COMPOUNDS FOR THE TREATMENT OF INFLAMMATORY DISORDERS AND MICROBIAL DISEASES

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates generally to tartaric acid functional compounds that can inhibit matrix metalloproteinases (MMPs), a disintegrin and metalloproteases (ADAMs), aggrecanase or aggrecan degrading metallo protease (ADMP) and/or tumor necrosis factor alpha - converting enzyme (TACE) and in so doing prevent the release of tumor necrosis factor alpha (TNF-α), pharmaceutical compositions comprising such compounds, and methods of treatment using such compounds. The invention also relates to tartaric acid functional compounds that can inhibit UDP-3-*O*-(R-3-hydroxymyristoyl)-N-acetylglucosamine deacetylase (LpxC), and as a result have antimicrobiall activity.

Description

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. 52A (1970) 424-434). There are four classes of protein degradative enzymes in mammalian cells: serine, cysteine, aspartic and metalloproteases. The available evidence supports the belief that it is the metalloproteases that are responsible for the degradation of the extracellular matrix of articullar cartilage 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. 26, 1983, 63-68 and Ibid. 27, 1984, 305-312). In addition, aggrecanase (a newly identified metalloprotease) has been identified that

provides the specific cleavage product of proteoglycan, found in RA and OA patients (Lohmander L. S. et al. Arthritis Rheum. 36, 1993, 1214-22).

Metalloproteases (MPs) 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 (see Wahl et al. Ann. Rep. Med. Chem. 25, 175-184, AP, San Diego, 1990).

MMPs are a family of over 20 different enzymes that are involved in a variety of biological processes 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 RA and OA, 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 alpha-2-macroglobulins and TIMPs (tissue inhibitor of MPs), which form inactive complexes with the MMP's.

Tumor necrosis factor alpha (TNF-α) is a cell-associated cytokine that is processed from a 26 kDa precursor form to a 17 kd active form. *See* Black R.A. "Tumor necrosis factor-alpha converting enzyme" Int J Biochem Cell Biol. 2002 Jan;34(1):1-5 and Moss ML, White JM, Lambert MH, Andrews RC."TACE and other ADAM proteases as targets for drug discovery" Drug Discov Today. 2001 Apr 1;6(8):417-426, each of which is incorporated by reference herein.

TNF-α has been shown to play a pivotal role in immune and inflammatory responses. Inappropriate or over-expression of TNF-α is a hallmark of a number of diseases, including RA, Crohn's disease, multiple sclerosis, psoriasis and sepsis. Inhibition of TNF-α production has been shown to be beneficial in many preclinical models of inflammatory disease, making inhibition of TNF-α production or signaling an appealing target for the development of novel anti-inflammatory drugs.

TNF-α is a primary mediator in humans and animals of inflammation, fever and acute phase responses, similar to those observed during acute infection and shock. Excess TNF-α has been shown to be lethal. Blocking the effects of TNF-α with specific antibodies can be beneficial in a variety of conditions, including autoimmune diseases such as RA (Feldman et al, Lancet, (1994) 344, 1105), non-insulin dependent diabetes mellitus (Lohmander L. S. et al., Arthritis Rheum. 36 (1993) 1214-22) and Crohn's disease (Macdonald T. et al., Clin. Exp. Immunol. 81 (1990) 301).

Compounds that inhibit the production of TNF-α are therefore of therapeutic importance for the treatment of inflammatory disorders. Recently it has been shown that metalloproteases, such as TACE, are capable of converting TNF-α from its inactive to active form (Gearing et al Nature, 1994, 370, 555). Since excessive TNF-α production has been noted in several disease conditions also characterized by MMP-mediated tissue degradation, compounds which inhibit both MMPs and TNF-α production may also have a particular advantage in diseases where both mechanisms are involved.

One approach to inhibiting the harmful effects of TNF-α is to inhibit the enzyme, TACE before it can process TNF-α to its soluble form. TACE is a member of the ADAM family of type I membrane proteins and mediates the ectodomain shedding of various membrane-anchored signaling and adhesion proteins. TACE has become increasingly important in the study of several diseases, including inflammatory disease, because of its role in cleaving TNF-α from its "stalk" sequence and thus releasing the soluble form of the TNF-α protein (Black R.A. Int J Biochem Cell Biol. 2002 34,1-5).

Aggrecan is the major proteoglycan of cartilage and provides this tissue with its mechanical properties of compressibility and elasticity. In arthritic conditions one of the earliest changes observed in cartilage morphology is the depletion of aggrecan [Mankin et al. (1970) J. Bone Joint Surg. 52A, 424-434], which appears to be due to an increased rate of degradation.

The aggrecan molecule is composed of two N-terminal globular domains, G1 and G2, which are separated by an approximately 150 residue interglobular domain (IGD), followed by a long central glycosaminoglycan (GAG) attachment region and a C-terminal globular domain, G3 [Hardingham et al. (1992) in Articular Cartilage and Osteoarthritis: Aggrecan, The Chondroitin Sulfate/Keratan Sulfate Proteoglycan from Cartilage (Kuettner et al.) pp. 5- 20, Raven Press, New York and Paulson et al. (1987) Biochem. J. 245, 763-7721. These aggrecan molecules interact through the Gl domain with hyaluronic acid and a link protein to form large molecular weight aggregates which are trapped within the cartilage matrix [Hardingham et al. (1972) Biochim. Biophys. Acta 279, 401-405, Heinegard et al. (1974) J. Biol. Chem. 249, 4250-4256, and Hardingham, T.E. (1979) Biochem. J. 177, 237-247]. Loss of aggrecan from cartilage in arthritic conditions involves proteolytic cleavage of the aggrecan core protein within the IGD, producing a N-terminal G-1 fragment that remains bound to hyaluronic acid and the link protein within the matrix, releasing a large C-terminal GAG-containing aggrecan fragment that diffuses out of the cartilage matrix. Loss of the C-terminal fragment results in cartilage deficient in its mechanical properties. This deficiency arises because the GAGs which are present on the C-terminal portion of the aggrecan core protein are the components of aggrecan that impart the mechanical properties to the molecule through their high negative charge and water binding capacity.

Therefore compounds that exhibit inhibition against aggrecanase or aggrecan degrading metalloprotease (ADMP) could serve as potential therapeutic agents for treating aggrecanase-related disorders cited above, and are therefore desired.

Lipid A is the hydrophobic anchor of lipopolysaccharide (LPS) and forms the major lipid component of the outer monolayer of the outer membrane of gram-negative bacteria. Lipid A is required for bacterial growth and inhibition of its biosynthesis is lethal to the bacteria. Furthermore, blocking Lipid A biosynthesis increases the sensitivity of bacteria to other antibiotics.

One of the key enzymes of bacterial lipid A biosynthesis is LpxC. LpxC catalyzes the removal of the N-acetyl group of UDP-3-O-(R-3-hydroxymyristoyl)-N-acetylglucosamine. The LpxC enzyme is essential in gram negative bacteria for the biosynthesis of Lipid A, and it is notably absent from mammalian genomes. Since LpxC is essential for Lipid A biosynthesis and inhibition of Lipid A biosynthesis is lethal to bacteria, inhibitors of LpxC have utility as antibiotics. In addition, the absence of LpxC from mammalian genomes reduces potential toxicity of LpxC inhibitors in mammals. Accordingly, LpxC is an attractive target for antibacterial drug discovery.

There are several patents which disclose hydroxamate, carboxylate and/or lactam based MMP inhibitors.

US 6,677,355 and US 6,534,491(B2), describe compounds that are hydroxamic acid derivatives and MMP inhibitors.

US 6,495,565 discloses lactam derivatives that are potential inhibitors of matrix metalloproteases and/or TNF-α.

U.S. Patent Application Serial No. 11/142601 (filed June 1, 2005) discloses tartrate compounds that are useful TACE inhibitors.

U.S. Patent 5,925,659 teaches that certain heterocyclic hydroxamate compounds, in particular oxazoline compounds, have the ability to inhibit LpxC.

WO2004/00744 refers to N-Hydroxyamide derivatives having LpxC inhibitory activity and thus possessing antibacterial activity.

WO2004/062601 also refers to small molecule inhibitors of LpxC.

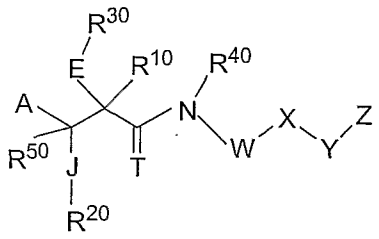
There is a need in the art for inhibitors of MMPs, ADAMs, aggrecanase, ADMP, TACE, and TNF-α, which can be useful as anti-inflammatory compounds and cartilage protecting therapeutics. The inhibition of TNF-α, ADMP, TACE and or other MMPs can prevent the degradation of cartilage by these enzymes, thereby alleviating the pathological conditions of OA and RA as well as many other auto-immune diseases.

There is also a need in the art for small molecule inhibitors of LpxC as potential antibacterial agents.

SUMMARY OF THE INVENTION

In its many embodiments, the present invention provides a novel class of compounds as inhibitors of LpxC, TACE, ADMP, aggrecanase, the production of TNF-α, MMPs, ADAMs or any combination thereof, methods of preparing such compounds, pharmaceutical compositions comprising one or more such compounds, methods of preparing pharmaceutical formulations comprising one or more such compounds, and methods of treatment, prevention, inhibition or amelioration of one or more diseases associated with LpxC, TACE, ADMP, aggrecanase,TNF-α, MMPs, ADAMs or any combination thereof using such compounds or pharmaceutical compositions.

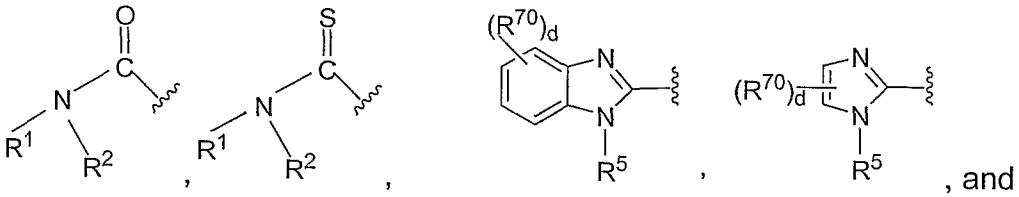
In one embodiment, the present application discloses a compound, or pharmaceutically acceptable salts or solvates of said compound, said compound having the general structure shown in formula (I):



formula (I)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

A is selected from the group consisting of:



, and

$-CO_2R^1$;

d is 0 to 4;

J is selected from the group consisting of: O, S, and NR^5;

E is selected from the group consisting of: O, S, and NR^5;

T is O or S;

R^1 and R^2 are the same or different, each being independently selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl, and heteroaryl; or alternatively R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 4-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein each of said alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl, heteroaryl and 4-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties below;

R^{10} is selected from the group consisting of H, alkyl, and fluoroalkyl;

R^{20} is selected from the group consisting of H, alkyl, and fluoroalkyl;

R^{30} is H or alkyl, or alternatively R^{30} and R^{40} taken together with the N to which R^{40} is shown attached to in Formula I, are joined to form a 4-7 membered heterocylic ring, wherein said heterocylic ring is unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties below;

R^{40} is H or alkyl;

R^{50} is H or alkyl;

W is $-(CR^{13}{}_2)_n-$, wherein n is 0 to 5 or a covalent bond, or alternatively two R^{13} groups can fuse to form a 3-8 membered cycloalkyl, wherein said 3-8 membered cycloalkyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^6 moieties below;

X is absent or present, and if present X is selected from the group consisting of a covalent bond, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl can be unsubstituted or optionally

independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties below;

Y is absent or present, and if present Y is selected from the group consisting of a covalent bond, $-[C(R^6)_2]_n-$ wherein n is 1 to 2, -O-, -S-, $-NR^1-$, $-SO_v-$ wherein v is 1 to 2, $-SO_n(CR^6_2)_p-$ wherein n is 1 or 2 and p is 1 to 4, $-O(CR^6_2)_q-$ or $-(CR^6_2)_qO-$ wherein q is 1 to 4, $-N(R^7)S(O)_n-$ or $-S(O)_nN(R^7)-$ wherein n is 1 or 2, and $-N(R^7)C(O)-$ or $-C(O)N(R^7)-$;

Z is selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, said cycloalkyl, heterocyclyl, aryl, and heteroaryl being optionally fused with aryl, heterocyclyl, heteroaryl or cycloalky; wherein each of said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties below;

R^5 is selected from the group consisting of hydrogen, alkyl, and alkylaryl;

each R^6 is the same or different and is independently selected from the group consisting of hydrogen, halogen, $-SR^{15}$, $-S(O)_qR^{15}$ wherein q is 1 to 2, alkyl, cycloalkyl, heterocyclyl, alkoxyl, hydroxy, nitro, cyano, amino, alkenyl, alkynyl, arylalkyl, aminocarbonyl, alkylcarbonyl, and alkoxycarbonyl;

each R^7 is the same or different and is independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, alkenyl, alkynyl, arylalkyl, alkylcarbonyl, and alkoxycarbonyl, wherein each of the aryl, heteroaryl and heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties below;

R^{13} is the same or different and is independently selected from the group consisting of hydrogen, halogen, -OH, $-OR^{14}$, alkyl, cycloalkyl, heterocyclyl, alkenyl, alkynyl, alkylaryl, alkylamino, and alkylcarbonyl;

R^{14} is alkyl;

each R^{70} is a substituent for H where indicated and is the same or different and is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, -CN, $-CF_3$, $-OCF_3$, $-OR^{15}$, $-C(O)R^{15}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, $-SR^{15}$, $-S(O)_qN(R^{15})(R^{16})$ wherein q is 1 to 2, $-C(=NOR^{15})R^{16}$, $-N(R^{15})(R^{16})$, -alkyl-$N(R^{15})(R^{16})$, $-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})S(O)_2R^{16}$, $-N(R^{17})S(O)_2N(R^{16})(R^{15})$, $-N(R^{17})S(O)N(R^{16})(R^{15})$, $-N(R^{17})C(O)N(R^{16})(R^{15})$, $-CH_2-N(R^{17})C(O)N(R^{16})(R^{15})$, $-N(R^{15})C(O)OR^{16}$, $-CH_2-N(R^{15})C(O)OR^{16}$, and $-S(O)_qR^{15}$ wherein q is 1 to 2; and wherein each of the alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl are independently unsubstituted or substituted by 1 to 5 groups independently selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, $-CF_3$, -CN, $-OR^{15}$, $-N(R^{15})(R^{16})$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, and $-N(R^{15})S(O)R^{16}$;

each R^{15}, R^{16} and R^{17} are independently selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, or alternatively R^{15} and R^{16} taken together with the N to which they are shown attached, are joined to form a 4-8 membered heterocylic ring, wherein said 4-8 membered cycloalkyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{75} moieties below;

each R^{75} is independently selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl, and wherein each of the alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl are independently

unsubstituted or substituted by 1 to 5 groups independently selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, $-CF_3$, -CN, $-OR^{19}$, $-N(R^{19})_2$, $-C(O)OR^{19}$, $-C(O)N(R^{19})_2$, and $-N(R^{19})S(O)R^{19}$; and

each R^{19} is independently selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl.

The compounds of Formula I can be useful as inhibitors and may be useful in the treatment and prevention of diseases associated with LpxC, TACE, aggrecanase, ADMP, TNF-α, MMPs, ADAMs or any combination thereof.

DETAILED DESCRIPTION OF THE INVENTION

In its several embodiments, the present invention provides a novel class of inhibitors of LpxC, TACE, aggrecanase, ADMP, the production of TNF-α, MMPs, ADAMs or any combination thereof, pharmaceutical compositions containing one or more of the compounds, methods of preparing pharmaceutical formulations comprising one or more such compounds, and methods of treatment, prevention or amelioration of one or more of the symptoms of inflammation.

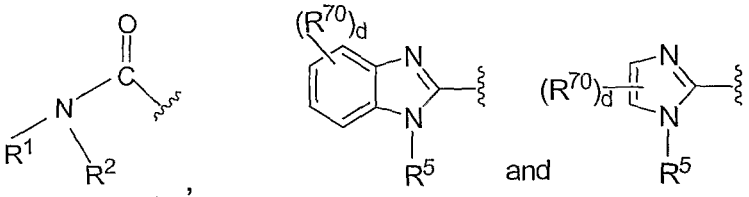
In one embodiment, the present invention provides compounds which are represented by structural Formula (I) above or a pharmaceutically acceptable salt, solvate or isomer thereof, wherein the various moieties are as described above.

In one embodiment, R^1 and R^2 are the same or different, each being independently selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl, and heteroaryl; or alternatively R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 4-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein each of said alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl, heteroaryl and 4-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more

moieties which can be the same or different, each moiety being independently selected from the group of R^{70}.

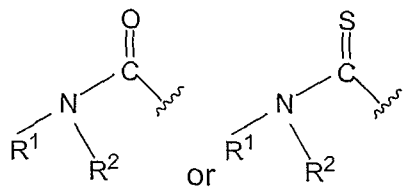
In one embodiment, R^1 and R^2 are the same or different, each being independently selected from the group consisting of H, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl, and heteroaryl; or alternatively R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 4-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein each of said alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl, heteroaryl and 4-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70}.

In one embodiment, A is selected from the group consisting of:



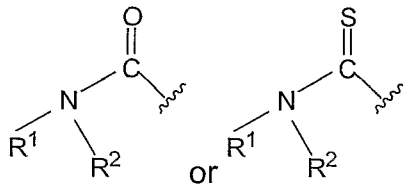
wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 4-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein said 4-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties.

In another embodiment, A is



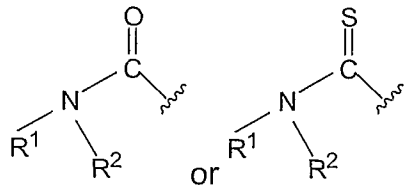
wherein R^1 and R^2 are the same or different, each being independently selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl, and heteroaryl; wherein said alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl and heteroaryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties.

In another embodiment, A is



wherein R^1 and R^2 are the same or different, each being independently selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl, and heteroaryl; wherein said alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl and heteroaryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties.

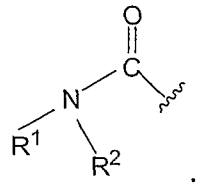
In another embodiment, A is



wherein R^1 and R^2 are the same or different, each being independently selected from the group consisting of H, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl, and heteroaryl; wherein said alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl and heteroaryl can be unsubstituted

or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties.

In another embodiment, A is



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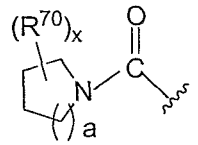
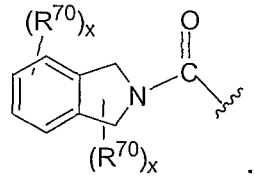
In another embodiment, A is



wherein a is 0 to 4 and x is 0 to 4.

In another embodiment, A is



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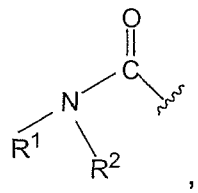
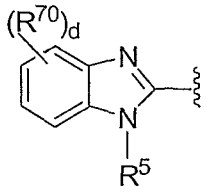
wherein each x idependently is 0 to 4.

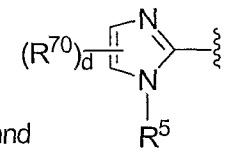
In another embodiment, A is selected from the group consisting of:



,

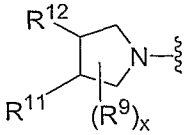


and



wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 3-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein said 3-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties;

wherein a ring is formed from -NR^1R^2 and said ring is



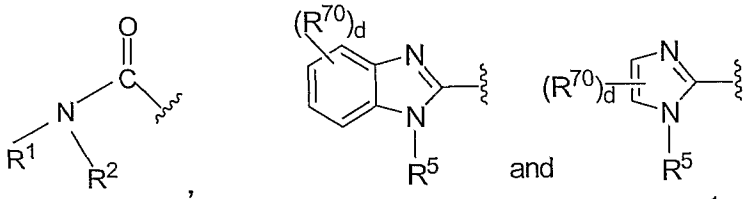
wherein

each R^9 is a substituent for H where indicated and can be the same or different, each being independently selected from the group consisting of -OH, $-OR^{14}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, alkyl, aryl, heteroaryl, alkenyl, alkynyl, cycloalkyl and heterocyclyl, wherein said alkyl, aryl, heteroaryl, alkenyl, alkynyl, cycloalkyl and heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties;

$R^{11}$and R^{12} taken together with the carbon to which each $R^{11}$and R^{12} are shown attached are fused heteroaryl or fused cycloalkyl, wherein said fused heteroaryl and fused cycloalkyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties; and

x is 0 to 4, and when x is greater than 1, each R^9 moiety can be the same or different, each moiety being independently selected from the group of R^9 moieties.

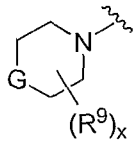
In another embodiment, A is selected from the group consisting of:



wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 3-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein said 3-8 membered heterocyclic ring can be unsubstituted or optionally

independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties;

wherein a ring is formed from $-NR^1R^2$ and said ring is



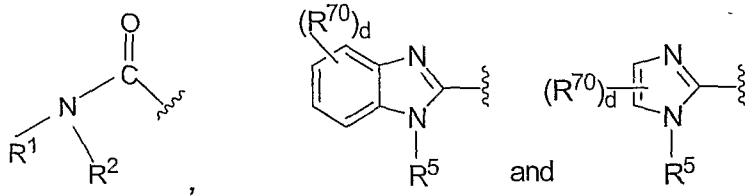
wherein

each R^9 is a substituent for H where indicated and can be the same or different, each being independently selected from the group consisting of -OH, $-OR^{14}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, alkyl, aryl, heteroaryl, alkenyl, alkynyl, cycloalkyl and heterocyclyl, wherein said alkyl, aryl, heteroaryl, alkenyl, alkynyl, cycloalkyl and heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties;

x is 0 to 4, and when x is greater than 1, each R^9 moiety can be the same or different, each moiety being independently selected from the group of R^9 moieties; and

G is selected from the group consisting of CH_2, NR^7, O, S, or SO_2.

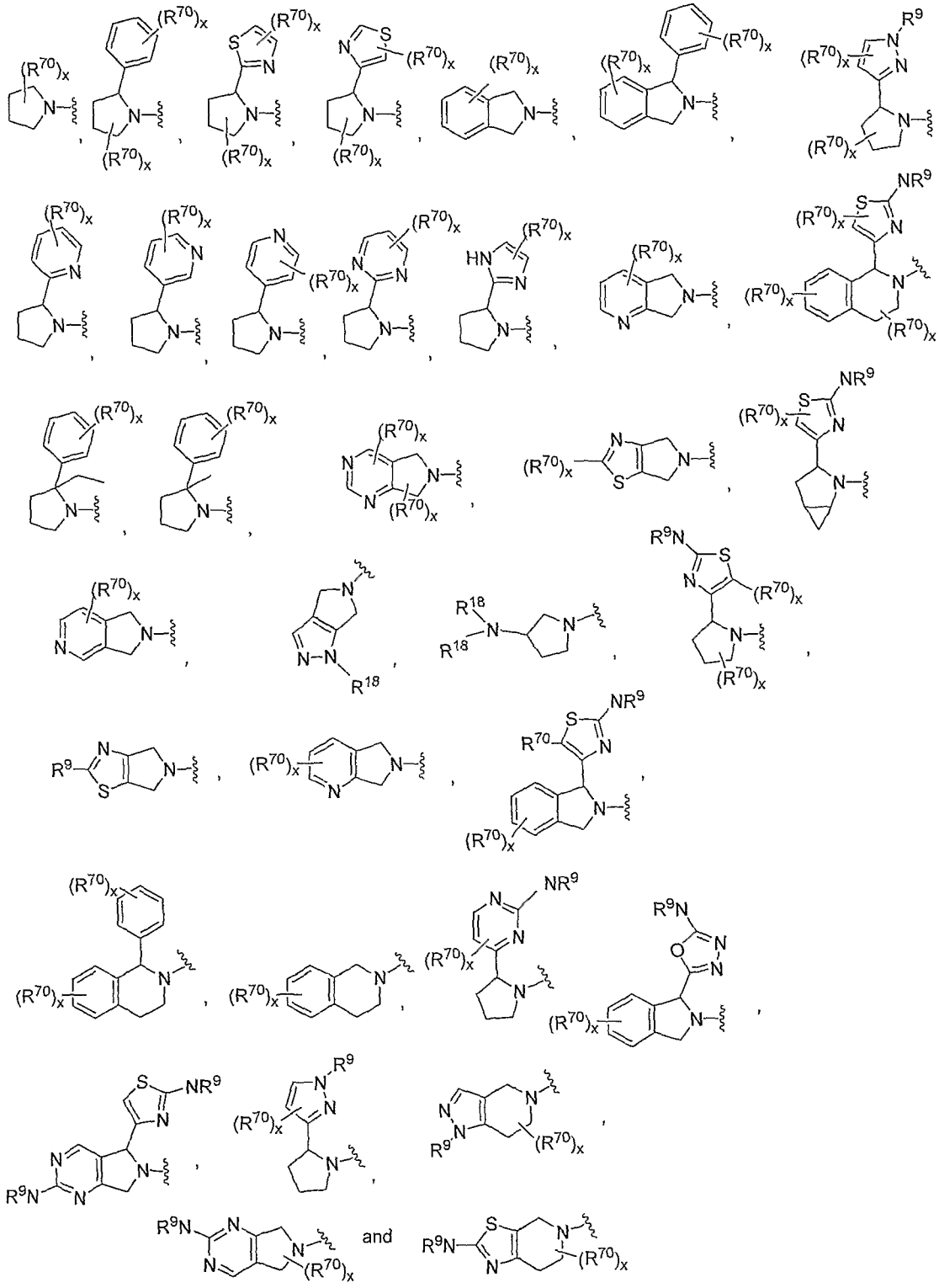
In another embodiment, A is selected from the group consisting of:



wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 3-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein said 3-8 membered heterocyclic ring can be

unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties;

a ring is formed from $-NR^1R^2$ and said ring is selected from the group consisting of



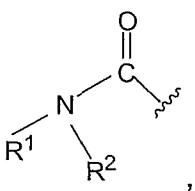
and

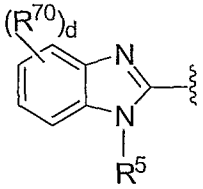
wherein

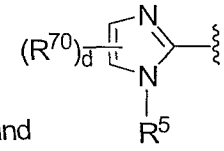
x is 0 to 4, and when x is greater than 1, each R^{70} moiety can be the same or different, each moiety being independently selected from the group of R^{70} moieties; and

each R^{18} is the same or different and is independently H or alkyl.

In another embodiment, A is selected from the group consisting of:

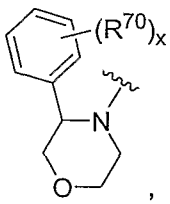


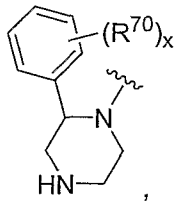
,


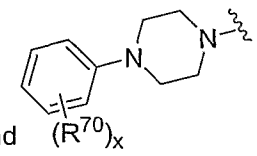
and


wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 3-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein said 3-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties;

a ring is formed from $-NR^1R^2$ and said ring is selected from the group consisting of



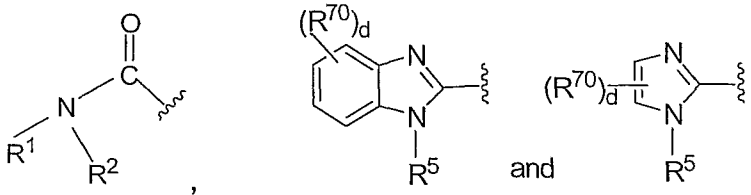
,


,
and


wherein

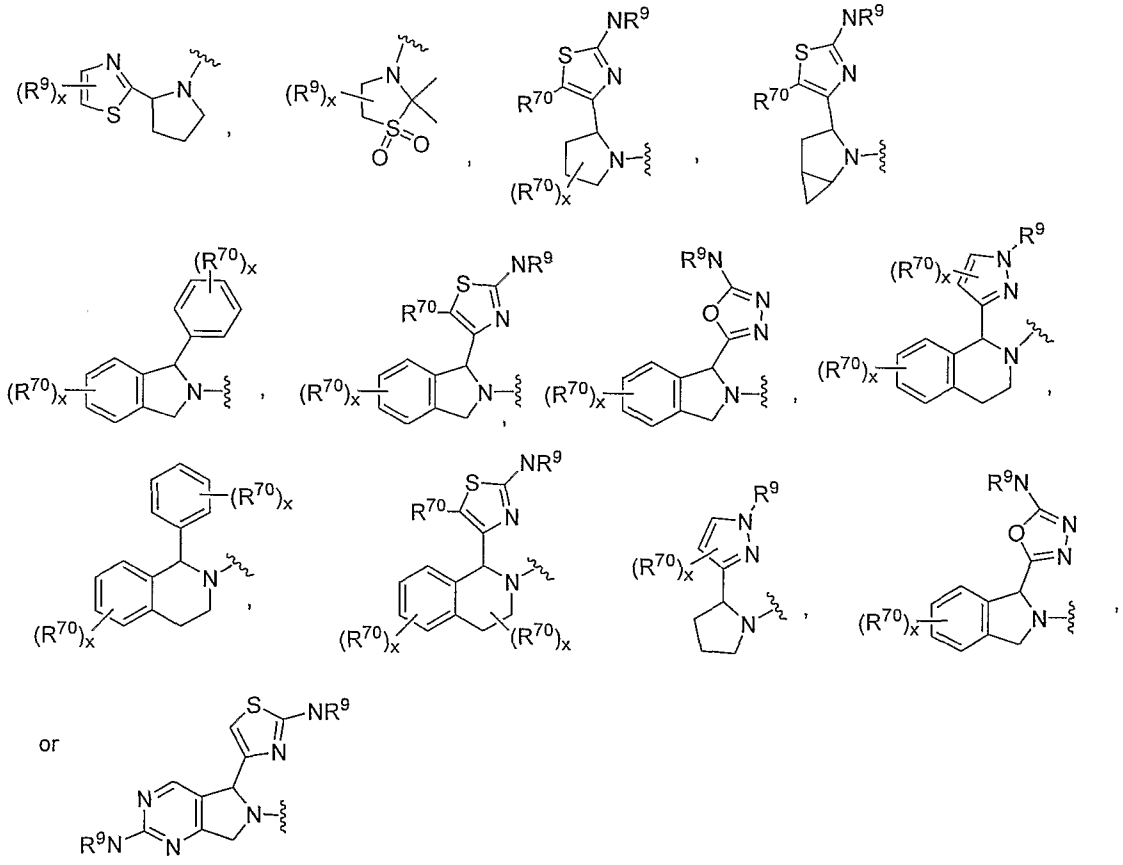
x is 0 to 4, and when x is greater than 1, each R^{70} moiety can be the same or different, each moiety being independently selected from the group of R^{70} moieties.

In another embodiment, A is selected from the group consisting of:



wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 3-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein said 3-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties;

a ring is formed from $-NR^1R^2$ and said ring is



wherein

each R^9 is a substituent for H where indicated and can be the same or different, each being independently selected from the group consisting of -OH,

$-OR^{14}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, alkyl, aryl, heteroaryl, alkenyl, alkynyl, cycloalkyl and heterocyclyl, wherein said alkyl, aryl, heteroaryl, alkenyl, alkynyl, cycloalkyl and heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties; and

x is 0 to 4, and when x is greater than 1, each R^9moiety can be the same or different, each moiety being independently selected from the group of R^9moieties.

In another embodiment, J is O.

In another embodiment, E is O.

In another embodiment, R^{10} is H or alkyl.

In another embodiment, R^{20}, R^{30}, R^{40}, and R^{50} are all the same and are H.

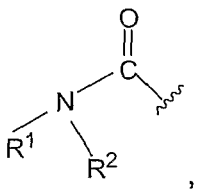
In another embodiment, R^6 is H or alkyl.

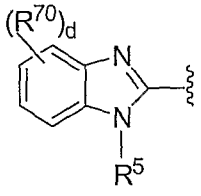
In another embodiment, R^6 is H.

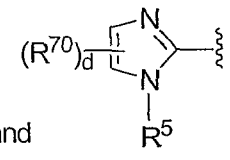
In another embodiment, R^{13} is H or alkyl.

In another embodiment, R^{13} is H or $-CH_3$.

In another embodiment, A is selected from the group consisting of



,


and


wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 4-6 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with R^{70}, wherein R^{70} is aryl.

In another embodiment, Y is a covalent bond or $-[C(R^6)_2]_n-$ wherein n is 1 to 2, $-CH_2-$.

In another embodiment, Y is selected from the group consisting of a covalent bond, $-CH_2-$, -C(H)(OH)-, -C(O)- and –O-.

In another embodiment, Y is a covalent bond or $-CH_2-$.

In another embodiment, Y is a covalent bond.

In another embodiment, W is $-(CR^{13}{}_2)_n-$, in which n is 0-5.

In another embodiment, W is $-(CR^{13}{}_2)_n-$, in which n is 1-5 and each R^{13} is H or alkyl.

In another embodiment, W is selected from the group consisting of $-CH_2-$, $-C(H)(CH_3)-$, $-C(CH_3)_2-$ and $-CH_2CH_2-$.

In another embodiment, W is $-CH_2-$.

In another embodiment, W is $-C(H)(CH_3)-$.

In another embodiment, X is selected from the group consisting of alkyl, aryl, heterocyclyl and heteroaryl.

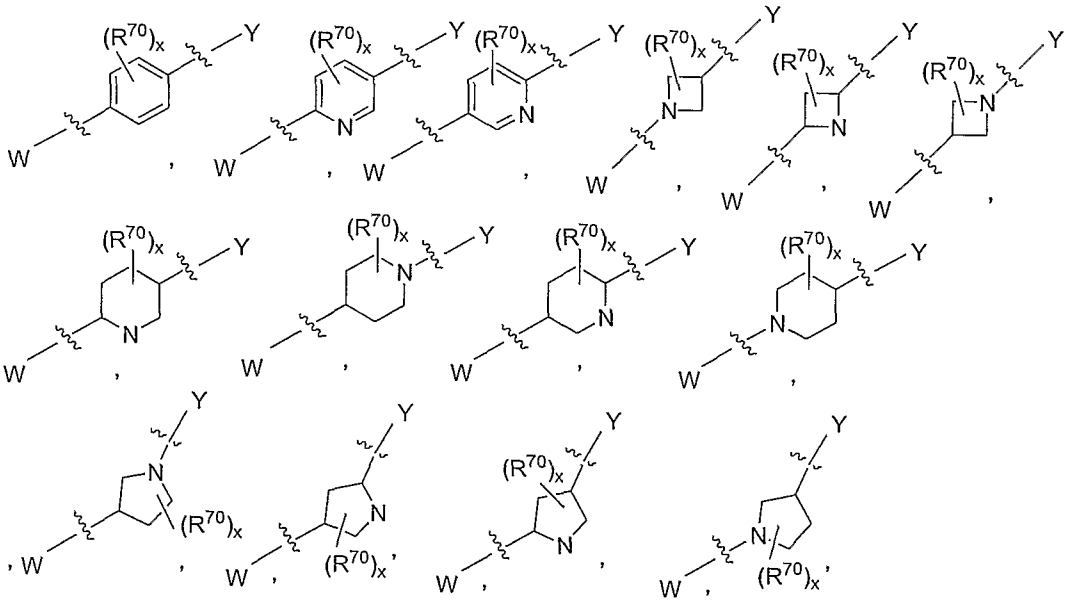
In another embodiment, X is aryl.

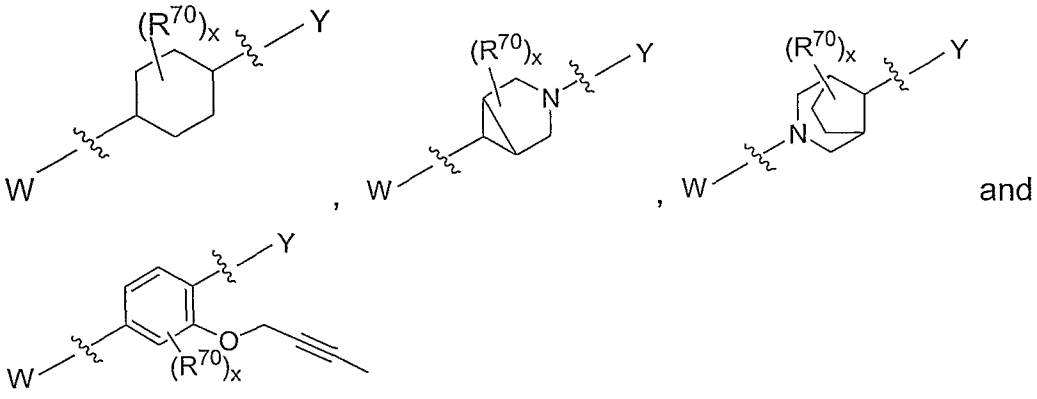
In another embodiment, X is heteroaryl.

In another embodiment, X is selected from the group consisting of phenyl, azetidinyl, pyrrolidinyl, piperidinyl, pyridinyl, thienyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl.

In another embodiment, X is selected from the group consisting of phenyl, pyridinyl and piperidinyl.

In another embodiment, X is selected from the group consisting of



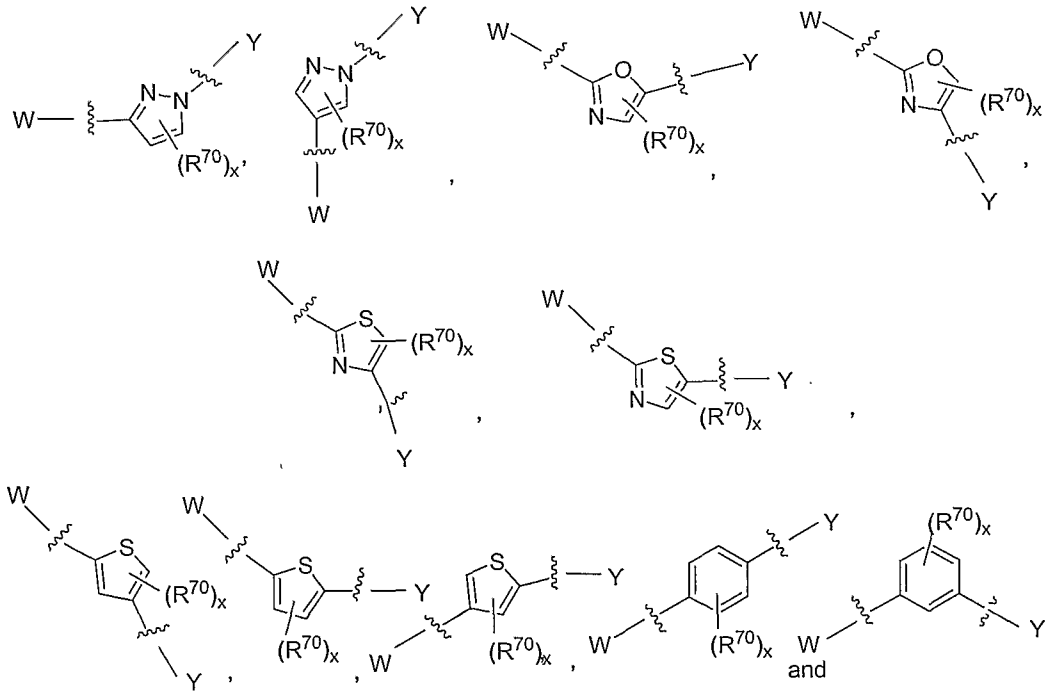


wherein

x is 0 to 4, and wherein x is greater than 1, each R^{70} moiety can be the same or different, each moiety being independently selected from the group of R^{70} moieties.

In the above shown moieties for X, X is the moiety enclosed by and W and Y are shown only to indicate which end of the X is attached to W and which end to Y. Similar depictions occur throughout this application with similar connotations.

In another embodiment X is selected from the group consisting of

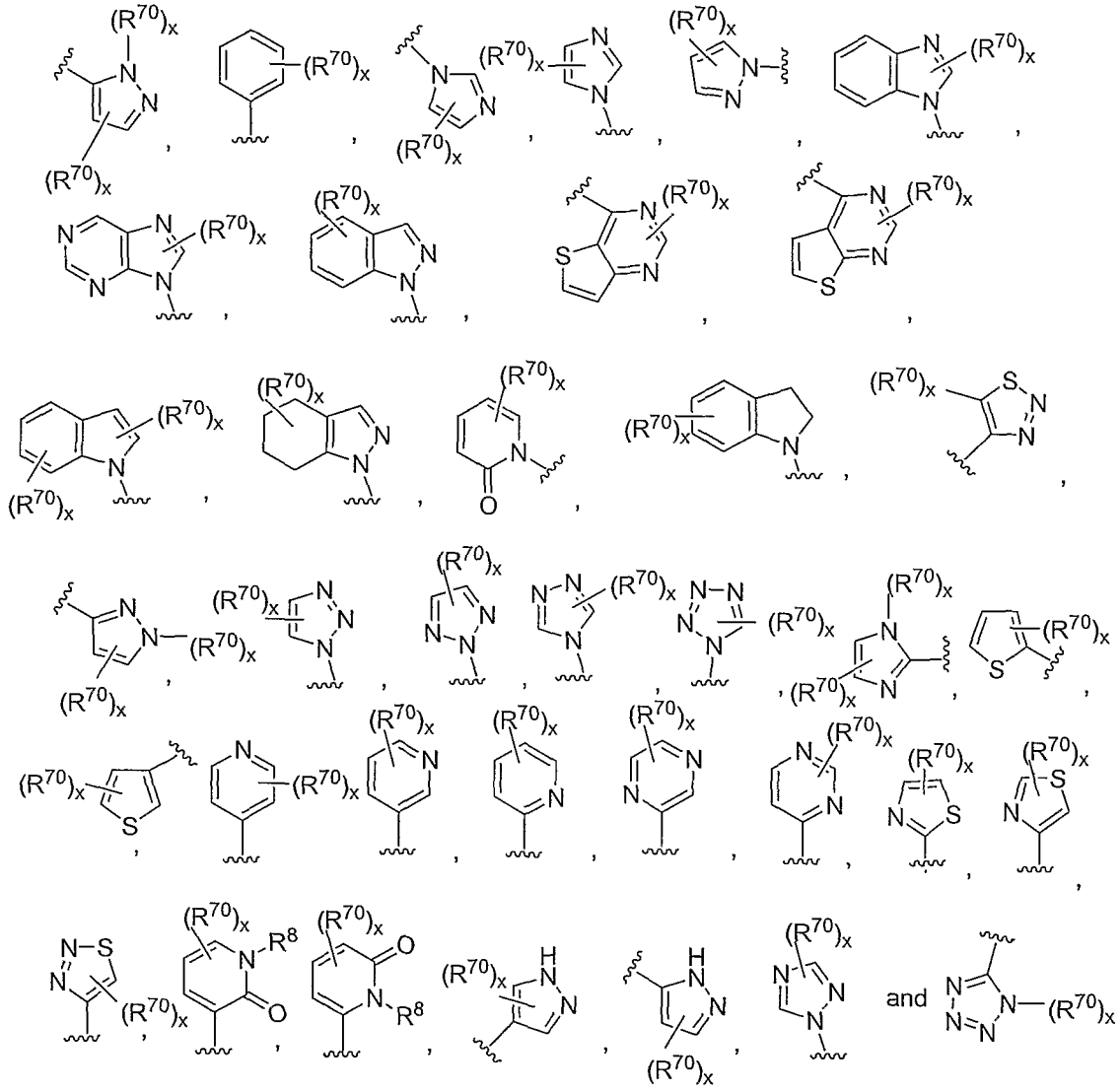


wherein x is 0 to 4, and when x is greater than 1, each R^{70} moiety can be the same or different, each moiety being independently selected from the group of R^{70} moieties.

In another embodiment, Z is selected from the group consisting of H, aryl and heteroaryl.

In another embodiment, Z is selected from the group consisting of H, phenyl, indolyl, benzimidazolyl, pyrazolyl, thienyl, pyridinyl, thiazolyl, thiadiazolyl, imidazolyl, pyrrolidinyl, pyrazinyl, triazolyl, tetrazolyl and tetrazinyl, wherein said phenyl, indolyl, benzimidazolyl, pyrazolyl, thienyl, pyridinyl, thiazolyl, thiadiazolyl, imidazolyl, pyrrolidinyl, pyrazinyl, triazolyl, tetrazolyl and tetrazinyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of R^{70} moieties.

In another embodiment, Z is selected from the group consisting of



wherein x is 0 to 4, and when x is greater than 1, each R^{70} moiety can be the same or different, each moiety being independently selected from the group of R^{70} moieties.

In another embodiment, Z is phenyl.

In another embodiment, Z is a phenyl substituted with at least one substituent selected from the group consisting of cyano, alkoxy, halogen, alkyl, haloalkyl, hydroxy, aryl, heteroaryl, aryloxy, amino and tetrazole.

In another embodiment, Z is thienyl.

In another embodiment, Z is a thienyl substituted with at least one substituent selected from the group consisting of cyano, alkoxy, halogen, alkyl, haloalkyl, hydroxy, aryl, heteroaryl, aryloxy, amino and tetrazole.

In another embodiment, Z is pyrazolyl.

In another embodiment, Z is a pyrazolyl substituted with at least one substituent selected from the group consisting of cyano, alkoxy, halogen, alkyl, haloalkyl, hydroxy, aryl, heteroaryl, aryloxy, amino and tetrazole.

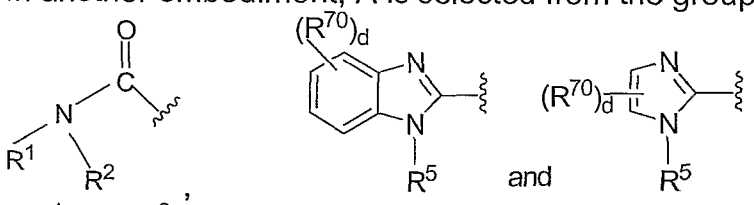
In another embodiment, Z is pyridinyl.

In another embodiment, Z is a pyridinyl substituted with at least one substituent selected from the group consisting of cyano, alkoxy, halogen, alkyl, haloalkyl, hydroxy, aryl, heteroaryl, aryloxy, amino and tetrazole.

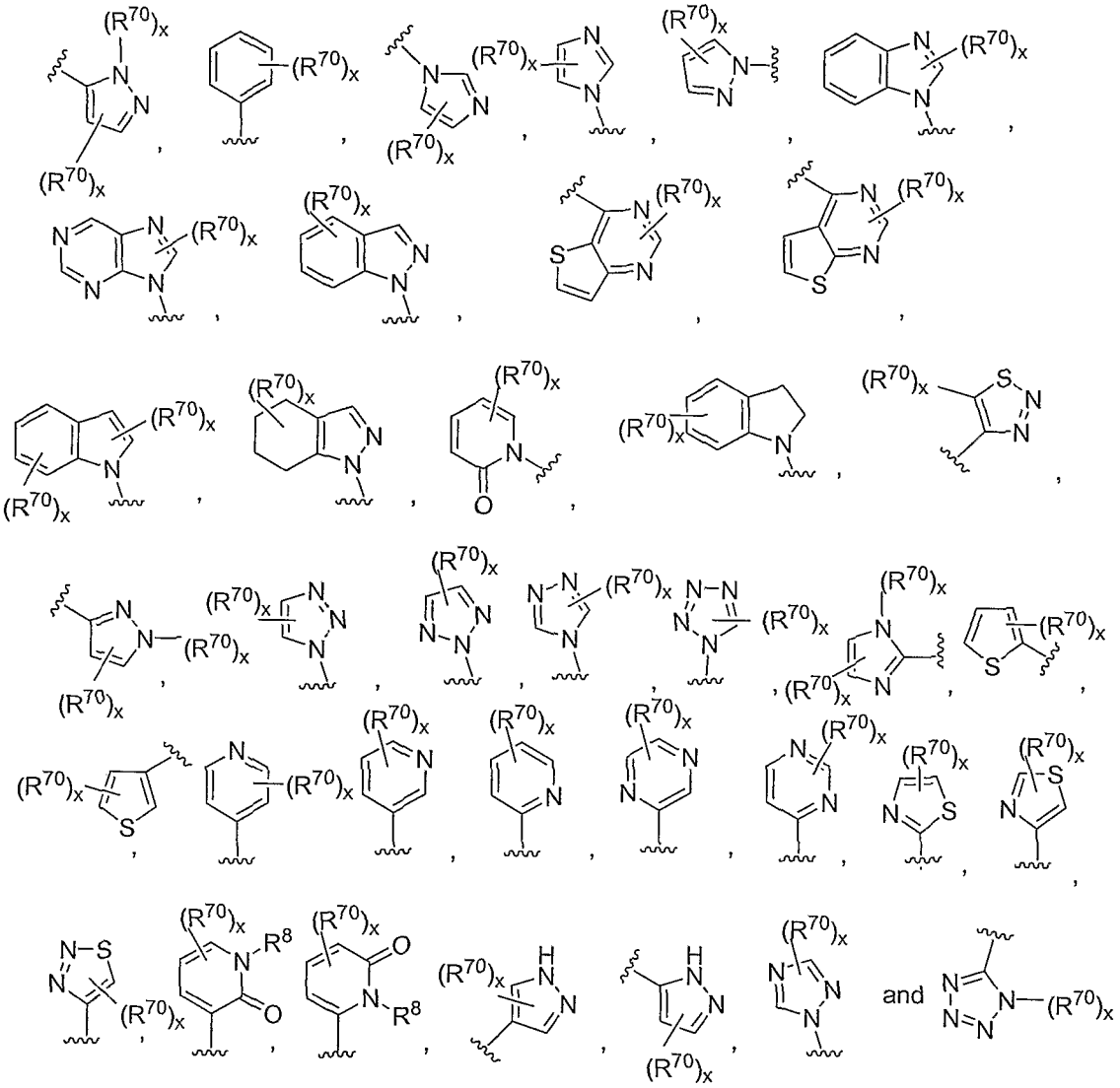
In another embodiment, Z is imidazolyl.

In another embodiment, Z is an imidazolyl substituted with at least one substituent selected from the group consisting of cyano, alkoxy, halogen, alkyl, haloalkyl, hydroxy, aryl, heteroaryl, aryloxy, amino and tetrazole.

In another embodiment, A is selected from the group consisting of:

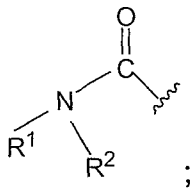


wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 4-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with one or more R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein said 4-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties; E, J and T are the same and are O; R^{10} is H or alkyl; R^{20}, R^{30}, R^{40}, and R^{50} are the same and are H; W is $-(CR^{13}{}_2)_n-$,wherein n is 0 to 5; X is selected from the group consisting of aryl, heteroaryl and heterocyclyl; Y is selected from the group consisting of a covalent bond, $-[C(R^6)_2]_n-$ wherein n is 1 to 2, -O-, -S-, and $-NR^1-$; and Z is selected from the group consisting of



.

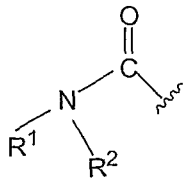
In another embodiment, A is:



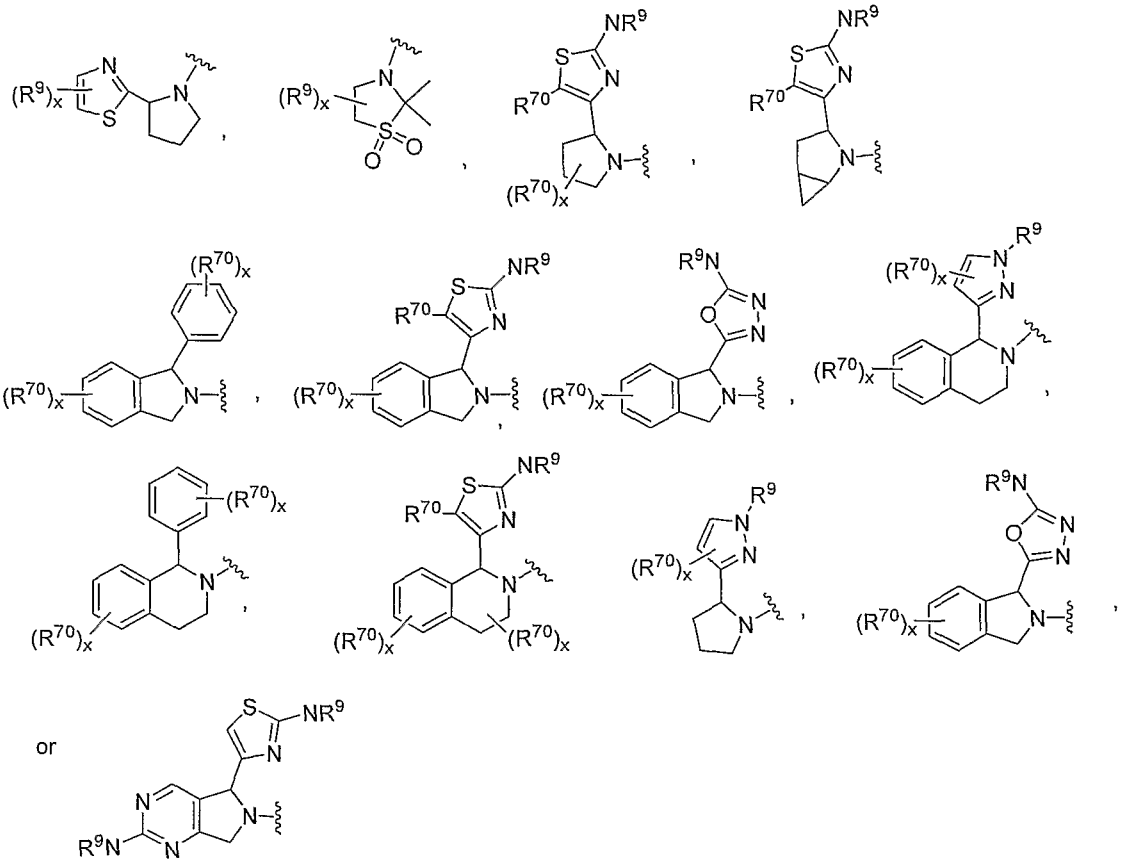
;

wherein;

the $-NR^1R^2$ of



is



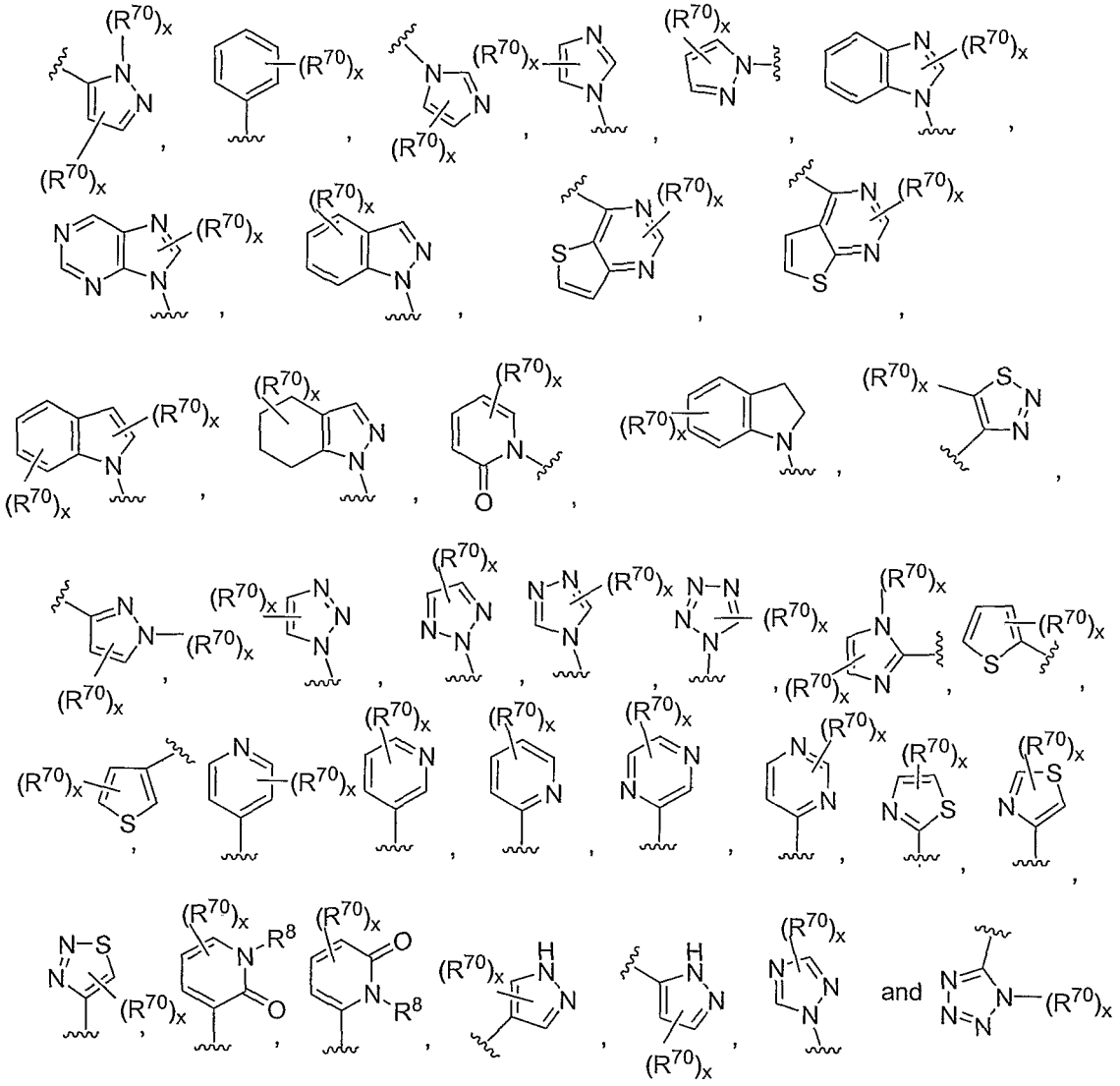
wherein

each R^9 is a substituent for H where indicated and can be the same or different, each being independently selected from the group consisting of -OH, $-OR^{14}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, alkyl, aryl, heteroaryl, alkenyl, alkynyl, cycloalkyl and heterocyclyl, wherein said alkyl, aryl, heteroaryl, alkenyl, alkynyl, cycloalkyl and heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties; and

x is 0 to 4, and when x is greater than 1, each R^9moiety can be the same or different, each moiety being independently selected from the group of R^9 moieties;

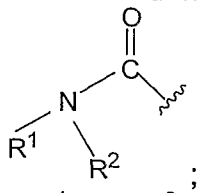
E, J and T are the same and are O; R^{10} is H or alkyl; R^{20}, R^{30}, R^{40}, and R^{50} are the same and are H; W is $-(CR^{13}{}_2)_n-$,wherein n is 0 to 5; X is selected from the group consisting of aryl, heteroaryl and heterocyclyl; Y is selected

from the group consisting of a covalent bond, -[C(R^6)$_2$]$_n$- wherein n is 1 to 2, -O-, -S-, and -NR^1-; and Z is selected from the group consisting of



.

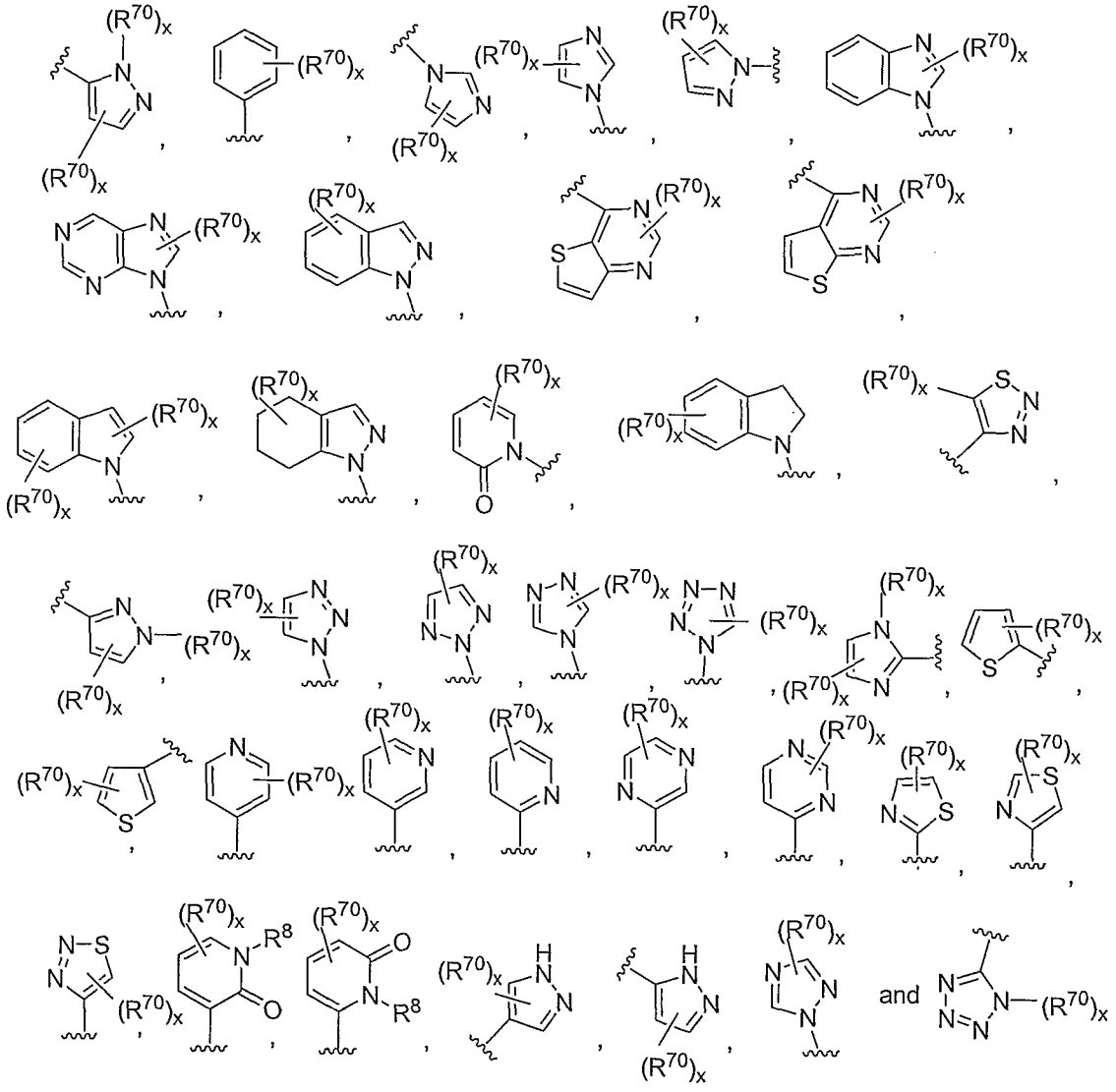
In another embodiment, A is:



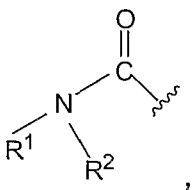
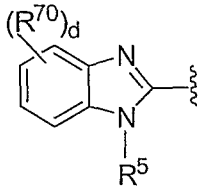
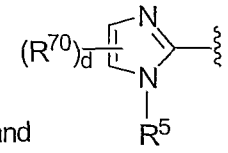
;

wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 4-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with one or more R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein said 4-8 membered heterocyclic ring can be unsubstituted or

optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties; E, J and T are the same and are O; R^{10} is H or alkyl; R^{20}, R^{30}, R^{40}, and R^{50} are the same and are H; W is $-(CR^{13}_2)_n-$,wherein n is 0 to 5; X is selected from the group consisting of aryl, heteroaryl and heterocyclyl; Y is selected from the group consisting of a covalent bond, $-[C(R^6)_2]_n-$ wherein n is 1 to 2, -O-, -S-, and $-NR^1-$; and Z is selected from the group consisting of

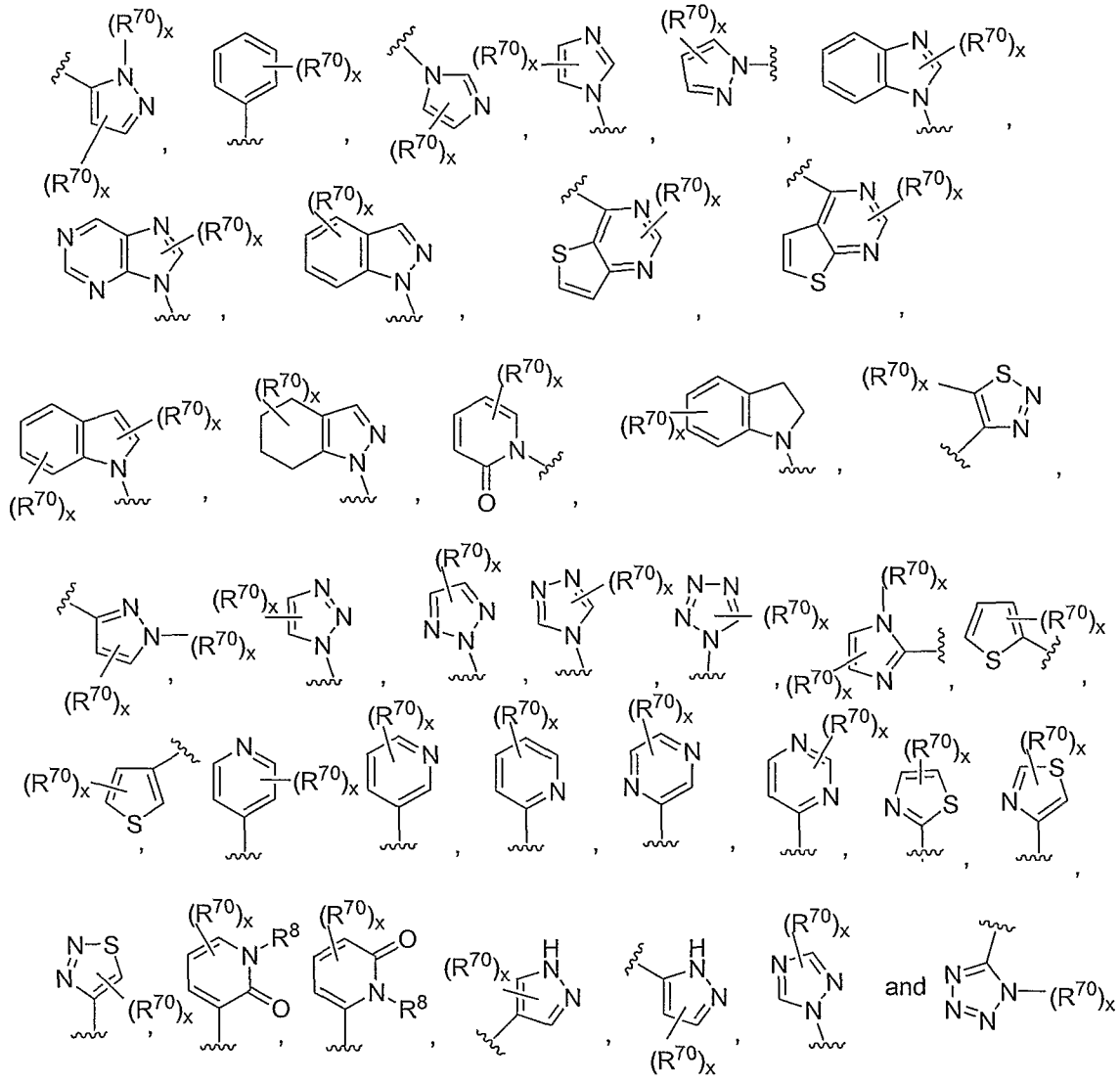


In another embodiment, A is selected from the group consisting of:

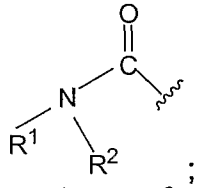


and


wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 3-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with one or more R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein said 3-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties;

wherein E, J and T are the same and are O; R^{10} is H or alkyl; R^{20}, R^{30}, R^{40}, and R^{50} are the same and are H; W is $-(CR^6{}_2)_n-$, wherein n is 0 to 5; X is selected from the group consisting of phenyl, piperidinyl, pyridinyl, thienyl, thiazolyl, oxazolyl and pyrazolyl; Y is $-[C(R^6)_2]_n-$ wherein n is 1 to 2; and Z is selected from the group consisting of



In another embodiment, A is:

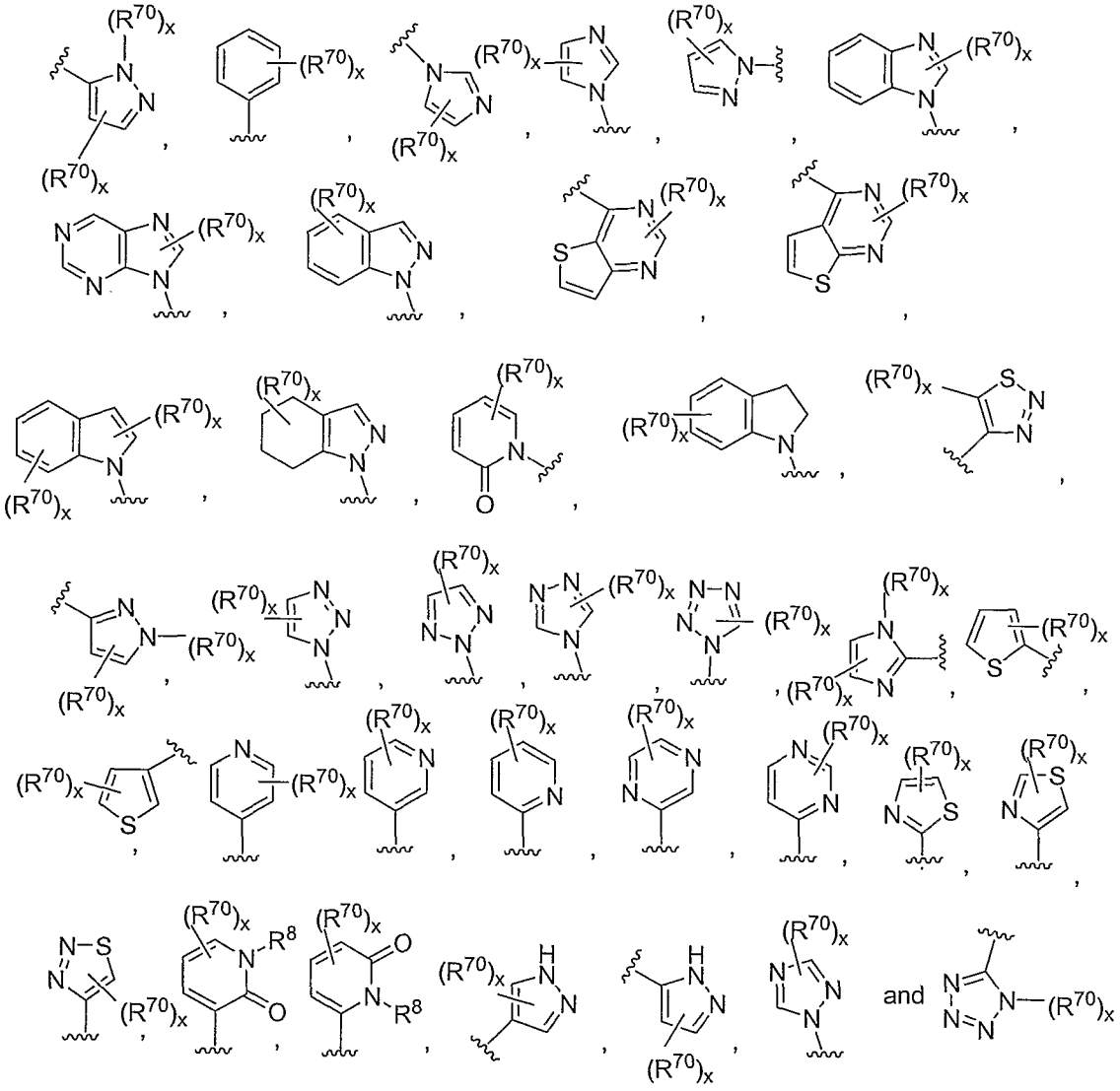


;

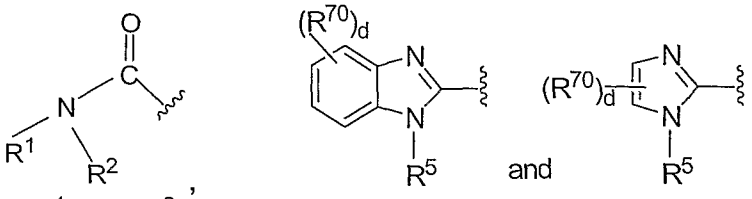
wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 3-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with one or more R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein said 3-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be

the same or different, each moiety being independently selected from the group of R^{70} moieties;

wherein E, J and T are the same and are O; R^{10} is H or alkyl; R^{20}, R^{30}, R^{40}, and R^{50} are the same and are H; W is $-(CR^6{}_2)_n-$, wherein n is 0 to 5; X is selected from the group consisting of phenyl, piperidinyl, pyridinyl, thienyl, thiazolyl, oxazolyl and pyrazolyl; Y is $-[C(R^6)_2]_n-$ wherein n is 1 to 2; and Z is selected from the group consisting of

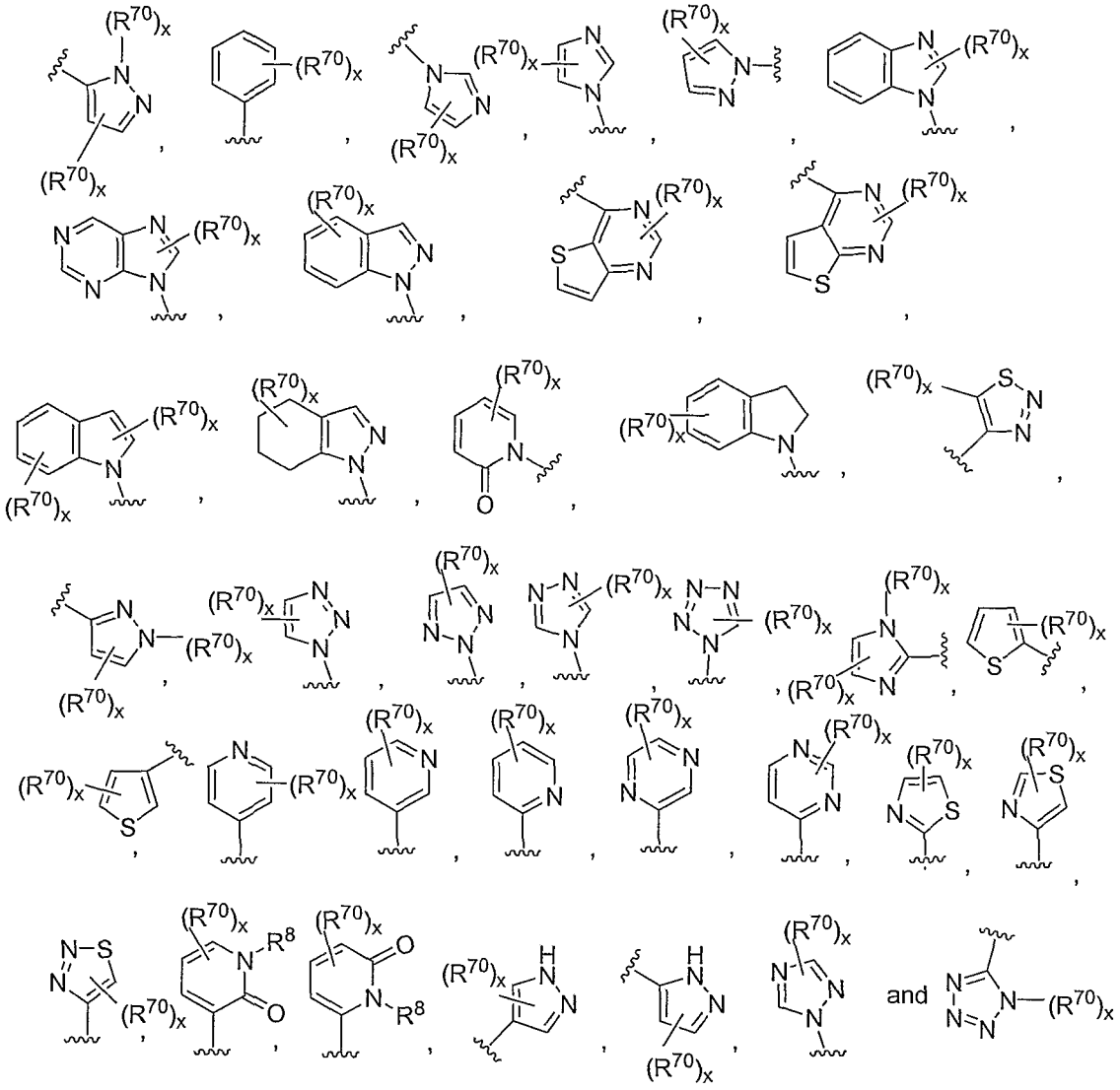


In another embodiment, A is selected from the group consisting of:

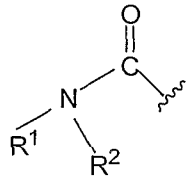


wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 3-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with one or more R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein said 3-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties;

E, J and T are the same and are O; R^{10} is H or alkyl; R^{20}, R^{30}, R^{40}, and R^{50} are the same and are H; W is $-(CR^6{}_2)_n-$, wherein n is 0 to 5; X is selected from the group consisting of phenyl, piperidinyl, pyridinyl, thienyl, thiazolyl, oxazolyl and pyrazolyl; Y is selected from the group consisting of O-, -S-, and $-NR^1-$; and Z is selected from the group consisting of



In another embodiment, A is

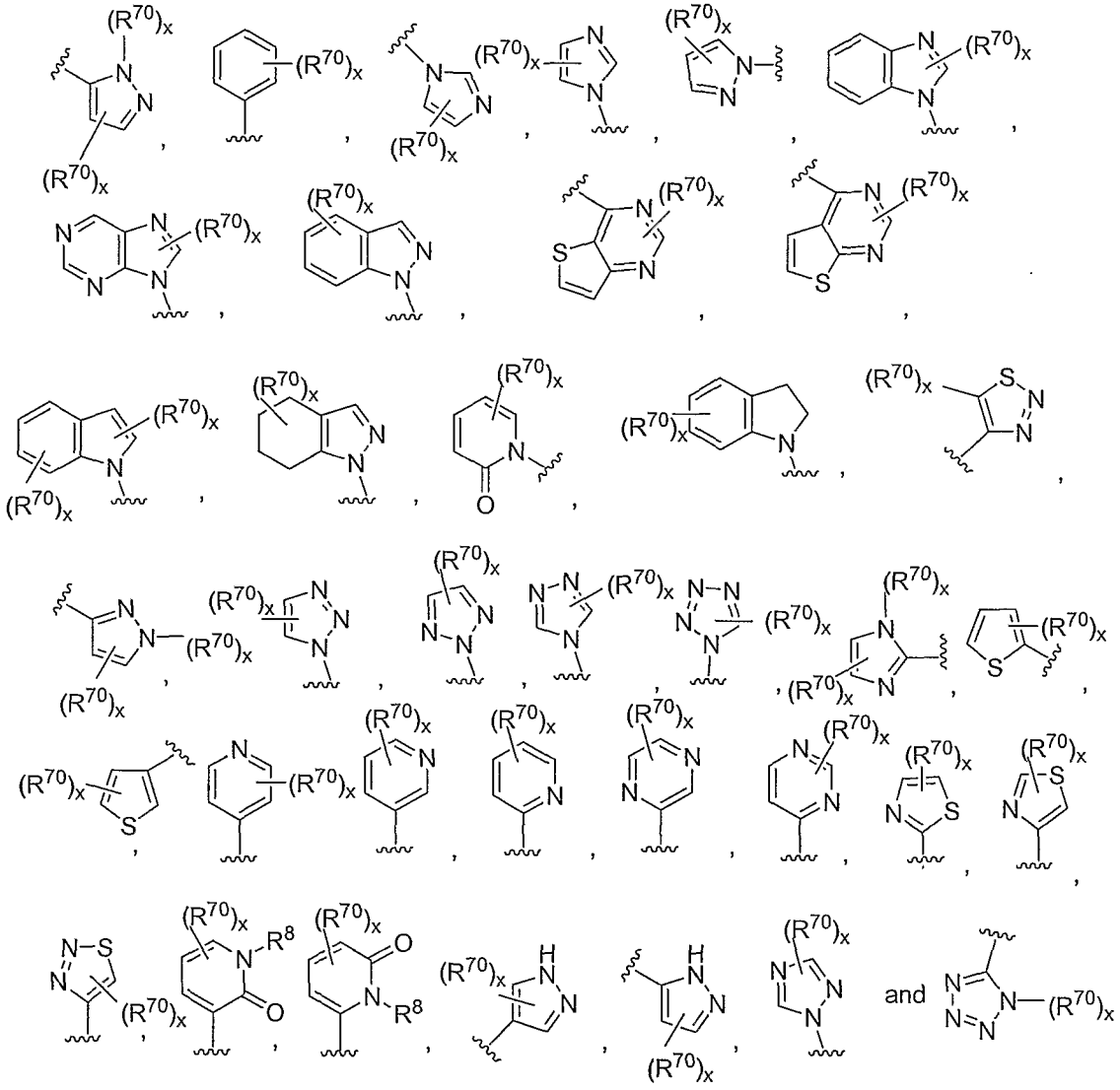


;

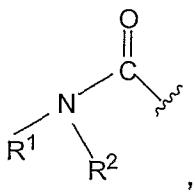
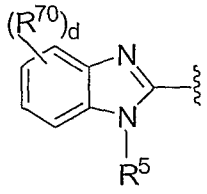
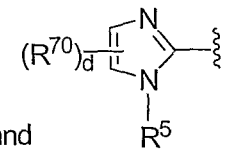
wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 3-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with one or more R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein said 3-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be

the same or different, each moiety being independently selected from the group of R^{70} moieties;

wherein E, J and T are the same and are O; R^{10} is H or alkyl; R^{20}, R^{30}, R^{40}, and R^{50} are the same and are H; W is $-(CR^6_2)_n-$, wherein n is 0 to 5; X is selected from the group consisting of phenyl, piperidinyl, pyridinyl, thienyl, thiazolyl, oxazolyl and pyrazolyl; Y is selected from the group consisting of O-, -S-, and $-NR^1-$; and Z is selected from the group consisting of

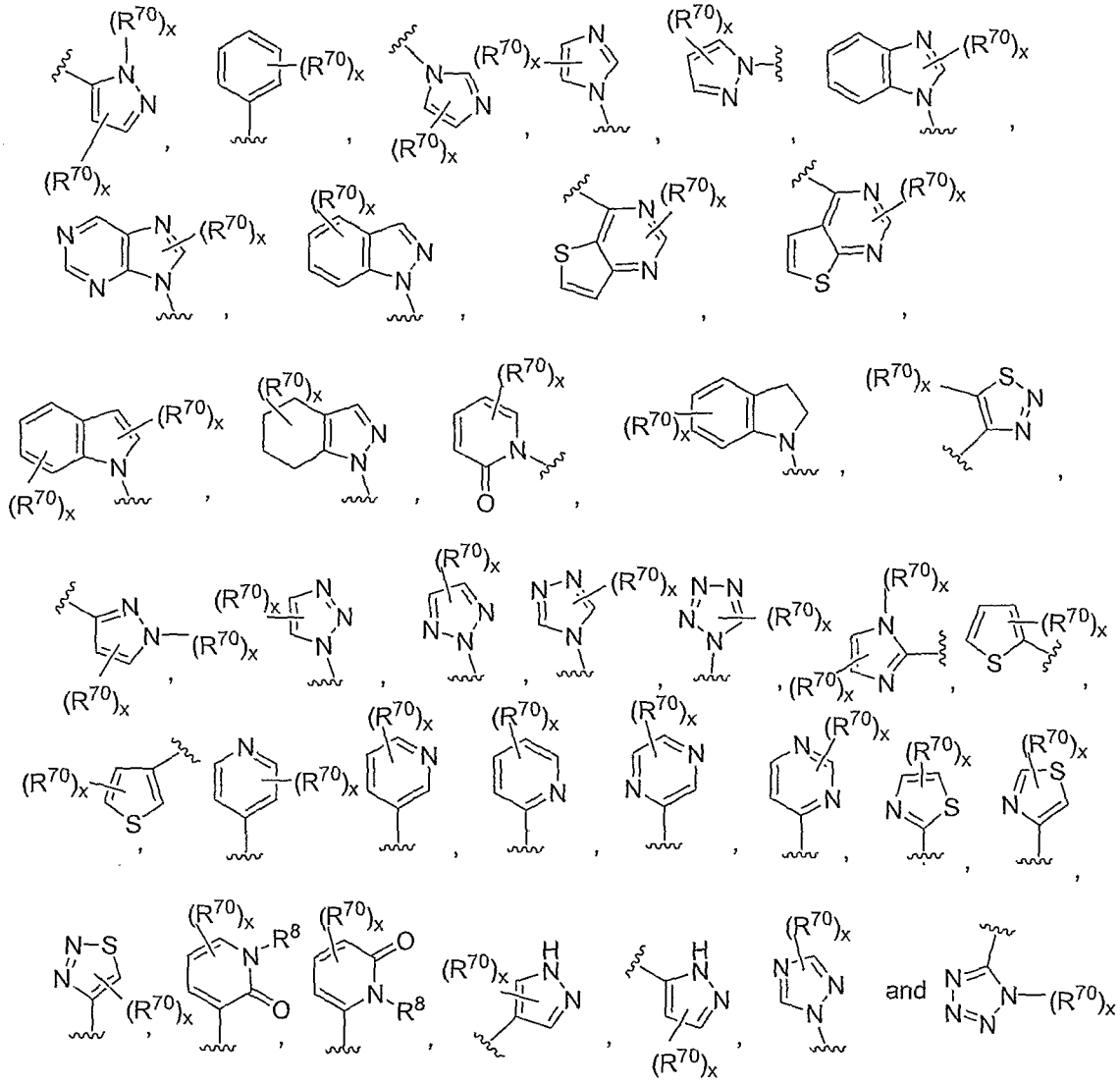


In another embodiment, A is selected from the group consisting of:

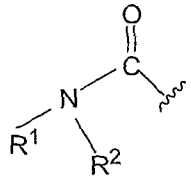

,

and


wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 3-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with one or more R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein said 3-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties;

wherein E, J and T are the same and are O; R^{10} is H or alkyl; R^{20}, R^{30}, R^{40}, and R^{50} are the same and are H; W is $-(CR^{13}{}_2)_n-$ wherein n is 1 or 2; X is selected from the group consisting of phenyl, piperidinyl, pyridinyl, thienyl, thiazolyl, oxazolyl and pyrazolyl; Y is a covalent bond and Z is selected from the group consisting of



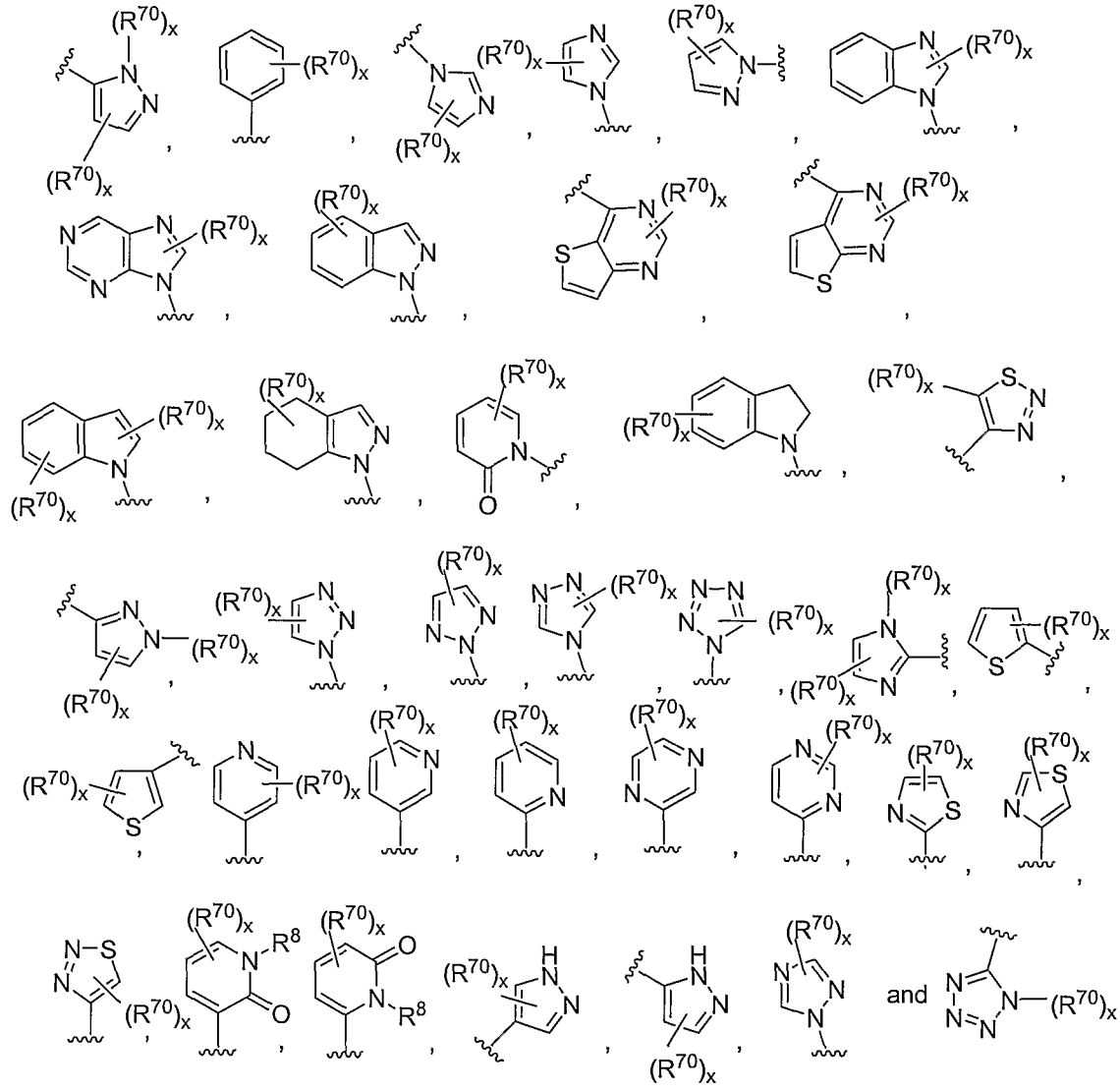
In another embodiment, A is



;

wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 3-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with one or more R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein said 3-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties; wherein E, J and T are the same and

are O; R^{10} is H or alkyl; R^{20}, R^{30}, R^{40}, and R^{50} are the same and are H; W is -$(CR^{13}{}_2)_n$- wherein n is 1 or 2; X is selected from the group consisting of phenyl, piperidinyl, pyridinyl, thienyl, thiazolyl, oxazolyl and pyrazolyl; Y is a covalent bond and Z is selected from the group consisting of



In another embodiment, X is selected from the group consisting of phenyl, piperidinyl, pyridinyl, thienyl, thiazolyl, oxazolyl, and pyrazolyl.

In another embodiment, X is selected from the group consisting of phenyl, piperidinyl, thienyl, and pyridinyl and Y is selected from the group consisting of a covalent bond, -$[C(R^6)_2]_n$- wherein n is 1 to 2 and -O-.

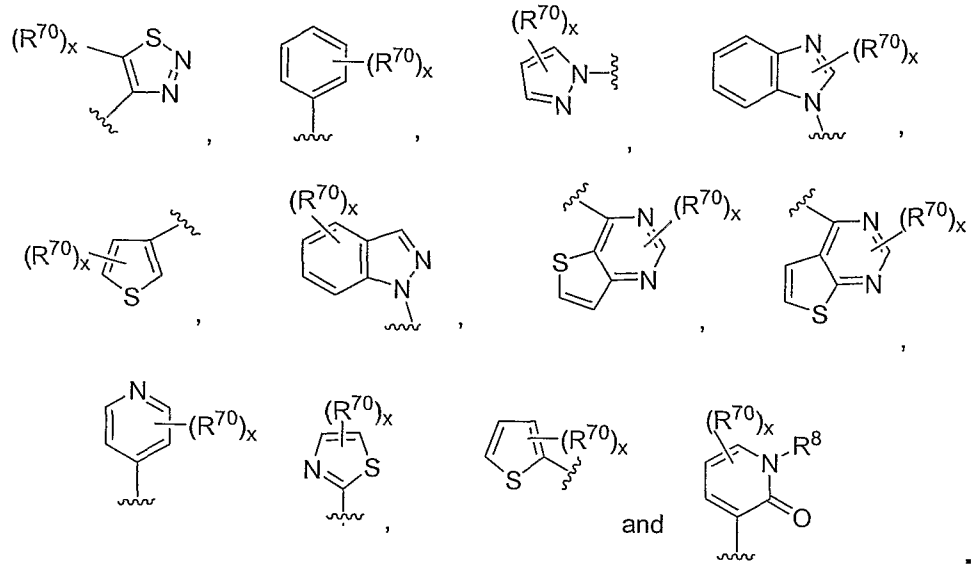
In another embodiment, X is phenyl and Y is selected from the group consisting of a covalent bond, -CH_2- and -O-.

In another embodiment, X is piperidinyl, Y is a covalent bond, and Z is aryl or heteroaryl having two substituents which can be the same or different, each moiety being independently selected from the group consisting of cyano, alkoxy, halogen, alkyl, haloalkyl, hydroxy, aryl, heteroaryl, aryloxy and amino.

In another embodiment, W is selected from the group consisting of -CH_2-, –C(H)CH_3-, -$C(CH_3)_2$- and Y is a covalent bond.

In another embodiment, W is -CH_2- and Y is -CH_2-.

In another embodiment, Z is selected from the group consisting of



and

Another embodiment of the invention discloses the compounds shown in Table 1 below.

As used above, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"Patient" includes both human and animals.

"Mammal" means humans and other mammalian animals.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl,

ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. The term "substituted alkyl" means that the alkyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), -$N(alkyl)_2$, carboxy and –C(O)O-alkyl. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl. The term "Fluoroalkyl" means an alkyl group in which alkyl is as previously described wherein one or more hydrogens are replaced with fluorine atoms.

"Alkenyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl.

"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl. The term "substituted alkynyl" means that the alkynyl group may be substituted by one or more substituents which may be the same or

different, each substituent being independently selected from the group consisting of alkyl, aryl and cycloalkyl.

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like. The term “heteroaryl” also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like.

"Aralkyl" or “arylalkyl” means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-

phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the alkyl.

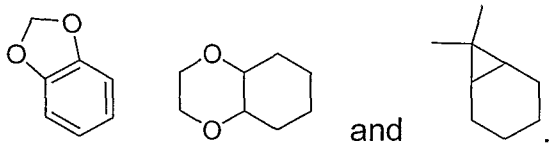
"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described. Preferred alkylaryls comprise a lower alkyl group. Non-limiting example of a suitable alkylaryl group is tolyl. The bond to the parent moiety is through the aryl.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like, as well as partially saturated species such as, for example, indanyl, tetrahydronaphthyl and the like.

"Halogen" means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine and bromine.

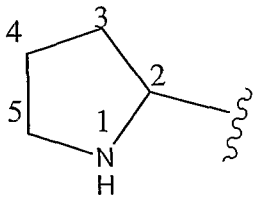
"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, alkylaryl, heteroaralkyl, heteroarylalkenyl, heteroarylalkynyl, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, heterocyclyl, -C(=N-CN)-NH_2, -C(=NH)-NH_2, -C(=NH)-NH(alkyl), Y_1Y_2N-, Y_1Y_2N-alkyl-, $Y_1Y_2NC(O)$-, $Y_1Y_2NSO_2$- and -$SO_2NY_1Y_2$, wherein Y_1 and Y_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, and aralkyl. "Ring system substituent" may also mean a single

moiety which simultaneously replaces two available hydrogens on two adjacent carbon atoms (one H on each carbon) on a ring system. Examples of such moiety are methylene dioxy, ethylenedioxy, $-C(CH_3)_2-$ and the like which form moieties such as, for example:

 and .

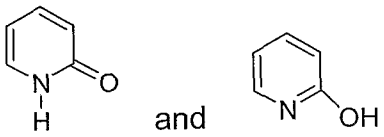
"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any –NH in a heterocyclyl ring may exist protected such as, for example, as an -N(Boc), -N(CBz), -N(Tos) group and the like; such protections are also considered part of this invention. The heterocyclyl can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, lactam, lactone, and the like.

It should be noted that in hetero-atom containing ring systems of this invention, there are no hydroxyl groups on carbon atoms adjacent to a N, O or S, as well as there are no N or S groups on carbon adjacent to another heteroatom. Thus, for example, in the ring:



there is no -OH attached directly to carbons marked 2 and 5.

It should also be noted that tautomeric forms such as, for example, the moieties:



are considered equivalent in certain embodiments of this invention.

"Alkynylalkyl" means an alkynyl-alkyl- group in which the alkynyl and alkyl are as previously described. Preferred alkynylalkyls contain a lower alkynyl and a lower alkyl group. The bond to the parent moiety is through the alkyl. Non-limiting examples of suitable alkynylalkyl groups include propargylmethyl.

"Heteroaralkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl group. Non-limiting examples of suitable aralkyl groups include pyridylmethyl, and quinolin-3-ylmethyl. The bond to the parent moiety is through the alkyl.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Acyl" means an H-C(O)-, alkyl-C(O)- or cycloalkyl-C(O)-, group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl and propanoyl.

"Aroyl" means an aryl-C(O)- group in which the aryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include benzoyl and 1- naphthoyl.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Non-limiting examples of suitable aryloxy groups include phenoxy and naphthoxy. The bond to the parent moiety is through the ether oxygen.

"Aralkyloxy" means an aralkyl-O- group in which the aralkyl group is as previously described. Non-limiting examples of suitable aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy. The bond to the parent moiety is through the ether oxygen.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkylthio groups include methylthio and ethylthio. The bond to the parent moiety is through the sulfur.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups include phenylthio and naphthylthio. The bond to the parent moiety is through the sulfur.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. Non-limiting example of a suitable aralkylthio group is benzylthio. The bond to the parent moiety is through the sulfur.

"Alkoxycarbonyl" means an alkyl-O-CO- group. Non-limiting examples of suitable alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aryloxycarbonyl" means an aryl-O-C(O)- group. Non-limiting examples of suitable aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aralkoxycarbonyl" means an aralkyl-O-C(O)- group. Non-limiting example of a suitable aralkoxycarbonyl group is benzyloxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Alkylsulfonyl" means an alkyl-$S(O_2)$- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfonyl.

"Arylsulfonyl" means an aryl-$S(O_2)$- group. The bond to the parent moiety is through the sulfonyl.

The term "substituted" means that 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 under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound' or "stable structure" is meant 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.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

The term "isolated" or "in isolated form" for a compound refers to the physical state of said compound after being isolated from a synthetic process or natural source or combination thereof. The term "purified" or "in purified form" for a compound refers to the physical state of said compound after being obtained from a purification process or processes described herein or well known to the skilled artisan, in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W.

Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

When any variable (e.g., aryl, heterocycle, R^2, etc.) occurs more than one time in any constituent or in Formula I, its definition on each occurrence is independent of its definition at every other occurrence.

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

Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug", as employed herein, denotes a compound that is a drug precursor which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of Formula I or a salt and/or solvate thereof. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design,* (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, both of which are incorporated herein by reference thereto.

"Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in inhibiting the CDK(s) and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

The compounds of Formula I can form salts which are also within the scope of this invention. Reference to a compound of Formula I herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula I contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of the Formula I may be formed, for example, by reacting a compound of Formula I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Compounds of Formula I, and salts, solvates and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates and prodrugs of the compounds as well as the salts and solvates of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate" "prodrug" and the like, is intended to equally apply to the salt, solvate and

prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

Polymorphic forms of the compounds of Formula I, and of the salts, solvates and prodrugs of the compounds of Formula I, are intended to be included in the present invention.

The compounds according to the invention have pharmacological properties; in particular, the compounds of Formula I can be inhibitors of LpxC, TACE, aggrecanase, ADMP, TNF-α, ADAM and/or MMP activity.

In one aspect, the invention provides a pharmaceutical composition comprising as an active ingredient at least one compound of formula 1.

In another aspect, the invention provides a pharmaceutical composition of formula 1 additionally comprising at least one pharmaceutically acceptable carrier.

In another aspect, the invention provides a method of treating disorders associated with LpxC, TACE, aggrecanase, ADMP, TNF-α, MMPs, ADAMs or any combination thereof or any combination thereof, said method comprising administering to a patient in need of such treatment a pharmaceutical composition which comprises therapeutically effective amounts of at least one compound of formula 1.

In another aspect, the invention provides a use of a compound of formula 1 for the manufacture of a medicament to treat disorders associated with LpxC, TACE, ADMP, aggrecanase, TNF-α, MMPs, ADAMs or any combination thereof.

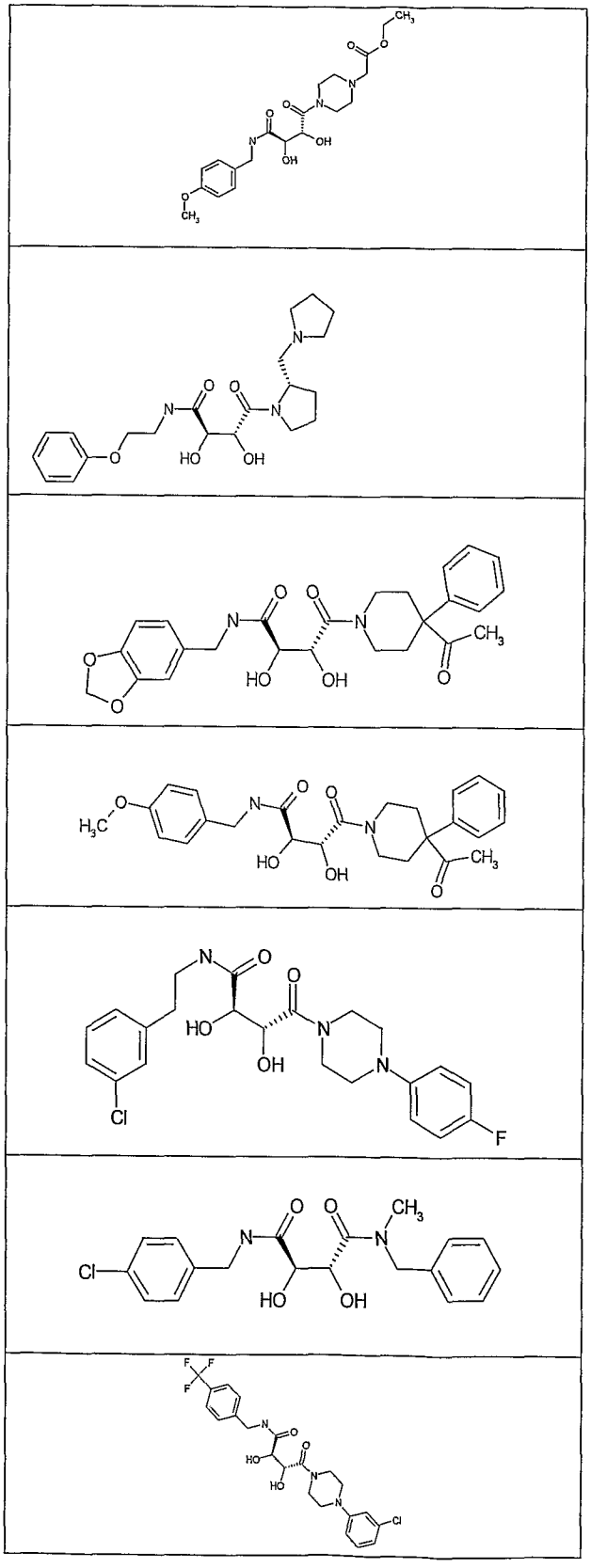
The compounds of Formula I can have anti-inflammatory activity and/or immunomodulatory activity and can be useful in the treatment of diseases including but not limited to septic shock, haemodynamic shock, sepsis syndrome, post ischaemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic diseases, cachexia, graft rejection, cancers such as cutaneous T-cell lymphoma, diseases involving angiogenesis, autoimmune diseases, skin inflammatory diseases, inflammatory bowel diseases such as Crohn's disease and colitis, OA and RA, ankylosing spondylitis, psoriatic arthritis, adult Still's disease, ureitis,

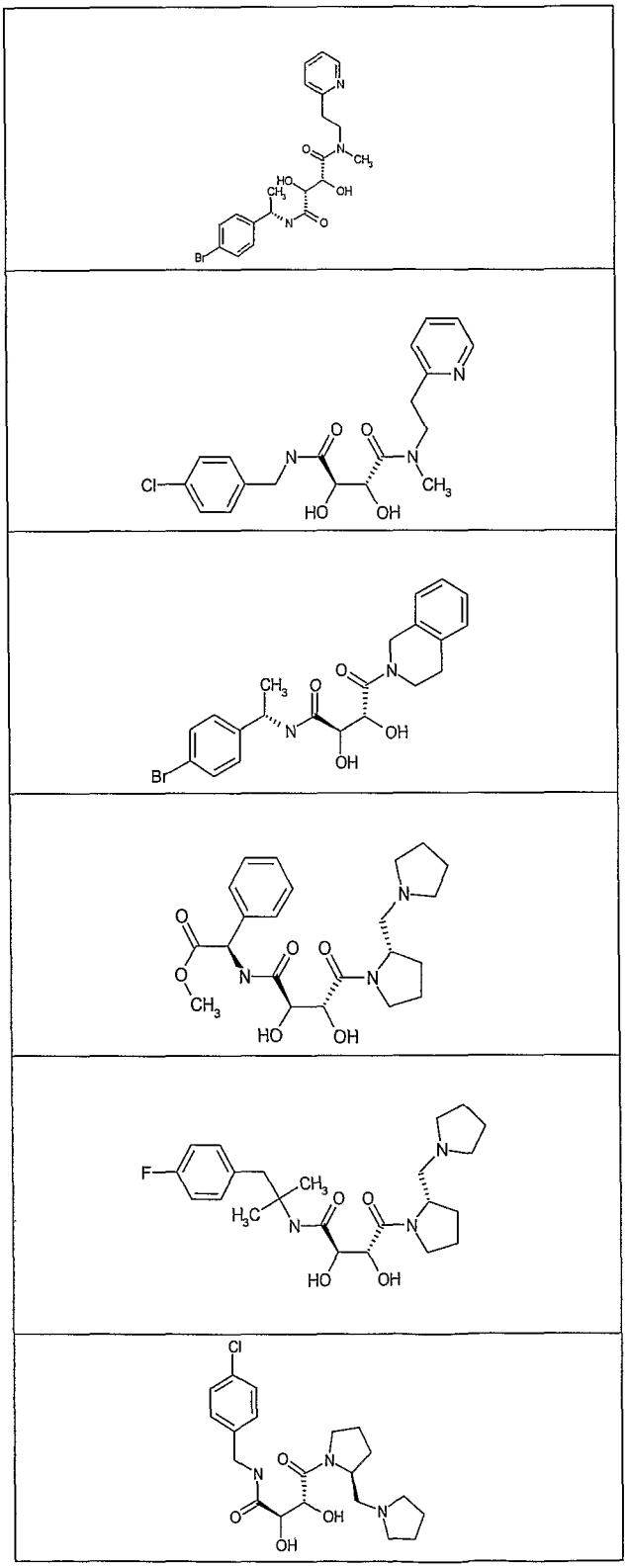
Wegener's granulomatosis, Behcehe disease, Sjogren's syndrome, sarcoidosis, polymyositis, dermatomyositis, multiple sclerosis, sciatica, complex regional pain syndrome, radiation damage, hyperoxic alveolar injury, periodontal disease, HIV, non-insulin dependent diabetes mellitus, systemic lupus erythematosus, glaucoma, sarcoidosis, idiopathic pulmonary fibrosis, bronchopulmonary dysplasia, retinal disease, scleroderma, osteoporosis, renal ischemia, myocardial infarction, cerebral stroke, cerebral ischemia, nephritis, hepatitis, glomerulonephritis, cryptogenic fibrosing aveolitis, psoriasis, transplant rejection, atopic dermatitis, vasculitis, allergy, seasonal allergic rhinitis, reversible airway obstruction, adult respiratory distress syndrome, asthma, chronic obstructive pulmonary disease (COPD) and/or bronchitis. It is contemplated that a compound of this invention may be useful in treating one or more of the diseases listed.

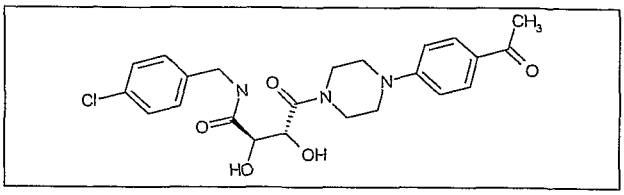
The compounds of formula I can also have antibacterial activitity and can be useful in the treatment of a microbial infection, including gram negative and gram positive infections.

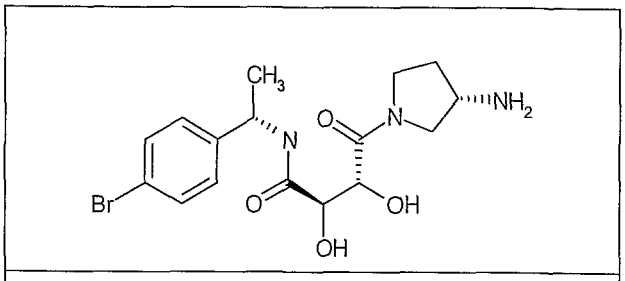
In another aspect, the invention provides a method of preparing a pharmaceutical composition for treating the disorders associated with LpxC, TACE, aggrecanase, ADMP, TNF-α, MMPs, ADAMs or any combination thereof, said method comprising bringing into intimate contact at least one compound of formula 1 and at least one pharmaceutically acceptable carrier.

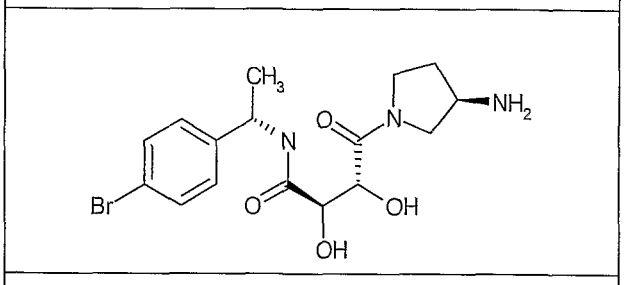
In another aspect, the invention provides a compound of formula (I) exhibiting LpxC, TACE, aggrecanase, ADMP, TNF-α, MMPs, ADAMs or any combination thereof inhibitory activity, including enantiomers, stereoisomers and tautomers of said compound, and pharmaceutically acceptable salts or solvates of said compound, said compound being selected from the compounds of structures listed below:

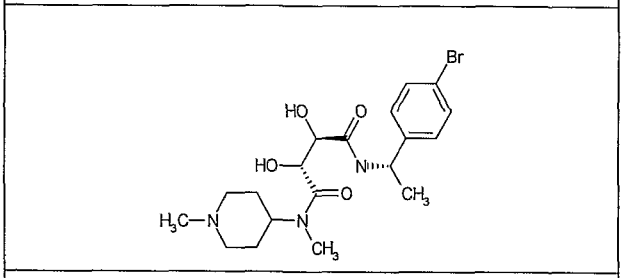


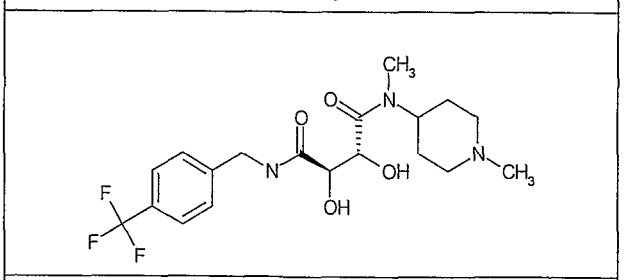


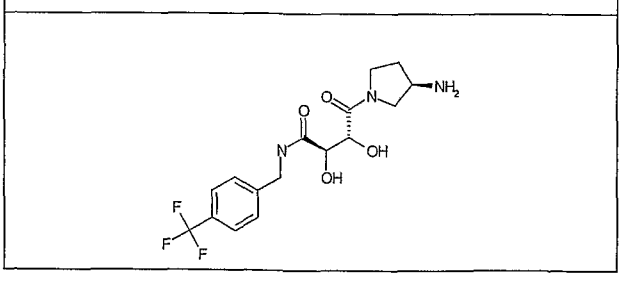


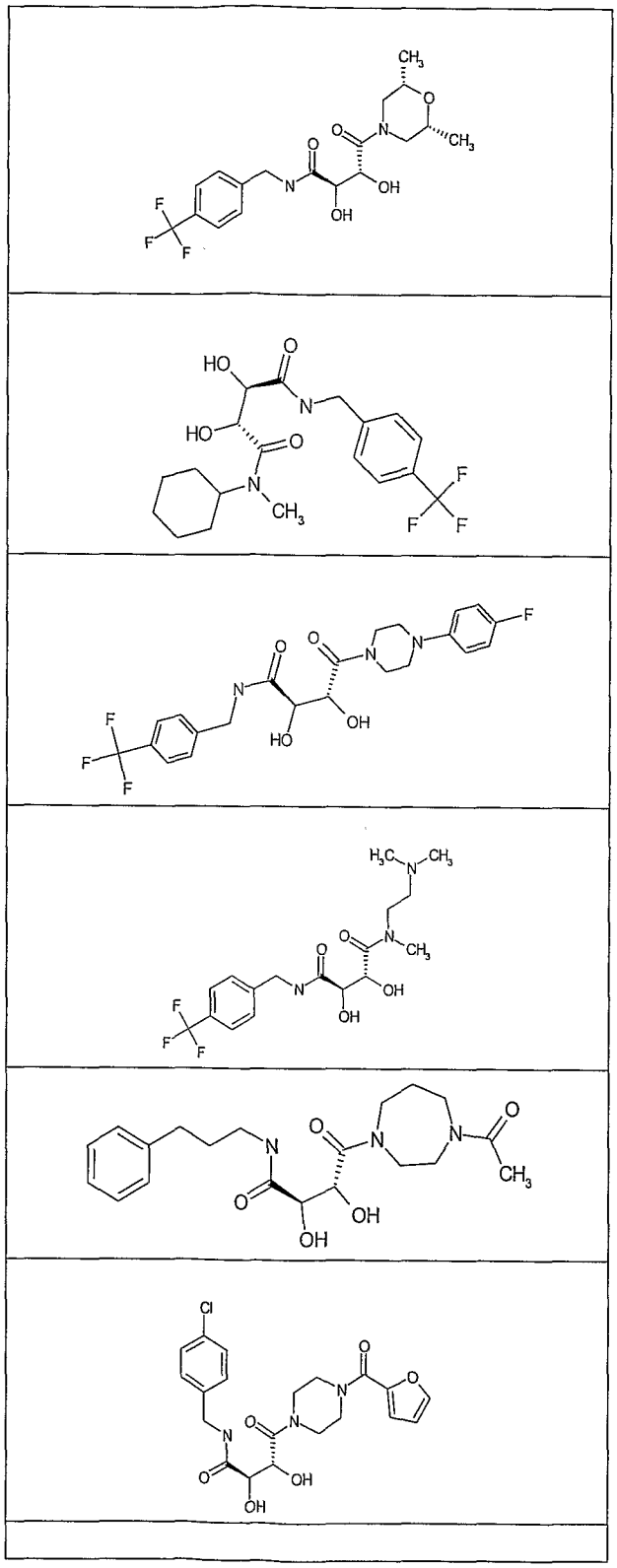


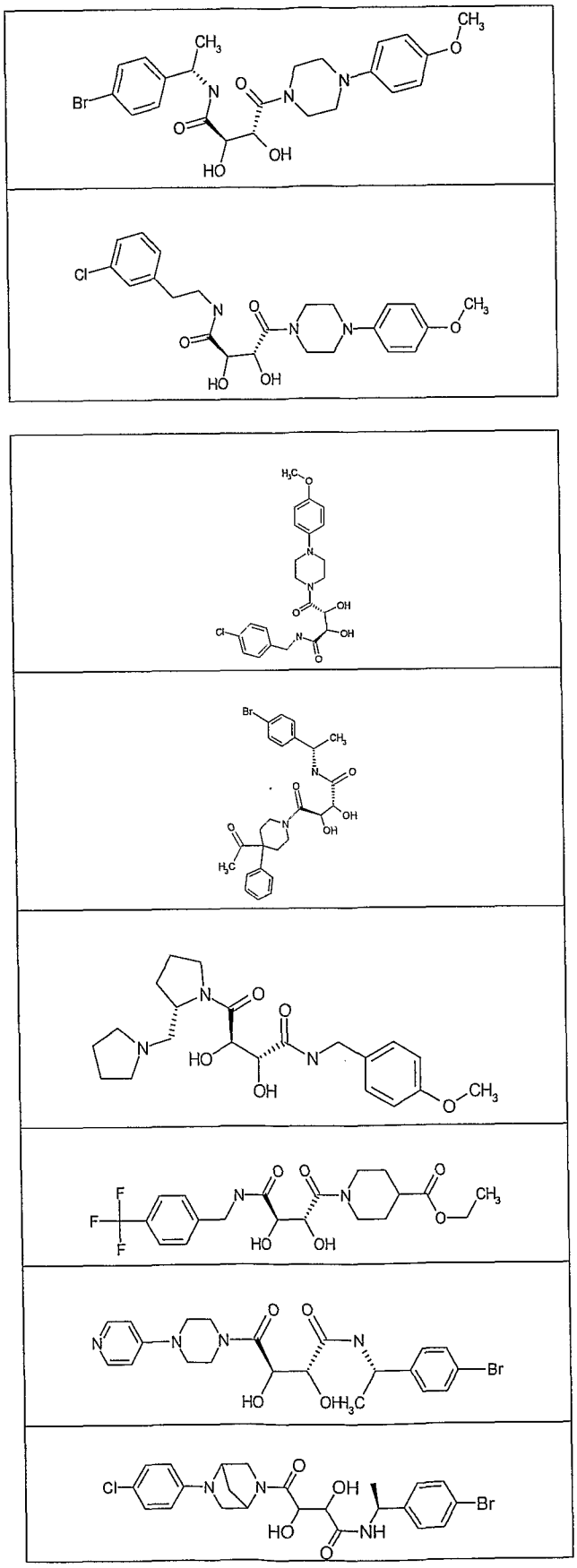


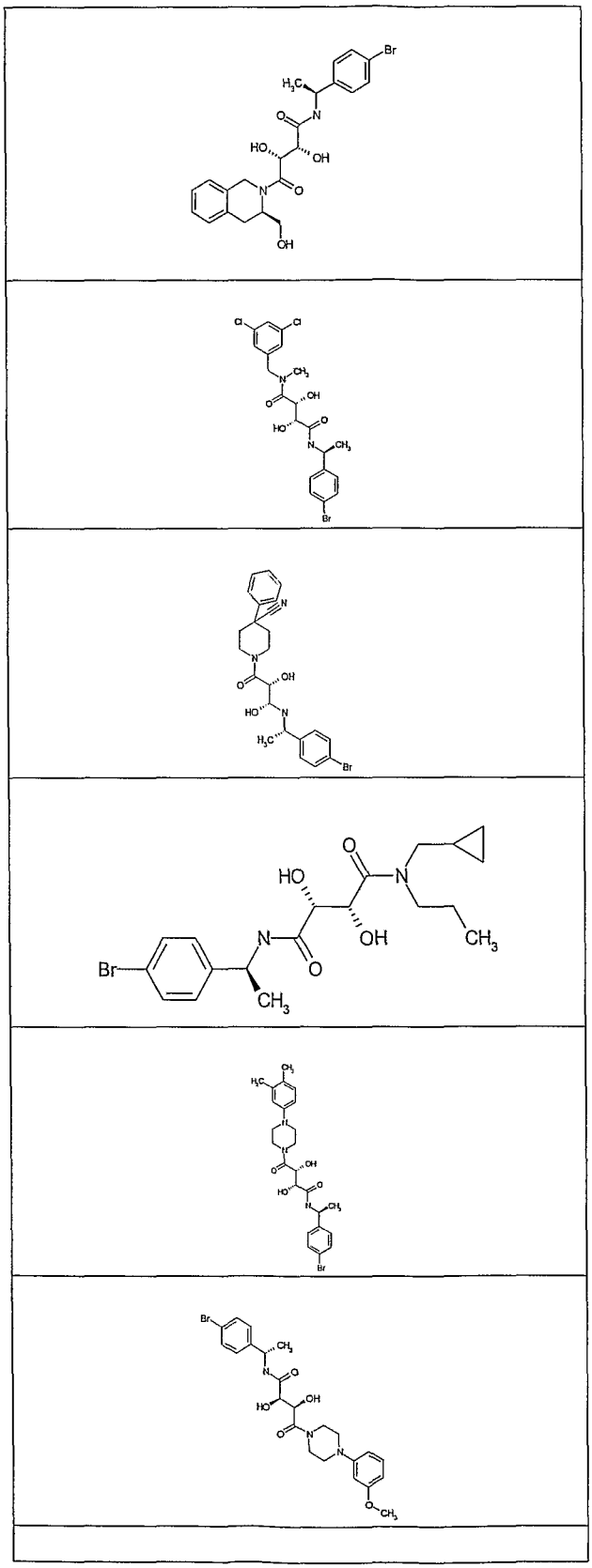


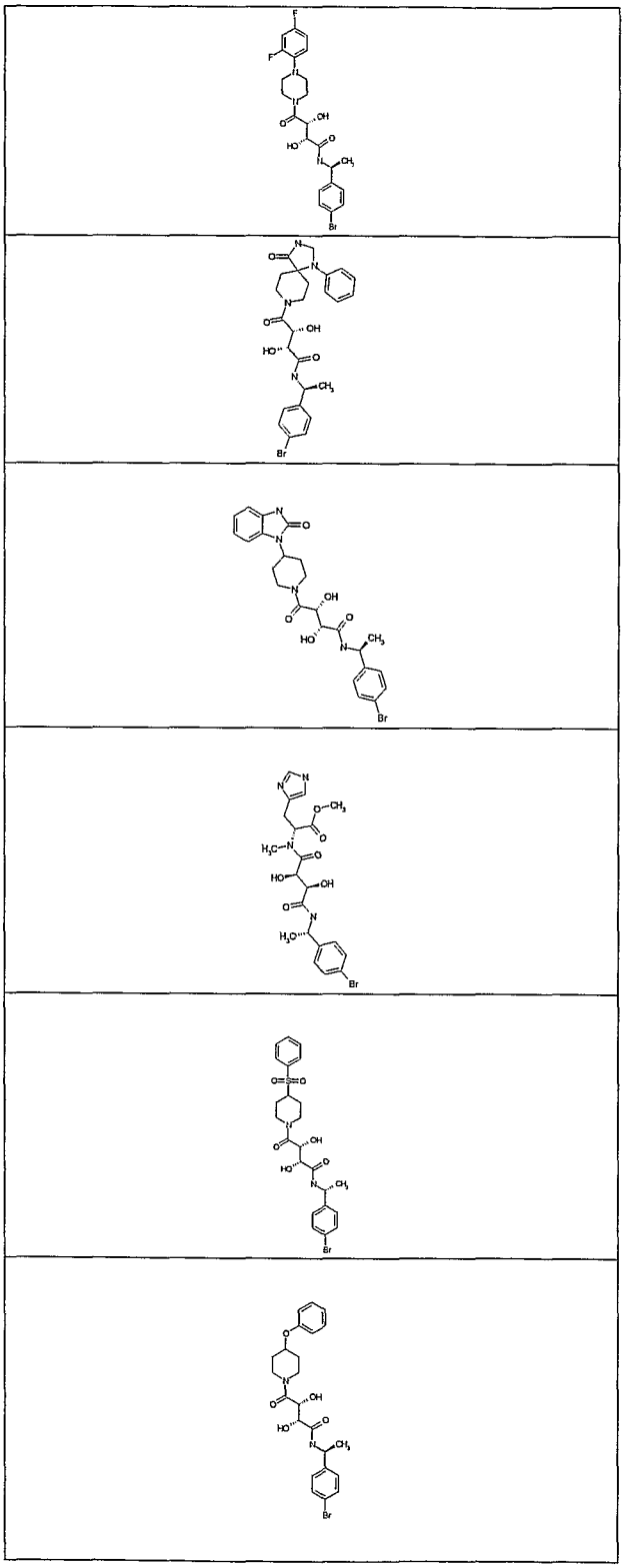


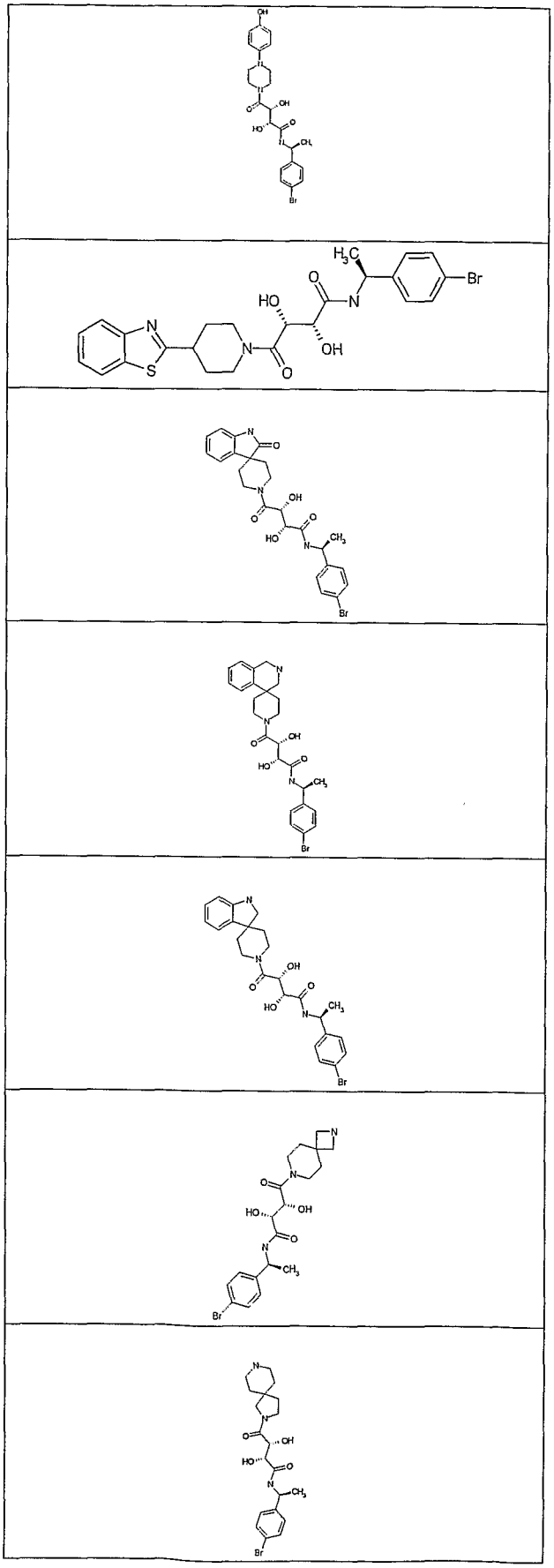


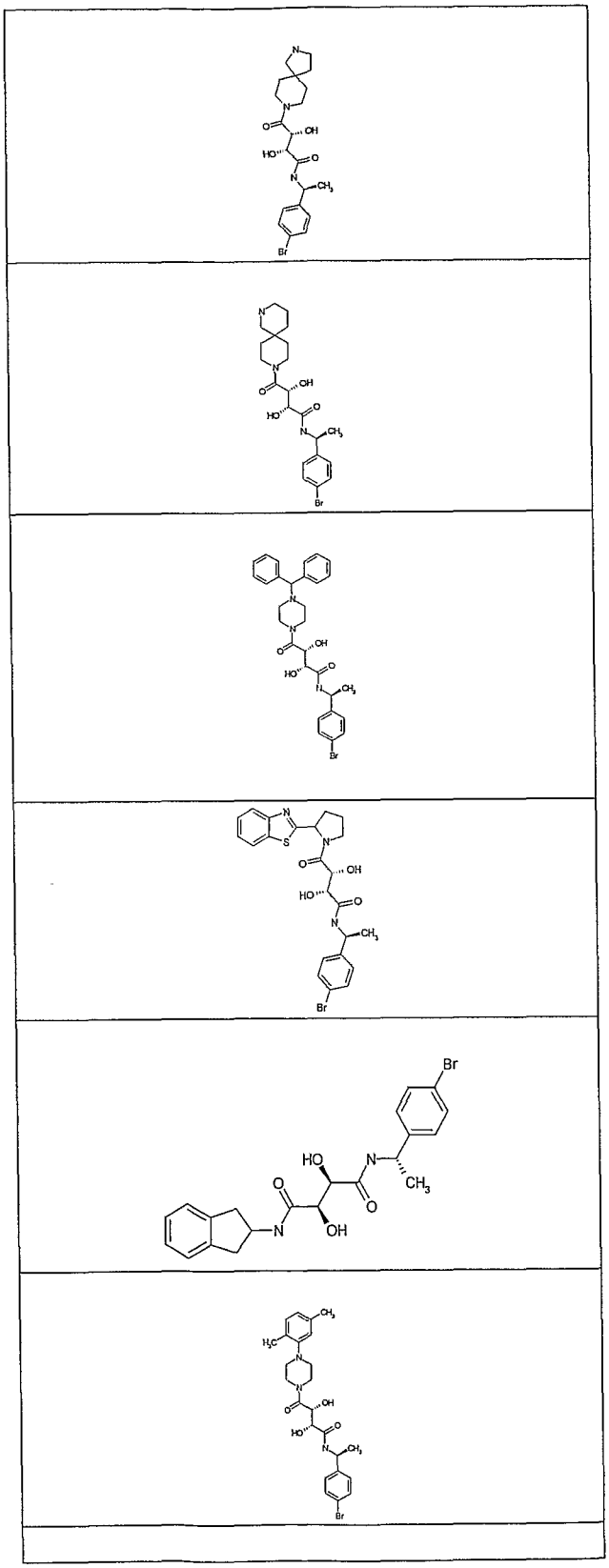


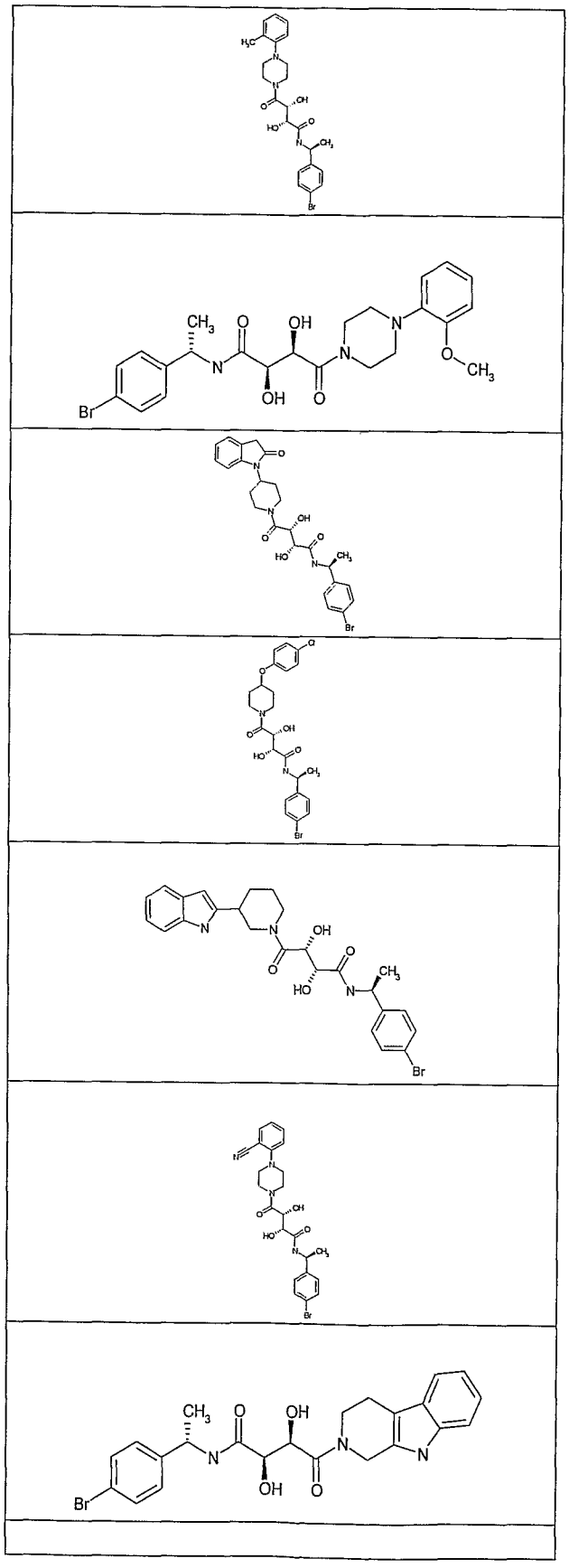


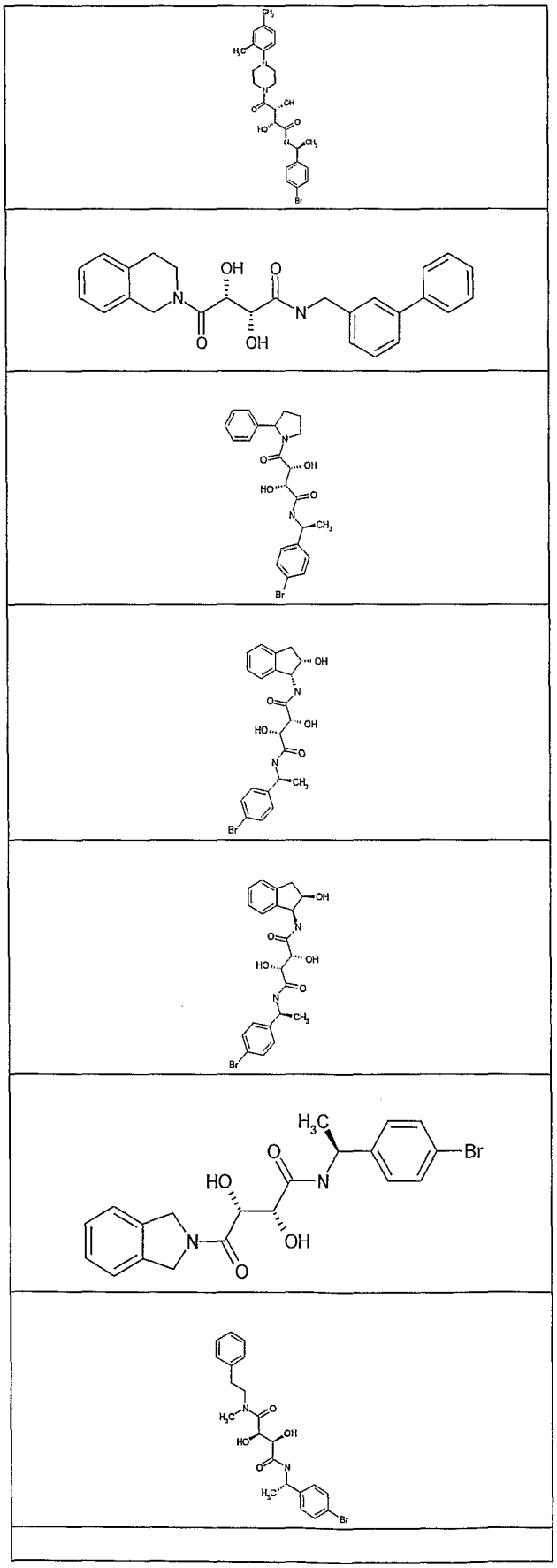


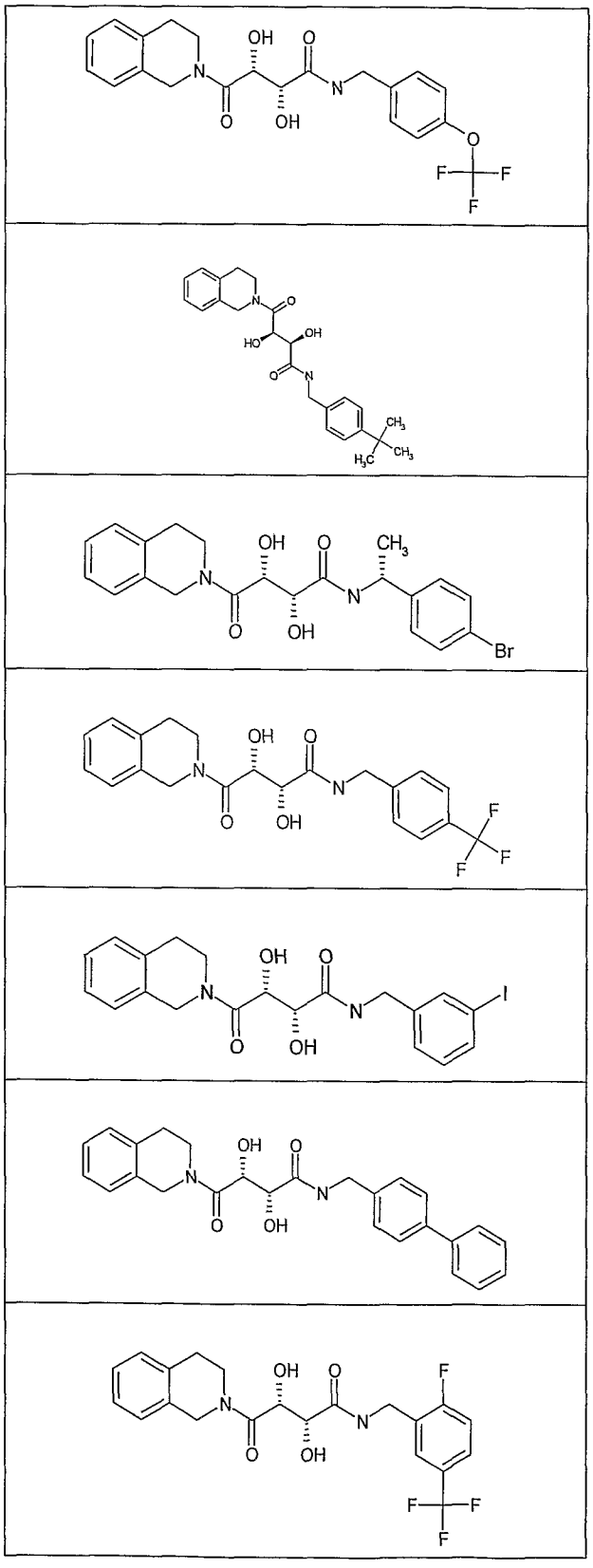


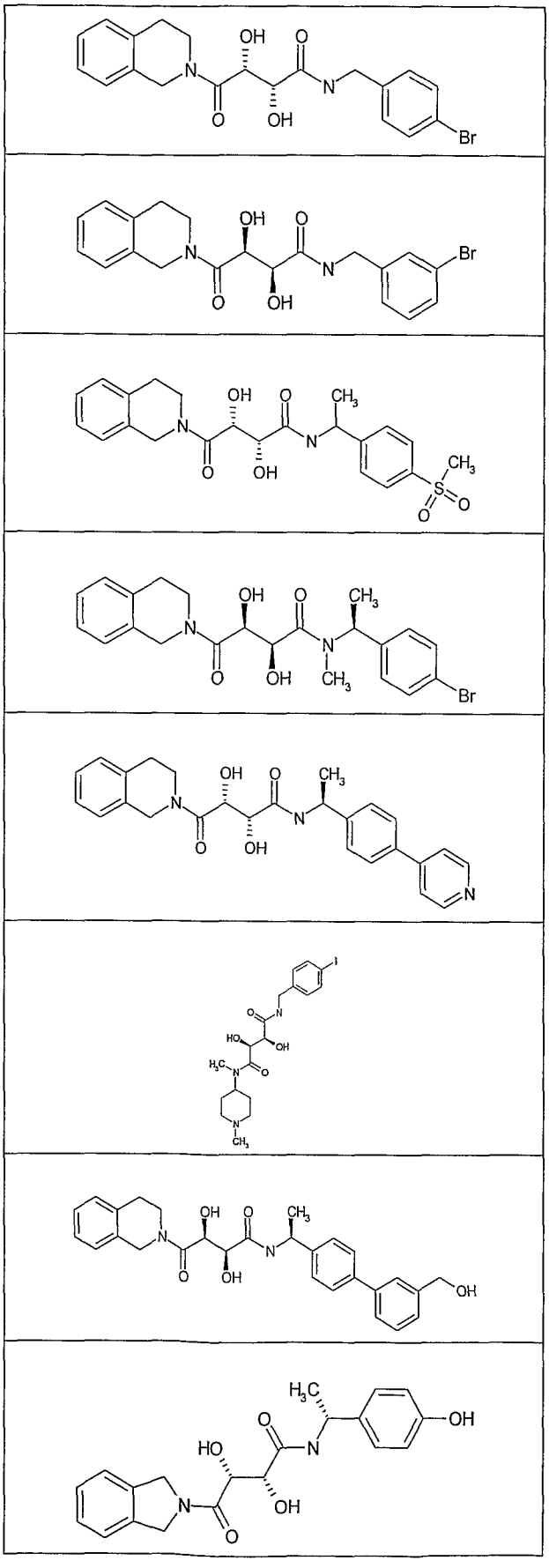


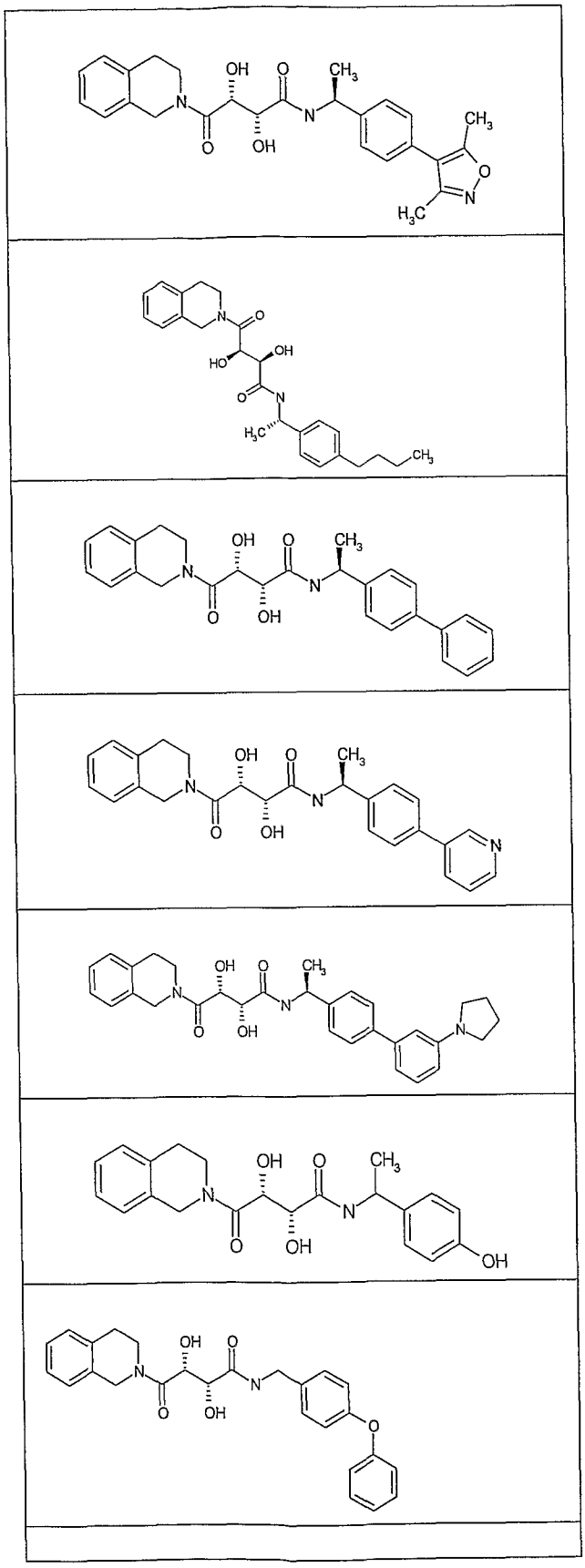


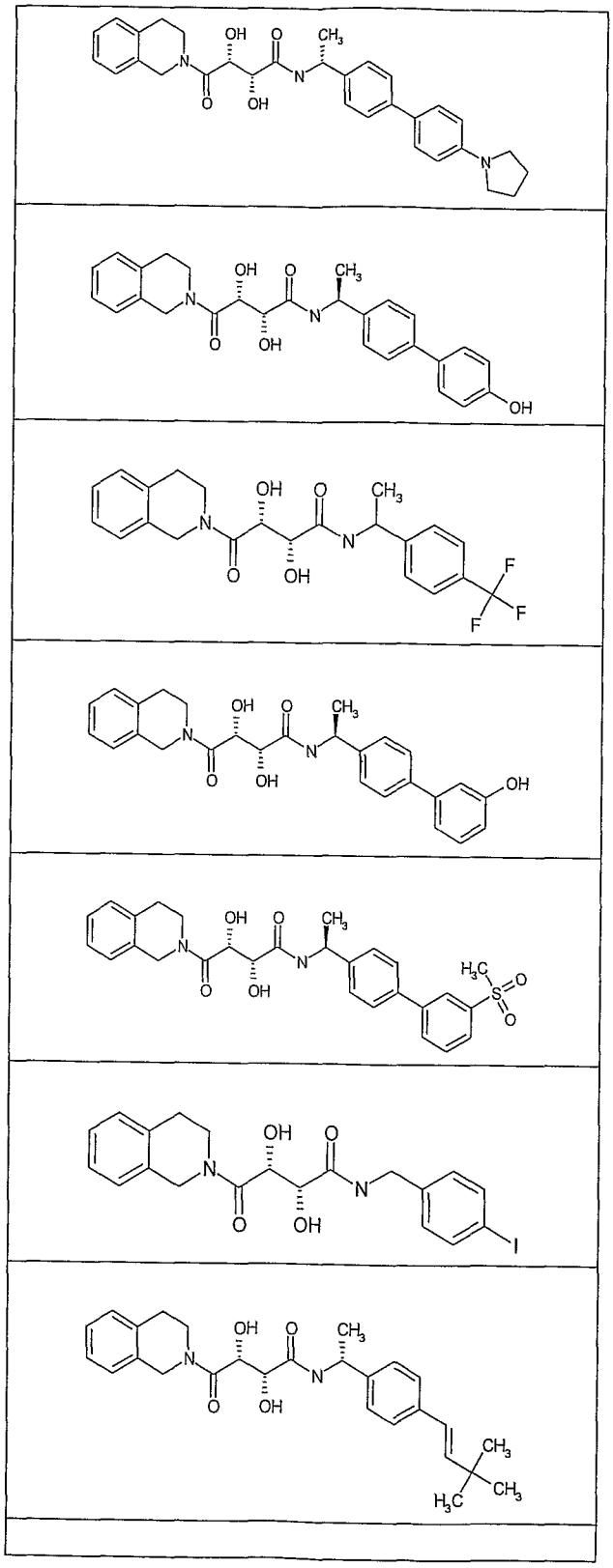


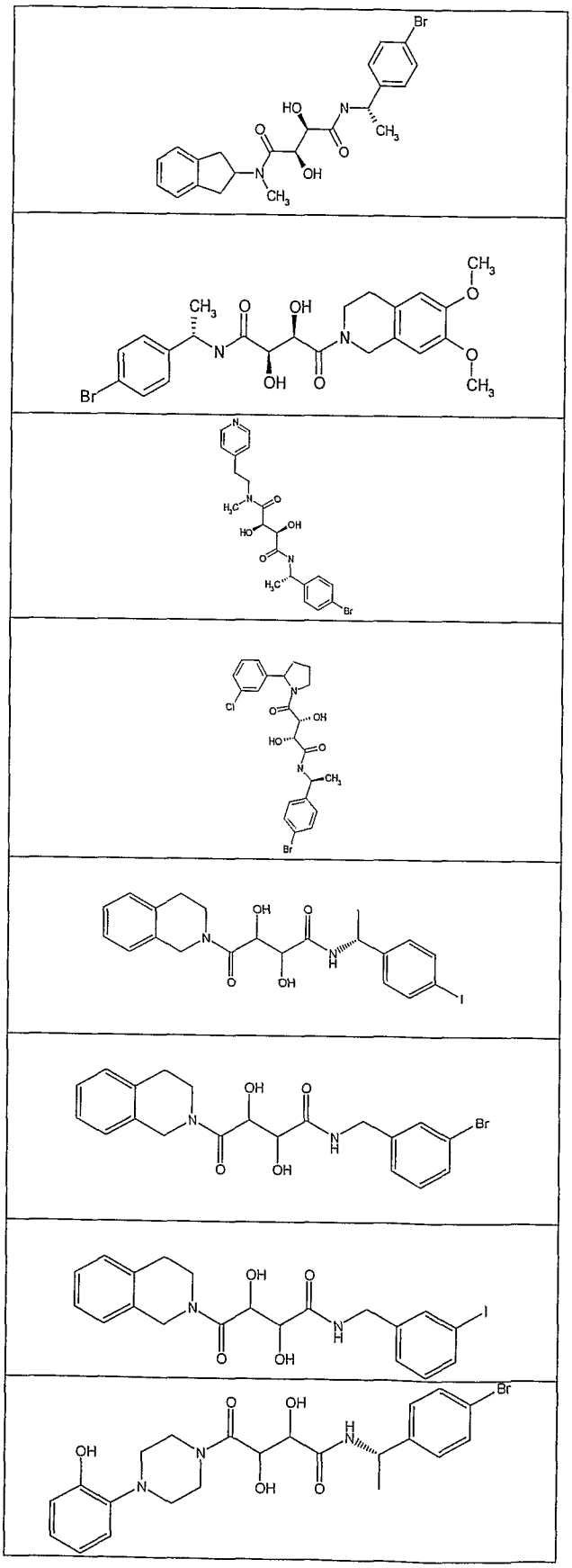


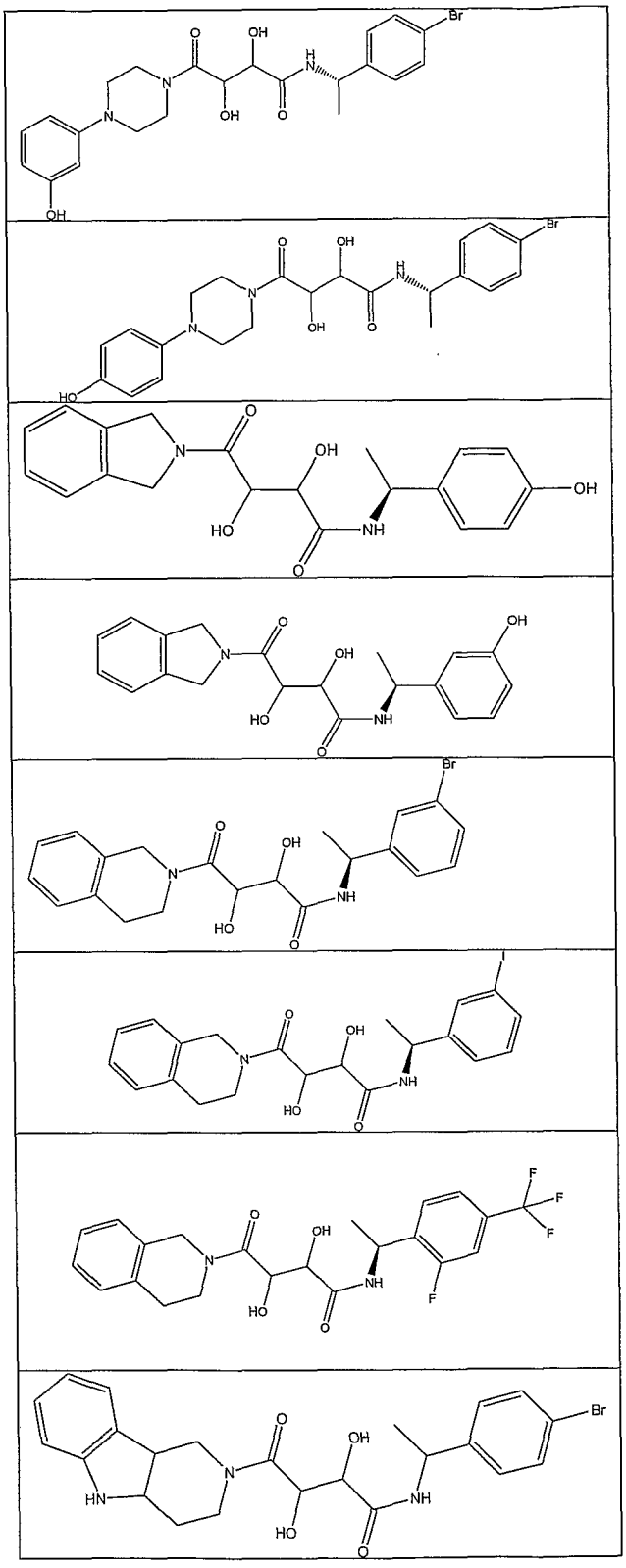


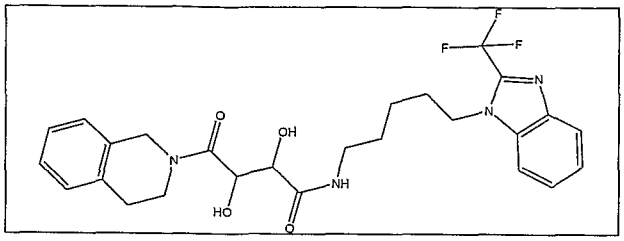


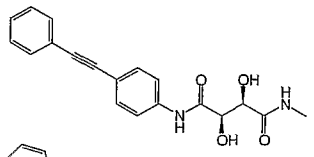


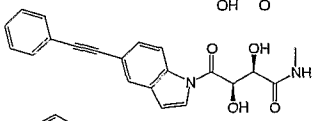


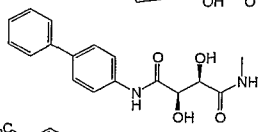


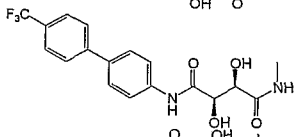


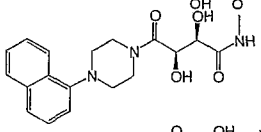


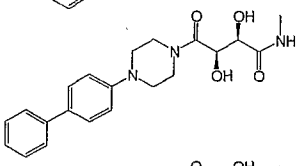


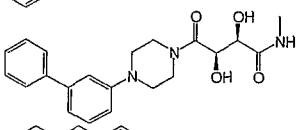


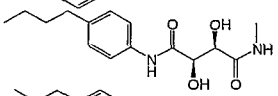


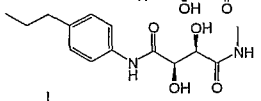


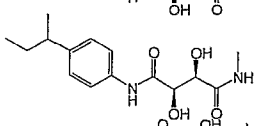


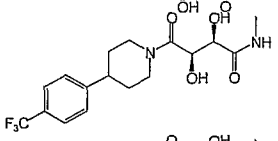


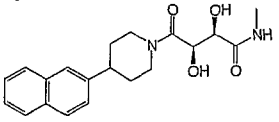


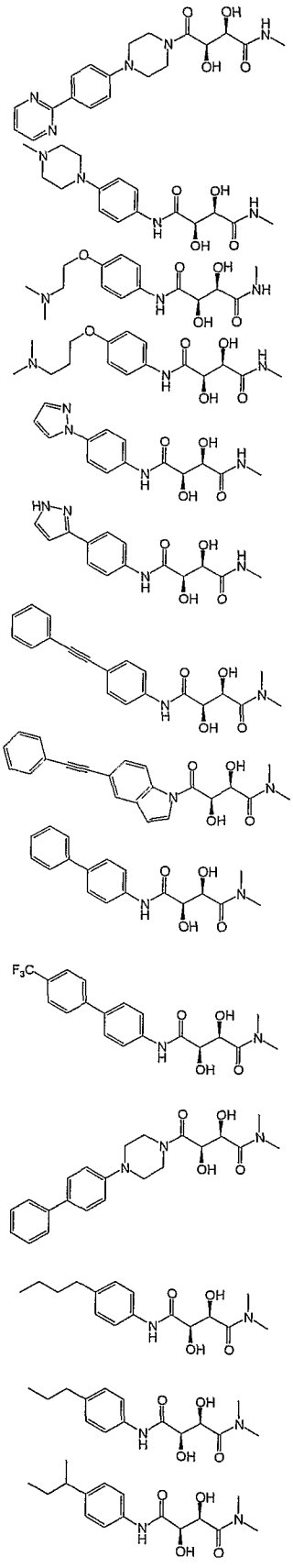


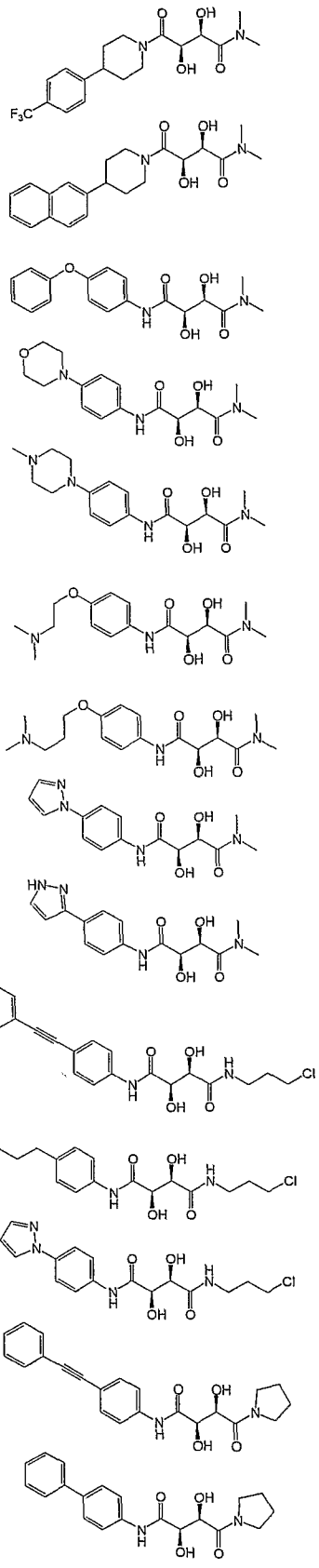


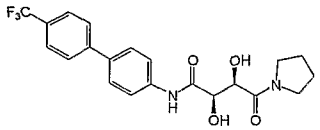


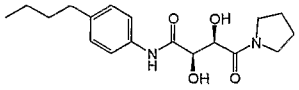


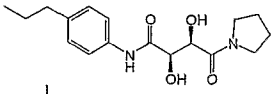


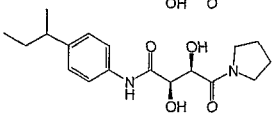


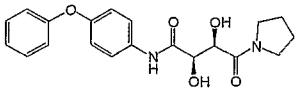


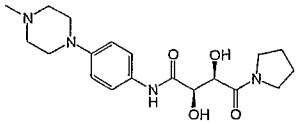


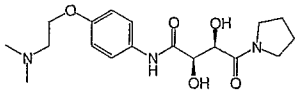


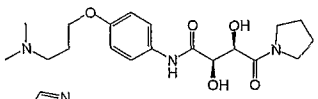


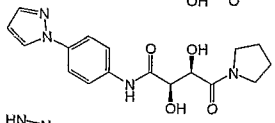


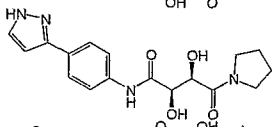


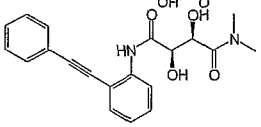


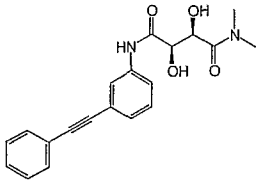


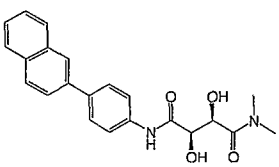


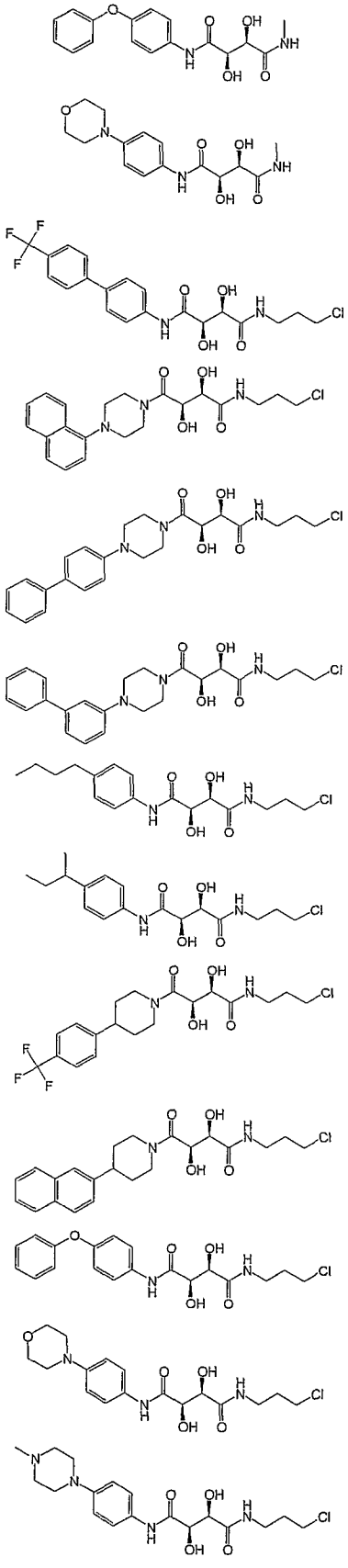


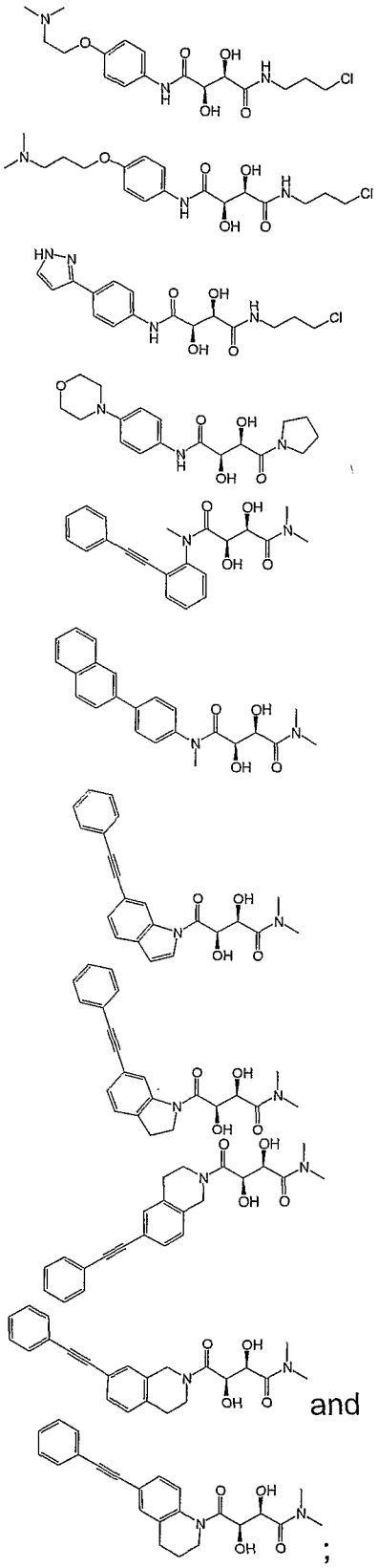












and

;

or a pharmaceutically acceptable salt, solvate or ester thereof.

In another aspect, the invention provides a pharmaceutical composition for treating disorders associated with LpxC, TACE, aggrecanase, ADMP, TNF-α, MMP, ADAM or any combination thereof in a subject comprising, administering to the subject in need of such treatment a therapeutically effective amount of a compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a compound of formula 1 in purified form.

In another aspect, the invention provides a method of treating a condition or disease mediated by LpxC, TACE, aggrecanase, ADMP, MMPs, TNF-α, aggrecanase (such as aggrecanase 1, aggrecanase 2, aggrecanase 3, aggrecanase 4, or aggrecanase 5), or any combination thereof in a subject comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease selected from the group consisting of rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, solid tumor growth and tumor invasion by secondary metastases, neovascular glaucoma, inflammatory bowel disease, multiple sclerosis and psoriasis in a subject, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease selected from the group consisting of fever, cardiovascular conditions, hemorrhage, coagulation, cachexia, anorexia, alcoholism, acute phase response, acute infection, shock, graft versus host reaction, autoimmune disease and HIV infection in a subject comprising administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease selected from the group consisting of septic shock, haemodynamic shock, sepsis syndrome, post ischaemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic diseases, cachexia, graft rejection, cancers such as cutaneous T-cell lymphoma, diseases involving angiogenesis, autoimmune diseases, skin inflammatory diseases, inflammatory bowel diseases such as Crohn's disease and colitis, osteo and rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, adult Still's disease, ureitis, Wegener's granulomatosis, Behcehe disease, Sjogren's syndrome, sarcoidosis, polymyositis, dermatomyositis, multiple sclerosis, sciatica, complex regional pain syndrome, radiation damage, hyperoxic alveolar injury, periodontal disease, HIV, non-insulin dependent diabetes mellitus, systemic lupus erythematosus, glaucoma, sarcoidosis, idiopathic pulmonary fibrosis, bronchopulmonary dysplasia, retinal disease, scleroderma, osteoporosis, renal ischemia, myocardial infarction, cerebral stroke, cerebral ischemia, nephritis, hepatitis, glomerulonephritis, cryptogenic fibrosing aveolitis, psoriasis, transplant rejection, atopic dermatitis, vasculitis, allergy, seasonal allergic rhinitis, reversible airway obstruction, adult respiratory distress syndrome, asthma, chronic obstructive pulmonary disease (COPD) and bronchitis in a subject comprising administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with COPD, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with rheumatoid arthritis, comprising: administering to the subject in need of such treatment a therapeutically

effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with Crohn's disease, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with psoriasis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with ankylosing spondylitis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with sciatica, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with complex regional pain syndrome, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with psoriatic arthritis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with multiple sclerosis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof, in combination with a compound selected from the group consisting of Avonex®, Betaseron, Copaxone or other compounds indicated for the treatment of multiple sclerosis.

Additionally, a compound of the present invention may be co-administered or used in combination with disease-modifying antirheumatic drugs (DMARDS) such as methotrexate, azathioprine, leflunomide, pencillinamine, gold salts, mycophenolate mofetil, cyclophosphamide and other similar drugs. They may also be co-administered with or used in combination with NSAIDS such as piroxicam, naproxen, indomethacin, ibuprofen and the like; COX-2 selective inhibitors such as Vioxx® and Celebrex®; immunosuppressives such as steroids, cyclosporin, Tacrolimus, rapamycin and the like; biological response modifiers (BRMs) such as Enbrel®, Remicade®, IL-1 antagonists, anti-CD40, anti-CD28, IL-10, anti-adhesion molecules and the like; and other anti-inflammatory agents such as p38 kinase inhibitors, PDE4 inhibitors, other chemically different TACE inhibitors, chemokine receptor antagonists, Thalidomide and other small molecule inhibitors of pro-inflammatory cytokine production.

Also, a compound of the present invention may be co-administered or used in combination with an H1 antagonist for the treatment of seasonal allergic rhinitis and/or asthma. Suitable H1 antagonists may be, for example, Claritin®, Clarinex®, Allegra®, or Zyrtec®.

In another aspect, the invention provides a method of treating a condition or disease mediated by TACE, aggrecanase, ADMP, MMPs, TNF-α, aggrecanase, or any combination thereof in a subject comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof in combination with a therapeutically effective amount of at least one medicament selected from the group

consisting of disease modifying anti-rheumatic drugs (DMARDS), NSAIDs, COX-2 inhibitors, COX-1 inhibitors, immunosuppressives, biological response modifiers (BRMs), anti-infammatory agents and H1 antagonists.

In another aspect, the invention provides a method of treating a condition or disease selected from the group consisting of rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, solid tumor growth and tumor invasion by secondary metastases, neovascular glaucoma, inflammatory bowel disease, multiple sclerosis and psoriasis in a subject, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof in combination with a therapeutically effective amount of at least one medicament selected from the group consisting of DMARDS, NSAIDs, COX-2 inhibitors, COX-1 inhibitors, immunosuppressives, BRMs, anti-infammatory agents and H1 antagonists.

In another aspect, the invention provides a method of treating a condition or disease selected from the group consisting of septic shock, haemodynamic shock, sepsis syndrome, post ischaemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic diseases, cachexia, graft rejection, cancers such as cutaneous T-cell lymphoma, diseases involving angiogenesis, autoimmune diseases, skin inflammatory diseases, inflammatory bowel diseases such as Crohn's disease and colitis, osteo and rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, adult Still's disease, ureitis, Wegener's granulomatosis, Behcehe disease, Sjogren's syndrome, sarcoidosis, polymyositis, dermatomyositis, multiple sclerosis, sciatica, complex regional pain syndrome, radiation damage, hyperoxic alveolar injury, periodontal disease, HIV, non-insulin dependent diabetes mellitus, systemic lupus erythematosus, glaucoma, sarcoidosis, idiopathic pulmonary fibrosis, bronchopulmonary dysplasia, retinal disease, scleroderma, osteoporosis, renal ischemia, myocardial infarction, cerebral stroke, cerebral ischemia, nephritis, hepatitis, glomerulonephritis, cryptogenic fibrosing aveolitis, psoriasis, transplant

rejection, atopic dermatitis, vasculitis, allergy, seasonal allergic rhinitis, reversible airway obstruction, adult respiratory distress syndrome, asthma, chronic obstructive pulmonary disease (COPD) and bronchitis in a subject comprising administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof in combination with a therapeutically effective amount of at least one medicament selected from the group consisting of DMARDS, NSAIDs, COX-2 inhibitors, COX-1 inhibitors, immunosuppressives, BRMs, anti-infammatory agents and H1 antagonists.

In another aspect, the invention provides a method for treating RA comprising administering a compound of the formula I in combination with compound selected from the class consisting of a COX-2 inhibitor e.g. Celebrex® or Vioxx®; a COX-1 inhibitor e.g. Feldene®; an immunosuppressive e.g. methotrexate or cyclosporin; a steroid e.g. β-methasone; and anti-TNF-α compound, e.g. Enbrel® or Remicade®; a PDE IV inhibitor, or other classes of compounds indicated for the treatment of RA.

In another aspect, the invention provides a method for treating multiple sclerosis comprising administering a compound of the formula I in combination with a compound selected from the group consisting of Avonex®, Betaseron, Copaxone or other compounds indicated for the treatment of multiple sclerosis.

In another aspect, the invention provides a method for the treatment of a microbial infection in a mammal, comprising administering to said mammal a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt, solvate or ester thereof. In one embodiment, the microbe causing the infection is a bacteria, in another embodiment it is a fungus. In one embodiment, the microbial infection is a gram negative infection; in another embodiment, it is a gram negative infection.

In another aspect, the invention provides a method for the treatment of a microbial infection in a mammal, comprising administering to said mammal

a therapeutically effective amount of a compound of formula I in combination with one or more additional antibacterial or antifungal agent. In one embodiment, said additional antibacterial agent is active against gram negative bacteria. In onother embodiment, said additional antibacterial agent is active against gram positive bacteria.

In another embodiment, the bacterial infection is caused by at least one organism selected from the group consisting of *Acinetobacter baumannii, Acinetobacter calcoaceticus, Acinetobacter haemolyticus, Acinetobacter hydrophila, Actinobacillus actinomycetemcomitans, Aeromonas hydrophila, Alcaligenes xylosoxidans, Bacteroides distasonis, Bacteroides fragilis, Bacteroides melaninogenicus, Bacteroides ovatus, Bacteroides thetaiotaomicron, Bacteroides vulgatus, Bartonella henselae, Bordetella pertussis, Branhamella catarrhalis, Brucella melitensis, Brucella abortus, Brucella canis,Burkholderia cepacia, Burkholderia mallei,Burkholderia pseudomallei, Campylobacter coli, Campylobacter fetus, Campylobacter jejuni, Citrobacter diversus, Citrobacter freundii, Citrobacter koseri, Coxiella burnetli, Edwarsiella tarda, Ehrlichia chafeenis, Eikenella corrondens, Enterobacter aerogenes, Enterobacter agglomerans, Enterobacter cloacae, Escherichia coli, Flavobacterium meningosepticum, Francisella tularensis, Fusobacterium spp., Haemophilus ducreyi, Haemophilus influenzae,Haemophilus parainfluenzae, Helicobacter pylori, Kingella kingae, Klebsiella oxytoca,Klebsiella ozaenae, Klebsiella pneumoniae, Klebsiella rhinoscleromatis, Legionella pneumophila, Moraxella catarrhalis, Morganella morganii, Neisseria gonorrhoeae, Neisseria meningitides, Pasteurella multocida, Plesiomonas shigelloides, Porphyromonas asaccharolytica, Porphyromonas gingivalis, Prevotella bivia,Prevotella buccae, Prevotella corporis, Prevotella endodontalis, Prevotella intermedia,Prevotella melaninogenica,Prevotella oralis, Proteus mirabilis, Proteus myxofaciens, Proteus penner, Proteus vulgaris, Providencia alcalifaciens, Providencia rettgeri, Providencia stuarfii, Pseudomonas aeruginosa, Pseudomonas fluorescens, Ricketsia prowozekii, Salmonella enterica,Serratia marcescens, Shigella boydii, Shigella dysenteriae, Shigella flexneri,Shigella sonnei,*

Stenotrophomonas maltophilia, Streptobacillus moniliformis, Vibrio alginolyticus, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vuluificus, Yersinia enterocolitica, Yersinia pestis, and *Yersinia pseudotuberculosis.*

In another embodiment, the bacterial infection is caused by at least one organism selected from the group consisting of *Acinetobacter baumannii, Acinetobacter spp., Aeromonas hydrophila, Bacteroides fragilis, Bacteroides spp., Bordetella pertussis, Campylobacter jejuni, Campylobacter spp., Citrobacter freundii, Citrobacter spp., Enterobacter cloacae, Enterobacter spp., Escherichia coli, Fusobacterium spp., Haemophilus influenzae, Haemophilus parainfluenzae, Helicobacter pylori, Klebsiella pneumoniae, Klebsiella spp., Legionella pneumophila, Moraxella catarrhalis, Morganella morganii, Neisseria gonorrhoeae, Neisseria meningitides, Pasteurella multocida, Prevotella spp., Proteus mirabilis, Proteus spp., Providencia stuartii, Pseudomonas aeruginosa, Pseudomonas spp., Salmonella enterica, Salmonella typhi, Serratia marcescens, Shigella spp.,Stenotrophomonas maltophilia, Vibrio cholerae, Vibrio spp.,* and *Yersinia spp.*

TACE activity is determined by a kinetic assay measuring the rate of increase in fluorescent intensity generated by TACE catalyzed cleavage of an internally quenched peptide substrate (SPDL-3). The purified catalytic domain of recombinant human TACE (rhTACEc, Residue 215 to 477 with two mutation (S266A and N452Q) and a 6xHis tail) is used in the assay. It is purified from the baculovirus/Hi5 cells expression system using affinity chromatography. The substrate SPDL-3 is an internally quenched peptide (MCA-Pro-Leu-Ala-Gln-Ala-Val-Arg-Ser-Ser-Ser-Dpa-Arg-NH2), with its sequence derived from the pro-TNFα cleavage site. MCA is (7-Methoxycoumarin-4-yl)acetyl. Dpa is N-3-(2,4-Dinitrophenyl)-L-2,3-diaminopropionyl.

A 50 μl assay mixture contains 20 mM HEPES, pH 7.3, 5 mM $CaCl_2$, 100 μM $ZnCl_2$, 2 % DMSO, 0.04% Methylcellulose, 30 μM SPDL-3, 70 pM rhTACEc and a test compound. RhTACEc is pre-incubated with the testing compound for 90 min. at 25 °C. Reaction is started by addition of the substrate. The fluorescent intensity (excitation at 320 nm, emission at 405

nm) was measured every 45 seconds for 30 min. using a fluorospectrometer (GEMINI XS, Molecular Devices). Rate of enzymatic reaction is shown as Units per second. Effect of a test compound is shown as % of TACE activity in the absence of the compound.

The procedures of International Patent Publication WO00/05256 (published February 3, 2000) were followed for detection of ADMP Activity and for measuring the IC_{50} of the compounds of the present invention. This was indicative of activity against a desintgrin and metallopropeinase thrombo spondin 4 and 5 (ADAMTS-4-5).

The enzyme was purchased commercially from Calbiochem (Cat# PF113) and the peptide substrate described in the patent was custom-ordered from AnaSpec.

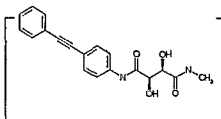
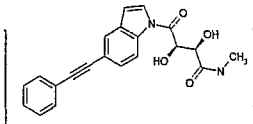
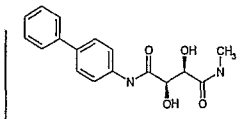
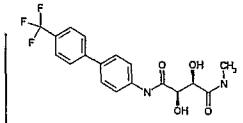
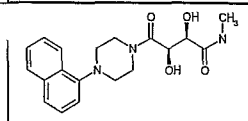
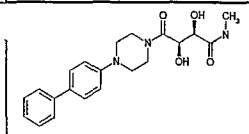
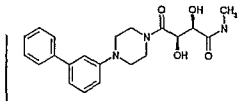
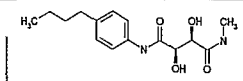
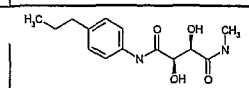
The standard LpxC assay consists of 0.2 nM LpxC enzyme, 1.0 μM UDP-3-*O*-(*R*-3-hydroxymyristoyl)-*N*-acetylglucosamine, and test compound, in assay buffer and 2% DMSO. Assay buffer is comprised of 25 mM HEPES, pH 7.3, 150 mM NaCl, 2.0 mM DTT, and 0.01% BSA. The enzyme reaction is carried out in a 96-well assay plate, in a final volume of 102 μL. Solutions of test compounds are prepared in 100% DMSO. Reaction additions, in order, are (1) 2.0 μL compound solution , (2) 80 μL of assay buffer, (3) 10 μL of 10 μM UDP-3-*O*-(*R*-3-hydroxymyristoyl)-*N*-acetylglucosamine (in assay buffer) and, (4) 10 μL of LpxC enzyme (20 nM in assay buffer) to initiate the reaction. In positive control reactions, addition (1) has 2.0 μL of 100% DMSO (without compound); these reactions are used as the total signal (TSB) value. Reactions are incubated at room temperature for 60 minutes when 10 μL of 1 N HCl is added to stop the reaction. The plate is shaken by hand for 10 seconds to ensure complete quenching. Assay plates are sealed with foil tape, and stored at -80 ^{0}C for 24 - 48 hr prior to analysis.

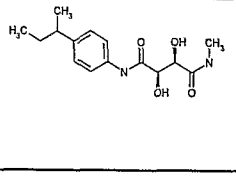
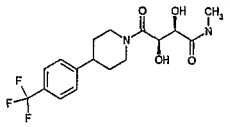
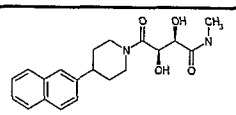
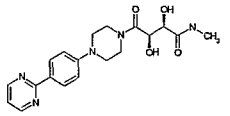
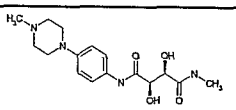
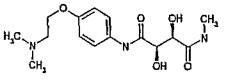
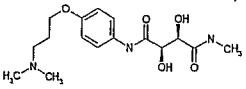
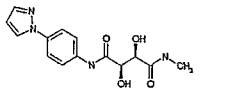
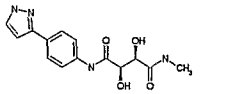
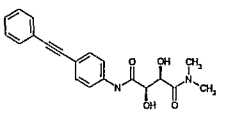
The concentrations of substrate and product in the reaction mixtures are determined with BioTrove's proprietary RapidFire™ high-throughput mass spectrometry (HTMS). Assay mixtures are partially purified with reverse phase chromatography, where they are washed with water containing 5 mM

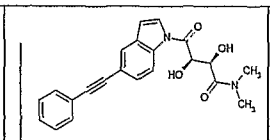
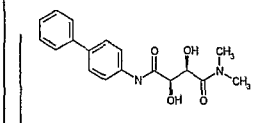
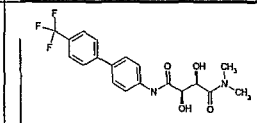
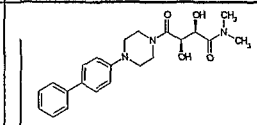
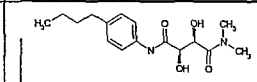
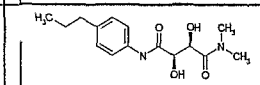
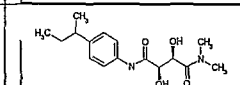
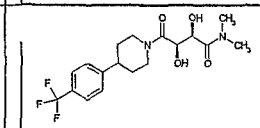
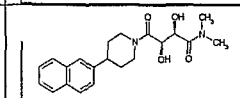
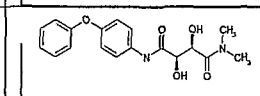
ammonium formate and eluted onto the mass spectrometer in 80% acetonitrile, 20% water, and 5 mM ammonium formate. The mass spectrometry peak areas of the substrate and product are measured to determine the concentration of these analytes. The assay signal is the percentage of substrate that is converted to product. Percent inhibition, %I, in test samples is determined from the following equation:

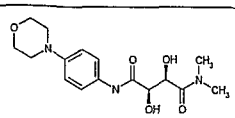
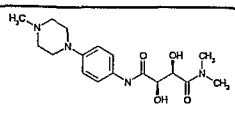
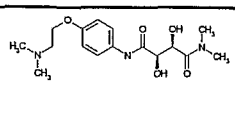
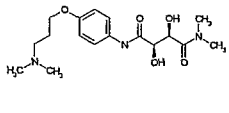
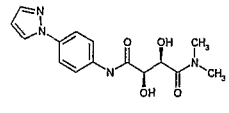
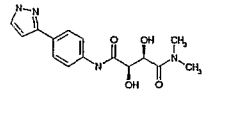
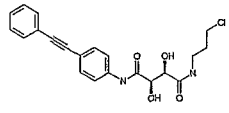
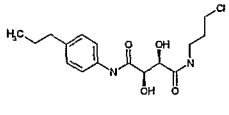
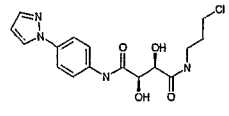
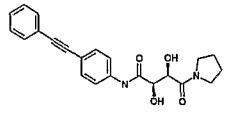
$$\%I = 100 * \frac{(TSB - SampleSignal)}{(TSB)}.$$

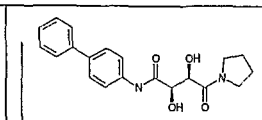
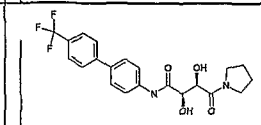
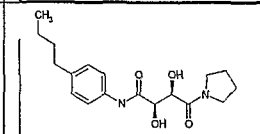
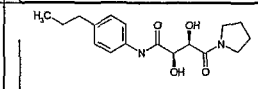
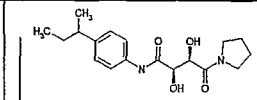
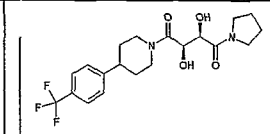
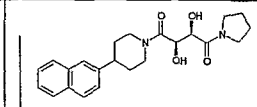
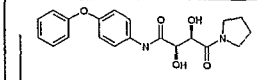
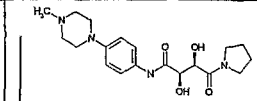
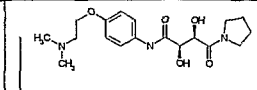
Inhibitory activities of representative compounds of the present invention are set forth in the table below. In this table below, greater than 30% inhibition is assigned a rating of "A", 10-30% inhibition is assigned a rating of "B", and less than 10% inhibition is assigned a rating of "C".

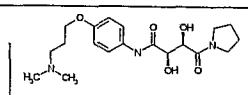
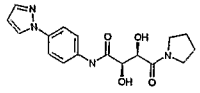
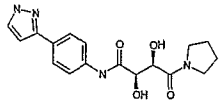
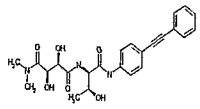
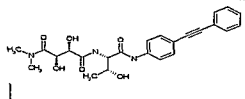
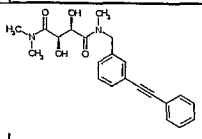
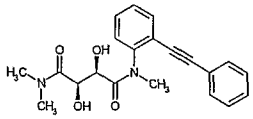
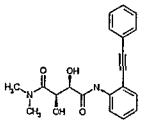
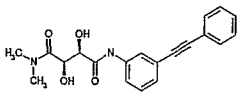
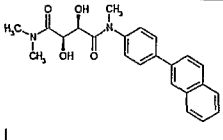
S.No	Structure	LpxC enzyme assay rating (% inhibition at indicated concentrations)									
		50	25	12.50	6.25	3.13	1.56	0.78	0.39	0.20	0.10
25		C	C	B	C	C	C	C	C	C	C
26		B	C	B	C	C	C	C	C	C	C
27		B	B	B	B	B	C	C	C	C	C
28		C	C	B	C	C	C	C	C	C	C
29		B	B	B	B	B	B	C	C	C	C
30		A	B	B	B	B	C	C	B	B	C
31		B	B	B	C	B	B	B	C	B	C
32		B	B	B	C	B	C	B	B	B	B
33		C	C	C	B	B	B	C	C	C	C

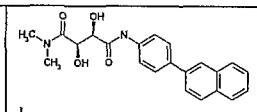
34		B	B	C	B	C	B	B	C	B	C
35		B	C	C	C	C	B	C	C	C	C
36		C	C	C	C	C	C	C	C	C	C
37		C	B	C	B	C	C	C	C	C	C
38		B	C	C	C	C	C	C	C	C	C
39		B	C	C	B	B	C	B	C	C	C
40		C	B	B	C	C	C	B	C	C	C
41		B	B	C	B	B	B	C	C	C	C
42		C	B	B	B	C	B	B	B	C	C
43		A	A	A	B	B	B	C	C	B	C

44		A	A	A	B	B	C	C	C	B	C
45		C	C	C	C	C	C	C	C	C	C
46		A	B	B	C	C	C	C	C	C	C
47		B	C	B	B	B	C	B	C	B	B
48		B	C	B	C	B	C	C	C	C	B
49		C	B	C	C	C	C	C	B	C	C
50		B	C	B	B	C	C	B	C	C	C
51		B	B	C	C	C	B	C	C	C	B
52		A	B	B	B	C	C	C	C	C	C
53		C	C	C	C	C	C	B	C	C	C

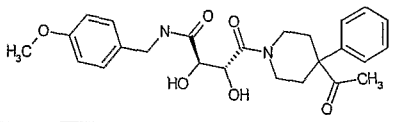
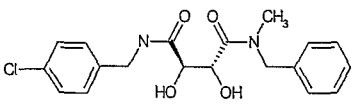
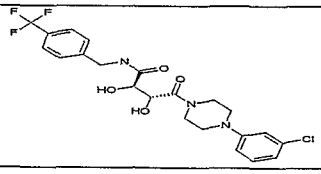
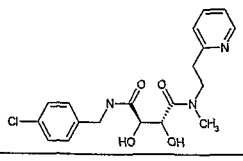
54		C	C	C	C	B	C	C	C	C	C
55		B	B	C	C	B	B	B	C	B	C
56		C	C	C	B	C	C	C	C	B	C
57		C	B	C	C	C	C	C	B	C	B
58		B	C	B	B	B	C	B	C	B	C
59		C	B	C	C	C	C	C	B	C	B
60		C	C	B	B	B	C	B	B	C	C
61		B	B	C	C	C	C	C	C	C	C
62		C	B	B	B	C	B	C	C	C	C
63		A	A	A	B	B	B	C	B	B	B

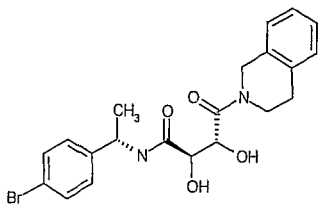
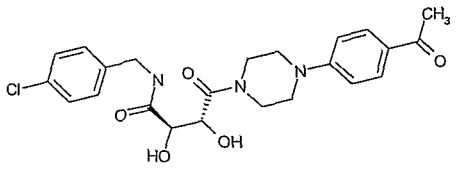
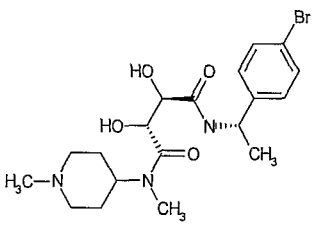
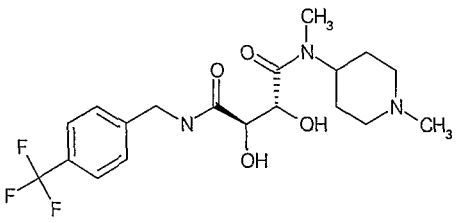
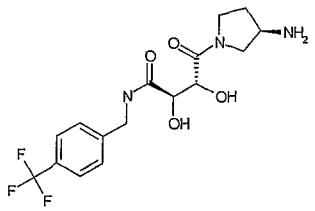
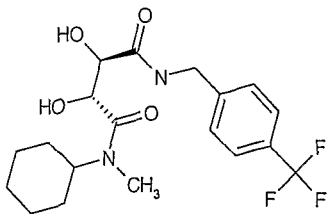
64		B	B	B	B	B	C	B	C	B	B
65		B	B	B	B	B	B	C	B	B	B
66		B	A	B	B	B	B	C	B	C	C
67		B	B	C	B	C	C	C	B	B	B
68		B	B	C	B	B	C	C	C	C	C
69		C	C	C	C	C	C	C	C	C	C
70		C	B	C	C	C	C	B	C	C	C
71		C	C	C	C	B	B	B	B	C	B
72		B	C	C	C	C	C	C	C	C	B
73		C	C	C	C	C	C	B	C	B	C

74		C	C	C	C	B	B	C	C	C	B
75		B	C	C	B	B	C	B	C	C	C
76		C	C	C	B	C	B	C	C	C	C
77			A	B	C	C	C	C	C	C	C
78			A	B	B	B	C	C	B	C	C
79			A	B	B	C	C	C	C	C	C
103			C	B	C	B	B	B	B	C	C
80			C	B	C	C	C	C	C	C	C
81			C	C	C	C	C	C	C	C	C
104			B	C	C	C	C	C	C	C	C

82			A	A	B	B	C	C	C	B	C

ADMP inhibitory activities for representative compounds are shown in the table below. Compounds possessing IC_{50} values greater than 5 μM (>5 μM) are designated as "D" class. Compounds possessing IC_{50} values greater than 1 μM but up to 5 μM (>0.1 μM – 5 μM) are designated as "C" class. IC_{50} values between 0.25 μM to 1.0 μM (0.25 μM – 1 μM) are designated as "B" class. IC_{50} values less than 0.25 μM (<0.25 μM) are designated as "A" class.

S. No.	Structure	IC_{50} rating
108		B
110		B
111		B
113		B

114		A
118		D
121		C
122		B
123		C
125		B
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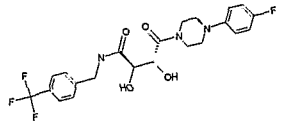
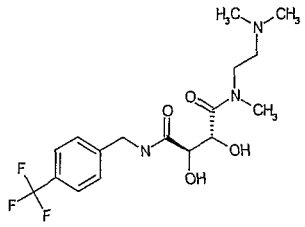
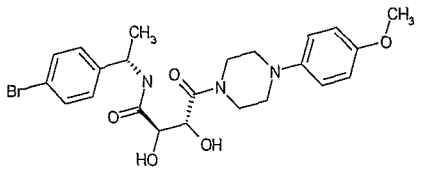
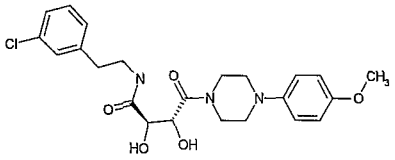
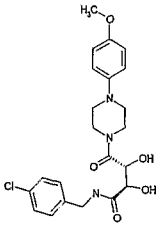
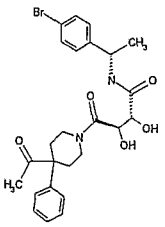
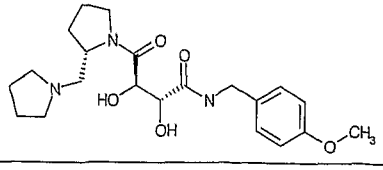
		
127		D
130		A
131		B
132		B
133		A
134		B
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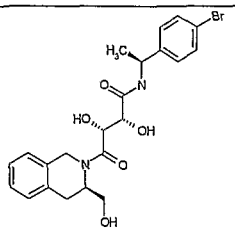
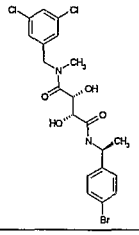
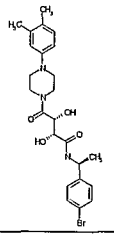
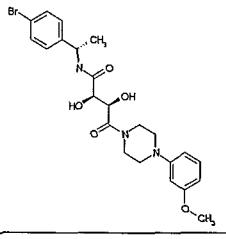
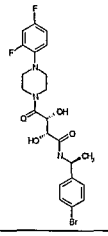
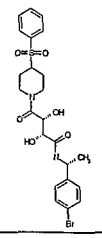
		
139		B
142		B
143		A
144		A
148		A
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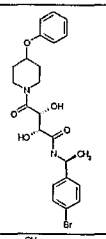
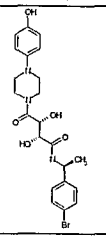
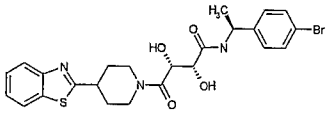
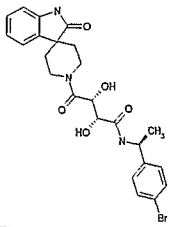
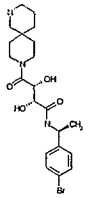
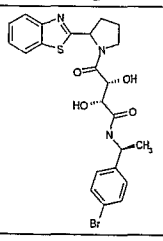
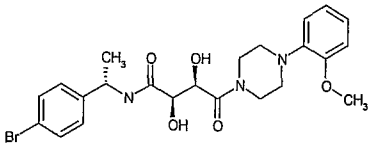
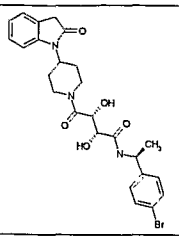
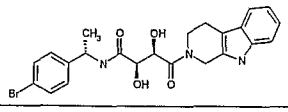
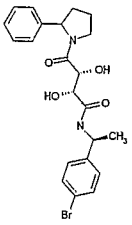
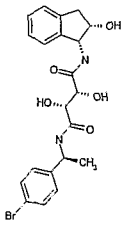
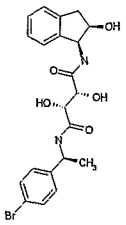
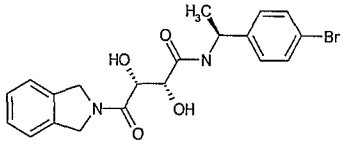
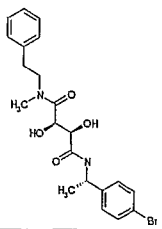
		
150		C
151		A
152		C
158		D
160		A
164		B

165		C
169		B
172		B
173		D
174		D
175		B
176		B
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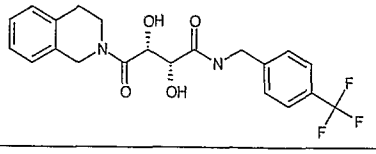
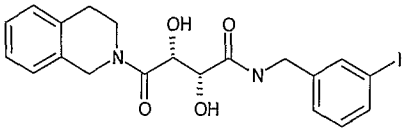
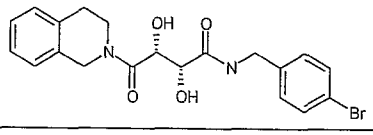
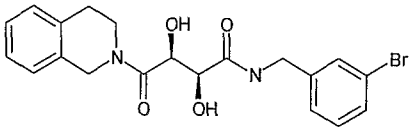
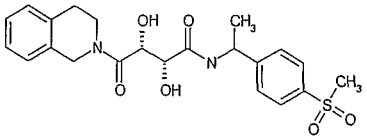
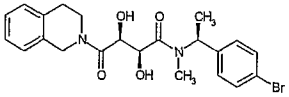
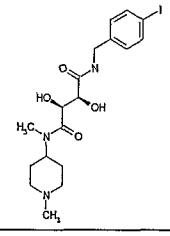
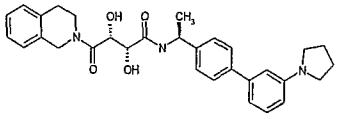
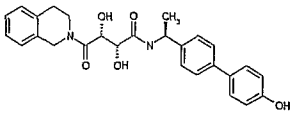
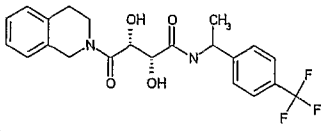
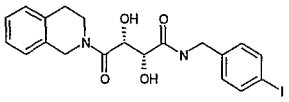
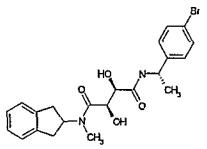
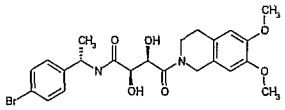
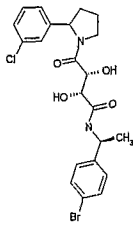
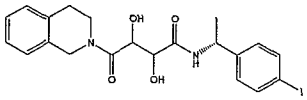
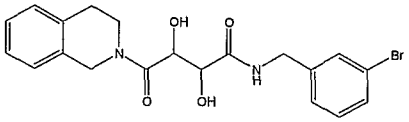
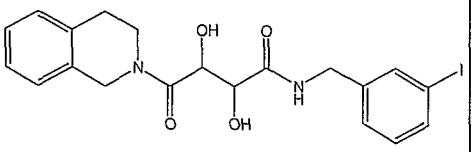
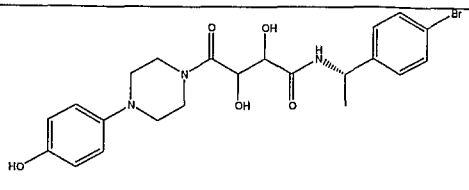
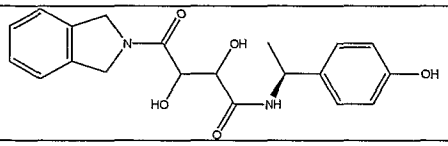
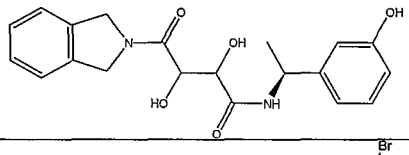
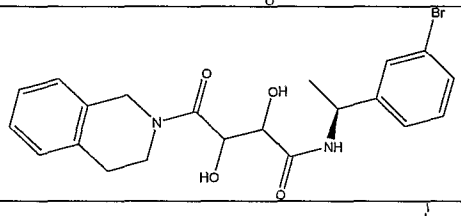
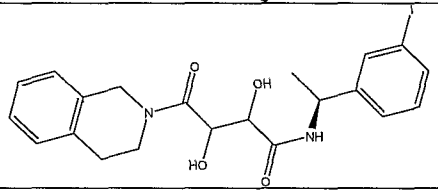
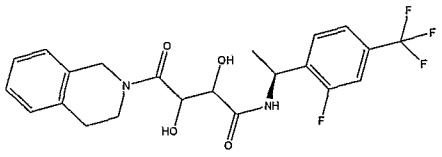
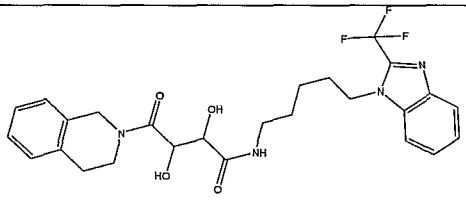
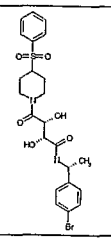
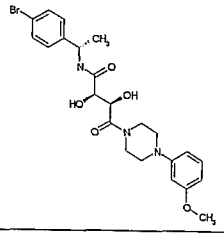
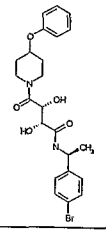
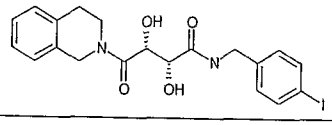
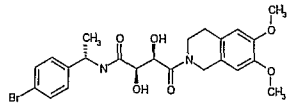
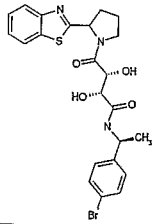
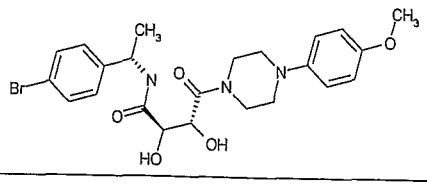
		
181		D
184		B
185		D
186		D
187		D
189		D
196		A
200		A

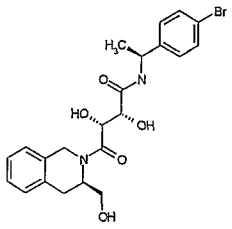
201		B
204		A
206		B
207		A
209		A
210		B
211		D
212		D
215		C

216		A
217		C
218		D
219		C
220		D
221		D

Representative examples of compounds of the invention with specific IC_{50} values (ADMP inhibition) are listed in the table below:

S. No.	Structure	IC_{50} (μM)
148		0.047

		
143		0.09
149		0.09
204		0.09
207		0.096
160		0.16
130		0.17

138		0.19

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Pat. Nos. 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for controlled release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredients is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or a soft gelatin

capsules where in the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example, polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example, ethyl or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example, arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example, beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending

agents are exemplified by those already mentioned above. Additional excipients, e.g., sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsion. The oily phase may be a vegetable oil, e.g., olive oil or arachis oil, or a mineral oil, e.g., liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, e.g., soy beans, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, e.g., polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, e.g., as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of the invention may also be administered in the form of suppositories for rectal administration of the drug. The compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will

therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of The invention are employed. (For purposes of this application, topical application shall include mouthwashes and gargles.)

The compounds for the present invention can be administered in the intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen. Compounds of the present invention may also be delivered as a suppository employing bases such as cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound thereof employed. A physician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the drug required to prevent, counter, arrest or reverse the progress of the condition. Optimal precision in achieving concentration of drug within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the drug's availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of a drug. Preferably, doses of the compound of Formula I useful in the method of the present invention range from 0.01 to 1000 mg per day. More preferably, dosages range from 0.1 to 1000 mg/day. Most preferably, dosages range from 0.1 to 500 mg/day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01 to 1000 milligrams of the active ingredient, particularly 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0,

25.0, 50.0, 100 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.0002 mg/kg to about 50 mg/kg of body weight per day. The range is more particularly from about 0.001 mg/kg to 1 mg/kg of body weight per day.

Advantageously, the active agent of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in dividend doses of two, three or four time daily.

The amount of active ingredient that may be combined with the carrier materials to produce single dosage form will vary depending upon the host treated and the particular mode of administration.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route or administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The compounds of the invention may be produced by processes known to those skilled in the art and as shown in the following reaction schemes and in the preparations and examples described below.

EXAMPLES

The following abbreviations are used in the procedures and schemes:

ACN	Acetonitrile
AcOH	Acetic acid
ADDP	1,1[1]-(Azodicarbonyl)dipiperidine
Anh.	Anhydrous
Aq	Aqueous
BOC	tert-Butoxycarbonyl
°C	degrees Celsius
CBZCl	Benzyl chloroformate
CDI	Carbodiimide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
(DHQ)2PHAL	Hydroquinine 1,4-phthalazinediyl diether
DIAD	Diisopropylazodicarboxylate
DIEA	Diisopropylethylamine
DMA	N,N-Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMFDMA	N,N-Dimethylformamide dimethylacetal
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1h)-pyrimidinone
DMSO	Dimethyl sulfoxide
EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EI	Electron ionization
Eq	Equivalents
EtOAc	Ethyl acetate
EtOH	Ethanol
g	grams
h.	hours

^1H	proton
HATU	N,N,N',N'-Tetramethyl-O-(7-Azabenzotriazol-1-yl)Uronium hexafluorophosphate
Hex	hexanes
HOBt	1-Hydroxybenzotriazole
HPLC	High pressure liquid chromatography
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
M	Molar
mCPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
min	Minutes
mg	Milligrams
MHz	Megahertz
ml	Milliliter
MS	Mass Spectroscopy
NMM	N-Methylmorpholine
NMP	1-methyl-2-pyrrolidone
ON	Overnight
$Pd(^tBu_3P)_2$	Bis-(tri-*tert*-butylophosphine)palladium
$Pd(TPP)_4$	Tetrakis-(triphenylphosphine)palladium
$Pd(Oac)_2$	Palladium(II) acetate
$PdCl_2(TPP)_2$	Bis-(triphenylphosphine)palladium(II) chloride
$PdCl_2$(ddppf)	Dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(ii) dichloride
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
PyBrOP	Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
Pyr	Pyridine
RT	Room temperature
SiO_2	Silica gel 60 chromatography

sgc	Silica gel 60 chromatography
tBOC	tert-Butoxycarbonyl
TACE	TNF-alpha converting enzyme
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TPP	Triphenylphosphine
t_R	Retention time

NMR spectra were acquired on a Mercuryplus 400 MHz NMR Spectrometer (Varian), using CDCl3 or DMSO-d6 as solvents. LC-MS data was obtained using an Agilent 1100 Series LC/MSD (quadrupole, API-ES (Atmospheric Pressure Interface Electrospray)) with a capillary voltage set to 3500 V and running in positive mode. Reported analytical HPLC (LC/MS) retention times were obtained using a C18 (150 x 4.6 mm) reverse-phase column eluting with a 5 or 10 minute gradient of 0.1 % trifluoroacetic acid in water to 95:5 acetonitrile:water at a flow rate of 3 mL/min.

Purification via reverse phase chromatography was accomplished using a C18 reverse phase column with a gradient of 0.1 % trifluoroacetic acid in water to 95:5 acetonitrile:water at a flow rate of 20 mL/min. Samples were collected using a UV (Gilson, 254 nm) or mass spectra (Agilent 1100 Series LC/MSD model SL) signal.

Normal phase silica gel chromatography on a Biotage instrument was accomplished using a Quad UV System (P/N 07052) utilizing KP-SIL 32-63 um columns, 60Å with flash cartridges 12+M or 25+M.

The compounds of formula (I) may be produced by processes known to those skilled in the art and as shown in the following reaction schemes and in the preparations and examples described below. These preparations and examples should not be construed to limit the scope of the disclosure. Alternate mechanistic pathways and analogous structures may be apparent to those skilled in the art. Some of the compounds made by these processes

are listed in Table 1. All kinds of isomeric forms of the compounds are considered to be within the scope of this invention.

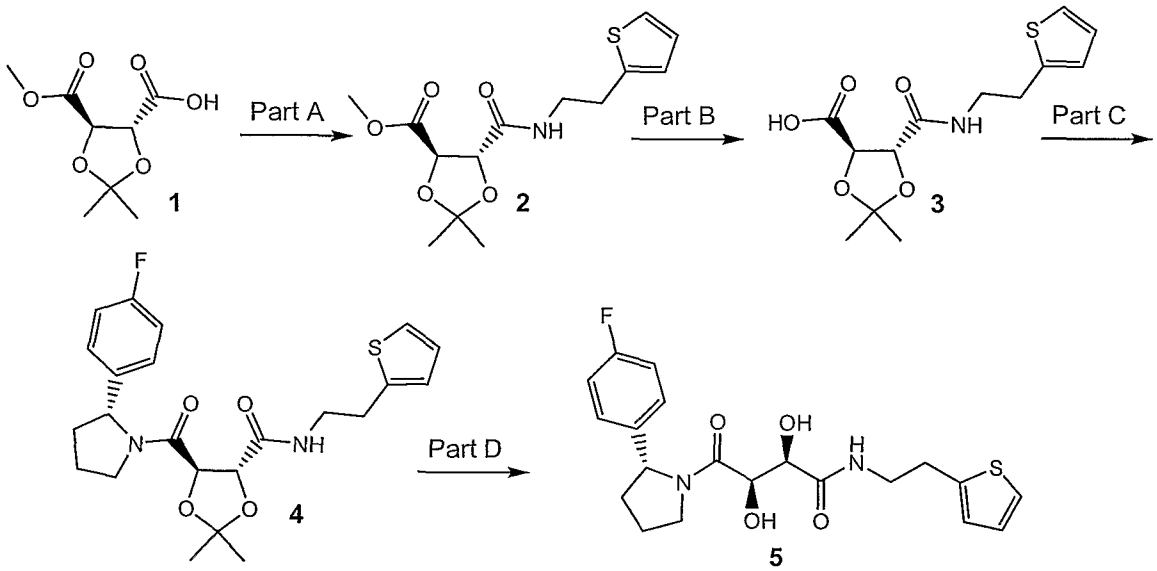
Example 1: General synthesis of tartrate inhibitors

Two general routes exist for the synthesis of tartrate diamides from amines. The first (Example 1) utilizes an acetonide-protected monoacid/monoester intermediate prepared from the commercially available acetonide dimethyl ester using a literature procedure (*J. Am. Chem. Soc.* **1978**, *100*, 4865-4872). In general either Example 1 or Example 2 could be used interchangeably, although Example 2 was found to be more preferred for compounds that contained functional groups that were unstable towards acidic deprotection conditions (such as **113**).

A variety of amide bond coupling reagents were acceptable, including HATU, CDI, EDC, DCC/HOBt, PyBrOP, polymer supported CDI with HOBt, polymer supported carbodiimide, and polymer supported EDC (PS-EDC) with HOBt. These coupling reagents could be used with a variety of bases, including triethylamine (TEA), diisopropylethylamine (DIEA), N-methyl morpholine, pyridine, dimethylaminopyridine (DMAP) and imidazole. In some cases the excess amines in the peptide coupling steps were removed using liquid/liquid extraction or polymeric scavenging resins such as polymer supported isocyanate (PS-NCO) and/or polymer supported tosic acid (MP-TsOH). Unreacted acids could be removed using MP-carbonate resin or polymer resins containing basic functional groups such as trisamine (i.e. PS-trisamine), amberlite, or morpholine. Peptide couplings were conducted in a variety of solvents, including DMF, THF, dioxane, acetonitrile, NMP, and DCM. These solvents can also be combined in various proportions to optimize the reaction conditions. A less preferred but viable route using pentafluorophenyl (PFP) ester intermediates may be also utilized to prepare mono or diamides; preferred solvents for this approach should include THF. General peptide coupling strategies, including PFP-based approaches, can be

found in Bodanszky & Bodanszky, *The Practice of Peptide Synthesis, second edition, Springer-Verlag, **1994***.

Cleavage (saponification) of the intermediate methyl ester could be accomplished under a variety of well-known conditions; including: a slight excess (1.1-3 equivalents) of base, KOH in methanol, LiOH in THF/water, LiOH in methanol/water, and NaOH/THF/MeOH/water. Removal of the acetonide protecting group could be afforded using a variety of acidic conditions, including TFA:water combinations (such as 80:20).



Part A:

To 2,2-dimethyl-[1,3]dioxolane-4R,5R-dicarboxylic acid monomethyl ester **(1)** (Musich, J.A.; Rapoport, H.; *J. Am. Chem. Soc.* **1978**, *100*, 4865-4872) (500 mg, 2.45 mmol) in DMF (5 mL) was added 2-thiopheneethylamine (316 µL, 2.70 mmol), DIEA (0.94 mL, 5.4 mmol) and HATU (989 mg, 2.60 mmol). The reaction mixture was stirred overnight and the DMF was removed in vacuo. The residue was dissolved in EtOAc, washed with water, saturated bicarbonate solution, 0.1 N HCl, and brine. The organic layer was dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 10% EtOAc/DCM) afforded **2** as an oil (491 mg, 64%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (dd, 1H , J = 1.2, 5.2 Hz), 6.95 (dd, 1H, J = 2.1, 5.2 Hz), 6.84 (d, 1H, J = 2.4 Hz), 6.66 (bs, 1H, NH), 4.72 (ABq, 2H, J = 13.2 Hz), 3.84

(s, 3H), 3.65 (m, 1H), 3.57 (m, 1H), 3.09 (t, 2H, J = 6.4 Hz), 1.47 (s, 3H), 1.40 (s, 3H); HPLC-MS t_R = 1.63 min ($UV_{254\ nm}$); Mass calculated for formula $C_{14}H_{19}NO_5S$ 313.1, observed LCMS m/z 314.2 (M+H).

Part B:

To **2** (869 mg, 2.77 mmol) in THF (10 mL) was added 1.0 M LiOH (3 mL, 3 mmol) and the reaction was stirred overnight at room temperature. The reaction mixture was diluted with water (10 mL) and the THF was removed in vacuo. The basic aqueous layer was extracted with diethyl ether and the ether wash was discarded. The aqueous layer was made acidic with 1.0 N HCl and extracted with diethyl ether. The combined organic layers were dried over sodium sulfate and concentrated to afford **3** as a yellow solid (443 mg, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, 1H, J = 1.2, 5.2 Hz), 6.97 (dd, 1H, J = 3.6, 5.2 Hz), 6.90 (bs, 1H, NH), 6.86 (d, 1H, J = 3.2 Hz), 4.48 (ABq, 2H, J = 9.2 Hz), 3.76 (m, 1H), 3.60 (m, 1H), 3.15 (m, 2H), 1.53 (s, 3H), 1.41 (s, 3H); HPLC-MS t_R = 1.34 min ($UV_{254\ nm}$); Mass calculated for formula $C_{13}H_{17}NO_5S$ 299.1, observed LCMS m/z 300.1 (M+H).

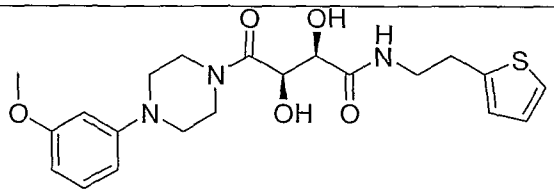
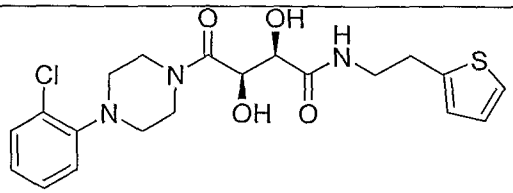
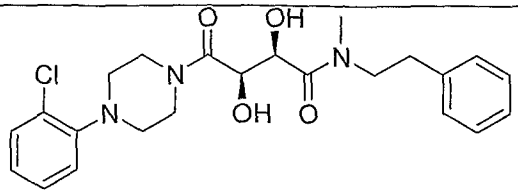
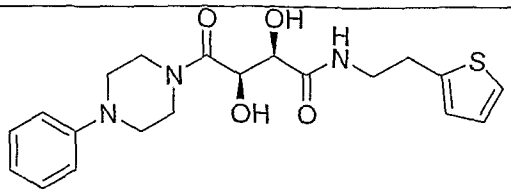
Part C:

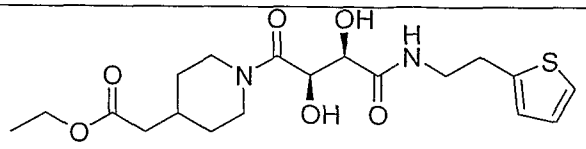
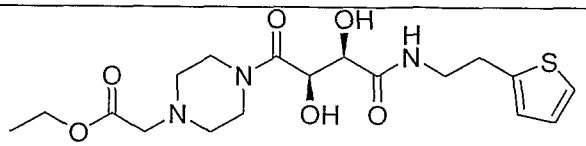
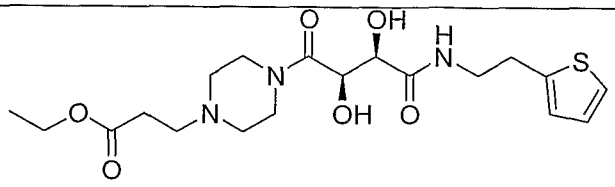
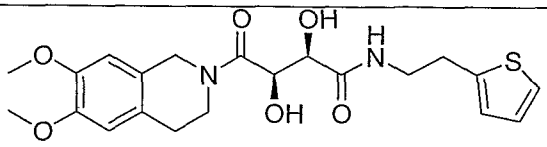
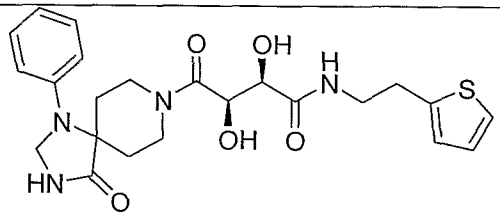
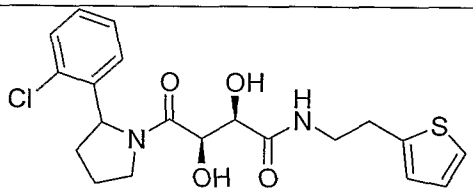
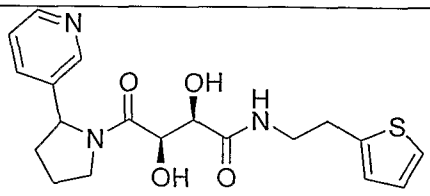
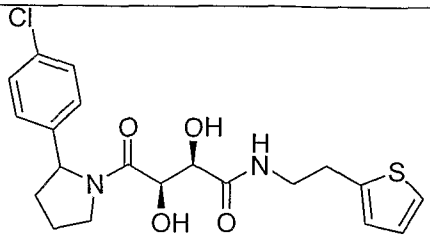
To **3** (150 mg, 0.5 mmol) in DMF (2 mL) was added racemic 2-(4-fluoro-phenyl)-pyrrolidine (99 mg, 0.6 mmol), DIEA (261 µL, 1.5 mmol), and HATU (228 mg, 0.6 mmol) and the reaction mixture was stirred overnight at room temperature. The DMF was removed in vacuo and the residue was dissolved in ethyl acetate. The organic layer was washed with 0.1 N NaOH, 0.1 N HCl, water, and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 10% to 50% EtOAc/DCM) afforded an oil (220 mg, 99%). The diastereomers were resolved (as described in Example 18) by reverse phase HPLC to afford **4** the desired isomer (78 mg, 35%) after lypholization. HPLC-MS t_R = 1.93 min ($UV_{254\ nm}$); Mass calculated for formula $C_{23}H_{27}FN_2O_4S$ 446.2, observed LCMS m/z 447.3 (M+H).

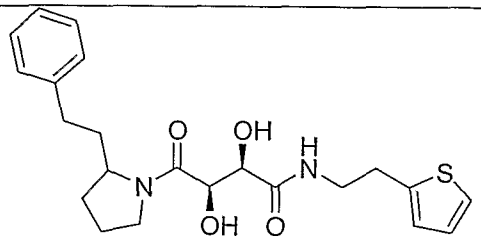
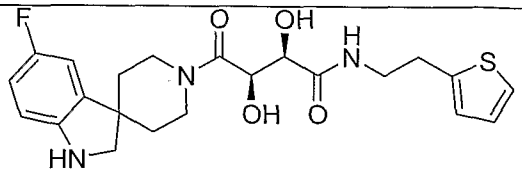
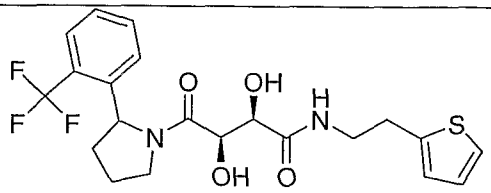
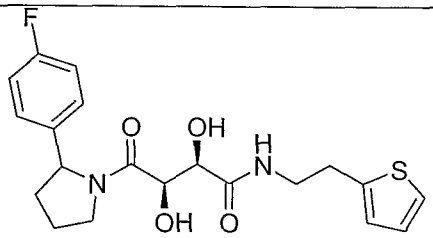
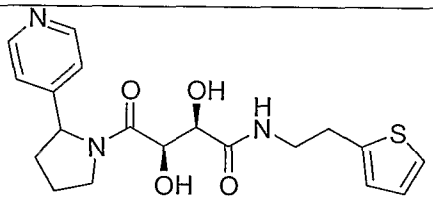
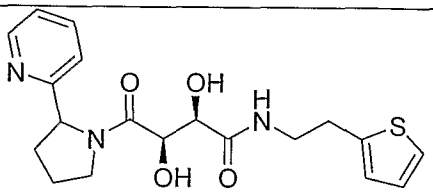
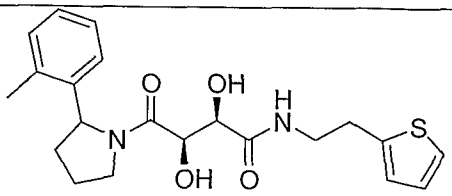
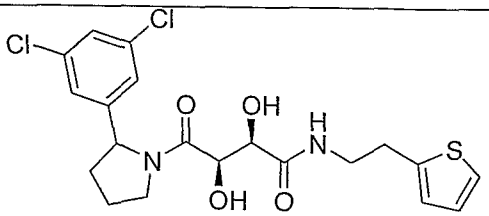
Part D:

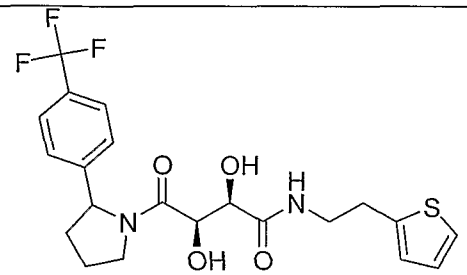
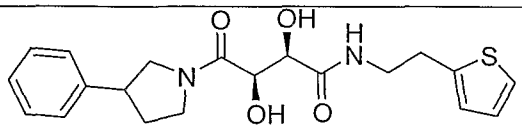
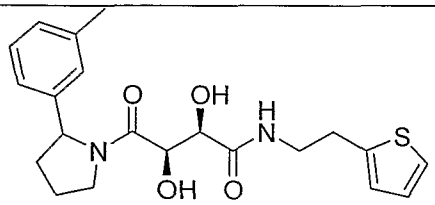
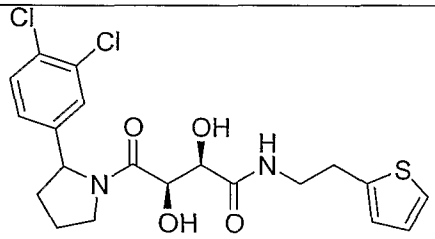
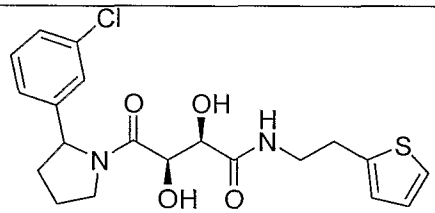
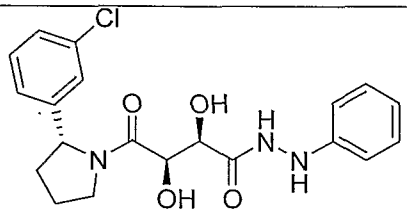
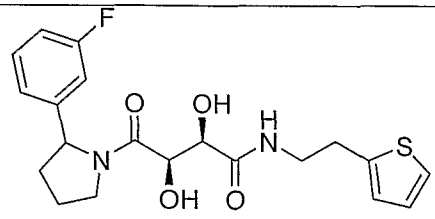
Compound **4** (78 mg, 0.17 mmol) was dissolved in 90:10 TFA:water (5 mL) and stirred for 4 hours at room temperature. The reaction mixture was quenched with 1:1 ACN:water (10 mL) and concentrated. The residue was re-dissolved in 1:1 ACN:water (10 mL) and concentrated. Lypholization afforded **5** as white solid (62 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) mixture of rotomers δ 7.16- 6.8 (m, 8H), 5.23-5.11 (m, 1H), 4.85 (m, 1H), 4.40-4.15 (m, 1H), 3.90-3.48 (m, 6H), 3.00 (m, 2H), 2.33 (m, 1H), 2.05-1.83 (m, 3H); HPLC-MS t_R = 1.50 min ($UV_{254\ nm}$); Mass calculated for formula $C_{20}H_{23}FN_2O_4S$ 406.1, observed LCMS m/z 407.2 (M+H).

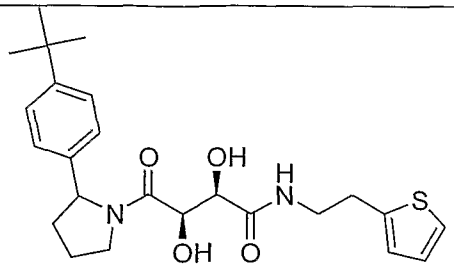
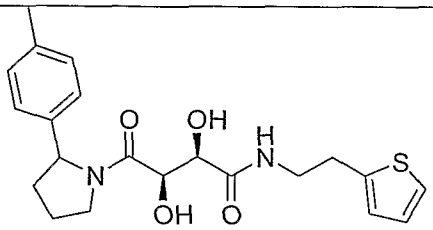
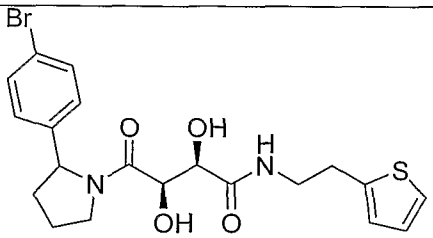
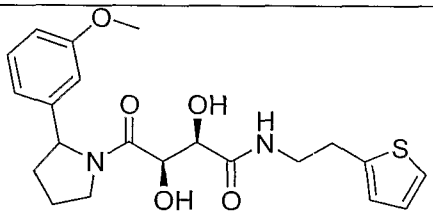
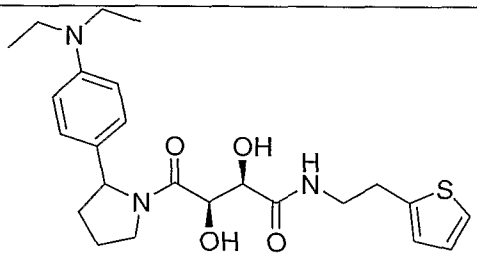
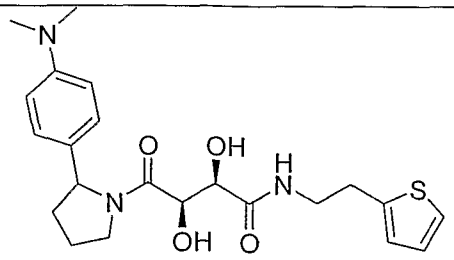
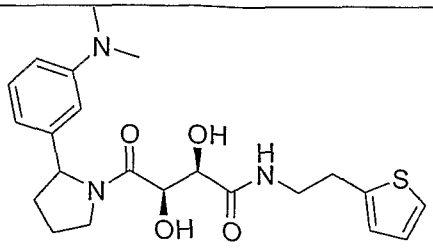
The following table contains compounds synthesized using the above procedures.

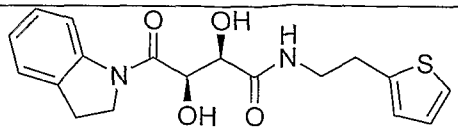
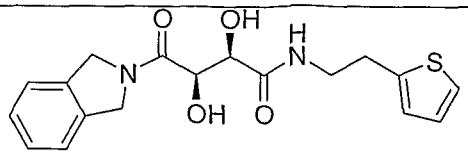
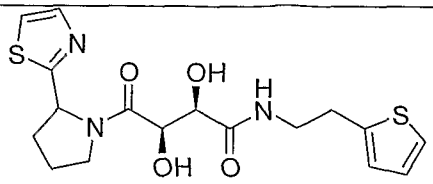
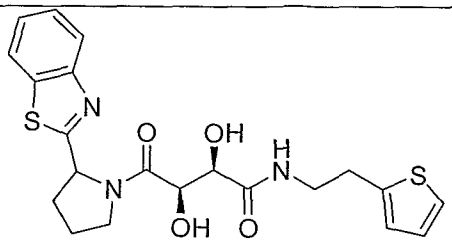
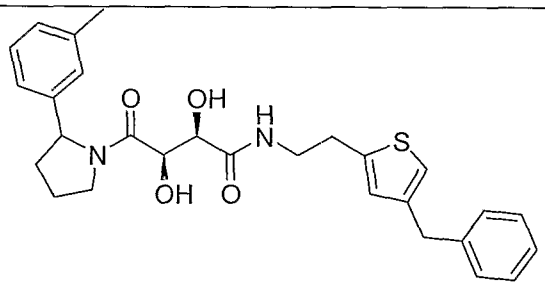
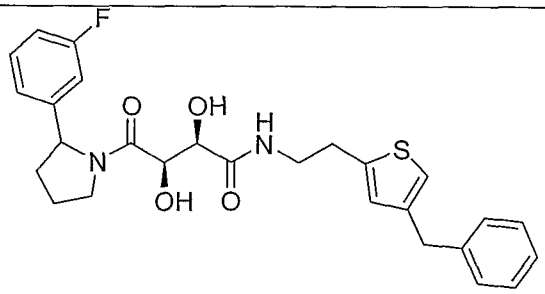
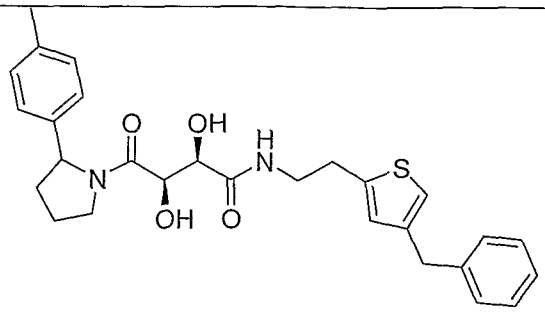
Compound #	Structure	Exact mass	MS m/z (M+H)
6		433.2	434.1
7A		437.1	438.0
7B		445.2	446.1
8		403.2	404.1

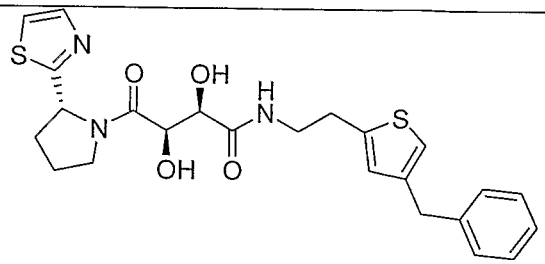
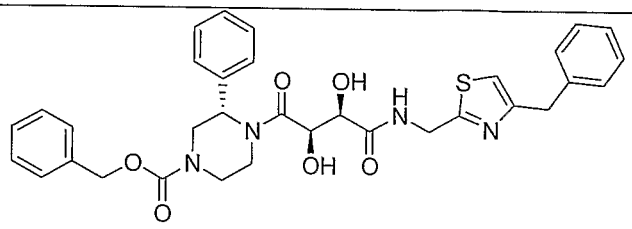
9		412.2	413.2
10		413.2	414.0
11		427.2	428.2
12		434.2	435.1
13		472.2	473.2
14		422.1	423.4
15		389.1	390.1
16		422.1	423.3

17		416.2	417.2
18		447.2	448.1
19		456.1	457.1
20		406.1	407.2
21		389.1	390.1
22		389.1	390.1
23		402.2	403.1
24		456.1	457.0

25		456.1	457.1
26		388.2	389.2
27		402.2	403.1
28		456.1	457.0
29A		422.1	423.1
29B		403.1	404.1
30		406.1	407.2

31		444.2	445.3
32		402.2	403.1
33		466.1	467.0
34		418.2	419.2
35		459.2	460.3
36		431.2	432.2
37		431.2	432.2

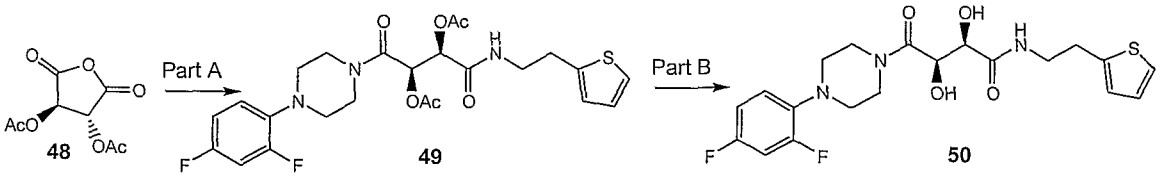
38		360.1	361.1
39		360.1	361.1
40		395.1	396.1
41		445.1	446.2
42		492.2	493.1
43		496.2	497.2
44		492.2	493.1

46		485.1	486.1
47		614.2	615.0

Example 2: Anhydride route to tartrate diamide inhibitors

A second general route to diamide compounds starting from an anhydride intermediate is delineated below in Example 2. (+)-Diacetyl –L-tartaric anhydride **(48)** is an article of commerce and reacts readily with a variety of amines to generate monoacid/monoamide intermediate. The preferred solvent for the ring opening is DCM; although DMF, THF or dioxane may also be compatible. The subsequent peptide coupling step proceeds under a variety of standard conditions which are given for Example 1. The acetate groups can be removed using a variety of conditions, including hydrazine/methanol, NaOMe in methanol, ammonia/methanol, lithium hydroxide/THF/water (saponification), potassium carbonate in methanol, or MP-carbonate. Often times the preferred set of conditions for parallel synthesis is to use the MP-carbonate. It has also been observed that one or both of the acetate protecting groups can be cleaved during synthetic transformations involving nucleophiles, basic reagents, heating in protic solvents or exposure to organometallic reagents.

Example 2A:



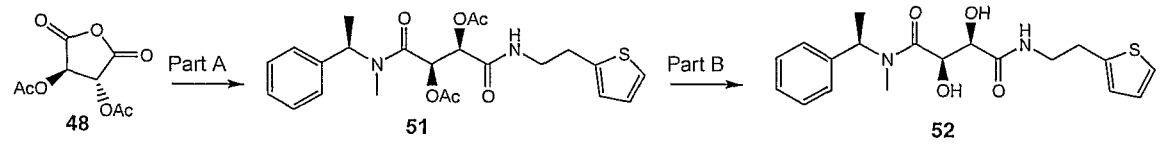
Part A:

To **48** (26 mg, 0.1 mmol) in DMF (1 mL) was added 2,4-difluorophenylpiperazine (20 mg, 0.1 mmol). The reaction mixture was stirred for 1.5 hours. To the crude mixture was added 2-thiopheneethylamine (14 µL, 0.12 mmol), DIEA (38 µL, 0.22 mmol) and HATU (42 mg, 0.11 mmol). The reaction was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with EtOAc. The combined organic layers were washed with 0.1 N NaOH, 0.1 N HCl, and brine; dried over sodium sulfate and concentrated in vacuo to yield **49** as an oil (49 mg, 94%). HPLC-MS t_R = 2.10 min ($UV_{254\ nm}$); mass calculated for formula $C_{24}H_{27}F_2N_3O_6S$ 523.2, observed LCMS m/z 524.4 (M+H); purity > 95% (ELSD).

Part B:

To **49** (49 mg, 0.09 mmol) in MeOH (2 mL) was added anhydrous hydrazine (5 µL, 0.16 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated in vacuo and freeze-dried to afford **50** as a white powder (40 mg, 100%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, 1H, J = 5.2 Hz), 6.96 (m, 2H), 6.85 (m, 4H), 4.87 (s, 1H), 4.24 (s, 1H), 3.90 (m, 2H), 3.72 (m, 2H), 3.60 (m, 4H), 3.08 (m, 4H); HPLC-MS t_R = 1.85 min ($UV_{254\ nm}$); mass calculated for formula $C_{20}H_{23}F_2N_3O_4S$ 439.1, observed LCMS m/z 440.2 (M+H).

Example 2B:



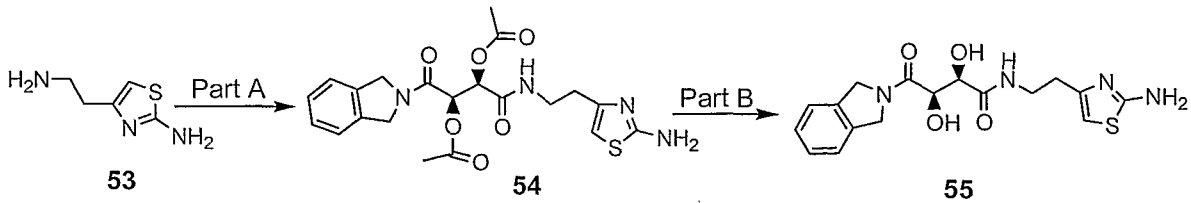
Part A:

To **48** (26 mg, 0.1 mmol) in DMF (1 mL) was added N-methyl-(1*R*-phenyl-ethyl)-amine (15 µL, 0.1 mmol). The reaction mixture was stirred for 1 hour. To the crude mixture was added 2-thiopheneethylamine (47 µL, 0.4 mmol), HOBt (27 mg, 0.2 mmol), PS-carbodiimide resin (312 mg, 0.4 mmol). To the reaction mixture was added PS-TsOH resin (0.6 mmol) and MP-carbonate resin (0.4 mmol). The reaction was tumbled overnight, filtered and concentrated. Compound **51** was used without further purification. HPLC-MS t_R = 1.82 min ($UV_{254\ nm}$); mass calculated for formula $C_{23}H_{28}N_2O_6S$ 460.2, observed LCMS m/z 461.1 (M+H).

Part B:

To **51** in MeOH (2 mL) was added anhydrous hydrazine (5 µL, 0.16 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated in vacuo, purified by reverse phase prep-HPLC and freeze-dried to afford **52** as a white powder (6.7 mg, 18% overall). ^1H NMR (400 MHz, $CDCl_3$) major rotomer δ 7.40- 7.25 (m, 6H), 7.16 (d, 1H, J = 4.8 Hz), 6.95 (app. t, 1H, J = 4.8 Hz), 6.87 (bs, 1H, NH), 5.96 (q, 1H, J = 7.2 Hz), 4.91 (d, 1H, J = 1.2 Hz), 4.22 (d, 1H, J = 1.2 Hz), 3.60 (m, 2H), 3.08 (m, 2H), 2.79 (s, 3H), 1.56 (d, 3H, J = 5.7Hz); HPLC-MS t_R = 3.80 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{19}H_{24}N_2O_4S$ 376.2, observed LCMS m/z 377.2 (M+H).

Example 2C:

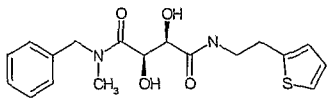
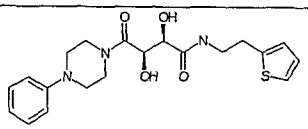
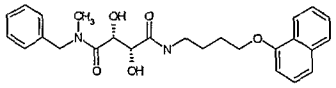
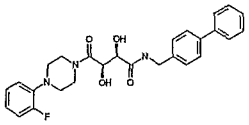


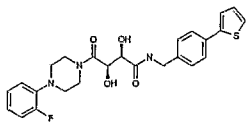
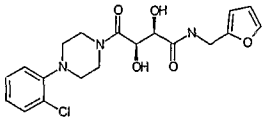
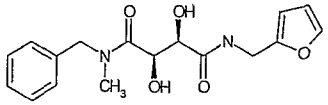
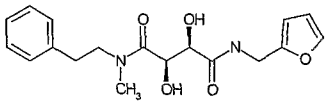
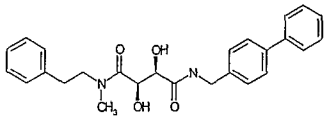
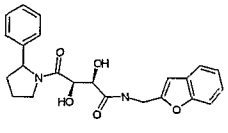
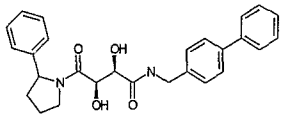
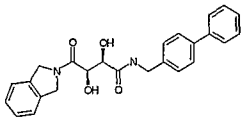
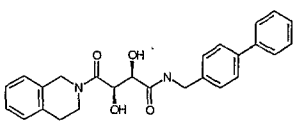
Compound **53** was prepared according to the procedure described by D. Miller et al (*J. Med. Chem.* **1999**, 42, 2287).

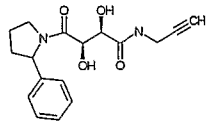
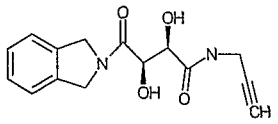
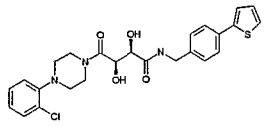
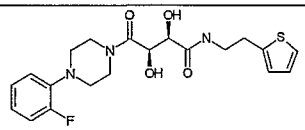
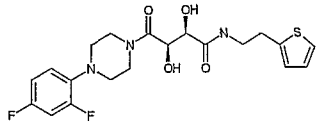
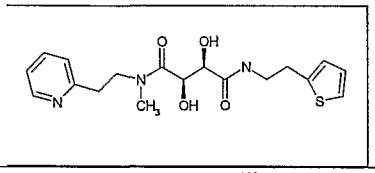
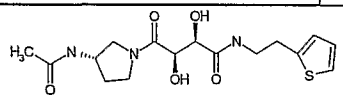
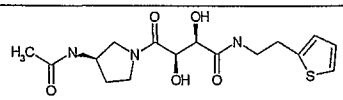
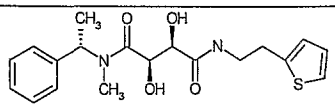
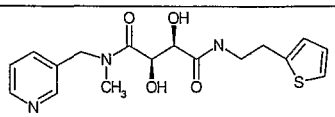
Parts A & B:

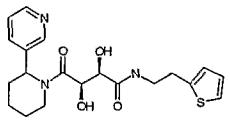
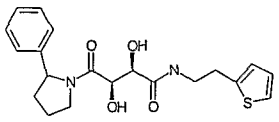
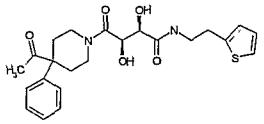
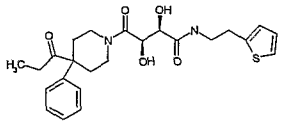
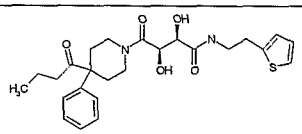
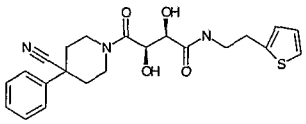
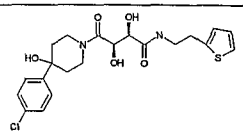
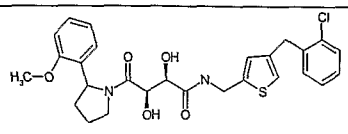
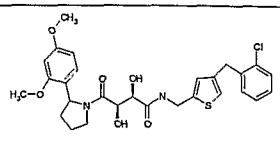
Compound **55** was prepared using procedures similar to those described in Example 14, Parts D & E.

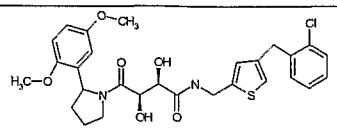
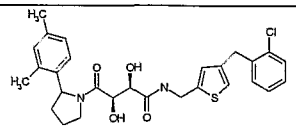
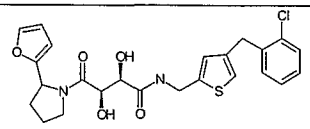
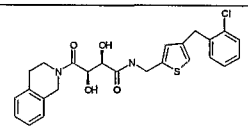
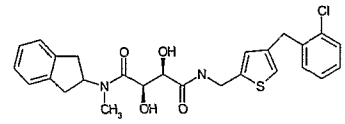
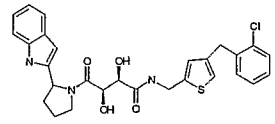
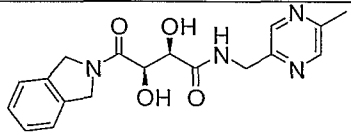
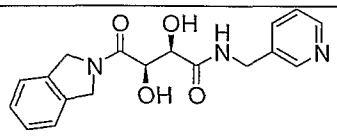
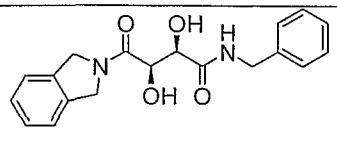
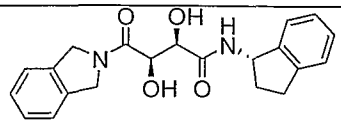
Data for **54**: ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.51-7.25 (m, 6H), 6.22 (s, 1H), 5.75-5.67 (m, 2H), 5.36 (s, 2H), 5.28-4.61 (m, 4H), 3.69-3.40 (m, 2H), 2.74 (s, 1H), 2.24 (s, 3H), 2.18 (s, 3H). Data for **55**: ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.54-7.26 (m, 6H), 6.24 (s, 1H), 5.22-5.02 (m, 2H), 4.94-4.82 (m, 3H) 4.42 (s, 1H), 3.72-3.50 (m, 2H), 2.92-2.76 (m, 2H) MS (EI) m/z M+H Obsd 377.1

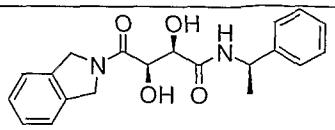
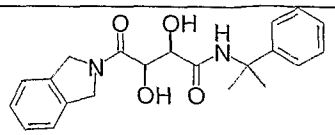
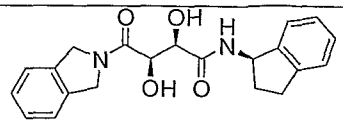
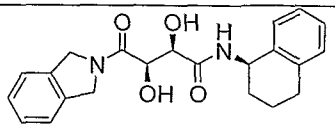
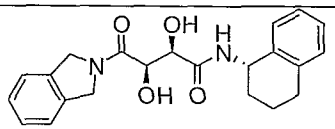
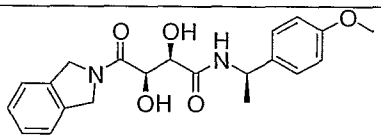
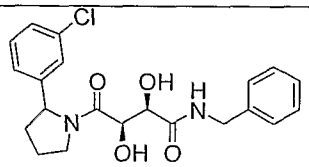
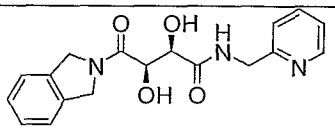
Compound #	Structure	Exact mass	MS m/z (M+H)
56		362.1	363.1
57		403.2	404.1
58		450.2	451.1
59		477.2	478.2

60		483.2	484.2
61		407.1	408.1
62		332.1	333.1
63		346.15	347.2
64		432.2	433.2
65		408.2	409.2
66		444.2	445.1
67		416.2	417.1
68		430.2	431.1

69		316.1	317.1
70		288.1	289.1
71		499.1	500.1
72		421.2	422.1
73		439.1	440.2
74		377.1	378.1
75		369.1	370.1
76		369.1	370.1
77		376.2	377.10
78		363.1	364.1

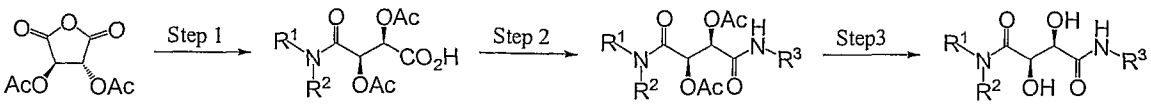
79		403.2	404.2
80		388.2	389.2
81		444.2	445.1
82		458.2	459.1
83		472.2	473.2
84		427.2	428.2
85		452.1	453.1
86		528.2	529.2
87		558.2	559.2

88		558.2	559.2
89		526.2	527.2
90		488.1	489.1
91		484.1	485.0
92		498.1	499.1
93		537.2	538.2
94		356.2	357.2
95		341.1	342.1
96		340.1	341.1
97		366.16	367.1

98		354.16	355.1
99		368.17	369.1
100		366.16	367.1
101		380.17	381.2
102		380.2	381.2
103		384.2	385.1
104		402.1	403.1
105		341.1	342.1

Example 2D:

Method A



48 106 107 108

Method A, Step 1:

Compound **106** (R1 = R2 = CH_2Ph) was prepared from **48** following the procedure described in Example 4A, Part C.

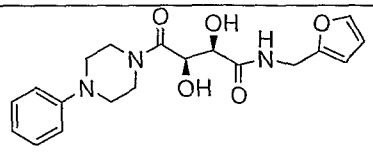
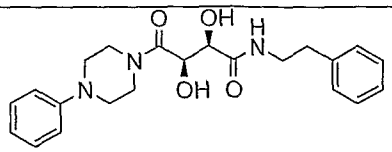
Method A, Step 2:

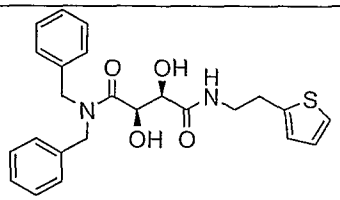
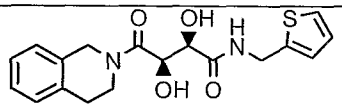
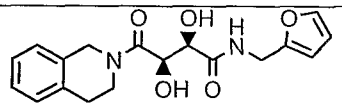
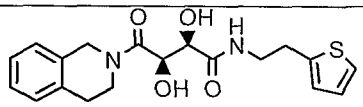
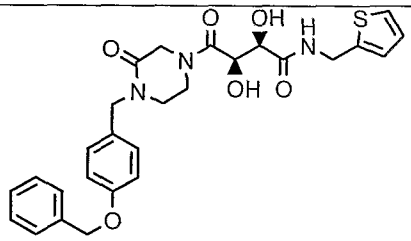
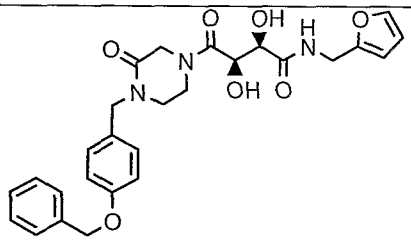
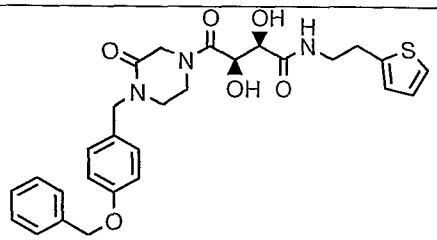
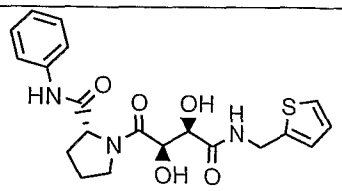
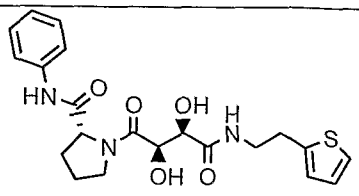
To a THF/MeCN (1:1, 0.5 mL) solution of polystyrene EDC resin (57 mg, 3 eq) in a 6 mL fritted cartridge was added a THF/MeCN (1:1) solution of **106** (0.028 mmol), a THF solution of HOBT (0.3 mL, 1.5 eq) and a 1M THF/MeCN (1:1) solution of 2-furanethylamine (0.056 mL, 2 eq). The cartridge was capped and let shake at 25°C for 20 h. Polystryrene isocyanate resin (57 mg, 3 eq) and polystyrene trisamine (39 mg, 6 eq) was added followed by 0.5 mL of THF and the mixture was shaken for 6 h. The suspension was filtered and the filtrate was concentrated to afford **107** (R1 = R2 = CH_2Ph, R3 = $CH_2CH_2(C_4H_4O)$.

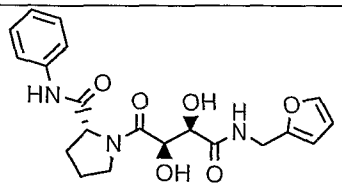
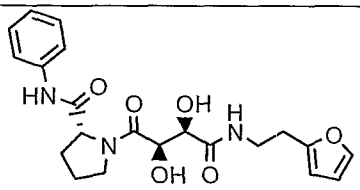
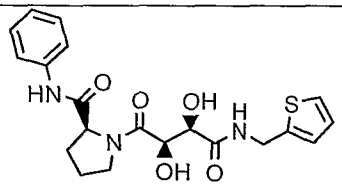
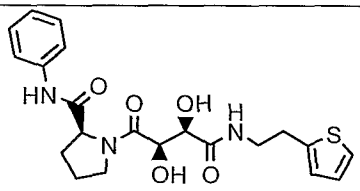
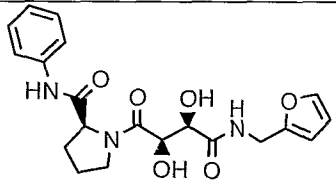
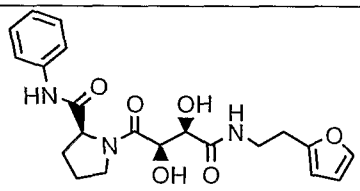
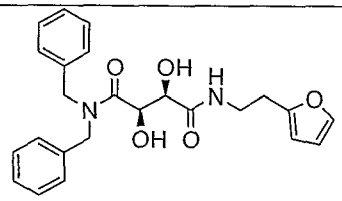
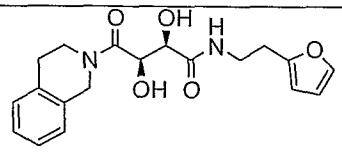
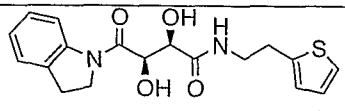
Method A, Step 3:

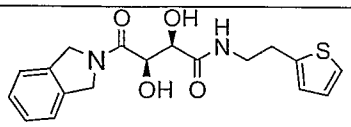
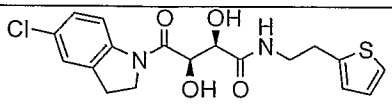
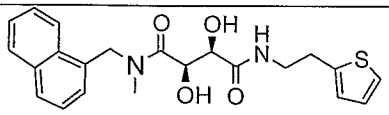
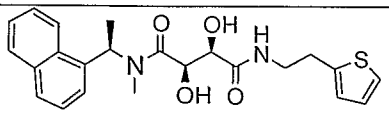
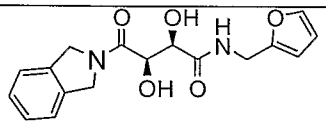
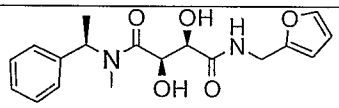
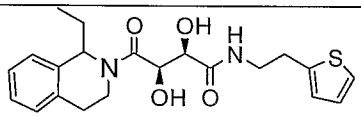
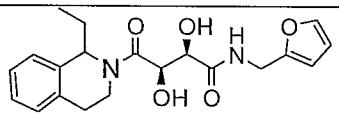
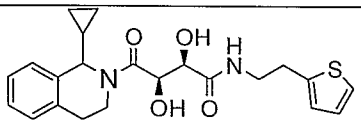
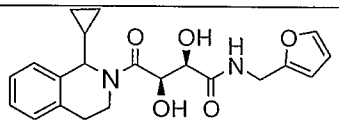
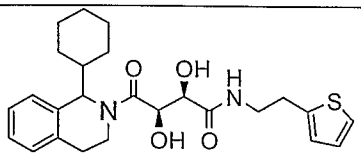
Compound **107** was treated with a 2N solution of NH_3 in MeOH (3 mL) for 1.5 h. The solvent was then removed in vacuo to provide **108** (R1 = R2 = CH_2Ph, R3 = $CH_2CH_2(C_4H_4O)$.

Example 2D Table A

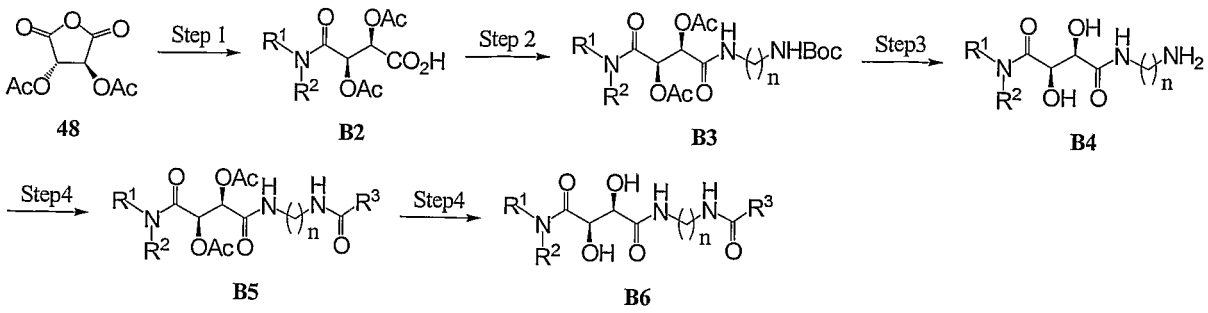
Compound #	Structure	Exact mass	MS m/e (M+H)
109		373.2	374.2
110		397.2	398.2

111		438.2	439.1
112		360.1	361.1
113		344.1	345.1
114		374.1	375.1
115		523.2	524.1
116		507.2	508.1
117		537.2	538.1
118A		417.1	418.1
118B		431.2	432.2

119		401.2	402.1
120		415.2	416.1
121		417.1	418.1
122		431.2	432.2
123		401.2	402.1
124		415.2	416.1
108		422.2	423.1
125		358.2	359.1
38		360.1	361.2

39		360.1	361.2
126		394.1	395.2
127		412.2	413.2
128		426.2	427.2
129		330.1	331.2
130		346.2	347.2
131		402.2	403.1
132		372.2	373.1
133		414.2	415.1
134		384.2	385.1
135		456.2	457.1

Method B



Method B, Step 1:

Compound **B2** (R^1 = CH_2Ph, R^2 = CH_3) was prepared from **48** following the procedure described in Example 4A Part C.

Method B, Step 2:

To a DMF (40 mL) solution of **B2** (2.0 g, 5.93 mmol), HOBT (880 mg, 6.52 mmol), and N-Boc-1,3-propylenediamine (1.14 g, 6.52 mmol) was added EDCI (1.48 g, 7.61 mmol) at 25 °C under N_2. After stirring for 20 h, 1N HCl was added, the products were extracted with ethyl acetate (3X), combined, then washed with sat. $NaHCO_3$, water (3x), and dried over $MgSO_4$. The products were then filtered and concentrated in vacuo to give **B3** (R^1 = CH_2Ph, R^2 = CH_3, n = 3).

Method B, Step 3:

To a MeCN (30 mL) solution of **B3** (1.18 g, 2.4 mmol) at 25°C was added 20 mL of a 4N solution of HCl in dioxane. The solution was capped and stirred at 25 °C for 2.5 h. The solvent was then removed in vacuo. The product was then dissolved in 45 mL of THF/MeCN/DMF (4:4:1) and polystyrene NEt_2 resin (4.5 g, 14.4 mmol) added. After stirring for 1.5 h, the solution was filtered off and the resin washed with THF:MeCN (1:1). The filtrates were then diluted to 120 mL with additional THF/MeCN (1:1) and **B4** (R^1 = CH_2Ph, R^2 = CH_3, n = 3) was used in the preparation of the following library:

Method B, Step 4:

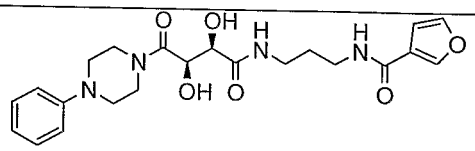
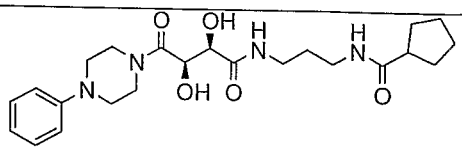
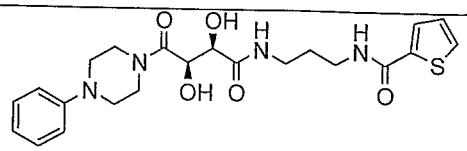
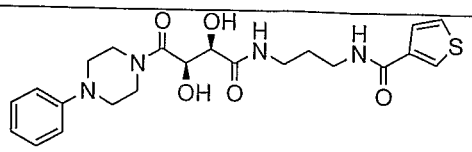
Polystyrene EDC resin (30mg, 0.045 mmol) was added to 96-wells of a deep well polypropylene microtiter plate followed by a MeCN/THF/DMF (6:6:1) stock solution (1 mL) of **B4** (0.015 mmol) and HOBT (0.0225 mmol). Then 1M stock solutions of each of the individual acids (R^1-96COOH) (0.023 mL, 0.021

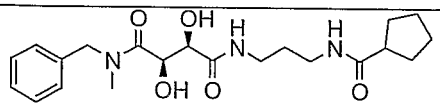
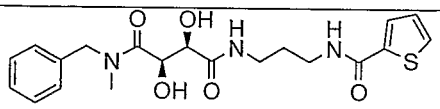
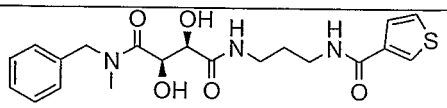
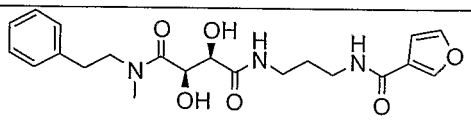
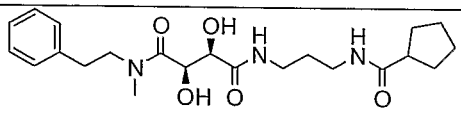
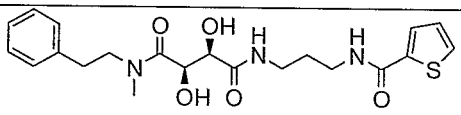
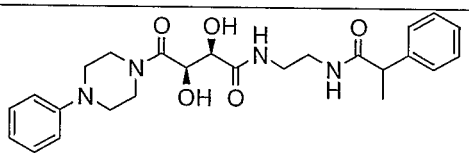
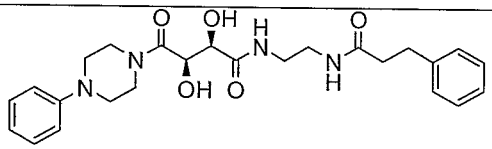
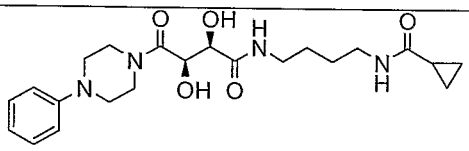
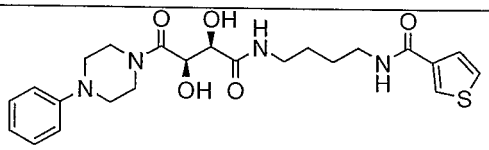
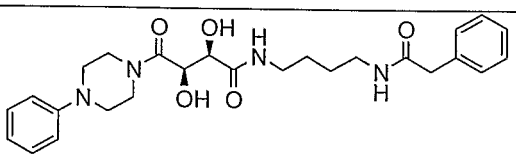
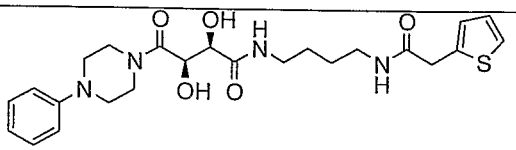
mmol) were added to the wells, which was then sealed and shaken at 25 °C for 20h. The solutions were filtered through a polypropylene frit into a 2nd microtiter plate containing polystyrene isocyanate resin (3 equivalents, 0.045 mmol) and polystyrene trisamine resin (6 equivalents, 0.09 mmol). After the top plate was washed with MeCN (0.5 mL), the plate was removed, the bottom microtiter plate sealed and shaken at 25 °C for 16h. Then the solutions were filtered through a polypropylene frit into a 96-well collection plate. The wells of the top plate were then washed with MeCN (0.5 mL), and the plate removed. Then the resultant solutions in the collection plate were transferred into vials and the solvents removed in vacuo via a SpeedVac to provide amides **B5**.

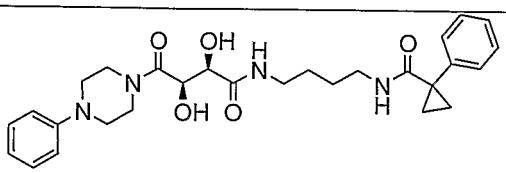
Method B, Step 5:

Compounds **B6** were prepared from **B5** following the procedure described in Method A, Step 3 (see above).

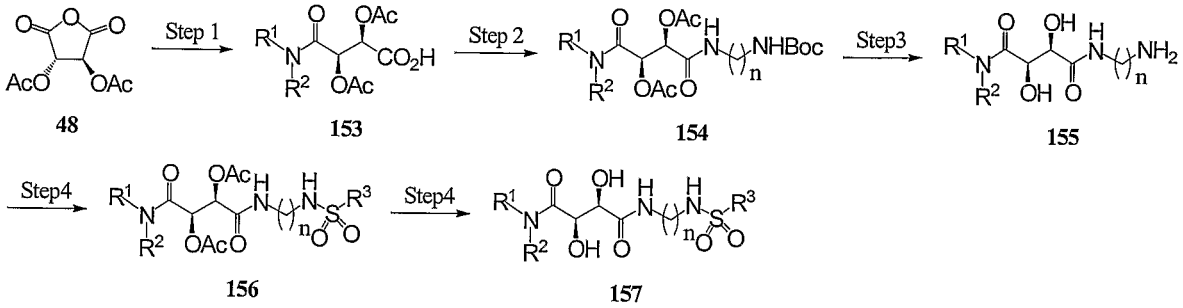
Example 2D Table B

Compound #	Structure	Exact mass	MS m/e (M+H)
136		444.2	445.2
137		446.3	447.3
138		460.2	461.3
139		460.2	461.3

140		405.2	406.2
141		419.2	420.2
142		419.2	420.2
143		417.2	418.2
144		419.2	420.2
145		433.2	434.2
146		468.2	469.3
147		468.2	469.3
148		432.2	433.2
149		474.2	475.3
150		482.3	483.3
151		488.2	489.3

152		508.3	509.3

Method C



Method C, Step 1:

Compound **153** (R^1R^2N = 4-phenylpiperazine) was prepared from **48** following the procedure described in Method B, Step 1 (see above).

Method C, Step 2:

Compound **154** (R^1R^2N = 4-phenylpiperazine, n = 3) was prepared from **153** following the procedure described in Method B, Step 2 (see above).

Method C, Step 3:

Compound **155** (R^1R^2N = 4-phenylpiperazine, n = 3) was prepared from **154** following the procedure described in Method B, Step 3 (see above) and was used in the preparation of the following library:

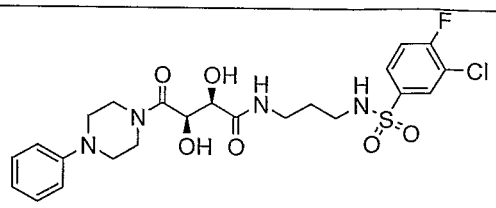
Method C, Step 4:

Polystyrene DIEA resin (30mg, 0.045 mmol) was added to 72-wells of a deep well polypropylene microtiter plate followed by a MeCN/THF/DMF (6:6:1) stock solution (1 mL) of **155** (0.015 mmol). Then 1M stock solutions of each of the individual sulfonyl chlorides (R^1-$72SO_2Cl$) (0.023 mL, 0.021 mmol) were added to the wells, which was then sealed and shaken at 25 °C for 20h. The solutions were filtered through a polypropylene frit into a 2nd microtiter plate containing polystyrene isocyanate resin (3 equivalents, 0.045 mmol) and polystyrene trisamine resin (6 equivalents, 0.09 mmol). After the top plate was washed with MeCN (0.5 mL), the plate was removed, the bottom microtiter plate sealed and shaken at 25 °C for 16h. Then the solutions were filtered through a polypropylene frit into a 96-well collection plate. The wells of the top plate were then washed with MeCN (0.5 mL), and the plate removed. Then the resultant solutions in the collection plate were transferred into vials and the solvents removed in vacuo via a SpeedVac to provide sulfonamides **156**.

Method C, Step 5:

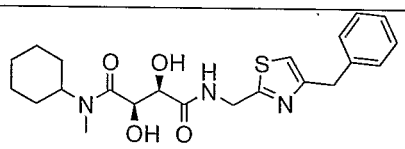
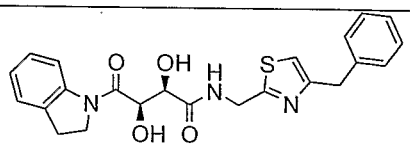
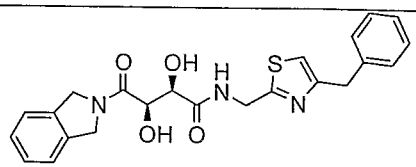
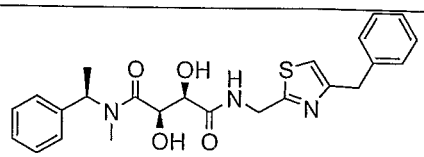
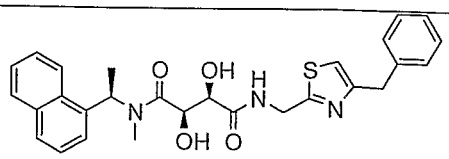
Compounds **157** were prepared from **156** following the procedure described in Method A, Step 3 (see above).

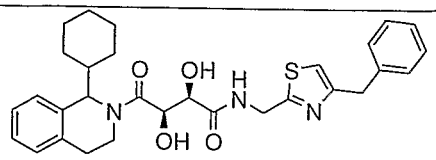
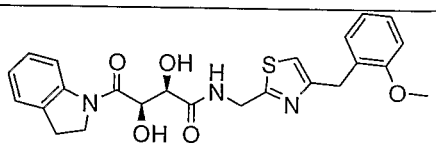
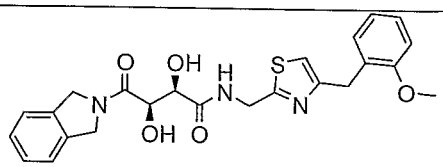
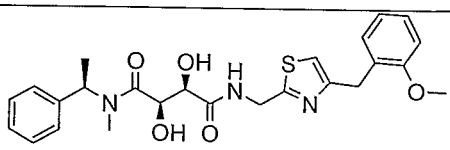
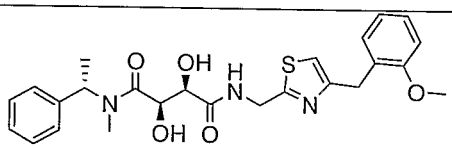
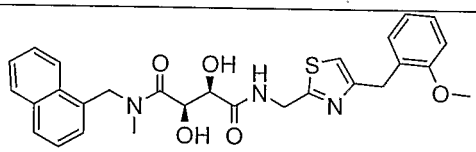
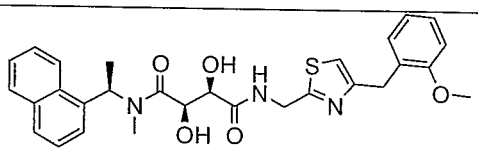
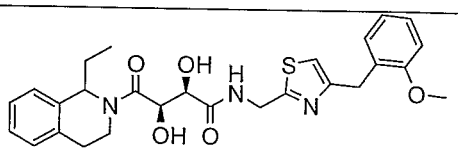
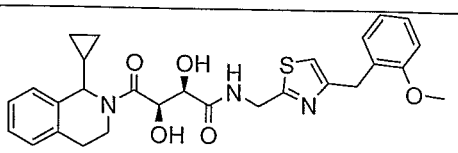
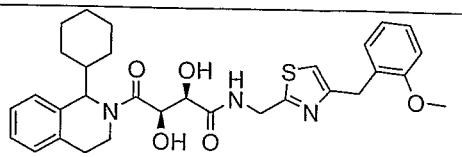
Example 2D Table C

Compound #	Structure	Exact mass	MS m/e (M+H)
157		542.2	543.3

These compounds were prepared using Method A:

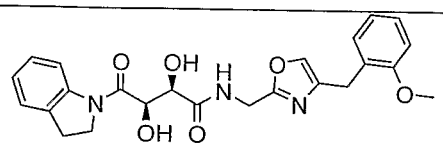
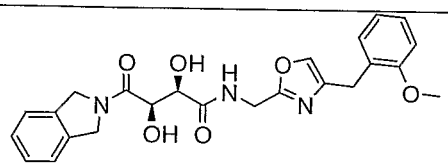
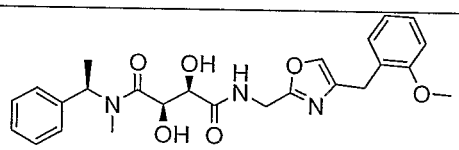
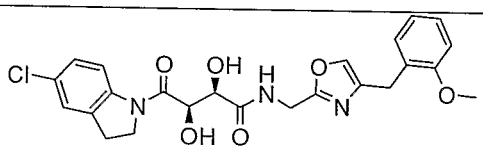
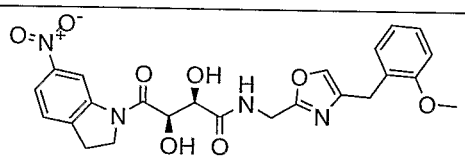
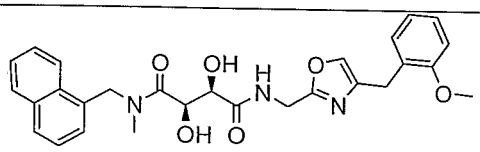
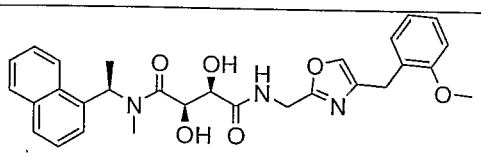
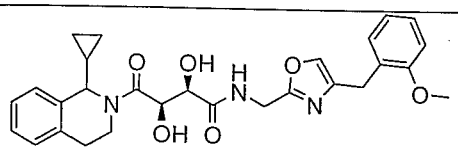
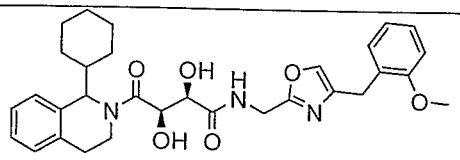
Example 2D Table D

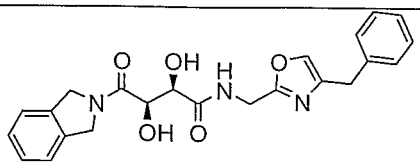
Compound #	Structure	Exact mass	MS m/e (M+H)
158		431.2	432.2
159		437.1	438.2
160		437.1	438.2
161		453.2	454.3
162		503.2	504.3

163		533.2	534.2
164		467.2	468.3
165		467.2	468.3
166		483.2	484.3
167		483.2	484.3
168		519.2	520.3
169		533.2	534.3
170		509.2	510.3
171		521.2	522.3
172		563.2	564.3

These compounds were prepared using Method A:

Example 2D Table E

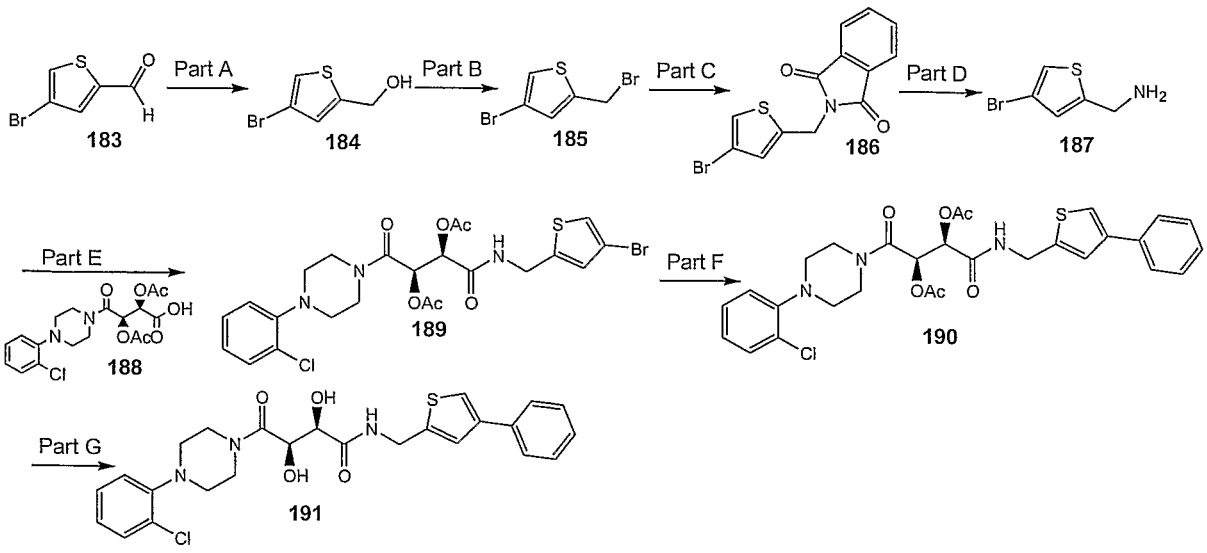
Compound #	Structure	Exact mass	MS m/e (M+H)
173		451.2	452.3
174		451.2	452.3
175		467.2	468.3
176		485.1	486.3
177		496.2	497.3
178		503.2	504.3
179		517.2	518.3
180		505.2	506.3
181		547.3	548.3

182		421.2	422.2

Example 3: Heteroaryl biaryl compounds

A compound precursor may be prepared such that the synthesis of direct analogs is facilitated. Examples of schemes for biaryl synthesis are listed below. Aryl halides and 'pseudo-halides' (i.e. triflates) are known to react with boronic acids under a variety of established conditions (*Top. Curr. Chem.* **2002,** *219*, 12-49). A variety of bases for this reaction are known in the literature, including sodium carbonate, potassium carbonate, cesium carbonate, potassium t-butoxide, sodium t-butoxide, TEA, DIEA, potassium fluoride, and potassium phosphate. For most applications potassium phosphate was preferred and gave acceptable yields and chemoselectivity. A number of solvents have also been used in the literature for Suzuki reactions, including THF, dioxane, NMP, DMF, DME, DMA, toluene, and water. In general we have found that THF or dioxane are preferred solvents. Solvents may also be mixed in various proportions to enhance reactivity and/or chemoselectivity. Palladium sources for this reaction are numerous as well, including $Pd(TPP)_4$, $Pd(OAc)_2$, $PdCl_2(TPP)_2$, $PdCl_2(dppf)$, $Pd_2(dba)_3$. In general $PdCl_2(dppf)$ was found to be a preferred palladium source.

Example 3A:



Part A:

To an ice cold methanol (100 mL) solution of 4-bromo-thiophene-2-carbaldehyde **(183)** (90%, 11.1 g, 58.1 mmol, 1.00 equiv) was added sodium borohydride in portions (2.20 g, 58.1 mmol, 1.00 equiv) over ca. 10 minutes. The cooling bath was removed and the reaction solution was aged 30 min. The reaction was quenched at rt by the addition of acetone (until evolution of gas ceased), concentrated, and partitioned between ethyl acetate and 0.1 N HCl. The organic phase was washed with water, brine, dried (sodium sulfate), filtered, and then concentrated to give **184** as an orange oil (10.5 g, 95%) that was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 1H), 6.93 (s, 1H), 4.81 (s, 2H).

Part B:

To **184** (4.38 g, 22.7 mmol) in toluene (25 mL) was added phosphorous tribromide (2.36 mL, 25 mmol). The reaction mixture was heated in an oil bath at 90 °C for 15 minutes. After cooling to room temperature the reaction mixture was poured over ice and extracted with ethyl acetate. The combined organic layer was washed with water (2x), saturated sodium bicarbonate solution (1x) and saturated sodium chloride solution, dried over magnesium sulfate and concentrated to afford **185** as a light brown oil (5.51 g, 95%). The material was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (s, 1H), 7.03 (s, 1H), 4.66 (s, 2H).

Part C:

To **185** (5.51 g, 21.5 mmol) in DMF (20 mL) was added phthalimide (3.80 g, 25.8 mmol) and cesium carbonate (7.72 g, 23.7 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was filtered and the filtrate was concentrated. The residue was dissolved in ethyl acetate and water. The organic layer was separated, washed with saturated sodium chloride solution, dried over sodium sulfate and concentrated to afford a brown solid. Recrystallization from ~30 % ethyl acetate/hexanes afforded **186** as a peach solid (6.38 g, 2 crops, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (m, 2H), 7.72 (m, 2H), 7.11 (s, 1H), 7.07 (s, 1H), 4.97 (s, 2H). HPLC-MS t_R = 2.02 min ($UV_{254\ nm}$); mass calculated for formula $C_{13}H_8BrNO_2S$ 321.0, observed LCMS m/z 322.0 (M+H).

Part D:

A suspension of **186** (5.76 g, 17.8 mmol) and hydrazine hydrate (3.5 mL, 72 mmol) in ethanol (50 mL) was heated to reflux. The suspension cleared upon heating before a thick white precipitate formed. The reaction mixture was heated for 1 hour and cooled. The white precipitate was broken up by the addition of ethanol (50 mL) and sonication of the mixture. The precipitate was removed by filtration and the solids were thoroughly washed with ethanol and ethyl acetate. The filtrate was concentrated in vacuo. The residue was dissolved in ethyl acetate and water. The layers were separated. The organic layer was washed with saturated sodium chloride solution, dried over sodium sulfate and concentrated to afford **187** as an orange-brown oil (2.66 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (s, 1H), 6.84 (s, 1H), 4.04 (s, 2H). HPLC-MS t_R = 0.58 min ($UV_{254\ nm}$); Mass calculated for formula C_5H_6BrNS 190.9, observed LCMS m/z 192.0(M+H).

Part E:

Following the procedure described in Example 1 part A: To **188** (prepared as described in Example 4 Part C from (+)-diacetyl –L-tartaric anhydride (48) and 2-chlorophenylpiperazine) (916 mg, 2.22 mmol) in DMF (5 mL) was added **187** (502

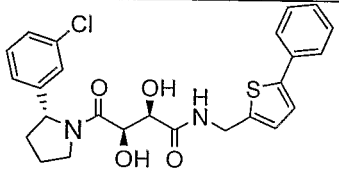
mg, 2.61 mmol), DIEA (850 µL, 4.88 mmol) and HATU (928 mg, 2.44 mmol). Purification by column chromatography (SiO_2, 20% to 50% EtOAc/DCM) afforded **189** as an off-white foam (652 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, 1H, J = 1.2, 7.6 Hz), 7.25 (dt, 1H, J = 1.2, 7.6 Hz), 7.14 (d, 1H, J = 1.2 Hz), 7.03 (m, 2H), 6.92 (d, 1H, J = 1.2 Hz), 6.74 (m, 1H, NH), 5.92 (d, 1H, J = 3.6 Hz), 5.70 (d, 1H, J = 4.0 Hz), 4.73 (dd, 1H, J = 6.4, 15.2 Hz), 4.50 (dd, 1H, J = 5.6, 15.6 Hz), 3.83 (m, 3H), 3.65 (m, 1H), 3.20 – 3.00 (m, 4H), 2.21 (s, 3H), 2.11 (s, 3H); Mass calculated for formula $C_{23}H_{25}BrClN_3O_6S$ 585.0, observed LCMS m/z 586.1 (M+H).

Part F:

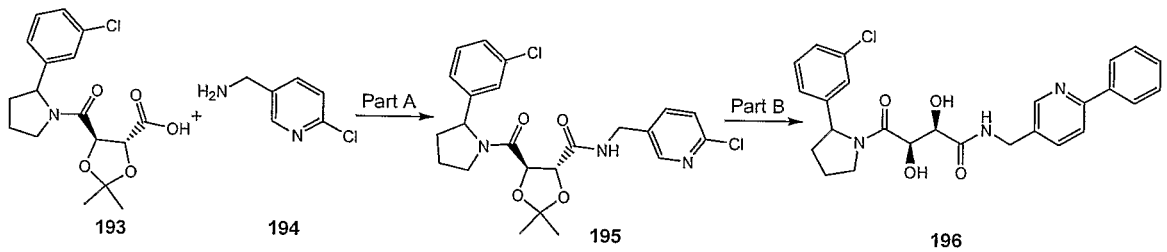
To **189** (59 mg, 0.1 mmol), phenyl boronic acid (13 mg, 0.11 mmol), potassium phosphate (42 mg, 0.2 mmol), and $PdCl_2$(dppf) (4 mg, 0.005 mmol) was added dioxane (2 mL). The reaction mixture was flushed with argon and heated to 80 °C overnight. The reaction mixture was cooled, poured into water and extracted with EtOAc. The combined organics were washed with brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 20% EtOAc/DCM) afforded **190** as an off-white foam (36 mg, 58%, 94% purity). HPLC-MS t_R = 5.61 min ($UV_{254\ nm}$, 10 min.); mass calculated for formula $C_{29}H_{30}ClN_3O_6S$ 583.2, observed LCMS m/z 584.2 (M+H).

Part G:

To **190** (36 mg, 0.062 mmol) in methanol was added 0.5 M sodium methoxide in methanol (6 µL, 0.003 mmol). The reaction mixture was stirred for 1.5 hours at room temperature, quenched with 0.1 N HCl and concentrated. Purification by reverse-phase prep-LC afforded **191** as a white solid (3.2 mg, 10%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, 2H, J = 1.2, 8.4 Hz), 7.40 to 7.20 (m, 9H), 7.09 (m, 1H, NH), 4.91 (d, 1H, J = 2.4 Hz), 4.70 (m, 2H), 4.33 (d, 1H, J = 2.0 Hz), 4.00 (m, 2H), 3.85 (m, 2H), 3.20 (m, 4H); HPLC-MS t_R = 1.94 min ($UV_{254\ nm}$); Mass calculated for formula $C_{25}H_{26}ClN_3O_4S$ 499.1, observed LCMS m/z 500.2 (M+H).

Compound #	Structure	Exact mass	MS m/e (M+H)
192		484.1	485.0

Example 3B: 3-Pyridyl-Biaryl



193 194 195 196

Part A:

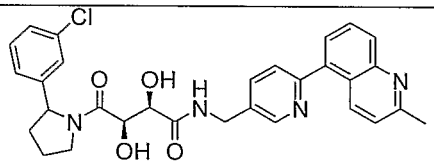
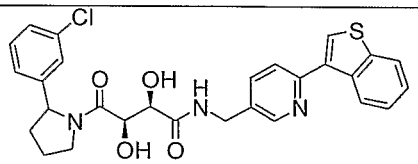
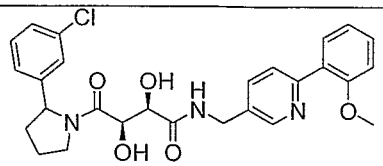
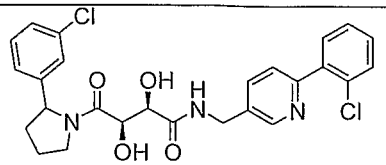
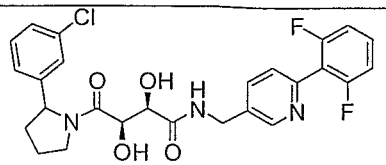
To **193** (prepared as described in Example 1) (1.5 g, 4.24 mmol) in DMF (10 mL) was added **194** (0.725 g, 5.09 mmol) and HATU (1.94 g, 5.09 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 80% ethyl acetate/hexanes) afforded **195** as a colorless oil (1.73 g, 86%). HPLC-MS t_R = 1.92 and 1.97 min ($UV_{254\ nm}$); Mass calculated for formula $C_{23}H_{25}Cl_2N_3O_4$ 477.1, observed LCMS m/z 478.1 (M+H).

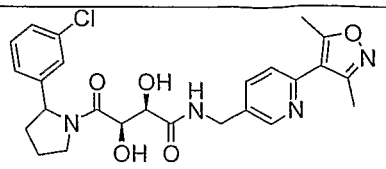
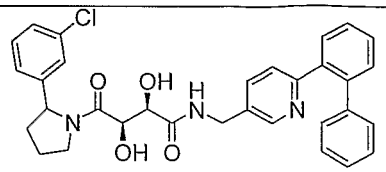
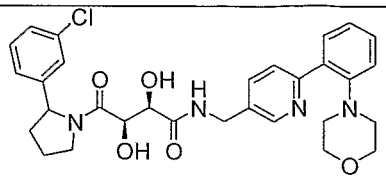
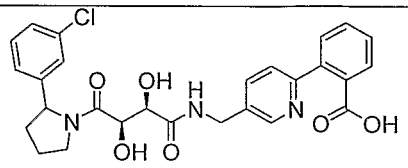
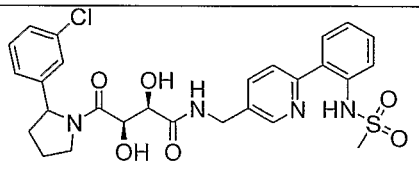
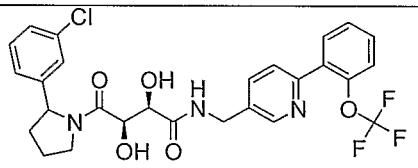
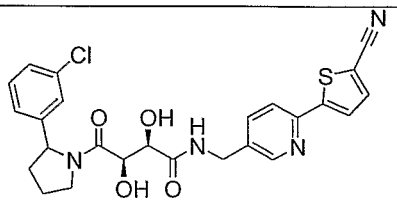
Part B:

Step1: To phenyl boronic acid (10 mg, 0.084 mmol), potassium phosphate (36 mg, 0.168 mmol) and $PdCl_2$(dppf) (3.1 mg, 10 mol%) under argon in a 4-mL vial was added **195** (20 mg, 0.042 mmol) in dioxane (0.5 mL). The

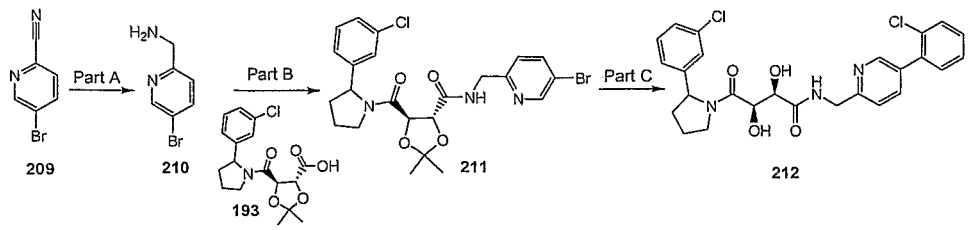
reaction mixture was heated at 100 °C for 16 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and filtered through celite. The filtrate was concentrated. HPLC-MS t_R = 2.01 min ($UV_{254\ nm}$); Mass calculated for formula $C_{29}H_{30}ClN_3O_4$ 519.2, observed LCMS m/z 520.2 (M+H).

Step 2: The crude material from Step 1 was dissolved in 80:20 TFA:water (1 mL) at 0 °C and stirred at room temperature for 2 hours. The reaction mixture was quenched with 1:1 water:acetonitrile (2 mL) and concentrated. Purification by reverse phase prep-LC afforded **196** as a solid after lypholization. HPLC-MS t_R = 3.54 min ($UV_{254\ nm}$, 10 min); Mass calculated for formula $C_{26}H_{26}ClN_3O_4$ 479.2, observed LCMS m/z 480.2 (M+H).

Compound #	Structure	Exact mass	MS m/z (M+H)
197		544.2	454.2
198		535.1	536.2
199		509.2	510.1
200		513.1	514.2
201		515.1	516.2

202		498.2	499.2
203		555.2	556.2
204		564.2	565.2
205		523.2	524.2
206		572.2	573.2
207		563.1	564.2
208		510.0	511.1

Example 3C: 2-Pyridyl-Biaryl



Part A:

To 5-bromo-pyridine-2-carbonitrile **(209)** (1.0 g, 5.46 mmol) in tetrahydrofuran (10 mL) at –78 °C was added lithium aluminum hydride (1.0 M, 13.66 mL, 13.66 mmol). The reaction was stirred for 2 hours at –78 °C. The mixture was quenched at –78 °C with 10:1 THF:water. The mixture was warmed to room temperature, diluted with ethyl acetate and stirred with 1.0 N sodium hydroxide for 10 minutes. The reaction mixture was filtered through celite and the layers were separated. The organic layer was washed with 1.0 N sodium hydroxide and brine, dried over sodium sulfate and concentrated to afford **210** as an oil (600 mg). The material was used without further purification.

Part B:

To **193** (1.13 g, 3.2 mmol) in DMF (10 mL) was added **210** (0.600 g, 3.2 mmol) and HATU (1.34 g, 3.52 mmol). The reaction mixture was stirred for 5 hours at room temperature. The reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate and brine, dried over sodium sulfate and concentrated to afford **211** as an oil (380 mg). HPLC-MS t_R = 2.00 and 2.05 min ($UV_{254\ nm}$); Mass calculated for formula $C_{23}H_{25}BrClN_3O_4$ 521.1, observed LCMS m/z 522.1 (M+H).

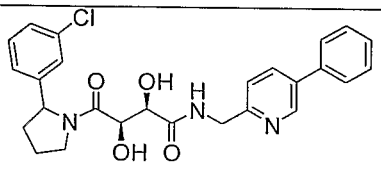
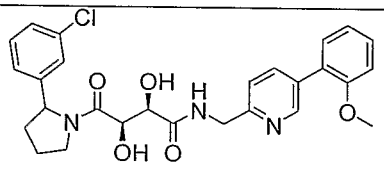
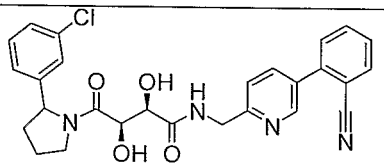
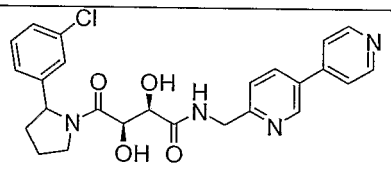
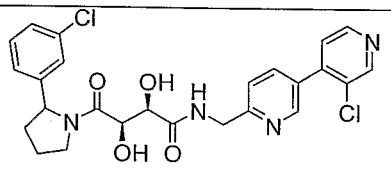
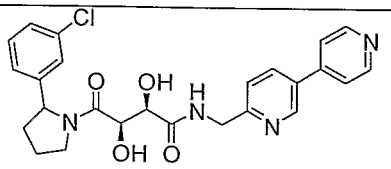
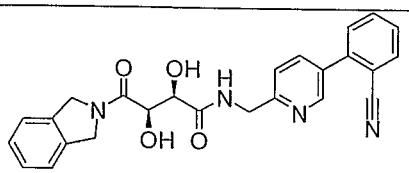
Part C:

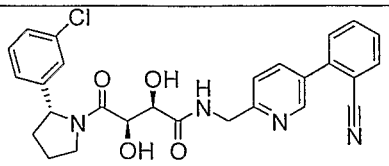
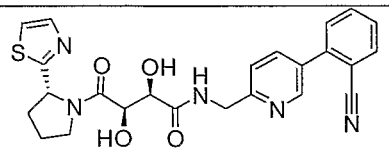
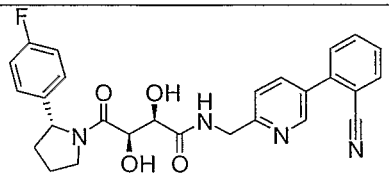
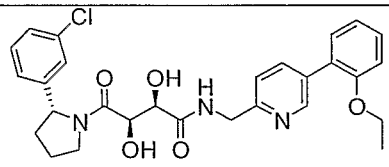
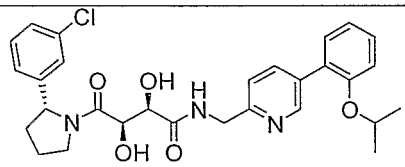
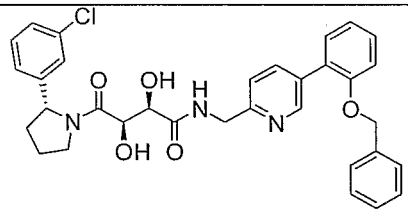
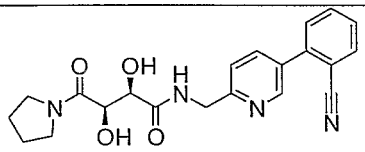
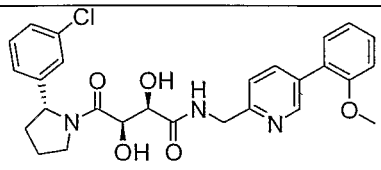
Step1: To 2-chlorophenyl boronic acid (24 mg, 0.152 mmol), potassium phosphate (65 mg, 0.306 mmol) and $PdCl_2$(dppf) (3.1 mg, 5 mol%) under argon in a 4-mL vial was added **211** (40 mg, 0.076 mmol) in dioxane (0.5 mL). The reaction mixture was heated at 100 °C for 16 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and filtered through celite. The filtrate was concentrated.

Step 2: The crude material from Step 1 was dissolved in 80:20 TFA:water (1 mL) at 0 °C and stirred at room temperature for 2 hours. The reaction mixture was quenched with 1:1 water:acetonitrile (2 mL) and concentrated. Purification by reverse phase prep-LC afforded **212** as a solid after

lypholization. HPLC-MS t_R = 4.10 and 4.13 min ($UV_{254\ nm}$, 10 min); Mass calculated for formula $C_{26}H_{25}Cl_2N_3O_4$ 513.2, observed LCMS m/z 514.2 (M+H).

The following compounds were prepared using the above procedures.

Compond #	Structure	Exact mass	MS m/z (M+H)
213		479.2	480.1
214		509.2	510.1
215		504.2	505.1
216		480.2	481.1
217		514.1	515.0
218		481.2	482.2
219		442.2	443.2

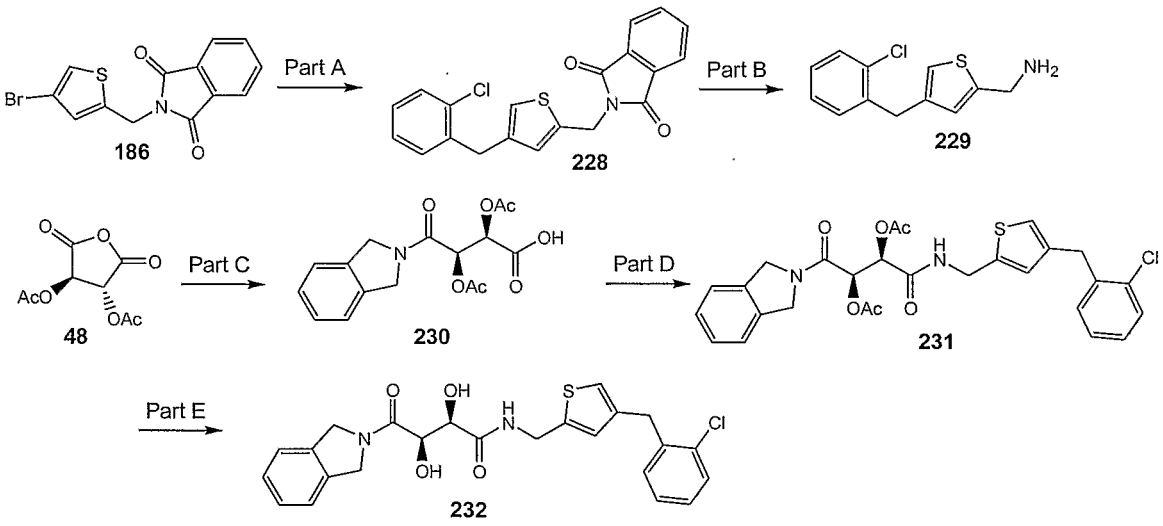
220		504.2	505.1
221		477.2	478.1
222		488.2	489.1
223		523.2	524.2
224		537.2	538.2
225		585.2	586.2
226		394.2	395.2
227		509.2	510.1

Example 4: Thiophene-benzyl compounds

Pd-mediated Negishi-type couplings were an efficient way to generate a set of relevant compounds for this series where Ar was a phenyl ring. While a range

of palladium sources are known we found that $Pd(P^tBu_3)_2$ was preferred. The reaction can be run in a variety of solvent systems, including dioxane, THF, or DMA. A preferred method utilized the solvent from the zinc reagent, which was typically available as a THF stock solution. Removal of the t-BOC group can be completed using a range of acidic conditions including TFA/water, HCl in methanol, and HCl in dioxane; all of which proceeded equally well with most reaction substrates. The reactions are typically concentrated and freeze-dried to give HCl or TFA salts. The Negishi reactions proceed comparably, and in many cases better, when the amine was protected by a phthalimide. The phthalimide protecting group could be removed by heating in ethanol containing hydrazine hydrate.

Example 4A:



Part A:

To **186** (3.47 g, 10.8 mmol) and bis-(tri-*tert*-butyl-phosphine) palladium (0.28 g, 0.54 mmol) in a flask under argon was added 2-chlorobenzyl zinc chloride (0.5 M in THF, 54 mL, 27 mmol). The reaction was stirred at room temperature for 3 hours. The reaction mixture was diluted with EtOAc (200 mL) and washed with saturated ammonium chloride solution (100 mL), bicarbonate solution (100 mL) and brine (100 mL). The organic layer was dried over sodium sulfate and concentrated. Purification

by column chromatography (SiO_2, 20% EtOAc/Hex) afforded **228** as a white solid (3.59 g, 91%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, 2H, J = 3.2, 5.6 Hz), 7.71 (dd, 2H, J = 3.2, 5.6 Hz), 7.36 (m, 1H), 7.17 (m, 3H), 6.99 (d, 1H, J = 1.0 Hz), 6.78 (d, 1H, J = 1.0 Hz), 4.95 (s, 2H), 4.00 (s, 2H).

Part B:

To **228** (3.55 g, 9.72 mmol) suspended in ethanol (35 mL) was added hydrazine monohydrate (1.9 mL, 38.9 mmol). The reaction mixture was heated at reflux for 2 hours. After cooling the solids were removed by filtration and washed with ethanol (100 mL) and ethyl acetate (50 mL). The filtrate was concentrated and the residue was dissolved in ethyl acetate (150 mL) and water (100 mL). The organic layer was separated, washed with brine (100 ml), dried over sodium sulfate and concentrated to yield **229** as a yellow oil (2.54 g, 99%).

Part C:

To **48** (2.16 mg, 10.0 mmol) in DCM (10 mL) was added isoindoline (1.13 mL, 10.0 mmol). The reaction was stirred at room temperature for 2 hours. The solvent was removed in vacuo and the residue was partitioned between ethyl acetate and 1.0 N HCl. The organic layer was separated, washed with water and brine, dried over sodium sulfate and concentrated to afford **230** as a dark solid (3.35 g, 100%). ^1H NMR (400 MHz, DMSO-d_6) δ 13.63 (bs, 1H), 7.38 – 7.28 (m, 4H), 5.01 (d, 1H, J = 13.2 Hz), 4.93 (d, 1H, J = 14.0 Hz), 4.71 (d, 1H, J = 16.4 Hz), 4.56 (d, 1H, J = 15.6 Hz), 2.12 (s, 3H), 2.07 (s, 3H); HPLC-MS t_R = 1.10 min ($UV_{254\ nm}$); mass calculated for formula $C_{16}H_{17}NO_7$ 335.1, observed LCMS m/z 336.1 (M+H).

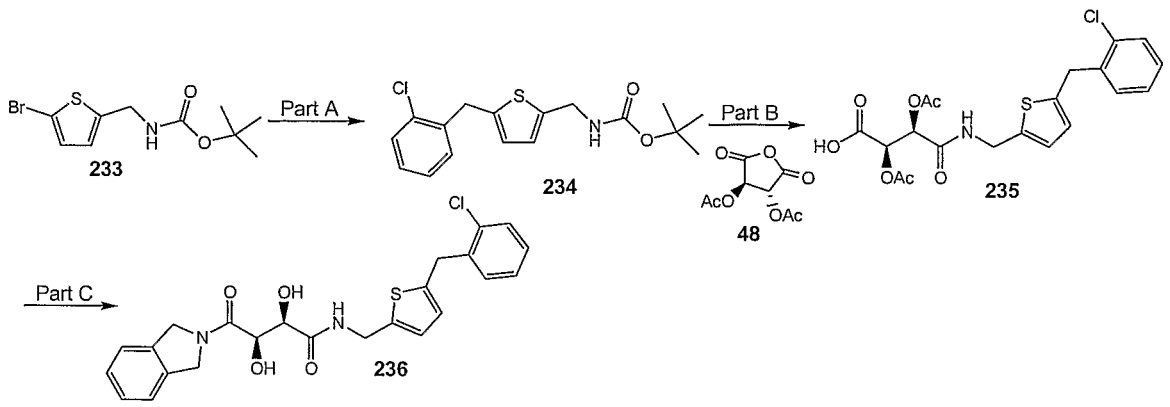
Part D:

To **230** (18 mg, 0.053 mmol) in NMP (2 mL) was added **229** (19 mg, 0.08 mmol), DIEA (26 µL, 0.148 mmol) and HATU (30 mg, 0.08 mmol). The reaction mixture was stirred overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layer was washed with 0.1 N NaOH, 0.1 N HCl and brine, dried over sodium sulfate and concentrated to afford **231**.

Part E:

To **231** (118 mg, 0.216 mmol) in methanol (3 mL) and DCM (3 mL) was added MP-carbonate resin (2.54 mmol/g, 85 mg). The reaction was stirred for 3 hours, filtered and concentrated to afford **232** as a white solid (94 mg, 92%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (t, 1H, J = 2.0 Hz) 7.79 (dd 1H, J = 0.8, 8.0 Hz), 7.64 (dt, 1H, J =1.6, 8.0 Hz), 7.47 (d, 1H, J = 7.6 Hz), 7.40 (dt, 1H, J = 0.8, 7.6 Hz), 7.35 – 7.27 (m, 4H), 6.97 (d, 1H, J = 1.6 Hz), 6.81 (d, 1H, J = 1.2 Hz), 5.67 (d, 1H, J = 6.4 Hz), 5.05 (d, 1H, J = 12.8 Hz), 4.97 (d, 1H, J = 8.0 Hz), 4.90 (d, 1H, J = 13.2 Hz), 4.75 (d, 1H, J = 13.2 Hz), 4.60 (m, 2H), 4.36 (m, 2H, J = 6.4, 15.2 Hz) 4.24 (dd, 1H, J = 3.2, 6.8 Hz); HPLC-MS t_R = 1.85 ($UV_{254\ nm}$); mass calculated for formula $C_{24}H_{23}ClN_2O_4S$ 470.1, observed LCMS m/z 471.1

Example 4B:



Part A:

To **233** (4.00 g, 13.7 mmol) and bis-(tri-*tert*-butyl-phosphine) palladium (0.28 g, 0.54 mmol) in a flask under argon was added 2-chlorobenzyl zinc chloride (0.5 M in THF, 69 mL, 34.5 mmol). The reaction was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc (200 mL) and washed with saturated ammonium chloride solution (100 mL), bicarbonate solution (100 mL) and brine (100 mL). The organic layer was dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 15% EtOAc/Hex) afforded **234** as a white solid (4.5 g, 95%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, 1H J =3.6 Hz), 7.25 – 7.18 (m, 4H), 6.74 (s, 1H), 6.64 (d, 1H, J = 3.6 Hz), 4.40 (d, 2H, J = 5.2 Hz), 4.22 (s, 2H).

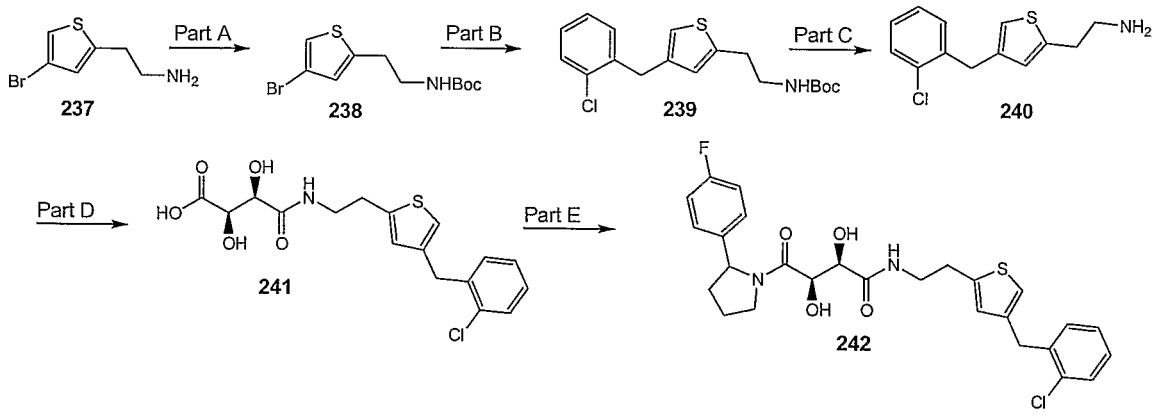
Part B:

To **234** (450 mg, 1.34 mmol) was added 4M HCl in dioxane (1.5 mL) and the reaction was stirred for 30 minutes. The dioxane was removed in vacuo. The residue was dissolved in THF (10 mL) and DIEA (500 µL, 2.68 mmol) and **48** (275 mg, 1.27 mmol) were added. The reaction was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate (60 mL) and washed with 1.0 N HCl. The organic layer was dried over sodium sulfate and concentrated to afford **235** as a yellow foam (505 mg, 90%).

Part C:

To **235** (40 mg, 0.09 mmol) in DMF (2 mL) were added DIEA (50 µL, 0.29 mmol), isoindoline (14 mg, 0.12 mmol), and HATU (45 mg, 0.12 mmol). The reaction mixture was stirred for 6 hours. The reaction mixture was diluted with ethyl acetate (30 mL) and washed with 0.1 N NaOH, 0.1 N HCl and brine. The organic layer was dried over sodium sulfate. The crude product was dissolved in methanol (3 mL) and potassium carbonate (100 mg) in water (1 mL) was added. After stirring for 30 minutes the reaction mixture was diluted with ethyl acetate (20 mL) and washed with brine. The organic layer was dried over sodium sulfate and concentrated. Purification by reverse phase prep-LC afforded **236** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (t, 1H, J = 6.4 Hz) 7.42 (dd, 1H, J = 1.6, 7.8 Hz), 7.37 – 7.23 (m, 7H), 6.74 (d, 1H, J = 3.6 Hz), 6.65 (d, 1H, J = 3.2 Hz), 5.66 (d, 1H, J = 5.6 Hz), 5.04 (d, 1H, J = 14.8 Hz), 4.97 (bs, 1H), 4.89 (d, 1H, J = 15.2 Hz), 4.75 (d, 1H, J = 16.4 Hz), 4.60 (m, 2H), 4.38 (dd, 1H, J = 6.4, 15.2 Hz), 4.23 (bs, 1H), 4.15 (s, 2H); HPLC-MS t_R = 4.92 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{24}H_{23}ClN_2O_4S$ 470.1, observed LCMS m/z 471.1

Example 4C: Thiophene-Benzyl



Compound **237** was prepared according to the procedure described by A. J. Hutchison et al (European Patent 0323807 A2, Dec. 7, 1989)

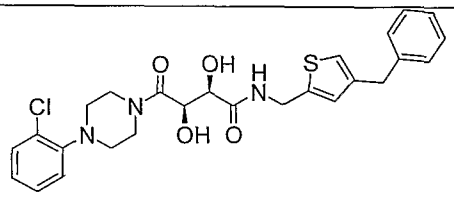
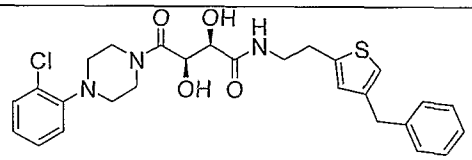
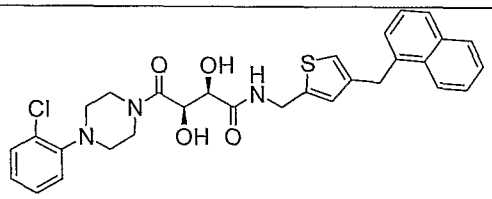
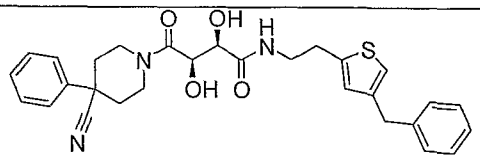
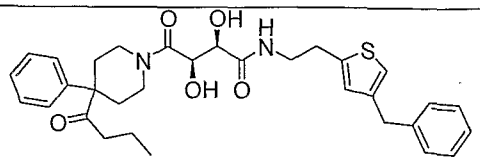
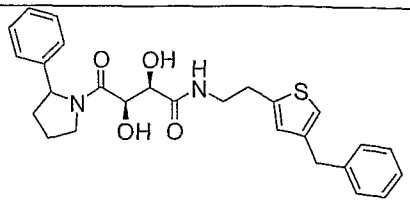
Parts A:

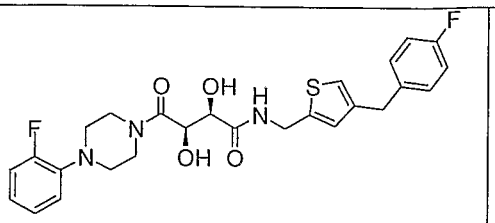
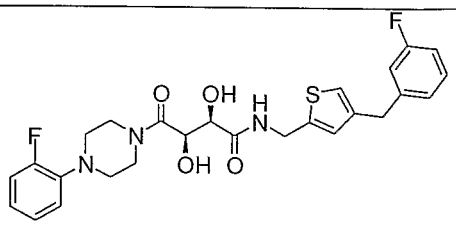
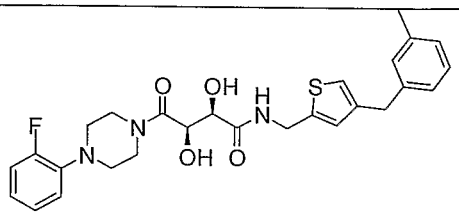
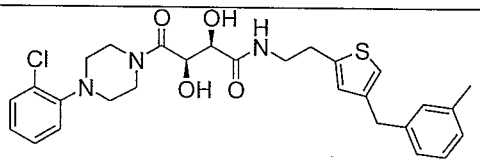
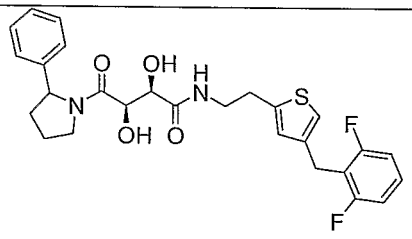
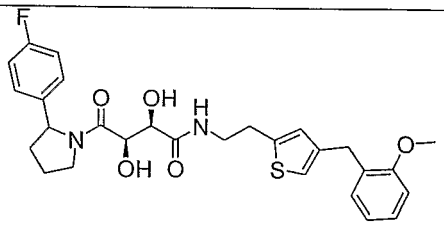
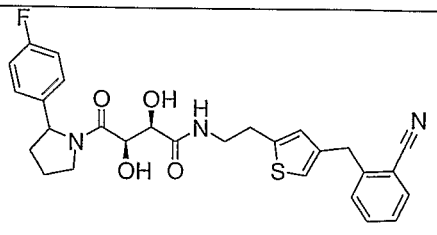
Compound **238** was prepared by procedures similar to those described in Example 5 Part A.

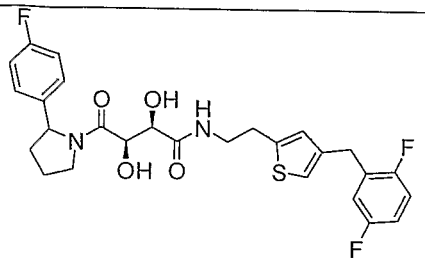
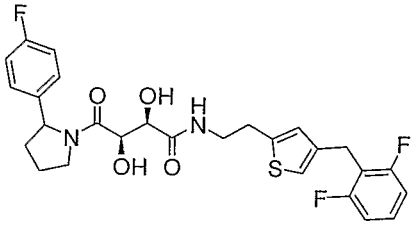
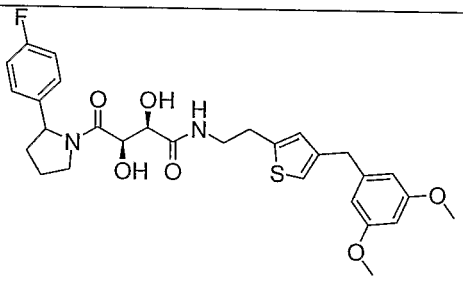
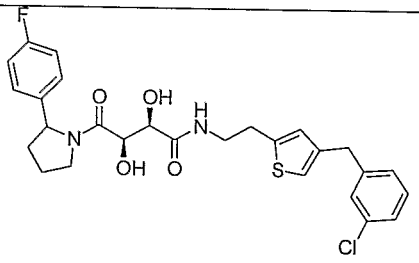
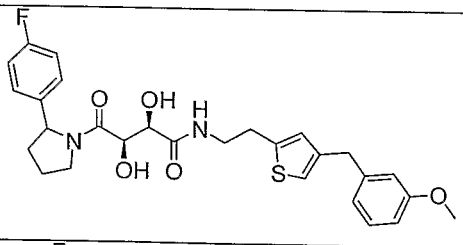
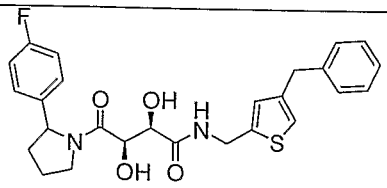
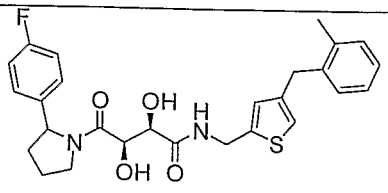
Parts B-E:

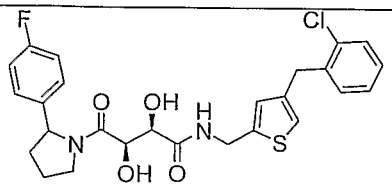
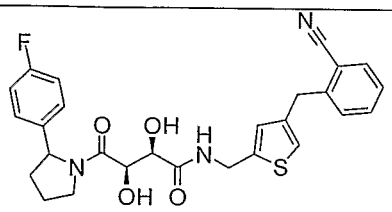
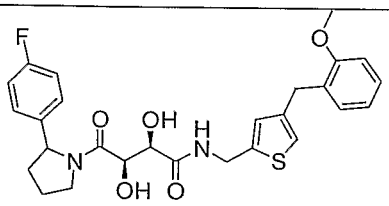
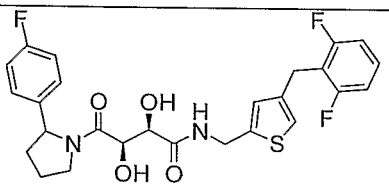
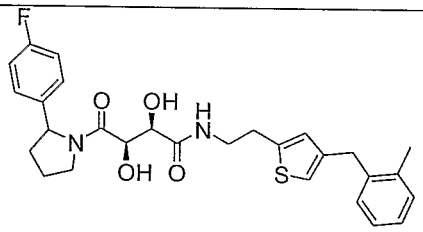
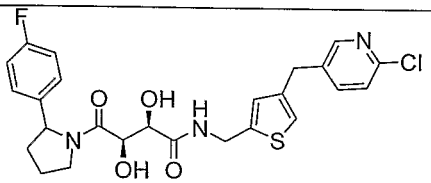
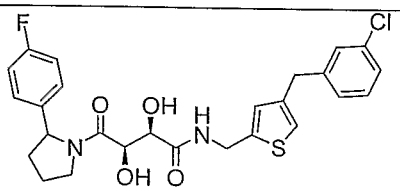
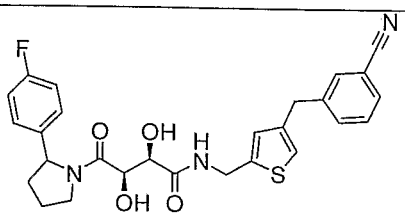
Compound **242** was prepared by procedures similar to those described in Example 4B Parts A to C. HPLC-MS t_R = 2.05 min ($UV_{254\ nm}$); mass calculated for formula $C_{27}H_{28}ClFN_2O_4S$ 530.1, observed LCMS m/z 531.1 (M+H).

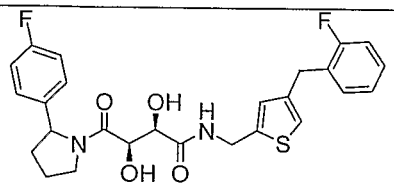
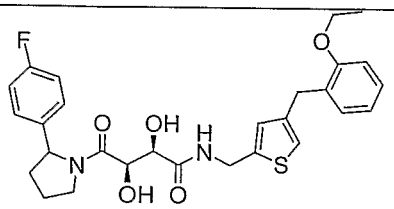
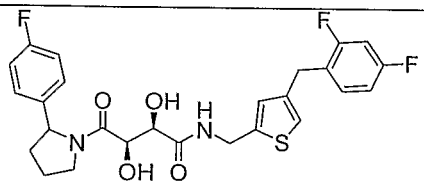
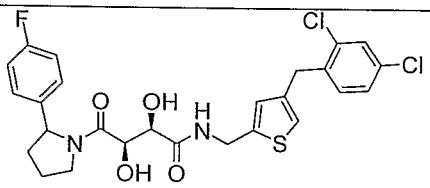
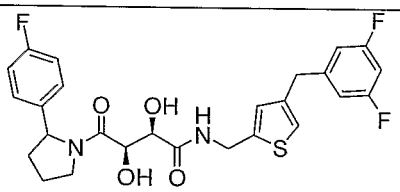
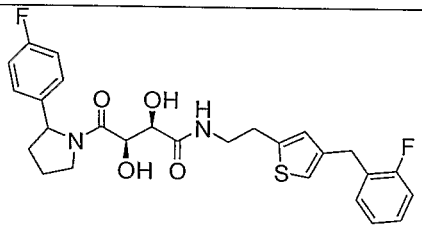
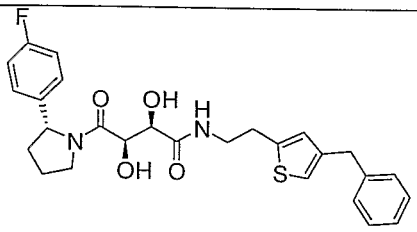
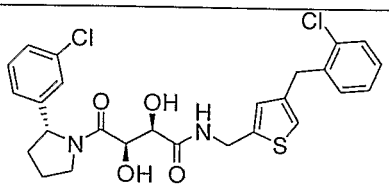
The following compounds were prepared by the procdures desribed in Example 4A – 4C.

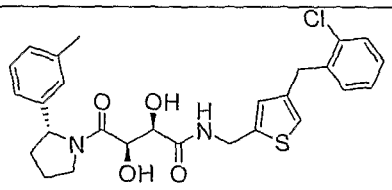
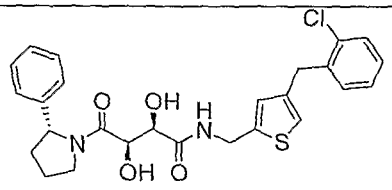
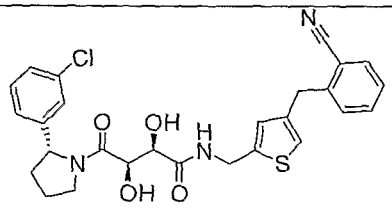
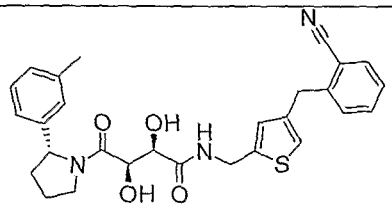
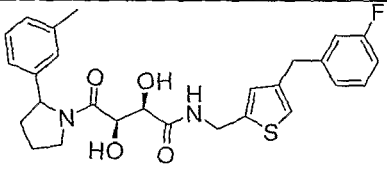
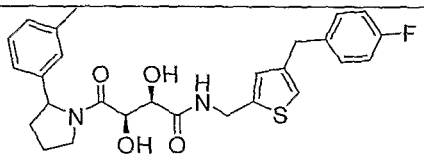
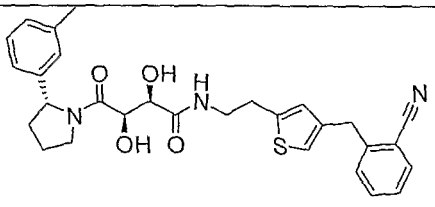
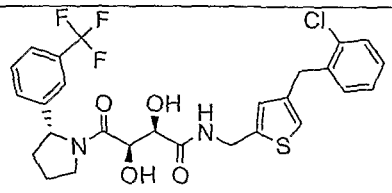
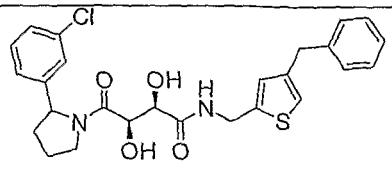
Compound #	Structure	Exact mass	MS m/z (M+H)
243		513.2	514.2
244		527.2	528.1
245		563.2	564.2
246		517.2	518.2
247		562.3	563.2
248		478.2	479.2

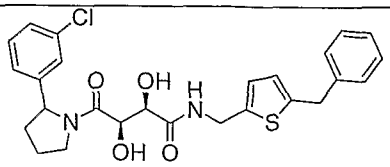
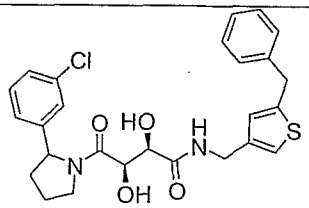
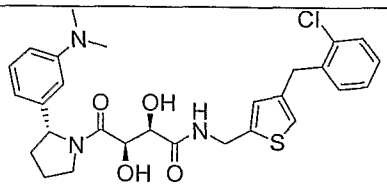
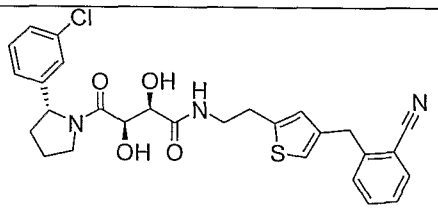
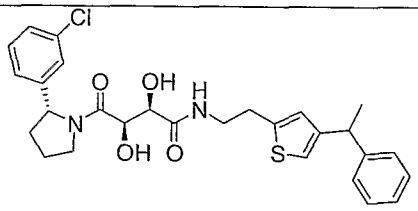
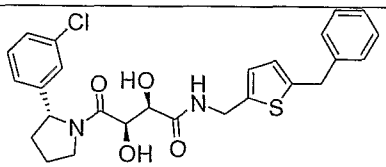
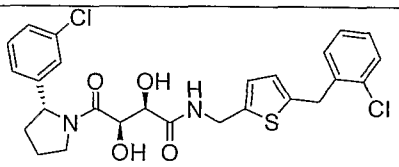
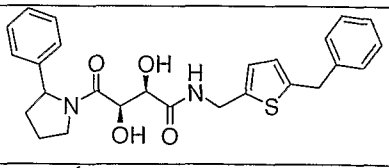
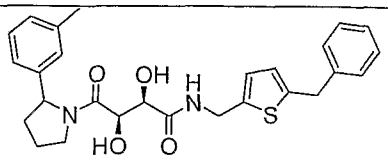
249		515.2	516.0
250		515.2	516.0
251		511.2	512.2
252		541.2	542.2
253		514.2	515.2
254		526.2	527.2
255		521.2	522.1

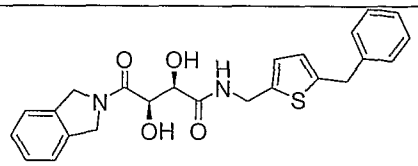
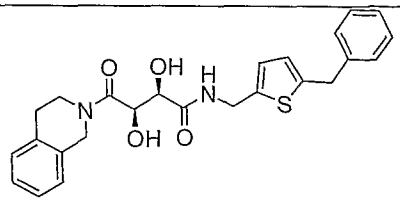
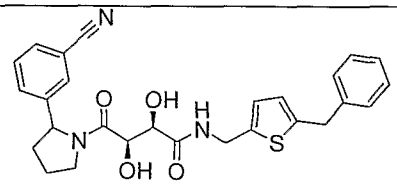
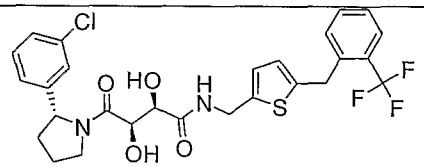
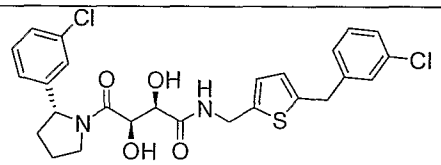
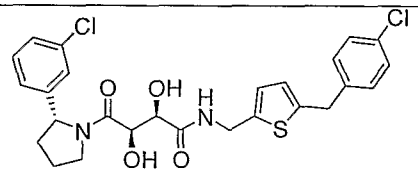
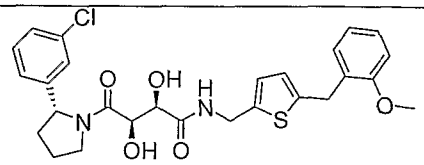
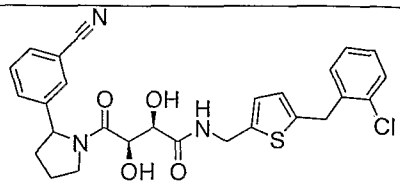
256		532.2	533.2
257		532.2	533.2
258		556.2	557.2
259		530.1	531.1
260		526.2	527.2
261		482.2	483.1
262		496.2	497.2

263		516.1	517.2
264		507.2	508.1
265		512.2	513.2
266		518.2	519.1
267		510.2	511.1
268		517.1	518.0
269		516.1	517.2
270		507.2	508.1

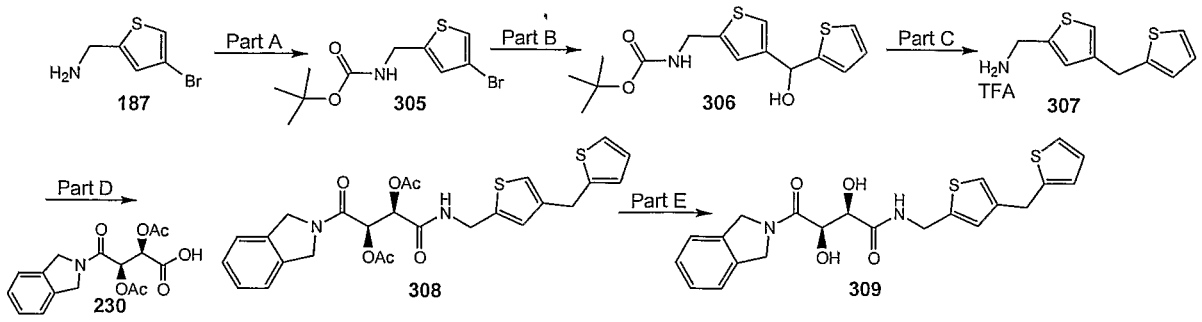
271		500.2	501.1
272		526.2	527.2
273		518.2	519.1
274		550.1	551.0
275		518.2	519.1
276		514.2	515.2
277		496.2	497.1
278		532.1	533.0

279		512.2	513.1
280		498.1	499.0
281		523.1	524.1
282		503.2	504.1
283		496.2	497.2
284		496.2	497.2
285		517.2	518.2
286		566.12	567.1
287		498.1	499.1

288		498.1	499.1
289		498.1	499.1
290		541.2	542.2
291		537.2	538.2
292		526.2	527.0
293		498.1	499.1
294		532.1	533.0
295		464.2	465.1
296		478.2	479.2

297		436.2	437.2
298		450.2	451.1
299		489.2	490.1
300		566.1	567.1
301		532.1	533.0
302		532.1	533.0
303		528.2	529.2
304		523.1	524.2

Example 5:



Part A:

To a solution of **187** (2.68 g, 14.0 mmol) and pyridine (2.26 mL, 28 mmol) in dichloromethane (25 mL) was added di-*tert*-butyl dicarbonate (3.21 g, 14.7 mmol). The mixture was stirred overnight at room temperature. The reaction mixture was poured into water (25 mL) and the layers were separated. The organic layer was washed with 1.0 N HCl (20 mL), water (20 mL), and saturated sodium chloride solution (20 mL), dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, DCM) afforded **305** as a light orange solid (3.64 g, 89%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.11 (s, 1H), 6.87 (s, 1H), 4.01 (bs, 1H), 4.44 (d, 2H, J = 6.0 Hz), 1.48 (s, 9H).

Part B:

To *n*-butyl lithium (2.5 M, 0.31 mL, 0.78 mmol) in THF (2 mL) at –78 °C under argon was added **305** (100 mg, 0.34 mmol) in THF (1.5 mL) dropwise. The reaction mixture was stirred for 30 minutes at –78 °C. Then 2-thiophene carbaldehyde (60 µL, 0.68 mmol) was added. The reaction mixture was stirred for 30 minutes at –78 °C. The reaction mixture was quenched with saturated ammonium chloride solution and warmed to room temperature. The mixture was diluted with ethyl acetate (10 mL) and the layers were separated. The organic layer was washed with water and brine. Dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 20% EtOAc/hexane) afforded **306** (47 mg, 42%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 1H), 7.16 (s, 1H) 6.95 (m, 2H), 6.93 (s, 1H), 6.05 (s, 1H). 4.88 (bs, 1H), 4.43 (d, 2H, J = 5.6 Hz), 2.43 (bs, 1H), 1.48 (s, 9H).

Part C:

To **306** (47 mg, 0.14 mmol) in DCM (2 mL) was added triethylsilane (0.2 mL). The mixture was cooled in an ice bath and TFA (0.2 mL) was added. The mixture was warmed to room temperature and stirred overnight. The solvents were removed in vacuo and **307** was used without further purification. ^{1}H NMR (400 MHz, CD_3OD) δ 7.20 (m, 2H), 7.09 (s, 1H) 6.90 (m, 1H), 6.86 (m, 1H), 4.26(s, 2H), 4.15 (s, 2H).

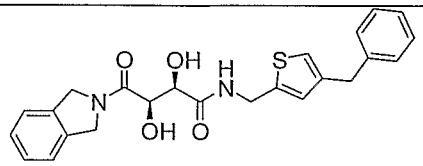
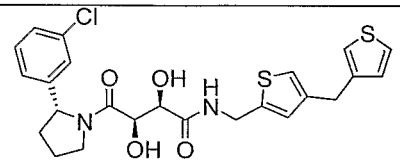
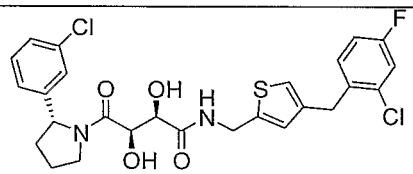
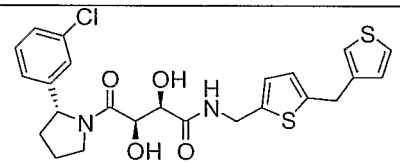
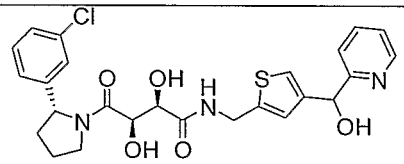
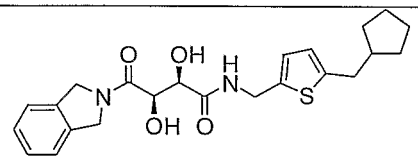
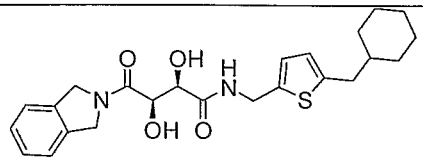
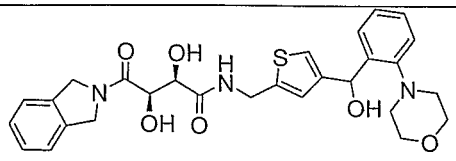
Part D:

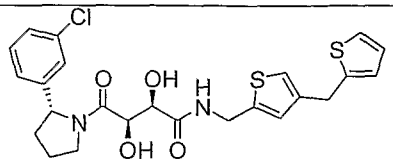
To **230** (19 mg, 0.06 mmol) in DMF (2 mL) was added **307** (18 mg, 0.06 mmol), DIEA (29 µL, 0.17 mmol) and HATU (28 mg, 0.07 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate (20 mL) and water (20 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with sodium bicarbonate solution and brine, dried over sodium sulfate and concentrated. Compound **308** was used without further purification. HPLC-MS t_R = 1.91 min ($UV_{254\ nm}$); mass calculated for formula $C_{26}H_{26}N_2O_6S_2$ 526.1, observed LCMS m/z 269.9 (M+H).

Part E:

Compound **308** and potassium carbonate (20 mg) were mixed in methanol (2.5 mL) and water (0.5 mL) and were stirred for 30 minutes. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over sodium sulfate and concentrated. Purification by reverse phase prep-LC afforded **309** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (t, 1H, J = 5.6 Hz), 7.30 (m, 5H), 7.03 (s, 1H), 6.92 (s, 1H), 6.67 (s, 1H), 6.82 (s, 1H), 5.04 (d, 1H, J = 14.0 Hz), 4.90 (d, 1H, J = 14.0 Hz), 4.75 (d, 1H, J = 16.0 Hz), 4.60 (m, 2H), 4.41 (dd, 1H, J = 6.8, 14.8 Hz), 4.33 (dd, 1H, J = 5.6, 14.4 Hz), 4.25 (s, 1H), 4.04 (s, 2H); HPLC-MS t_R = 4.45 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{22}H_{22}N_2O_4S_2$ 442.1, observed LCMS m/z 443.0 (M+H).

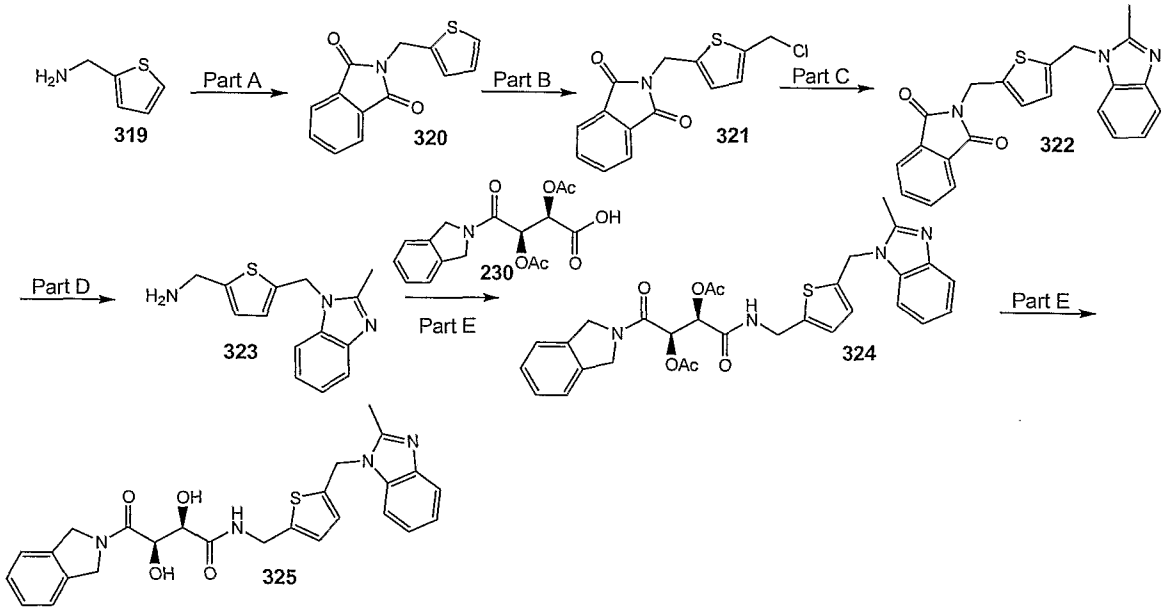
The following compounds were prepared using the procedures described above. Part C did not result in dehydration for compounds like **314** and **317**.

Compound #	Structure	Exact mass	MS m/z (M+H)
310		436.2	437.3
311		504.1	505.1
312		550.1	551.0
313		504.1	505.1
314		515.1	516.1
315		428.2	429.1
316		442.2	443.0
317		537.2	538.0

318		504.09	505.0

Example 6

Example 6A:



Part A:

A mixture of 2-(aminomethyl)thiophene **(319)** (1.57 g, 13.8 mmol), monomethyl phthalate (2.75 g, 15.3 mmol), EDC (3.26 g, 16.6 mmol), HOBt (2.79 g, 20.7 mmol) and triethylamine (5 mL, 27.6 mmol) in DCM (40 mL) was stirred for 12 hours. The reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with 1.0 N HCl, bicarbonate solution and brine, dried over sodium sulfate and concentrated. Recrystallization of the mixture from ethyl acetate/hexanes afforded **320** as a solid (2.20 g, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (m, 2H), 7.71 (m, 2H), 7.21 (m, 1H), 7.15 (m, 1H), 6.94 (m, 1H), 5.03 (s, 2H).

Part B: (Feigel, M., Lugert, G., Heichert, C.; *Liebigs Ann. Chem.* **1987**, 367) To paraformaldehyde (250 mg) in HCl (conc., 5 mL) was added 0.5 M zinc chloride in THF (1.7 mL, 0.85 mmol). To this mixture was added **320** (235 mg, 0.85 mmol) in portions and then dioxane (3 mL). The reaction mixture was stirred at 60 °C for 45 minutes. The reaction mixture was cooled and

diluted with water (50 mL) and ethyl acetate (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 30 mL). The combined organic layers were dried over sodium sulfate and concentrated. Recrystallization from ethyl acetate / hexane afforded **321** as a solid (190 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, 2H, J = 3.2, 5.6 Hz), 7.72 (dd, 2H, J = 3.2, 5.6 Hz), 6.98 (d, 1H, J = 3.6 Hz), 6.90 (d, 1H, J = 3.6 Hz), 4.98 (s, 2H), 4.72 (s, 2H).

Part C:

A mixture **321** (190 mg, 0.65 mmol), 2-methylbenzimidazole (112 mg, 0.85 mmol), sodium iodide (catalytic) and cesium carbonate (275 mg, 0.85 mmol) in DMF (6 mL) were stirred overnight at room temperature. The reaction mixture was partitioned between ethyl acetate and water. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with sodium bicarbonate solution and brine, dried over sodium sulfate and concentrated. Recrystallization from ethyl acetate / hexane afforded **322** (65 mg) and **322** contaminated with 2-methylbenzimidazole (120 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, 2H, J = 3.2, 5.6 Hz), 7.70 (dd, 2H, J = 3.2, 5.6 Hz), 7.68 (m, 1H), 7.29 (m, 1H), 7.23 (m, 2H), 6.95 (d, 1H, J = 3.6 Hz), 6.70 (d, 1H, J = 3.6 Hz), 5.36 (s, 2H), 4.91 (s, 2H), 2.64 (s, 3H); HPLC-MS t_R = 1.14 min ($UV_{254\ nm}$); mass calculated for formula $C_{22}H_{17}N_3O_2S$ 387.1, observed LCMS m/z 388.1 (M+H).

Part D:

Compound **322** (90 mg, 0.23 mmol) and hydrazine hydrate (50 µL, 0.93 mmol) in ethanol (10 mL) and DCM (5 mL) were refluxed for 1.5 hours. The reaction mixture was cooled and filtered. The filtrate was concentrated and the crude product was used without further purification.

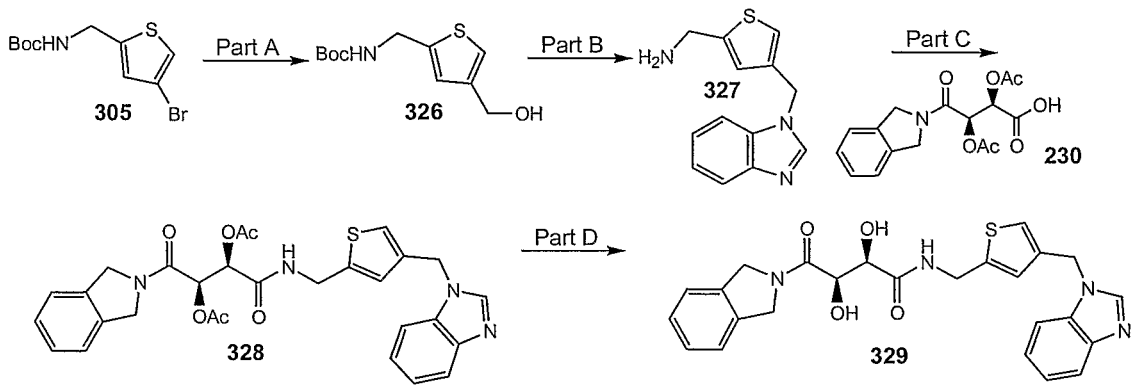
Part E:

To **230** (83 mg, 0.24 mmol) in DMF (5 mL) was added **323** (82 mg, 0.32 mmol), DIEA (300 µL, 1.6 mmol) and HATU (135 mg, 0.36 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate (50 mL) and water (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with sodium bicarbonate solution and brine, dried over sodium sulfate and concentrated. Compound **324** was used without further purification. HPLC-MS t_R = 1.13 min ($UV_{254\ nm}$); mass calculated for formula $C_{30}H_{30}N_4O_6S$ 574.2, observed LCMS m/z 575.1 (M+H).

Part F:

Compound **324** (~120 mg, 0.21 mmol) and potassium carbonate (100 mg) were mixed in methanol (5 mL) and water (1 mL). After 5 minutes a solid precipitated and the reaction was stirred for 30 minutes. The solid was collected by filtration. Purification by reverse phase prep-LC afforded **325** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (t, 1H, J = 6.0 Hz), 7.93 (d, 1H, J = 8.0 Hz), 7.73 (d, 1H, J = 6.8 Hz), 7.48 (m, 2H), 7.33 (m, 1H), 7.27 (m, 3H), 7.08 (d, 1H, J = 3.6 Hz), 6.82 (d, 1H, J = 3.6 Hz), 5.80 (s, 2H), 5.02 (d, 1H, J = 14.4 Hz), 4.86 (d, 1H, J = 15.2 Hz), 4.74 (d, 1H, J = 16.8 Hz), 4.58 (d, 1H, J = 16.4 Hz), 4.57 (s, 1H), 4.33 (m, 2H), 4.22 (s, 1H), 2.84 (s, 3H); HPLC-MS t_R = 2.74 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{26}H_{26}N_4O_4S$ 490.2, observed LCMS m/z 491.2 (M+H).

Example 6B:



Part A:

To *n*-butyl lithium (2.5 M, 0.91 mL, 2.28 mmol) in THF (5 mL) at –78 °C under argon was added **305** (300 mg, 1.03 mmol) in THF (5 mL) dropwise. The reaction mixture was stirred for 30 minutes at –78 °C. Then dimethyl formamide (151 mg, 2.06 mmol) was added. The reaction mixture was stirred for 30 minutes at –78 °C. The reaction mixture was quenched with saturated ammonium chloride solution and warmed to room temperature. The mixture was diluted with ethyl acetate (10 mL) and the layers were separated. The organic layer was washed with water and brine. Dried over sodium sulfate and concentrated. The residue was dissolved in methanol and sodium borohydride (156 mg, 4.12 mmol) was added. The reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate and washed with 0.1 N HCl, water and brine. The organic layer was dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 25% EtOAc/hexane) afforded **326** (147 mg, 58%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.10 (s, 1H), 6.94 (s, 1H), 4.63 (s, 2H), 4.45 (d, 2H, J = 4.7 Hz), 1.48 (s, 9H).

Part B:

To **326** (30 mg, 0.12 mmol) in THF (2 mL) was added benzimidazole (19 mg, 0.16 mmol), triphenylphosphine (42 mg, 0.16 mmol) and DIAD (32 mg, 0.16 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated. The residue was dissolved in dichloromethane (2 mL)

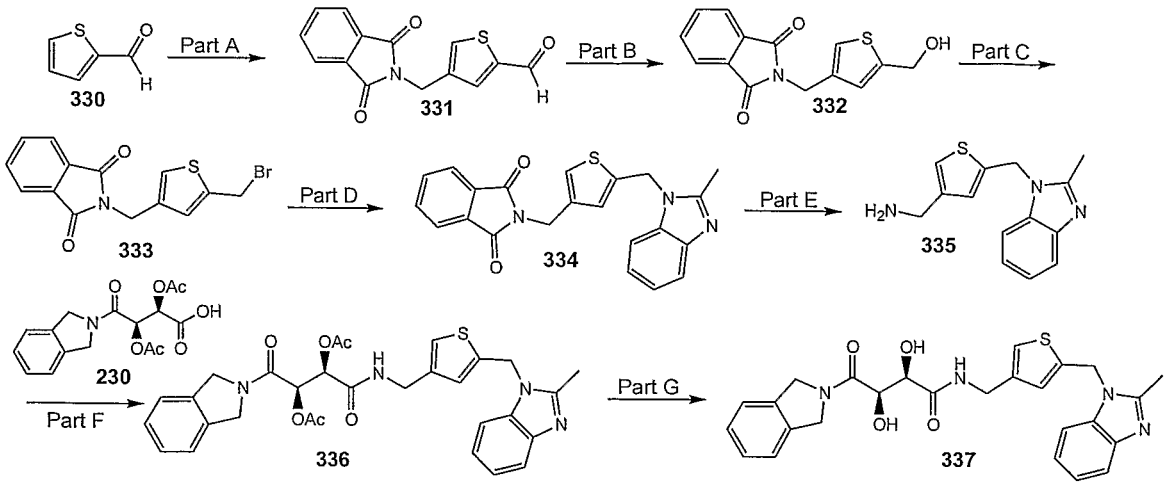
and TFA (0.5 mL) was added. The reaction mixture was stirred for 30 minutes and concentrated. The residue was dissolved in diethyl ether and washed twice with water. The combined aqueous layer was made basic DIEA and extracted with ethyl acetate. The combined organic layer was washed with brine, dried and concentrated to afford **327** as a film (41 mg). The material was used without further purification.

Part C:

To **230** (20 mg, 0.06 mmol) in DMF (2 mL) was added **327** (19 mg, 0.08 mmol), DIEA (31 µL, 0.18 mmol), DMAP (1 mg) and HATU (30 mg, 0.08 mmol). The reaction mixture was stirred overnight. The mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with 0.1 N NaOH, water and brine, dried over sodium sulfate and concentrated. Compound **328** was used without further purification.
Mass calculated for formula $C_{29}H_{28}N_4O_6S$ 560.2, observed LCMS m/z 561.2 (M+H).

Part D:
Compound **328** and potassium carbonate (20 mg) were mixed in methanol (2.5 mL) and water (0.5 mL) and were stirred for 30 minutes. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over sodium sulfate and concentrated. Purification by reverse phase prep-LC afforded **329** as a white solid (8 mg). HPLC-MS t_R = 2.77 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{25}H_{24}N_4O_4S$ 476.2, observed LCMS m/z 477.1 (M+H).

Example 6C



Part A:

N-(Hydroxymethyl)phthalimide (1.0 g, 5.6 mmol) was dissolved in 1% triflic acid in trifluoroacetic acid (10 mL) at 0 °C. To this mixture was added **330** (0.52 mL, 5.6 mmol). The reaction mixture was warmed to room temperature slowly and stirred overnight. The reaction mixture was poured into ice water (100 mL) and extracted with DCM. The combined organic layers were washed with sodium bicarbonate solution and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 30% EtOAc/Hex) afforded **331** (619 mg, 41%). ^1H NMR (400 MHz, $CDCl_3$) δ 9.85 (d, 1H, J = 1.6 Hz), 7.86 (m, 2H), 7.81 (d, 1H, J = 1.6 Hz), 7.76 (s, 1H), 7.73 (m, 2H), 4.87 (s, 2H).

Part B:

Compound **331** (315 mg, 1.16 mmol) was dissolved in 1:1 methylene chloride:methanol (10 mL) and cooled in an ice bath. To this solution was added sodium borohydride (11 mg, 0.29 mmol) and the reaction was stirred for 30 minutes. Additional sodium borohydride (3 mg, 0.08 mmol) was added and the reaction was stirred for 30 minutes. The reaction mixture was diluted with methylene chloride and washed with saturated ammonium chloride solution, water and brine. The reaction mixture was dried over sodium sulfate and concentrated to afford **332** as a white solid (310 mg, 98%). ^1H NMR (400

MHz, CD_3OD) δ 7.83 (m, 2H), 7.79 (m, 2H), 7.24 (s, 1H), 6.97 (s, 1H), 4.76 (s, 2H), 4.65 (s, 2H).

Part C:

A mixture of **332** (97 mg, 0.36 mmol) and phosphorous tribromide (34 µL, 0.39 mmol) in DCM (5 mL) was stirred for 30 minutes at room temperature. The reaction mixture was poured into ice water and extracted with ethyl acetate. The combined organic layers were washed with sodium bicarbonate solution and brine, dried over sodium sulfate and concentrated to afford **333** as a white solid (104 mg, 87%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, 2H, J = 2.8, 5.2 Hz), 7.72 (dd, 2H, J = 2.8, 5.2 Hz), 7.32 (s, 1H), 7.15 (s, 1H), 4.77 (s, 2H), 4.66 (s, 2H).

Part D:

A mixture of **333** (450 mg, 1.34 mmol), 2-methyl-benzimidazole (355 mg, 2.69 mmol) and cesium carbonate (875 mg, 2.69 mmol) in DMF (5 mL) was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate and washed with water and brine, dried over sodium sulfate and concentrated. Recrystallization from ethyl acetate / hexanes afforded **334** as a white solid (252 mg, 49%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, 2H, J = 2.8, 5.2 Hz), 7.72 (dd, 2H, J = 2.8, 5.2 Hz), 7.68 (m, 1H), 7.23 (m, 3H), 7.19 (s, 1H), 7.05 (s, 1H), 5.38 (s, 2H), 4.75 (s, 2H), 2.66 (s, 3H).

Part E:

A mixture of **334** (225 mg, 0.58 mmol) and hydrazine hydrate (113 µL, 2.32 mmol) in ethanol (4 mL) was refluxed for 4 hours. The reaction mixture was cooled and filtered. The filtrate was concentrated and the residue was dissolved in ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate and concentrated to afford a **335** as yellow solid (148 mg, 99%).

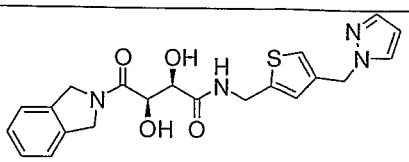
Part F:

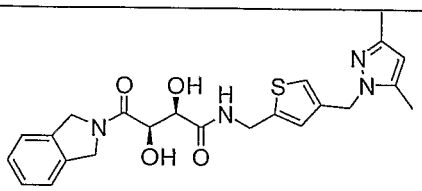
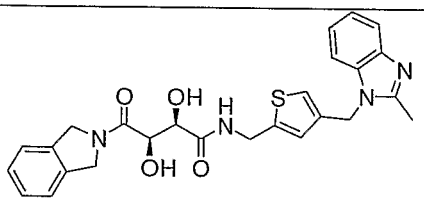
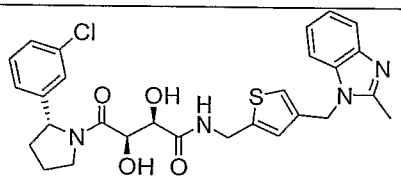
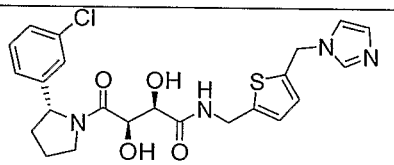
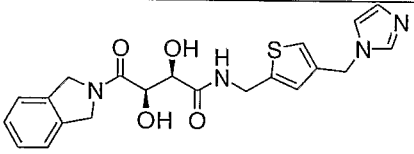
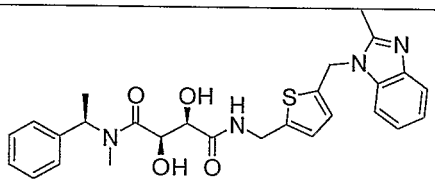
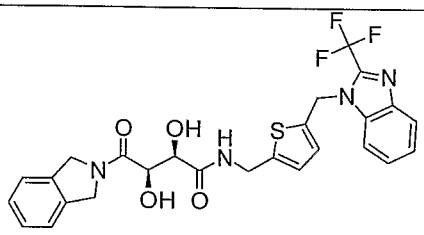
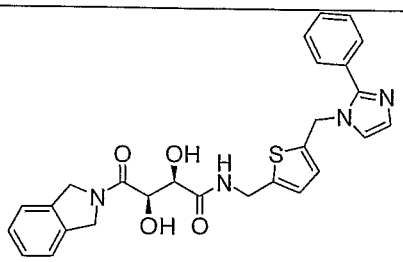
To **230** (12 mg, 0.036 mmol) in DMF (2 mL) was added **335** (12 mg, 0.045 mmol), DIEA (18 µL, 0.11 mmol) and HATU (17 mg, 0.045 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate (20 mL) and water (20 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with sodium bicarbonate solution and brine, dried over sodium sulfate and concentrated. Compound **336** was used without further purification. HPLC-MS t_R = 1.22 min (UV_{254} nm); mass calculated for formula $C_{30}H_{30}N_4O_6S$ 574.2, observed LCMS m/z 575.0 (M+H).

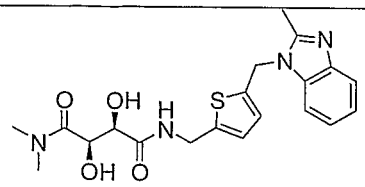
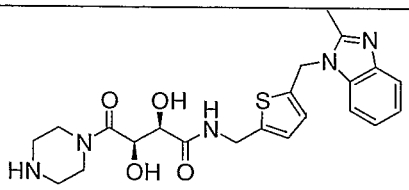
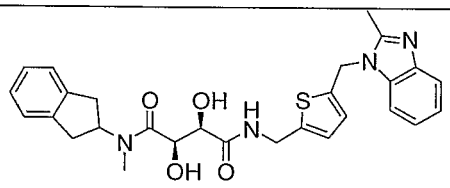
Part G:

Compound **336** and potassium carbonate (20 mg) were mixed in methanol (1.5 mL) and stirred for 30 minutes. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over sodium sulfate and concentrated. Purification by reverse phase prep-LC afforded **337** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (t, 1H, J = 6.4 Hz), 7.89 (m, 1H), 7.70 (m, 1H), 7.44 (m, 2H), 7.33 (m, 1H), 7.27 (m, 3H), 7.20 (s, 1H), 7.14 (s, 1H), 5.80 (s, 2H), 5.04 (d, 1H, J = 13.2 Hz), 4.88 (d, 1H, J = 15.2 Hz), 4.73 (m, 2H), 4.60 (m, 2H), 4.25 (m, 2H), 2.83 (s, 3H); HPLC-MS t_R = 2.04 min (UV_{254} nm, 10 min); mass calculated for formula $C_{26}H_{26}N_4O_4S$ 490.2, observed LCMS m/z 491.1 (M+H).

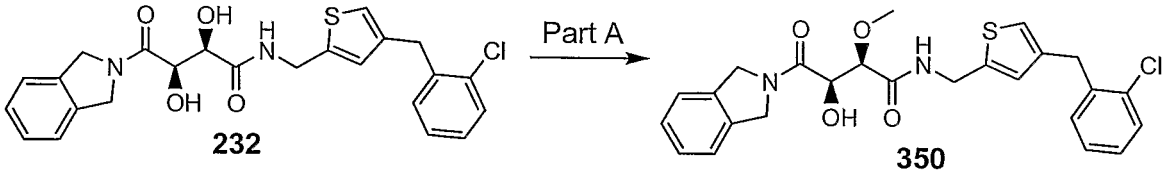
The following compounds were prepared using the procedures described in Example 6A to 6C.

Compound #	Structure	Exact mass	MS m/z (M+H)
338		426.1	427.1

339		454.2	455.2
340		490.2	491.2
341		552.2	553.2
342		488.1	489.0
343		426.1	427.1
344		506.2	507.2
345		544.1	545.1
346		502.2	503.2

347		416.2	417.2
348		457.2	458.1
349		518.2	519.2

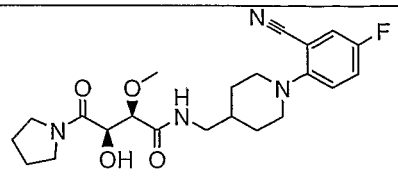
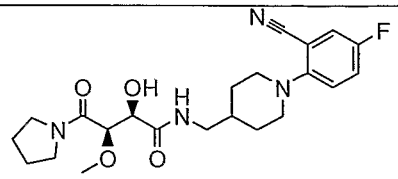
Example 7:



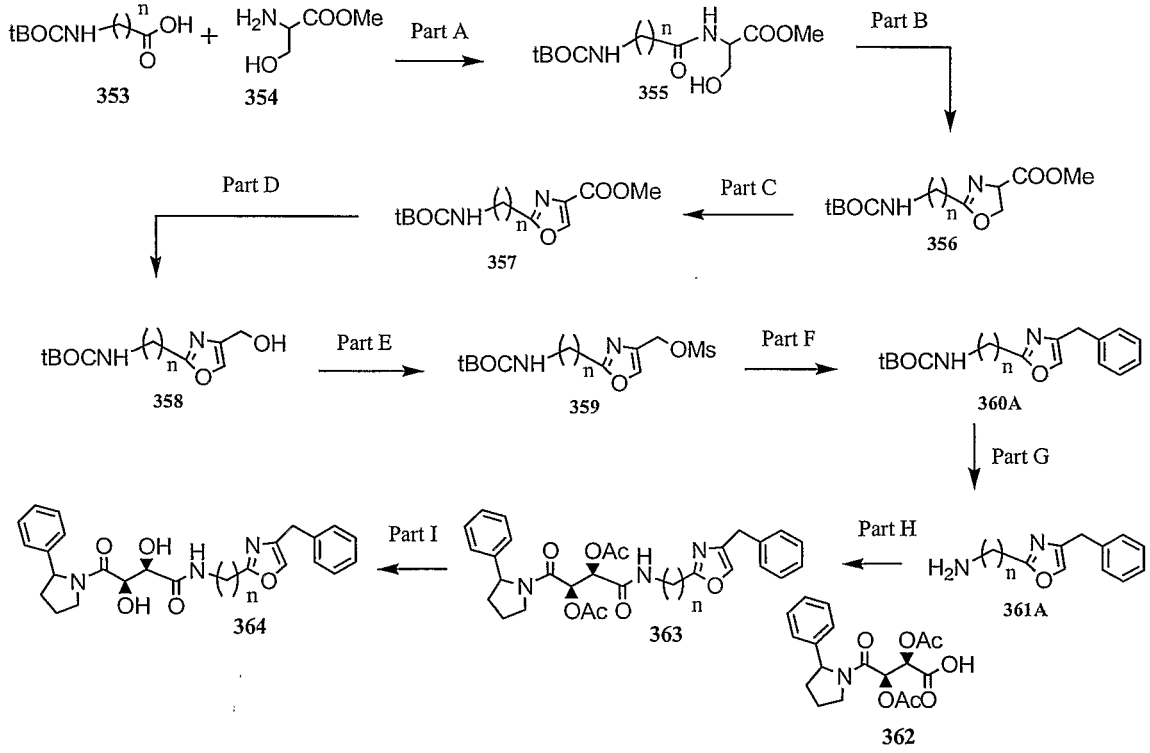
232 **350**

Part A:

To **232** (26 mg, 0.056 mmol) in toluene (5 mL) was added dibutyltin oxide (20 mg, 0.08 mmol). The mixture was heated for 3 hours at reflux with a Dean Stark trap. The mixture was concentrated. The residue was dissolved in NMP (3 mL) and treated with cesium fluoride (8.5 mg, 0.056 mmol) and iodomethane (14 µL, 0.224 mmol). The reaction mixture was heated at 50 °C overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated. Purification by prep-HPLC afforded **350** (3.4 mg, 13%). HPLC-MS t_R = 5.26 min (UV_{254} nm, 10 min.); mass calculated for formula $C_{25}H_{25}ClN_2O_4S$ 484.1, observed LCMS m/z 485.0 (M+H).

Compound #	Structure	Exact mass	MS m/e (M+H)
351		432.2	433.2
352		432.2	433.2

Example 8:



Part A:

To BOC-glycine **(353)** (25.0 g, 0.143 mol) dissolved in dry THF (100 mL) and cooled to -20 °C under a nitrogen atmosphere was added Hunig's base (23.1 g, 31.1 mL, 0.357 mol) then isobutylchloroformate (21.4 g, 20.4 mL, 0.157 mol). Stirred at -20 °C for 60 mins. Serine methyl ester **(354)** (24.4 g, 0.157

mol) then Hunig's base (23.1 g, 31.1 mL, 0.357 mol) was added. The reaction mixture was warmed to room temperature, stirred for 18 h and concentrated. The residue was partitioned between 0.5 N NaOH (300 mL) CH_2Cl_2. The layers were separated and the acqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over magnesium sulfate and concentrated. Purified by silica gel chromatography (eluant: 1% MeOH-CH_2Cl_2 to 3% MeOH-CH_2Cl_2) to give 20.5 g (52%) of the product **355** as a yellow oil. MS m/e: 277 (M+H).
For n=2: MS m/e: 291 (M+H)

Part B:
To compound **355** (4.55g, 16.5 mmol) dissolved in CH_2Cl_2 (200 mL) and cooled to -50 °C under a nitrogen atmosphere was added diethylaminosulfur trifluoride (3.19 g, 2.4 mL, 19.8 mmol) dropwise via syringe. Stirred at -50 °C for 2 h, added potassium carbonate (3.88 g, 28.1 mmol), and warmed slowly to room temperature over 2 h. Added 0.2 N NaOH (100 mL) and separated layers. Extracted aqueous layer with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 2% MeOH-CH_2Cl_2 to 4% MeOH-CH_2Cl_2) to give 3.06 g (72%) of the product **356** as a yellow oil. MS m/e: 259 (M+H).
For n=2: MS m/e: 273 (M+H)

Part C:
To compound **356** (6.10 g, 23.6 mmol) dissolved in CH_2Cl_2 (250 mL) and cooled to 0 °C was added DBU (12.59 g, 12.4 mL, 82.7 mmol) and bromotrichloromethane (16.40 g, 8.1 mL, 82.7 mmol). Warmed slowly to room temperature over 2 h and stirred for 16 h. Added 0.1 N NaOH (200 mL) and separated layers. Extracted aqueous layer with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 2% MeOH-CH_2Cl_2 to 3% MeOH-CH_2Cl_2) to give 4.27 g (71%) of the product **357** as an orange oil. MS m/e: 257 (M+H).
For n=2: MS m/e: 271 (M+H)

Part D:

To compound **357** (4.25 g, 16.6 mmol) dissolved in Et_2O (100 mL) was added lithium borohydride (1.44 g, 66.3 mmol) and MeOH (2.13 g, 2.7 mL, 66.3 mmol). Refluxed for 3 h, cooled to room temperature, and concentrated. Added water (100 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 5% MeOH-CH_2Cl_2 to 10% MeOH-CH_2Cl_2) to give 2.43 g (64%) of the product **358** as a yellow oil. MS m/e: 229 (M+H).
For n=2: MS m/e: 243 (M+H)

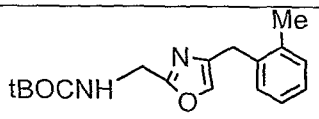
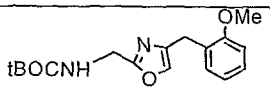
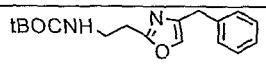
Part E:

To compound **358** (1.41 g, 6.18 mmol) dissolved in CH_2Cl_2 (35 mL) and cooled to -25 °C was added triethylamine (1.25 g, 1.7 mL, 12.4 mmol) then mesyl chloride (0.85 g, 0.57 mL, 7.41 mmol) dropwise. Warmed to 0 °C slowly over 60 mins. Added water (50 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated to give 1.89 g (100%) of the product **359** as a yellow oil. MS m/e: 251 (M+2-tBu).
For n=2: MS m/e: 265 (M+2-tBu)

Part F:

Suspended copper cyanide (1.66 g, 18.5 mmol) in dry THF (70 mL) under a nitrogen atmosphere and cooled to -25 °C. Added phenyl magnesium bromide (3.0 M in Et_2O, 12.3 mL, 37.0 mmol) dropwise via syringe such that internal temperature < -20 °C. Stirred at -20 °C for 30 mins then at 0 °C for 30 mins. Warmed to 15 °C internal temperature then recooled to -25 °C. Added compound **359** (1.89 g, 6.18 mmol) dissolved in dry THF (20 mL) dropwise via syringe. Stirred at -25 °C internal temperature for 2 h then at 0 °C for 16 h. Concentrated, added 2 N NH_4OH (100 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 5% EtOAc-hexane to 20% EtOAc-hexane) to give 0.82 g (46%) of the product **360A** as a yellow oil. MS m/e: 289 (M+H).

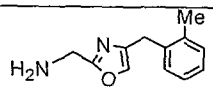
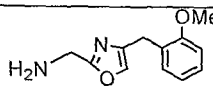
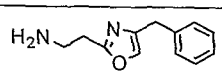
The following intermediates were prepared according to the above procedure:

Compound #	Intermediate Structure	MS
360B		303 (M+H)
360C		319 (M+H)
360D		303 (M+H)

Part G:

To compound **360A** (1.00 g, 3.47 mmol) dissolved in 1:1 CH_2Cl_2:MeOH (30 mL) was added 4 N HCl in dioxane (7.8 mL, 31.2 mmol). Stirred at room temperature for 4 h then concentrated to give 0.78 g (100%) of the product **361A** (hydrochloride salt) as a yellow solid. MS m/e: 189 (M+H).

The following intermediates were prepared according to the above procedure:

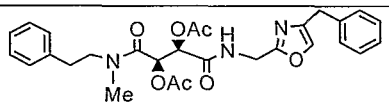
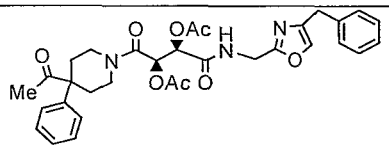
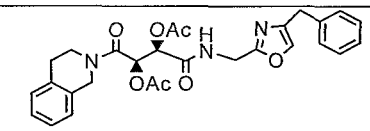
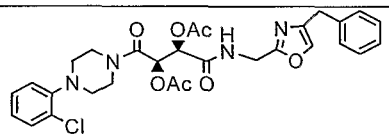
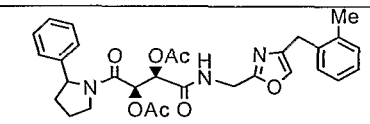
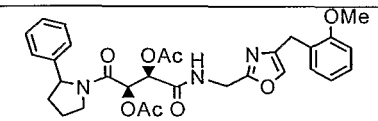
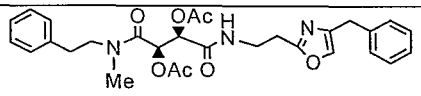
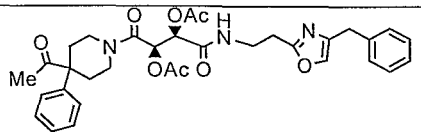
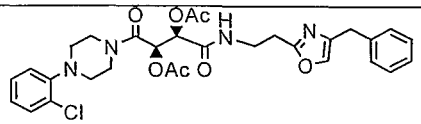
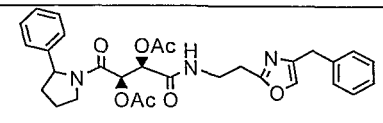
Compound #	Intermediate Structure	MS
361B		303 (M+H)
361C		219 (M+H)
361D		203 (M+H)

Part H: (JFL 80324-023)

Combined compound **361A** (0.20 g, 0.677 mmol), compound **362** (0.30 g, 0.812 mmol), HATU (0.51 g, 1.35 mmol), and triethylamine (0.21 g, 0.28 mL, 2.03 mmol) in dry DMF (8 mL). Stirred at room temperature for 16 h. Concentrated, added 0.5 N NaOH (15 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by

silica gel chromatography (eluant: 3% MeOH-CH_2Cl_2) to give 0.25 g (70%) of the product **363** as a beige oil. MS m/e: 534 (M+H).

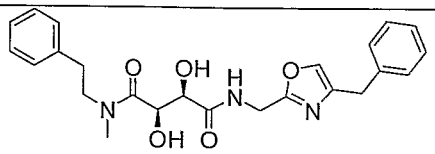
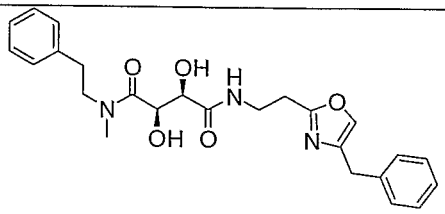
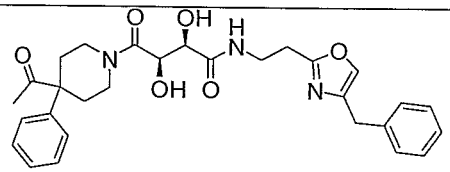
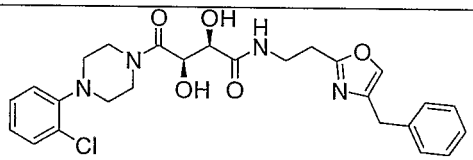
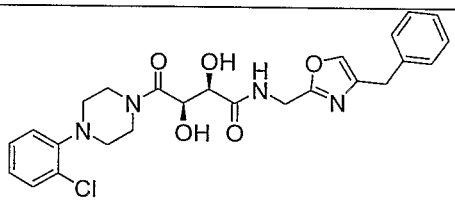
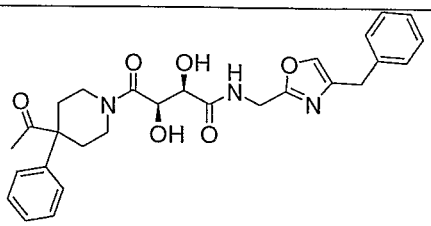
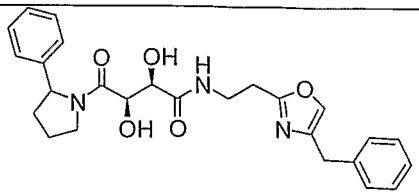
The following intermediates were prepared according to the above procedure:

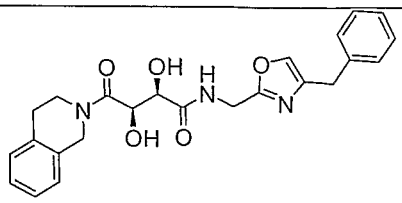
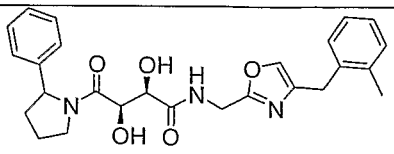
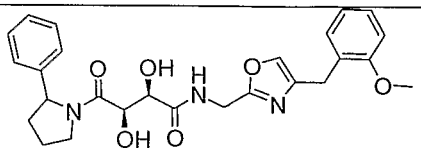
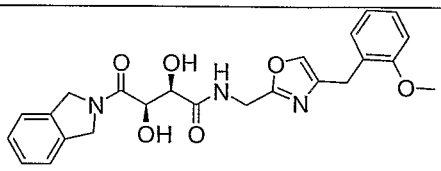
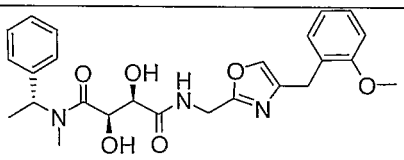
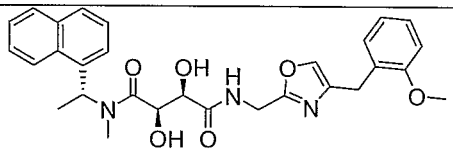
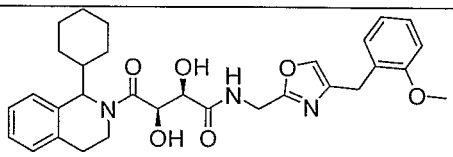
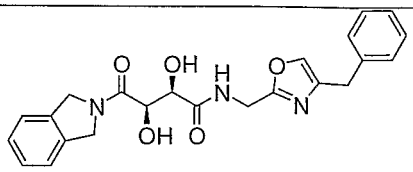
Compound #	Intermediate Structure	MS
365		522 (M+H)
366		590 (M+H)
367		520 (M+H)
368		583 (M+H)
369		548 (M+H)
370		564 (M+H)
371		536 (M+H)
372		604 (M+H)
373		597 (M+H)
374		548 (M+H)

Part I:

To compound **363** (0.24 g, 0.450 mmol) dissolved in MeOH (10 mL) was added 0.5 M NaOMe in MeOH (0.09 mL, 0.045 mmol). Stirred at room temperature for 60 mins. Added 4 N HCl in dioxane (0.11 mL, 0.450 mmol) and concentrated to give 0.20 g (100%) of the product **364** as a brown foam. MS m/e: 450 (M+H).

The following compounds were prepared according to Example 8:

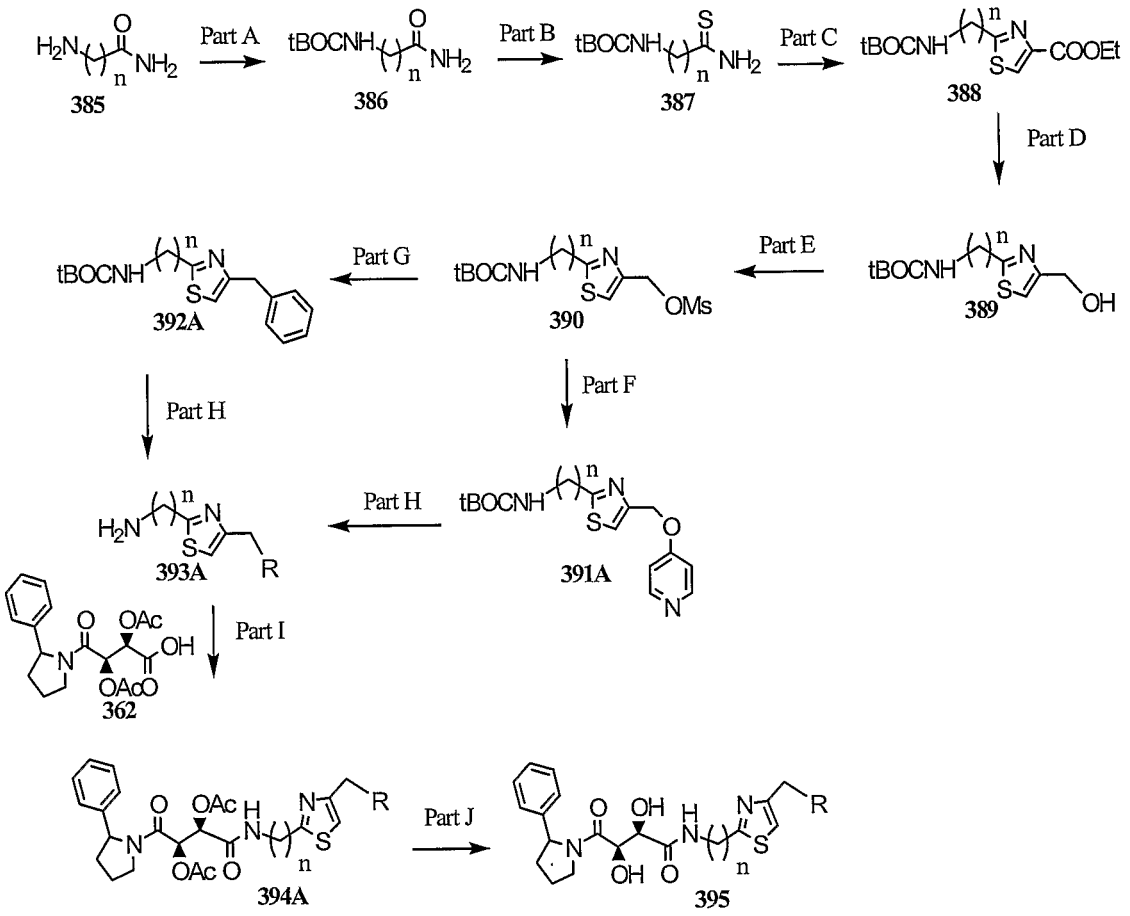
Compound #	Structure	Exact mass	MS m/z (M+H)
375		437.2	438.0
376		451.2	452.0
377		519.2	520.0
378		512.2	513.0
379		498.2	499.2
380		505.2	506.3
381		463.2	464.2

382		435.2	436.2
383		463.2	464.2
384		479.2	480.2
174		451.2	452.2
175		467.2	468.3
179		517.2	518.3
181		547.3	548.3
182		421.2	422.2

Example 9: Thiazole-benzyl inhibitors

Example 9A:

Scheme 1



Part A:

To glycinamide HCl **385** (60.0 g, 0.543 mol) suspended in MeOH (1000 mL) and cooled to 0 °C was added triethylamine (109.9 g, 151.4 mL, 1.09 mol) and tBOC anhydride (148.0 g, 0.678 mol) portionwise. Warmed to room temperature and stirred for 24 h. Concentrated, added 1 N NaOH (600 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated to give 53.0 g (56%) of the product **396** as a white solid. MS m/e: 175 (M+H).

For n=2: MS m/e: 189 (M+H)

Part B:

To compound **386** (21.63 g, 0.124 mol) dissolved in THF (400 mL) was added Lawesson reagent (30.13 g, 0.074 mol). Stirred at room temperature for 16 h then concentrated. Purified by silica gel chromatography (eluant: 3% MeOH-CH_2Cl_2) then re-purified by silica gel chromatography (eluant: 2% MeOH-CH_2Cl_2) to give 23.59 g (100%) of the product **387** as a light green solid. MS m/e: 135 (M+2-tBu).
For n=2: MS m/e: 149 (M+2-tBu)

Part C:
To compound **387** (6.00 g, 31.5 mmol) dissolved in CH_2Cl_2 (150 mL) was added ethyl bromopyruvate (6.76 g, 4.4 mL, 34.7 mmol). Stirred at room temperature for 5 h then concentrated. Added 3 A sieves (6 g) and EtOH (150 mL) and refluxed for 16 h. Filtered and concentrated to give a dark foam. Dissolved foam in 1:1 CH_2Cl_2:EtOH (100 mL) and added triethylamine (6.40 g, 8.8 mL, 63.1 mmol) and tBOC anhydride (7.60 g, 34.7 mmol). Stirred at room temperature for 5 h then concentrated. Added 0.25 N NaOH (100 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 10% EtOAc-CH_2Cl_2 to 30% EtOAc-CH_2Cl_2) to give 6.00 g (67%) of the product **388** as a brown oil. MS m/e: 287 (M+H).
For n=2: MS m/e: 301 (M+H)

Part D:
To compound **388** (4.70 g, 16.4 mmol) dissolved in Et_2O (140 mL) was added lithium borohydride (1.43 g, 65.7 mmol) and MeOH (2.10 g, 2.7 mL, 65.7 mmol). Refluxed for 16 h, cooled to room temperature, and concentrated. Added water (100 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 2% MeOH-CH_2Cl_2 to 5% MeOH-CH_2Cl_2) to give 3.70 g (92%) of the product **389** as a yellow solid. MS m/e: 245 (M+H).
For n=2: MS m/e: 259 (M+H)

Part E:

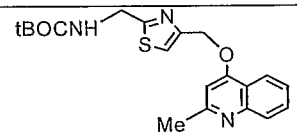
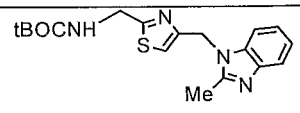
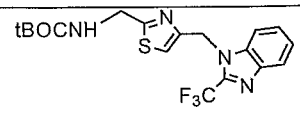
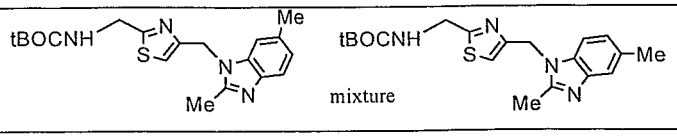
To compound **389** (5.30 g, 21.7 mmol) dissolved in CH_2Cl_2 (130 mL) and cooled to -25 °C was added triethylamine (4.40 g, 6.0 mL, 43.4 mmol) then mesyl chloride (3.00 g, 2.0 mL, 26.0 mmol) dropwise. Warmed to 0 °C slowly over 60 mins. Added water (100 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated to give 7.00 g (100%) of the product **390** as a yellow oil. MS m/e: 223 (M+2-tBOC).

For n=2: MS m/e: 237 (M+2-tBOC)

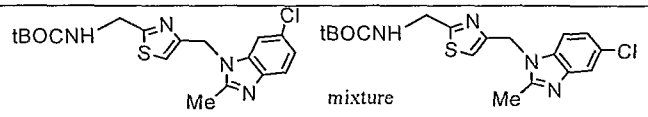
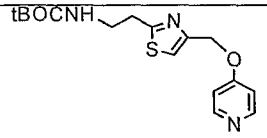
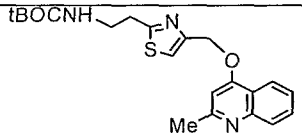
Part F:

To compound **390** (0.60 g, 1.86 mmol) dissolved in dry DMF (25 mL) was added 4-hydroxypyridine (0.22 g, 2.30 mmol) and cesium carbonate (1.20 g, 3.72 mmol). Stirred at room temperature for 16 h then concentrated. Added water (25 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 10% MeOH with NH_3-CH_2Cl_2) to give 0.40 g (68%) of the product **391A** as a colorless oil. MS m/e: 322 (M+H).

The following intermediates were prepared according to the above procedure:

Compound #	Intermediate Structure	MS
391B		386 (M+H)
391C		359 (M+H)
391D		413 (M+H)
391E		373 (M+H)

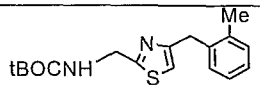
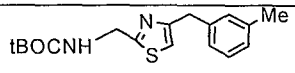
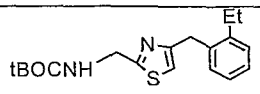
mixture

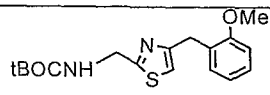
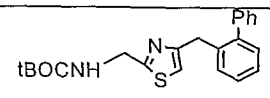
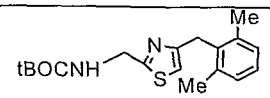
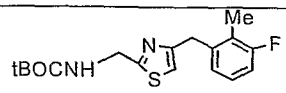
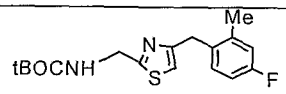
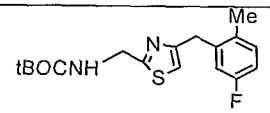
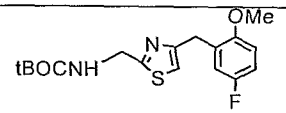
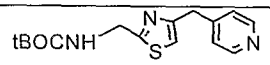
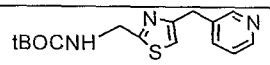
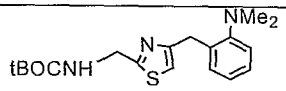
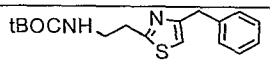
391F		393 (M+H)
391G		336 (M+H)
391H		400 (M+H)

Part G:

Suspended copper cyanide (1.65 g, 18.4 mmol) in dry THF (70 mL) under a nitrogen atmosphere and cooled to -25 °C. Added phenyl magnesium bromide (3.0 M in Et_2O, 12.3 mL, 37.0 mmol) dropwise via syringe such that internal temperature < -20 °C. Stirred at -20 °C for 30 mins then at 0 °C for 30 mins. Warmed to 15 °C internal temperature then recooled to -25 °C. Added compound **390** (1.98 g, 6.14 mmol) dissolved in dry THF (20 mL) dropwise via syringe. Stirred at -25 °C internal temperature for 2 h then at 0 °C for 16 h. Concentrated, added 2 N NH_4OH (100 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 5% EtOAc-hexane to 20% EtOAc-hexane) to give 1.14 g (66%) of the product **392A** as a yellow oil. MS m/e: 305 (M+H).

The following intermediates were prepared according to the above procedure:

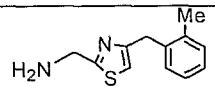
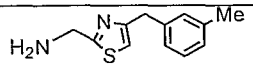
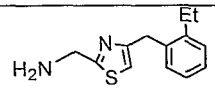
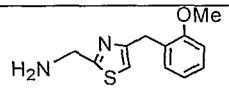
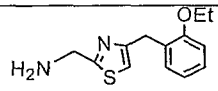
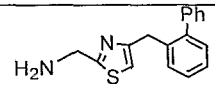
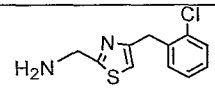
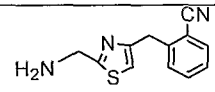
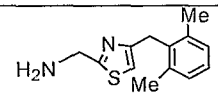
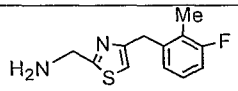
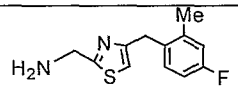
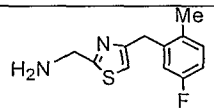
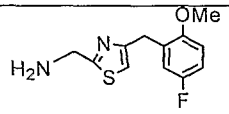
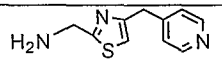
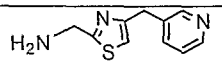
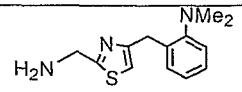
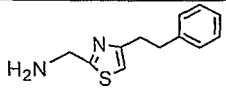
Compound #	Intermediate Structure	MS
392B		319 (M+H)
392C		319 (M+H)
392D		333 (M+H)

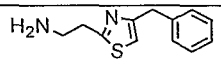
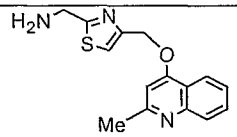
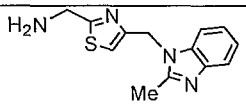
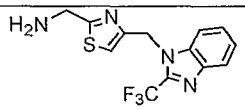
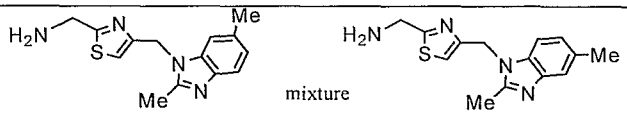
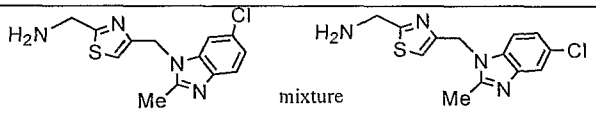
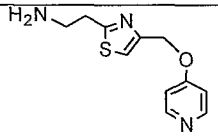
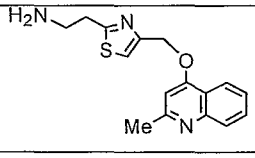
392E		335 (M+H)
392F		381 (M+H)
392G		333 (M+H)
392H		337 (M+H)
392I		337 (M+H)
392J		337 (M+H)
392K		353 (M+H)
392L		306 (M+H)
392M		306 (M+H)
392N		348 (M+H)
392O		319 (M+H)

Part H:

To compound **392A** (0.30 g, 0.986 mmol) dissolved in 1:1 CH_2Cl_2:MeOH (10 mL) was added 4 N HCl in dioxane (2.4 mL, 9.86 mmol). Stirred at room temperature for 16 h then concentrated to give 0.23 g (100%) of the product **393A** (hydrochloride salt) as a beige foam. MS m/e: 205 (M+H).

The following intermediates were prepared according to the above procedure:

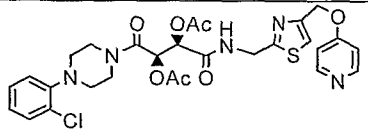
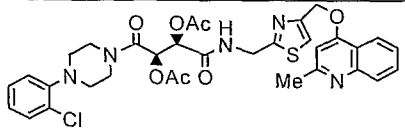
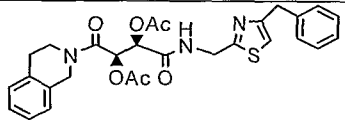
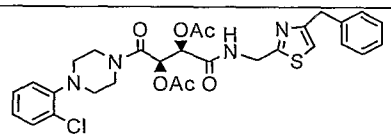
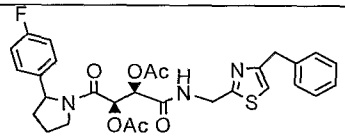
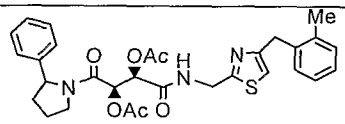
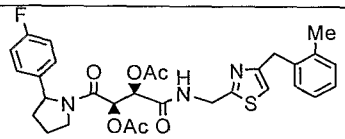
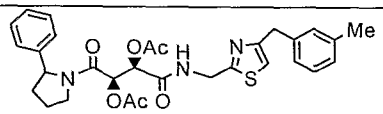
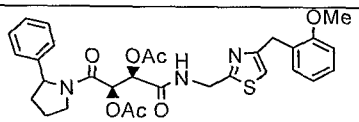
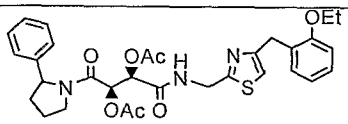
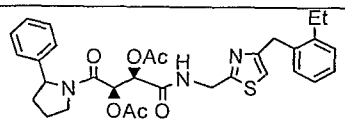
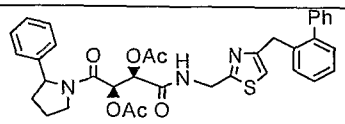
Compound #	Intermediate Structure	MS
393B		219 (M+H)
393C		219 (M+H)
393D		233 (M+H)
393E		235 (M+H)
393F		249 (M+H)
393G		281 (M+H)
393H		239 (M+H)
393I		230 (M+H)
393J		233 (M+H)
393K		237 (M+H)
393L		237 (M+H)
393M		237 (M+H)
393N		253 (M+H)
393O		206 (M+H)
393P		206 (M+H)
393Q		248 (M+H)
393R		219 (M+H)

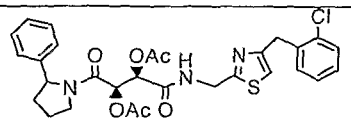
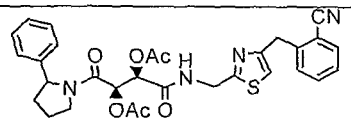
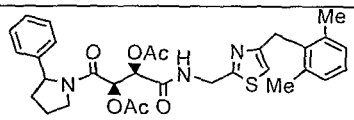
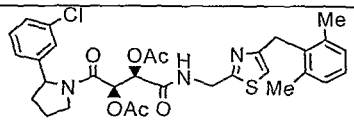
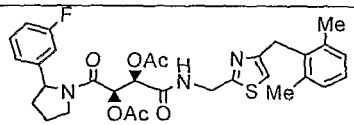
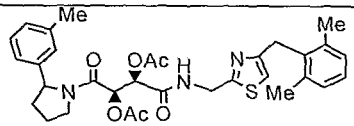
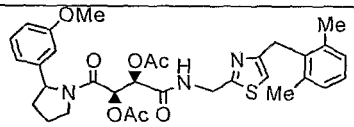
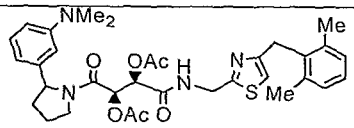
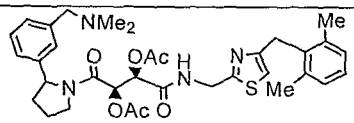
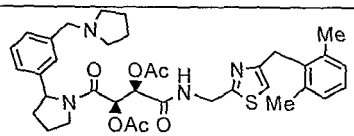
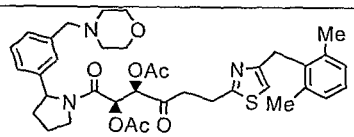
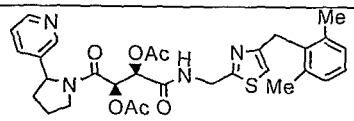
393S		219 (M+H)
393T		286 (M+H)
393U		259 (M+H)
393V		313 (M+H)
393W		273 (M+H)
393X		293 (M+H)
393Y		236 (M+H)
393Z		300 (M+H)

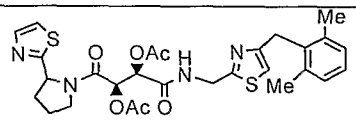
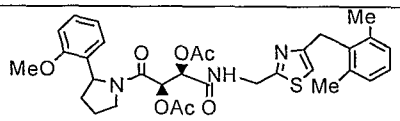
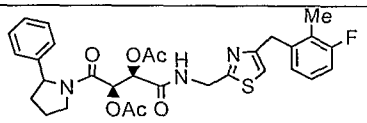
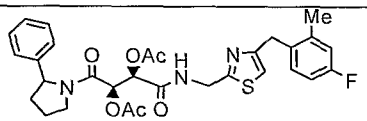
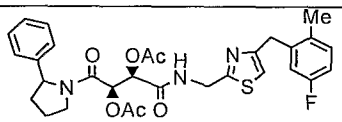
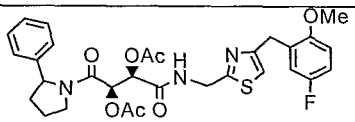
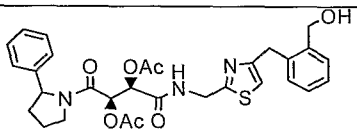
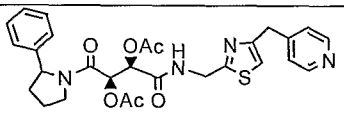
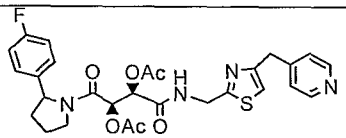
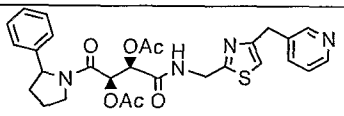
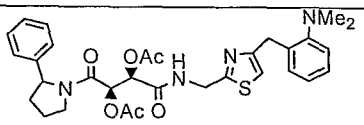
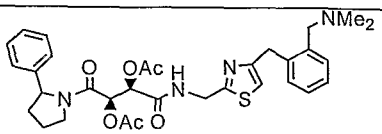
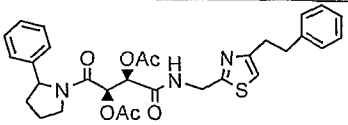
Part I:

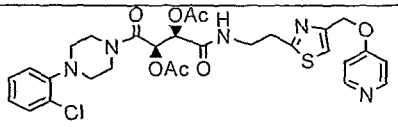
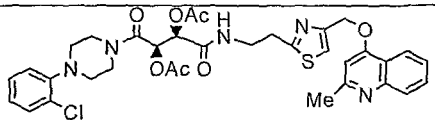
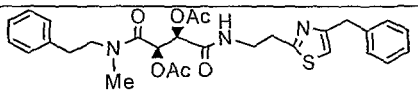
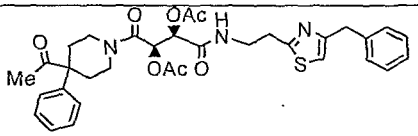
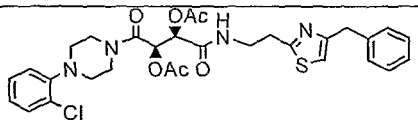
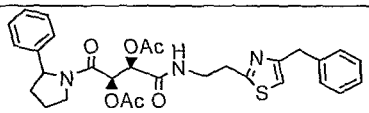
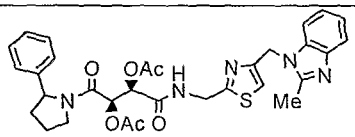
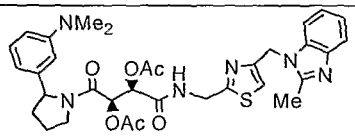
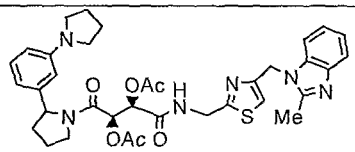
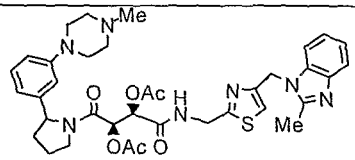
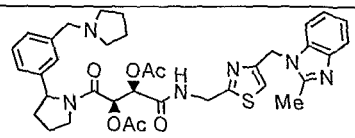
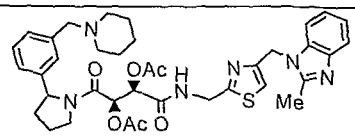
Combined compound **393A** (100 mg, 0.416 mmol), compound **362** (181 mg, 0.499 mmol), HATU (316 mg, 0.832 mmol), and triethylamine (126 mg, 0.17 mL, 1.25 mmol) in dry DMF (6 mL). Stirred at room temperature for 16 h. Concentrated, added 0.5 N NaOH (15 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 3% MeOH-CH_2Cl_2) to give 120 mg (52%) of the product **394A** as a colorless oil. MS m/e: 550 (M+H).

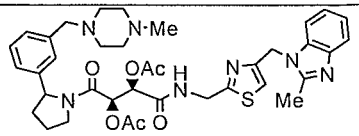
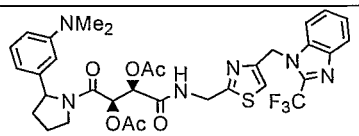
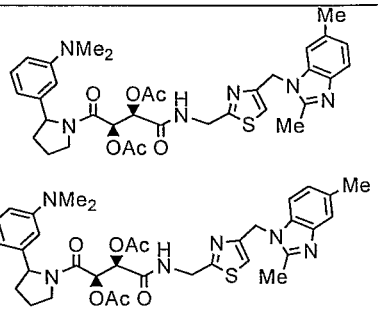
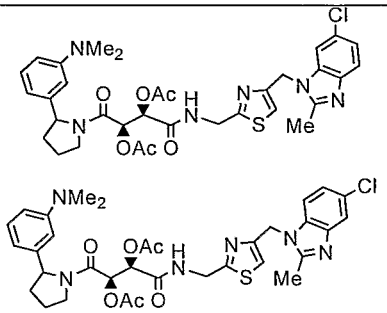
The following intermediates were prepared according to the above procedure:

Compound #	Intermediate Structure	MS
394B		616 (M+H)
394C		680 (M+H)
394D		536 (M+H)
394E		600 (M+H)
394F		568 (M+H)
394G		564 (M+H)
394H		582 (M+H)
394I		564 (M+H)
394J		580 (M+H)
394K		594 (M+H)
394L		578 (M+H)
394M		626 (M+H)

394N		584 (M+H)
394O		575 (M+H)
394P		578 (M+H)
394Q		612 (M+H)
394R		596 (M+H)
394S		592 (M+H)
394T		608 (M+H)
394U		621 (M+H)
394V		635 (M+H)
394W		661 (M+H)
394X		677 (M+H)
394Y		579 (M+H)

394Z		585 (M+H)
394AA		608 (M+H)
394BB		582 (M+H)
394CC		582 (M+H)
394DD		582 (M+H)
394EE		598 (M+H)
394FF		580 (M+H)
394GG		551 (M+H)
394HH		569 (M+H)
394II		551 (M+H)
394JJ		593 (M+H)
394KK		607 (M+H)
394LL		564 (M+H)

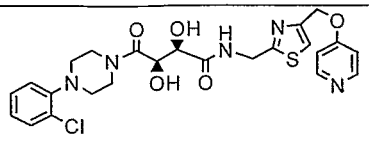
394MM		630 (M+H)
394NN		694 (M+H)
394OO		552 (M+H)
394PP		620 (M+H)
394QQ		613 (M+H)
394RR		564 (M+H)
394SS		604 (M+H)
394TT		647 (M+H)
394UU		673 (M+H)
394VV		702 (M+H)
394WW		687 (M+H)
394XX		701 (M+H)

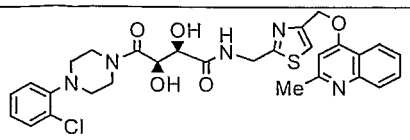
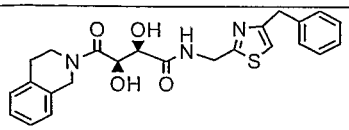
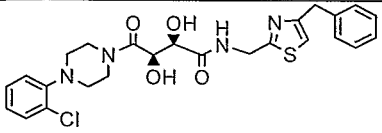
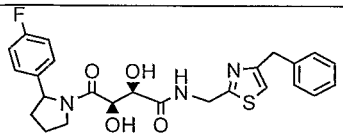
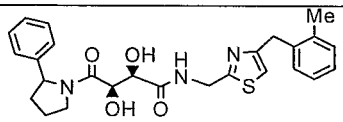
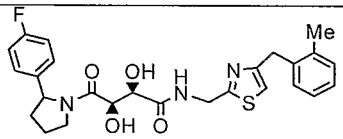
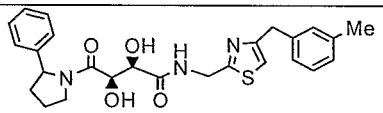
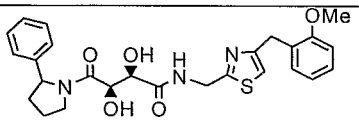
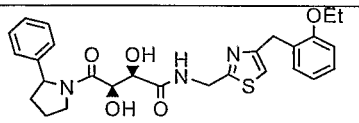
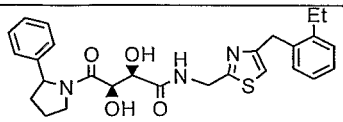
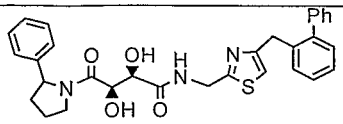
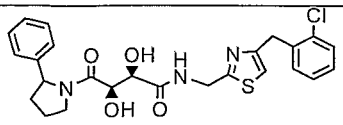
394YY		716 (M+H)
394ZZ		701 (M+H)
394AAA		661 (M+H)
394BBB		682 (M+H)

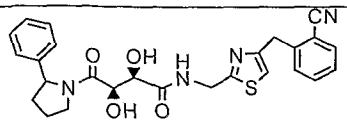
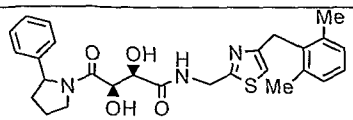
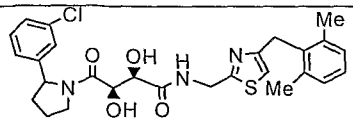
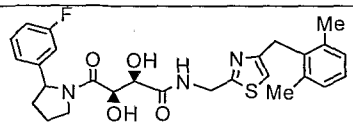
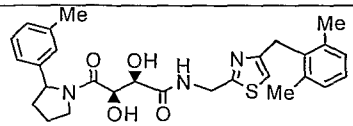
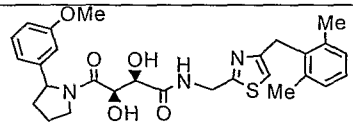
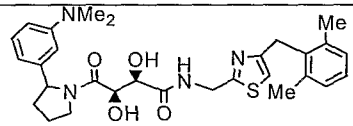
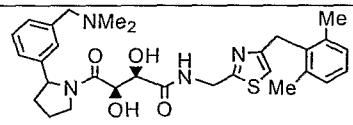
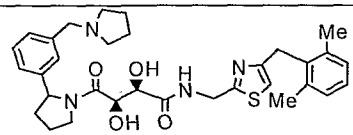
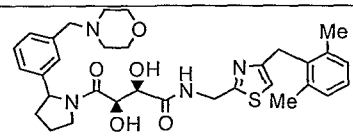
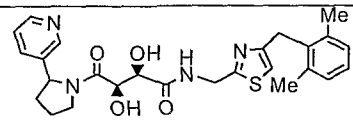
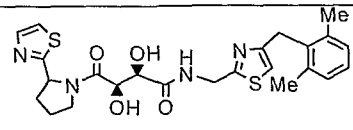
Part J:

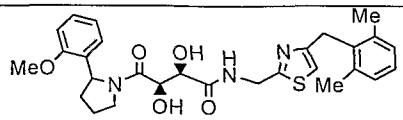
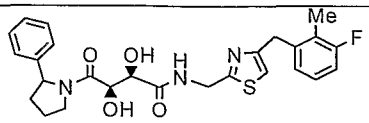
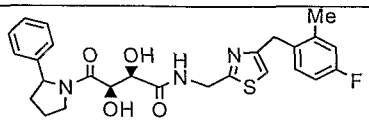
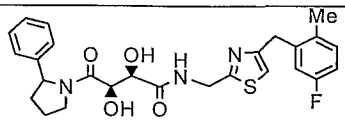
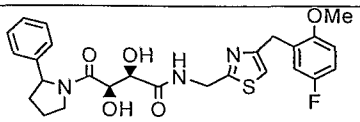
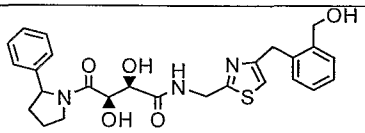
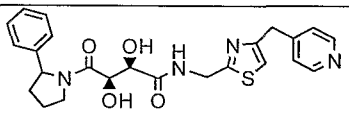
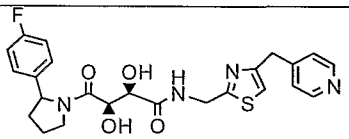
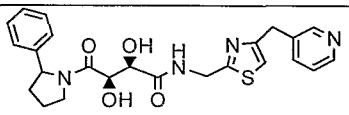
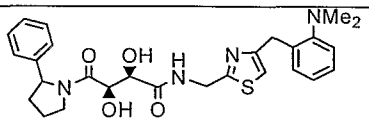
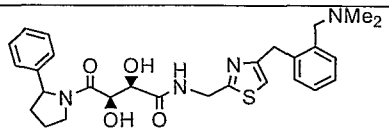
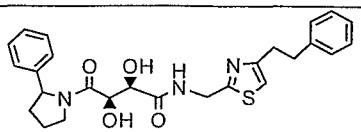
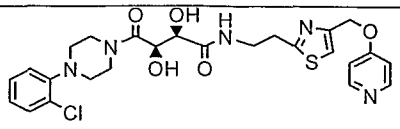
To compound **394A** (0.12 g, 0.218 mmol) dissolved in MeOH (6 mL) was added 0.5 M NaOMe in MeOH (0.044 mL, 0.0218 mmol). Stirred at room temperature for 60 mins. Added 4 N HCl in dioxane (0.055 mL, 0.218 mmol) and concentrated to give 0.10 g (100%) of the product **395** as a light yellow foam. MS m/e: 466 (M+H).

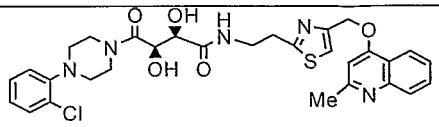
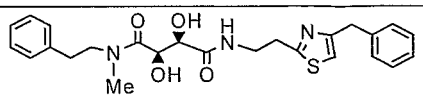
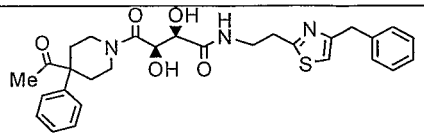
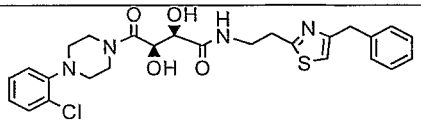
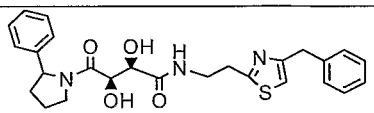
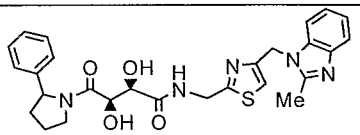
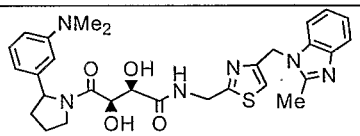
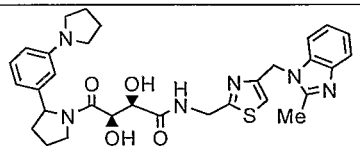
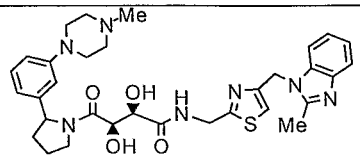
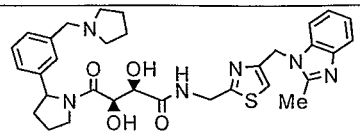
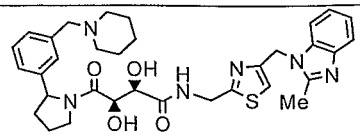
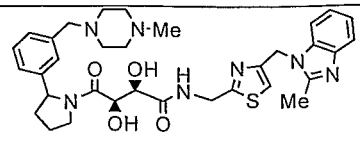
The following compounds were prepared according to the above procedure:

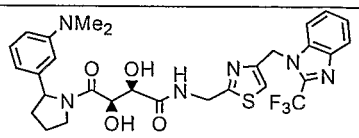
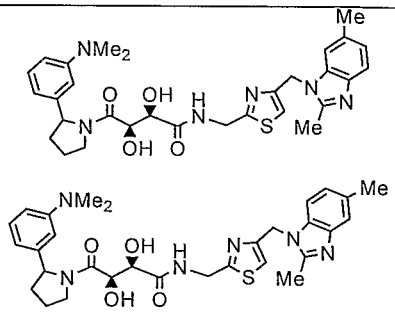
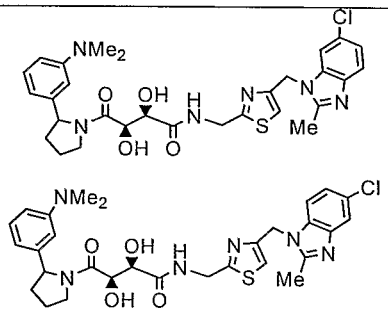
Compound #	Compound	MS
396		532 (M+H)

397		596 (M+H)
398		452 (M+H)
399		515 (M+H)
400		484 (M+H)
401		480 (M+H)
402		498 (M+H)
403		480 (M+H)
404		496 (M+H)
405		510 (M+H)
406		494 (M+H)
407		542 (M+H)
408		500 (M+H)

409		491 (M+H)
410		494 (M+H)
411		528 (M+H)
412		512 (M+H)
413		508 (M+H)
414		524 (M+H)
415		537 (M+H)
416		551 (M+H)
417		577 (M+H)
418		593 (M+H)
419		495 (M+H)
420		501 (M+H)

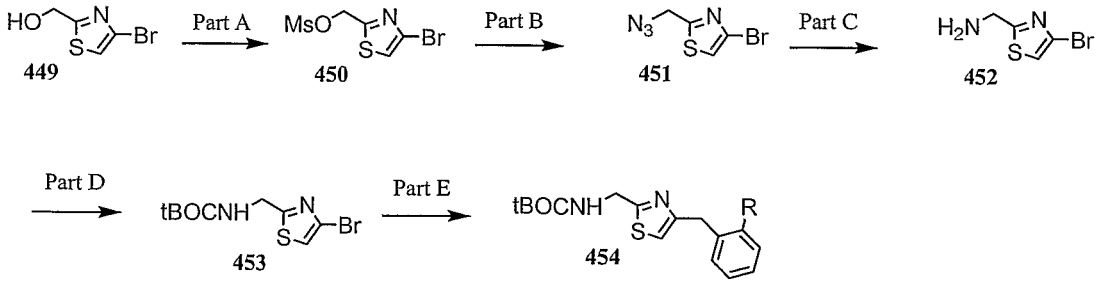
421		524 (M+H)
422		498 (M+H)
423		498 (M+H)
424		498 (M+H)
425		514 (M+H)
426		496 (M+H)
427		467 (M+H)
428		485 (M+H)
429		467 (M+H)
430		509 (M+H)
431		523 (M+H)
432		480 (M+H)
433		546 (M+H)

434		610 (M+H)
435		468 (M+H)
436		536 (M+H)
437		529 (M+H)
438		480 (M+H)
439		520 (M+H)
440		563 (M+H)
441		589 (M+H)
442		618 (M+H)
443		603 (M+H)
444		617 (M+H)
445		632 (M+H)

446		617 (M+H)
447		577 (M+H)
448		597 (M+H)

Example 9B

Scheme 1



Reference for compound **449**:

K. C. Nicolaou, N. P. King, M. R. V. Finlay, Y. He, F. Roschangar, D. Vourloumis, H. Vallberg, F. Sarabia, S. Ninkovic, D. Hepworth; *Bioorg. Med. Chem.* **1999**, *7*, 665-697.

Part A:

To compound **449** (4.86 g, 25.0 mmol) dissolved in CH_2Cl_2 (200 mL) and cooled to -30 °C was added triethylamine (5.07 g, 7.0 mL, 50.1 mmol) and then mesyl chloride (3.44 g, 2.3 mL, 30.1 mmol) dropwise via syringe. Warmed slowly to 0 °C over 60 mins. Added water (200 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated to give 6.80 g (100%) of the product **450** as an orange oil. MS m/e: 272 (M+H).

Part B:

To compound **450** (6.80 g, 25.0 mmol) dissolved in DMF (100 mL) was added sodium azide (3.25 g, 50.0 mmol) and heated at 80 °C for 2 h. Cooled to room temperature and concentrated. Added water (200 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 5% EtOAc-hexane to 10% EtOAc-hexane) to give 4.18 g (76%) of the product **451** as an orange oil. MS m/e: 219 (M+H).

Part C:

To compound **451** (4.18 g, 19.1 mmol) dissolved in 10:1 THF:water by volume (150 mL) was added triphenylphosphine (20.0 g, 76.3 mmol) and refluxed for 2 h. Cooled to room temperature and concentrated. Purified by silica gel chromatography (eluant: 3% MeOH with NH_3-CH_2Cl_2) to give 6.18 g of the product **452** (with triphenylphosphine oxide) as a yellow solid. 100% yield of product **452** would be 3.68 g. MS m/e: 194 (M+H).

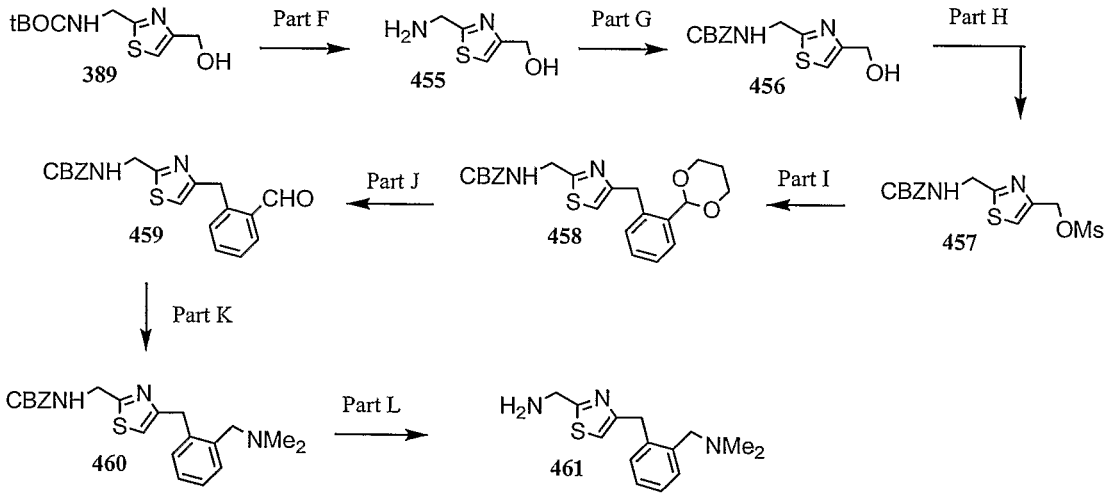
Part D:

To compound **452** (3.68 g, 19.1 mmol) dissolved in CH_2Cl_2 (100 mL) was added tBOC anhydride (5.21 g, 23.9 mmol). Stirred at room temperature for 2 h then concentrated. Purified by silica gel chromatography (eluant: 3% MeOH-CH_2Cl_2) to give 3.97 g (71%) of the product **453** as a yellow oil. MS m/e: 293 (M+H).

Part E:

To compound **453** (1.07 g, 3.65 mmol) dissolved in dry THF (10 mL) under a nitrogen atmosphere was added 2-chlorobenzylzinc chloride (0.5 M in THF, 14.6 mL, 7.30 mmol) and bis(tri-t-butylphosphine)palladium (0.14 g, 0.274 mmol). Heated at 60 °C for 2 h. Cooled to room temperature and concentrated. Added 0.2 N HCl (30 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 5% EtOAc-hexane to 15% EtOAc-hexane) to give 0.61 g (49%) of the product **454** as a yellow oil. MS m/e: 339 (M+H).

Scheme 2



Part F:

To compound **389** (2.00 g, 8.18 mmol) dissolved in MeOH (40 mL) was added 4 N HCl in dioxane (20.5 mL, 81.8 mmol). Stirred at room temperature for 3 h. Concentrated to give 1.48 g (100%) of the product **455** as a white solid. MS m/e: 145 (M+H).

Part G:

To compound **455** (1.48 g, 8.18 mmol) suspended in CH_2Cl_2 (50 mL) was added triethylamine (2.48 g, 3.4 mL, 24.5 mmol) and cooled to 0 °C. Added CBZCl (1.54 g, 1.3 mL, 9.00 mmol) dissolved in CH_2Cl_2 (10 mL) dropwise via

addition funnel. Stirred at 0 °C for 30 mins then at room temperature for 2 h. Added 0.2 N NaOH (100 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 5% MeOH-CH_2Cl_2 to 10% MeOH-CH_2Cl_2) to give 1.41 g (62%) of the product **456** as a white solid. MS m/e: 279 (M+H).

Part H:

To compound **456** (1.40 g, 5.03 mmol) dissolved in CH_2Cl_2 (40 mL) and cooled to -30 °C was added triethylamine (1.02 g, 1.4 mL, 10.1 mmol) and then mesyl chloride (0.69 g, 0.47 mL, 6.04 mmol) dropwise via syringe. Warmed slowly to 0 °C over 60 mins. Added water (50 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated to give 1.79 g (100%) of the product **457** as a yellow oil. MS m/e: 357 (M+H).

Part I:

To 2-(1,3-dioxan-2-yl)phenylmagnesium bromide (0.25 M in THF, 100 mL, 25.0 mmol) under a nitrogen atmosphere and cooled to -25 °C internal temperature was added copper cyanide (1.12 g, 12.5 mmol). Stirred at -25 °C for 1 h then at 0 °C for 1 h. Warmed to 15 °C internal temperature then recooled to -25 °C. Added compound **457** (1.78 g, 4.99 mmol) dissolved in dry THF (15 mL) dropwise via syringe. Stirred at -25 °C internal temperature for 1 h then at 0 °C for 16 h. Concentrated, added 2 N NH_4OH (100 mL) and CH_2Cl_2 (100 mL), and filtered through celite. Separated layers of filtrate, extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 10% EtOAc-hexane to 40% EtOAc-hexane) to give 1.35 g (64%) of the product **458** as a white solid. MS m/e: 425 (M+H).

Part J:

To compound **458** (1.34 g, 3.16 mmol) dissolved in CH_2Cl_2 (10 mL) was added water (2 mL) and TFA (8 mL). Stirred at room temperature for 5 h then concentrated. Added 1 N NaOH (50 mL), extracted with CH_2Cl_2, dried

combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 20% EtOAc-CH_2Cl_2 to 30% EtOAc-CH_2Cl_2) to give 1.05 g (91%) of the product **459** as a yellow oil. MS m/e: 367 (M+H).

Part K:

To compound **459** (0.74 g, 2.02 mmol) dissolved in CH_2Cl_2 (20 mL) was added dimethylamine (2 M in THF, 2.0 mL, 4.04 mmol), 3A sieves (0.60 g), glacial acetic acid (0.12 g, 0.12 mL, 2.02 mmol), then sodium triacetoxyborohydride (0.64 g, 3.03 mmol). Stirred at room temperature for 16 h. Added 0.5 N NaOH (25 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), filtered, and concentrated. Purified by silica gel chromatography (eluant: 5% MeOH with NH_3-CH_2Cl_2 to 15% MeOH with NH_3-CH_2Cl_2) to give 0.65 g (81%) of the product **460** as a yellow oil. MS m/e: 396 (M+H).

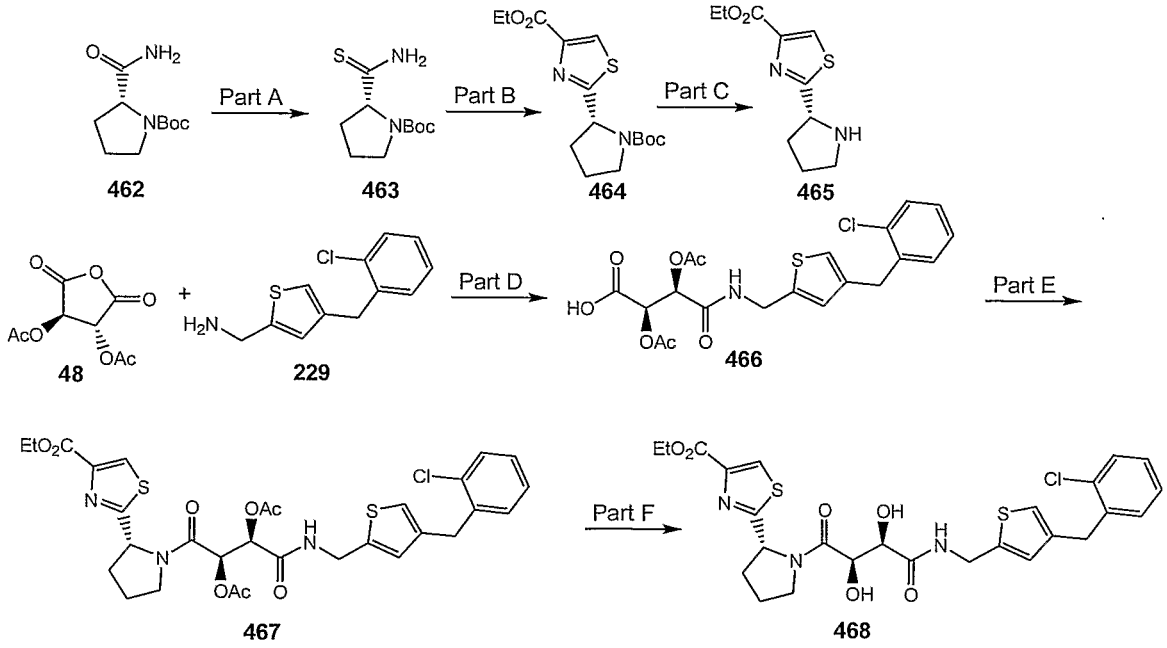
Part L:

To compound **460** (0.64 g, 1.62 mmol) dissolved in MeOH (5 mL) was added THF (2 mL) and 6.25 N NaOH (5 mL). Refluxed for 3 h. Cooled to room temperature and concentrated. Purified by silica gel chromatography (eluant: 10% MeOH with NH_3-CH_2Cl_2 to 15% MeOH with NH_3-CH_2Cl_2) to give 0.31 g (74%) of the product **461** as an orange oil. MS m/e: 262 (M+H).

Select compounds prepared using the procedures from Example 9B are exemplified in the preceding table.

Example 10: 2-Heteroaryl pyrrolidines & derivatives

Example 10A:



Part A:

To D-1-N-Boc-prolinamide **(462)** (2.5 g, 11.7 mmol) in THF (15 mL) was added Lawesson's reagent (2.36 g, 5.8 mmol) portionwise at room temperature. The reaction mixture was stirred for 3.5 hours under argon atmosphere. The solvents were removed in vacuo. Purification by column chromatography (SiO_2, 5% MeOH/DCM) afforded **463** as a light yellow solid (2.5 g, 93%).

Part B:

A mixture of **463** (500 mg, 2.15 mmol) and potassium hydrogencarbonate (1.74 g, 17.35 mmol) in DME (12 mL) was stirred for 10 minutes. Ethyl bromopyruvate (0.81 mL, 6.45 mmol) was added dropwise via a syringe to the reaction mixture. The reaction mixture was stirred for 30 minutes. The reaction mixture was cooled to 0 °C and a mixture of trifluoroacetic anhydride (1.21 mL, 8.6 mmol) and 2,6-lutidine (2.12 mL, 18.3 mmol) was added dropwise via syringe over 10 minutes. The reaction mixture was stirred for 30 minutes at 0 °C. The solvents were removed in vacuo. The residue was dissolved in chloroform, washed with 1.0 N HCl, bicarbonate solution and

brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 30% EtOAc/hexane) afforded **464** as a light yellow solid (520 mg, 74%). HPLC-MS t_R = 1.88 min ($UV_{254\ nm}$); Mass calculated for formula $C_{15}H_{22}N_2O_4S$ 326.1, observed LCMS m/z 327.1 (M+H).

Part C:

To **464** (486 mg, 1.49 mmol) in dioxane (1 mL) was added 4 N HCl in dioxane (1 mL). The reaction mixture was stirred for 1 hour at room temperature and concentrated. HPLC-MS t_R = 0.60 min ($UV_{254\ nm}$); Mass calculated for formula $C_{10}H_{14}N_2O_2S$ 226.1, observed LCMS m/z 227.1 (M+H).

Part D:

To **48** (216 mg, 1.0 mmol) in THF (2 mL) was added material from **229** (238 mg, 1 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated and freeze-dried to afford a white powder (410 mg, 90%). HPLC-MS t_R = 1.74 min ($UV_{254\ nm}$); Mass calculated for formula $C_{20}H_{20}ClNO_7S$ 453.0, observed LCMS m/z 454.0 (M+H).

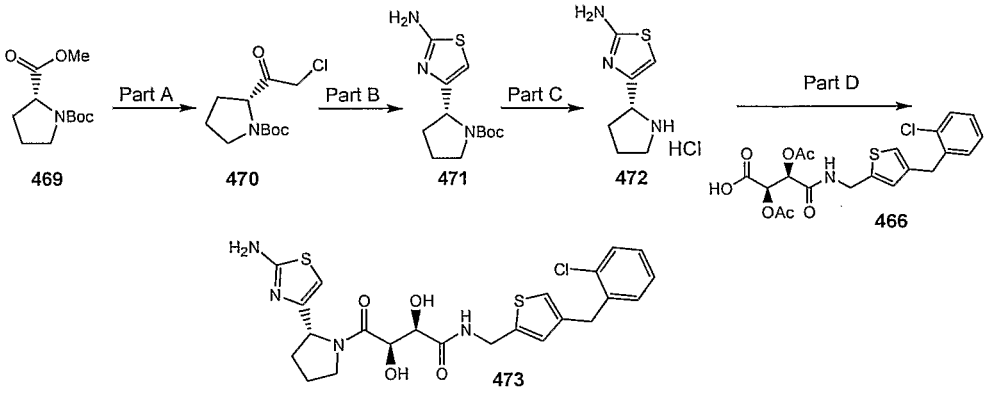
Part E:

To **465** (26 mg, 0.1 mmol) in DMF (0.5 mL) was added DIEA (35 µL, 0.2 mmol), **466** (54 mg, 0.12 mmol) in DMF (1 mL) and then HATU (57 mg, 0.15 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate (20 mL) and water (20 mL) and the layers were separated. The organic layer was washed with 0.1 N NaOH, 0.1 N HCl and brine, dried over sodium sulfate and concentrated. Compound **467** was used without further purification. HPLC-MS t_R = 2.06 min ($UV_{254\ nm}$); Mass calculated for formula $C_{30}H_{32}ClN_3O_8S_2$ 661.1, observed LCMS m/z 662.0 (M+H).

Part F:

To **467** in methanol (1 mL) was added 7.0 M ammonia in methanol (1 mL). The reaction mixture was stirred for 1 hour at room temperature and concentrated. Purification by reverse phase prep-LC afforded **468** as a white powder (2 mg). HPLC-MS t_R = 5.04 min ($UV_{254\ nm}$, 10 min); Mass calculated for formula $C_{26}H_{28}ClN_3O_6S_2$ 577.1, observed LCMS m/z 578.0 (M+H).

Example 10B:



Part A:

A solution of LDA was formed by the addition of 1.6 M *n*-butyl lithium (34 mL, 54.5 mmol) to diisopropylamine (8.47 mL, 60 mmoL) in THF (20 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 20 minutes and warmed to 0 °C gradually. The LDA solution was added dropwise to a mixture of N-Boc-D-proline methyl ester **(469)** (2.5 g, 10.9 mmol) and chloroiodomethane (3.17 mL, 43.6 mmol) in THF (20 mL) at – 78 °C via a cannula over 30 minutes. The reaction mixture was stirred at –78 °C for 30 minutes. A solution of acetic acid (15 mL) in THF (15 mL) was added slowly over 20 minutes at –78 °C. The reaction mixture was stirred for 20 minutes and then warmed to room temperature. The reaction mixture was diluted with ethyl acetate and washed with water, sodium bicarbonate solution and brine. The organic layer was dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 20% EtOAc/hexane) afforded **470** as a light brown

solid (2.0 g, 74%). HPLC-MS t_R = 1.80 min ($UV_{254\ nm}$); Mass calculated for formula $C_{11}H_{18}ClNO_3$ 247.1, observed LCMS m/z 248.1 (M+H).

Part B:

A mixture of **470** (250 mg, 1.0 mmol) and thiourea (152 mg, 2 mmol) were stirred for 72 hours. The reaction mixture was diluted with ethyl acetate and washed with sodium bicarbonate solution and brine. The organic layer was dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 80% EtOAc/hexane) afforded **471** as a white solid (201 mg, 75%). HPLC-MS t_R = 0.67 min ($UV_{254\ nm}$); Mass calculated for formula $C_{12}H_{19}N_3O_2S$ 269.1, observed LCMS m/z 270.1 (M+H).

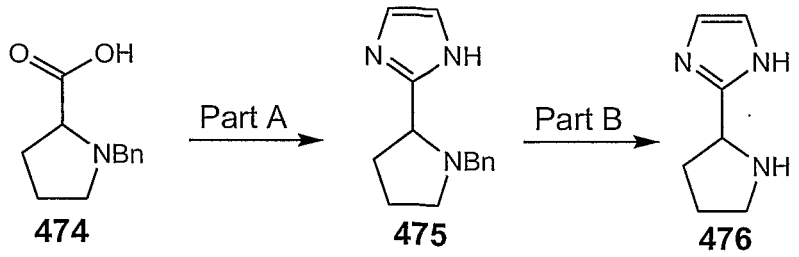
Part C:

To **471** (201 mg, 0.75 mmol) in dioxane (1 mL) was added 4 N HCl in dioxane (1 mL). The reaction mixture was stirred for 1 hour at room temperature and concentrated.

Part D:

A mixture of **466** (45 mg, 0.1 mmol), **472** (29 mg, 0.12 mmol), DIEA (50 µL, 0.28 mmol) and HATU (57 mg, 0.15 mmol) in DMF (2 mL) was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate (20 mL) and water (20 mL) and the layers were separated. The organic layer was washed with 0.1 N NaOH, 0.1 N HCl and brine, dried over sodium sulfate and concentrated. The residue was dissolved in methanol (1 mL) and 7.0 M ammonia in methanol (1 mL) was added. The reaction mixture was stirred for 1 hour at room temperature and concentrated. Purification by reverse phase prep-LC afforded **473** as a white powder. HPLC-MS t_R = 1.42 min ($UV_{254\ nm}$); Mass calculated for formula $C_{23}H_{25}ClN_4O_4S_2$ 520.1, observed LCMS m/z 521.1 (M+H).

Example 10C:



474 475 476

Part A:

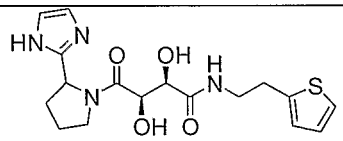
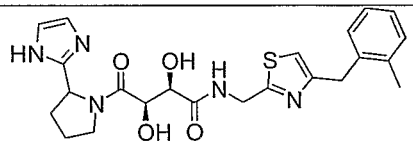
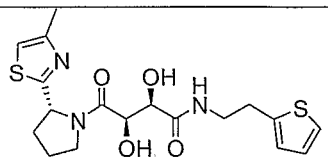
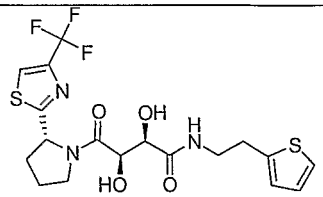
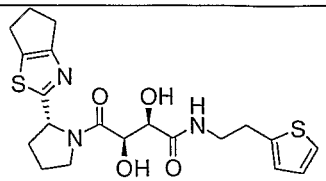
To 1-Benzyl-pyrrolidine-2-carboxylic acid **(474)** (Belokon, Y. N. at al; Tetrahedron Asymmetry **1998**, *9*, 4249-4252) in CH_2Cl_2 (20 mL) was added 2,2-dimethoxy-ethylamine (614 mg, 5.84 mmol), EDCI (1.12 g, 5.84 mmol), HOBT (658 mg, 4.87 mmol), and NMM (1.08 mL, 9.8 mmol). The reaction mixture was stirred overnight at 25 °C. Saturated aqueous $NaHCO_3$ solution (50 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (50 mL x3). The combined organic layers was washed with brine (50 mL), dried over Na_2SO_4, and concentrated by rotary evaporator to give 1-benzyl-pyrrolidine-2-carboxylic acid (2,2-dimethoxy-ethyl)-amide as yellow oil. To 1-benzyl-pyrrolidine-2-carboxylic acid (2,2-dimethoxy-ethyl)-amide was added acetic acid (10 mL) and ammonium acetate (11 g). The reaction mixture was heated to 140 °C overnight. After it was cooled down, it was poured into 100 mL ice-water with stirring. Solid $NaHCO_3$ was added in small portion with stirring to adjust the pH of the solution to 8~9. The aqueous solution was extracted with EtOAc (100 mL x2). The combined organic layers was washed with brine, dried over Na_2SO_4, and concentrated with rotary evaporator. Compound **475** (110 mg) was isolated by SiO_2 chromatography (CH_2Cl_2/MeOH/NH_3: 40:1:0.1 to 20:1:0.1). MS: m/z 228.3 $[M+H]^+$.

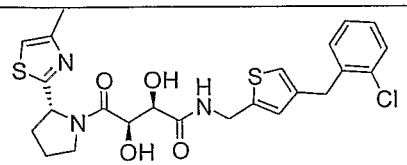
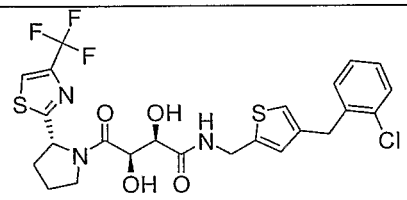
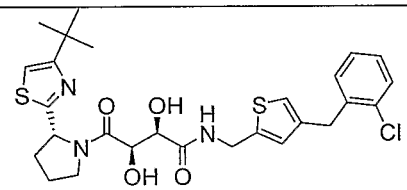
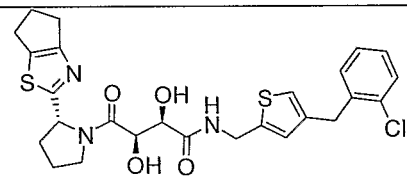
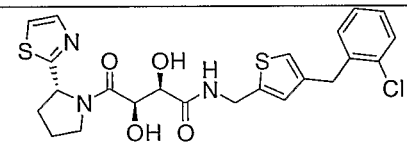
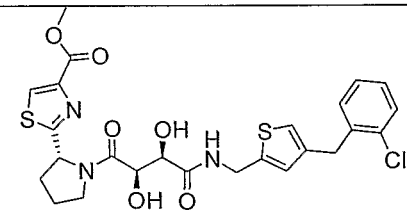
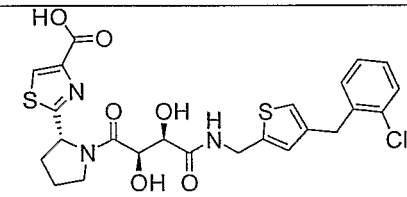
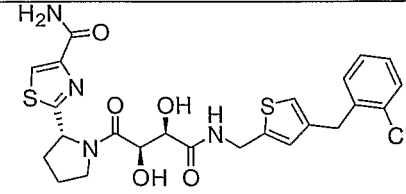
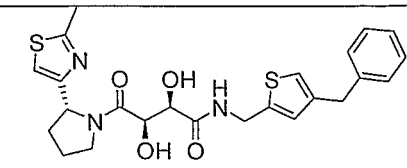
Part B: 5-Pyrrolidine-2-yl-1*H*-imidazole:

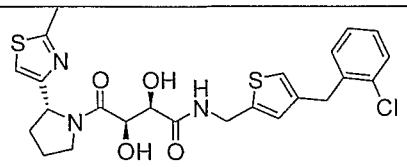
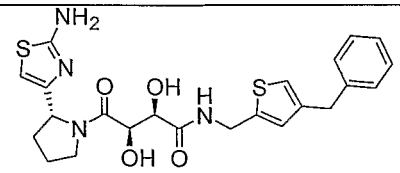
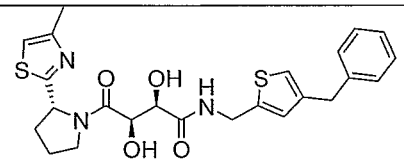
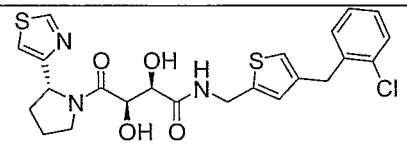
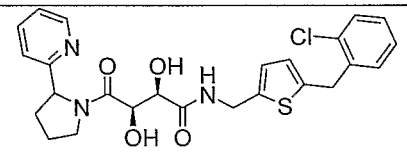
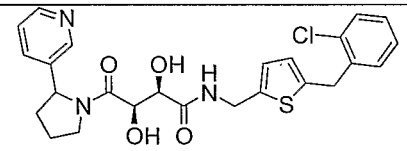
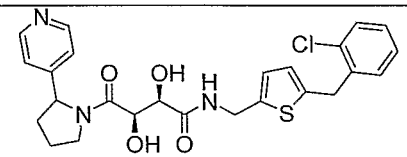
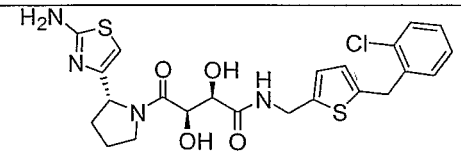
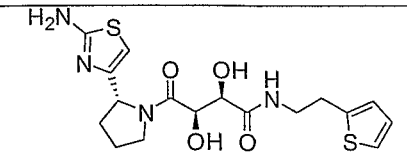
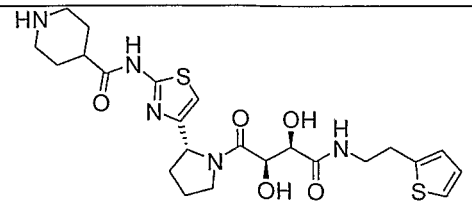
To **475** (110 mg) in 10 mL EtOH was added Pd/C (10%, 50 mg). The reaction mixture was hydrogenated under hydrogen (50 psi) for 24 hours. The solid was filtrated and the solution was evaporated by rotary evaporator to give 5-Pyrrolidine-2-yl-1*H*-imidazole (476) (67 mg). MS m/z 138.2 $[M+H]^+$.^{1}H-NMR

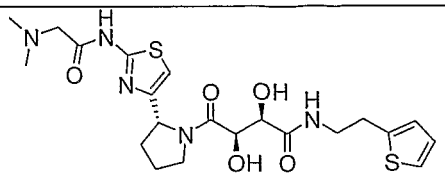
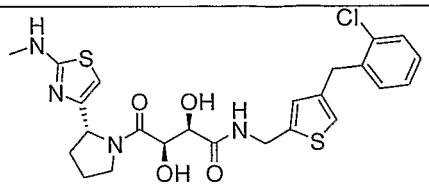
(300 MHz, $CDCl_3$): δ ppm: 6.95 (s, 2H), 4.35 (t, 1H, J = 7.4 Hz), 3.00 (m, 2H), 2.22~2.03 (m, 2H), 1.85 (m, 3H).

The following compounds were prepared by procedures described in Example 11. The 2-(pyridyl)-pyrrolidines are commericial amines (entries **495** - **497**). The amino-thiazole of **471** was further functionalized via acylation chemistry to afford **500** – **501**.

Compound #	Structure	Exact mass	MS m/z (M+H)
477		378.1	379.1
478		469.2	470.1
479		409.1	410.1
480		463.1	464.0
481		435.1	436.1

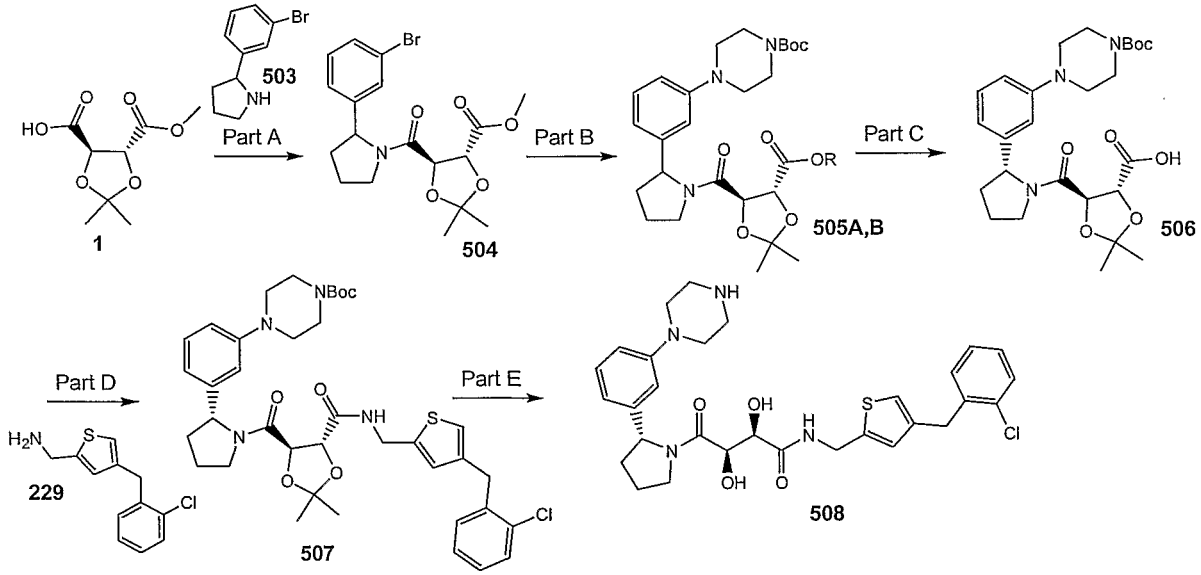
482		519.1	520.0
483		573.1	574.0
484		561.2	562.2
485		545.1	546.1
486		505.1	506.0
487		563.1	564.1
488		549.1	550.0
489		548.1	549.1
490		485.1	486.1

491		519.1	520.0
492		486.1	487.1
493		485.1	486.1
494		505.1	505.9
495		499.1	499.9
496		499.1	499.9
497		499.1	499.9
498		520.1	520.9
499		521.2	522.1
500		522.2	522.1

501		495.2	496.1
502		534.1	535.0

Example 11: 2-Phenyl pyrrolidines & derivatives

Example 11A:



Part A:

To **1** (925 mg, 4.53 mmol) in DMF (5 mL) was added 2-(3-bromophenyl)-pyrrolidine **(503)** (prepared by the method of Sorgi, K.L.; Maryanoff, C. A.; McComsey, D. F.; Graden, D. W.; Maryanoff, B. E.; *J. Am. Chem. Soc.* **1990**, *112*, 3567) (1.12 g, 4.95 mmol), DIEA (1.75 mL, 10.0 mmol) and HATU (1.88 g, 4.95 mmol). The reaction mixture was stirred overnight at room temperature. The DMF was removed in vacuo and the residue was partitioned between ethyl acetate (20 mL) and water (20 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate. The

combined organic layers were washed with sodium bicarbonate solution, 1.0 N HCl and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 10 - 20% EtOAc/DCM) afforded **504** (1.22 g, 65%). HPLC-MS t_R = 2.00 min ($UV_{254\ nm}$); mass calculated for formula $C_{18}H_{22}BrNO_5$ 411.1, observed LCMS m/z 412.2 (M+H).

Part B:

To piperazine-1-carboxylic acid tert-butyl ester (279 mg, 1.5 mmol), potassium phosphate (530 mg, 2.5 mmol), $Pd_2(dba)_3$ (23 mg, 0.025 mmol) and 2-(dicyclohexylphosphino)biphenyl (35 mg, 0.1 mmol) under argon atmosphere was added the material from Part A (414 mg, 1.0 mmol). The reaction mixture was evacuated and flushed with argon. The mixture was heated overnight at 90 °C. The reaction mixture was diluted with ethyl acetate, filtered through celite and concentrated to give a mixture of methyl ester **505A** and acid **505B** as an orange film (679 mg). The material was used without further purification. **505A**: HPLC-MS t_R = 2.08 & 2.14 min (ester, UV_{254} nm); mass calculated for formula $C_{27}H_{39}N_3O_7$ 517.3, observed LCMS m/z 518.0 (M+H). **505B**: HPLC-MS t_R = 1.83 & 1.91 min (acid, UV_{254} nm); mass calculated for formula $C_{26}H_{37}N_3O_7$ 503.3, observed LCMS m/z 504.1 (M+H)

Part C:

To the mixture of **505A** and **505B** (~1 mmol) in THF (4 mL) and water (1 mL) was added 1.0 M lithium hydroxide (1.2 mL, 1.2 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with water (10 mL) and the THF was removed in vacuo. The aqueous layer was washed with diethyl ether (3 x 10 mL), made acidic with 1.0 N HCl and extracted with ethyl acetate (3 x 10 mL). The combined ethyl acetate layers were dried over sodium sulfate and concentrated. Purification by reverse phase prep-LC afforded the desired isomer **506** (107 mg, 96% purity). HPLC-MS t_R = 1.83 min ($UV_{254\ nm}$); mass calculated for formula $C_{26}H_{37}N_3O_7$ 503.3, observed LCMS m/z 504.1 (M+H).

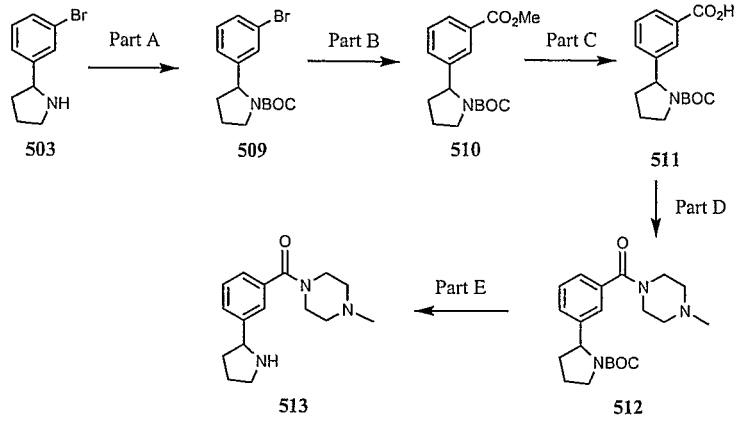
Part D:

To **506** (107 mg, 0.21 mmol) in DMF (5 mL) was added **229** (55 mg, 0.23 mmol), DIEA (80 µL, 0.46 mmol) and HATU (87 mg, 0.23 mmol). The reaction mixture was stirred overnight at room temperature. The DMF was removed in vacuo and the residue was partitioned between ethyl acetate and water. The layers were separated. The organic layer was washed with 0.1 N NaOH, 0.1 N HCl, and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 50% EtOAc/hexane) afforded **507** (98 mg, 64%). HPLC-MS t_R = 2.49 min ($UV_{254\ nm}$); mass calculated for formula $C_{38}H_{47}ClN_4O_6S$ 722.2, observed LCMS m/z 723.1 (M+H).

Part E:

To **507** (98 mg, 0.14 mmol) was added 80:20 TFA:water (4 mL) and the mixture was stirred for 4 hours at room temperature. The reaction was quenched with 1:1 acetonitrile:water (10 mL) and concentrated. The residue was dissolved in ethyl acetate and washed with sodium bicarbonate solution. To the aqueous layer was added sodium chloride and it was extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate and concentrated. The residue was dissolve in acetonitrile (2 mL) and 1.0 N HCl (0.3 mL) and concentrated. The material was lyophilized to afford **508** as the HCl salt as a white powder (75 mg, 86%). HPLC-MS t_R = 1.27 min ($UV_{254\ nm}$); mass calculated for formula $C_{30}H_{35}ClN_4O_4S$ 582.2, observed LCMS m/z 583.2 (M+H).

Example 11B



Part A

To a solution of compound **503** (5.0 g, 22.1 mmol) in dry CH_2Cl_2 (80 mL) was added di-tert-butyl dicarbonate (5.55 g, 25.4 mmol). The solution was stirred at room temperature for 2 hours. The solvent was removed by rotary evaporator. The product was isolated by silica gel chromatography (Hexane/EtOAc 5:1 to 3:1) to give compound **509** (5.7 g, 79%).

Part B

To a two neck flask was charged with compound **509** (1.0 g, 3.06 mmol), MeOH (8 mL), triethylamine (6 mL), DMF (6 mL), and $Pd(PPh_3)_2Cl_2$. A condenser with a three-way-valve on the top was attached to the flask. A balloon and a carbon monoxide tank were attached to the three-way-valve. The balloon was filled with CO and flashed the system twice. Then the balloon was filled with CO and was connected to the flask system. The flask was heated in a 80 °C oil bath for 36 hours. After cooling down to room temperature, water (50 mL) and EtOAc (100 mL) were added. The organic phase was separated, washed with water (50 mL) twice and brine, dried over Na_2SO_4, concentrated with rotary evaporator, the product was isolated with silica gel chromatography (Hexane/EtOAc 10:1 to 5:1) to give compound **510** (610 mg, 65%).

Part C

Compound **510** (384 mg, 1.26 mmol) was dissolved in dioxane/water (3:1, 4 mL) and LiOH (100 mg. 2.38 mmol) was added. The solution was stirred at room temperature for four hours. Saturated NH_4Cl solution (20 mL) was added. The aqueous phase was extracted with EtOAc (25 mL) twice. The organic phases were combined, washed with brine, dried over Na_2SO_4, concentrated by rotary evaporator, and dried under vacuum to give compound **511** (368 mg, 100%).

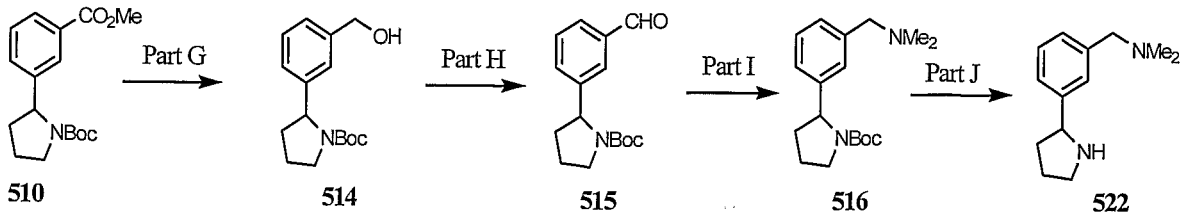
Part E

Compound **511** (76 mg, 0.26 mmol) was dissolved in dry CH_2Cl_2 (1.5 mL). N-methyl piperazine (0.035 mL, 0.31 mmol), EDCI (75 mg, 0.39 mmol), HOBT (43 mg, 0.31 mmol), and NMM (0.086 mL, 0.78 mmol) were added. The solution was stirred at room temperature for 16 hours. Saturated $NaHCO_3$ solution (5 mL) and CH_2Cl_2 (5 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (5 mL) twice. The organic phases were combined, dried over Na_2SO_4, concentrated by rotary evaporator. The product was isolated by silica gel chromatography to give compound **512** (90 mg, 92%).

Part F

Compound **512** (90 mg, 0.24 mmol) was dissolved in MeOH (1 mL) and HCl (4M in dioxane, 0.25 mL, 1 mmol) was added. The solution was stirred at room temperature for overnight. The solvent was removed by rotary evaporator to give compound **513** (83 mg, 100%).

Example 11C:



Part G:

Compound **510** (3.68 g, 12.0 mmol) was dissolved in dry THF (60 mL), and lithium borohydride (0.78 g, 36.2 mmol) was added. The solution was heated at reflux for 16 h then cooled to room temperature. MeOH (4 mL) was added, and the solvent was removed by rotary evaporator. Water (75 mL) was added, and the aqueous solution was extracted with CH_2Cl_2 (75 mL) three times. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The product was purified by silica gel chromatography (eluant: 5% MeOH-CH_2Cl_2 to 10% MeOH-CH_2Cl_2) to give 3.28 g (98%) of compound **514**. MS (m/e for M+1): 278.

Part H:

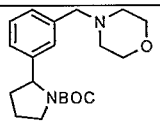
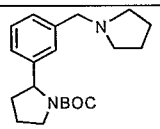
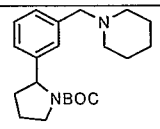
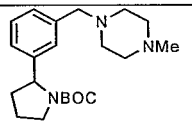
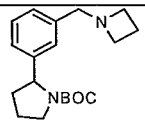
Oxalyl chloride (1.87 g, 1.3 mL, 14.7 mmol) was dissolved in dry CH_2Cl_2 (35 mL) and cooled to -78° C under a nitrogen atmosphere. DMSO (2.30 g, 2.1 mL, 29.5 mmol) dissolved in dry CH_2Cl_2 (5 mL) was added dropwise via addition funnel. The solution was stirred at -78° C for 15 mins then compound **514** (3.27 g, 11.8 mmol) dissolved in CH_2Cl_2 (15 mL) was added. The reaction mixture was stirred at -78° C for 60 mins then triethylamine (3.58 g, 4.9 mL, 35.4 mmol) was added. The reaction mixture was stirred at -78° C for 15 mins then warmed to 0° C. Water (75 mL) was added, and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (75 mL) two times. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The product was purified by silica gel chromatography (eluant: 5% EtOAc-CH_2Cl_2 to 10% EtOAc-CH_2Cl_2) to give 2.94 g (90%) of the product **515**. MS (m/e for M+1): 276.

Part I:

Compound **515** (0.50 g, 1.82 mmol) was dissolved in CH_2Cl_2 (10 mL), and 3A sieves (0.50 g), dimethylamine in THF (2 M, 1.8 mL, 3.64 mmol), glacial acetic acid (0.109 g, 1.82 mmol), and sodium triacetoxyborohydride (0.579 g, 2.73 mmol) were added. The reaction mixture was stirred at room temperature for 24 h. 1 N NaOH (25 mL) was added, and the aqueous solution was extracted

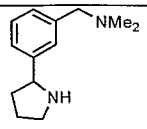
with CH_2Cl_2 (25 mL) four times. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The product was purified by silica gel chromatography (eluant: 5% MeOH-CH_2Cl_2 to 15% MeOH-CH_2Cl_2) to give 0.396 g (72%) of the product **516**. MS (m/e for M+1): 305.

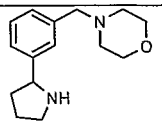
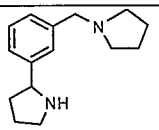
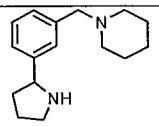
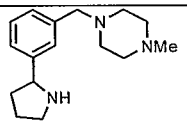
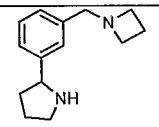
The following intermediates were also prepared.

Compound #	Intermediate	MS (m/e for M+1)
517		347
518		331
519		345
520		360
521		317

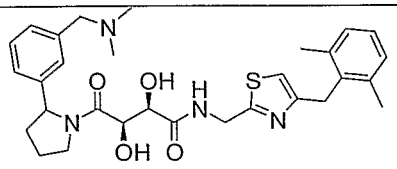
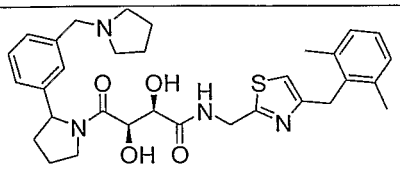
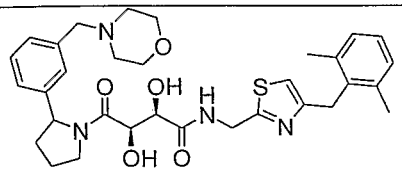
Part J:

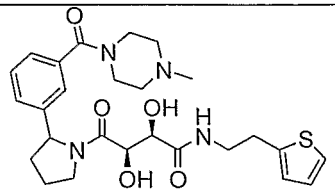
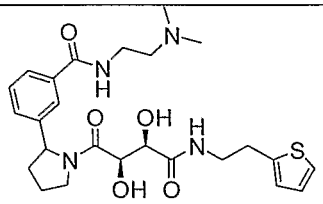
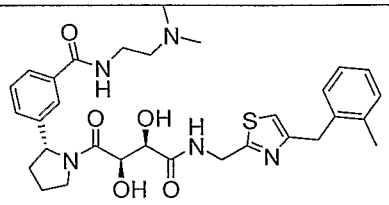
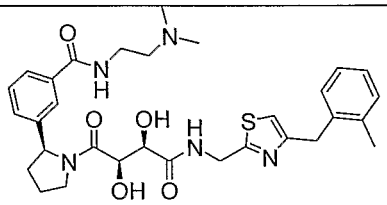
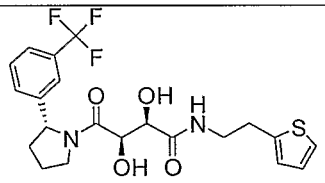
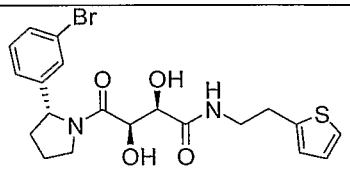
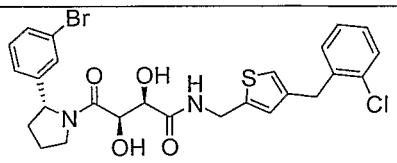
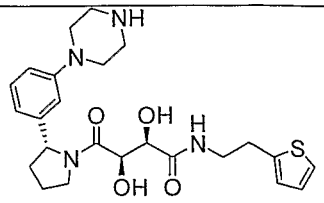
The following compounds were prepared using procedure described in Example 11B Part F.

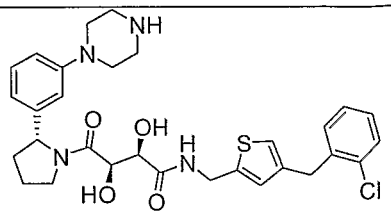
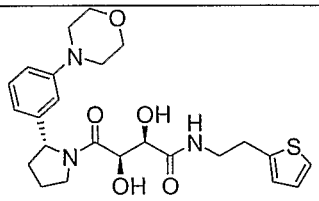
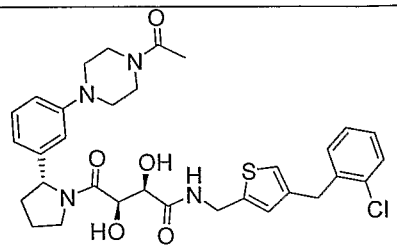
Compound #	Intermediate	MS (m/e for M+1)
522		205

523		247
524		231
525		245
526		260
527		217

The following compounds were prepared using the procedures described in Example 11.

Compound #	Structure	Exact mass	MS m/e (M+H)
416		550.3	551.3
417		576.3	577.3
418		592.3	593.3

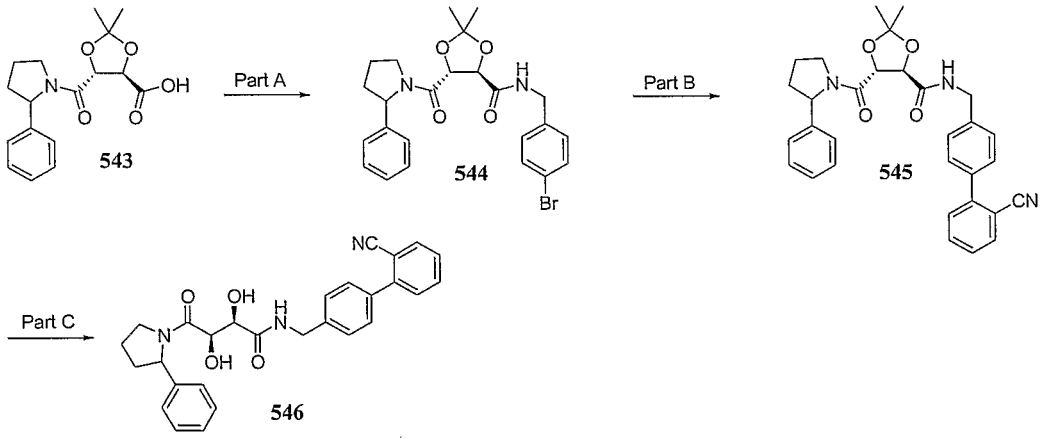
529		514.2	515.0
530		502.2	503.1
531		593.3	594.1
532		593.3	594.1
536		456.1	457.1
537		466.1	467.0
538		576.1	577.0
539		472.2	473.2

540		582.2	583.2
541		473.2	474.2
542		624.2	625.1

Example 12: Suzuki Aryl-Aryl couplings

Example 12A:

Scheme 1 Biaryl Preparation (preferred method)



Compound **543** was prepared by procedures described in Example 1.

Part A:

To a solution of **543** (1.01 g, 3.17 mmol) and 4-bromobenzyl amine (0.71 g, 3.83 mmol) in CH_2Cl_2 (10 mL) cooled to 0 °C was added DIEA (1.10 mL, 6.31

mmol) followed by PyBrOP (1.10 g, 3.43 mmol). The reaction was warmed to room temperature and stirred for 16 hours. The liquid was concentrated, and the thick oil was taken up in EtOAc. The organic layer was washed with 0.5 N $KHSO_4$ (1x), sat. $NaHCO_3$ (1x), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel chromatography (eluting 0% to 100% EtOAc/hexanes) to furnish **544** (1.27 g, 2.61 mmol, 82% yield) as a tan oil. MS m/e: 487.1 (M+H).

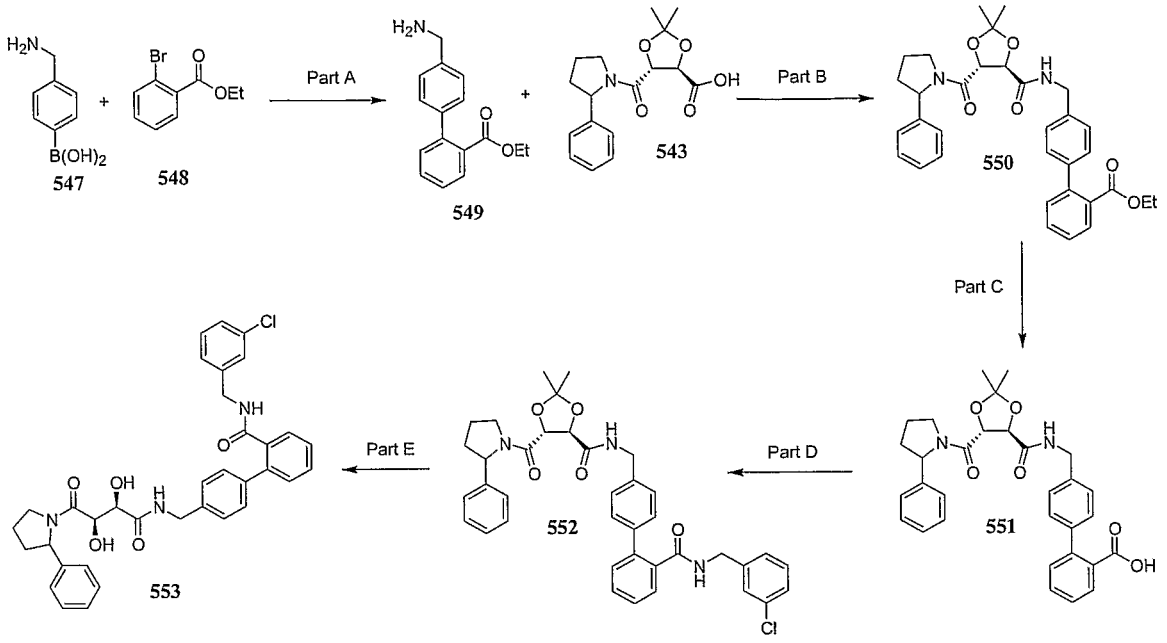
Part B:

A solution of **544** (0.105 g, 0.215 mmol), 2-cyanophenyl boronic acid (0.032 g, 0.215 mmol), and $Pd(dppf)Cl_2$ (0.016 g, 0.021 mmol) in CH_3CN (1 mL) and 1 N K_2CO_3 (1 mL) was heated in a SmithCreator microwave (2-5 mL vessel, 150 °C for 10 minutes). The mixture was concentrated and the residue was purified by silica gel chromatography (eluting 0% to 100 % EtOAc/hexanes) to furnish **545** (0.062 g, 0.12 mmol, 56% yield) as a tan oil. MS m/e: 510.1 (M+H).

Part C:

A solution of **545** (0.049 g, 0.096 mmol) in a 70% TFA/20% CH_2Cl_2/10% H_2O mixture was stirred at room temperature for 2 hours. The mixture was concentrated, and the residue was purified by reverse phase HPLC (eluting 5:95 to 95:5 CH_3CN/H_2O (0.1% HCO_2H)) to provide **546** (0.023 g, 0.049 mmol, 51% yield) as a white solid. MS m/e: 470.1 (M+H).

Example 12B:



Part A:

A solution of ethyl 2-bromobenzoate **(548)** (0.25 g, 1.1 mmol), (4-aminomethylphenyl)boronic acid **(547)** (0.20 g, 1.1 mmol), and $Pd(dppf)Cl_2$ (0.040 g, 0.055 mmol) in CH_3CN (1 mL) and 1 N K_2CO_3 (1 mL) was heated in a SmithCreator microwave (2-5 mL vessel, 100 °C for 5 minutes). The reaction was diluted with H_2O and EtOAc. The organic layer was removed, and the aqueous phase was extracted with EtOAc (3x). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel chromatography (eluting 0% to 20% CH_2Cl_2/MeOH) to furnish **549** (0.14 g, 0.55 mmol, 50 % yield) as a brown oil. MS m/e: 256.1 (M+H).

Part B:

To a solution of **549** (0.21 g, 0.82 mmol) and **543** (0.19 g, 0.59 mmol) in CH_2Cl_2 (5 mL) cooled to 0 °C was added DIEA followed by PyBrOP. The reaction was stirred for 20 hours gradually warming to room temperature. The mixture was concentrated, and the brown oil was taken up in EtOAc. The organic phase was washed with 0.5 N $KHSO_4$ (1x), sat. $NaHCO_3$ (1x), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel

chromatography (eluting 0% to 100% EtOAc/hexanes) to furnish **550** (0.29 g, 0.51 mmol, 87% yield) as a brown oil. MS m/e: 557.1 (M+H).

Part C:

To a solution of **550** (0.26 g, 0.47 mmol) in a THF (2 mL)/MeOH (2 mL)/H_2O (1 mL) mixture was added $LiOH•H_2O$ (0.052 g, 1.24 mmol) in one solid portion. The reaction was stirred overnight and then acidified to pH ~ 3 with 1N HCl. After dilution with EtOAc, the organic layer was removed, and the aqueous phase was extracted with EtOAc (3x). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by reverse phase HPLC (eluting 10:90 to 100:0 CH_3CN/H_2O (0.1% HCO_2H) to furnish **551** (0.22 g, 0.38 mmol, 88 % yield). MS m/e: 529.1 (M+H).

Part D:

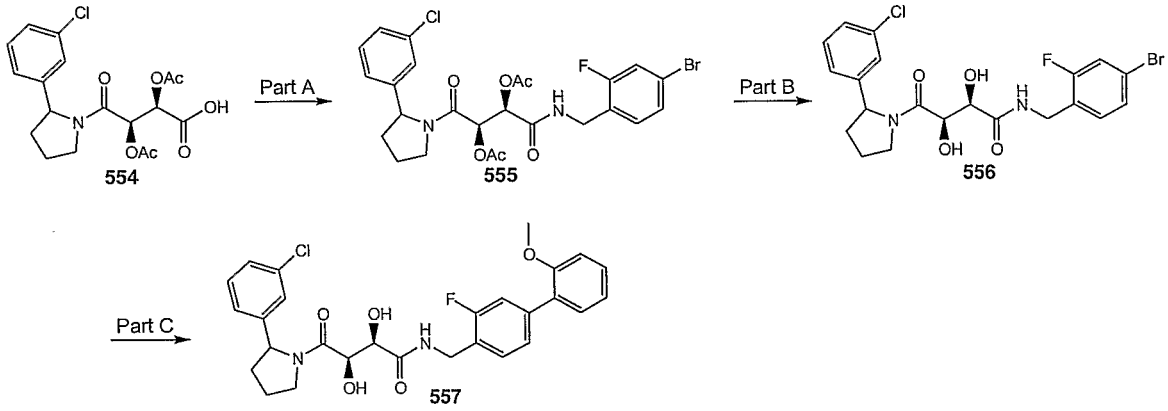
To a solution of **551** (55 mg, 0.104 mmol) in CH_2Cl_2 (1 mL) was added polystyrene-bound HOBt (109 mg, 0.095 mmol), DIC (0.067 mL, 0.427 mmol), and DMAP (7 mg, 0.057 mmol) and was shaken overnight. The mixture was filtered, then washed with DMF (3 x 3 mL), CH_2Cl_2 (3 x 3 mL), DMF (3 x 3 mL), and THF (3 x 3 mL). The resin was dried under vacuum overnight. To the dried resin-bound acid (82 mg, 0.034 mmol) was added 3-chlorobenzylamine (8.33 µL, 0.068 mmol) in CH_2Cl_2 (1 mL) and the mixture was shaken overnight. To the mixture was added polystyrene-bound isocyanate resin (70 mg, 0.102 mmol) and shaken for 5 hours. Filter the desired product and wash the filtrate with CH_2Cl_2 (3 x 3 mL) and THF (3 x 3 mL). Concentrate the organic portions *in vacuo* to afford **552** (14.6 mg, 0.022 mmol, 66 % yield). MS m/e: 652.2 (M+H).

Part E:

To **552** (14.6mg, 0.022 mmol) was added a 2 mL of a mixture of TFA/CH_2Cl_2/H_2O (7/2/1) and stirred at room temperature for 2 h. The mixture was concentrated *in vacuo*. The mixture was purified via reverse-phase

HPLC to furnish **553** (3.7 mg, 0.006 mmol, 27 % yield). MS m/e: 612.1 (M+H).

Example 12C:



Compound **554** was prepared by the procedure desribed in Example 4 Part C. HPLC-MS t_R = 1.39 min ($UV_{254\ nm}$); mass calculated for formula $C_{14}H_{16}ClNO_5$ 397.1, observed LCMS m/z 398.1 (M+H).

Part A:

To **554** (355 mg, 0.89 mmol) in DMF (5 mL) was added 2-fluoro-4-bromobenzylamine hydrochloride (257 mg, 1.07 mmol), DIEA (530 uL, 3.03 mmol) and HATU (407 mg, 1.07 mmol). The reaction was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with EtOAc. The combined organic layers were washed with 0.1 N NaOH, 0.1 N HCl, and brine; dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 80% ethyl acetate/hexanes) afforded **555** as a foam (320 mg, 62%). HPLC-MS t_R = 2.03 min ($UV_{254\ nm}$); mass calculated for formula $C_{25}H_{25}BrClFN_2O_6$ 582.1, observed LCMS m/z 583.0 (M+H).

Part B:

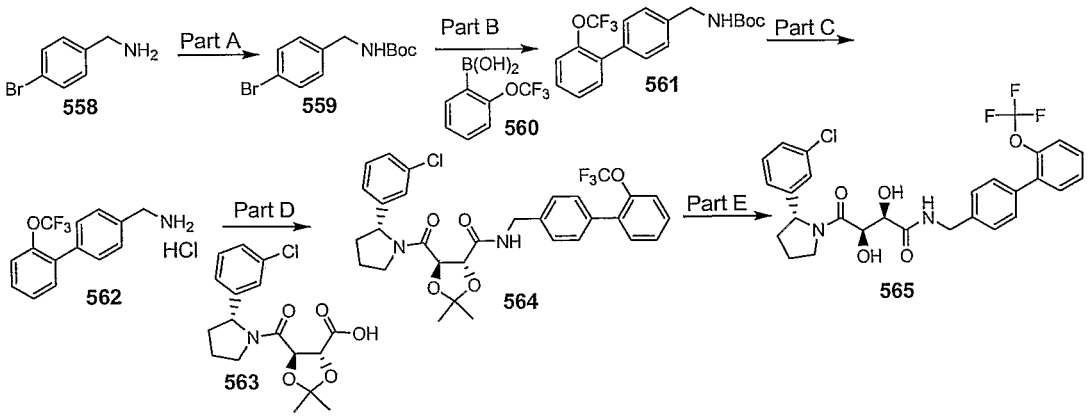
To **555** (320 mg, 0.55 mmol) in MeOH (5 mL) was added anhydrous hydrazine (28 µL, 0.88 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated in vacuo and lypholized to afford **556** as a white powder (275 mg, 100%). HPLC-MS t_R =

1.81 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{21}BrClFN_2O_4$ 498.0, observed LCMS m/z 499.0 (M+H).

Part C:

Compound **556** (46 mg, 0.092 mmol) in dioxane (1 mL) was added to a solution of 2-methoxyphenyl boronic acid (22 mg, 0.14 mmol), potassium phosphate (42 mg, 0.2 mmol), and $PdCl_2$(dppf) (4 mg, 0.005 mmol) under argon atmosphere. The reaction mixture was heated to 80 °C overnight. After cooling the mixture was filtered through celite and the pad was rinsed with ethyl acetate. The filtrate was concentrated. Purification by reverse phase prep-LC afforded **557** as a white solid (26 mg) after lypholization. HPLC-MS t_R = 1.97 min ($UV_{254\ nm}$); mass calculated for formula $C_{28}H_{28}ClFN_2O_5$ 526.2, observed LCMS m/z 527.0 (M+H).

Example 12D:



Part A:

A mixture of 4-bromo-benzylamine hydrochloride **(558)** (1.0 g, 4.5 mmol), di-*tert*-butyl dicarbonate (1.48 g, 6.8 mmol) and DIEA (2.4 mL, 13.8 mmol) in chloroform (40 mL) was stirred overnight at room temperature. The reaction mixture was washed with 1.0 N HCl, water and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 20% ethyl acetate/hexane) afforded a mixture of **559** (1.17 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, 2H, J = 8.8 Hz), 7.15 (d, 2H, J = 8.8 Hz), 4.85 (bs, 1H), 4.27 (d, 2H, J = 5.7 Hz), 1.48 (s, 9H).

Part B:

A mixture of **559** (100 mg, 0.35 mmol), **560** (107 mg, 0.52 mmol) potassium phosphate (223 mg, 1.05 mmol) and $PdCl_2$(dppf) (14 mg, 0.018 mmol) in dioxane (5 mL) was under argon atmosphere was heated to 80 °C overnight. The reaction mixture was cooled and filtered through celite. The celite pad was washed with ethyl acetate. The filtrate was washed with saturated sodium bicarbonate, water and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 20% ethyl acetate/hexane) afforded slightly impure **561** (146 mg). HPLC-MS t_R = 2.35 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{20}F_3NO_3$ 367.1, observed LCMS m/z 390.1 (M+Na).

Part C:

Compound **561** (129 mg, 0.35 mmol) in 3:1 DCM:TFA (4 mL) was stirred for 1 hour. The residue was dissolved in DCM (5 mL) and concentrated. The residue was dissolved in diethyl ether (20 mL) and treated with 1.0 M HCl in diethyl ether (2 mL). The resulting white solid was collected by filtration and washed with diethyl ether to afford **562** (90 mg, 85% 2 steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.3 (bs, 3H), 7.50 (m, 8H), 4.09 (s, 2H).

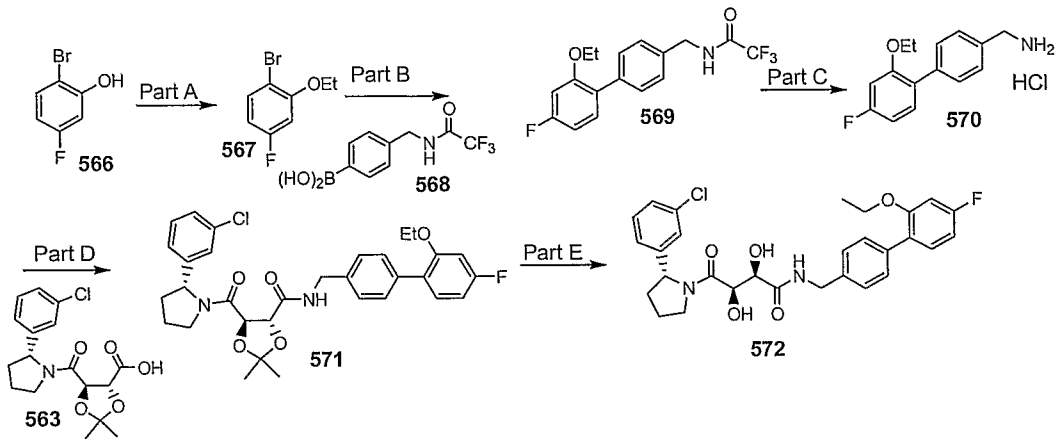
Part D:

Compound **563** was prepared using procedures similar to those described in Example 11A. Compound **564** was prepared from **562** and **563** using procedures similar to those described in Example 1 Part A. HPLC-MS t_R = 2.49 min ($UV_{254\ nm}$); mass calculated for formula $C_{31}H_{30}ClF_3N_2O_5$ 602.2, observed LCMS m/z 603.2 (M+H).

Part E:

Compound **565** was prepared using the procedures described in Example 1 Part B. HPLC-MS t_R = 2.16 min ($UV_{254\ nm}$); mass calculated for formula $C_{28}H_{26}ClF_3N_2O_5$ 562.2, observed LCMS m/z 563.0 (M+H).

Example 12E:



Part A:

To 2-bromo-5-fluoro-phenol **(566)** (2.28 g, 11.94 mmol) in DMF (15 mL) was added iodoethane (1.16 mL, 14.32 mmol) and cesium carbonate (4.28 g, 13.13 mmol). The reaction mixture was stirred for 72 hours. The mixture was filtered and the DMF was removed in vacuo. The residue was partitioned in ethyl acetate and water. The layers were separated and the organic layer was washed with water and brine, dried over sodium sulfate and concentrated to afford **567** (1.76 g, 67%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, 1H, J = 6.3, 8.8 Hz), 6.62 (dd, 1H, J = 2.7, 10.5 Hz), 6.57 (m, 1H, J = 2.7), 4.08 (q, 2H, J = 6.9 Hz), 1.50 (t, 3H, J = 7.0 Hz).

Part B:

Compound **569** (607 mg, 58%) was prepared from **567** and **568** (prepared by the procedures of Maku, S. et. al. (*J. Comb. Chem.* **2003**, 5, 379)) using the procedures described in Example 12D Part B. HPLC-MS t_R = 2.13 min ($UV_{254\ nm}$); mass calculated for formula $C_{17}H_{15}F_4NO_2$ 341.1, observed LCMS m/z 342.1 (M+H).

Part C:

To **569** (607 mg, 1.78 mmol) in methanol (6 mL) was added 10% potassium carbonate in 2:1 methanol:water (20 ml). To obtain a clear solution additional water (5 mL) was added. The reaction mixture was stirred overnight at room

temperature. The methanol was removed in vacuo. The residue was portioned between water and ethyl acetate. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated. The residue was dissolved in diethyl ether (20 mL) and treated with 1.0 M HCl in diethyl ether (5 mL). The resulting white solid was collected by filtration and washed with diethyl ether to afford **570** (377 mg, 75%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (bs, 3H), 7.49 (m, 4H), 7.29 (dd, 1H, J = 6.9, 8.3 Hz), 7.00 (dd, 1h J = 2.5, 11.4 Hz), 6.83 (dt, 1H, J = 2.8, 8.6, 10.8Hz) 4.05 (m, 4H), 1.27 (t, 3H, J = 6.5 Hz).

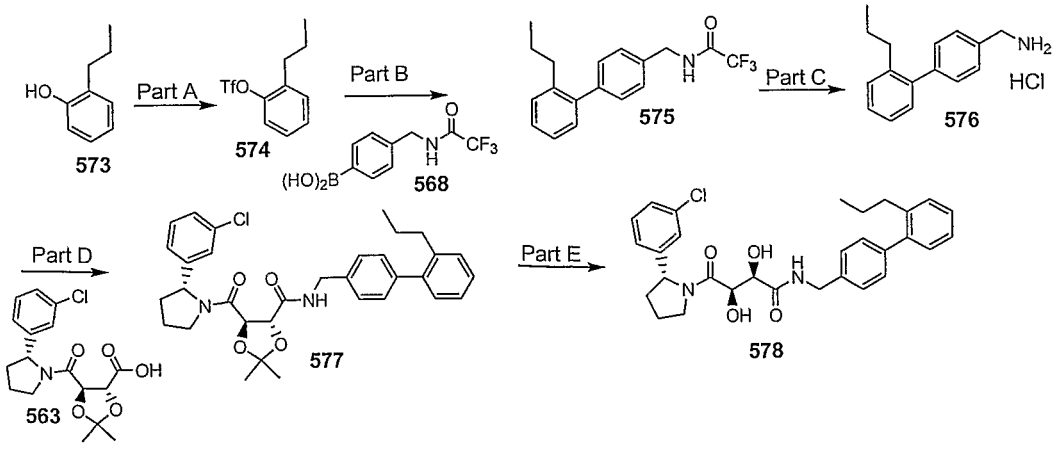
Part D:

Compound **571** was prepared using procedures described in Example 12E Part D. Purification by column chromatography (SiO_2, 20% ethyl acetate/hexane) afforded **571** (104 mg, 95%). HPLC-MS t_R = 2.40 min ($UV_{254\ nm}$); mass calculated for formula C32H34ClFN2O5 580.2, observed LCMS m/z 581.2 (M+H).

Part E:

Compound **572** was prepared using the procedures described in Example 12D Part E. HPLC-MS t_R = 2.06 min ($UV_{254\ nm}$); mass calculated for formula $C_{29}H_{30}ClFN_2O_5$ 540.2, observed LCMS m/z 541.2 (M+H).

Example 12F:



Part A:

To a mixture of 2-propyl phenol **(573)** (0.5 mL, 3.63 mmol) and DIEA (0.950 mL, 5.45 mmol) in DCM (20 mL) at 0 °C was added triflic anhydride (0.734 mL, 4.36 mmol) in DCM (10 mL) via an addition funnel. The reaction mixture was stirred for 45 minutes. The mixture was poured into water. The layers were separated and the organic layer was washed with saturated sodium bicarbonate solution and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 5% ethyl acetate/hexane) afforded **574** (916 mg, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 2H), 7.26 (m, 2H), 2.70 (m, 2H), 1.68 (m, 2H), 1.00 (t, 3H, J = 7.3 Hz).

Part B:

Compound **575** (288 mg, 89%) was prepared using the procedures described in Example 12D Part B and a reaction temperature of 100 °C. HPLC-MS t_R = 2.30 min ($UV_{254\ nm}$); mass calculated for formula $C_{18}H_{18}F_3NO$ 321.1, observed LCMS m/z 322.2 (M+H).

Part C:

Compound **576** (203 mg, 86%) was prepared using the procedure described in Example 12E Part C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (bs, 3H), 7.52 (d, 2H, J = 8.0 Hz), 7.32 (d, 2H, J = 8.1 Hz), 7.31 (m, 2H), 7.22 (m, 1H), 7.10 (d, 1H, J = 7.1 Hz), 4.08 (s, 2H,) 2.54 (m, 2H), 1.44 (m, 2H), 0.75 (t, 3H, J = 7.7 Hz).

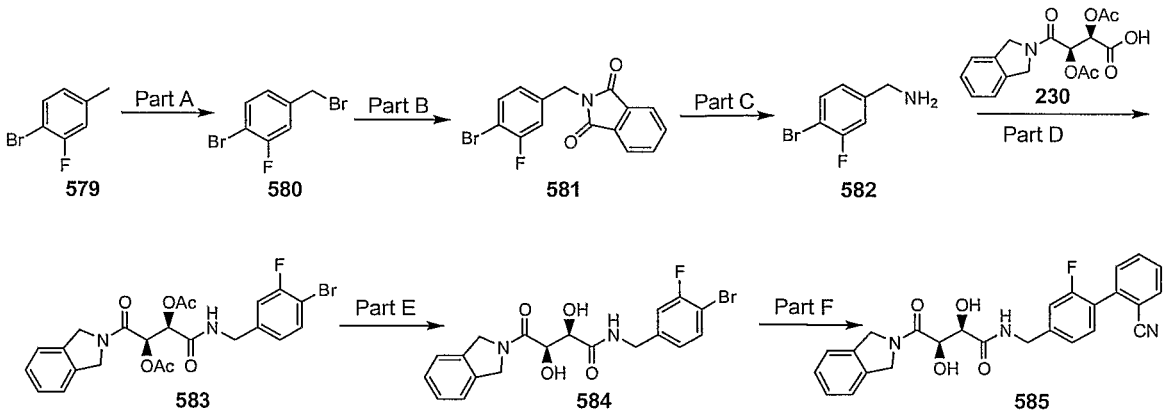
Part D:

Compound **577** (62 mg, 92%) was prepared according to the procedure described in Example 12D Part D. HPLC-MS t_R = 2.55 min ($UV_{254\ nm}$); mass calculated for formula $C_{33}H_{37}ClN_2O_4$ 560.2, observed LCMS m/z 561.2 (M+H).

Part E:

Compound **578** (53 mg, 93%) was prepared according to the procedure described in Example 12D Part E. . HPLC-MS t_R = 2.21 min ($UV_{254\ nm}$); mass calculated for formula $C_{30}H_{33}ClN_2O_4$ 520.2, observed LCMS m/z 521.2 (M+H).

Example 12G:



Part A:

A mixture of 4-bromo-3-fluoro-toluene **(579)** (2.0 mL, 15.8 mmol), N-bromosuccinimide (3.38 g, 19.0 mmol) and benzoylperoxide (48 mg, 0.2 mmol) in carbon tetrachloride (50 mL) was heated to reflux under a nitrogen atmosphere for 16 hours. The reaction mixture was cooled and filtered. The filtrate was washed with water (2x), saturated sodium bicarbonate solution and brine, dried over sodium sulfate and concentrated to afford a mixture of **580** and dibromonated product (4.02 g). The material was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, 1H, J = 6.6, 7.6 Hz), 7.17 (dd, 1H, J = 2.0, 8.9 Hz), 7.11 (dd, 1H, J = 2.0, 8.2 Hz), 4.42 (s, 2H).

Part B:

A mixture of **580** (4.02 g, 15.0 mmol), phthalimide (2.65 g, 18 mmol) and cesium carbonate (5.38 g, 16.5 mmol) in DMF (30 mL) was stirred for 72 hours. The reaction mixture was poured into water (100 mL) and extracted with ethyl acetate. The combined organic layers were washed with water (3X) and brine, dried over sodium sulfate and concentrated. Recrystallization from 30% ethyl acetate/hexanes afforded slightly impure **581** (3.28 g) as a yellow

solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (m, 2H), 7.74 (m, 2H), 7.49 (dd, 1H, J = 7.3, 8.4 Hz), 7.20 (dd, 1H, J = 1.9, 9.3 Hz), 7.06 (dd, 1H, J = 2.0, 7.9 Hz), 4.80 (s, 2H).

Part C:

A mixture of **581** (1.00 g, 3.0 mmol) and hydrazine monohydrate (580 uL, 12.0 mmol) in ethanol (25 mL) was heated to reflux for 1 hour. The reaction mixture was diluted with ethyl acetate and filtered. The precipitate was washed with ethyl acetate. The filtrate was concentrated and the residue was dissolved in water and ethyl acetate. The layers were separated. The organic layer was washed with saturated sodium bicarbonate solution, water and brine, dried over sodium sulfate and concentrated to afford **582** (375 mg) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (t, 1H, J = 8.5 Hz), 7.12 (dd, 1H, J = 2.2, 9.5 Hz), 6.99 (dd, 1H, J = 1.6, 8.2 Hz), 3.86 (s, 2H).

Part D:

Compound **583** was prepared using procedures similar to those described in Example 12C Part A. HPLC-MS t_R = 1.82 min ($UV_{254\ nm}$); mass calculated for formula $C_{23}H_{22}BrFN_2O_6$ 520.0, observed LCMS m/z 521.0 (M+H).

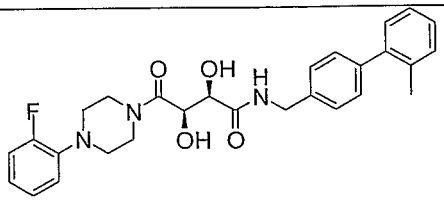
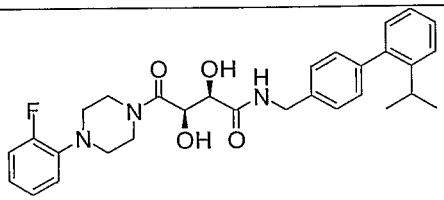
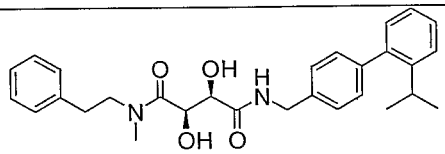
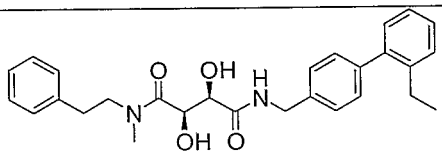
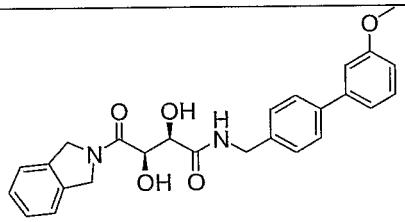
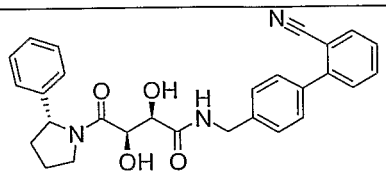
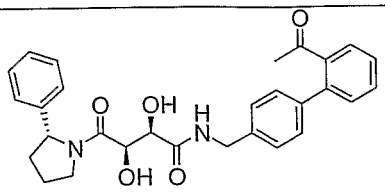
Part E:

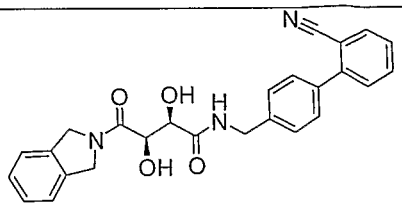
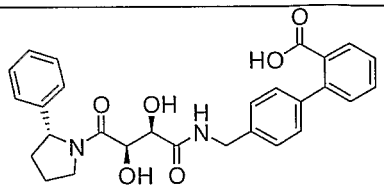
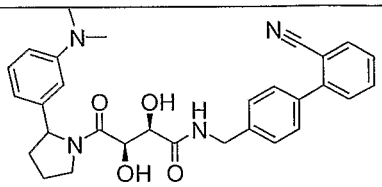
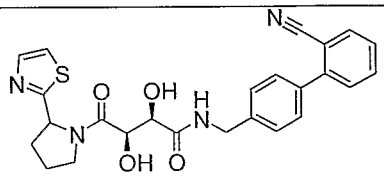
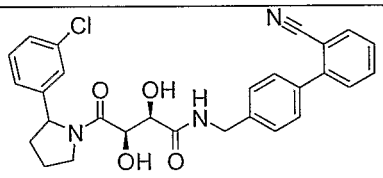
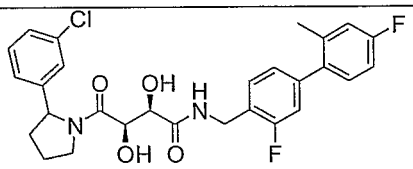
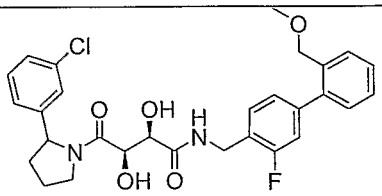
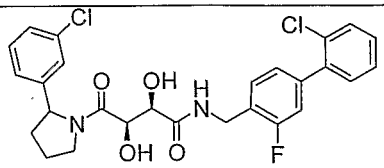
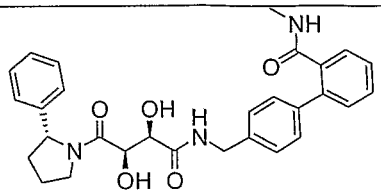
Compound **584** was prepared using the procedures described in Example 12C Part B. HPLC-MS t_R = 1.81 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{18}BrFN_2O_4$ 436.0, observed LCMS m/z 437.0 (M+H).

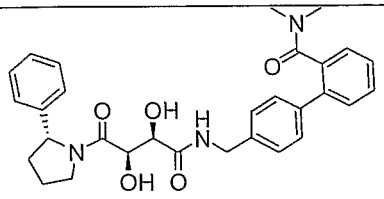
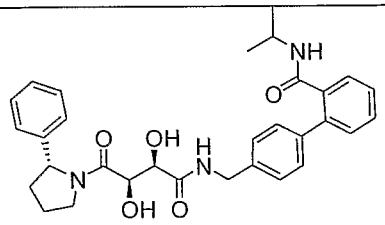
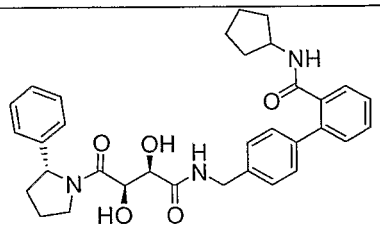
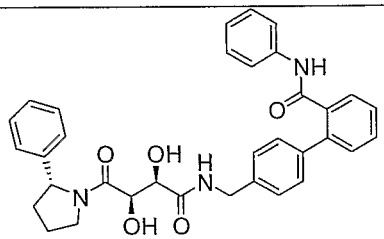
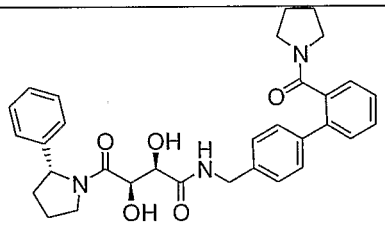
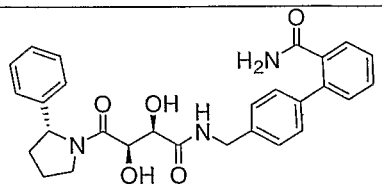
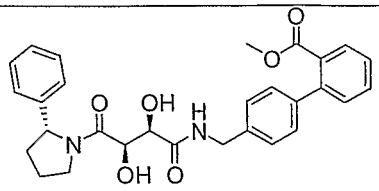
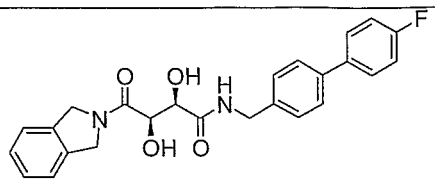
Part F:

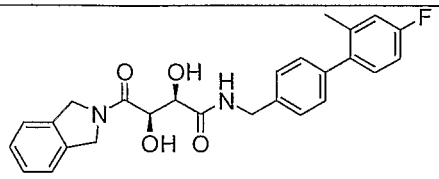
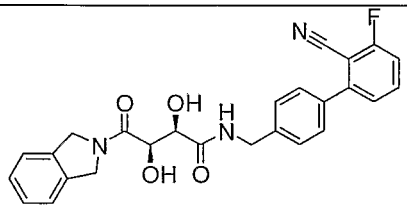
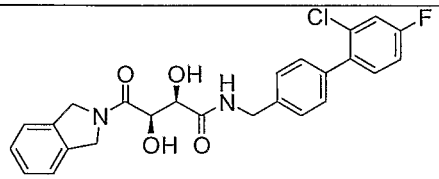
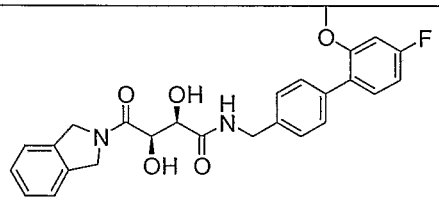
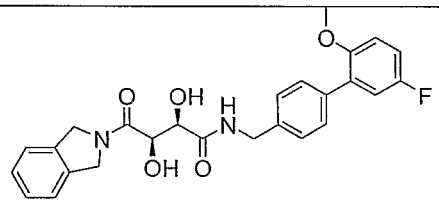
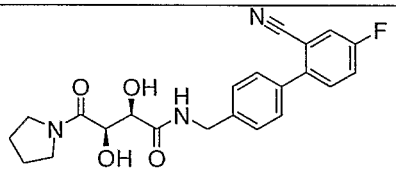
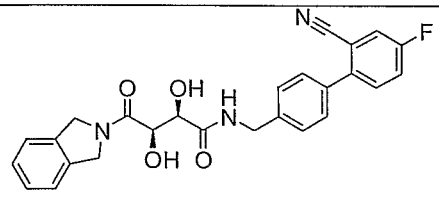
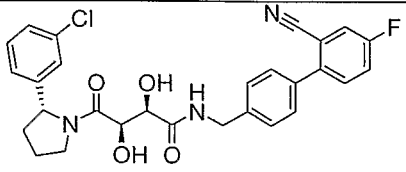
Compound **585** was prepared using procedures similar to those described in Example 12C Part C. HPLC-MS t_R = 4.12 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{26}H_{22}FN_3O_4$ 459.2, observed LCMS m/z 460.1 (M+H).

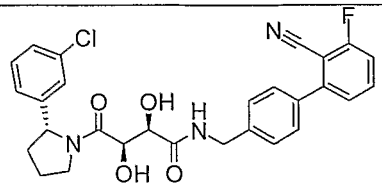
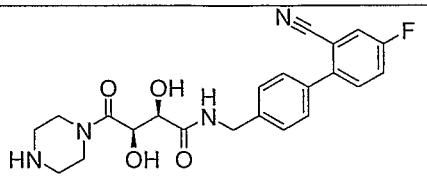
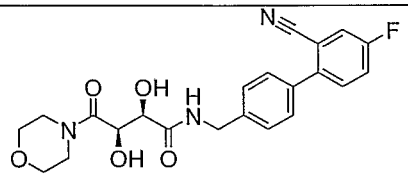
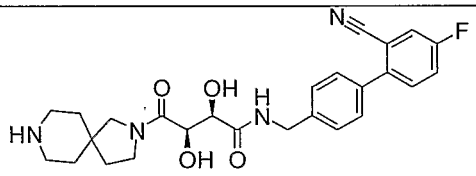
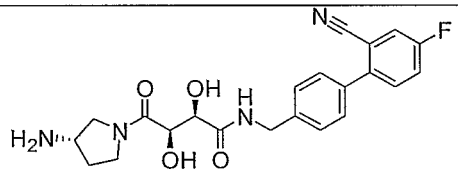
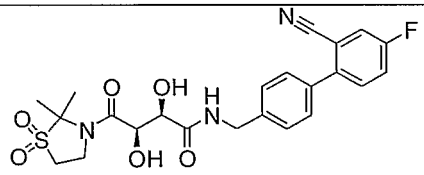
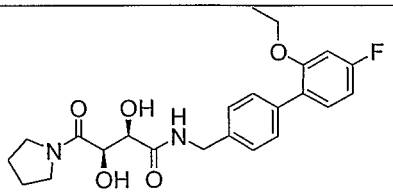
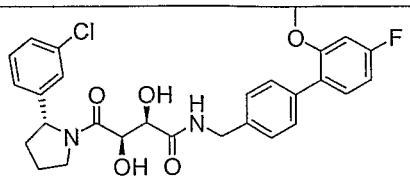
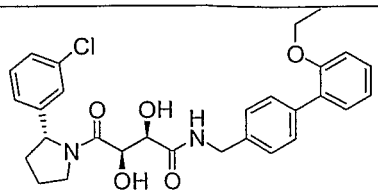
The following table contains compounds prepared using the procedures described in Example 12 A – G.

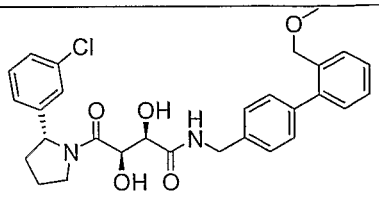
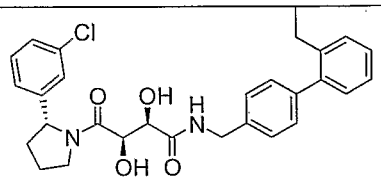
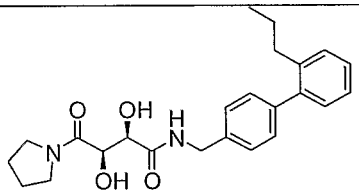
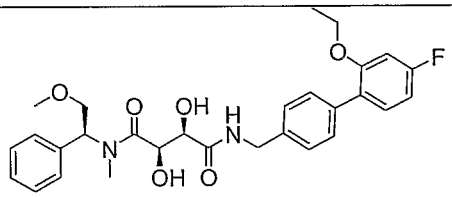
Compound #	Structure	Exact mass	MS m/e (M+H)
586		491.2	492.2
587		519.3	520.3
588		474.3	475.3
589		460.2	461.2
590		446.2	447.2
591		469.2	470.1
592		486.2	487.1

593		441.2	442.1
594		488.2	489.1
595		512.2	513.3
596		476.2	477.2
597		503.2	504.2
598		528.2	529.2
599		540.2	541.2
600		530.1	531.0
601		501.2	502.3

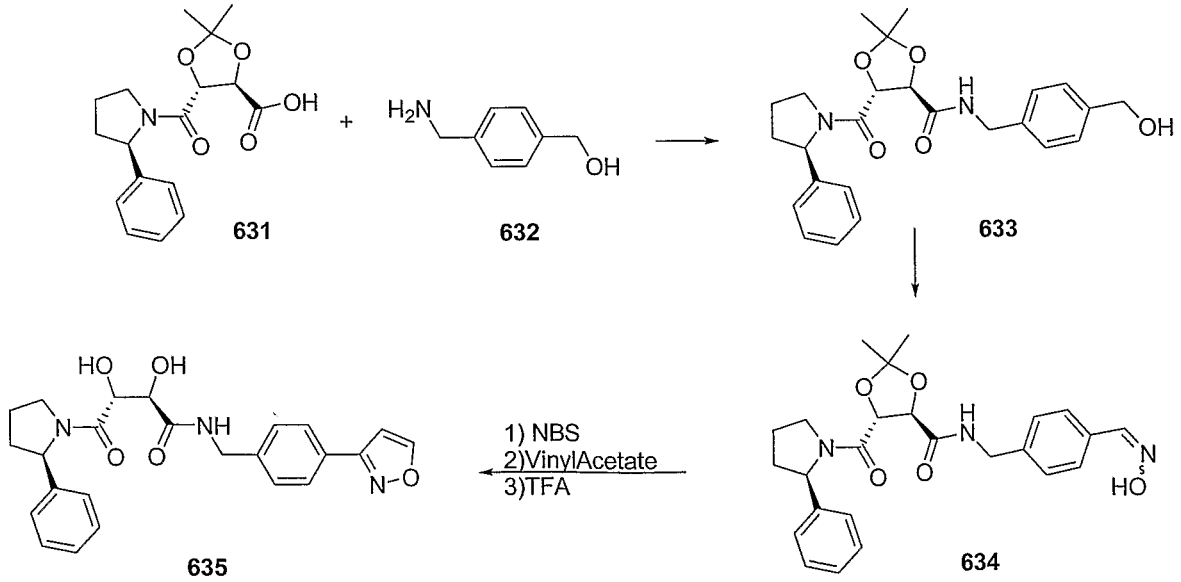
602		515.2	516.3
603		529.3	530.3
604		555.3	556.3
605		563.2	564.3
606		541.3	542.3
607		487.2	488.1
608		502.2	503.1
609		434.2	435.2

610		448.2	449.2
611		459.2	460.1
612		468.1	469.1
613		464.2	465.1
614		464.2	465.1
615		411.2	412.1
616		459.2	460.1
617		521.2	522.1

618		521.2	522.1
619		426.2	427.1
620		427.2	428.1
621		480.2	481.2
622		426.2	427.1
623		489.1	490.1
624		430.2	431.2
625		526.2	527.2
626		522.2	523.2

627		522.2	523.2
628		506.2	507.2
629		410.2	411.2
630		524.2	525.2

Example 13



Compound **631** was prepared by the procedures described in Example 11A. Part A.

To a solution of **631** (0.46 g) and **632** (1.2 eq) in 10 ml DMF at 0C were added HATU (1.5 eq) and HOBt (1.5 eq). The reaction was stirred at r.t. overnight before the solvent was removed in vacuo and residue chromatographed using Ethyl Acetate in Hexane (0 - 100 %) to give 0.46 gram of desired product **633**.

Part B.

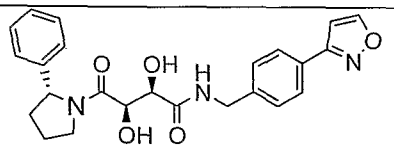
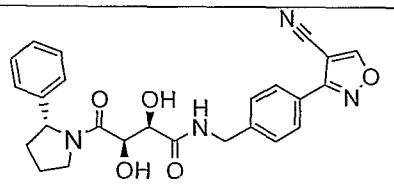
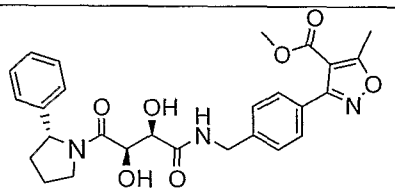
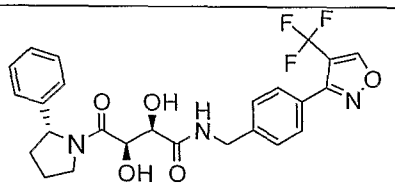
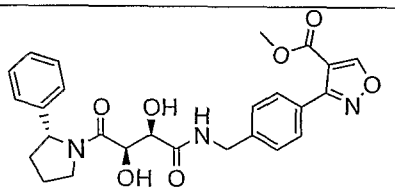
To a solution of 0.46 g of **633** in 10 ml of DCM was added Dess-Martin Reagent (1.1 eq) and the reaction was stirred at r.t. for 30 min before it was treated with sat. aqueous solution of sodium bicarbonate and sodium thiosulfate 7:1 (w/w). The aqueous layer was extracted with DCM (2X) and the combined organic layers was dried over anhydrous sodium sulfate. After removal of solvent, the crude reaction product was dissolved in 2 ml pyridine. To the solution was added 1.5 eq of hydroxylamine hydrochloride and the solution was heated to reflux for 30 min before the solvent was removed in vacuo and residue chromatographed using Ethyl Acetate in Hexane (0 - 100 %) to give 0.4 gram of product **634**.

Part C

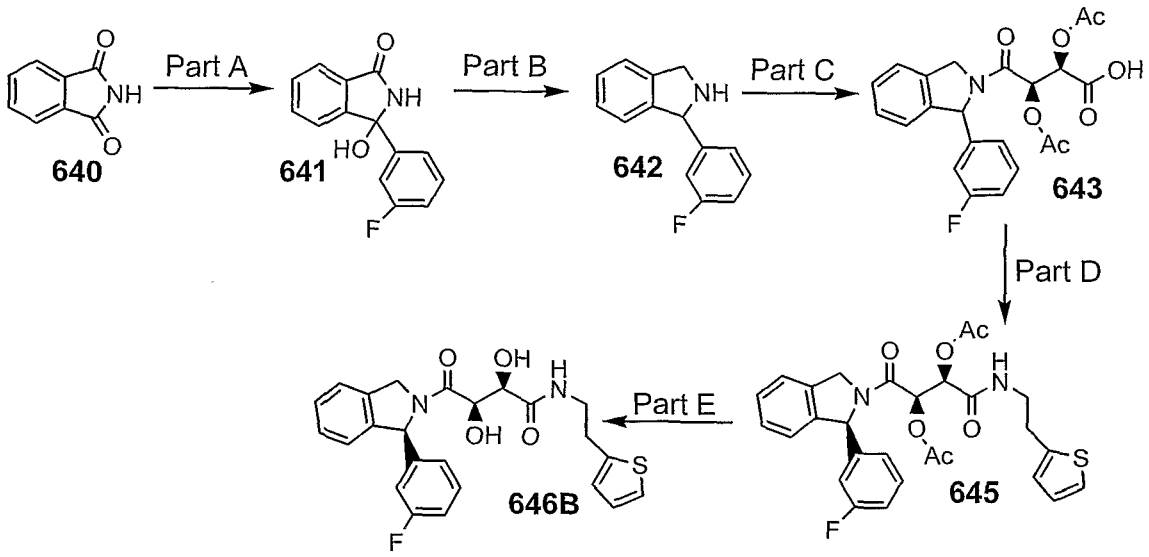
To a flask containing **634** (0.42 g) in anhydrous DMF at 0 °C was added NBS (1 eq) and the solution was allowed to warm up to r.t. overnight before another equivalent of NBS was added and solution stirred for another overnight. The final reaction mixture was poured over ice and extracted with DCM. The organic phase was washed with water and brine, dried over sodium sulfate. After removal of the solvent, the residue was chromatographed using Ethyl Acetate in Hexane (0 - 100 %) to give 0.38 gram of desired product.

To a solution of 0.035 gram of above compound in 2 ml DCM was added vinylacetate (2 eq) and DIEA (3.5 eq) and the solution was stirred at r.t. overnight. After removal of solvent, the residue was chromatographed using Ethyl Acetate in Hexane (0 - 100 %) to give 20 mg product which was treated with 50% TFA in DCM for 2h. before it was purified using a RP HPLC system to give 10 mg of desired product **635**.

The following compounds were generated using similar procedures.

Compound #	Structure	Exact mass	MS m/z (M+H)
635		435.2	436.0
636		460.2	461.0
637		507.2	508.0
638		503.2	504.0
639		493.2	494.0

Example 14:



Part A:

A Schlenck flask was flame dried under N_2 flow, capped with a septum, and allowed to cool to rt. Phthalimide **(640)** (4.13 g, 28.1 mmol) was added followed by anhydrous THF (100 mL). After the phthalimide had dissolved, the flask was placed in an ice water bath and allowed to cool for 20 min. A 1 M solution of 3-fluorophenyl magnesium bromide in THF (25 mL) was added causing a precipitate to form. DMPU (5 mL) was added, causing the reaction mixture to become clear again. Additional 3-fluorophenyl magnesium bromide was added (35 mL) over 10 min. The reaction mixture was stirred at 0 °C for 3.5 h, then quenched with 1.0 M pH 6.5 sodium phosphate buffer. The resulting mixture was diluted with EtOAc and the layers were separated. The organic layer was washed with water and brine, then dried with $MgSO_4$. Evaporation of the solvent gave and off white solid (7.4 g). This material was triturated in CH_2Cl_2/hexanes to give 4.0 g of pure **641**. MS (EI) m/z Obsd. M+H 244.0

Part B:

A Schlenck flask was flame dried under N_2 flow, capped with a septum, and allowed to cool to rt. $LiAlH_4$ (1.26 g, 33.2 mmol) and $AlCl_3$ (1.47 g, 11.0 mmol)

were added to the flask, followed by anhydrous THF. The flask was placed in an ice-water bath immediately and allowed to cool with stirring. Compound **641** was added to the flask in portions. The reaction mixture was stirred for 3 h during which time it warmed to 15 °C. The reaction was recooled to 0 °C and water (3 mL) was added. Aqueous 3.0 N sodium hydroxide was added (6 mL) followed by water (9 mL). The reaction mixture was filtered through a pad of Celite which was rinsed with EtOAc. The resulting filtrate was concentrated to dryness giving a green solid. The crude product was partially purified via flash sgc using a 40%-50% EtOAc/hexanes gradient, followed by 98%EtOAc/2% Et_3N. The fractions containing the impure desired product were combined to give a blue oil. This material was dissolved in CH_2Cl_2 (6 mL). TFA (4 mL) and triethyl silane (2 mL) were added and the reaction mixture was left stirring ON. The reaction mixture was concentrated to give a green oil. This material was purified via flash sgc using 2:1 hexanes:EtOAc, followed by 98%EtOAc/2% Et_3N as the mobile phase. Compound **642** was isolated as a yellow oil (0.56 g). MS (EI) m/z Obsd M+H 214.2.

Part C:

Compound **642** (0.56 g, 2.6 mmol) was dissolved in CH_2Cl_2 (8 mL). Triethyl amine was added (1 mL) followed by (+)-diacetyl-(L)-tartaric anhydride (0.65 g, 3.00 mmol). The reaction mixture was left stirring at rt ON. The reaction mixture was concentrated to dryness and purified via sgc using 2%-5% MeoH/ CH_2Cl_2 mobile phase with 1% acetic acid added to it. After evaporating the solvent and azeotopic removal of the acetic acid with heptane, compound **643** was obtained as a white solid (0.33 g). MS (EI) m/z Obsd M+H 430.1

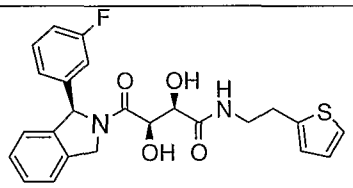
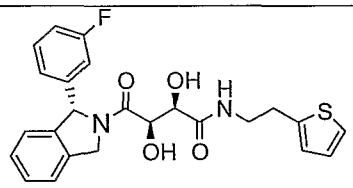
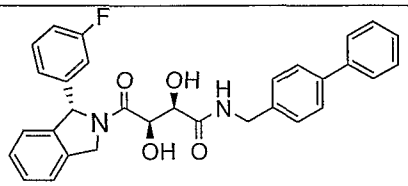
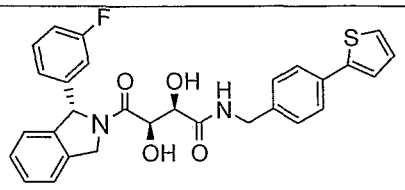
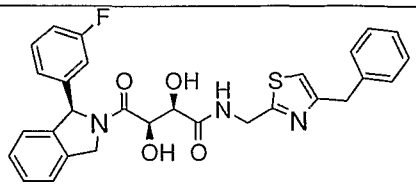
Part D:

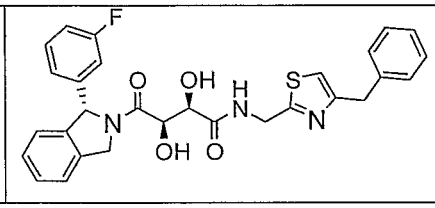
Compound **643** (92 mg, 0.214 mmol), HOBT (36 mg, 0.26 mmol), DMF(1.5 mL), 2-thiophene ethylamine (44 mg, 0.34 mmol), and N-methylmorpholine (50 µL) were added to a flask. EDC was added and the reaction mixture was left stirring ON at rt. The reaction mixture was diluted with EtOAc and washed with aqueous $NaHCO_3$, citric acid, water, and brine. The organic layer was

dried with $MgSO_4$ and concentrated to give a brown oil. The crude product was purified via flash sgc using a 10%-80% EtOAc/Hexanes gradient. Two diastereomeric compounds were isolated-**644** Diastereomer A (0.02 g) MS (EI) m/z Obsd M+H 539.06 and **645** Diastereomer B (0.03 g) MS (EI) m/z Obsd M+H 539.03.

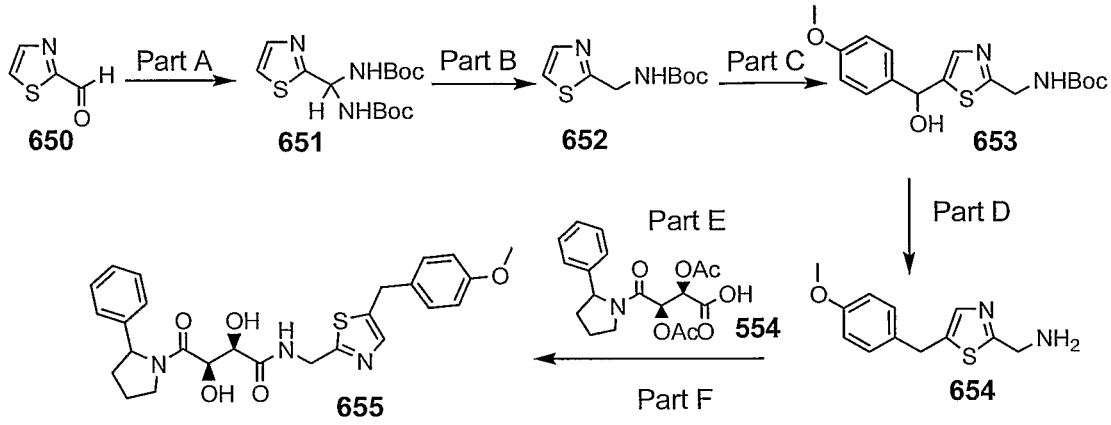
Part E:

Compound **645** was dissolved in 2 M methanolic ammonia and stirred at rt for 30 m. The reaction was purified to dryness. The crude product was purified via prep TLC on silica plates using 1:1 EtOAc: Hexanes as the mobile phase. **646B**: MS (EI) m/z Obsd M+H 455.1.

Compound #	Structure	Exact mass	MS m/z (M+H)
646A		454.1	455.1
646B		454.1	455.1
647		510.2	511.1
648		516.2	517.1
649A		531.2	532.1

649B		531.2	532.1

Example 15:



Part A:

Compound **650** (8.36 g, 73.9 mmol) and tert-butyl carbamate (25.96 g, 222 mmol) were dissolved in acetonitrile (300 mL) and trifluoroacetic acid was added. The reaction was stirred overnight at rt under N_2, then concentrated. The resulting mixture was dissolved in EtOAc and washed with water. The organic layer was dried with Na_2SO_4 and concentrated to dryness. The crude product was purified via flash sgc using 1:3 EtOAc: Hexanes as the mobile phase to give 30.27 g of product **651**. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.40 (s, 1H), 6.38-6.30 (m, 1H), 1.51 (s, 18H) MS (EI) m/z Obsd M+H 330.1

Part B:

Compound **651** (30.27 g, 91.89 mmol) was dissolved in 2-propanol (1500 mL) and sodium borohydride (17.0 g, 46 mmol) was added. The reaction mixture was refluxed for 3 h, then concentrated on the rotovap. The resulting material was diluted with EtOAc, washed with water, and dried with Na_2SO_4. The solvents were evaporated and the crude product was purified via flash sgc

using 1:2 EtOAc: Hexanes as the mobile phase to give 11.58 g of **652**. Yield = 73% over steps one and two. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.33 (s, 1H), 5.35 (s, 1H), 4.69 (s, 2H), 1.53 (s, 9H); MS (EI) MS (EI) m/z Obsd M+H 215.0

Part C:

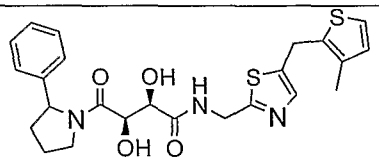
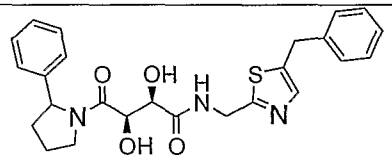
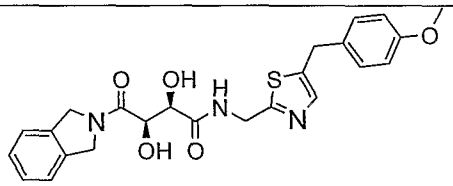
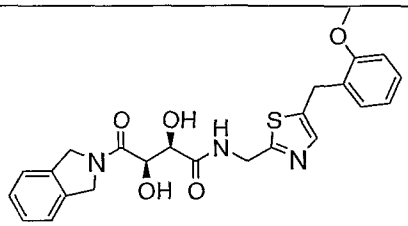
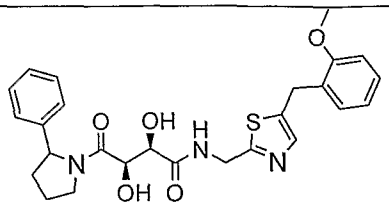
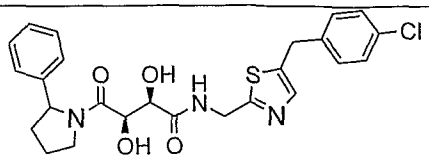
Compound **652** (0.30 g, 1.40 mmol) was dissolved in 5 mL of anhydrous THF (5 mL). The flask was capped with a septum, placed under N_2 blanket, and cooled in a dry ice/2-propanol bath. A solution of LDA (1.71 mL, 1.8 M) was added via syringe and the reaction mixture was stirred for 0.5 h. A solution of 4-methoxy benzaldehyde (0.21 g, 1.54 mmol) in 5 mL of anhydrous THF was added via syringe. The reaction mixture was stirred for 1 h. The ice bath was removed and the reaction was left stirring overnight at rt. Water was added and the reaction mixture was diluted with EtOAc. The layers were separated. The organic layer was washed with water and dried with Na_2SO_4. The solvent was evaporated and the crude product was purified via flash sgc using 1:1 EtOAc: Hexanes to give 0.28 g of **653**. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.37-7.32 (m, 2H), 6.89-6.94 (m, 2H), 6.02 (s, 1H), 5.38 (broad s, 1H), 4.55 (s, 2H), 3.86 (s, 3H) 3.28 (s, 1H), 1.49 (s, 9H).

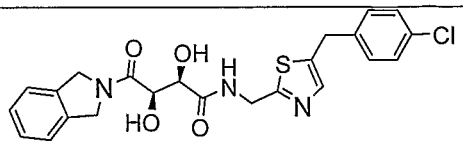
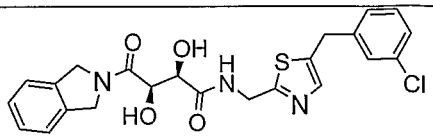
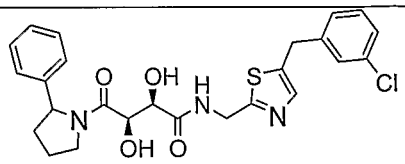
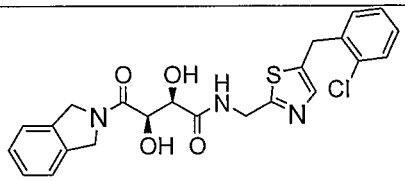
Part D:

Compound **653** (0.28 g, 0.80 mmol) was dissolved in triethylsilane (2 mL) and TFA (0.6 mL). The reaction mixture was refluxed for 3 h then allowed to cool to rt and stirred overnight. The reaction mixture was concentrated. Methanol was added and the reaction mixture was concentrated. Lithium hydroxide (10 mL, 1.0 M aq) and dioxane (10 mL) were added. The reaction mixture was stirred for 3 h then partially concentrated. EtOAc was added and the layers were separated. The organic layer was washed with water and dried with Na_2SO_4. The reaction mixture was concentrated to give 0.23 g of compound **654**. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.19 (d, J=9 Hz, 2 H), 6.89 (d, J=9 Hz, 2H), 4.16 (s, 2H), 4.11 (s, 2H), 3.84 (s, 3H), 1.77 (broad s, 2H).

Parts E and F:

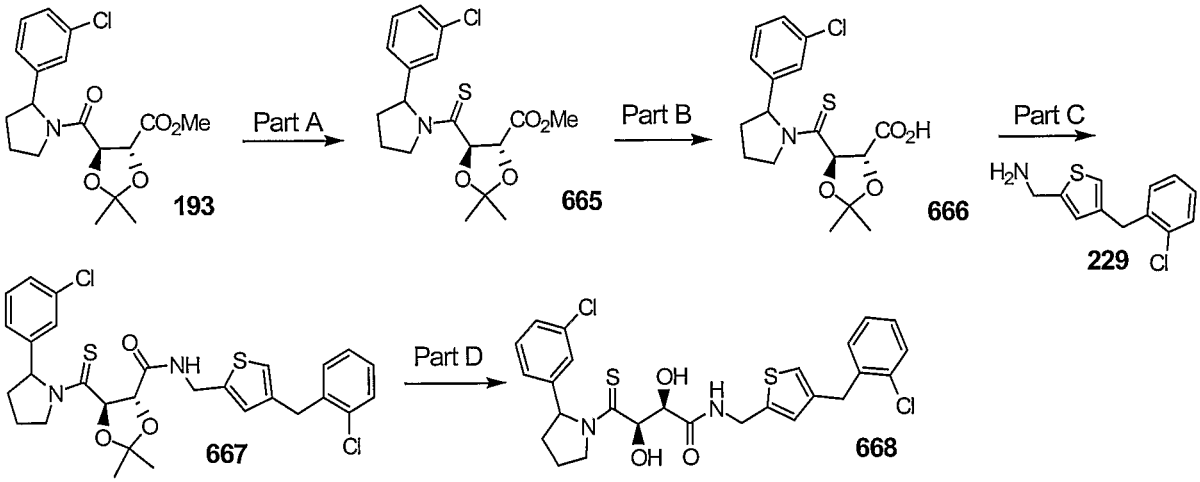
Compound **654** was converted to compound **655** using procedures described in Example 2. Data for **655**: ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.41-7.26 (m, 5H), 7.22-7.14 (M, 4H), 6.89-6.81 (m, 2H), 5.50-5.17 (m, 1H), 4.98-4.54 (m, 4H), 4.53-4.31 (m, 2H), 4.06-3.98 (m, 2H), 3.84 (s, 3H), 2.47-2.27 (m, 1H), 2.12-1.75 (m, 1H). MS (EI) m/z Obsd M+H 496.1.

Compound #	Structure	Exact mass	MS m/z (M+H)
656A		485.1	486.3
656B		465.2	466.1
657		467.2	468.1
658		467.2	468.1
659		495.2	496.1
660		499.1	500.1

661		471.1	472.1
662		471.1	472.1
663		499.1	500.1
664		471.1	472.1

Example 16: Thioamides

Example 16A:



Part A:

To a solution of compound **193** (200 mg, 0.54 mmol) in THF (5 mL) was added portionwise of Lawesson's reagent (203 mg, 0.5 mmol). The reaction mixture was stirred overnight under argon at room temperature, and diluted with EtOAc. The organic layer was washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated. Column chromatography over silica gel

(EtOAc/hexane, 20:80) afforded compound **665**. Mass calculated for formula $C_{18}H_{22}ClNO_4S$ 383.1, observed LCMS m/z 384.1 (M+H).

Part B:

To compound **665** in MeOH (5 mL) was added powdered K_2CO_3 (50 mg). Mixture was stirred at room temperature for 1 h and the solvent was removed in vacuo. The residue was dissolved in water and acidified with 1 N HCl. It was extracted with EtOAc, the combined organic layers was washed with 1N HCl, brine, dried over Na_2SO_4, and concentrated to afford compound **666** as an oil (45 mg). Mass calculated for formula $C_{17}H_{20}ClNO_4S$ 369.1, observed LCMS m/z 370.1 (M+H).

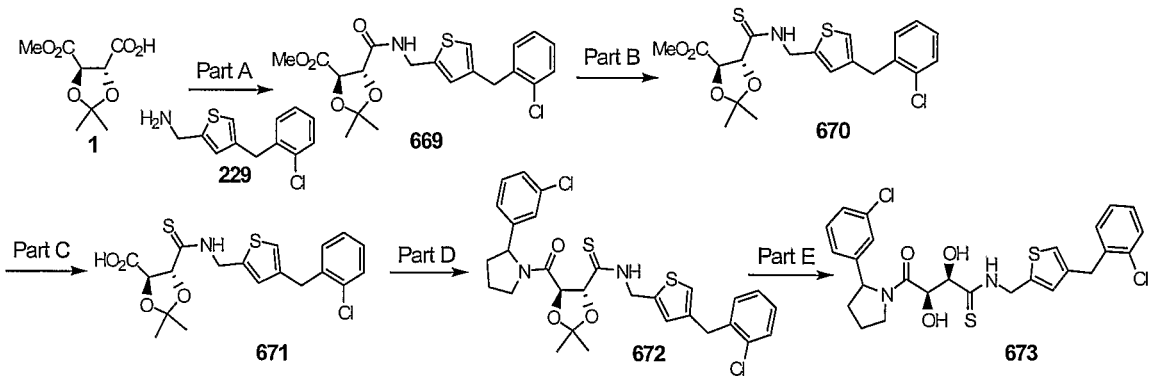
Part D:

To compound **666** (10 mg, 0.027 mmol) in DMF (0.5 mL) was **229** (11 mg, 0.041 mmol) and HATU (20.5 mg, 0.054 mmol). The reaction mixture was stirred at room temperature for 4 h, and diluted with ethyl acetate and water. The organic layer was washed with 1 N HCl, saturated $NaHCO_3$, and brine. It was dried over Na_2SO_4, and concentrated, resulting in compound **667** as an oil. Mass calculated for formula $C_{29}H_{30}Cl_2N_2O_3S_2$ 588.1, observed LCMS m/z 589.1 (M+H).

Part E:

Compound **667** was dissolved in 0.5 mL of TFA/H_2O (80:20) and stirred at room temperature for 2 h. The reaction mixture was quenched with ACN/H_2O (50:50) and concentrated in vacuo. Purification by reverse phase prep-LC afforded compound **668** as a white solid. HPLC-MS t_R = 6.97 min ($UV_{254\ nm}$, 10 min), Mass calculated for formula $C_{26}H_{26}Cl_2N_2O_3S_2$ 548.1, observed LCMS m/z 549.1 (M+H).

Example 16B:



Part A:

To **1** (204 mg, 1mmol) in DMF (2 mL) was added **229** (320 mmol, 1.2 mmol) and HATU (570 mg, 1.5 mmol). The reaction mixture was stirred overnight at room temperature, and diluted with ethyl acetate and water. The organic layer was washed with 1 N HCl, saturated $NaHCO_3$, and brine. It was dried over Na_2SO_4, and concentrated, resulting in **669** as a slightly yellow oil (280 mg, 66%).

Part B:

To a solution of **669** (280 mg, 0.54 mmol) in THF (5 mL) was added portionwise of Lawesson's reagent (202 mg, 0.5 mmol). The reaction mixture was stirred overnight under argon at room temperature, and diluted with EtOAc. The organic layer was washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated. Column chromatography over silica gel (EtOAc/hexane, 20:80) afforded compound **670**. Mass calculated for formula $C_{20}H_{22}ClNO_4S$ 439.1, observed LCMS m/z 440.1 (M+H).

Part C:

To **670** in MeOH (5 mL) was added powdered K_2CO_3 (50 mg). The mixture was stirred at room temperature for 1 h and the solvent was removed in vacuo. The residue was dissolved in water and acidified with 1 N HCl. It was extracted with EtOAc, the combined organic layers was washed with 1N HCl, Brine, dried over Na_2SO_4, and concentrated to afford compound **671** as an oil

(80 mg). Mass calculated for formula $C_{17}H_{20}ClNO_4S$ 425.1, observed LCMS m/z 426.1 (M+H).

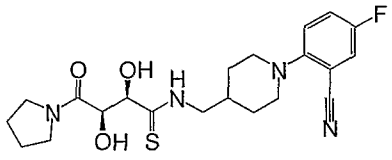
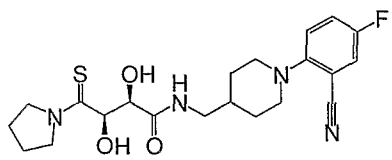
Part D:

To compound **671** (10 mg, 0.027 mmol) in DMF (0.5 mL) was added racemic 2-(3-chlorophenyl)pyrrolidine (6.5 mg, 0.035 mmol) and HATU (17.5 mg, 0.046 mmol). The reaction mixture was stirred at room temperature for 4 h, and diluted with ethyl acetate and water. The organic layer was washed with 1 N HCl, saturated $NaHCO_3$, and brine. It was dried over Na_2SO_4, and concentrated, resulting in compound **672** as an oil. Mass calculated for formula $C_{29}H_{30}Cl_2N_2O_3S_2$ 588.1, observed LCMS m/z 589.1 (M+H).

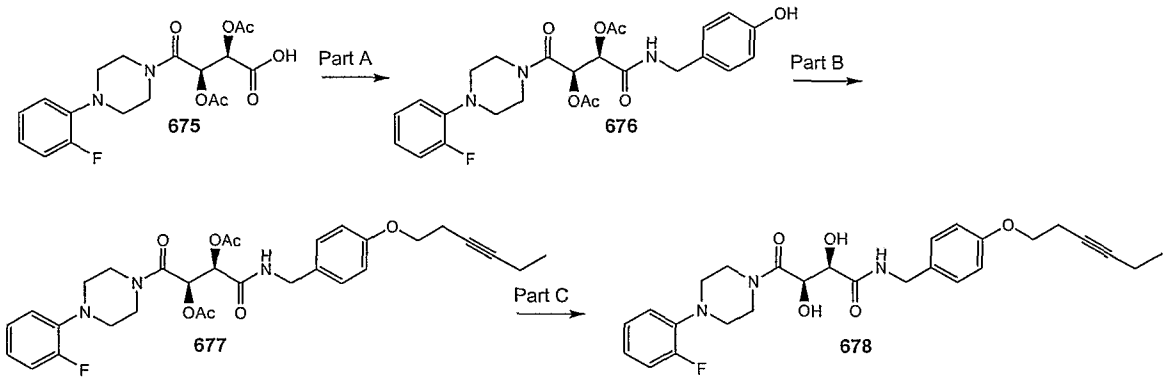
Part E:

Compound **672** was dissolved in 0.5 mL of TFA/H_2O (80:20) and stirred at room temperature for 2 h. The reaction mixture was quenched with ACN/H_2O (50:50) and concentrated in vacuo. Purification by reverse phase prep-LC afforded compound **673** as a white solid. HPLC-MS t_R = 7.04 min ($UV_{254\ nm}$, 10 min), Mass calculated for formula $C_{26}H_{26}Cl_2N_2O_3S_2$ 548.1, observed LCMS m/z 549.1 (M+H).

The following compounds were prepared by the methods described above. Belleau's reagent was substituted for Lawesson's reagent.

Compound #	Structure	Exact mass	MS m/e (M+H)
673		434.2	435.2
674		434.2	435.1

Example 17



Compound **675** was prepared as described in Example 4A Part C.

Part A:

To **675** (1.34 g, 3.38 mmol) in DMF (20 mL) was added 4-hydroxybenzylamine (0.5 g, 4.06 mmol), DIEA (0.71 mL, 4.06 mmol) and HATU (1.54 g, 4.06 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with water and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 80% EtOAc/hexane) afforded **676** (1.41 g, 83%). HPLC-MS t_R = 1.56 min ($UV_{254\ nm}$); Mass calculated for formula $C_{25}H_{28}FN_3O_7$ 501.2, observed LCMS m/z 502.1 (M+H).

Part B:

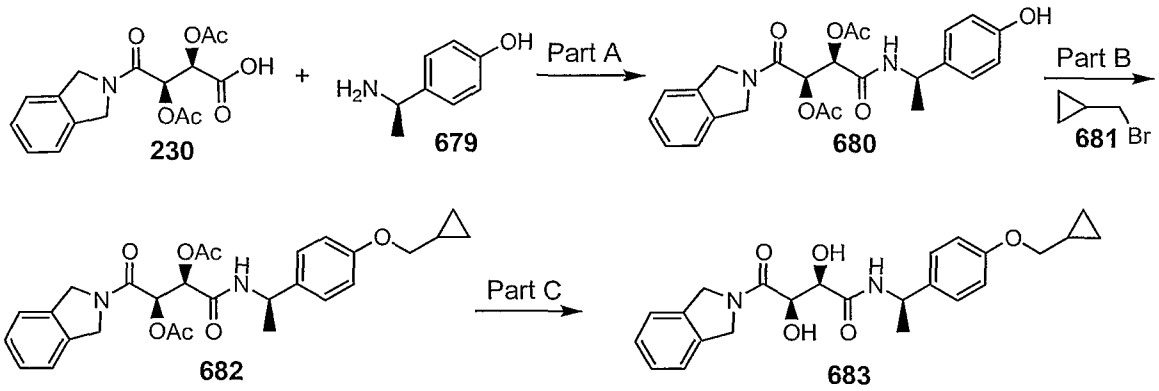
To a mixture of **676** (50 mg, 0.1 mmol), triphenylphosphine (79 mg, 0.3 mmol), 3-hexyn-1-ol (33 µL, 0.3 mmol) in THF (0.5 mL) at 0 °C was added DEAD (47 µL, 0.3 mmol). The reaction mixture was warmed to room temperature and stirred for 5 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 20% EtOAc/hexane to 100% EtOAc) afforded **677** (9

mg, 15%). HPLC-MS t_R = 2.09 min ($UV_{254\ nm}$); Mass calculated for formula $C_{31}H_{36}FN_3O_7$ 581.3, observed LCMS m/z 582.2 (M+H).

Part C:

To **677** (9 mg, 0.02 mmol) in methanol (0.5 mL) was added anhydrous hydrazine (2 µL, 0.04 mmol). The reaction mixture was stirred overnight at room temperature. The solvents were removed in vacuo and the material was freeze-dried to yield **678** as a white powder (2 mg). HPLC-MS t_R = 1.89 min ($UV_{254\ nm}$); Mass calculated for formula $C_{27}H_{32}FN_3O_5$ 497.2, observed LCMS m/z 498.2 (M+H).

Example 17B:



Part A:

Compound **680** was prepared from compounds **230** & **679** using procedures described in Example 17A Part A. HPLC-MS t_R = 1.37 min ($UV_{254\ nm}$); Mass calculated for formula $C_{24}H_{26}N_2O_7$ 454.2, observed LCMS m/z 455.2 (M+H).

Part B:

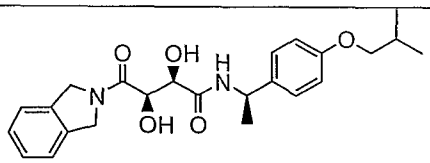
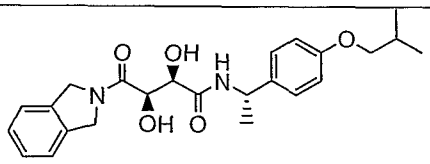
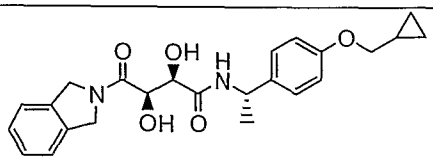
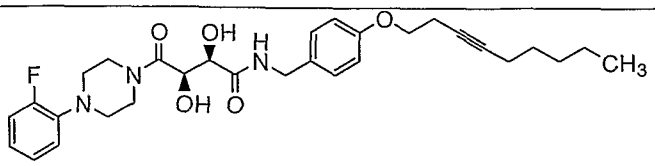
A mixture of **680** (49 mg, 0.11 mmol), **681** (14 uL, 0.14 mmol) and cesium carbonate (46 mg, 0.14 mmol) in DMF (2 mL) was stirred 24 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate

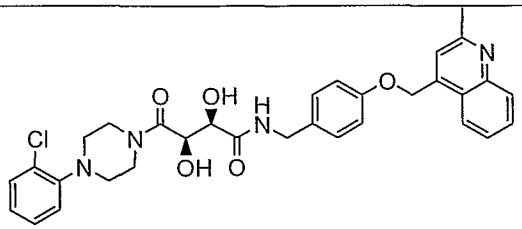
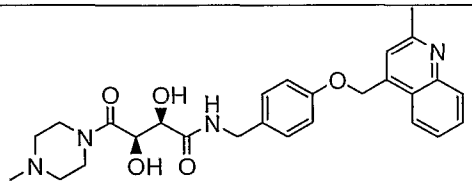
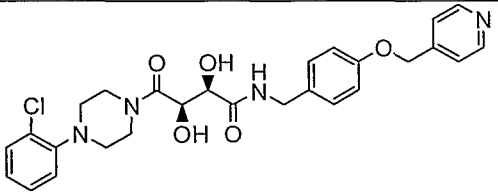
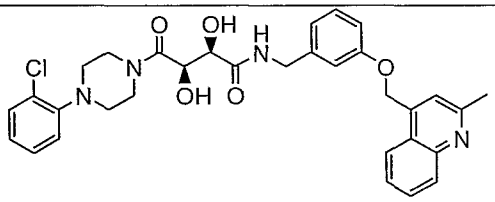
and concentrated to afford **682** (33 mg). The material was used without further purification. HPLC-MS t_R = 1.91 min ($UV_{254\ nm}$); Mass calculated for formula $C_{28}H_{32}N_2O_7$ 508.2, observed LCMS m/z 509.2 (M+H).

Part C:

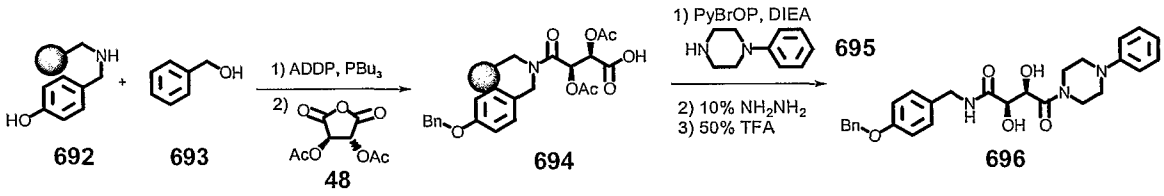
To compound **682** (33 mg, 0.06 mmol) in methanol (2 mL) was added 7.0 M ammonia in methanol (2 ml). The reaction mixture was stirred for 1 hour and concentrated. Purification by reverse phase prep-HPLC afforded **683** (8 mg). HPLC-MS t_R = 4.28 min ($UV_{254\ nm}$, 10 min); Mass calculated for formula $C_{24}H_{28}N_2O_5$ 424.2, observed LCMS m/z 425.2 (M+H).

The following compounds were prepared using procedures described in Example 17A & 17B.

Compound #	Structure	Exact Mass	Mass Obsvd
684		426.2	427.1
685		426.2	427.1
686		424.2	425.2
687		539.3	540.3

688		588.2	589
689		492.2	493
690		524.1	525
691		588.2	589

Example 17C:



Step A1:

To pre-swelled MB-CHO resin (5.0 g, 1.0 mmol/g) in 40 ml DCE was added 4-hydroxybenzylamine (1.5 eq) and triacetoxyborohydride (2 eq) and the mixture was agitated overnight before the solution was drained and resin washed with MeOH, DCM and THF 5 cycles to give resin **692** after drying in *vacuo* overnight.

Step A2:

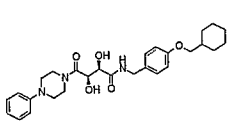
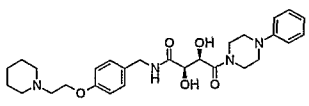
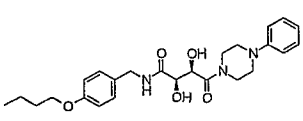
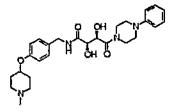
To a pre-swelled resin **692** (150 mg, 1 mmol/g) in anhydrous THF was added benzylalcohol (5 eq) and PPh_3 (7 eq) in 1.5 ml of THF and ADDP (5 eq) in 0.5

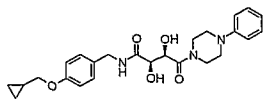
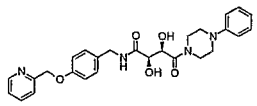
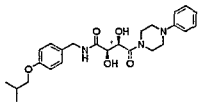
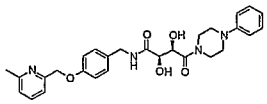
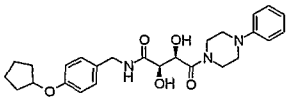
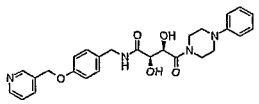
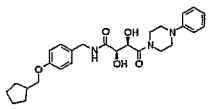
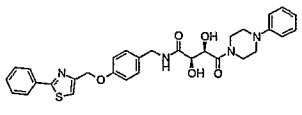
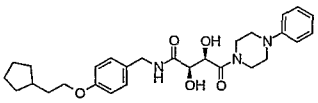
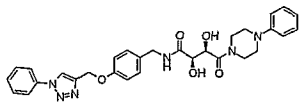
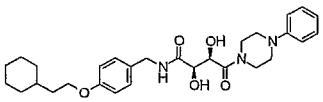
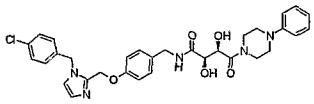
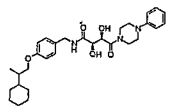
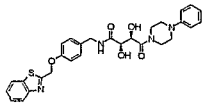
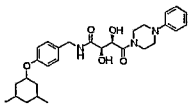
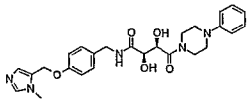
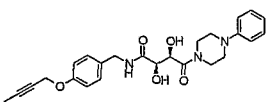
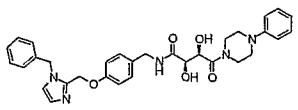
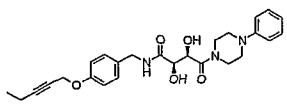
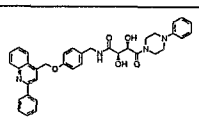
ml of DCM. The reaction was agitated at room temperature over the weekend. The reaction solution was drained and resin washed with 5 cycles of MeOH, DCM and THF and dried in vaccuo before it was swelled in NMP followed by addition of 1.5 ml 1M NMP solution of compound **48**. The reaction mixture was agitated overnight before the solution was drained and resin washed with 5 cycles of MeOH, DCM and THF and dried in vacuo to give resin **694**.

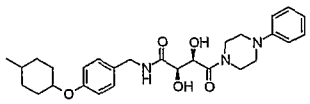
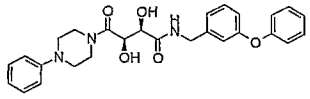
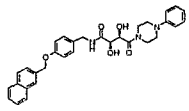
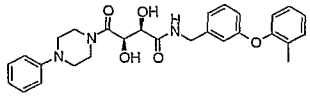
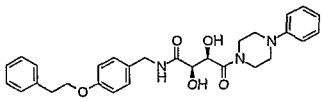
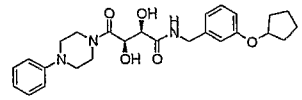
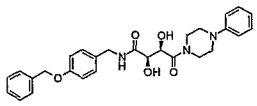
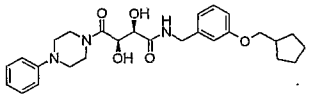
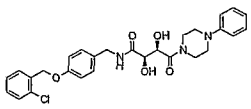
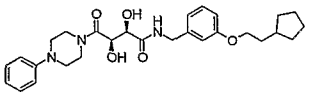
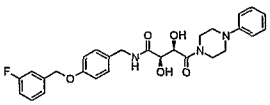
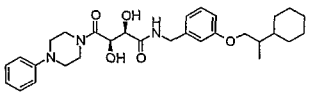
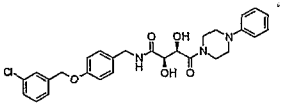
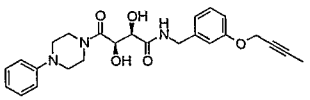
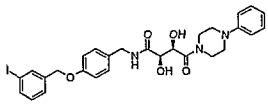
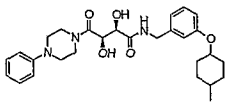
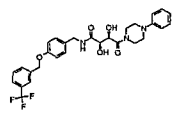
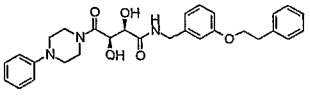
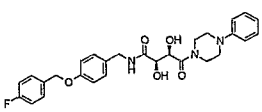
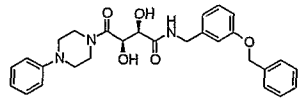
Step B:

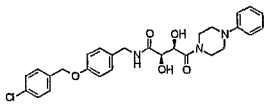
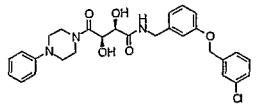
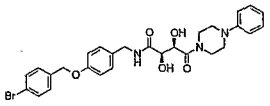
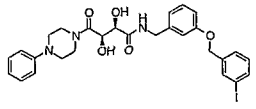
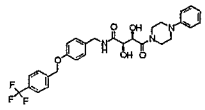
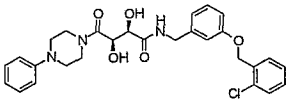
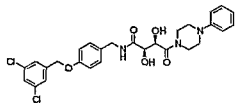
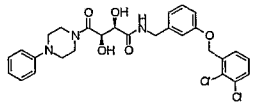
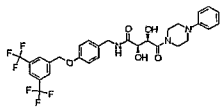
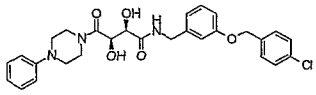
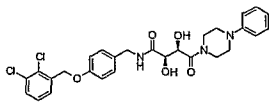
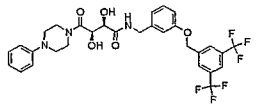
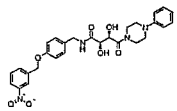
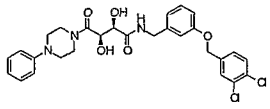
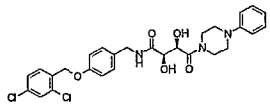
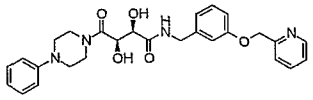
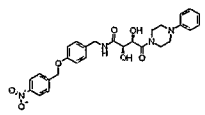
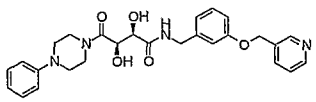
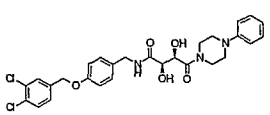
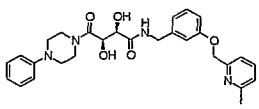
Resin **694** was pre-swelled in DCM, before 1-phenylpiperazine hydrochloric salt (695)(6 eq) was added followed by addition of PyBrop (3 eq) and DIEA (9 eq) in 3 ml of DCM. The reaction solution was agitated overnight before it was drained and resin washed with 5 cycles of MeOH, DCM and THF before it was treated with 10% hydrazine in methanol for 2h. The resin was then further washed with 5 cycles of MeOH, DCM and THF followed by cleavage using 50% of TFA in DCM. The cleavage solution was evaporated and residue purified with a RP-HPLC system to give 5 mg of desired product **696**.

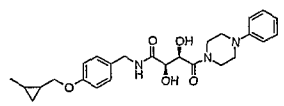
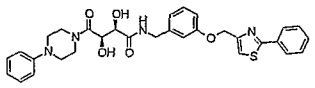
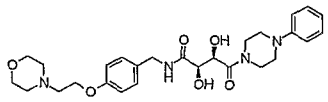
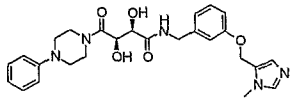
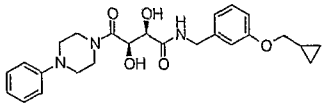
The following compounds were generated using similar methods.

Compound #	Structure	Obs. MS		Compound #	Structure	Obs. MS
697		496		**698**		511
699		456		**700**		497

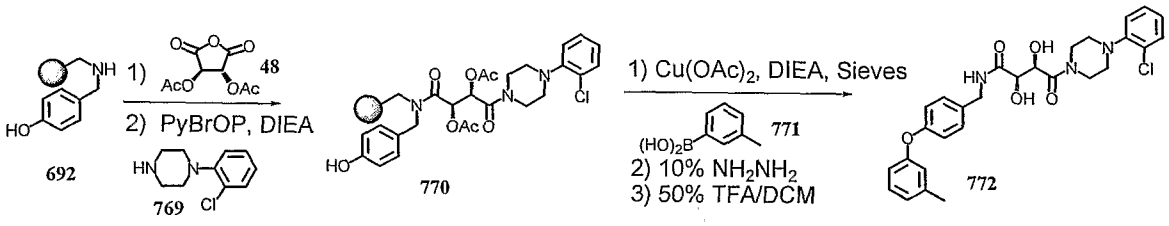
701		454		**702**		491
703		456		**704**		505
705		468		**706**		491
707		482		**708**		573
709		496		**710**		557
711		510		**712**		604
713		524		**714**		547
715		510		**716**		494
717		452		**718**		570
719		466		**720**		617

721		496		**722**		476
723		540		**724**		490
725		504		**726**		468
696		490		**728**		482
729		524		**730**		496
731		508		**732**		524
733		524		**734**		452
735		616		**736**		496
737		558		**738**		504
739		508		**740**		490

741		524	**742**		524
743		569	**744**		616
745		558	**746**		524
747		558	**748**		558
749		626	**750**		524
751		558	**752**		626
753		535	**754**		558
755		558	**756**		491
757		535	**758**		491
759		558	**760**		505

761		468		**762**		573
763		513		**764**		494
765		454				

Example 17D:



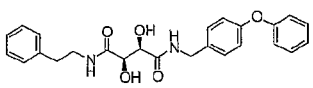
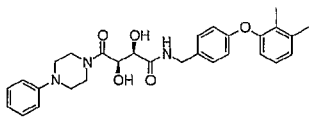
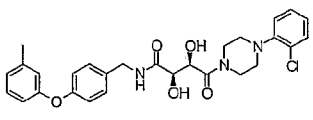
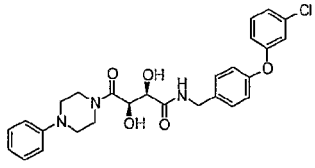
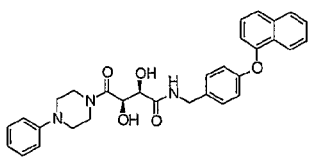
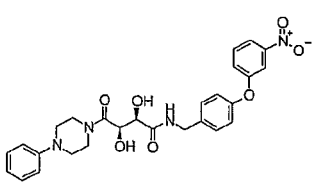
Step A.

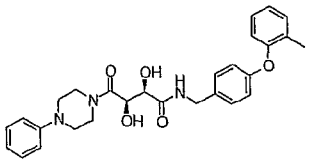
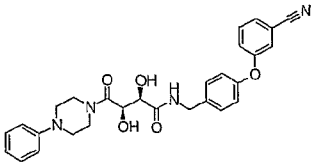
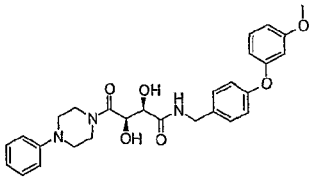
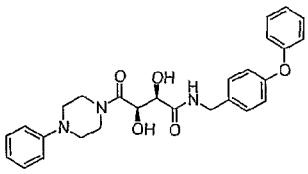
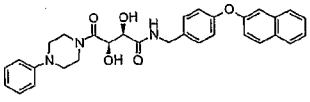
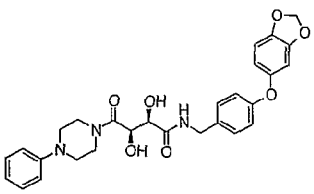
To resin **692** (2.6 g, 1mmol/g), preswelled in NMP was added **48** (5 eq) and the mixture was agitated for 48 h. before the solution was drained and resin washed with 5 cycles of MeOH, DCM and THF and dried in vacuo. The resin was then swelled in anhydrous DCM (25 ml) before **769** (6 eq, HCl salt) and DIEA (9 eq) were added followed by addition of PyBrop. The reaction was agitated at r.t. overnight before the solution was drained and resin washed with 5 cycles of MeOH, DCM and THF and dried in vacuo to give resin **770** (0.9 mmol/g loading).

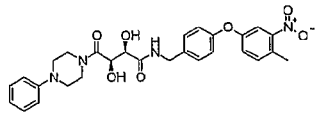
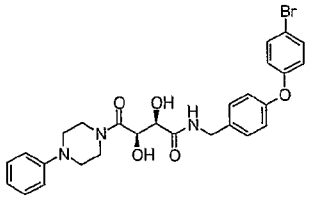
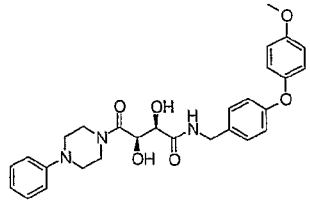
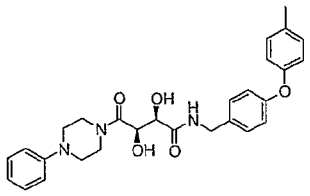
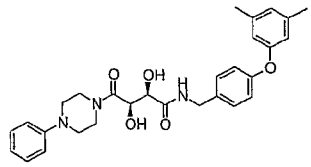
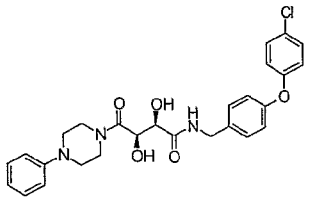
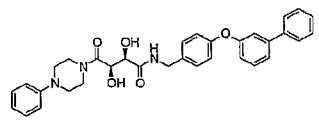
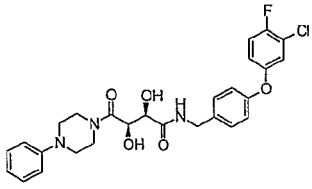
Step B.

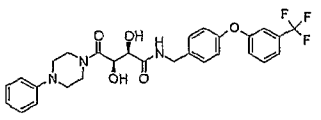
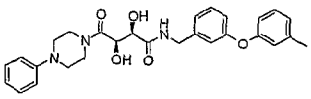
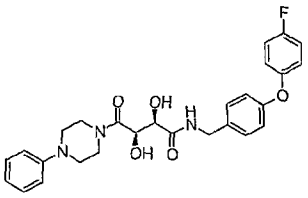
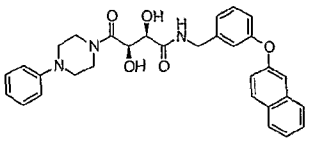
To a pre-swelled resin **770** (0.095 g, 0.9 mmol/g) in anhydrous DCM was added anhydrous $Cu(OAc)_2$ (3 eq), **771** (5 eq), 4 A molecular sieves (5micron particle size, 100 mg) and DIEA (7eq) in 2 ml anh. DCM. The reaction was agitated for 48 h. before the mixture was drained and resin washed with 5 cycles of H_2O, MeOH, DCM and THF before it was treated with 10% hydrazine in Methanol for 2h. The resin was then further washed with 5 cycles of MeOH, DCM and THF followed by cleavage using 50% of TFA in DCM. The cleavage solution was evaporated and residue purified with a RP-HPLC system to give 5 mg of desired product **772.**

The following compounds were synthesized in similar fashion.

Comound #	Structure	OBS. Mass		Compound #	Structure	OBS. Mass
773		435		**774**		504
772		524		**776**		510
777		526		**778**		521

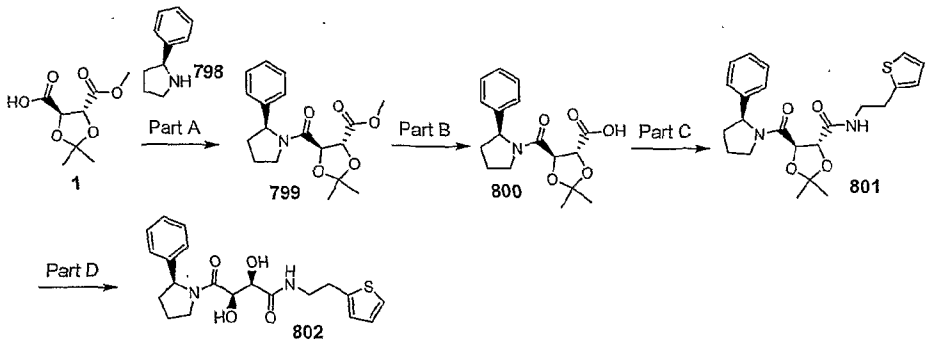
779		490		**780**		501	
781		506		**782**		476	
783		526		**784**		520	

785		535		**786**		555
787		506		**788**		490
789		504		**790**		510
791		552		**792**		528

793		544		**794**		490
795		494		**796**		526

Example 18

Example 18A:



Part A:

Following the procedure described in Example 1 Part A, **1** (163 mg, 0.8 mmol), 2S-phenyl-pyrrolidine **(798)** (Burgess, L.E.; Meyers, A.I.; *J. Org. Chem.* **1991**, *56*, 2294) (147 mg, 0.8 mmol), DIEA (560 µL, 3.2 mmol) and HATU (304 mg, 0.8 mmol) were mixed together in DMF (2 mL). Purification

by column chromatography (SiO_2, 5%-20% EtOAc/DCM) afforded **799** as an oil (115 mg, 43%). HPLC-MS t_R = 1.82 min ($UV_{254\ nm}$); Mass calculated for formula $C_{18}H_{23}NO_5$ 333.2, observed LCMS m/z 334.1 (M+H).

Part B:

Following the procedure in Example 1 Part B the material from Part A was saponified. **800**: HPLC-MS t_R = 1.54 min ($UV_{254\ nm}$); Mass calculated for formula $C_{17}H_{21}NO_5$ 319.1, observed LCMS m/z 320.2 (M+H).

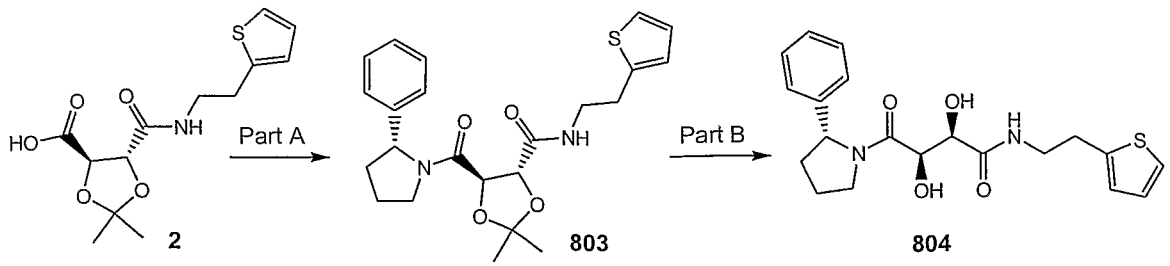
Part C:

Compound **800**, 2-thiopheneethylamine (6 µL, 0.05 mmol), DIEA (18 µL, 0.103 mmol) and HATU (19 mg, 0.05 mmol) were mixed together following the procedure described in Example 1 Part A. **801**: HPLC-MS t_R = 2.01 min ($UV_{254\ nm}$); Mass calculated for formula $C_{23}H_{28}N_2O_4S$ 428.2, observed LCMS m/z 429.2 (M+H).

Part D:

Compound **801** was dissolved in 90:10 TFA:water (2 mL) and stirred for 4 hours. The reaction mixture was quenched with 1:1 acetonitrile:water (4 mL) and concentrated. Purification by reverse phase prep-LC afforded **802** as a white powder (9 mg, 50%, 2 steps). HPLC-MS t_R = 1.54 min ($UV_{254\ nm}$); Mass calculated for formula $C_{20}H_{24}N_2O_4S$ 388.2, observed LCMS m/z 389.2 (M+H).

Example 18B:

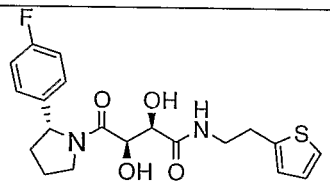
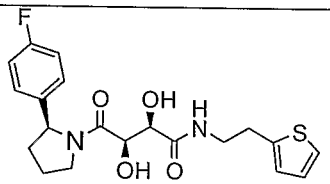
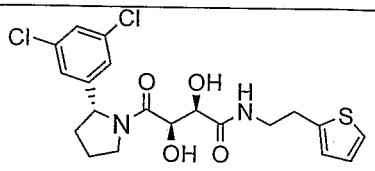
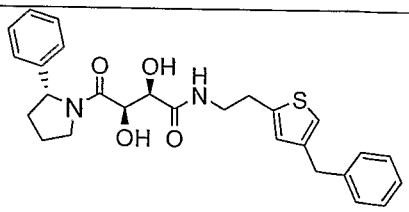


Part A:

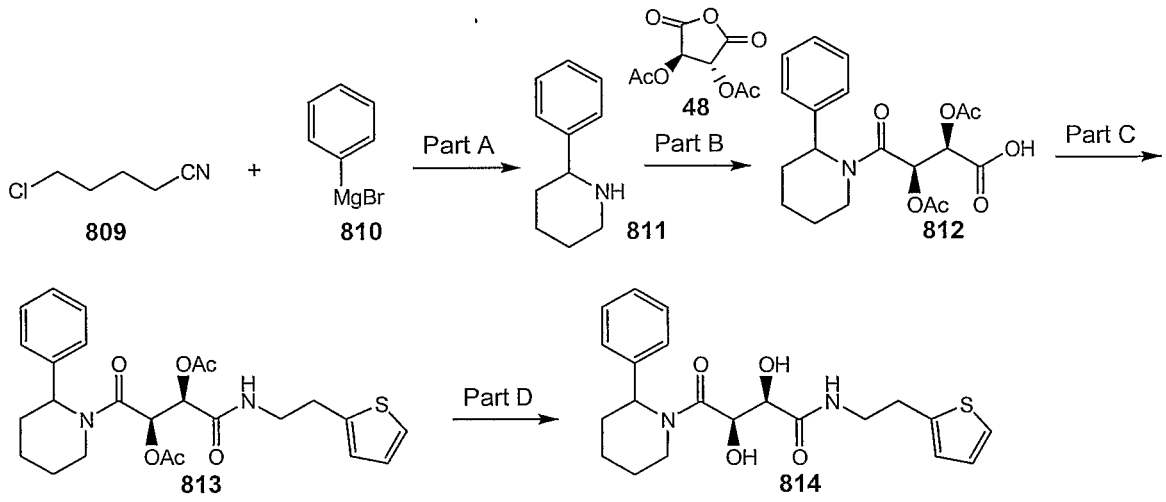
Compound **2** (42 mg, 0.14 mmol), 2-phenyl pyrrolidine (22 mg, 0.15 mmol), DIEA (63 µL, 0.36 mmol) and HATU (61 mg, 0.16 mmol) were mixed together following the procedure described in Example 1 Part A. The desired isomer was separated by reverse phase prep-LC to afford **803** as a white solid. HPLC-MS t_R = 1.96 min ($UV_{254\ nm}$); Mass calculated for formula $C_{23}H_{28}N_2O_4S$ 428.2, observed LCMS m/z 429.1 (M+H).

Part B:

Compound **803** was deprotected using the procedure described in Example 1 Part D to afford **804** as a white powder (5 mg, 19% 2 steps). HPLC-MS t_R = 1.50 min ($UV_{254\ nm}$); Mass calculated for formula $C_{20}H_{24}N_2O_4S$ 388.2, observed LCMS m/z 389.2 (M+H).

Compound #	Structure	Exact mass	MS m/e (M+H)
805		406.1	407.2
806		406.1	407.2
807		456.1	457.1
808		478.2	479.2

Example 19:



Part A: 2-Phenyl piperidine

To 5-chlorovaleronitrile **(809)** (1.23 mL, 11 mmol) and trimethylsilylchloride (4.32 mL, 34 mmol) in toluene (50 mL) under argon at 0 °C was added phenylmagnesium bromide **(810)** (3M in diethyl ether, 3.67 mL, 11 mmol) dropwise. The reaction mixture was stirred at 0 °C for 1 hour. To the reaction mixture was added methanol (50 mL). Sodium borohydride (1.04 g, 27.5 mmol) was added portionwise. After the vigorous bubbling had subsided the reaction mixture was stirred for 1 hour at room temperature. A solution of 50% sodium hydroxide (5 mL) was added to the mixture and it was stirred overnight. The reaction mixture was filtered to remove the precipitate and the solids were washed with ethyl acetate. The filtrate was concentrated in vacuo. The crude reaction mixture was dissolved in ethyl acetate and water. The aqueous layer had a pH of 9. The layers were separated and the organic layer was washed with brine solution, dried over sodium sulfate and concentrated in vacuo to afford an orange oil. The product was purified by column chromatography (SiO_2, 20% ethyl acetate/hexane to 20% ethyl acetate hexane + 2% triethylamine) to afford **811** as a polar yellow oil (927 mg, 52%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.4 – 7.3 (m, 4H), 7.24 (m, 1H), 3.60 (dd, 1H, J = 2.4, 10.4 Hz), 3.21 (m, 1H), 2.81 (dt, 1H, J = 3.2, 10.8 Hz), 1.90 (m, 1H), 1.81 (m, 1H), 1.68 (m, 1H), 1.56 (m, 3H); HPLC-MS t_R = 0.73 min (MS); mass calculated for formula $C_{11}H_{15}N$ 161.1, observed LCMS m/z 162.1 (M+H).

Part B:

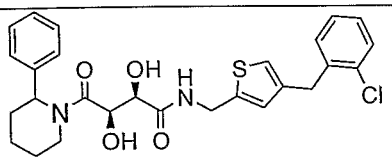
To **48** (108 mg, 0.5 mmol) in DCM (3 mL) was added **811** (80 mg, 0.5 mmol). The reaction mixture was stirred overnight before being poured into 1.0 N HCl and extracted with DCM. The combined organic layers were dried over sodium sulfate, concentrated and freeze-dried to afford **812** as a white solid (119 mg, 63%). Mass calculated for formula $C_{19}H_{23}NO_7$ 377.2, observed LCMS m/z 378.1 (M+H).

Part C:

Prepared as described in Example 1 Part A using **812** (19 mg, 0.05 mmol) to afford a foam **813** (24 mg, 100%). Mass calculated for formula $C_{19}H_{23}NO_7$ 486.2, observed LCMS m/z 487.1 (M+H).

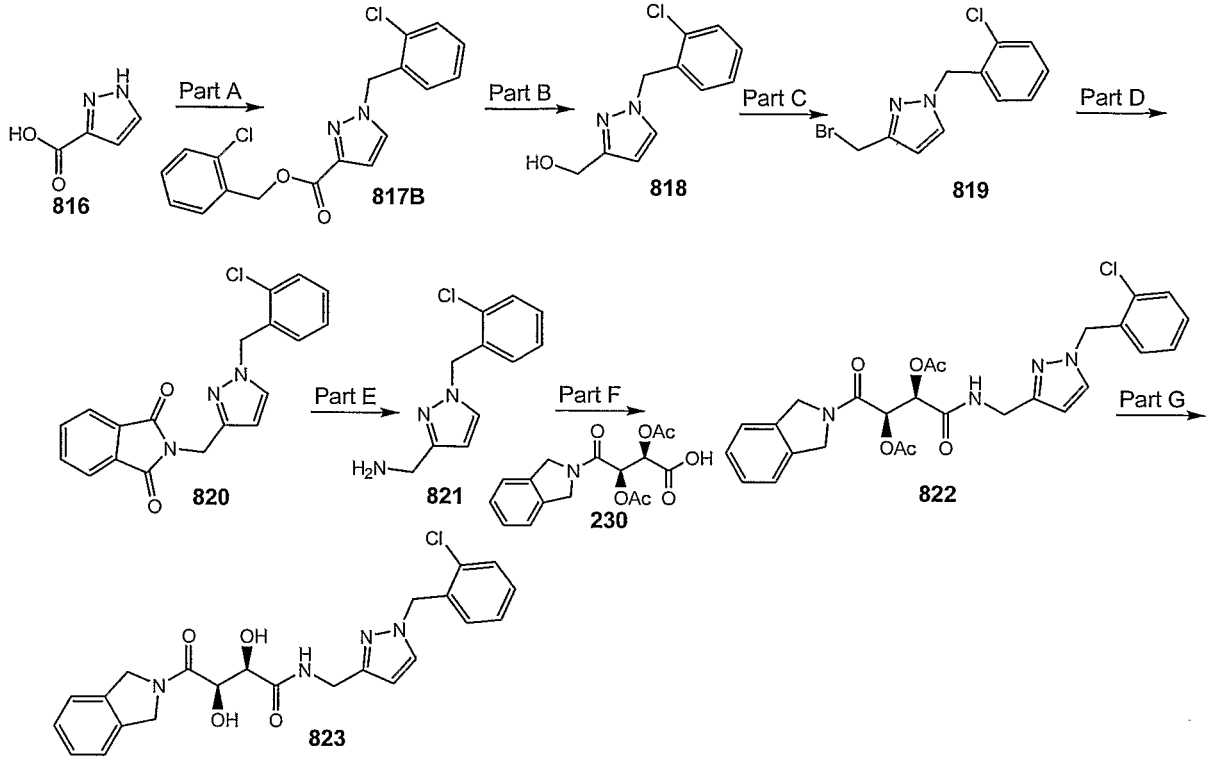
Part D:

Compound **813** (24 mg, 0.05 mmol) was deprotected using the procedure described in Example 2A Part B. Purification by reverse-phase prep-LC afforded **814** as a white powder (9 mg, 45%). HPLC-MS t_R = 4.38 and 4.42 min ($UV_{254\ nm}$, 10 min); Mass calculated for formula $C_{21}H_{26}N_2O_4S$ 402.2, observed LCMS m/z 403.1 (M+H).

Compound #	Structure	Exact mass	MS m/e (M+H)
815		512.2	513.1

Example 20:

Example 20A:



Part A:

To 1H-Pyrazole-3-carboxylic acid (**816**) (274 mg, 2.44 mmol) in DMF (10 mL) was added 2-chlorobenzyl bromide (698 µL, 5.38 mmol) and cesium carbonate (1.67 g, 5.12 mmol). The reaction mixture was stirred overnight at room temperature. The solids were removed by filtration and the filtrate was concentrated. Purification by column chromatography (SiO_2, 20% to 30% EtOAc/Hex) separated the regioisomers to afford the **817A** as an oil (136 mg, 15%) and **817B** as a white solid (685 mg, 78%).

1-(2-Chloro-benzyl)-1H-pyrazole-5-carboxylic acid 2-chloro-benzyl ester (**817A**): ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, 1H, J = 2.0 Hz), 7.37 (m, 3H), 7.31 - 7.11 (m, 4H), 7.02 (d, 1H, J = 2.0 Hz), 6.53 (dd. 1H, J = 2.0, 7.6 Hz), 5.91 (s, 2H), 5.39 (s, 2H). HPLC-MS t_R = 2.40 min ($UV_{254\ nm}$); mass

calculated for formula $C_{18}H_{14}Cl_2N_2O_2$ 360.0, observed LCMS m/z 361.0 (M+H).

1-(2-Chloro-benzyl)-1H-pyrazole-3-carboxylic acid 2-chloro-benzyl ester (**817B**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (m, 1H), 7.44 (d, 1H, J = 2.4 Hz), 7.40 (m, 2H), 7.27 (m, 4H), 7.08 (dd, 1H, J = 1.6, 7.6 Hz), 6.87 (d, 1H, J = 2.4 Hz), 5.54 (s, 2H), 5.51 (s, 2H); HPLC-MS t_R = 2.22 min (UV_{254} nM); mass calculated for formula $C_{18}H_{14}Cl_2N_2O_2$ 360.0, observed LCMS m/z 361.0 (M+H).

Part B:

To **817B** (685 mg, 1.90 mmol) in THF (10 mL) was added 1.0 M $LiAlH_4$ (1.14 mL, 1.14 mmol) with ice cooling. The reaction mixture was stirred for 1 hour. The reaction was quenched with water (1 mL), 3 M NaOH (1 mL) and water (3 mL). The organic layer was decanted and the precipitate was washed with EtOAc. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 1:1 DCM:EtOAc) yielded **818** as an oil (350 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, 1H, J = 2.4 Hz), 7.39 (dd, 1H, J = 2.4, 8.0 Hz), 7.25 (m, 2H), 7.02 (dd, 1H, J = 1.6, 7.2 Hz), 6.30 (d, 1H, J = 2.4 Hz), 5.43 (s, 2H), 4.73 (s, 2H), 2.5 (bs, 1H, OH); HPLC-MS t_R = 1.29 min ($UV_{254\ nm}$); mass calculated for formula $C_{11}H_{11}ClN_2O$ 222.1, observed LCMS m/z 223.1 (M+H).

Part C:

To **818** (350 mg, 1.57 mmol) in toluene (5 mL) was added phosphorous tribromide (163 µL, 1.73 mmol). The reaction mixture was heated to reflux in a pre-heated oil bath for 15 minutes. The mixture was cooled, poured over ice and extracted with EtOAc. The combined organic layer was washed with bicarbonate solution and brine, dried over sodium sulfate and concentrated to yield **819** as a white solid (414 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (m, 2H), 7.25 (m, 2H), 7.00 (dd, 1H, J = 2.0, 7.2 Hz), 6.36 (d, 1H, J = 2.4 Hz), 5.41 (s, 2H), 4.53 (s, 2H); HPLC-MS t_R = 1.96 min ($UV_{254\ nm}$); mass calculated for formula $C_{11}H_{10}BrClN_2$ 284.0, observed LCMS m/z 285.1 (M+H).

Part D:

To **819** (412 mg, 1.44 mmol) in DMF (5 mL) was added phthalimide (255 mg, 1.73 mmol) and cesium carbonate (515 mg, 1.58 mmol). The reaction mixture was stirred overnight at room temperature. The solids were removed by filtration and the filtrate was concentrated. The residue was dissolved in EtOAc and water. The layers were separated. The organic layer was washed with brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 5% EtOAc/DCM) yielded **820** as a solid (418 mg, 82%). HPLC-MS t_R = 1.96 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{14}ClN_3O_2$ 351.1, observed LCMS m/z 352.2 (M+H).

Part E:

To **820** (418 mg, 1.19 mmol) in ethanol (20 mL) was added hydrazine monohydrate (231 µL, 4.75 mmol) and the reaction was heated to reflux for 3 hours. The mixture was cooled and diluted with 50% EtOAc/hexanes (40 mL). The solids were removed by filtration and were thoroughly washed with 50% EtOAc/hexanes (30 mL). The filtrate was concentrated. The residue was dissolved in EtOAc and washed with water and brine, dried over sodium sulfate and concentrated to afford **821** as a semi-solid (205 mg, 78%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (m, 1H), 7.38 (d, 1H, J = 2.0 Hz), 7.23 (m, 2H), 6.92 (dd, 1H, J = 2.0, 7.2 Hz), 6.22 (d, 1H, J = 2.0 Hz), 5.39 (s, 2H), 3.91 (s, 2H); HPLC-MS t_R = 0.91 min ($UV_{254\ nm}$); mass calculated for formula $C_{11}H_{12}ClN_3$ 221.07, observed LCMS m/z 222.1 (M+H).

Part F:

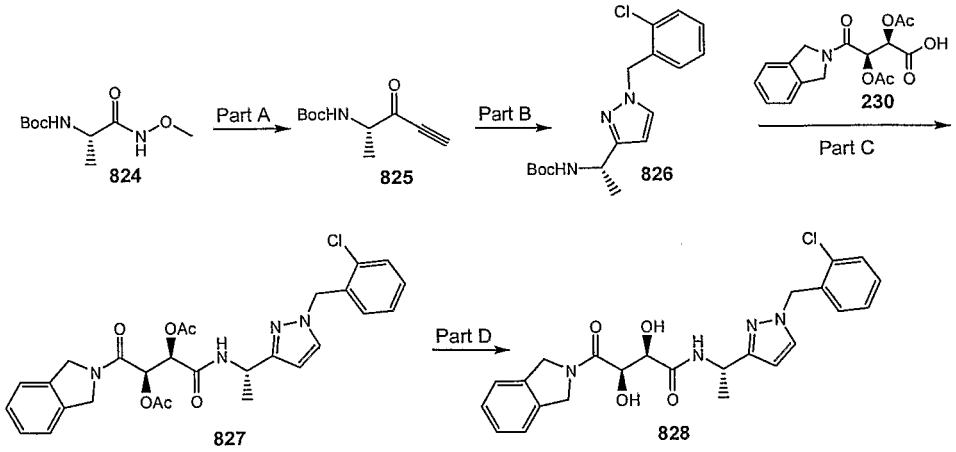
To **821** (49 mg, 0.22 mmol) in DMF (2 ml) was added **230** (67 mg, 0.2 mmol), DIEA (77 µL, 0.44 mmol) and HATU (84 mg, 0.22 mmol). The reaction mixture was stirred overnight. The DMF was removed in vacuo and the residue was dissolved in EtOAc. The organic layer was washed with bicarbonate solution, 0.1 N HCl, and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 80%

EtOAc/Hex) yielded **822** as a solid (70 mg, 65%). HPLC-MS t_R = 1.80 min ($UV_{254\ nm}$); mass calculated for formula $C_{27}H_{27}ClN_4O_6$ 538.2, observed LCMS m/z 539.2 (M+H).

Part G:

A mixture of **822** (70 mg, 0.13 mmol) and potassium carbonate (90 mg, 0.65 mmol) in MeOH (2 mL) was stirred 1 hour. The reaction was diluted with EtOAc and poured into brine solution. Additional salt was added and the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic layer was dried over sodium sulfate and concentrated to yield **823** as a white solid (45 mg, 76%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (t, 1H, J = 6.0 Hz), 7.70 (d, 1H, J = 2.0 Hz), 7.46 (dd, 1H, J = 2.0, 8.0 Hz), 7.36 – 7.27 (m, 6H), 6.94 (dd, 1H, J = 2.0, 7.6 Hz), 6.20 (d, 1H, J = 2.0 Hz), 5.68 (d, 1H, J = 6.8 Hz), 5.35 (s, 2H), 5.06 (d, 1H, J = 14.4 Hz), 5.03 (d, 1H, J = 7.6 Hz), 4.91 (d, 1H, J = 14.4 Hz), 4.76 (d, 1H, J = 15.6 Hz), 4.62 (dd, 1H, J = 2.8, 7.6 Hz), 4.61 (d, 1H, J = 14.8 Hz), 4.26 (m, 3H); HPLC-MS t_R = 1.55 min ($UV_{254\ nm}$); mass calculated for formula $C_{23}H_{23}ClN_4O_4$ 454.1, observed LCMS m/z 455.2 (M+H).

Example 20B: Pyrazole Spacer



Part A:

To the Weinreb amide **824** (prepared using the method of De Luca, L.; Giacomelli, G.; Taddei, M. *J. Org. Chem.* **2001**, *66*, 2534) (200 mg, 0.85

mmol) in THF (15 mL) was added lithium (trimethylsilyl)acetylide (4.3 mL, 2.14 mmol) dropwise at 0 °C. The reaction mixture was stirred for 1 hour then diluted with EtOAc (50 mL). The mixture was washed with 0.1 N HCl (50 mL), dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 20% EtOAc/Hex) afforded **825** (91 mg, 54%).

Part B:

A mixture of **825** (71 mg, 0.33 mmol), (2-chloro-phenyl)-hydrazine dihydrochloride (89 mg, 0.39 mmol) and potassium carbonate (200 mg, 1.64 mmol) in methanol (5 mL) were stirred at reflux for 12 hours. The reaction mixture was cooled and diluted with EtOAc (50 mL) and water (50 mL). The organic layer was separated, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 20% EtOAc/Hex) afforded **826** (50 mg, 15%). HPLC-MS t_R = 2.10 min (ELSD); mass calculated for formula $C_{17}H_{22}ClN_3O_2$ 335.1, observed LCMS m/z 336.2 (M+H).

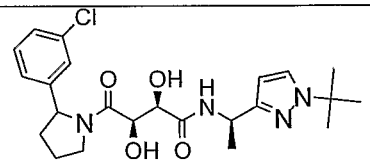
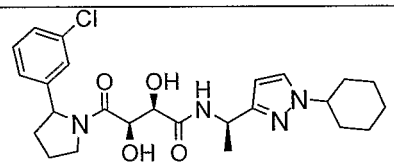
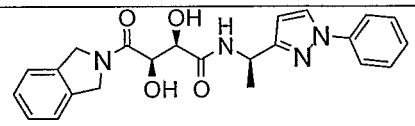
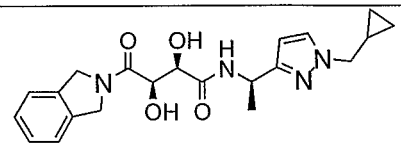
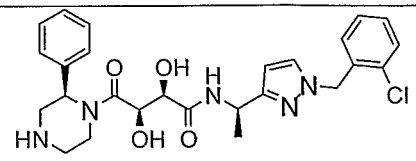
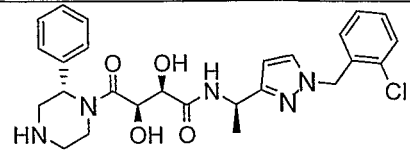
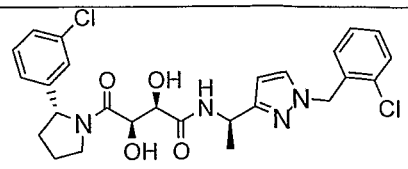
Part C:

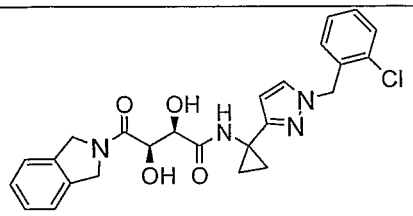
Compound **826** (45 mg, 0.13 mmol) was dissolved in 25% TFA/DCM (4 mL) and stirred for 30 minutes. The solvents were removed in vacuo and the material was used without further purification. The residue was dissolved in DMF (5 mL) and **230** (25 mg, 0.07 mmol), DIEA (300 µL, 1.68 mmol) and HATU (32 mg, 0.09 mmol) were added. The reaction mixture was stirred overnight. The DMF was removed in vacuo and the residue was dissolved in EtOAc and water. The organic layer was separated and washed with 0.1 N NaOH, 0.1 N HCl and brine, dried over sodium sulfate and concentrated. Compound **827** was used without further purification.

Part D:

Compound **827** (~25 mg, 0.05 mmol) was dissolved in methanol (5 mL) and a solution on potassium carbonate (50 mg) in water (1 mL) was added. The reaction was stirred for 30 minutes. The reaction mixture was diluted with ethyl acetate and brine. The organic layer was separated, dried over sodium

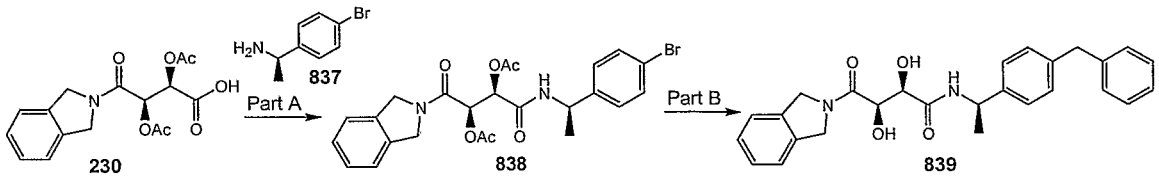
sulfate and concentrated. Purification by reverse phase prep-LC afforded **828** as a white powder (15 mg, 65%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (d, 1H, J = 8.0 Hz), 7.70 (d, 1H, J = 1.6 Hz), 7.47 (dd, 1H, J = 1.6, 7.6 Hz), 7.35 – 7.26 (m, 6H), 6.89 (dd, 1H, J = 1.6, 7.2 Hz), 6.29 (d, 1H, J = 2.0 Hz), 5.38 (s, 2H), 5.04 (d, 1H, J = 15.2 Hz), 4.97 (m, 2H), 4.90 (d, 1H, J = 14.0 Hz), 4.76 (d, 1H, J = 16.4 Hz), 4.61 (m, 2H), 4.27 (d, 1H, J = 2.4 Hz), 1.39 (d, 3H, J = 6.8 Hz); HPLC-MS t_R = 4.25 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{24}H_{25}ClN_4O_4$ 468.2, observed LCMS m/z 469.1 (M+H).

Compound #	Structure	Exact mass	MS m/e (M+H)
829		462.2	463.1
830		488.2	489.2
831		420.2	421.1
832		398.2	399.1
833		511.2	512.2
834		511.2	512.2
835		530.2	531.1

836		480.2	481.1

Example 21: α-Methyl benzyl amines

Example 21A:



Part A:

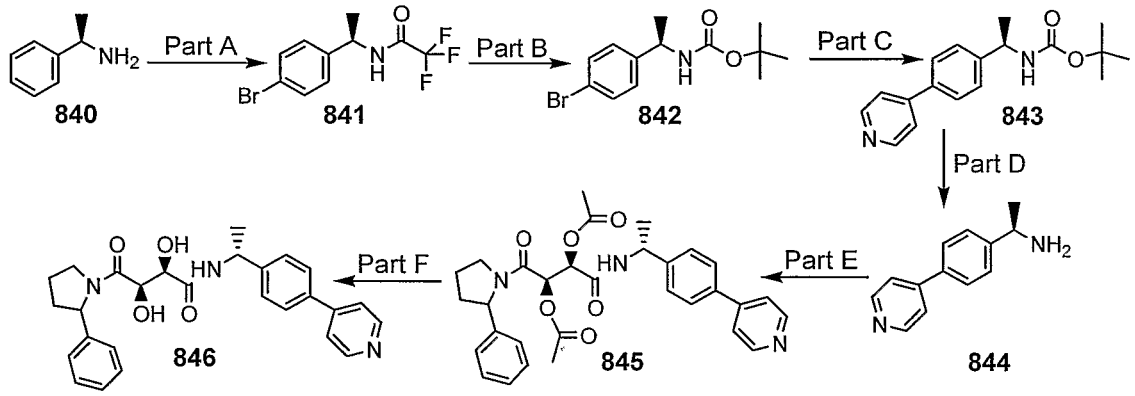
A mixture of 1R-(4-bromo-phenyl)-ethylamine (837) (0.18 mL, 1.25 mmol), **230** (349 mg, 1.0 mmol), DIEA (357 µL, 2.0 mmol) and HATU (456 mg, 1.2 mmol) in NMP (10 mL) was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with bicarbonate solution, 0.1 N HCl, and brine, dried over sodium sulfate and concentrated. **838**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 (d, 1H, J = 7.6 Hz), 7.49 (dd, 2H, J = 2.0, 6.8 Hz), 7.37 – 7.25 (m, 6H), 5.56 (ABq, 2H, J = 6.8 Hz), 4.99 (d, 1H. J = 13.2 Hz), 4.89 (m, 2H), 4.70 (d, 1H, J = 16.0 Hz), 4.51 (d, 1H, J = 16.4 Hz), 2.09 (s, 3H), 2.03 (s, 3H), 1.32 (d, 3H, J = 7.2 Hz).

Part B:

To **838** (135 mg, 0.26 mmol), $PdCl_2$(dppf) (22 mg, 0.03 mmol), potassium phosphate (166 mg, 0.78 mmol) in dioxane (5 mL) under argon atmosphere was added benzyl-9-BBN (0.5 M in THF, 1.3 mL, 0.65 mmol). The reaction mixture was heated to 60 °C overnight. The reaction mixture was filtered through a celite pad and the pad was rinsed with ethyl acetate. The filtrate

was concentrated. The crude product was dissolved in methanol (5 mL) and potassium carbonate (4 mg) was added. The reaction mixture was stirred for 1 hour, filtered and concentrated to afford **839** as a solid (50 mg, 42%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (d, 1H, J = 7.6 Hz), 7.34 – 7.10 (m, 13H), 5.03 (d, 1H. J = 14.4 Hz), 4.90 (m, 2H), 4.72 (d, 1H, J = 16.8 Hz), 4.58 (m, 2H), 4.20 (d, 1H, J = 3.2 Hz), 3.87 (s, 2H), 1.37 (d, 3H, J = 7.2 Hz); HPLC-MS t_R = 1.89 min (UV_{254nm}); mass calculated for formula $C_{27}H_{28}N_2O_4$ 444.2, observed LCMS m/z 445.1 (M+H).

Example 21B:



Part A:

CH_2Cl_2 (300 mL) and trifluoroacetic anhydride (100 g, 0.476 mol) were added to a 2 liter 3-necked flask. The flask was equipped with a drying tube and cooled in an ice-water bath. A solution of (R)-α-methylbenzylamine **(840)** (53.72 g, 0.443 mol) dissolved in 100 mL of CH_2Cl_2 was added over 40 min. The ice bath was removed and the reaction mixture was stirred at rt for 3 h. The reaction mixture was cooled with an ice-water bath and methanesulfonic acid (110 mL, 1.69 mol) was added. Dibromodimethylhydantoin (65 g, 0.227 mol) was added in portions over 1 hr 15 min. The reaction mixture was left stirring overnight then poured into a solution prepared from 60 mL of 1 M $NaHSO_3$ and 500 mL of ice and water. The layers were separated and the aqueous layer was extracted with 100 mL of CH_2Cl_2. The combined organic layer was washed with water and brine, then dried with $MgSO_4$. The solvent

was evaporated to give a white solid. This material was recrystallized from Et_2O/Hexanes to give compound **841**. MS (EI) m/z M+H Obsd 297.16

Part B:

Compound **841** (8.09 g, 27.3 mmol) was dissolved in 40 mL of dioxane, 10 mL of methanol, and 40 mL of 1 M aqueous LiOH. The reaction mixture was stirred at rt for 2.5 h under N_2. Boc anhydride (7.45 g, 34.1 mmol) and EtOAc (25 mL) were added and the reaction mixture was stirred at rt under N_2 for 1.5 h. The reaction mixture was diluted with EtOAc and brine. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with citric acid, water, and brine, then dried with $MgSO_4$. The solvents were evaporated and the crude product was purified via flash sgc using a 5%-10% EtOAc/Hexanes gradient as the mobile phase. White solid **842** (7.95 g) was obtained as product. MS (EI) m/z M+Na Obsd 324.01

Part C:

Compound **842** (1.11 g, 3.69) and 4-pyridine boronic acid (0.55 g, 4.48 mmol) were suspended in 1-propanol (8 mL) and stirred for 25 min at 40 °C. Palladium (II) acetate (55 mg, 0.24 mmol) and water (4 mL), were added, followed by sodium carbonate (0.47 g, 4.43 mmol) and triphenyl phosphine (197 mg 0.75 mmol). The reaction mixture was stirred under N_2 at 80 °C for 21 h. The reaction mixture was allowed to cool to rt and diluted with EtOAc and 0.5 M $NaHCO_3$. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried with $MgSO_4$, filtered, and concentrated to give an orange solid. The crude product was purified via sgc using 30% EtOAc/Hexanes, followed by 30% EtOAc/Hexanes with 2% added diisopropylethylamine added, followed by 40% EtOAc/Hexanes as the mobile phase. White solid **843** was obtained as product (0.71 g). MS (EI) m/z M+H Obsd 299.10.

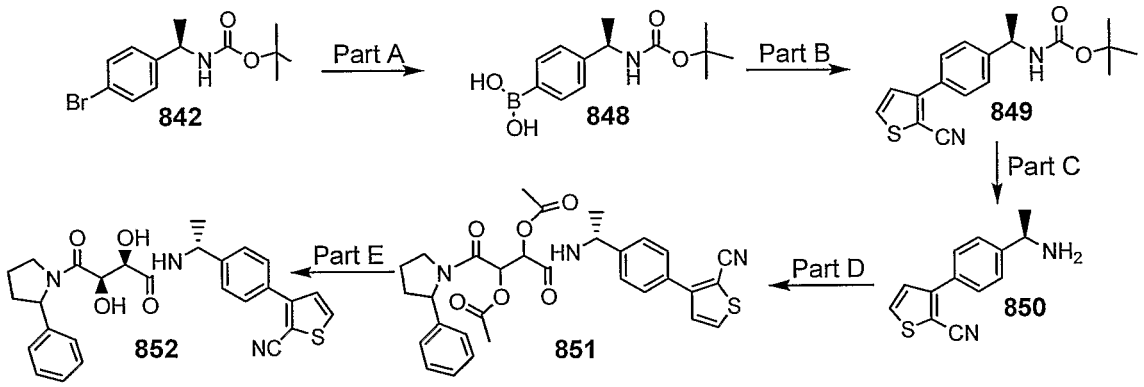
Part D:

Compound **843** (0.70, 2.3 mmol) was suspended in 22 mL of 4 M HCl in dioxane and 8 mL of CH_2Cl_2. The reaction mixture was stirred under N_2 at rt for 6 h, then concentrated to give white solid **844** (0.70 g). MS (EI) m/z M+H Obsd 199.09.

Parts E & F:

Compound **846** was prepared using procedures similar to those described in Example 14, Steps E&F. MS (EI) m/z M+H Obsd 460.1

Example 21C:



Part A:

A 500 mL Schlenck Flask equipped with a stir bar was flame dried under N_2 flow, capped with a septum, and allowed to cool to rt. A solution of n-butyl lithium in hexanes (55 mL, 2.5 Molar, 137.4 mmol) was added via syringe. The flask was cooled in a dry ice/2-propanol bath. Tetramethylethylene diamine (TMEDA-19.0 g, 167 mmol) was added. Compound **842** (20 g, 66.8 mmol) was dissolved in anhydrous THF (200 mL) and added to the reaction mixture over 30 min via addition funnel. The reaction mixture was stirred at -78 C for 15 min. Triethyl borate was added (21.4 mL, 176 mmol) as a solution in 40 mL of anhydrous THF. The reaction mixture was stirred for 30 min. The reaction mixture was quenched at -78 °C with 1.0 M aq HCl to a pH of 2, then

allowed to warm to rt. The reaction mixture was extracted with EtOAc. The organic layer was dried with $MgSO_4$ and concentrated to dryness. The crude product was purified via sgc using 5:95 MeOH:CH_2Cl_2 as the mobile phase. White solid **848** was obtained as product (3.8 grams). Data for **848**: ^{1}HNMR (400 MHz, CD_3OD) δ 7.56 (d, J = 8Hz, 2H), 7.29 (d, J = 8Hz, 2H), 4.58-4.64 (m, 1H), 1.41-1.36 (m, 12H).

Part B:

Compound **848** (300 mg, 1.13 mmol), 3-bromo-2-cyanothiophene (192 mg, 1.02 mmol), acetonitrile (4 mL), Dichloro[1, 1'-bis(diphenylphosphino) ferrocene] palladium(II) dichloride (Strem, 171 mg, 0.23 mmol), and 1.25 mL of 1 M aq K_2CO_3 were added to a microwave tube equipped with a stir bar. N_2 was bubbled through the soln. and the tube was capped. The reaction mixture was irradiated at 150 °C for 5 min in a Personal Chemistry "Companion" microwave oven. The resulting material was filtered through Celite which was washed with EtOAc. The filtrate was partitioned between EtOAc and water. The organic layer was washed with water and treated with Na_2SO_4 and Darco activated carbon. The mixture was filtered and concentrated to dryness. The crude product was purified via sgc using 60:40 Hexanes: EtOAc as the mobile phase. Compound **849** was obtained as a yellow oil (224 mg) which crystallized on standing. m/z Obsd. M+Na 350.93

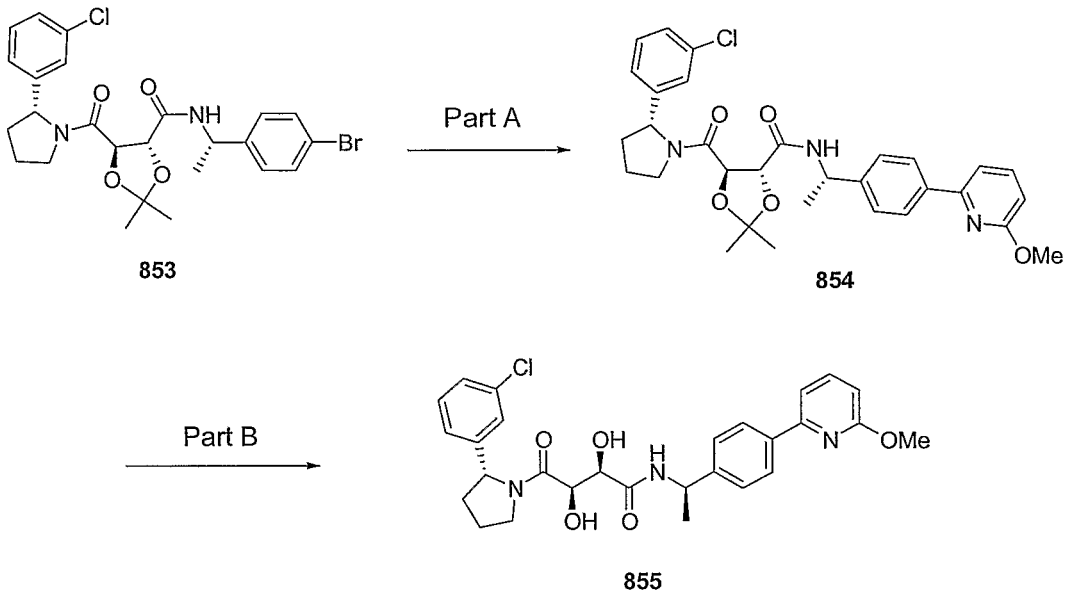
Part C:

Compound **849** (224 mg, 0.682 mmol) was dissolved in 2.8 mL of CH_2Cl_2 and 1.2 mL of trifluoroacetic acid. The reaction mixture was stirred at rt for 2 hours, then concentrated to dryness. The crude product was purified via sgc using 9:1 CH_2Cl_2 :MeOH (NH_3) as the mobile phase to give 110 mg of **850** as an oil. m/z Obsd. M+H 229.10

Parts D and E:

Compounds **851** and **852** were prepared via procedures similar to those described in Example 14, Parts D and E. Data for **851:** m/z Obsd. M+H 574.05. Data for **852**: m/z Obsd. M+Na 511.91.

Example: 21D:



853 854 855

Compound **853** was synthesized using the procedures described in Example 1.

Part A:

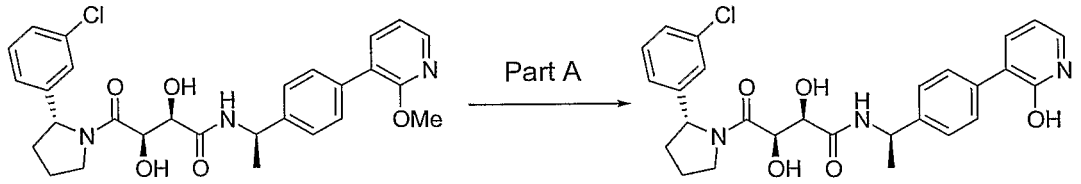
Compound **853** (25 mg, 0.050 mmol) was dissolved in THF (1mL) and $PdP(t\text{-}Bu_3)_2$ (5 mg, 0.0097 mmol) was added under an argon atmosphere. 6-Methoxy-2-pyridylzinc bromide (0.5 M in THF, 0.2 mL) was added and the reaction was stirred at 50 °C overnight. The reaction mixture was filtered over a bed of celite and then evaporated under reduced pressure. Purification by reverse phase prep-LC afforded an off-white solid **854** (10 mg, 38%) after lyophilization. HPLC-MS t_R = 6.138 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{31}H_{34}ClN_3O_5$ 563.2, observed LCMS m/z 564.1 (M+H).

Part B:

Compound **854** (10 mg, 0.0188 mmol) was dissolved in MeOH (0.3 mL) and TFA (4 mL) and stirred for 2 hours at room temperature. The solvent was removed to provide the pure product **855** (9.36 mg, 95%). HPLC-MS t_R =

5.098 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{28}H_{30}ClN_3O_5$ 523.1, observed LCMS m/z 524.1 (M+H).

Example: 21E:



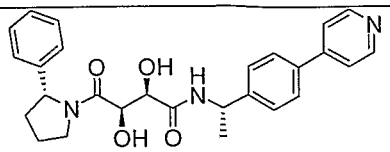
856 857

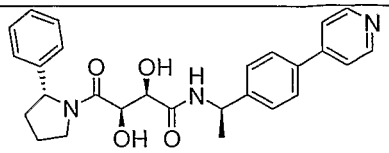
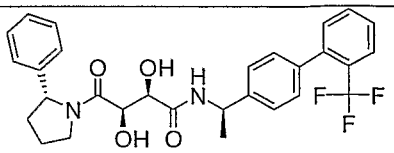
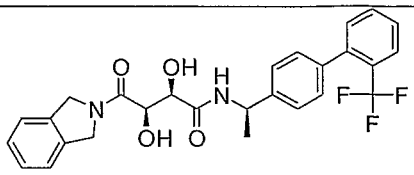
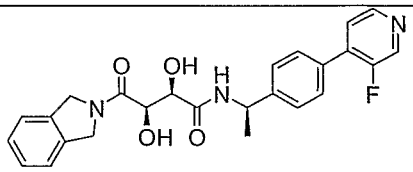
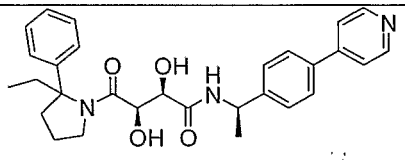
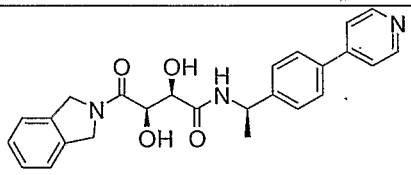
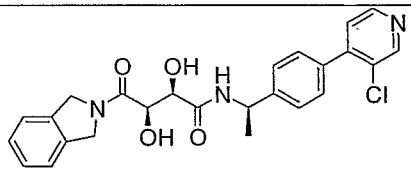
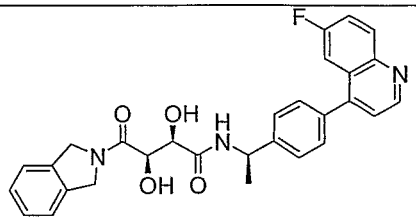
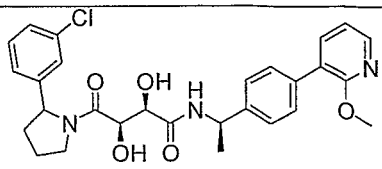
Compound **856** was synthesized using the Suzuki procedures desribed in Example 12.

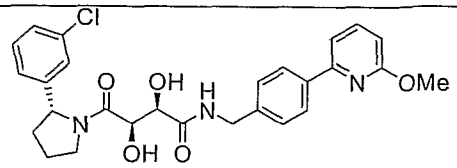
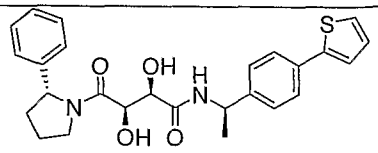
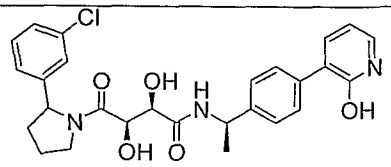
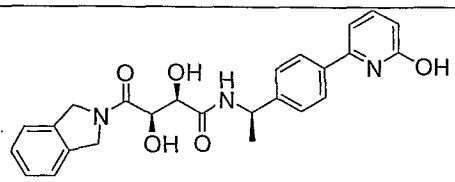
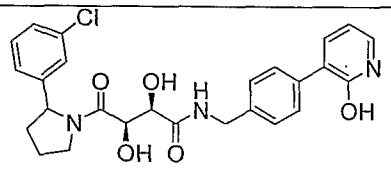
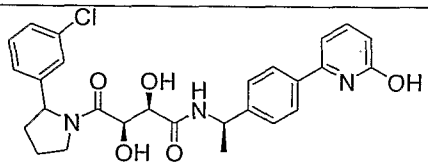
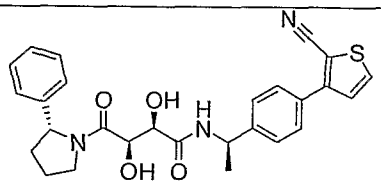
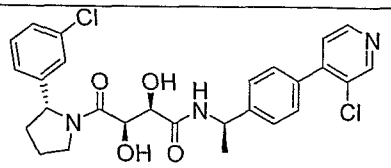
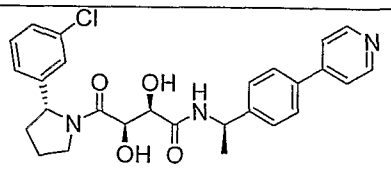
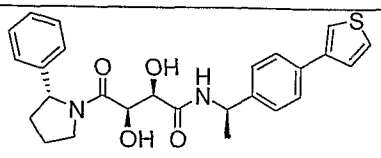
Part A:

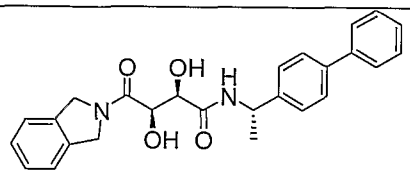
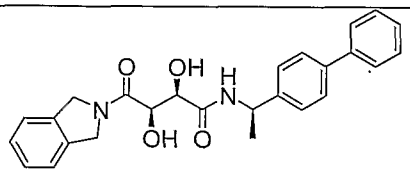
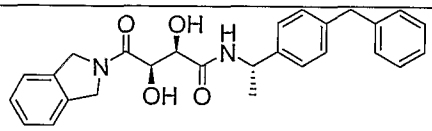
Compound **856** (160 mg, 0.30 mmol) was dissolved in acetonitrile (5 mL) and sodium iodide (140 mg, 1.0 mmol) was added followed by trimethylsilylchloride (105 mg, 1.0 mmol). Water (0.1 mL) was added and the reaction mixture was stirred at reflux for 4 hours. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with bicarbonate solution and brine; dried over sodium sulfate and concentrated. Purification by reverse phase prep-LC afforded an off-white solid **857** (86 mg, 56%) after lyophilization. HPLC-MS t_R = 3.72 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{27}H_{28}ClN_3O_5$ 509.1, observed LCMS m/z 510.1 (M+H).

The following table contains compounds made using the procedures described in Example 21 A – E.

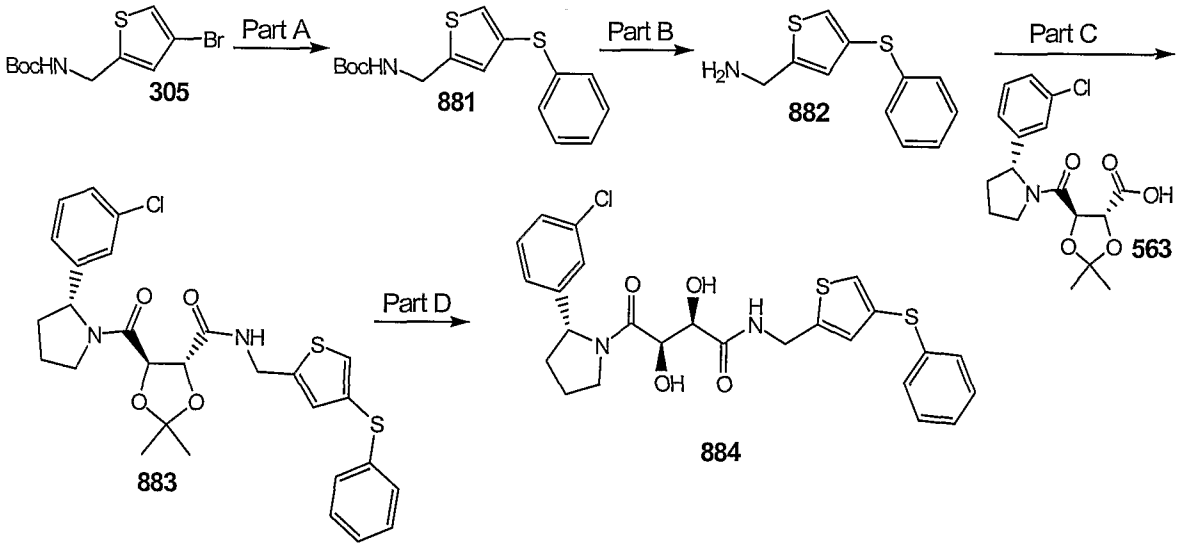
Compound #	Structure	Exact mass	MS m/e (M+H)
858		459.2	460.1

859		459.2	460.1
860		526.2	527.7
861		498.2	499.0
862		449.2	450.0
863		487.3	488.1
864		431.2	432.1
865		465.2	466.1
866		499.2	500.0
867		523.2	524.2

868		509.2	510.1
869		464.2	464.9
870		509.2	510.2
871		447.2	448.2
872		495.2	496.2
873		509.2	510.2
874		489.2	511.9 (M+Na)
875		527.1	528.1
876		493.1	494.1
877		464.2	464.9

878		430.2	431.2
879		430.2	431.2
880		444.2	445.2

Example 22



Part A:

To **305** (100 mg, 0.34 mmol) in THF (2 mL) at –90 °C under argon was added n-butyl lithium (1.6 M, 0.140 mL, 0.22 mmol) dropwise. The reaction mixture was stirred for 30 minutes at –90 °C. Then diphenyl disulfide (90 mg, 0.4 mmol) in THF (1 mL) was added slowly. The reaction mixture was stirred for 30 minutes at –90 °C. The reaction mixture was quenched with saturated ammonium chloride solution and warmed to room temperature. The mixture was diluted with ethyl acetate (10 mL) and the layers were separated. The organic layer was washed with water and brine. Dried over sodium sulfate and

organic layer was washed with water and brine. Dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 5% EtOAc/hexane) afforded **881** (19 mg, 59%). HPLC-MS t_R = 2.28 min ($UV_{254\ nm}$,); mass calculated for formula $C_{16}H_{19}NO_2S_2$ 321.09, observed LCMS m/z 322.2 (M+H).

Part B:

To **881** (66 mg, 0.2 mmol) was added 4N HCl in dioxane (1 mL). The reaction mixture was stirred for 1 hour. The solvents were removed in vacuo and the crude product was used without further purification. HPLC-MS t_R = 1.12 min ($UV_{254\ nm}$); mass calculated for formula $C_{11}H_{11}NS_2$ 221.0, observed LCMS m/z 222.1 (M+H).

Part C:

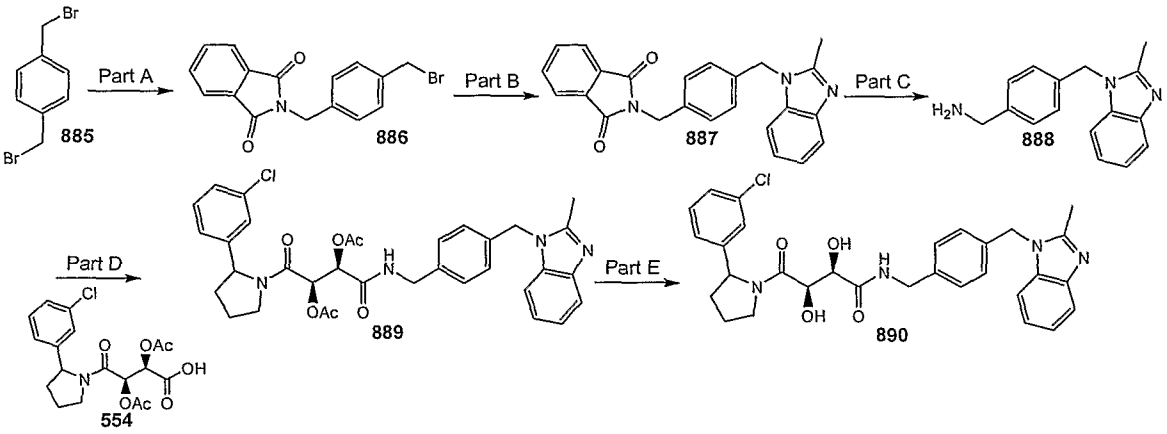
To **563** (56 mg, 0.16 mmol) in DMF (2 mL) was added **882** (66 mg, 0.26 mmol), DIEA (82 µL, 0.46 mmol) and HATU (78 mg, 0.24 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate (20 mL) and water (20 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with sodium bicarbonate solution and brine, dried over sodium sulfate and concentrated. Compound **883** (43 mg, 48%) was used without further purification. HPLC-MS t_R = 2.40 min ($UV_{254\ nm}$); mass calculated for formula $C_{28}H_{29}ClN_2O_4S_2$ 556.1, observed LCMS m/z 557.0 (M+H).

Part D:

Compound **883** (25 mg, 0.04 mmol) was dissolved in 80:20 TFA:water (1 mL) and stirred for 1.5 hours. The reaction was quenched with 1:1 water:acetonitrile (1 mL) and the solvents were removed in vacuo. Purification by reverse phase prep-LC afforded **884** as a white solid (5 mg,

22%). HPLC-MS t_R = 2.04 min ($UV_{254\ nm}$); mass calculated for formula $C_{25}H_{25}ClN_2O_4S_2$ 516.1, observed LCMS m/z 517.1 (M+H).

Example 23:



Part A:

A mixture of □□'-dibromo-p-xylene (**885**) (528 mg, 2.0 mmol), phthalimide (294 mg, 2.0 mmol) and cesium carbonate (717 mg, 2.2 mmol) in DMF (5 mL) was stirred for 4 hours. The reaction mixture was filtered and the filtrate was concentrated. The residue was dissolved in DCM and washed with bicarbonate solution and brine. The organic layer was dried over sodium sulfate and concentrated. Recrystallization from 75% EtOAc/hexanes removed the dialkylated product. The mother liquor was concentrated and the monoalkylated product **886** was isolated by column chromatography (SiO_2, 50% DCM/Hex) as a white solid (110 mg, 16%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, 2H, J = 2.4 Hz), 7.72 (d, 2H, J = 2.4 Hz), 7.41 (d, 2H, J = 7.2 Hz), 7.34 (d, 2H, J = 7.2 Hz), 4.84 (s, 2H), 4.46 (s, 2H).

Part B:

A mixture of **886** (110 mg, 0.33 mmol), 2-methyl benzimidazole (44 mg, 0.33 mmol) and cesium carbonate (114 mg, 0.35 mmol) in DMF (5 mL) was stirred

overnight at room temperature. The reaction mixture was filtered and concentrated. The residue was partitioned between bicarbonate solution and ethyl acetate. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulfate and concentrated to afford **887** as an off-white solid (120 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (m, 2H), 7.70 (m, 2H), 7.37 (d, 2H, J = 8.0 Hz), 7.25 – 7.18 (m, 4H), 7.00 (d, 2H, J = 8.7 Hz), 5.30 (s, 2H), 4.82 (s, 2H), 2.57 (s, 3H).

Part C:

A mixture of **887** (120 mg, 0.31 mmol) and hydrazine hydrate (61 µL, 1.26 mmol) in ethanol (10 mL) was heated to reflux for 3 hours. The reaction mixture was concentrated. The residue was dissolved in ethyl acetate and washed with bicarbonate solution. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulfate and concentrated to afford **888** as a yellow oil (31 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, 1H, J = 1.2, 8.4 Hz), 7.51 (dd, 1H, J = 3.2, 6.4 Hz), 7.26 – 7.17 (m, 4H), 7.01 (d, 2H, J = 8 Hz), 5.30 (s, 2H), 3.85 (s, 2H), 2.60 (s, 2H), 2.57 (s, 3H).

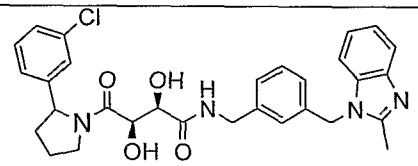
Part D:

A mixture of **888** (31 mg, 0.12 mmol), **554** (40 mg, 0.1 mmol), DIEA (38 µL, 0.22 mmol) and HATU (46 mg, 0.12 mmol) in DMF (2 mL) was stirred overnight. The DMF was removed in vacuo. The residue was dissolved in ethyl acetate, washed with bicarbonate solution and brine, dried over sodium sulfate and concentrated to afford **889** as a film (61 mg, 96%). HPLC-MS t_R = 1.38 min ($UV_{254\ nm}$); mass calculated for formula C34H35ClN4O6 630.2, observed LCMS m/z 631.2 (M+H).

Part E:

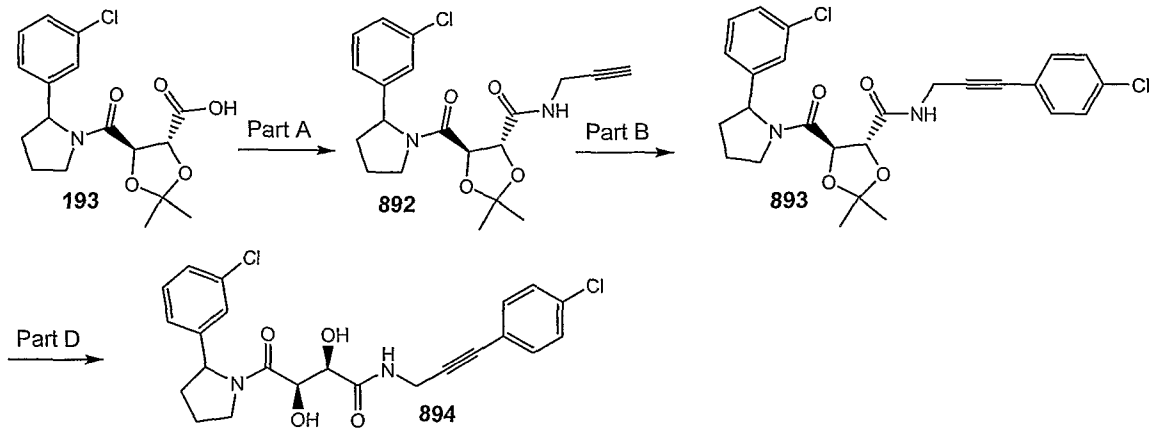
To **889** (61 mg, 0.097 mmol) in methanol (2 mL) was added anhydrous hydrazine (5 µL, 0.16 mmol). The reaction mixture was stirred overnight,

concentrated, purified by reverse phase prep-LC and treated with HCl to afford **890** as an HCl salt (19 mg, 33%). HPLC-MS t_R = 3.42 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{30}H_{31}ClN_4O_4$ 546.2, observed LCMS m/z 547.2 (M+H).

Compound #	Structure	Exact mass	MS m/e (M+H)
891		546.2	547.2

Example 24: Alkyne linkages

Example 24A:



Part A:

To **193** (200 mg, 0.57 mmol) in DCM (5 mL) was added propargyl amine (62 mg, 1.13 mmol), DIEA (396 µL, 1.71 mmol), DMAP (7 mg, 0.06 mmol) and EDC (140 mg, 0.74 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 60% ethyl acetate/hexanes) afforded **892** as an oil (136 mg, 62%). HPLC-MS t_R = 1.76 and 1.83 min ($UV_{254\ nm}$); Mass calculated for formula $C_{20}H_{23}ClN_2O_4$ 390.1, observed LCMS m/z 391.1 (M+H).

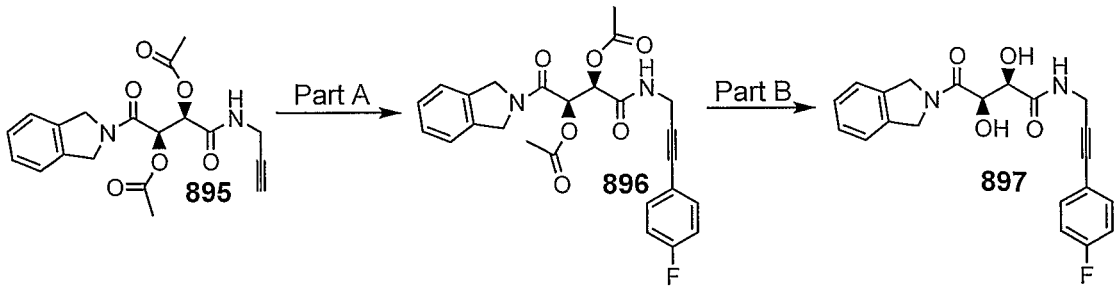
Part B:

To **892** (20 mg, 0.05 mmol) in DMF(1 mL) was added 4-chloro-iodobenzene (24 mg, 0.10 mmol), copper(I) iodide (1 mg, 0.005 mmol), $PdCl_2(Ph_3P)_2$ (1.8 mg, 0.003 mmol) and triethylamine (1 mL). The reaction mixture was stirred overnight at 50 °C under argon atmosphere. The reaction mixture was diluted with ethyl acetate, washed with 0.1 N HCl, dried over sodium sulfate and concentrated. The material was used without further purification. **893**: HPLC-MS t_R = 2.28 and 2.32 min ($UV_{254\ nm}$); Mass calculated for formula $C_{26}H_{26}Cl_2N_2O_4$ 500.1, observed LCMS m/z 501.1 (M+H).

Part C:

Compound **893** was dissolved in 4:1 TFA:water (2 mL) and stirred at room temperature for 1.5 hours. The reaction was quenched with 1:1 water:acetonitrile (2 mL) and concentrated. Purification by reverse phase prep-LC afforded **894** as a solid (2 mg). HPLC-MS t_R = 5.02 min ($UV_{254\ nm}$, 10 min); Mass calculated for formula $C_{23}H_{22}Cl_2N_2O_4$ 460.1, observed LCMS m/z 461.2 (M+H).

Example 24 B:



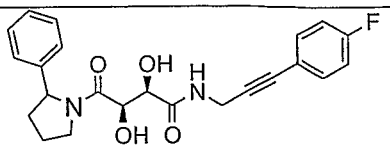
Compound **895** was obtained via procedures described in Example 2A Part A using isoindoline to open the (+)-diacetyl-L-tartaric anhydride and propargyl amine in the coupling procedure.

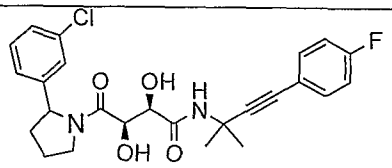
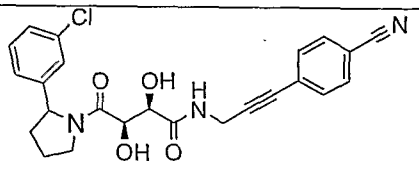
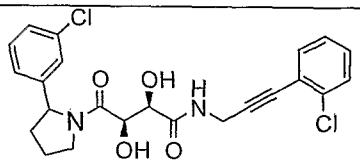
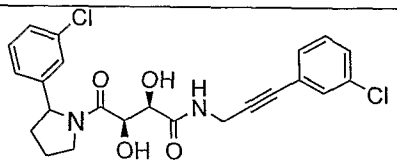
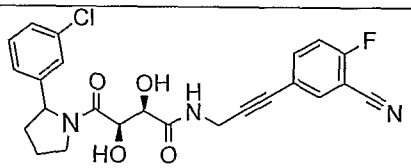
Part A:

Compound **895** (138 mg, 0.371 mmol), p-bromofluorobenzene (244 mg, 1.39 mmol), and dichlorobis(triphenylphosphine) palladium (II) (26 mg, 0.037 mmol) were dissolved in 1.5 mL CH_3CN and 1.5 mL Et_3N. The reaction mixture was heated in a sealed tube under N_2 at 80 °C for 2 h. The reaction mixture was allowed to cool to rt. EOAc and 1.0 M pH 7.0 sodium phosphate buffer were added. The layers were separated. The organic layer was washed with water and dried with $MgSO_4$. The solvent was evaporated and the crude product was purified via sgc using 3:1 EtOAc:hexanes as the mobile phase to give 20 mg of compound **896**. MS (EI) m/z Obsd M+H 467.19

Part B:

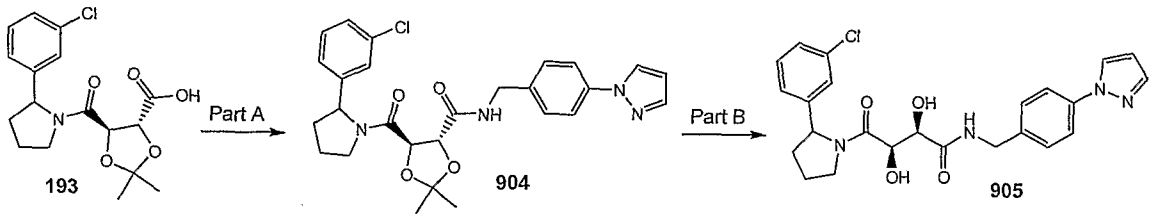
Compound **896** (20 mg, 0.043 mmol) was dissolved in 3 mL of 2 M methanolic ammonia. The reaction mixture was stirred at rt for 1 h. The reaction mixture was concentrated to dryness. The crude product was purified via prep TLC on silica plates using 97:3 CH_2Cl_2 :MeOH as the mobile phase to give 12 mg of **897**. MS (EI) m/z Obsd M+H 383.2.

Compound #	Structure	Exact mass	MS m/z (M+H)
898		410.2	411.1

899		472.2	473.2
900		451.1	452.1
901		460.1	461.2
902		460.1	461.2
903		469.1	470.2

Example 25: N-Linked biaryls

Example 25A:



Part A:

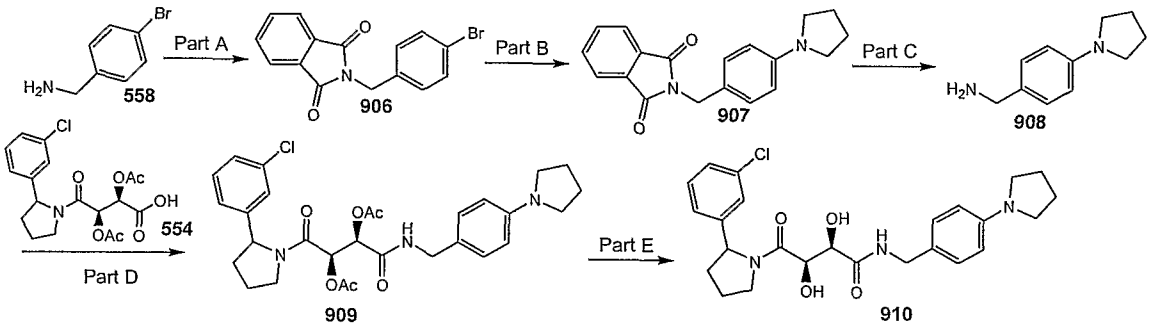
To **193** (42 mg, 0.12 mmol) in DMF (2 mL) was added 4-pyrazol-1-yl-benzylamine (25 mg, 0.14 mmol), DIEA (50 µL, 0.29 mmol) and HATU (53 mg, 0.13 mmol). The reaction mixture was stirred overnight at room

temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with 0.1 N NaOH and brine, dried over sodium sulfate and concentrated. The crude material was used without further purification. **904**: HPLC-MS t_R = 1.97 and 2.03 min ($UV_{254\ nm}$); Mass calculated for formula $C_{27}H_{29}ClN_4O_4$ 508.2, observed LCMS m/z 509.2 (M+H).

Part B:

Compound **904** was dissolved in 4:1 TFA:water (2 mL) and stirred at room temperature for 2 hours. The reaction was quenched by the addition of 1:1 acetonitrile:water (4 mL) and the solvents were removed in vacuo. Purification by reverse phase prep-LC afforded **905** as a white solid (33 mg). HPLC-MS t_R = 4.16 min ($UV_{254\ nm}$, 10 min); Mass calculated for formula $C_{24}H_{25}ClN_4O_4$ 468.2, observed LCMS m/z 469.2 (M+H).

Example 25B:



Part A:

A mixture of 4-bromobenzyl amine hydrochloride (**558**) (2.0 g, 9.0 mmol), monomethyl phthalate (1.94 g, 10.8 mmol), EDC (2.07 g, 10.8 mmol), HOBt (1.82 g, 13.5 mmol) and triethylamine (3.8 mL, 27.0 mmol) in DCM (50 mL) was stirred overnight. The reaction mixture was diluted DCM and washed with 1.0 N HCl, water, bicarbonate solution and brine, dried over sodium sulfate and concentrated. Recrystallization of the mixture from ethyl acetate afforded **906** as a solid (1.72 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (m,

2H), 7.70 (m, 2H), 7.42 (d, 2H, J = 8.2 Hz), 7.29 (d, 2H, J = 8.2 Hz), 4.79 (s, 2H). HPLC-MS t_R = 2.05 min ($UV_{254\ nm}$); Mass calculated for formula $C_{15}H_{10}BrNO_2$ 315.0, observed LCMS m/z 316.0 (M+H).

Part B:

A mixture of **906** (100 mg, 0.32 mmol), pyrrolidine (34 mg, 0.48 mmol), potassium phosphate (171 mg, 0.80 mmol), $Pd_2(dba)_3$ (8 mg, 0.008 mmol) and 2-(dicyclohexylphosphino)biphenyl (11 mg, 0.032 mmol) in dioxane (3 mL) were stirred under argon atmosphere at 90 °C overnight. The reaction mixture was filtered through celite and concentrated. The yellow residue was purified by column chromatography (SiO_2, 5% EtOAc/DCM) to afford **907** (82 mg, 84%). HPLC-MS t_R = 2.13 min (UV_{254nm}); Mass calculated for formula $C_{19}H_{18}N_2O_2$ 306.1, observed LCMS m/z 307.2 (M+H).

Part C:

To **907** (82 mg, 0.268 mmol) in 1:1 ethanol:DCM (4 mL) was added hydrazine monohydrate (52 µL, 1.07 mmol). The reaction mixture was heated to reflux overnight. The precipitate was removed by filtration and the filtrate was concentrated. The residue was dissolved in ethyl acetate, washed with water and brine, dried over sodium sulfate and concentrated to afford **908** as a white solid (23 mg, 49%). HPLC-MS t_R = 0.86 min (UV_{254nm}); Mass calculated for formula $C_{11}H_{16}N_2$ 176.1, observed LCMS m/z 177.1 (M+H).

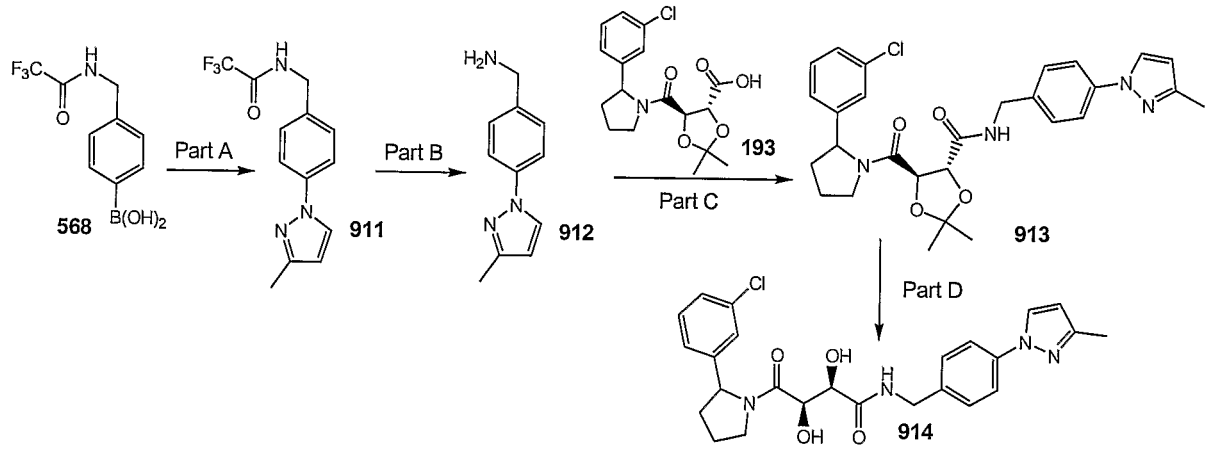
Part D:

A mixture of **554** (30 mg, 0.076 mmol), **908** (17.3 mg, 0.098 mmol), DIEA (40 µL, 0.226 mmol), DMAP (1 mg) and HATU (37 mg, 0.098 mmol) in DMF (1 mL) was stirred overnight. The reaction mixture was poured in water and extracted with ethyl acetate. The combined organic layers were washed with 0.1 N NaOH, water and brine, dried over sodium sulfate and concentrated. Compound **909** was used without further purification.

Part E:

To **909** in 3:1 methanol:water (2 mL) was added potassium carbonate (20 mg). The reaction mixture was stirred for 30 minutes. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over sodium sulfate and concentrated. Purification by reverse phase prep-LC afforded **910** as a solid (2 mg). HPLC-MS t_R = 3.57 min ($UV_{254\ nm}$ 10 min); Mass calculated for formula $C_{25}H_{30}ClN_3O_4$ 471.2, observed LCMS m/z 472.2 (M+H).

Example 25C:



Compound **568** was prepared according to the procedure of Maku, S. et. al. (*J. Comb. Chem.* **2003**, *5*, 379)

Part A:

A mixture of compound **568** (740 mg, 3 mmol), 3-methylpyrazole (123 mg, 1.5 mmol), copper (II) acetate (409 mg, 2.25 mmol), pyridine (0.25 ml), 3 mmol) in tetrahydrofuran (10 mL) was stirred at room temperature open to the air for 60 hours. The reaction mixture was diluted with ethyl acetate, filtered through celite and concentrated. Purification by column chromatography (SiO_2, 30% ethyl acetate/hexanes to 50% ethyl acetate/ hexane) afforded the product as an impure white solid (450 mg). Further purification by column chromatography (SiO_2, dichloromethane to 5% ethyl acetate /

dichloromethane) afforded **911** as a solid (295 mg, 70% purity). ^{1}H NMR (400 MHz, acetone-d_6) δ 8.97 (bs, 1H, NH), 8.16 (d, 1H, J = 2.4 Hz), 7.76 (d, 2H, J = 8.4 Hz), 7.42 (d, 2H, J = 8.8 Hz), 6.27 (d, 1H, J = 2.4 Hz), 4.55 (d, 2H, J = 5.6 Hz), 2.28 (s, 3H); HPLC-MS t_R = 1.62 min ($UV_{254\ nm}$); Mass calculated for formula $C_{13}H_{12}F_3N_3O$ 283.1, observed LCMS m/z 284.2 (M+H).

Part B:

To **911** (165 mg, 0.43 mmol) in 1:1 methanol: water (2 mL) was added 10% potassium carbonate in 2:1 methanol:water (7mL). The reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated and the residue was dissolved in ethyl acetate. The ethyl acetate layer was washed with water and brine, dried over sodium sulfate and concentrated to afford **912** as a white solid (69 mg, 86%). HPLC-MS t_R = 0.75 min ($UV_{254\ nm}$); Mass calculated for formula $C_{11}H_{13}N_3$ 187.1, observed LCMS m/z 188.1 (M+H).

Part C:

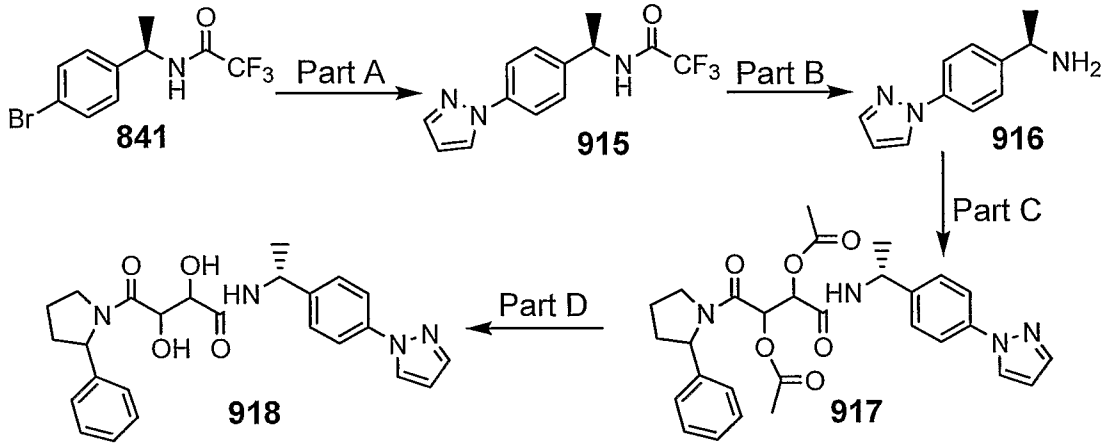
To **193** (65 mg, 0.18 mmol) in DMF (2 mL) was added **912** (38 mg, 0.2 mmol), DIEA (70 µL, 0.4 mmol) and HATU (76 mg, 0.21 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with 0.1 N NaOH and brine, dried over sodium sulfate and concentrated. Compound **913** was used without further purification. HPLC-MS t_R = 2.05 and 2.09 min ($UV_{254\ nm}$); Mass calculated for formula $C_{28}H_{31}ClN_4O_4$ 522.2, observed LCMS m/z 523.2 (M+H).

Part D:

Compound **913** was dissolved in 4:1 TFA:water (2 mL) and stirred at room temperature for 2 hours. The reaction was quenched by the addition of 1:1 acetonitrile:water (4 mL) and the solvents were removed in vacuo. Purification by reverse phase prep-LC afforded **914** as a white solid (35 mg).

HPLC-MS t_R = 4.31 min ($UV_{254\ nm}$, 10 min); Mass calculated for formula $C_{25}H_{27}ClN_4O_4$ 482.1, observed LCMS m/z 483.1 (M+H).

Example 25D:



Part A:

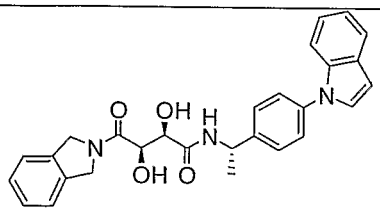
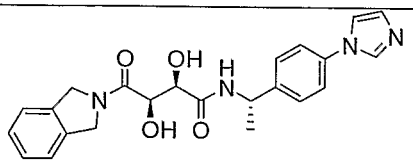
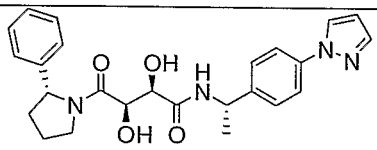
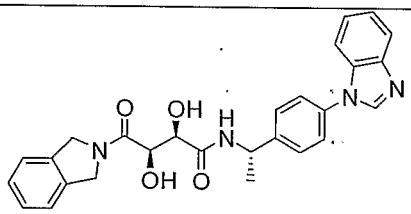
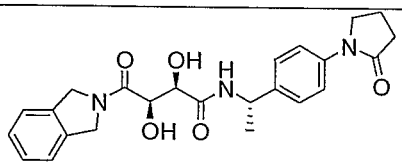
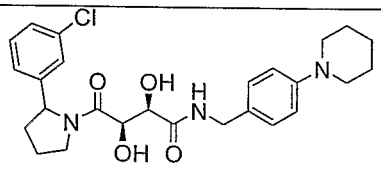
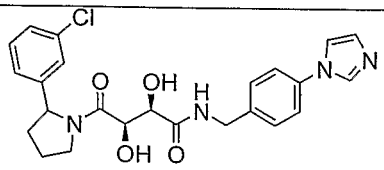
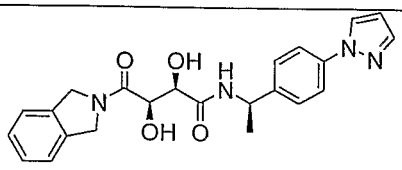
Compound **841** (0.5 g, 1.69 mmol), pyrazole (0.14 g, 2.05 mmol), CuI (0.064 g, 0.336 mmol), 1,10-phenanthroline (0.12 g, 0.66 mmol), and Cs_2CO_3 (1.1 g, 3.37 mmol) were dissolved in dimethylacetamide and stirred for 20 h at 140 °C under N_2. The reaction mixture was allowed to cool to rt and diluted with EtOAc. The resulting mixture was washed with water and concentrated to dryness. The resulting material was purified via flash sgc using CH_2Cl_2:MeOH:conc NH_4OH- (200:10:1) as the mobile phase to give 0.30 g of **915**. Data for **915**: ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.80-7.74 (m, 3H), 7.48 (d, 2H), 6.55 (s, 1H), 5.23 (m, 1H), 1.68 (d, J=4 Hz, 2H). MS (EI) of m/z Obsd. M+H 283.97

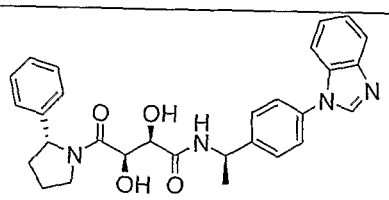
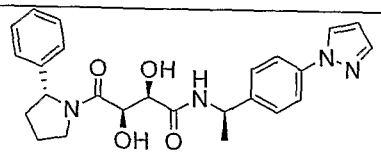
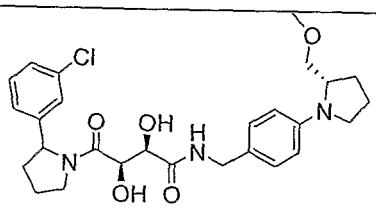
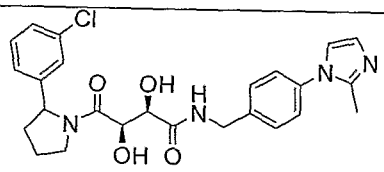
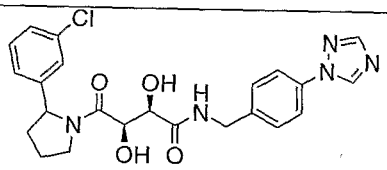
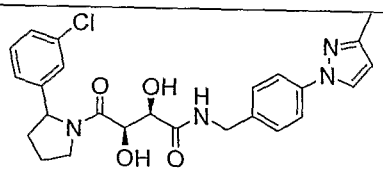
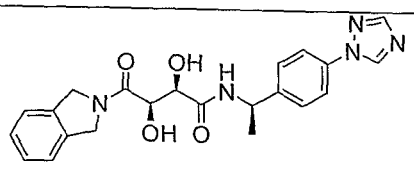
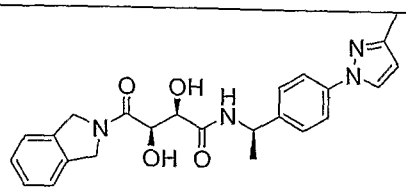
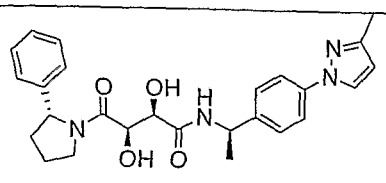
Part B:

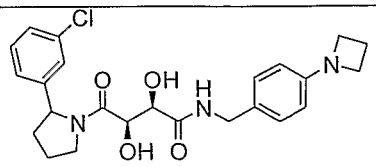
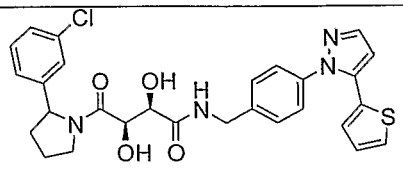
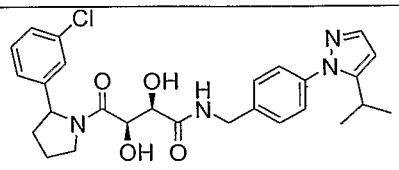
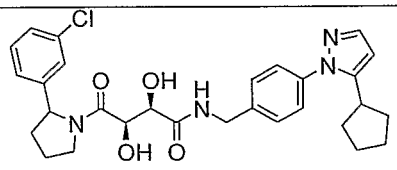
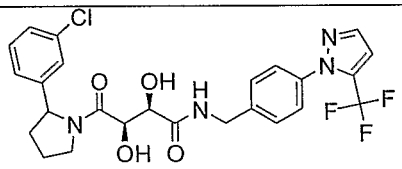
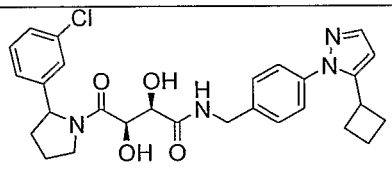
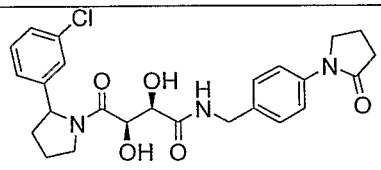
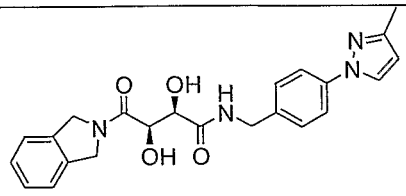
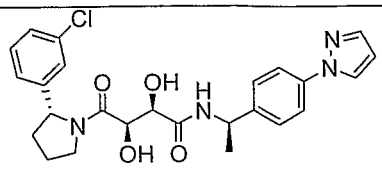
Compound **915** (0.20 g, 0.67 mmol) was dissolved in 10 mL of MeOH. Aqueous LiOH (10 mL/ 1.0 M) was added. The reaction mixture was stirred at rt for 4 h. The solution was partially concentrated in vacuo to remove the MeOH. The resulting material was extracted with EtOAc. The organic layer was washed with water, dried with Na_2SO_4, filtered, and concentrated to give 0.14 g of **916**. Data for **916**: ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.75 (s, 1H), 7.68 (d, J= 9 Hz, 2H), 7.47 (d, J= 9 Hz, 2H), 4.26-4.13 (m, 1H), 1.44 (d, J= 7 Hz, 3H).

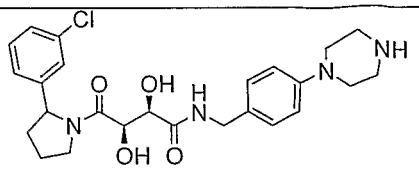
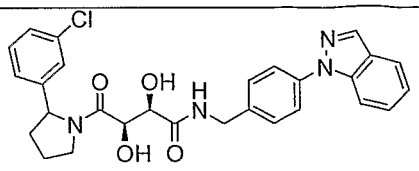
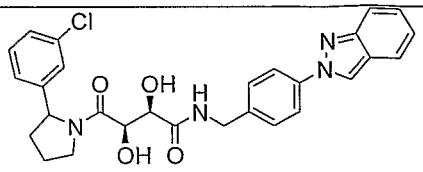
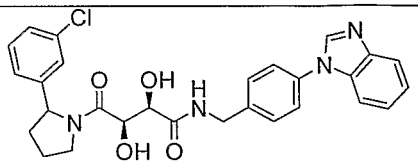
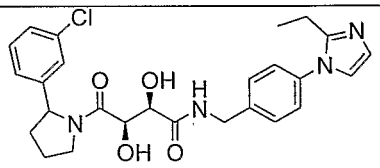
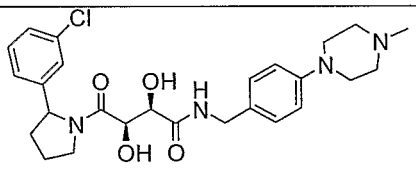
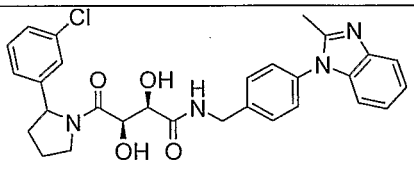
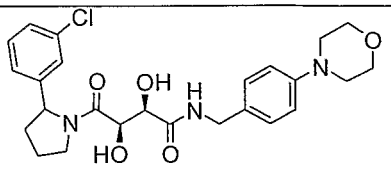
Parts C and D:

Compounds **917** and **918** were prepared via procedures similar to those described in Example 14 -Parts D and E. Data for **917**: ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.98-7.62 (m, 4H), 7.46-7.13 (m, 8H), 6.68-6.47 (m, 2H), 5.86-5.41 (m, 2H), 5.24-5.10 (m, 2H), 4.05-3.48 (m, 2H), 2.22-1.79 (m, 10H), 1.58-1.55 (m, 2H). Data for **918**: ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.80 (s, 1H), 7.75-7.59 (m, 2H), 7.48-6.95 (m, 8H), 6.52 (s, 1H), 5.32-5.13 (m, 2H), 4.97-4.05 (m, 2H), 3.99-3.68 (m, 3H), 2.46-1.80 (m, 4H), 1.62-1.51 (m, 3H); MS (EI) m/z Obsd. M+H 449.1.

Compound #	Structure	Exact mass	MS m/e (M+H)
919		469.2	470.1
920		420.2	421.1
921		448.2	449.1
922		470.2	471.1
923		437.2	438.2
924		485.2	486.2
925		468.2	469.1
926		420.2	421.1

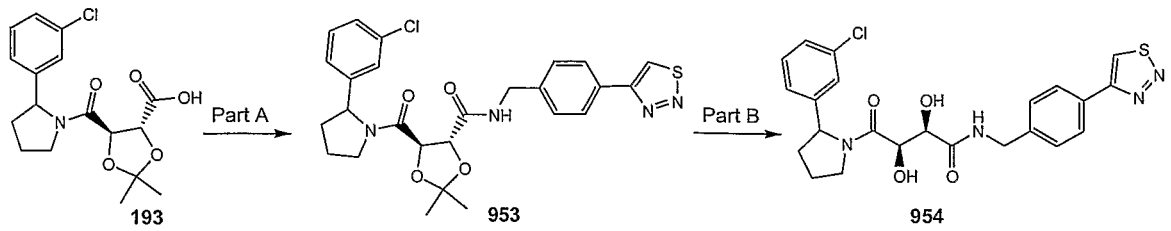
927		498.2	499.1
928		448.2	449.1
929		515.2	516.3
930		482.2	483.1
931		469.2	470.0
932		482.2	483.1
933		421.2	422.1
934		434.2	435.1
935		462.2	463.1

936		457.2	458.2
937		550.1	551.0
938		510.2	511.1
939		536.2	537.1
940		536.1	537.1
941		522.2	523.2
942		485.2	486.1
943		420.2	421.1
944		482.1	483.1

945		486.2	487.3
946		518.2	519.2
947		518.2	519.2
948		518.2	519.2
949		496.2	497.2
950		500.2	501.2
951		532.2	533.2
952		487.2	488.2

Example 26: Aryl-heteroaryl biaryl compounds

Example 26A:



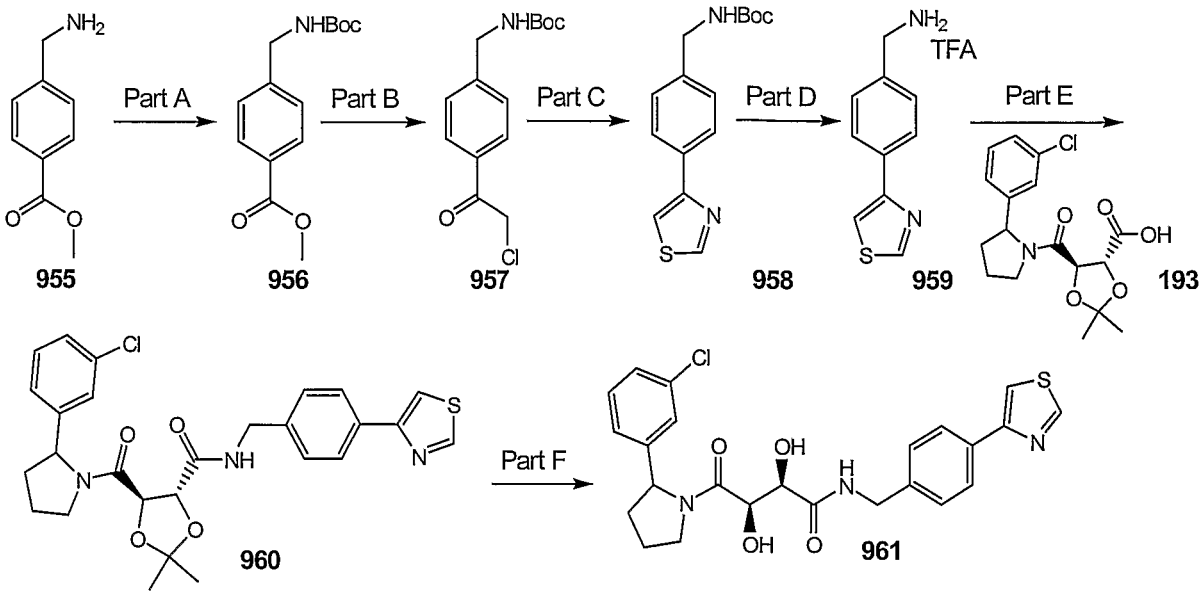
Part A:

To **193** (42 mg, 0.12 mmol) in DMF (2 mL) was added 4-[1,2,3]thiadiazol-4-yl-benzylamine (25 mg, 0.13 mmol), DIEA (45 µL, 0.26 mmol) and HATU (50 mg, 0.13 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with 0.1 N NaOH and brine, dried over sodium sulfate and concentrated. The crude material was used without further purification. **953**: Mass calculated for formula C26H27ClN4O4S 526.1, observed LCMS m/z 527.1 (M+H).

Part B:

Compound **953** was dissolved in 4:1 TFA:water (2 mL) and stirred at room temperature for 2 hours. The reaction was quenched by the addition of 1:1 acetonitrile:water (4 mL) and the solvents were removed in vacuo. Purification by reverse phase prep-LC afforded **954** as a white solid (21 mg). HPLC-MS t_R = 4.21 min ($UV_{254\ nm}$, 10 min); Mass calculated for formula $C_{23}H_{23}ClN_4O_4S$ 486.1, observed LCMS m/z 487.1 (M+H).

Example 26B: Biaryl C-C linkage



Part A:

To 4-aminomethyl-benzoic acid methyl ester (**955**) (2 g, 9.92 mmol) in dichloromethane (25 mL) was added Boc anhydride (2.27 g, 10.4 mmol) and triethylamine (2.76 mL, 19.84 mmol). The reaction mixture was stirred overnight. The reaction mixture was diluted with dichloromethane, washed with water and brine, dried over sodium sulfate and concentrated to afford **956** as a white solid (2.40 g, 91%). HPLC-MS t_R = 1.76 min (UV_{254nm}); Mass calculated for formula $C_{14}H_{19}NO_4$ 265.1, observed LCMS m/z 288.2 (M+Na).

Part B:

Compound **957** (257 mg, 80%) was synthesized following the procedure described in Example 10B Part A. HPLC-MS t_R = 1.77 min (UV_{254nm}); Mass calculated for formula $C_{14}H_{18}ClNO_3$ 283.1, observed LCMS m/z 306.1 (M+Na).

Part C:

To **957** (49 mg, 0.17 mmol) in DMF (2 mL) was added thioformamide (21 mg, 0.35 mmol) and pyridine (50 µL). The reaction mixture was stirred for 72 hours. The mixture diluted with ethyl acetate, washed with 0.1 N sodium hydroxide, water and brine, dried over sodium sulfate and concentrated.

Purification by column chromatography (SiO_2, 25% ethyl acetate/hexanes) afforded **958** (25 mg, 50%). HPLC-MS t_R = 1.80 min (UV_{254nm}); Mass calculated for formula $C_{15}H_{18}N_2O_2S$ 290.1, observed LCMS m/z 291.1 (M+H).

Part D:

Compound **958** (25 mg, 0.084 mmol) was stirred in dichloromethane (2 mL) and TFA (1 mL) at room temperature for 1 hour. The solvents were removed in vacuo to afford **959** as an oil (26 mg). ^1H NMR (400 MHz, CD_3OD) δ 9.07 (d, 1H, J = 2.0 Hz), 8.03 (d, 2H, J = 8.4 Hz), 7.96 (d, 1H, J = 1.6 Hz), 7.52 (d, 2H, J = 8.0 Hz), 4.16 (s, 2H).

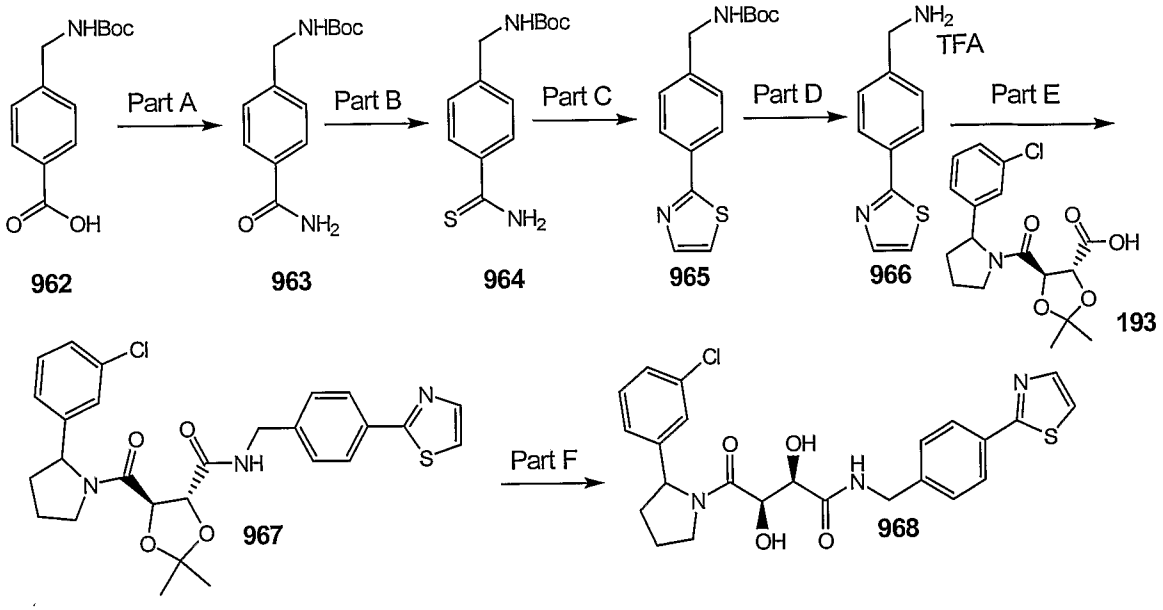
Part E:

To **193** (23 mg, 0.065 mmol) in DMF (2 mL) was added **959** (26 mg, 0.084 mmol), DIEA (34 µL, 0.20 mmol) and HATU (32 mg, 0.084 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with 0.1 N NaOH and brine, dried over sodium sulfate and concentrated. The crude material was used without further purification. **960**: HPLC-MS t_R = 2.00 and 2.05 min ($UV_{254\ nm}$); Mass calculated for formula $C_{27}H_{28}ClN_3O_4S$ 525.2, observed LCMS m/z 526.1 (M+H).

Part F:

Compound **960** was dissolved in 4:1 TFA:water (2 ml) and stirred at room temperature for 2 hours. The reaction was quenched by the addition of 1:1 acetonitrile:water (4 mL) and the solvents were removed in vacuo. Purification by reverse phase prep-LC afforded **961** as a white solid (14 mg). HPLC-MS t_R = 4.17 min ($UV_{254\ nm}$, 10 min); Mass calculated for formula $C_{24}H_{24}ClN_3O_4S$ 485.1, observed LCMS m/z 486.1 (M+H).

Example 26C: Biaryl C-C linkage



Part A:

To 4-(tert-butoxycarbonylamino-methyl)-benzoic acid (**962**) (500 mg, 1.99 mmol) in tetrahydrofuran (5 mL) in an ice bath was added DIEA (347 µL, 1.99 mmol). The reaction mixture was stirred for 15 minutes and ethyl chloroformate (190 µL, 1.99 mmol) was added. The reaction mixture was stirred for an additional 15 minutes and ammonia in dioxane (0.5 M, 4.18 mL, 2.09 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 2 hours. The solvent was removed in vacuo and the residue was partitioned between ethyl acetate and water. The layers were separated and the aqueous layer was saturated with sodium chloride and extracted with ethyl acetate. The combined organic layers were washed brine, dried over sodium sulfate and concentrated to afford **963** as a white solid (540 mg), which contained some mixed anhydride as an impurity. ^{1}H NMR (400 MHz, CD_3OD) δ7.81 (d, 2H, J = 8.0 Hz), 7.35 (d, 2H, J = 8.4 Hz), 7.21 (bs, 1H, NH), 4.28 (s, 2H), 1.47 (s, 9H).

Part B:

To **963** (500 mg, 2.0 mmol) in tetrahydrofuran (20 mL) was added Lawesson's reagent (485 mg, 1.2 mmol). The reaction mixture was stirred overnight at room temperature. The solvent was removed in vacuo and the residue was dissolved in ethyl acetate. The mixture was washed with 0.1 N sodium hydroxide, water and brine, dried over sodium sulfate and concentrated to a yellow residue. Purification by column chromatography (SiO_2, 40% ethyl acetate/hexanes) afforded **964** as a pale yellow solid (432 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, 2H, J = 8.4 Hz), 7.32 (d, 2H, J = 8.4 Hz), 4.36 (d, 2H, J = 5.6 Hz), 1.48 (s, 9H).

Part C:

To **964** (70 mg, 0.263 mmol) in DMF (2 mL) was added chloroacetaldehyde (50% in water, 41 mg, 0.526 mmol). The reaction was stirred overnight at room temperature. An additional 2 equivalents of chloroacetaldehyde was added and the reaction was stirred for 24 hours. The reaction was still not complete so the mixture was heated to 50 °C for 2 days. The mixture diluted with ethyl acetate, washed with 0.1 N sodium hydroxide, water and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 25% ethyl acetate/hexanes) afforded **965** (31 mg). HPLC-MS t_R = 1.84 min ($UV_{254\ nm}$); Mass calculated for formula $C_{15}H_{18}N_2O_2S$ 290.1, observed LCMS m/z 291.1 (M+H).

Part D:

Compound **965** (31 mg, 0.106 mmol) was stirred in dichloromethane (2 mL) and TFA (1 mL) at room temperature for 1 hour. The solvents were removed in vacuo to afford **966** as an oil (60 mg). ^{1}H NMR (400 MHz, CD_3OD) δ 8.03 (d, 2H, J = 8.8 Hz), 7.90 (d, 1H, J = 3.2 Hz), 7.65 (d, 1H, J = 3.6 Hz), 7.56 (d, 2H, J = 8.8 Hz), 4.18 (s, 2H).

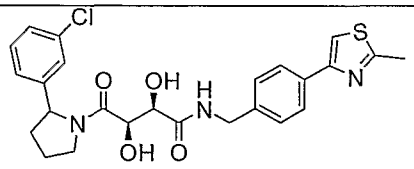
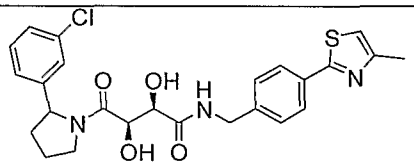
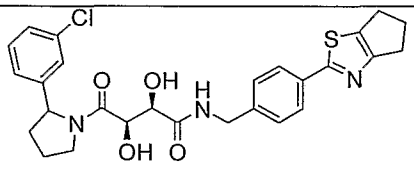
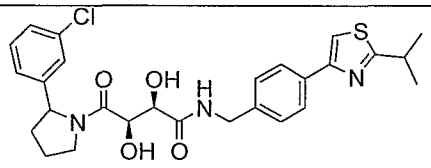
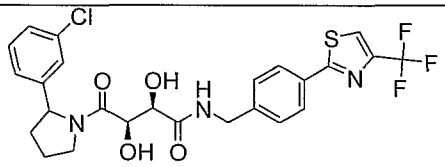
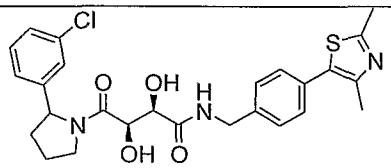
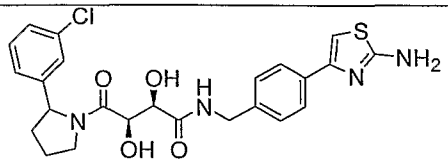
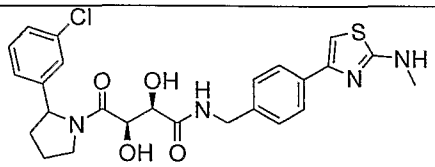
Part E:

To **193** (29 mg, 0.082 mmol) in DMF (2 mL) was added **966** (32 mg, 0.106 mmol), DIEA (43 µL, 0.25 mmol) and HATU (40 mg, 0.106 mmol). The

reaction mixture was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with 0.1 N NaOH and brine, dried over sodium sulfate and concentrated. The crude material was used without further purification. **967**: HPLC-MS t_R = 2.03 and 2.08 min ($UV_{254\ nm}$); Mass calculated for formula $C_{27}H_{28}ClN_3O_4S$ 525.2, observed LCMS m/z 526.1 (M+H).

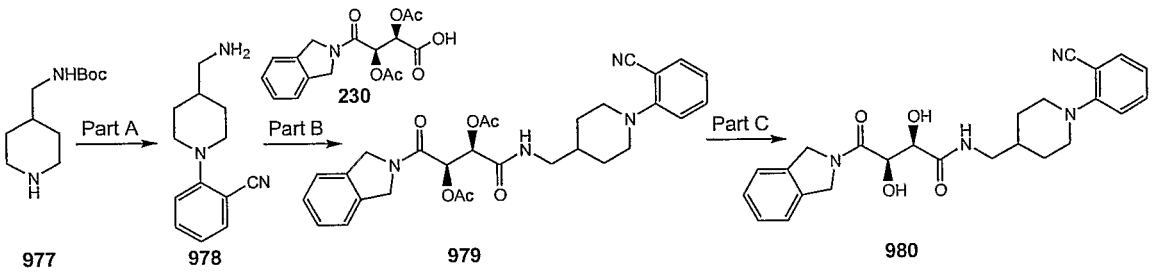
Part F:

Compound **967** was dissolved in 4:1 TFA:water (2 mL) and stirred at room temperature for 2 hours. The reaction was quenched by the addition of 1:1 acetonitrile:water (4 mL) and the solvents were removed in vacuo. Purification by reverse phase prep-LC afforded **968** as a white solid (15 mg). HPLC-MS t_R = 4.21 min ($UV_{254\ nm}$, 10 min); Mass calculated for formula $C_{24}H_{24}ClN_3O_4S$ 485.1, observed LCMS m/z 486.1 (M+H).

Compound #	Structure	Exact mass	MS m/e (M+H)
969		499.1	500.1
970		499.1	500.1
971		525.2	526.2
972		527.2	528.1
973		553.1	554.0
974		513.2	514.2
975		500.1	501.1
976		514.1	515.1

Example 27: Piperidine-aryl compounds

Example 27A: Piperidine-aryl



Part A:

Step 1: A mixture of piperidin-4-ylmethyl-carbamic acid tert-butyl ester (**977**) (2.5 g, 11.66 mmol), 2-fluoro-3-cyanobenzene (1.55 g, 12.8 mmol) and DIEA (3 mL, 17.5 mmol) in NMP (5 mL) under argon atmosphere was stirred overnight at 120 °C. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 25% ethyl acetate/hexanes) afforded a white solid (3.1 g).

Step 2: To the material from Step 1 (2 g) in dichloromethane (5 mL) at 0 °C was added TFA (5 mL). The mixture was stirred at room temperature for 1 hour. The mixture was quenched with acetonitrile and concentrated. The residue was dissolved in ethyl acetate, washed with sodium carbonate solution and brine, dried over sodium sulfate and concentrated to yield **978** as an oil which solidified to a waxy solid (920 mg). HPLC-MS t_R = 0.63 min ($UV_{254\ nm}$); Mass calculated for formula $C_{13}H_{17}N_3$ 215.1, observed LCMS m/z 216.2 (M+H).

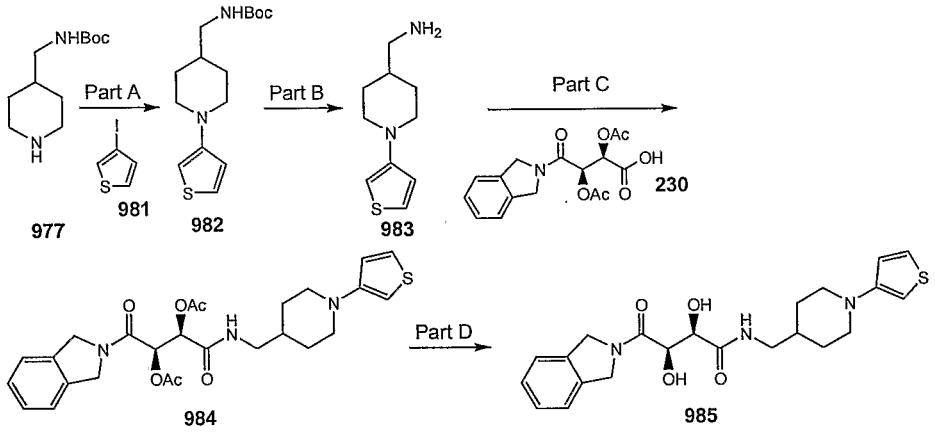
Part B:

To **978** (120 mg, 0.55 mmol) in DMF (2 mL) was added **230** (167 mg, 0.5 mmol), DIEA (0.21 mL, 1.2 mmol) and HATU (211 mg, 0.55 mmol). The mixture was stirred for 3 hours at room temperature. The reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate and brine, dried over sodium sulfate and concentrated. The material was used without further purification.

Part C:

To **979** in methanol (4 mL) was added 7.0 N ammonia in methanol (2 mL) was added. The mixture was stirred for 2 hours at room temperature and concentrated. Purification by reverse phase prep-LC afforded **980** as a white powder (80 mg) upon lypholization. HPLC-MS t_R = 4.03 min ($UV_{254\ nm}$); Mass calculated for formula $C_{25}H_{28}N_4O_4$ 448.2, observed LCMS m/z 449.2 (M+H).

Example 27B: Piperidine-aryl



Part A:

A mixture of **977** (200 mg, 0.93 mmol), 3-iodothiophene (981) (294 mg, 1.4 mmol), copper(I)iodide (36 mg, 0.19 mmol), proline (43 mg, 0.37 mmol) and potassium carbonate (258 mg, 1.87 mmol) in DMSO (1.5 mL) was stirred overnight at 80 °C in a 4 mL vial. The reaction mixture was diluted with ethyl acetate and washed with water (3X) and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 25% ethyl acetate / hexanes) afforded **982** (94 mg, 34%).

Part B:

Compound **982** (42 mg, 0.14 mmol) was dissolved in DCM (2 mL) and TFA (1 mL). The mixture was stirred for 1 hour and concentrated to afford **983** in quantitative yield. HPLC-MS t_R = 0.35 min ($UV_{254\ nm}$); Mass calculated for formula $C_{10}H_{16}N_2S$ 196.1, observed LCMS m/z 197.2 (M+H).

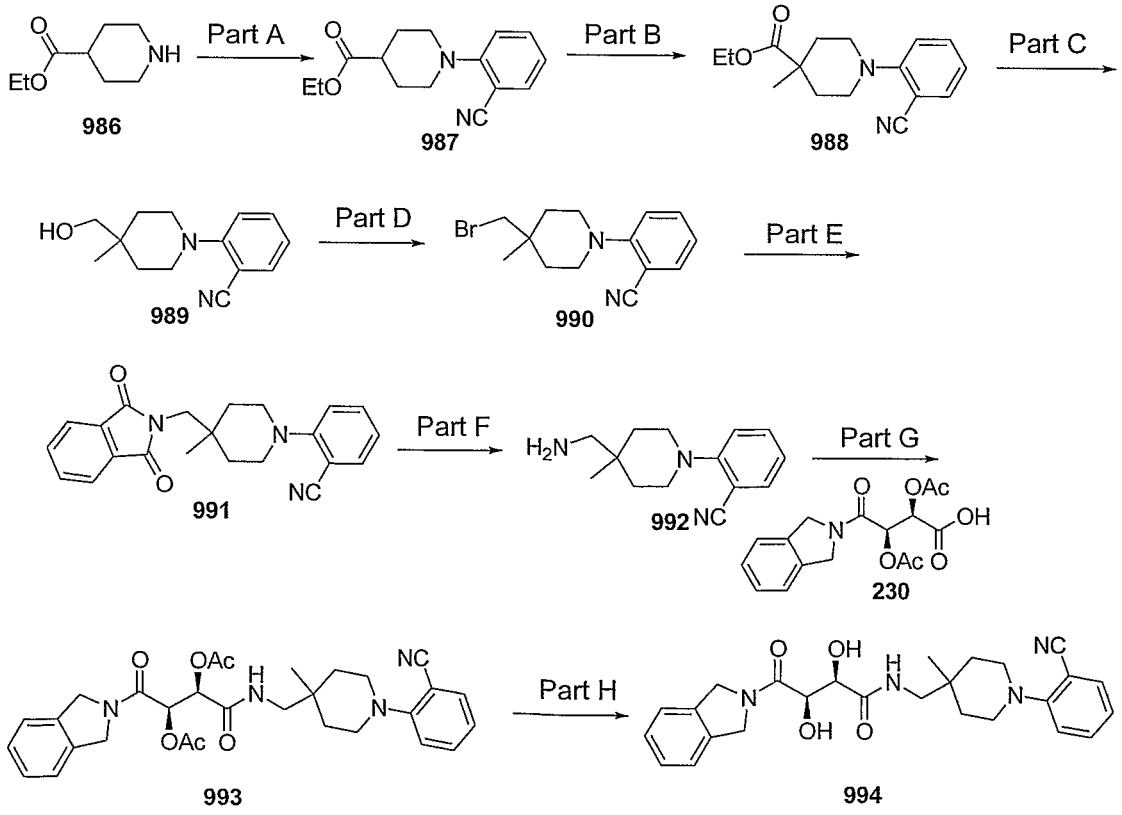
Part C:

Compound **984** was prepared according to the procedure described in Example 27A Part B. HPLC-MS t_R = 1.36 min (UV_{254nm}); Mass calculated for formula $C_{26}H_{31}N_3O_6S$ 513.2, observed LCMS m/z 514.2 (M+H).

Part D:

Compound **985** was prepared according to the method described in Example 25 Part E. HPLC-MS t_R = 2.85 min ($UV_{254nm,}$ 10 min.); Mass calculated for formula $C_{22}H_{27}N_3O_4S$ 429.2, observed LCMS m/z 430.1 (M+H).

Example 27C:



Part A:

Compound **986** (1.13 g, 7.23 mmol) was dissolved in N-methylpyrrolidinone (4 mL) and 2-fluorobenzonitrile (0.90 g, 7.5 mmol) was added followed by DIEA (2.5 mL, 14.4 mmol). The reaction was stirred at 120 °C overnight. The cooled reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with bicarbonate solution and brine; dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 25% ethyl acetate/hexanes) afforded a white solid **987** (1.5 g, 81%). HPLC-MS t_R = 1.95 (UV_{254nm}); mass calculated for formula $C_{15}H_{18}N_2O_2$ 258.14, observed LCMS m/z 259.1 (M+H).

Part B:

Diisopropylamine (0.330 mL, 2.32 mmol) was dissolved in THF (20 mL) and cooled in an ice bath. A solution of n-BuLi (2.5M in hexanes, 1 mL) was added dropwise and stirred for 15 minutes. The reaction mixture was then cooled to –78 °C and a solution of compound **987** (400 mg, 1.6 mmol) in THF (10 mL) was added dropwise. Stirring was continued at this temperature for 30 minutes before a solution of iodomethane (450 mg, 3.2 mmol) in THF (10 mL) was added dropwise. The reaction was stirred for 30 minutes at this temperature and then 1 hour at room temperature. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with bicarbonate solution and brine; dried over sodium sulfate and concentrated to provide the product **988** that was used without purification. HPLC-MS t_R = 2.10 (UV_{254nm}); mass calculated for formula $C_{16}H_{20}N_2O_2$ 272.15, observed LCMS m/z 273.2 (M+H).

Part C:

Compound **988** was dissolved in THF (20 mL) and lithium borohydride (60 mg, 2.6 mmol) was added. The reaction mixture was refluxed for 5 hours. The cooled reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with bicarbonate

solution and brine; dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 50% ethyl acetate/hexanes) afforded a white solid **989** (300 mg). HPLC-MS t_R = 1.57 ($UV_{254\ nm}$); mass calculated for formula $C_{14}H_{18}N_2O$ 230.1, observed LCMS m/z 231.3 (M+H).

Part D:
Compound **989** (300 mg, 1.3 mmol) was dissolved in toluene (5 mL) and phosphorus tribromide (0.06 mL, 0.52 mmol) was added. The reaction was stirred at reflux for 3 hours. The cooled reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with bicarbonate solution and brine; dried over sodium sulfate and concentrated to provide the product **990** that was used without purification.

Part E:
Compound **990** was dissolved in DMF (10 mL) and cesium carbonate (850 mg, 2.6 mmol) and phthalimide (190 mg, 1.3 mmol) were added and stirred overnight. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with bicarbonate solution and brine; dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 25% ethyl acetate/hexanes) afforded a white solid **991** (90 mg). HPLC-MS t_R = 2.14 min ($UV_{254\ nm}$); mass calculated for formula $C_{22}H_{21}N_3O_2$ 359.1, observed LCMS m/z 360.1.

Part F:
Compound **991** (90 mg, 0.25 mmol) was dissolved in ethanol (3 mL) and hydrazine hydrate (0.5 mL) was added. The reaction was stirred for 3 hours and the solids were filtered. The solvent was evaporated to provide the desired product **992** that was used without purification.

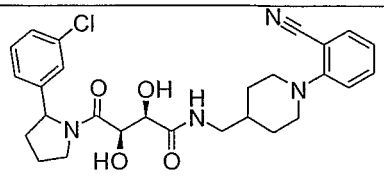
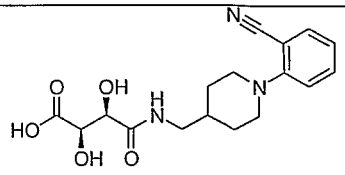
Part G:
Compound **992** was dissolved in DMF (5 mL) and compound **230** (84 mg, 0.25 mmol) and HATU (114 mg, 0.30 mmol) were added and stirred

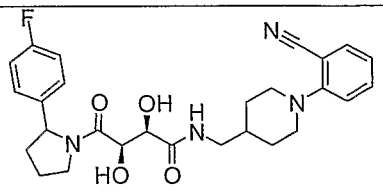
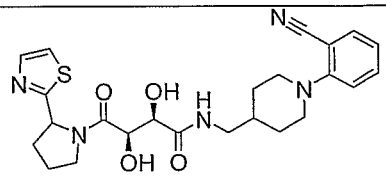
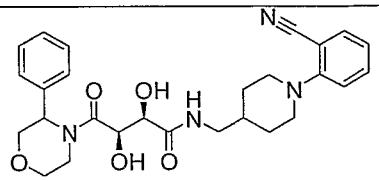
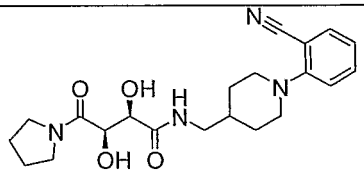
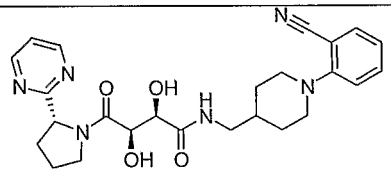
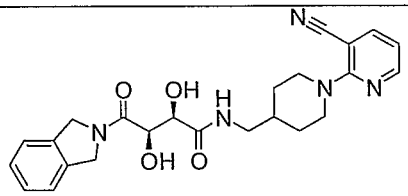
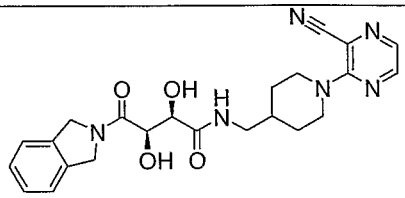
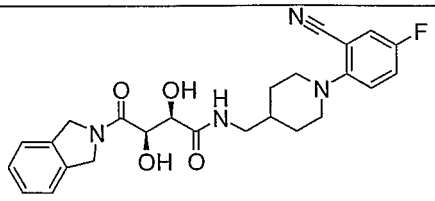
overnight. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with bicarbonate solution and brine; dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, ethyl acetate) afforded a white foam **993** (100 mg). HPLC-MS t_R = 1.99 min ($UV_{254\ nm}$); mass calculated for formula $C_{30}H_{34}N_4O_6$ 546.2, observed LCMS m/z 547.2.

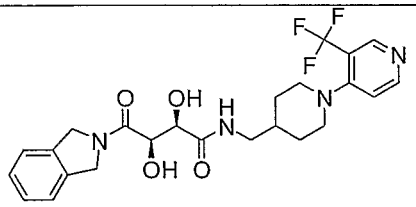
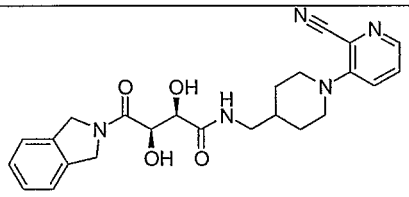
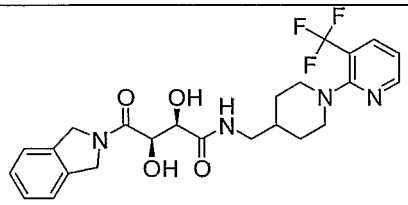
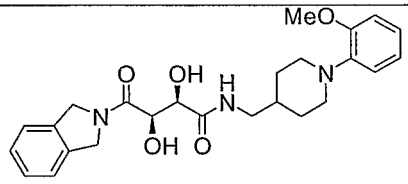
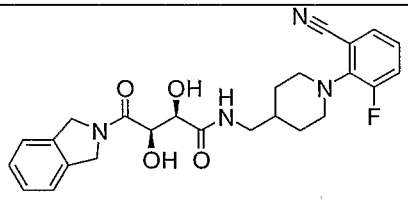
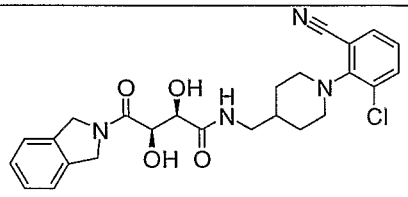
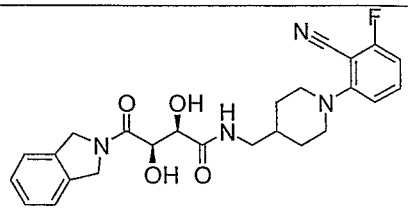
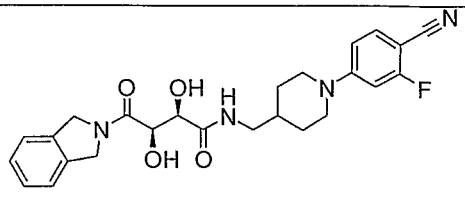
Part H:

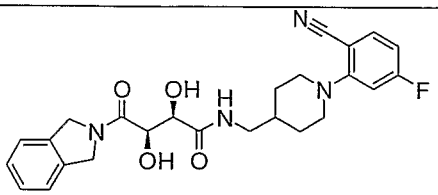
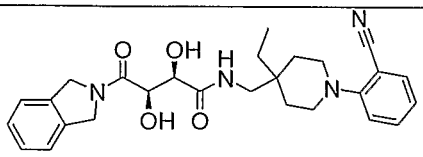
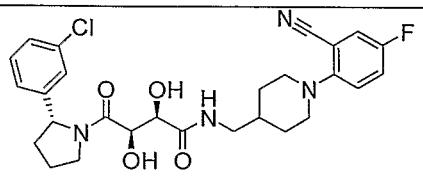
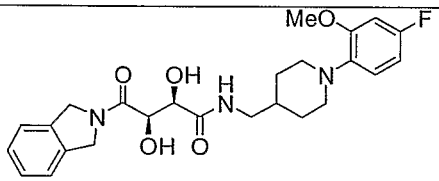
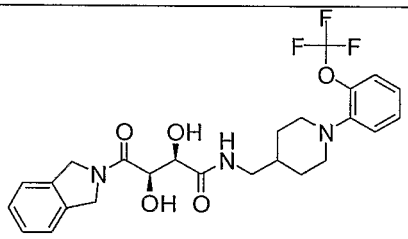
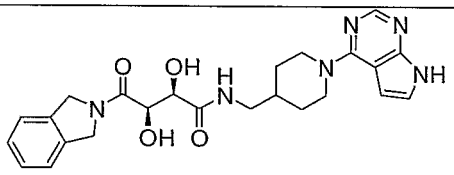
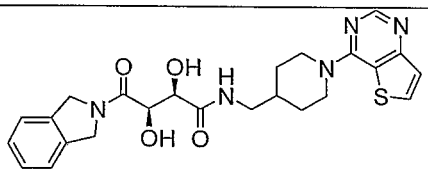
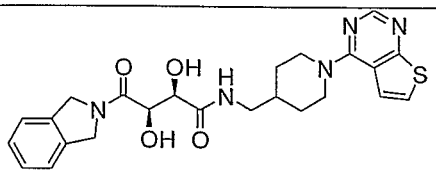
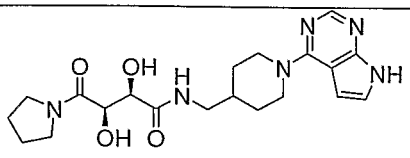
Compound **993** (100 mg, 0.182 mmol) was dissolved in methanol (5 mL) and potassium carbonate (100 mg) was added and stirred for 30 minutes. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with bicarbonate solution and brine; dried over sodium sulfate and concentrated. Purification by reverse phase prep-LC afforded a white solid **994** (7 mg, 8%) after lyophilization. HPLC-MS t_R = 4.32 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{26}H_{30}N_4O_4$ 462.23, observed LCMS m/z 463.1 (M+H).

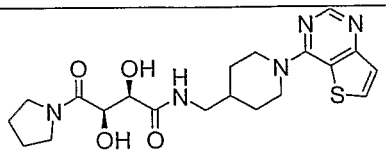
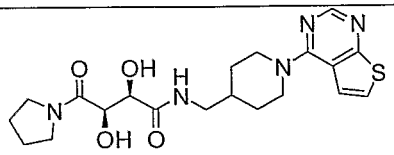
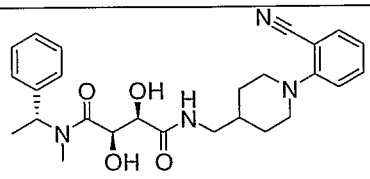
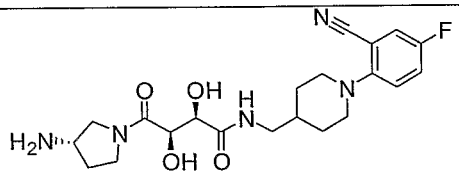
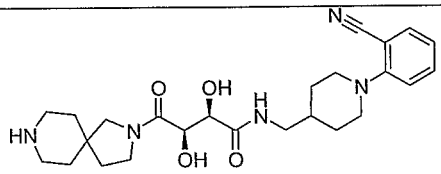
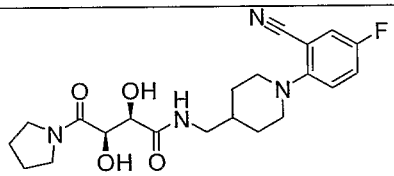
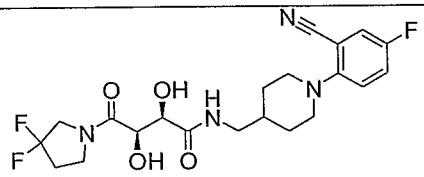
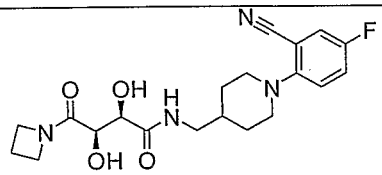
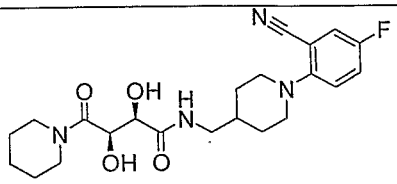
The following table contains compounds that were prepared using the procedures described in Example 27 A – C. Compounds such as **1002** were made from the chloropyridyl precursor using the procedures described in Example 27A Part A.

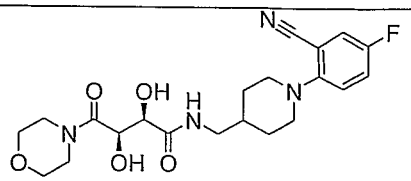
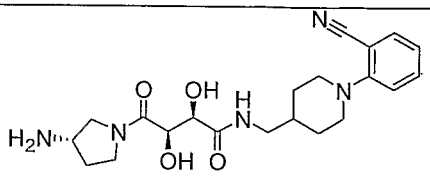
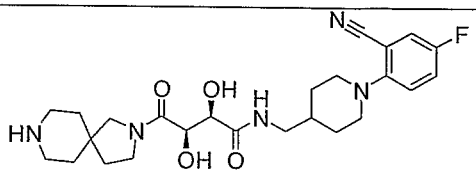
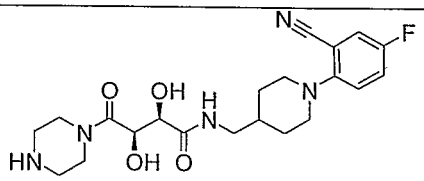
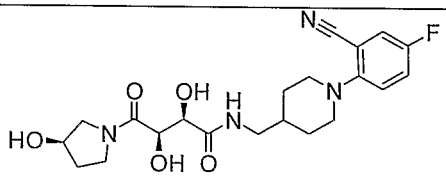
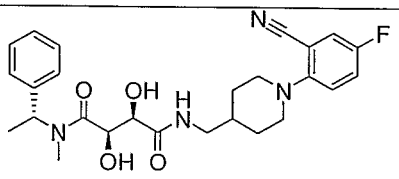
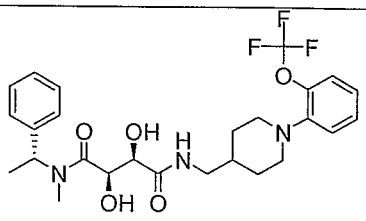
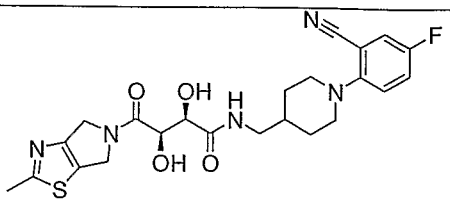
Compound #	Structure	Exact mass	MS m/z (M+H)
995		510.2	511.1
996		347.1	348.3

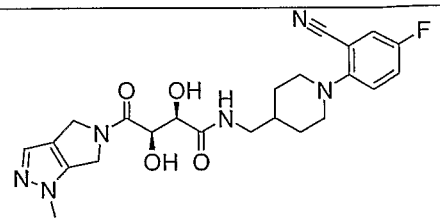
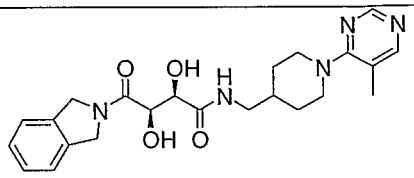
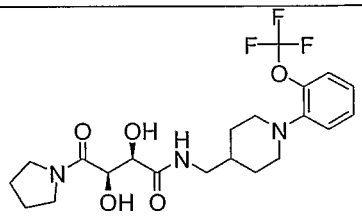
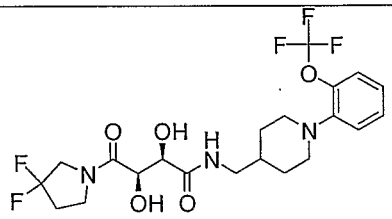
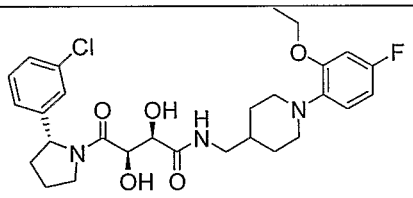
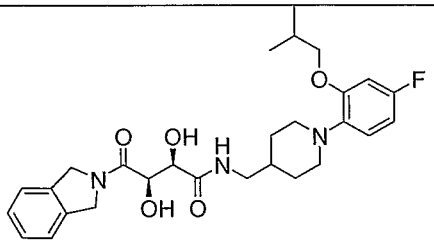
997		494.2	495.2
998		483.2	484.1
999		492.2	493.1
1000		400.2	401.2
1001		478.2	479.2
1002		449.2	450.2
1003		450.2	451.1
1004		466.2	467.2

1005		492.2	493.1
1006		449.2	450.1
1007		492.2	493.1
1008		453.2	454.2
1009		466.2	467.2
1010		482.2	483.1
1011		466.2	467.2
1012		466.2	467.2

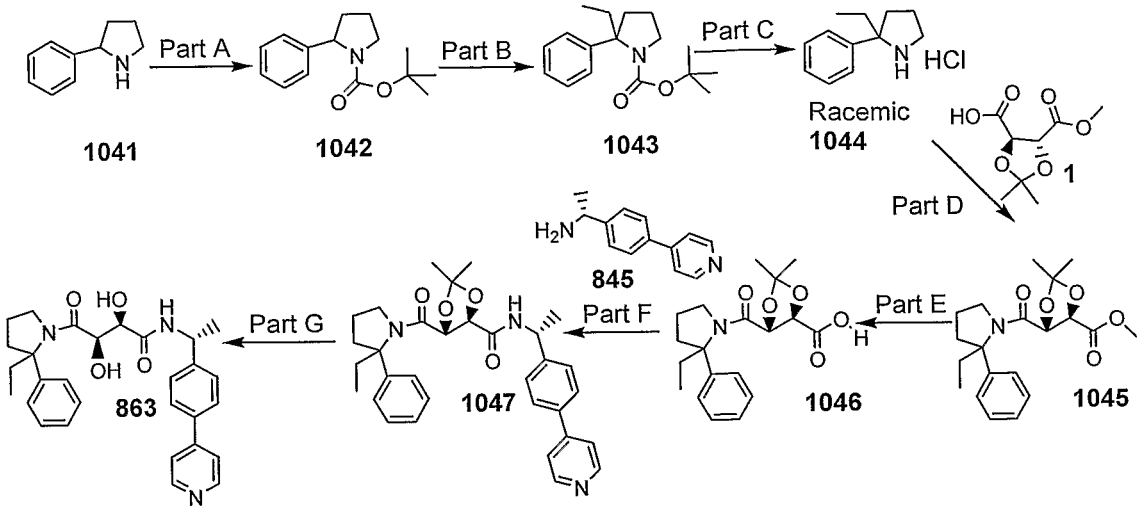
1013		466.2	467.2
1014		476.2	477.1
1015		528.2	529.2
1016		471.2	472.1
1017		507.2	508.2
1018		464.2	465.2
1019		481.2	482.2
1020		481.2	482.2
1021		416.2	417.3

1022		433.2	434.2
1023		433.2	434.2
1024		464.2	465.2
1025		433.2	434.2
1026		469.3	470.2
1027A		418.2	419.2
1027B		454.2	455.2
1027C		404.2	405.2
1028		432.2	433.2

1029		434.2	435.2
1030		415.2	416.2
1031		487.3	488.2
1032		433.2	434.2
1033		434.2	435.2
1034A		482.2	483.3
1034B		523.2	524.2
1035		487.2	488.2

1036		470.2	471.2
1037		439.2	440.2
1038A		459.2	460.1
1038B		495.2	496.2
1039		547.2	548.2
1040		513.3	514.3

Example 28: Alkylated phenyl pyrrolidines



Part A:

2-Phenyl pyrrolidine (**1041**) (3.14 g, 21.4 mmol) was dissolved in THF (40 mL). Aqueous NaOH (12 mL, 25%) was added, followed by Boc anhydride. The reaction mixture was stirred at rt for 70 h. The layers were separated. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with 1.0 M pH=7.0 sodium phosphate buffer and brine, then dried with $MgSO_4$. Evaporation of the solvents gave a yellow oil which was purified by column chromatography (SiO_2, 9:1 Hexanes:EtOAc) to give a 5.1 g of a clear oil as product **1042**. MS (EI) m/z M+Na Obsd 270.08

Part B:

A 100 mL Schlenck flask was equipped with a stir bar, flame dried under N_2 flow, capped with a septum, and allowed to cool to rt. Compound **1042** (0.50 g, 2.02 mmol) was added and the flask was recapped. Anhydrous THF (8.5 mL) was added via syringe and the flask was cooled in a dry ice/2-propanol bath. Sec butyl lithium (1.6 mL, 2.34 mmol) was added via syringe. The reaction mixture was left stirring at -78 °C for 30 m. Iodoethane (180 µL, 2.25 mmol) was added and the reaction mixture was stirred for 2 hr. Additional iodoethane was added (80 µL, 1.0 mmol) was added and the reaction mixture was stirred for 45 minutes. The reaction mixture was quenched with 1.0 M pH 7.0 sodium phosphate buffer and diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined

organic layer was washed with water and brine, then dried with $MgSO_4$ and concentrated to a clear oil. The crude product was purified by column chromatography (SiO_2, 0%-20% EtOAc/Hexanes) to give 0.12 g of compound **1043**. MS (EI) m/z M+Na Obsd 298.15.

Part C:

Compound **1043** (0.12 g, 0.43 mmol) was dissolved in 10 mL of 4 M HCl in dioxane. The reaction mixture was stirred at rt for 2.25 h. The reaction mixture was concentrated to dryness giving white solid **1044** (112 mg). MS (EI) m/z Obsd M+H 176.12.

Part D:

Compound **1044** (104 mg, 0.49 mmol) and **1** (0.120 g, 0.588 mmol) were dissolved in CH_2Cl_2 (2 mL). Diisopropyl ethylamine (200 µL, 1.12 mmol) was added, followed by PyBrop (249 mg, 0.78 mmol). The reaction mixture was left stirring overnight at rt under N_2. The reaction mixture was diluted with CH_2Cl_2 then washed with 1.0 m pH 7.0 sodium phosphate buffer, aq $NaHCO_3$, and brine. The organic layer was dried with $MgSO_4$ and concentrated to a clear oil. The crude product was purified purified by column chromatography (SiO_2, 0%-40% EtOAc/Hexanes) to give 0.16 g of compound **1045.** MS (EI) m/z Obsd M+H 362.08

Part E:

Compound **1045** (0.15 g, 0.42 mmol) was dissolved in dioxane (1.6 mL) and water (0.4 mL). Lithium hydroxide was added (19 mg, 0.45 mmol). The reaction mixture was stirred at rt for 2 h 15 m. The solution was concentrated to give **1046** as a clear oil. MS (EI) m/z Obsd M+H 348.09

Part F:

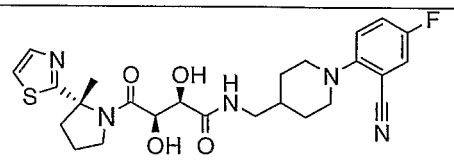
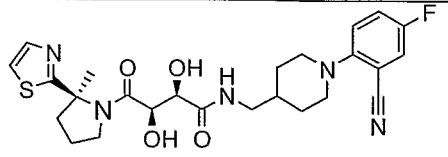
Compound **1046** (69 mg, 0.19 mmol) and **845** (51 mg, 0.22 mmol) were dissolved in DMF (1 mL) and diisopropylamine (100 µL, 0.58 mmol). PyBrop was added (108 mg, 0.338 mmol) and the reaction was stirred overnight at rt.

The reaction mixture was diluted with EtOAc and washed with 1.0 M pH 8.0 sodium phosphate buffer and brine. The organic layer was dried with $MgSO_4$ and concentrated to a yellow oil. The crude product was purified via prep TLC on silica plates using 95:5 CH_2Cl_2:MeOH as the mobile phase. Compound **1047** was obtained as a clear oil (74 mg). MS (EI) m/z Obsd M+H 528.20.

Part G:

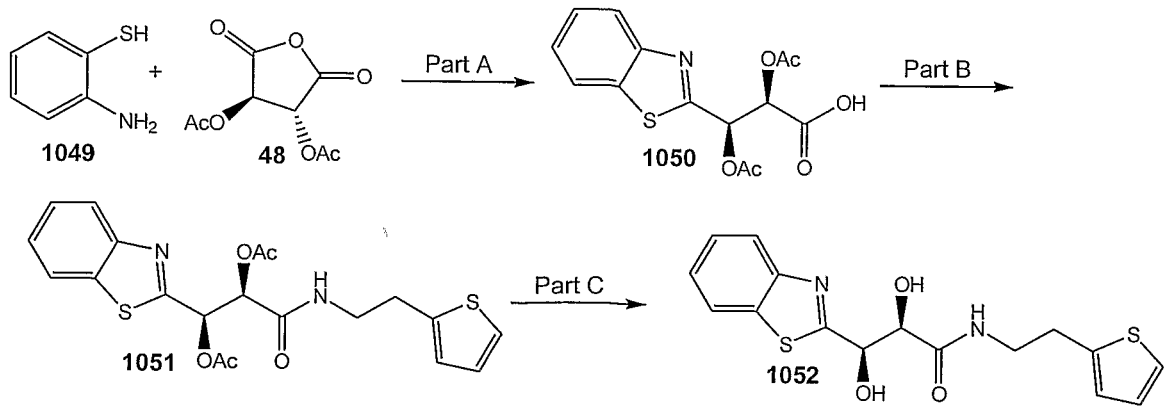
Compound **1047** (74 mg, 0.14 mmol) was dissolved in 5 mL of 9:1 trifluoroacetic acid:water solution. The reaction mixture was stirred at rt for 3 h 10 m, then concentrated to dryness. The crude product was purified purified by column chromatography (SiO_2, 0%-7% MeOH/ CH_2Cl_2) to give 26 mg of compound **863**. MS (EI) m/z Obsd M+H 488.1.

Compound **1048A,B** was prepared from Boc-proline OMe using the above alkylation procedures and the thiazole ring was constructed as described in Example 10A.

Compound #	Structure	Exact mass	MS m/e (M+H)
1048A		515.2	516.2
1048B		515.2	516.2

Example 29:

Example 29A:



Part A:

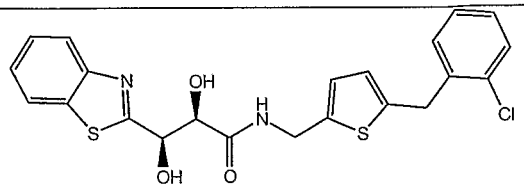
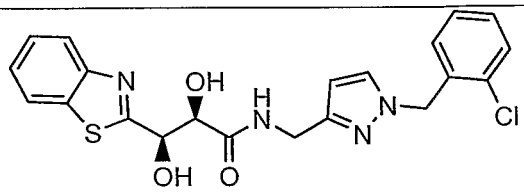
A mixture of 2-amino-benzenethiol (**1049**) (247 uL, 2.31 mmol) and **48** (500 mg, 2.31 mmol) in benzene was heated at reflux overnight with a dean-stark trap. The reaction mixture was cooled and concentrated. The mixture was recrystallized from 30% ethyl acetate/hexanes to afford **1050** (267 mg) as a brown powder. HPLC-MS t_R = 1.35 min ($UV_{254\ nm}$); mass calculated for formula $C_{14}H_{13}NO_6S$ 323.1, observed LCMS m/z 324.1 (M+H).

Part B:

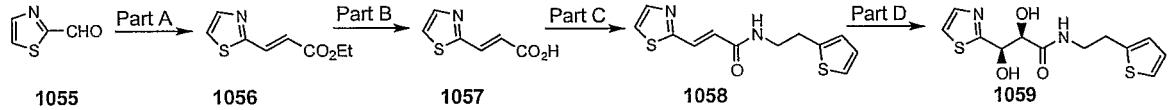
Compound **1051** was prepared from compound **1050** (32 mg, 0.1 mmol) using the standard HATU coupling strategy described in Example 2 Part A. Purification by column chromatography (SiO_2, 10% ethyl acetate/dichloromethane) afforded the product as an orange solid (27 mg). HPLC-MS t_R = 1.78 min ($UV_{254\ nm}$); mass calculated for formula $C_{20}H_{20}N_2O_5S_2$ 432.1, observed LCMS m/z 433.0 (M+H).

Part C:

Compound **1052** was prepared following the procedure described in Example 2 Part B. HPLC-MS t_R = 1.39 min ($UV_{254\ nm}$); mass calculated for formula $C_{16}H_{16}N_2O_3S_2$ 348.1, observed LCMS m/z 349.0 (M+H).

Compound #	Structure	Exact mass	MS m/z (M+H)
1053		458.1	459.0
1054		442.1	443.0

Example 29B:



Part A:

To sodium hydride (95%, 115 mg, 4.55 mmol) in DME (10 mL) under argon was added triethylphophonacetate dropwise. Within a few minutes the reaction mixture was clear. After 1 hour the aldehyde **1055** (400 uL, 4.55 mmol) was added. After 15 minutes water and diethyl ether were added to the reaction mixture. The layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic layer was washed with brine, dried over sodium sulfate and concentrated to afford **1056** as an orange oil (666 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, 1H, J = 3.2 Hz), 7.79 (d, 1H, J = 16.0 Hz), 7.43 (d, 1H, J = 3.2 Hz), 6.71 (d, 1H, J = 16.0 Hz), 4.29 (q, 2H, J = 7.5 Hz), 1.36 (t, 3H, J = 7.5 Hz).

Part B:

To ester **1056** (84 mg, 0.46 mmol) in THF (2 mL) was added 1.0 M lithium hydroxide solution (0.5 mL, 0.5 mmol). The reaction mixture was stirred

overnight. The reaction mixture was made acidic with 1.0 N HCl solution and extracted with ethyl acetate. Sodium chloride was added to the aqueous layer during the extractions. The combined organic layer was dried over sodium sulfate and concentrated to afford **1057** as a film (65 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, 1H, J = 3.0 Hz), 7.89 (d, 1H, J = 15.7 Hz), 7.49 (d, 1H, J = 3.0 Hz), 6.75 (d, 1H, J = 15.7 Hz).

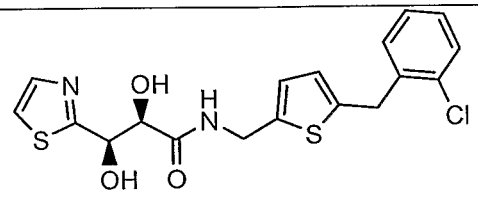
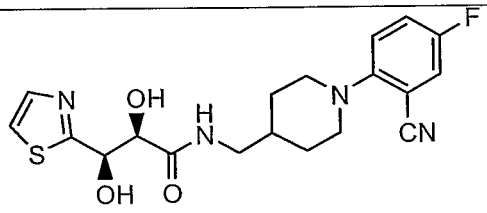
Part C:

Compound **1058** was prepared from Compound **1057** (32 mg, 0.21 mmol) using the standard HATU coupling strategy described in Example 2 Part A. Purification by column chromatography (SiO_2, 50% ethyl acetate/hexane) afforded the product as a film (35 mg, 63%). HPLC-MS t_R = 1.35 min ($UV_{254\ nm}$); mass calculated for formula $C_{12}H_{12}N_2OS_2$ 264.0, observed LCMS m/z 265.1 (M+H).

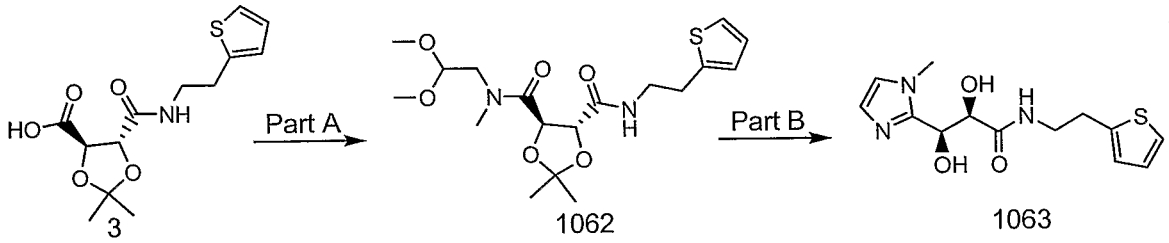
Part D:

Compound **1059** was prepared using a modified Sharpless dihydroxylation procedure (*Chem. Rev.* **1994**, *94*, 2483). A flask was charged with $(DHQ)_2PHAL$ (10 mg, 10 mol %), $K_3Fe(CN)_6$ (128 mg, 0.39 mmol), postassium carbonate (54 mg, 0.39 mmol), methane sulfonamide (24 mg, 0.26 mmol) and potassium osmium tetraoxide dihydrate (1 mg, 2 mol%). To the solids was added alkene 4 (35 mg, 0.13 mmol) in tert-butanol:water (1:1, 2.5 mL). The reaction mixture was stirred overnight at room temperature. The reaction mixture was cooled in an ice bath and sodium metabisulfite (38 mg, 0.2 mmol) was added. The mixture was stirred for 30 minutes. The reaction mixture was diluted with ethyl acetate and water. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with 2.0 N potassium hydroxide solution and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 80% ethyl acetate/hexane) afforded the product as a white solid after lypholization (5 mg, 13%). HPLC-MS t_R = 1.00 min (UV_{254}

$_{nm}$); mass calculated for formula $C_{12}H_{14}N_2O_3S_2$ 298.0, observed LCMS m/z 299.0 (M+H).

Compound #	Structure	Exact mass	MS m/z (M+H)
1060		408.0	409.0
1061		404.1	405.1

Example 29C:



Part A:

Compound **1062** was prepared following the procedures described in Example 1.

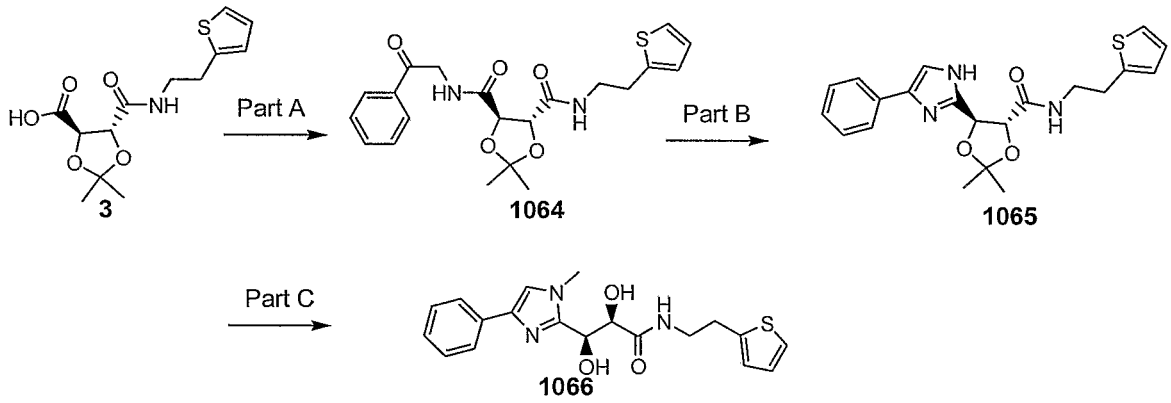
HPLC-MS t_R = 1.69 min ($UV_{254\ nm}$); mass calculated for formula $C_{18}H_{28}N_2O_6S$ 400.2, observed LCMS m/z 401.2 (M+H).

Part B:

Compound **1062** (198 mg, 0.69 mmol) and ammonium acetate (1.9 g, 24.7 mmol) in acetic acid (6 ml) were heated overnight at 110 °C. The reaction mixture was concentrated. The residue was suspended in DCM and the

solids removed by filtration. The filtrate was concentrated to afford a mixture of acetonide protected product and **1063**. The residue was treated with 80% TFA:water (2 mL) and stirred overnight. The solvents were removed. Purification by prep-HPLC afforded **1063** (11 mg, 4%) as a TFA salt. HPLC-MS t_R = 0.79 min ($UV_{254\ nm}$); mass calculated for formula C13H17N3O3S 295.1, observed LCMS m/z 296.1 (M+H).

Example 29D:



Part A:

Compound **1064** was prepared following the procedures described in Example 1.

HPLC-MS t_R = 1.77 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{24}N_2O_5S$ 416.14, observed LCMS m/z 417.1 (M+H).

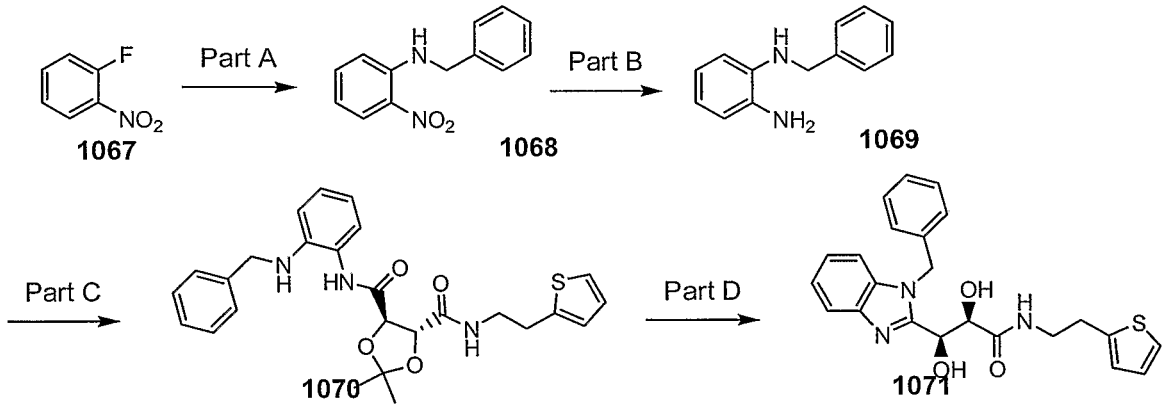
Part B:

Compound **1064** (216 mg, 0.52 mmol) and ammonium acetate (2 g, 25.9 mmol) in acetic acid (6 ml) were heated overnight at 110 °C. The reaction mixture was concentrated. The residue was suspended in DCM and the solids removed by filtration. The filtrate was concentrated and purified by reverse phase chromatography (Gilson) to afford **1065** (80 mg, 30%) as a TFA salt (80% purity). HPLC-MS t_R = 1.38 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{23}N_3O_3S$ 397.1, observed LCMS m/z 398.2 (M+H).

Part C:

A mixture of compound **1065** (63 mg, 0.127 mmol), iodomethane (10 µL, 0.16 mmol) and cesium carbonate (206 mg, 0.634 mmol) in DMF (6 ml) was stirred overnight at room temperature. The reaction mixture was concentrated. The residue was suspended in ethyl acetate and the solids removed by filtration. The filtrate was concentrated to afford the crude acetonide protected product. The residue was treated with 90% TFA:water (3 mL) and stirred for 3 h at 50 °C. The solvents were removed. Purification by prep-HPLC afforded **1066** (12 mg, 19%) as a TFA salt. HPLC-MS t_R = 2.87 min (10 min; $UV_{254\ nm}$); mass calculated for formula $C_{19}H_{21}N_3O_3S$ 371.1, observed LCMS m/z 372.1 (M+H).

Example 29E:



Part A:

According to a modification of a procedure by Goker, H. et. al. *(Il Farmaco* **1998**, *53*, 415-420) a mixture of 1-fluoro-2-nitro-benzene (**1067**) (1.1 mL, 10.4 mmol) and benzylamine (2.35 mL, 21.5 mmol) in DMF (5 mL) was heated overnight at 80 °C. The reaction mixture was concentrated to give an orange solid which was filtered, washed with water and dried to afford benzyl-(2-nitro-phenyl)-amine (**1068**) (2.5 g, 100%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.44 (b, 1H, NH), 8.22-8.19 (dd, 1H), 7.41-7.27 (m, 6H), 6.84-6.81 (dd, 1H), 6.70-6.66 (m, 1H), 4.58-4.57 (d, 2H).

Part B:

To a solution of benzyl-(2-nitro-phenyl)-amine (**1068**) (2.5 g, 10.43 mmol) in ethanol (150 mL) and water (10 mL) was added iron (8.7 g, 155.7 mmol) followed by 30 drops of concentrated HCl, and the resulting mixture was heated overnight at reflux. The reaction mixture was quenched with water, diluted with DCM and the layers were separated. The organic layer was washed with saturated sodium bicarbonate solution, brine, dried over sodium sulfate and concentrated to give a brown oily residue. Further purification by column chromatography (SiO_2, 20 % ethyl acetate/hexanes) afforded N-benzyl-benzene-1,2-diamine (**1069**) as a dark yellow oil (1.18 g, 57%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.24 (m, 5H), 6.82-6.67 (m, 4H), 4.32 (s, 2H), 3.56 (b, 3H, NH).

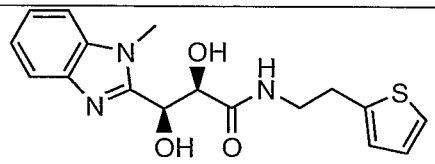
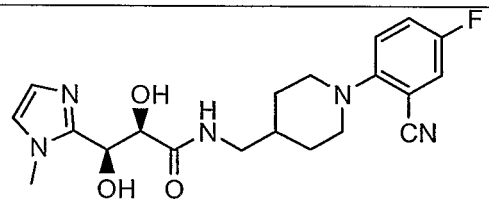
Part C:

Compound **1070** was prepared following the procedures described in Example 29C Part A. HPLC-MS t_R = 2.13 min ($UV_{254\ nm}$); mass calculated for formula $C_{26}H_{29}N_3O_4S$ 479.2, observed LCMS m/z 480.1 (M+H).

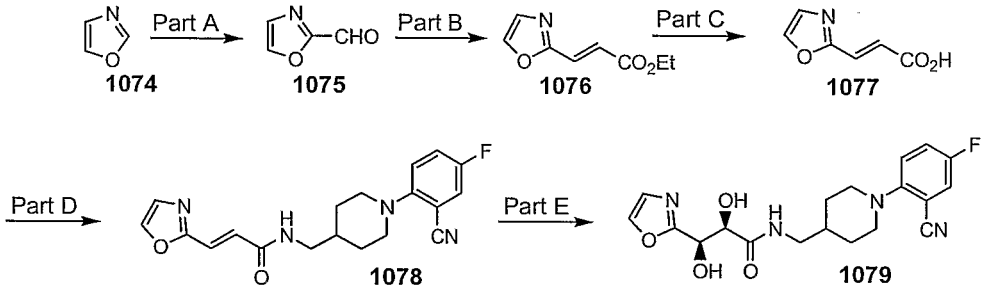
Part D:

A mixture of compound **1070** (75 mg, 0.156 mmol) and p-toluenesulfonic acid monohydrate (30 mg, 0.156 mmol) in toluene (3 ml) was heated overnight at reflux. The reaction mixture was concentrated to a residue identified as the acetonide deprotected product by LC-MS. Further purification by reverse phase chromatography afforded **1071** (40 mg, 48%) as a TFA salt (95% purity). HPLC-MS t_R = 3.52 min (10 min; $UV_{254\ nm}$); mass calculated for formula $C_{23}H_{23}N_3O_3S$ 421.1, observed LCMS m/z 422.2 (M+H).

The following compounds were synthesized by procedures described in Example 29C-E.

Compound #	Structure	Exact mass	MS m/z (M+H)
1072		345.1	346.1
1073		401.2	402.2

Example 29F:



Part A:

According to a procedure Hodges, J. C. et al (*J. Org. Chem.* **1991**, *56*, 449-452) to a cold (–78 °C) solution of oxazole **(1074)** (1g, 14.4 mmol) in 45 mL of THF was added dropwise nBuLi (9 mL, 14.4 mmol, 1.6 M soln in hexane), and the resulting solution was stirred at –78 °C for 25 min. Then DMF (1.12 mL, 14.4 mmol) was added dropwise, followed by THF (5 mL) and the resulting mixture was allowed to warm up slowly to room temperature, and was stirred overnight. The reaction mixture was quenched by the addition of silica gel (3 g), concentrated, and the resulting slurry was diluted with DCM and loaded on a silica gel column. Flash chromatography (3% ethyl acetate/DCM) afforded

oxazole-2-carbaldehyde **(1075)** (165 mg, 12%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.9 (s, 1H), 7.46 (s, 1H).

Part B:

Compound **1076** was prepared from compound **1075** (165 mg, 1.7 mmol) using the procedure described in Example 29B Part A. Purification by column chromatography (SiO_2, 20% ethyl acetate/hexane) afforded the product as a yellow solid (107 mg, 34%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.45 (d, 1H, J = 16.0 Hz), 7.27 (s, 1H), 6.74 (d, 1H, J = 16.0 Hz), 4.29 (q, 2H, J = 7.3 Hz), 1.36 (t, 3H, J = 7.3 Hz).

Part C:

Compound **1077** was prepared from compound **1076** (107 mg, 0.58 mmol) using the procedure described in Example 29B Part B. Work-up afforded the product as a pale yellow solid (77 mg, 85%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.9 (s, 1H), 8.25 (s, 1H), 7.44 (s, 1H), 7.27 (d, 1H, J = 16.0 Hz), 6.62 (d, 1H, J = 16.0 Hz).

Part D:

Compound **1078** was prepared from compound **1077** (165 mg, 1.7 mmol) using the procedure described in Example 29B Part C. After standard HATU coupling work-up the solid residue was triturated with 1:1 DCM/hexane, filtered and washed with 1:1 DCM/hexane to give **1078** (123 mg, 70%) as a pale yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (t, 1H), 8.20 (s, 1H), 7.69-7.66 (dd, 1H), 7.49-7.44 (m, 1H), 7.38 (s, 1H), 7.20-7.16 (dd, 1H), 7.14 (d, 1H, J = 16.0 Hz), 6.94 (d, 1H, J = 16.0 Hz), 3.41-3.38 (d, 2H), 3.16 (t, 2H), 2.72 (t, 2H), 1.81-1.78 (d, 2H), 1.64-1.58 (m, 1H), 1.40-1.30 (m, 2H). HPLC-MS t_R = 1.63 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{19}FN_4O_2$ 354.15, observed LCMS m/z 355.1 (M+H).

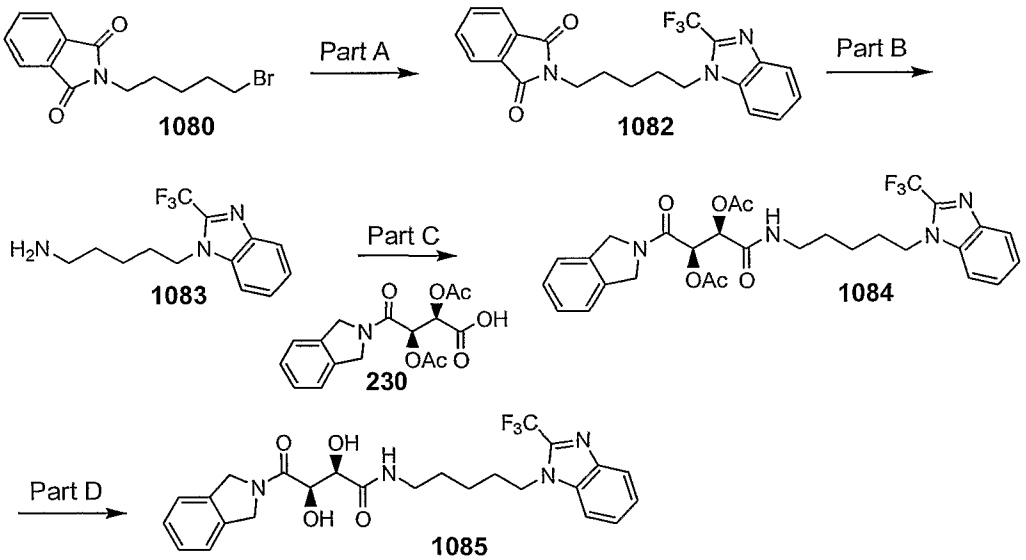
Part E:

Compound **1079** was prepared from compound **1078** (118 mg, 0.33 mmol) using the procedure described in Example 29B Part D. Purification by column

chromatography (SiO_2, 5% MeOH/DCM) afforded the product as a white solid (28 mg, 22%); ^1H NMR (400 MHz, DMSO-d_6) δ 8.02 (s, 1H), 7.88 (t, 1H), 7.69-7.66 (dd, 1H), 7.48-7.43 (m, 1H), 7.20-7.16 (dd, H), 7.14 (s, 1H), 5.83-5.81 (d, 1H), 5.72-5.70 (d, 1H), 4.93-4.90 (dd, 1H), 4.23-4.21 (d of d, 1H), 3.38-3.36 (d, 2H), 3.04 (t, 2H), 2.69 (t, 2H), 1.77-1.72 (d, 2H), 1.62-1.56 (m, 1H), 1.32-1.23 (m, 2H). ^{19}F NMR (400 MHz, DMSO-d_6) δ -120.6 ppm. HPLC-MS t_R = 3.32 min (10 min; $UV_{254\ nm}$); mass calculated for formula $C_{19}H_{21}FN_4O_4$ 388.15, observed LCMS m/z 389.2 (M+H).

Example 30:

Example 30A:



Part A:

A mixture of 2-(5-bromo-pentyl)-isoindole-1,3-dione (**1080**) (2.0 g, 6.77 mmol), 2-trifluoromethyl-1H-benzoimidazole (1.2 g, 6.45 mmol) and potassium carbonate (1.78 g, 12.9 mmol) in NMP (5 ml) was stirred overnight at room temperature. The reaction mixture was partitioned between ethyl acetate and water, and the resulting organic layer was washed with water, brine, dried over sodium sulfate and concentrated to give an oil. Further purification by column chromatography (SiO_2, 25 % ethyl acetate/hexanes) afforded compound **1082** as a colorless oil (1.88 g, 73%). ^1H NMR (400 MHz, $CDCl_3$)

δ 7.88-7.86 (d, 1H), 7.85-7.83 (m, 2H), 7.73-7.71 (m, 2H), 7.49-7.34 (m, 3H), 4.31 (t, 2H), 3.72 (t, 2H), 1.99-1.92 (m, 2H), 1.80-1.73 (m, 2H), 1.53-1.45 (m, 2H).

Part B:

To a solution of compound **1082** (1.88 g, 4.68 mmol) in EtOH (50 mL) was added hydrazine monohydrate (0.45 mL, 9.36 mmol) and the resulting mixture was heated for 3 h at 60 °C, during which time a white precipitate formed. The reaction mixture was filtered, washed with EtOH and the filtrate was concentrated. The residue was suspended in ether, stirred for 10 min at room temperature, filtered and washed with ether, and the resulting filtrate was concentrated to afford compound **1083** as an oil (1.10 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.88 (d, 1H), 7.46-7.37 (m, 3H), 4.33 (t, 2H), 2.76 (t, 2H), 2.02-1.40 (m, 6H).

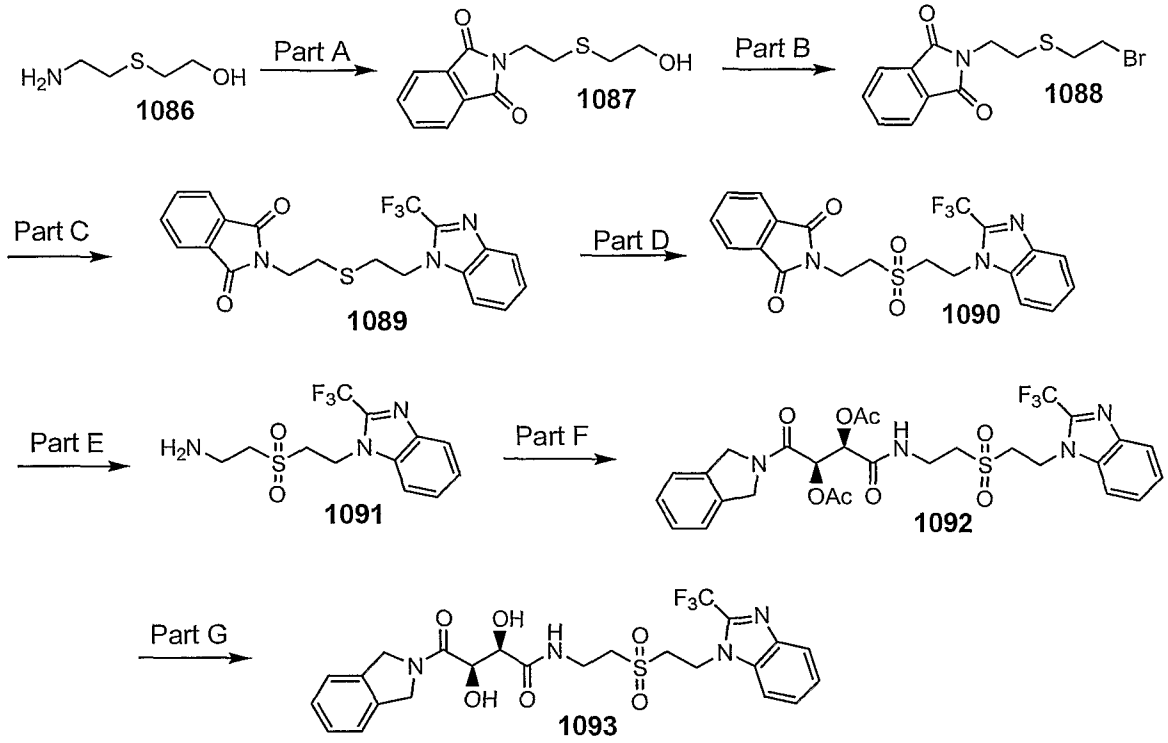
Part C:

Compound **1084** was prepared from **1083** and **230** following the procedures described in Example 2.

Part D:

Compound **1085** was prepared following the procedures described in Example 2. HPLC-MS t_R = 4.14 min (10 min; $UV_{254\ nm}$); mass calculated for formula $C_{25}H_{27}F_3N_4O_4$ 504.2, observed LCMS m/z 505.1 (M+H).

Example 30B:



Part A:

According to a modification of a procedure by Lown, J. W. et. al. (*J. Org. Chem.* **1982**, *47*, 2027-2033) a mixture of 2-(2-amino-ethylsulfanyl)-ethanol (**1086**) (1.82, 15 mmol) and phthalimide (2.22 g, 15 mmol) in toluene (35 ml) was heated overnight at reflux. The reaction mixture was concentrated to a residue, which was purified by column chromatography (SiO_2, 25 % ethyl acetate/DCM to 50% ethyl acetate/DCM) to afford compound **1087** as an off-white solid (2.98 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.87-7.85 (m, 2H), 7.75-7.72 (m, 2H), 3.94 (t, 2H), 3.80 (t, 2H), 2.89-2.82 (m, 4H).

Part B:

According to a modification of a procedure by Nair, S. A. et. al. (*Synthesis* **1995**, 810-814) to an ice-cold solution of compound **1087** (628 mg, 2.5 mmol) and carbon tetrabromide (1.04 g, 3.12 mmol) in DCM (25 mL) was added triphenylphosphine (920 mg, 3.5 mmol) in two portions over 10 min. The reaction mixture was allowed to warm up to room temperature and stirred

overnight at room temperature. The mixture was concentrated and the resulting residue was purified by column chromatography (SiO_2, 30 % ethyl acetate/hexanes) to afford compound **1088** as a white solid (733 mg, 93%). ^1H NMR (400 MHz, $CDCl_3$) δ7.88-7.86 (m, 2H), 7.75-7.73 (m, 2H), 3.92 (t, 2H), 3.53 (t, 2H), 3.04 (t, 2H), 2.90 (t, 2H).

Part C:

Compound **1089** was prepared following the procedures described in Example 30A, Part A. ^1H NMR (400 MHz, $CDCl_3$) δ7.89-7.87 (d, 1H), 7.86-7.84 (m, 2H), 7.74-7.72 (m, 2H), 7.58-7.56 (d, 1H), 7.46 (t, 1H), 7.38 (t, 1H), 4.52 (t, 2H), 3.92 (t, 2H), 3.02 (t, 2H), 2.89 (t, 2H); ^{19}F NMR (400 MHz, $CDCl_3$) δ–64.7 ppm.

Part D:

To a solution of compound **1089** (250 mg, 0.6 mmol) in DCM (5 mL) was added m-chloroperoxybenzoic acid (336 mg, 1.5 mmol) and the resulting mixture was stirred overnight at room temperature. The reaction mixture was diluted with DCM, washed with saturated sodium bicarbonate solution, brine, dried over sodium sulfate and concentrated to give compound **1090** (284 mg) as a white solid which was used without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ7.92-7.90 (d, 1H), 7.90-7.88 (m, 2H), 7.78-7.76 (m, 2H), 7.66-7.62 (d of t, 1H), 7.54-7.51 (t of d, 1H), 7.46-7.44 (t of d, 1H), 4.89 (t, 2H), 4.20 (t, 2H), 3.65 (t, 2H), 3.46 (t, 2H); ^{19}F NMR (400 MHz, $CDCl_3$) δ –62.5 ppm.

Part E:

Compound **1091** was prepared following the procedures described in Example 30A, Part B. ^1H NMR (400 MHz, $CDCl_3$) δ7.91-7.89 (d, 1H), 7.63-7.61 (d, 1H), 7.51-7.48 (t of d, 1H), 7.44-7.40 (t of d, 1H), 4.90 (t, 2H), 3.71 (t, 2H), 3.31 (t, 2H), 3.12 (t, 2H); ^{19}F NMR (400 MHz, $CDCl_3$) δ–62.5 ppm.

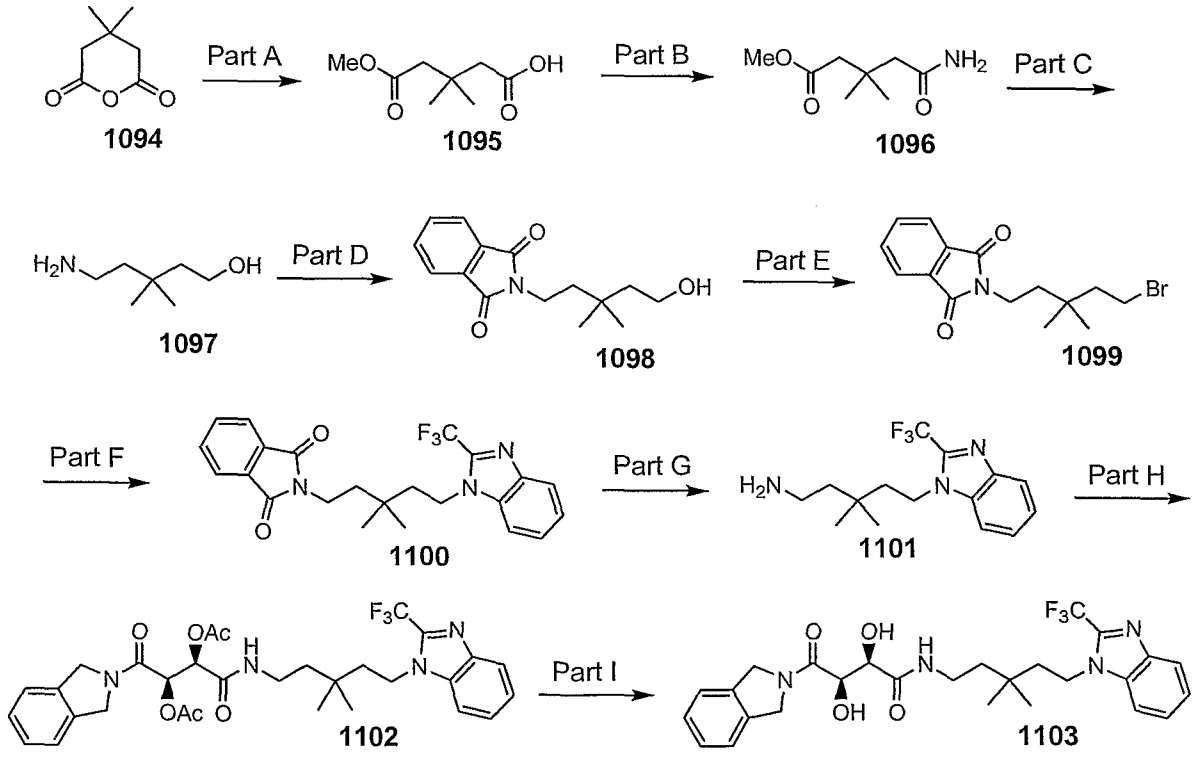
Part F:

Compound **1092** was prepared following the procedures described in Example 27A, Part B, and used without further purification. HPLC-MS t_R = 1.65 min ($UV_{254\ nm}$); mass calculated for formula $C_{28}H_{29}F_3N_4O_8S$ 638.17, observed LCMS m/z 639.1 (M+H).

Part G:

Compound **1093** was prepared following the procedures described in Example 27A, Part C. HPLC-MS t_R = 3.57 min (10 min; $UV_{254\ nm}$); mass calculated for formula $C_{24}H_{25}F_3N_4O_6S$ 554.14, observed LCMS m/z 555.1 (M+H).

Example 30 C:



Part A:

According to a modification of a procedure by Brown, R. F. et. al. (*J. Am. Chem.* Soc. **1955**, *77*, 1083-1089) a mixture of 3,3-dimethyl glutaric anhydride (**1094**) (7.1 g, 50 mmol) and methanol (40 mL) was heated overnight at reflux.

The reaction mixture was concentrated to give compound **1095** as a colorless oil (8.46 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (s, 3H), 2.50 (s, 2H), 2.48 (s, 2H), 1.16 (s, 6H).

Part B:

To an ice-cold solution of compound **1095** (8.46 g, 48.5 mmol) in DCM (30 mL) was added dropwise oxalyl chloride (7 mL, 80 mmol), followed by DMF (2 drops) and the resulting mixture was heated for 3.5 h at reflux. The reaction mixture was concentrated to give the corresponding acid chloride (4-chlorocarbonyl-3,3-dimethyl-butyric acid methyl ester) as a brown oil (7.89 g, 84%) which was used without further purification in the next step.

To an ice-cold solution of ammonia in 1,4-dioxane (30 mL of a solution containing 2.2 g ammonia dissolved in 100 mL of 1,4-dioxane, 38.8 mmol approx) was added dropwise a solution of 4-chlorocarbonyl-3,3-dimethyl-butyric acid methyl ester (3 g, 15.5 mmol) in 1,4-dioxane (3 mL) and after the addition was complete the resulting white slurry was stirred 45 min at room temperature. The reaction mixture was diluted with ethyl acetate, filtered and concentrated to give compound **1096** as a viscous yellow oil (2.62 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (s, 3H), 2.43 (s, 2H), 2.31 (s, 2H), 1.14 (s, 6H).

Part C:

To an ice-cold solution of LAH (42 mL, 1 M sol in THF, 42 mmol) was added dropwise a solution of compound **1096** (2.02 g, 11.6 mmol) in THF and the resulting mixture was heated overnight at reflux. The reaction mixture was cooled to 0 °C and quenched by dropwise addition of brine, when a paste-like solid formed. This solid was triturated and sonicated several times with ethyl acetate, and the combined organic extracts were concentrated to give compound **1097** as an oil (1.17 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (t, 2H), 2.71 (t, 2H), 1.53 (t, 2H), 1.41 (t, 2H), 0.92 (s, 6H).

Part D:

Compound **1098** was prepared following the procedures described in Example 30B, Part A. HPLC-MS t_R = 1.88 min ($UV_{254\ nm}$); mass calculated for formula $C_{15}H_{19}NO_3$ 261.14, observed LCMS m/z 262.0 (M+H).

Part E:

Compound **1099** was prepared following the procedures described in Example 30B, Part B. ^1H NMR (400 MHz, $CDCl_3$) δ 7.84-7.82 (m, 2H), 7.71-7.69 (m, 2H), 3.70-3.66 (m, 2H), 3.47-3.42 (m, 2H), 1.97-1.92 (m, 2H), 1.61-1.57 (m, 2H), 1.03 (s, 6H).

Part F:

Compound **1100** was prepared following the procedures described in Example 30B, Part C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.89-7.87 (d, 1H), 7.86-7.84 (m, 2H), 7.73-7.71 (m, 2H), 7.5-7.57 (d, 1H), 7.47-7.43 (t of d, 1H), 7.39-7.35 (t of d, 1H), 4.46-4.41 (m, 2H), 3.79-3.75 (m, 2H), 1.89-1.85 (m, 2H), 1.74-1.69 (m, 2H), 1.18 (s, 6H); ^{19}F NMR (400 MHz, $CDCl_3$) δ–62.7 ppm.

Part G:

Compound **1101** was prepared following the procedures described in Example 30B, Part E. HPLC-MS t_R = 1.13 min ($UV_{254\ nm}$); mass calculated for formula $C_{15}H_{20}F_3N_3$ 299.16, observed LCMS m/z 300.1 (M+H).

Part H:

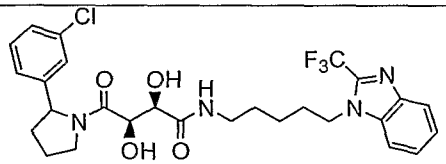
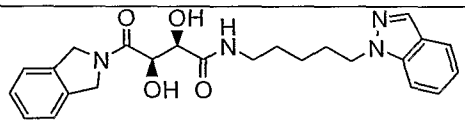
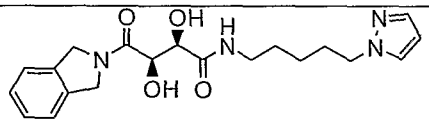
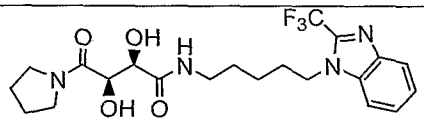
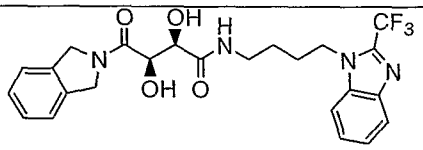
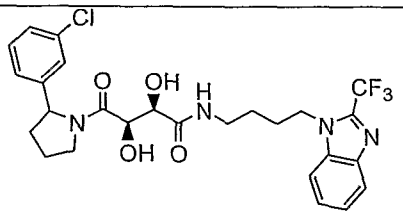
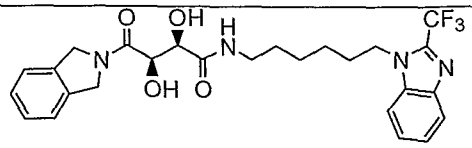
Compound **1102** was prepared following the procedures described in Example 27A, Part B, and used without further purification. HPLC-MS t_R = 2.0 min ($UV_{254\ nm}$); mass calculated for formula C31H35F3N4O6 616.25, observed LCMS m/z 617.2 (M+H).

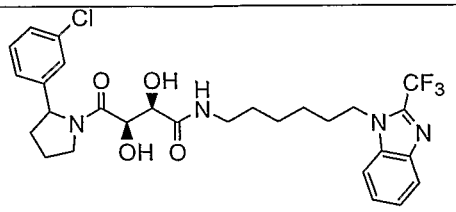
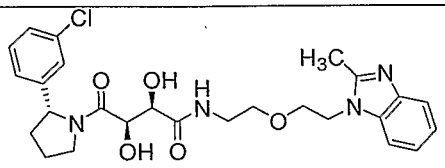
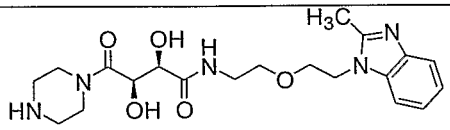
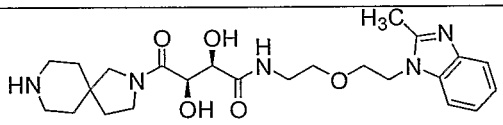
Part I:

Compound **1103** was prepared following the procedures described in Example 27A, Part C. HPLC-MS t_R = 4.52 min (10 min, $UV_{254\ nm}$); mass

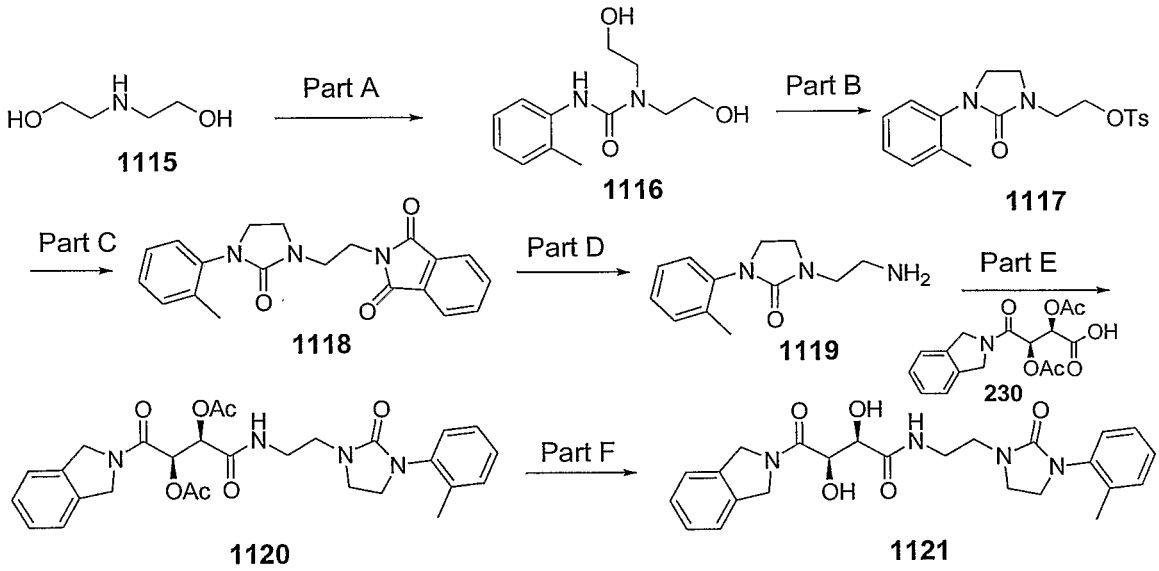
calculated for formula $C_{27}H_{31}F_3N_4O_4$ 532.23, observed LCMS m/z 533.2 (M+H).

The following compounds were synthesized using procedures described in Example 30 A-C.

Compound #	Structure	Exact mass	MS m/e (M+H)
1104		566.2	567.2
1105		436.21	437.2
1106		386.2	387.2
1107		456.2	457.1
1108		490.18	491.1
1109		552.18	553.2
1110		518.2	519.1

1111		580.21	581.2
1112		514.2	515.2
1113		419.2	420.2
1114		473.3	474.3

Example 31:



Part A:

Compound **1115** (790 mg, 7.5 mmol) was dissolved in THF (10 mL) and cooled in an ice bath. 2-Methylphenylisocyanate (500 mg, 3.75 mmol) was added in portions and the resulting solution was stirred at room temperature for 2 hours. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with 1 N HCl solution, bicarbonate solution and brine; dried over sodium sulfate and

concentrated. Purification by column chromatography (SiO_2, 50% ethyl acetate/hexanes) afforded a white solid **1116** (1.02 g, 56%). HPLC-MS t_R = 0.95 (UV_{254nm}); mass calculated for formula $C_{12}H_{18}N_2O_3$ 238.1, observed LCMS m/z 239.2 (M+H).

Part B:

Compound **1116** (1.02 g, 4.2 mmol) was dissolved in THF (25 mL) and cooled in an ice bath. Potassium *t*-butoxide (1.5 g, 13.2 mmol) was added in portions and the reaction mixture was stirred for 10 minutes. A solution of *p*-toluenesulfonyl chloride (1.91 g, 10.8 mmol) in THF (5 mL) was added dropwise and the reaction was stirred 30 minutes at 0°C and 30 minutes at room temperature. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with 1 N HCl solution, bicarbonate solution and brine; dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 50% ethyl acetate/hexanes) afforded a white solid **1117** (0.750 g, 48%). HPLC-MS t_R = 1.87 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{22}N_2O_4S$ 374.1, observed LCMS m/z 375.1 (M+H).

Part C:

Compound **1117** (750 mg, 2.0 mmol) was dissolved in DMF (10 mL) and phthalimide (441 mg, 3.0 mmol) and cesium carbonate (1.95 g, 6.0 mmol) were added and stirred overnight. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with 1 N HCl solution, bicarbonate solution and brine; dried over sodium sulfate and concentrated. The solid residue was recrystallized from ethyl acetate/hexanes to provide **1118** (500 mg, 72%) as a white solid. HPLC-MS t_R = 1.63 ($UV_{254\ nm}$); mass calculated for formula $C_{20}H_{19}N_3O_3$ 349.1, observed LCMS m/z 350.2 (M+H).

Part D:

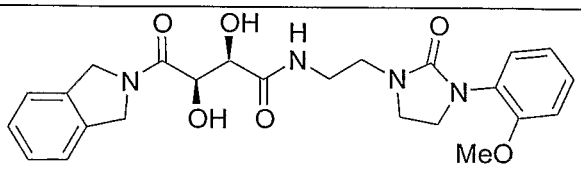
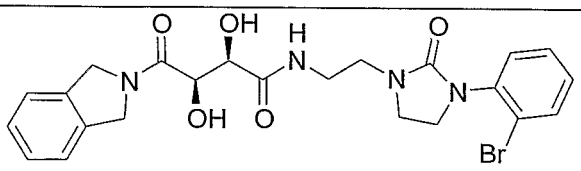
Compound **1118** (110 mg, 0.29 mmol) was dissolved in ethanol (3 mL) and hydrazine hydrate (0.10 mL) was added. The reaction was stirred for 3 hours at room temperature. The solids were removed by filtration and the solution was evaporated under reduced pressure. The residue was dissolved in 1 N NaOH solution and extracted with ethyl acetate. The combined organic layers were washed with brine; dried over sodium sulfate and concentrated to provide compound **1119** that was used without purification.

Part E:

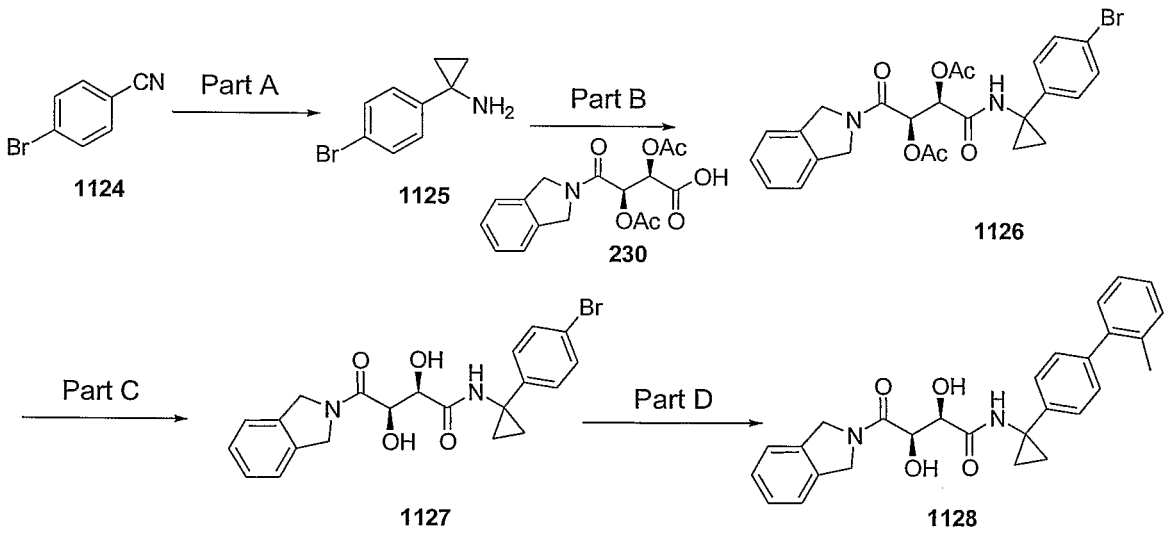
Compound **1119**, **230** (97 mg, 0.29 mmol), DIEA (0.125 mL, 0.7 mmol) and HATU (133 mg, 0.348 mmol) were combined in DMF (3 ml) and stirred overnight. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with 1 N HCl solution, bicarbonate solution and brine; dried over sodium sulfate and concentrated to provide compound **1120** that was used in the next step without purification. HPLC-MS t_R = 1.68 min ($UV_{254\ nm}$); mass calculated for formula $C_{28}H_{32}N_4O_7$ 536.2, observed LCMS m/z 537.3(M+H).

Part F:

Compound **1120** was dissolved in methanol (5 mL) and potassium carbonate (150 mg) was added and stirred for 30 minutes. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with 1 N HCl solution, bicarbonate solution and brine; dried over sodium sulfate and concentrated. Purification by reverse phase prep-LC afforded **1121** as a white solid (16 mg) after lyophilization. HPLC-MS t_R = 3.48 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{24}H_{28}N_4O_5$ 452.2, observed LCMS m/z 453.1(M+H).

Compound #	Structure	Exact mass	MS m/e (M+H)
1122		468.20	469.1
1123		516.10	517.0

Example 32:



Part A:

Compound **1124** (360 mg, 2.00 mmol) was dissolved in diethylether (10 mL) and cooled to -70 °C. Titanium isopropoxide (624 mg, 2.2 mmol) was added and stirred for 10 minutes. Ethylmagnesium chloride (1M in THF, 4 mL, 4 mmol) was added dropwise and the reaction was stirred another 10 minutes at this temperature before warming to room temperature and stirring for an additional 30 minutes. Boron trifluoroetherate (864 mg, 4 mmol) was added and the solution was stirred for 2 hours. The reaction was quenched with 1 N HCl and washed with diethylether. The aqueous layer was made basic by

addition of 1N NaOH solution and then extracted with ethyl acetate. The combined organic layers were washed with brine; dried over sodium sulfate and concentrated to provide compound **1125** that was used without purification.

Part B:

Compound **1125** was dissolved in DMF (5 mL) and compound **230** (50 mg, 0.140 mmol) and HATU (69 mg, 0.182 mmol) were added and stirred overnight. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with 1N HCl, bicarbonate solution and brine; dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 50% ethyl acetate/hexanes) afforded a white solid **1126** (60 mg, 81%). HPLC-MS t_R = 1.928 ($UV_{254\ nm}$); mass calculated for formula $C_{25}H_{25}BrN_2O_6$ 528.0, observed LCMS m/z 529.1 (M+H).

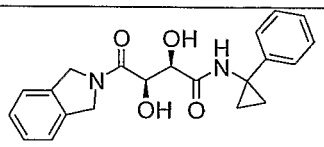
Part C:

Compound **1126** (60 mg, 0.1427 mmol) was dissolved in MeOH (5 mL) and potassium carbonate (100 mg) was added followed by stirring for 30 minutes. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with bicarbonate solution and brine; dried over sodium sulfate and concentrated. Purification by reverse phase prep-LC afforded a white solid **1127** (10 mg, 15.8%) after lyophilization. HPLC-MS t_R = 4.192 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{21}H_{21}BrN_2O_4$ 444.0, observed LCMS m/z 445.1 (M+H).

Part D:

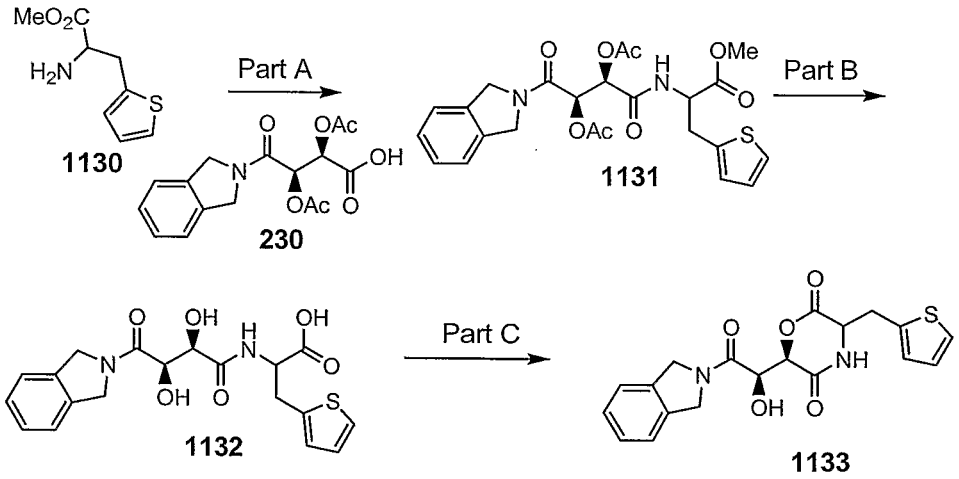
Compound **1127** (7.6 mg, 0.017 mmol) was dissolved in dioxane (2 mL) and $Pd(dba)_3$ (3 mg), triphenylphosphine (4.4 mg, 0.017 mmol), potassium phosphate (8 mg, 0.0377 mmol), and 2-methylphenylboronic acid (4.3 mg, 0.034 mmol) were added under a nitrogen atmosphere. The reaction mixture was heated to 90 °C overnight and then filtered over a bed of celite and concentrated. Purification by reverse phase prep-LC afforded a white solid

1128 (5 mg, 65%) after lyophilization. HPLC-MS t_R = 4.095 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{28}H_{28}N_2O_4$ 456.2, observed LCMS m/z 457.3 (M+H).

Compound #	Structure	Exact mass	MS m/e (M+H)
1129		366.16	367.1

Example 33: Constrained Analogs

Example 33A:



Part A:

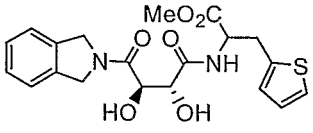
To 2-amino-3-thiophen-2-yl-propionic acid methyl ester hydrochloride **(1130)** (120 mg, 0.54 mmol) in DMF (2 mL) was added **230** (150 mg, 0.45 mmol), DIEA (160 □M, 0.9 mmol) and HATU (205 mg, 0.54 mmol). The reaction mixture was stirred overnight at room temperature, and diluted with ethyl acetate and water. The organic layer was washed with 1 N HCl, saturated $NaHCO_3$, and brine. It was dried over Na_2SO_4, and concentrated, resulting in compound **1131**.

Part B:

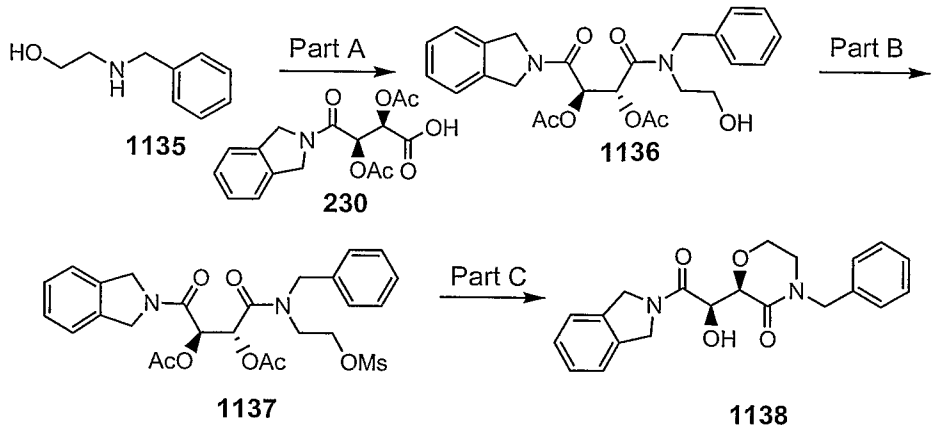
Compound **1131** was dissolved in 5 mL of MeOH, 10 mL of 10% K_2CO_3 aqueous solution was added. After stirring at room temperature for 1 h, the reaction mixture was concentrated in *vacuo*, and then acified with 1N HCL to PH 2. The solution was then extracted with EtOAc, the organic layer was washed with brine, dried over Na_2SO_4, and concentrated, affording compound **1132** as a white solid. Mass calculated for formula $C_{19}H_{20}N_2O_6S$ 404.1, observed LCMS m/z 405.0.0 (M+H).

Part C:

Compound **1132** (40 mg, 0.1 mmol) in 1 mL of DMF was added with PS carbodiimide resin (117 mg, 1.28 mmol/g loading, 0.15 mmol) and dimethylaminopyridine (3 mg, 0.024 mmol). After stirring overnight at 50 °C, the solid was filtered off, and the solution was concentrated in *vacuo*. Purification by reverse phase prep-LC afforded compound **1133** as a white solid. HPLC-MS t_R = 3.59 min ($UV_{254\ nm}$, 10 min), Mass calculated for formula $C_{25}H_{26}ClN_3O_4S$ 386.1, observed LCMS m/z 387.0 (M+H).

Compound #	Structure	Exact mass	MS m/e (M+H)
1134		418.1	419.0

Example 33B:



Part A:

2-Benzylamino-ethanol (1135) (0.676 g, 4.5 mmol) in DMF (10 mL) was added **230** (1.0 g, 3 mmol), and HATU (1.71 g, 4.5 mmol). The reaction mixture was stirred overnight at room temperature, and diluted with ethyl acetate and water. The organic layer was washed with 1 N HCl, saturated $NaHCO_3$, and brine. It was dried over Na_2SO_4, and concentrated, resulting in compound **1136** (1.1 g, 80%). Mass calculated for formula $C_{25}H_{28}N_2O_7$ 468.2, observed LCMS m/z 469.1 (M+H).

Part B:

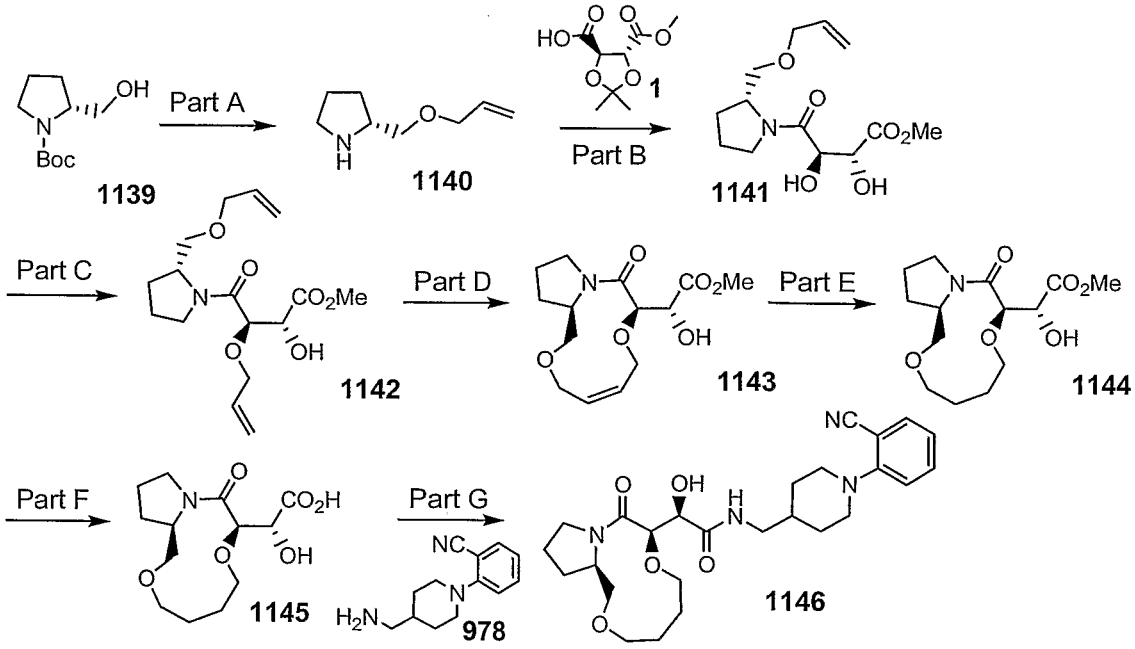
Compound **1136** (468 mg, 1 mmol) and DIEA (261 mL, 1.5 mmol) in CH_2Cl_2 (5 mL) was added dropwise with mesyl chloride (116 mL, 1.5 mmol) at 0 °C. After stirring at 0 °C for 10 min, the reaction mixture was allowed to stir at room temperature for 1.5 h, then concentrated to dryness. The residue was extracted with ethyl acetate, washed with 1 N HCl, saturated $NaHCO_3$, and brine. It was dried over Na_2SO_4, and concentrated, resulting in **1137** (511 mg, 93%).

Part C:

Compound **1137** (389 mg, 0.71 mmol) in MeOH (20 mL) was added with solid K_2CO_3 (323 mg, 2.34 mmol). After stirring at room temperature for 2 h, it was concentrated to remove the solvent, then dissolved in EtOAc and water. The organic layer was washed with 1 N HCl, saturated $NaHCO_3$, brine, and concentrated. Purification by reverse phase prep-LC afforded **1138** as a

white solid. HPLC-MS t_R = 3.89 min ($UV_{254\ nm}$, 10 min), Mass calculated for formula $C_{21}H_{22}N_2O_4$ 366.16, observed LCMS m/z 367.1 (M+H).

Example 33C:



Part A:

Step 1: (R)- Boc-prolinol (**1139**) (2.0 g, 9.94 mmol) in THF (5 mL) was added into NaH (0.437 g, 60% in mineral oil, 10.93 mmol) in 10 mL of THF at 0 °C. After stirring at 0 °C for 10 min, allyl bromide (1.32 g, 10.93 mmol) was added. Te reaction mixture was allowed to stir overnight at room temperature. After filtration, the solution was concentrated to dryness, the residue was taken up with EtOAc, washed with 1N citric acid, saturated $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated, resulting in a colorless oil (2.30 g, 96%).

Step 2: The above material in CH_2Cl_2 (10 mL) was added dropwise with 3 mL of TFA at 0 °C. After stirring at room temperature for 1 h, the solution was concentrated. The residue was dissolved in EtOAc, washed with concentrated Na_2CO_3, brine, dried over over Na_2SO_4, and concentrated, resulting in compound **1140** as a colorless oil (1.06 g, 75% for two steps).

Part B:

Step 1: To compound **1140** (500 mg, 3.54 mmol) in DMF (10 mL) was added **1** (867 mg, 4.25 mmol) DIEA (1.48 mL, 8.5 mmol) and HATU (1.616 g, 4.25 mmol) at 0 °C. After stirring at room temperature for 5 h, the reaction mixture was diluted with ethyl acetate and water. The organic phase was washed with 1 N citric acid, saturated $NaHCO_3$, and brine. It was dried over Na_2SO_4, and concentrated. Column purification (SiO_2, EtOAc/Hexane 40:60) afforded a colorless oil (650 mg, 57%).

Step 2: The above material was treated with 5 mL of TFA/H_2O (80:20) at 0 °C. After stirring at room temperature for 2 h, it was concentrated to dryness. Column purification (SiO_2, EtOAc/Hexane 70:30) afforded compound **1141** (500 mg, 88%) as a colorless oil.

Part C:

Step 1: To compound **1141** (250 mg, 0.87 mmol) in toluene (20 mL) was added dibutyltin oxide (217 mg, 0.87 mmol). The reaction mixture was refluxed for 1 h, using Dean-stark apparatus for azotropic removal of water. After cooling to room temperature, the solvent was stripped to dryness under reduced pressure. The resulting oil was dried in *vacuo* for 2 h.

Step 2: To the above oil was added CsF (198 mg, 1.30 mmol). The mixture was then placed in vacuo for 2 h. Allyl bromide (220 mg, 1.83 mmol) in DMF (10 mL) was added at 0 °C. After stirring at room temperature under argone for 30 h, the reaction mixture was concentrated, and then taken up with EtOAc. The solution was washed with saturated KF solution, and brine, dried over Na_2SO4, and concentrated. The organic layer was washed with 1 N HCl, saturated $NaHCO_3$, brine, and concentrated. Column chromatography (SiO_2, EtOAc/Hexane 60:40) afforded compound **1142** as a colorless oil (130 mg, 45%). Mass calculated for formula $C_{16}H_{25}NO_6$ 327.17, observed LCMS m/z 328.1 (M+H).

Part D:

Compound **1142** (110 mg, 0.33 mmol) in dichloromethane (200 mL) was added with Grubbs' second-generation catalyst (Scholl, M.; Ding, S.; Lee, C.W.; Grubbs, R.H., *Org. Lett,* **1999**, *1*, 953-956.). After stirring at room temperature under argone for 3.5 h, the solution was concentrated under reduced pressure. Column chromatography (SiO_2, EtOAc) afforded **1143** as a white solid (60 mg, 60%), Mass calculated for formula $C_{14}H_{21}NO_6$ 299.14, observed LCMS m/z 300.1 (M+H).

Part E:

To **1143** (60 mg, 0.2 mmol) in EtOAc (10 mL) was added 10% Pd/C (10 mg). The reaction mixture was allowed to stir at room temperature under H_2 for 2 h, then concentrated. Column chromatography (SiO_2, EtOAc) afforded **1144** as a white solid (50 mg, 83%), Mass calculated for formula $C_{14}H_{23}NO_6$ 301.15, observed LCMS m/z 302.1 (M+H).

Part F:

Compound **1144** (20 mg, 0.067 mmol) in MeOH (2 mL) was mixed with solid K_2CO_3 (20 mg, 0.14 mmol). After stirring at room temperature for 5 h, the reaction mixture was concentrated, and then taken up with EtOAc and water. It was acidified with 1N HCl. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated to afford **1145** as a white solid (12 mg, 63%), Mass calculated for formula $C_{13}H_{21}NO_6$ 287.1, observed LCMS m/z 288.1 (M+H).

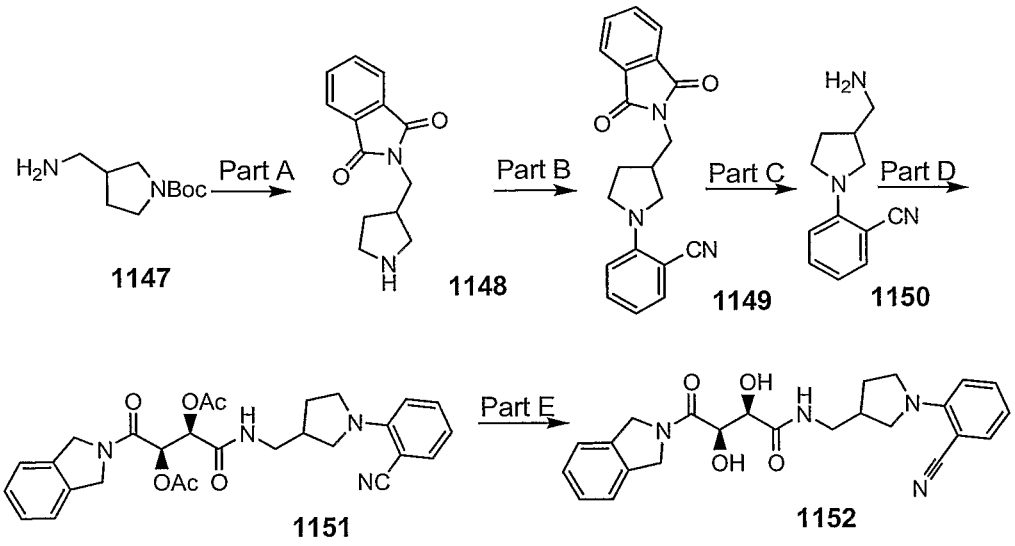
Part G:

A mixture of **1145** (12 mg, 0.042 mmol), **978** (13.5 mg, 0.063 mmol), DIEA (0.018 mL, 0.1 mmol) and HATU (24 mg, 0.063 mmol) in DMF (1 mL) was stirred overnight at room temperature, and then diluted with ethyl acetate and water. The organic layer was washed with 1 N HCl, saturated $NaHCO_3$, and brine. It was dried over Na_2SO_4, and concentrated. Purification by reverse phase prep-LC afforded **1146** as a white solid. HPLC-MS t_R = 4.22 min

(UV_{254} nm, 10 min), mass calculated for formula $C_{21}H_{22}N_2O_4$ 484.3, observed LCMS m/z 485.2 (M+H).

Example 34

Example 34A:



Part A

Step 1: A mixture of 3-(aminomethyl)-1-N-(*tert*-butoxycarbonyl)-pyrrolidine (**1147**) (200 mg, 1.0 mmol), monomethyl phthalate (216 mg, 1.2 mmol), EDC (229 mg, 1.2 mmol), HOBt (162 mg, 1.2 mmol) and triethylamine (0.79 mL, 2.0 mmol) in DCM (4 mL) was stirred overnight. The reaction mixture was diluted with DCM and washed with 0.1 N HCl, water, saturated sodium bicarbonate solution, water, and brine, dried over sodium sulfate and concentrated. The residue was purified by column chromatography (SiO_2, 33% EtOAc/hexane) to afford a white solid (110 mg, 33%). HPLC-MS t_R = 1.89 min ($UV_{254\ nm}$); mass calculated for formula $C_{18}H_{22}N_2O_4$ 330.2, observed LCMS m/z 353.2 (M+Na).

Step 2: Compound **1148** was prepared from the material from step 1 following the procedure as described in Example 27 Part A step 2.

Part B

Compound **1149** was prepared following the procedure as described in Example 27 Part A step 1. HPLC-MS t_R = 1.96 min ($UV_{254\ nm}$); mass calculated for formula $C_{20}H_{17}N_3O_2$ 331.1, observed LCMS m/z 332.2 (M+H).

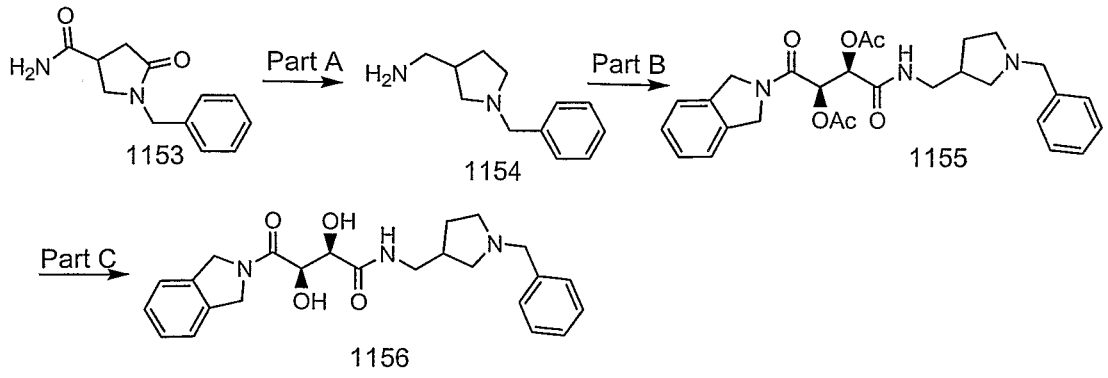
Part C

Compound **1149** (0.33 mmol) and hydrazine hydrate (65 µL, 1.34 mmol) in ethanol (3 mL) were refluxed for 2 hours. The reaction mixture was cooled and filtered. The filtrate was concentrated and **1150** was used without further purification.

Part D and E

Compounds **1151** and **1152** were prepared following the procedures described in Example 5 Part D and E. Data for **1151**: HPLC-MS t_R = 1.78 min ($UV_{254\ nm}$); mass calculated for formula C28H30N4O6 518.2, observed LCMS m/z 519.2 (M+H). Data for **1152**: HPLC-MS t_R = 1.52 min ($UV_{254\ nm}$); mass calculated for formula $C_{24}H_{26}N_4O_4$ 434.2, observed LCMS m/z 435.2 (M+H).

Example 34B:



Part A

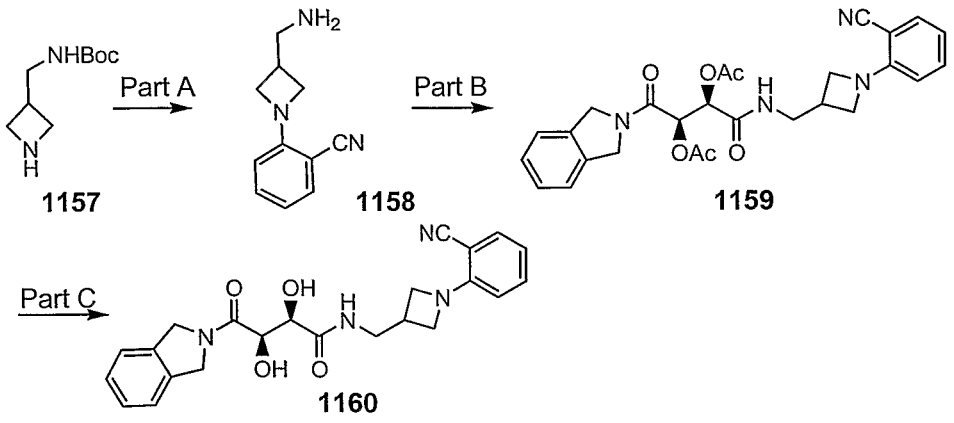
To a solution of 1-benzyl-5-oxo-3-pyrrolidinecarboxamide (**1153**) (50 mg, 0.23 mmol) in THF (1 mL) was added 1M solution of lithium aluminum hydride in THF (0.69 mL, 0.69 mmol). The reaction mixture was stirred at 50 °C for 3 hours, cooled, quenched with aqueous ammonium chloride solution. After addition of 1N sodium hydroxide solution, the mixture was diluted with ethyl acetate, stirred for 20 minutes, and filtered through a pad of Celite. The filtrate was washed with 1N sodium hydroxide solution and brine, dried over sodium sulfate and concentrated to give **1154** as an oil (14 mg, 32%). HPLC-MS t_R = 0.22 min ($UV_{254\ nm}$); mass calculated for formula $C_{12}H_{18}N_2$ 190.2, observed LCMS m/z 191.2 (M+H).

Part B and C

Compounds **1155** and **1156** were prepared following the procedures described in Example 5 Part D and E. Data for **1156**: HPLC-MS t_R = 0.91 min ($UV_{254\ nm}$); mass calculated for formula $C_{24}H_{29}N_3O_4$ 423.2, observed LCMS m/z 424.1 (M+H).

Example 35

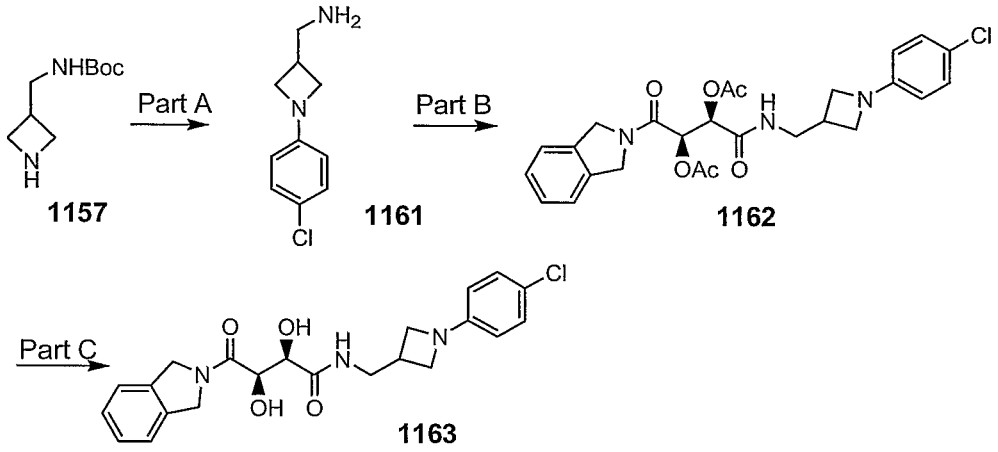
Example 35A:



Part A and B and C:

Compounds **1158, 1159** and **1160** were prepared following the procedures described in Example 27 Part A, B and C. Data for **1158**: HPLC-MS t_R = 0.76 min ($UV_{254\ nm}$); mass calculated for formula $C_{11}H_{13}N_3$ 187.1, observed LCMS m/z 188.1 (M+H). Data for **1159**: HPLC-MS t_R = 1.72 min ($UV_{254\ nm}$); mass calculated for formula $C_{27}H_{28}N_4O_6$ 504.2, observed LCMS m/z 505.1 (M+H). Data for **1160**: HPLC-MS t_R = 1.43 min ($UV_{254\ nm}$); mass calculated for formula $C_{23}H_{24}N_4O_4$ 420.2, observed LCMS m/z 421.1 (M+H).

Example 35B:



Part A

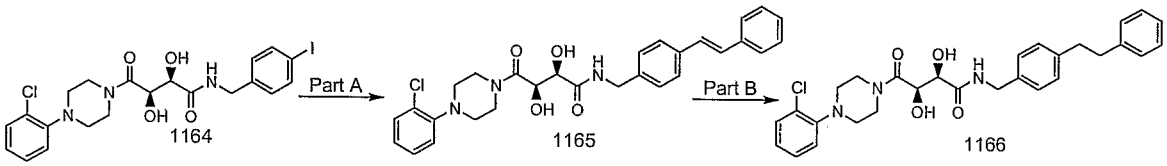
Step 1: A mixture of azetidin-3-ylmethyl-carbamic acid tert-butyl ester (**1157**) (20 mg, 0.107 mmol), 4-chloro-1-iodobenzene (38.4 mg, 0.161 mmol), copper iodide (4.0 mg, 0.021 mmol), L-proline (4.8 mg, 0.042 mmol) and potassium carbonate (29.6 mg, 0.214 mmol) in DMSO (2 mL) under Argon atmosphere was stirred at 80 °C overnight. The reaction mixture was diluted with EtOAc, washed with water and brine, dried over sodium sulfate and concentrated. HPLC-MS t_R = 2.13 min ($UV_{254\ nm}$); mass calculated for formula $C_{15}H_{21}ClN_2O_3$ 296.1, observed LCMS m/z 297.2 (M+H).

Step 2: Compound **1161** was prepared from the material from step 1 following the procedure as described in Example 27 Part A step 2.

Part B and C

Compounds **1162** and **1163** were prepared following the procedures described in Example 5 Part D and E. Data for **1162**: HPLC-MS t_R = 1.93 min ($UV_{254\ nm}$); mass calculated for formula C26H28ClN3O6 513.2, observed LCMS m/z 514.2 (M+H). Data for **1163**: HPLC-MS t_R = 1.63 min ($UV_{254\ nm}$); mass calculated for formula $C_{22}H_{24}ClN_3O_4$ 429.2, observed LCMS m/z 430.1 (M+H).

Example 36:



Compound **1164** was prepared using procedures described in Example 2. HPLC-MS t_R = 1.88 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{23}ClIN_3O_4$ 543.0, observed LCMS m/z 544.0 (M+H).

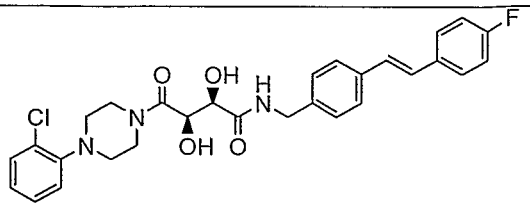
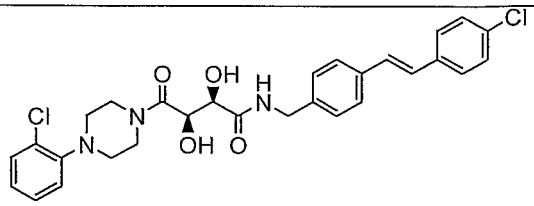
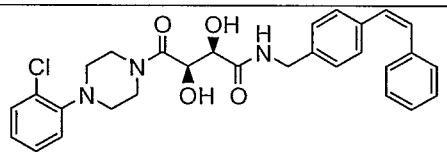
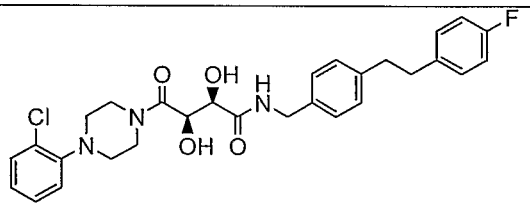
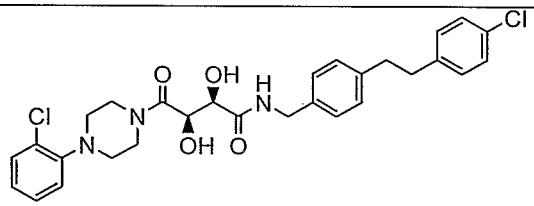
Part A:

Compound **1165** was prepared from **1164** and styrenyl boronic acid using the coupling conditions described in Example 3 Part F. HPLC-MS t_R = 2.11 min ($UV_{254\ nm}$); mass calculated for formula $C_{29}H_{30}ClN_3O_4$ 519.2, observed LCMS m/z 520.0 (M+H).

Part B:

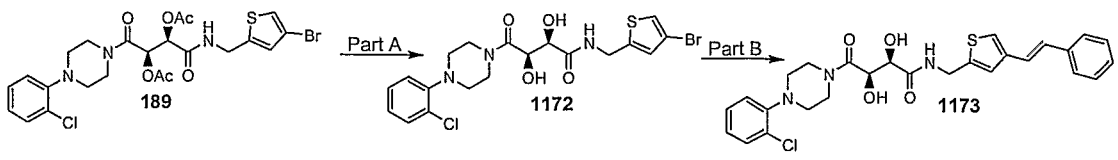
A mixture of **1165** (10 mg, 0.02 mmol) and palladium on carbon (10 wt%, 2 mg) in THF (2 mL) under hydrogen (atmospheric pressure) was stirred overnight. The reaction mixture was filtered through celite and concentrated.

Purification by prep-LC afforded **1166** as an off-white solid (5 mg). HPLC-MS t_R = 5.42 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{29}H_{32}ClN_3O_4$ 521.2, observed LCMS m/z 522.2 (M+H).

Compound #	Structure	Exact mass	MS m/e (M+H)
1167		537.2	538.1
1168		553.2	554.0
1169		519.2	520.2
1170		539.2	540.2
1171		555.2	556.0

Example 37: Alkyl Suzuki

Example 37A:



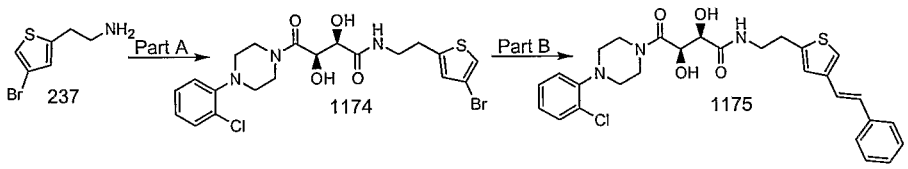
Part A:

Compound **1172** was prepared from **189** using the procedures described in Example 2A Part B. HPLC-MS t_R = 4.83 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{19}H_{21}BrClN_3O_4S$ 501.0, observed LCMS m/z 502.0 (M+H).

Part B:

Compound **1173** was prepared using the procedures described in Example 36 Part A. HPLC-MS t_R = 5.37 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{27}H_{28}ClN_3O_4S$ 525.2, observed LCMS m/z 526.2 (M+H).

Example 37B:



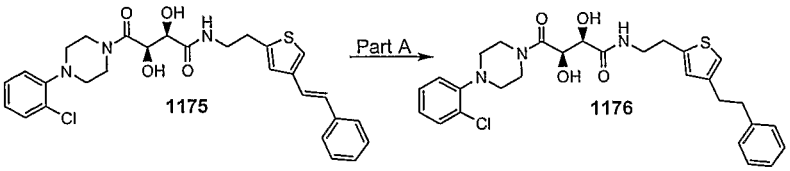
Part A:

Compound **1174** was prepared from **237** using the procedures described in Example 2. HPLC-MS t_R = 4.76 min ($UV_{254\ nm}$, 10 min); Mass calculated for formula $C_{20}H_{23}BrClN_3O_4S$ 515.0, observed LCMS m/z 516.0 (M+H).

Part B:

Compound **1175** was prepared using the procedures described in Example 36 Part A. HPLC-MS t_R = 2.29 min ($UV_{254\ nm}$,); mass calculated for formula $C_{28}H_{30}ClN_3O_4S$ 539.2, observed LCMS m/z 540.2 (M+H).

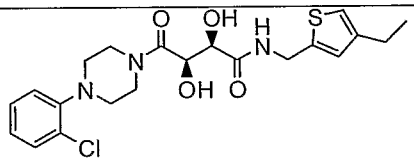
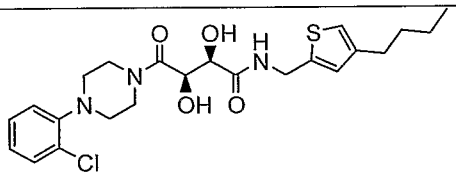
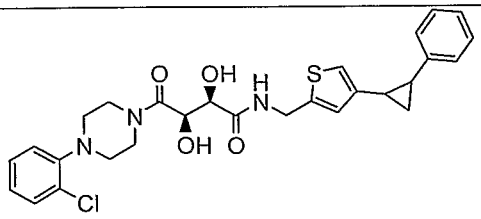
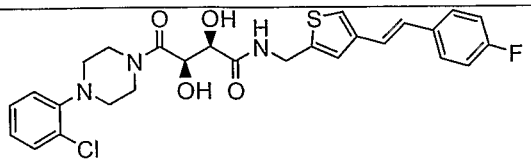
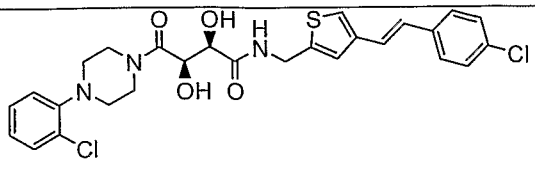
Example 37C:

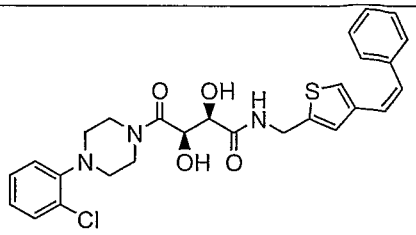
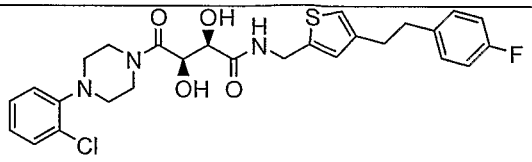
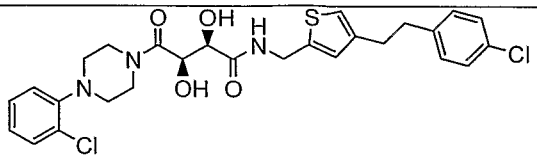
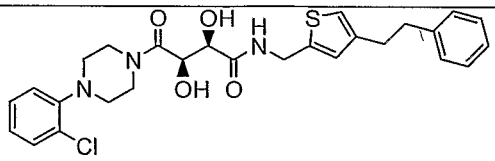
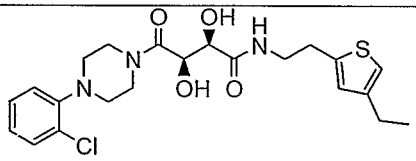
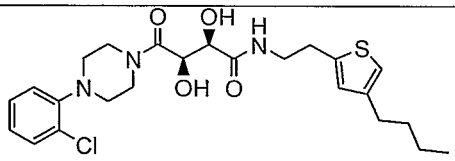
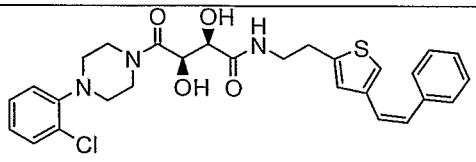


Part A:

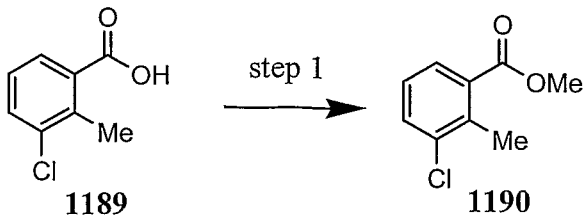
Compound **1176** was prepared using procedures described in Example 36 Part B.

HPLC-MS t_R = 5.50 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{28}H_{32}ClN_3O_4S$ 541.2, observed LCMS m/z 542.2 (M+H).

Compound #	Structure	Exact mass	MS m/e (M+H)
1177		451.1	452.2
1178		479.2	480.2
1179		539.2	540.1
1180		543.1	544.0
1181		559.1	560.0

1182		525.2	526.2
1183		545.2	546.1
1184		561.1	562.0
1185		527.2	528.1
1186		465.2	466.1
1187		493.2	494.1
1188		539.2	540.1

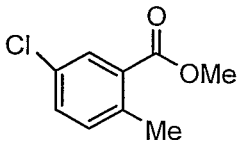
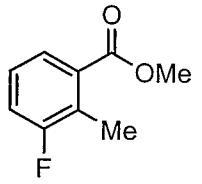
Example 38: Isoindoline analogs

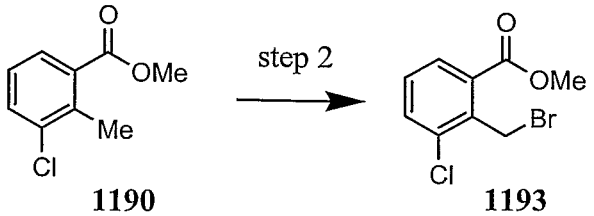


1189 **1190**

Step 1

To 3-chloro-2-methylbenzoic acid **1189** (4.95 g, 0.0290 mol) dissolved in DMF (70 mL) was added cesium carbonate (14.18 g, 0.0435 mol) and methyl iodide (5.35 g, 2.3 mL, 0.0377 mol). The reaction mixture was stirred at room temperature for 20 h. The reaction mixture was concentrated, and EtOAc (200 mL) was added. The organic solution was washed with water (2 x 100 mL), dried ($MgSO_4$), filtered, and concentrated to give 4.43 g (83%) of the product **1190** as a yellow oil. MS for M-Cl:149

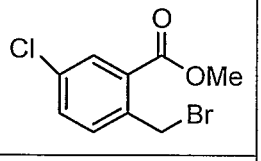
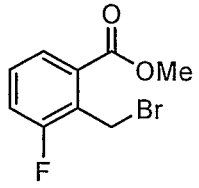
Compound #	Structure	MS
1191		M-Cl: 149
1192		M+1: 169

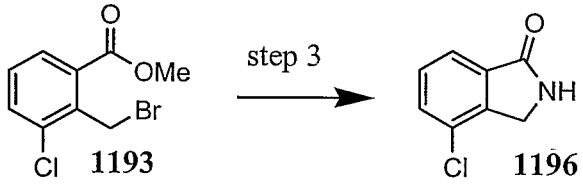


1190 **1193**

Step 2

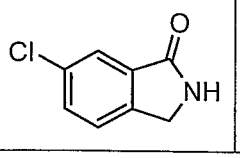
To compound **1190** (4.42 g, 0.0239 mol) dissolved in CCl_4 (100 mL) was added n-bromosuccinimide (5.11 g, 0.287 mol) and benzoyl peroxide (0.58 g, 0.00239 mol). The reaction mixture was heated at reflux for 16 h then cooled to room temperature. The solid was removed by filtration and washed with CH_2Cl_2. The filtrate was concentrated to give 7.80 g of the product **1193** with succinimide as a yellow oil and solid mixture.

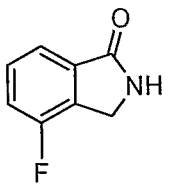
Compound #	Structure
1194	
1195	

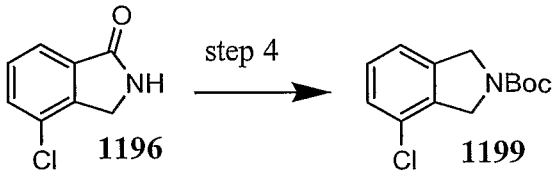


Step 3

Compound **1193** (6.31 g, 0.0239 mol) was dissolved in 7 N NH_3 in MeOH (50 mL) and stirred at room temperature for 3 h then heated at reflux for 4 h. The reaction mixture was cooled to room temperature and concentrated. The residue was suspended in CH_2Cl_2 (150 mL), and the solid was removed by filtration and washed with CH_2Cl_2. The filtrate was concentrated, and the crude product was purified by silica gel flash chromatography (eluant: 5% MeOH-CH_2Cl_2 to 10% MeOH-CH_2Cl_2) to give 3.68 g (92%) of the product **1196** as a white solid. MS for M+1: 168.

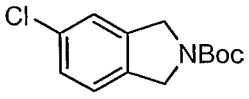
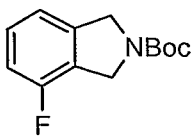
Compound #	Structure	MS (M+1)
1197		168

1198		152

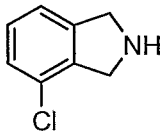
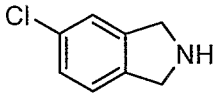
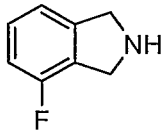


Step 4

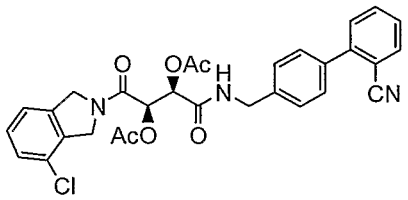
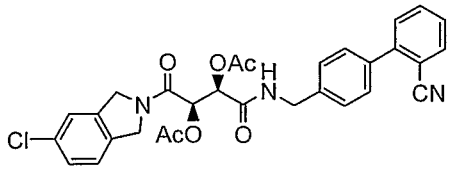
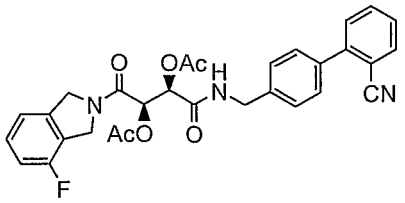
To compound **1196** (1.00 g, 5.97 mmol) suspended in dry THF (15 mL) was added borane (1 M in THF, 14.9 mL, 14.0 mmol). The reaction mixture was heated at reflux for 5 h then cooled to 0 °C. EtOH (15 mL) and potassium carbonate (2 g) were carefully added portionwise. The reaction mixture was heated at reflux for 16 h then cooled to 0 °C, and $(tBOC)_2O$ (1.95 g, 8.95 mmol) was added. The reaction mixture was stirred at room temperature for 3 h then concentrated. Water (30 mL) was added, and the aqueous solution was extracted with 3 x 30 mL of CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by silica gel flash chromatography (eluant: 5% EtOAc- CH_2Cl_2) to give 0.56 g (37%) of the product **1199** as a yellow oil. MS for M+1-tBu: 198.

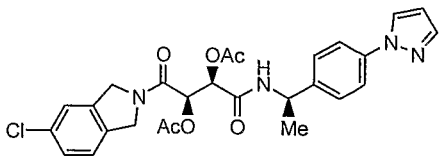
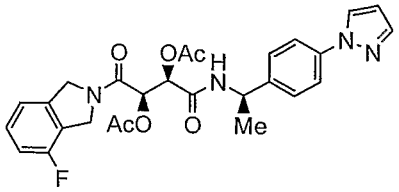
Compound #	Structure	MS
1200		M+2-tBu = 198
1201		M+2-tBu: 182

The following intermediates were prepared according to the procedure of Example 11B Part F.

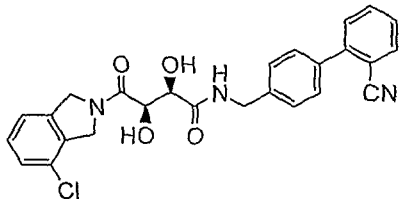
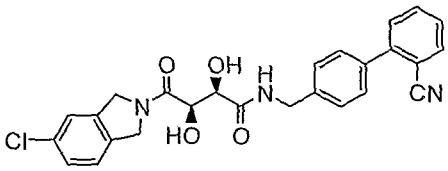
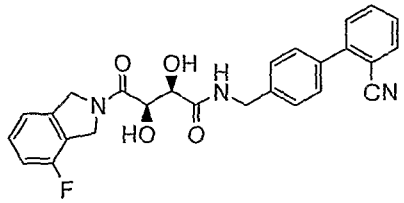
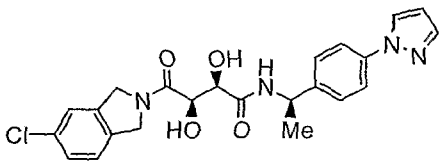
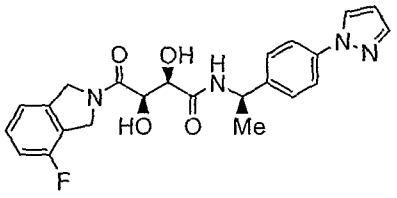
Compound #	Structure	MS (M+1)
1202		154
1203		154
1204		138

The following intermediates were prepared according to the procedure of Example 2

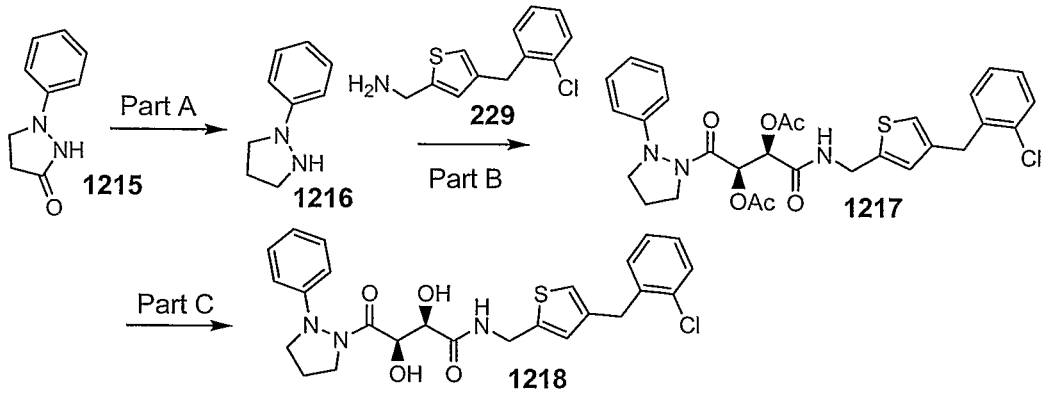
Compound #	Structure	MS (M+1)
1205		560
1206		560
1207		544

1208		539
1209		523

The following compounds were prepared according to the procedure of Example 2

Compound #	Structure	MS (M+1)
1210		476
1211		476
1212		460
1213		455
1214		439

Example 39: Hydrazinoamides



Part A:

1-Phenyl-pyrazolidin-3-one (**1215**)(1.0 g, 6.16 mmol) in 15 mL of THF was added dropwise to the mixture of $AlCl_3$ (0.82 g, 6.16 mmol) and 12 mL of 1 M $LiAlH_4$ (12 mmol) in THF at 0°C under argone. The reaction mixture was then allowed to stir at room temperature for 4 h. It was quenched with 10 mL of 1N NH4Cl solution, diluted with EtOAc and 15% NaOH aqueous solution. After filtration, the organic layer was separated, dried over Na_2SO_4, and concentrated. Column chromatography (SiO_2, EtOAc/Hexane, 20:80) afforded **1216** as colorless oil.

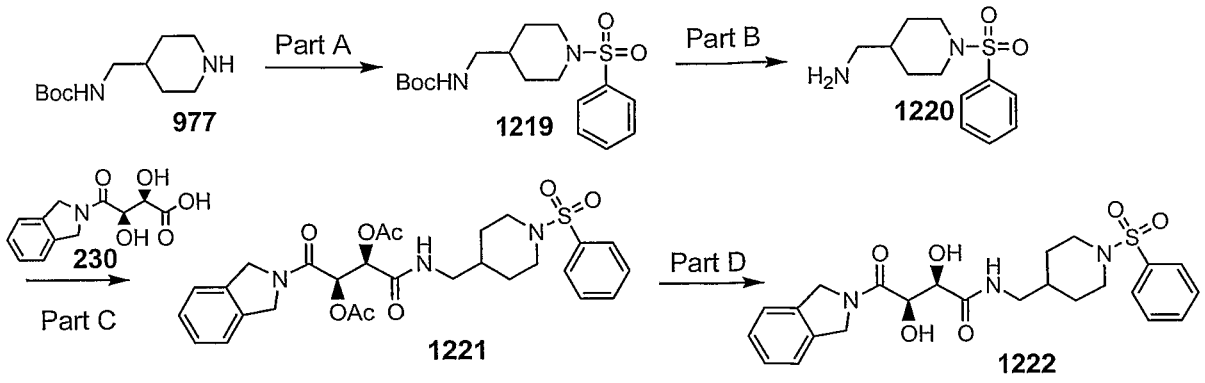
Part B:

Compound **1217** was prepared according to the procedure described in Example 2A Part A from **1216** (15 mg, 0.1 mmol).

Part C:

Compound **1217** was dissolved in 1 mL of MeOH, 0.5 mL of 7N NH_3 in MeOH was added. After stirring at room temperature for 1 h, the reaction mixture was concentrated in *vacuo*. Purification by reverse phase prep-LC afforded compound **1218** as a white solid. HPLC-MS t_R = 5.09 min ($UV_{254\ nm}$, 10 min), Mass calculated for formula $C_{25}H_{26}ClN_3O_4S$ 499.1, observed LCMS m/z 500.0 (M+H).

Example 40: Piperidine sulfonamides



Part A:

Phenylsulfonyl chloride (212 mg, 1.2 mmol) was slowly added to a solution of 4-(Boc-aminomethyl)piperidine (**977**) (214 mg, 1 mmol) in 1.0 mL of pyridine at 0 °C. The reaction mixture was allowed to stir at room temperature overnight, and diluted with ethyl acetate and water. The organic layer was washed with 1 N citric acid, saturated $NaHCO_3$, and brine. It was dried over Na_2SO_4, and concentrated, resulting in **1219** (320 mg, 90%). Mass calculated for formula $C_{17}H_{26}N_2O_4S$ 354.2, observed LCMS m/z 355.2 (M+H), 299.2 (M-55)

Part B:

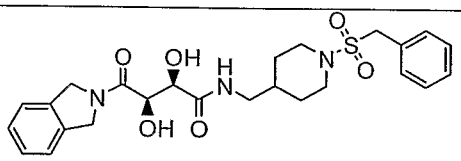
To the solution of **1219** (200 mg, 0.54 mmol) in THF (5 mL) was added 2 mL of 4 N HCl in dioxane. The reaction mixture was stirred at room temperature for 1 h, and concentrated to afford **1220** (105 mg, 66 %).

Part C:

To **1220** (105 mg, 0.36 mmol) in DMF (2 mL) was added **230** (100 mg, 0.3 mmol), DIEA (750 µL, 0.6 mmol) and HATU (137 mg, 0.36 mmol). The reaction mixture was stirred overnight at room temperature, and diluted with ethyl acetate and water. The organic layer was washed with 1 N HCl, saturated $NaHCO_3$, and brine. It was dried over Na_2SO_4, and concentrated, resulting in **1221**.

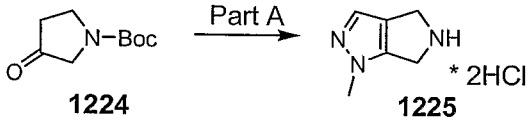
Part D:

Compound **1221** was dissolved in 4 mL of MeOH, 2 mL of 7N NH_3 in MeOH was added. After stirring at room temperature for 1 h, the reaction mixture was concentrated in vacuo. Purification by reverse phase prep-LC afforded **1222** as a white solid. HPLC-MS t_R = 3.59 min ($UV_{254\ nm}$, 10 min), Mass calculated for formula $C_{24}H_{29}N_3O_6S$ 488.2, observed LCMS m/z 488.1 (M+H).

Compound #	Structure	Exact mass	MS m/e (M+H)
1223		501.2	502.1

Example 41: Heterocyclic isoindoline analogs

Example 41A:

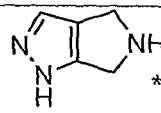
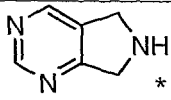
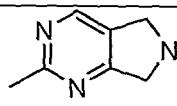


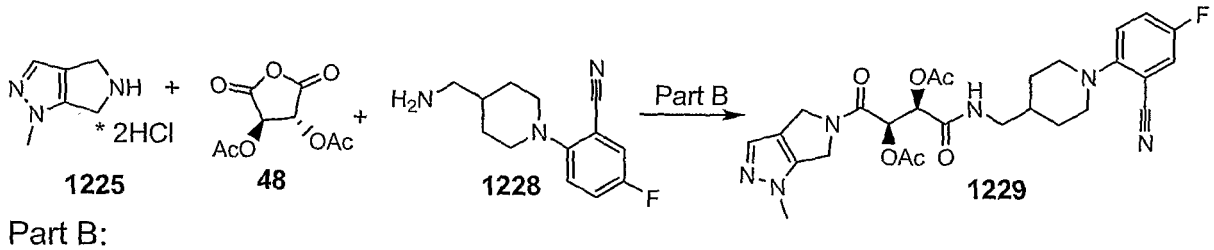
1224 **1225**

Part A:

Compound **1225** (70% overall yield) was prepared from **1** according to the procedures of Fukui, H. *et. al.* (*Heterocycles* **2002**, *56*, 257)

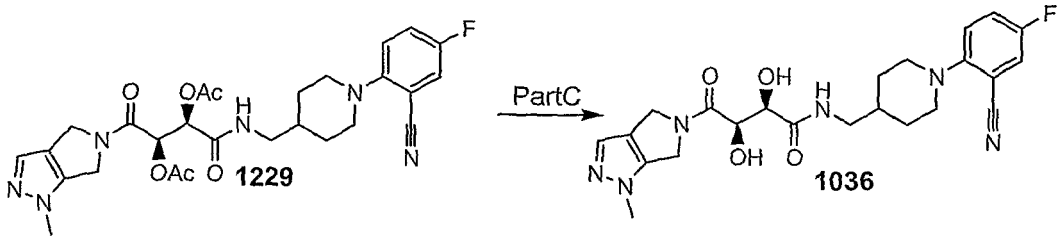
The following analogs were prepared according to this reference:

Compound #	Structure	Overall yield
1225		73%
1226		47%
1227		66%



Part B:

Compound **1228** was prepared according to procedures described in Example 27A. HPLC-MS t_R = 0.95 min (UV_{254nm}); mass calculated for formula C13H16FN3 233.1, observed LCMS m/z 234.2 (M+H). Compound **1229** was prepared according to the procedures described in Example 2A Part A. HPLC-MS t_R = 1.57 min ($UV_{254\ nM}$); mass calculated for formula $C_{27}H_{31}FN_6O_6$ 554.23, observed LCMS m/z 555.2 (M+H).

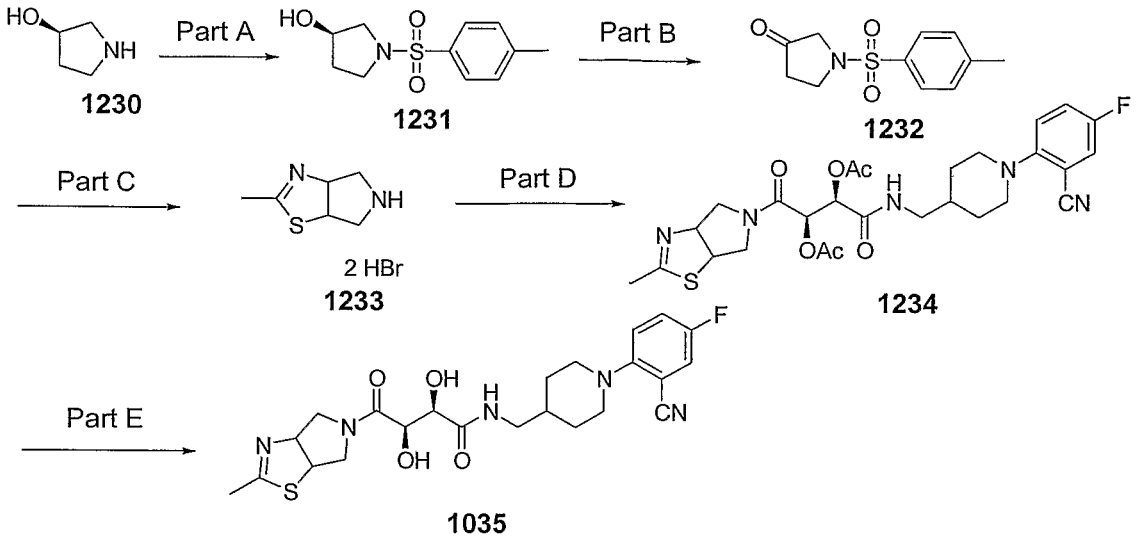


Part C:

Comppound **1036** was synthesized using the procedure found in Example 2A, Part B. Purification by reverse phase prep-LC afforded a white solid after

lyophilization. HPLC-MS t_R = 3.39 min ($UV_{254\ nM}$, 10 min); mass calculated for formula $C_{23}H_{27}FN_6O_4$ 470.21, observed LCMS m/z 471.2 (M+H).

Example 41B:



Part A:

Compound **1230** (2.18 g, 17.7 mmol) was dissolved in methylene chloride (35 mL) and cooled in an ice bath. Triethylamine (5 mL, 35.4 mmol) was added followed by p-toluenesulfonyl chloride (3.35 g, 17.7 mmol) in portions. The reaction mixture was stirred for 3 hours at room temperature and then quenched with water and extracted with methylene chloride. The combined organic layers were washed with 1 N HCl solution, bicarbonate solution and brine; dried over sodium sulfate and concentrated to provide the desired product **1231** (3.85 g), that was used without purification. HPLC-MS t_R = 1.26 min (UV_{254nm}); mass calculated for formula $C_{11}H_{15}NO_3S$ 241.08, observed LCMS m/z 242.2 (M+H).

Part B:

Compound **1231** (3.82 g, 15.78 mmol) was dissolved in methylene chloride (100 mL) and pyridinium chlorochromate (6.7 g, 31 mmol) was added followed

by crushed molecular sieves (3.5 g). The reaction was stirred overnight and then diethylether (150 mL) was added and stirring was continued for an additional hour. The solids were filtered and the solvent was evaporated under reduced pressure. Purification by column chromatography (SiO_2, 50% ethyl acetate/hexanes) afforded a white solid **1232** (3.20 g, 84%). HPLC-MS t_R = 1.43 min ($UV_{254\ nM}$); mass calculated for formula $C_{11}H_{13}NO_3S$ 239.06, observed LCMS m/z 240.1 (M+H).

Part C:

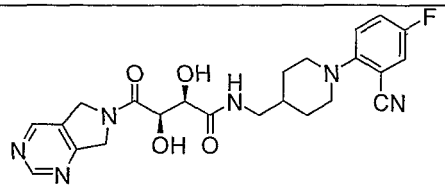
Reactions were performed using procedures from Heterocycles, Vol. 41, No. 7, 1995.

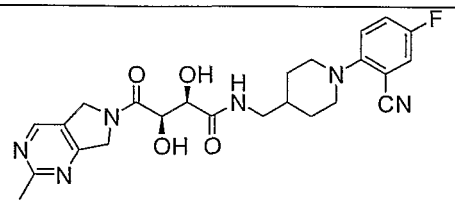
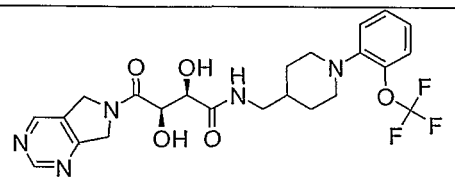
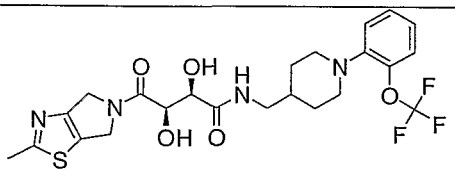
Part D:

Reaction was performed using the procedure found in Example 2A, Part A. **1234**: HPLC-MS t_R = 1.702 min ($UV_{254\ nM}$); mass calculated for formula $C_{27}H_{30}FN_5O_6S$ 571.19, observed LCMS m/z 572.2 (M+H).

Part E:

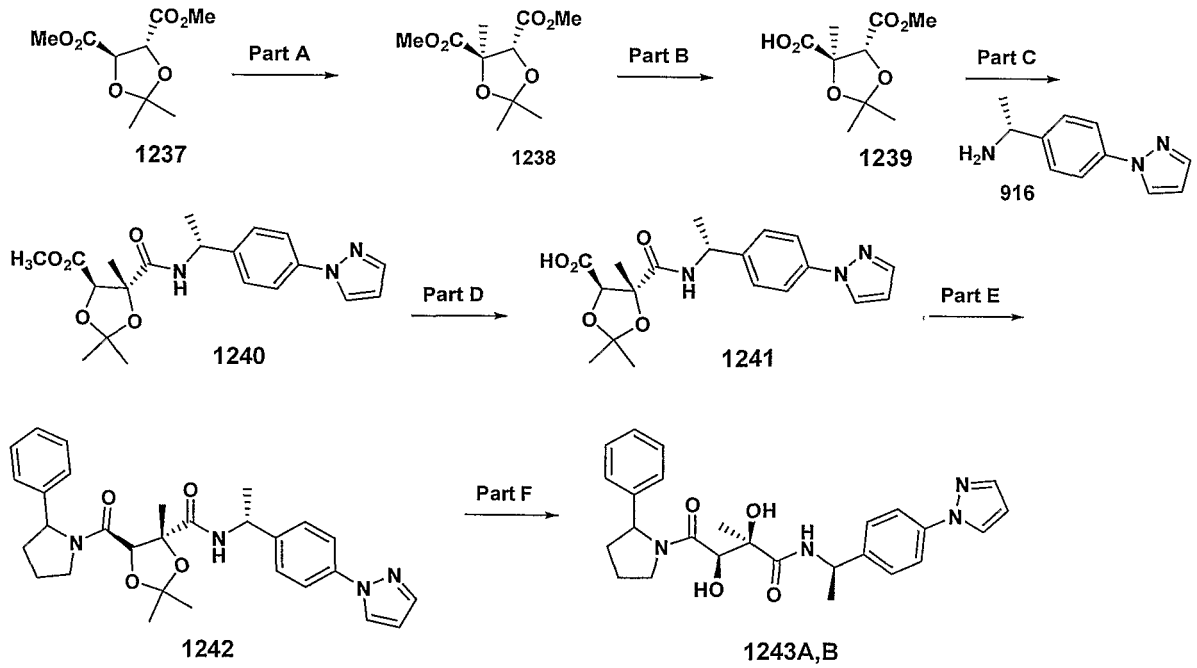
Reaction was performed using the procedure found in Example 2A, Part B. Purification by reverse phase prep-LC afforded a white solid after lyophilization. **1035**: HPLC-MS t_R = 3.66 min ($UV_{254\ nM}$, 10 min); mass calculated for formula $C_{23}H_{26}FN_5O_4S$ 487.2, observed LCMS m/z 488.2 (M+H).

Compound #	Structure	Exact mass	MS m/e (M+H)
1235A		468.2	469.2

1235B		482.2	483.2
1236A		509.2	510.2
1236B		528.2	529.2

Example 42:

Example 42A:



Part A:

To a solution of dimethyl 2,3-O-isopropylidene-L-tartrate **1237** (10.9 g, 50 mmol) in dry THF (150 mL) and DMPU (25 mL) was added methyl iodide (4.7

mL, 75.5 mmol). The reaction mixture was cooled to -78 °C and a 1M solution in THF of $LiN(TMS)_2$ (55mL, 55 mmol) was added via dropping funnel in 45 minutes period to the reaction mixture. THF reaction mixture was stirred at -78 °C for 2 hours then warmed to -20 °C and quenched carefully with water (20 mL). The reaction mixture was poured into EtOAc (150 mL) and the organic layer was separated and washed with water (1 x 50 mL) followed by brine (1 x 50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (SiO_2, 10% Et_2O/hexane followed by 15% Et_2O/hexane) afforded the desired compound **1238** as clear oil (9.7 g, 83%). LCMS m/z: 233.1 (M+H).

Part B:

A pH 8 buffer solution was prepared by titrating a solution of 0.1 M sodium phosphate (300 mL) with 1M HCl to final pH of 8. To a mixture of compound **1238** in pH 8 buffer solution was added esterase (41 units/mg,15 mg, 615 units). Added aq. 1N NaOH (6.5 mL) slowly via syringe during a period of 3.5 hours to the reaction mixture to maintain the pH of the reaction mixture in the range of 7.9-8.2. The reaction mixture was extracted with Et_2O (2 x 50 mL). The aqueous layer was acidified to pH 3 using 12N HCl then extracted with EtOAc (4 x 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo to afford the desired compound **1239** (1.36 g, 72%). LCMS m/z: 219.1 (M+H).

Part C:

To a solution of compound **916** (0.1 g, 0.535 mmol) in DMF (1.5 mL) was added compound **1239** (0.092 g, 0.5 mmol), triethyl amine (0.2 mL, 1.4 mmol) and HATU (0.365 g, 0.96 mmol). The reaction mixture was stirred for 18 hours and then diluted with CH_2Cl_2 (5 mL) and washed with aq. 0.5N NaOH solution (3 mL). The organic layer was dried over $MgSO_4$ and concentrated. Purification by column chromatography (SiO_2, 30% EtOAc/hexane followed by 40% EtOAc/hexane) afforded the compound **1240** as a white foam (0.162 g,

67%). LCMS m/z 388.1 (M+H).

Part D:

To a solution of compound **1240** (0.175 g, 0.452 mmol) in THF (2 mL) and MeOH (2 mL) at 0 °C was added aq. 1.0 M LiOH (0.91 mL, 0.91 mmol). The reaction mixture was warmed to room temperature and stirred for 1 hour. The reaction mixture was acidified with aq. 1N HCl (0.95 mL) and diluted with brine (1.5 mL) and extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to afford compound **1241** as a white foam (0.182 g, 100%). LCMS m/z: 374.1 (M+H).

Part E:

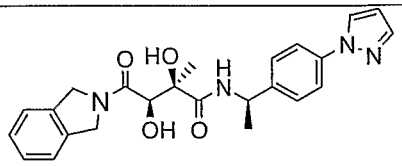
To a solution of compound **1241** (0.179 g, 0.48 mmol) in DMF (3 mL) was added 2-phenylpyrrolidine hydrogen chloride salt (0.092 g, 0.5 mmol), triethyl amine (0.2 mL, 1.4 mmol) and HATU (0.365 g, 0.96 mmol). The reaction mixture was stirred for 4.5 hours and then diluted with EtOAc (10 mL) and washed with water (1.5 mL) followed by brine (1.5 mL). The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by prep. plate chromatography (SiO_2, 66%EtOAc/hexane). Two diastereomeric compounds **1242** were isolated. Diastereomer compound **1242A** (0.067 g, 28%), LCMS m/z 503.1 (M+H) and diastereomer compound **1242B** (0.095 g, 28%), LCMS m/z 503.1 (M+H).

Part F:

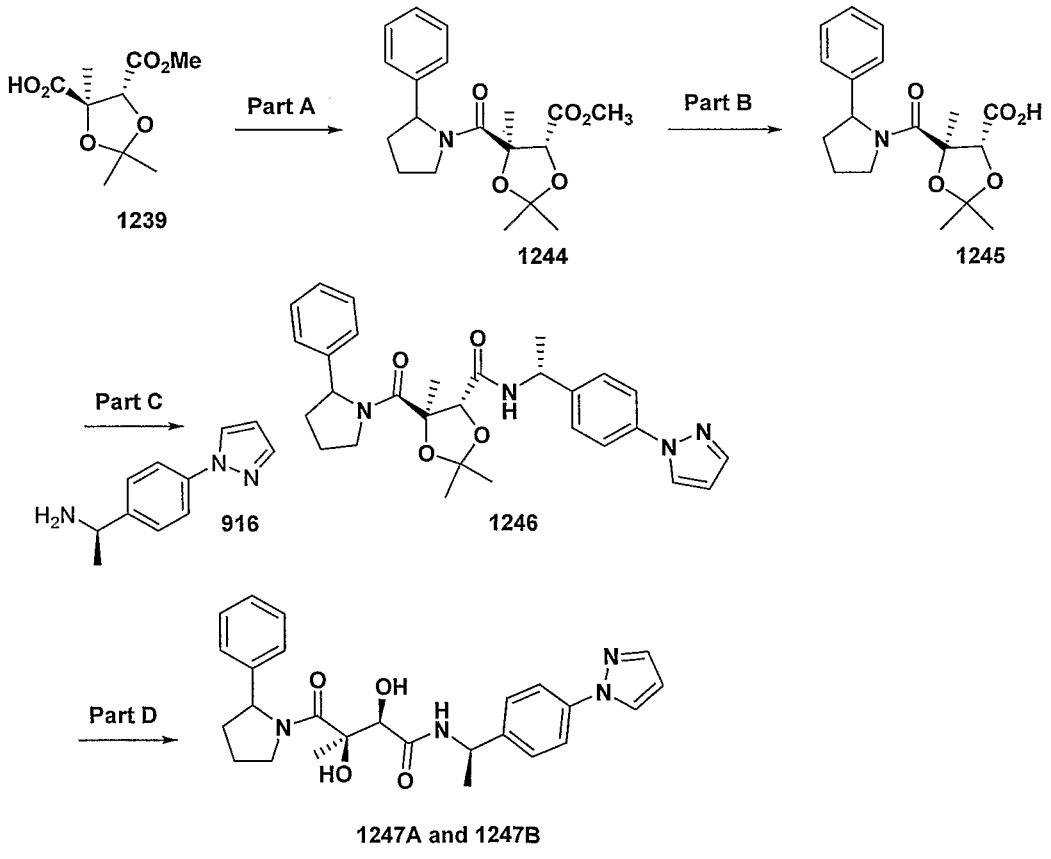
To a solution of compound **1242A** (0.06 g, 0.119 mmol) in CH_2Cl_2 (1 mL) was added TFA (4 mL) followed by water (0.5 mL). The reaction mixture was stirred at 80 °C temperature for 3 hours and then concentrated. The residue was purified by column chromatography (SiO_2, 5% MeOH/CH_2Cl_2) to afford **1243A** (0.012 g, 22%), LCMS m/z 463.1 (M+H).

To a solution of compound **1242B** (0.088 g, 0.18 mmol) in CH_2Cl_2 (1 mL) was added TFA (4 mL) followed by water (0.5 mL). The reaction mixture was stirred at 23 °C temperature for 18 hours and then concentrated. The

residue was purified by column chromatography (SiO_2, 5% MeOH/CH_2Cl_2) to afford **1243B** (0.05 g, 66%), LCMS m/z 463.1 (M+H).

Compound #	Structure	Exact mass	MS m/z (M+H)
1243C		434.2	435.1

Example 42B:



Part A:

To a solution of compound **1239** (200 mg, 0.917 mmol) and 2-phenylpyrrolidine (177 mg, 0.96 mmol) in CH_2Cl_2 (5 mL) at 23 °C was added DIEA (0.35 mL, 2.01 mmol) followed by PyBOP (0.367 g, 1.146 mmol) and the reaction mixture was stirred for 18 hours. The reaction mixture was concentrated and the residue was purified by column chromatography (SiO_2, 20% EtOAc/hexane followed by 30% EtOAc/hexane) to afford the desired compound **1244** as an oil (0.16 g, 50%). LCMS m/z: 348.1 (M+H).

Part B:

Compound **1244** was converted to compound **1245** using the procedure as described in Example 42A Part D. LCMS m/z: 374.1 (M+H).

Part C:

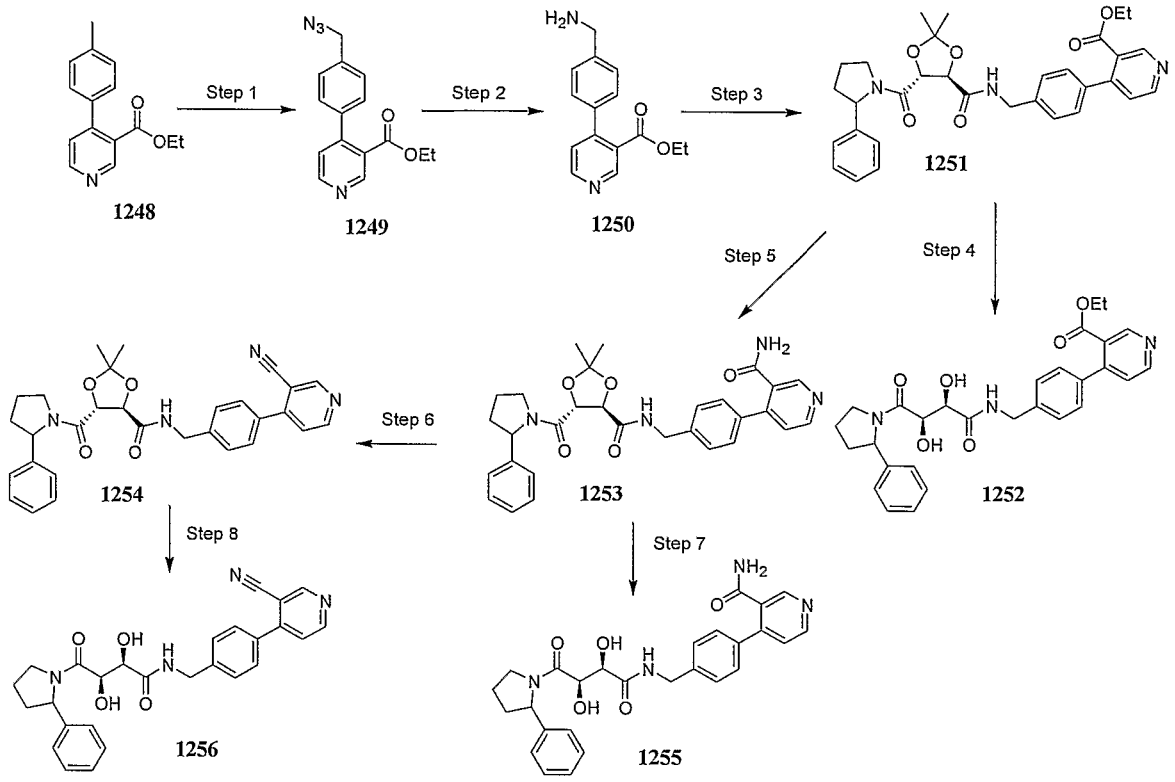
Compound **1245** was converted to compound **1246** using the procedure as described in Example 42A Part E. LCMS m/z: 503.1 (M+H).

Part D:

Compound **1246** was converted to **1247A** and **1247B** using the procedure as described in Example 42A Part F. Two diastereomeric compounds **1247** were isolated. Diastereomer **1247A** (16% yield), LCMS m/z: 463.1 (M+H) and diastereomer **1247B** (16% yield), LCMS m/z: 463.1 (M+H).

Example 43:

Example 43A:



Step 1:

Compound **1248** was prepared according to the literature procedure: Shiao, M.-J.; Liu, K.-H.; Lin, P.-Y *Hetereocycles* **1993**, *36*, 3, 507.

A solution of **1248** (2.20 g, 9.10 mmol), NBS (1.81 g, 10.20 mmol), 1,1'-azobis(cyclohexanecarbonitrile) (0.113 g, 0.46 mmol) in CCl_4 (40 mL) was stirred at 75 °C for 24 hours. The reaction was cooled to room temperature, and the mixture was diluted with CH_2Cl_2 and sat. Na_2CO_3. The organic layer was removed, and the aqueous phase was extracted with CH_2Cl_2 (4x). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The crude product mixture was used without further purification.

A solution of the crude product mixture prepared above and sodium azide (0.75 g, 11.5 mmol) in a MeOH (15 mL)/DMF(15 mL)/DMSO (15 mL) solvent mixture was stirred at room temperature for 24 hours. The reaction was diluted with H_2O and EtOAc. The organic layer was removed, and the aqueous phase was extracted with EtOAc (1x). The combined organics were

washed with H_2O (3x), brine (1x), dried (Na_2SO_4), filtered, and concentrated. The resulting brown oil was purified by silica gel chromatography to furnish **1249** (1.2 g, 4.25 mmol, 47% yield over 2 steps). MS m/e: 283.1 (M+H).

Step 2:

To a solution of **1249** (1.2 g, 4.2 mmol) in THF (20 mL) at room temperature was added PPh_3 (1.1g, 4.2 mmol). The reaction was stirred at room temperature for 1 hour at which time H_2O (2 mL) was added. The resulting mixture was stirred for 24 hours. After concentration, the mixture was taken up in Et_2O and 0.25 N HCl. The organic phase was removed, and the aqueous phase was basicified with sat. Na_2CO_3 and extracted with EtOAc (4x). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The compound was purified by silica gel chromatography to furnish **1250** (0.51 g, 47% yield). MS m/e: 257.1 (M+H).

Step 3:

Compound **1251** was prepared with **1250** in a similar manner as previously stated in Example 12B.

Step 4:

Compound **1252** was prepared in a similar fashion from **1251** as previously stated in Example 12B. MS m/e: 518.1 (M+H).

Step 5:

To a solution of **1251** (0.20 g, 0.36 mmol) in THF (2 mL)/MeOH (2 mL)/ H_2O (2 mL) was added LiOH (0.050 g, 1.2 mmol). The reaction was stirred at room temperature for 20 hours. The reaction was acidified to pH ~ 4 with 1 N HCl and diluted with EtOAc. The organic layer was removed and the aqueous phase was extracted with EtOAc (3x). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The compound was used without further purification.

To the crude product mixture prepared above in CH_2Cl_2 (2 mL) was added NMM (0.200 mL, 1.82 mmol), EDCI (0.100 g, 0.52 mmol), and HOBt

(0.059 g, 0.38 mmol). This mixture was stirred for 10 minutes at which time NH_4Cl (0.100 g, 1.86 mmol) was added. After 72 hours of stirring, the reaction was quenched with H_2O and diluted with EtOAc. The organic layer was removed, and the aqueous phase was extracted with EtOAc (3x). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel chromatography to yield **1253** (0.062 g, 61 % yield over 2 steps). MS m/e: 529.1 (M+H).

Step 6:

To a solution of **1253** (0.050 g, 0.095 mmol) in CH_2Cl_2 (2 mL) cooled to 0 °C was added DIEA (0.050 mL, 0.28 mmol) followed by TFAA (0.030 mL, 0.22 mmol). The reaction was stirred at 0 °C for 3 hours and then quenched with 1 N NaOH. The organic layer was removed, and the aqueous phase was acidified with 1 N HCl to pH ~ 4. The aqueous phase was then extracted with EtOAc (3x). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel chromatography to furnish **1254** (0.042 g, 0.082 mmol, 88% yield). MS m/e: 511.1 (M+H).

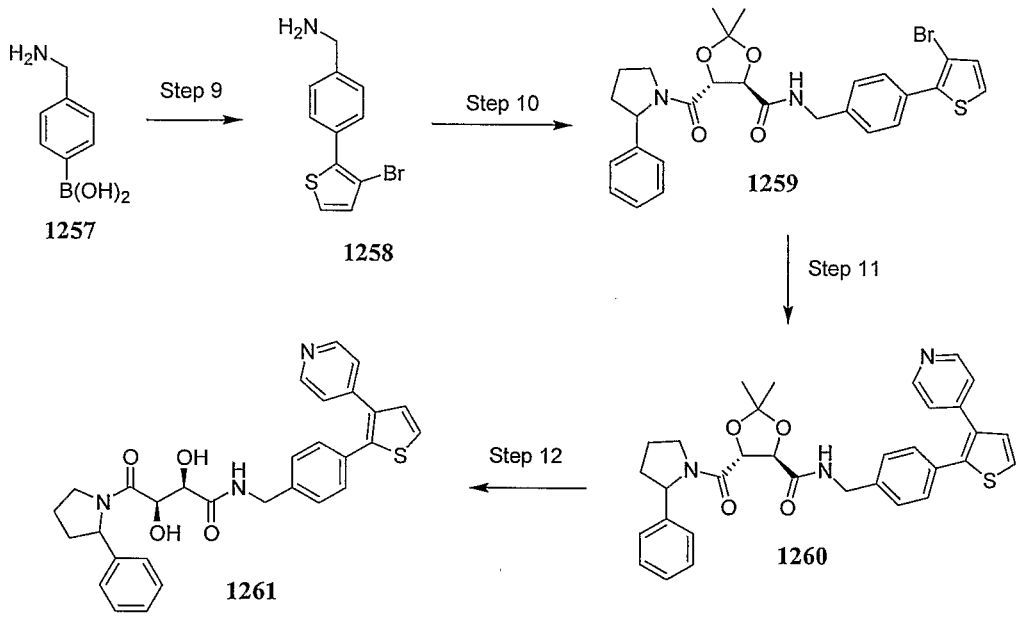
Step 7:

Compound **1255** was prepared in a similar fashion from **1253** as previously stated in Example 12B. MS m/e: 489.1 (M+H).

Step 8:

Compound **1256** was prepared in a similar fashion from **1254** as previously stated in Example12A. MS m/e: 471.1 (M+H).

Example 43B:



Step 9:

A solution of aminomethylphenyl boronic acid hydrochloride **(1257)** (2.0 g, 10.7 mmol), 2,3-dibromothiophene (2.7 g, 11.0 mmol), and $Pd(dppf)Cl_2$ (0.51 g, 0.69 mmol) in CH_3CN (40 mL)/1 M K_2CO_3 (40 mL) was stirred at 80 °C for 3 hours. The reaction was cooled to room temperature and diluted with EtOAc. The organic layer was removed, and the aqueous phase was extracted with EtOAc (3x). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The brown oil was purified by silica gel chromatography to furnish **1258** (1.4 g, 5.3 mmol, 50% yield) as a brown oil. MS m/e: 268.1 (M+H).

Step 10:

Compound **1259** was prepared in a similar fashion from **1258** as previously stated in Example 12B. MS m/e: 569.1 (M+H).

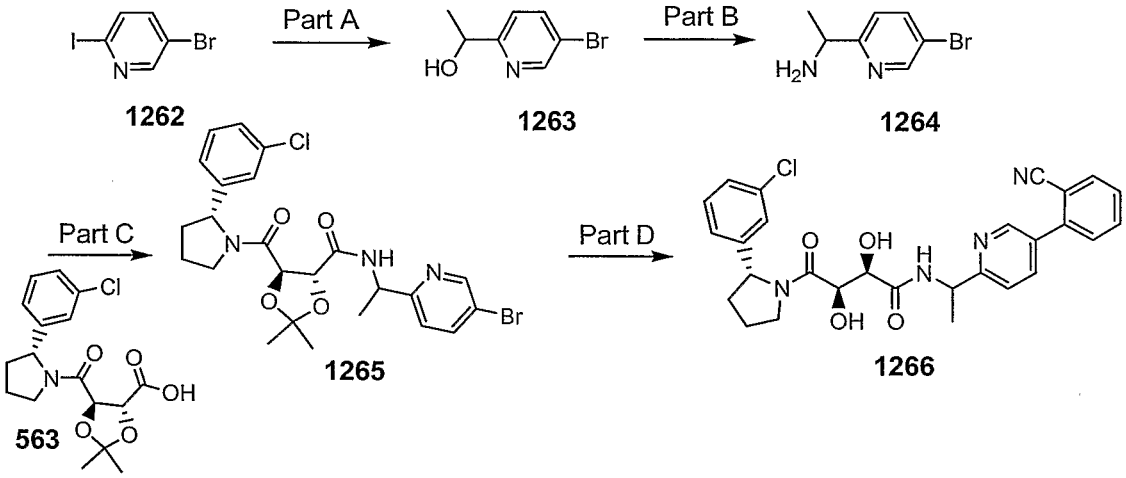
Step 11:

A solution of **1259** (0.059 g, 0.10 mmol), pyridine-4-yl boronic acid (0.017 g, 0.14 mmol), and $Pd(dppf)Cl_2$ (0.010 g, 0.014 mmol) in CH_3CN (1 mL)/1 M K_2CO_3 (1 mL) was heated in SmithCreator microwave (2-5 mL vessel, 150 °C for 5 minutes). The liquid was concentrated, and the residue was purified by silica gel chromatography to furnish **1260** (0.057 g, 0.10 mmol, 99% yield). MS m/e: 568.1 (M+H).

Step 12:

Compound **1261** was prepared in a similar fashion from **1260** as previously stated in Example 12A MS m/e: 528.1 (M+H).

Example 44:



Part A:

Isopropylmagnesium chloride (2.0 M solution in THF, 5 mL, 10 mmol) was added dropwise to the solution of 2-iodo-5-bromopyridine (1262) in THF (20 mL) at –40°C in an acetonitrile/dry ice bath. After stirring for 1 h at this temperature for 1 h, acetaldehyde (0.615 mL, 1 mmol) in 5 mL of THF was slowly added. The reaction mixture was allowed to stir at –40 °C for 0.5 h, then quenched with 1 N NH_4Cl (5 mL) solution, and concentrated under reduced pressure. The residue was dissolved in ethyl acetate and water. Organic layer was separated, washed with 1N NH_4Cl, brine, dried over Na_2SO_4, and concentrated, affording **1263** as a colorless oil (1.95 g, 97%). ^1H

NMR ($CDCl_3$, 300 MHz), δ 8.58 (d, *J* = 2.4 Hz, 1H), 7.80 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.21 (d, *J* = 8.6Hz, 1H), 4.87 (br q, *J* = 6.2 Hz, 1H), 3.79 (br s, 1H), 1.50 (d, *J* = 6.2 Hz, 3H). Mass calculated for formula C_7H_8BrNO 200.98, observed LCMS m/z 202.0 (M+H).

Part B:

Diisopropyl azodicaboxylate (1.2 g, 6 mmol) in THF (5 mL) was added into a solution of **1263** (1.0 g, 5 mmol), phththalimide (0.88 g, 6 mmol) and triphenylphosphine (1.57 g, 6 mmol) in 20 mL of THF. After stirring overnight at room temperature, the reaction mixture was concentrated to dryness. It was then dissolved in 30 mL of ethanol, added with hydrazine monohydrate (5 mL), heated to reflux for 3 h. The reaction mixture was filtered and the filtrate was concentrated. The residue was dissolved with ethyl acetate and 1 N HCl. The aqueous phase was backed extracted with ethyl acetate. The organic extract was discarded. The aqueous phase was added with 1N NaOH to pH 12. It was extracted with EtOAc (30 mL x 3). The ester extract was combined, washed with brine, dried over Na_2SO_4, and concentrated, resulting in **1264** (0.61 g, 61%). ^1H NMR ($CDCl_3$, 300 MHz), δ 8.58 (s, 1H), 7.75 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 4.15 (q, *J* = 6.5 Hz, 1H), 1.43 (d, *J* = 6.5 Hz, 3H). Mass calculated for formula $C_7H_9BrN_2$ 199.99, observed LCMS m/z 201.0 (M+H).

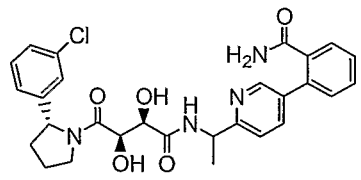
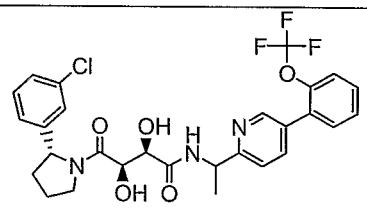
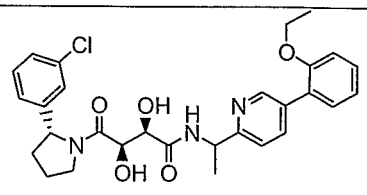
Part C:

To **1264** (400 mg, 2 mmol) in DMF (5 mL) was added **563** (707 mg, 2 mmol), and HATU (912 mg, 2.4 mmol). The reaction mixture was stirred overnight at room temperature, and diluted with ethyl acetate and water. The organic layer was washed with saturated $NaHCO_3$, and brine. It was dried over Na_2SO_4, and concentrated, resulting in **1265** (600 mg, 56%). Mass calculated for formula $C_{24}H_{27}BrClN_3O_4$ 535.09, observed LCMS m/z 534.1 (M+H).

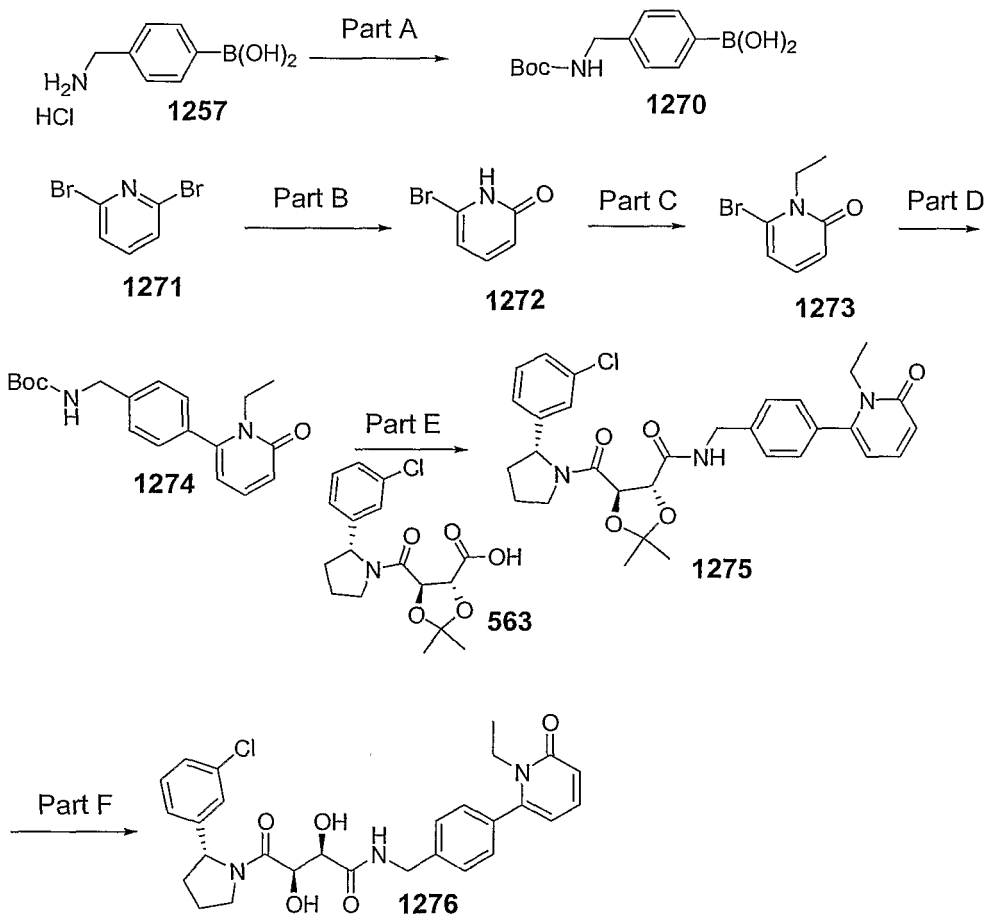
Part D:

Step 1: To **1265** (120 mg, 0.22 mmol) in 1 mL of dioxane, was added with 2-cyanophenylboronic acid (49 mg, 0.33 mmol), potassium phosphate (142 mg, 0.66 mmol) and $PdCl_2$(dppf) (7.2 mg, 0.0088 mmol, 4 mol%). The reaction mixture was stirred overnight at 80 °C under argon, then diluted with EtOAc and water, washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated.

Step 2: The above residue was dissolved in 0.5 mL of TFA/H_2O (80:20) and stirred at room temperature for 2 h. The reaction mixture was quenched with ACN/H_2O (50:50) and concentrated in *vacuo*. Purification by reverse phase prep-LC afforded **1266** as a white solid. HPLC-MS t_R = 4.04 min ($UV_{254\ nm}$, 10 min), Mass calculated for formula $C_{28}H_{27}ClN_4O_4$ 518.17, observed LCMS m/z 519.1 (M+H).

Compound #	Structure	Exact mass	MS m/e (M+H)
1267		536.2	537.1
1268		577.2	578.0
1269		537.20	538.2

Example 45:



Part A:

Compound **1257** (1.00 g, 5.34 mmol) was dissolved in THF (15 mL) and saturated sodium bicarbonate solution (20 mL). Di-*t*-butyldicarbonate (1.28 g, 5.88 mmol) was added and the solution was stirred overnight at room temperature. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with bicarbonate solution and brine; dried over sodium sulfate and concentrated to provide a white solid **1270** (560 mg, 42%). HPLC-MS t_R = 1.34 (UV_{254nm}); mass calculated for formula $C_{12}H_{18}BNO_4$ 251.13, observed LCMS m/z 274.1 (M+Na).

Part B:

Compound **1271** (2.0 g, 8.5 mmol) was dissolved in *t*-butanol (25 mL) and potassium *t*-butoxide (10g) was added and stirred at reflux for 24 hours. The

solvents were removed under reduced pressure and the reaction was quenched with water and extracted with chloroform. The aqueous layer was acidified and extracted with chloroform. The combined organic layers were dried over sodium sulfate and concentrated to provide a yellow solid **1272** (1.10 g, 74%). HPLC-MS t_R = 0.76 min ($UV_{254\ nm}$); mass calculated for formula C_5H_4BrNO 172.95, observed LCMS m/z 174.0 (M+H).

Part C:

Compound **1273** was prepared according to the procedure of Lui, H. et. al. (Tet. Lett. **1995**, 36, 8917). Data for **1273**: HPLC-MS t_R = 1.12 ($UV_{254\ nm}$); mass calculated for formula C_7H_8BrNO 200.98, observed LCMS m/z 202.0 (M+H).

Part D:

Compound **1273** (50 mg, 0.247 mmol) was dissolved in dioxane (5 mL) and compound **1270** (93 mg, 0.370 mmol), potassium phosphate (108 mg, 0.51 mmol), triphenylphosphine (10 mg), and $Pd(dba)_3$ (5 mg) were added and stirred at 90 °C overnight. The reaction was filtered through celite and purified by column chromatography (EtOAc) to provide the desired product **1274** as a white solid (60 mg, 75%). HPLC-MS t_R = 1.64 ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{24}N_2O_3$ 328.18, observed LCMS m/z 329.2 (M+H).

Part E:

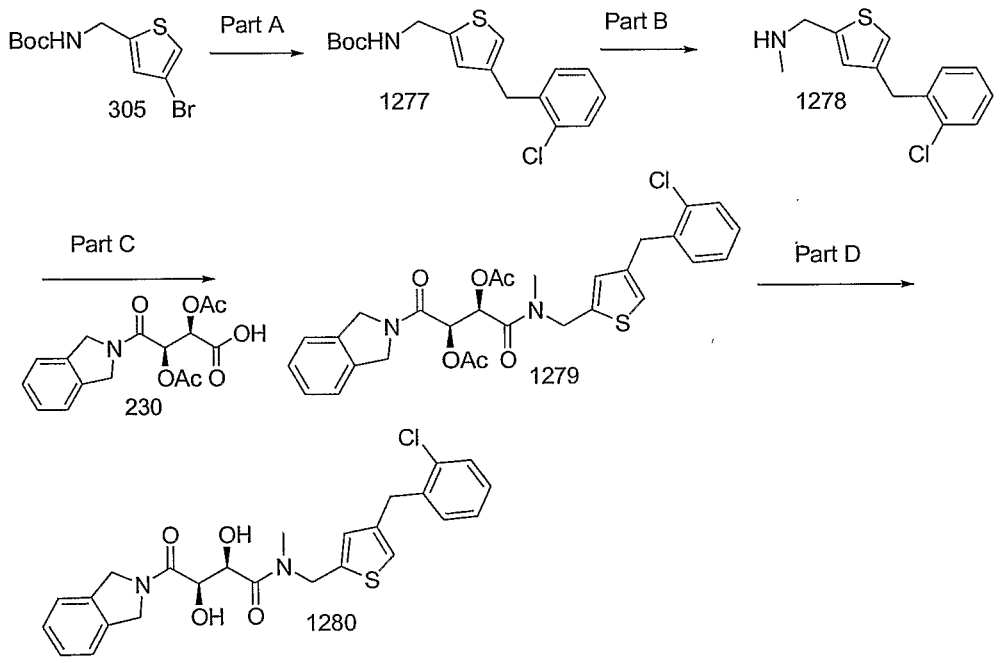
Compound **1274** (60 mg, 0.183 mmol) was dissolved in methylene chloride (4 mL) and TFA (1 mL) was added. The reaction mixture was stirred for 1 hour and then the solvent was removed under reduced pressure. The residue was dissolved in DMF (5 mL) and compound **563** (63.5 mg, 0.183 mmol), HATU (90.5 mg, .0.2379 mmol), and DIEA (0.5 mL) were added and stirred overnight. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with 1 N HCl solution, bicarbonate solution and brine; dried over sodium sulfate and concentrated. Purification of the residue by column chromatography (EtOAc) provided

compound **1275** as a white solid (87 mg, 85%). HPLC-MS t_R = 1.81 min ($UV_{254\ nm}$); mass calculated for formula $C_{31}H_{34}ClN_3O_5$ 563.22, observed LCMS m/z 564.1(M+H).

Part F:

Compound **1276** was synthesized using procedures similar to Example 1, Part D. HPLC-MS t_R = 1.48 min ($UV_{254\ nm}$); mass calculated for formula $C_{28}H_{30}ClN_3O_5$ 523.19, observed LCMS m/z 524.2(M+H).

Example 46:



Part A:

Compound **1277** was prepared from **305** according to the procedures described in Example 4A Part A.

Part B:

To **1277** (150 mg, 0.44 mmol) in THF (5 mL) was added lithium hexamethyldisilazide (1.0 M, 0.66 mL, 0.66 mmol) at 0 °C. The reaction

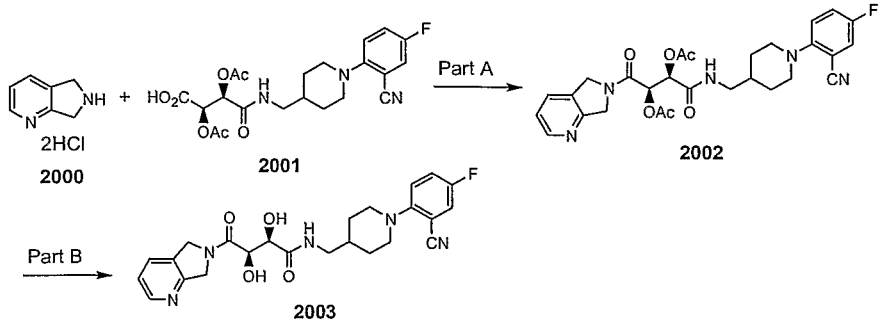
mixture was stirred for 10 minutes. To the reaction mixture was added methyl iodide (0.034 mL, 0.53 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate and washed with 1.0 N citric acid, satureated sodium bicarbonate solution and brine, dried over sodium sulfate and concentrated. The residue was dissolved in DCM (5 ml) and treated with 4N HCl in dioxane (2 mL). The reaction was stirred at room temperature and concentrated. Compound **1278** was used without further purification.

Part C and D:

Compound **1280** was obtained from **1278** and **230** using the procedures described in Example 4A Part D and E. Data for **1280**: HPLC-MS t_R = 5.05 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{25}H_{25}ClN_2O_4S$ 484.1, observed LCMS m/z 485.0 (M+H).

Example 47: Heterocyclic Isoindolines

Example 47A:



Compound **2000** was prepared according to the procedures in US Patent 5,371,090.

Compound **2001** was prepared using procedures described in Example 2 and 27. HPLC-MS t_R = min ($UV_{254\ nm}$); mass calculated for formula C21H24FN3O7 449.2, observed LCMS m/z 450.1 (M+H).

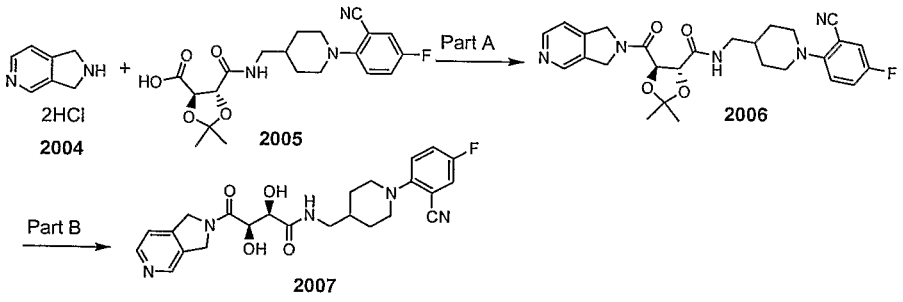
Part A:

Compound **2002** was prepared using the coupling conditions described in Example 2. HPLC-MS t_R = 1.60 min ($UV_{254\ nm}$); mass calculated for formula C28H30FN5O6 551.2, observed LCMS m/z 552.1 (M+H).

Part B:

Compound **2002** (50 mg) was dissolved in methanol (2 mL). To this solution was added 7.0 M ammonia in methanol (2 mL). The reaction mixture was stirred for 1 hour at room temperature and concentrated. Purification by prep-LC and conversion to a hydrochloric salt afforded **2003** as an off-white solid (32 mg). HPLC-MS t_R = 1.35 min ($UV_{254\ nm}$); mass calculated for formula C24H26FN5O4 467.2, observed LCMS m/z 468.1 (M+H).

Example 47B:



Compound **2004** was prepared according to the procedures in US Patent 5,371,090.

Compound **2005** was prepared using procedures described in Example 1 and 27.

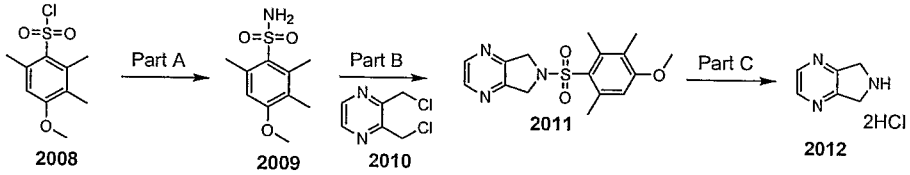
Part A:

Compound **2006** was prepared using the coupling conditions described in Example 1. HPLC-MS t_R = 1.40 min ($UV_{254\ nm}$); mass calculated for formula C27H30FN5O4 507.2, observed LCMS m/z 508.1 (M+H).

Part B:

Compound **2006** (50 mg) was deprotected using procedures described in Example 1. Purification by prep-LC and conversion to a hydrochloric salt afforded **2007** as an off-white solid (32 mg). HPLC-MS t_R = 1.09 min ($UV_{254\ nm}$); mass calculated for formula C24H26FN5O4 467.2, observed LCMS m/z 468.1 (M+H).

Example 47C:



Part A:

Sulfonyl chloride **2008** (2.44 g, 9.8 mmol) was dissolved in dioxane (40 mL) and cooled in an ice bath. Ammonia gas was bubbled into the reaction mixture for 10 minutes. The reaction mixture was warmed to room temperature and filtered. The filtrate was concentrated. The crude product was recrystallized from ethyl acetate/hexanes to afford **2009** as an off-white solid (1.74 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.09 (s, 2H), 6.74 (s, 1H), 3.80 (s, 3H), 2.57 (s, 3H), 2.48 (s, 3H), 2.08 (s, 3H); HPLC-MS t_R = 1.43 min ($UV_{254\ nm}$); mass calculated for formula C10H15NO3S 229.1, observed LCMS m/z 230.1 (M+H).

Part B:

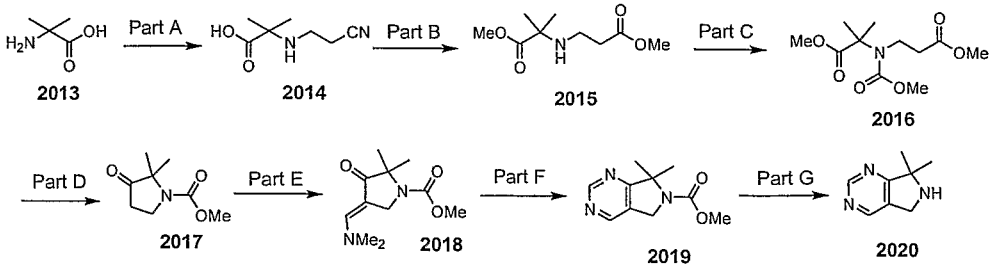
To sodium hydride (95%, 131 mg, 5.19 mmol) in DMF (10 mL) was added sulfonamide **2009** (596 mg, 2.6 mmol). The reaction mixture was heated to 70 °C and stirred for 45 minutes. To this mixture was added 2,3-bis(chloromethyl)pyrazine (**2010**) (Yoshiizumi, K. et. al. *Bioorg. Med. Chem.* **2003**, *11*, 433) (448 mg, 2.53 mmol) in DMF (3 mL). The reaction mixture

was heated at 70 °C overnight. The reaction mixture was cooled and poured into water. The aqueous layer was salted and extracted with chloroform. The combined organics were washed with water, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 30% ethyl acetate/hexanes) afforded recovered sulfonamide **2009** (218 mg) and **2011** (245 mg). HPLC-MS t_R = 1.82 min ($UV_{254\ nm}$); mass calculated for formula C16H19N3O3S 333.1, observed LCMS m/z 334.1 (M+H).

Part C:

A mixture of sulfonamide **2011** (245 mg, 0.73 mmol), anhydrous methanesulfonic acid (3 mL) and 1:9 thioanisole:trifluoroacetic acid (3 mL) was stirred for 3 hours at room temperature. The reaction mixture was poured over ice and treated with 50% sodium hydroxide (10 mL). The aqueous layer was salted and extracted with chloroform. The combined organics were dried over sodium sulfate and concentrated. The residue was dissolved in 1.0 M HCl (5 mL) and extracted with ether. The aqueous layer was lyophilized to afford **2012** (105 mg) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 (s, NH), 8.58 (s, 2H), 4.59 (m, 4H).

Example 47D:



Part A:

Compound **2014** was prepared according to the procedure in *Helv. Chim. Acta.* **1986**, 905-907.

Part B:

Acetyl chloride (20 mL) was added dropwise to methanol (130 mL) cooled in an ice bath. This solution was then added to compound **2014** (5.00 g, 31.8 mmol) and stirred overnight at reflux. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and 1N NaOH. The organic layer was washed with brine, dried over sodium sulfate, and concentrated to provide **2015** (5.0 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H), 3.69 (s, 3H), 2.77 (t, 2H), 2.5 (t, 2H), 1.32 (s, 6H).

Part C:

Compound **2015** (5.00 g, 24 mmol) was dissolved in THF (60 mL) and saturated sodium bicarbonate (60 mL) and cooled in an ice bath. Methyl chloroformate (2.93 g, 31.2 mmol) was added dropwise and the reaction was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with 1 N HCl, saturated sodium bicarbonate, brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 20% ethyl acetate/hexanes) afforded **2016** (5.5 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72-3.68 (m, 9H), 3.65-3.6 (t, 2H), 2.66 (t, 2H), 1.5 (s, 6H).

Part D:

Compound **2016** (1.66 g, 6.36 mmol) was dissolved in THF (20 mL) and cooled on an ice bath. Potassium hydride (35% in oil, 1.12 g, 9.54 mmol) was added in portions and stirring was continued for 2 hours at room temperature. The reaction was slowly quenched with water, acidified to pH 3, and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated (1.5 g). A portion of the residue (350 mg) was dissolved in MeOH (5 mL) and 6N HCl (5 mL) and stirred at reflux for 3 hours and room temperature overnight. The solvent was evaporated under reduced pressure and partitioned between ethyl acetate and water. The organic layer was washed with water, dried over sodium sulfate, and concentrated to yield **2017** (150 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72-3.55 (m, 5H), 2.5 (t, 2H), 1.4-1.25 (m, 6H).

Part E:

According to a modification of a procedure by Fukui, H. et al. (*Heterocycles* **2002**, *56*, 257-264) a mixture of ketone **2017** (200 mg, 1.17 mmol) and N,N-dimethylformamide dimethyl acetal (3 mL) was heated at 100 °C for 2h, and then concentrated to give enamino-ketone **2018** (244 mg, 92%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.31 (m, 1H), 4.54-4.51 (d, 2H), 3.78-3.22 (d, 3H), 3.12 (s, 6H), 1.48 (s, 3H), 1.40 (s, 3H).

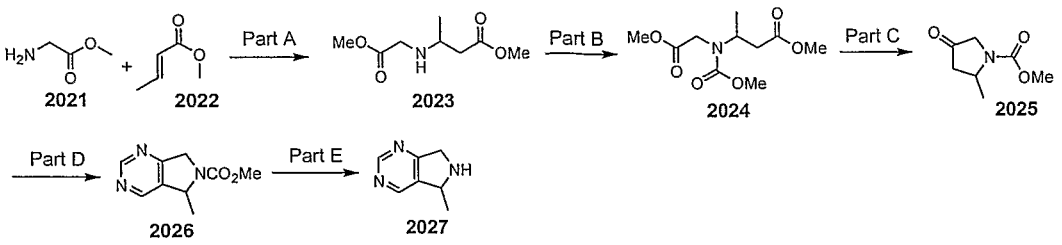
Part F:

According to a modification of a procedure by Fukui, H. et al. (*Heterocycles* **2002**, *56*, 257-264) a mixture of enamino-ketone **2018** (690 mg, 3.05 mmol) and formamidine acetate (3.17 g, 30.5 mmol) in ethanol (15 mL) was heated at reflux for 3 days, and then concentrated. The residue was partitioned between dichloromethane and water, and extracted with dichloromethane. The combined organic extracts were concentrated to give an oil which was chromatographed (SiO_2, 50%-80% ethyl acetate/hexane) to give pyrimidine **2019** (334 mg, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (s, 1H), 8.67 (s, 1H, broad), 4.76-4.71 (d, 2H), 3.84-3.77 (d, 3H), 1.75 (s, 3H), 1.67 (s, 3H).

Part G:

A mixture of compound **2019** (235 mg, 1.13 mmol), powder potassium hydroxide (900 mg, 16 mmol) and hydrazine monohydrate (1.36 mL, 28 mmol) in ethylene glycol (5 mL) was heated at 100 °C overnight. The reaction mixture was cooled to rt, poured into brine and extracted several times with dichloromethane. The combined organic extracts were washed with brine and concentrated to give compound **2020** (121 mg, 72 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.58 (s, 1H), 4.24 (s, 2H), 1.47 (s, 6H). HPLC-MS t_R = 0.2 min ($UV_{254\ nm}$); mass calculated for formula C8H11N3 149.1, observed LCMS m/z 150.1 (M+H).

Example 47E:



Part A:

To a mixture of methyl crotonate (**2022**) (2.0 g, 20 mmol) and methyl glycine hydrochloride (**2021**) (5.5 g, 44 mmol) in methanol (27 mL) was added triethylamine (6.4 mL, 46 mmol). The mixture was stirred at room temperature for 2 days and filtered to remove the white precipitate. The filtrate was concentrated and the residue was dissolved in ethyl acetate, washed with sodium bicarbonate solution, water and brine, dried over sodium sulfate and concentrated to afford **2023** as a light yellow oil (2.4 g, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.69 (s, 3H), 3.46 (d, J = 3.2 Hz, 2H), 3.14 (m, 1H), 2.45 (m, 2H), 1.15 (d, J = 7.2 Hz, 3H).

Part B:

Compound **2023** (2.42 g, 13 mmol) was dissolved in THF (20 mL) and saturated sodium bicarbonate (20 mL) and cooled in an ice bath. Methyl chloroformate (1.2 mL, 15 mmol) was added dropwise and the reaction was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with 1 N HCl, saturated sodium bicarbonate and brine, dried over sodium sulfate and concentrated to afford **2024** (2.9 g).

Part C:

Compound **2024** (1.30 g, 5.26 mmol) was dissolved in THF (20 mL) and cooled on an ice bath. Potassium hydride (35% in oil, 1.12 g, 9.54 mmol) was added in portions and the mixture was stirred at room temperature overnight. The reaction was slowly quenched with water, acidified to pH 3, and extracted

with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 25% ethyl acetate/hexane) afforded an oil (1.27 g). This oil (1.27 g) was dissolved in MeOH (5 mL) and 6N HCl (5 mL) and stirred at reflux overnight. The mixture was extracted with ethyl acetate and the combined organic layers were washed with sodium bicarbonate solution, water and brine, dried over sodium sulfate and concentrated to afford **2025** (663 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.5 (bs, 1H), 3.95 (m, 1H), 3.78 (s, 3H), 3.70 (m, 1H), 2.73 (m, 1H), 2.25 (m, 1H), 1.28 (m, 3H).

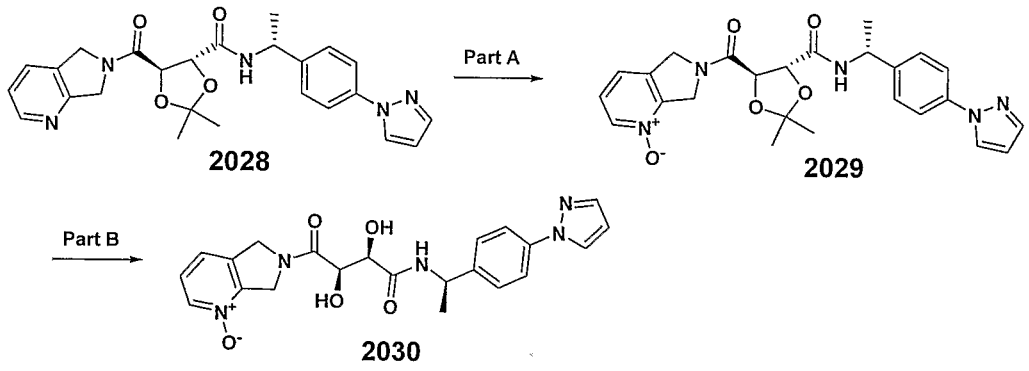
Part D:

Compound **2026** was prepared from the material from part C according to procedures described in Example 47D Part E and Part F. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.61 (m, 1H), 5.24 (m, 1H), 4.88 – 4.64 (m, 2H), 3.82 (m, 3H), 1.59 (m, 3H).

Part E:

A mixture of compound **2026** (300 mg, 1.45 mmol), powder potassium hydroxide (600 mg, 10.7 mmol) and hydrazine monohydrate (1.0 mL, 21 mmol) in ethylene glycol (5 mL) was heated at 100 °C overnight. The reaction mixture was cooled to rt, poured into brine and extracted several times with dichloromethane. The combined organic extracts were washed with brine and concentrated to give compound **2027** (105 mg, 54 %).

Example 47F:



2028 2029 2030

Part A:

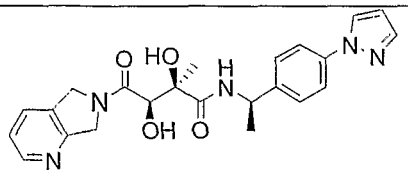
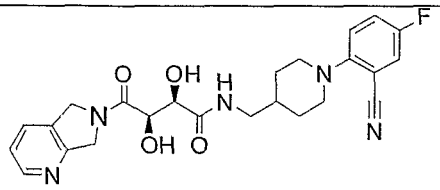
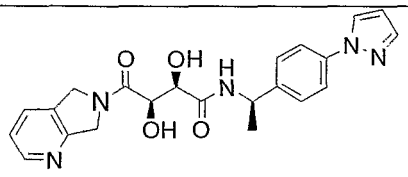
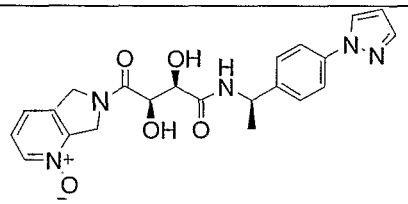
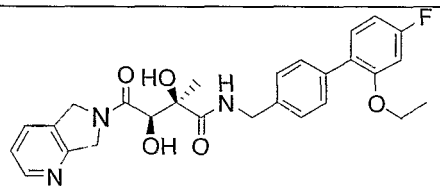
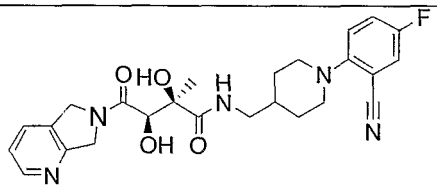
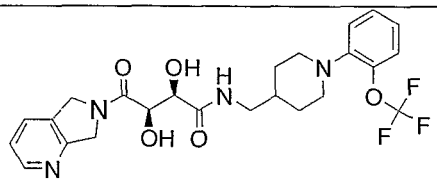
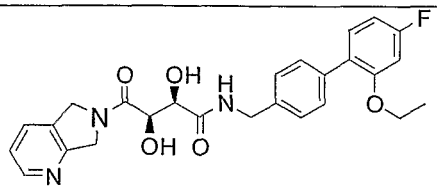
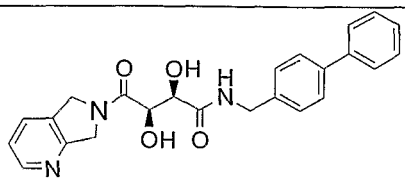
To a solution of compound **2028** (0.29 g, 0.63 mmol) in CH_2Cl_2 at 0 °C was added 70% m-CPBA (0.31 g, 1.26 mmol) and the reaction mixture was warmed to room temperature and stirred for 1 hour. Diluted with CH_2Cl_2 (5 mL) and washed with a solution of water (6 mL) and concentrated NH_4OH (0.5 mL). Aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and 5% MeOH/CH_2Cl_2 (2 x 5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (SiO_2, 5% MeOH/CH_2Cl_2) afforded the desired product with some impurity. Dissolved the impure product in EtOAc (15 mL) and washed with 10% NH_4OH (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers (EtOAc and CH_2Cl_2) were dried over $MgSO_4$, filtered and concentrated to give the desired compound **2029** (0.25 g, 92%).

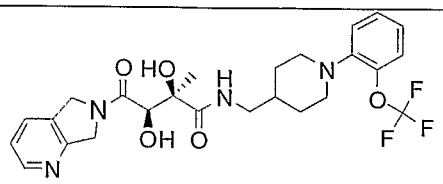
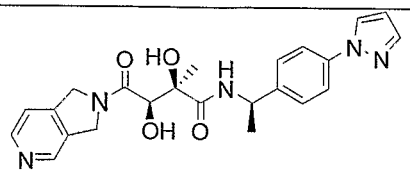
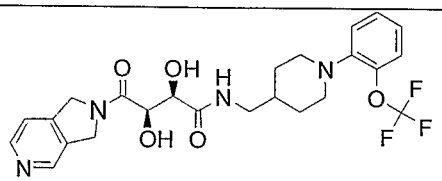
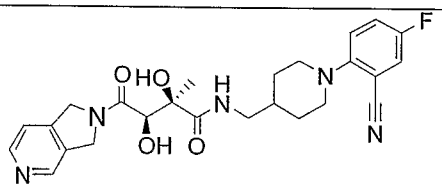
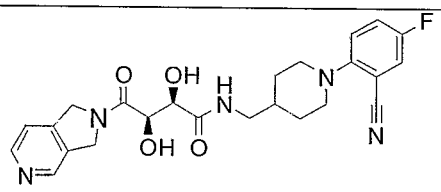
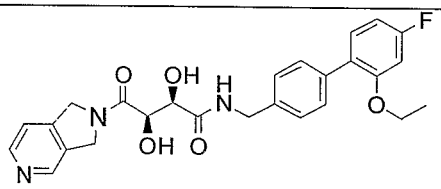
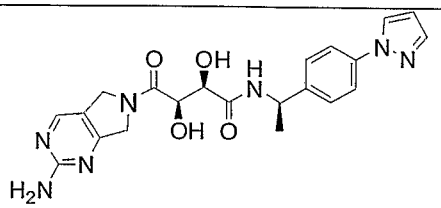
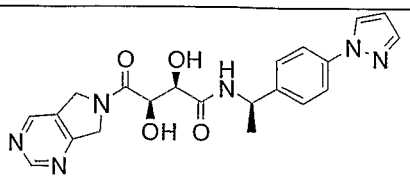
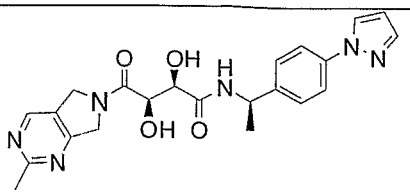
Part B:

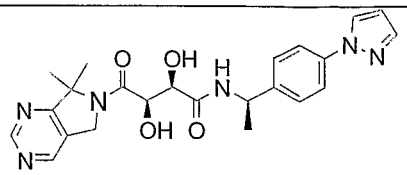
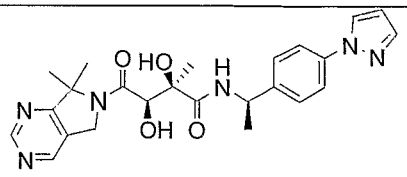
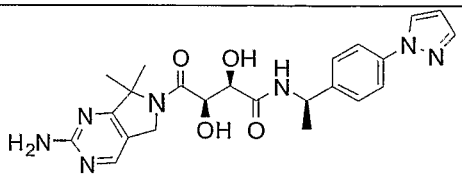
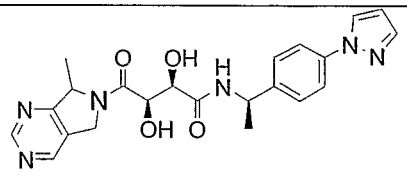
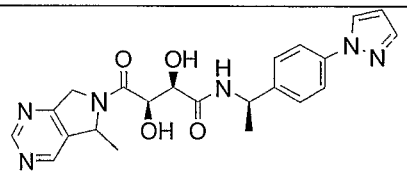
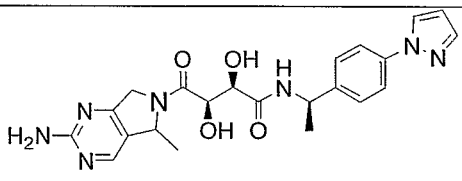
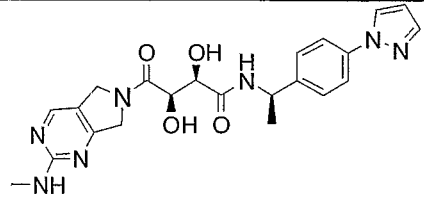
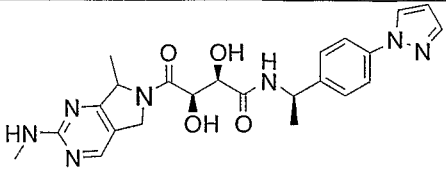
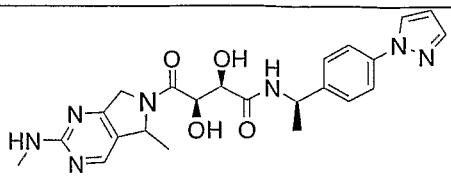
Compound **2030** was obtained from compound **2029** using the TFA deprotection procedure as described in Example 1.

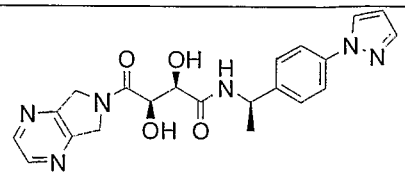
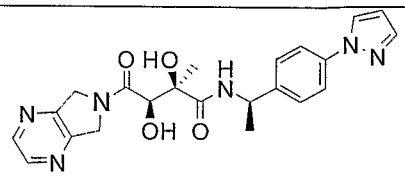
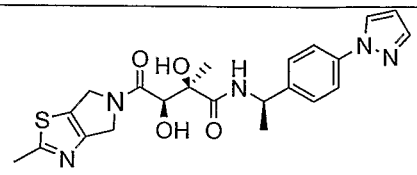
The following compounds were prepared using previously described procedures.

Compound #	Structure	Exact mass	MS m/z (M+H)

2031		435.2	436.2
2003		467.2	468.1
2032		421.2	422.1
2030		437.2	438.1
2033		493.2	494.1
2034		481.2	482.1
2035		508.2	509.1
2036		479.2	480.1
2037		417.2	418.2

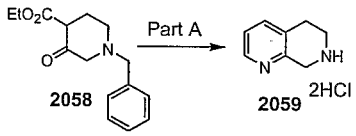
2038		522.2	523.2
2039		435.2	436.1
2040		508.2	509.1
2041		481.2	482.2
2007		467.2	468.1
2042		479.2	480.1
2043		437.2	438.1
2044		422.2	423.1
2045		436.2	437.2

2046		450.2	451.1
2047		464.2	465.1
2048		465.2	466.1
2049		436.2	437.0
2050		436.2	437.2
2051		451.2	452.2
2052		451.2	452.0
2053		465.2	466.1
2054		465.2	466.1

2055		422.2	423.1
2056		436.2	437.1
2057		455.2	456.1

Example 48: Heterocyclic tetrahydroisoquinoline analogs

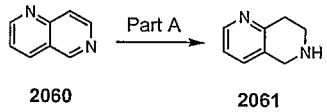
Example 48A:



Part A:

Compound **2059** was synthesized according to the literature procedures. (Dow, R.L.; Schneider, S.R. *J. Heterocyclic Chem.* **2001**, *38*, 535).

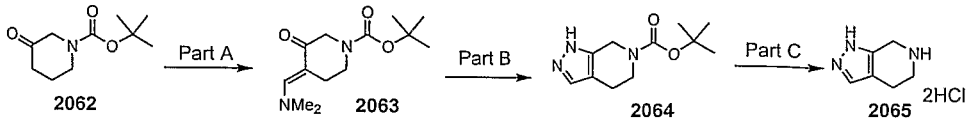
Example 48B:



Part A:

Compound **2061** was synthesized according to the procedures of US patent 5,037,834.

Example 48C:



2062 2063 2064 2065

Part A:

According to a modification of a procedure by Fukui, H. et al. (*Heterocycles* **2002**, *56*, 257-264) a mixture of ketone **2062** (2.5 g, 12.5 mmol) and N,N-dimethylformamide dimethyl acetal (21 mL) was heated at 100 °C for 2h. The mixture was concentrated to a residue which was passed through a short silica gel column (9:1:90 methanol:triethylamine:dichloromethane) to give enamino-ketone **2063** (3.1, 97%) as a viscous brown oil. HPLC-MS t_R = 1.34 min ($UV_{254\ nm}$); mass calculated for formula C13H22N2O3 254.1, observed LCMS m/z 255.1 (M+H).

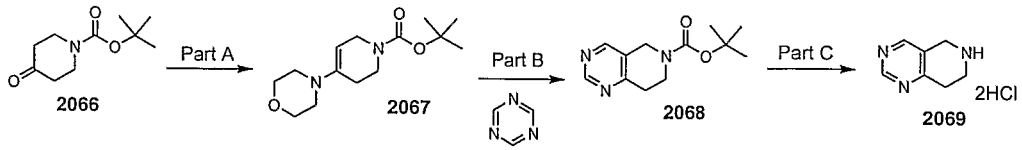
Part B:

According to a modification of a procedure by Fukui, H. et al. (*Heterocycles* **2002**, *56*, 257-264) a mixture of enamino-ketone **2063** (732 mg, 2.88 mmol) and hydrazine monohydrate (0.28 mL, 5.76 mmol) in ethanol (8 mL) was heated at reflux overnight, and then concentrated. The residue was partitioned between dichloromethane and water, and extracted with dichloromethane. The combined organic extracts were concentrated to give an oil which was chromatographed (SiO_2, 80% ethyl acetate/hexane) to give compound **2064** as an oil (major isomer, 300 mg, 46%). HPLC-MS t_R = 1.39 min ($UV_{254\ nm}$); mass calculated for formula C11H17N3O2 223.1, observed LCMS m/z 224.2 (M+H).

Part C:

Compound **2064** (300 mg, 1.34 mmol) was deprotected according to a procedure described by Fukui, H. et al. (*Heterocycles* **2002**, *56*, 257-264) to give compound **2065** (57 mg, 22 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.9 (s, 1H, broad), 9.4 (s, 1H, broad), 7.57 (s, 1H), 4.19 (t, 2H), 3.30-3.26 (m, 2H), 2.78 (t, 2H). HPLC-MS t_R = 0.2 min ($UV_{254\ nm}$); mass calculated for formula C6H9N3 123.1, observed LCMS m/z 124.2 (M+H).

Example 48D:



2066 2067 2068 2069

Part A:

A mixture of ketone **2066** (4.0 g, 20 mmol), morpholine (7.5 mL, 85 mmol) and p-toluenesulfonic acid monohydrate (160 mg, 0.84 mmol) in benzene (30 mL) was heated at reflux for 3 days using a Dean-Stark trap. The mixture was then washed with saturated sodium bicarbonate solution and concentrated to give **2067** as a yellow oil (4.36 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58 (s, 1H, broad), 3.96-3.95 (m, 2H), 3.77-3.73 (m, 4H), 3.55 (t, 2H), 2.83-2.80 (m, 4H), 2.18 (t, 2H), 1.49 (s, 9H).

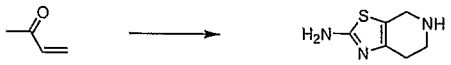
Part B:

According to a modification of a procedure by Gündisch, D. et. al. (*Bioorg. Med. Chem.* **2002**, *10*, 1-9) a mixture of enamine **2067** (2.27 g, 8.48 mmol) and 1,3,5-triazine (688 mg, 8.48 mmol) in 1,4-dioxane (10 mL) was heated at 100 °C in a sealed tube overnight. The reaction mixture was concentrated and chromatographed (SiO_2, 50-65% ethyl acetate/hexane) to give pyrimidine **2068** as a yellow oil (665 mg, 35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.49 (s, 1H), 4.64 (s, 2H), 3.80 (t, 2H), 3.00 (t, 2H), 1.54 (s, 9H). HPLC-MS t_R = 1.32 min ($UV_{254\ nm}$); mass calculated for formula C12H17N3O2 235.1, observed LCMS m/z 236.1 (M+H).

Part C:

Compound **2068** (100 mg) was deprotected using procedures described in Example 48C to give amine **2069** as a yellow solid (68 mg, 78%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.67 (s, 2H, broad), 9.01 (s, 1H), 8.67 (s, 1H), 4.33 (t, 2H), 3.50-3.45 (m, 2H), 3.09 (t, 2H). HPLC-MS t_R = 0.18 min ($UV_{254\ nm}$); mass calculated for formula C7H9N3 135.1, observed LCMS m/z 136.2 (M+H).

Example 48E:



2070

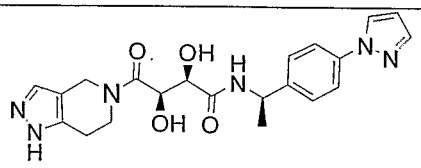
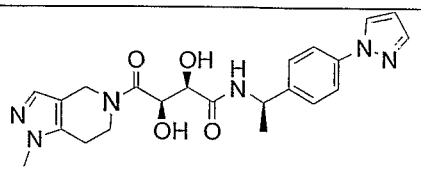
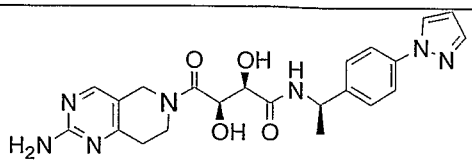
Compound **2070** was prepared from methyl vinyl ketone in 6 steps following procedures described in US Patent 5,037,834/1991.

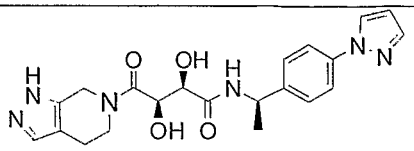
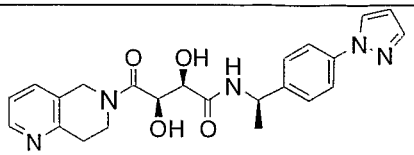
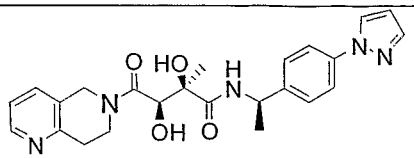
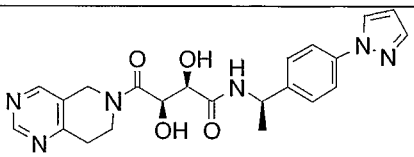
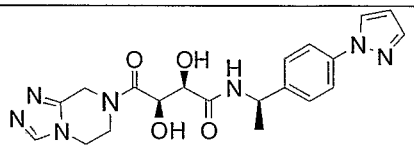
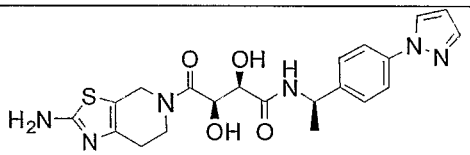
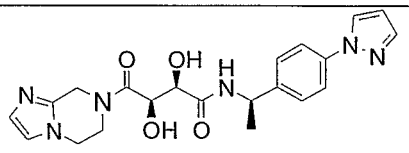
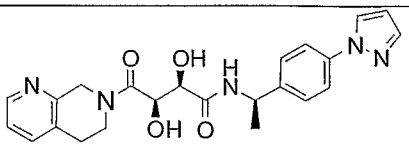
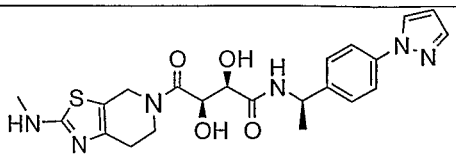
Example 48F:

2071 2072

Compound **2072** was prepared from 2-aminopyrazine (**2071**) in 2 steps following procedures described by Sablayrolles, C. et. al. (*J. Med. Chem.* **1984**, *27*, 206-212) and Bonnet, P. A. et. al. (*J. Chem. Res. Miniprint FR* **1984**, *2*, 0468-0480).

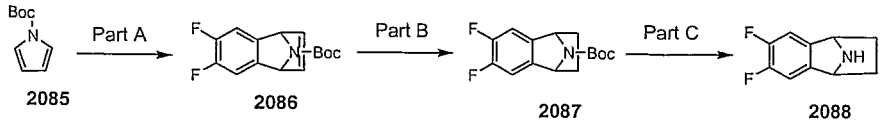
The following compounds were prepared using previously described procedures.

Compound #	Structure	Exact mass	MS m/z (M+H)
2073		424.2	425.0
2074		438.2	439.1
2075		451.2	452.0

2076		424.2	425.1
2077		435.2	436.1
2078		449.2	450.1
2079		436.2	437.1
2080		425.2	426.1
2081		456.2	457.1
2082		424.2	425.1
2083		435.2	436.1
2084		470.2	471.1

Example 49:

Example 49A:



Part A:

Compound **2086** was prepared according to the procedure in *Org. Lett.* **2002**, *4*, 24, 4353-4356.

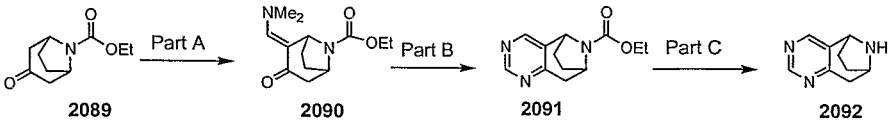
Part B:

Compound **2087** was prepared according to the procedure in *Org. Lett.* **2002**, *4*, 24, 4353-4356. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (t, 2H), 5.1 (bs, 2H), 2.15 (m, 2H), 1.4 (s, 9H), 1.3 (m, 2H).

Part C:

Compound **2087** (80 mg, 0.30 mmol) was dissolved in 4 M HCl in dioxane (2 mL) and stirred at room temperature for 1 hr. The reaction was diluted with diethyl ether (5 mL) and the resulting solid was filtered to provide **2088** as an HCl salt (45 mg).

Example 49B:



Part A:

Compound **2090** was prepared according to the procedure in *Bioorg. Med. Chem.* **2002**, *10*, 5, 1197-1206.

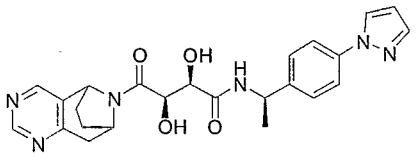
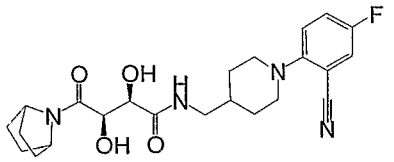
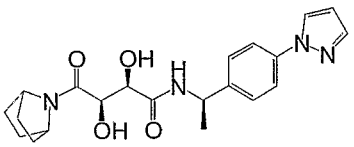
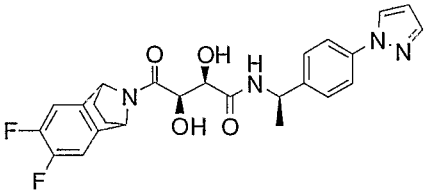
Part B:

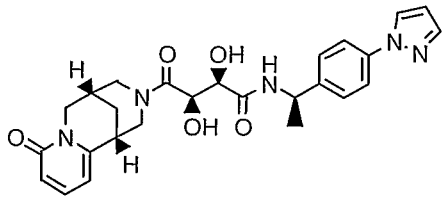
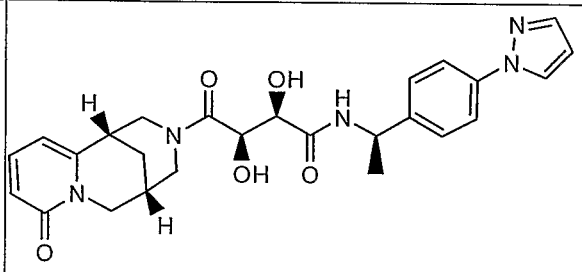
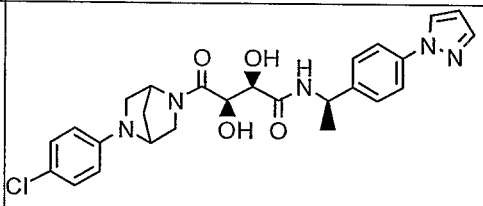
Compound **2091** was prepared according to the procedure in *Bioorg. Med. Chem.* **2002**, *10,* 5, 1197-1206. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.40 (s, 1H), 5.10 (bs, 1H), 4.70 (bs, 1H), 4.10 (m, 2H), 3.40 (bs, 1H), 2.50 (s, 1H), 2.40-2.30 (m, 2H), 1.80 (m, 2H), 1.75 (m, 2H), 1.25 (m, 3H).

Part C:

Compound **2091** (350 mg, 1.5 mmol) was dissolved in ethylene glycol (4 mL) and KOH (0.5 g) and hydrazine monohydrate (1 mL) were added and stirred at 100 °C for 12 hours. The reaction mixture was poured into brine and extracted with methylene chloride. The combined organic layers were washed with water, dried over sodium sulfate and concentrated to afford **2092** (150 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.40 (s, 1H), 4.30 (d, 1H), 4.00 (t, 1H), 3.20 (m, 1H), 2.80 (m, 1H), 2.20-2.10 (m, 2H), 2.00-1.90 (m, 2H), 1.80-1.60 (m, 2H).

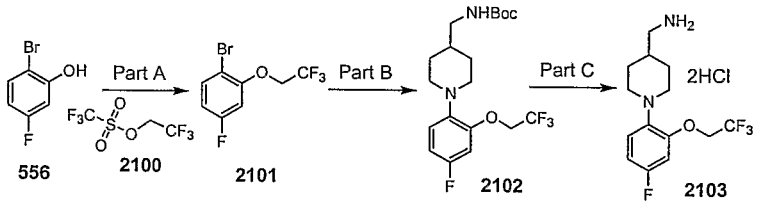
The following compounds were prepared using previously described procedures.

Compound #	Structure	Exact mass	MS m/z (M+H)
2093		462.2	463.1
2094		444.2	445.1
2095		398.2	399.3
2096		482.2	483.1

2097		491.2	492.1
2098		491.2	492.1
2099		509.2	510.1

Example 50: Piperidine-aryl compounds

Example 50A:



Part A:

A mixture of 2-bromo-5-fluorophenol (**556**) (0.111 mL, 1 mmol), 2,2,2-trifluoroethyl trifluoromethanesulfonate (**2100**) (279 mg, 1.2 mmol) and cesium carbonate (358 mg, 1.1 mmol) in NMP (5 mL) was stirred at room temperature overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with water (2x) and brine, dried over sodium sulfate and concentrated. Purification by column

chromatography (SiO_2, hexanes to 2% ethyl acetate/hexanes) afforded **2101** (232 mg) as an oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (m, 1H), 6.70 (m, 2H), 4.40 (q, 2H, J = 8.0 Hz).

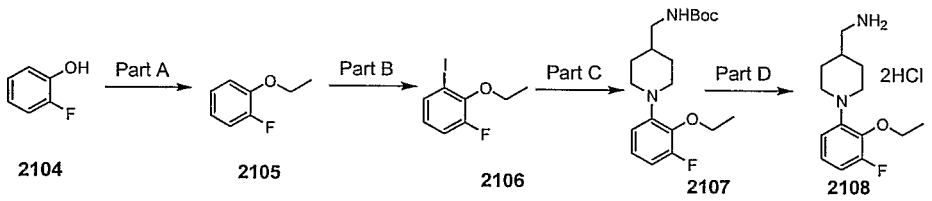
Part B:

Compound **2102** was prepared according to the procedures in Example 27B Part A. HPLC-MS t_R = 2.10 min ($UV_{254\ nm}$); mass calculated for formula C19H26F4N2O3 406.2, observed LCMS m/z 407.2 (M+H).

Part C:

Compound **2102** (8 mg, 0.02 mmol) was dissolved in 3:1 DCM:TFA (4 mL) and stirred for 1 hour at room temperature. The solvent was removed in vacuo. The residue was dissolved in ether and treated with 1.0 M HCl in ether (1 mL). The solvents were concentrated to afford **2103** as a white solid (8 mg).

Example 50B:



Part A:

A mixture of 2-fluorophenol (**2104**) (1.0 mL, 10.7 mmol), ethyl iodide (1.05 mL, 13 mmol) and potassium carbonate (1.66 g, 12 mmol) in acetone (20 mL) was stirred at room temperature overnight. Additional ethyl iodide (0.24 mL, 3 mmol) was added to the reaction and the mixture was stirred for 24 hours. The mixture was filtered and concentrated. The residue was partitioned between water and ethyl acetate. The layers were separated. The organic layer was washed with water and brine, dried over sodium sulfate and concentrated to afford **2105** (1.23 g) as an oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.07 (m, 2H), 6.96 (m, 1H), 6.87 (m, 1H), 4.12 (q, 2H, J = 7.1 Hz), 1.48 (t, 3H, J = 7.1 Hz).

Part B:

To arene **2105** (1.23 g, 8.8 mmol) and TMEDA (1.32 mL, 8.8 mmol) in THF (20 mL) at –78 °C under argon was added s-BuLi (1.4 M, 6.3 mL, 8.8 mmol). The reaction mixture was stirred for 2 hours at –78 °C. To the reaction mixture was added iodine (2.23 g, 8.8 mmol) in THF (10 mL) at –78 °C. The reaction was stirred for 10 minutes then warmed to 0 °C. The reaction mixture was poured into water and extracted with diethyl ether. The combined organics were washed with water (2x), 5% sodium hydrogensulfite and brine, dried over sodium sulfate and concentrated. The crude product **2106** (1.70 g) was a mixture of 75:25 product:starting material by ^{1}H NMR. It was used without further prurification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 1H), 6.94 (m, 1H), 6.81 (m, 1H), 4.11 (q, 2H, J = 7.1 Hz), 1.47 (t, 3H, J = 7.1 Hz).

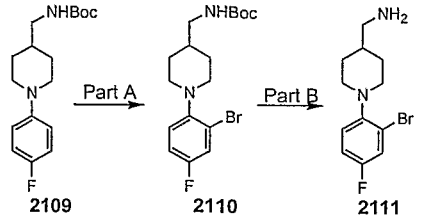
Part C:

Compound **2107** was prepared according to the procedures in Example 27B Part A. HPLC-MS t_R = 2.15 min ($UV_{254\ nm}$); mass calculated for formula C19H29FN2O3 352.2, observed LCMS m/z 353.2 (M+H).

Part D:

Compound **2107** (276 mg, 0.78 mmol) was dissolved in 3:1 DCM:TFA (4 mL) and stirred for 1 hour at room temperature. The solvent was removed in vacuo. The residue was dissolved in ether and treated with 1.0 M HCl in ether (1 mL). The solvents were concentrated to afford **2108** as a white solid (241 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (bs, NH), 6.97 (m, 1H), 6.75 (m, 1H), 6.63 (m, 1H), 4.04 (q, 2H, J = 6.9 Hz), 3.33 (m, 2H), 2.76 (m, 2H), 2.62 (m, 2H), 1.80 (m, 2H), 1.70 (m, 1H), 1.38 (m, 2H), 1.32 (t, 3H, J = 7.1 Hz).

Example 50C:



Compound **2109** was prepared using procedures described in Example 27. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 – 6.80 (m, 4H), 4.64 (m, 1H), 3.55 (m, 2H), 3.09 (m, 2H), 2.65 (m, 2H), 1.82 (m, 2H), 1.60-1.50 (m, 2H), 1.49 (s, 9H), 1.42 (m, 1H).

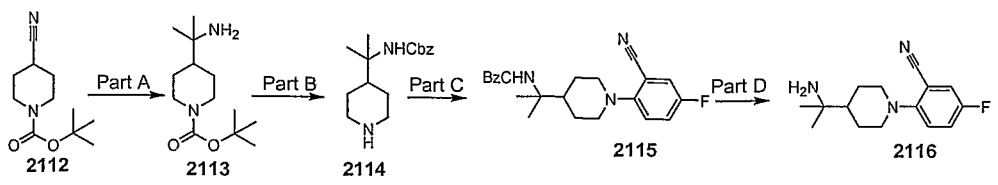
Part A:

To compound **2109** (100 mg, 0.32 mmol) and pyridine (0.026 mL, 0.32 mmol) in DMF (2 mL) was added NBS (115 mg, 0.64 mmol). The mixture was stirred at room temperature for 2 hours and diluted with ethyl acetate. The mixture was washed with sodium carbonate solution, water and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 5% ethyl acetate/hexane) afforded **2110** as a white solid (88 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.3 (m, 1H), 7.0 (m, 2H), 4.65 (bs, 1H), 3.28 (m, 2H), 3.10 (m, 2H), 2.61 (m, 2H), 1.8 (m, 2H), 1.65 – 1.4 (m, 12 H).

Part B:

To **2110** (21 mg, 0.055 mmol) in dichloromethane (2 mL) at 0 °C was added TFA (1 mL). The mixture was stirred at room temperature for 1 hour. The mixture was quenched with acetonitrile and concentrated. Compound **2111** was used without further purification.

Example 50D:



Part A:

Compound **2113** was prepared from 1-N-(*t*-butoxycarbonyl)-4-cyano-piperidine (**2112**) according to a procedure described in *J. Org. Chem.* **1992**, *57*, 4521-4527.

Part B:

Step 1: To **2113** (100 mg, 0.41 mmol) in THF (2 mL) were added benzyl chloroformate (0.089 mL, 0.619 mmol) and potassium carbonate (114 mg, 0.82 mmol). The mixture was stirred at room temperature overnight, diluted with ethyl acetate, washed with water, brine, dried over sodium sulfate and concentrated. The product was purified by column chromatography (SiO_2, 10% ethyl acetate/hexane to 25% ethyl acetate/hexane) to give a pale yellow oil (80 mg). HPLC-MS t_R = 2.14 min ($UV_{254\ nm}$); Mass calculated for C21H32N2O4 376.5, observed LSMS m/z 399.2 (M+Na).

Step 2: The material from step 1 (80 mg) was stirred in 4 N HCl in 1,4-dioxane (2mL) for 1 hour. The solvent was removed in vacuum and **2114** was used without further purification.

Part C:

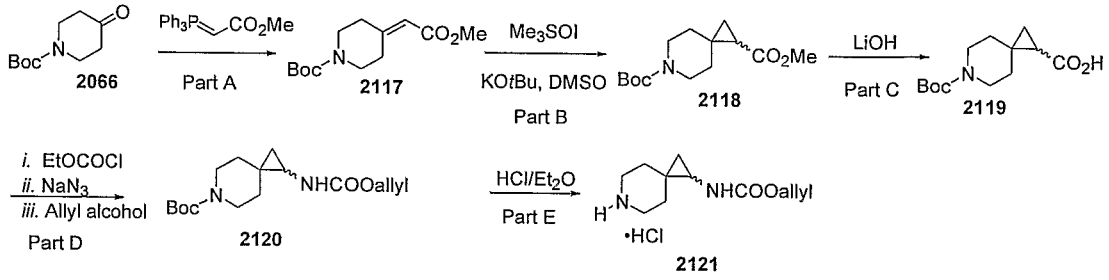
A mixture of **2114**, 2,5-difluorobenzonitrile (32.5 mg, 0.234 mmol) and DIEA (0.113 mL, 0.637 mmol) in NMP (2 mL) under argon atmosphere was stirred overnight at 100 °C. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 25% ethyl acetate/hexane) afforded **2115** as a yellow oil (26 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 7.3 – 7.2 (m, 6H), 7.2 (m, 1H), 7.0 (m, 1H), 5.05 (s, 2H), 4.7 (m, 1H), 3.52 (m, 2H), 2.77 (m, 2H), 2.15 (m, 1H), 1.8 (m, 2H), 1.63 (m, 2H), 1.32 (s, 6H).

Part D:

A mixture of **2115** (26 mg) and 10% palladium on carbon (5 mg) in ethanol (4 mL) under hydrogen atmosphere was stirred for 3 hours. The mixture was

filtered through a pad of celite and the filtrate was concentrated to give **2116** as a yellow residue (20 mg), which was used without further purification.

Example 50E:



Part A:

Methyl (triphenylphosphoranylidene)acetate (104.5 g, 0.31 mmol) was added to a solution of *N*-Boc-piperidinone (**2066**) (49.79 g, 0.25 mol) in toluene (625 mL). The resulting reaction mixture was heated to reflux and stirred for 17 h. The reaction mixture was then cooled to room temperature and concentrated under vacuum. The resulting residue was then pre-adsorbed on silica gel and purified by eluting it through a plug of silica gel with 50% ethyl acetate/hexanes, to yield unsaturated ester **2117** (62.16 g, 0.243 mol) as a white solid.

Part B:

Potassium *tert*-butoxide (450 g, 0.41 mol) was added to a solution of trimethylsulfoxonium iodide (90.0 g, 0.41 mol) in DMSO (700 mL), in one portion. The mixture was stirred at room temperature for 3 h. The unsaturated ester **2117** (59.64 g, 0.23 mol) was dissolved in DMSO (0.26 L) and added to the reaction mixture. The reaction mixture was stirred for 20 h at room temperature and then added to brine (1 L). Saturated aqueous NH_4Cl was then added to the reaction mixture in order to adjust the pH to approximately 7. The reaction mixture was then extracted several times with ether, the ether extracts combined, washed with water and brine, dried with anhydrous $MgSO_4$, filtered, and concentrated under vacuum to yield ester **2118** (53.5 g, 0.20 mol) as an oil.

Part C:

An aqueous LiOH solution (2N, 200 mL) was added to a solution of the ester **2118** (53.5 g, 0.20 mol) in THF (200 mL). The mixture was then stirred at room temperature for 17 h, diluted with water (750 mL) and washed with ether. The ether phase was discarded, and the aqueous phase acidified to a pH of 3-4 with 6N HCl. The acidified aqueous phase was then extracted with ether several times. The ether washes were combined, washed with water and brine, dried with anhydrous $MgSO_4$, filtered, and concentrated under vacuum to provide carboxylic acid **2119** (49.25 g, 0.19 mol) as a white solid.

Part D:

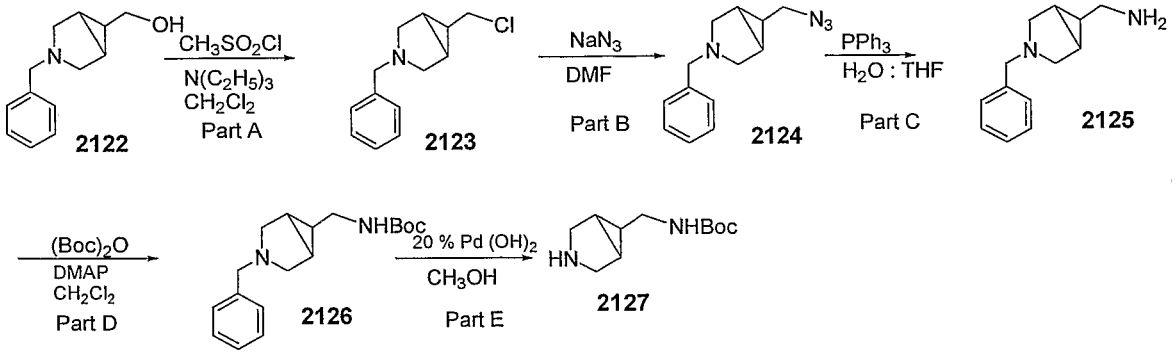
Triethylamine (8.7 g, 0.086 mol) followed by ethyl chloroformate (9.4 g, 0.086 mol) was added to a solution of carboxylic acid **2119** (20.0 g, 0.078 mol) in acetone (78 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 40 minutes. Sodium azide (10.2 g, 0.15 mol) in water (50 mL) was then added to the mixture. The mixture was then allowed to warm to room temperature and stirred for 4 h. Water was then added, and then the mixture was extracted several times with CH_2Cl_2. The organic extracts were combined and washed with water and brine, dried over magnesium sulfate and concentrated under vacuum to provide an oil. The oil was taken up into toluene (200 mL), allyl alcohol (5.5 g, 0.094 mol) was added, and the mixture was heated to reflux and stirred at reflux for 17 h. The reaction mixture was then cooled to room temperature and EtOAc (250 mL) was added. Then, the mixture was washed with water and brine, dried over magnesium sulfate and concentrated under vacuum. The resulting residue was purified by silica gel chromatography (35% ethyl acetate/hexanes) to provide the carbamate **2120** (24.4 g, 0.061 mol).

Part E:

A solution of HCl/Et_2O (2 N, 50 mL) was added to a solution of the carbamate **2120** (24.4 g, 0.061 mol) in CH_2Cl_2 (100 mL). The reaction mixture was stirred

overnight and then concentrated under vacuum to yield **2121** as a hygroscopic foam (17.4 g, 0.052 mol).

Example 50F:



Starting alcohol **(2122)** (1α, 5α, 6α)-3-benzyl-6-hydroxymethyl-3-azabicyclo[3.1.0]hexane was prepared by known methods (i.e., Brighty, K. E; Castaldi, M. J *Synlett,* **1996**, 1097).

Part A:

Alcohol **2122** (11 g, 54 mmol) and triethylamine (38 mL, 27 mmol) were dissolved in CH_2Cl_2 (200 mL) and cooled to 0 °C. The cooled solution was stirred, and CH_3SO_2Cl (as a CH_2Cl_2 solution; 6 mL, 78 mmol, 25 mL CH_2Cl_2) was added dropwise, and the stirring was continued for 3-4 h. The reaction mixture was then washed two times with 100 mL of water and two times with 100 ml of brine. The organic and aqueous phases were separated, and the organic phase was dried, and concentrated to provide a crude product. The crude product was purified by silica gel chromatography (eluted with 1:6 ethyl acetate:hexane). The appropriate fractions were collected from the chromatography column and concentrated to provide pure chloro compound **2123** as an oil (7 g, 59%).

Part B:

The chloro compound **2123** was dissolved in DMF (100 mL) and treated with NaN_3 (10.3 g, 157 mmol), and the mixture was stirred vigorously for 36-48 h. The reaction mixture was then diluted with 100 mL water and extracted with

ethyl acetate (2 x 100 mL). The organic extracts were combined, dried, and concentrated to yield pure azide **2124** (6.2 g, 87%).

Part C:

The azide **2124** (6.2 g, 27 mmol) and triphenylphosphine (15 g, 57 mmol) were dissolved in 100 mL of THF, and then water (6 mL, 333 mmol) was added. The resulting mixture was stirred vigorously for 16-24 h. The solvent was removed and the crude amine **2125** was obtained without further purification.

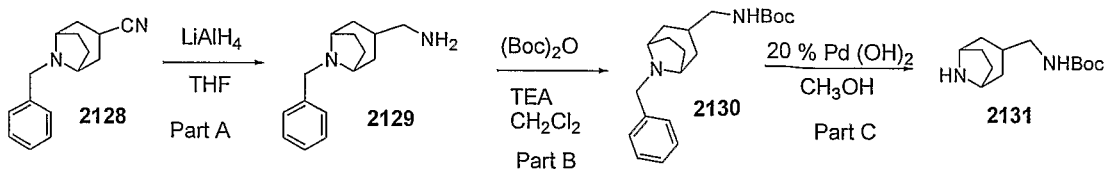
Part D:

The crude amine **2125** and N, N-dimethylaminopyridine (0.66 g, 5.4 mmol) were dissolved in CH_2Cl_2 (100 mL). To this solution was added di-tert-butyldicarbonate (7 g, 33 mmol), in portions, and the reaction mixture was stirred for 16 h. The reaction mixture was then washed two times (50 mL) with water and once with brine (50 mL). The organic phase was isolated and dried, and the solvent was removed under reduced pressure. The crude product was subjected to silica gel chromatography using 1:3 ethyl acetate:hexane as the eluting solvent. The eluted fractions were combined and concentrated to yield 6.9 g of pure carbamate **2126** (84%).

Part E:

The carbamate **2126** (1.9 g, 6.3 mmol) was dissolved in methanol (100 mL) and mixed with palladium hydroxide (20%, 0.4 g). The mixture was transferred to a Parr bottle, which was then charged with hydrogen (20 psi). The Parr bottle was shaken for 10 h. The remaining hydrogen was removed from the Parr bottle under vacuum, and the reaction was filtered through Celite. The filtrate was then concentrated to provide pure amine **2127** (1.4 g).

Example 50G:



2128 2129 2130 2131

N-Benzyltropinanecarbonitrile **2128** was prepared using known procedures (see, for example: Montzka, T. A.; Matiskella, J. D.; Partyka, R. A. *Tetrahedron Letters* **1974**, *14*, 1325; Lowe, J. A.; Drozda, S. E.; McLean, S.; Bryce, D. K.; Crawford, R.T.; Snider, R. M.;Tsuchiya, M. *J. Med. Chem.* **1994**, *37*, 2831).

Part A:

$LiAlH_4$ was added to dry THF (40 mL) and the mixture was then cooled to 0 °C. Then carbonitrile **2128** (0.9 g, 3.8 mmol, in a 10 mL THF solution) was added to the mixture dropwise. The reaction mixture was allowed to warm to ambient temperature and stirred for 48 h, then cooled to back to 0 °C and quenched by the sequential addition of 1 mL of water, 2 mL of 0.5 N aq. NaOH, and 1 mL of water. The resulting mixture was stirred vigorously for 2 h and then filtered through Celite. The filtrate was concentrated to yield pure **2129** as an oil (0.9 g, 100%).

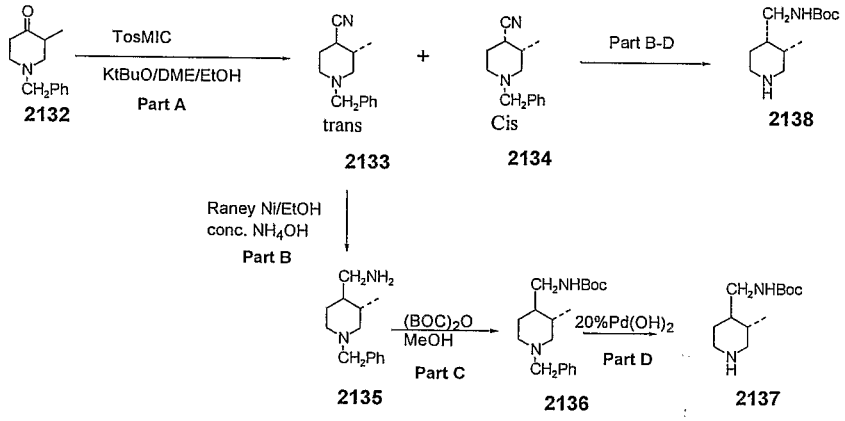
Part B:

The crude product **2129** and triethylamine (TEA) (0.6 mL, 4.3 mmol) were dissolved in CH_2Cl_2 (50 mL). Di-tert-butyldicarbonate (0.85 g, 3.9 mmol) was added to this solution in portions, and the reaction mixture was stirred for 16 h. The reaction mixture was then washed two times with 50 mL of water and once with 50 mL of brine. The organic phase was dried and the solvent was removed under reduced pressure. The crude product was subjected to silica gel chromatography using 2.5% ammonia saturated methanol in CH_2Cl_2 as the eluting solvent. The eluted fractions were combined and concentrated to yield 0.78 g of pure carbamate product **2130** (61%).

Part C:

The carbamate **2130** (0.8 g, 2.3 mmol) was dissolved in methanol (60 mL) and treated with palladium hydroxide (20%, 0.08 g). The mixture was transferred to a Parr bottle, which was then charged with hydrogen (20 psi). The Parr bottle was shaken for 10 h. The hydrogen was removed from the Parr bottle under vacuum, and the reaction mixture was filtered through Celite. The filtrate was then concentrated to provide pure amine **2131** (0.6 g).

Example 50H:



Part A:

Tosylmethyl isocyanide (TosMIC) (7.2 g, 37 mmol) was added to 3-methyl-N-benzyl piperidone (**2132**) (4.25 g, 20.93 mmol) in DME (150 mL) and cooled to 0 °C. Ethyl alcohol (2.9 mL) and potassium tert-butoxide (7 g, 62.4 mmol) were added to the reaction mixture and stirred at room temperature for 4 hours. The reaction mixture was poured into ice and extracted with ethyl acetate (2 x 50 mL). The organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under vacuum. The resulting residue was purified by silica gel chromatography (20% ethyl acetate/hexane) to give first **2133** (trans isomer, 1.85 g, 41%), and second **2134** (cis isomer, 1.05 g, 22%).

Part B:

The trans intermediate **2133** (2.0 g, 9.34 mmol) was dissolved in ethyl alcohol (50 mL) and Raney Nickel (wet, 5.0 g) was added under N_2, followed by addition of

conc. ammonium hydroxide (1.0 mL). The mixture was subjected to H_2 atmosphere at 50 p.s.i. for 16 hours with vigorous shaking. The reaction was filtered through celite under N_2 and the filtrate was concentrated under vacuum to provide 1.8 g (88%) of intermediate **2135.**

Part C:

Intermediate **2135** (1.0 g, 4.6 mmol) was dissolved in methyl alcohol (35 mL). A solution of BOC-anhydride (1.2 g, 5.5 mmol) in methyl alcohol (15 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for one hour, then at ambient temperature for an additional hour. The solvent was removed under vacuum to provide a crude product that was purified by silica-gel column chromatography using ethyl acetate as the eluting solvent. The relevant fractions were collected and concentrated under reduced pressure to yield 1.1 g (76%) of intermediate **2136.**

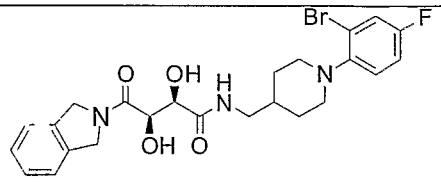
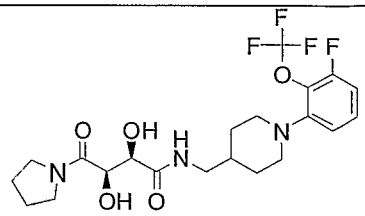
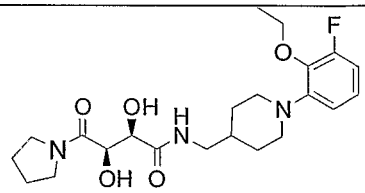
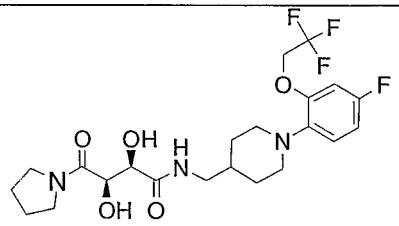
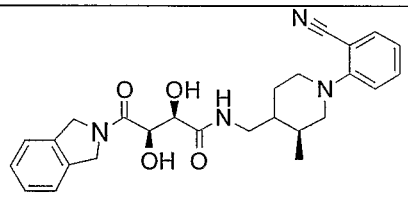
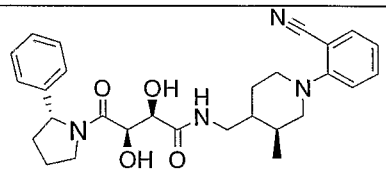
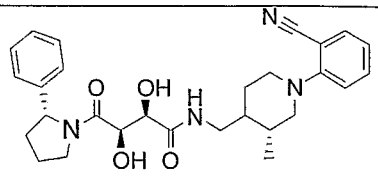
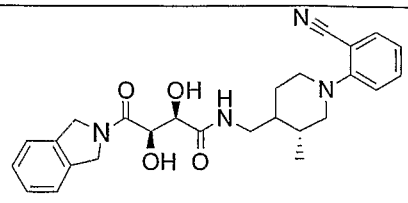
Part D:

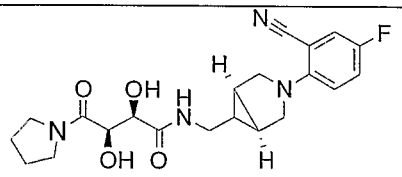
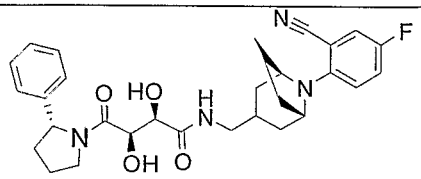
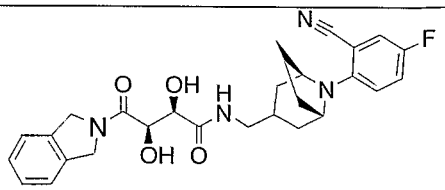
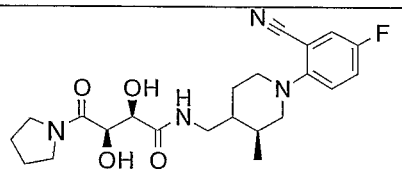
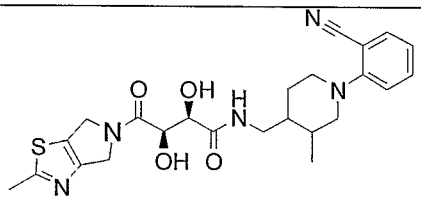
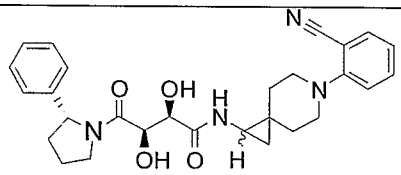
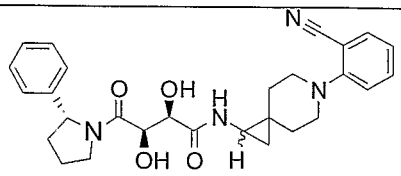
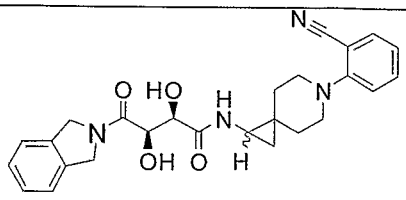
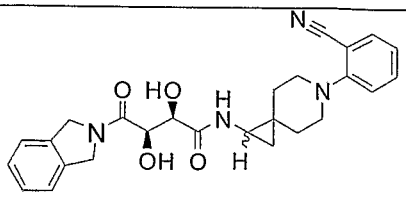
Intermediate **2136** (0.5 g, 1.57 mmol) was dissolved in methyl alcohol (25 mL). Palladium hydroxide (20 wt % Pd, 0.1 g) was added under N_2. The resulting mixture was exposed to H_2 atmosphere at 20 p.s.i. for 16 hours with vigorous shaking. The reaction mixture was filtered through celite and washed with methyl alcohol (1 X 25 mL). The filtrate was concentrated under vacuum to provide intermediate **2137** (0.38 g) as an oil which was used in the next step without further purification.

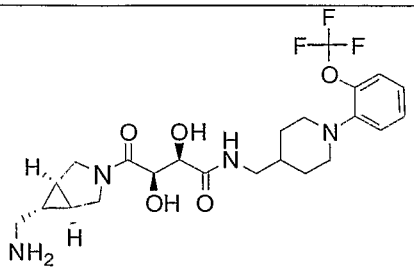
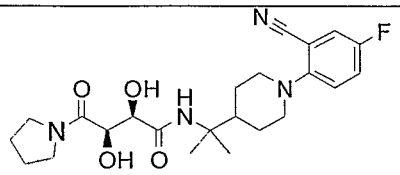
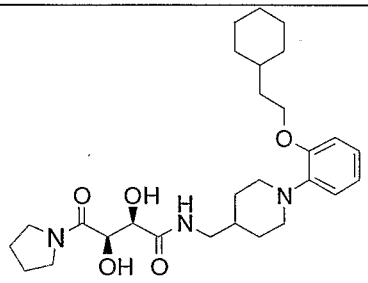
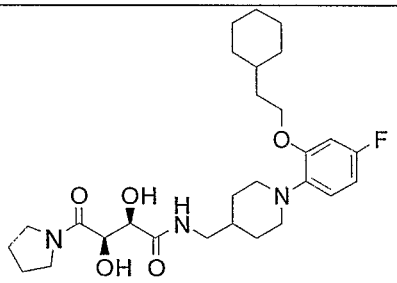
Intermediate **2138** was prepared using methods similar to those used in Part B-D.

The following compounds were prepared using previously described procedures.

Compound #	Structure	Exact mass	MS m/z (M+H)

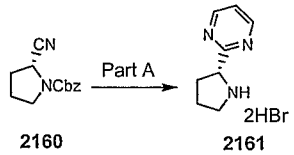
2139		519.1	520.1
2140		477.2	478.1
2141		437.2	438.1
2142		491.2	492.1
2143		462.2	463.1
2144		490.3	491.1
2145		490.3	491.3
2146		462.2	463.3

2147		416.2	417.2
2148		520.2	521.1
2149		492.2	493.3
2150		432.2	433.2
2151		483.2	484.1
2152		488.2	489.1
2153		488.2	489.1
2154		460.2	461.1
2155		460.2	461.3

2156		500.2	500.1
2157		446.2	447.3
2158		501.3	502.3
2159		519.3	520.3

Example 51:

Example 51A:

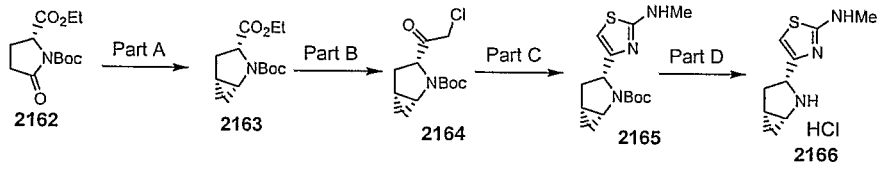


2160 **2161**

Part A:

Compound **2161** was synthesized according to the procedures of WO02060894A2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.58 (bs, NH), 8.89 (m, 2H), 7.57 (m, 1H), 4.88 (m, 1H), 3.80 (m, 2H), 2.06 (m, 4H).

Example 51B:



Part A:

Compound **2163** was synthesized from Compound **2162** (made according to the procedures of WO2004/052850) according to the procedures of Hanessian et. al.(*Bioorg. Med. Chem Lett.* **1998**, *8*, 2123 and the references therein.) HPLC-MS t_R = 1.90 min ($UV_{254\ nm}$); mass calculated for formula C13H21NO4 255.2, observed LCMS m/z 278.2 (M+Na).

Part B:

Compound **2164** was synthesized according to the procedures of Example 10B Part A. HPLC-MS t_R = 1.79 min ($UV_{254\ nm}$); mass calculated for formula C12H18ClNO3 259.1, observed LCMS m/z 282.1 (M+Na).

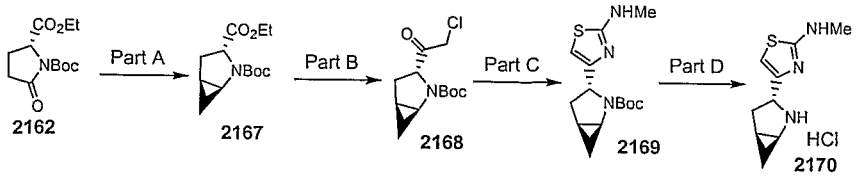
Part C:

Compound **2164** (190 mg) was cyclized with N-methylthiourea in DMF (2 mL) to afford **2165** (81 mg) according to the procedures of Example 10B Part B. HPLC-MS t_R = 1.27 min ($UV_{254\ nm}$); mass calculated for formula C14H21N3O2S 295.1, observed LCMS m/z 296.2 (M+H).

Part D:

To compound **2165** (81 mg) in methanol (2 mL) was added 4.0 M HCl/dioxane (1 mL) with ice bath cooling. The reaction mixture was stirred for 1.5 hours and concentrated. The residue was suspended in DCM (5 mL) and concentrated to afford impure **2166**. The material was used without purification.

Example 51C:



Part A:

Compound **2167** was synthesized from Compound **2162** (made according to the procedures of WO2004/052850) according to the procedures of Hanessian et. al. *Bioorg. Med. Chem Lett.* **1998**, *8*, 2123 and the references therein. HPLC-MS t_R = 1.83 min (MS); mass calculated for formula C13H21NO4 255.2, observed LCMS m/z 278.2 (M+Na).

Part B:

Compound **2168** was synthesized according to the procedures of Example 10B Part A. HPLC-MS t_R = 1.78 min (MS); mass calculated for formula C12H18ClNO3 259.1, observed LCMS m/z 282.1 (M+Na).

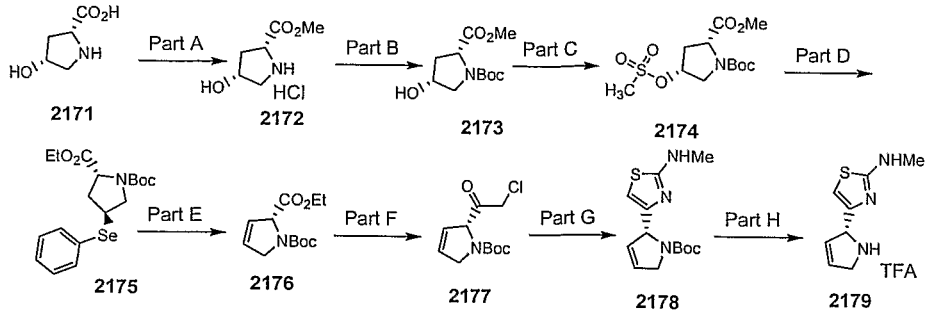
Part C:

Compound **2168** (117 mg) was cyclized with N-methylthiourea in DMF (2 mL) to afford **2169** (35 mg) according to the procedures of Example 10B Part B. HPLC-MS t_R = 1.16 min ($UV_{254\ nm}$); mass calculated for formula C14H21N3O2S 295.1, observed LCMS m/z 296.2 (M+H).

Part D:

To compound **2169** (35 mg) in methanol (2 mL) was added 4.0 M HCl/dioxane (1 mL) with ice bath cooling. The reaction mixture was stirred for 1.5 hours and concentrated. The residue was suspended in DCM (5 mL) and concentrated to afford impure **2170**. The material was used without purification.

Example 51D:



Part A:

To hydroxy proline **2171** (1.52 g, 11.6 mmol) in methanol (25 mL) in an ice bath was added thionyl chloride (0.95 mL, 13 mmol). The ice bath was removed and the reaction mixture was heated to reflux overnight. The reaction mixture was cooled and concentrated. The residue was dissolved in methanol and concentrated. The residue was dissolved in diethyl ether and concentrated to afford **2172** quantitatively. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (bs, 1H), 8.95 (bs, 1H), 4.50 (d, 1H, J = 7.0 Hz), 4.36 (m, 1H), 3.75 (s, 3H), 3.16 (m, 2H), 2.31 (m, 1H), 2.13 (m, 1H).

Part B:

To compound **2172** (2.11 g, 11.6 mmol) in DCM (25 mL) was added DIEA (4.2 mL, 24 mmol) and a solution of BOC-anhydride (3.03 g, 13. 9 mmol) in DCM (25 mL) with ice bath cooling. The reaction mixture was slowly warmed to room temperature and stirred overnight. The reaction mixture was washed with water, 0.1 N HCl, bicarbonate solution and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, loaded with ethyl acetate and eluted with 30% ethyl acetate/hexane to ethyl acetate) afforded **2173** (2.66 g) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ rotomers 4.40-4.29 (m, 2H), 3.81 and 3.80 (s, 3H), 3.75 –3.64 (m, 1H), 3.57-3.50 (m, 1H), 2.35 (m, 1H), 2.11 (m, 1H), 1.48 and 1.44 (s, 9H).

Part C:

To compound **2173** (2.66 g, 10.8 mmol) in DCM (50 mL) in an ice bath was added triethyl amine (1.66 mL, 11.9 mmol) and methanesulfonyl chloride

(1.09 mL, 14.1 mmol) dropwise. The reaction mixture was slowly warmed to room temperature and stirred overnight. The reaction mixture was quenched with ice water and the layers were separated. The aqueous layer was extracted with DCM. The combined organic layers were washed with 0.1 N HCl and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 50% ethyl acetate/hexanes) afforded **2174** (3.36 g) as an oil. HPLC-MS t_R = 1.49 min (ELSD); mass calculated for formula C12H21NO7S 323.1, observed LCMS m/z 346.1 (M+Na).

Part D:

To diphenylselenide (1.97 g, 6.3 mmol) in ethanol (20 mL) in an ice bath was added sodium borohydride (472 mg, 12.5 mmol) portion wise. The reaction mixture was stirred for 10 minutes after the bubbling had ceased. The above solution was added to compound **2174** (3.36 g, 10. 4 mmol) in ethanol (10 mL). The reaction mixture was heated to reflux for 2 hours. The reaction was cooled and the solvents removed in vacuo. The residue was partitioned between water (50 mL) and ethyl acetate (50 mL). The layers were separated. The organic layer was washed with water and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 5% to 20% ethyl acetate/hexanes) afforded **2175** (2.91 g) as an oil. HPLC-MS t_R = 2.32 min ($UV_{254\ nm}$); mass calculated for formula C18H25NO4Se 399.1, observed LCMS m/z 422.0 (M+Na).

Part E:

To **2175** (481 mg, 1.21 mmol) in DCM (5 mL) in an ice bath was added dropwise pyridine (0.162 mL, 2.0 mmol) and 50% hydrogen peroxide (0.161 mL, 2.63 mmol). The ice bath was removed and the reaction mixture was stirred at room temperature for 1.25 hours. The reaction mixture was diluted with ethyl acetate (50 mL), washed with 0.1 N HCl, bicarbonate solution and brine, dried over sodium sulfate and concentrated to afford **2176** (272 mg) as a yellow oil. HPLC-MS t_R = 1.81 min (MS); mass calculated for formula C12H19NO4 241.1, observed LCMS m/z 264.1 (M+Na).

Part F:

Compound **2177** (123 mg) was prepared from **2176** (202 mg, 0.84 mmol) according to the procedure described in Example 10B Part B. HPLC-MS t_R = 1.70 min (MS); mass calculated for formula C11H16ClNO3 245.1, observed LCMS m/z 264.1 (M+Na).

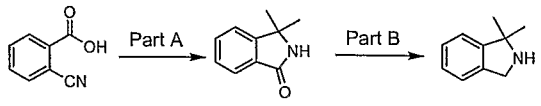
Part G:

Compound **2178** (48 mg) was prepared as described in Example 51B Part C from compound **2177** (123 mg, 0.5 mmol). HPLC-MS t_R = 1.12 min ($UV_{254\ nm}$); mass calculated for formula C13H19N3O2S 281.1, observed LCMS m/z 282.1 (M+H).

Part H:

A mixture of compound **2178** (48 mg, 0.17 mmol), TFA (2 mL) and DCM (2 mL) were stirred at room temperature for 1 hour. The solvents were removed and the residue was dissolved in DCM (5 ml) and concentrated to afford **2179** (70 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (bs, NH), 6.75 (s, 1H), 6.26 (d, 1H, J = 6.3 Hz), 5.92 (d, 1H, J = 7.5 Hz), 5.77 (m, 1H), 4.43 (d, 1H, J =17.2 Hz), 4.28 (d, 1H, J =17.2 Hz), 3.11 (s, 3H).

Example 51E:



2180 2181 2182

Part A:

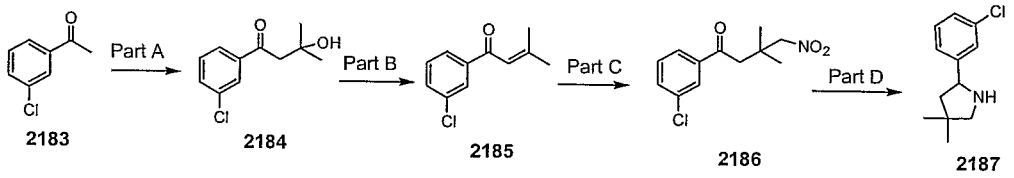
Compound **2180** was prepared using a modification of the procedure in *J. Org. Chem.* **1998**, *63*, 8, 2451-2455. Compound **2180** (0.400 g, 2.72 mmol) was dissolved in THF (60 mL) and cooled in a dry ice/acetone bath. A solution of methyllithium (1.6 M in diethylether, 18 mL) was added dropwise and the solution was warmed to room temperature. The reaction was quenched with brine after 10 minutes. The reaction mixture was poured into

water and extracted with ethyl acetate. The combined organics were washed with 1N HCl, saturated sodium bicarbonate and water, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 50% ethyl acetate/hexanes) afforded **2181** (0.200 g). HPLC-MS t_R = 1.126 min ($UV_{254\ nm}$); mass calculated for formula $C_{10}H_{11}NO$ 161.1, observed LCMS m/z 162 (M+H).

Part B:

Compound **2181** (0.200 g, 1.24 mmol) was dissolved in THF (10 mL) and a solution of borane (2.5 M in THF, 3 mL) was added dropwise and the solution was stirred at reflux overnight. The reaction was quenched with a solution of 1 M sodium hydroxide (2 mL) and methanol (2 mL) and reflux was continued for 5 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organics were washed with saturated sodium bicarbonate, water, dried over sodium sulfate and concentrated to afford **2182** (65 mg). HPLC-MS t_R = 0.595 min ($UV_{254\ nm}$); mass calculated for formula $C_{10}H_{11}N$ 147.1, observed LCMS m/z 148 (M+H).

Example 51F:



Part A:

Compound **2184** was prepared using a modification of the procedure in *J. Med.Chem.*. **1994**, *37*, 23, 3878-3881. Compound **2183** (2.0 g, 12.9 mmol) was dissolved in methylene chloride and cooled in an ice bath. Triethylamine (3.61 mL, 26 mmol) was added followed by the dropwise addition of TMSOTf (2.81 mL, 15.5 mmol). The reaction was warmed to room temperature and stirred for 30 minutes. Saturated sodium bicarbonate was added slowly to quench the reaction and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate. In a separate flask $TiCl_4$ (1M in toluene, 20 mL) was added to

methylene chloride (80 mL) at –78 °C. Acetone (1.2 g, 22 mmol) was added and stirred for 2 minutes. The silyl enol ether from the earlier was added and the reaction was stirred for 4 hours. After warming to room temperature, the reaction was quenched with saturated sodium bicarbonate and extracted with methylene chloride. The combined organic layers were dried over sodium sulfate and evaporated. Purification by column chromatography (SiO_2, 33% ethyl acetate/hexanes) afforded **2184** (600 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, 1H), 7.80 (d, 1H), 7.55 (d, 1H), 7.40 (t, 1H), 3.15 (s, 2H), 1.40 (s, 6H).

Part B:

Compound **2184** (600 mg, 2.84 mmol) was dissolved in methylene chloride (2 mL) and pyridine (2 mL) and cooled in an ice bath. TFAA (0.894 g, 4.26 mmol) was added dropwise and stirred 1 hour at room temperature. The reaction mixture was partitioned between ethyl acetate and water. The organic layers were washed with 1N HCl, saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated. The residue was dissolved in methylene chloride (5 mL) and DBU (0.5 mL) was added and stirred for 1 hour at room temperature. The reaction mixture was partitioned between methylene chloride and water. The organic layers were washed with 1N HCl, saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated. Purification by column chromatography (SiO_2, 10% ethyl acetate/hexanes) afforded **2185** (460 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, 1H), 7.80 (d, 1H), 7.50 (d, 1H), 7.40 (t, 1H), 6.70 (m, 1H), 2.20 (d, 3H), 2.05 (d, 3H).

Part C:

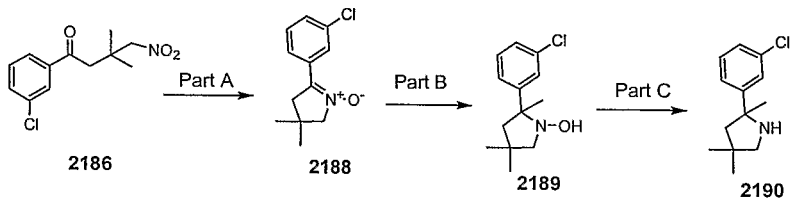
Compound **2185** (460 mg, 2.38 mmol) was dissolved in nitromethane (295 mg, 4.76 mmol) and benzyltrimethylammonium hydroxide (40% weight in MeOH, 200 mg) and stirred for 2 hours at room temperature. The reaction was quenched with acetic acid (1 mL) and partitioned between diethyl ether and water. The organic layer was dried over sodium sulfate and concentrated

to afford **2186** (550 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, 1H), 7.80 (d, 1H), 7.58 (d, 1H), 7.40 (t, 1H), 4.70 (s, 2H), 3.10 (s, 2H), 1.30 (s, 6H).

Part D:

Compound **2187** was prepared according to the procedure in *Chem. Ber.* **1958**, *91*, 1978-1980. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (m, 1H), 7.22 (m, 2H), 7.18 (m, 1H), 4.30 (m, 1H), 2.90-2.80 (dd, 2H), 2.00 (m, 1H), 1.50 (m, 1H), 1.15 (d, 6H).

Example 51G:



2186 2188 2189 2190

Part A:

Compound **2186** (500 mg, 1.96 mmol) and ammonium chloride (104 mg, 1.96 mmol) were dissolved in THF (5 mL) and water (5 mL) and cooled in an ice bath. Zn dust (637 mg, 9.8 mmol) was added in portions and stirred overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layers were washed with saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated. The residue was dissolved in methylene chloride (10 mL) and m-CPBA (510 mg, 2.94 mmol) was added and stirred for 2 hours. The reaction mixture was partitioned between methylene chloride and water. The organic layers were washed with saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated to yield **2188** (300 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (m, 1H), 7.65 (m, 2H), 7.40-7.30 (m, 2H), 3.80 (t, 2H), 2.80 (t, 2H), 1.20 (s, 6H).

Part B:

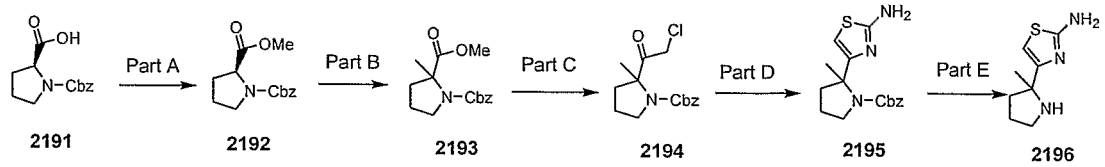
Compound **2188** (300 mg, 1.35 mmol) was dissolved in THF (10 mL) and MeMgBr (3M in THF, 5 mL) was added dropwise. After stirring for 30 minutes

at room temperature the reaction mixture was partitioned between ethyl acetate and water. The organic layers were washed with saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated to afford **2189** (280 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (t, 1H), 7.42 (m, 1H), 7.30-7.20 (m, 2H), 3.20 (m, 2H), 2.00 (m, 2H), 1.55 (s, 3H), 1.20 (s, 3H), 1.15 (s, 3H).

Part C:

Compound **2189** (280 mg, 1.26 mmol) was dissolved in 1N HCl (10 mL) and Zn dust (0.5 g) was added. The reaction mixture was stirred at 60 °C for 12 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layers were washed with saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated to afford **2190** (110 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (bs, 1H), 7.38 (m, 1H), 7.30-7.20 (m, 2H), 2.85 (m, 1H), 2.75 (m, 1H), 2.05 (m, 1H), 1.85 (m, 1H), 1.50 (s, 3H), 1.20 (s, 3H), 0.95 (s, 3H).

Example 51H:



Part A:

Compound **2191** (2.8 g, 11.2 mmol) was dissolved in toluene (10 mL) and MeOH (10 mL) and cooled in an ice bath. A solution of TMS diazomethane in hexanes (2M, 8.4 mL) was added dropwise until yellow color persisted. The reaction was quenched with acetic acid until color became clear and the solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was washed with 1N HCl, saturated sodium bicarbonate, brine, dried over sodium sulfate and concentrated to afford **2192** (3.1 g). The product was used without purification.

Part B:

Diisopropylamine (3.9 mL, 28 mmol) was dissolved in THF (20 mL) and cooled to –40 °C. A solution of n-BuLi (2.5M in hexanes, 8.9 mL) was added dropwise and the reaction was stirred for 30 minutes. Compound **2192** (3.1 g, 11.2 mmol) dissolved in THF (10 mL) was added dropwise at –78 °C and stirred for another 30 minutes. Iodomethane (3.1 g, 22.4 mmol) was added dropwise and the reaction was stirred for one additional hour. The reaction was warmed to room temperature and quenched with brine and extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over sodium sulfate and concentrated to provide **2193** (2.5 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.20 (m, 5H), 5.20-5.00 (m, 2H), 3.70-3.40 (d, 3H), 3.70-3.60 (m, 2H), 2.20 (m, 1H), 1.90 (m, 3H), 1.60 (d, 3H).

Part C:

Diisopropylamine (1.24 mL, 8.85 mmol) was dissolved in THF (10 mL) and cooled to –40 °C. A solution of n-BuLi (2.5M in hexanes, 3.5 mL) was added dropwise and the reaction was stirred for 30 minutes. This solution was added dropwise to a solution of compound **2193** (450 mg, 1.61 mmol) and chloroiodomethane (1.12 g, 6.44 mmol) in THF (10 mL) at –78 °C. The reaction was stirred for 30 minutes and then quenched by the dropwise addition of acetic acid (1 mL) in THF (5 mL). After 10 minutes of stirring the reaction mixture was partitioned between ethyl acetate and water. The organic layers were washed with saturated sodium bicarbonate, brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 25% ethyl acetate/hexanes) afforded **2194** (330 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.20 (m, 5H), 5.20-5.00 (m, 2H), 4.40-4.00 (m, 2H), 3.80-3.60 (m, 2H), 2.20 (m, 1H), 2.00-1.8 (m, 3H), 1.60-1.40 (m, 3H).

Part D:

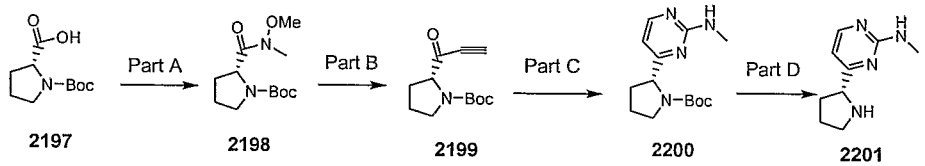
Compound **2194** (175 mg, 0.59 mmol) was dissolved in DMF (5 mL) and thiourea (91 mg, 1.2 mmol) was added and stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layers were washed with saturated sodium bicarbonate,

brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 50% ethyl acetate/hexanes) afforded **2195** (115 mg). HPLC-MS t_R = 1.17 min ($UV_{254\ nm}$); mass calculated for formula $C_{16}H_{19}N_3O_2S$ 317.1, observed LCMS m/z 318.1 (M+H).

Part E:

Compound **2195** (115 mg, 0.36 mmol) was dissolved in 30% HBr/AcOH (2 mL) and stirred for 2 hours. The solvent was removed under reduced pressure and the residue was dissolved in water and washed with diethyl ether. The aqueous layer was lyophilized to provide **2196** as a di-HBr salt (100 mg).

Example 51I:



2197 2198 2199 2200 2201

Part A:

Compound **2197** (2.3 g, 10.6 mmol), 4-chloro-2,6-dimethoxytriazine (2.4 g, 13.9 mmol) and NMM (7.3 mL, 53 mmol) were dissolved in THF (50 mL) and stirred for 1 hour. N,O- dimethylhydroxylamine hydrochloride (2.05 g, 21.2 mmol) was added and the reaction mixture was stirred overnight at room temperature. The reaction mixture was partitioned between ethyl acetate and water. The organic layers were washed with 1N HCl, saturated sodium bicarbonate, brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 50% ethyl acetate/hexanes) afforded **2198** (2.0 g). ^1H NMR (400 MHz, $CDCl_3$) δ 4.70-4.60 (m, 1H), 3.75 (m, 3H), 3.60-3.40 (m, 2H), 3.20 (s, 3H), 2.20 (m, 1H), 2.00-1.80 (m, 3H), 1.50-1.40 (m, 9H).

Part B:

Compound **2198** (550 mg, 2.13 mmol) was dissolved in THF (10 mL) and a solution of lithium (trimethylsilyl)acetylide (0.5 M in THF, 12 mL) was added dropwise and stirred overnight. The reaction mixture was partitioned between

ethyl acetate and 1N HCl. The organic layer was washed with 1N HCl, saturated sodium bicarbonate, brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 20% ethyl acetate/hexanes) afforded **2199** (370 mg). HPLC-MS t_R = 1.69 min ($UV_{254\ nm}$); mass calculated for formula $C_{12}H_{17}NO_3$ 223.1, observed LCMS m/z 168.1 (M-(t-butyl)).

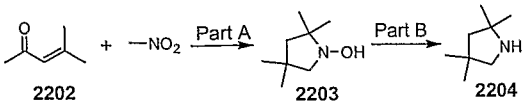
Part C:

Compound **2199** (350 mg, 1.56 mmol) and diethylamine (228 mg, 3.13 mmol) were dissolved in EtOH (1.5 mL) and water (1.5 mL) and stirred for 3 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layers were washed with saturated sodium bicarbonate, brine, dried over sodium sulfate and concentrated. The residue was combined with methyl guanidine hydrochloride (756 mg, 7.8 mmol) and sodium carbonate (826 mg, 7.8 mmol) in EtOH (6 mL) and refluxed for 48 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with saturated sodium bicarbonate, brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 80% ethyl acetate/hexanes) afforded **2200** (210 mg). HPLC-MS t_R = 1.26 min ($UV_{254\ nm}$); mass calculated for formula $C_{14}H_{22}N_4O_2$ 278.1, observed LCMS m/z 279.1 (M+H).

Part D:

Compound **2200** (105 mg, 0.377 mmol) was dissolved in 4 M HCl in dioxane (2 mL) and methanol (0.5 mL) and stirred at room temperature for 1 hr. The reaction mixture was concentrated and triturated with diethyl ether to afford **2201** (74 mg) as an HCl salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.00 (bs, 1H), 8.70 (bs, 1H), 8.30 (s, 1H), 6.70 (d, 1H), 4.60 (bs, 1H), 3.40 (m, 2H), 2.75 (s, 3H), 2.40 (m, 1H), 2.00-1.80 (m, 3H).

Example 51J:



2202 2203 2204

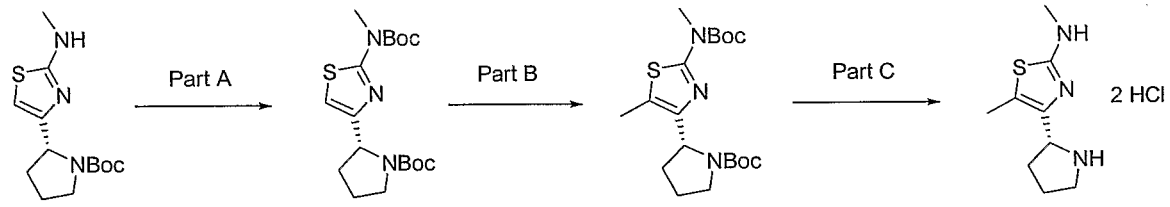
Part A:

Compound **2203** was prepared according to a procedure described in *J. Org. Chem.* **1991**, *57*, 7034-7038.

Part B:

A mixture of **2203** (200 mg, 1.42 mmol) and zinc dust (278 mg, 4.25 mmol) in concentrated hydrochloric acid (1.4 mL) and water (5.8 mL) was stirred at reflux overnight. The mixture was made basic with potassium hydroxide pellets, decanted and the aqueous solution extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated to give **2204** as a yellow sticky solid (95 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.35 (m, 2H), 1.88 (s, 2H), 1.66 (s, 6H), 1.30 (s, 6H).

Example 51K:



2205 **2206** **2207** **2208**

Compound **2205** was prepared using procedures described in Example 10B.

Part A:

To the solution of 2-methylaminothiazole **2205** (100 mg, 0.35 mmol) and DMAP (135 mg, 1.0 mmol) in THF (5 mL), Boc_2O (218 mg, 1.0 mmol) was added at room temperature. The resulting mixture was stirred overnight and then diluted with ethyl acetate (30 mL). The organics was washed with water, Brine and dried over sodium sulfate and concentrated. The residue which was purified by column chromatography (SiO_2, 20% ethyl acetate/hexanes) afforded the protected product **2206** (130 mg) as semi-oil. HPLC-MS t_R = 2.42

min ($UV_{254\ nm}$); mass calculated for formula C18H29N3O4S 383.2, observed LCMS m/z 384.1 (M+H).

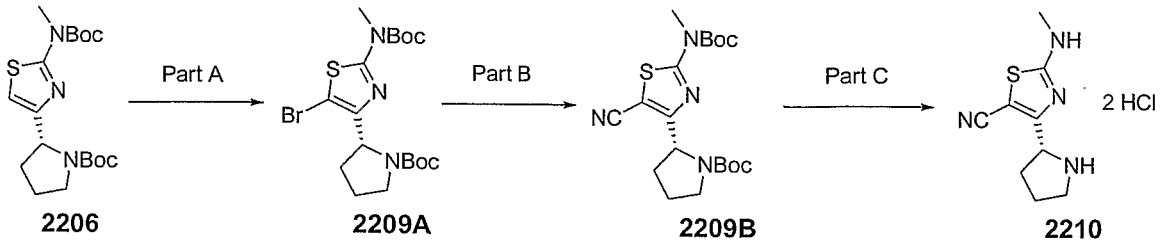
Part B:

The solution of thiazole **2206** (150 mg, 0.39 mmol) in THF (5 mL) was cooled to –78 °C, and *n*-BuLi (2.5 M in hexane, 0.19 mL, 0.47 mmol) was added slowly. The resulting mixture was stirred at –78 °C for 30 min, and then iodomethane (0.1 mL, 1.55 mmol) was added. The mixture was stirred for another 30 min followed by the addition of saturated NH_4Cl solution (15 mL). The aqueous layer was extracted with ethyl acetate. The combined organics were washed with water, brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 10% ethyl acetate/hexanes) afforded recovered thiazole **2206** (36 mg) and **2207** (100 mg). HPLC-MS t_R = 2.51 min ($UV_{254\ nm}$); mass calculated for formula C19H31N3O4S 397.2, observed LCMS m/z 398.2 (M+H).

Part C:

To a solution of 5-methylthiazole **2207** (100 mg, 0.25 mmol) in dioxane (2 mL) was added HCl (4N in dioxane, 4 mL) followed by water (0.5 mL). The mixture was stirred at room temperature for 1 hour and concentrated. The resulting residue **2208** (72 mg) was dried under vacuum and used in the next step without further purification.

Example 51L:



2206 **2209A** **2209B** **2210**

Part A:

To the solution of thiazole **2206** (190 mg, 0.5 mmol) in chloroform (5 mL), NBS (107 mg, 0.6 mmol) was added. The mixture was heated to 50 °C and stirred for 1 hour. After cooling to room temperature, the mixture was concentrated and purified by column chromatography (SiO_2, 10% ethyl acetate/hexanes) to afford 5-bromothiazole **2209A** (221 mg). HPLC-MS t_R = 2.65 min ($UV_{254\ nm}$); mass calculated for formula C18H28BrN3O4S 461.1, observed LCMS m/z 462.1 (M+H).

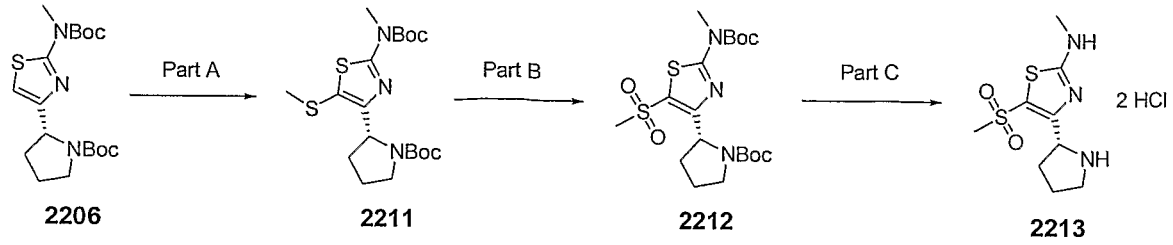
Part B:

A mixture of 5-bromothiazole **2209A** (221 mg, 0.48 mmol), $Zn(CN)_2$ (117 mg, 1.0 mmol), $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and DPPF (55 mg, 0.1 mmol) in a 25-ml round bottom flask was flushed with argon for 3 min. Under the argon, DMA (3 mL) was added and the flask was sealed under the argon atmosphere. The mixture was heated to 85 °C and stirred overnight. After cooling to room temperature, ethyl acetate (30 mL) was added to dilute the reaction mixture and the solution was filtered through celite. The filtrate was concentrated and purified by column chromatography (SiO_2, 10% ethyl acetate/hexanes) to afford 5-cyanothiazole **2209B** (167 mg) as oil. HPLC-MS t_R = 2.39 min ($UV_{254\ nm}$); mass calculated for formula C19H28N4O4S 408.2, observed LCMS m/z 409.2 (M+H).

Part C:

Compound **2210** (110 mg) was prepared from **2209B** (167 mg, 0.41 mmol) according to the procedure described in Example 51K Part C. HPLC-MS t_R = 0.62 min ($UV_{254\ nm}$); mass calculated for formula C9H12N4S 208.1, observed LCMS m/z 209.1 (M+H).

Example 51M:



2206 2211 2212 2213

Part A:

A solution of *n*-BuLi (2.5 M in hexane, 0.24 mL, 0.6 mmol) was added slowly to a solution of thiazole **2206** (190 mg, 0.5 mmol) in THF (5 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 1 hour, and then methyl disulfide (94 mg, 1.0 mmol) was added. The mixture was stirred for another one hour, and then warmed to room temperature slowly. Then saturated NH_4Cl solution was added to quench the reaction. The mixture was extracted with ethyl acetate (30 mL x 3). The combined organics were dried over sodium sulfate, concentrated and purified by column chromatography (SiO_2, 10% ethyl acetate/hexanes) to afford 5-methylsulfidethiazole **2211** (137 mg) and recovered thiazole **2206** (38 mg). HPLC-MS t_R = 2.62 min ($UV_{254\ nm}$); mass calculated for formula C19H31N3O4S2 429.2, observed LCMS m/z 430.1 (M+H).

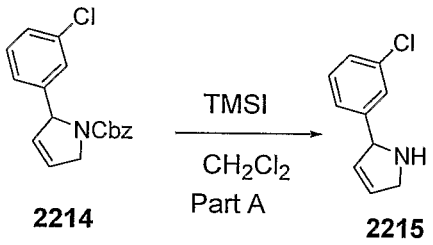
Part B:

A mixture of sulfide **2211** (137 mg, 0.32 mmol) and m-CPBA (~77%, 230 mg, 1.0 mmol) in dichloromethane (10 mL) was stirred at room temperature overnight. Ethyl acetate (80 mL) was added to dilute the mixture and the organics were washed with saturated sodium bicarbonate solution twice followed by brine, dried over sodium sulfate, concentrated. The residue was purified by column chromatography (SiO_2, 20% ethyl acetate/hexanes) afforded 5-methylsulfonethiazole **2212** (141 mg). HPLC-MS t_R = 2.62 min ($UV_{254\ nm}$); mass calculated for formula C19H31N3O6S2 461.2, observed LCMS m/z 406.1 (M+H- *t*-Bu).

Part C:

Compound **2213** (110 mg) was prepared from **2212** (141 mg, 0.30 mmol) according to the procedure described in Example 51K Part C. HPLC-MS t_R = 0.63 min ($UV_{254\ nm}$); mass calculated for formula C9H15N3O2S2 261.1, observed LCMS m/z 262.0 (M+H).

Example 51N:



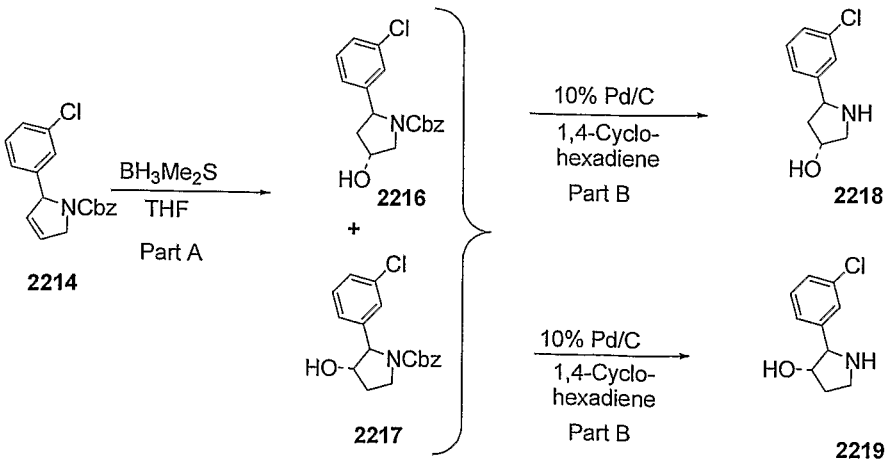
2214 **2215**

Starting pyrroline derivative **2214** was prepared by known methods (Billet, M; Schoenfelder, A; Klotz, P.; Mann, A.. *Tetrahedron Letters,* 2002, 1453).

Part A:

Trimethylsilyl iodide (0.44 g, 2.24 mmol) was added dropwise to a solution of **2214** (0.47 g, 1.5 mmol; 20 mL CH_2Cl_2) at room temperature and stirred for 3 hours. The mixture was cooled to 0 °C before quenching with methanol (5 mL). The solvent was removed under reduced pressure to provide crude amine **2215,** which was used without further purification.

Example 51O:



2214 **2216** + **2217** **2218** **2219**

Part A:

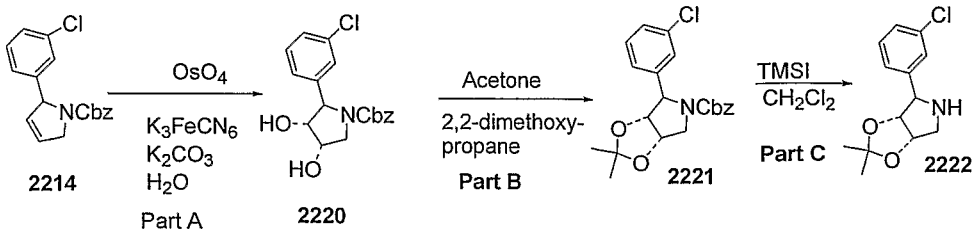
Borane dimethyl sulfide (2.0 M solution in toluene, 1.45 mL, 2.9 mmol) was added dropwise to a solution of intermediate **2214** (0.65 g, 2 mmol) in THF (10 mL) at 0 °C. After addition, the mixture was stirred at room temperature for 3 hours. The reaction mixture was quenched with dropwise addition of water (1.0 mL) and 3N NaOH (3.0 mL). The resulting mixture was stirred for 5 minutes and then cooled to 0 °C before adding 30% H_2O_2 (6.0 mL) dropwise. The mixture was stirred at ambient temperature for 2 hours and then treated with 5% $Na_2S_2O_3$ (25 mL) and stirred additional half hour. The reaction mixture was diluted with ethyl acetate (100 mL), and the organics were washed with brine, dried (Na_2SO_4), filtered, and concentrated under vacuum to provide a crude residue which was purified by silica-gel column chromatography (1:3 to 1:2 ethyl acetate / hexane) to give first intermediate **2217** (0.3 g, 44%) followed by intermediate **2216** (0.2 g, 29%).

Part B:

Intermediate **2216** (0.075 g, 0.22 mmol) was dissolved in ethyl alcohol (1.5 mL). Then 1,4-cyclohexadiene (0.21 mL, 2.24 mmol) was added, followed by addition of 10% Pd/C under N_2. The reaction mixture was stirred at r.t. for 2 hours, filtered through celite and concentrated under vacuum to give intermediate **2218** (0.035 g, 80%).

Compound **2219** was prepared by using methods similar to those described in Parts A-B for intermediate **2218.**

Example 51P:



Part A:

Intermediate **2214** (0.1 g, 0.3 mmol) was dissolved in *t*-butanol (3 mL) and water (3 mL). Potassium hexacyanoferrate (0.31 g, 0.94 mmol) and potassium

carbonate (0.13 g, 0.94 mmol) were added and stirred for 15 minutes. To this mixture osmium tetraoxide (0.005 g, 0.02 mmol) was added and stirred for 16 h. The reaction was diluted with ethyl acetate (50 mL) and the organics were washed once with brine (10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to provide intermediate **2220** (0.1 g, 91%).

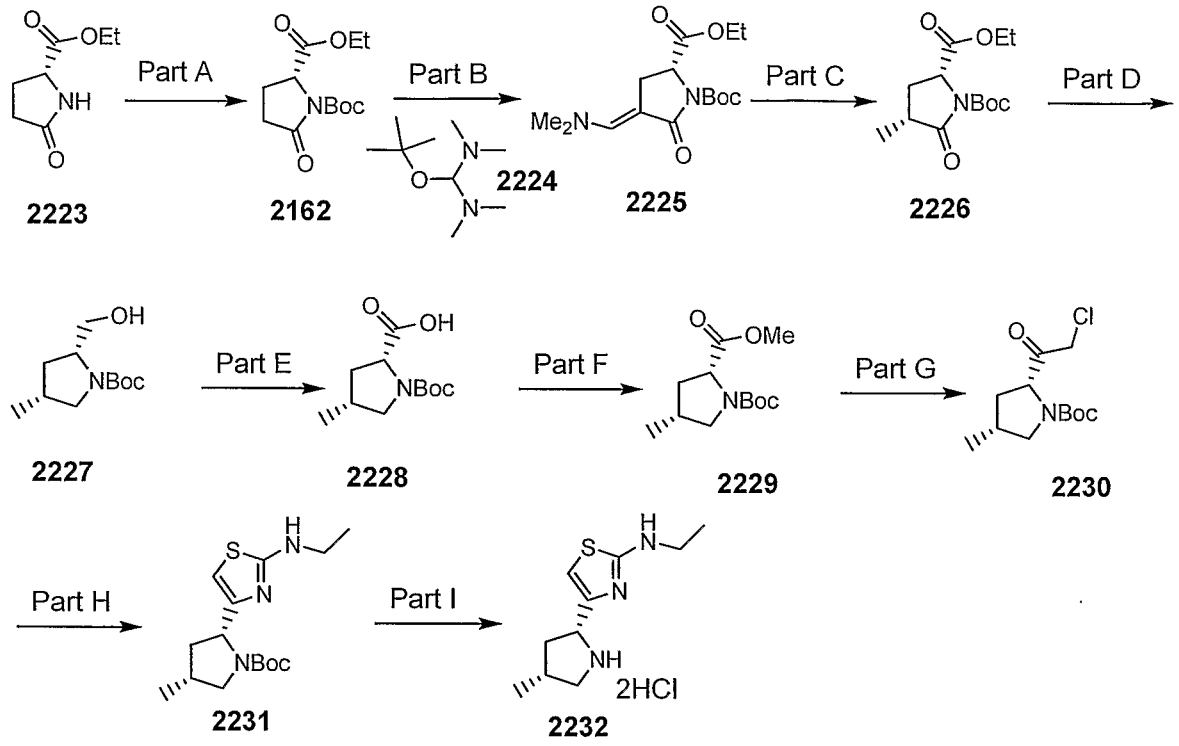
Part B:

Diol **2220** (0.1 g, 0.28 mmol) was dissolved in acetone (5 mL) and 2,2-dimethoxypropane (0.045 g, 0.43 mmol) was added, followed by addition of catalytic amount of p-toluenesulfonic acid (0.06 g, 0.03 mmol). The reaction mixture was stirred at room temperature for 14 h. The solvent was removed under vacuum to provide a crude product which was purified by silica-gel preparative chromatography using ethyl acetate/hexane (1/3) as the eluting solvent to yield **2221** (0.075 g, 68%).

Part C:

Intermediate **2221** (0.06 g, 0.15 mmol) was dissolved in CH_2Cl_2 (0.5 mL), followed by addition of trimethylsilyl iodide (0.034 mL, 0.24 mmol) at 0 °C. The mixture was stirred at r.t. for 2 hours. The reaction was quenched with methanol (5 mL) and stirred for another 2 hours. The reaction mixture was concentrated to provide the crude amine **2222**, which was used without additional purification.

Example 51Q:



Part A:

Compound **2223** (2.2 g, 13.9 mmol) was dissolved in methylene chloride (25 mL) and triethylamine (3.9 mL, 27.8 mmol), DMAP (100 mg), and di-*t*-butyldicarbonate (3.33 g, 15.3 mmol) were added. The reaction mixture was stirred for 5 hours at room temperature and then diluted with water and methylene chloride. The organic layers were washed with 1N HCl, saturated sodium bicarbonate, water, brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 33% ethyl acetate/hexanes) afforded the desired product (3.0 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.60 (m, 1H), 4.20 (q, 2H), 2.70-2.60 (m, 1H), 2.50 (m, 1H), 2.40-2.30 (m, 1H), 2.05 (m, 1H), 1.50 (s, 9H), 1.20 (t, 3H).

Part B:

Compound **2162** (630 mg, 2.44 mmol) was added to *t*-butoxy-bis(dimethylamino)methane (**2224**) (0.705 mL, 3.42 mmol) and stirred at 80 °C overnight. The excess reagent was removed under reduced pressure to provide **2225** that was used without purification (750 mg). ^{1}H NMR (400

MHz, $CDCl_3$) δ 7.10 (m, 1H), 4.50 (m, 1H), 4.30-4.20 (m, 2H), 3.30 (m, 1H), 3.00 (s, 6H), 2.80 (m, 1H), 1.50 (s, 9H), 1.30 (m, 3H).

Part C:

Compound **2225** (750 mg, 2.4 mmol) was dissolved in ethyl acetate (12 mL) and 10% Pd-C (200 mg) was added under an argon atmosphere. The reaction mixture was placed under a hydrogen atmosphere and stirred for 96 hours at room temperature. The reaction was filtered and the solvent was evaporated. Purification by column chromatography (SiO_2, 33% ethyl acetate/hexanes) afforded the desired product (350 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 4.50 (m, 1H), 4.25 (q, 2H), 2.60 (m, 2H), 1.65 (m, 1H), 1.50 (s, 9H), 1.32 (t, 3H), 1.28 (d, 3H).

Part D:

Compound **2226** (200 mg, 0.73 mmol) was dissolved in THF (2 mL) and borane dimethyl sulfide (2M in THF, 1.5 mL) was added. The reaction mixture was stirred for 40 hours and then cooled in an ice bath and quenched slowly with methanol. The solvent was evaporated and the residue was purified by column chromatography (SiO_2, 33% ethyl acetate/hexanes) to afford the desired product (80 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 3.95 (m, 1H), 3.75-3.50 (m, 3H), 2.75 (t, 1H), 2.25 (m, 2H), 1.50 (s, 9H), 1.20 (m, 1H), 1.00 (d, 3H).

Part E:

Compound **2227** (70 mg, 0.32 mmol) was dissolved in acetone (3 mL) and Jones Reagent (1 mL) was added dropwise. The reaction mixture was stirred overnight and then quenched with methanol. The mixture was then filtered and concentrated. The residue was dissolved in saturated sodium bicarbonate and washed with diethyl ether. The aqueous layer was acidified to pH 2 and then extracted with ethyl acetate. The ethyl acetate layers were dried over sodium sulfate and concentrated to provide the desired product (55 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 4.30-4.20 (m, 1H), 3.80-3.70 (m, 1H), 2.95

(m, 1H), 2.50-2.30 (m, 1H), 2.25 (m, 1H), 1.80-1.60 (m, 1H), 1.50 (d, 9H), 1.05 (m, 3H).

Part F:

Compound **2228** (370 mg, 1.62 mmol) was dissolved in toluene (2 mL) and methanol (2 mL) and cooled in an ice bath. A solution of trimethylsilyl diazomethane (2M in hexanes, 1.5 mL) was added dropwise. The solution was stirred for 1 hour and then concentrated. The residue was dissolved in ethyl acetate and water. The organic layer was washed with 1N HCl, saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated to provide the methyl ester **2229** (310 mg).

Part G:

In a separate flask diisopropylamine (1.0 mL) was dissolved in THF (10 mL) and cooled to -78 °C. A solution of *n*-butyl lithium (2.5 M in hexanes, 2.55 mL) was added dropwise and stirred for 30 minutes. This solution was added dropwise to a solution of the methyl ester **2229** (310 mg, 1.27 mmol) and chloroiodomethane (0.9 g, 5.08 mmol) in THF (5 mL) at -78 °C. After thirty minutes the reaction was quenched dropwise with acetic acid (1 mL) in THF (5 mL). The reaction mixture was warmed to room temperature and diluted with water and ethyl acetate. The organic layer was dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 25% ethyl acetate/hexanes) afforded the desired alpha-chloro ketone **2230** (150 mg).

Part H:

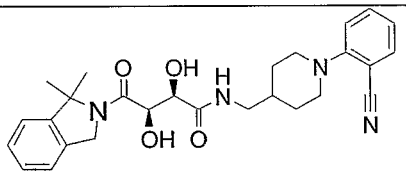
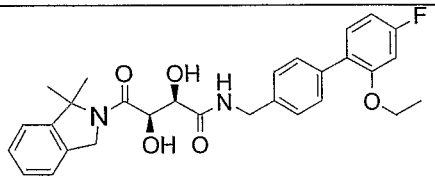
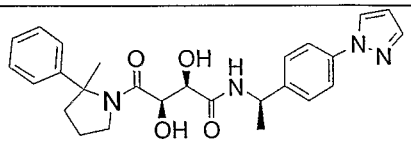
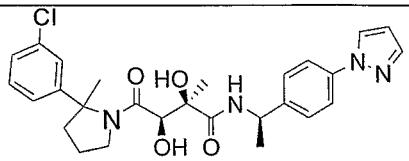
The alpha-chloro ketone **2230** (150 mg, 0.575 mmol) was dissolved in DMF (5 mL) and ethyl thiourea (134 mg, 1.15 mmol) was added and stirred at 80 °C overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, ethyl acetate) afforded the desired product **2231** (85 mg). HPLC-MS t_R = 1.35 min

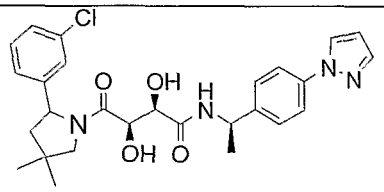
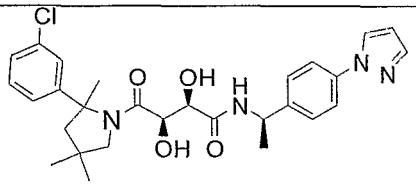
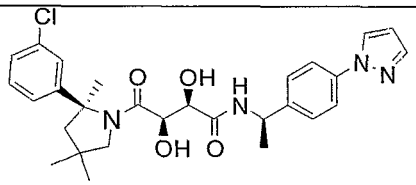
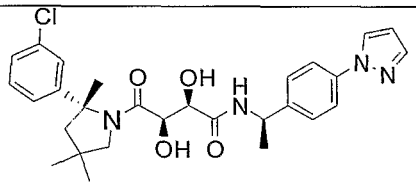
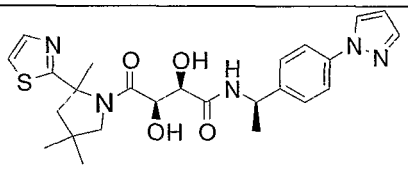
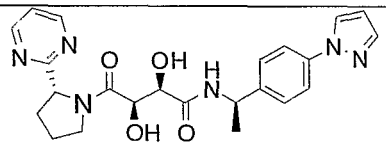
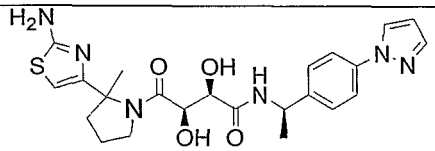
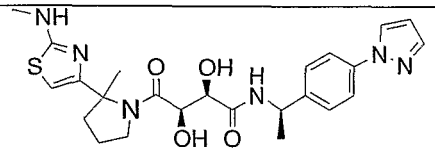
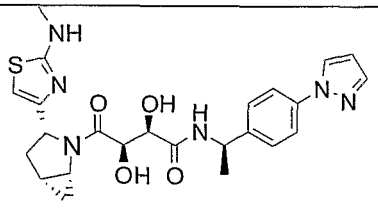
($UV_{254\ nm}$); mass calculated for formula $C_{15}H_{25}N_3O_2S$ 311.1, observed LCMS m/z 312.1 (M+H).

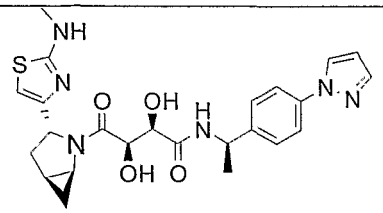
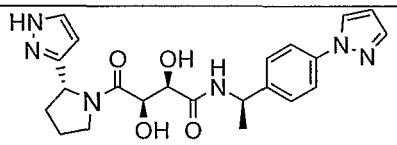
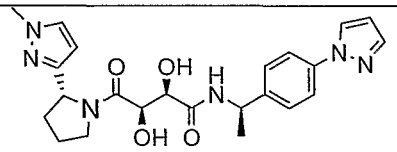
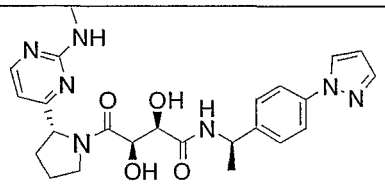
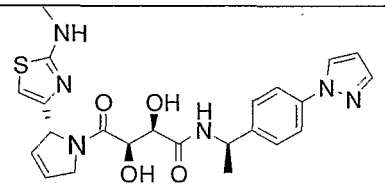
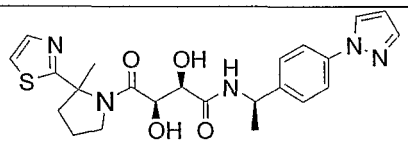
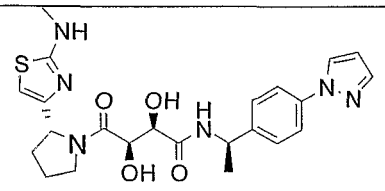
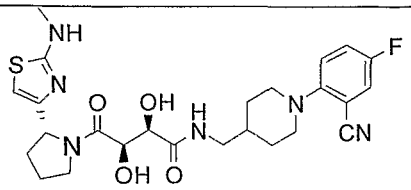
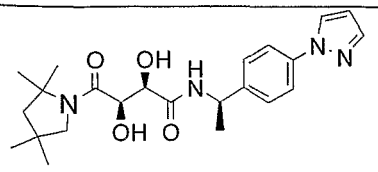
Part I:

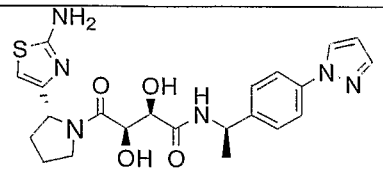
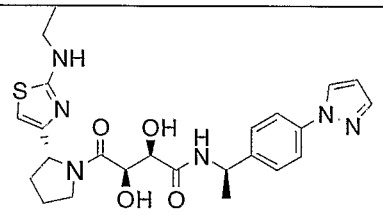
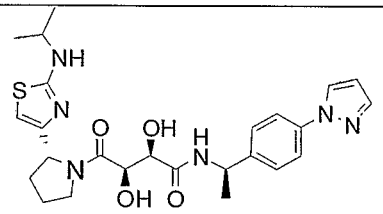
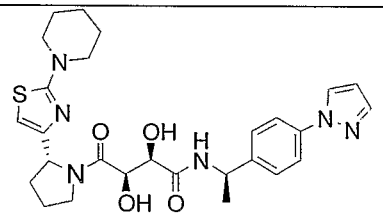
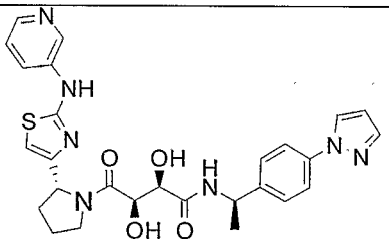
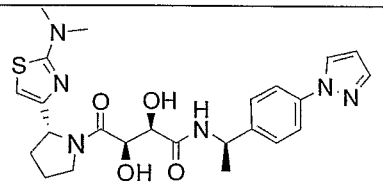
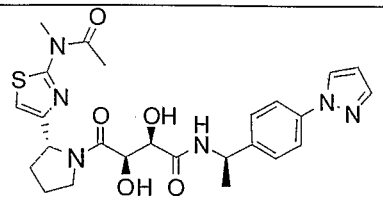
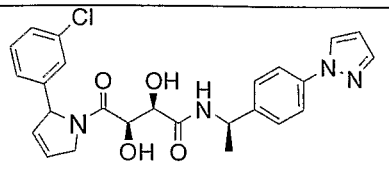
Compound **2231** (85 mg, 0.30 mmol) was dissolved in 4M HCl in dioxane (2mL) and methanol (0.5 mL) and stirred for 30 minutes. The solvents were removed to provide **2232** as a di-HCl salt (65 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.50 (bs, 1H), 8.70 (bs, 1H), 7.80 (bs, 1H), 6.70 (s, 1H), 4.50 (m, 1H), 3.30-3.20 (m, 2H), 2.75-2.65 (m, 2H), 2.40 (m, 2H), 1.70 (m, 1H), 1.15 (t, 3H), 1.10 (d, 3H).

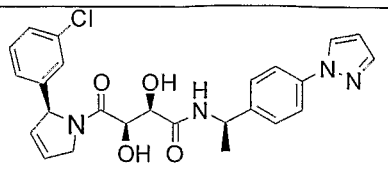
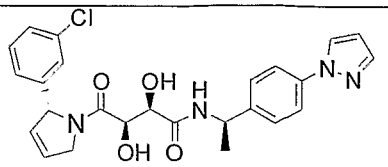
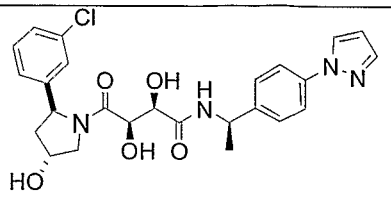
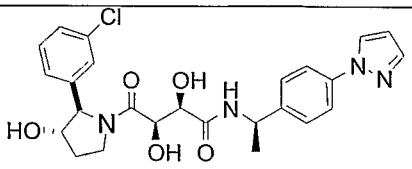
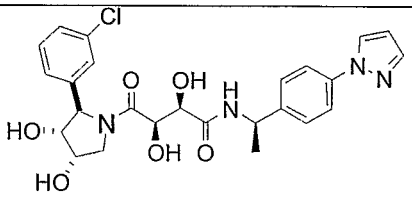
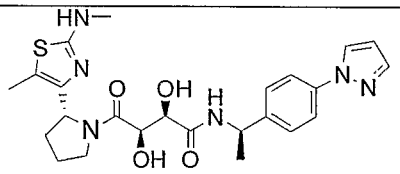
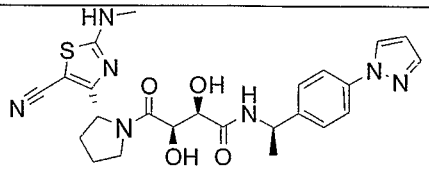
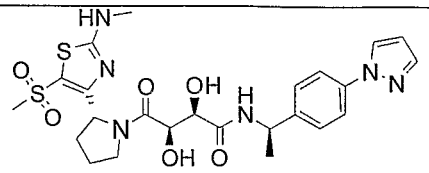
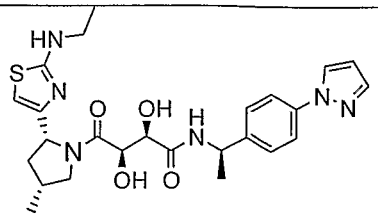
The following compounds were prepared using previously described procedures.

Compound #	Structure	Exact mass	MS m/z (M+H)
2233		494.2	495.2
2234		506.2	507.1
2235		462.2	463.1
2236		510.2	511.1

2237		510.2	511.1
2238		524.2	525.1
2239		524.2	525.1
2240		524.2	525.1
2241		497.2	498.1
2242		450.2	451.1
2243		484.1	485.0
2244		498.2	499.1
2245		496.2	497.1

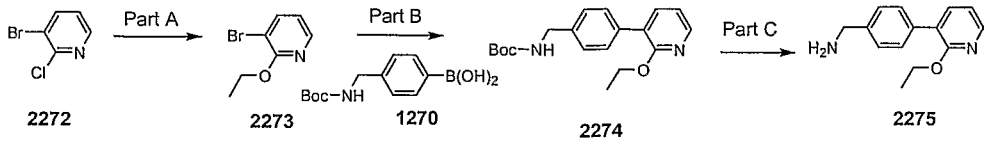
2246		496.2	497.1
2247		438.2	439.1
2248		452.2	453.1
2249		479.2	480.1
2250		482.2	483.1
2251		469.2	470.0
2252		484.2	485.1
2253		530.2	531.1
2254		428.2	429.2

2255		470.2	471.1
2256		498.2	499.1
2257		512.2	513.1
2258		538.2	539.2
2259		547.2	548.2
2260		498.2	499.1
2261		526.2	527.1
2262		480.2	481.1

2263		480.2	481.1
2264		480.2	481.3
2265		498.2	499.1
2266		498.2	499.1
2267		514.2	515.1
2268		498.2	499.1
2269		509.2	510.1
2270		562.2	563.0
2271		512.2	513.1

Example 52:

Example 52A:



Part A:

Sodium pellets (1.0 g, 43 mmol) were dissolved in ethanol (35 mL). Compound **2272** (1.4 g, 7.2 mmol) was added to the solution and the reaction was refluxed overnight. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated to afford **2273** (1.3 g). The product was used without further purification. HPLC-MS t_R = 1.92 min ($UV_{254\ nm}$); mass calculated for formula C_7H_8NOBr 201.0, observed LCMS m/z 202.1 (M+H).

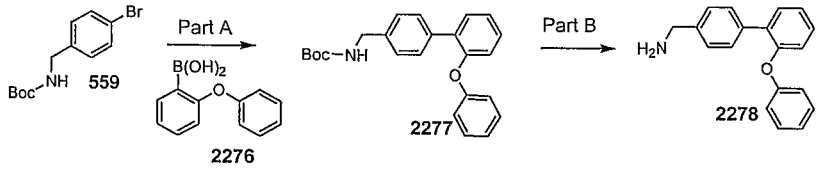
Part B:

Compound **2273** (171 mg, 0.8592 mmol) was dissolved in toluene (10 mL). The boronic acid **1270** (409 mg, 1.69 mmol), $Pd_2(dba)_3$ (38 mg, 0.0423 mmol), S-PHOS (34 mg, 0.084 mmol), potassium phosphate (358 mg, 1.69 mmol) were added to the solution and stirred at reflux overnight. The reaction mixture was cooled to room temperature and filtered, and the toluene was removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The combined organic layers were dried over sodium sulfate and concentrated to afford **2274** (190 mg). The material was used without further purification. HPLC-MS t_R = 2.21 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{24}N_2O_3$ 328.2, observed LCMS m/z 329.2 (M+H).

Part C:

Compound **2274** (190 mg, 0.584 mmol) was dissolved in methylene chloride (4 mL) and TFA (1 mL) and stirred for 30 minutes. The solvents were removed to provide **2275** as the TFA salt (190 mg).

Example 52B:



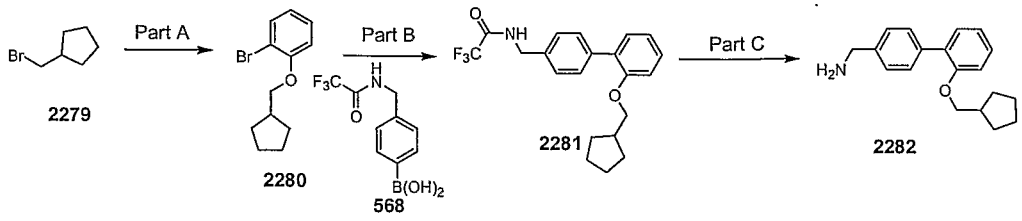
Part A:

Compound **559** (100 mg, 0.35 mmol) was dissolved in dioxane (5 mL). Then boronic acid **2276** (113 mg, 0.52 mmol), $Pd_2(dba)_3$ (27 mg, 0.03 mmol), triphenylphosphine (13.7 mg, 0.052 mmol), potassium phosphate (148 mg, 0.70 mmol) were added to the solution and stirred at reflux overnight. The reaction mixture was cooled to room temperature and filtered, and the toluene was removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The combined organic layers were dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 25% ethyl acetate/hexanes) afforded **2277** (80 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, 1H), 7.45 (m, 2H), 7.30-7.15 (m, 5H), 7.20-7.10 (m, 2H), 7.00-6.90 (m, 3H), 4.30 (d, 2H), 1.45 (s, 9H).

Part B:

Compound **2277** (80 mg, 0.21 mmol) was dissolved in 4 M HCl in dioxane (2 mL) and stirred at room temperature for 1 hr. The reaction was diluted with diethyl ether (5 mL) and **2278** (60 mg) was collected by filtration.

Example 52C:



Part A:

Compound **2279** (500 mg, 3.08 mmol), cesium carbonate (3.0 g, 9.25 mmol), and 2-bromophenol (527 mg, 3.08 mmol) were dissolved in DMF (15 mL) and

stirred at 60 °C for 2 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layers were washed with saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated. Purification by column chromatography (SiO_2, 10% ethyl acetate/hexanes) afforded **2280** (400 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 1H), 7.20 (m, 1H), 6.85 (d, 1H), 6.80 (t, 1H), 3.90 (d, 2H), 2.40 (m, 1H), 1.85 (m, 2H), 1.60-1.45 (m, 4H), 1.40 (m, 2H).

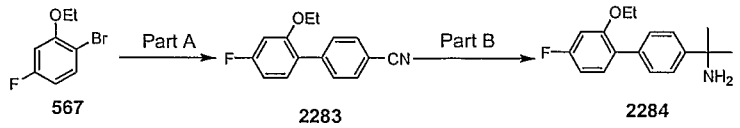
Part B:

Compound **2280** (157 mg, 0.50 mmol), compound **568** (250 mg, 1.02 mmol), $Pd_2(dba)_3$ (9.1 mg, 0.01 mmol), S-PHOS (8.3 mg, 0.02 mmol), potassium fluoride (350 mg, 3.0 mmol) were dissolved in dioxane (8 mL) and stirred at reflux overnight. The reaction mixture was cooled to room temperature and filtered, and the toluene was removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The combined organic layers were dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 10% ethyl acetate/hexanes) afforded **2281** (200 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (m, 2H), 7.40 (m, 2H), 7.30 (m, 2H), 7.00 (m, 2H), 4.60 (d, 2H), 3.85 (d, 2H), 2.35 (m, 1H), 1.80 (m, 2H), 1.60 (m, 4H), 1.30 (m, 2H).

Part C:

Compound **2281** (100 mg, 0.317 mmol) was dissolved in MeOH (5 mL) and a saturated solution of potassium carbonate (1 mL) was added and the reaction was stirred for 3 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layers were washed with saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated to afford **2282** (40 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, 2H), 7.40 (m, 4H), 7.00 (m, 2H), 4.60 (d, 2H), 3.85 (d, 2H), 2.35 (m, 1H), 1.80 (m, 2H), 1.60 (m, 4H), 1.35 (m, 2H).

Example 52D:



567 2283 2284

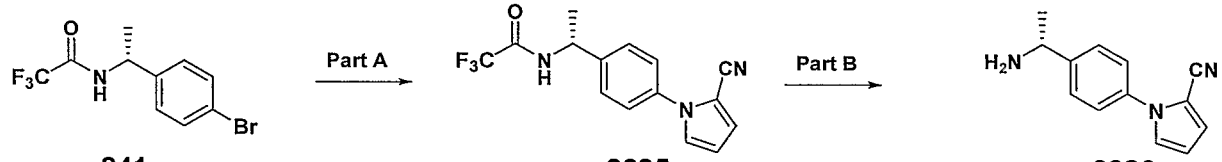
Part A:

Compound **567** (500 mg, 2.29 mmol), 4-cyanophenylboronic acid (483 mg, 3.43 mmol), $Pd_2(dba)_3$ (70 mg, 0.08 mmol), triphenylphosphine (70 mg, 0.26 mmol), potassium phosphate (970 mg, 4.58 mmol) were dissolved in dioxane (15 mL) and stirred at reflux overnight. The reaction mixture was cooled to room temperature and filtered and the dioxane was removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The combined organic layers were dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 5% ethyl acetate/hexanes) afforded **2283** (240 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 7.70-7.58 (m, 4H), 7.27-7.23 (m, 1H), 6.75-6.70 (m, 2H), 4.05 (q, 2H), 1.38 (t, 3H).

Part B:

Compound **2284** was prepared according to the procedure in *J. Org. Chem.* **1992**, *57*, 4521-4527.

Example 52E:



841 2285 2286

Part A:

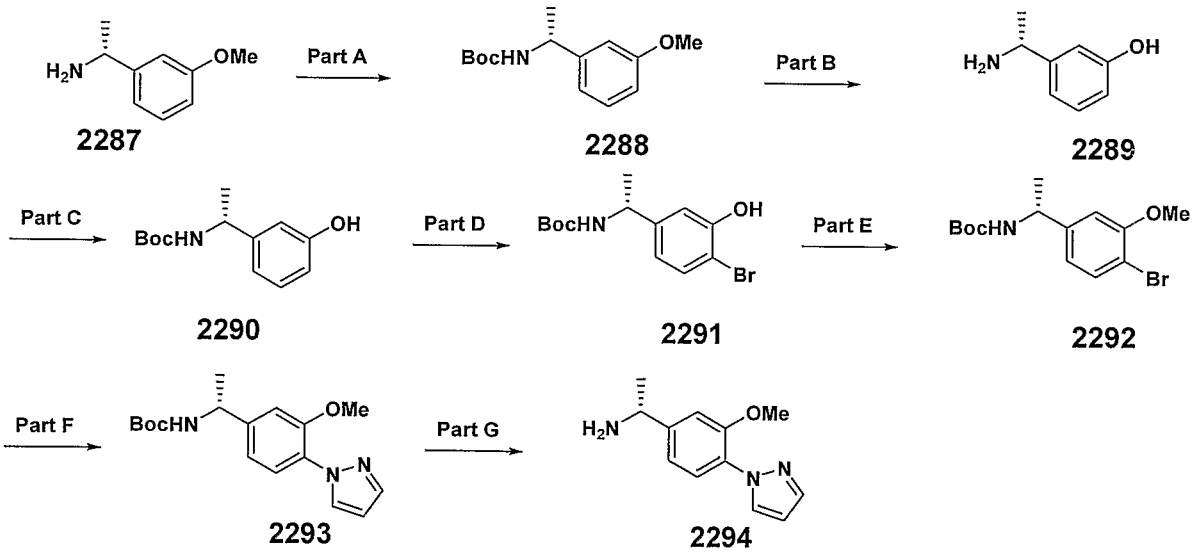
To a mixture of compound **841** (2.96 g, 10 mmol), pyrrole-2-carbonitrile (1.1 g, 12 mmol) and 1,10-phenanthroline (1.17 g, 6.5 mmol) in DMA (10 mL) was added cesium carbonate (6.52 g, 20 mmol) and CuI (0.42 g, 2.2 mmol) and the mixture was heated at 150 °C for 18 hours. The mixture was filtered and rinsed with EtOAc (100 mL). The filtrate was washed with water (2 x 10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated. Purification by column chromatography (SiO_2, 10% EtOAc/hexane followed by 20%

EtOAc/hexane) afforded compound **2285** as an oil (0.17 g, 5.7%).

Part B:

A mixture of compound **2285** (0.17 g, 0.57 mmol) and aq. 1M LiOH (1 mL, 1 mmol) in dioxane (3 mL) was stirred at room temperature for 18 hours. The reaction mixture was concentrated and added water (2 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (SiO_2, 1% MeOH/ CH_2Cl_2 followed by 5% MeOH/ CH_2Cl_2) afforded compound **2286** as an oil (0.085 g, 71%).

Example 52F:



Part A:

To a solution of compound **2287** (20.6 g, 136.4 mmol) in CH_2Cl_2 (200 mL) was added triethylamine (27.5 g, 272.8 mmol) and the reaction mixture was cooled to 0 °C, and $(Boc)_2O$ (32.7 g, 150 mmol) was added. The mixture was stirred at 0 °C for 10 minutes and then warmed to room temperature and stirred for 4 hours. The reaction mixture was washed with aq. sat. NH_4Cl (100 mL) and dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (SiO_2, 10% EtOAc/hexane followed by 15% EtOAc/hexane)

afforded the compound **2288** as white solid (32.7 g, 95%).

Part B:

To a solution of compound **2288** (3.95 g, 15.7 mmol) in CH_2Cl_2 (200 mL) at -78 °C was added a solution of 1M BBr_3/CH_2Cl_2 (37 mL) dropwise via a dropping funnel over 15 minutes. The reaction mixture was stirred at -78 °C for 2 hours, then poured carefully into MeOH (100 mL) and concentrated to a brown tar (3.6 g). Trituration with ether (3 x 20 mL) and concentrated afforded compound **2289** as brown tar which was used in next reaction without further purification.

Part C:

The crude compound **2289** was suspended in CH_2Cl_2 (100 mL) and triethylamine (8.8 mL, 63 mmol) was added. The reaction mixture was cooled to 0 °C and $(Boc)_2O$ (3.77 g, 17.3 mmol) was added. The mixture was stirred at room temperature for 1 hour. The reaction mixture was then washed with water (100 mL), sat. $NaHCO_3$ (25 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (SiO_2, 10% EtOAc/hexane followed by 15% EtOAc/hexane and 20% EtOAc/hexane) afforded compound **2290** as an oil (1.85 g, 62% over two steps).

Part D:

To a solution of compound **2290** (0.45 g, 1.9 mmol) in CH_2Cl_2 (10 mL) was added a solution of NBS (0.34 g, 1.9 mmol) in CH_2Cl_2 (10 mL) via a dropping funnel. Stirred at room temperature for 3.5 hours and then washed with aq. 10% H_2SO_4 (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (SiO_2, 100% CH_2Cl_2 followed by 1% EtOAc/CH_2Cl_2) afforded compound **2291** (0.13 g, 21%).

Part E:

To a solution of compound **2291** (0.22 g, 0.7 mmol) in acetone (6 mL) was

added K_2CO_3 (0.288 g, 2.1 mmol) followed by a solution of methyl iodide (0.065 mL, 1.05 mmol) and the reaction mixture was stirred at room temperature for 18 hours. The mixture was filtered and concentrated to dryness. The residue was dissolved in EtOAc (20 mL) and washed with water (2 mL) followed by brine (2 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to afford the compound **2292** (0.2 g, 86%).

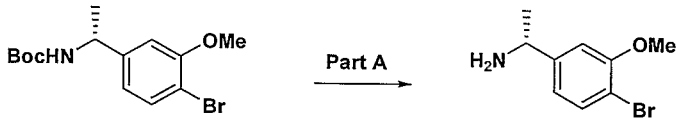
Part F:

Compound **2293** was prepared following the procedure described in Example 52E, Part A.

Part G:

Compound **2294** was prepared from compound **2293** via TFA deprotection as described in Example 1.

Example 52G:

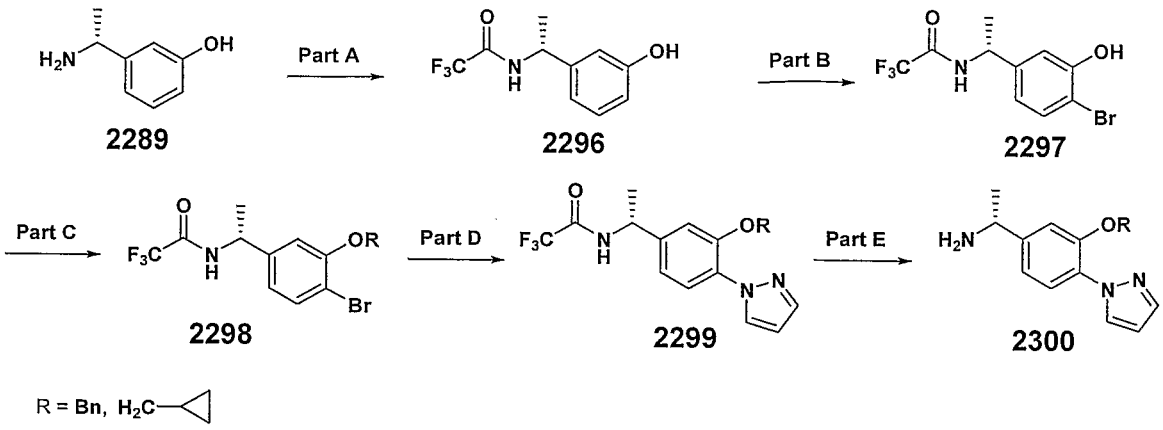


2292 **2295**

Part A:

Compound **2295** was prepared from compound **2292 2293** via TFA as described in Example 1.

Examples 52H:



Part A:

Compound **2289** was converted to compound **2296** via the procedure described in Example 52F Part C and using trifluoroacetic anhydride in place of Boc_2O.

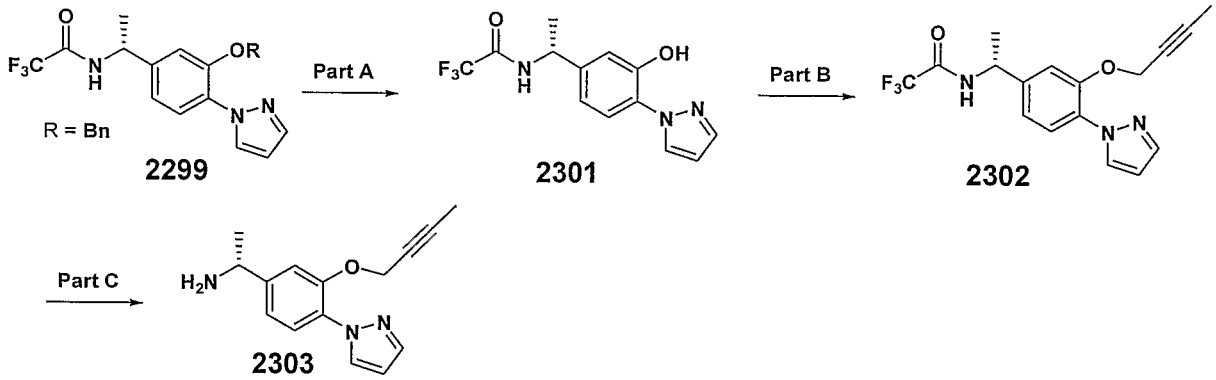
Part B,C,D:

Compounds **2297, 2298** and **2299** were prepared following the procedures described in Example 52F, Part D, E and F using benzyl bromide and cyclopropyl bromide in place of methyl iodide.

Part E:

Compound **2300** were prepared from compound **2299** following the procedures described in Example 52E, Part B.

Example 52I:



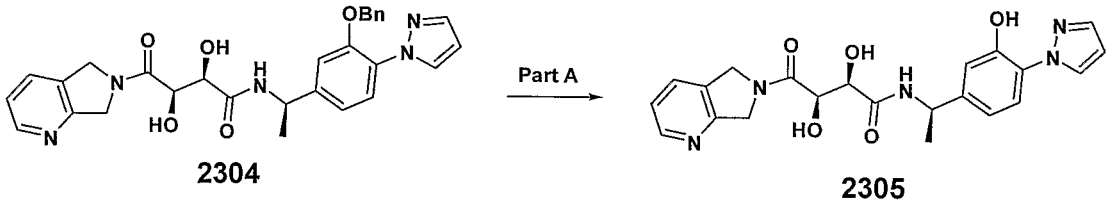
Part A:

A mixture of compound **2299** (0.27 g, 0.69 mmol), 10% Pd-C (0.18 g) and EtOH (25 mL) was stirred under hydrogen atmosphere at 55 psi for 18 hours. Filtered through celite and rinsed with CH_2Cl_2 and concentrated to afford the desired compound **2301** (0.21 g, 100%).

Part B,C:

Compounds **2302** and **2303** were prepared following the procedures described in Example 52H, Part C and E and using 1-bromo-2-butyne as the alkylating reagent.

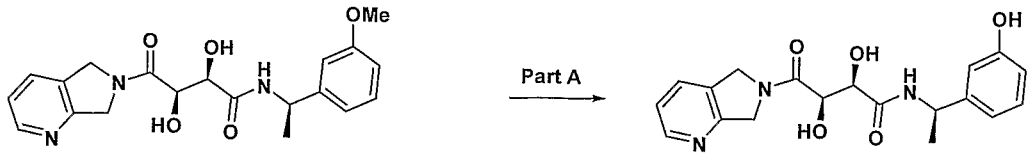
Example 52J:



Part A:

A mixture of compound **2304** (60 mg), 10% Pd-C (30 mg) and MeOH (10 mL) was stirred at room temperature under hydrogen atmosphere for 18 hours. Filtered and rinsed with CH_2Cl_2 and concentrated to afford the desired product **2305** (50 mg).

Example 52K:

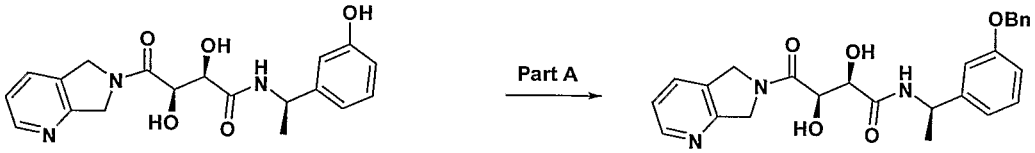


2306 **2307**

Part A:

Compound **2307** was prepared from compound **2306** following the procedure described in Example 52F, Part B.

Example 52L:

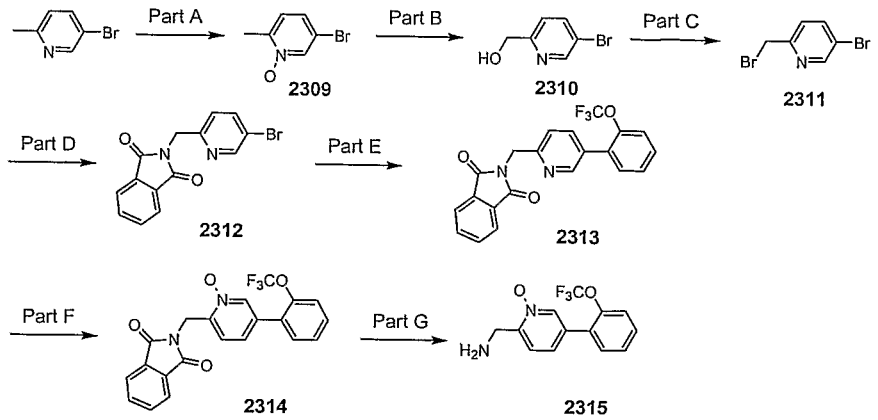


2307 **2308**

Part A:

To a mixture of **2307** (0.065 g, 0.18 mmol) in acetone (10 mL) was added K_2CO_3 (0.082 g, 0.59 mmol) followed by benzyl bromide (0.022 mL, 0.19 mmol) and the reaction mixture was refluxed for 18 hours. DMF (0.5 mL) was added to the reaction mixture and heated at 70 °C for 18 hours. The reaction mixture was cooled to room temperature and EtOAc (5 mL) was added, then was washed with water (2 x 1 mL) followed by brine (1 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (SiO_2, 5% MeOH (NH_3)/CH_2Cl_2) afforded **2308** (0.019 g, 23%).

Example 52M:



Part A:

To a solution of 5-bromopicoline (20 g, 116 mmol) in chloroform (100 mL) at 0 °C was added portionwise 77% mCPBA (28.7 g, 128 mmol) over 20 min. The reaction mixture was allowed to stir at room temperature overnight, after which time the solid was filtered off, the filtrate was washed with saturated Na_2CO_3, dried over Na_2SO_4, and concentrated to afford **2309** (17.83 g, 82%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 8.3 Hz, 1H), 2.47 (s, 3H).

Part B:

Compound **2309** (15 g, 80 mmol) was cooled to 0 °C, and trifluoroacetic anhydride (35 mL, 250 mmol) was slowly added under argon. The mixture was allowed to stir at room temperature for 30 min, then at 55 °C for 30 min after which it was cooled to 0 °C in an ice bath. $NaHCO_3$ aqueous solution (10%, 150 mL) was slowly added with caution. After the completion of addition, the mixture was allowed to stir at room temperature for 6 h. The solution was extracted with dichloromethane, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane 50:50), affording product **2310** as a white solid (9.2 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 1.9 Hz, 1H), 7.80 (dd, J = 7.9, 2.4 Hz, 1H), 7.19 (dd, J = 8.3, 0.9 Hz, 1H), 4.73 (s, 2H), 3.37 (br s, 1H).

Part C:

To a solution of **2310** (9.0 g, 47.86 mmol) in toluene (40 mL) was added PBr_3 (5 mL, 52.6 mmol) dropwise. After the completion of addition, the mixture was stirred at 100 °C for 2 h. It was cooled to room temperature; the solid was collected by filtration to afford **2311** as a yellow solid (HBr salt, 14.83 g, 93%). ^1H NMR (400 MHz, DMSO-d_6) δ 9.74 (br, 1H), 8.66 (d, *J* = 1.8 Hz, 1H), 8.06 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.19 (dd, *J* = 8.3, 0.9 Hz, 1H), 4.67 (s, 2H).

Part D:

To a solution of **2311** (14.83 g, 44.7 mmol) in DMF at 0 °C was slowly added Cs_2CO_3 (29.1 g, 89.4 mmol) and potassium phthalimde (9.1 g, 49.2 mmol). The reaction mixture was allowed to stir at room temperature for 6h after which the solvent was evaporated to dryness. The resulting solid was washed with H_2O. The solid cake was recrystallized in hot EtOH, affording compound **2312** (7.64 g, 54%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.54 (d, *J* = 1.9 Hz, 1H), 8.00 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.90-7.83 (m, 4H), 7.41 (d, *J* = 7.8 Hz, 1H), 4.88 (s, 2H).

Part E:

A mixture of $Pd(OAc)_2$ (45 mg, 0.2 mmol), 2-bis(tert-butyl)phosphino-biphenyl (120 mg, 0.4 mmol), compound **2312** (3.17 g, 10 mmol), 2-trifluoromethoxyphenyl boronic acid (2.47 g, 12 mmol) and KF (2.1 g, 36 mmol) was charged into a 250-mL round bottom flask. Then THF (30 mL) was added under argon, and the reaction mixture was allowed at stir at 50 °C overnight, after which it was cooled to room temperature, filtered through celite and concentrated. Flash column chromatography on silica gel (EtOAc/hexane (5:95) provided compound **2313** (3.27 g, 82%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 1.5 Hz, 1H), 7.91-7.89 (m, 2H), 7.77-7.73 (m, 3H), 7.44-7.34 (m, 5H), 5.08 (s, 2H).

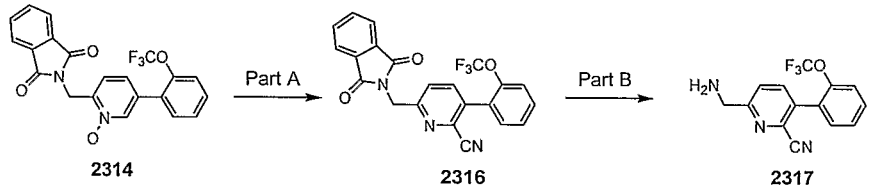
Part F:

Compound **2314** was prepared according to the same procedure as in Example 52M Part A. HPLC-MS t_R = 1.74 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{13}F_3N_2O_4$ 414.1, observed LCMS m/z 415.0 (M+H).

Part G:

To a solution of compound **2314** (210 mg, 0.51 mmol) in EtOH (10 mL) was added with hydrazine (0.5 mL). The solution was refluxed for 3 h, then cooled to room temperature. After removing the precipitate by filtration, the solution was concentrated. The resulting residue was extracted with Et_2O and concentrated, affording compound **2315** as a pale yellow oil (160 mg, 91%). HPLC-MS t_R = 1.74 min ($UV_{254\ nm}$); mass calculated for formula $C_{13}H_{11}F_3N_2O_2$ 284.1, observed LCMS m/z 285.1 (M+H).

Example 52N:



2314 2316 2317

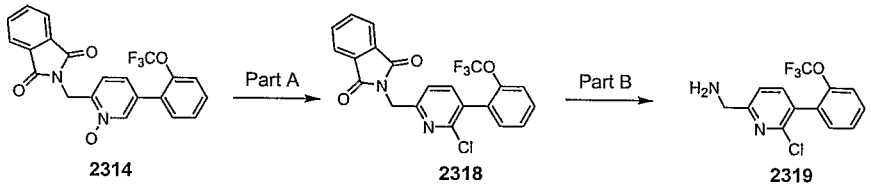
Part A:

To compound **2314** (200 mg, 0.48 mmol) in acetonitrile (1 mL) was added Et_3N (0.094 mL, 0.672 mmol) and Me_3SiCN (0.225 mL, 1.69 mmol) subsequently under argon. The reaction mixture was stirred at 80 °C for 48 h, after which it was cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in EtOAc, washed with saturated $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated. Flash column chromatography (EtOAc/hexane 40:60) afforded compound **2316** (130 mg, 64%). HPLC-MS t_R = 2.06 min ($UV_{254\ nm}$); mass calculated for formula $C_{22}H_{12}F_3N_3O_3$ 423.1, observed LCMS m/z 424.0 (M+H).

Part B:

Compound **2317** was prepared using the procedure described in Example 52M Part G. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.1 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.47-7.42 (m, 4H), 4.12 (s, 2H). 1.98 (br s, 2H).

Example 52O:



2314 **2318** **2319**

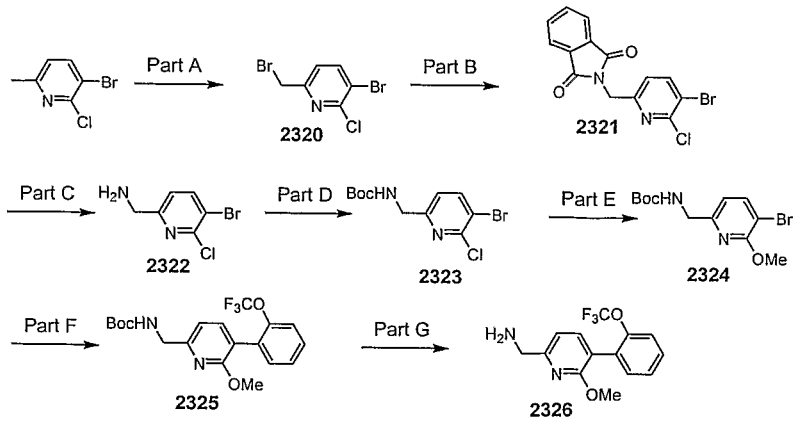
Part A:

Phosphorous trichloride (0.330 mL, 3.62 mmol) was added to a solution of **2314** (300 mg, 0.72 mmol) in $CHCl_3$ (1 mL). The reaction mixture was stirred at 60 °C overnight, after which it was cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in EtOAc, washed with saturated $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated. Flash column chromatography (EtOAc/hexane 30:70) afforded **2318** (180 mg, 58%). HPLC-MS t_R = 2.33 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{12}ClF_3N_2O_3$ 432.1, observed LCMS m/z 433.0 (M+H).

Part B:

Compound **2319** was prepared using the procedure described in Example 52M Part G. HPLC-MS t_R = 1.26 min ($UV_{254\ nm}$); mass calculated for formula $C_{13}H_{10}ClF_3N_2O$ 302.0, observed LCMS m/z 303.0 (M+H).

Example 52P:



Part A:

3-Bromo-2-chloro-6-picoline (1.0 g, 4.84 mmol) and NBS (1.20 g, 6.78 mmol) were dissolved in CCl_4 (20 mL). The solution was briefly flushed with argon, then AIBN (16 mg, 0.097 mmol) was added. The mixture was stirred at room temperature overnight, after which the solvent was evaporated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane 5:95) providing compound **2320** as a white solid (1.28 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.2 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 4.19 (s, 2H).

Part B:

Compound **2321** was prepared according to the procedure described in Example 52M, Part D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (d, *J* = 8.0 Hz, 1H), 7.92-7.84 (m, 4H), 7.41 (d, *J* = 8.0 Hz, 1H), 4.86 (s, 2H).

Part C:

Compound **2322** was prepared according to the procedure described in Example 52M, Part G. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 3.93 (s, 2H), 1.78 (br s, 2H).

Part D:

Compound **2322** (370 mg, 1.67 mmol) in THF (10 mL) was added dropwise into the solution of Boc_2O (437 mg, 2.0 mmol) in THF (10 mL), followed by DIEA (300 mL). The mixture was stirred at room temperature overnight and concentrated. Column chromatography on silica gel (EtOAc/hexane 20:80)

provided compound **2323** (450 mg, 84%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.5 Hz, 1H), 7.12 (d, *J* = 8.2 Hz, 1H), 5.35 (br s, 1H), 4.37 (d, *J* = 5.9 Hz, 2H), 1.47 (s, 9H).

Part E:

Sodium (4 pellets) was dissolved in MeOH (15 mL). The mixture was stirred at room temperature for 10 min until all the sodium had reacted. To this solution was added compound **2323** (450 mg, 1.4 mmol) in MeOH (5 mL) via syringe. The reaction mixture was stirred at 60 °C for 48 h and concentrated. The residue was dissolved with EtOAc and 1N NH_4Cl solution, washed with brine, dried over Na_2SO_4, and concentrated. Column chromatography (SiO_2, EtOAc/hexane 20:80) afforded compound **2324** as a white solid (350 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.3 Hz, 1H), 6.73 (d, *J* = 7.5 Hz, 1H), 5.26 (br s, 1H), 4.32 (d, *J* = 5.1 Hz, 2H), 4.02 (s, 3H), 1.48 (s, 9H).

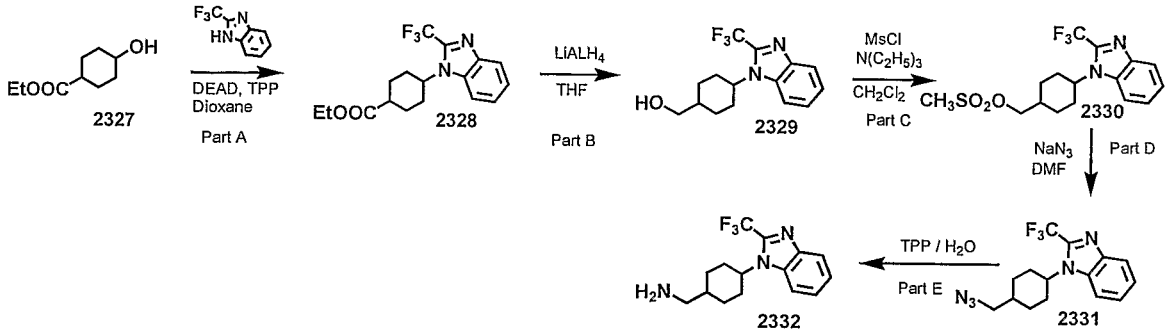
Part F:

Compound **2325** was prepared according to the same procedure as in Example 52M Part E for the Suzuki coupling. HPLC-MS t_R = 2.35 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{21}F_3N_2O_4$ 398.2, observed LCMS m/z 399.1 (M+H).

Part G:

Compound **2325** was deprotected with TFA in CH_2Cl_2. HPLC-MS t_R = 1.12 min ($UV_{254\ nm}$); mass calculated for formula $C_{14}H_{13}F_3N_2O_2$ 298.1, observed LCMS m/z 299.0 (M+H).

Example 52Q:



Part A:

Ethyl-4-hydroxycyclohexylcarboxylate (2327) (cis/trans mixture) (4.3 g, 25 mmol), 2-trifluoromethylbenzimidazole (4.65 g, 25 mmol), and triphenylphosphine (9.8 g, 37.5 mmol) were dissolved in dioxane (60 mL). The resulting solution was treated with diethyldiazodicarboxylate (6.5 g, 37.5 mmol), dropwise, over a period of 1h and stirred for 16h. The reaction mixture was diluted with ethyl acetate (200 mL) and washed in sequence with water (2 X 100 mL) and brine (1 X 100 mL). The organics were dried and concentrated to yield a crude which was subjected to silica-gel column chromatography (10% ethyl acetate/hexane) to yield pure **2328** (0.2 g, 0.6 mmol).

Part B:

$LiAlH_4$ was added to dry THF (40 mL) and the mixture was then cooled to 0 °C. Then ester **2328** (0.2 g, 0.6 mmol) in THF (5 mL) was added to the mixture dropwise. The reaction mixture was allowed to warm to ambient temperature and stirred for 48 h, then cooled back to 0 °C and quenched by the sequential addition of 1 mL of water, 2 mL of 0.5 N NaOH, and 1 mL of water. The resulting mixture was stirred vigorously for 2 h and then filtered through Celite. The filtrate was concentrated to yield pure **2329** as an oil (0.2 g, 0.6 mmol).

Part C:

Alcohol **2329** (0.2 g, 0.6 mmol) and triethylamine (0.18 g, 1.8 mmol) were dissolved in CH_2Cl_2 (200 mL) and cooled to 0 °C. The cooled solution was stirred, and CH_3SO_2Cl (as a CH_2Cl_2 solution; 0.2 g, 1.8 mmol, 5 mL CH_2Cl_2)

was added dropwise, and the stirring was continued for 24 h. The reaction mixture was then washed two times with 50 mL of water and two times with 50 mL of brine. The organic and aqueous phases were separated, and the organic phase was dried, and concentrated to provide pure product **2330** as an oil (0.21 g).

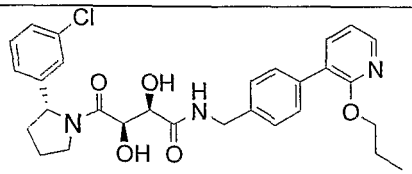
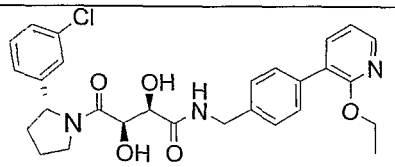
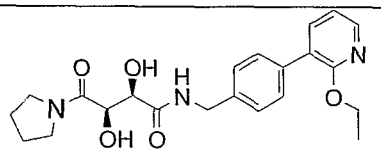
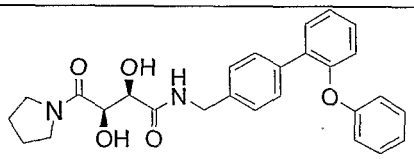
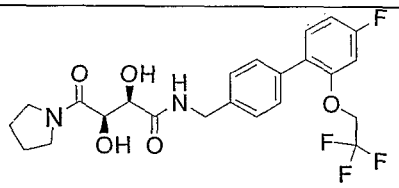
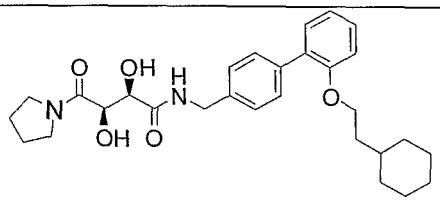
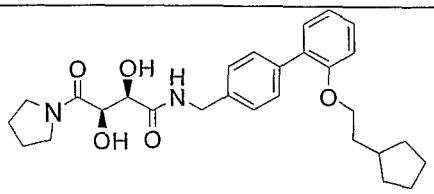
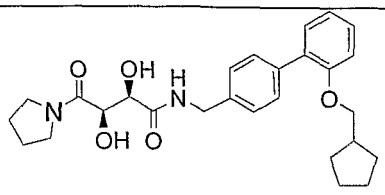
Part D:

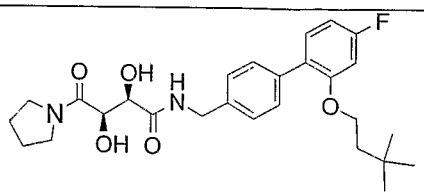
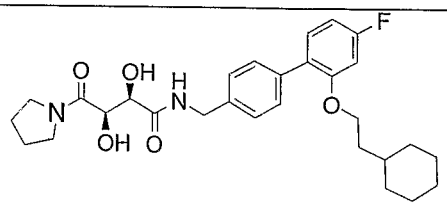
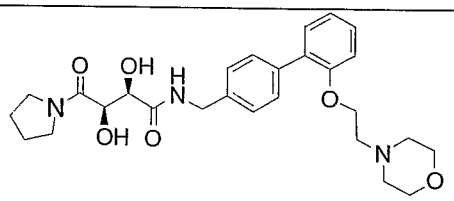
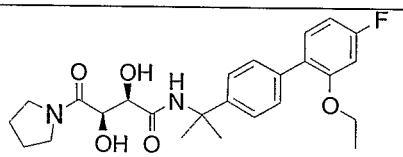
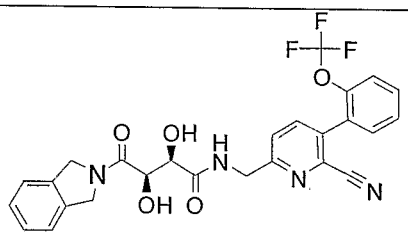
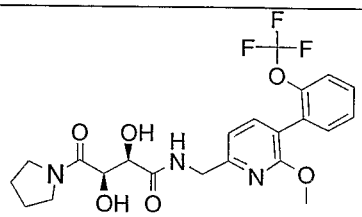
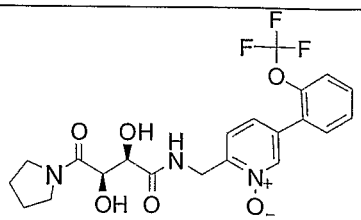
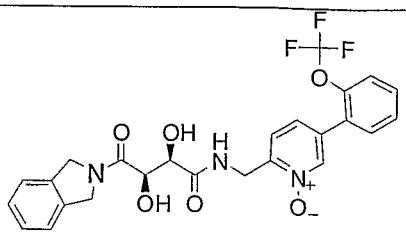
The mesylate **2330** was dissolved in DMF (10 mL) and treated with NaN_3 (0.23 g, 1.8 mmol), and the mixture was stirred vigorously for 36-72 h. The reaction mixture was then diluted with 100 mL water and extracted with ethyl acetate (2 x 100 mL). The organic phases were combined, dried, and concentrated to yield pure azide **2331** (0.19 g, 87%).

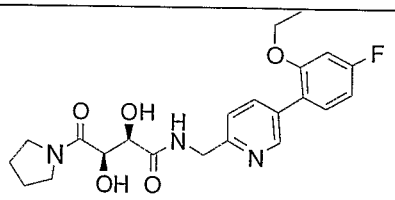
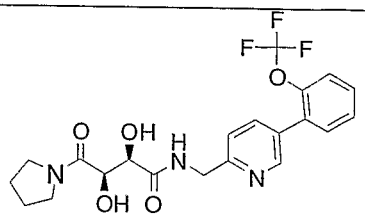
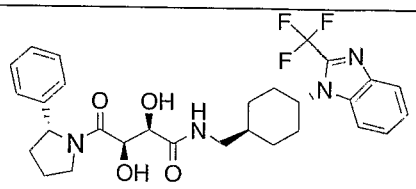
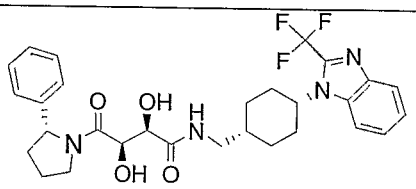
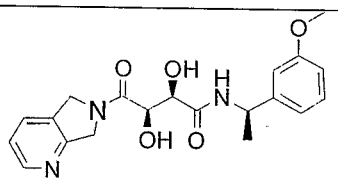
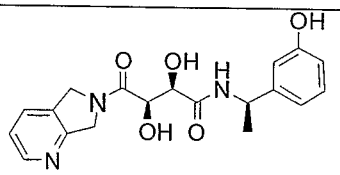
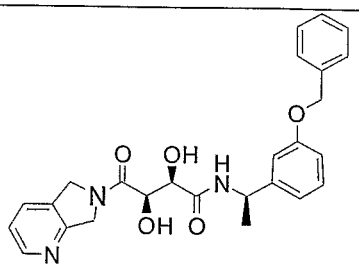
Part E:

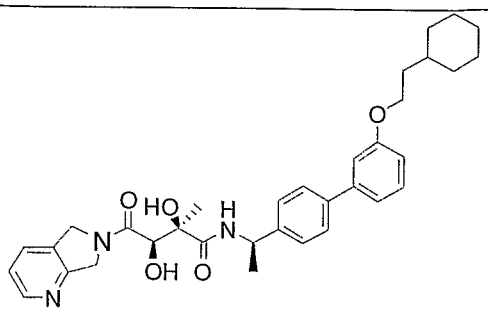
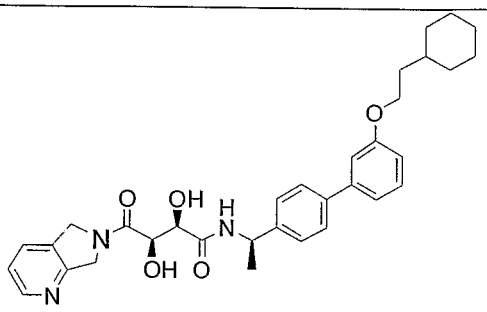
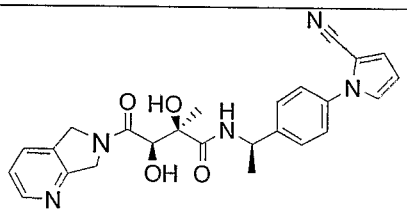
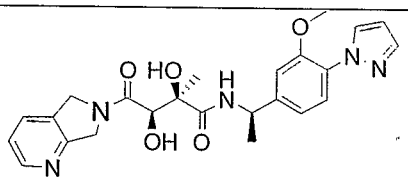
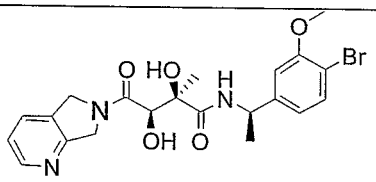
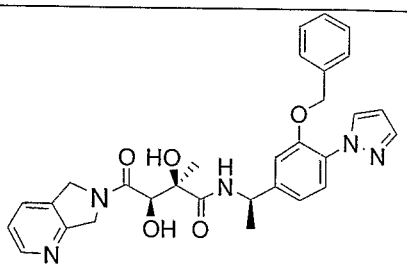
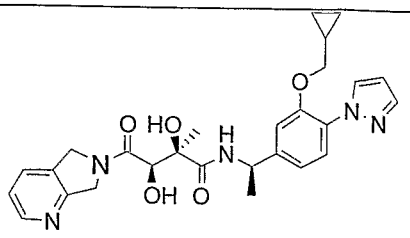
The azide **2331** (0.19 g, 0.6 mmol)) and triphenylphosphine (0.15 g, 0.6 mmol) were dissolved in 5 mL of THF, and then water (0.6 mL, 33.3 mmol) was added. The resulting mixture was stirred vigorously for 16-24 h. The solvent was removed and the crude amine **2332** was taken to the next step without further purification.

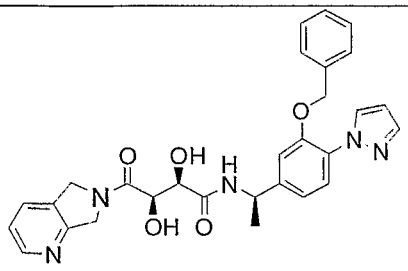
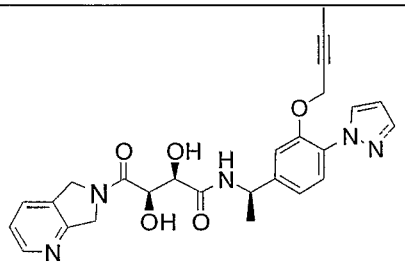
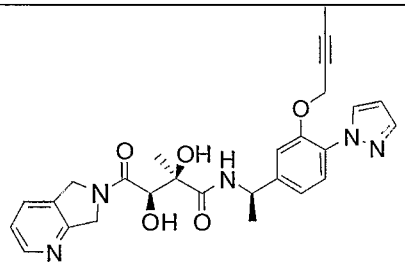
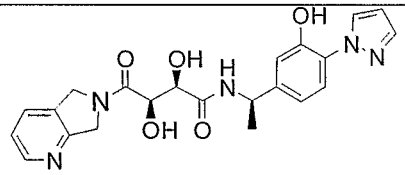
The following compounds were prepared using previously described procedures.

Compound #	Structure	Exact mass	MS m/z (M+H)
2333		537.2	538.1
2334		523.2	524.1
2335		413.2	414.2
2336		460.2	461.0
2337		484.2	485.2
2338		494.3	495.2
2339		480.3	481.1
2340		466.3	467.2

2341		486.3	487.2
2342		512.3	513.2
2343		497.3	498.2
2344		458.2	459.2
2345		526.2	527.0
2346		483.2	484.0
2347		469.2	470.0
2348		517.2	518.0

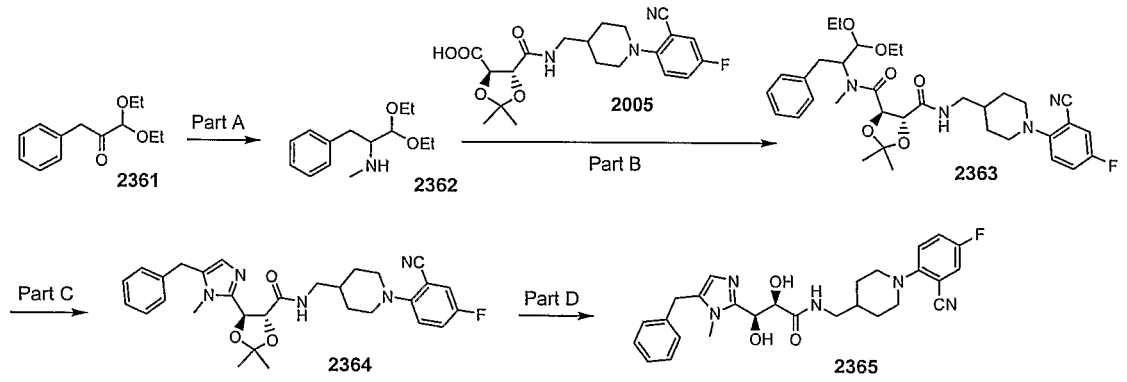
2349		431.2	432.1
2350		453.2	454.1
2351		558.2	559.1
2352		558.2	559.1
2306		385.2	386.1
2307		371.2	372.1
2308		461.2	462.1

2353A		571.3	572.3
2353B		557.3	558.1
2354		459.2	460.1
2355		465.2	466.3
2356		477.1	478.3
2357		541.2	542.3
2358		505.2	506.3

2304		527.2	528.3
2359		489.2	490.3
2360		503.2	504.3
2305		437.2	438.1

Example 53:

Example 53A:



Part A:

Compound **2361** was prepared using procedures described in Adamczyk, M. et al. *Synth. Commun.* **2002**, *32*, 3199-3205.

According to a modification of a procedure by Neidigh, K. A. et al. *(J. Chem. Soc. Perkin Trans. 1* **1998**, 2527-2531) a mixture of ketone **2361** (1.56 g, 7 mmol), titanium (IV) isopropoxide (4.1 mL, 14 mmol), methylamine hydrochloride (0.94 g, 14 mmol) and triethylamine (1.95 mL, 14 mmol) in ethanol (15 mL) was stirred at rt overnight. Then sodium borohydride (0.4 g, 10.5 mmol) was added and the resulting mixture was stirred at rt for 8 h. The reaction mixture was then poured into aqueous ammonium hydroxide (40 mL), the resulting white inorganic precipitate was filtered off, and washed several times with dichloromethane. The organic layer was separated, and the aqueous phase was extracted with dichloromethane. Combined dichloromethane extracts were washed with brine, concentrated and chromatographed (SiO_2, 5% methanol/dichloromethane) to give **2362** (1.03 g, 62%). ^1H NMR (400 Mhz, $CDCl_3$) δ 7.30-7.17 (m, 5H), 4.31-4.30 (d, 1H), 3.78-3.62 (m, 2H), 3.57-3.47 (m, 2H), 2.97-2.70 (m, 3H), 2.43 (s, 3H), 1.27-1.20 (m, 6H).

Part B:

Compound **2005** was prepared using procedures described in Example 27.

Compound **2363** was prepared using the coupling conditions described in Example 1. HPLC-MS t_R = 2.42 min ($UV_{254\ nm}$); mass calculated for formula C34H45FN4O6 624.3, observed LCMS m/z 625.2 (M+H).

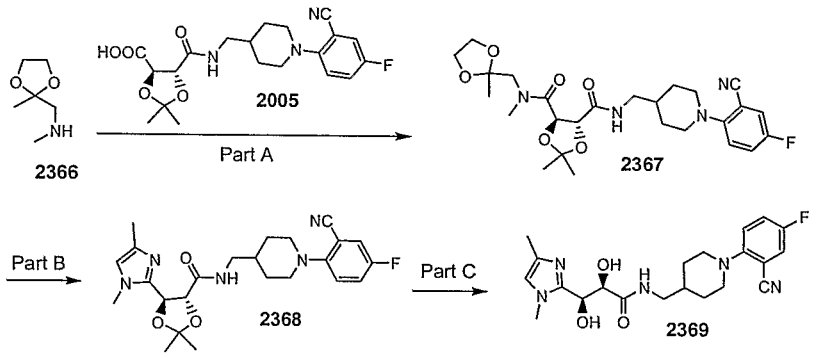
Part C:

Compound **2364** was prepared using the cyclization conditions described in Example 29. HPLC-MS t_R = 1.66 min ($UV_{254\ nm}$); mass calculated for formula C30H34FN5O3 531.3, observed LCMS m/z 532.2 (M+H).

Part D:

Compound **2364** was deprotected using procedures described in Example 29. Purification by prep-LC and conversion to a hydrochloric salt afforded **2365** as an off-white solid. HPLC-MS t_R = 3.54 min (10 min; $UV_{254\ nm}$); mass calculated for formula C27H30FN5O3 491.2, observed LCMS m/z 492.1 (M+H).

Example 53B:



Part A:

Compound **2366** was prepared using procedures described in Waldvogel, E. et al. *Helv. Chim. Acta*. **1997**, *80*, 2084-2099.

Compound **2367** was prepared using the coupling conditions described in Example 1. HPLC-MS t_R = 1.88 min ($UV_{254\ nm}$); mass calculated for formula C26H35FN4O6 518.2, observed LCMS m/z 519.2 (M+H).

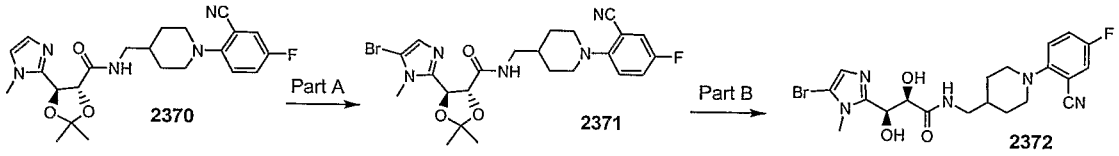
Part B:

Compound **2368** was prepared using the cyclization conditions described in Example 29. HPLC-MS t_R = 1.40 min ($UV_{254\ nm}$); mass calculated for formula C24H30FN5O3 455.2, observed LCMS m/z 456.1 (M+H).

Part C:

Compound **2368** was deprotected using procedures described in Example 29. Purification by prep-LC and conversion to a hydrochloric salt afforded **2369** as an off-white solid. HPLC-MS t_R = 2.99 min (10 min; $UV_{254\ nm}$); mass calculated for formula C21H26FN5O3 415.2, observed LCMS m/z 416.2 (M+H).

Example 53C:



Part A:

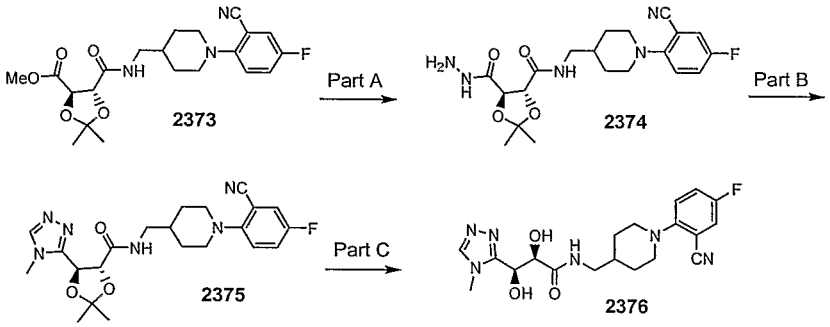
Compound **2370** was prepared using previously described procedures in Example 29. HPLC-MS t_R = 1.30 min ($UV_{254\ nm}$); mass calculated for formula C23H28FN5O3 441.2, observed LCMS m/z 442.1 (M+H).

According to a modification of a procedure by Miller, R. D. et al. *(Chem. Mater.* **1994**, *6*, 1023-1032) to an ice cold solution of compound **2370** (104 mg, 0.23 mmol) and pyridine (0.039 mL, 0.48 mmol) in dichloromethane (3 mL) was added dropwise a solution of bromine (0.016 mL, 0.31 mmol) in dichloromethane (1 mL) and the resulting solution was stirred at 0 °C for 20 min. The reaction mixture was quenched with 10% sodium thiosulfate solution, and extracted with dichloromethane. Combined organic extracts were dried, concentrated and chromatographed (SiO_2, gradient elution 50% to 80% ethyl acetate/hexane, ethyl acetate followed by 5% methanol/ethyl acetate) to give **2371** as a white solid (35 mg, 37% based on reacted starting material). HPLC-MS t_R = 1.94 min ($UV_{254\ nm}$); mass calculated for formula C23H27BrFN5O3 519.1, observed LCMS m/z 520.0 (M+H).

Part B:

Compound **2371** was deprotected using procedures described in Example 29. Purification by prep-LC and conversion to a hydrochloric salt afforded **2372** as a white solid. HPLC-MS t_R = 3.1 min (10 min; $UV_{254\ nm}$); mass calculated for formula C20H23BrFN5O3 479.1, observed LCMS m/z 480.0 (M+H).

Example 53D:



Part A:

Compound **2373** was prepared using previously described procedures in Examples 1 and 27.

To a solution of **2373** (300 mg, 0.71 mmol) in methanol (7 mL) was added hydrazine monohydrate (0.35 mL, 7.1 mmol) and the resulting mixture was heated at 70 °C in a sealed tube overnight. The mixture was then cooled to rt, concentrated, diluted with ethyl acetate, washed with water, brine and concentrated to give **2374** (220 mg, 73%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.24 (m, 1H), 7.22-7.17 (m, 1H), 7.00 (t, 1H, NH), 6.99-6.96 (m, 2H), 4.62-4.57 (dd, 2H), 3.51-3.48 (d, 2H), 3.38-3.24 (m, 2H), 2.80-2.74 (m, 2H), 1.88-1.84 (d, 2H), 1.79-1.69 (m, 1H), 1.61-1.50 (m, 2H), 1.53 (s, 3H), 1.52 (s, 3H). HPLC-MS t_R = 1.49 min ($UV_{254\ nm}$); mass calculated for formula C20H26FN5O4 419.2 observed LCMS m/z 420.1 (M+H).

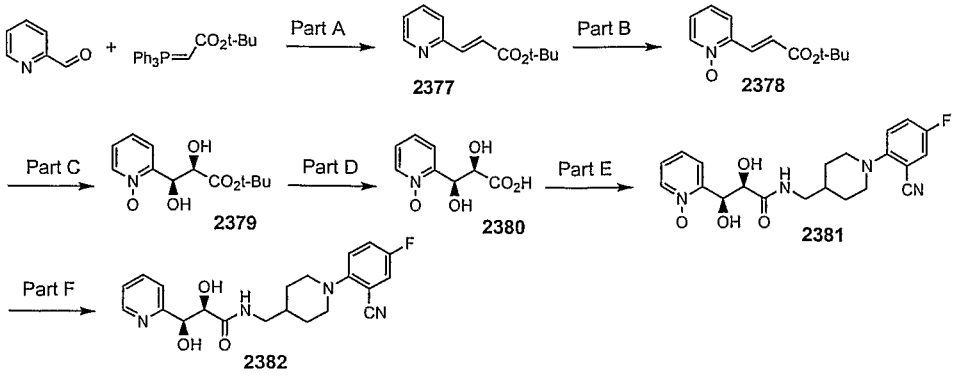
Part B:

According to a modification of a procedure by Stocks, M. J. et al. *(Org. Lett.* **2004**, *17*, 2969-2971) to a solution of hydrazide **2374** (110 mg, 0.26 mmol) in acetonitrile (1 mL) was added N,N-dimethylformamide dimethyl acetal (0.035 mL, 0.26 mmol) and the mixture was heated at 50 °C for 50 min. Then methylamine (0.18 mL of 2 M solution in THF, 0.36 mmol) was added, followed by acetic acid (1 mL) and the resulting mixture was heated at 80 °C overnight. The reaction mixture was then concentrated and chromatographed (SiO_2, 9:1:90 methanol:triethylamine:dichloromethane) to give **2375**. ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.27-7.24 (m, 1H), 7.21-7.18 (m, 1H), 7.02-6.97 (m, 1H), 6.92 (t, 1H, NH), 5.48-5.37 (dd, 2H), 3.51-3.47 (m, 2H), 3.36-3.23 (m, 2H), 2.80-2.74 (m, 2H), 1.88-1.81 (m, 2H), 1.76-1.70 (m, 1H), 1.58-1.54 (m, 2H), 1.58 (s, 3H), 1.43 (s, 3H). HPLC-MS t_R = 1.58 min ($UV_{254\ nm}$); mass calculated for formula C22H27FN6O3 442.2 observed LCMS m/z 443.2 (M+H).

Part C:

Compound **2375** was deprotected with 4 M HCl in dioxane (3 mL) and water (0.3 mL) at 55 °C for 1 hour. Purification by prep-LC and conversion to a hydrochloric salt afforded **2376** as an off-white solid (20 mg). HPLC-MS t_R = 1.23 min ($UV_{254\ nm}$); mass calculated for formula C19H23FN6O3 402.2, observed LCMS m/z 403.1 (M+H).

Example 53E:



Part A:

(*tert*-Butoxycarbonylmethylene)triphenylphosphorane (15.1 g, 40 mmol) was added portionwise to a solution of 2-pyridinecarboxaldehyde (4.28 g, 40 mmol) in THF (60 mL) at 0 °C over a period of 5 min. The reaction mixture was allowed to stir at room temperature overnight. The solution was concentrated, extracted with hexane (120 mL). After filtration to remove the solid, the filtrate was concentrated to give a yellow oil. Purification by flash chromatography on silica gel (EtOAc/hexane 15:85) yielded the desired product **2377** (4.5 g, 55%) as slightly yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 4.9 Hz, 1H), 7.69 (td, *J* = 6.6, 1.7 Hz, 1H), 7.58 (d, *J* = 15.5 Hz, 1H), 7,41(dd, *J* = 7.8, 0.6 Hz, 1H), 7.23 (m, 1H), 6.82 (d, *J* = 16.1 Hz, 1H), 1.54 (s, 9H).

Part B:

Compound **2377** (4.5 g, 21.92 mmol) was dissolved in dry DCM (40 mL) and cooled to 0 °C, then 77% *m*-CPBA (5.41 g, 24.12 mmol) was added in three portions over 5 min. The reaction mixture was allowed to stir overnight at room temperature. It was poured into saturated aqueous $NaHCO_3$ (100 mL) and the product was extracted into DCM. The organic layer was washed with water and brine and dried (Na_2SO_4). Flash chromatography on silica gel (MeOH/DCM 5:95) afforded compound **2378** as a pale yellow solid (3.2 g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (m, 1H), 7.96 (d, *J* = 16.0 Hz, 1H), 7.51 (m, 1H), 7.22 (m, 1H), 6.85 (d, *J* = 16.0 Hz, 1H), 1.55 (s, 1H).

Part C:

A 250-mL round bottom flask filled with H_2O (30 mL) was cooled to 0 °C in an ice bath. Reagents $K_3[Fe(CN)_6]$ (9.88 g, 30 mmol), K_2CO_3 (6.91 g, 50 mmol), and $MeSO_2NH_2$ (0.95 g, 10 mmol) were subsequently added, followed by $K_2[OsO_2(OH)_4]$ (14.7 mg, 0.04 mmol), (DHQ)PHAL (233.7 mg, 0.3 mmol), compound **2378** (2.21 g, 10 mmol) and *t*-BuOH (20 mL). The reaction mixture was stirred at 0 °C for 24 h. The solid was filtered off and washed with excess EtOAc. The organic layer was separated. The aqueous solution was

concentrated to dryness, and the resulting solid was extracted with CH_2Cl_2. The above EtOAc and CH_2Cl_2 solutions were combined and concentrated. Flash chromatography on silica gel (MeOH/CH_2Cl_2 10:90) provided compound **2379** as a white solid (2.2 g, 86%). Recrystallization from EtOAc afforded analytically pure material (1.51 g, 52% yield). ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.24 (d, *J* = 6.5 Hz, 1H), 7.54 (dd, *J* = 7.7, 2.0 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.30 (m, 1H), 5.41 (d, *J* = 2.6 Hz, 1H), 4.69 (d, *J* = 2.7 Hz, 1H), 1.54 (s, 9H).

Part D:

Compound **2379** (1.0 g, 3.9 mmol) in CH_2Cl_2 (10 mL) was treated with TFA (4 mL). The solution was allowed to stir at room temperature for 2 h, and then concentrated to afford compound **2380** as a white solid (750 mg, 96%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (dd, *J* = 6.3, 1.2 Hz, 1H), 7.54 (dd, *J* = 6.4, 2.2 Hz, 1H), 7.37 – 7.32 (m, 2H), 5.38 (d, *J* = 2.1 Hz, 1H), 4.62 (d, *J* = 2.3 Hz, 1H).

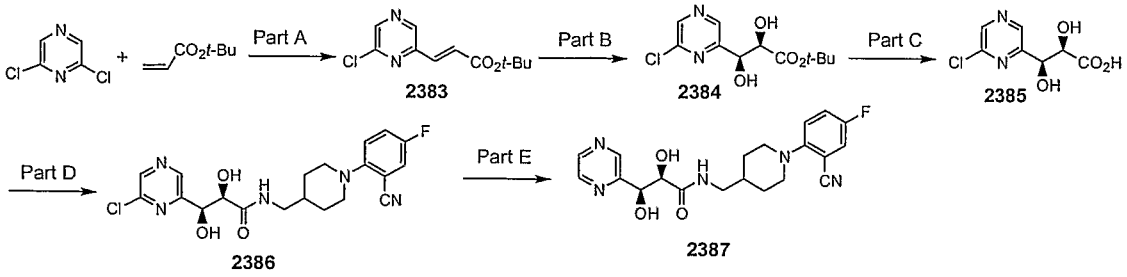
Part E:

Compound **2381** was prepared using the coupling conditions described in Example 1. Purification by prep-LC afforded **2381** as a white solid (63 mg). HPLC-MS t_R = 1.30 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{23}FN_4O_4$, 414.2, observed LCMS m/z 415.1 (M+H).

Part F:

To compound **2381** (25 mg, 0.06 mmol) in EtOH (5 mL) was added with saturated NH_4Cl aqueous solution (5 mL) and indium (16.6 mg, 0.072 mmol). The reaction mixture was allowed to reflux for 24 h. After cooling to room temperature, it was concentrated and extracted with DCM. The DCM extract was filtered and concentrated. Purification by column chromatography on silica gel (Et_3N / MeOH / EtOAc 5:5:95) afforded compound **2382** as a white solid (8.5 mg, 35%). HPLC-MS t_R = 1.16 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{23}FN_4O_3$, 398.2, observed LCMS m/z 399.1 (M+H).

Example 53F:



Part A:

Under argon, to a mixture of $Pd_2(dba)_3$ (384 mg, 0.42 mmol), tri(t-butyl)phosphinium tetrafluoroborate (243 mg, 0.84 mmol), and 2,6-dichloropyrizine (5.0 g, 33.56 mmol) were added sequentially NMP (10 mL), *t*-butyl acrylate (2.46 mL, 16.78 mmol) and Et_3N (3.51 mL, 25.17 mmol). The reaction mixture was allowed to stir at 50 °C for 12 h. After cooling to room temperature, the mixture was diluted with EtOAc and water, filtered through a pad of celite, washed with water, brine, dried (Na_2SO4), and concentrated. Flash column chromatography on silica gel (EtOAc / hexane 15:85) afforded compound **2383** as a pale yellow solid (2.32 g, 57%). ^1H NMR (400 MHz, acetone-d_6) δ 8.84 (s, 1H), 8.68 (s, 1H), 7.61 (d, J = 15.7 Hz, 1H), 6.92 (d, J = 15.5 Hz, 1H), 1.55 (s, 9H).

Part B:

A 50-mL round bottom flask filled with H_2O (9 mL) was cooled to 0 °C in an ice bath. Reagents $K_3[Fe(CN)_6]$ (1.29 g, 3.93 mmol), K_2CO_3 (905 mg, 6.55 mmol), and $MeSO_2NH_2$ (124.6 mg, 1.31 mmol) were subsequently added, followed by $K_2[OsO_2(OH)_4]$ (2.0 mg, 0.005 mmol), (DHQ)PHAL (31.0 mg, 0.04 mmol), compound **2383** (315 mg, 1 mmol) and *t*-BuOH (6 mL). The reaction mixture was stirred at 0 °C for 36 h. Then EtOAc and H_2O were added to dissolve the solid. The organic layer was separated and the aqueous layer was back extracted with EtOAc. The EtOAc extracts were combined, washed with water and brine, dried (Na_2SO_4), and concentrated. Flash chromatography on silica gel (EtOAc/hexane 40:60) provided compound **2384**

as a white solid (285 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.54 (s, 1H), 5.13 (d, *J* = 2.3 Hz, 1H), 4.55 (d, *J* = 2.9 Hz, 1H), 1.55 (s, 9H). HPLC-MS t_R = 1.73 min ($UV_{254\ nm}$); mass calculated for formula $C_{11}H_{15}ClN_2O_4$, 274.1, observed LCMS m/z 275.0 (M+H).

Part C:

Compound **2384** (285 mg, 1.04 mmol) in dioxane (5 mL) was treated with 4N HCl in dioxane (5 mL). After stirring at room temperature for 2 h, the solution was concentrated to afford compound **2385** (200 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.66 (s, 1H), 5.00 (d, *J* = 2.6 Hz, 1H), 4.31 (d, *J* = 2.2 Hz, 1H), 1.55 (s, 9H).

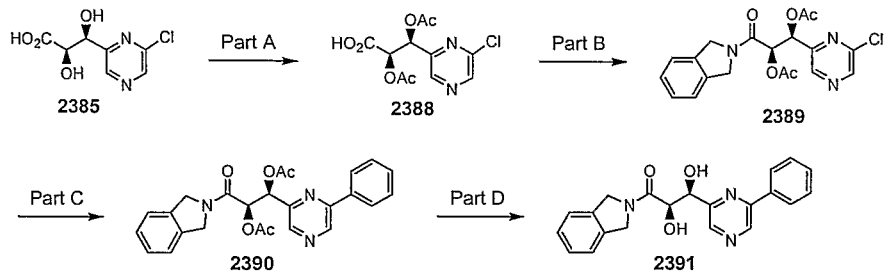
Part D:

Compound **2386** was prepared using the coupling conditions described in Example 1. Purification by prep-LC afforded **2386** as a white solid (42 mg). HPLC-MS t_R = 1.55 min ($UV_{254\ nm}$); mass calculated for formula $C_{20}H_{21}ClFN_5O_3$, 433.1, observed LCMS m/z 434.0

Part E:

Compound **2386** (20 mg, 0.046 mmol) along with 10% Pd/C (20 mg) in EtOAc (10 mL) was stirred at room temperature for 12 h under hydrogen atmosphere (1 atm). The solution was filtered through celite and concentrated. Purification by prep-LC afforded **2387** as a white solid (15 mg, 81%). HPLC-MS t_R = 1.35 min ($UV_{254\ nm}$); mass calculated for formula $C_{20}H_{22}FN_5O_3$, 399.2, observed LCMS m/z 400.1

Example 53G:



Part A:

To compound **2385** (150 mg, 0.69 mmol) in acetic acid (2 mL) was added acetic anhydride (0.5 mL). The reaction mixture was stirred at room temperature for 2 h, and then concentrated. The residue was dissolved in EtOAc, washed with H_2O, brine, dried over Na_2SO_4, and concentrated, giving rise to compound **2388** as oily solid (180 mg, 86%). HPLC-MS t_R = 1.10 min ($UV_{254\ nm}$); mass calculated for formula $C_{11}H_{11}ClN_2O_6$ 302.0, observed LCMS m/z 303.0 (M+H).

Part B:

To compound **2388** (180 mg, 0.59 mmol) and HATU (269 mg, 0.71 mmol) in DMF (4 mL) was added isoindoline (84 mg, 0.71 mmol). The reaction mixture was stirred at room temperature for 12 h, and concentrated. The residue was dissolved with EtOAc and water, washed with saturated bicarbonate solution, and brine, dried over Na_2SO_4, and concentrated. Purification by column chromatography on silica gel (EtOAc/hexane 60:40) afforded the desired product **2389** as a pale yellow solid (150 mg, 63%). ^1H NMR (400 MHz, CDCl3) δ 8.67 (s, 1H), 8.51 (s, 1H), 7.29 (m, 4H), 6.39 (d, *J* = 7.1 Hz, 1H), 5.93 (d, *J* = 6.7 Hz, 1H), 5.21 (d, *J* = 5.4 Hz, 1H), 5.05 (d, *J* = 4.1 Hz, 1H), 4.78 (d, *J* = 5.6 Hz, 1H), 4.52 (d, *J* = 4.7 Hz, 1H), 2.18 (s, 3H), 2.16 (s, 3H). HPLC-MS t_R = 1.70 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{18}ClN_3O_5$ 403.1, observed LCMS m/z 404.0 (M+H).

Part C:

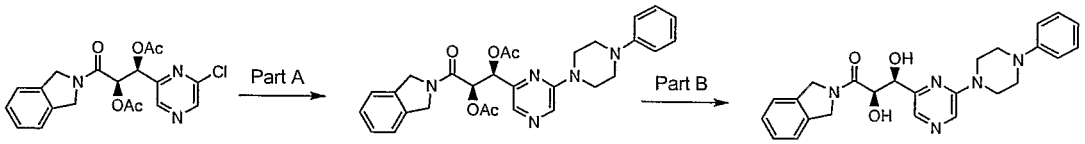
A 4-mL vial was charged with $Pd_2(dba)_3$ (2.3 mg, 0.0025 mmol), tri(t-butyl)phosphonium tetrafluoroborate (1.5 mg, 0.0025 mmol), compound **2389** (20 mg, 0.05 mmol), phenylboronic acid (9.1 mg, 0.075 mmol) and potassium

fluoride (13 mg, 0.225 mmol). Under argon, dioxane (1 mL) was added via syringe. The vial was sealed with a Teflon coated screw cap and placed into an oil bath preheated to 80 °C. The reaction mixture was allowed to stir at 80 °C for 12 h. LC-MS indicated the reaction was completed. After cooling to room temperature, the reaction mixture was filtered through celite with the aid of EtOAc. The filtrate was washed with saturated NaHCO3, brine, dried over Na2SO4, and concentrated. The resulting solid (21 mg) was used for next step without purification. HPLC-MS t_R = 1.89 min ($UV_{254\ nm}$); mass calculated for formula $C_{25}H_{23}N_3O_5$ 445.1, observed LCMS m/z 446.0 (M+H).

Part D:

Compound **2390** (21 mg) was deprotected using procedures described in Example 2. Purification by prep-LC afforded **2391** as an off-white solid (8.3 mg). HPLC-MS t_R = 4.02 min (10 min method) ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{19}N_3O_5$ 361.1, observed LCMS m/z 362.0 (M+H).

Example 53H:



2389 2392 2393

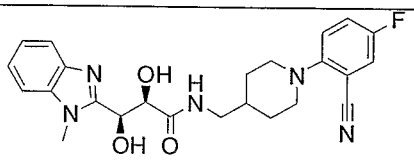
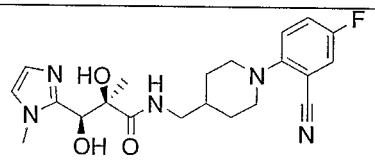
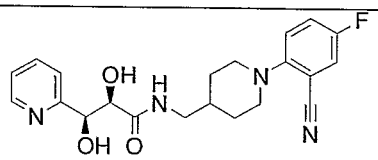
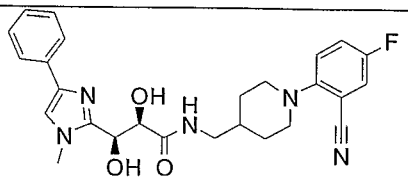
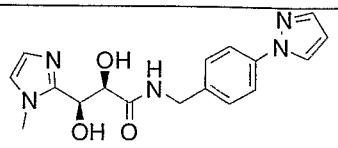
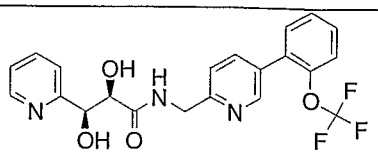
Part A:

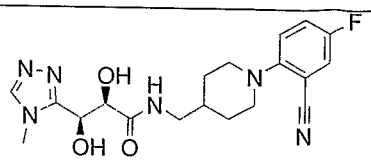
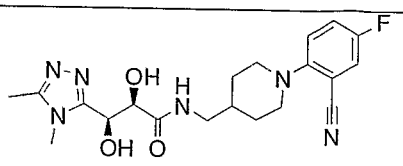
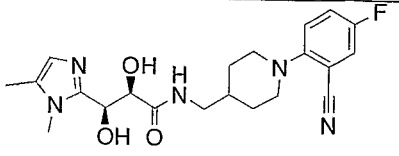
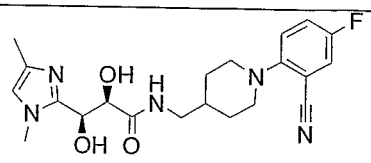
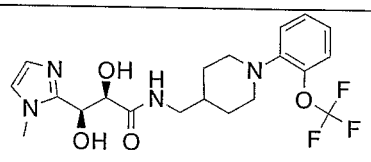
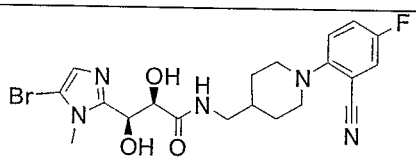
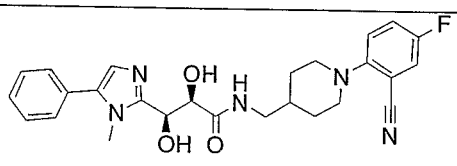
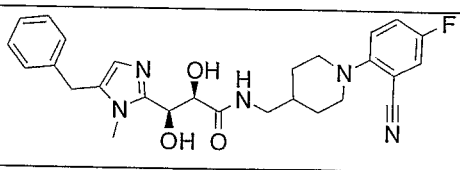
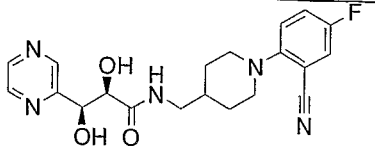
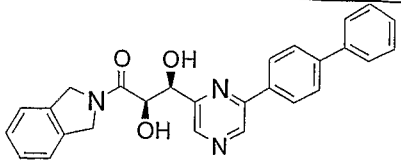
To compound **2389** (50 mg, 0.12 mmol) in NMP (1 mL) was added 4-N-phenylpipyzine (29 mg, 0.18 mmol) and DIEA (0.032 mL, 0.18 mmol). The reaction mixture was allowed to stir at 80 °C for 16 h. After cooling to room temperature, the solution was diluted with EtOAc, washed with water and brine, dried over Na2SO4, and concentrated. The resulting oily solid (52 mg) was utilized for next step without further purification. HPLC-MS t_R = 1.96 min ($UV_{254\ nm}$); mass calculated for formula $C_{29}H_{31}N_5O_5$ 529.2, observed LCMS m/z 530.2 (M+H).

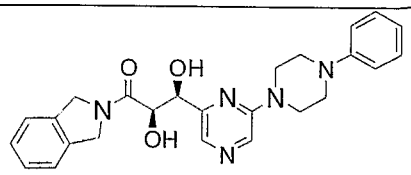
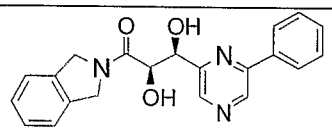
Part B:

Compound **2392** (52 mg) was deprotected using procedures described in Example 2. Purification by prep-LC afforded **2393** as an off-white solid (15 mg). HPLC-MS t_R = 1.60 min ($UV_{254\ nm}$); mass calculated for formula $C_{25}H_{27}N_5O_3$ 445.2, observed LCMS m/z 446.1 (M+H).

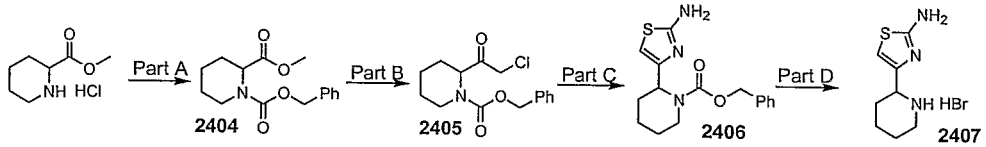
The following compounds were prepared using previously described procedures.

Compound #	Structure	Exact mass	MS m/z (M+H)
2394		451.2	452.2
2395		415.2	416.2
2382		398.2	399.1
2396		477.2	478.2
2397		341.2	342.1
2398		433.1	434.0

2376		402.2	403.1
2399		416.2	417.1
2400		415.2	416.2
2369		415.2	416.2
2401		442.2	443.2
2372		479.1	480.0
2402		477.2	478.1
2365		491.2	492.1
2387		399.2	400.1
2403		437.2	438.0

2393		445.2	446.1
2391		361.1	362.0

Example 54:



Part A:

Methyl pipecolinate hydrochloride (2.0 g, 11 mmol) was dissolved in THF (20 mL) and saturated sodium bicarbonate (20 mL) and cooled in an ice bath. Benzyl chloroformate (1.5 mL, 11 mmol) was added dropwise and the reaction was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with 1 N HCl, saturated sodium bicarbonate, water and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 10% ethyl acetate/hexane to 15% ethyl acetate/hexane) afforded **2404** as a clear oil (2.9 g, 93%).

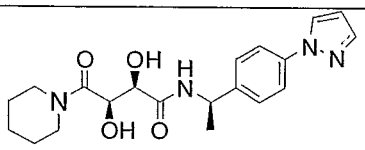
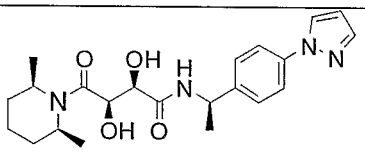
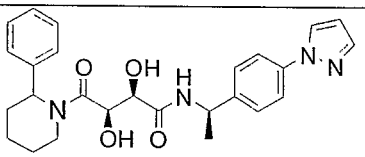
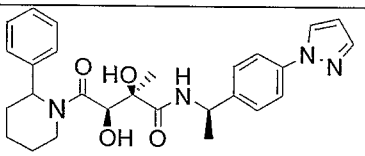
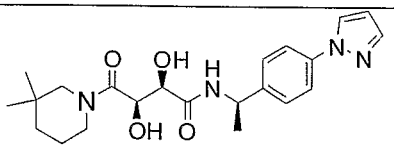
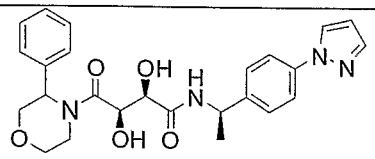
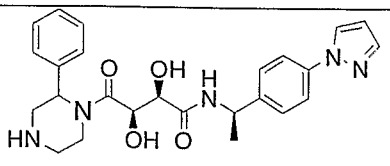
Part B and C:

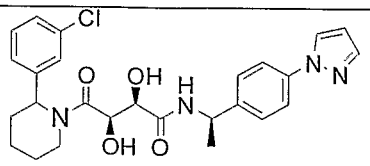
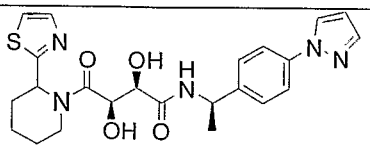
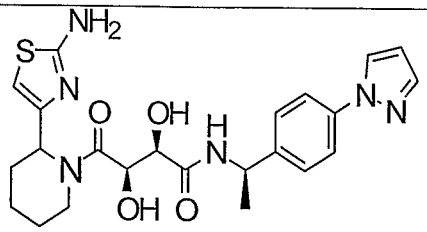
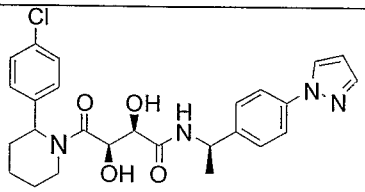
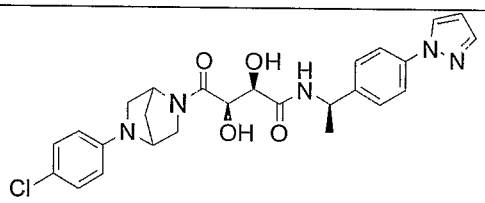
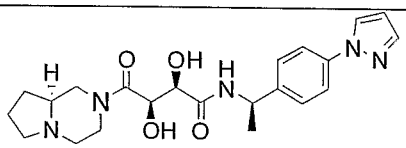
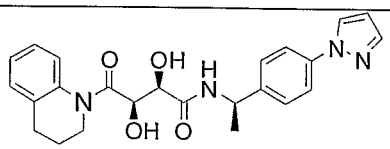
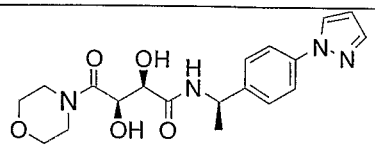
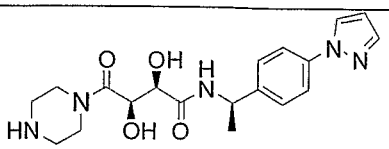
Compounds **2405** and **2406** were prepared following the procedures described in Example 10B part A and part B. Compound **2406**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 5H), 6.11 (s, 1H), 5.36 (m, 1H), 5.18 (s, 2H), 3.72 (m, 1H), 3.00 (m, 1H), 2.33 (m, 1H), 1.90 – 1.40 (m, 7H). HPLC-MS t_R = 1.34min ($UV_{254\ nm}$); Mass calculated for C16H19N3O2S 317.4, observed LSMS m/z 318.1 (M+H).

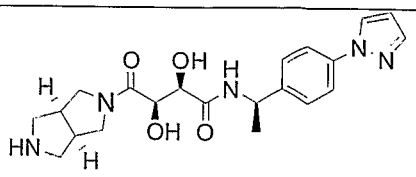
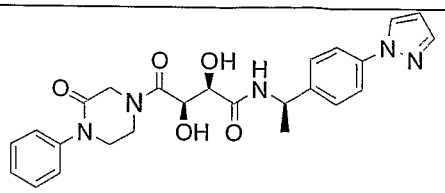
Part D:

Compound **2406** (75 mg, 0.24 mmol) was stirred in 30% HBr in acetic acid (2 mL) for 1 hour at room temperature. The solvent was evaporated and the residue was dissolved in water and lyophilized to afford **2407** (66 mg) as a red solid.

The following compounds were prepared using previously described procedures.

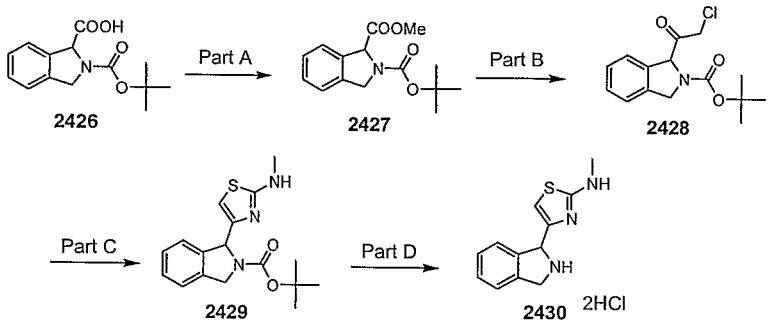
Compound #	Structure	Exact mass	MS m/z (M+H)
2408		386.2	387.1
2409		414.2	415.1
2410		462.2	463.1
2411		476.2	477.1
2412		414.2	415.1
2413		464.2	465.1
2414		463.2	464.2

2415		496.2	497.0
2416		469.2	470.0
2417		484.2	485.0
2418		496.2	497.0
2419		509.2	510.1
2420		427.2	428.2
2421		434.2	435.1
2422		388.2	389.1
2423		387.2	388.1

2424		413.2	414.1
2425		477.2	478.1

Example 55:

Example 55A:



Part A:

To an ice cold solution of acid **2426** (1.0 g, 3.8 mmol) in 1:1 methanol:toluene (10 mL) was added dropwise TMS-diazomethane (3.2 mL of 2 M solution in hexane, 6.4 mmol) and the resulting solution was stirred at rt for 1 h. The reaction mixture was concentrated, partitioned between ethyl acetate and water and extracted with ethyl acetate. The combined organic extracts were washed with saturated sodium bicarbonate solution, brine, dried and evaporated to give ester **2427** as an off-white solid (0.907 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.28 (m, 4H), 5.53-5.46 (dd, 1H), 4.86-4.69 (m, 2H), 3.77-3.75 (d, 3H), 1.54-1.49 (d, 9H).

Part B:

Chloroketone **2428** was prepared using procedures described in Example 10. ^{1}H NMR (400 MHz, CDCl3) δ 7.46-7.30 (m, 4H), 5.65-5.48 (d of d, 1H), 4.90-4.71 (m, 2H), 4.42-4.06 (m, 2H), 1.57-1.52 (d, 9H).

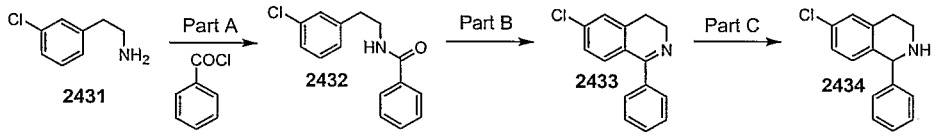
Part C:

Compound **2429** was prepared using procedures described in Example 10. HPLC-MS t_R = 1.51 min ($UV_{254\ nm}$); mass calculated for formula C17H21N3O2S 331.1, observed LCMS m/z 332.1 (M+H).

Part D:

Compound **2430** was prepared using procedures described in Example 10. HPLC-MS t_R = 0.80 min ($UV_{254\ nm}$); mass calculated for formula C12H13N3S 231.1, observed LCMS m/z 232.1 (M+H).

Example 55B:



Part A:

According to a modification of a procedure by Mach, U. R. et al. (*ChemBioChem* **2004**, *5*, 508-518) to a mixture of 3-chlorophenethylamine **2431** (3.89 g, 25 mmol) and 2 M potassium hydroxide solution (35 mL) was added dropwise benzoyl chloride (3.48 mL, 30 mmol). Within minutes a white precipitate formed, it was filtered and washed thoroughly with water, dried (air) and recrystallized (ethanol) to give amide **2432** as a white solid (4.22 g, 65%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (t, 1H, NH), 7.78-7.76 (d, 2H), 7.50-7.17 (m, 7H), 3.50-3.46 (m, 2H), 2.85 (t, 2H). HPLC-MS t_R = 1.81 min ($UV_{254\ nm}$); mass calculated for formula C15H14ClNO 259.1, observed LCMS m/z 260.0 (M+H).

Part B:

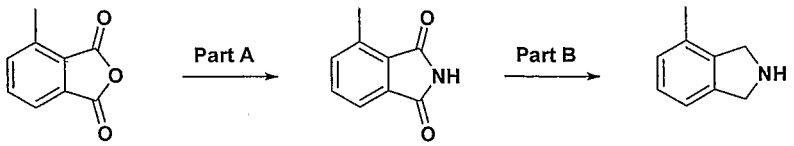
According to a modification of a procedure by Mach, U. R. et al. (*ChemBioChem* **2004**, *5*, 508-518) to a mixture of amide **2432** (1.79 g, 6.9 mmol) and powder zinc chloride (3.29 g, 24.1 mmol) in toluene (30 mL) was added dropwise phosphorus oxychloride (4.4 mL, 48.3 mmol) and the mixture

was heated at reflux for 2 h, during which time a polymer-like residue formed. The reaction mixture was cooled in an ice bath, quenched by the addition of 2 M sodium hydroxide solution, extracted and sonicated with dichloromethane (the residue dissolved). The combined dichloromethane extracts were concentrated to a solid residue, which was then triturated with THF. The resulting white solid was filtered and dried to give compound **2433** (1.23 g, 74%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82-7.67 (m, 6H), 7.58-7.55 (dd, 1H), 7.41-7.39 (d, 1H), 3.98 (t, 2H), 3.23 (t, 2H). HPLC-MS t_R = 0.96 min ($UV_{254\ nm}$); mass calculated for formula C15H12ClN 241.1, observed LCMS m/z 242.1 (M+H).

Part C:

According to a modification of a procedure by Mach, U. R. et al. (*ChemBioChem* **2004**, *5*, 508-518) to a solution of imine **2433** (760 mg, 3.14 mmol) in ethanol (50 mL) was added portionwise sodium borohydride (300 mg, 7.86 mmol) and the resulting mixture was heated at reflux overnight. The reaction mixture was cooled, quenched with water, concentrated, partitioned between ethyl acetate and water, and extracted with ethyl acetate. The combined organic extracts were dried and concentrated to give amine **2434** (418 mg, 55%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33-7.04 (m, 7H), 6.62-6.60 (d, 1H), 5.00 (s, 1H), 3.36-3.26 (m, 1H), 3.11-3.06 (m, 1H), 2.98-2.73 (m, 2H). HPLC-MS t_R = 1.14 min ($UV_{254\ nm}$); mass calculated for formula C15H14ClN 243.1, observed LCMS m/z 244.1 (M+H).

Example 55C:



2435 **2436** **2437**

Part A:

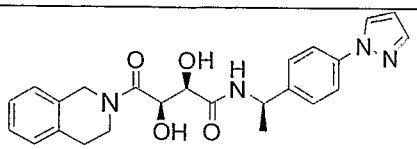
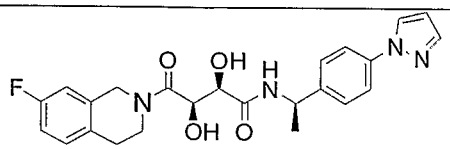
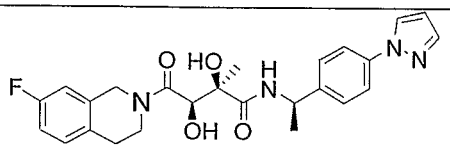
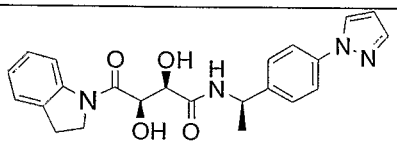
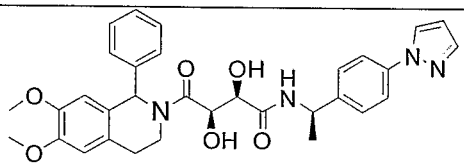
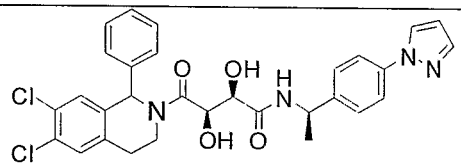
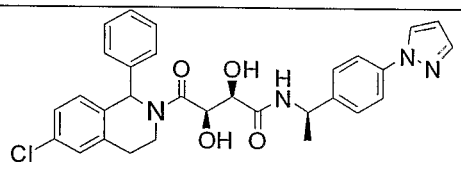
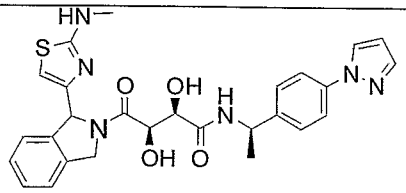
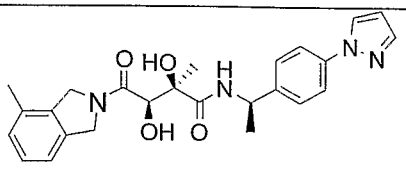
A mixture of compound **2435** (6 g, 36.5 mmol) and urea (1.95 g, 32.5 mmol) was heated over a sand bath at 350 °C for 30 minutes. The resulting black tar was cooled down to 100 °C and water (25 mL) was carefully added. This mixture was stirred for 1 hour. The solid was collected by filtration, dissolved in DMF (40 mL) and stirred with Darco (1 g) for 1 hour. The mixture was filtered and water (100 mL) was added to the filtrate to precipitate out a brown solid. The solid was collected by filtration and air dried. The the solid was dissolved in boiling MeOH (120 mL) with Darco (1 g). The mixture was filtered and the filtrate was concentrated to dryness. The residue was suspended in EtOAc and filtered to afford the desired compound **2436** as brown solid (2.5 g, 43%).

Part B:

Compound **2436** (1 g, 6.2 mmol) was added to a solution of 1M borane/THF (21 mL, 21 mmol) at 0 °C and the mixture was warmed to room temperature and then refluxed for 18 hours. The reaction mixture was cooled to room temperature and 6N HCl (50 mL) was added dropwise. The reaction mixture was concentrated to remove THF and then cooled to 0 °C and sodium hydroxide pellets (13 g) were added carefully to the reaction mixture. The reaction mixture was extracted with CH_2Cl_2 (1 x 50 mL, 1 x 20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (SiO_2, 3% MeOH(NH_3)/CH_2Cl_2, followed by 5% MeOH(NH_3)/CH_2Cl_2) afforded the desired compound **2437** as tan solid (64 mg, 7.7%).

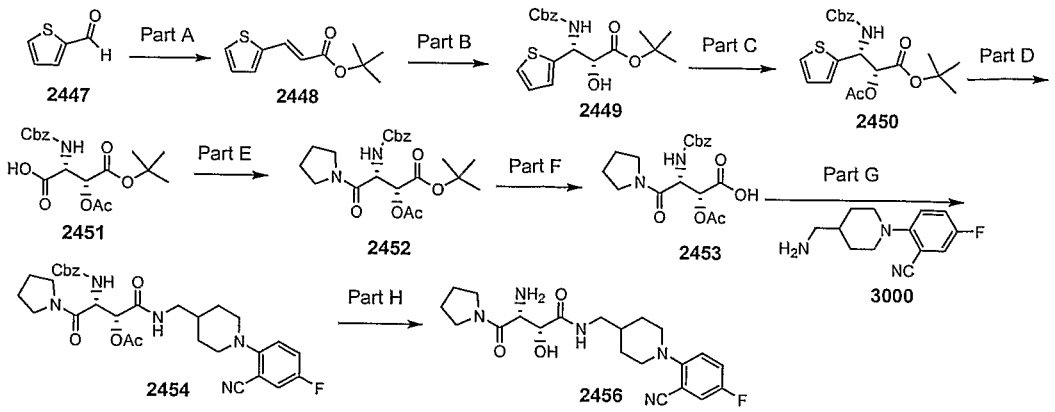
The following compounds were prepared using previously described procedures.

Compound #	Structure	Exact mass	MS m/z (M+H)

2438		434.2	435.1
2439		452.2	453.1
2440		466.2	467.0
2441		420.2	421.1
2442		570.2	571.1
2443		578.2	579.1
2444		544.2	545.0
2445		532.2	533.0
2446		448.2	449.1

Example 56:

Example 56A:



Parts A-D:

Compounds **2448-2451** were prepared according to the procedures in *Syn. Lett.* **1999**, 12, 1907-1910.

Part E:

Compound **2451** (200 mg, 0.52 mmol), HATU (260 mg, 0.68 mmol), pyrrolidine (0.052 mL, 0.624 mmol), and DIEA (0.1 mL) were dissolved in DMF (5 mL). The reaction mixture was stirred overnight at room temperature and then partitioned between ethyl acetate and water. The organic layers were washed with 1 M HCl, saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated. Purification by column chromatography (SiO_2, 50% ethyl acetate/hexanes) afforded the desired product (200 mg). HPLC-MS t_R = 1.91 min ($UV_{254\ nm}$); mass calculated for formula $C_{22}H_{30}N_2O_7$ 434.21, observed LCMS m/z 435.1 (M+H).

Part F:

Compound **2452** (200 mg, 0.46 mmol) was dissolved in methylene chloride (4 mL) and trifluoroacetic acid (1 mL). The reaction mixture was stirred at room temperature for 4 hours. The solvent was evaporated and the material was used without further purification (160 mg). HPLC-MS t_R = 1.31 min ($UV_{254\ nm}$); mass calculated for formula $C_{18}H_{22}N_2O_7$ 434.21, observed LCMS m/z 379.1 (M+H).

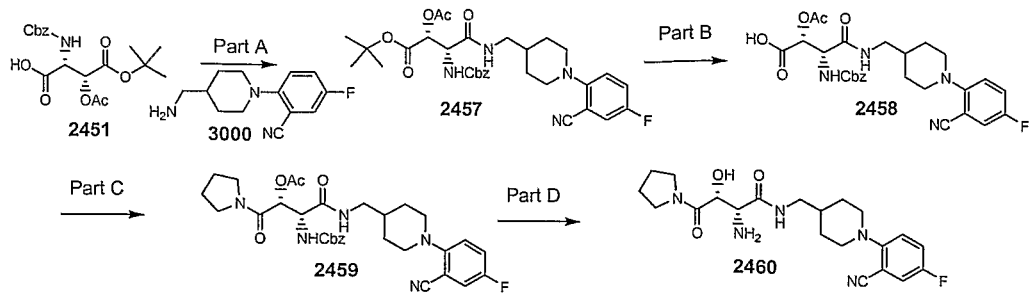
Part G:

Compound **2453** (160 mg, 0.423 mmol), compound **3000** (prepared as described in Example 27A) (122 mg, 0.423 mmol), HATU (210 mg, 0.55 mmol), and DIEA (0.5 mL) were dissolved in DMF (10 mL). The reaction mixture was stirred overnight at room temperature and then partitioned between ethyl acetate and water. The organic layers were washed with 1 M HCl, saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated. Purification by column chromatography (SiO_2, 25% ethyl acetate/hexanes to 100% ethyl acetate) afforded the desired product (175 mg). HPLC-MS t_R = 1.94 min ($UV_{254\ nm}$); mass calculated for formula $C_{31}H_{36}FN_5O_6$ 593.2, observed LCMS m/z 594.2 (M+H).

Part H:

Compound **2454** (50 mg, 0.084 mmol) was dissolved in 7 M ammonia in MeOH (0.5 mL) and MeOH (2 mL) and stirred for 30 minutes. The solvent was removed under reduced pressure. The residue was dissolved in MeOH (5 mL) and acetic acid (0.3 mL) and Pd-C (100 mg) was added under an argon atmosphere. The reaction was stirred under a hydrogen atmosphere for 3 hours and then filtered through a pad of celite. The solvent was evaporated and the residue was partitioned between ethyl acetate and water. The combined organic layers were washed with saturated sodium bicarbonate, brine, dried over sodium sulfate and concentrated. The residue was dissolved in ethyl acetate (2 mL) and treated with 4 M HCl in dioxane (0.1 mL). The solids were filtered and washed several times with ethyl acetate to obtain the desired product as an HCl salt (23 mg). HPLC-MS t_R = 1.15 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{28}FN_5O_3$ 417.2, observed LCMS m/z 418.1 (M+H).

Example 56B:



Part A:

Compound **2451** (200 mg, 0.52 mmol), compound **3000** (194 mg, 0.68 mmol), HATU (260 mg, 0.68 mmol), and DIEA (0.5 mL) were dissolved in DMF (5 mL). The reaction mixture was stirred overnight at room temperature and then partitioned between ethyl acetate and water. The organic layers were washed with 1 M HCl, saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated. Purification by column chromatography (SiO_2, 33% ethyl acetate/hexanes to 100% ethyl acetate) afforded the desired product (230 mg). HPLC-MS t_R = 2.20 min ($UV_{254\ nm}$); mass calculated for formula $C_{31}H_{37}FN_4O_7$ 596.2, observed LCMS m/z 597.2 (M+H).

Part B:

Compound **2457** (230 mg, 0.386 mmol) was dissolved in methylene chloride (4 mL) and trifluoroacetic acid (1 mL). The reaction mixture was stirred at room temperature for 4 hours. The solvent was evaporated and **2458** (190 mg) was used without further purification. HPLC-MS t_R = 1.77 min ($UV_{254\ nm}$); mass calculated for formula $C_{27}H_{29}FN_4O_7$ 540.2, observed LCMS m/z 541.2 (M+H).

Part C:

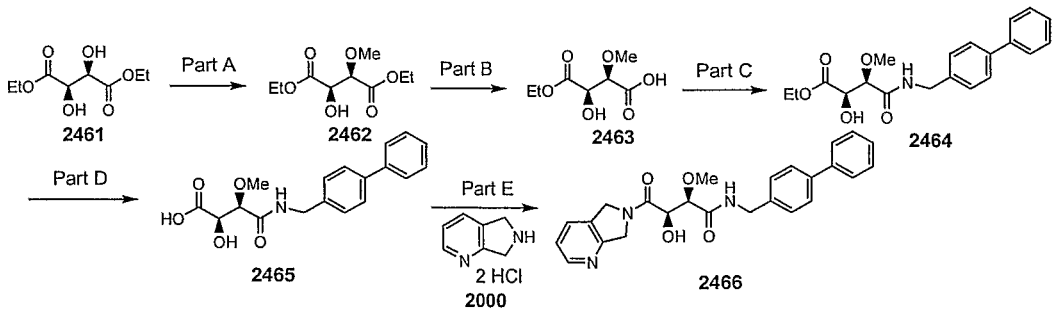
Compound **2458** (190 mg, 0.32 mmol), HATU (160 mg, 0.416 mmol), pyrrolidine (0.035 mL, 0.416 mmol), and DIEA (0.5 mL) were dissolved in DMF (5 mL). The reaction mixture was stirred overnight at room temperature and then partitioned between ethyl acetate and water. The organic layers were washed with 1 M HCl, saturated sodium bicarbonate, brine, dried over

sodium sulfate, and concentrated. Purification by column chromatography (SiO_2, 25% ethyl acetate/hexanes to 100% ethyl acetate) afforded the desired product (200 mg). HPLC-MS t_R = 1.92 min ($UV_{254\ nm}$); mass calculated for formula $C_{31}H_{36}FN_5O_6$ 593.2, observed LCMS m/z 594.2 (M+H).

Part D:

Compound **2459** (55 mg, 0.092 mmol) was dissolved in 7 M ammonia in MeOH (0.5 mL) and MeOH (2 mL) and stirred for 30 minutes. The solvent was removed under reduced pressure. The residue was dissolved in MeOH (5 mL) and acetic acid (0.3 mL) and Pd-C (100 mg) was added under an argon atmosphere. The reaction was stirred under a hydrogen atmosphere for 3 hours and then filtered over a bed of celite. The solvent was evaporated and the residue was partitioned between ethyl acetate and water. The combined organic layers were washed with saturated sodium bicarbonate, brine, dried over sodium sulfate and concentrated. The residue was dissolved in ethyl acetate (2 mL) and treated with 4 M HCl in dioxane (0.1 mL). The solids were filtered and washed several times with ethyl acetate to obtain **2460** as an HCl salt (29 mg). HPLC-MS t_R = 1.15 min ($UV_{254\ nm}$); mass calculated for formula $C_{21}H_{28}FN_5O_3$ 417.2, observed LCMS m/z 418.1 (M+H).

Example 56C:



Part A:

Compound **2462** was prepared using a modification of the procedure in *Chem. Pharm. Bull.* **1991**, 39, 8, 1972-1982. Compound **2461** (1.06 g, 5.14 mmol) and Bu_2SnO (1.28 g, 5.14 mmol) were dissolved in toluene (20 mL) and stirred at reflux for 1.5 hours using a Dean-Stark trap to azeotrope the

water formed in the reaction. The solvent was evaporated under reduced pressure and placed under vacuum for 1 hr. Cesium fluoride (1.08 g, 6.68 mmol) was added to the residue and placed under vacuum for an additional 2 hours. The mixture was then dissolved in DMF (20 mL) and iodomethane (2.99 g, 22.1 mmol) and stirred overnight at room temperature. The reaction mixture was partitioned between ethyl acetate and water. The organic layers were washed with 1 N HCl, saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated. Purification by column chromatography (SiO_2, 33% ethyl acetate/hexanes) afforded the desired product (800 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 4.60 (d, 1H), 4.30 (m, 4H), 4.15 (d, 1H), 3.50 (s, 3H), 1.35 (t, 6H).

Part B:

Compound **2463** was prepared using a modification to a procedure found in *Tetrahedron* **1993**, 49, 37, 8381-8396. The diester **2462** (0.837 g, 3.6 mmol) was suspended in pH 8 phosphate buffer (75 mL) and pH was monitored at 8.33. Pig liver esterase (20 mg) was added to the suspension and the reaction mixture was stirred at room temperature. The pH of the reaction was maintained between 7.9-8.2 by the dropwise addition of 1M NaOH (3.27 mL, 3.24 mmol) over 1.5 hours. The reaction mixture was partitioned between diethyl ether and water. The aqueous layer was acidified to pH 2 and extracted with ethyl acetate. The combined ethyl acetate layers were dried over sodium sulfate and evaporated to provide the desired product as a 4.5:1 mixture of inseparable acids (275 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 4.60 (d, 1H), 4.40 (m, 2H), 4.25 (d, 1H), 3.50 (s, 3H), 1.35 (t, 3H).

Part C:

Compound **2463** (130 mg, 0.65 mmol), HATU (322 mg, 0.845 mmol), 4-phenylbenzylamine (153 mg, 0.845 mmol), and DIEA (0.2 mL) were dissolved in DMF (6 mL). The reaction mixture was stirred overnight at room temperature and then partitioned between ethyl acetate and water. The organic layers were washed with 1 M HCl, saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated. Recrystallization from

ethyl acetate provided pure product (50 mg) and slightly impure product (150 mg). HPLC-MS t_R = 1.70 min ($UV_{254\ nm}$); mass calculated for formula $C_{20}H_{23}NO_5$ 357.1, observed LCMS m/z 358.1 (M+H).

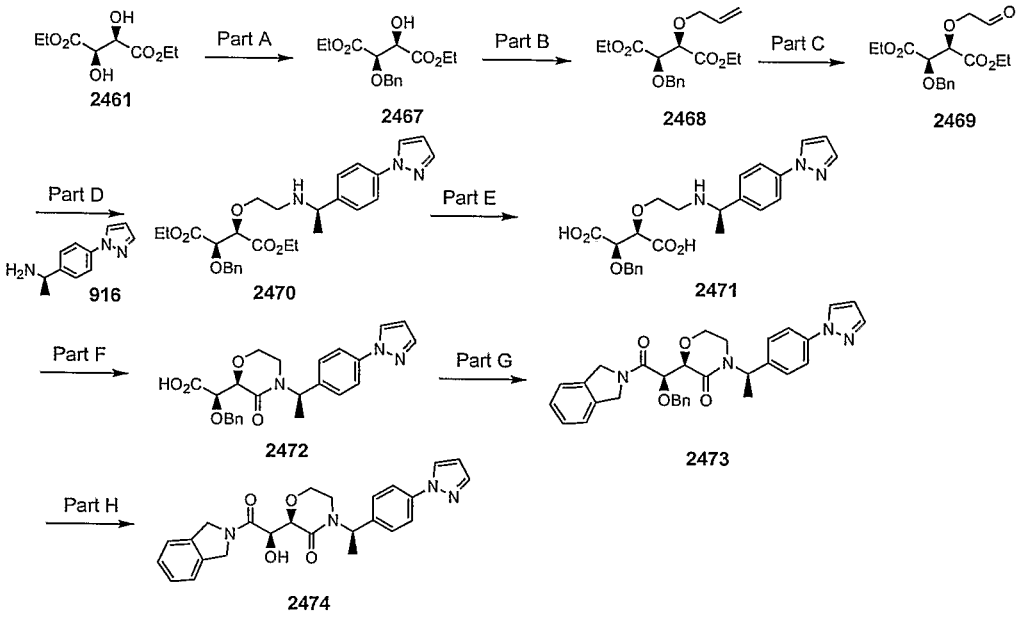
Part D:

Compound **2464** (50 mg, 0.140 mmol) was dissolved in 1 M LiOH (0.151 mL, 0.151 mmol) and THF (5 mL) and stirred for 1 hour. The reaction mixture was partitioned between ethyl acetate and water and the aqueous layer was acidified to pH 2 using 1N HCl. The organic layers were dried over sodium sulfate and concentrated to provide the desired product (46 mg). HPLC-MS t_R = 1.43 min ($UV_{254\ nm}$); mass calculated for formula $C_{18}H_{19}NO_5$ 329.1, observed LCMS m/z 330.1 (M+H).

Part E:

Compound **2465** (46 mg, 0.140 mmol), HATU (70 mg, 0.182 mmol), compound **2000** (35 mg, 0.182 mmol), and DIEA (0.12 mL) were dissolved in DMF (6 mL). The reaction mixture was stirred overnight at room temperature and then partitioned between ethyl acetate and water. The organic layers were washed with saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated. Recrystallization from ethyl acetate provided pure product (30 mg). HPLC-MS (10 min) t_R = 3.51 min ($UV_{254\ nm}$); mass calculated for formula $C_{25}H_{25}N_3O_4$ 431.2, observed LCMS m/z 432.1 (M+H).

Example 56D:



Part A:

Compound **2467** was prepared according to a modified literature procedure (Nagashima, N. and Ohno, M., *Chem. Pharm. Bull.*, **1991**, *39*, 1972-1982.)

L-Diethyl tartrate (2461) (6.18 g, 30 mmol) and dibutyltin oxide (7.47 g, 30 mmol) in toluene (100 mL) was heated under reflux for 1h, removing water formed as the azotropic mixture. The solution was evaporated to complete dryness *in vacuo* to afford a white solid. To this solid was added dry CsF (8.66 g, 59 mmol) and DMF (60 mL). The resulting mixture was cooled to 0 °C, and benzyl bromide (6 mL, 51 mmol) was added dropwise via a syringe. After the completion of addition, the reaction mixture was allowed to stir rigorously at room temperature for 12 h. The solvent was removed under vacuum and the obtained residue was dissolved in EtOAc and H_2O. The organic layer was washed with $NaHCO_3$ aqueous solution, brine, dried over Na_2SO_4, and concentrated. Purification by flask column chromatography on silica gel (EtOAc / hexane 30:70) afforded compound **2467** as colorless liquid (8.10 g, 91%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.25 (m, 5H), 4.87 (d, J = 12.0 Hz, 1H), 4.58 (br s, 1H), 4.02 (d, J = 12.0 Hz, 1H), 4.34 – 4.25 (m, 3H),

4.23-4.21 (m, 1H), 4.08 – 4.03 (m, 1H), 3.12 (br s, 1H), 1.35 (t, J = 7.0 Hz, 3H), 1.19 (t, J = 6.9 Hz, 3H).

Part B:

To compound **2467** (2.96 g, 10 mmol) in toluene (10 mL) was added with Ag_2O (4.63 g, 20 mmol) and allyl bromide (1.31 mL, 15 mmol). The reaction mixture was allowed to stir at 110 °C for 16 h and cooled to room temperature. After filtering through a pad of celite, the solution was concentrated. Flash column chromatography on silica gel (EtOAc / hexane 20: 80) afforded the desired product **2468** (2.65 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.25 (m, 5H), 4.87 (d, J = 12.0 Hz, 1H), 5.89-5.79 (m, 1H), 5.26-5.15 (m, 2H), 4.87 (d, J = 11.4 Hz, 1H), 4.46 (d, J = 11.7 Hz, 1H), 4.41-4.38 (m, 2H), 4.34 – 3.92 (m, 6H), 1.32 (t, J = 7.2 Hz, 3H), 1.19 (t, J = 7.2 Hz, 3H).

Part C:

To an ice-cold mixture of compound **2468** (1.0 g, 3 mmol) and N-methylmorpholine monohydrate (703 mg, 6 mmol) in THF / H_2O 3:1 (20 mL) was added OsO_4 (2.5 wt% in *t*-BuOH, 610 mg, 0.06 mmol). After stirring for 30 min, the ice bath was removed and the reaction mixture was stirred at room temperature overnight. Solid $NaHSO_3$ (750 mg, 7.2 mmol) was added, and the mixture was stirred for an additional 30 min. The mixture was filtered through a pad of silica and the solution was concentrated *in vacuo* giving rise to an oil. This material was dissolved in THF/H_2O 3:1 (20 mL) and $NaIO_4$ (1.28 g, 6 mmol) was added. The mixture was allowed to stir at room temperature for 1 h. It was filtered through silica, and the solvent was evaporated. Flash column chromatography on silica gel (EtOAc/ hexane 50:50) provided the aldehyde **2469** (760 mg, 75%) as a colorless oil). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.35-7.26 (m, 5H), 4.89 (d, J = 11.8 Hz, 1H), 4.52-4.48 (m, 2H), 4.45 – 4.04 (m, 7H), 1.34 (t, J = 7.7 Hz, 3H), 1.19 (t, J = 7.4 Hz, 3H).

Part D:

Compound **2469** (340 mg, 1 mmol) and amine **916** (187 mg, 1 mmol) in 1,2-dichloroethane (5 mL) were stirred at room temperature for 5 min, after which sodium tri(acetoxyl)borohydride (254 mg, 1.2 mmol) was added slowly. The reaction mixture was allowed to stir at room temperature overnight. The solution was concentrated, the crude residue was purified by flash column chromatography on silica gel (MeOH/EtOAc 10:90), affording desired product **2470** (350 mg, 69%) as a colorless oil. HPLC-MS t_R = 1.49 min ($UV_{254\ nm}$); mass calculated for formula $C_{28}H_{35}N_3O_6$ 509.2, observed LCMS m/z 510.1 (M+H).

Part E:

To a solution of compound **2470** (170 mg, 0.33 mmol) in dioxane / water 1:1 (10 mL) was added LiOH (1M, 1.32 mL, 1.32 mmol) dropwise. The mixture was stirred at room temperature for 2h after which it was neutralized with 1 M HCl and concentrated. The residue was utilized for the following step without further purification. HPLC-MS t_R = 1.12 min ($UV_{254\ nm}$); mass calculated for formula $C_{24}H_{27}N_3O_6$ 453.2, observed LCMS m/z 454.1 (M+H).

Part F:

The crude compound **2471** was dissolved in DMF (10 mL) and cooled to 0 °C in an ice bath, HATU (304 mg, 0.8 mmol) was added slowly and the reaction mixture was stirred at 0 °C for 2h. LC-MS indicated the disappearance of diacid and the formation of the cyclized product **2472**. HPLC-MS t_R = 1.65 min ($UV_{254\ nm}$); mass calculated for formula $C_{24}H_{25}N_3O_5$ 435.2, observed LCMS m/z 436.1 (M+H).

Part G:

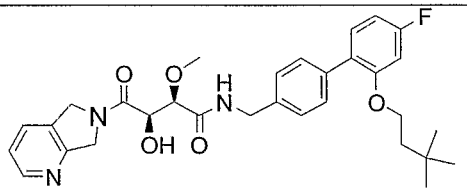
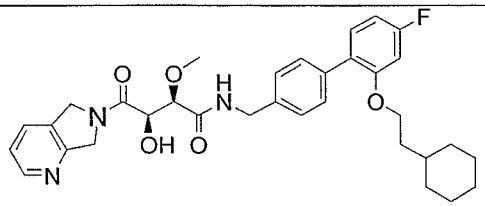
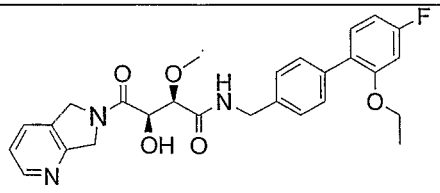
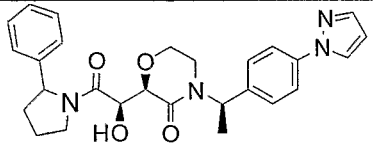
To the above solution at 0 °C was added isoindoline (48 mg, 0.4 mmol) and the reaction mixture was stirred at room temperature overnight. The DMF was evaporated, the residue was dissolved inn EtOAc and water, washed with 1N HCl, saturated NaHCO3 and brine, dried over Na2SO4 and concentrated to afford **2437** as an oily solid (85 mg, 47% yield over three steps). HPLC-MS

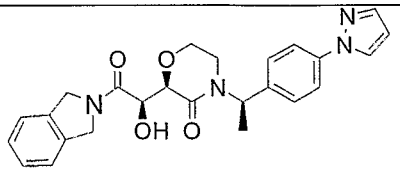
t_R = 2.00 min ($UV_{254\ nm}$); mass calculated for formula $C_{32}H_{32}N_4O_4$ 536.1, observed LCMS m/z 537.1 (M+H).

Part H:

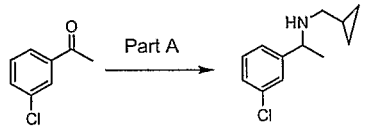
Crude compound **2473** was dissolved in EtOH (20 mL), and palladium on carbon (10%, 40 mg) was added. The mixture was hydrogenated (atmospheric pressure) at room temperature overnight. The suspension was filtered through celite and concentrated. The resulting residue was purified by preparative LC affording **2474** as a white solid (9.4 mg). HPLC-MS t_R = 3.57 min (10 min method, $UV_{254\ nm}$); mass calculated for formula $C_{25}H_{26}N_4O_4$ 446.2, observed LCMS m/z 447.1 (M+H).

The following compounds were prepared using previously described procedures.

Compound #	Structure	Exact mass	MS m/z (M+H)
2475		549.3	550.2
2476		575.3	576.1
2477		493.2	494.2
2478		474.2	475.1

2474		446.2	447.1

Example 57:

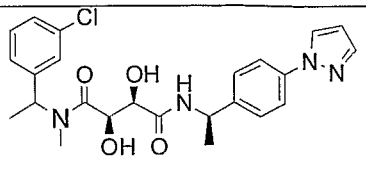


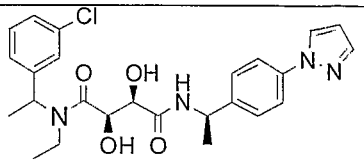
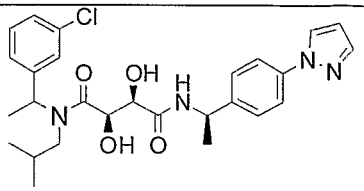
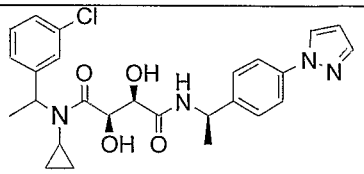
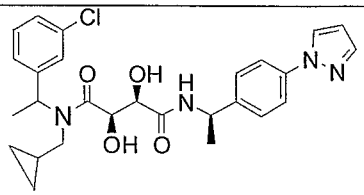
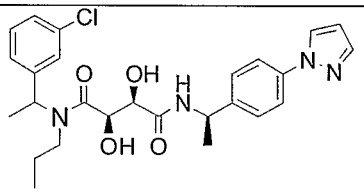
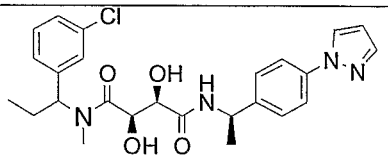
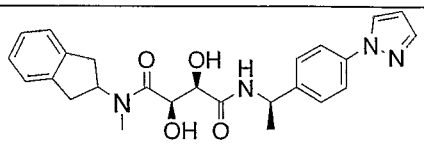
2183 **2479**

Part A:

Compound **2183**(200 mg, 1.3 mmol) and cyclopropylmethyl amine (0.16 mL) were dissolved in MeOH (5 mL) and stirred at 50 °C overnight. Then sodium borohydride (42 mg, 1.3 mmol) was added and the mixture was stirred for 2 hours. The solvent was removed under reduced pressure and the residue was partitioned between diethyl ether and 1 N HCl. The aqueous layer was made basic and extracted with ethyl acetate. The combined ethyl acetate layers were dried over sodium sulfate and concentrated to provide the desired product **2479** (130 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 1H), 7.28-7.18 (m, 3H), 3.79 (m, 1H), 2.50-2.25 (m, 2H), 1.38 (d, 3H), 1.00-0.90 (m, 1H), 0.50-0.45 (m, 2H), 0.10-0.00 (m, 2H).

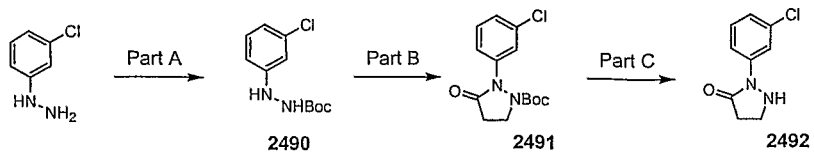
The following compounds were prepared using previously described procedures.

Compound #	Structure	Exact mass	MS m/z (M+H)
2480		470.2	471.1

2481		484.2	485.0
2482		512.2	513.1
2483		496.2	497.0
2485		510.2	511.1
2486		498.2	499.1
2487		484.2	485.0
2489		448.2	449.1

Example 58:

Example 58A:



Part A:

To a solution of Boc_2O (6.1 g, 28 mmol) and Et_3N (7.8 mL, 56 mmol) in DMF (20 mL) at 0 °C was added portionwise 3-chlorophenylhyrazine hydrocloride (5.0 g, 28 mmol) in DMF (20 mL). The reaction mixture was allowed to stir at room temperature for 2 h and concentrated. The residue was dissolved in EtOAc and H_2O, washed with 1N citric acid and saturated $NaHCO_3$, dried over Na_2SO_4 and concentrated, affording **2490** (17.83 g, 97%) as a off-white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (t, *J* = 8.3 Hz, 1H), 6.86-6.81 (m, 2H), 6.70-6.66 (m, 1H), 6.36 (br s, 1H), 1.48 (s, 10H).

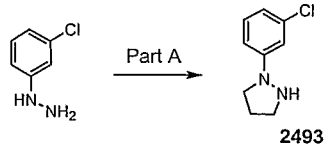
Part B:

3-Chloropropionyl chloride (0.400 mL, 4.12 mmol) was added dropwise into a solution of compound **2490** (1.0 g, 4.12 mmol) and K_2CO_3 (1.14 g, 8.24 mmol) in DMF (10 mL) at 0 °C. The reaction mixture was allowed to stir at 80°C overnight and concentrated. The residue was dissolved in EtOAc and H_2O, washed with 1N citric acid and saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated. Column chromatography (EtOAc/hexane 25:75) provided compound **2491** (600 mg, 49%) as an off-white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (t, *J* = 2.3 Hz, 1H), 7.51-7.48 (m, 1H), 7.27 (t, *J* = 8.3 Hz, 1H), 7.12-7.09 (m, 1H), 4.16 (t, *J* = 7.2 Hz, 2H), 2.77 (t, *J* = 7.3 Hz, 2H), 1.34 (s, 9H).

Part C:

Compound **2491** was deprotected with TFA in CH_2Cl_2. The material was used without further purification.

Example 58B:

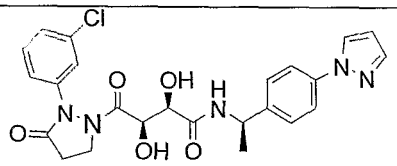
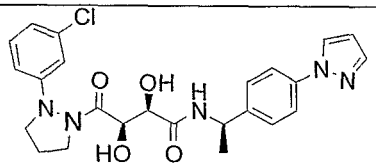
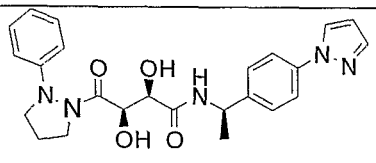


2493

Part A:

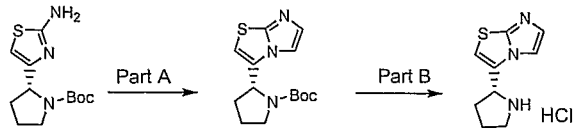
To a suspension of NaH (60% in mineral oil, 1.56 g, 39 mmol) in benzene (40 mL) at 0 °C was added with 3-chlorophenylhyrazine (2.13 g, 15 mmol). The mixture was stirred at 80 °C for 1 h, after which 1,3-dibromopropane (2.0 g, 10 mmol) was added slowly via syringe. It was stirred at 80 °C overnight and quenched by adding water (20 mL). The organic layer was separated, washed with water and brine, dried over Na_2SO_4, and concentrated. Column chromatography (DCM) provided compound **2493** (850 mg, 47%) as pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (t, *J* = 8.2 Hz, 1H), 7.04 (t, *J* = 2.3 Hz, 1H), 6.84-6.81 (m, 1H), 6.74-6.71 (m, 1H), 3.75 (bs, 1H), 3.35 (t, *J* = 7.5 Hz, 2H), 3.00 (t, *J* = 6.7 Hz, 2H), 2.16-2.11 (m, 2H).

The following compounds were prepared using previously described procedures.

Compound #	Structure	Exact mass	MS m/z (M+H)
2494		497.2	498.1
2495		483.2	484.1
2496		449.2	450.1

Example 59:

Example 59A:



471 2500 2501

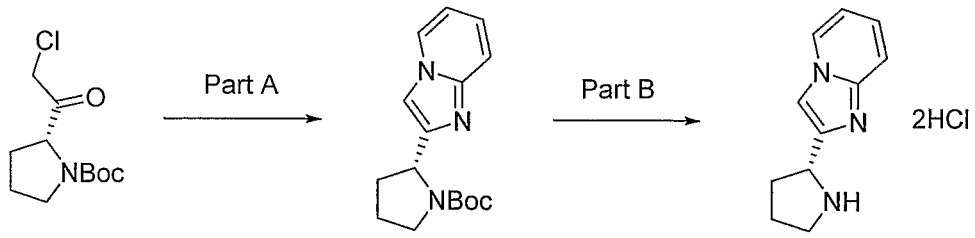
Part A:

To compound **471** (100 mg, 0.37 mmol) in EtOH (2 mL) was added chloroacetaldehyde (50 wt.% in water, 233 mg, 1.48 mmol). The reaction mixture was allowed to stir at 90 °C overnight and concentrated. The residue was dissolved in EtOAc , washed with water and brine, dried (Na_2SO_4) and concentrated. The crude product **2500** (90 mg, 82%) was used without further purification. HPLC-MS t_R = 1.10 min; Mass calculated for formula $C_{14}H_{19}N_3O_2S$ 293.1, observed m/z 294.1(M+H).

Part B:

Compound 2500 (90 mg) was dissolved in 2 mL of 4 N HCL in dioxane/H2O (1:1). After stirring at room temperature for 1 h, the solution was concentrated, affording a brown solid (80 mg, 90%). HPLC-MS t_R = 0.22 min; Mass calculated for formula $C_9H_{11}N_3S$ 193.1, observed m/z 194.1(M+H).

Example 59B:



470 **2502** **2503**

Part A:

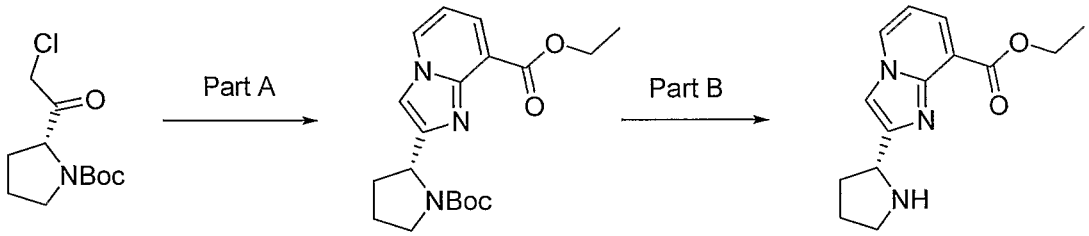
A mixture of chloroketone **470** (200 mg, 0.81 mmol) and 2-aminopyridine (77 mg, 0.82 mmol) in ethanol (5 ml) was heated to reflux and stirred overnight. The reaction mixture was concentrated and purified by prep-HPLC to afford

2502 (103 mg). HPLC-MS t_R = 1.00 min ($UV_{254\ nm}$); mass calculated for formula C16H21N3O2 287.2, observed LCMS m/z 288.3 (M+H).

Part B:

To a solution of imidazopyridine **2502** (103 mg, 0.56 mmol) in dioxane (2 mL) was added HCl (4N in dioxane, 4 mL) and water (0.5 mL). The mixture was stirred at room temperature for 1 hour and concentrated. The resulting residue **2503** (81 mg) was dried under vacuum and used in the next step without further purification. HPLC-MS t_R = 0.19 min ($UV_{254\ nm}$); mass calculated for formula C11H13N3 187.1, observed LCMS m/z 188.1 (M+H).

Example 59C:



470 **2504** **2505**

Part A:

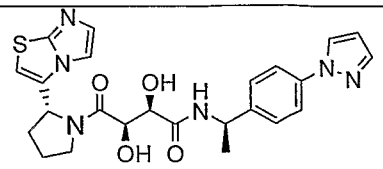
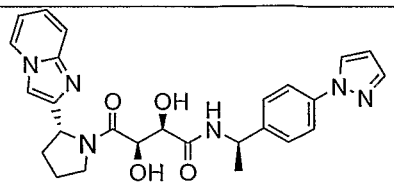
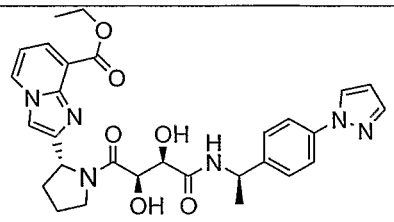
A mixture of chloroketone **471** (200 mg, 0.81 mmol) and 2-aminopyridine (140 mg, 0.81 mmol) in ethanol (5 ml) was heated up to reflux and stirred overnight. The reaction mixture was concentrated and purified by prep-HPLC to afford **2504** (119 mg). HPLC-MS t_R = 1.22 min ($UV_{254\ nm}$); mass calculated for formula C19H25N3O4 359.2, observed LCMS m/z 360.1 (M+H).

Part B:

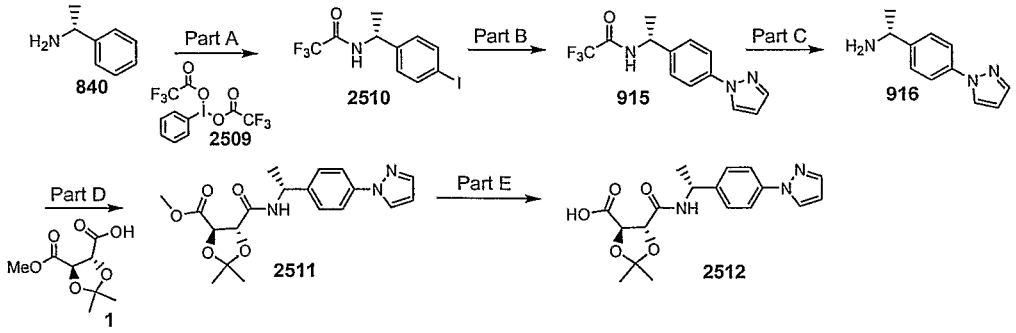
To a solution of imidazopyridine **2504** (119 mg, 0.33 mmol) in dioxane (2 mL) was added HCl (4N in dioxane, 4 mL) and water (0.5 mL). The mixture was stirred at room temperature for 1 hour and concentrated. The resulting residue **2505** (83 mg) was dried under vacuum and used in the next step without

further purification. HPLC-MS t_R = 0.70 min ($UV_{254\ nm}$); mass calculated for formula C14H17N3O2 259.1, observed LCMS m/z 260.1 (M+H).

The following compounds were prepared using previously described procedures.

Compound #	Structure	Exact mass	MS m/z (M+H)
2506		494.2	495.1
2507		488.2	489.1
2508		560.2	561.2

Example 60:



Part A:

Trifluoroacetic anhydride (16 mL, 115.1 mmol) was dissolved in methylene chloride (60 mL) and cooled in an ice bath. Compound **840** (10.0 g, 82.6 mmol) was added dropwise in methylene chloride (40 mL) and stirred at room temperature for one hour. The solution was cooled in an ice bath and iodine (11.0 g, 43.2 mmol) and compound **2509** (9.8 g, 22 mmol) were added and stirred for 12 hours in the dark (cover flask with aluminum foil). Additional compound **2509** (9.5 g, 20 mmol) was added and stirring was continued for 12 hours. The reaction mixture was added to a cooled solution of methylene

chloride and 5% sodium bisulfite and stirred for one hour. The organic layer was washed with saturated sodium bicarbonate, filtered through a pad of silica, and concentrated. The residue was suspended in diethyl ether (30 mL) and hexanes (90 mL) and stirred for 30 minutes. The mixture was filtered to provide compound **2510** as a white solid (15.5 g). The product was stored in the dark at room temperature. ^{1}H NMR (400 MHz, $CDCl_3$) □□□d, 2H), 7.06 (d, 2H), 5.10 (m, 1H), 1.60 (d, 3H).

Part B:

Compound **2510** (4.0 g, 11.66 mmol), pyrazole (0.953 g, 14 mmol), copper (I) iodide (444 mg, 2.33 mmol), cesium carbonate (7.6 g, 23.3 mmol), 1,10 phenanthroline (844 mg, 4.66 mmol) and dimethylacetamide (40 mL) were combined in a 80 mL screw-capped vial and stirred in the dark at 120 °C for 12 hours. The reaction mixture was poured into ethyl acetate (200 mL) and filtered. The organic layer was washed with water several times followed by 1N citric acid solution. The organic layer was dried over sodium sulfate and concentrated. The residue was recrystallized from ethyl acetate and hexanes to provide 2.45 g of compound **915**. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.92 (m, 1H), 7.70 (m, 2H), 7.40 (d, 1H), 6.45 (t, 1H), 5.20 (m, 1H), 1.65 (d, 3H).

Part C:

Compound **915** (2.43 g, 9.13 mmol) was dissolved in methanol (20 mL) and 1N lithium hydroxide (20 mL) and stirred for 6 hours. The reaction mixture was poured into ethyl acetate and water. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated to provide compound **916** (1.45 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.90 (d, 1H), 7.70 (d, 1H), 7.64 (d, 2H), 7.43 (d, 2H), 6.46 (t, 1H), 1.44 (d, 3H).

Part D:

Compound **916** (1.45 g, 7.7 mmol), compound **1** (1.5 g, 7.35 mmol), HATU (3.63 g, 9.55 mmol), and diisopropylethylamine (1.28 mL, 7.35 mmol) were

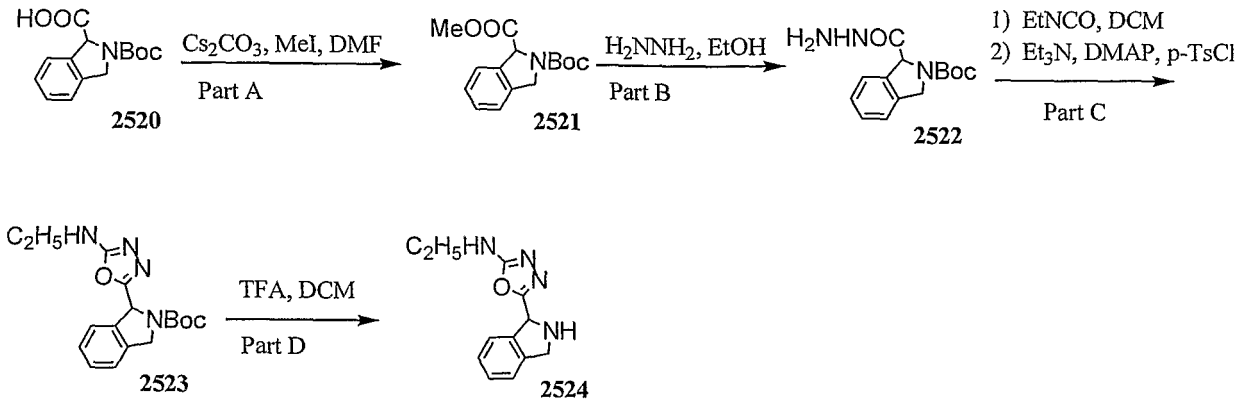
dissolved in DMF (20 mL) at 0 °C. The reaction mixture was stirred for 12 hours and then diluted with water and extracted with ethyl acetate. The combined organic layers were washed with 1N HCl, saturated sodium bicarbonate, brine and water, dried over sodium sulfate and concentrated. The residue was purified by column chromatography (2:1 hexanes/ethyl acetate) to provide compound **2511** (2.15 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.90 (d, 1H), 7.72 (m, 1H), 7.66 (d, 2H), 7.40 (d, 2H), 6.75 (d, 1H), 6.49 (d, 1H), 5.20 (m, 1H), 4.82-4.75 (dd, 2H), 3.83 (s, 3H), 1.57 (d, 3H), 1.54 (s, 3H), 1.50 (s, 3H).

Part E:

Compound **2511** (2.15 g, 5.76 mmol) was dissolved in THF (20 mL) and 1N lithium hydroxide and stirred for 2 hours. Diethyl ether was added and the aqueous layer was acidified to pH 2 with 1 N HCl and extracted with ethyl acetate. The combined ethyl acetate layers were dried over sodium sulfate and concentrated to provide compound **2512** as a white solid (1.95 g). 1H NMP (400MHz, $CDCl_3$) δ7.9 (d, 1H), 7.74 (m, 1H), 7.70 (d, 2H), 7.42 (d, 2H), 6.96 (d, 1H), 6.49 (t, 1H), 5.2 (m, 1H), 4.60-4.50 (dd, 2H), 1.64 (d, 3H), 1.54 (d, 3H).

Example 61:

Example 61A:



Part A:

(R,S)-BOC-1,3-Dihydro-2H-Isoindole carboxylic acid **2520** (3.0 g, 11.39 mmol) and cesium carbonate (4.05 g, 12.43 mmol) were stirred together in DMF (25mL) at r.t. for one hour. Iodomethane (1.05 mL, 16.86 mmol) was added and the reaction mixture was stirred at ambient temperature overnight. The reaction mixture was diluted with ethyl acetate then washed several times with water, brine (1 x 50 mL), dried over Na_2SO_4 and concentrated to give light yellow oil. Purification by column chromatography (SiO2, 25% ethyl acetate / hexane) afforded **2521** (2.66 g, 84 %) as white solid.

Part B:

A mixture of **2521** (0.2 g, 0.72 mmol) and hydrazine (0.22 mL, 7.0mmol) in ethanol (20 mL) was heated at 70 °C for 5 hours. The solvent was removed under reduced pressure and the resulting residue was dissolved in ethyl acetate, washed with water (2 x 30mL), brine (1 x 20 mL), dried over Na_2SO_4 and concentrated to provide **2522** (0.18 g, 86%) as an yellow oil, which was used in the next step without further purification.

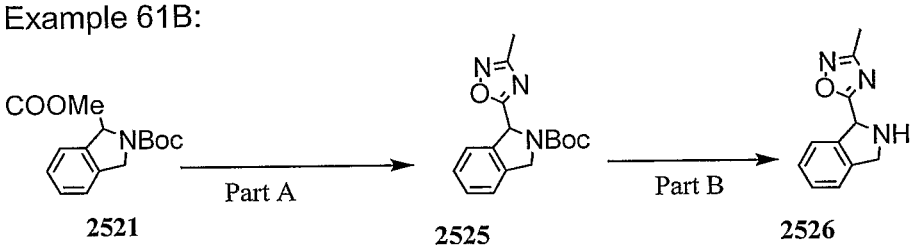
Part C:

A mixture of **2522** (0.2 g, 0.72 mmol) and ethyl isocyanate (0.077 g, 1.083 mmol) in DCM (5 mL) was stirred at r.t. for 16 hours. Additional ethyl isocyanate (0.077 g, 1.083 mmol) was added and reaction was stirred for another two hours. The solvent was removed under reduced pressure to provide the crude product as a white gum. It was dissolved in DCM (20 mL) and treated triethyl amine (0.5 mL, 3.6 mmol) , DMAP (0.017 g, 0.139 mmol) and *p*-toluene sulphonyl chloride (0.16 g, 0.83 mmol). The mixture was stirred at room temperature for 64 hours and the solvent was removed. The residue was purified by preparative chromatography using 5% MeOH/CH_2Cl_2, to provide the product which was again purified using ethyl acetate/Hexane (3/1) to yield intermediate **2523** (0.1 g, 44%) as a light brown solid.

Part D:

Intermediate **2523** (0.05 g, 0.15 mmol) was dissolved in DCM (10 mL) then trifluoroacetic acid (0.06 mL, 0.77 mmol) was added. Reaction was stirred at ambient temperature for 3 hours and then concentrated. The residue was dissolved in DCM and washed with saturated sodium bicarbonate solution (1 x 0.8 mL), saline(1 x 0.8 mL), dried over sodium sulfate and concentrated under vacuum to provide amine **2524** (0.03 g, 86%) as a brown oil. It was used in the next step without additional purification.

Example 61B:



2521 **2525** **2526**

Part A:

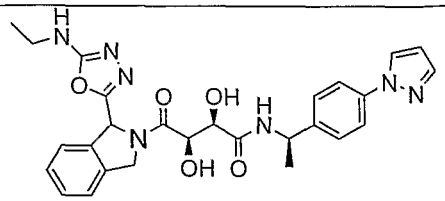
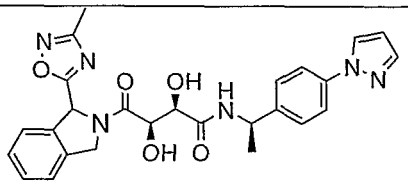
Intermediate **2525** was prepared by known methods (Showell , G.A.; Gibbons, T.L.; Kneen, C.O.; Macleod, A.M..; Merchant, K.; Saunders, J.; Freedman, S.B.; Patel, S; Baker, R.. *J Med Chem.* **1991**, *34* (3), 1086-1094).

Part B:

Intermediate **2526** was prepared using the method described in Example 61A Part D.

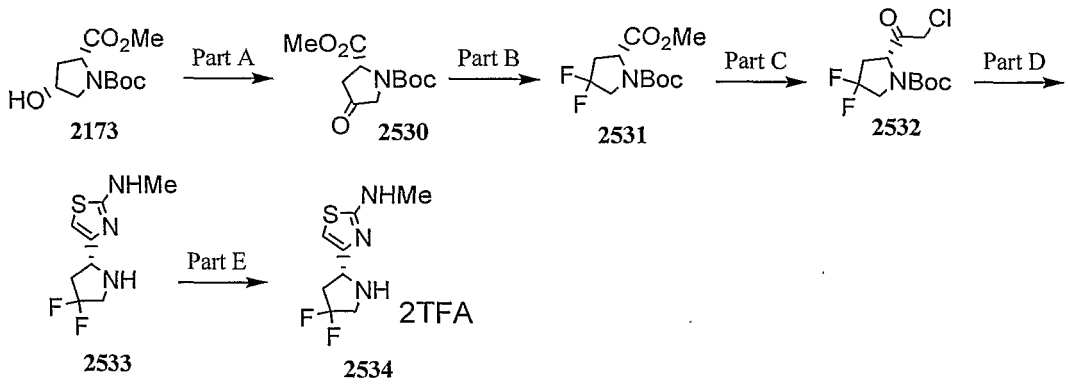
The following compounds were prepared using previously described procedures.

Compound #	SCH	Structure	Exact mass	MS m/z (M+H)

2527	786656		531.2	532.2
2528	7867566		502.2	503.2

Example 62:

Example 62A:



Part A:

A mixture of **2173** (1.54 g, 6.28 mmol) and Dess-Martin periodinane (2.72 g, 6.41 mmol) in DCM (30 ml) was stirred at room temperature overnight. To the reaction mixture was add saturated sodium bicarbonate solution and the mixture was stirred for 2 hours. The solids were removed by filtration. The filtrate was separated and the organic layer was washed with brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 30% ethyl acetate / hexane) afforded **2530** (939 mg, 61%) as an oil. HPLC-MS t_R = 1.10 min (MS); Mass calculated for formula C11H17NO5 243.1, observed m/z 266.1 (M+Na).

Part B:

To ketone **2530** (939 mg, 3.86 mmol) in DCM (30 mL) at -78 oC under argon was added (diethylamino)sulfur trifluoride (2.53 mL, 19.3 mmol). The bath was slowly warmed to room temperature while the mixture was stirred overnight. The reaction mixture was poured into saturated sodium bicarbonate and the layers were separated. The organic layer was washed with brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 10% to 30% ethyl acetate / hexane) afforded **2531** (751 mg, 74%) as an oil. HPLC-MS t_R = 4.72 min (10 min, MS); Mass calculated for formula C11H17F2NO4 265.1, observed m/z 288.1 (M+Na).

Part C:

Compound **2531** (751 mg, 2.83 mmol) was converted to **2532** (418 mg, 52 %) using the procedures described in Example 10 Part A. HPLC-MS t_R = 1.85 min (MS); Mass calculated for formula C11H16ClF2NO3 283.1, observed m/z 228.1 (M-55).

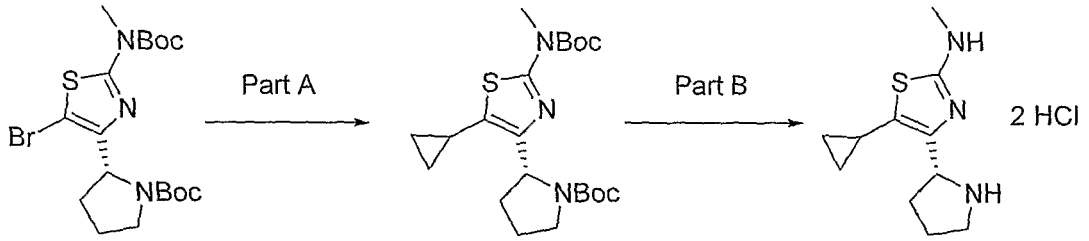
Part D:

Compound **2532** (418 mg, 1.47 mmol) was cyclized with N-methylthiourea according to the procedures described in Example 51B Part C to afford **2533** (200 mg, 42%). HPLC-MS t_R = 1.38 min (UV $_{254\ nm}$); Mass calculated for formula C8H11F2N3S 319.1, observed m/z 320.1 (M+H).

Part E:

Compound **2534** was synthesized in quantitative yield using the procedure described in Example 51D Part H. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (s, 1H), 4.98 (dd, 1H, J = 7.2, 11.7 Hz), 3.89 (m, 1H), 3.72 (m, 1H), 3.13 (s, 3H), 3.09-2.85 (m, 2H).

Example 62B:



2209A **2535** **2536**

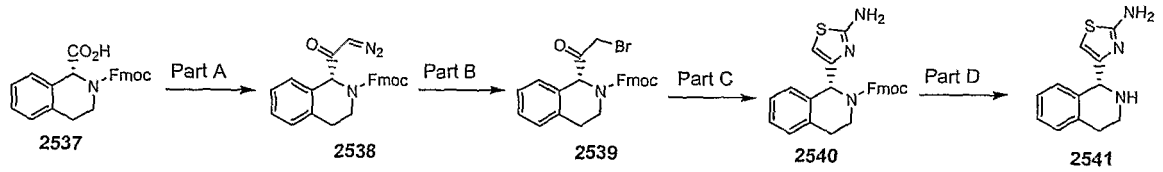
Part A:

The mixture of 5-bromothiazole **2209A** (210 mg, 0.45 mmol), cyclopropylboronic acid (80 mg, 1.0 mmol), $Pd(dppf)Cl_2$ (41 mg, 0.05 mmol) and K_3PO_4 (424 mg, 2.0 mmol) in 20-ml vial was flushed with argon for 3 min. Under the argon, dioxane (5 mL) was added and the vial was sealed under the argon atmosphere. The mixture was heated to 80 °C and stirred overnight. After cooling to room temperature, ethyl acetate (30 mL) was added to the reaction mixture and the solution was filtered through celite. The filtrate was concentrated and purified by column chromatography (SiO_2, 10% ethyl acetate/hexanes) to afford 5-cyclopropylthiazole **2535** (166 mg) as oil. HPLC-MS t_R = 2.65 min ($UV_{254\ nm}$); mass calculated for formula C21H33N3O4S 423.2, observed LCMS m/z 424.1 (M+H).

Part B:

To the solution of 5-cyclopropylthiazole **2535** (166 mg, 0.39 mmol) in dioxane (2 mL), HCl (4N in dioxane, 4 mL) was added followed by the addition of water (0.5 mL). The mixture was stirred at room temperature for 1 hour and concentrated. The resulting residue **2536** (111 mg) was dried under vacuum and used in the next step without further purification. HPLC-MS t_R = 0.86 min ($UV_{254\ nm}$); mass calculated for formula C11H17N3S 223.1, observed LCMS m/z 224.1 (M+H).

Example 62C:



Part A:

To Fmoc-D-Tiq-OH (**2537**) (1.0 g, 2.5 mmol) in dichloromethane (20 mL) at 0 °C was added $(COCl)_2$ (0.262 mL, 3.0 mmol) and DMF (2 drops, catalytic) under argon. The reaction mixture was stirred at 0 °C for 2 hr and concentrated to dryness in *vacuo*. The resulting syrup was dissolved in dry THF (20 mL) and cooled to 0 °C. Trimethylsilyldiazomethane (2.0 M in Et2O, 5 mL, 10 mmol) was added dropwise under argon during a period of 30 min. After the completion of addition, the solution was stirred at 0 °C for 3 hr and concentrated under reduced pressure. Flash column chromatography on silica (EtOAc/hexane 25:75) afforded **2538** (630 mg, 60%) as a yellow oily solid. HPLC-MS t_R = 2.23 min ($UV_{254\ nm}$); mass calculated for formula $C_{26}H_{21}N_3O_3$ 423.2, observed LCMS m/z 446.2 (M+Na).

Part B:

Compound **2538** (630 mg, 1.49 mmol) in Et_2O (20 mL) was cooled to 0 °C. To this solution was added 2.15 M hydrobromide acid in Et_2O (830 □L, 1.79 mmol) dropwise. The reaction mixture was stirred for 20 min at 0 °C and concentrated. The residue was dissolved in EtOAc, the solution was than washed with saturated bicarbonate solution, brine, dried (Na_2SO_4) and concentrated in *vacuo* to afford **2539** (630 mg, 89%) as an off white solid. HPLC-MS t_R = 2.40 min ($UV_{254\ nm}$); mass calculated for formula $C_{26}H_{22}BrNO_3$ 475.1, observed LCMS m/z 476.0 (M+H).

Part C:

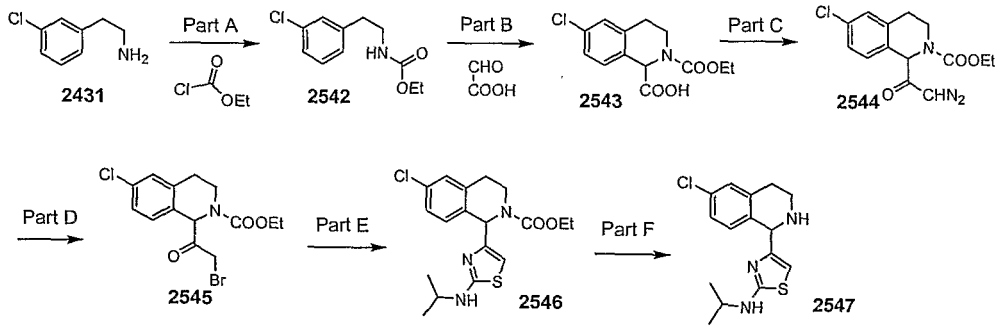
Compound **2539** (150 mg, 0.31 mmol) and thiourea (36 mg, 0.47 mmol) in DMF (2 mL) was allowed to stir at room temperature for 3 hr. The solution

was concentrated and the residue was dissolved with EtOAc and saturated $NaHCO_3$ solution. The organic phase was washed with H_2O, brine, dried over Na_2SO_4, and concentrated. Flash column chromatography on silica (EtOAc / hexane 60:40) afforded **2540** (120 mg, 84%) as a white solid. HPLC-MS t_R = 1.96 min ($UV_{254\ nm}$); mass calculated for formula $C_{27}H_{23}N_3O_2S$ 453.2, observed LCMS m/z 454.1 (M+H).

Part D:

Compound **2540** (150 mg, 0.26 mmol) was treated with 20% piperidine in DMF (10 mL). The solution was stirred at room temperature for 2 hr and concentrated. LC-MS indicated the clean deprotection of the Fmoc group. HPLC-MS t_R = 0.72 min ($UV_{254\ nm}$); mass calculated for formula $C_{12}H_{13}N_3S$ 231.1, observed LCMS m/z 232.1 (M+H).

Example 62D:



Part A:

According to a modification of a procedure by Ortwine, D. F. et al. (*J. Med. Chem.* **1992**, 35, 1345-1370) to an ice-cold solution of 3-chlorophenethylamine **2431** (10 g, 64.6 mmol) and triethylamine (6.46 mL, 67.8 mmol) in DCM (200 mL) was added dropwise ethyl chloroformate (9.45 mL, 67.8 mmol), and the resulting solution was stirred at 0 °C for 1 h, and then at rt for 1.5 h. The reaction mixture was washed with saturated sodium bicarbonate solution, brine, dried and concentrated to give ethyl carbamate **2542** as a colorless oil (14.36 g, 98%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.24-7.19 (m, 3H), 7.09-7.07 (d, 1H), 4.66 (s, broad, NH), 4.12 (q, 2H), 3.44 (q, 2H), 2.81 (t, 2H), 1.25 (t, 3H).

Part B:

According to a modification of a procedure by Ortwine, D. F. et al. (*J. Med. Chem.* **1992**, *35*, 1345-1370) to an ice-cold mixture of carbamate **2542** (6.81 g, 29.9 mmol) and 3:1 glacial acetic acid:sulfuric acid (64 mL) was added (in two portions) glyoxylic acid monohydrate (3.03 g, 32.9 mmol) and the mixture was stirred at rt overnight. The reaction mixture was poured in ice, and extracted with dichloromethane (5 times). The combined dichloromethane extracts were dried and concentrated to an oily residue, which was then taken in toluene and concentrated (3 times) and dried under vacuum overnight to give compound **2543** (7.91 g, 93%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.9 (s, broad, COOH), 7.50-7.12 (m, 3H), 5.42 (s, 1H), 4.12-4.03 (m, 2H), 3.77-3.50 (m, 2H), 2.89-2.79 (m, 2H), 1.24-1.16 (m, 3H). HPLC-MS t_R = 1.68 min ($UV_{254\ nm}$); mass calculated for formula C13H14ClNO4 283.1, observed LCMS m/z 284.0 (M+H).

Part C:

Diazoketone **2544** was prepared using procedures described in Example 62C Part A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.18 (m, 3H), 5.60-5.41 (m, 2H), 4.26-4.22 (m, 2H), 3.90-3.65 (m, 2H), 2.97-2.82 (m, 2H), 1.36-1.32 (m, 3H). HPLC-MS t_R = 1.8 min ($UV_{254\ nm}$); mass calculated for formula C14H14ClN3O3 307.1, observed LCMS m/z 280.1 (M-N2+H), and 330.1 (M+Na).

Part D:

Bromoketone **2545** was prepared using procedures described in Example 62C Part B. ^{1}H NMR (400 MHz, CDCl3) δ 7.31-7.20 (m, 3H), 5.87-5.81 (m, 1H), 4.25-4.04 (m, 4H), 3.90-3.82 (m, 1H), 3.60-3.51 (m, 1H), 2.98-2.79 (m, 2H), 1.34-1.31 (m, 3H). HPLC-MS t_R = 2.07 min ($UV_{254\ nm}$); mass calculated for formula C14H15BrClNO3 359.0, observed LCMS m/z 360.0 (M+H).

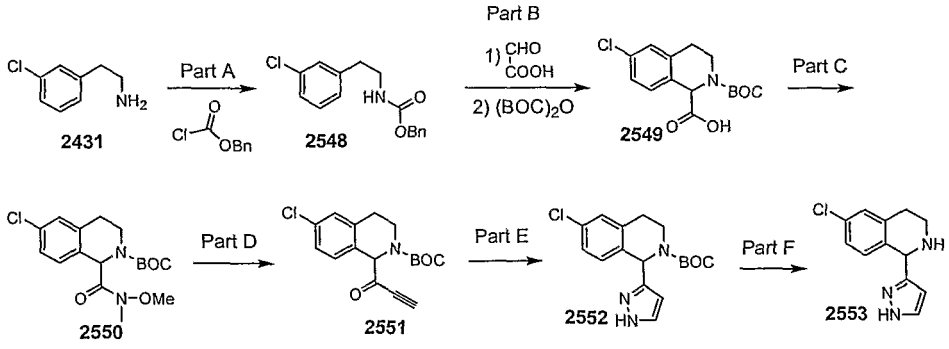
Part E:

Thiazole **2546** was prepared using procedures described in Example 10. HPLC-MS t_R = 2.05 min ($UV_{254\ nm}$); mass calculated for formula C18H22ClN3O2S 379.1, observed LCMS m/z 380.1 (M+H).

Part F:

To a solution of thiazole **2546** (117 mg, 0.31 mmol) in chloroform (1.5 mL) was added iodotrimethylsilane (0.32 mL, 2.24 mmol) and the resulting mixture was heated at 50 °C for 2 h. The reaction mixture was diluted with dichloromethane, washed with saturated sodium bicarbonate, brine and concentrated to give amine **2547** as a dark yellow solid (93 mg, 97%). ^{1}H NMR (400 MHz, CDCl3) δ 7.12-6.97 (m, 3H), 6.01(s, 1H), 5.26 (s, broad, 1H), 5.15 (s, 1H), 3.60-3.53 (m, 1H), 3.18-2.80 (m, 4H), 1.28-1.26 (d of d, 6H). HPLC-MS t_R = 1.24 min ($UV_{254\ nm}$); mass calculated for formula C15H18ClN3S 307.1, observed LCMS m/z 308.2 (M+H).

Example 62E:



Part A:

According to a modification of a procedure by Ortwine, D. F. et al. (*J. Med. Chem.* **1992**, 35, 1345-1370) to an ice-cold solution of 3-chlorophenethylamine **2431** (11.6 g, 75 mmol) and triethylamine (10.9 mL, 78.7 mmol) in DCM (300 mL) was added dropwise benzyl chloroformate (11.1 mL, 78.1 mmol), and the resulting solution was stirred at 0 °C for 30 min, and

then at rt overnight. The reaction mixture was washed with saturated sodium bicarbonate solution, brine, dried and concentrated to give benzyl carbamate **2548** as a colorless oil (21.4 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.30 (m, 5H), 7.23-7.05 (m, 4H), 5.1 (s, 2H), 4.75 (s, broad, NH), 3.46 (q, 2H), 2.82 (t, 2H).

Part B:

According to a modification of a procedure by Ortwine, D. F. et al. (*J. Med. Chem.* **1992**, 35, 1345-1370) to an ice-cold mixture of benzyl carbamate **2548** (8.6 g, 31.4 mmol) and 3:1 glacial acetic acid:sulfuric acid (64 mL) was added (in two portions) glyoxylic acid monohydrate (3.0 g, 32.6 mmol) and the mixture was stirred at rt overnight. The reaction mixture was poured in ice, and washed with dichloromethane (4 times). The aqueous phase was concentrated, diluted with tetrahydrofuran (200 mL), and treated with 6M NaOH solution (130 mL) to pH 12-13, followed by di-tert-butyl dicarbonate (7.94 g, 36.4 mmol), and then stirred at rt overnight. The reaction mixture was concentrated, diluted with water, acidified with 2 M HCl solution to pH 2, and extracted with ethyl acetate. The combined organic extracts were concentrated and chromatographed (SiO_2, 5% methanol/dichloromethane) to give compound **2549** (0.95 g, 15% based on reacted starting material). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.27 (m, 3H), 5.67-5.50 (d, 1H), 3.87-3.79 (m, 2H), 3.01-2.88 (m, 2H), 1.61-1.57 (9H).

Part C:

Weinreb amide **2550** was prepared using procedures described in Example 51I, Part A. ^{1}H NMR (400 MHz, CDCl3) δ 7.37-7.14 (m, 3H), 6.1-5.88 (d, 1H), 4.0 (s, 3H), 3.84-3.67 (m, 2H), 3.21 (s, 3H), 3.17-3.09 (m, 1H), 2.79-2.72 (m, 1H), 1.5 (s, 9H). HPLC-MS t_R = 2.15 min ($UV_{254\ nm}$); mass calculated for formula C17H23ClN2O4 354.1, observed LCMS m/z 255.1 (M-BOC+H).

Part D:

Acetylene **2551** was prepared using procedures described in Example 51I, Part B. HPLC-MS t_R = 2.22 min ($UV_{254\ nm}$); mass calculated for formula C17H18ClNO3 319.1, observed LCMS m/z 264.0 (M-(t-butyl)).

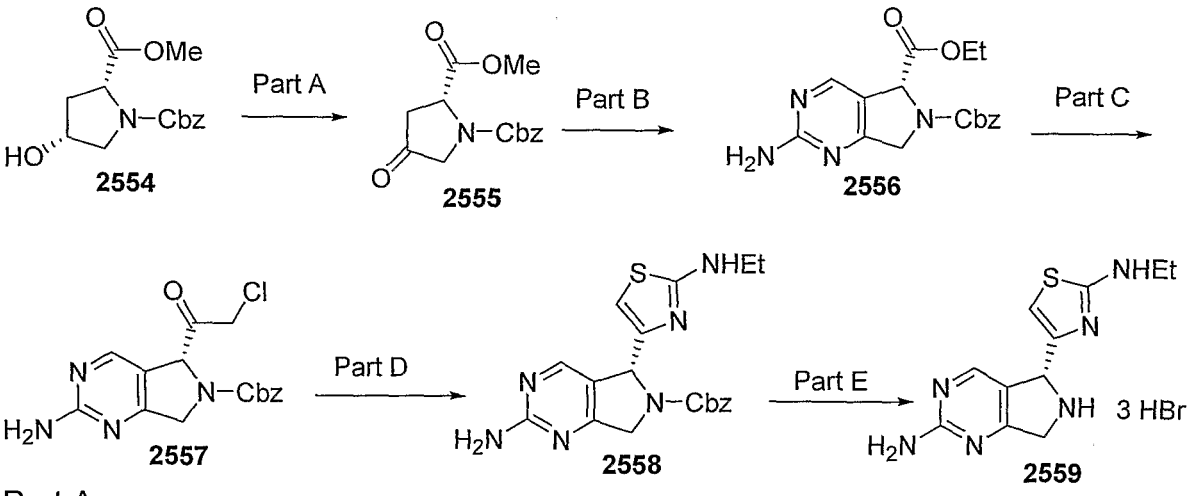
Part E:

Pyrazole **2552** was prepared using procedures described in Example 62G Part A. HPLC-MS t_R = 1.97 min ($UV_{254\ nm}$); mass calculated for formula C17H20ClN3O2 333.1, observed LCMS m/z 234 (M-BOC+H).

Part F:

Amine **2553** was prepared using a procedure similar to that described in Example 51I, Part D. HPLC-MS t_R = 0.89 min ($UV_{254\ nm}$); mass calculated for formula C12H12ClN3 233.1, observed LCMS m/z 234.1 (M+H).

Example 62F:



Part A:

Compound **2554** (3.7 g, 13.4 mmol) was dissolved in methylene chloride (35 mL) and Dess-Martin periodinane (8.55 g, 20.18 mmol) was added and stirred at room temperature overnight. The reaction was quenched with saturated sodium bicarbonate and stirred for 1 hour. The reaction mixture was filtered through celite. The aqueous layer was extracted with methylene chloride. The combined organic layers were dried over sodium sulfate and

concentrated. Purification by column chromatography (SiO_2, 50% ethyl acetate/hexanes) afforded **2555** (1.75 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.30 (m, 5 H), 5.25-5.20 (m, 2H), 4.90-4.80 (m, 1H), 4.00-3.80 (m, 2H), 3.80-3.60 (m, 3H), 3.00 (m, 1H), 2.60 (m, 1H).

Part B:

Compound **2556** was prepared according to the procedure in *Bioorg. Med. Chem.* **2002**, *10, 5,* 1197-1206. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.4-7.3 (m, 5 H), 5.3-5.15 (m, 3H), 4.7-4.55 (m, 2H), 4.3-4.2 (m, 2H), 1.3 (t, 3H).

Part C:

Compound **2557** was prepared from compound **2556** according to the procedure described in Example 10B Part B. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (m, 1H), 7.60-7.40 (m, 5H), 5.30-5.20 (m, 2H), 5.10 (m, 2H), 4.80-4.60 (m, 1H).

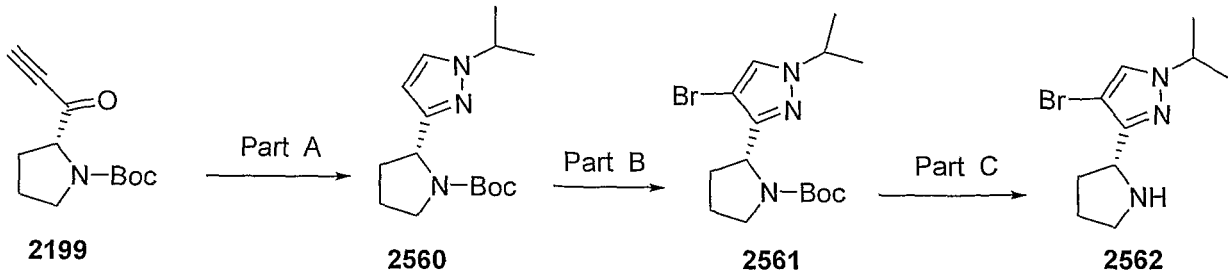
Part D:

Compound **2558** was prepared as described in Example 51B Part C from compound **2557**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.40-7.20 (m, 5H), 6.20 (s, 1H), 5.30-5.00 (m, 3H), 4.70 (m, 2H), 3.25 (m, 2H), 1.30 (m, 3H).

Part E:

Compound **2558** (80 mg, 0.202 mmol) was dissolved in 30% HBr in acetic acid (3 mL) and stirred for 2 hours. The solvent was removed and the residue was dissolved in water and washed with ethyl acetate. The aqueous layer was lyophilized to provide **2559** as a red solid (100 mg). HPLC-MS t_R = 0.414 min ($UV_{254\ nm}$); mass calculated for formula C11H14N6S 262.1, observed LCMS m/z 263.1 (M+H).

Example 62G:



2199 2560 2561 2562

Part A:

Compound **2199** (1.11 g, 3.7 mmol), isopropyl hydrazine hydrochloride (616 mg, 5.55 mmol), and sodium carbonate (980 mg, 9.25 mmol) were dissolved in ethanol (12 mL) and stirred at 80 °C for 5 hours. The reaction mixture was cooled to room temperature and diluted with ethyl acetate and water. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 33% ethyl acetate/hexanes) afforded **2560** (750 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, 1 H), 6.00 (d, 1H), 5.10-4.90 (m, 1H), 4.50 (m, 1H), 3.60-3.40 (m, 2H), 2.30-2.10 (m, 1H), 2.10-1.80 (m, 3H), 1.50 (m, 9H), 1.30 (s, 6H).

Part B:

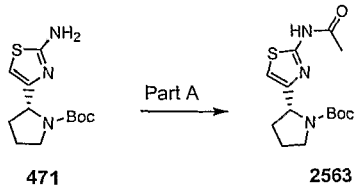
Compound **2560** (541 mg, 1.93 mmol) was dissolved in chloroform (10 mL) and N-bromosuccinimide (412 mg, 2.31 mmol) was added and stirred at room temperature overnight. The reaction was diluted with methylene chloride and water. The organic layer was washed with 1N NaOH, brine, dried over sodium sulfate, and concentrated. Purification by column chromatography (SiO_2, 15% ethyl acetate/hexanes) afforded **2561** (350 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 1 H), 5.00-4.80 (m, 1H), 4.40 (m, 1H), 3.60-3.40 (m, 2H), 2.30-2.20 (m, 1H), 2.10-2.00 (m, 1H), 2.00-1.80 (m, 2H), 1.40 (m, 9H), 1.20 (s, 6H).

Part C:

Compound **2561** (86 mg, 0.238 mmol) was dissolved in 4M HCl in dioxane (2.0 mL) and stirred for 1 hour. The solvent was removed to provide **2562** as

a white solid (82 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.60 (bs, 1H), 8.80 (bs, 1H), 8.18 (s, 1 H), 4.60 (m, 1H), 4.50 (m, 1H), 3.25 (m, 2H), 2.35 (m, 1H), 2.10-1.90 (m, 3H), 1.40 (d, 6H).

Example 62H:

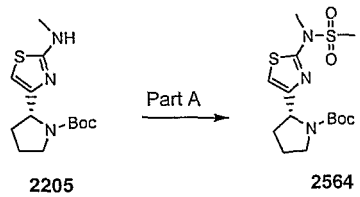


471 2563

Part A:

To **471** (81 mg, 0.30 mmol) and DIEA (0.156 mL, 0.90 mmol) in dichloromethane (5 mL) was added slowly acetyl chloride (0.052 mL, 0.72 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature for 2 hr and concentrated. The residue was then dissolved in EtOAc and H_2O, washed with 1N citric acid, $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated. The resulting sticky solid was dissolved in methanol (5 mL) and stirred with solid K_2CO_3 (100 mg) for 2 hr. After removing the solvent, the residue was dissolved in EtOAc and H_2O, washed with H_2O, brine, dried (Na_2SO_4) and concentrated to afford **2563** (82 mg, 87 %) as an oily solid. HPLC-MS t_R = 1.60 min ($UV_{254\ nm}$); mass calculated for formula $C_{14}H_{21}N_3O_4S$ 311.1, observed LCMS m/z 312.1 (M+H).

Example 62I:



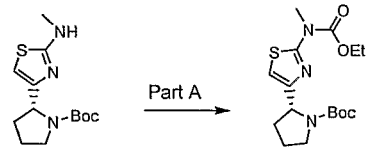
2205 2564

Part A:

To compound **2205** (100 mg, 0.35 mmol) and DIEA (0.092 mL, 0.53 mmol) in dichloromethane (5 mL) was slowly added methylsulfonic chloride (0.033 mL,

0.42 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature for 2 hr and concentrated. The residue was dissolved in EtOAc, washed with water, 1N citric acid, $NaHCO_3$, and brine, dried over Na_2SO_4 and concentrated to afford **2564** (120 mg, 94%) as an oily solid. HPLC-MS t_R = 1.96 min ($UV_{254\ nm}$); mass calculated for formula $C_{14}H_{23}N_3O_4S_2$ 361.1, observed LCMS m/z 362.0 (M+H).

Example 62J:

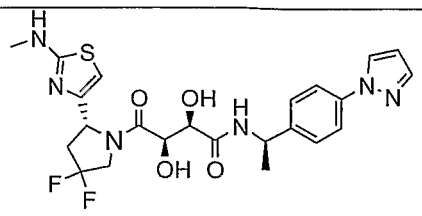


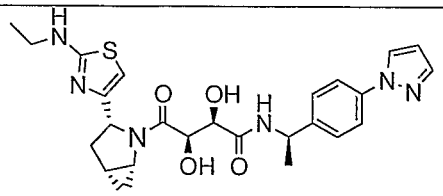
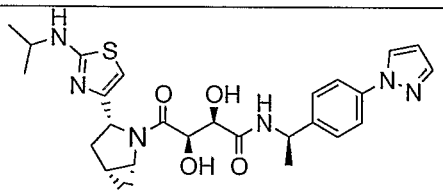
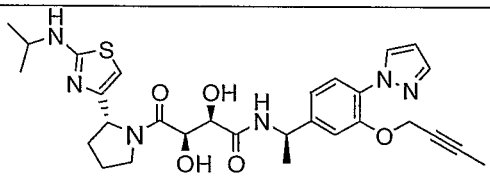
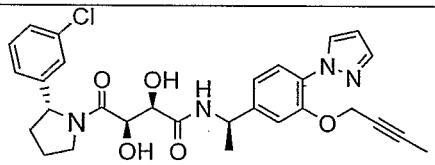
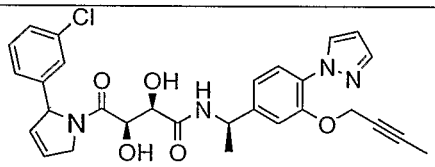
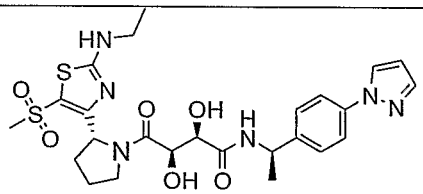
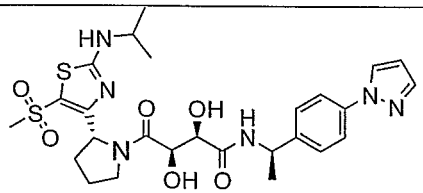
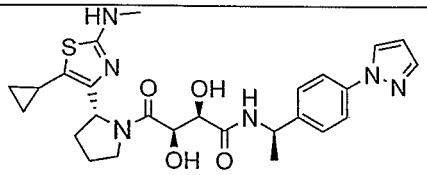
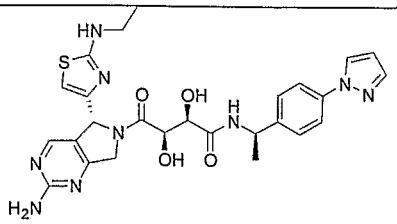
2205 **2565**

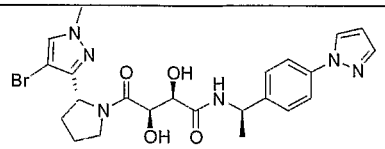
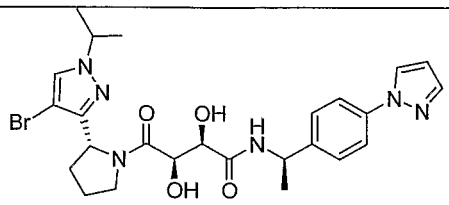
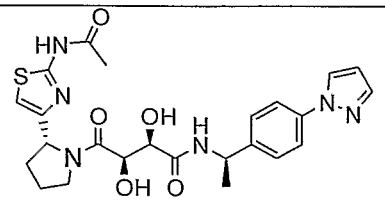
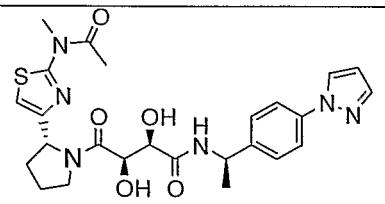
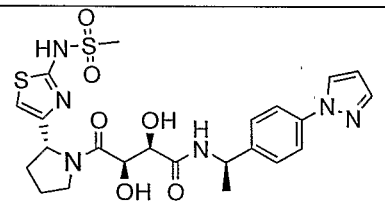
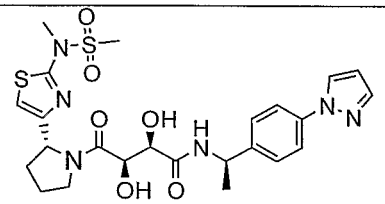
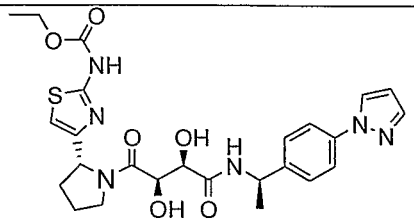
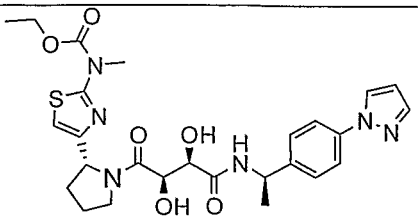
Part A:

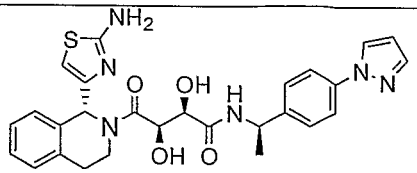
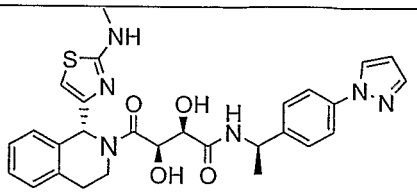
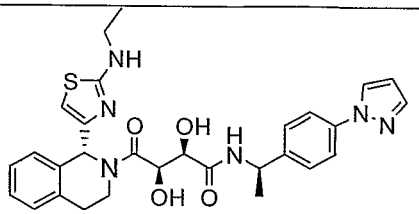
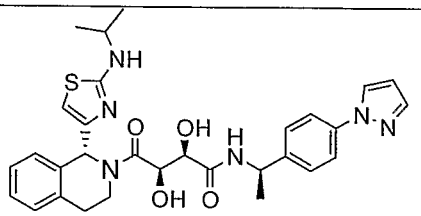
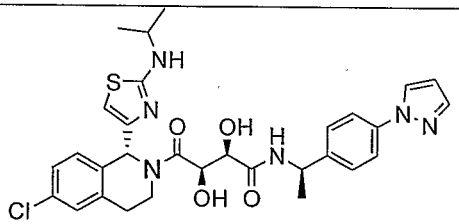
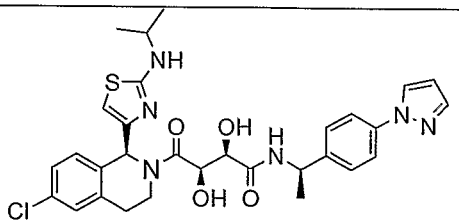
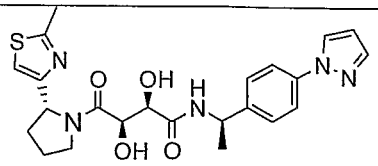
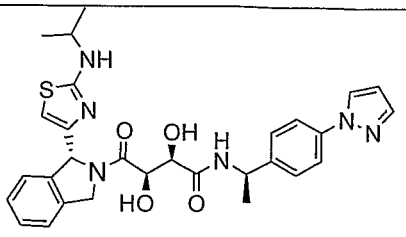
To compound **2205** (80 mg, 0.28 mmol) and DIEA (0.098 mL, 0.56 mmol) in dichloromethane (5 mL) was added slowly ethyl chloroformate (0.054 mL, 0.56 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature for 2 hr and concentrated. The residue was dissolved in EtOAc, washed with water, 1N citric acid, $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated to afford **2565**(88 mg, 88%) as an oily solid. HPLC-MS t_R = 2.23 min ($UV_{254\ nm}$); mass calculated for formula $C_{11}H_{25}N_3O_4S$ 355.2, observed LCMS m/z 356.2 (M+H).

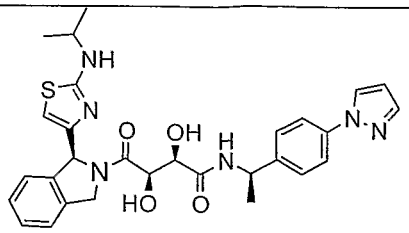
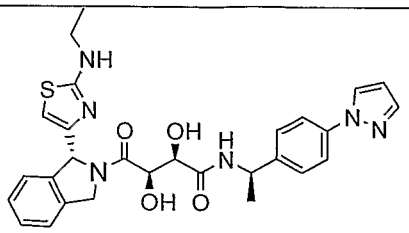
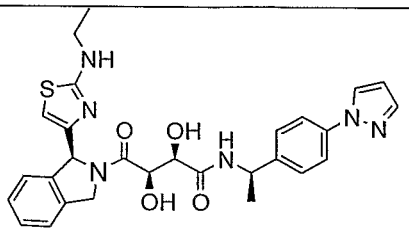
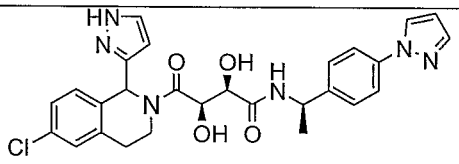
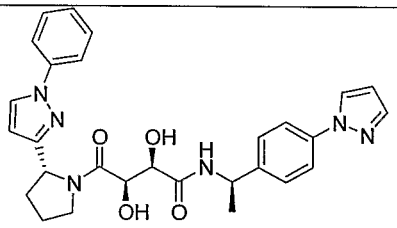
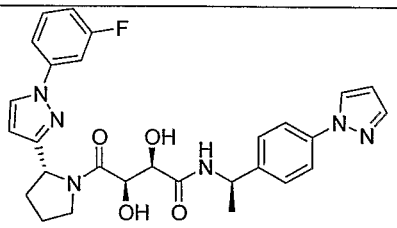
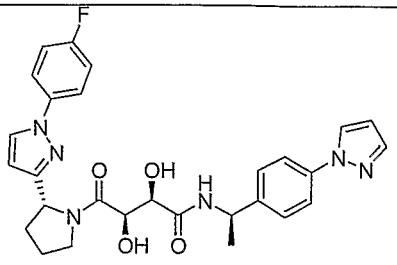
The following compounds were prepared using previously described procedures.

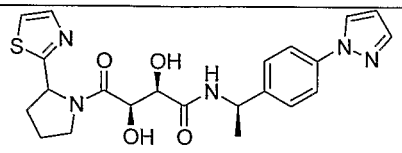
Compound #	Structure	Exact mass	MS m/z (M+H)
2567		520.17	521.0

2568		510.2	511.1
2569		524.2	525.3
2570		580.2	581.2
2571		550.2	551.0
2572		548.2	549.2
2573		576.2	577.3
2574		590.2	591.3
2575		524.2	525.2
2576		563.2	564.2

2577		530.1	531.1
2578		558.2	559.2
2579		512.2	513.2
2580		526.2	527.2
2581		548.2	549.2
2582		562.2	563.2
2583		542.2	543.2
2584		556.2	557.2

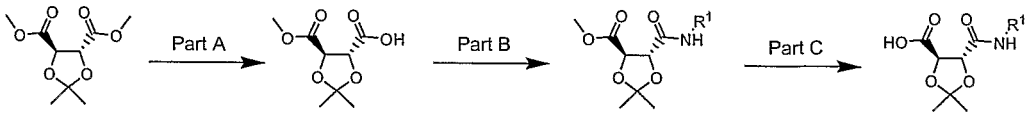
2585		532.2	533.2
2586		546.2	547.2
2587		560.2	561.1
2588		574.2	575.2
2589		608.2	609.2
2590		608.2	609.2
2591		469.2	470.2
2592		560.2	561.1

2593		560.2	561.1
2594		546.2	547.2
2595		546.2	547.2
2596		534.2	535.2
2597		514.2	515.2
2598		532.2	533.2
2599		532.2	533.2

2600		455.2	456.2

Additional Examples:

Additional Example 1:



Part A:

To a stirred solution of L-tartrate dimethylester (1) (29.8 g, 136 mmol) in methanol (60 mL) at 0 °C (ice-bath) was added a solution of potassium hydroxide (6.9 g, 123 mmol) in water (20 mL) over 30 minutes. The reaction mixture was stirred at room temperature for 3 hours. The volatiles were removed *in vacuo*, water (40 mL) was added and the basic solution washed with diethyl ether (30 mL x3). The basic solution was acidified to p*H* 2.0 with 6*N* HCl, saturated with solid sodium chloride and the product extracted into diethyl ether (40 mL x4). Drying over magnesium sulfate and concentration afforded compound 2 (22.2 g, 79 % yield) as a colorless oil.

Part B:

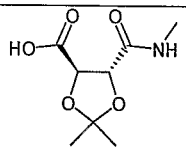
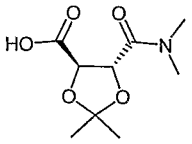
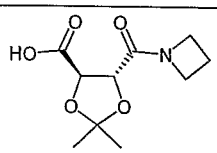
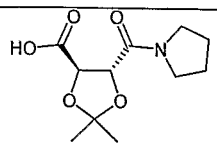
To a mixture of compound 2 (1.13 g, 5.53 mmol) and *O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) (3.2 g, 8.3 mmol) in DMF (20 mL) was added amine building block (1.2 equivalents) and diisopropylethylamine (2.89 mL, 16.59 mmol). The reaction mixture was stirred at room temperature for 3 hours. LC-MS analysis of the reaction indicated that the reaction was complete. The volatiles were removed *in vacuo*, ethyl acetate was added, and the organic solution washed successively with saturated $NaHCO_3$ (x1), water (x1), brine (x1), dried over magnesium sulfate and concentrated. Purification by flash column

chromatography (SiO_2, 20 % ethyl acetate in hexanes) afforded compound 3 (60 – 80 % yield).

Part C:

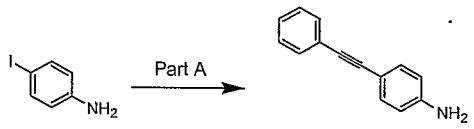
A mixture of compound 3 (850 mg, 3.9 mmol) and LiOH (1*M*, 5.85 mL, 5.85 mmol) in THF (30 mL) and water (10 mL) was stirred at room temperature for 5 hours. LC-MS analysis of the reaction indicated that the reaction was complete. The volatiles were removed *in vacuo*, water was added and the aqueous acidified to p*H* 4.0 with 1*N* HCl. The acidic solution was saturated with solid sodium chloride, the product extracted into ethyl acetate (x2), dried over magnesium sulfate and concentrated to afford compound 4-7 (60 - 70 % yield).

The following scaffolds were synthesized using this procedure:

Serial #	Structure	Exact mass	MS m/z (M^++H)	Ret. Time (min)
4		203.1	204.1	0.58
5		217.1	218.1	0.84
6		229.1	230.1	0.85
7		243.1	244.1	1.01

Additional Example 2:

Additional Example 2A:

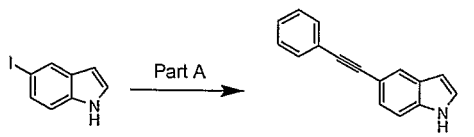


8 9

Part A:

To a mixture of 4-iodoaniline (8) (440 mg, 2 mmol), copper iodide (7.6 mg, 0.04 mmol) and dichlorobis(triphenylphosphine)palladium (II) (14 mg, 0.02 mmol) in THF (5 mL) was added phenylacetylene (244.8 mg, 2.4 mmol) and triethylamine (556 uL, 4 mmol). The reaction vessel was flushed with argon, and the reaction mixture stirred at room temperature for 16 hours. LC-MS analysis of the reaction indicated that the reaction was complete. Ethyl acetate (5 mL) was added, and the precipitates removed by passing through a plug of celite. The filtrate was concentrated, and the crude purified by flash column chromatography (SiO_2, 6 % ethyl acetate in hexanes) to afford compound 9 as a brown solid (321 mg, 82 % yield). HPLC-MS t_R = 1.88 min ($UV_{254\ nm}$); mass calculated for formula C14H11N 193.1, observed LCMS m/z 194.1 (M+H).

Additional Example 2B:

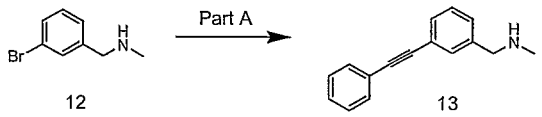


10 11

Part A:

Compound 11 was prepared from 5-iodoindole (10) using the Sonogashira Coupling conditions described in Additional Example 2A, Part A. HPLC-MS t_R = 2.06 min ($UV_{254\ nm}$); mass calculated for formula C16H11N 217.1, observed LCMS m/z 218.1 (M+H).

Additional Example 2C:

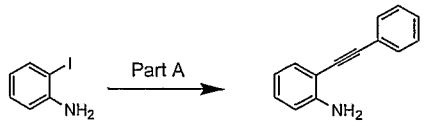


12 13

Part A:

To a mixture of 3-bromo-*N*-methylbenzylamine (12) (400 mg, 2 mmol), copper iodide (15.2 mg, 0.08 mmol) and dichlorobis(triphenylphosphine)palladium (II) (28 mg, 0.04 mmol) in DMF (3 mL) was added phenylacetylene (244.8 mg, 2.4 mmol) and triethylamine (556 uL, 4 mmol). The reaction vessel was flushed with argon, and the reaction mixture heated in the microwave for 5 minutes at 110 °C. The volatiles were removed *in vacuo*, ethyl acetate was added, and the organic solution washed successively with saturated $NaHCO_3$ (x1), water (x1), brine (x1) and then extracted with 1*N* HCl. The acidic solution was basified to p*H* 9.0 with 1*M* NaOH, and then re-extracted with ethyl acetate, dried over magnesium sulfate and concentrated. Compound 13 was used without further purification. HPLC-MS t_R = 1.24 min ($UV_{254\ nm}$); mass calculated for formula C16H15N 221.1, observed LCMS m/z 222.1 (M+H).

Additional Example 2D:

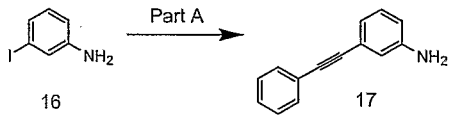


14 15

Part A:

Compound 15 was prepared from 2-iodoaniline (14) using the Sonogashira Coupling conditions described in Additional Example 2A, Part A. HPLC-MS t_R = 2.01 min ($UV_{254\ nm}$); mass calculated for formula C14H11N 193.1, observed LCMS m/z 194.1 (M+H).

Additional Example 2E:

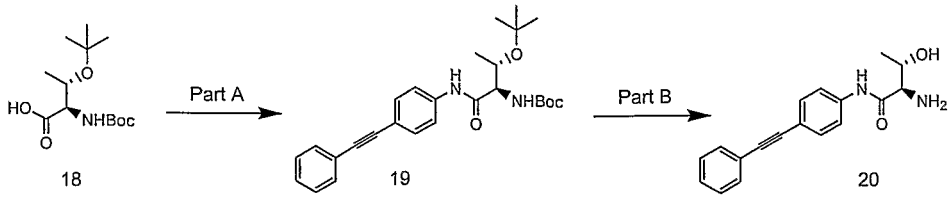


16 17

Part A:

Compound 17 was prepared from 3-iodoaniline (16) using the Sonogashira Coupling conditions described in Additional Example 2A, Part A. HPLC-MS t_R = 1.94 min ($UV_{254\ nm}$); mass calculated for formula C14H11N 193.1, observed LCMS m/z 194.1 (M+H).

Additional Example 2F:



18 19 20

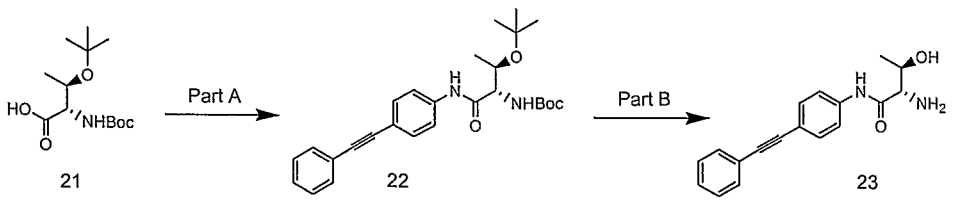
Part A:

To a mixture of Boc-D-Thr(t-Bu)-OH (100 mg, 0.36 mmol) and HATU (207 mg, 0.54 mmol) in NMP (2 mL) was added compound 9 (77 mg, 0.4 mmol) and diisopropylethylamine (209 uL, 1.2 mmol). The reaction mixture was heated at 55 °C for 16 hours. Ethyl acetate (5 mL) was added, and the organic solution washed successively with saturated $NaHCO_3$ (x1), brine (x1), 0.5*N* HCl (x1), dried over magnesium sulfate and concentrated. Purification by flash column chromatography (SiO_2, 20 % ethyl acetate in hexanes) afforded compound 19 as a white solid. HPLC-MS t_R = 2.52 min ($UV_{254\ nm}$); mass calculated for formula C27H34N2O4 450.3, observed LCMS m/z 339.1 (M-(2x t-Bu)+H).

Part B:

To a solution of compound 19 (0.1 mmol) in dioxane (1 mL) at 0 °C (ice-bath) was added 4 *N* HCl in dioxane (2 mL) and water (0.2 mL). The reaction mixture was stirred at room temperature for 3 hours. LC-MS analysis of the reaction indicated that the reaction was complete. The volatiles were removed *in vacuo*, acetonitrile was added, concentrated and dried to afford compound 20 (100 % yield) as a white solid. HPLC-MS t_R = 1.32 min ($UV_{254\ nm}$); mass calculated for formula C18H18N2O2 294.1, observed LCMS m/z 295.1 (M+H).

Additional Example 2G:



Part A:

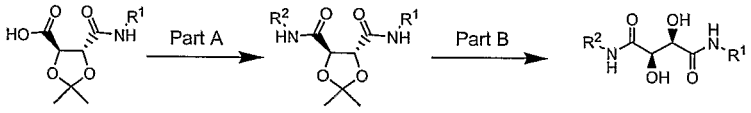
Compound 22 was prepared from Boc-L-Thr(t-Bu)-OH (21) and compound 9 using the coupling conditions described in Additional Example 2F, Part A.

HPLC-MS t_R = 2.62 min ($UV_{254\ nm}$); mass calculated for formula C27H34N2O4 450.3, observed LCMS m/z 339.1 (M-(2x t-Bu)+H).

Part B:

Compound 23 was prepared from compound 22 using the hydrolysis conditions described in Additional Example 2F, Part B. HPLC-MS t_R = 1.35 min ($UV_{254\ nm}$); mass calculated for formula C18H18N2O2 294.1, observed LCMS m/z 295.1 (M+H).

Additional Example 3:



Part A:

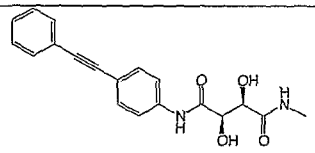
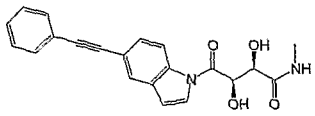
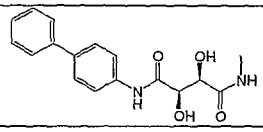
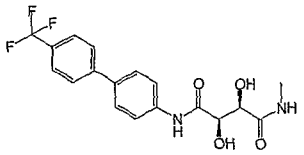
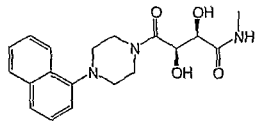
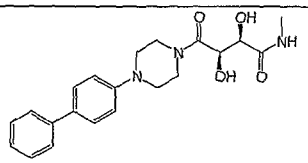
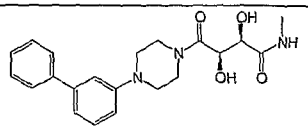
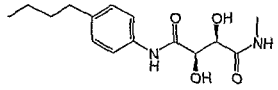
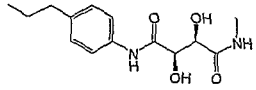
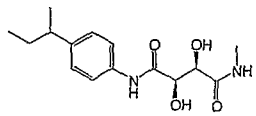
To a mixture of monoacid (4–7) (25 mg, 0.12 mmol) and HATU (68 mg, 0.18 mmol) in NMP (2 mL) was added amine building block (1.2 equivalents) and diisopropylethylamine (69 uL, 0.40 mmol). The reaction mixture was heated at 55 °C for 16 hours. LC-MS analysis of the reaction indicated that the reaction was complete. The volatiles were removed *in vacuo*, ethyl acetate was added, and the organic solution washed successively with saturated $NaHCO_3$ (x1), water (x1), brine (x1), dried over magnesium sulfate and concentrated. Purification by Prep.LC afforded compounds 24 (80 – 90 % yield).

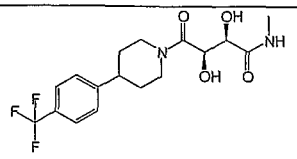
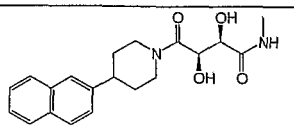
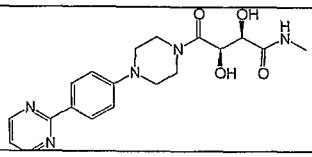
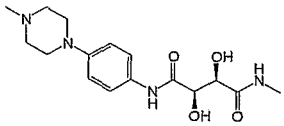
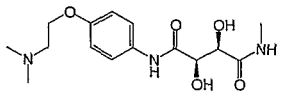
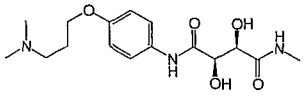
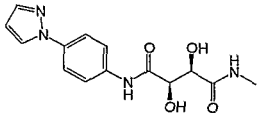
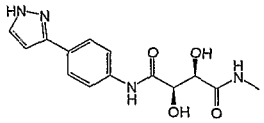
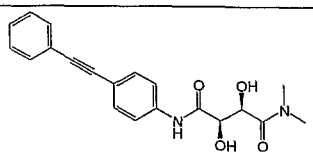
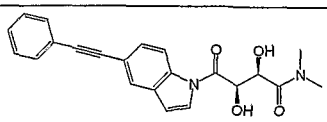
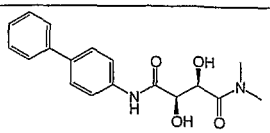
Part B:

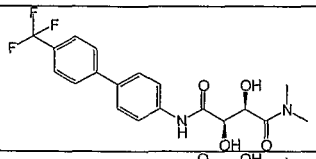
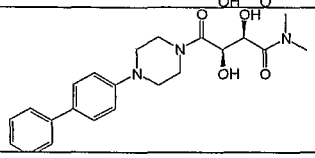
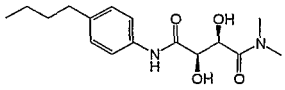
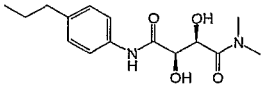
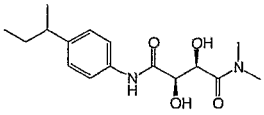
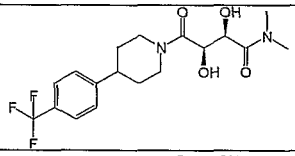
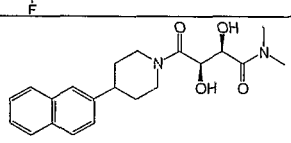
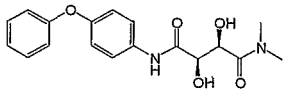
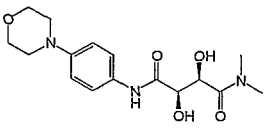
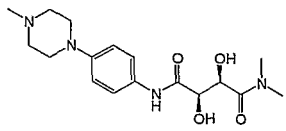
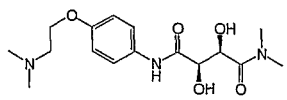
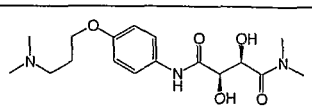
To a solution of compound 24 (0.1 mmol) in dioxane (1 mL) at 0 °C (ice-bath) was added 4 *N* HCl in dioxane (2 mL) and water (0.2 mL). The reaction mixture was stirred at room temperature for 3 hours. LC-MS analysis of the reaction indicated that the reaction was complete. The volatiles were

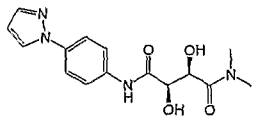
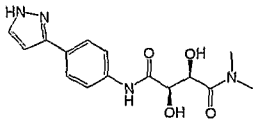
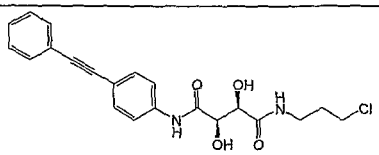
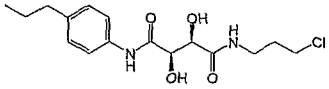
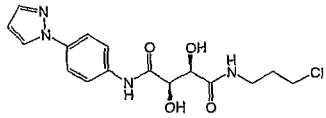
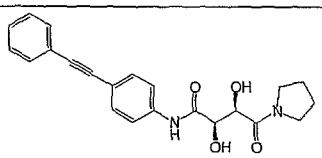
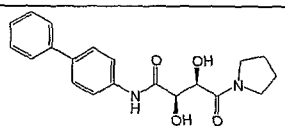
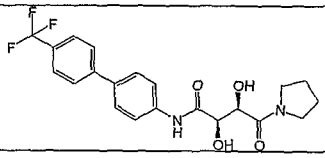
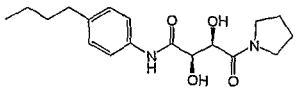
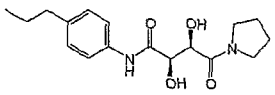
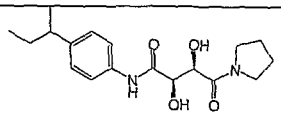
removed *in vacuo*, acetonitrile was added, concentrated and dried to afford compounds 25 - 101 (100 % yield). Purification by Prep-LC and conversion to a hydrochloric salt afforded compounds 25 - 101 as white solids.

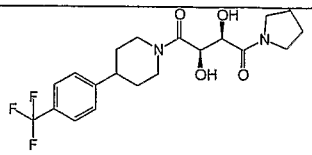
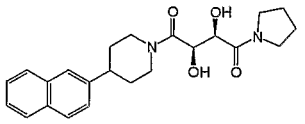
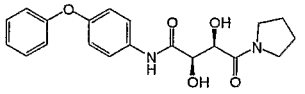
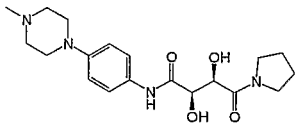
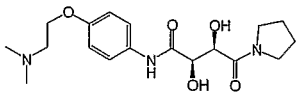
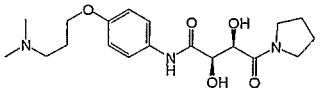
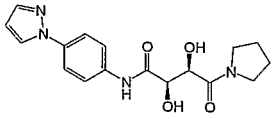
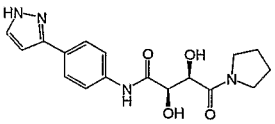
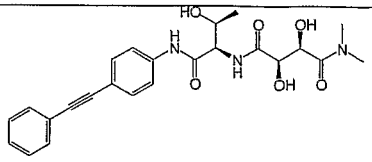
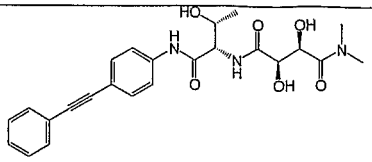
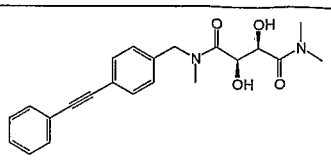
The following ligands were synthesized using this procedure:

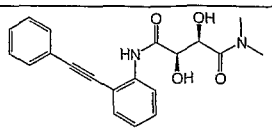
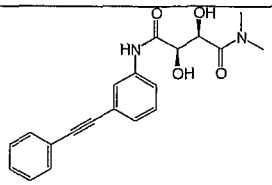
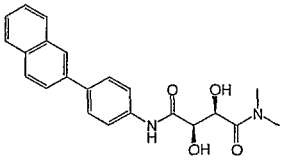
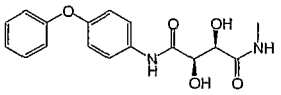
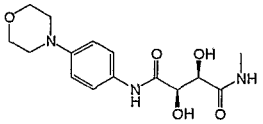
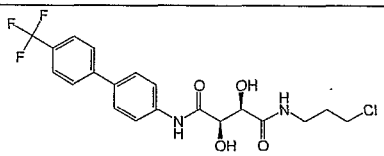
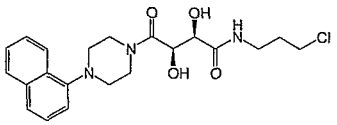
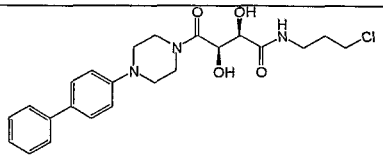
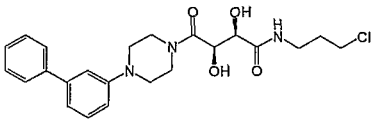
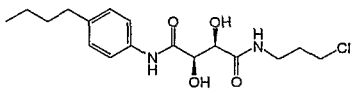
Serial #	Structure	Exact mass	MS m/z (M^++H)	Ret. Time (min)
25		338.1	339.1	4.17
26		362.1	363.1	4.82
27		314.1	315.1	1.35
28		382.1	383.1	1.63
29		357.2	358.2	1.42
30		383.2	384.2	1.53
31		383.2	384.2	1.52
32		294.2	295.1	1.49
33		280.1	281.2	1.32
34		294.2	295.1	1.45

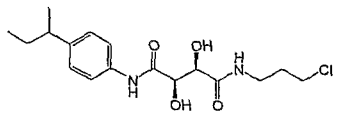
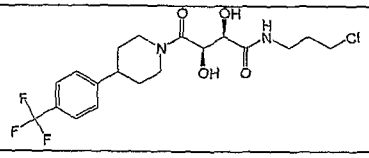
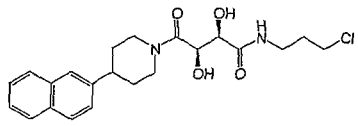
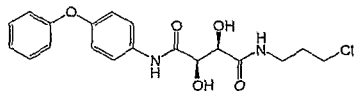
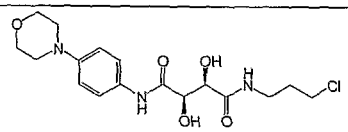
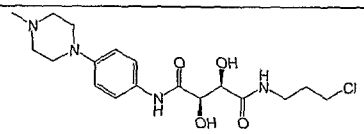
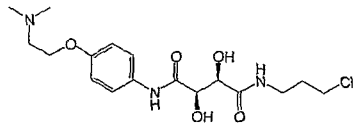
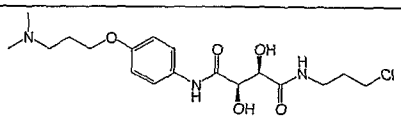
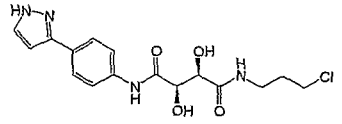
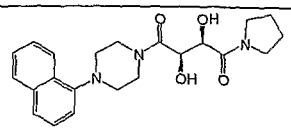
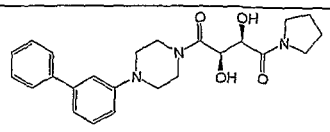
35		374.1	375.1	4.04
36		356.2	357.2	1.49
37		385.2	386.2	2.42
38		336.2	337.1	0.21
39		325.2	326.2	0.22
40		339.2	340.1	0.22
41		304.1	305.2	0.87
42		304.1	305.2	0.72
43		352.1	353.2	1.69
44		376.1	377.2	1.88
45		328.1	329.2	1.48

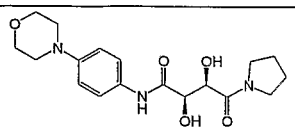
46		396.1	397.1	1.75
47		397.2	398.1	3.88
48		308.2	309.2	1.62
49		294.2	295.1	1.45
50		308.2	309.2	1.58
51		388.2	389.2	1.56
52		370.2	371.2	1.56
53		344.1	345.1	1.47
54		337.2	338.2	0.77
55		350.2	351.2	0.23
56		339.2	340.1	0.24
57		353.2	354.2	0.24

58		318.1	319.1	0.99
59		318.1	319.1	0.80
60		400.1	401.1	4.76
61		342.1	343.1	4.16
62		366.1	367.1	2.90
63		378.2	379.1	1.75
64		354.2	355.1	1.55
65		422.1	423.1	1.81
66		334.2	335.2	1.69
67		320.2	321.2	1.54
68		334.2	335.2	1.66

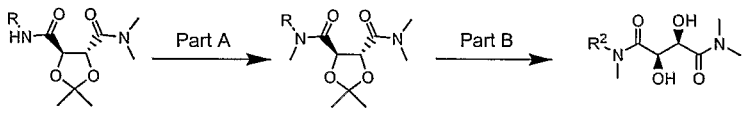
69		414.2	415.1	1.64
70		396.2	396.1	1.69
71		370.2	371.2	1.56
72		376.2	377.2	0.32
73		365.2	366.3	0.32
74		379.2	380.2	1.81
75		344.1	345.1	1.10
76		344.1	345.2	0.98
77		453.2	454.2	4.31
78		453.2	454.2	4.35
79		380.2	381.2	4.51

80		352.1	353.1	4.59
81		352.1	353.1	4.44
82		378.2	379.2	4.63
83		330.1	331.1	1.35
84		323.1	324.2	0.23
85		444.1	445.1	4.93
86		419.2	420.2	4.47
87		445.2	446.2	4.59
88		445.2	446.2	4.58
89		356.2	357.2	4.61

90		356.2	357.2	4.49
91		436.1	437.1	4.69
92		418.2	419.2	4.68
93		392.1	393.1	4.19
94		385.1	386.1	2.06
95		398.2	399.2	1.73
96		387.2	388.2	1.75
97		401.2	402.2	1.93
98		366.1	367.1	2.43
99		397.2	398.2	4.21
100		423.2	424.2	4.28

101		363.2	364.2	1.96

Additional Example 4:



80, 82 102 103, 104

Part A:

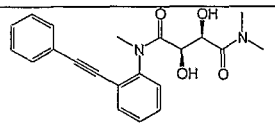
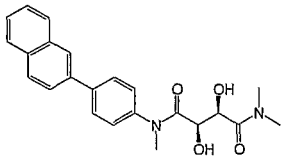
To a mixture of compound 80 (28 mg, 0.071 mmol) and iodomethane (13.4 uL, 0.21 mmol) in THF (2 mL) was added sodium hydride (60 % dispersion in oil, 3.1 mg, 0.079 mmol). The reaction mixture was stirred at room temperature for 3 hours. LC-MS analysis of the reaction indicated that the reaction was complete. Ethyl acetate was added, and the organic solution washed successively with saturated $NaHCO_3$ (x1), water (x1), brine (x1), dried over magnesium sulfate and concentrated. Compound 102 was used without further purification.

Part B:

Compounds 103 and 104 were prepared using the procedure described in Additional Example 3, Part B.

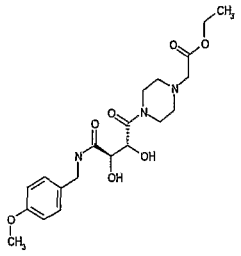
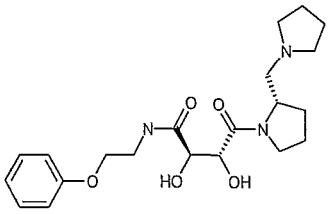
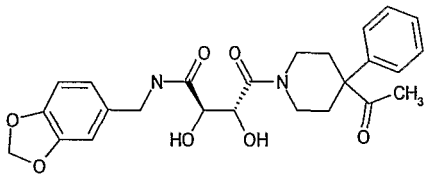
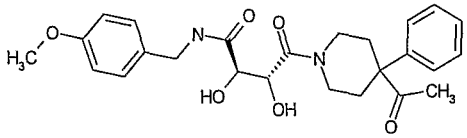
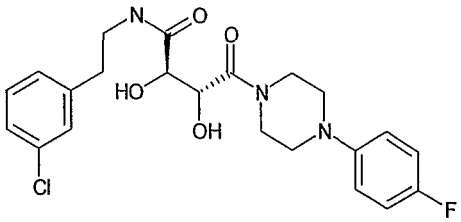
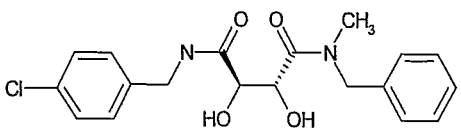
The following ligands were synthesized using this procedure:

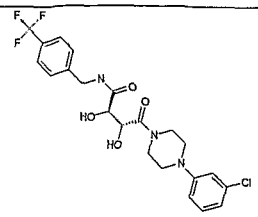
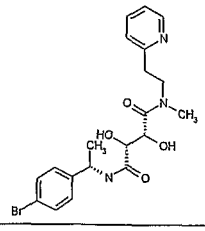
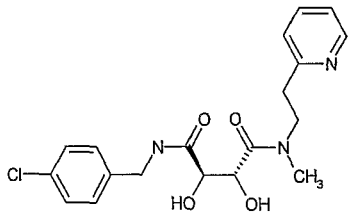
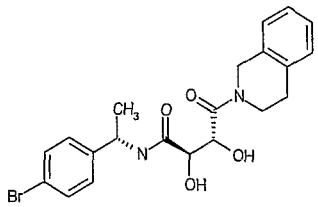
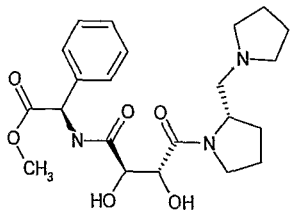
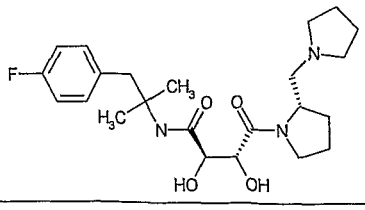
Serial #	Structure	Exact mass	MS m/z (M^++H)	Ret. Time (min)

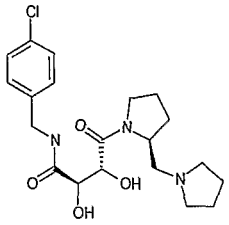
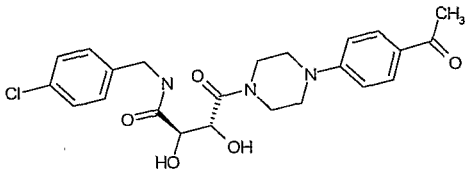
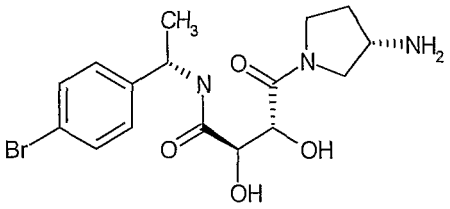
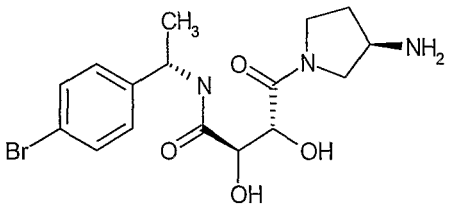
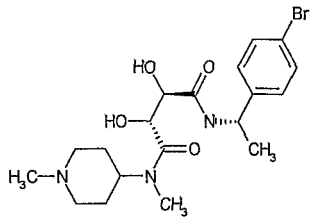
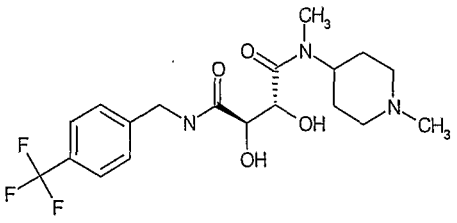
103		366.2	367.2	4.31
104		392.2	393.2	4.63

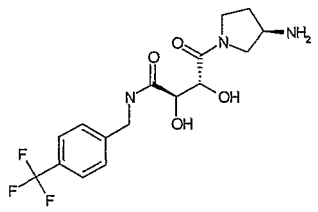
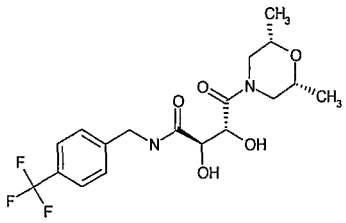
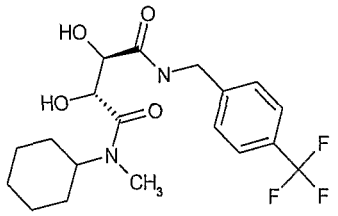
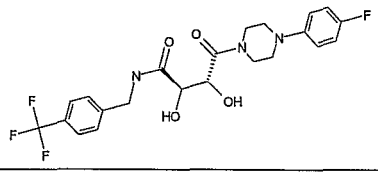
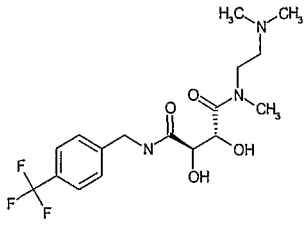
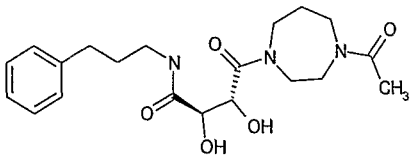
The following compounds in the table-2 can be prepared essentially following the procedures explained in Additional Example 1, part A, B,C and Additional Example 3 part A and B.

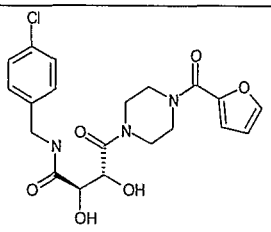
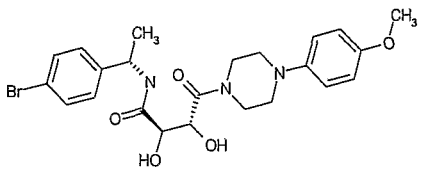
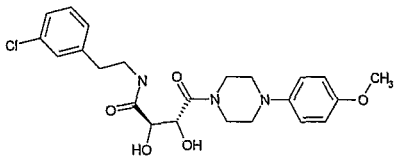
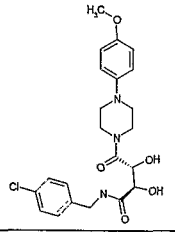
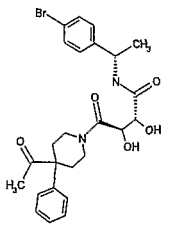
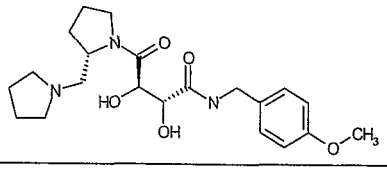
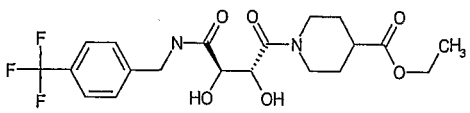
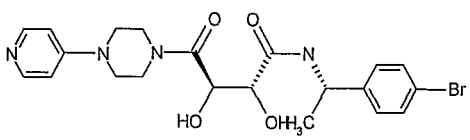
Table-2

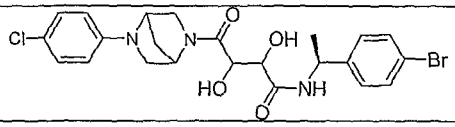
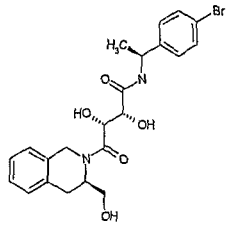
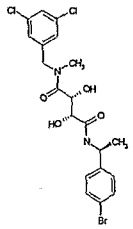
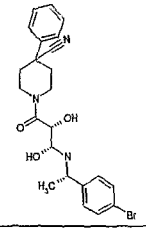
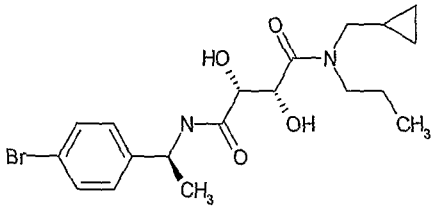
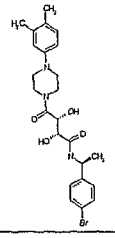
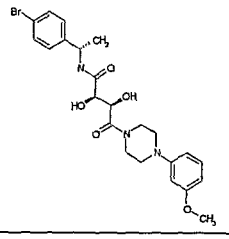
S.No.	Structure	MWt	MS m/z (M+H)	Retention time (min)
105		423.46	424.1	2.20
106		405.49	406.1	2.27
107		468.50	469.1	3.95
108		454.52	455.2	3.98
109		449.90	450.1	4.20
110		376.83	377.2	4.10

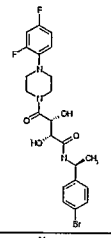
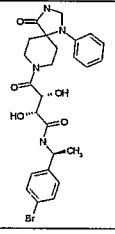
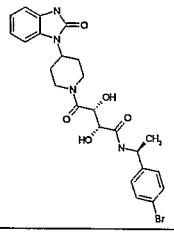
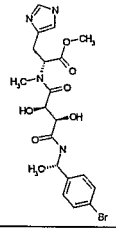
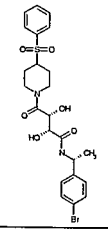
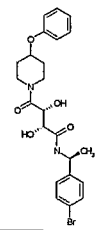
111		485.88	486.10	4.95
112		450.33	451.1	2.50
113		391.80	392.00	2.60
114		447.32	448.00	4.25
115		433.50	434.20	2.26
116		435.53	436.30	3.40

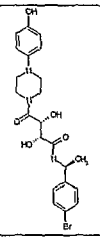
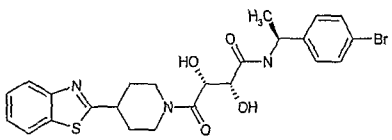
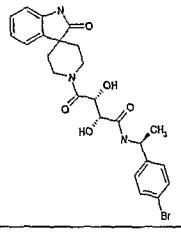
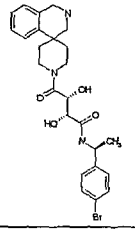
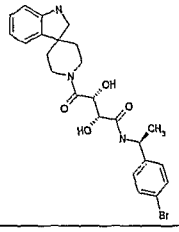
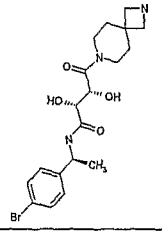
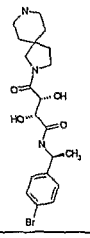
117		409.91	410.20	2.80
118		459.92	460.10	3.8
119		400.27 1	401.10	2.70
120		400.27	401.10	2.70
121		442.35	443.10	2.90
122		417.42	418.10	2.85

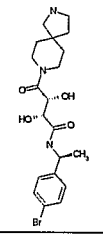
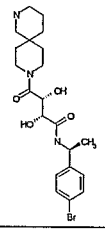
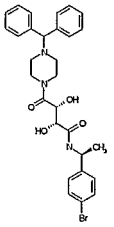
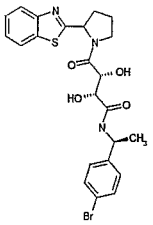
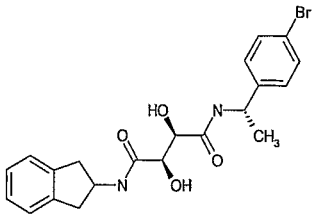
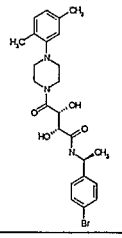
123		375.34	376.10	2.65
124		404.38	405.10	3.81
125		402.41	403.10	4.45
126		469.43	470.10	4.40
127		391.38	392.20	2.85
128		391.46	392.20	2.95
129		435.86	436.10	3.25

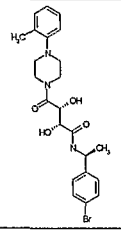
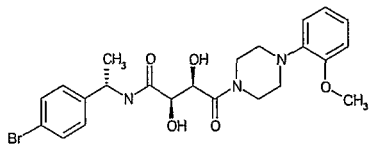
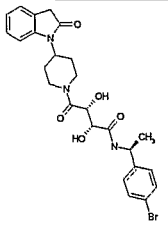
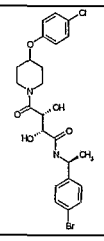
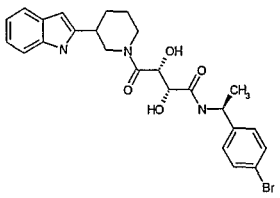
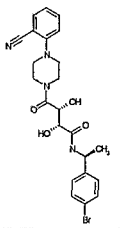
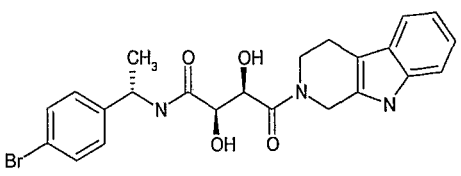
				
130		506.39	507.10	3.75
131		461.34	462.10	3.65
132		447.31	448.10	3.45
133		517.14	519.00	4.65
134		405.49	406.20	2.30
135		446.41	447.10	4.10
136		477.35	478.10	2.95

137		22.21	523.10	4.90
138		477.35	478.00	3.35
139		504.20	505.10	5.15
140		472.35	473.10	4.50
141		427.33	428.00	4.55
142		504.42	505.00	4.25
143		506.39	507.10	4.28

144		512.34	513.10	4.75
145		545.43	546.10	4.20
146		531.40	532.00	3.85
147		497.34	498.10	4.00
148		539.44	540.10	4.05
149		491.37	492.10	4.75

150		492.36	493.10	3.00
151		532.45	533.10	4.60
152		516.38	517.10	3.95
153		516.43	517.10	3.25
154		502.40	503.10	3.25
155		440.33	441.20	2.80
156		454.36	455.10	2.75

157		454.36	455.00	2.85
158		468.38	469.10	2.95
159		566.49	567.10	4.00
160		518.43	519.10	4.50
161		447.32	449.10	4.20
162		504.40	505.10	5.00

163		490.39	491.10	4.7
164		506.39	507.10	3.75
165		530.41	531.10	4.15
166		525.42	526.10	5.00
167		514.41	515.10	4.30
168		501.37	502.10	4.20
169		486.36	487.10	4.25
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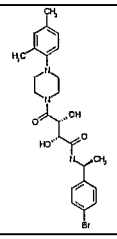
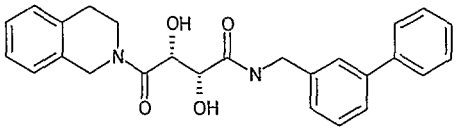
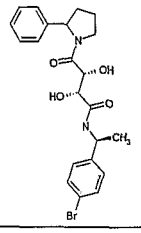
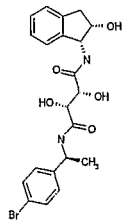
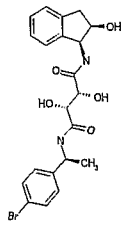
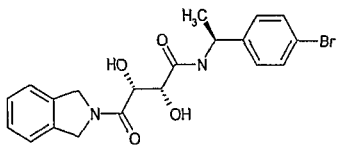
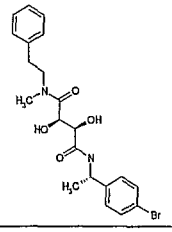
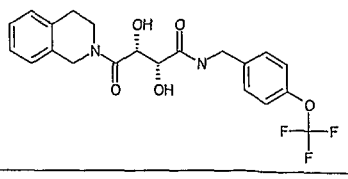
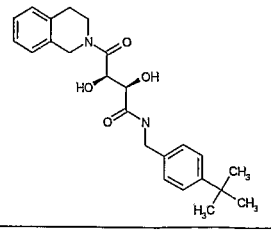
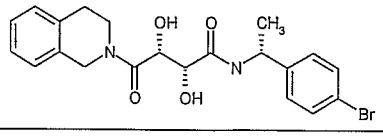
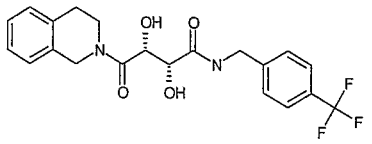
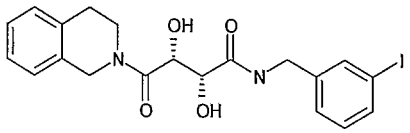
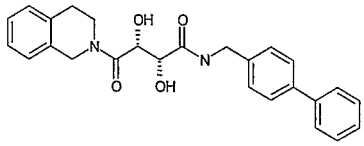
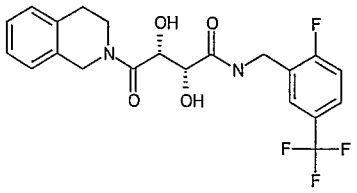
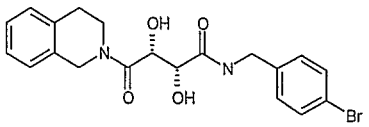
				

171		430.50	431.20	4.30
172		461.35	462.10	1.80
173		463.32	464.10	1.50
174		463.32	464.10	1.50
175		433.30	434.10	1.75
176		449.34	450.10	1.80
177		438.40	439.10	1.75

178		410.51	411.20	1.90
179		447.32	448.10	1.75
180		422.40	423.10	1.70
181		480.29	481.10	4.15
182		430.50	431.20	1.80
183		440.39	441.20	4.50
184		433.30	434.10	1.60
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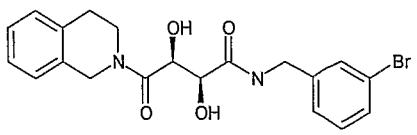
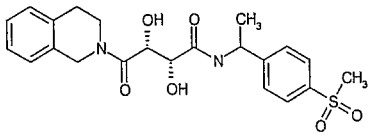
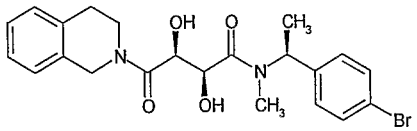
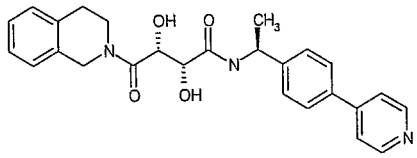
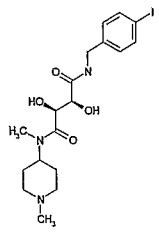
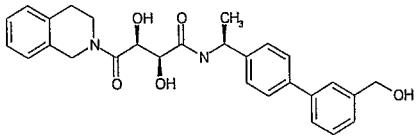
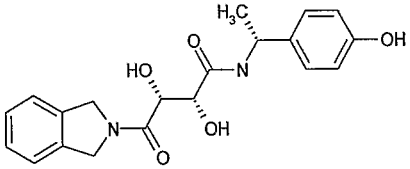
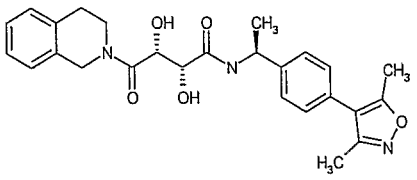
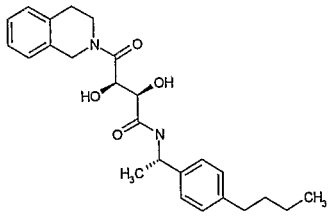
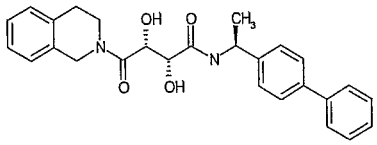
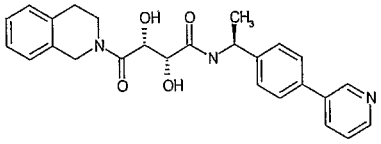
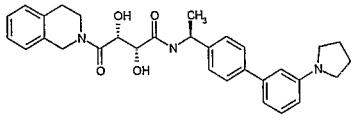
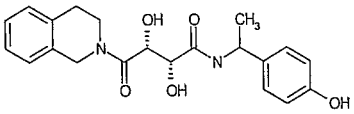
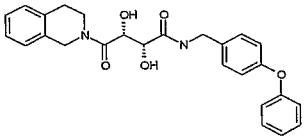
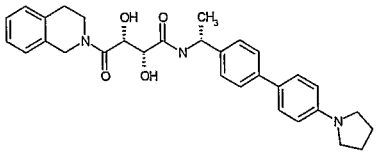
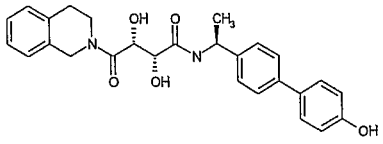
				

186		446.40	447.10	1.25
187		461.35	462.10	4.00
188		445.31	446.10	1.52
189		475.32	476.20	1.20
190		474.55	475.10	1.70
191		370.40	371.20	2.90
192		463.53	464.20	1.60
193		424.53	425.20	2.00

				
194		444.52	445.10	1.90
195		445.51	446.10	1.25
196		513.36	514.10	2.15
197		384.43	385.10	1.20
198		446.50	447.10	1.80
199		513..36	514.10	1.80
200		460.52	461.10	1.50
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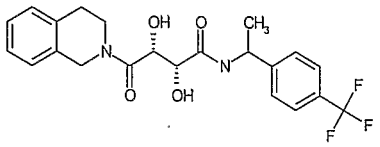
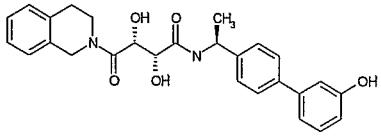
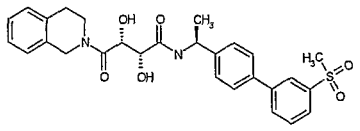
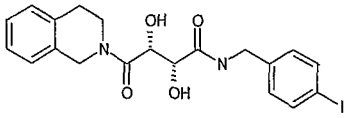
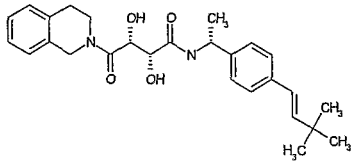
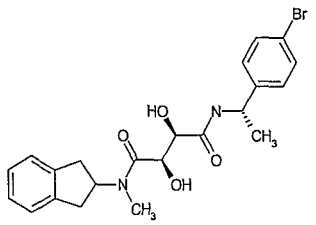
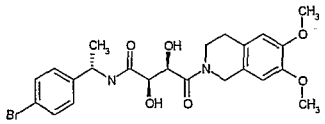
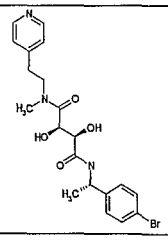
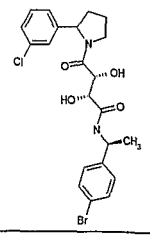
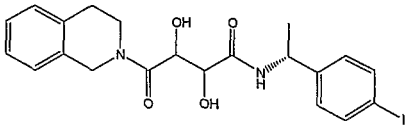
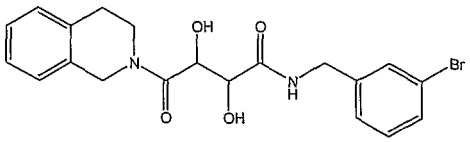
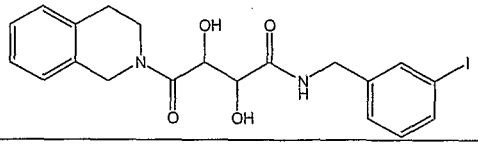
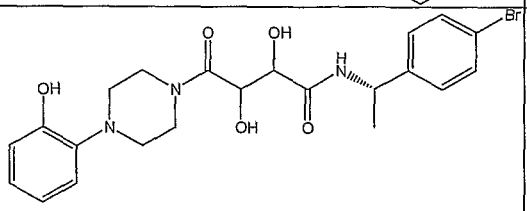
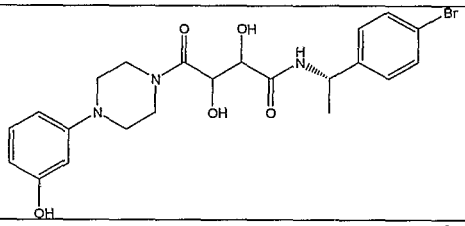
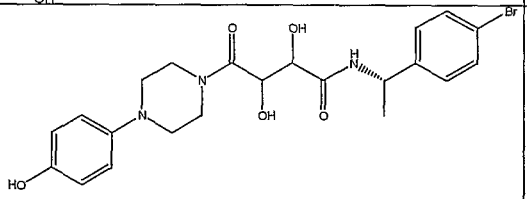
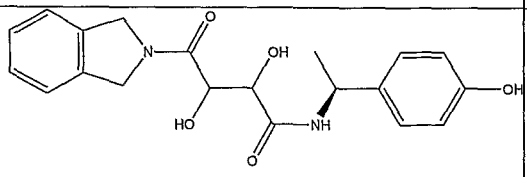
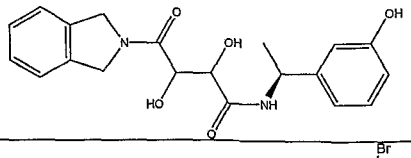
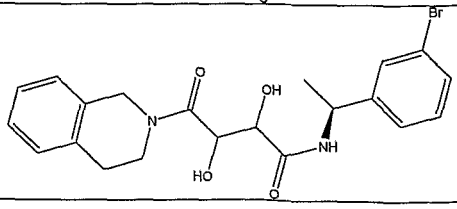
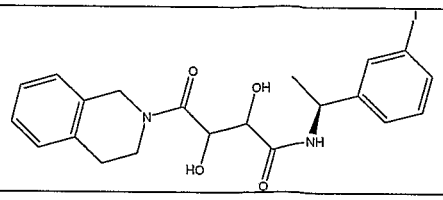
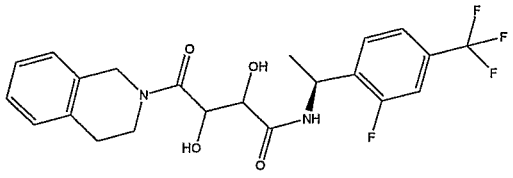
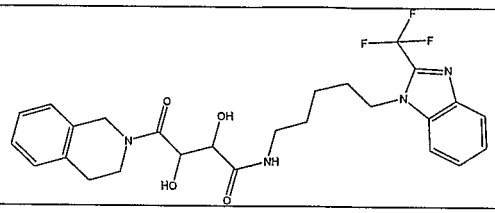
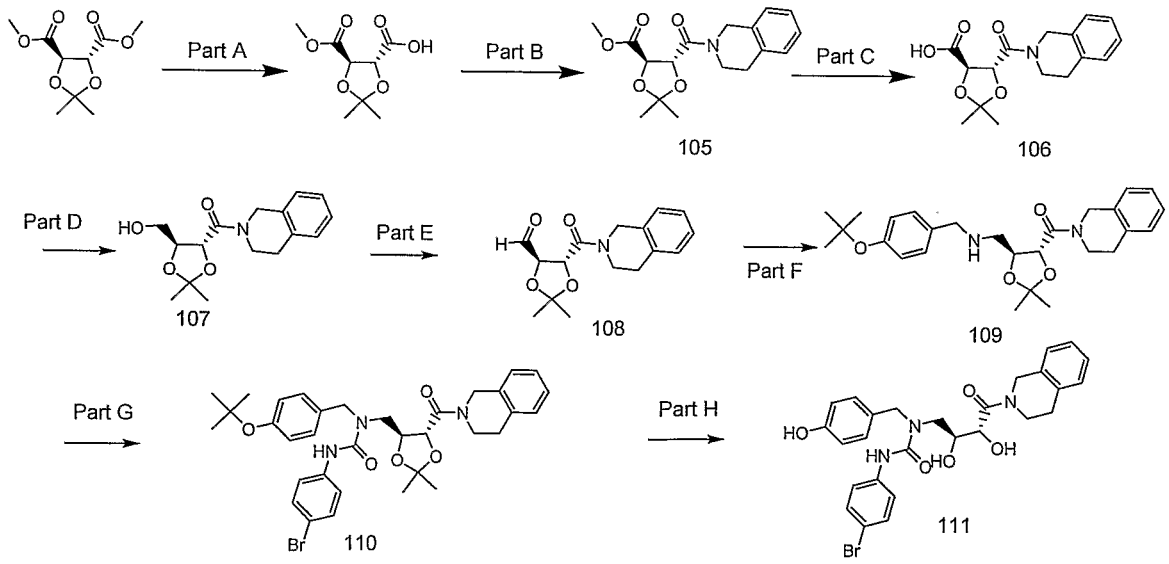
				
202		460.52	461.20	1.65

203		522.46	523.20	1.50
204		480.29	481.10	1.75
205		450.57	451.20	2.25
206		461.35	462.10	1.90
207		507.37	508.10	1.65
208		450.33	451.10	1.05
209		495.60	496.10	2.00
210		494.29	495.10	4.50

211		432.21	433.10	4.20
212		480.29	481.10	4.15
213		491.25	492.10	1.50
214		491.25	492.10	1.50
215		491.25	492.10	1.50
216		370.15	371.00	2.15
217		370.15	371.00	2.15
218		447.32	448.10	4.50

219		494.32	495.10	4.60
220		454.25	455.10	4.20
221		518.25	519.00	4.50

Additional Example -5



Part A, B (compound 105), and C (compound 106) are performed as described in Additional Example 1.

Part D:

Compound 106 (1.0gm) dissolved in dry THF and cooled to - 40° C and kept under nitrogen atmosphere. Two equivalents of BH_3 in THF(2.0 M) solution was added to it drop wise and the solution stirred at -40 ^{0}C for one hour followed by allowing the reaction mixture to warm to room temperature and continued stirring for overnight.

The solvent evaporated and extracted with ethyl acetate (200m). The organic layer washed with water, brine, and dried over anhydrous $MgSO_4$. Filtered and concentrated to dryness to provide the product 107. Purified on silica column using eluants Hexane and Ethyl acetate (8:2)

Part E:

The compound 107 (250mg) dissolved in dichloromethane and large excess (10 equivalents) of TEMPO resin was added to it. The reaction mixture stirred at room temperature for overnight. The LCMS analysis showed the completion. The mixture was filtered and the organic layer evaporated under vacuum. Compound 108 was used without further purification. HPLC-MS t_R = 1.50 min ($UV_{254\ nm}$); mass calculated for formula $C_{16}H_{19}NO_4$, 289.33, observed LCMS m/z 290.1 (M+H).

Part F:

Compound 108 (145mg, 0.5 mmol) and 4-ter-butoxy benzyl amine (0.6 mmol, 98 mg,1.1 equivalents) were dissolved in dichloromethane and the solution was added with 100 uL of acetic acid, followed by addition of sodium triacetoxy borohydride (3 equivalents) and the solution was stirred at room temperature for overnight. The analysis showed the completion of the reaction. The reaction mixture was added with 200mL of dichloromethane and washed with water, brine and DCM layer was dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum to provide compound 109, which was purified on silica gel column using the eluants hexane- ethyl acetate. HPLC-MS t_R = 2.75 min ($UV_{254\ nm}$); mass calculated for formula $C_{27}H_{36}N_2O_4$, 452.27, observed LCMS m/z 453.1 (M+H).

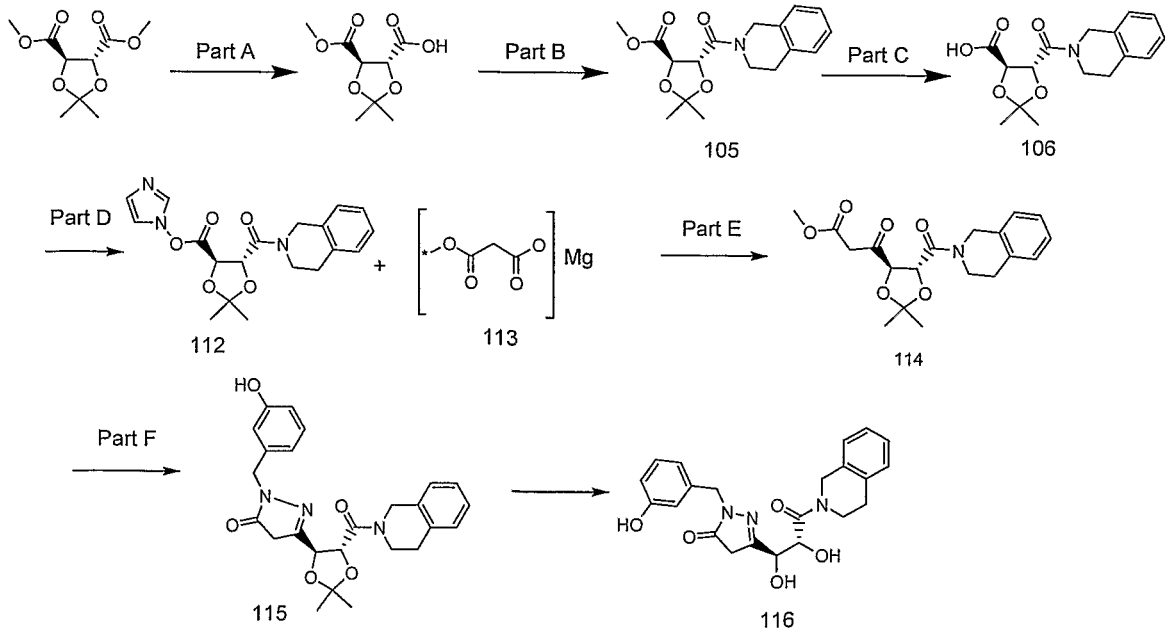
Part G:

Compound 109 (110mg, 0.25mmol) and 4-bromo isocyanate (0.3 mmol, 60 mg,1.2 equivalents) were dissolved in dichloromethane and the solution was stirred at room temperature for overnight. The analysis showed the completion of the reaction. The reaction mixture was added with 100mL of dichloromethane and washed with water, brine and DCM layer was dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum to provide compound 110, which was purified on silica gel column using the eluants hexane- ethyl acetate. HPLC-MS t_R = 3.25 min ($UV_{254\ nm}$); mass calculated for formula $C_{34}H_{40}N_3O_5Br$, 649.22, observed LCMS m/z 650.0 (M+H).

Part H:

Compound 110 (25mg) was dissolved in dichloromethane(2mL) and added 90% aqueous Trifluoroacetic acid and stirred at room temperature for 45 minutes. The solvent evaporated under vacuum and the resulting material purified on Prep HPLC to give the product 111. HPLC-MS t_R = 1.80min ($UV_{254\ nm}$); mass calculated for formula $C_{27}H_{28}N_3O_5Br$, 553.12, observed LCMS m/z 554.1 (M+H).

Additional Example 6:



Part A,B,C can be prepared as described in Additional Example 1 (parts a,b,c)

Part D:

Compound 106 (2 mmol, 610 mg) was dissolved in THF (50 mL) and cooled to 0 °C and kept under nitrogen atmosphere. To the above solution while stirring, a solution of N,N' carbonyldiimidazole (2.2 mmol, 356 mg) in THf was added and stirring continued for overnight. The removal of solvent provided the activated ester in quantitative yield and is used in the next step with out purification.

HPLC-MS t_R = 3.25 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{21}N_3O_5$, 371.15, observed LCMS m/z 372.10 (M+H).

Part E:

Compound 113 generated in situ, [addition of dibutyl magnesium to ethyl hydrogen malonate in THF at -78 ^{0}C stirred at -78 ^{0}C for 1 hr] was added to a solution containing the compound 112 in THF and stirred at room temperature for 24hrs. The solvent was evaporated and ethyl acetate (100mL) added. Organic layer washed with water, brine, dried over anhydrous MgSO4, filtered and evaporated to give a gummy material, purified on silica gel column to afford compound 114. HPLC-MS t_R =1.95 min ($UV_{254\ nm}$); mass calculated for formula $C_{20}H_{25}NO_6$, 375.17, observed LCMS m/z 376.10 (M+H).

Part F:

Compound 114 (0.2 mmol, 75 mg) in ethanol (5mL) was added with 3-hydroxybenzylhydrazide dihydrochloride (0.22 mmol, 50mg) and triethyl amine (140 uL, 1 mmol, 5 equivalents) and refluxed overnight.. The LCMS analysis showed the product formation. The ethanol was evaporated and compound was purified by Preparatory HPLC to afford the product 115.

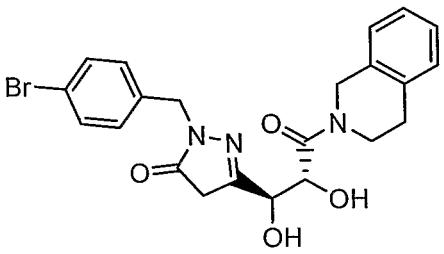
HPLC-MS t_R =1.50 min ($UV_{254\ nm}$); mass calculated for formula $C_{25}H_{27}N3O_5$, 449.17, observed LCMS m/z 450.10 (M+H).

Part G:

Compound 116 was prepared using the procedure described in Additional Example 3 part B. HPLC-MS t_R =1.40 min ($UV_{254\ nm}$); mass calculated for formula $C_{25}H_{27}N3O_5$, 409.16, observed LCMS m/z 410.10 (M+H).

Additional Example 7

Compound 117

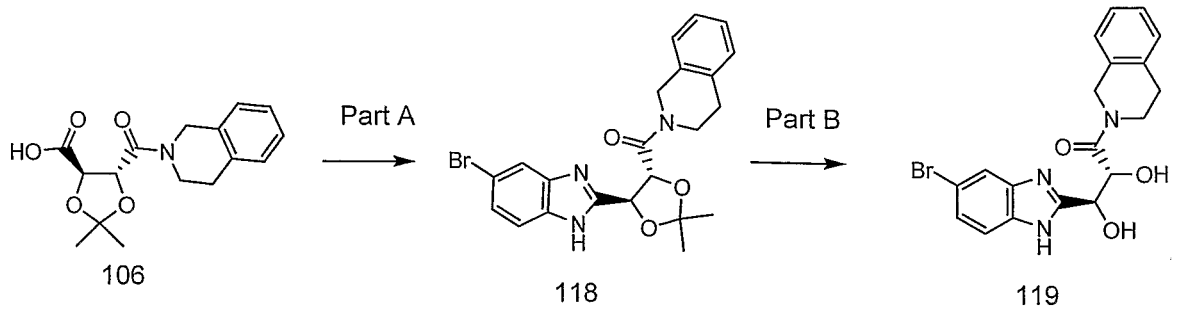


Compound 117 was synthesized similar to the procedure described in the synthesis of compound 116, Additional Example 6 (Part A-F)

HPLC-MS t_R =1.40 min ($UV_{254\ nm}$); mass calculated for formula $C_{22}H_{22}BrN_3O_4$, 471.08, observed LCMS m/z 472.00 (M+H).

Additional Example 8:

Compound 119:



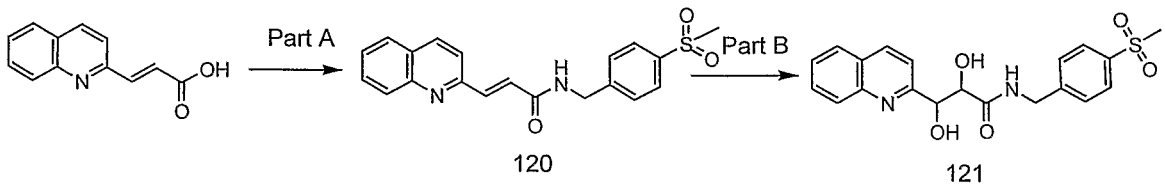
Part A:

Compound 106 made as described in example 6,

Compound 106 (305 mg. 1mmol) was dissolved in dimethylformamide and HATU (408 mg, 1.1 mmol), diisopropylethylamine amine (525 uL, 3 mmol) were added and stirred at room temperature. After ten minutes, 4-bromo o-phenylene diamine was added to the reaction mixture and stirring continued for overnight. LCMS analysis showed the completion of the reaction. Reaction mixture diluted

Additional Example 9

Compound 121



Compound 120:

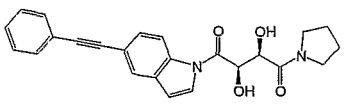
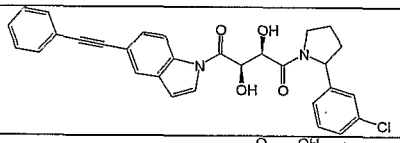
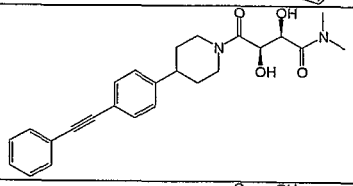
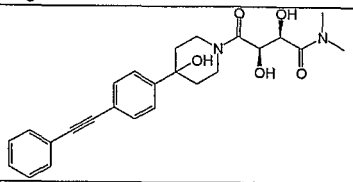
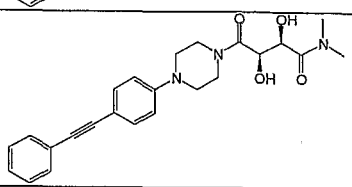
3-Quinolin-2-yl-acrylic acid (400mg, 2 mmol) is dissolved in dimethylformamide and HATU (800mg, 2.2 mmol) and diisopropylethylamine(1.2 ml, 6 mmol), was added to it and stirred at room temperature. To this solution, 4-methyl sulfonyl benzyl amine hydrochloride is added and stirring continued for 4hrs. The reaction mixture diluted with ethyl acetate and washed with water, brine and dried over anhydrous $MgSO_4$, Filtered and evaporation of the organic solvent provide the ptoduct 120.

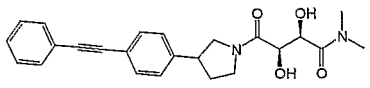
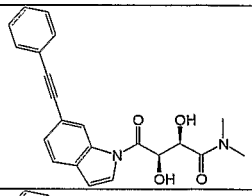
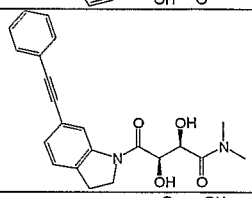
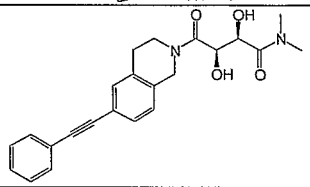
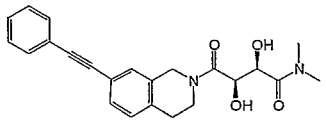
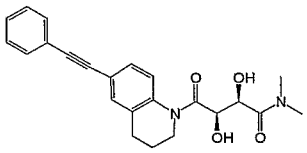
Compound 121:

Compound 120 (185 mg, 0.5 mmol) was dissolved in dichloromethane and osmium tetroxide (254 mg, 1 mmol) is added to it and stirred the mixture for overnight. LC analysis indicate the product formation. Evaporation of sovent and purification of the product by passing through the silica gel column followed by preparative HPLC result in the product 121.

Example 10:

The compounds listed in the table below can be prepared from the procedures described in experimental 2A or 2C utilizing Sonogashira coupling followed by coupling with compound 5 or 7 with HATU and hydrolysis as described in example 3 A and B.

S. NO.	Structure	MWt	MS m/z (M+H)
122		402.16	403.10
123		512.15	513.10
124		420.20	421.10
125		436.20	437.10
126		421.20	422.10

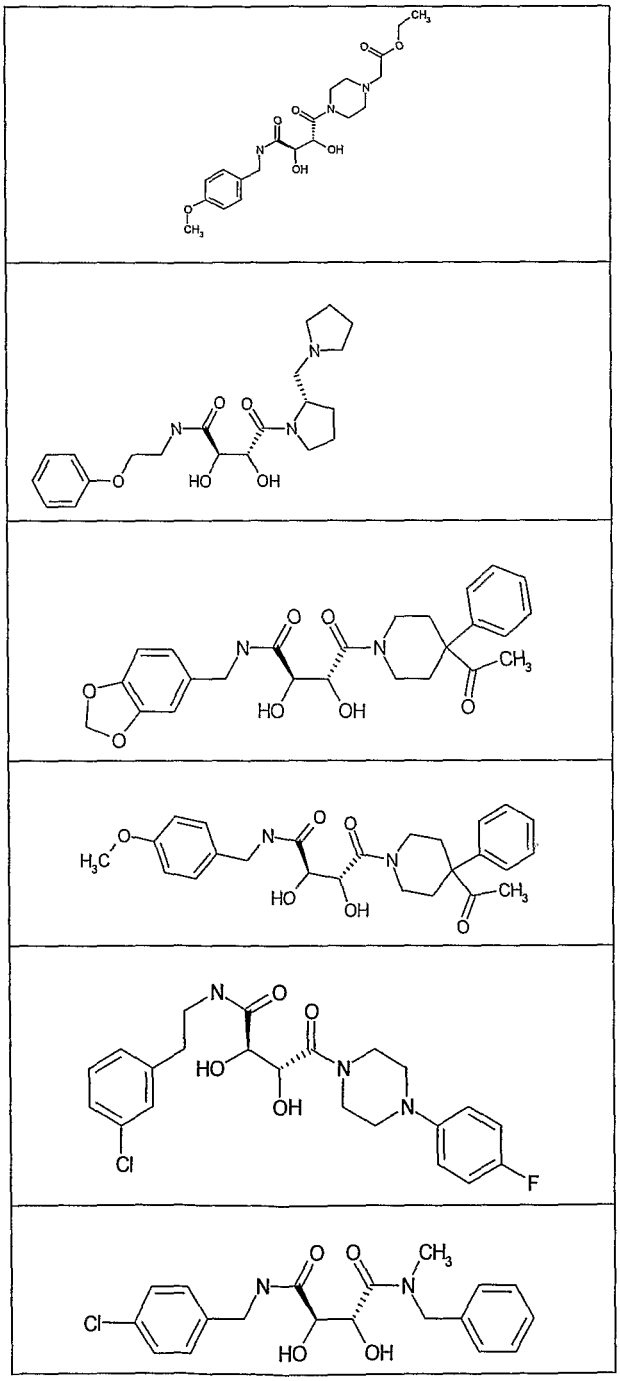
127		406.19	407.20
128		376.14	377.10
129		378.16	379.10
130		392.17	393.10
131		392.17	393.10
132		392.17	393.10

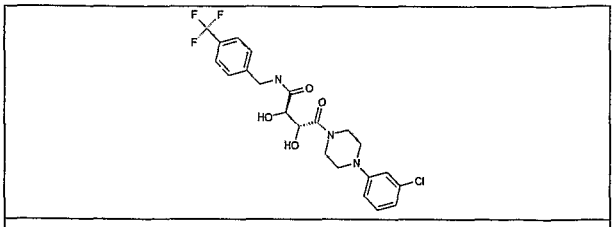
It will be appreciated by those skilled in the art that changes could be made to the embodiments described above without departing from the broad inventive concept thereof. It is understood, therefore, that this invention is not limited to the particular embodiments disclosed, but it is intended to cover modifications that are within the spirit and scope of the invention, as defined by the appended claims.

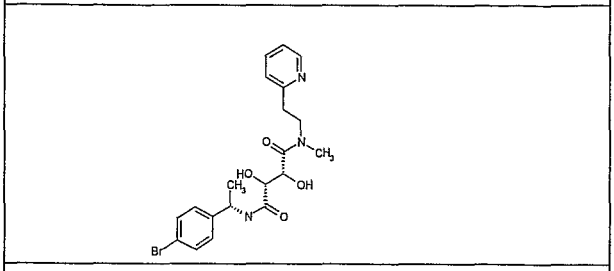
Each and every document referred to in this patent application is incorporated herein by reference in its entirety for all purposes.

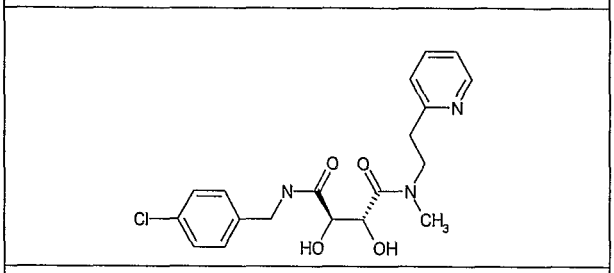
What is claimed is:

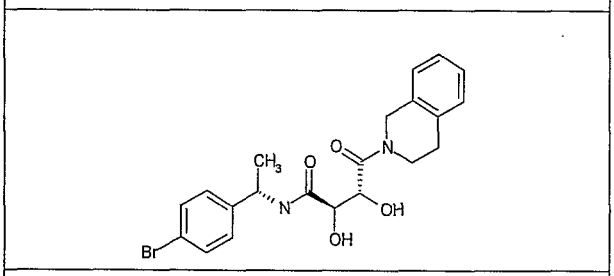
1. A compound selected from the group consisting of:

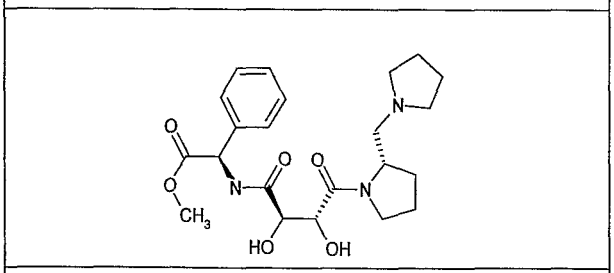


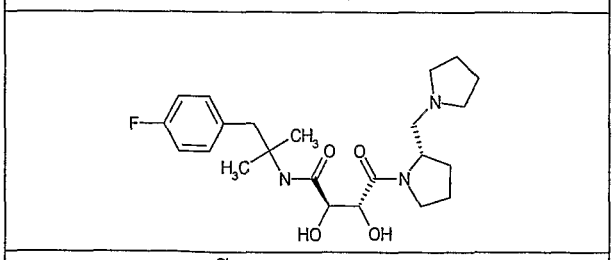


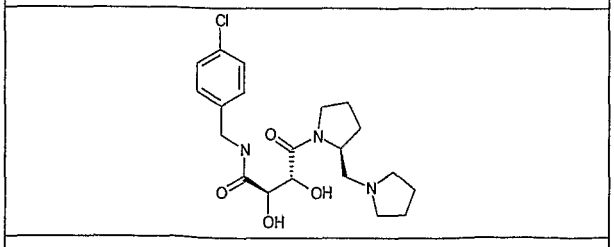


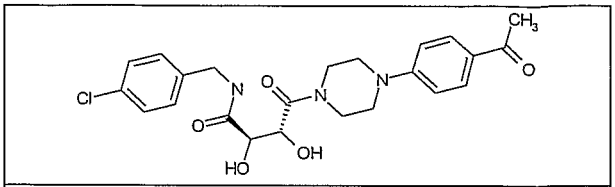


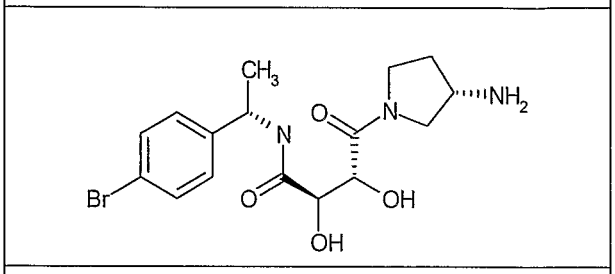


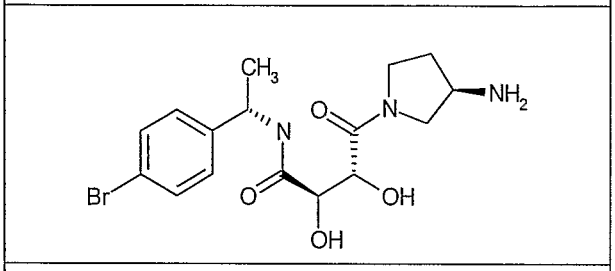


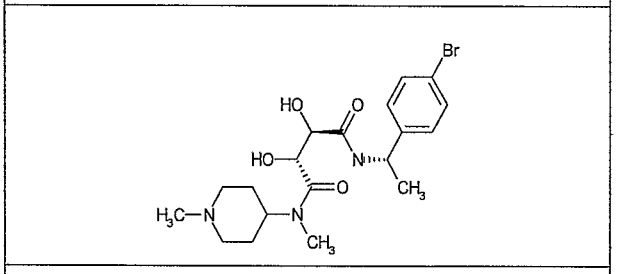


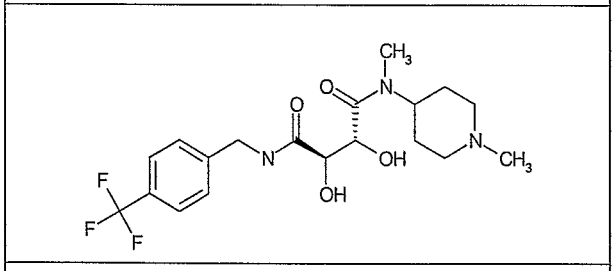


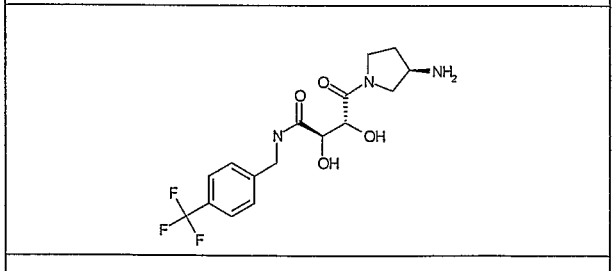


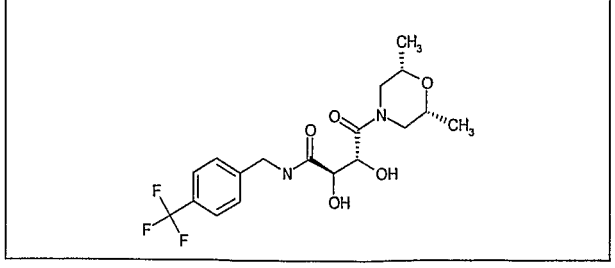


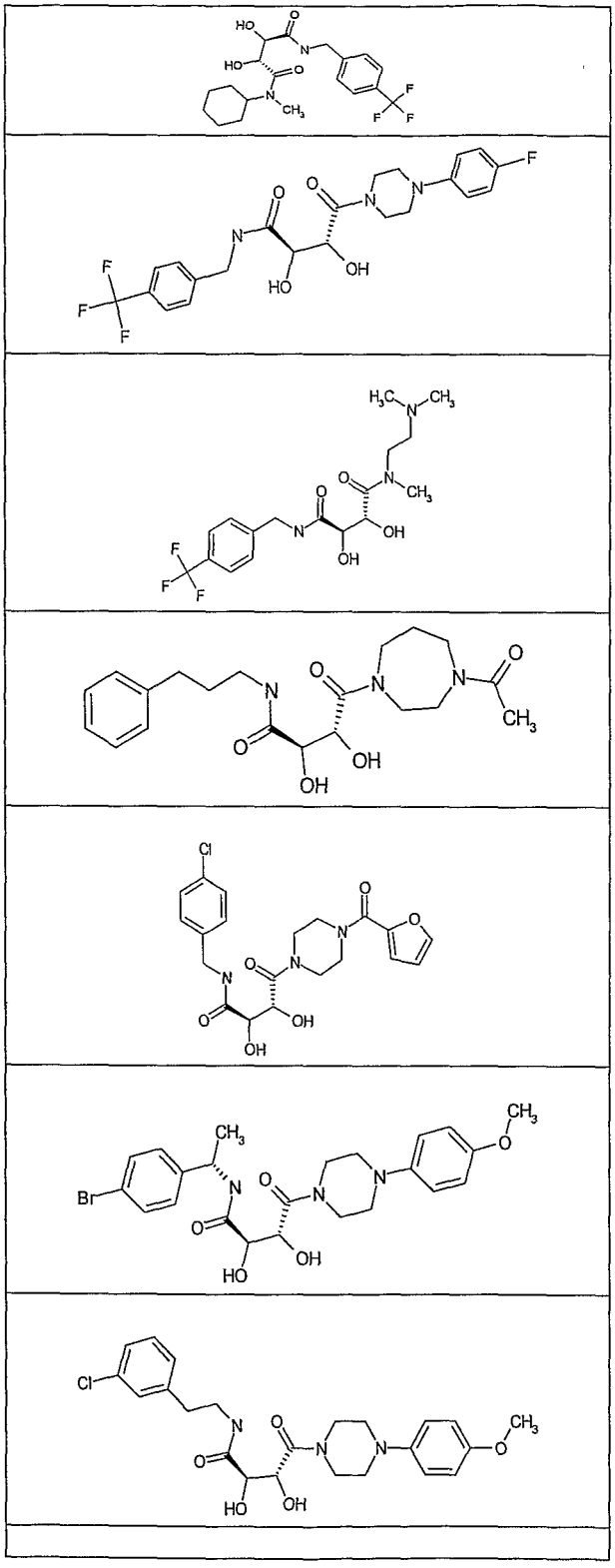


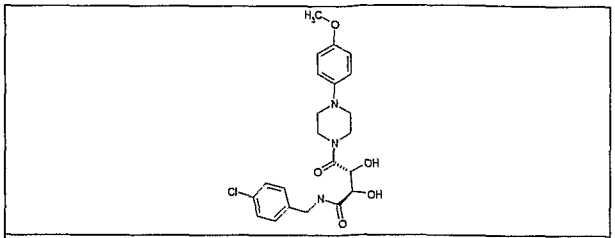


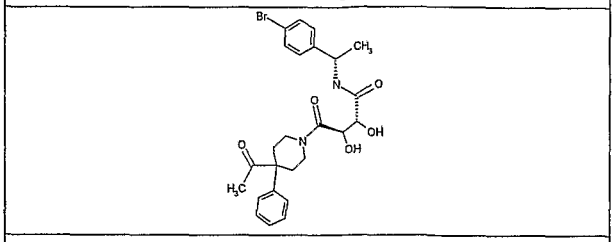


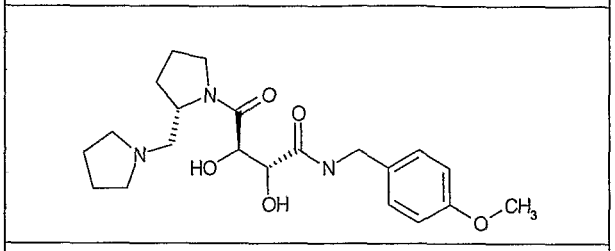


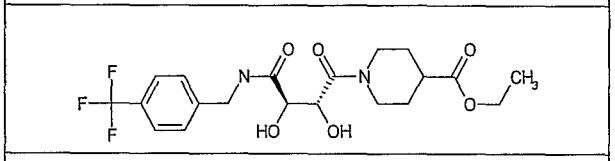


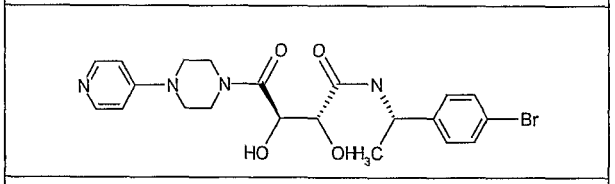


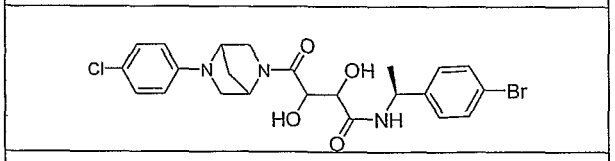


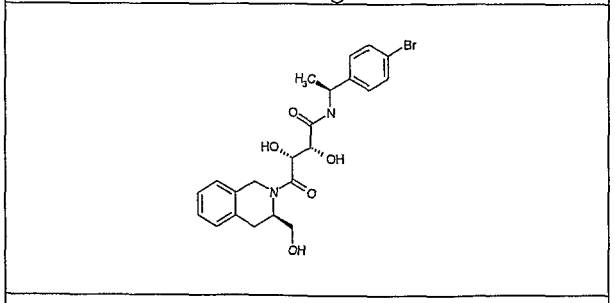


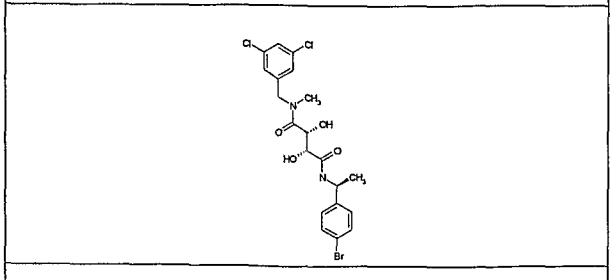


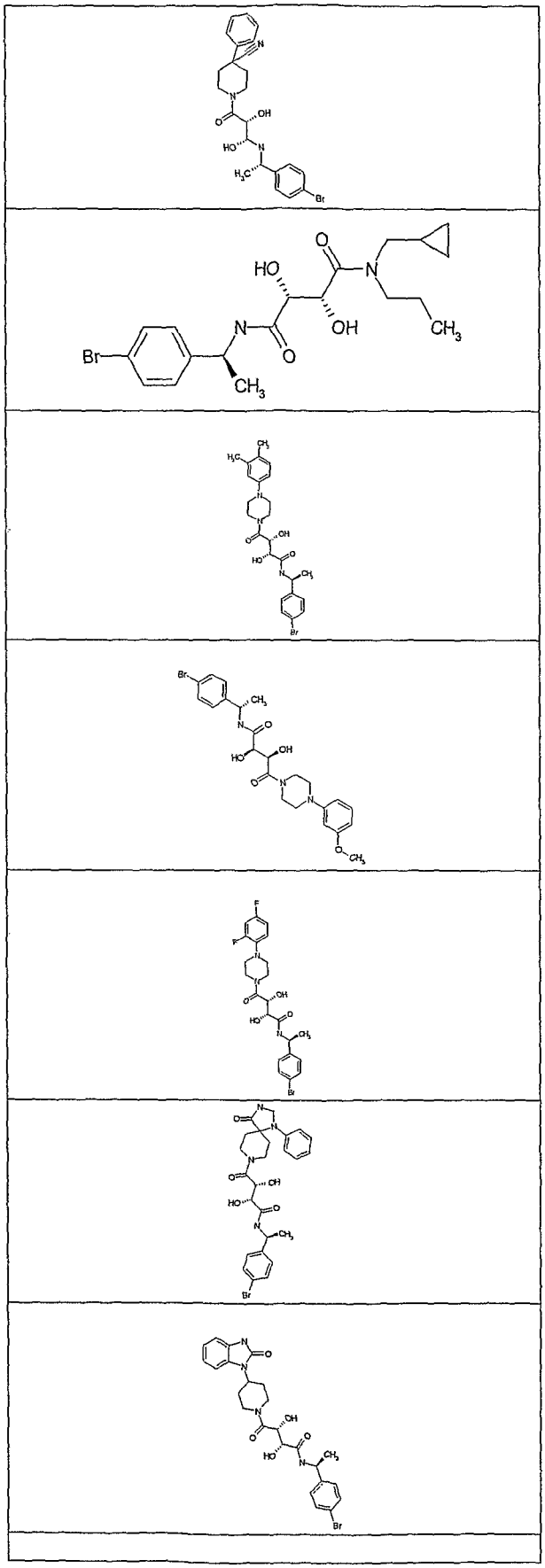


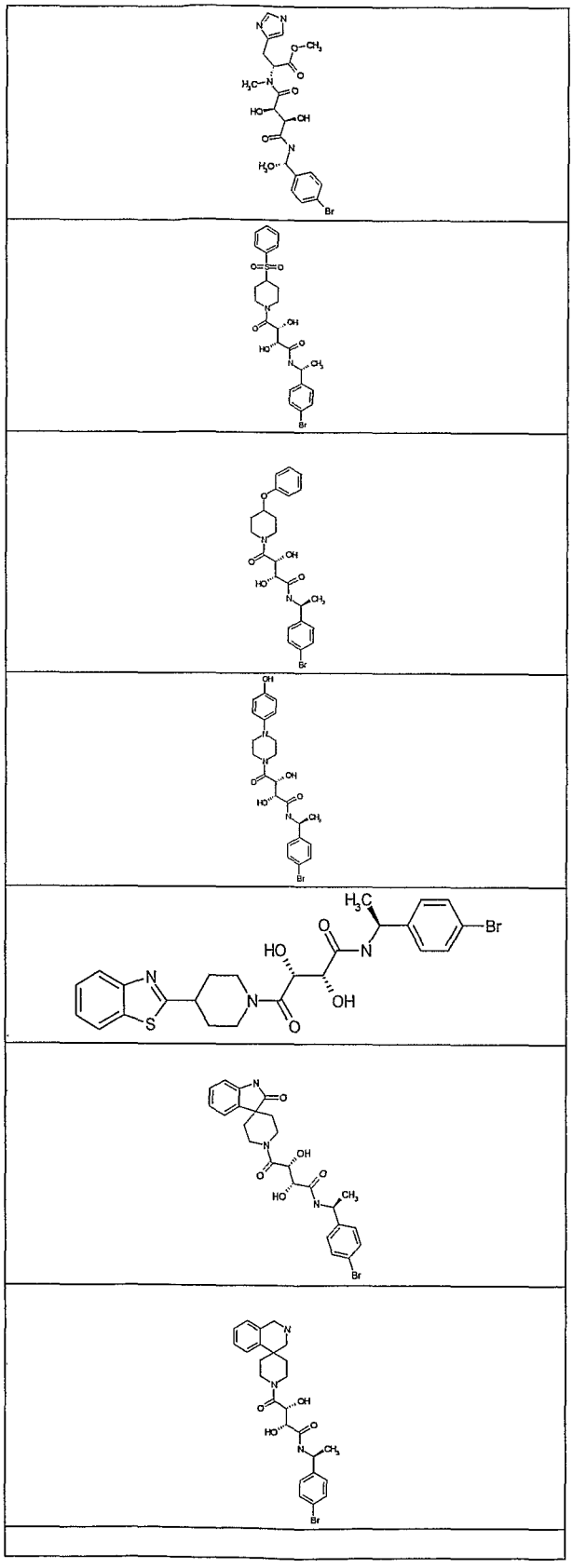


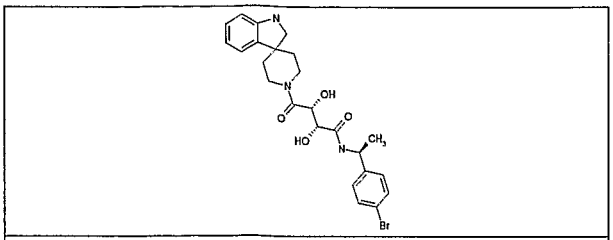


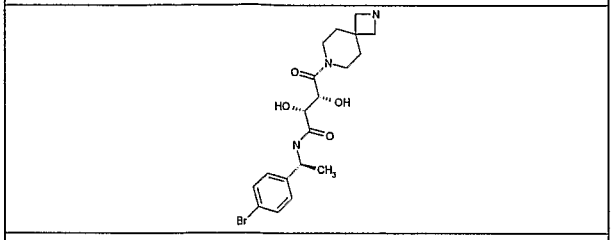


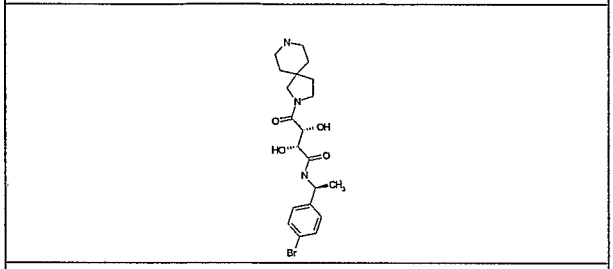


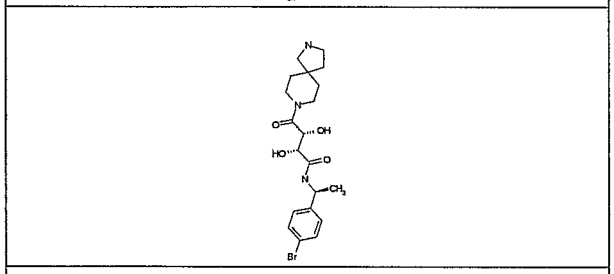


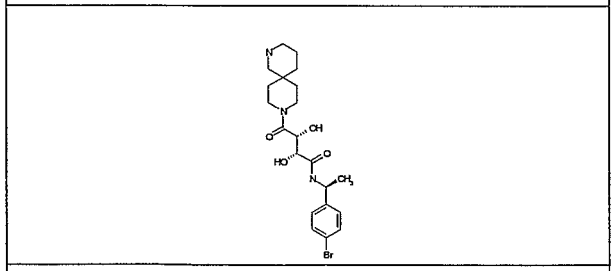


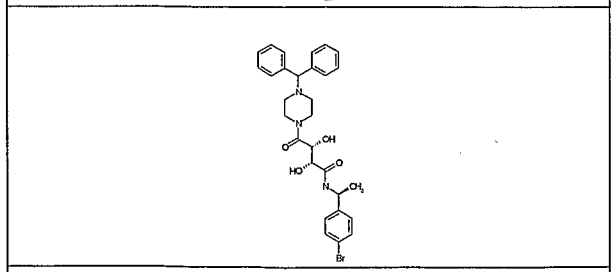


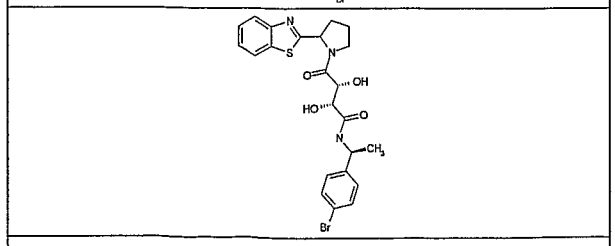


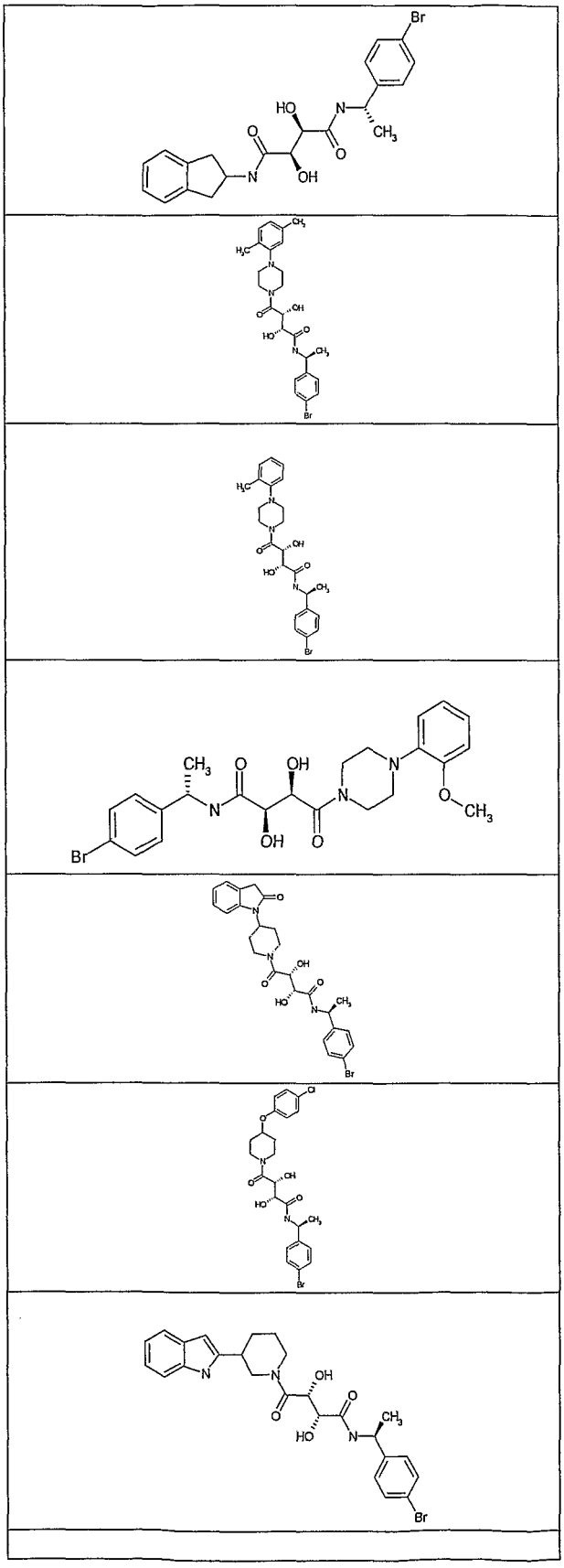


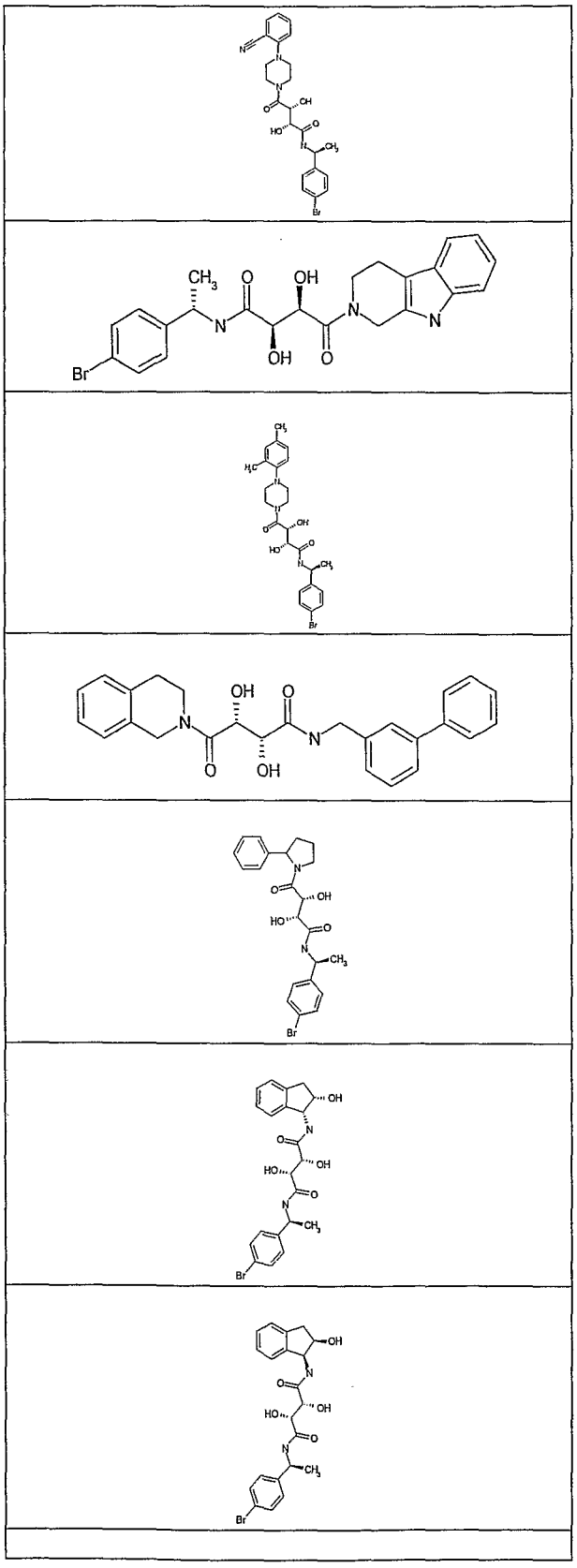


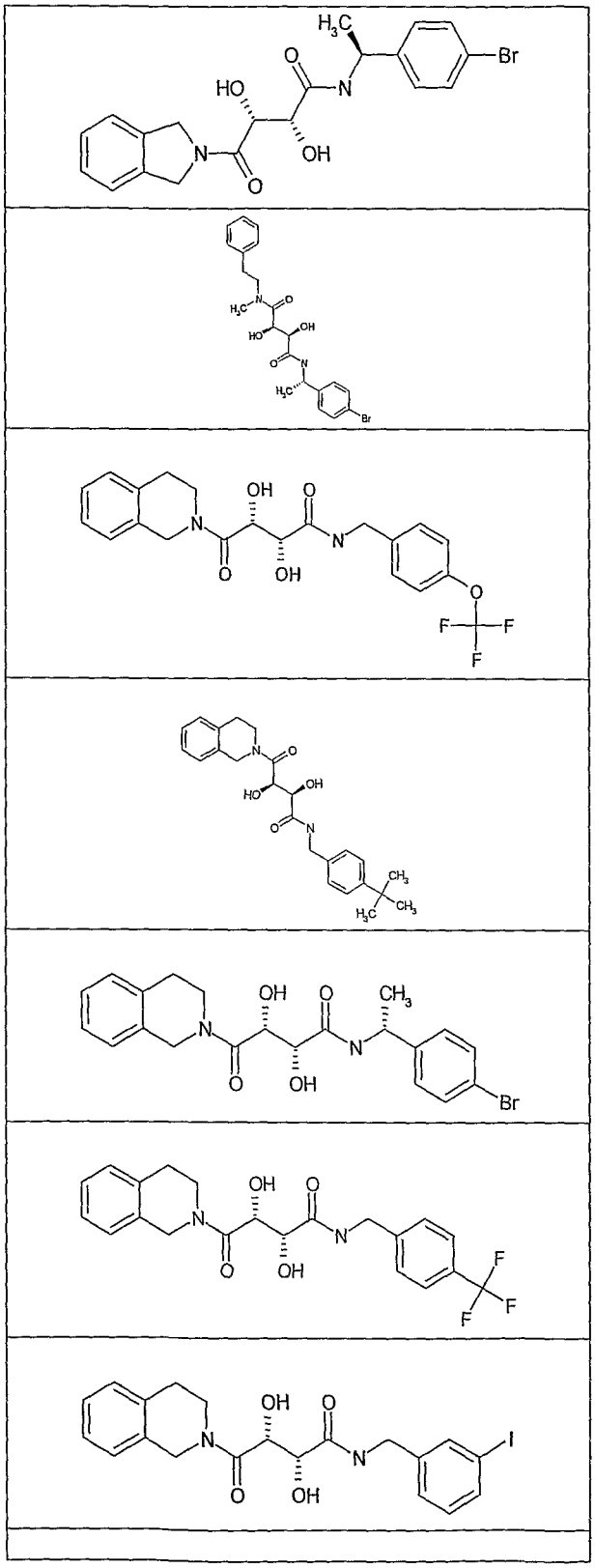


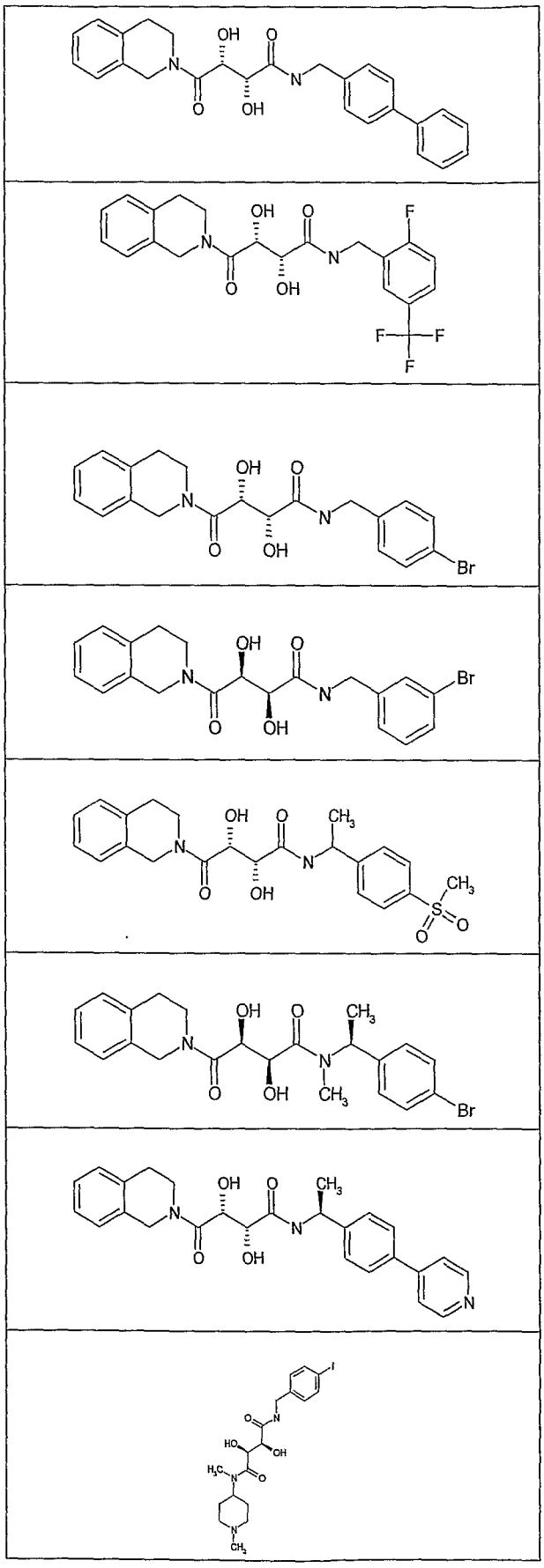


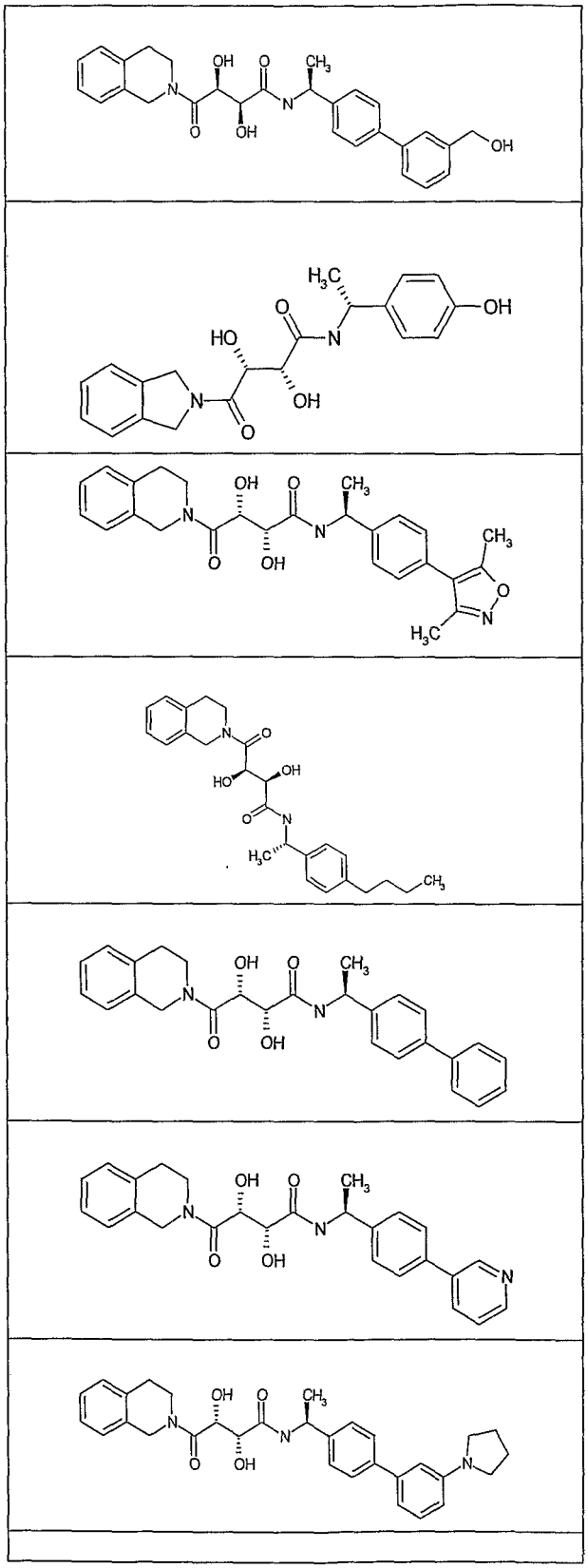


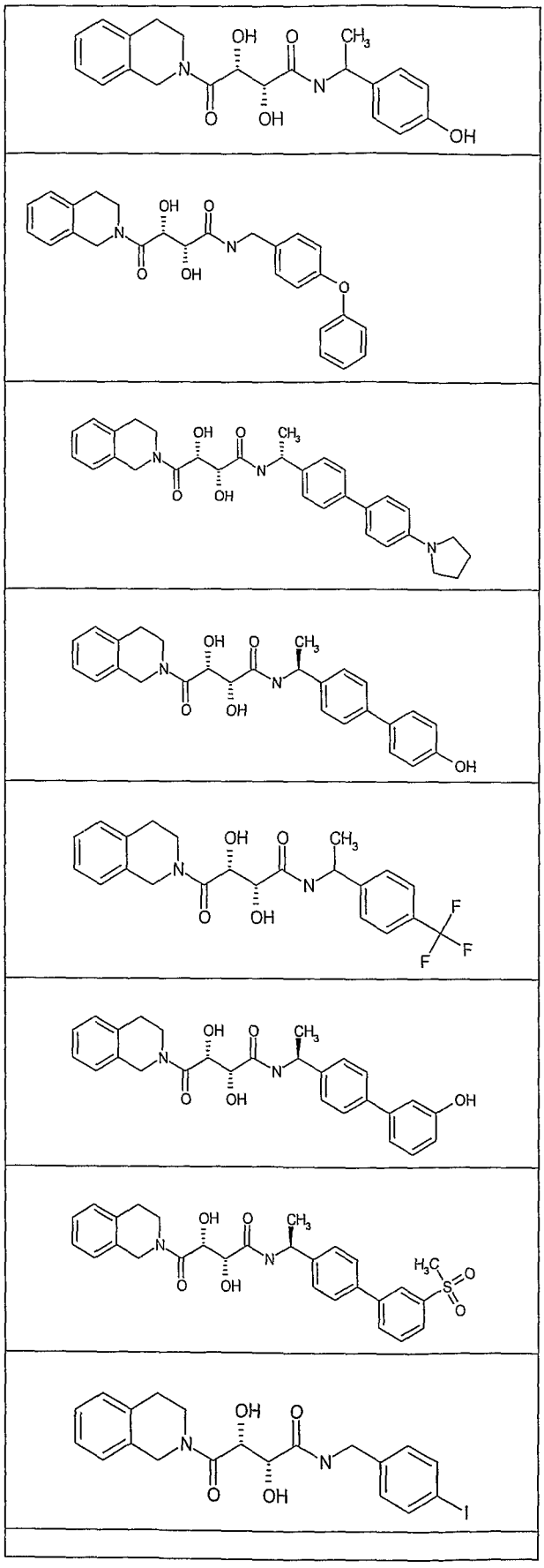


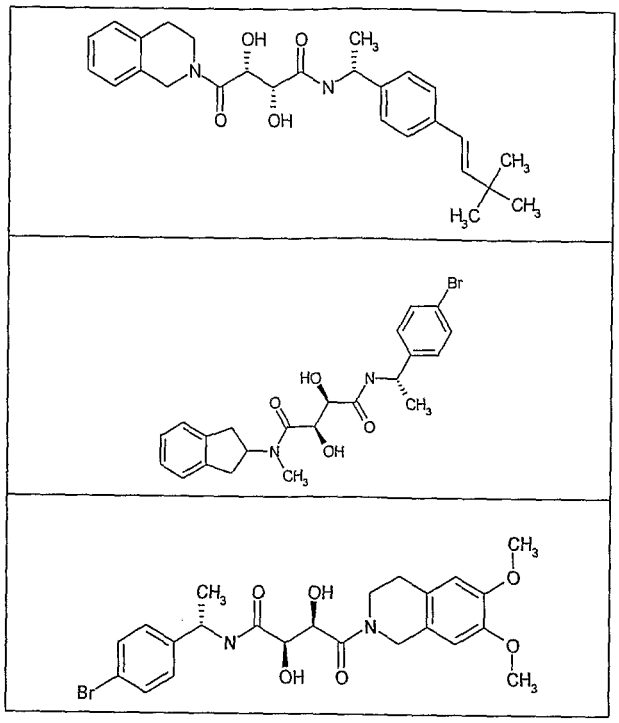


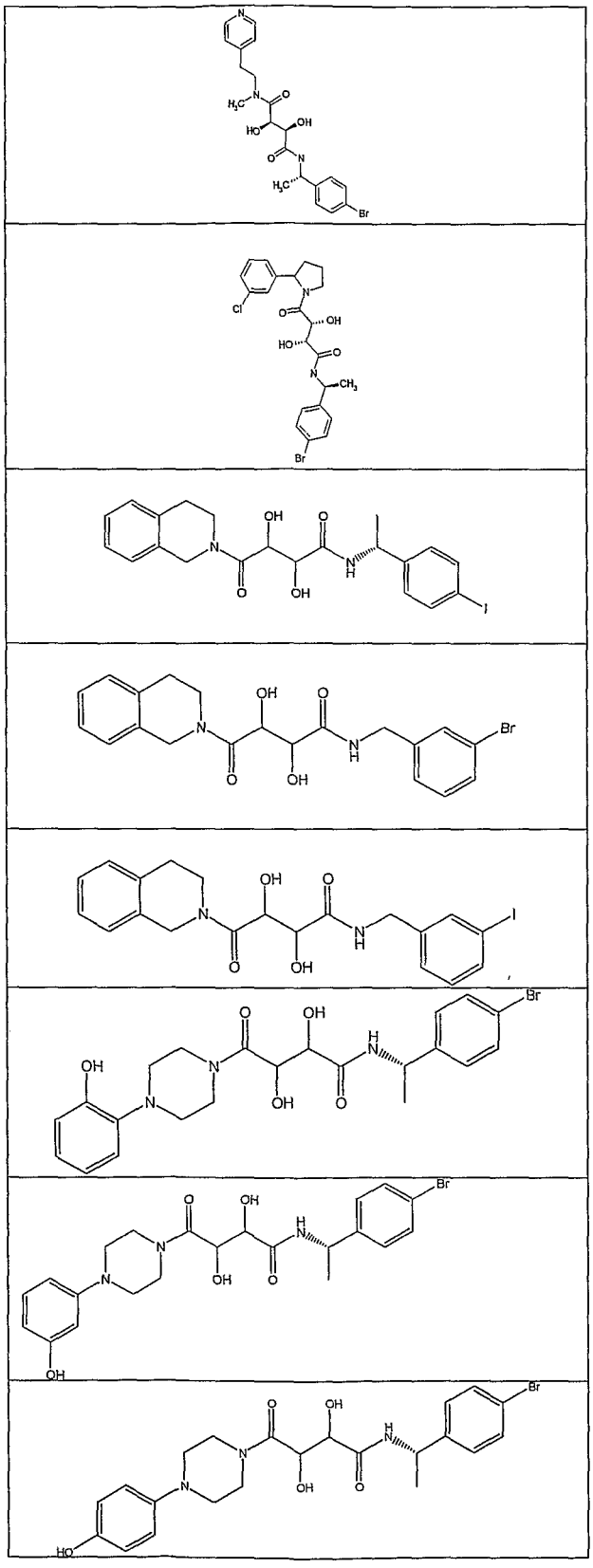


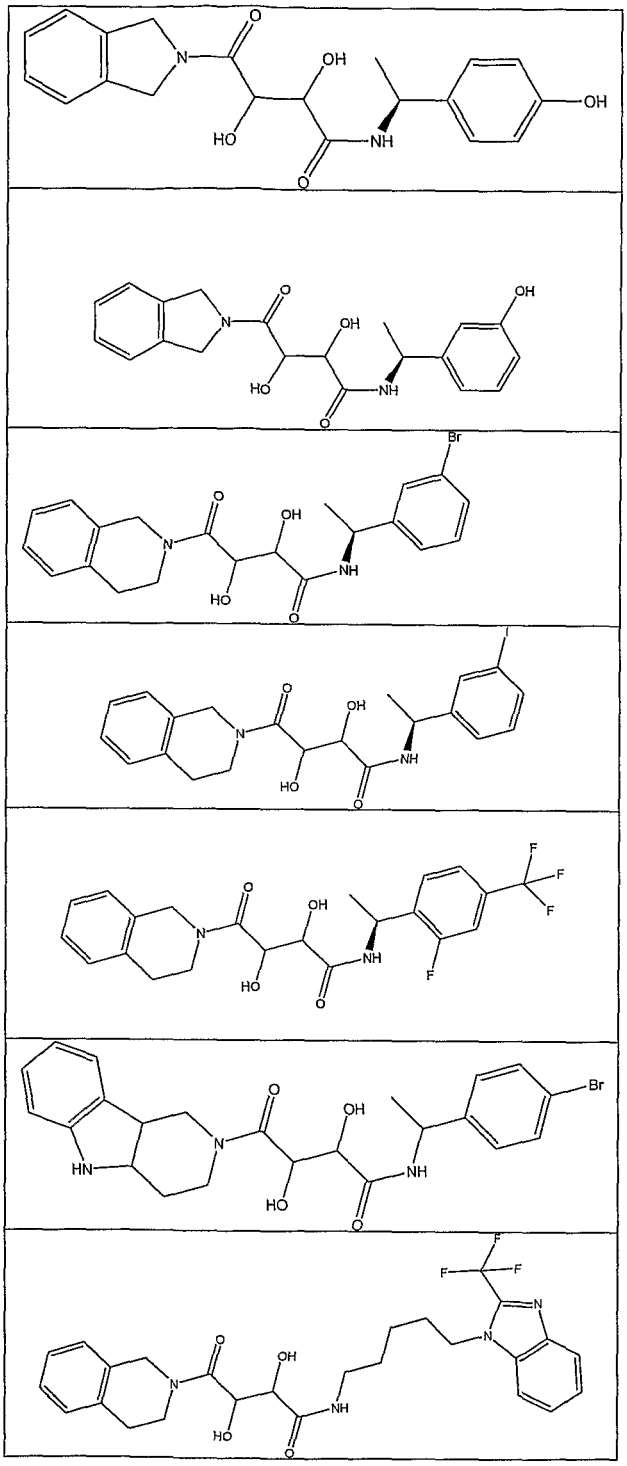


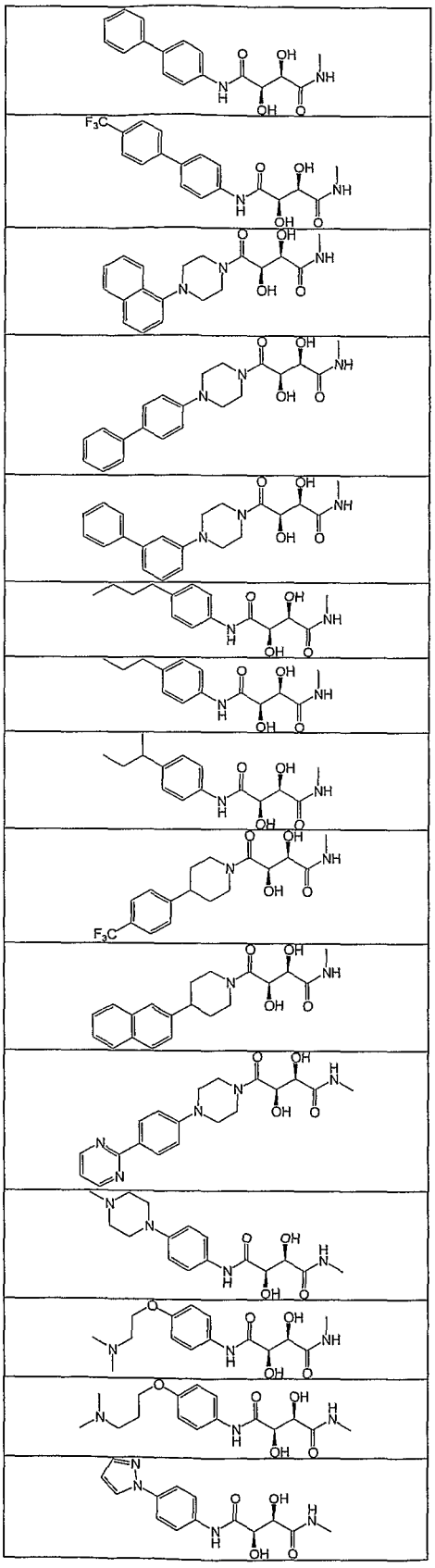


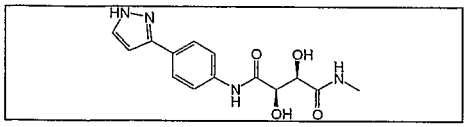


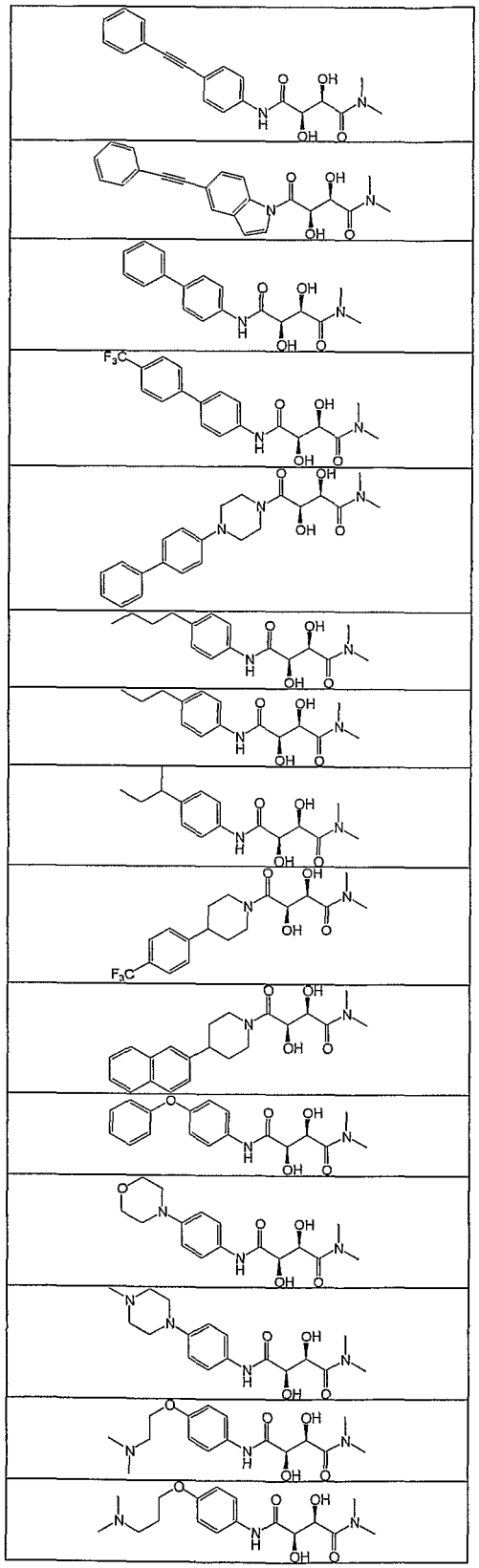


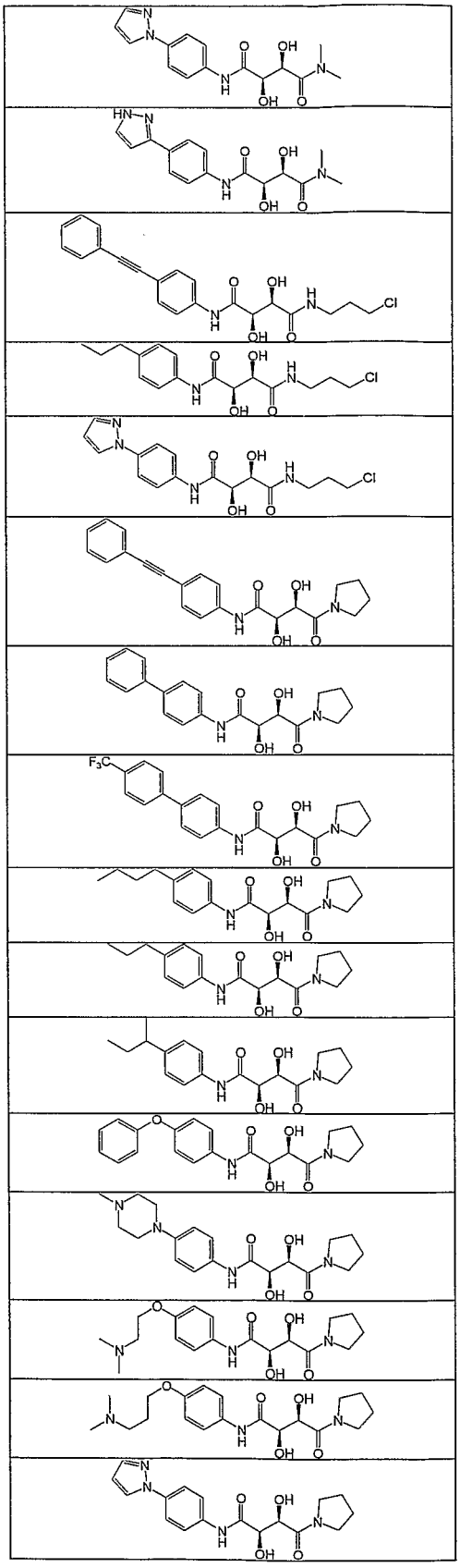


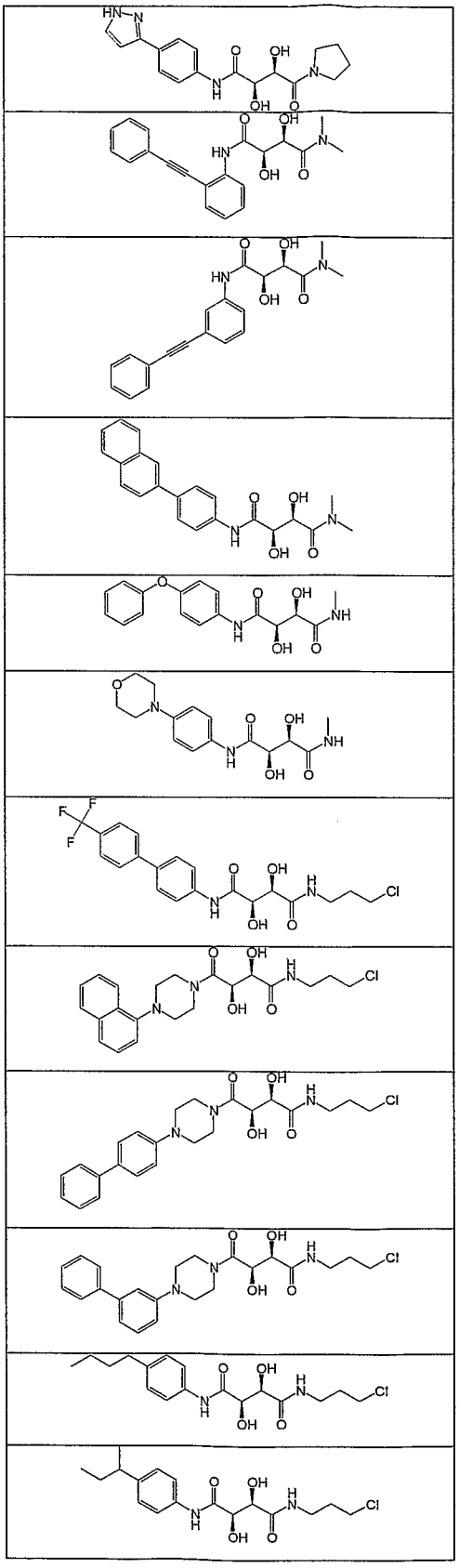


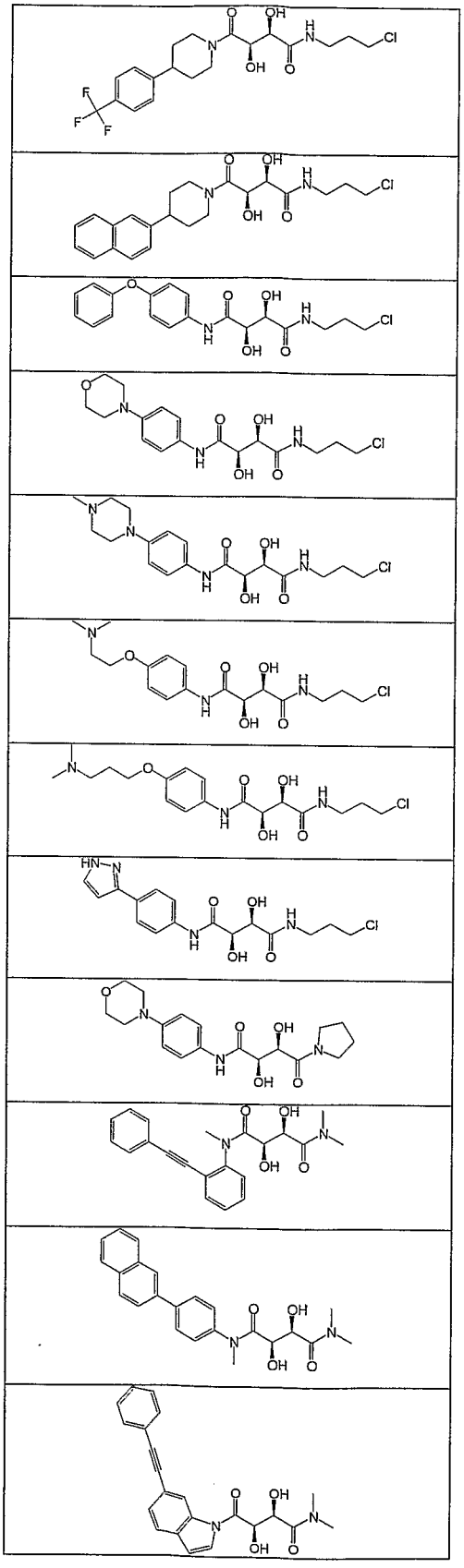


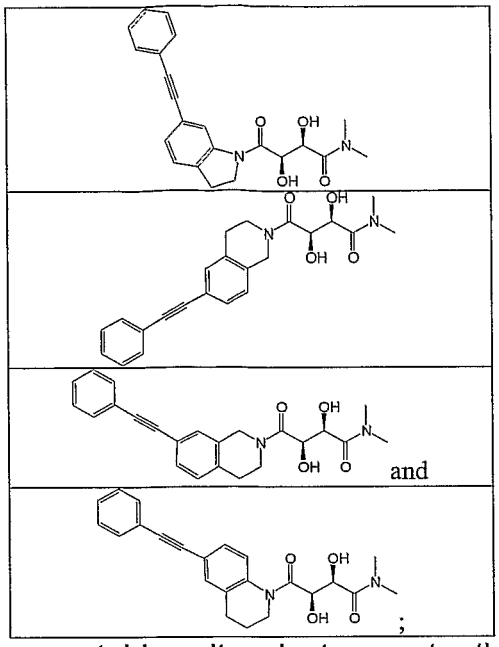






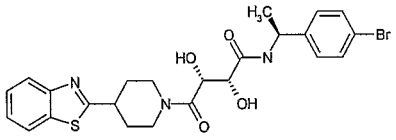


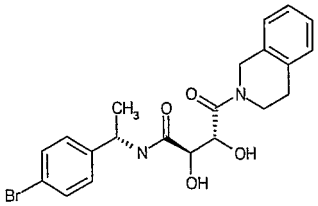


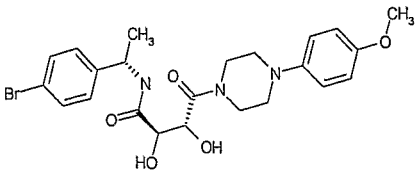


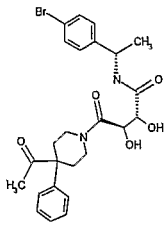
or a pharmaceutically acceptable salt, solvate or ester thereof.

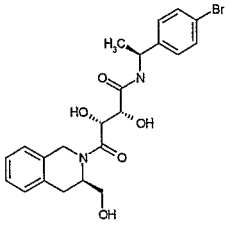
2. The compound of claim 1, wherein said compound is selected from the group consisting of

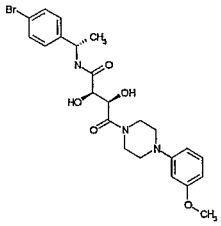


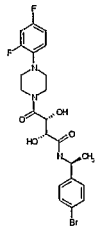


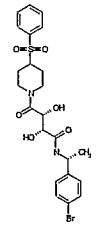


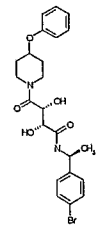


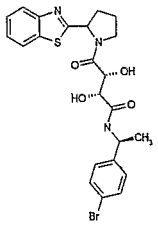


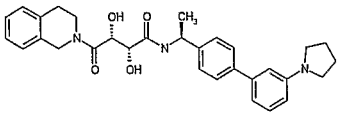


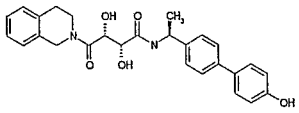


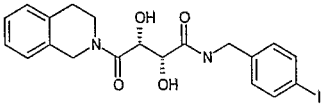


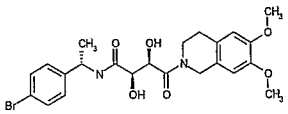


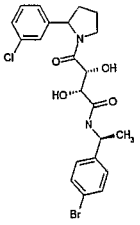




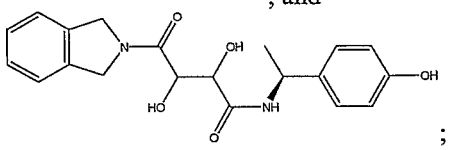








, and



;

or a pharmaceutically acceptable salt, solvate or ester thereof.

3. A pharmaceutical composition comprising as an active ingredient at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or ester thereof.

4. The pharmaceutical composition of claim 3, additionally comprising at least one pharmaceutically acceptable carrier.

5. A method of treating disorders associated with tumor necrosis factor-alpha-converting enzyme (TACE), aggrecanase, aggrecan degrading metallo protease (ADMP), UDP-3-O-(R-3-hydroxymyristoyl)-N-

acetylglucosamine deacetylase (LpxC), tumor necrosis factor-alpha (TNF-α), matrix metalloproteinases (MMPs), a disintegrin and metalloproteases (ADAMs) or any combination thereof, said method comprising administering to a patient in need of such treatment a pharmaceutical composition which comprises therapeutically effective amounts of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or ester thereof.

6. A method of preparing a pharmaceutical composition for treating the disorders associated with TACE, LpxC, aggrecanase, ADMP, TNF-α, MMPs, ADAMs or any combination thereof, said method comprising bringing into intimate contact at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or ester thereof, and at least one pharmaceutically acceptable carrier.

7. A pharmaceutical composition for treating disorders associated with TACE, aggrecanase, ADMP, TNF-α, MMP, ADAM or any combination thereof in a subject comprising, administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or ester thereof.

8. A compound of claim 1 or a pharmaceutically acceptable salt, solvate or ester thereof in purified form.

9. A method of treating a condition or disease mediated by TACE, LpxC, MMPs, ADMP, TNF-α, aggrecanase, or any combination thereof in a subject comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or ester thereof.

10. The method of claim 9, wherein said aggrecanase is aggrecanase 1, aggrecanase 2, aggrecanase 3, or aggrecanase 4.

11. A method of treating a condition or disease selected from the group consisting of rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, solid tumor growth and tumor invasion by secondary metastases, neovascular glaucoma, inflammatory bowel disease, multiple sclerosis and psoriasis in a subject, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one

compound of claim 1 or a pharmaceutically acceptable salt, solvate or ester thereof.

12. A method of treating a condition or disease selected from the group consisting of fever, cardiovascular conditions, hemorrhage, coagulation, cachexia, anorexia, alcoholism, acute phase response, acute infection, shock, graft versus host reaction, autoimmune disease and HIV infection in a subject comprising administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or ester thereof.

13. A method of treating a condition or disease selected from the group consisting of septic shock, haemodynamic shock, sepsis syndrome, post ischaemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic diseases, cachexia, graft rejection, cancers such as cutaneous T-cell lymphoma, diseases involving angiogenesis, autoimmune diseases, skin inflammatory diseases, inflammatory bowel diseases such as Crohn's disease and colitis, osteo and rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, adult Still's disease, ureitis, Wegener's granulomatosis, Behcehe disease, Sjogren's syndrome, sarcoidosis, polymyositis, dermatomyositis, multiple sclerosis, sciatica, complex regional pain syndrome, radiation damage, hyperoxic alveolar injury, periodontal disease, HIV, non-insulin dependent diabetes mellitus, systemic lupus erythematosus, glaucoma, sarcoidosis, idiopathic pulmonary fibrosis, bronchopulmonary dysplasia, retinal disease, scleroderma, osteoporosis, renal ischemia, myocardial infarction, cerebral stroke, cerebral ischemia, nephritis, hepatitis, glomerulonephritis, cryptogenic fibrosing aveolitis, psoriasis, transplant rejection, atopic dermatitis, vasculitis, allergy, seasonal allergic rhinitis, reversible airway obstruction, adult respiratory distress syndrome, asthma, chronic obstructive pulmonary disease (COPD) and bronchitis in a subject comprising administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or ester thereof.

14. A method of treating a condition or disease associated with COPD, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or ester thereof.

15. A method of treating a condition or disease associated with rheumatoid arthritis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or ester thereof.

16. A method of treating a condition or disease associated with Crohn's disease, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or ester thereof.

17. A method of treating a condition or disease associated with psoriasis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or ester thereof.

18. A method of treating a condition or disease associated with ankylosing spondylitis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or ester thereof.

19. A method of treating a condition or disease associated with sciatica, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or ester thereof.

20. A method of treating a condition or disease associated with complex regional pain syndrome, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or ester thereof.

21. A method of treating a condition or disease associated with psoriatic arthritis, comprising: administering to the subject in need of such

treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or ester thereof.

22. A method of treating a condition or disease associated with multiple sclerosis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or ester thereof, in combination with a compound selected from the group consisting of Avonex®, Betaseron, Copaxone or other compounds indicated for the treatment of multiple sclerosis.

23. The method of claim 11 further comprising administering to said subject a therapeutically effective amount of at least one medicament selected from the group consisting of disease modifying anti-rheumatic drugs (DMARDS), NSAIDs, COX-2 inhibitors, COX-1 inhibitors, immunosuppressives, biological response modifiers (BRMs), anti-infammatory agents and H1 antagonists.

24. A method of claim 12, further comprising administering to said subject a therapeutically effective amount of at least one medicament selected from the group consisting of DMARDS, NSAIDs, COX-2 inhibitors, COX-1 inhibitors, immunosuppressives, BRMs, anti-infammatory agents and H1 antagonists.

25. A method of claim 13, further comprising administering to said subject a therapeutically effective amount of at least one medicament selected from the group consisting of DMARDS, NSAIDs, COX-2 inhibitors, COX-1 inhibitors, immunosuppressives, BRMs, anti-infammatory agents and H1 antagonists.

26. A method for the treatment of a microbial infection in a mammal, comprising administering to said mammal a therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt, solvate or ester thereof.

27. The method of claim 26, wherein said infection is a gram negative infection.

28. The method of claim 26, wherein said infection is a gram positive infection.

29. The method of claim 26, further comprising administering one or more additional antibacterial agents.

30. The method of claim 29, wherein said antibacterial agent is active against gram negative bacteria.

31. The method of claim 29, wherein said antibacterial agent is active against gram positive bacteria.

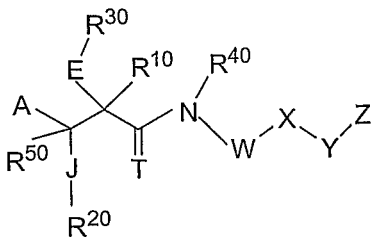
32. The method of claim 26, wherein said microbial infection is caused by at least one organism selected from the group consisting of *Acinetobacter baumannii, Acinetobacter calcoaceticus, Acinetobacter haemolyticus, Acinetobacter hydrophila, Actinobacillus actinomycetemcomitans, Aeromonas hydrophila, Alcaligenes xylosoxidans, Bacteroides distasonis, Bacteroides fragilis, Bacteroides melaninogenicus, Bacteroides ovatus, Bacteroides thetaiotaomicron, Bacteroides vulgatus, Bartonella henselae, Bordetella pertussis, Branhamella catarrhalis, Brucella melitensis, Brucella abortus, Brucella canis,Burkholderia cepacia, Burkholderia mallei,Burkholderia pseudomallei, Campylobacter coli, Campylobacter fetus, Campylobacter jejuni, Citrobacter diversus, Citrobacter freundii, Citrobacter koseri, Coxiella burnetli, Edwarsiella tarda, Ehrlichia chafeenis, Eikenella corrondens, Enterobacter aerogenes, Enterobacter agglomerans, Enterobacter cloacae, Escherichia coli, Flavobacterium meningosepticum, Francisella tularensis, Fusobacterium spp., Haemophilus ducreyi, Haemophilus influenzae,Haemophilus parainfluenzae, Helicobacter pylori, Kingella kingae, Klebsiella oxytoca,Klebsiella ozaenae, Klebsiella pneumoniae, Klebsiella rhinoscleromatis, Legionella pneumophila, Moraxella catarrhalis, Morganella morganii, Neisseria gonorrhoeae, Neisseria meningitides, Pasteurella multocida, Plesiomonas shigelloides, Porphyromonas asaccharolytica, Porphyromonas gingivalis, Prevotella bivia,Prevotella buccae, Prevotella corporis, Prevotella endodontalis, Prevotella intermedia,Prevotella melaninogenica,Prevotella oralis, Proteus mirabilis, Proteus myxofaciens,*

Proteus penner, Proteus vulgaris, Providencia alcalifaciens, Providencia rettgeri, Providencia stuarfii, Pseudomonas aeruginosa, Pseudomonas fluorescens, Ricketsia prowozekii, Salmonella enterica,Serratia marcescens, Shigella boydii, Shigella dysenteriae, Shigella flexneri,Shigella sonnei, Stenotrophomonas maltophilia, Streptobacillus moniliformis, Vibrio alginolyticus, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vuluificus, Yersinia enterocolitica, Yersinia pestis, and *Yersinia pseudotuberculosis.*

33. The method of claim 26, wherein the organism is selected from the group consisting of *Acinetobacter baumannii, Acinetobacter spp., Aeromonas hydrophila, Bacteroides fragilis, Bacteroides spp., Bordetella pertussis, Campylobacter jejuni, Campylobacter spp., Citrobacter freundii, Citrobacter spp., Enterobacter cloacae, Enterobacter spp., Escherichia coli, Fusobacterium spp., Haemophilus influenzae, Haemophilus parainfluenzae, Helicobacter pylori, Klebsiella pneumoniae, Klebsiella spp., Legionella pneumophila, Moraxella catarrhalis, Morganella morganii, Neisseria gonorrhoeae, Neisseria meningitides, Pasteurella multocida, Prevotella spp., Proteus mirabilis, Proteus spp., Providencia stuartii, Pseudomonas aeruginosa, Pseudomonas spp., Salmonella enterica, Salmonella typhi, Serratia marcescens, Shigella spp.,Stenotrophomonas maltophilia, Vibrio cholerae, Vibrio spp.,* and *Yersinia spp.*

34. The method of claim 26, wherein said microbial infection is a fungal infection.

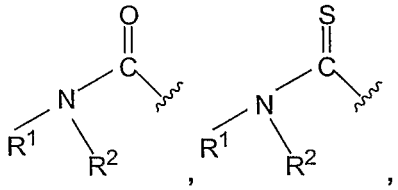
35. A method of treating a disorder associated with UDP-3-*O*-(R-3-hydroxymyristoyl)-N-acetylglucosamine deacetylase (LpxC), said method comprising administering to a subject in need of such treatment a therapeutically effective amount of at least one compound of formula (I):



formula (I)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

A is selected from the group consisting of: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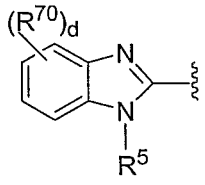
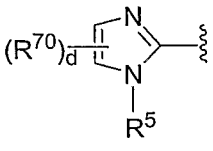
, 
, 
, and $-CO_2R^1$;

d is 0 to 4;

J is selected from the group consisting of O, S, and NR^5;

E is selected from the group consisting of: O, S, and NR^5;

T is O or S;

R^1 and R^2 are the same or different, each being independently selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl, and heteroaryl; or alternatively R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 4-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein each of said alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl, heteroaryl and 4-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties below;

R^{10} is selected from the group consisting of H, alkyl, and fluoroalkyl;

R^{20} is selected from the group consisting of H, alkyl, and fluoroalkyl;

R^{30} is H or alkyl, or alternatively R^{30} and R^{40} taken together with the N to which R^{40} is shown attached to in Formula I, are joined to form a 4-7 membered heterocylic ring, wherein said heterocylic ring is unsubstituted or optionally independently substituted with one or more moieties which can be

the same or different, each moiety being independently selected from the group of R^{70} moieties below;

R^{40} is H or alkyl;

R^{50} is H or alkyl;

W is $-(CR^{13}{}_2)_n-$, wherein n is 0 to 5 or a covalent bond, or alternatively two R^{13} groups can fuse to form a 3-8 membered cycloalkyl, wherein said 3-8 membered cycloalkyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^6 moieties below;

X is absent or present, and if present X is selected from the group consisting of a covalent bond, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties below;

Y is absent or present, and if present Y is selected from the group consisting of a covalent bond, $-[C(R^6)_2]_n-$ wherein n is 1 or 2, -O-, -S-, $-NR^1-$, $-SO_v-$ wherein v is 1 to 2, $-SO_n(CR^6{}_2)_p-$ wherein n is 1 or 2 and p is 1 to 4, $-O(CR^6{}_2)_q-$ or $-(CR^6{}_2)_qO-$ wherein q is 1 to 4, $-N(R^7)S(O)_n-$ or $-S(O)_nN(R^7)-$ wherein n is 1 or 2, and $-N(R^7)C(O)-$ or $-C(O)N(R^7)-$;

Z is selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, said cycloalkyl, heterocyclyl, aryl, and heteroaryl being optionally fused with aryl, heterocyclyl, heteroaryl or cycloalky; wherein each of said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties below;

R^5 is selected from the group consisting of hydrogen, alkyl, and alkylaryl;

each R^6 is the same or different and is independently selected from the group consisting of hydrogen, halogen, $-SR^{15}$, $-S(O)_qR^{15}$ wherein q is 1 to 2, alkyl, cycloalkyl, heterocyclyl, alkoxyl, hydroxy, nitro, cyano, amino, alkenyl, alkynyl, arylalkyl, aminocarbonyl, alkylcarbonyl, and alkoxycarbonyl;

each R^7 is the same or different and is independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, alkenyl, alkynyl, arylalkyl, alkylcarbonyl, and alkoxycarbonyl, wherein each of the aryl, heteroaryl and heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties below;

R^{13} is the same or different and is independently selected from the group consisting of hydrogen, halogen, -OH, $-OR^{14}$, alkyl, cycloalkyl, heterocyclyl, alkenyl, alkynyl, alkylaryl, alkylamino, and alkylcarbonyl;

R^{14} is alkyl;

each R^{70} is a substituent for H where indicated and is the same or different and is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, -CN, $-CF_3$, $-OCF_3$, $-OR^{15}$, $-C(O)R^{15}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, $-SR^{15}$, $-S(O)_qN(R^{15})(R^{16})$ wherein q is 1 to 2, $-C(=NOR^{15})R^{16}$, $-N(R^{15})(R^{16})$, -alkyl-$N(R^{15})(R^{16})$, $-N(R^{15})C(O)R^{16}$, $-CH_2-N(R^{15})C(O)R^{16}$, $-N(R^{15})S(O)R^{16}$, $-N(R^{15})S(O)_2R^{16}$, $-CH_2-N(R^{15})S(O)_2R^{16}$, $-N(R^{17})S(O)_2N(R^{16})(R^{15})$, $-N(R^{17})S(O)N(R^{16})(R^{15})$, $-N(R^{17})C(O)N(R^{16})(R^{15})$, $-CH_2-N(R^{17})C(O)N(R^{16})(R^{15})$, $-N(R^{15})C(O)OR^{16}$, $-CH_2-N(R^{15})C(O)OR^{16}$, and $-S(O)_qR^{15}$ wherein q is 1 to 2; and wherein each of the alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl are independently unsubstituted or substituted by 1 to 5 groups independently selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl,

heteroaryl, halo, $-CF_3$, -CN, $-OR^{15}$, $-N(R^{15})(R^{16})$, $-C(O)OR^{15}$,- $C(O)N(R^{15})(R^{16})$, and $-N(R^{15})S(O)R^{16}$; and

each R^{15}, R^{16} and R^{17} are independently selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, or alternatively R^{15} and R^{16} taken together with the N to which they are shown attached, are joined to form a 4-8 membered heterocylic ring, wherein said 4-8 membered cycloalkyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{75} moieties below;

each R^{75} is independently selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl, and wherein each of the alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl are independently unsubstituted or substituted by 1 to 5 groups independently selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, $-CF_3$, -CN, $-OR^{19}$, $-N(R^{19})_2$, $-C(O)OR^{19}$, $-C(O)N(R^{19})_2$, and $-N(R^{19})S(O)R^{19}$; and

each R^{19} is independently selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl.

36. The method of claim 35, wherein said disorder is a microbial infection.

37. The method of claim 36, wherein said microbial infection is a bacterial or fungal infection.

38. The method of claim 37, wherein said bacterial infection is a gram negative infection.

39. The method of claim 37, wherein said bacterial infection is a gram positive infection.