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CA 2569111 A1 2005/12/22

(21) 2 569 111

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2005/06/01
(87) Date publication PCT/PCT Publication Date: 2005/12/22
(85) Entrée phase nationale/National Entry: 2006/11/28
(86) N° demande PCT/PCT Application No.: US 2005/019131
(87) N° publication PCT/PCT Publication No.: 2005/121130
(30) Priorité/Priority: 2004/06/02 (US60/576,153)

(51) Cl.Int./Int.Cl. *C07D 409/12* (2006.01),
C07C 233/18 (2006.01), *C07D 207/20* (2006.01),
C07D 207/26 (2006.01), *C07D 209/44* (2006.01),
C07D 217/06 (2006.01), *C07D 295/18* (2006.01),
C07D 307/52 (2006.01), *C07D 333/20* (2006.01),
C07D 403/12 (2006.01), *C07D 405/12* (2006.01),
C07D 409/14 (2006.01), ...

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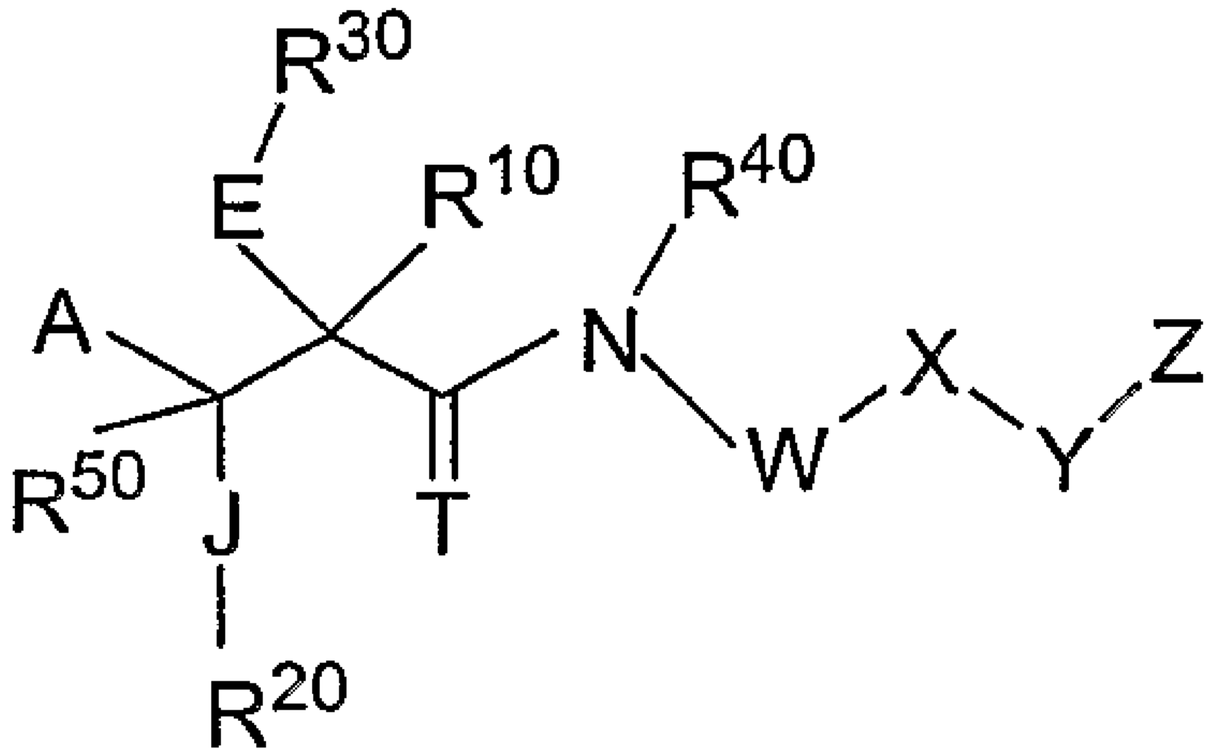
(54) Titre : COMPOSES POUR LE TRAITEMENT DE TROUBLES INFLAMMATOIRES
(54) Title: CHEMICAL COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM FOR THE TREATMENT OF INFLAMMATORY DISORDERS



(I)

(57) Abrégé/Abstract:
This invention relates to compounds of the Formula (I) or a pharmaceutically acceptable salt, solvate or isomer thereof, which can be useful for the treatment of diseases or conditions mediated by MMPs, ADAMs, TACE, TNF-α or combinations thereof.

CA 2569111 A1 2005/12/22

(21) 2 569 111

(13) A1

(51) Cl.Int./Int.Cl. (suite/continued) *C07D 417/12* (2006.01), *C07D 417/14* (2006.01), *C07D 471/10* (2006.01)

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 December 2005 (22.12.2005)

PCT

(10) International Publication Number
WO 2005/121130 A3

(51) International Patent Classification:
C07D 409/12 (2006.01) *C07C 233/18* (2006.01)
C07D 333/20 (2006.01) *C07D 307/52* (2006.01)
C07D 295/18 (2006.01) *C07D 405/12* (2006.01)
C07D 471/10 (2006.01) *C07D 209/44* (2006.01)
C07D 409/14 (2006.01) *C07D 217/06* (2006.01)
C07D 207/26 (2006.01) *C07D 207/20* (2006.01)
C07D 417/14 (2006.01) *C07D 403/12* (2006.01)
C07D 417/12 (2006.01)

(21) International Application Number:
PCT/US2005/019131

(22) International Filing Date: 1 June 2005 (01.06.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/576,153 2 June 2004 (02.06.2004) US

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

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

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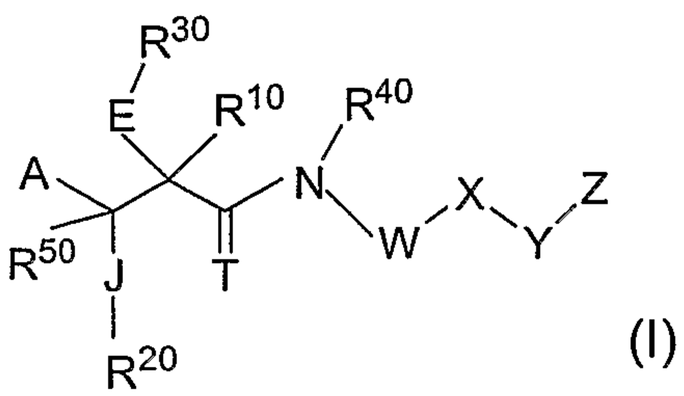
WO 2005/121130 A3

(54) Title: CHEMICAL COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM FOR THE TREATMENT OF INFLAMMATORY DISORDERS



(I)

(57) Abstract: This invention relates to compounds of the Formula (I) or a pharmaceutically acceptable salt, solvate or isomer thereof, which can be useful for the treatment of diseases or conditions mediated by MMPs, ADAMs, TACE, TNF-α or combinations thereof.

WO 2005/121130 A3

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
20 July 2006

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

DEMANDE OU BREVET VOLUMINEUX

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CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 535

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CONTAINING PAGES 1 TO 535

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NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

COMPOUNDS FOR THE TREATMENT OF INFLAMMATORY DISORDERS

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) 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.

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).

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.

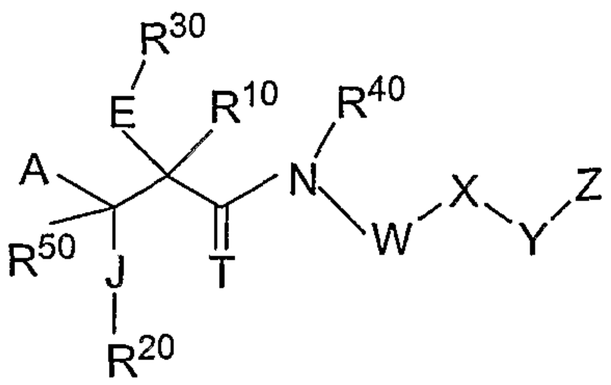
There is a need in the art for inhibitors of MMPs, ADAMs, TACE, and TNF-α, which can be useful as anti-inflammatory compounds and cartilage protecting therapeutics. The inhibition of TNF-α, TACE and or other MMPs can prevent the degradation of cartilage by these enzymes, thereby alleviating the pathological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

SUMMARY OF THE INVENTION

In its many embodiments, the present invention provides a novel class of compounds as inhibitors of TACE, 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 TACE, TNF-α, MMPs, ADAMs or any combination thereof using such compounds or pharmaceutical compositions.

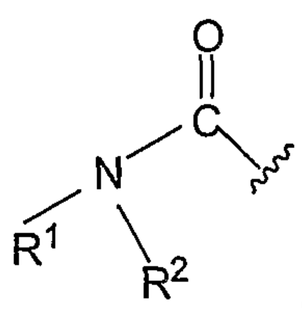
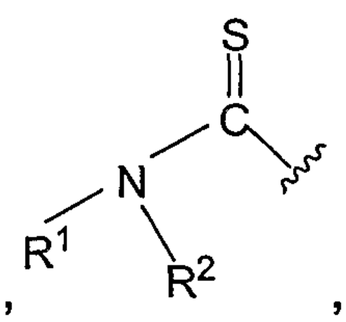
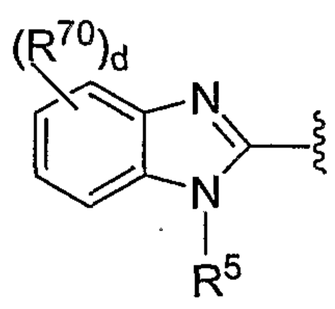
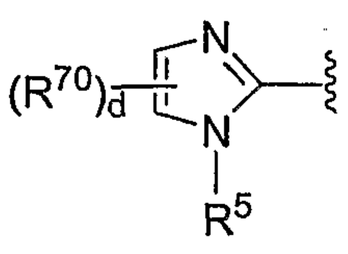
In one embodiment, the present application discloses a compound, or pharmaceutically acceptable salts or solvates of said compound, said compound having the general structure shown in formula (I):



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)$_2$N(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)$_q R^{15}$ 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 TACE, TNF-α, MMPs, ADAMs or any combination thereof.

DETAILED DESCRIPTION OF THE INVENTION

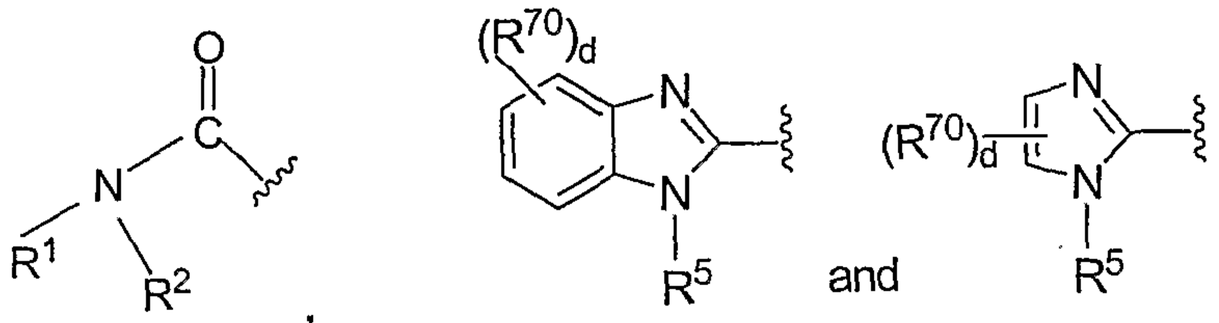
In its several embodiments, the present invention provides a novel class of inhibitors of TACE, the production of TNF-α, MMPs, ADAMs or any combination thereof, pharmaceutical compositions containing one or more of the compounds, methods of preparing pharmaceutical formulations comprising one or more 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}.

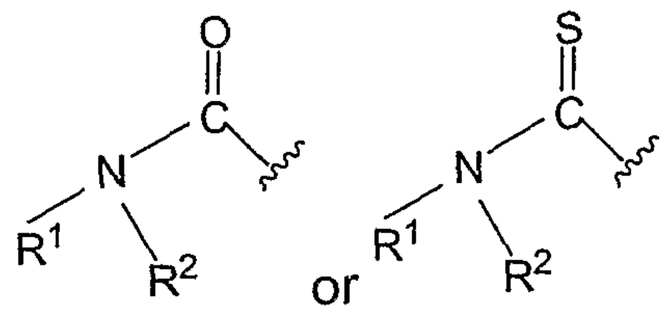
In one embodiment, R^1 and R^2 are the same or different, each being independently selected from the group consisting of H, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl, and heteroaryl; or alternatively R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent 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:



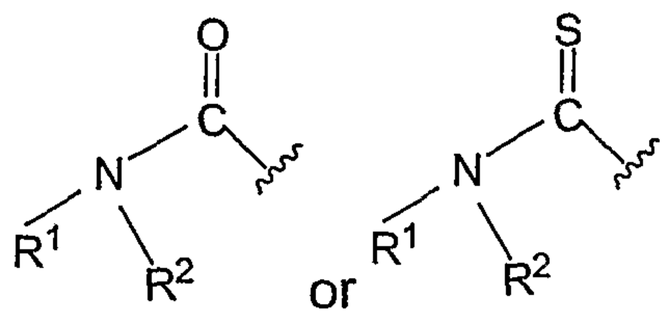
wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 4-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl,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



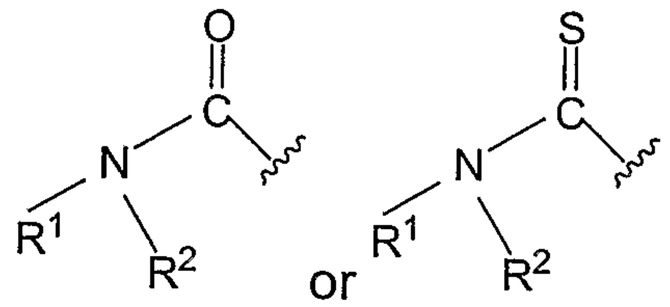
wherein R^1 and R^2 are the same or different, each being independently selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl, and heteroaryl; wherein said alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl and heteroaryl can be unsubstituted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



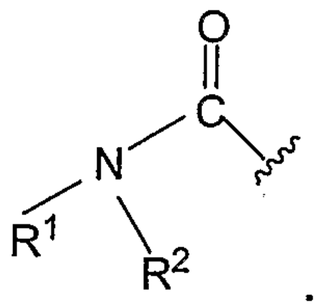
wherein R^1 and R^2 are the same or different, each being independently selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl, and heteroaryl; wherein said alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl and heteroaryl can be unsubstituted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

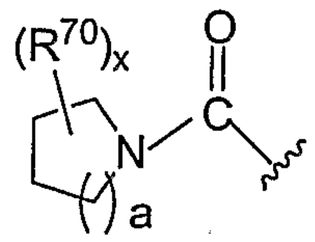


wherein R^1 and R^2 are the same or different, each being independently selected from the group consisting of H, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl, and heteroaryl; wherein said alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl and heteroaryl can be unsubstituted or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

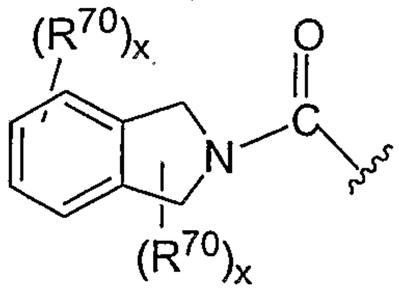


In another embodiment, A is



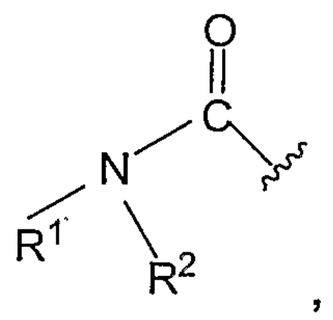
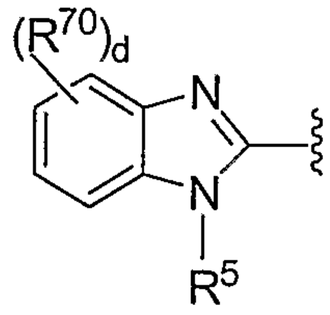
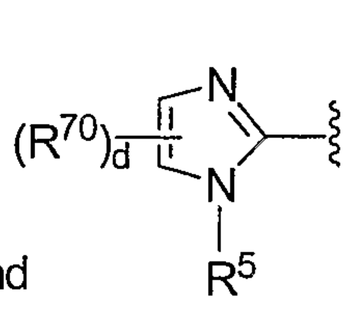
wherein a is 0 to 4 and x is 0 to 4.

In another embodiment, A is

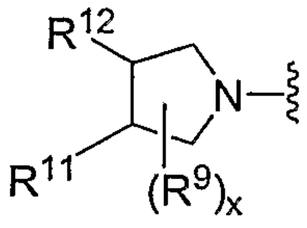


wherein each x idependently is 0 to 4.

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

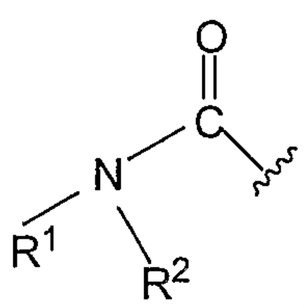
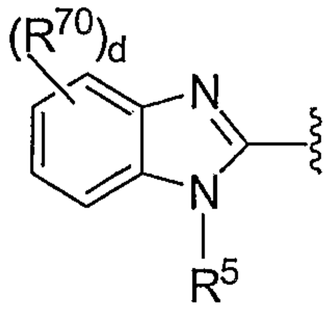
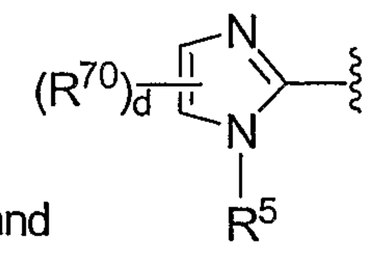
each R^9 is a substituent for H where indicated and can be the same or different, each being independently selected from the group consisting of -OH, $-OR^{14}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, alkyl, aryl, heteroaryl, alkenyl, alkynyl, cycloalkyl and heterocyclyl, wherein said alkyl, aryl,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

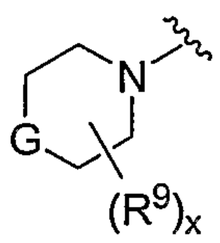
x is 0 to 4, and when x is greater than 1, each R^9 moiety can be the same or different, each moiety being independently selected from the group of R^9 moieties.

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



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



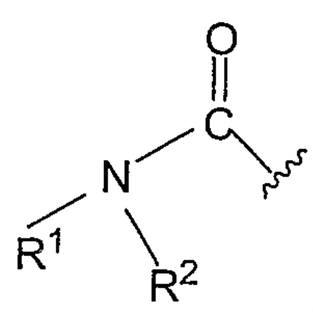
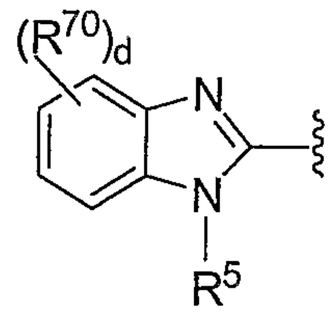
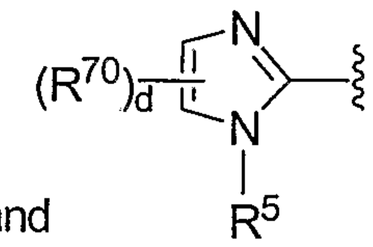
wherein

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;

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

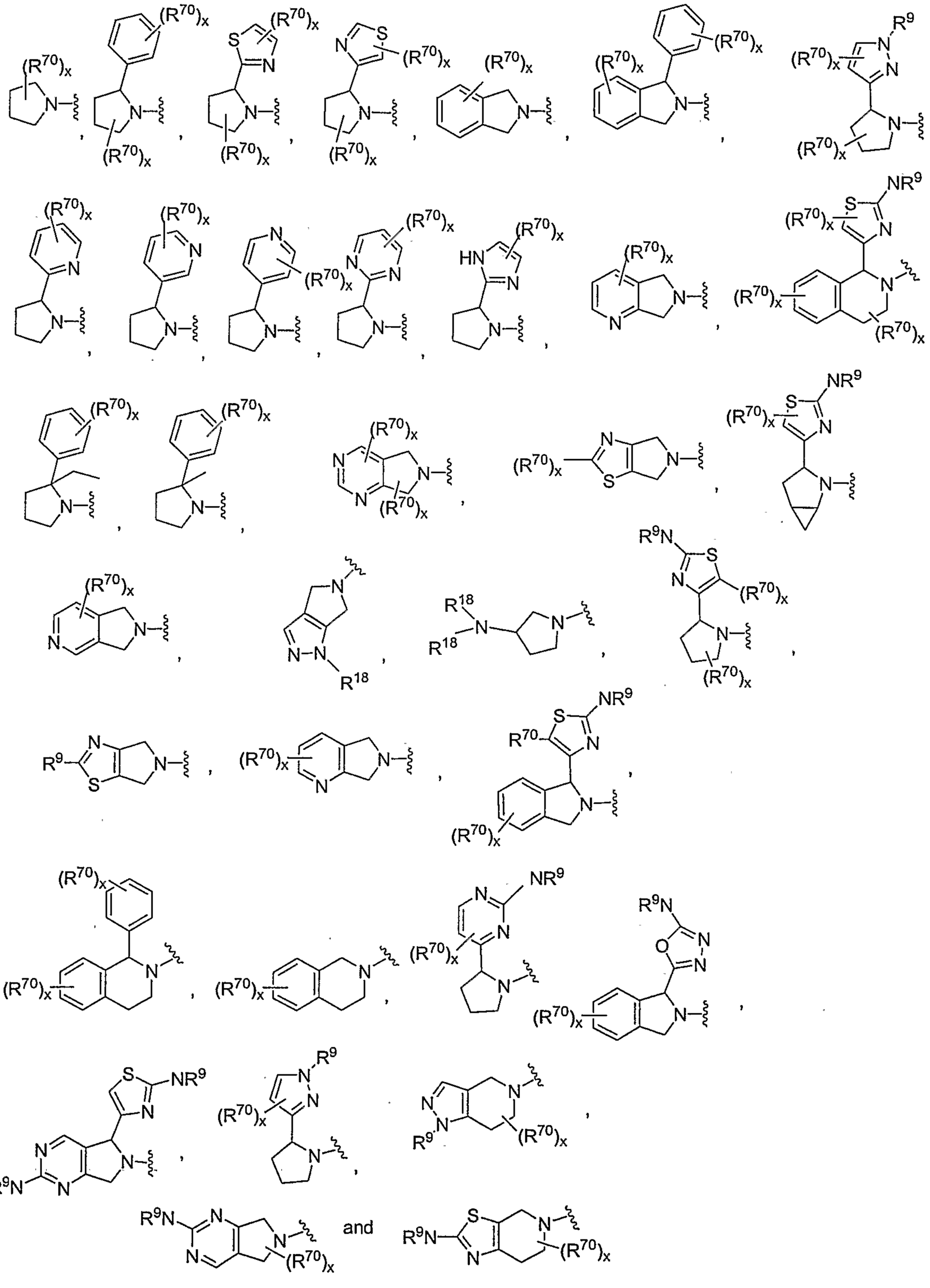
G is selected from the group consisting of CH_2, NR^7, O, S, or SO_2.

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

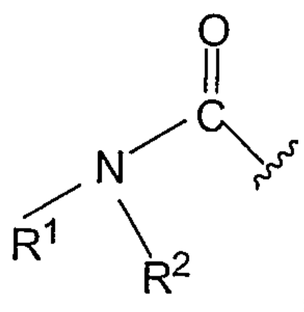
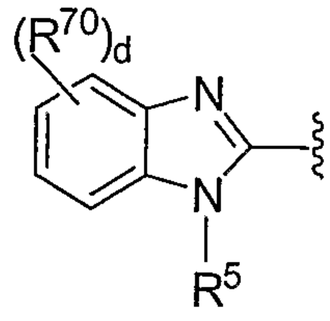
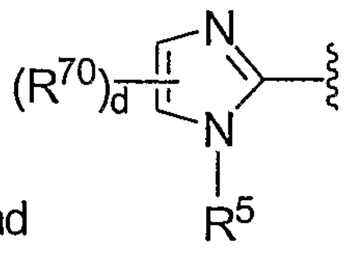


wherein

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

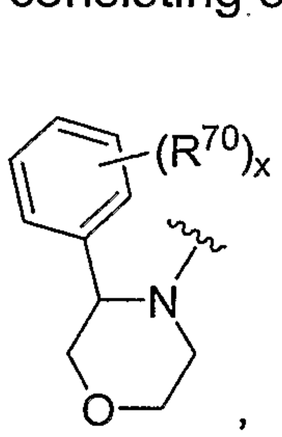
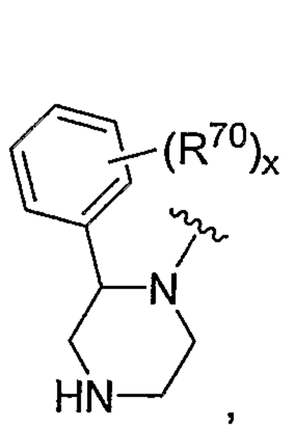
each R^{18} is the same or different and is independently H or alkyl.

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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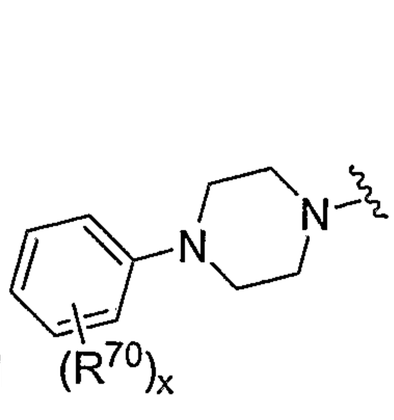
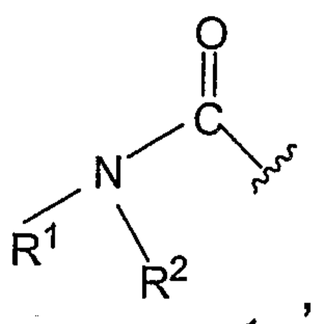
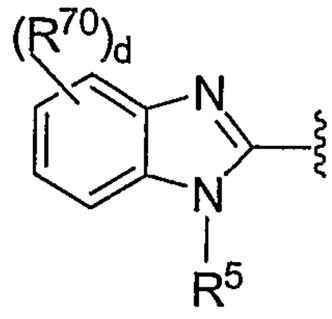


wherein

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: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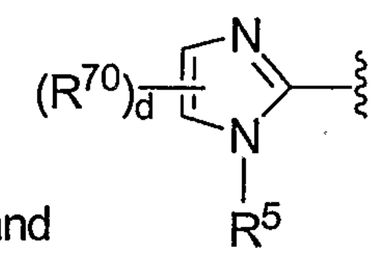
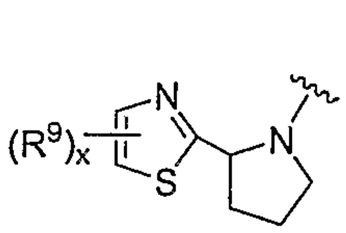


wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 3-8 membered heterocyclic ring having 1-3

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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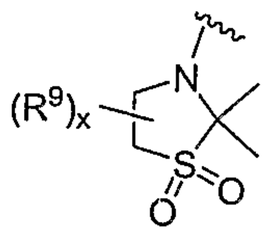
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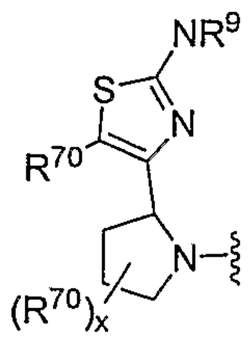
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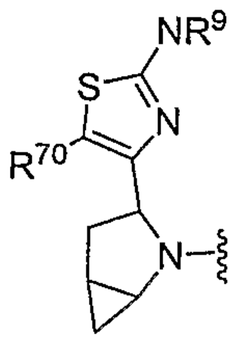
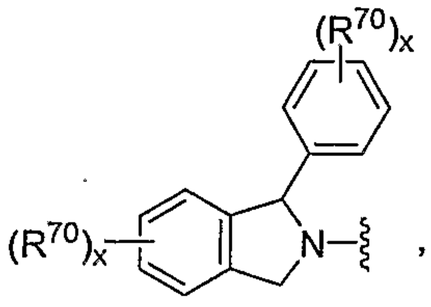
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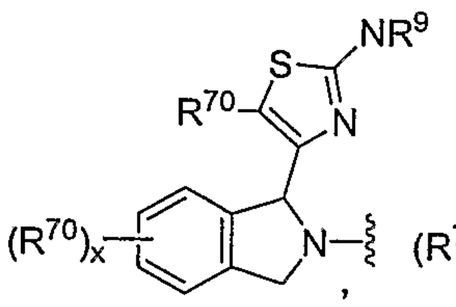
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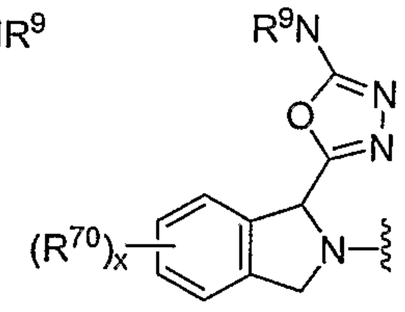
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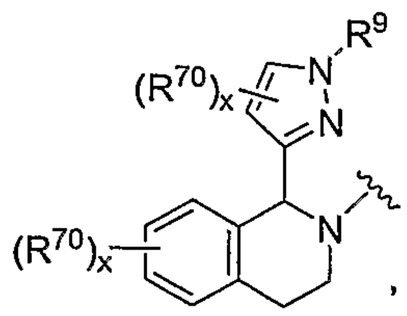
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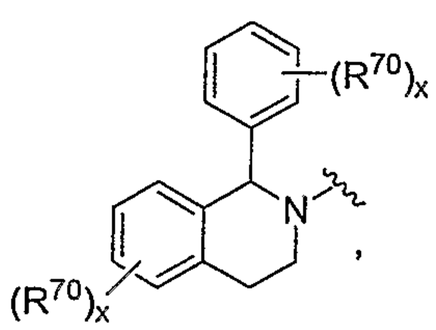
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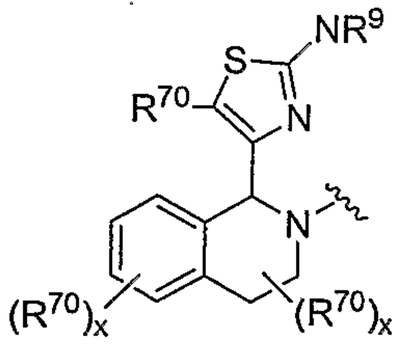
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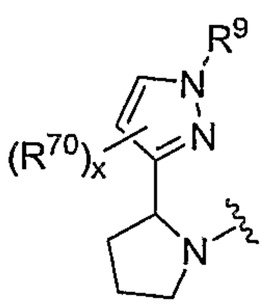
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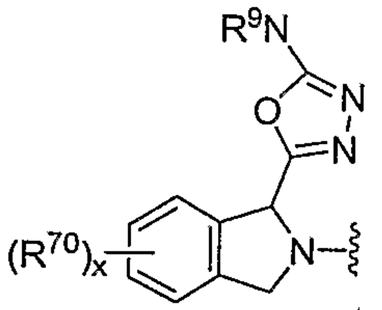
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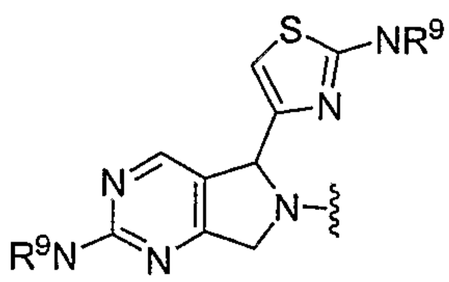
or


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.

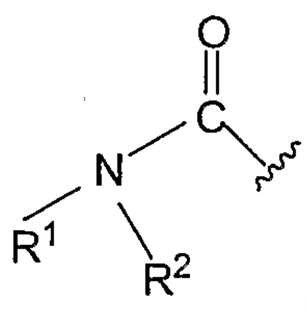
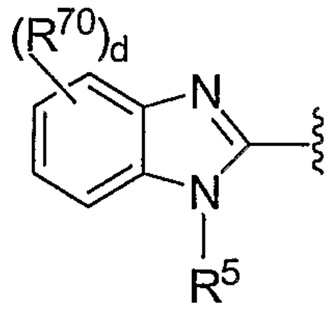
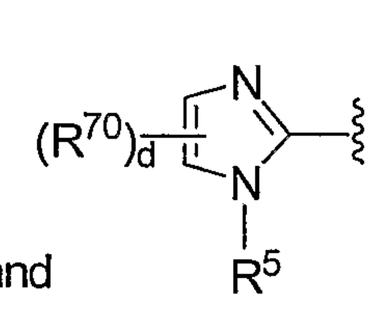
In another embodiment, R^6 is H or alkyl.

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

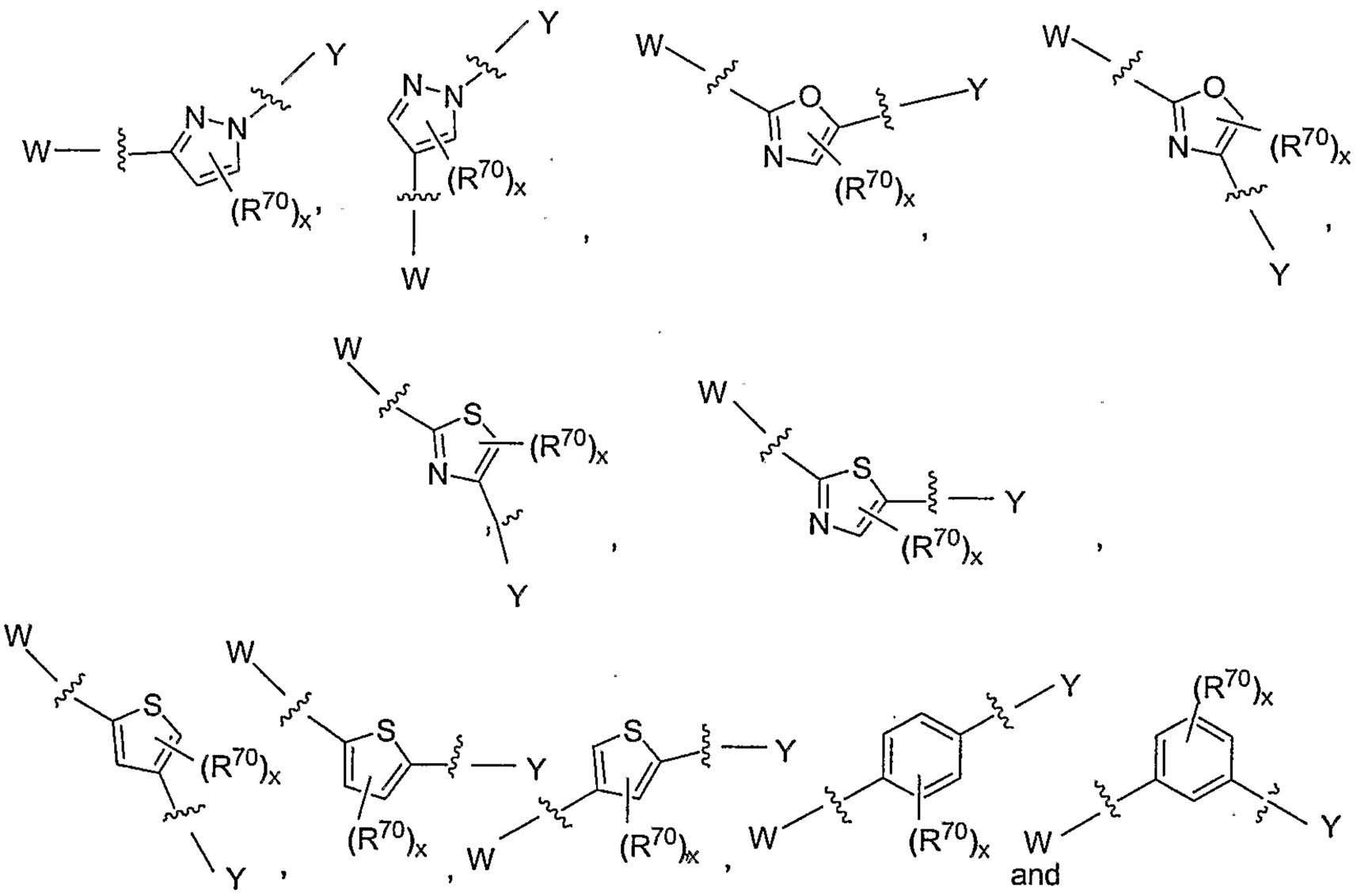
and

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 $\S\!\!-\!\!\S$ 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



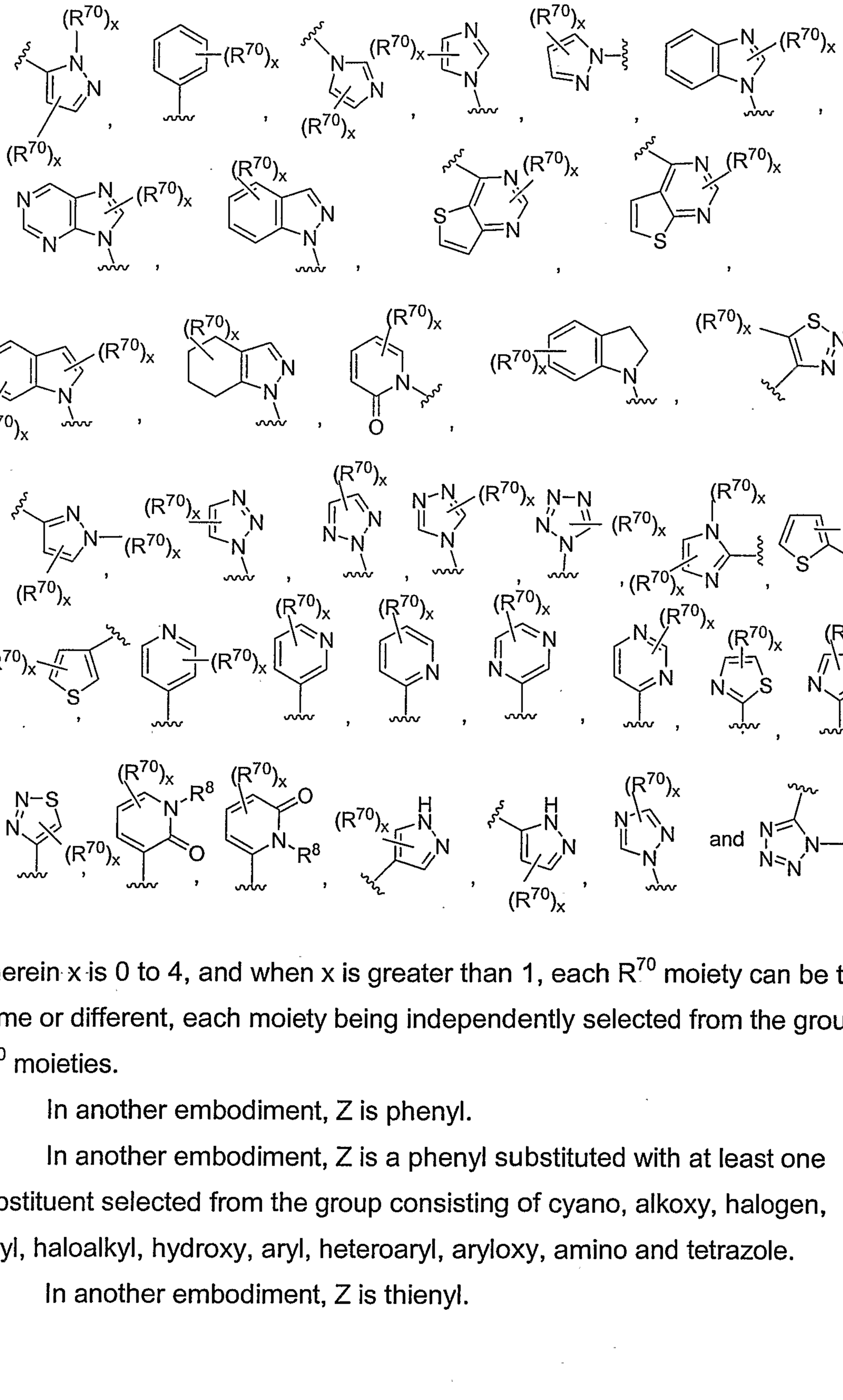
wherein x is 0 to 4, and when x is greater than 1, each R^{70} moiety can be the same or different, each moiety being independently selected from the group of R^{70} moieties.

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.

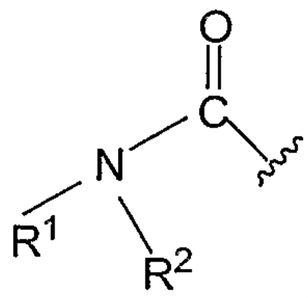
In another embodiment, Z is pyridinyl.

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:



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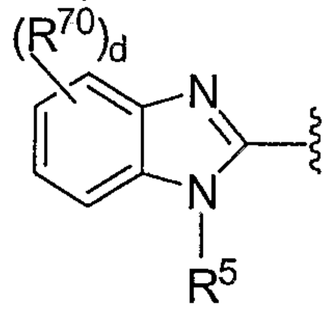
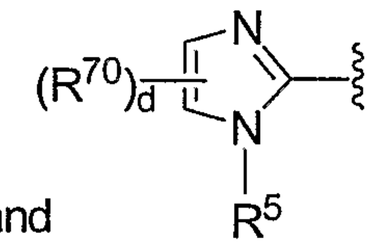
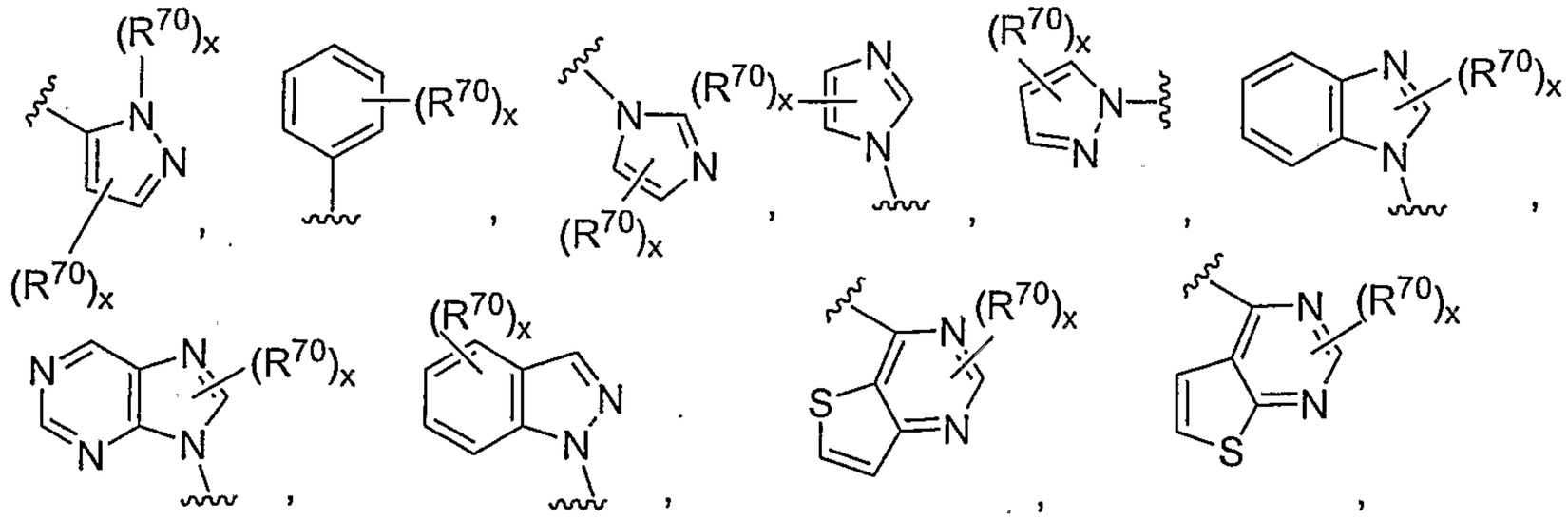
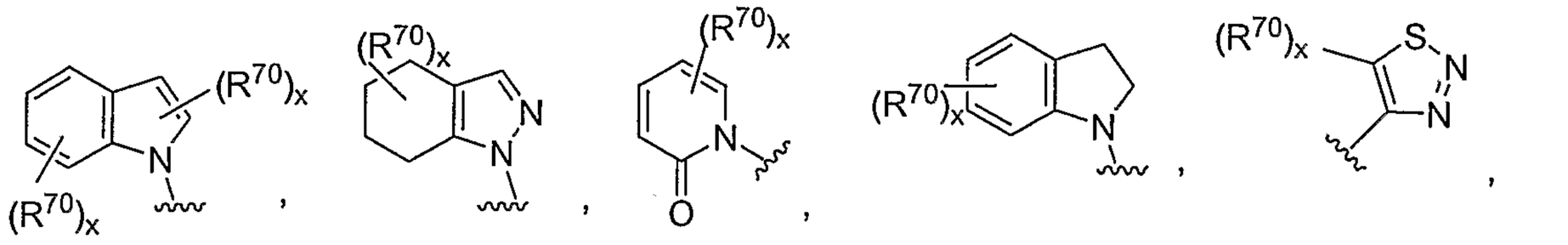
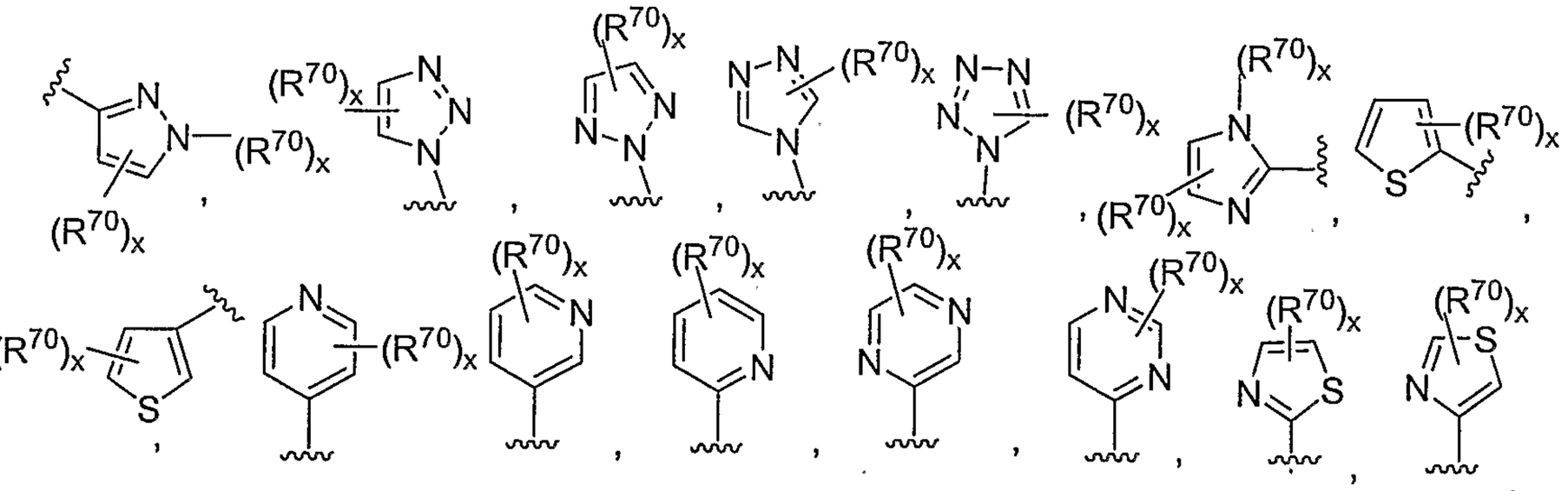


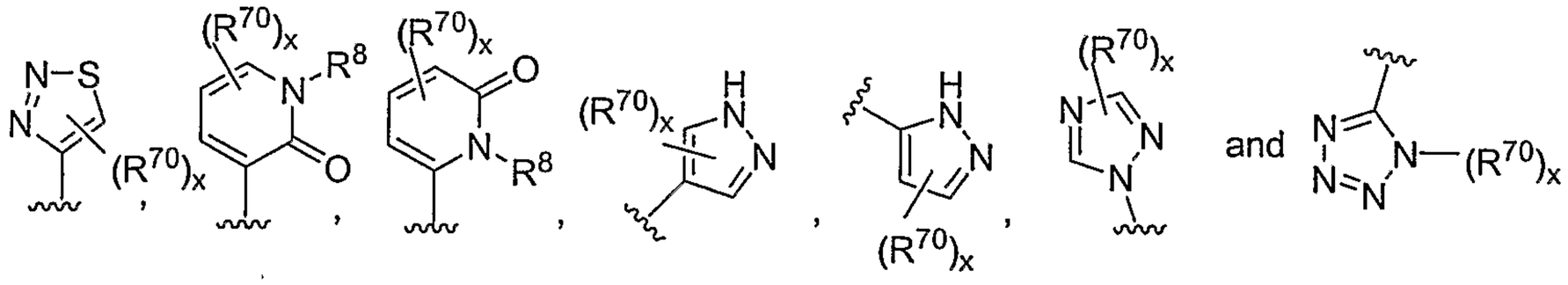
and


wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 4-8 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

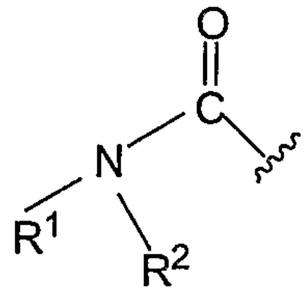








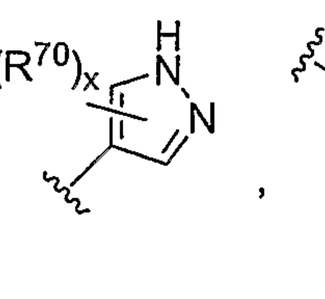
In another embodiment, A is:



;

wherein;

the $-NR^1R^2$ of



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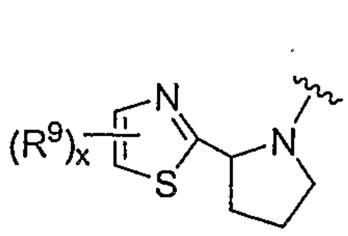
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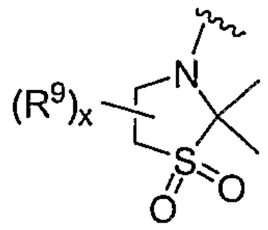
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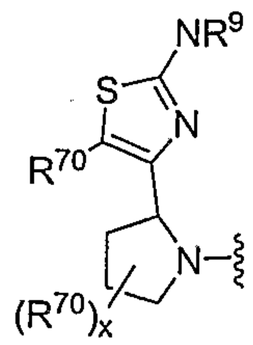
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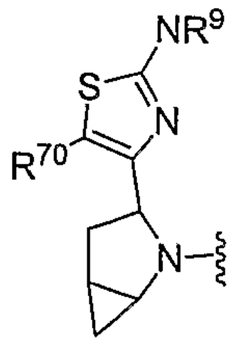

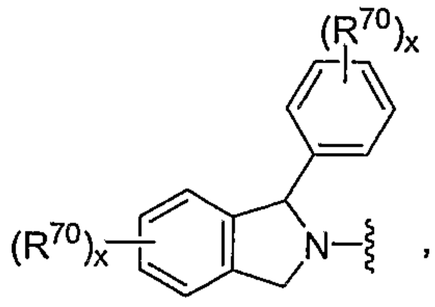
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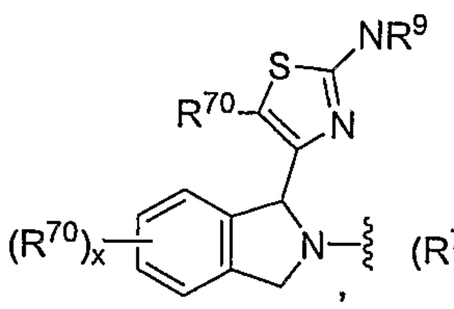
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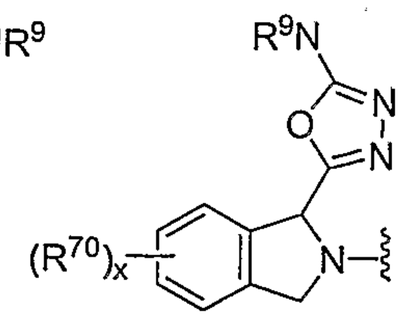
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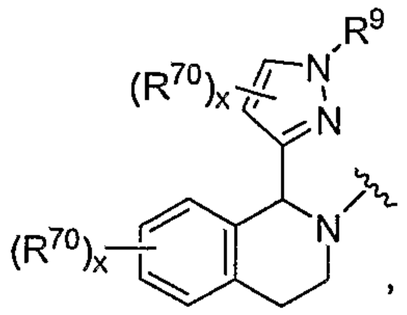
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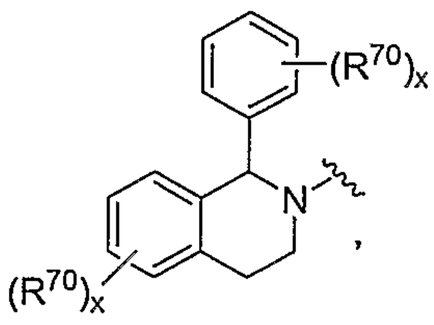
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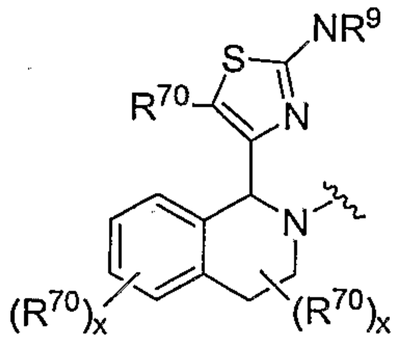
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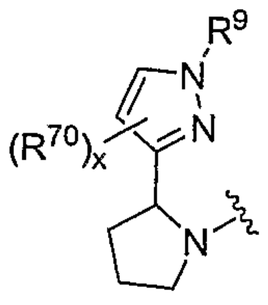
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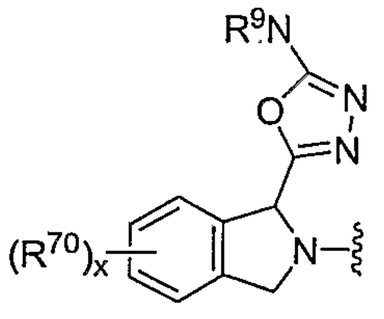
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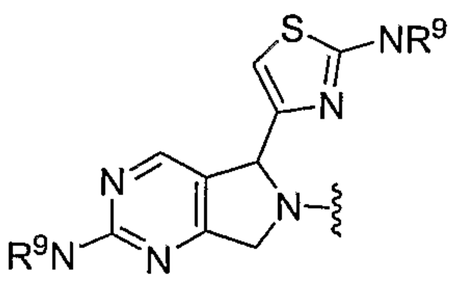
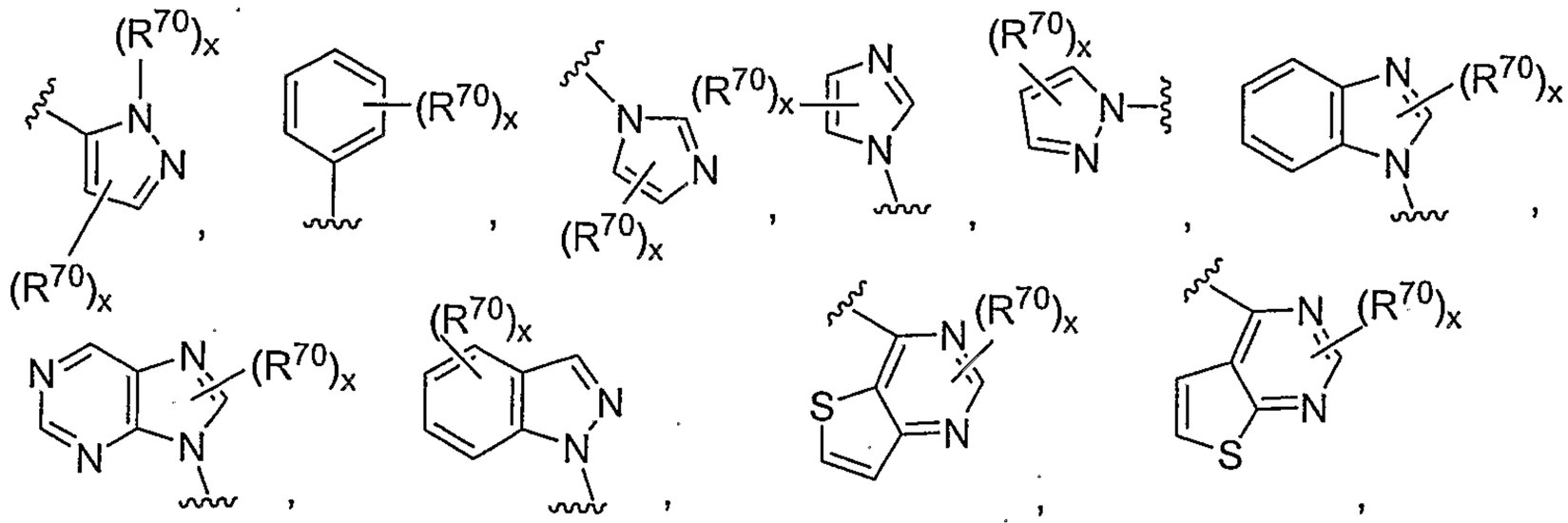
or


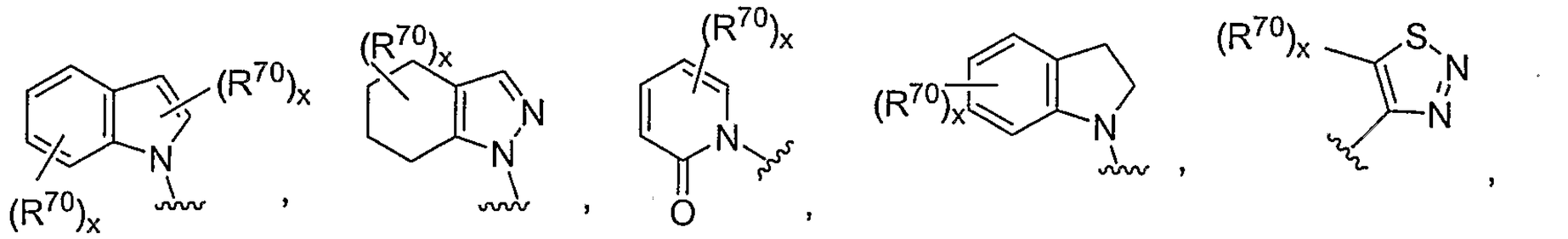
wherein

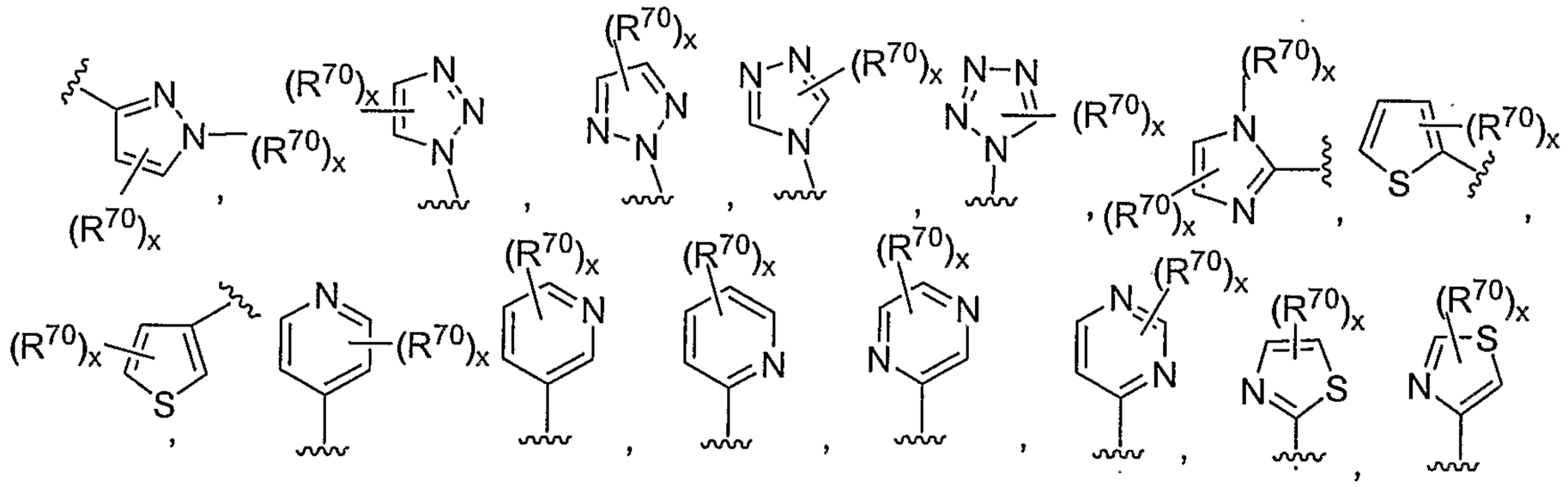
each R^9 is a substituent for H where indicated and can be the same or different, each being independently selected from the group consisting of -OH, $-OR^{14}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, alkyl, aryl, heteroaryl, alkenyl, alkynyl, cycloalkyl and heterocyclyl, wherein said alkyl, aryl,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

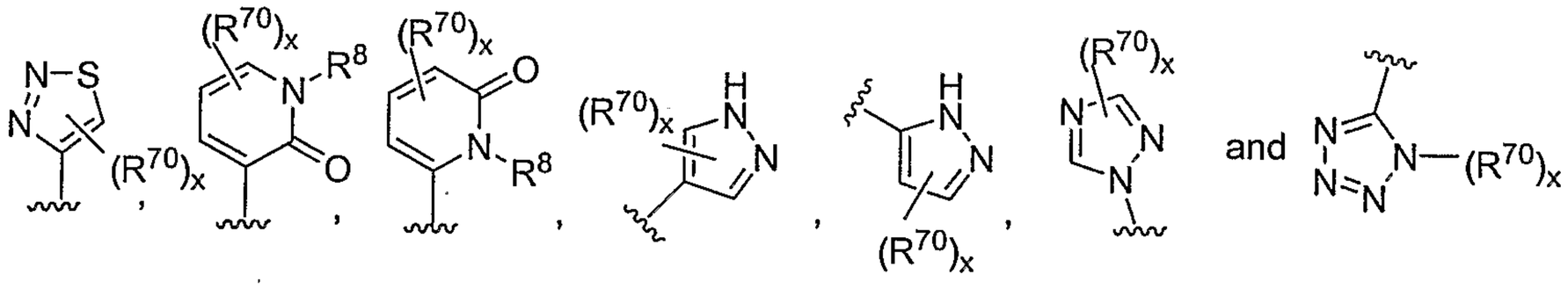
x is 0 to 4, and when x is greater than 1, each R^9moiety can be the same or different, each moiety being independently selected from the group of R^9 moieties;

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

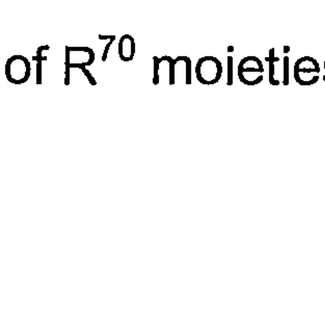








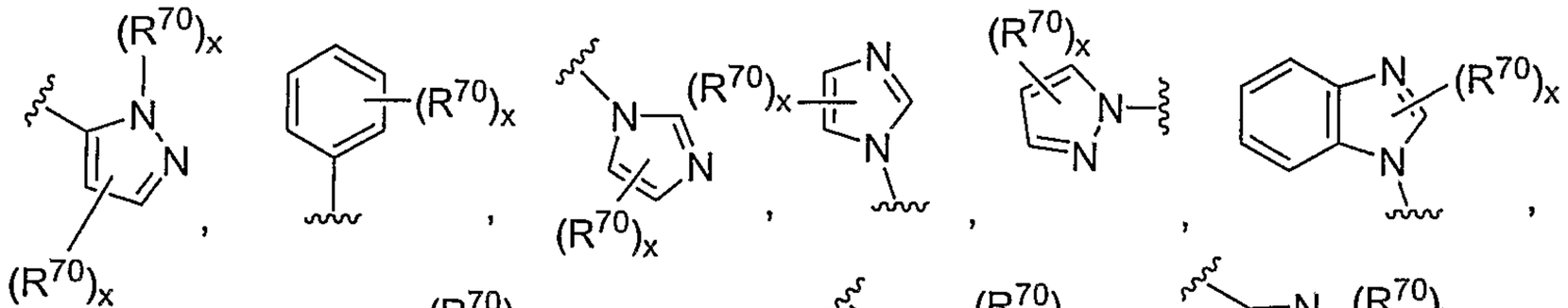
In another embodiment, A is:

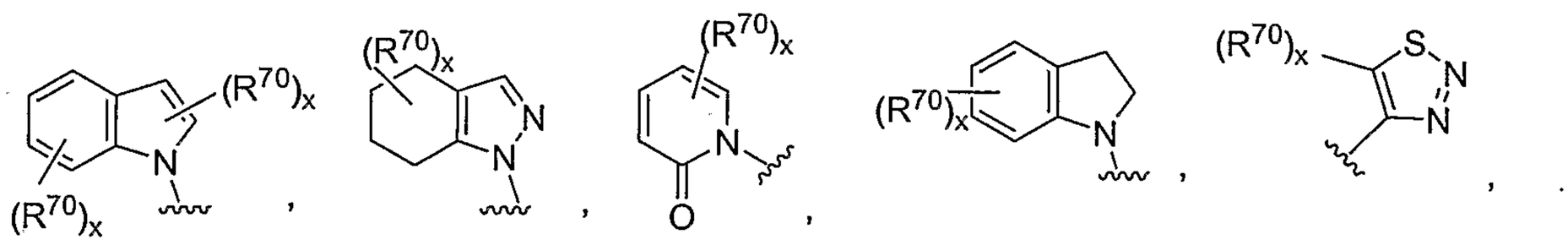


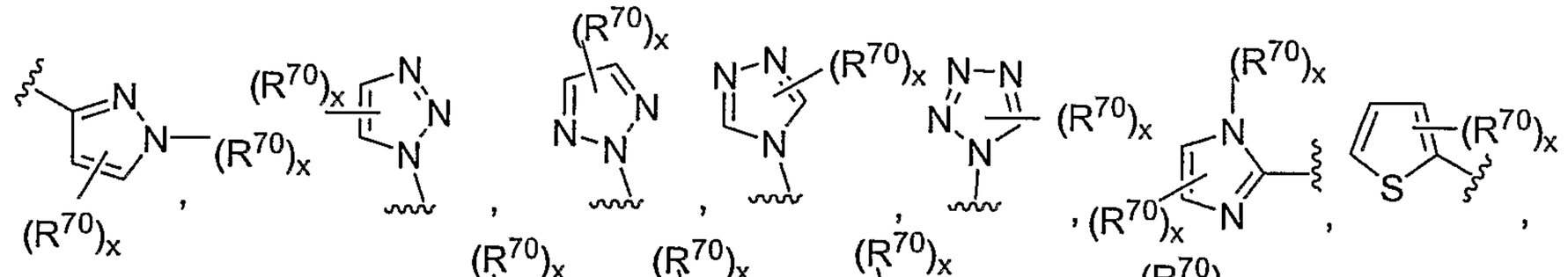
;

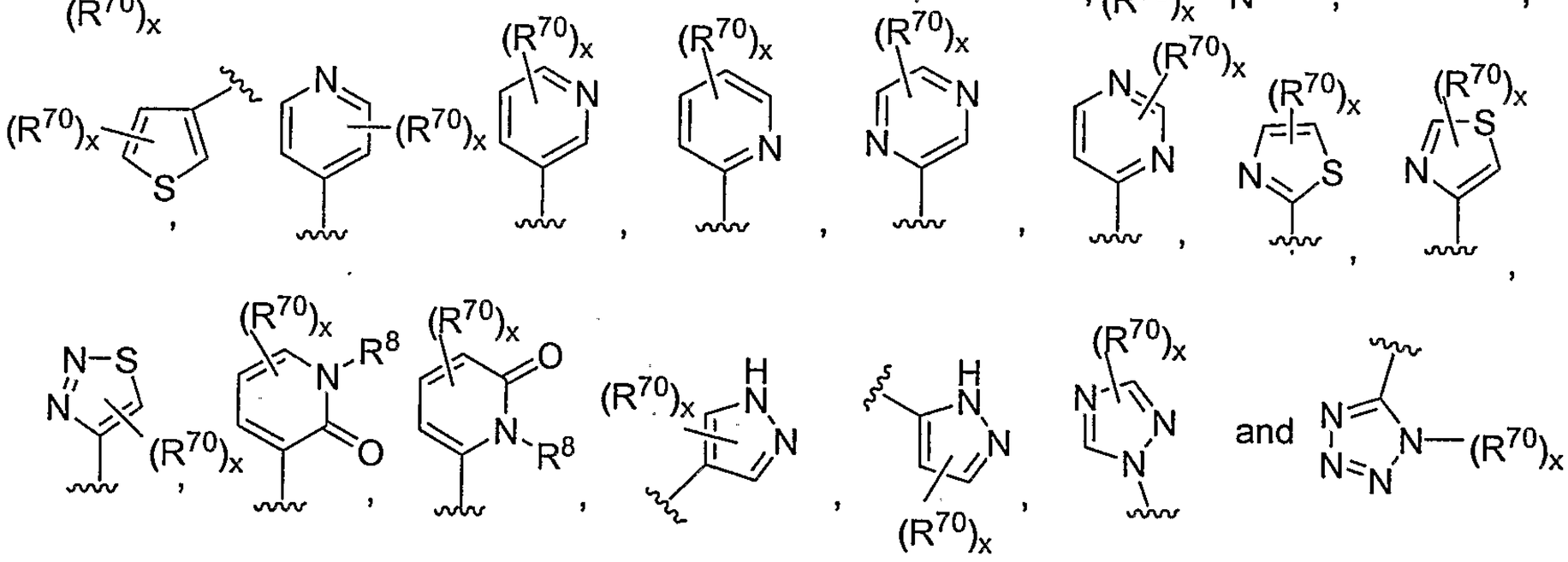
wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 4-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with one or more R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl,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

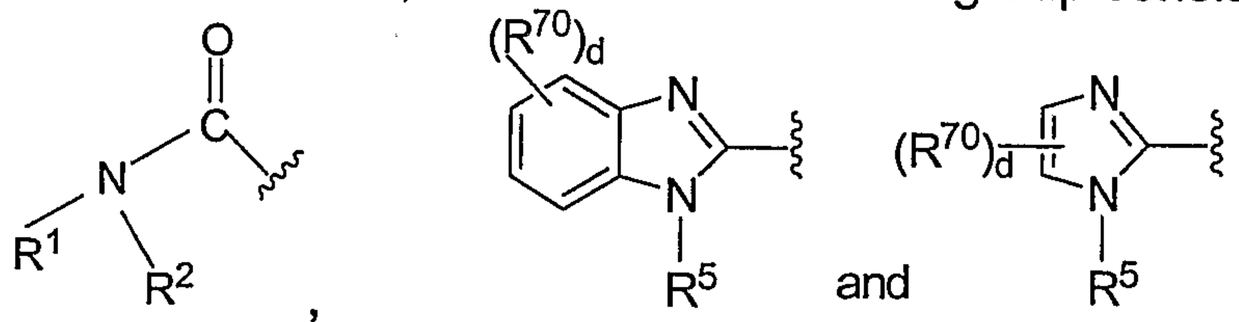








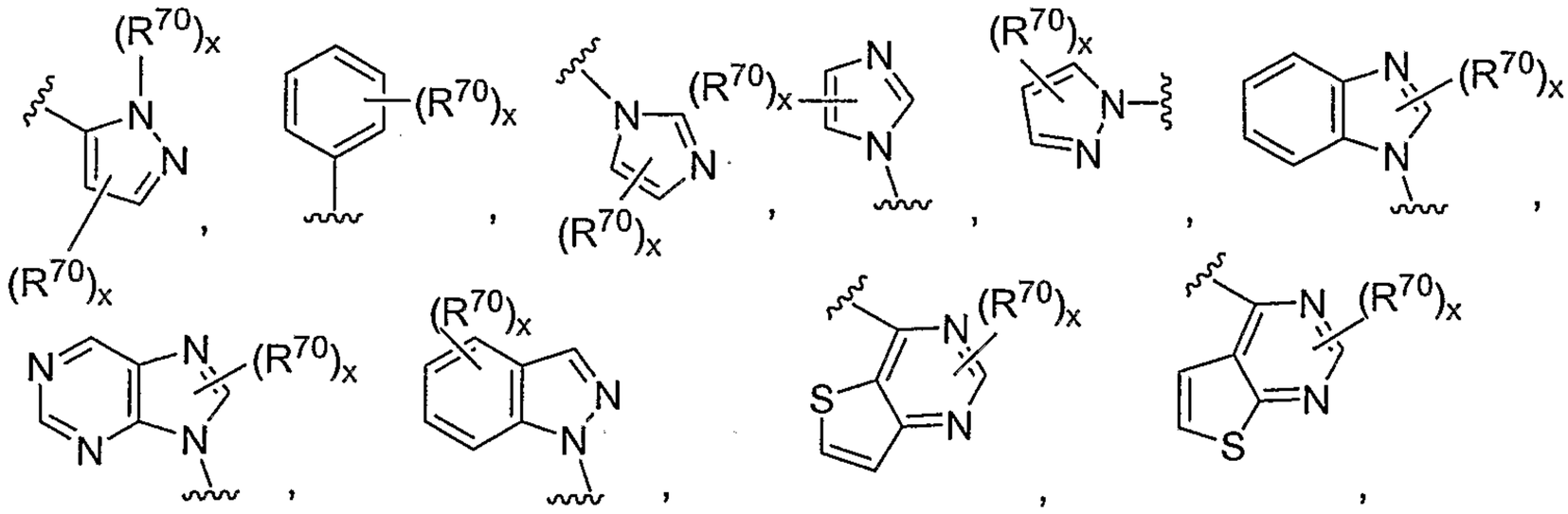
In another embodiment, A is selected from the group consisting of:

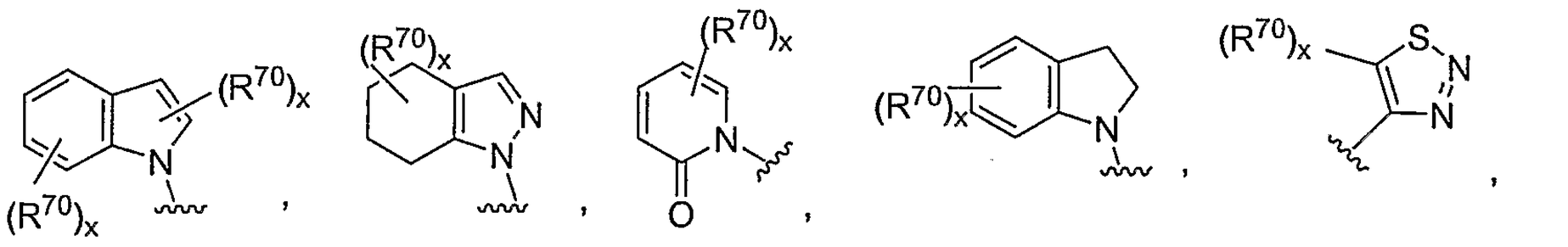


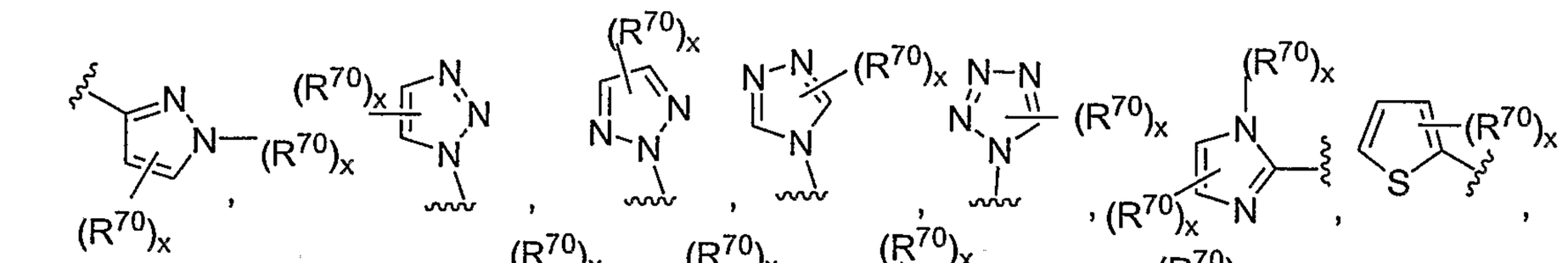
wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 3-8 membered heterocyclic ring having 1-3 heteroatoms

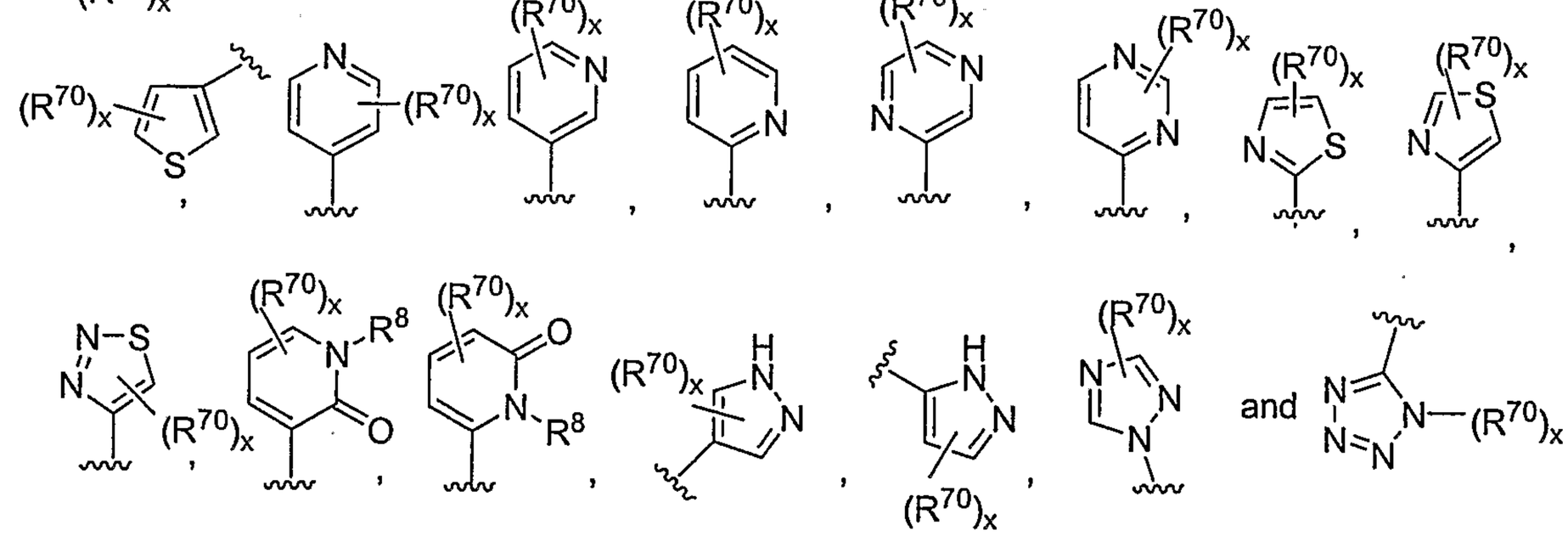
including said N, said heterocyclic ring being optionally substituted with one or more R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl, or heterocyclyl, wherein said 3-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which 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

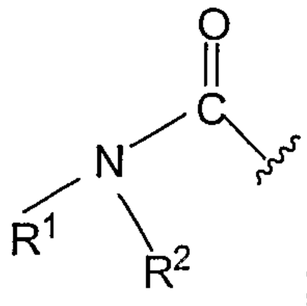








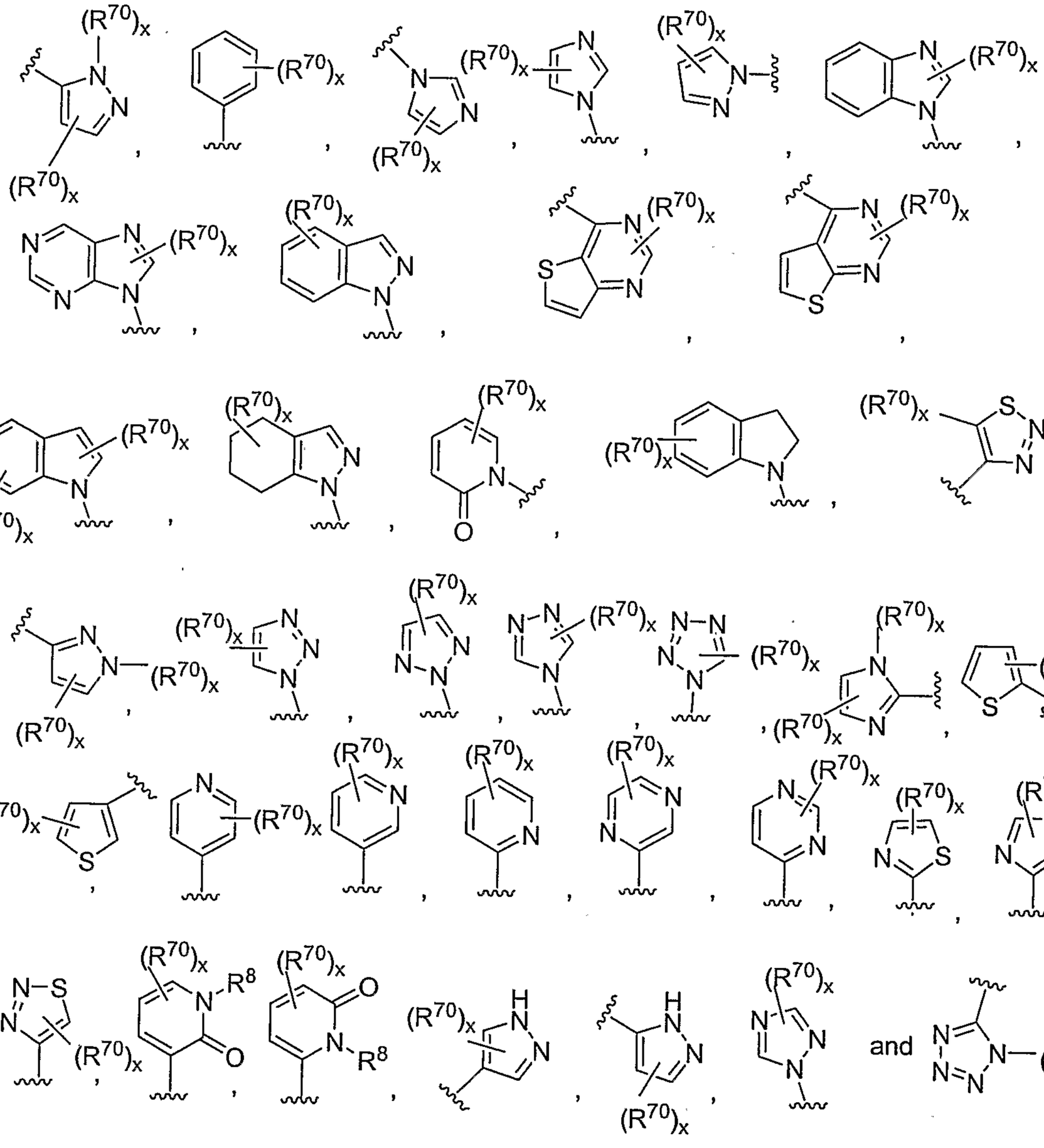
In another embodiment, A is:



;

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

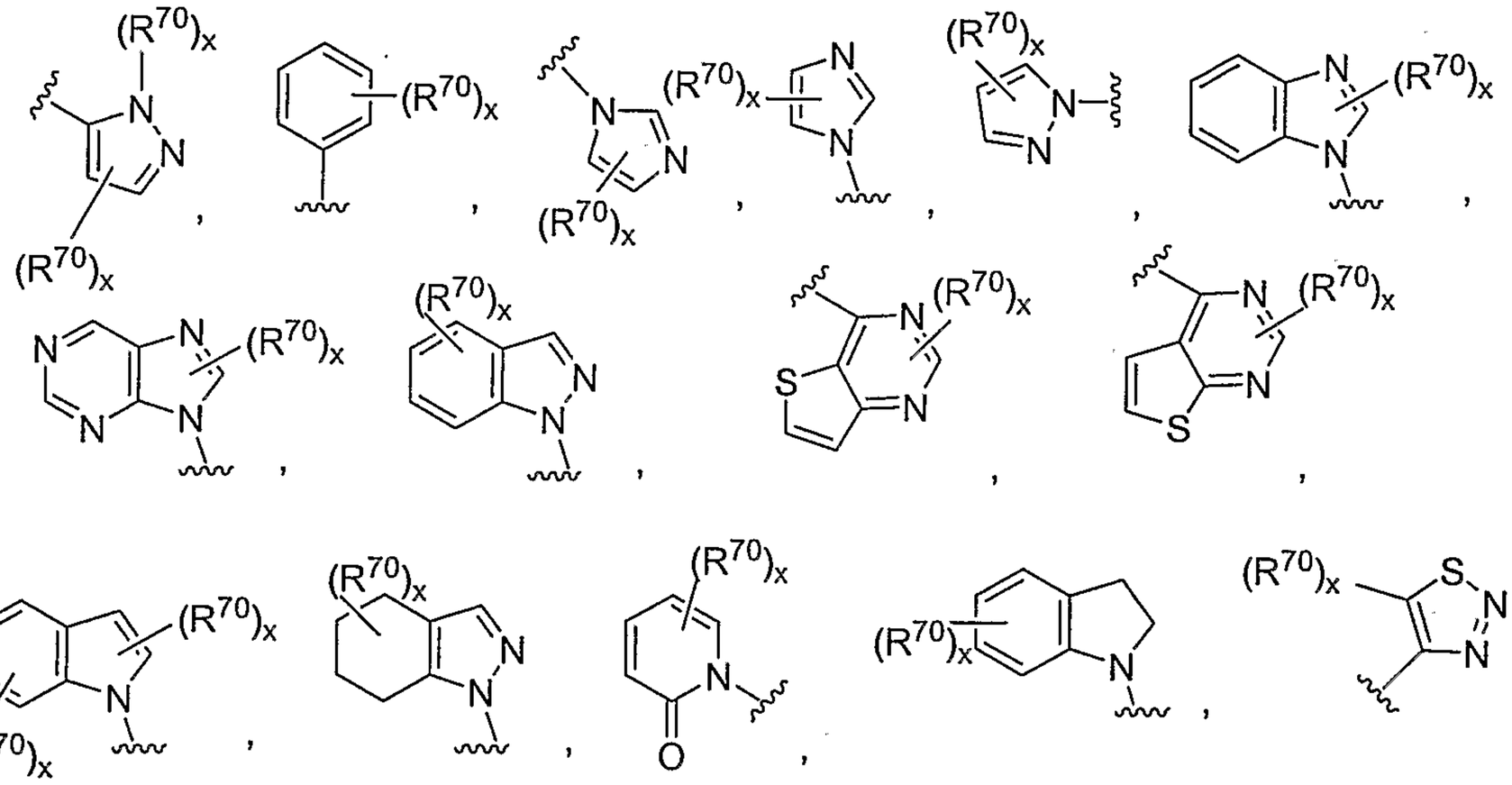


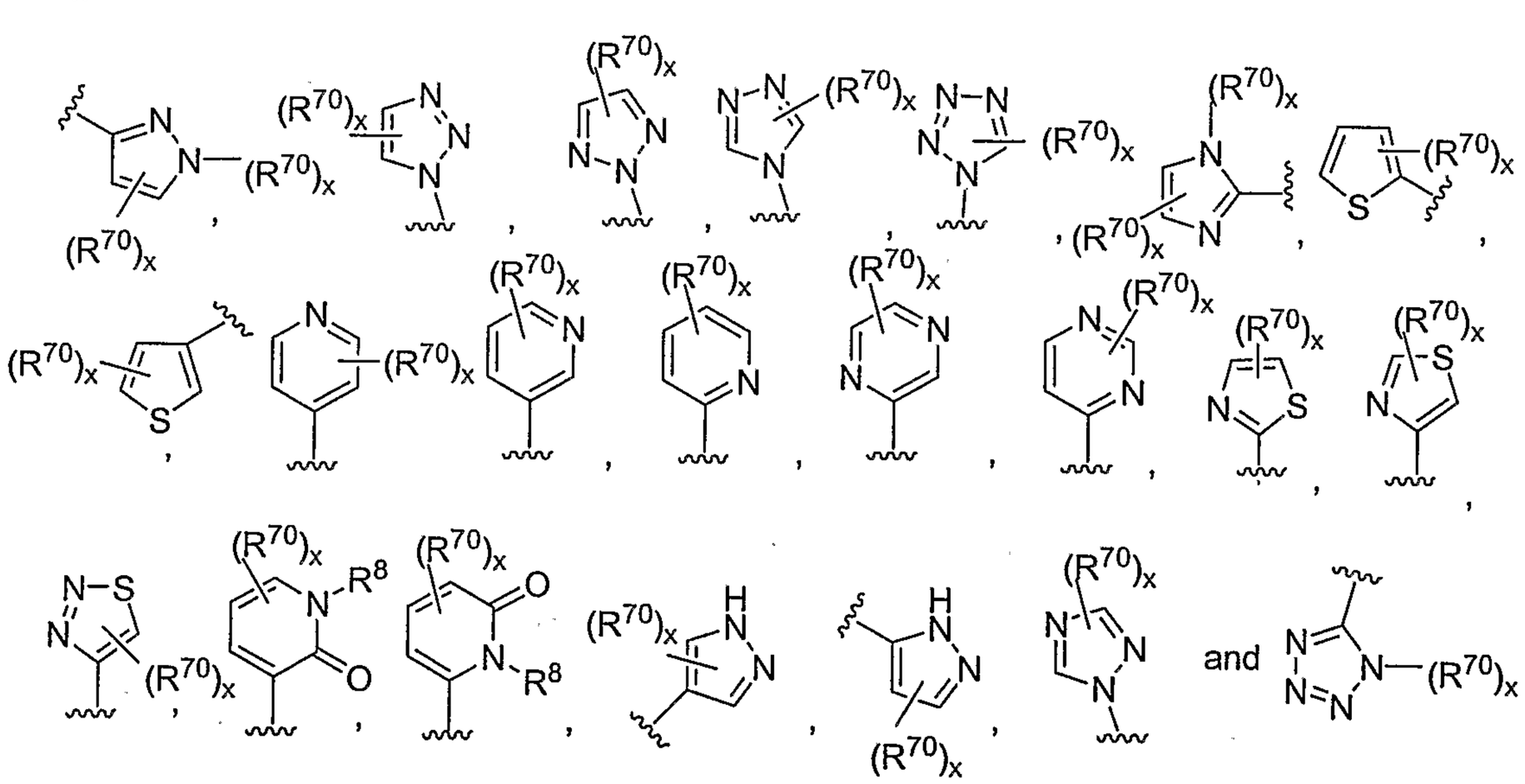
In another embodiment, A is selected from the group consisting of:

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;

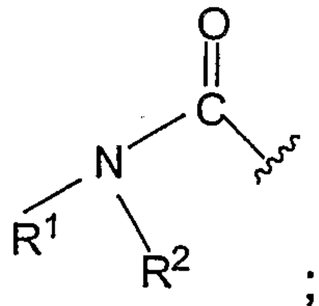
E, J and T are the same and are O; R^{10} is H or alkyl; R^{20}, R^{30}, R^{40}, and R^{50} are the same and are H; W is $-(CR^6{}_2)_n-$, wherein n is 0 to 5; X is selected from the group consisting of phenyl, piperidinyl, pyridinyl, thienyl, thiazolyl, oxazolyl and pyrazolyl; Y is selected from the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





.

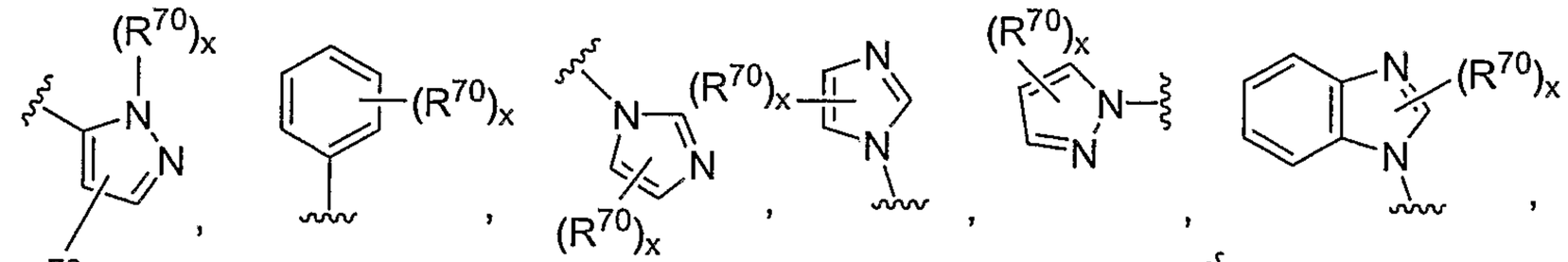
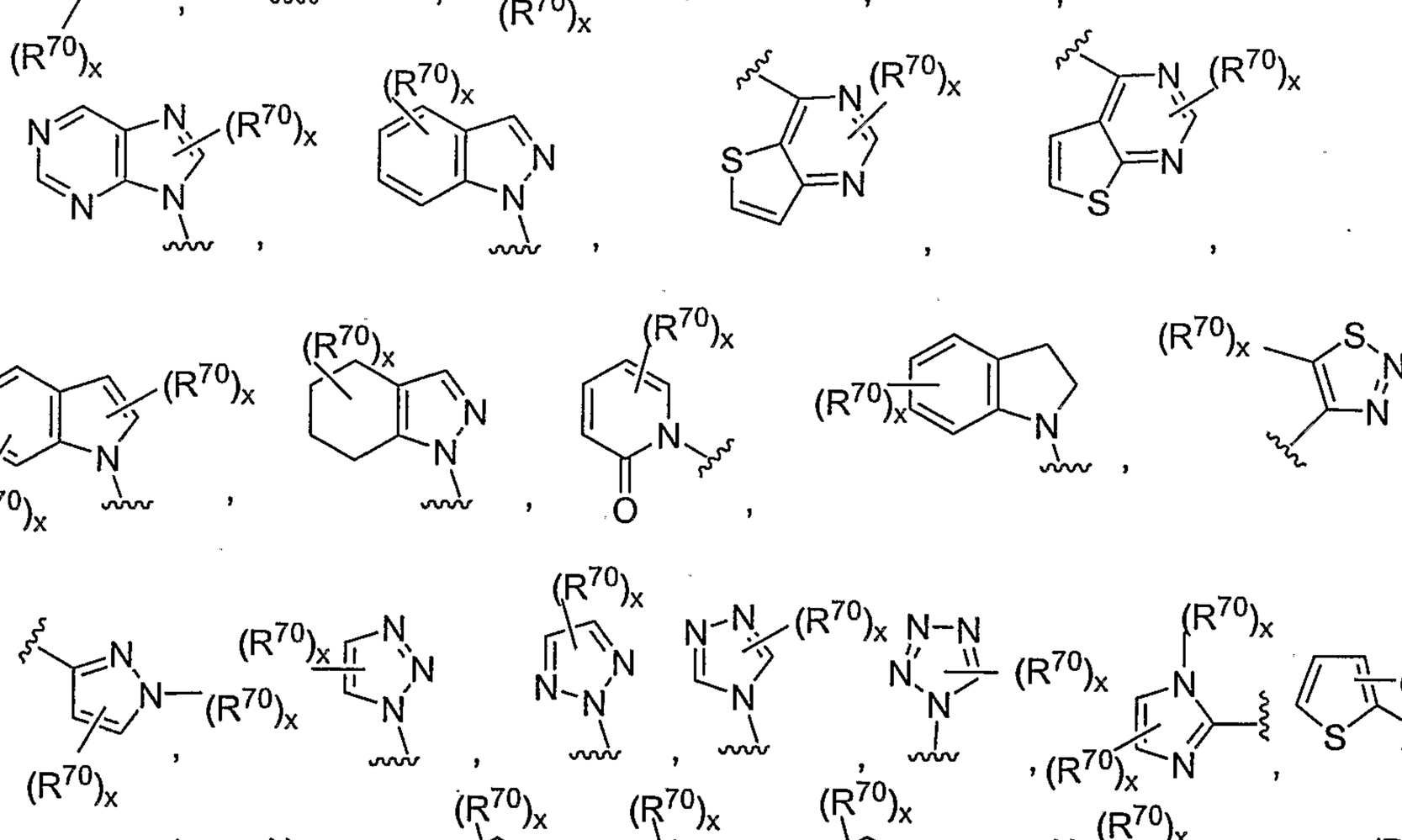
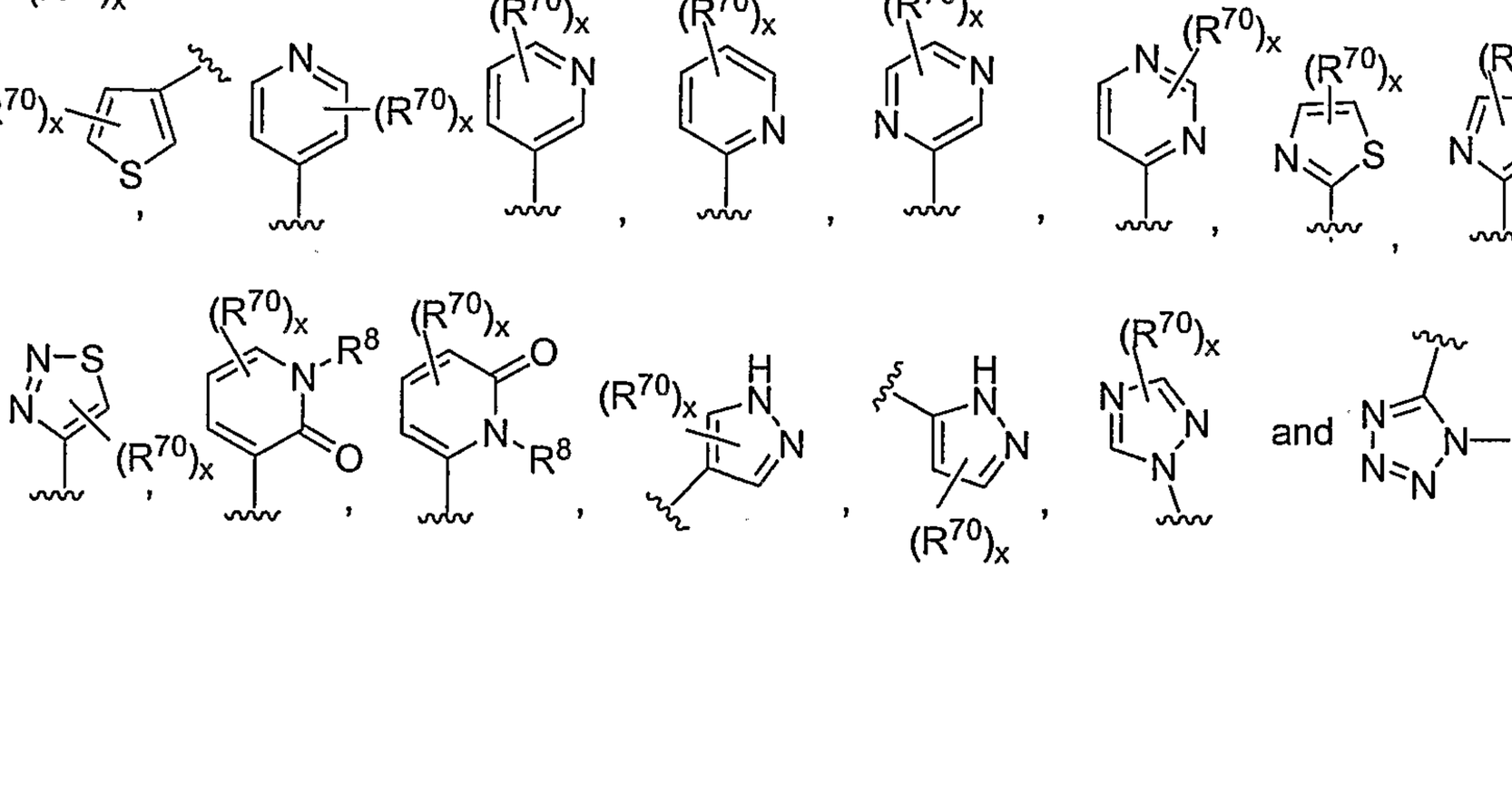
In another embodiment, A is



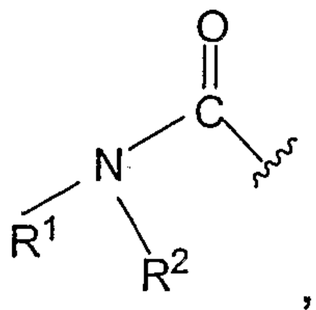
;

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: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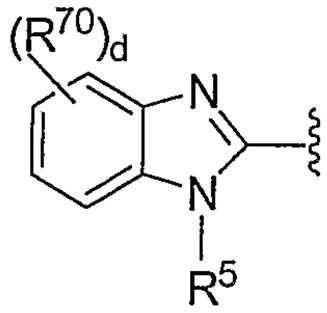
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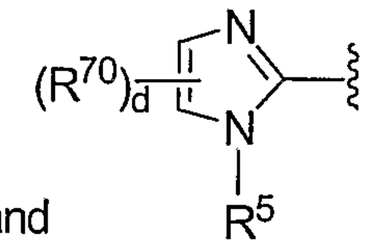
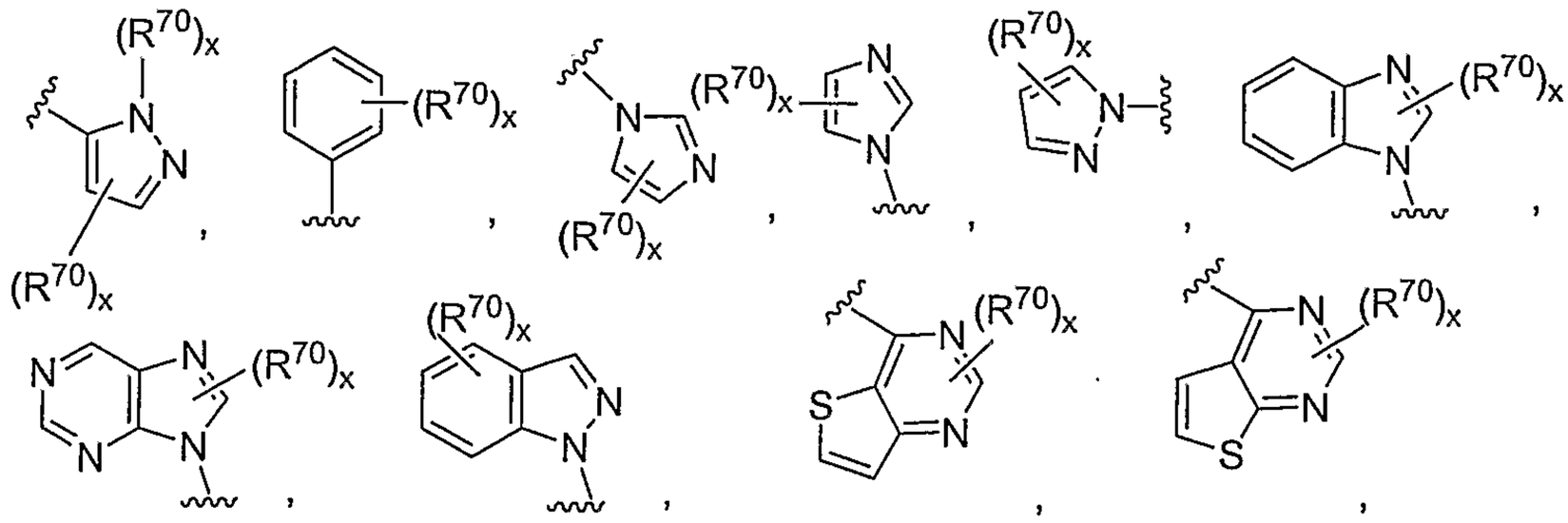
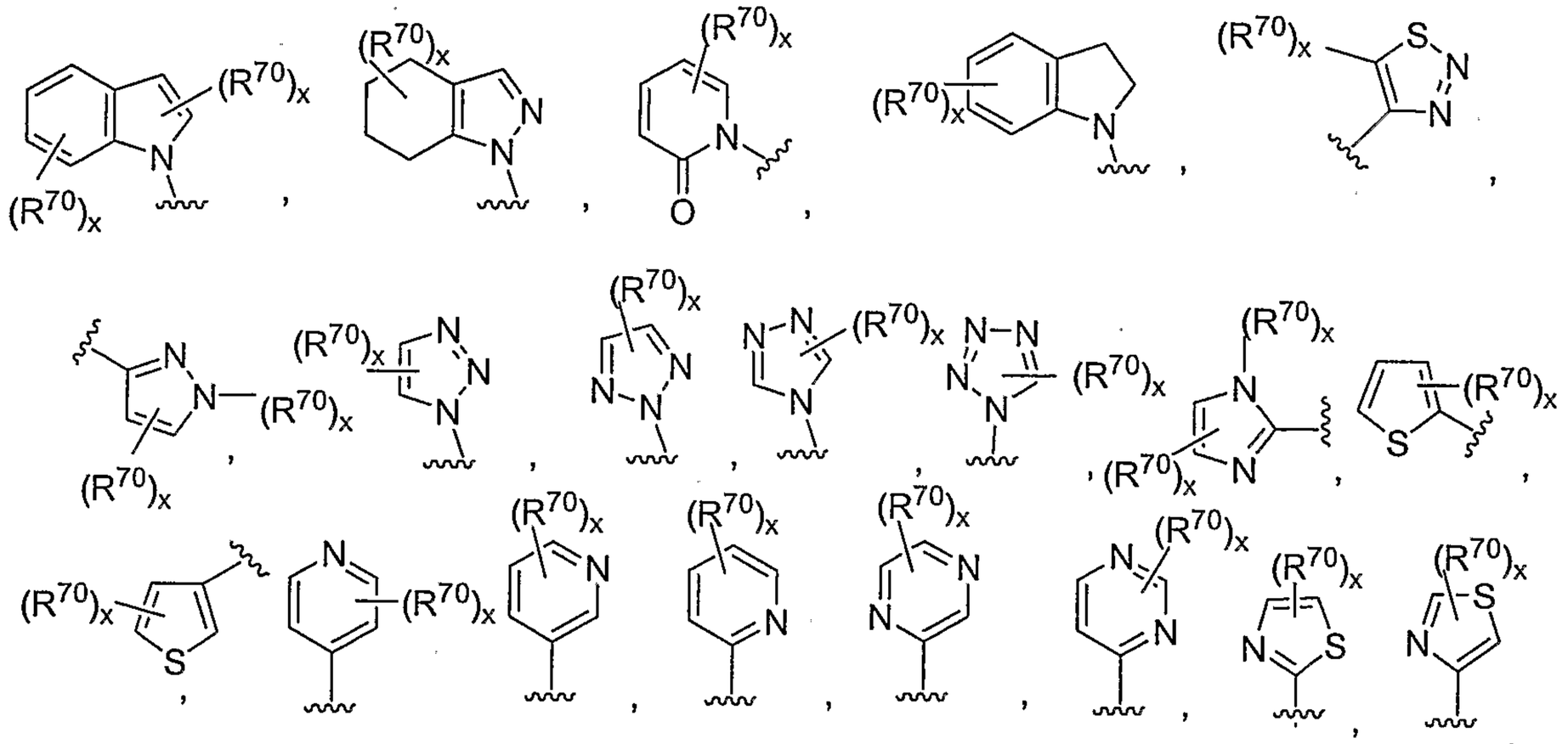


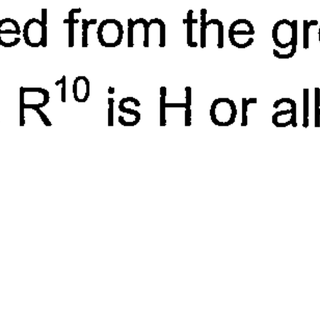
wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 3-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with one or more R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl,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





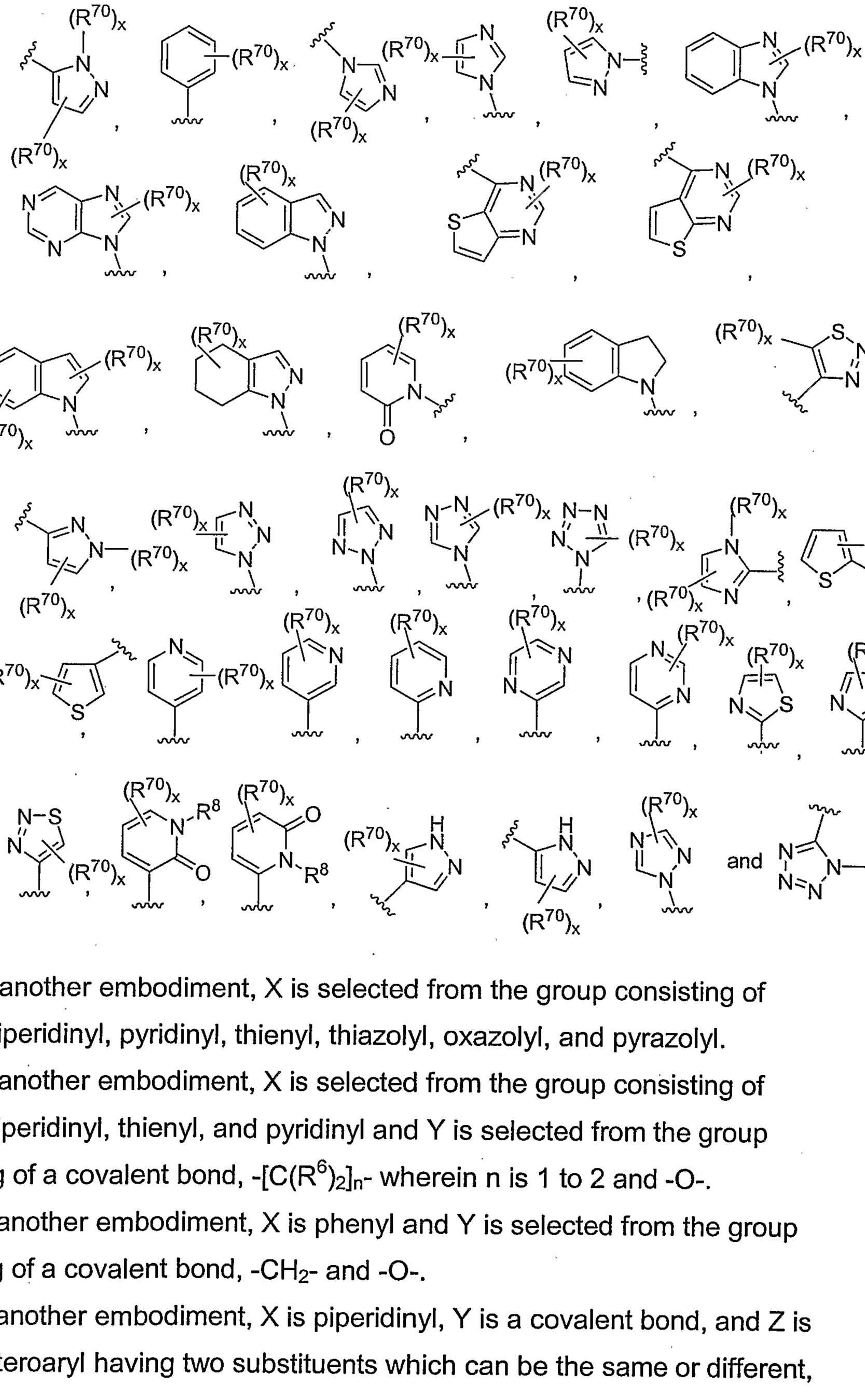
In another embodiment, A is



;

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-.

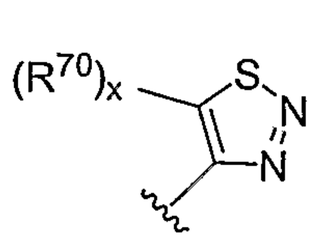
In another embodiment, X is piperidinyl, Y is a covalent bond, and Z is aryl or heteroaryl having two substituents which can be the same or different,

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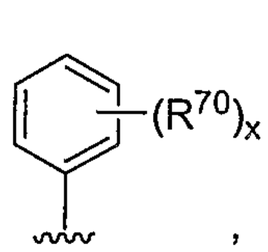
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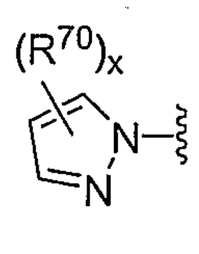
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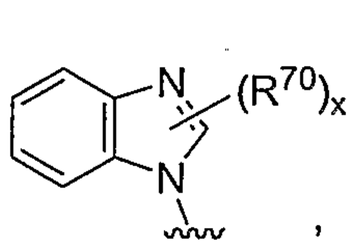
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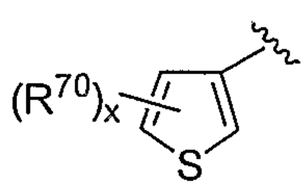
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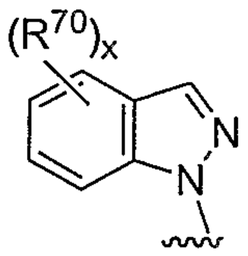
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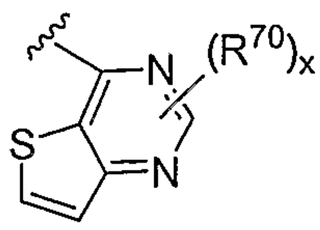
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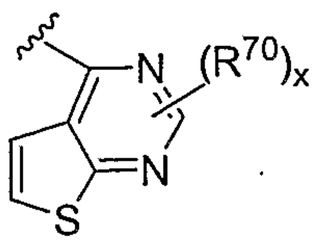
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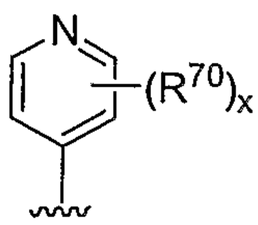
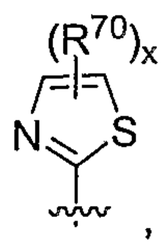
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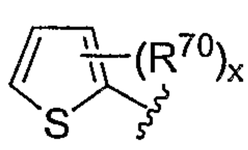
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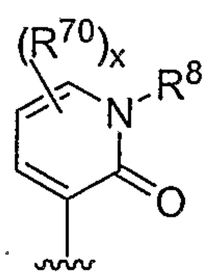
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Another embodiment of the invention discloses the compounds shown in Table 1 below.

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.

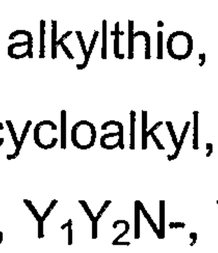
"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described. Preferred alkylaryls comprise a lower alkyl group. Non-limiting example of a suitable alkylaryl group is tolyl. The bond to the parent moiety is through the aryl.

"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: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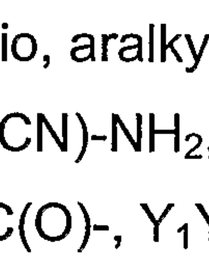
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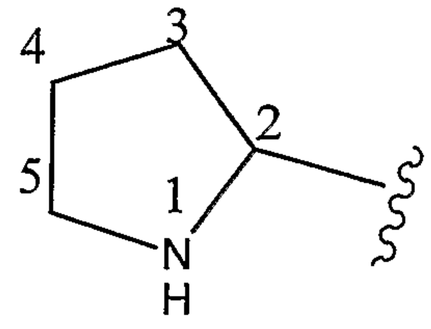
"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or

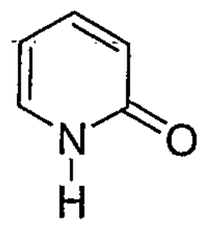
sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively 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:



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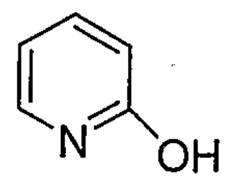


are considered equivalent in certain embodiments of this invention.

"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 TACE, 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 TACE, 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.

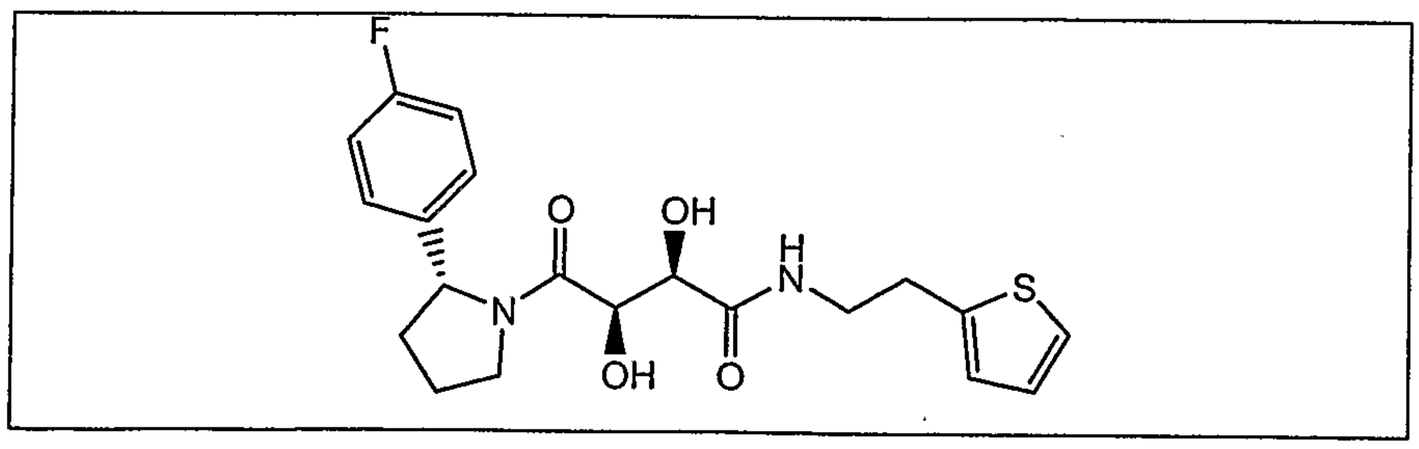
In another aspect, the invention provides a use of a compound of formula 1 for the manufacture of a medicament to treat disorders associated with TACE, TNF-*α*, MMPs, ADAMs or any combination thereof.

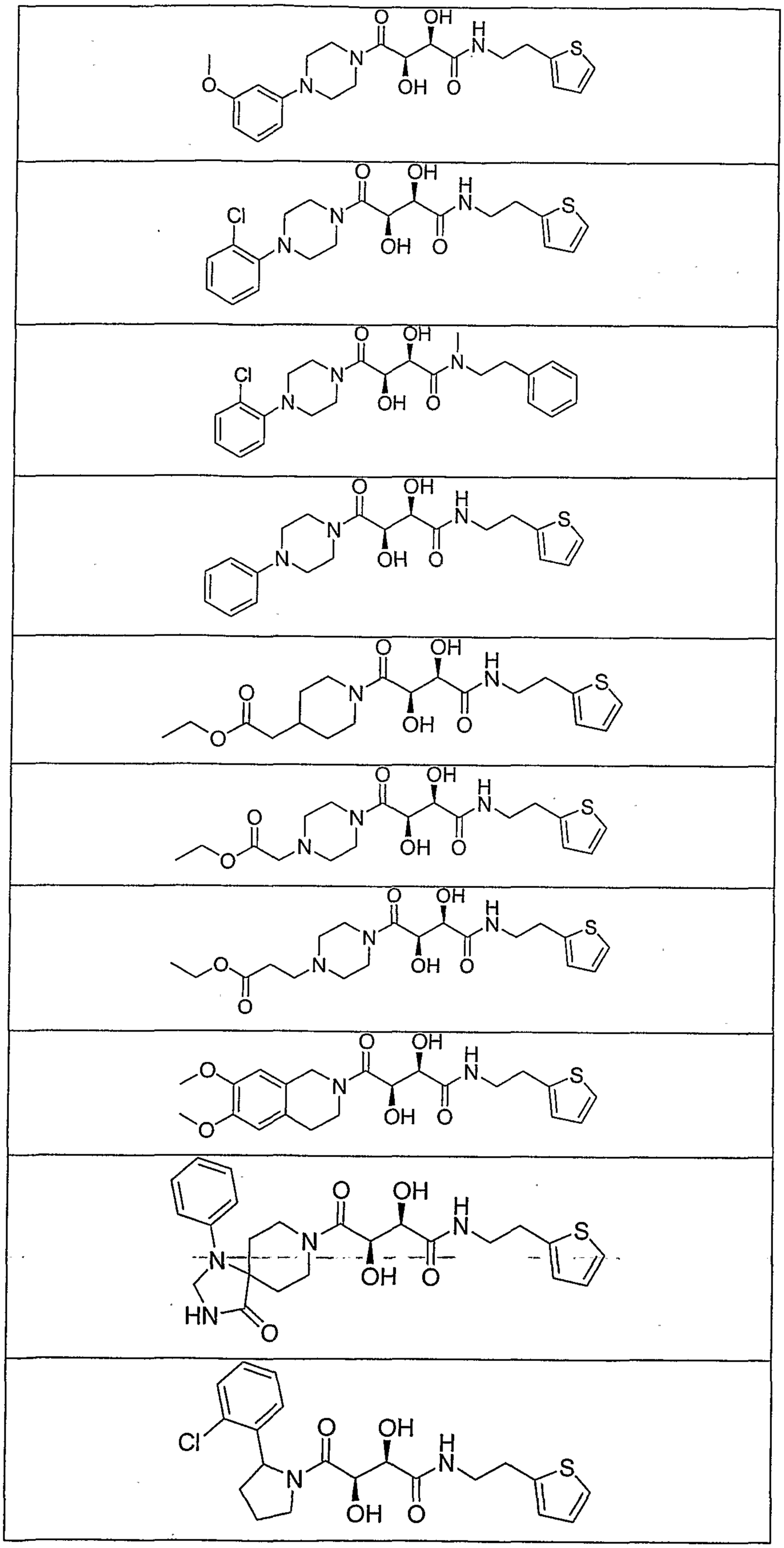
The compounds of Formula I can have anti-inflammatory activity and/or immunomodulatory activity and can be useful in the treatment of diseases including but not limited to septic shock, haemodynamic shock, sepsis syndrome, post ischaemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic diseases, cachexia, graft rejection, cancers such as cutaneous T-cell lymphoma, diseases

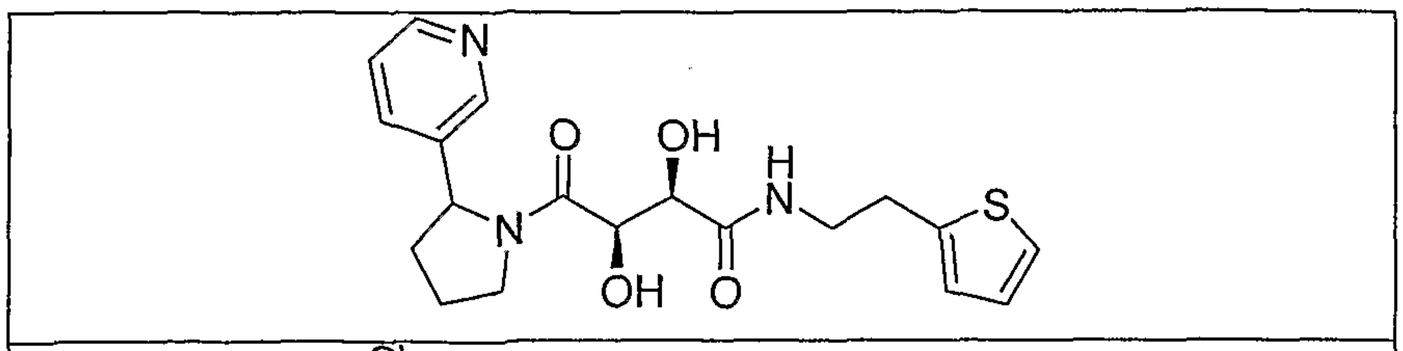
involving angiogenesis, autoimmune diseases, skin inflammatory diseases, inflammatory bowel diseases such as Crohn's disease and colitis, OA and RA, ankylosing spondylitis, psoriatic arthritis, adult Still's disease, ureitis, Wegener's granulomatosis, Behcehe disease, Sjogren's syndrome, sarcoidosis, 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.

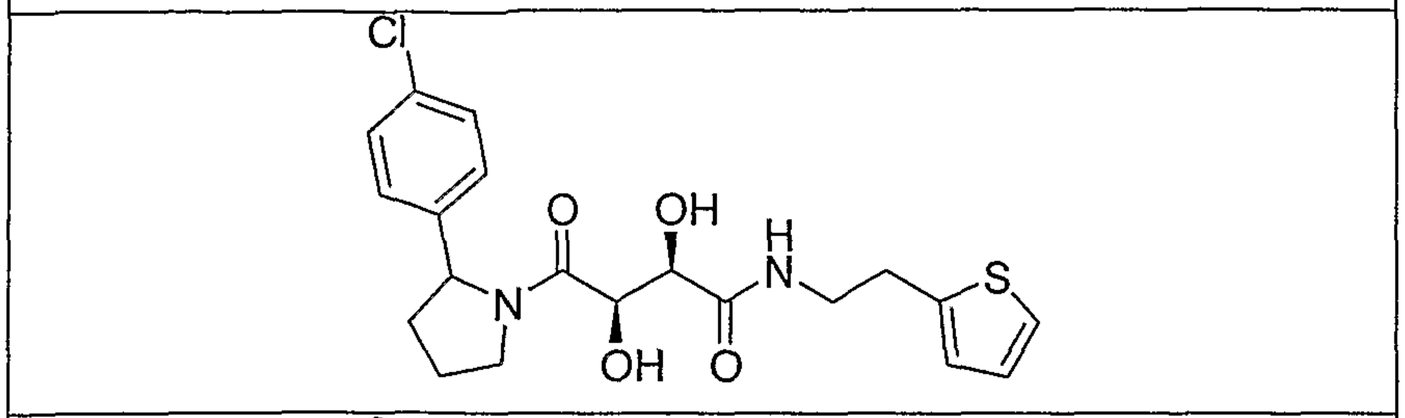
In another aspect, the invention provides a method of preparing a pharmaceutical composition for treating the disorders associated with TACE, TNF-α, MMPs, ADAMs or any combination thereof, said method comprising bringing into intimate contact at least one compound of formula 1 and at least one pharmaceutically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

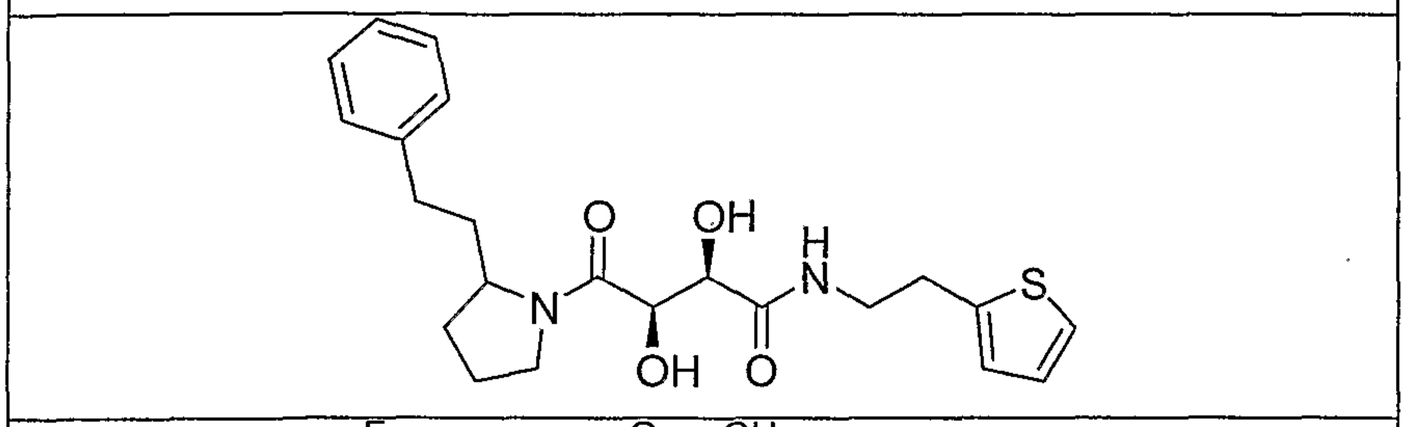
In another aspect, the invention provides a compound of formula (I) exhibiting TACE, TNF-α, MMPs, ADAMs or any combination thereof inhibitory activity, including enantiomers, stereoisomers and tautomers of said compound, and pharmaceutically acceptable salts or solvates of said compound, said compound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

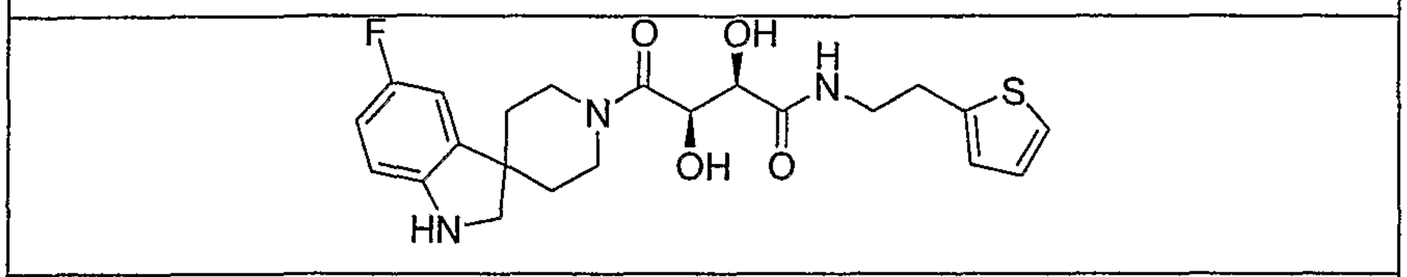


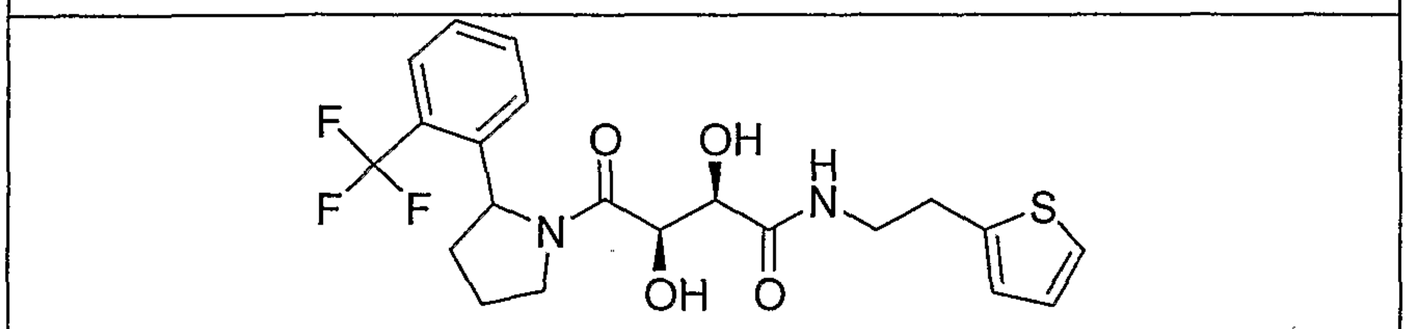


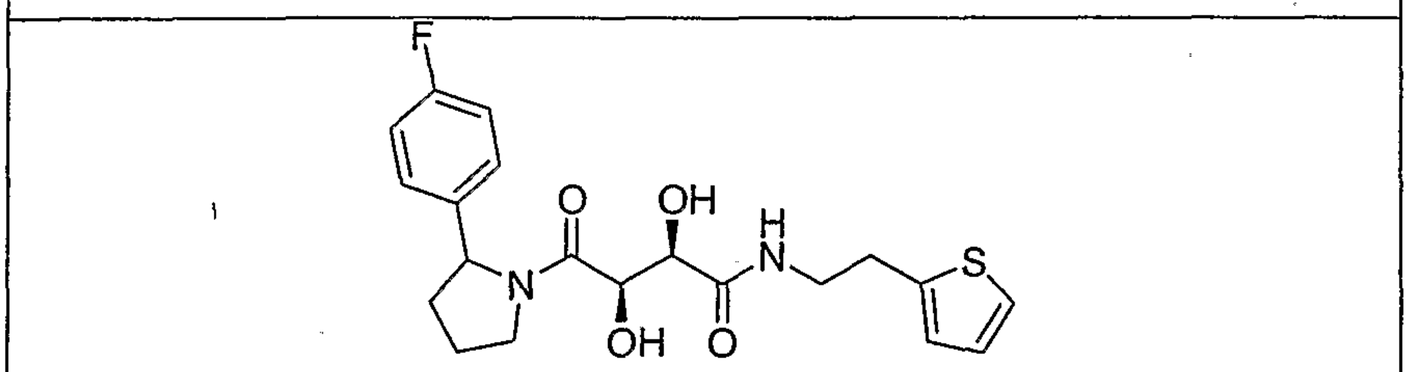


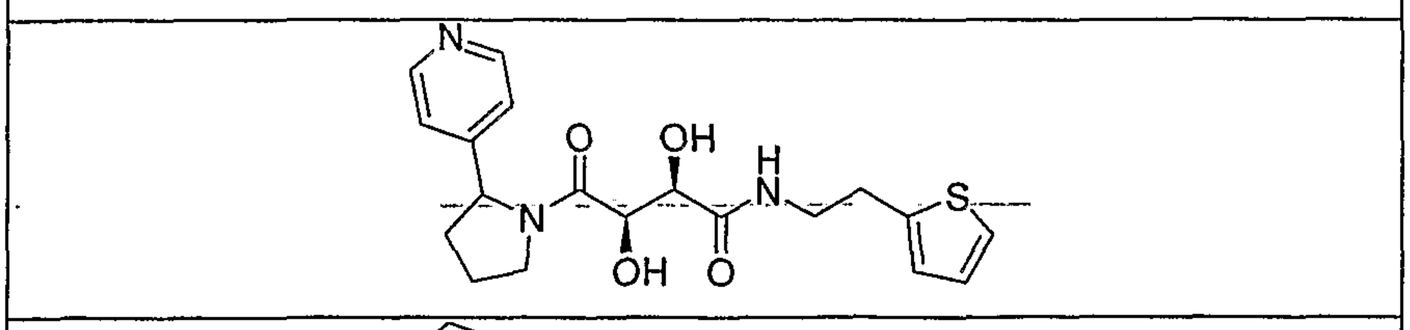


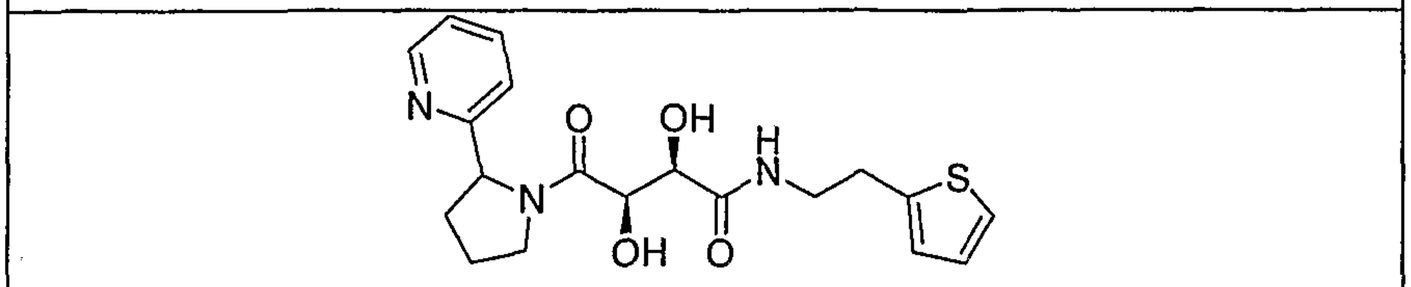


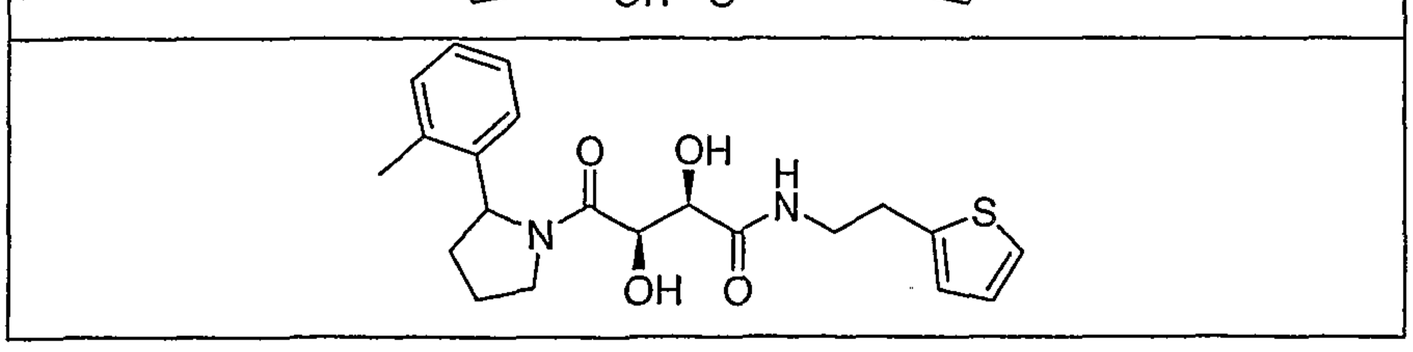


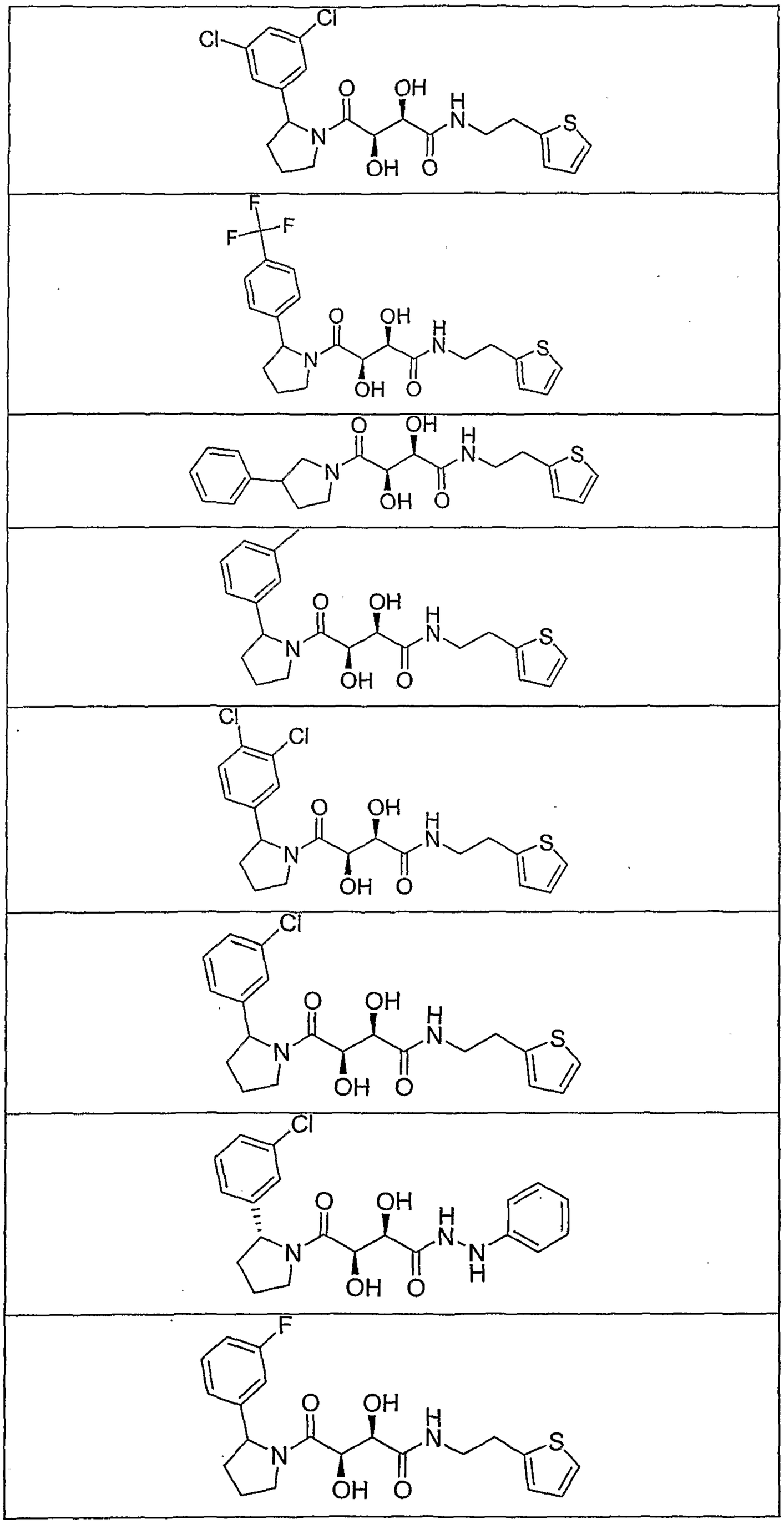


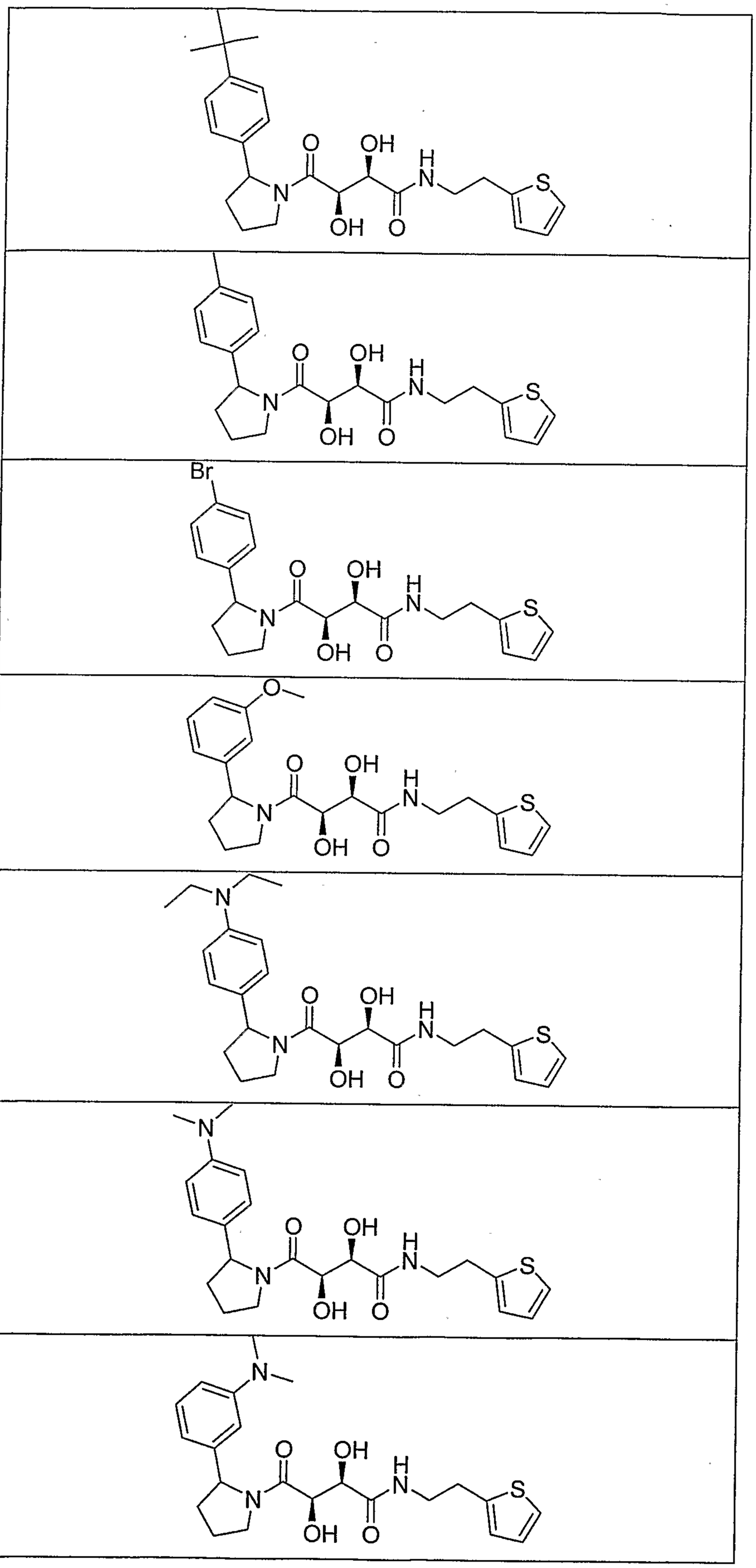


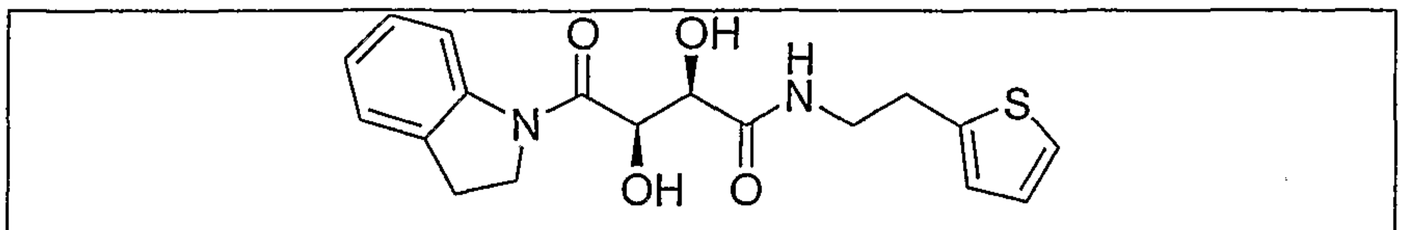


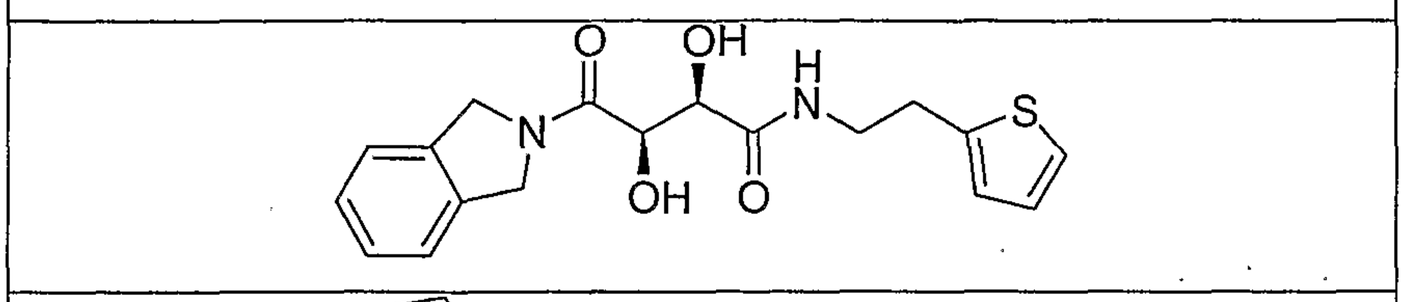


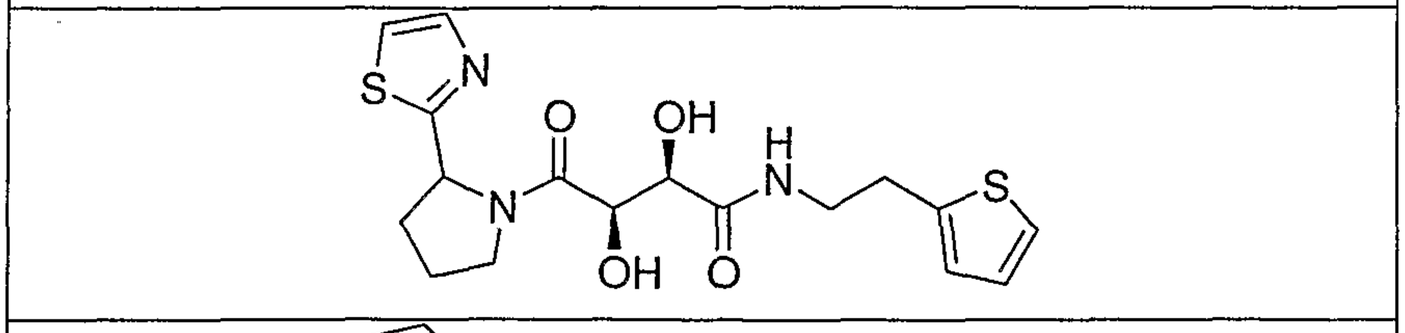


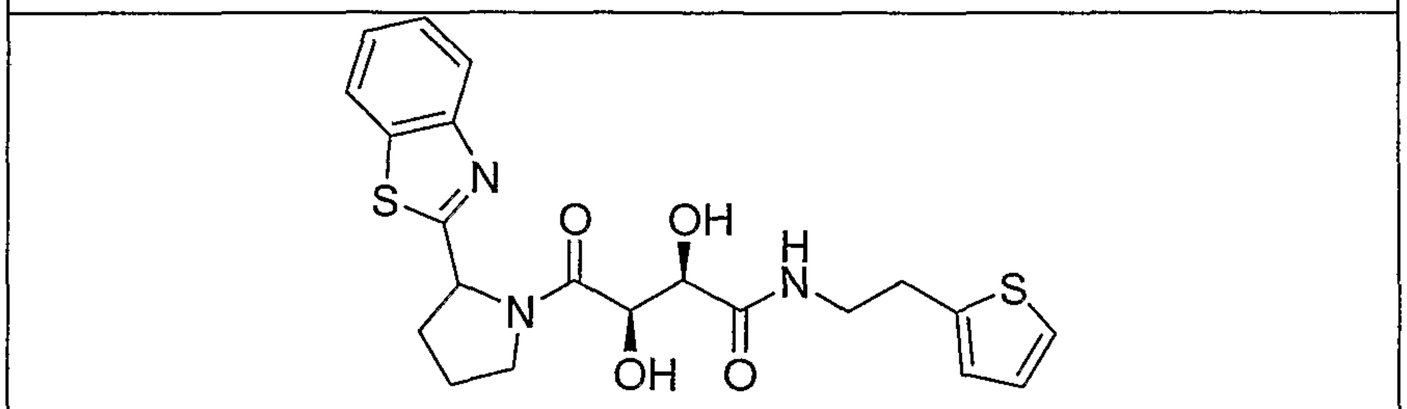


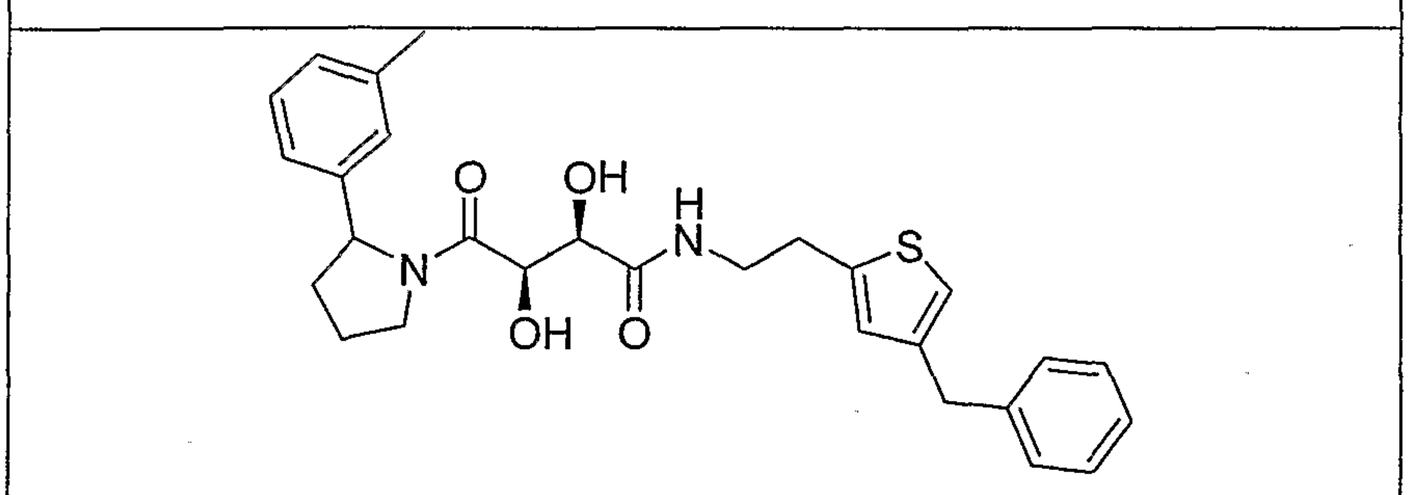


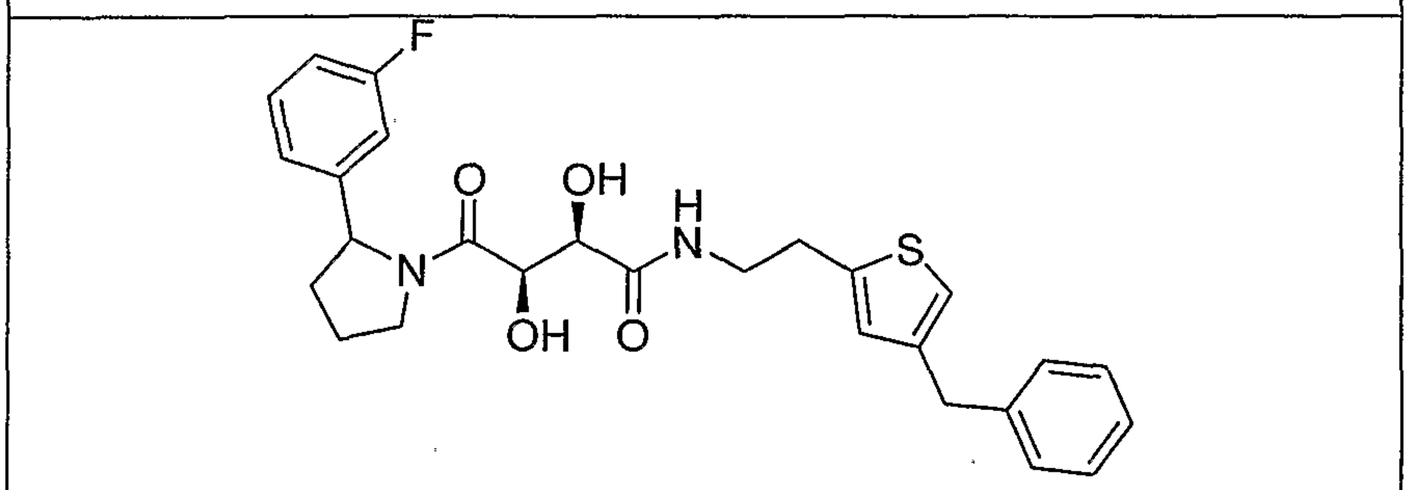


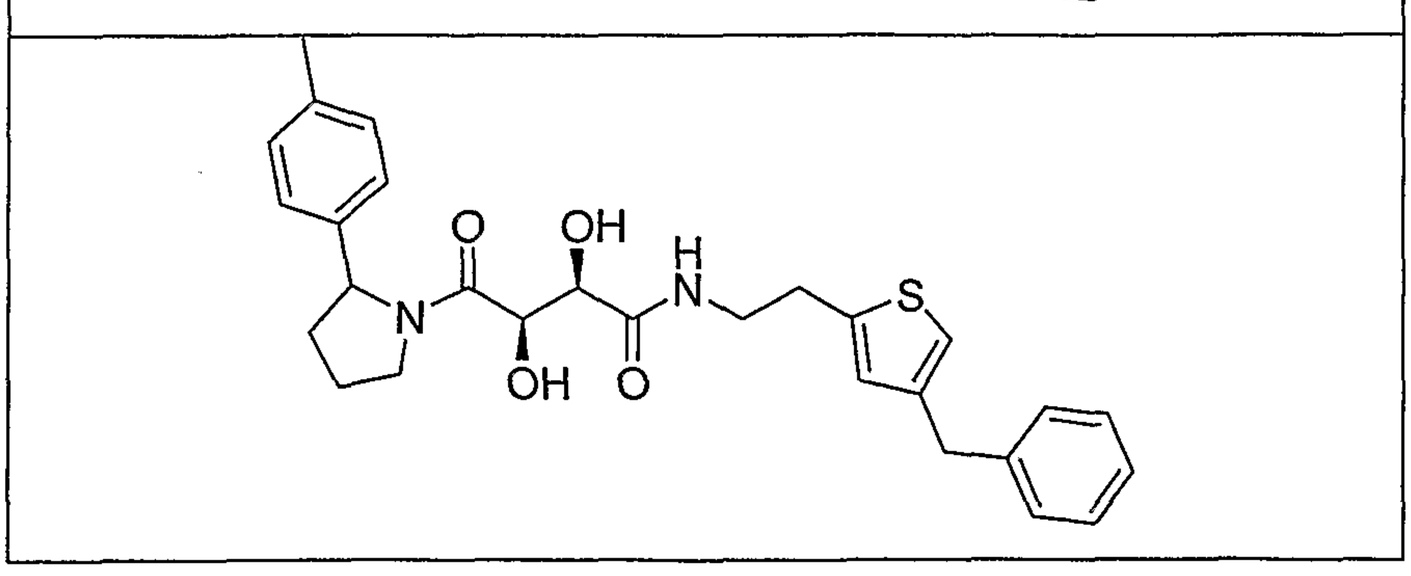


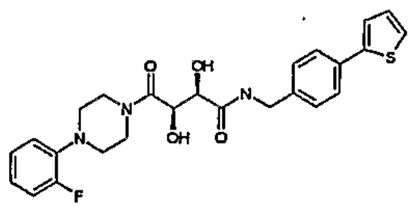


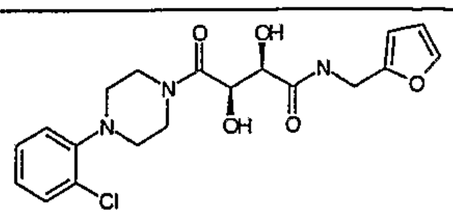


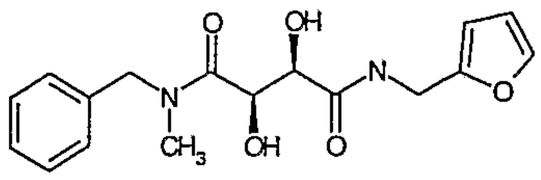


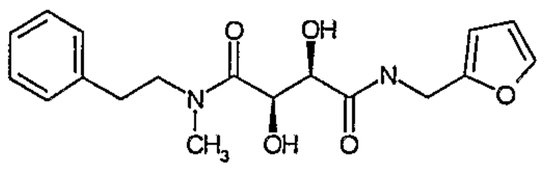


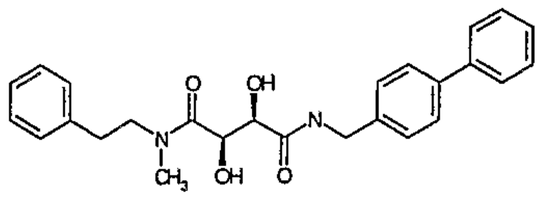


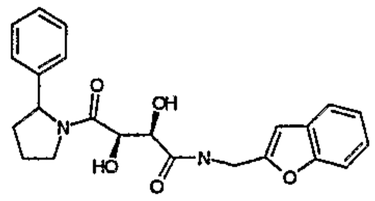


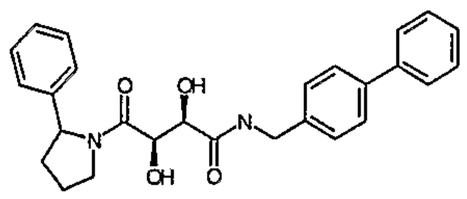


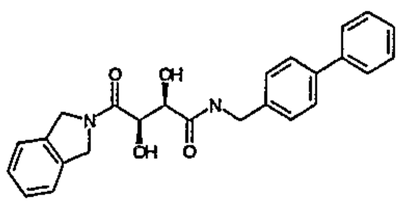


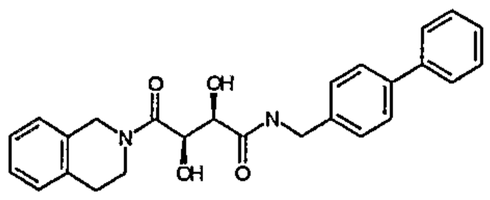


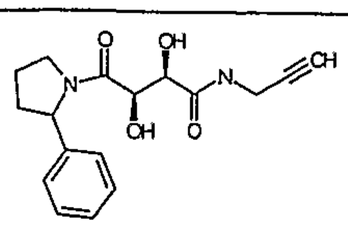


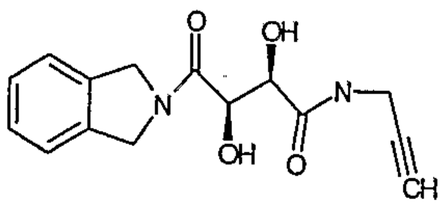


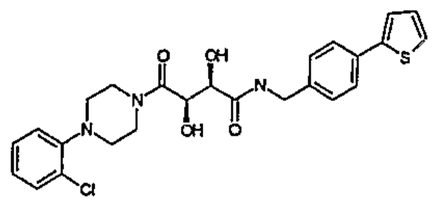


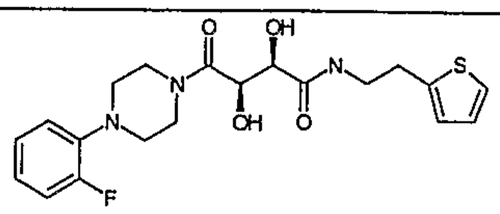


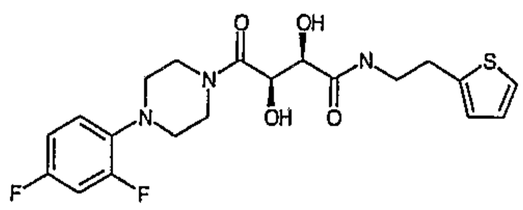


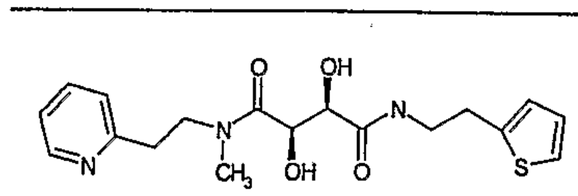


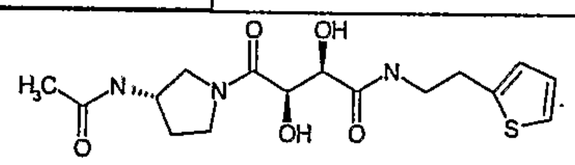


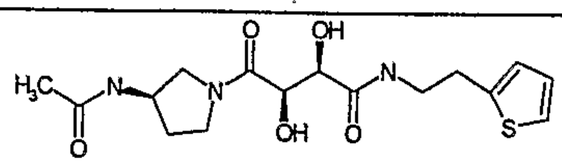


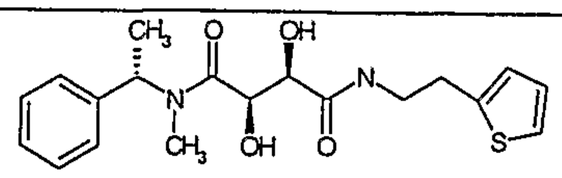


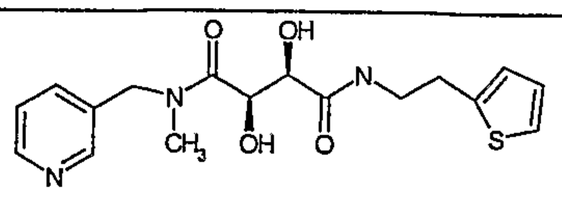


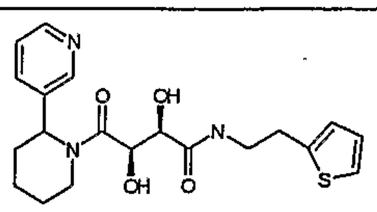


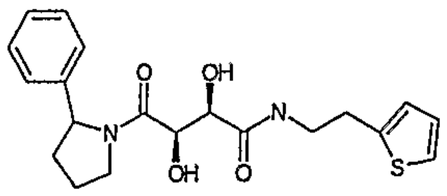


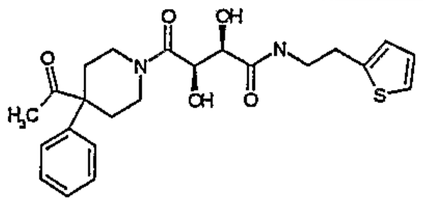


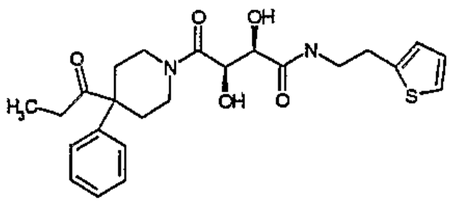


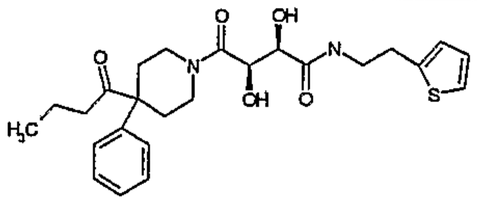


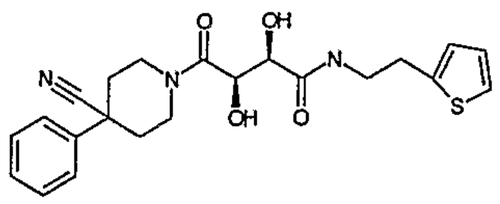


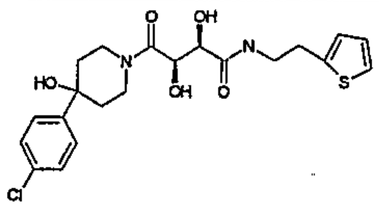


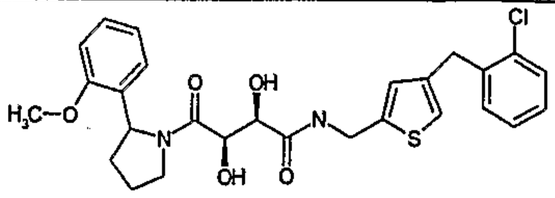


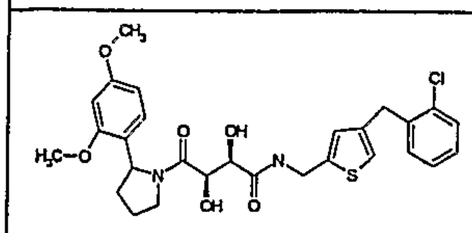


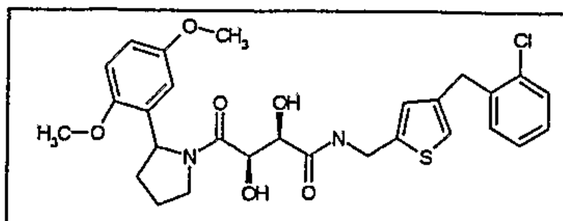


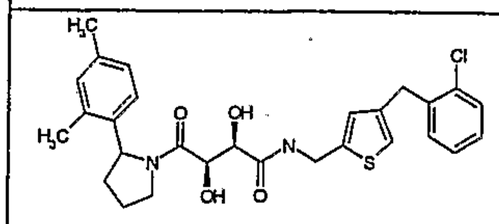


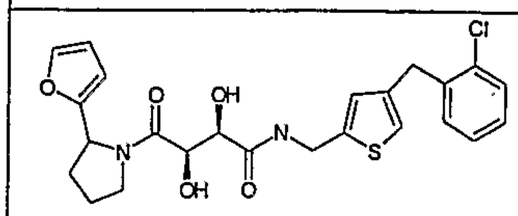


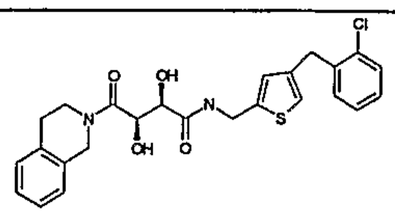


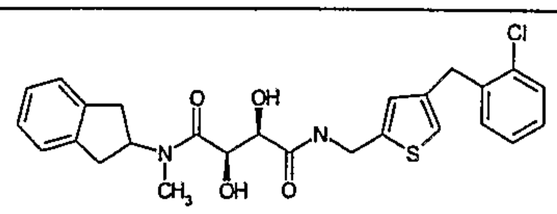


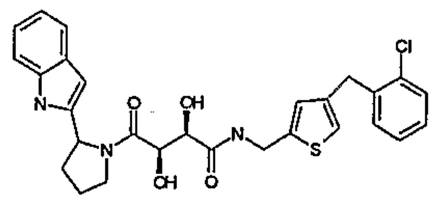


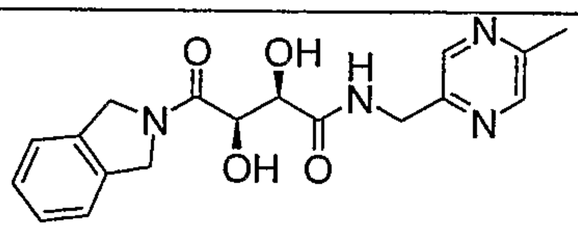


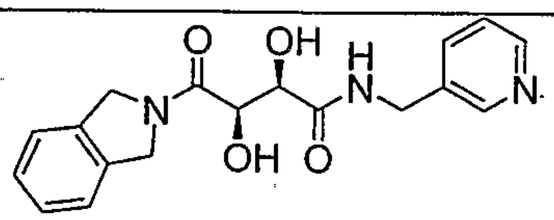


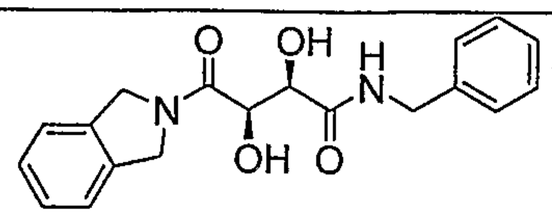


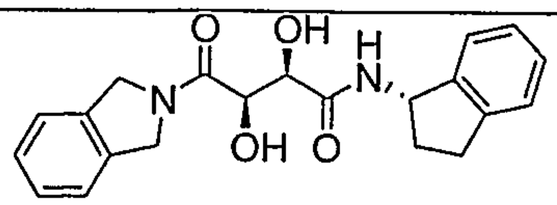


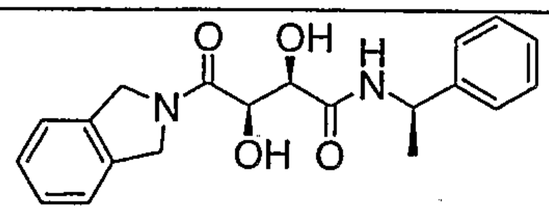


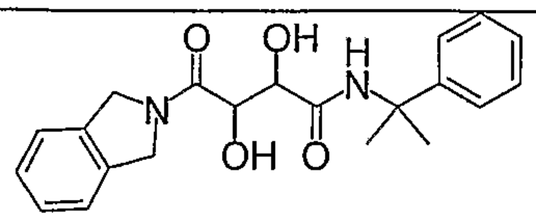
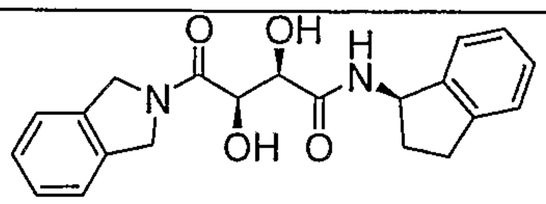
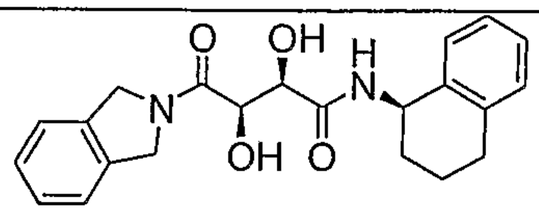
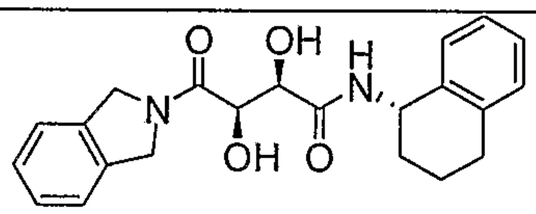
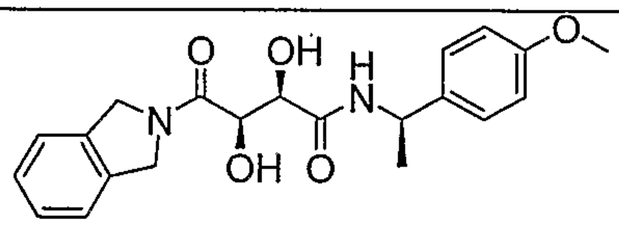
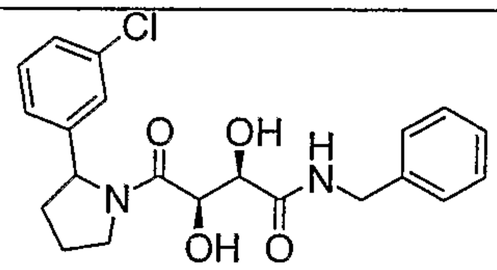
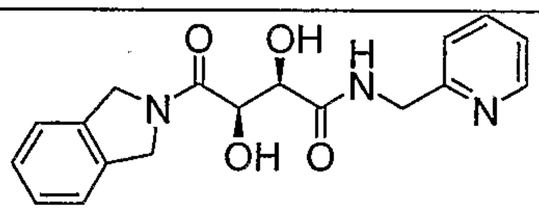
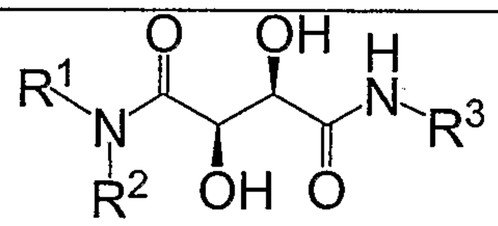
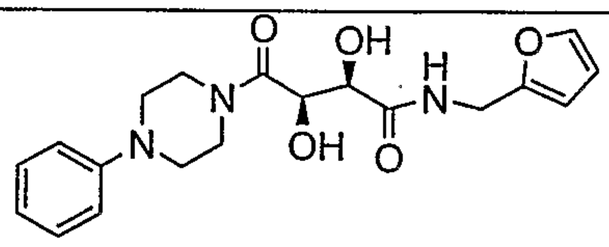
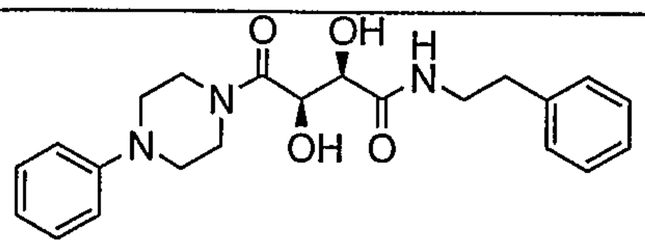
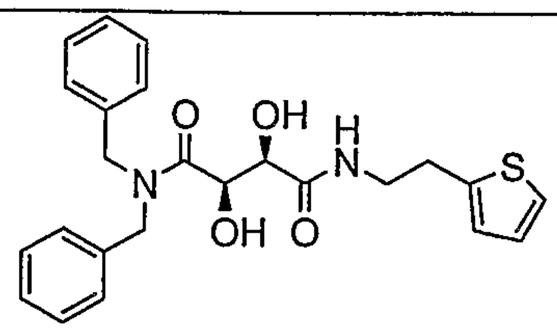


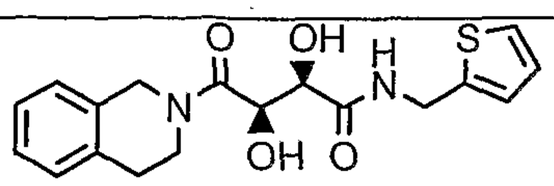


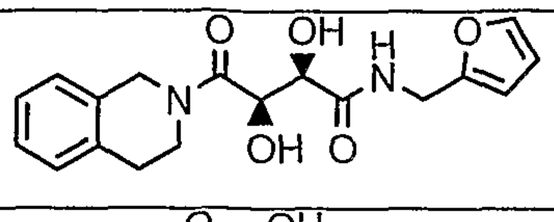


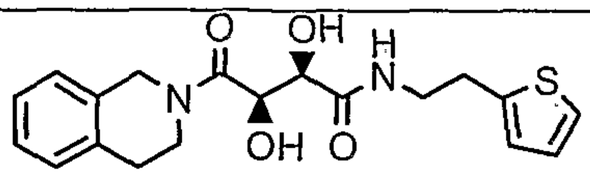


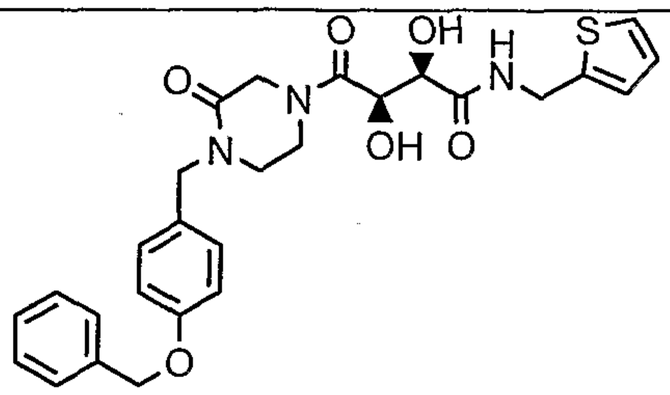


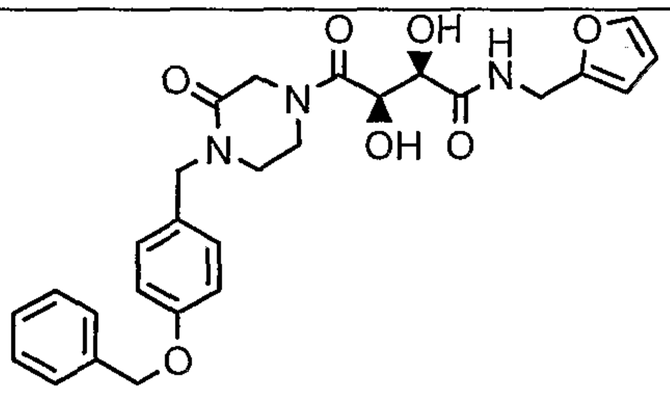







 (R1 = R2 = CH_2Ph, R3 = $CH_2CH_2(C_4H_4O)$




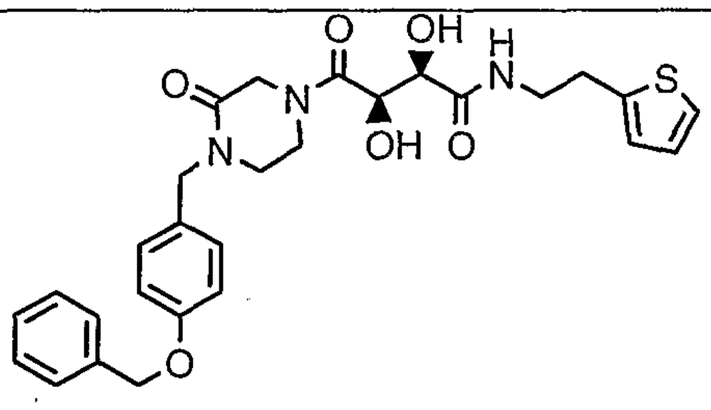


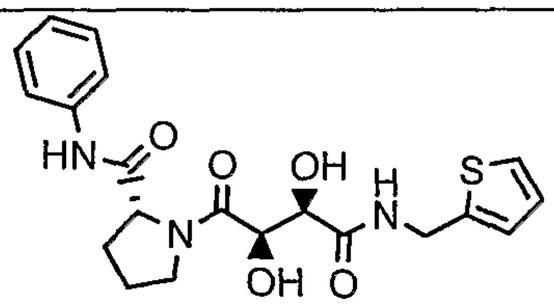


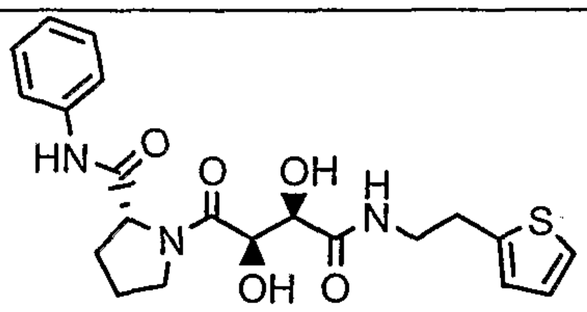


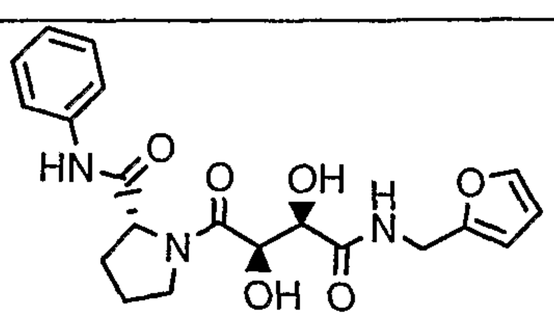


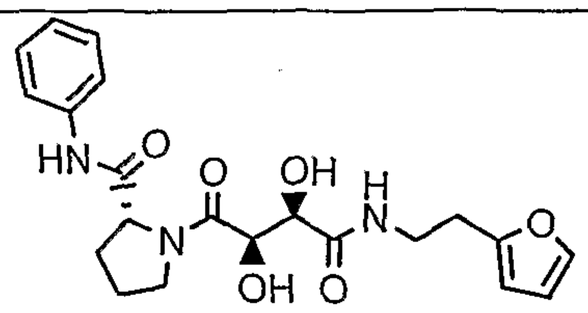
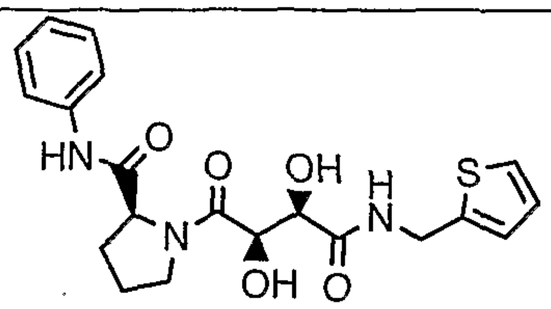
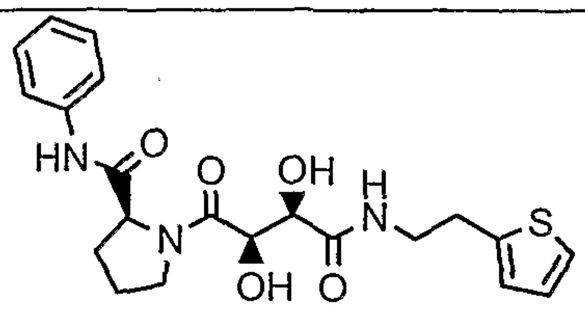
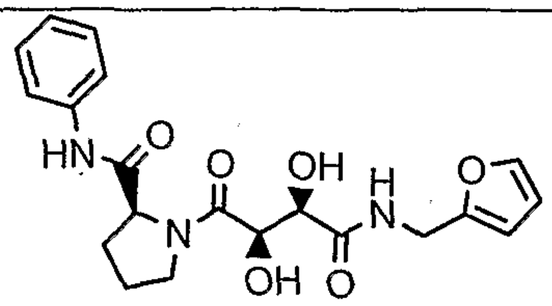
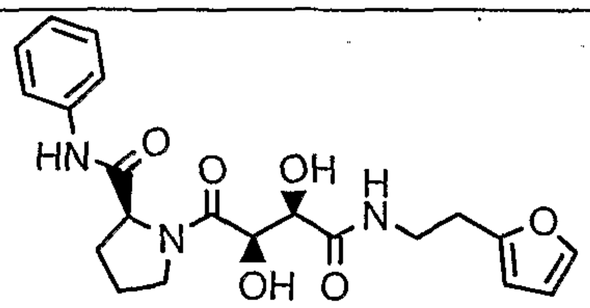
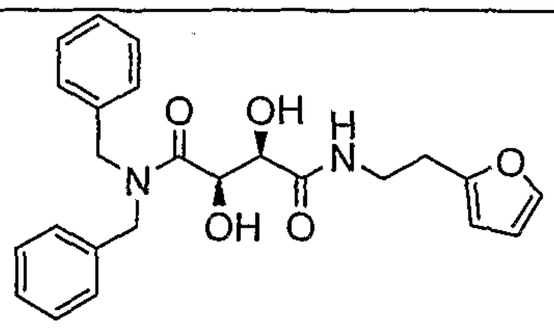
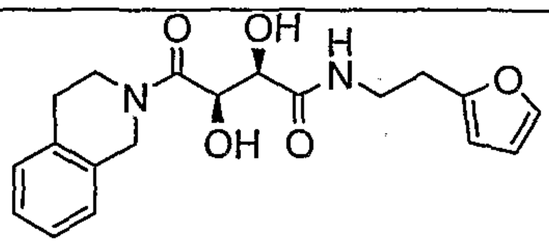
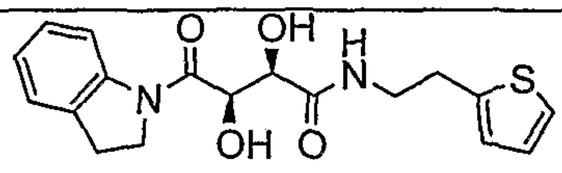
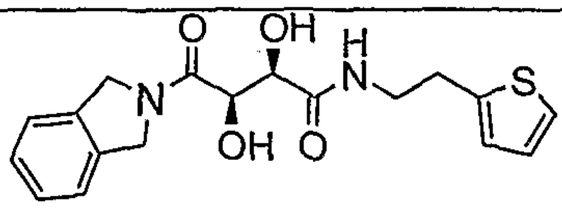
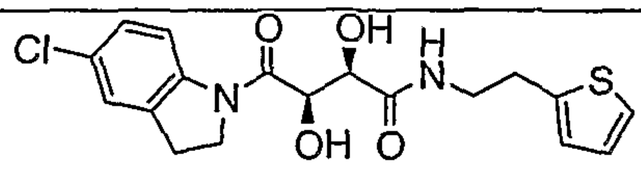
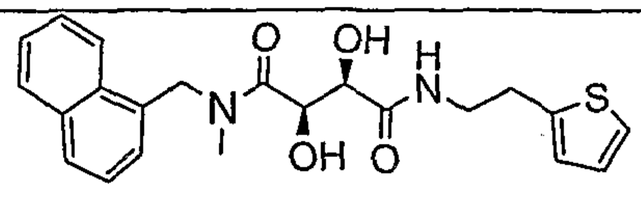


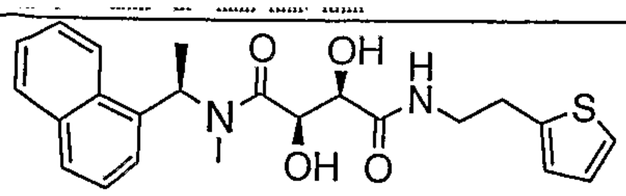
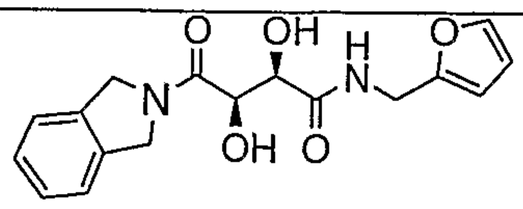
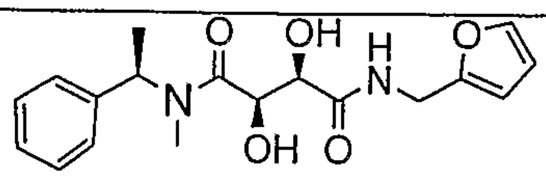
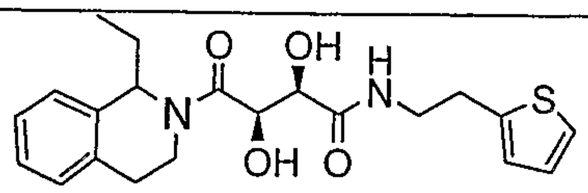
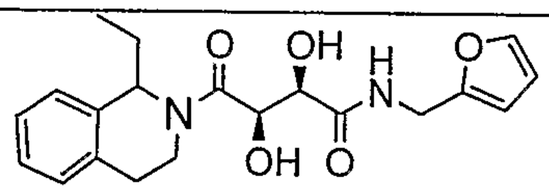
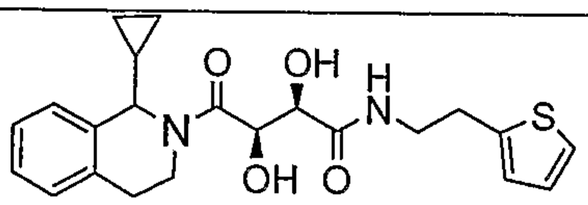
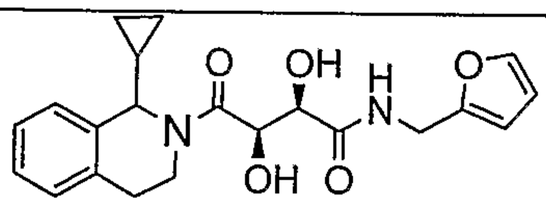
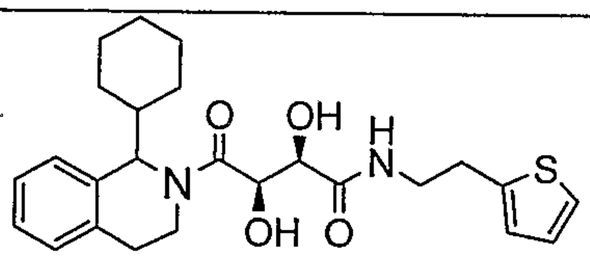
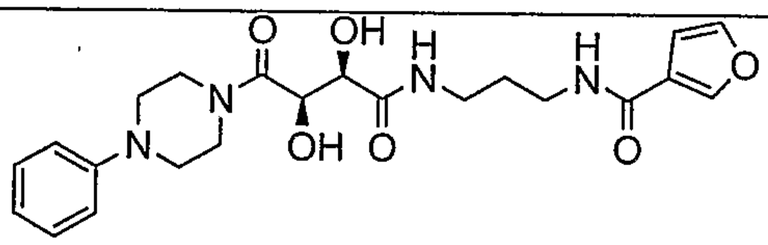
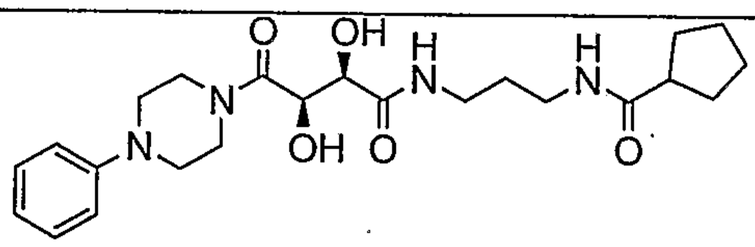
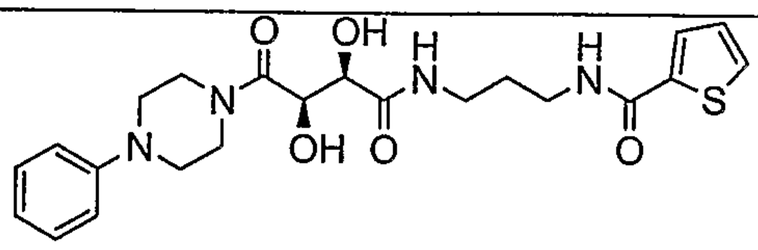
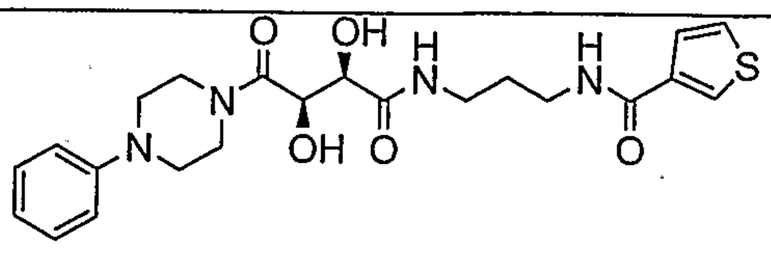
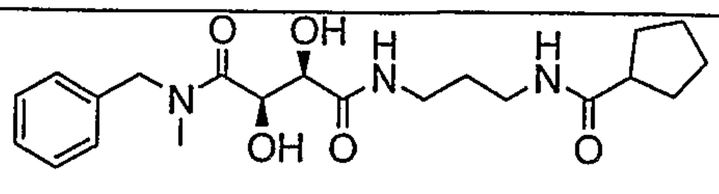


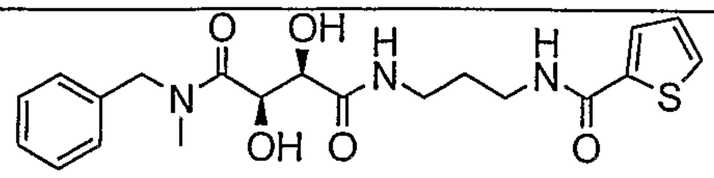
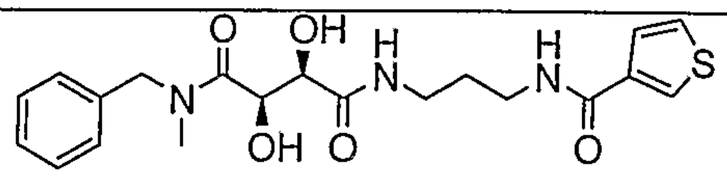
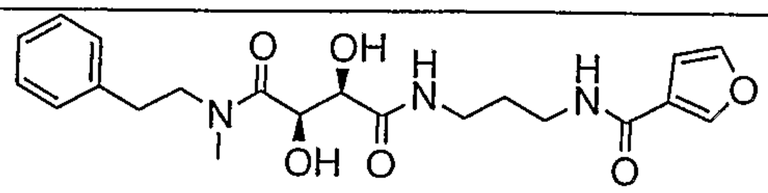
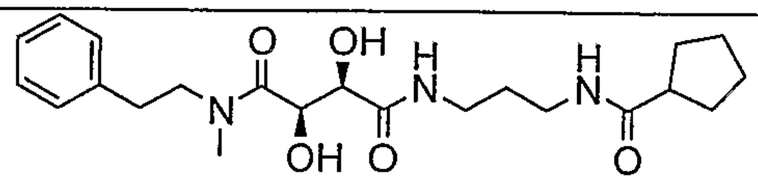
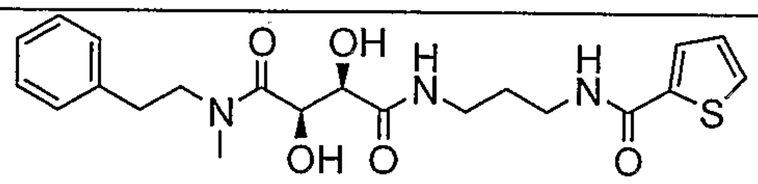
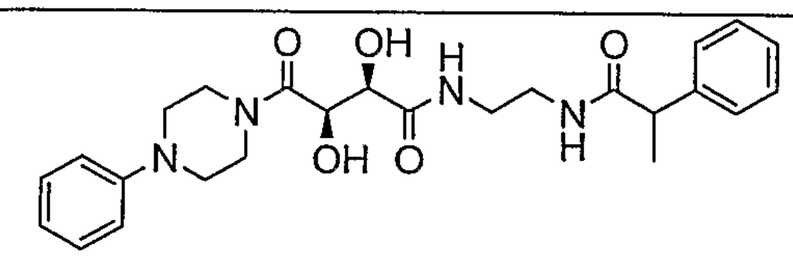
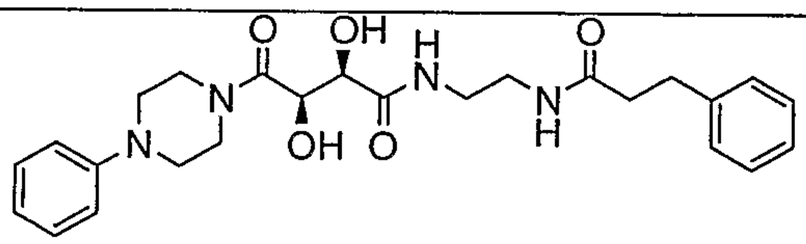
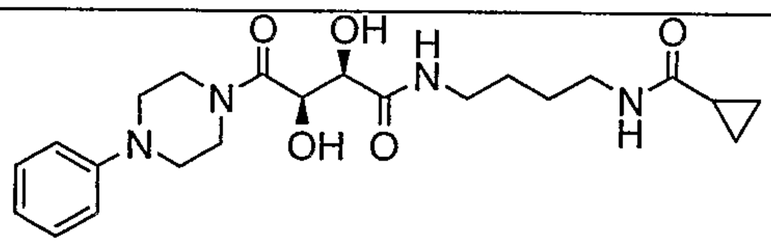
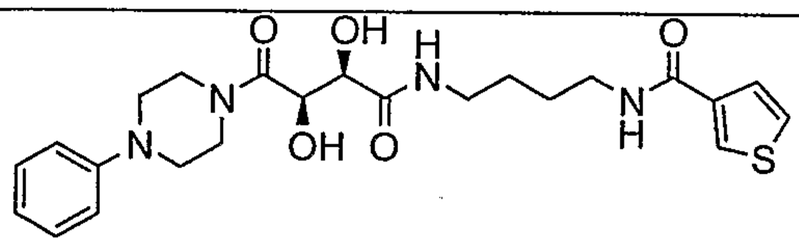
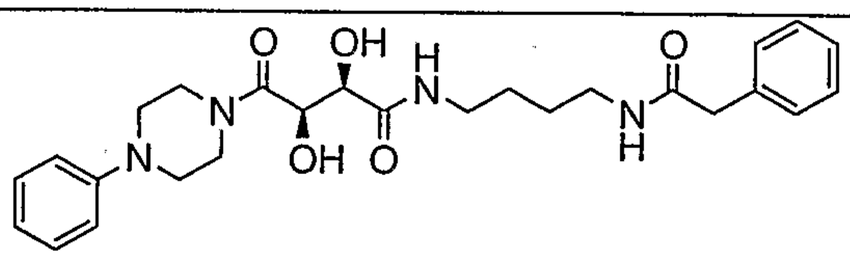
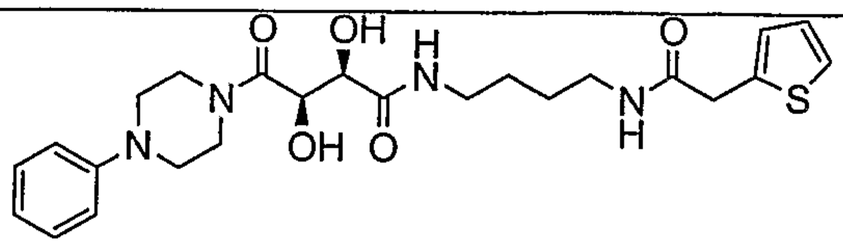
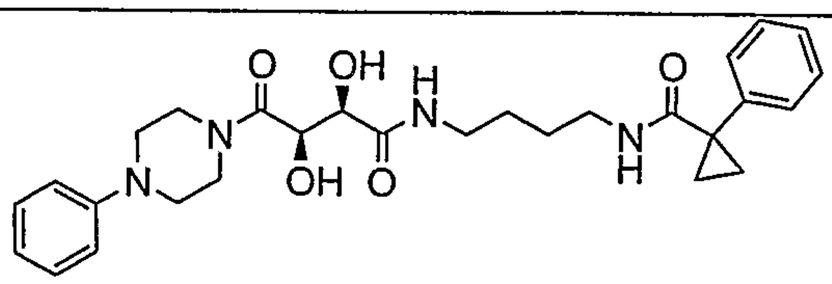


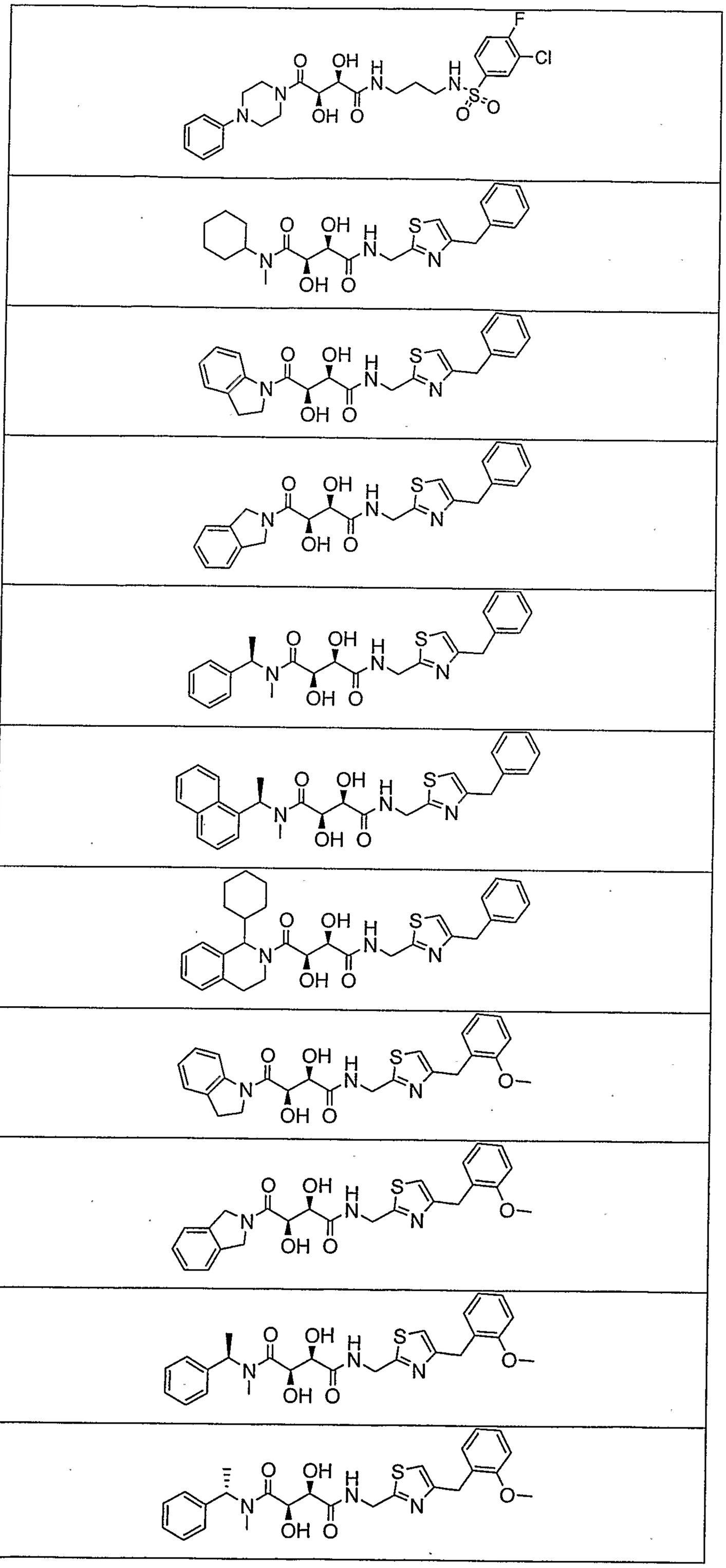


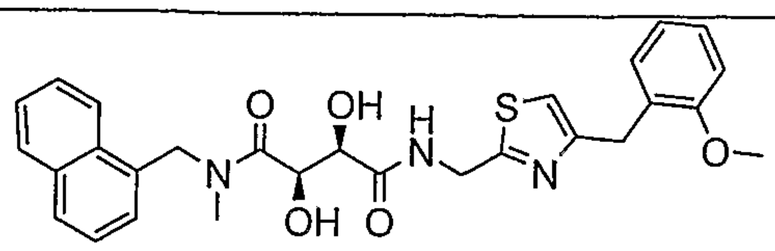


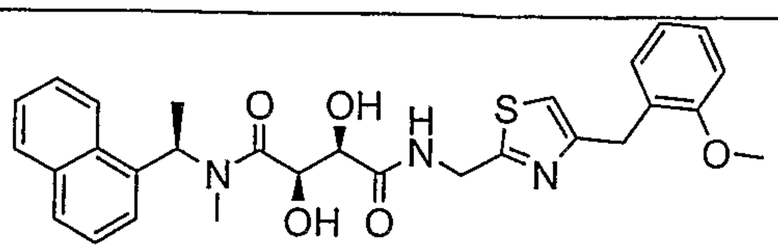












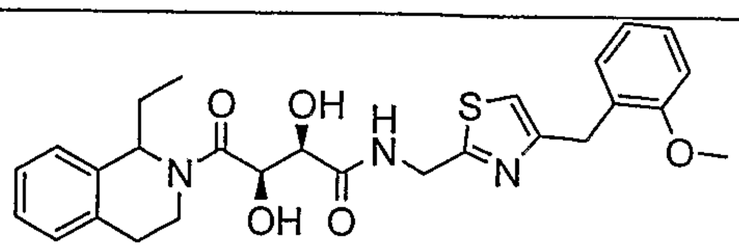














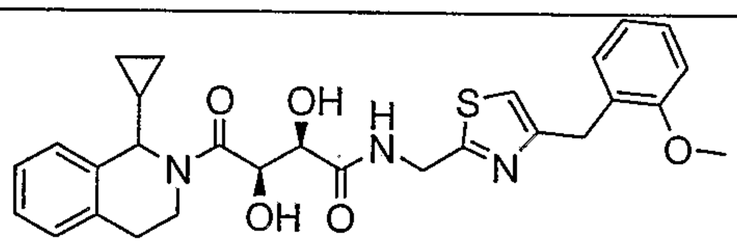













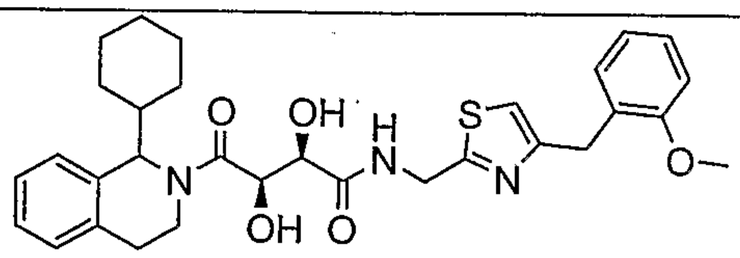


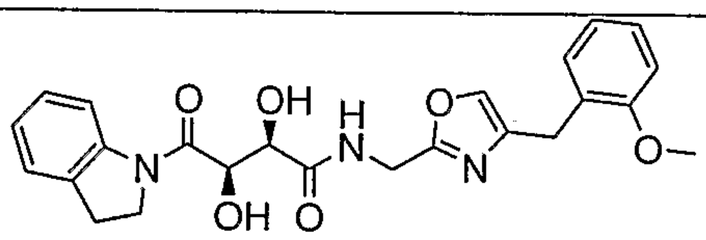


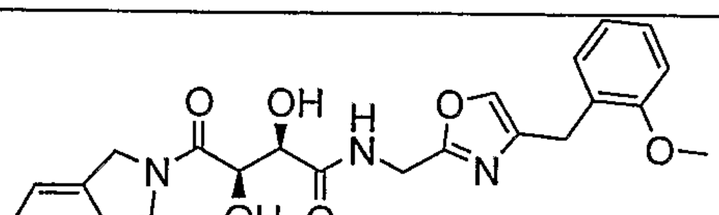


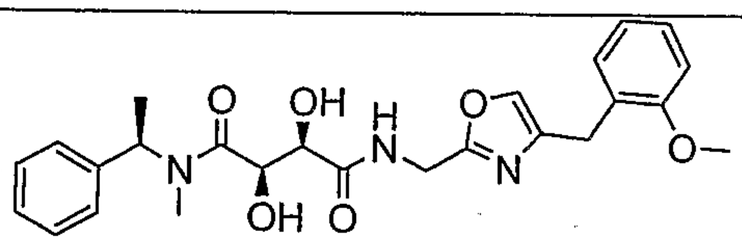


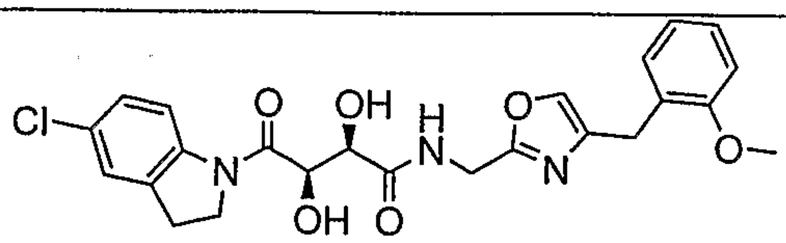


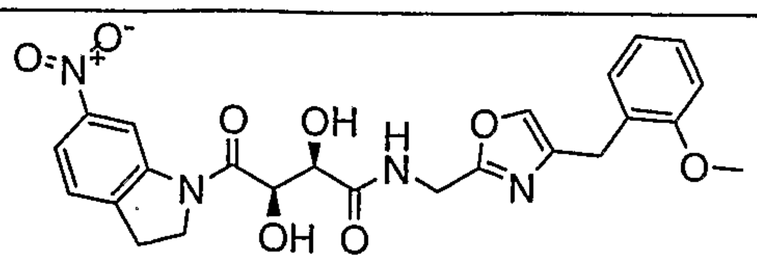


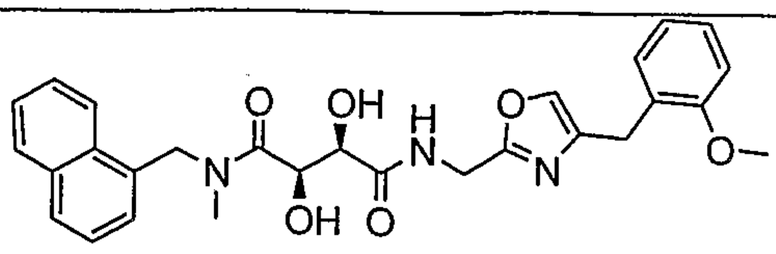


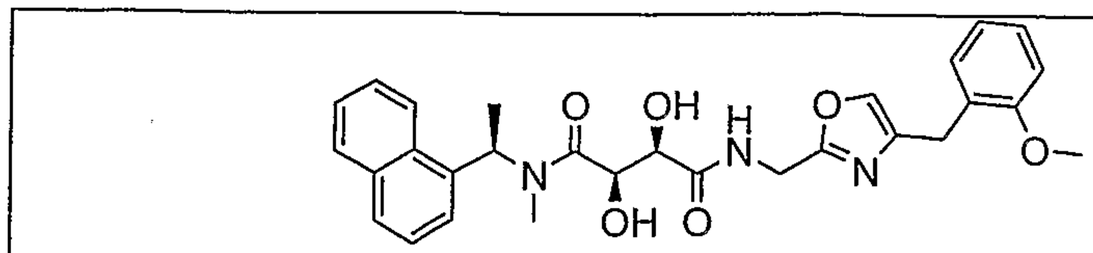


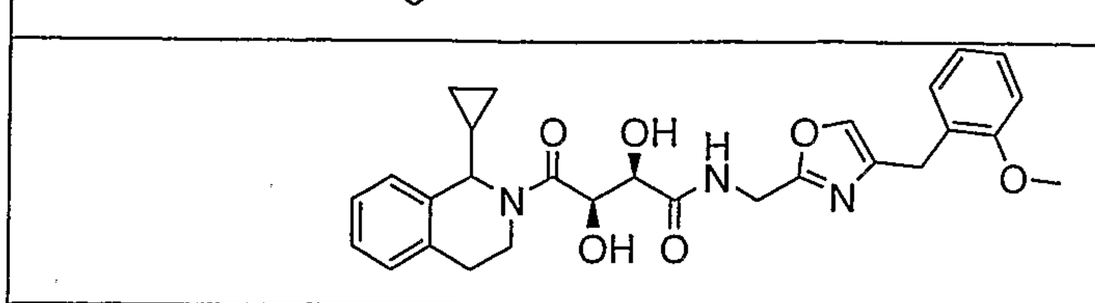


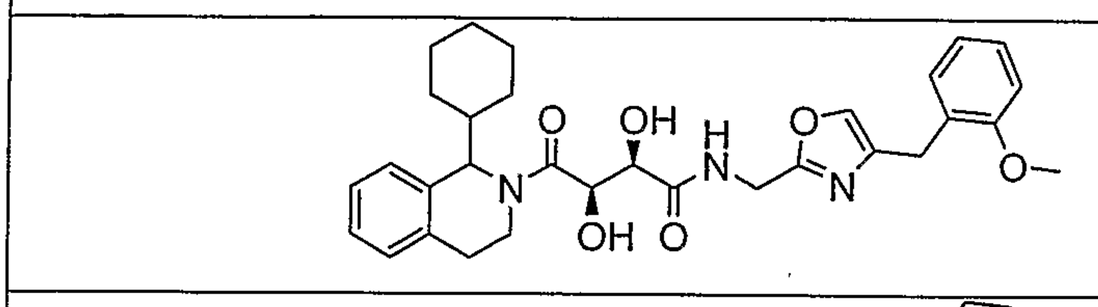


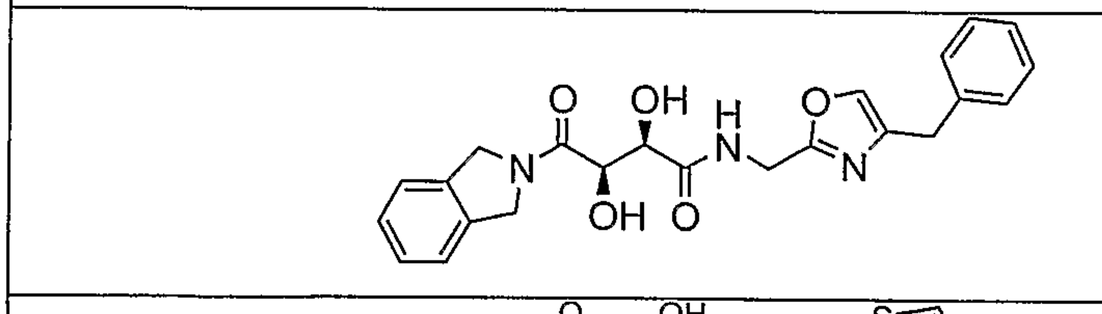


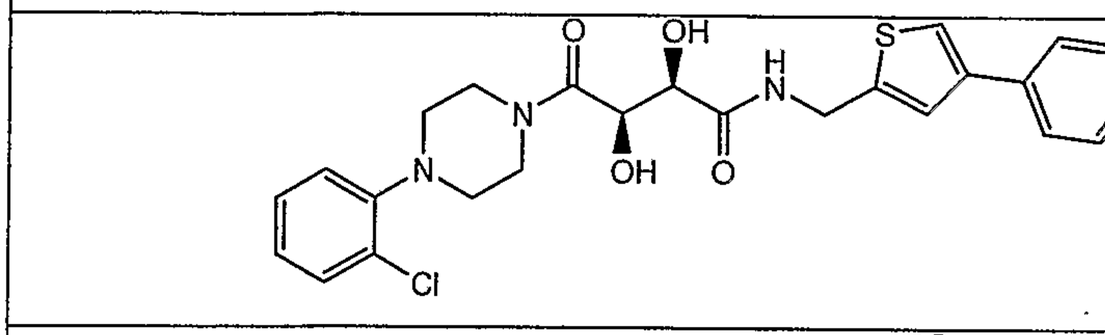


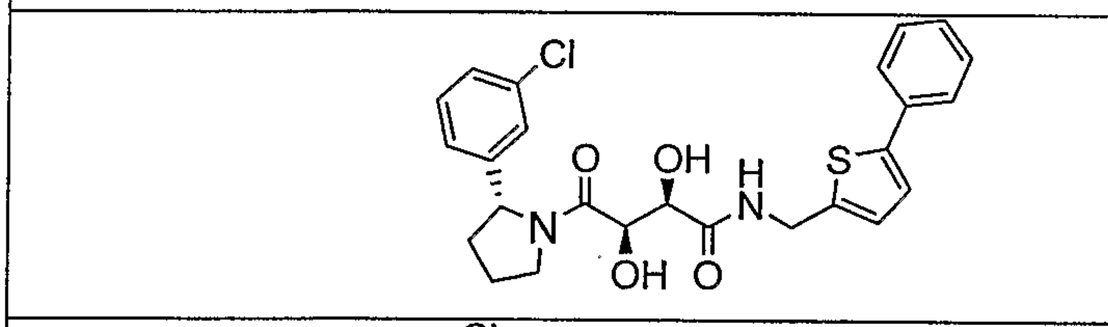


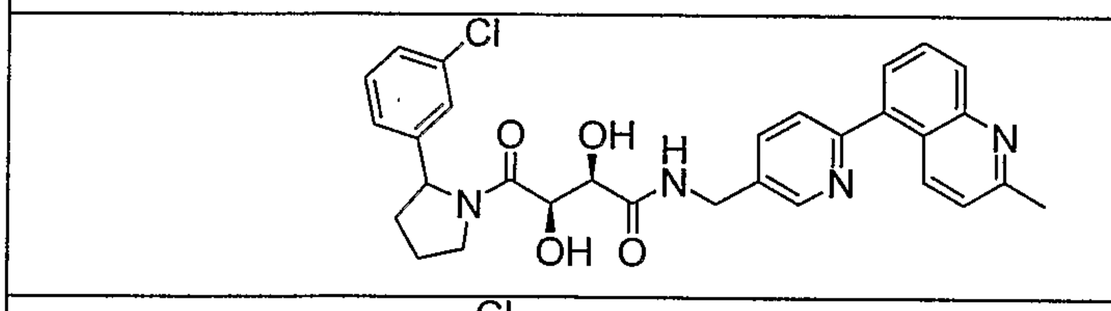


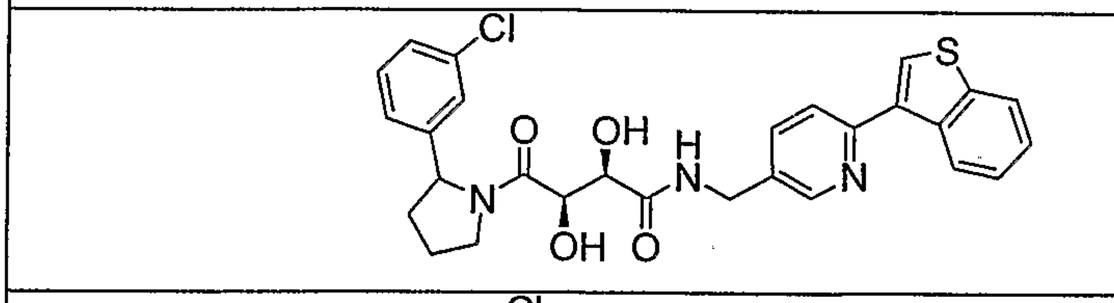


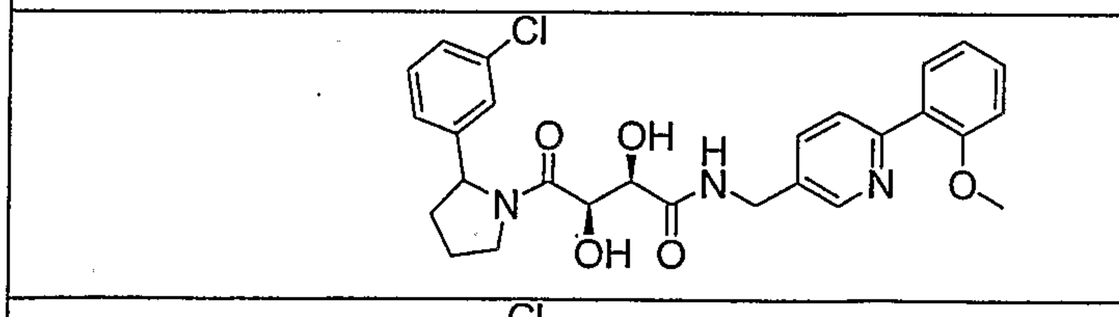


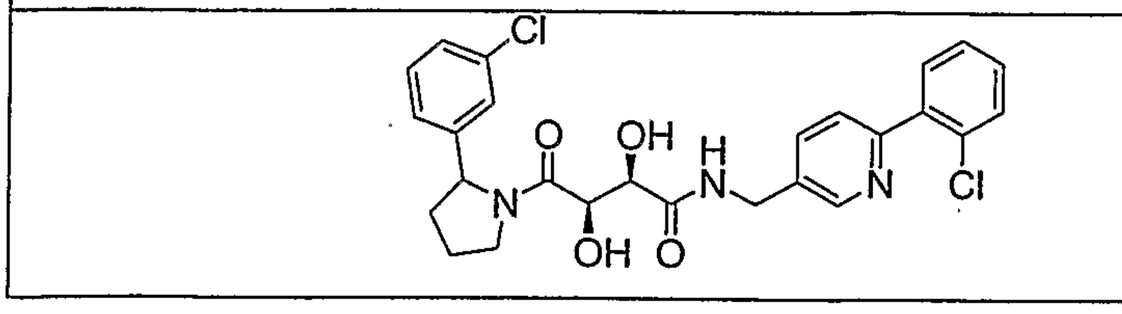


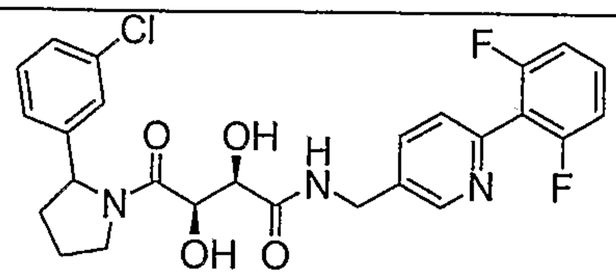


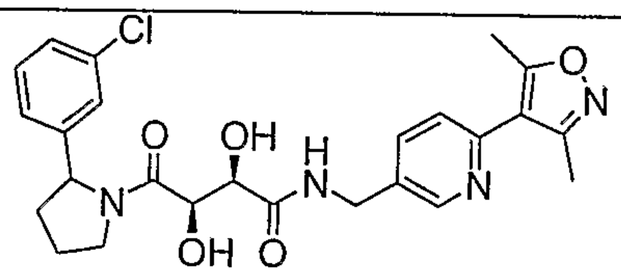


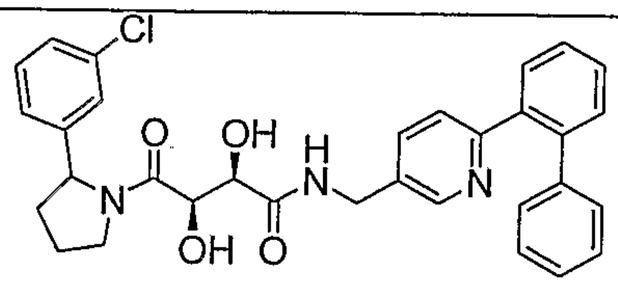


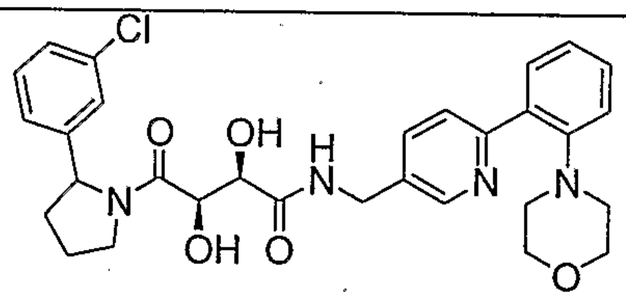


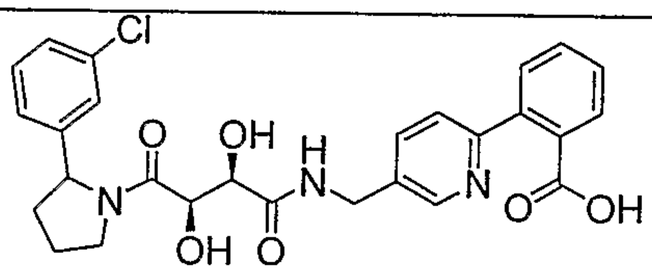


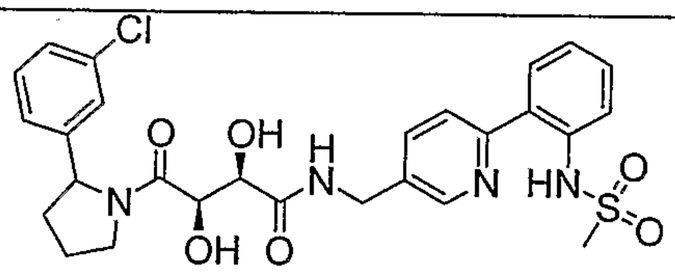


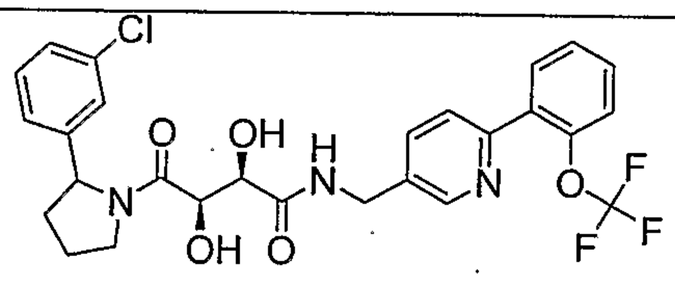


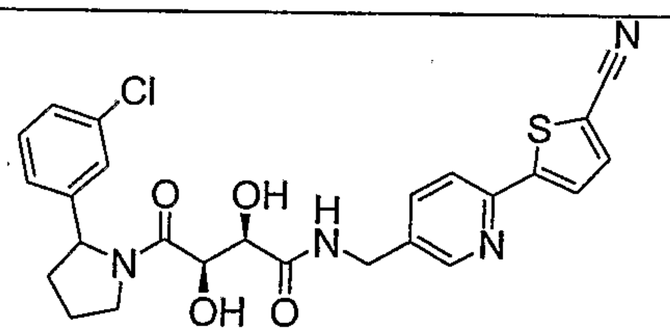


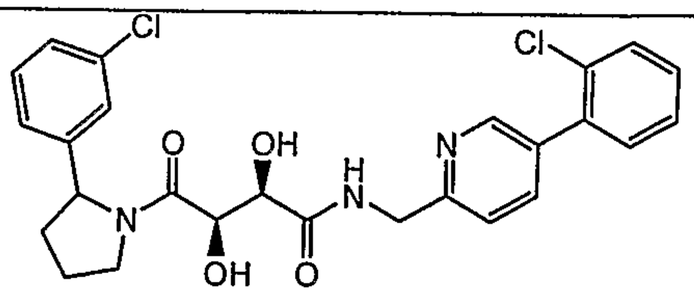


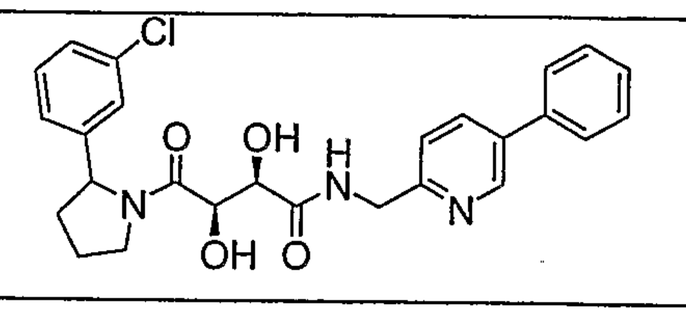


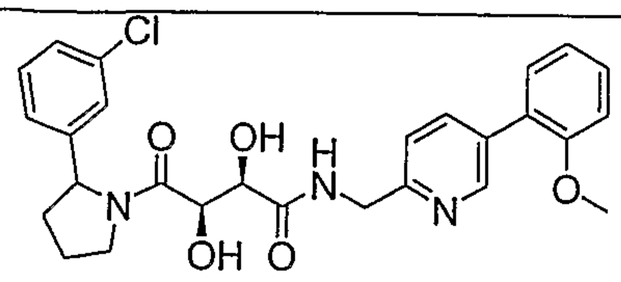
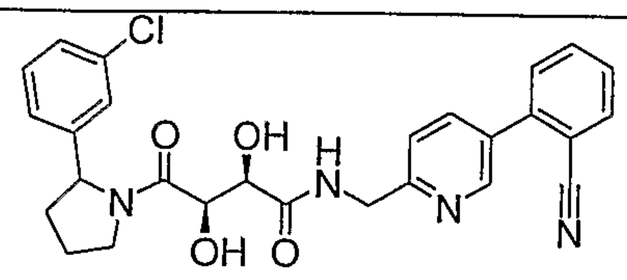
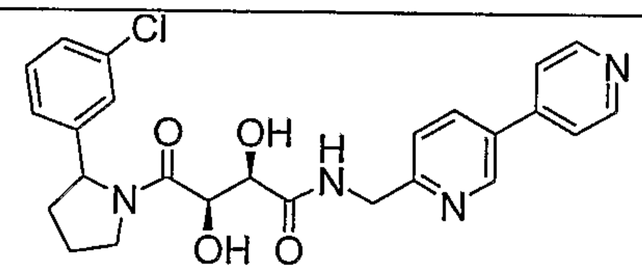
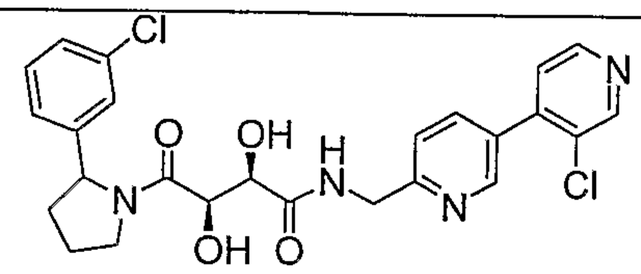
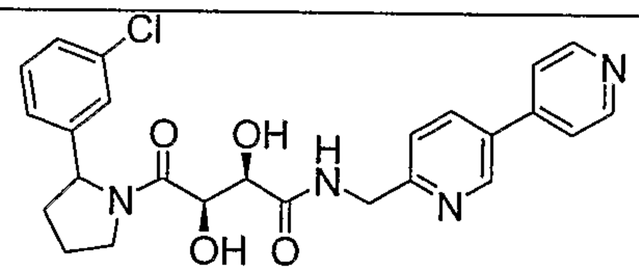
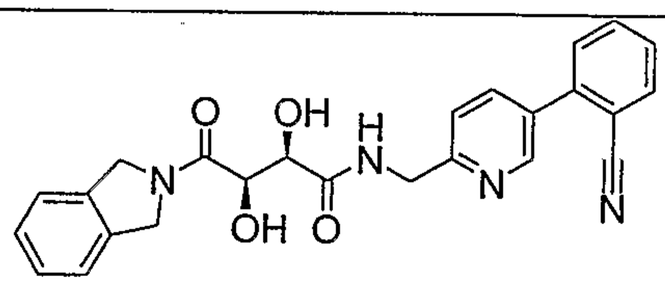
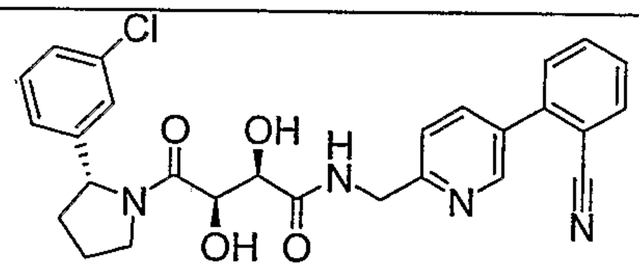
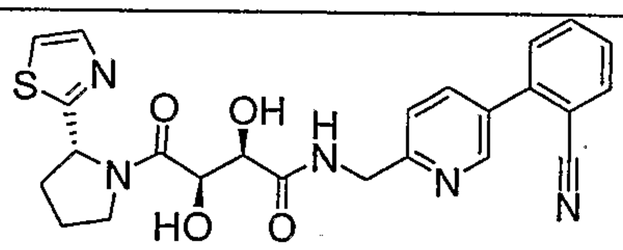
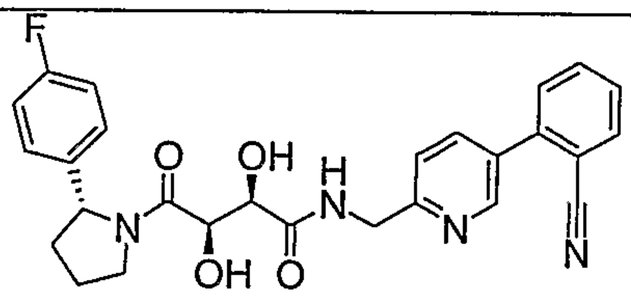
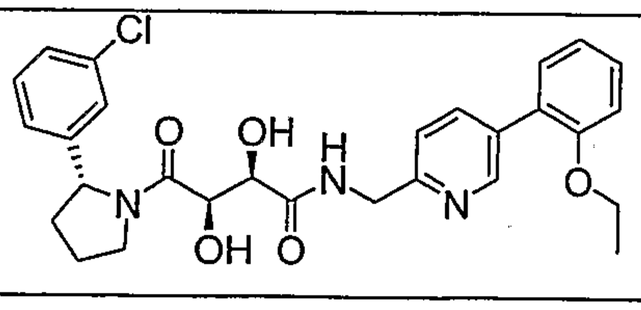


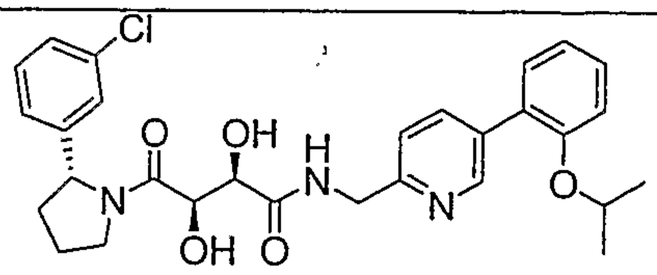
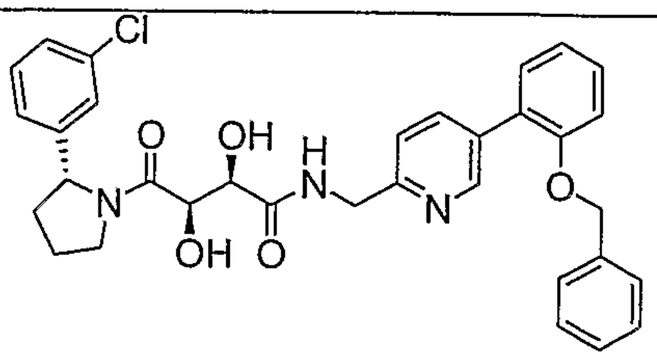
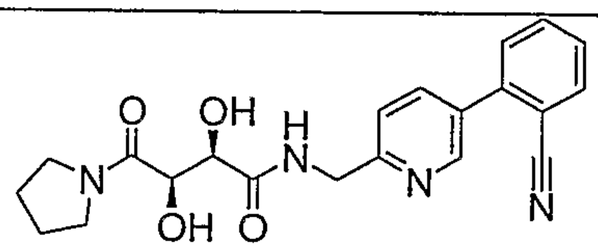
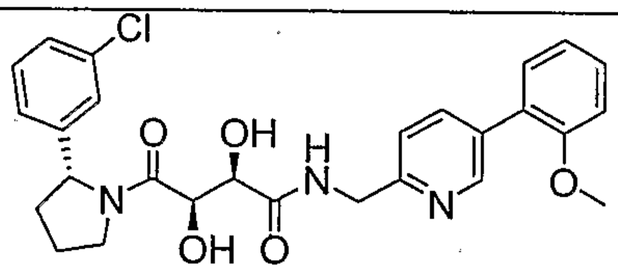
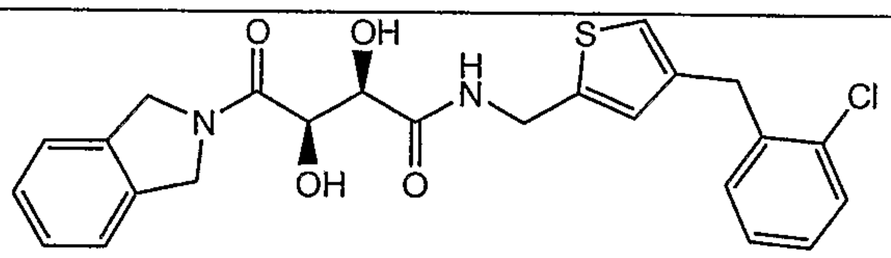
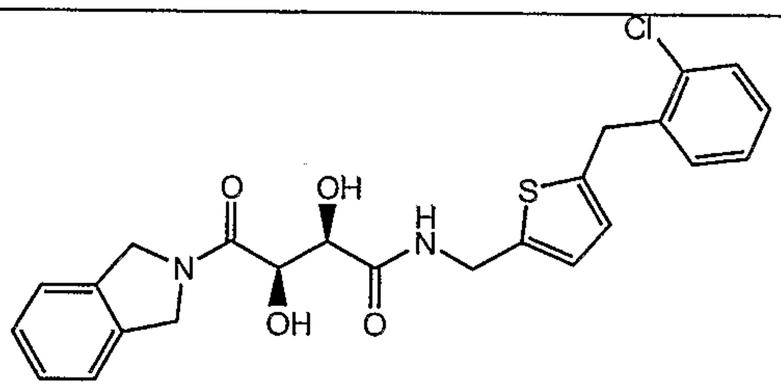
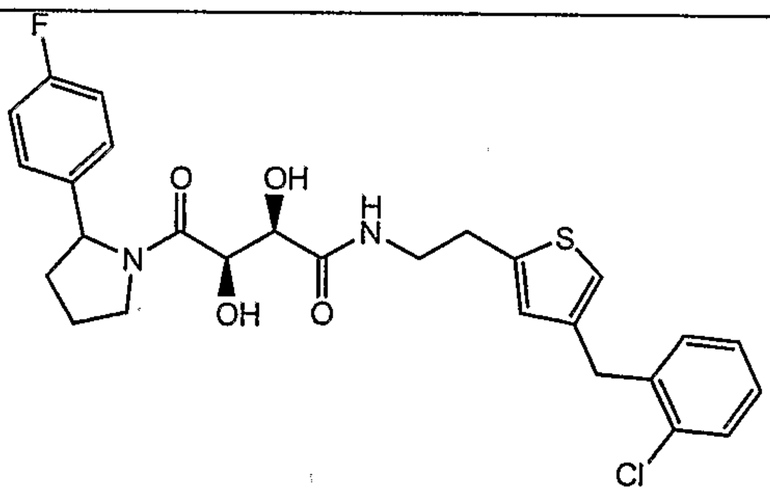
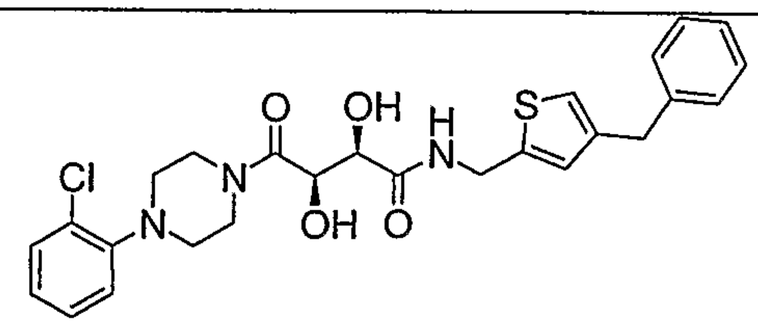
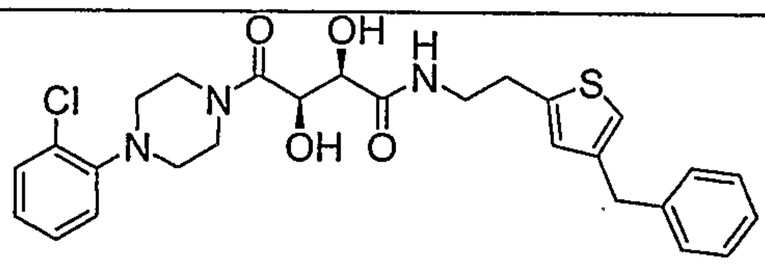


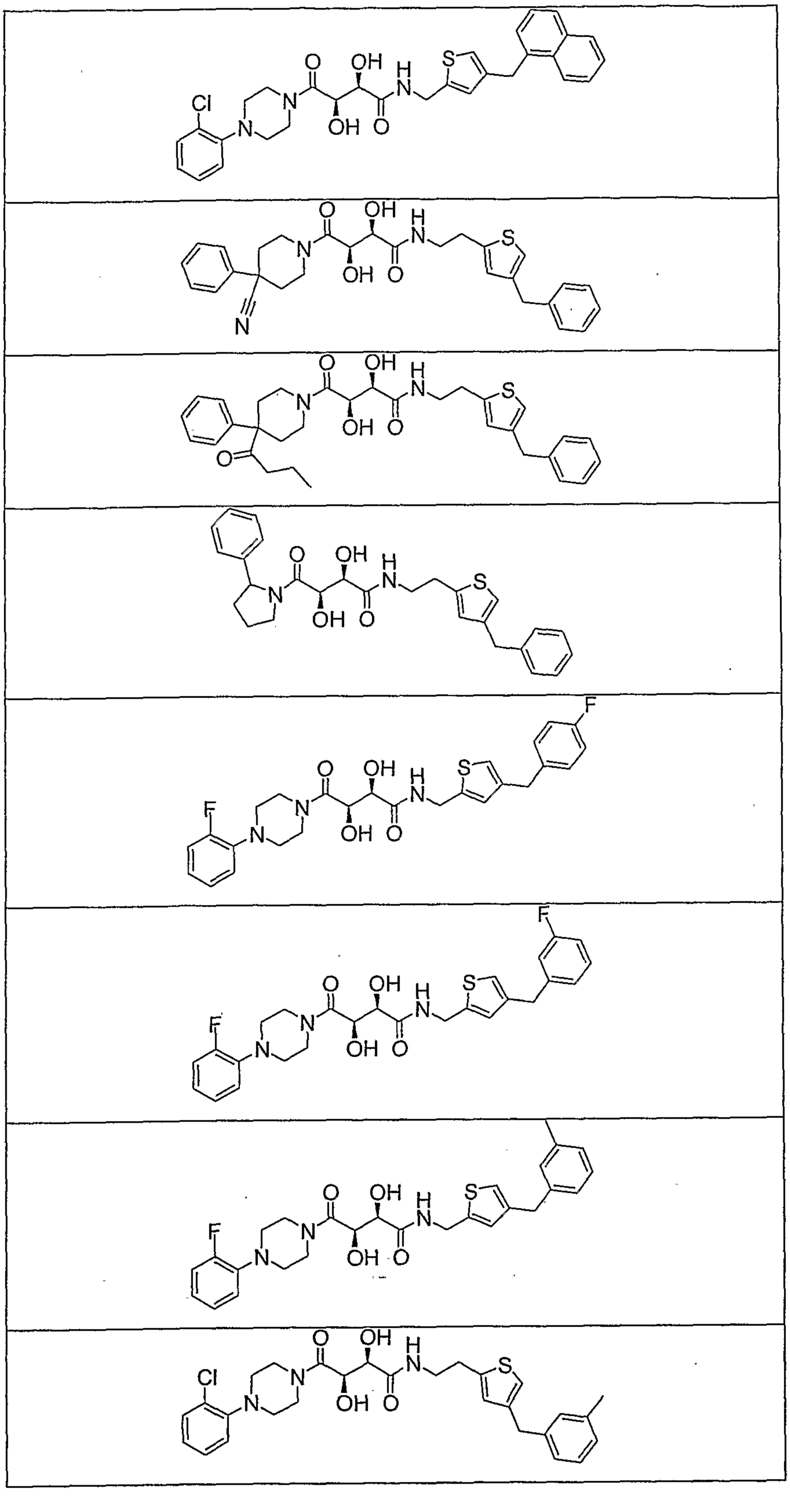




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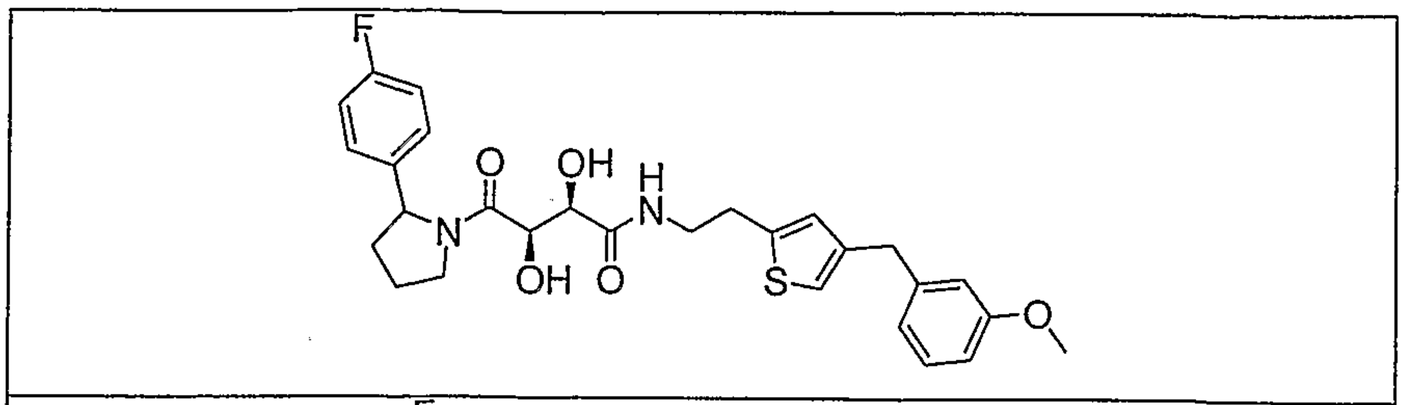

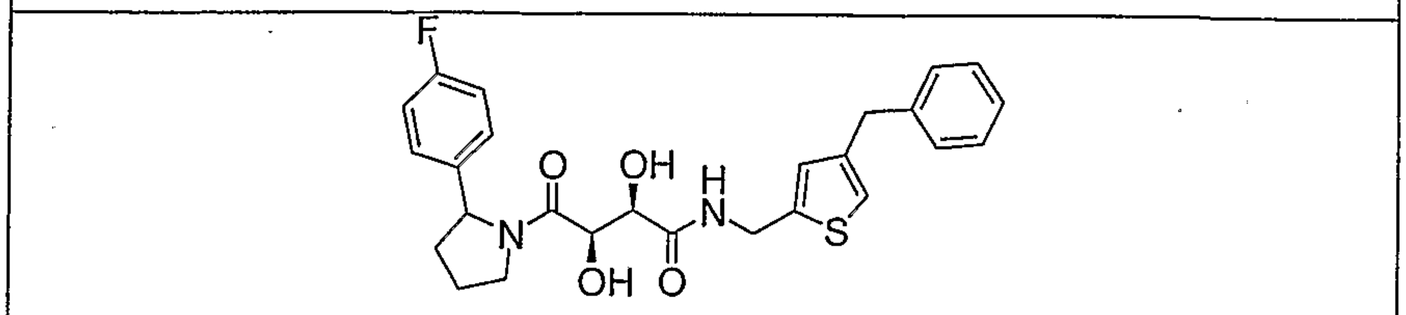

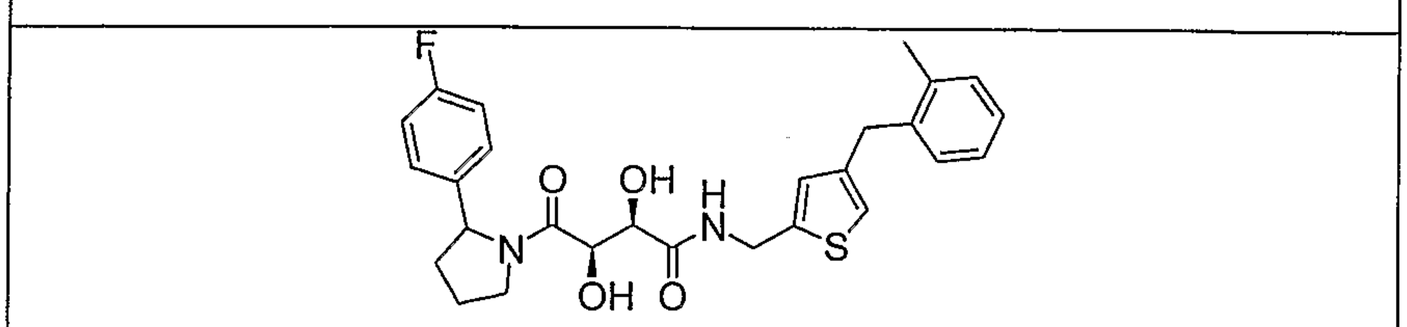

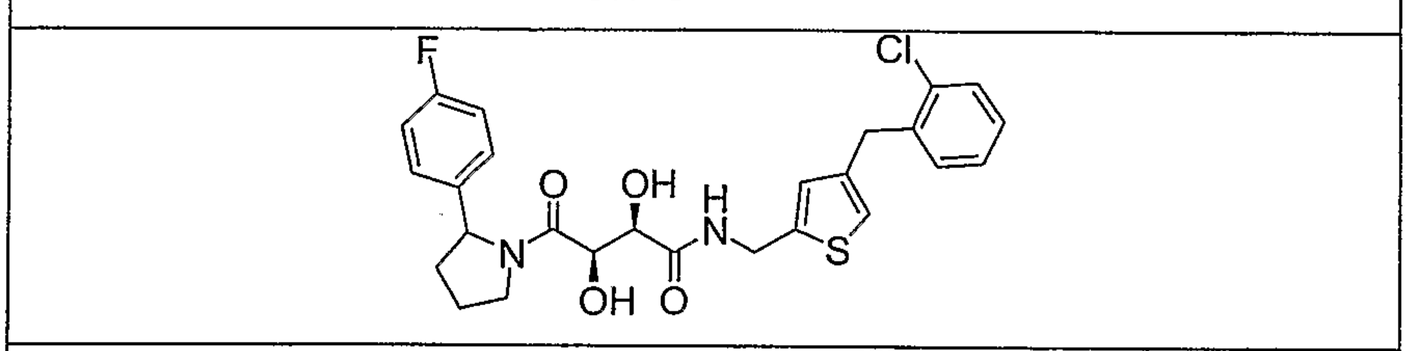

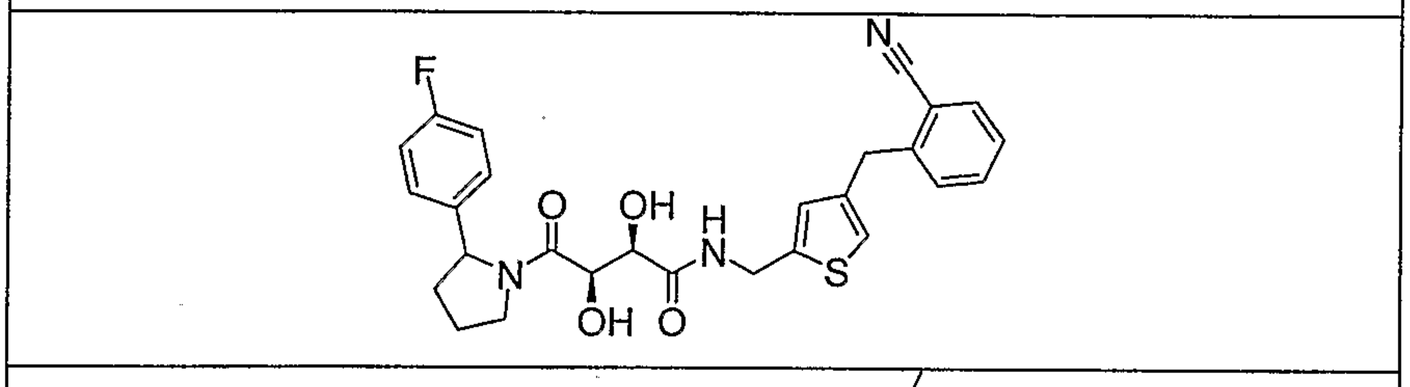

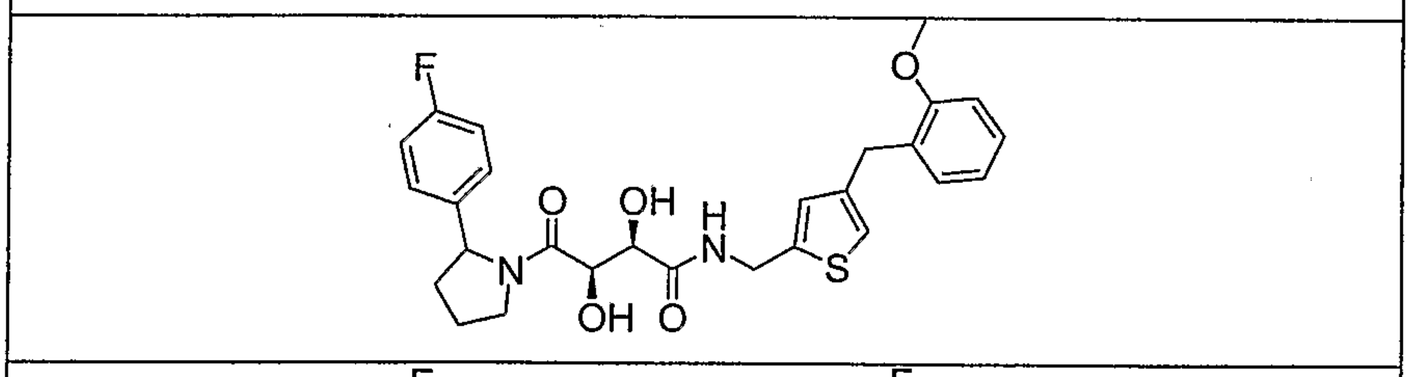

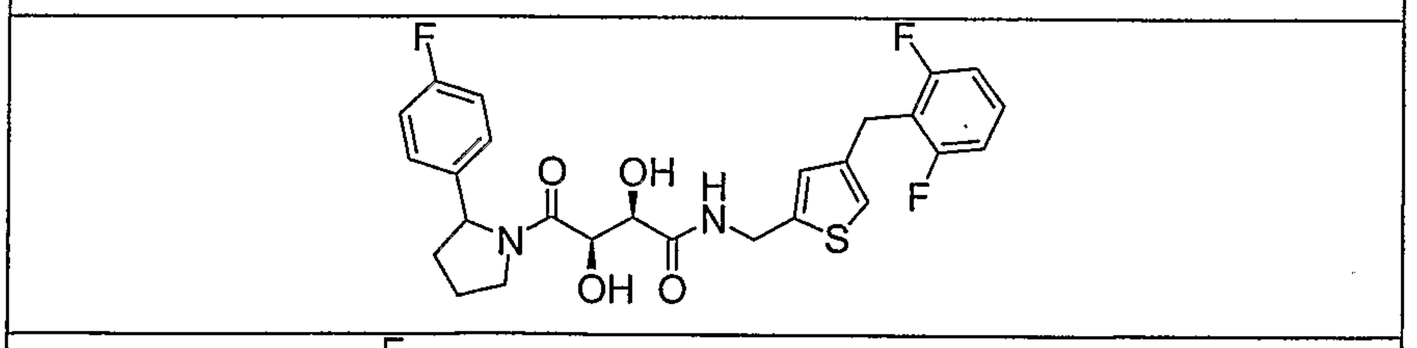

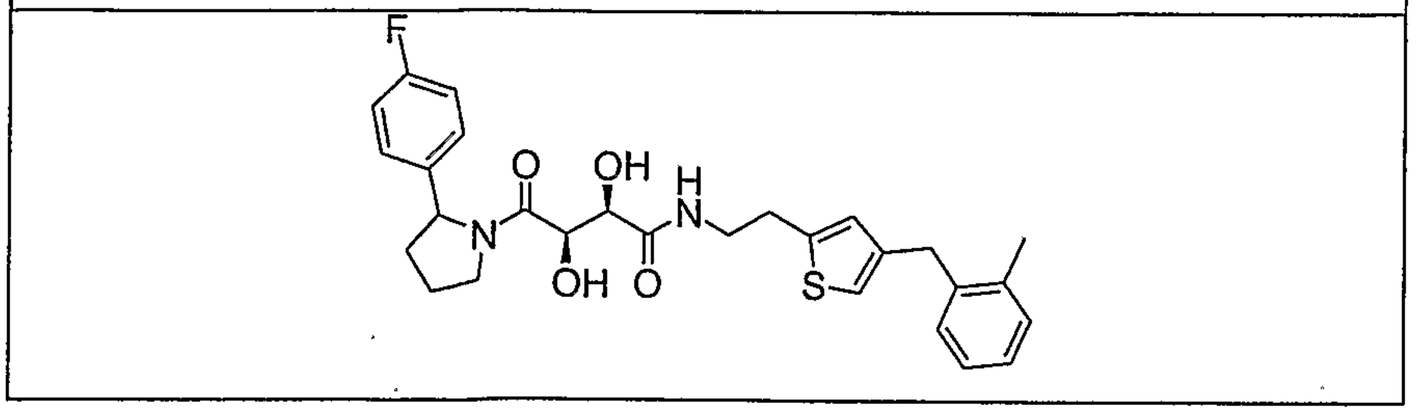

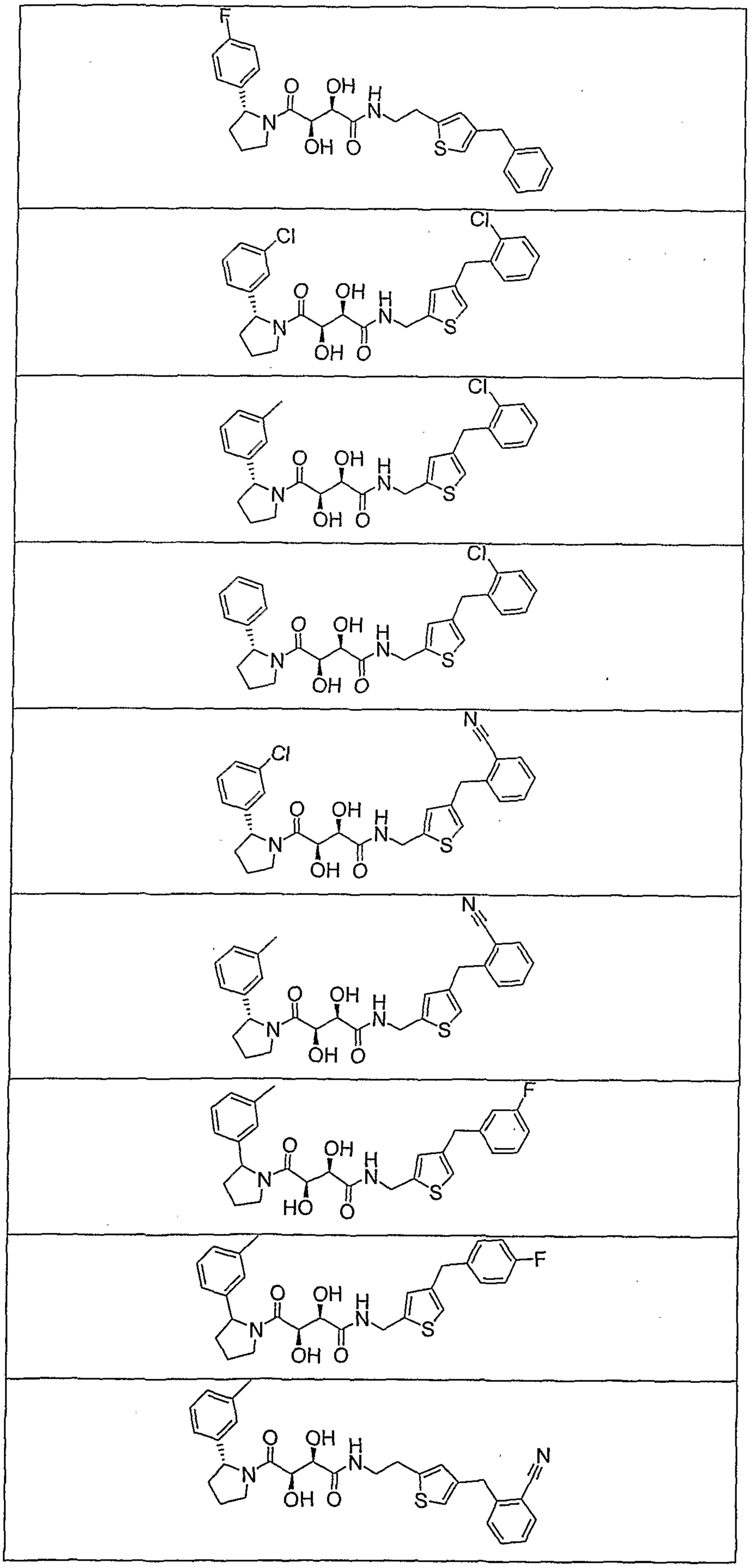

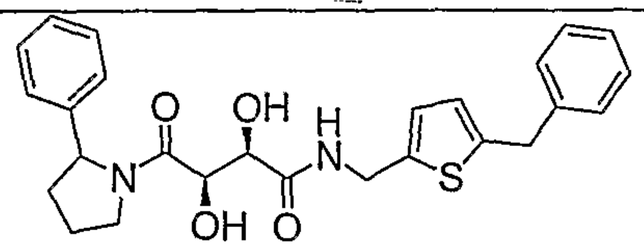
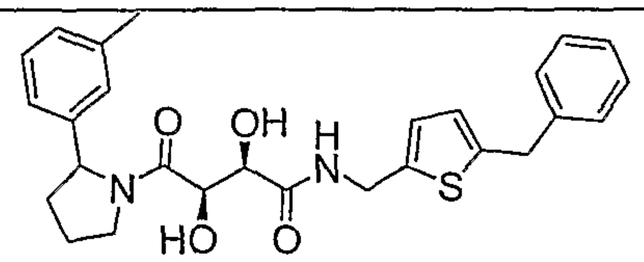
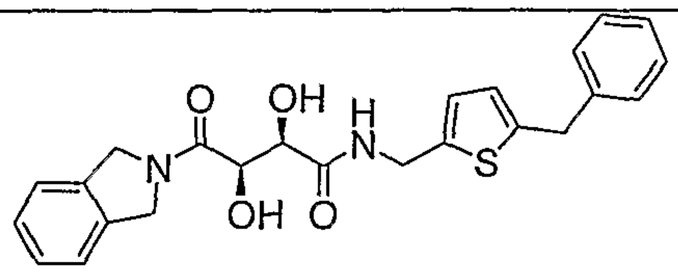
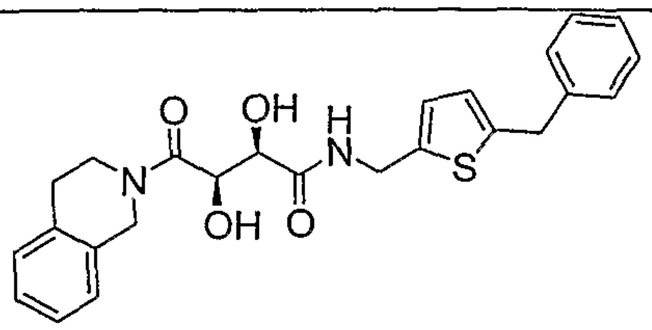
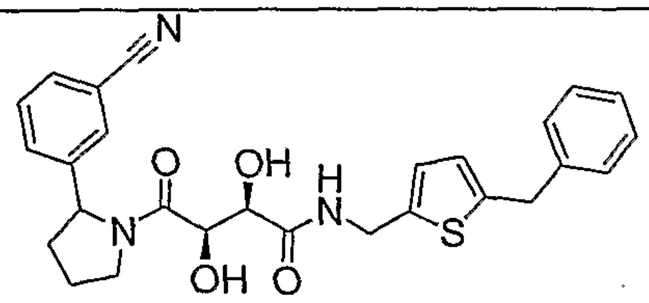
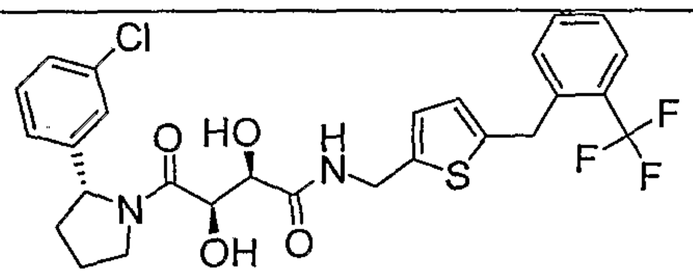
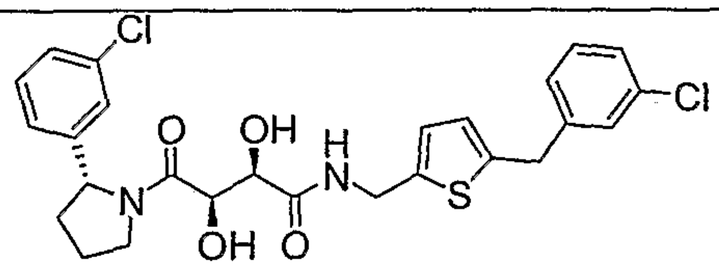
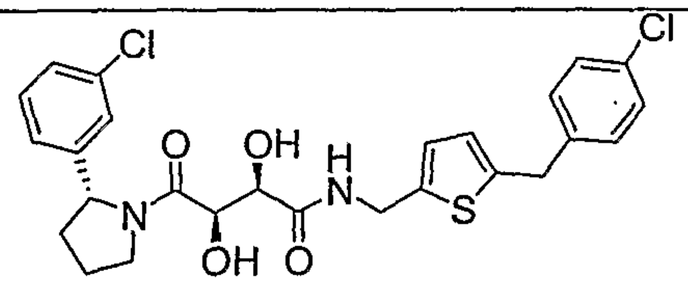
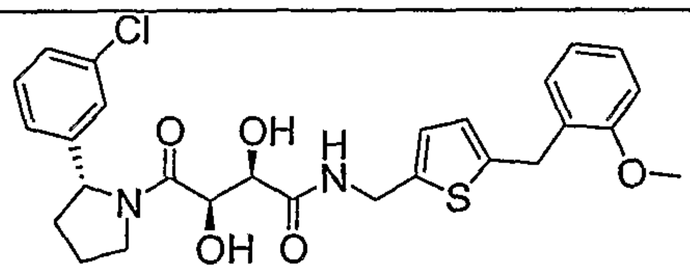
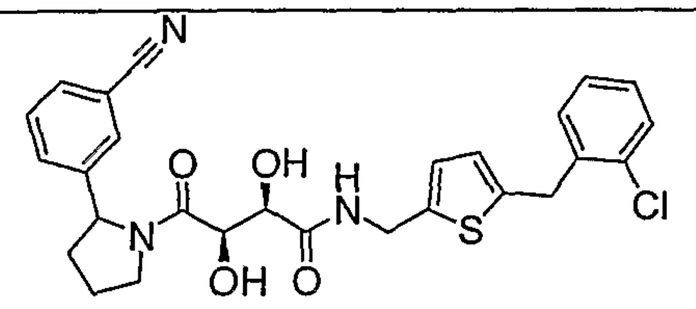

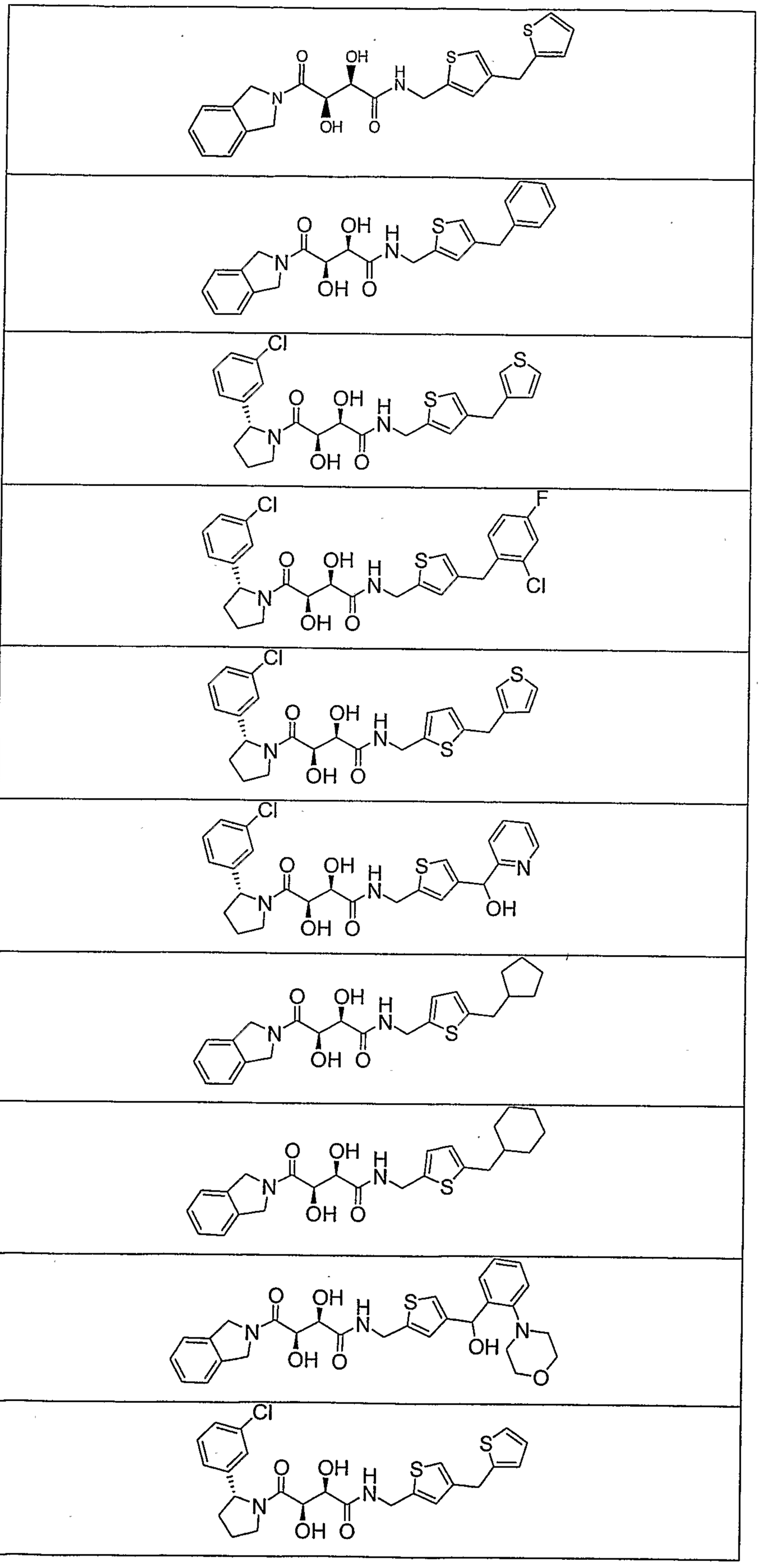

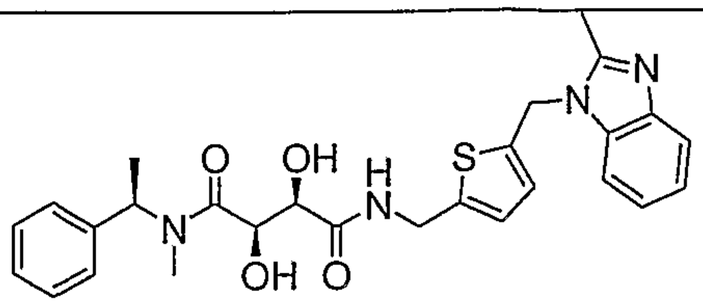

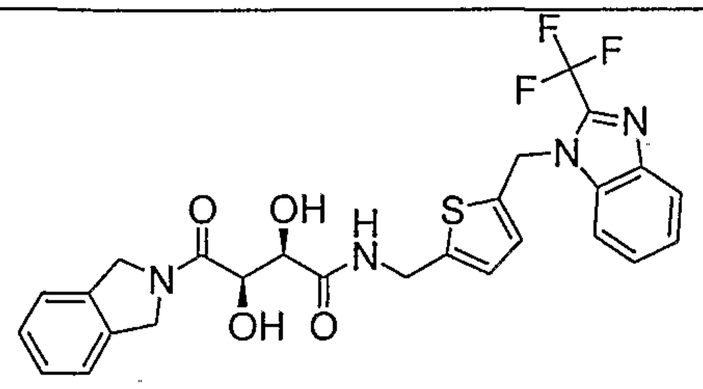

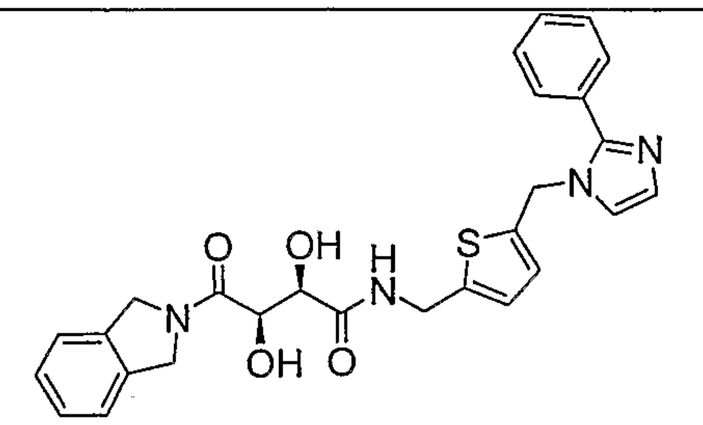

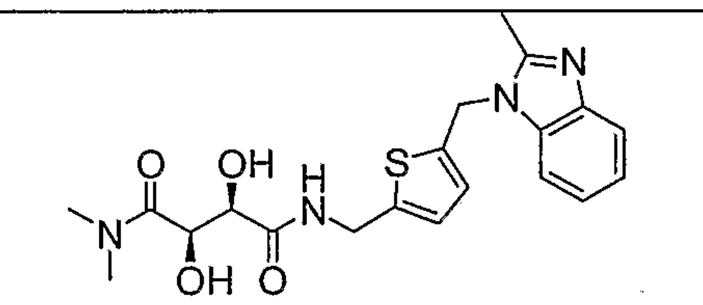

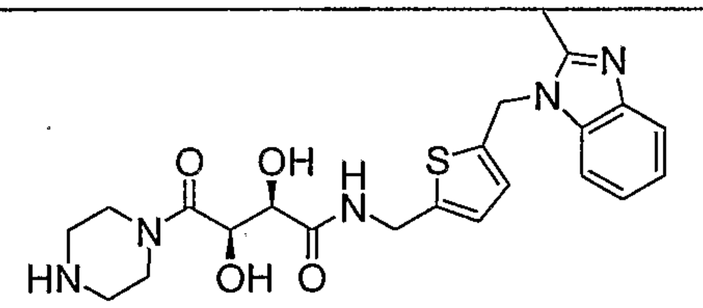

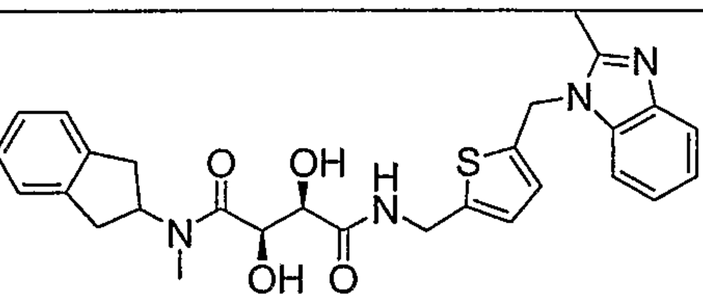

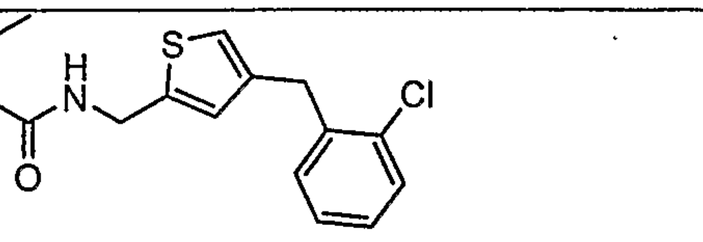

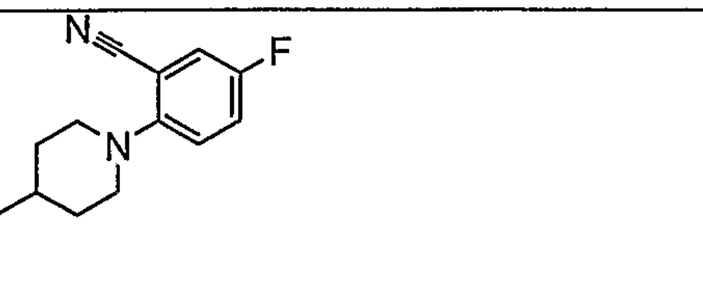

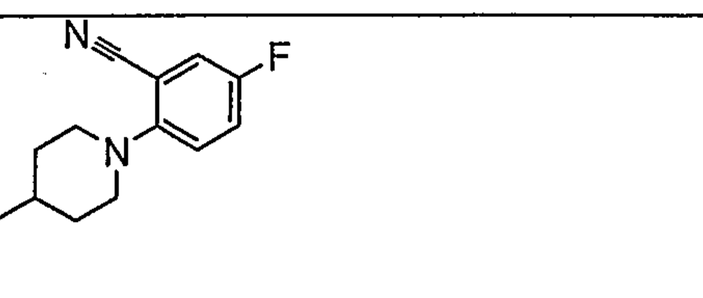

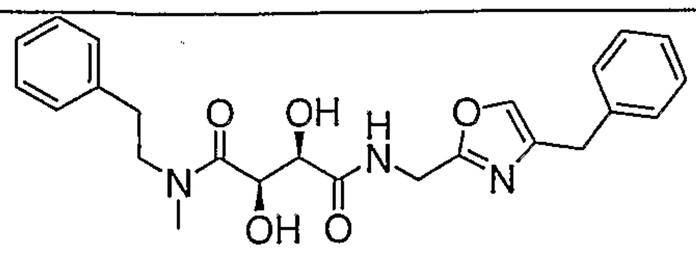
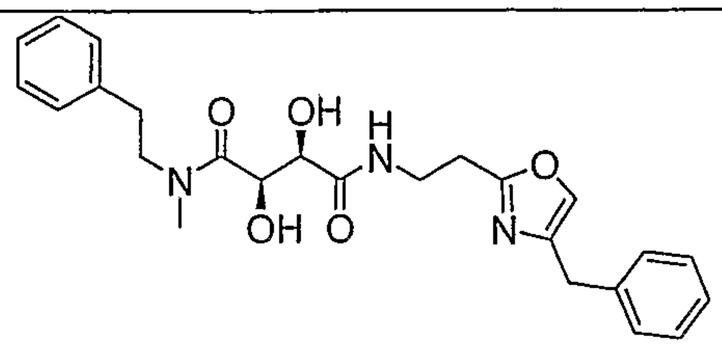
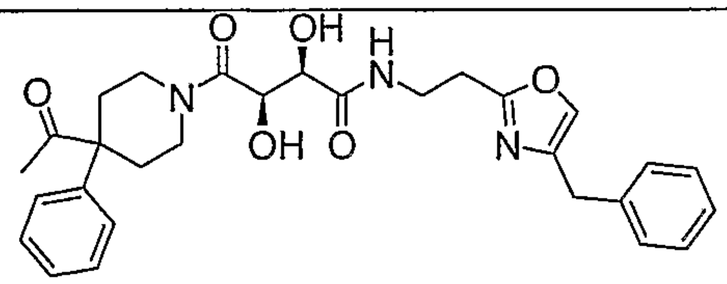
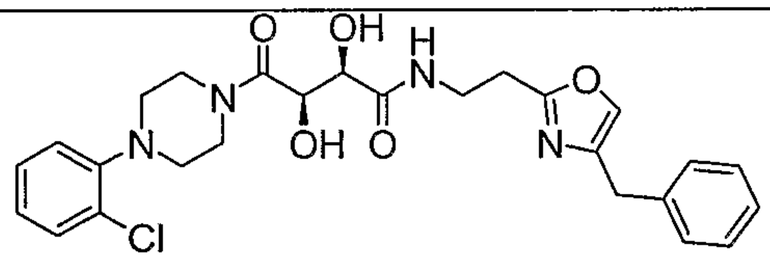
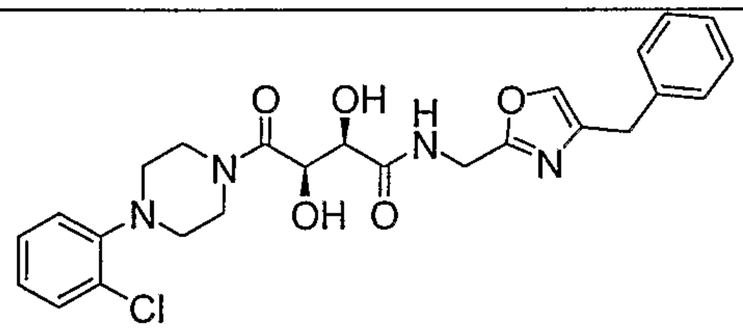
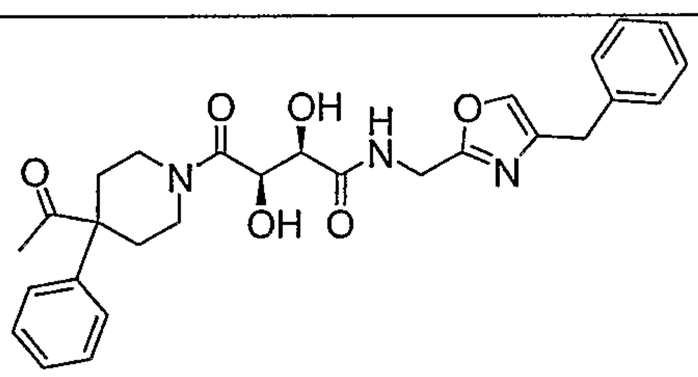
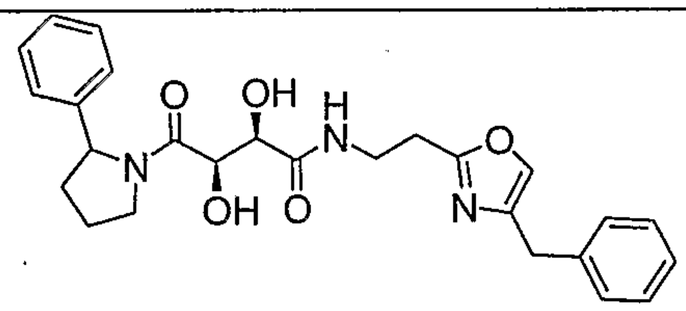
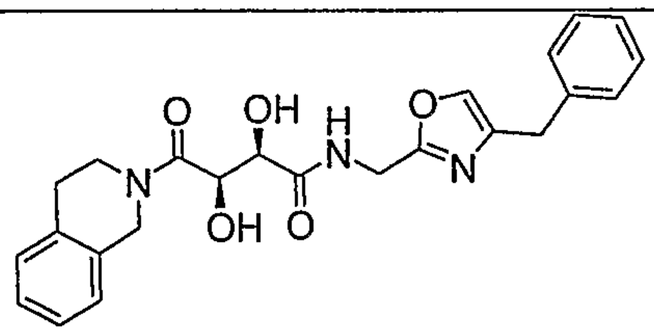
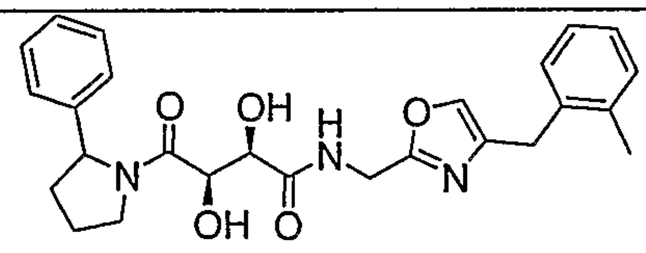

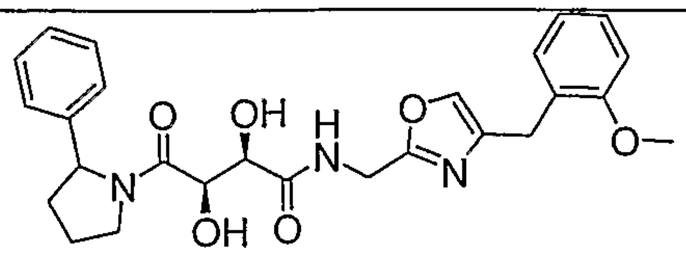
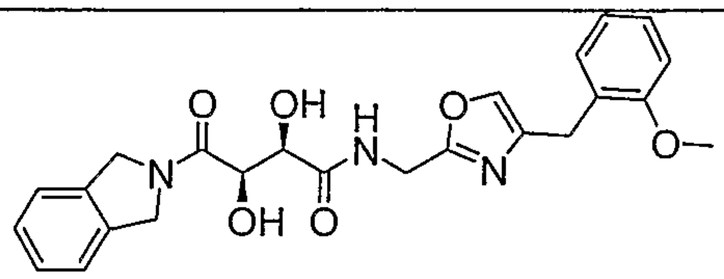
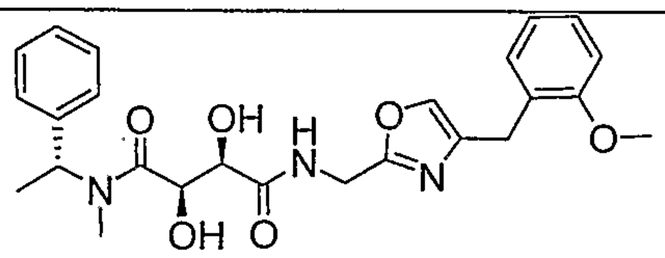
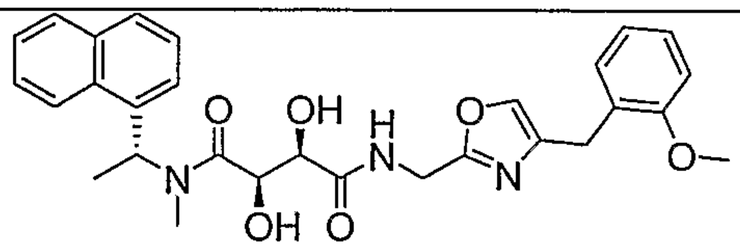
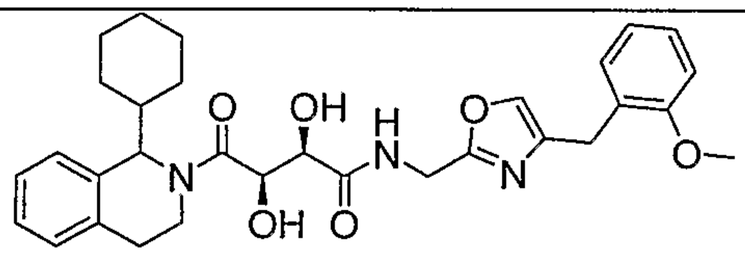
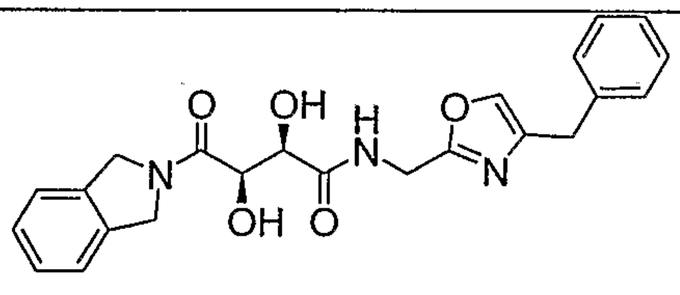
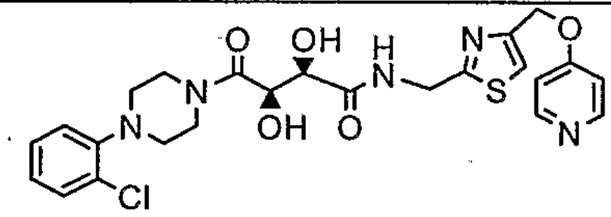
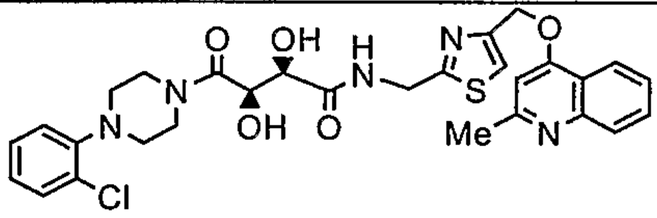
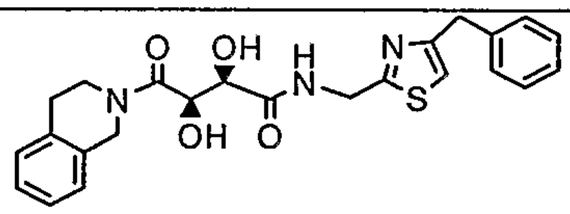
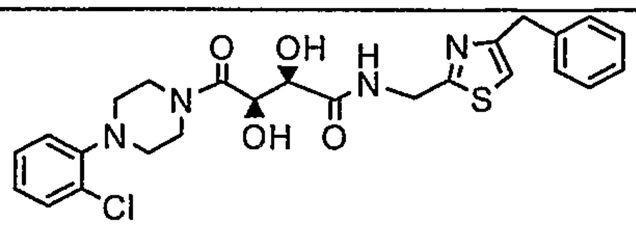
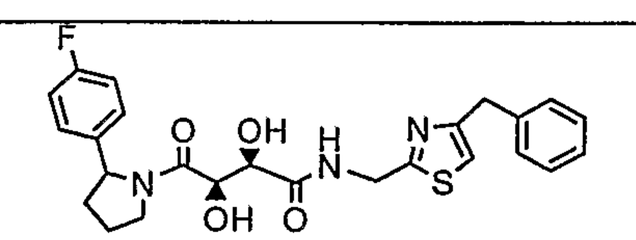

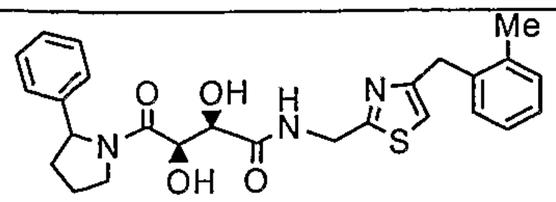
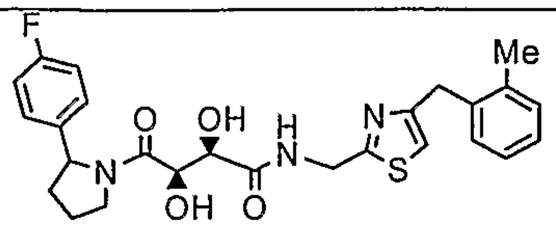
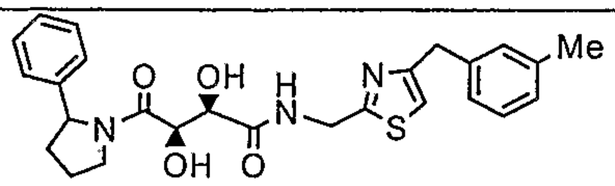
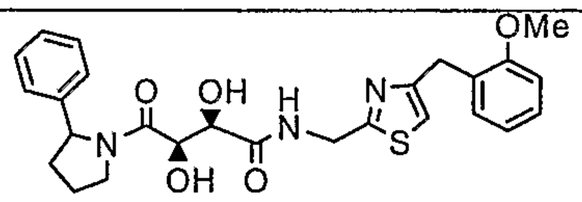
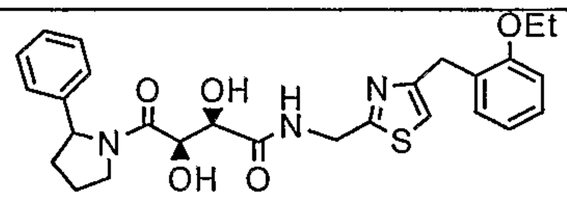
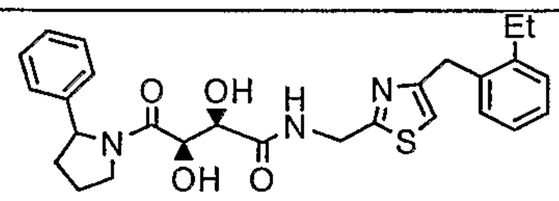
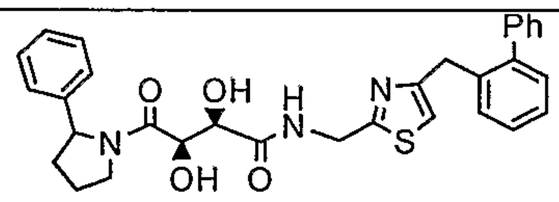
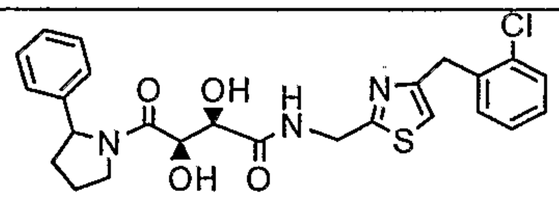
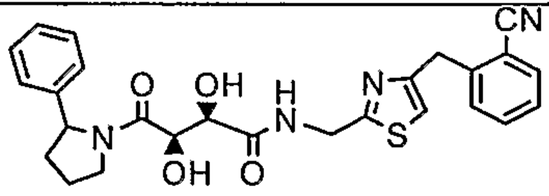
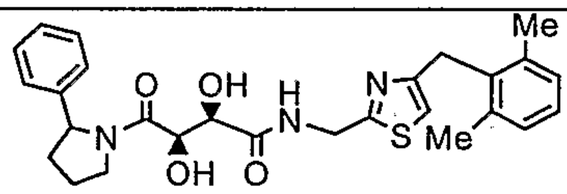
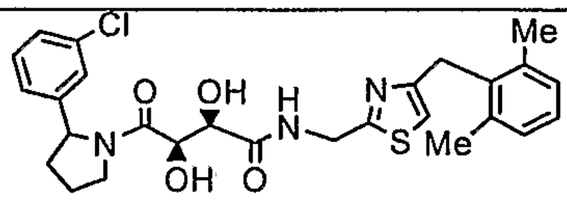
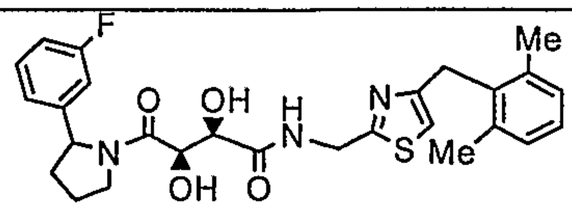
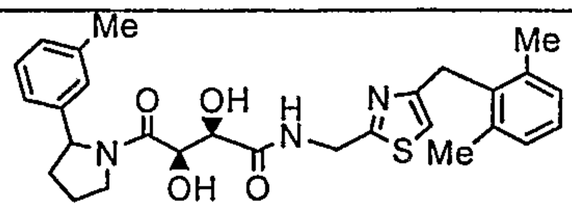

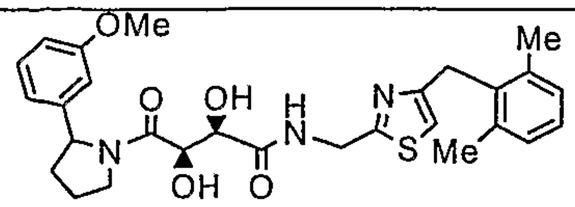
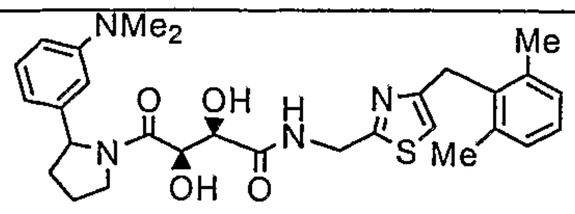
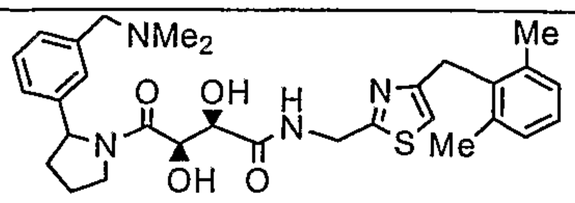
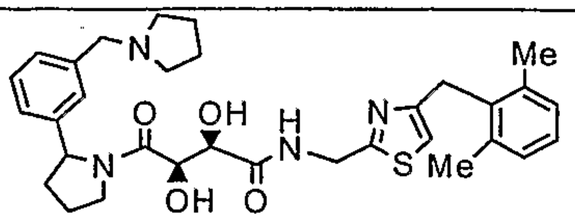
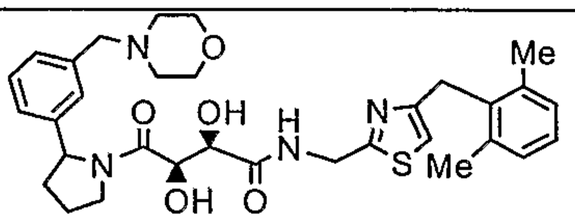
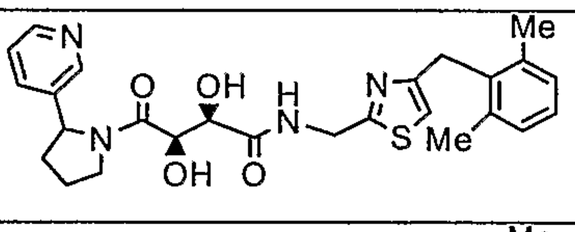
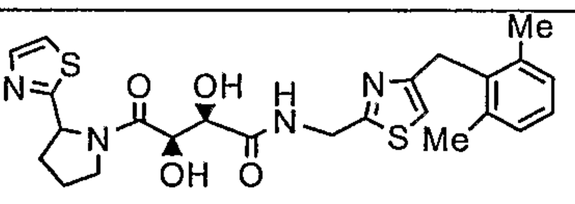
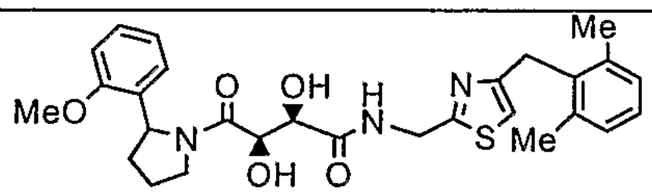
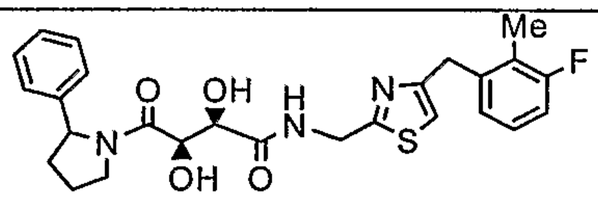
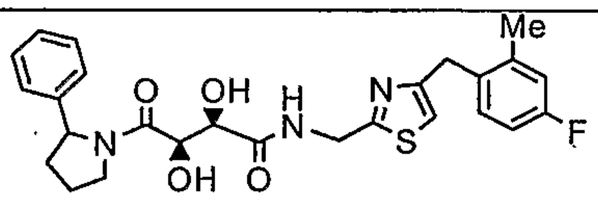
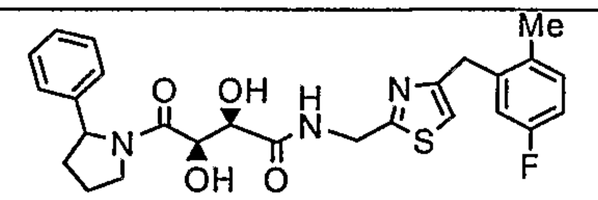
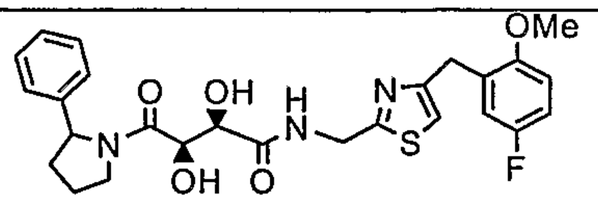
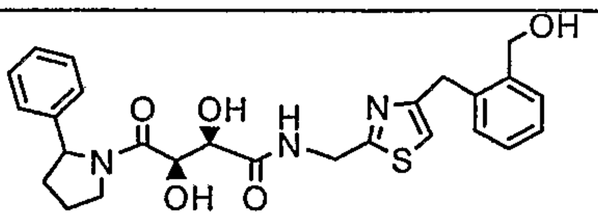

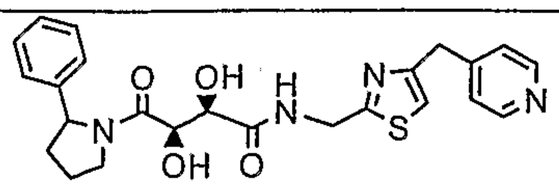
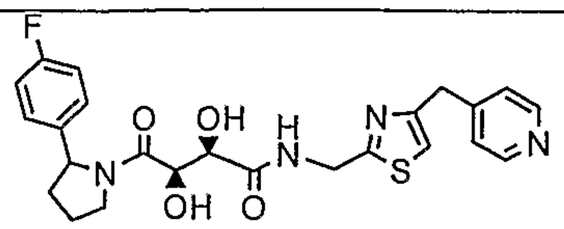
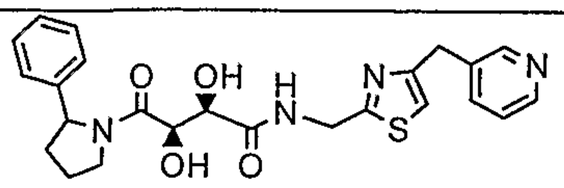
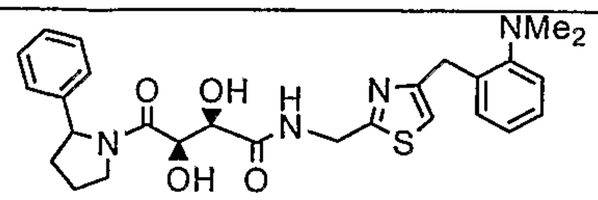
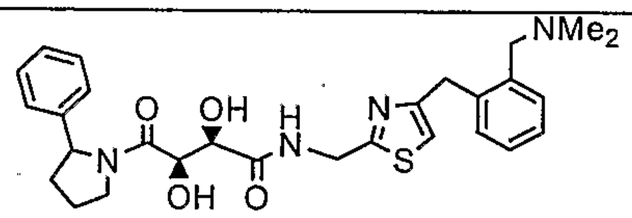
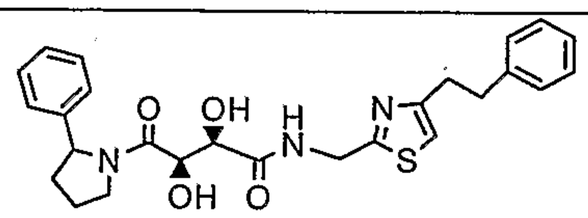
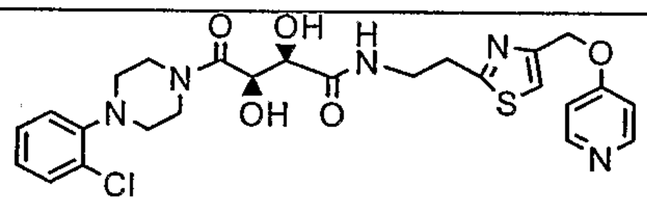
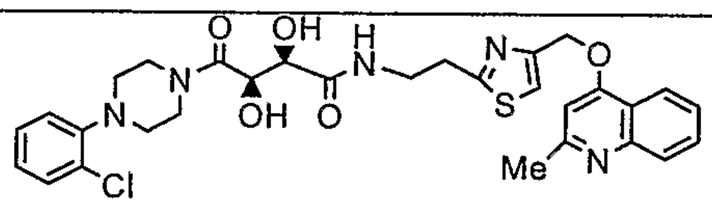
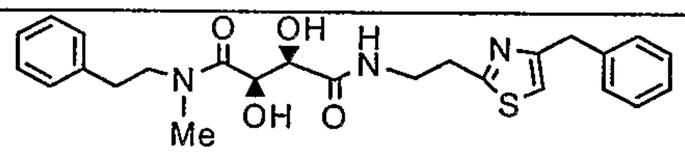
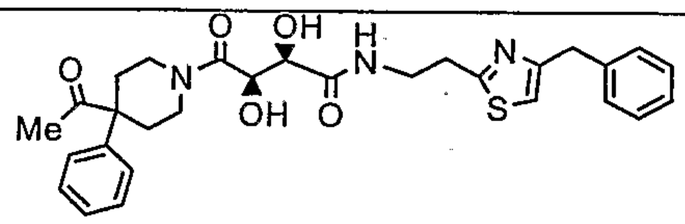
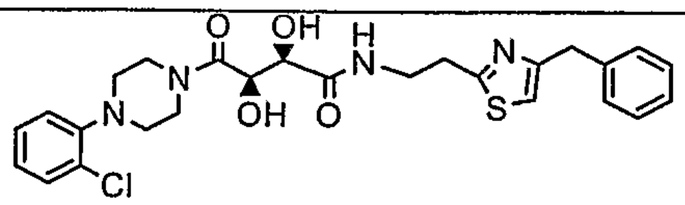
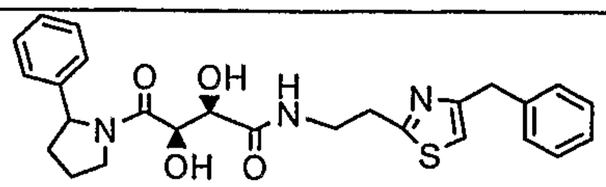
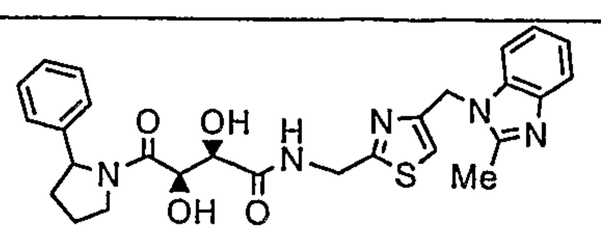

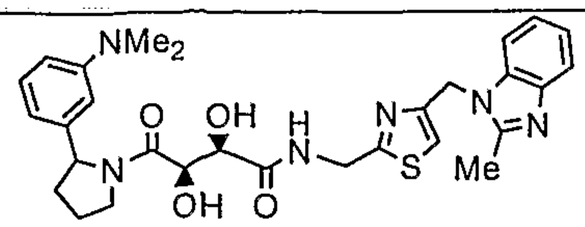
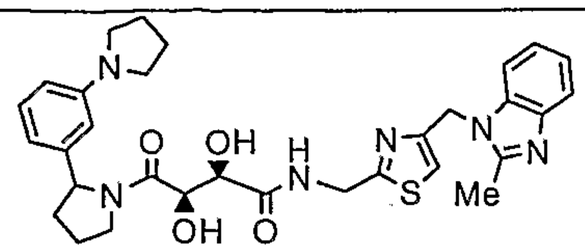
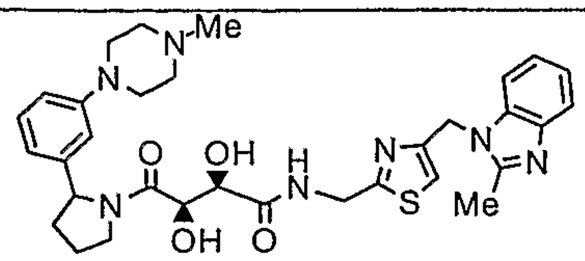
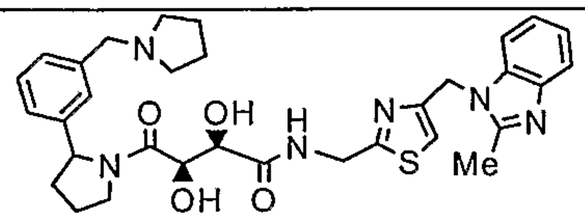
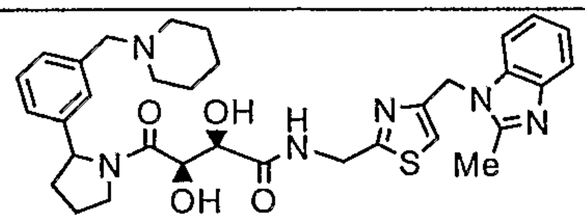
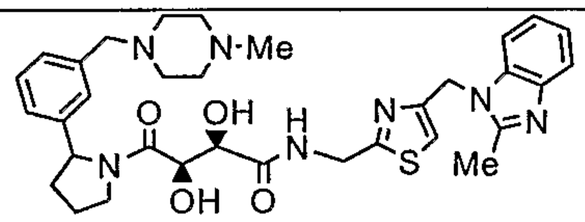
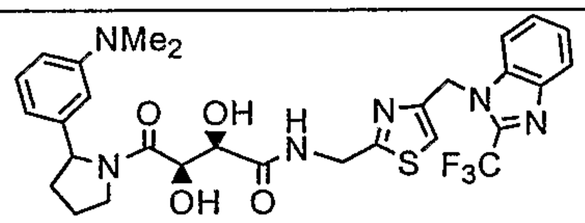
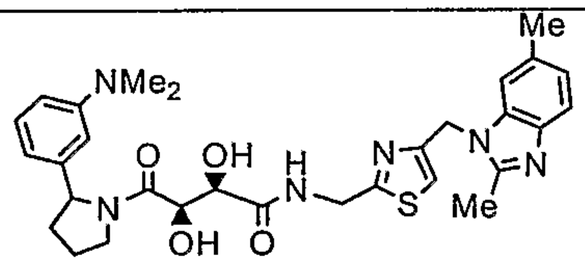 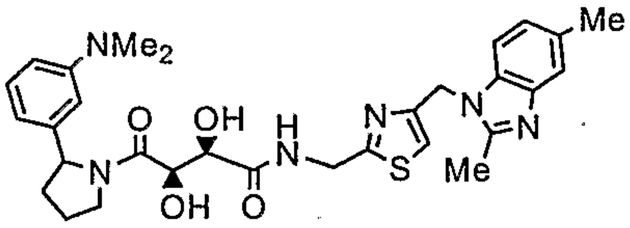
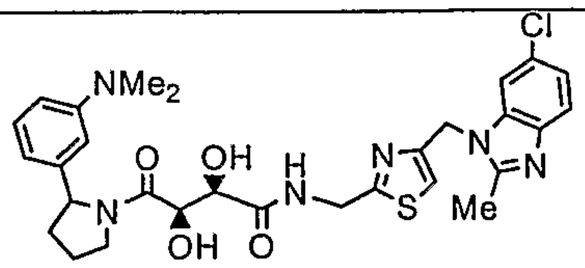 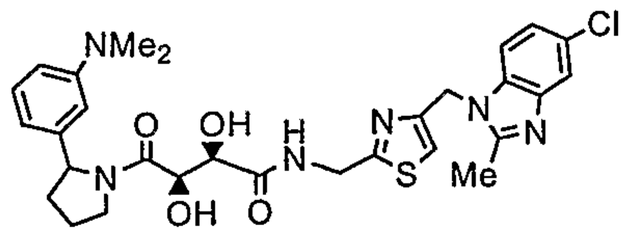

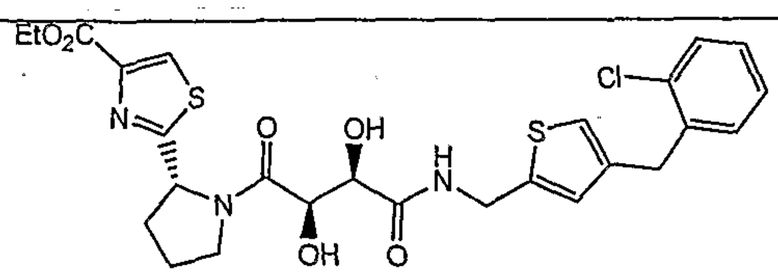
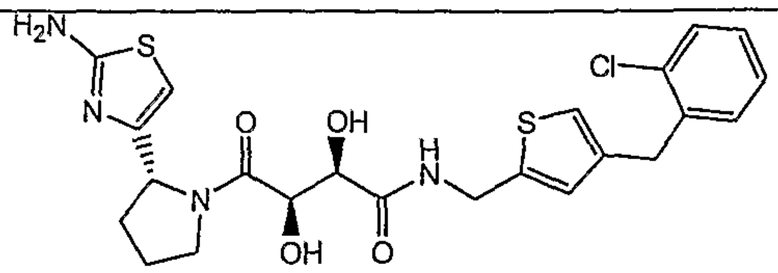
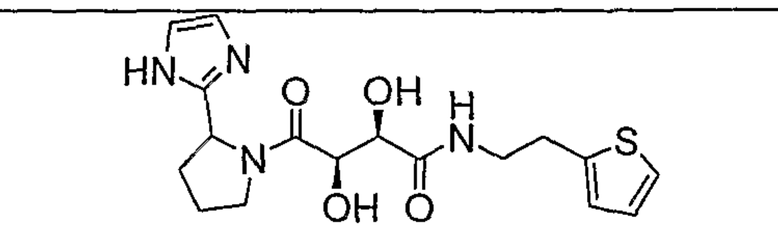
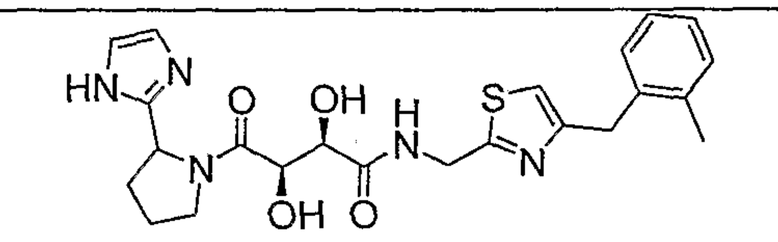
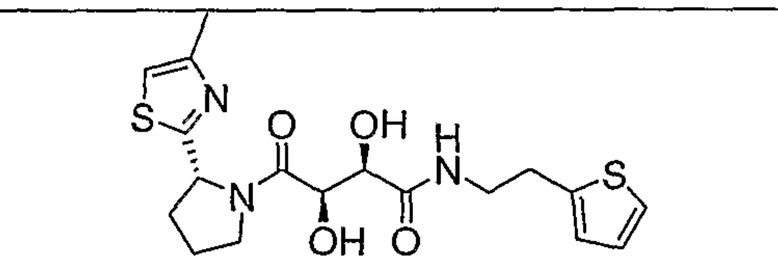
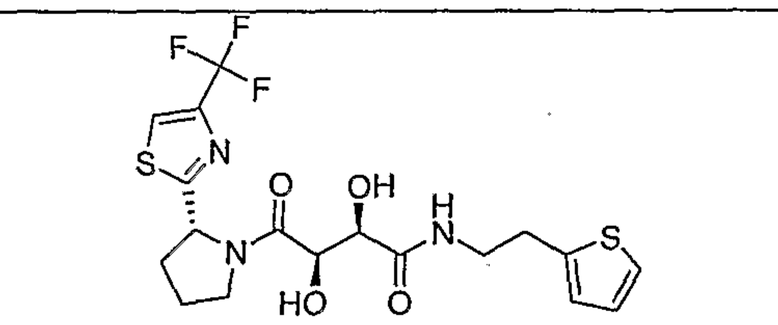
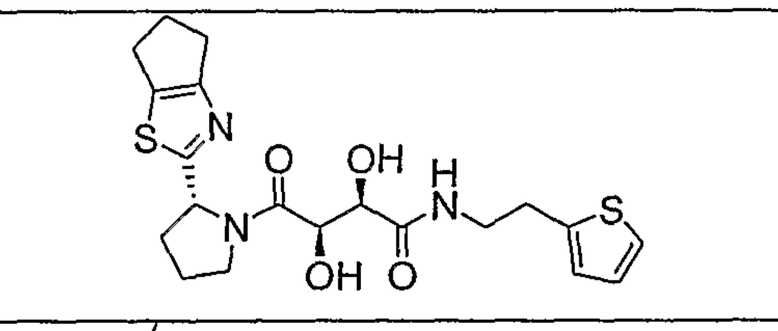
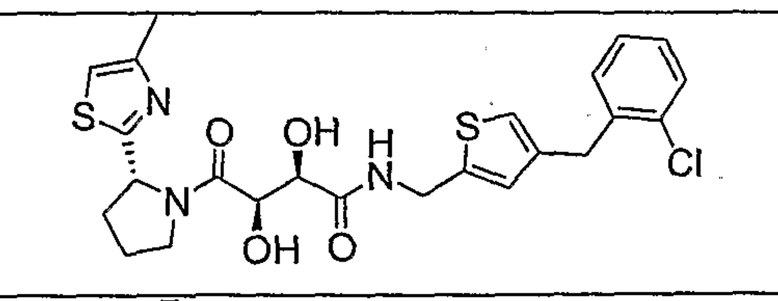
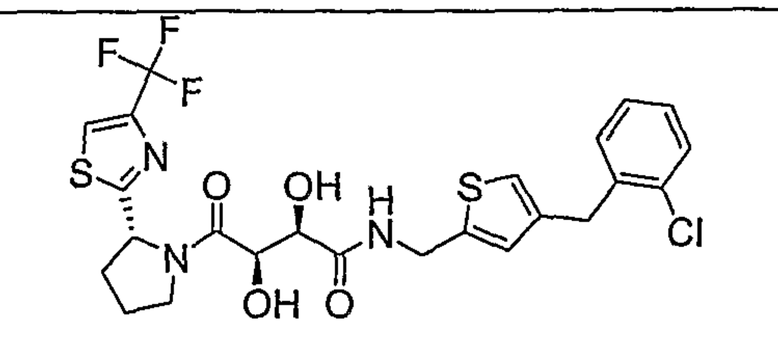
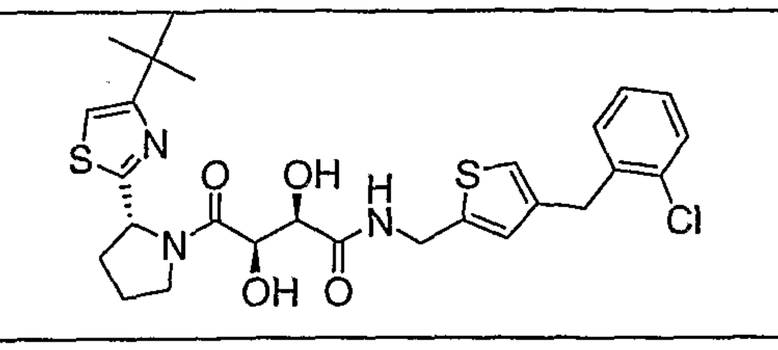

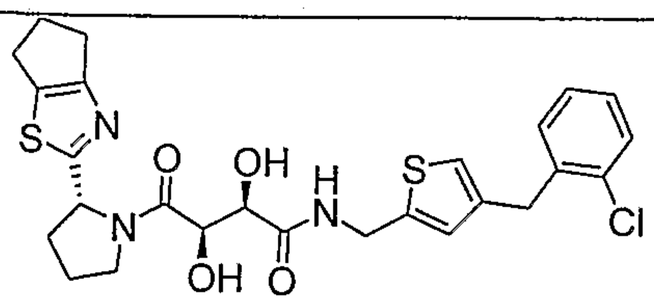
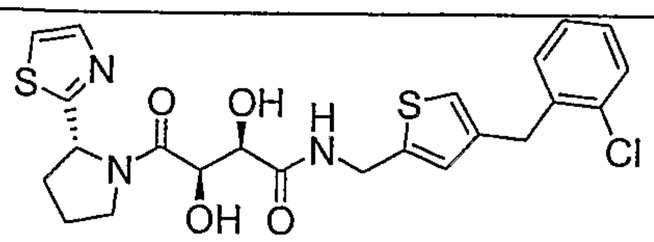
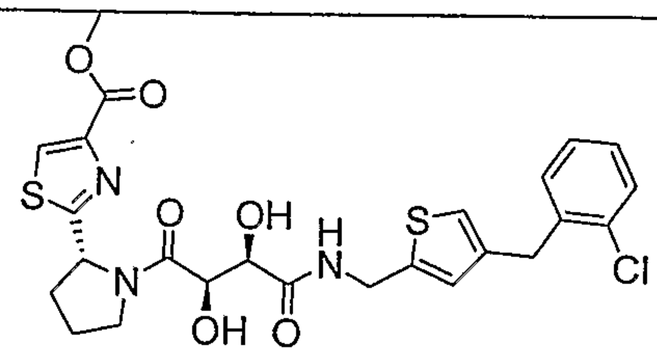
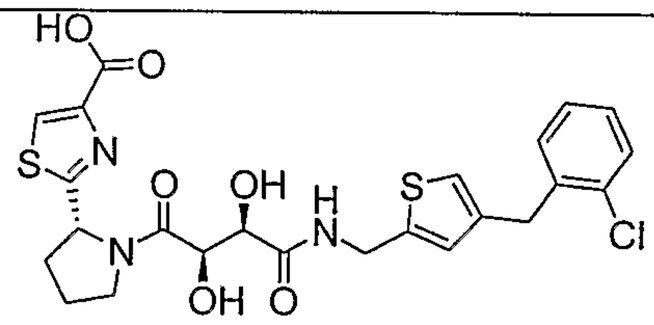
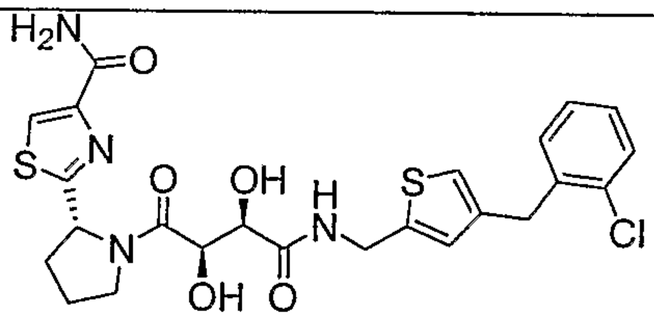
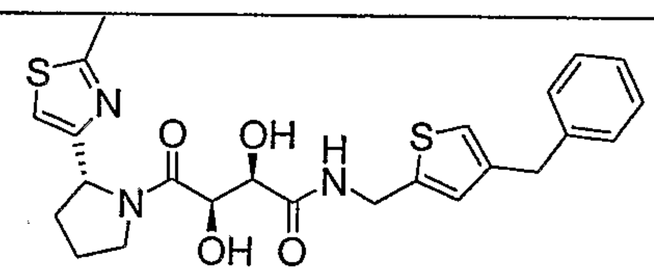
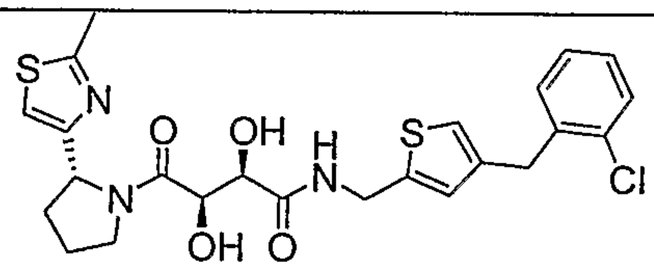
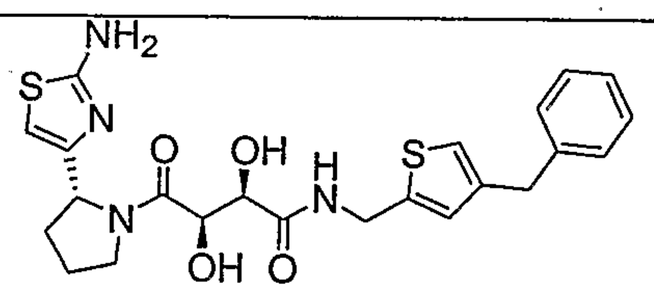
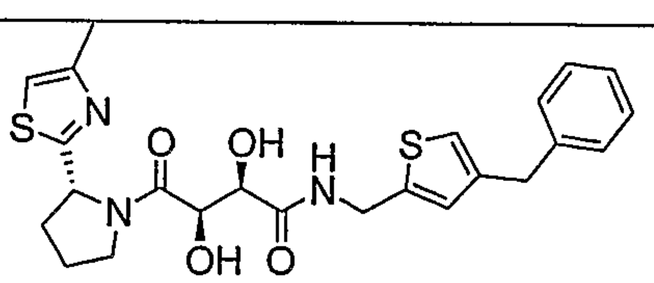
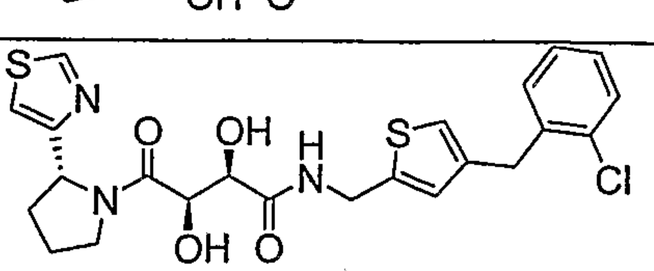

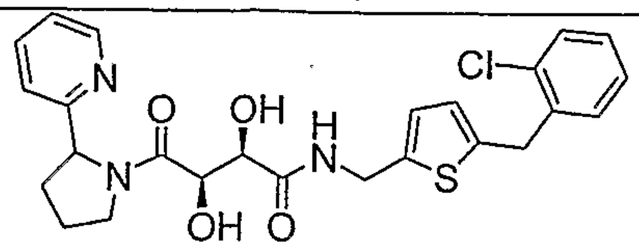
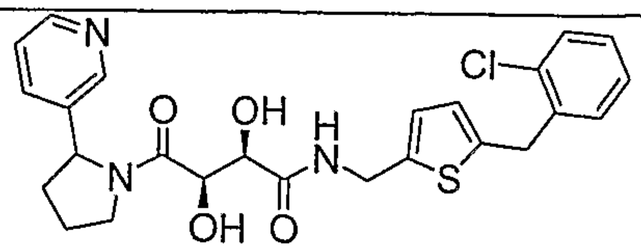
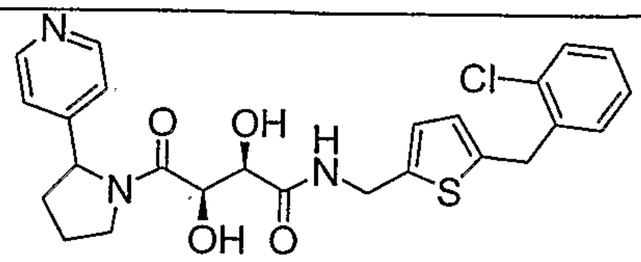
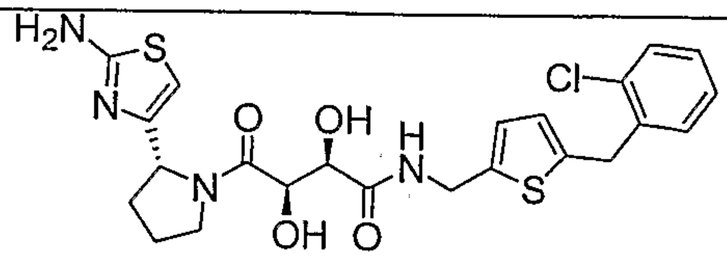
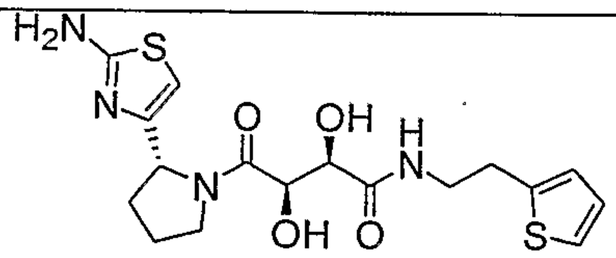
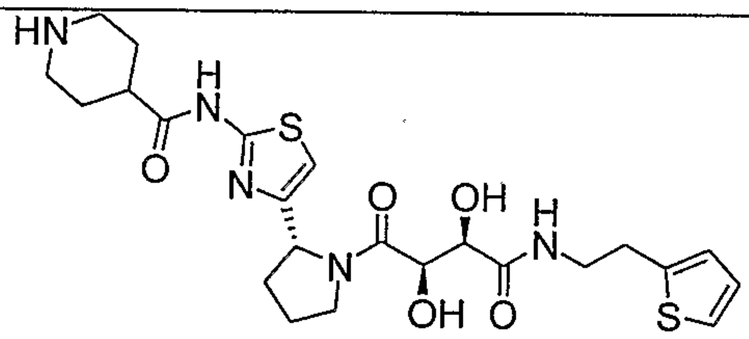
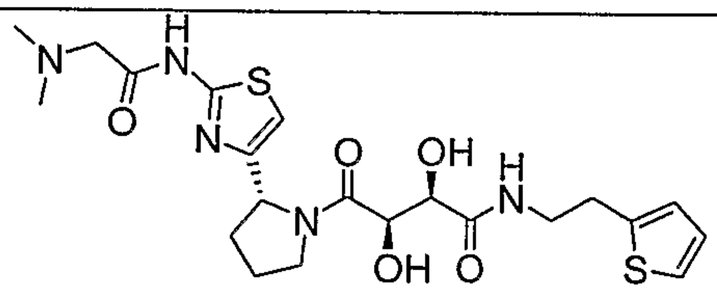
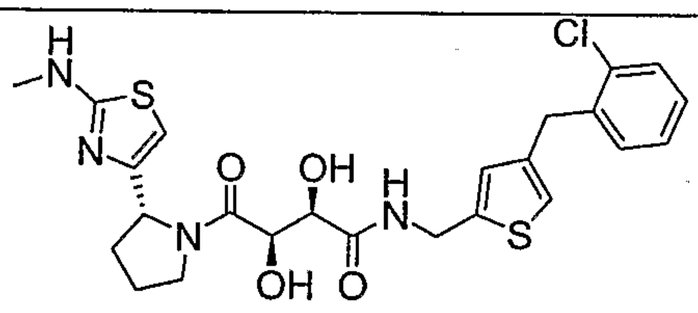
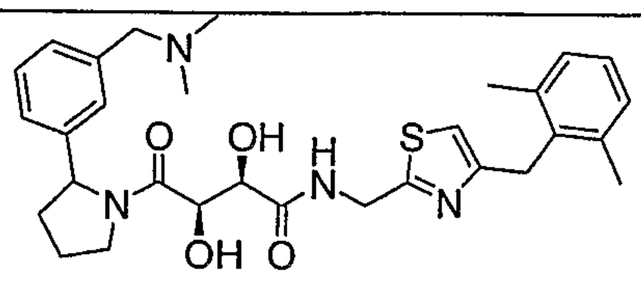
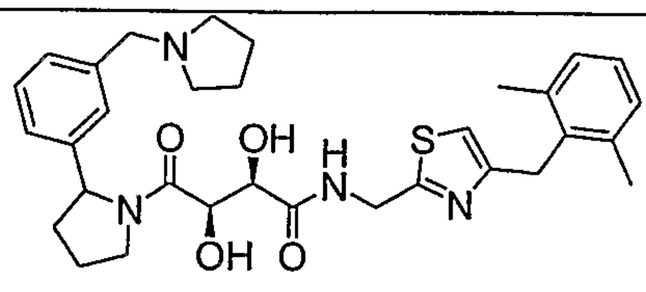

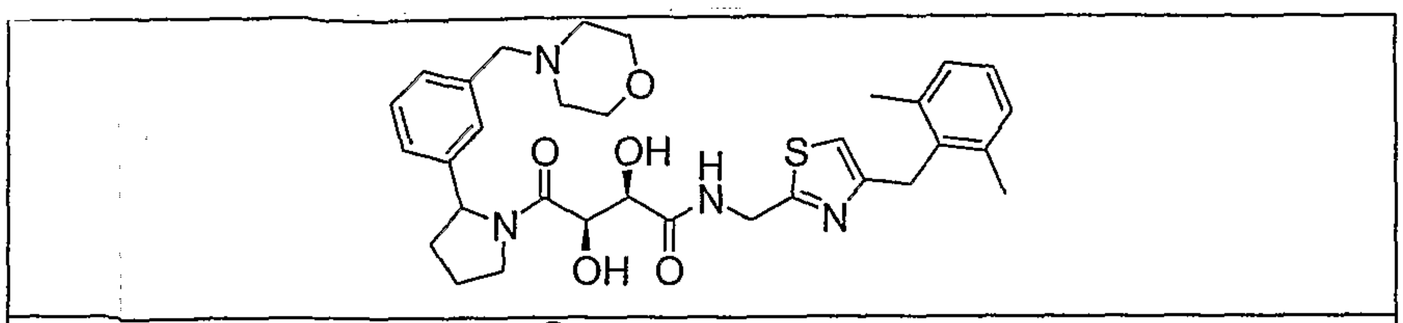

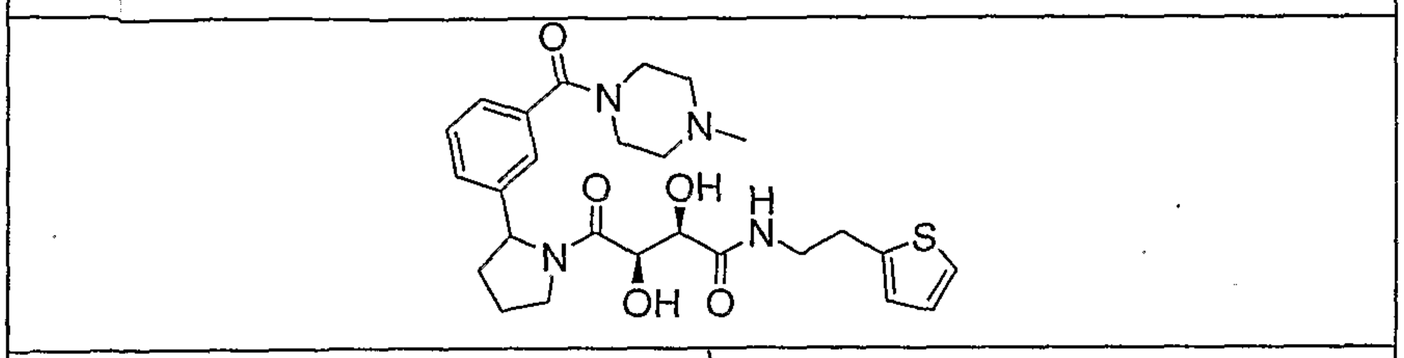

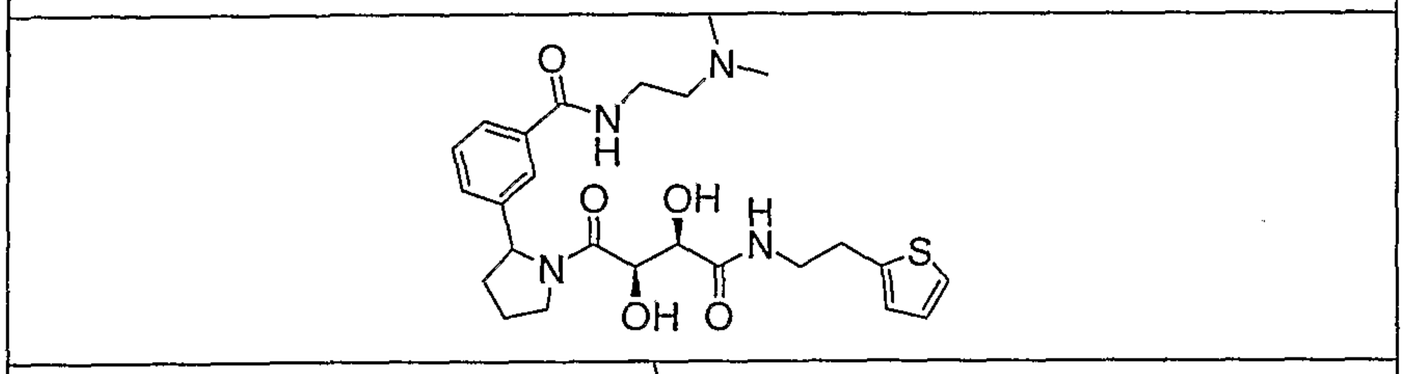

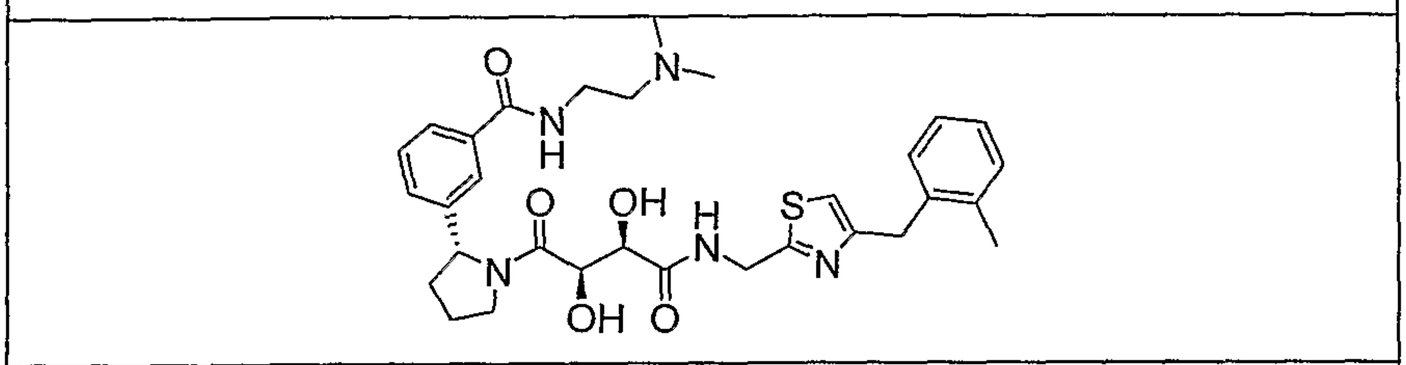

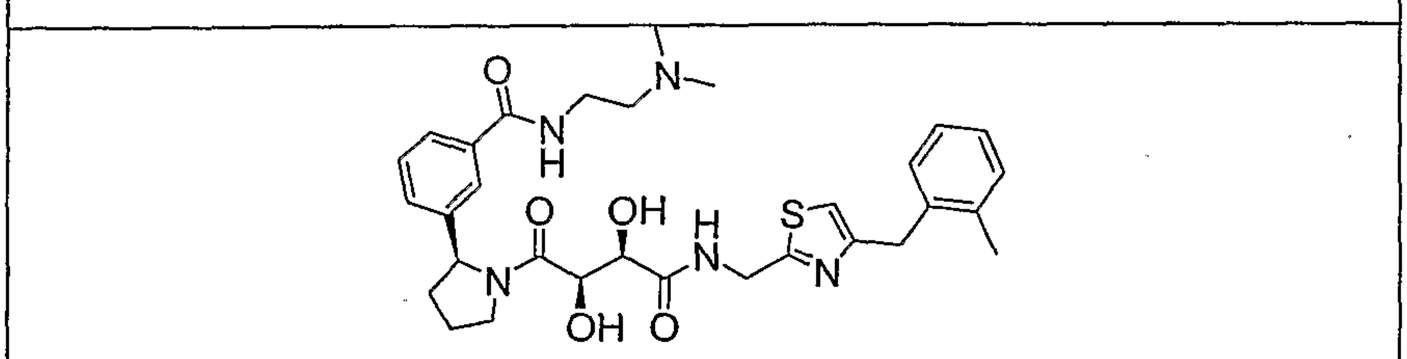

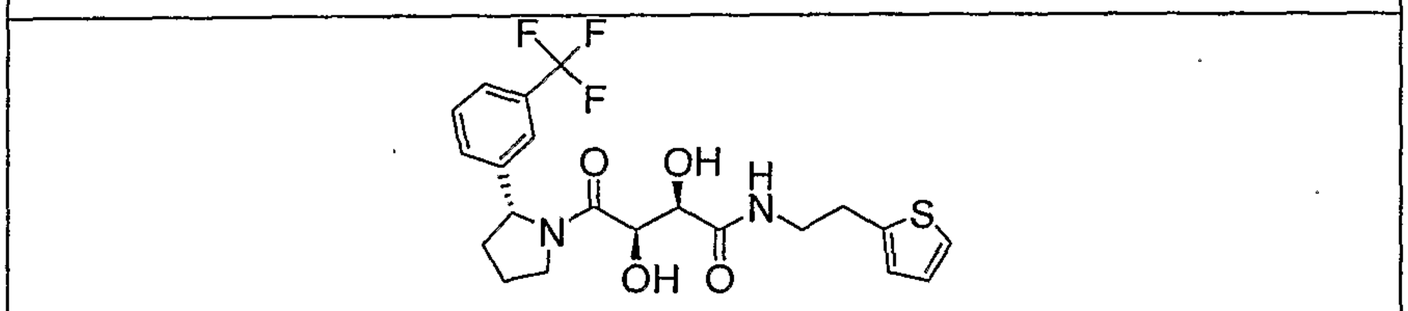

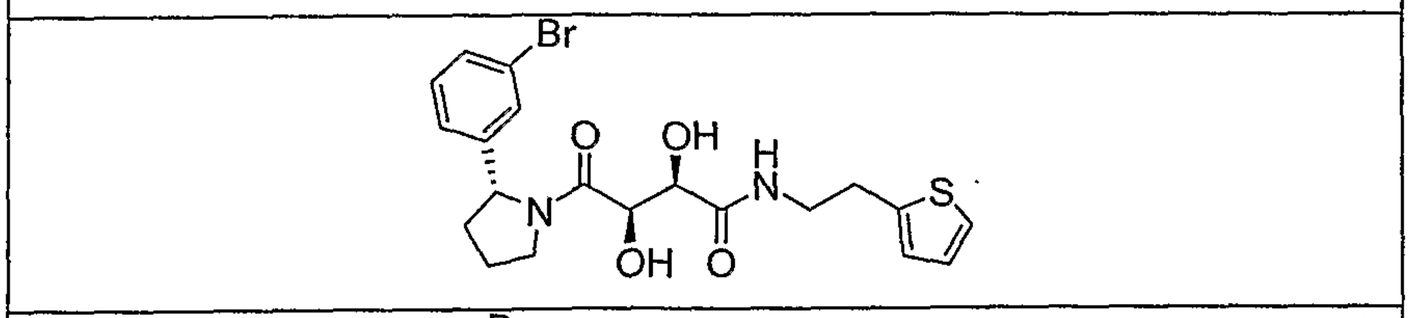

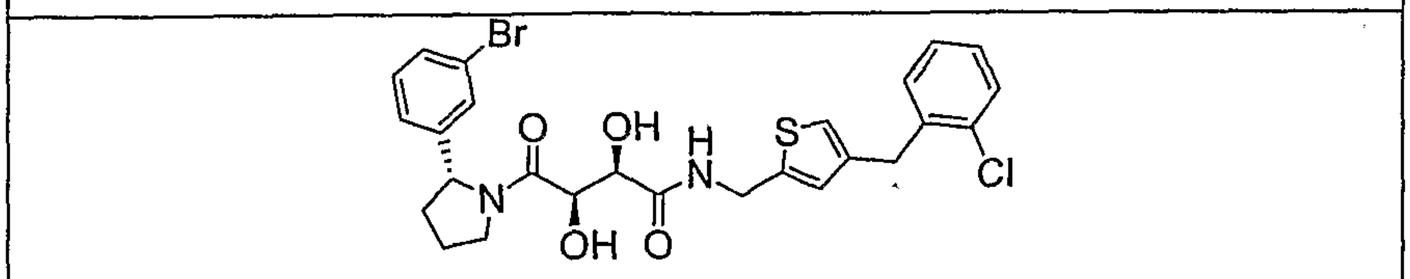

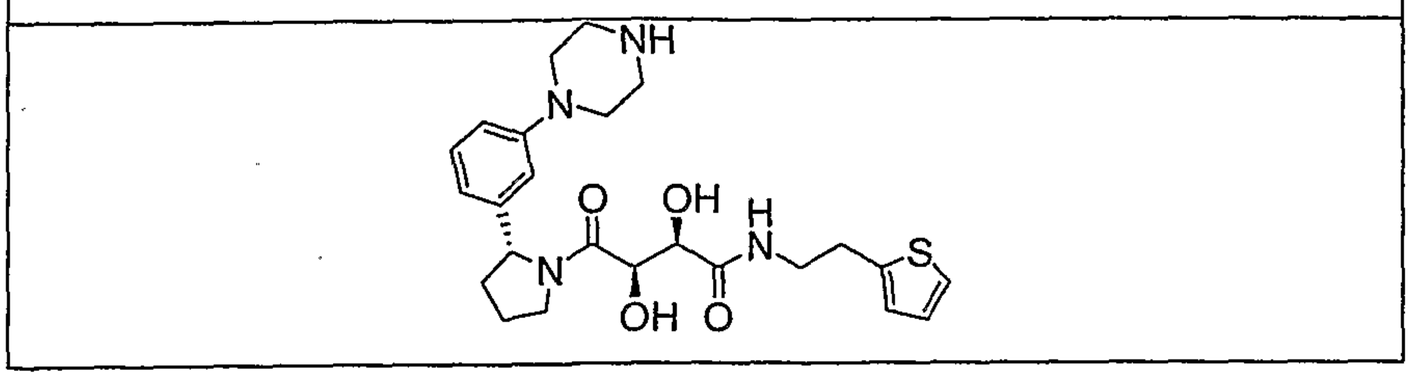

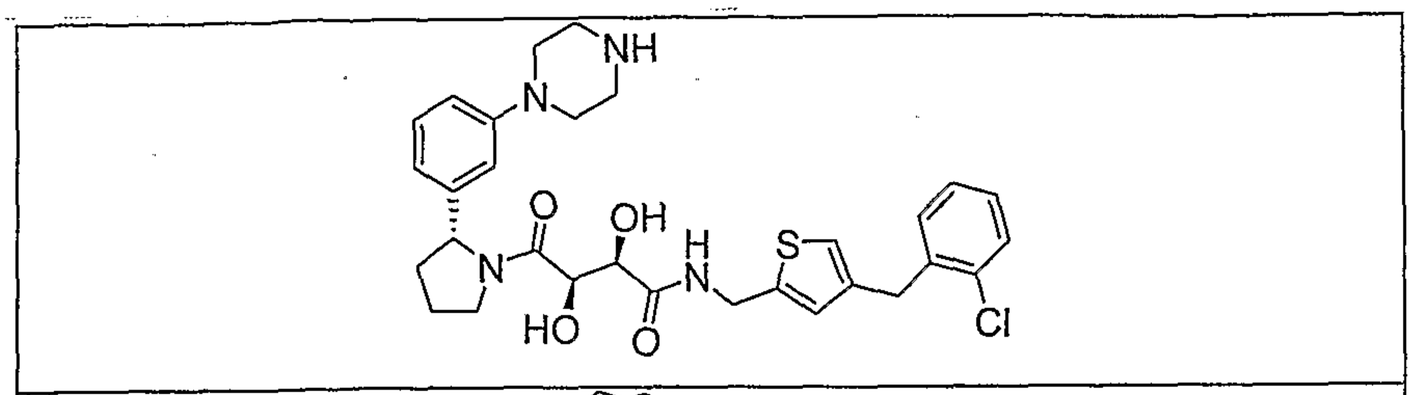

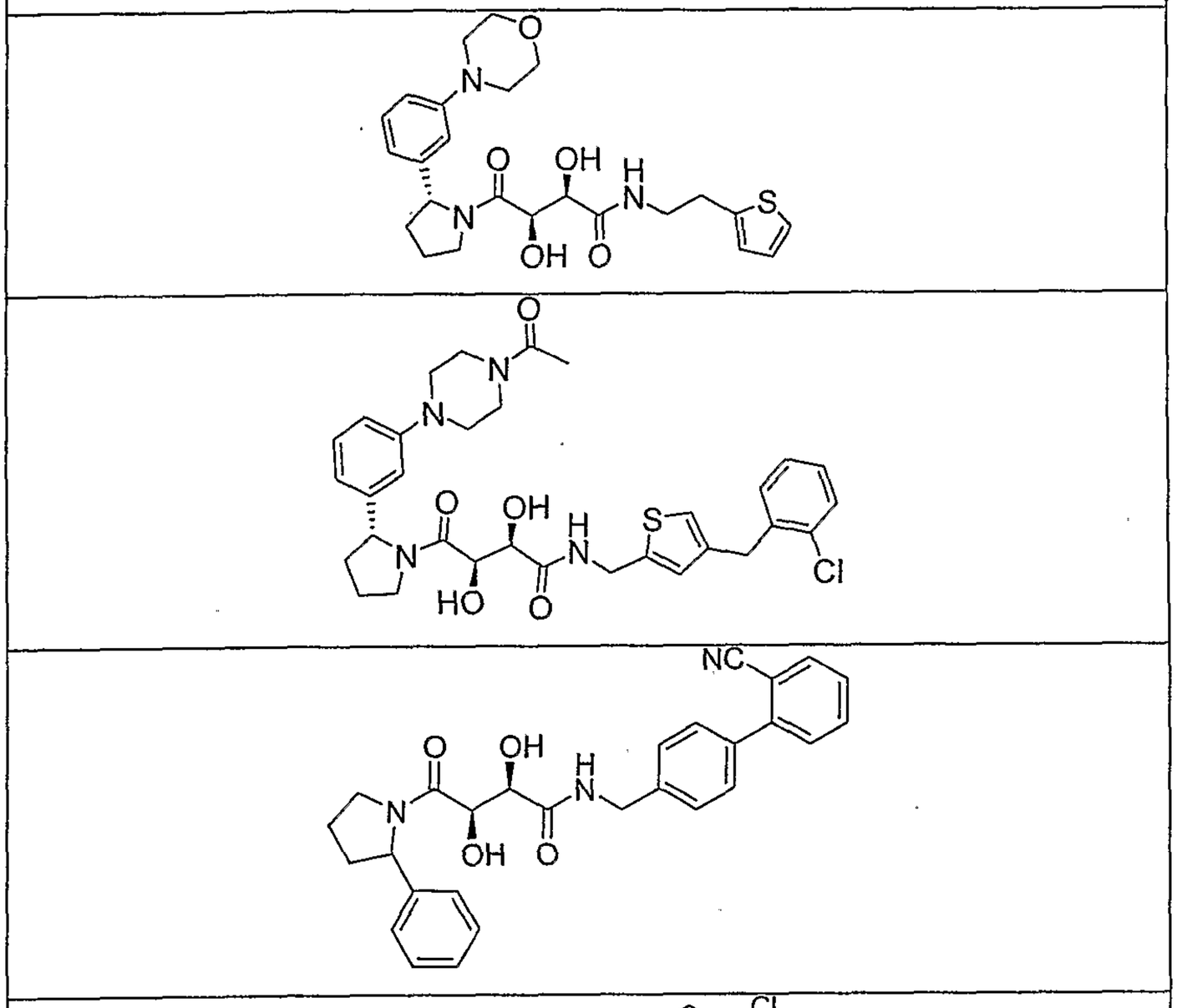

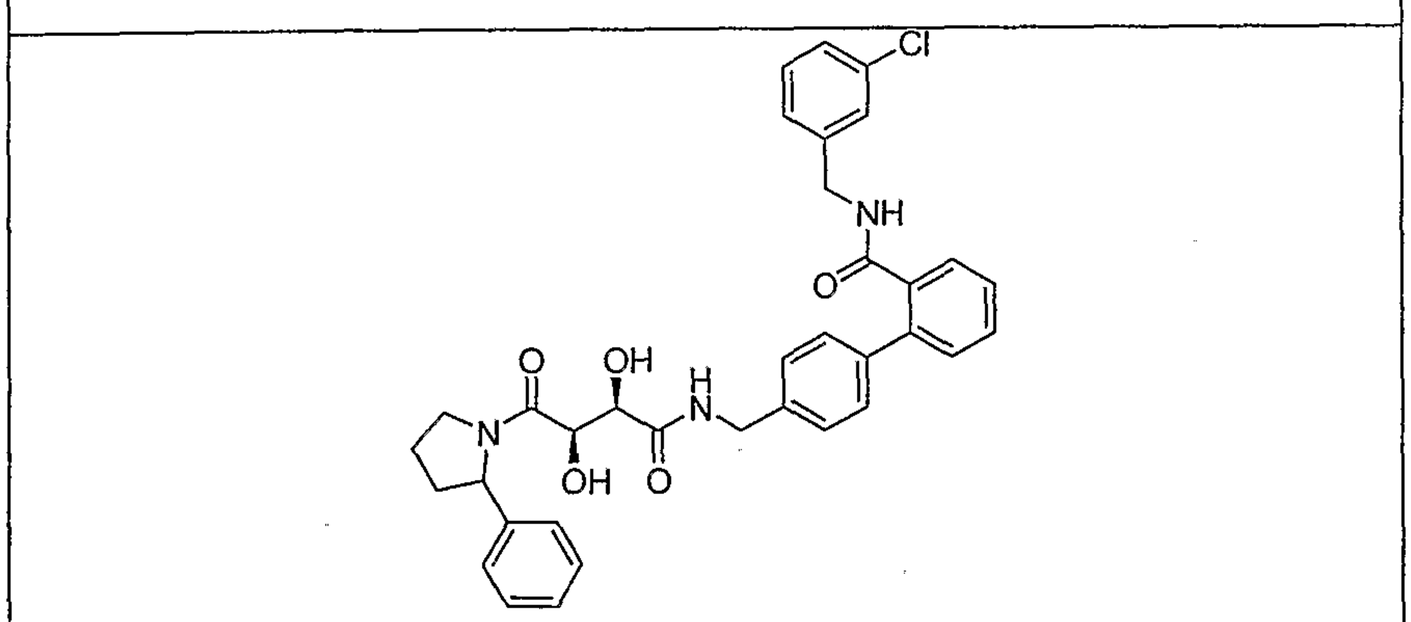

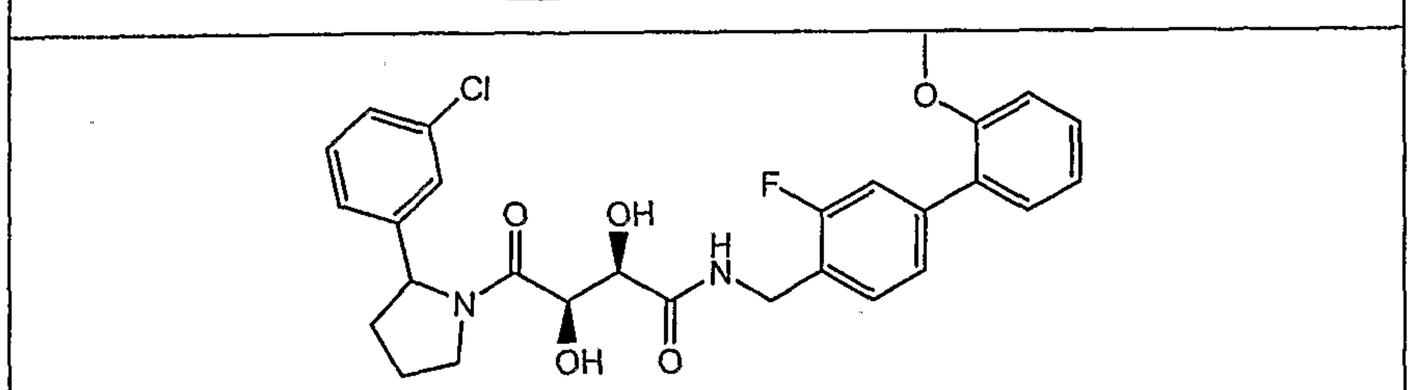

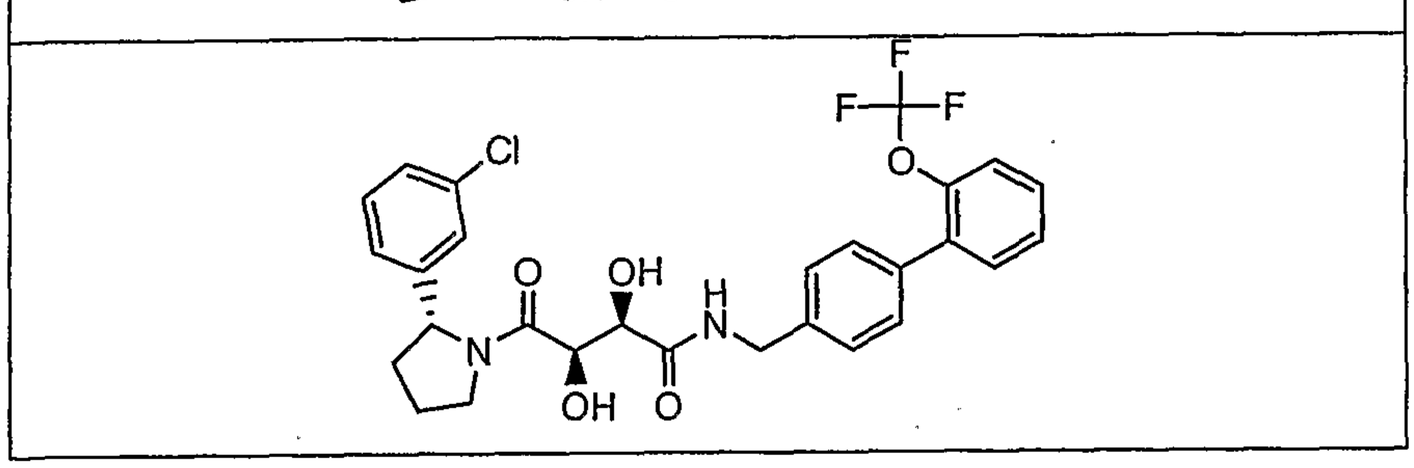

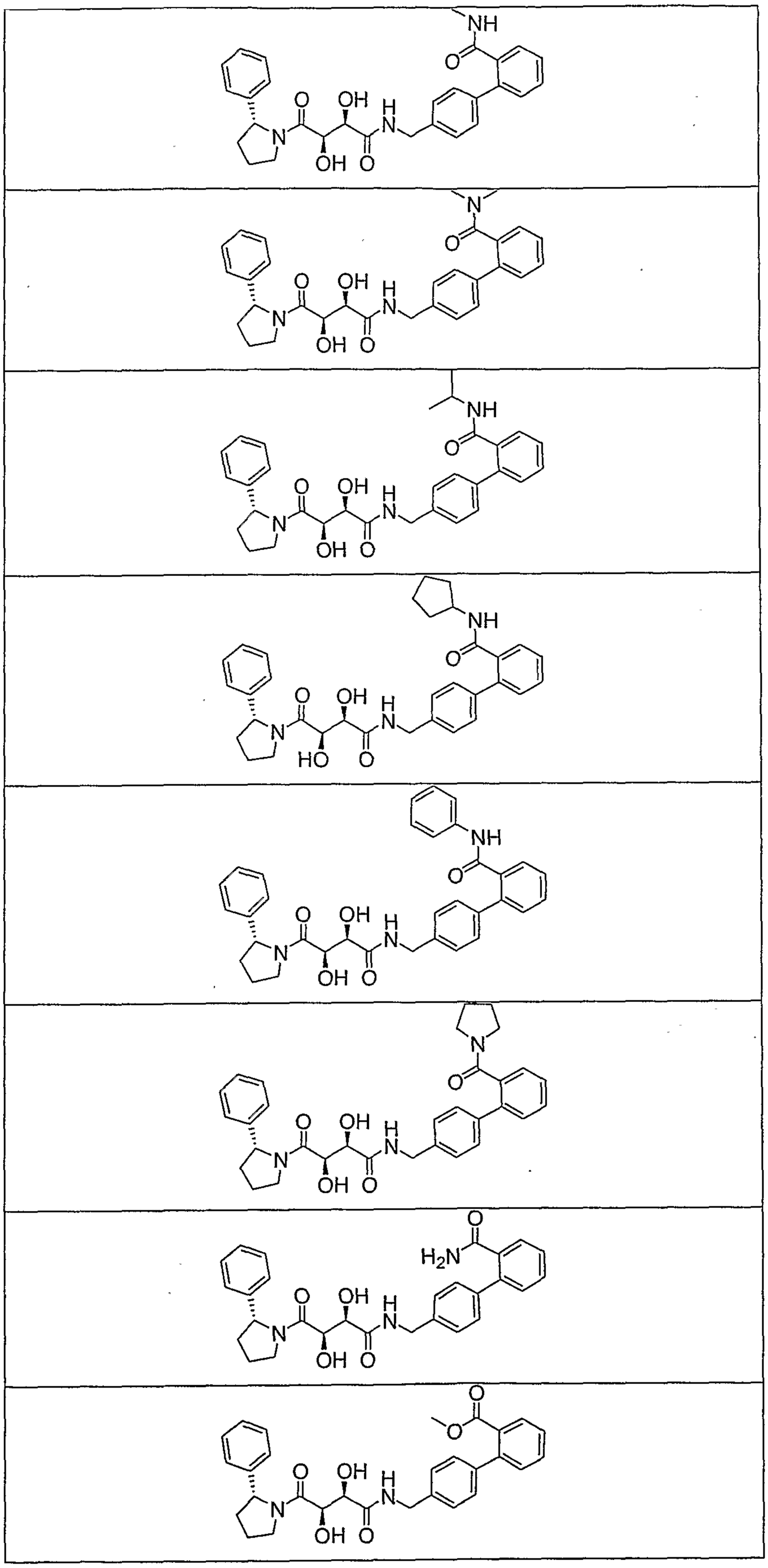

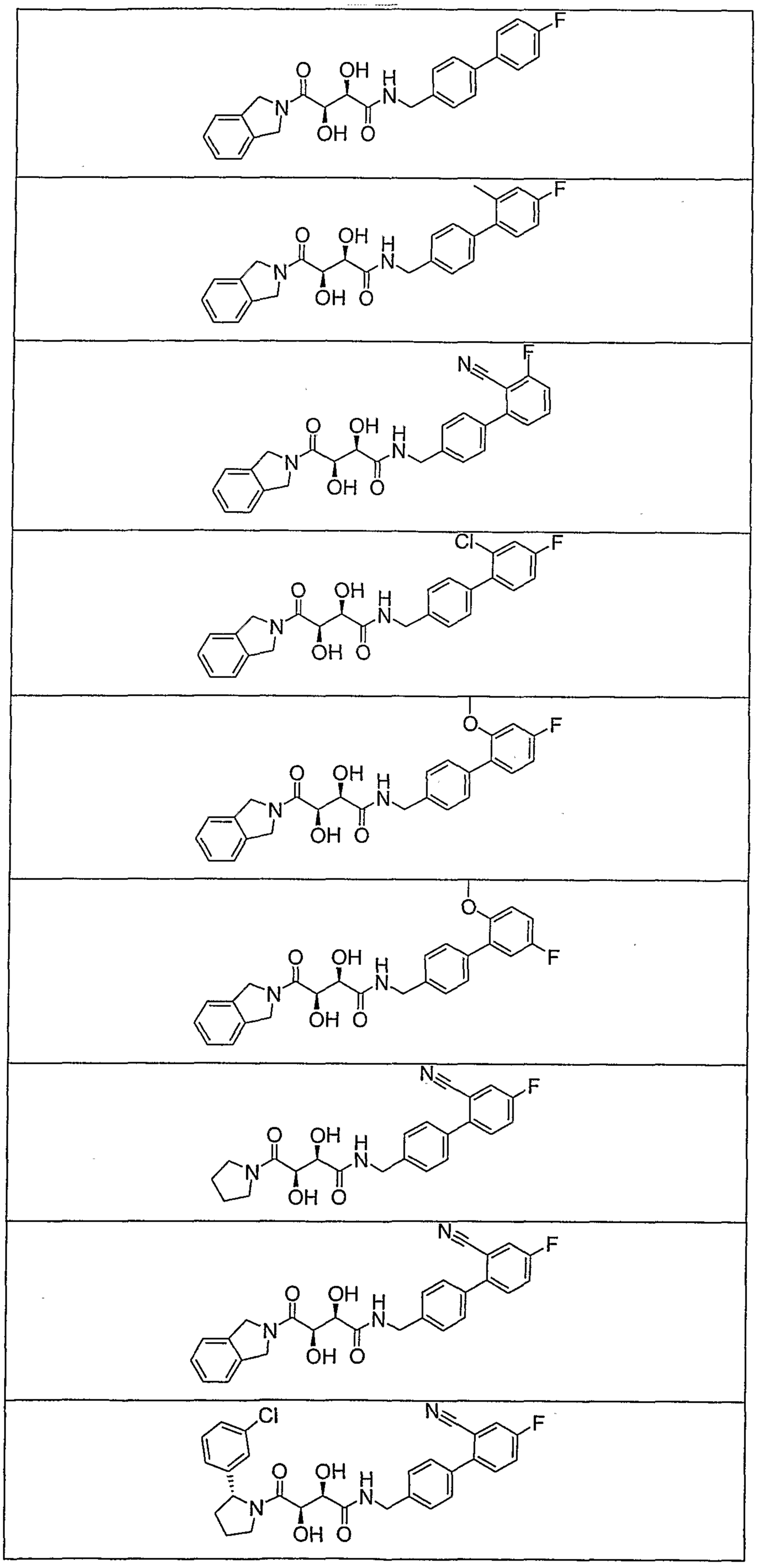

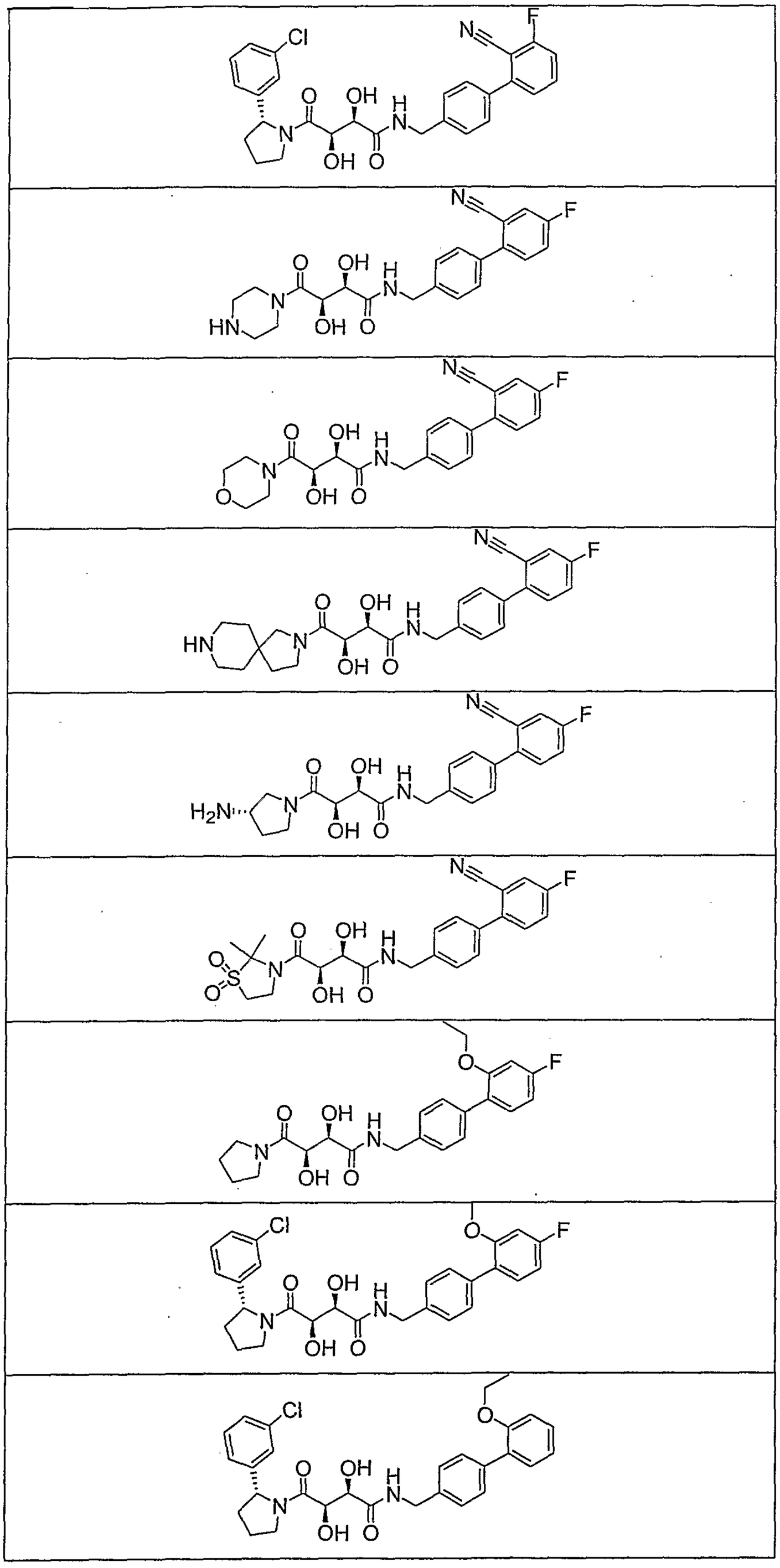

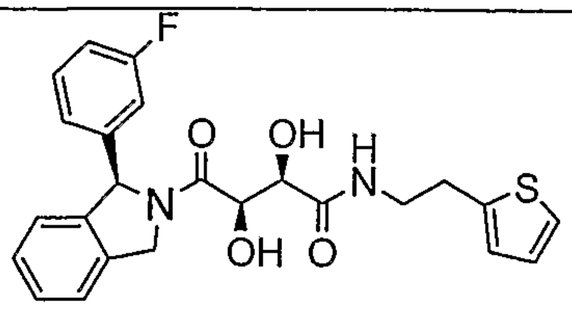

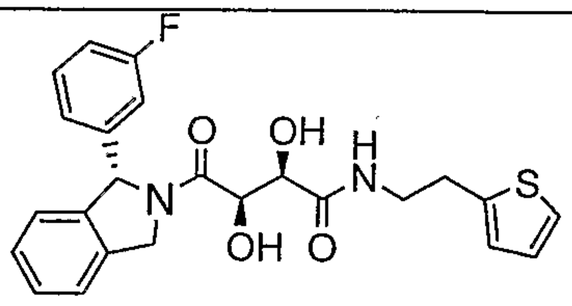

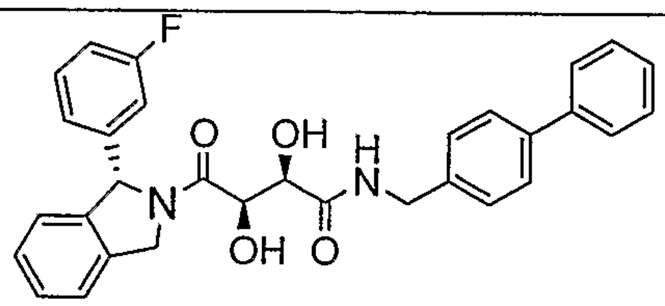

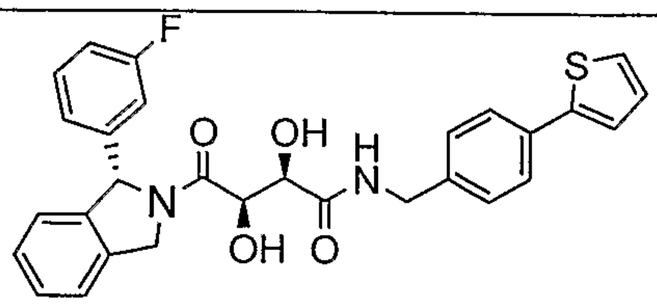

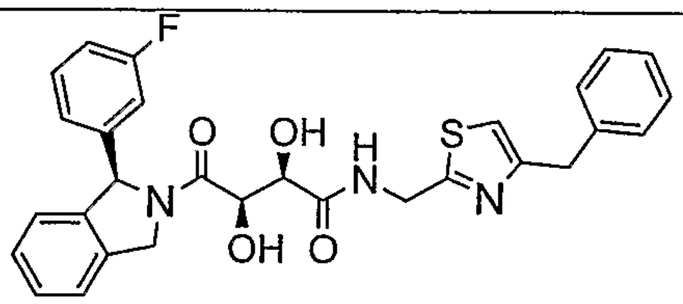

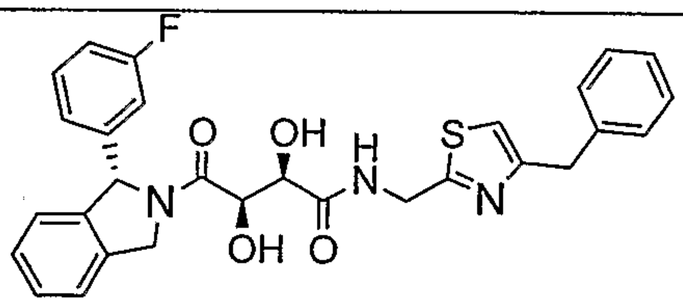

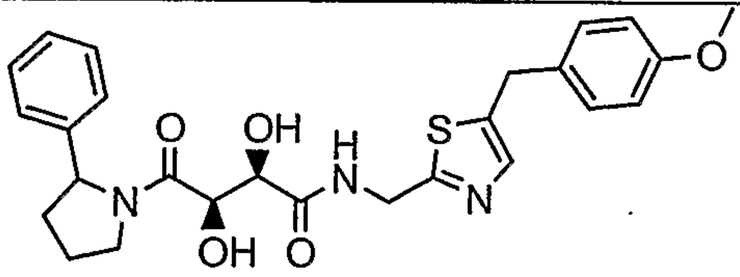

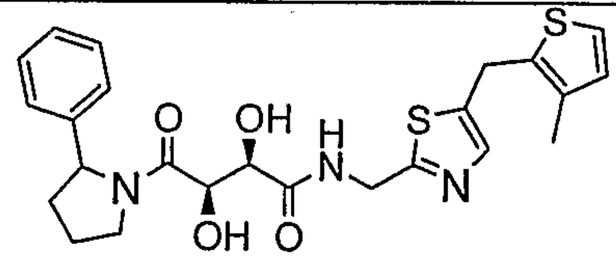

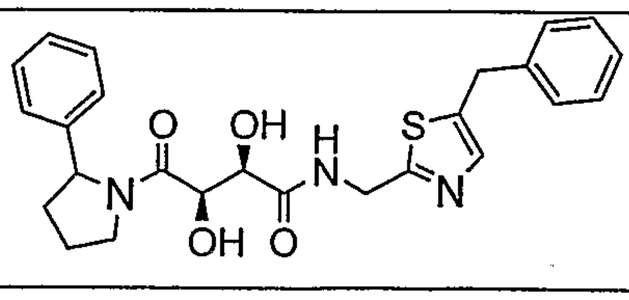

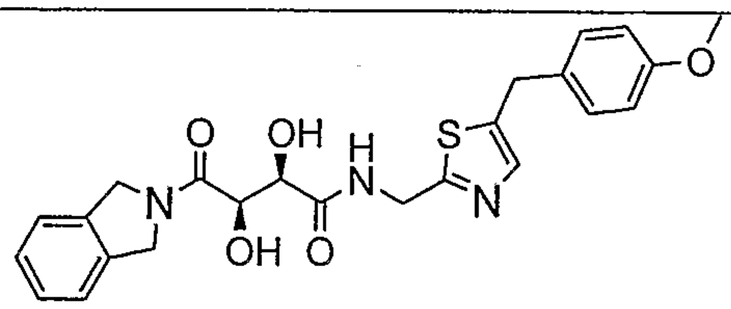
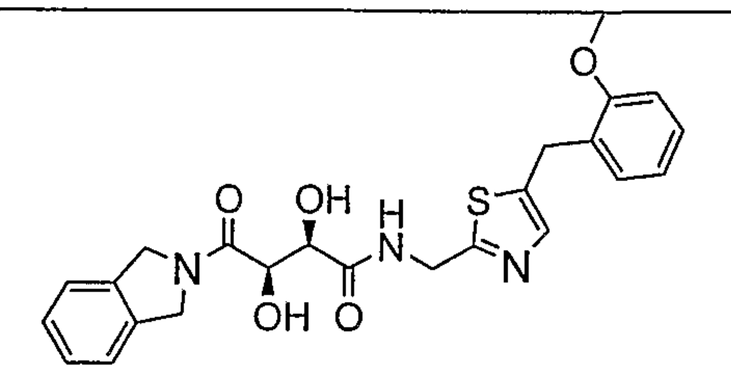
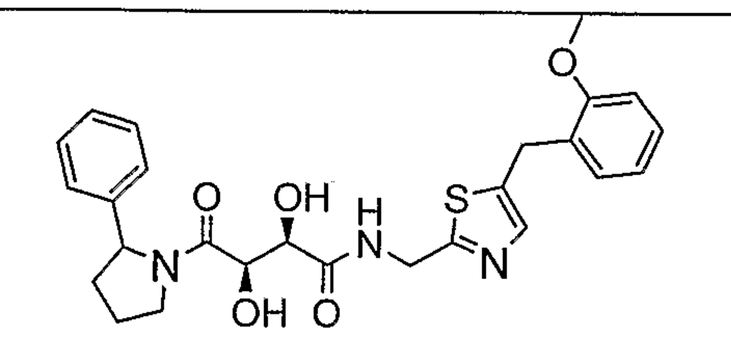
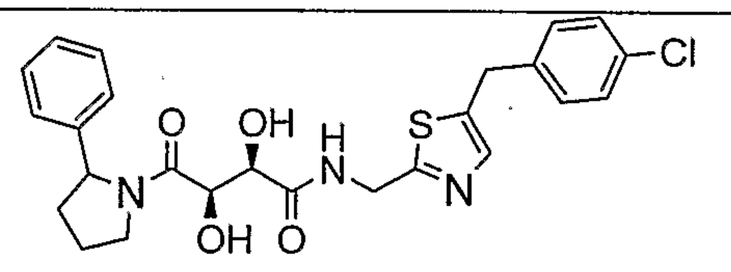
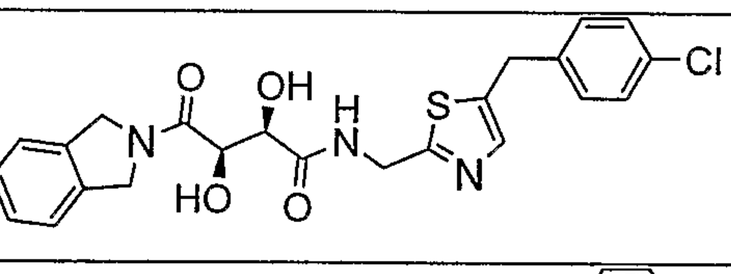
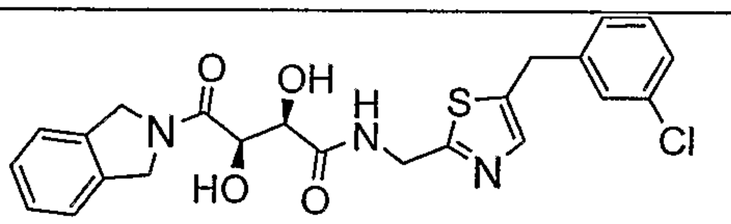
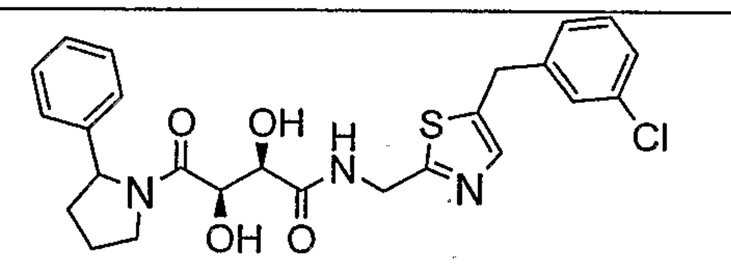
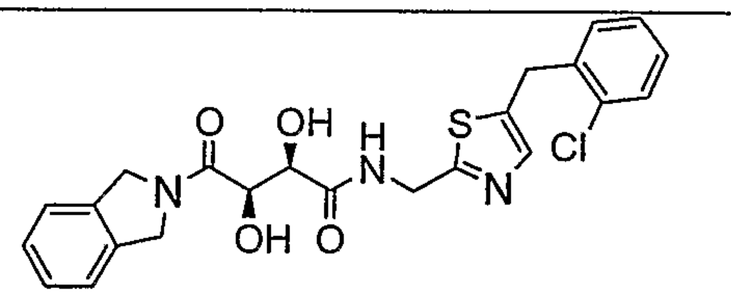
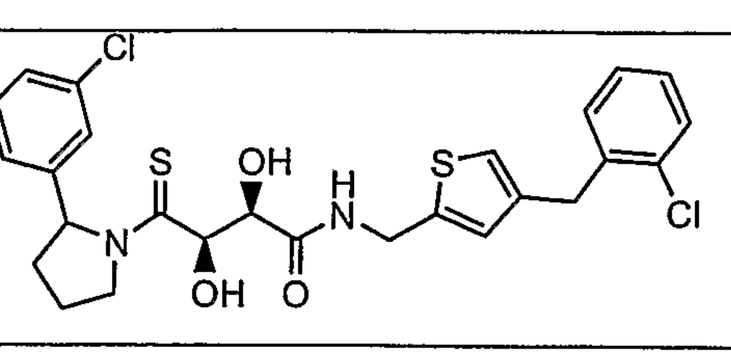

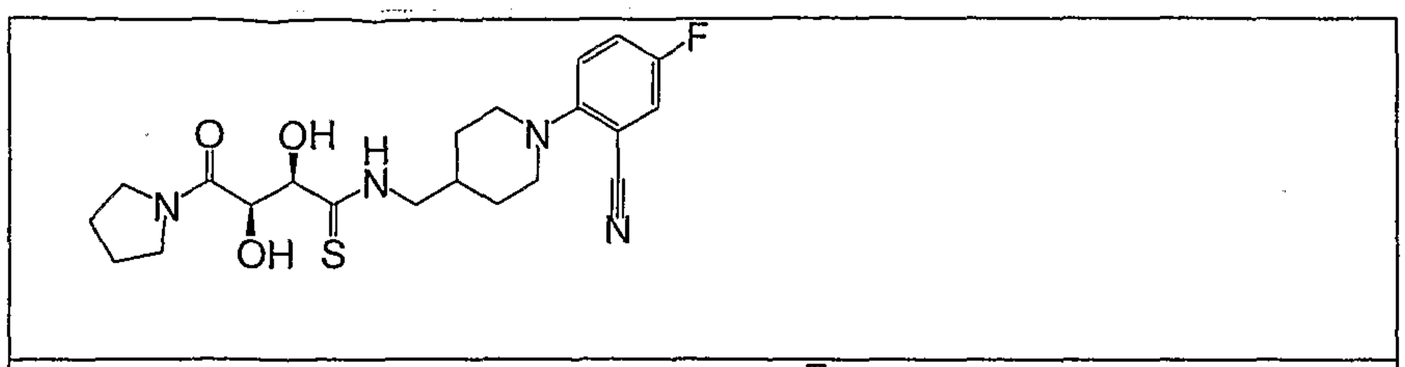

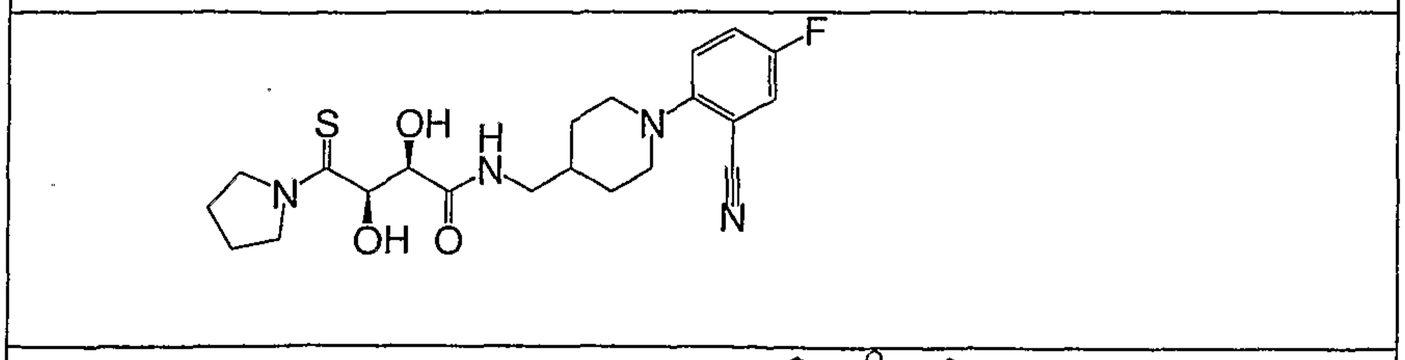

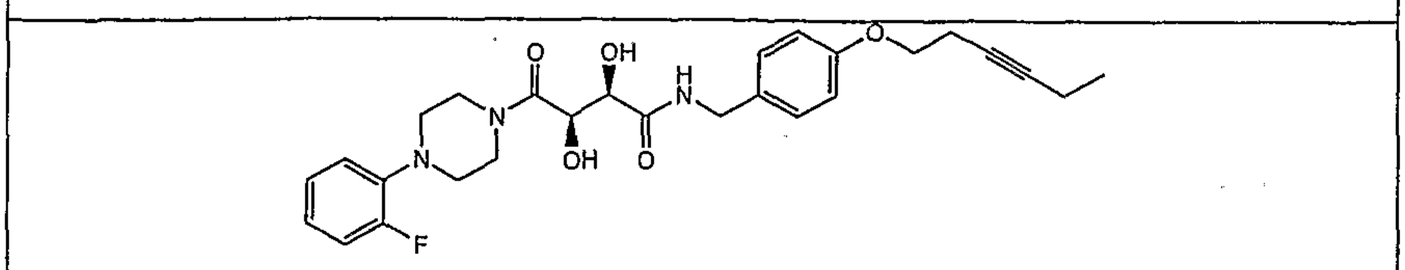

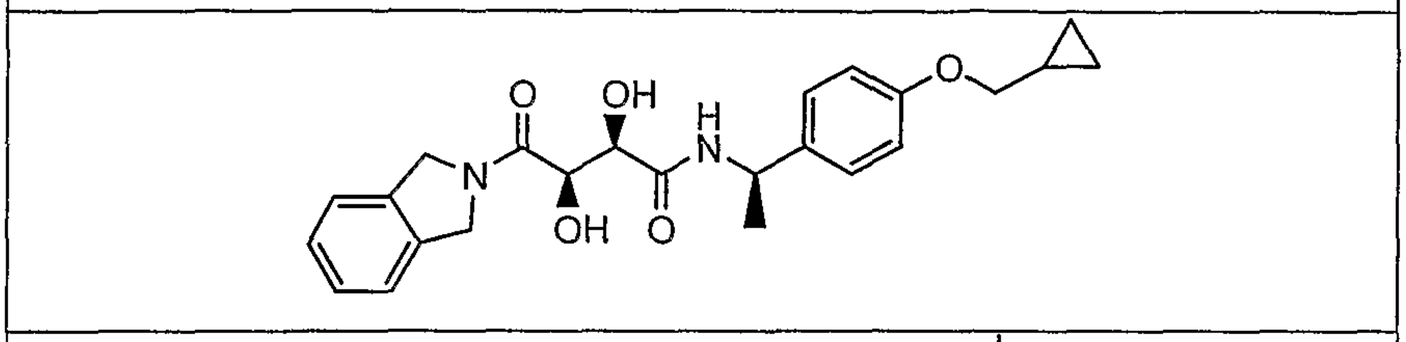

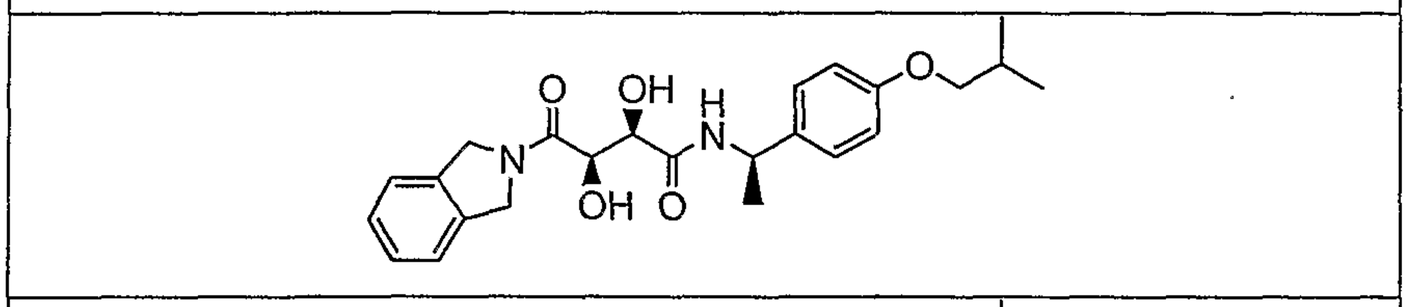

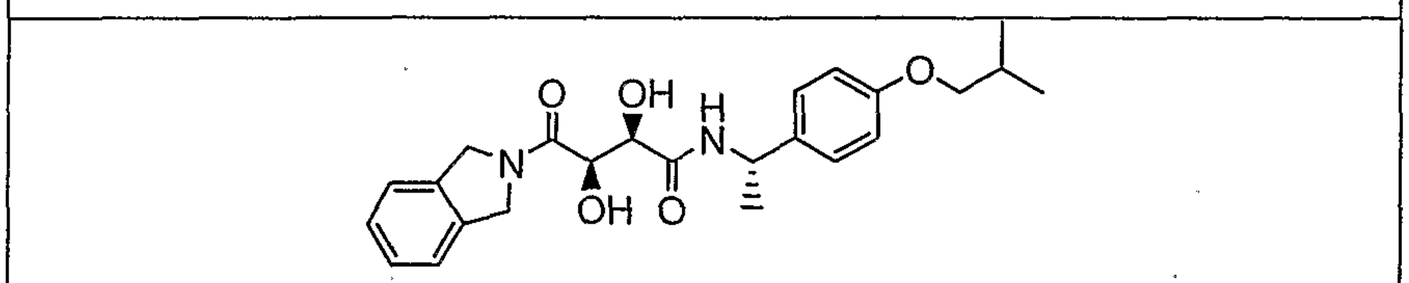

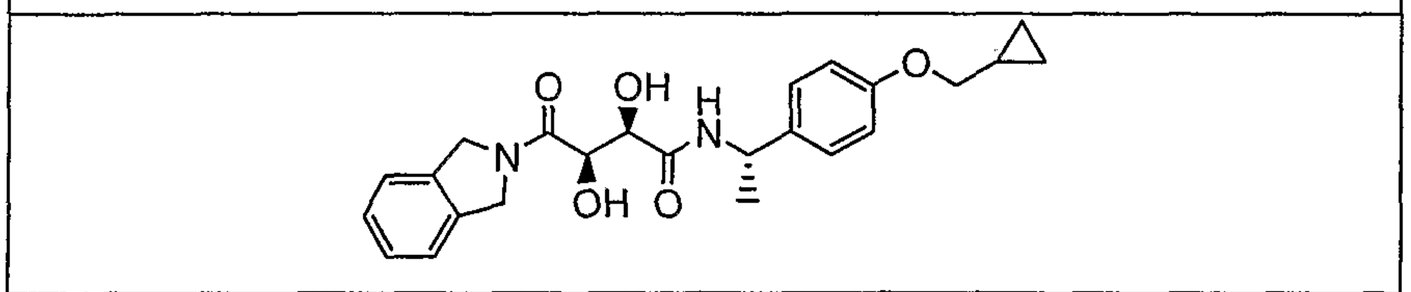

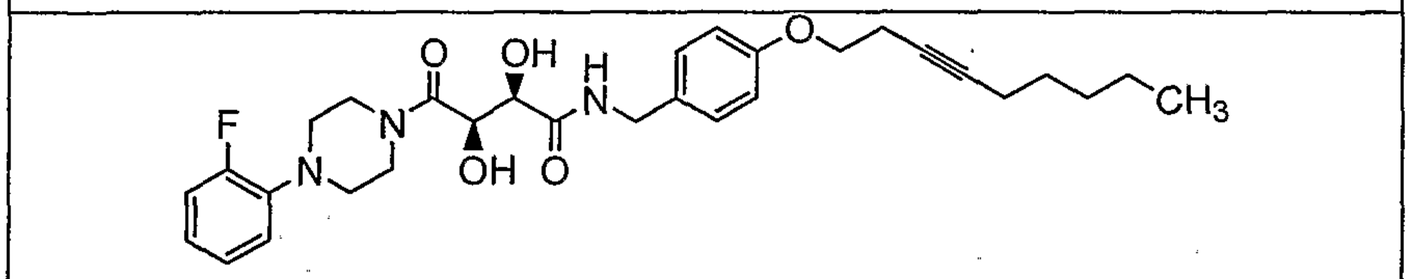

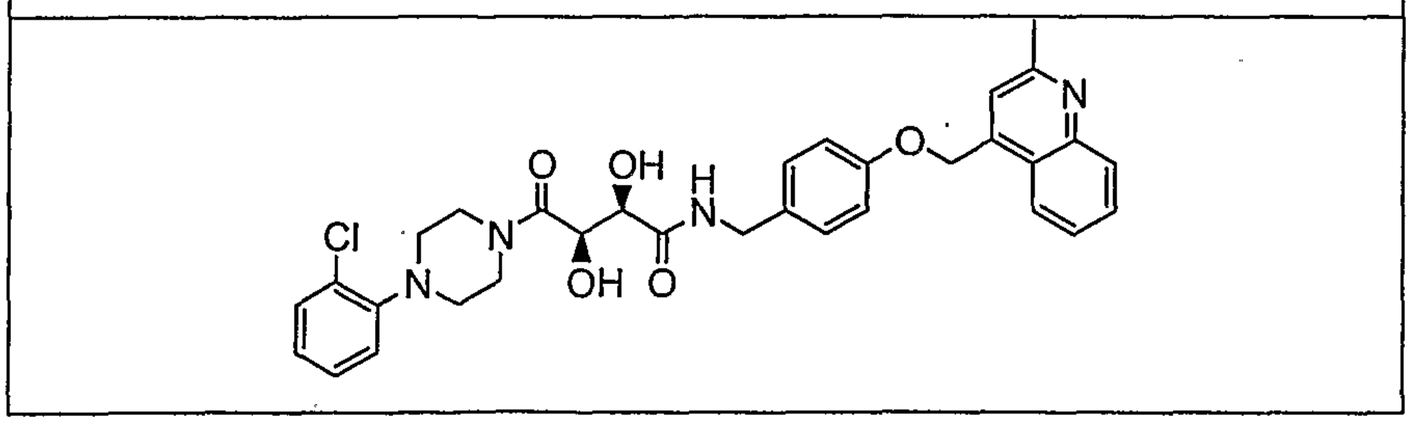

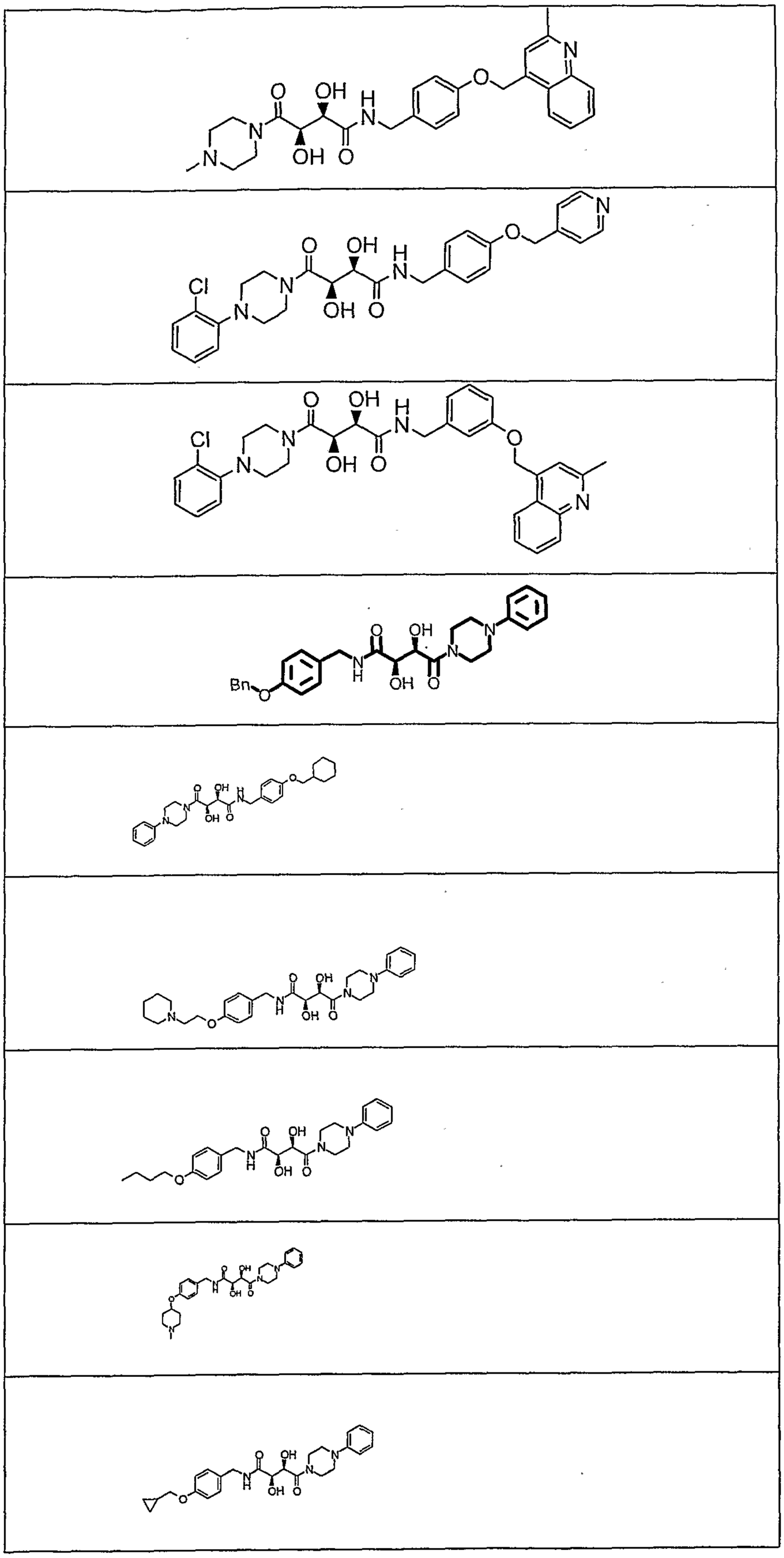

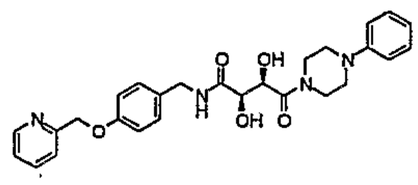
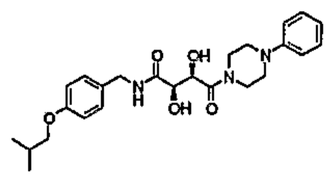
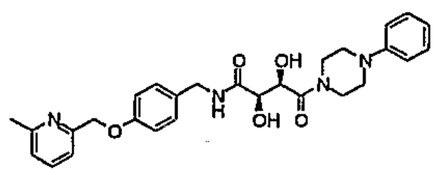
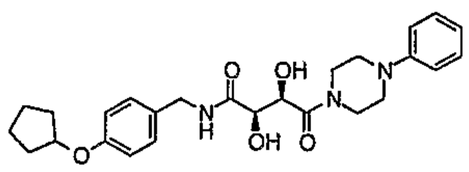
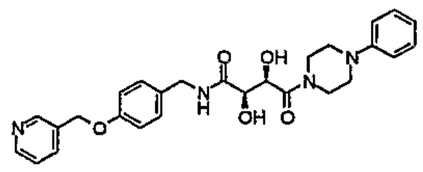
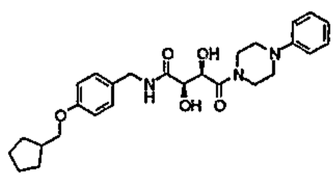
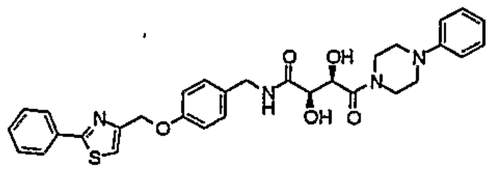
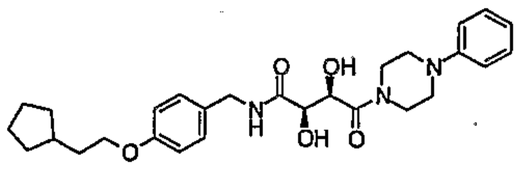
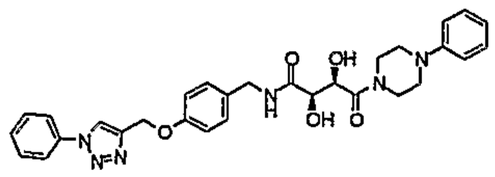
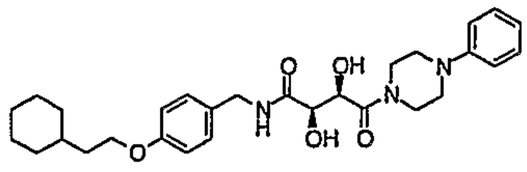

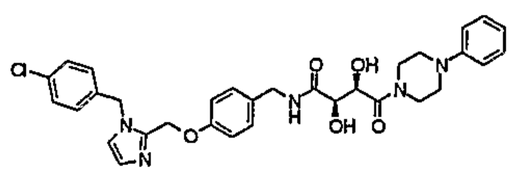

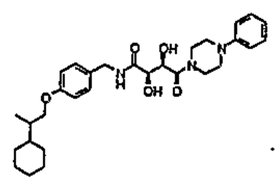

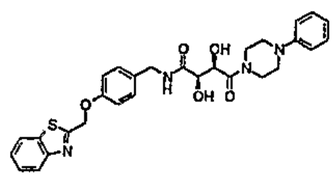

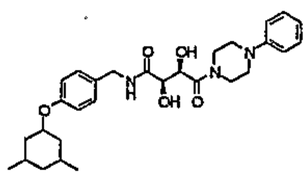

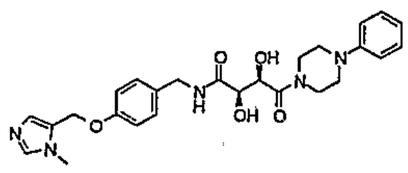

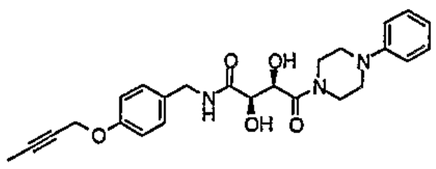

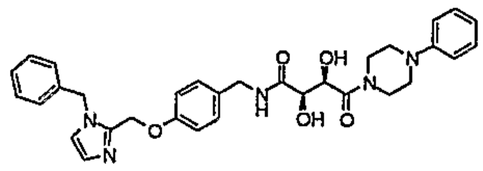

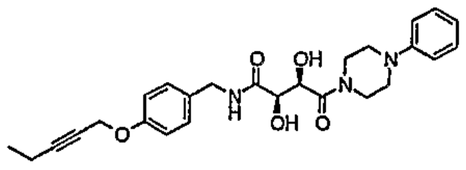

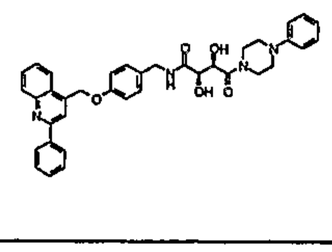

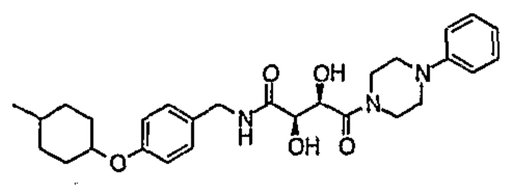

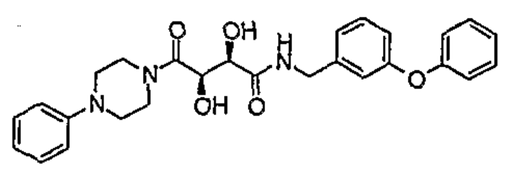

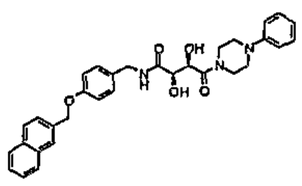

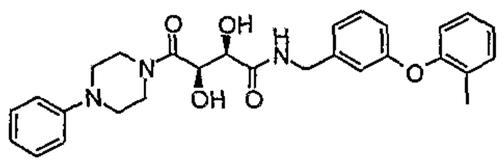

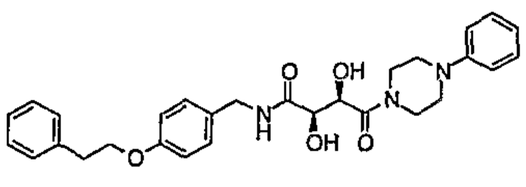

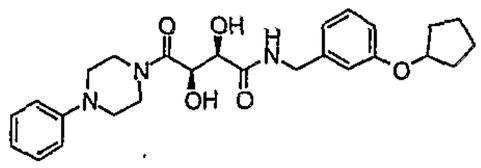

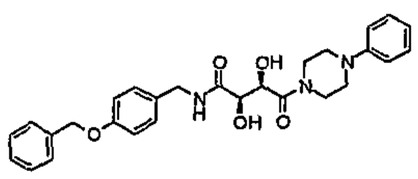

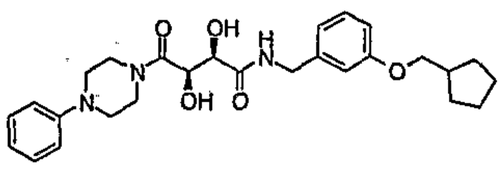

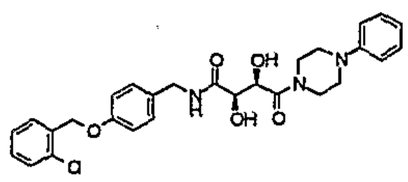

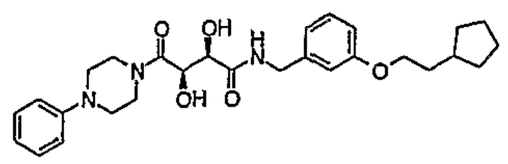

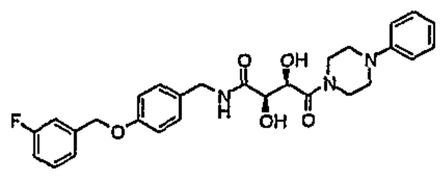

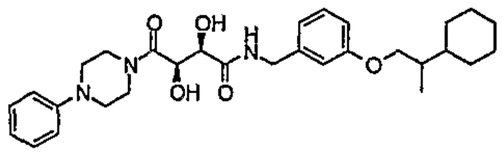

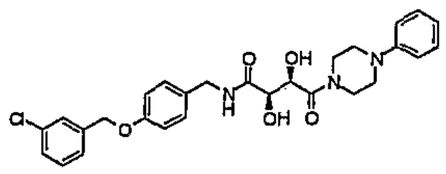

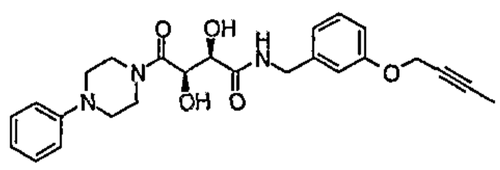

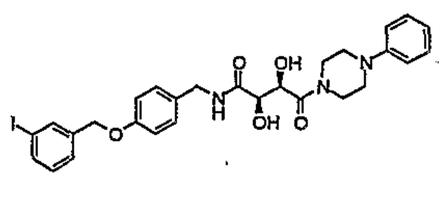

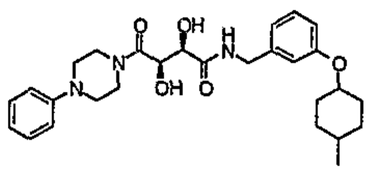

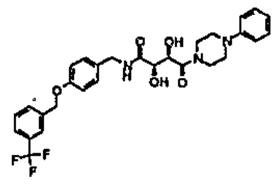

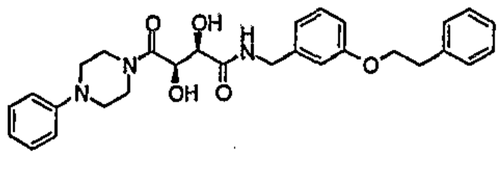

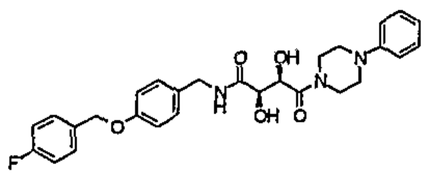

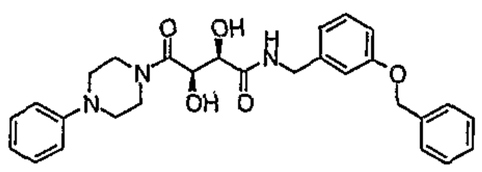

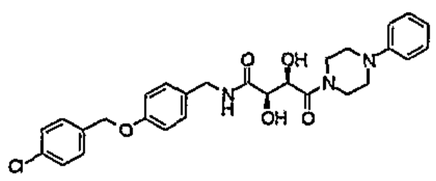

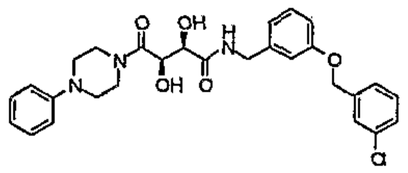

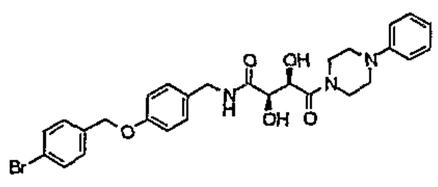

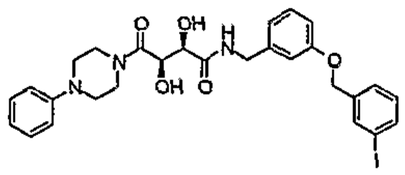

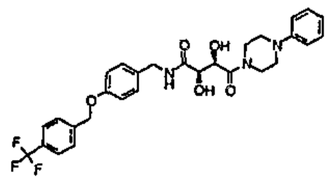

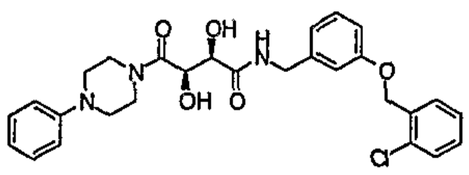

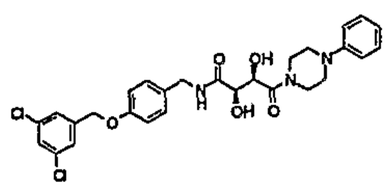

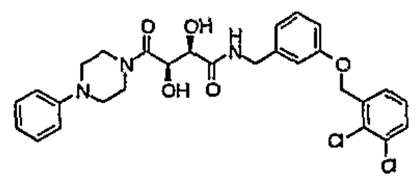
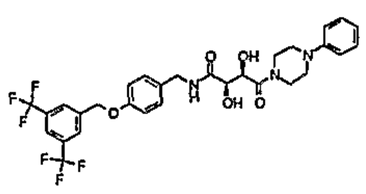
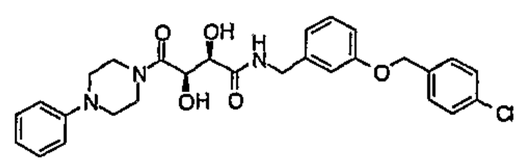
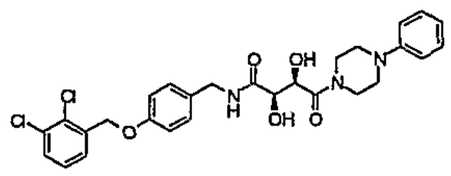
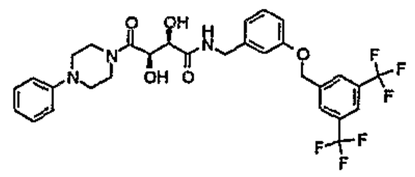
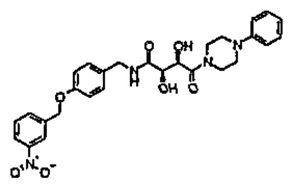
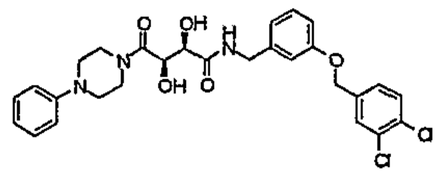
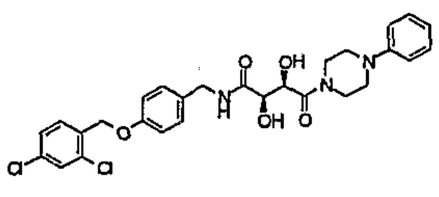
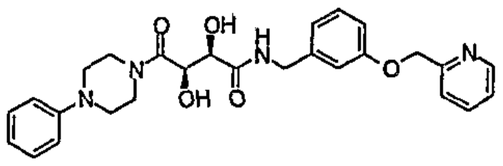

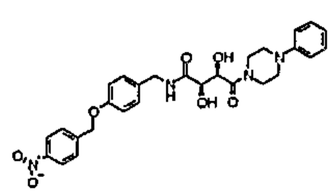

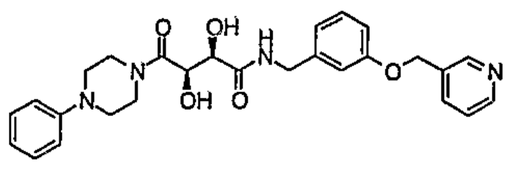

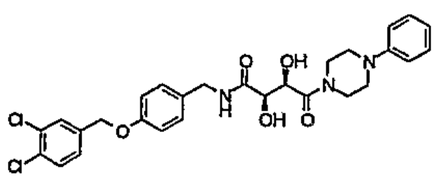

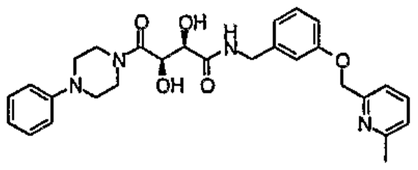

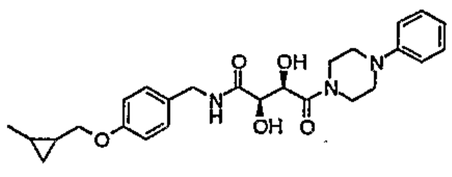

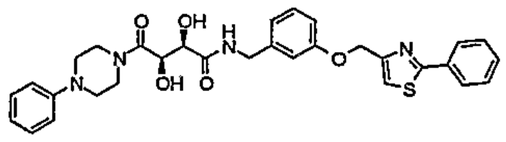

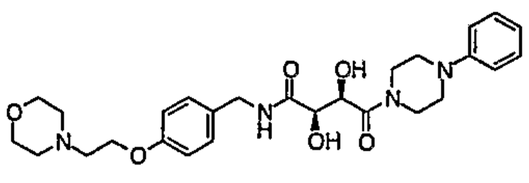

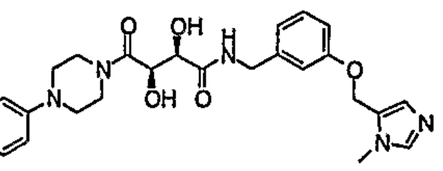

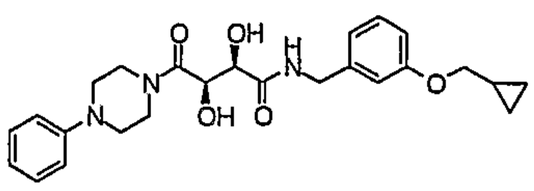

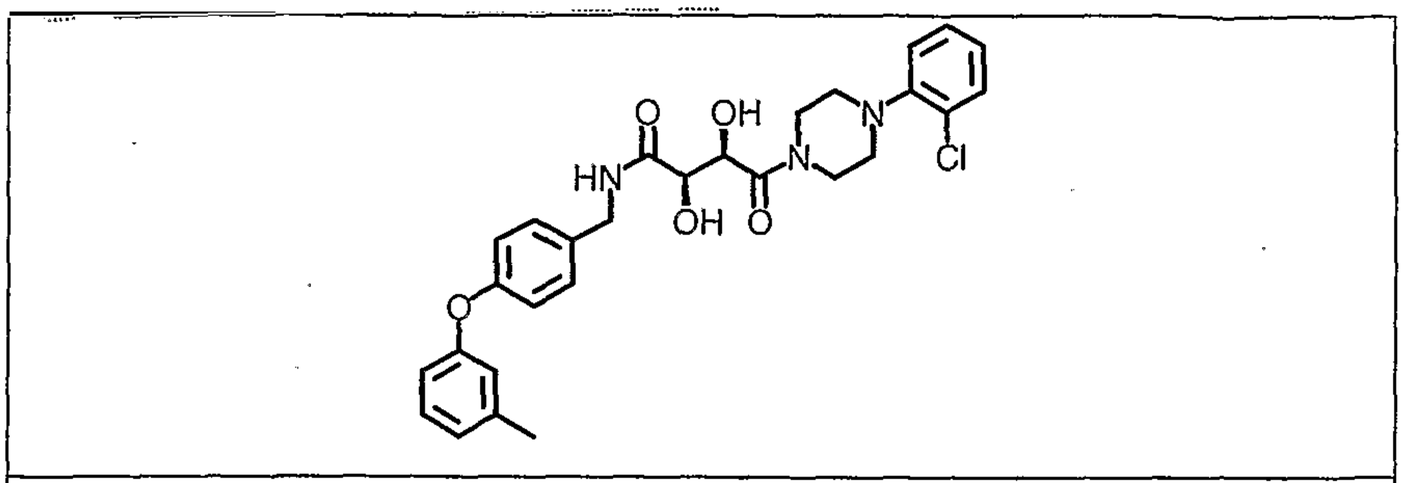

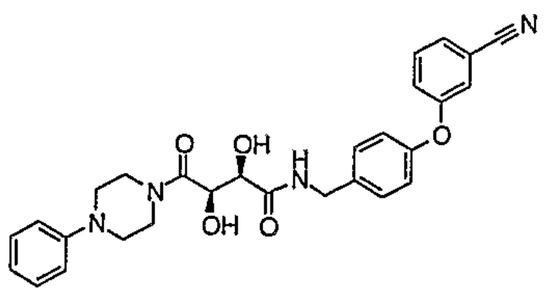

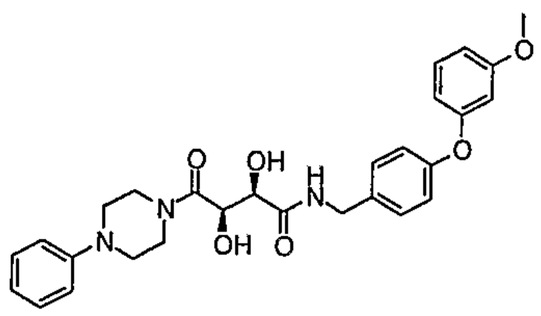

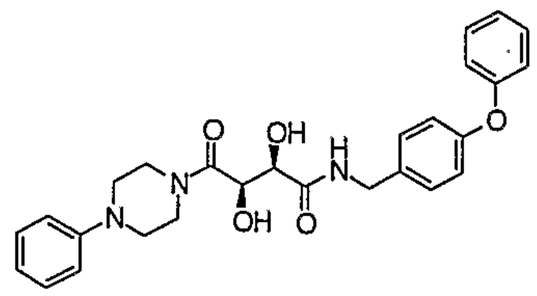

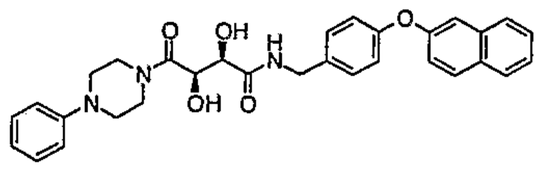

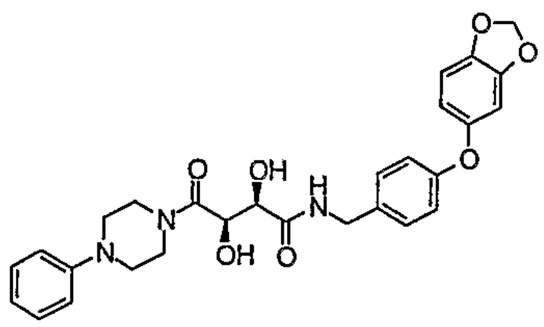

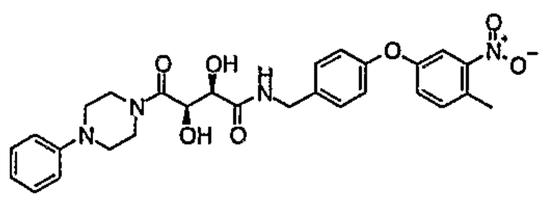

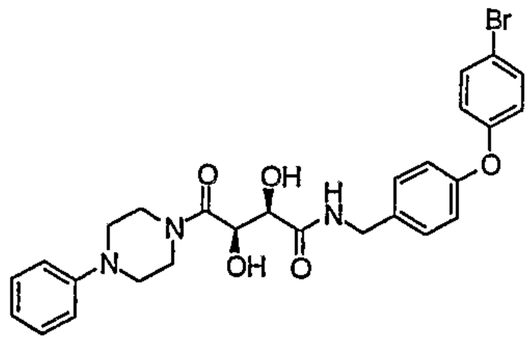

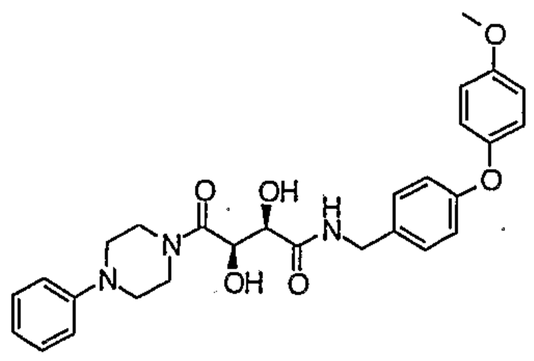
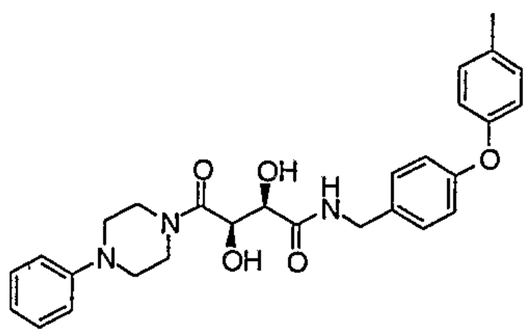
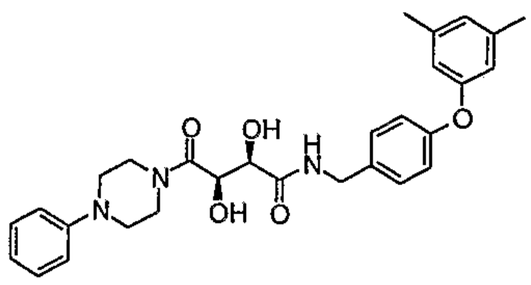
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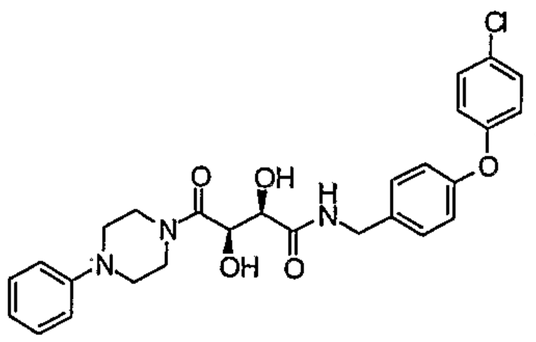
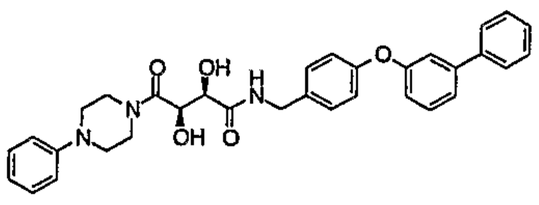
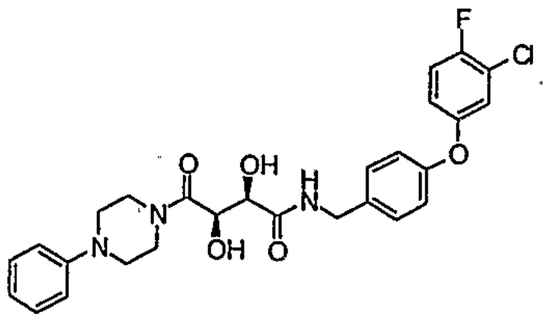
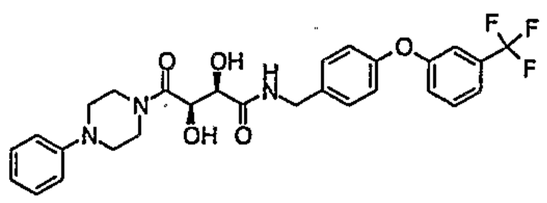

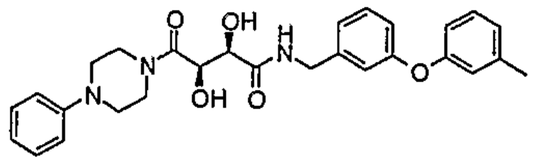

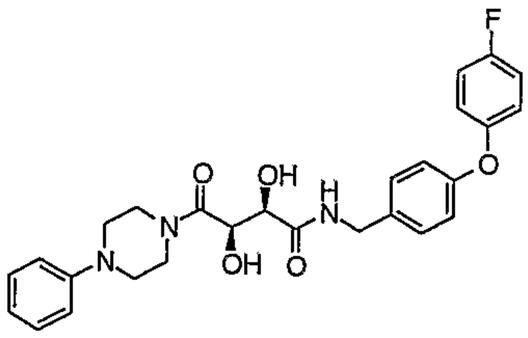

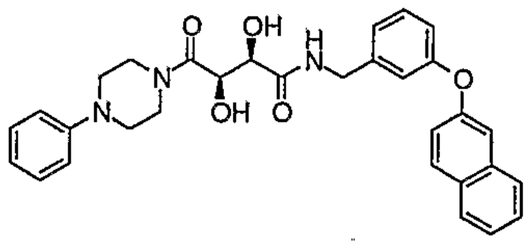

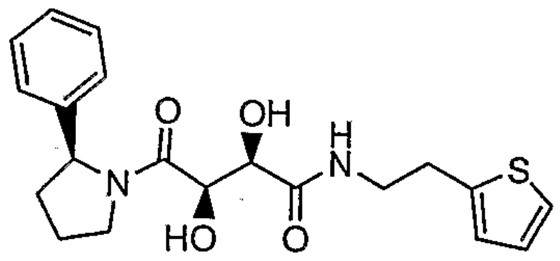

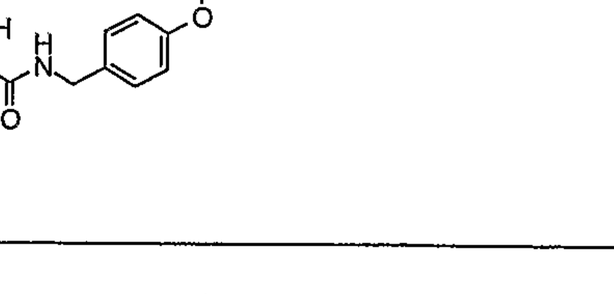

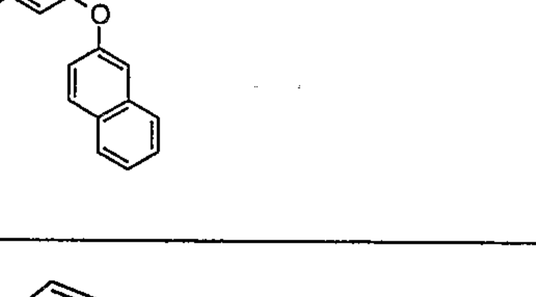

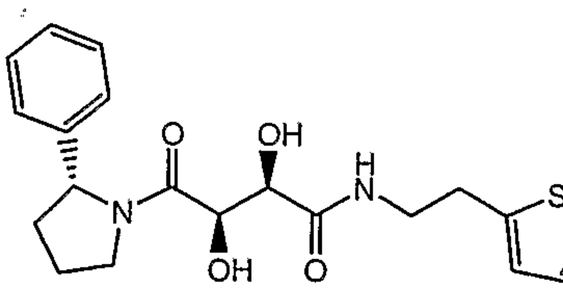

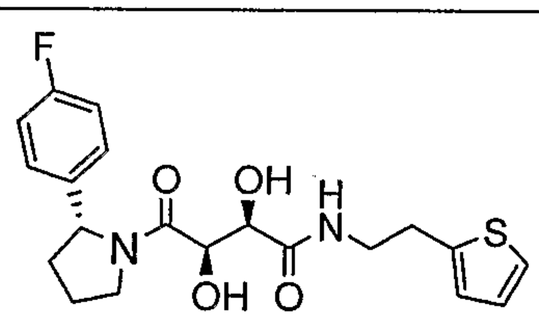

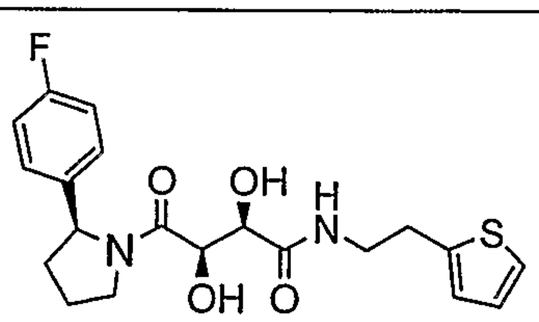

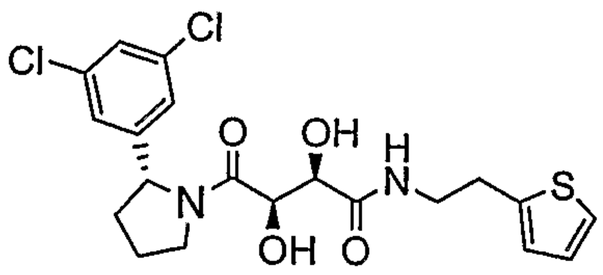

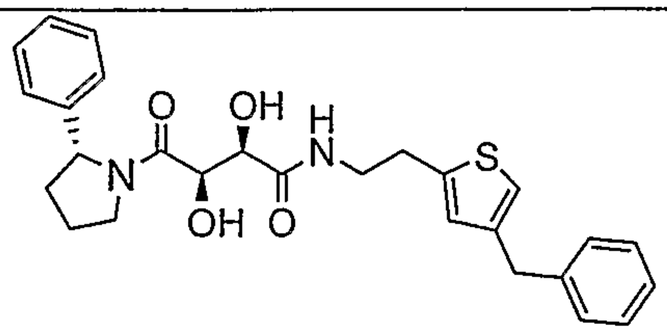
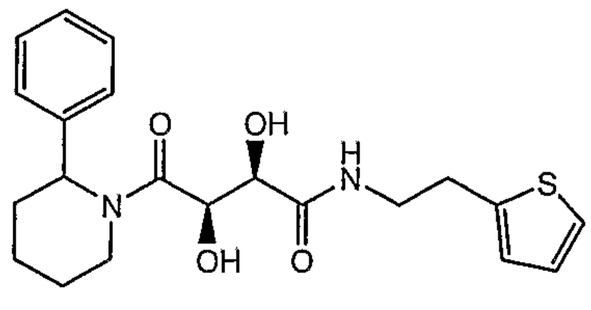
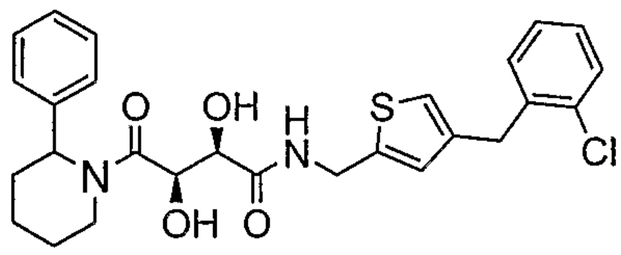
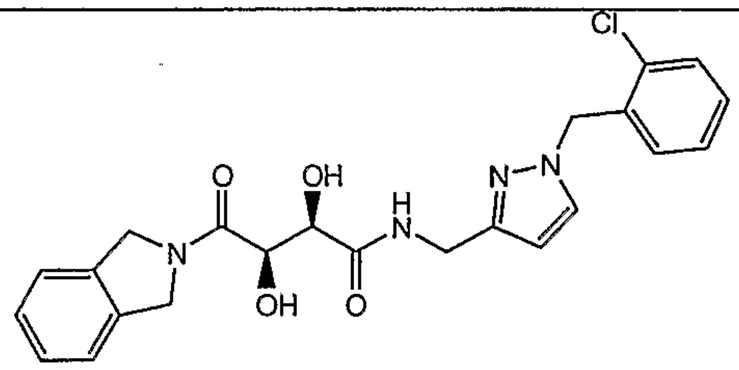
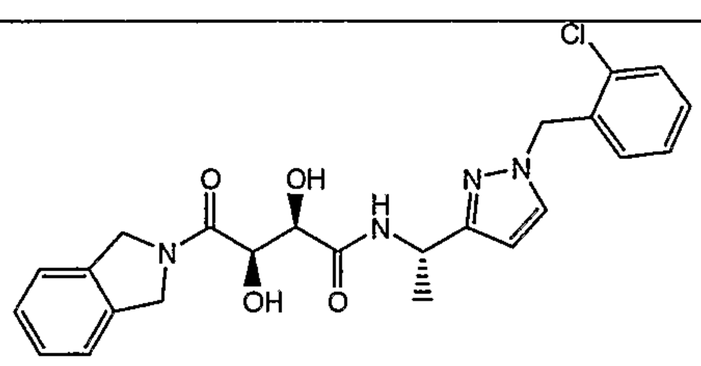
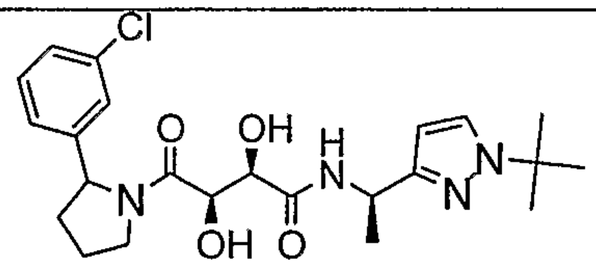
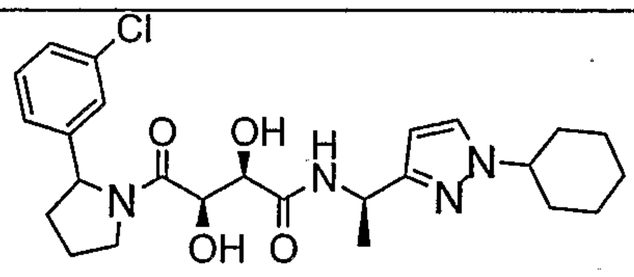
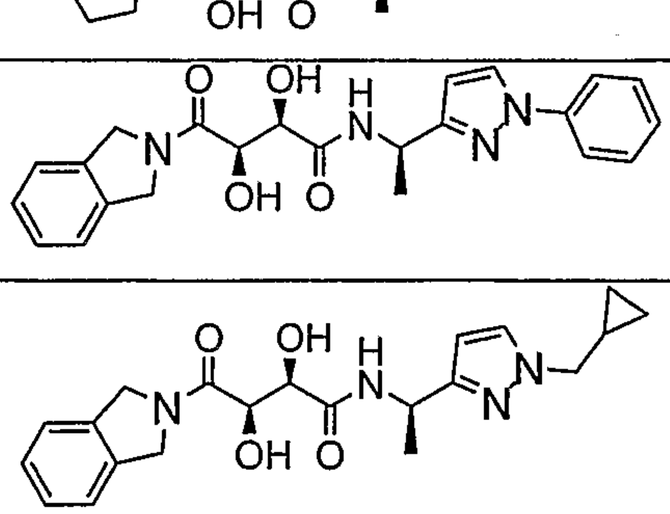

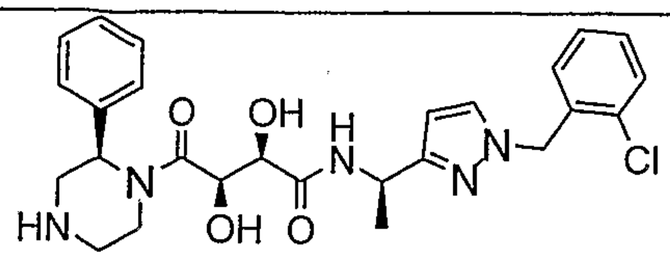
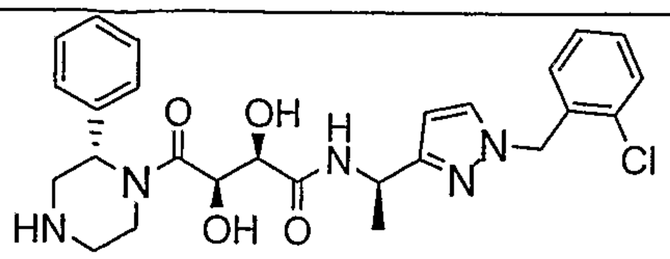
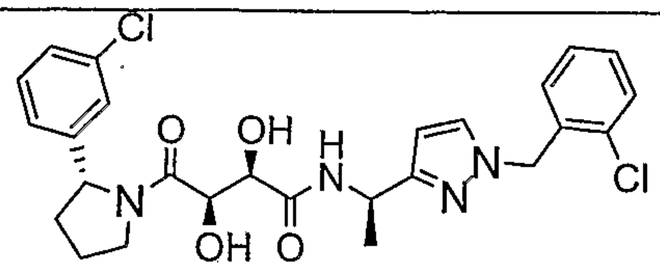
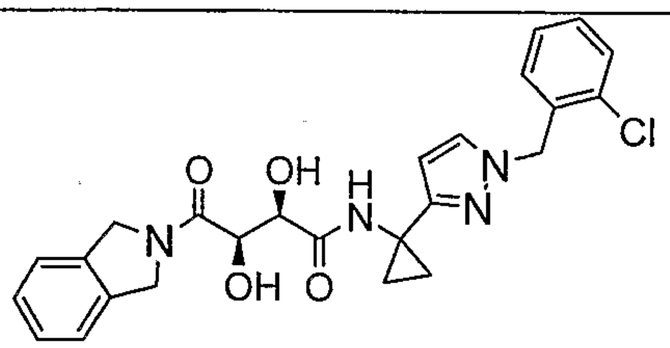
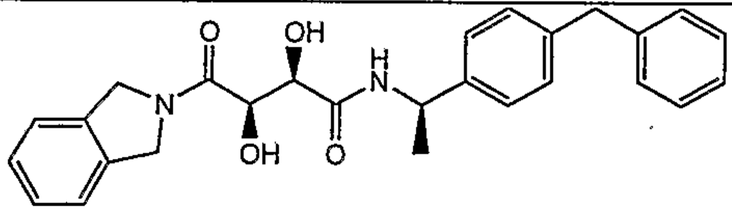
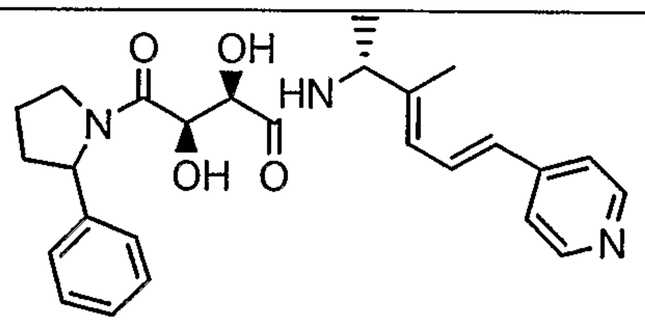
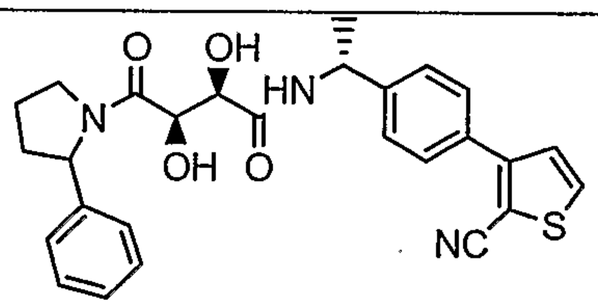
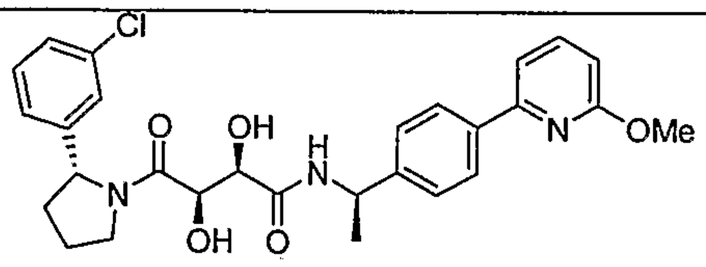
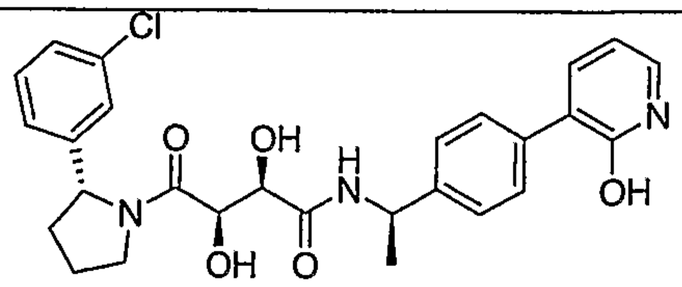
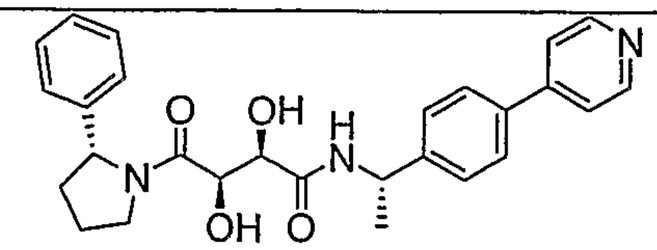

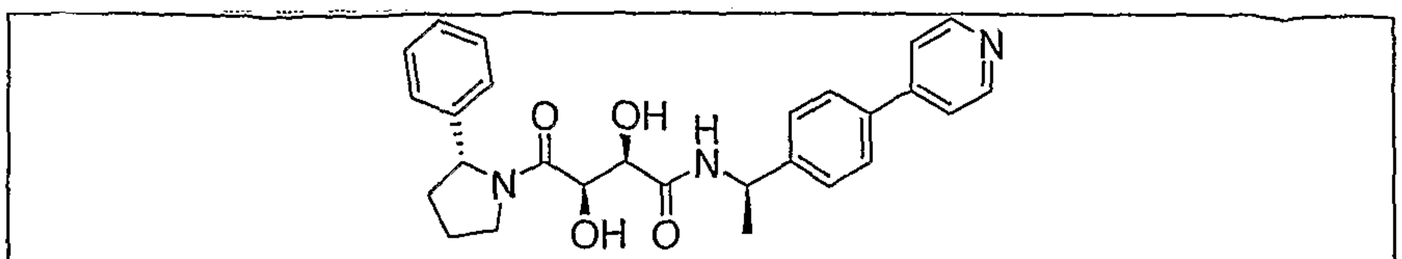

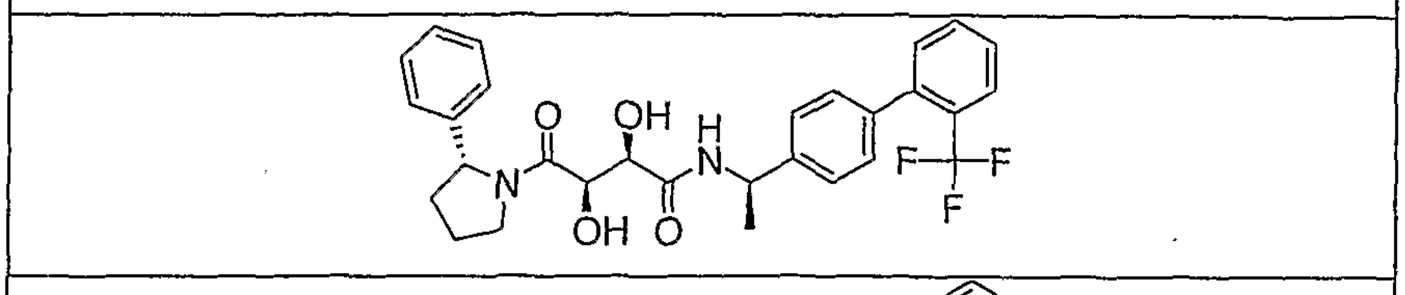

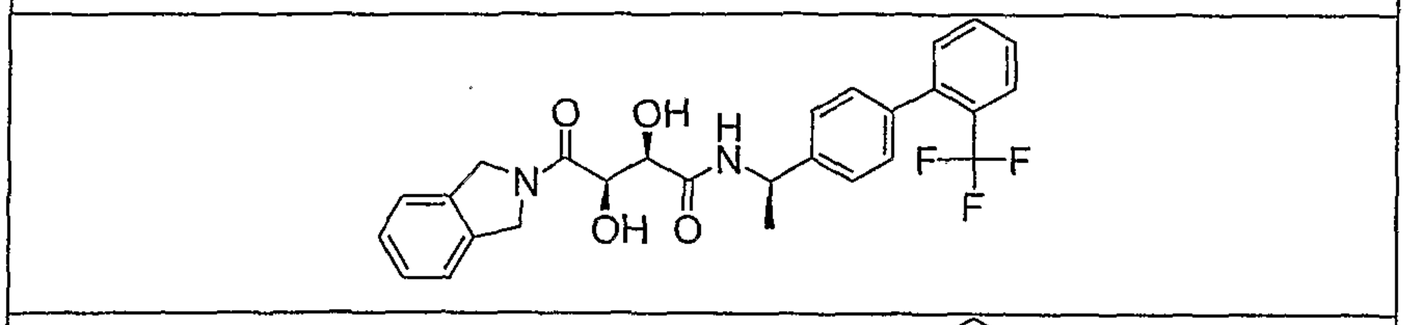

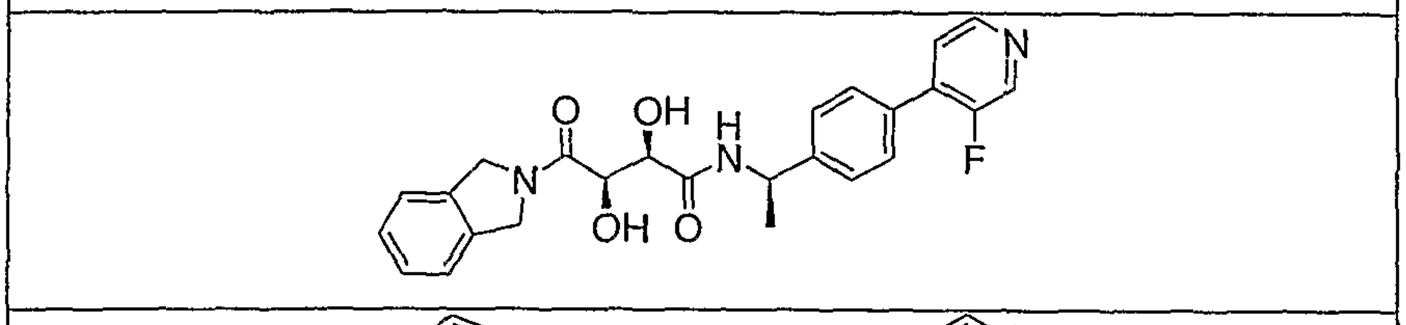

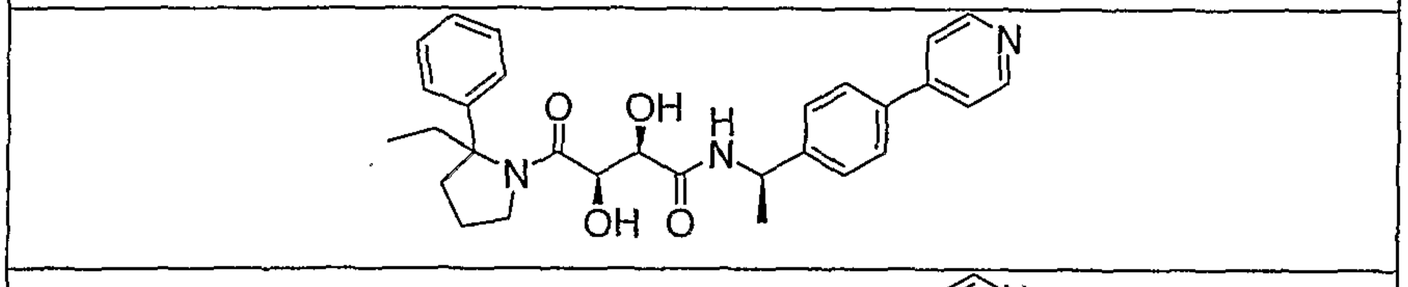

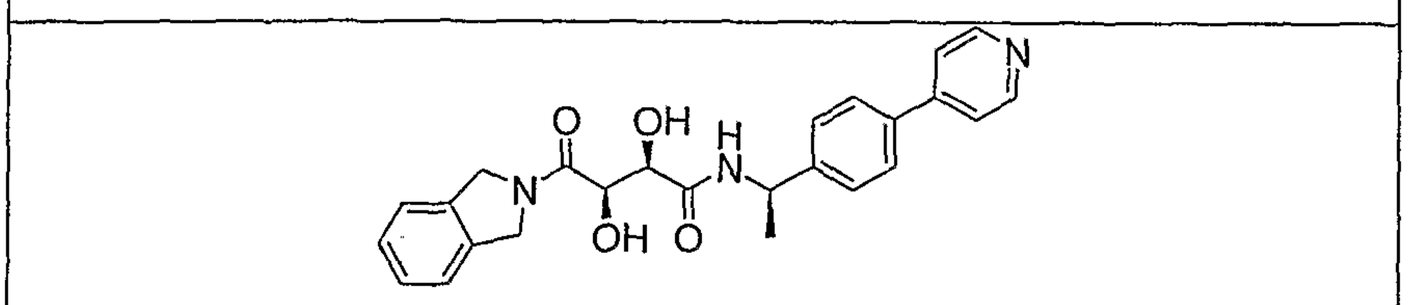

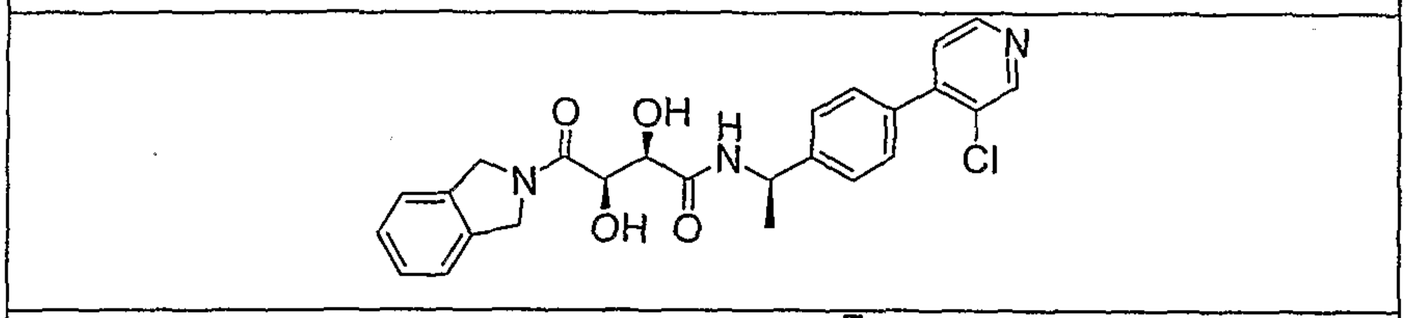

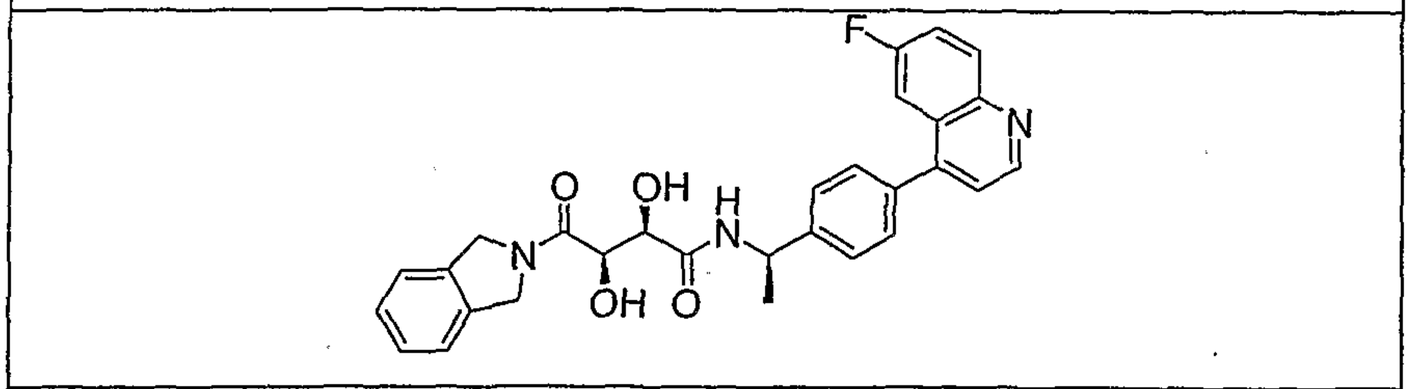

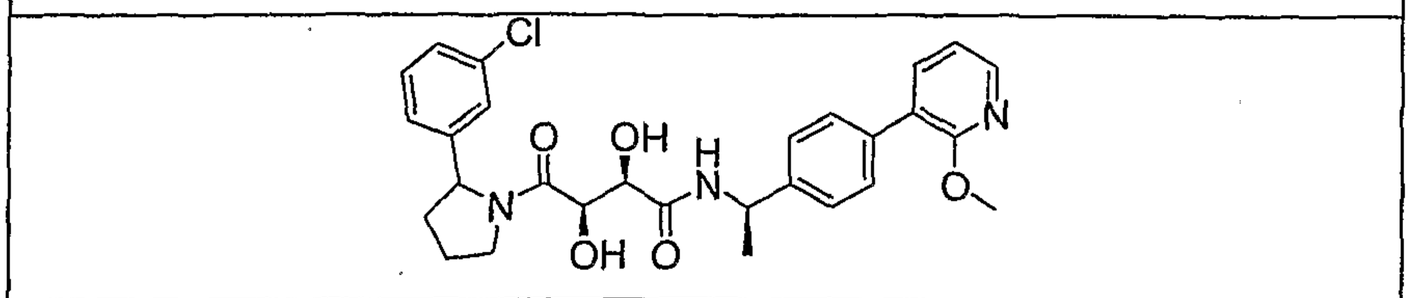

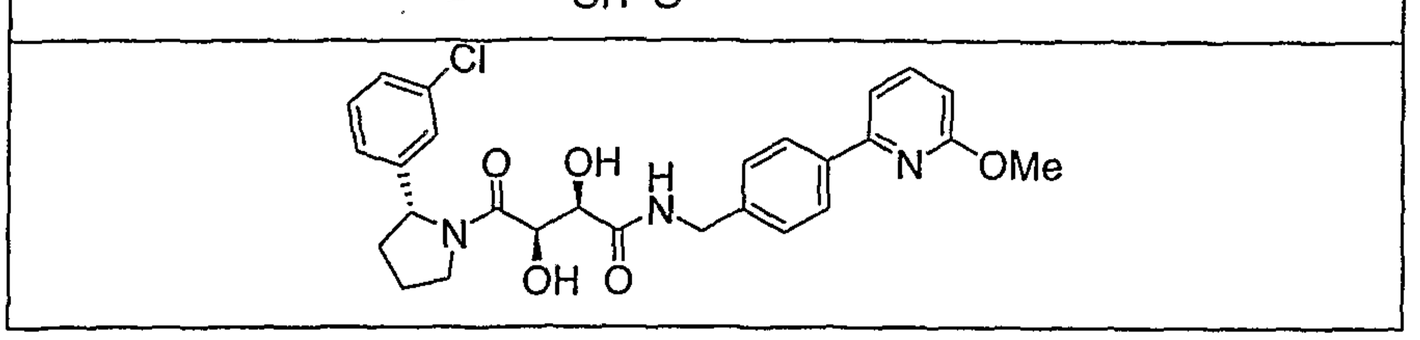

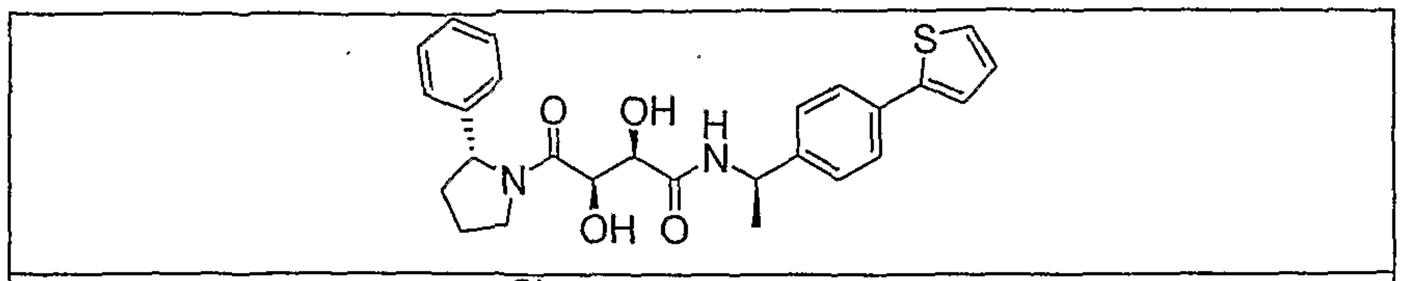

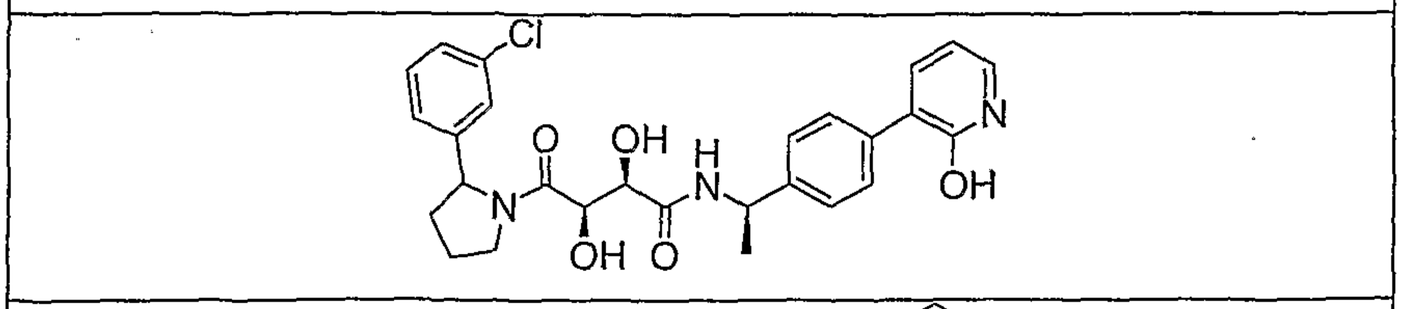

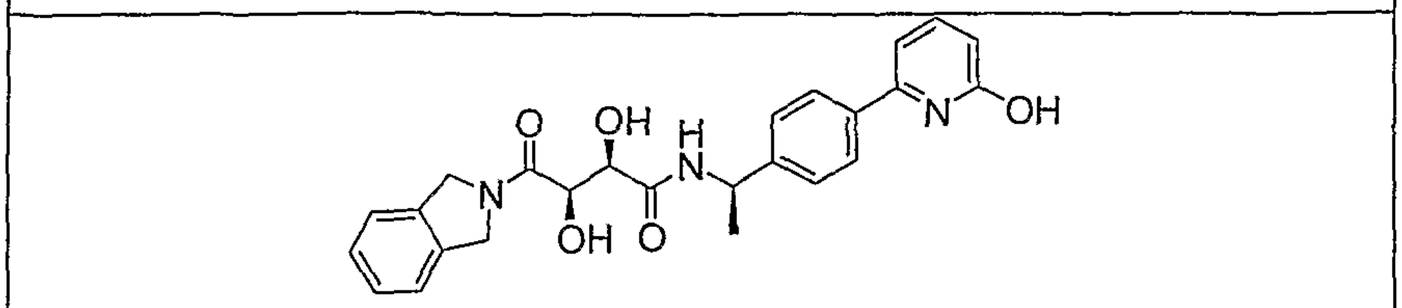

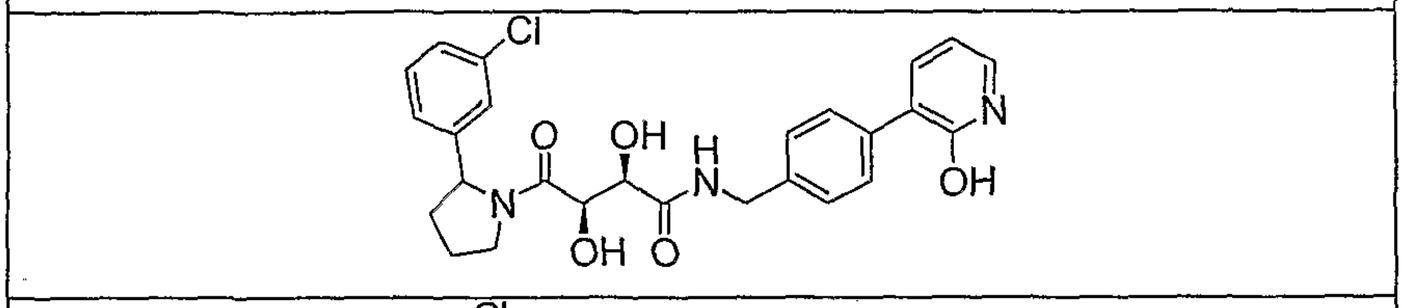

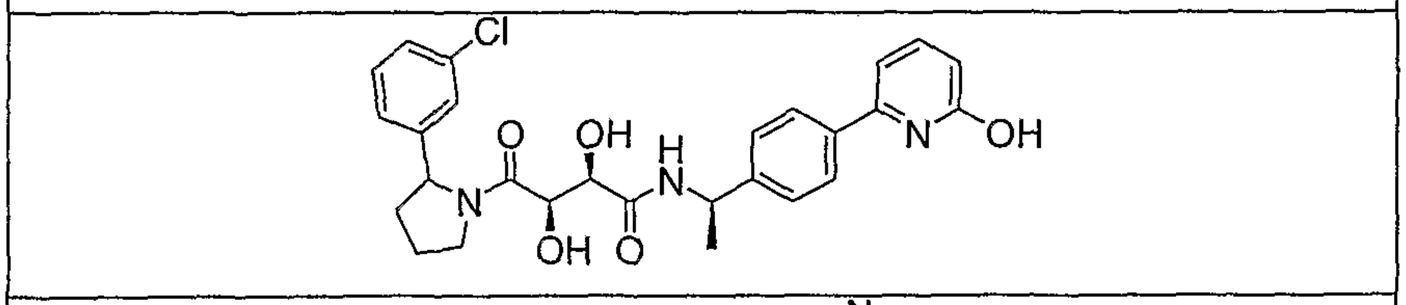

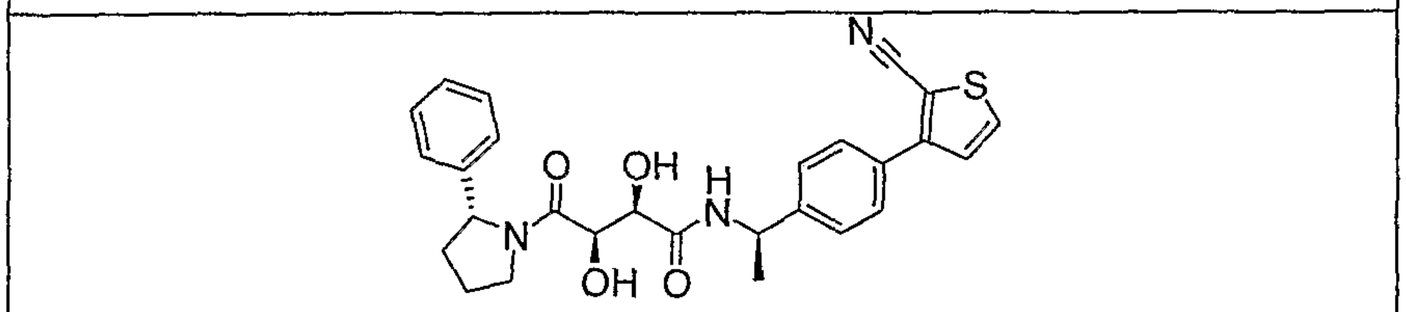

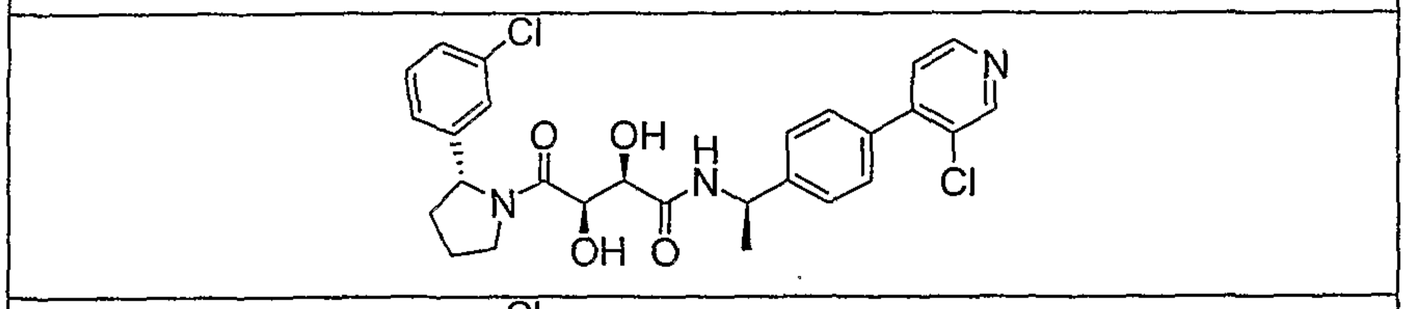

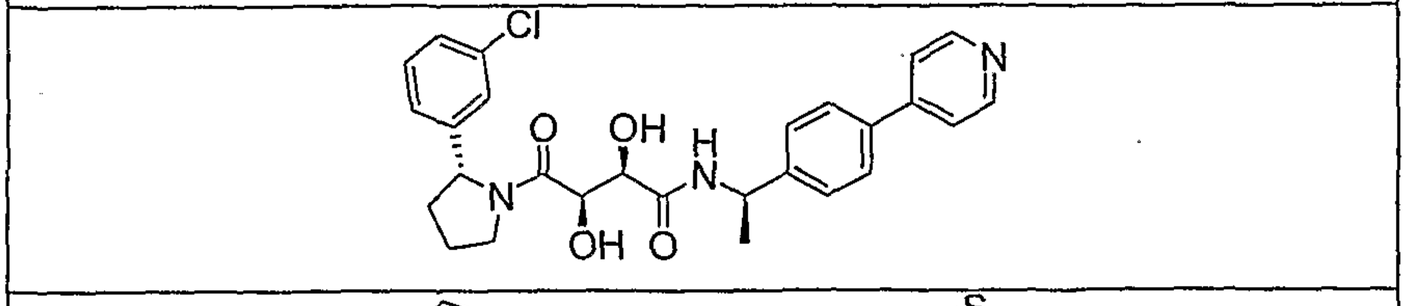

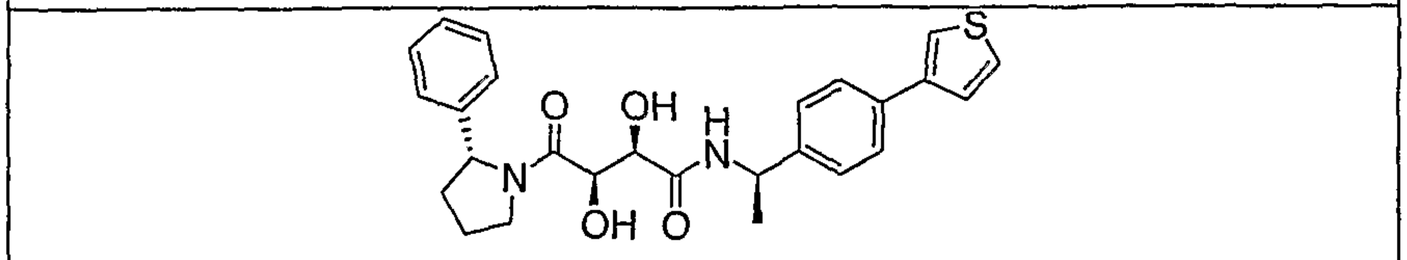

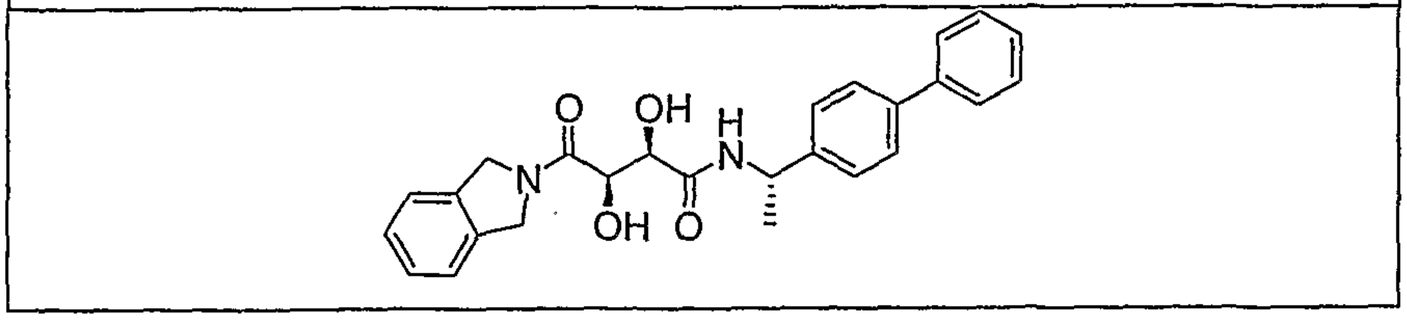

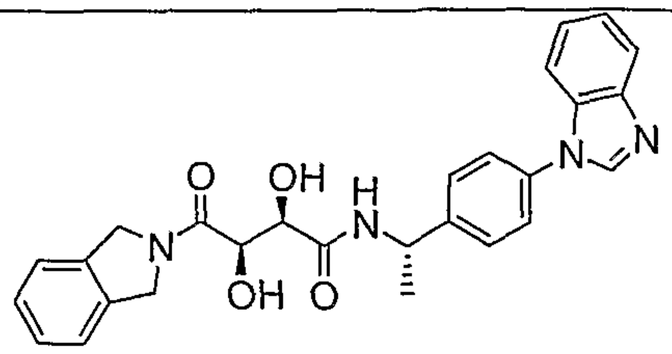
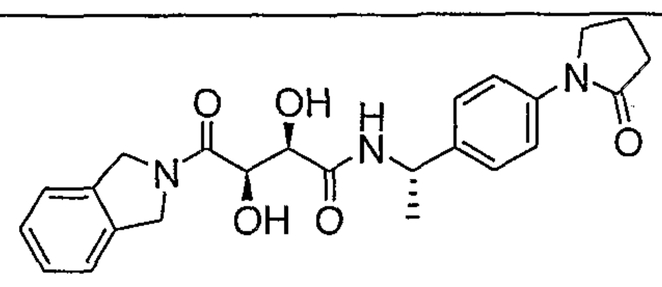
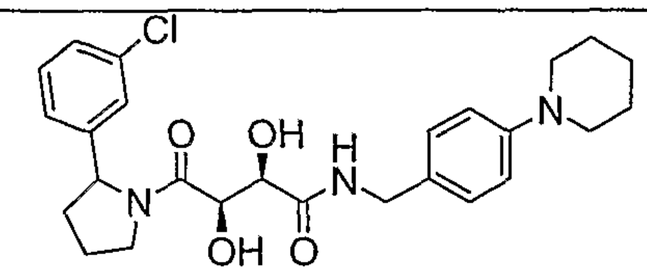
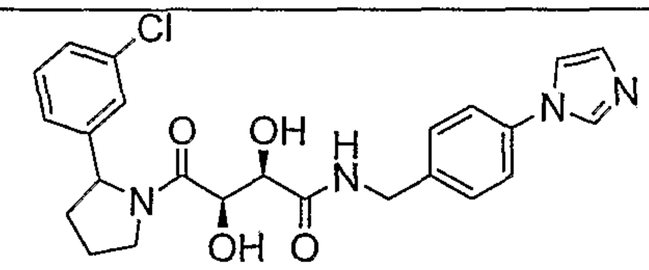
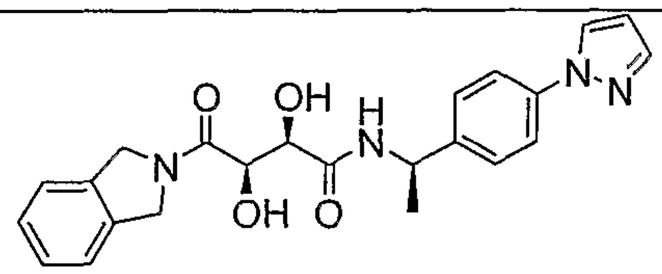
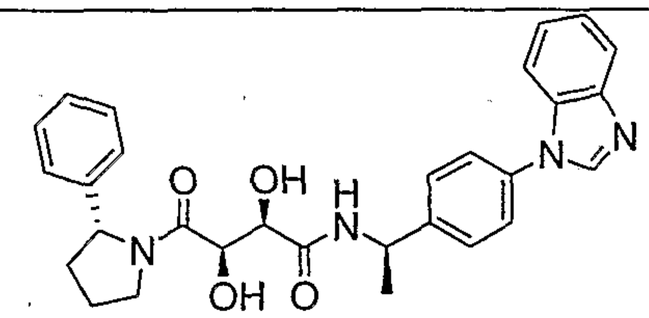
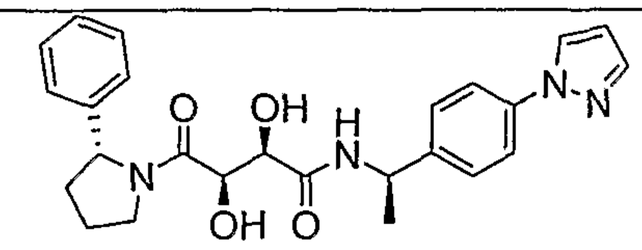
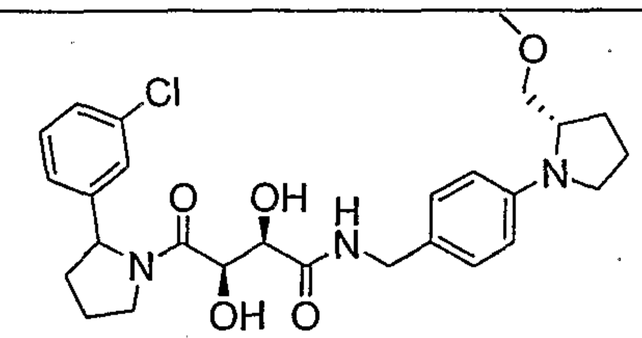
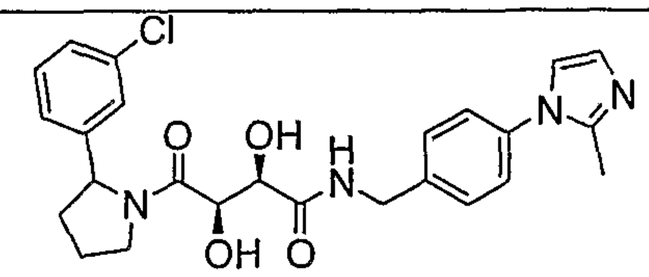
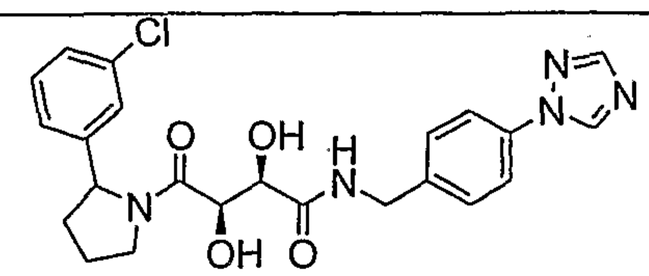

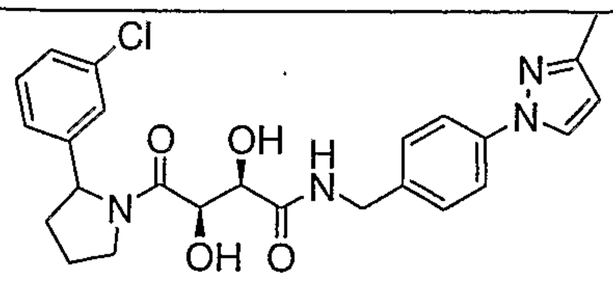
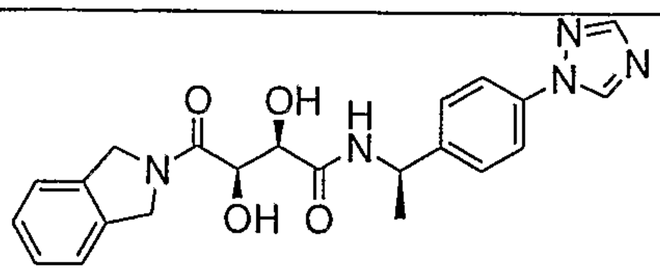
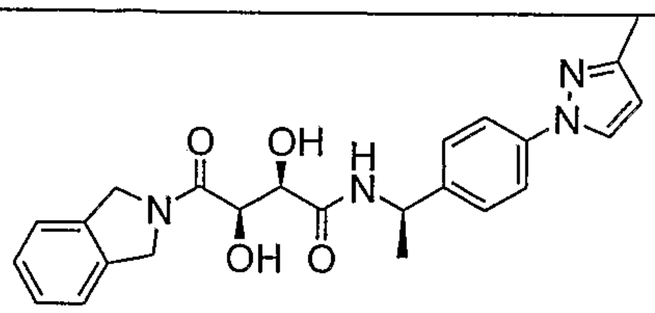
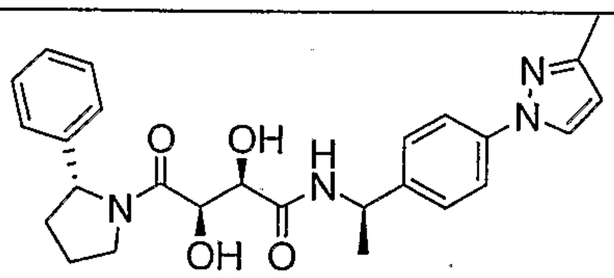
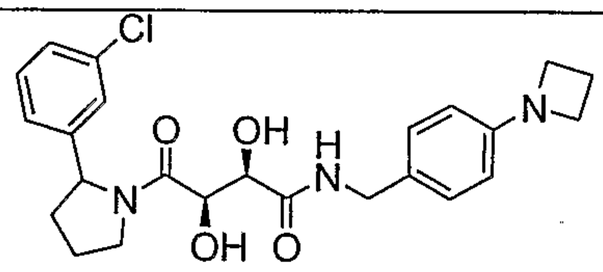
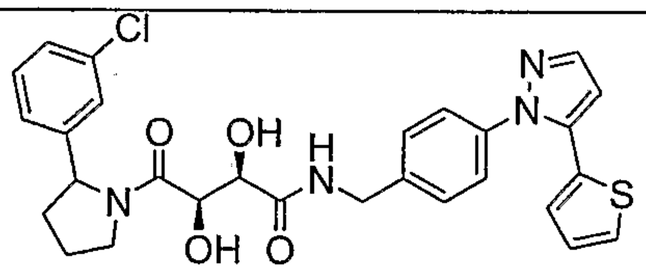
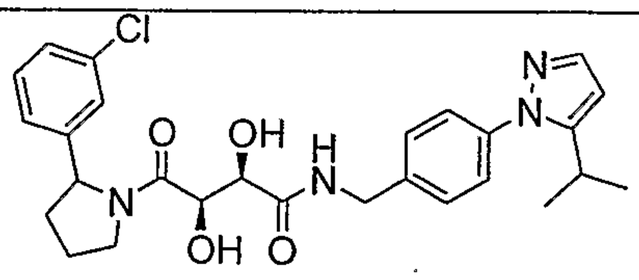
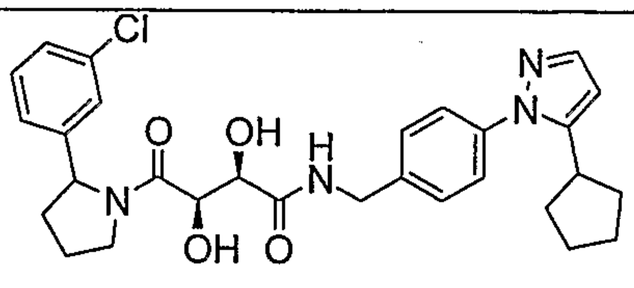
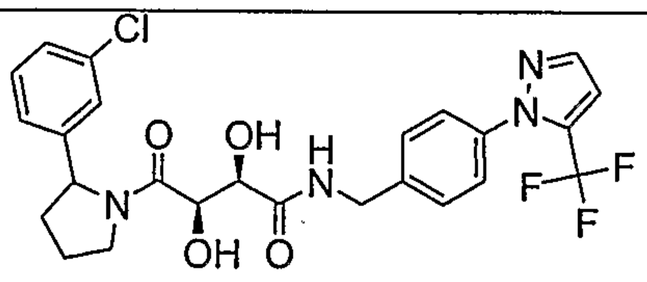
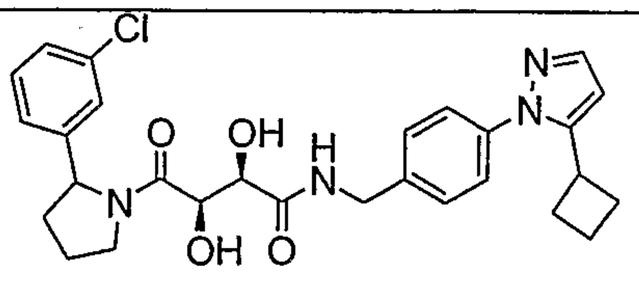

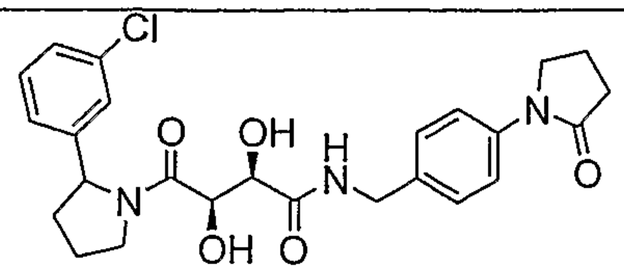
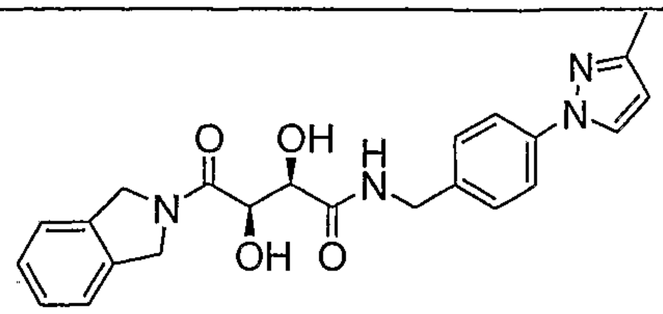
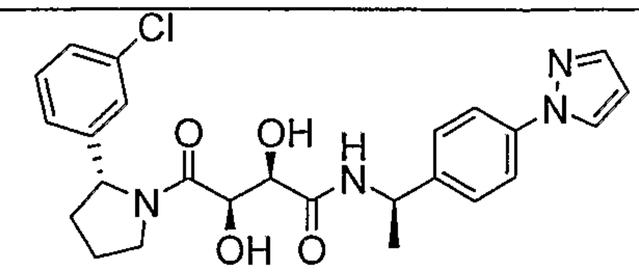
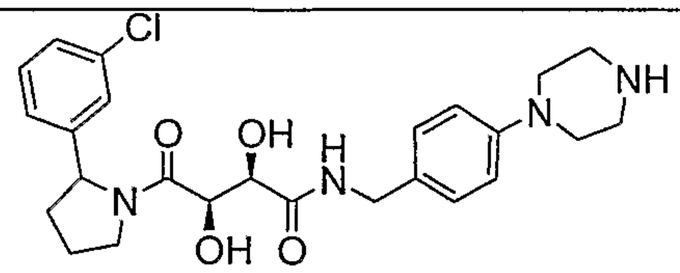
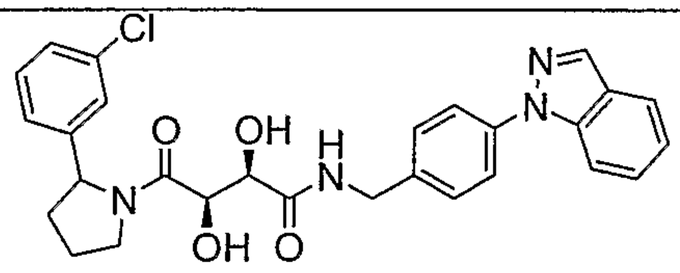
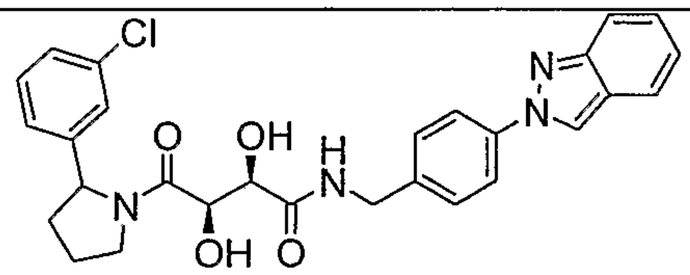
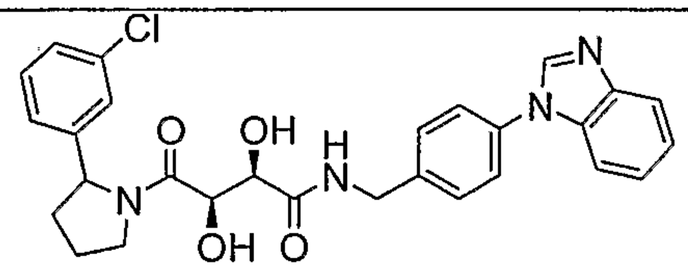
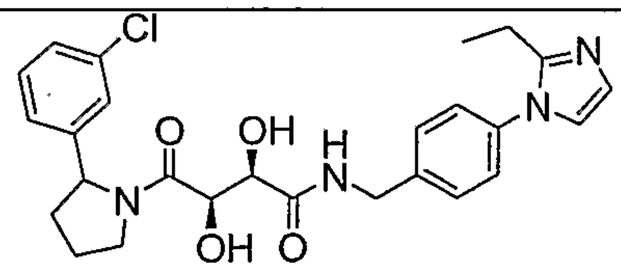
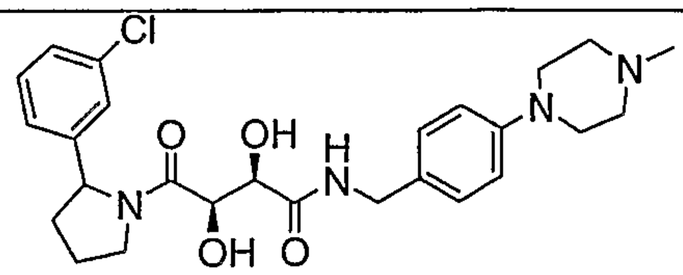
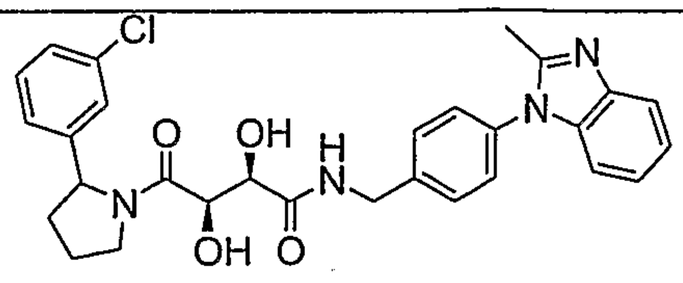

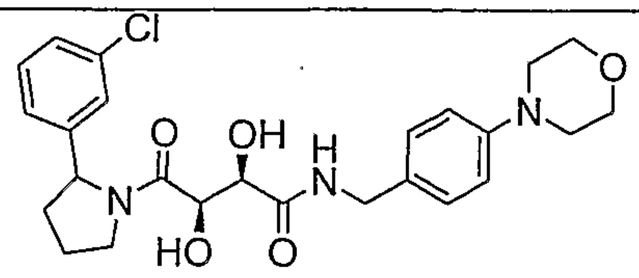
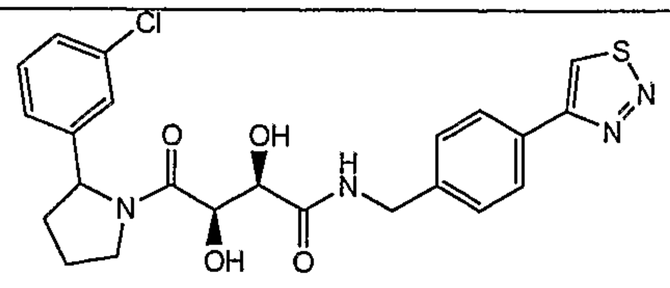
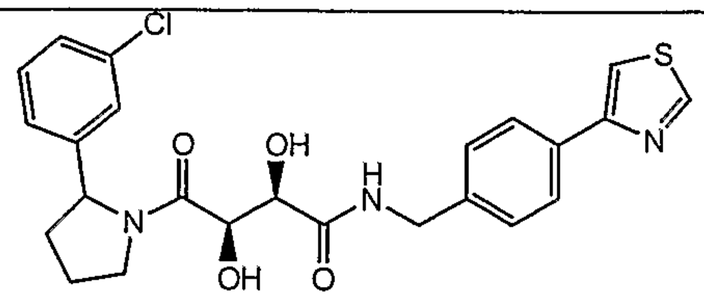
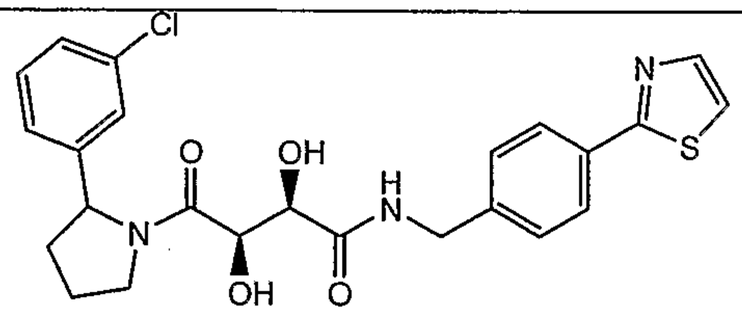
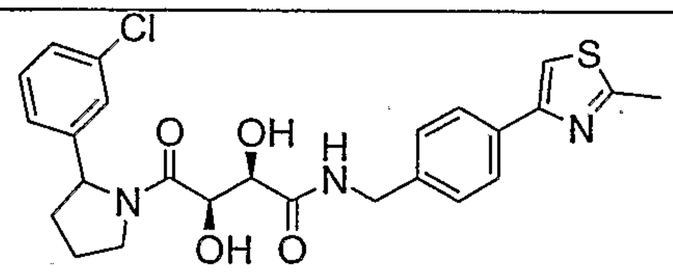
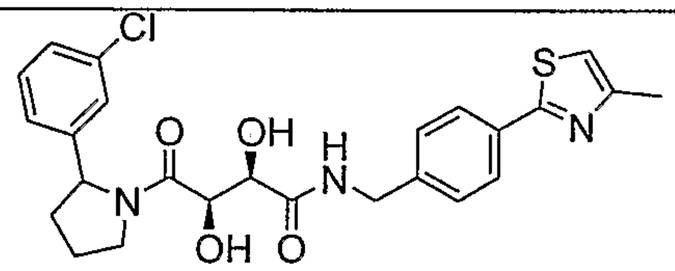
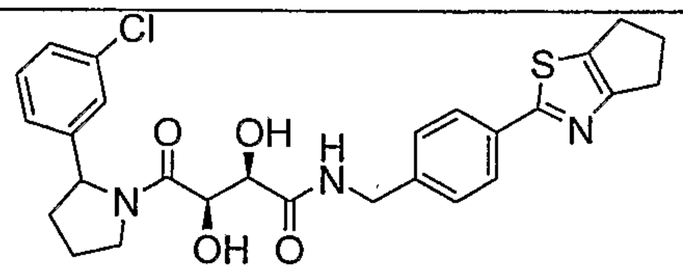
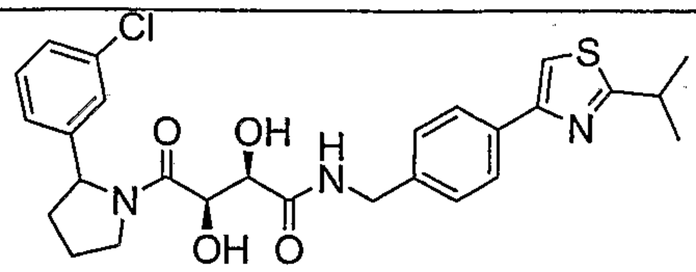
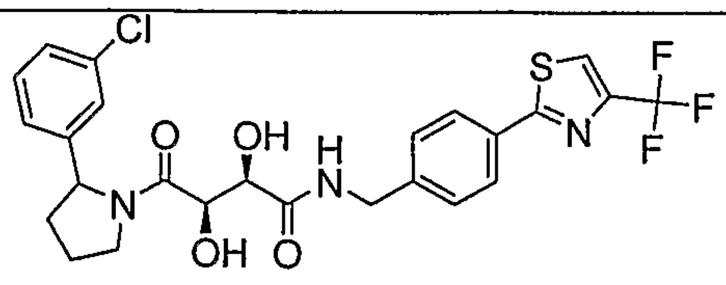
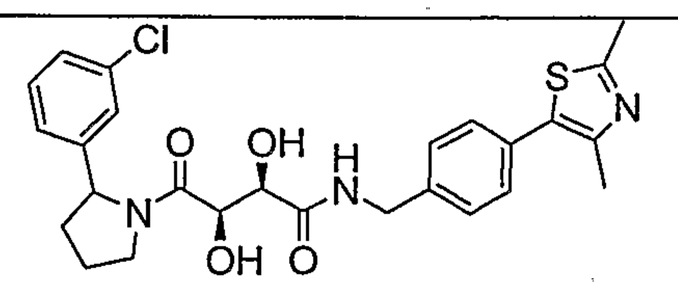

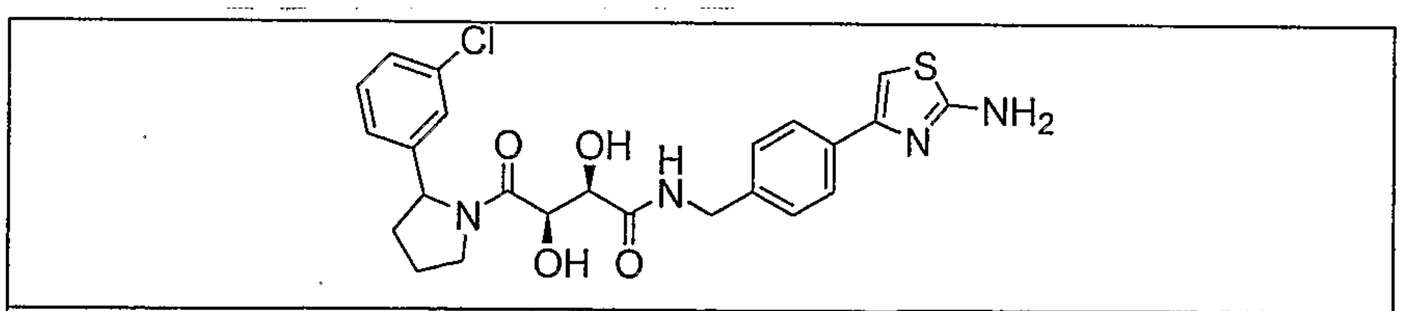

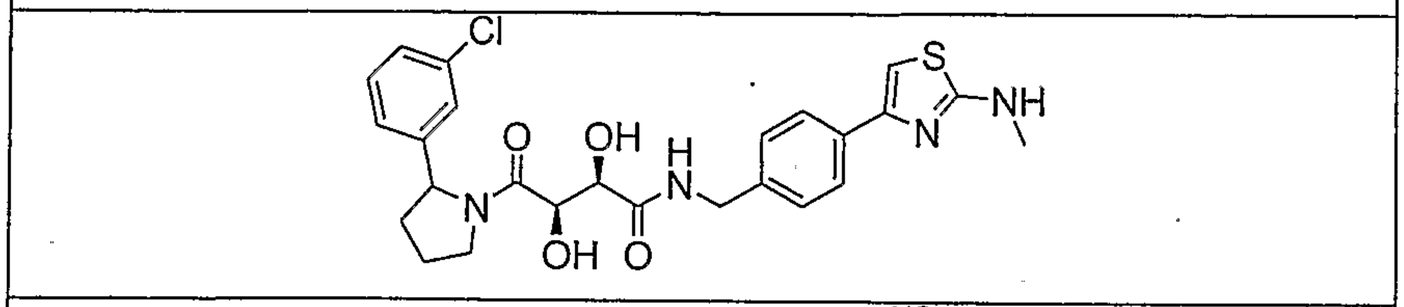

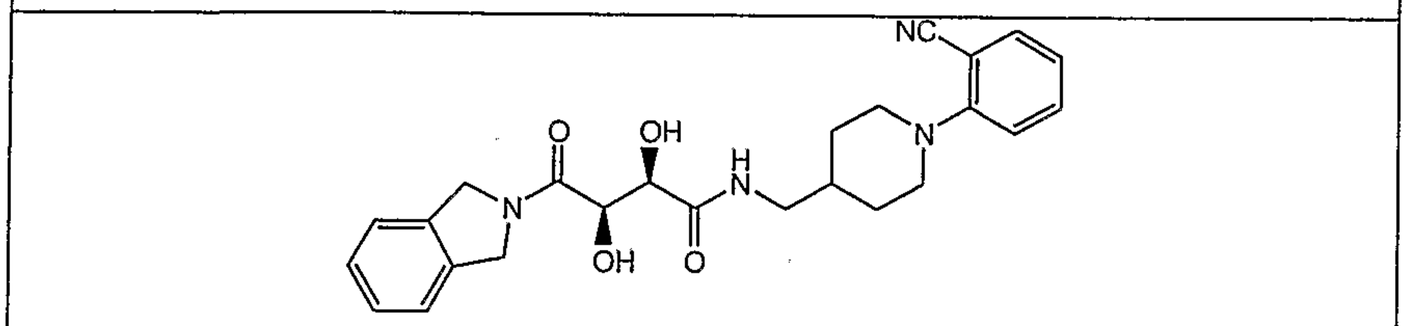

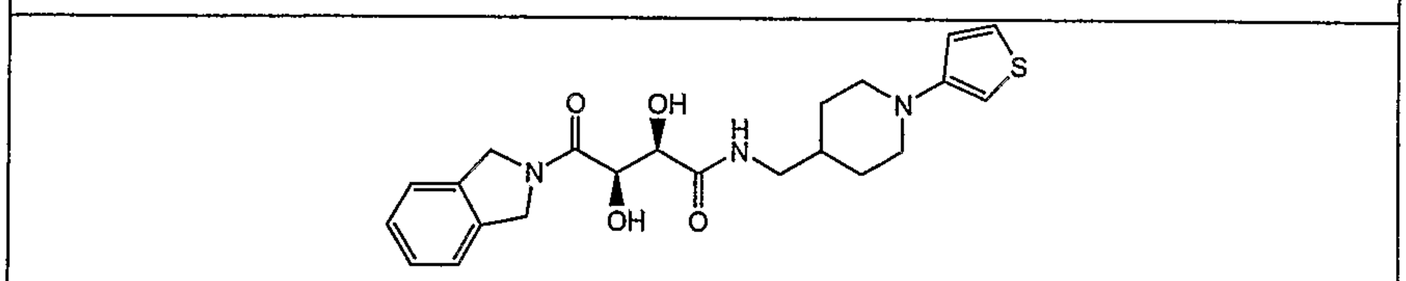

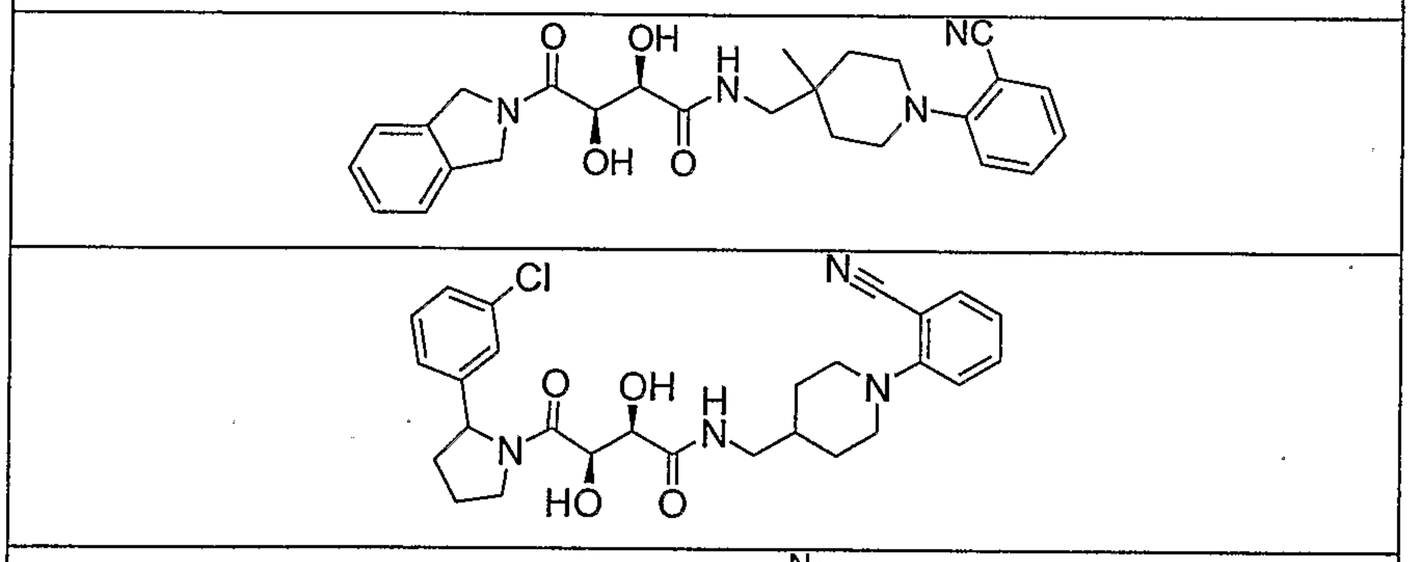

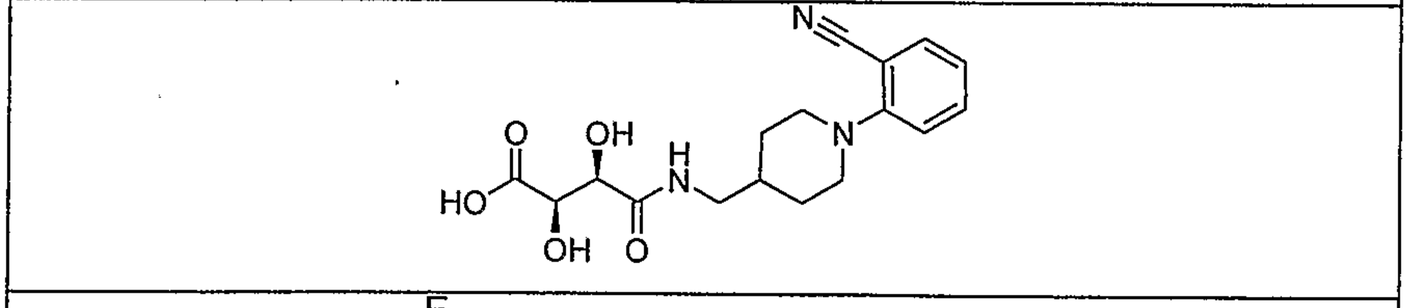

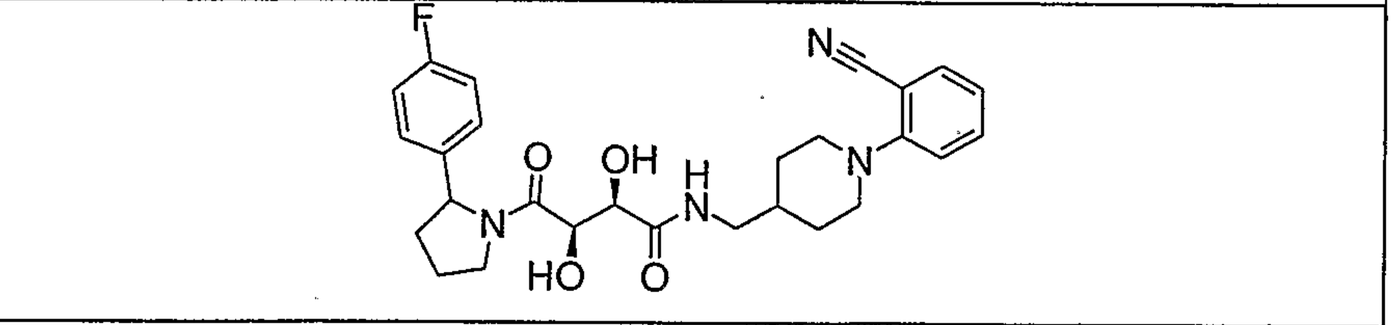

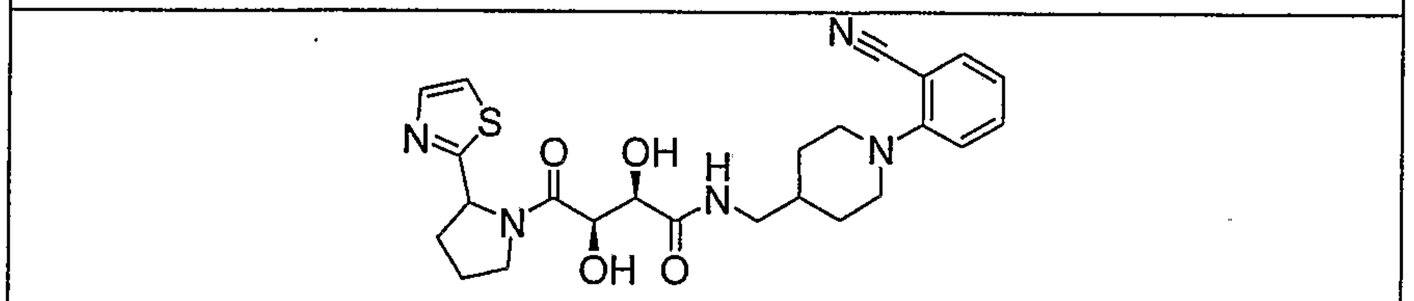

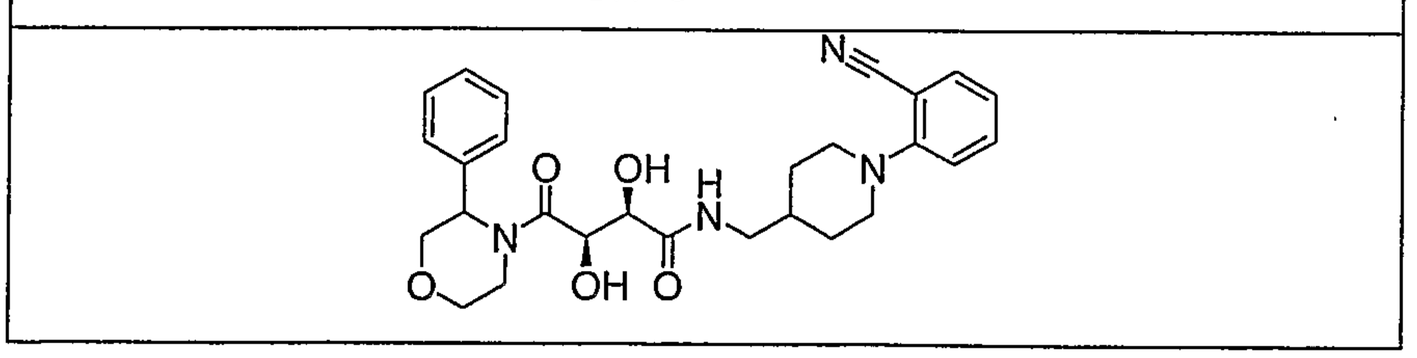

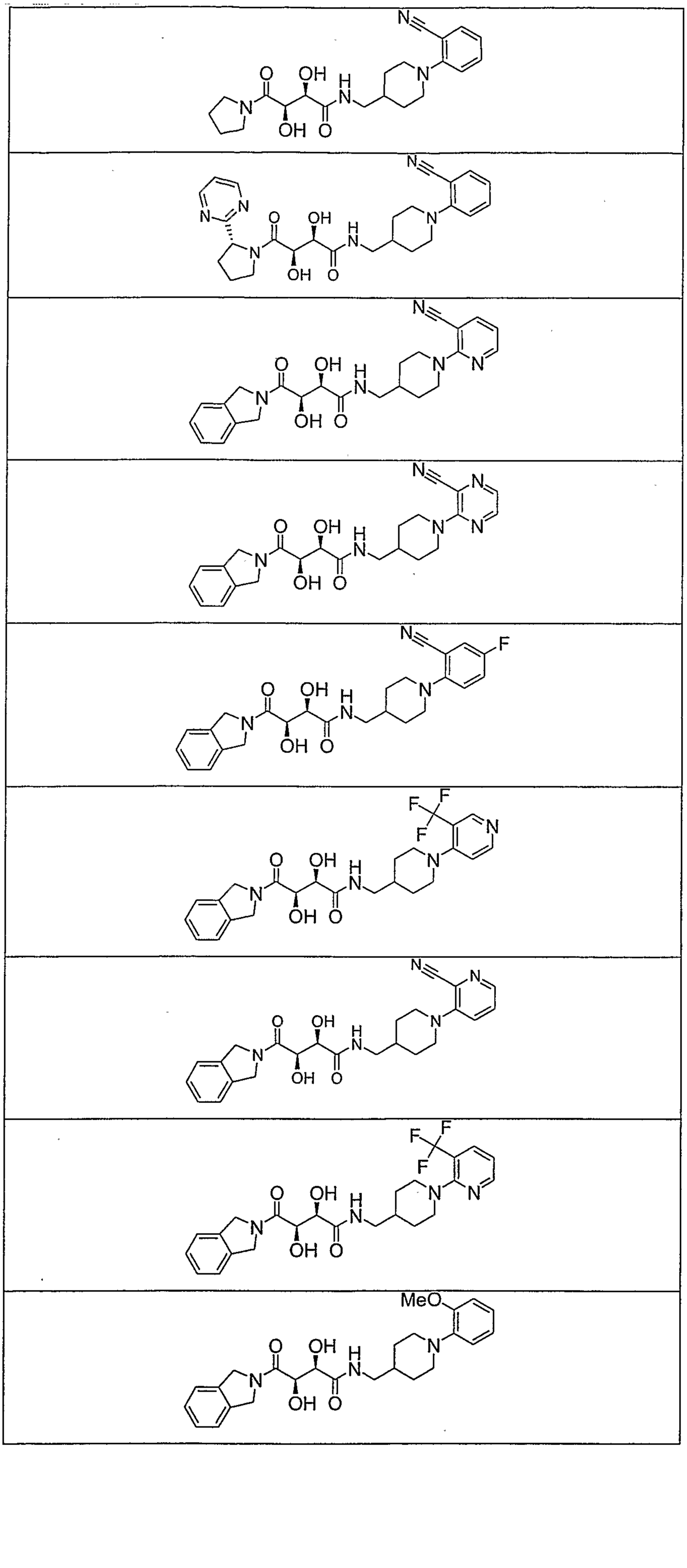

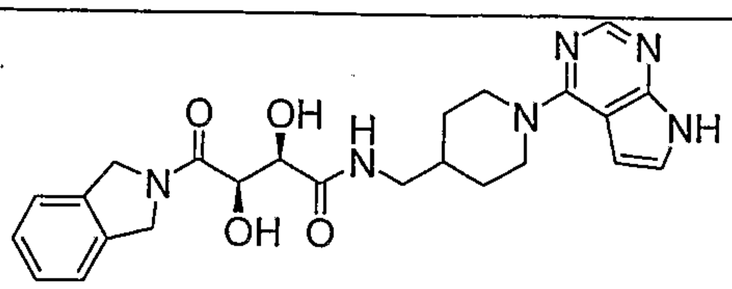

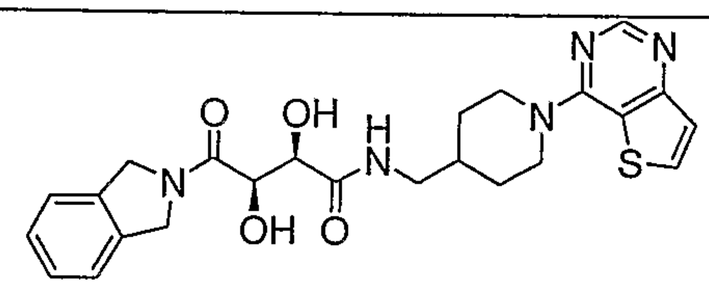

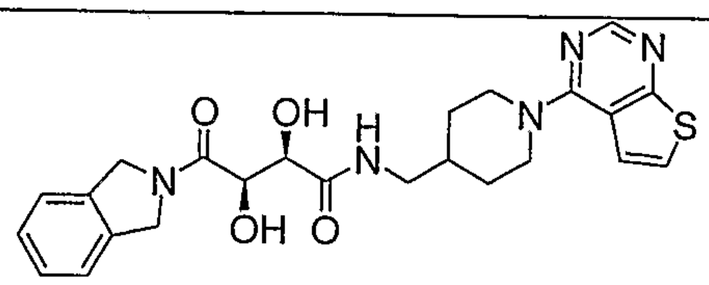

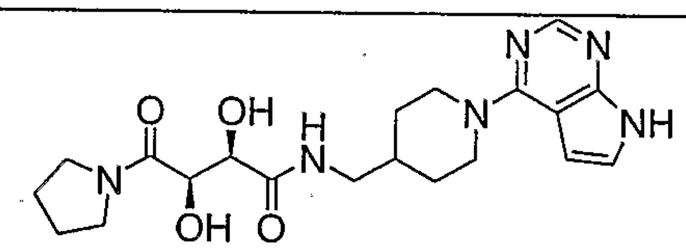

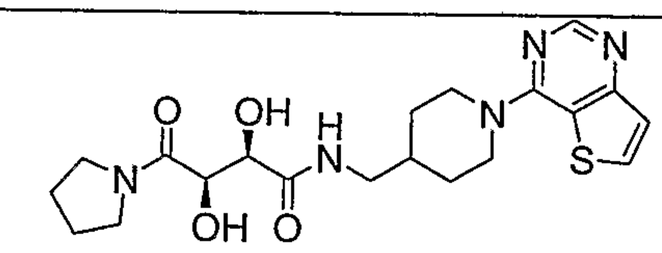

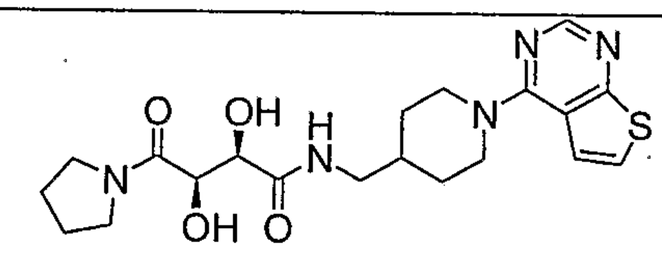

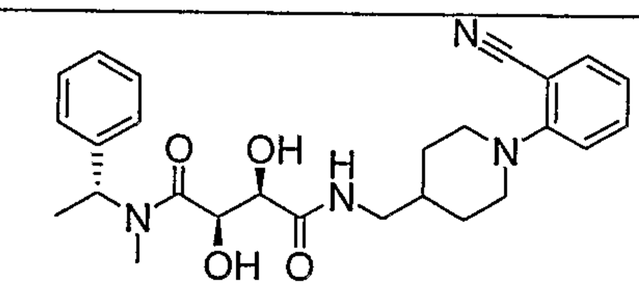

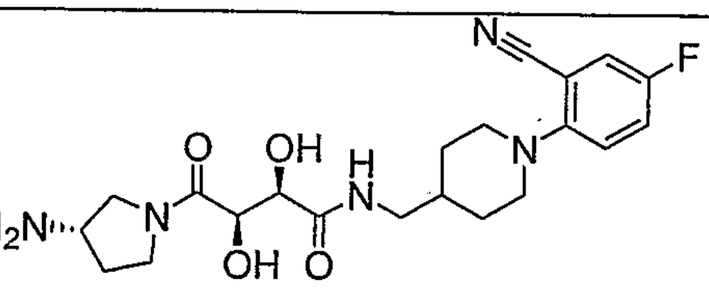

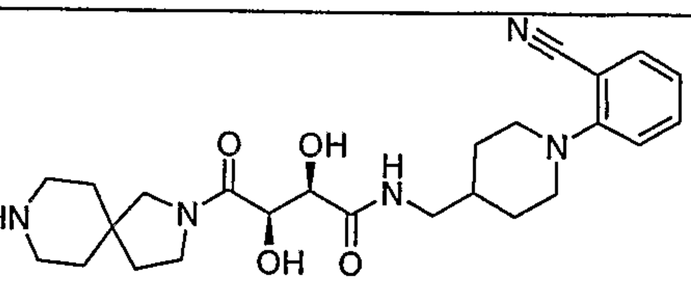

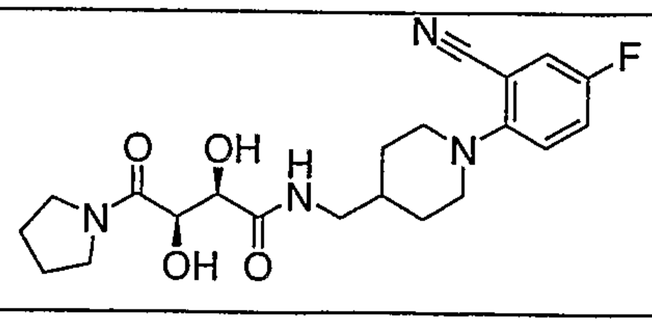

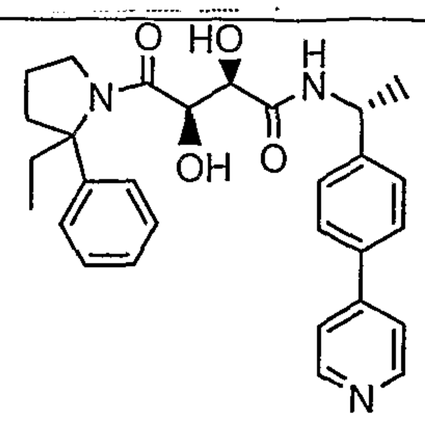
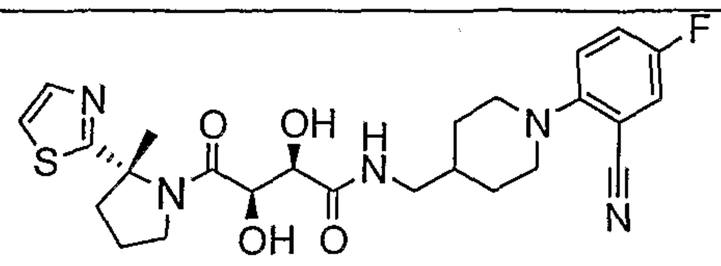
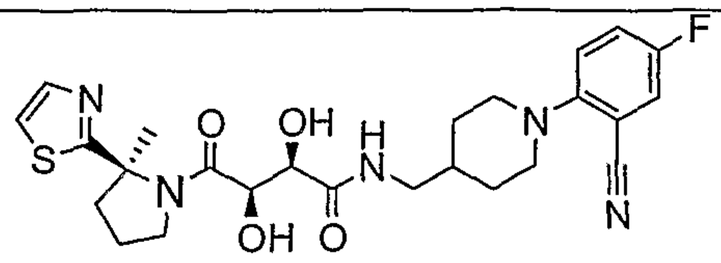
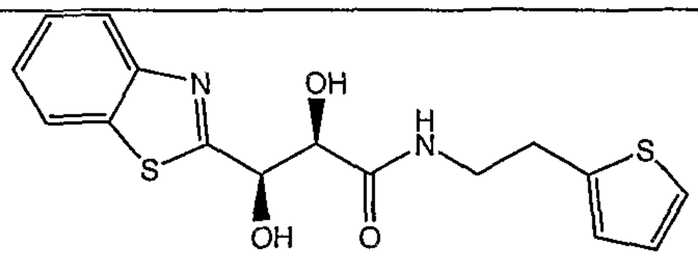
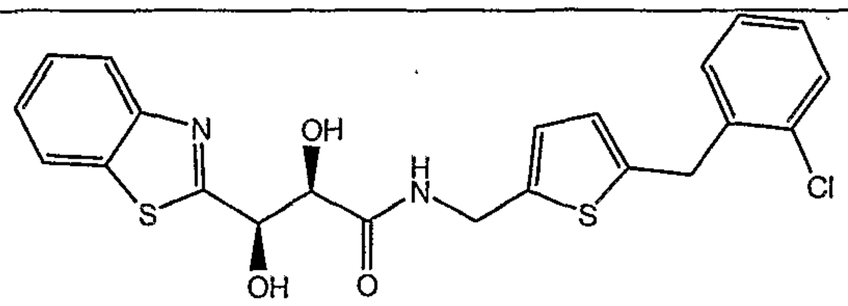
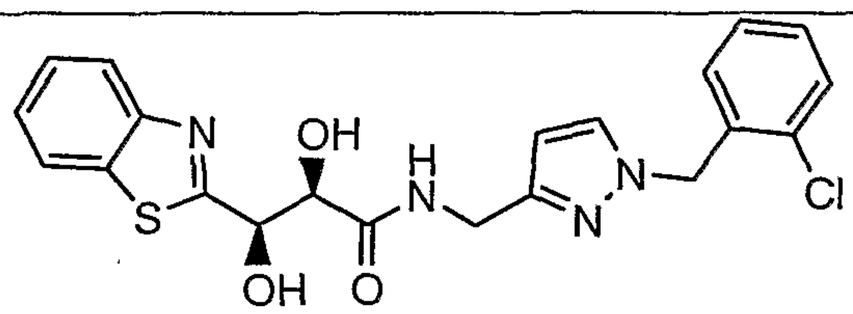
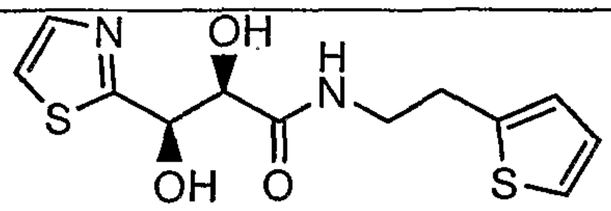
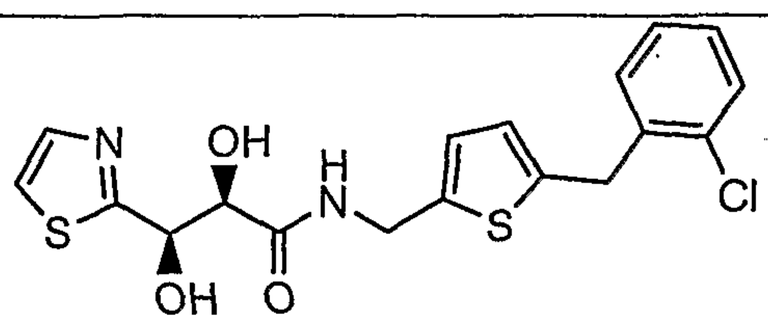
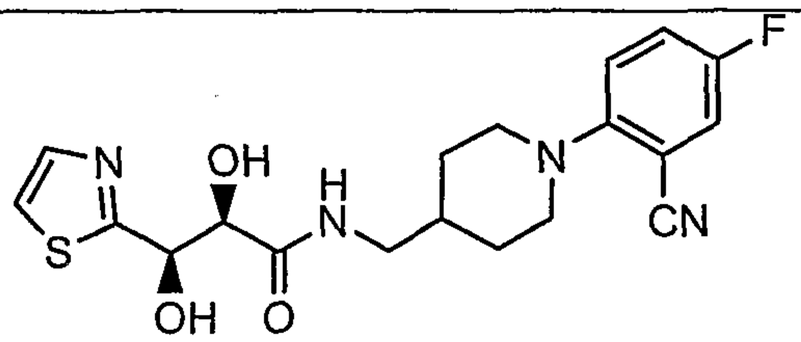

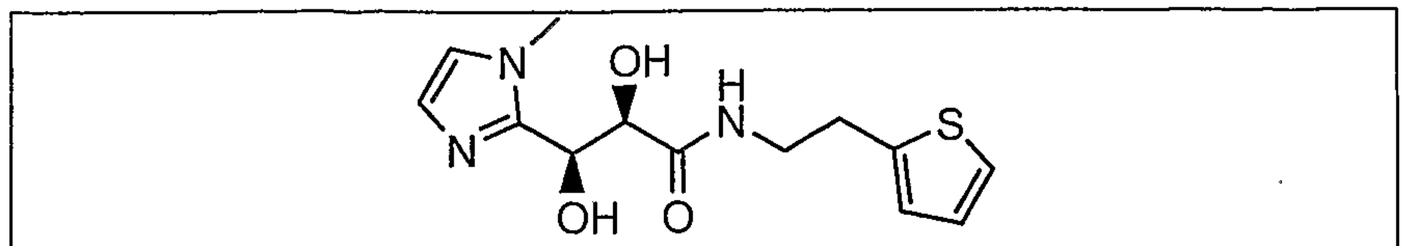

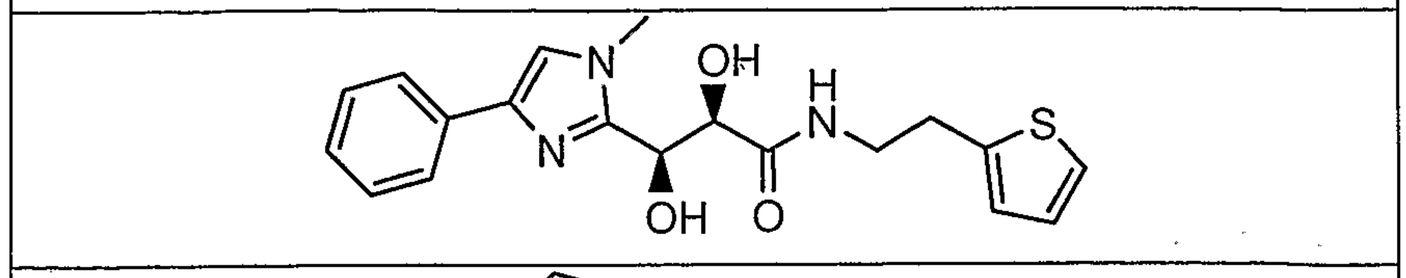

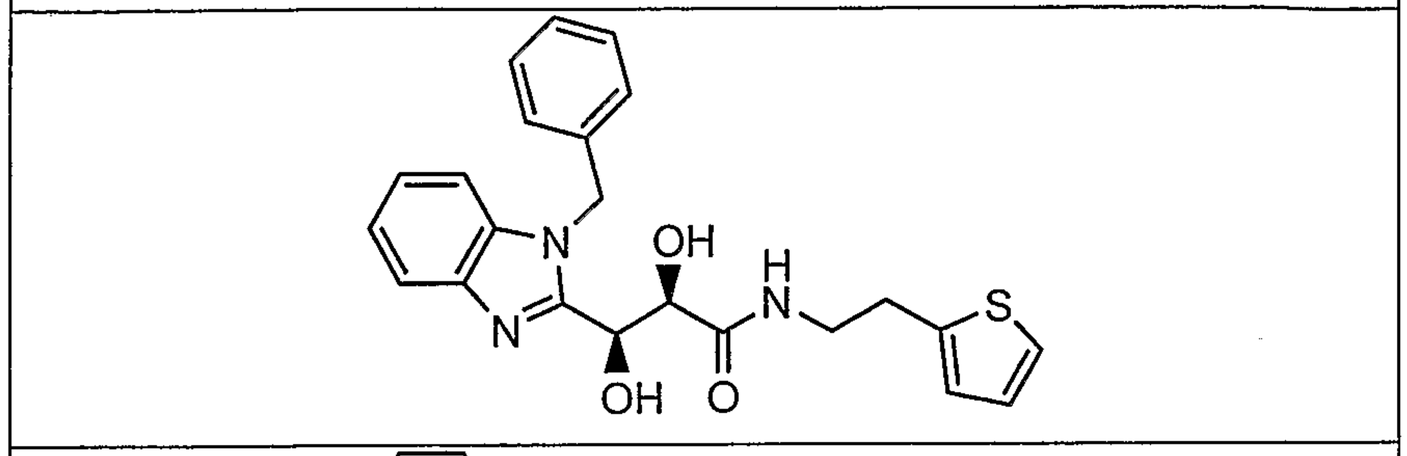

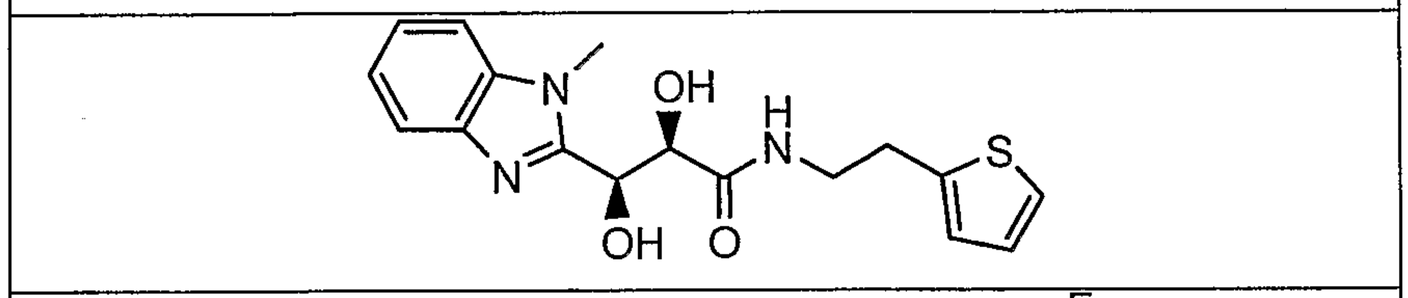

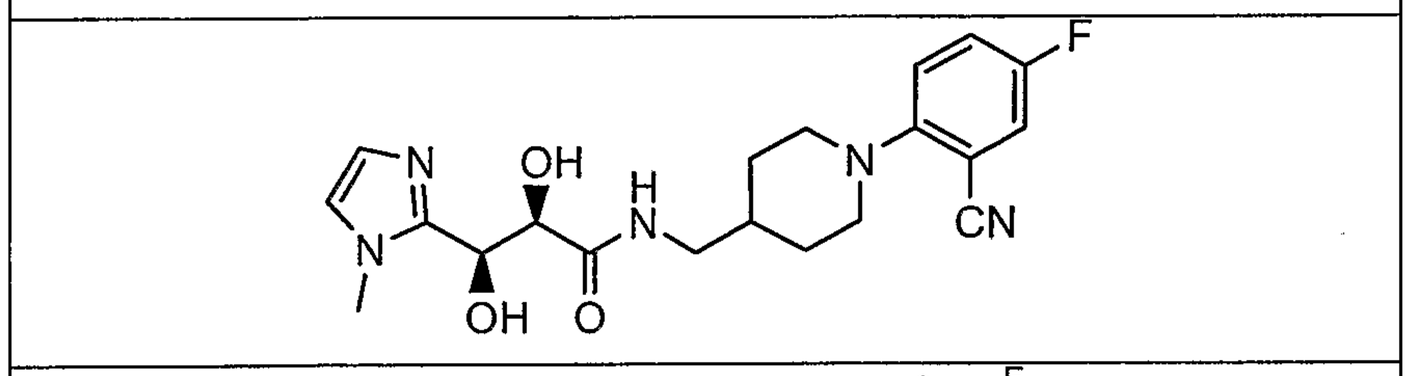

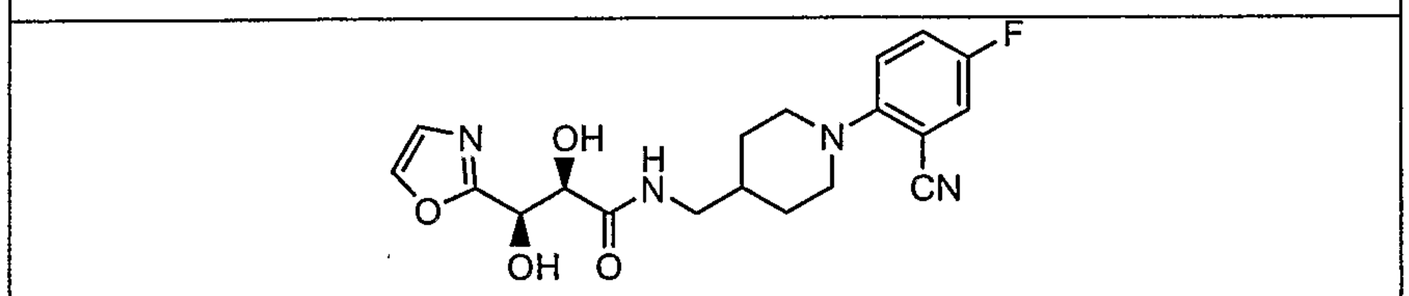

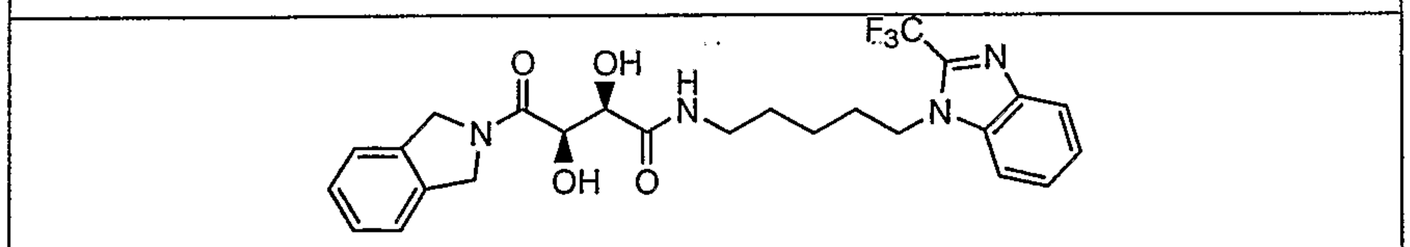

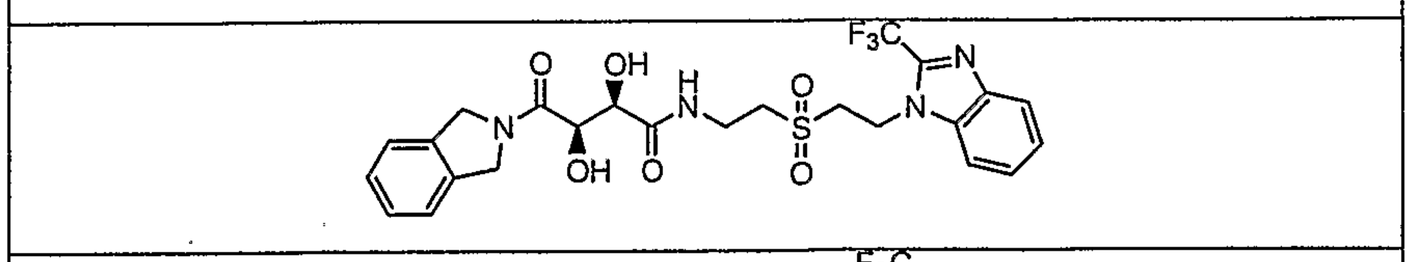

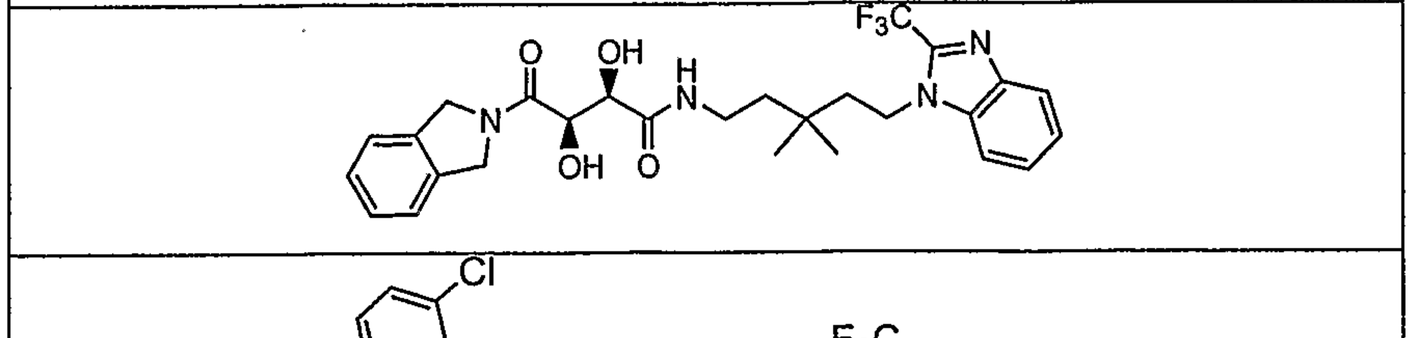

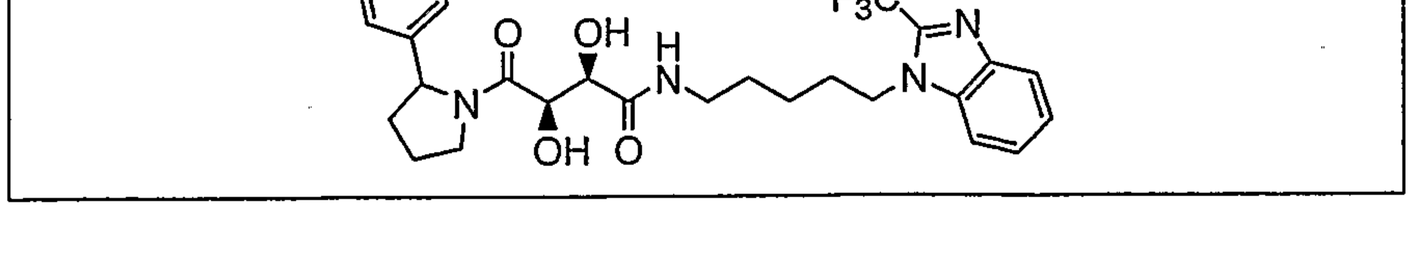

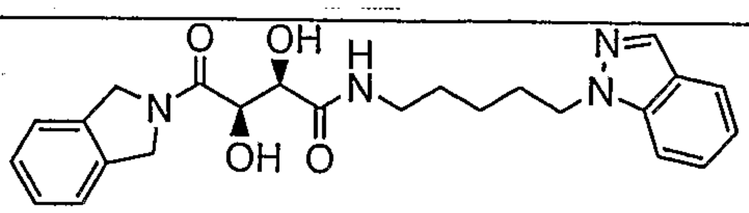

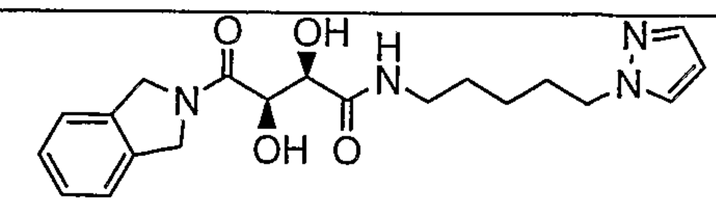

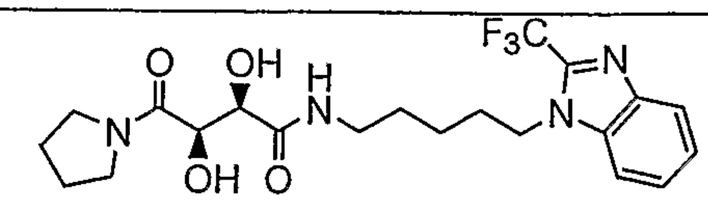

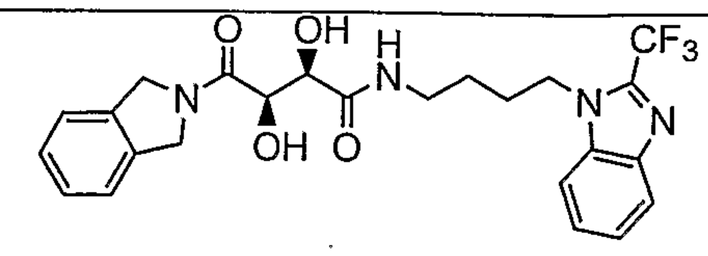

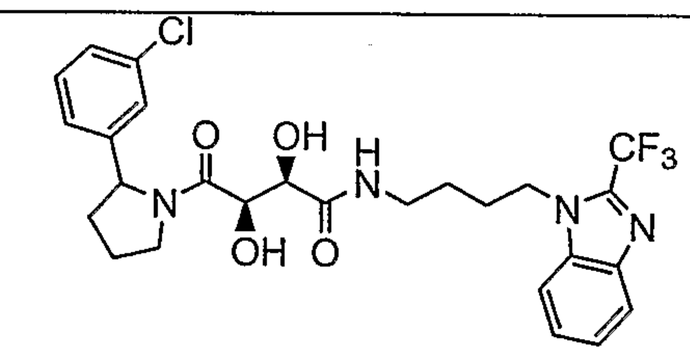

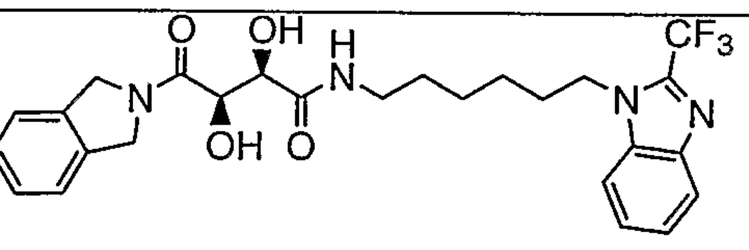

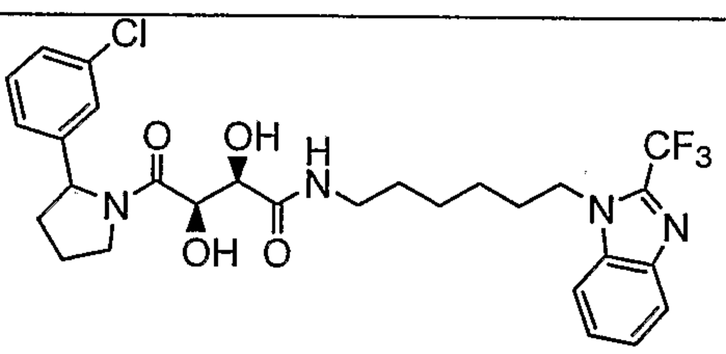

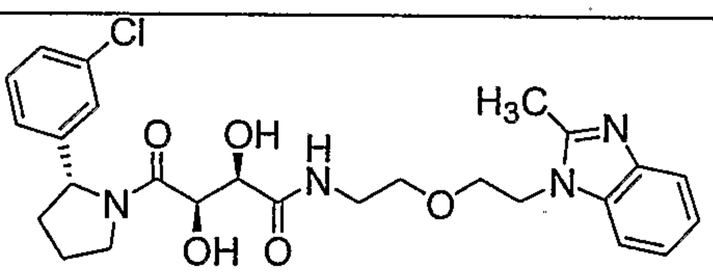

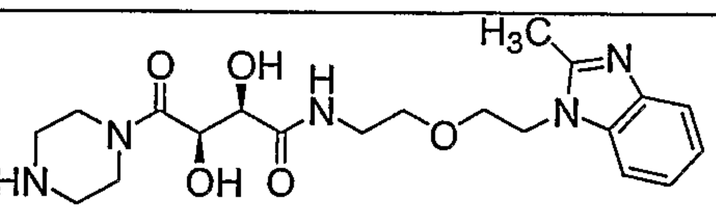

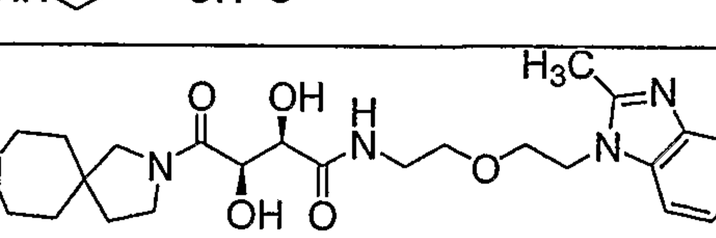

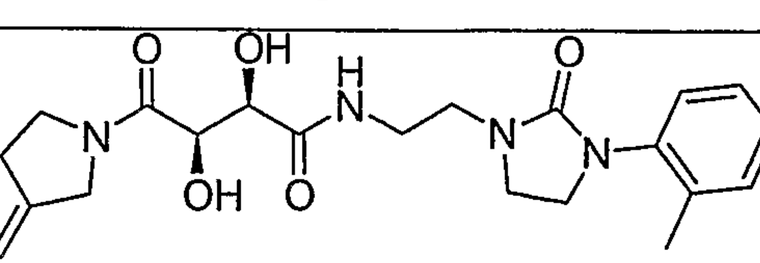

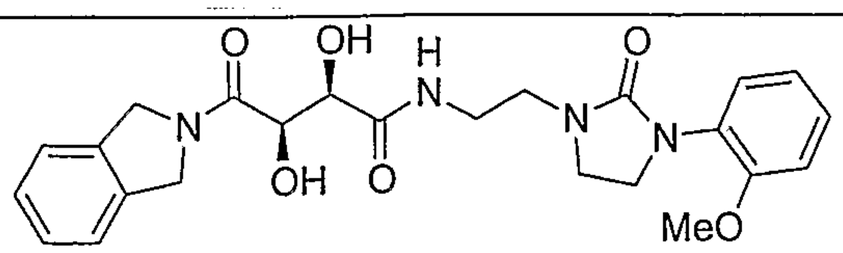

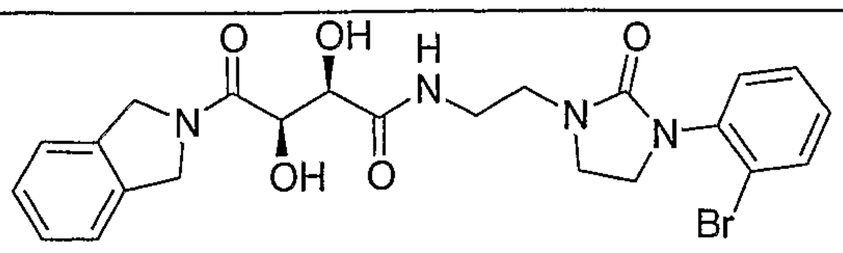

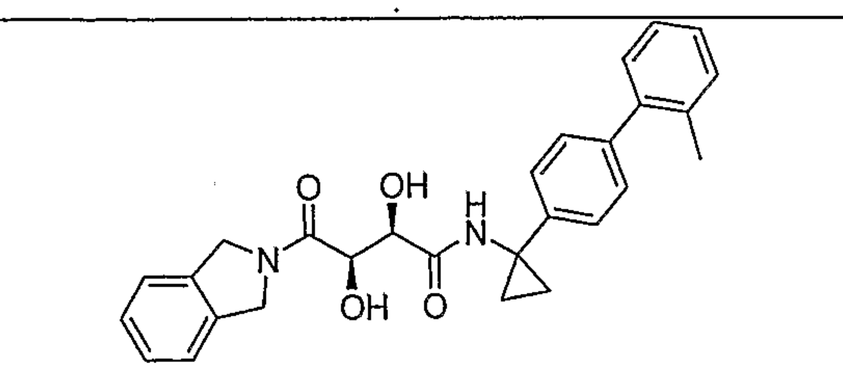

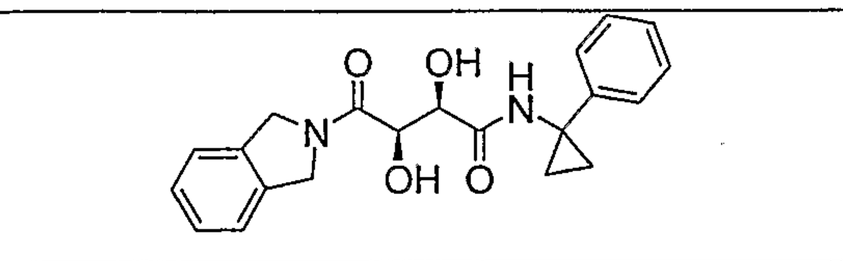

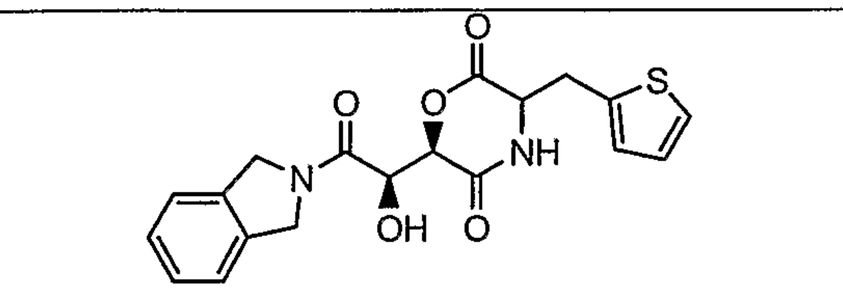

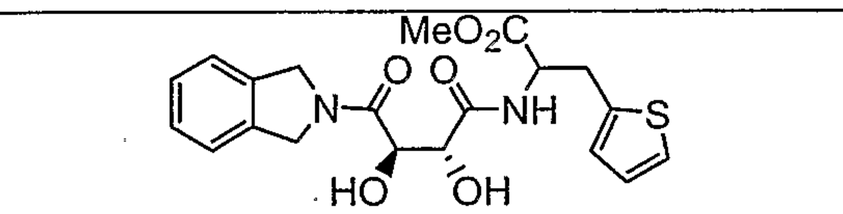

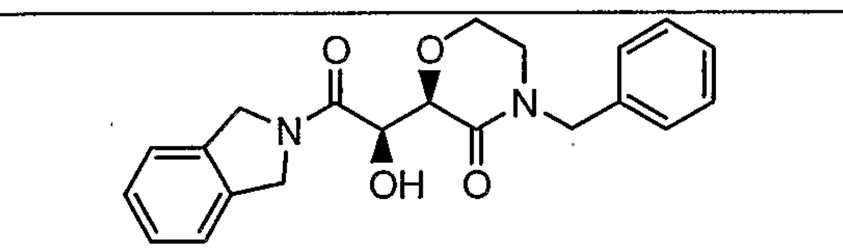

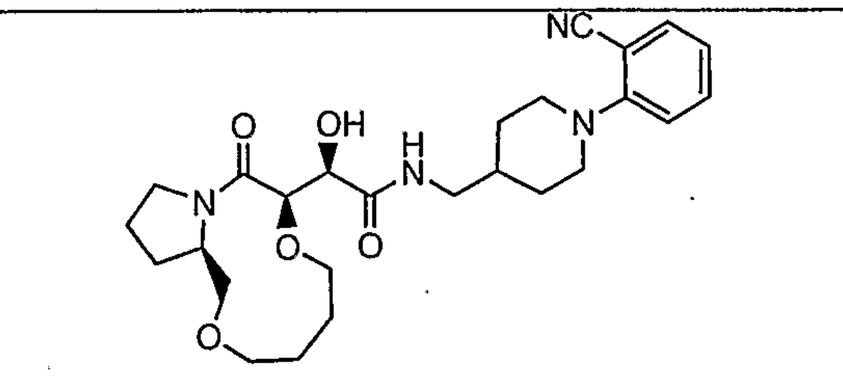

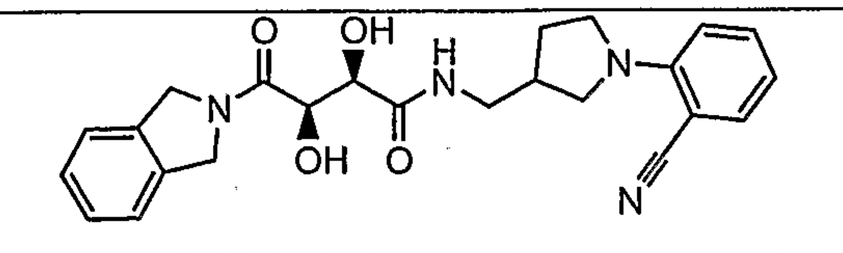

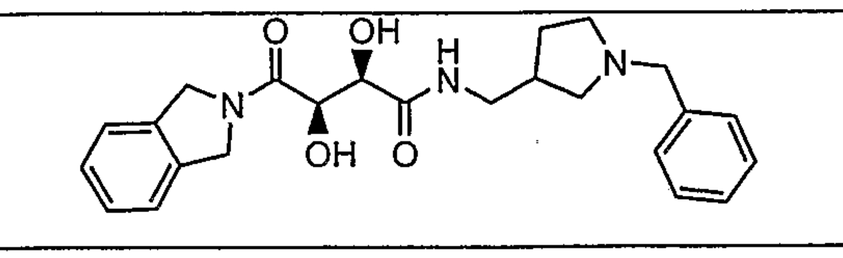

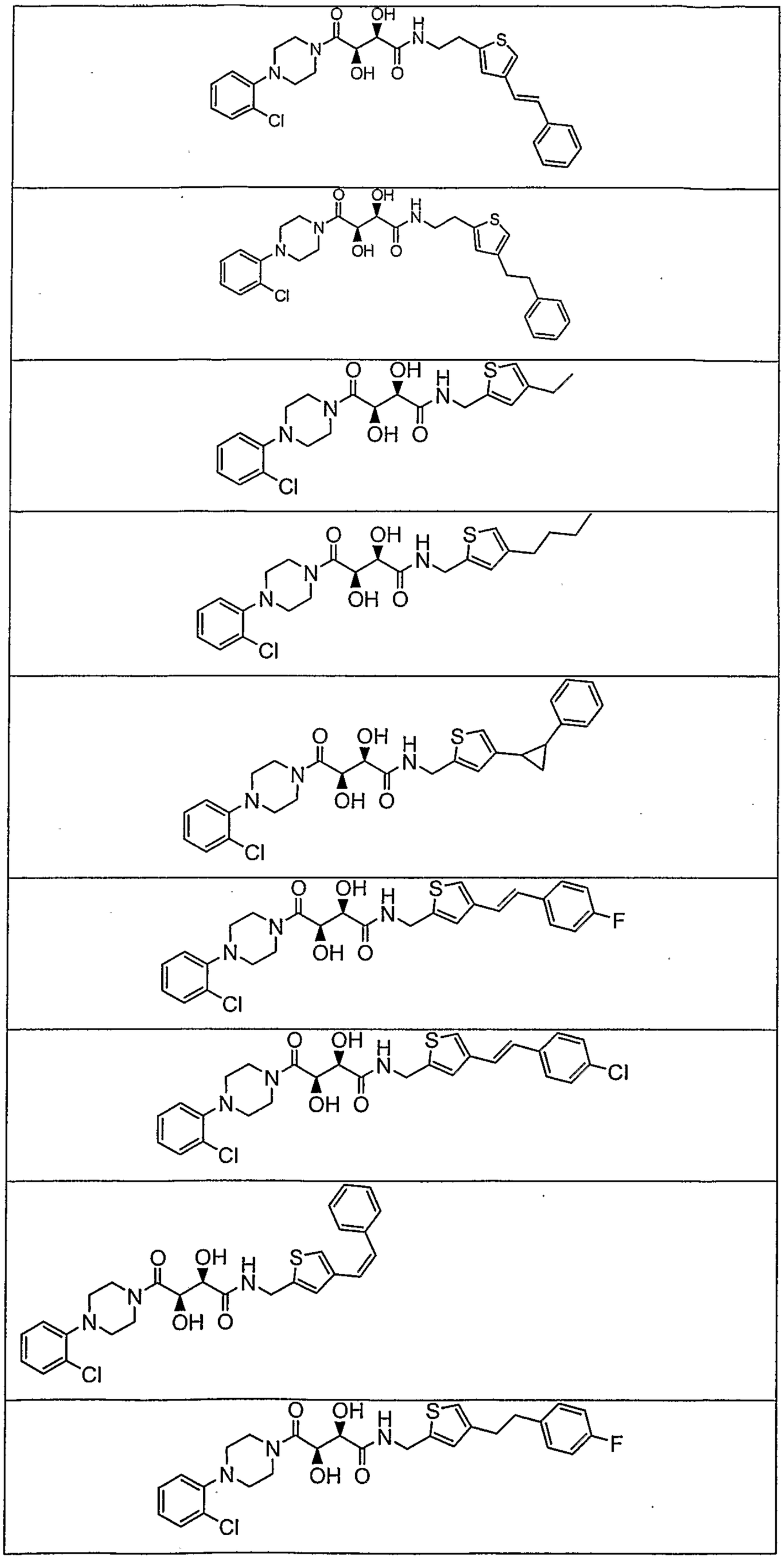

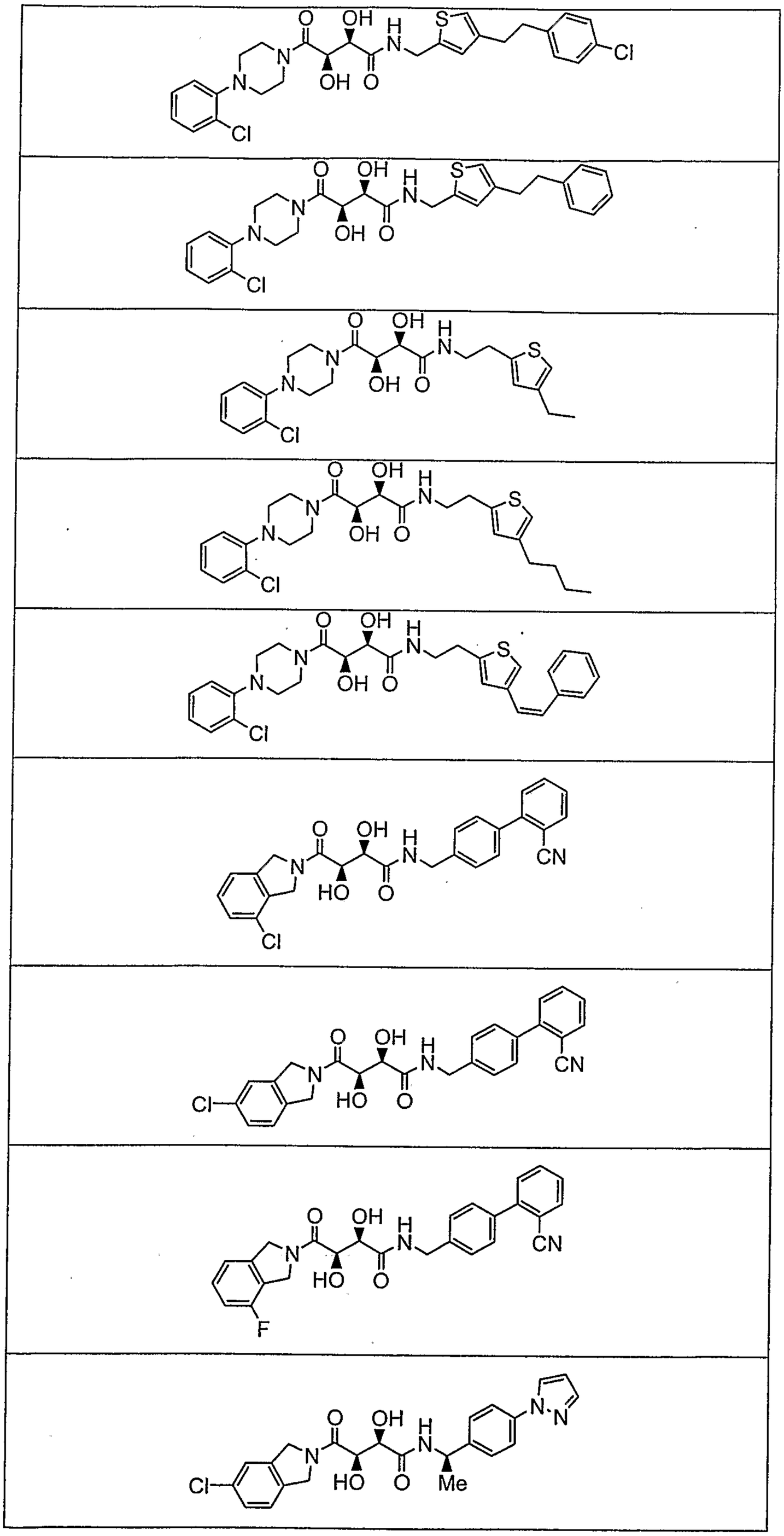

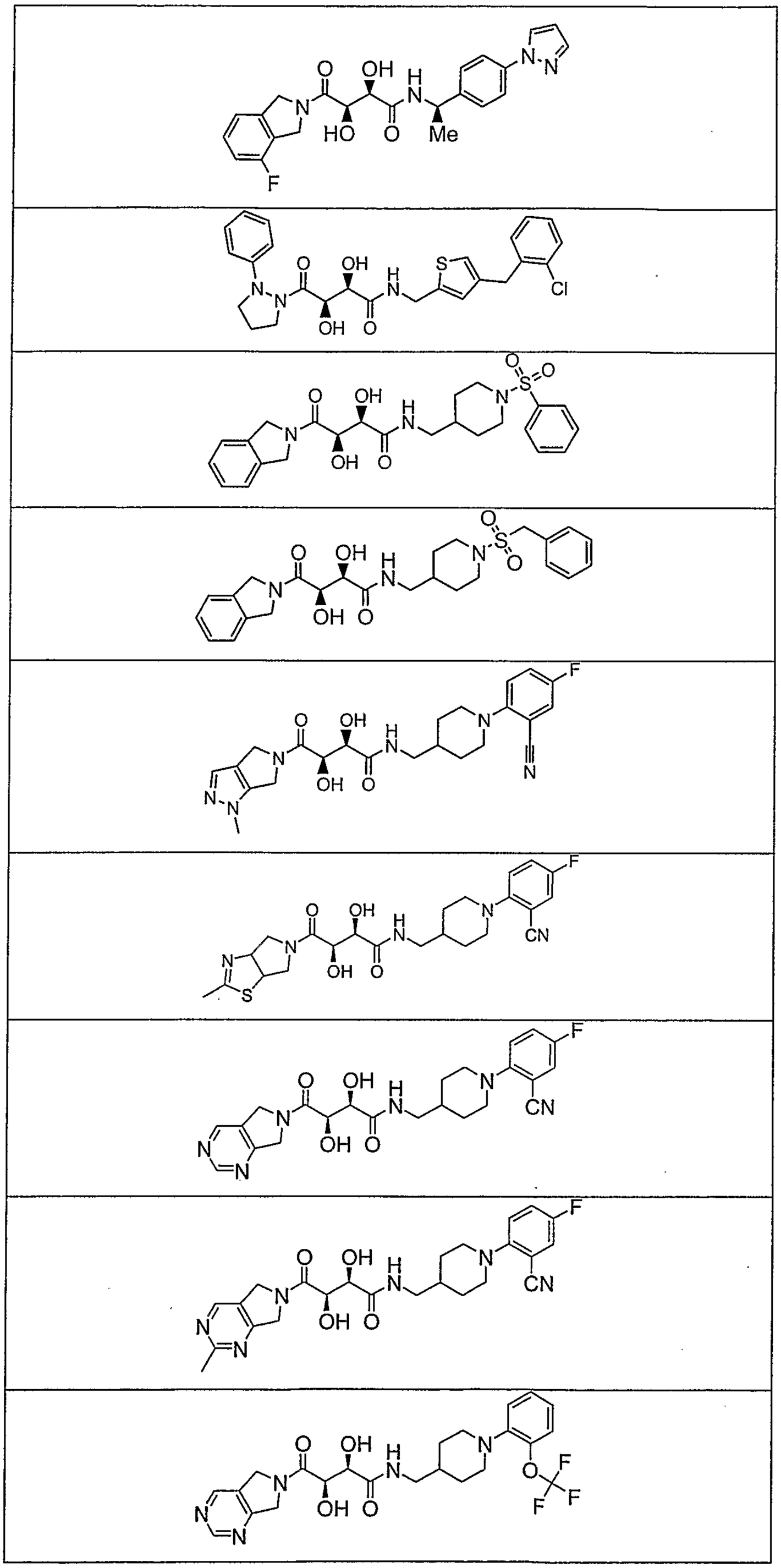

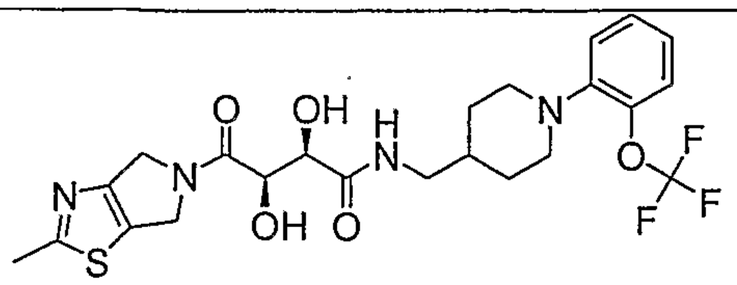

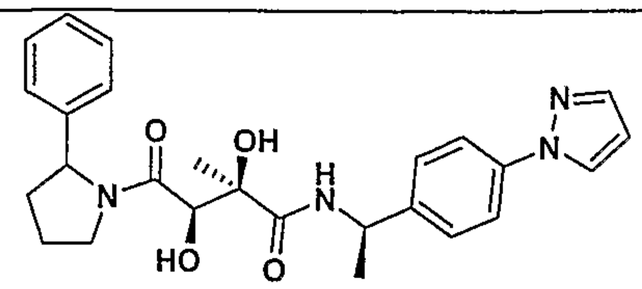

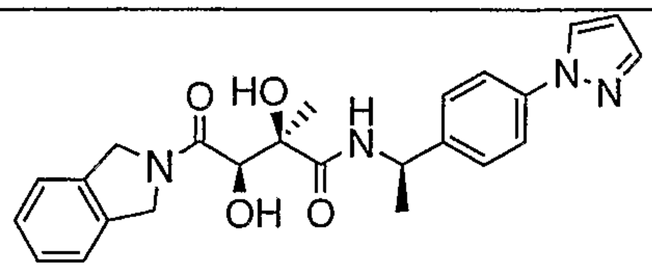

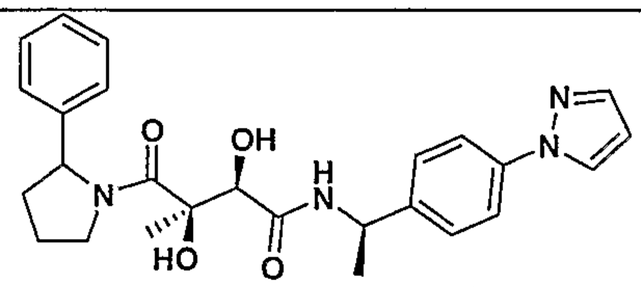

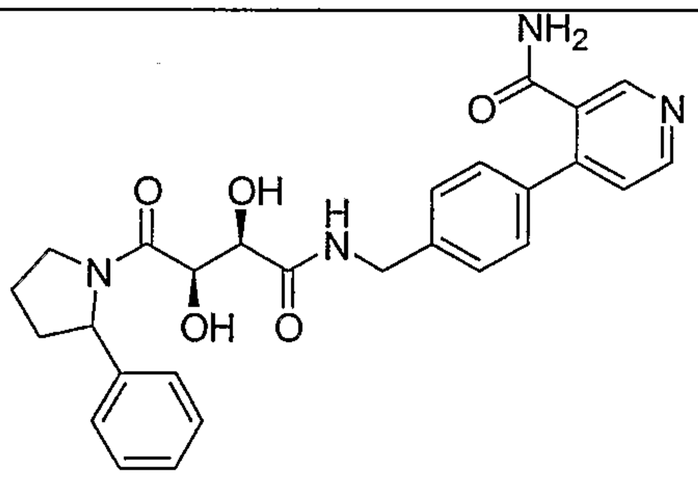

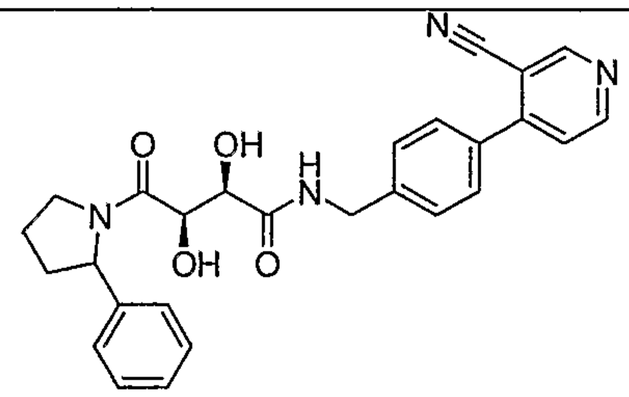

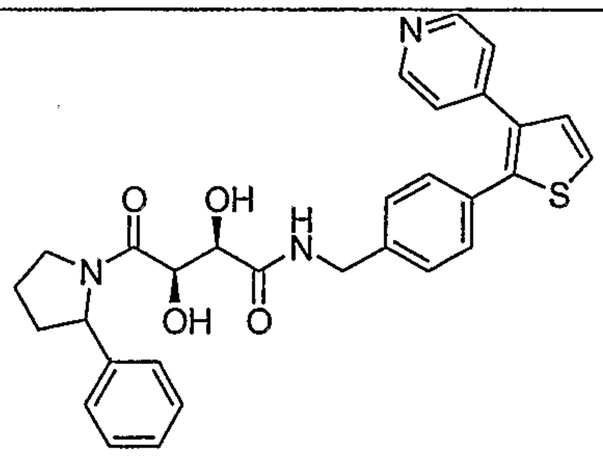

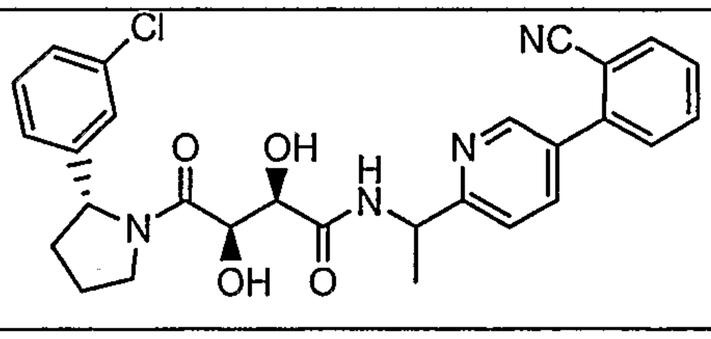

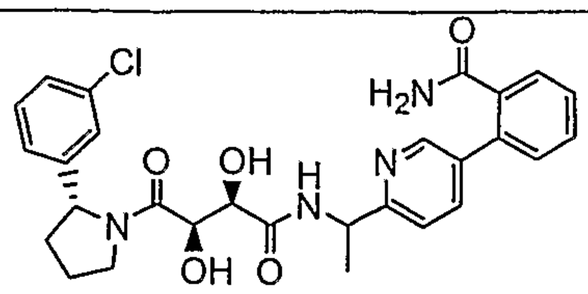

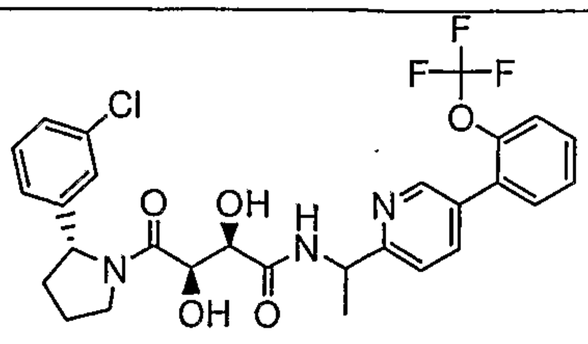

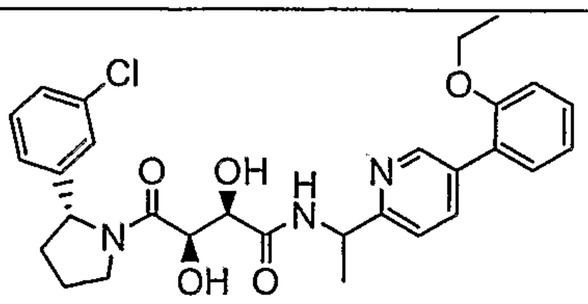

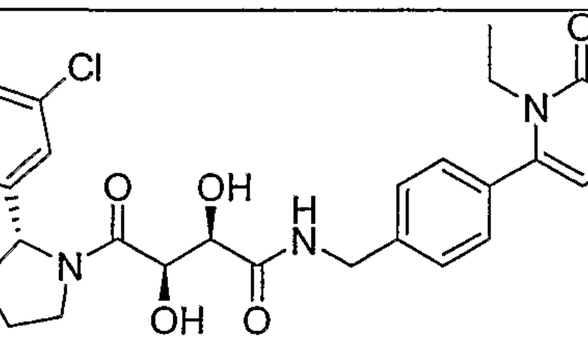

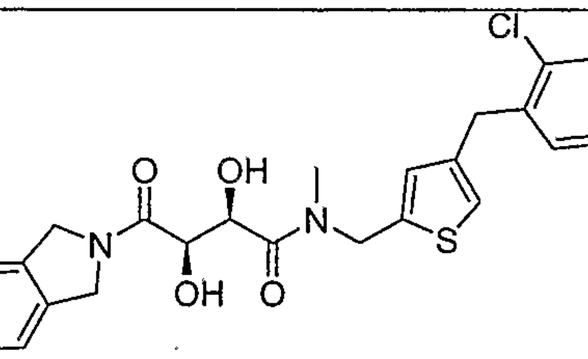

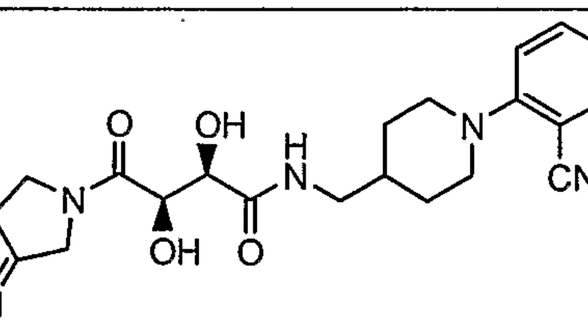

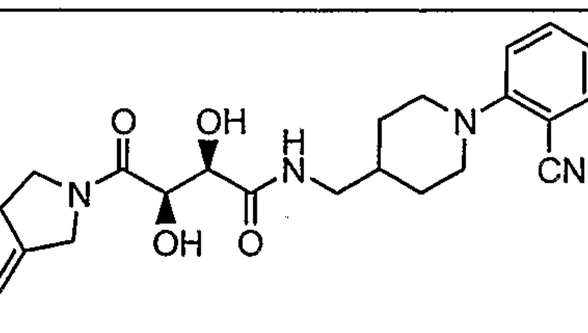

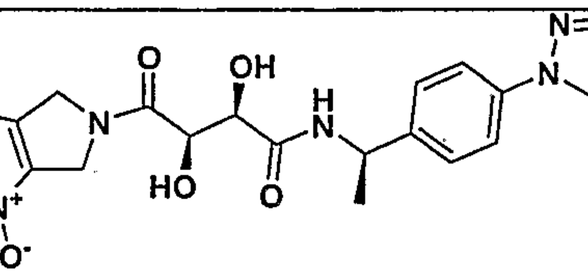

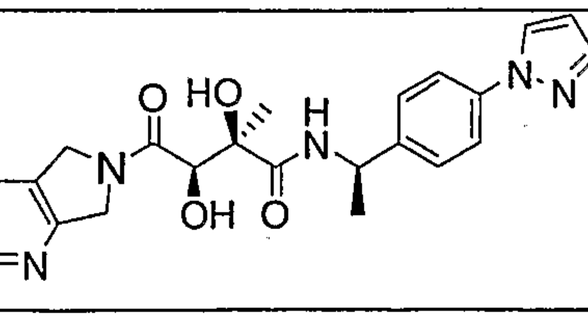

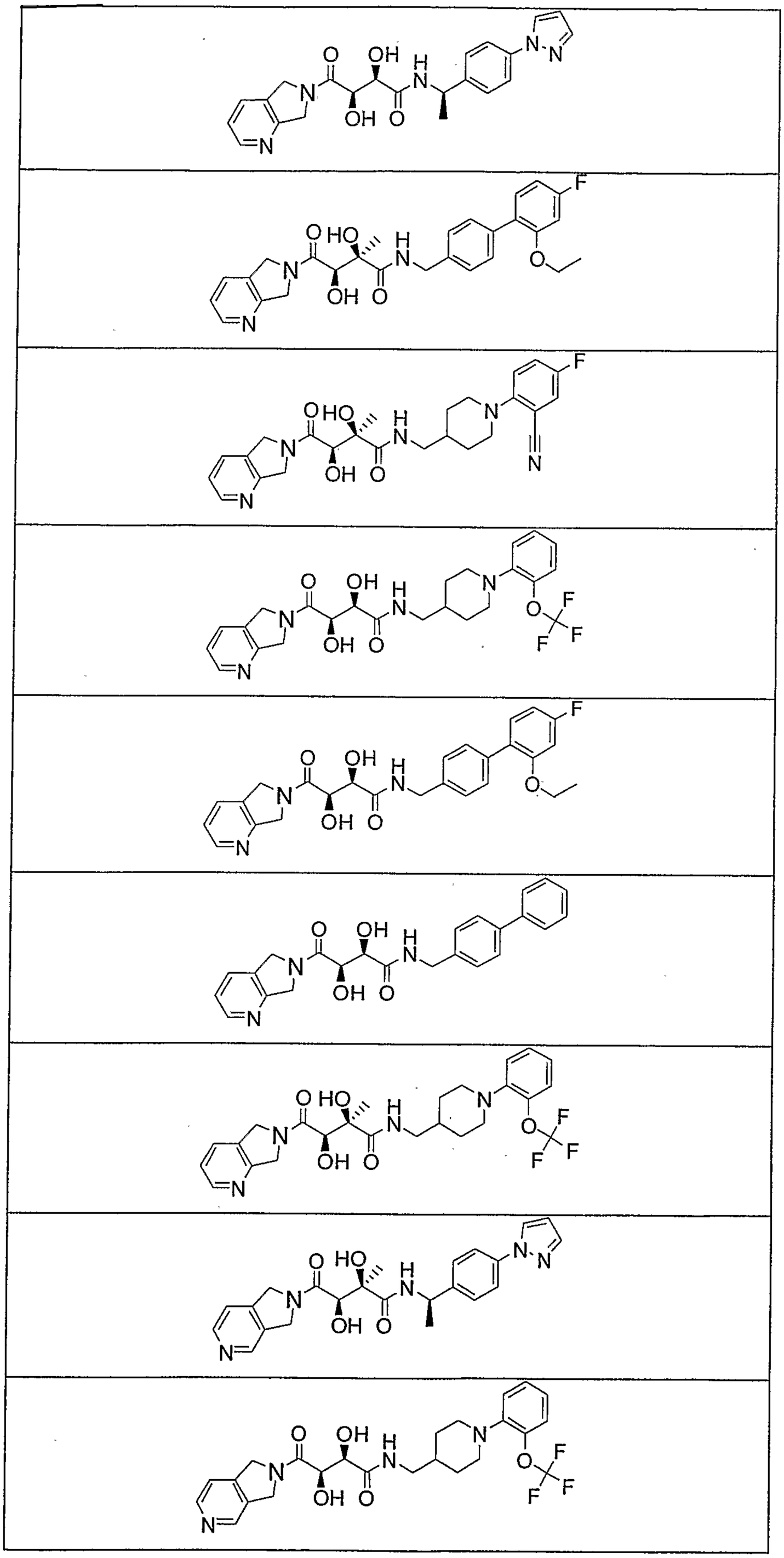

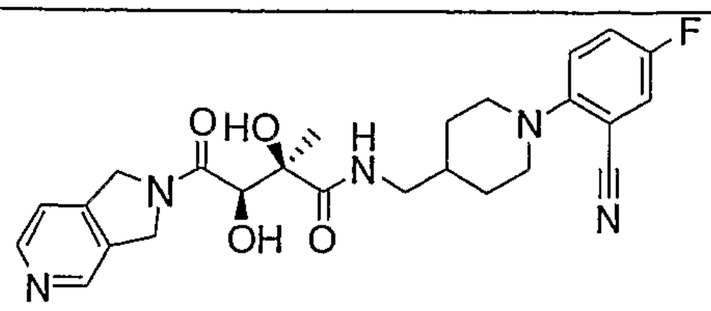

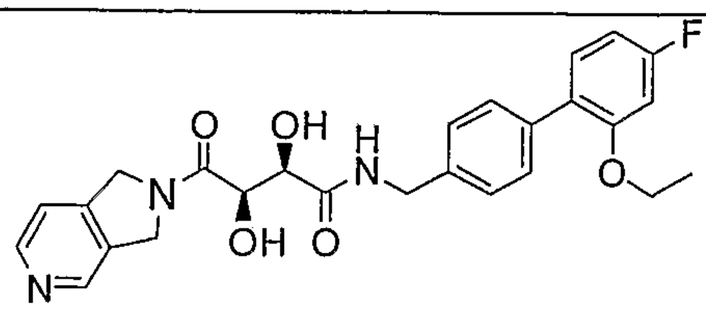

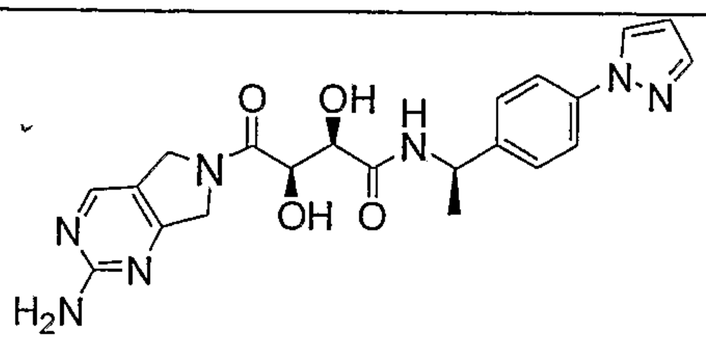

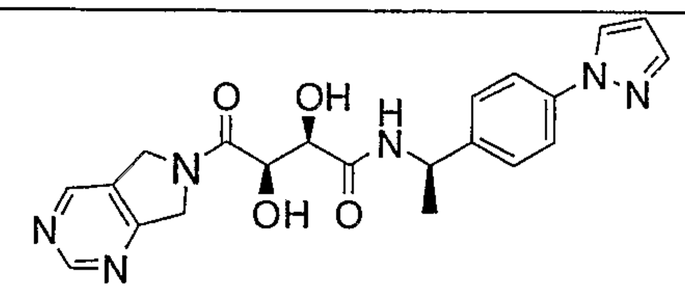

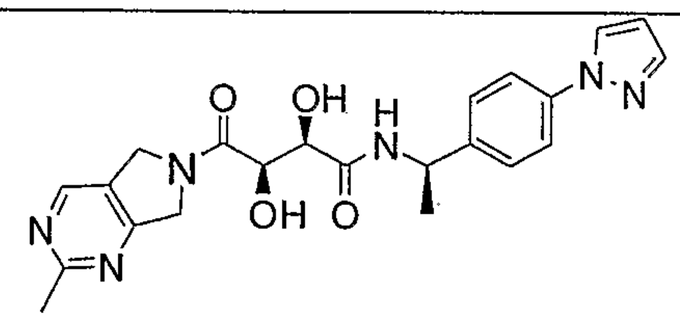

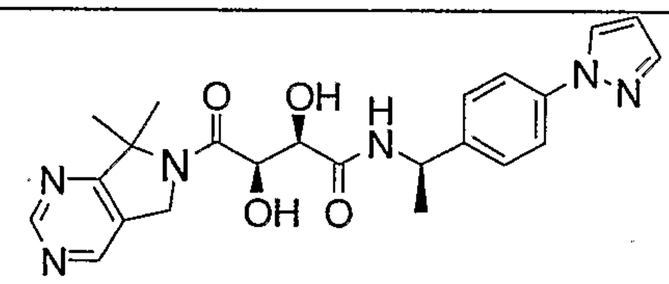

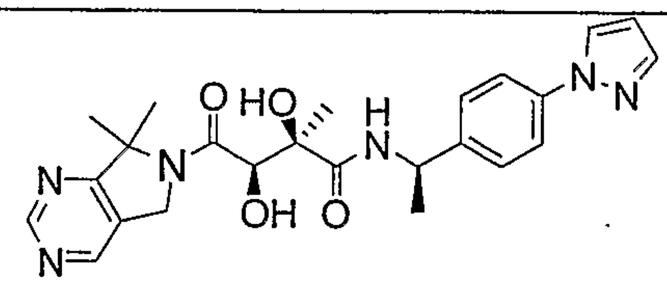

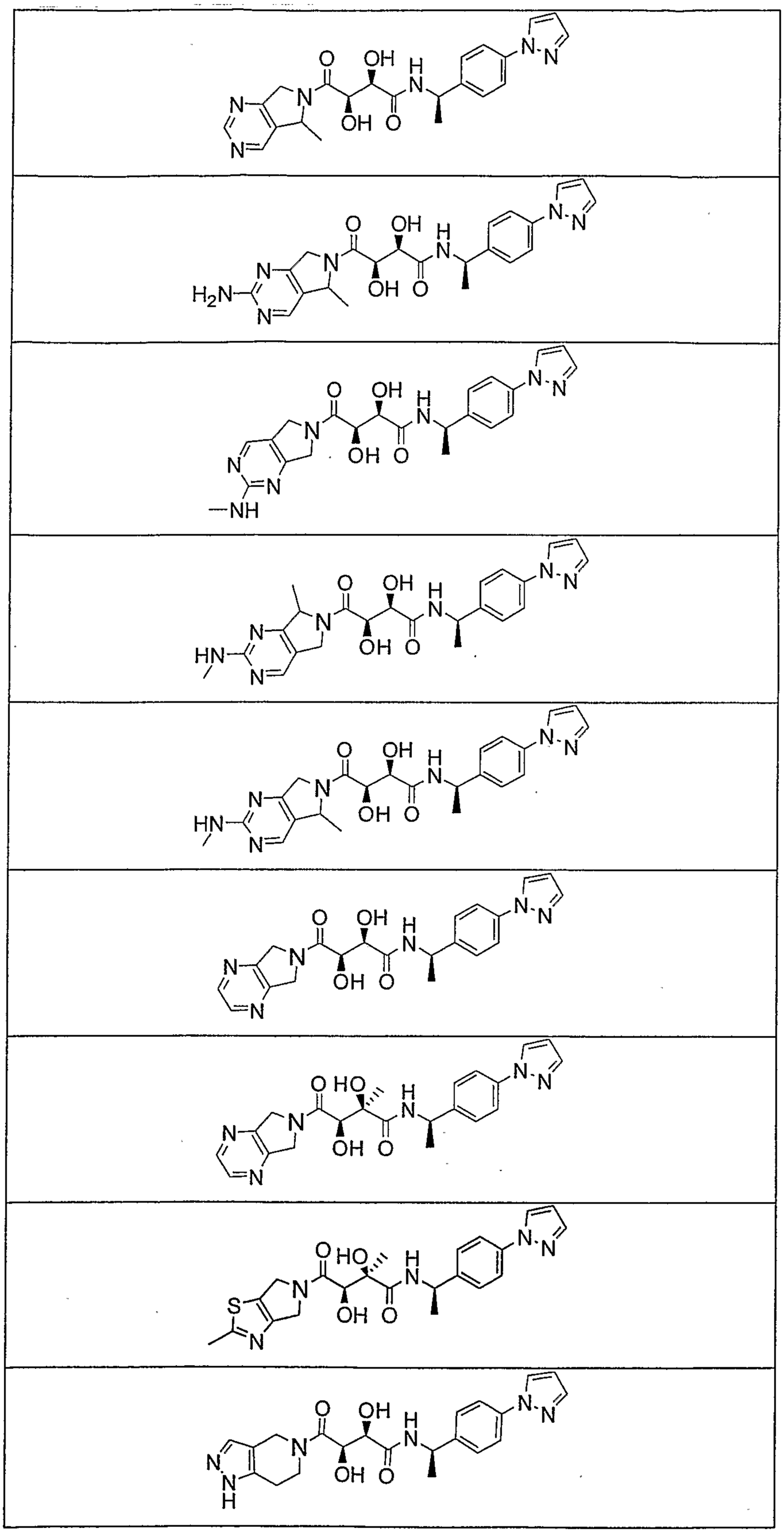

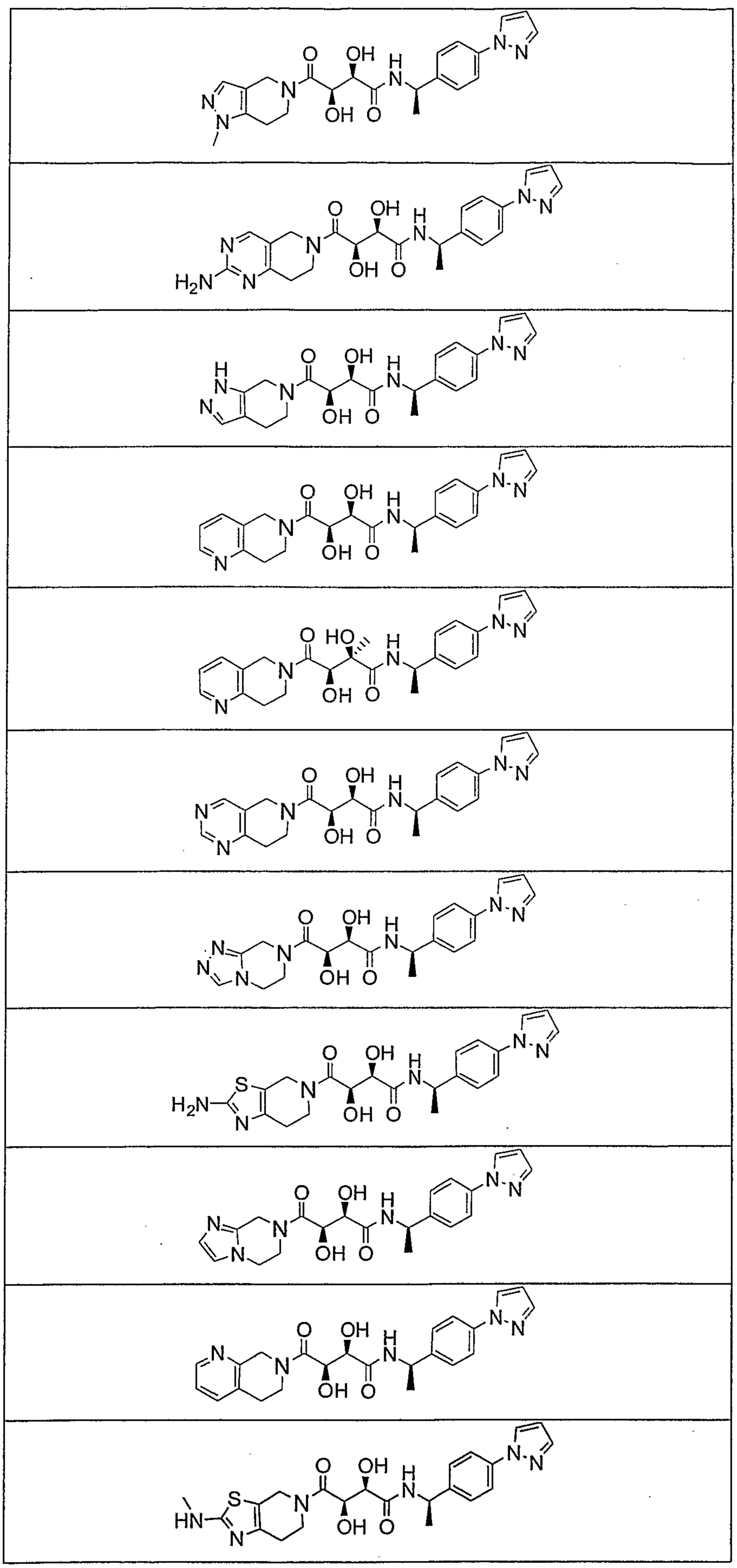

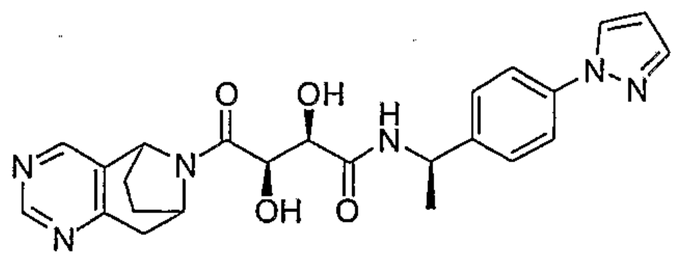

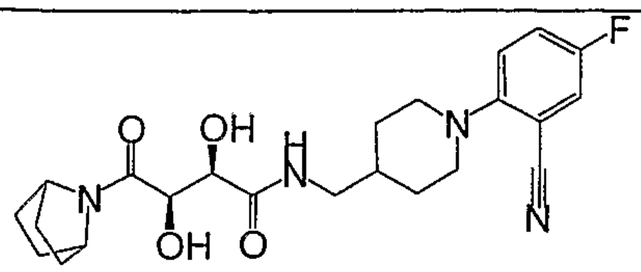

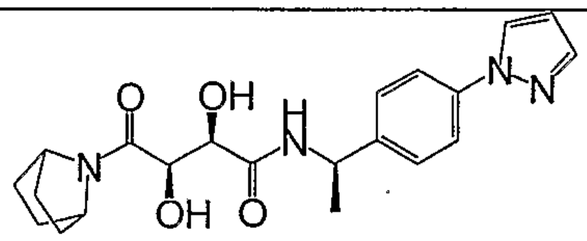

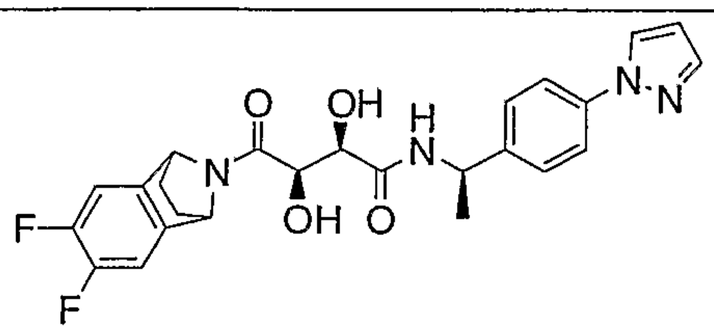

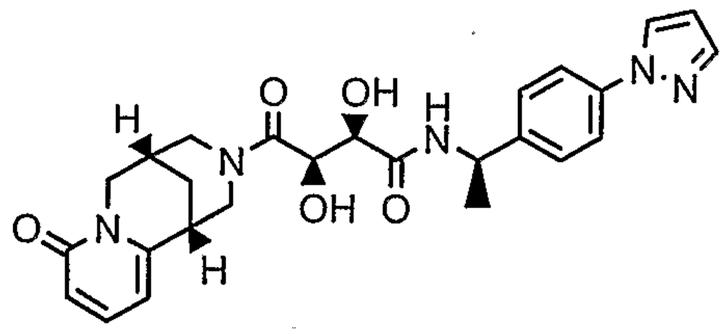

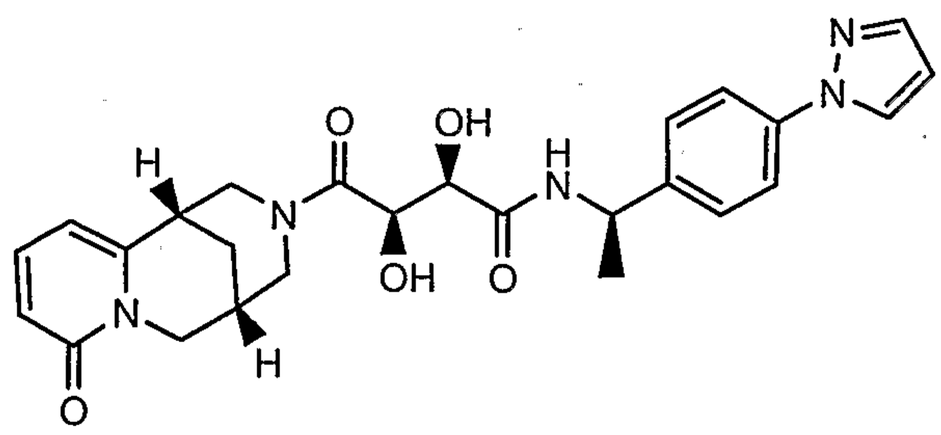

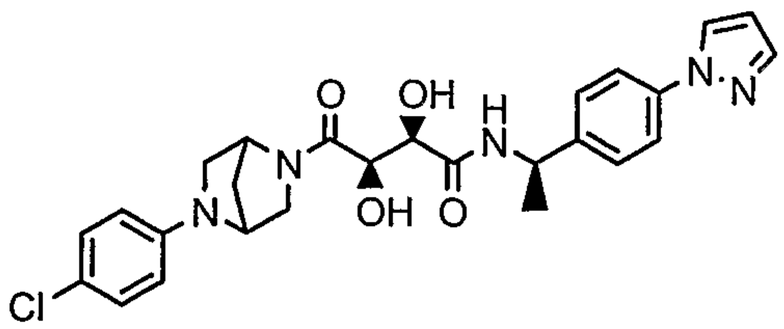

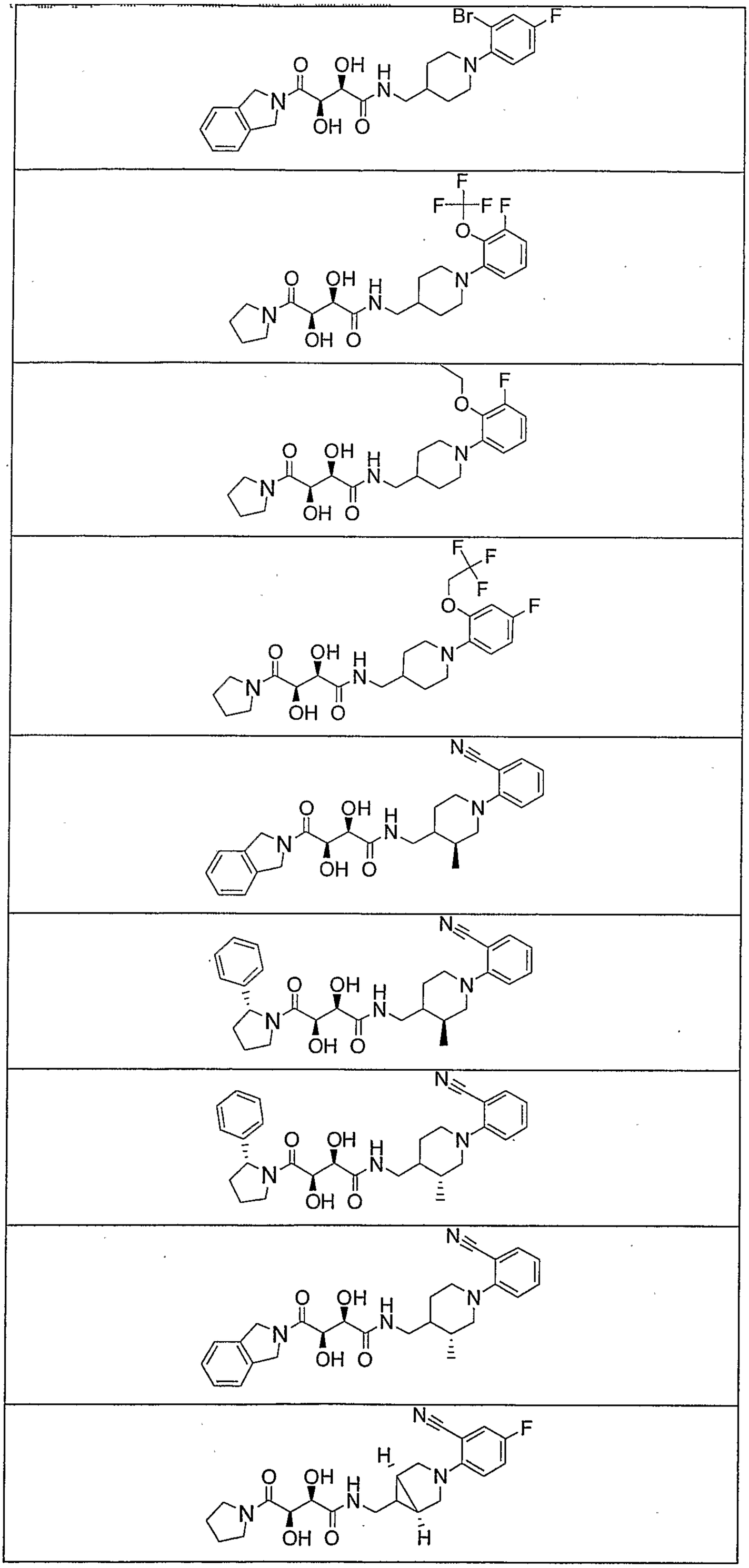
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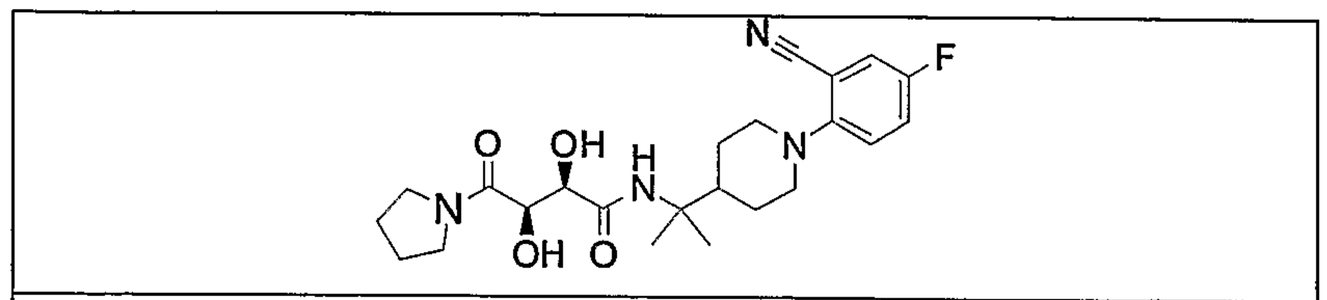

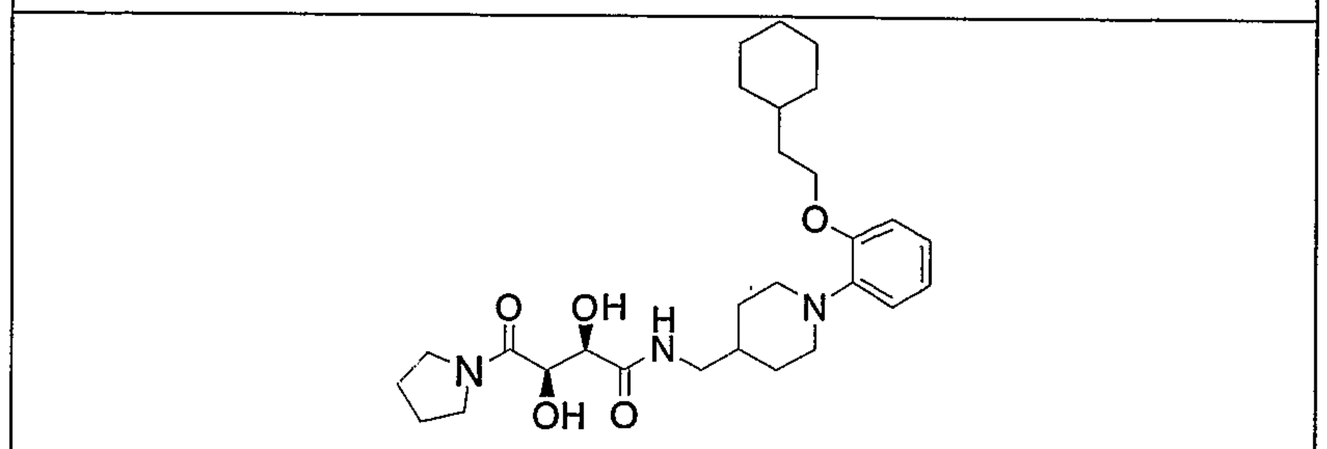

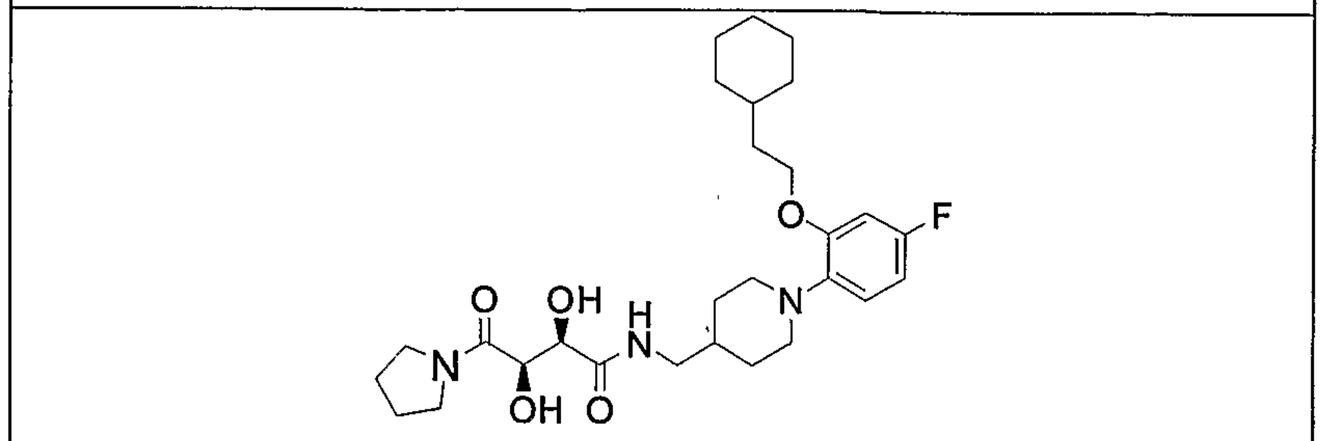

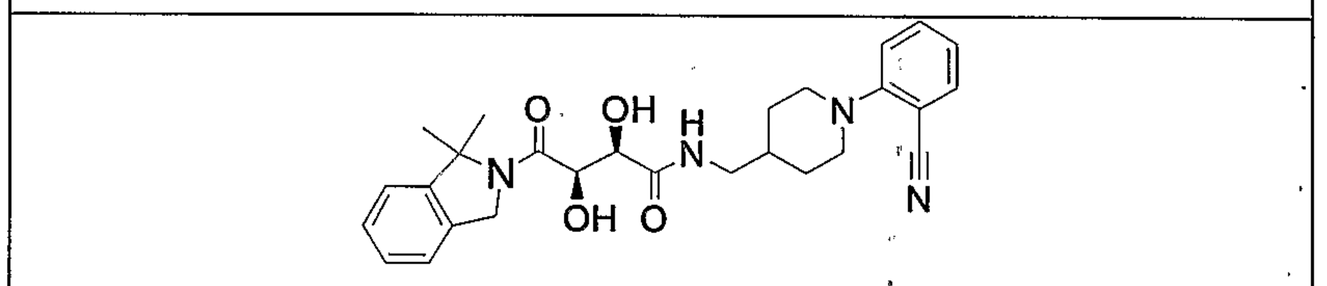

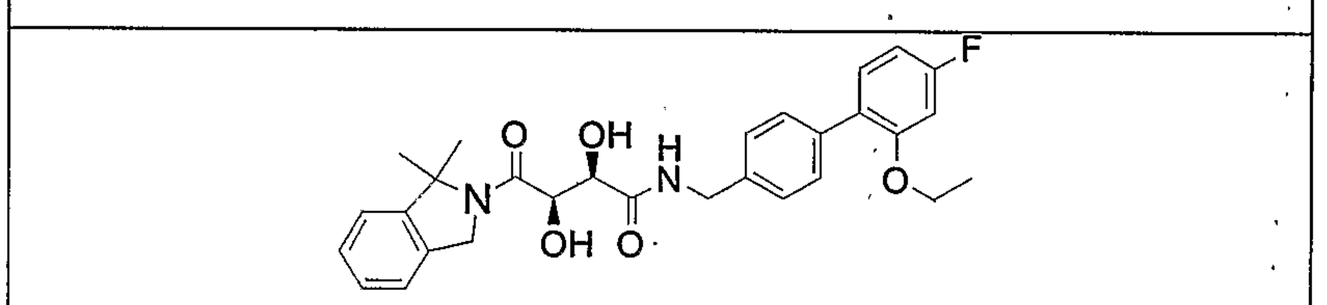

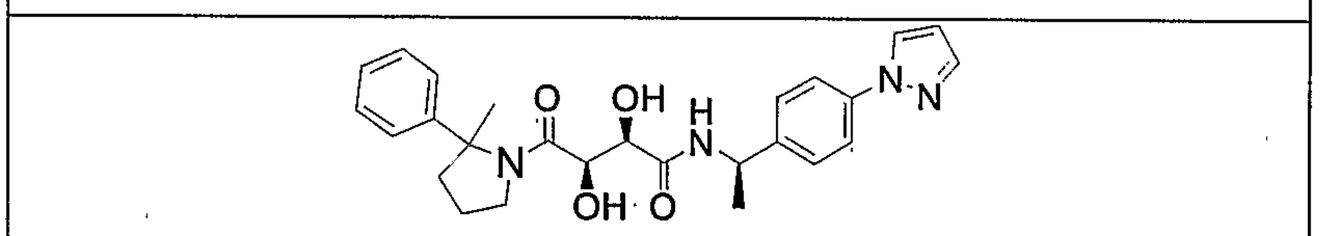

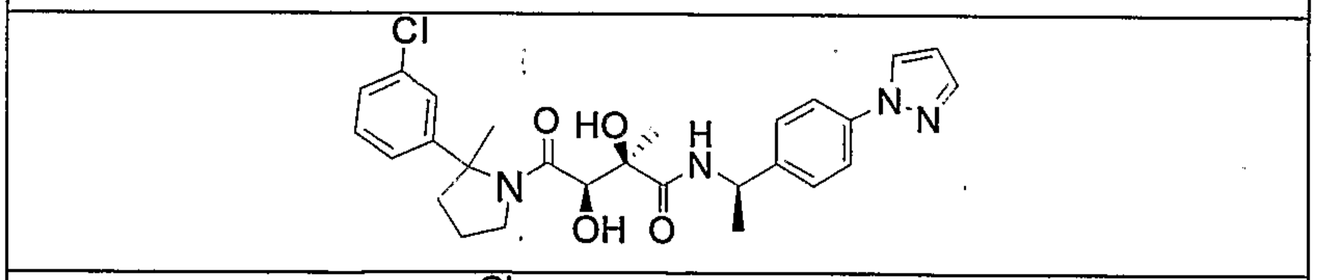

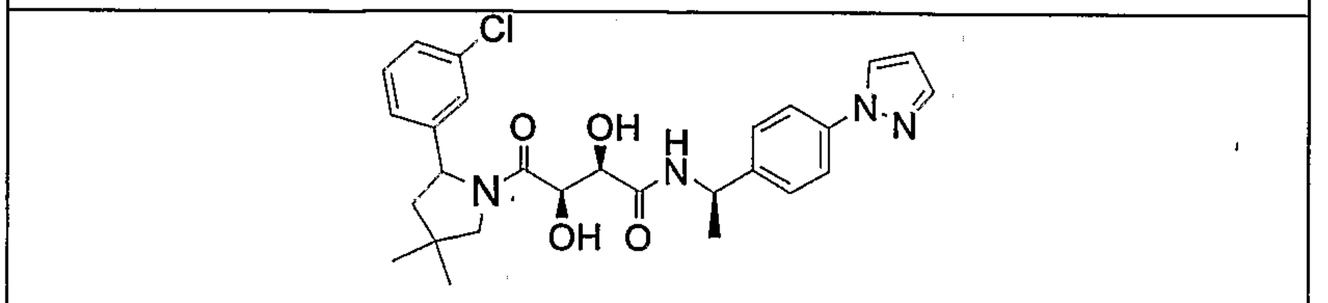

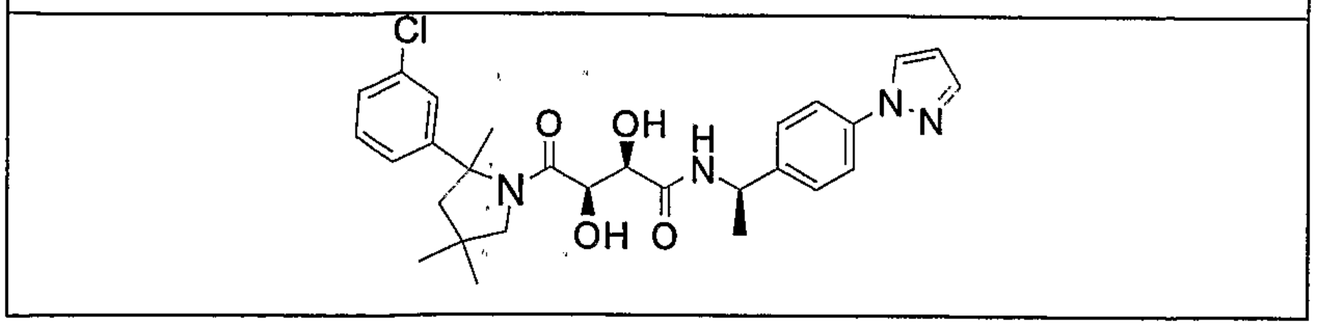

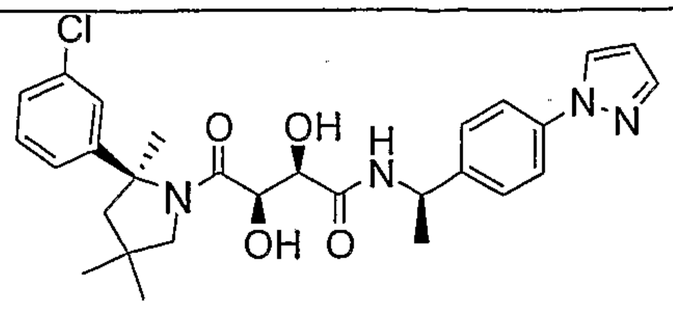
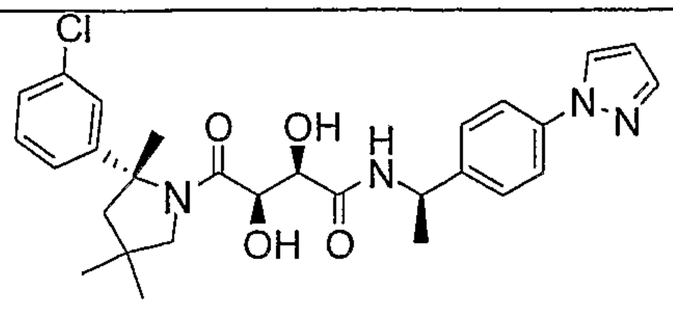
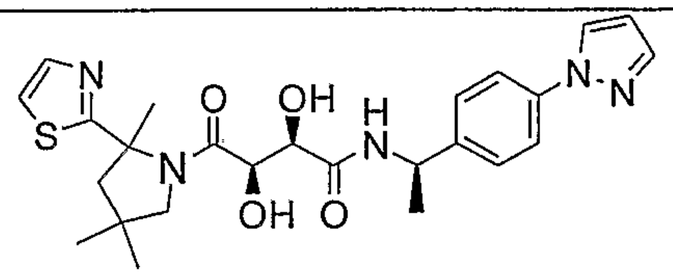
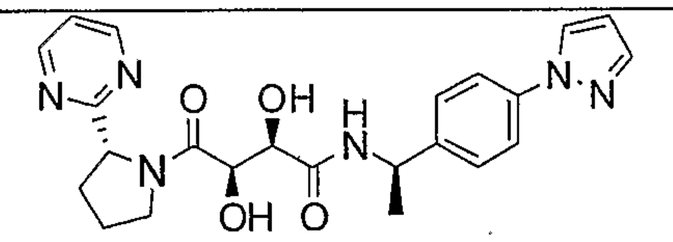
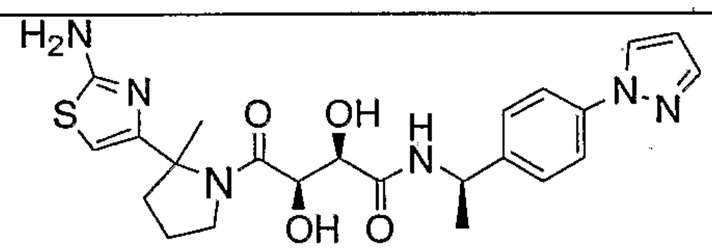
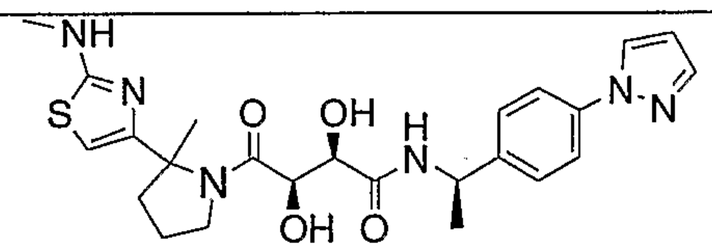
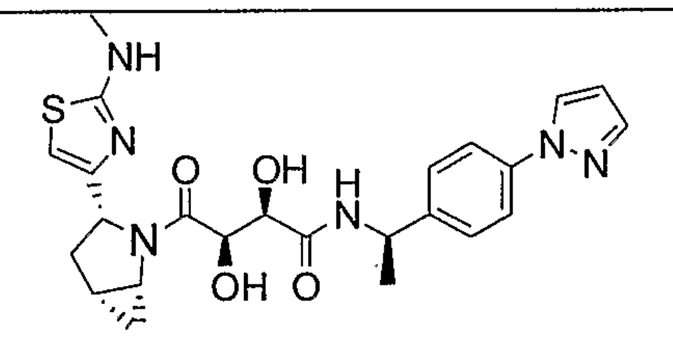
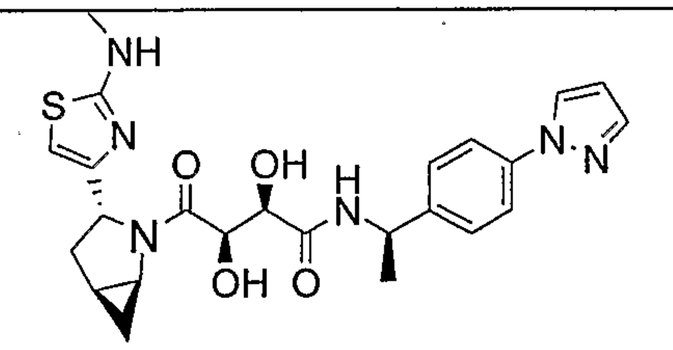
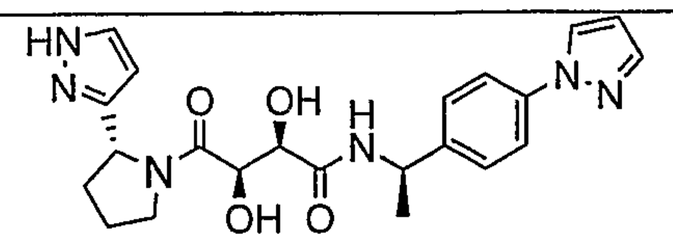
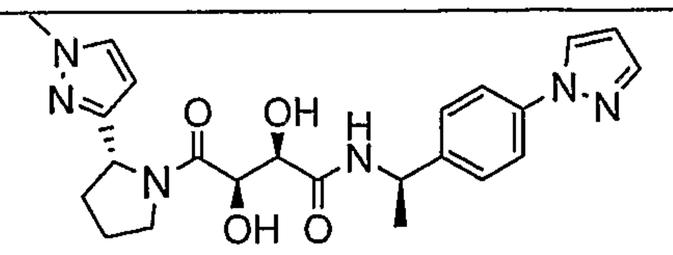

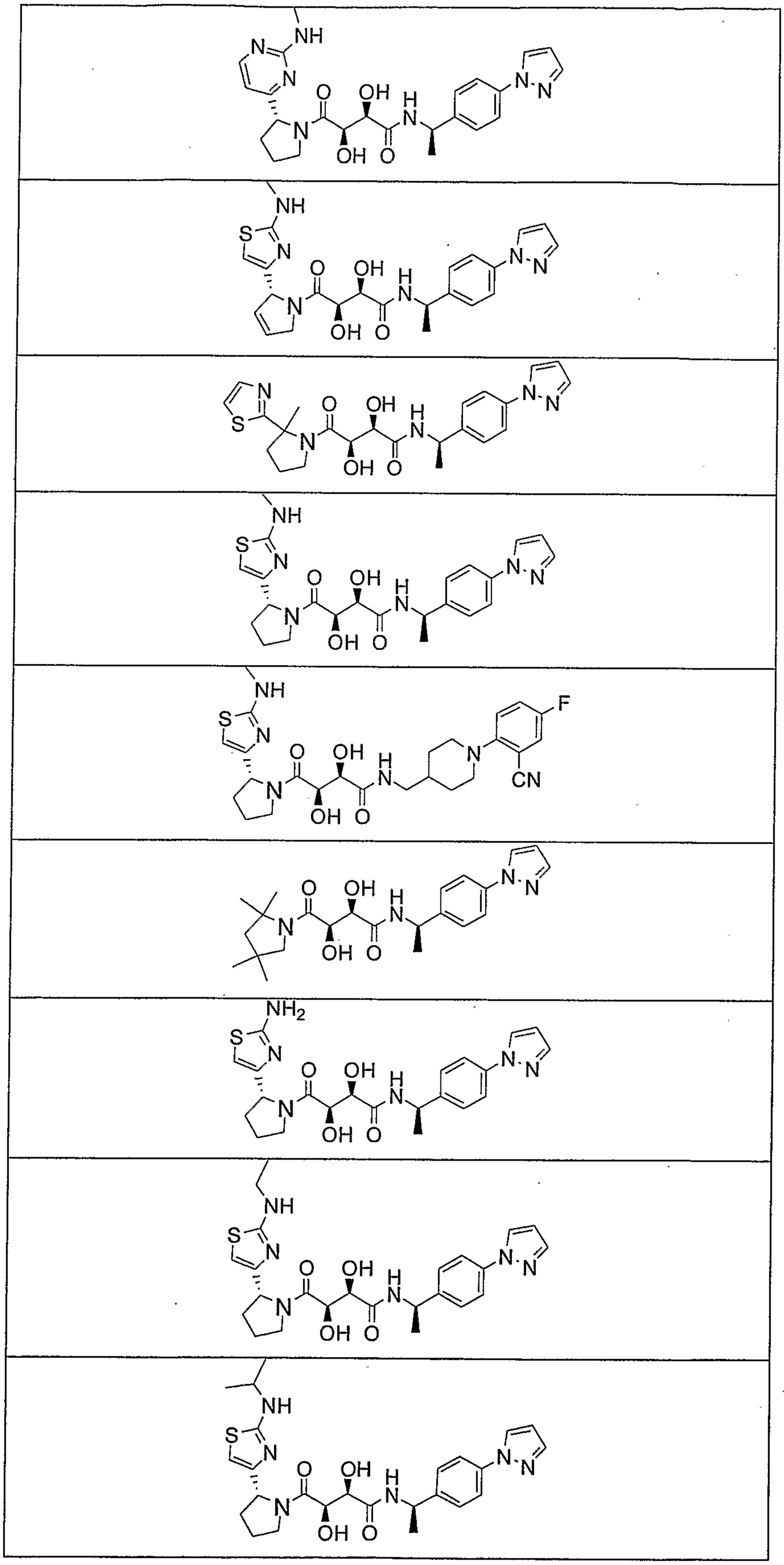

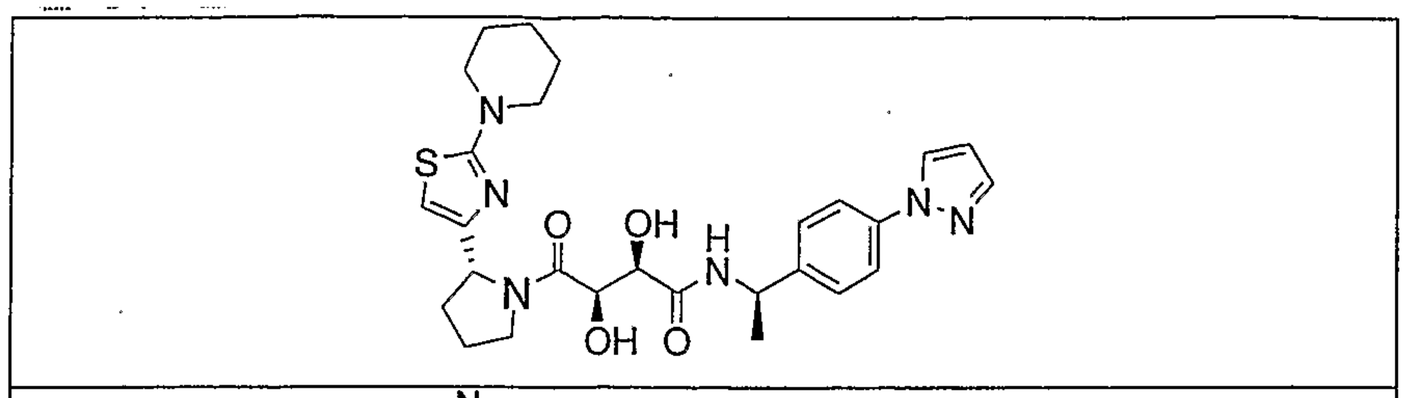

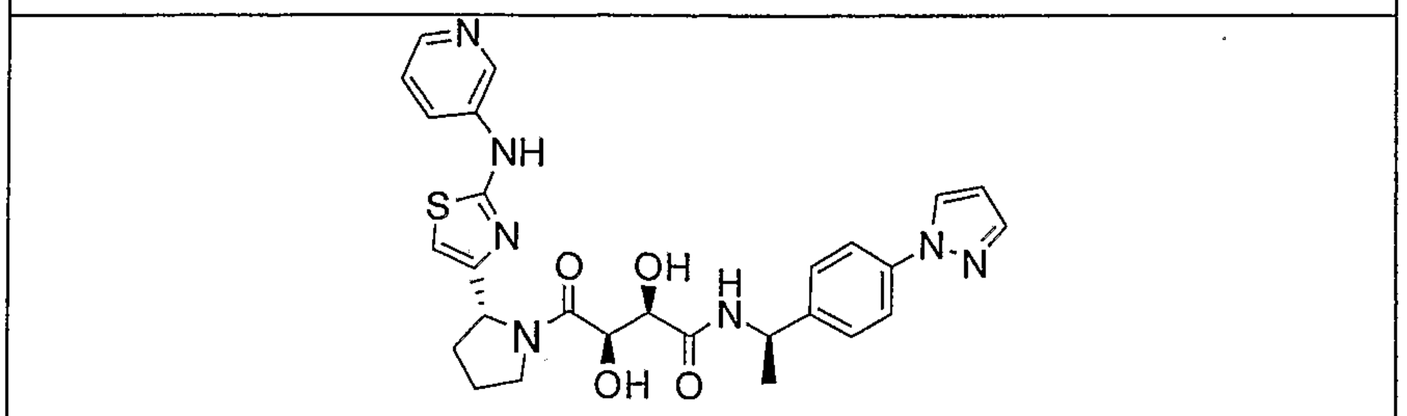

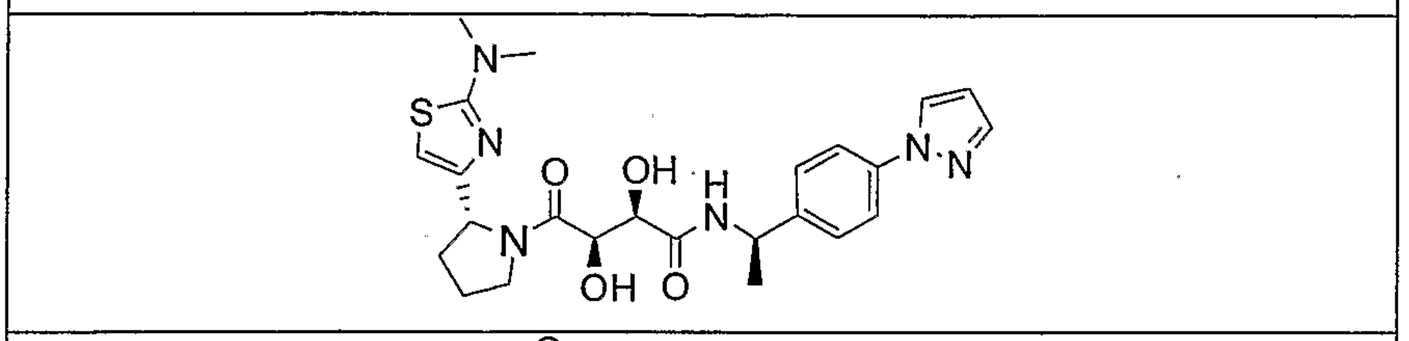

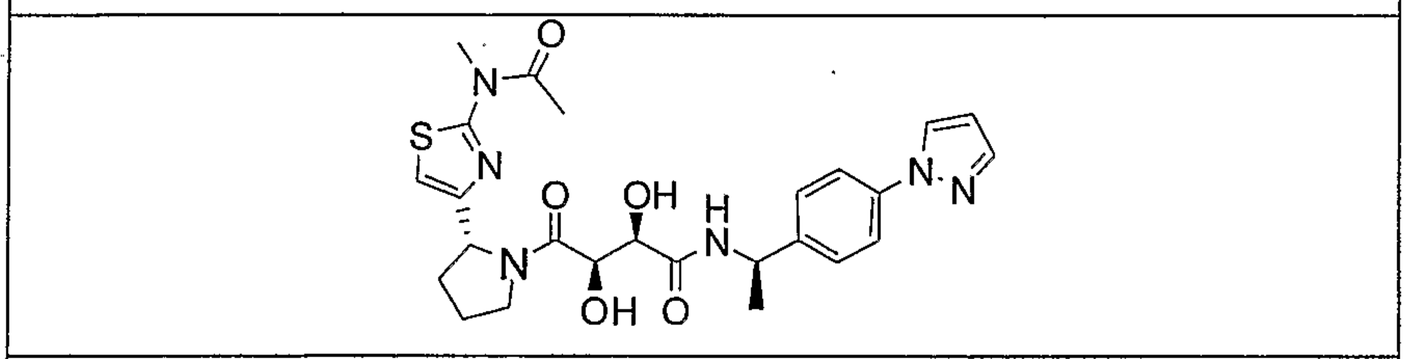

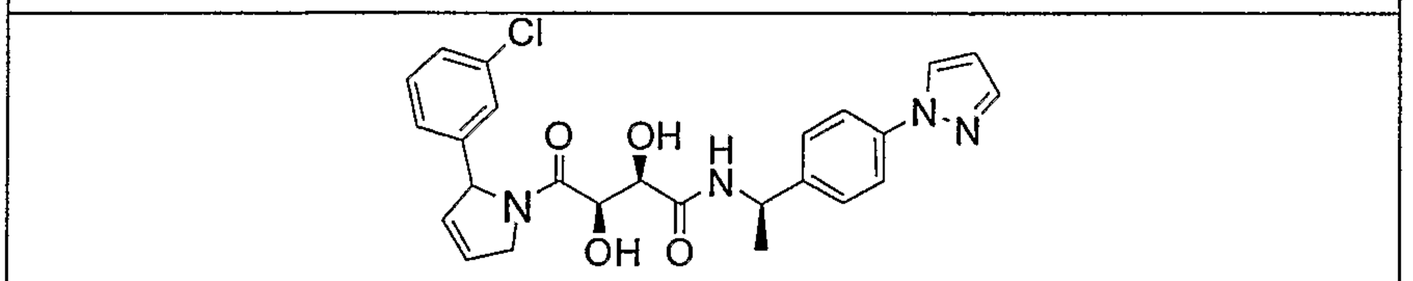

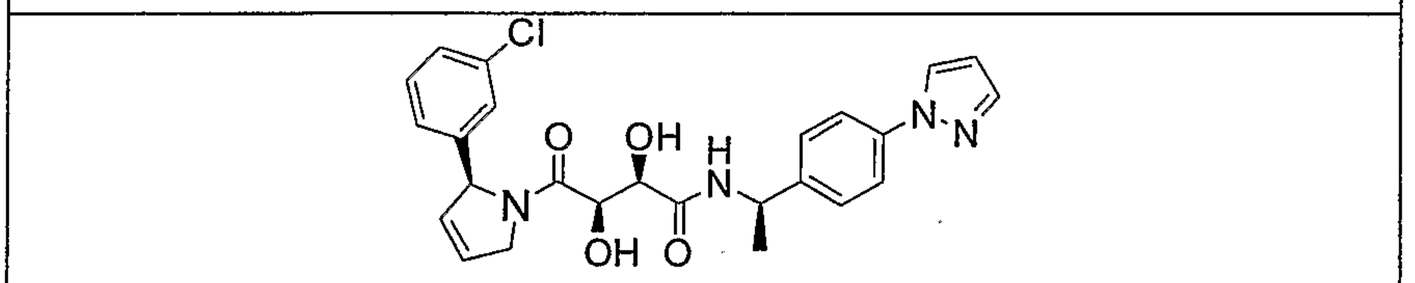

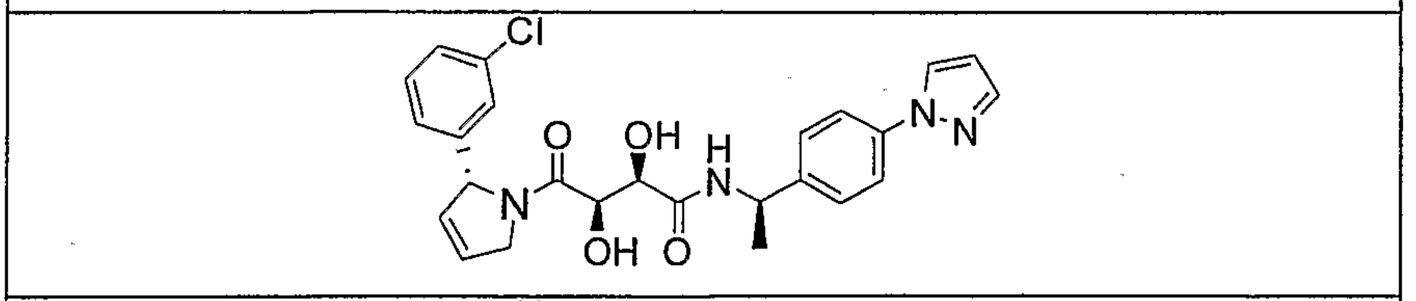

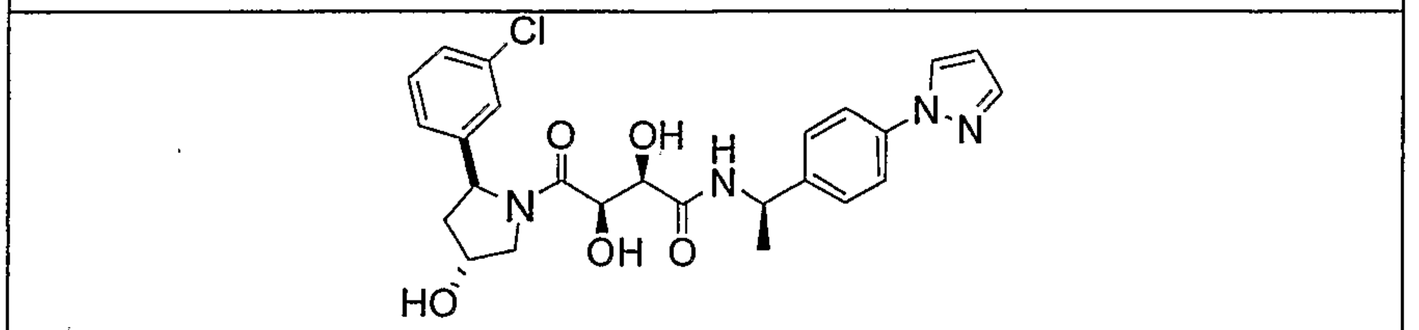

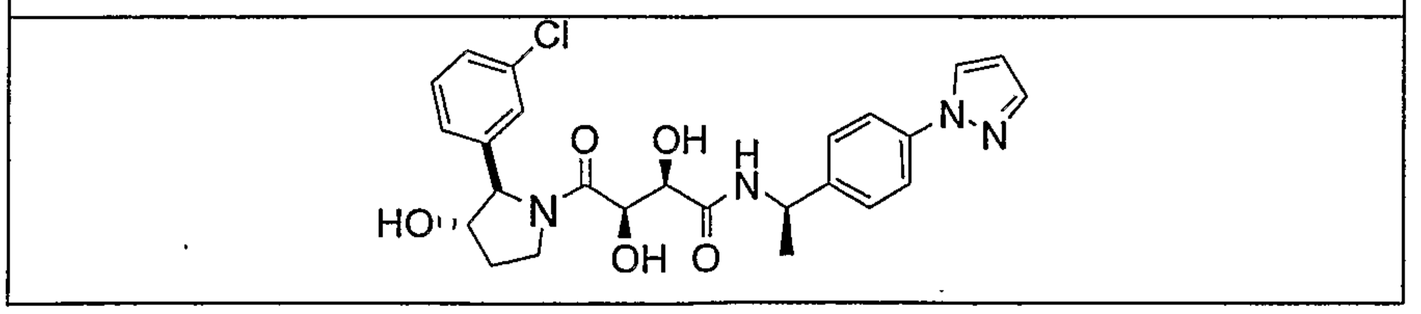

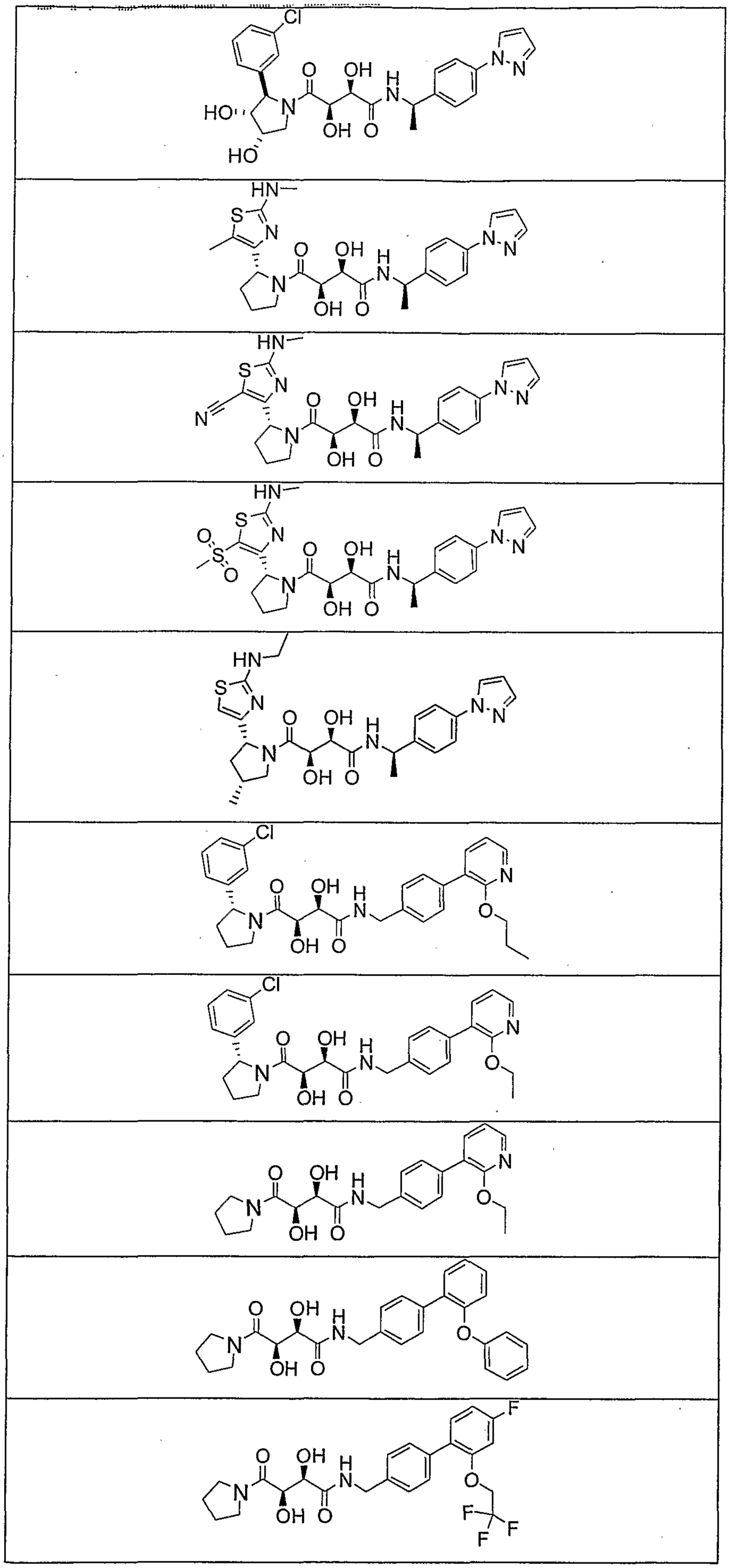

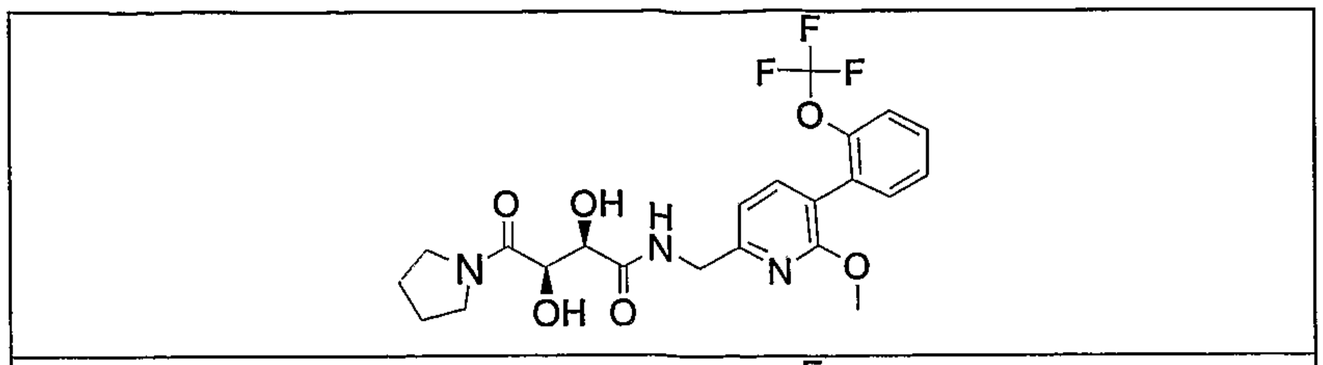

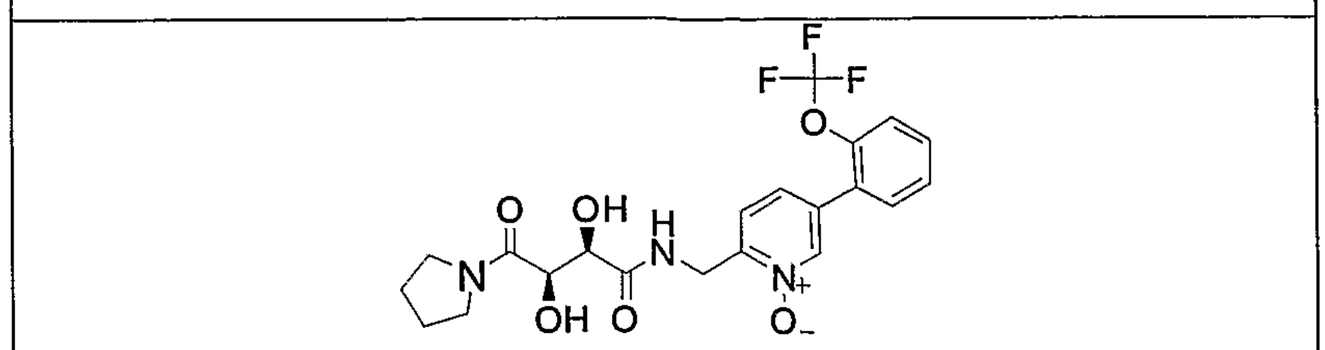

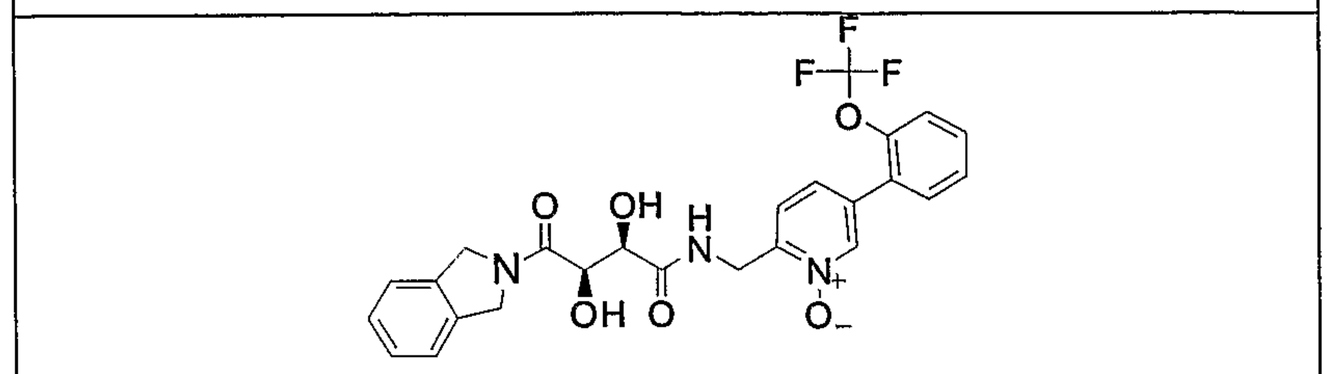

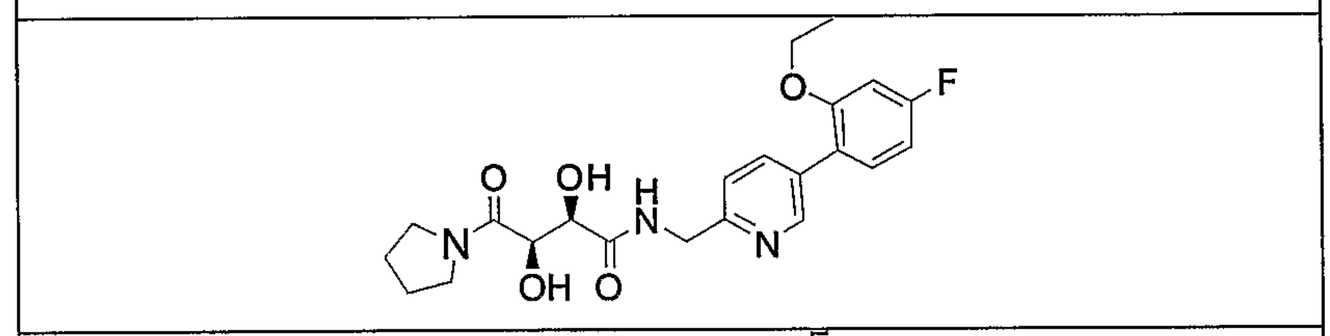

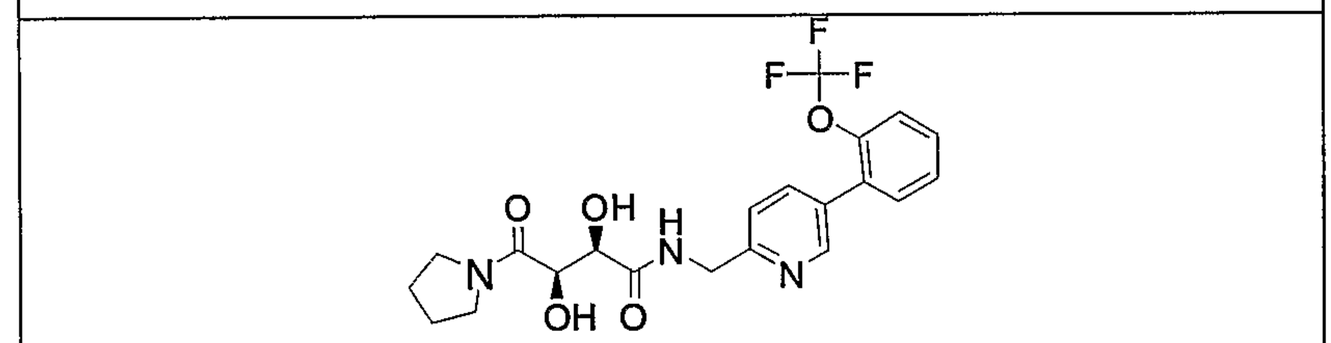

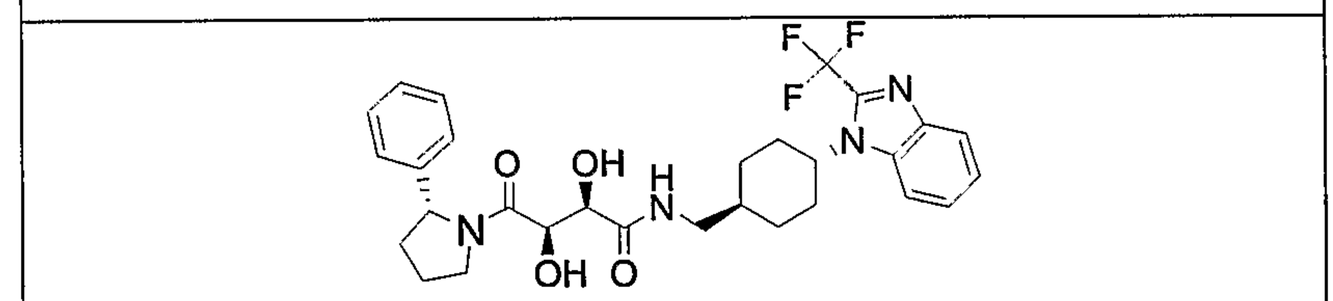

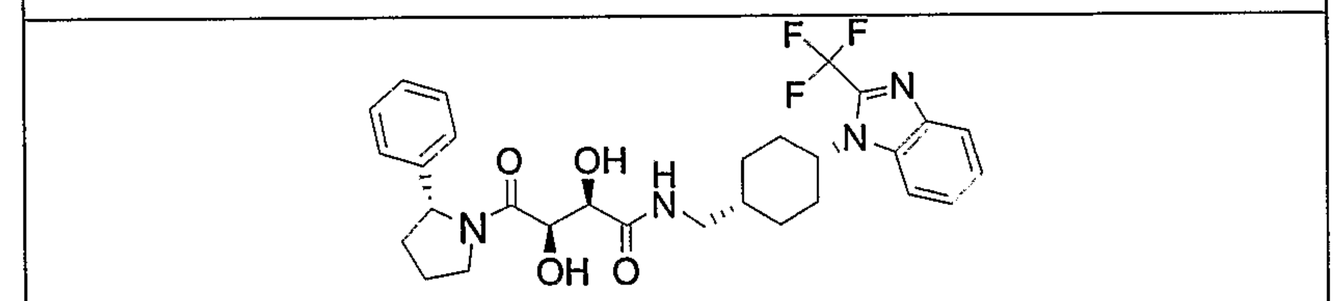

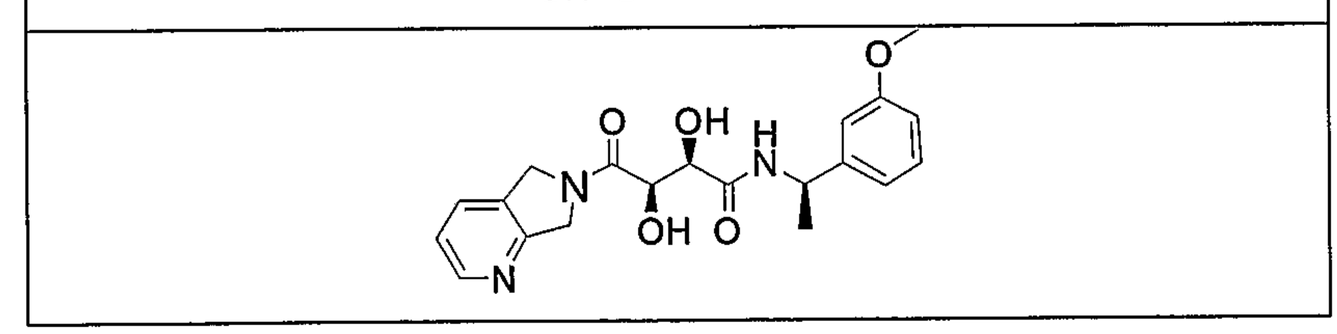

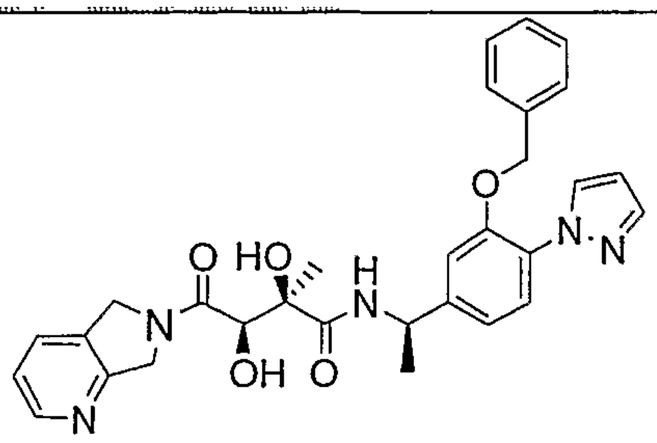
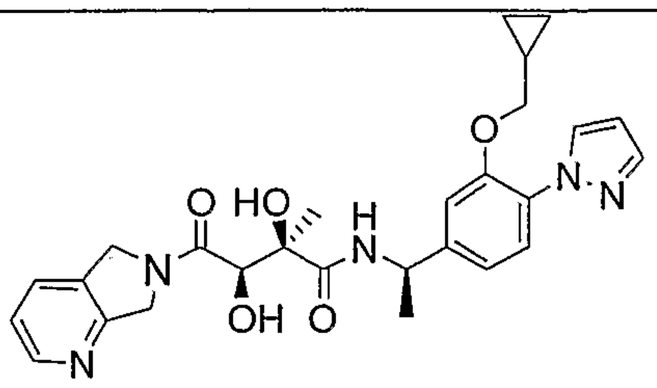
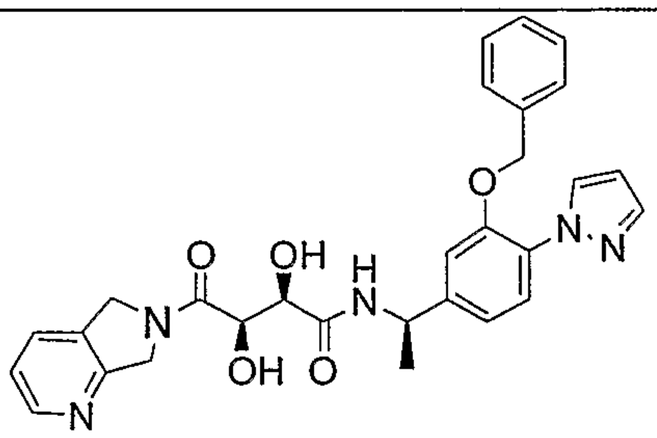
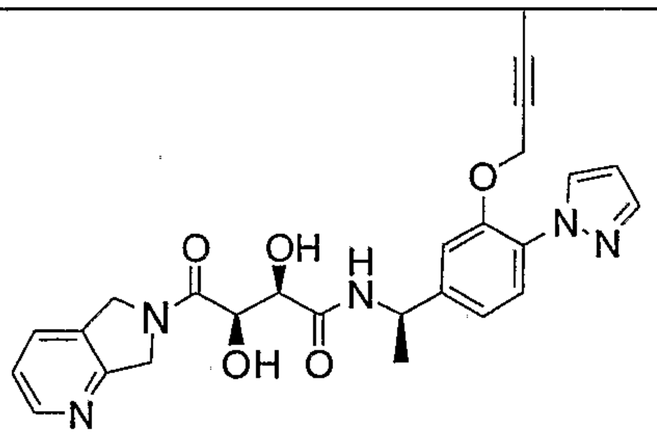
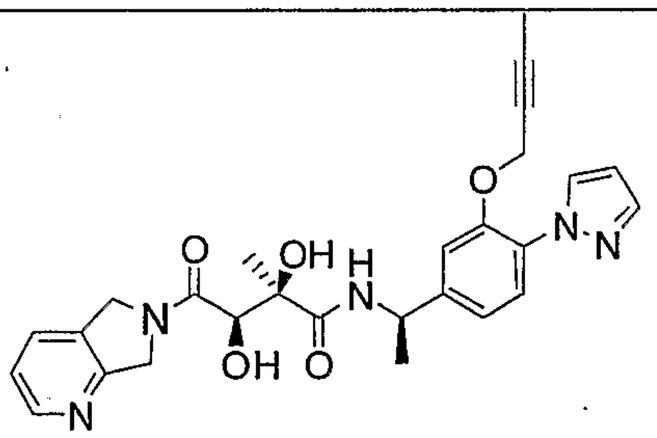
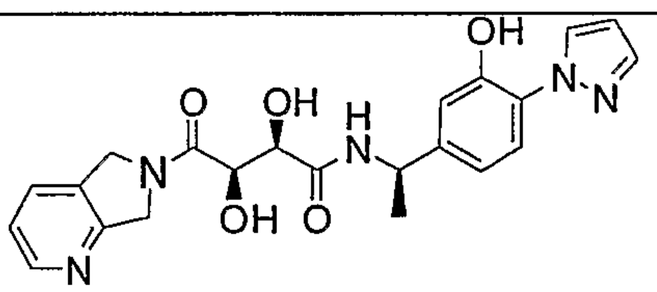
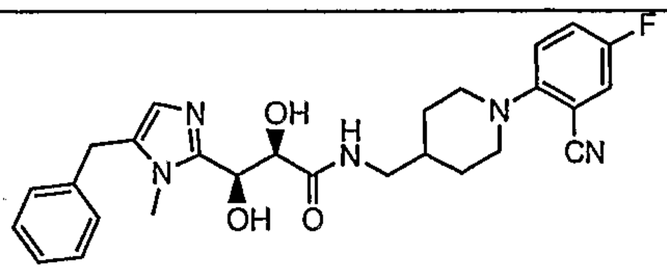

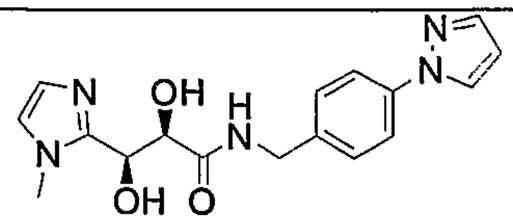
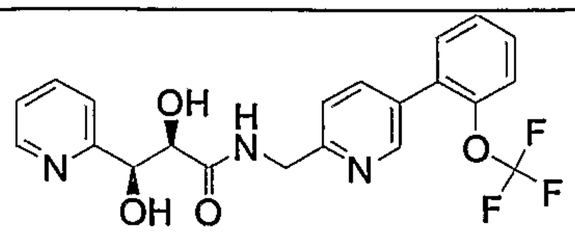
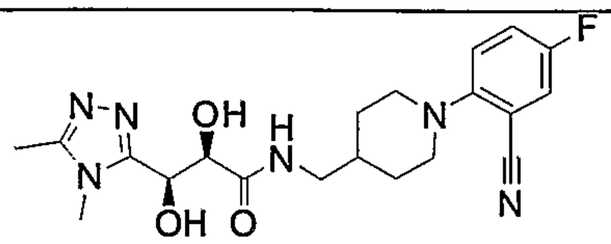
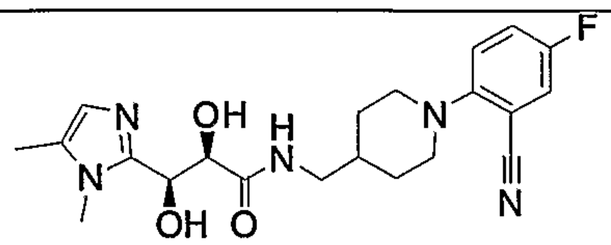
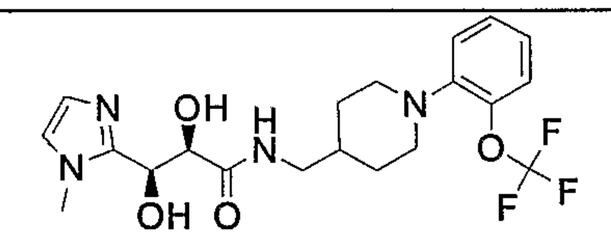
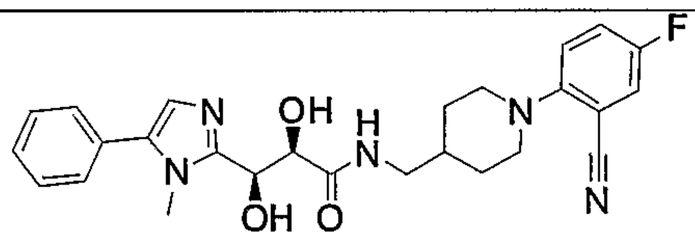
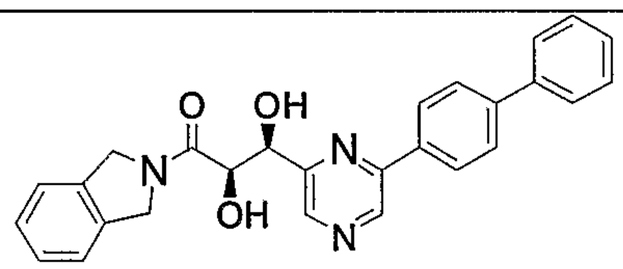
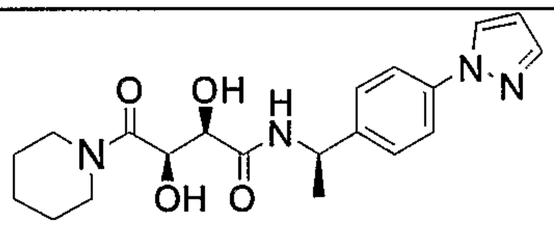
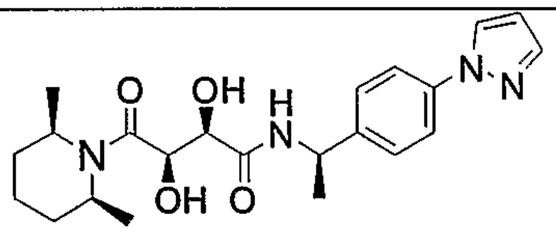
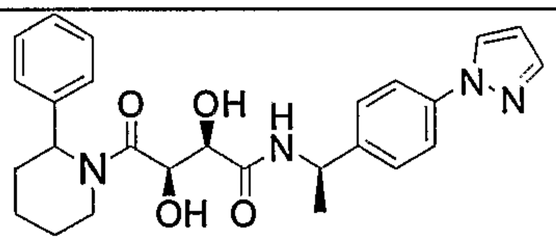
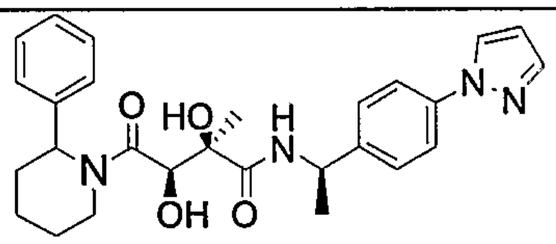

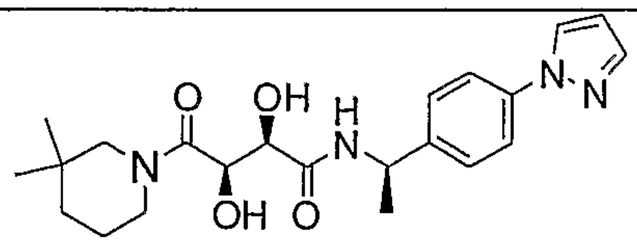
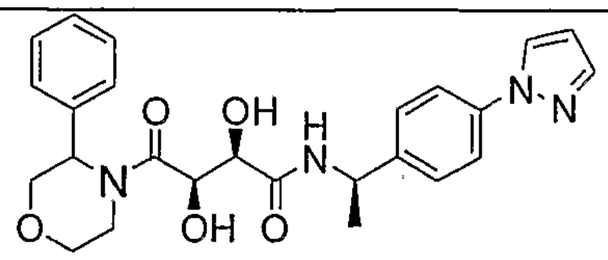
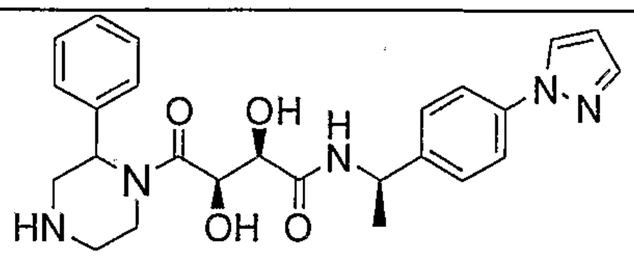
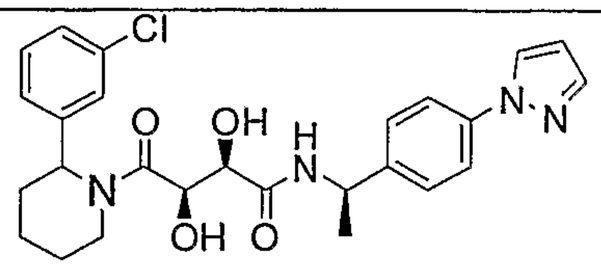
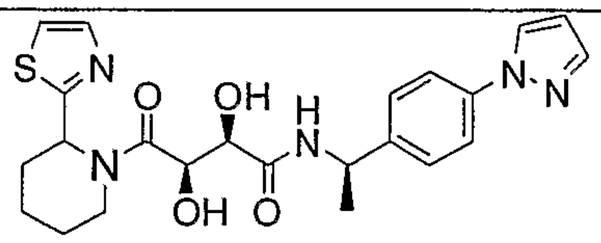
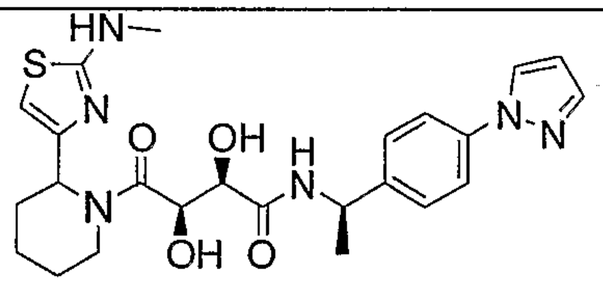
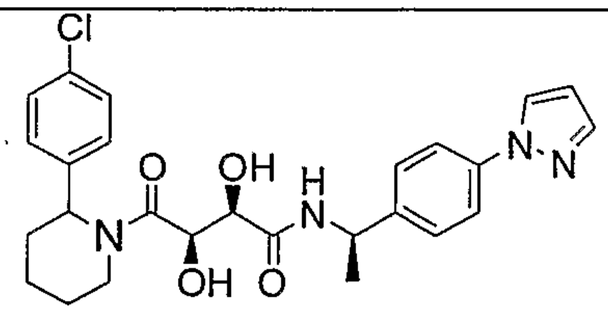
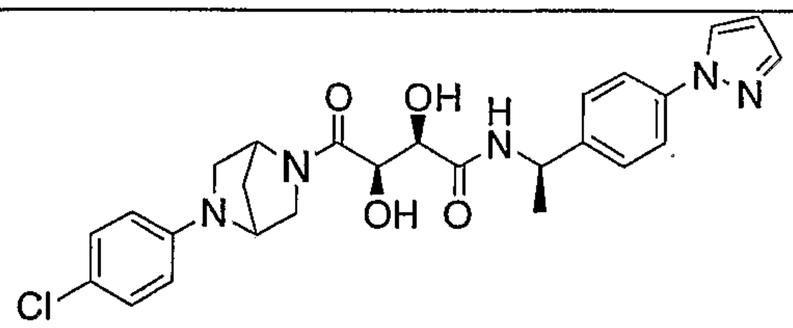
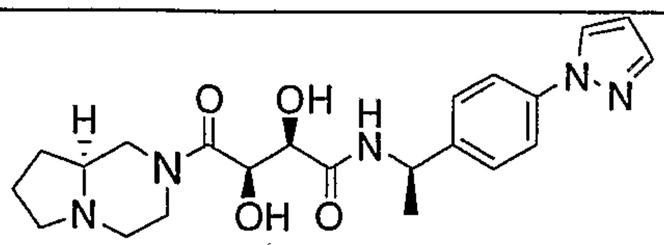
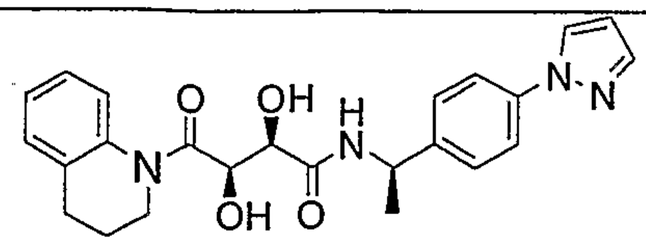

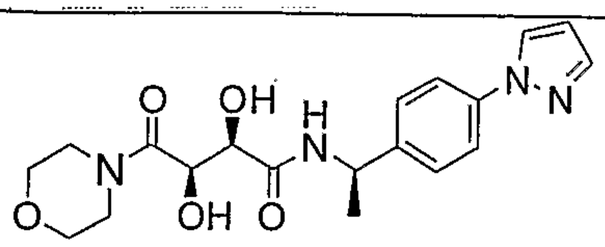

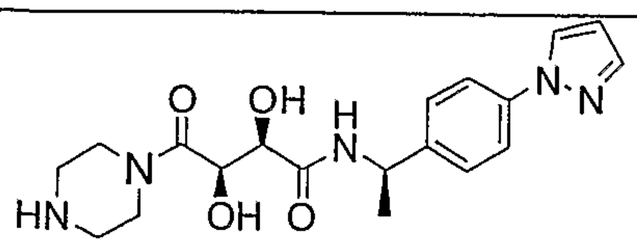

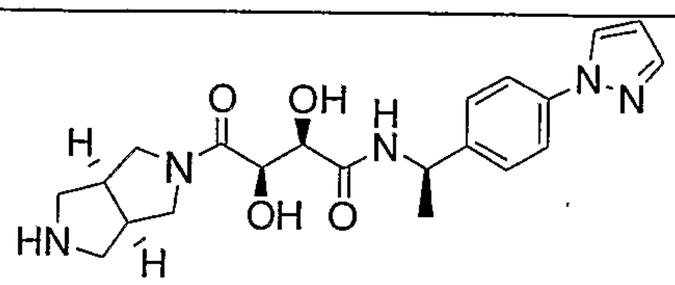

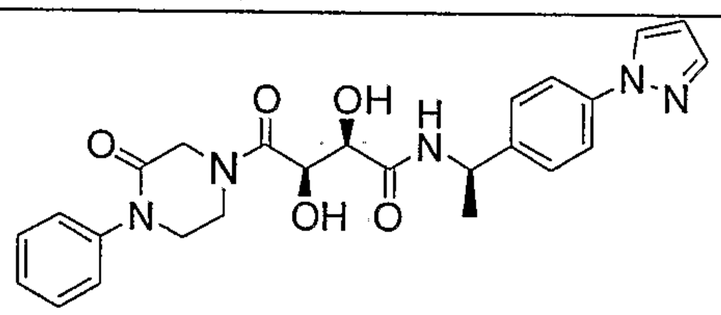

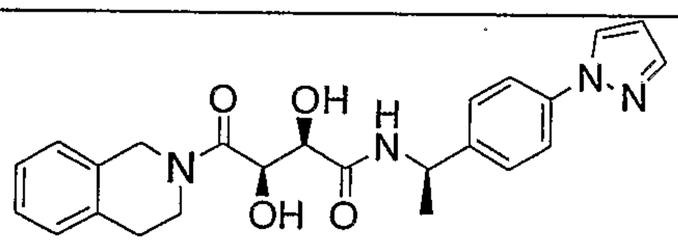

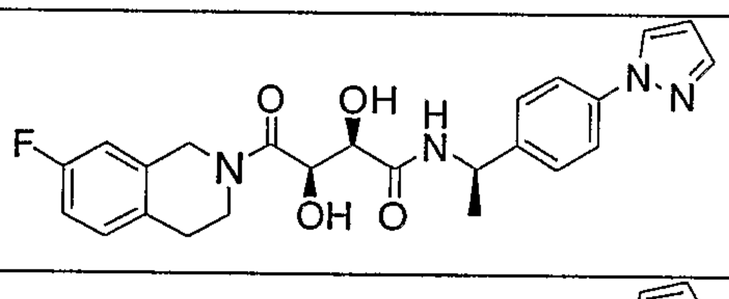

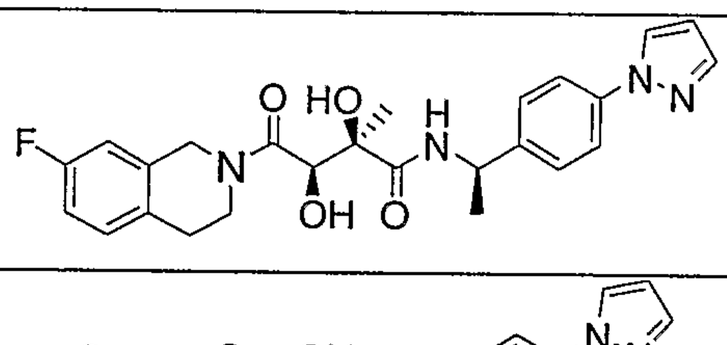

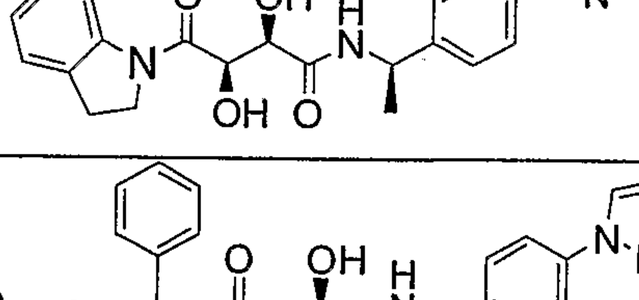

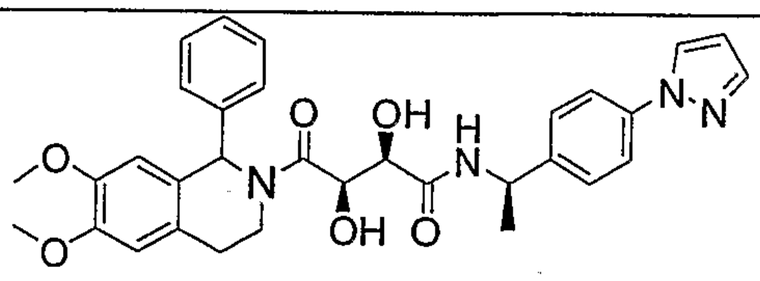

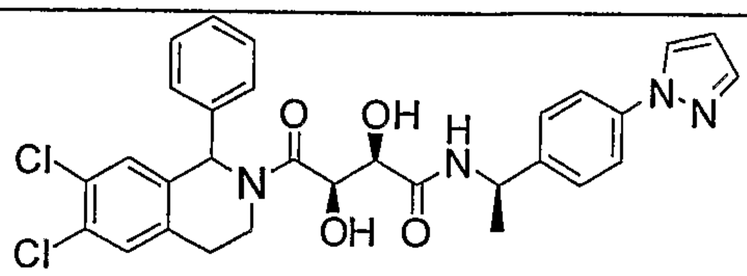

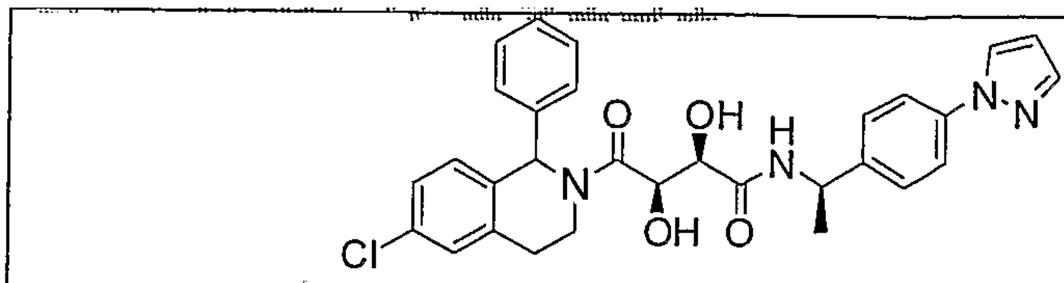

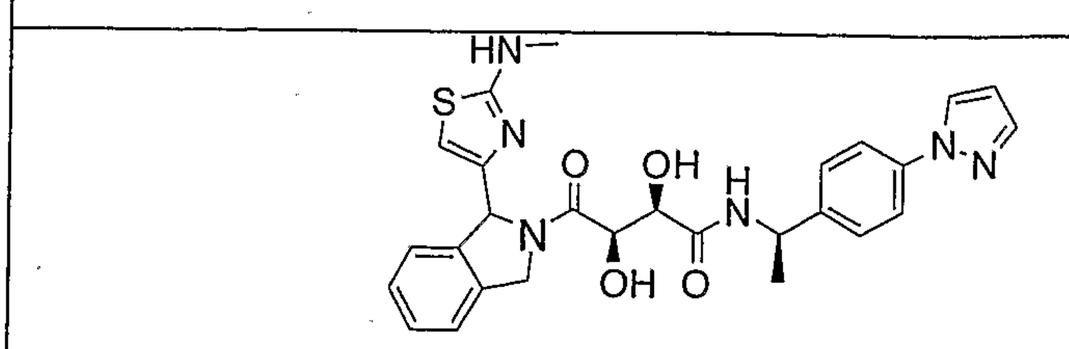

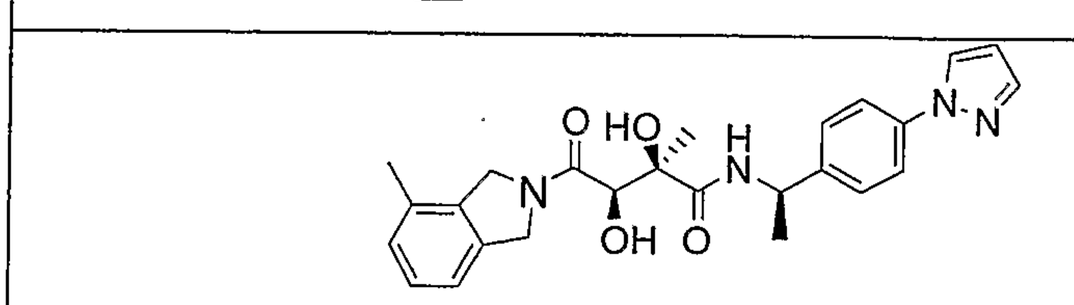

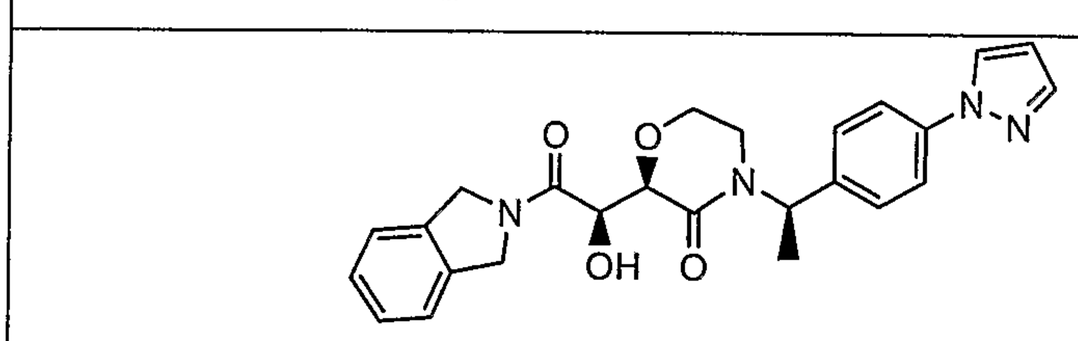

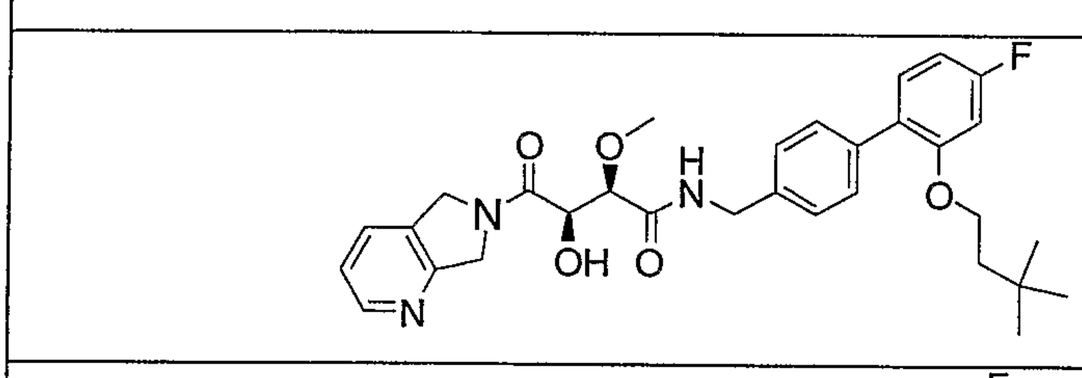

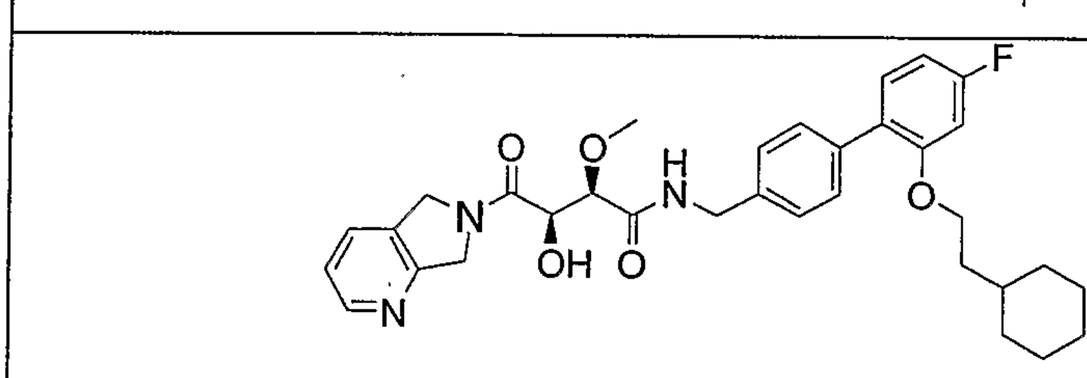

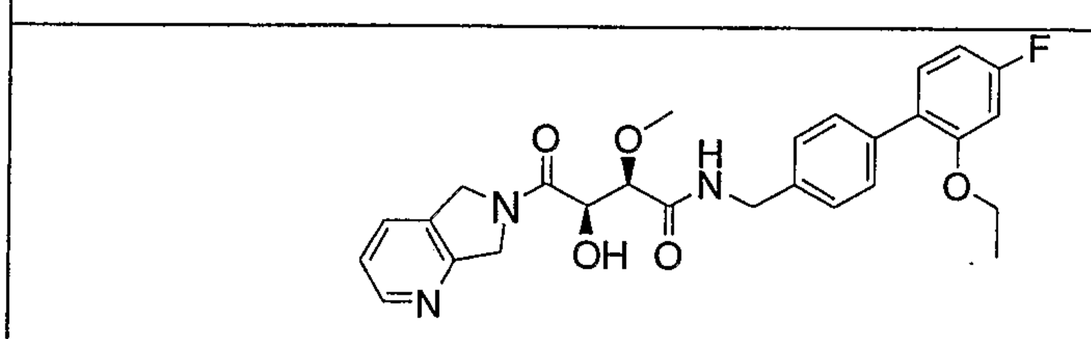

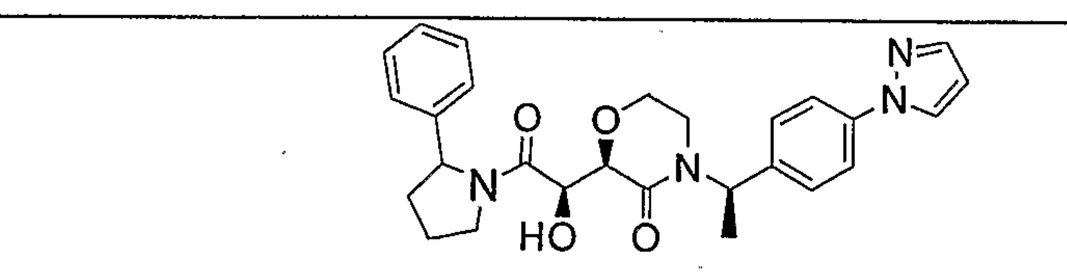

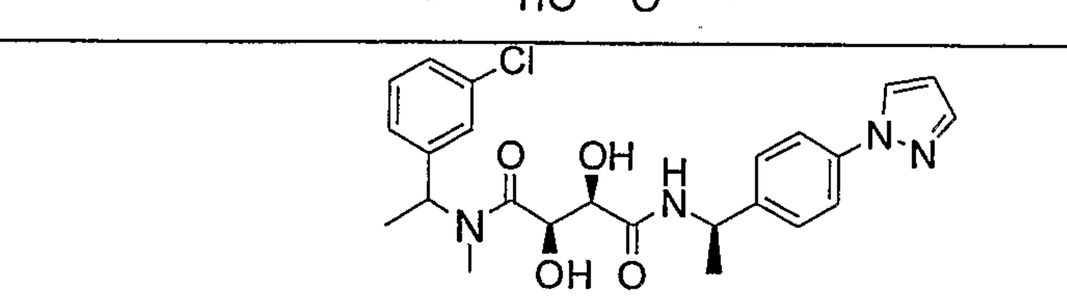

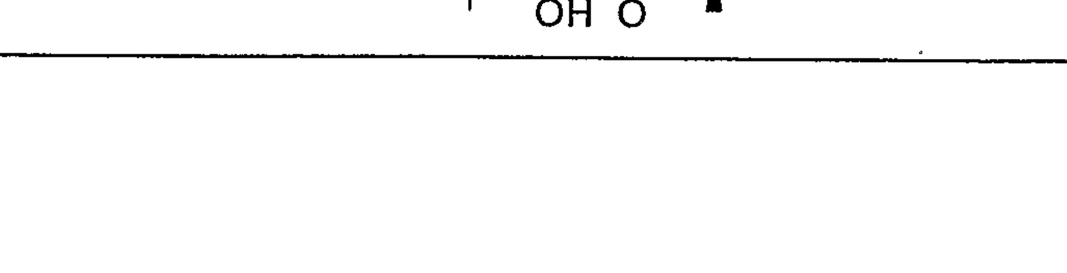

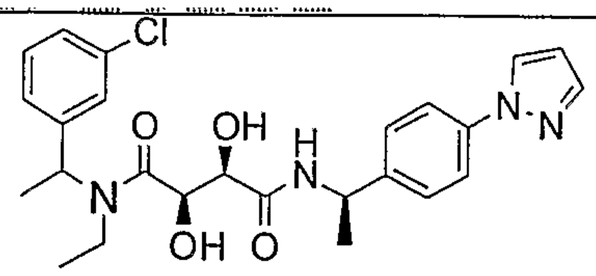
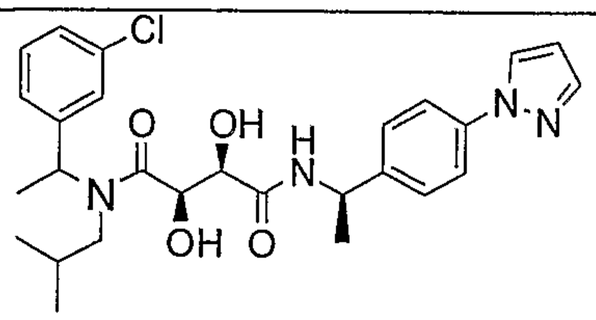
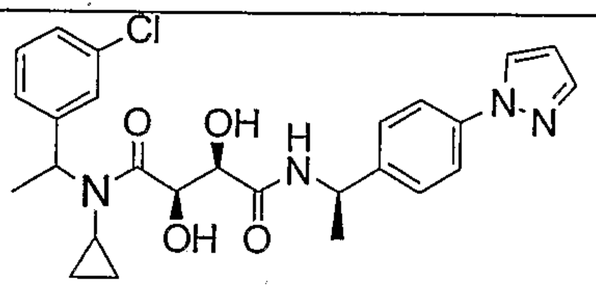
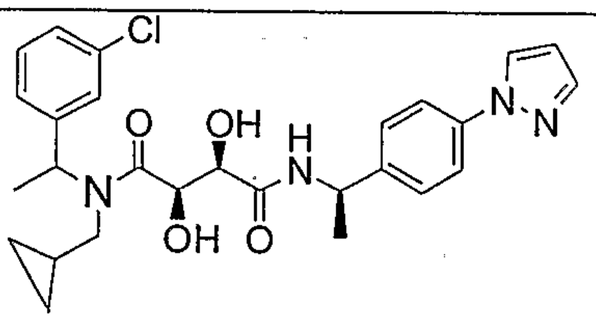
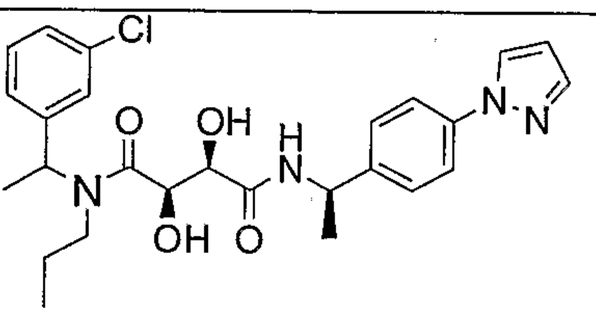
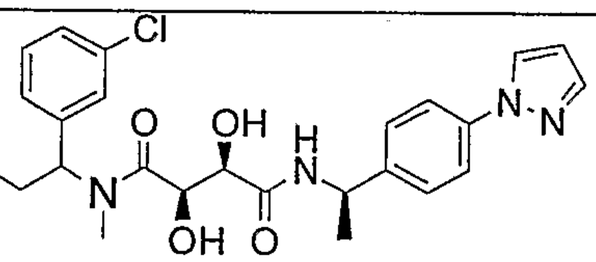
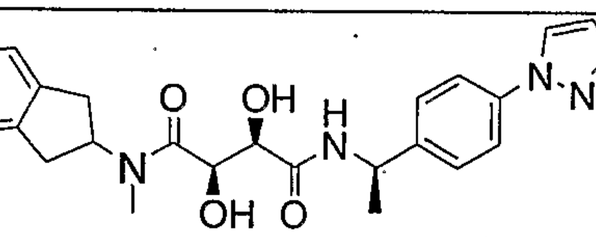
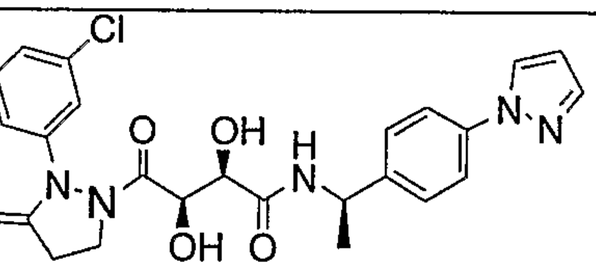
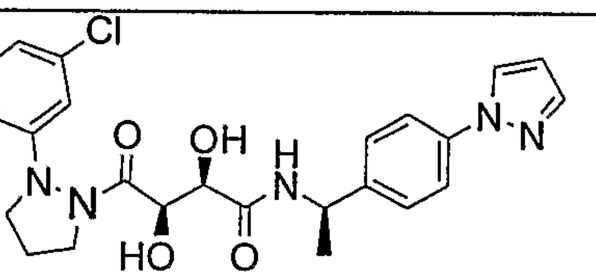
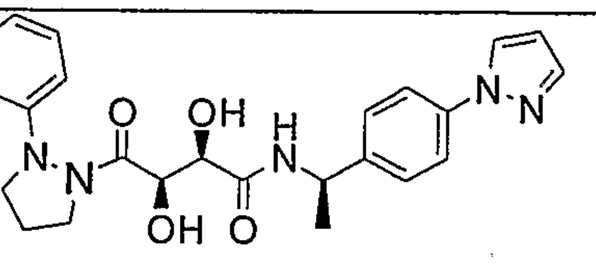

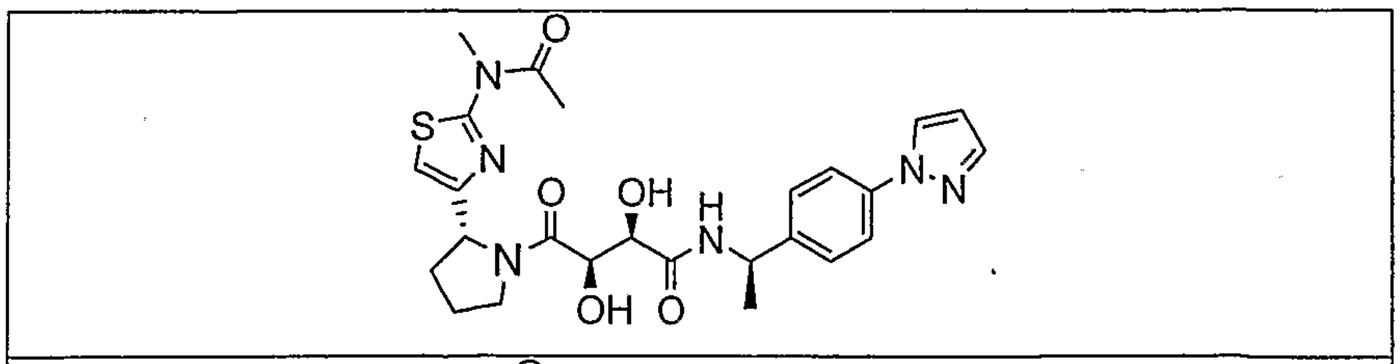

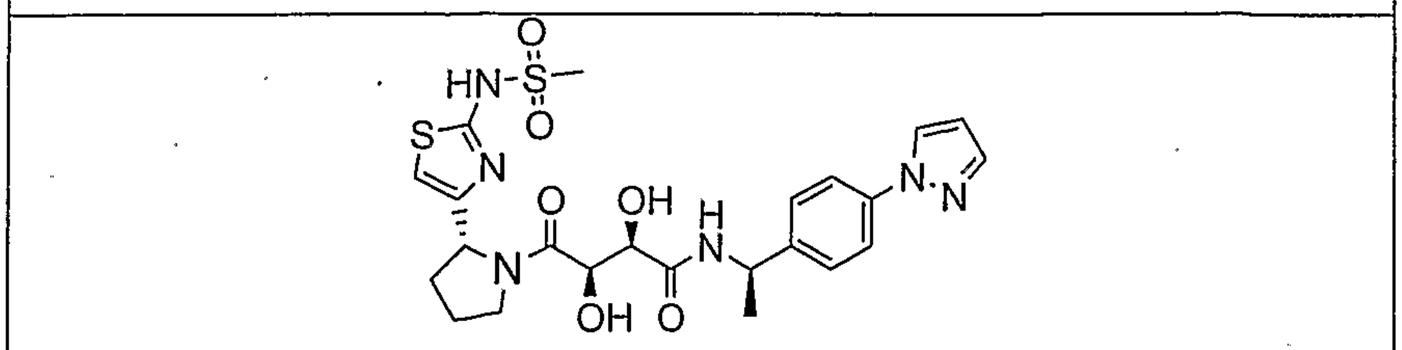

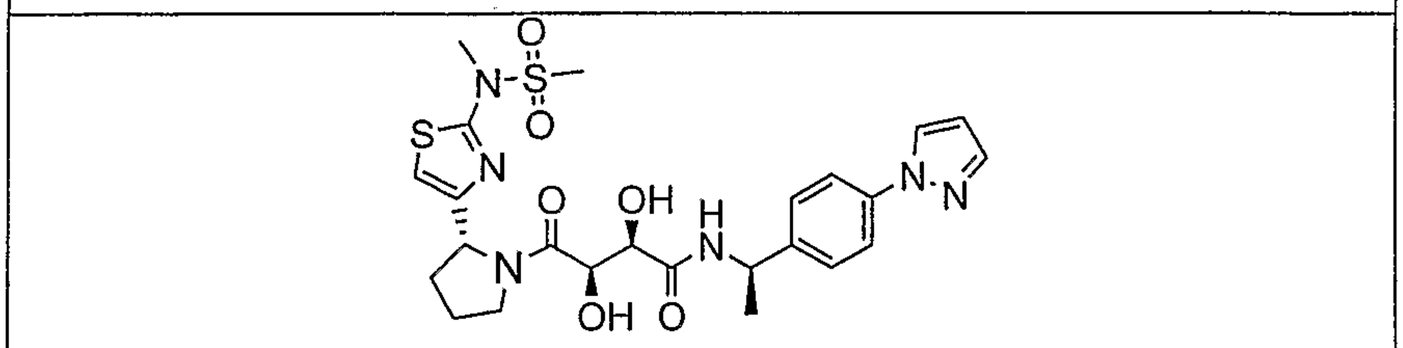

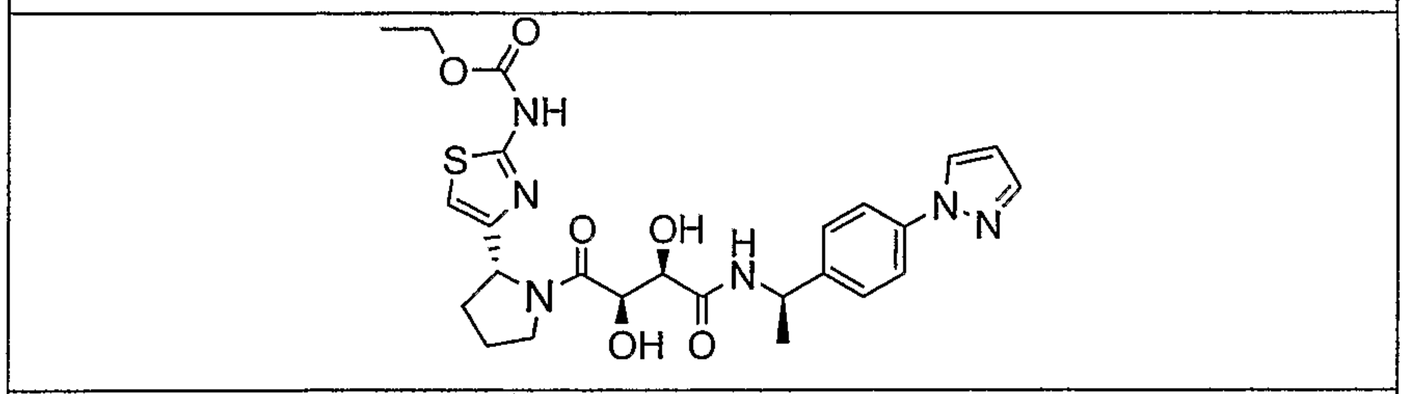

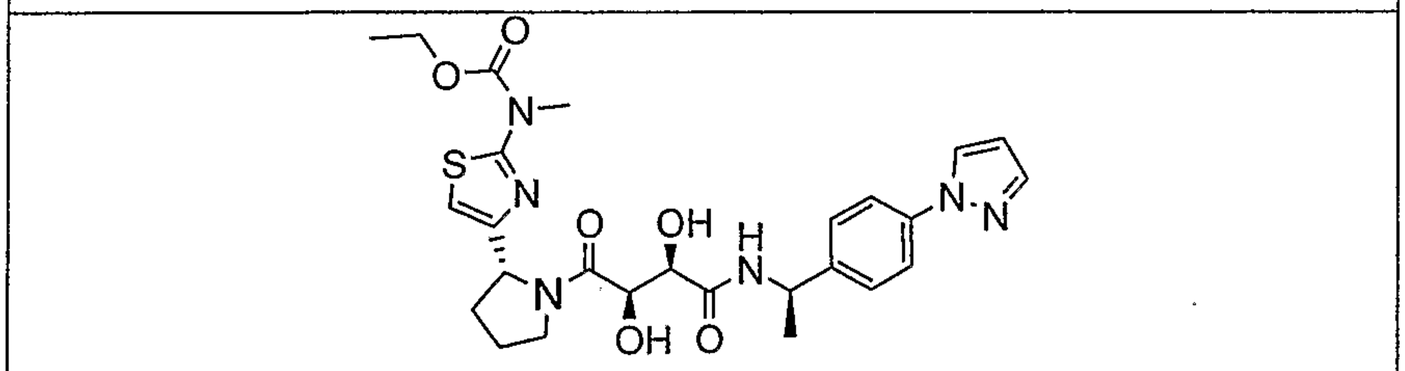

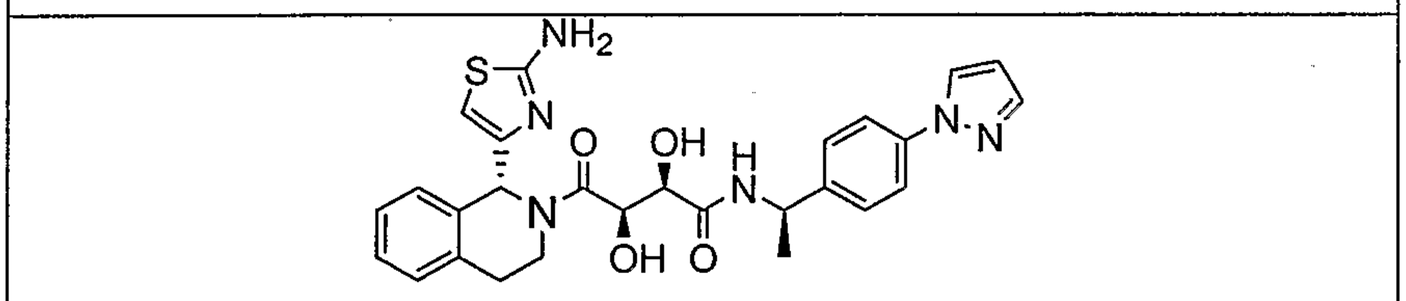

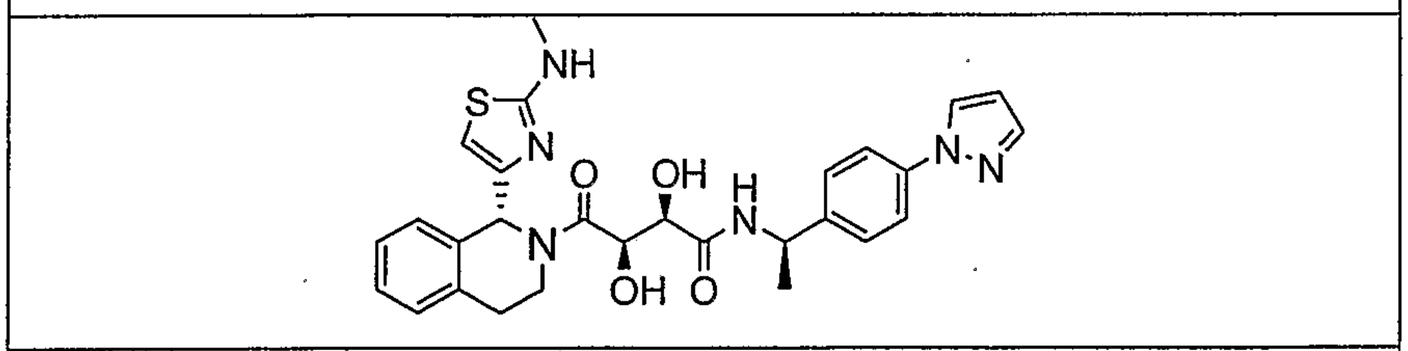

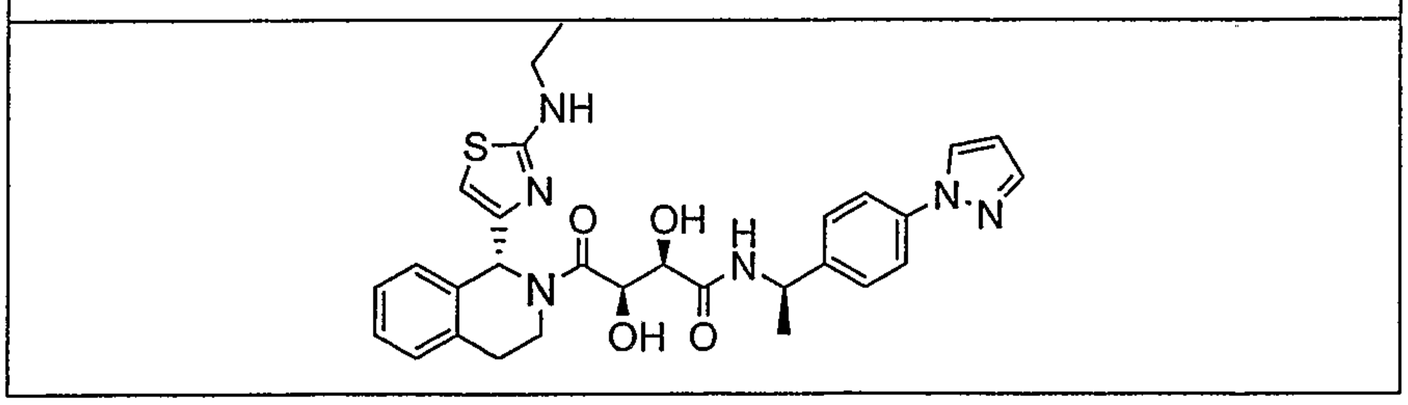

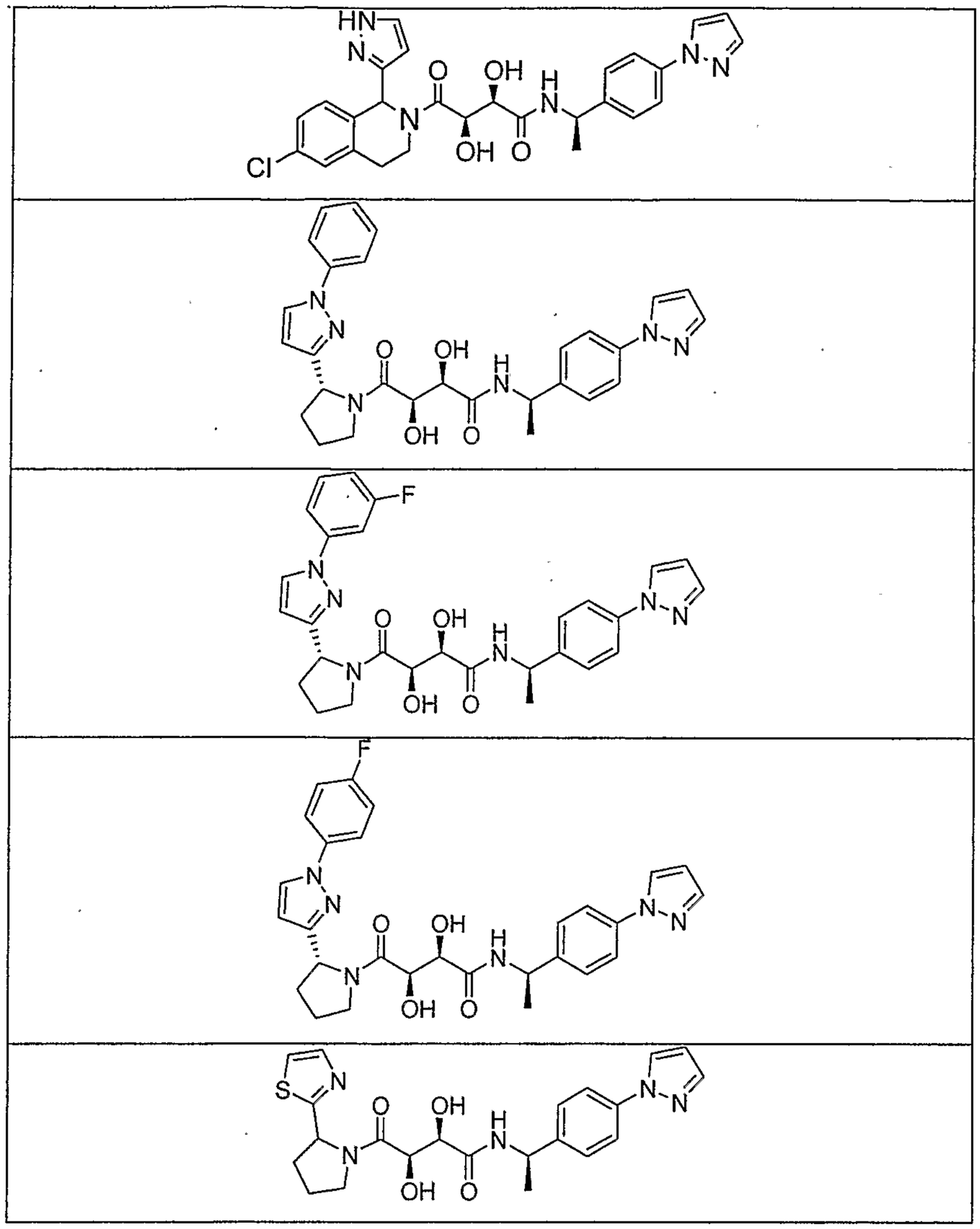

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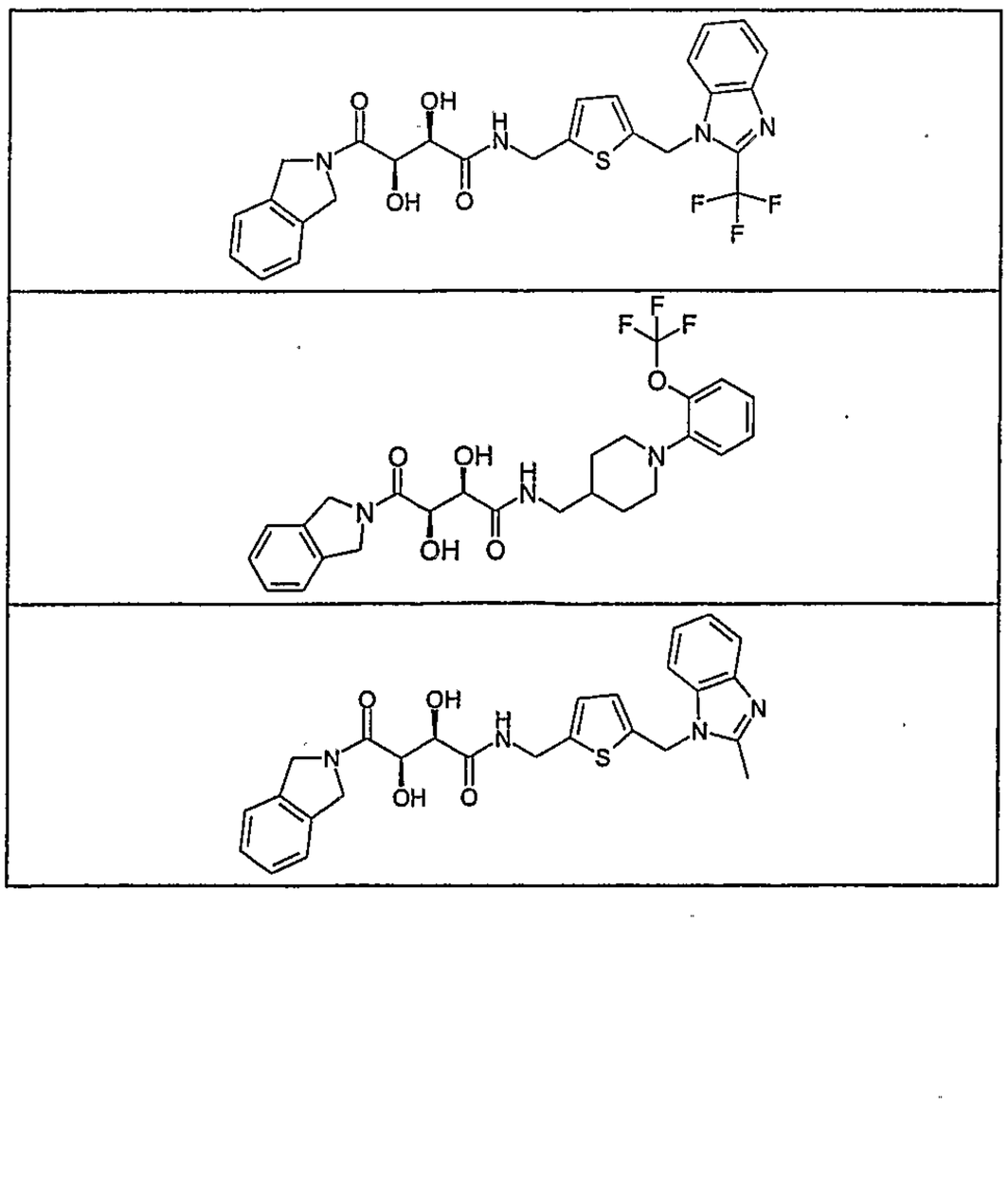

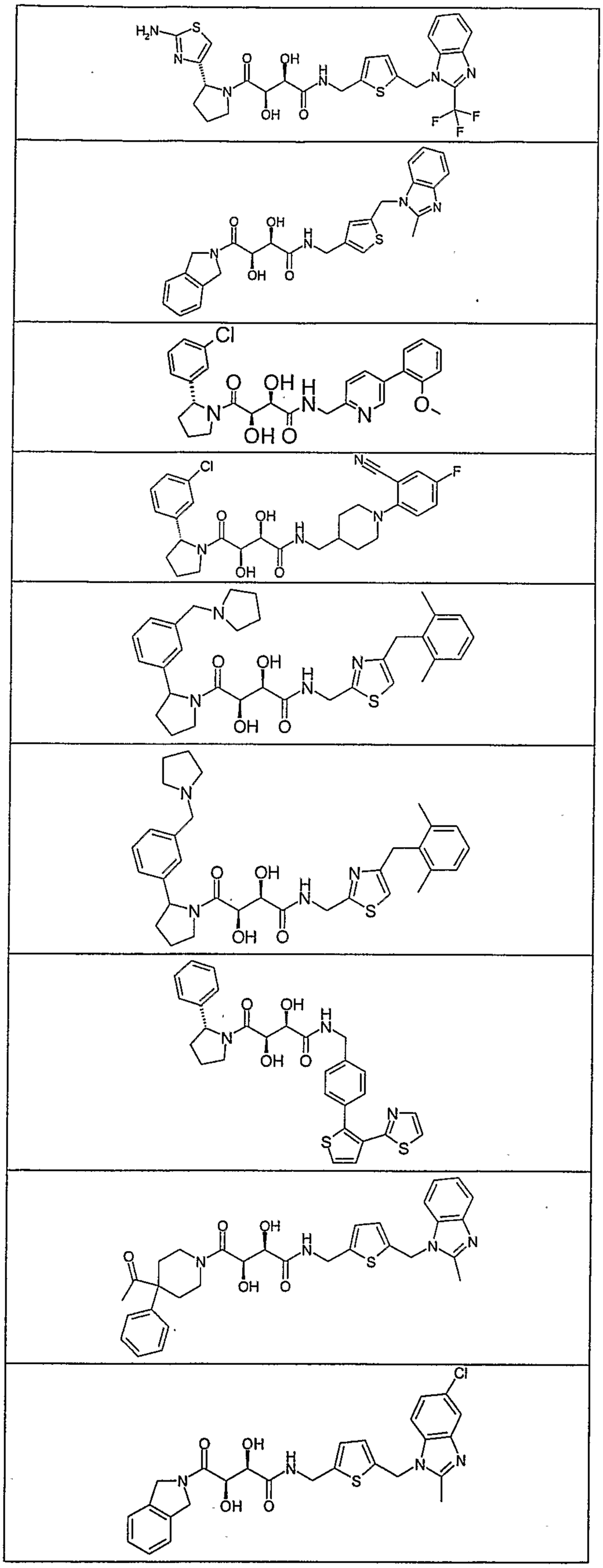

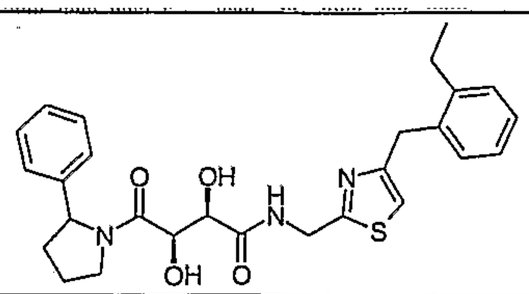
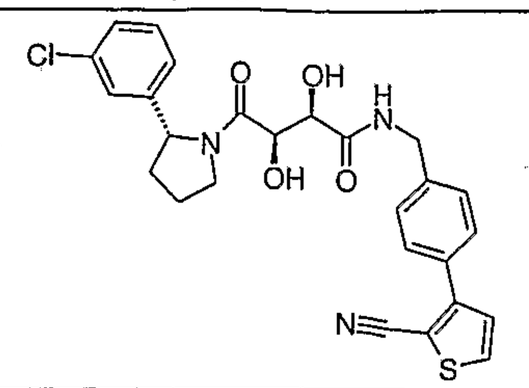
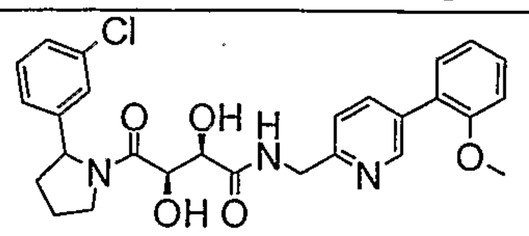
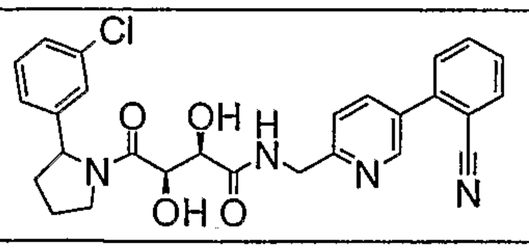
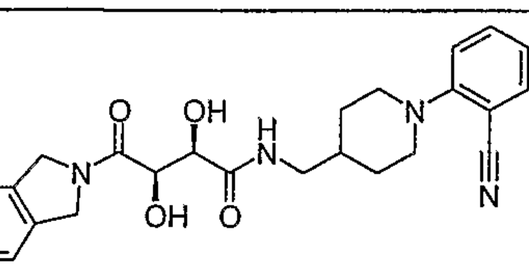
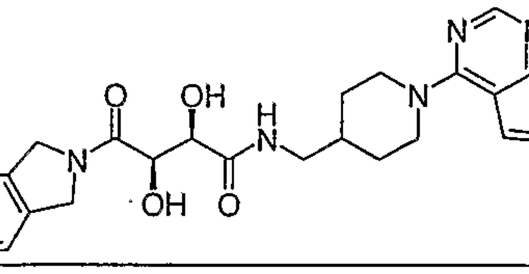
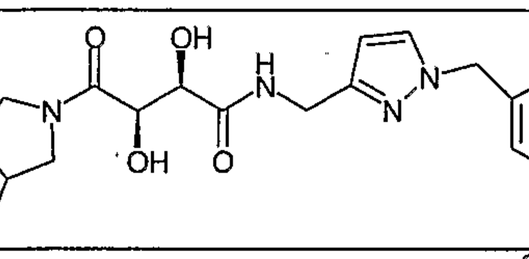
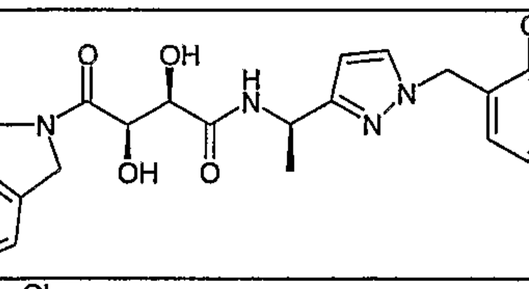
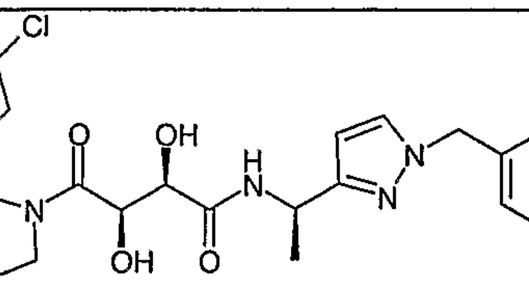
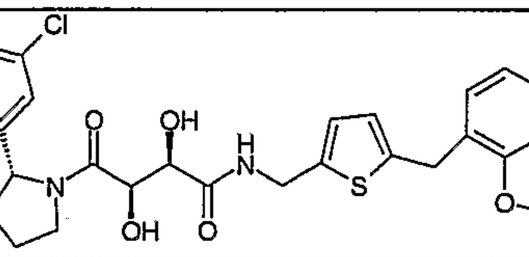
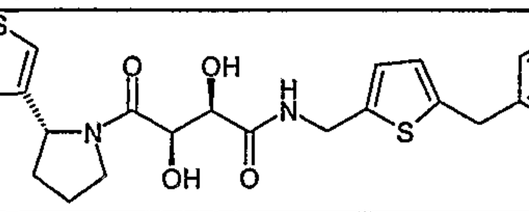

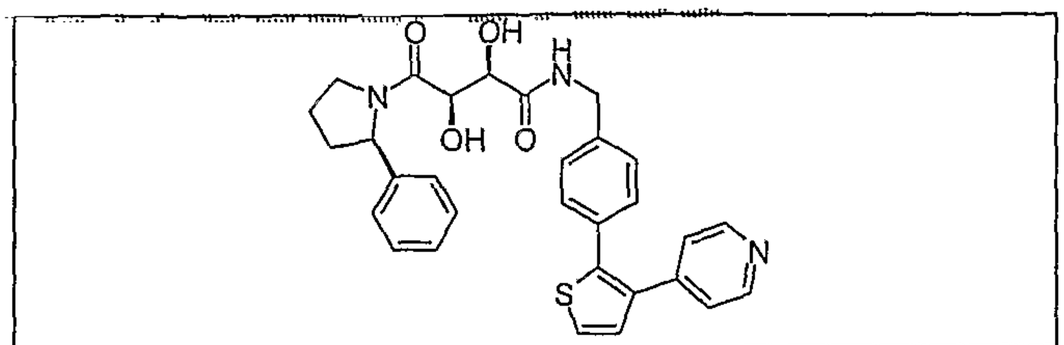

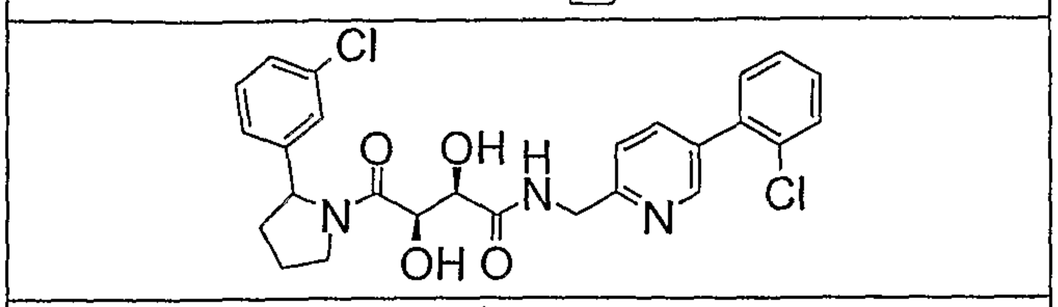

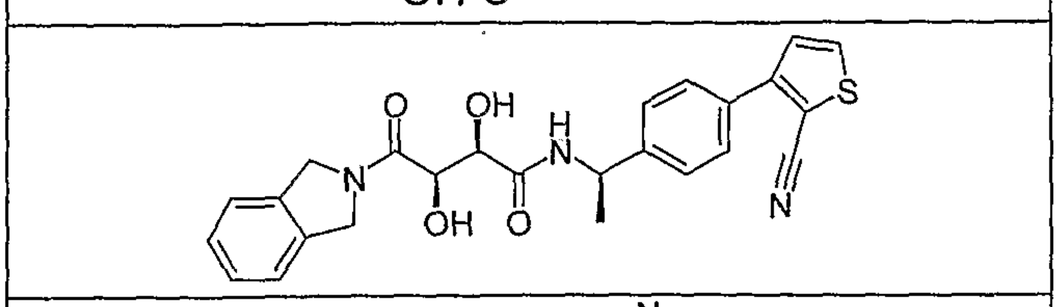

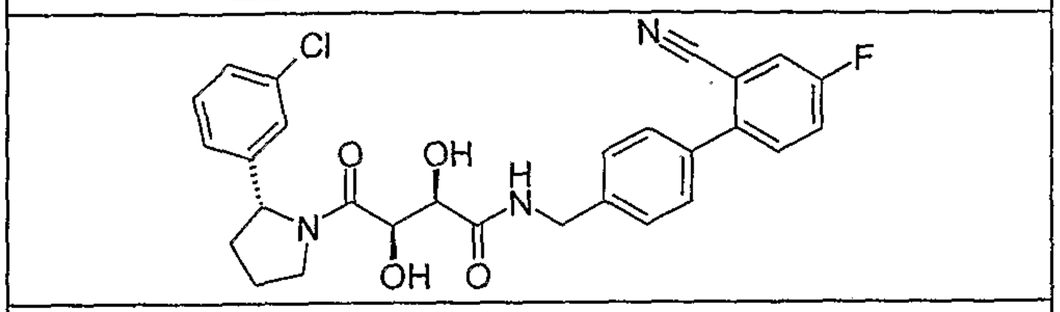

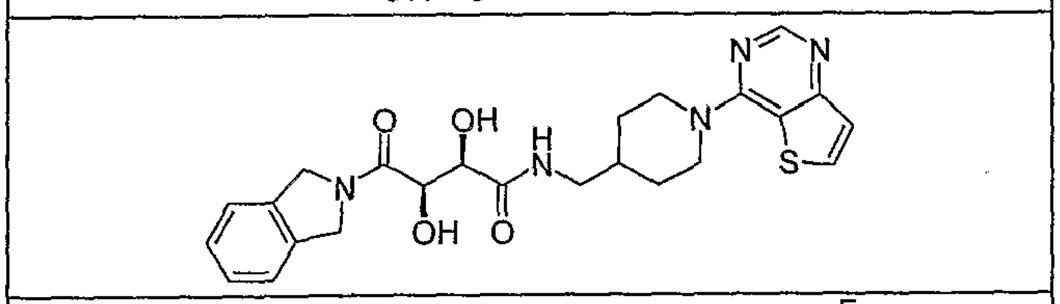

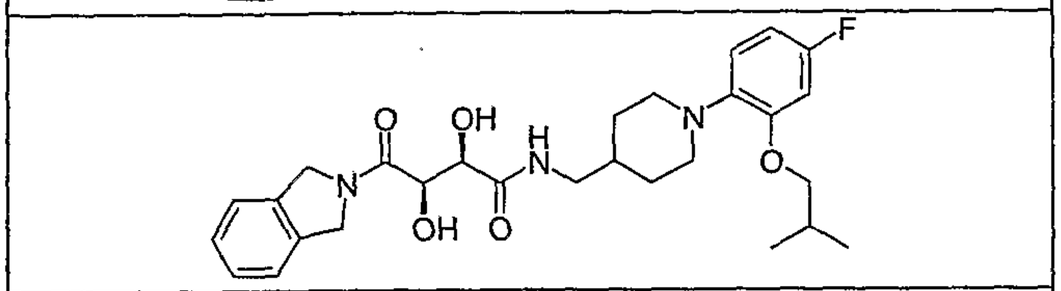

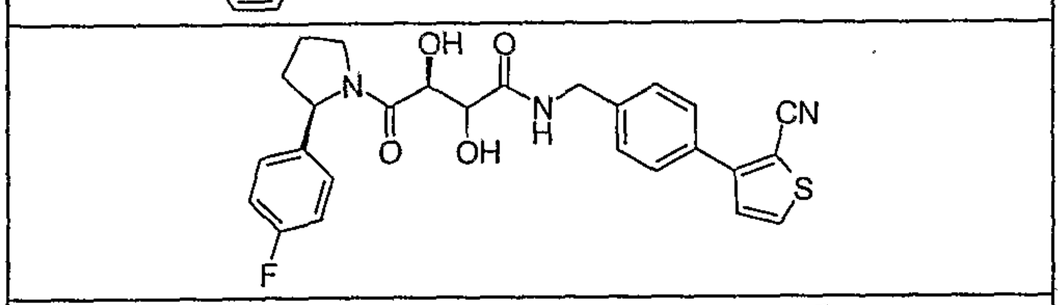

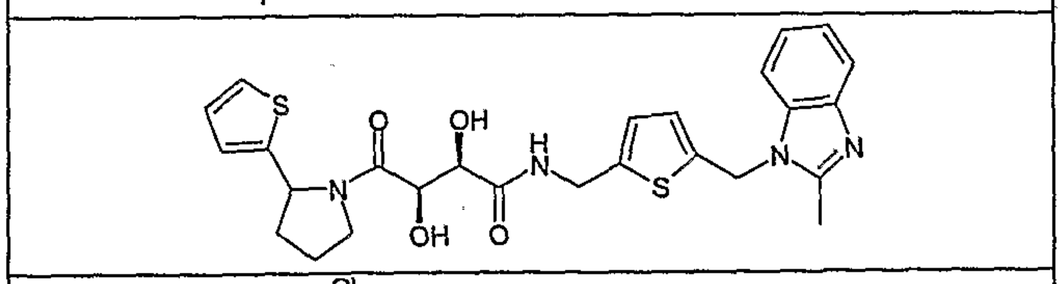

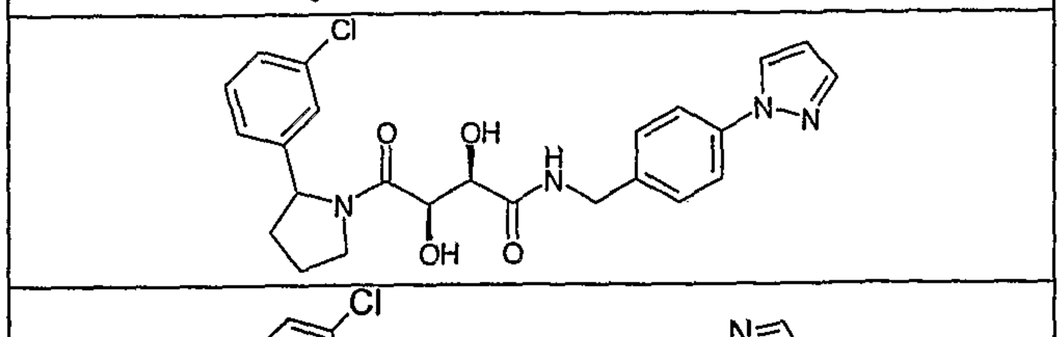

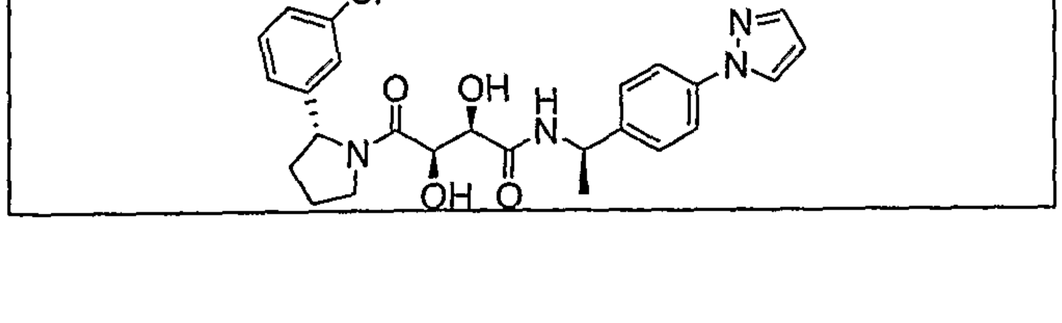

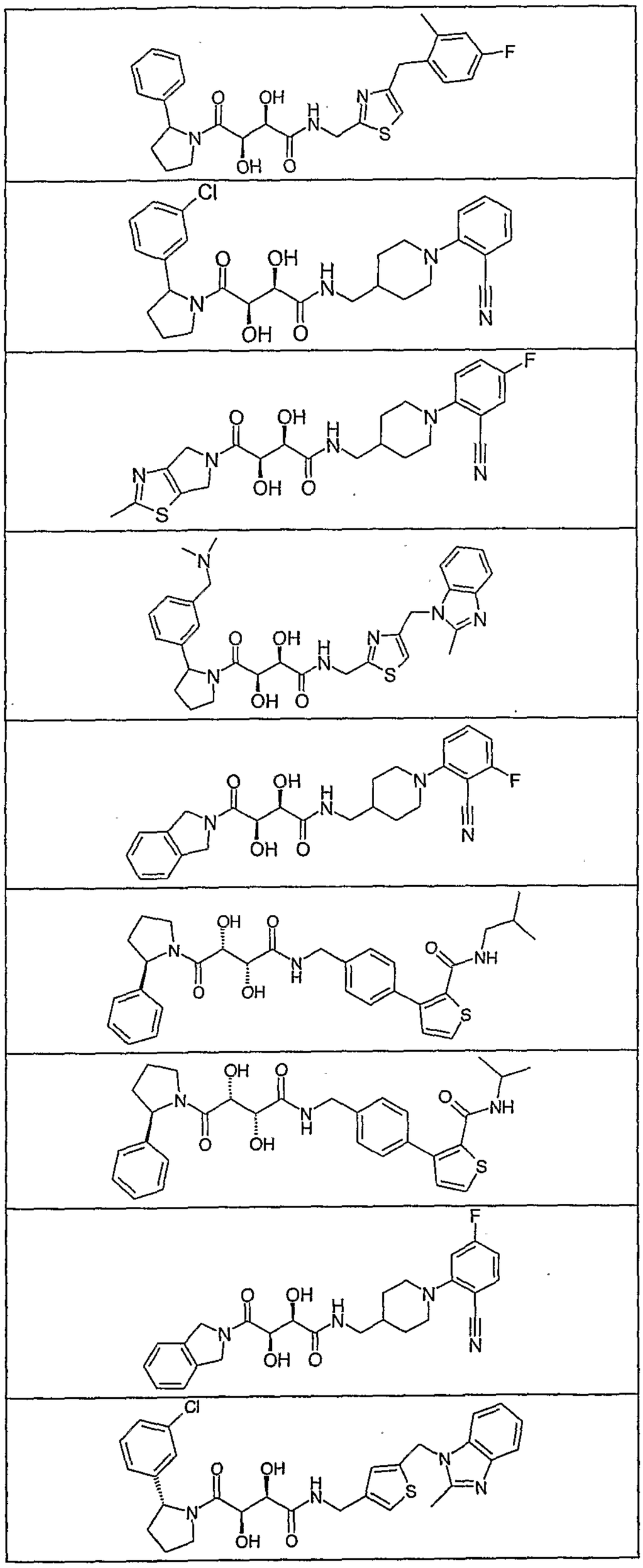

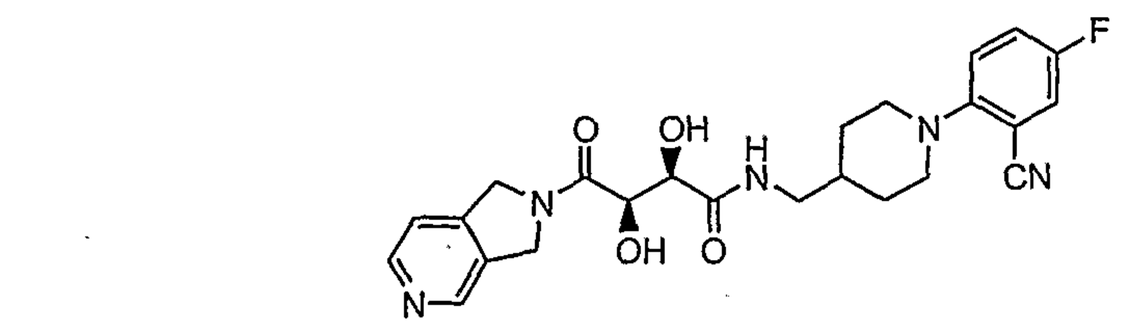

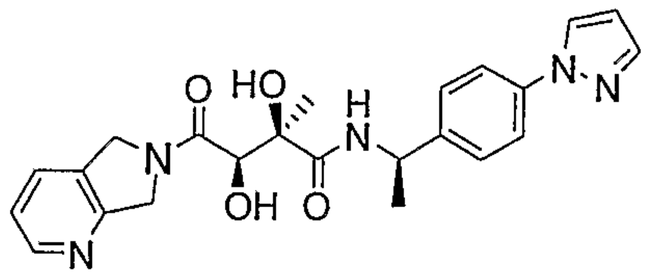

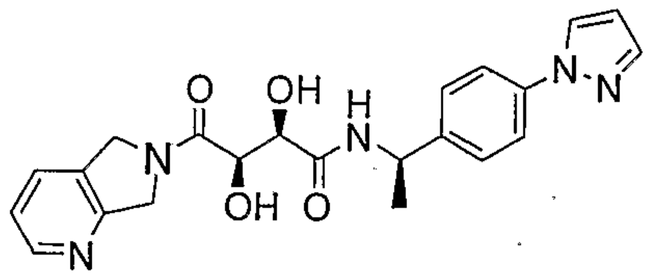

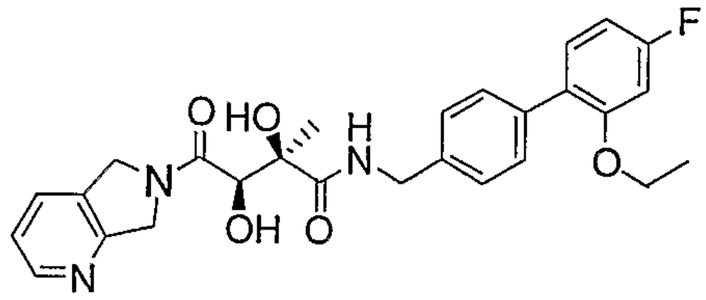

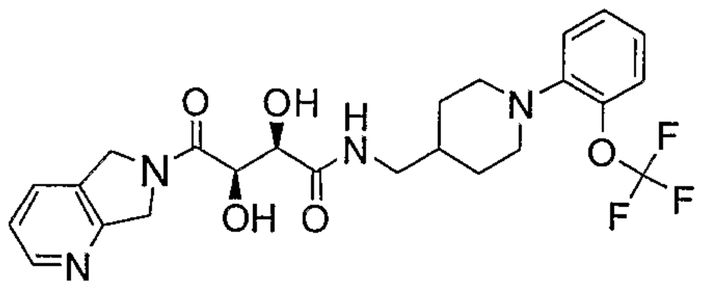

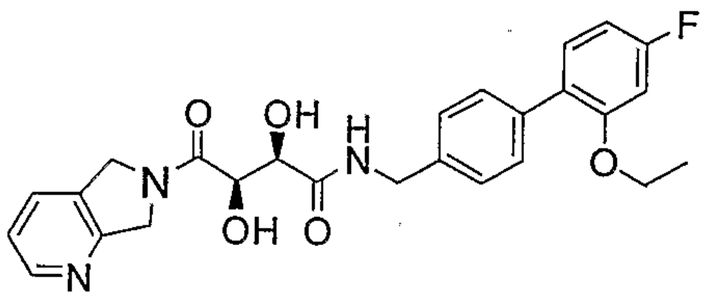

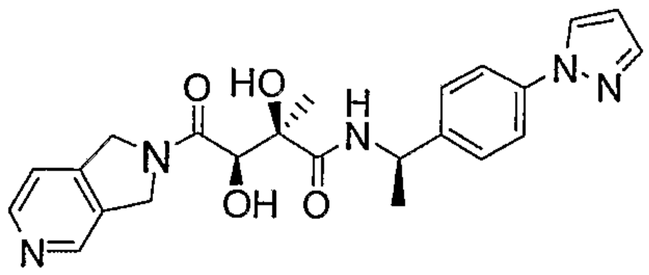

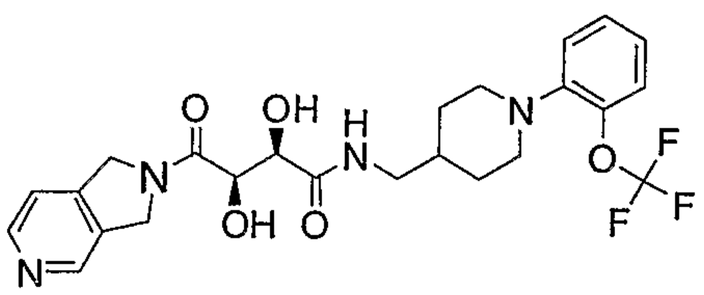

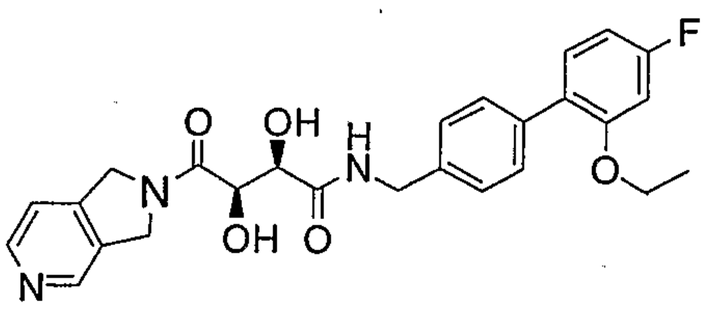

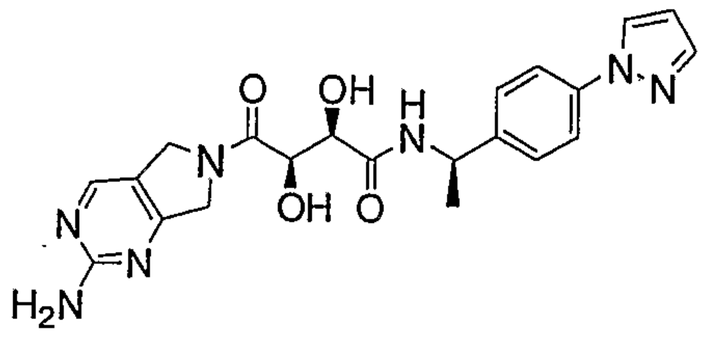

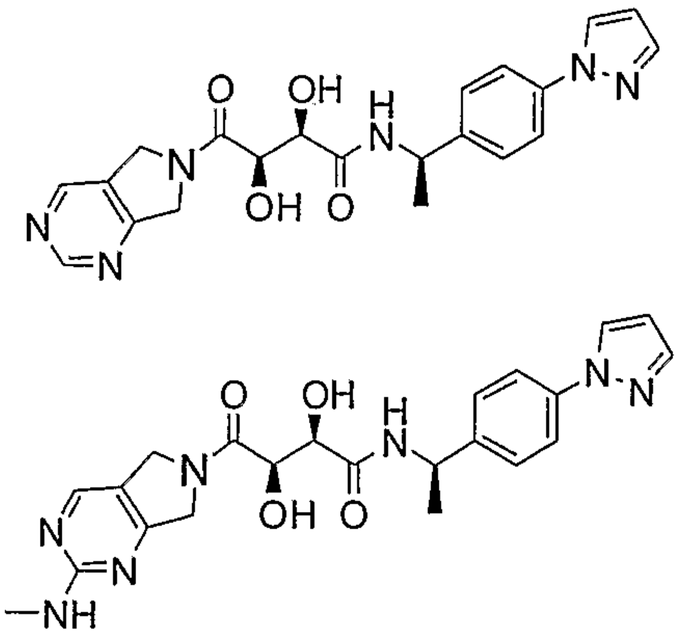

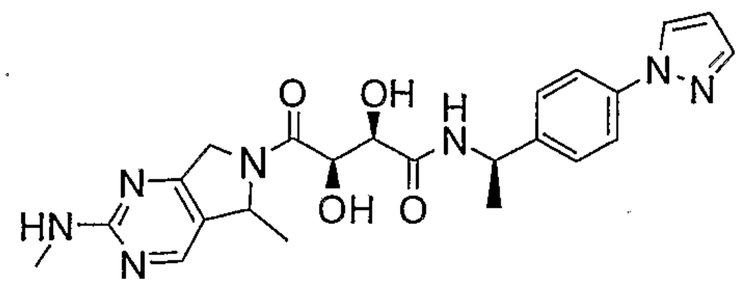

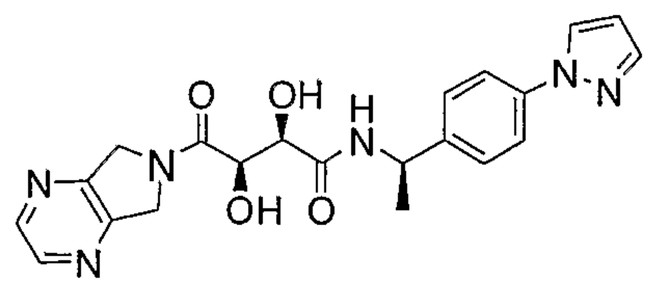

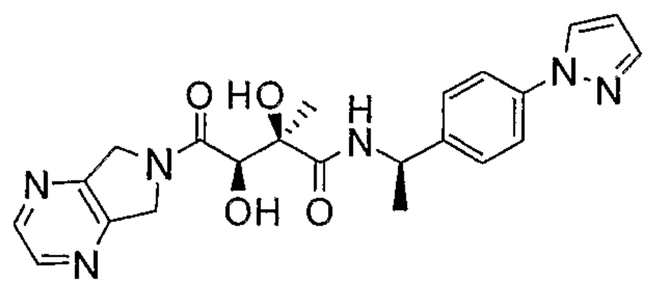

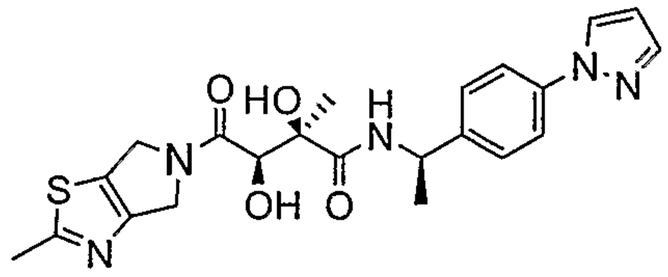

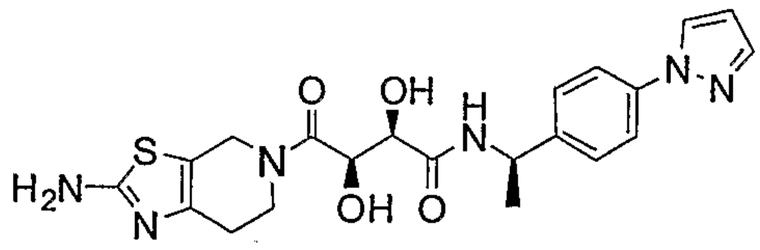

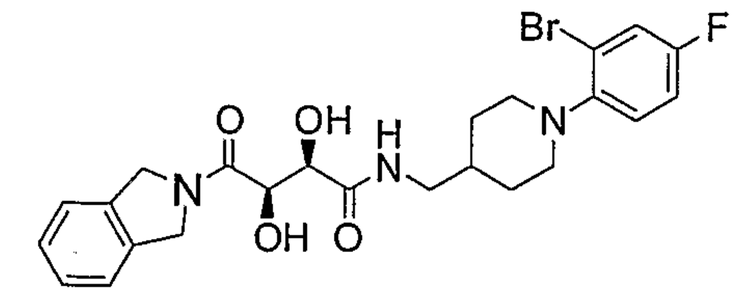

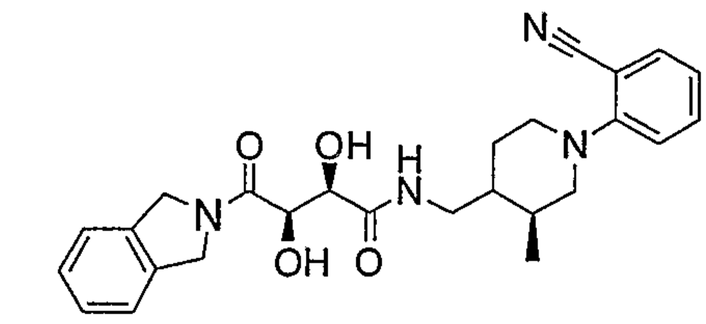

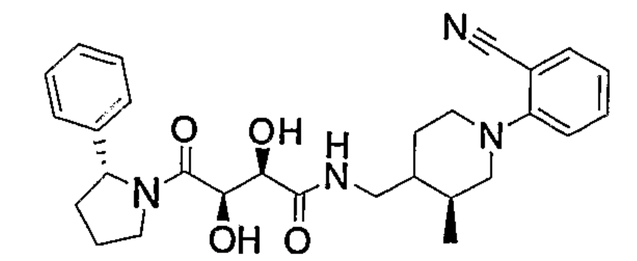

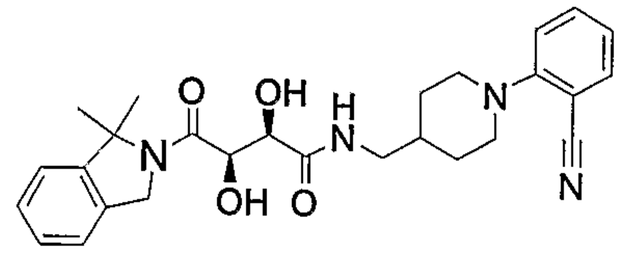

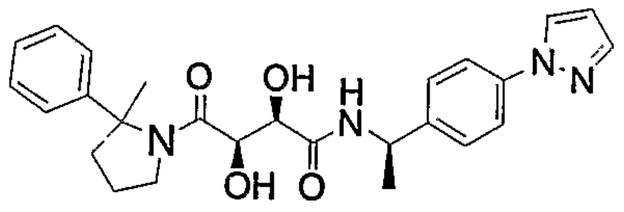

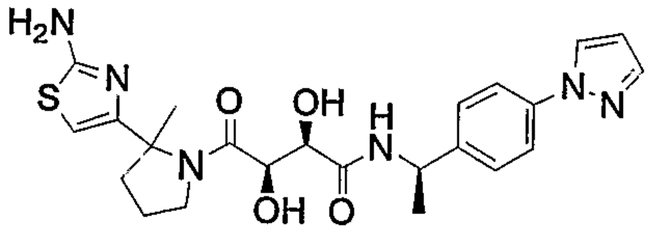

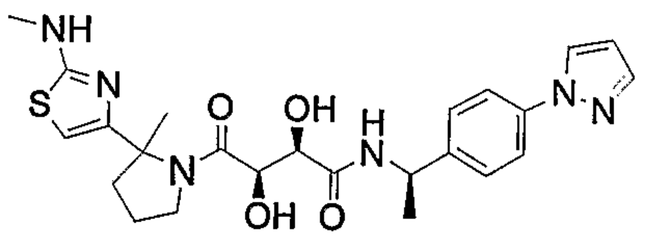

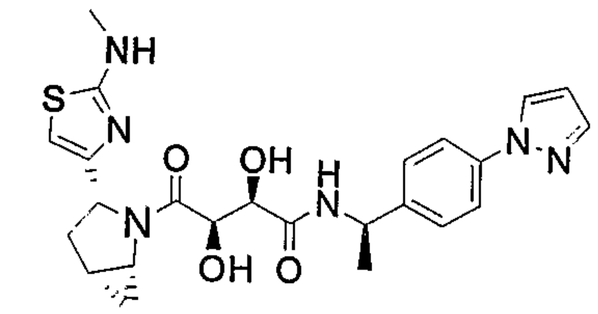

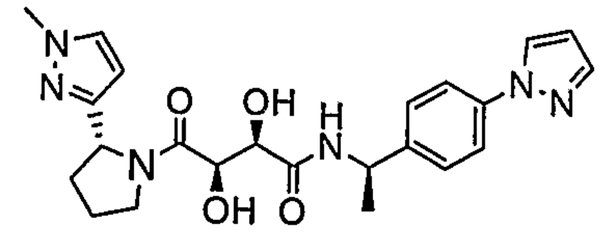

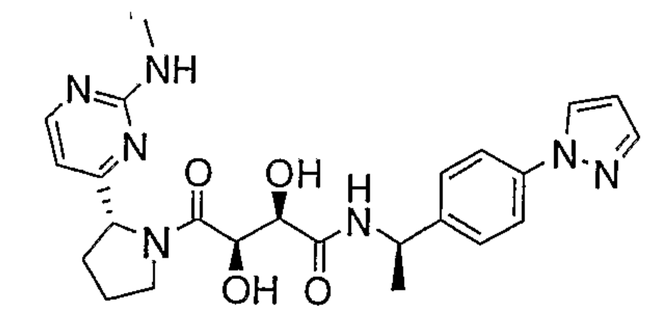

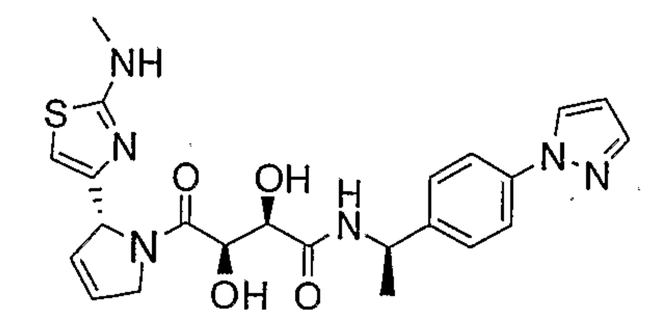

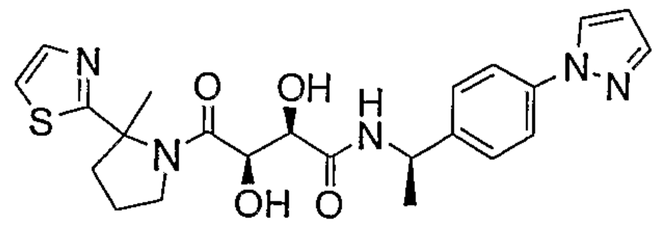

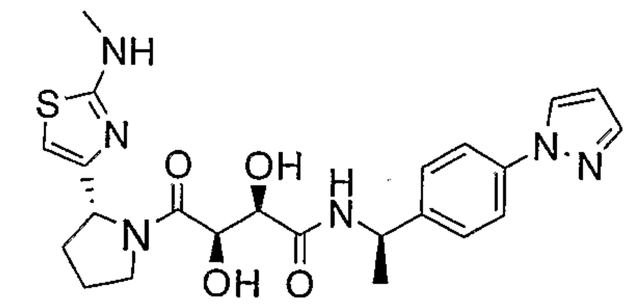

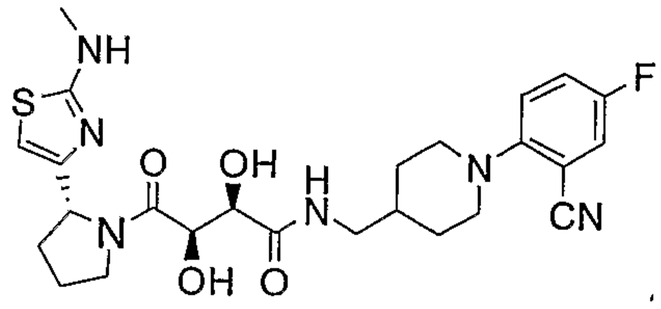

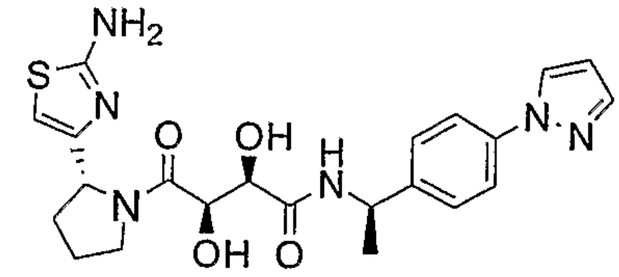

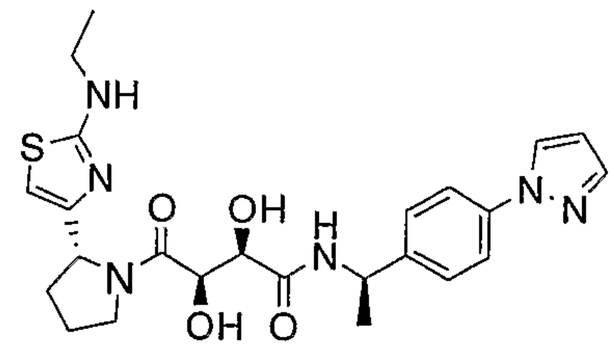

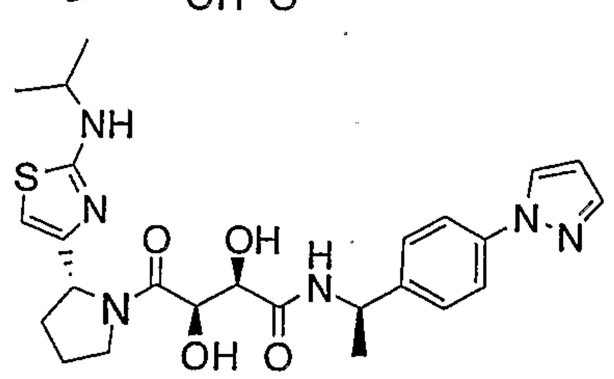

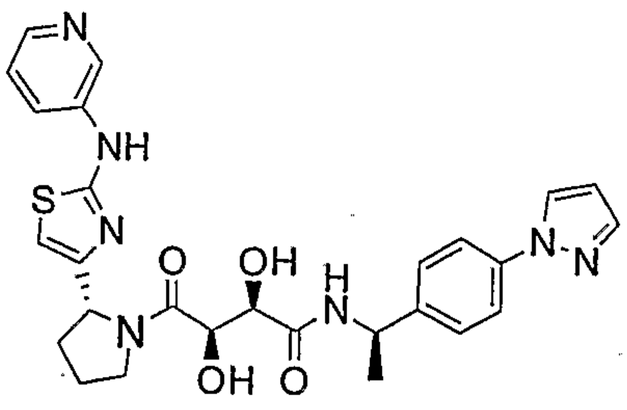

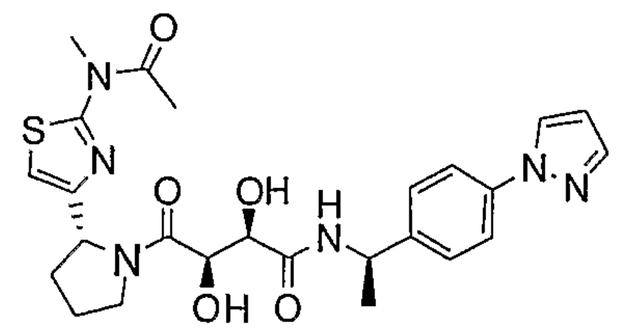

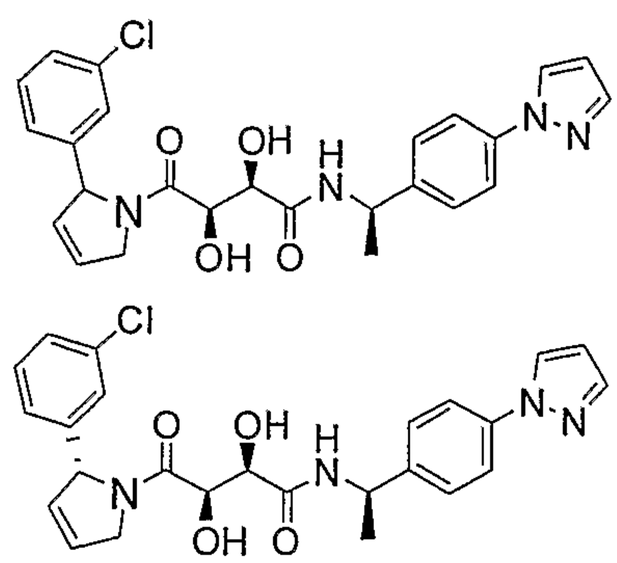

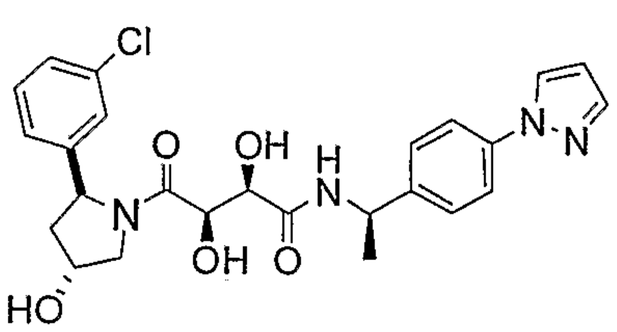

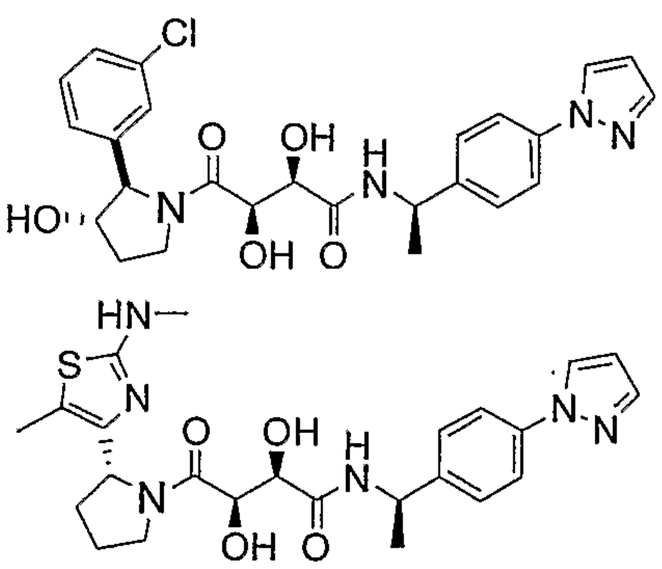

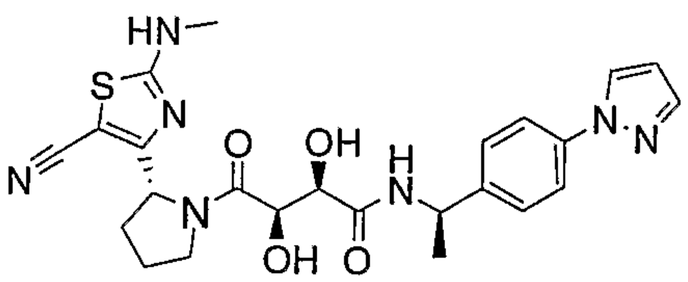

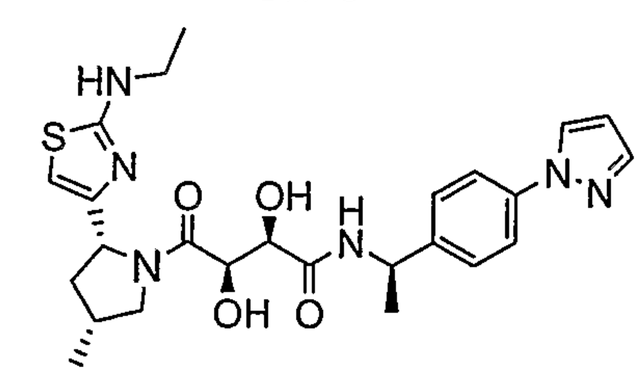

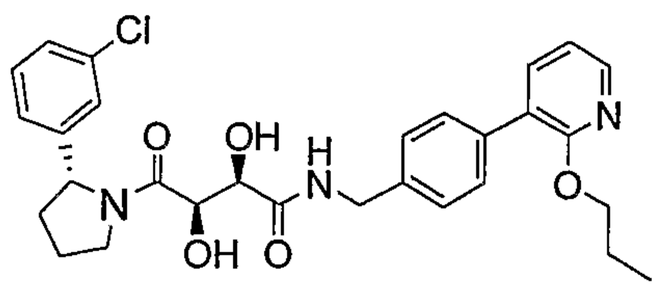

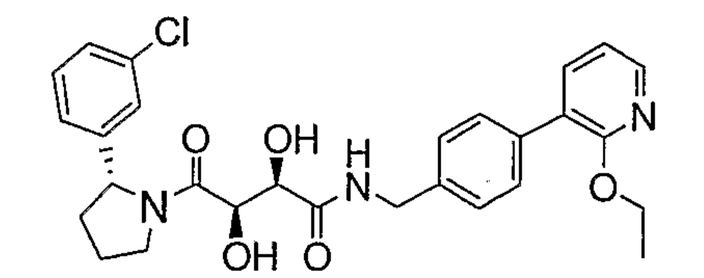

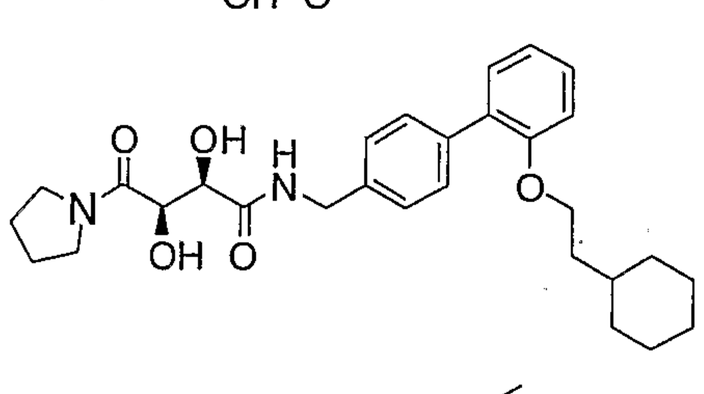

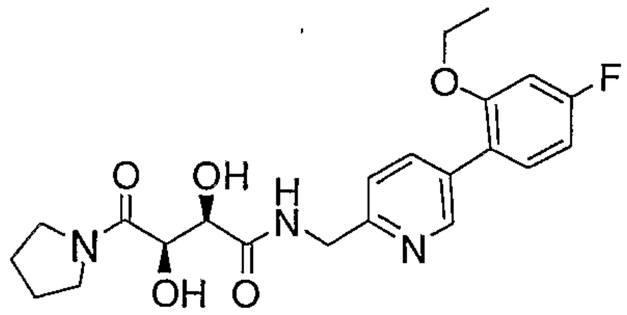

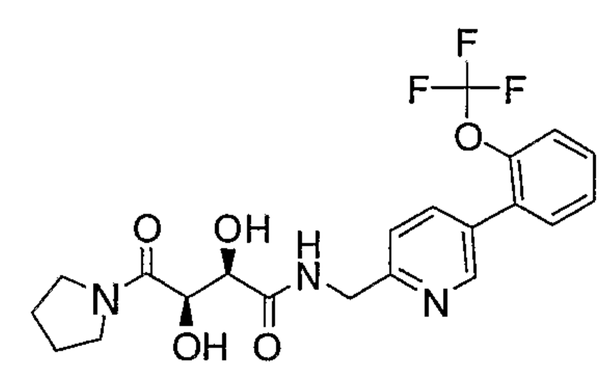

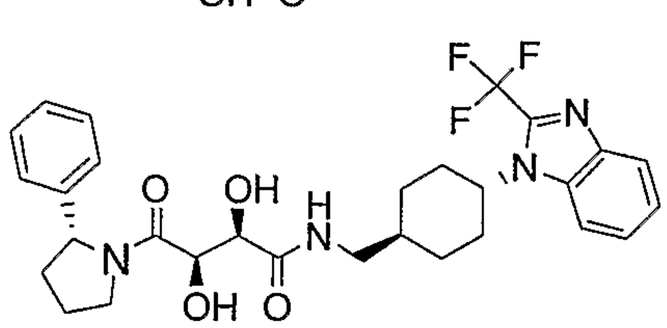

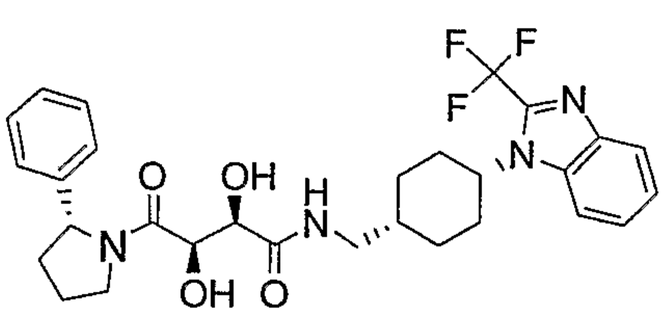

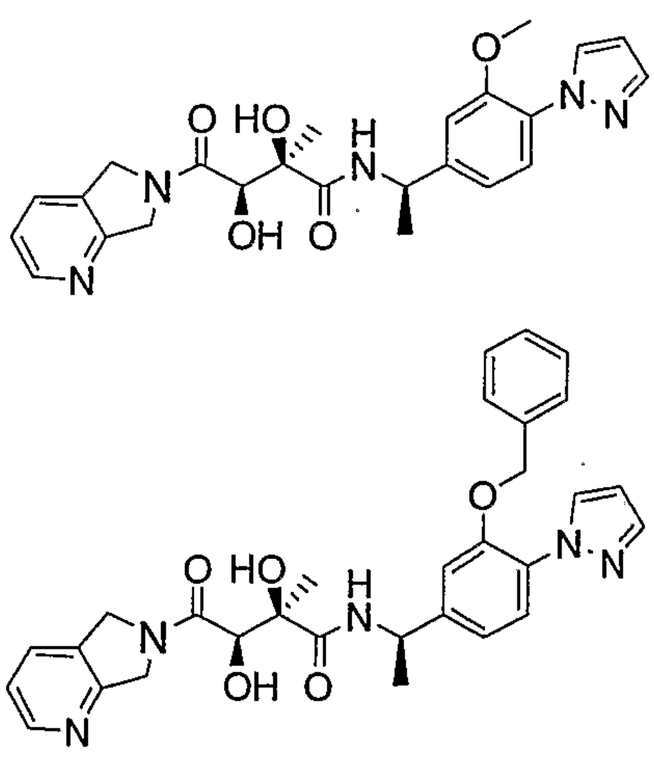

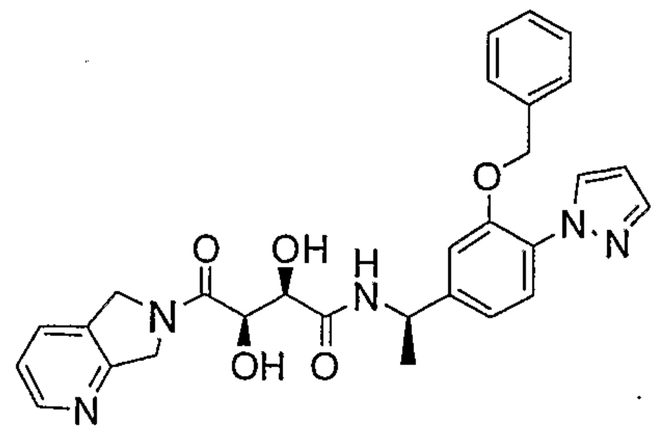

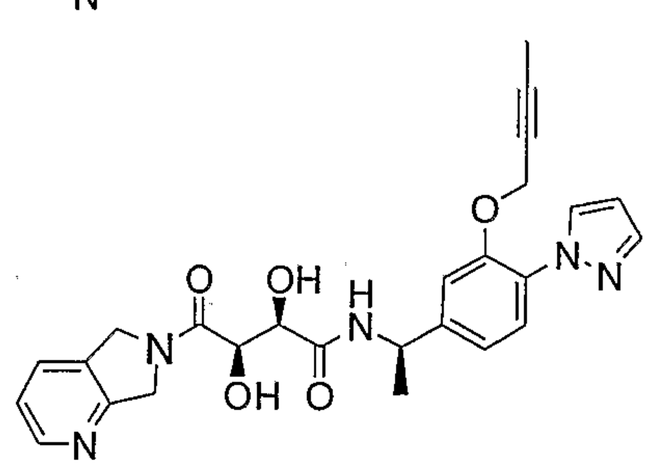

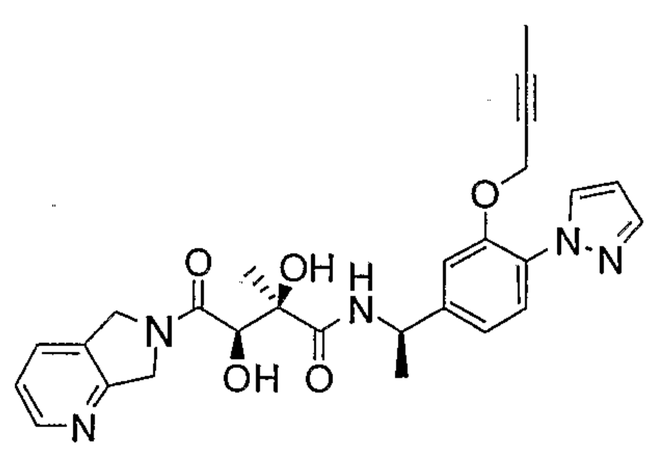

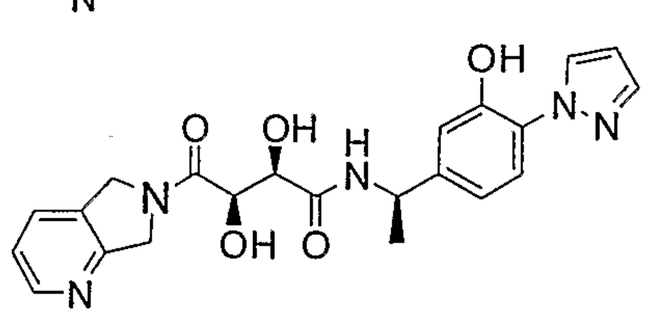

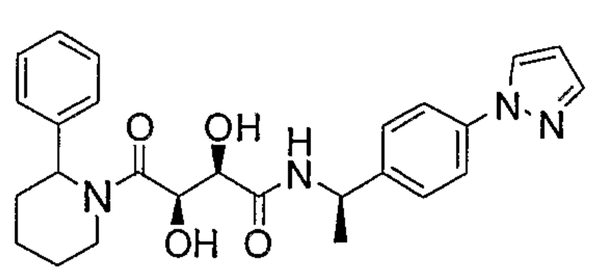

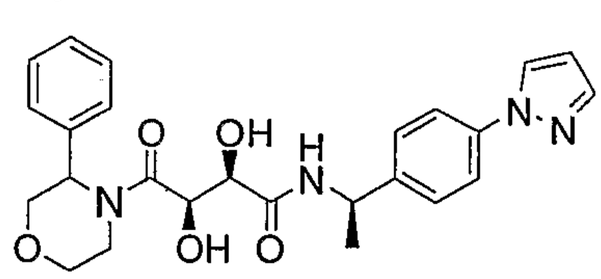

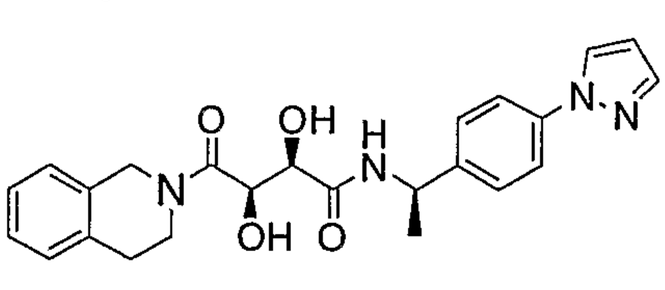

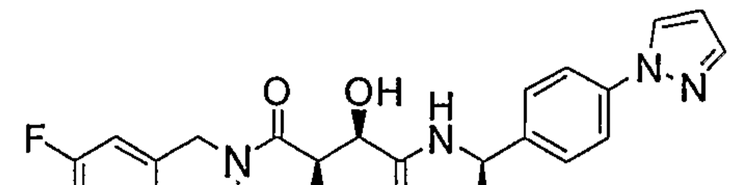

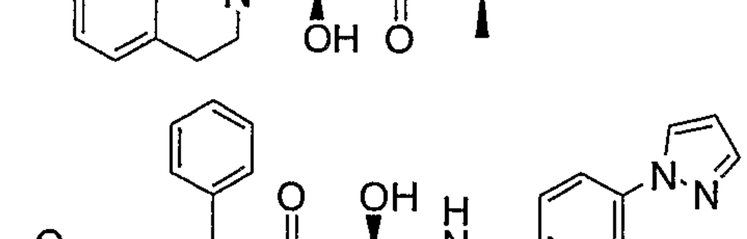

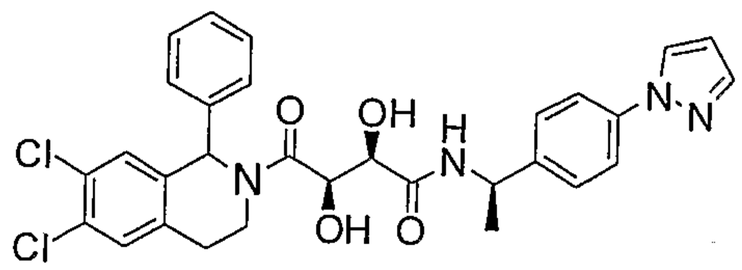

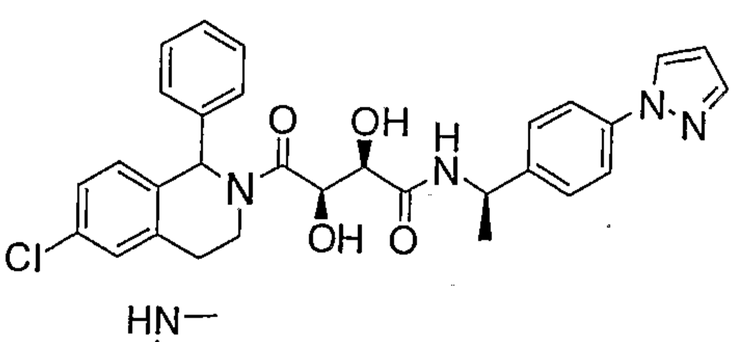

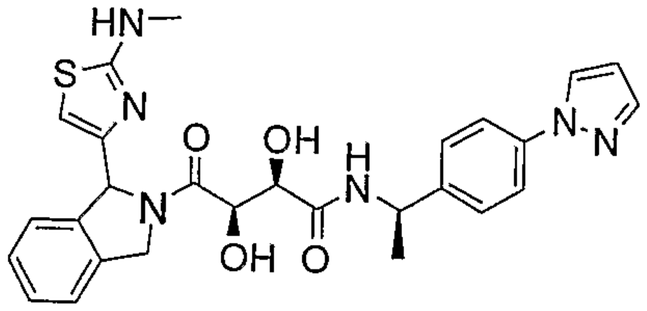

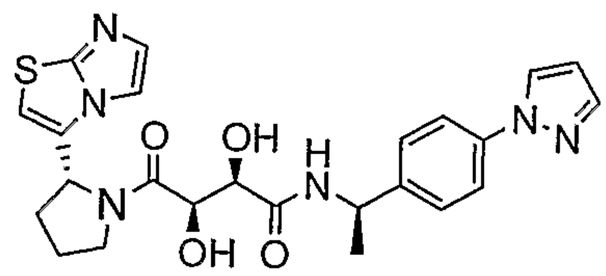

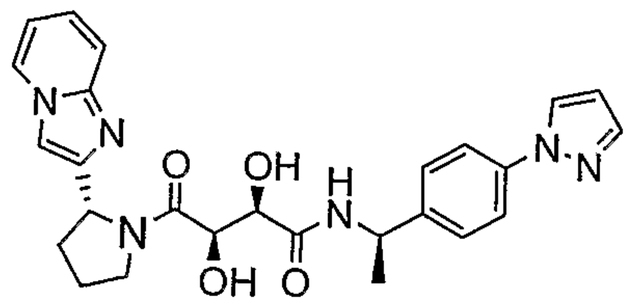

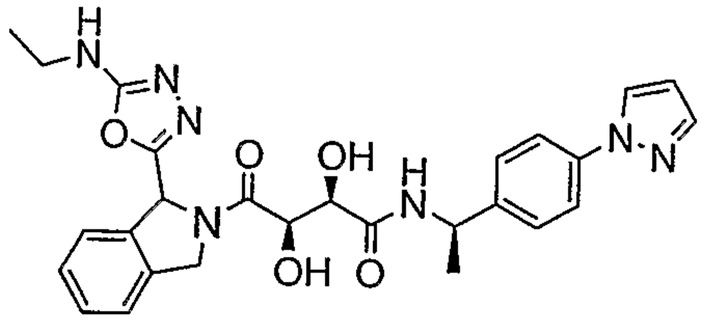

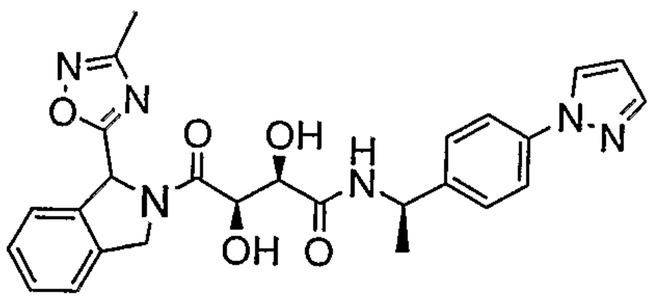

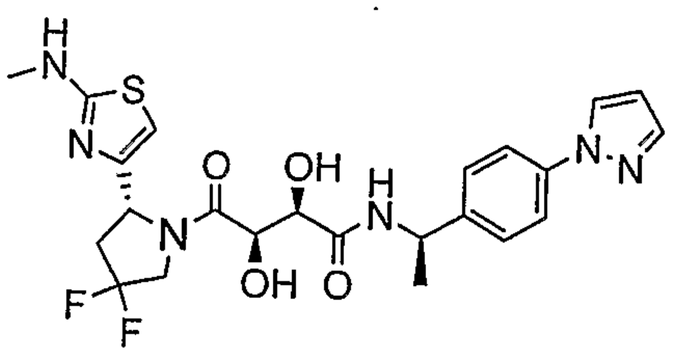

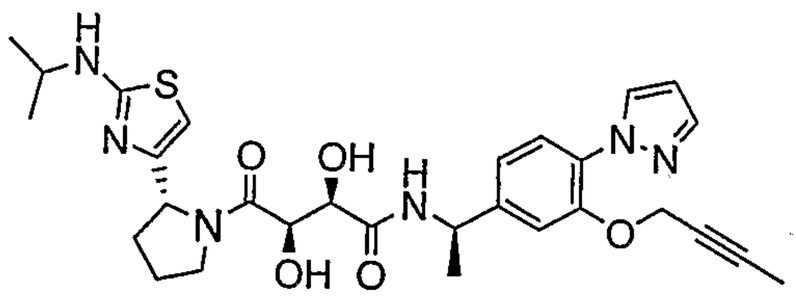

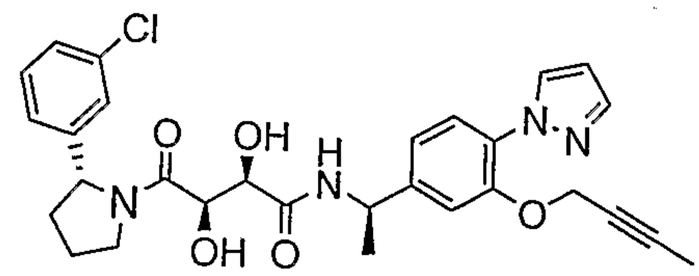

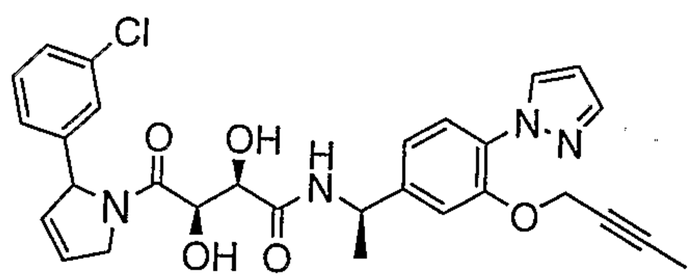

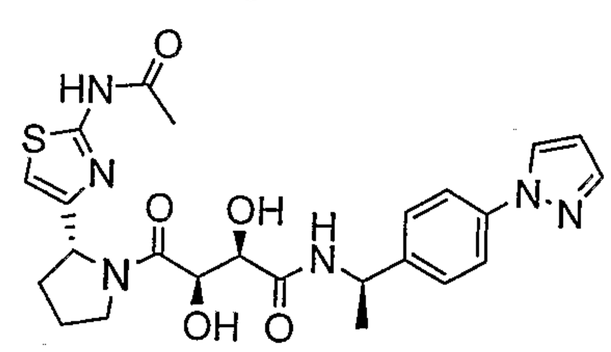

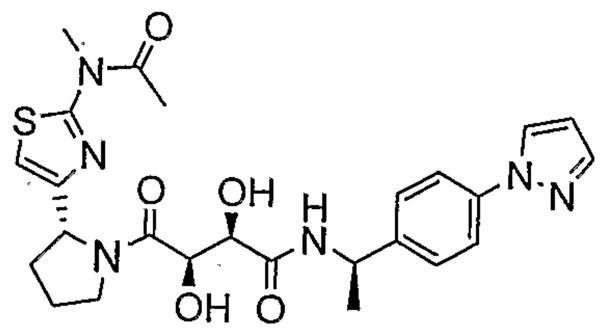

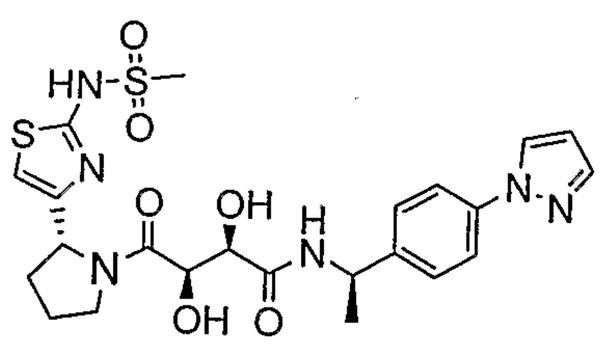

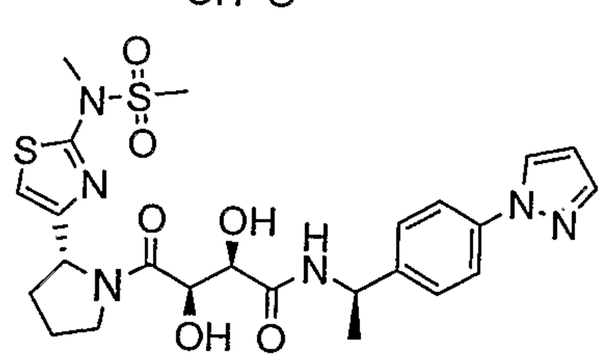

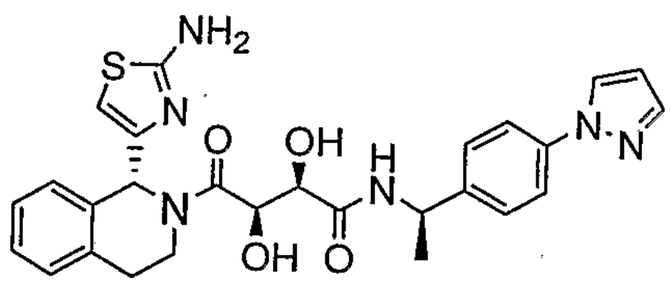

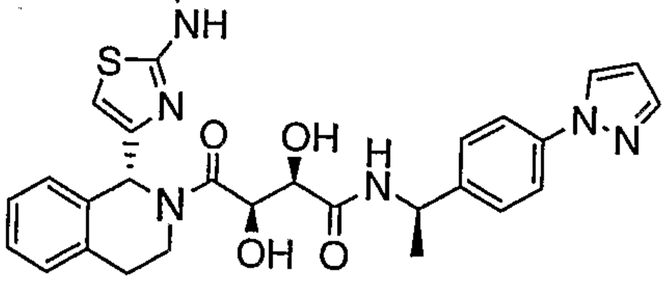

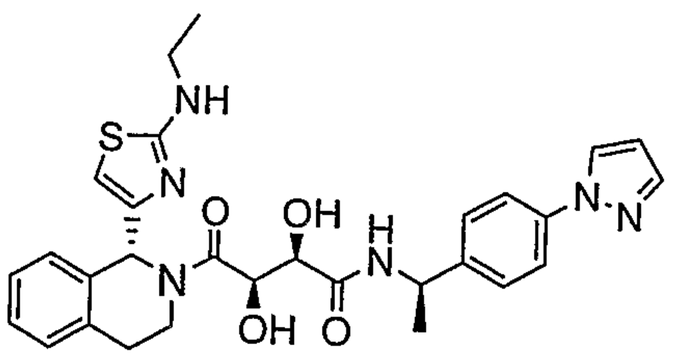

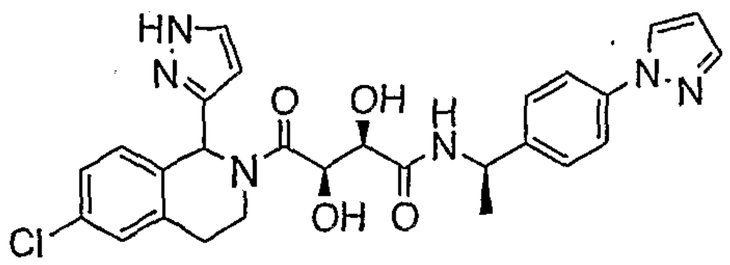

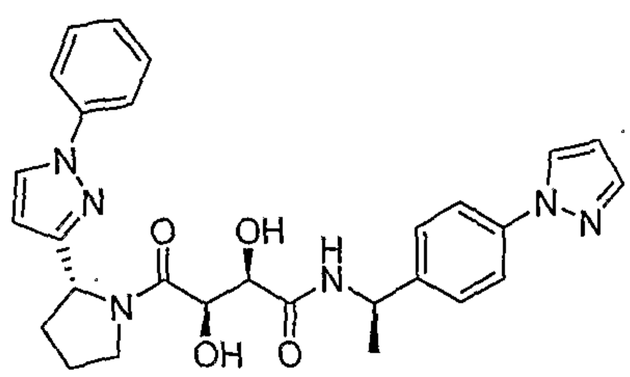

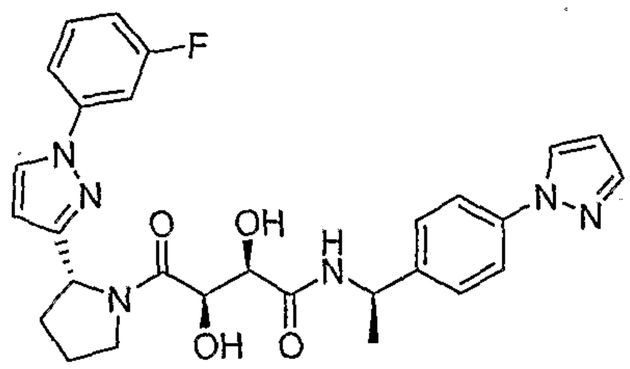

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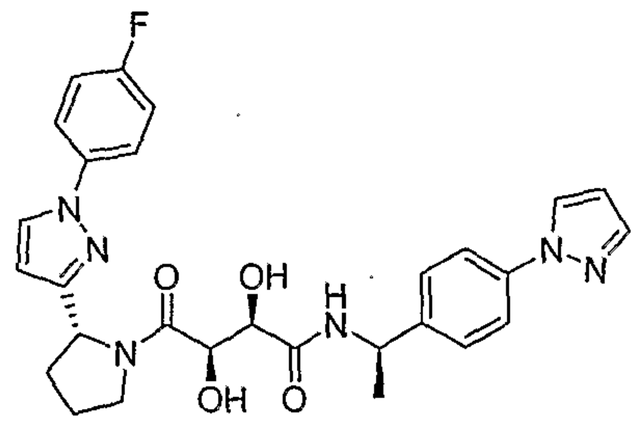
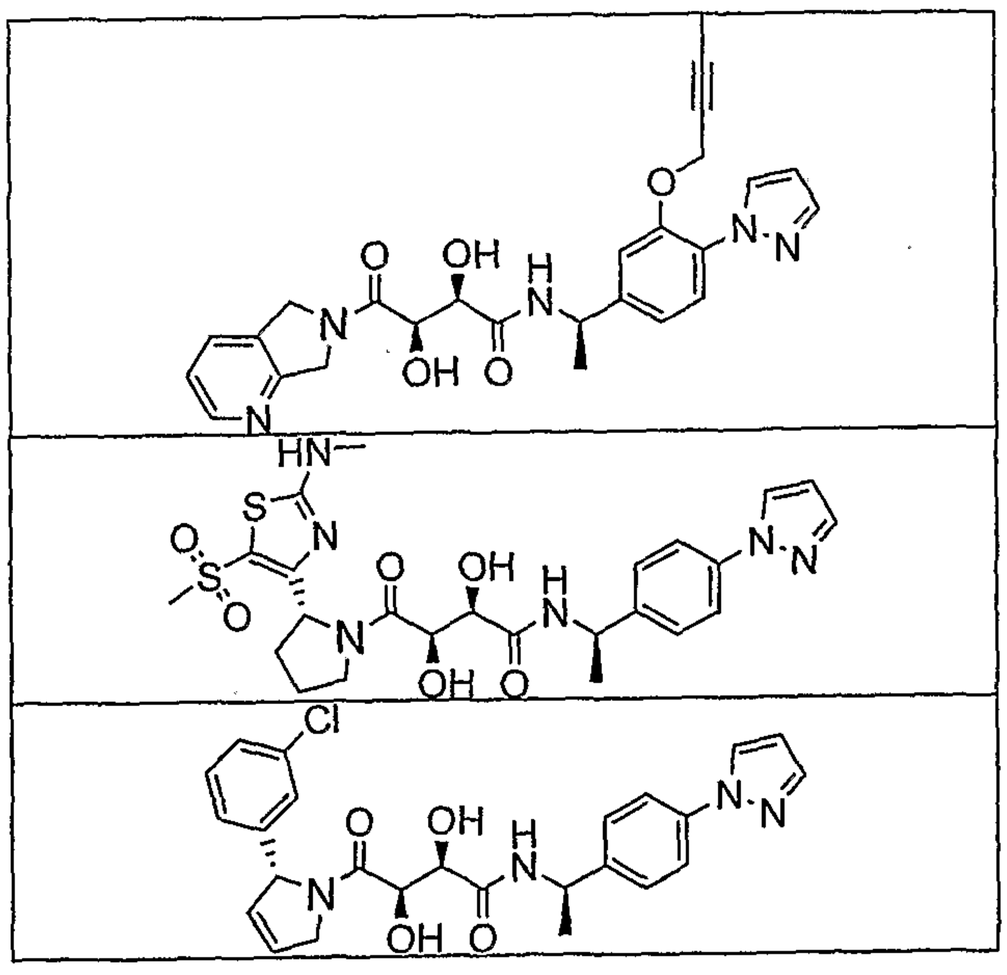
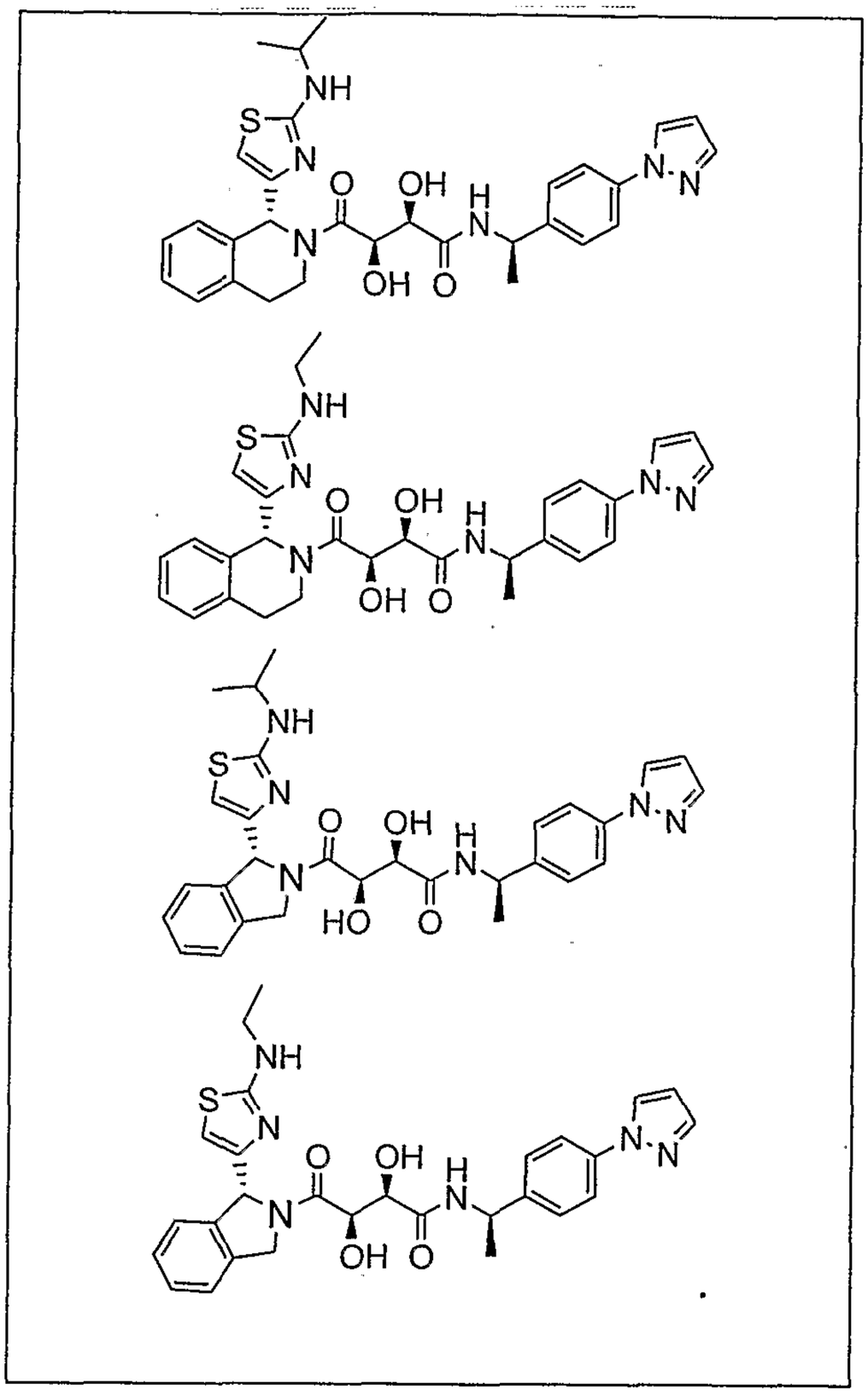


The above preferred compounds have TACE K_i values of less than 20nM.

In a more preferred embodiment, the compound is selected from the group consting of :





The above more preferred compounds have TACE K_i values of less than 5 nM.

In another aspect, the invention provides a pharmaceutical composition for treating disorders associated with TACE, 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 TACE, MMPs, TNF-α, aggrecanase (such as aggrecanase 1 or aggrecanase 2), 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 claim 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, 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.

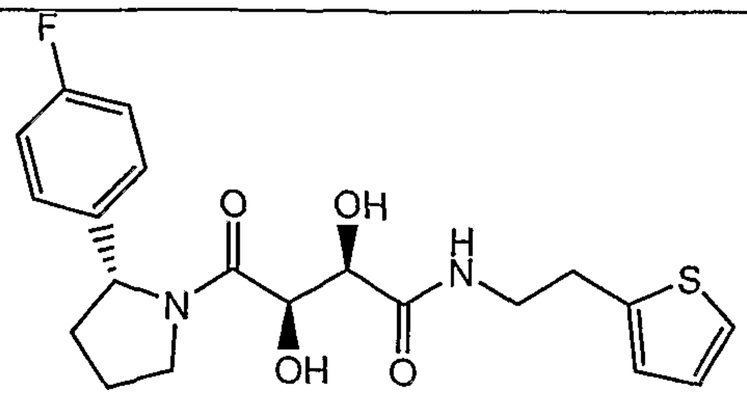
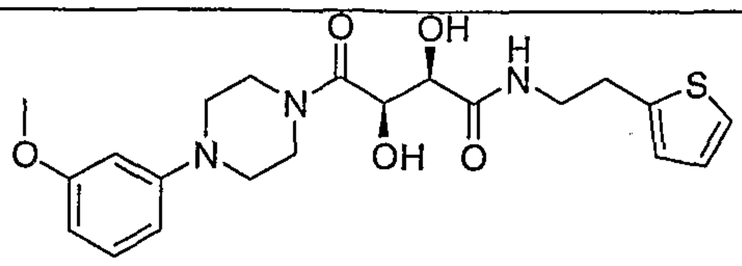
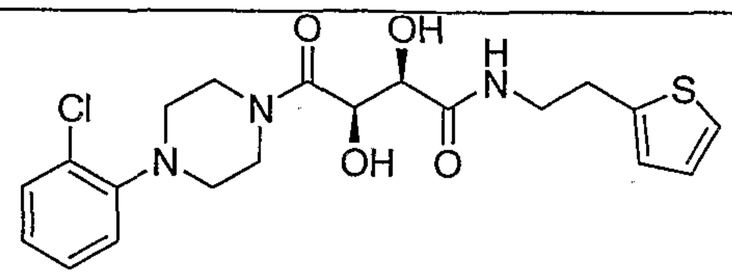
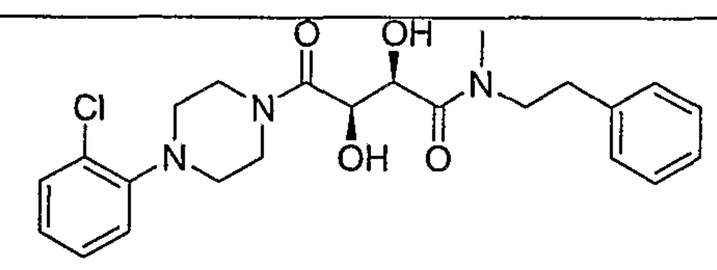
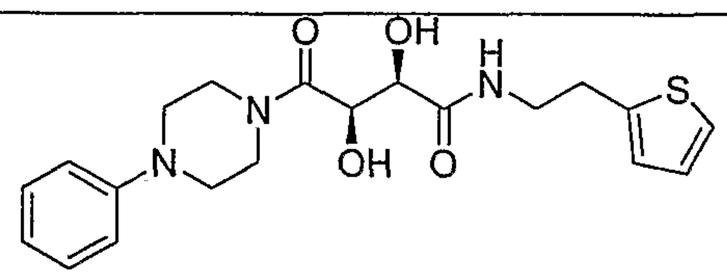
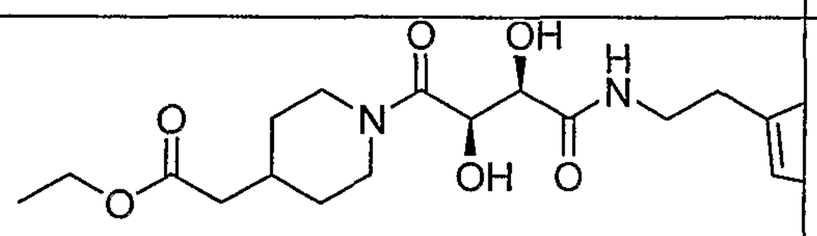
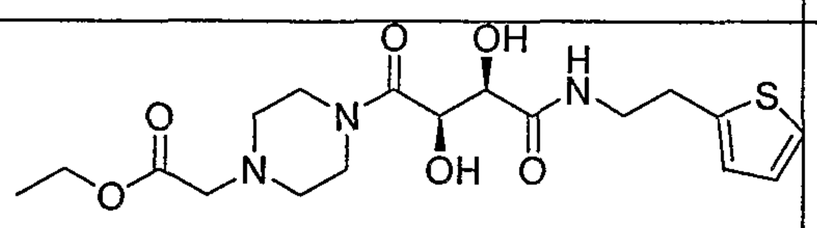
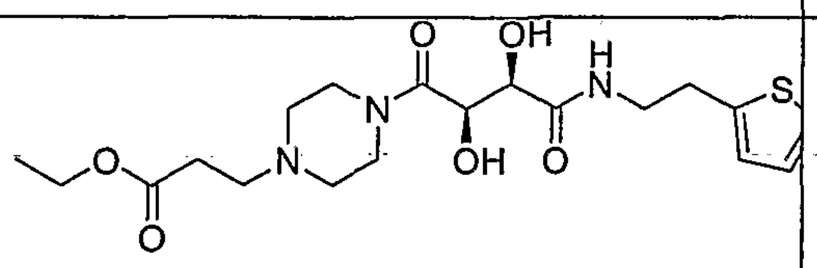
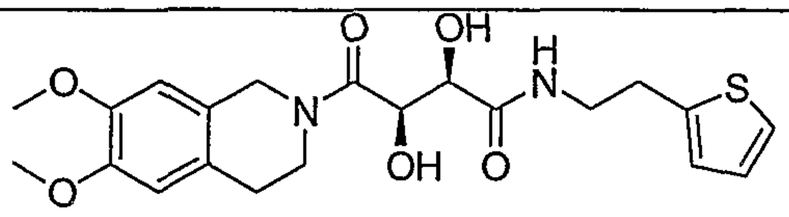
In another aspect, the invention provides a method for treating multiple sclerosis comprising administering a compound of the formula I in combination with a compound selected from the group consisting of Avonex®, Betaseron, Copaxone or other compounds indicated for the treatment of multiple sclerosis.

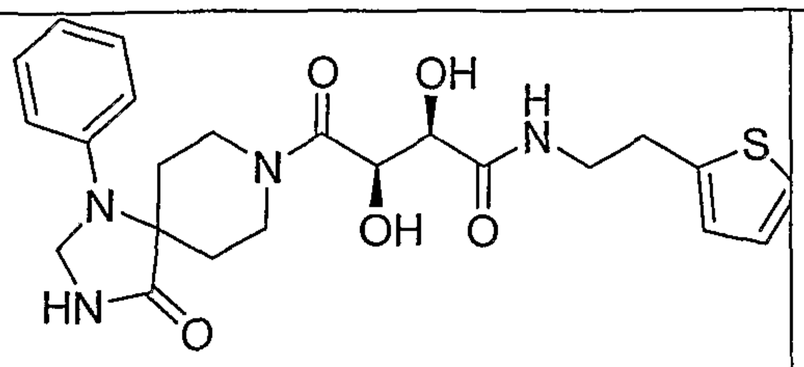
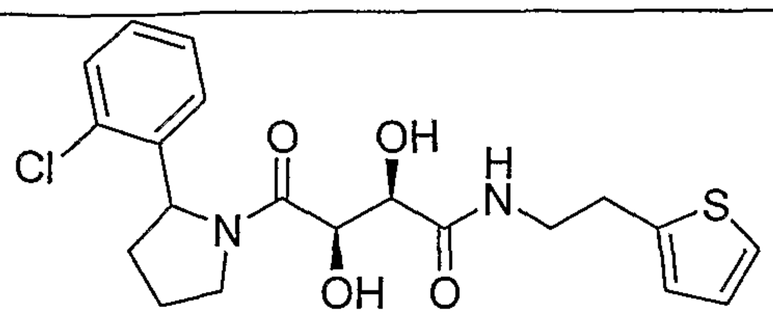
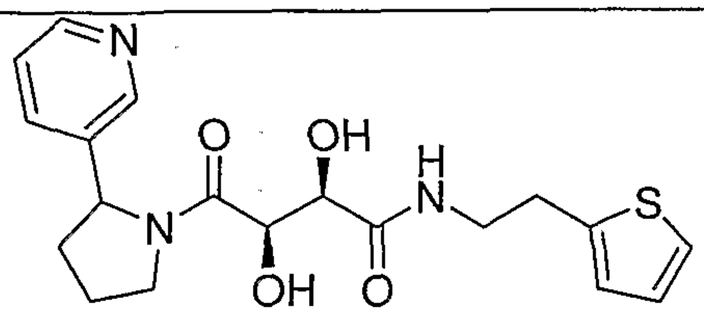
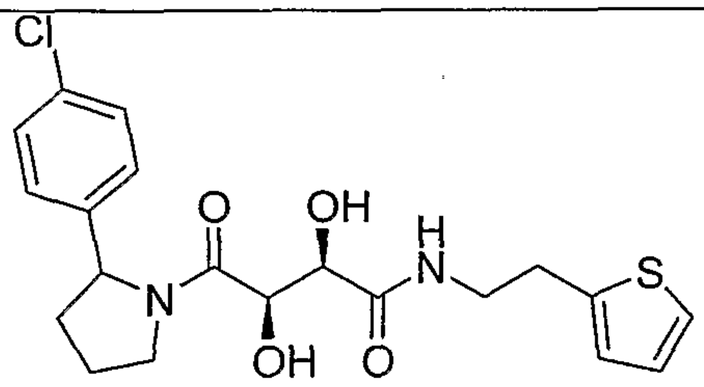
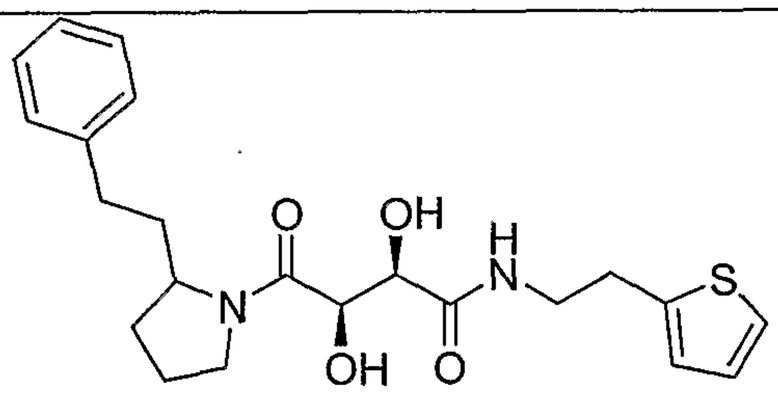
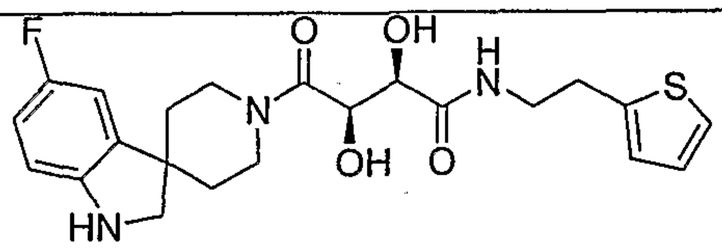
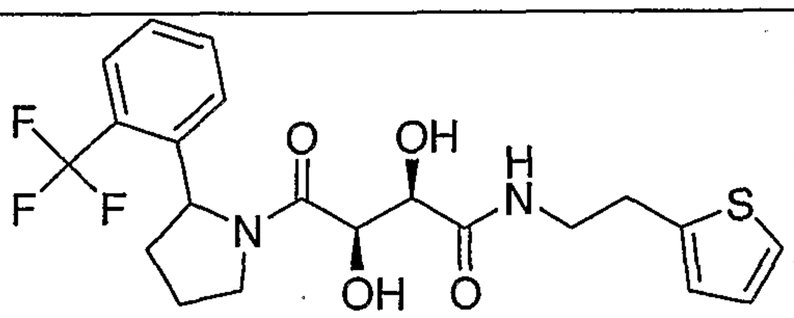
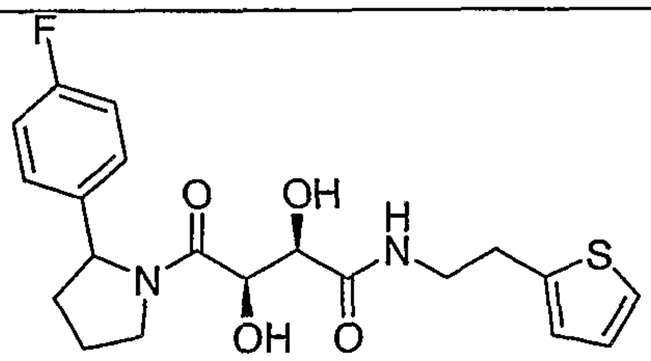
TACE activity is determined by a kinetic assay measuring the rate of increase in fluorescent intensity generated by TACE catalyzed cleavage of an internally quenched peptide substrate (SPDL-3). The purified catalytic domain of recombinant human TACE (rhTACEc, Residue 215 to 477 with two mutation (S266A 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.

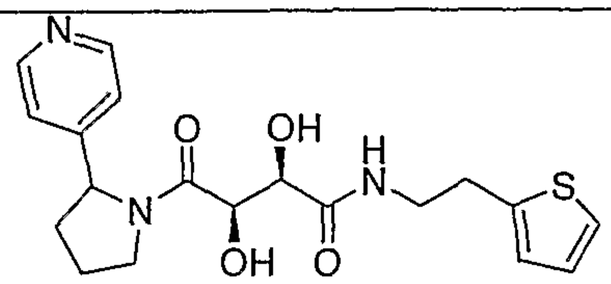
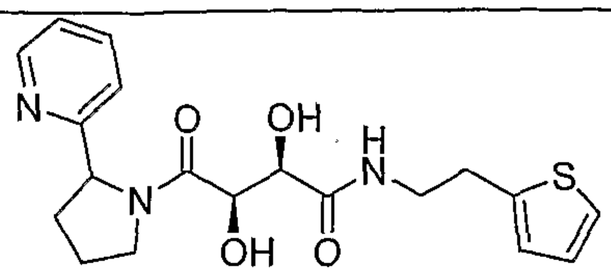
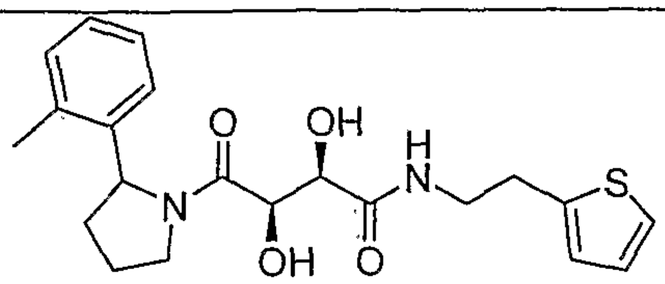
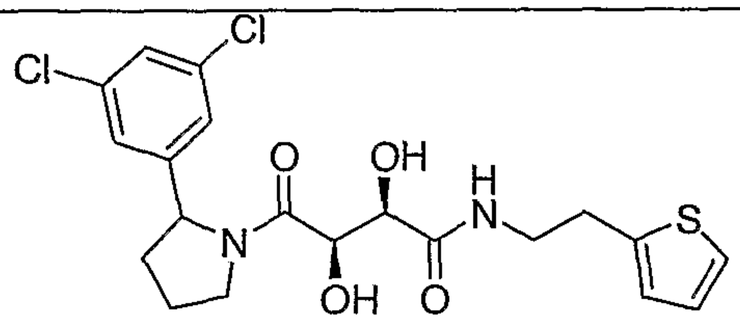
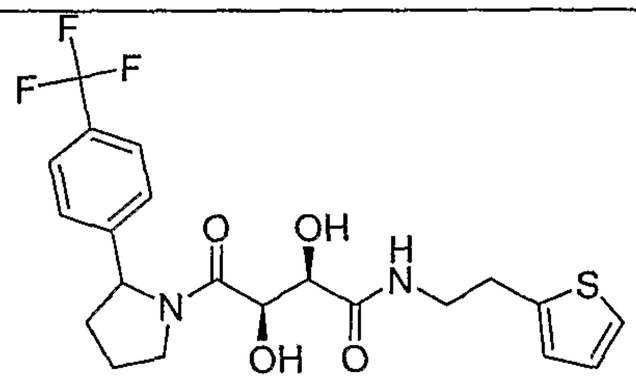
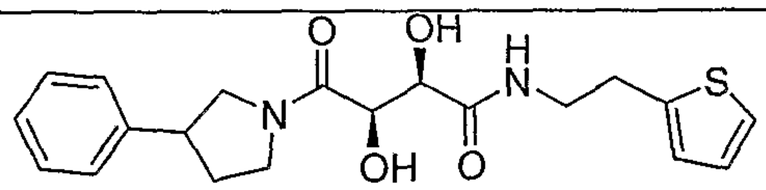
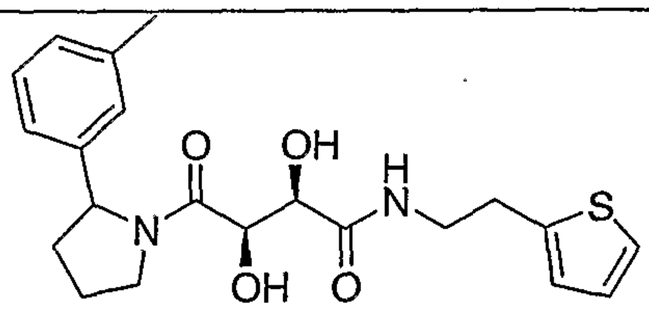
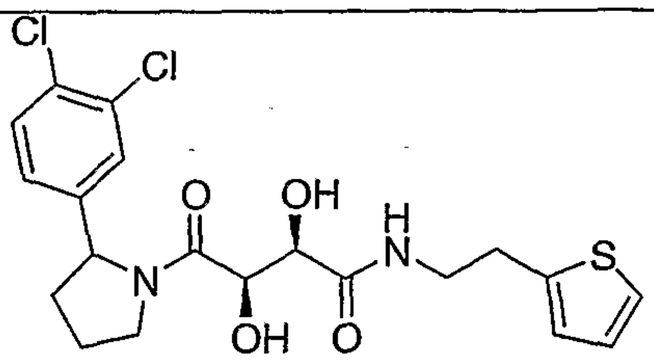
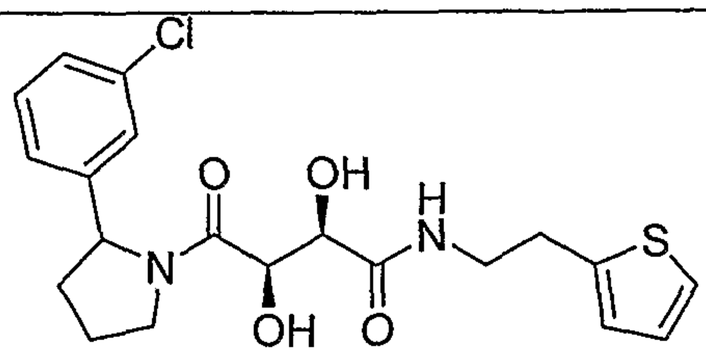
A 50 μl assay mixture contains 20 mM HEPES, pH 7.3, 5 mM $CaCl_2$, 100 μM $ZnCl_2$, 2 % DMSO, 0.04% Methylcellulose, 30 μM SPDL-3, 70 pM rhTACEc and a test compound. RhTACEc is pre-incubated with the testing compound for 90 min. at 25 °C. Reaction is started by addition of the substrate. The fluorescent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

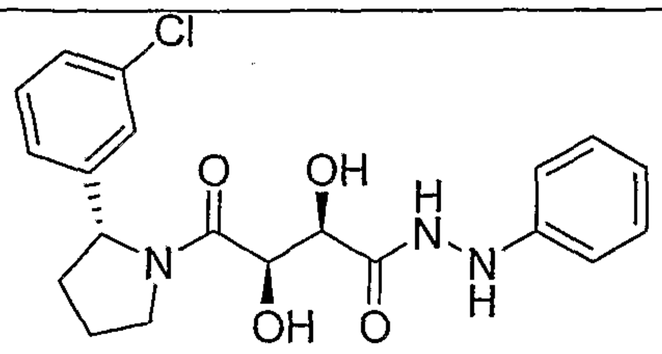
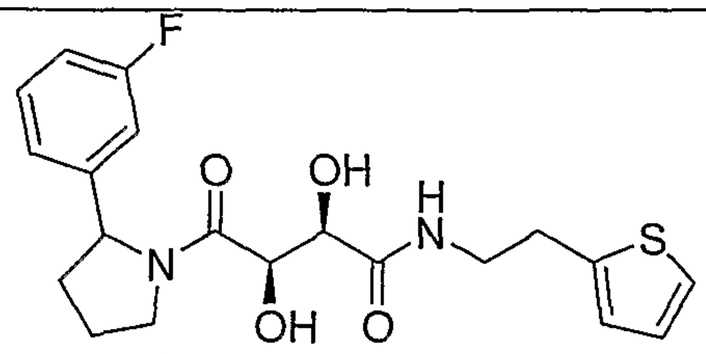
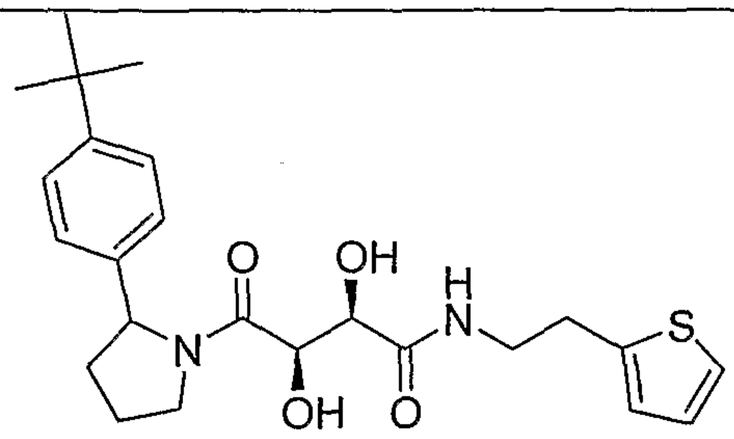
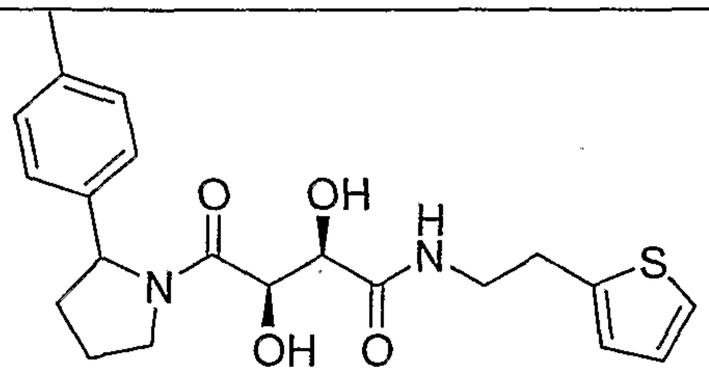
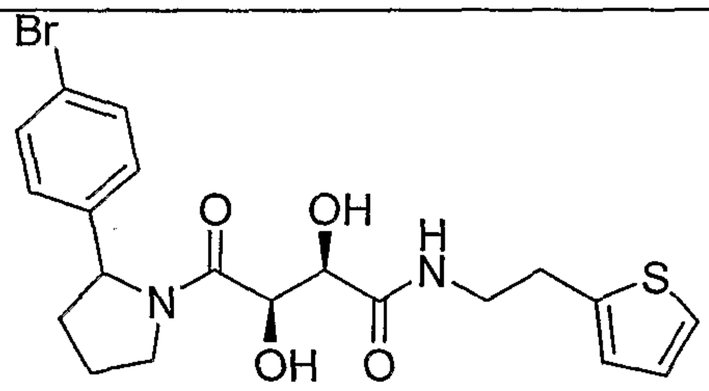
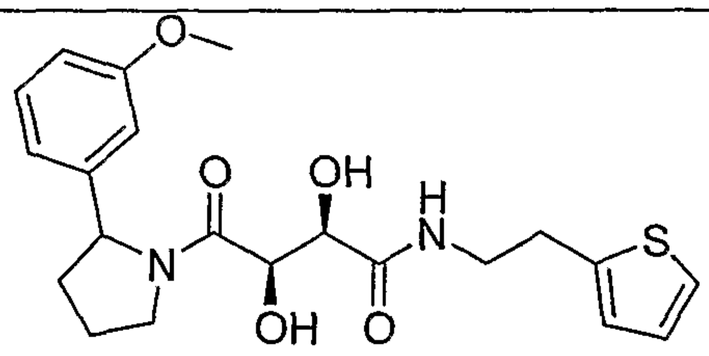
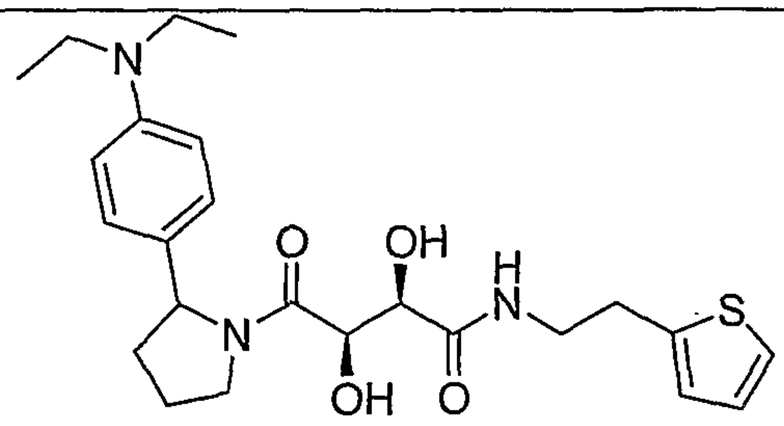
TACE inhibitory activities for representative compounds are shown in the table below. K_i values greater than 1000 nM (1 μM) are designated as D class. K_i values between 100 nM (0.1 μM) and 1000 nM (1 μM)are designated as C class. K_i values between 20 nM (0.02 μM) and 100 nM (0.1 μM) are designated as B class. K_i values less than 20 nM (0.02 μM) are designated as A class.

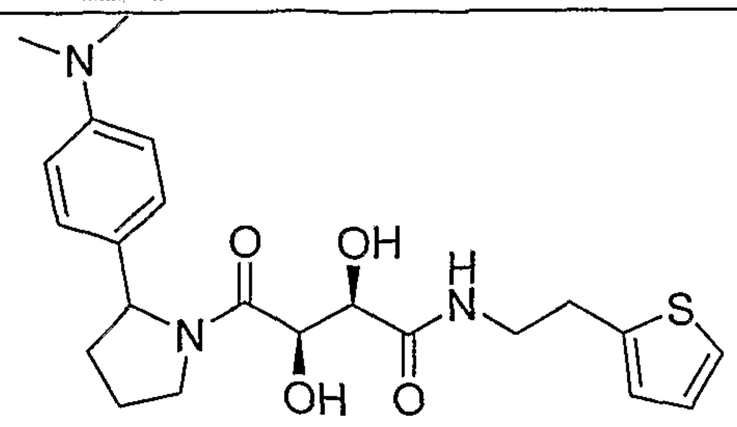
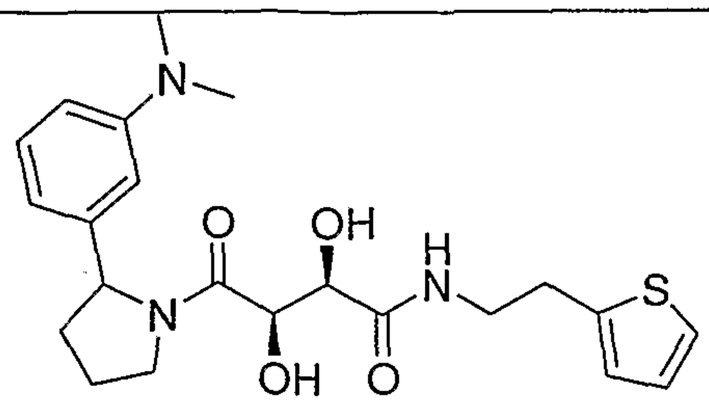
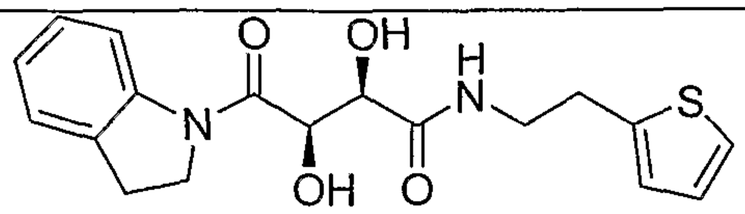
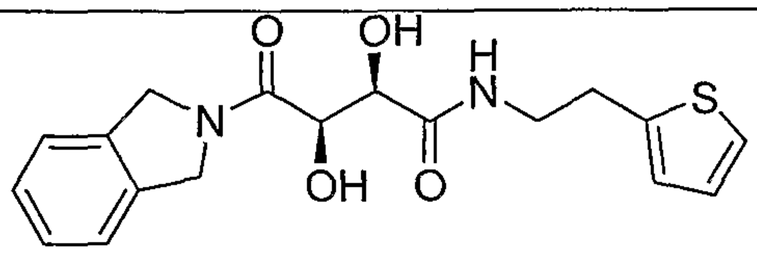
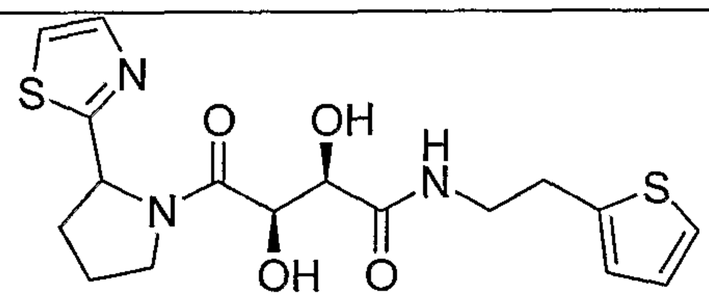
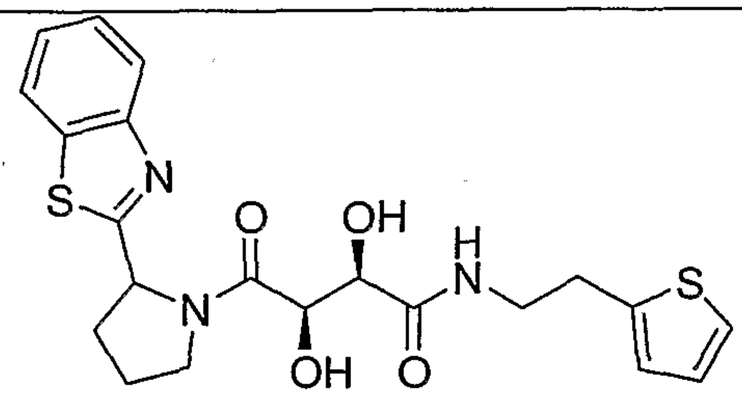
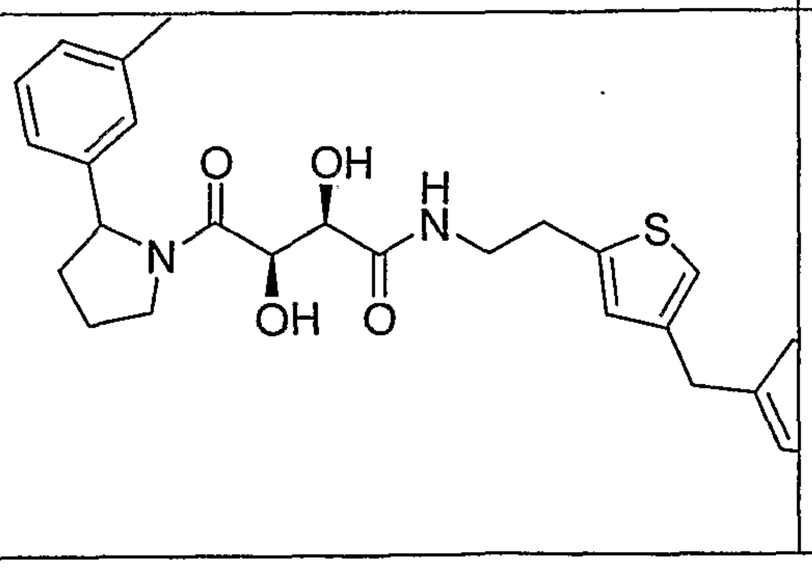
Compound #	Structure	K_i (nM)

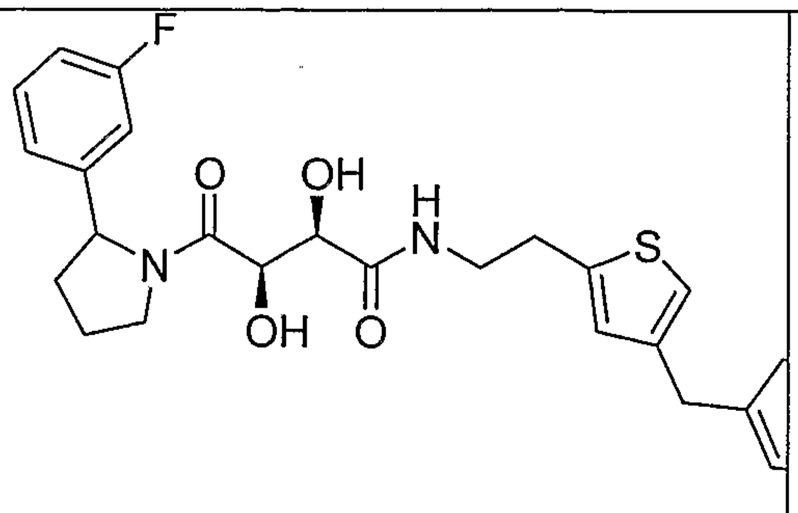
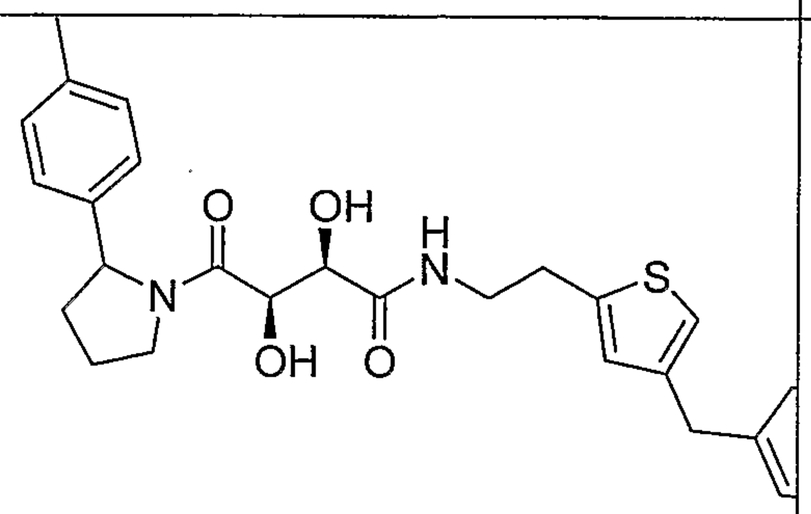
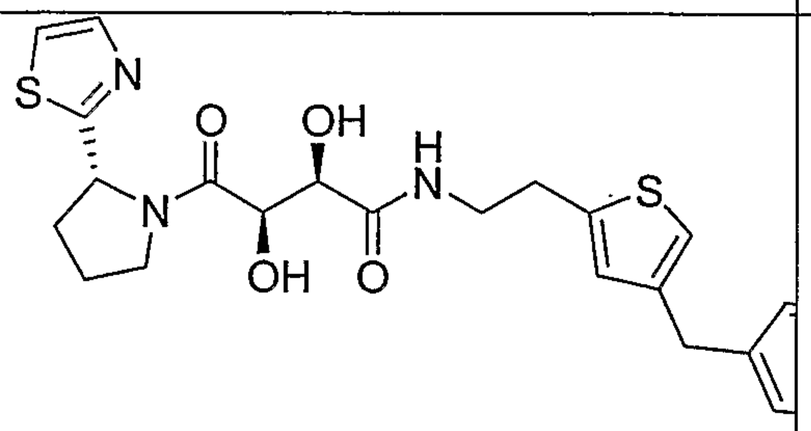
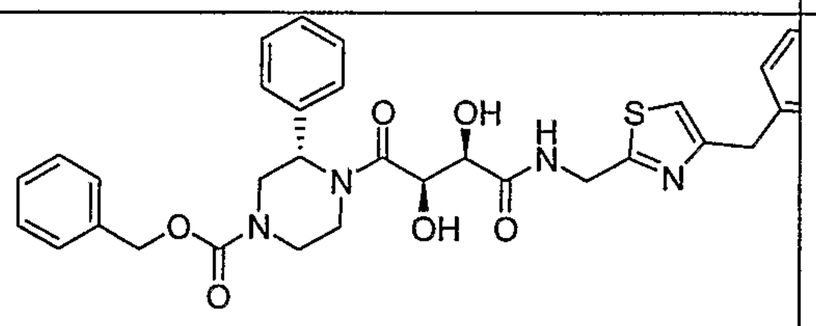
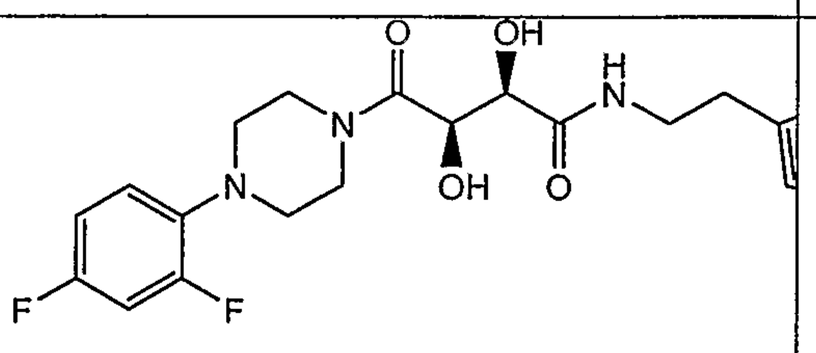
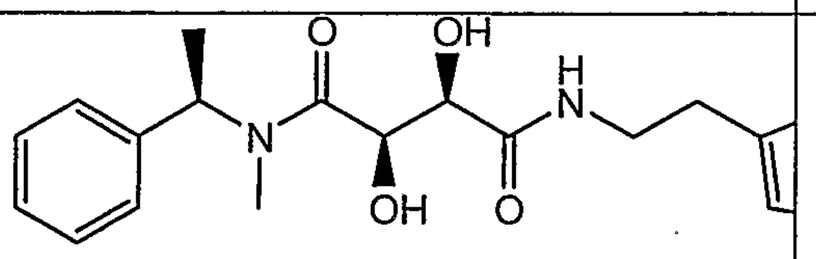
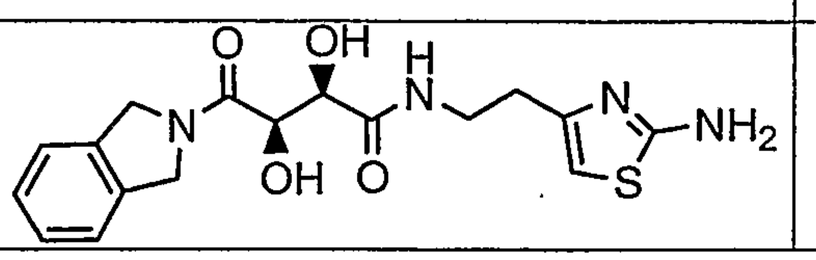
5		
6		
7A		
7B		
8		
9		
10		
11		
12		

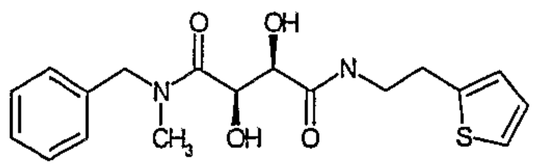
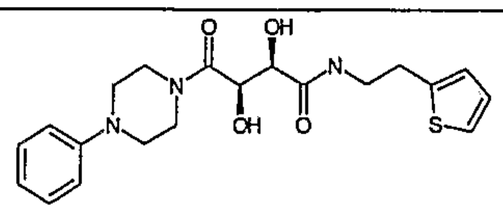
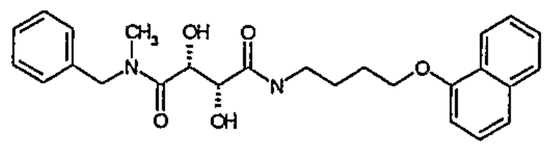
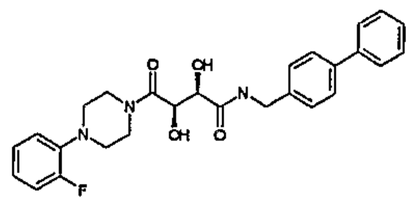
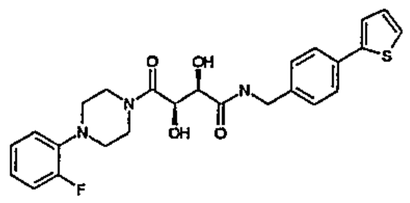
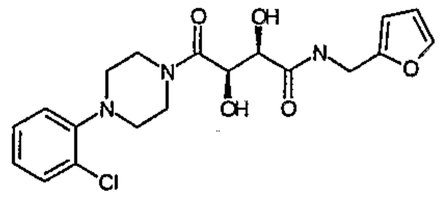
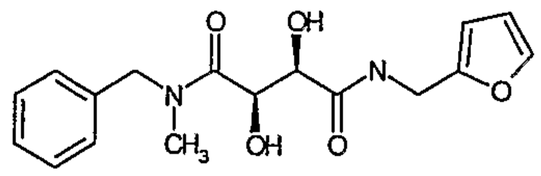
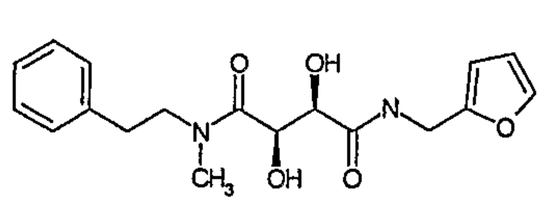
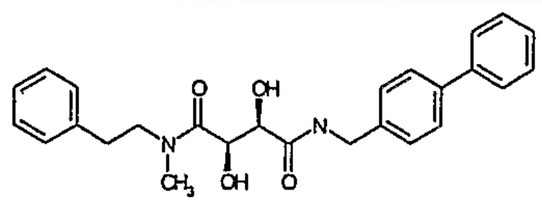
13		
14		
15		
16		
17		
18		
19		
20		

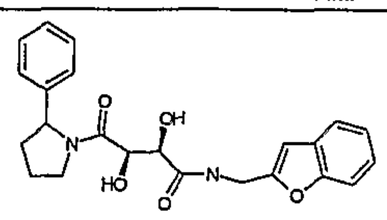
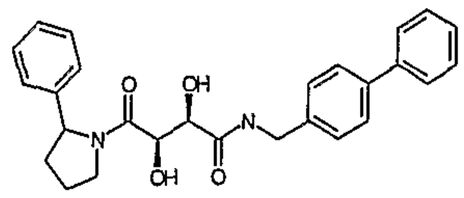
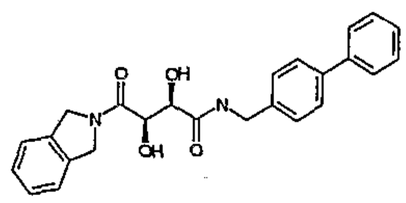
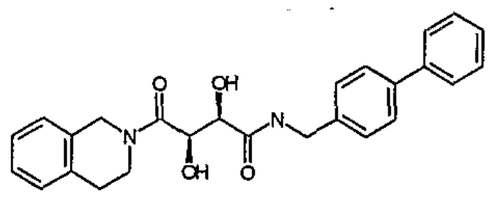
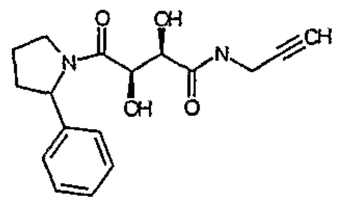
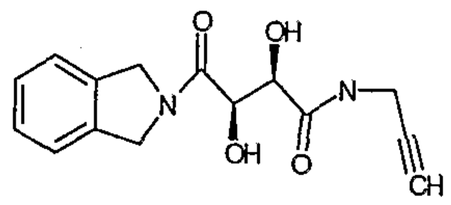
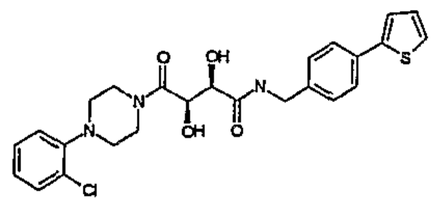
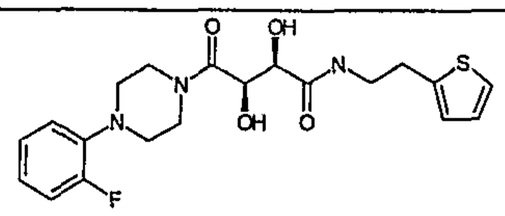
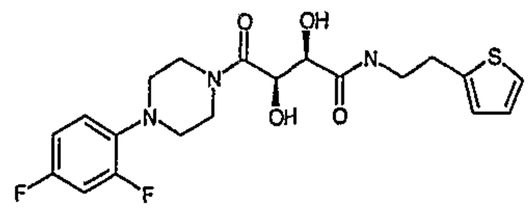
21		
22		
23		
24		
25		
26		
27		
28		
29A		

29B		
30		
31		
32		
33		
34		
35		

36		
37		
38		
39		
40		
41		
42		

43		
44		
46		
47		
50		
52		
55		

56		
57		
58		
59		
60		
61		
62		
63		
64		

65		
66		
67		
68		
69		
70		
71		
72		
73		
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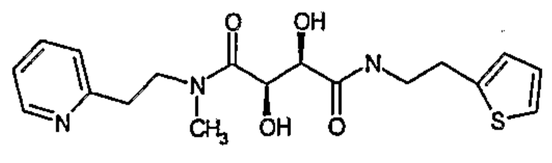
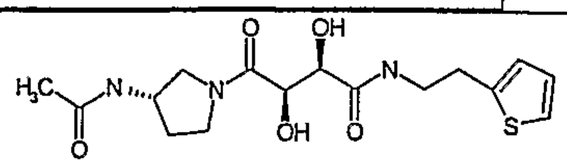
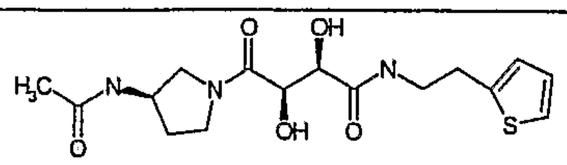
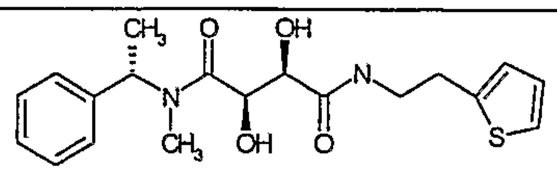
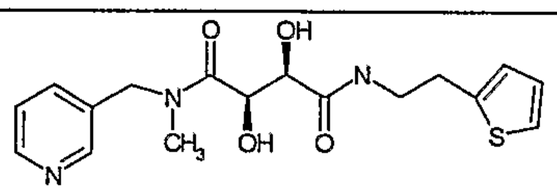
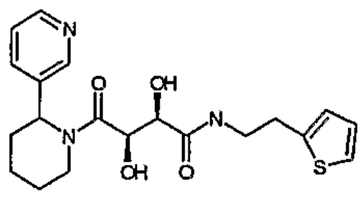
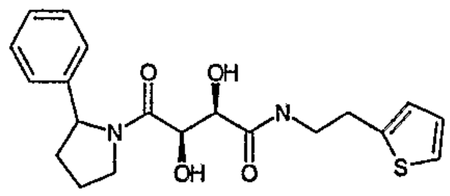
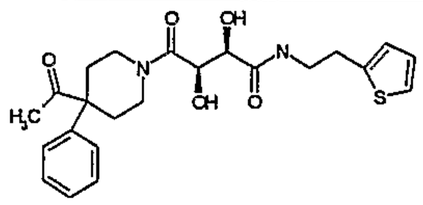
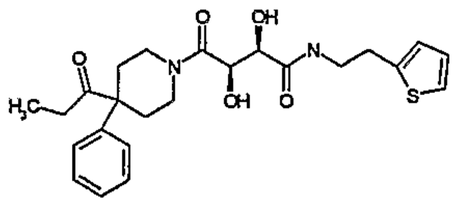
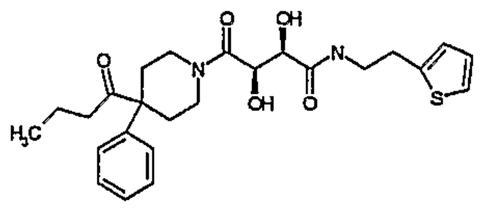
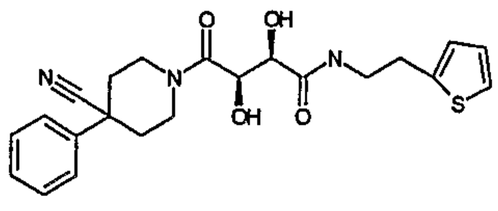
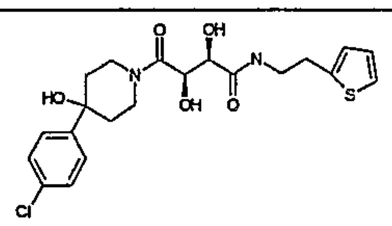
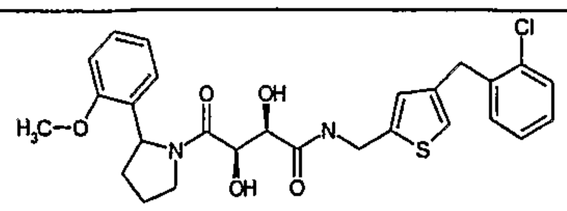
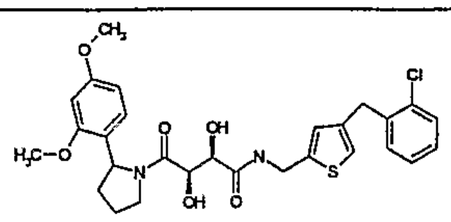
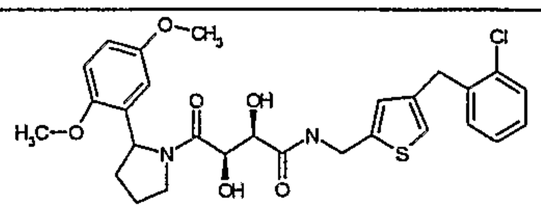
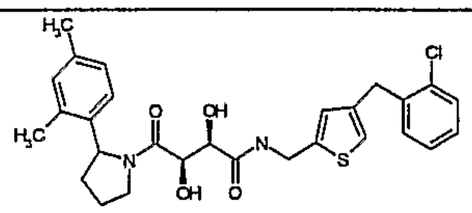
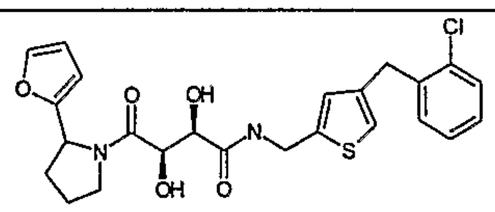
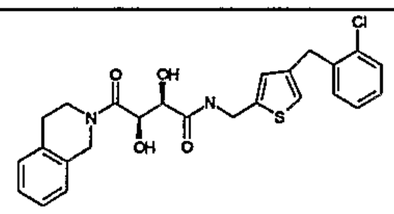
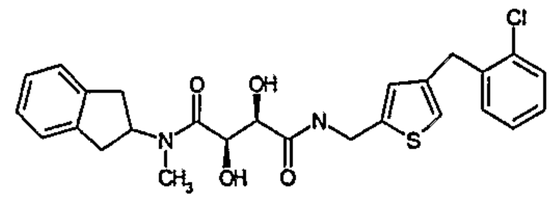
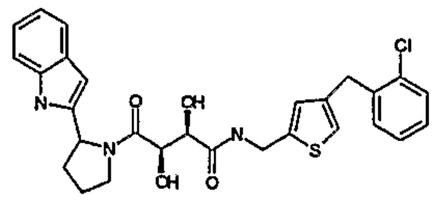
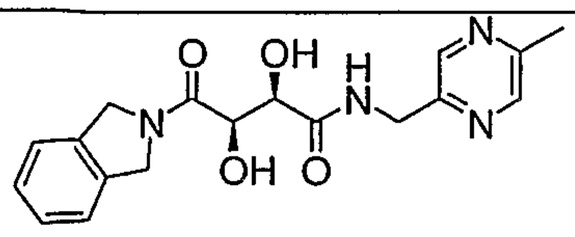
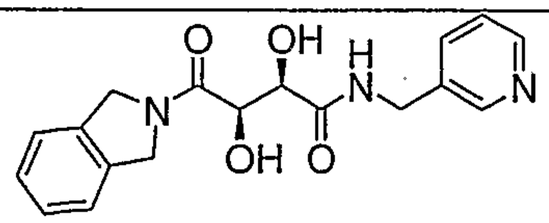
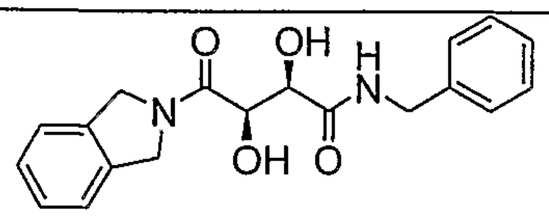
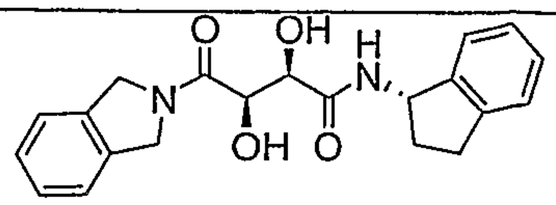
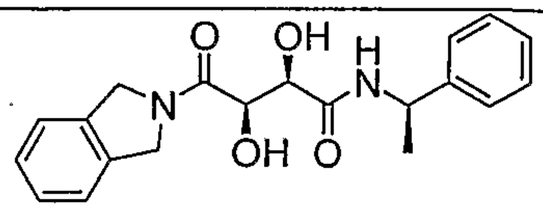
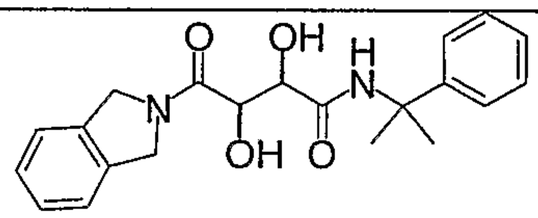
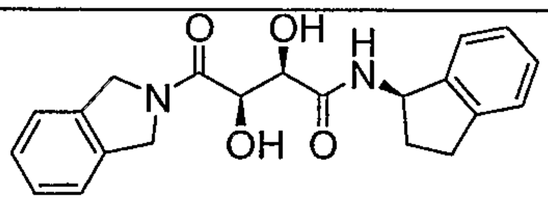
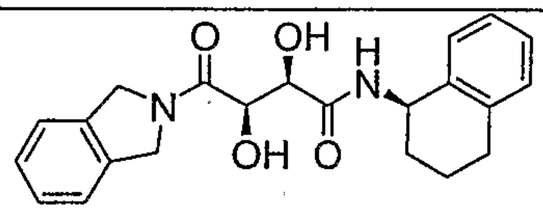
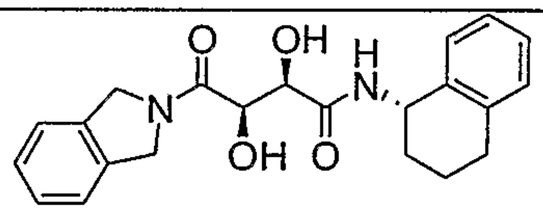
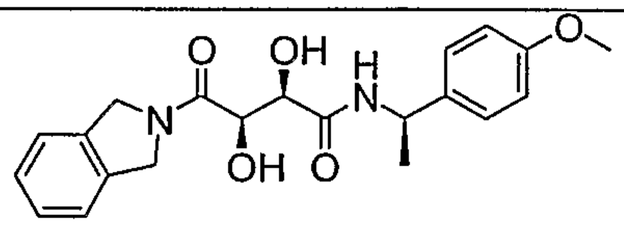
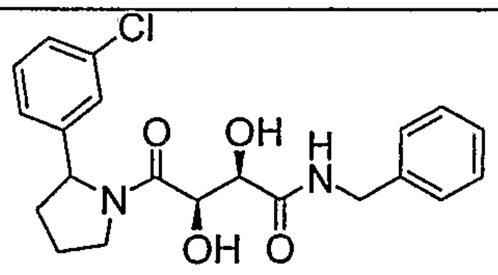
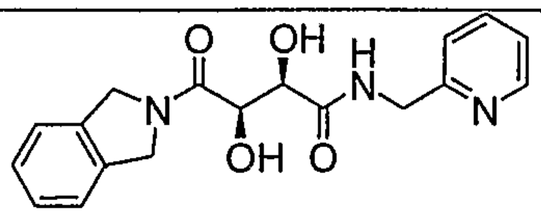
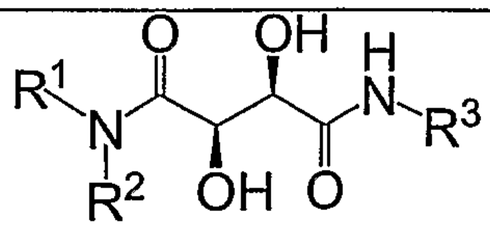
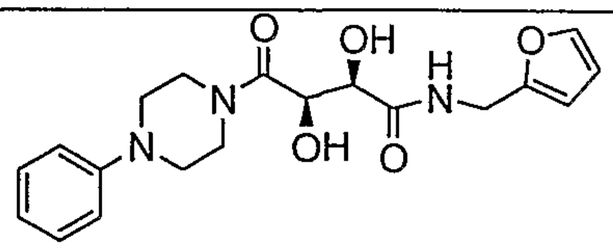
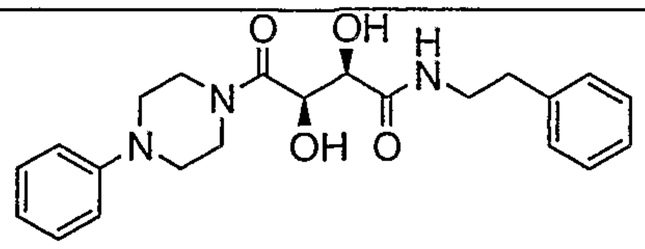
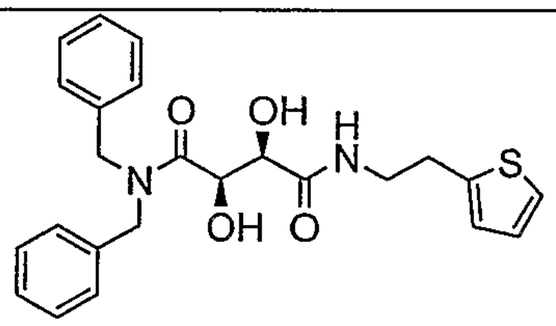
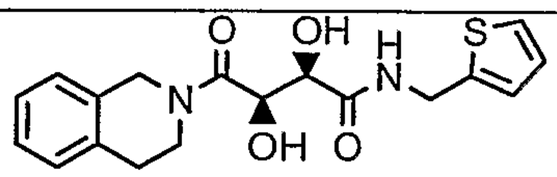
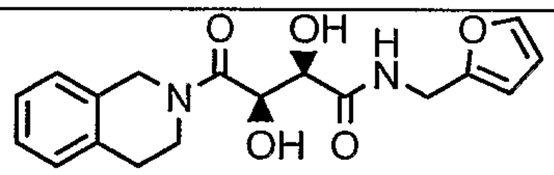
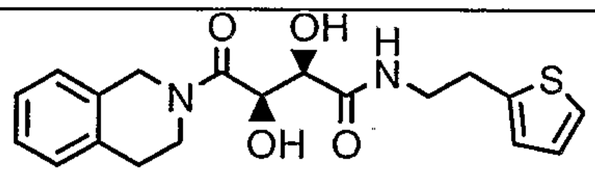
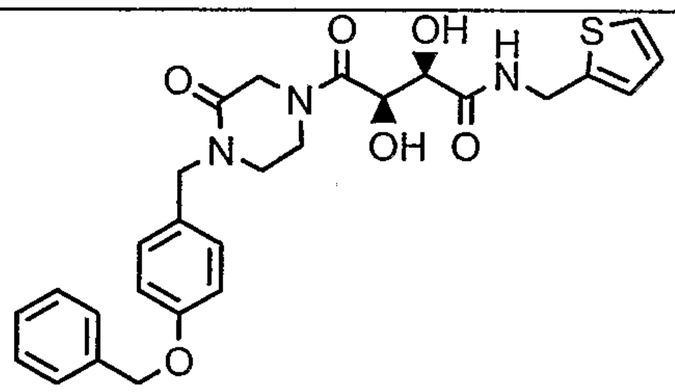
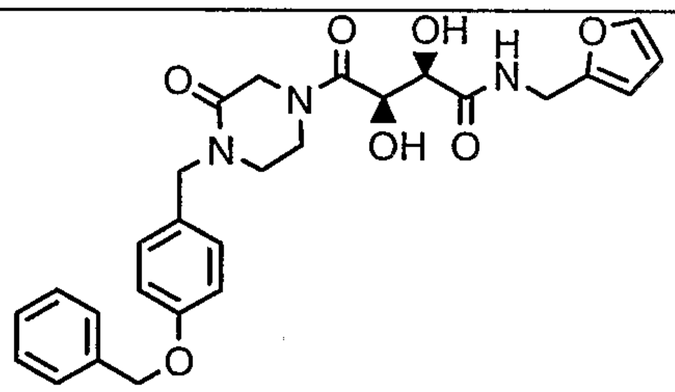
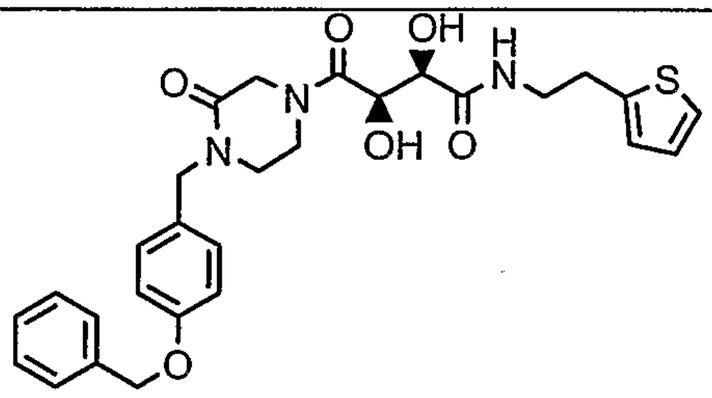
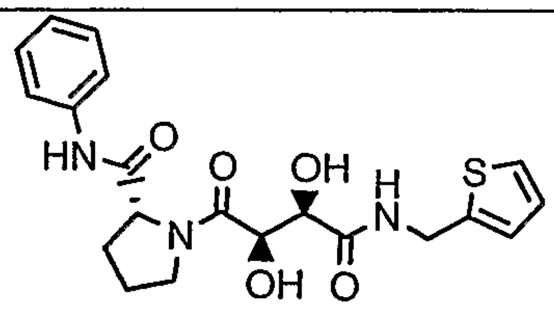
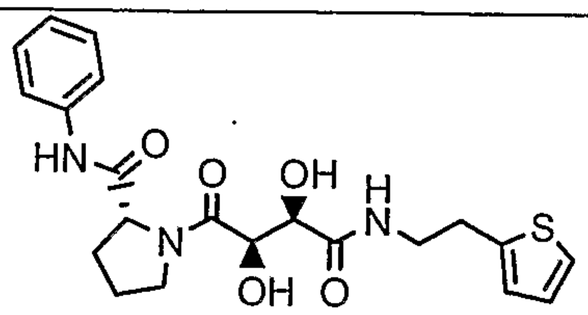
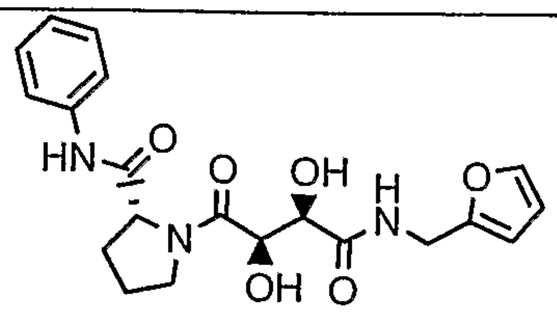
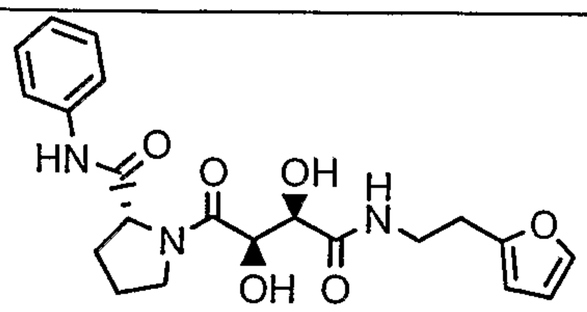
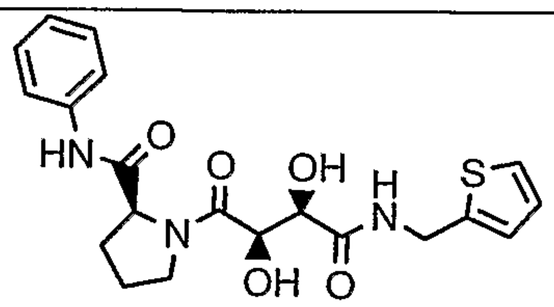
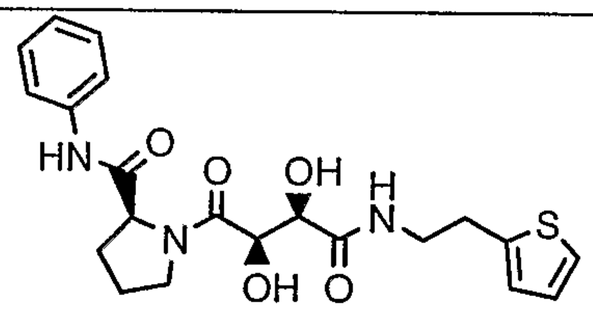
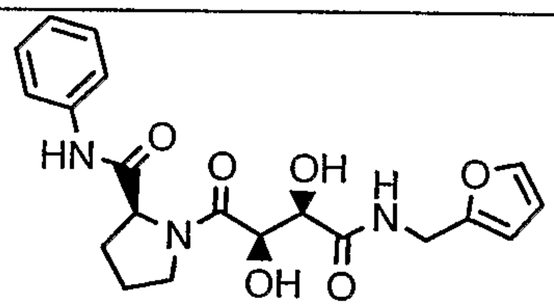
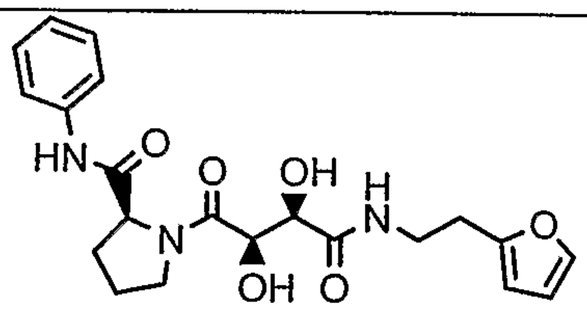
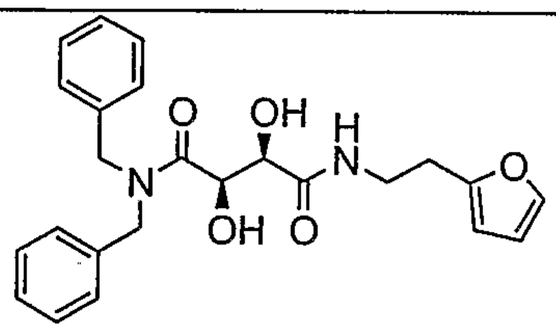
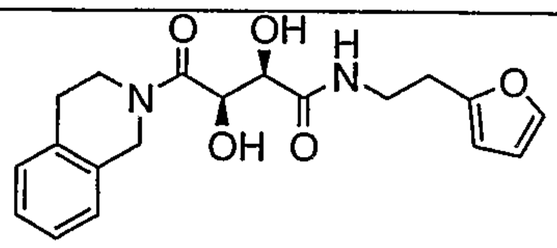
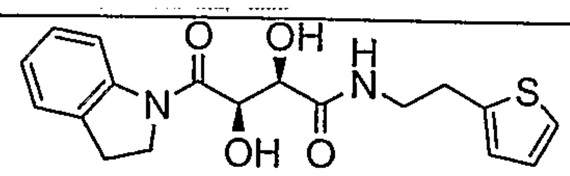
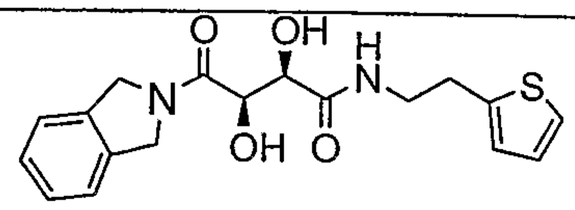
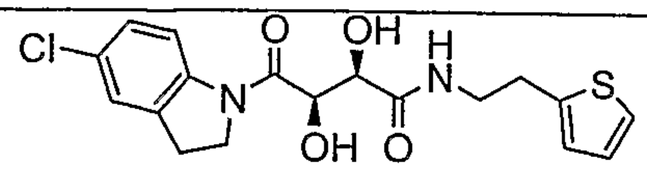
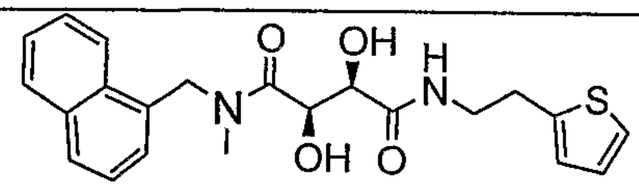
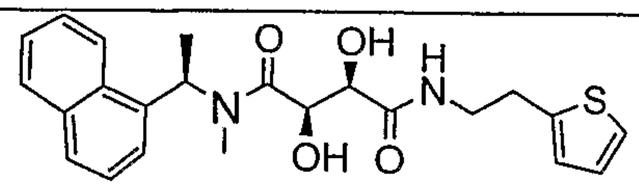
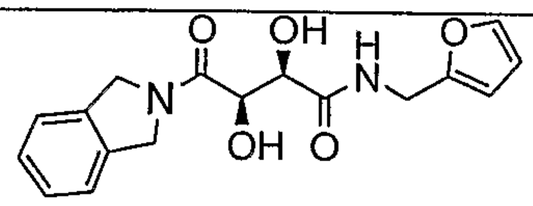
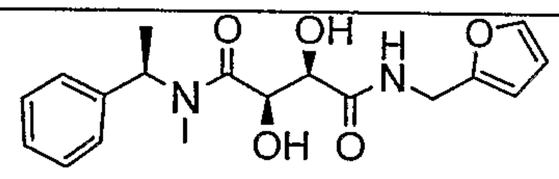
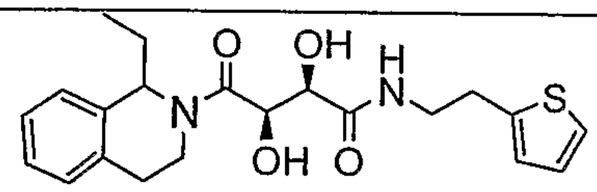
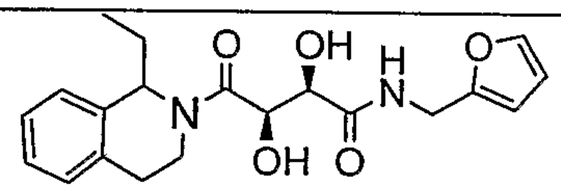
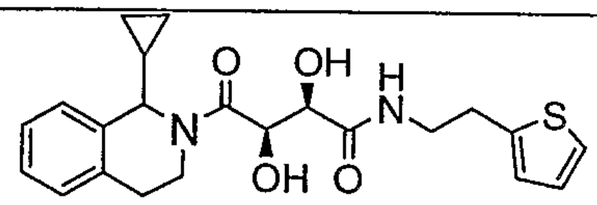
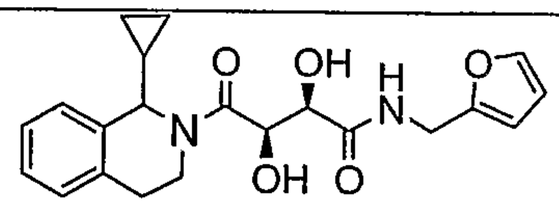
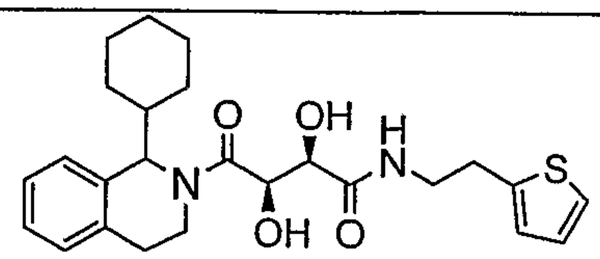
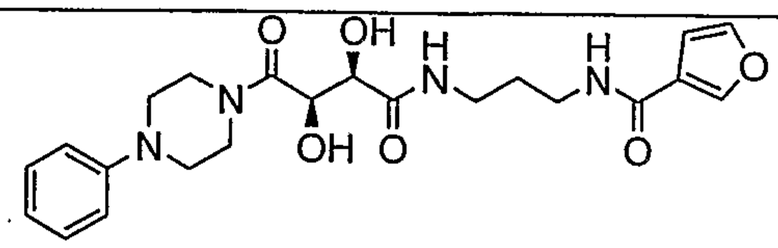
			
75			
76			
77			
78			
79			
80			
81			
82			
83			
84			

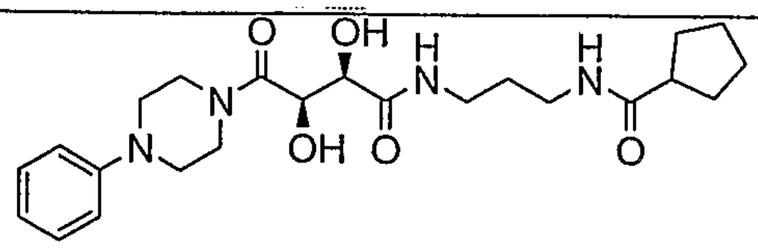
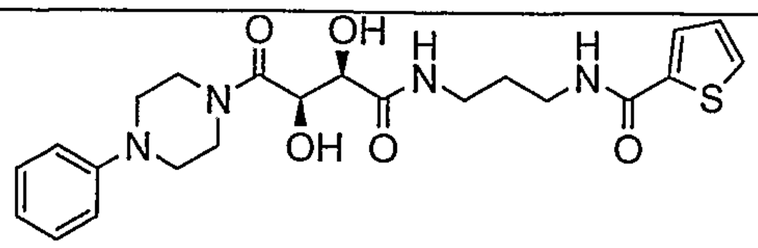
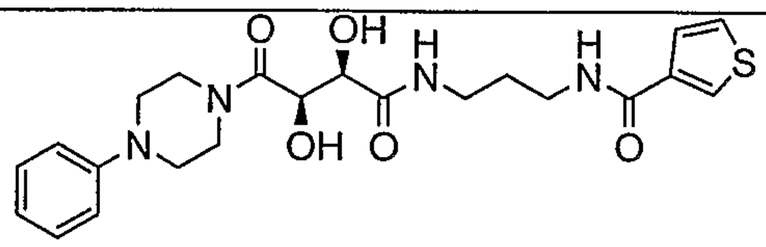
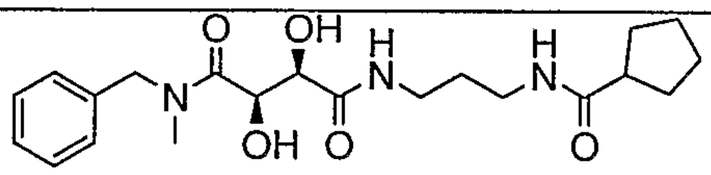
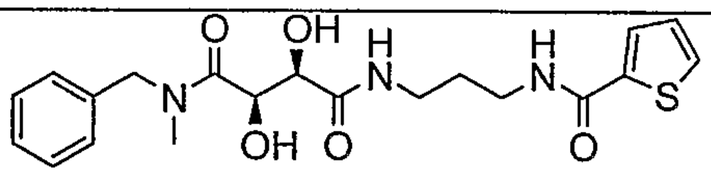
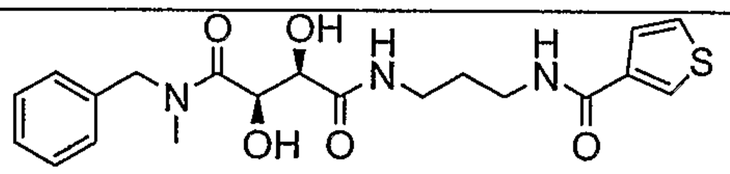
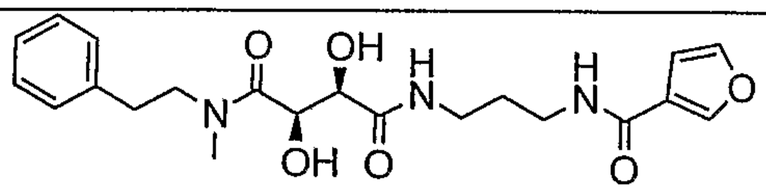
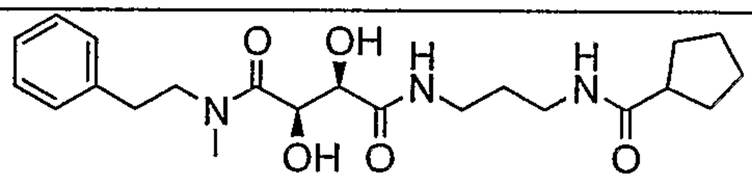
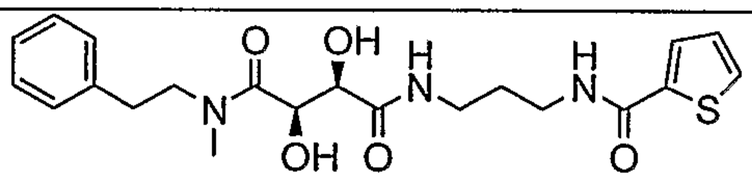
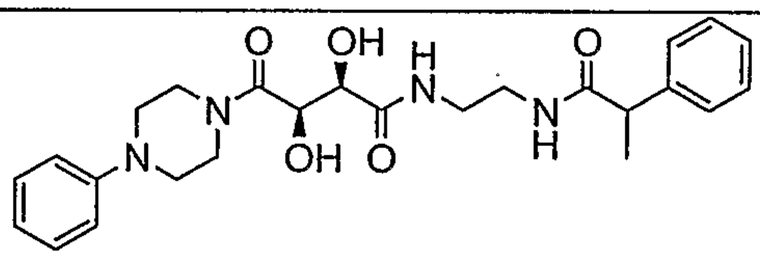
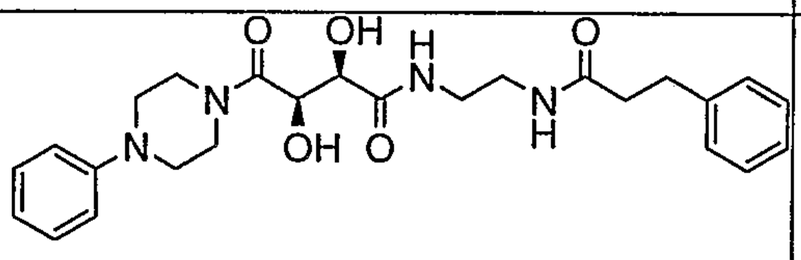
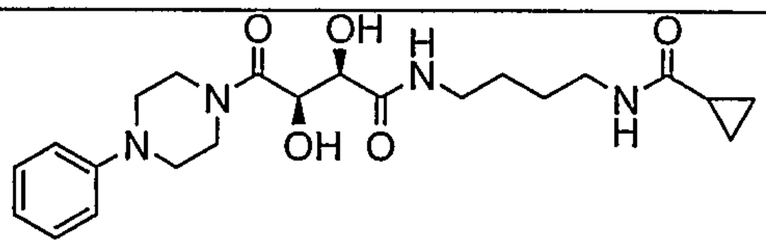
85		
86		
87		
88		
89		
90		
91		
92		
93		
94		

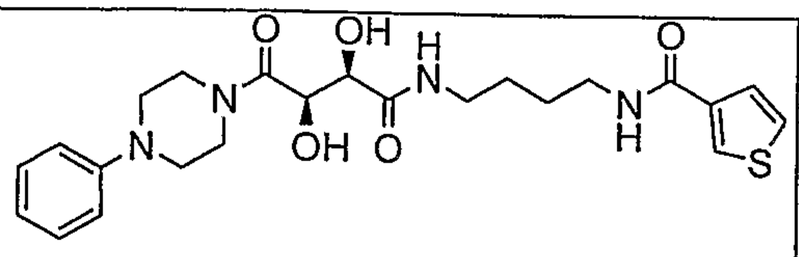
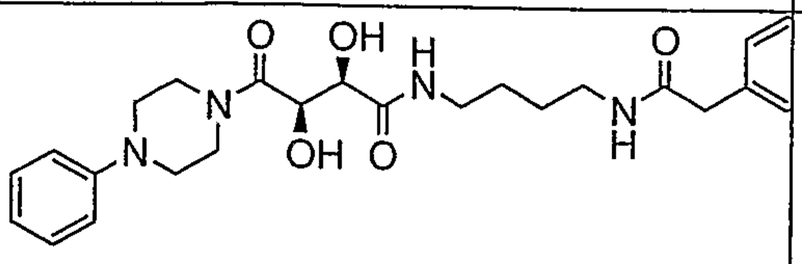
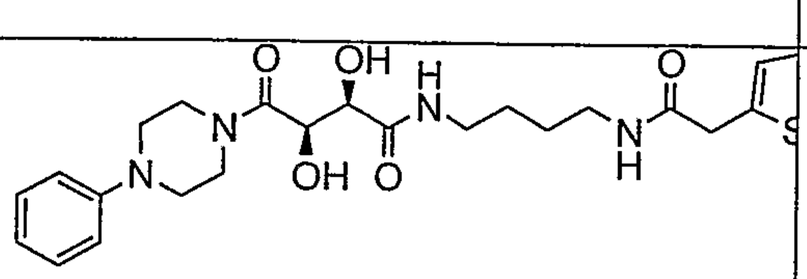
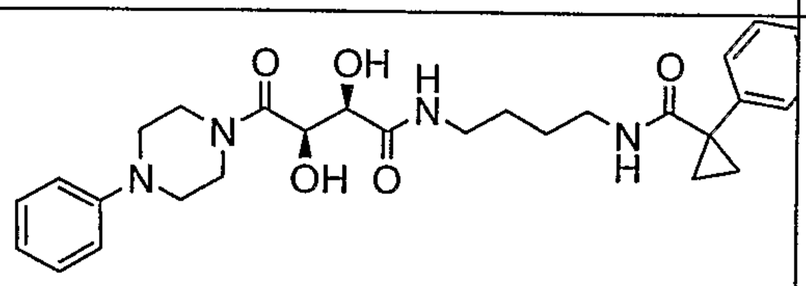
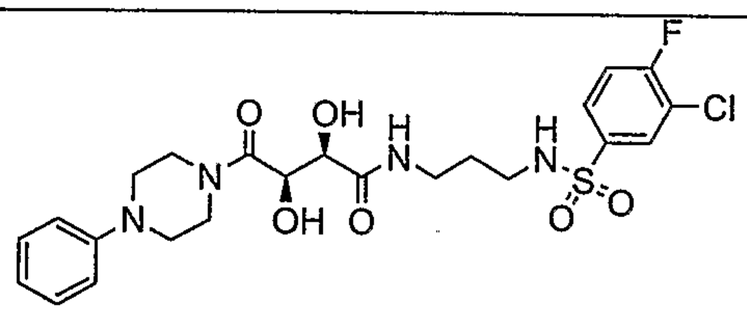
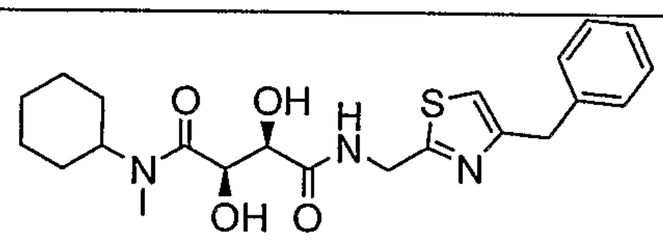
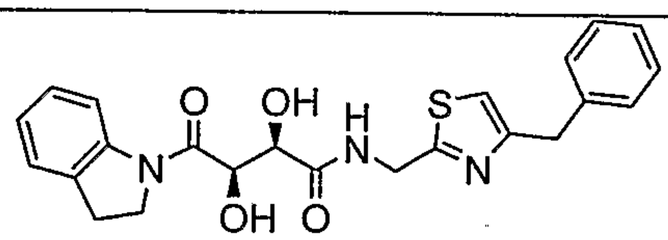
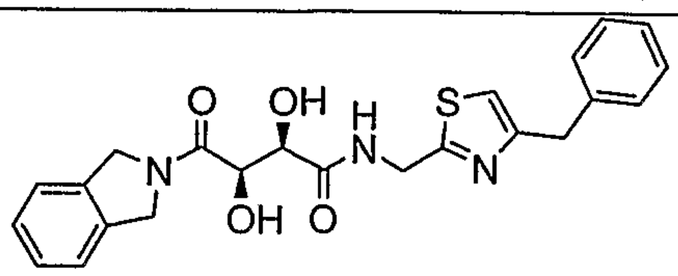
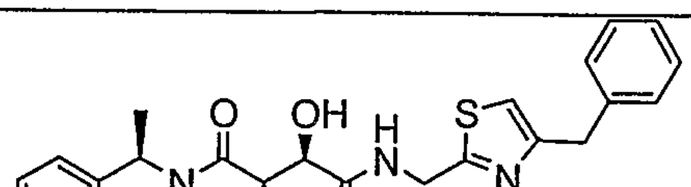
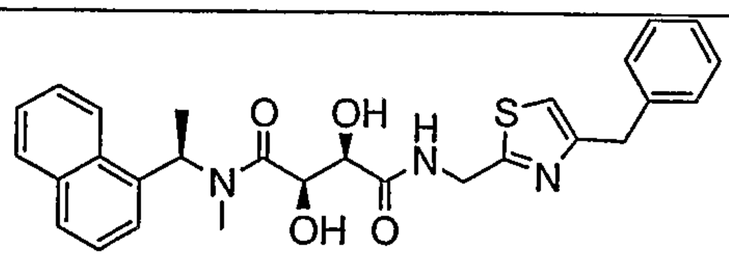
95		
96		
97		
98		
99		
100		
101		
102		
103		
104		
105		
108	 (R1 = R2 = CH_2Ph, R3 = $CH_2CH_2(C_4H_4O)$	

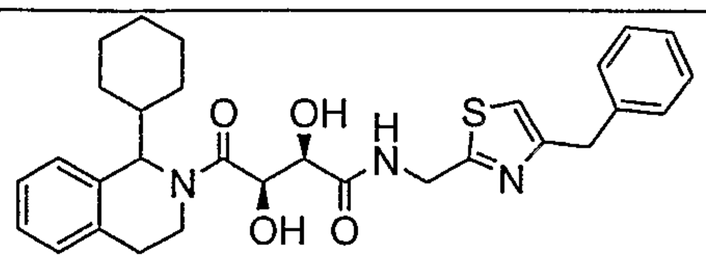
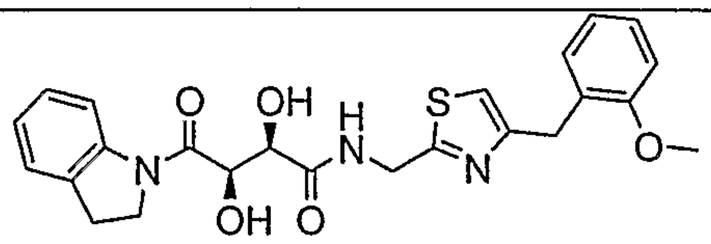
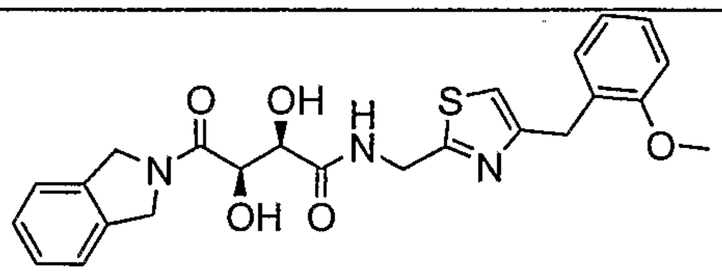
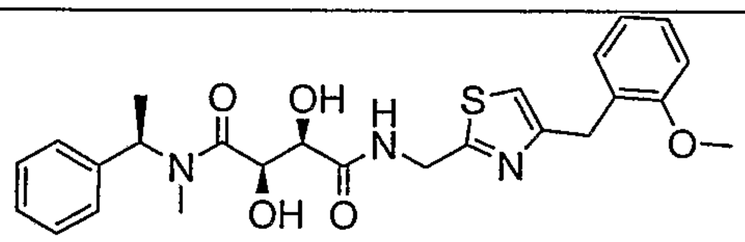
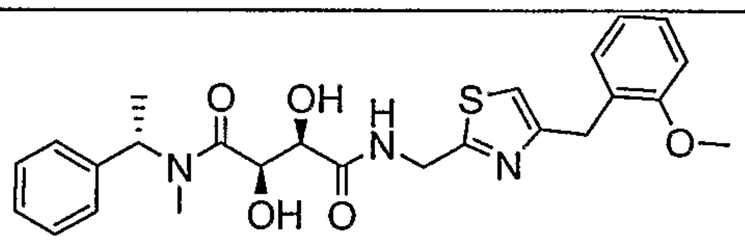
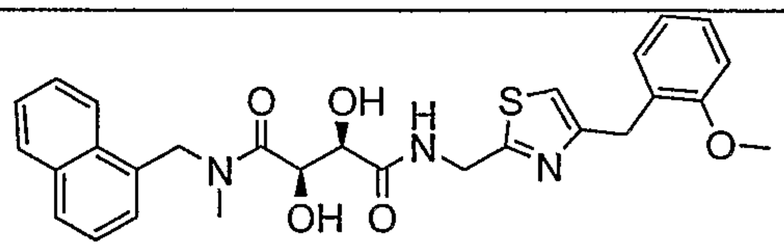
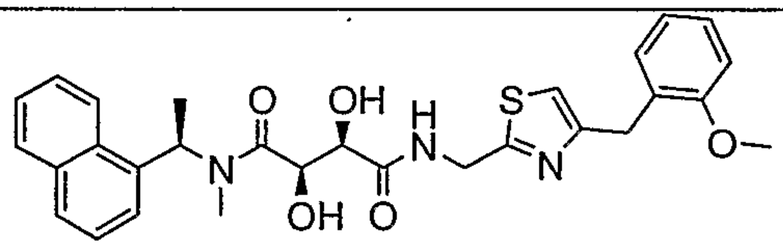
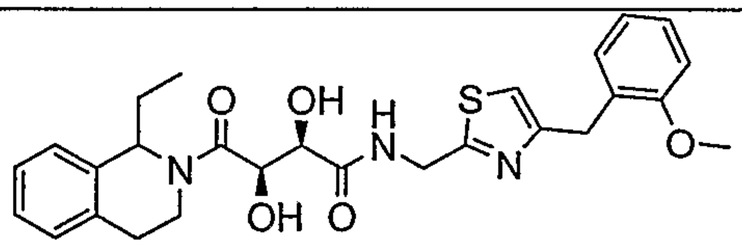
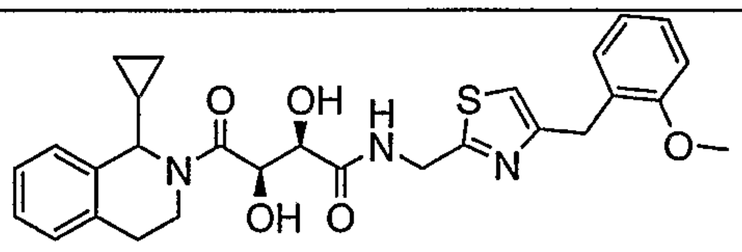
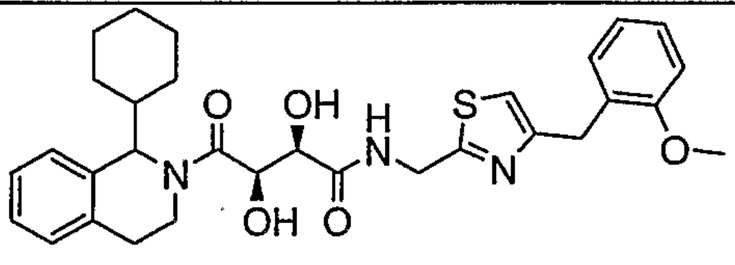
109		
110		
111		
112		
113		
114		
115		
116		
117		
118A		

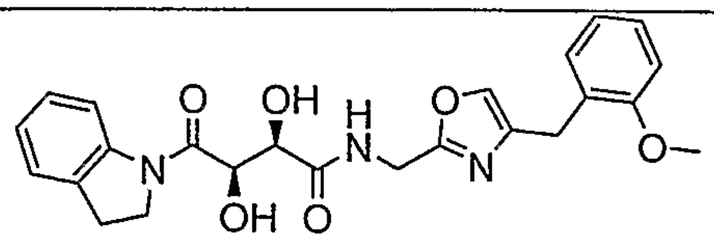
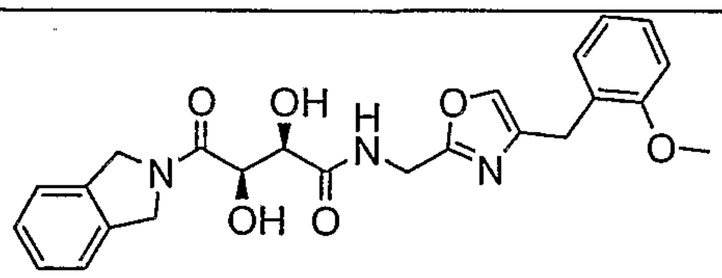
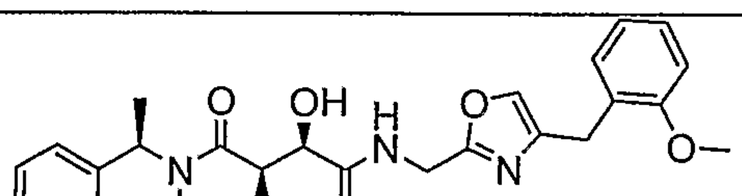
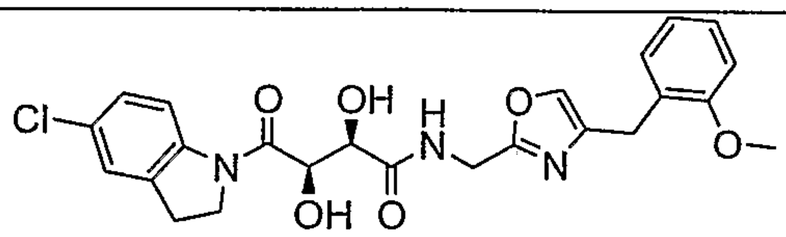
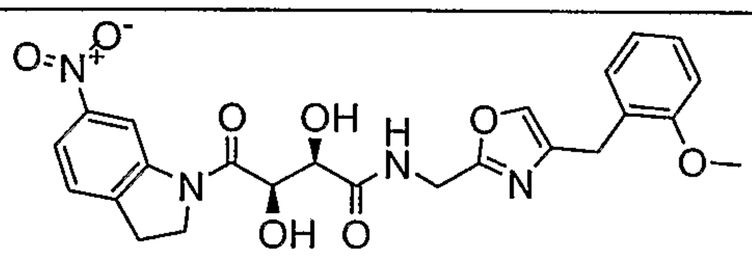
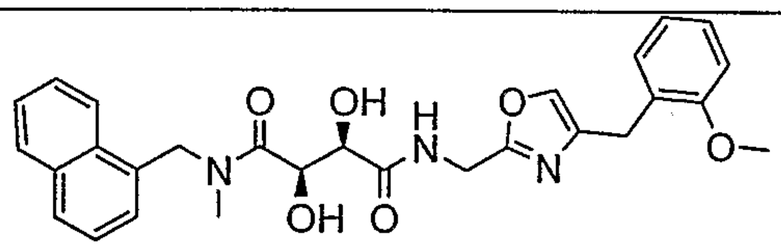
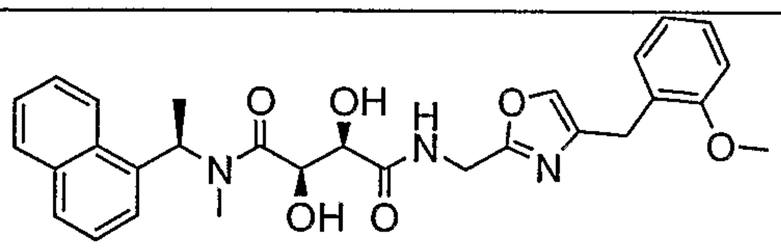
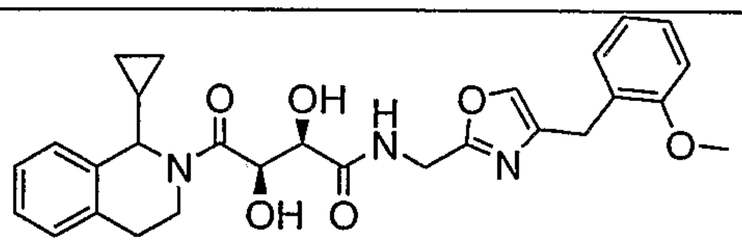
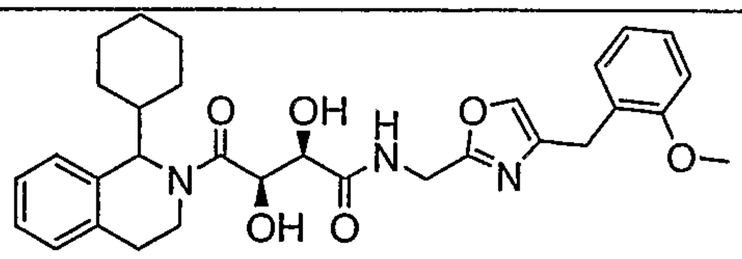
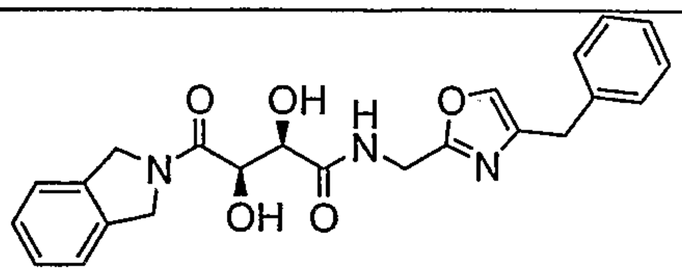
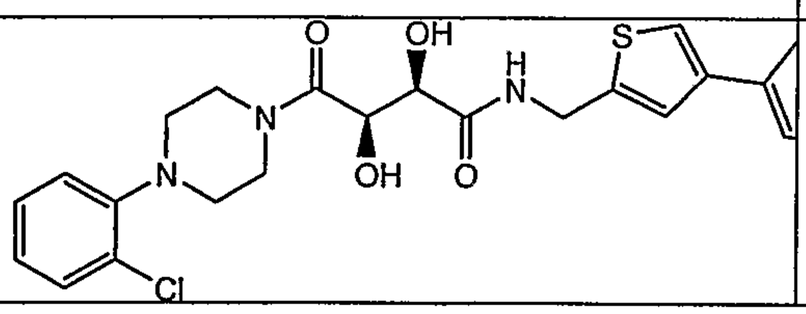
118B		
119		
120		
121		
122		
123		
124		
108		
125		

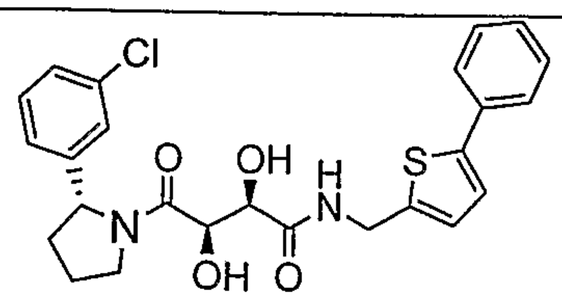
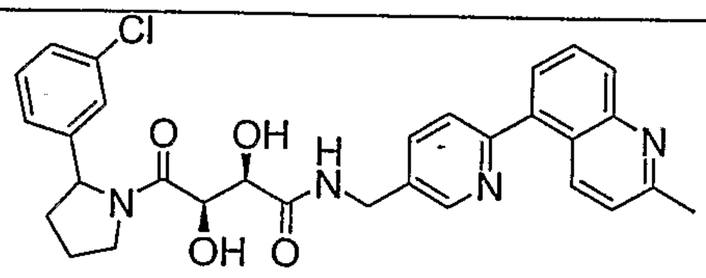
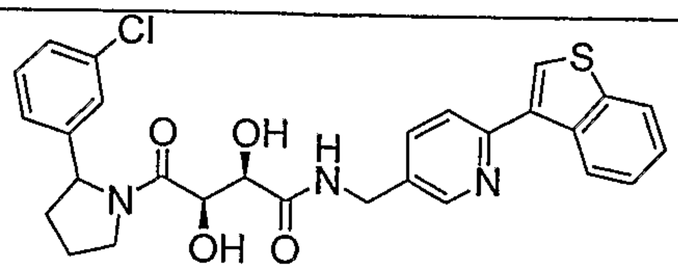
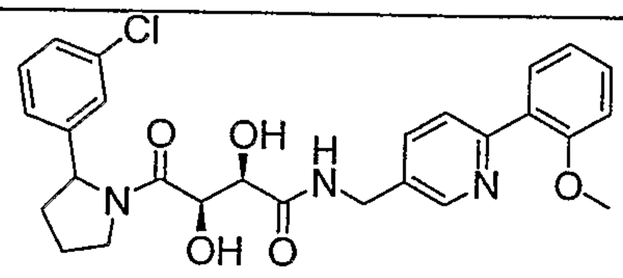
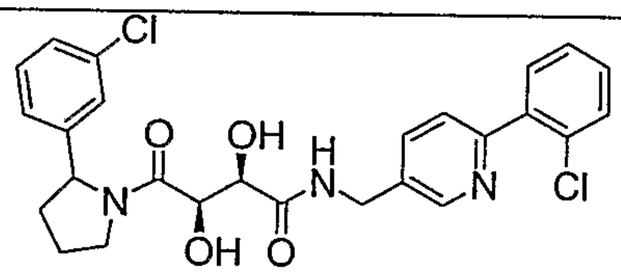
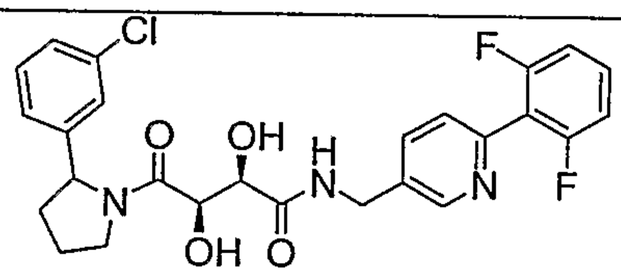
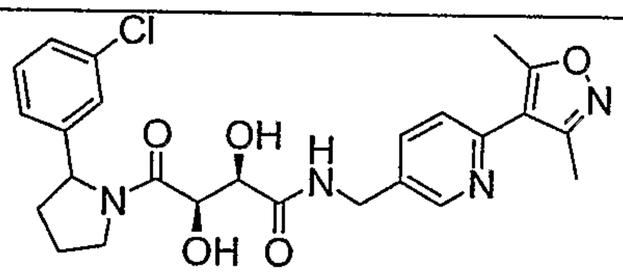
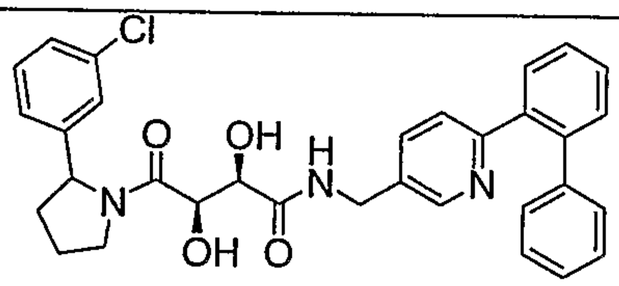
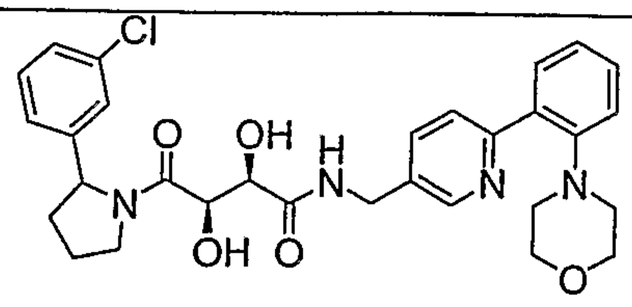
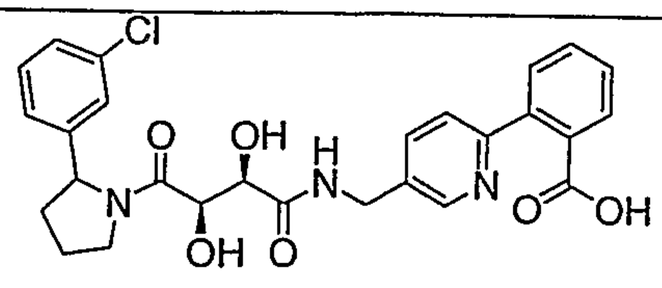
38		
39		
126		
127		
128		
129		
130		
131		
132		
133		
134		
135		
136		

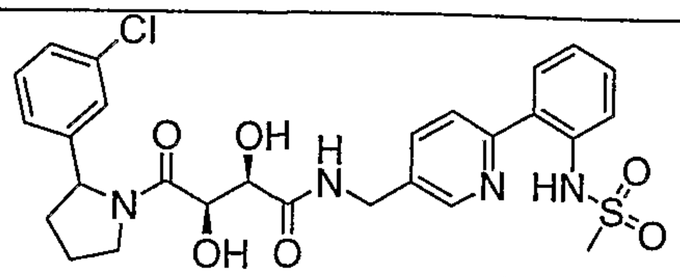
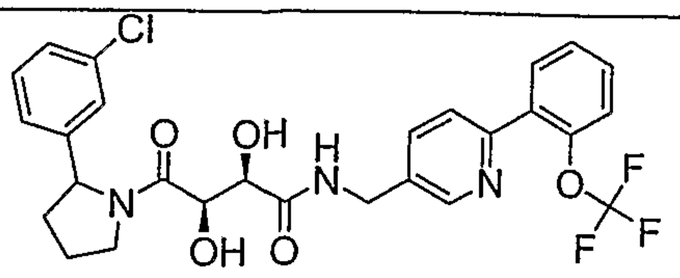
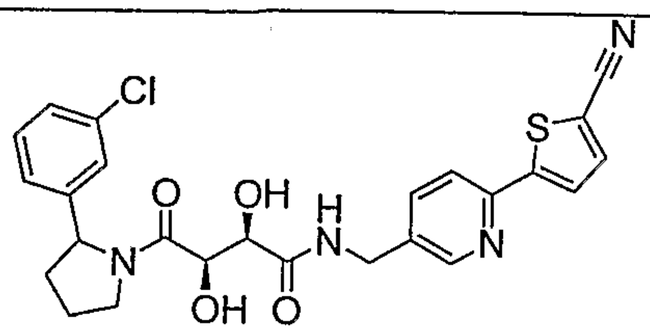
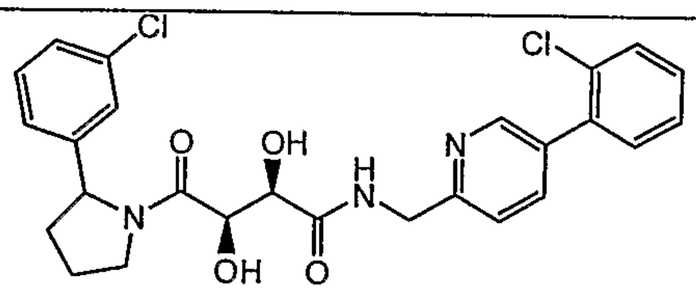
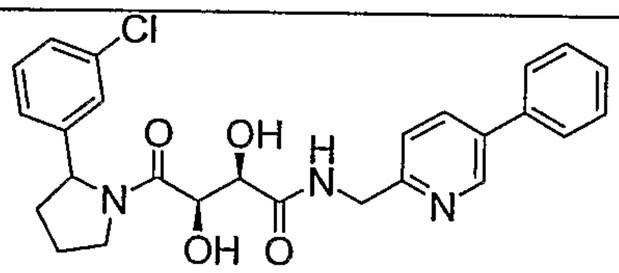
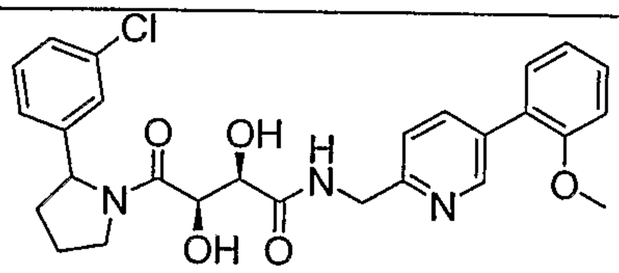
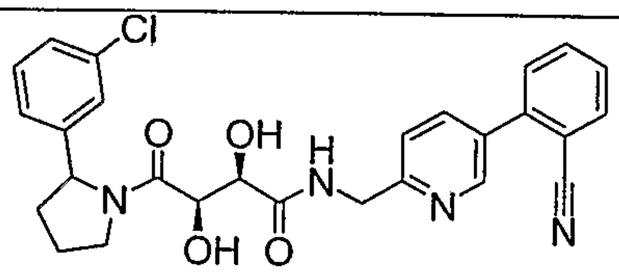
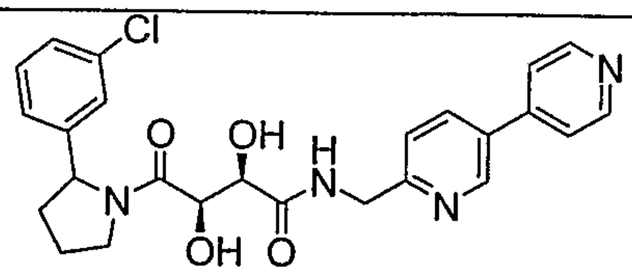
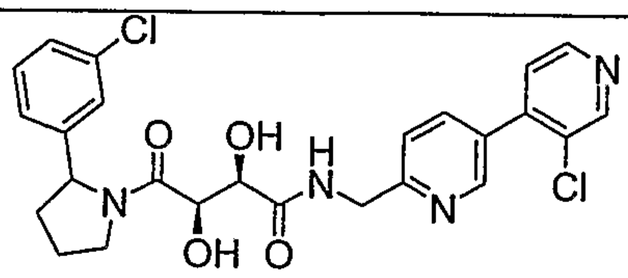
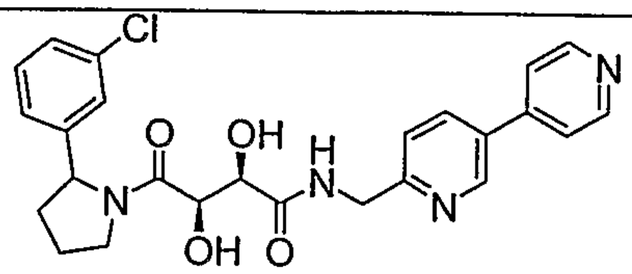
137		
138		
139		
140		
141		
142		
143		
144		
145		
146		
147		
148		

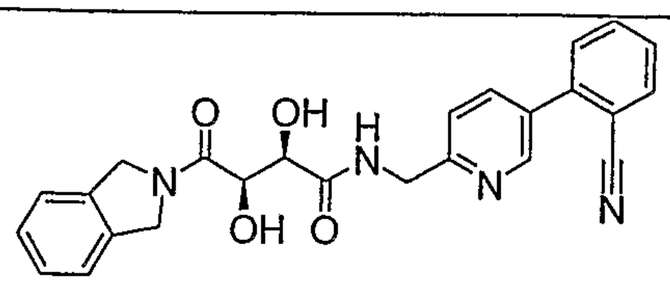
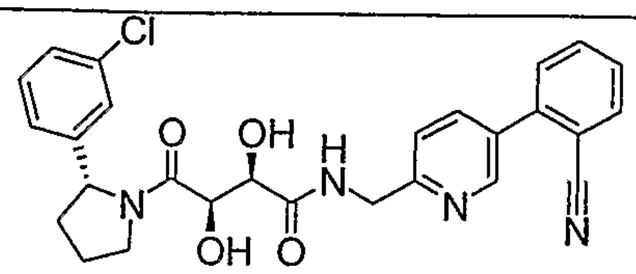
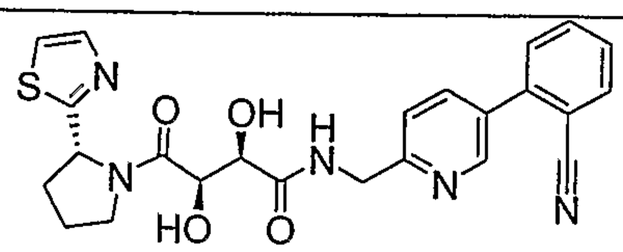
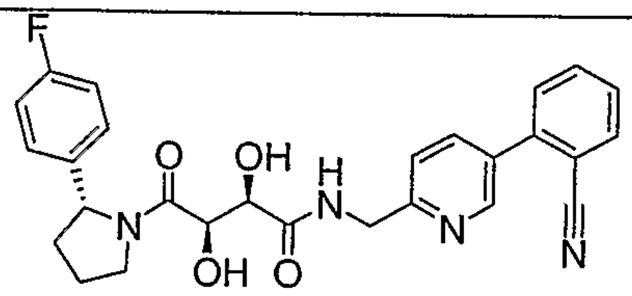
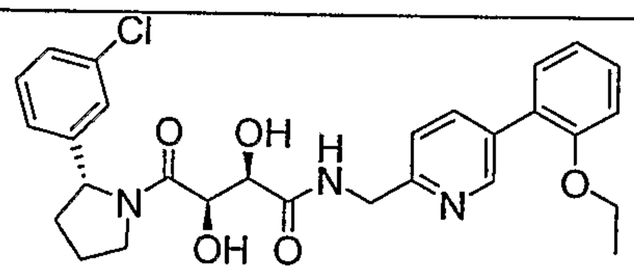
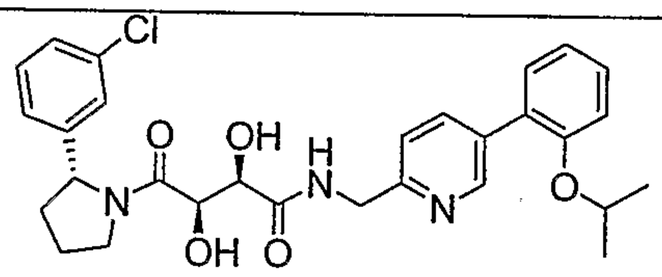
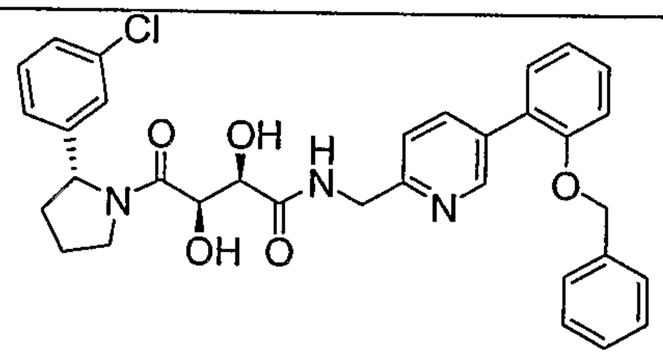
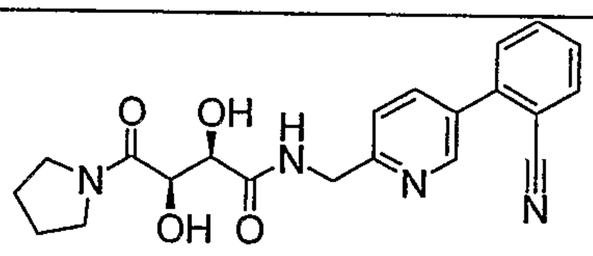
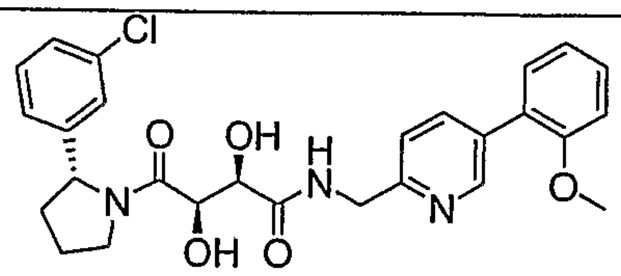
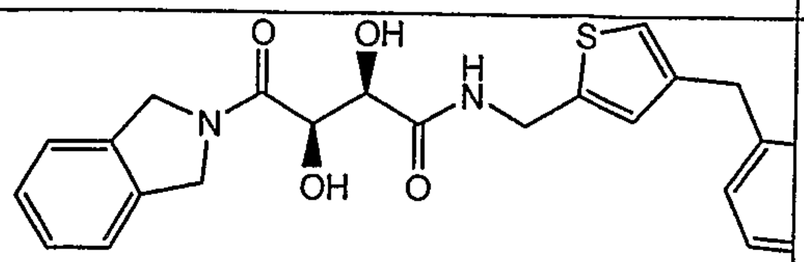
149		
150		
151		
152		
157		
158		
159		
160		
161		
162		

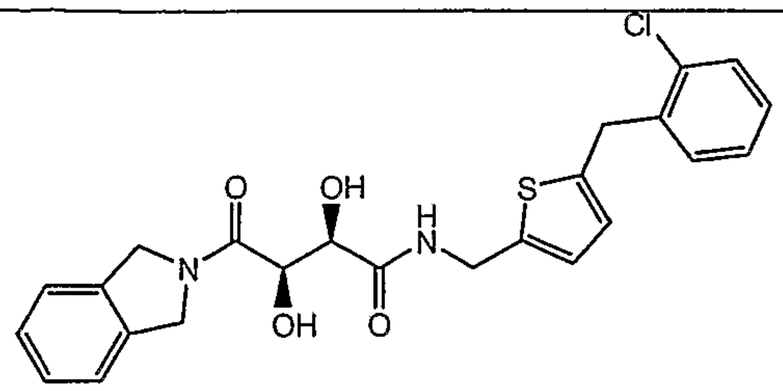
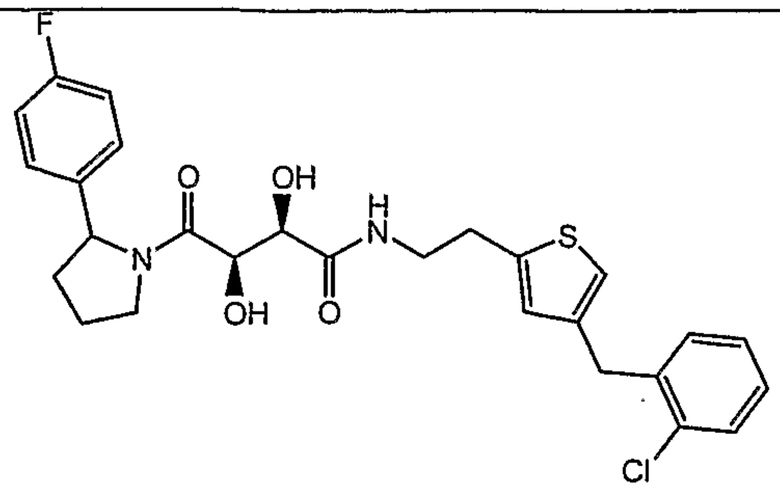
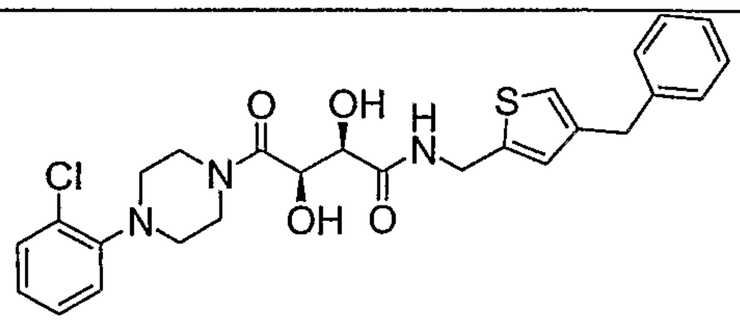
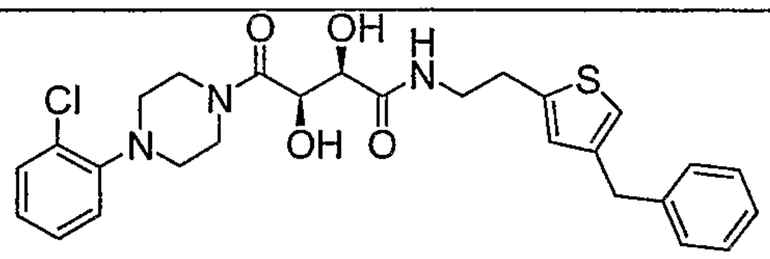
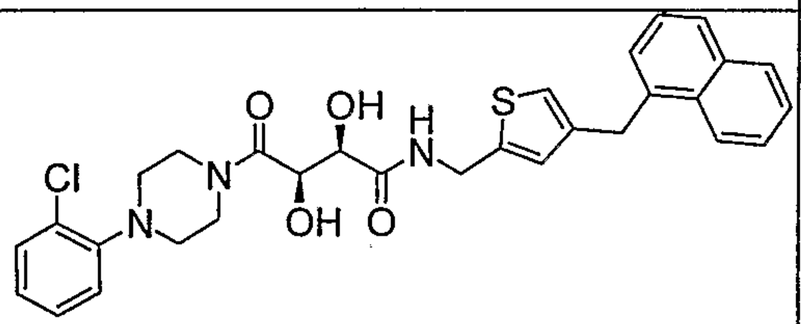
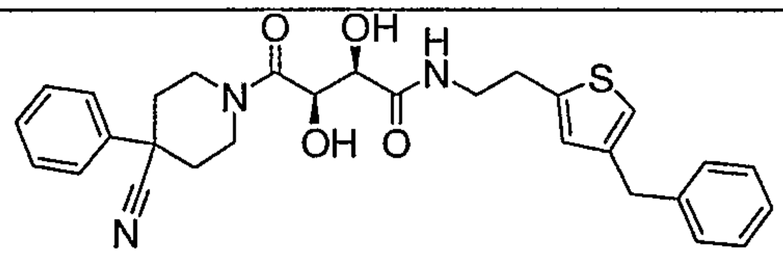
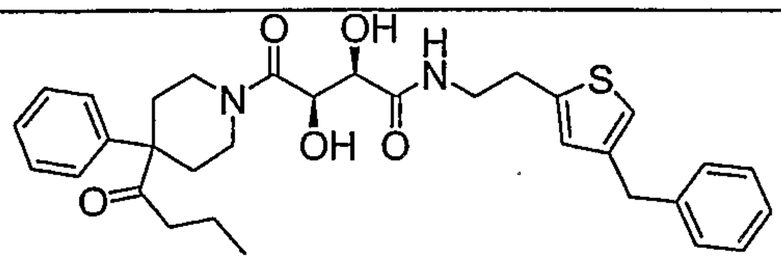
163		
164		
165		
166		
167		
168		
169		
170		
171		
172		

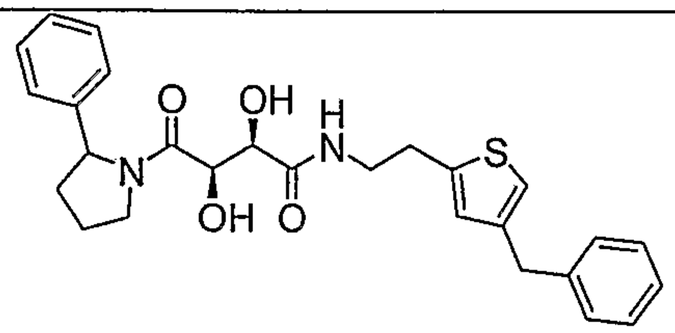
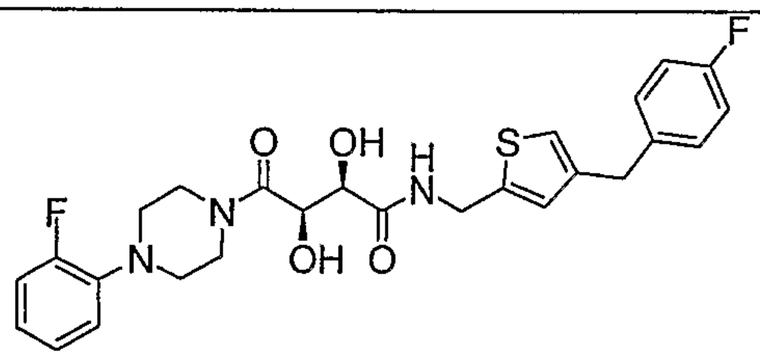
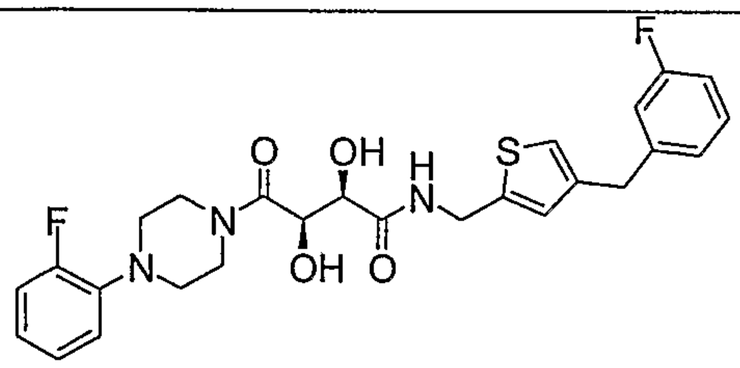
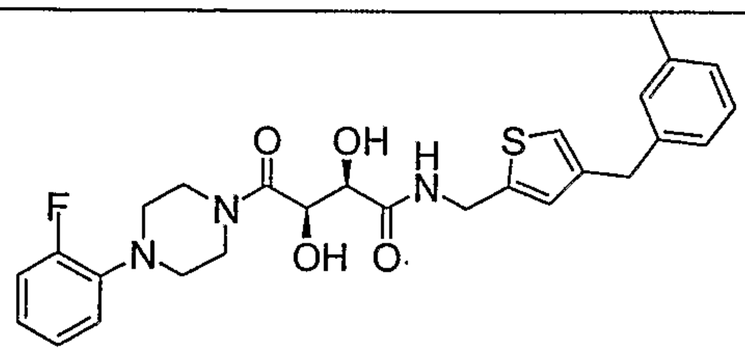
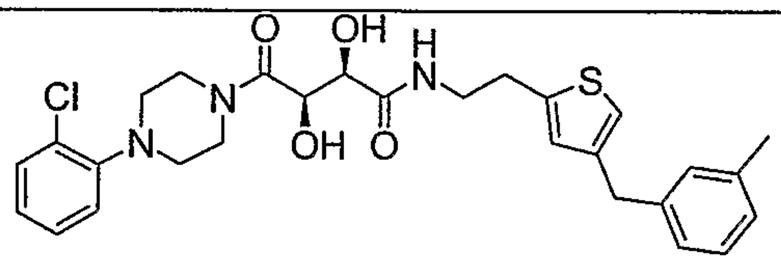
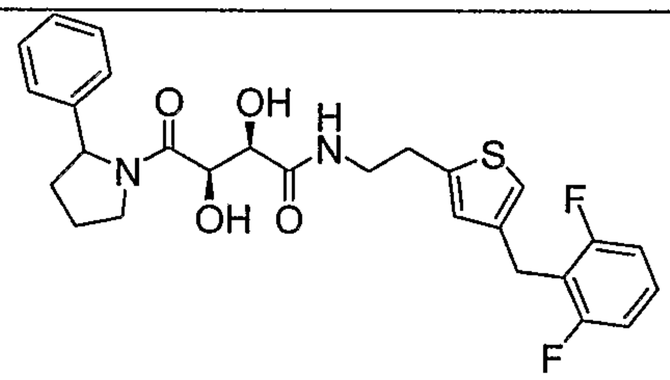
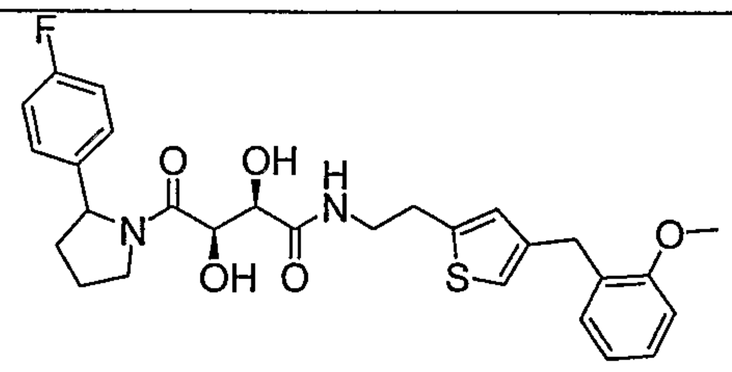
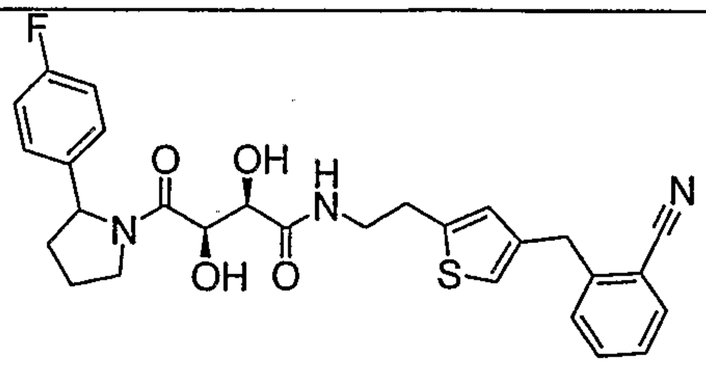
173		
174		
175		
176		
177		
178		
179		
180		
181		
182		
191		

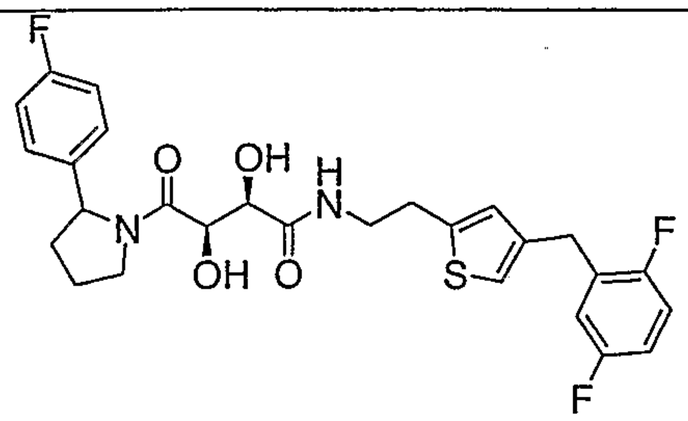
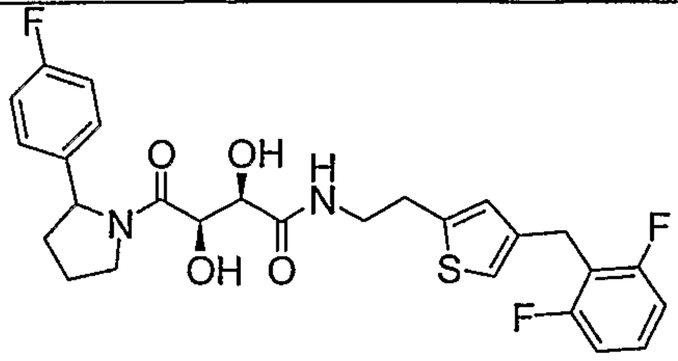
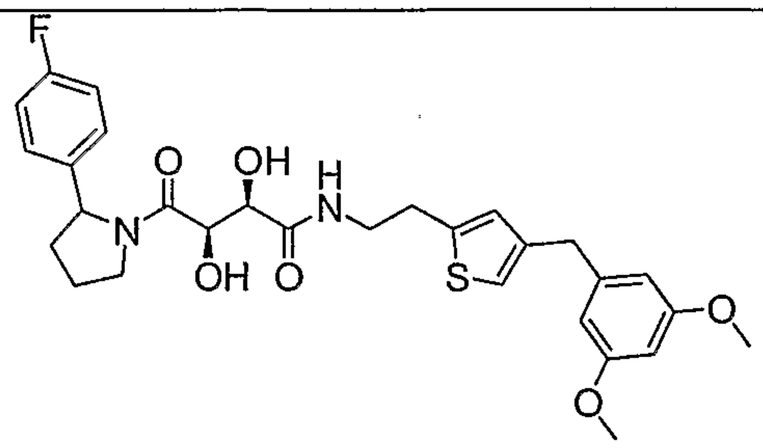
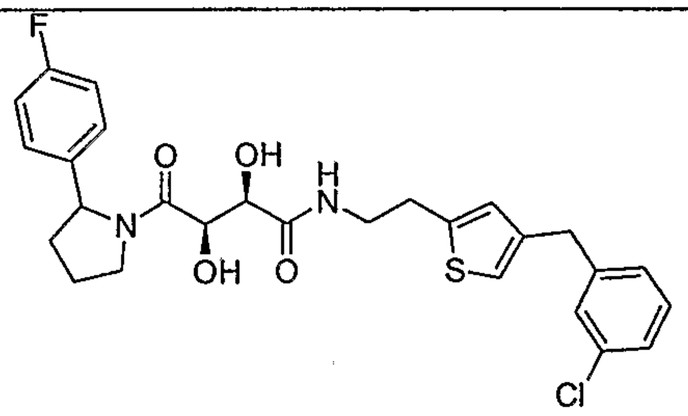
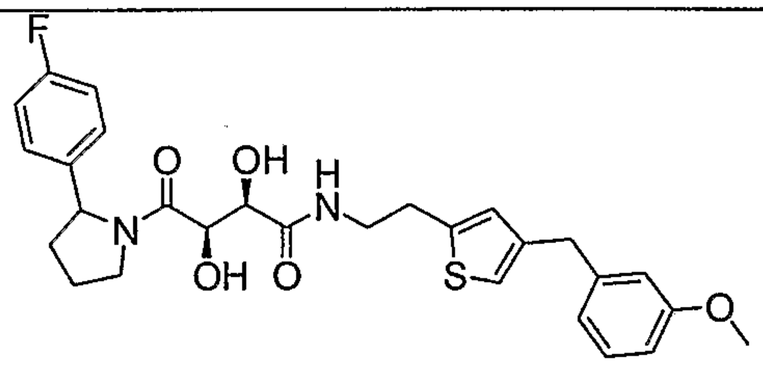
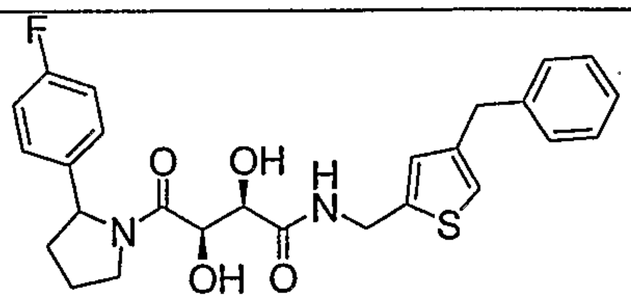
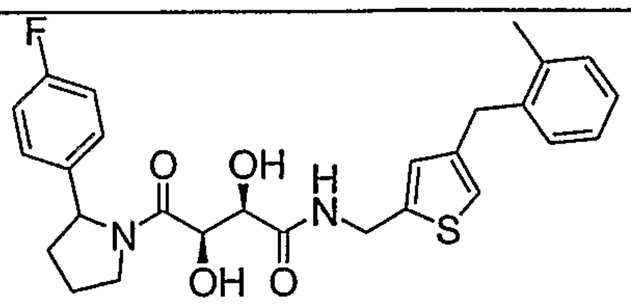
192		
197		
198		
199		
200		
201		
202		
203		
204		
205		

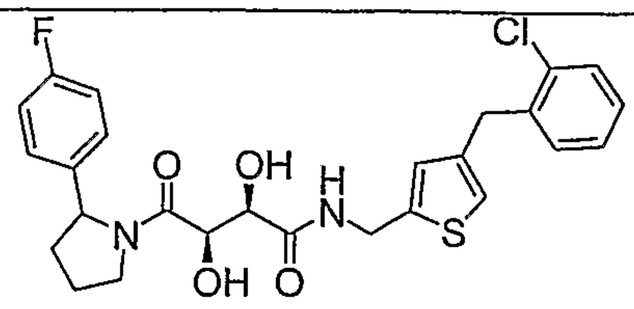
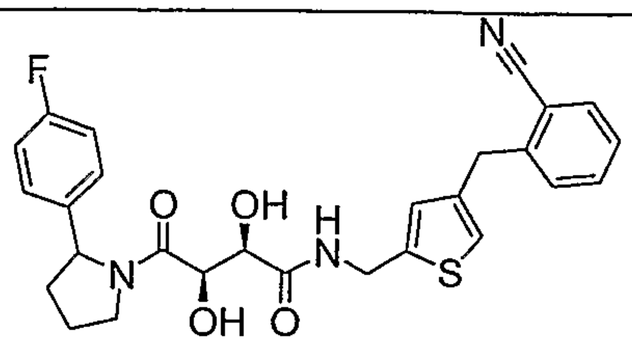
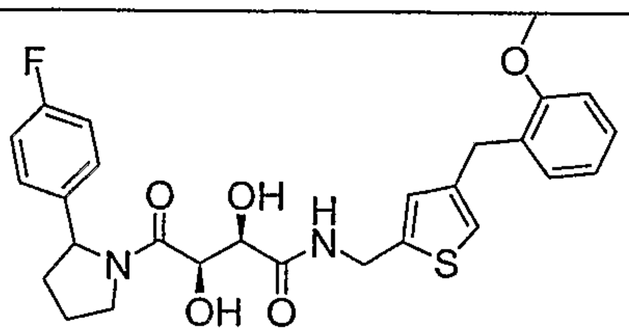
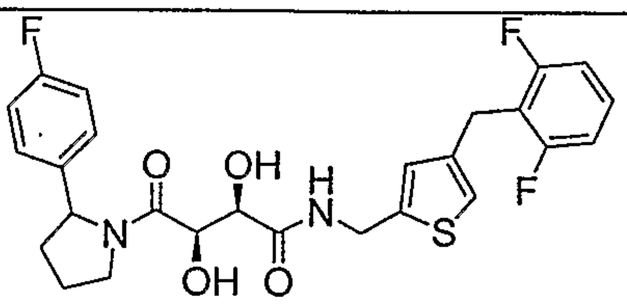
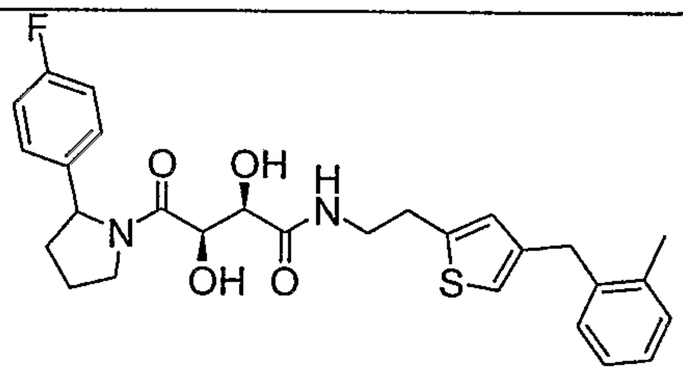
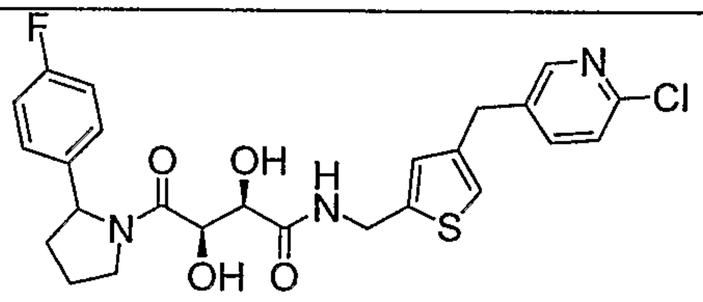
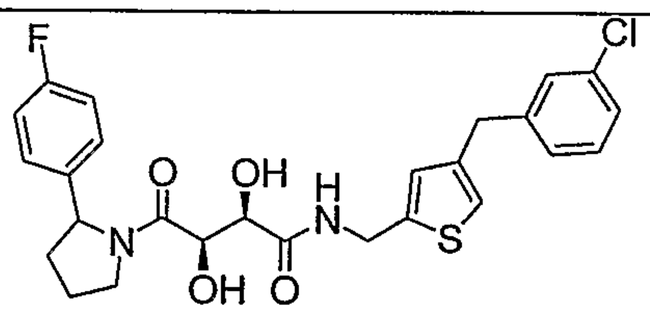
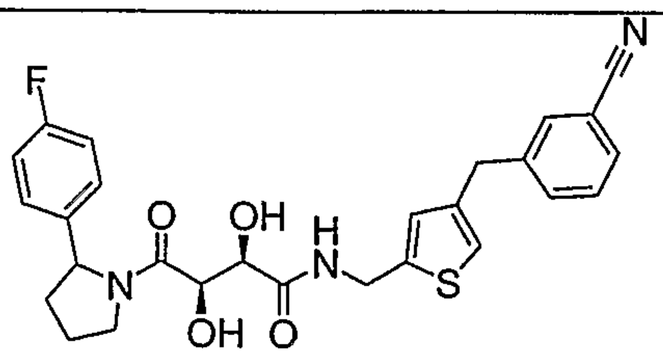
206		
207		
208		
212		
213		
214		
215		
216		
217		
218		

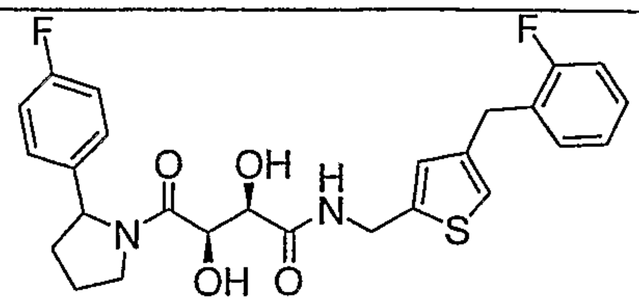
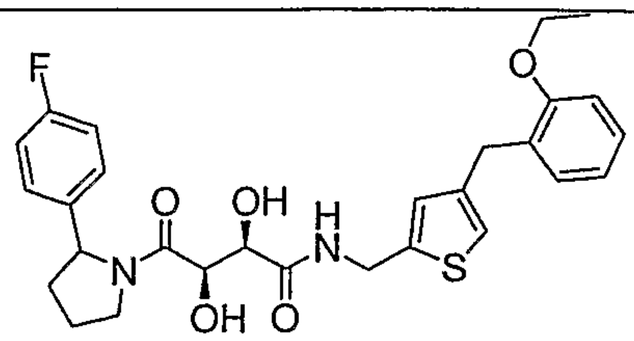
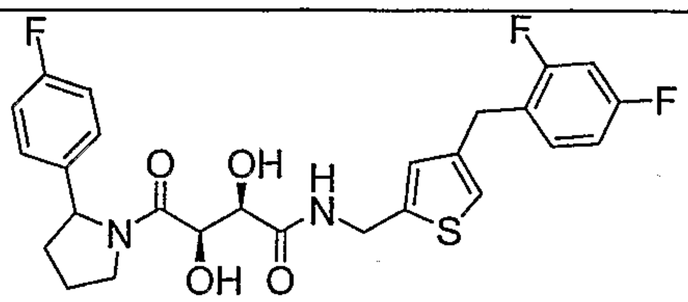
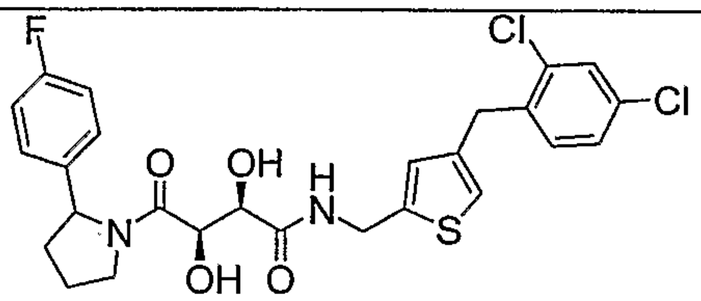
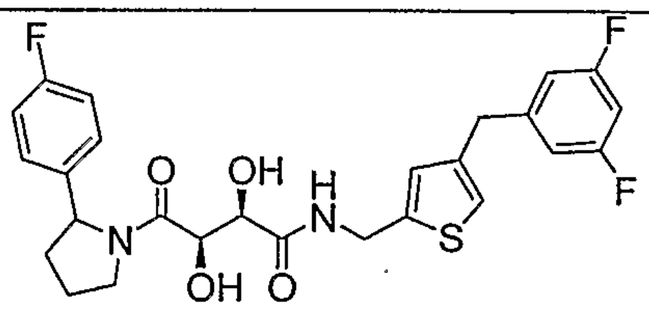
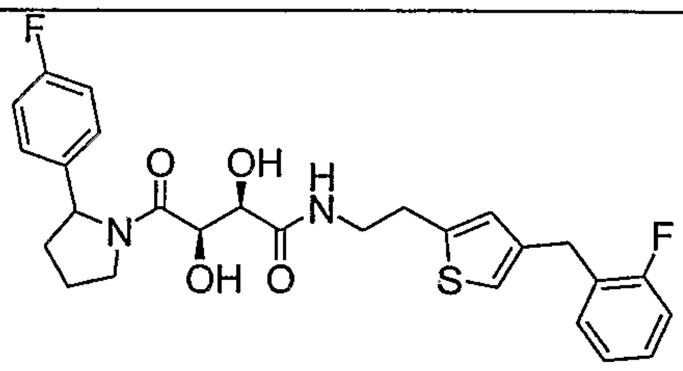
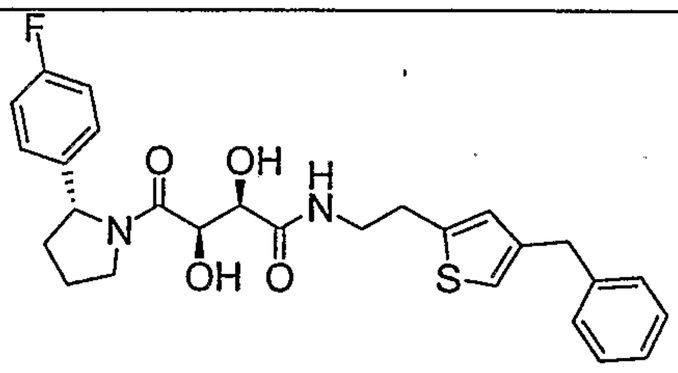
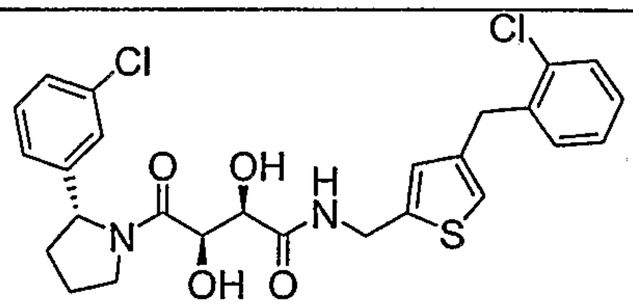
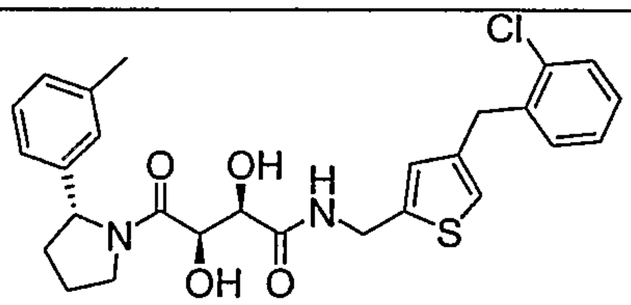
219		
220		
221		
222		
223		
224		
225		
226		
227		
232		

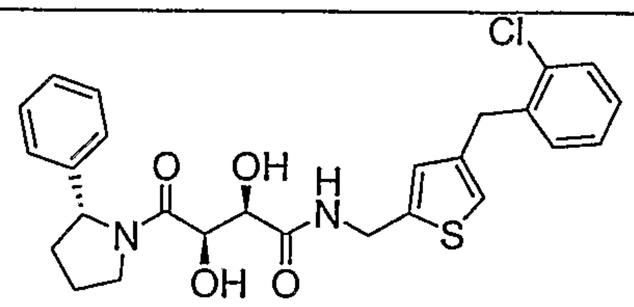
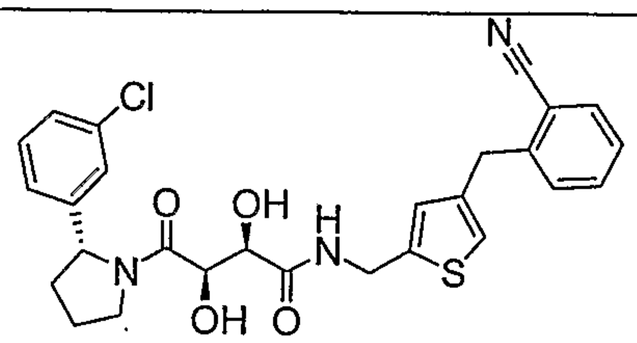
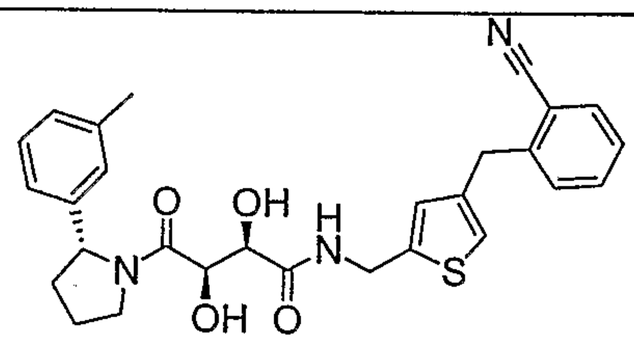
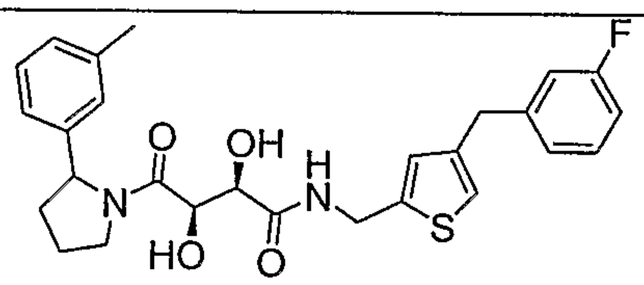
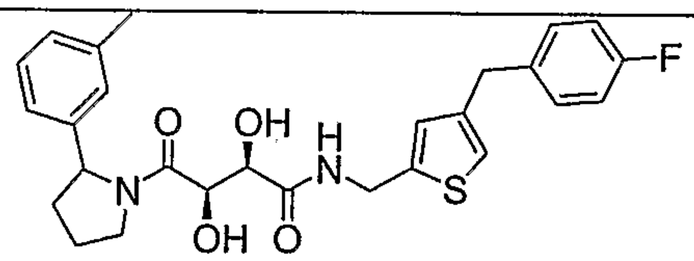
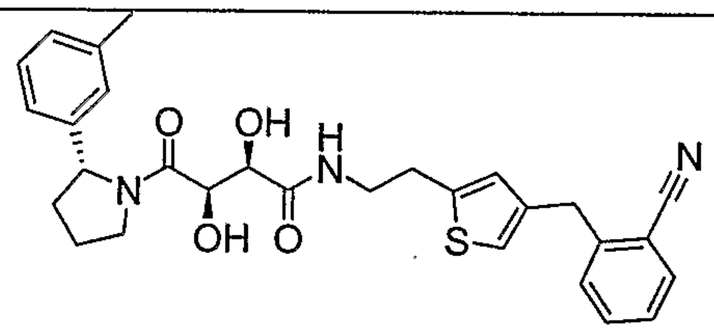
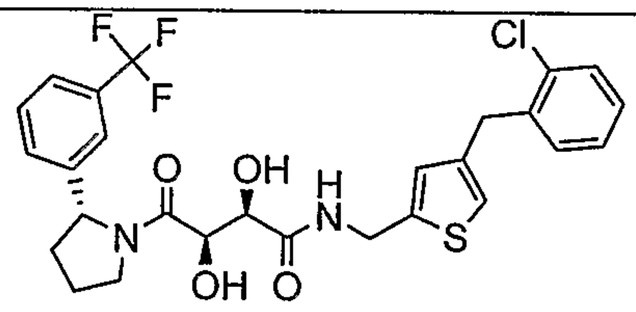
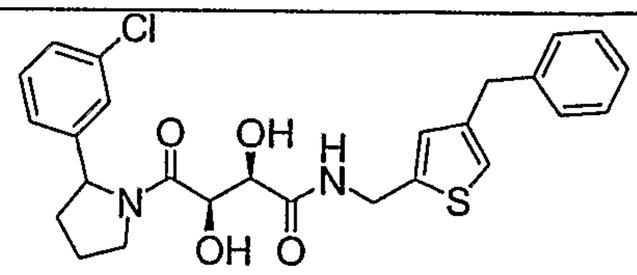
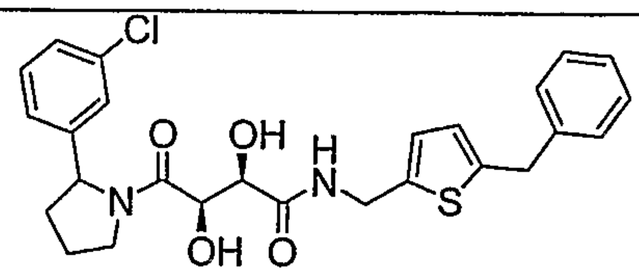
236		
242		
243		
244		
245		
246		
247		

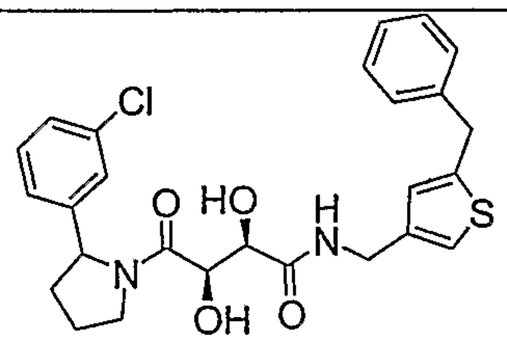
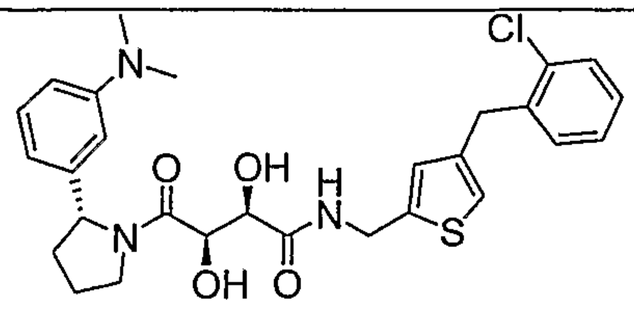
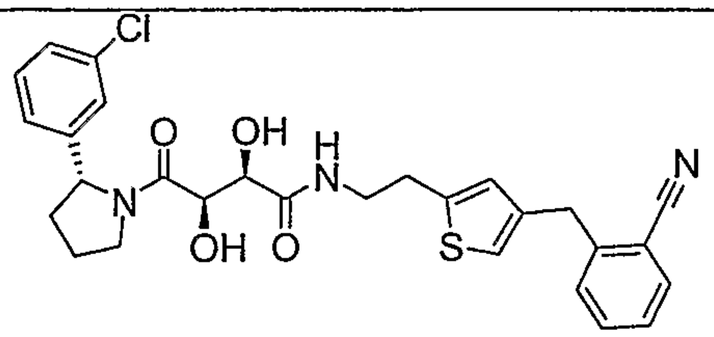
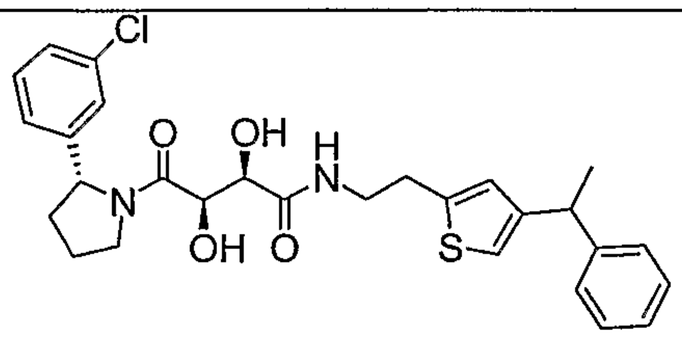
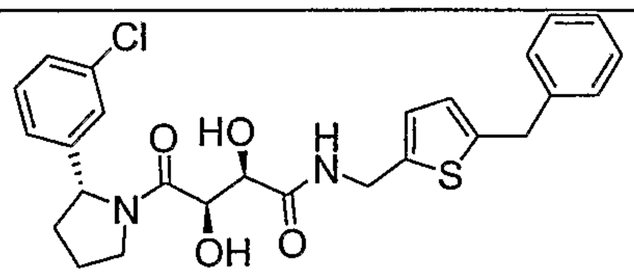
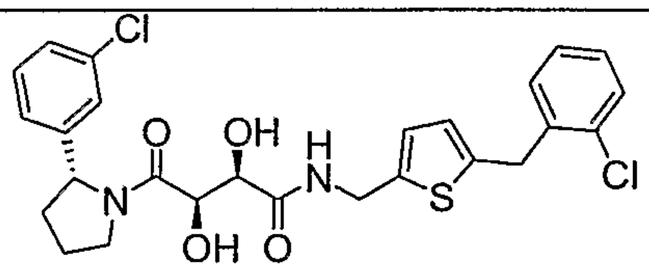
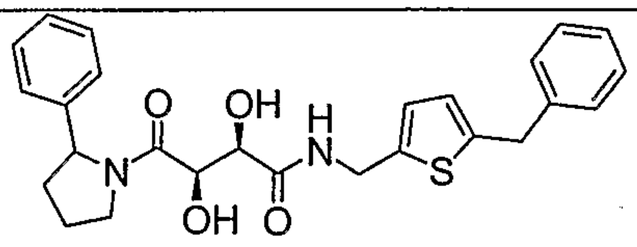
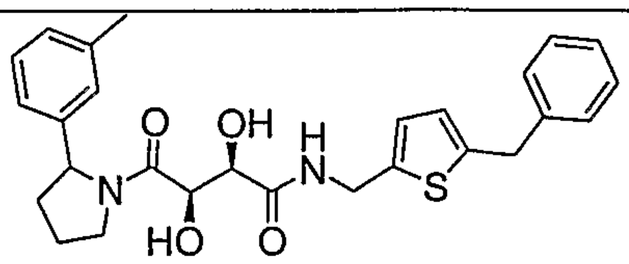
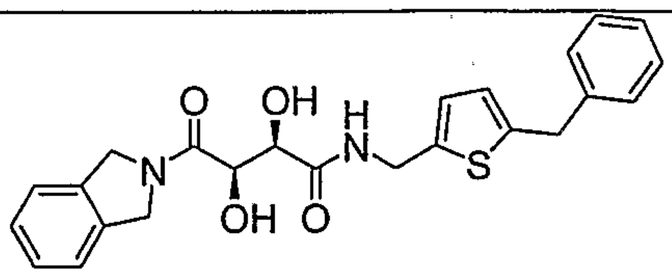
248		
249		
250		
251		
252		
253		
254		
255		

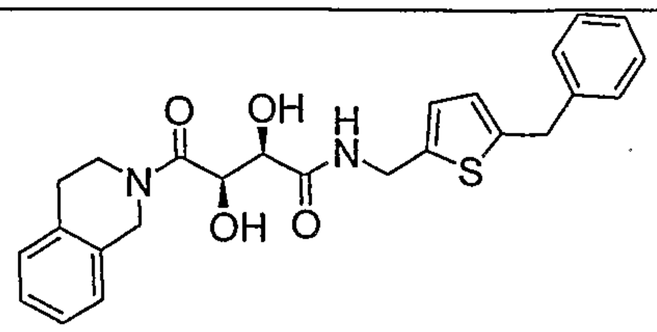
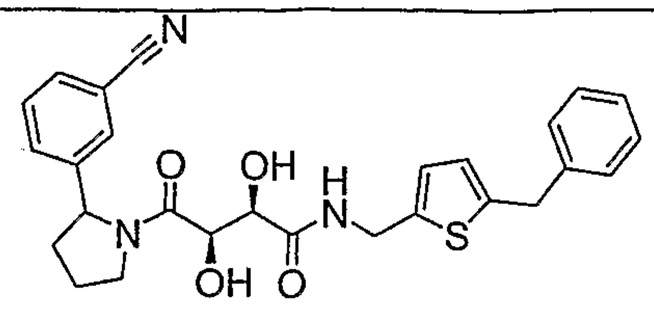
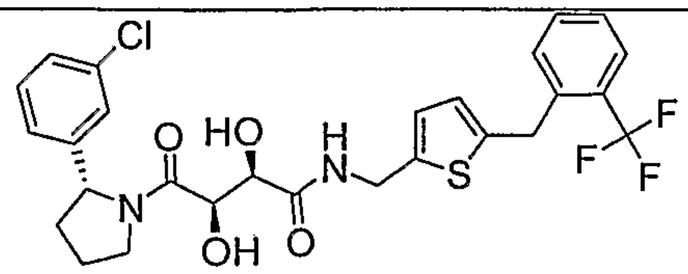
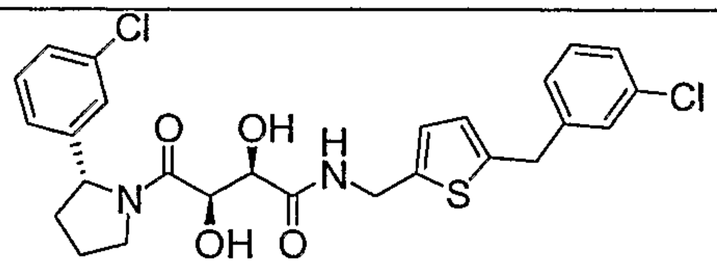
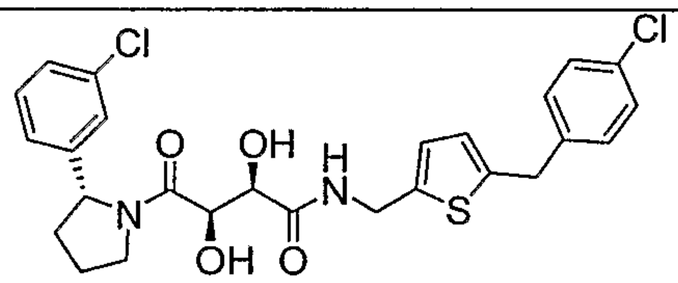
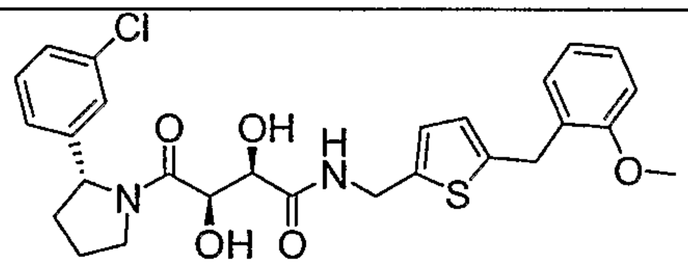
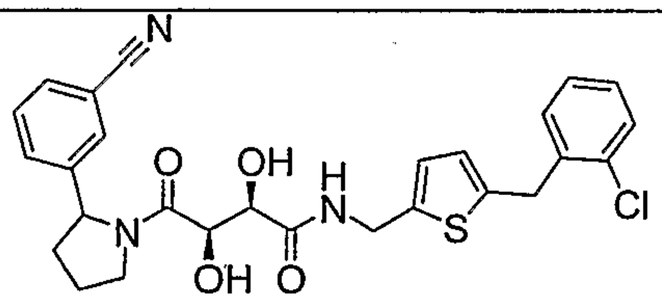
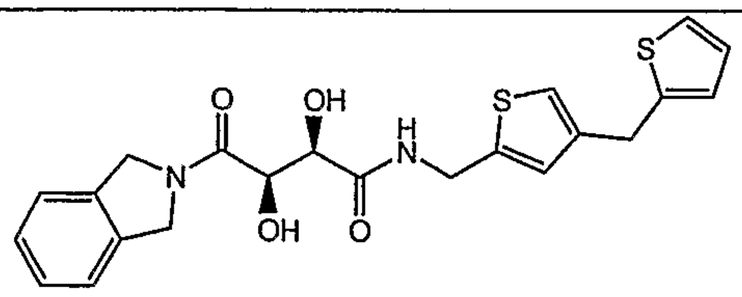
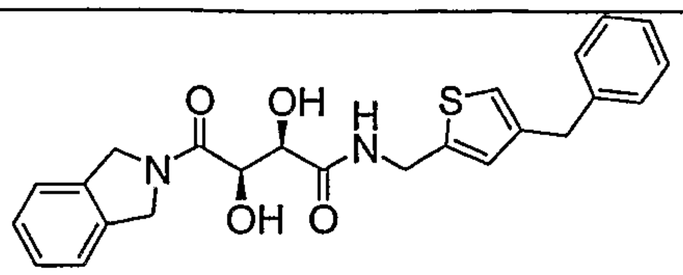
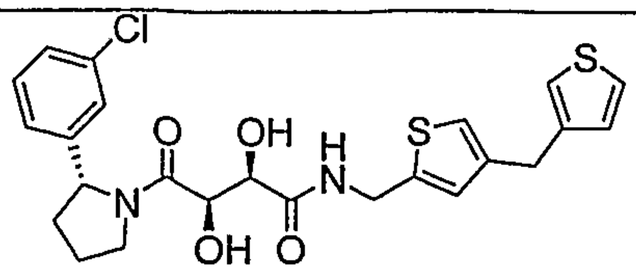
256		
257		
258		
259		
260		
261		
262		

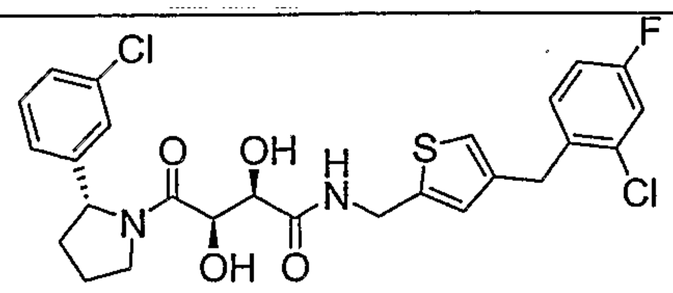
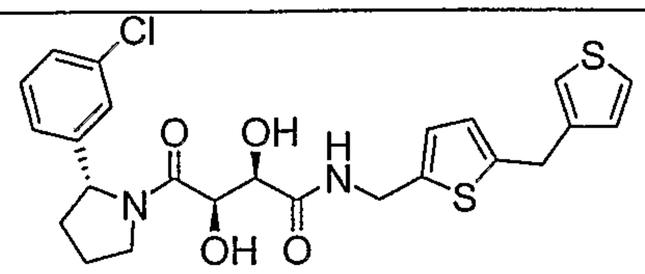
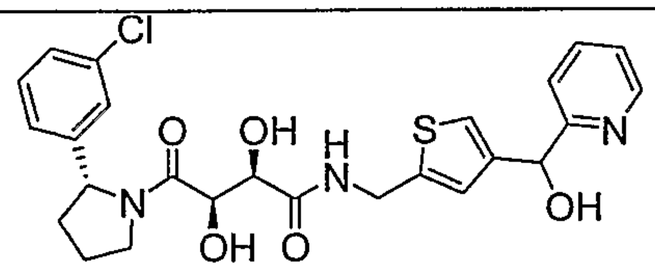
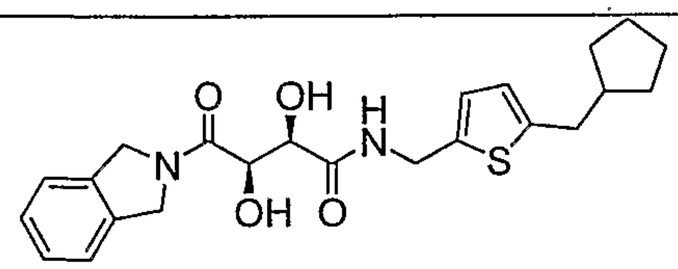
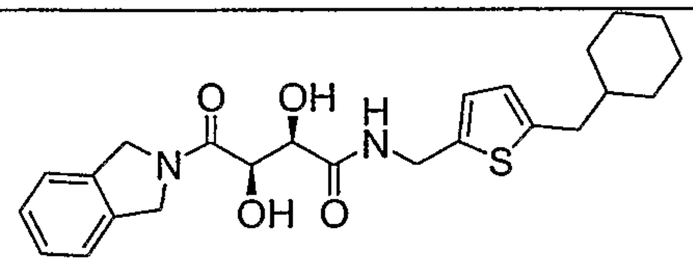
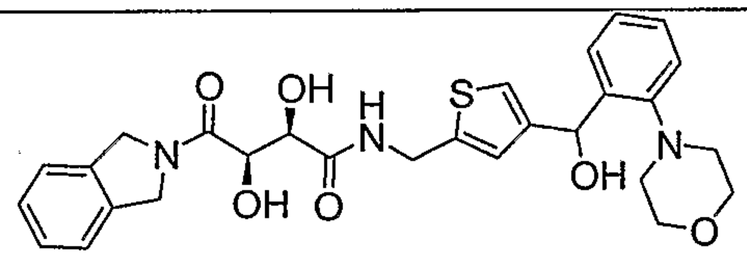
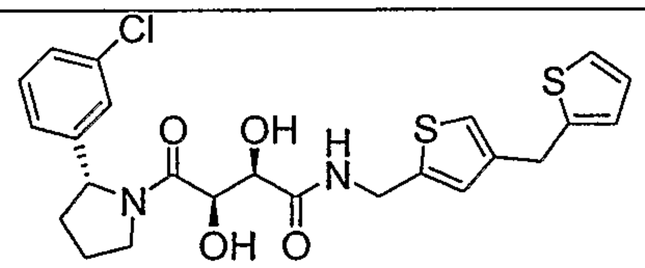
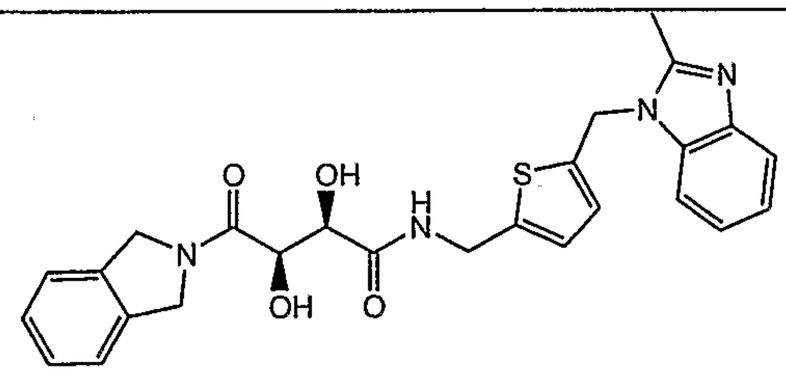
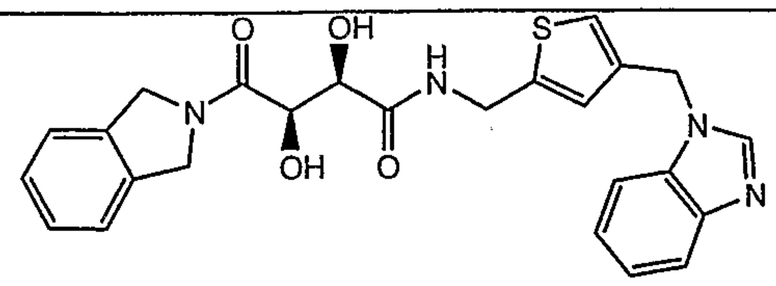
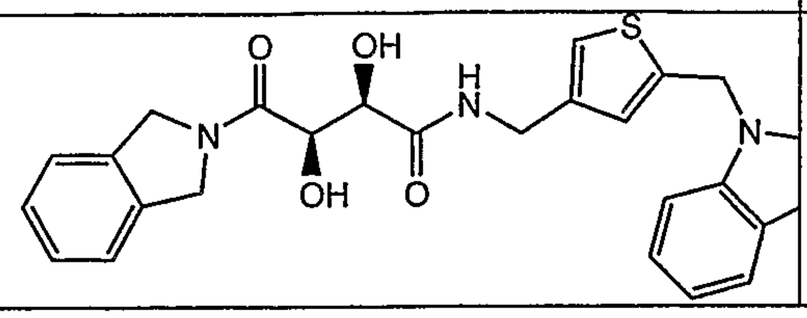
263		
264		
265		
266		
267		
268		
269		
270		

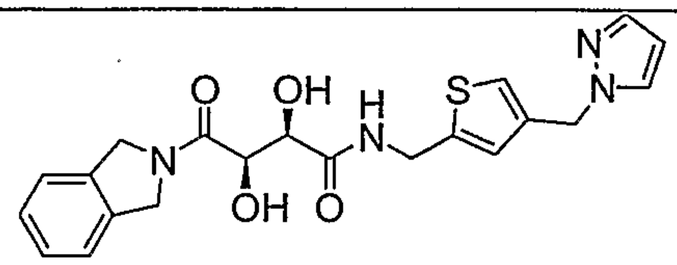
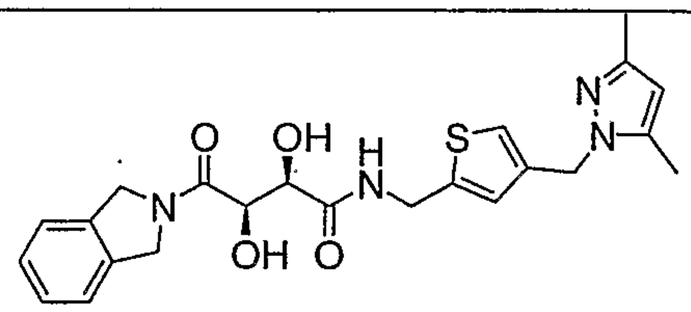
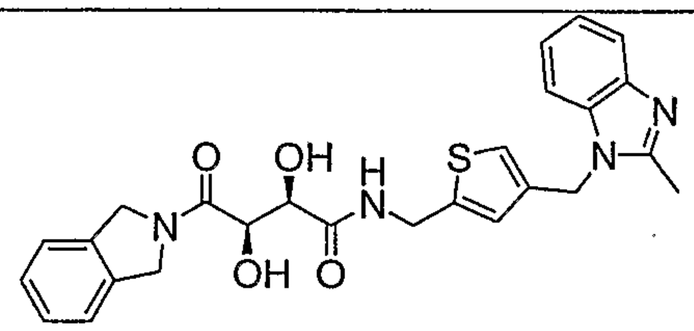
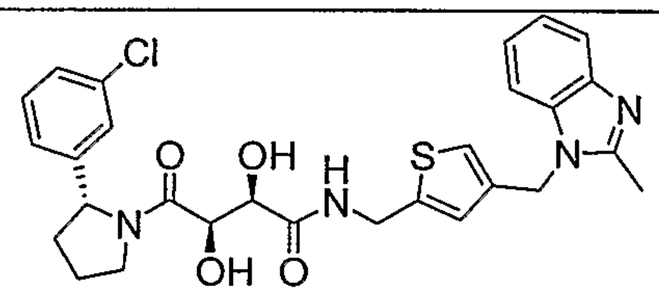
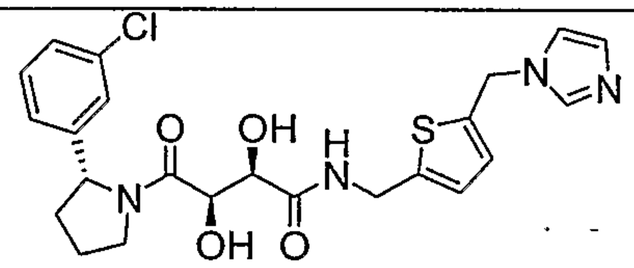
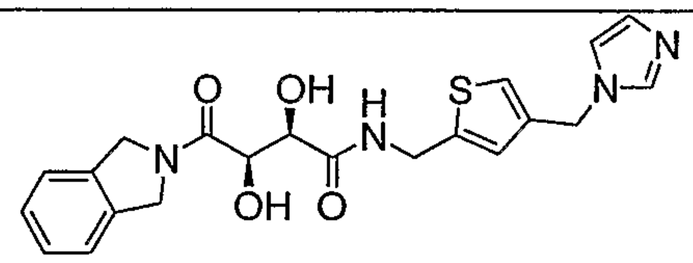
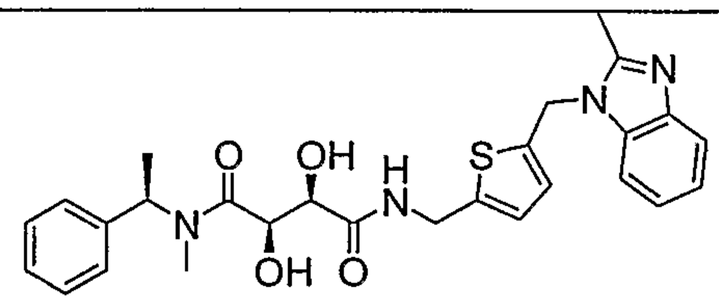
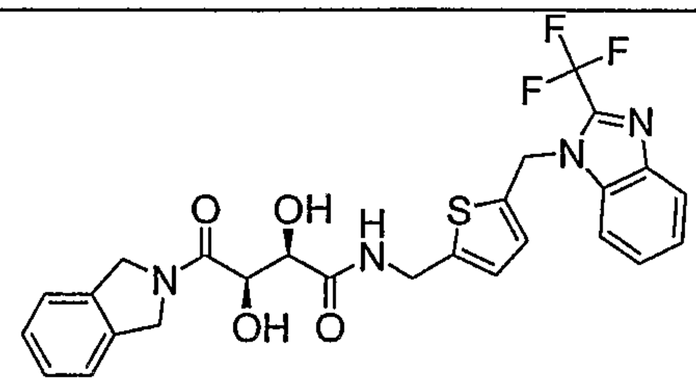
271		
272		
273		
274		
275		
276		
277		
278		
279		

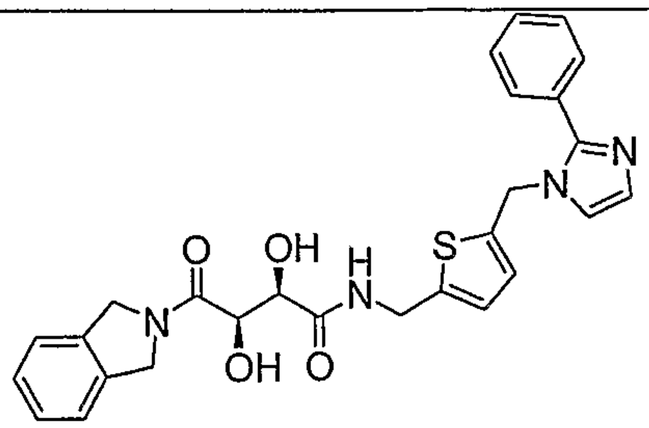
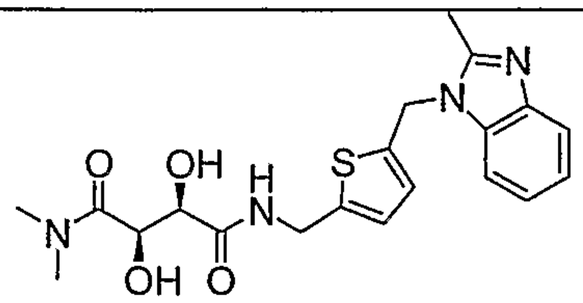
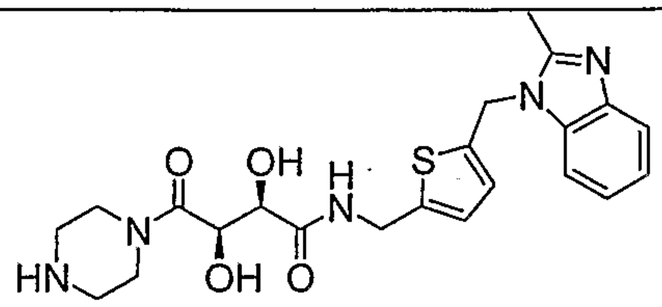
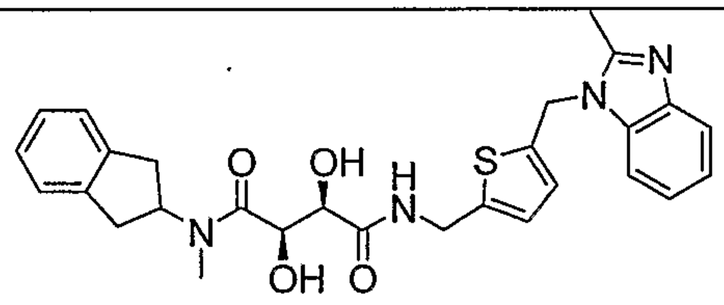
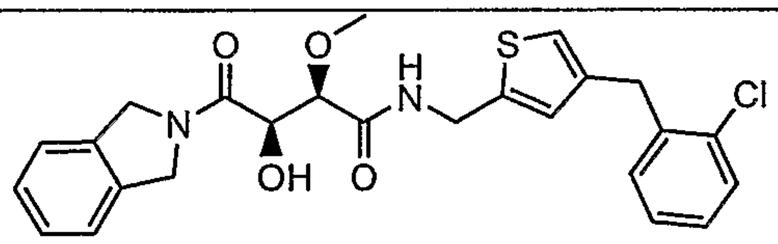
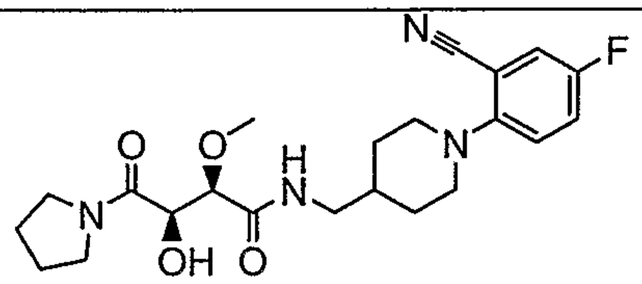
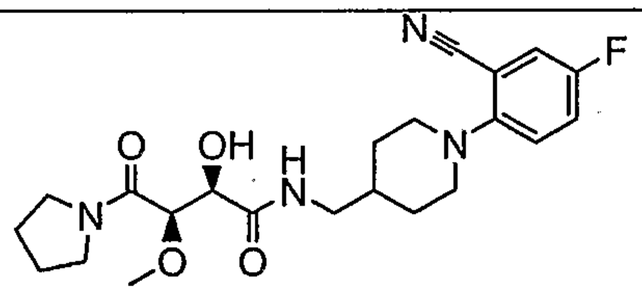
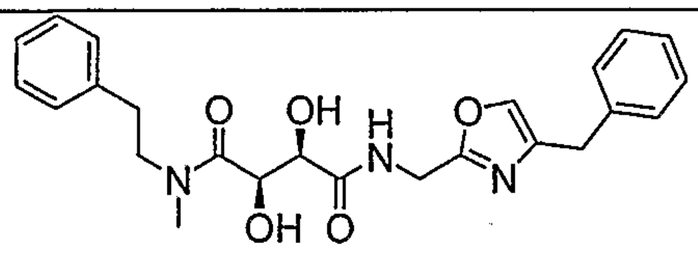
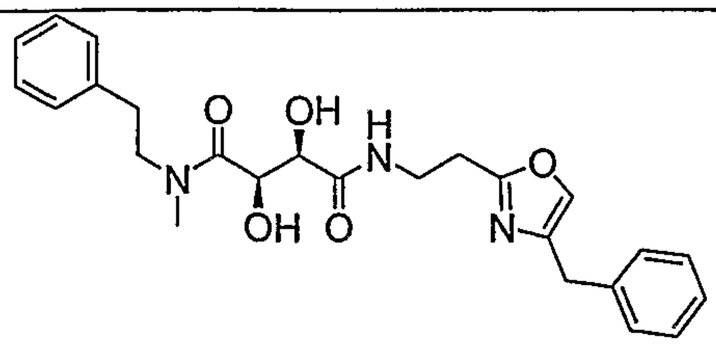
280		
281		
282		
283		
284		
285		
286		
287		
288		

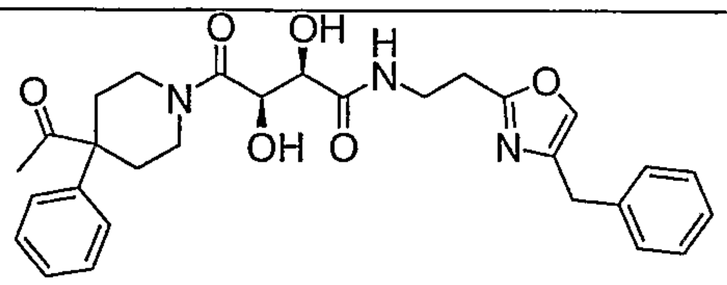
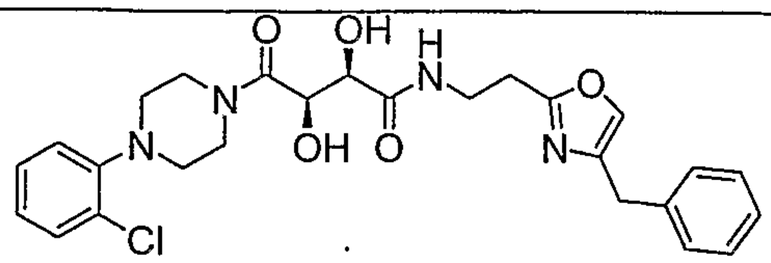
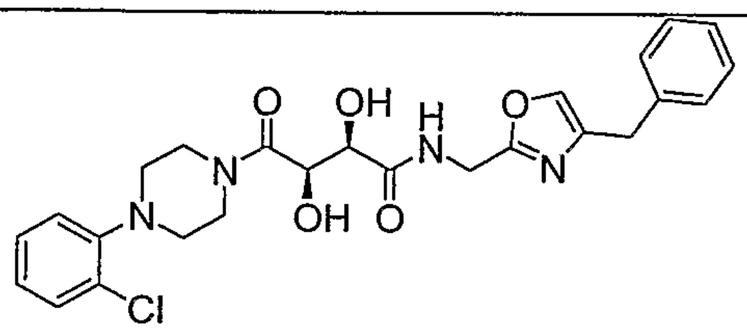
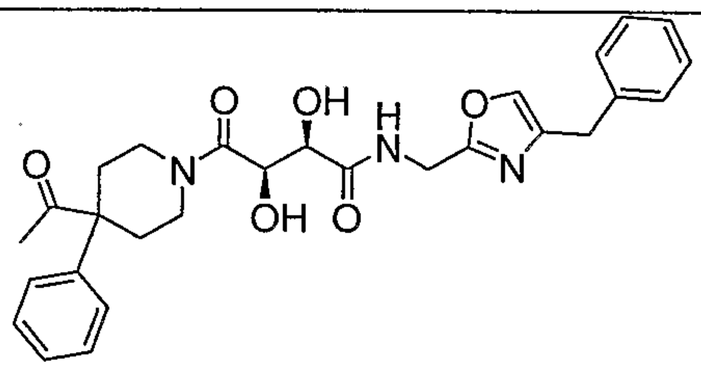
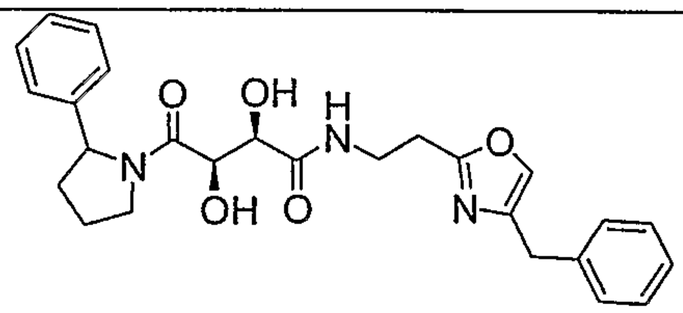
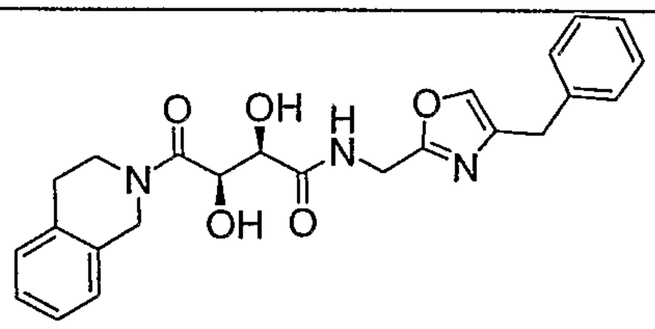
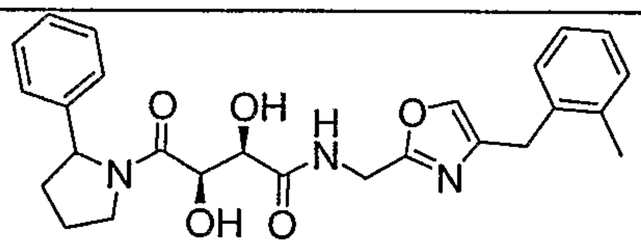
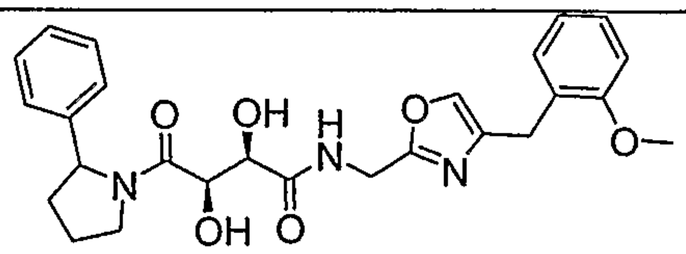
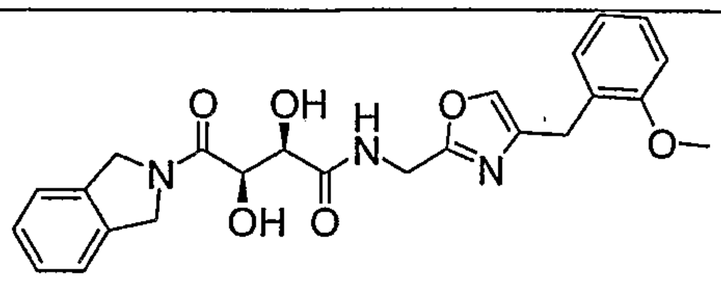
289		
290		
291		
292		
293		
294		
295		
296		
297		

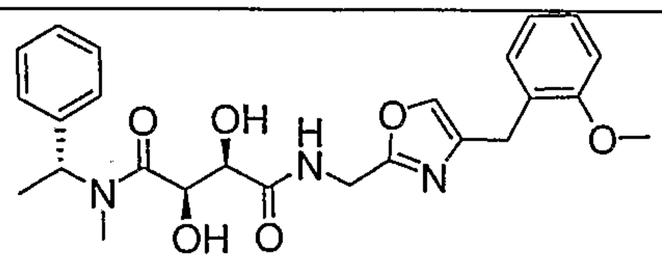
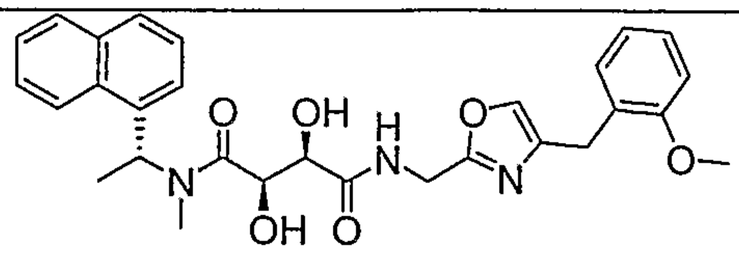
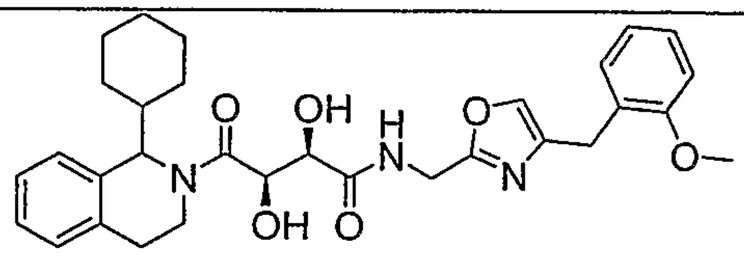
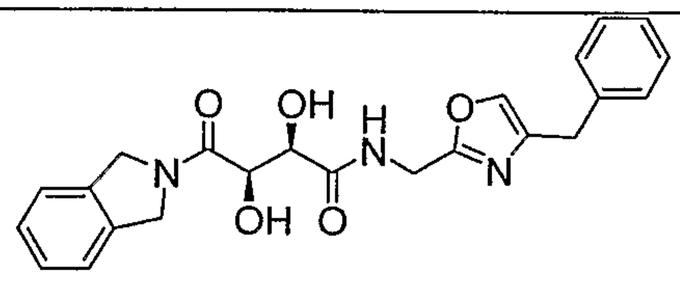
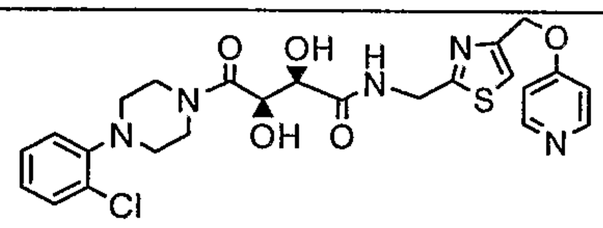
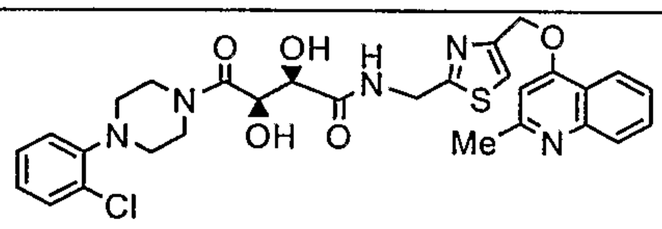
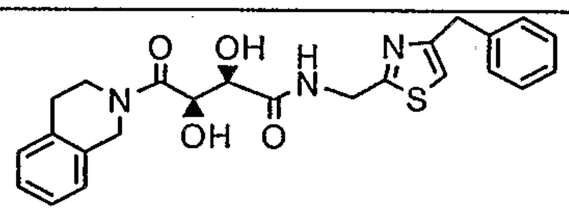
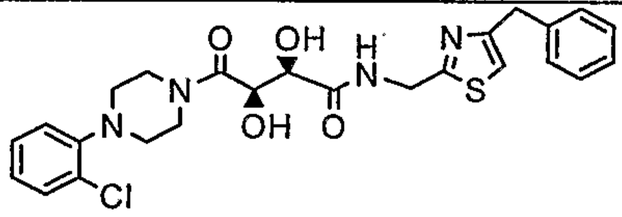
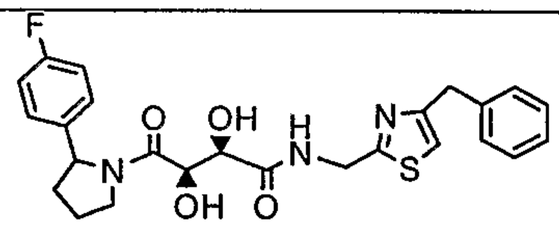
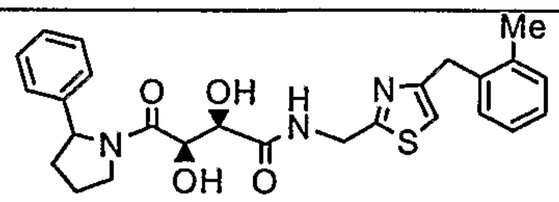
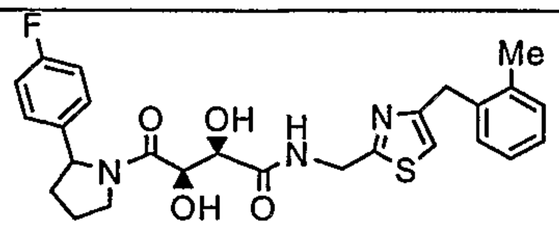
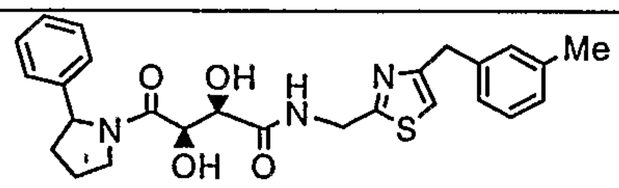
298		
299		
300		
301		
302		
303		
304		
309		
310		
311		

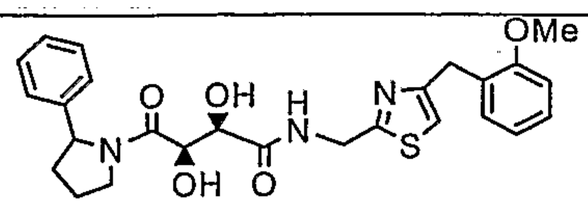
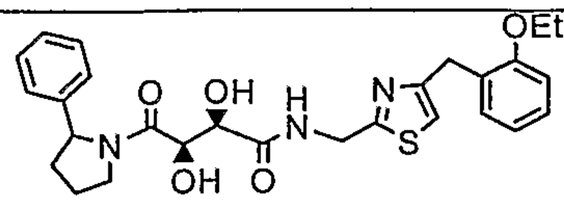
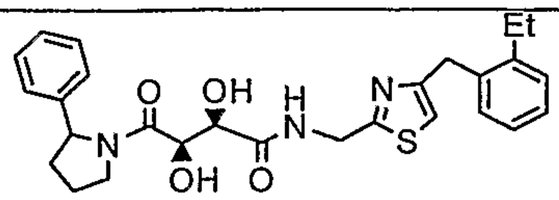
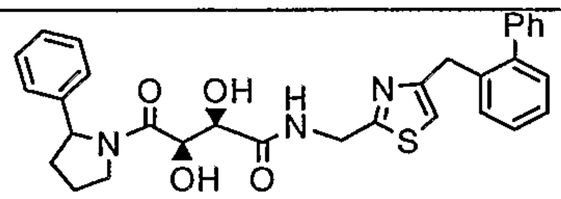
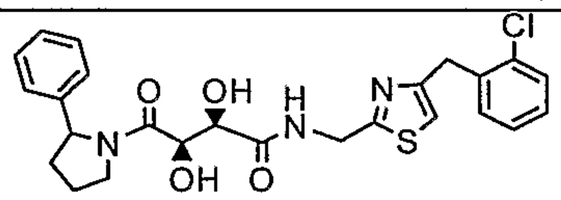
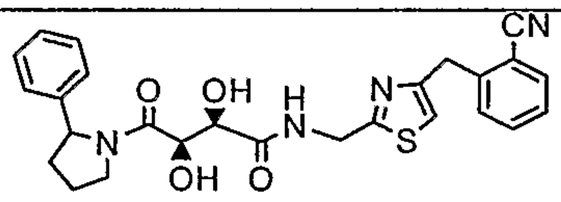
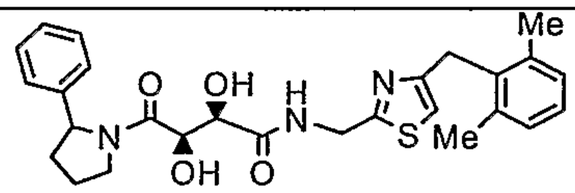
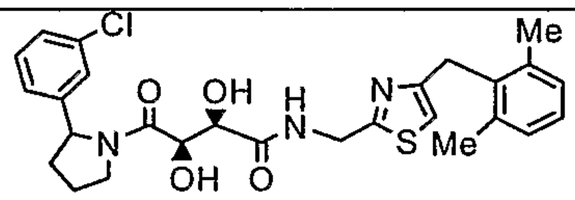
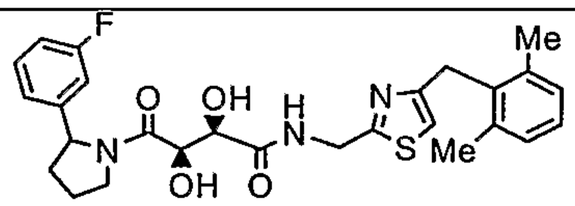
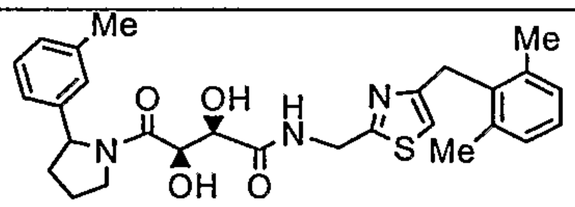
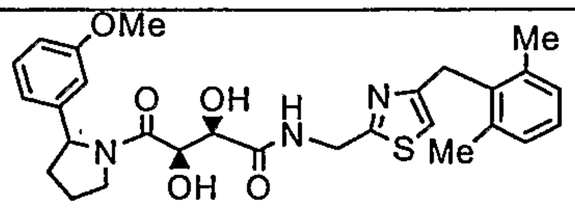
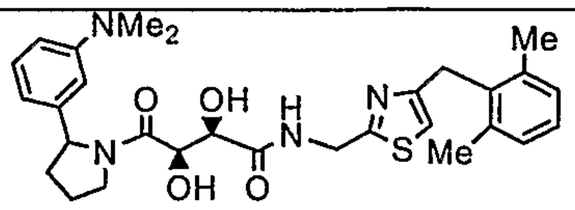
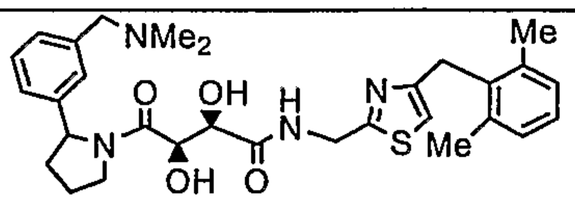
312		
313		
314		
315		
316		
317		
318		
325		
329		
327		

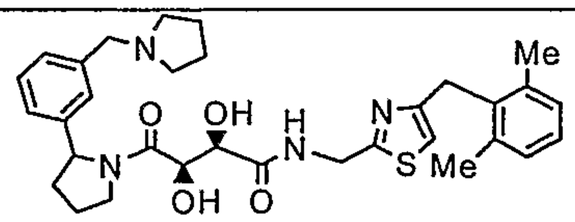
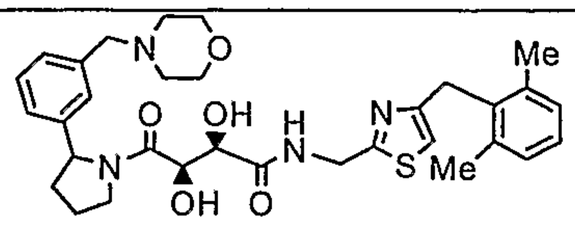
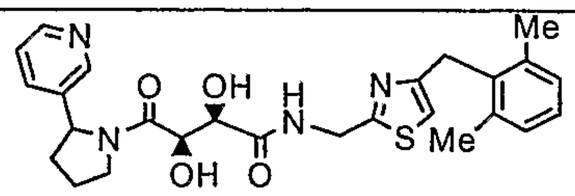
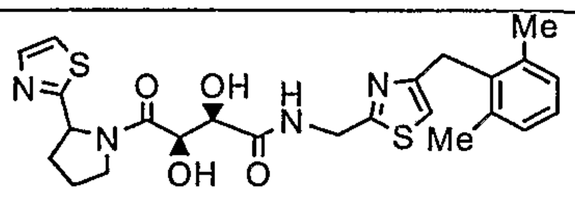
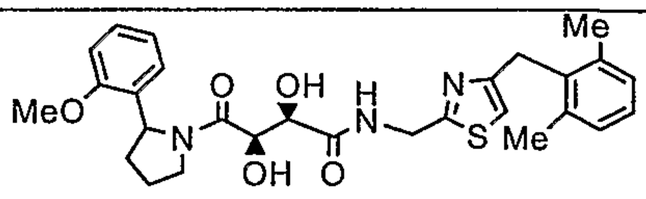
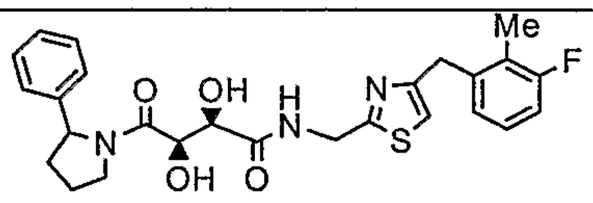
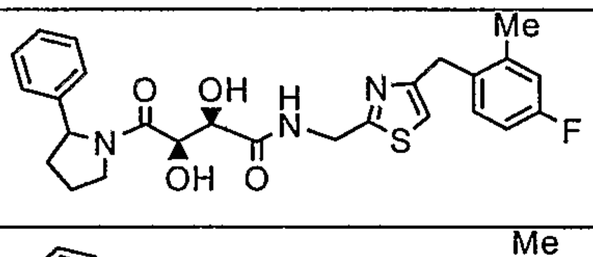
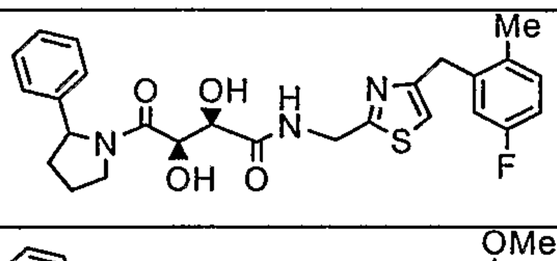
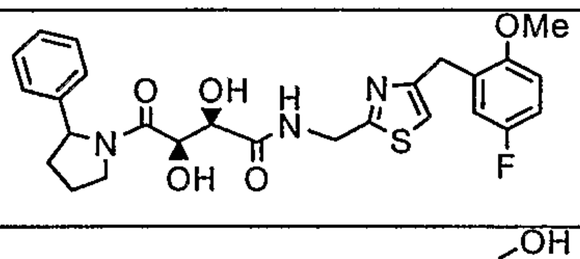
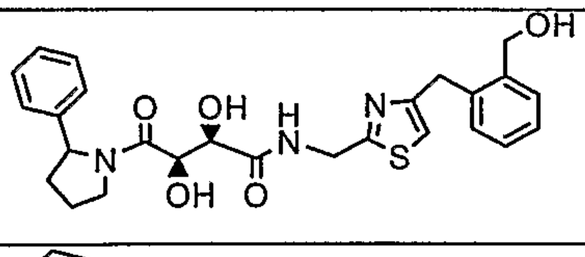
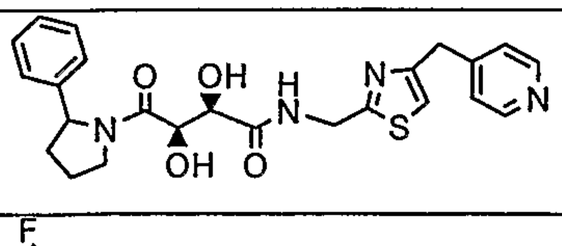
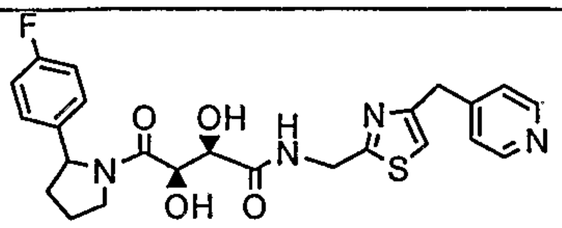
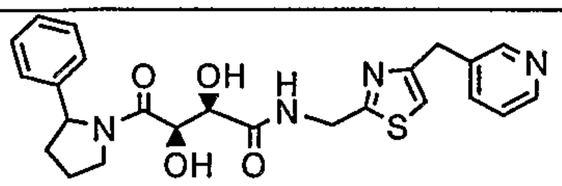
338		
339		
340		
341		
342		
343		
344		
345		

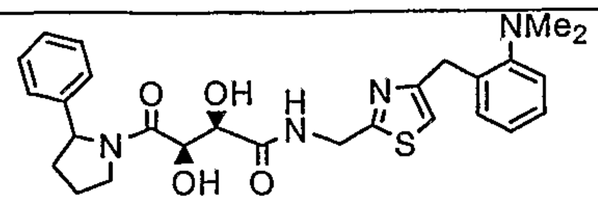
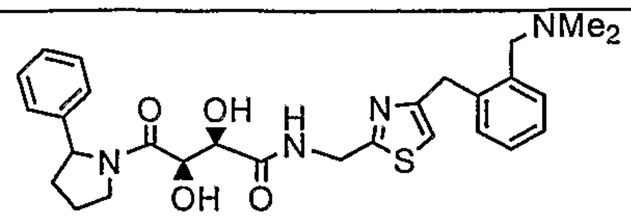
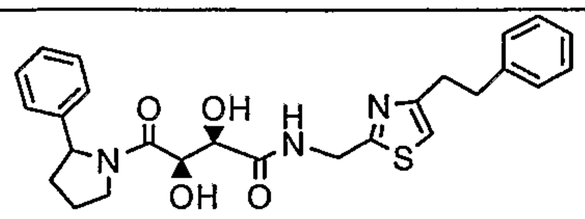
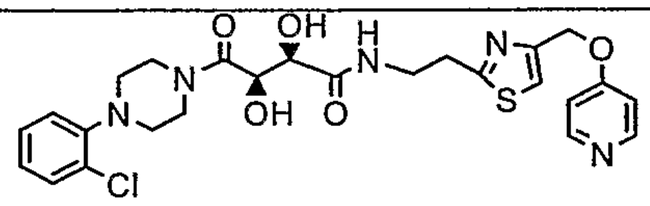
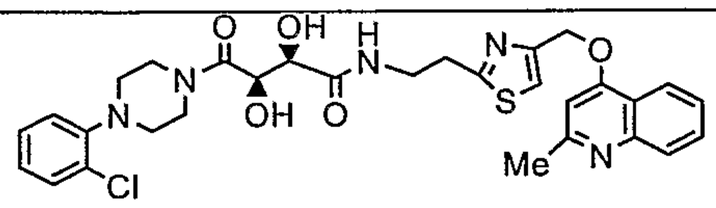
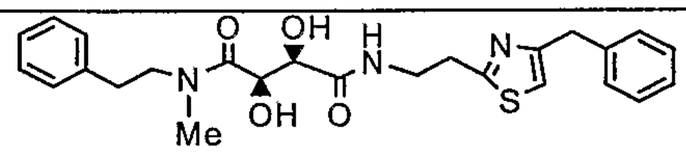
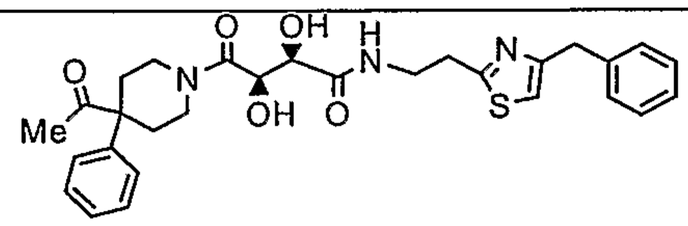
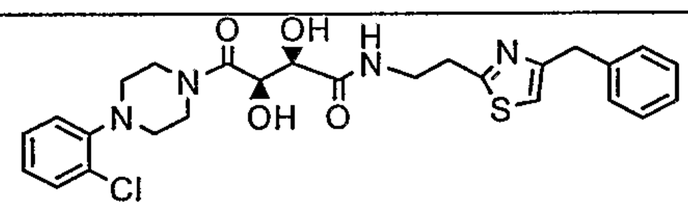
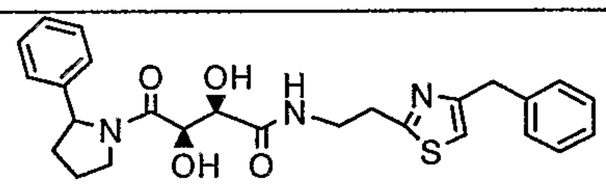
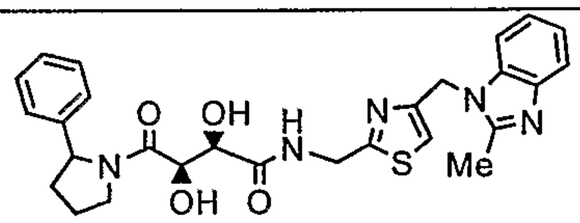
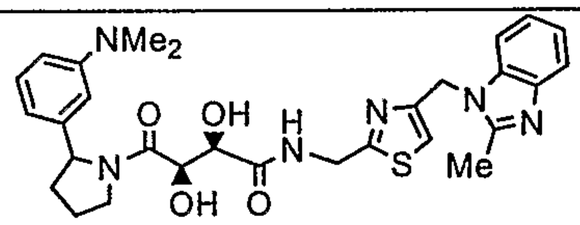
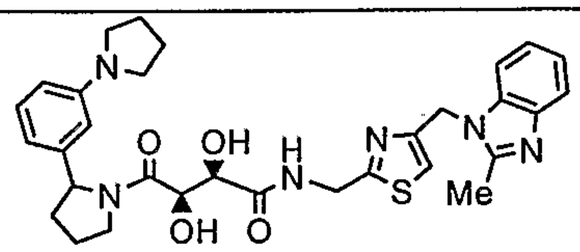
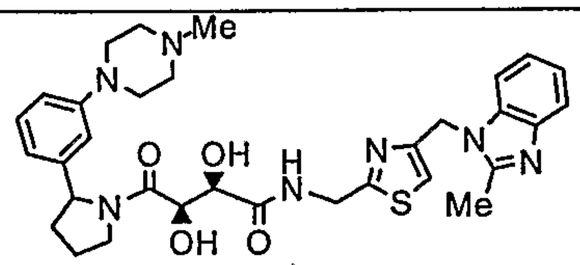
346		
347		
348		
349		
350		
351		
352		
375		
376		

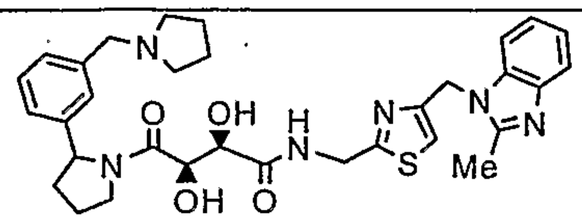
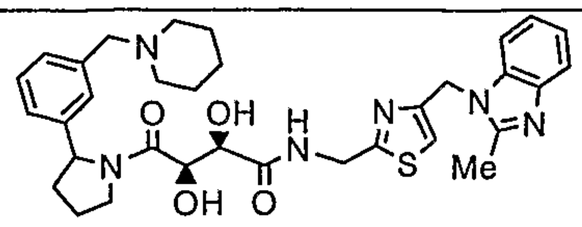
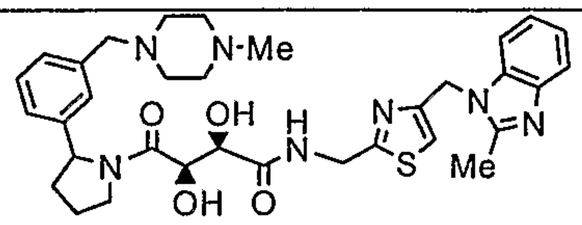
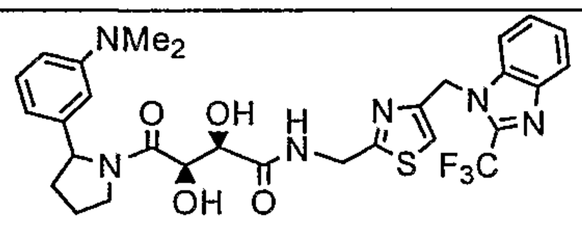
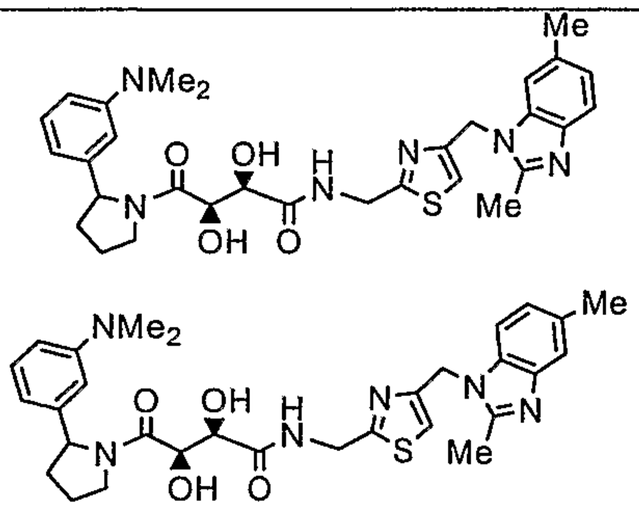
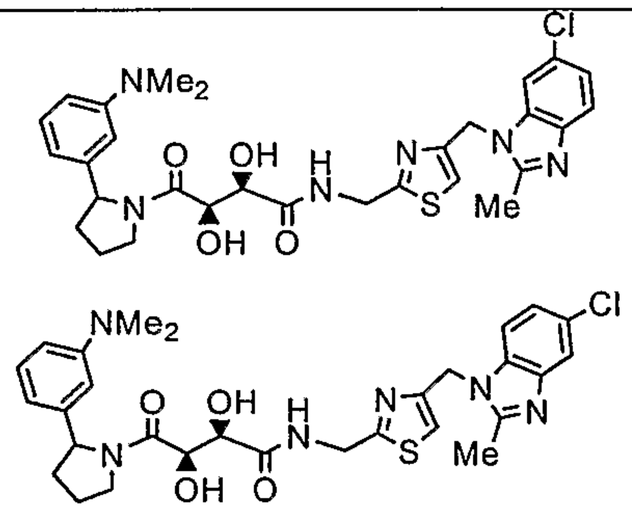
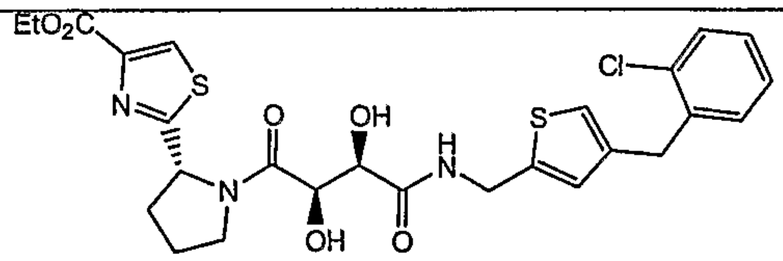
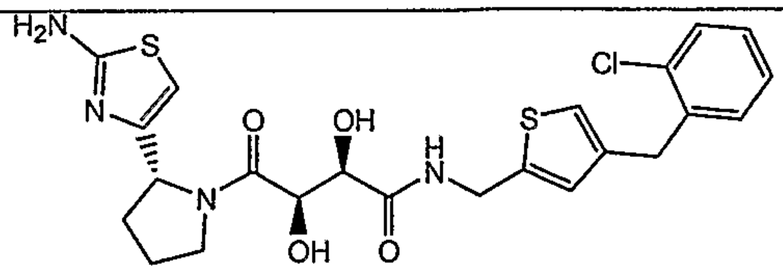
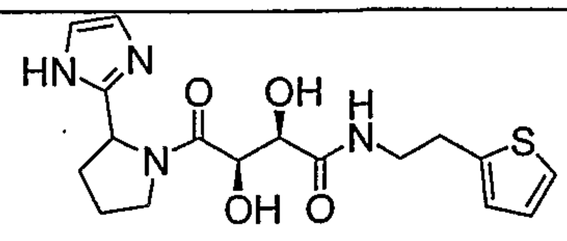
377		
378		
379		
380		
381		
382		
383		
384		
174		

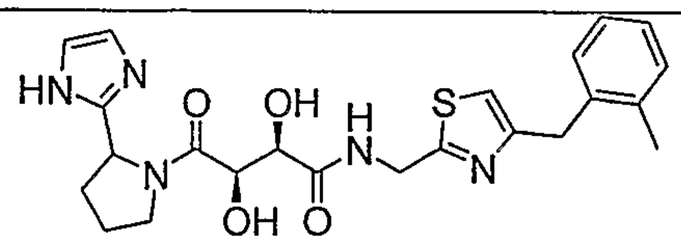
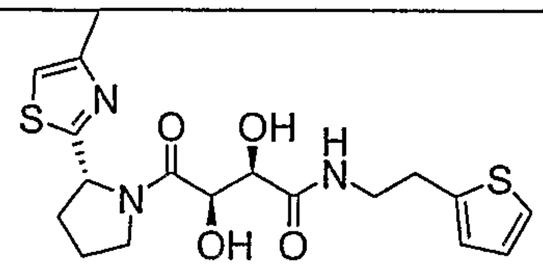
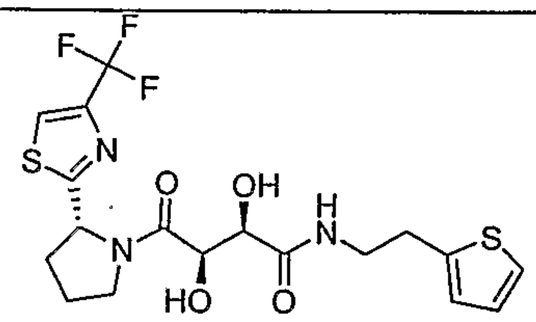
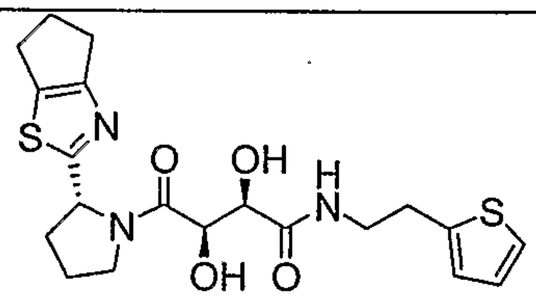
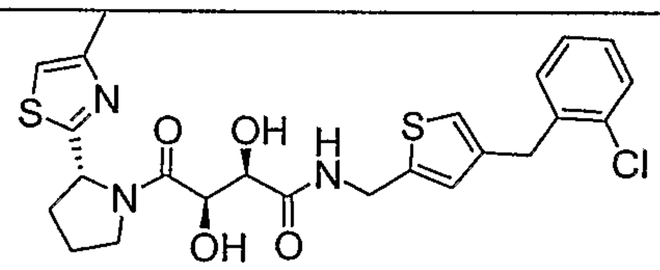
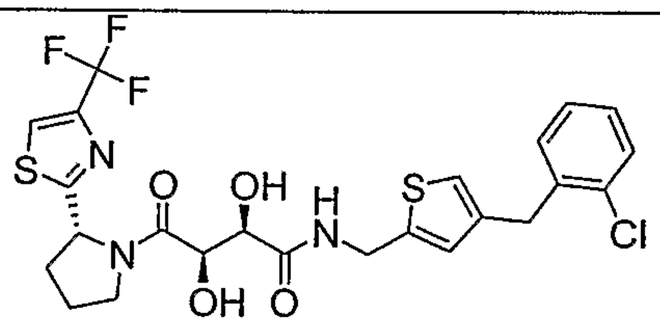
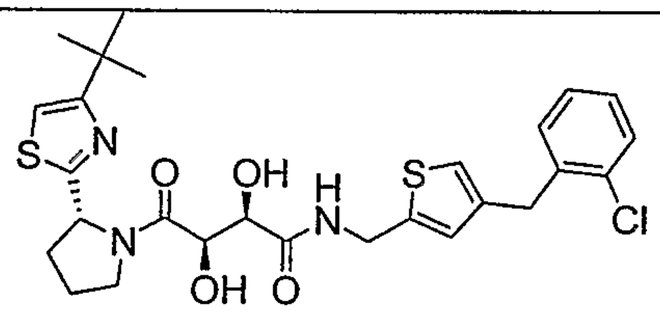
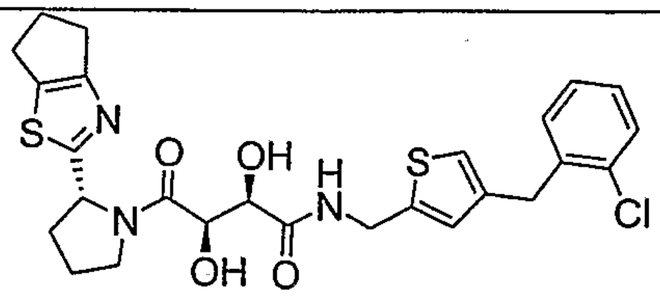
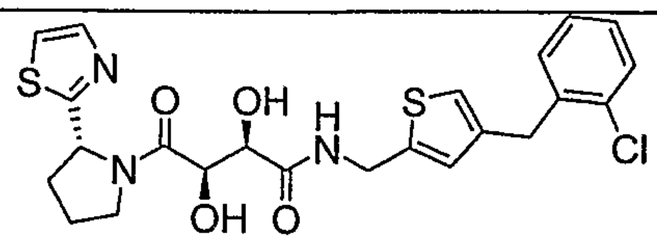
175		
179		
181		
182		
396		
397		
398		
399		
400		
401		
402		
403		

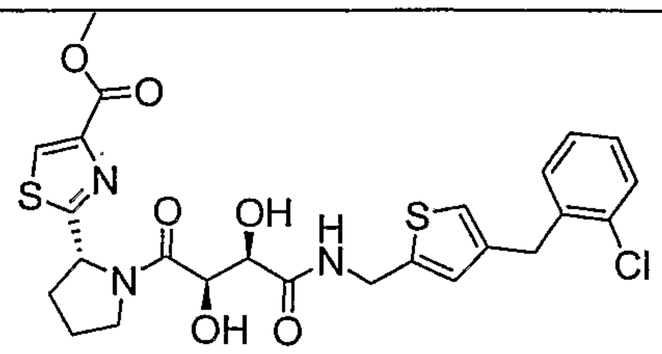
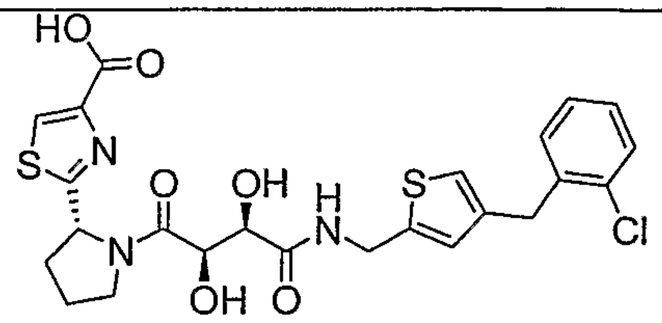
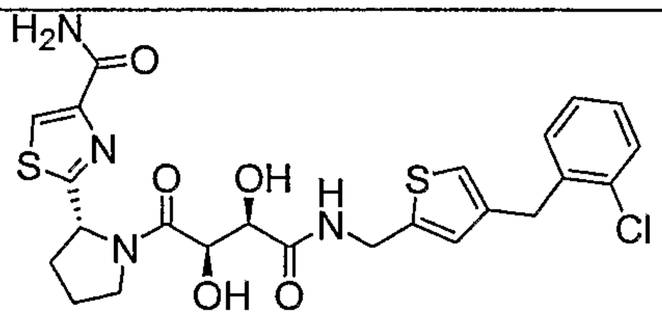
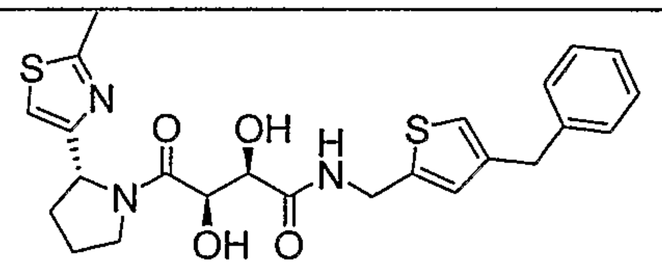
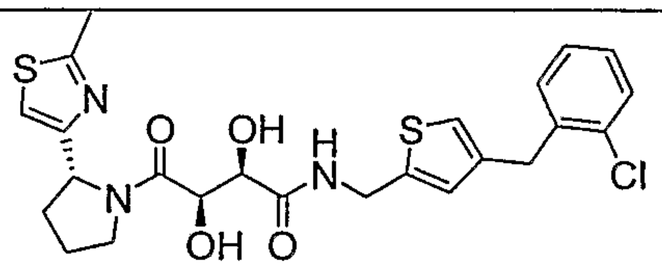
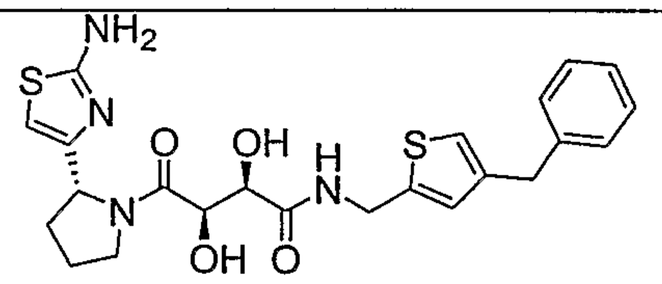
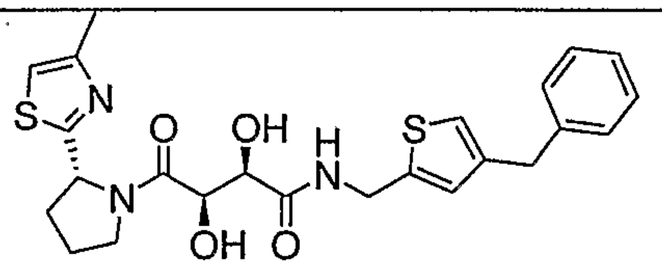
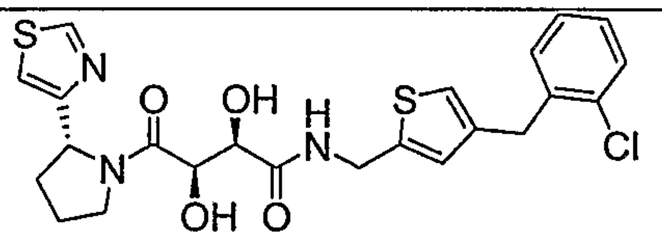
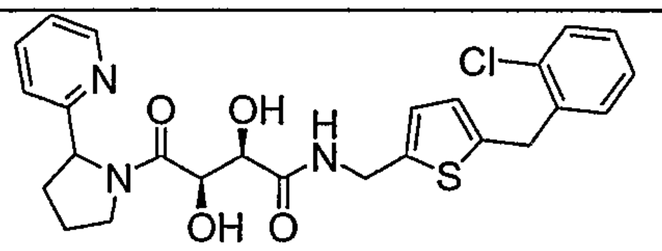
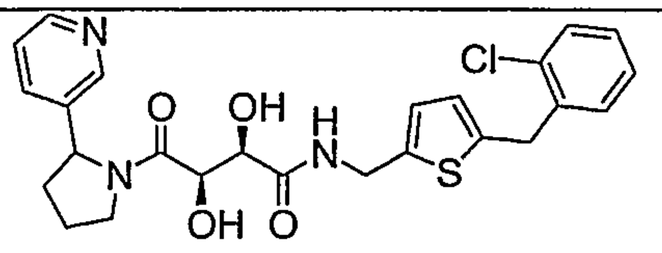
404		
405		
406		
407		
408		
409		
410		
411		
412		
413		
414		
415		
416		

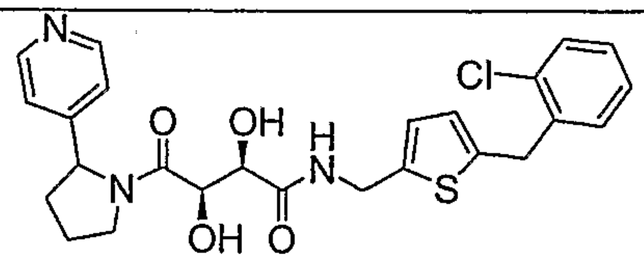
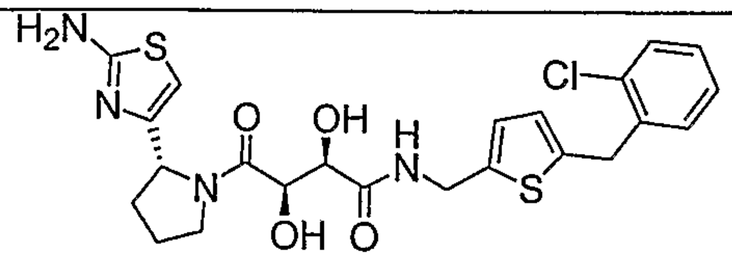
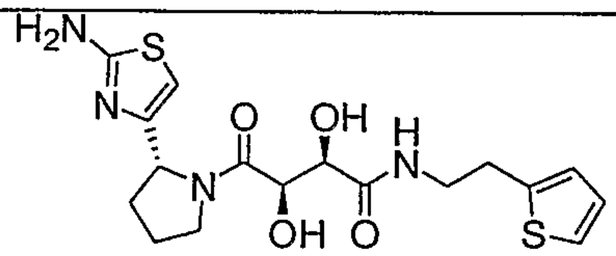
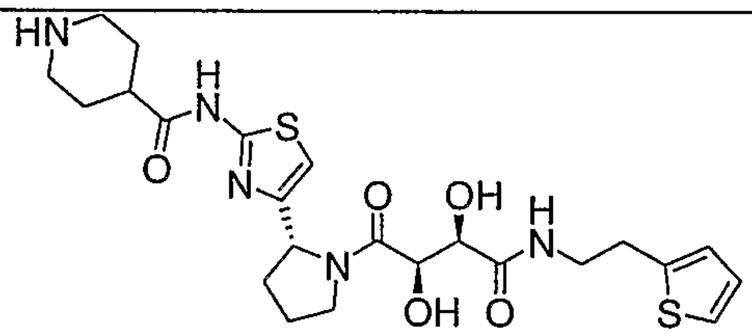
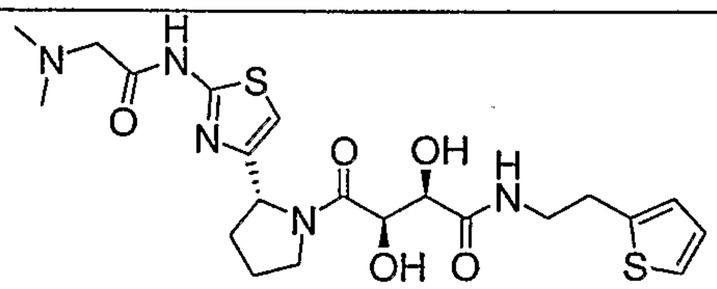
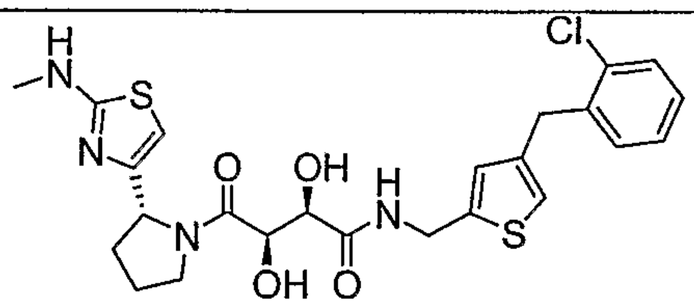
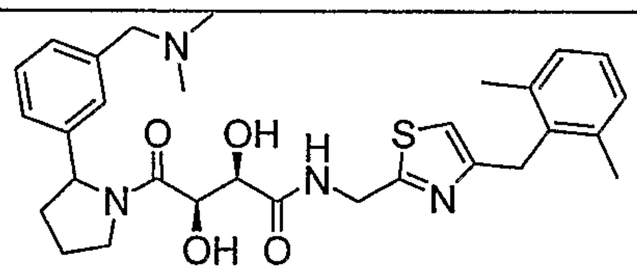
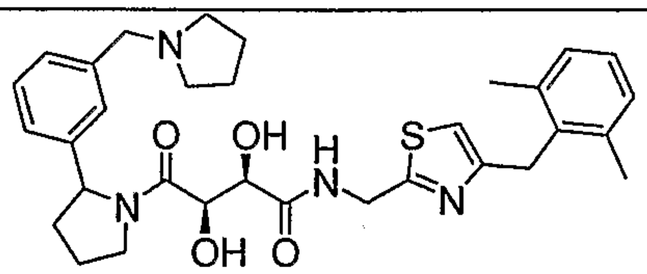
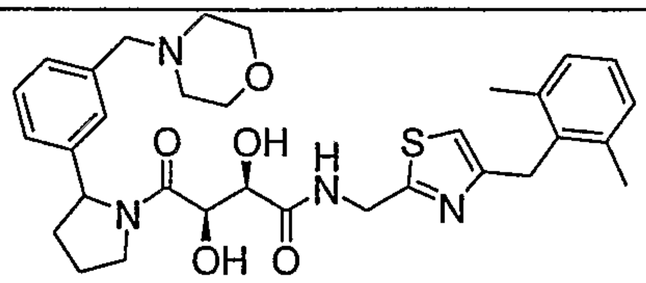
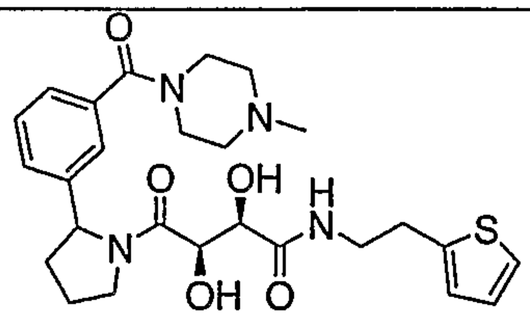
417		
418		
419		
420		
421		
422		
423		
424		
425		
426		
427		
428		
429		

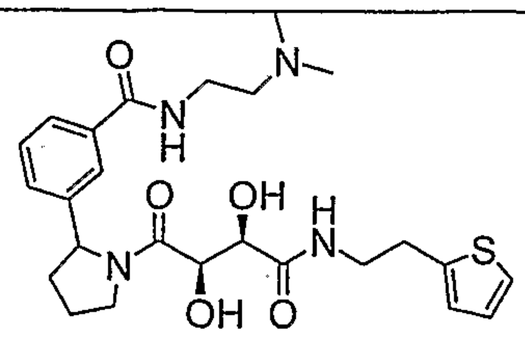
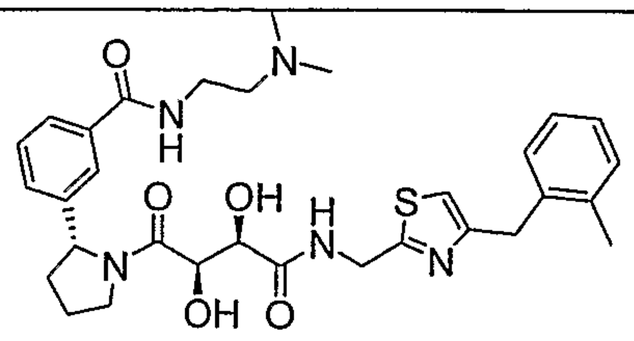
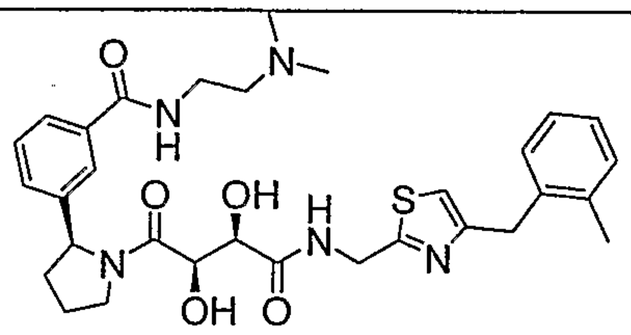
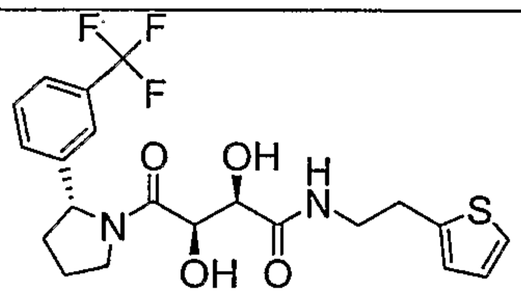
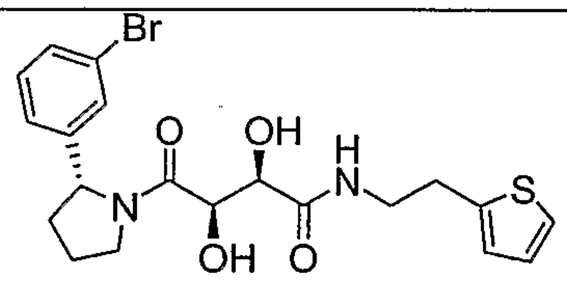
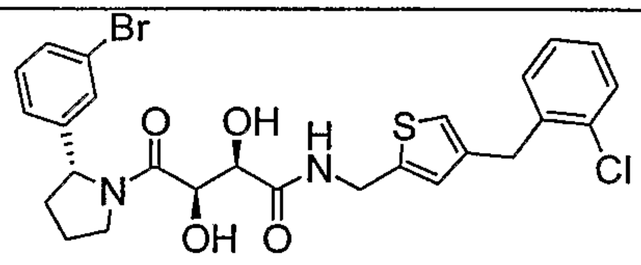
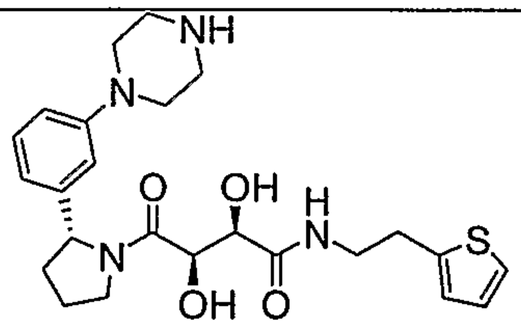
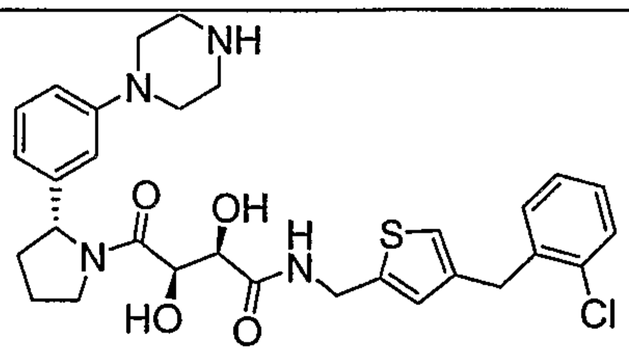
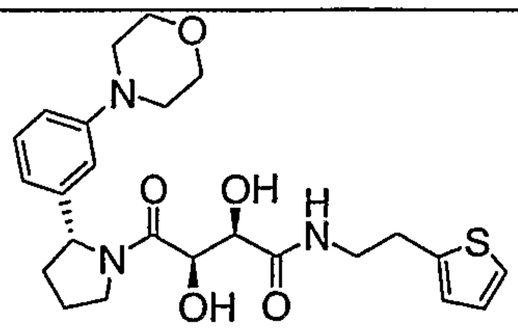
430		
431		
432		
433		
434		
435		
436		
437		
438		
439		
440		
441		
442		

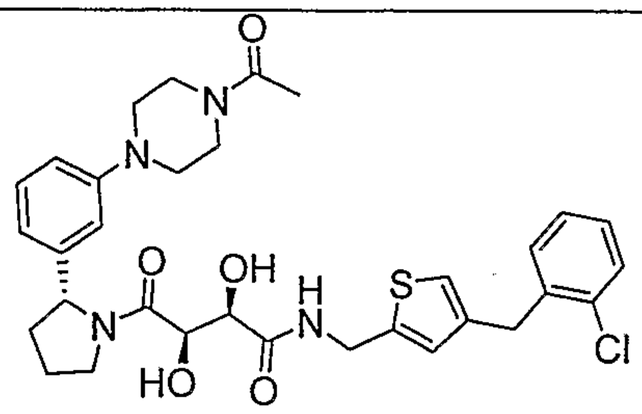
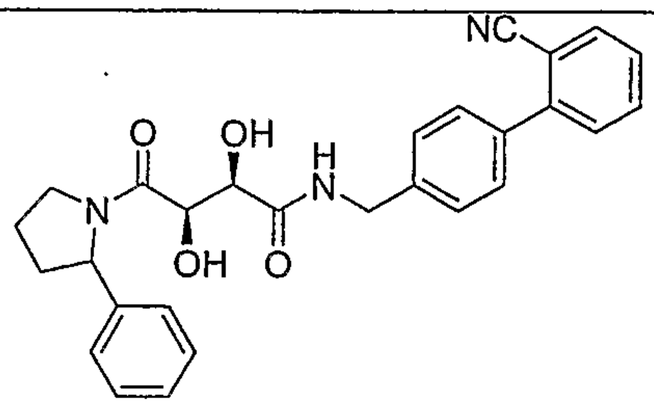
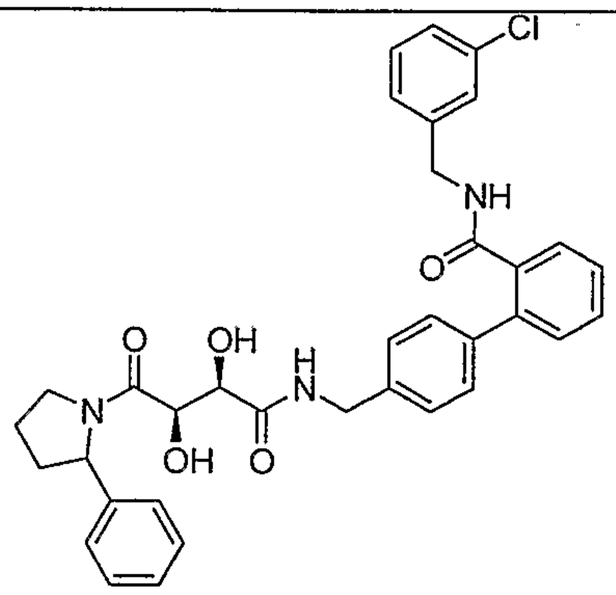
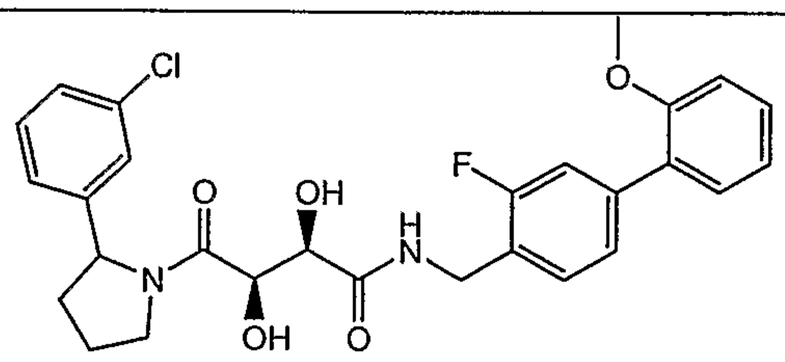
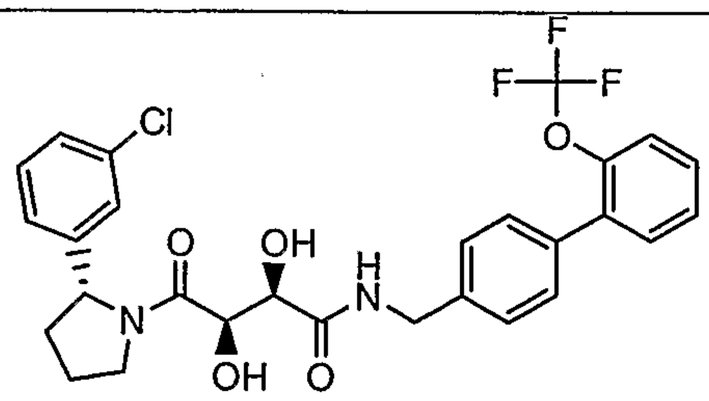
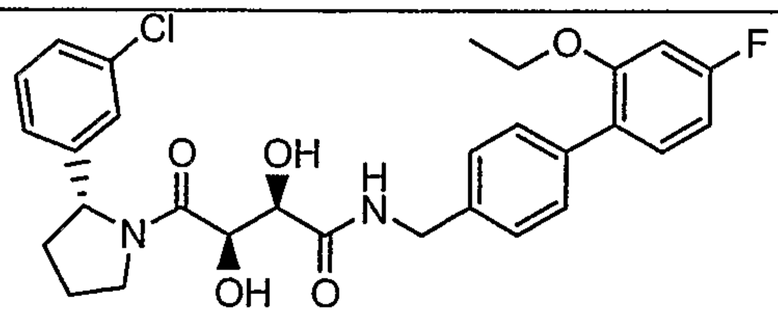
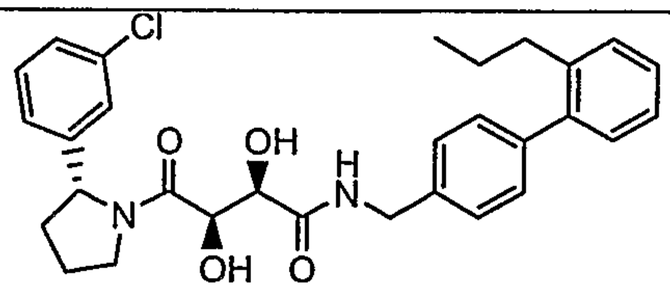
443		
444		
445		
446		
447		
448		
468		
473		
477		

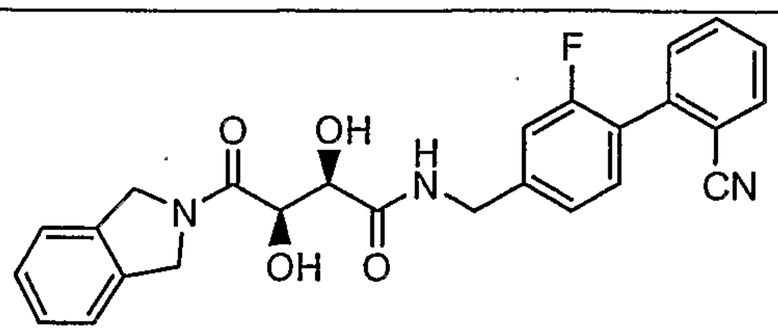
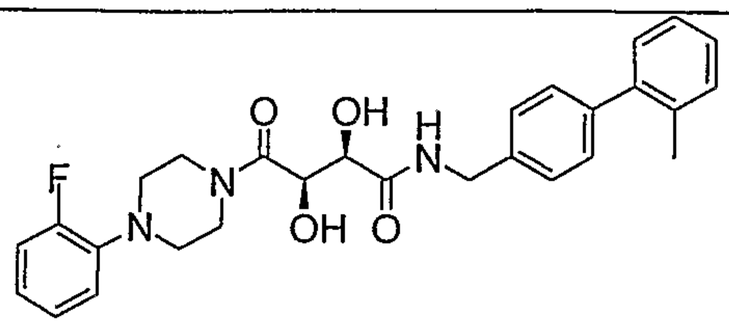
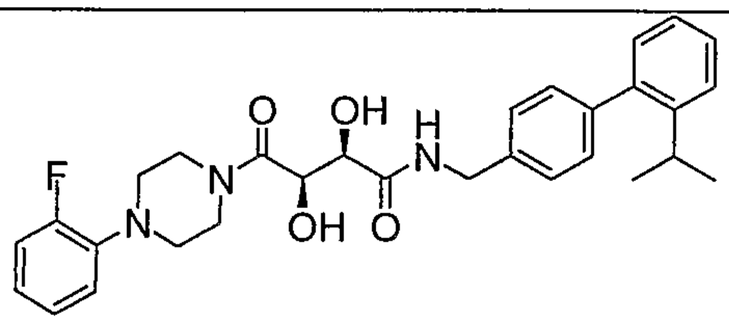
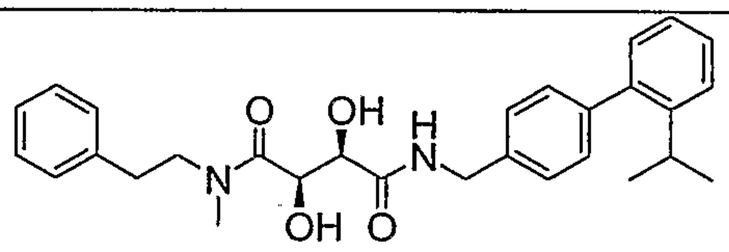
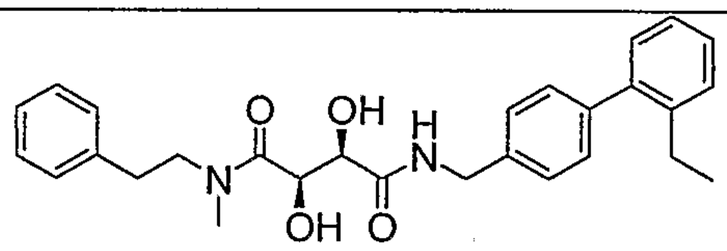
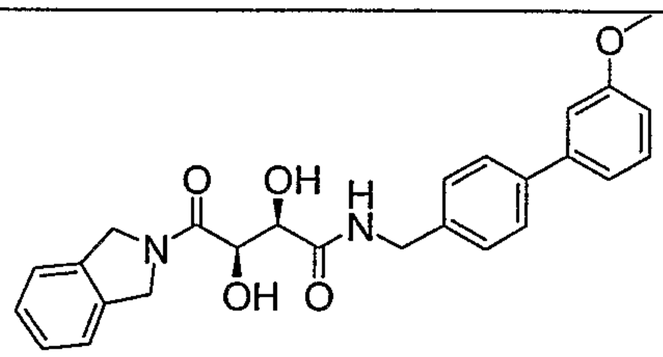
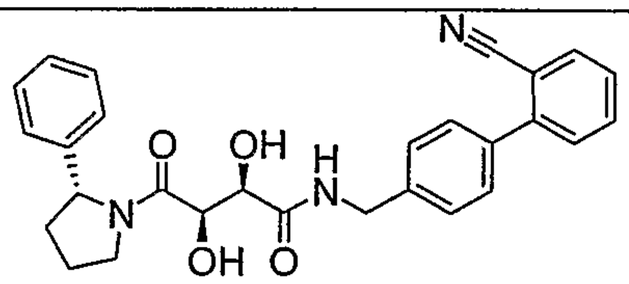
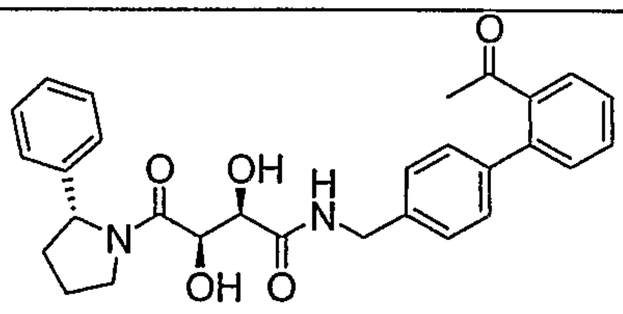
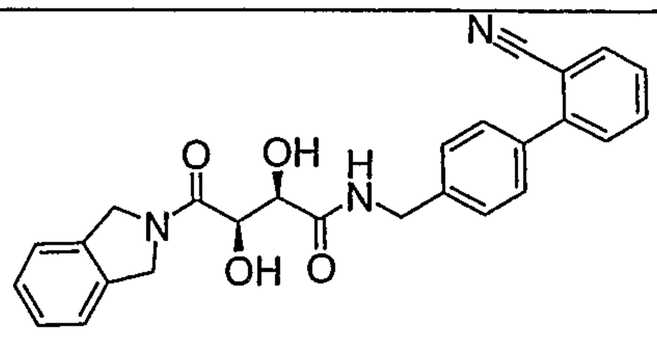
478		
479		
480		
481		
482		
483		
484		
485		
486		

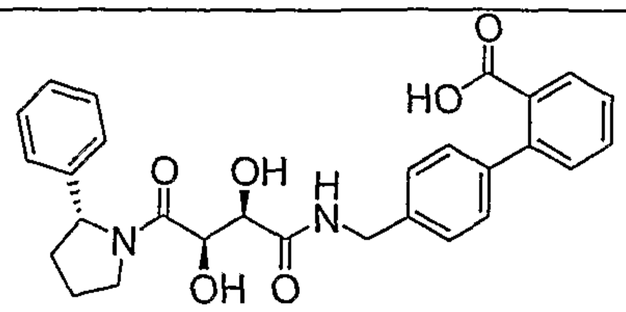
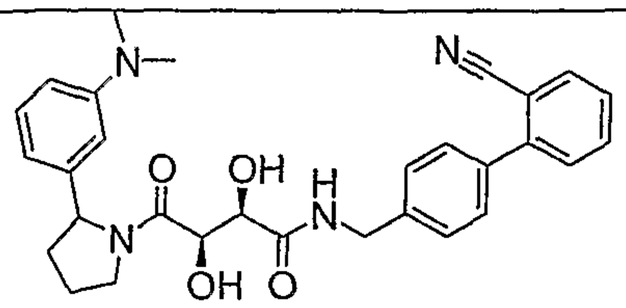
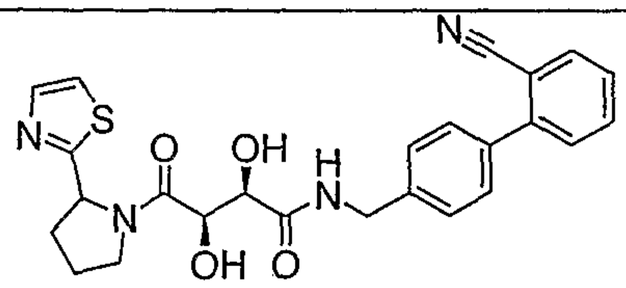
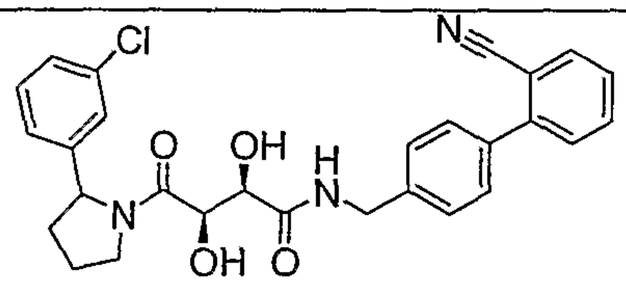
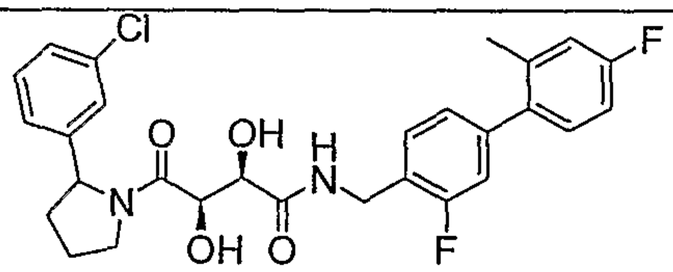
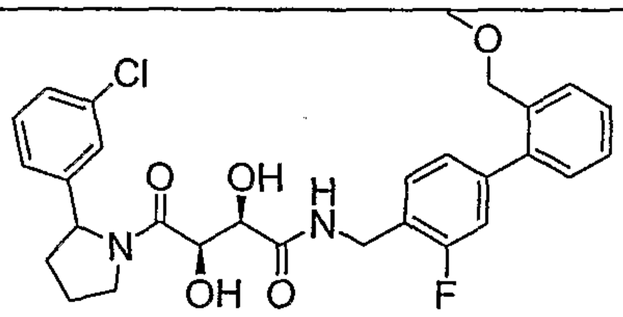
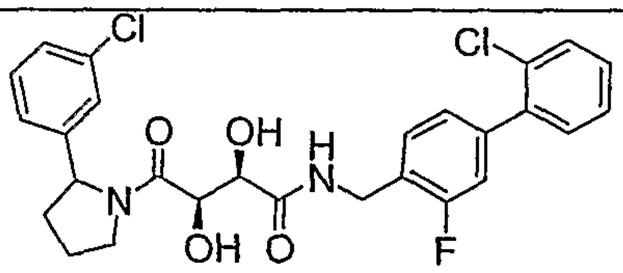
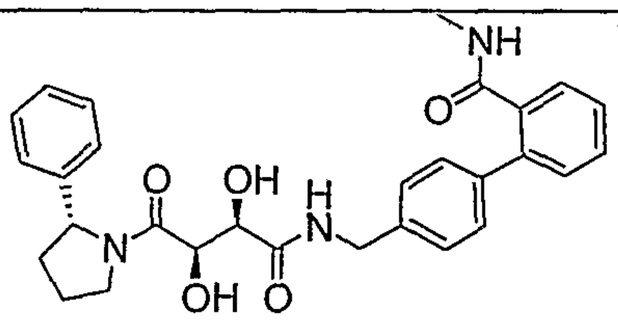
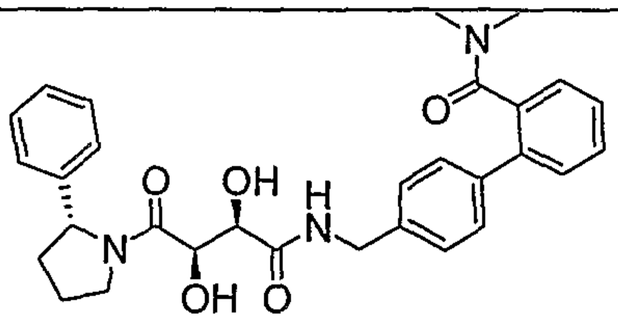
487		
488		
489		
490		
491		
492		
493		
494		
495		
496		

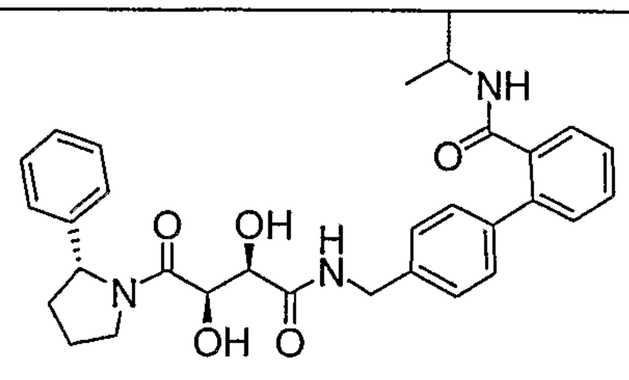
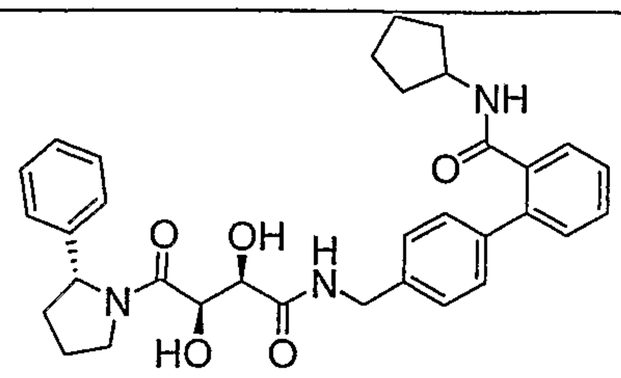
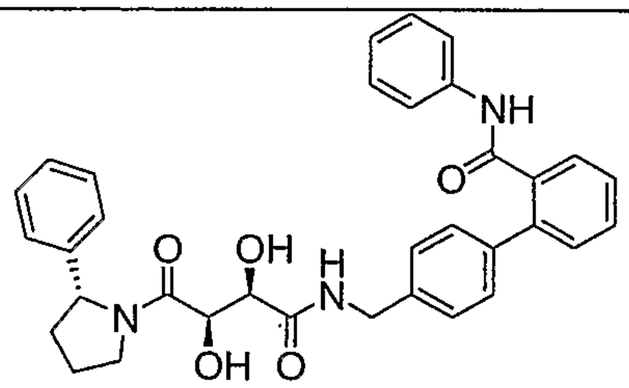
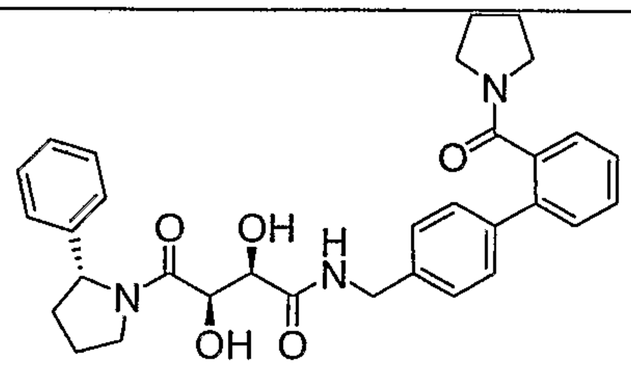
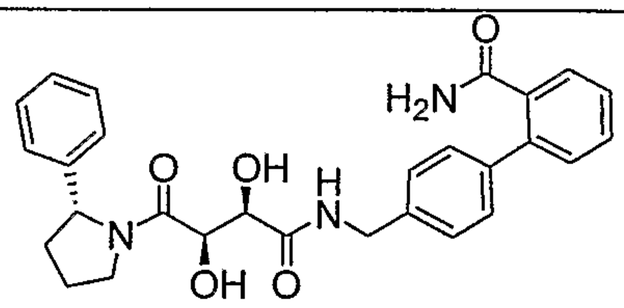
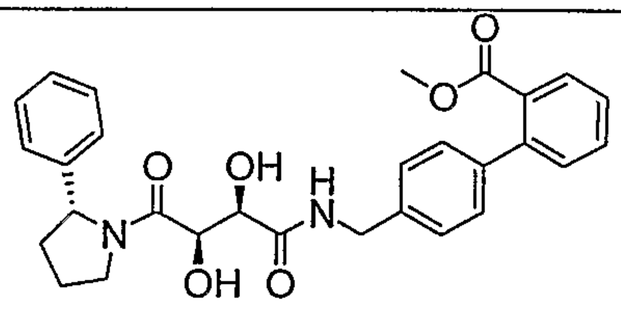
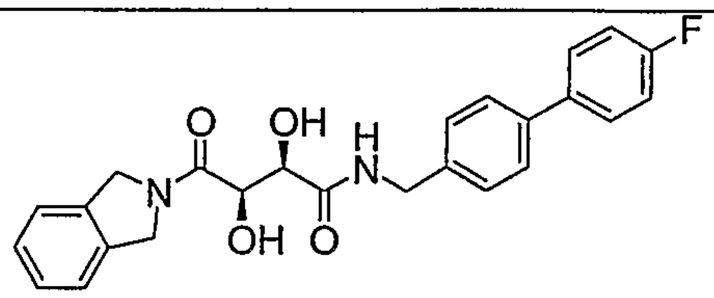
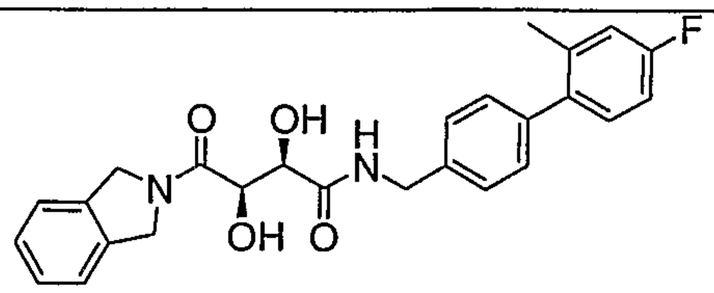
497		
498		
499		
500		
501		
502		
416		
417		
418		
529		

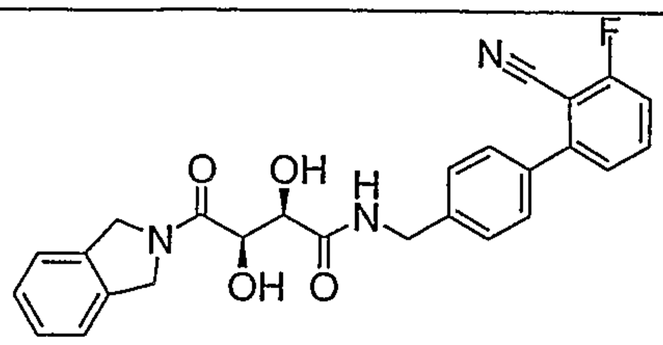
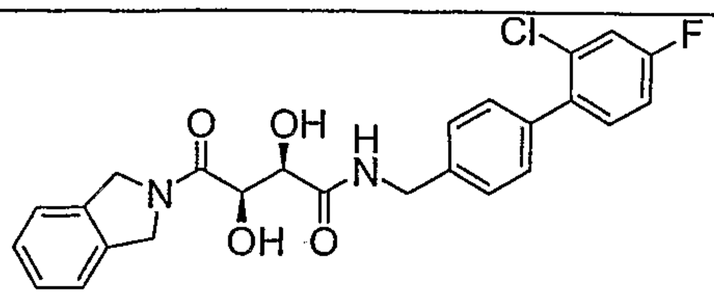
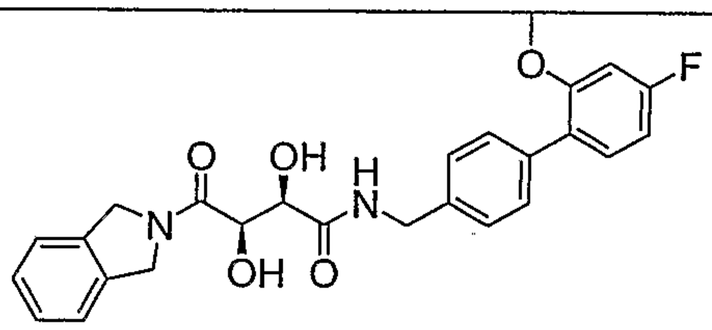
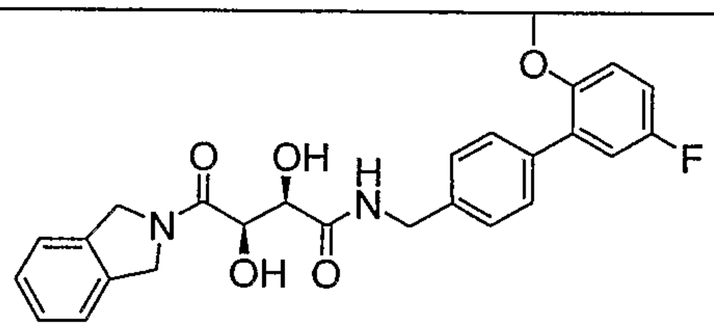
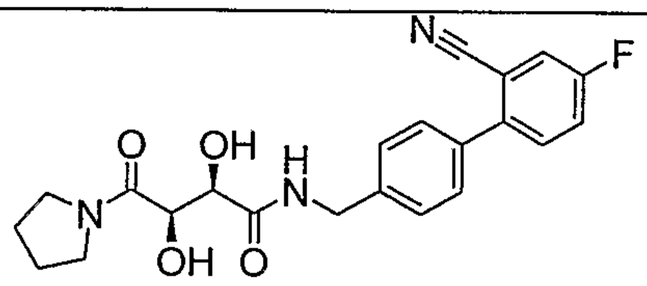
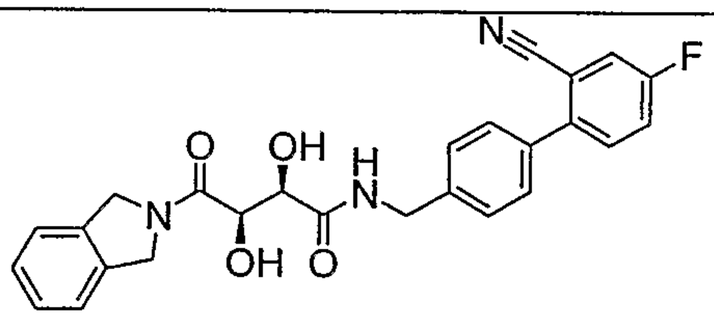
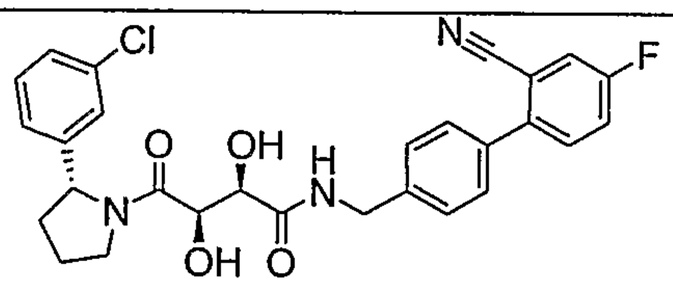
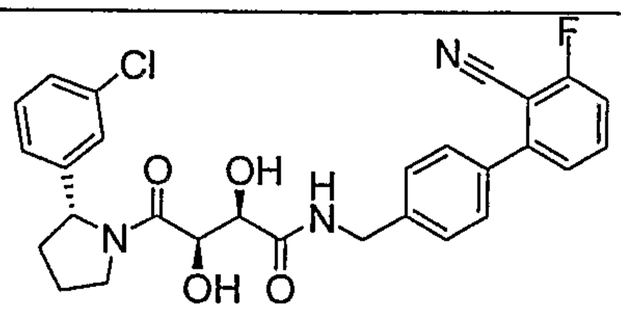
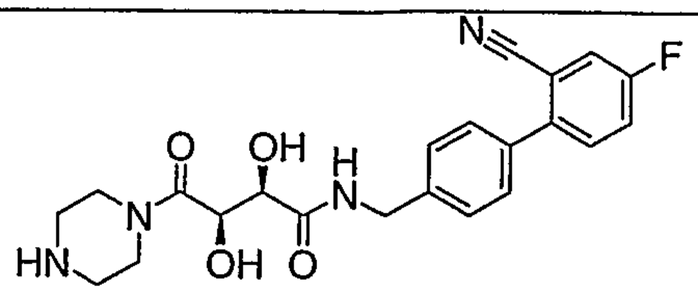
530		
531		
532		
536		
537		
538		
539		
540		
541		

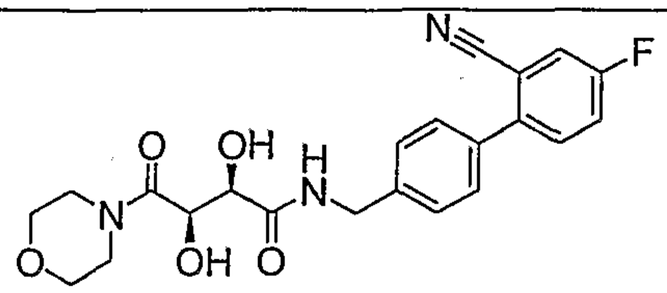
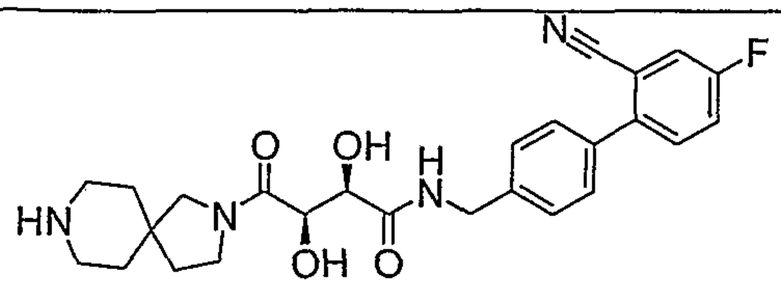
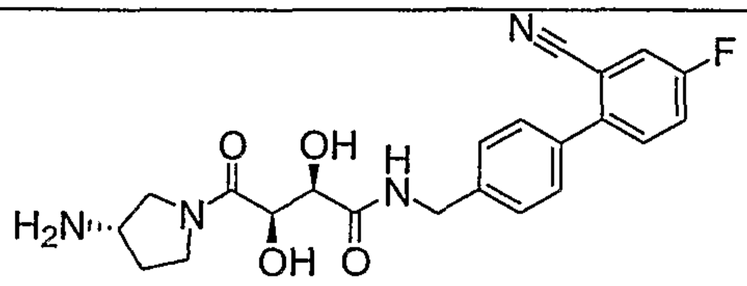
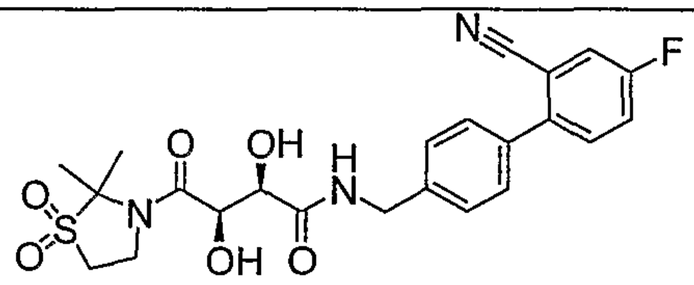
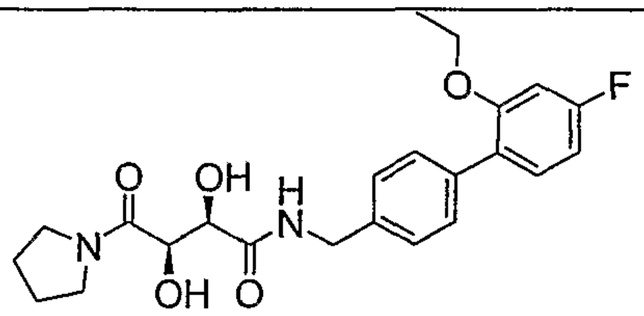
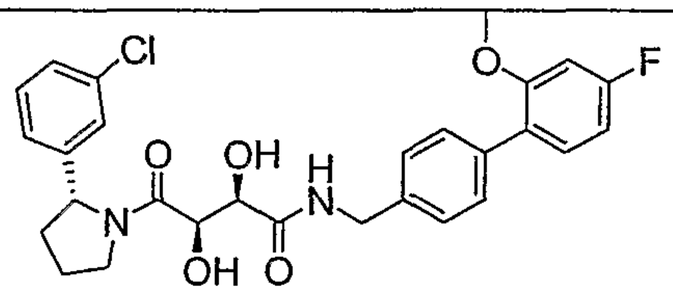
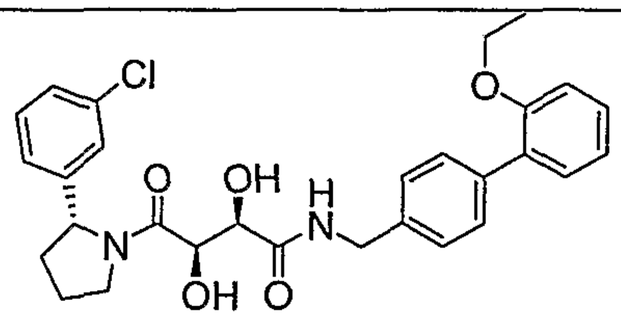
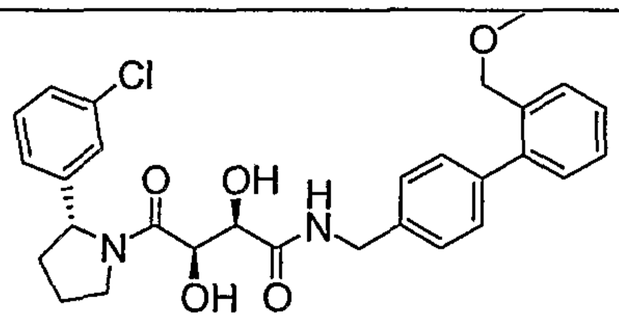
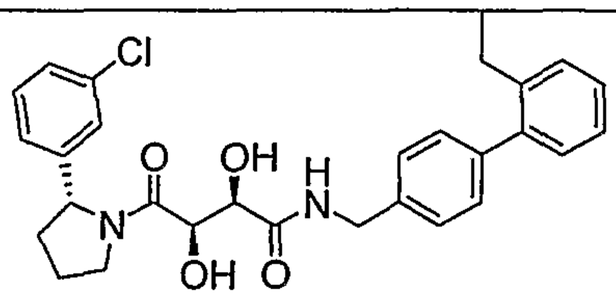
542		
546		
553		
557		
565		
572		
578		

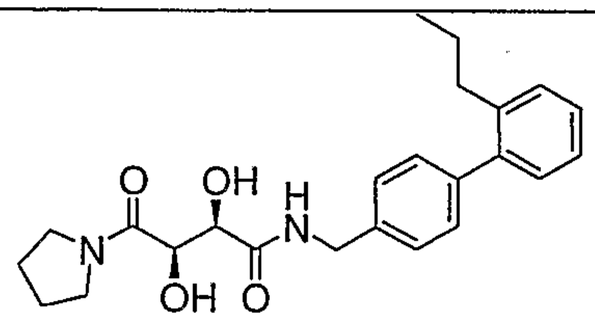
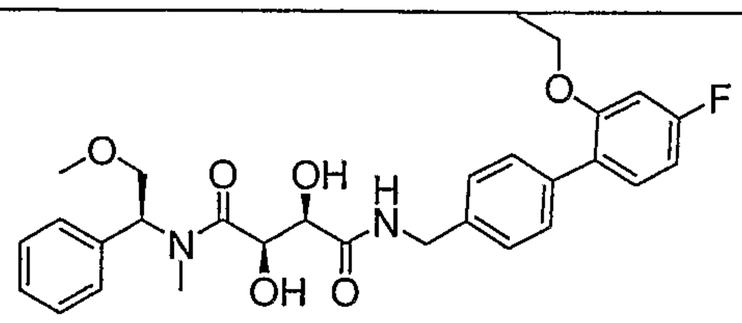
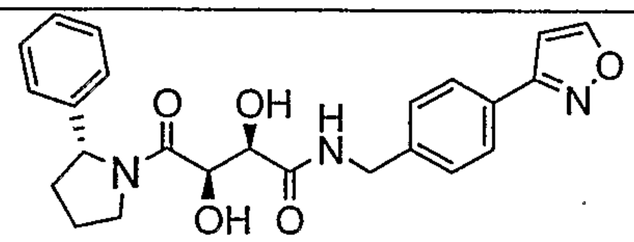
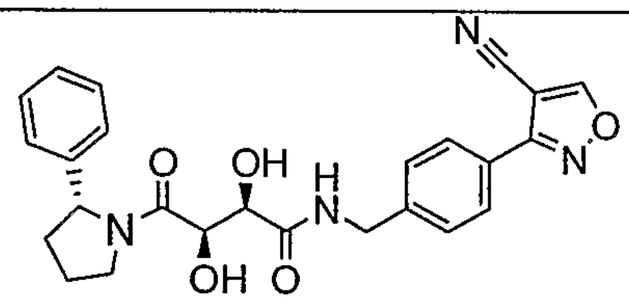
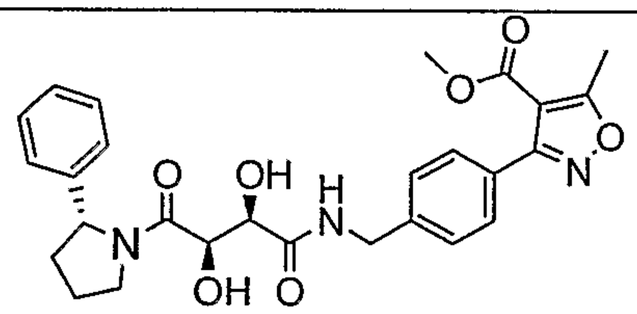
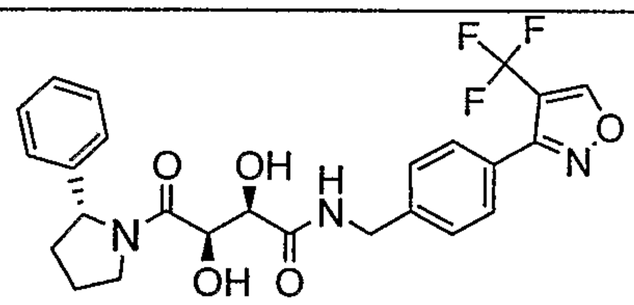
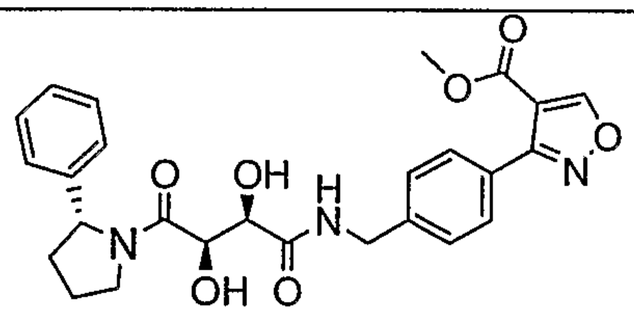
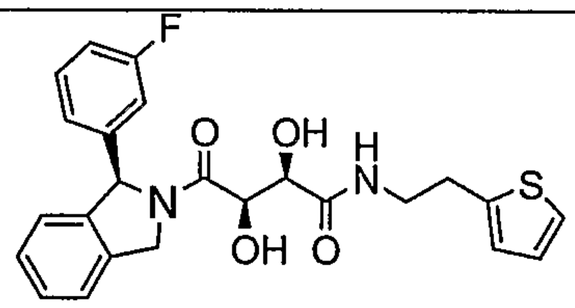
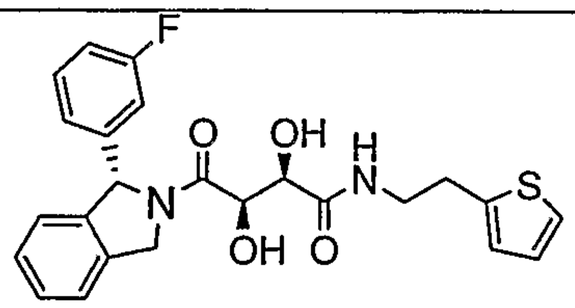
585		
586		
587		
588		
589		
590		
591		
592		
593		

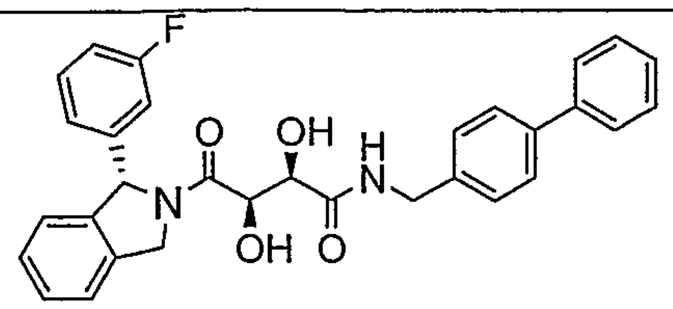
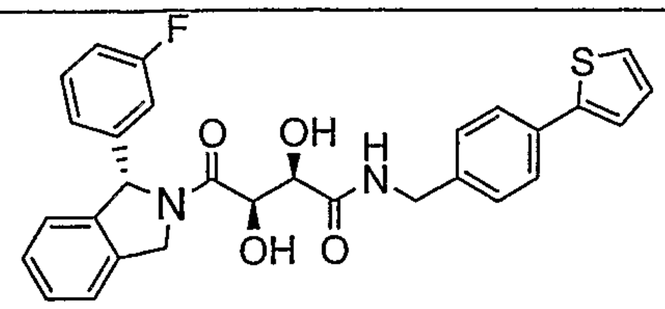
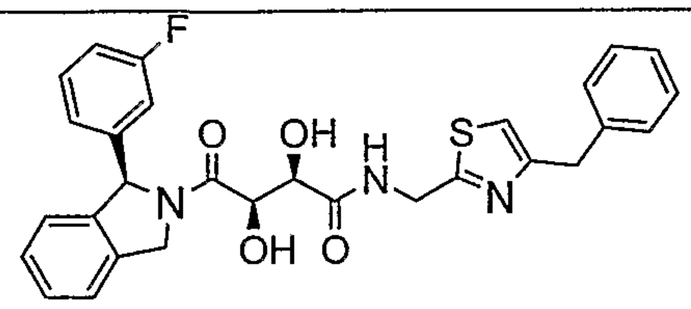
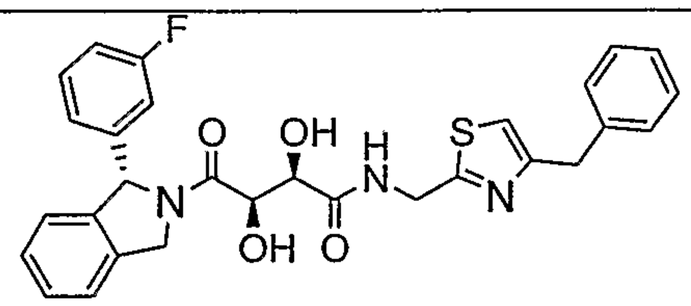
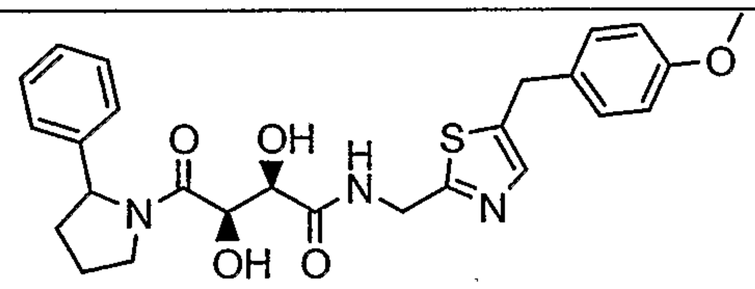
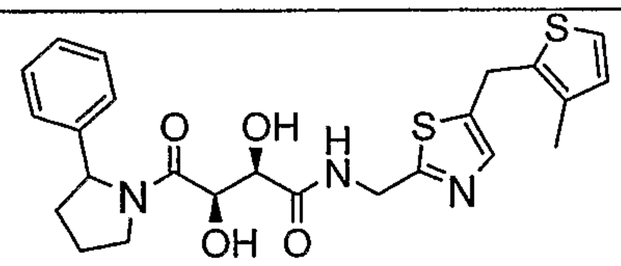
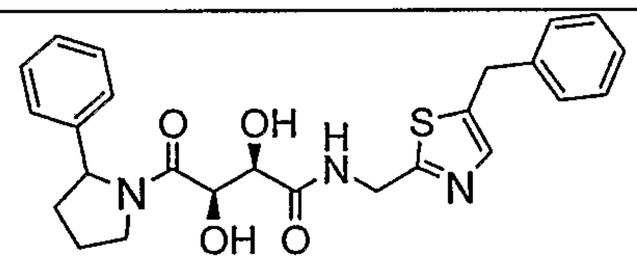
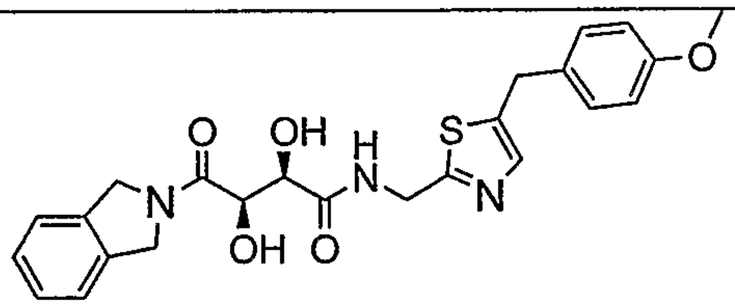
594		
595		
596		
597		
598		
599		
600		
601		
602		

603		
604		
605		
606		
607		
608		
609		
610		

611		
612		
613		
614		
615		
616		
617		
618		
619		

620		
621		
622		
623		
624		
625		
626		
627		
628		

629		
630		
635		
636		
637		
638		
639		
646A		
646B		

647		
648		
649A		
649B		
655		
656A		
656B		
657		
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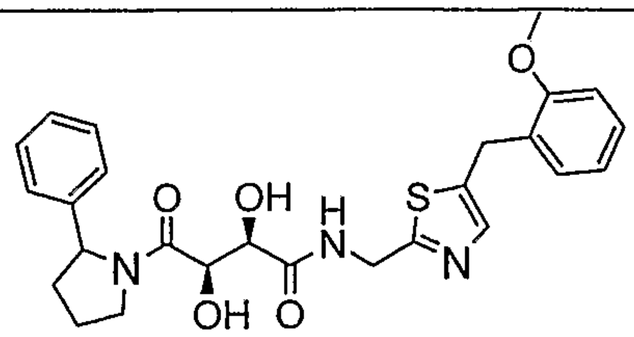
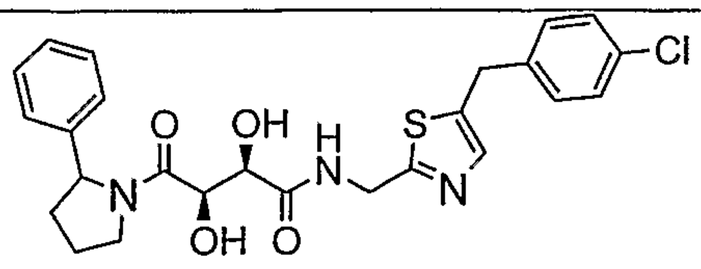
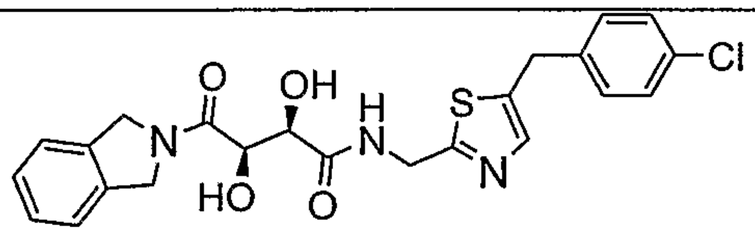
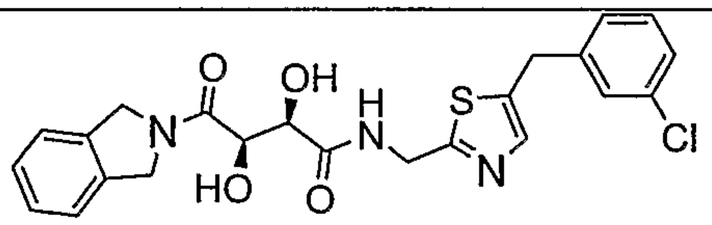
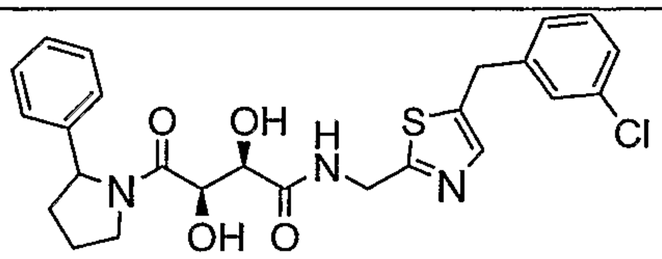
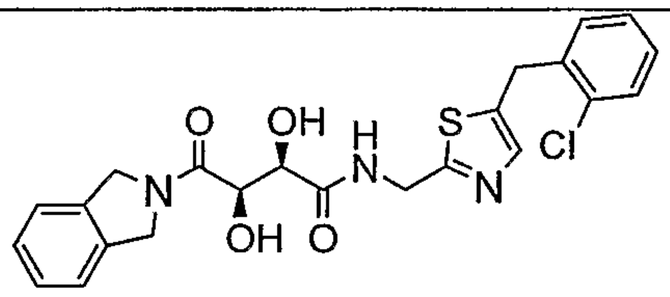
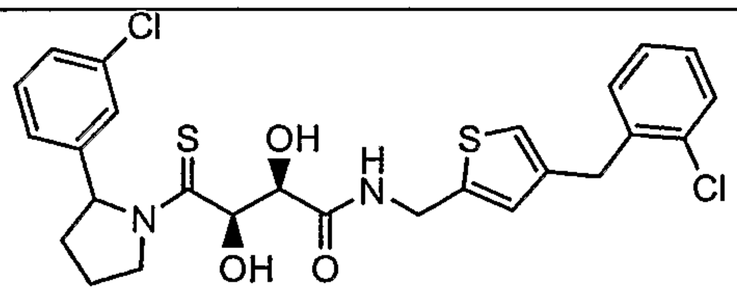
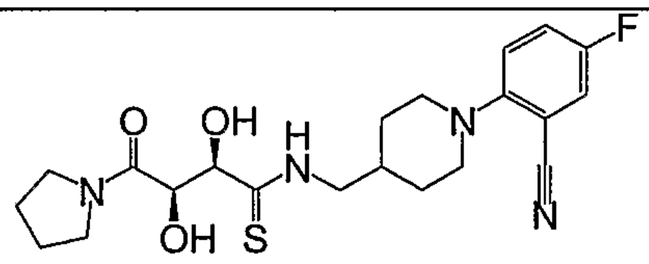
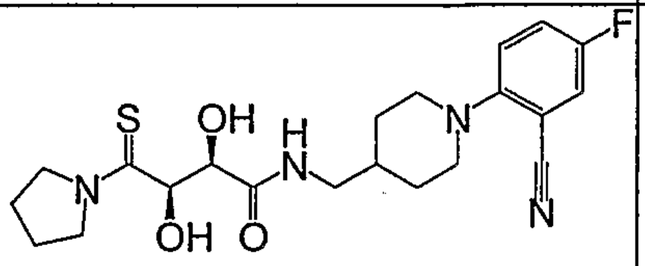
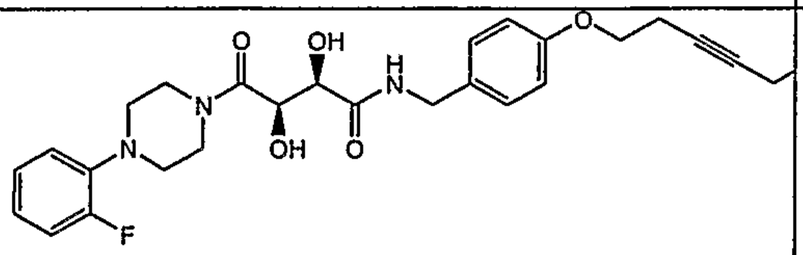
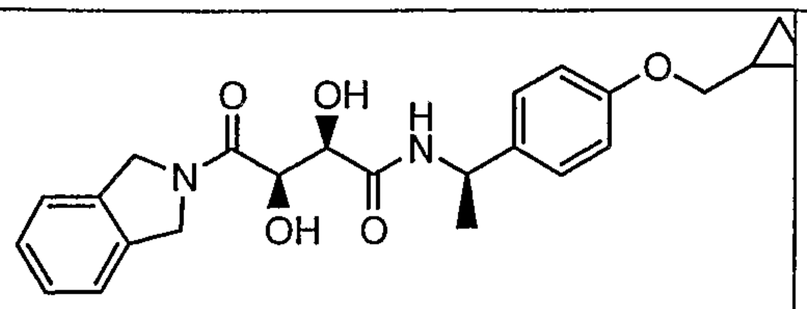
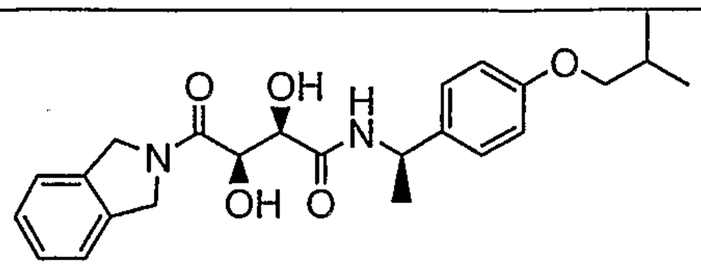
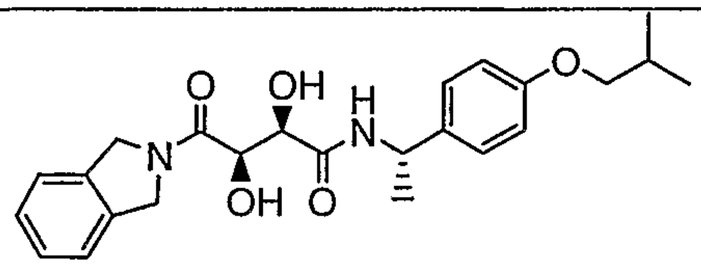
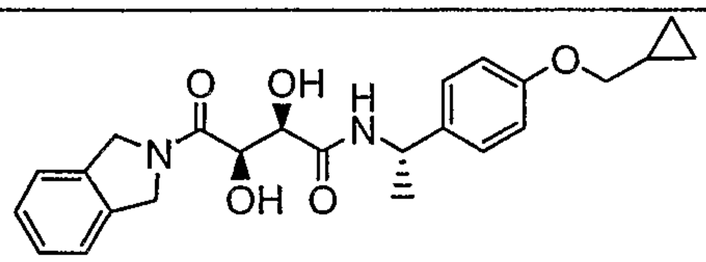
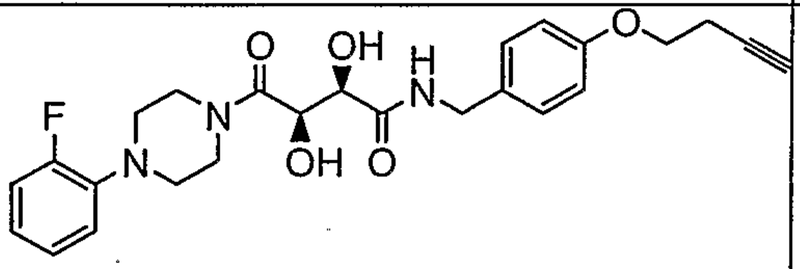
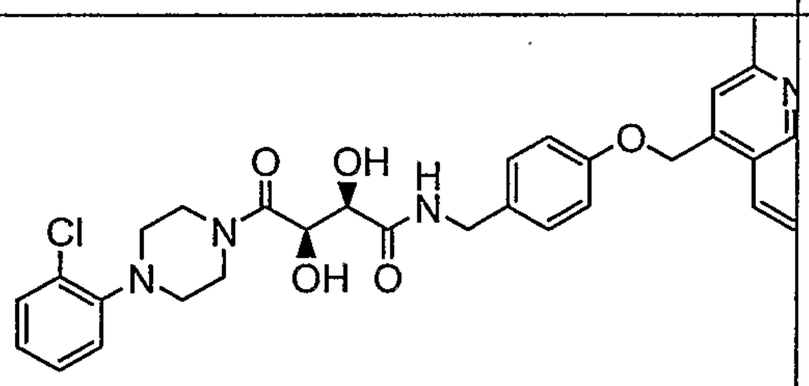
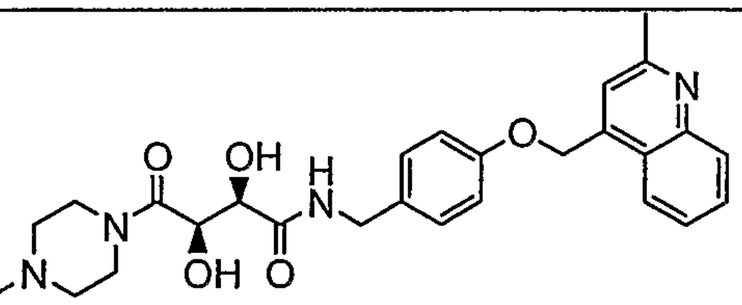
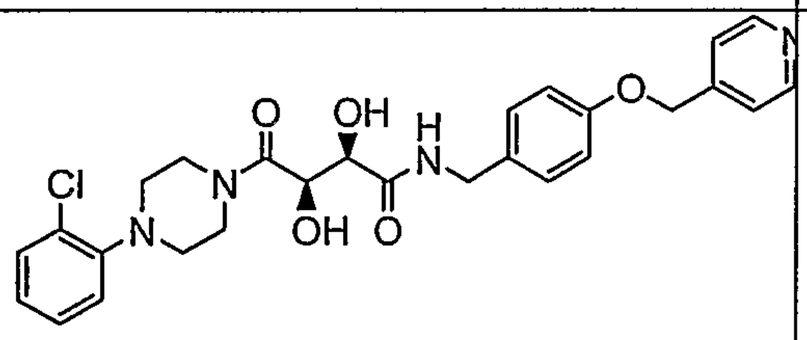
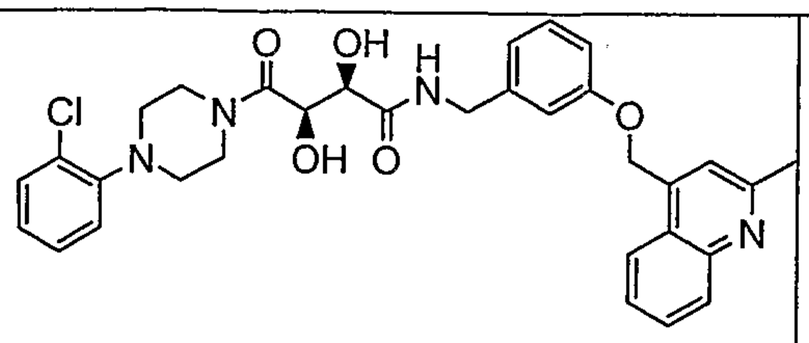
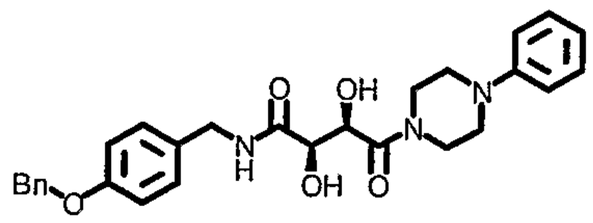
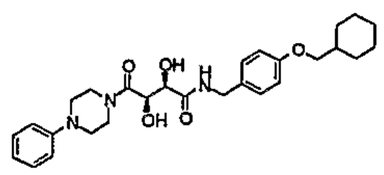
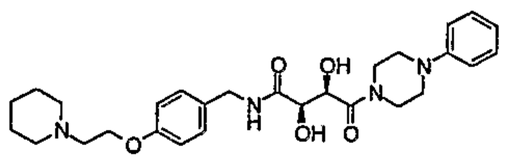
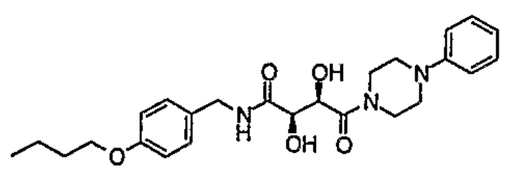
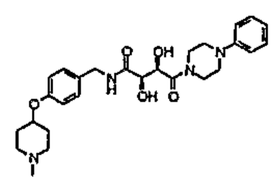
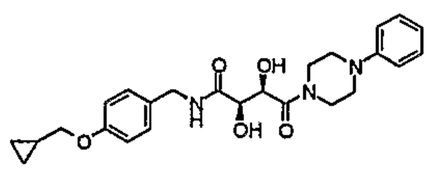
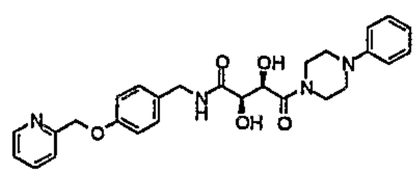
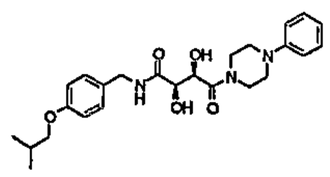
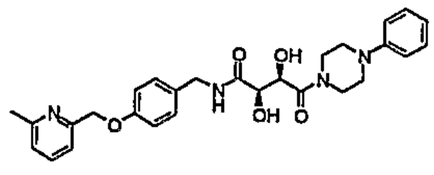
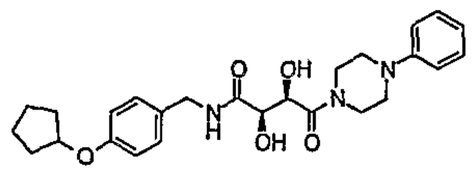
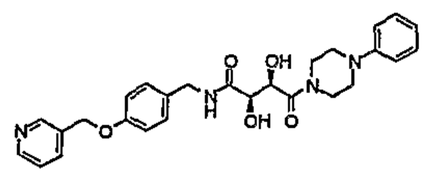
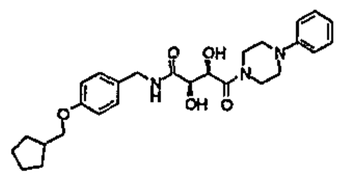
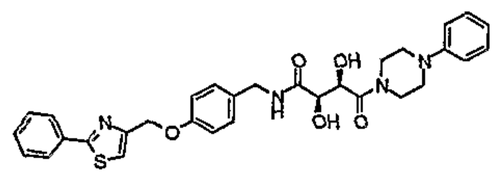
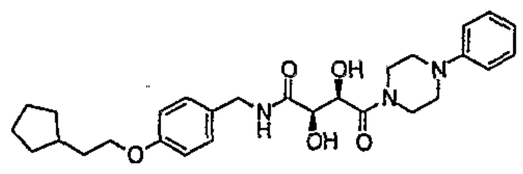
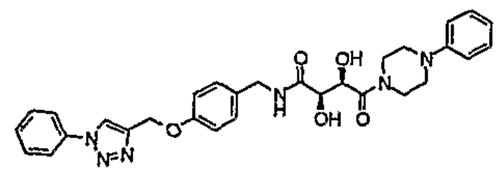
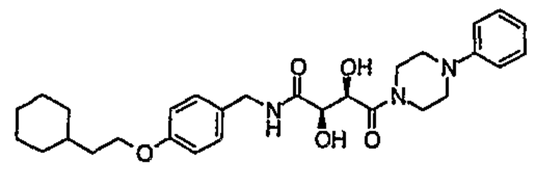
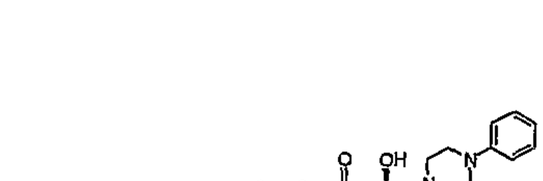
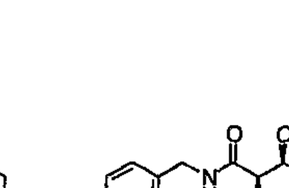
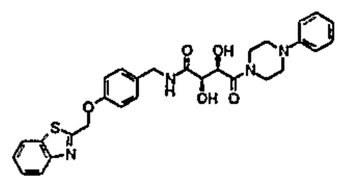
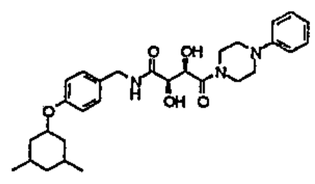
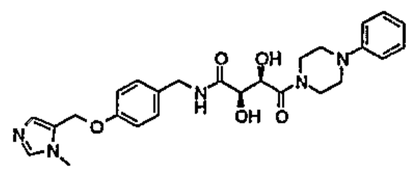
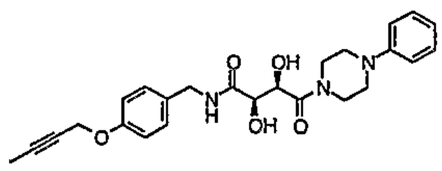
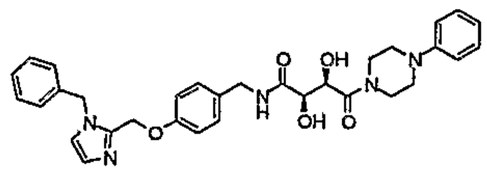
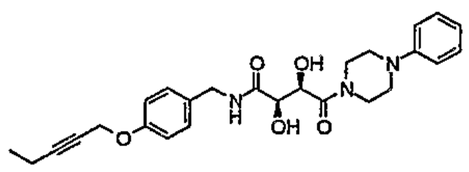
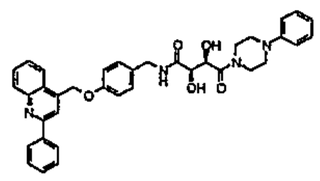
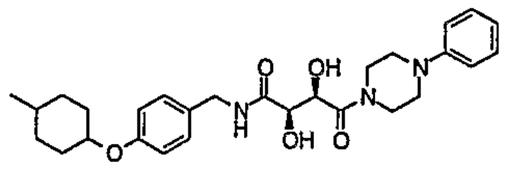
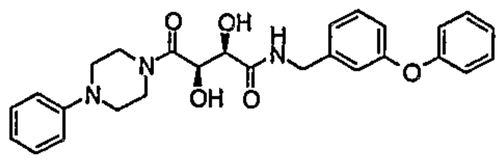
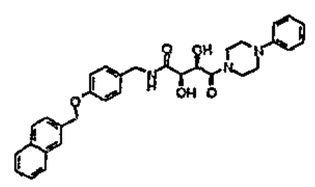
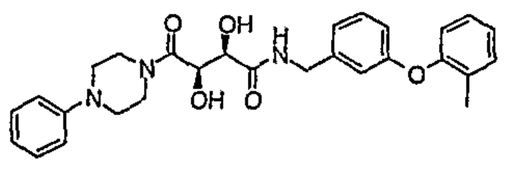
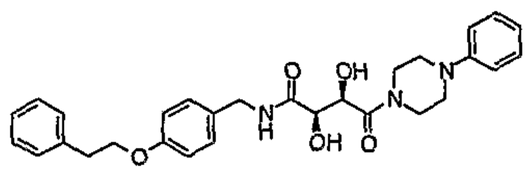
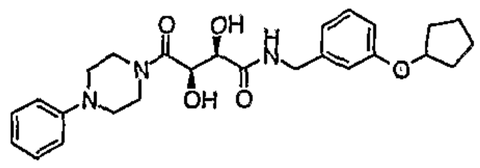
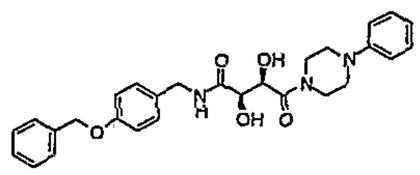
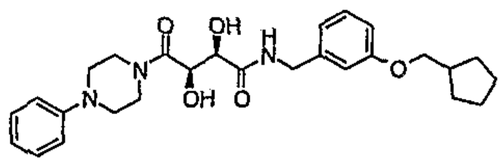
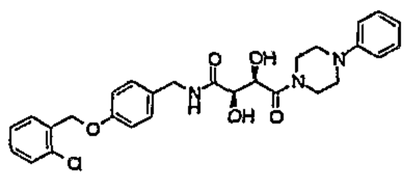
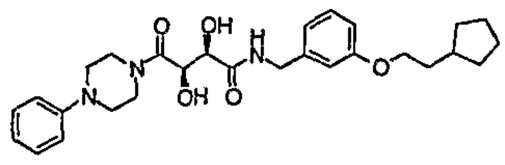
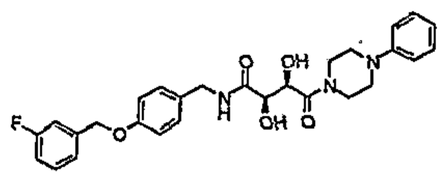
659		
660		
661		
662		
663		
664		
668		
673		
674		
678		

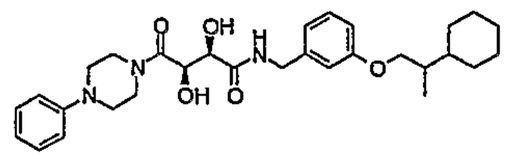
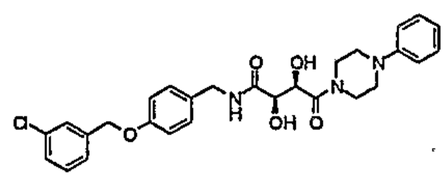
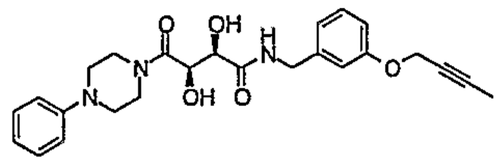
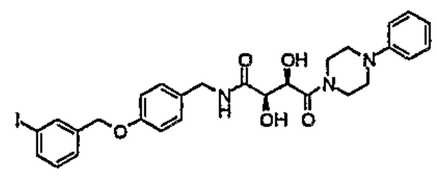
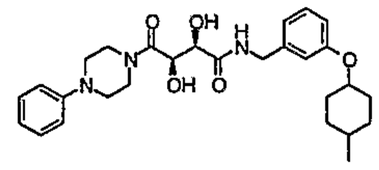
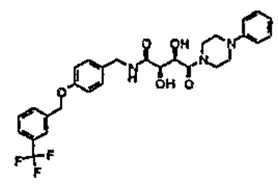
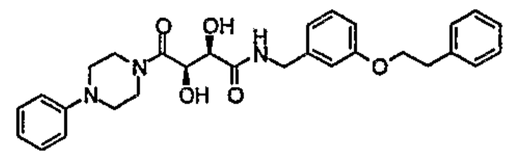
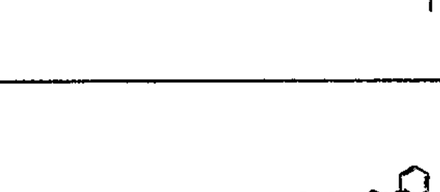
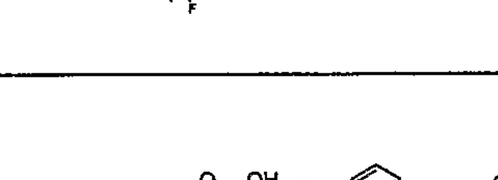
683		
684		
685		
686		
687		
688		
689		
690		

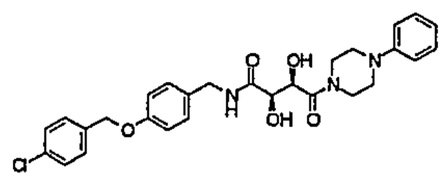
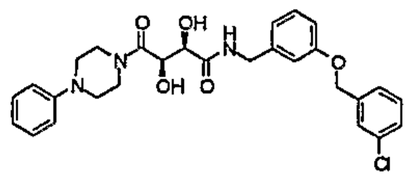
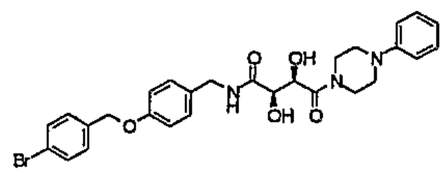
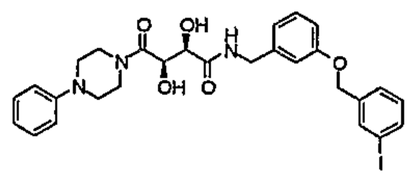
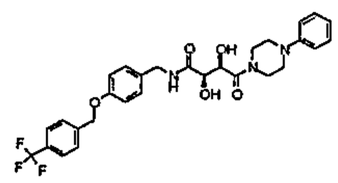
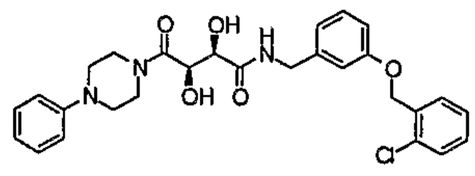
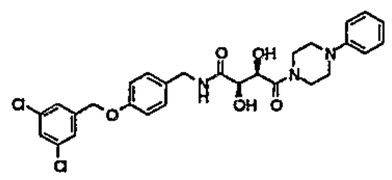
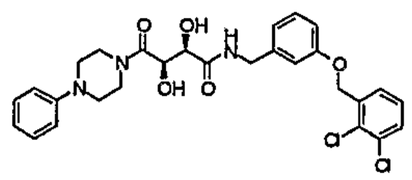
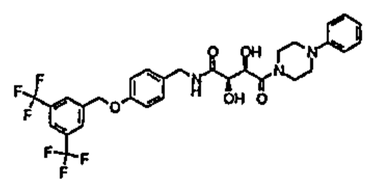
691		
696		
697		
698		
699		
700		
701		
702		
703		
704		

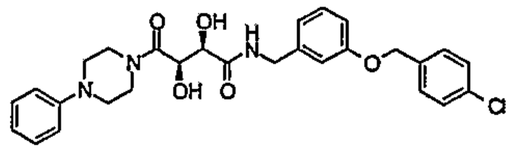
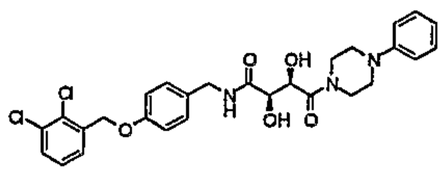
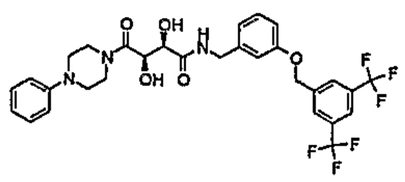
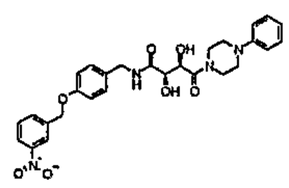
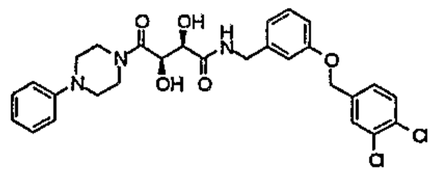
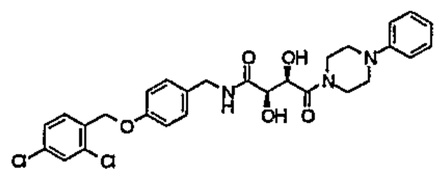
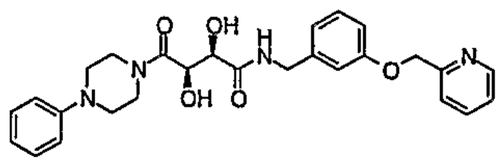
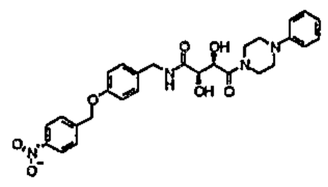
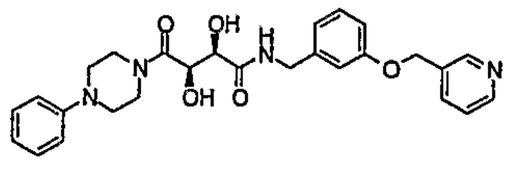
705		
706		
707		
708		
709		
710		
711		
712		
713		

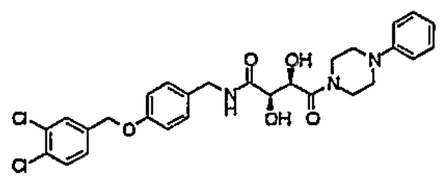
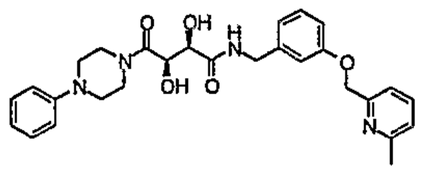
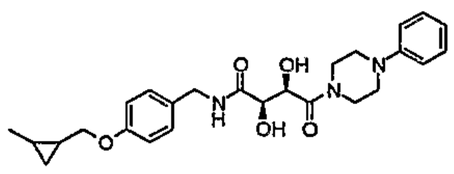
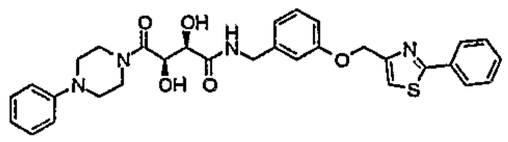
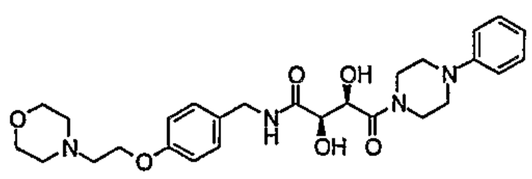
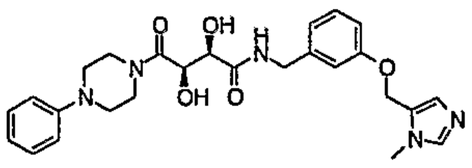
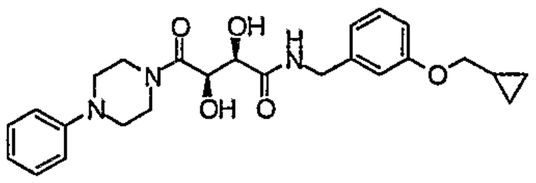
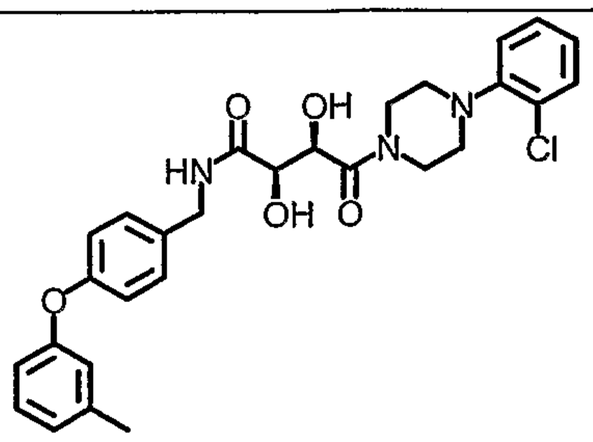
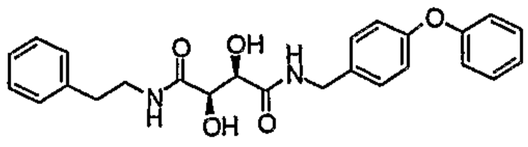
714		
715		
716		
717		
718		
719		
720		
721		
722		

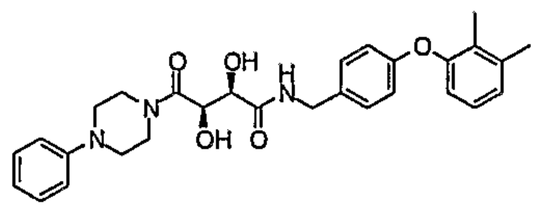
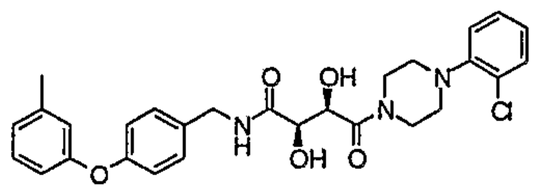
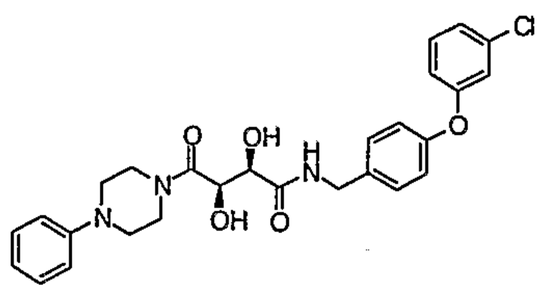
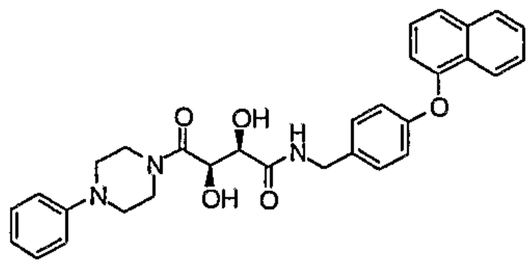
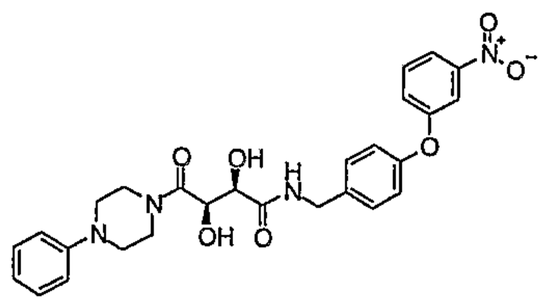
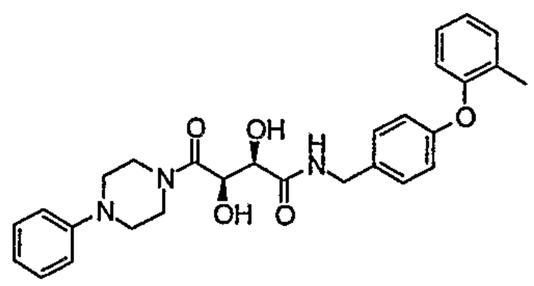
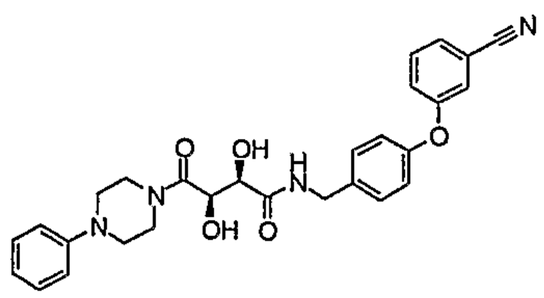
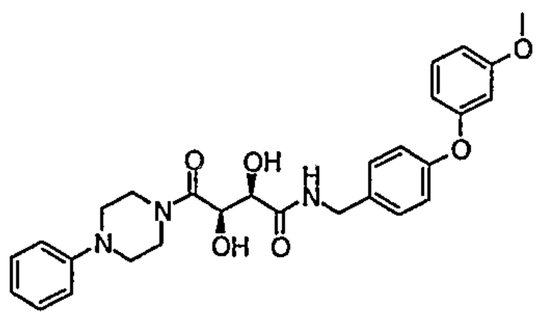
723		
724		
725		
726		
696		
728		
729		
730		
731		

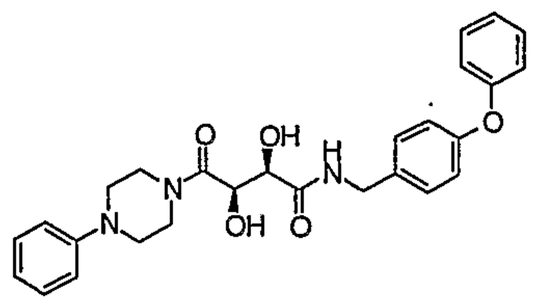
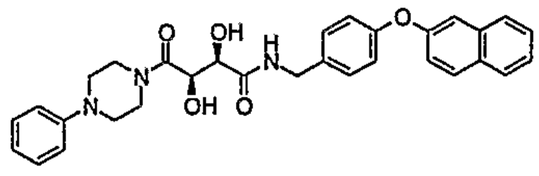
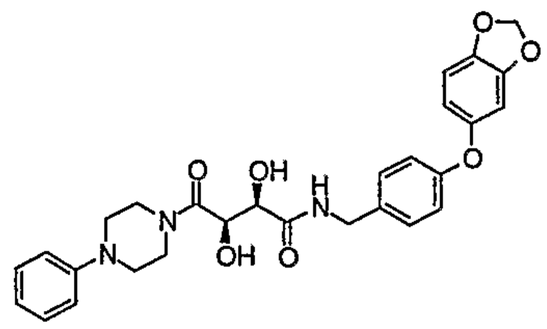
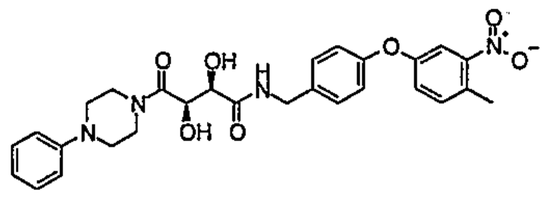
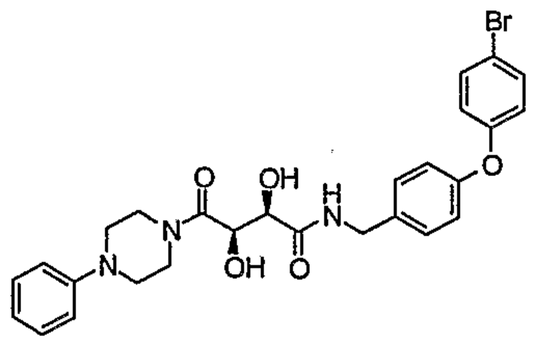
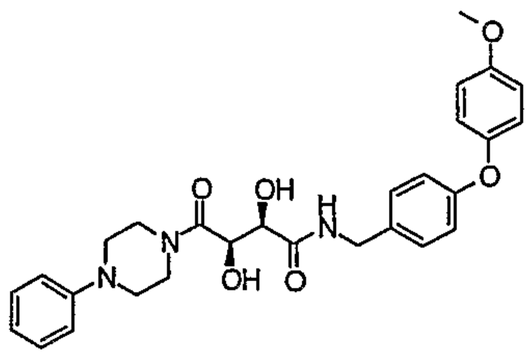
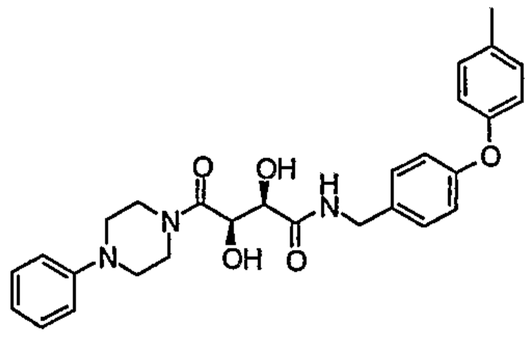
732		
733		
734		
735		
736		
737		
738		
739		
740		

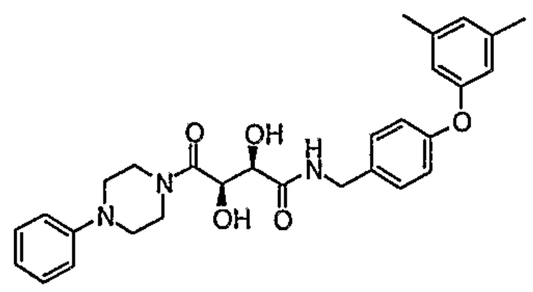
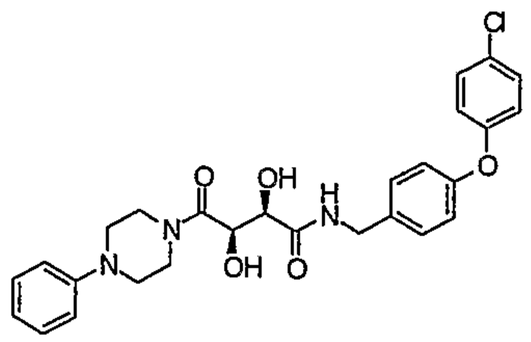
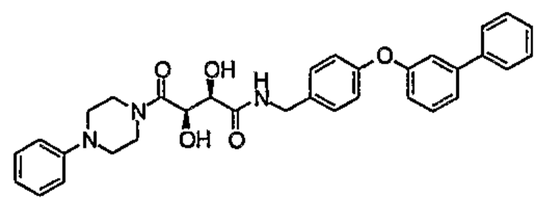
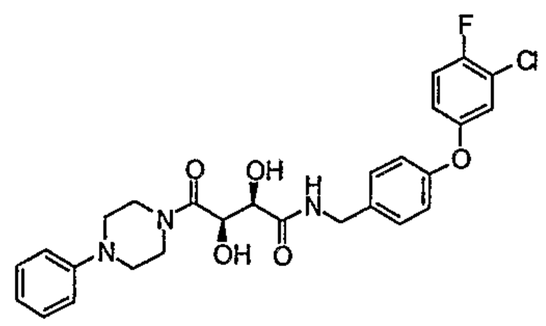
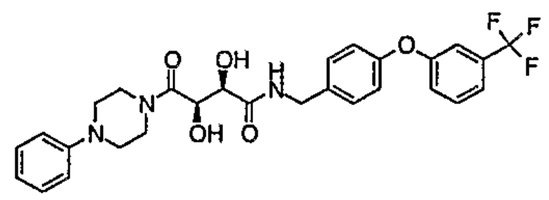
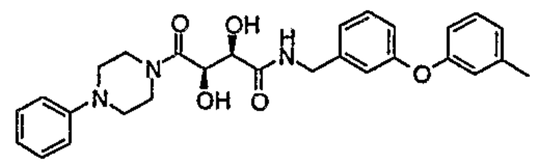
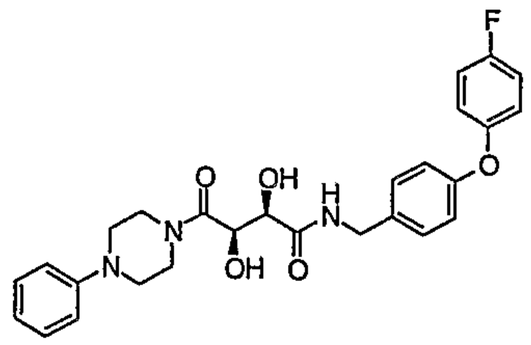
741		
742		
743		
744		
745		
746		
747		
748		
749		

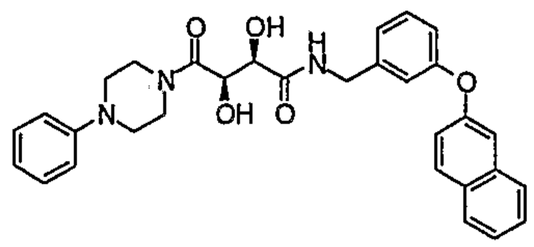
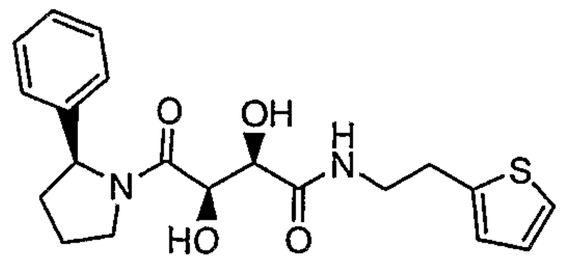
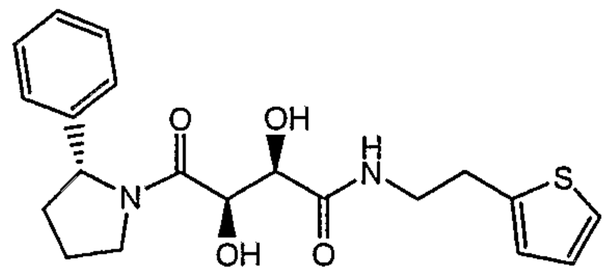
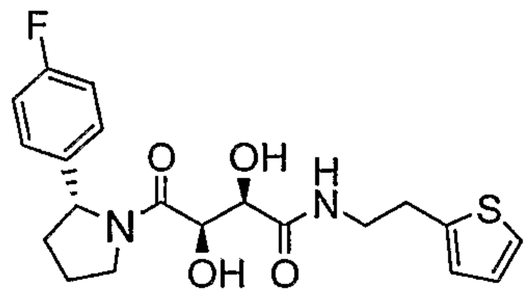
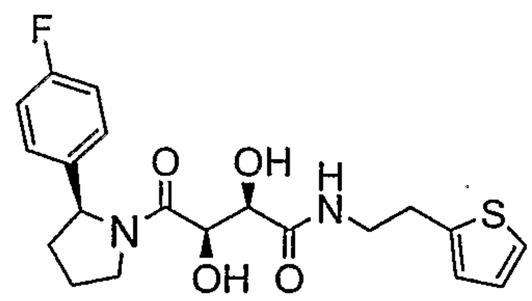
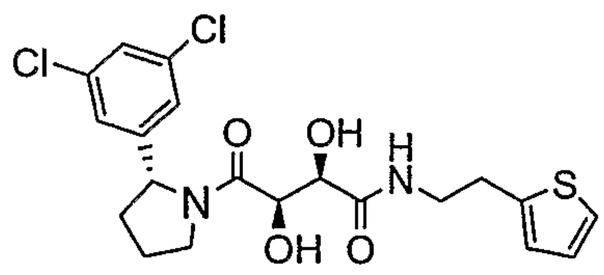
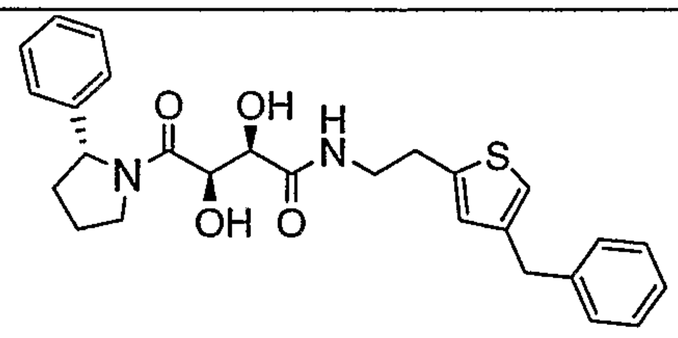
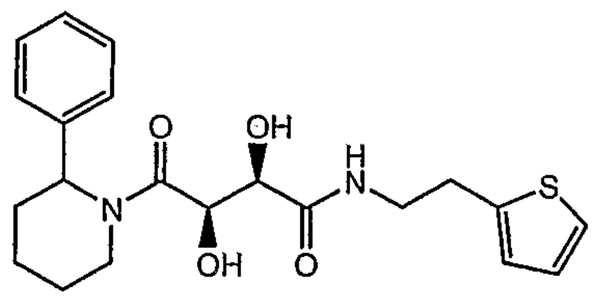
750		
751		
752		
753		
754		
755		
756		
757		
758		

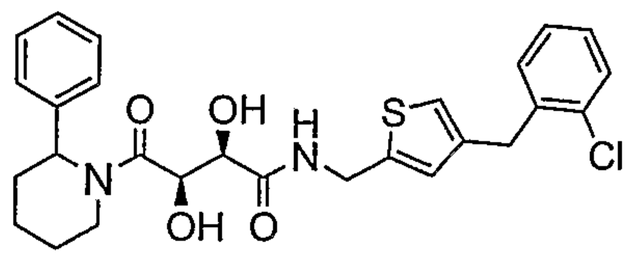
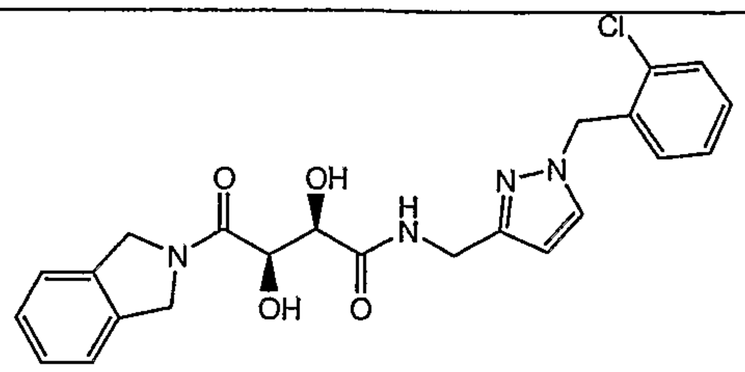
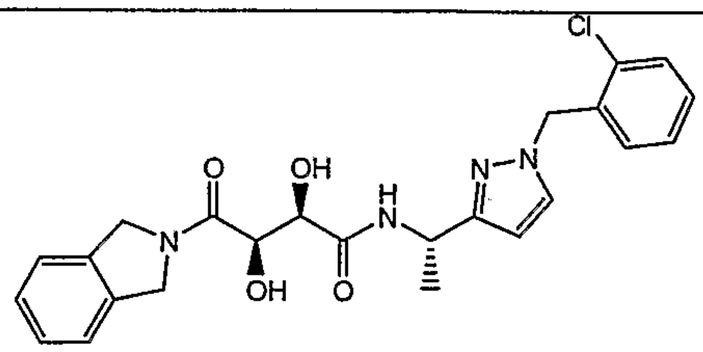
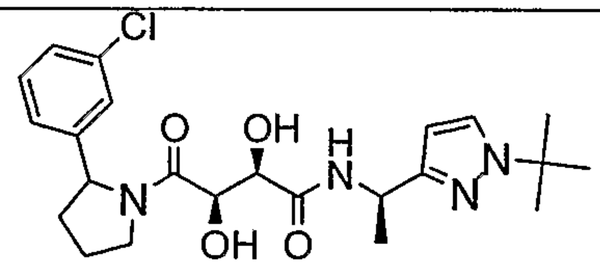
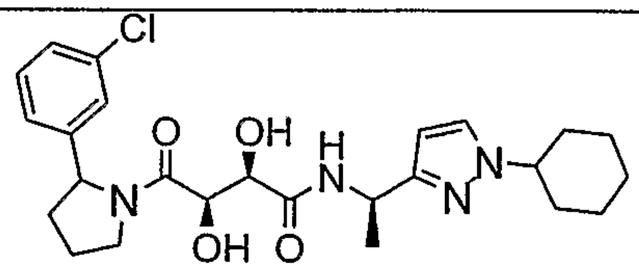
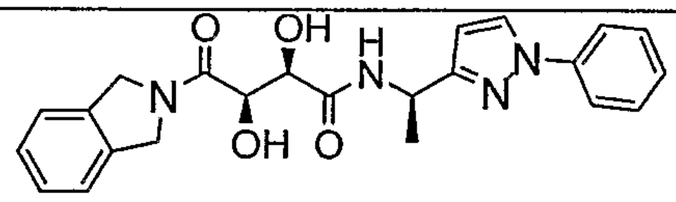
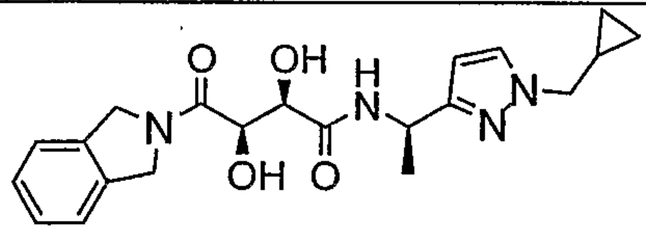
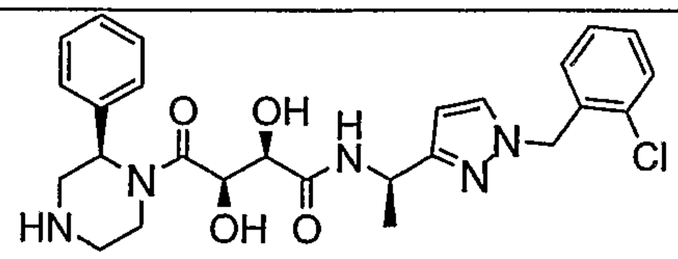
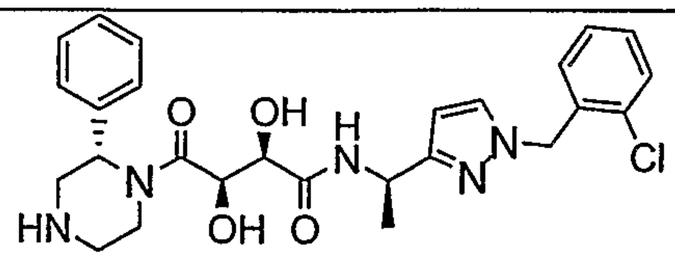
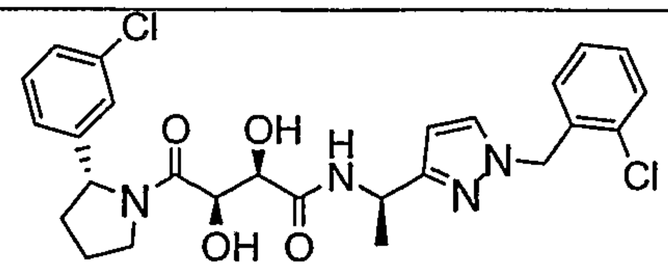
759		
760		
761		
762		
763		
764		
765		
772		
773		

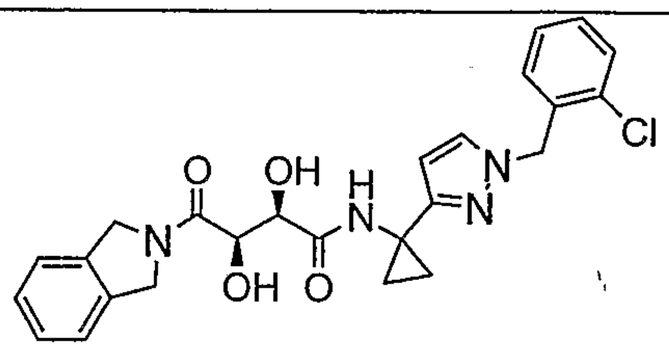
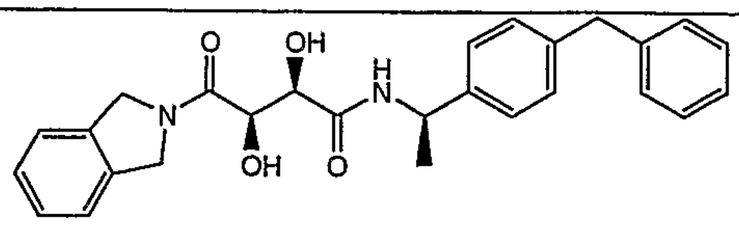
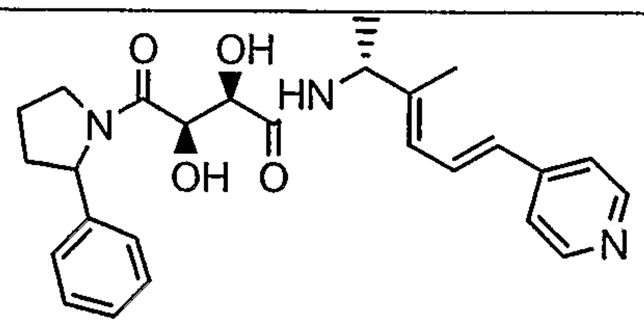
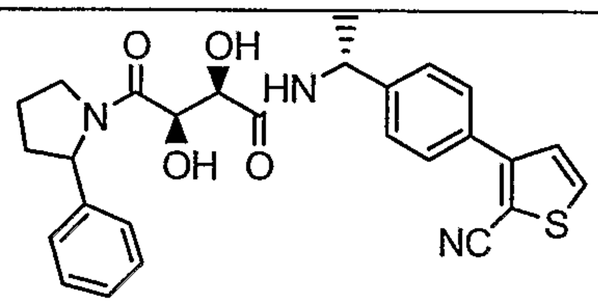
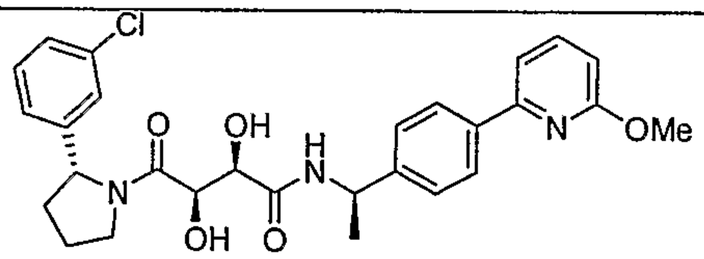
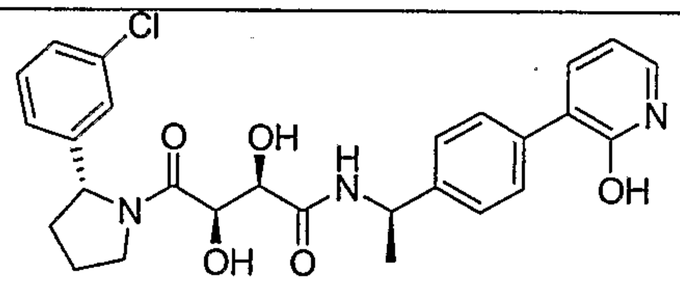
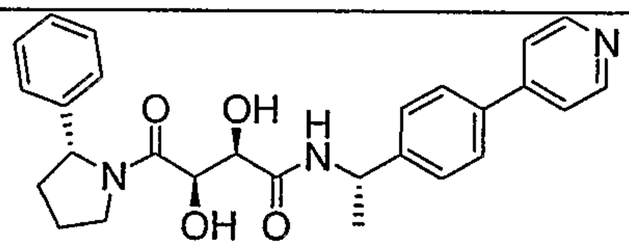
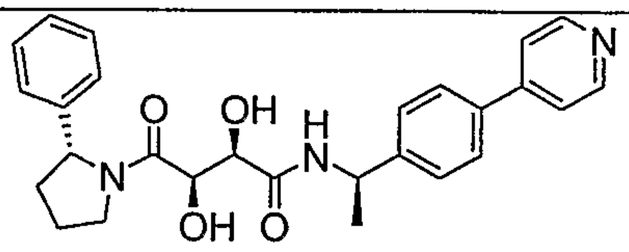
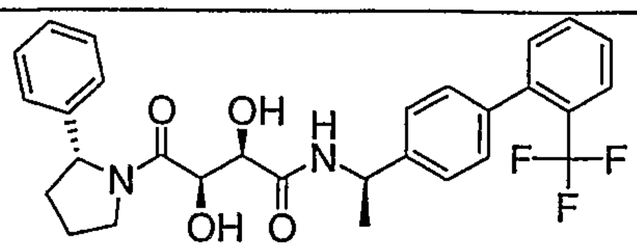
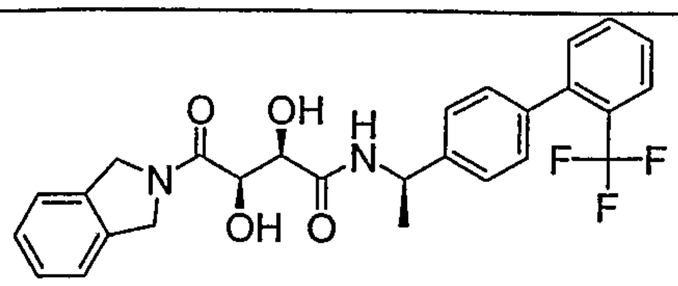
774		
772		
776		
777		
778		
779		
780		
781		

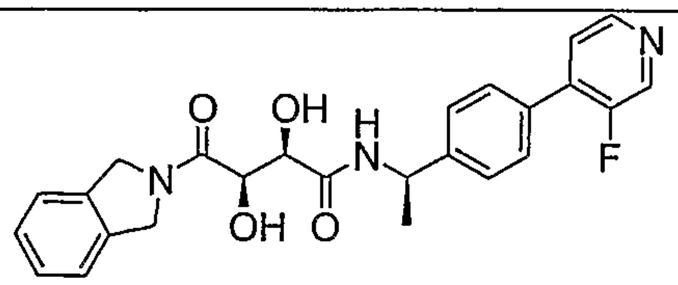
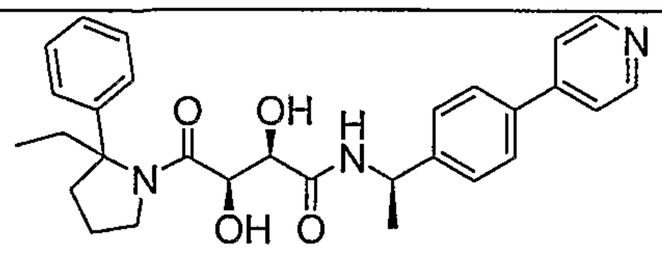
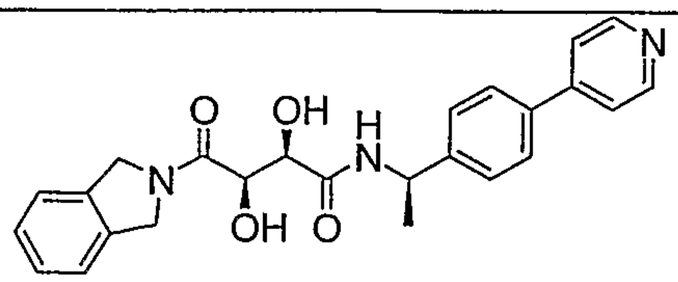
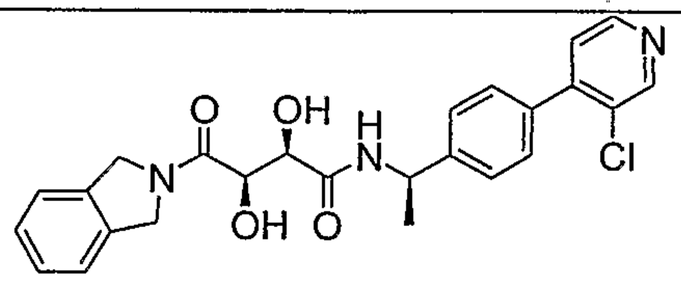
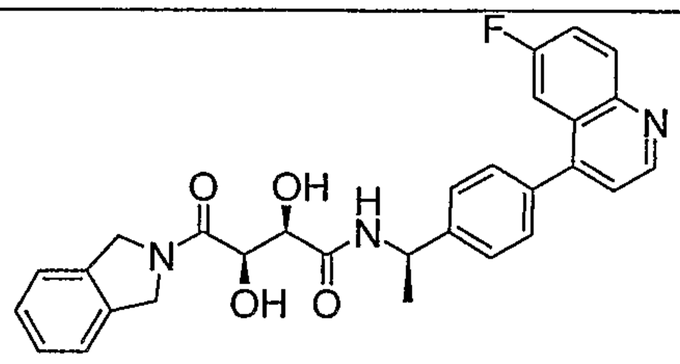
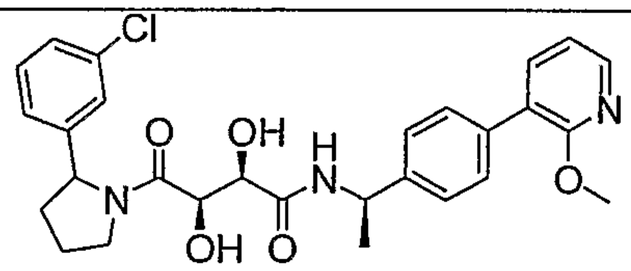
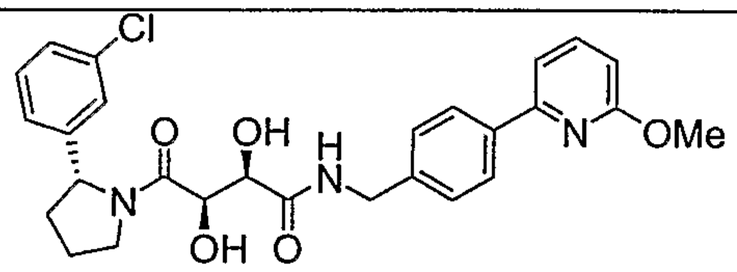
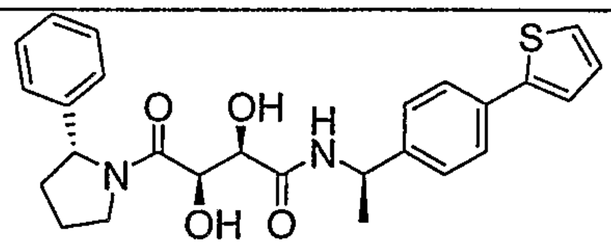
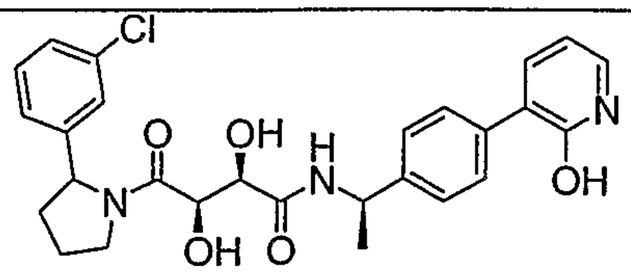
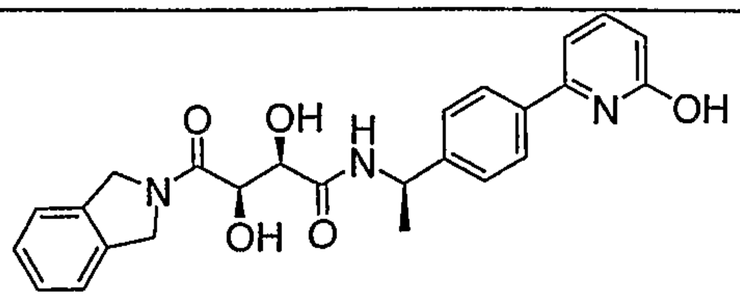
782		
783		
784		
785		
786		
787		
788		

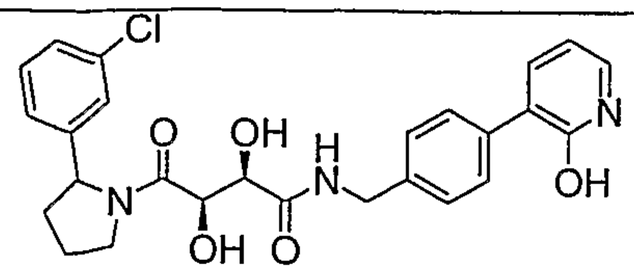
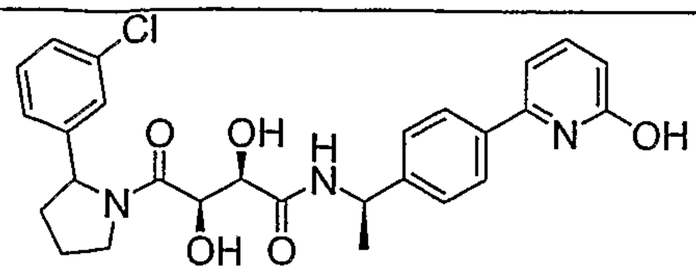
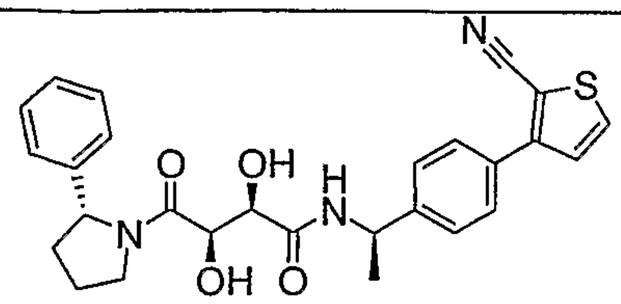
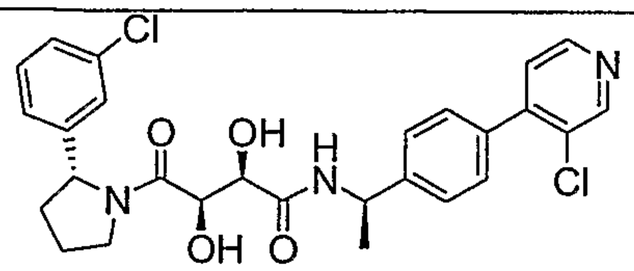
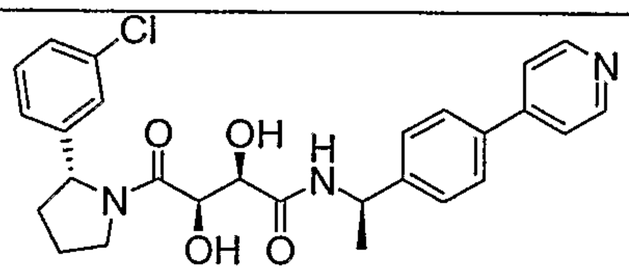
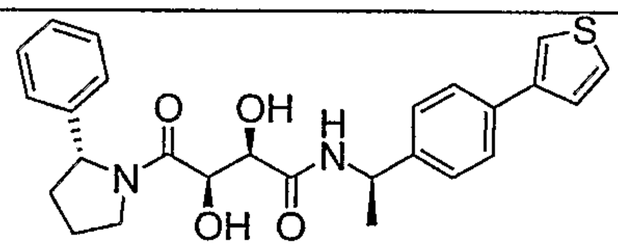
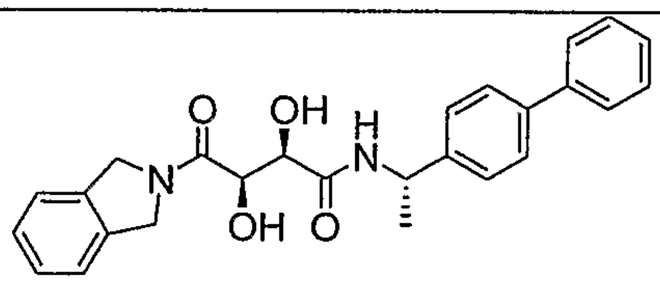
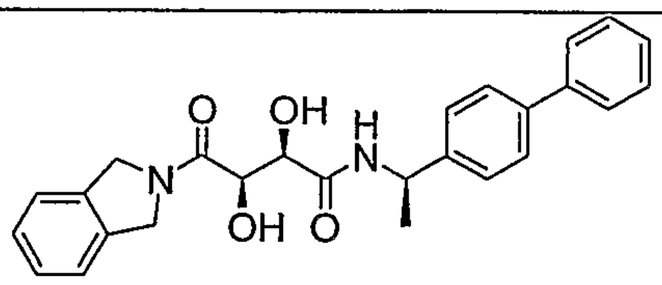
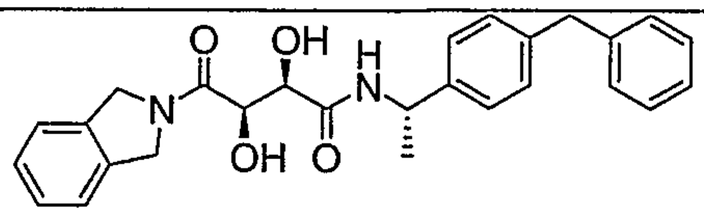
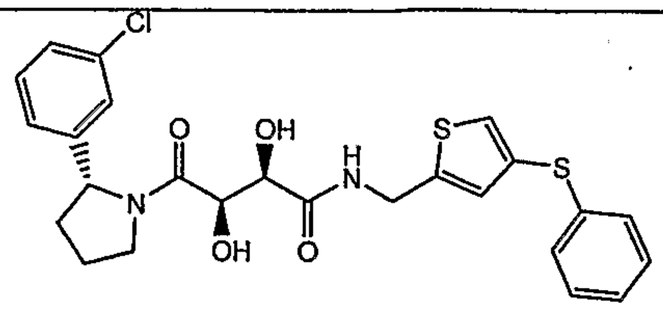
789		
790		
791		
792		
793		
794		
795		

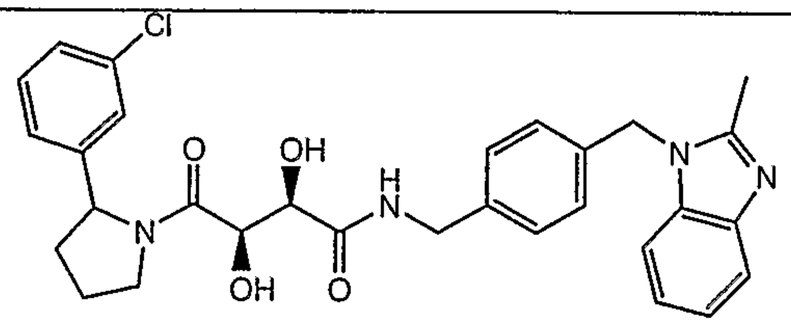
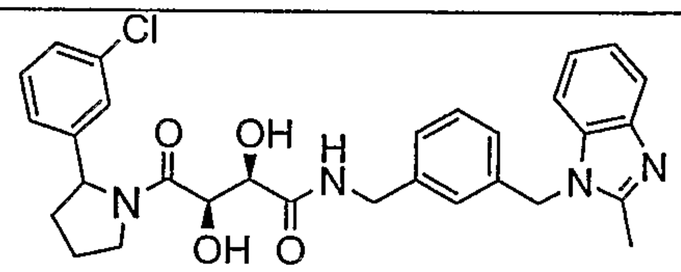
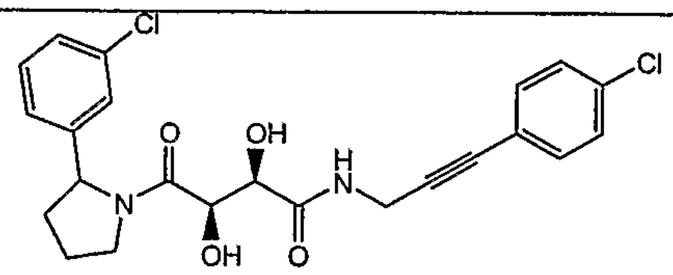
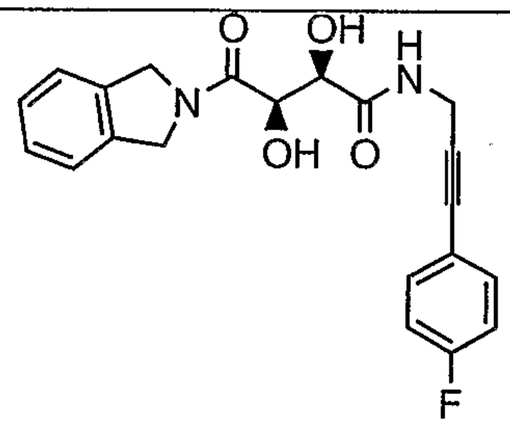
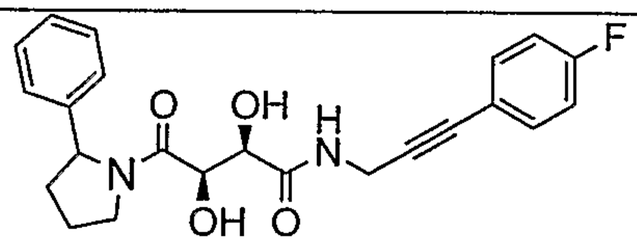
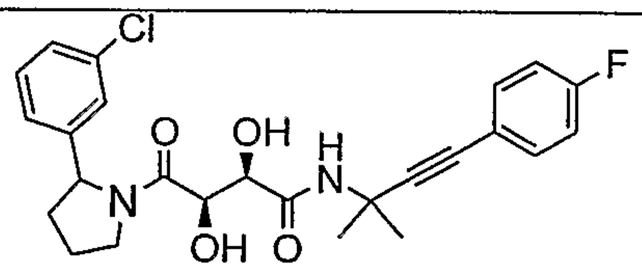
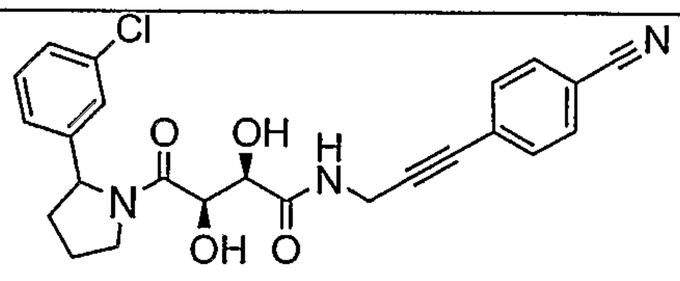
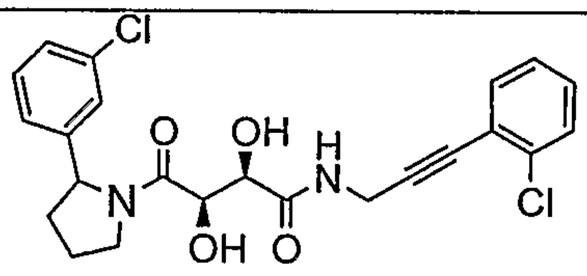
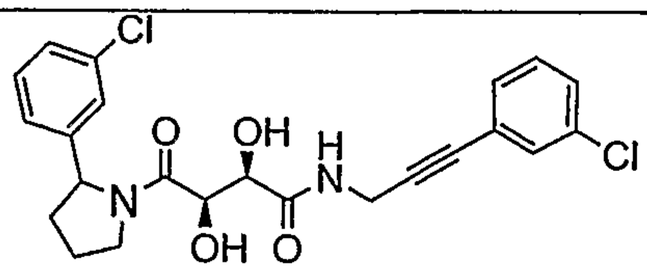
796		
802		
804		
805		
806		
807		
808		
814		

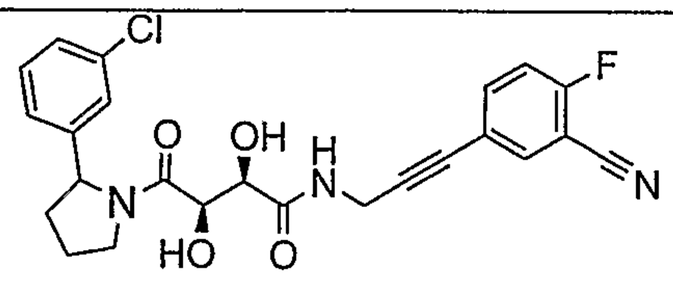
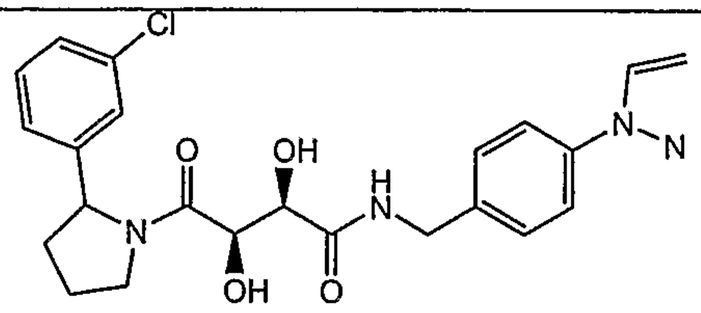
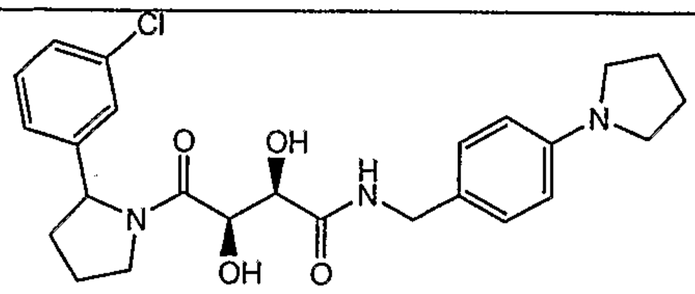
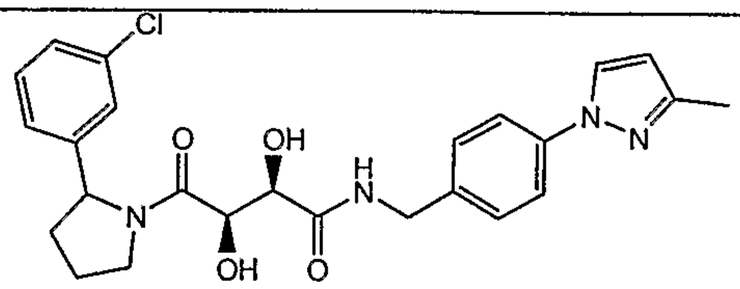
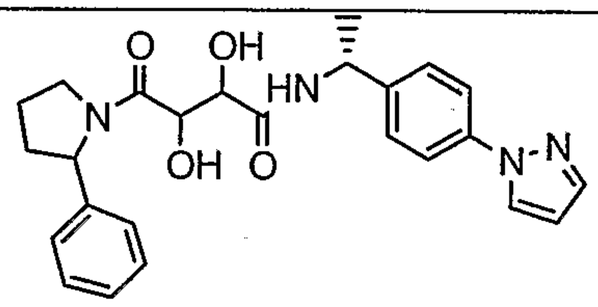
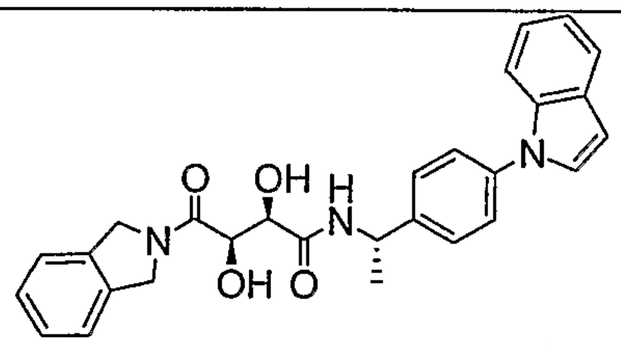
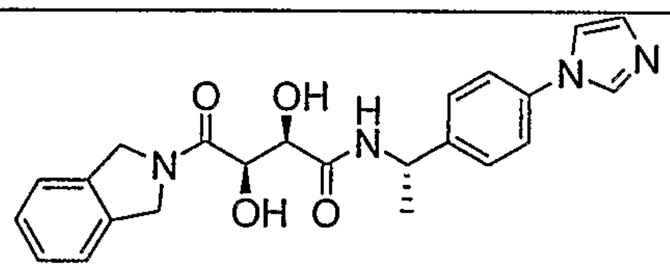
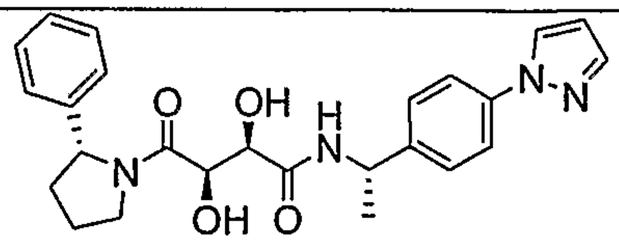
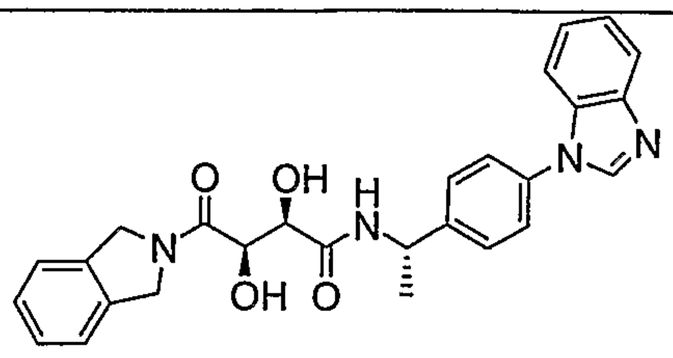
815		
823		
828		
829		
830		
831		
832		
833		
834		
835		

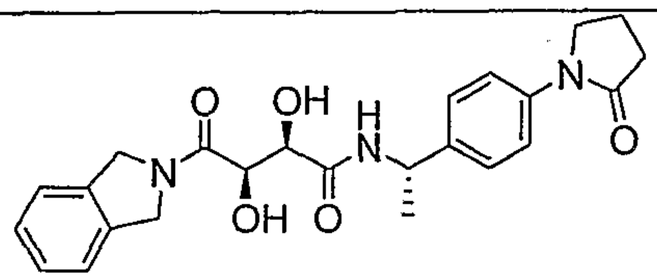
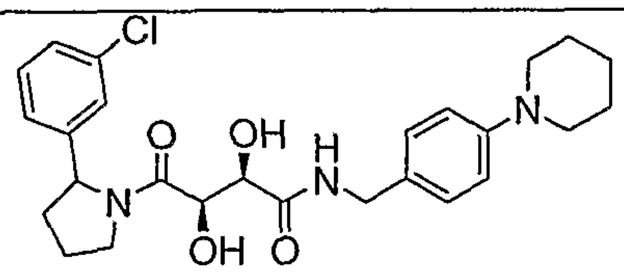
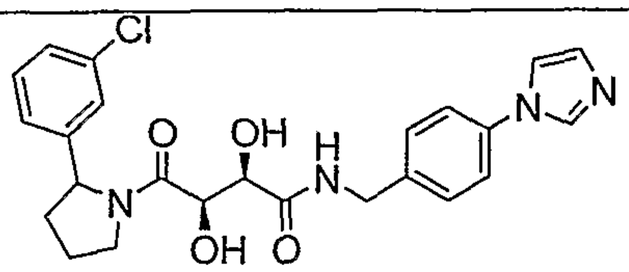
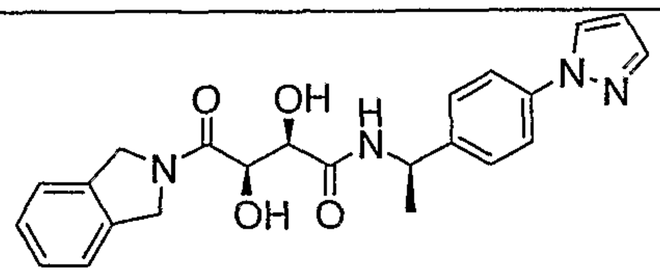
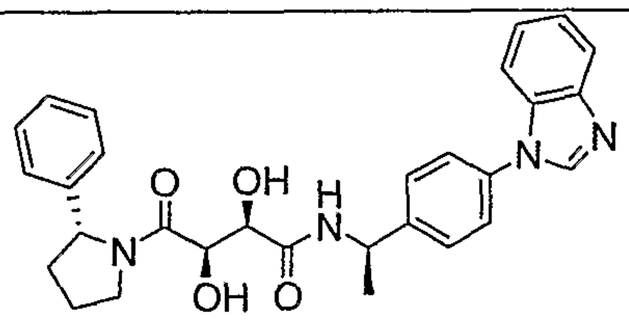
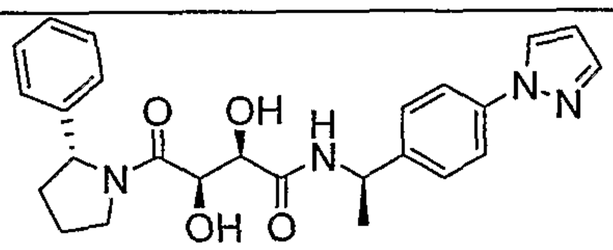
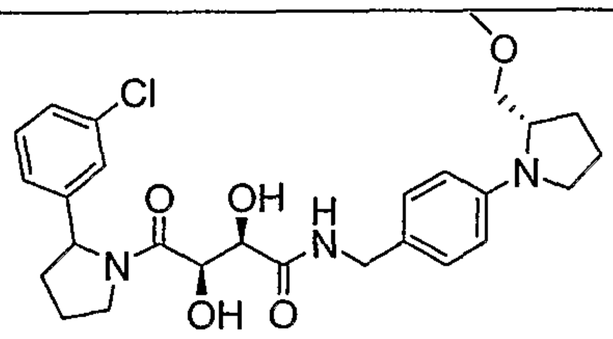
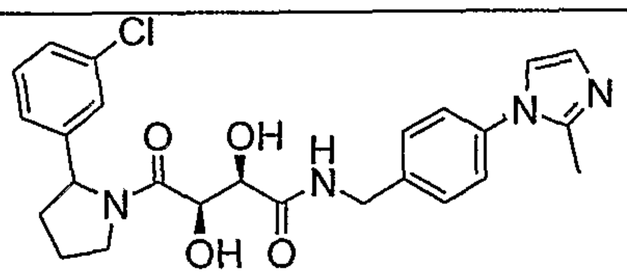
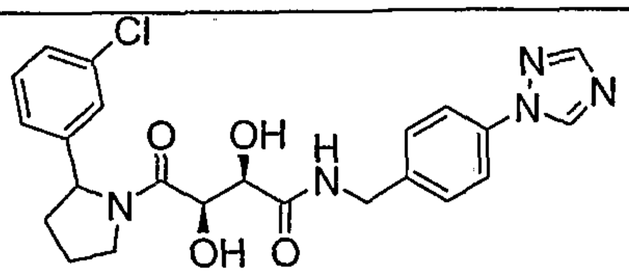
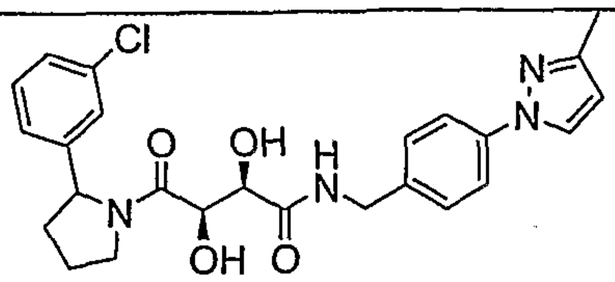
836		
839		
846		
852		
855		
857		
858		
859		
860		
861		

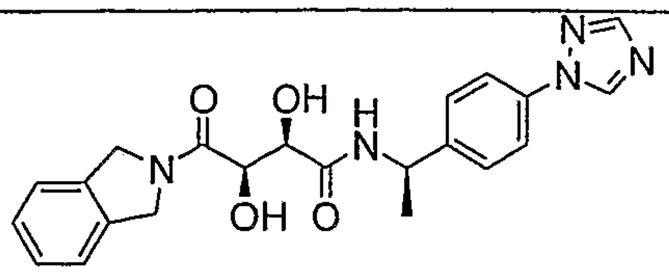
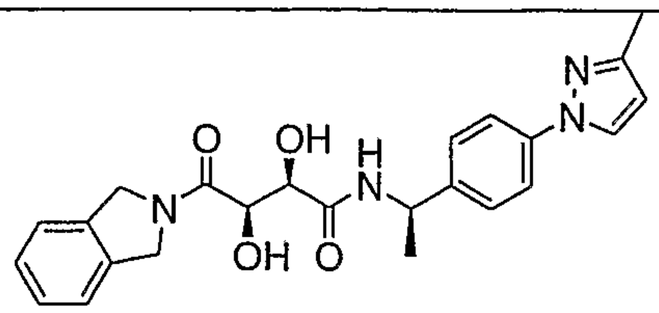
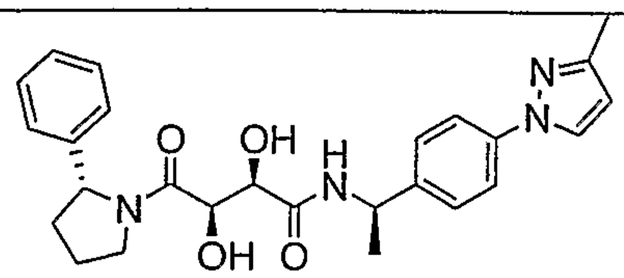
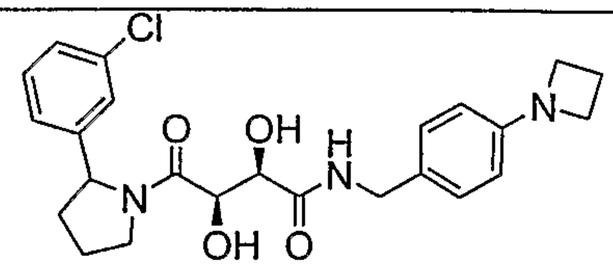
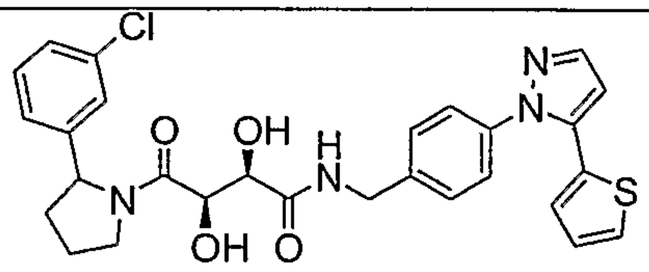
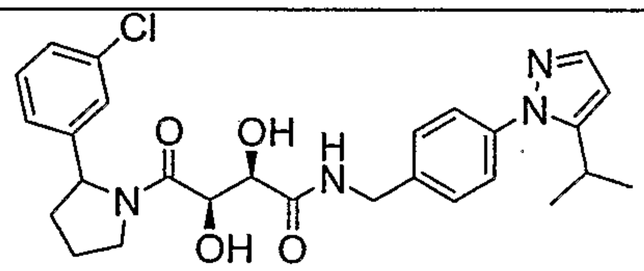
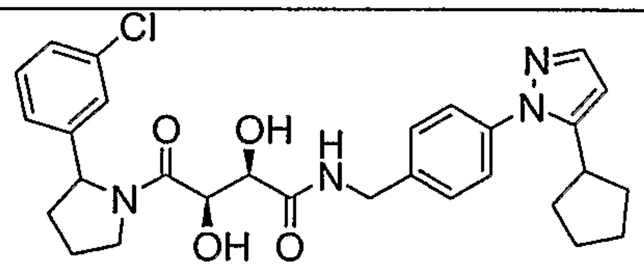
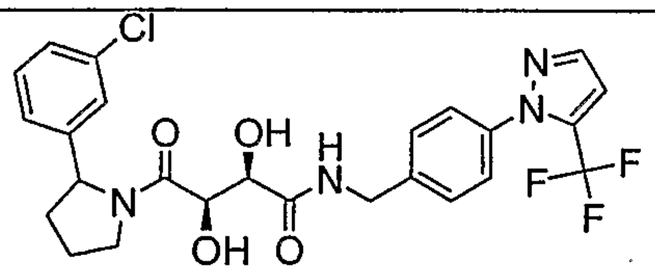
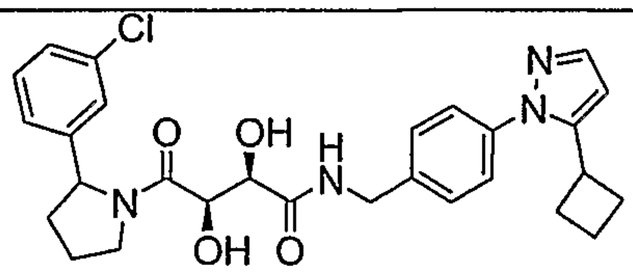
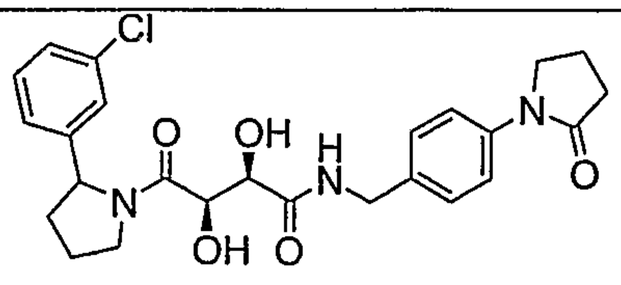
862		
863		
864		
865		
866		
867		
868		
869		
870		
871		

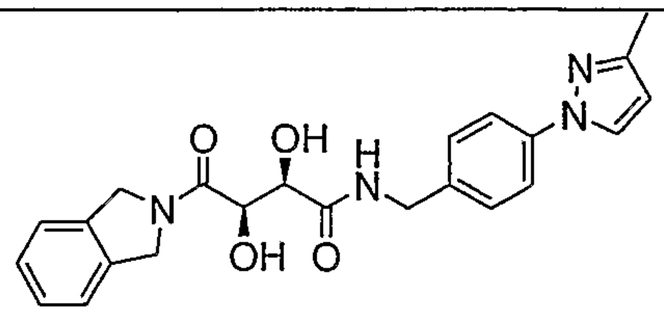
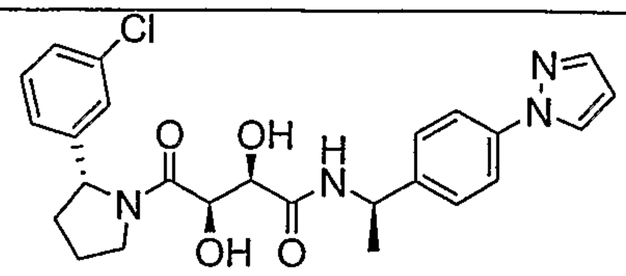
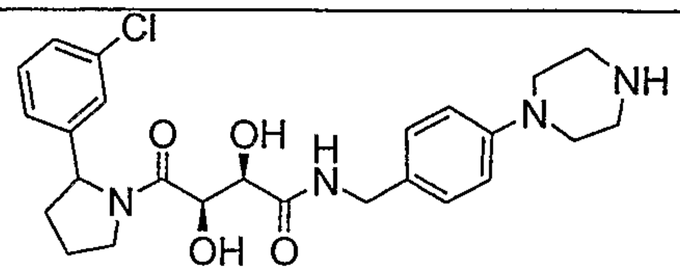
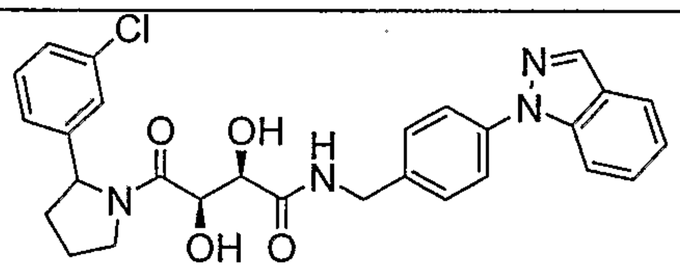
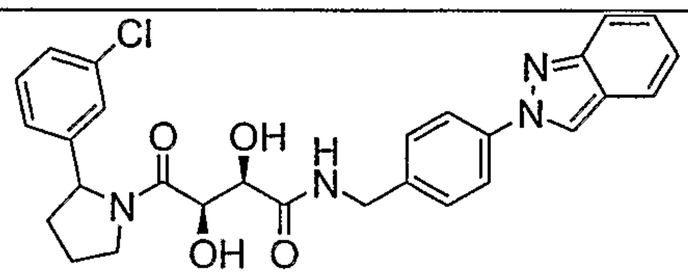
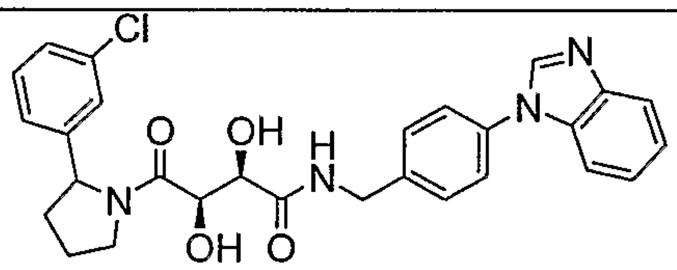
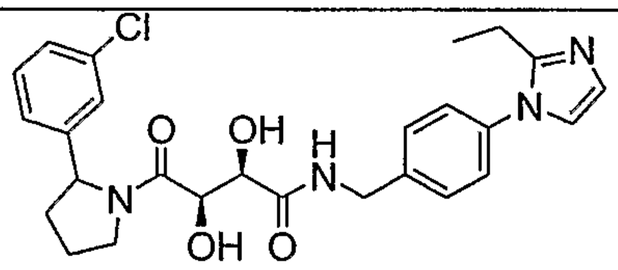
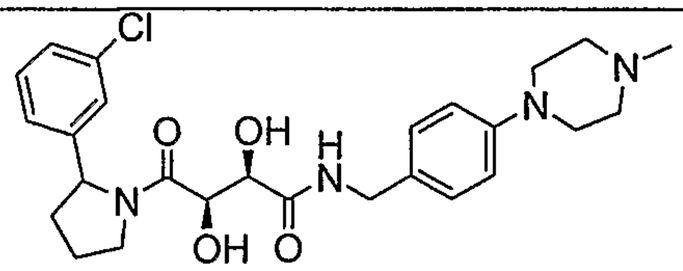
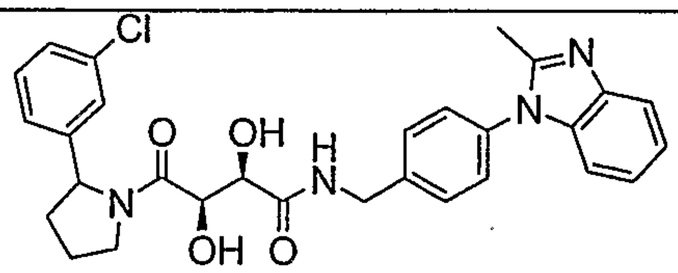
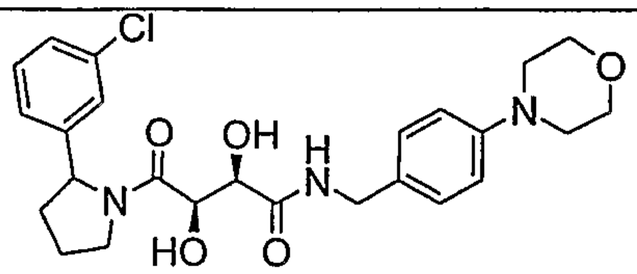
872		
873		
874		
875		
876		
877		
878		
879		
880		
884		

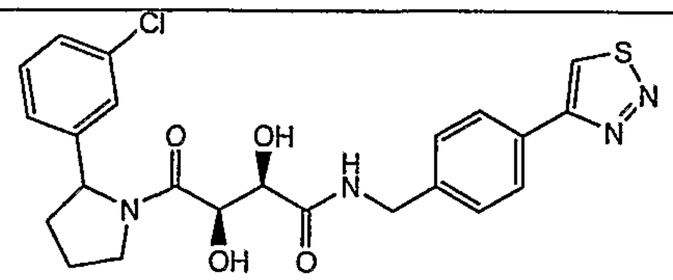
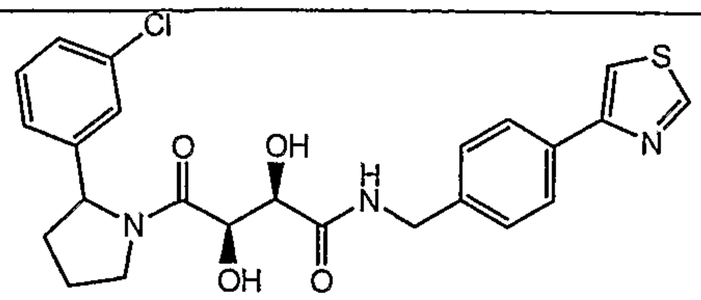
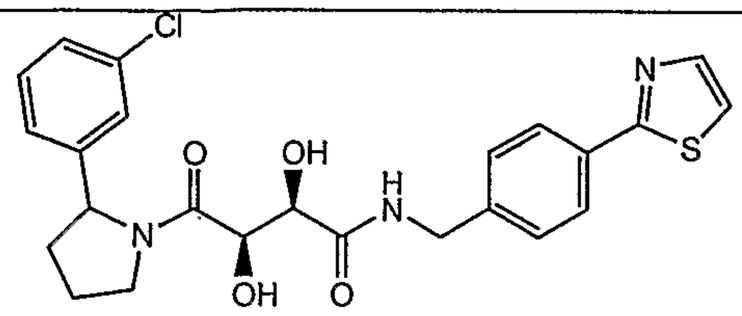
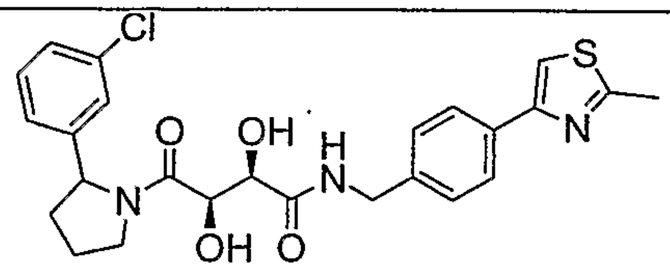
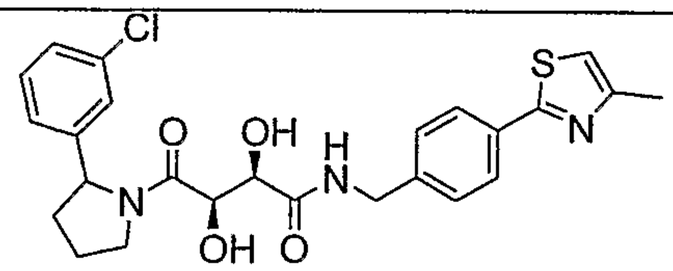
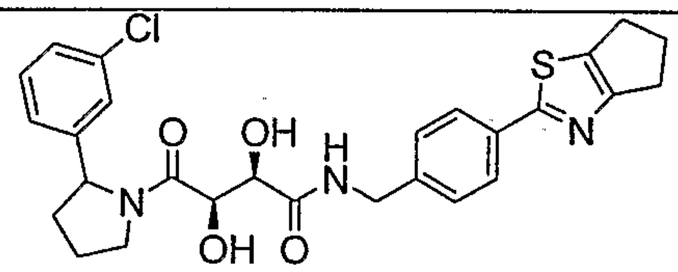
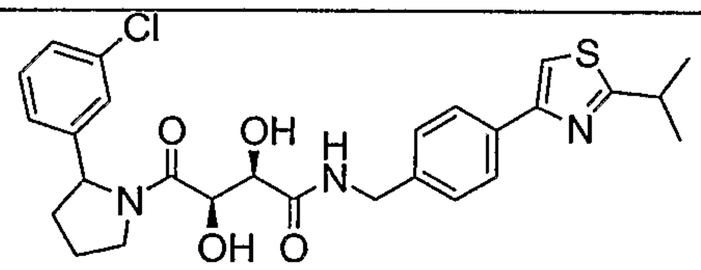
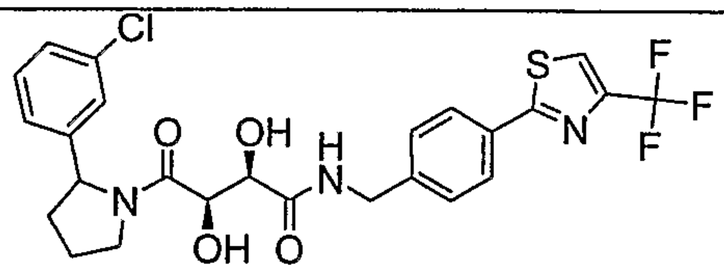
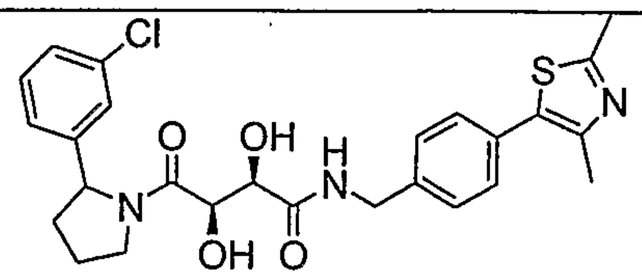
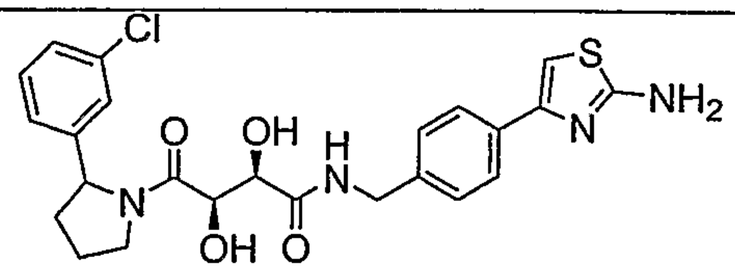
890		
891		
894		
897		
898		
899		
900		
901		
902		

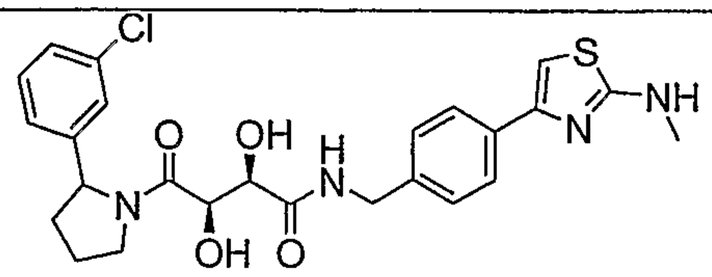
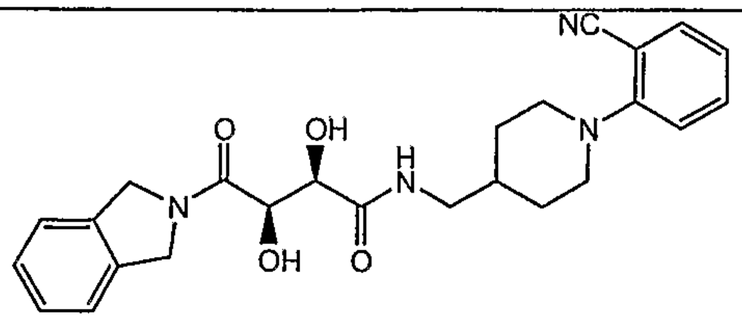
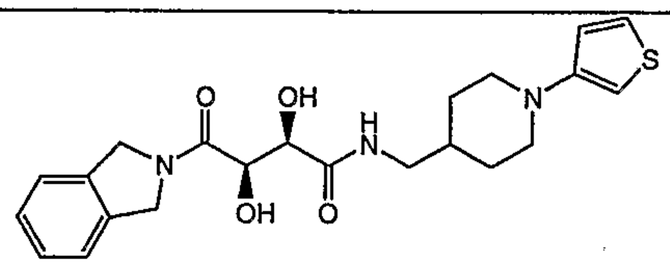
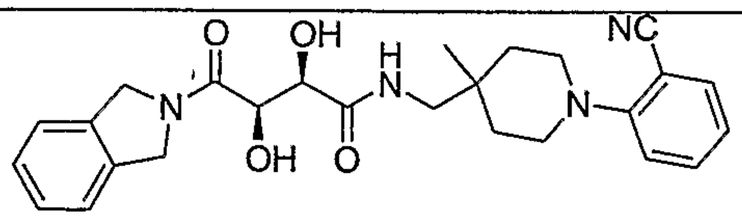
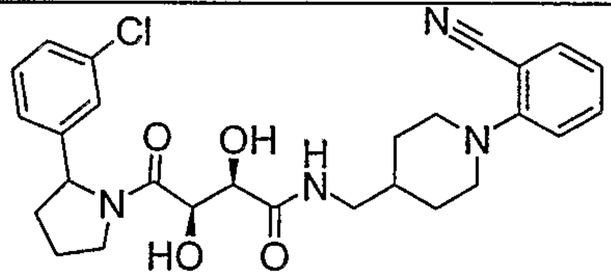
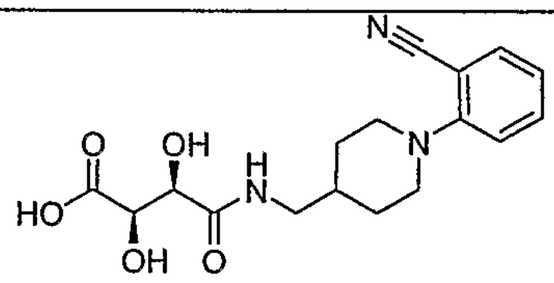
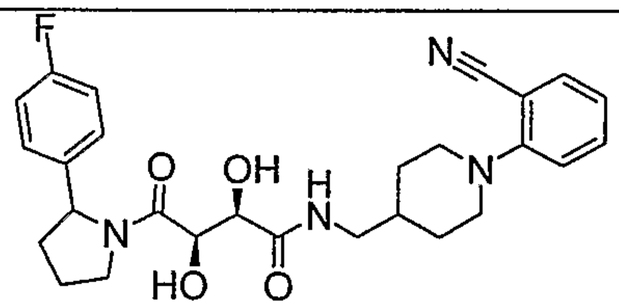
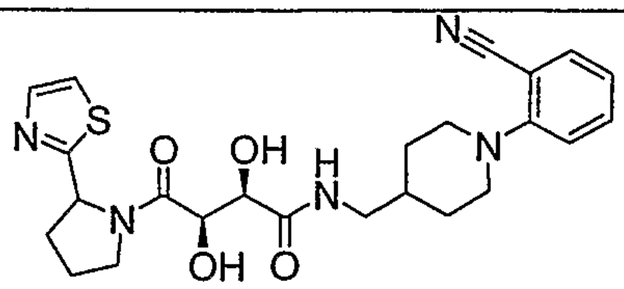
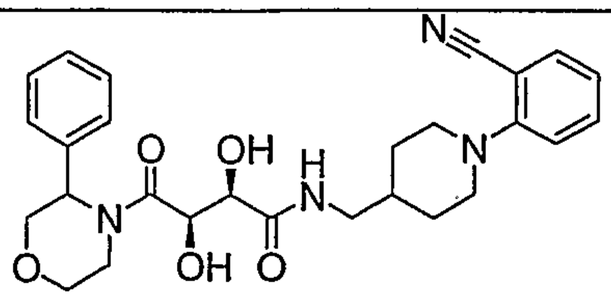
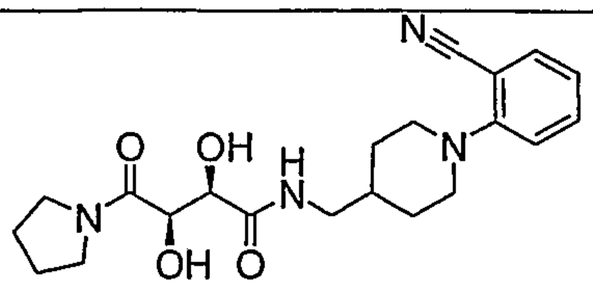
903		
905		
910		
914		
918		
919		
920		
921		
922		

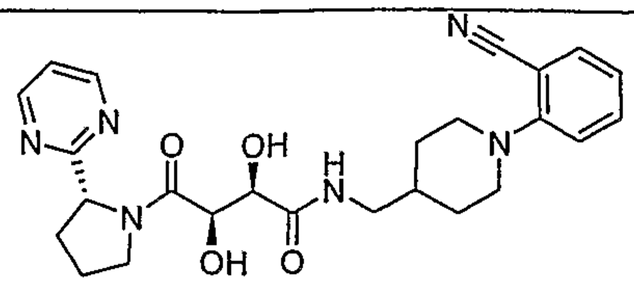
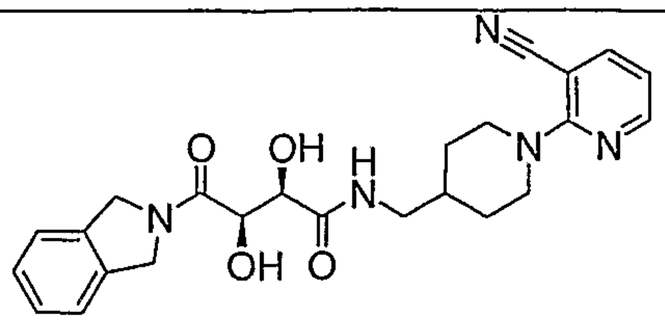
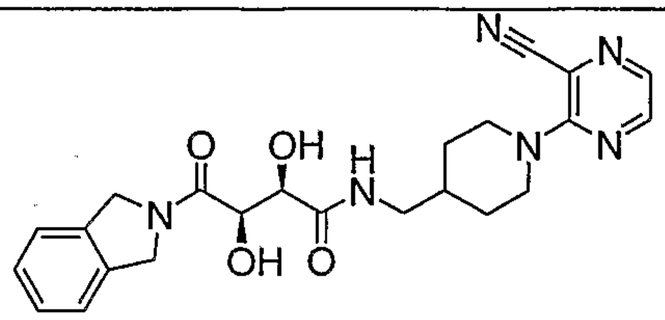
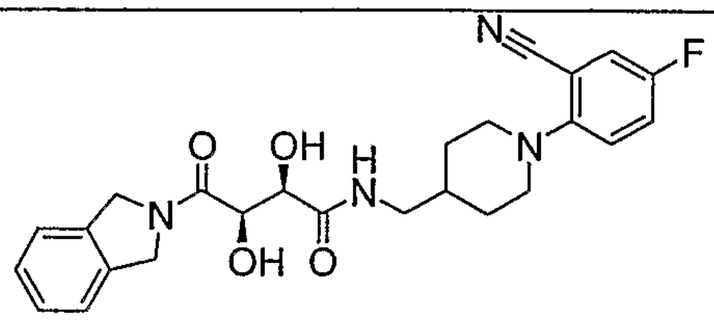
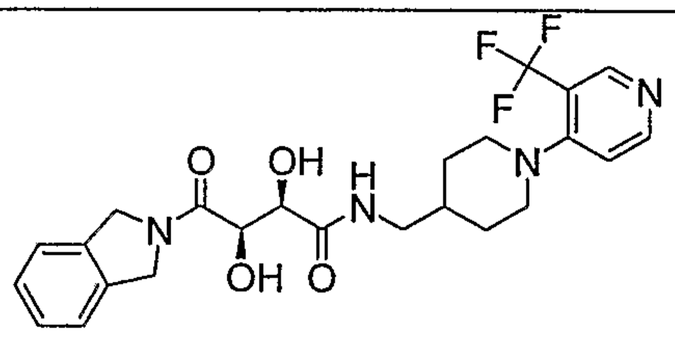
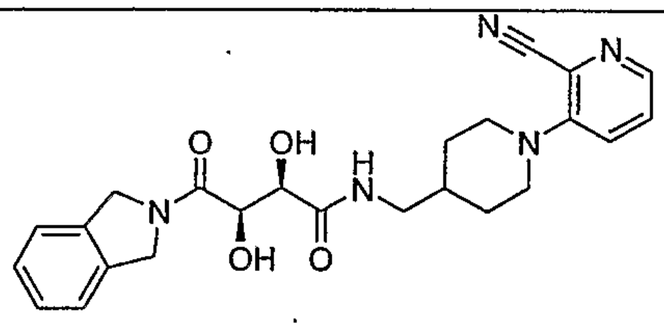
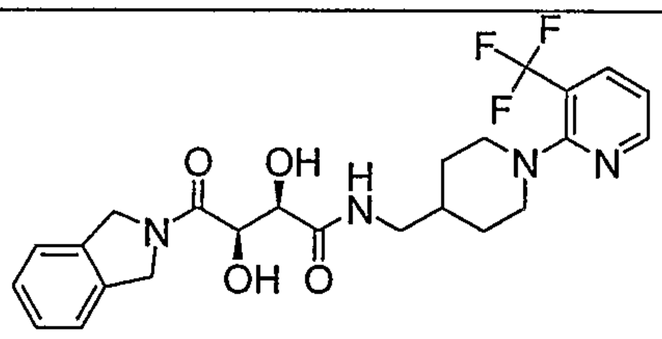
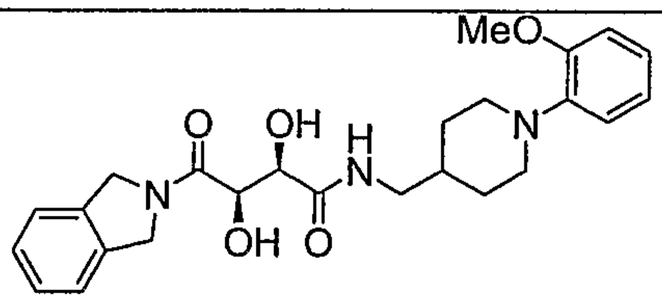
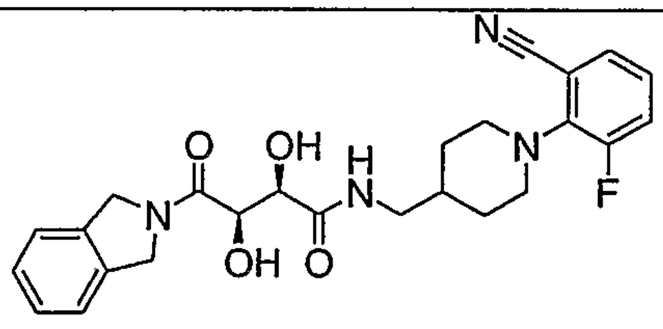
923		
924		
925		
926		
927		
928		
929		
930		
931		
932		

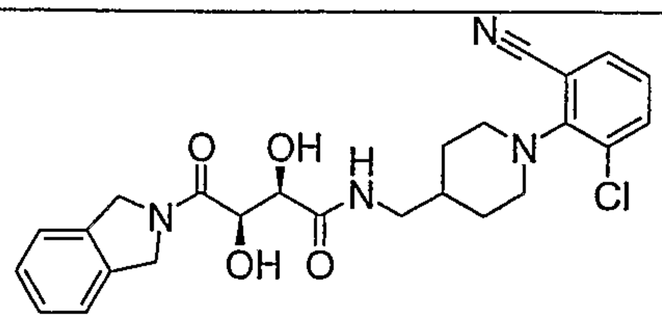
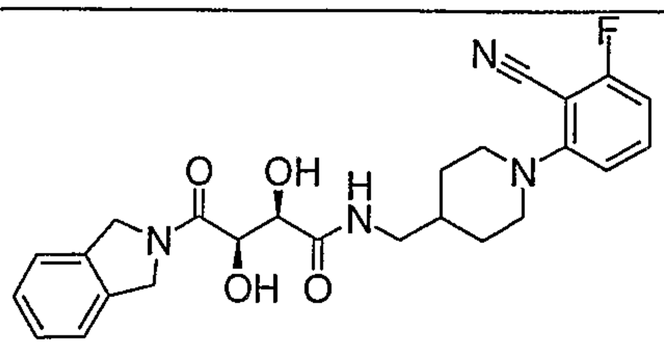
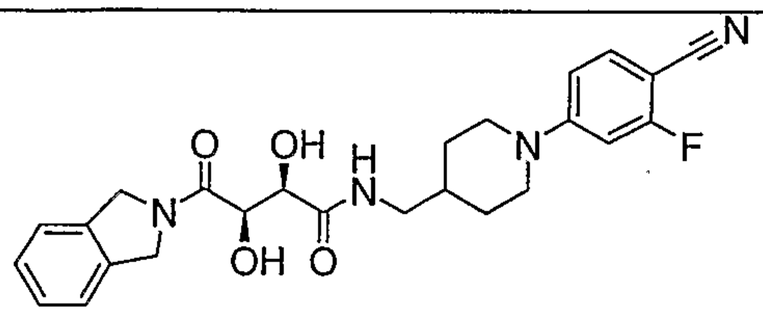
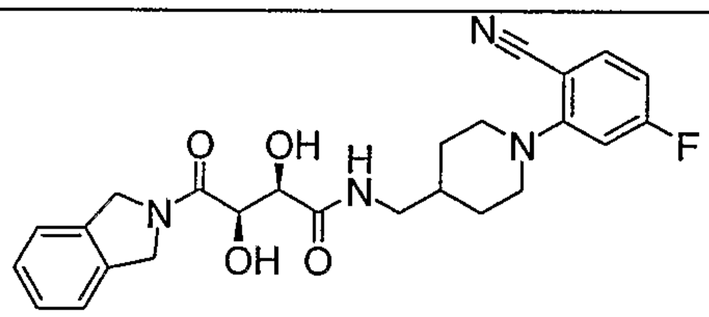
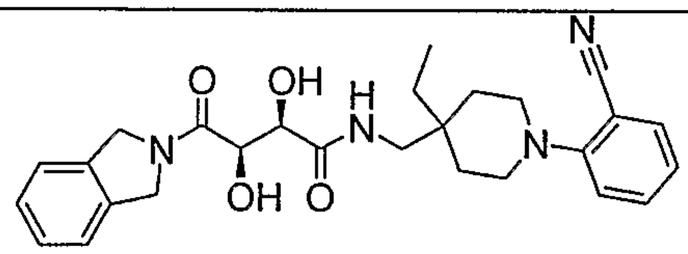
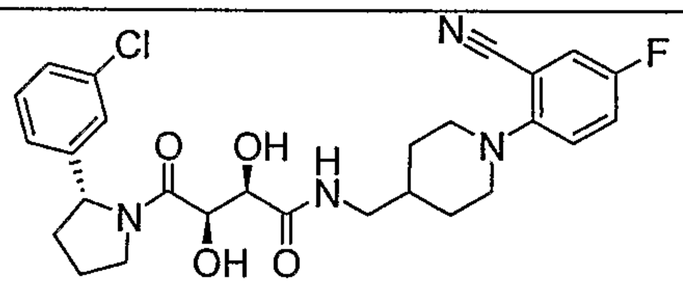
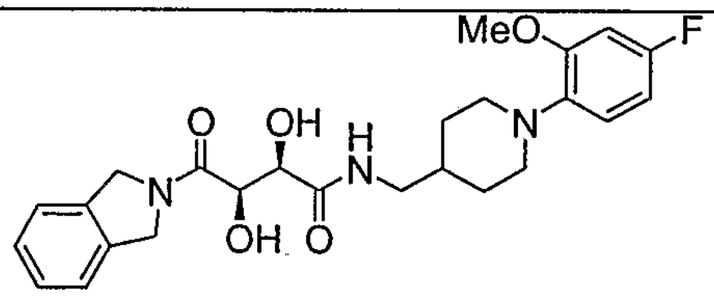
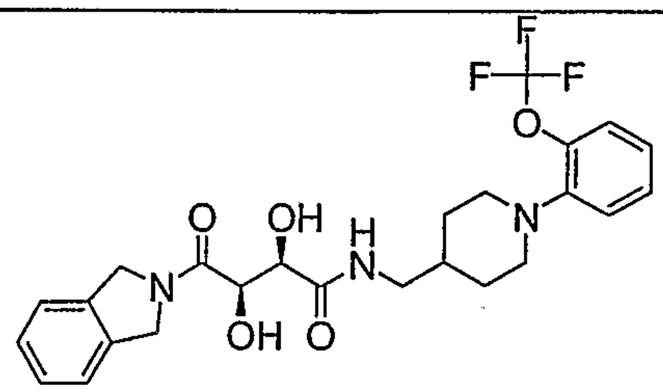
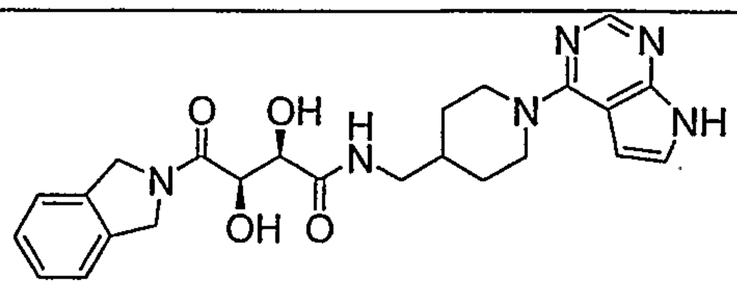
933		
934		
935		
936		
937		
938		
939		
940		
941		
942		

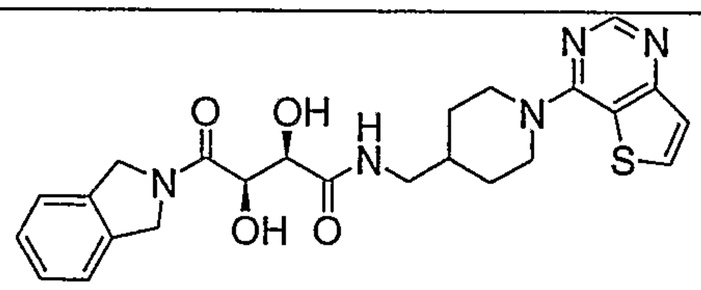
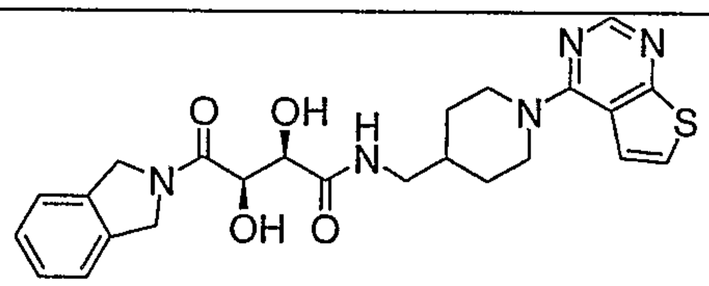
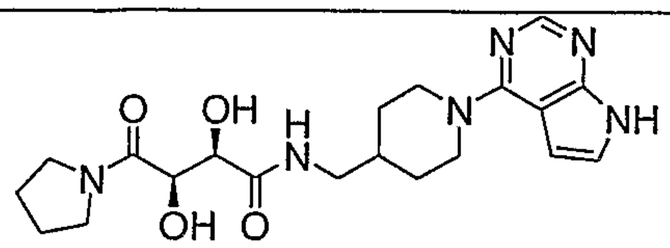
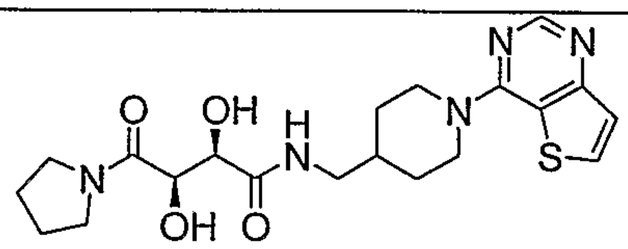
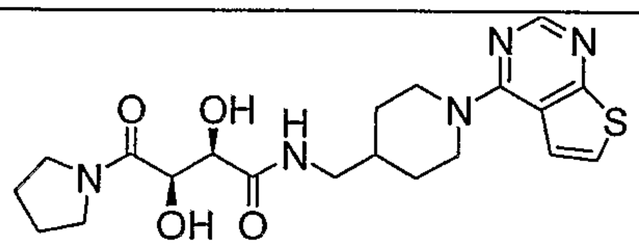
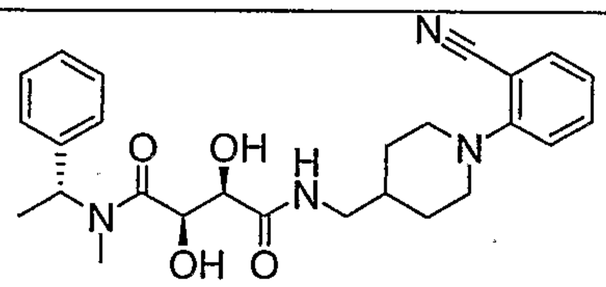
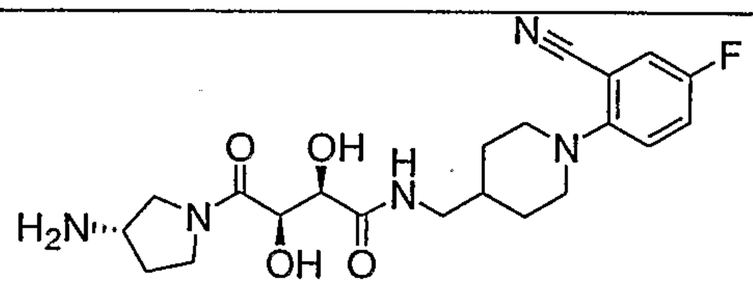
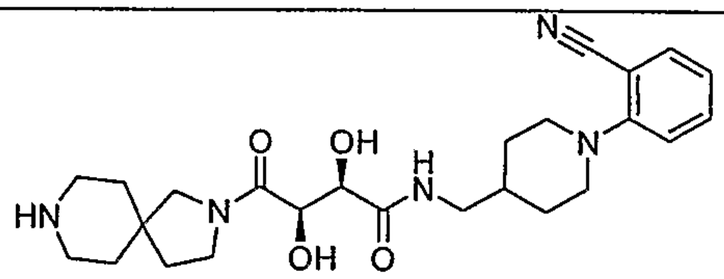
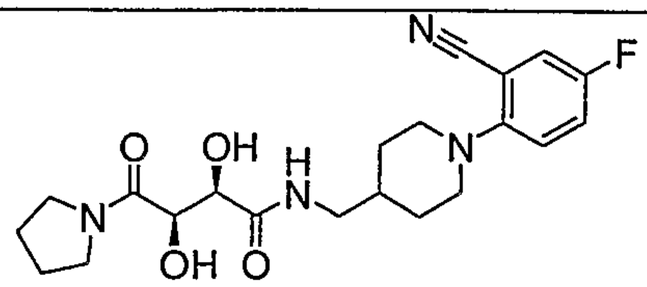
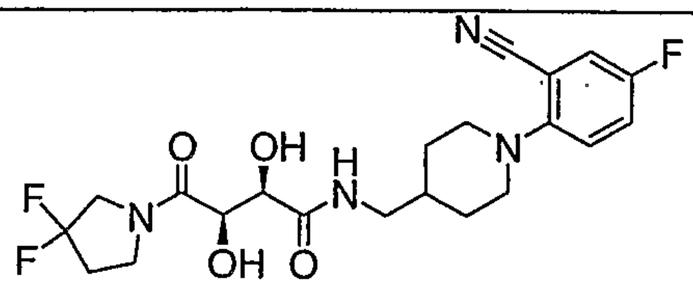
943		
944		A
945		
946		
947		
948		
949		
950		
951		
952		

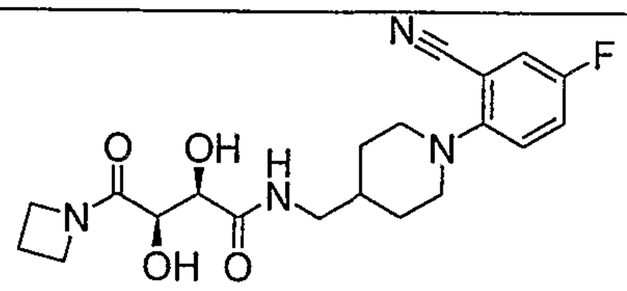
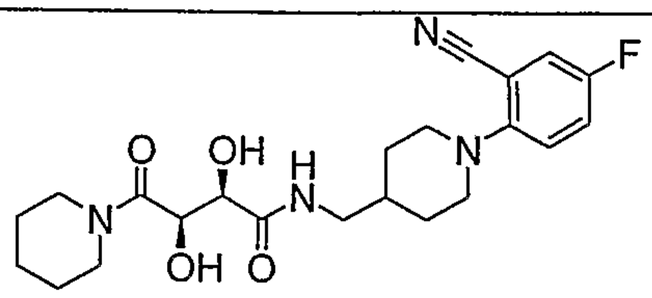
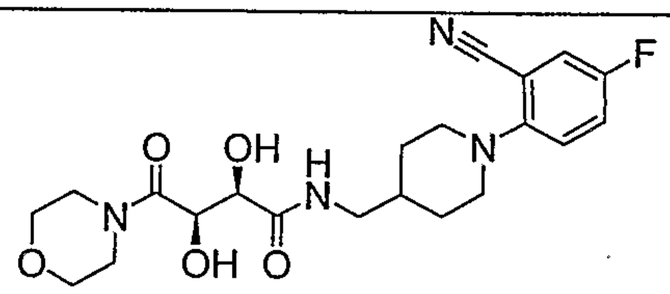
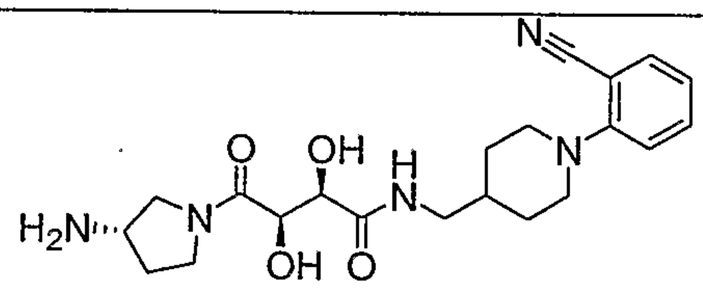
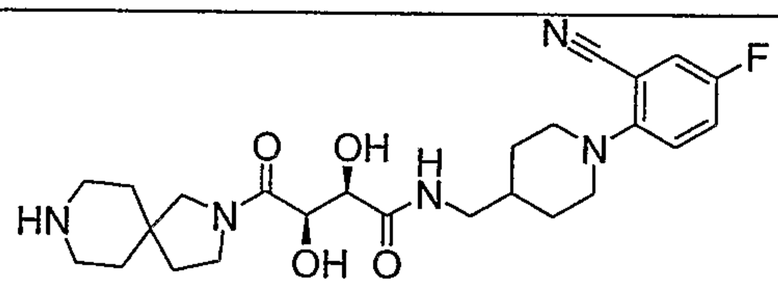
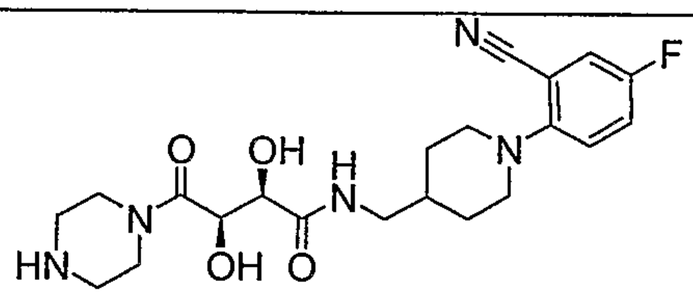
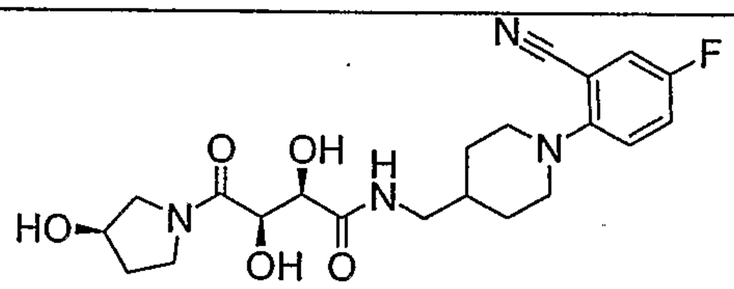
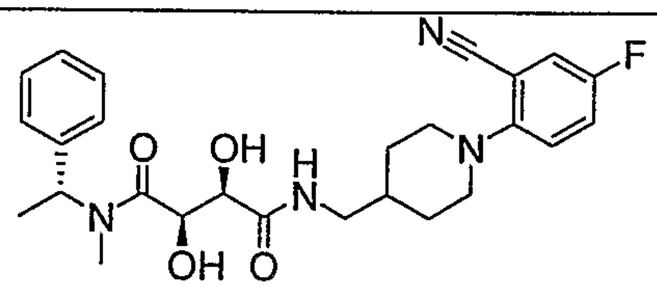
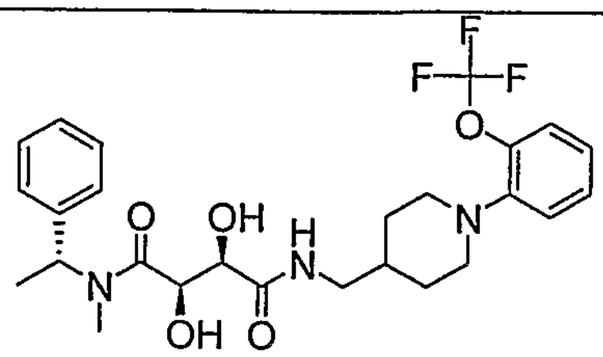
954		
961		
968		
969		
970		
971		
972		
973		
974		
975		

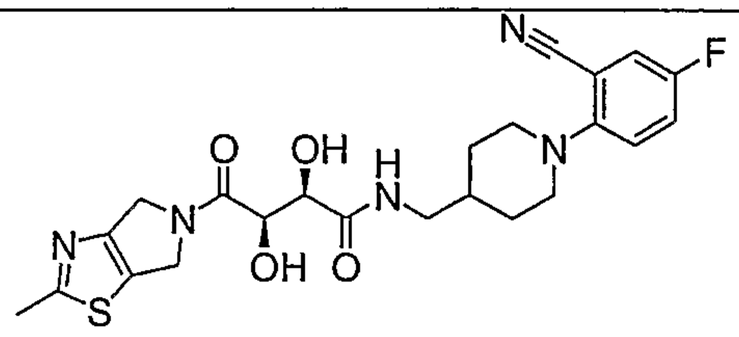
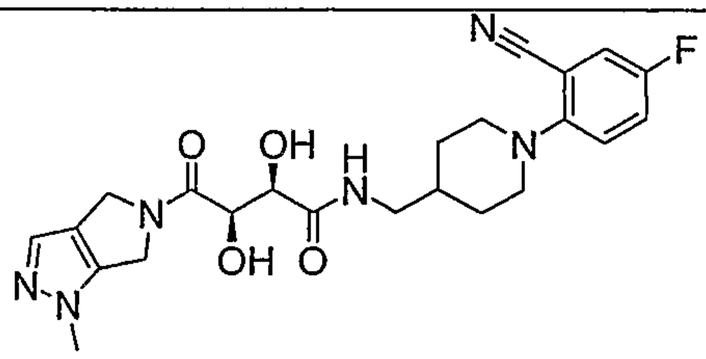
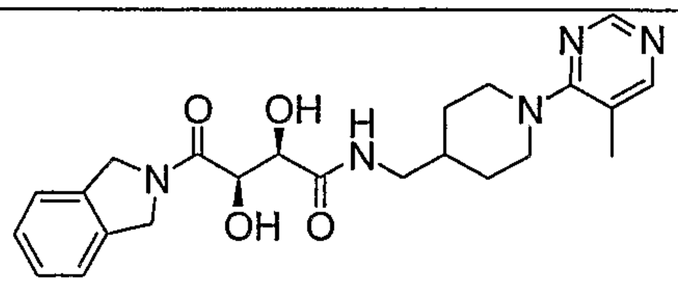
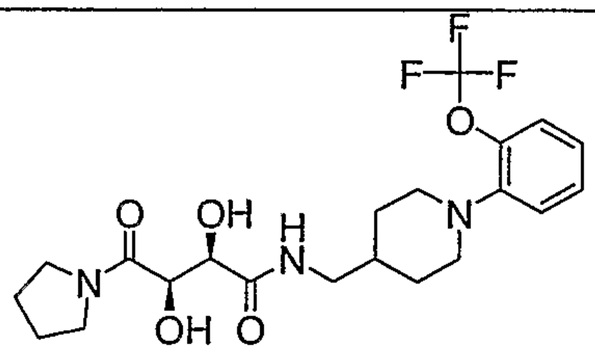
976		
980		
985		
994		
995		
996		
997		
998		
999		
1000		

1001		
1002		
1003		
1004		
1005		
1006		
1007		
1008		
1009		

1010		
1011		
1012		
1013		
1014		
1015		
1016		
1017		
1018		

1019		
1020		
1021		
1022		
1023		
1024		
1025		
1026		
1027A		
1027B		

1027C		
1028		
1029		
1030		
1031		
1032		
1033		
1034A		
1034B		

1035		
1036		
1037		
1038A		
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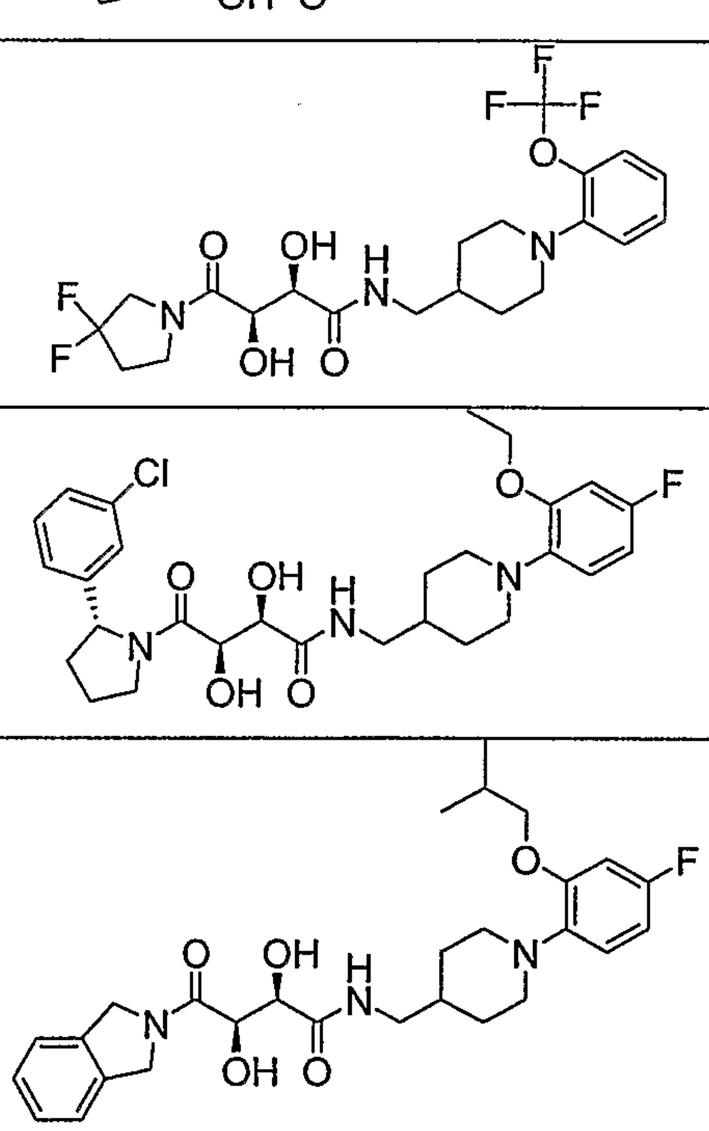
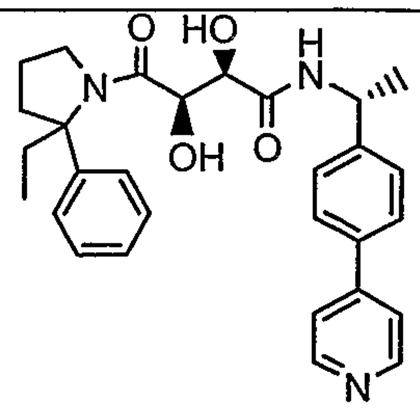
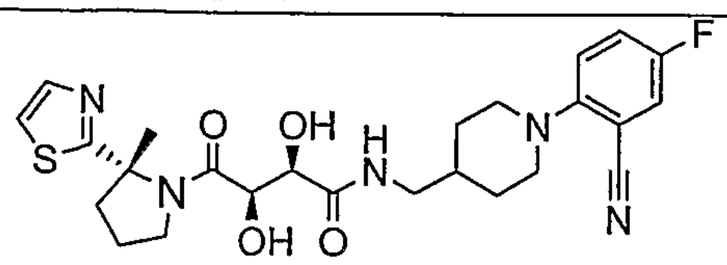
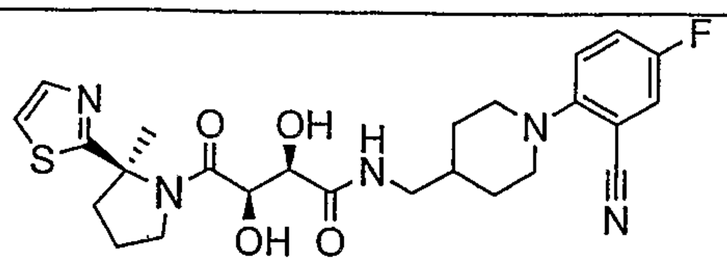
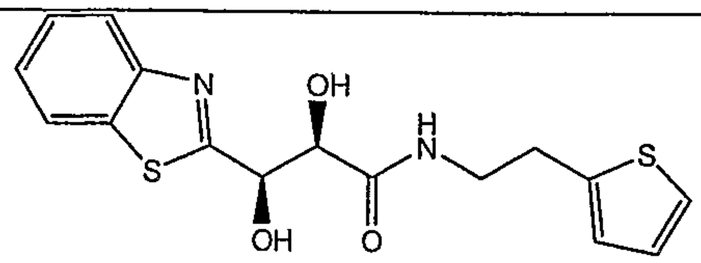
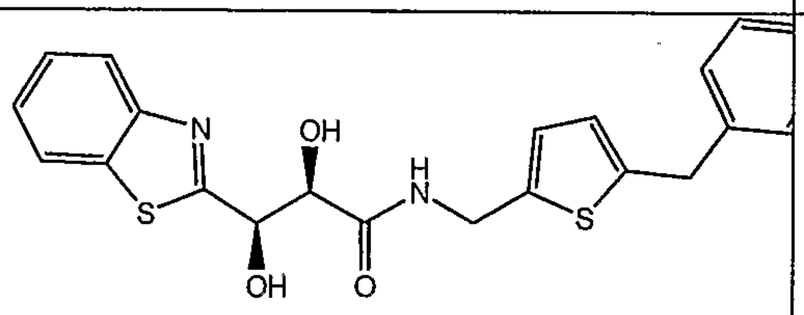
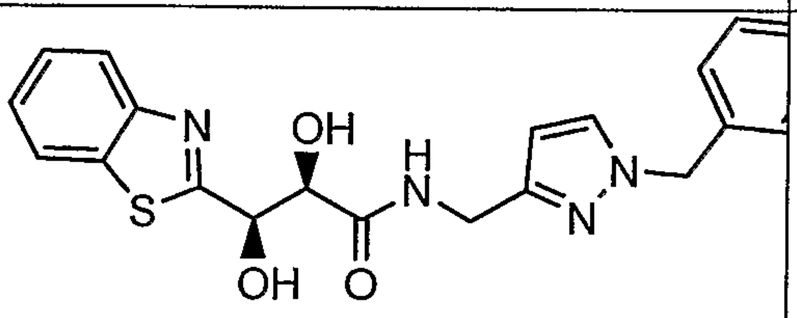
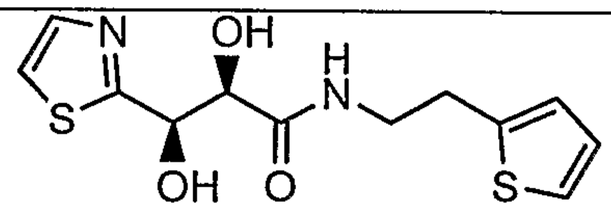
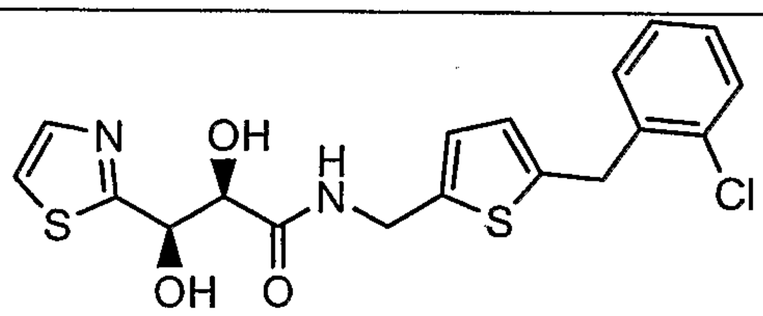
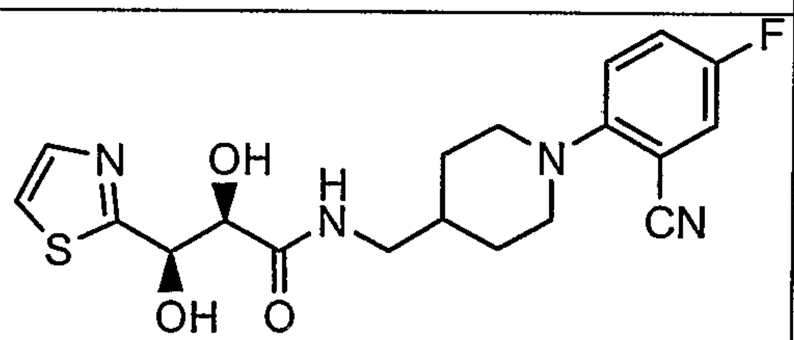
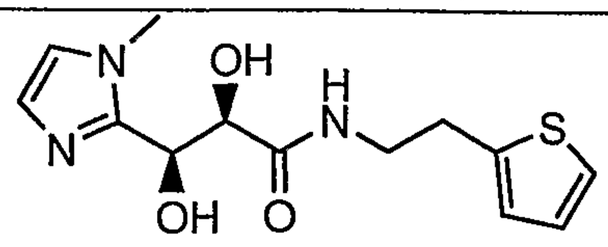
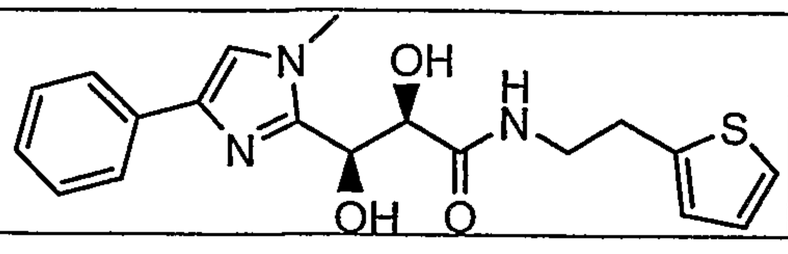
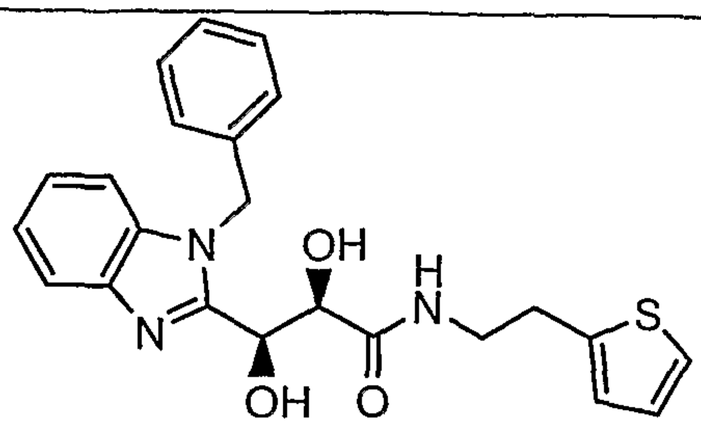
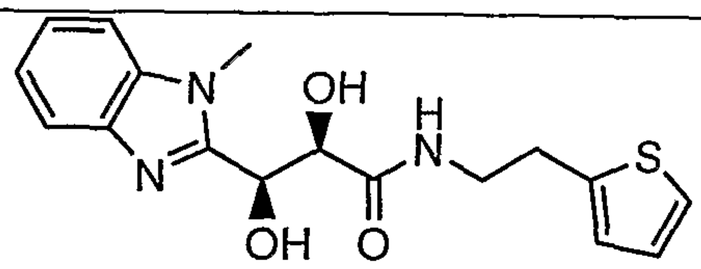
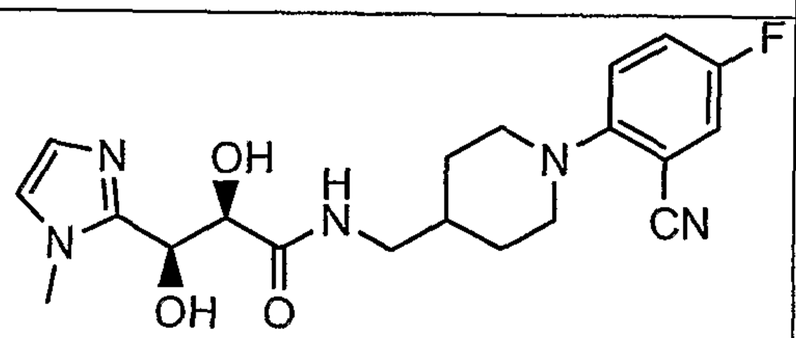
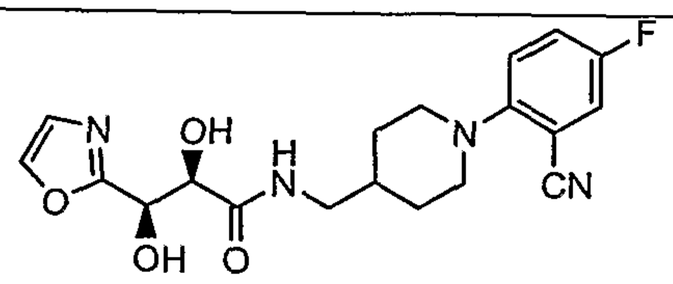
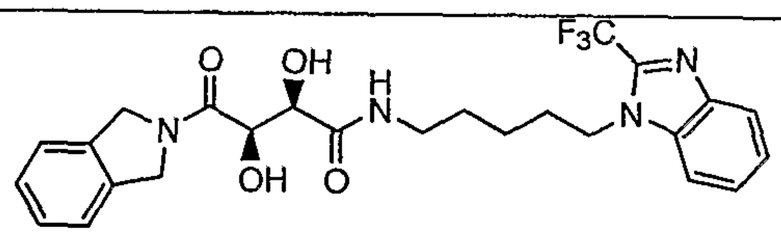
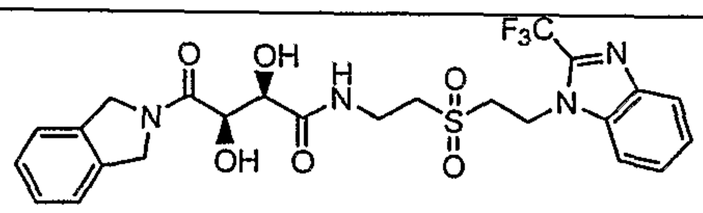
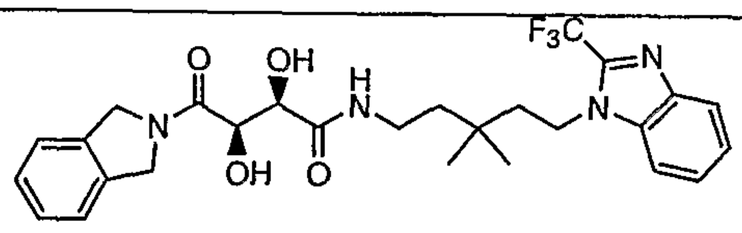
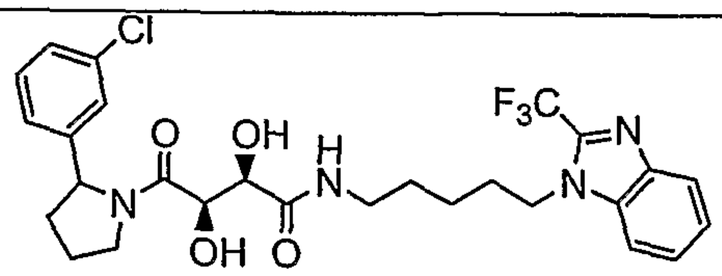
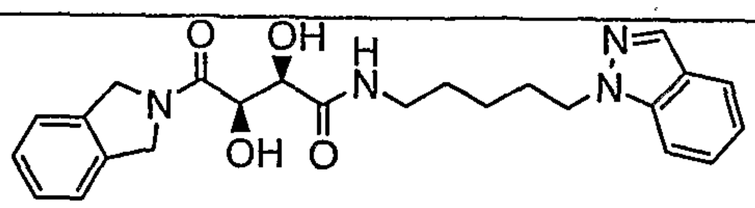
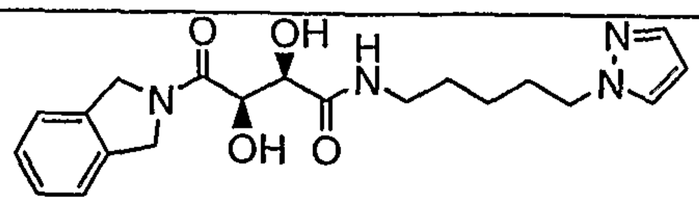
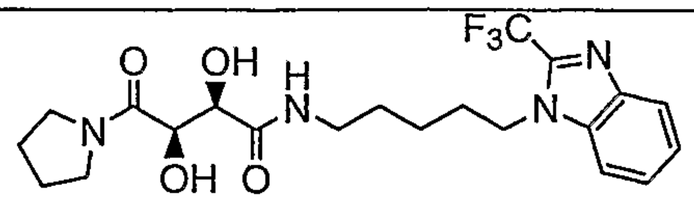
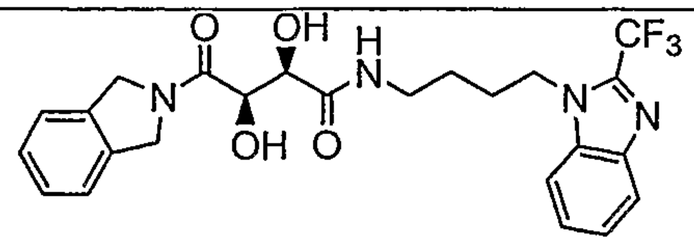
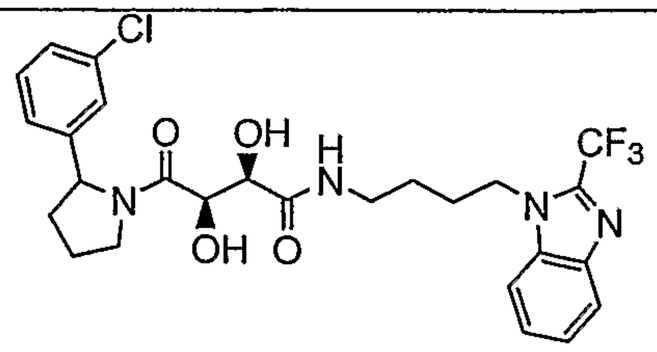
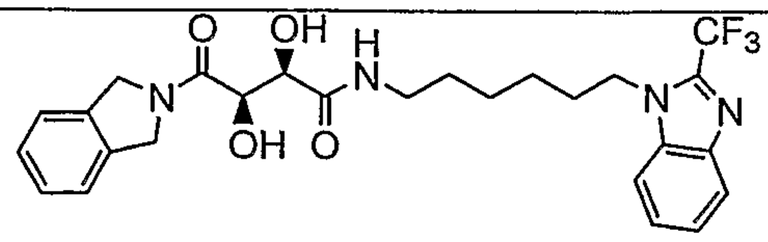
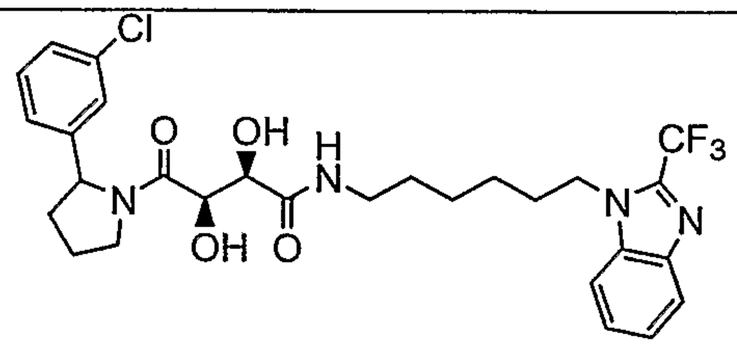
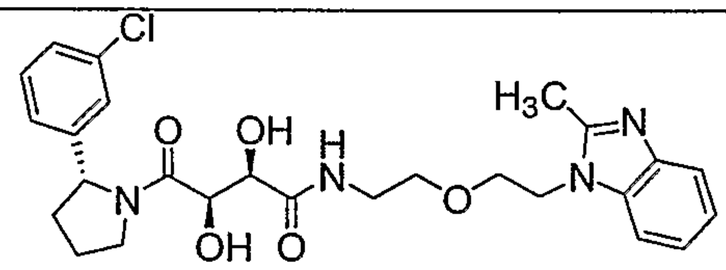
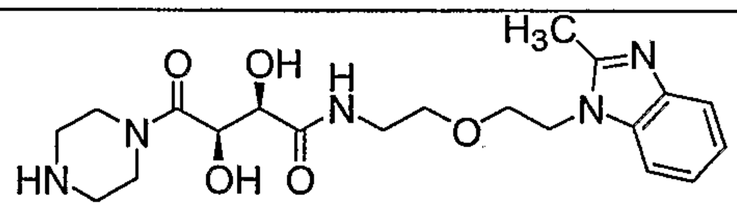
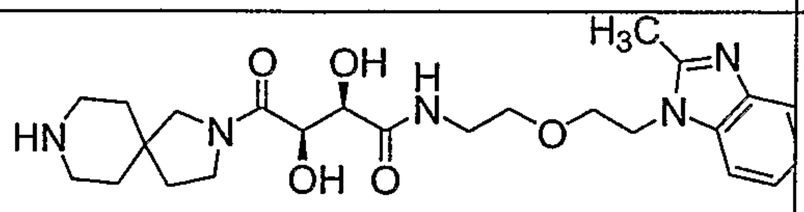
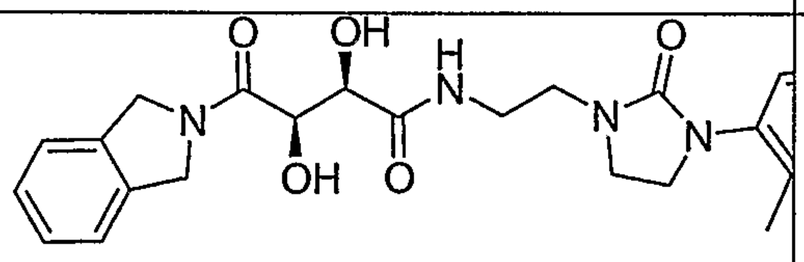
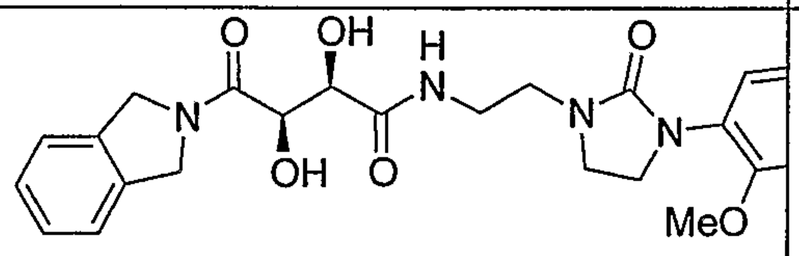
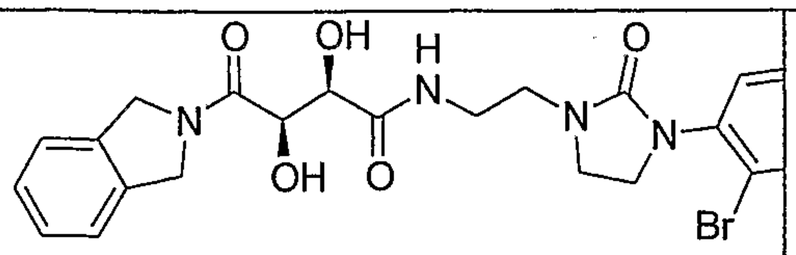
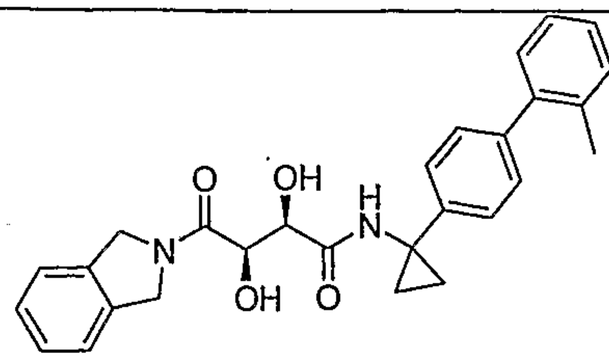
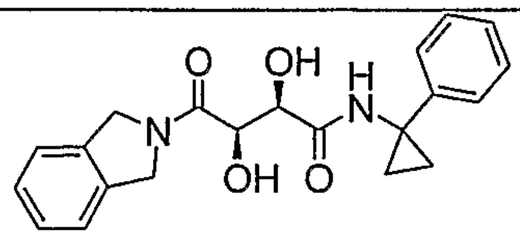
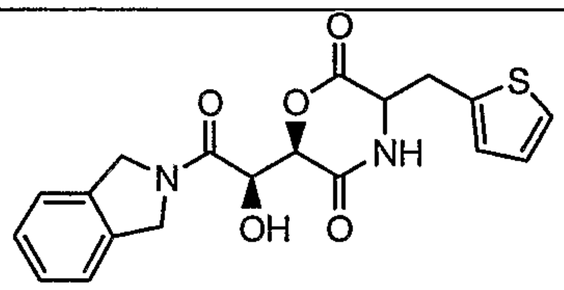
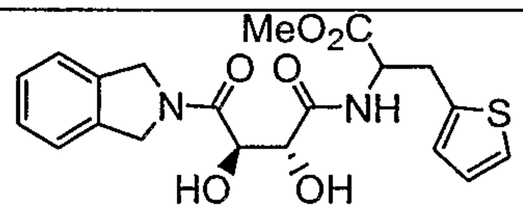
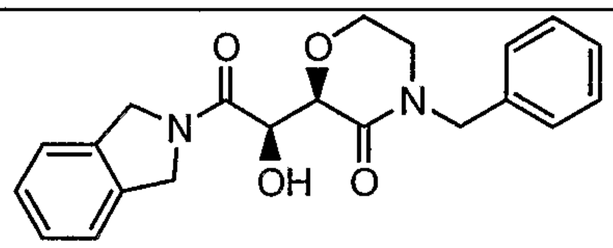
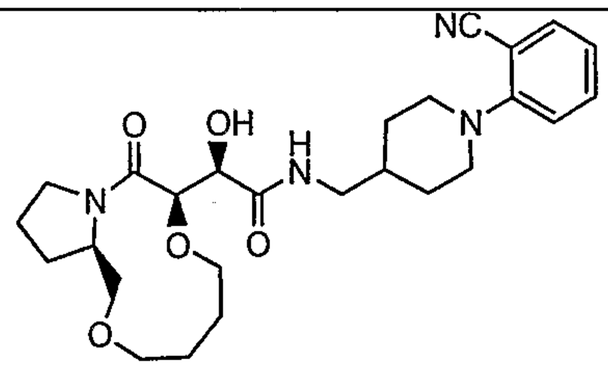
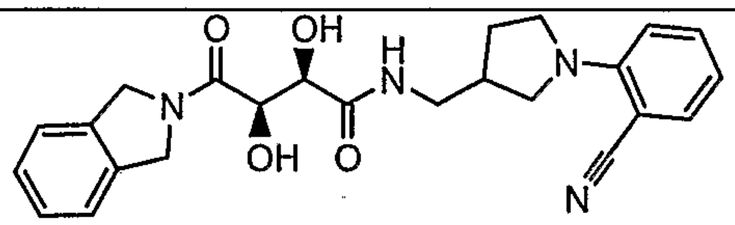
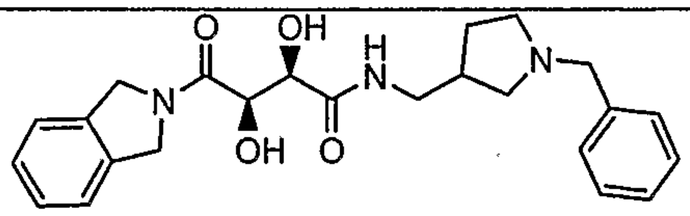
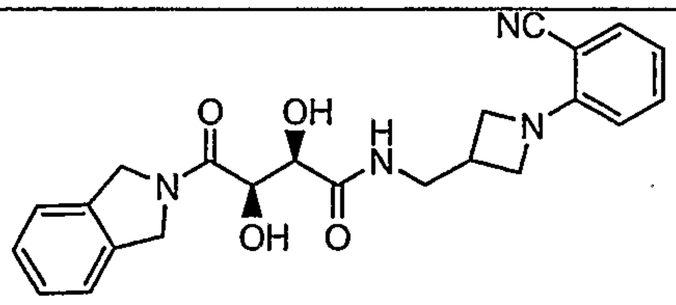
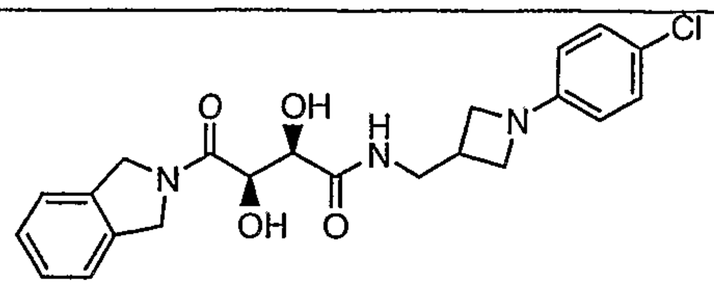
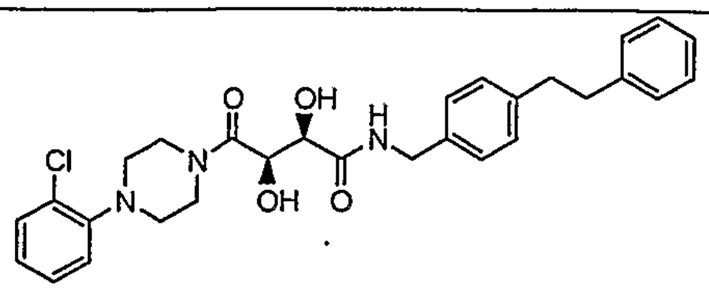
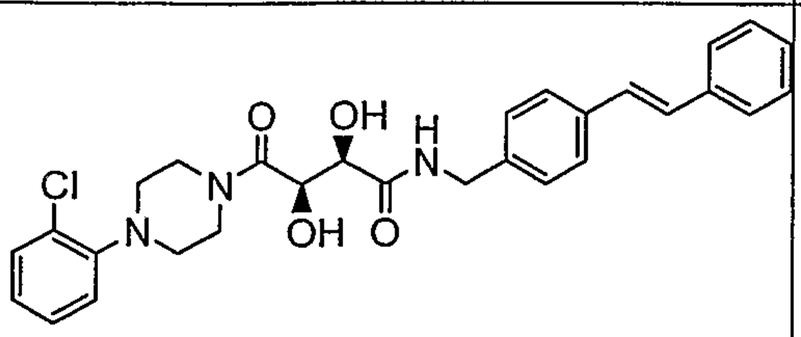
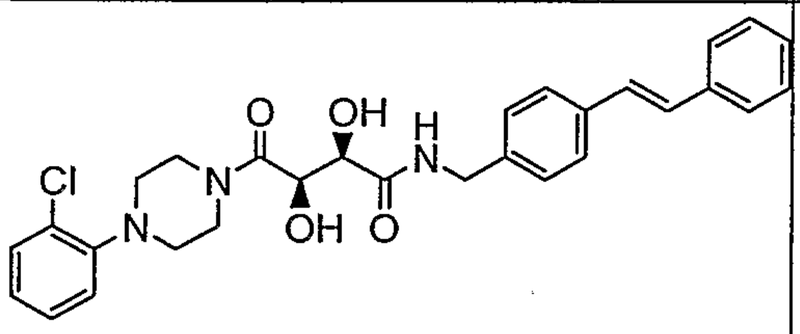
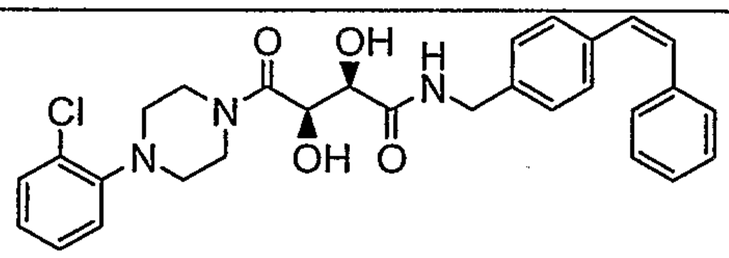
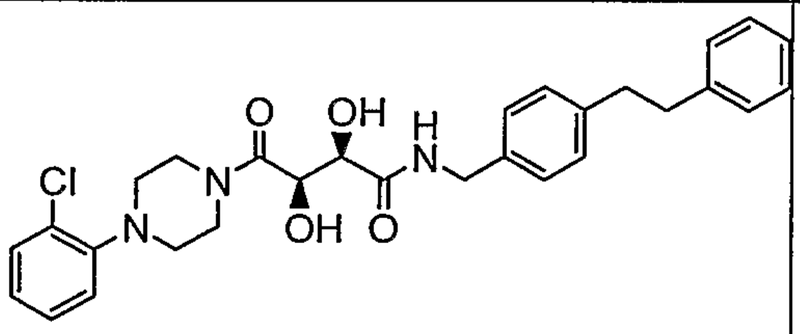
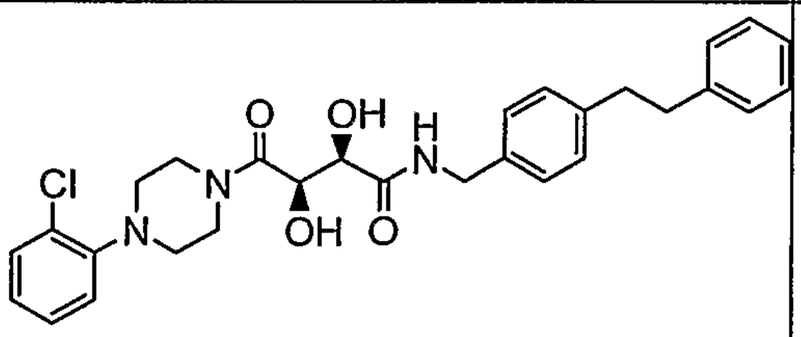
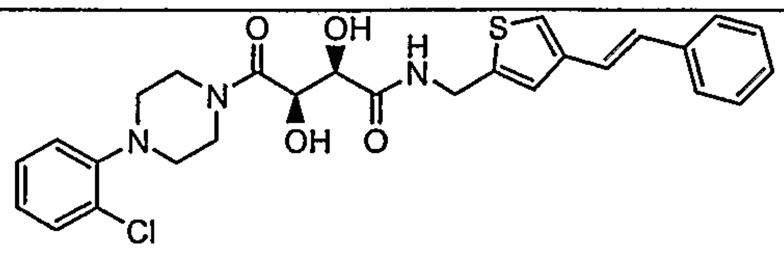
1040		
863		

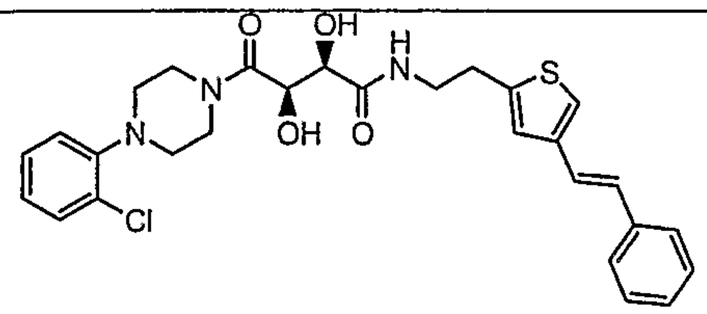
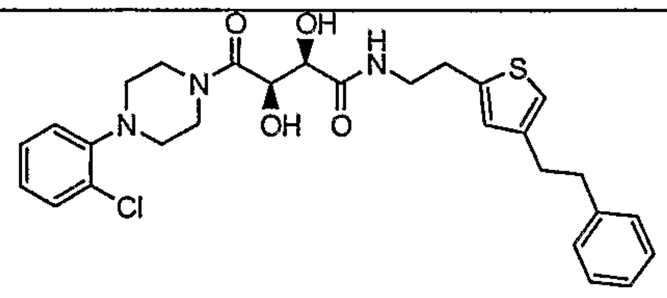
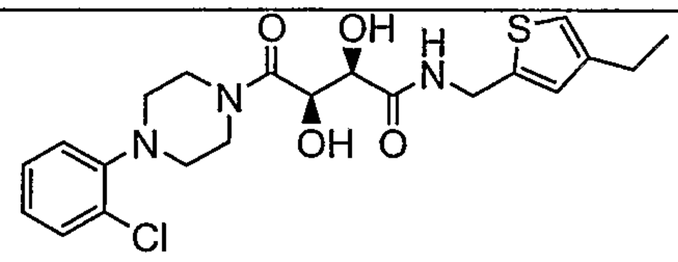
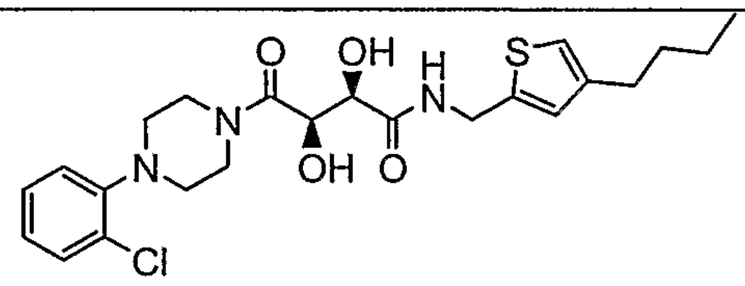
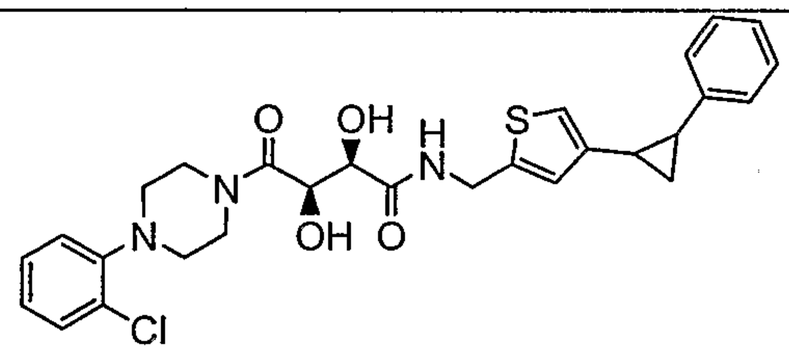
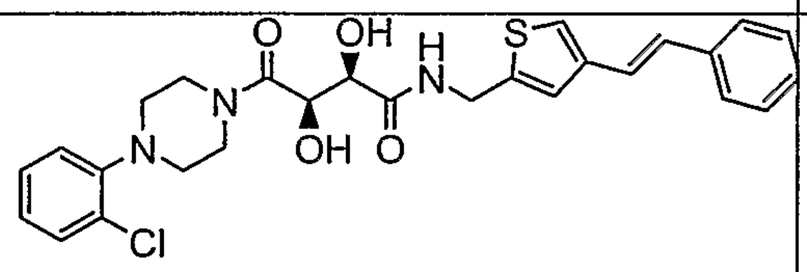
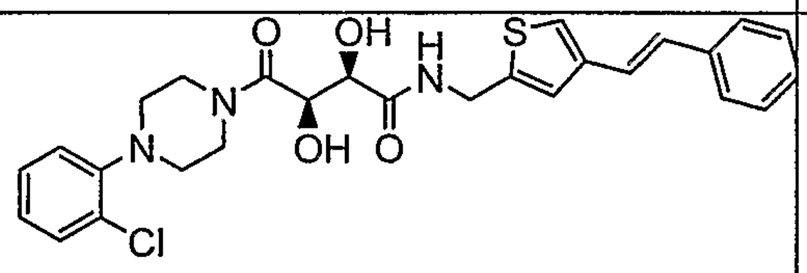
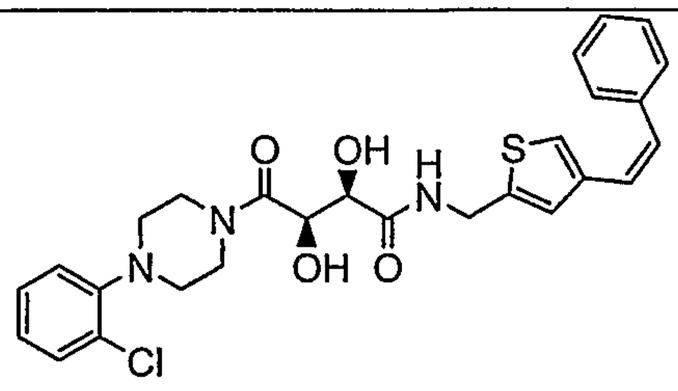
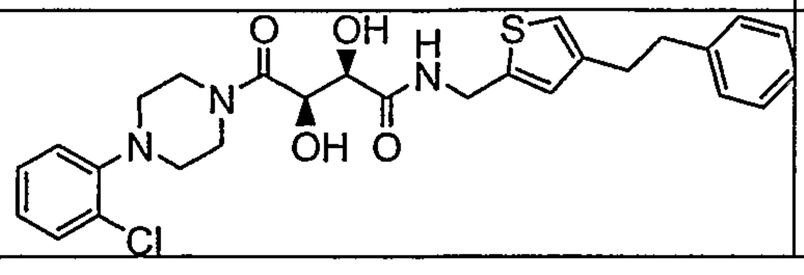
1048A		
1048B		
1052		
1053		
1054		
1059		
1060		
1061		
1063		
1066		

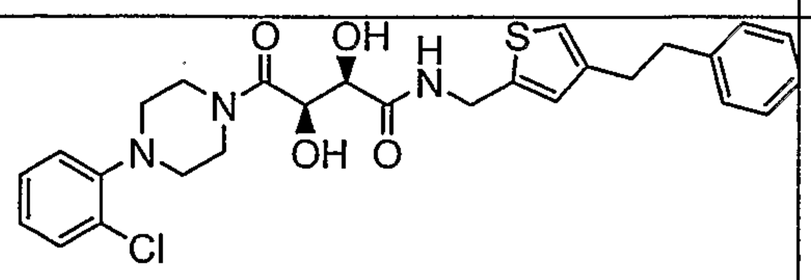
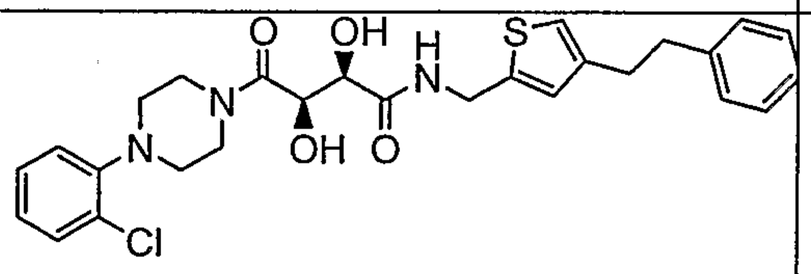
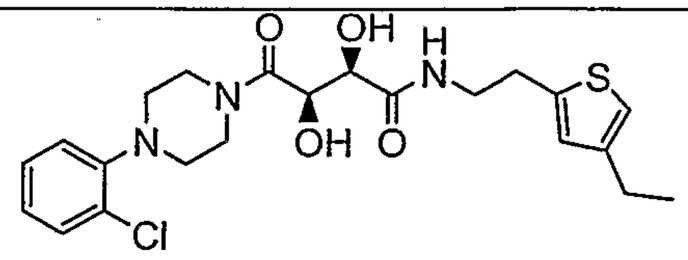
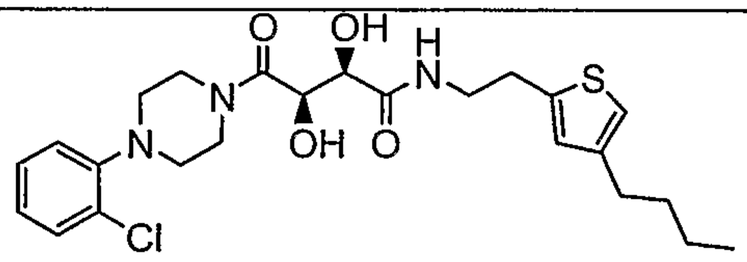
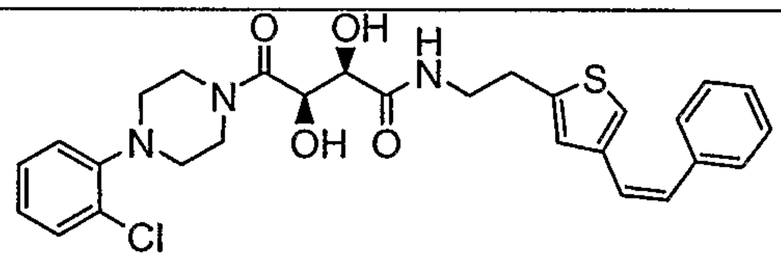
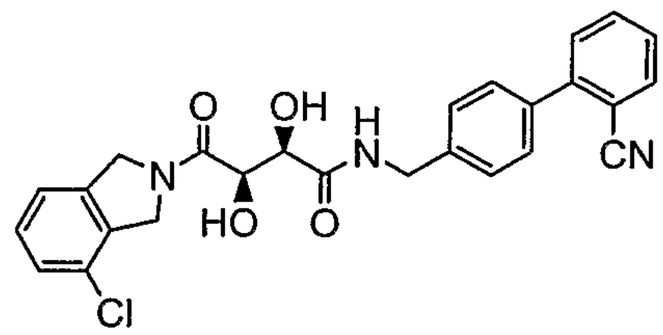
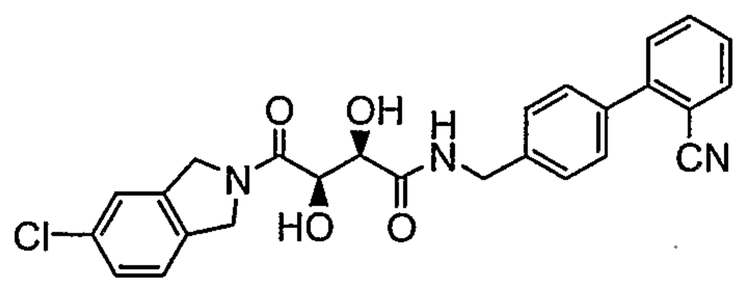
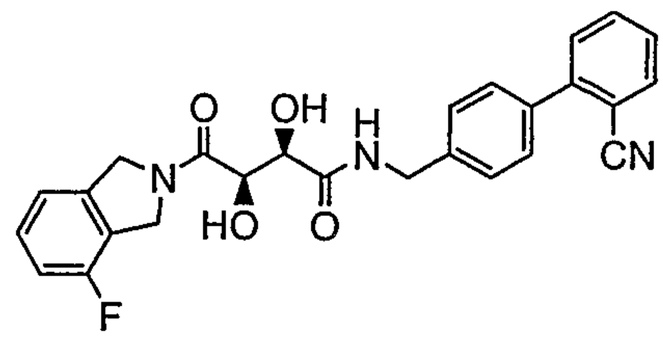
1071		
1072		
1073		
1079		
1085		
1093		
1103		
1104		
1105		
1106		

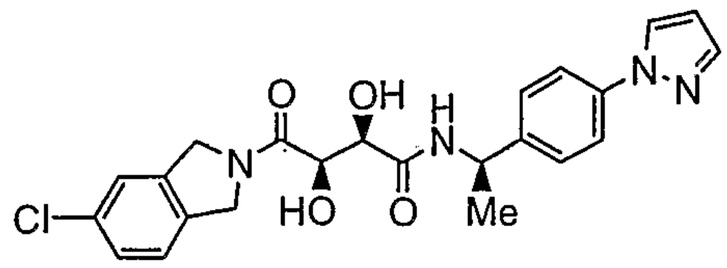
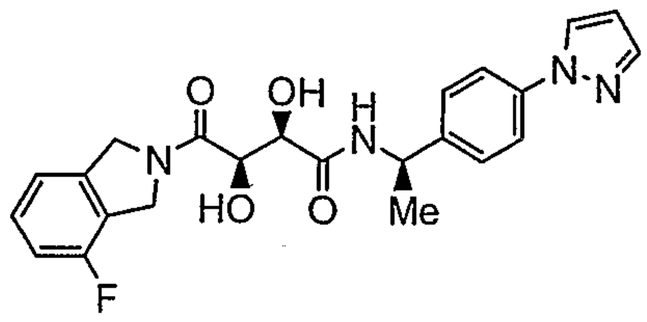
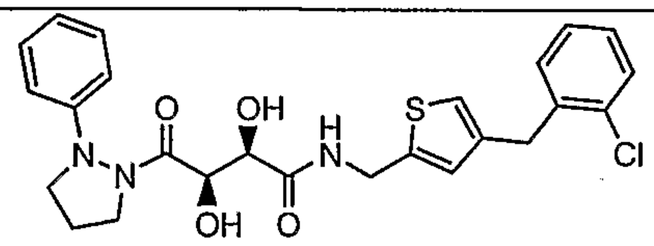
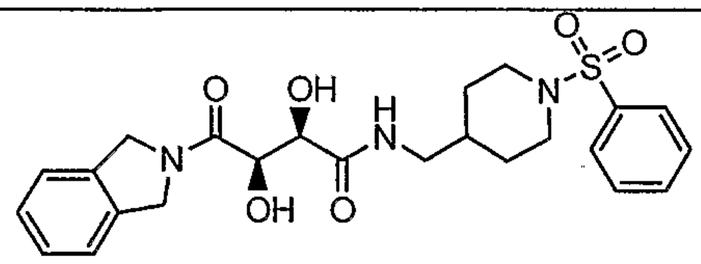
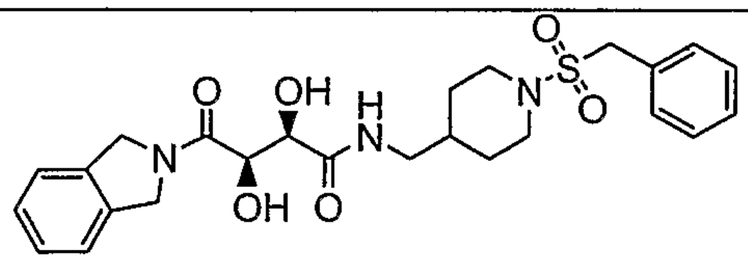
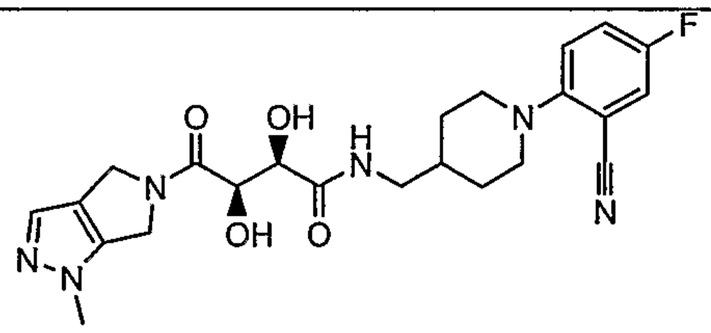
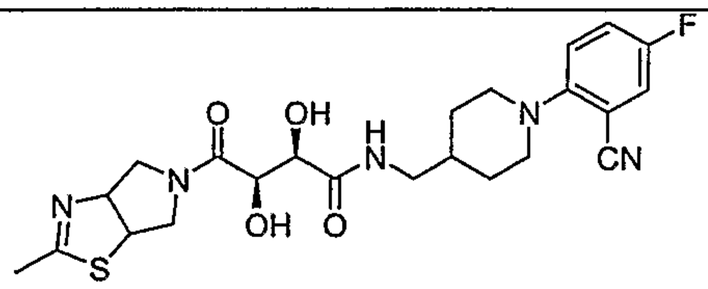
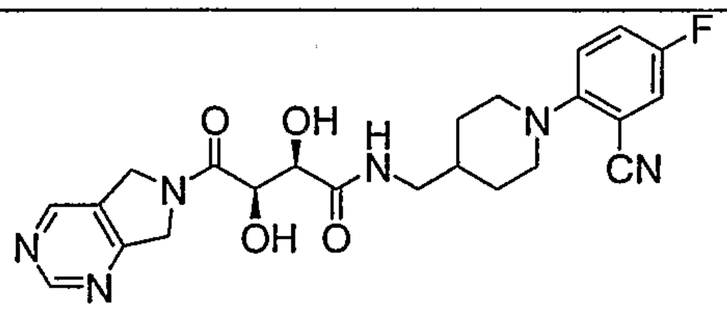
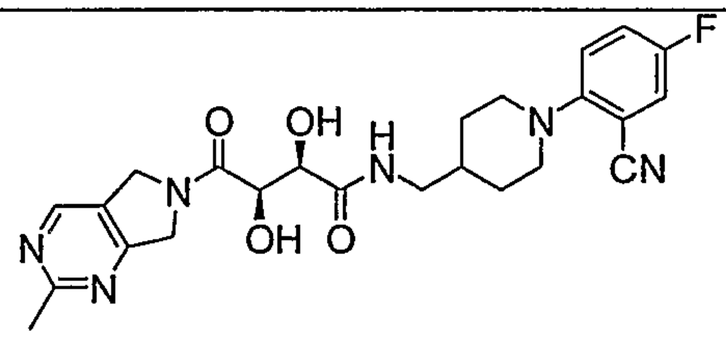
1107		
1108		
1109		
1110		
1111		
1112		
1113		
1114		
1121		
1122		

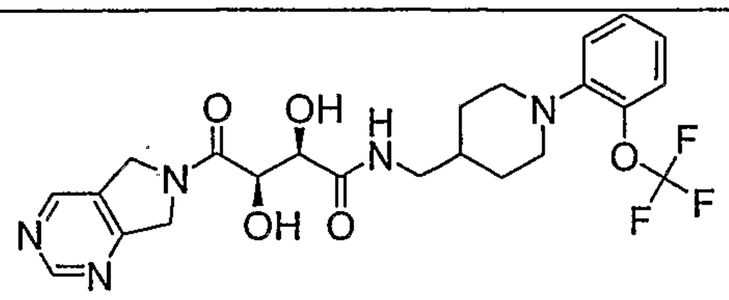
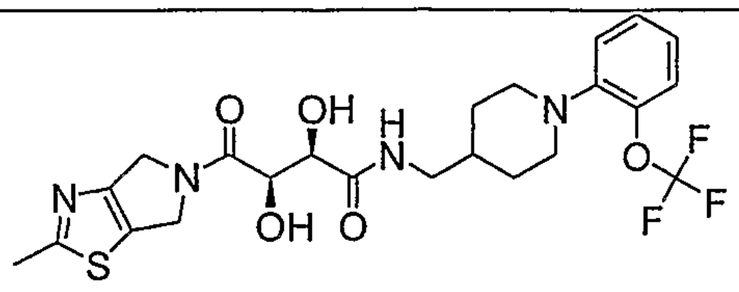
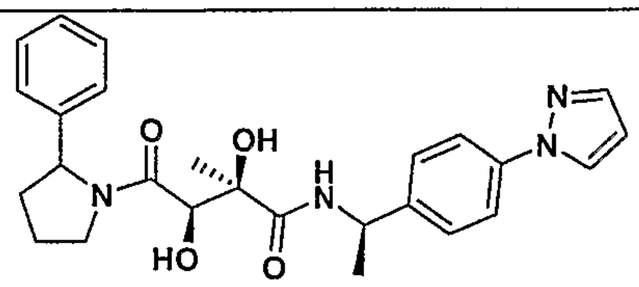
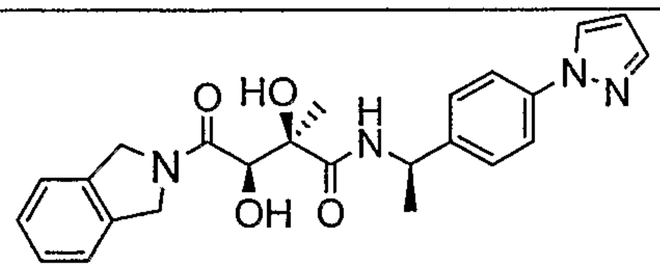
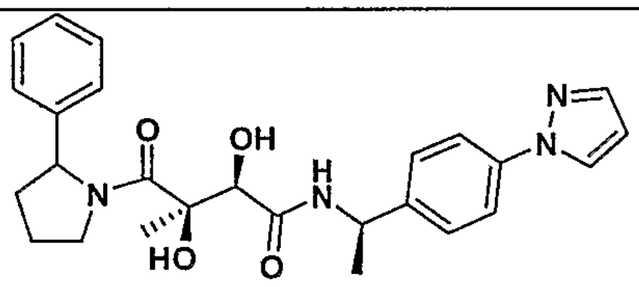
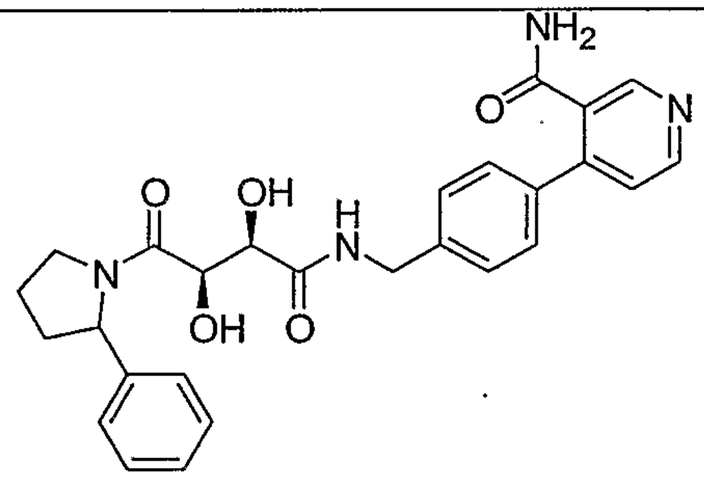
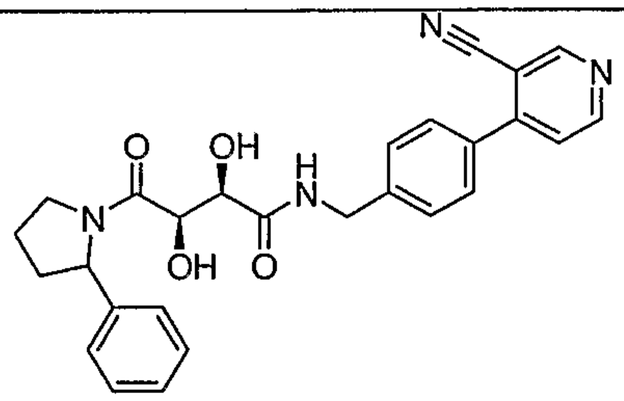
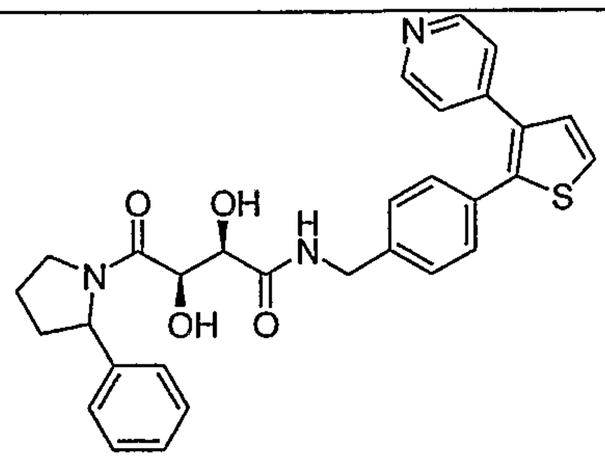
1123		
1128		
1129		
1133		
1134		
1138		
1146		
1152		
1156		
1160		

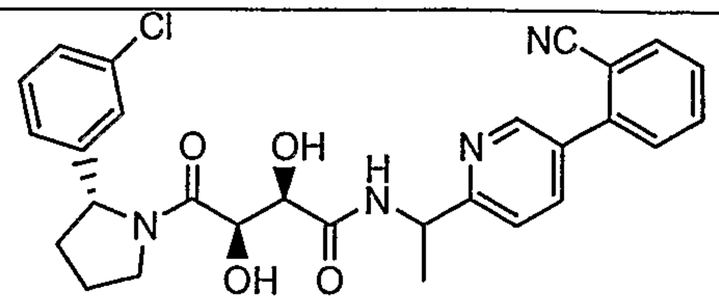
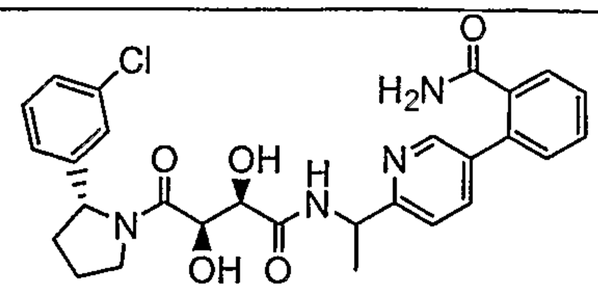
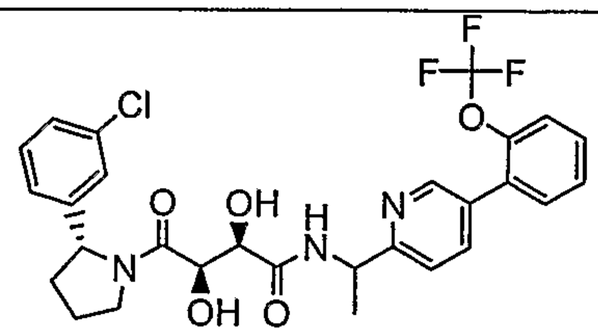
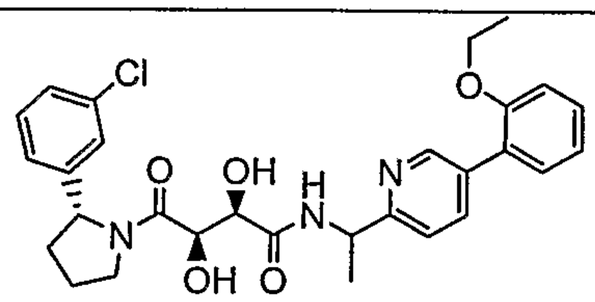
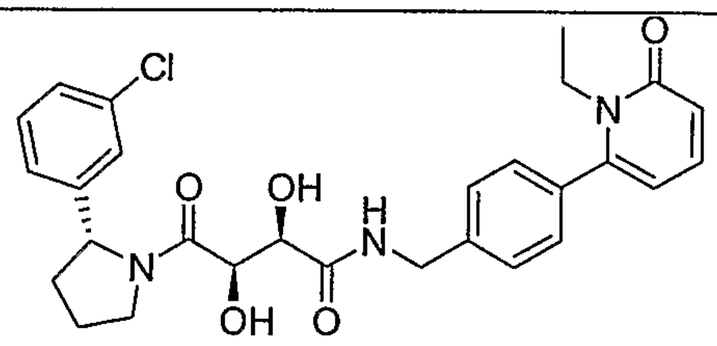
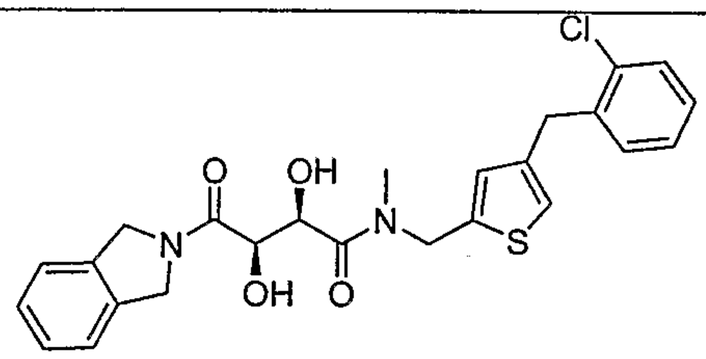
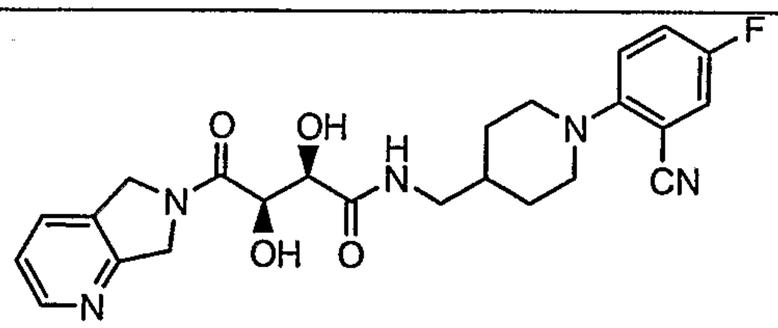
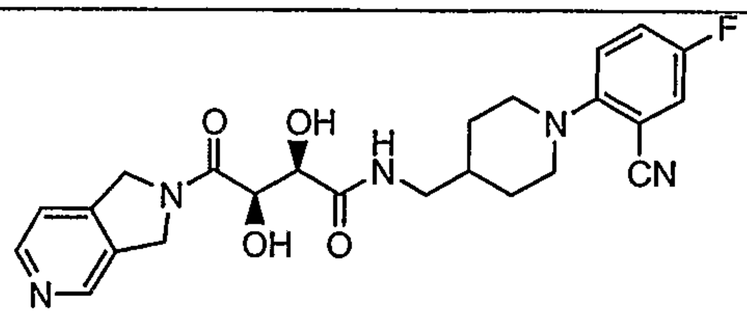
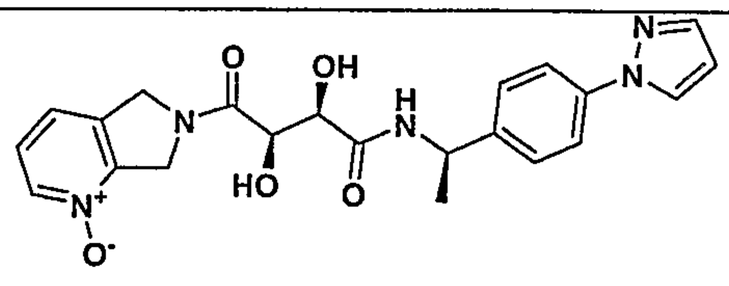
1163		
1166		
1167		
1168		
1169		
1170		
1171		
1173		

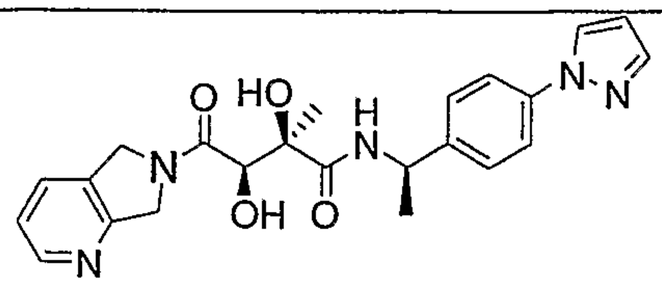
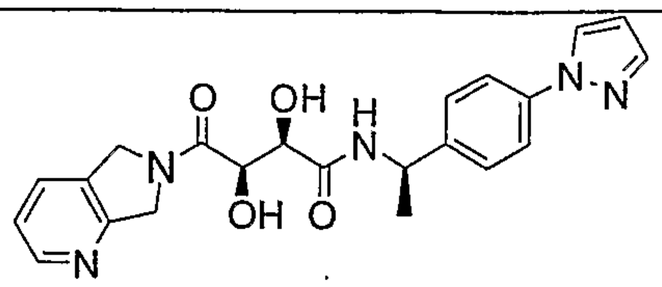
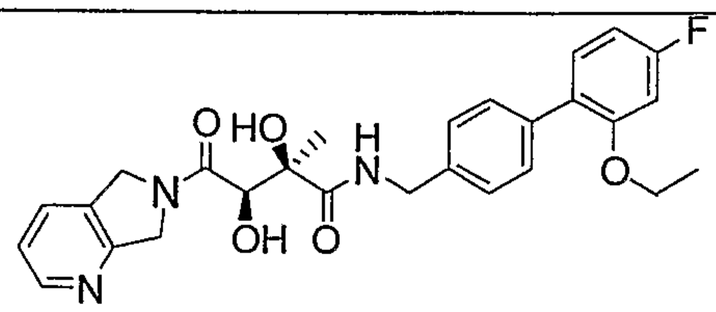
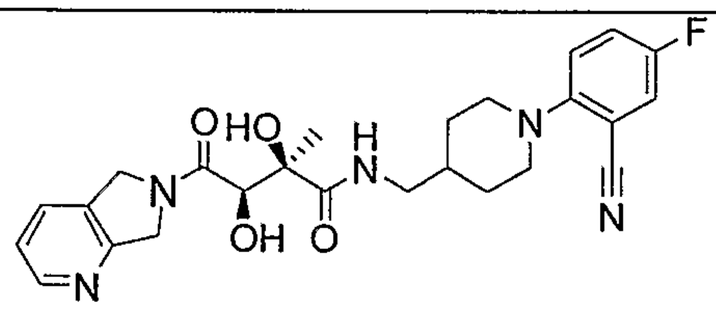
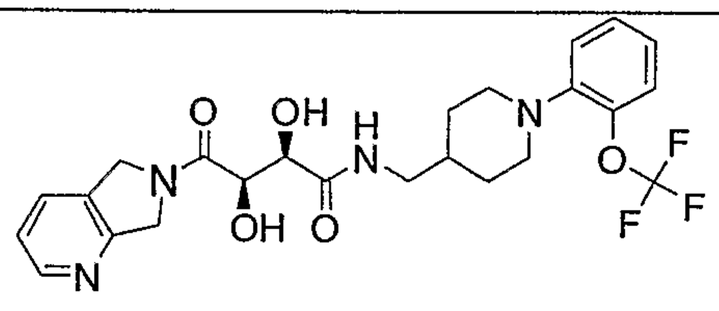
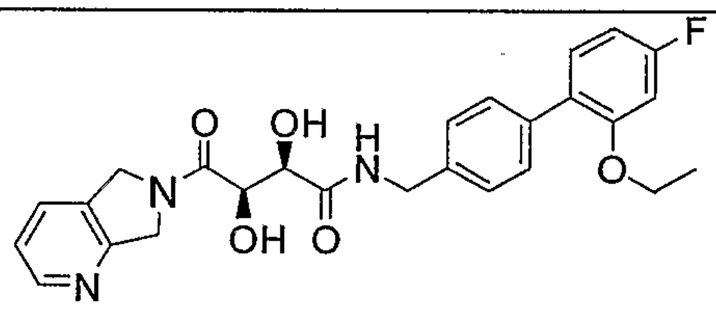
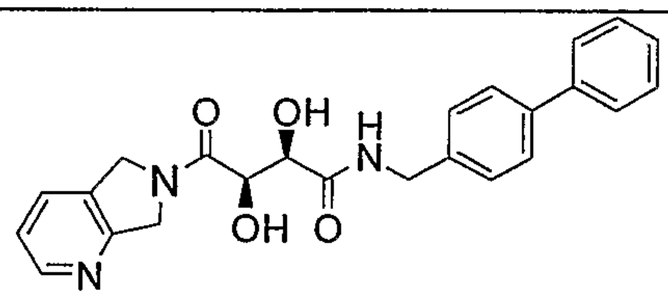
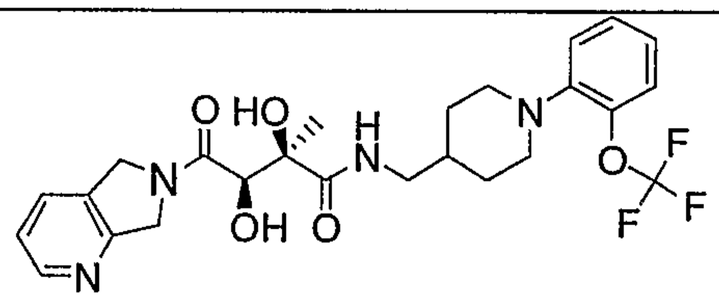
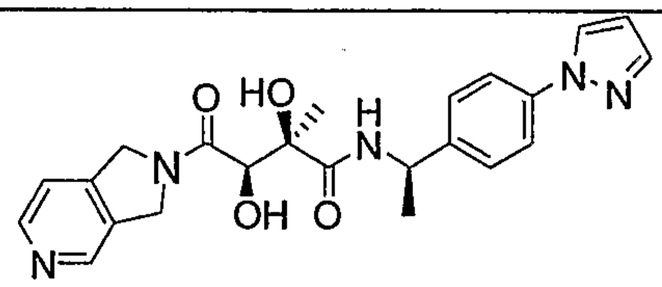
1175		
1176		
1177		
1178		
1179		
1180		
1181		
1182		
1183		

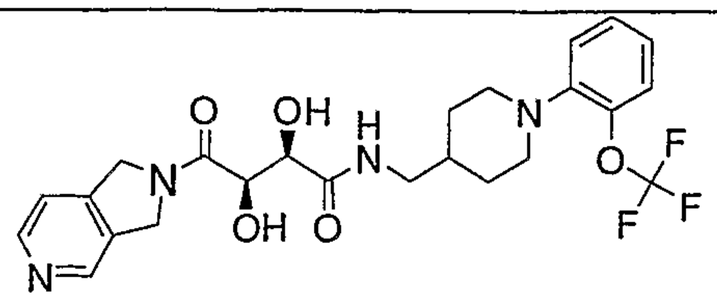
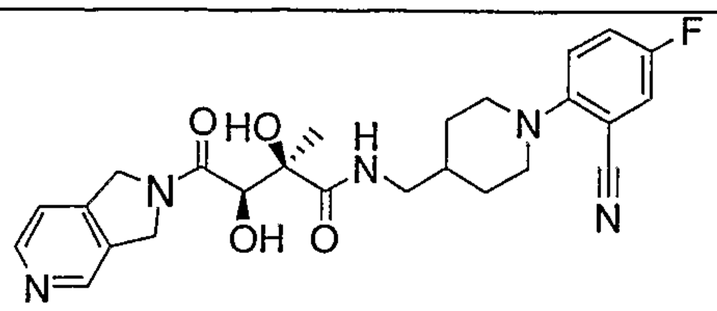
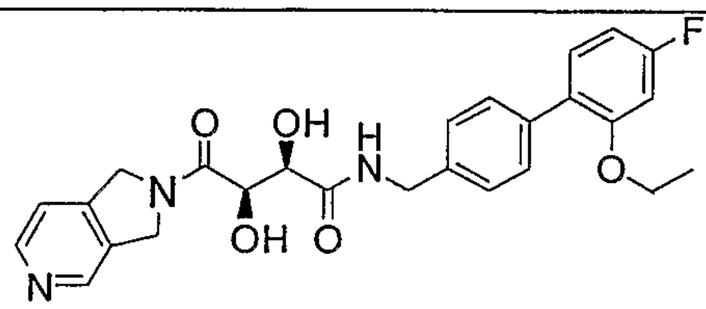
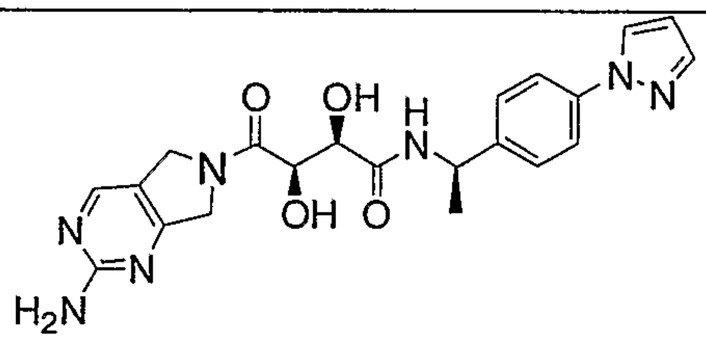
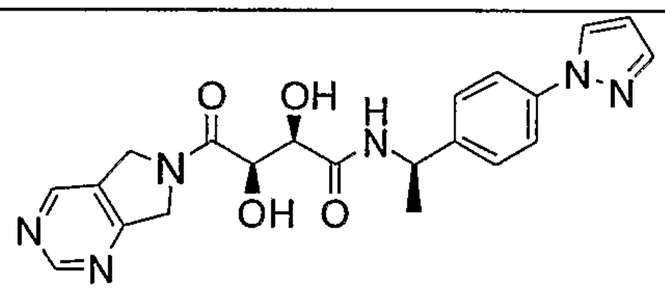
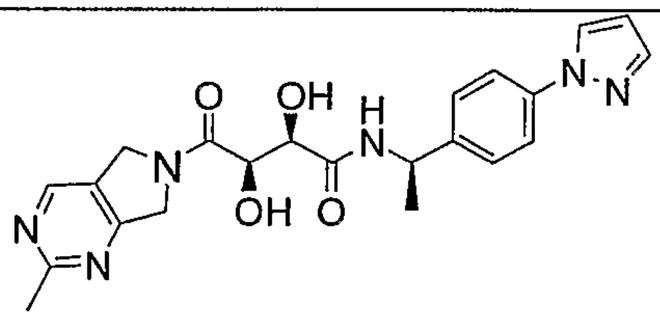
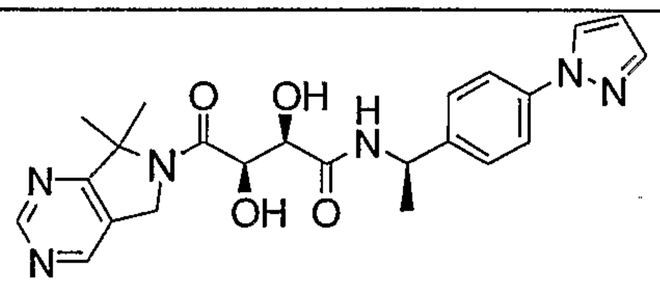
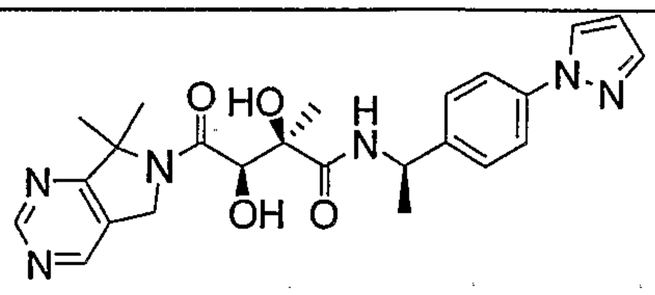
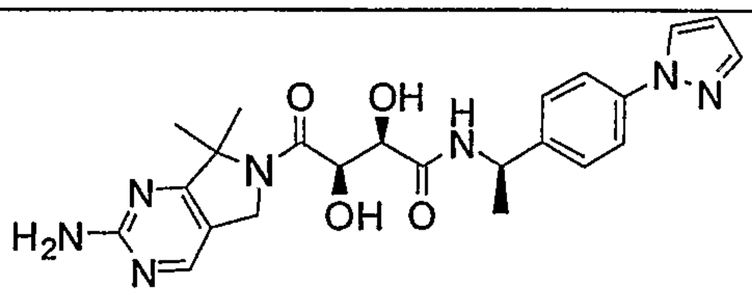
1184		
1185		
1186		
1187		
1188		
1210		
1211		
1212		

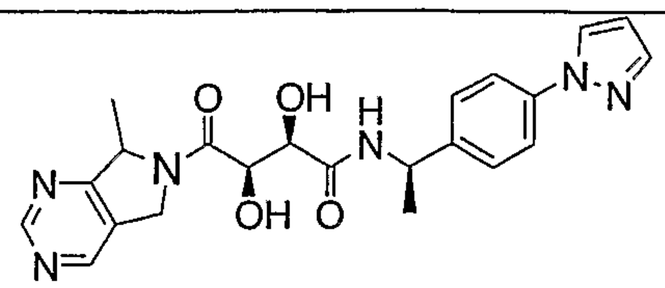
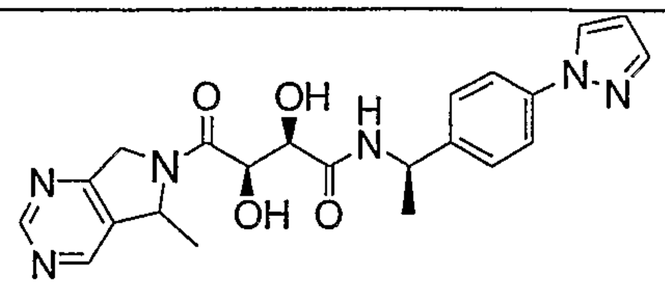
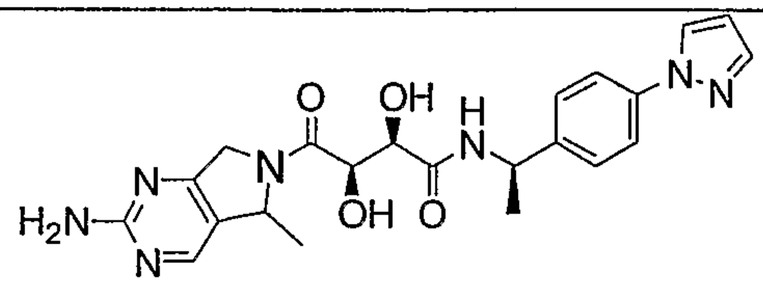
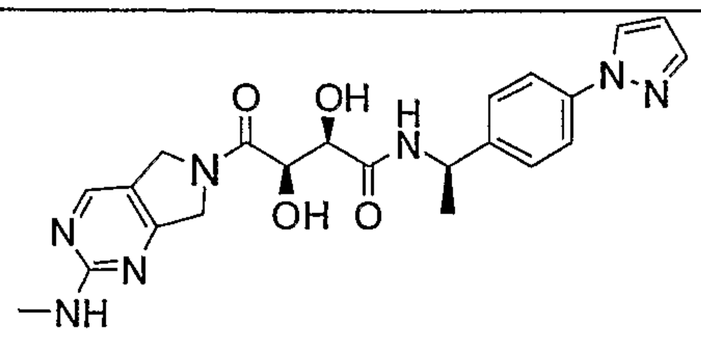
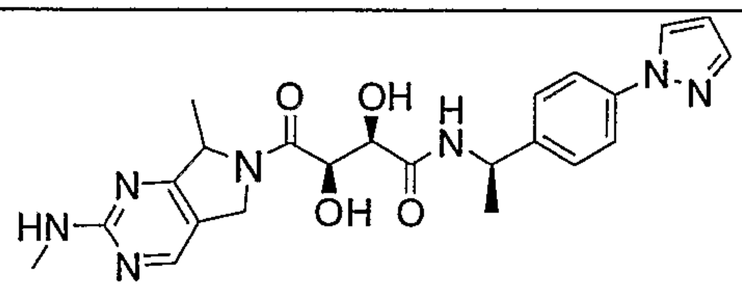
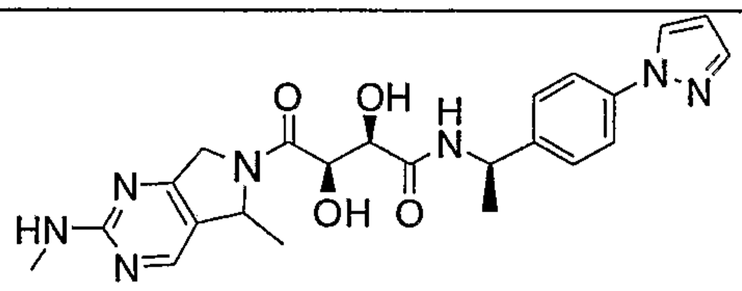
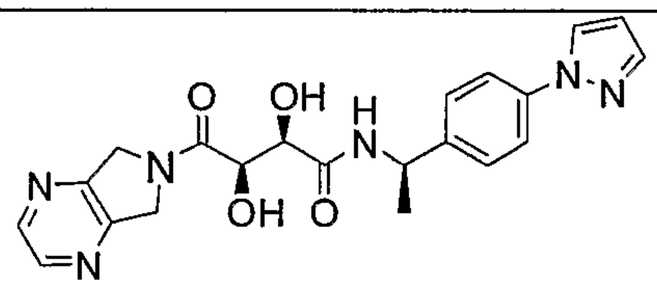
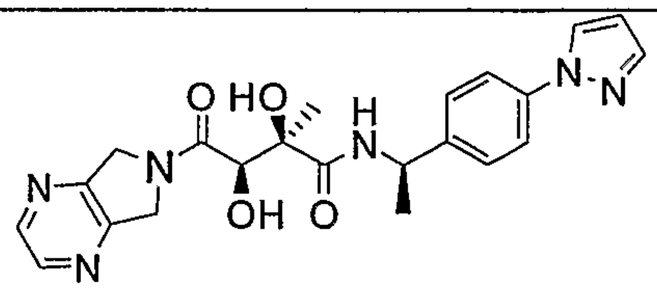
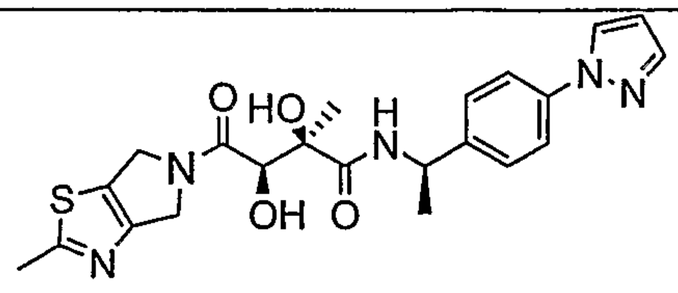
1213		
1214		
1218		
1222		
1223		
1036		
1035		
1235A		
1235B		

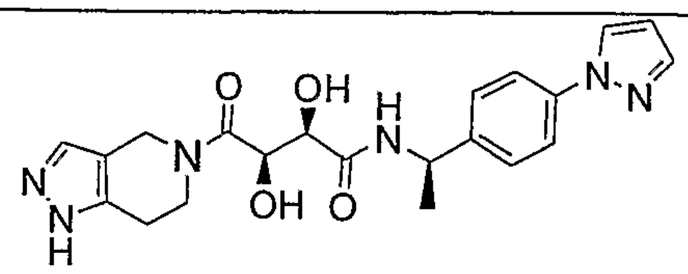
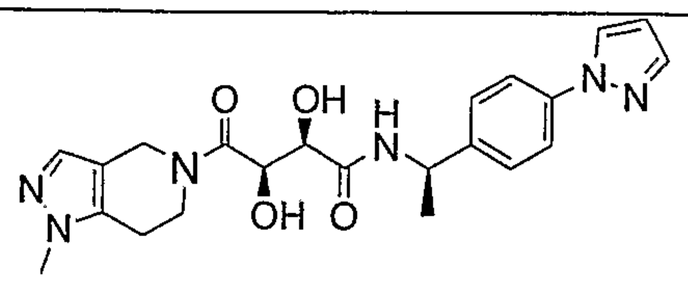
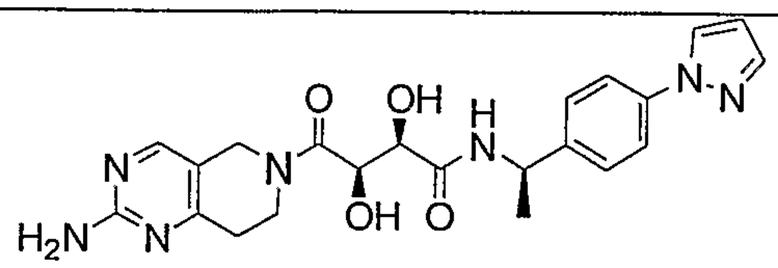
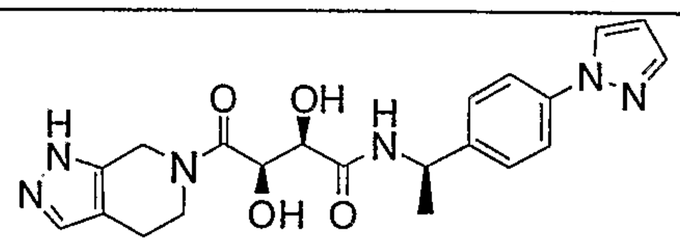
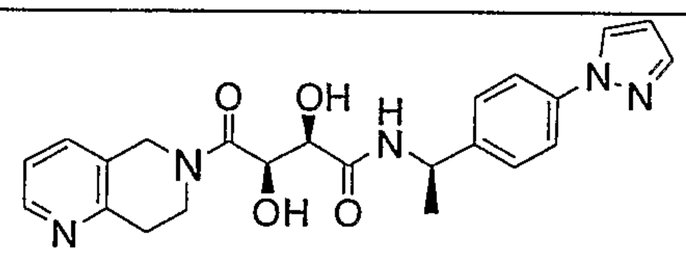
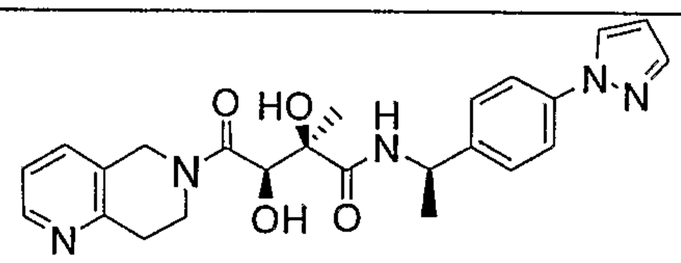
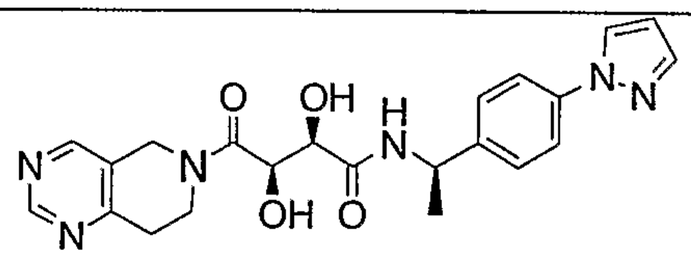
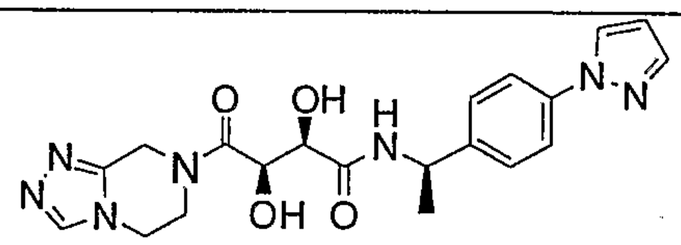
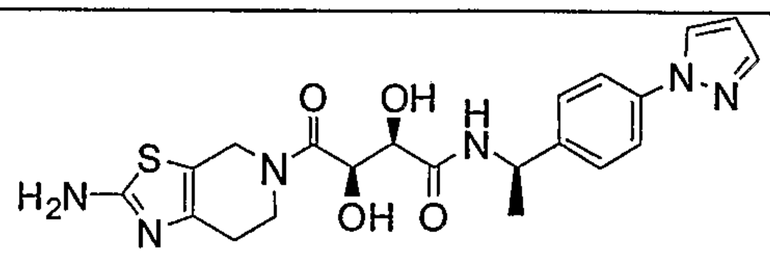
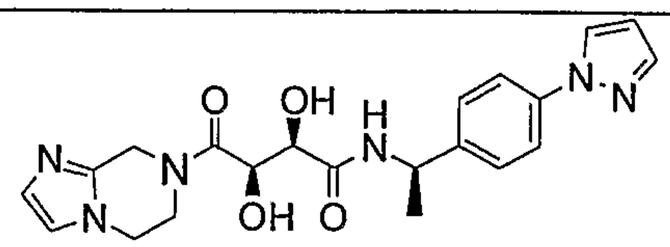
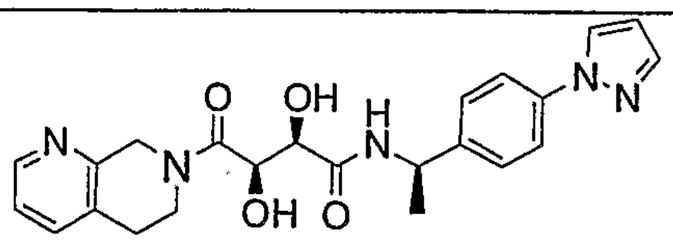
1236A		
1236B		
1243A, B (diastereomers)		
1243C		
1247A, B (diastereomers) (?)		
1255		
1256		
1261		

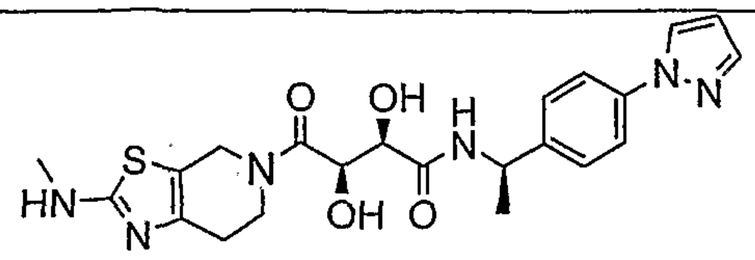
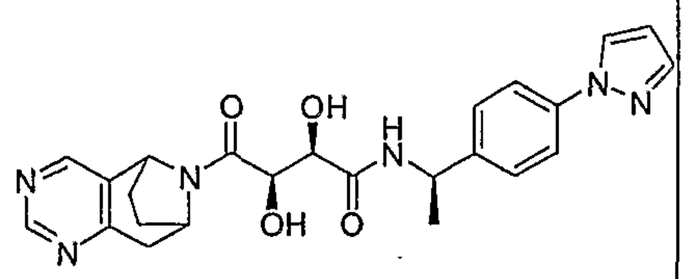
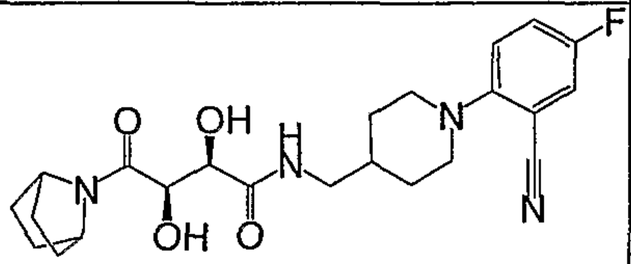
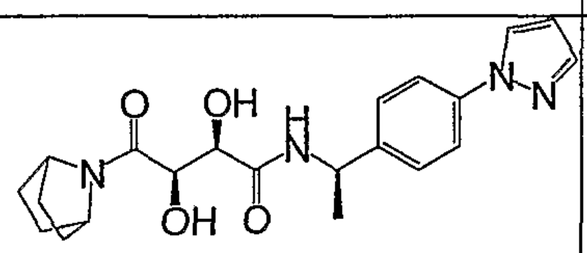
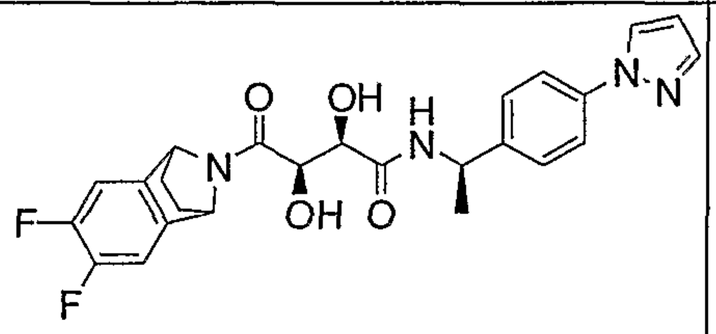
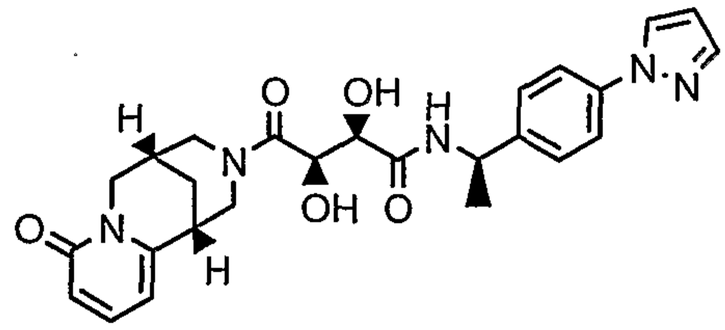
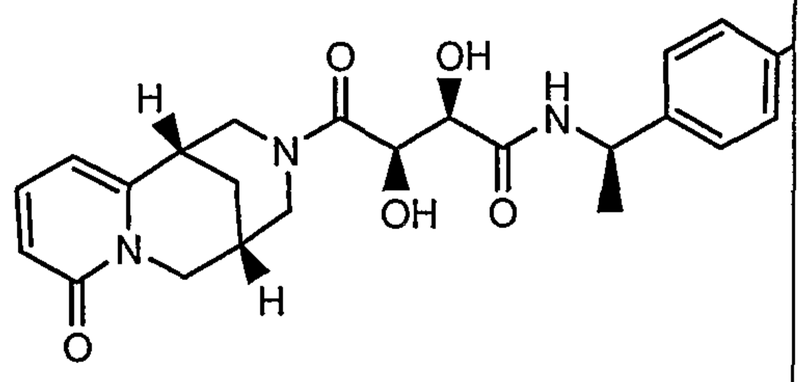
1266		
1267		
1268		
1269		
1276		
1280		
2003		B
2007		A
2030		B

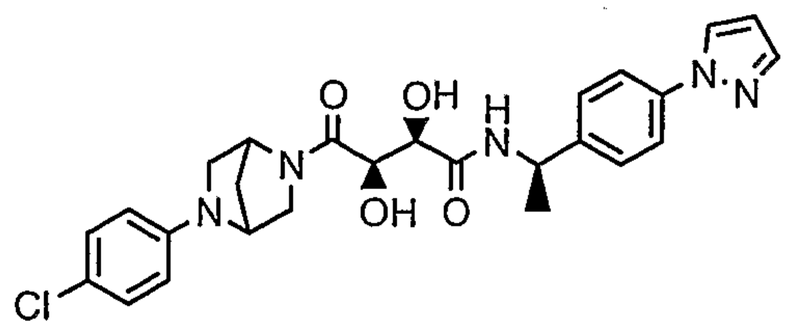
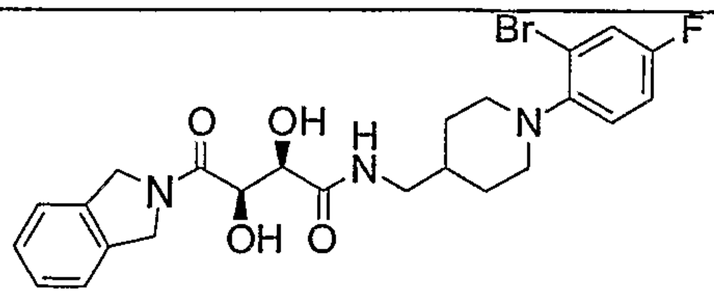
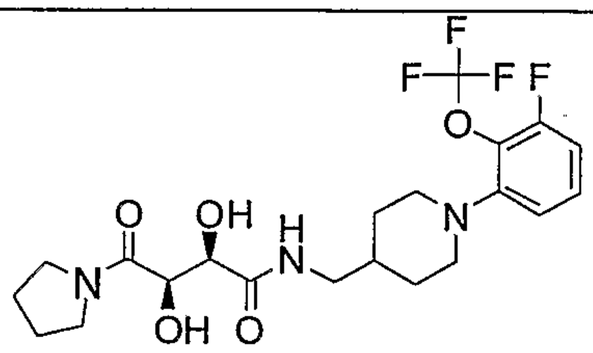
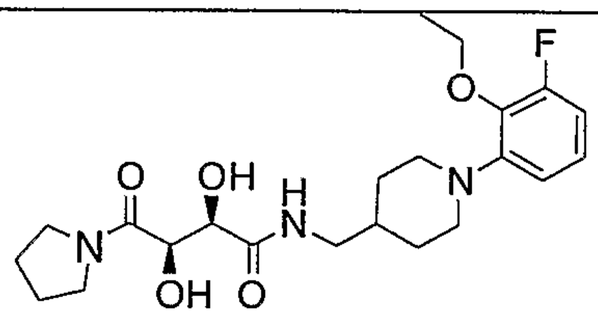
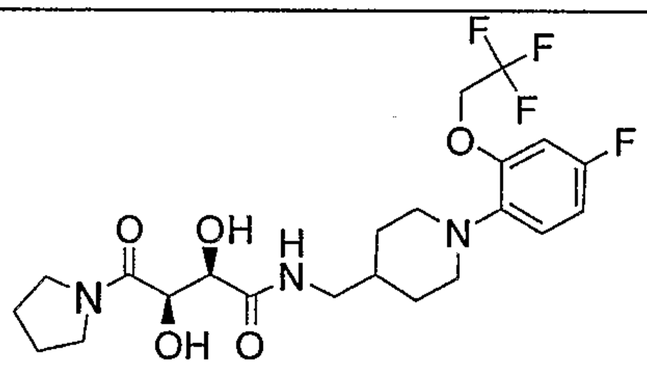
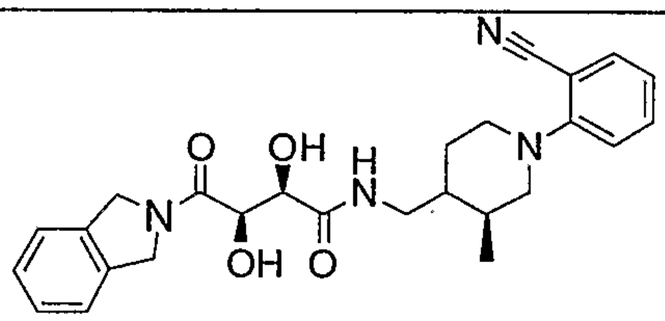
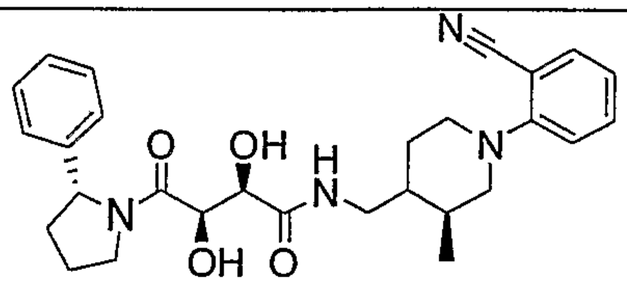
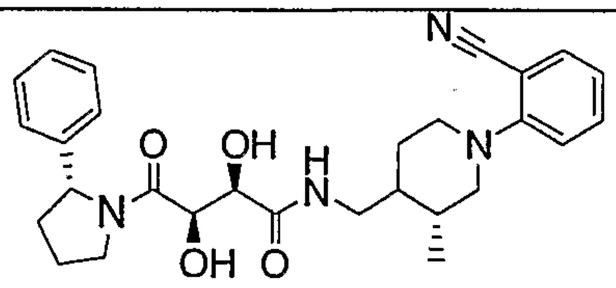
2031		A
2032		A
2033		A
2034		B
2035		A
2036		A
2037		B
2038		B
2039		A

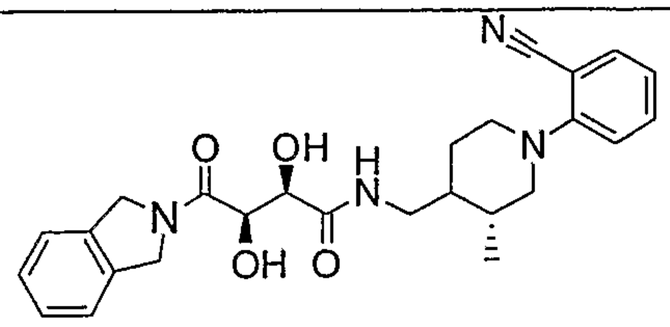
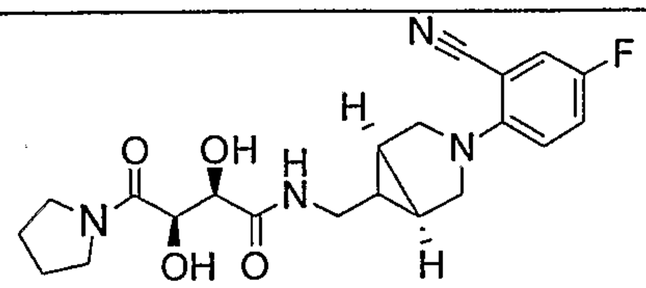
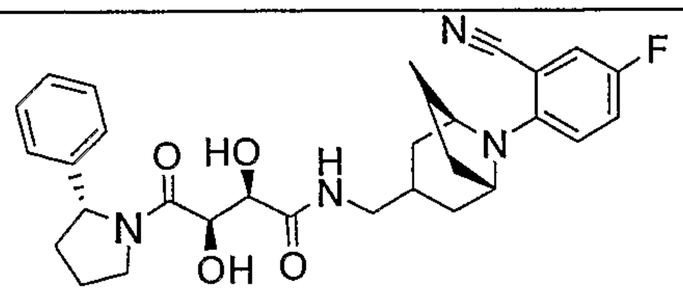
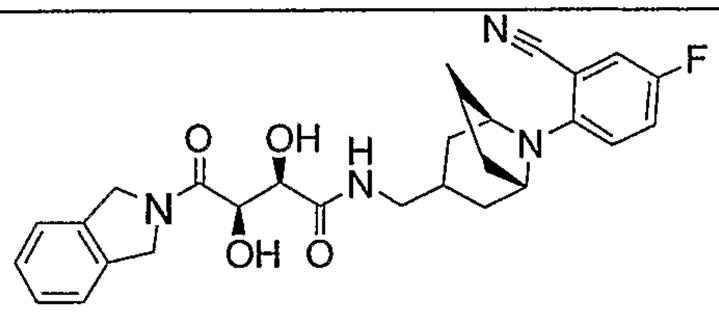
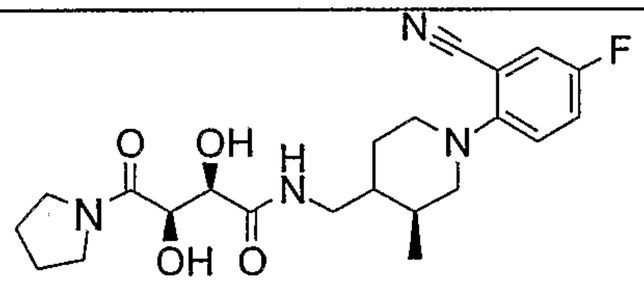
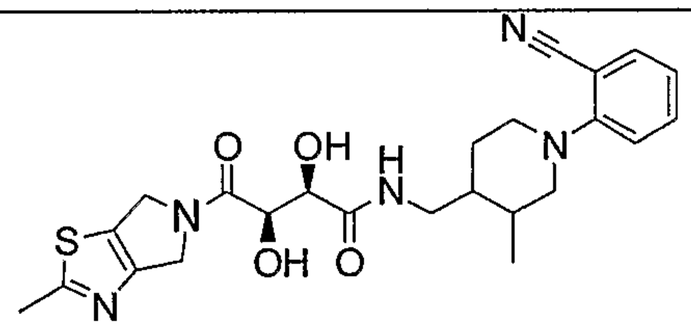
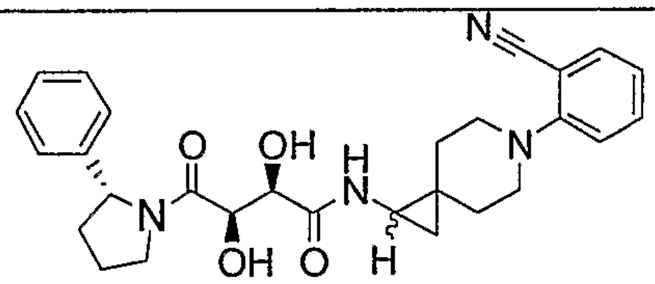
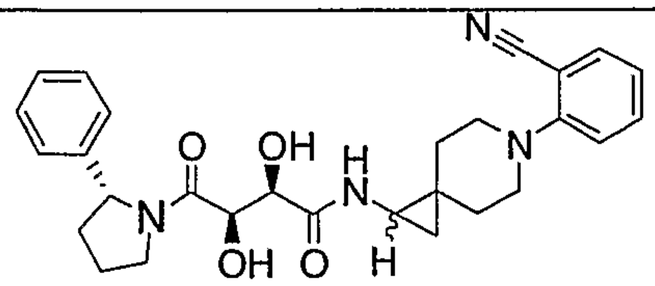
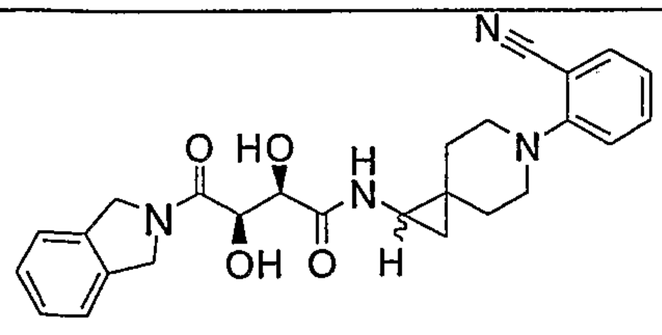
2040		A
2041		B
2042		A
2043		A
2044		A
2045		C
2046		C
2047		C
2048		B

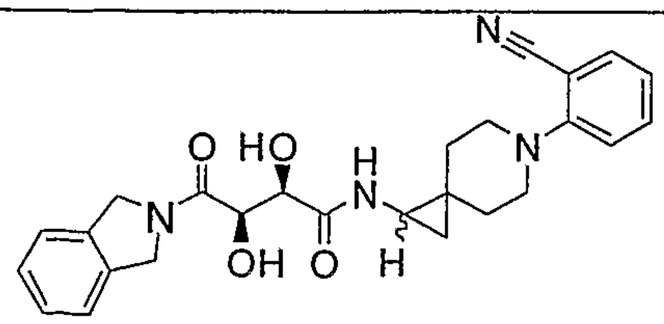
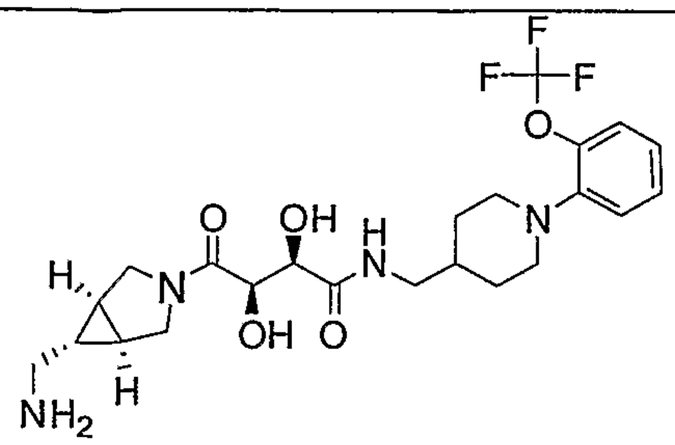
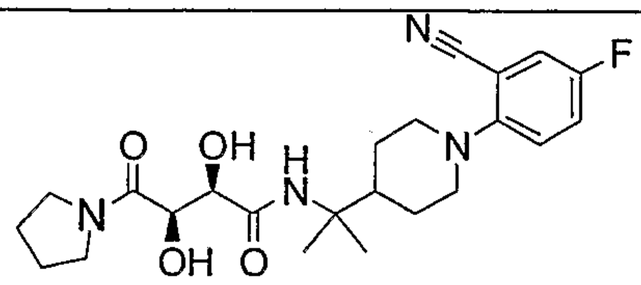
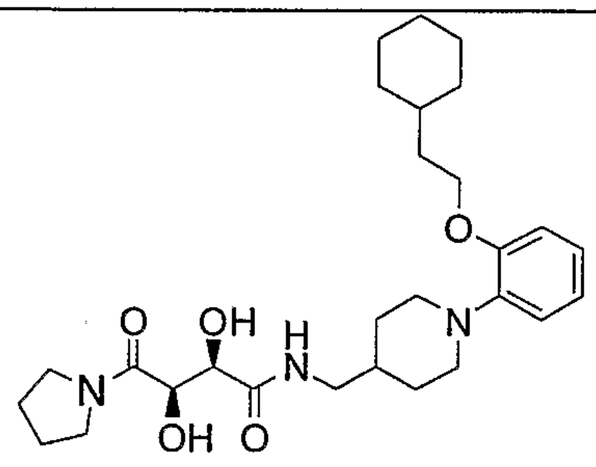
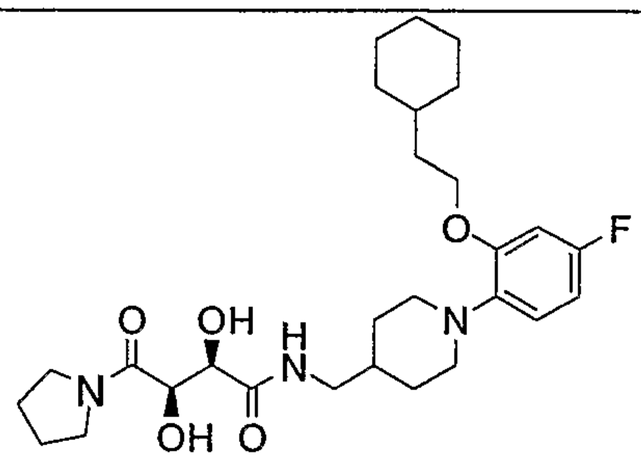
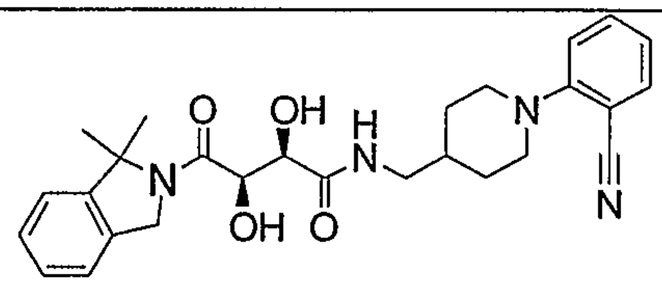
2049		B
2050		B
2051		B
2052		A
2053		B
2054		A
2055		A
2056		A
2057		A

2073		B
2074		B
2075		B
2076		B
2077		B
2078		C
2079		C
2080		C
2081		A
2082		C
2083		B

2084		B
2093		D
2094		D
2095		C
2096		C
2097		C
2098		C

2099		C
2139		A
2140		D
2141		D
2142		B
2143		A
2144		A
2145		C

2146		C
2147		C
2148		C
2149		C
2150		B
2151		A
2152		D
2153		D
2154		D

2155		D
2156		B
2157		B
2158		B
2159		B
2233		A
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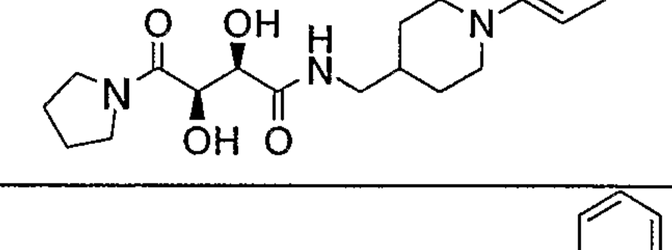
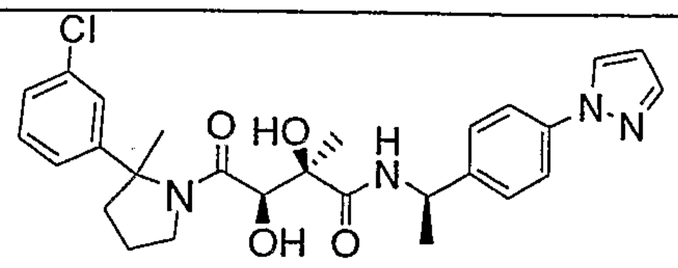
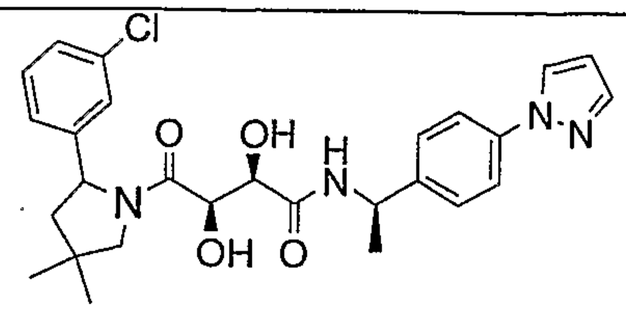
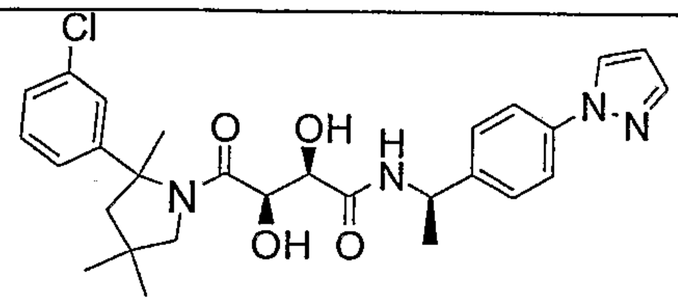
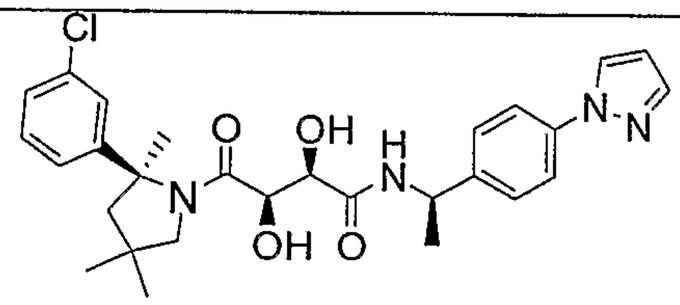
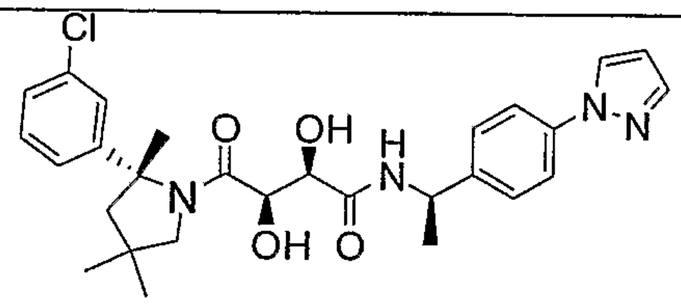
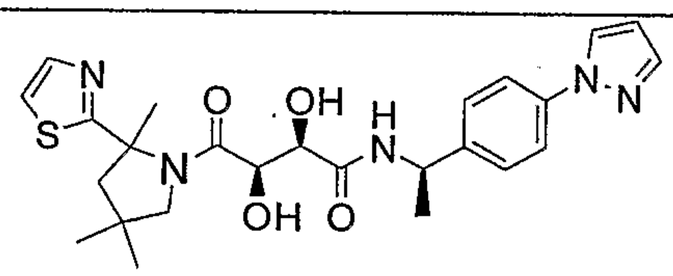
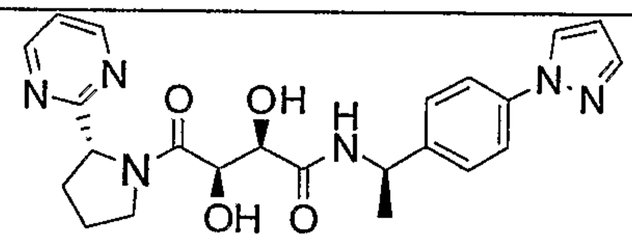
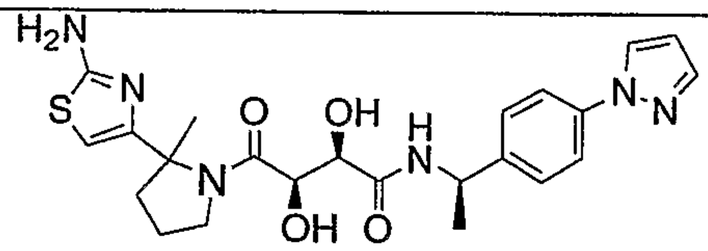
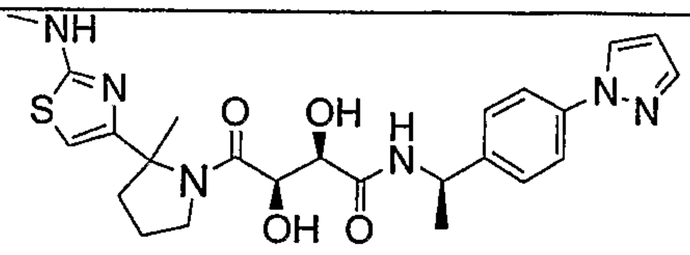
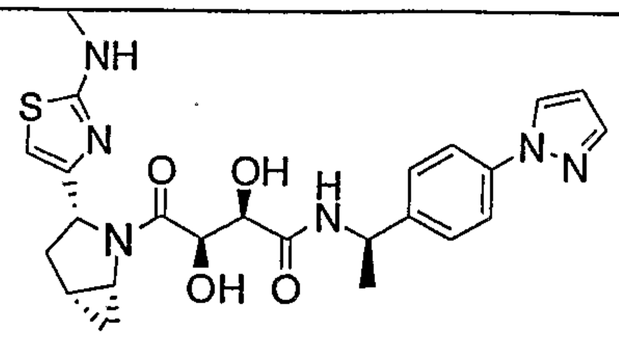
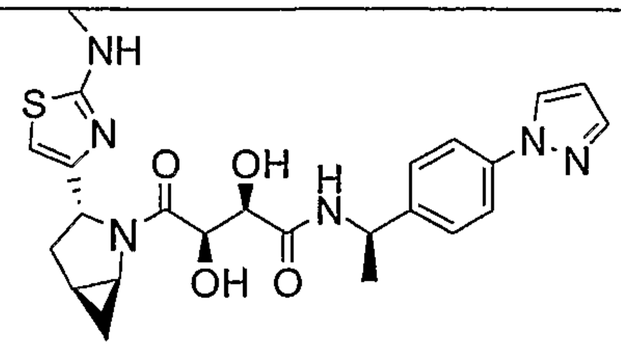
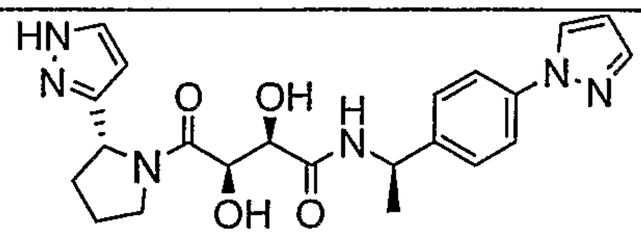
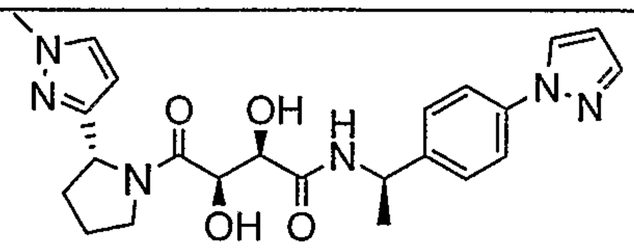
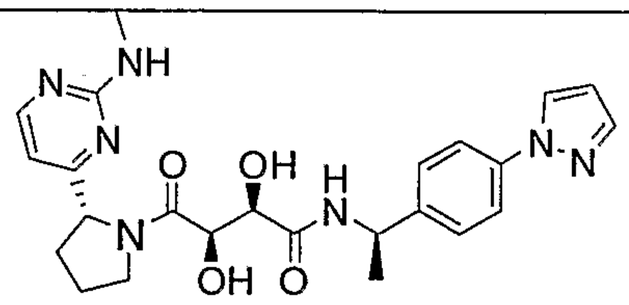
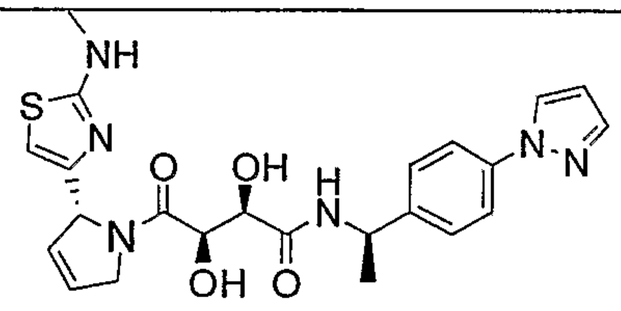
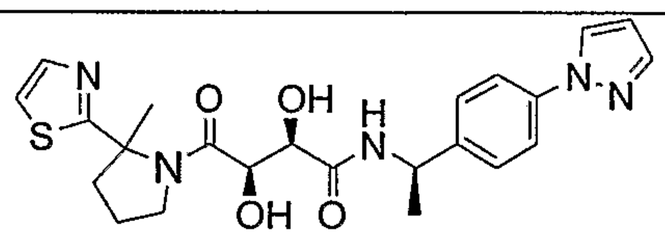
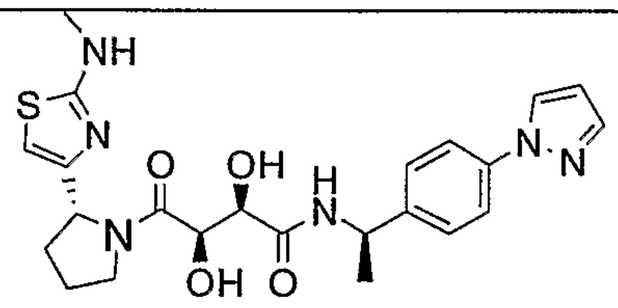
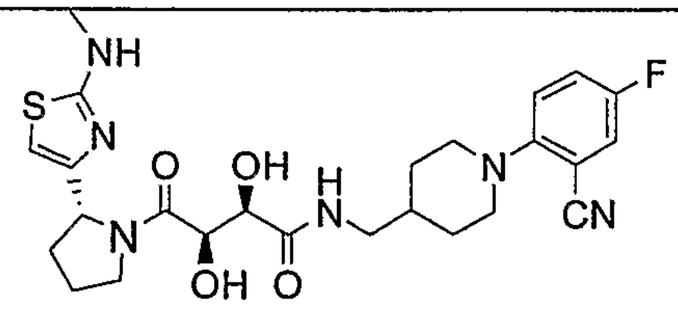
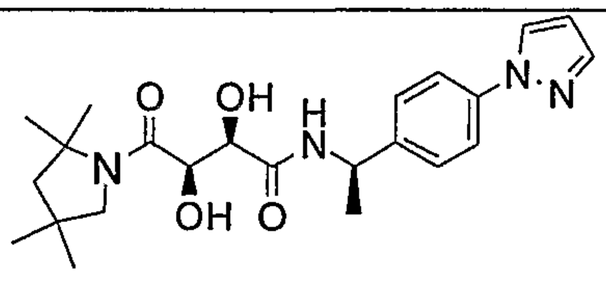
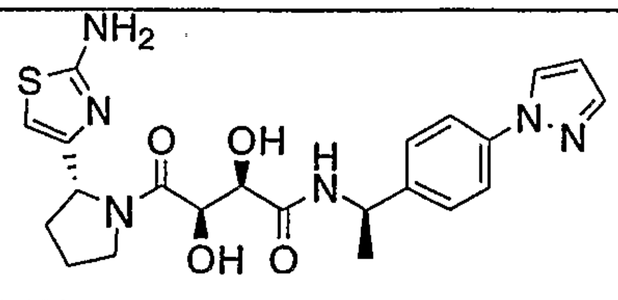
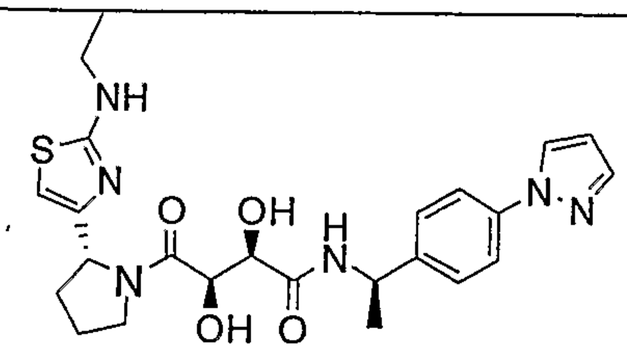
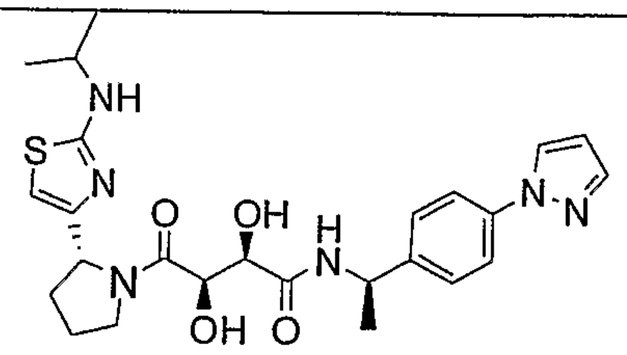
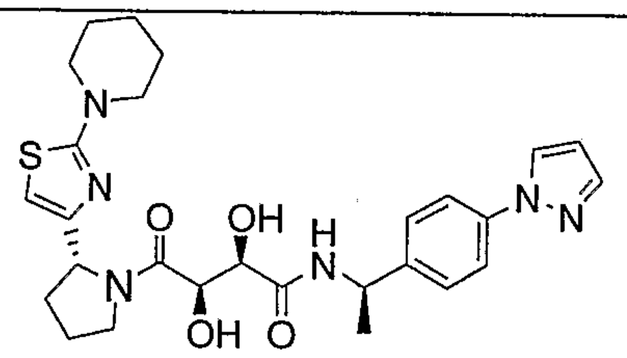
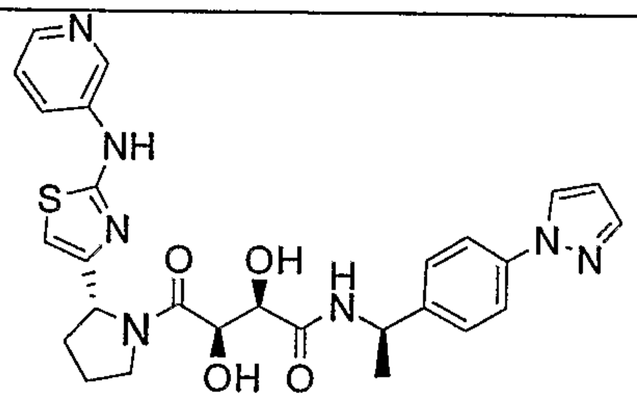
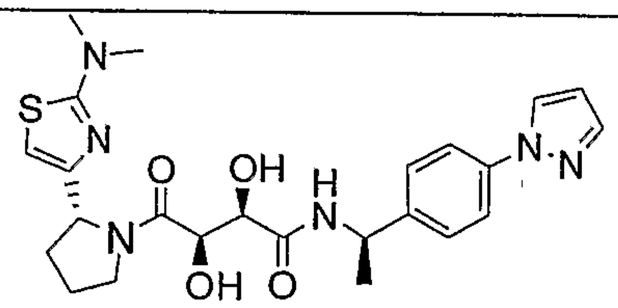
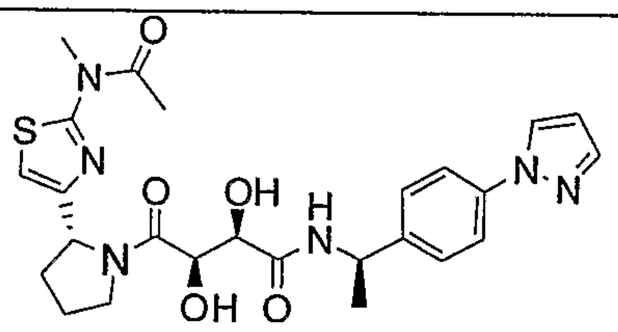
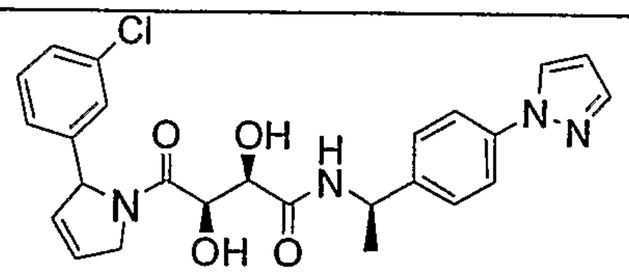
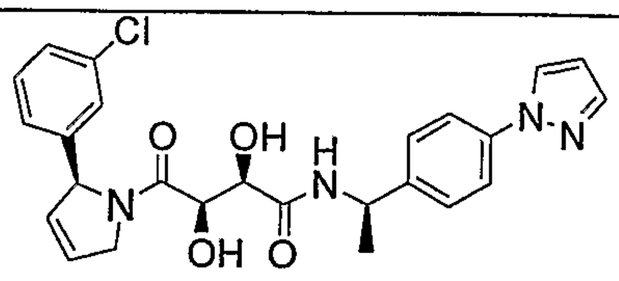
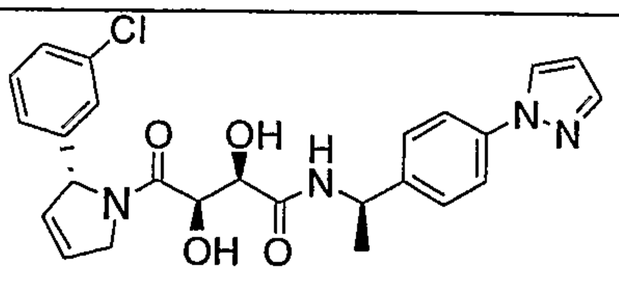
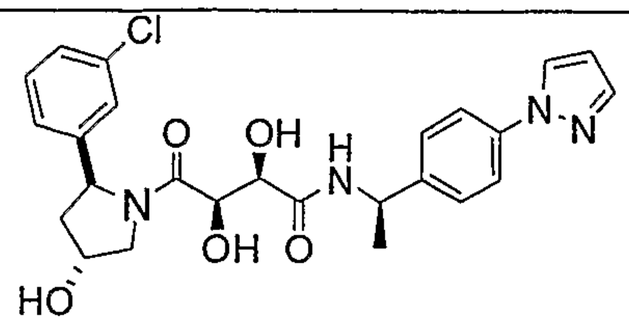
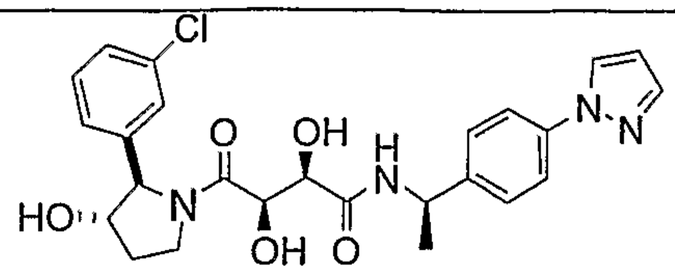
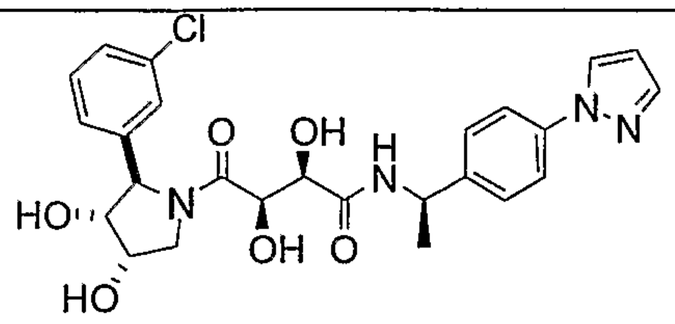
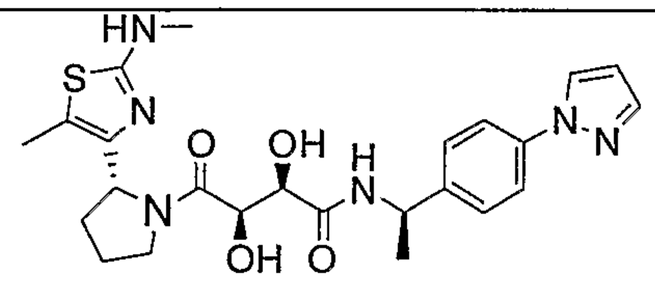
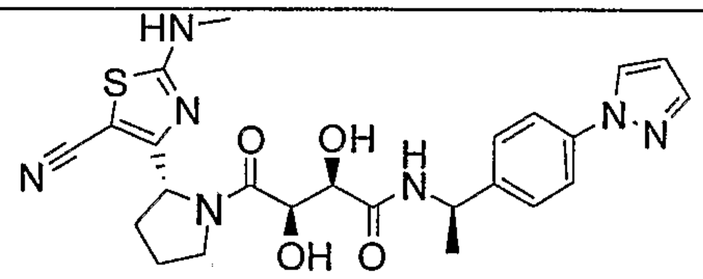
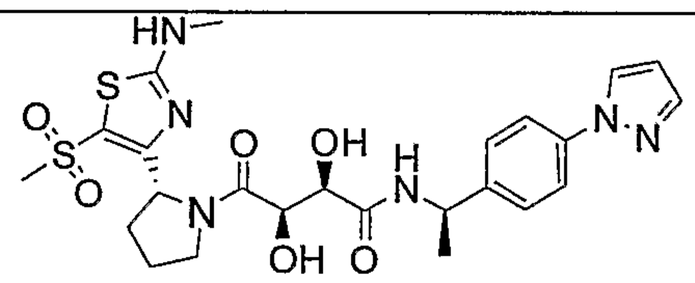
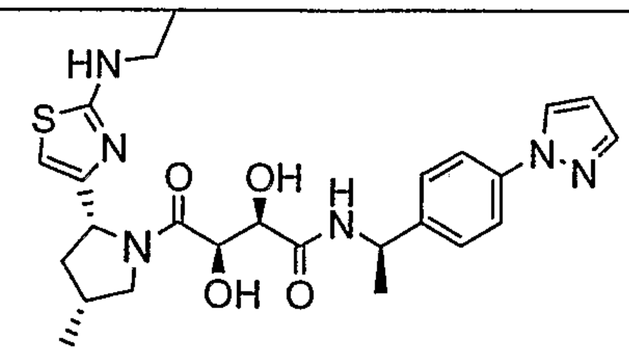
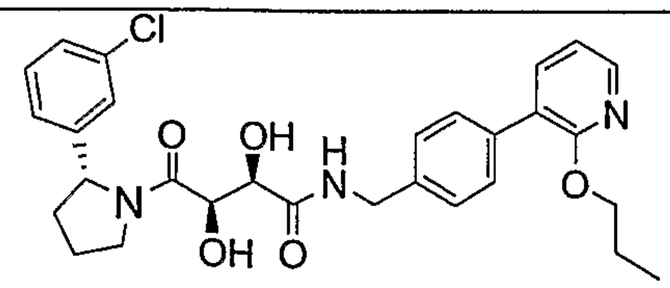
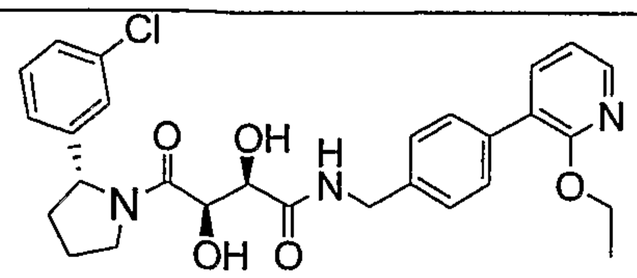
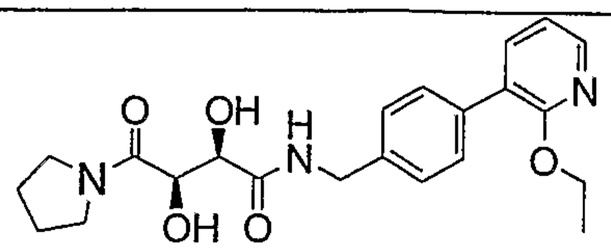
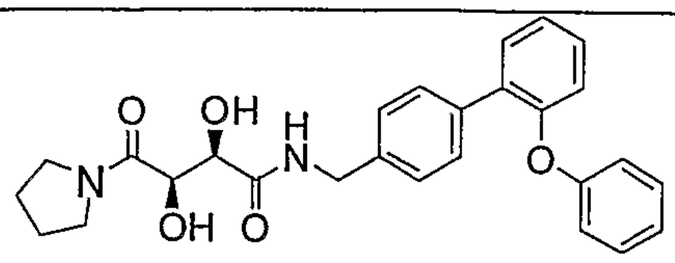
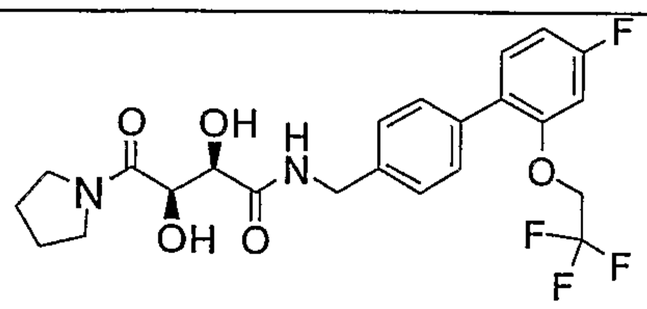
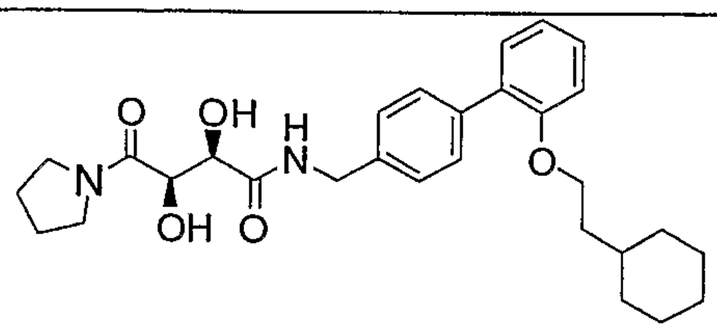
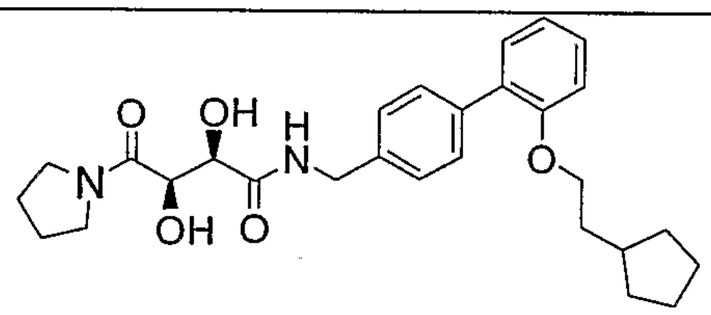
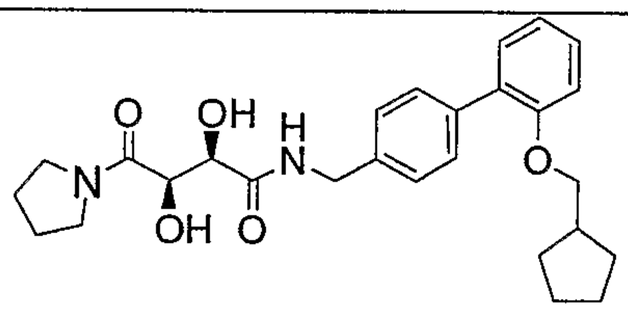
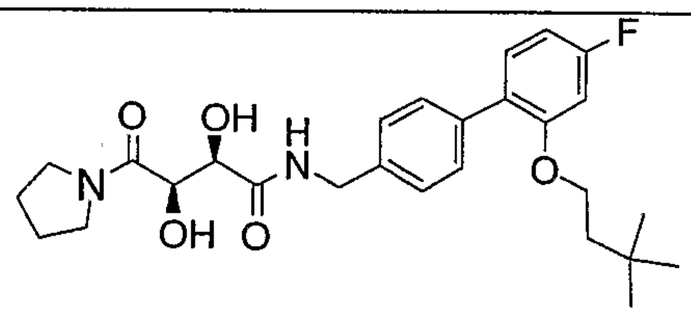
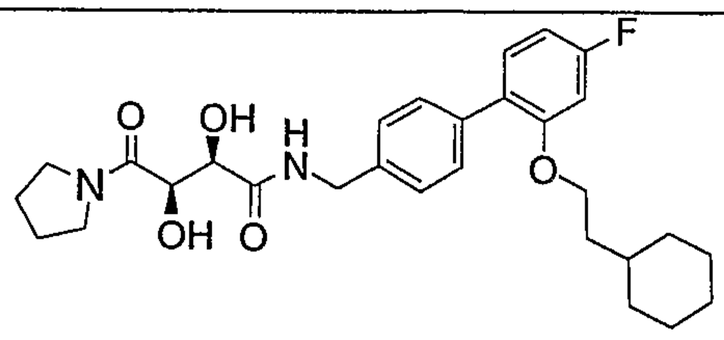
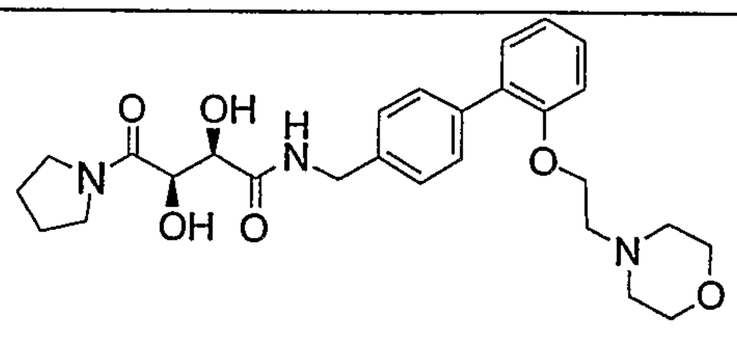
2235		A

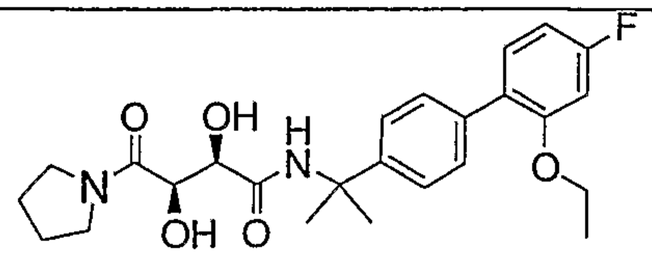
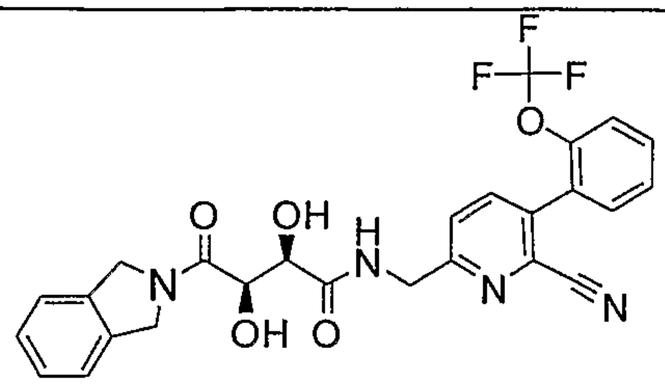
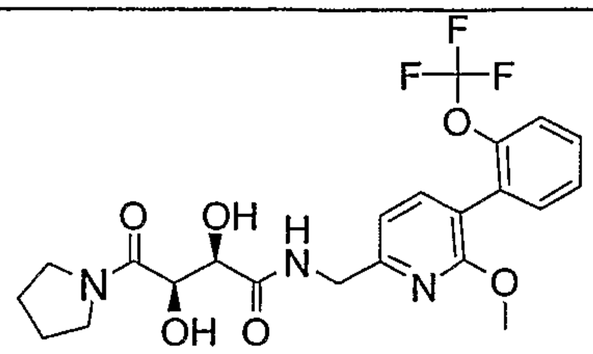
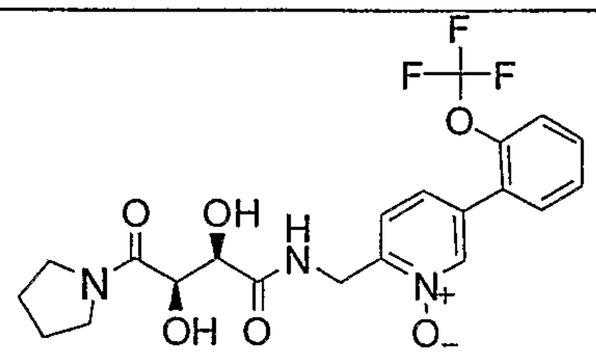
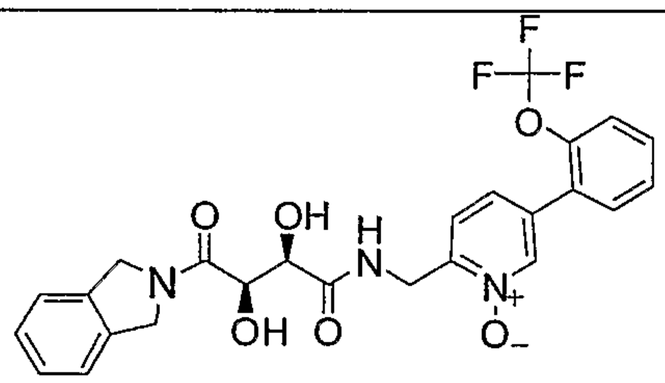
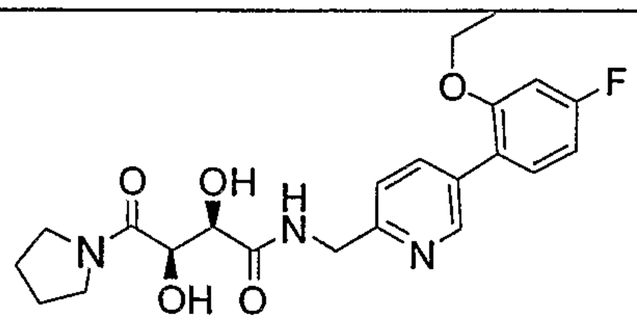
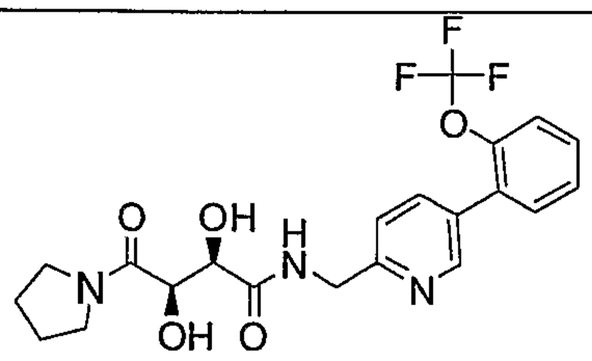
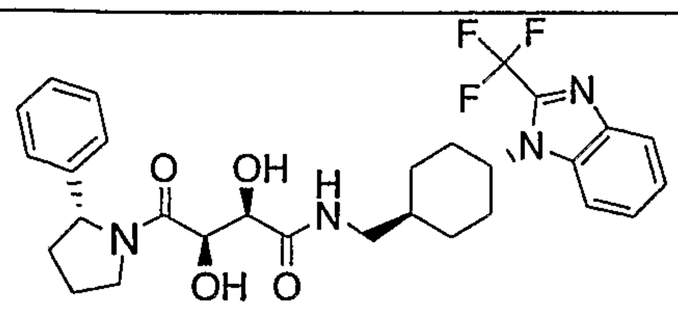
2236		D
2237		C
2238		B
2239		D
2240		B
2241		C
2242		A
2243		A
2244		A
2245		A

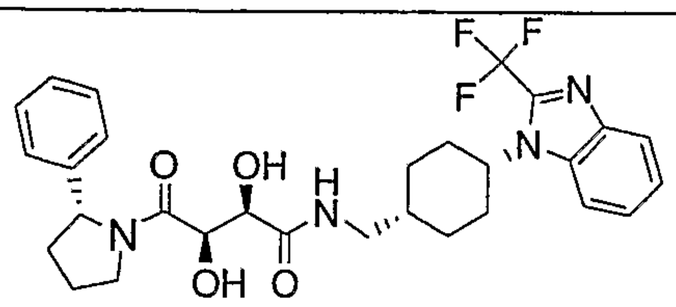
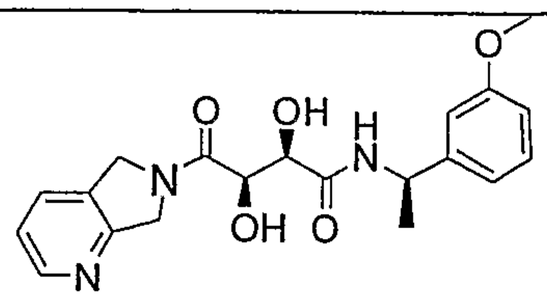
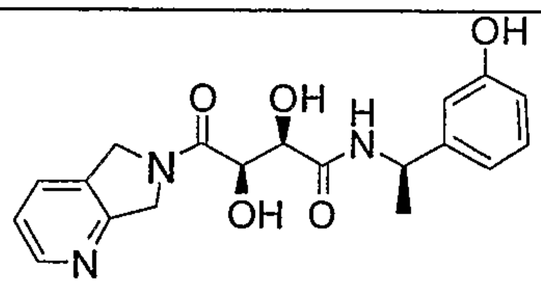
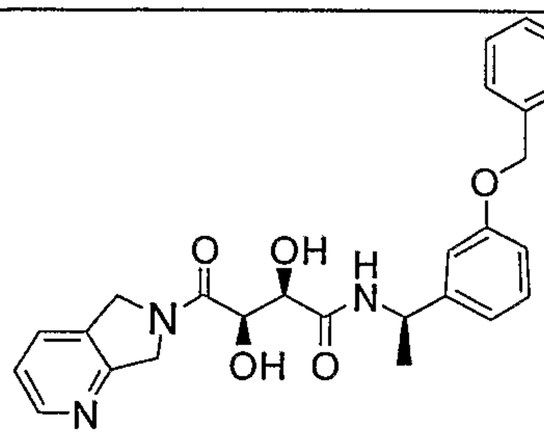
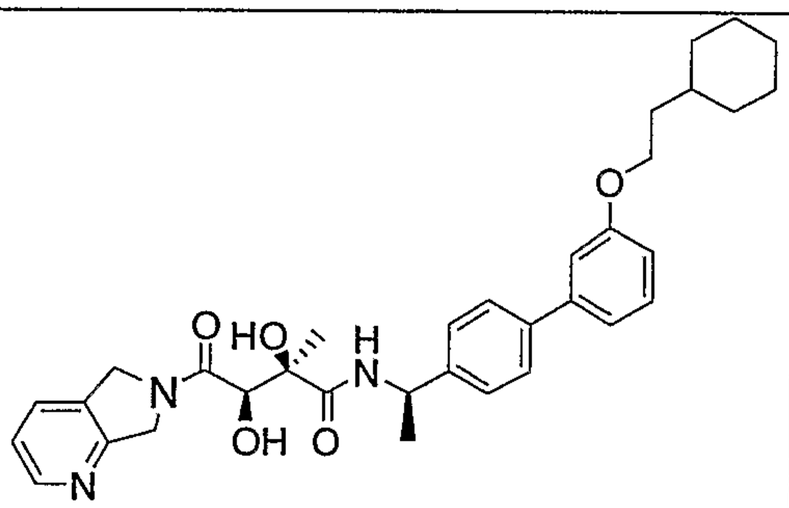
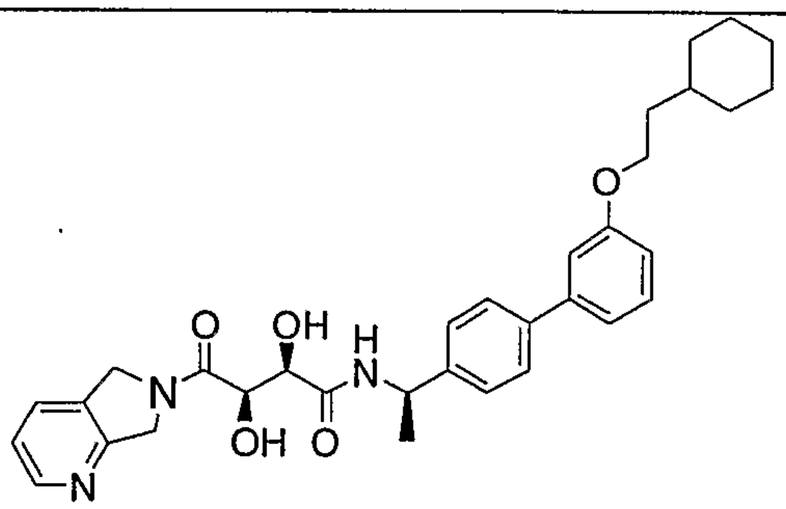
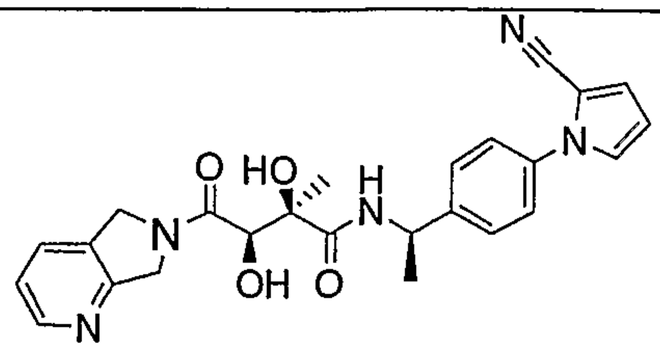
2246		B
2247		A
2248		A
2249		A
2250		A
2251		A
2252		A
2253		A
2254		C
2255		A

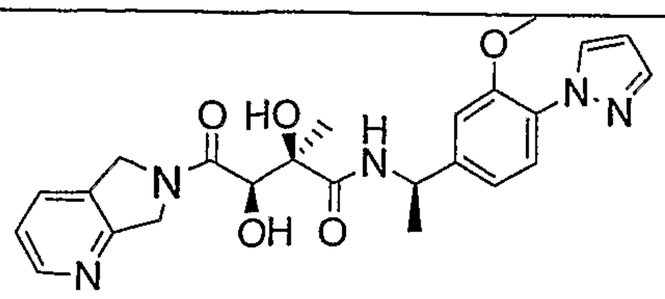
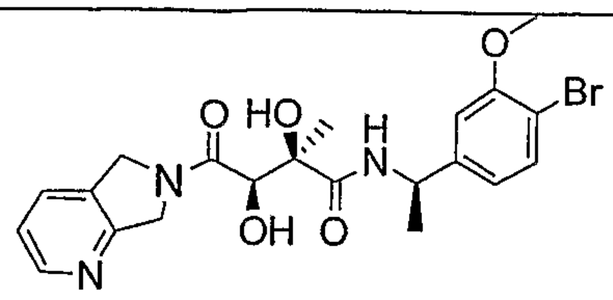
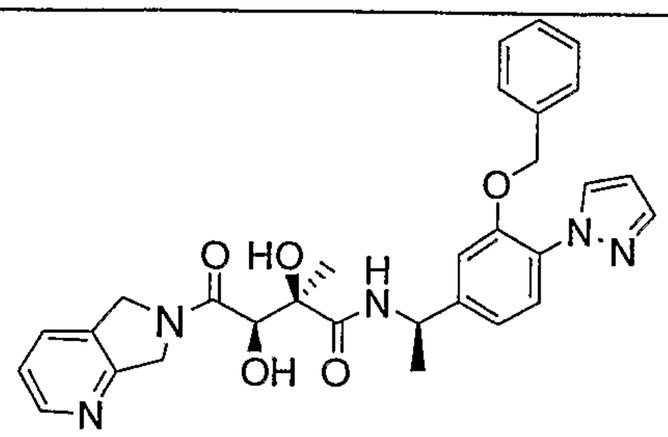
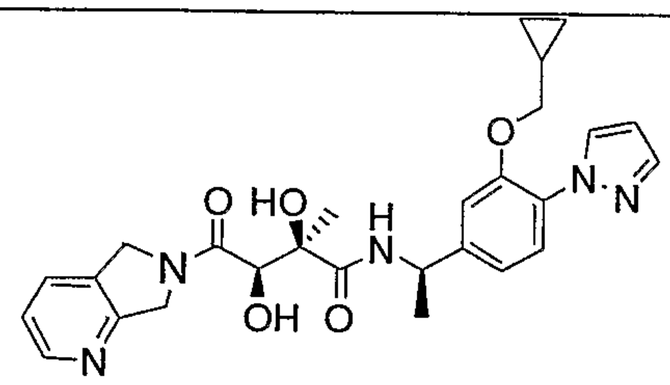
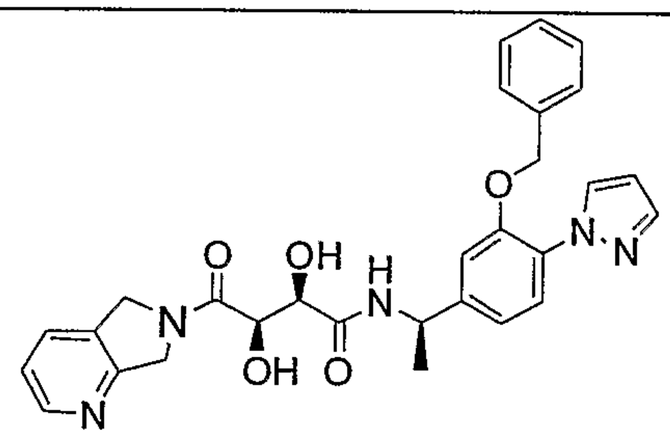
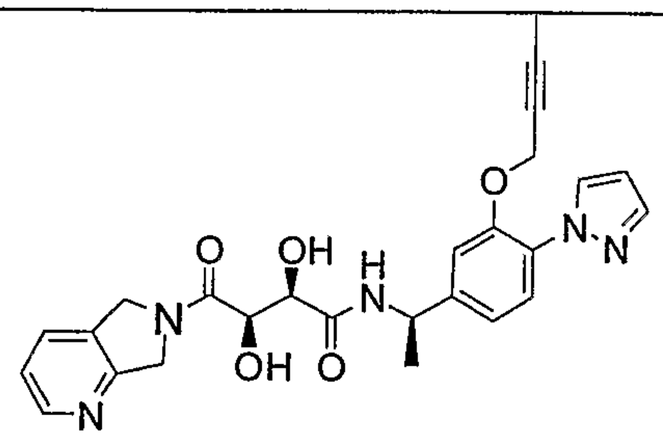
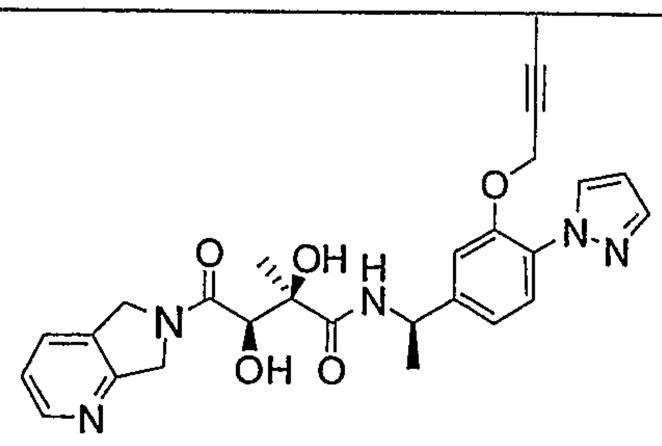
2256		A
2257		A
2258		B
2259		A
2260		B
2261		A
2262		A
2263		C
2264		A

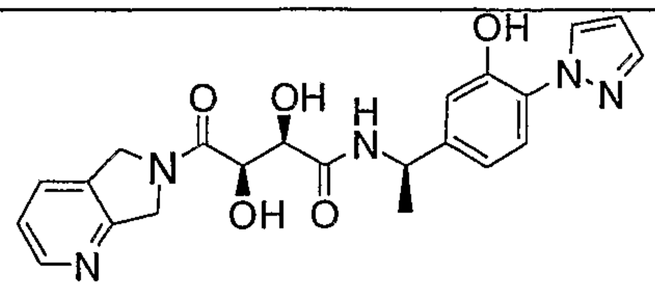
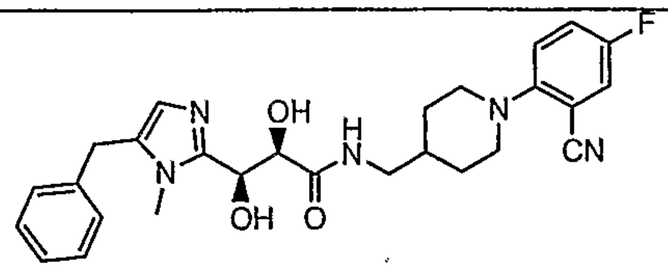
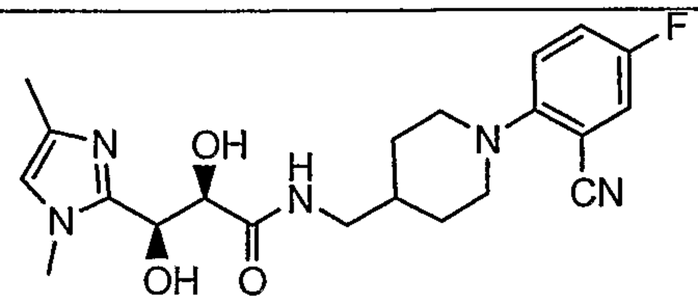
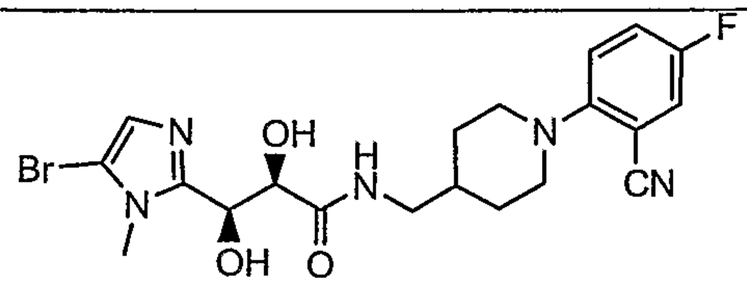
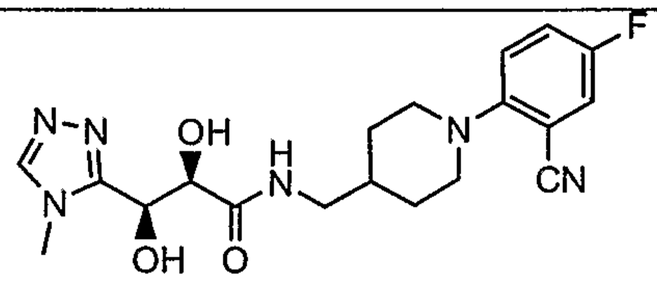
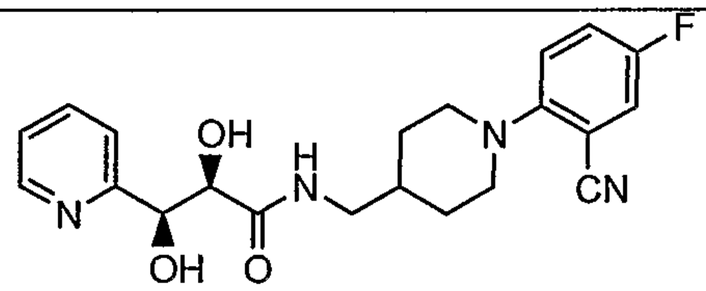
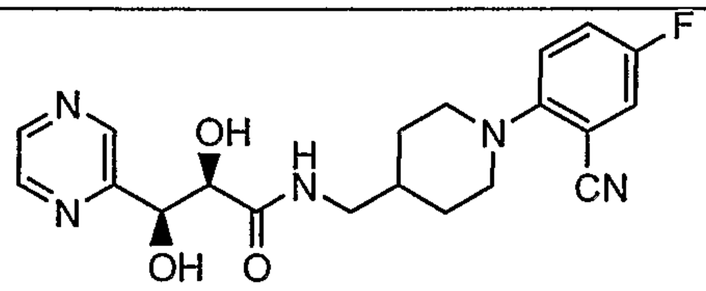
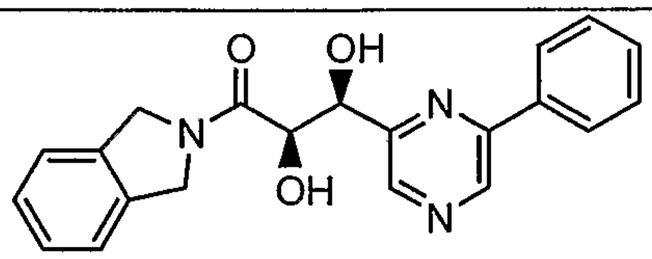
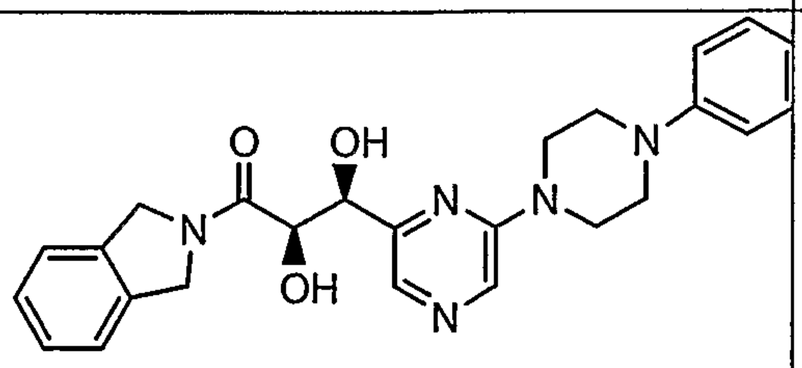
2265		A
2266		A
2267		C
2268		A
2269		A
2270		A
2271		A
2333		A
2334		A

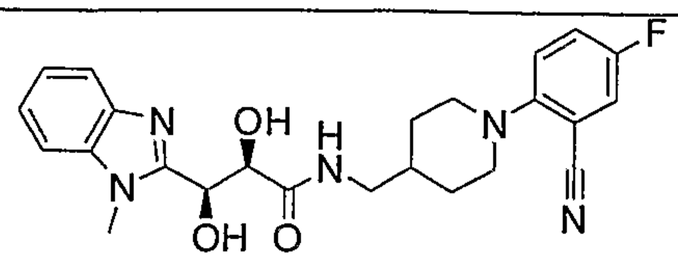
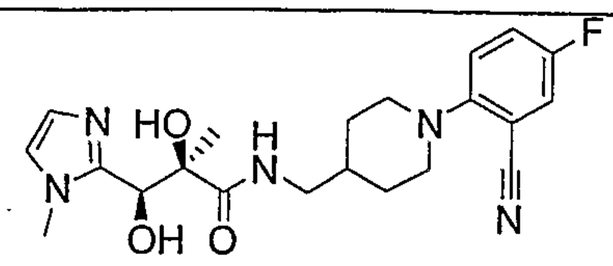
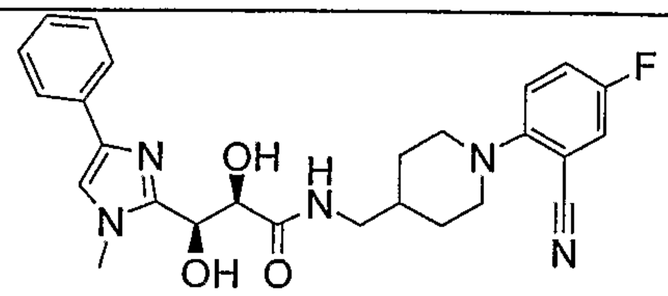
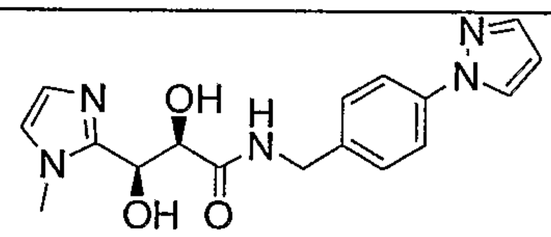
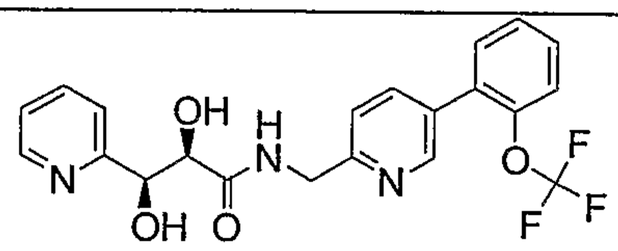
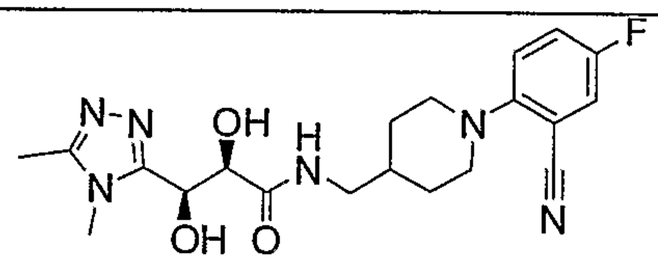
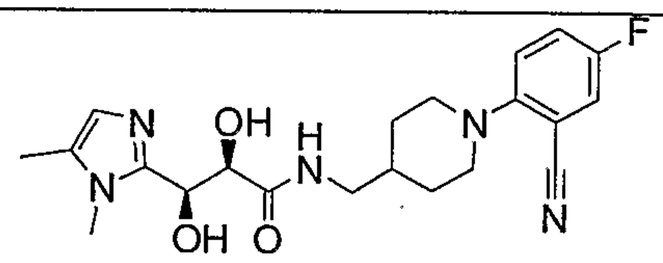
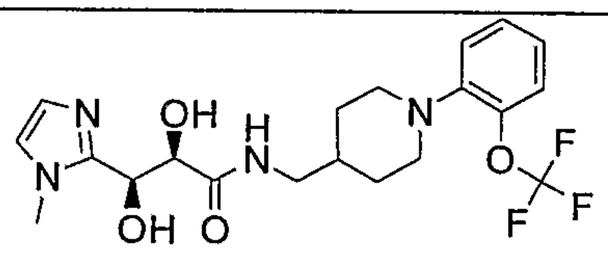
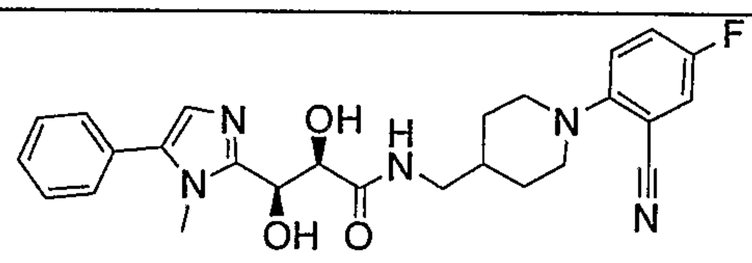
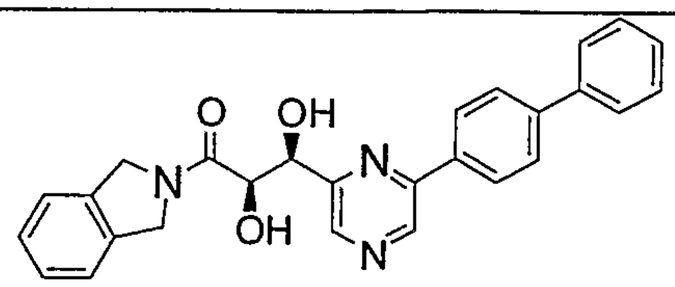
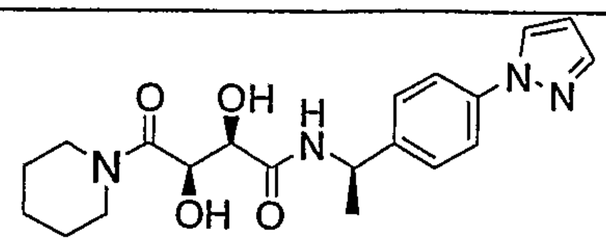
2335		C
2336		C
2337		B
2338		A
2339		B
2340		B
2341		C
2342		C
2343		D

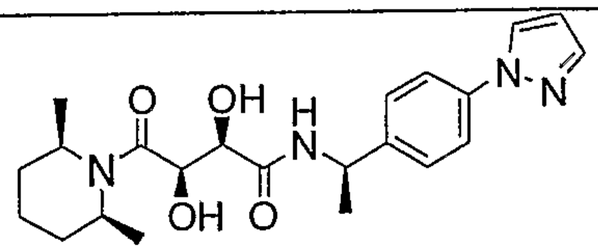
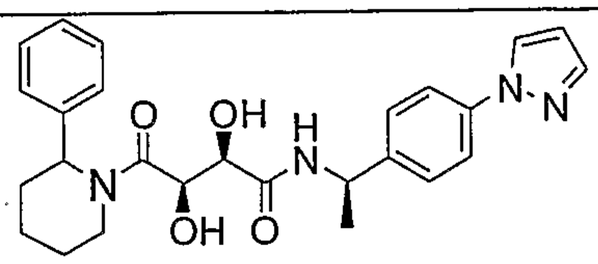
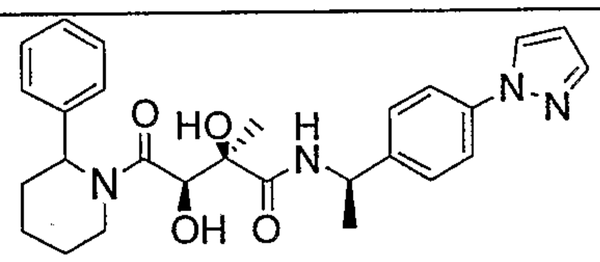
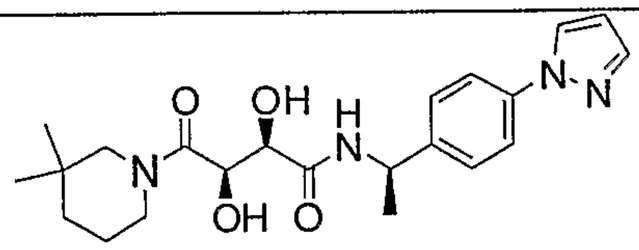
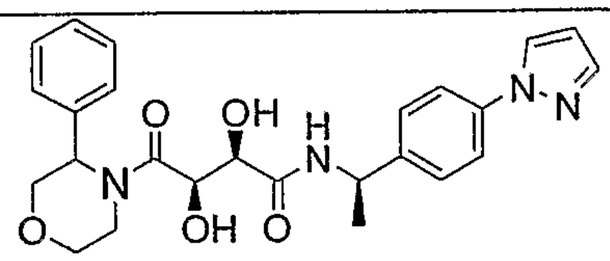
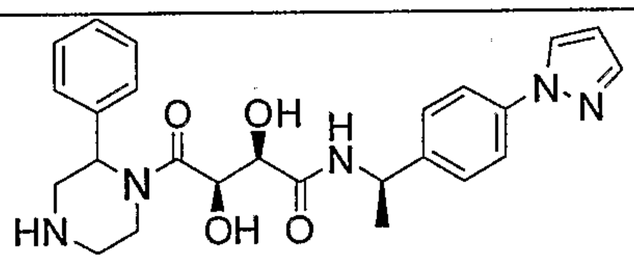
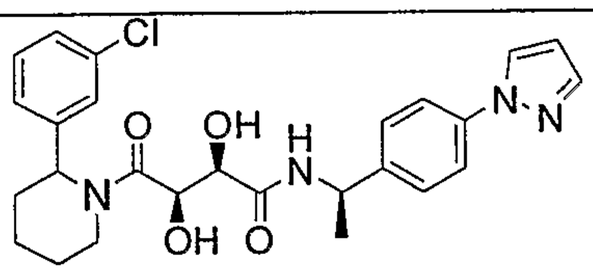
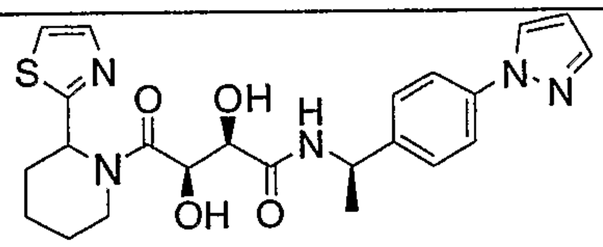
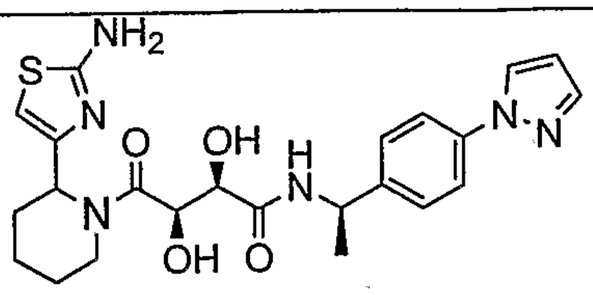
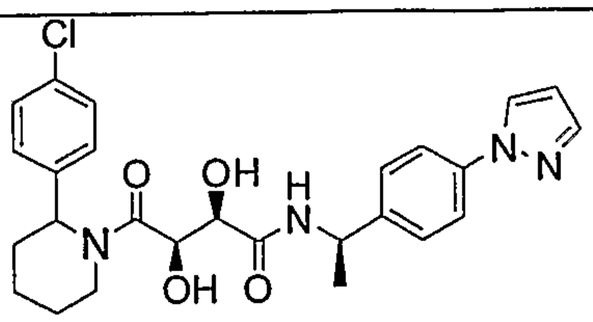
2344		D
2345		D
2346		D
2347		D
2348		C
2349		A
2350		A
2351		A

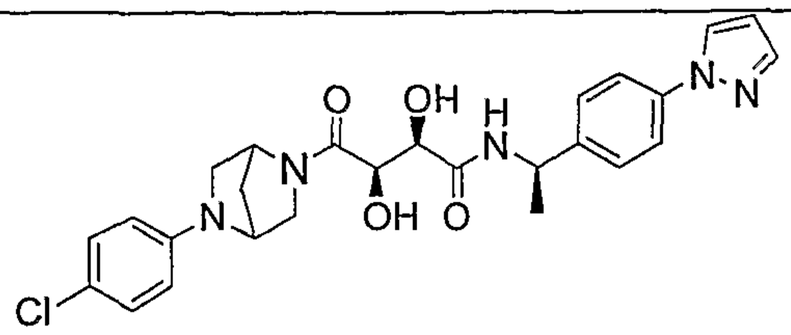
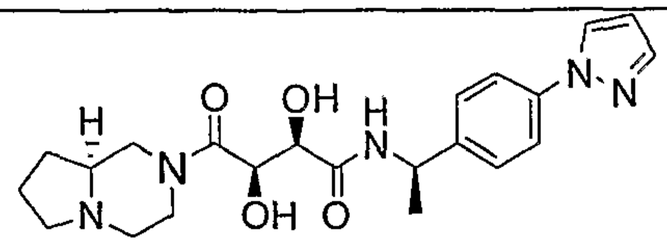
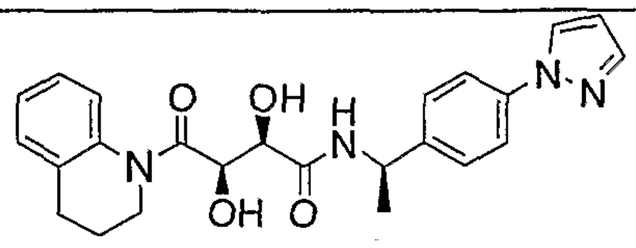
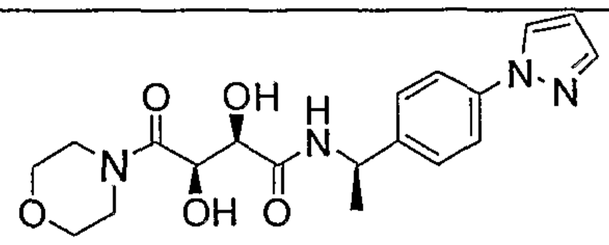
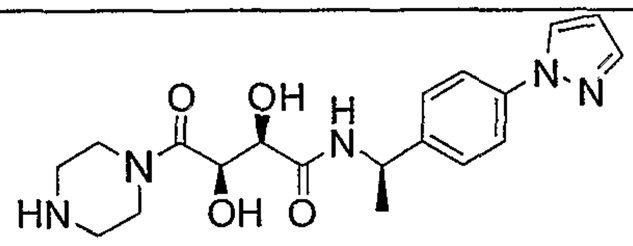
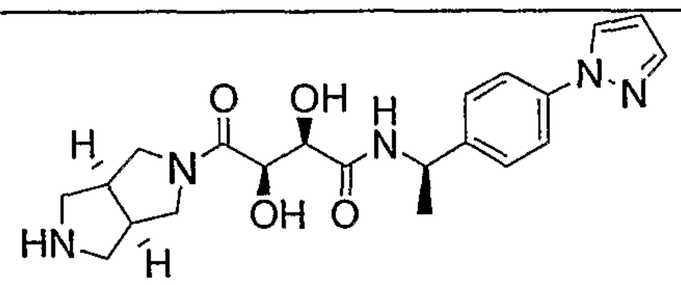
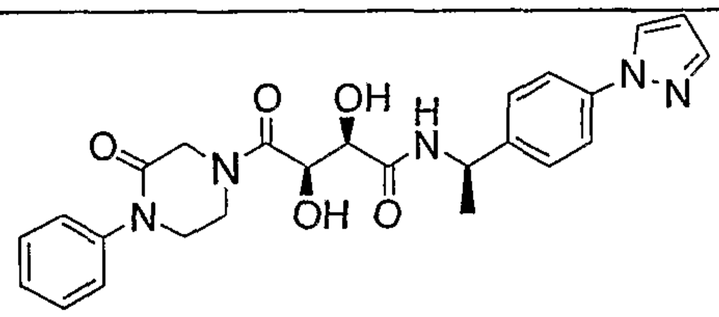
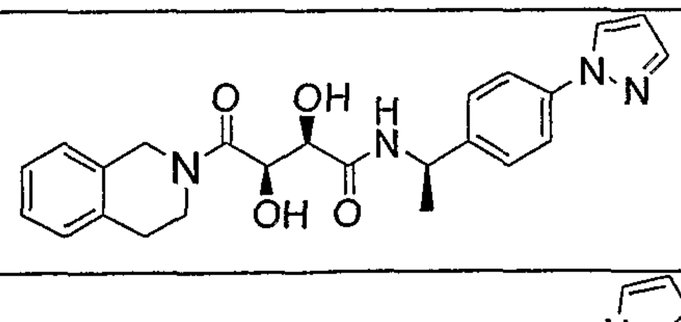
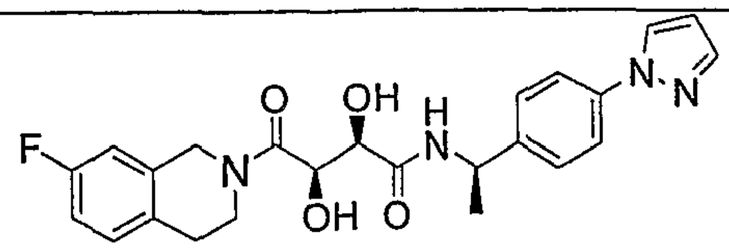
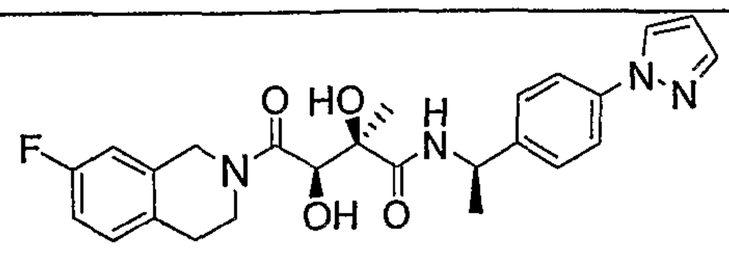
2352		A
2306		D
2307		D
2308		D
2353A		C
2353B		B
2354		B

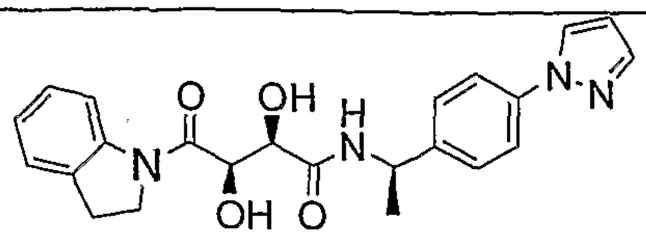
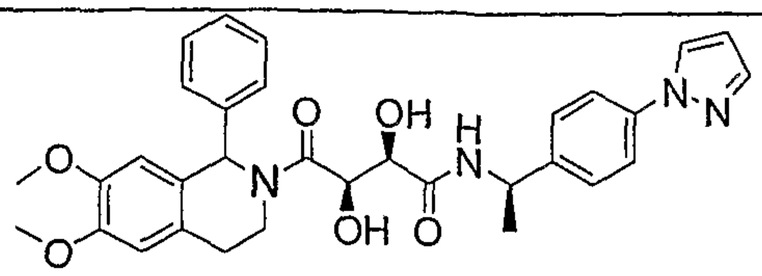
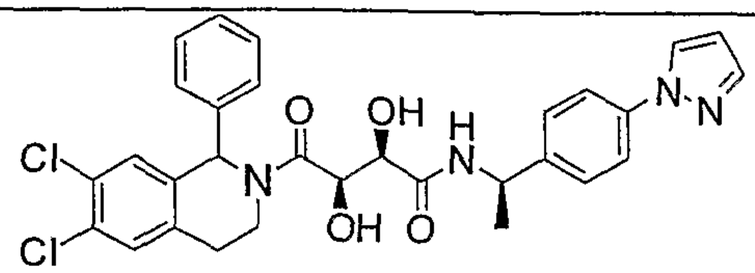
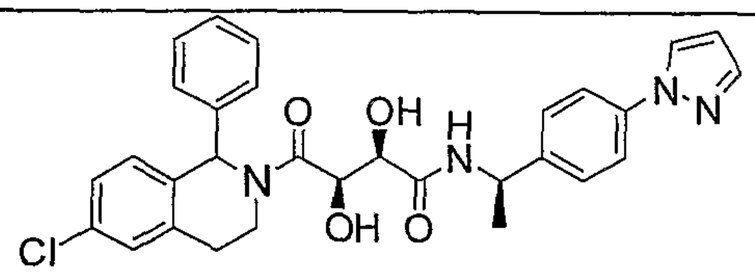
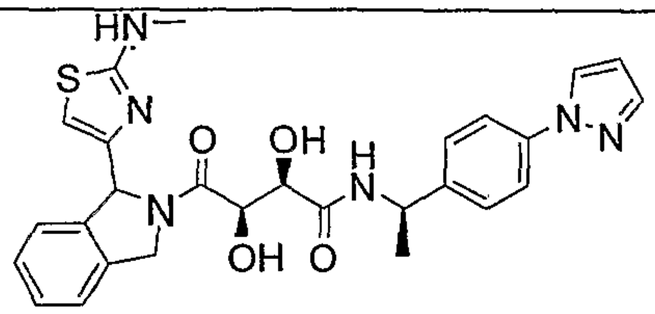
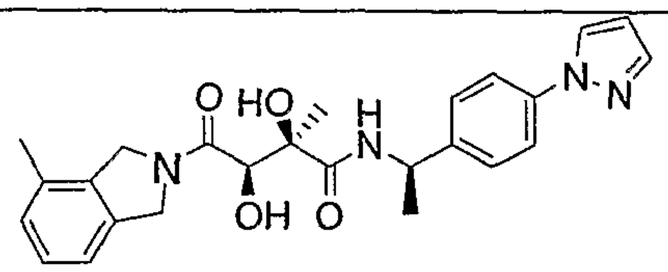
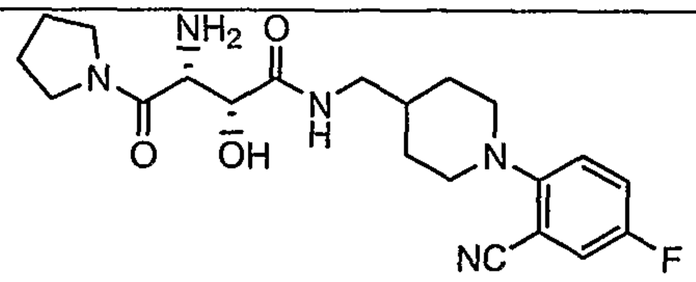
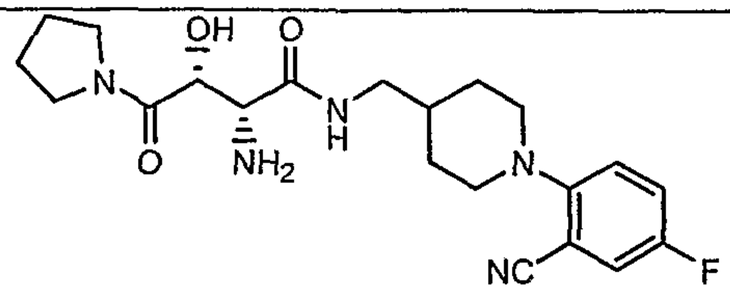
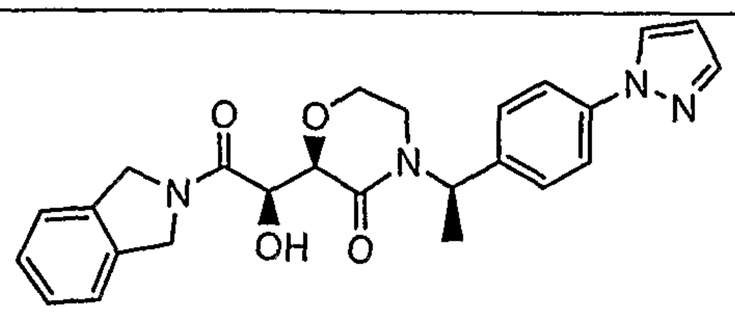
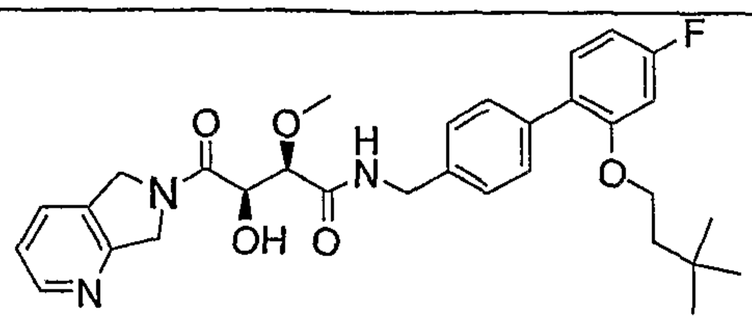
2355		A
2356		D
2357		A
2358		C
2304		A
2359		A
2360		A

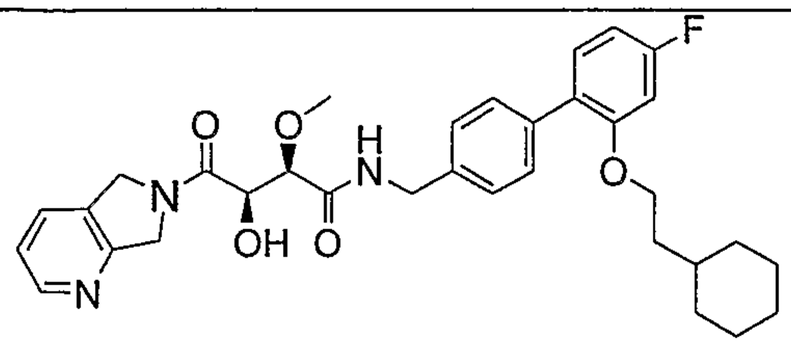
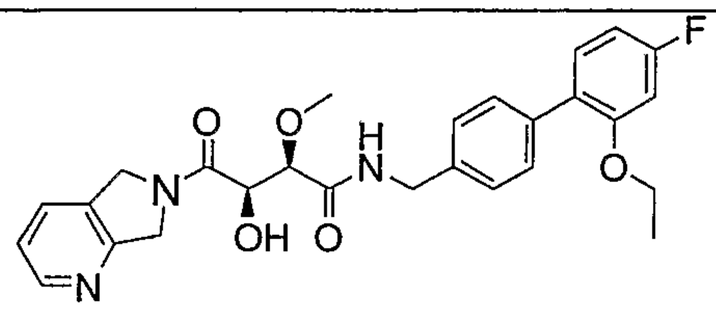
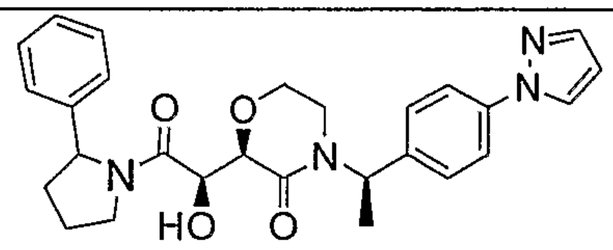
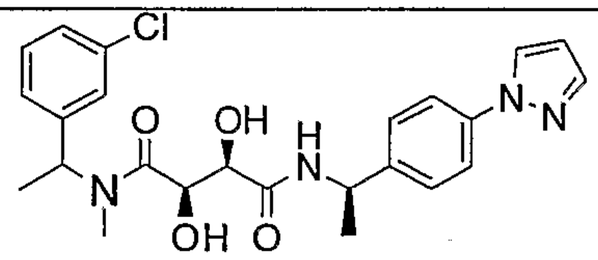
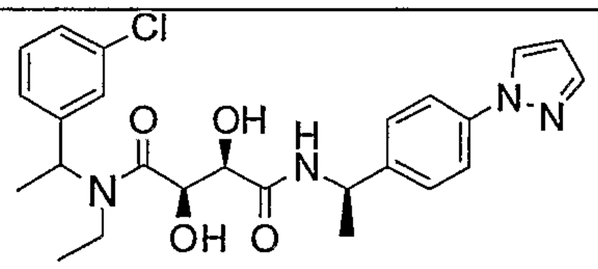
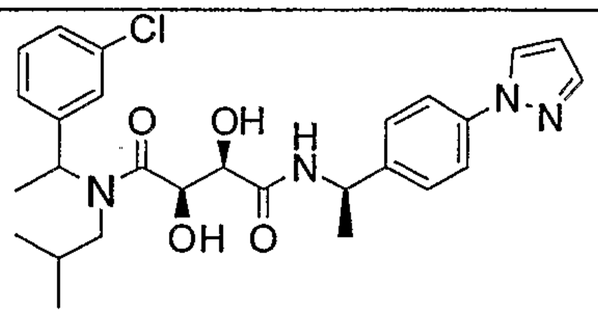
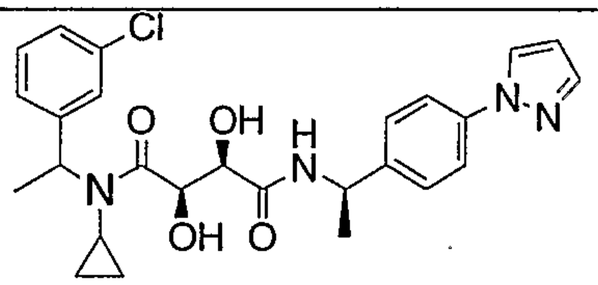
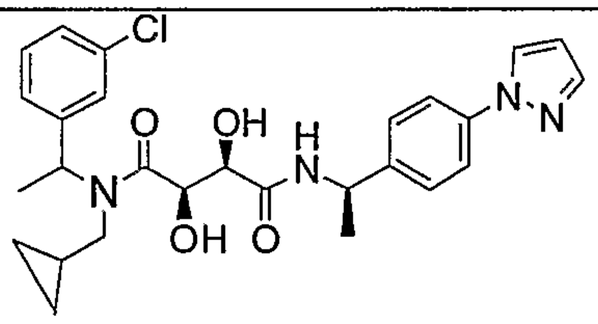
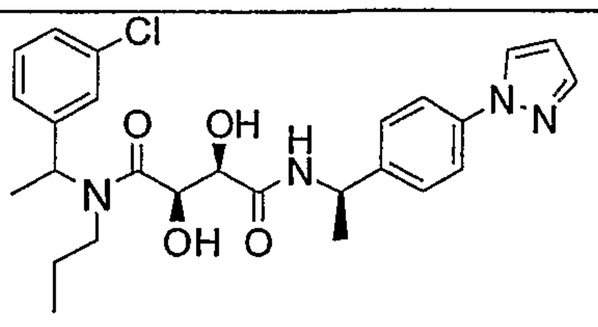
2305		A
2365		C
2369		
2372		D
2376		D
2382		D
2387		D
2391		D
2393		D

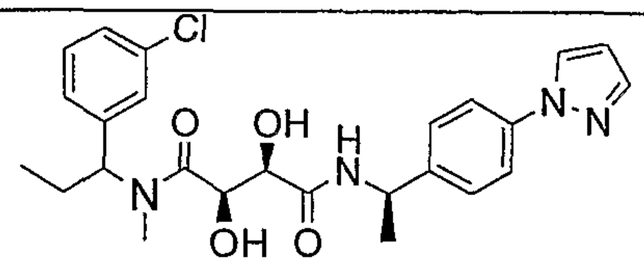
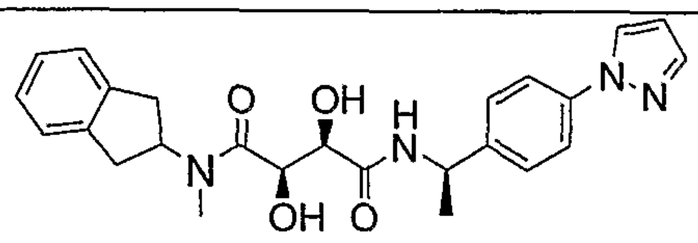
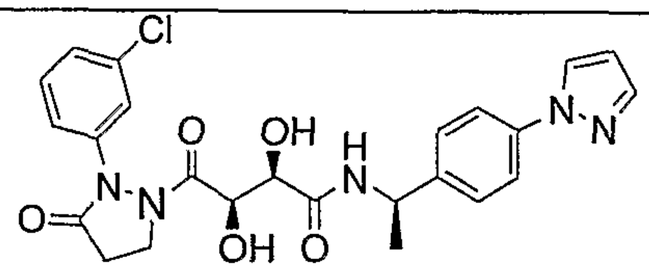
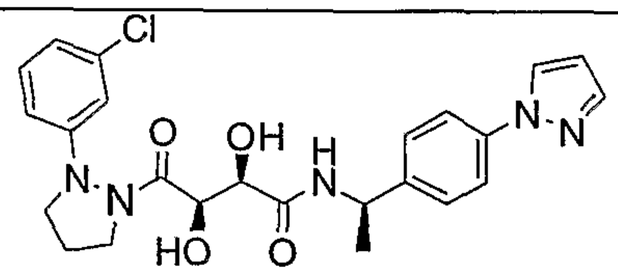
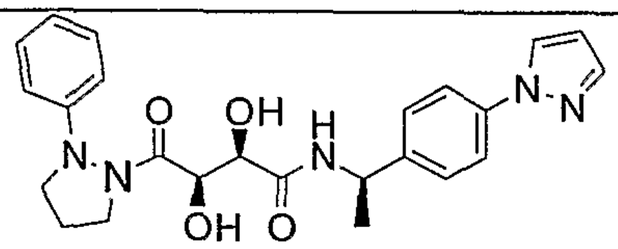
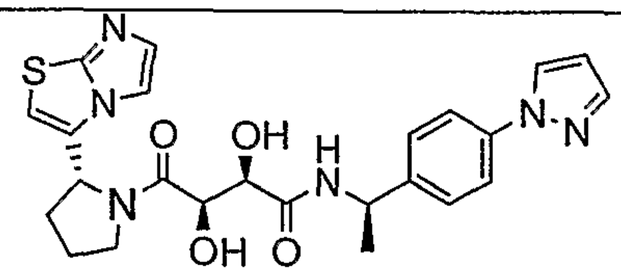
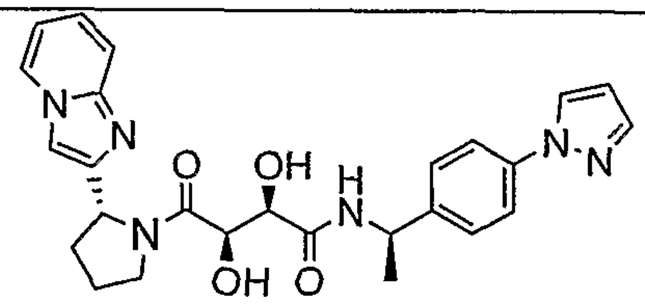
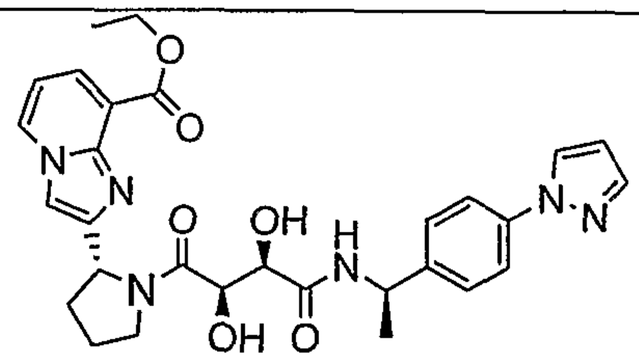
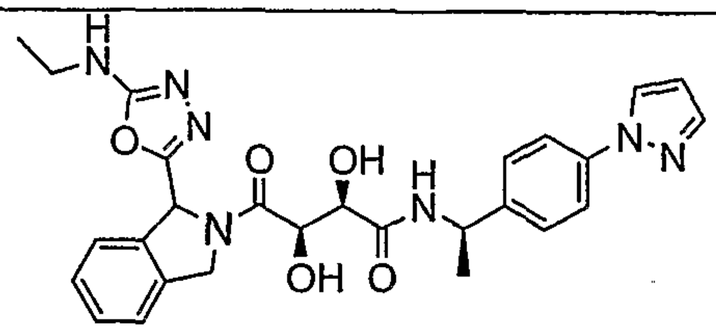
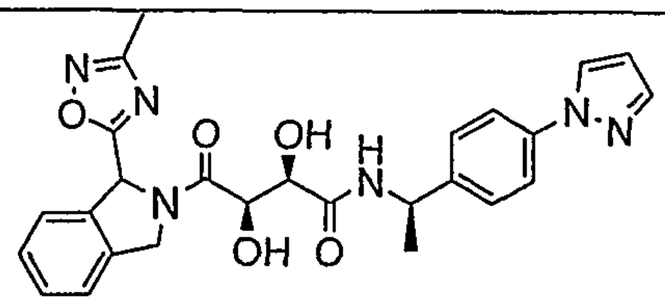
2394		D
2395		C
2396		D
2397		D
2398		D
2399		D
2400		C
2401		C
2402		D
2403		D
2408		B

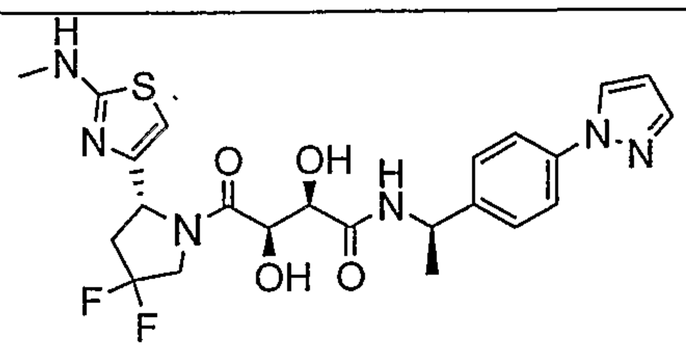
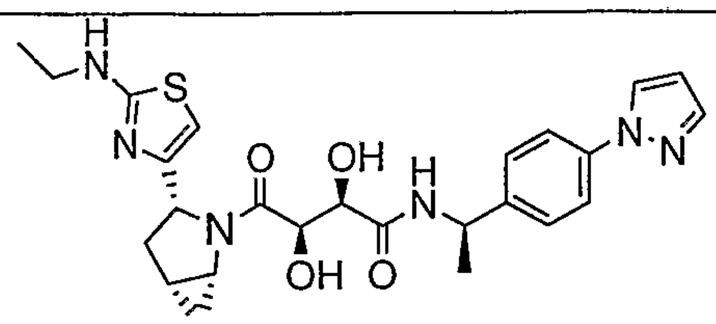
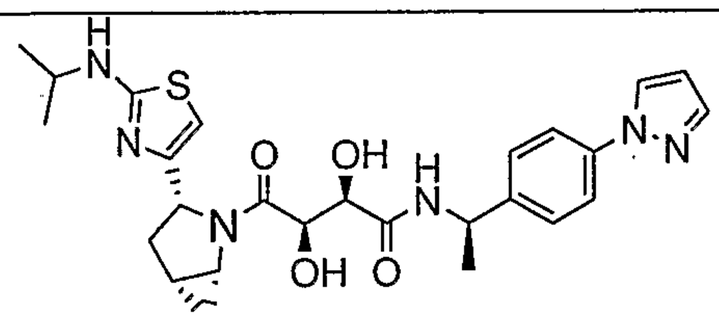
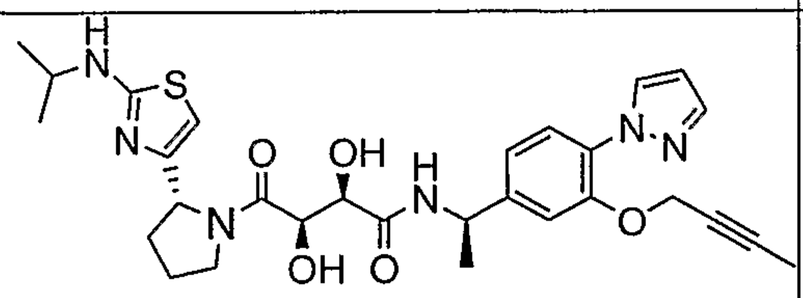
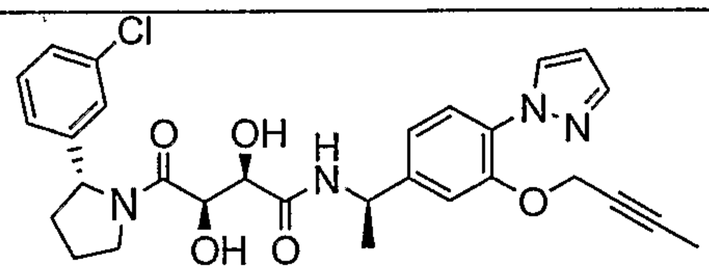
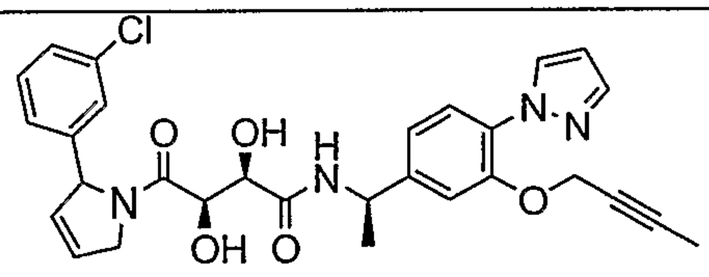
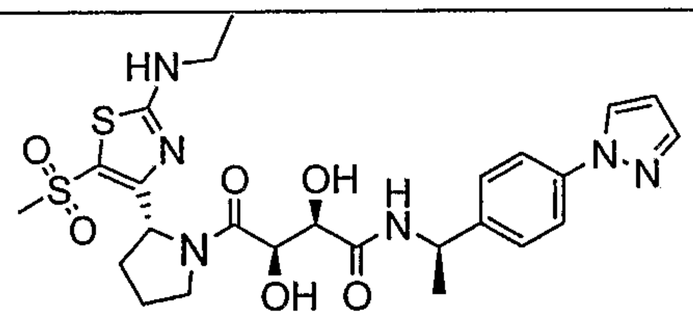
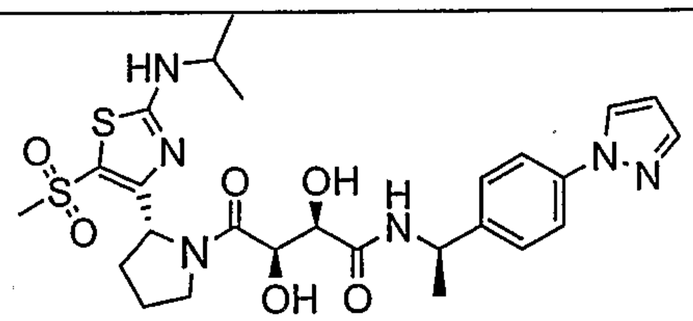
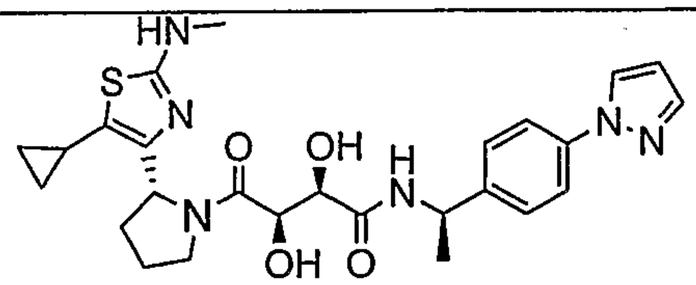
2409		C
2410		A
2411		D
2412		C
2413		A
2414		B
2415		B
2416		B
2417		B
2418		B

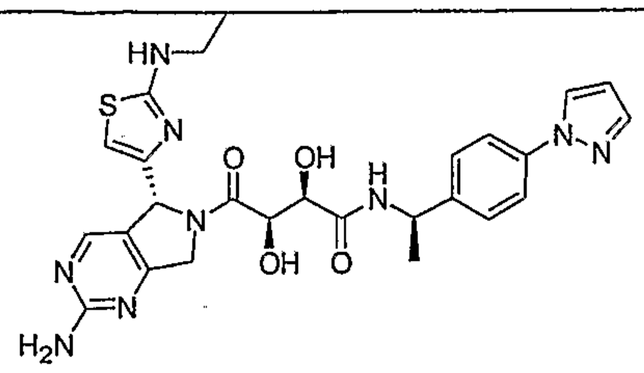
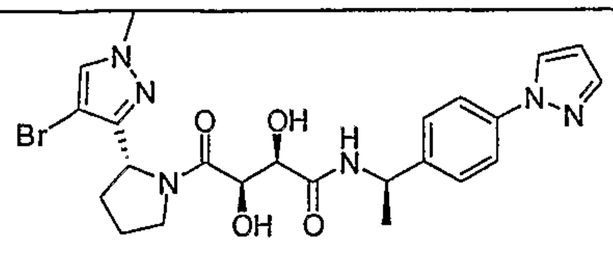
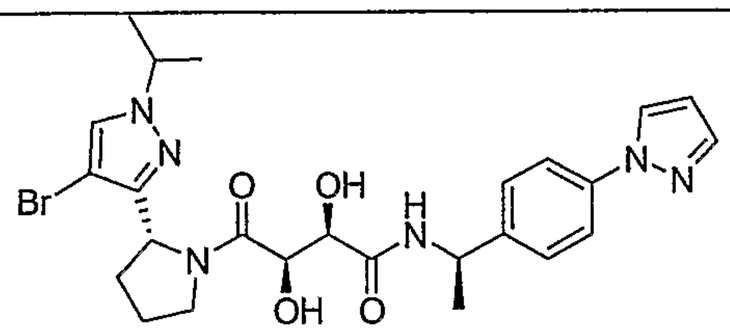
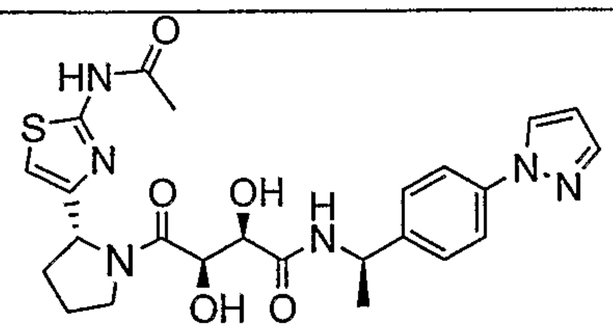
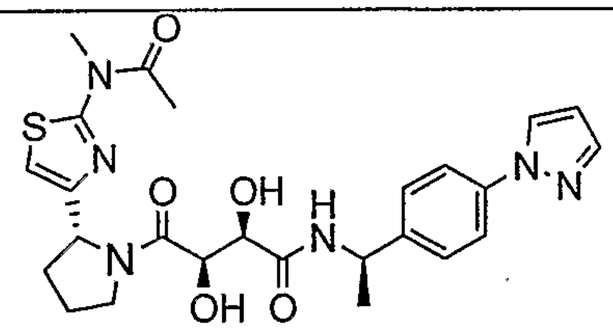
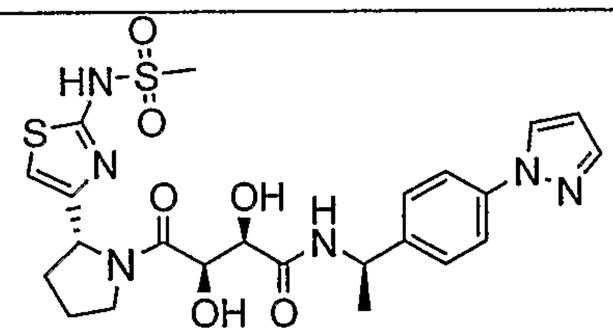
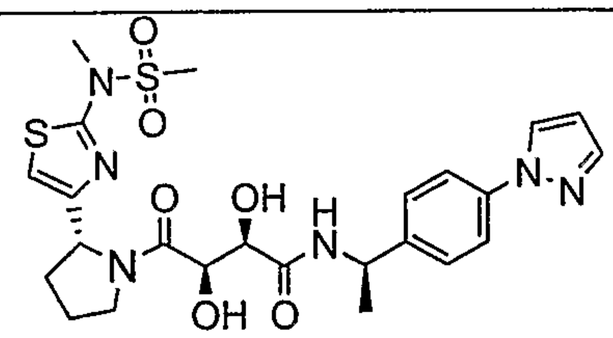
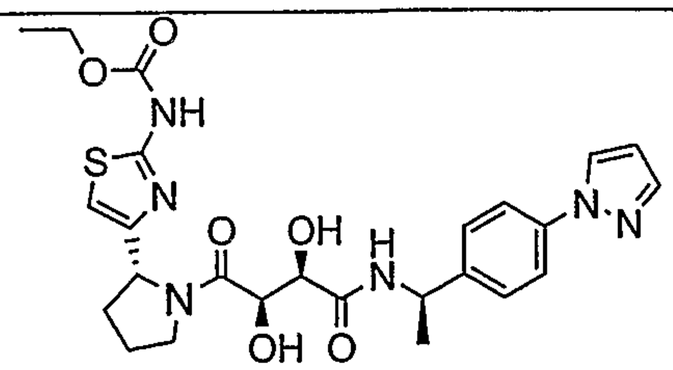
2419		C
2420		C
2421		C
2422		B
2423		C
2424		C
2425		C
2438		A
2439		A
2440		B

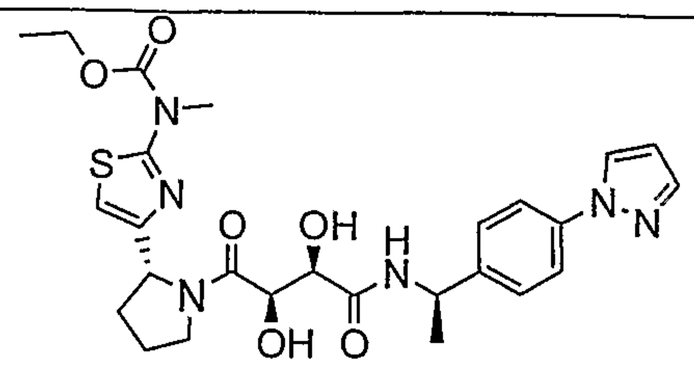
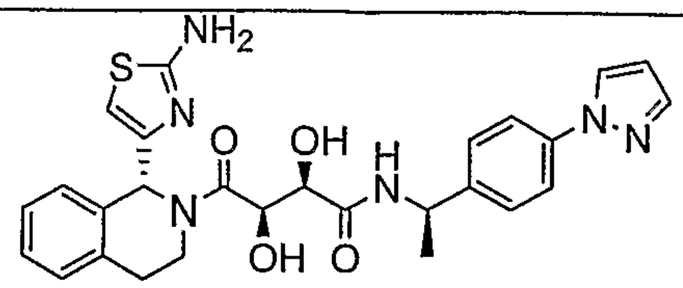
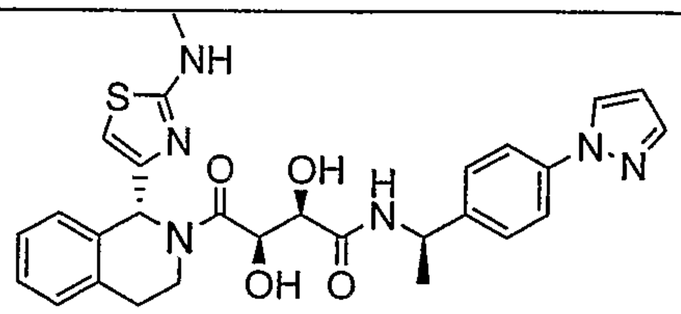
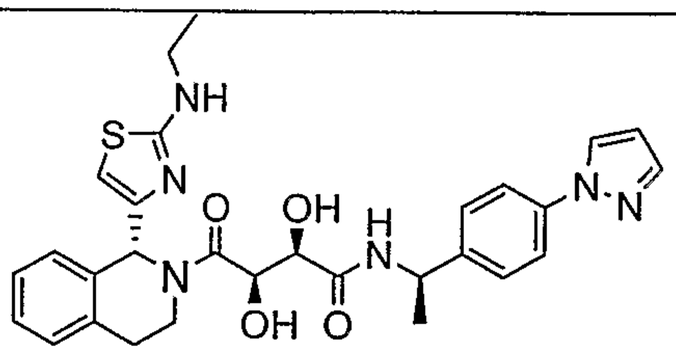
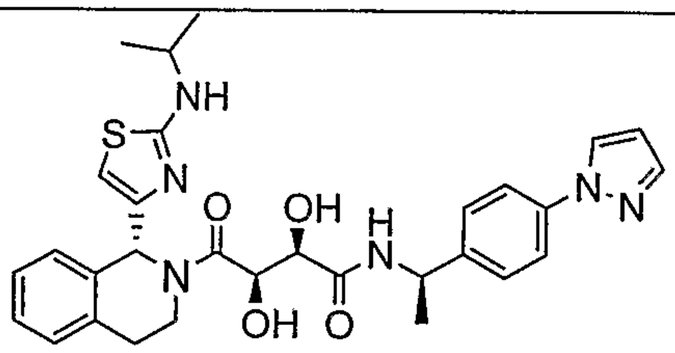
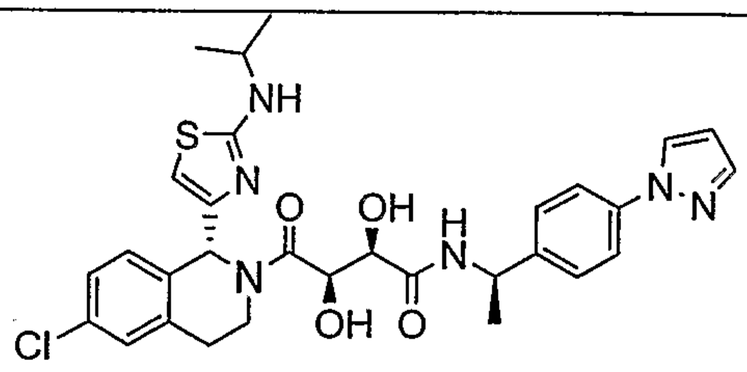
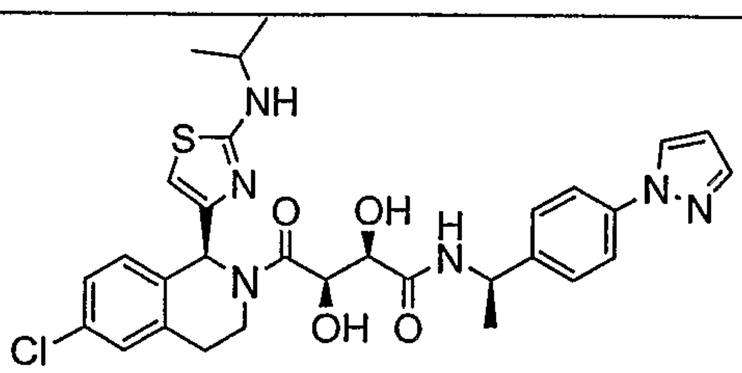
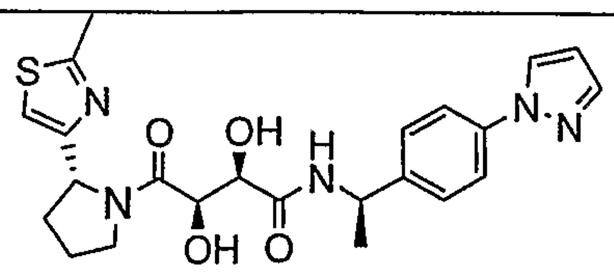
2441		B
2442		A
2443		A
2444		A
2445		A
2446		B
2456		D
2460		D
2474		D
2475		B

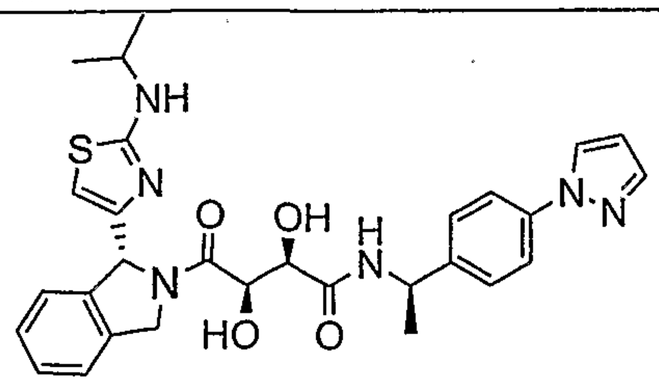
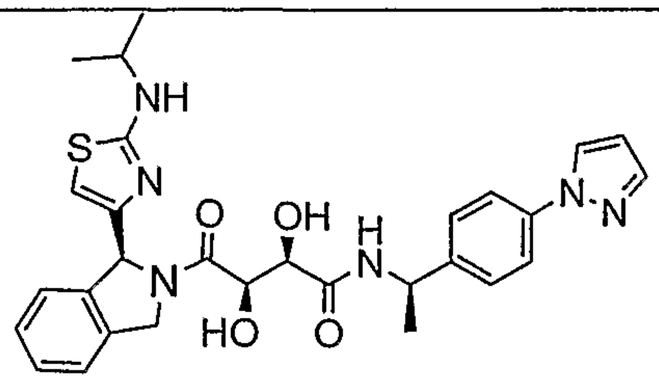
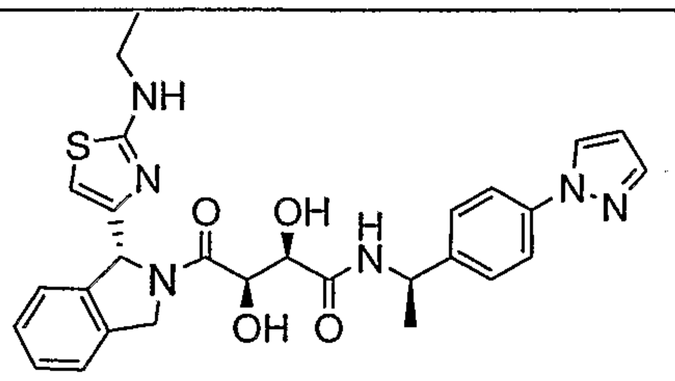
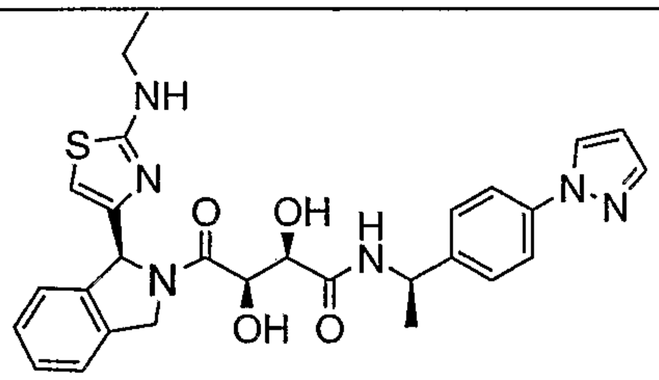
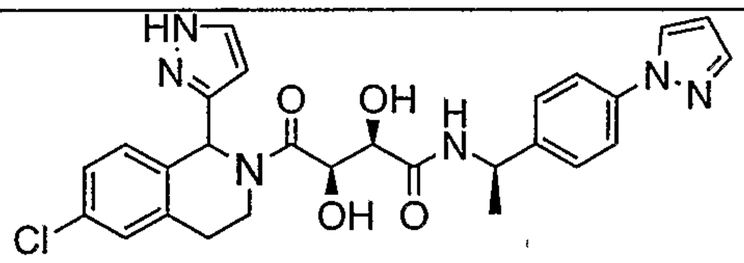
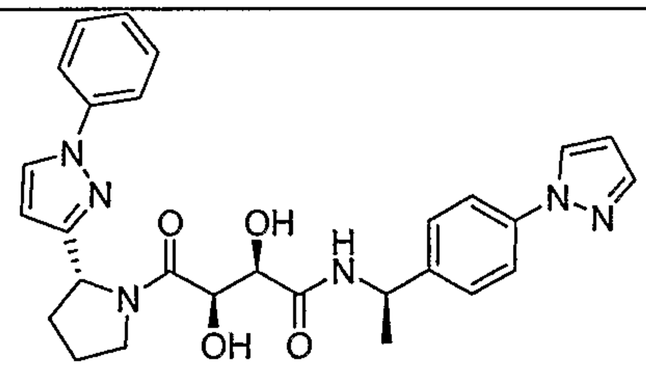
2476		B
2477		C
2478		D
2480		B
2481		C
2482		D
2483		D
2485		D
2486		D

2487		B
2489		B
2494		C
2495		C
2496		C
2506		A
2507		A
2508		B
2527		A
2528		A

2567		A
2568		--
2569		--
2570		A
2571		A
2572		A
2573		--
2574		--
2575		--

2576		--
2577		--
2578		--
2579		A
2580		A
2581		A
2582		A
2583		--

2584		--
2585		A
2586		A
2587		A
2588		A
2589		A
2590		A
2591		A

2592		A
2593		A
2594		A
2595		
2596		A
2597		A
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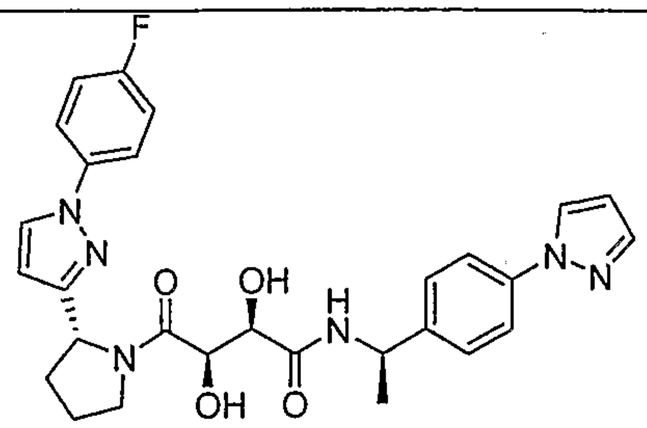
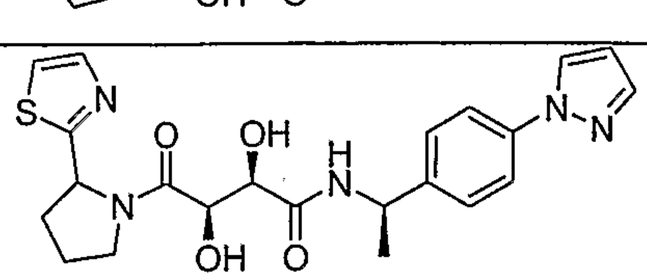
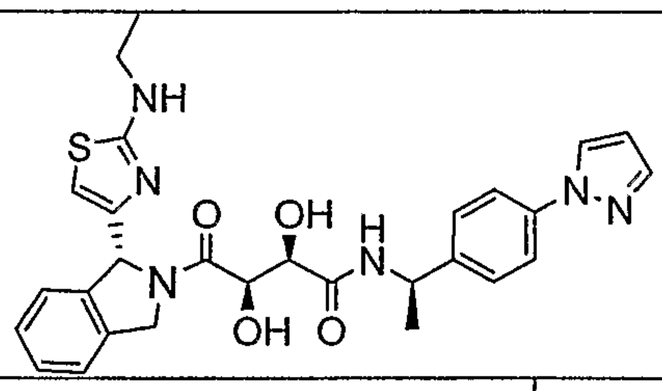
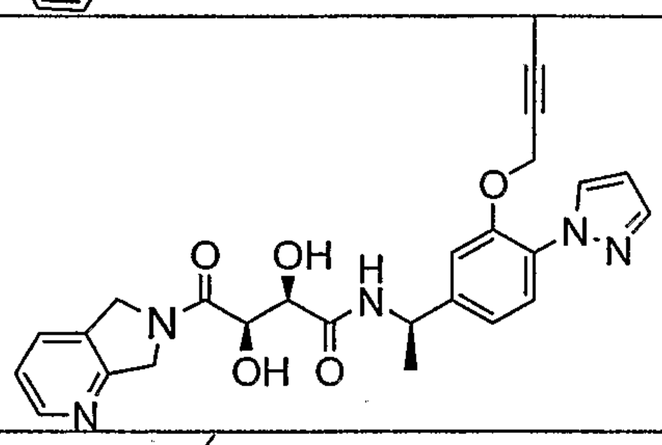
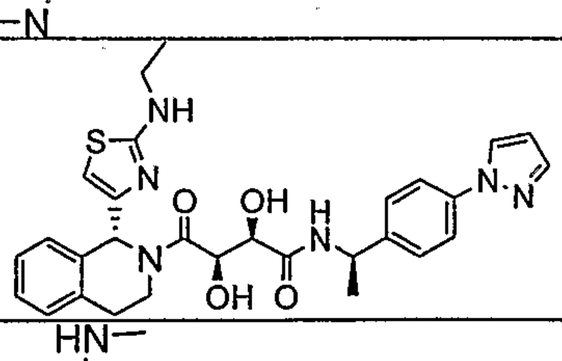
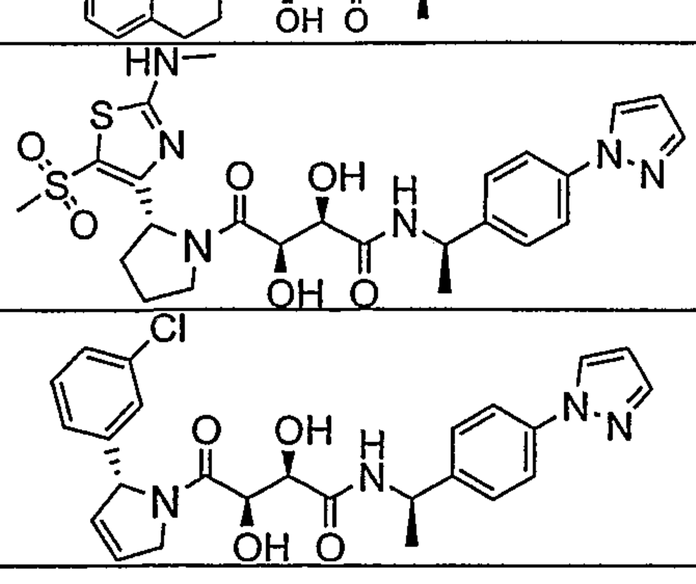
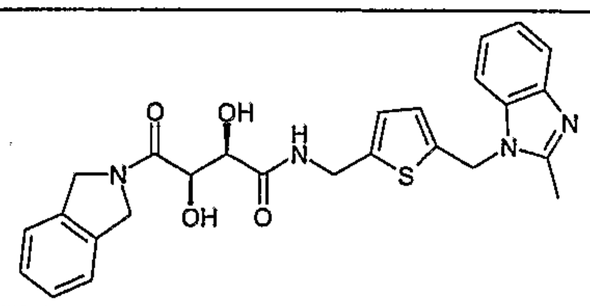
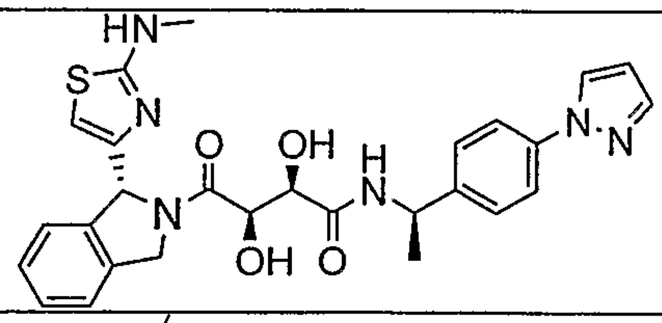
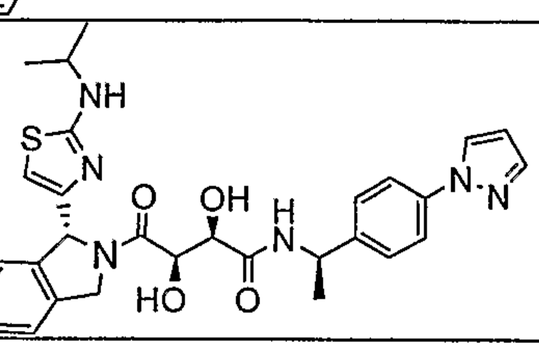
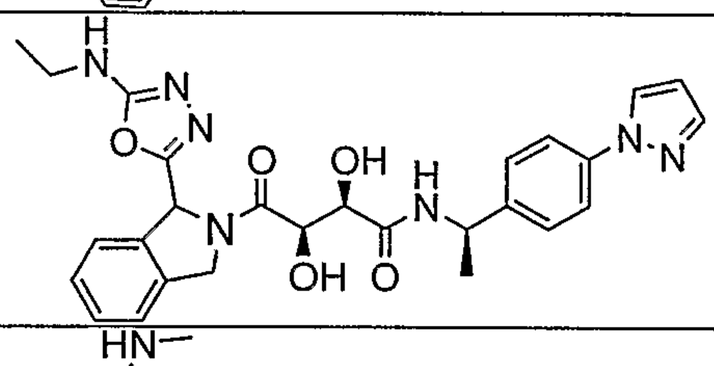
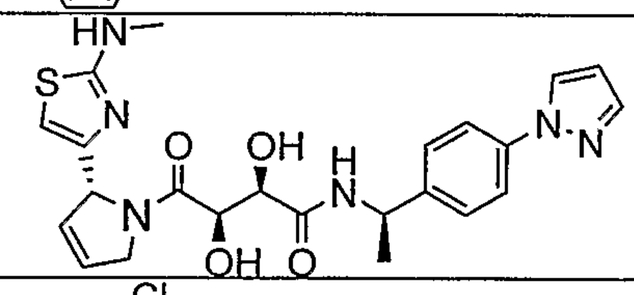
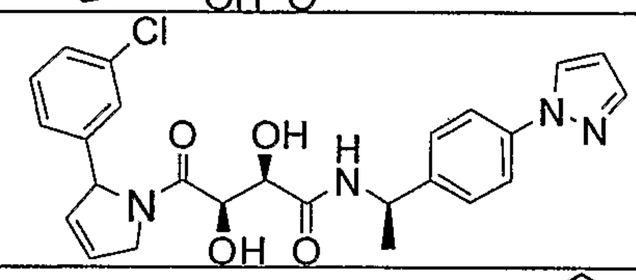
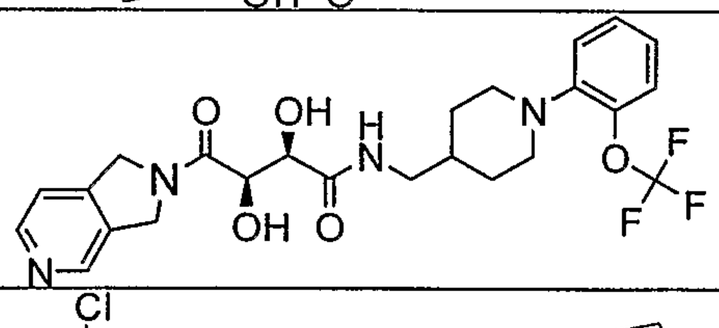
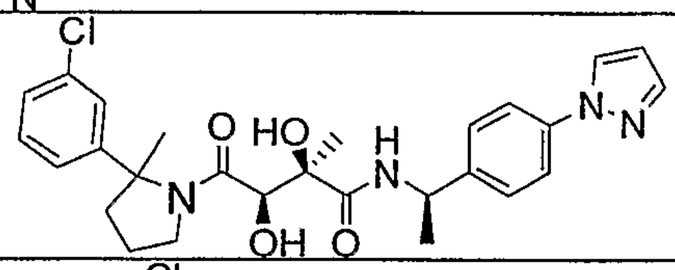
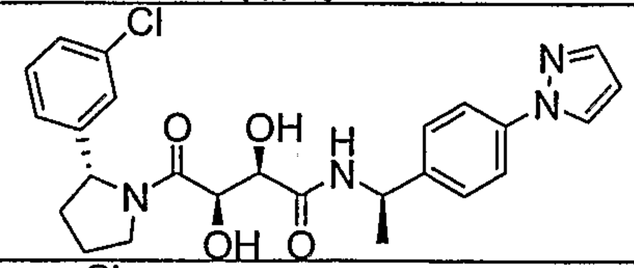
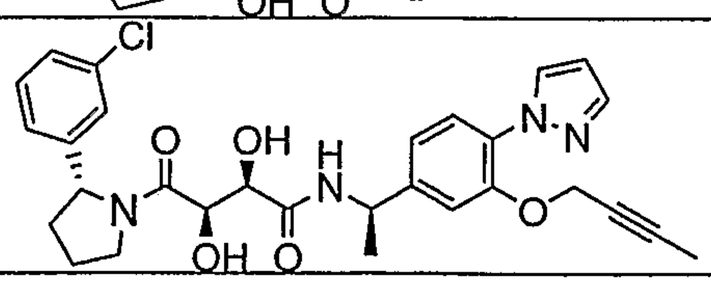
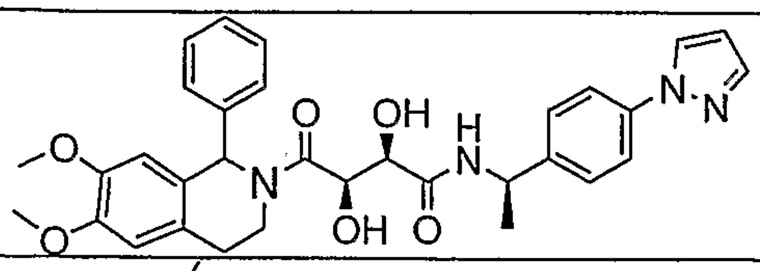
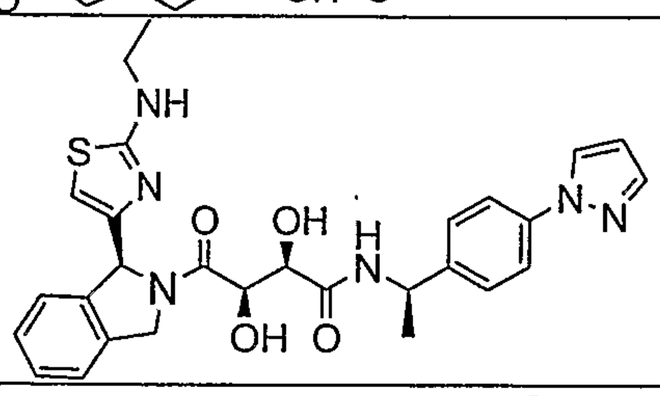
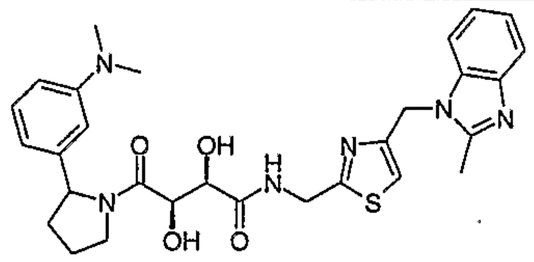
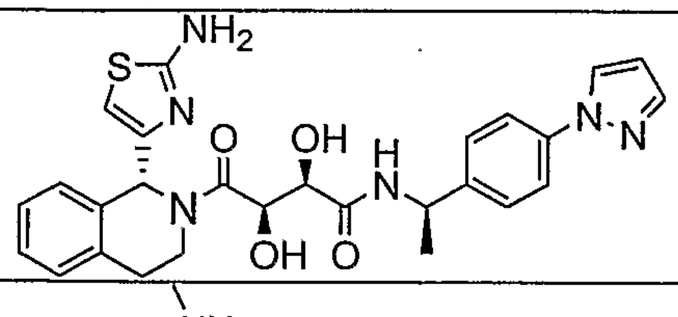
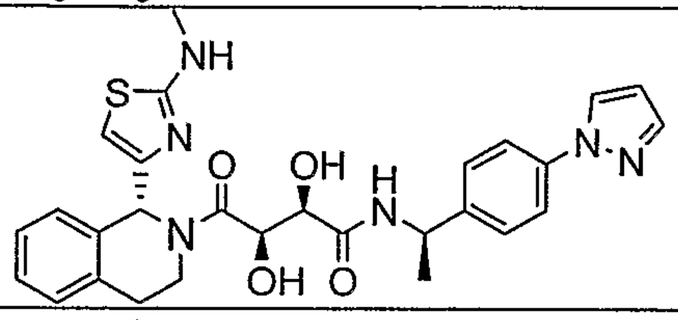
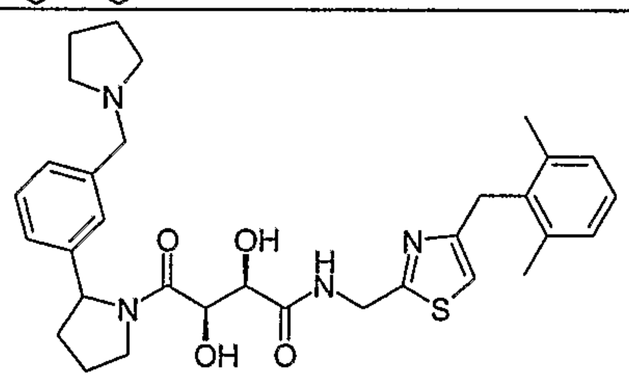
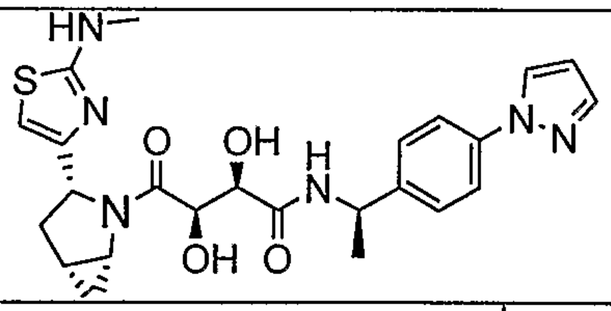
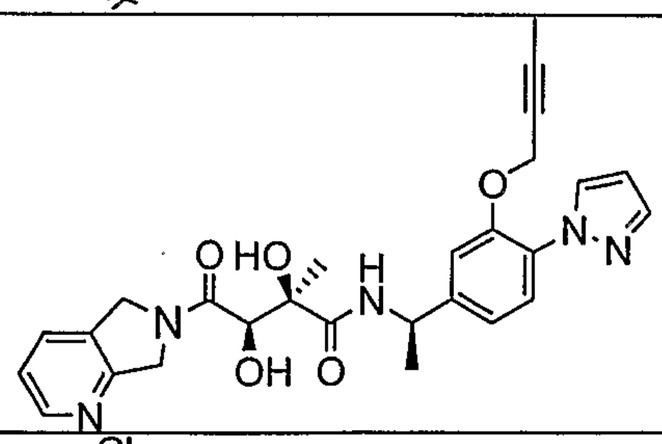
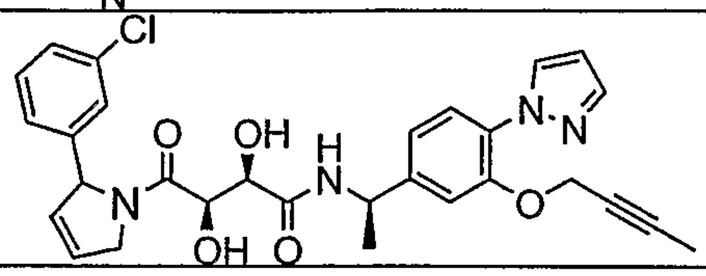
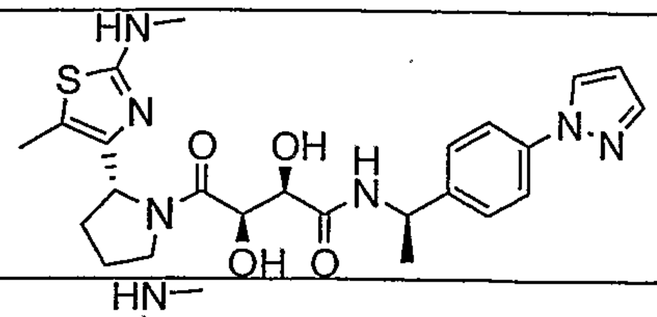
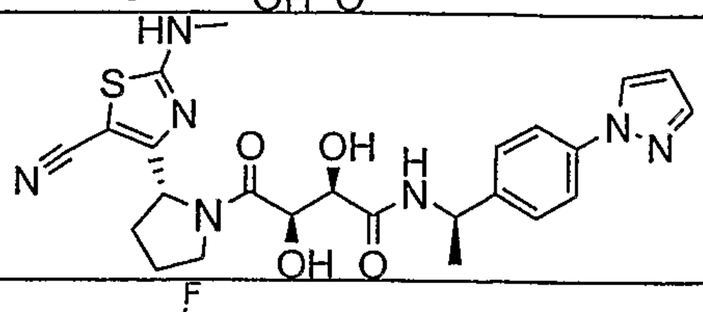
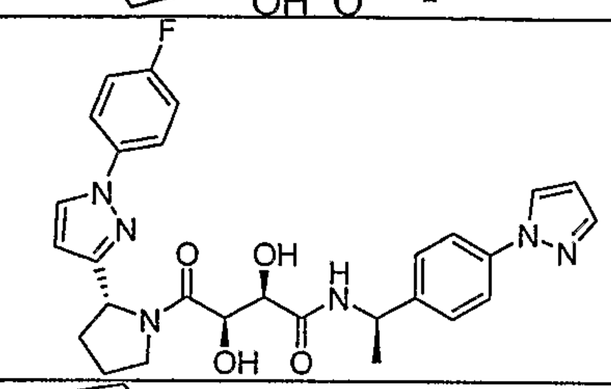
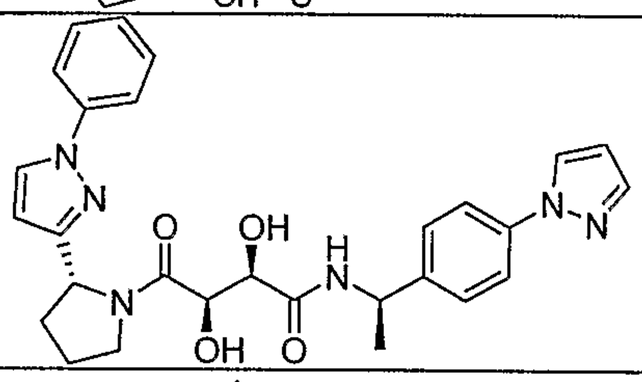
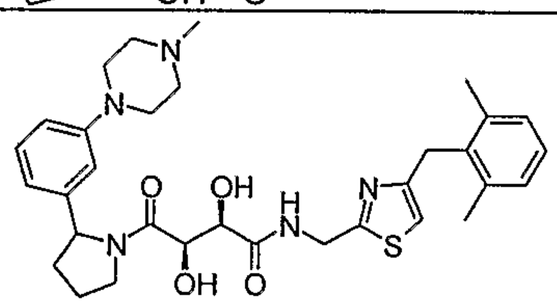
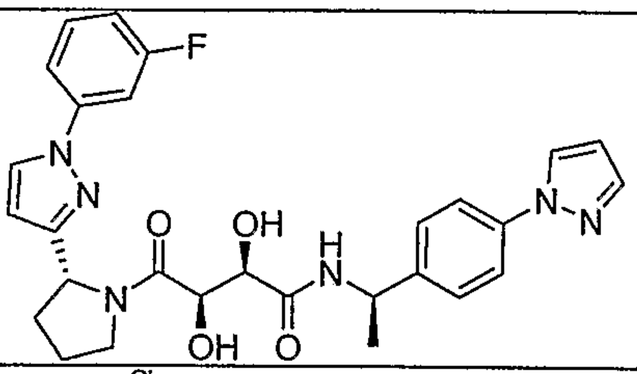
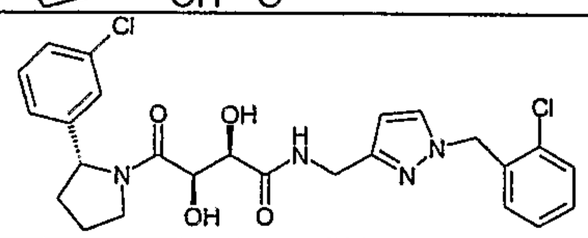
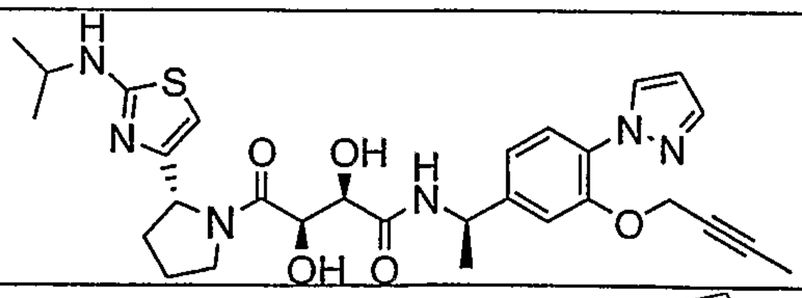
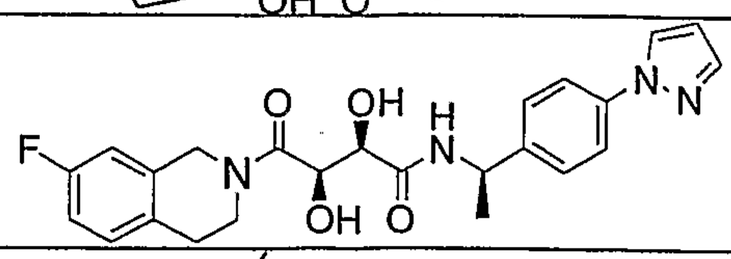
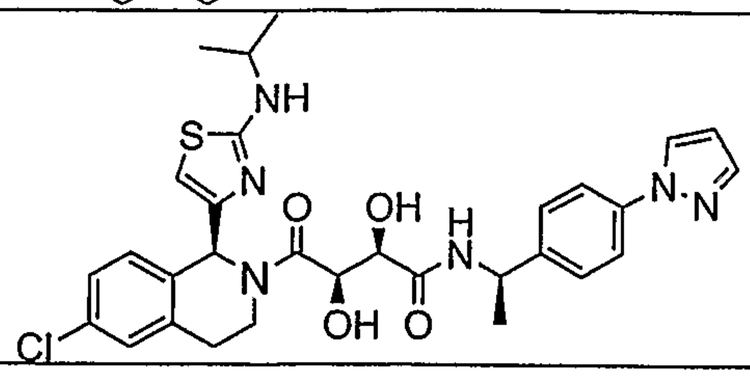
2599		A
2600		A

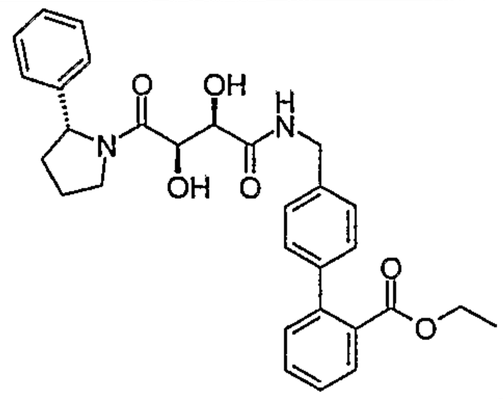
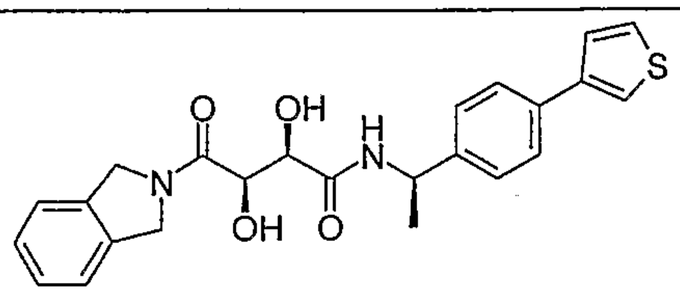
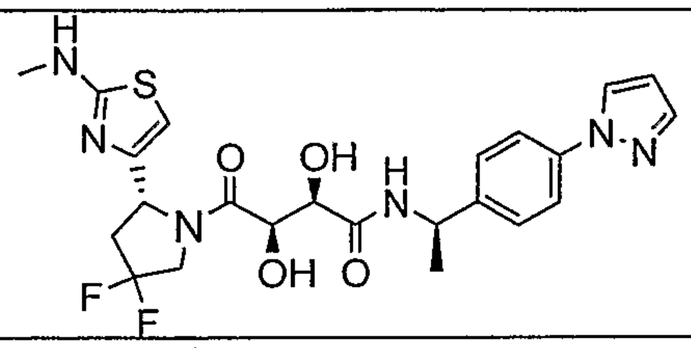
Representative examples of compounds of the invention with their respective K_i values are listed in the table below:

	Structure	Ki (nM)
		0.16
		0.25
		0.3
		0.38
		0.49

		0.5
		0.5
		0.54
		0.56
		0.57
		0.6
		0.74
		0.75
		0.8
		0.85

		0.86
		0.89
Mixture of diastereomers		1
		1.1
		1.4
One diastereomer		1.4
		1.4
		1.44
		1.54

		2
		2
		2.0
		2.3
Mixture of diastereomers		2.5
		2.7
		2.7
		2.9
		3.0
		3.3

		3.6
		3.8
		3.9

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
^{1}H	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.

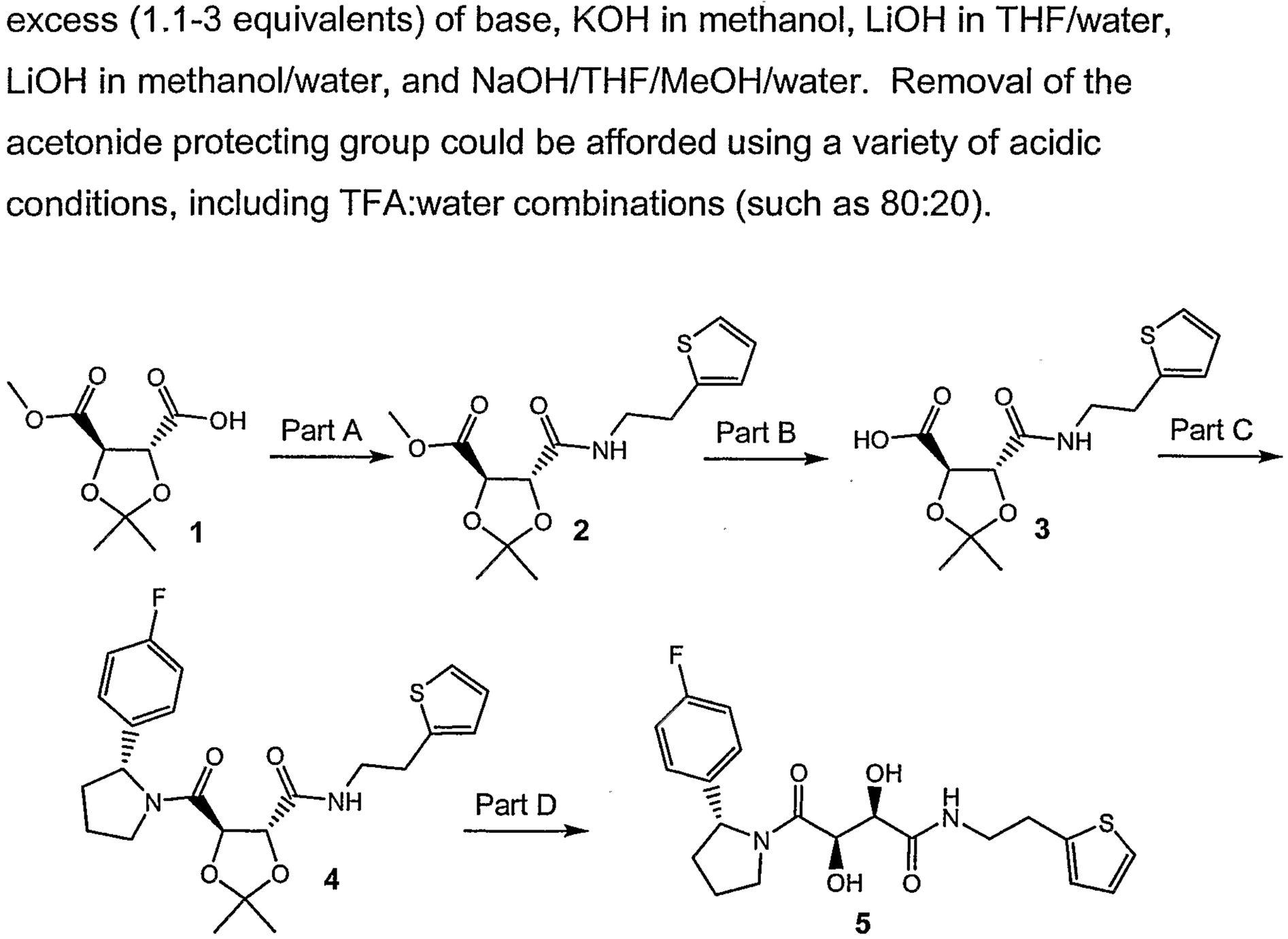
Example 1: General synthesis of tartrate inhibitors

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%). ^{1}H 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:

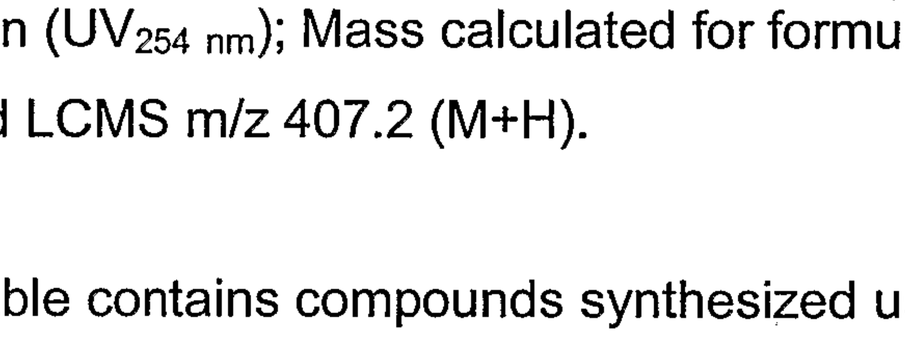
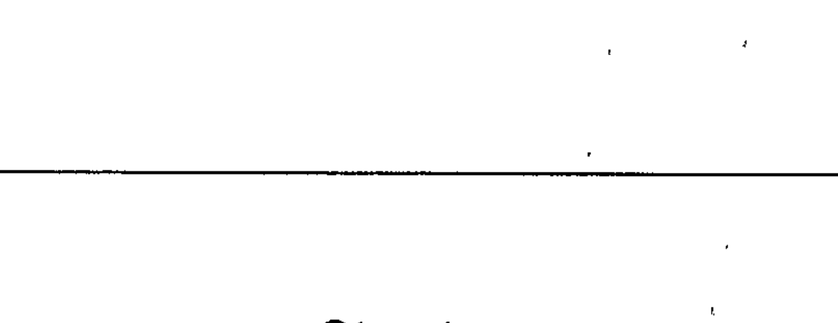
To **3** (150 mg, 0.5 mmol) in DMF (2 mL) was added racemic 2-(4-fluoro-phenyl)-pyrrolidine (99 mg, 0.6 mmol), DIEA (261 µL, 1.5 mmol), and HATU (228 mg, 0.6 mmol) and the reaction mixture was stirred overnight at room temperature. The DMF was removed in vacuo and the residue was dissolved

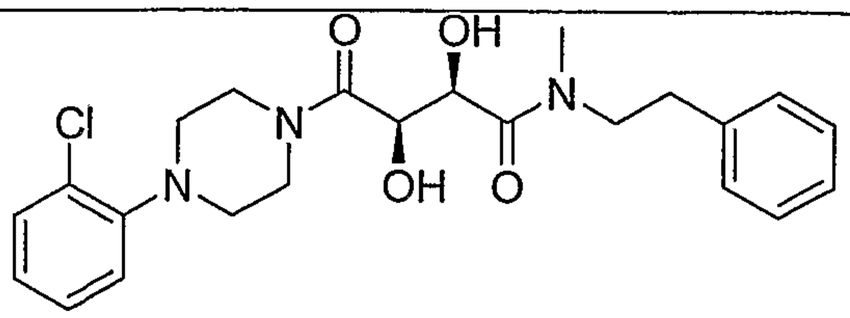
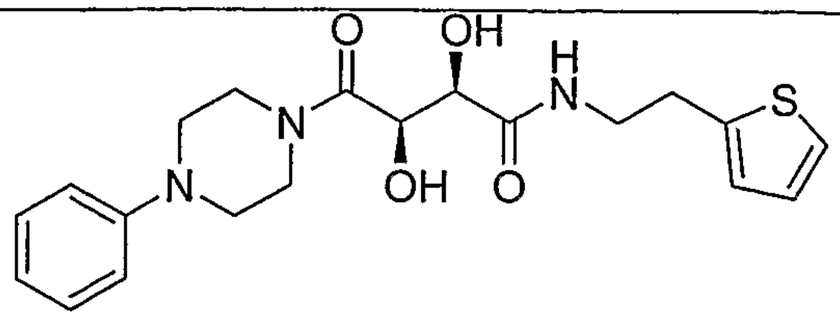
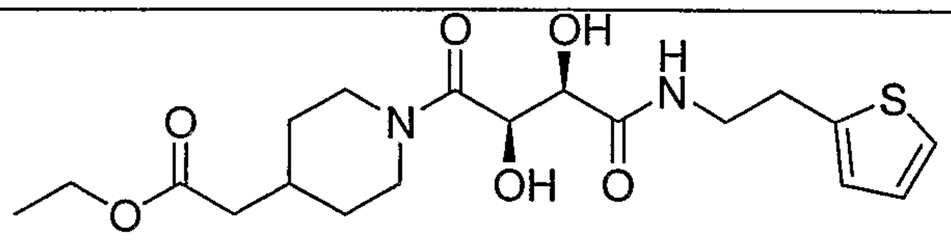
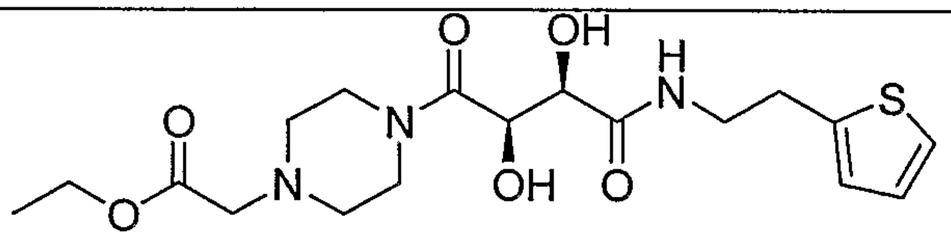
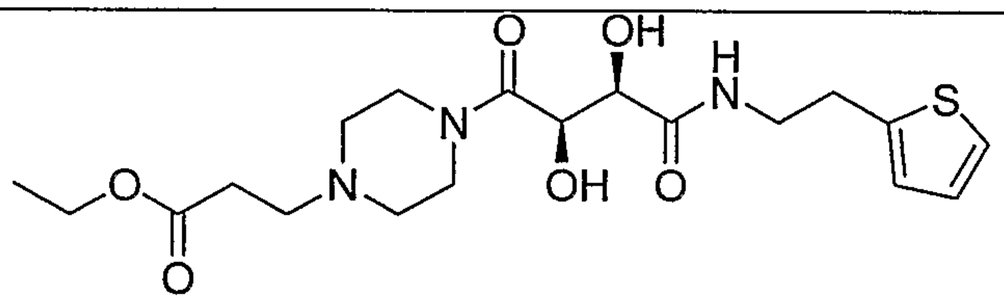
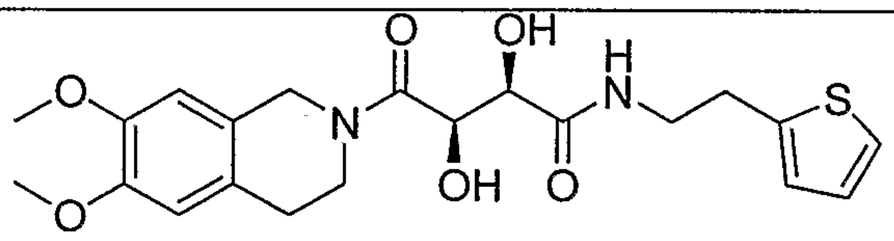
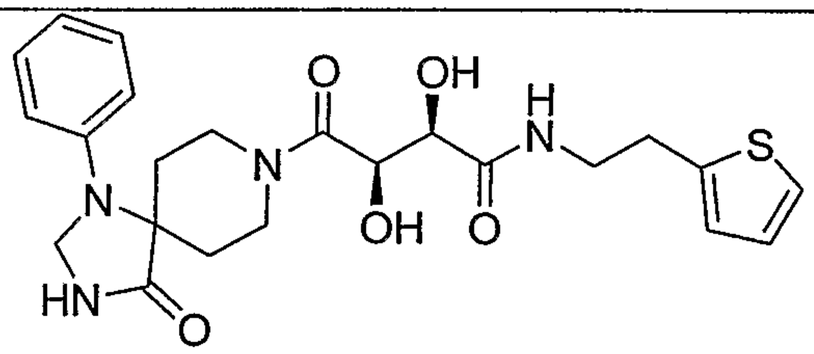
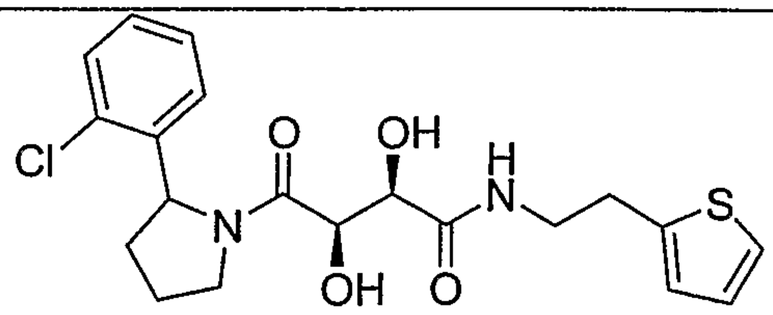
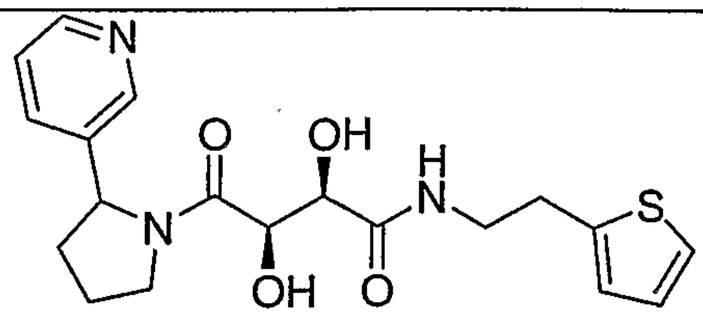
in ethyl acetate. The organic layer was washed with 0.1 N NaOH, 0.1 N HCl, water, and brine, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 10% to 50% EtOAc/DCM) afforded an oil (220 mg, 99%). The diastereomers were resolved (as described in Example 18) by reverse 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).

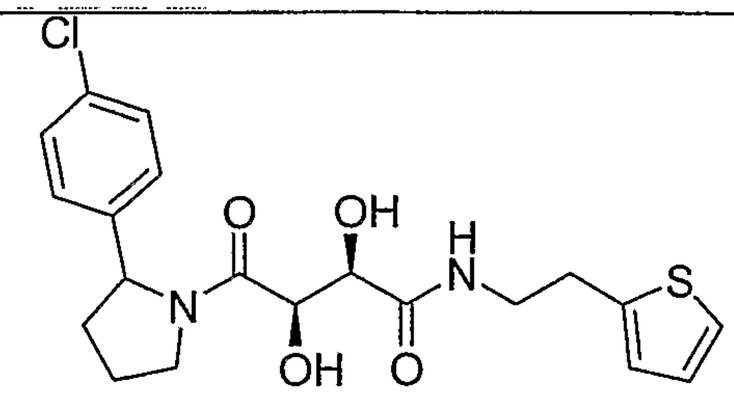
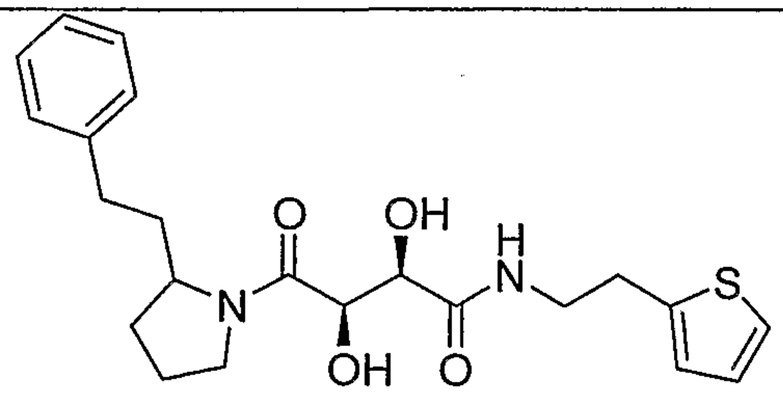
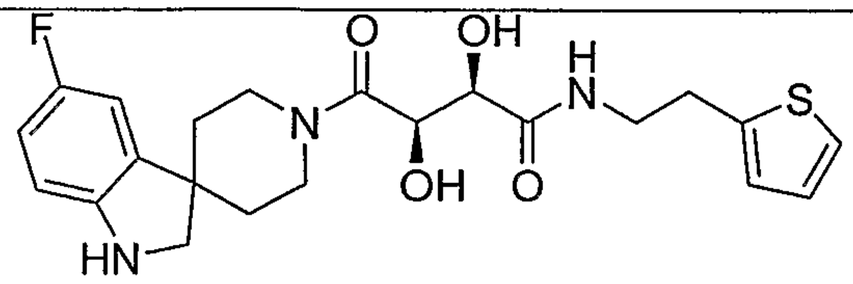
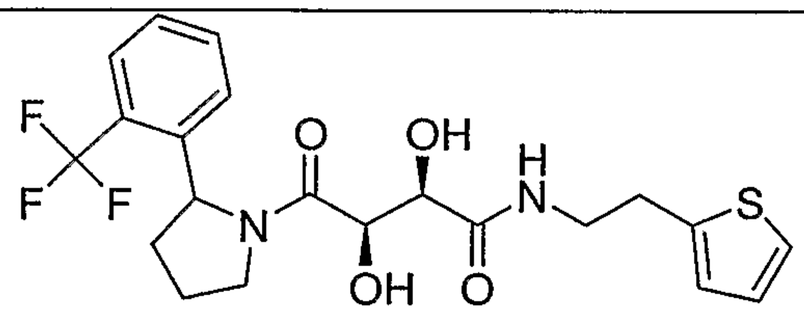
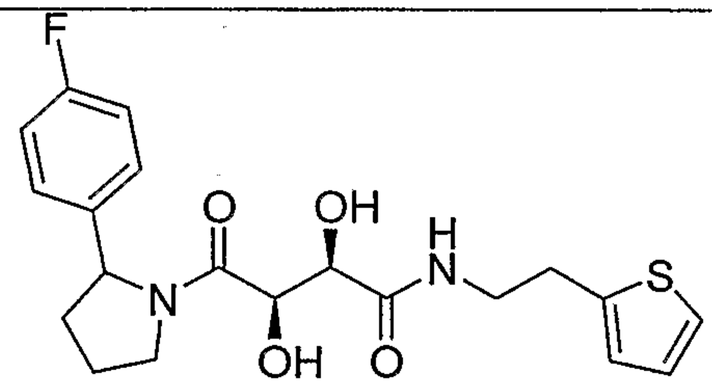
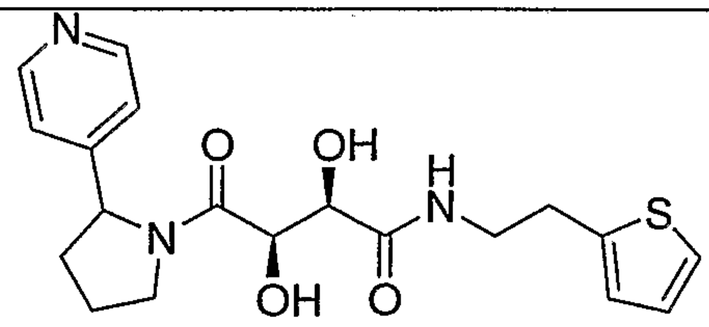
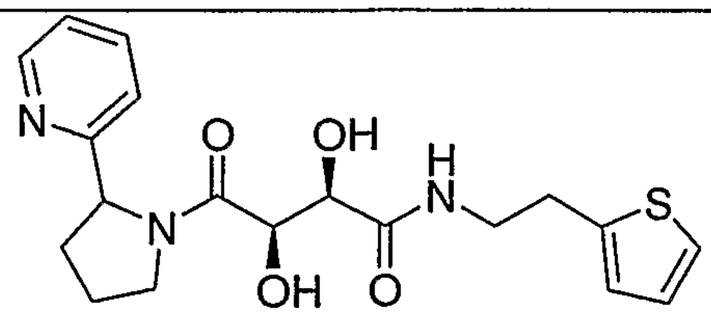
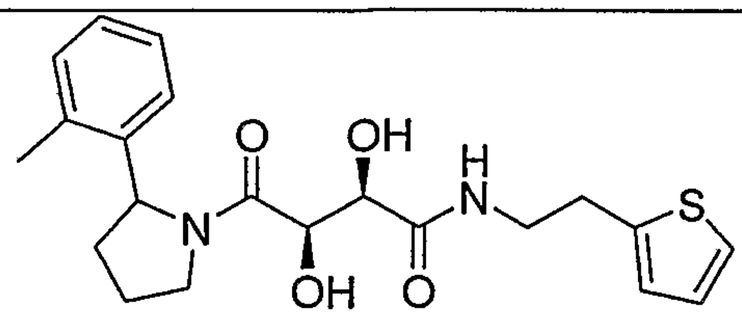
Part D:

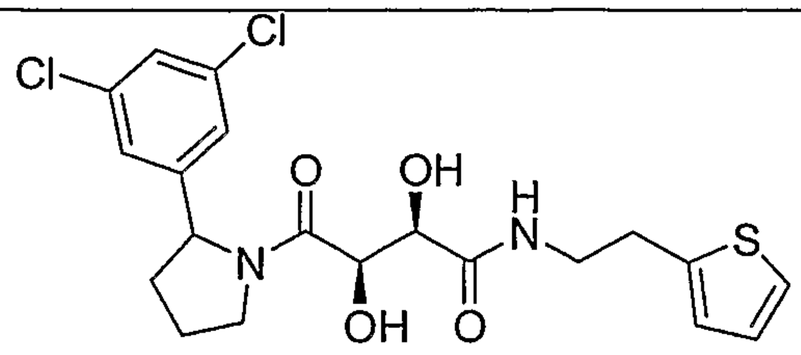
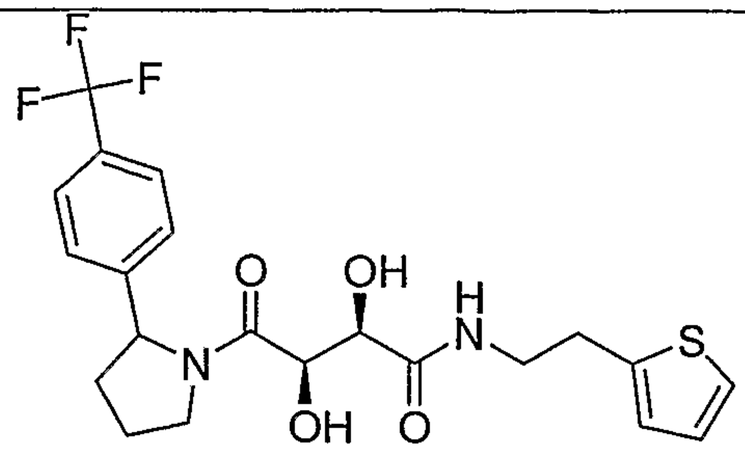
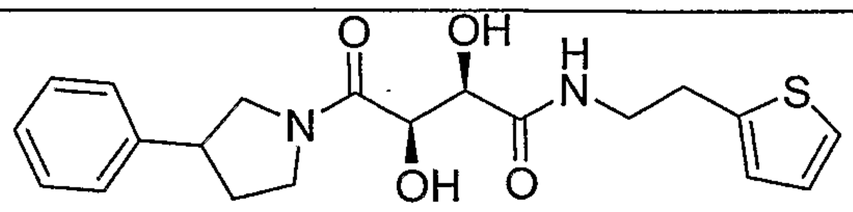
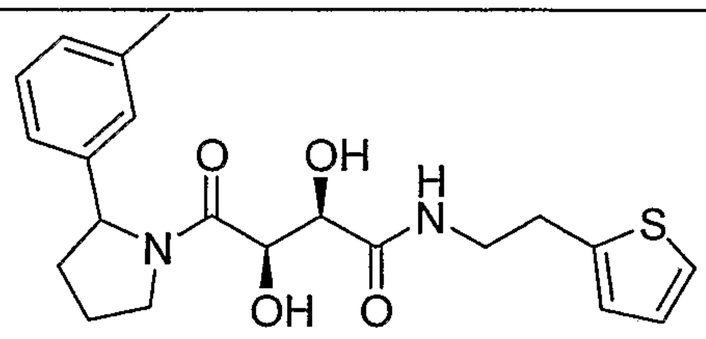
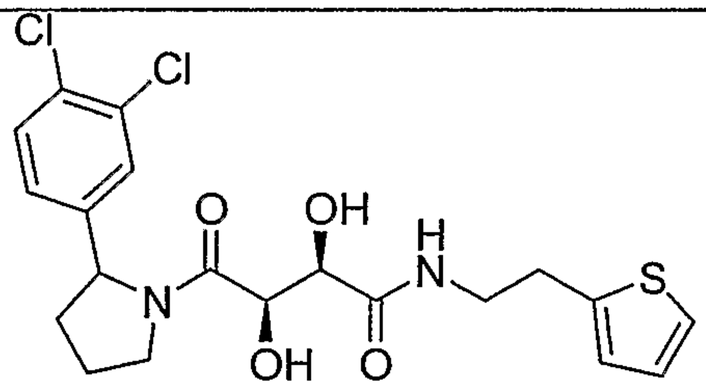
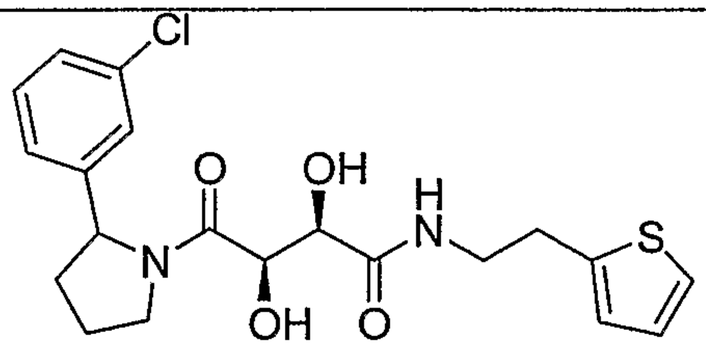
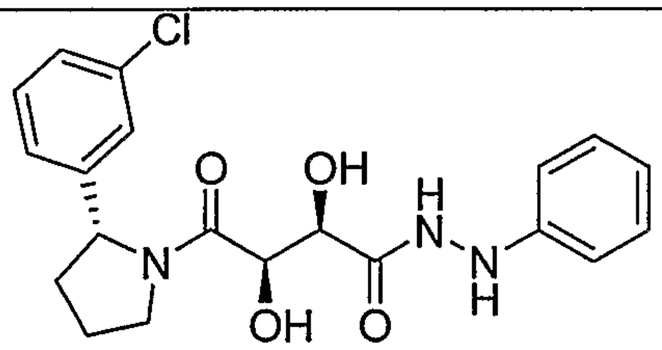
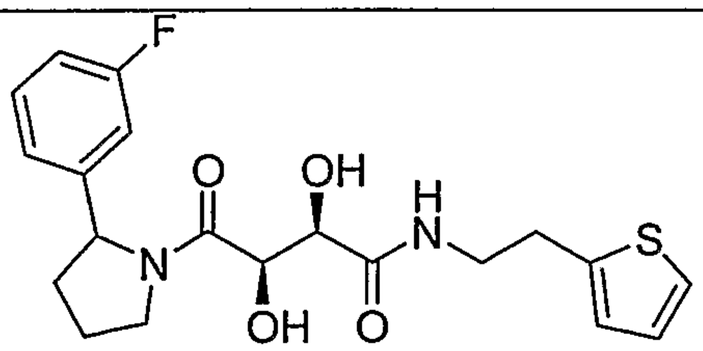
Compound **4** (78 mg, 0.17 mmol) was dissolved in 90:10 TFA:water (5 mL) and stirred for 4 hours at room temperature. The reaction mixture was quenched with 1:1 ACN:water (10 mL) and concentrated. The residue was re-dissolved in 1:1 ACN:water (10 mL) and concentrated. Lypholization afforded **5** as white solid (62 mg, 87%). ^1H 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).

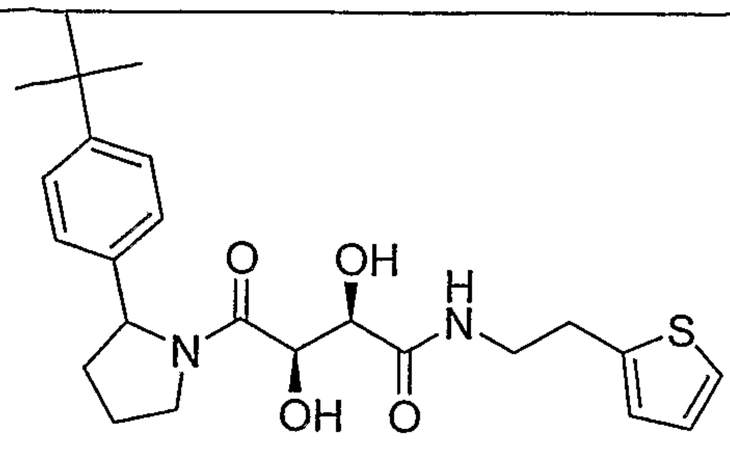
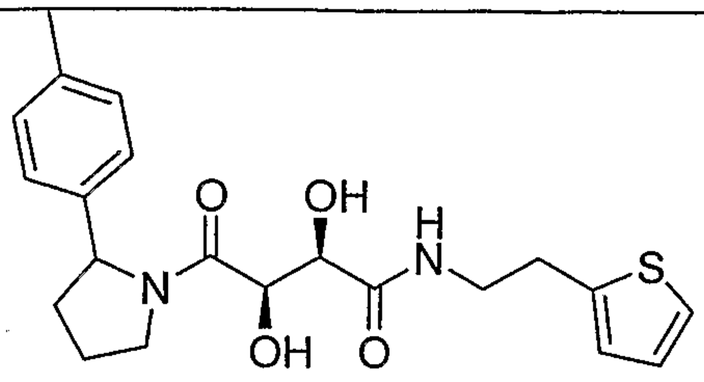
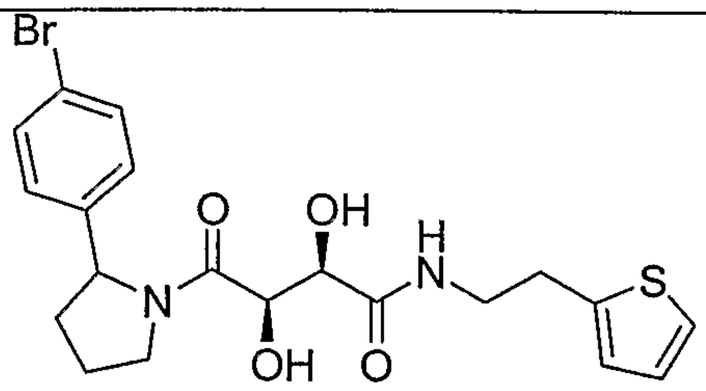
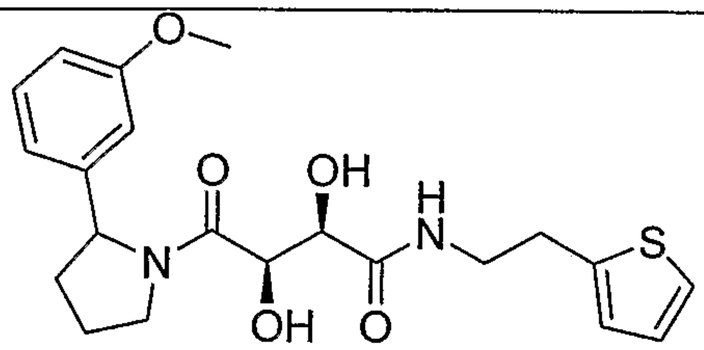
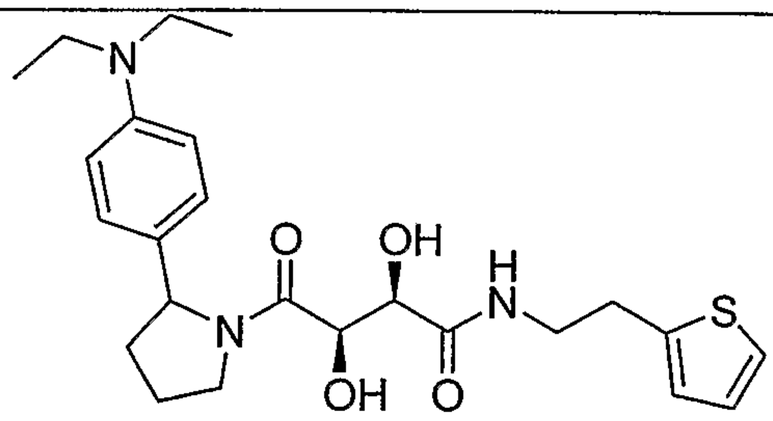
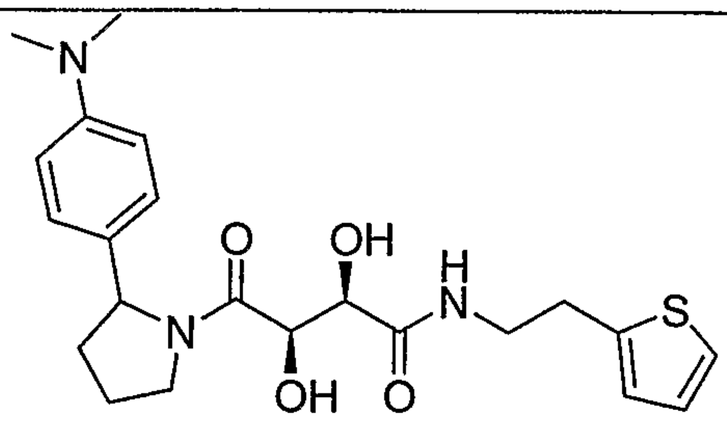
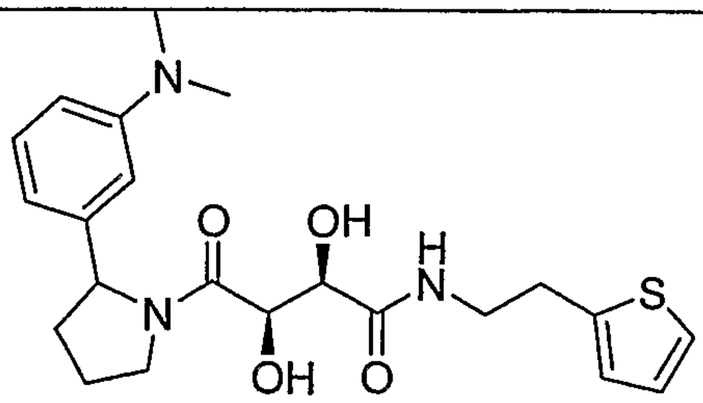
The following table contains compounds synthesized using the above procedures.

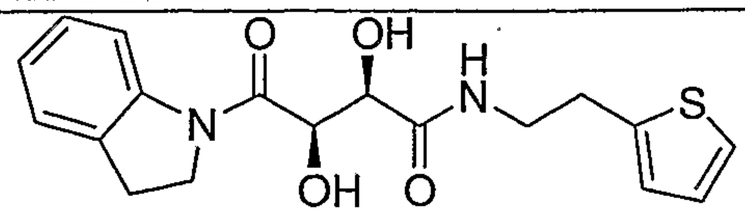
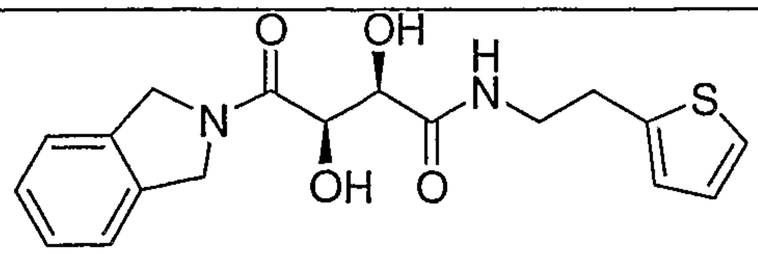
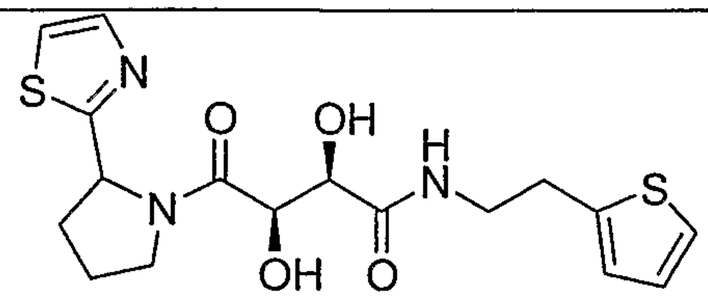
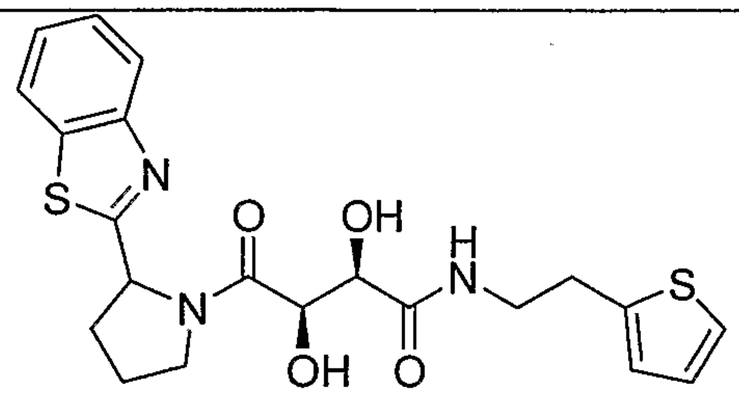
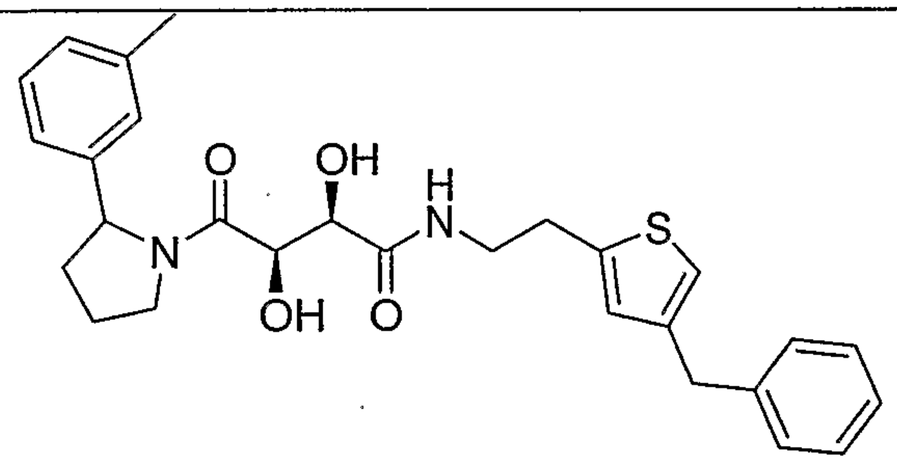
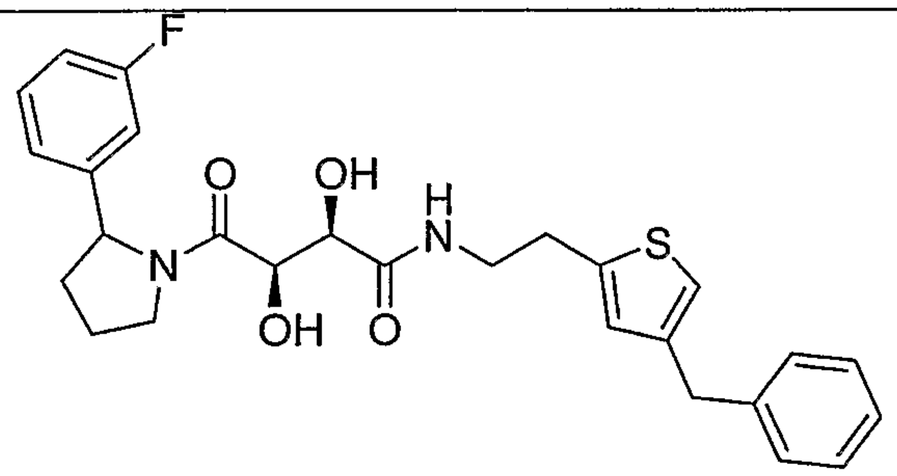
Compound #	Structure	Exact mass	MS m/z (M+H)
6		433.2	434.1
7A		437.1	438.0

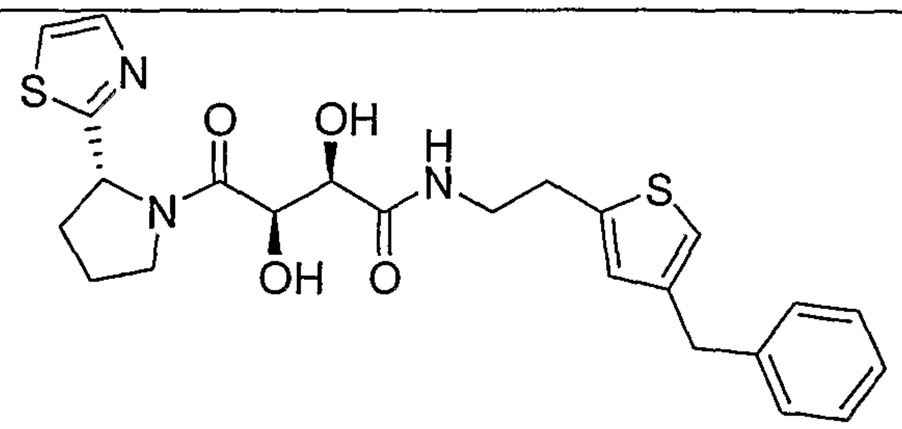
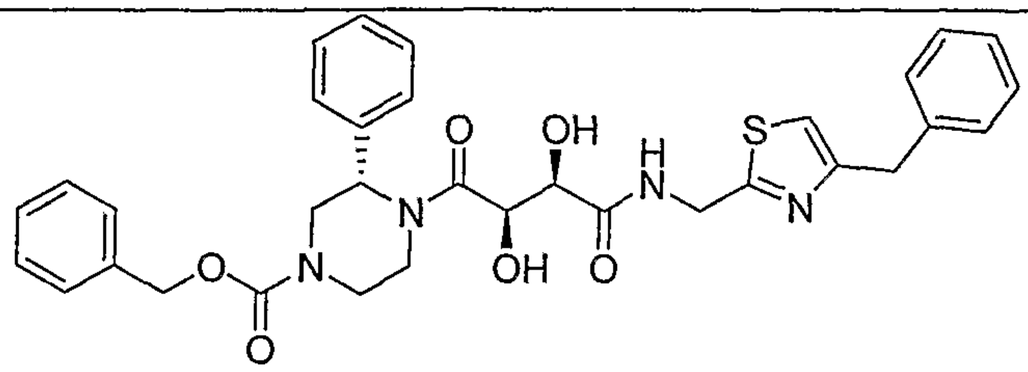
7B		445.2	446.1
8		403.2	404.1
9		412.2	413.2
10		413.2	414.0
11		427.2	428.2
12		434.2	435.1
13		472.2	473.2
14		422.1	423.4
15		389.1	390.1

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

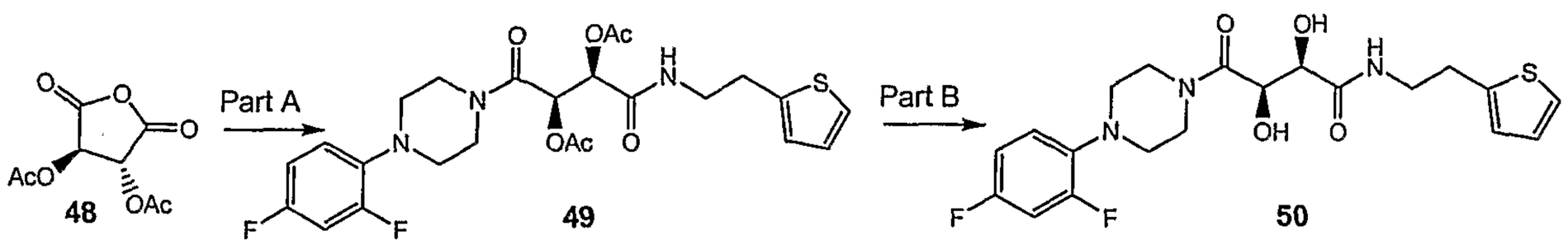
38		360.1	361.1
39		360.1	361.1
40		395.1	396.1
41		445.1	446.2
42		492.2	493.1
43		496.2	497.2
44		492.2	493.1

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:



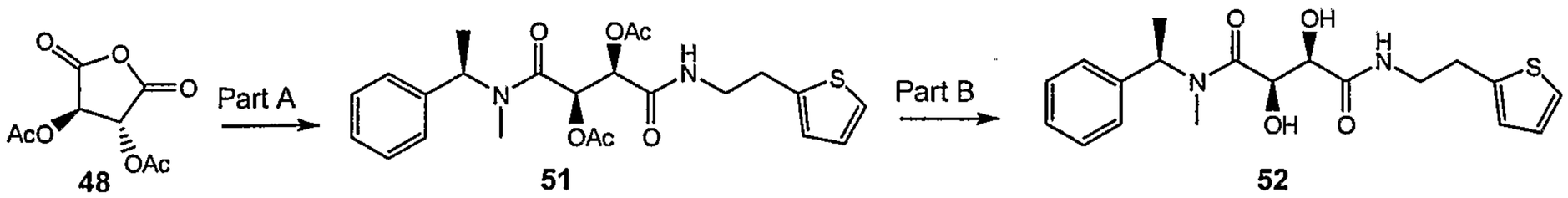
Part A:

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:

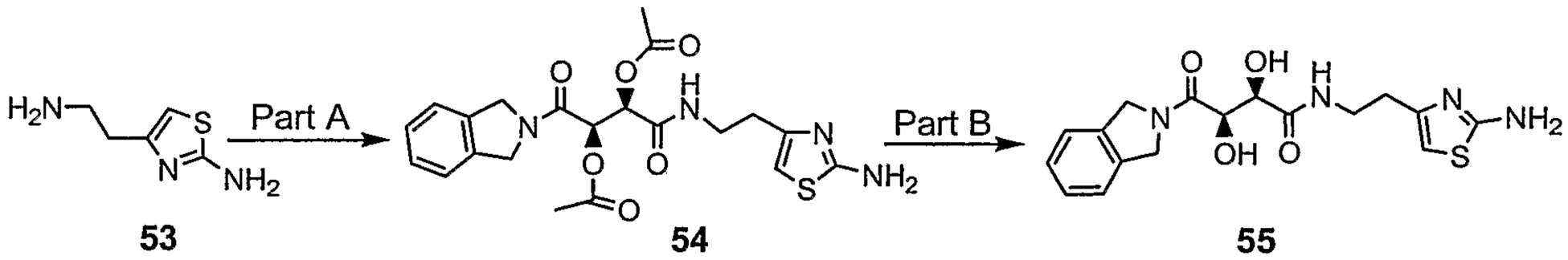
To **48** (26 mg, 0.1 mmol) in DMF (1 mL) was added N-methyl-(1*R*-phenyl-ethyl)-amine (15 µL, 0.1 mmol). The reaction mixture was stirred for 1 hour. To the crude mixture was added 2-thiopheneethylamine (47 µL, 0.4 mmol), HOBt (27 mg, 0.2 mmol), PS-carbodiimide resin (312 mg, 0.4 mmol). To the reaction 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). ^{1}H 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:



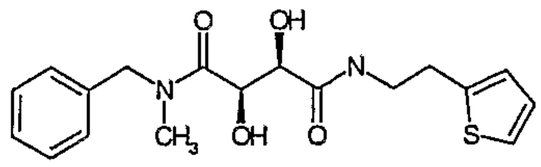
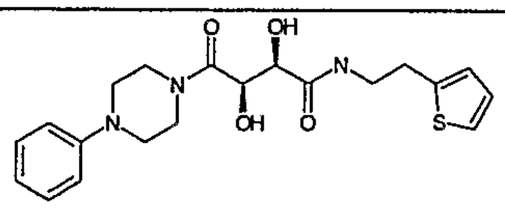
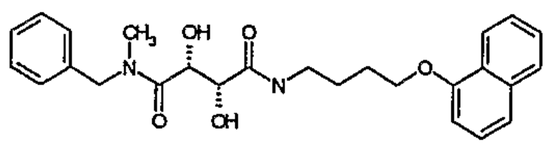
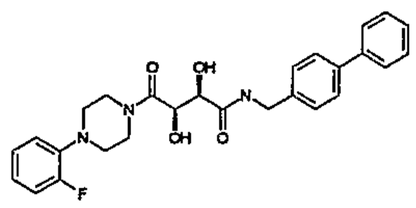
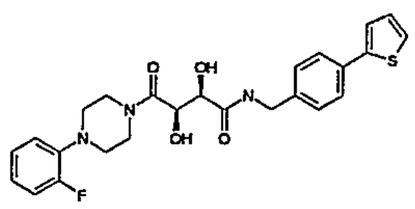
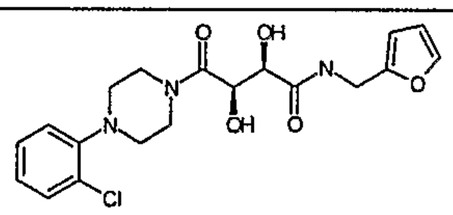
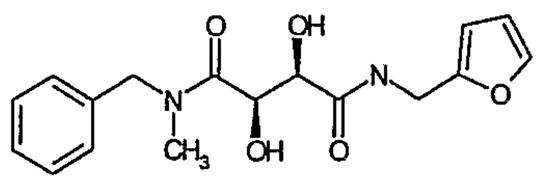
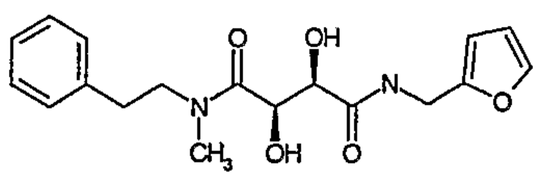
53 **54** **55**

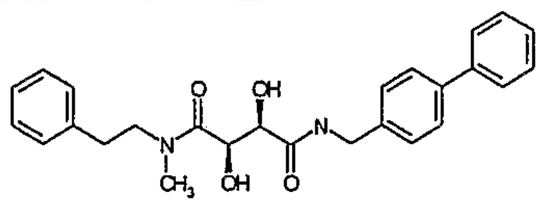
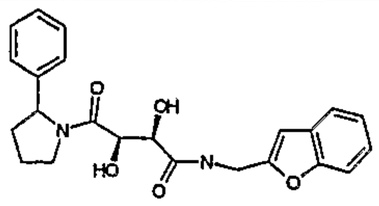
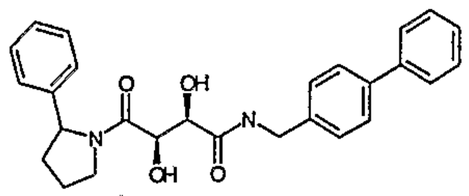
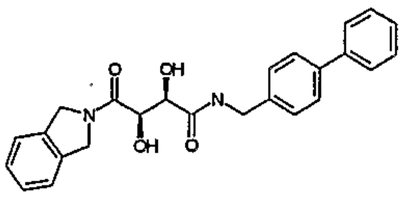
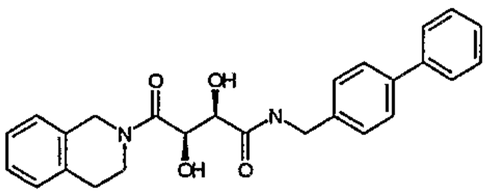
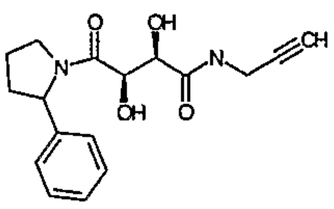
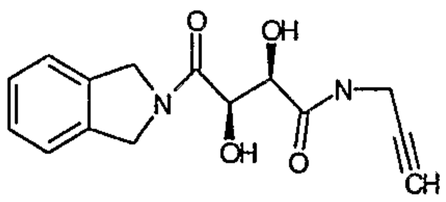
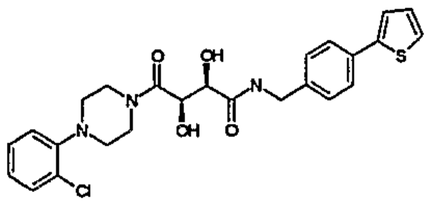
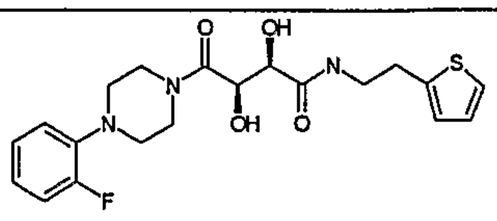
Compound **53** was prepared according to the procedure described by D. Miller et al (*J. Med. Chem.* **1999**, 42, 2287).

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
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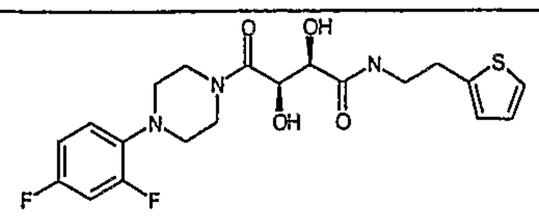
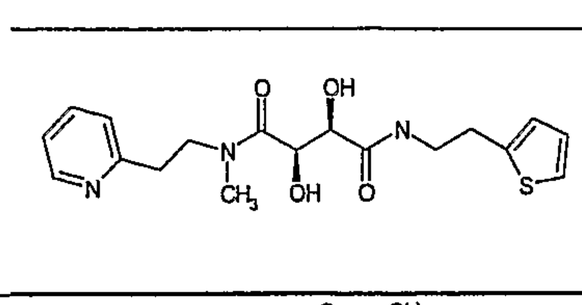
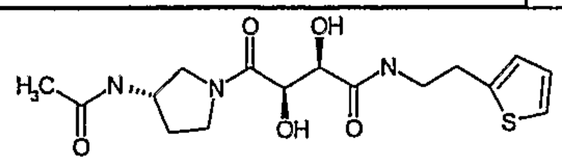
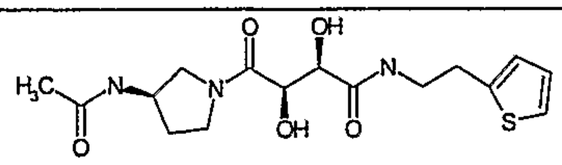
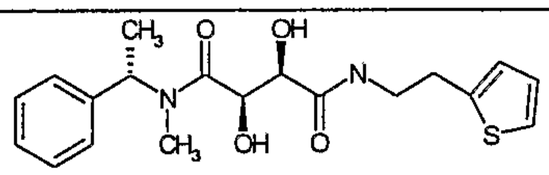
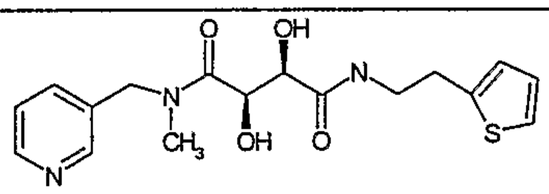
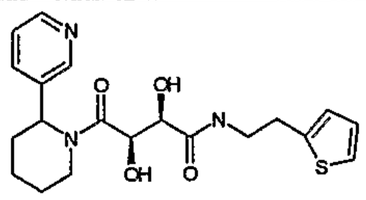
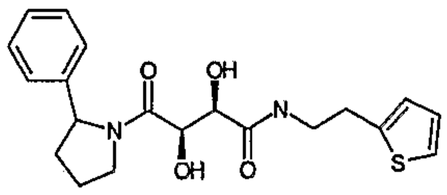
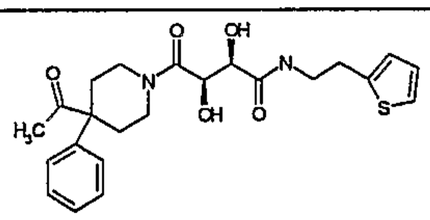
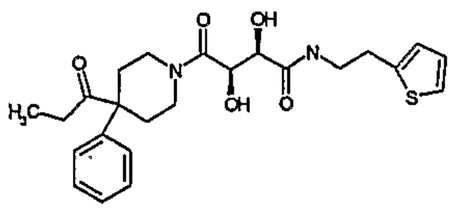
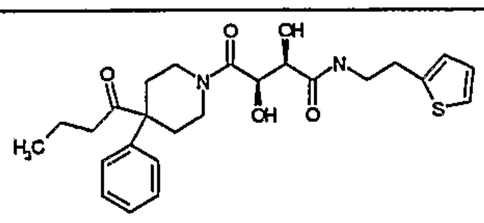
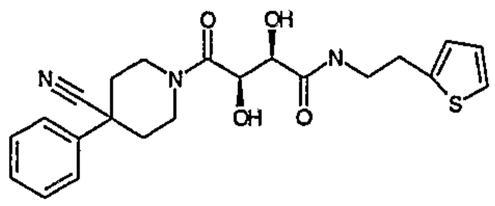
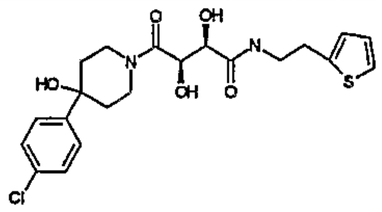
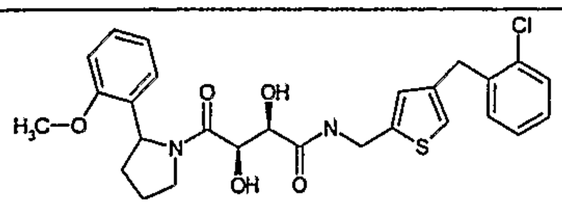
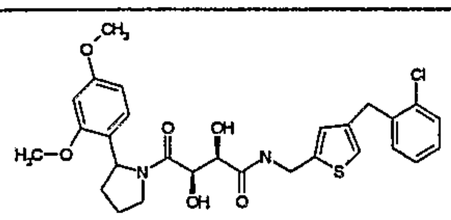
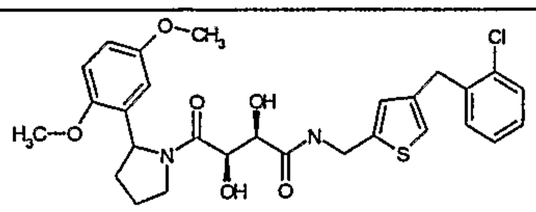
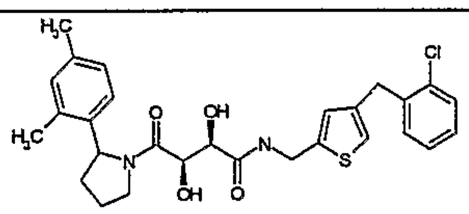
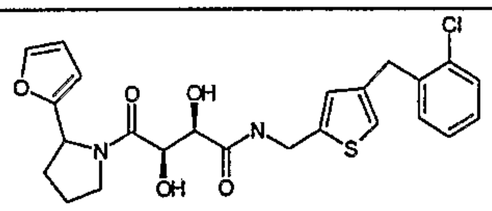
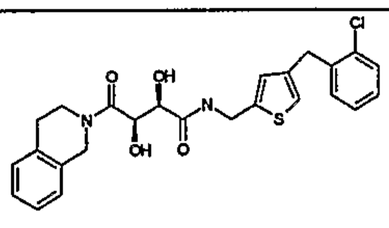
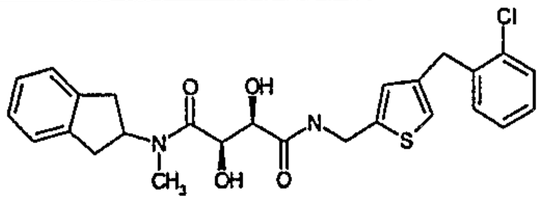
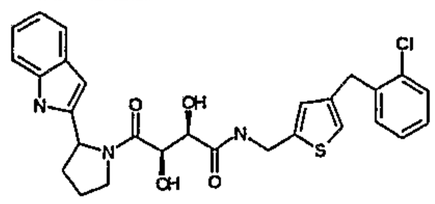
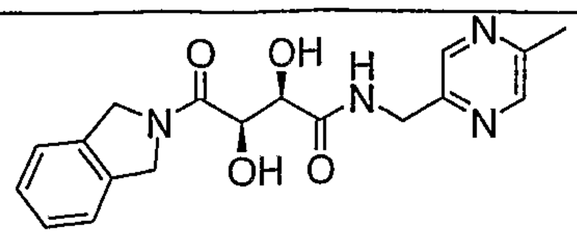
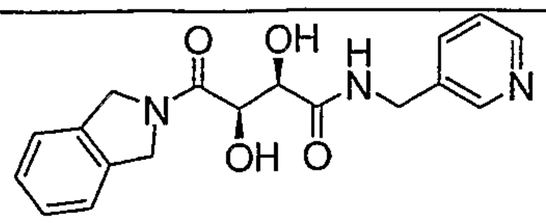
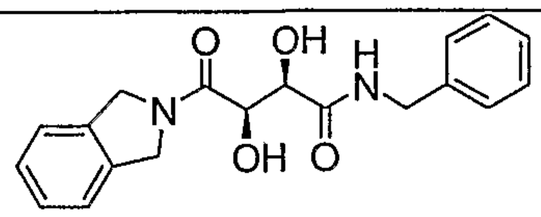
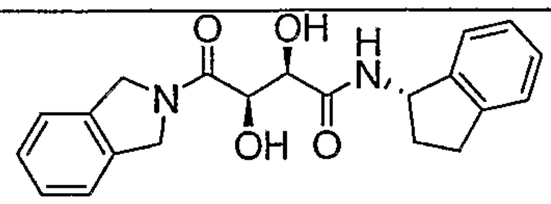
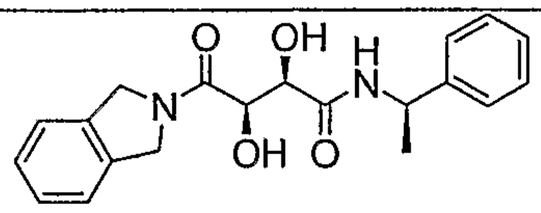
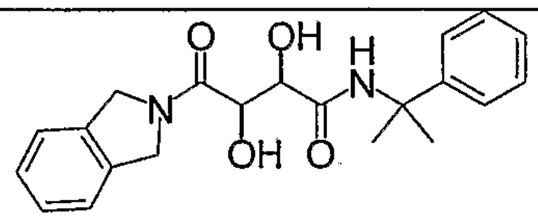
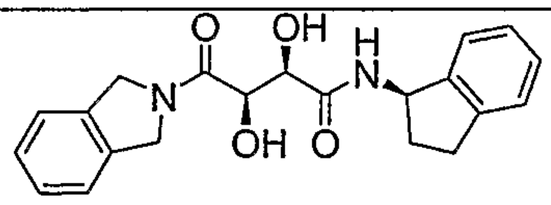
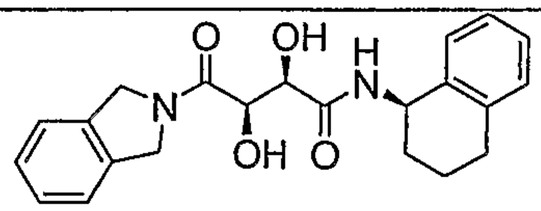
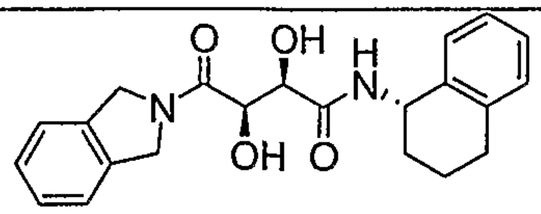
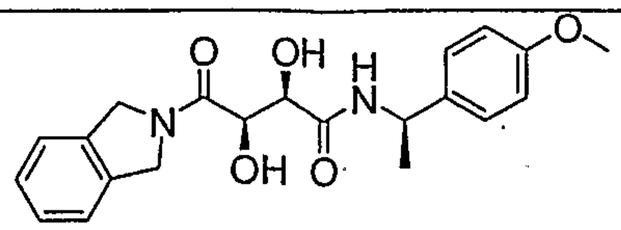
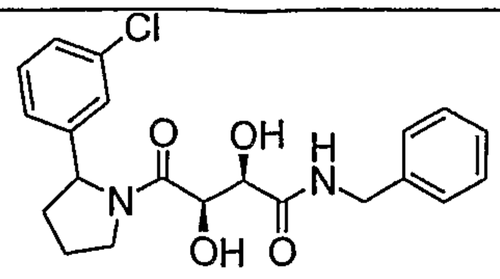
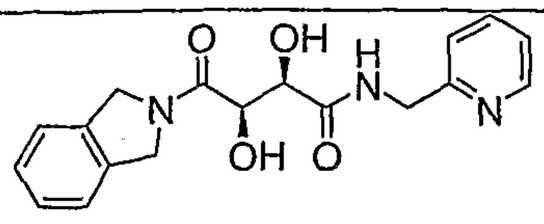
			
74		377.1	378.1
75		369.1	370.1
76		369.1	370.1
77		376.2	377.10
78		363.1	364.1
79		403.2	404.2
80		388.2	389.2
81		444.2	445.1
82		458.2	459.1
83		472.2	473.2

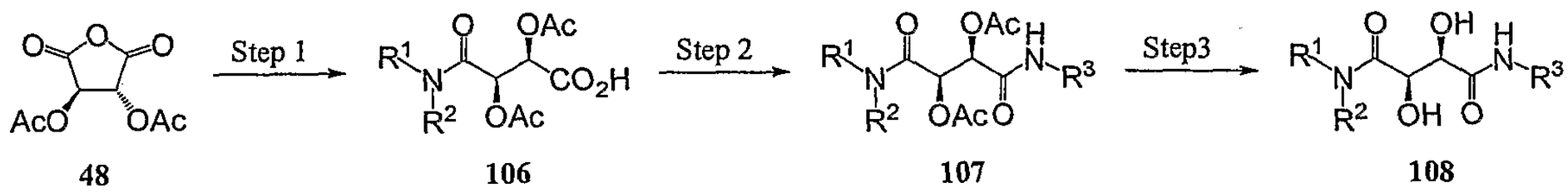
84		427.2	428.2
85		452.1	453.1
86		528.2	529.2
87		558.2	559.2
88		558.2	559.2
89		526.2	527.2
90		488.1	489.1
91		484.1	485.0
92		498.1	499.1

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.

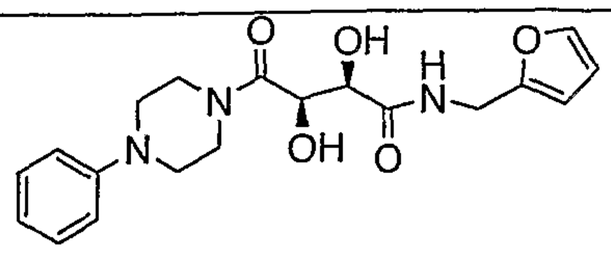
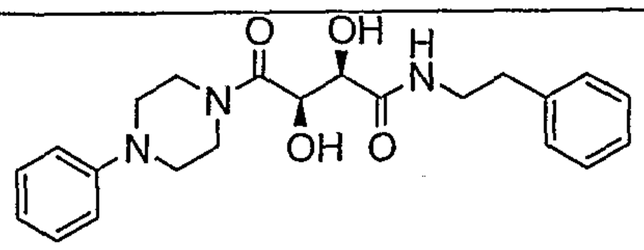
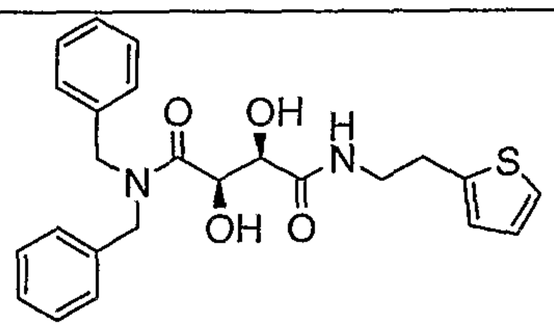
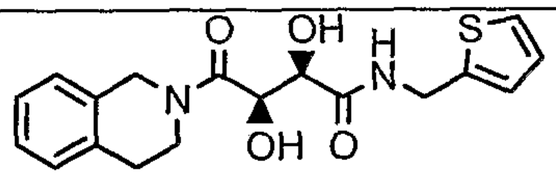
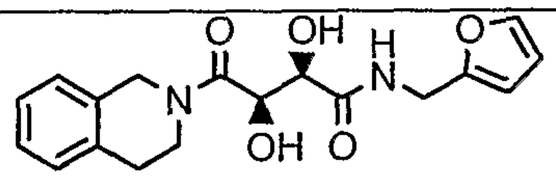
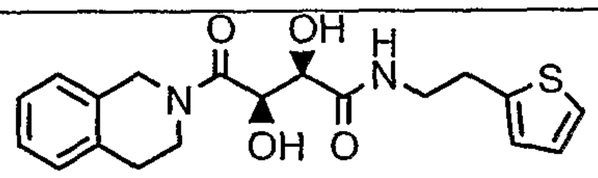
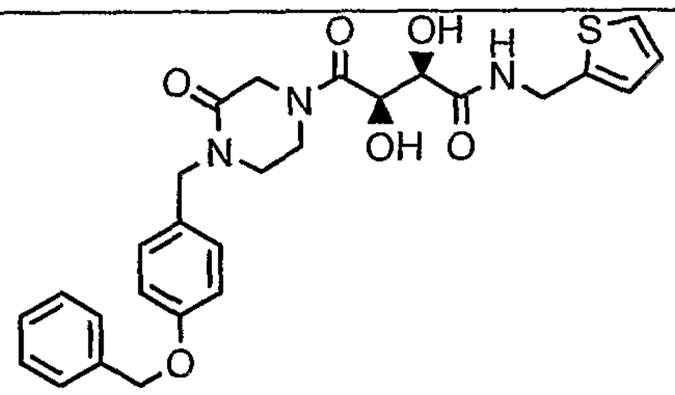
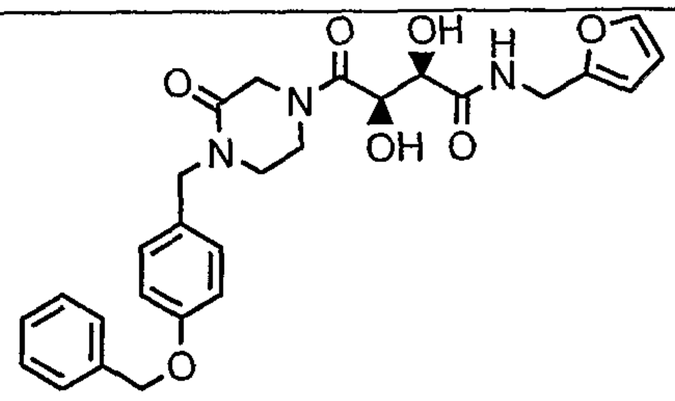
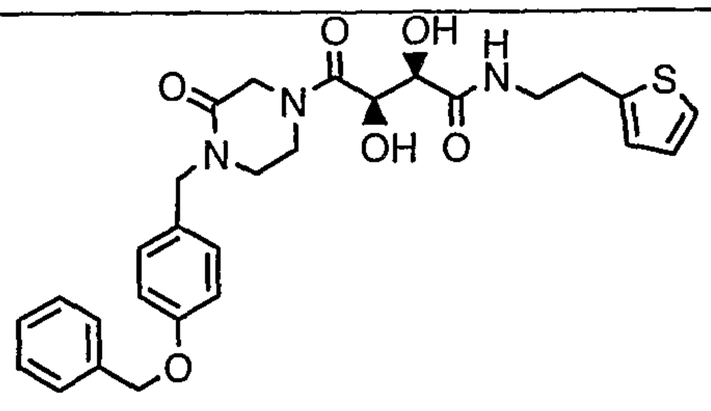
Method A, Step 2:

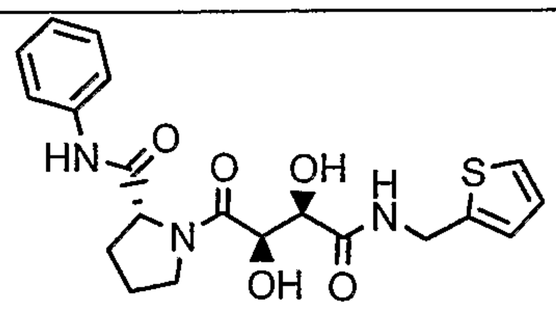
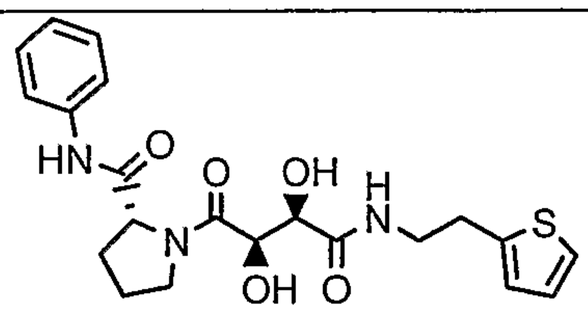
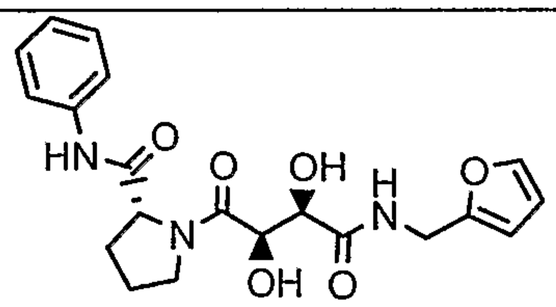
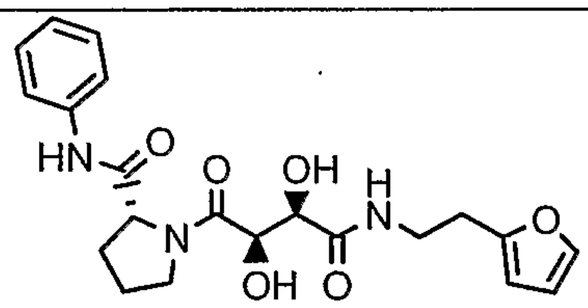
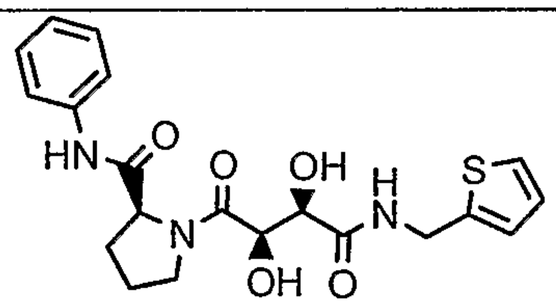
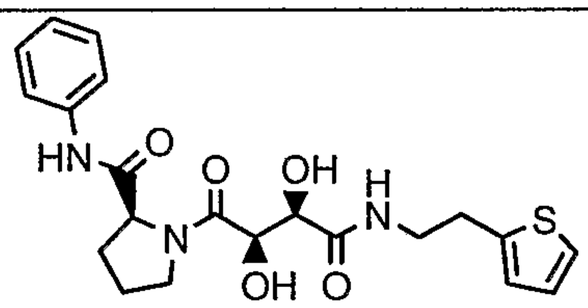
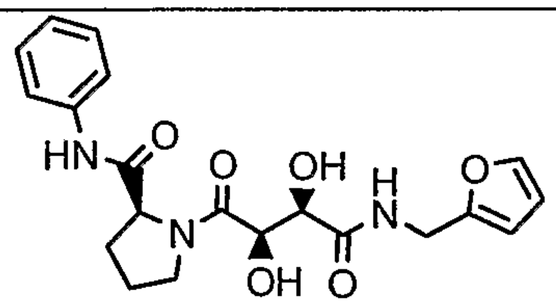
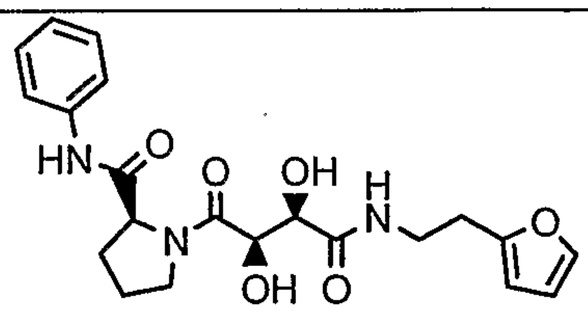
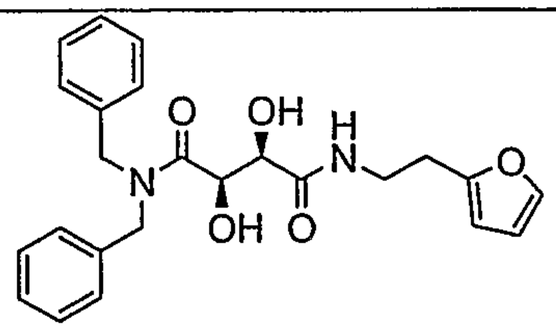
To a THF/MeCN (1:1, 0.5 mL) solution of polystyrene EDC resin (57 mg, 3 eq) in a 6 mL fritted cartridge was added a THF/MeCN (1:1) solution of **106** (0.028 mmol), a THF solution of HOBT (0.3 mL, 1.5 eq) and a 1M THF/MeCN (1:1) solution of 2-furanethylamine (0.056 mL, 2 eq). The cartridge was capped 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 = $CH_2CH_2(C_4H_4O)$.

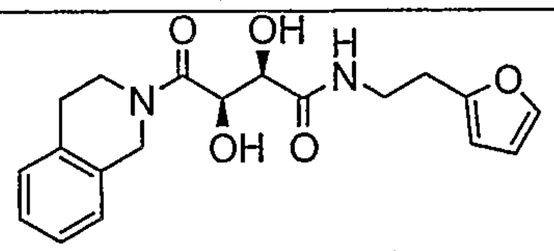
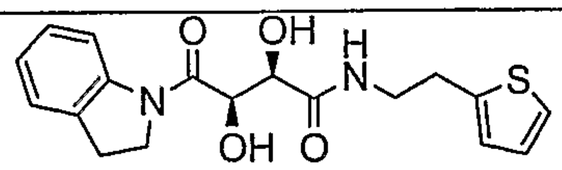
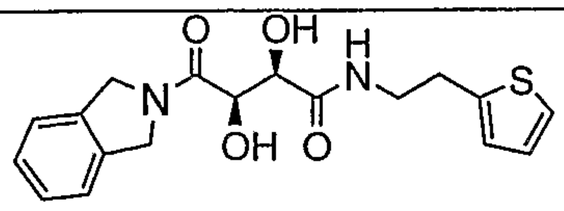
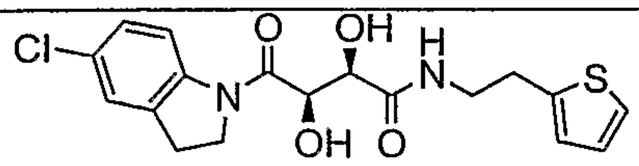
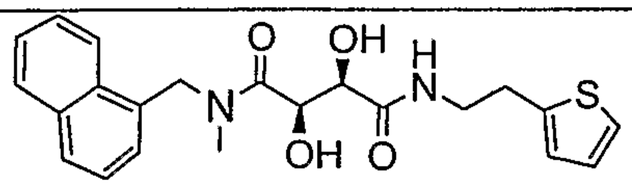
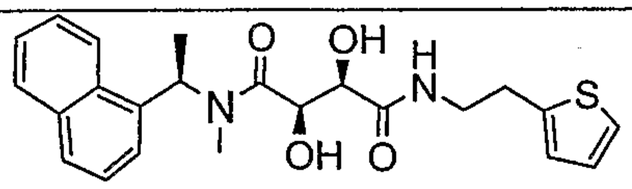
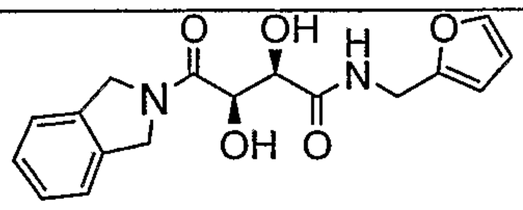
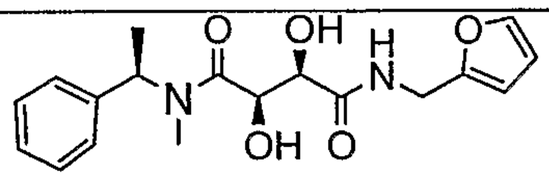
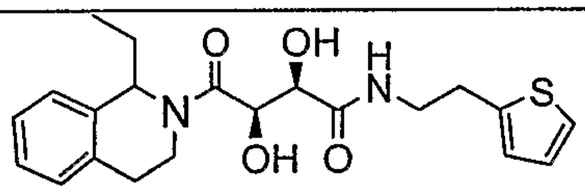
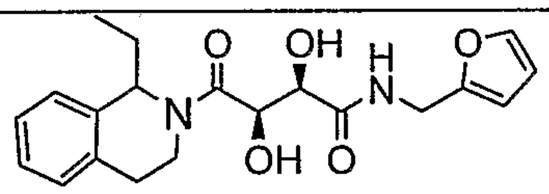
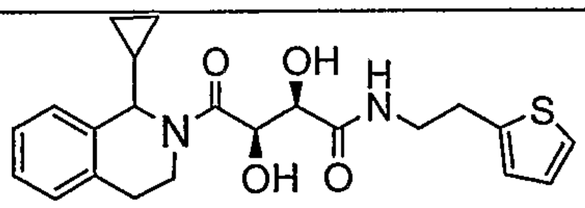
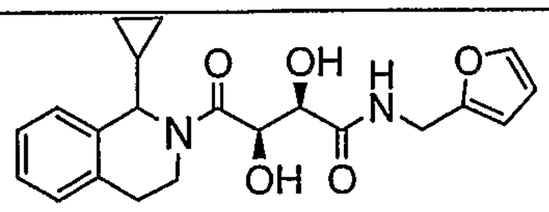
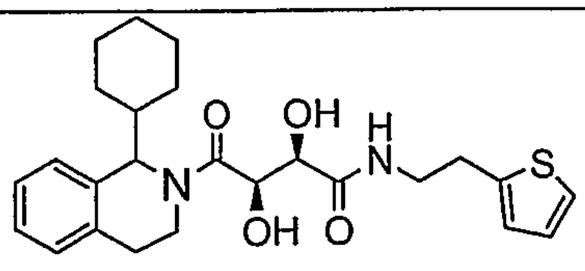
Method A, Step 3:

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 = $CH_2CH_2(C_4H_4O)$.

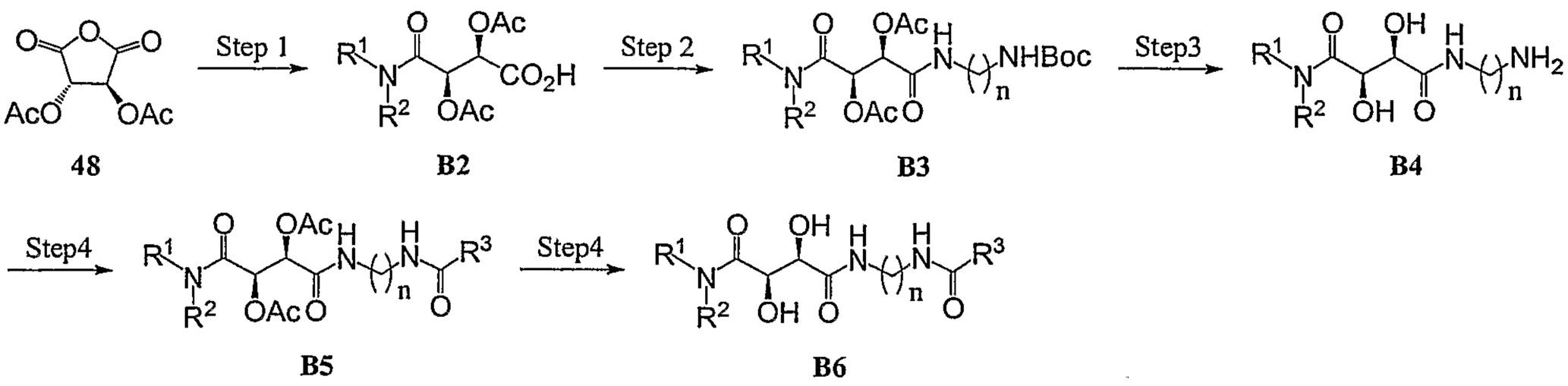
Example 2D Table A

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:

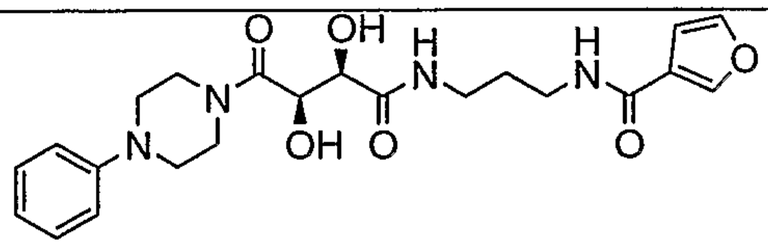
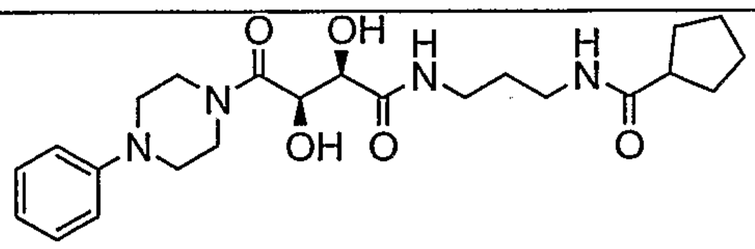
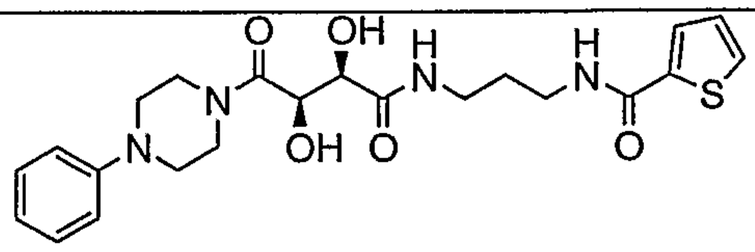
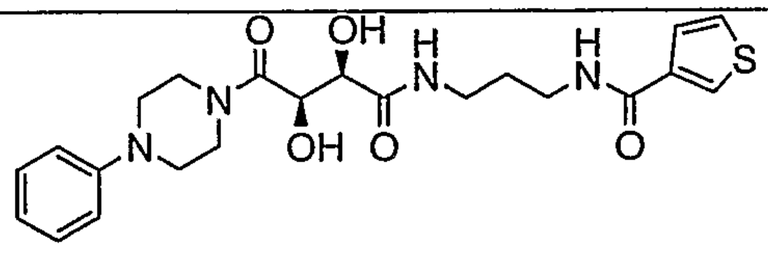
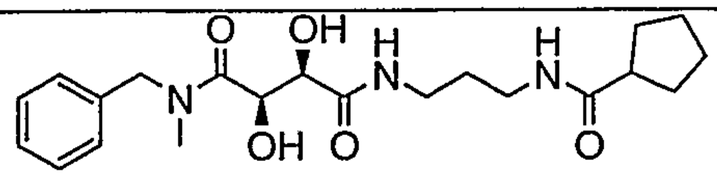
Polystyrene EDC resin (30mg, 0.045 mmol) was added to 96-wells of a deep well polypropylene microtiter plate followed by a MeCN/THF/DMF (6:6:1) stock solution (1 mL) of **B4** (0.015 mmol) and HOBT (0.0225 mmol). Then 1M

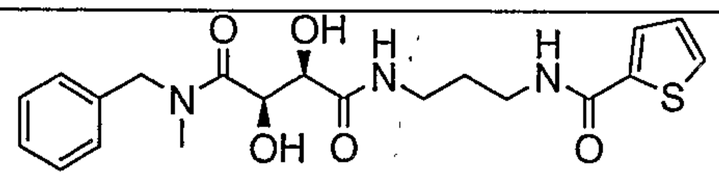
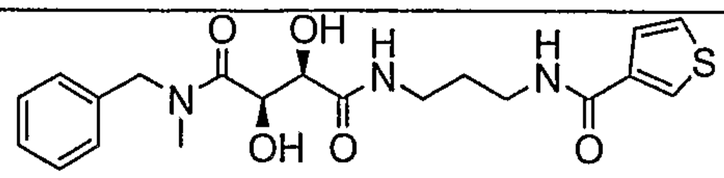
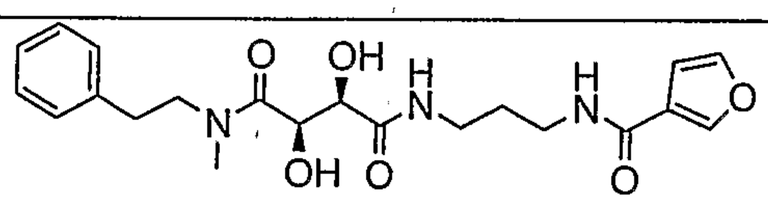
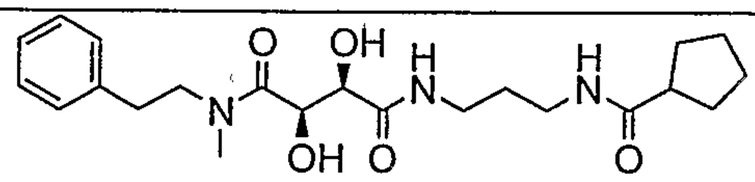
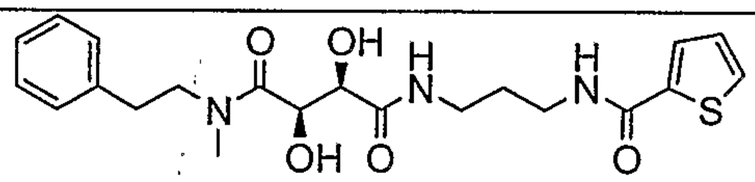
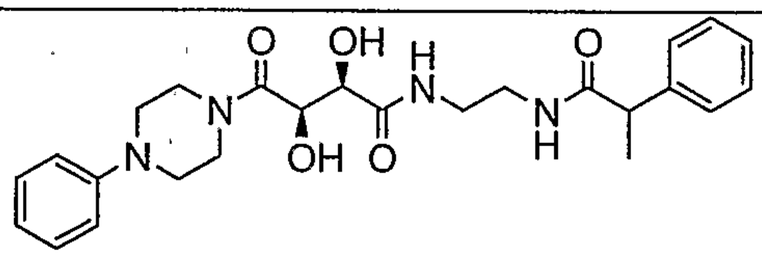
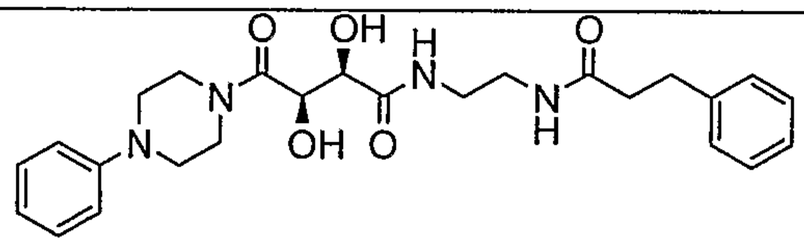
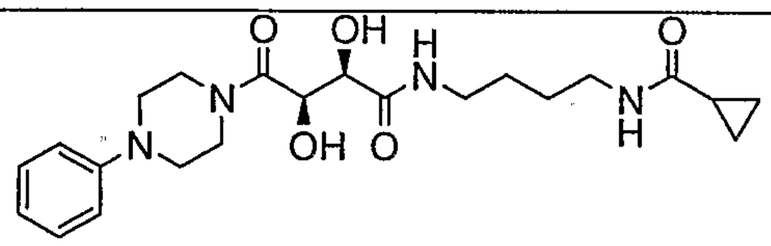
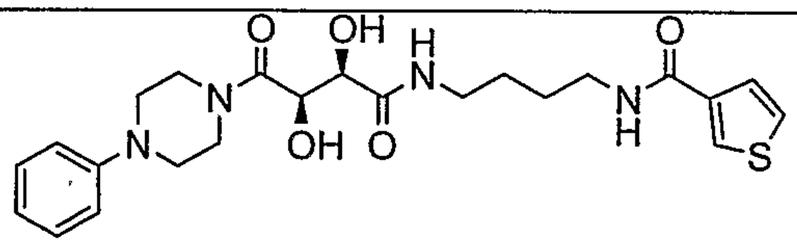
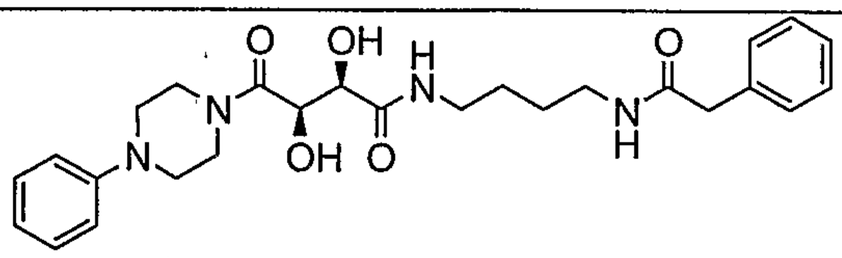
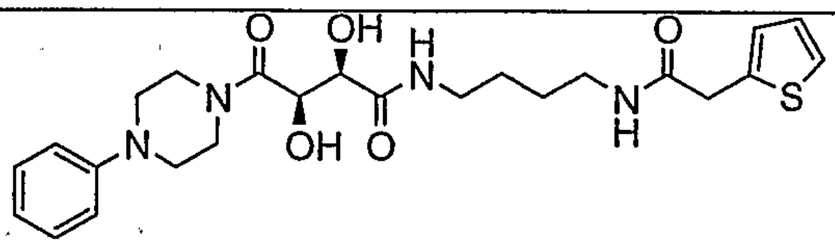
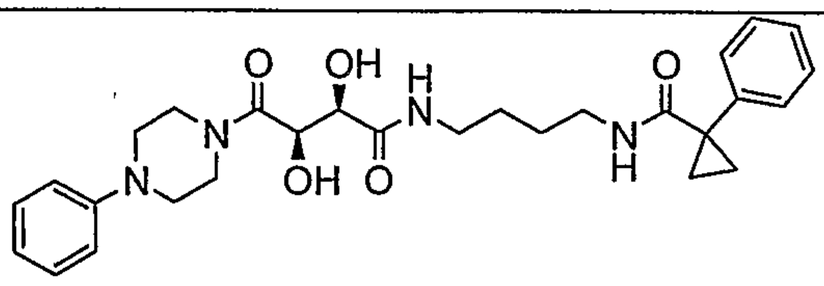
stock solutions of each of the individual acids (R^1-96COOH) (0.023 mL, 0.021 mmol) were added to the wells, which was then sealed and shaken at 25 °C for 20h. The solutions were filtered through a polypropylene frit into a 2nd microtiter plate containing polystyrene isocyanate resin (3 equivalents, 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:

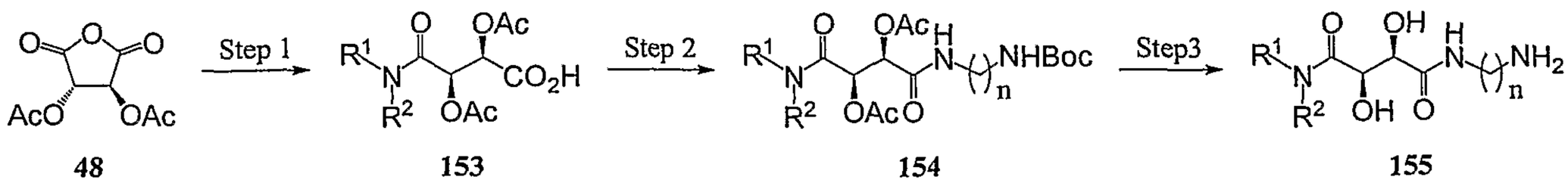
Compounds **B6** were prepared from **B5** following the procedure described in Method A, Step 3 (see above).

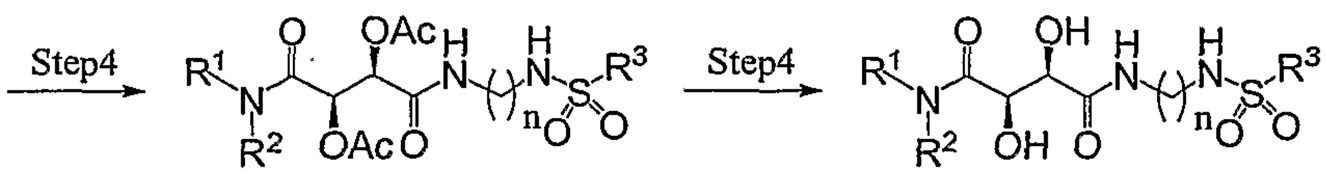
Example 2D Table B

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:

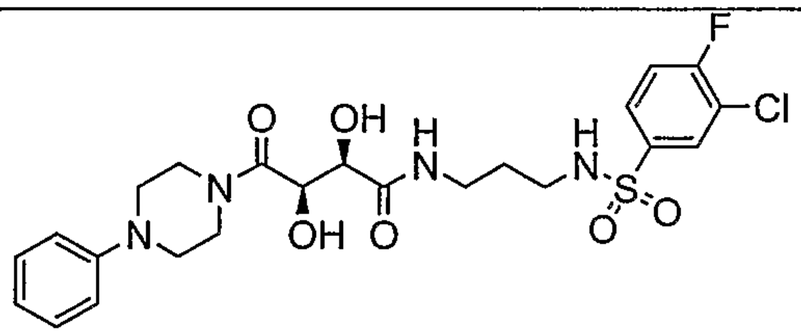
Polystyrene DIEA resin (30mg, 0.045 mmol) was added to 72-wells of a deep well polypropylene microtiter plate followed by a MeCN/THF/DMF (6:6:1) stock solution (1 mL) of **155** (0.015 mmol). Then 1M stock solutions of each of the individual sulfonyl chlorides (R^1-$72SO_2Cl$) (0.023 mL, 0.021 mmol) 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:

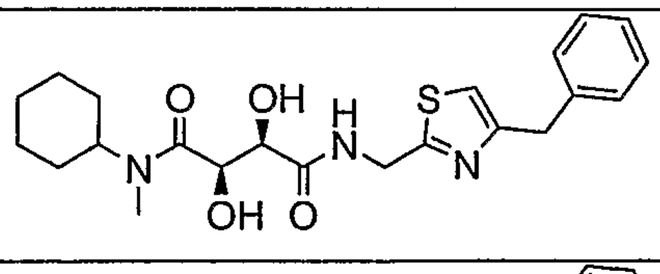
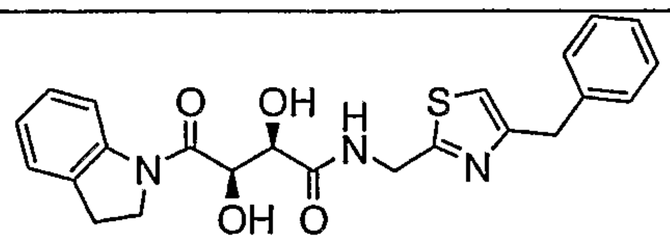
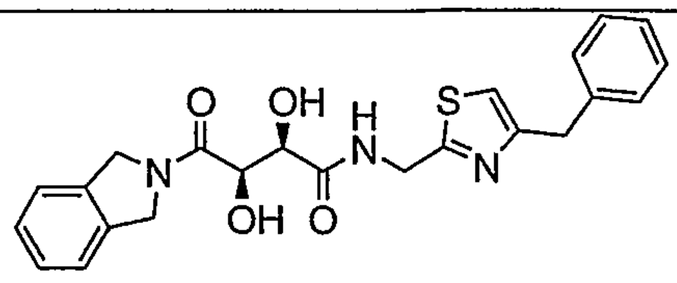
Compounds **157** were prepared from **156** following the procedure described in Method A, Step 3 (see above).

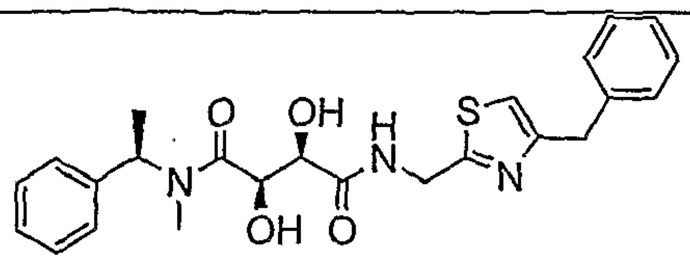
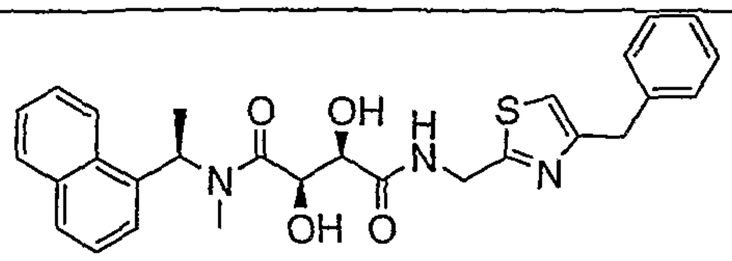
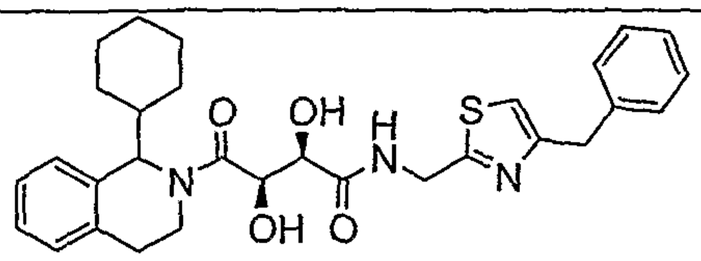
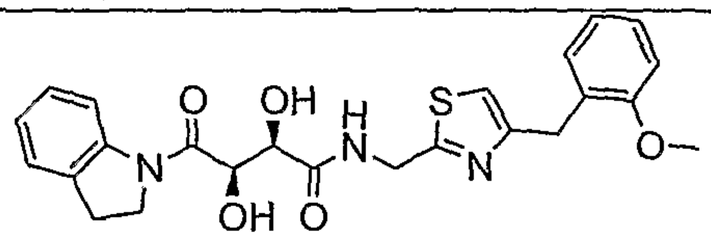
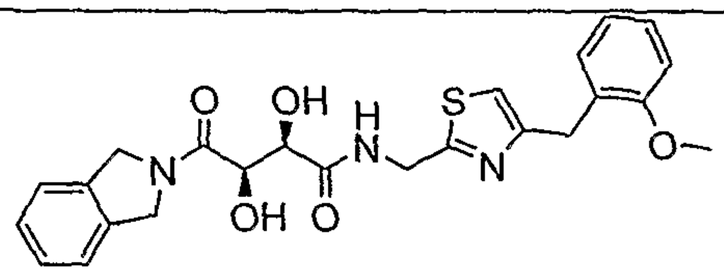
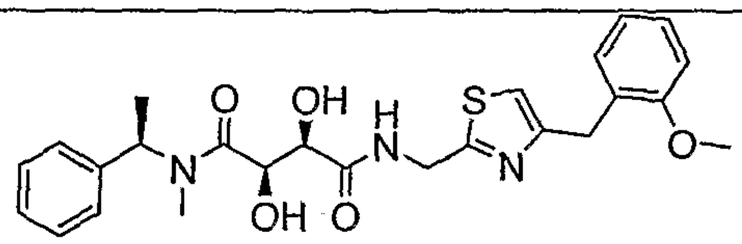
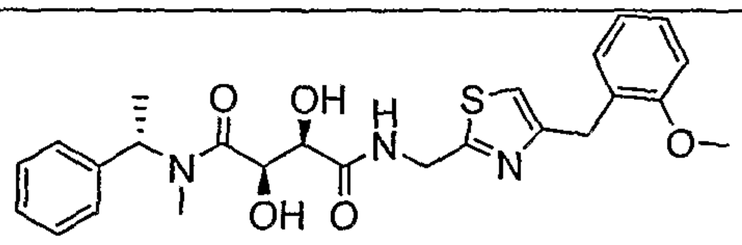
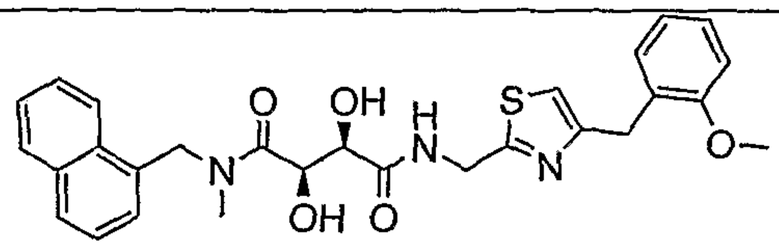
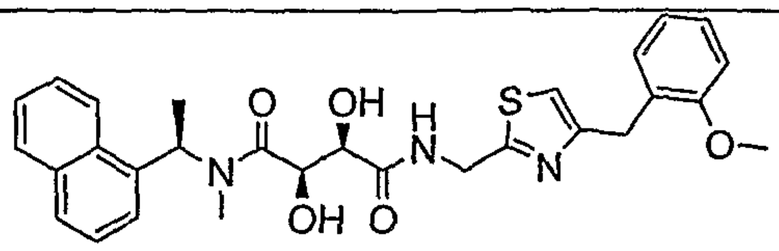
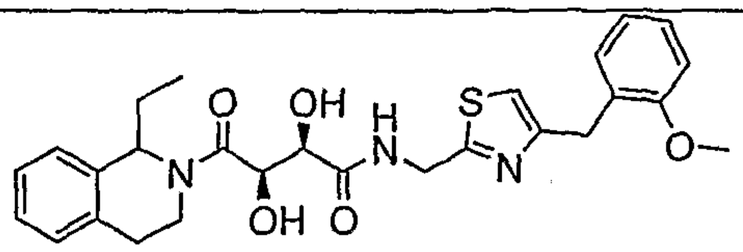
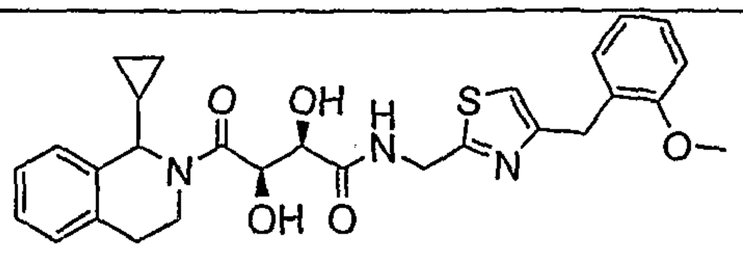
Example 2D Table C

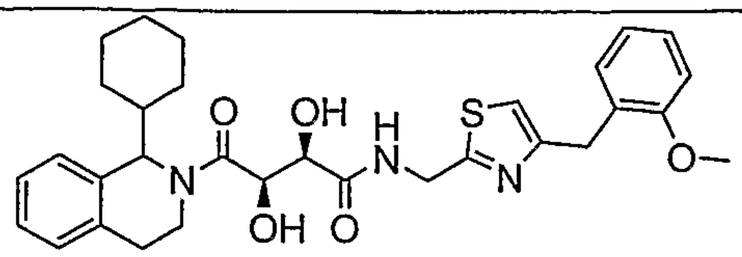
Compound #	Structure	Exact mass	MS m/e (M+H)
157		542.2	543.3

These compounds were prepared using Method A:

Example 2D Table D

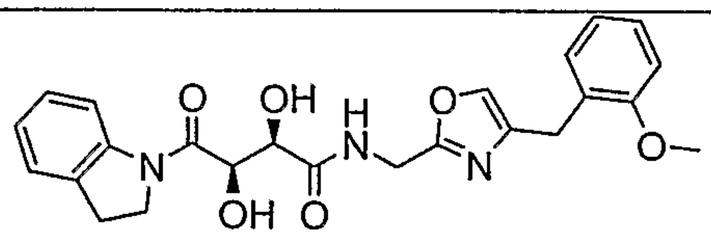
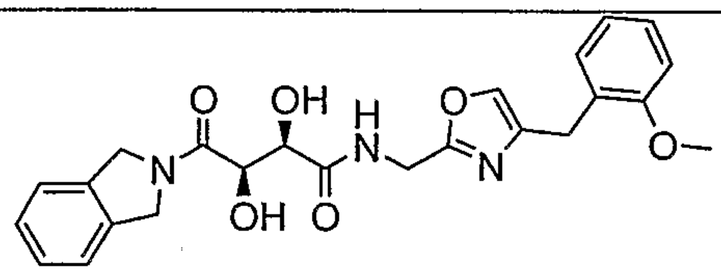
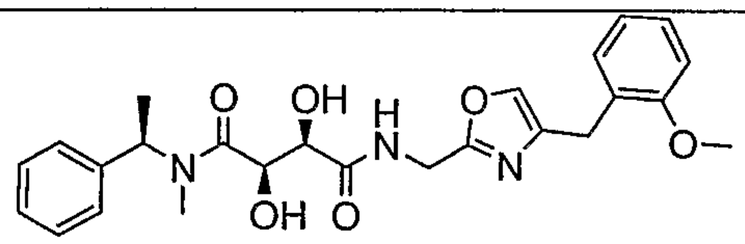
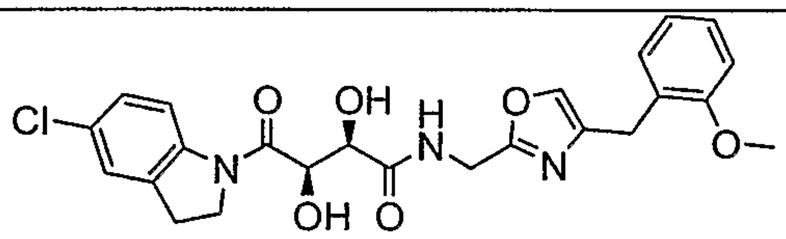
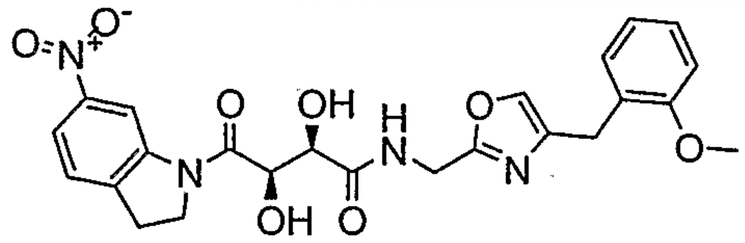
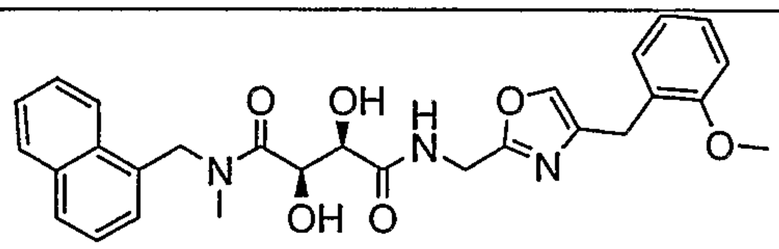
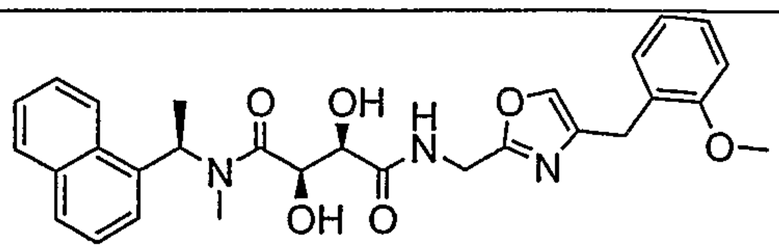
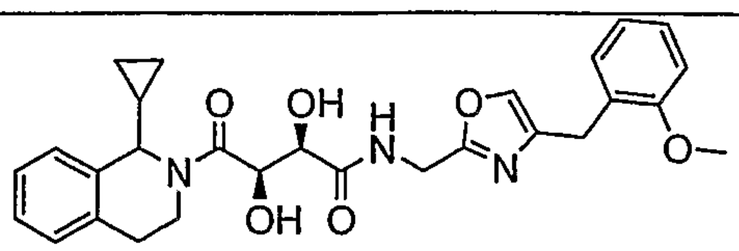
Compound #	Structure	Exact mass	MS m/e (M+H)
158		431.2	432.2
159		437.1	438.2
160		437.1	438.2

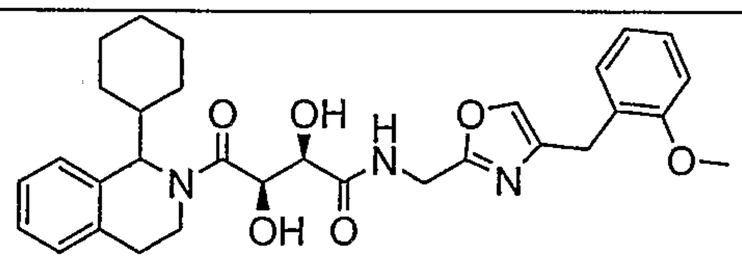
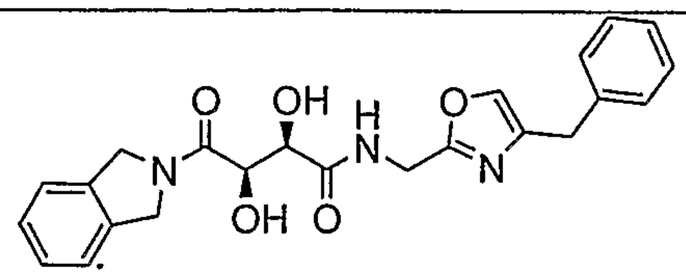
161		453.2	454.3
162		503.2	504.3
163		533.2	534.2
164		467.2	468.3
165		467.2	468.3
166		483.2	484.3
167		483.2	484.3
168		519.2	520.3
169		533.2	534.3
170		509.2	510.3
171		521.2	522.3

172		563.2	564.3

These compounds were prepared using Method A:

Example 2D Table E

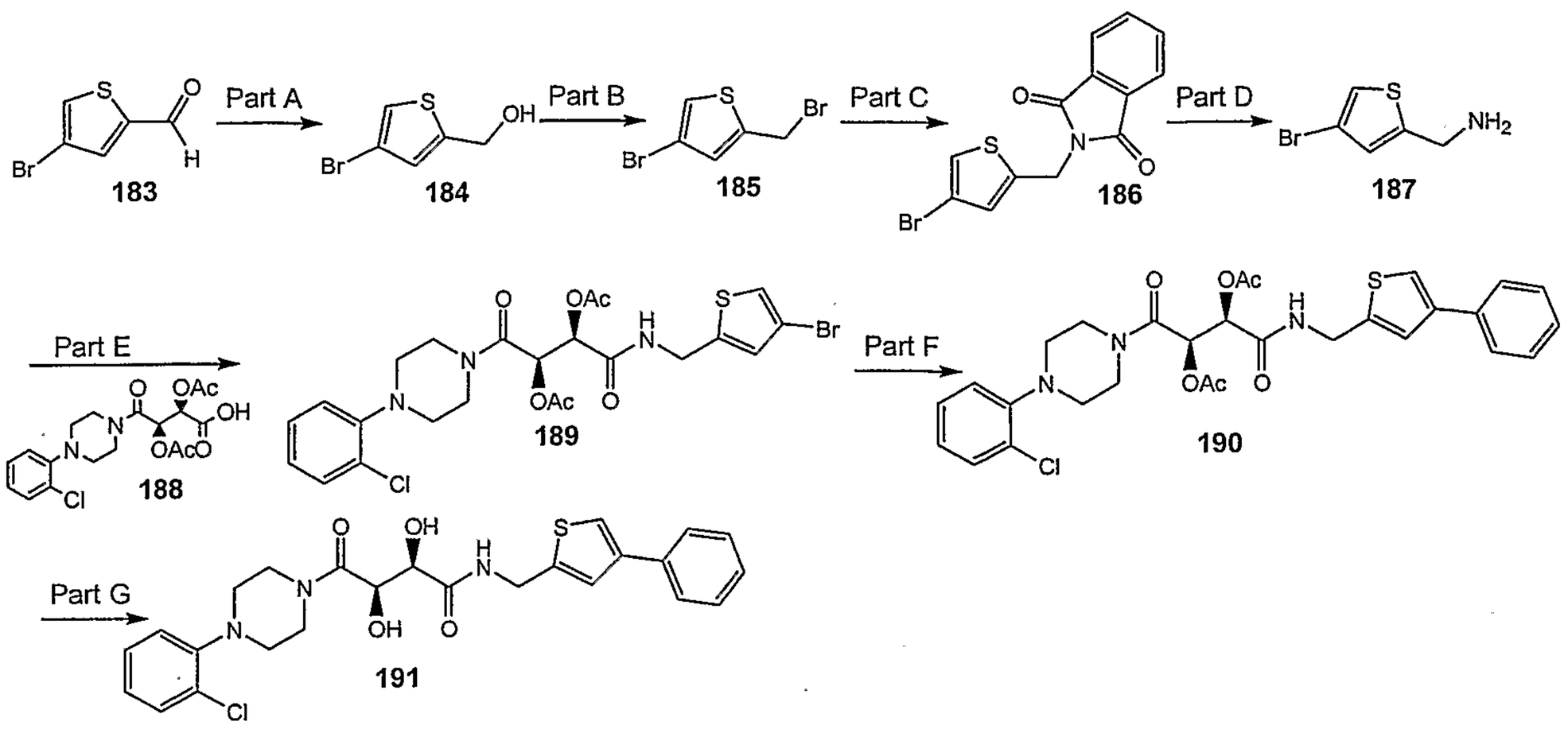
Compound #	Structure	Exact mass	MS m/e (M+H)
173		451.2	452.3
174		451.2	452.3
175		467.2	468.3
176		485.1	486.3
177		496.2	497.3
178		503.2	504.3
179		517.2	518.3
180		505.2	506.3

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 ^{o}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),

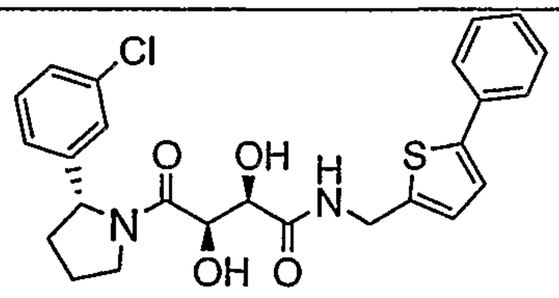
6.92 (d, 1H, J = 1.2 Hz), 6.74 (m, 1H, NH), 5.92 (d, 1H, J = 3.6 Hz), 5.70 (d, 1H, J = 4.0 Hz), 4.73 (dd, 1H, J = 6.4, 15.2 Hz), 4.50 (dd, 1H, J = 5.6, 15.6 Hz), 3.83 (m, 3H), 3.65 (m, 1H), 3.20 – 3.00 (m, 4H), 2.21 (s, 3H), 2.11 (s, 3H); Mass calculated for formula $C_{23}H_{25}BrClN_3O_6S$ 585.0, observed LCMS m/z 586.1 (M+H).

Part F:

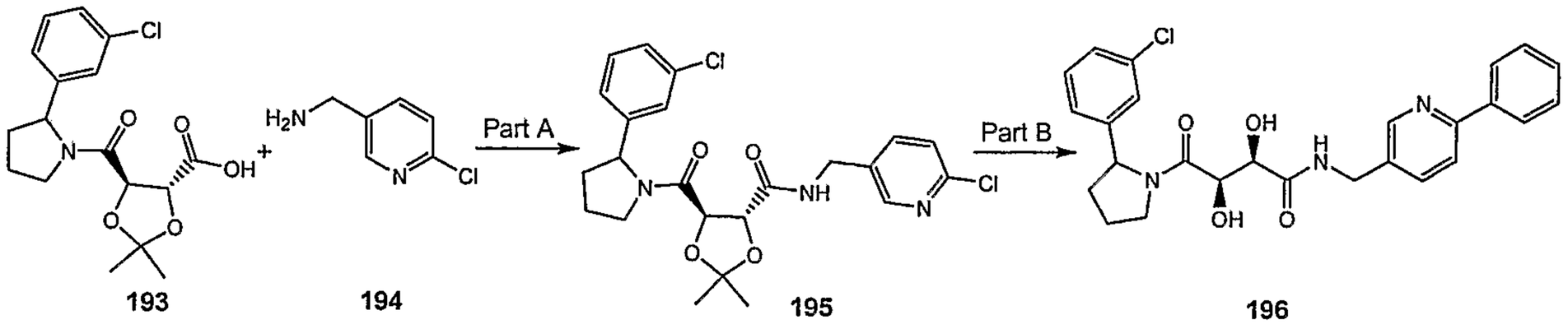
To **189** (59 mg, 0.1 mmol), phenyl boronic acid (13 mg, 0.11 mmol), potassium phosphate (42 mg, 0.2 mmol), and $PdCl_2$(dppf) (4 mg, 0.005 mmol) was added dioxane (2 mL). The reaction mixture was flushed with argon and heated to 80 °C overnight. The reaction mixture was cooled, poured into water and 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:

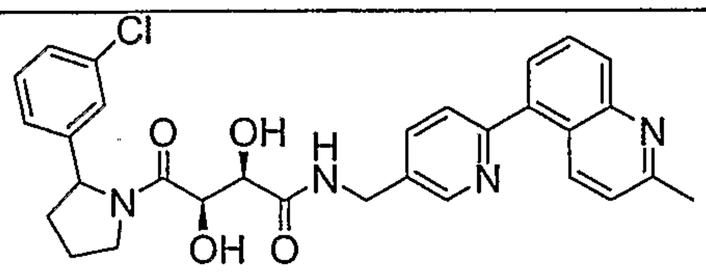
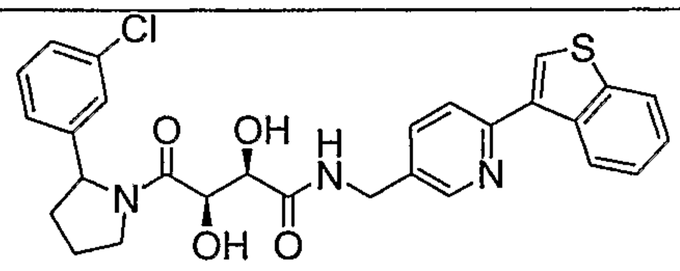
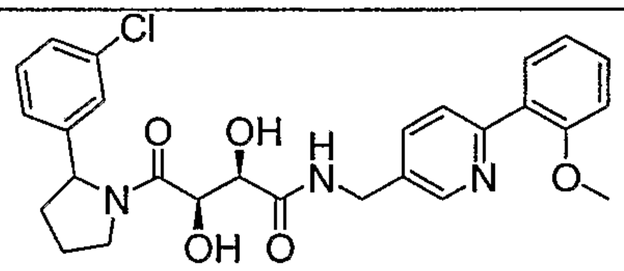
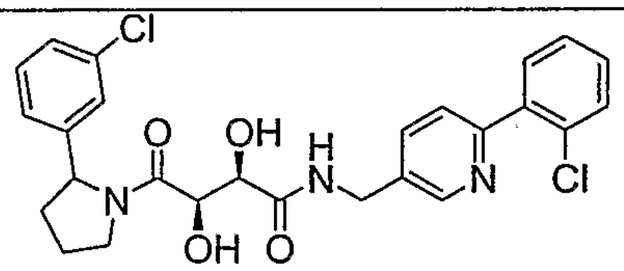
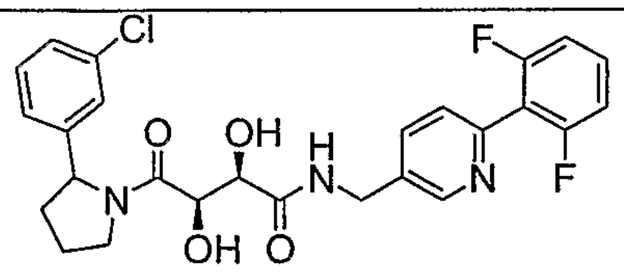
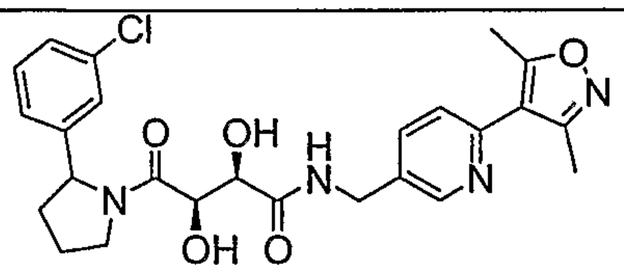
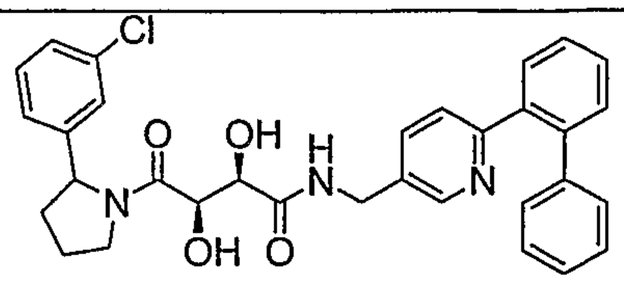
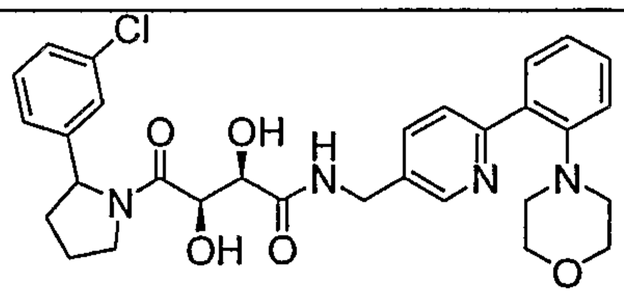
To **193** (prepared as described in Example 1) (1.5 g, 4.24 mmol) in DMF (10 mL) was added **194** (0.725 g, 5.09 mmol) and HATU (1.94 g, 5.09 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate 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).

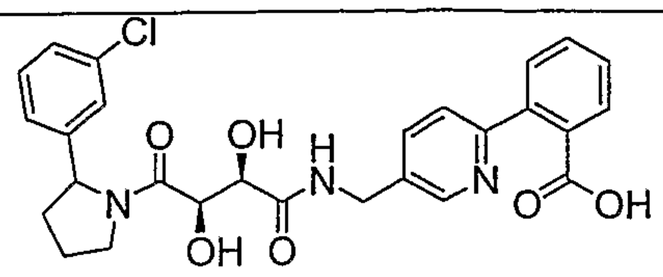
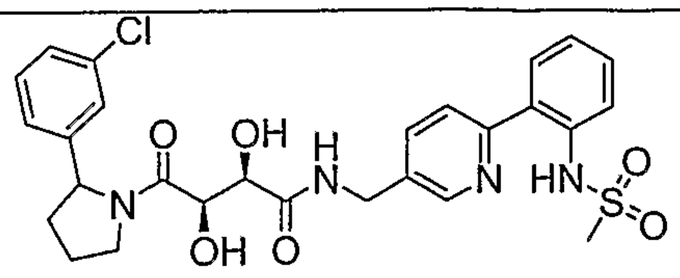
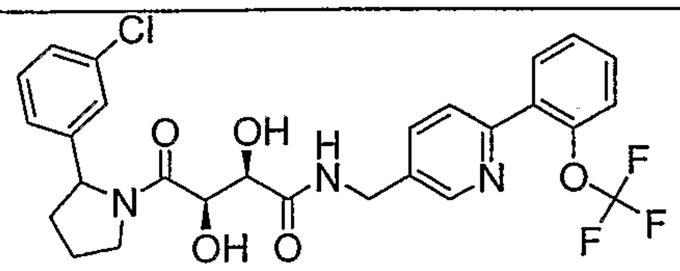
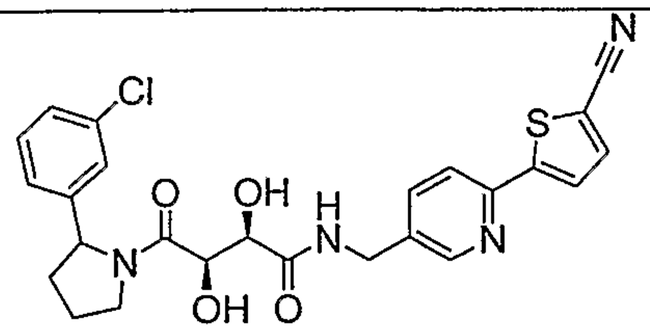
Part B:

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).

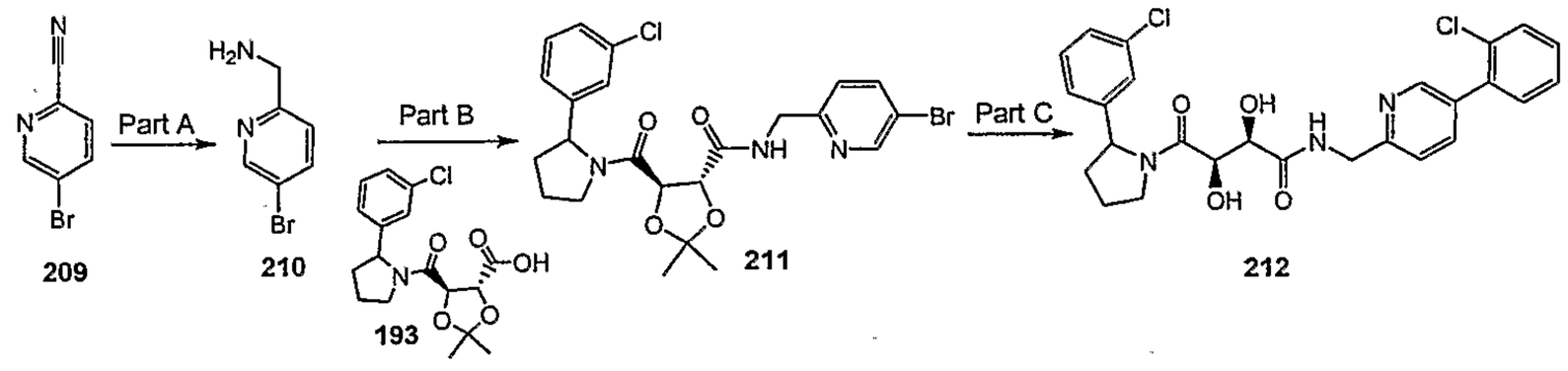
Step 2: The crude material from Step 1 was dissolved in 80:20 TFA:water (1 mL) at 0 °C and stirred at room temperature for 2 hours. The reaction mixture was quenched with 1:1 water:acetonitrile (2 mL) and concentrated.

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:

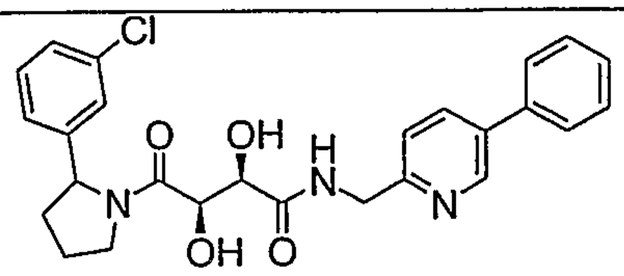
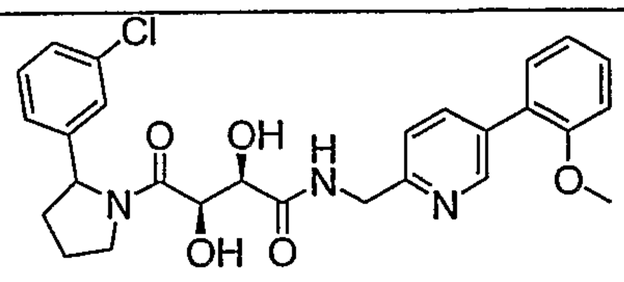
To **193** (1.13 g, 3.2 mmol) in DMF (10 mL) was added **210** (0.600 g, 3.2 mmol) and HATU (1.34 g, 3.52 mmol). The reaction mixture was stirred for 5 hours at room temperature. The reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate and brine, dried over sodium 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).

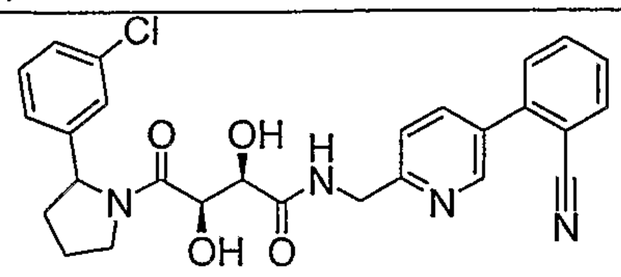
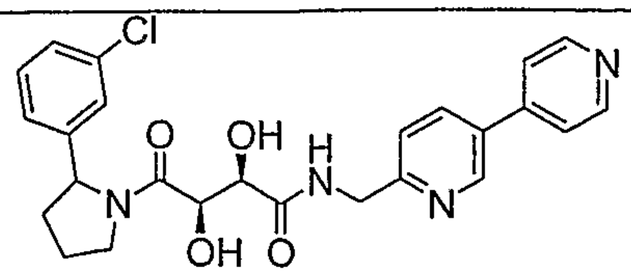
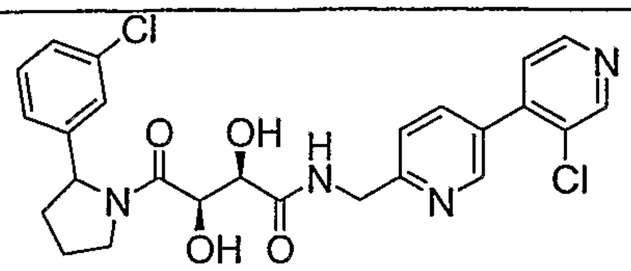
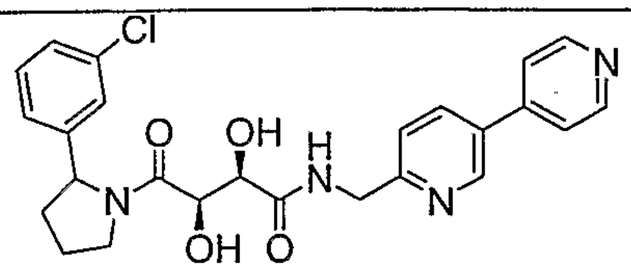
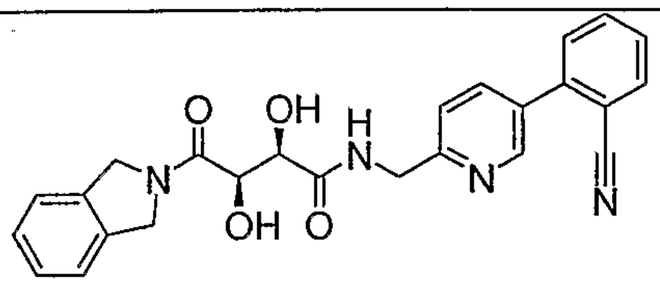
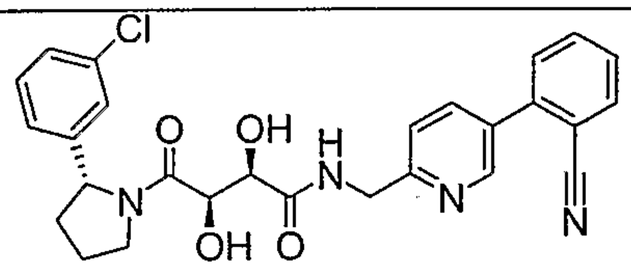
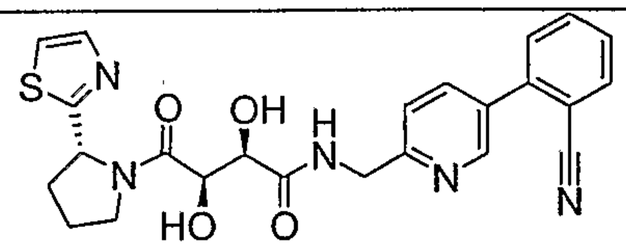
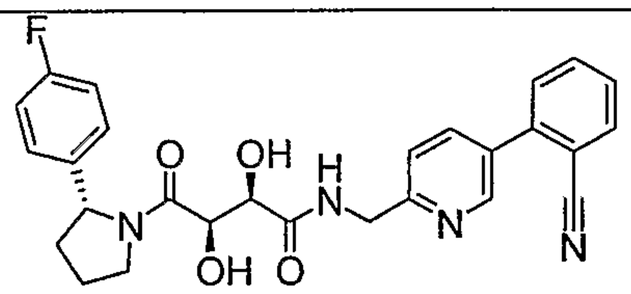
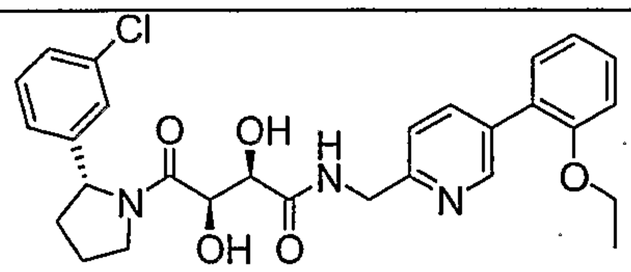
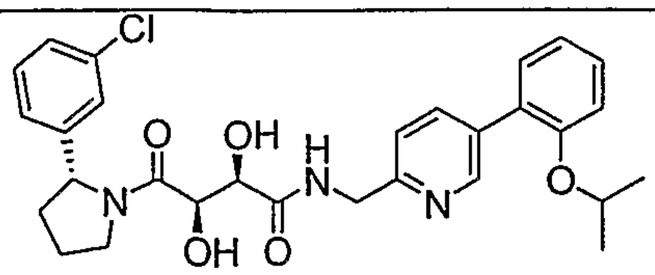
Part C:

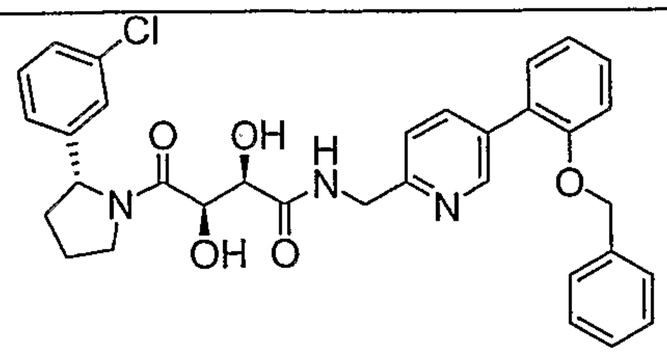
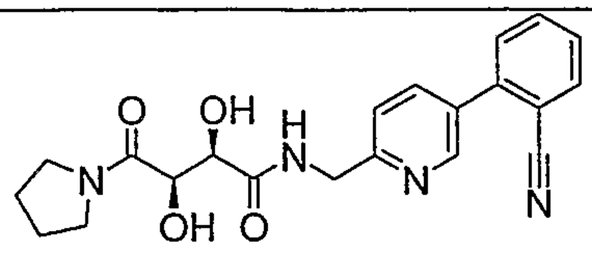
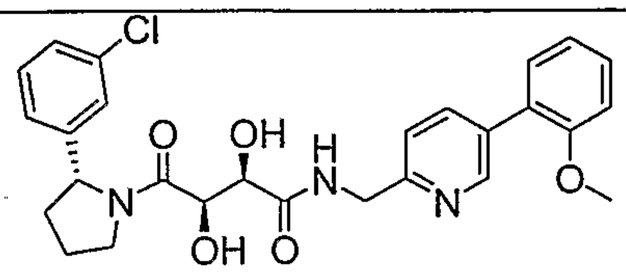
Step1: To 2-chlorophenyl boronic acid (24 mg, 0.152 mmol), potassium phosphate (65 mg, 0.306 mmol) and $PdCl_2$(dppf) (3.1 mg, 5 mol%) under argon in a 4-mL vial was added **211** (40 mg, 0.076 mmol) in dioxane (0.5 mL). The reaction mixture was heated at 100 °C for 16 hours. The reaction mixture was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

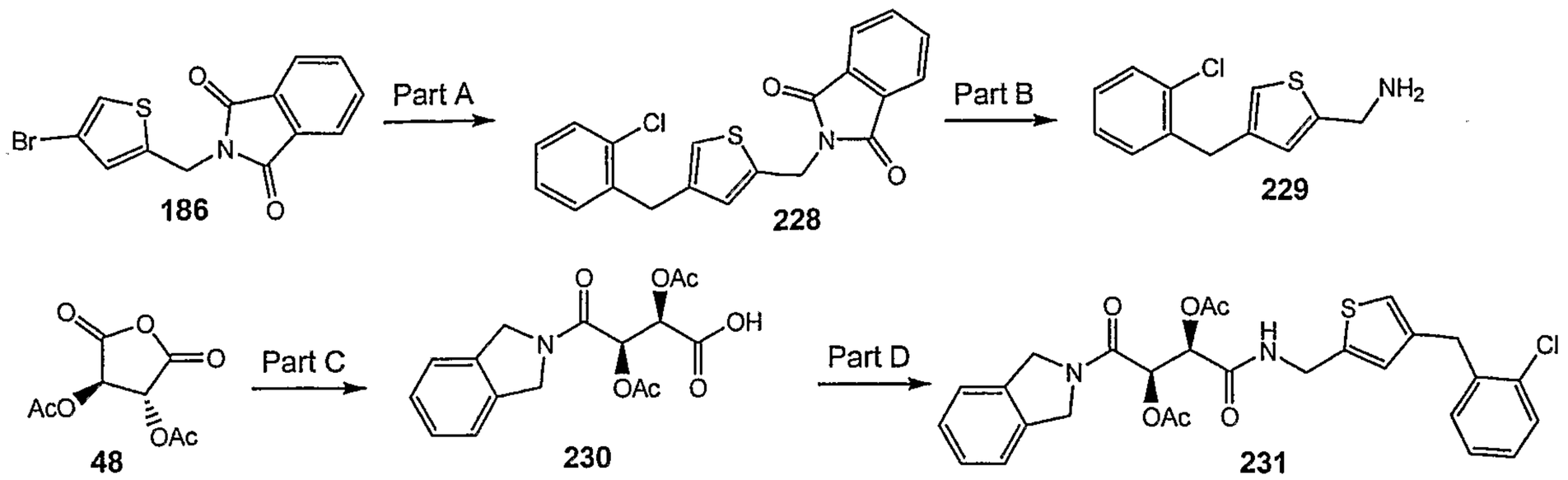
215		504.2	505.1
216		480.2	481.1
217		514.1	515.0
218		481.2	482.2
219		442.2	443.2
220		504.2	505.1
221		477.2	478.1
222		488.2	489.1
223		523.2	524.2
224		537.2	538.2

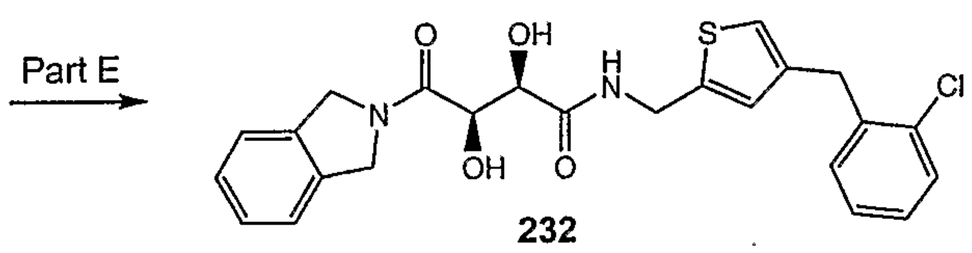
225		585.2	586.2
226		394.2	395.2
227		509.2	510.1

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%). ^{1}H 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).

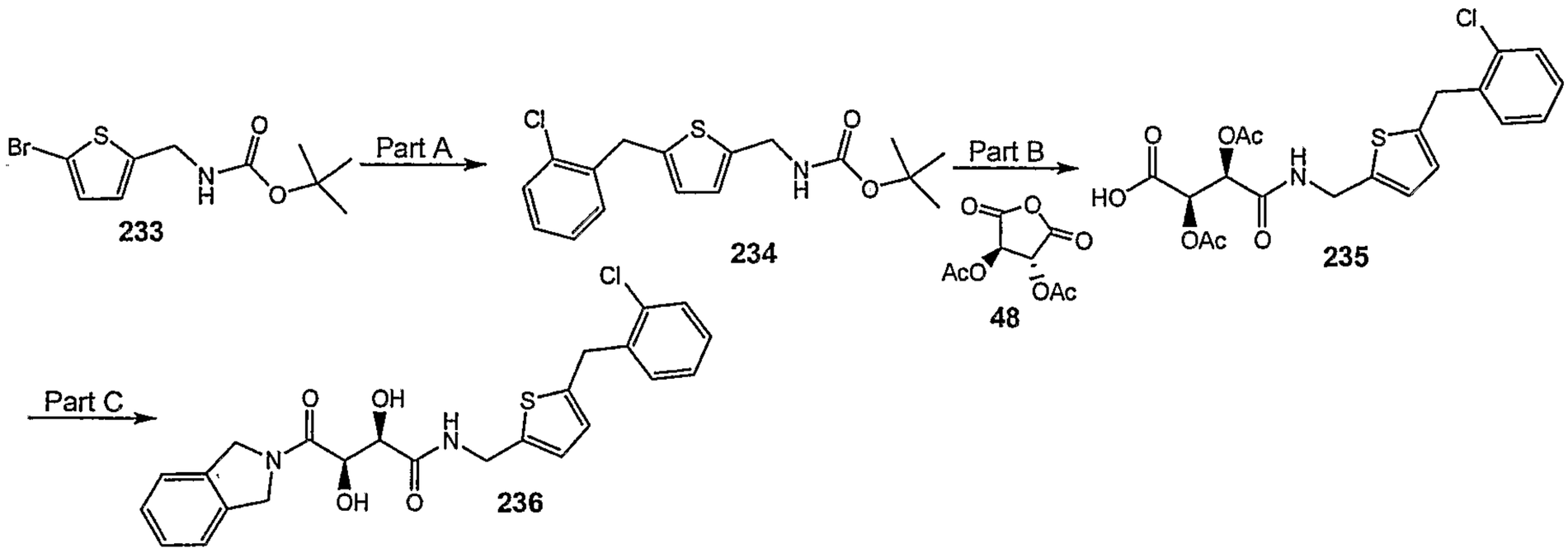
Part D:

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%). ^{1}H 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:

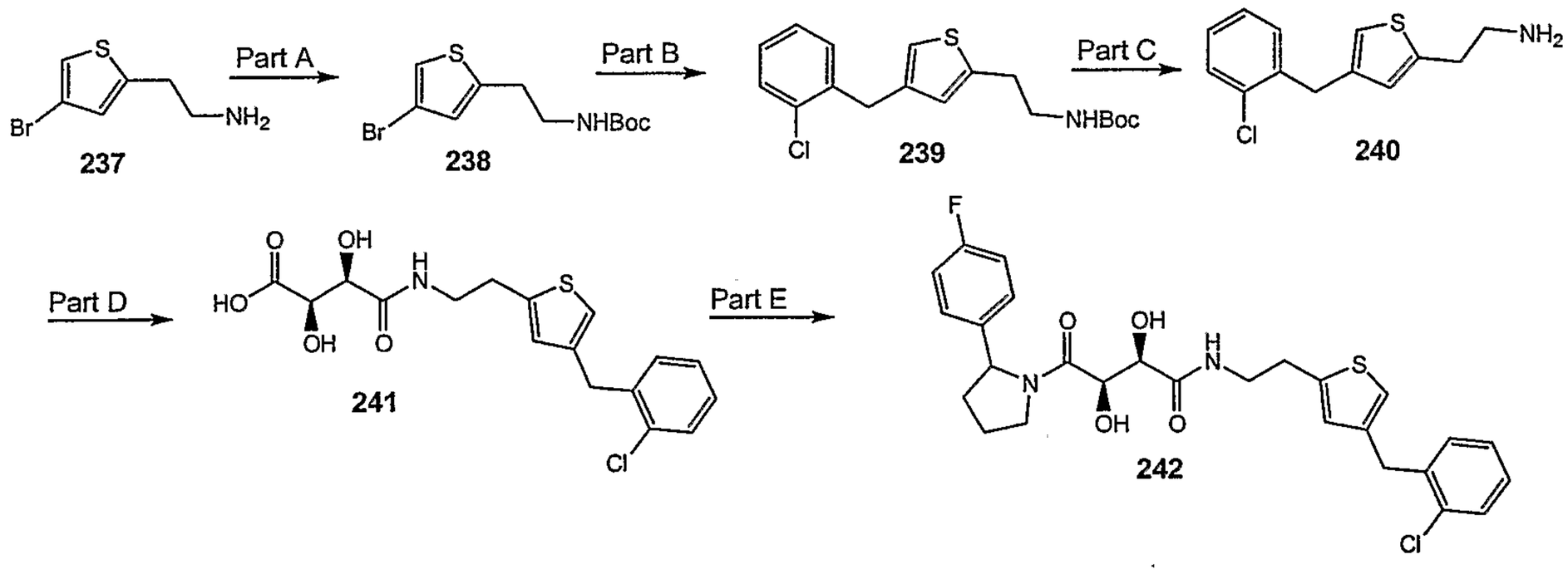
To **234** (450 mg, 1.34 mmol) was added 4M HCl in dioxane (1.5 mL) and the reaction was stirred for 30 minutes. The dioxane was removed in vacuo. The residue was dissolved in THF (10 mL) and DIEA (500 µL, 2.68 mmol) and **48** (275 mg, 1.27 mmol) were added. The reaction was stirred overnight at room 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)

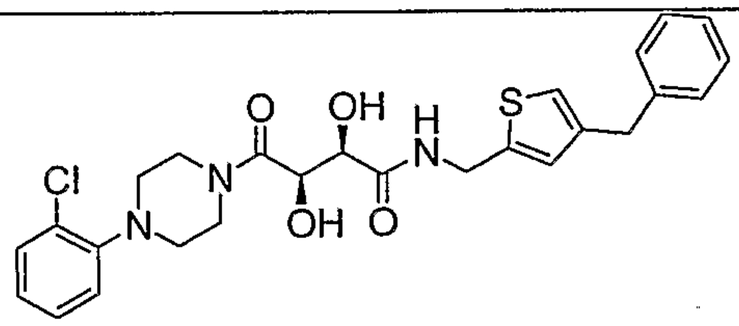
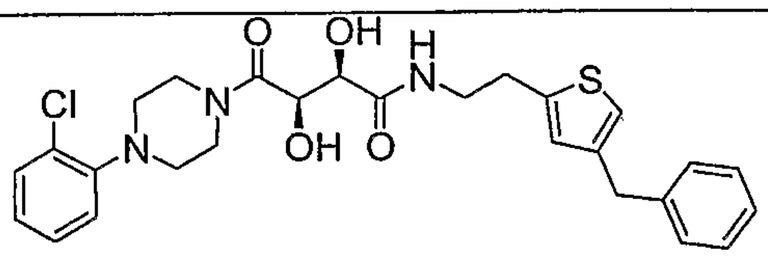
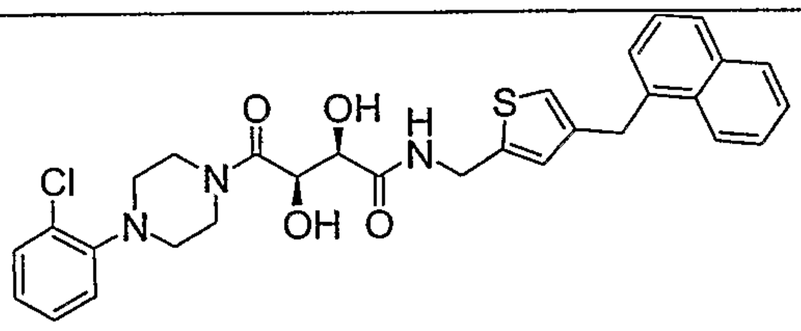
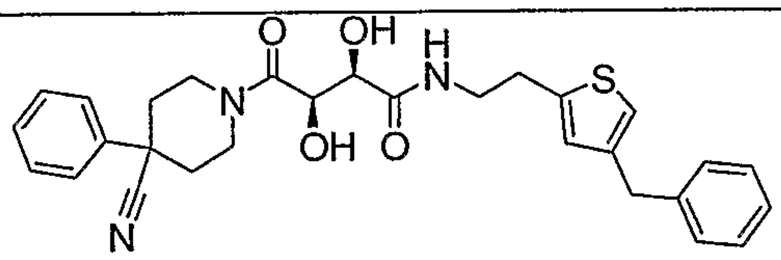
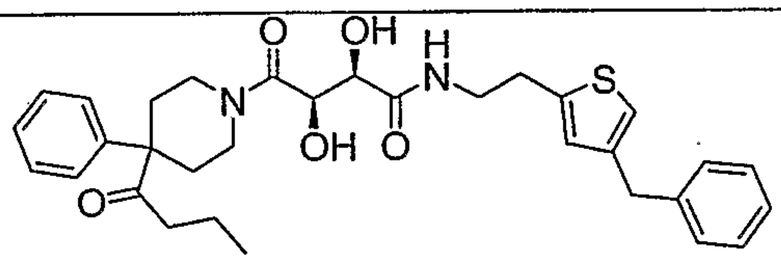
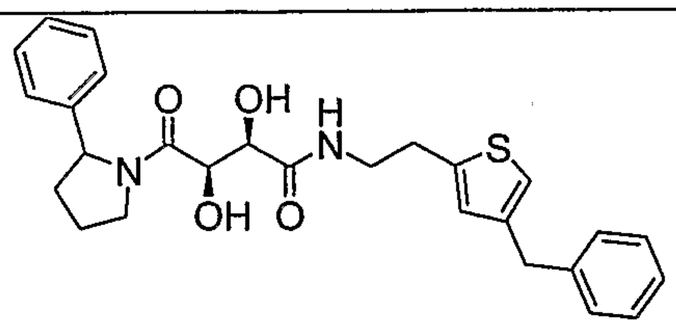
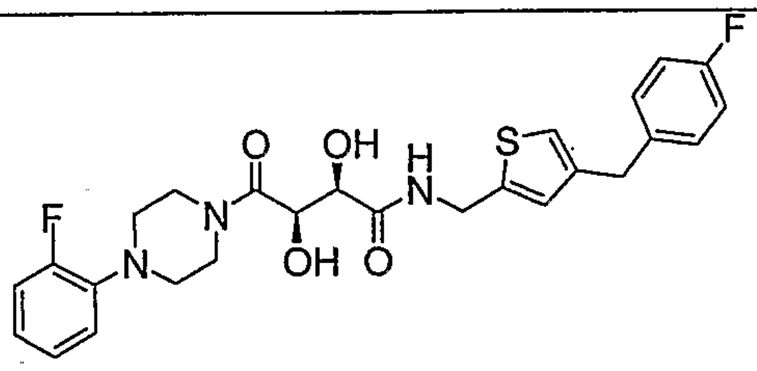
Parts A:

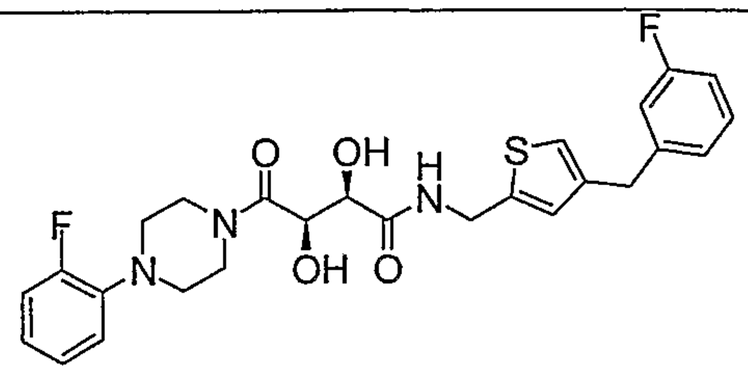
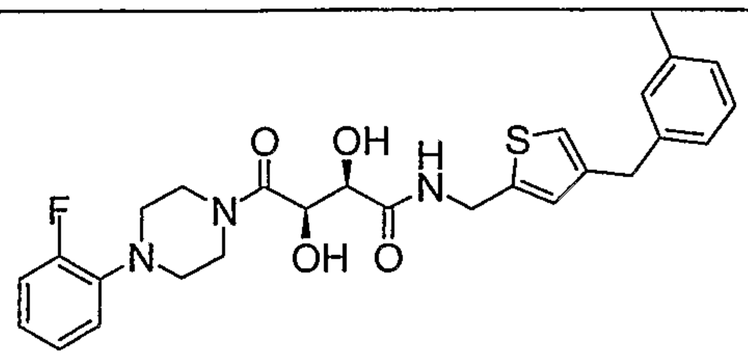
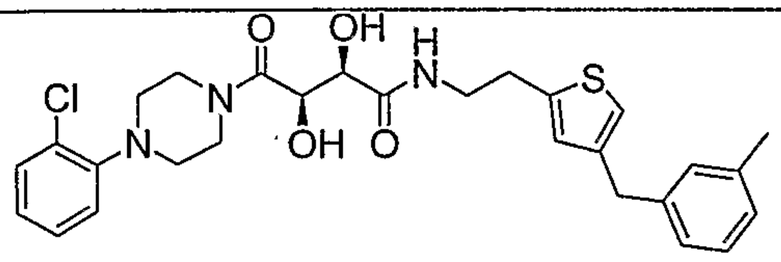
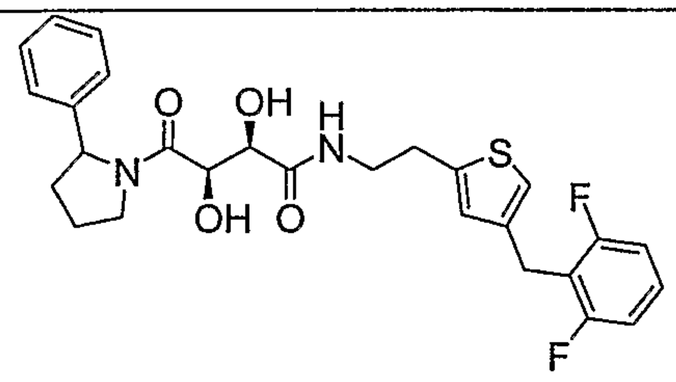
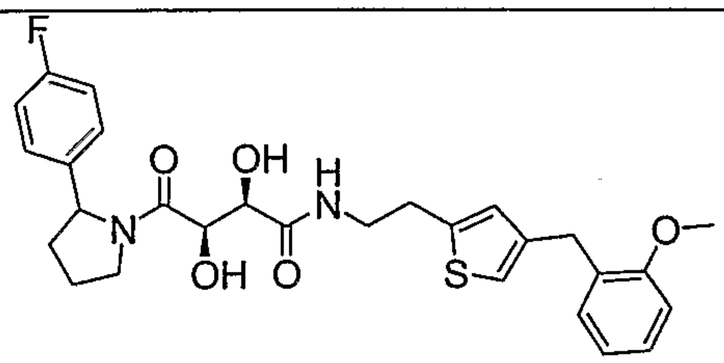
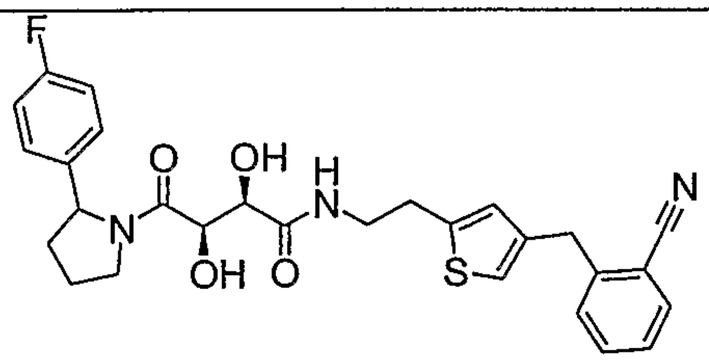
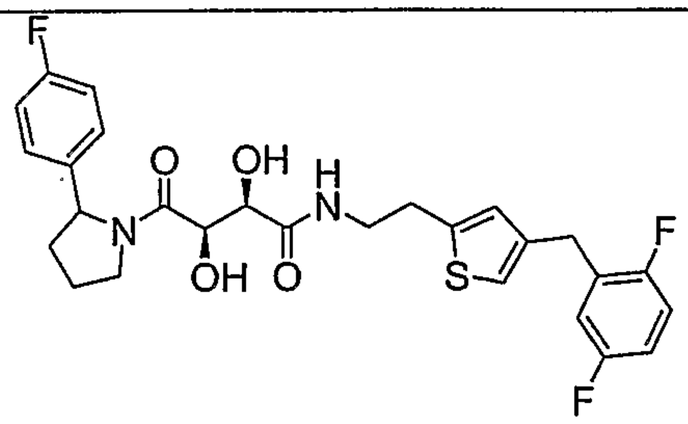
Compound **238** was prepared by procedures similar to those described in Example 5 Part A.

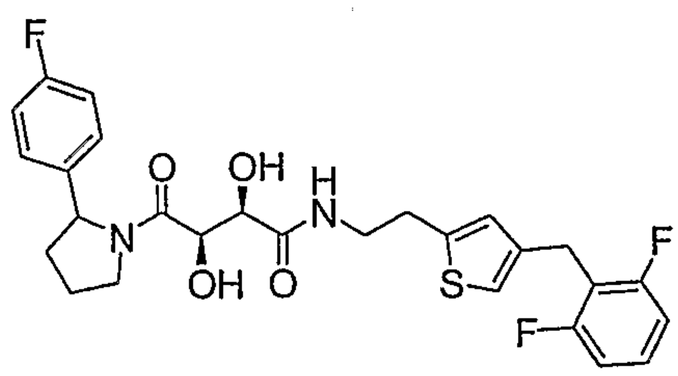
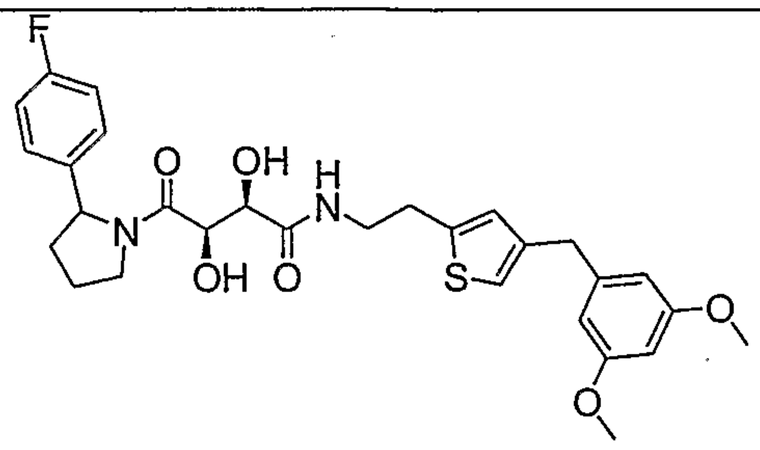
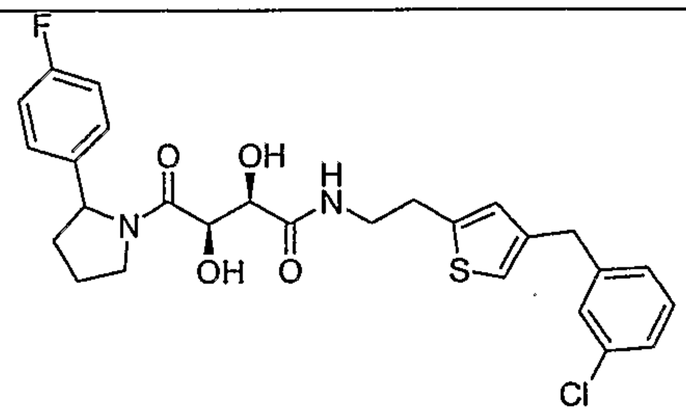
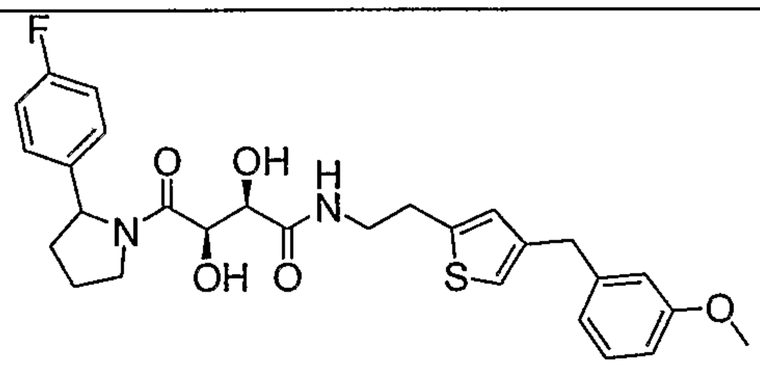
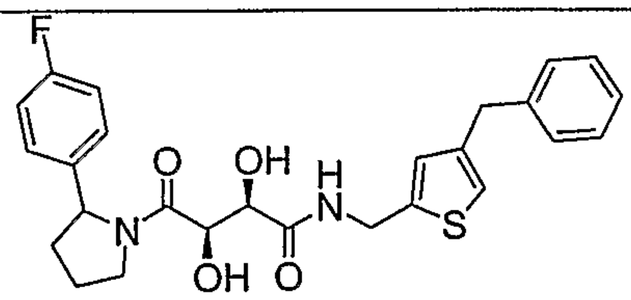
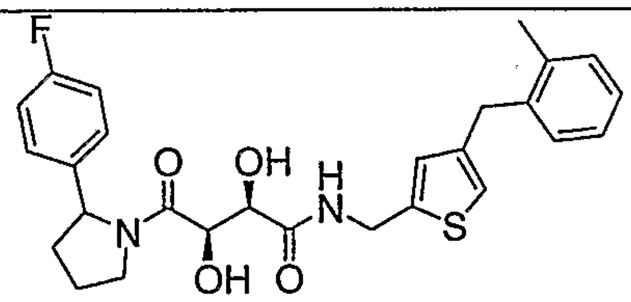
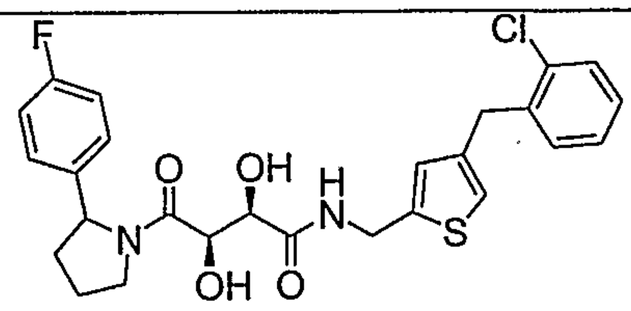
Parts B-E:

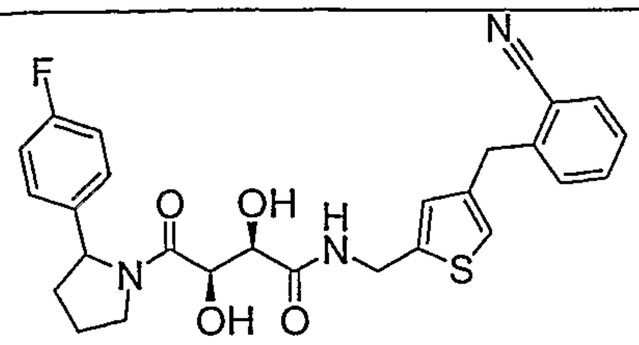
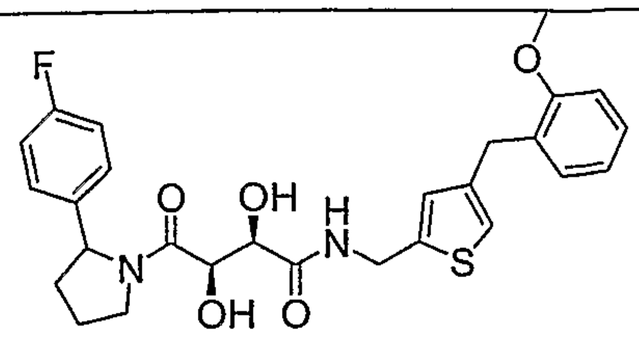
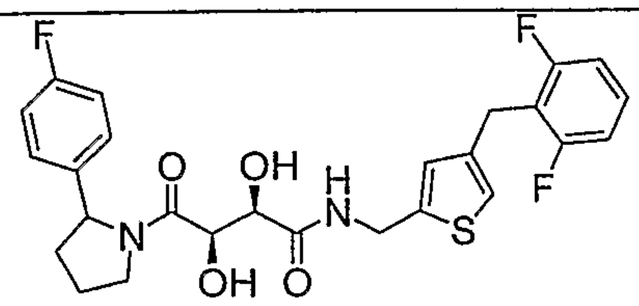
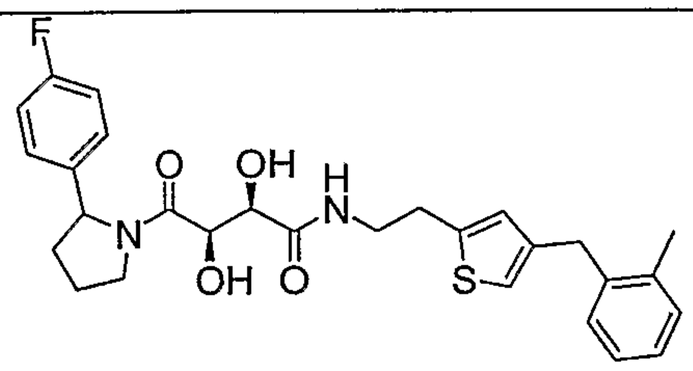
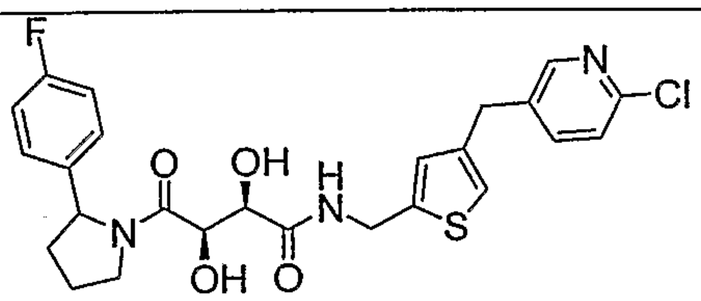
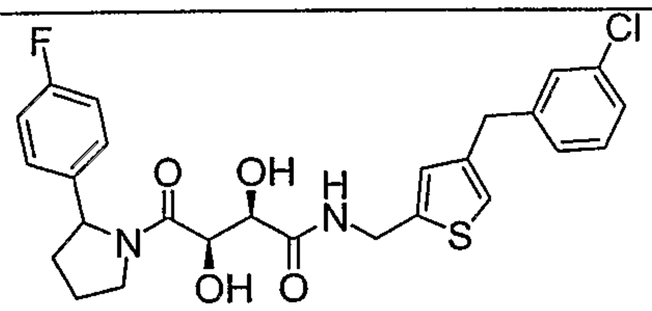
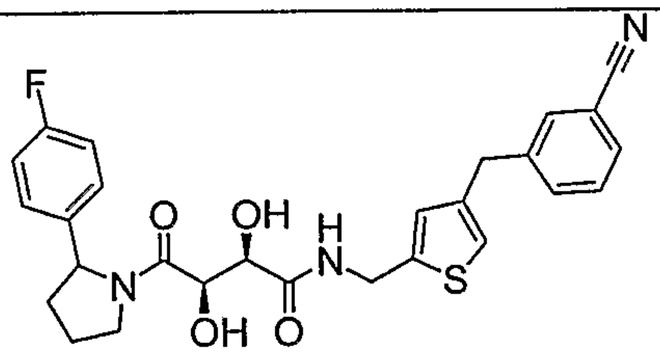
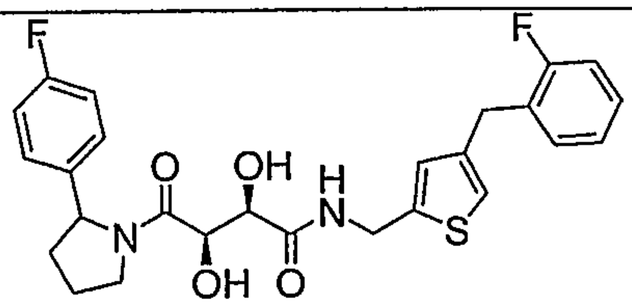
Compound **242** was prepared by procedures similar to those described in Example 4B Parts A to C. HPLC-MS t_R = 2.05 min ($UV_{254\ nm}$); mass calculated for formula $C_{27}H_{28}ClFN_2O_4S$ 530.1, observed LCMS m/z 531.1 (M+H).

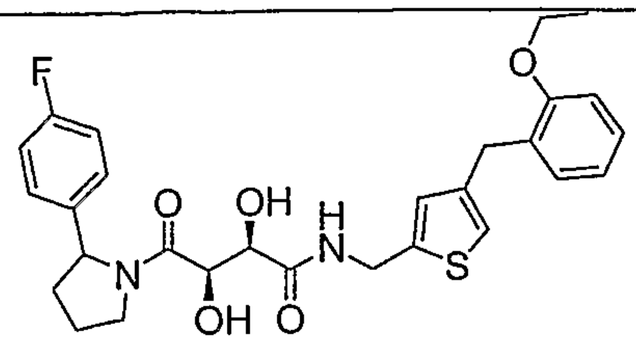
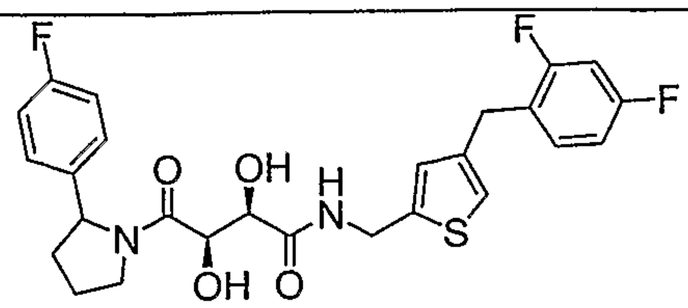
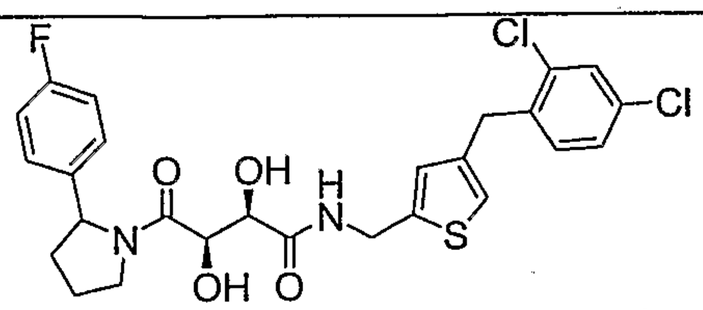
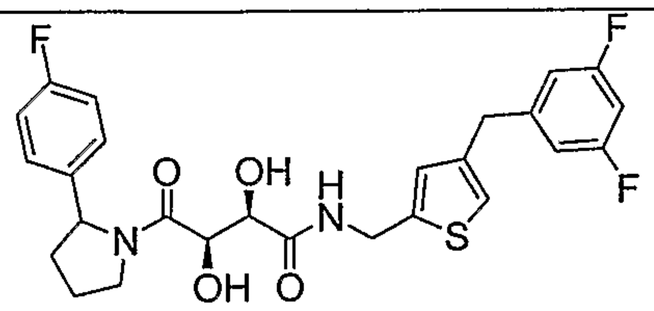
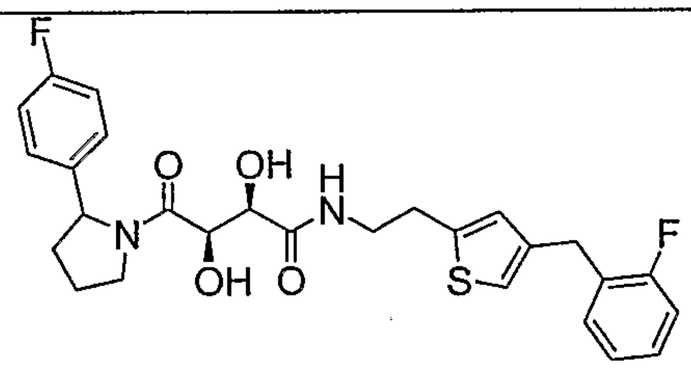
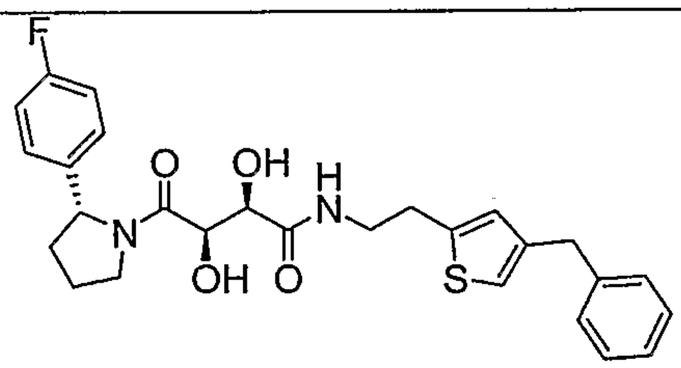
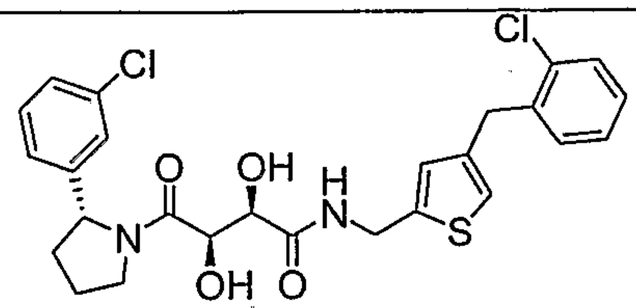
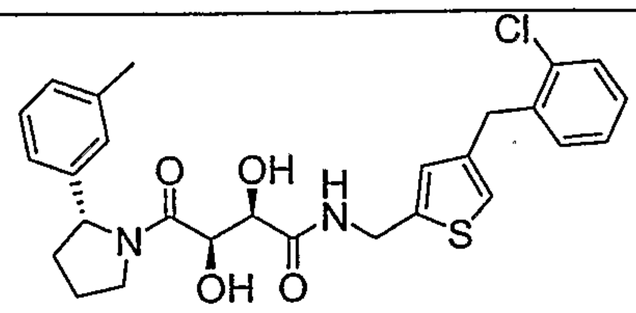
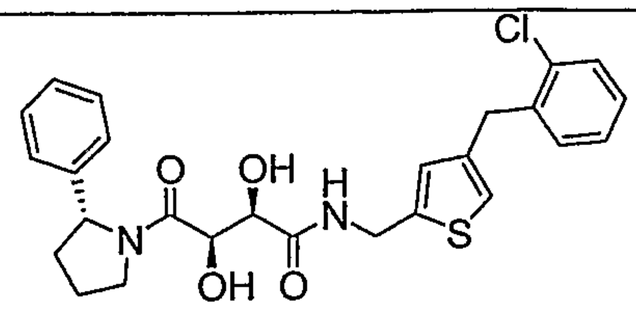
The following compounds were prepared by the procdures desribed in Example 4A – 4C.

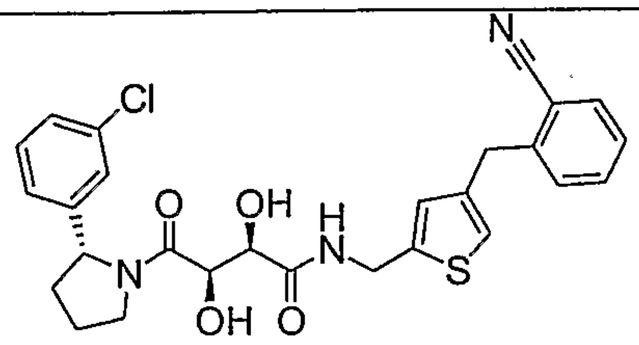
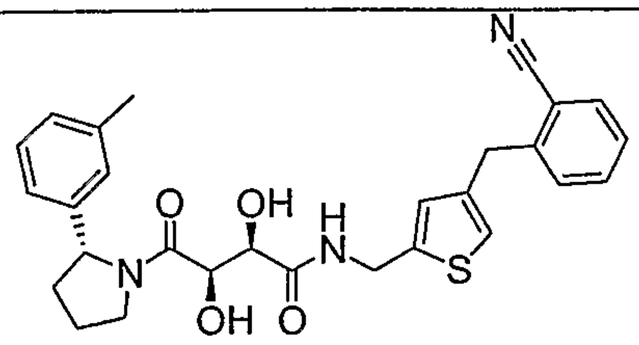
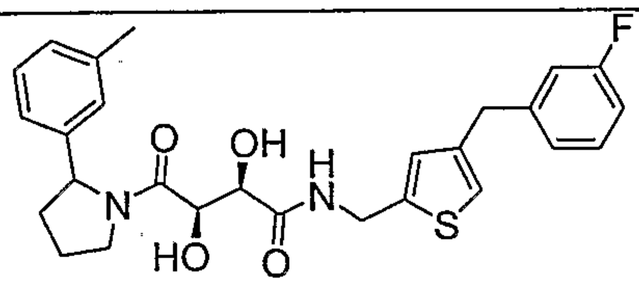
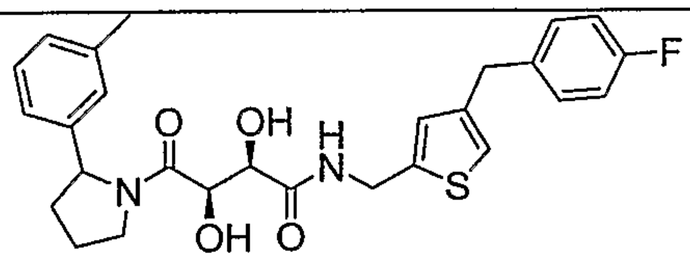
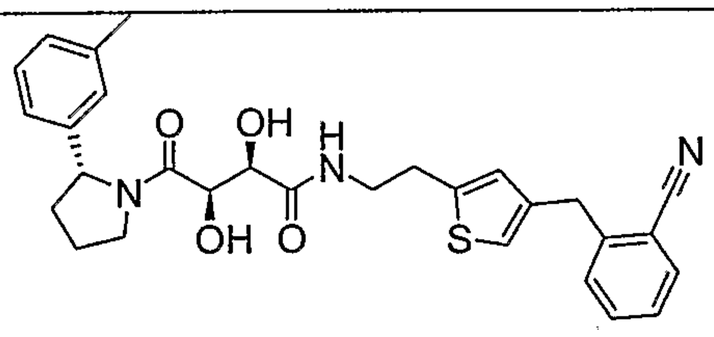
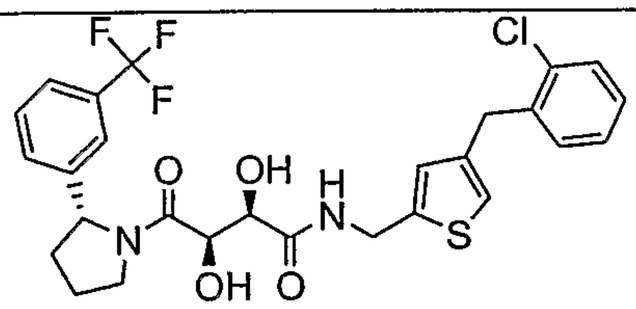
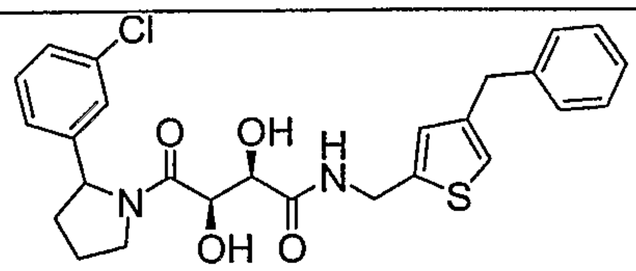
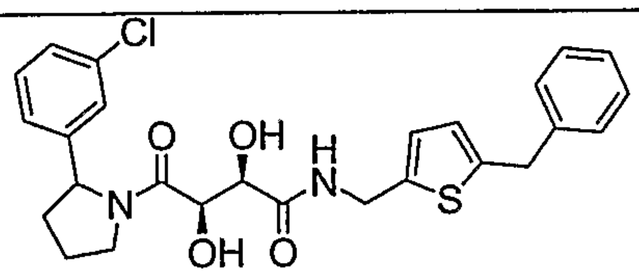
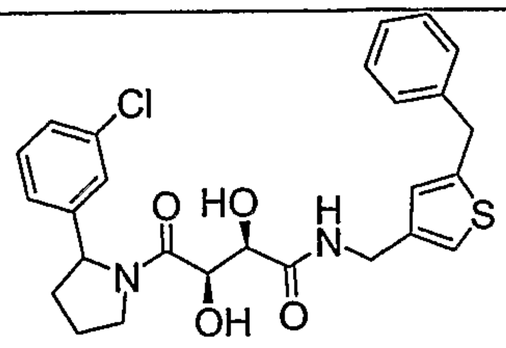
Compound #	Structure	Exact mass	MS m/z (M+H)
243		513.2	514.2
244		527.2	528.1
245		563.2	564.2
246		517.2	518.2
247		562.3	563.2
248		478.2	479.2
249		515.2	516.0

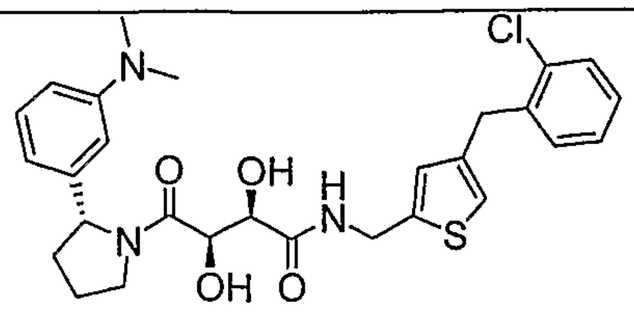
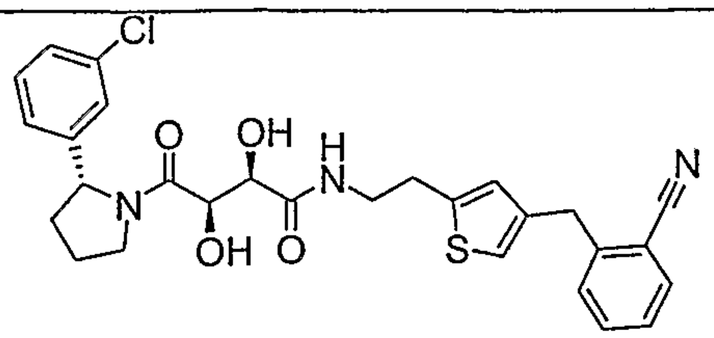
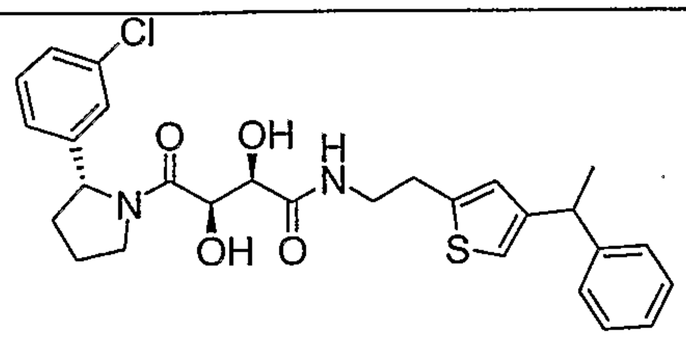
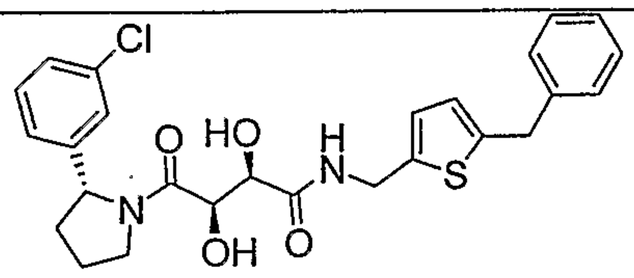
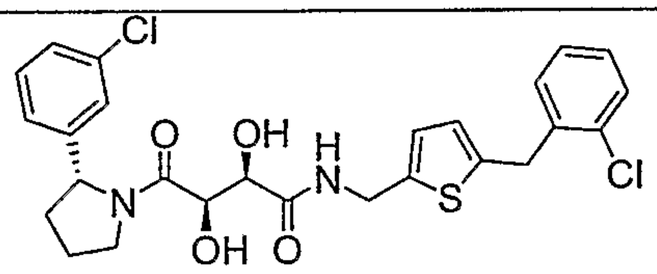
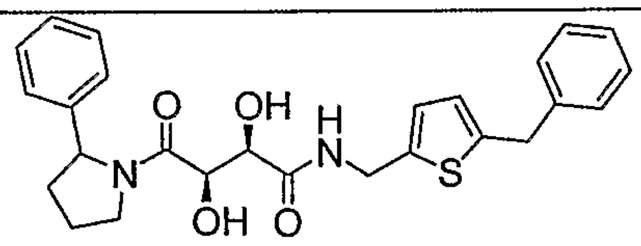
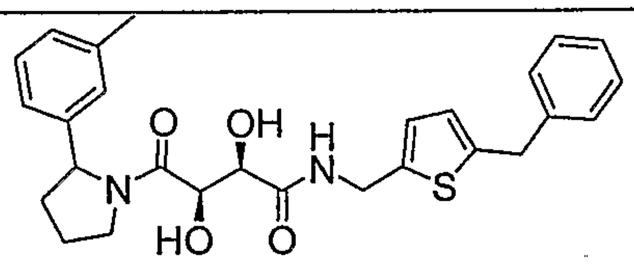
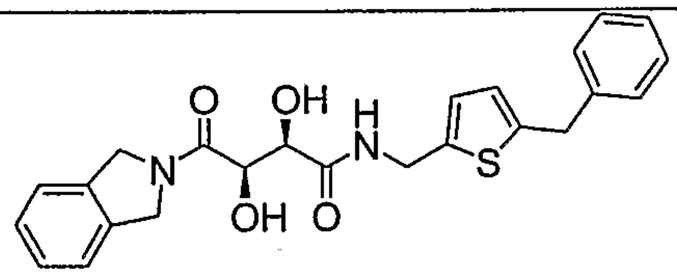
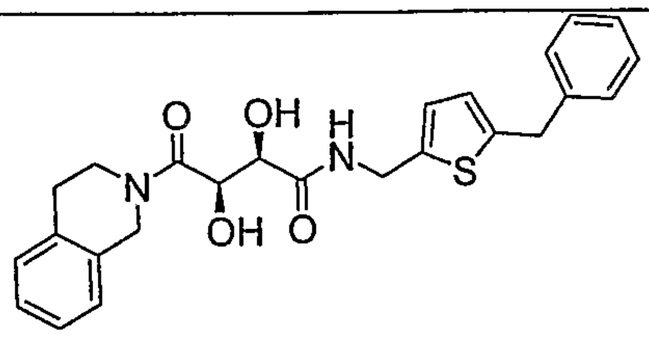
250		515.2	516.0
251		511.2	512.2
252		541.2	542.2
253		514.2	515.2
254		526.2	527.2
255		521.2	522.1
256		532.2	533.2

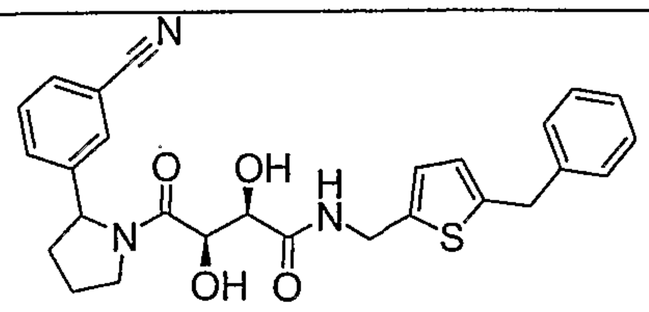
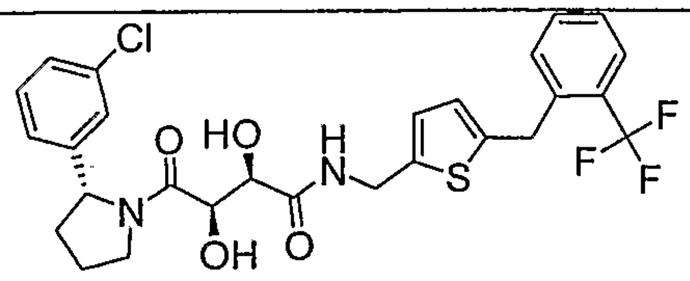
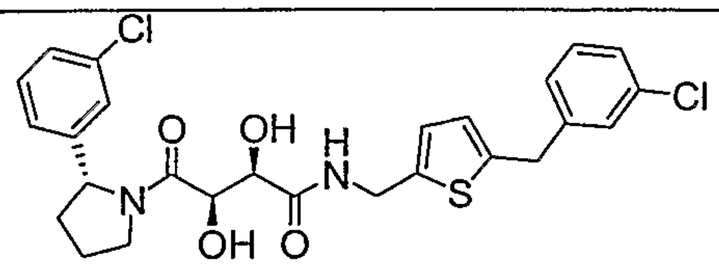
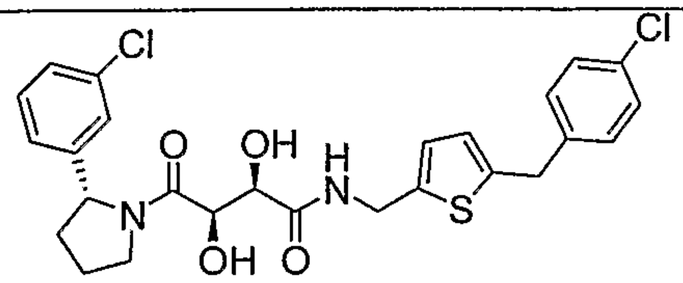
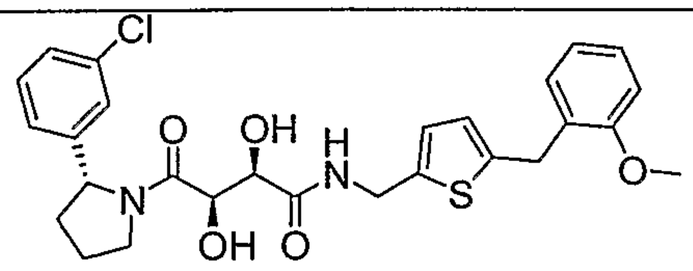
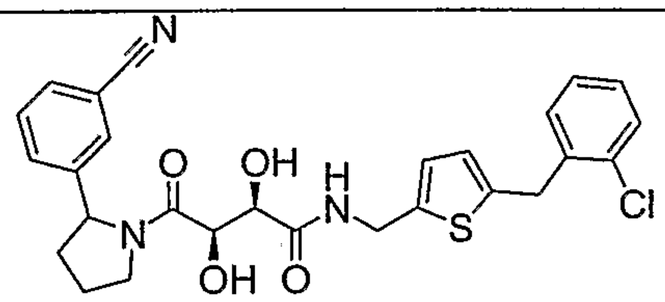
257		532.2	533.2
258		556.2	557.2
259		530.1	531.1
260		526.2	527.2
261		482.2	483.1
262		496.2	497.2
263		516.1	517.2

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

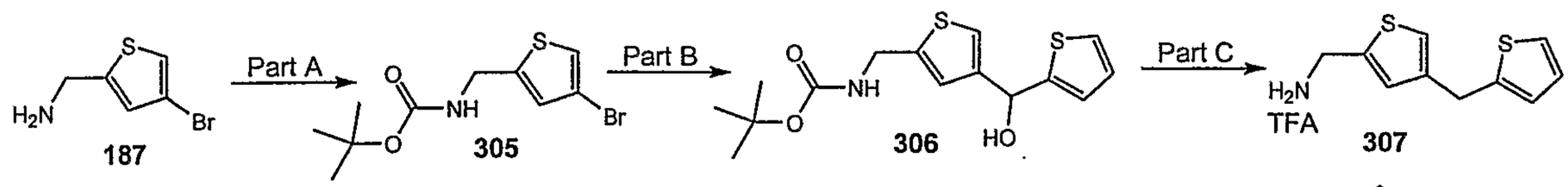
272		526.2	527.2
273		518.2	519.1
274		550.1	551.0
275		518.2	519.1
276		514.2	515.2
277		496.2	497.1
278		532.1	533.0
279		512.2	513.1
280		498.1	499.0

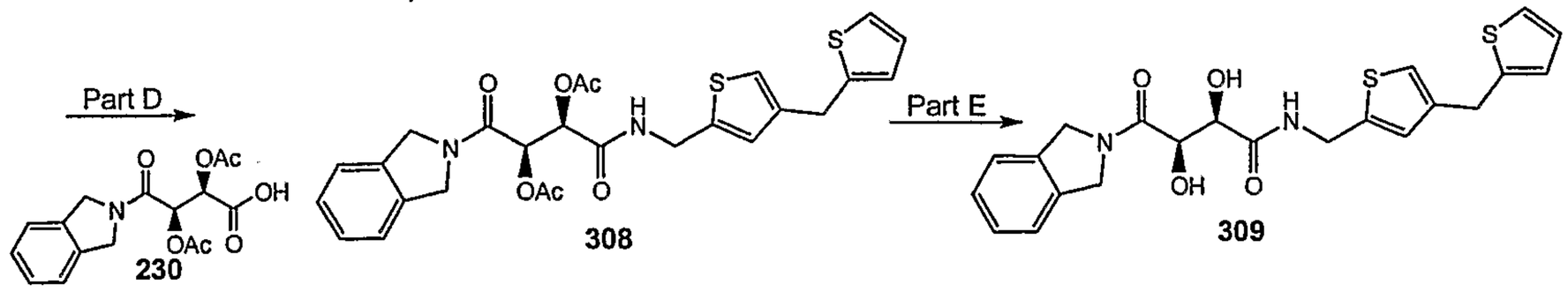
281		523.1	524.1
282		503.2	504.1
283		496.2	497.2
284		496.2	497.2
285		517.2	518.2
286		566.12	567.1
287		498.1	499.1
288		498.1	499.1
289		498.1	499.1

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. ^1H 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:

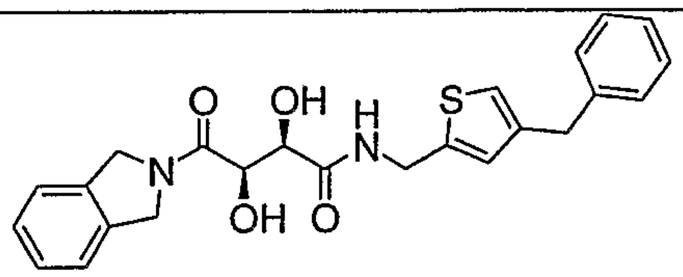
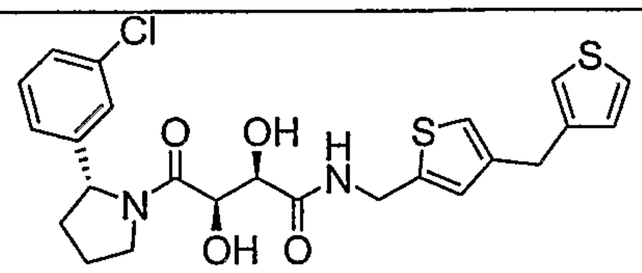
To **230** (19 mg, 0.06 mmol) in DMF (2 mL) was added **307** (18 mg, 0.06 mmol), DIEA (29 µL, 0.17 mmol) and HATU (28 mg, 0.07 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate (20 mL) and water (20 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed

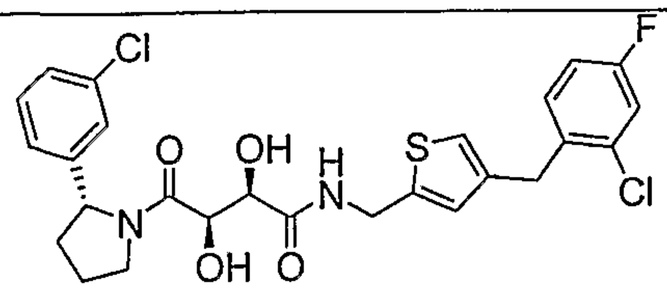
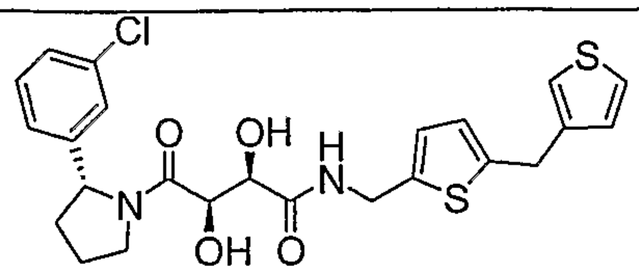
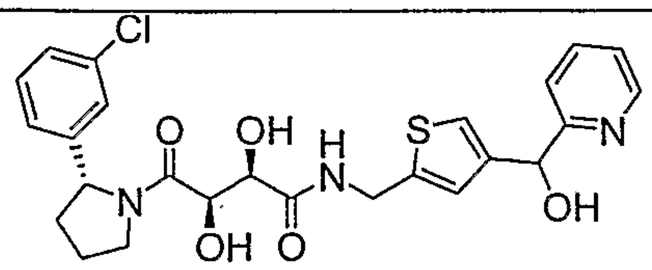
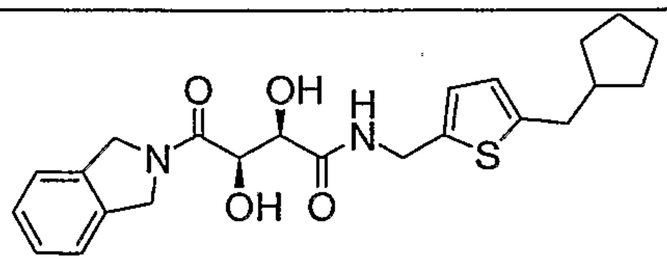
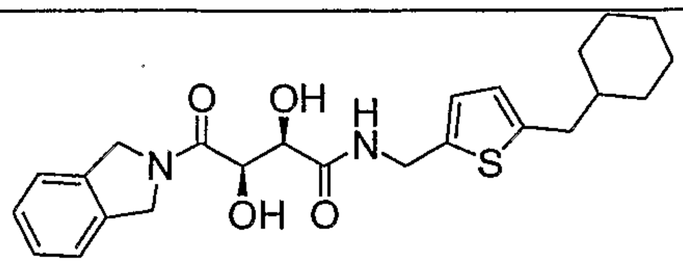
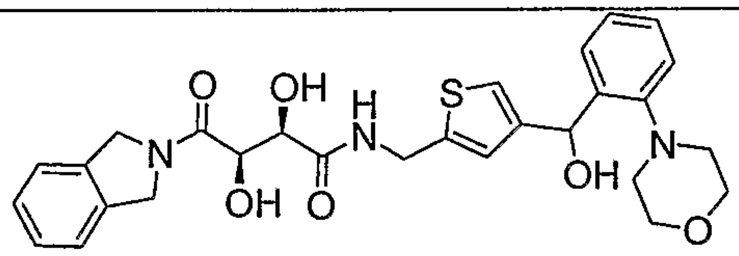
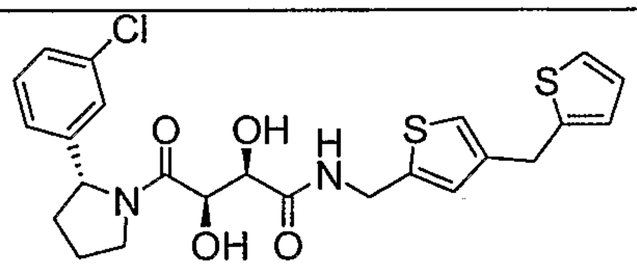
with sodium bicarbonate solution and brine, dried over sodium sulfate and concentrated. Compound **308** was used without further purification. HPLC-MS t_R = 1.91 min ($UV_{254\ nm}$); mass calculated for formula $C_{26}H_{26}N_2O_6S_2$ 526.1, observed LCMS m/z 269.9 (M+H).

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).

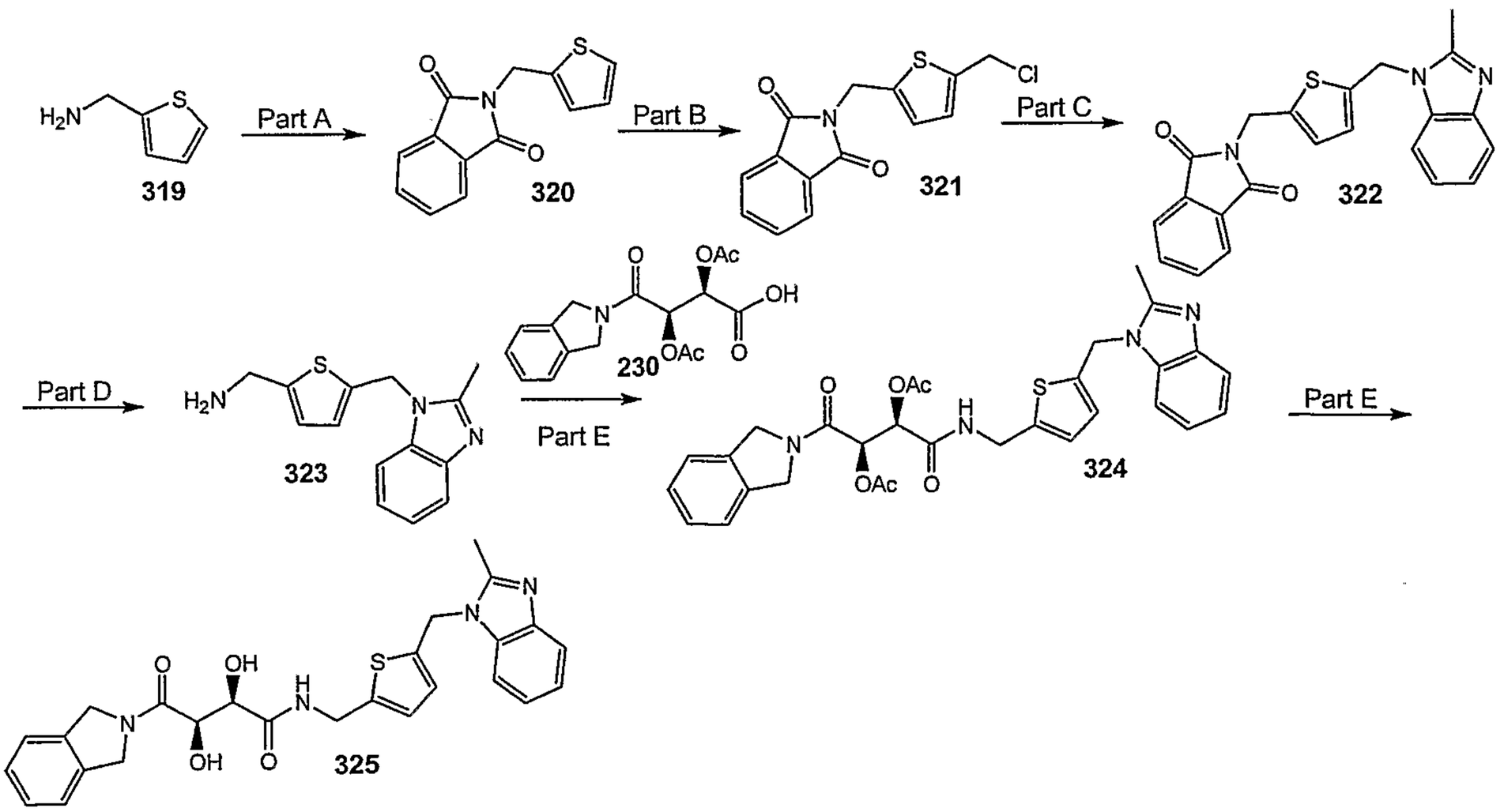
The following compounds were prepared using the procedures described above. Part C did not result in dehydration for compounds like **314** and **317**.

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:

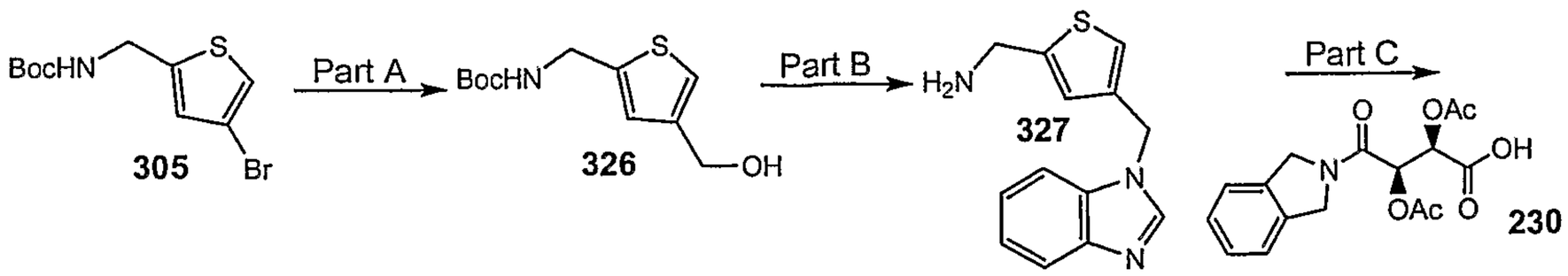
To **230** (83 mg, 0.24 mmol) in DMF (5 mL) was added **323** (82 mg, 0.32 mmol), DIEA (300 µL, 1.6 mmol) and HATU (135 mg, 0.36 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate (50 mL) and water (50 mL). The layers were separated 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

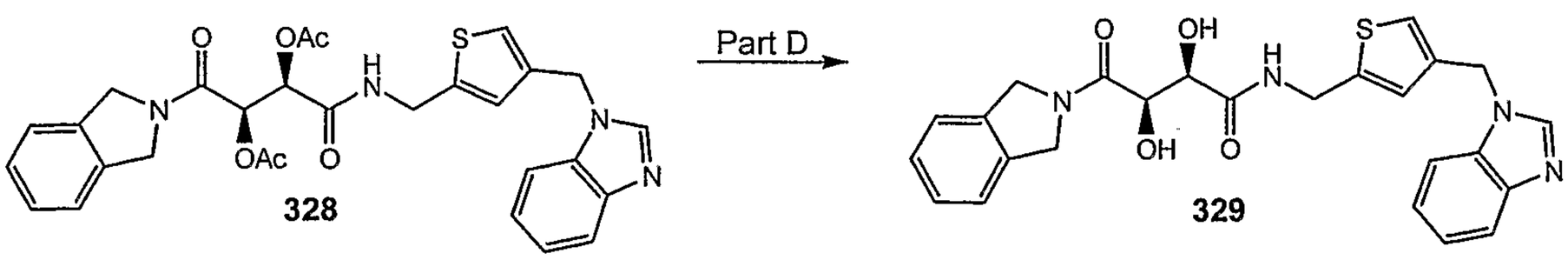
without further purification. HPLC-MS t_R = 1.13 min ($UV_{254\ nm}$); mass calculated for formula $C_{30}H_{30}N_4O_6S$ 574.2, observed LCMS m/z 575.1 (M+H).

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. ^1H 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%). ^{1}H 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.

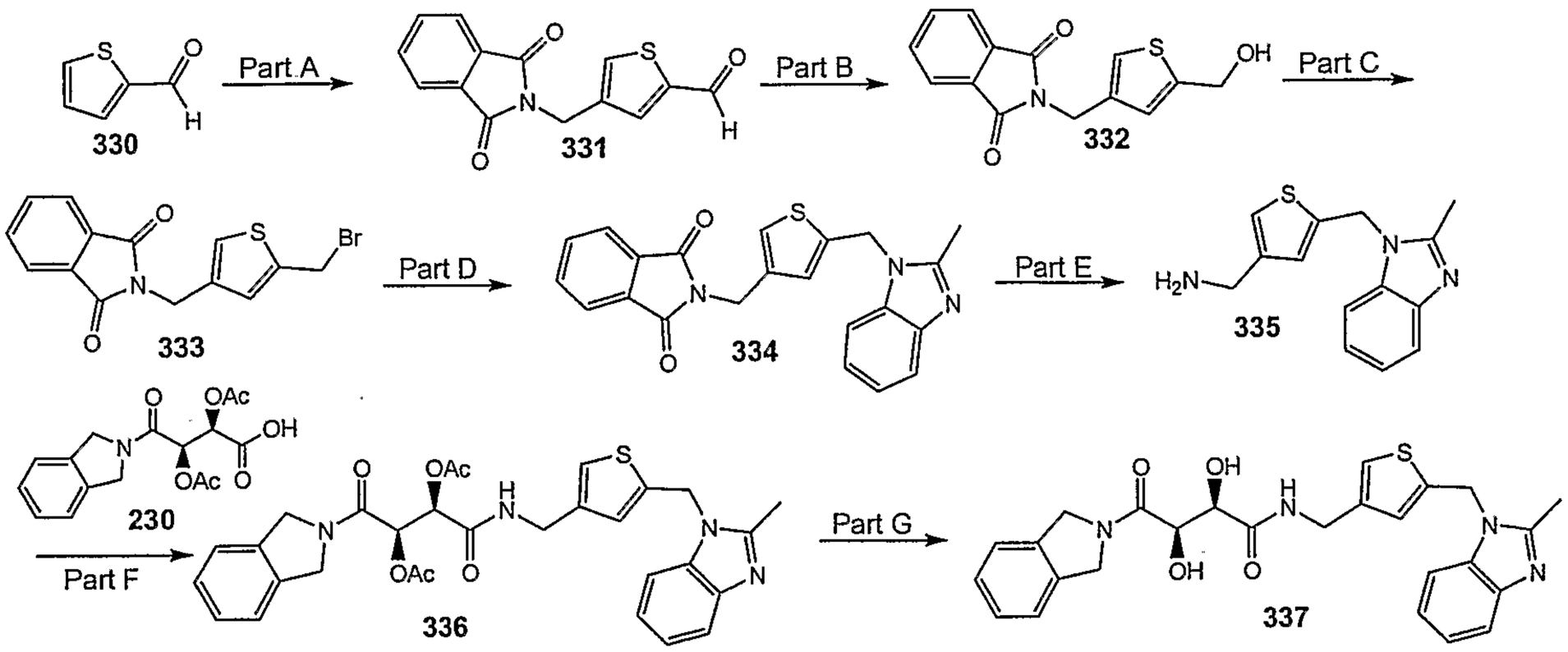
Part C:

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%). ^{1}H 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%). ^{1}H 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:

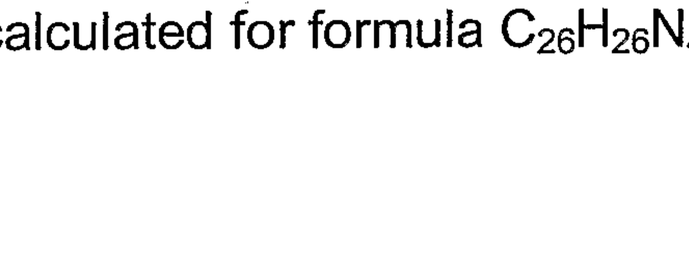
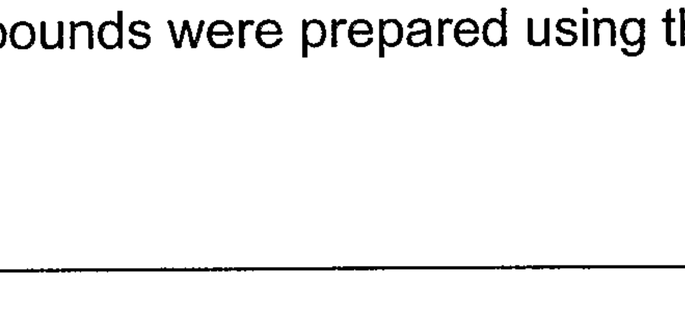
To **230** (12 mg, 0.036 mmol) in DMF (2 mL) was added **335** (12 mg, 0.045 mmol), DIEA (18 µL, 0.11 mmol) and HATU (17 mg, 0.045 mmol). The reaction mixture was stirred overnight at room temperature. The reaction

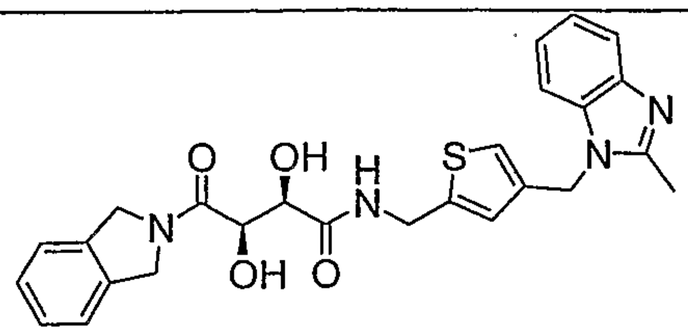
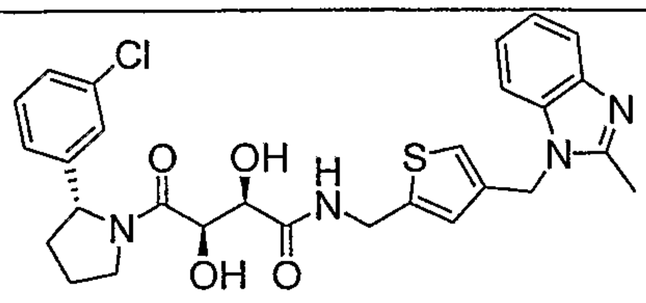
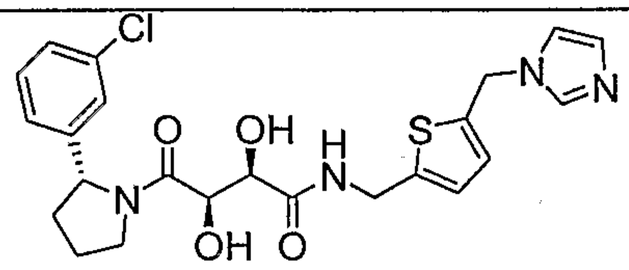
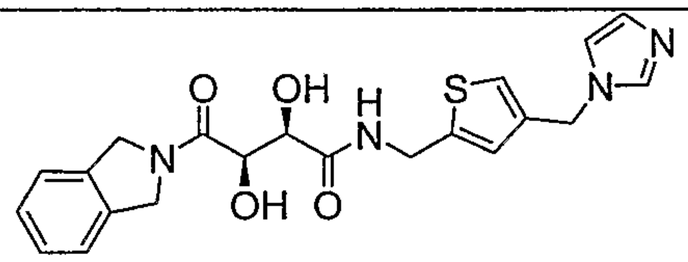
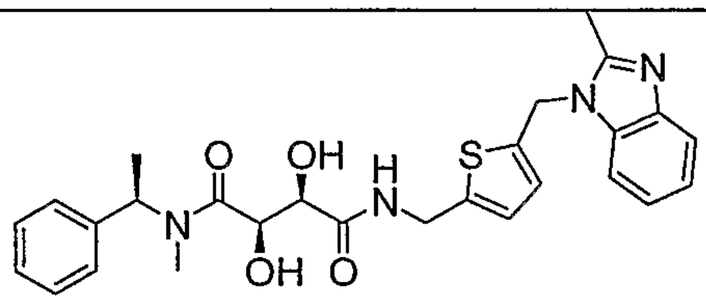
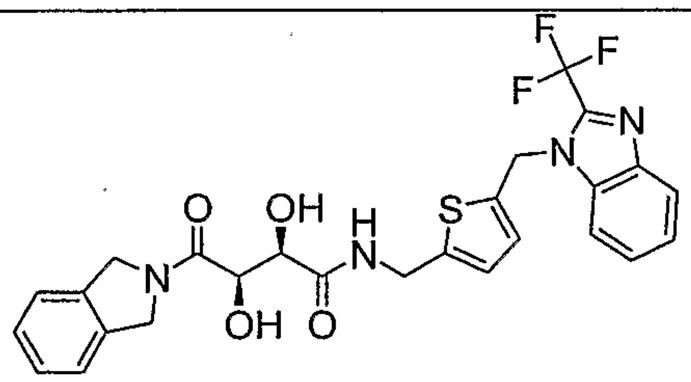
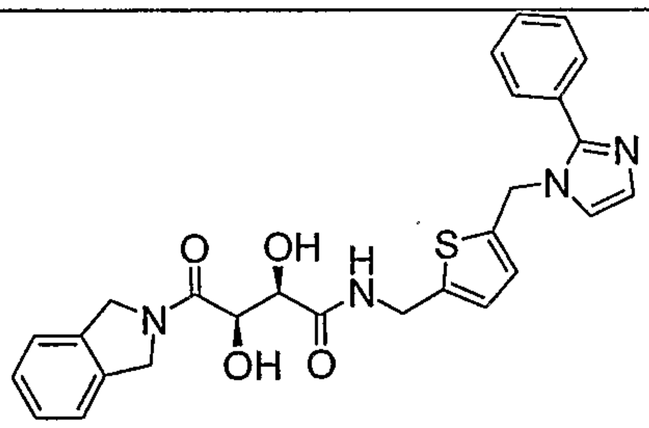
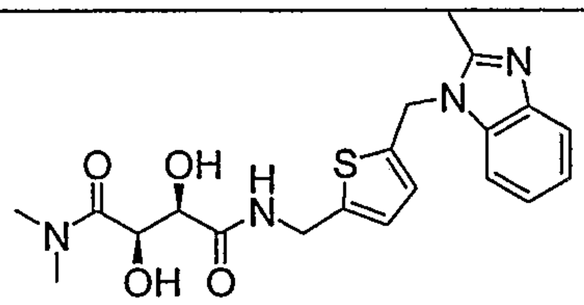
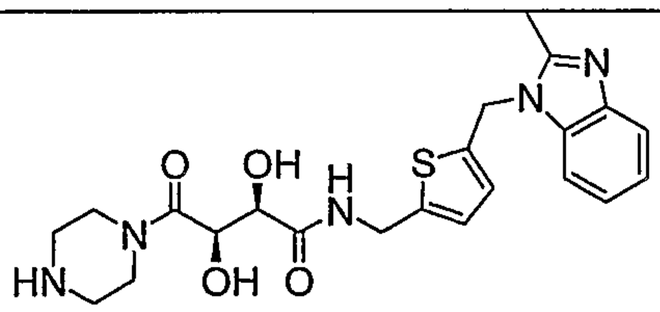
mixture was diluted with ethyl acetate (20 mL) and water (20 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with sodium bicarbonate solution and brine, dried over sodium sulfate and concentrated. Compound **336** was used 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).

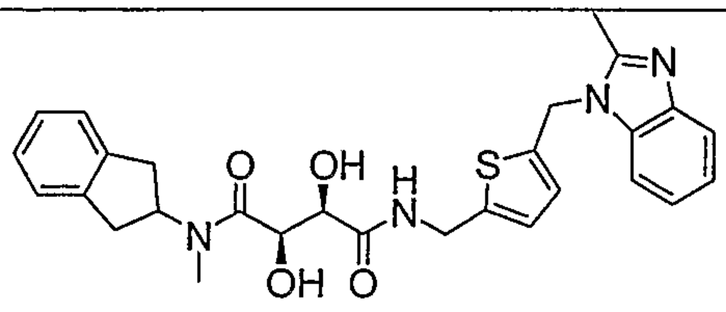
Part G:

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).

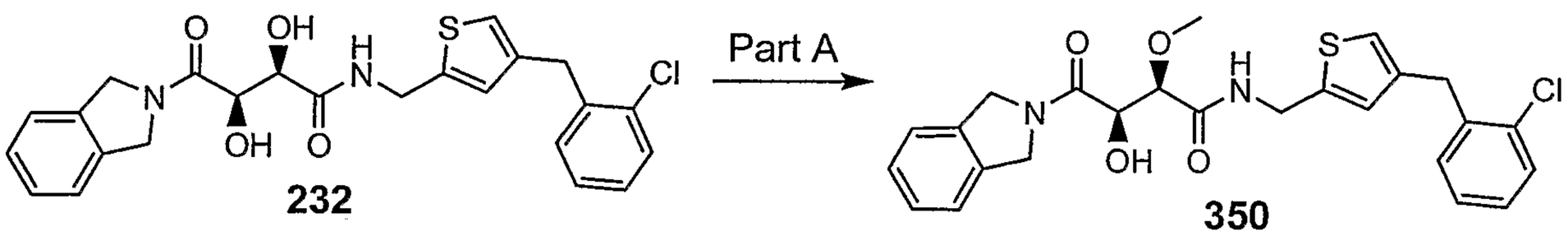
The following compounds were prepared using the procedures described in Example 6A to 6C.

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

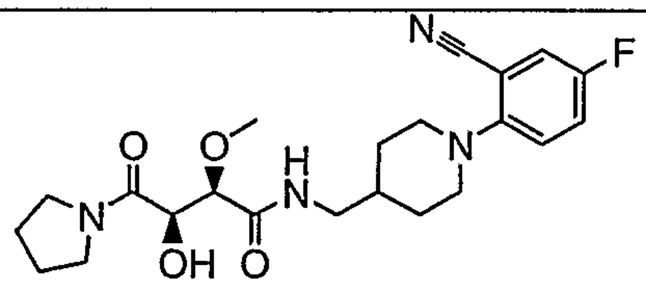
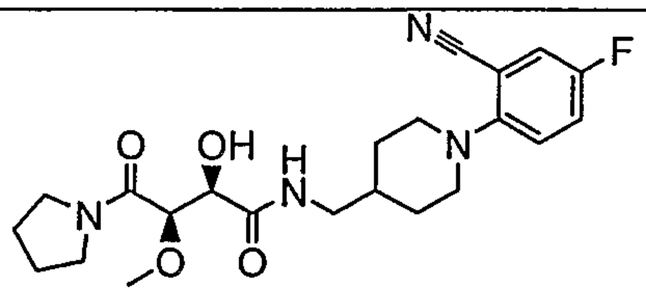
349		518.2	519.2

Example 7:

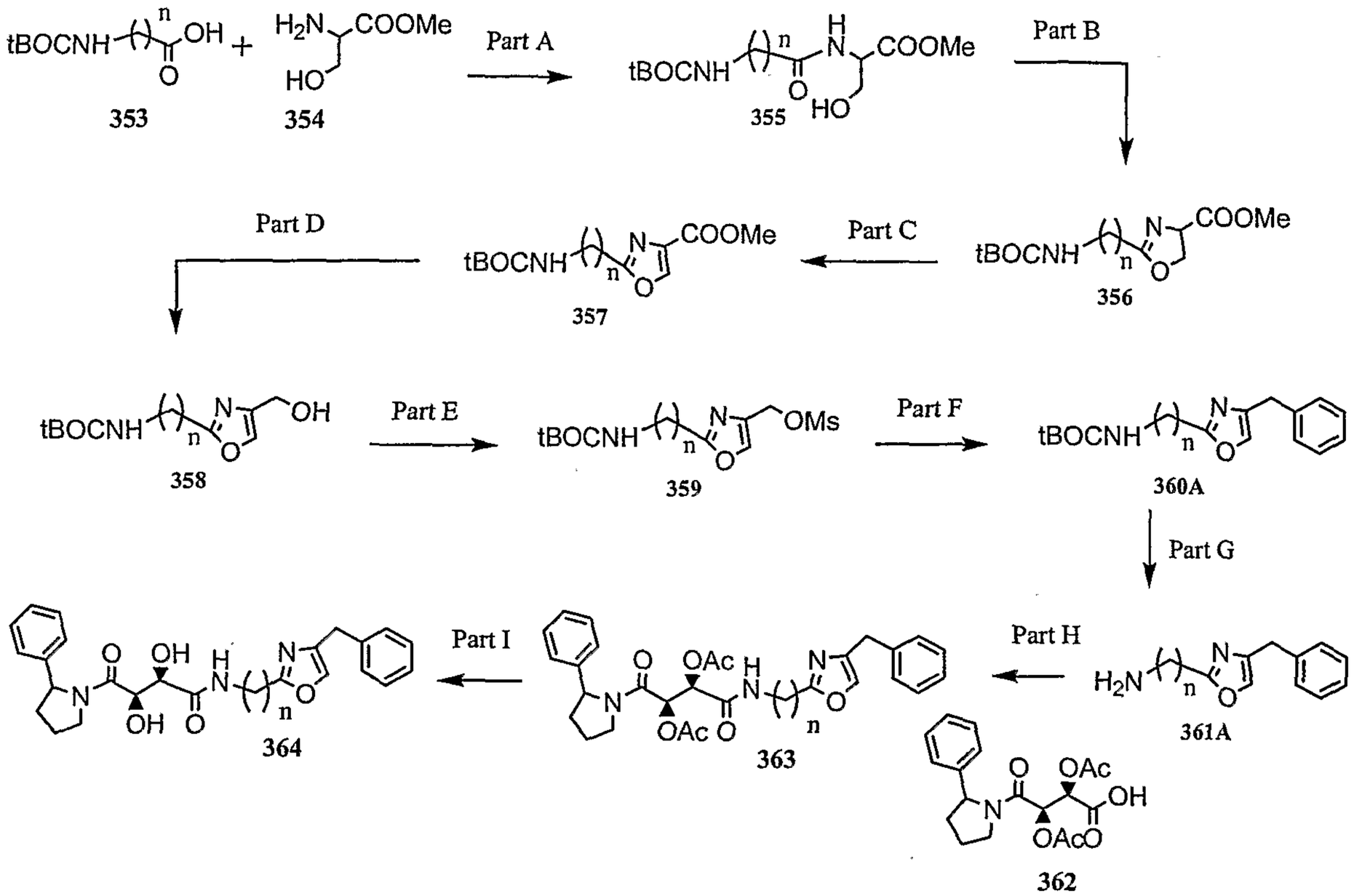


Part A:

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:

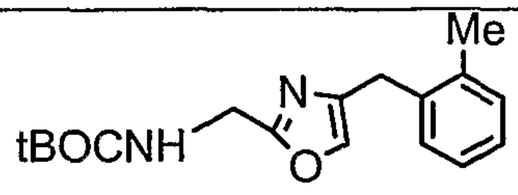
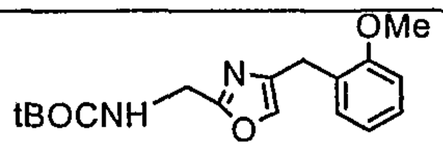
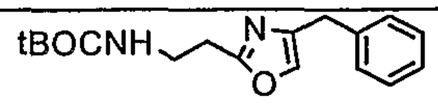
To compound **357** (4.25 g, 16.6 mmol) dissolved in Et_2O (100 mL) was added lithium borohydride (1.44 g, 66.3 mmol) and MeOH (2.13 g, 2.7 mL, 66.3 mmol). Refluxed for 3 h, cooled to room temperature, and concentrated. Added water (100 mL), extracted with CH_2Cl_2, dried combined organic extracts ($MgSO_4$), 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).

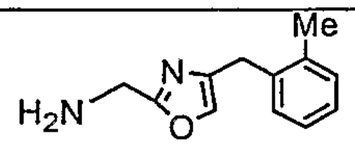
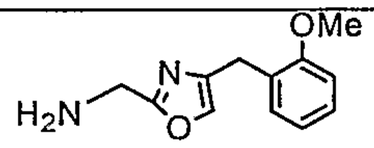
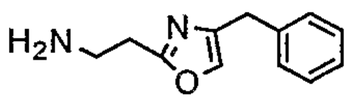
The following intermediates were prepared according to the above procedure:

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).

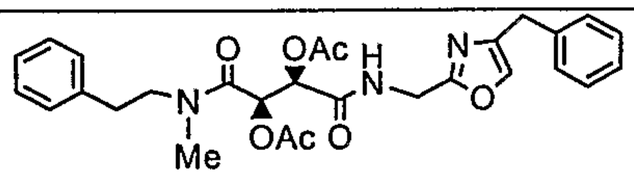
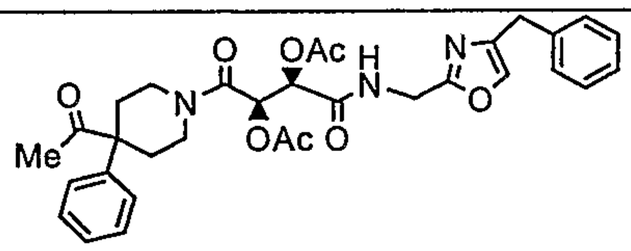
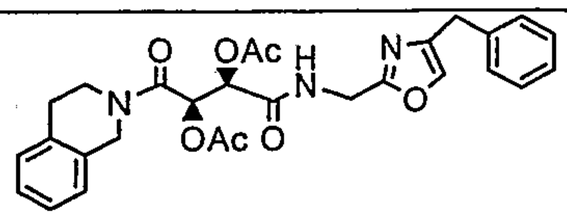
The following intermediates were prepared according to the above procedure:

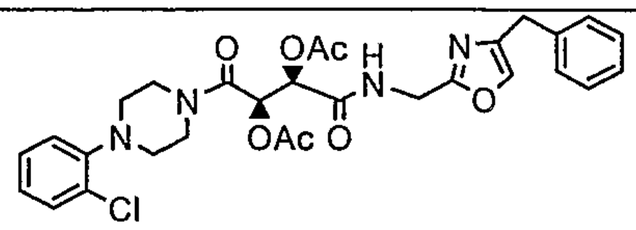
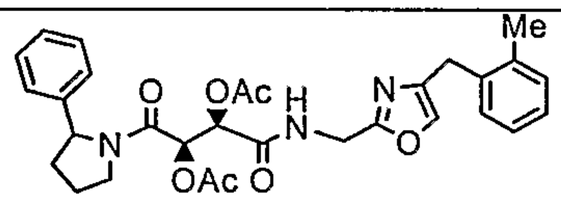
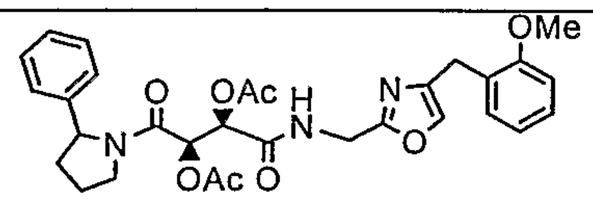
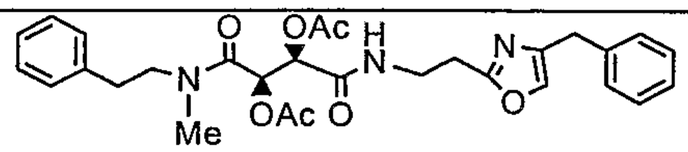
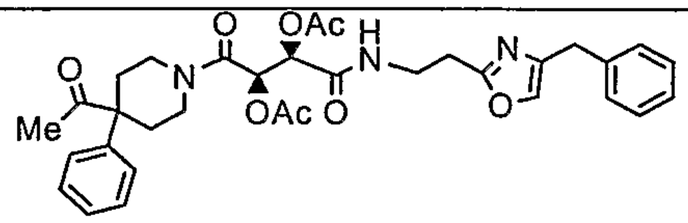
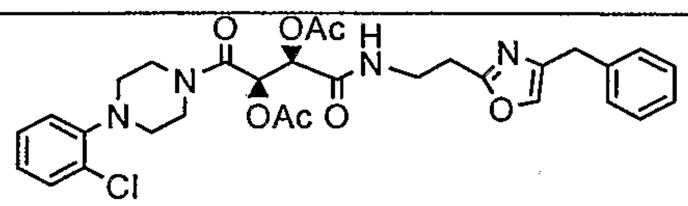
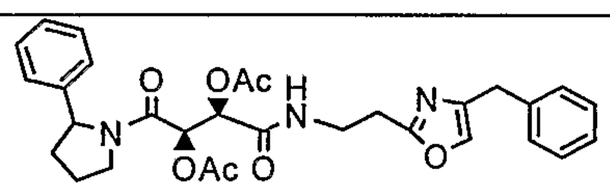
Compound #	Intermediate Structure	MS
361B		303 (M+H)
361C		219 (M+H)
361D		203 (M+H)

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:

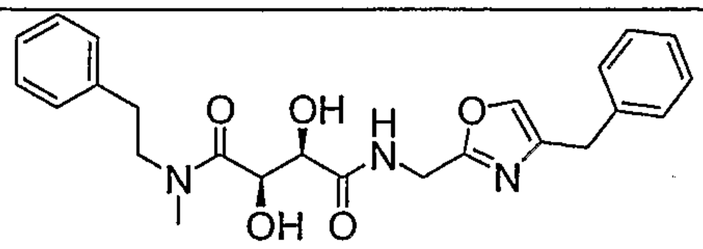
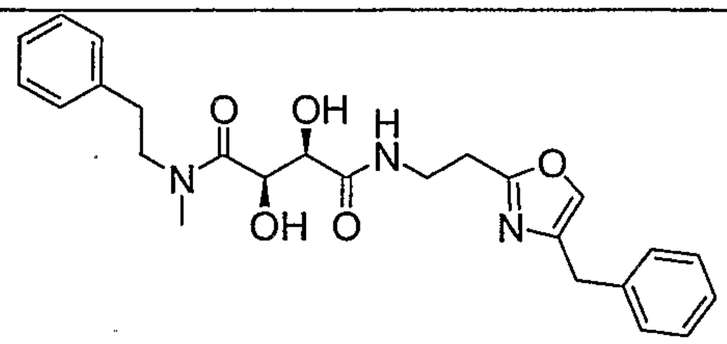
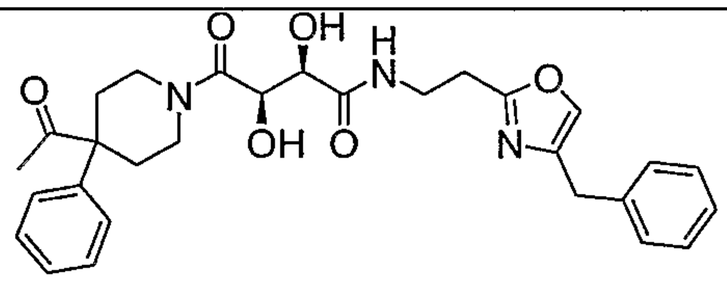
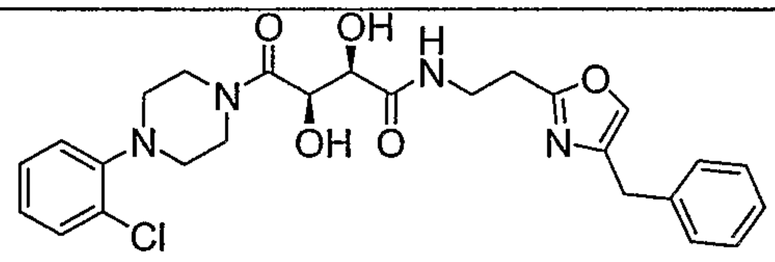
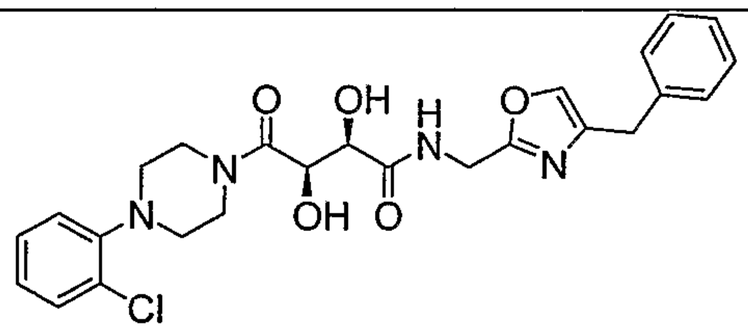
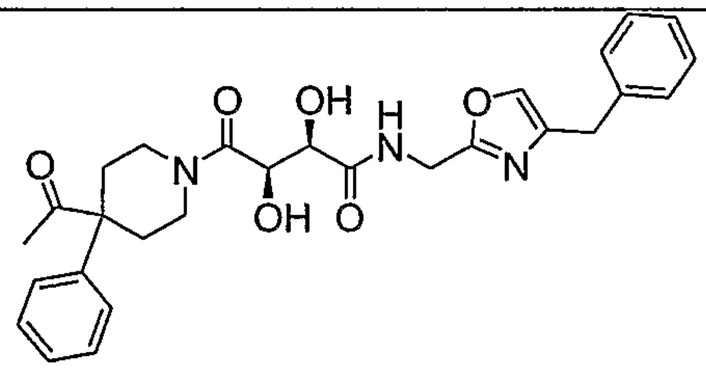
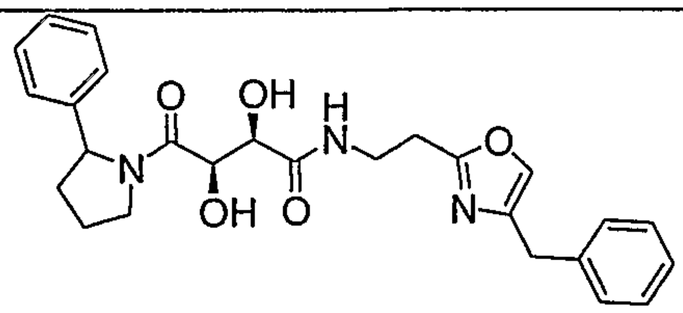
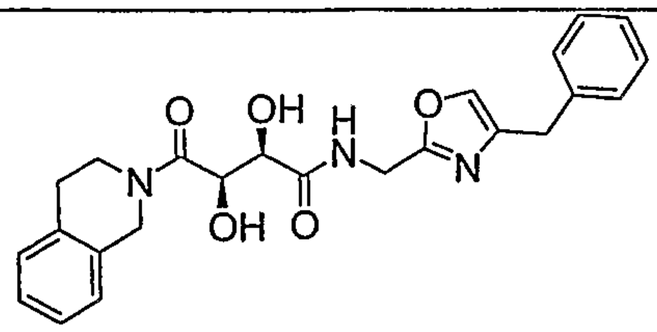
Compound #	Intermediate Structure	MS
365		522 (M+H)
366		590 (M+H)
367		520 (M+H)

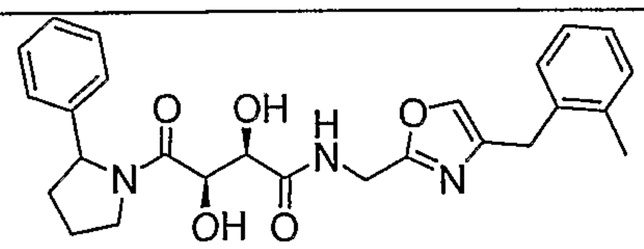
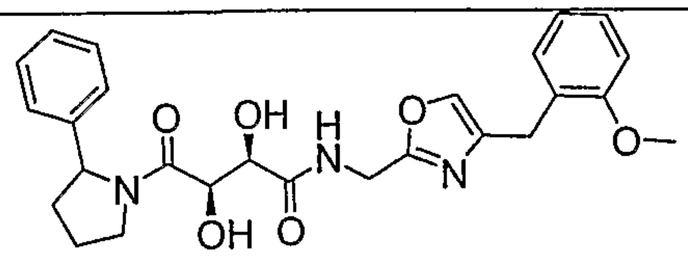
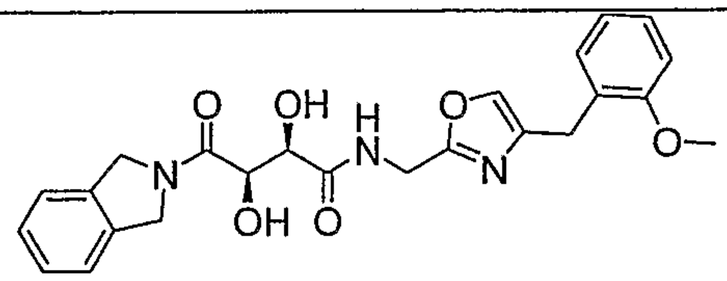
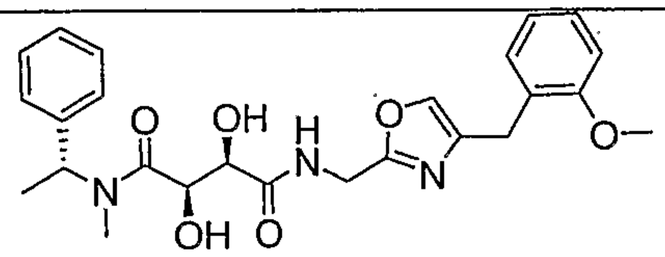
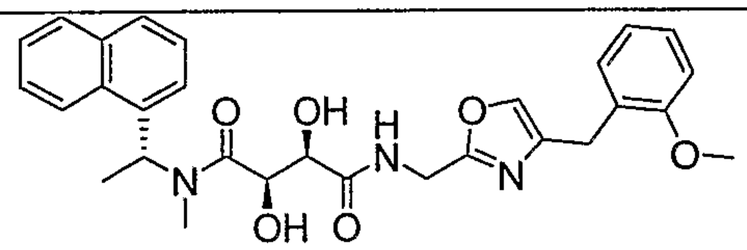
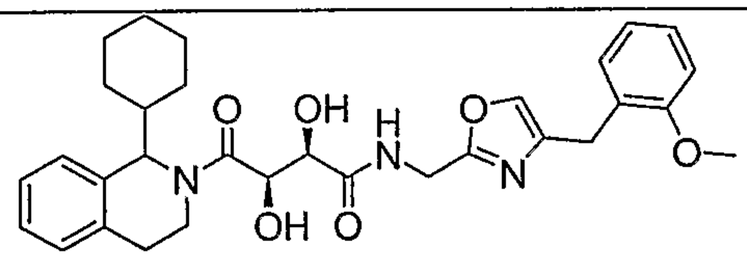
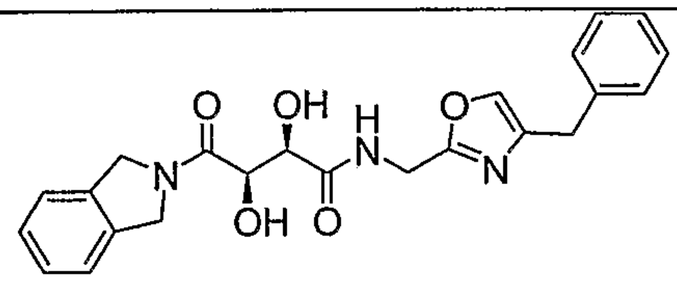
368		583 (M+H)
369		548 (M+H)
370		564 (M+H)
371		536 (M+H)
372		604 (M+H)
373		597 (M+H)
374		548 (M+H)

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:

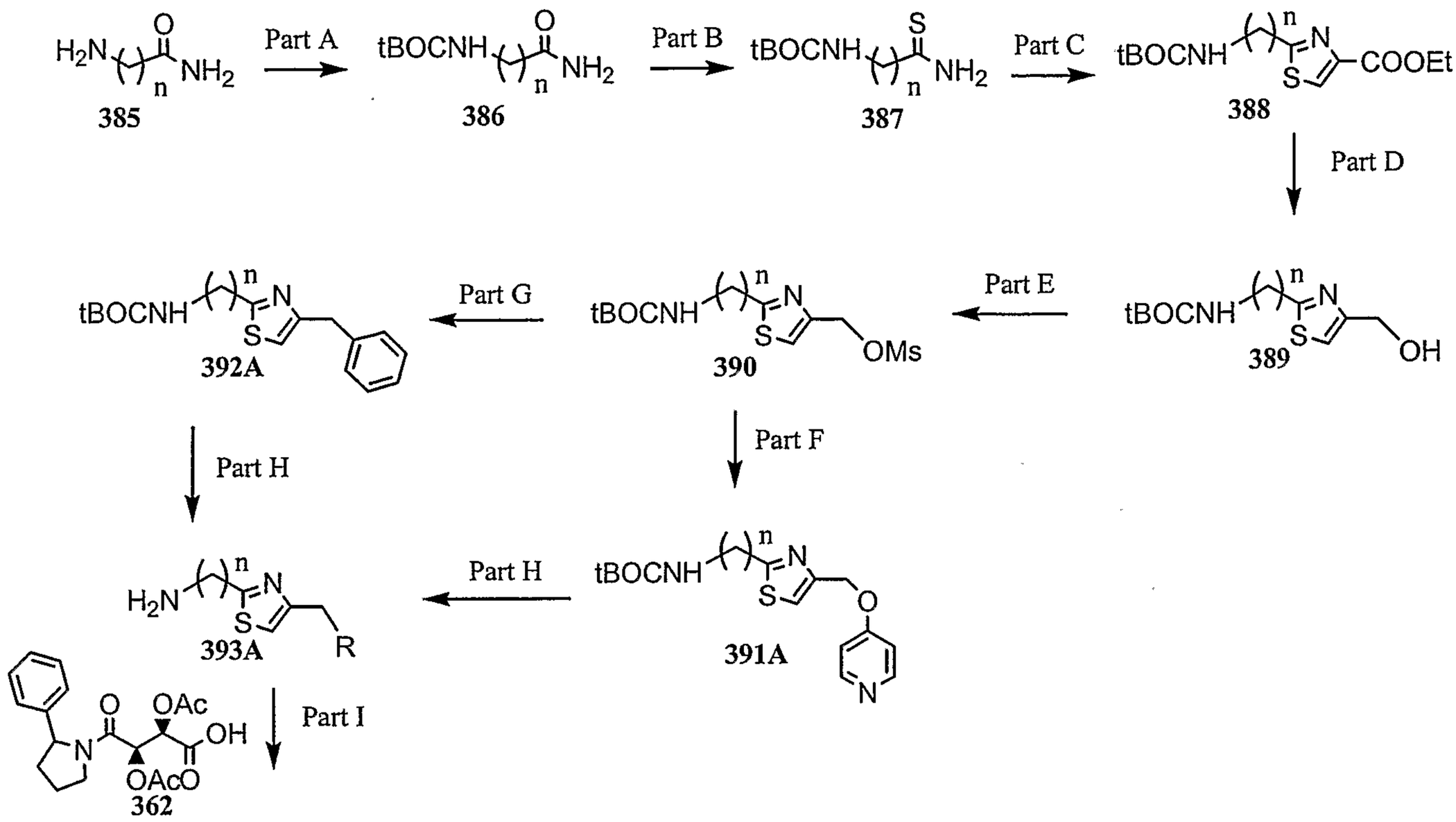
Compound #	Structure	Exact mass	MS m/z (M+H)
375		437.2	438.0
376		451.2	452.0
377		519.2	520.0
378		512.2	513.0
379		498.2	499.2
380		505.2	506.3
381		463.2	464.2
382		435.2	436.2

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)

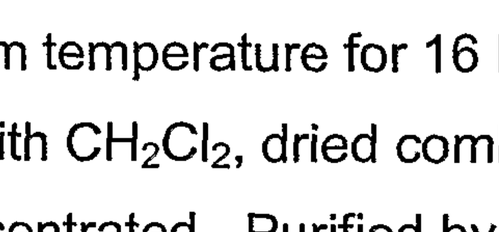
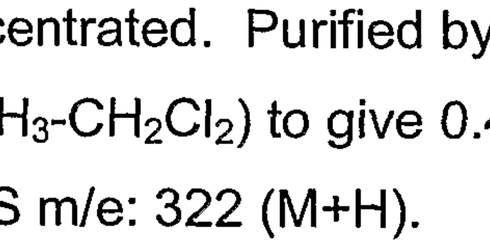
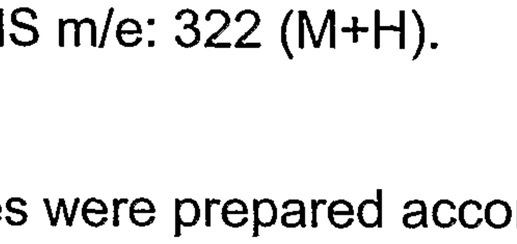
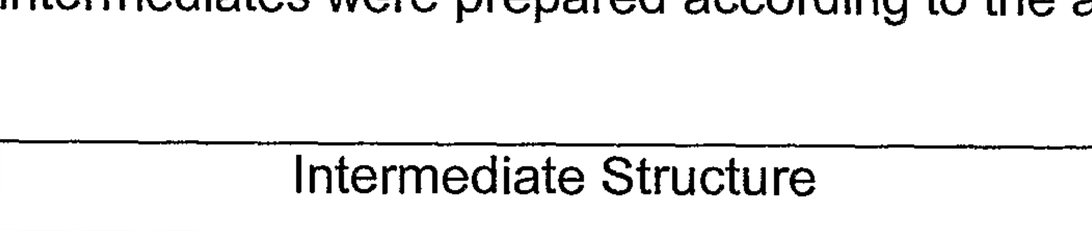
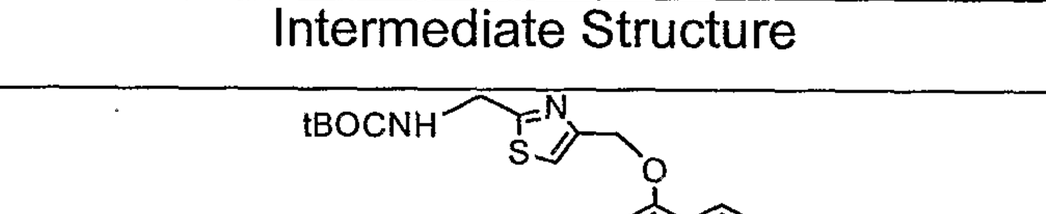
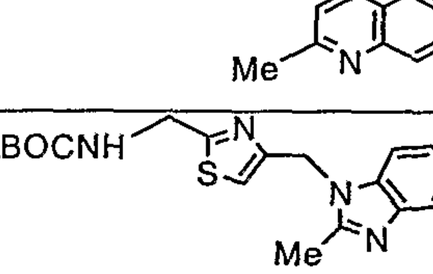
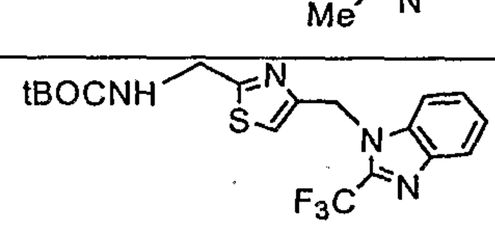
Part E:
To compound **389** (5.30 g, 21.7 mmol) dissolved in CH_2Cl_2 (130 mL) and cooled to -25 °C was added triethylamine (4.40 g, 6.0 mL, 43.4 mmol) then mesyl chloride (3.00 g, 2.0 mL, 26.0 mmol) dropwise. Warmed to 0 °C slowly over 60 mins. Added water (100 mL), extracted with CH_2Cl_2, dried combined

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).

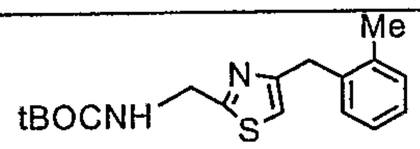
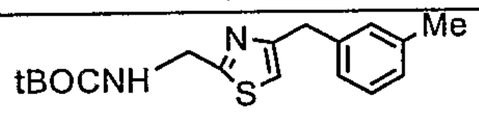
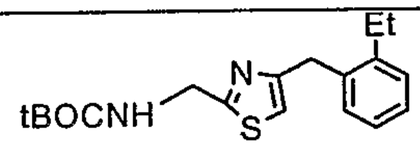
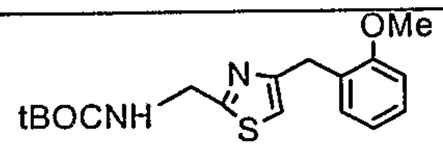
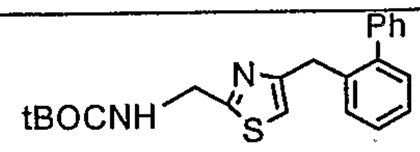
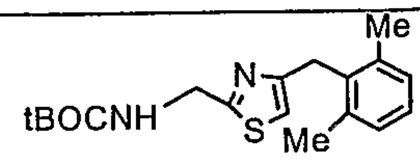
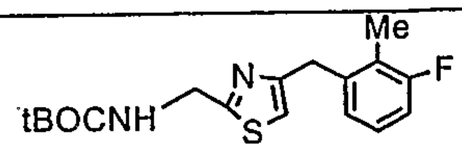
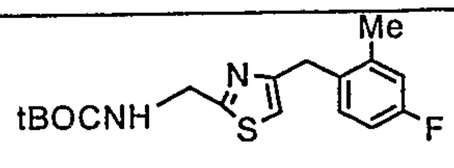
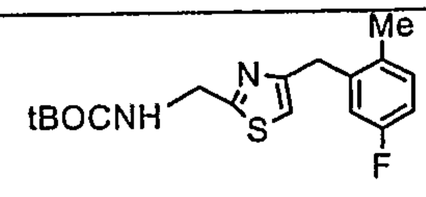
The following intermediates were prepared according to the above procedure:

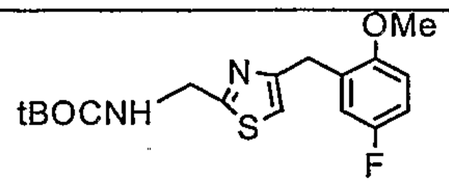
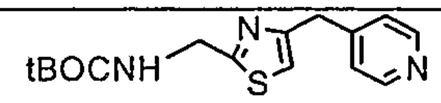
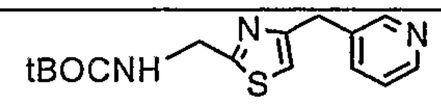
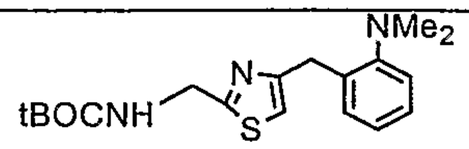
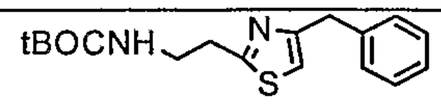
Compound #	Intermediate Structure	MS
391B		386 (M+H)
391C		359 (M+H)
391D		413 (M+H)
391E	 mixture	373 (M+H)
391F	 mixture	393 (M+H)
391G		336 (M+H)
391H		400 (M+H)

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:

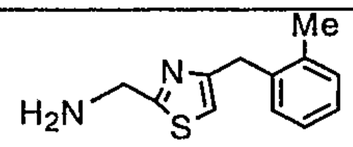
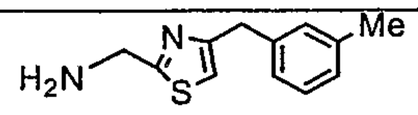
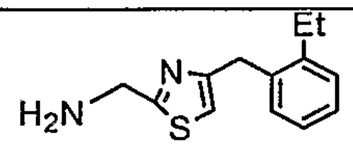
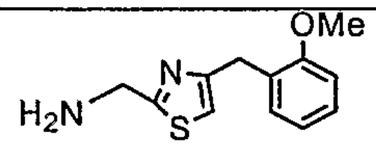
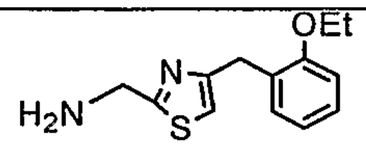
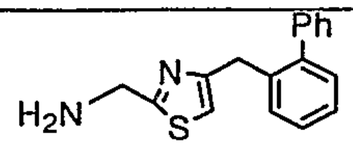
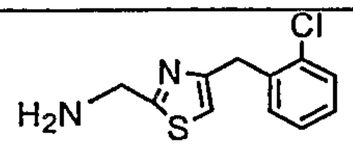
Compound #	Intermediate Structure	MS
392B		319 (M+H)
392C		319 (M+H)
392D		333 (M+H)
392E		335 (M+H)
392F		381 (M+H)
392G		333 (M+H)
392H		337 (M+H)
392I		337 (M+H)
392J		337 (M+H)

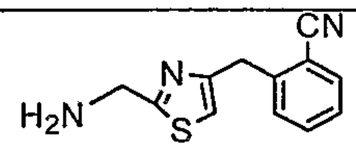
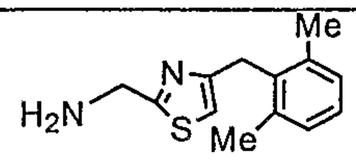
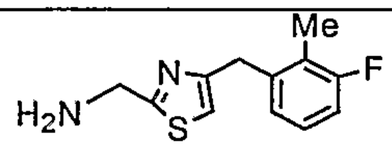
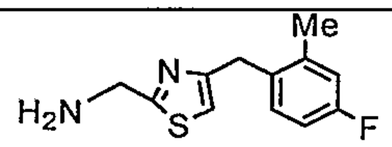
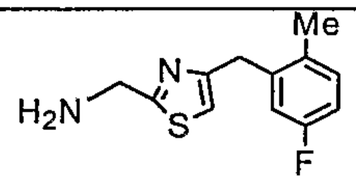
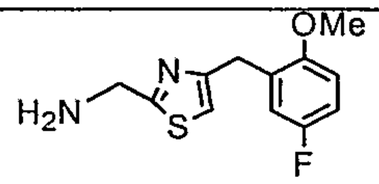
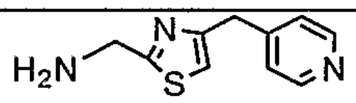
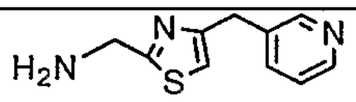
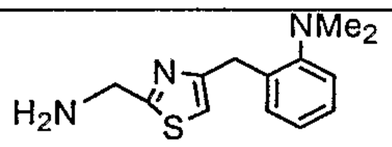
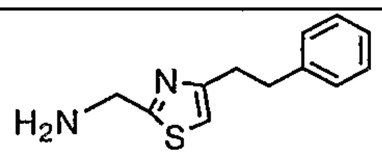
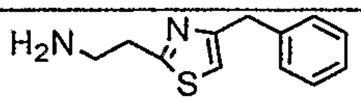
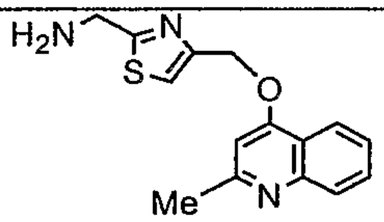
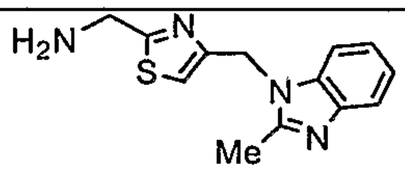
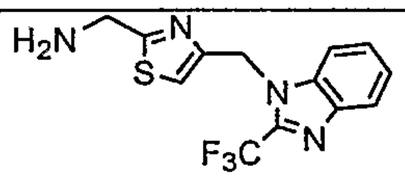
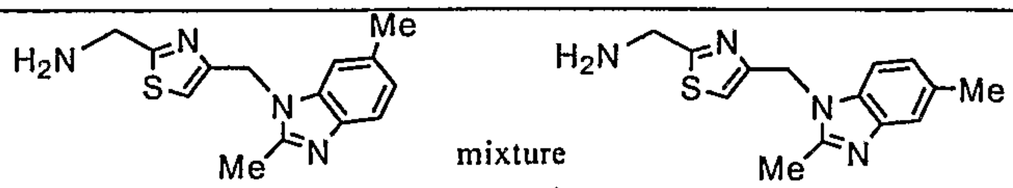
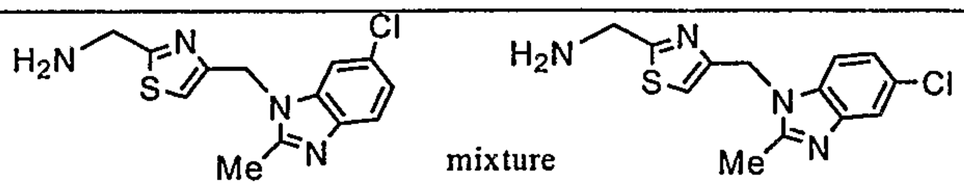
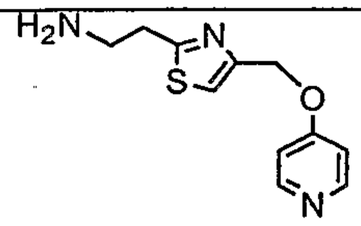
392K		353 (M+H)
392L		306 (M+H)
392M		306 (M+H)
392N		348 (M+H)
392O		319 (M+H)

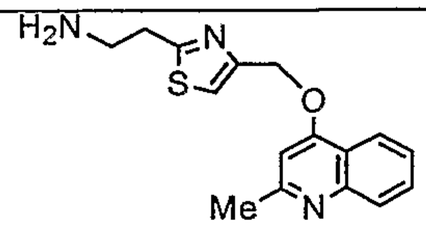
Part H:

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)

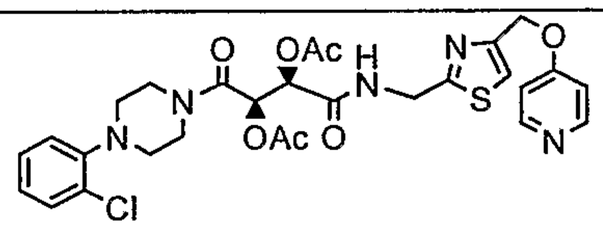
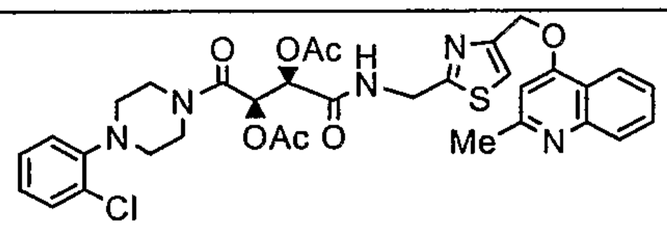
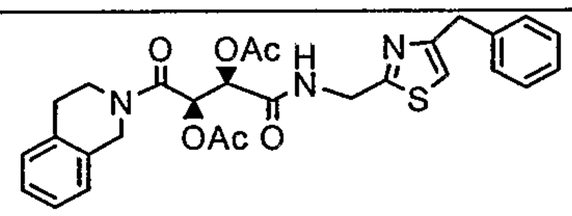
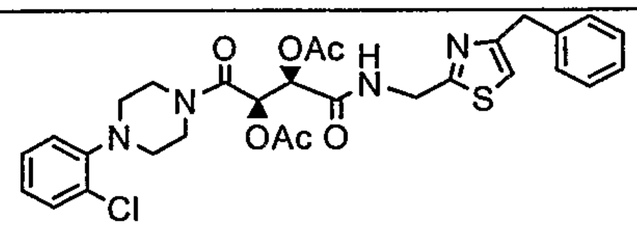
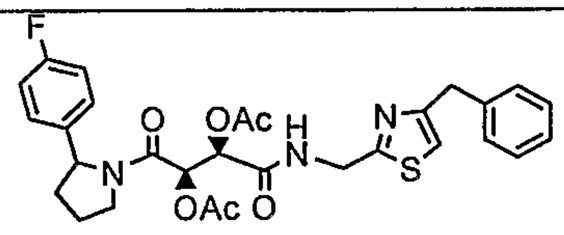
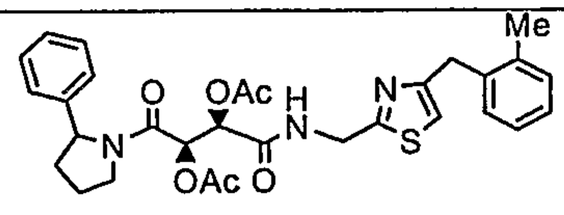
393I		230 (M+H)
393J		233 (M+H)
393K		237 (M+H)
393L		237 (M+H)
393M		237 (M+H)
393N		253 (M+H)
393O		206 (M+H)
393P		206 (M+H)
393Q		248 (M+H)
393R		219 (M+H)
393S		219 (M+H)
393T		286 (M+H)
393U		259 (M+H)
393V		313 (M+H)
393W	 mixture	273 (M+H)
393X	 mixture	293 (M+H)
393Y		236 (M+H)

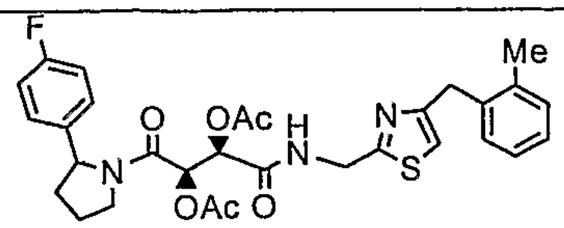
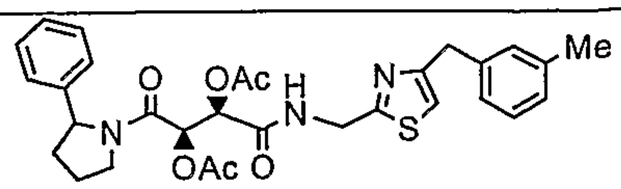
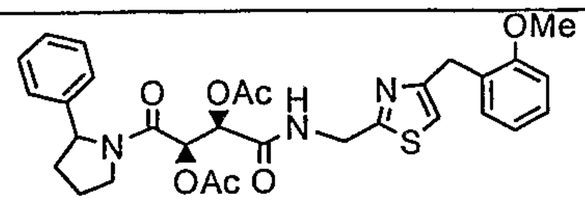
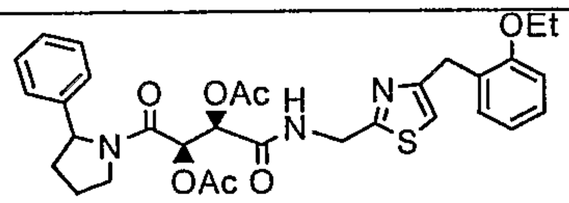
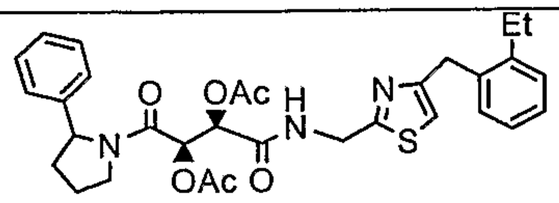
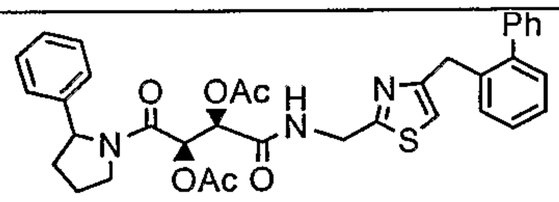
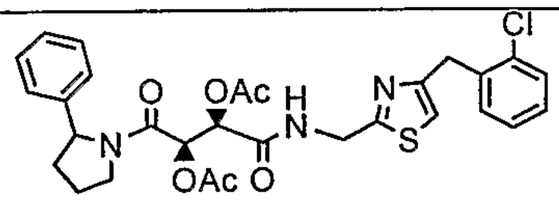
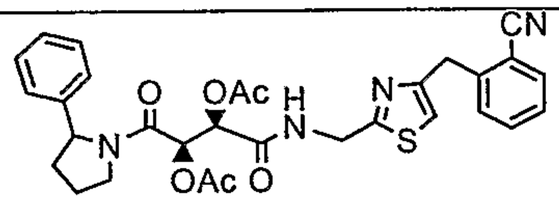
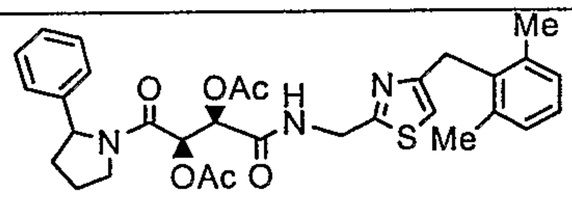
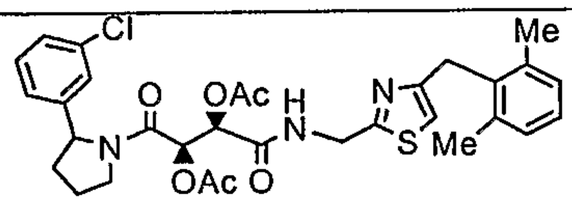
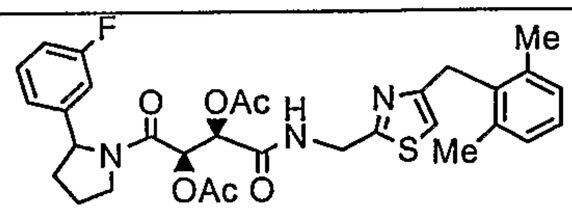
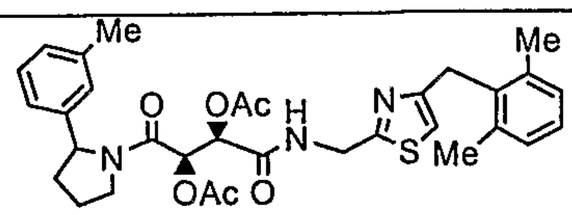
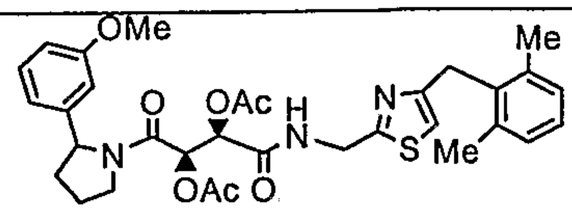
393Z		300 (M+H)

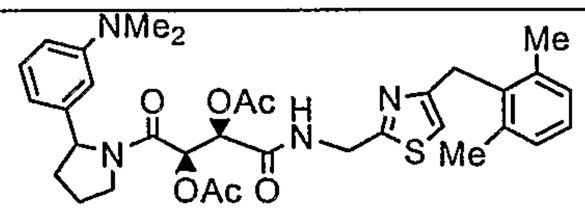
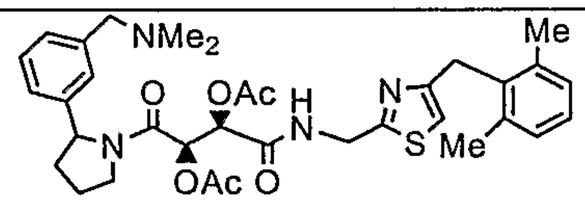
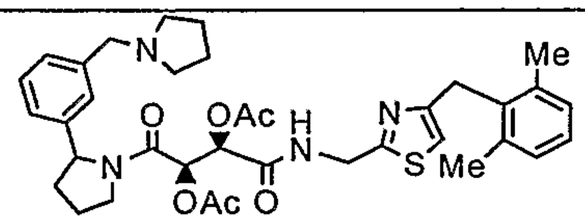
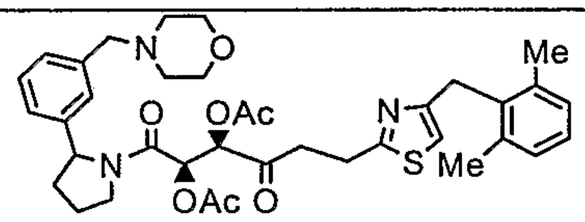
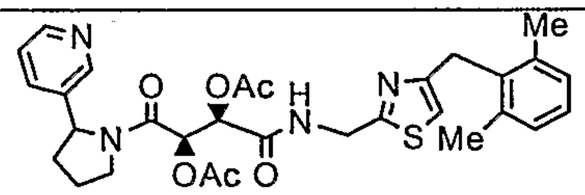
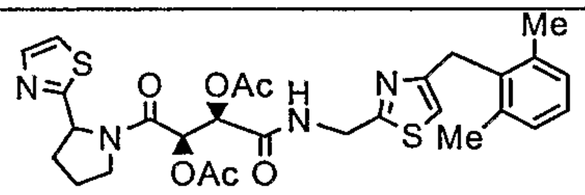
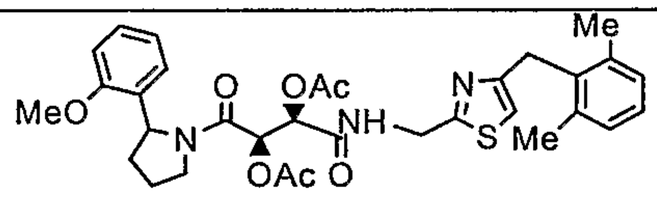
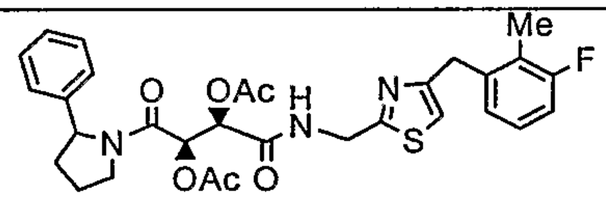
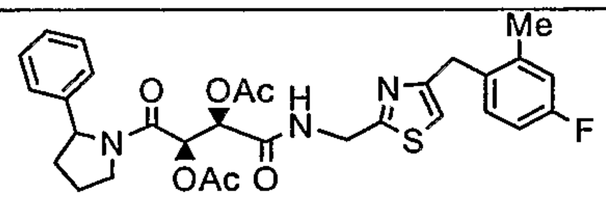
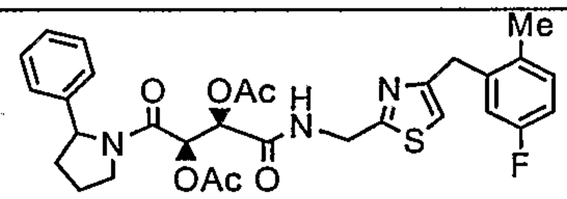
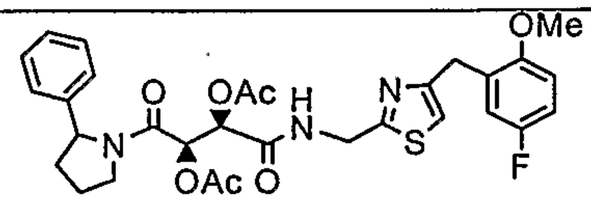
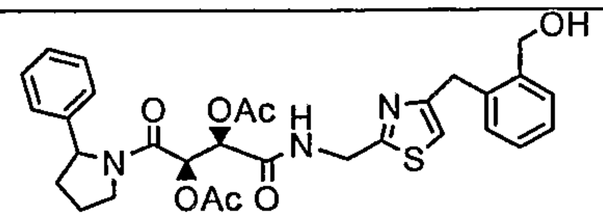
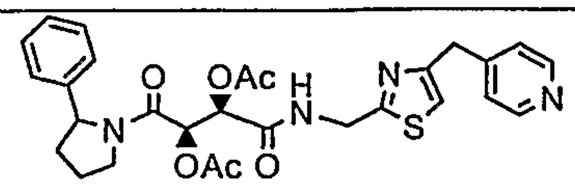
Part I:

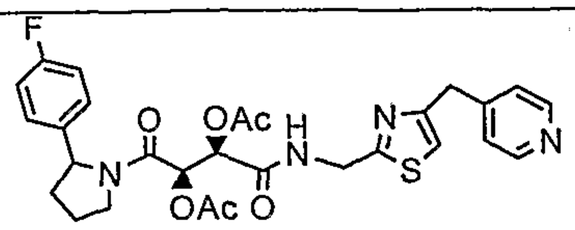
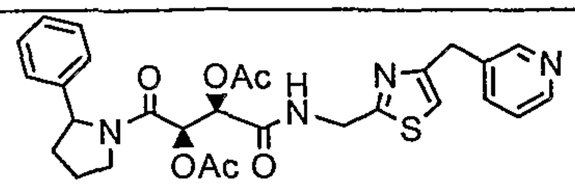
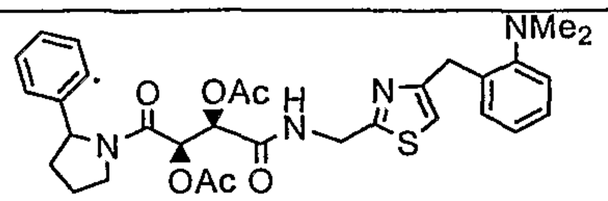
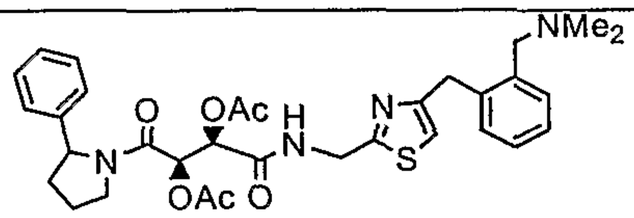
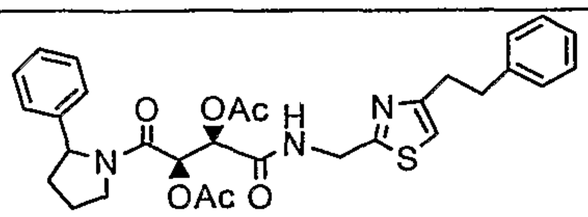
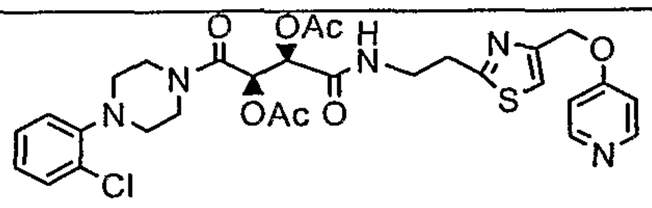
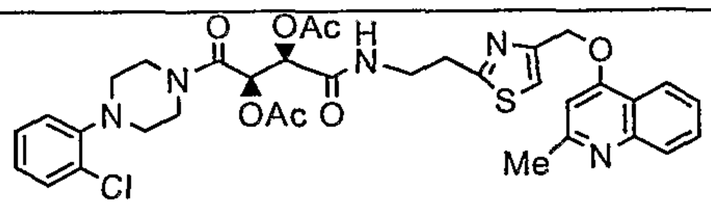
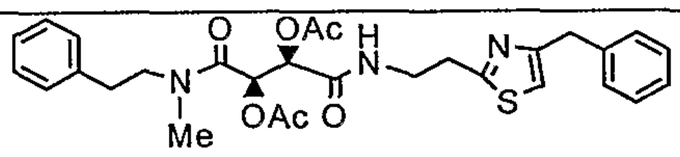
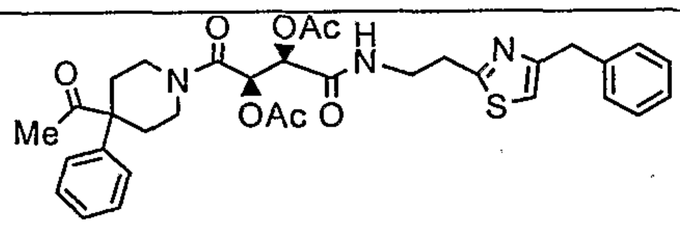
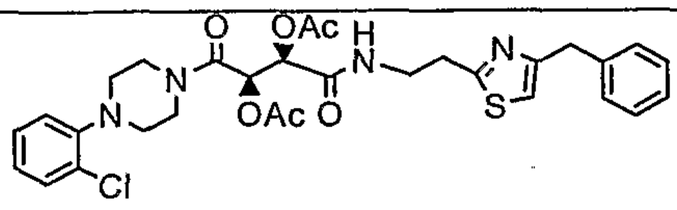
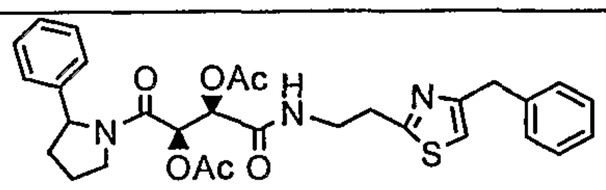
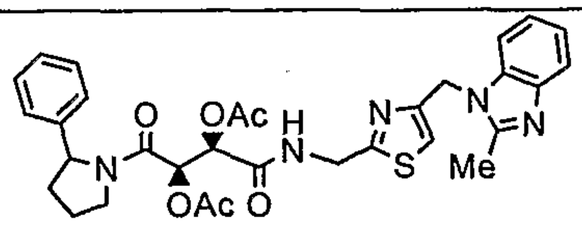
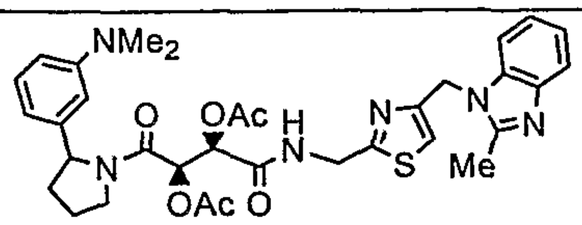
Combined compound **393A** (100 mg, 0.416 mmol), compound **362** (181 mg, 0.499 mmol), HATU (316 mg, 0.832 mmol), and triethylamine (126 mg, 0.17 mL, 1.25 mmol) in dry DMF (6 mL). Stirred at room temperature for 16 h. Concentrated, added 0.5 N NaOH (15 mL), extracted with CH_2Cl_2, dried combined organic 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).

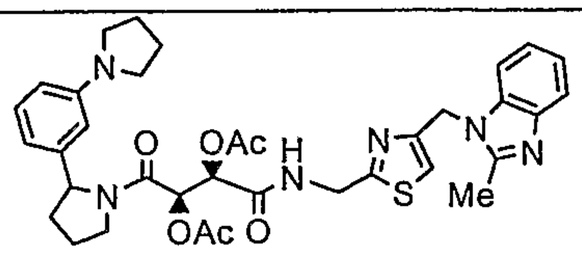
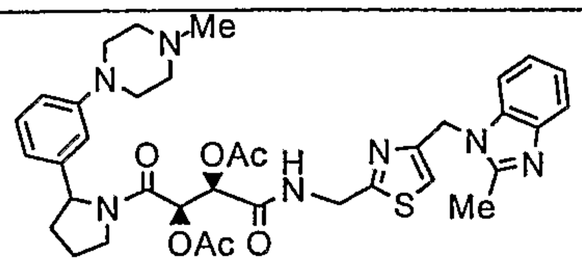
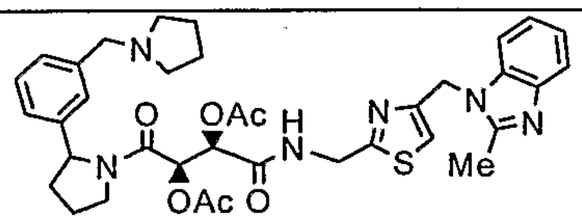
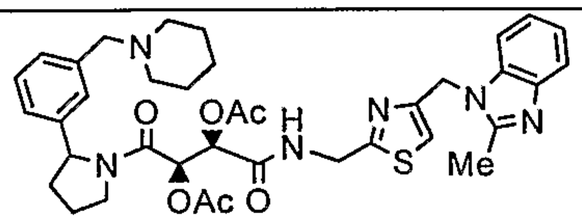
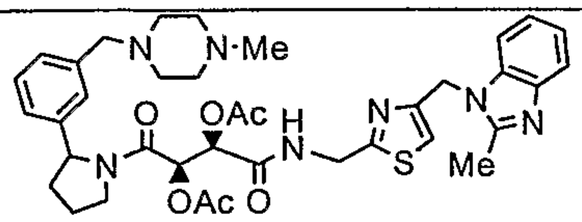
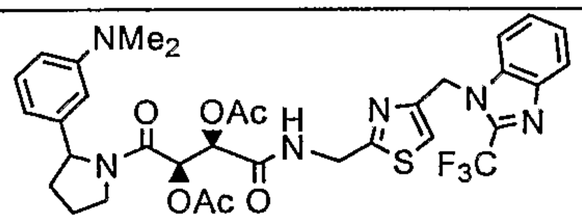
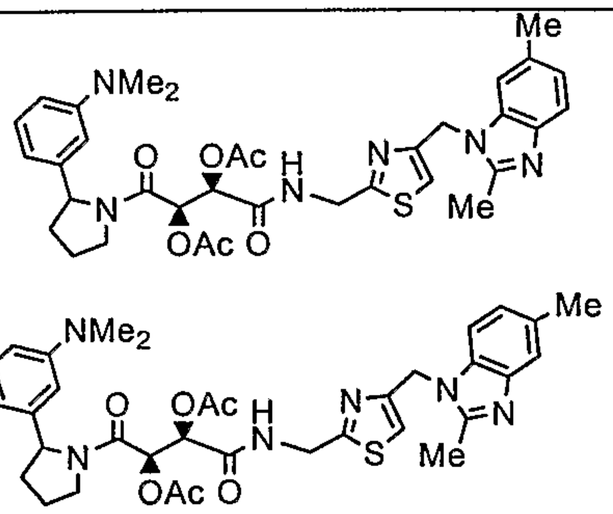
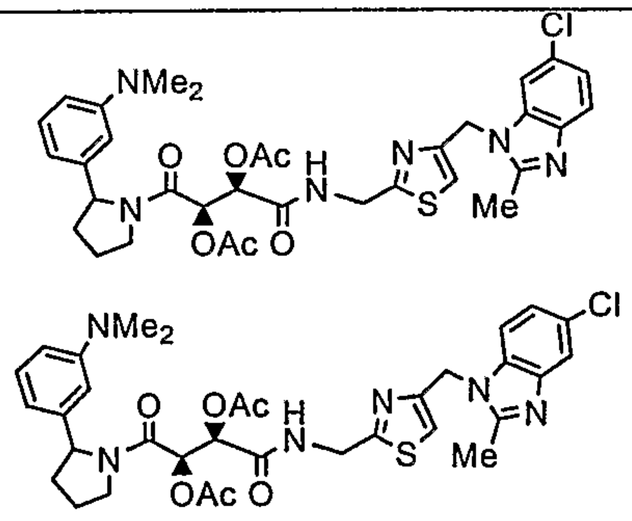
The following intermediates were prepared according to the above procedure:

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)

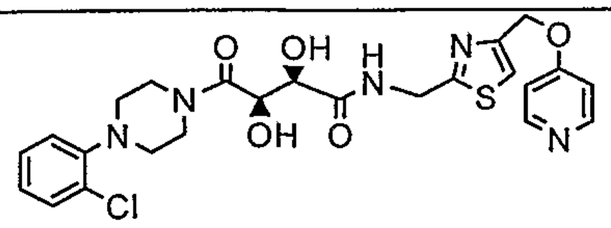
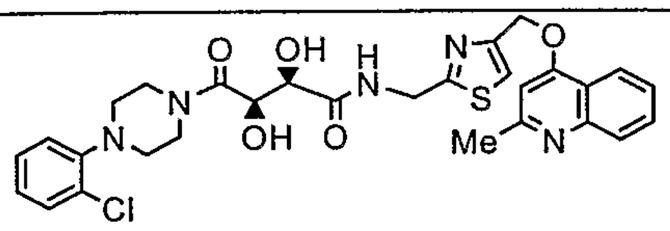
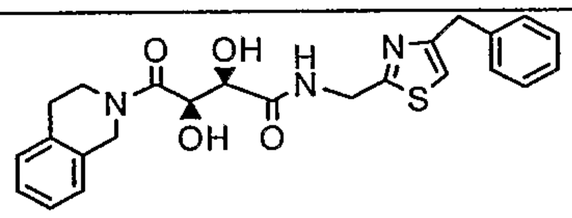
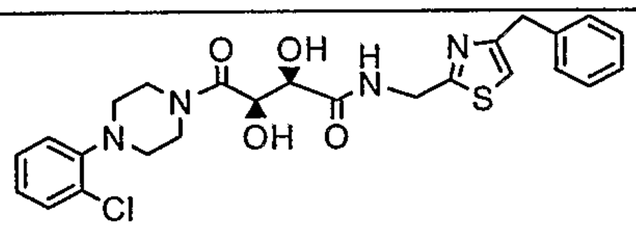
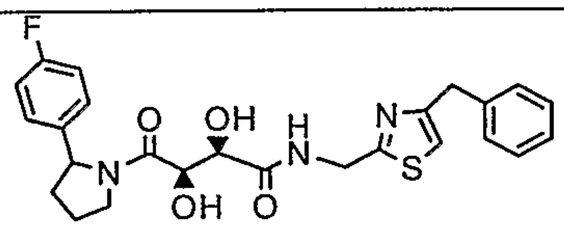
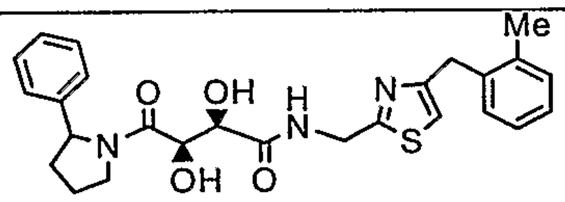
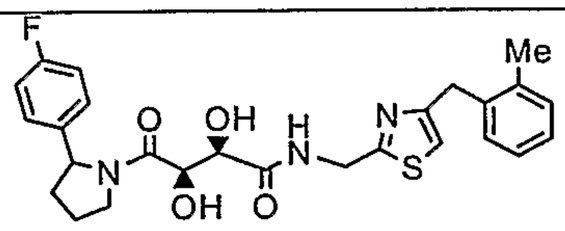
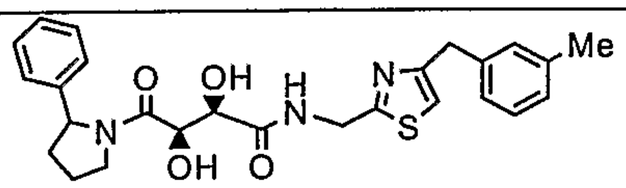
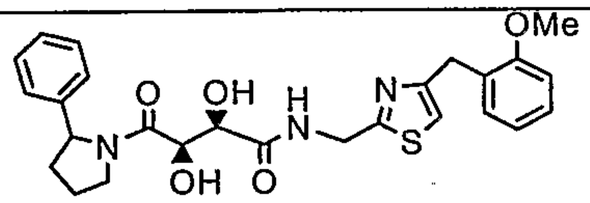
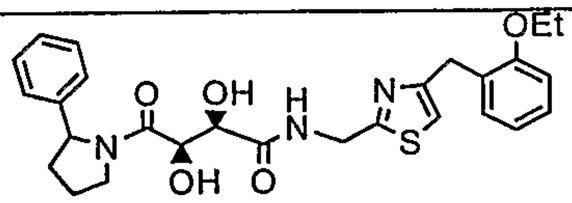
394UU		673 (M+H)
394VV		702 (M+H)
394WW		687 (M+H)
394XX		701 (M+H)
394YY		716 (M+H)
394ZZ		701 (M+H)
394AAA		661 (M+H)
394BBB		682 (M+H)

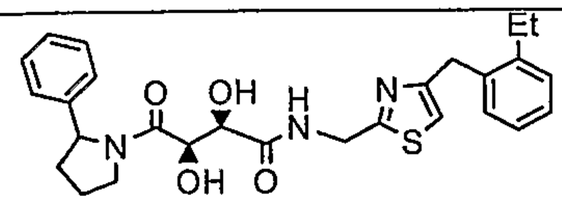
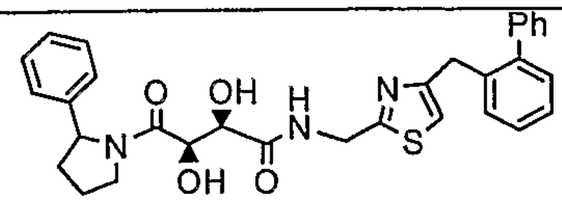
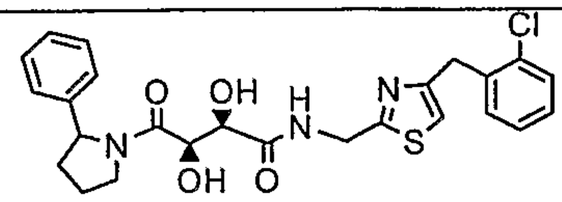
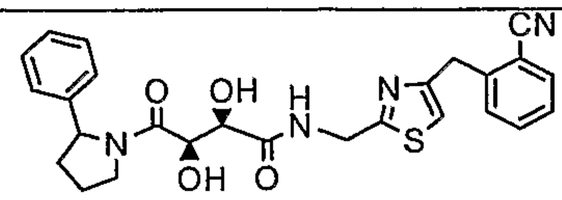
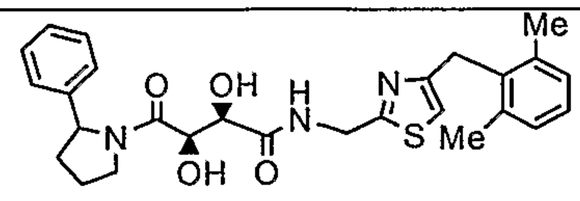
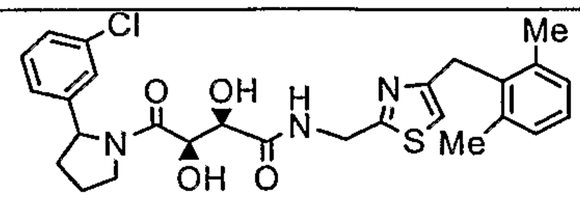
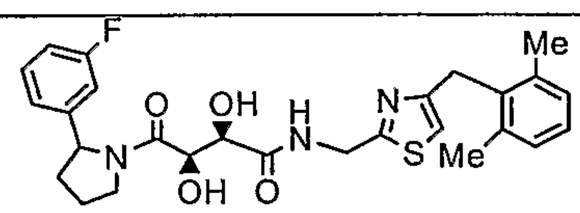
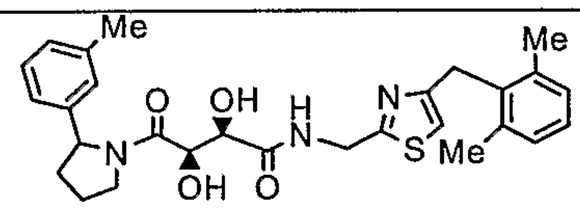
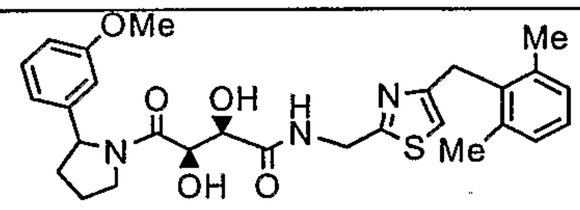
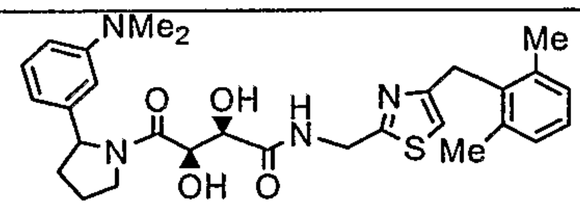
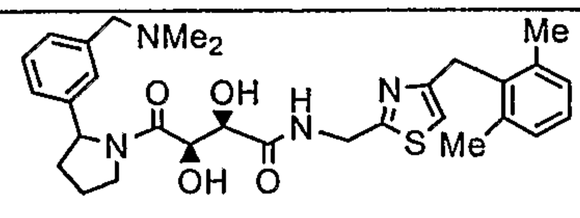
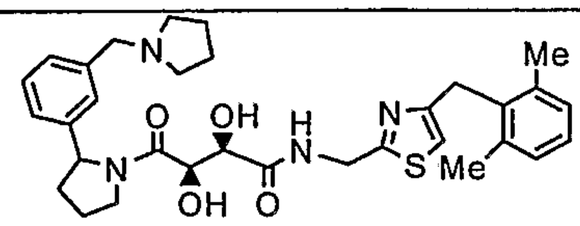
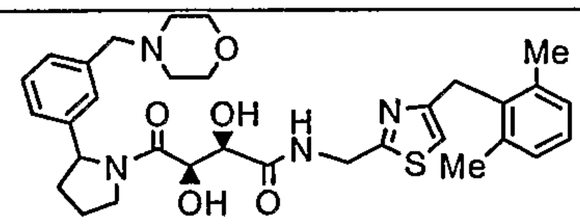
Part J:

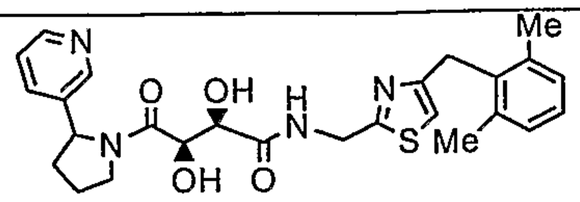
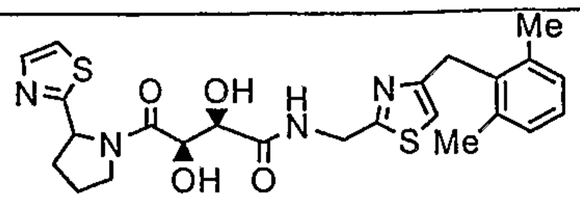
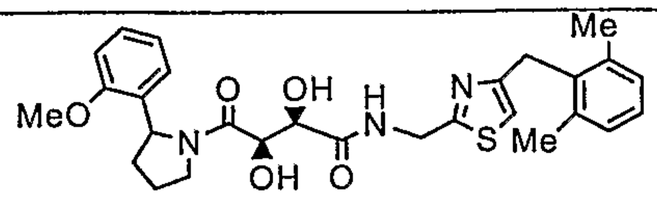
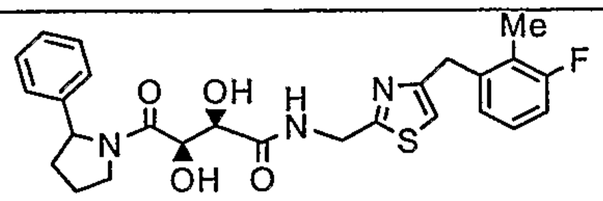
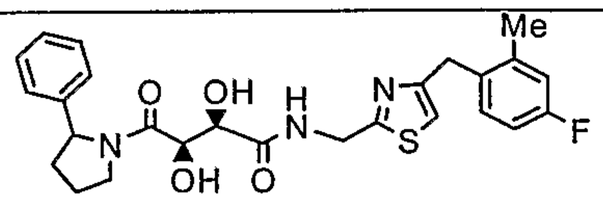
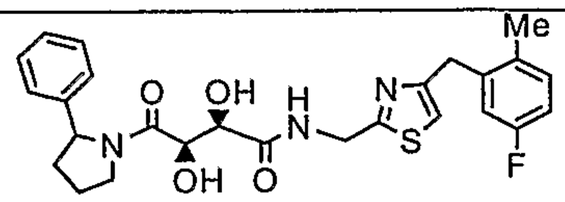
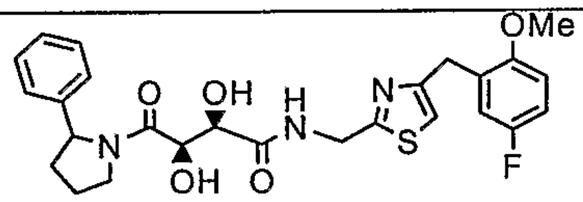
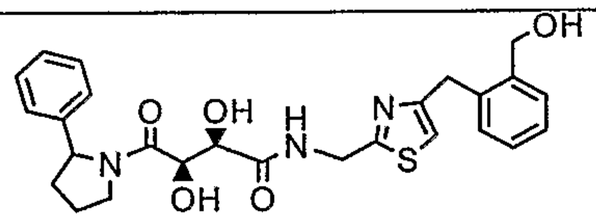
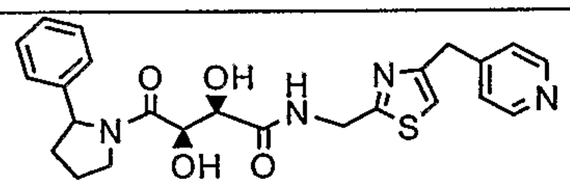
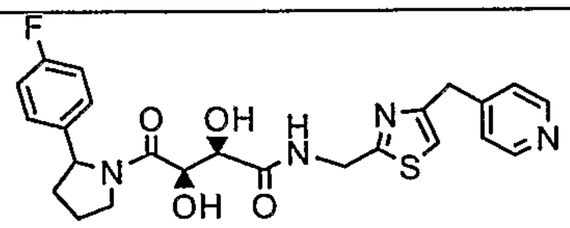
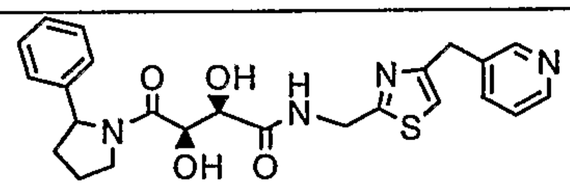
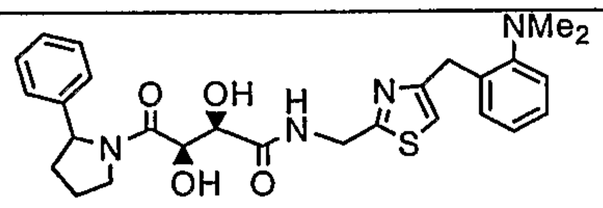
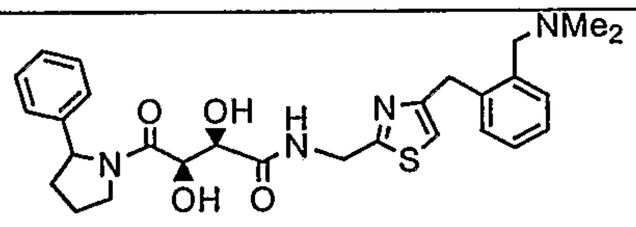
To compound **394A** (0.12 g, 0.218 mmol) dissolved in MeOH (6 mL) was added 0.5 M NaOMe in MeOH (0.044 mL, 0.0218 mmol). Stirred at room temperature for 60 mins. Added 4 N HCl in dioxane (0.055 mL, 0.218 mmol)

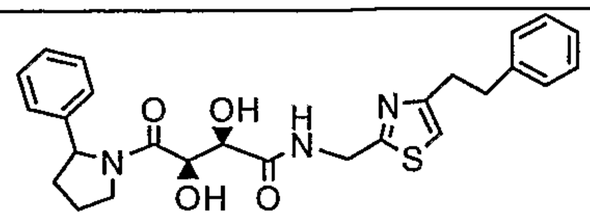
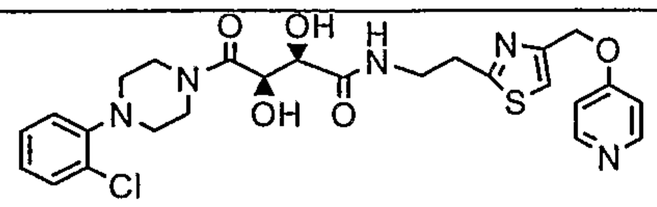
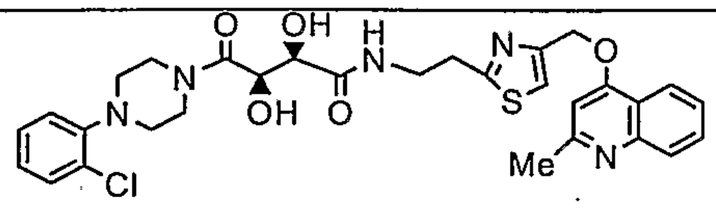
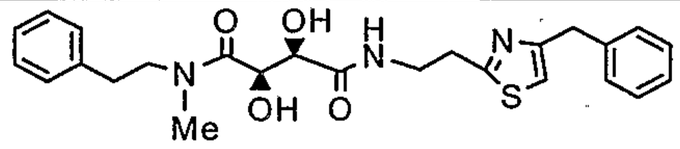
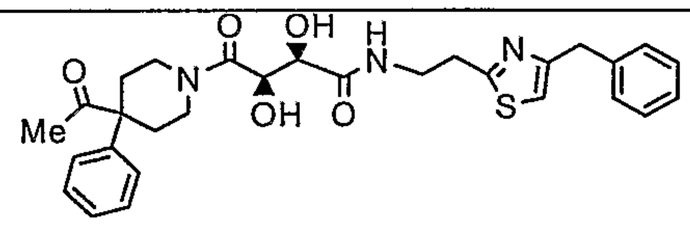
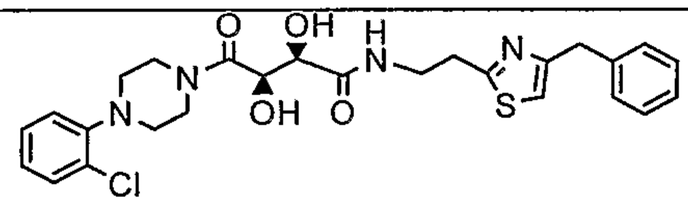
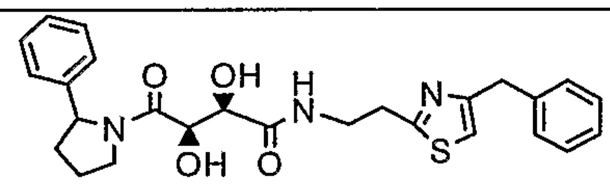
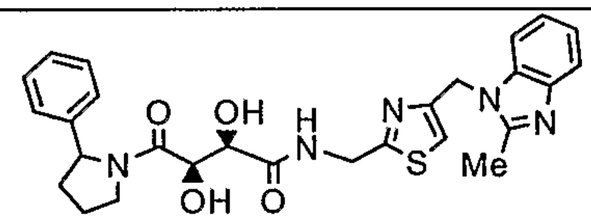
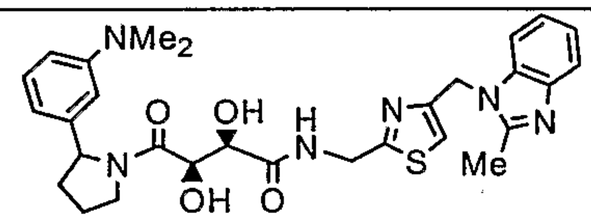
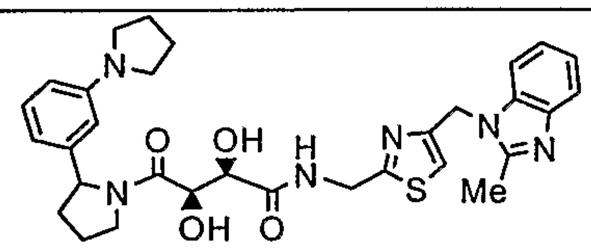
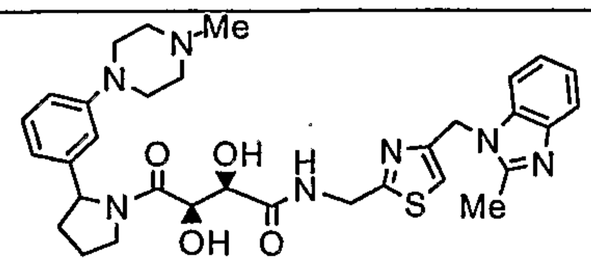
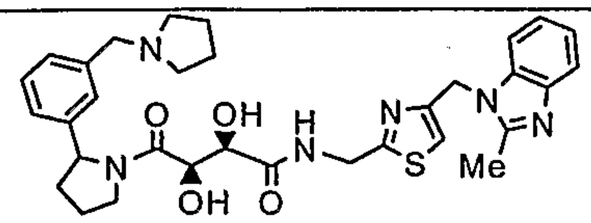
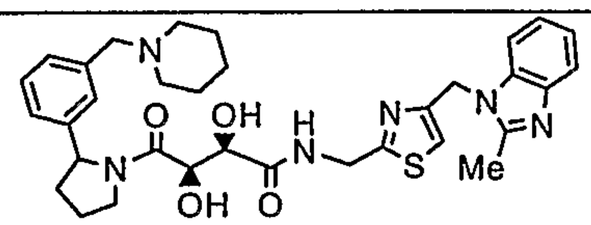
and concentrated to give 0.10 g (100%) of the product **395** as a light yellow foam. MS m/e: 466 (M+H).

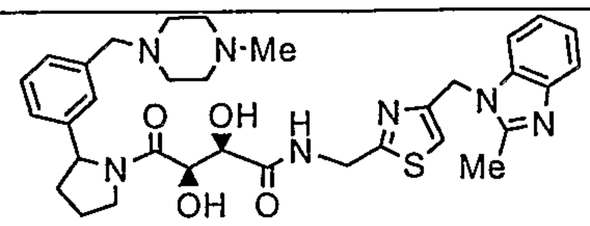
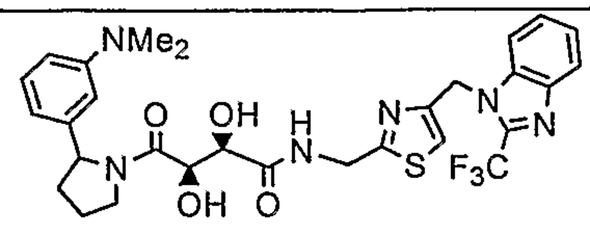
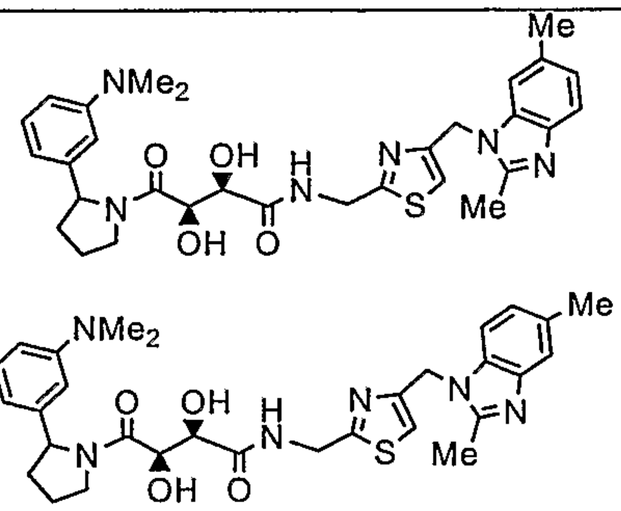
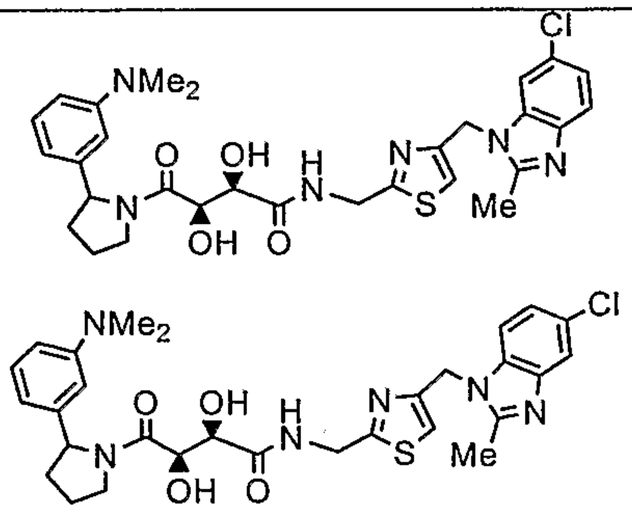
The following compounds were prepared according to the above procedure:

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)

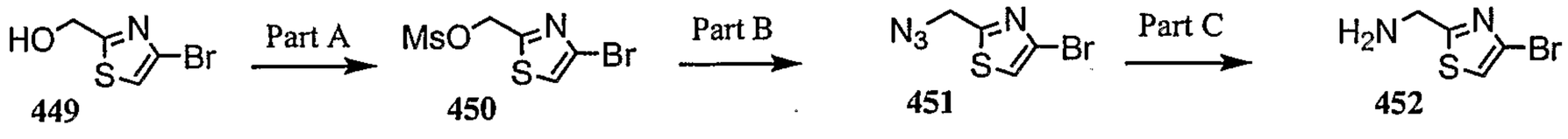
419		495 (M+H)
420		501 (M+H)
421		524 (M+H)
422		498 (M+H)
423		498 (M+H)
424		498 (M+H)
425		514 (M+H)
426		496 (M+H)
427		467 (M+H)
428		485 (M+H)
429		467 (M+H)
430		509 (M+H)
431		523 (M+H)

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



449 450 451 452 453 454

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).

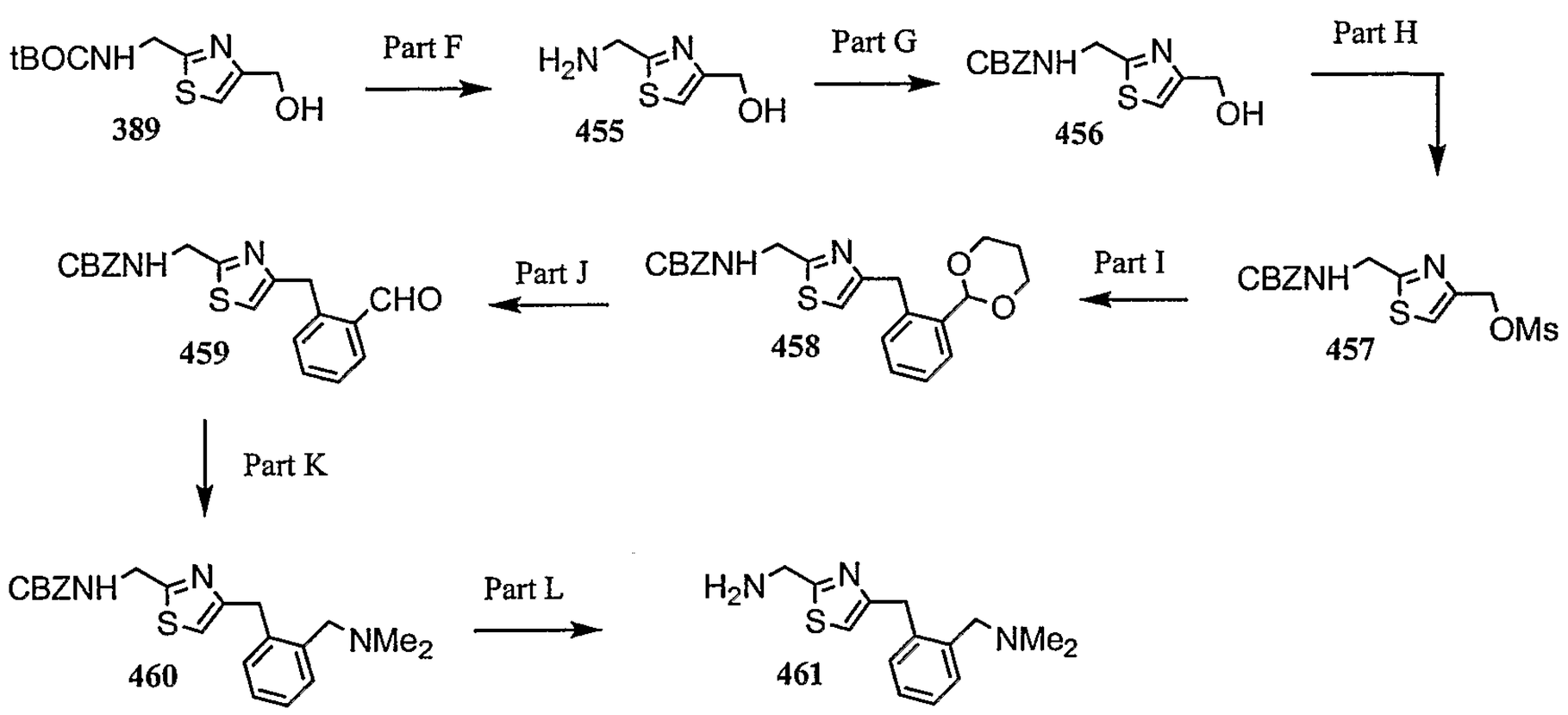
Part D:

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).

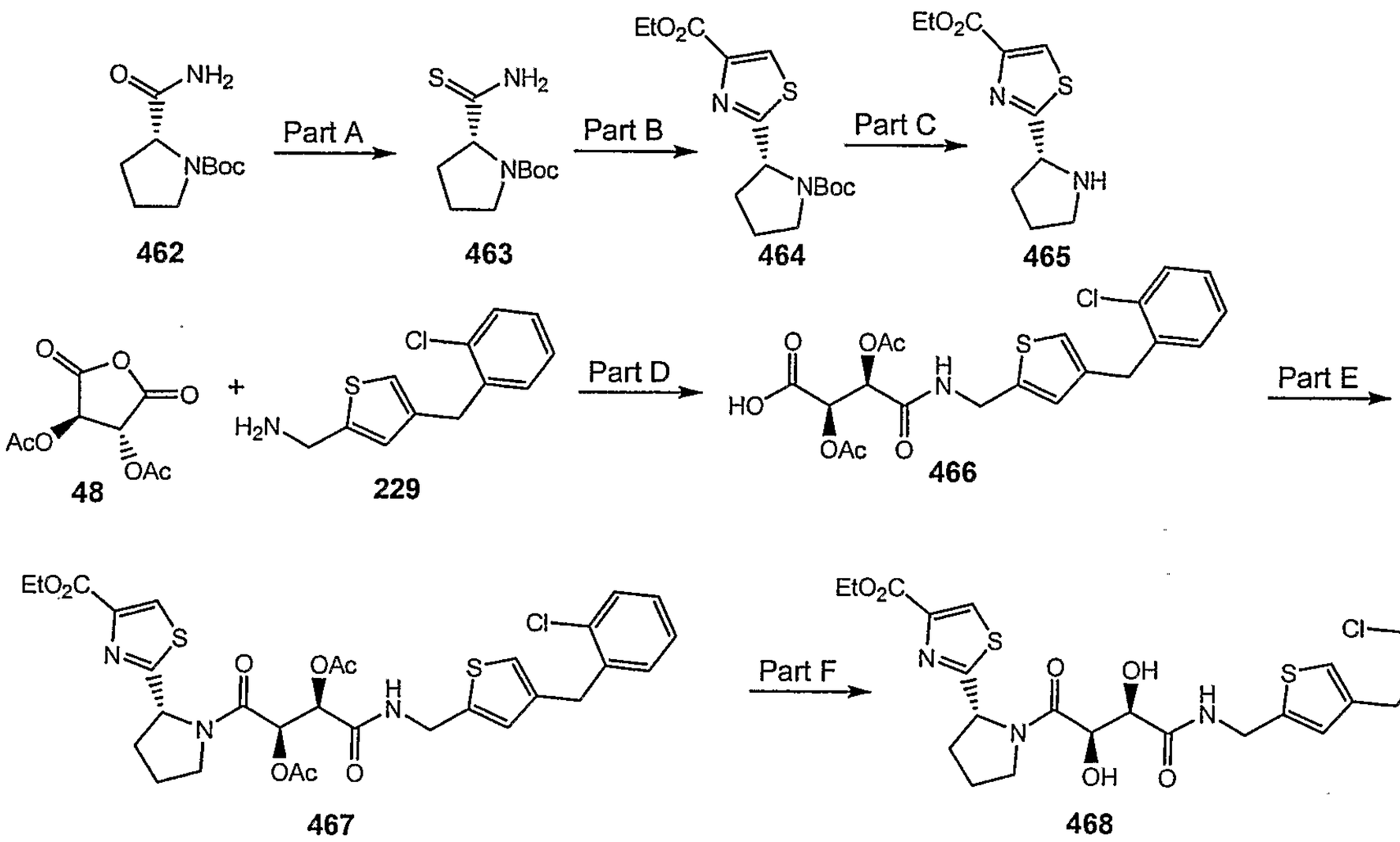
Part L:

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).

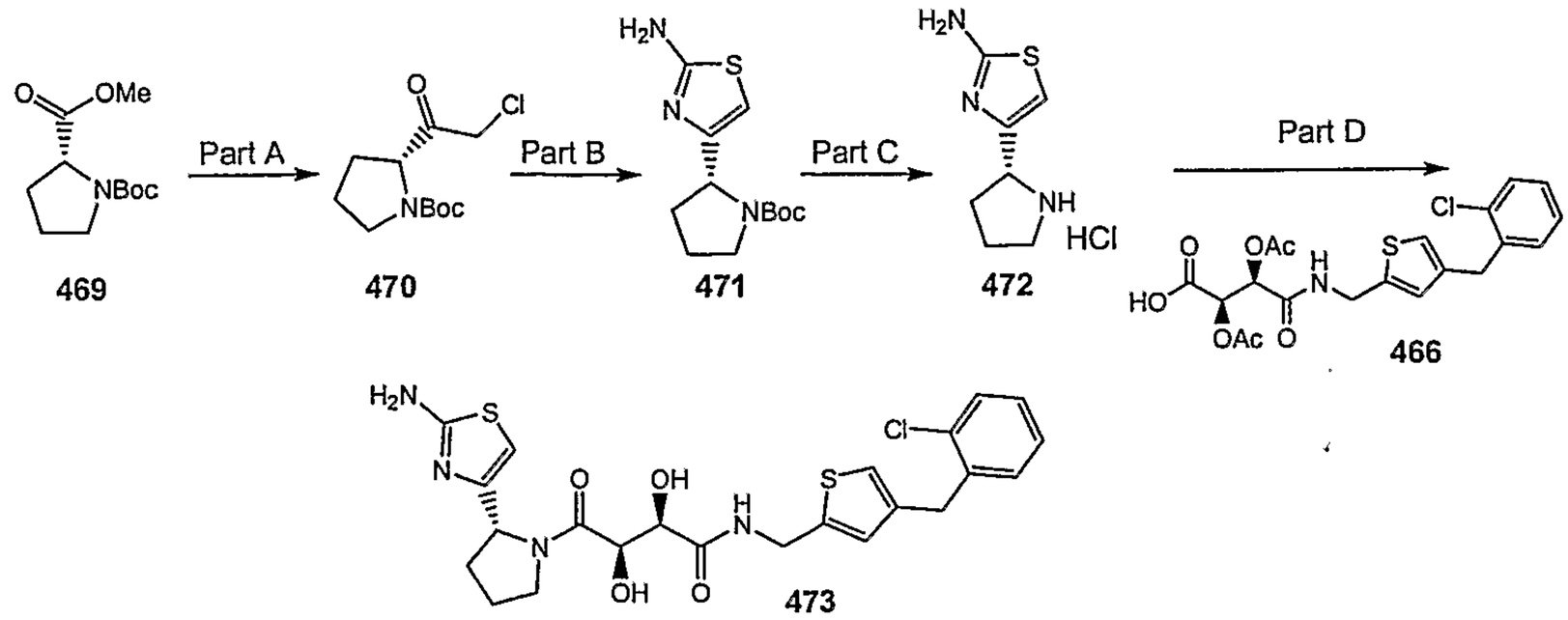
Part E:

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).

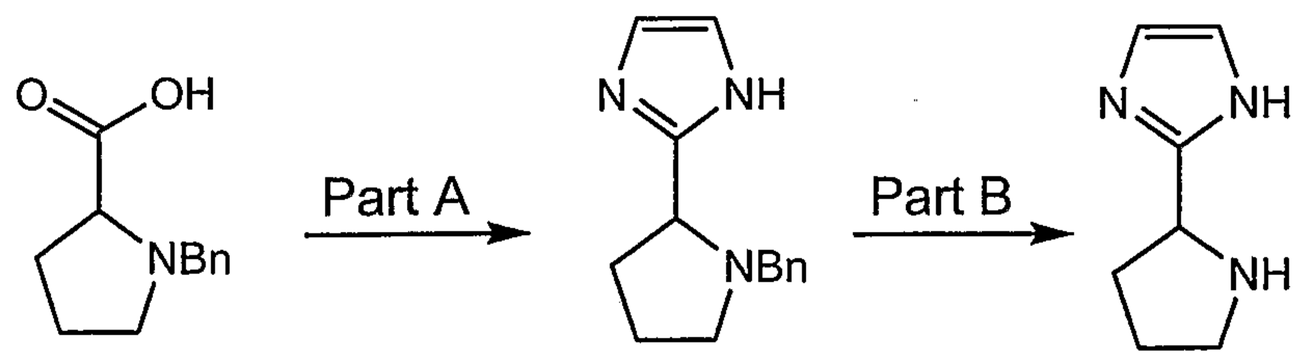
Part C:

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),

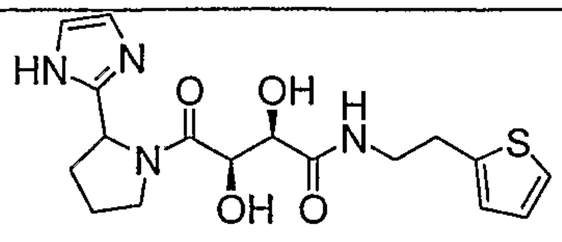
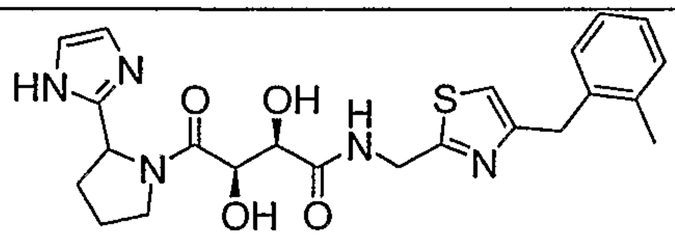
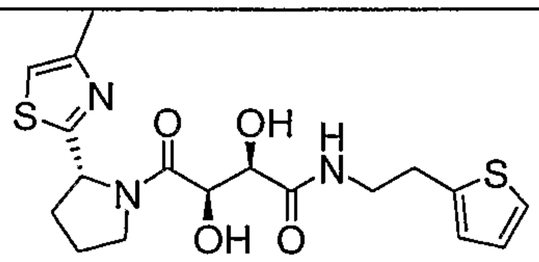
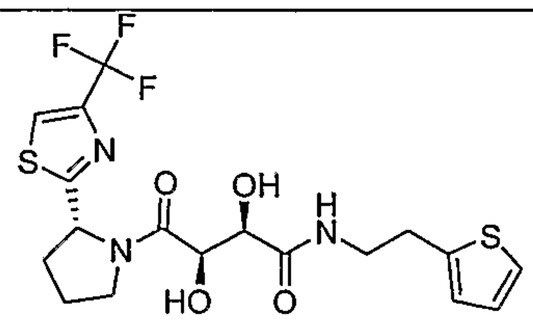
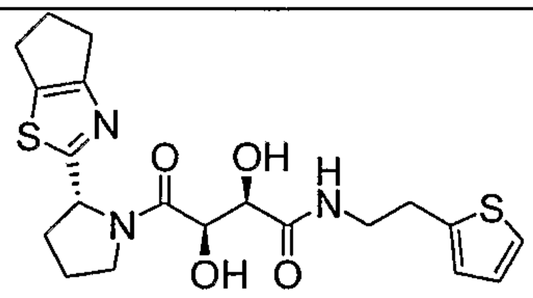
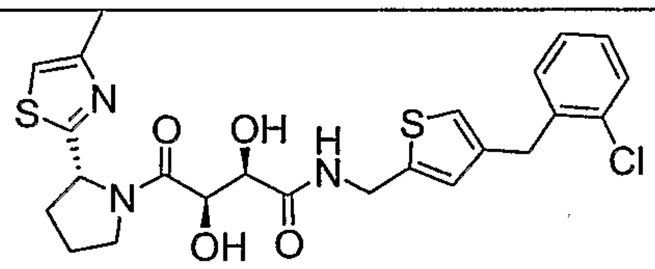
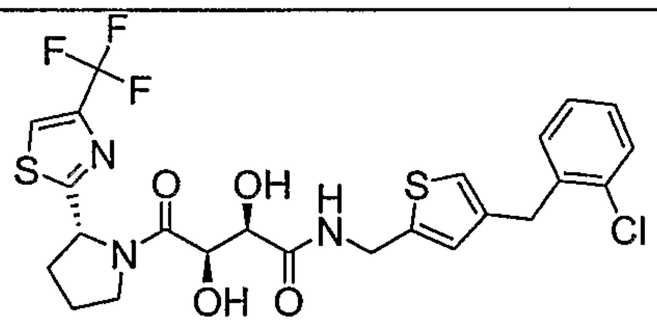
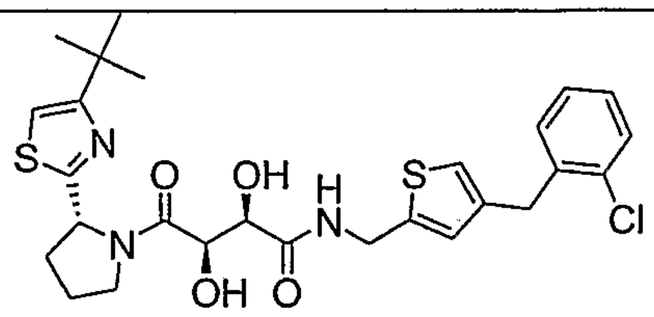
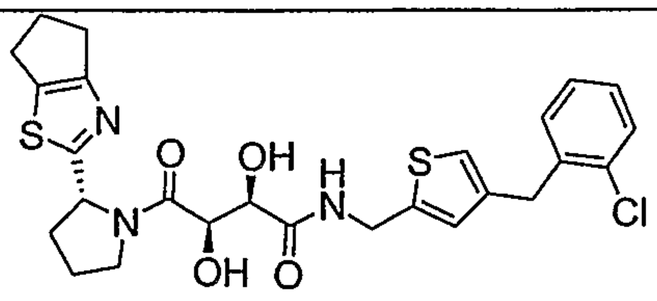
HOBT (658 mg, 4.87 mmol), and NMM (1.08 mL, 9.8 mmol). The reaction mixture was stirred overnight at 25 °C. Saturated aqueous $NaHCO_3$ solution (50 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (50 mL x3). The combined organic layers was washed with brine (50 mL), dried over Na_2SO_4, 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 $[M+H]^+$.

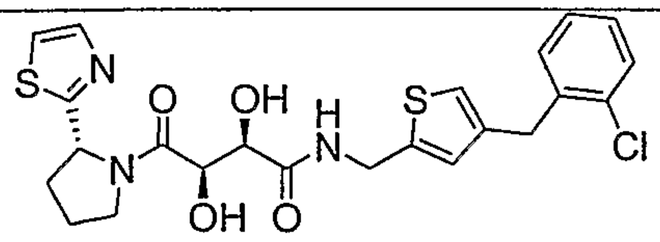
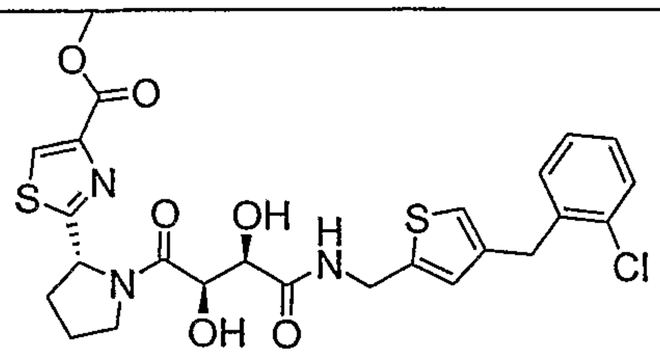
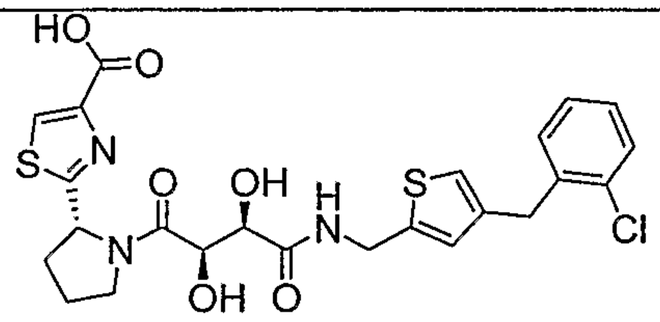
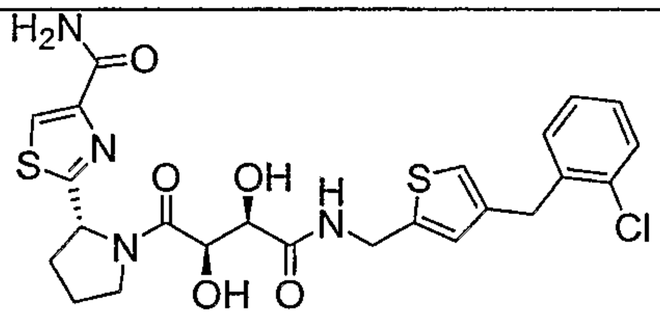
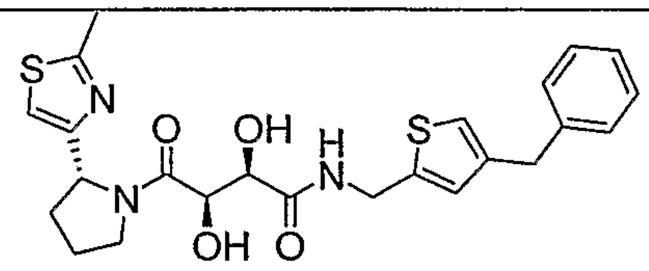
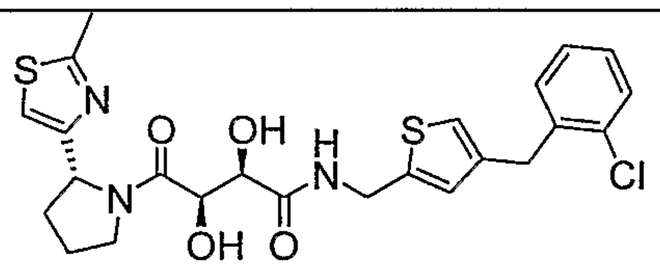
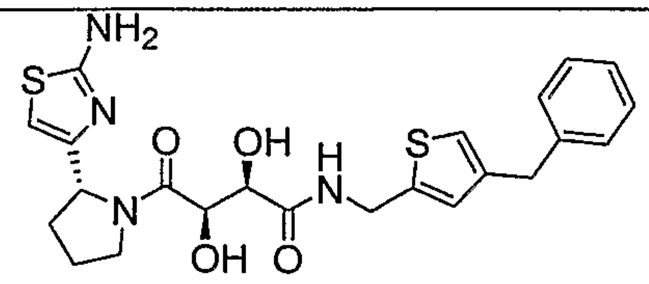
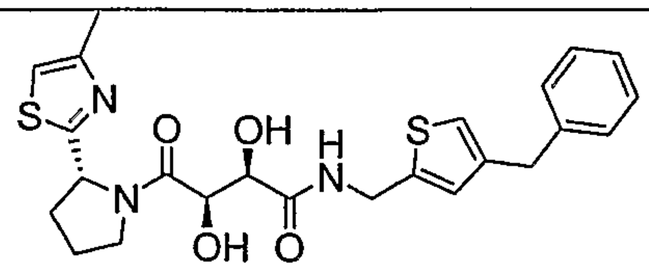
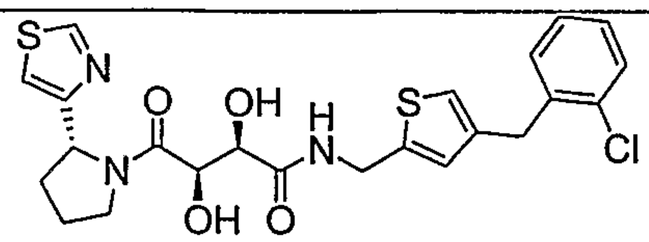
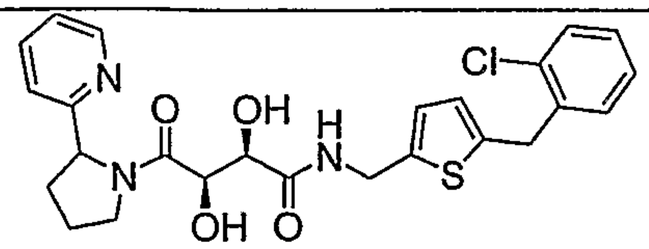
Part B: 5-Pyrrolidine-2-yl-1*H*-imidazole:

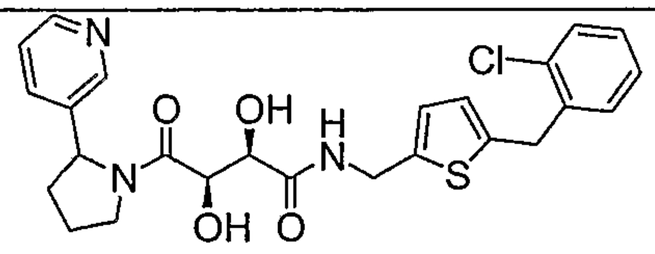
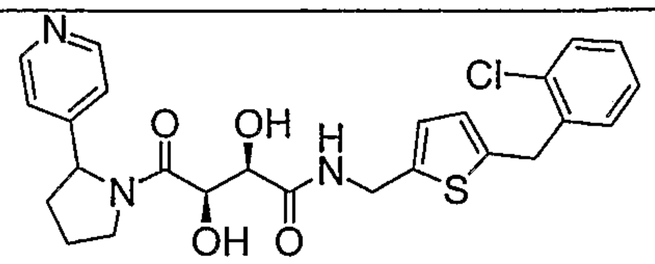
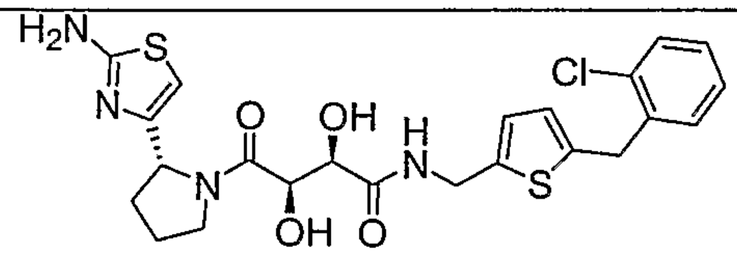
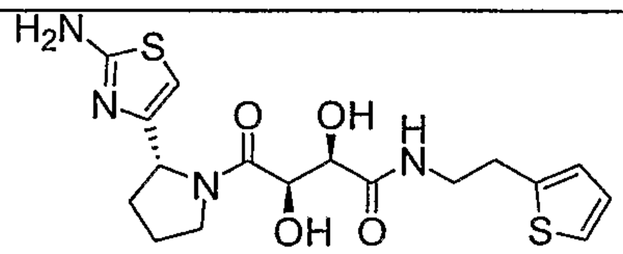
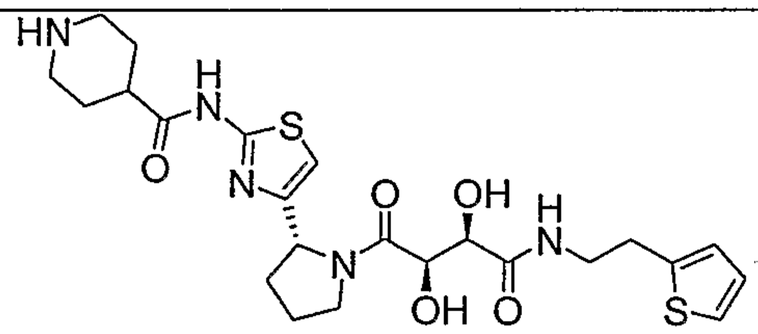
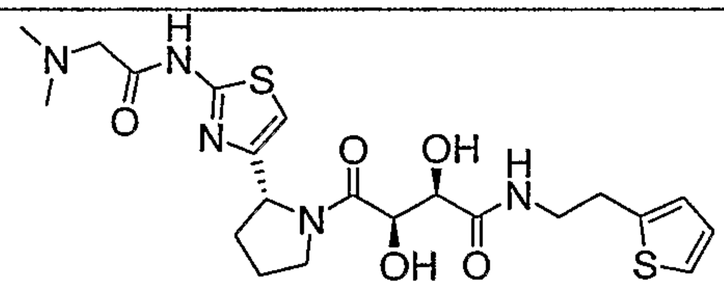
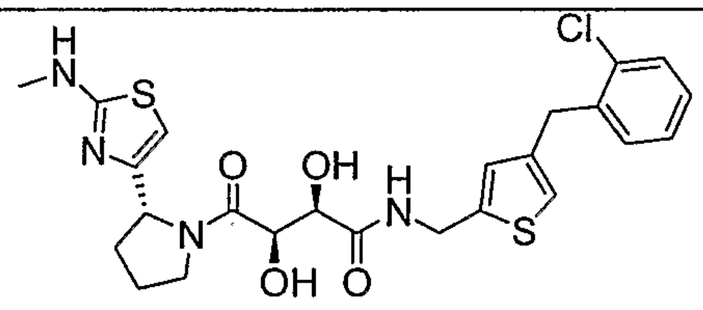
To **475** (110 mg) in 10 mL EtOH was added Pd/C (10%, 50 mg). The reaction mixture was hydrogenated under hydrogen (50 psi) for 24 hours. The solid was filtrated and the solution was evaporated by rotary evaporator to give 5-Pyrrolidine-2-yl-1*H*-imidazole (476) (67 mg). MS m/z 138.2 $[M+H]^+$.^{1}H-NMR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

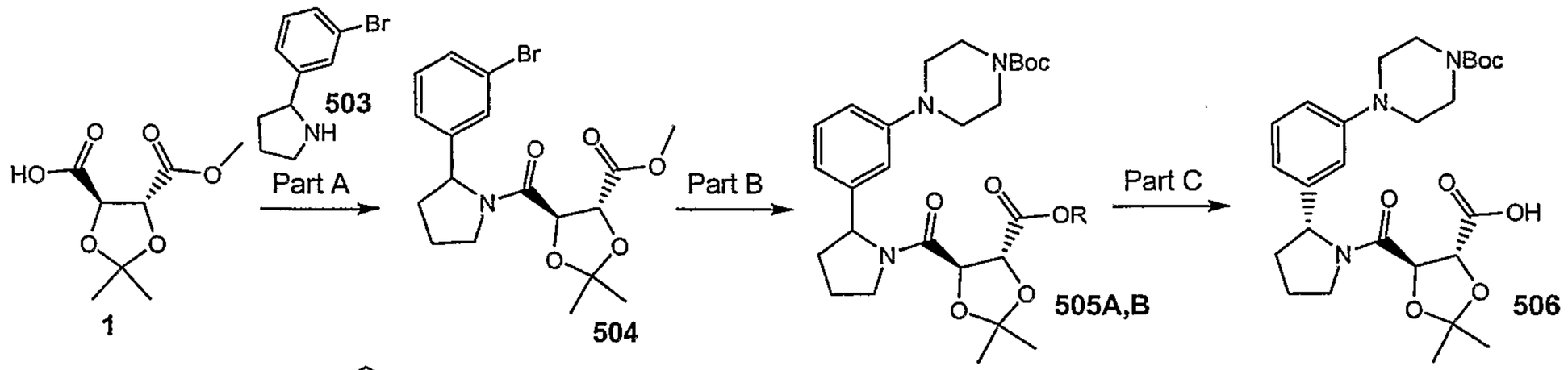
Compound #	Structure	Exact mass	MS m/z (M+H)
477		378.1	379.1
478		469.2	470.1
479		409.1	410.1
480		463.1	464.0
481		435.1	436.1
482		519.1	520.0
483		573.1	574.0
484		561.2	562.2
485		545.1	546.1

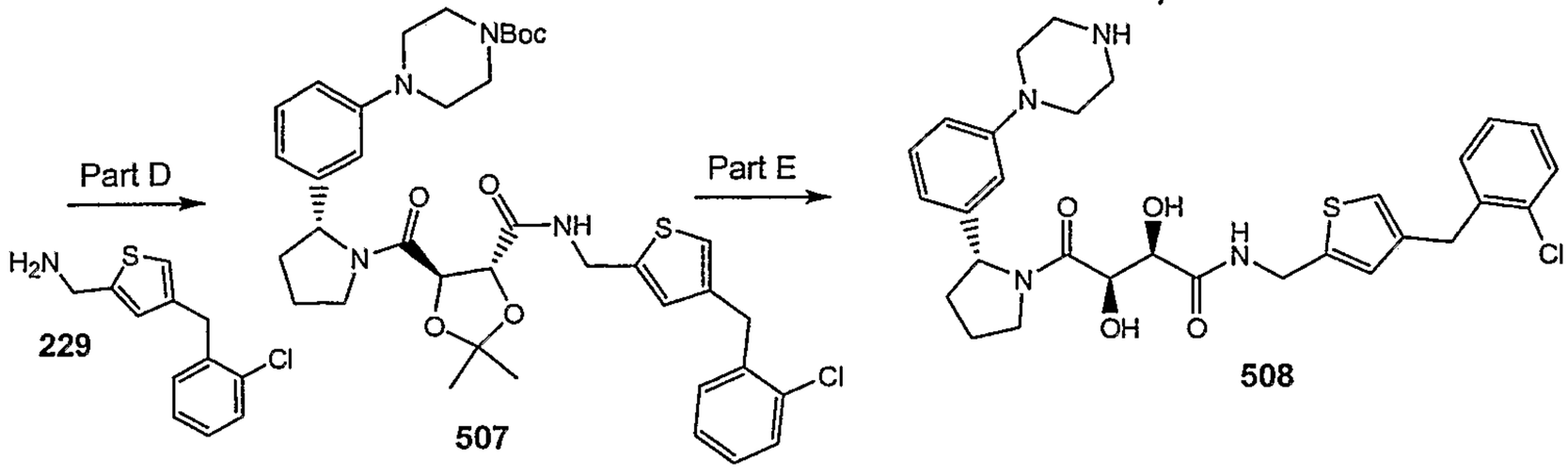
486		505.1	506.0
487		563.1	564.1
488		549.1	550.0
489		548.1	549.1
490		485.1	486.1
491		519.1	520.0
492		486.1	487.1
493		485.1	486.1
494		505.1	505.9
495		499.1	499.9

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:

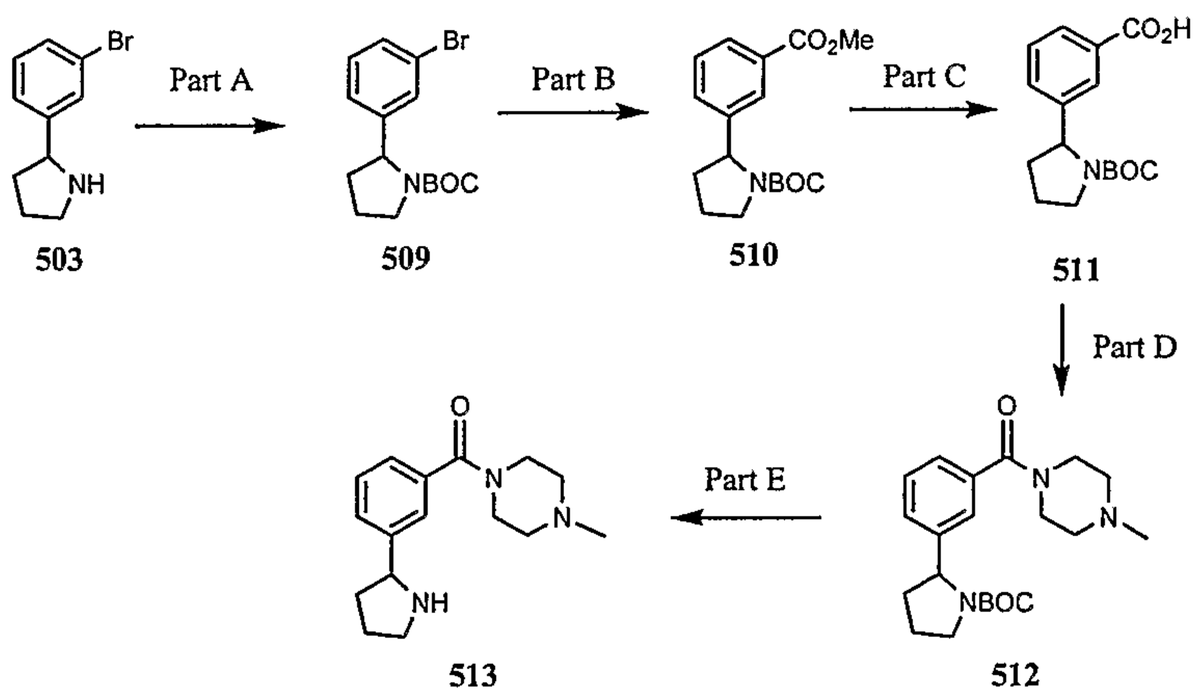
To **506** (107 mg, 0.21 mmol) in DMF (5 mL) was added **229** (55 mg, 0.23 mmol), DIEA (80 µL, 0.46 mmol) and HATU (87 mg, 0.23 mmol). The reaction mixture was stirred overnight at room temperature. The DMF was removed in vacuo and the residue was partitioned between ethyl acetate and water. The layers 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%).

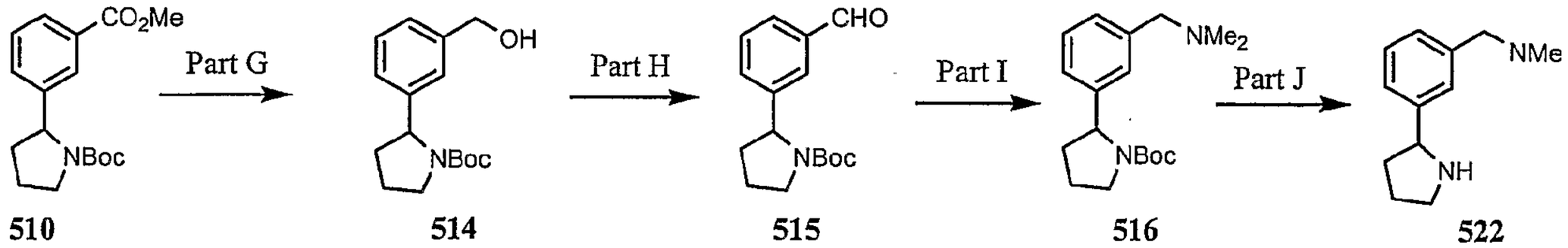
Part E

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:



510 **514** **515** **516** **522**

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.

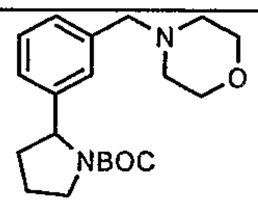
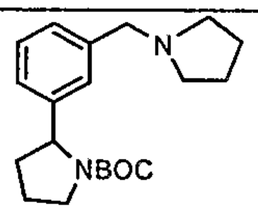
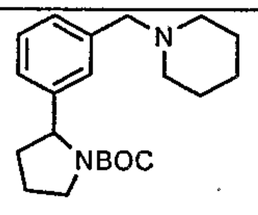
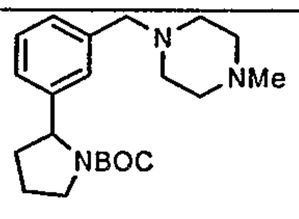
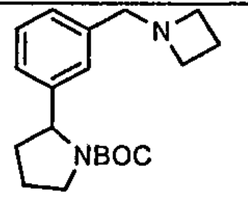
Part H:

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:

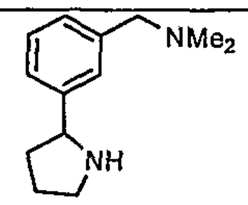
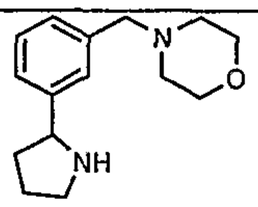
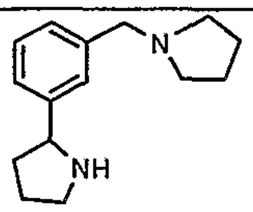
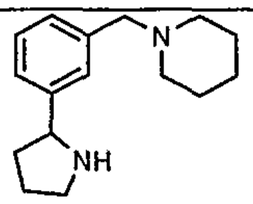
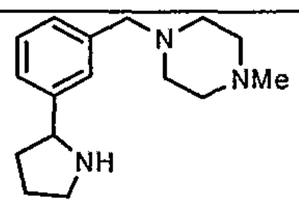
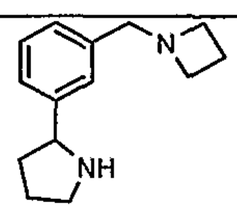
Compound **515** (0.50 g, 1.82 mmol) was dissolved in CH_2Cl_2 (10 mL), and 3A sieves (0.50 g), dimethylamine in THF (2 M, 1.8 mL, 3.64 mmol), glacial acetic acid (0.109 g, 1.82 mmol), and sodium triacetoxyborohydride (0.579 g, 2.73 mmol) were added. The reaction mixture was stirred at room temperature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

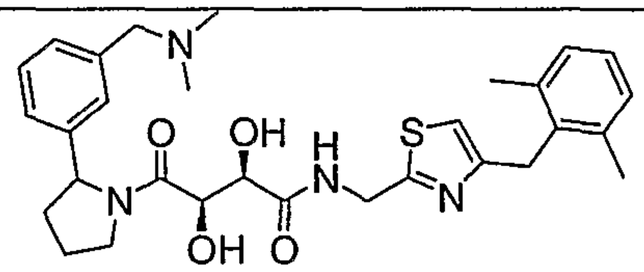
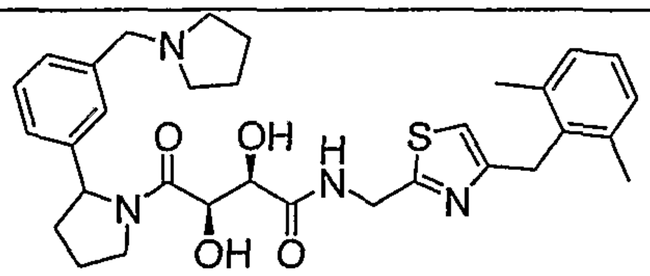
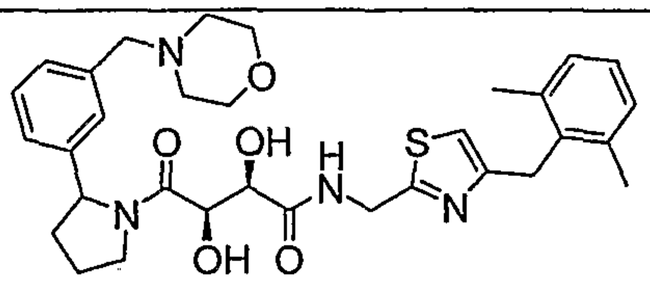
Compound #	Intermediate	MS (m/e for M+1)
517		347
518		331
519		345
520		360
521		317

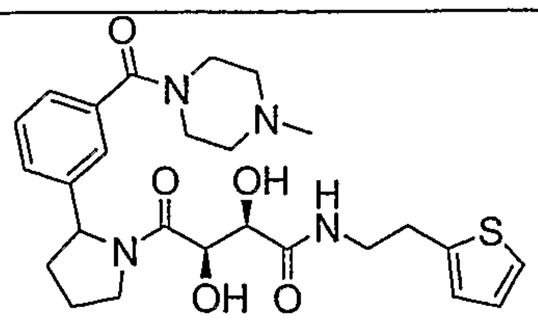
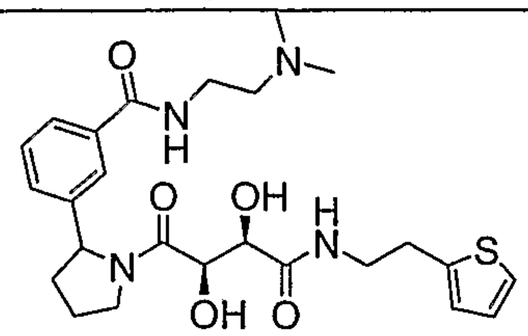
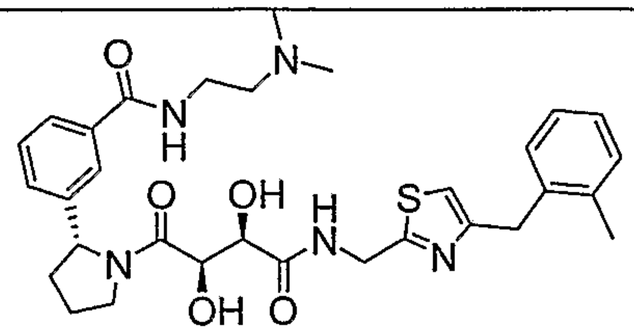
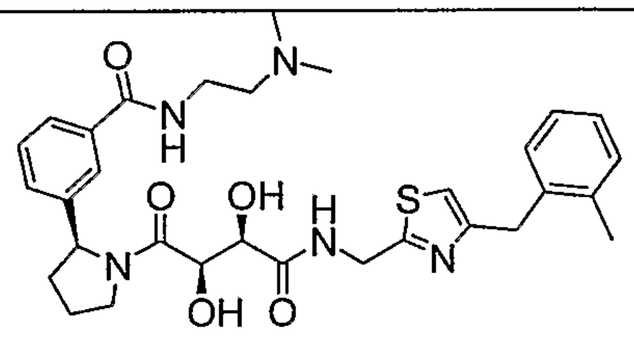
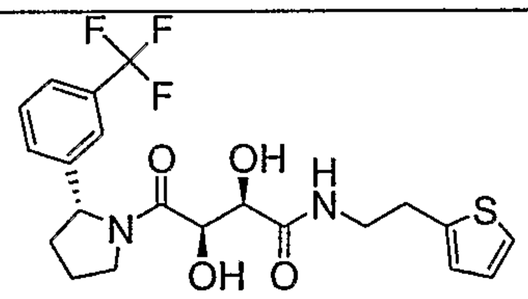
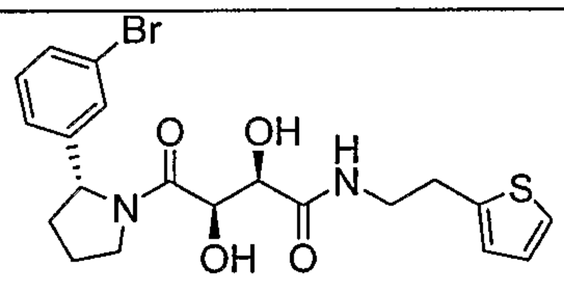
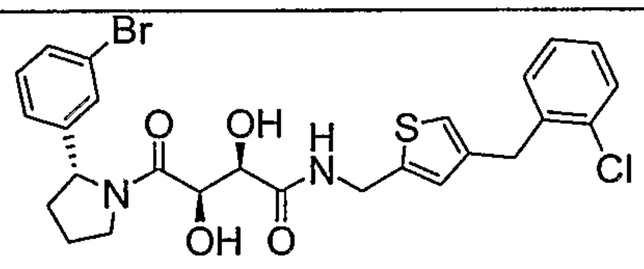
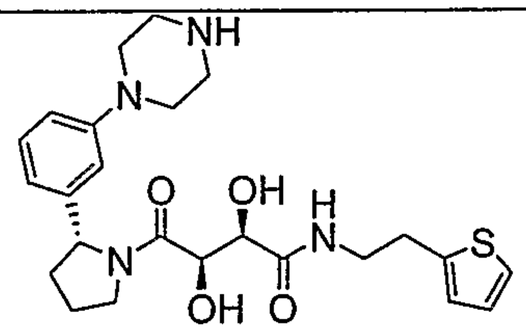
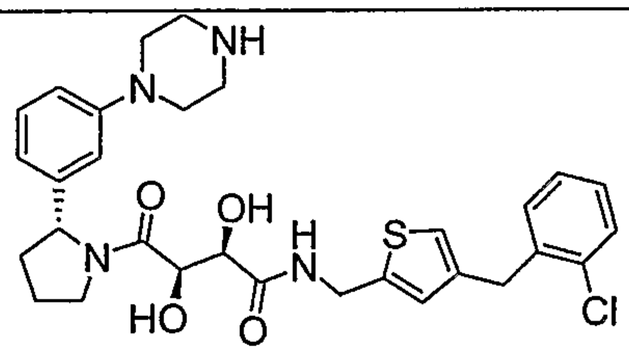
Part J:

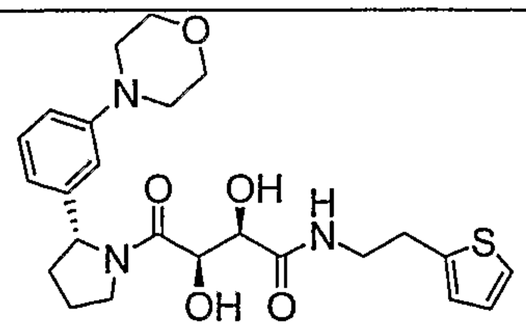
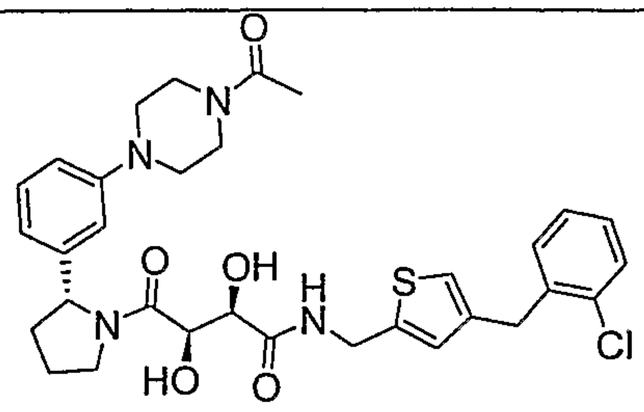
The following compounds were prepared using procedure described in Example 11B Part F.

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

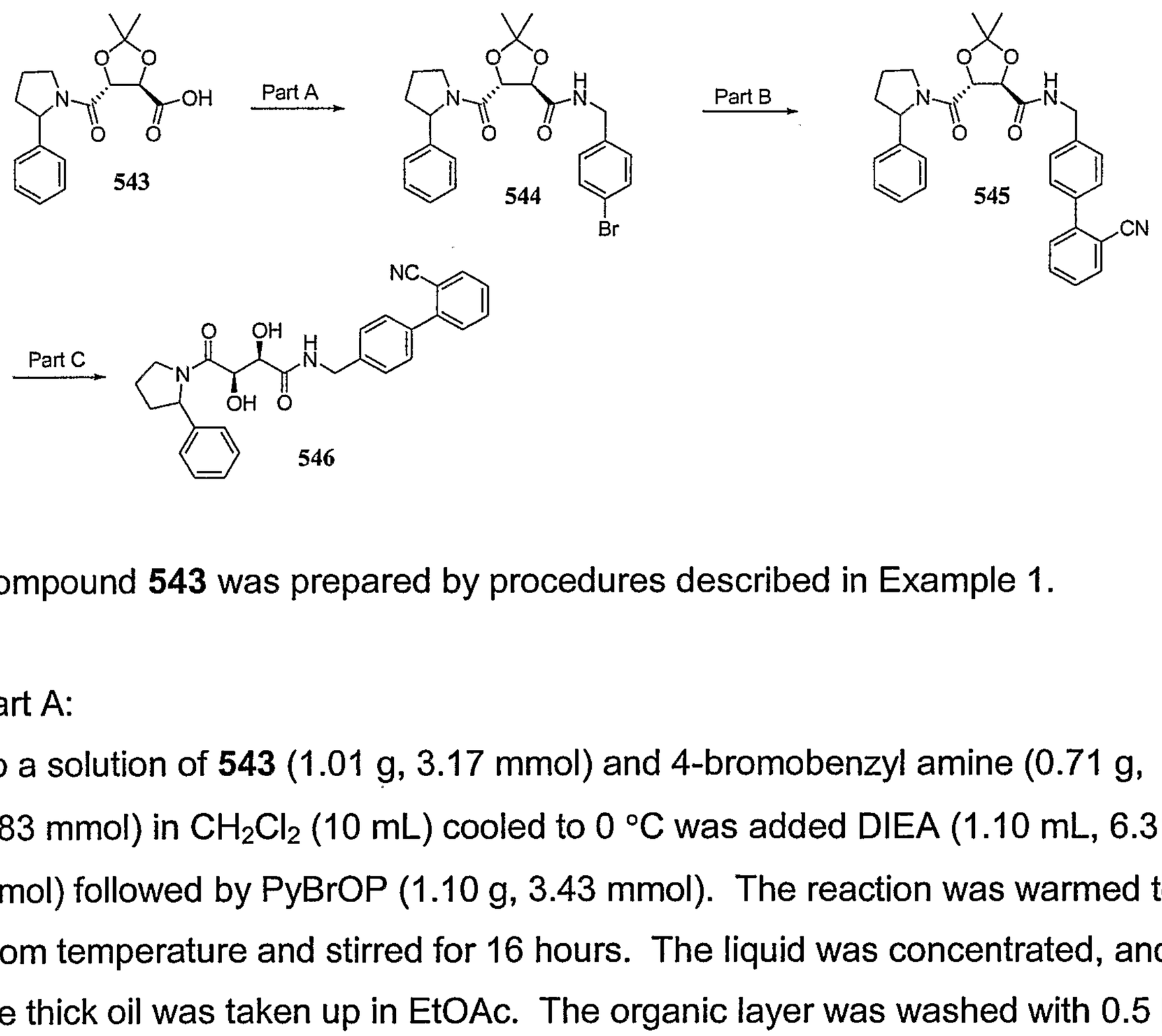
529		514.2	515.0
530		502.2	503.1
531		593.3	594.1
532		593.3	594.1
536		456.1	457.1
537		466.1	467.0
538		576.1	577.0
539		472.2	473.2
540		582.2	583.2

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 $LiOH \bullet H_2O$ (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).

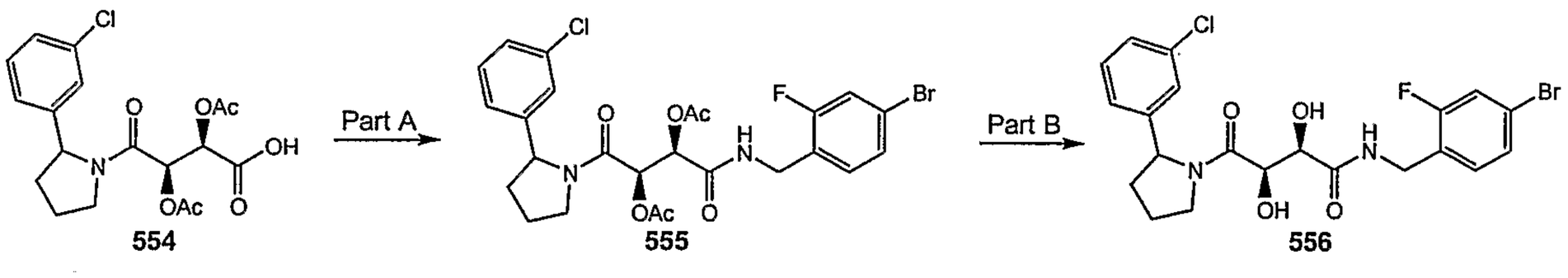
Part D:

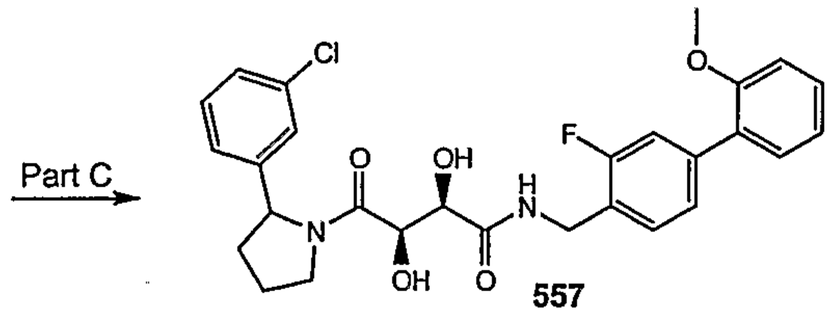
To a solution of **551** (55 mg, 0.104 mmol) in CH_2Cl_2 (1 mL) was added polystyrene-bound HOBt (109 mg, 0.095 mmol), DIC (0.067 mL, 0.427 mmol), and DMAP (7 mg, 0.057 mmol) and was shaken overnight. The mixture was filtered, then washed with DMF (3 x 3 mL), CH_2Cl_2 (3 x 3 mL), DMF (3 x 3 mL), and 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).

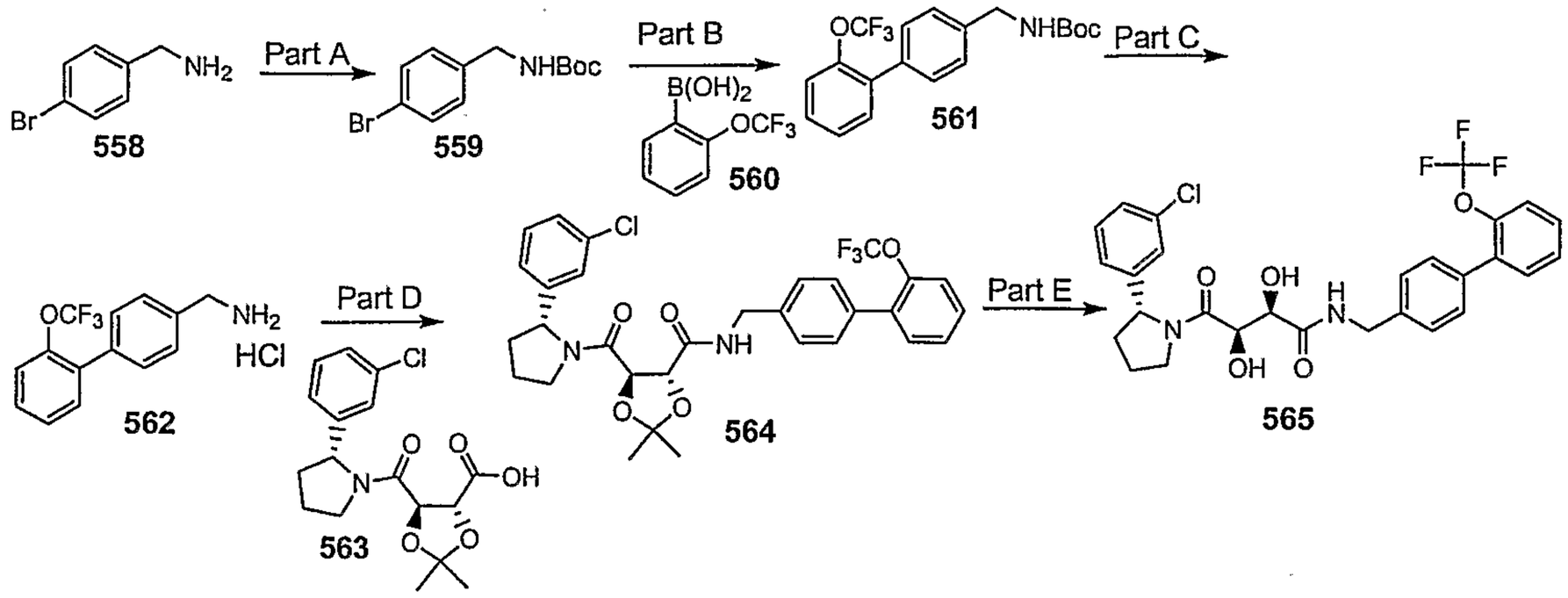
Part B:

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%). ^1H 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).

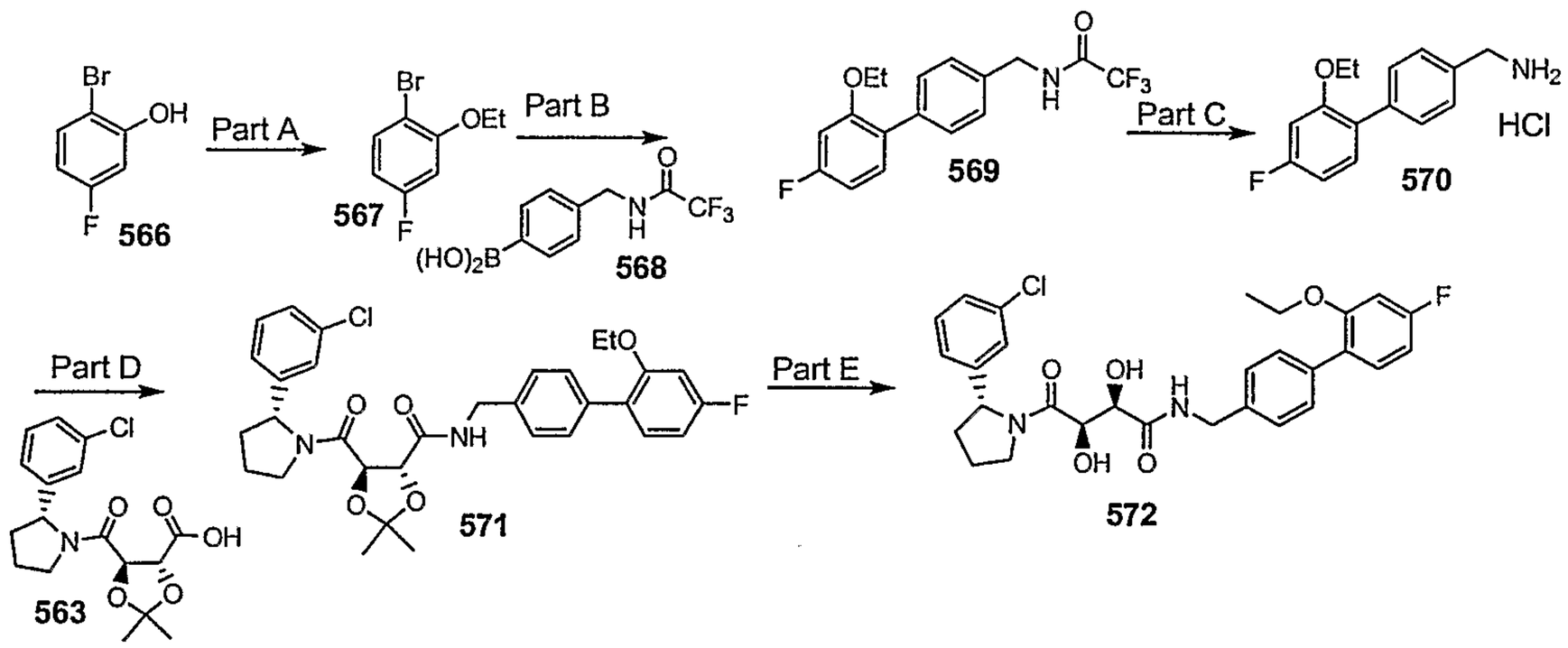
Part D:

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).

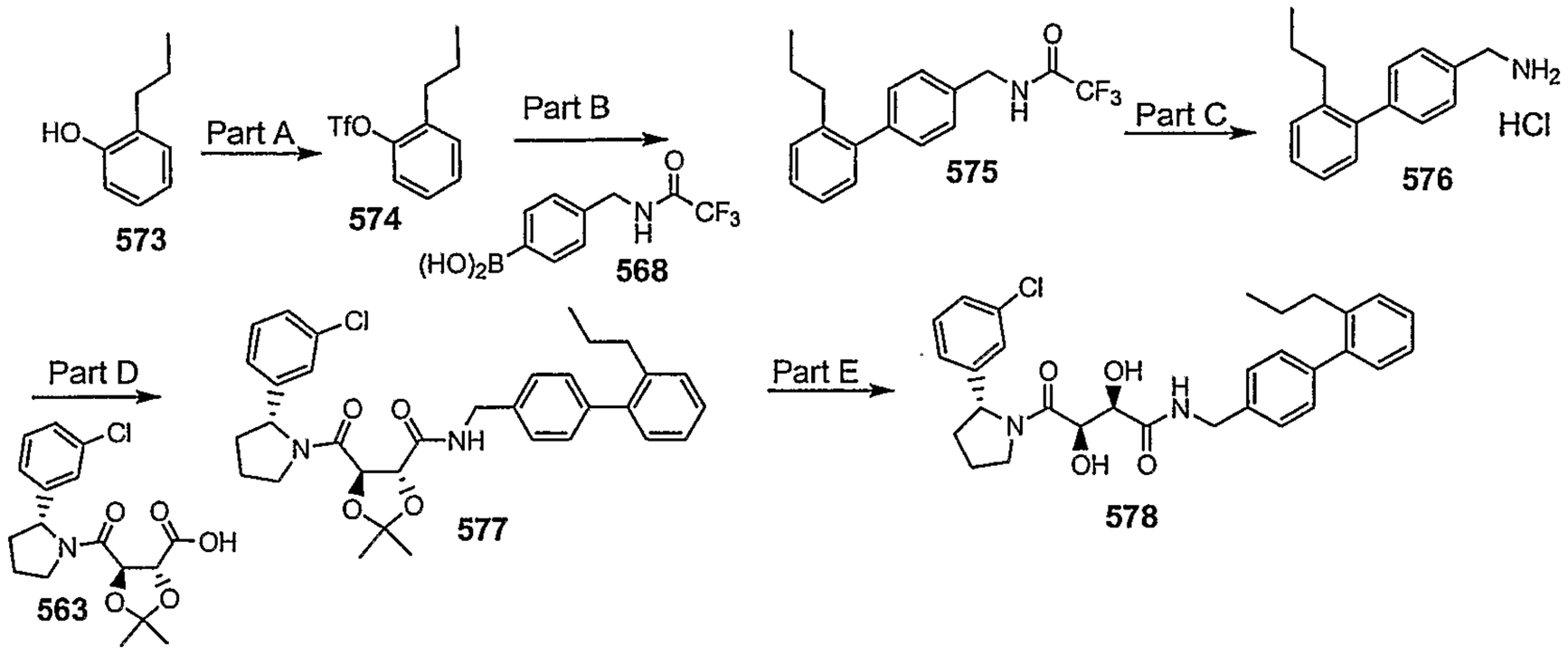
Part D:

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%). ^1H 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).

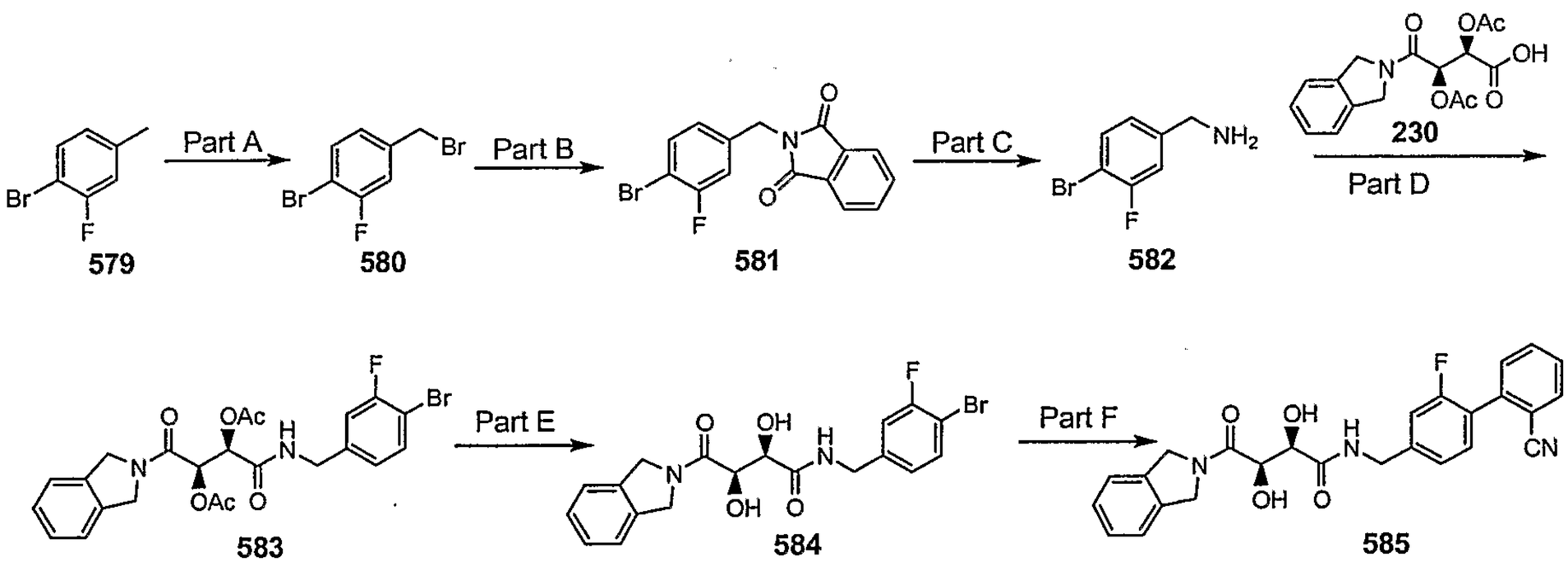
Part D:

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).

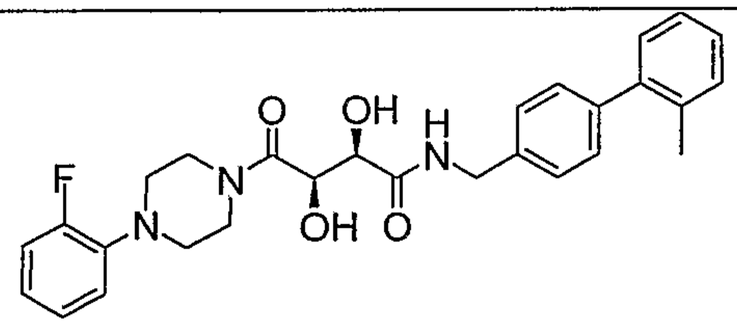
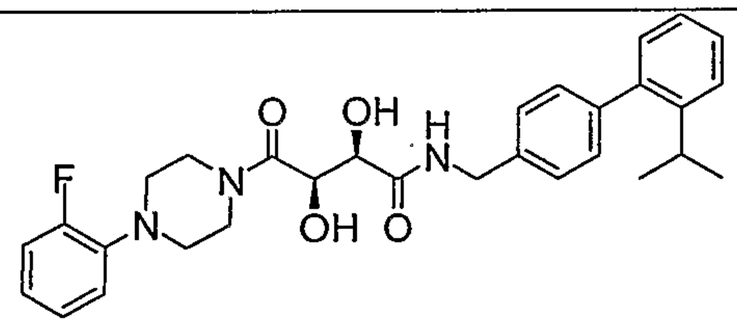
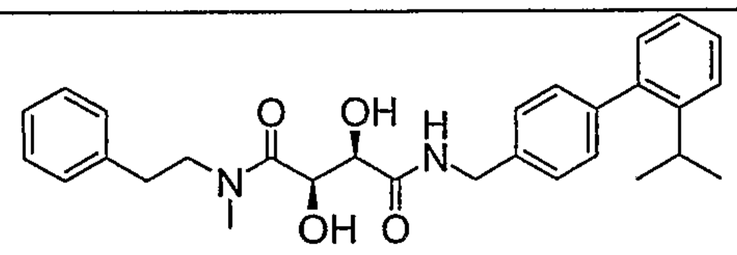
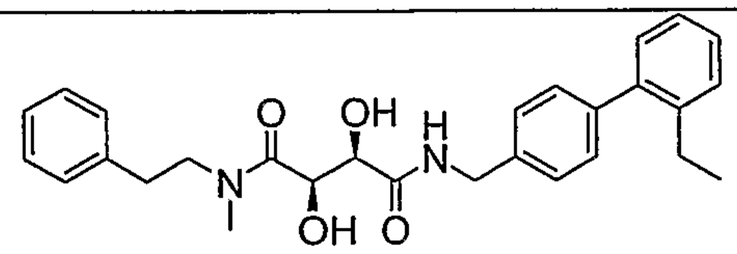
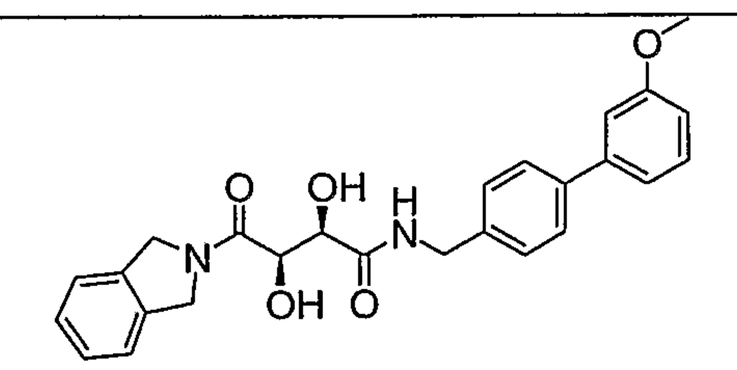
Part E:

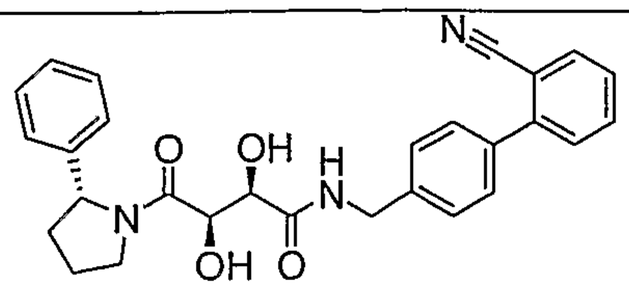
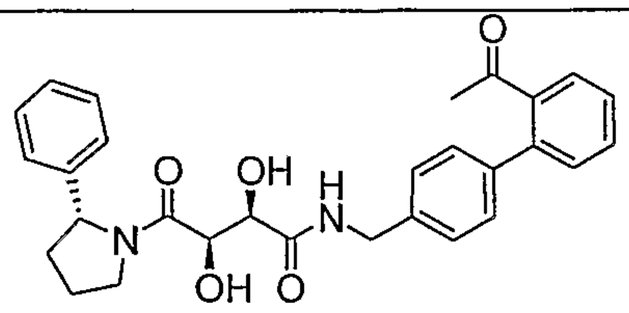
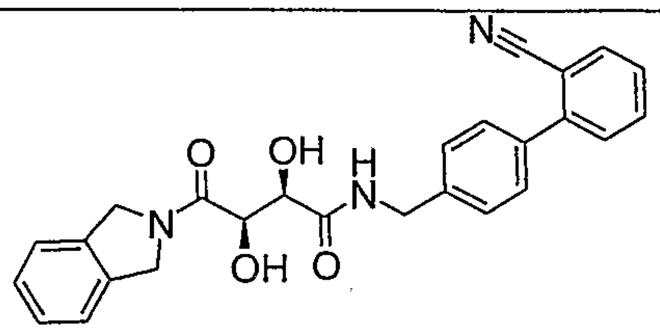
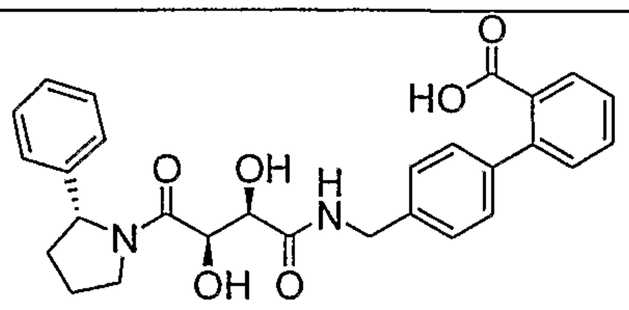
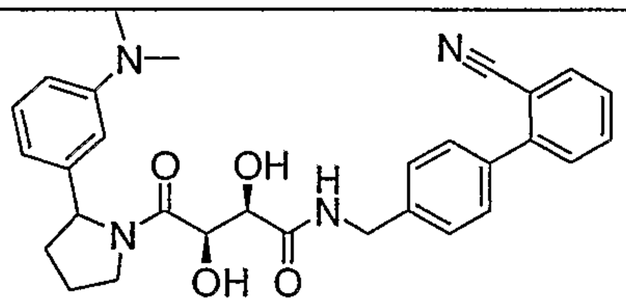
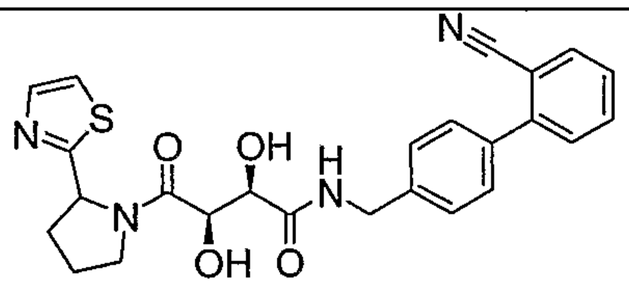
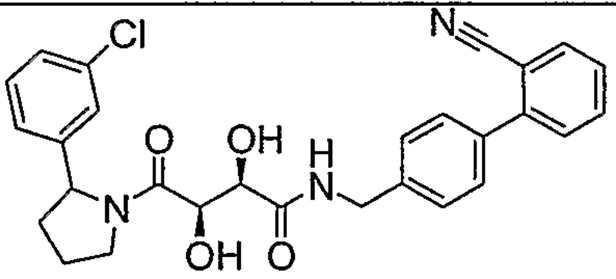
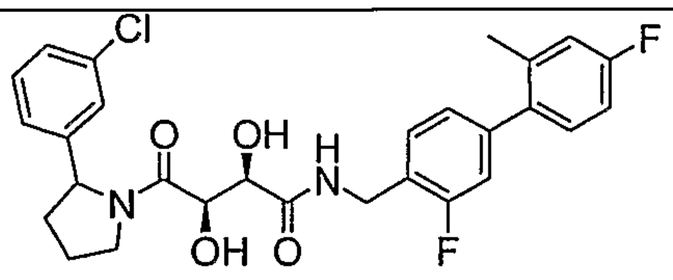
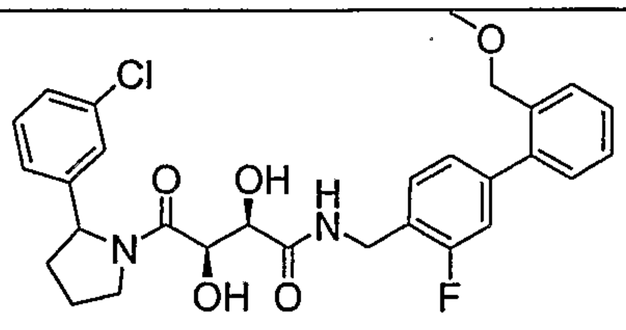
Compound **584** was prepared using the procedures described in Example 12C Part B. HPLC-MS t_R = 1.81 min ($UV_{254\ nm}$); mass calculated for formula $C_{19}H_{18}BrFN_2O_4$ 436.0, observed LCMS m/z 437.0 (M+H).

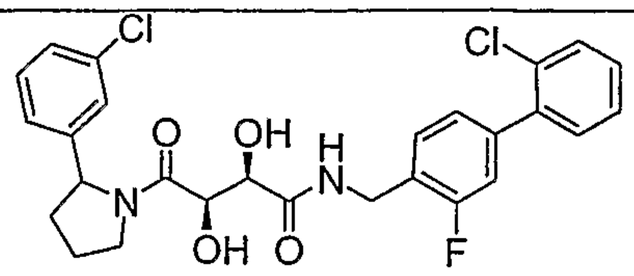
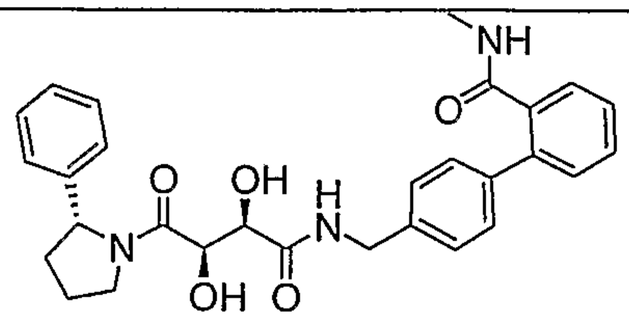
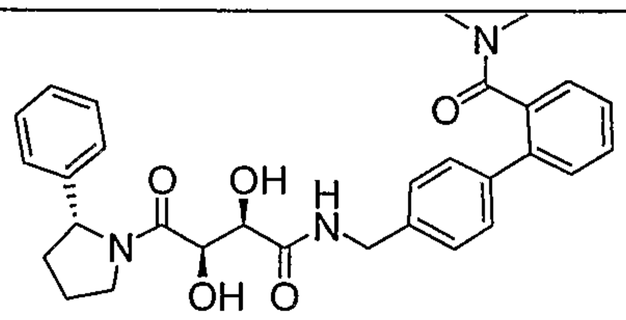
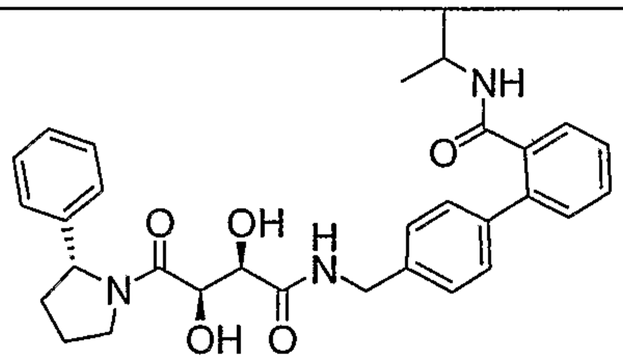
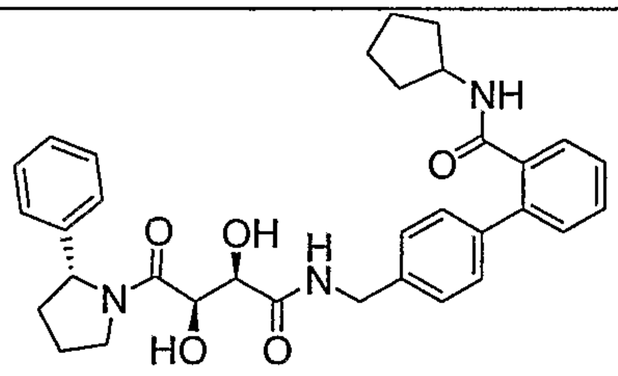
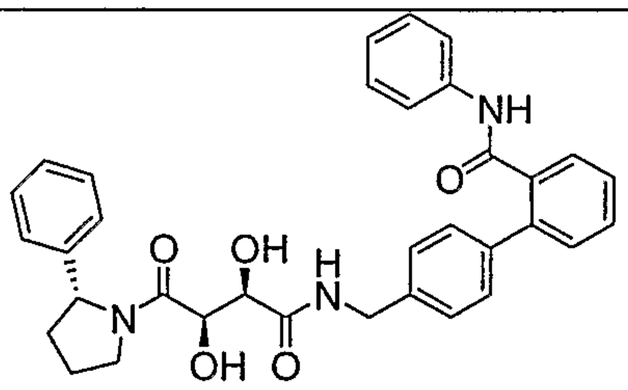
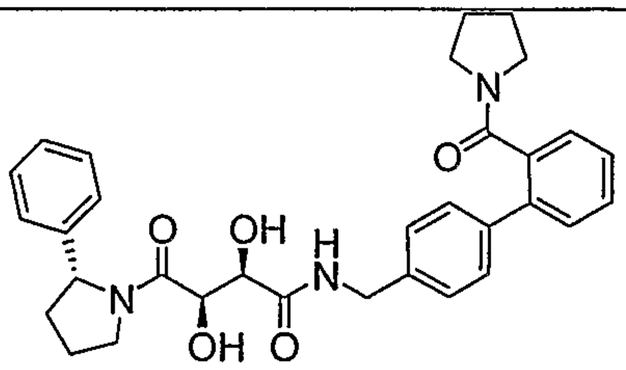
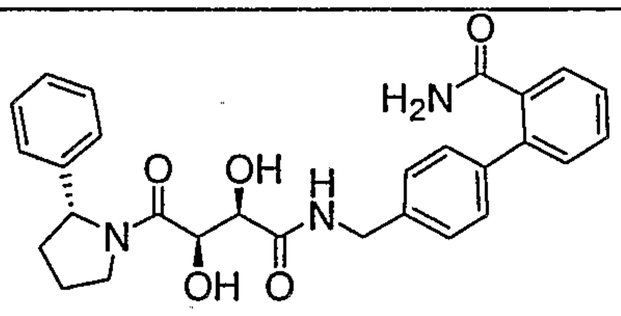
Part F:

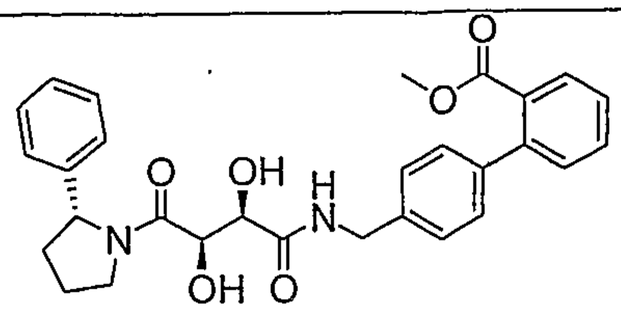
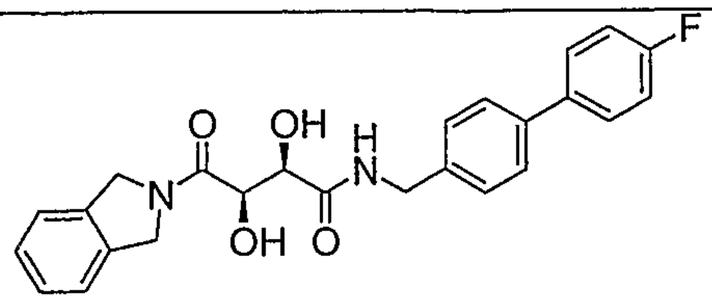
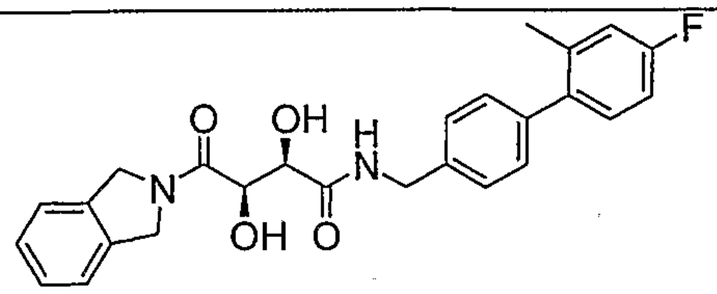
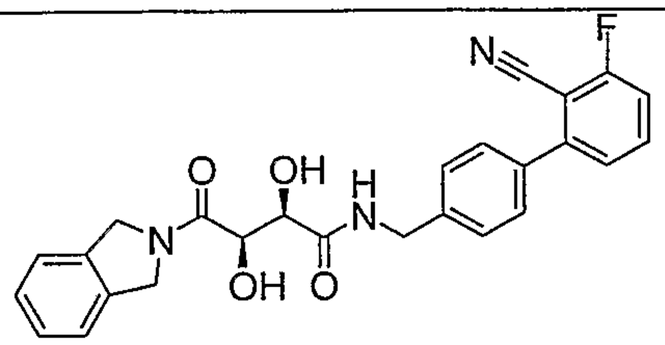
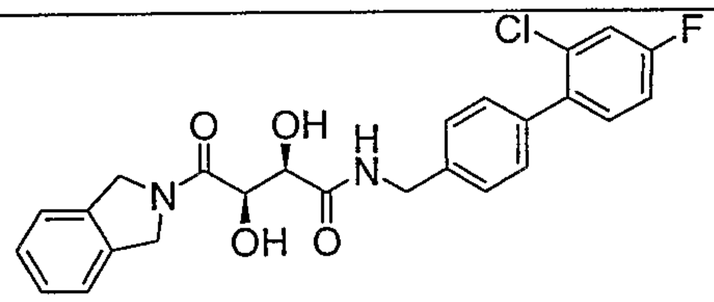
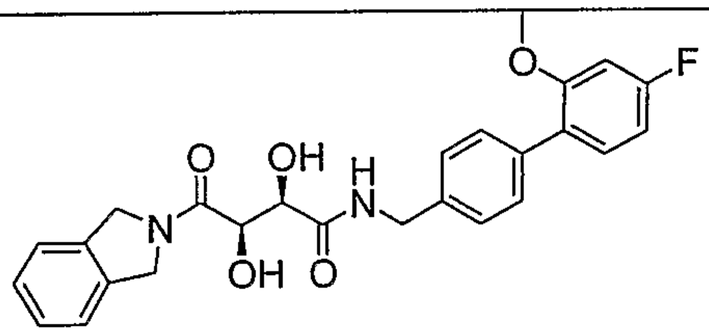
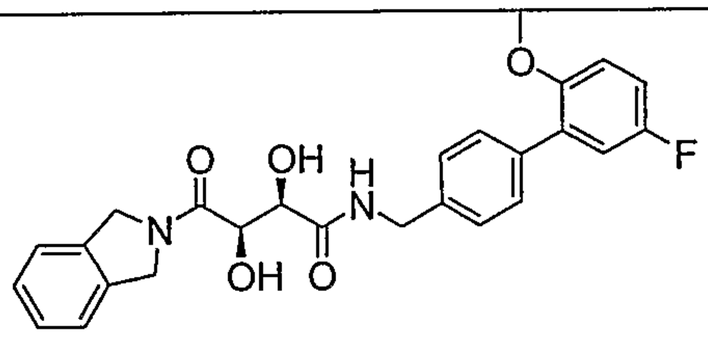
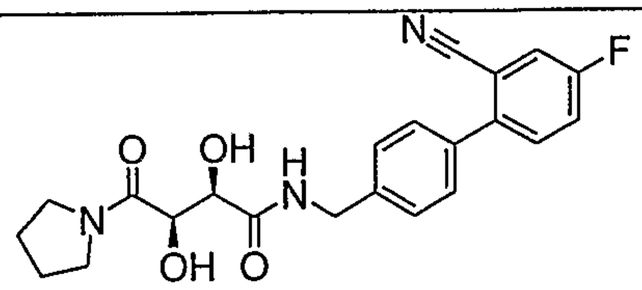
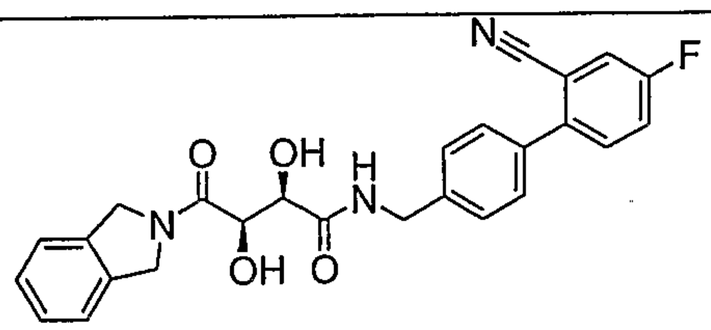
Compound **585** was prepared using procedures similar to those described in Example 12C Part C. HPLC-MS t_R = 4.12 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{26}H_{22}FN_3O_4$ 459.2, observed LCMS m/z 460.1 (M+H).

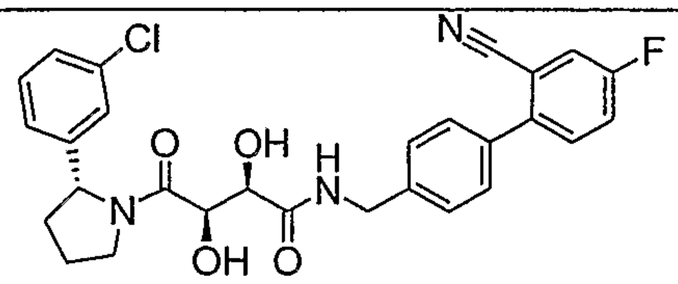
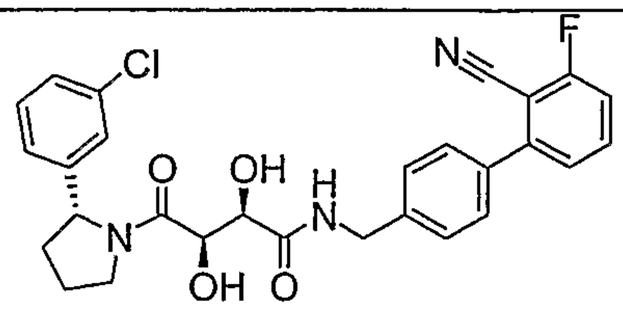
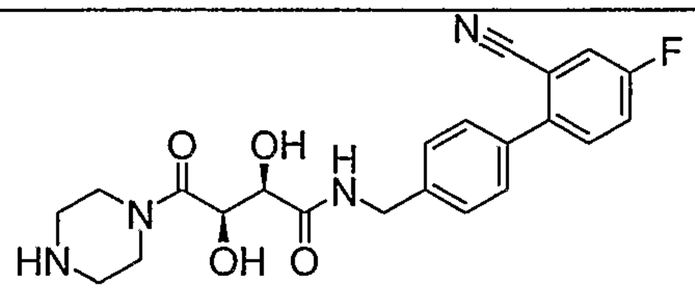
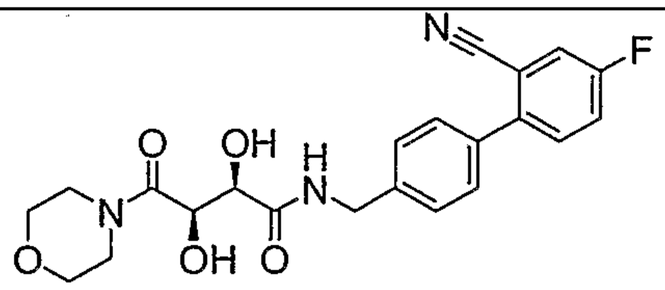
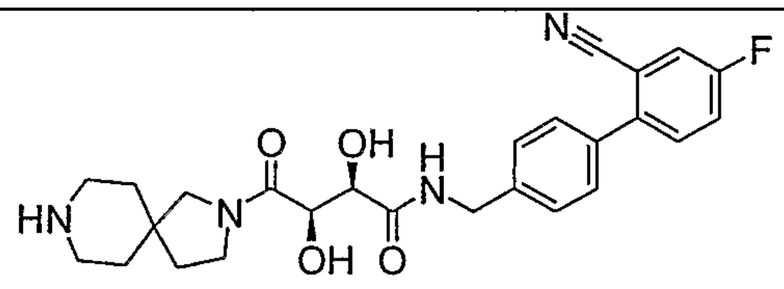
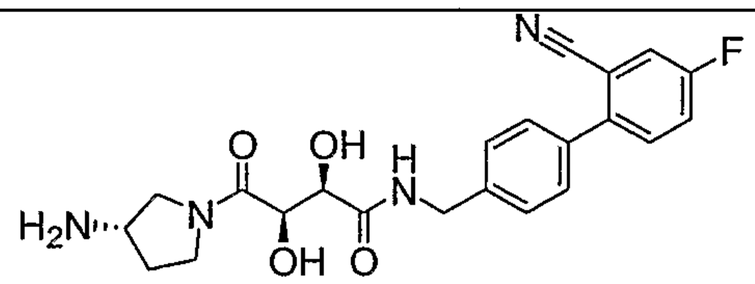
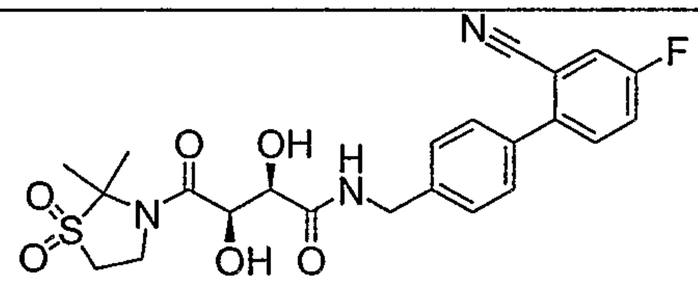
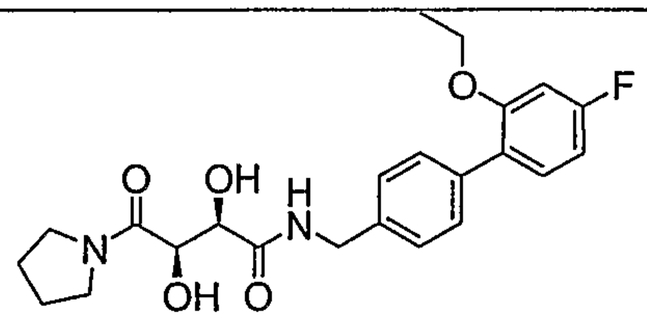
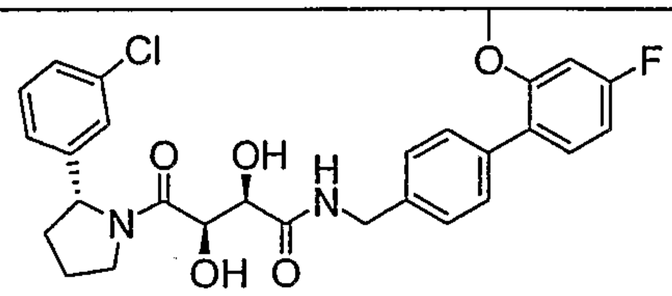
The following table contains compounds prepared using the procedures described in Example 12 A – G.

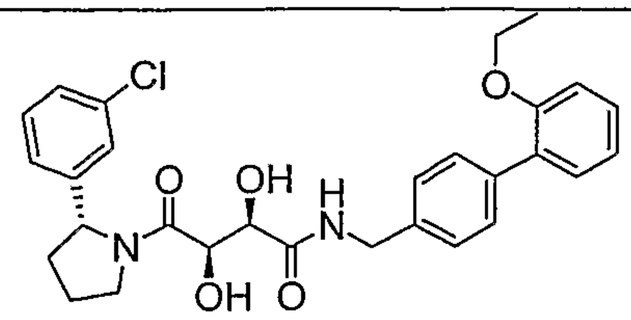
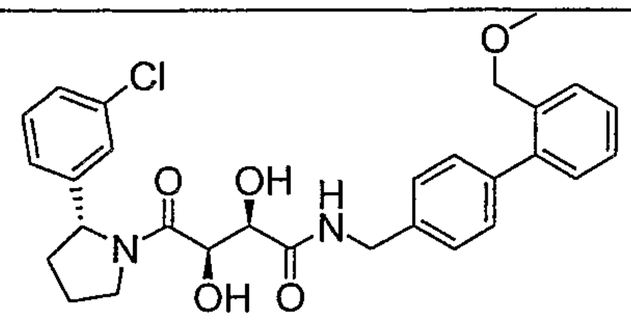
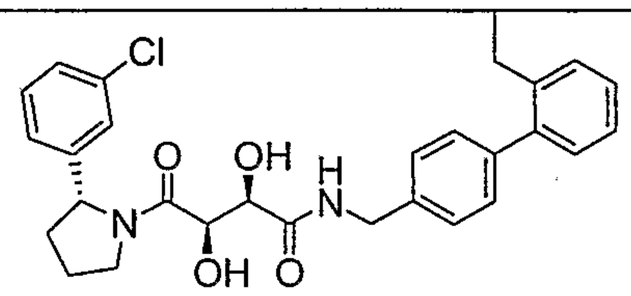
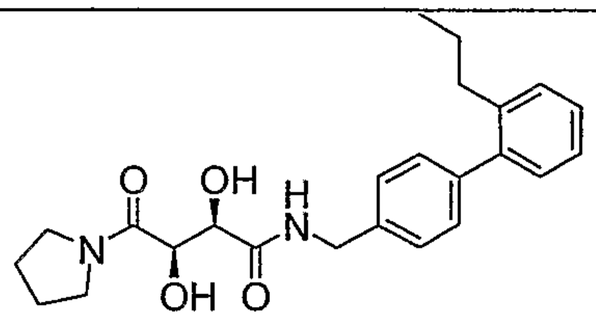
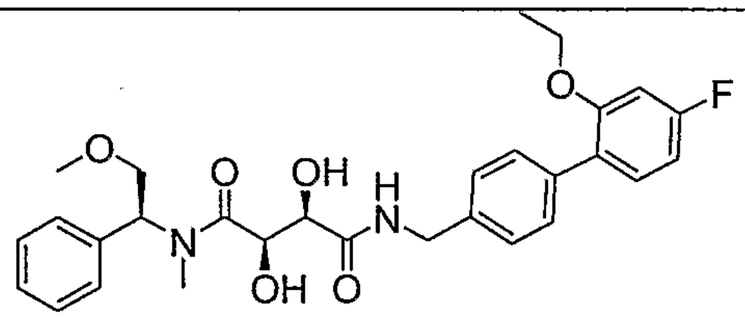
Compound #	Structure	Exact mass	MS m/e (M+H)
586		491.2	492.2
587		519.3	520.3
588		474.3	475.3
589		460.2	461.2
590		446.2	447.2

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

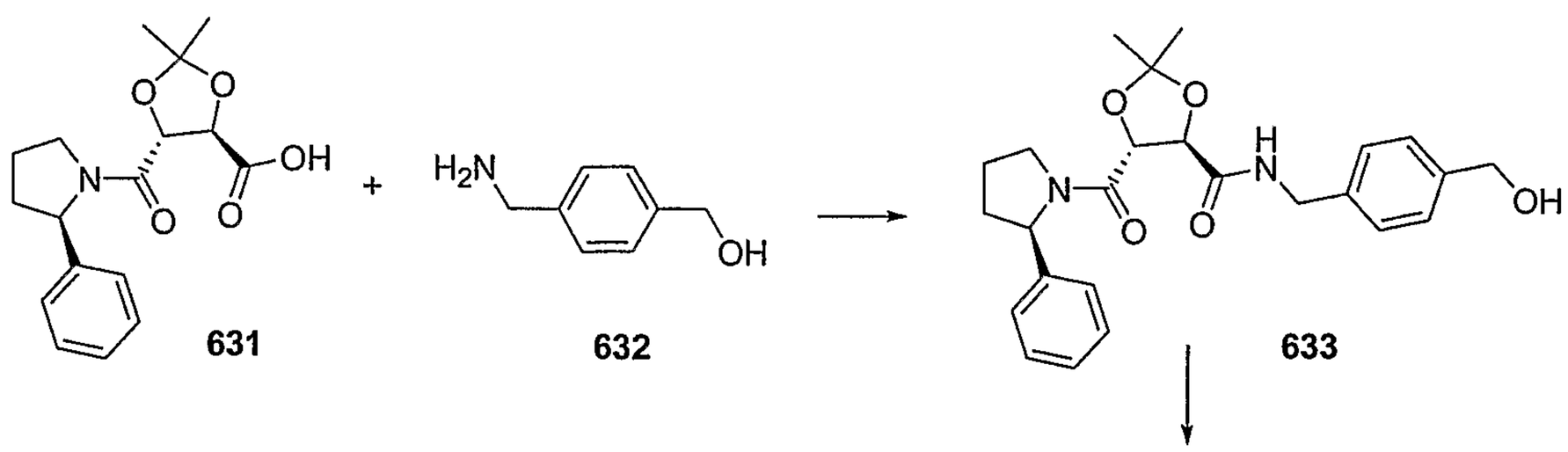
600		530.1	531.0
601		501.2	502.3
602		515.2	516.3
603		529.3	530.3
604		555.3	556.3
605		563.2	564.3
606		541.3	542.3
607		487.2	488.1

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.

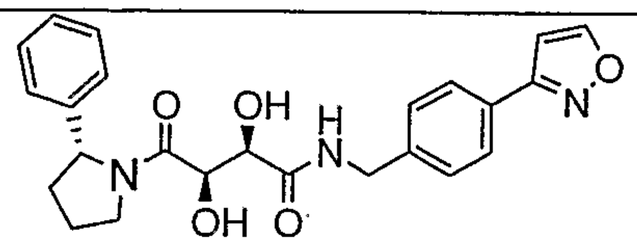
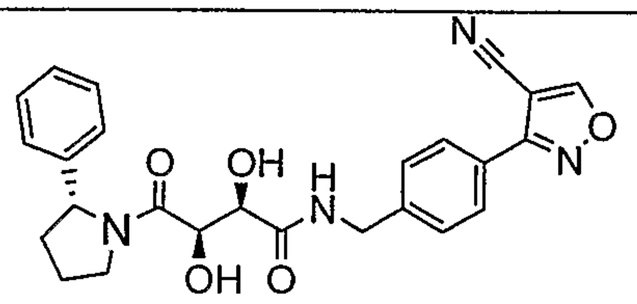
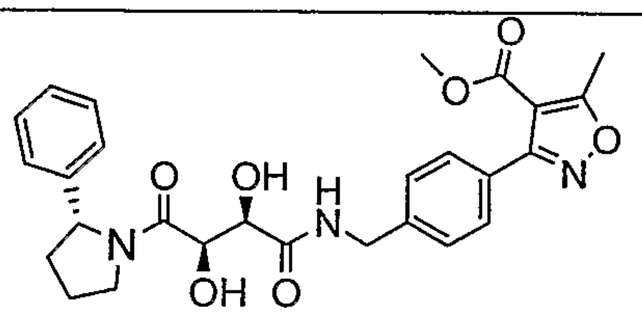
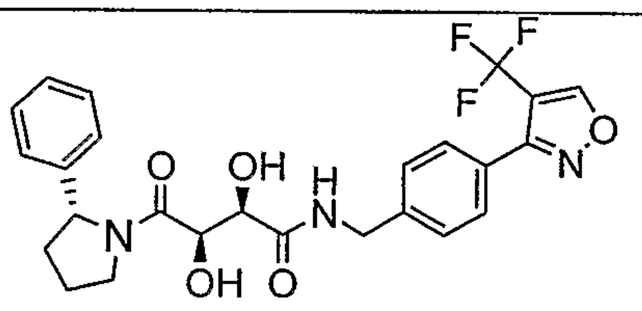
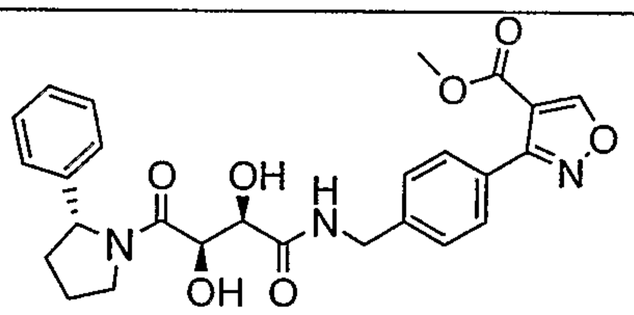
To a solution of 0.46 g of **633** in 10 ml of DCM was added Dess-Martin Reagent (1.1 eq) and the reaction was stirred at r.t. for 30 min before it was treated with sat. aqueous solution of sodium bicarbonate and sodium thiosulfate 7:1 (w/w). The aqueous layer was extracted with DCM (2X) and the combined 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

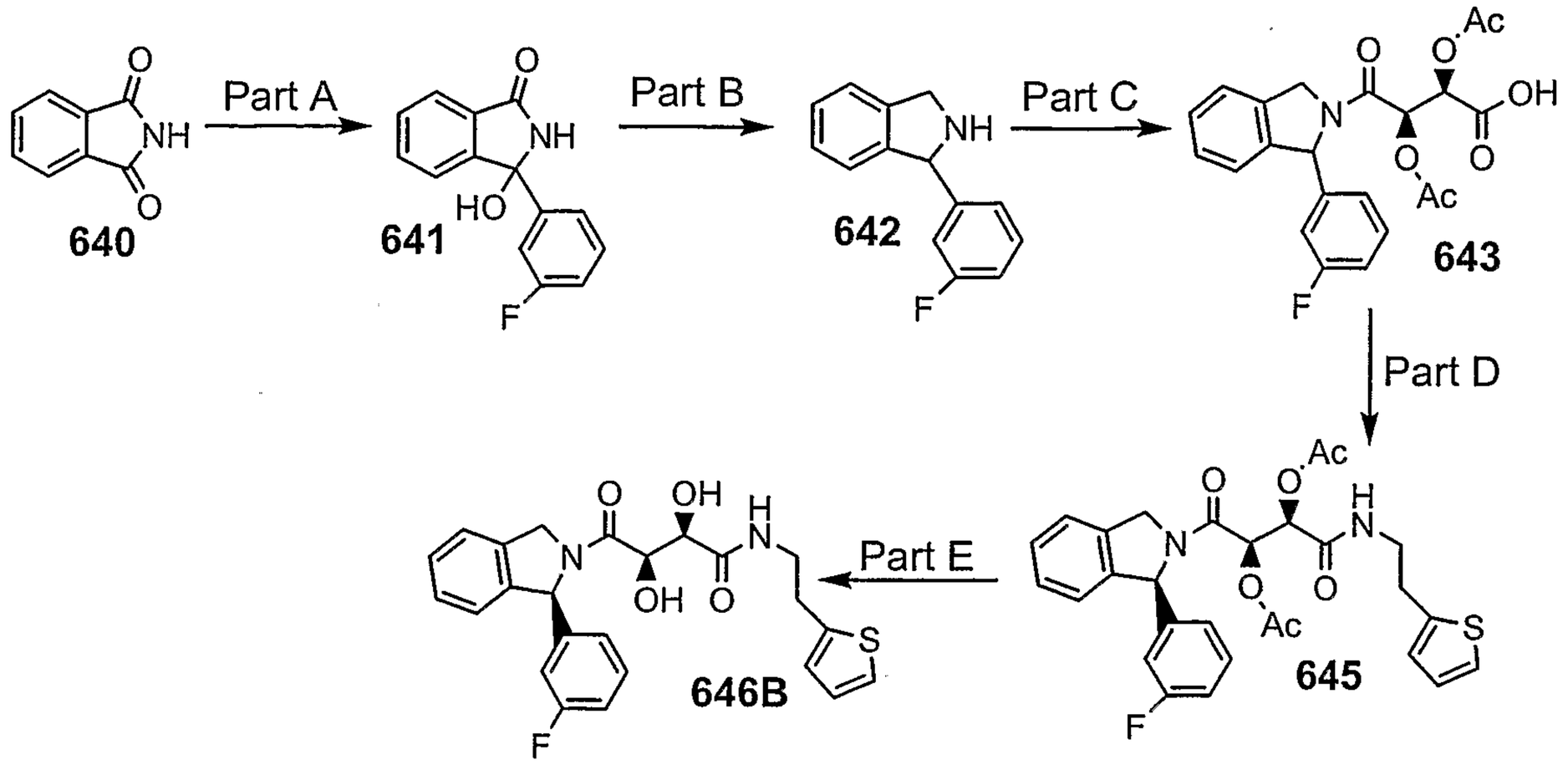
To a flask containing **634** (0.42 g) in anhydrous DMF at 0 °C was added NBS (1 eq) and the solution was allowed to warm up to r.t. overnight before another equivalent of NBS was added and solution stirred for another overnight. The final reaction mixture was poured over ice and extracted with DCM. 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:

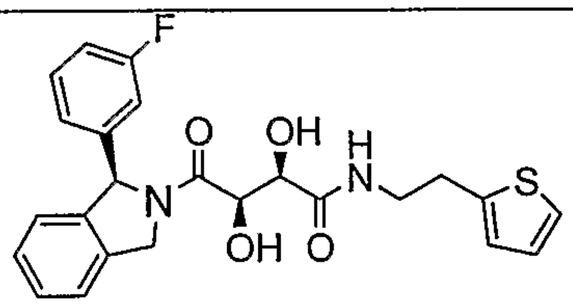
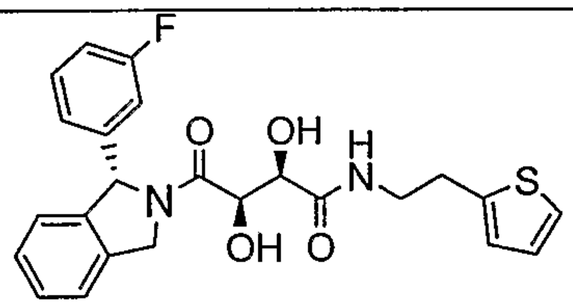
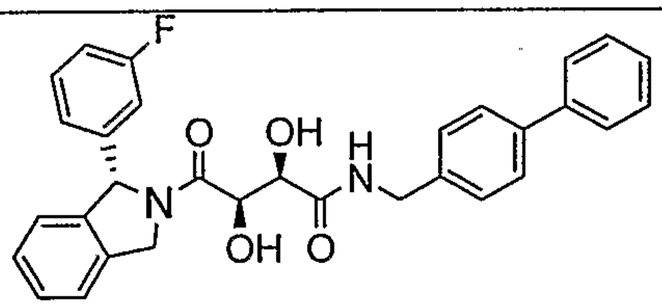
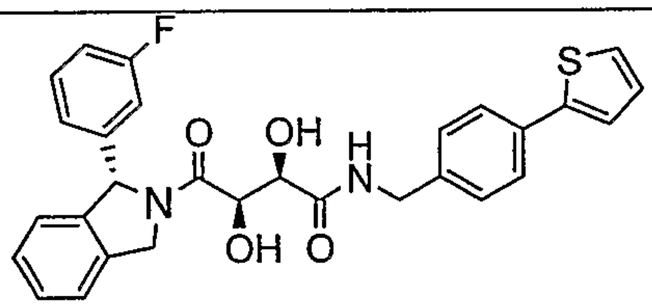
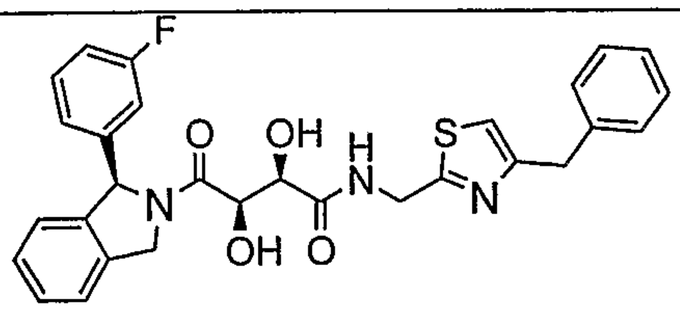
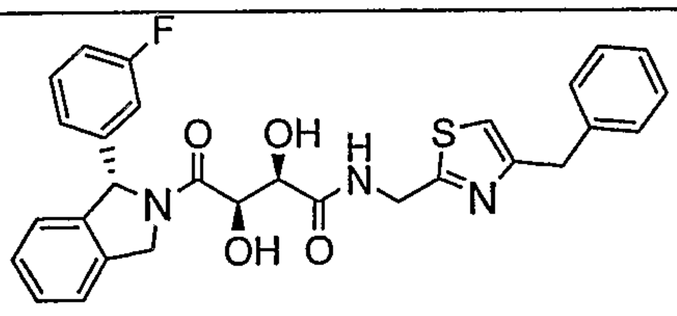
Compound **643** (92 mg, 0.214 mmol), HOBT (36 mg, 0.26 mmol), DMF(1.5 mL), 2-thiophene ethylamine (44 mg, 0.34 mmol), and N-methylmorpholine (50 µL) were added to a flask. EDC was added and the reaction mixture was left stirring ON at rt. The reaction mixture was diluted with EtOAc and washed with aqueous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

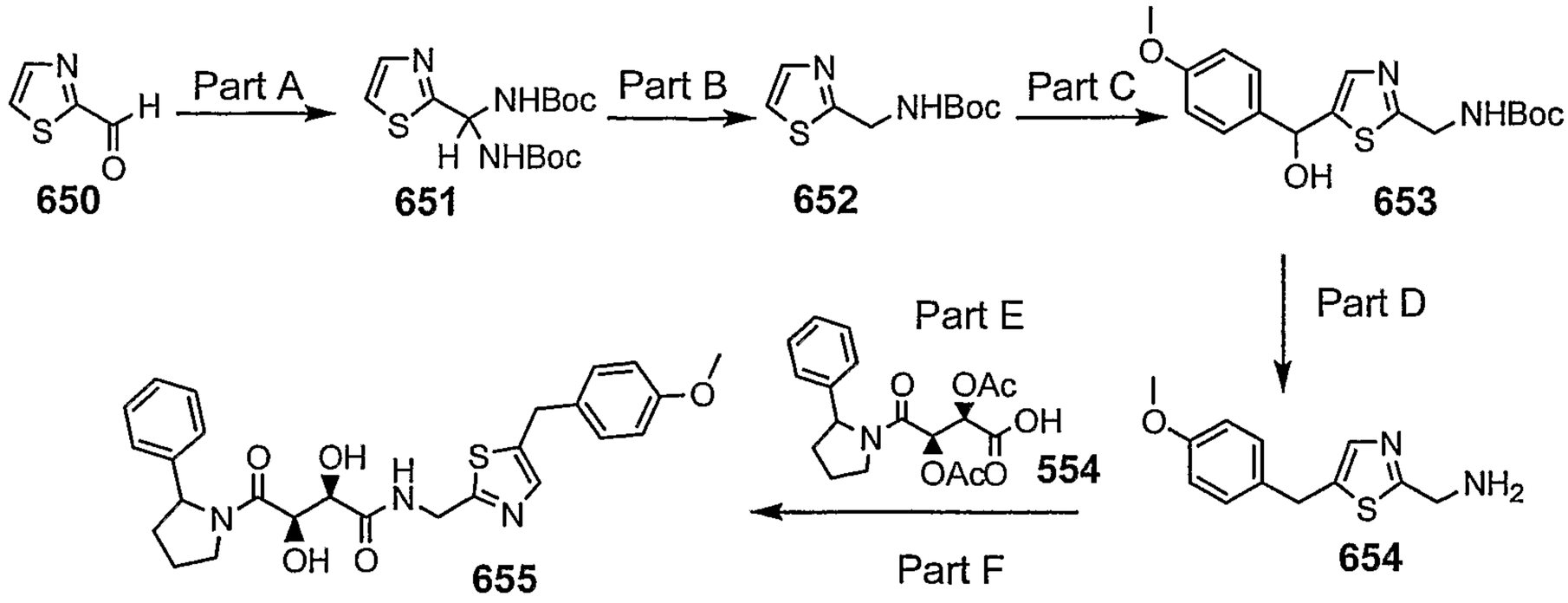
Part E:

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:

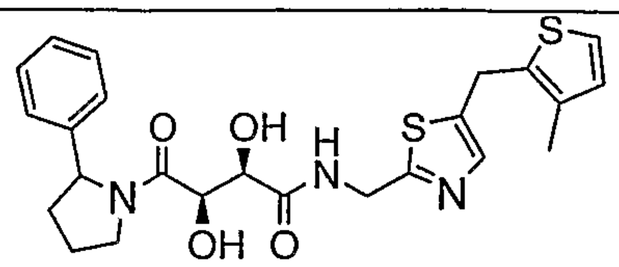
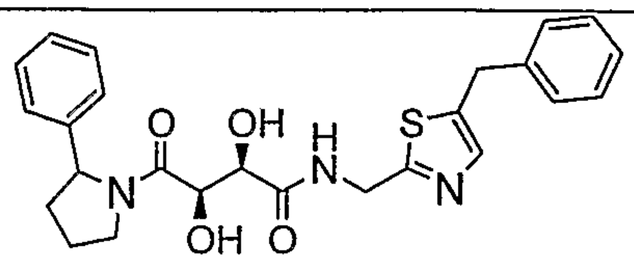
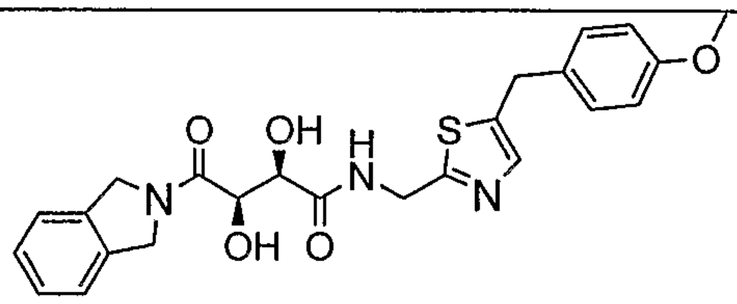
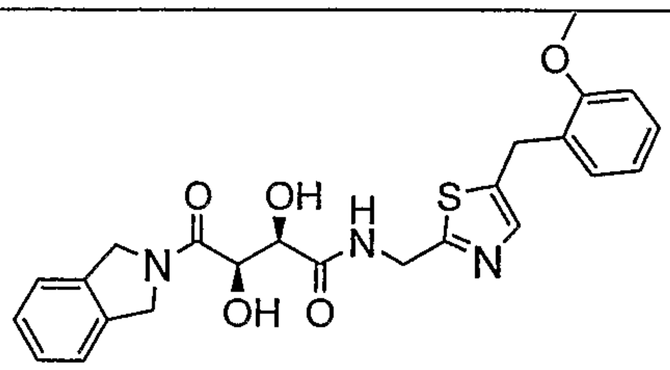
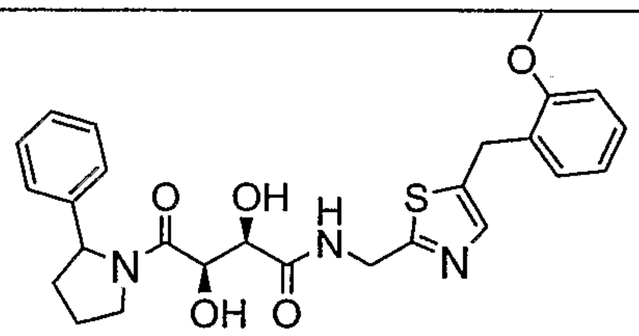
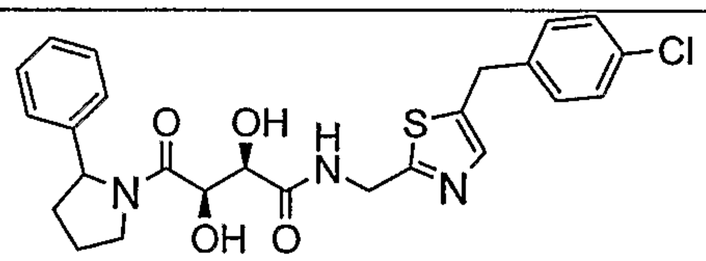
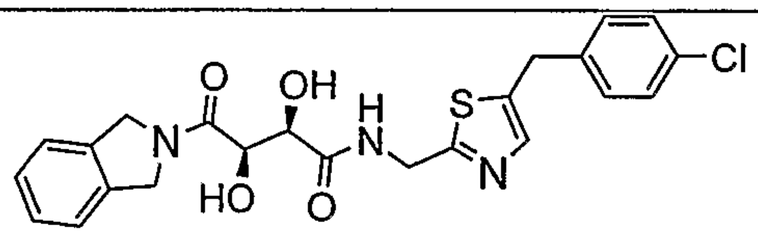
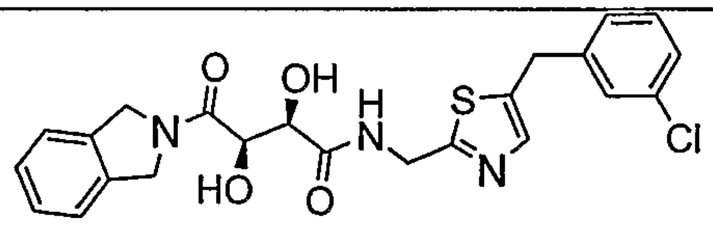
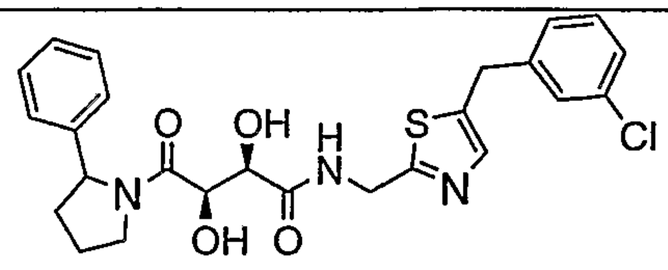
Compound **652** (0.30 g, 1.40 mmol) was dissolved in 5 mL of anhydrous THF (5 mL). The flask was capped with a septum, placed under N_2 blanket, and cooled in a dry ice/2-propanol bath. A solution of LDA (1.71 mL, 1.8 M) was added via syringe and the reaction mixture was stirred for 0.5 h. A solution 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).

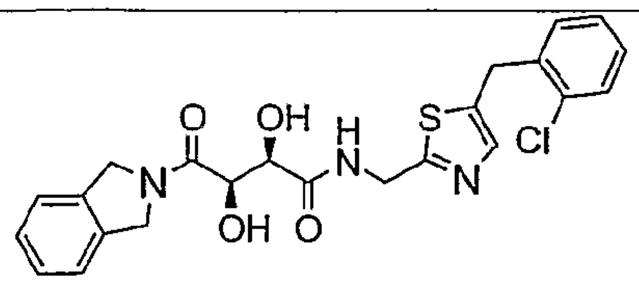
Part D:

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:

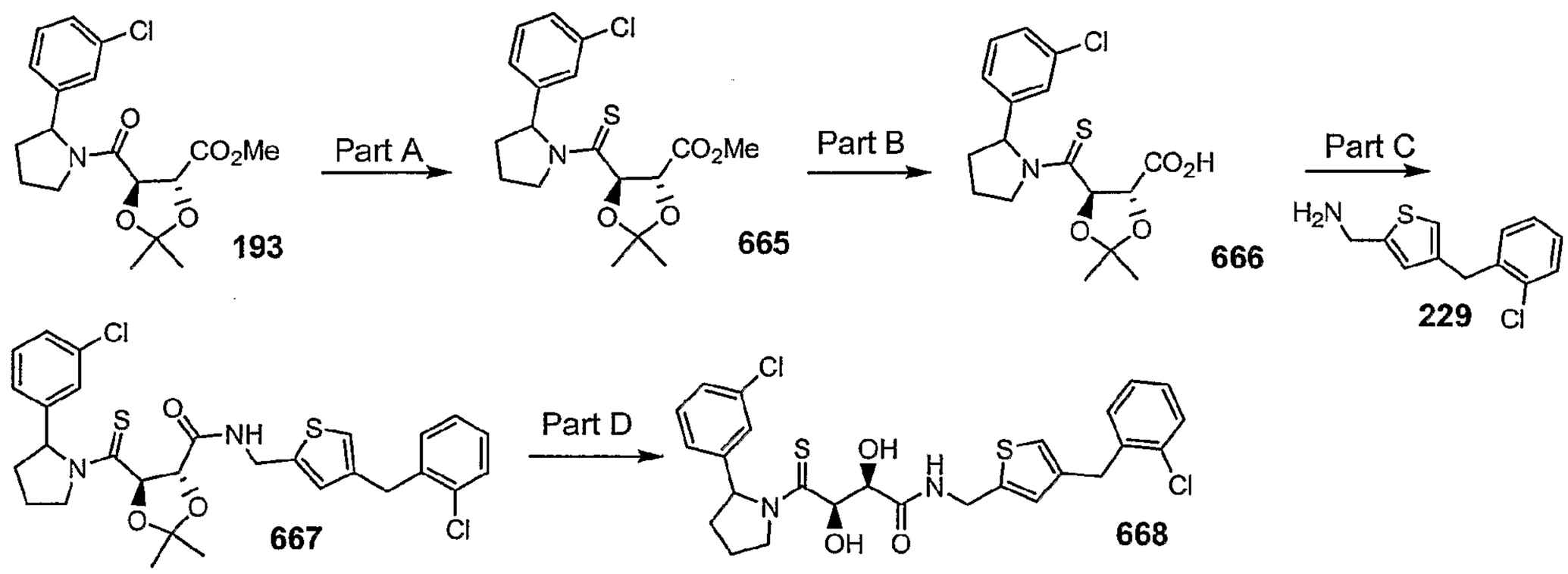
Compound **654** was converted to compound **655** using procedures described in Example 2. Data for **655**: ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.41-7.26 (m, 5H), 7.22-7.14 (M, 4H), 6.89-6.81 (m, 2H), 5.50-5.17 (m, 1H), 4.98-4.54 (m, 4H), 4.53-4.31 (m, 2H), 4.06-3.98 (m, 2H), 3.84 (s, 3H), 2.47-2.27 (m,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

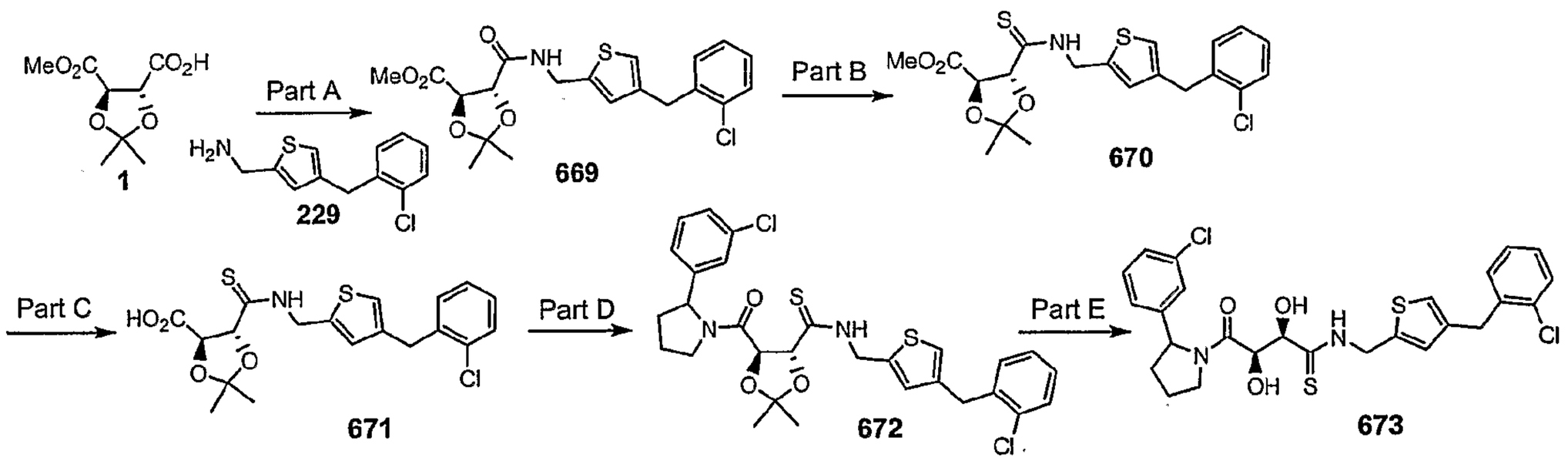
Part D:

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:

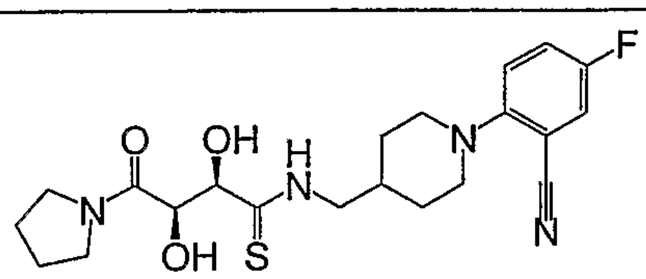
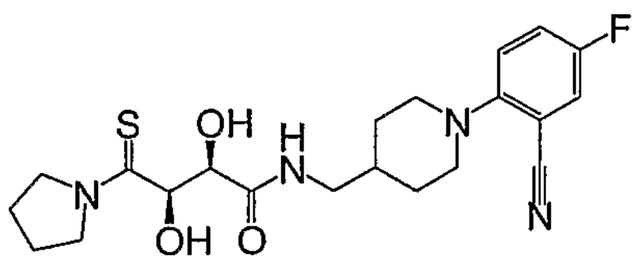
To compound **671** (10 mg, 0.027 mmol) in DMF (0.5 mL) was added racemic 2-(3-chlorophenyl)pyrrolidine (6.5 mg, 0.035 mmol) and HATU (17.5 mg, 0.046 mmol). The reaction mixture was stirred at room temperature for 4 h, and diluted with ethyl acetate and water. The organic layer was washed with 1 N HCl, 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:

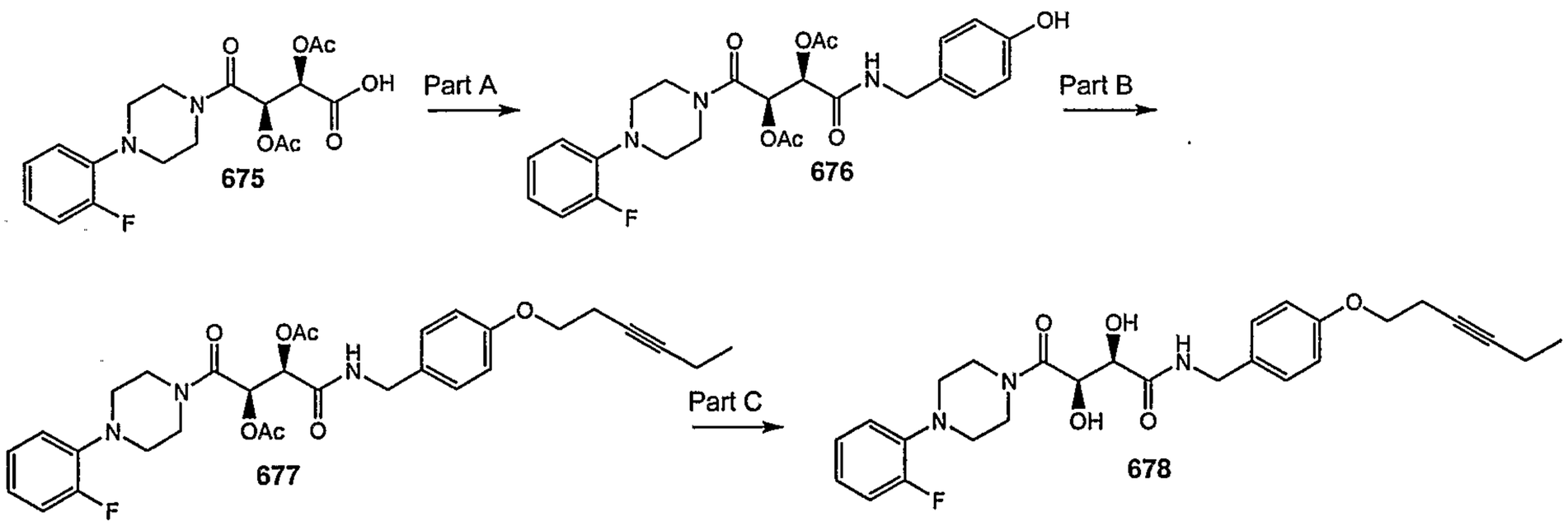
Compound **672** was dissolved in 0.5 mL of TFA/H_2O (80:20) and stirred at room temperature for 2 h. The reaction mixture was quenched with ACN/H_2O

(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).

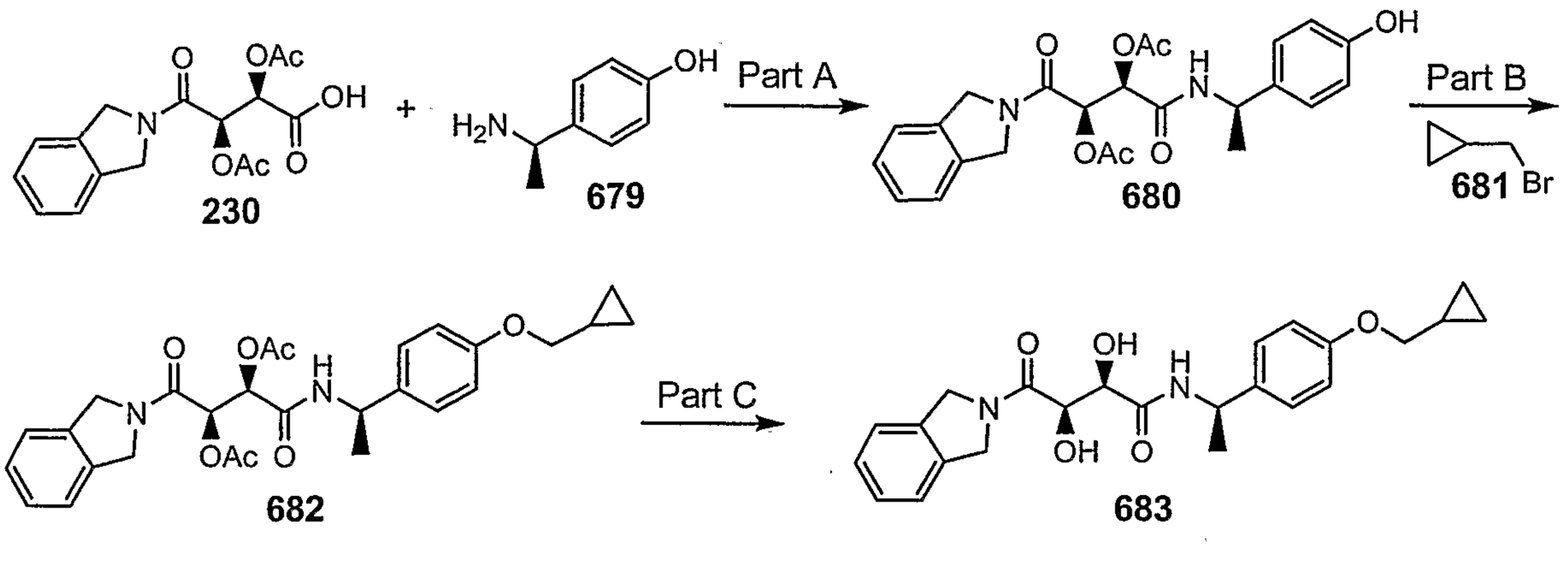
Part B:

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).

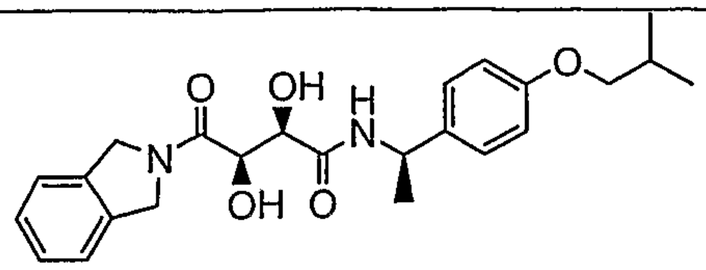
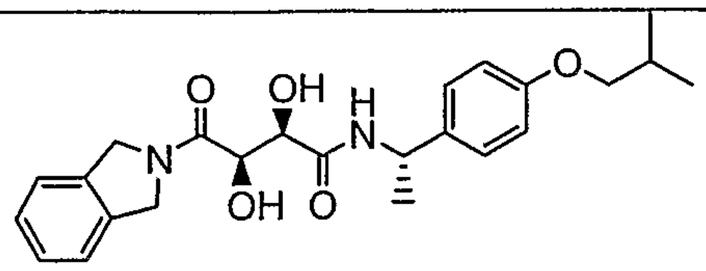
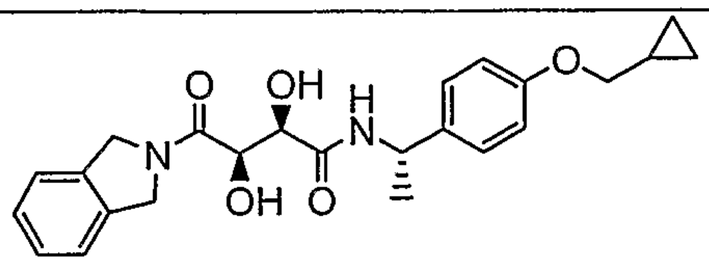
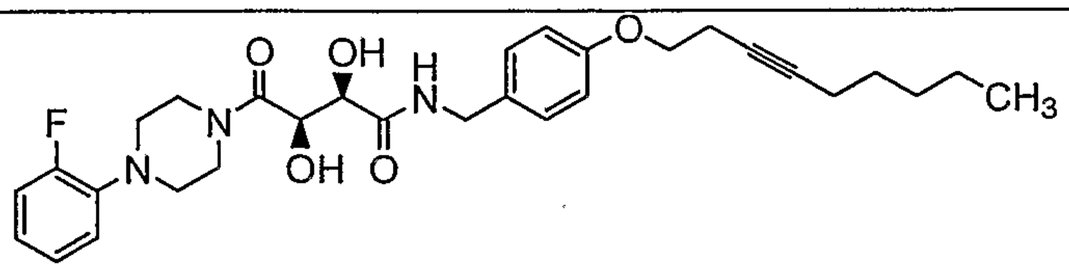
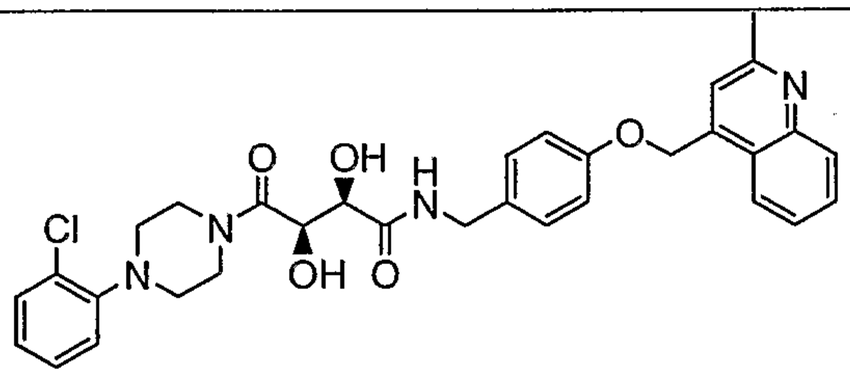
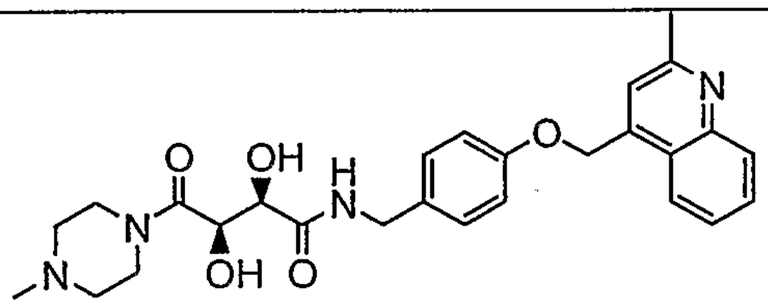
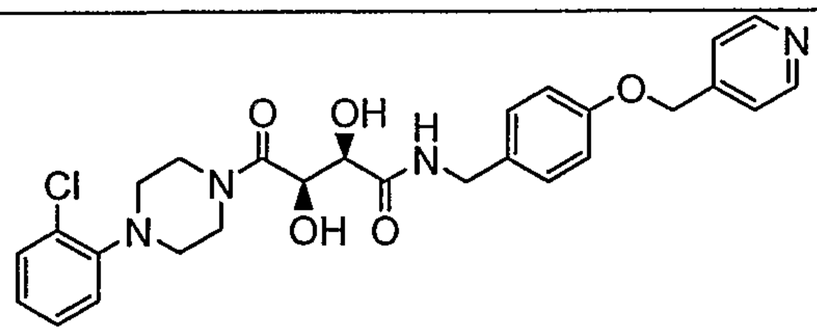
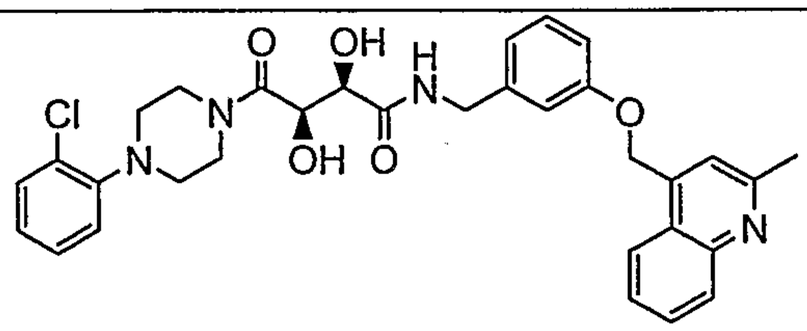
Part B:

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).

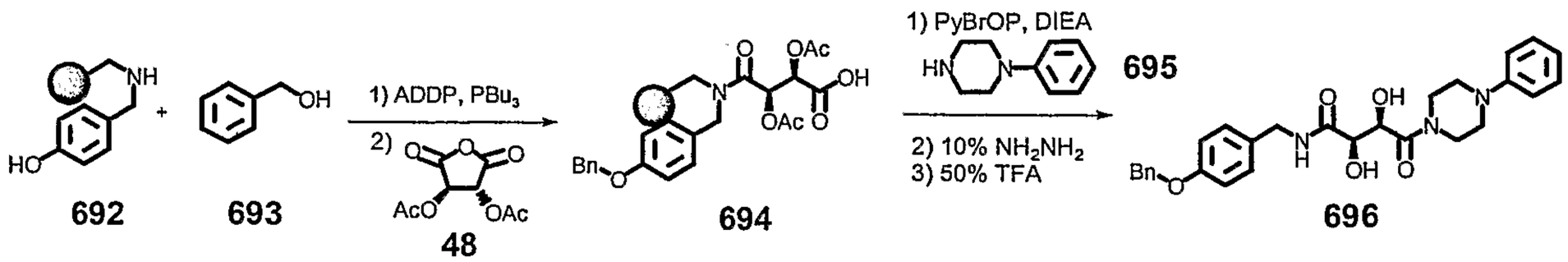
Part C:

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.

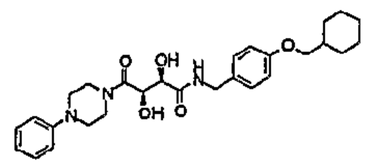
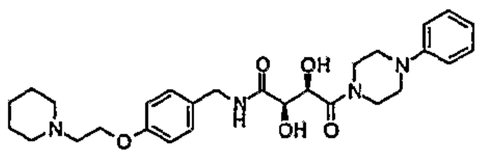
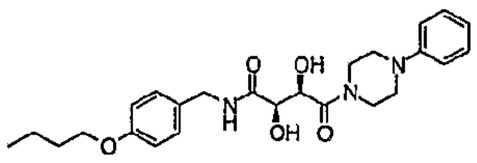
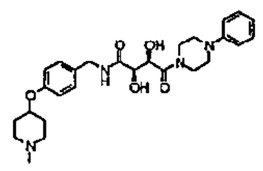
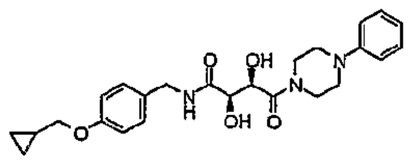
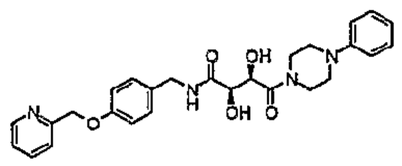
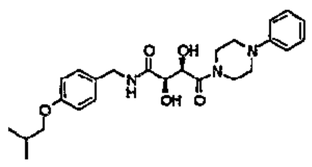
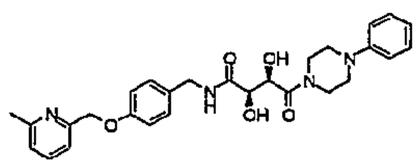
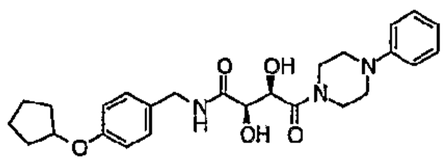
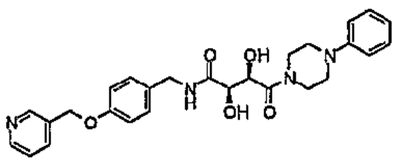
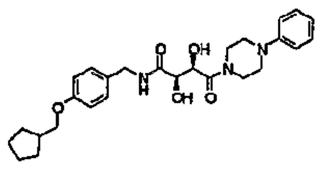
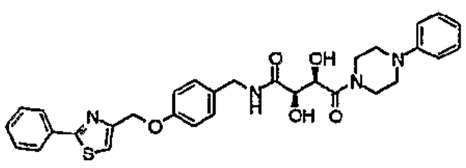
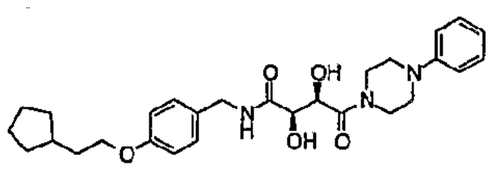
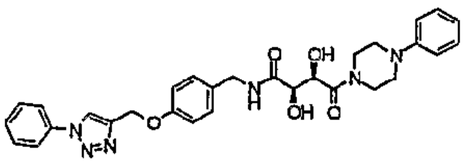
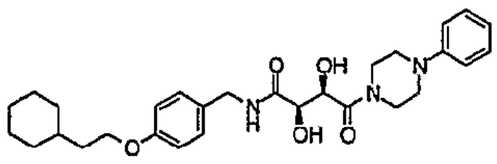
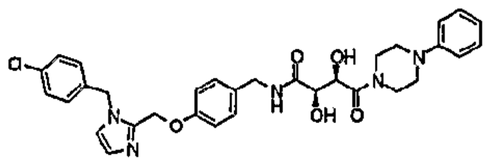
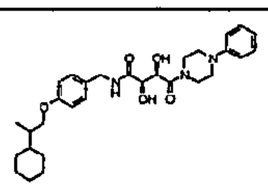
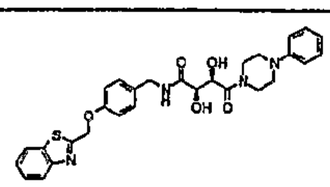
Step A2:

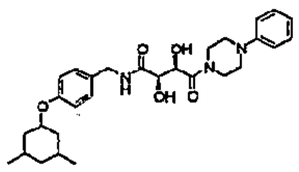
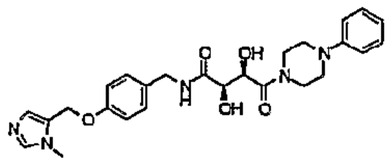
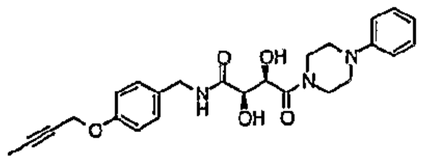
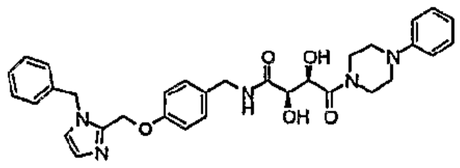
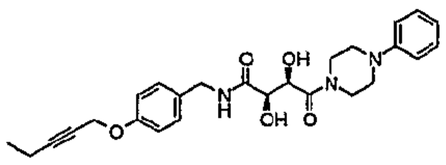
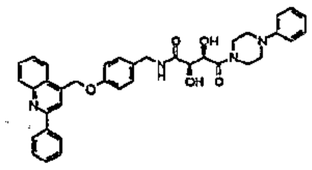
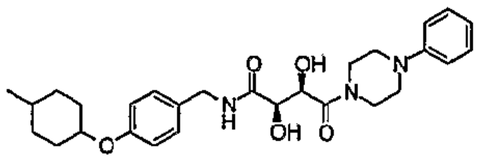
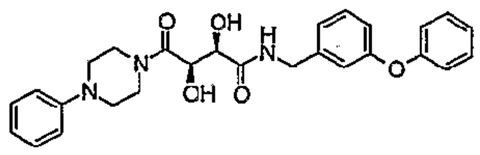
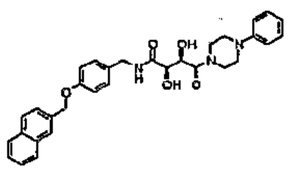
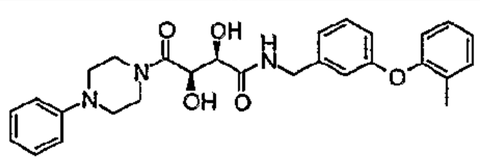
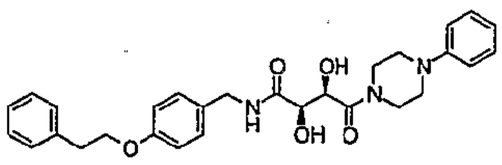
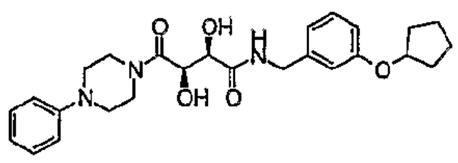
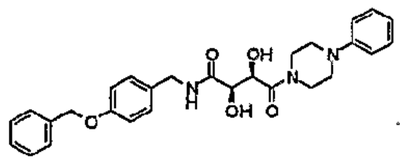
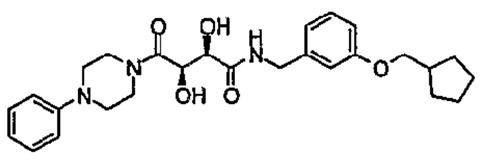
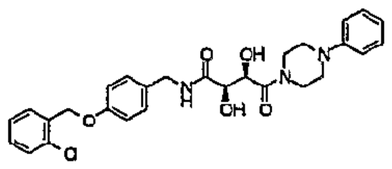
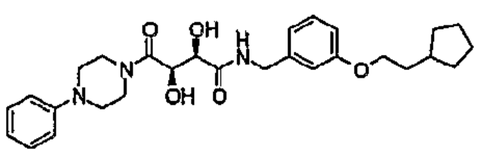
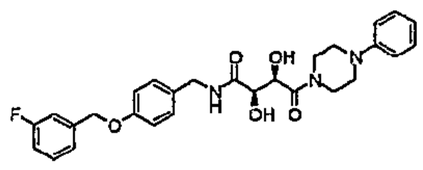
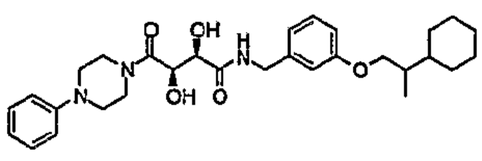
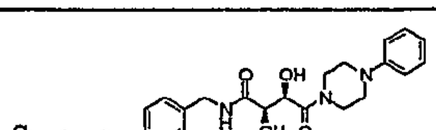
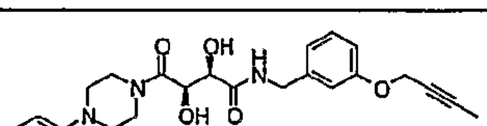
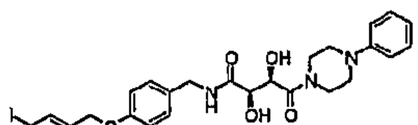
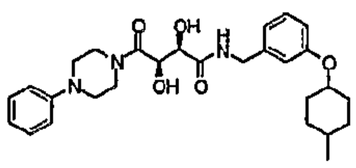
To a pre-swelled resin **692** (150 mg, 1 mmol/g) in anhydrous THF was added benzylalcohol (5 eq) and PPh_3 (7 eq) in 1.5 ml of THF and ADDP (5 eq) in 0.5 ml of DCM. The reaction was agitated at room temperature over the weekend. The reaction solution was drained and resin washed with 5 cycles of MeOH, 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**.

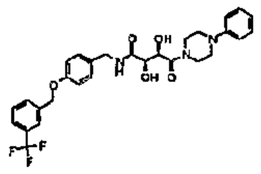
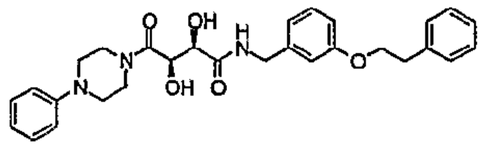
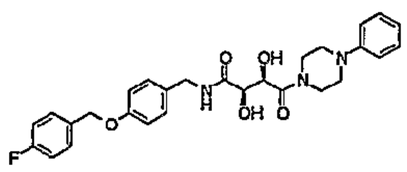
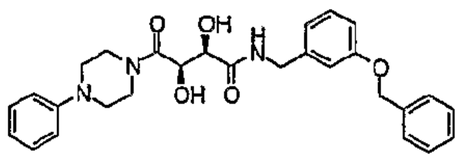
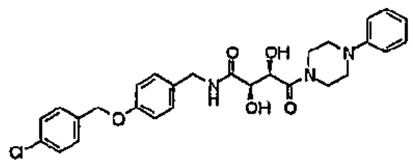
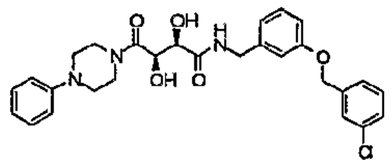
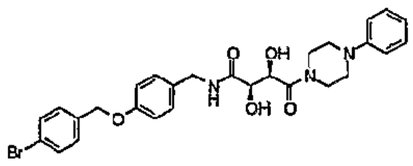
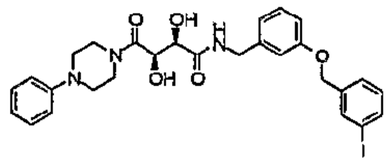
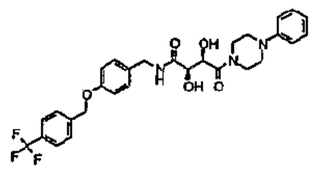
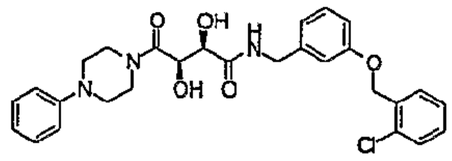
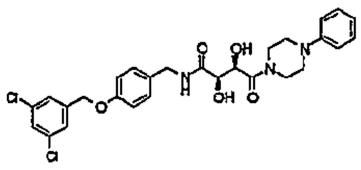
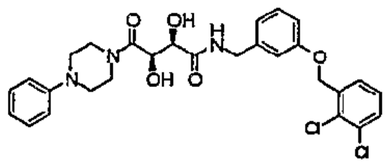
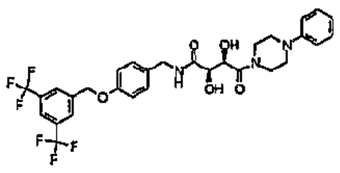
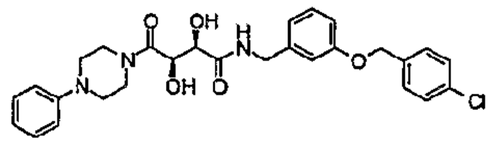
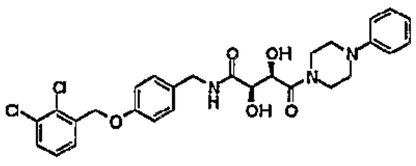
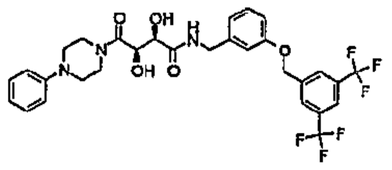
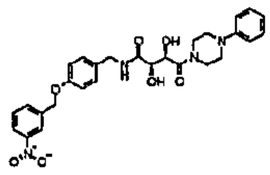
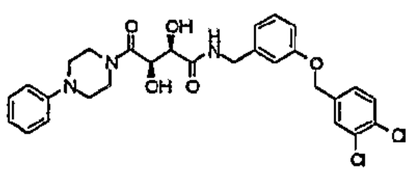
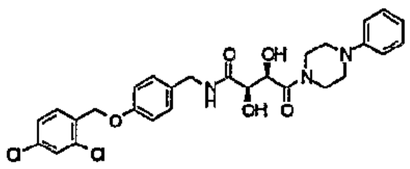
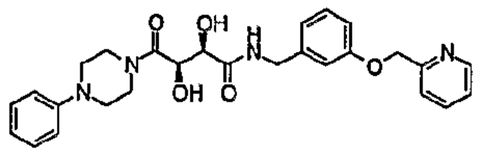
Step B:

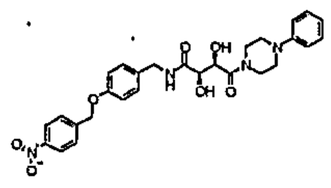
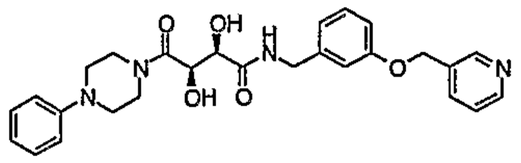
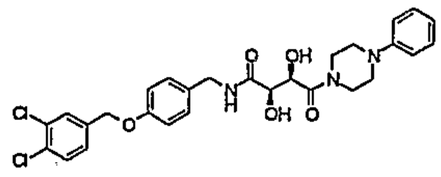
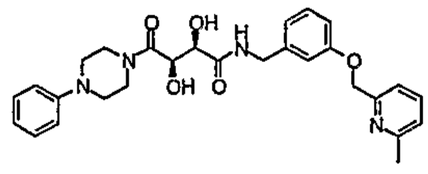
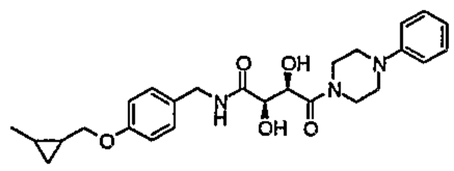
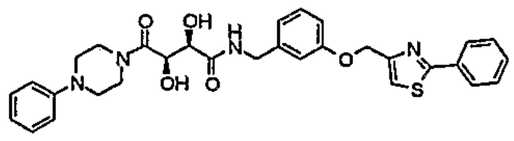
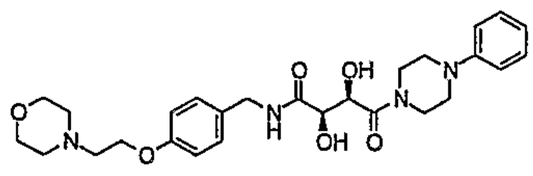
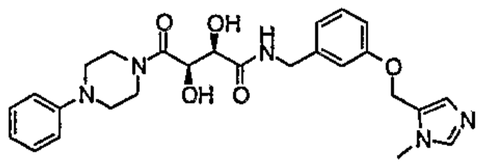
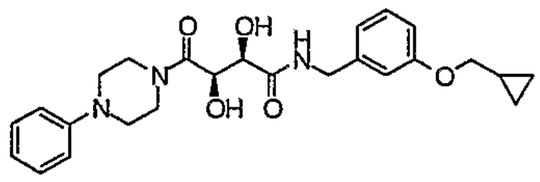
Resin **694** was pre-swelled in DCM, before 1-phenylpiperazine hydrochloric salt (695)(6 eq) was added followed by addition of PyBrop (3 eq) and DIEA (9 eq) in 3 ml of DCM. The reaction solution was agitated overnight before it was drained and resin washed with 5 cycles of MeOH, DCM and THF before it 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.

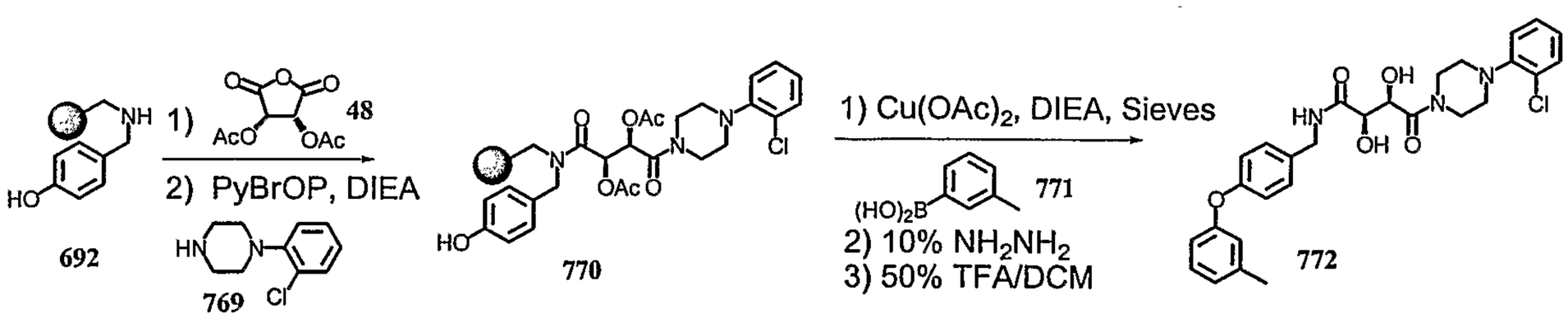
Compound #	Structure	Obs. MS		Compound #	Structure	Obs. MS
697		496		**698**		511
699		456		**700**		497
701		454		**702**		491
703		456		**704**		505
705		468		**706**		491
707		482		**708**		573
709		496		**710**		557
711		510		**712**		604
713		524		**714**		547

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.

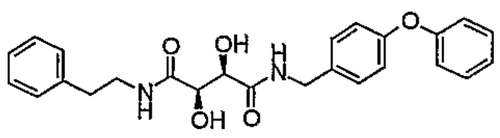
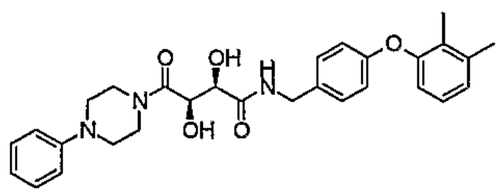
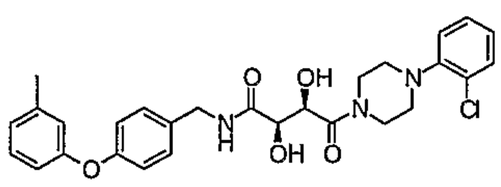
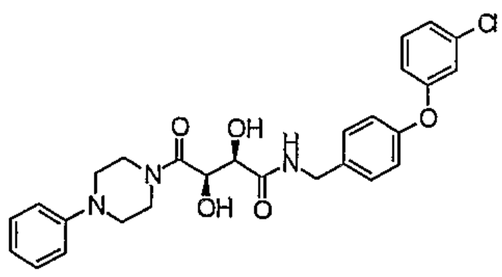
To resin **692** (2.6 g, 1mmol/g), preswelled in NMP was added **48** (5 eq) and the mixture was agitated for 48 h. before the solution was drained and resin washed with 5 cycles of MeOH, DCM and THF and dried in vacuo. The resin was then swelled in anhydrous DCM (25 ml) before **769** (6 eq, HCl salt)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

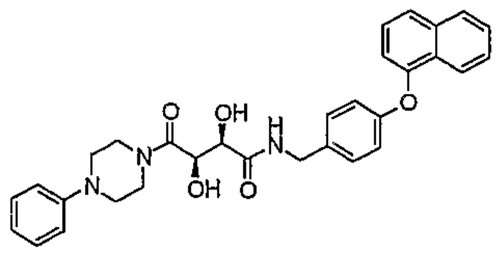
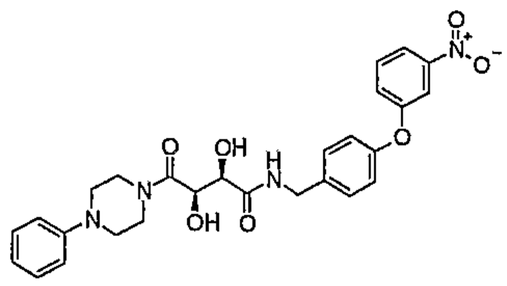
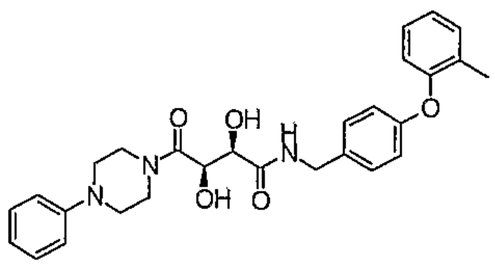
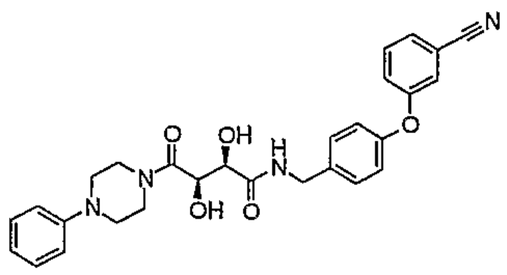
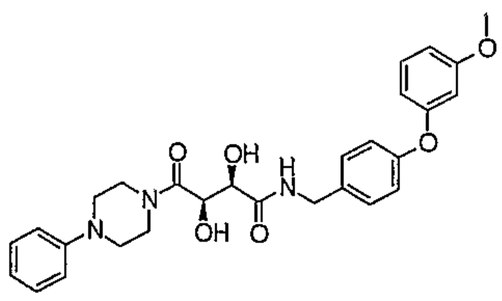
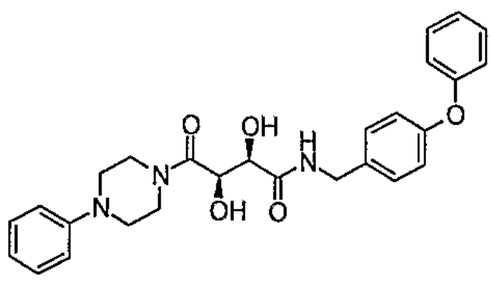
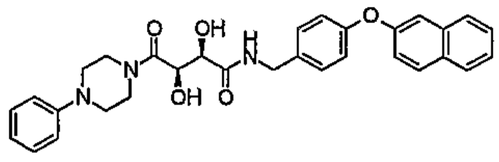
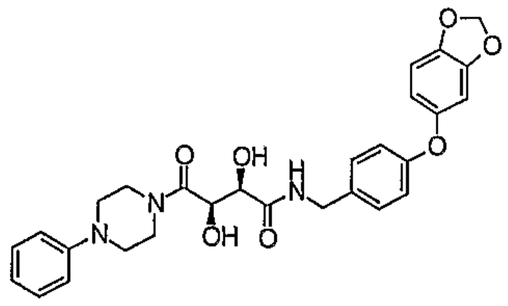
agitated at r.t. overnight before the solution was drained and resin washed with 5 cycles of MeOH, DCM and THF and dried in vacuo to give resin **770** (0.9 mmol/g loading).

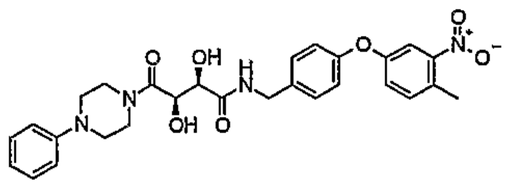
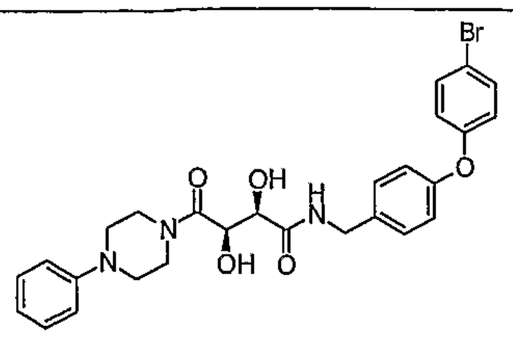
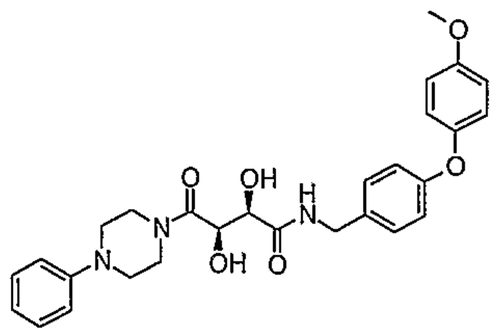
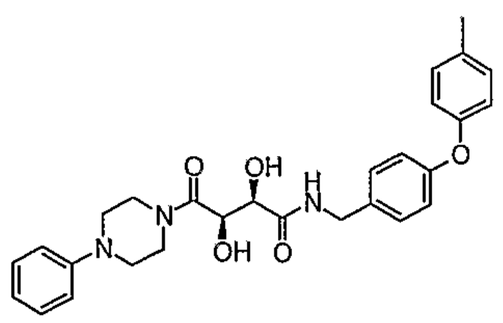
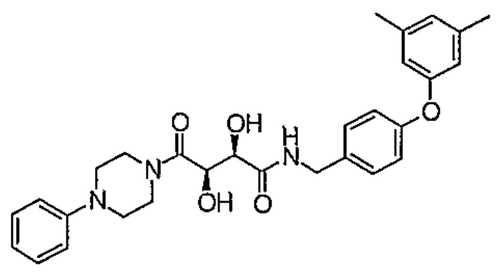
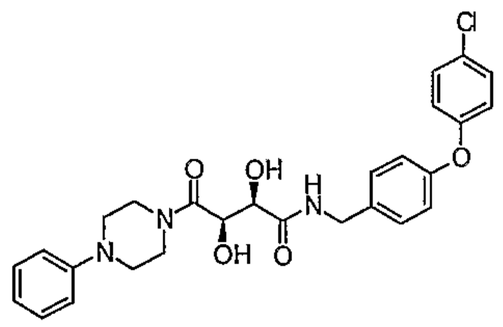
Step B.

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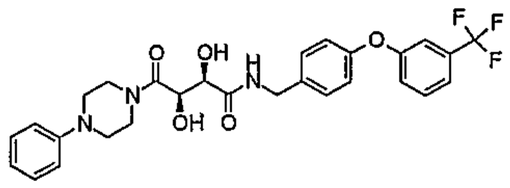
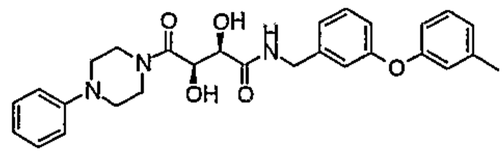
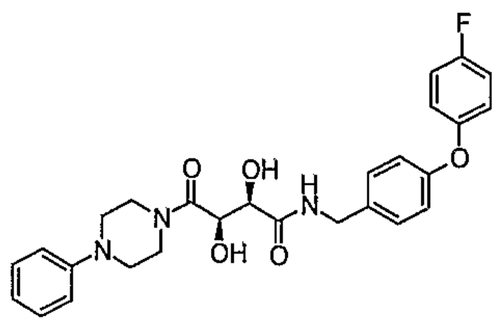
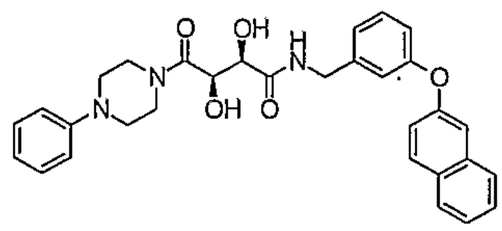
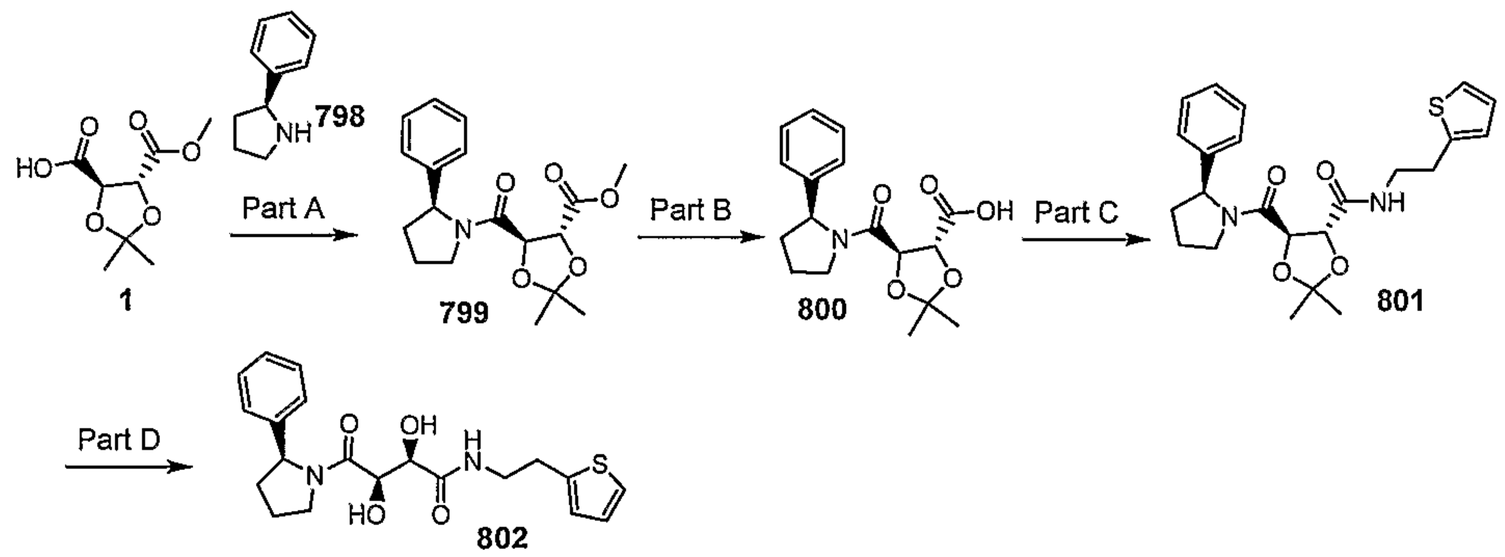
793		544		**794**		490
795		494		**796**		526

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).

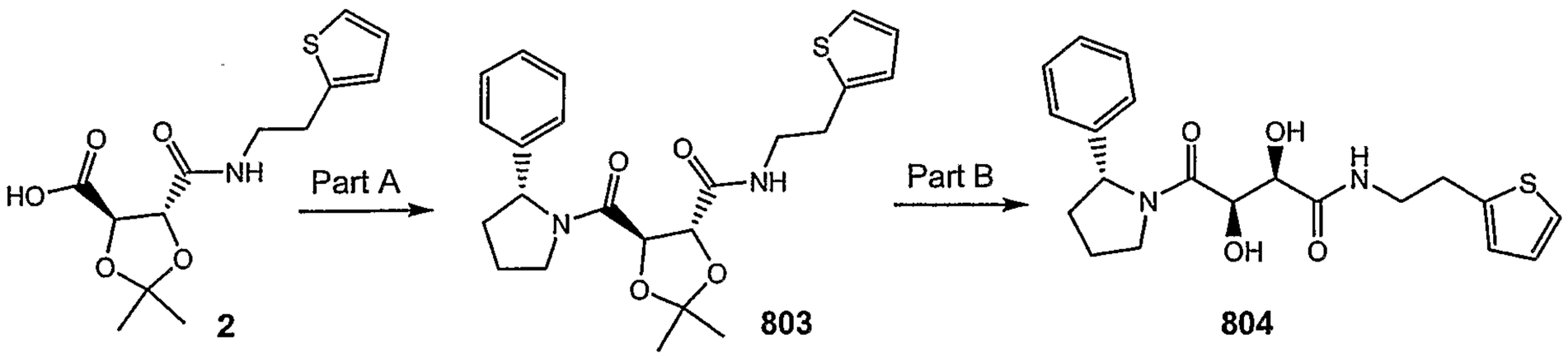
Part C:

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:



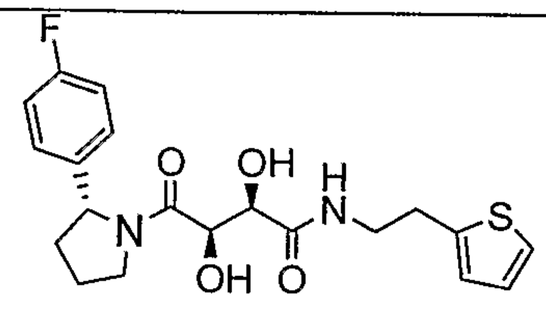
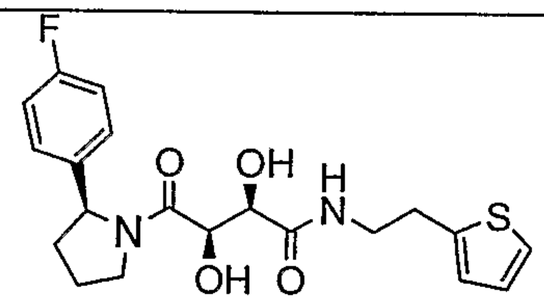
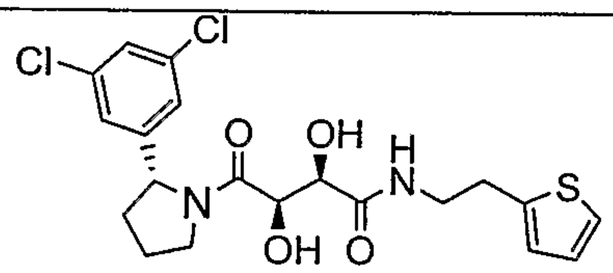
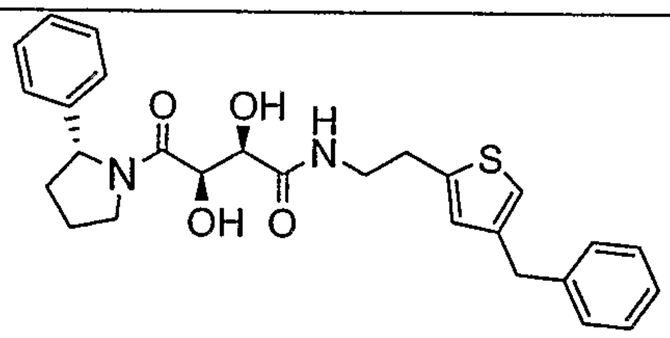
Part A:

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

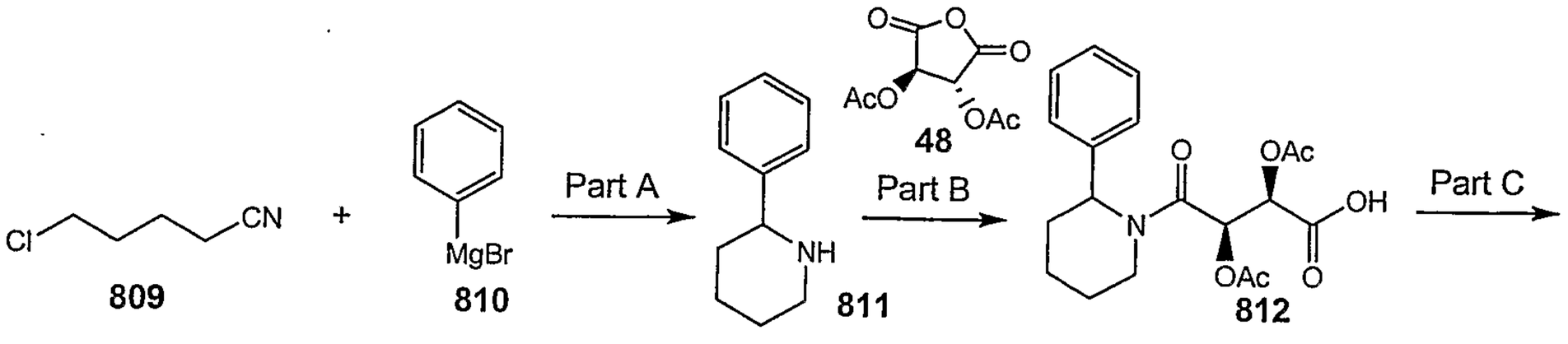
following the procedure described in Example 1 Part A. The desired isomer was separated by reverse phase prep-LC to afford **803** as a white solid. HPLC-MS t_R = 1.96 min ($UV_{254\ nm}$); Mass calculated for formula $C_{23}H_{28}N_2O_4S$ 428.2, observed LCMS m/z 429.1 (M+H).

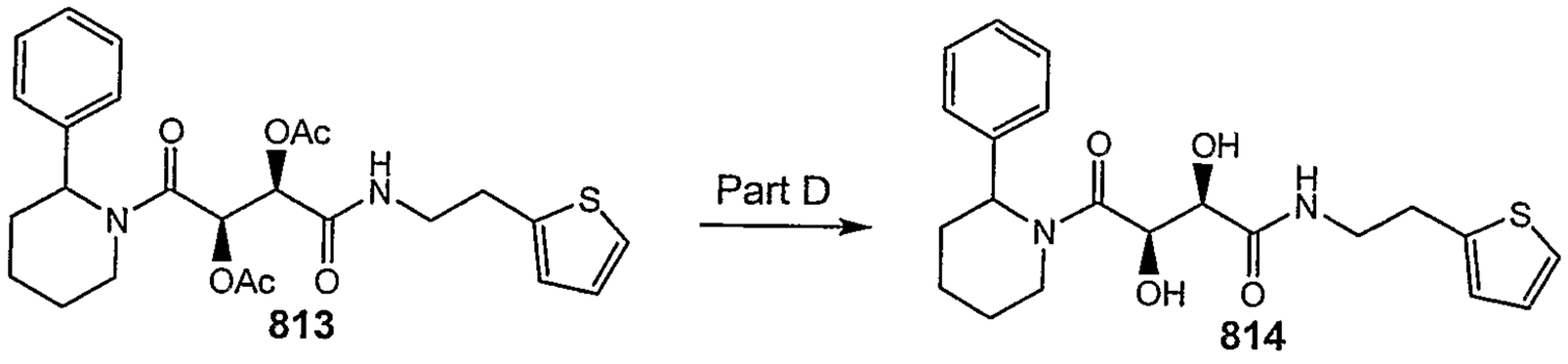
Part B:

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:

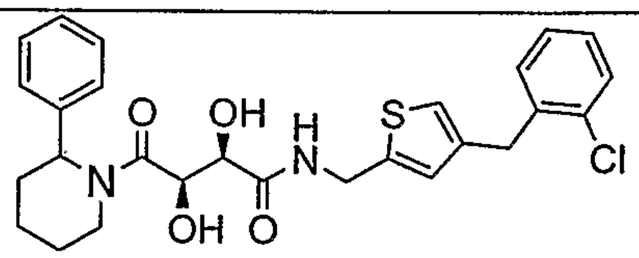
To **48** (108 mg, 0.5 mmol) in DCM (3 mL) was added **811** (80 mg, 0.5 mmol). The reaction mixture was stirred overnight before being poured into 1.0 N HCl and extracted with DCM. The combined organic layers were dried over sodium sulfate, concentrated and freeze-dried to afford **812** as a white 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).

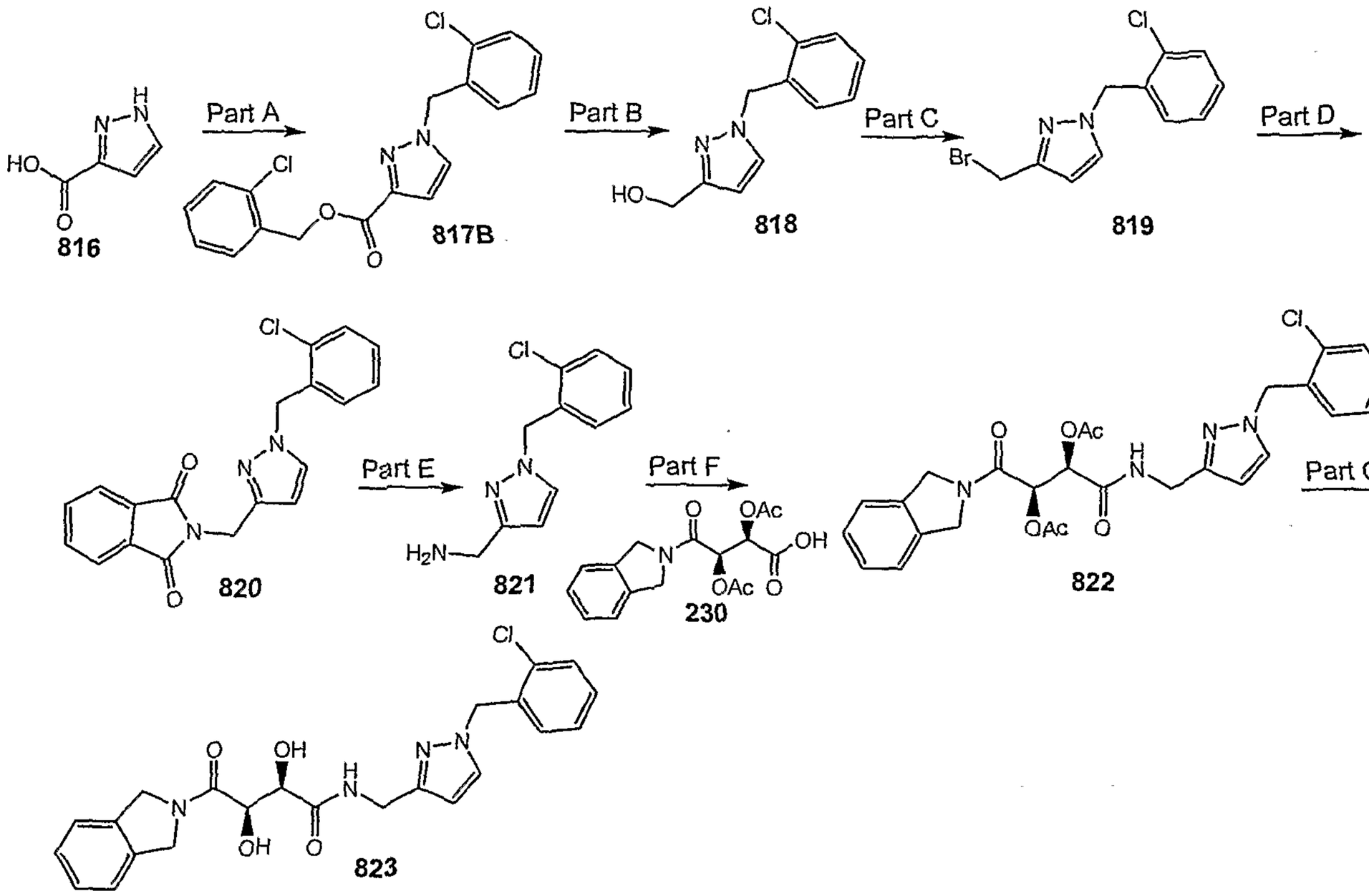
Part D:

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).

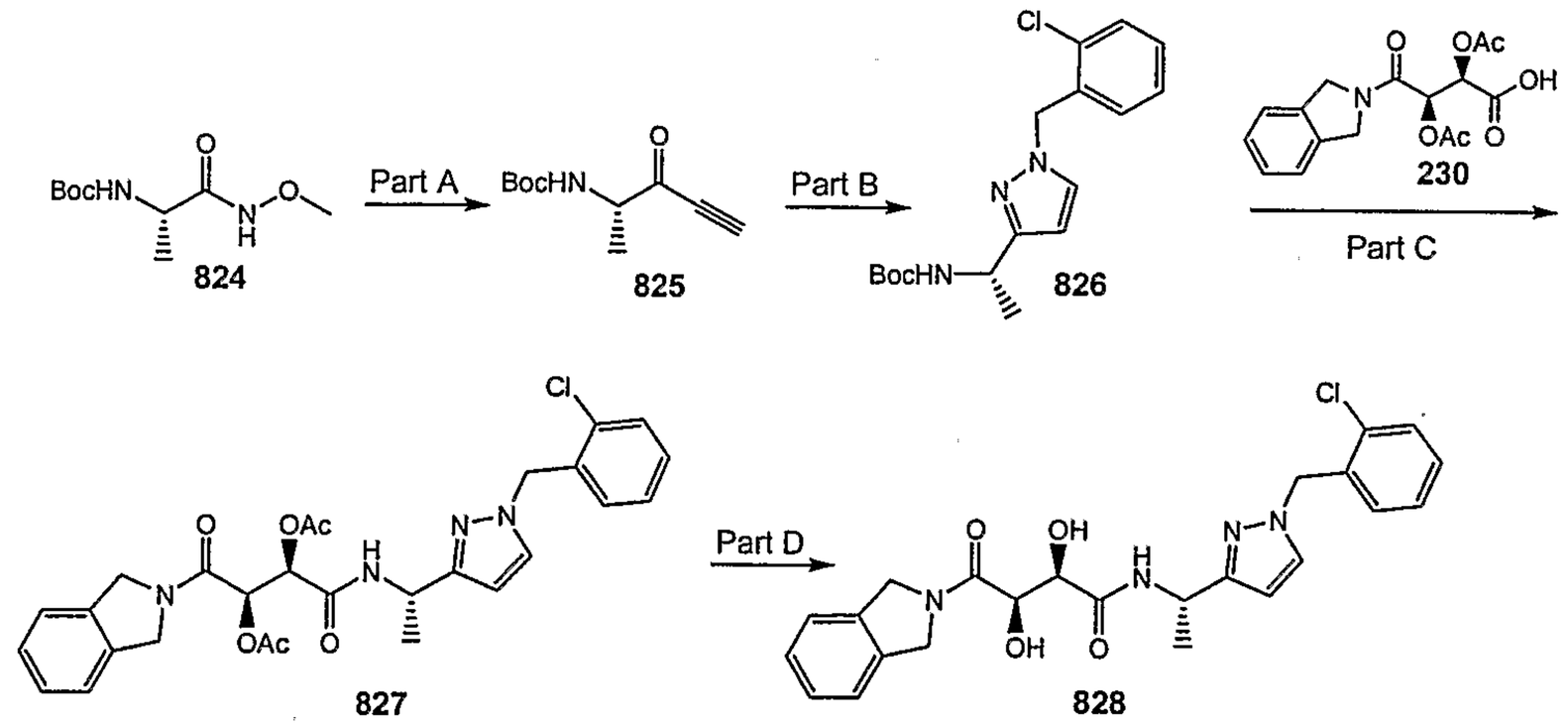
Part F:

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).

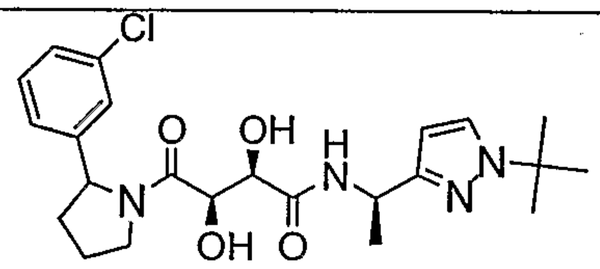
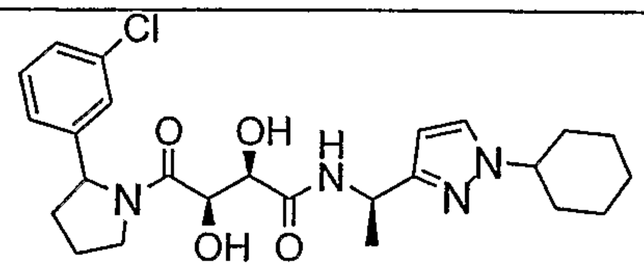
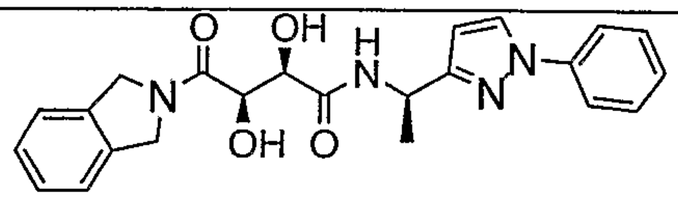
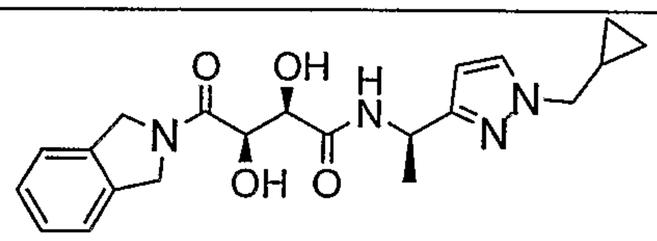
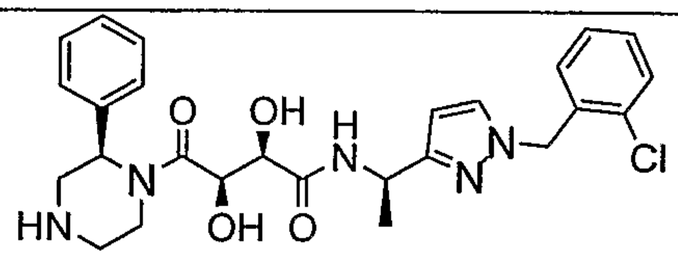
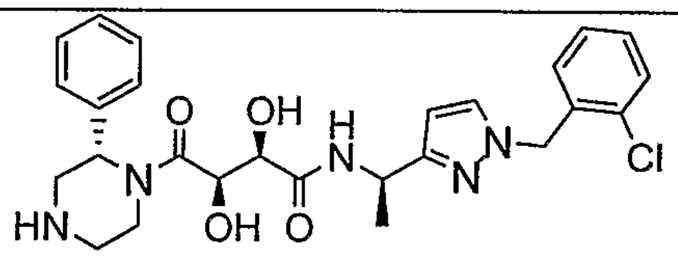
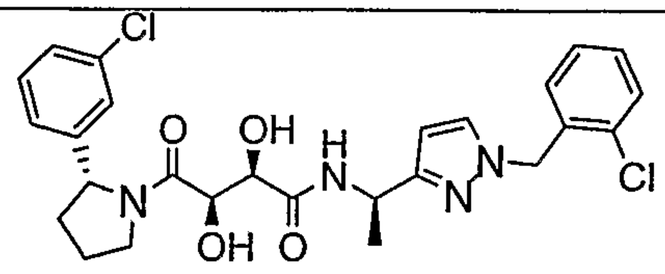
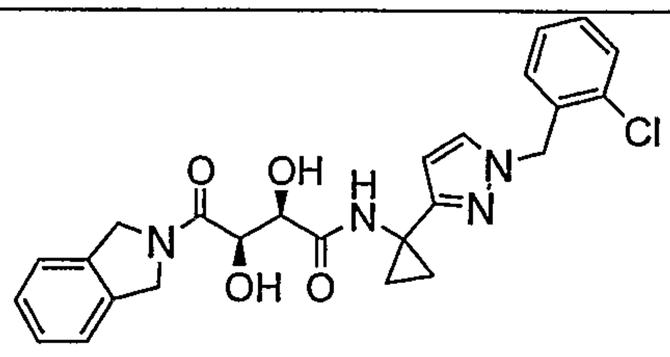
Part C:

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:

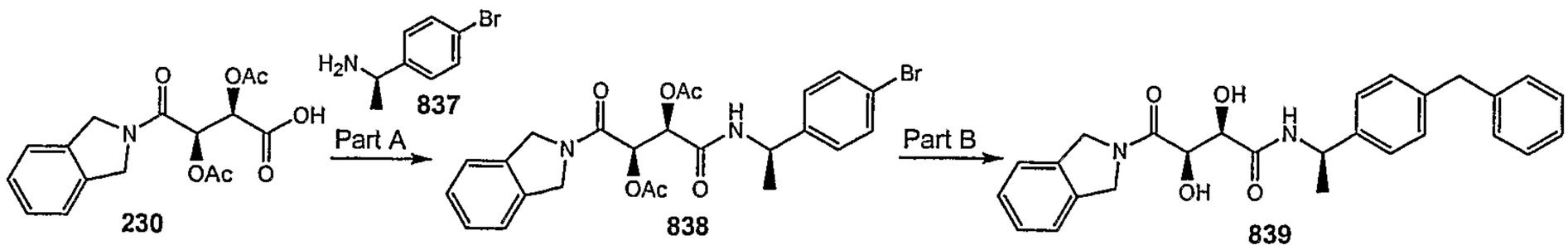
Compound **827** (~25 mg, 0.05 mmol) was dissolved in methanol (5 mL) and a solution on potassium carbonate (50 mg) in water (1 mL) was added. The reaction was stirred for 30 minutes. The reaction mixture was diluted with ethyl acetate and brine. The organic layer was separated, dried over sodium sulfate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



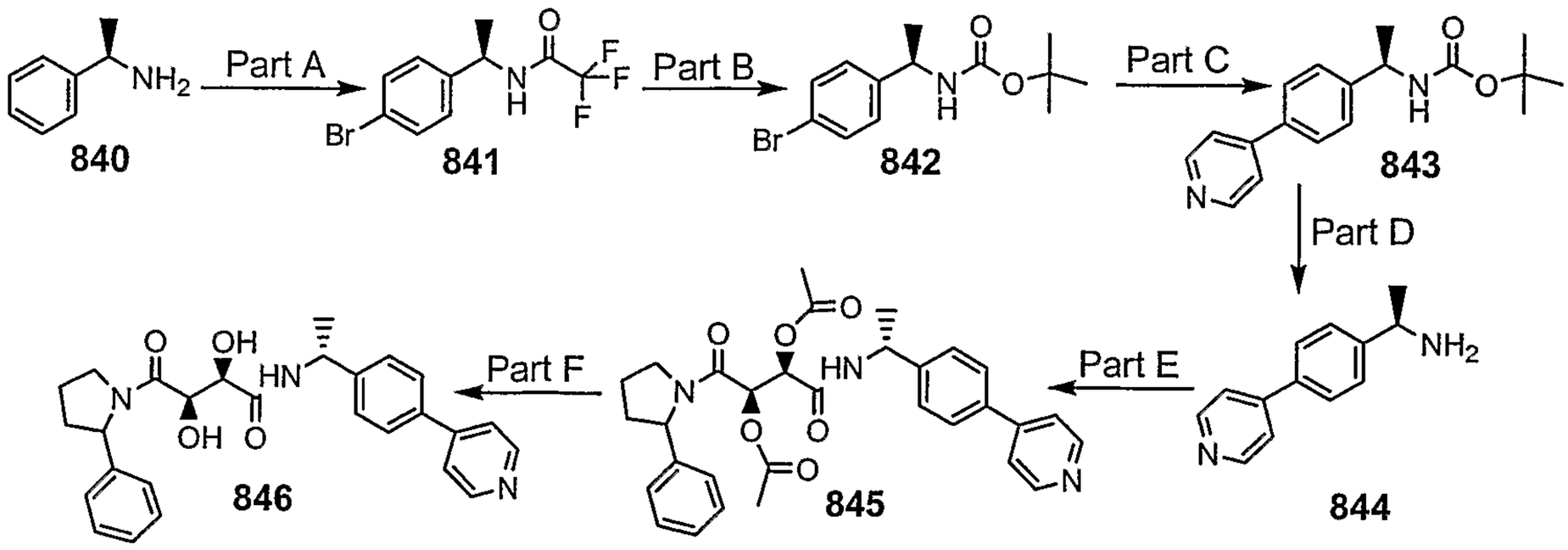
Part A:

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:


NH2
Part A
Br
F
F
F
Part B
Br
Part C
Part D
NH2
Part E
Part F
OH
OH
HN
HN
N
O
O
O

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.

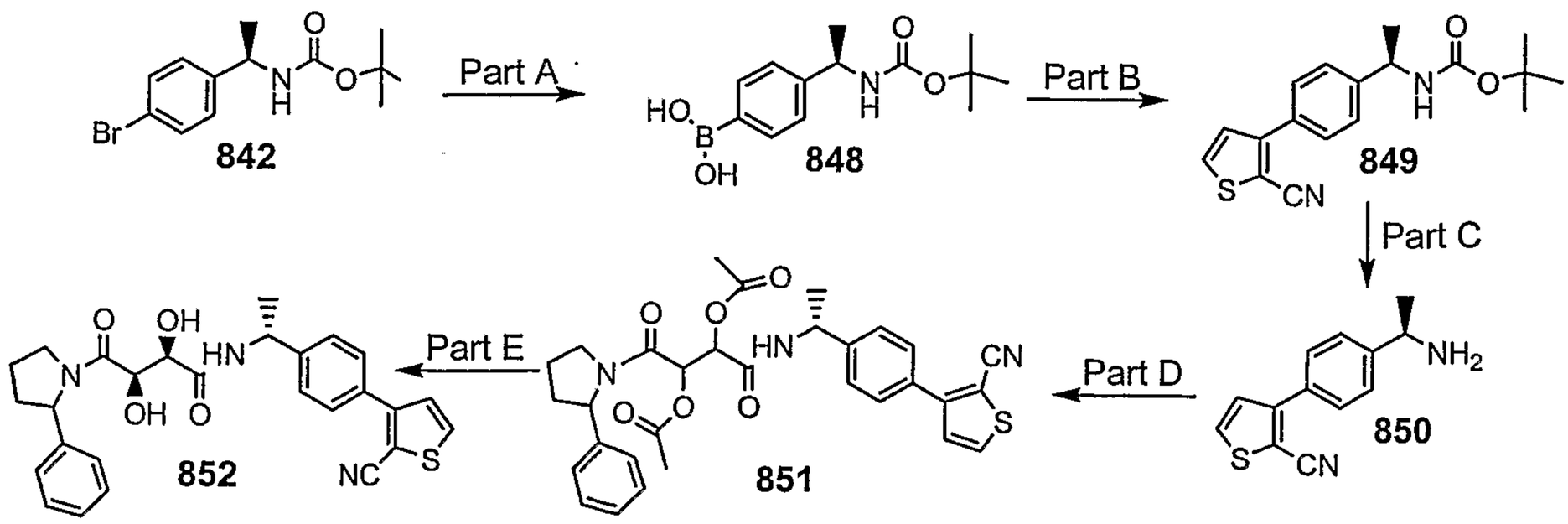
Part D:

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

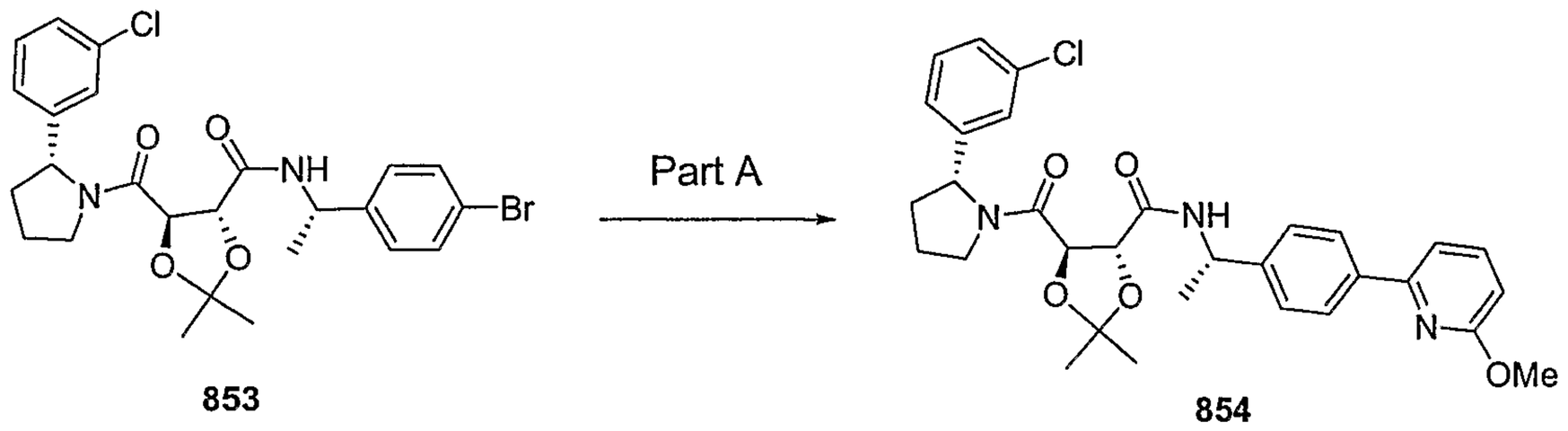
Part C:

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

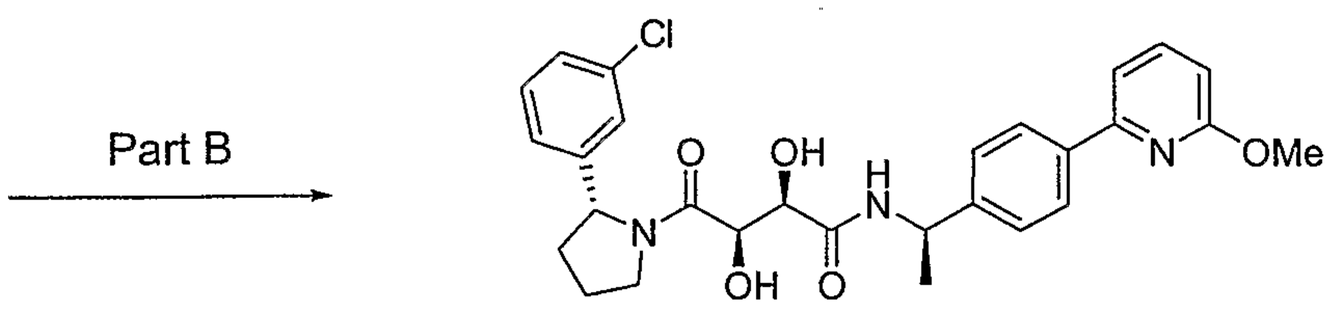
Parts D and E:

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.

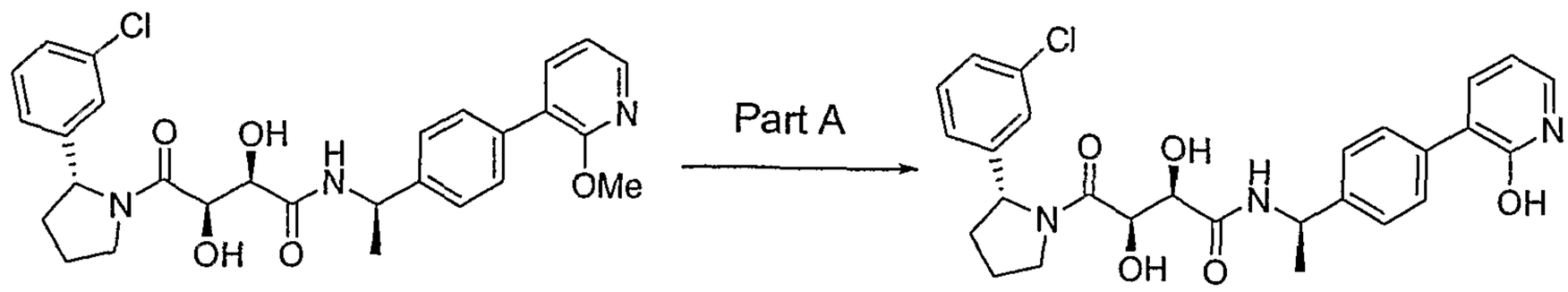
Part A:

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:



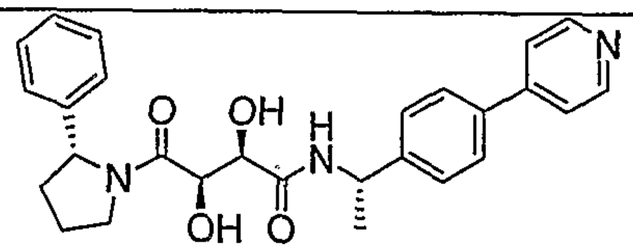
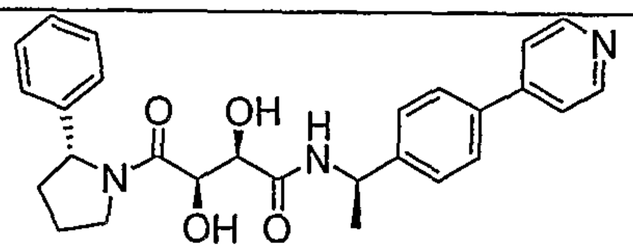
856 857

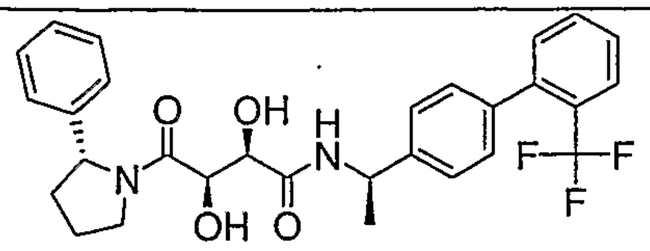
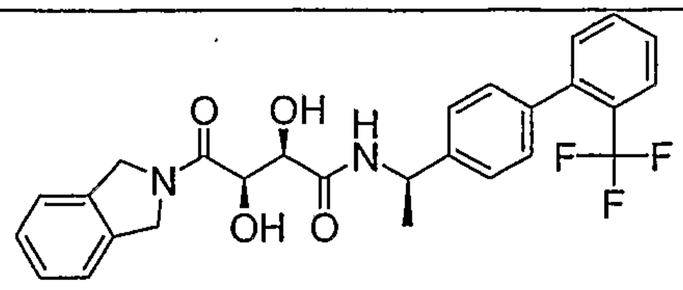
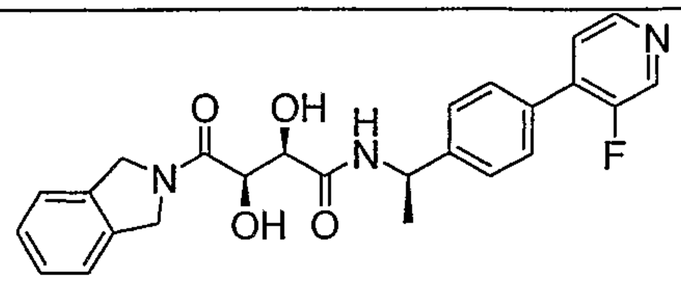
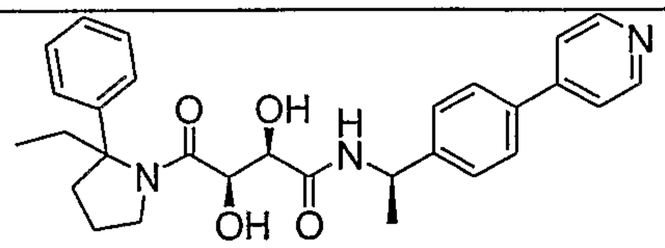
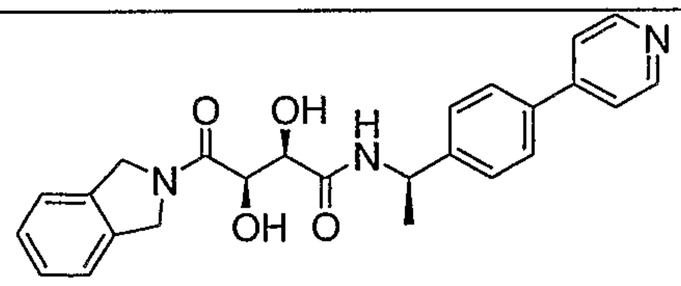
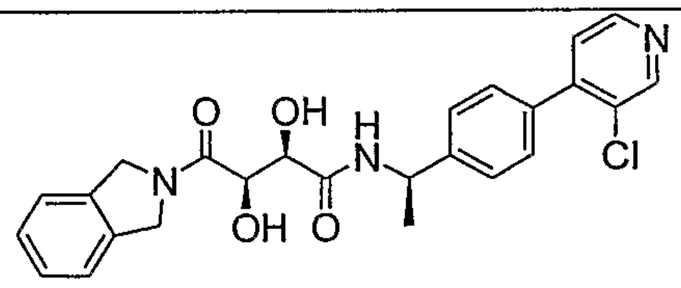
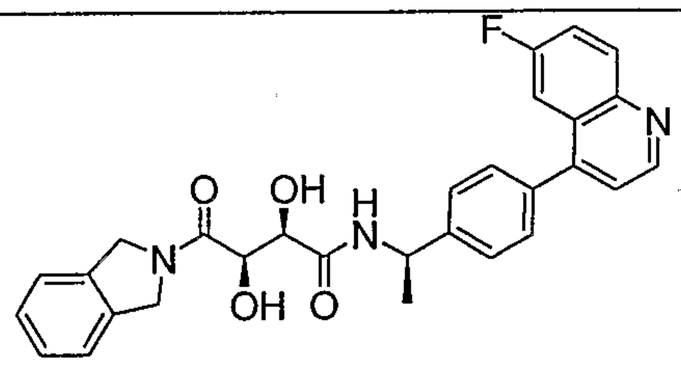
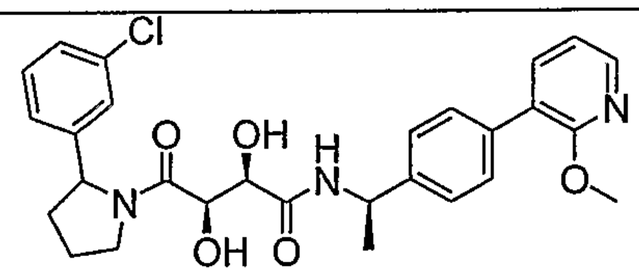
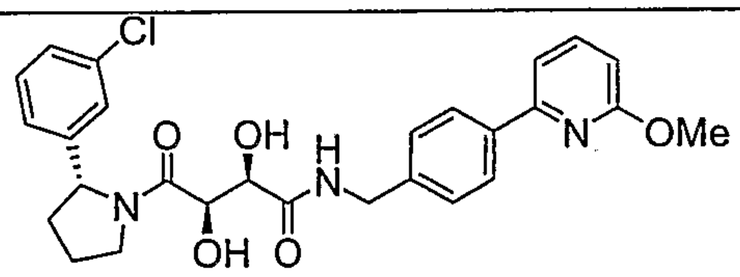
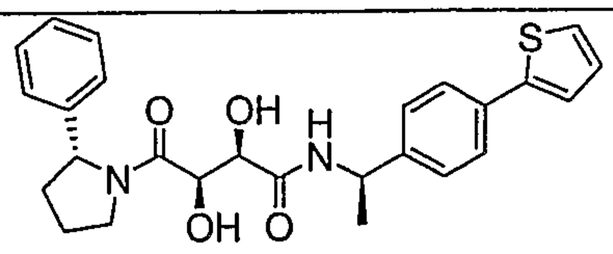
Compound **856** was synthesized using the Suzuki procedures desribed in Example 12.

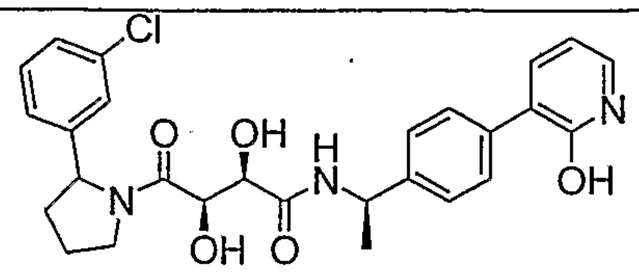
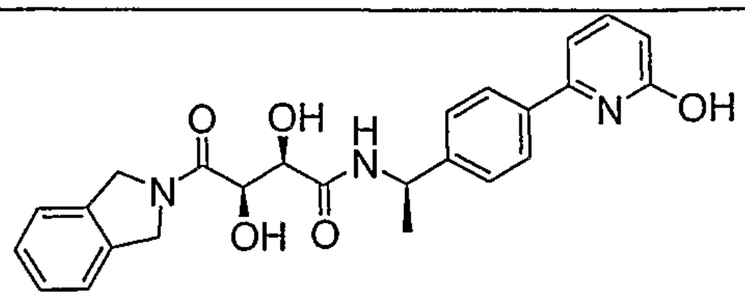
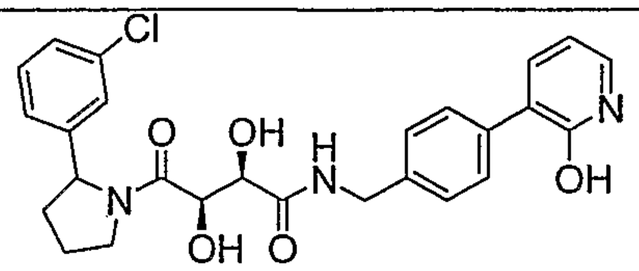
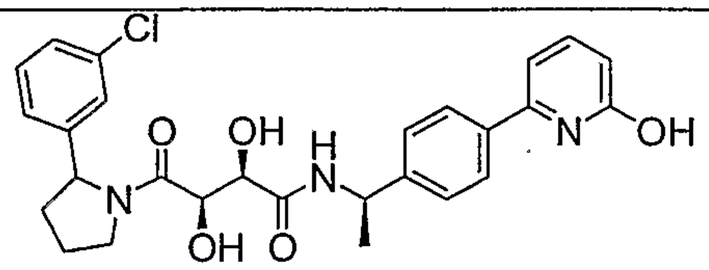
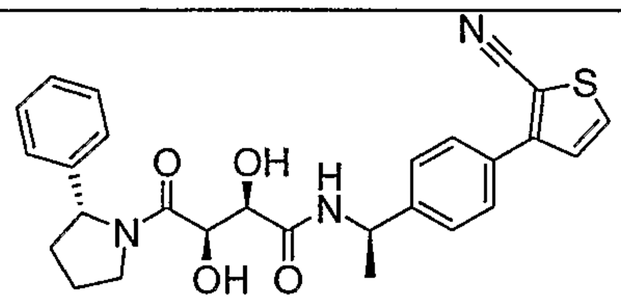
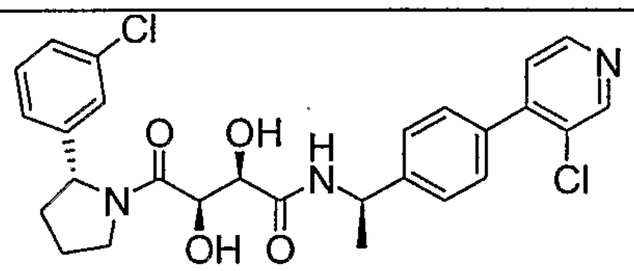
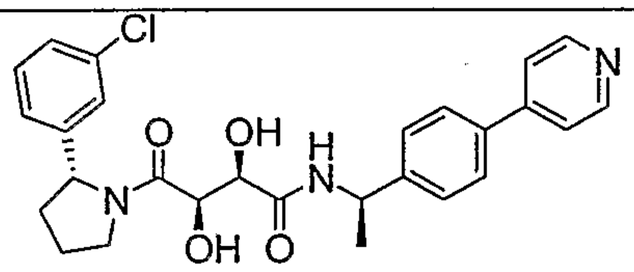
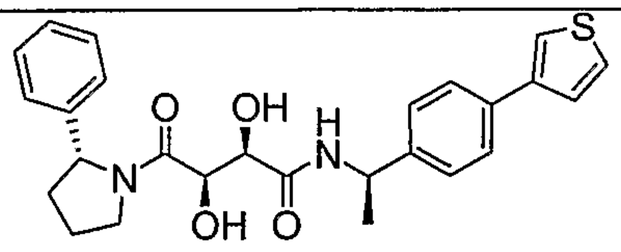
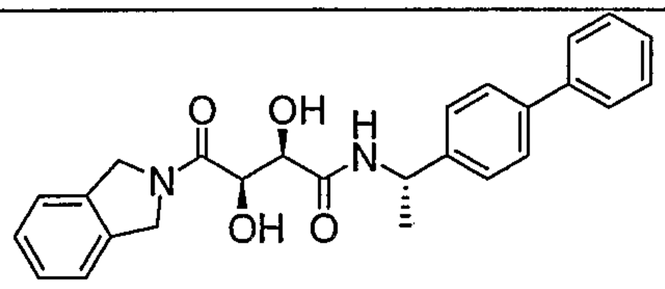
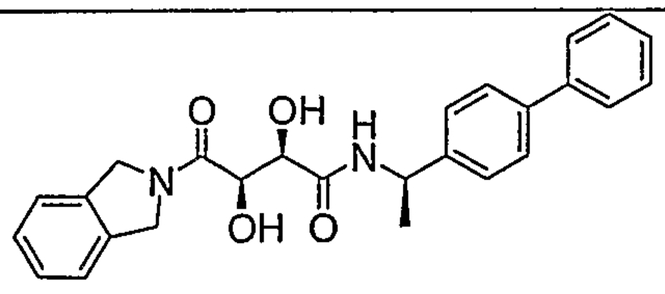
Part A:

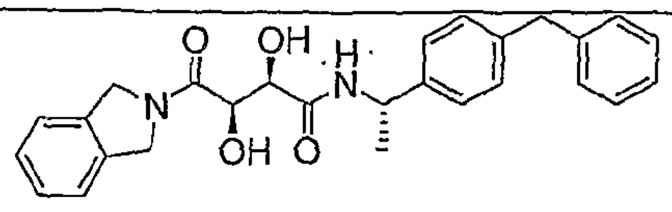
Compound **856** (160 mg, 0.30 mmol) was dissolved in acetonitrile (5 mL) and sodium iodide (140 mg, 1.0 mmol) was added followed by trimethylsilylchloride (105 mg, 1.0 mmol). Water (0.1 mL) was added and the reaction mixture was stirred at reflux for 4 hours. The reaction was quenched with water and 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.

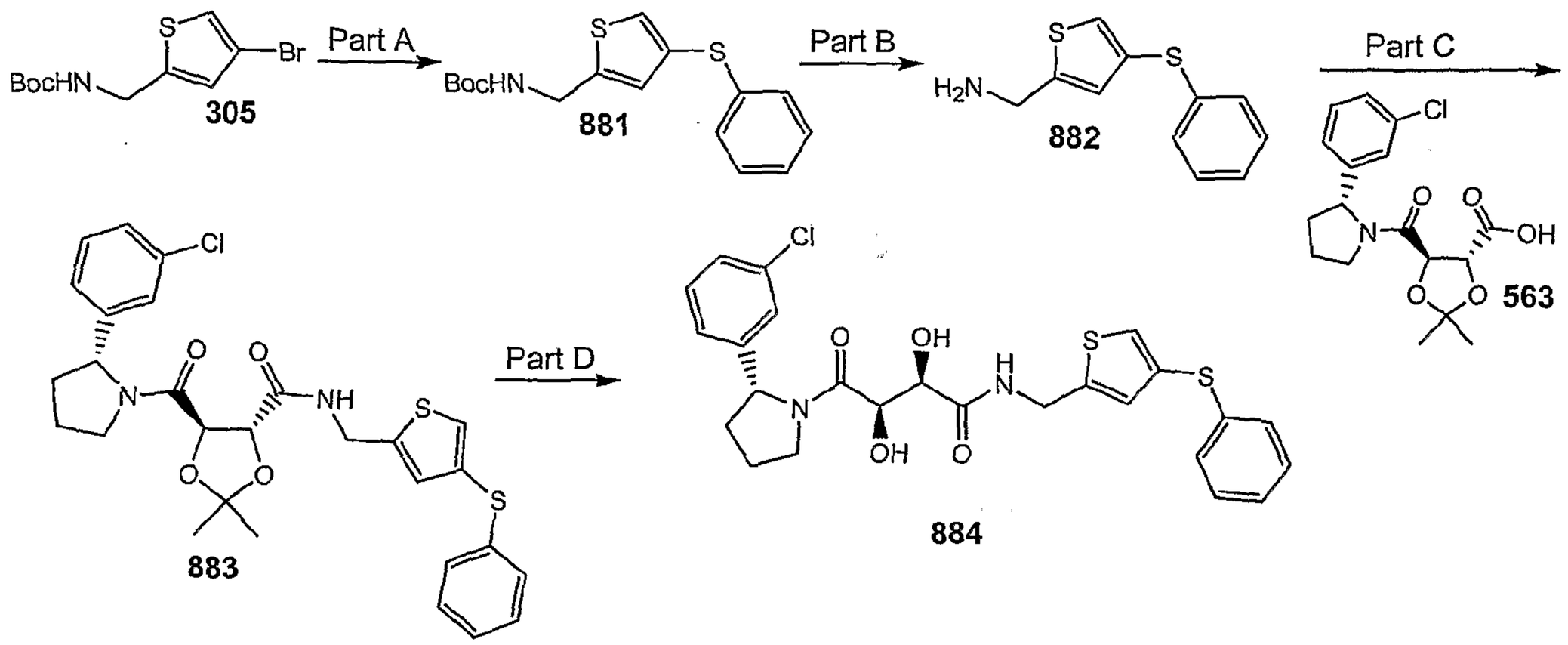
Compound #	Structure	Exact mass	MS m/e (M+H)
858		459.2	460.1
859		459.2	460.1

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 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).

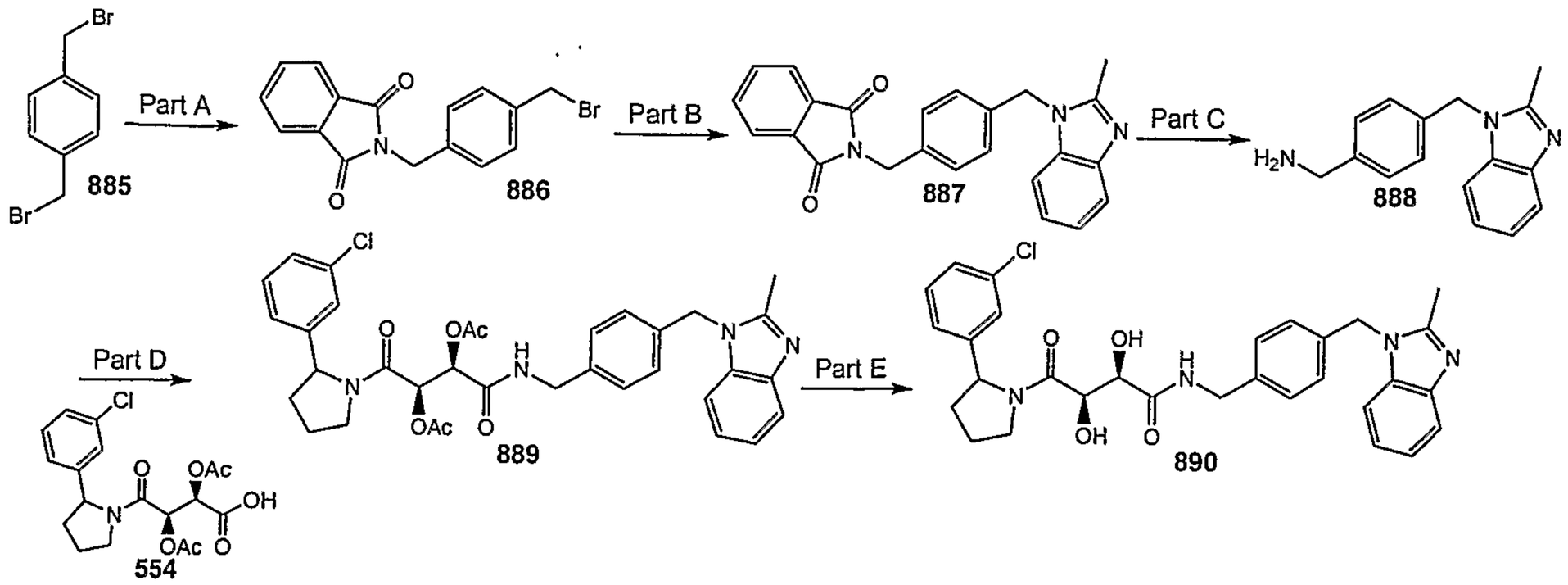
Part C:

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%). ^{1}H 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:

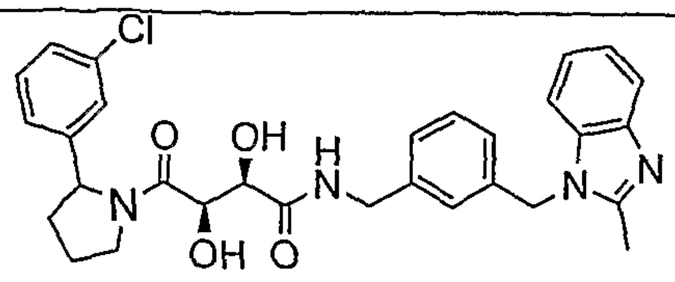
A mixture of **887** (120 mg, 0.31 mmol) and hydrazine hydrate (61 µL, 1.26 mmol) in ethanol (10 mL) was heated to reflux for 3 hours. The reaction mixture was concentrated. The residue was dissolved in ethyl acetate and washed with bicarbonate solution. The aqueous layer was extracted with ethyl acetate. 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).

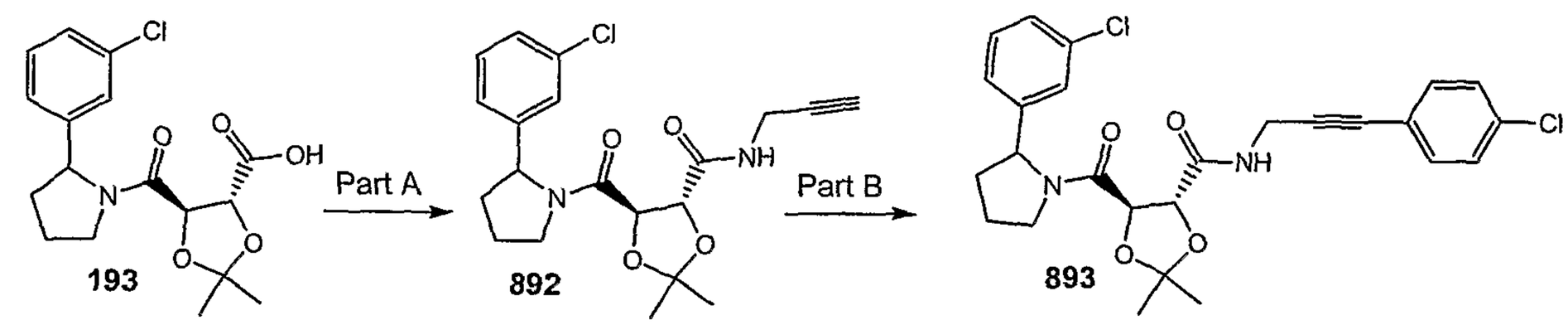
Part E:

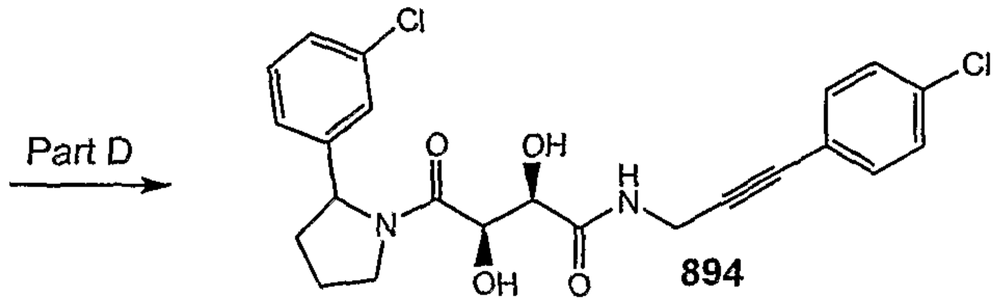
To **889** (61 mg, 0.097 mmol) in methanol (2 mL) was added anhydrous hydrazine (5 µL, 0.16 mmol). The reaction mixture was stirred overnight, concentrated, purified by reverse phase prep-LC and treated with HCl to afford **890** as an HCl salt (19 mg, 33%). HPLC-MS t_R = 3.42 min ($UV_{254\ nm}$, 10 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).

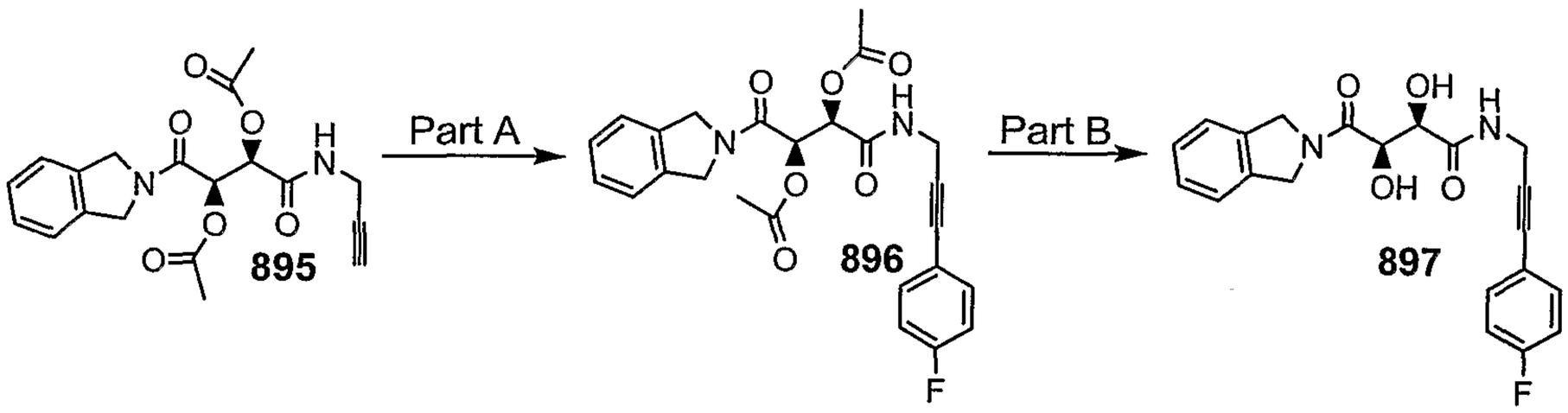
Part B:

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.

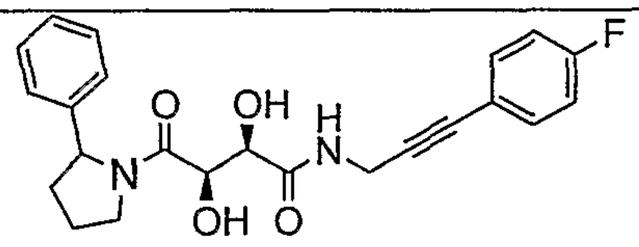
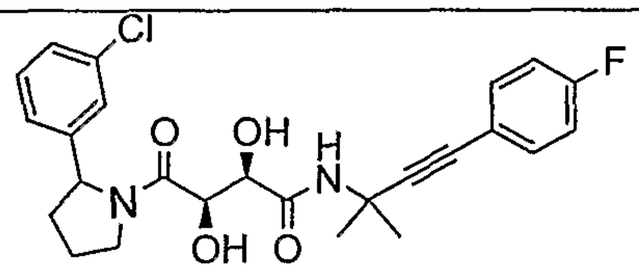
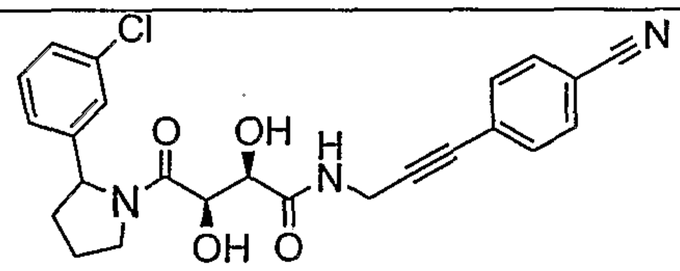
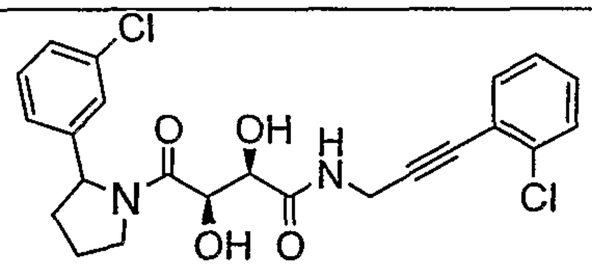
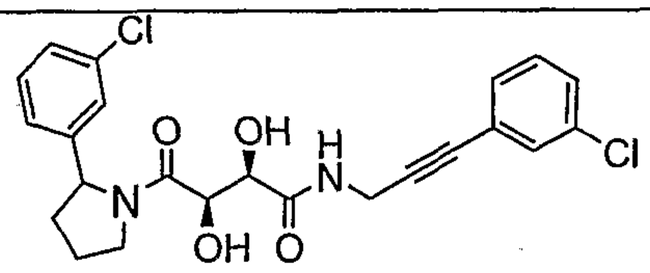
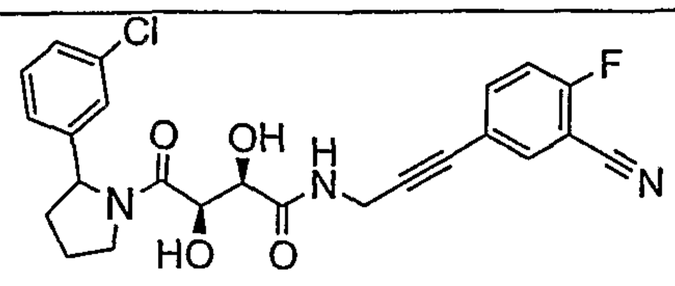
Part A:

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

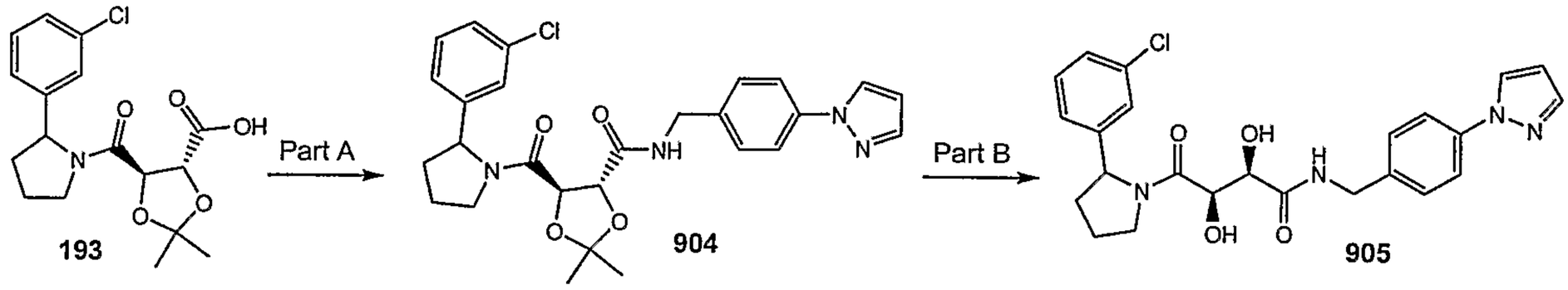
Part B:

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:



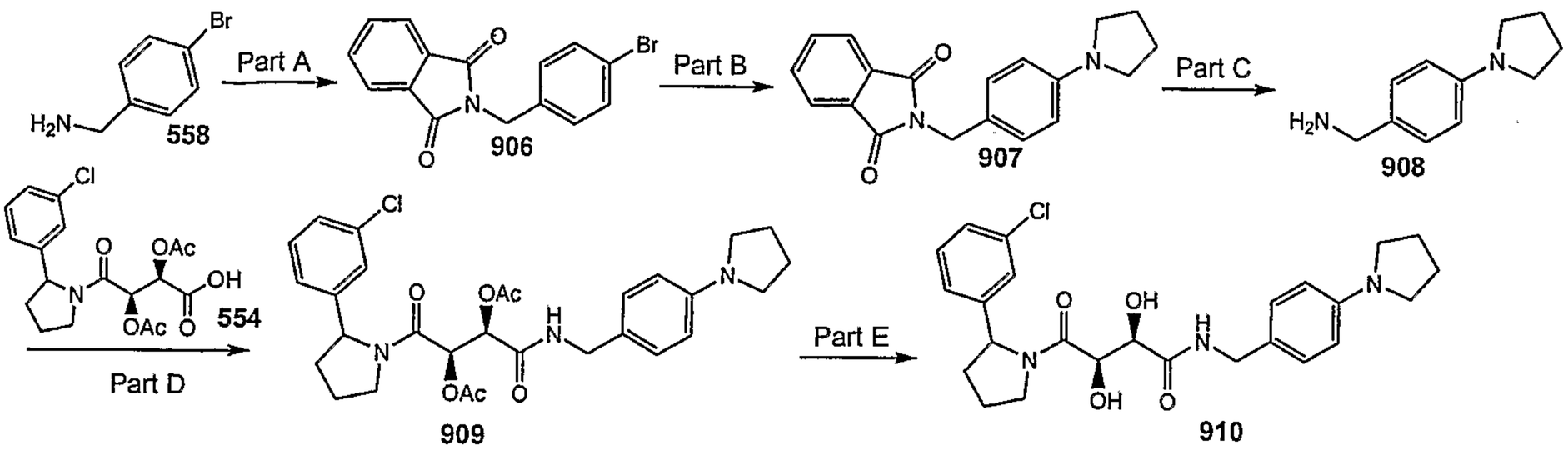
Part A:

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).

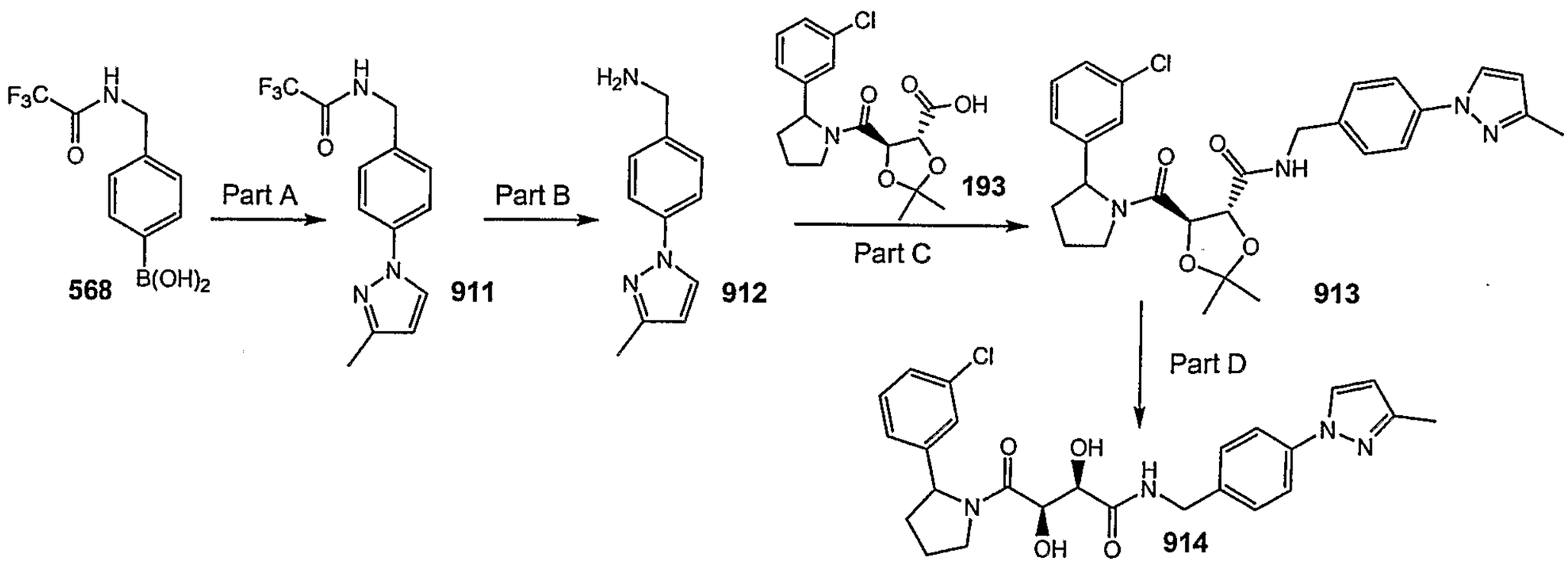
Part D:

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:

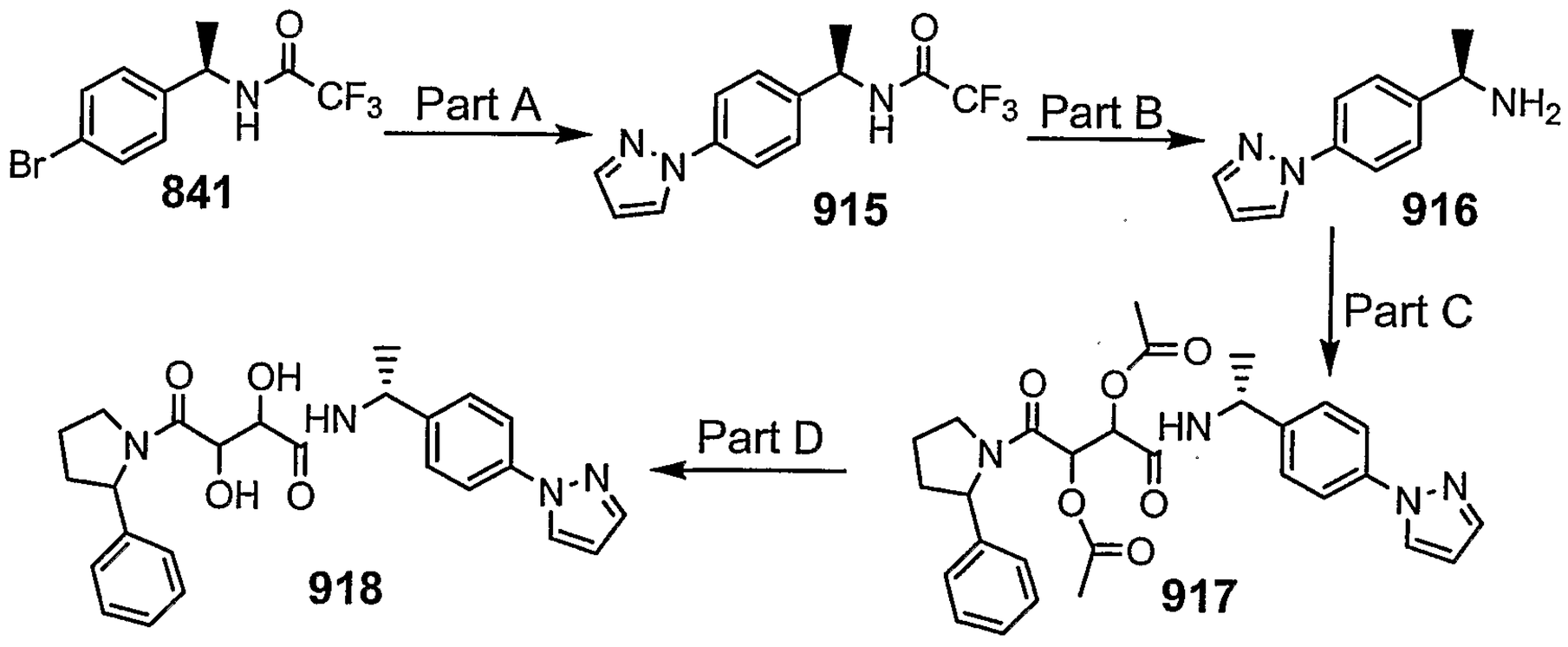
To **193** (65 mg, 0.18 mmol) in DMF (2 mL) was added **912** (38 mg, 0.2 mmol), DIEA (70 μL, 0.4 mmol) and HATU (76 mg, 0.21 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers

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

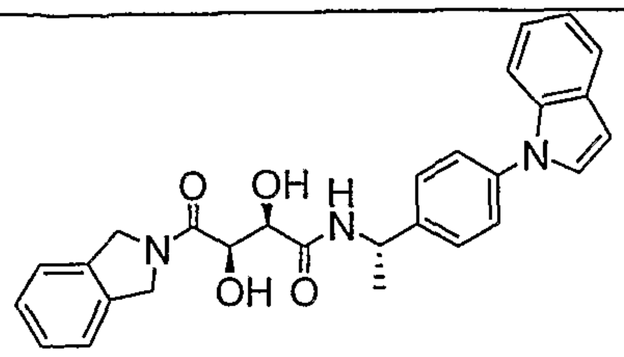
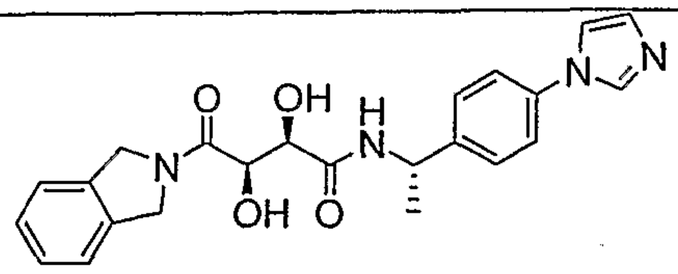
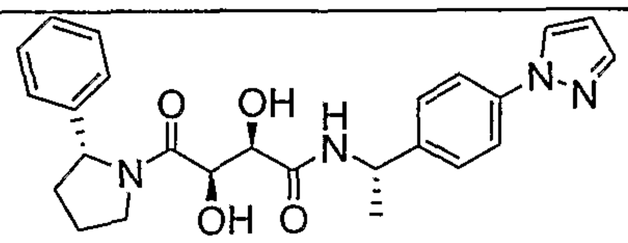
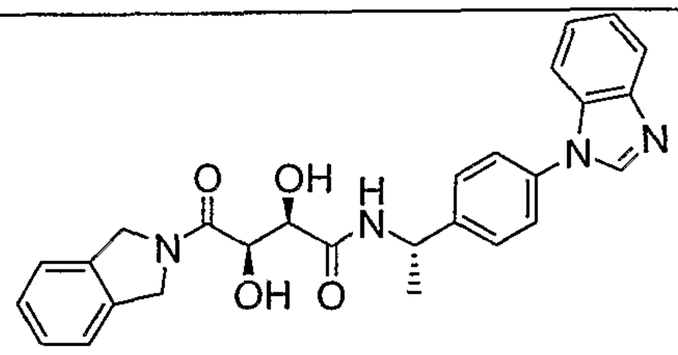
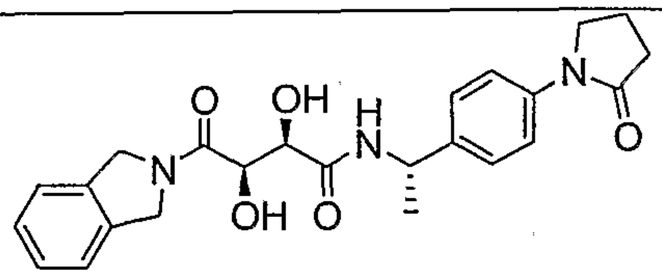
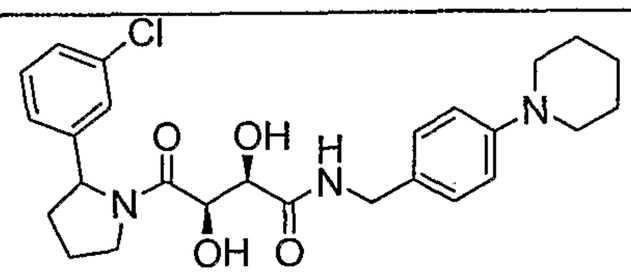
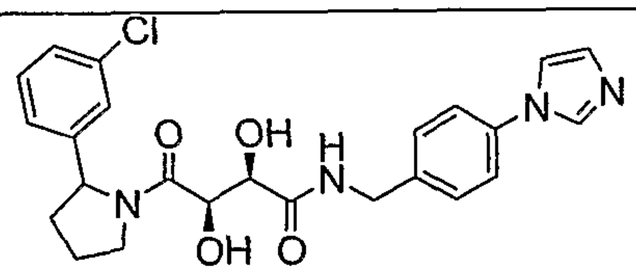
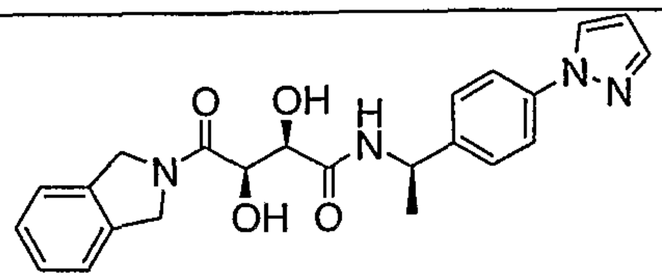
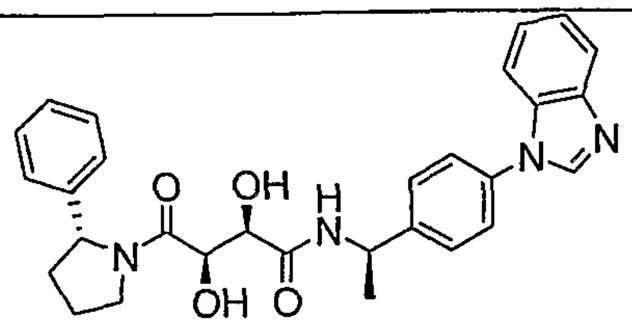
Part B:

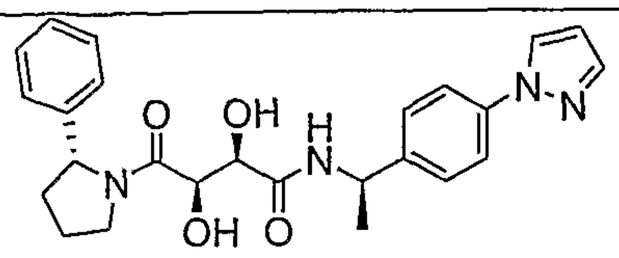
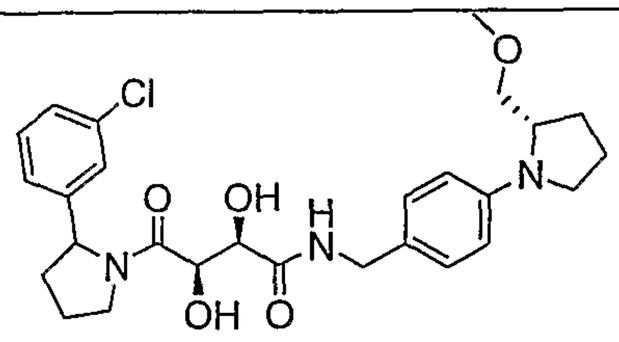
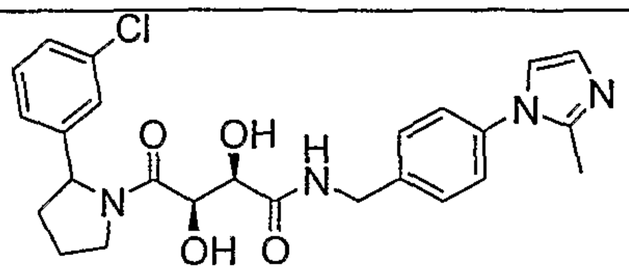
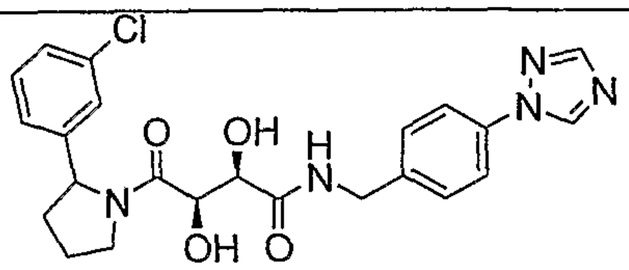
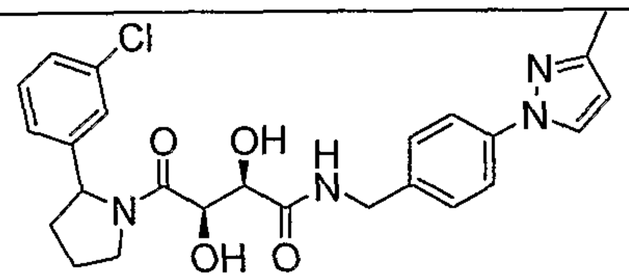
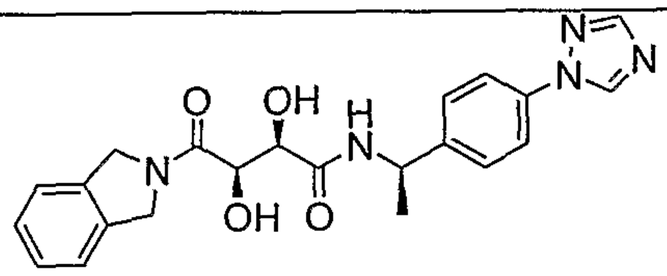
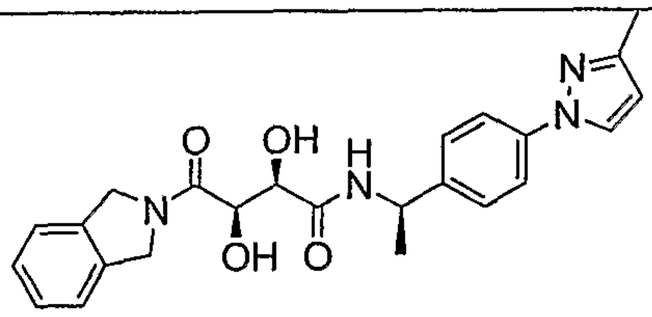
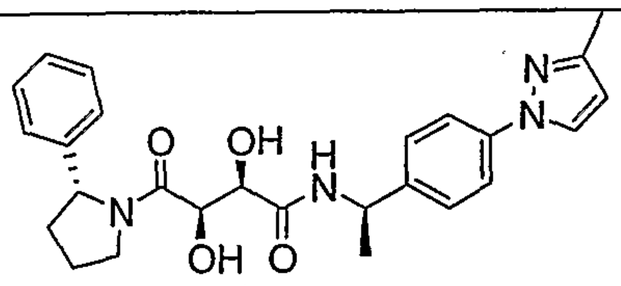
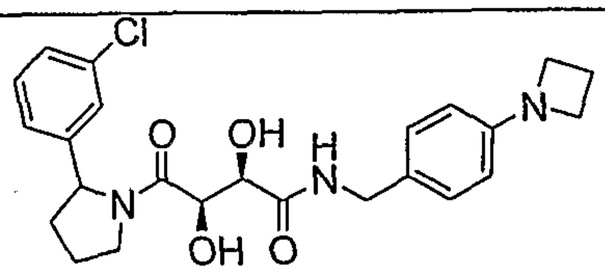
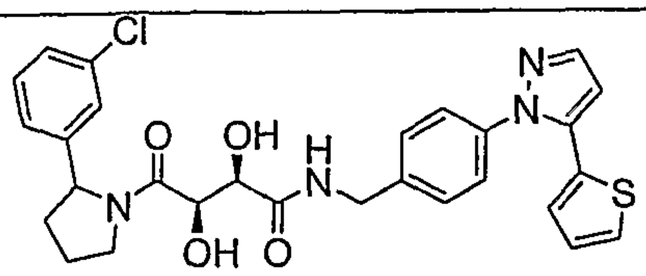
Compound **915** (0.20 g, 0.67 mmol) was dissolved in 10 mL of MeOH. Aqueous LiOH (10 mL/ 1.0 M) was added. The reaction mixture was stirred at rt for 4 h. The solution was partially concentrated in vacuo to remove the MeOH. The resulting material was extracted with EtOAc. The organic layer was washed 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).

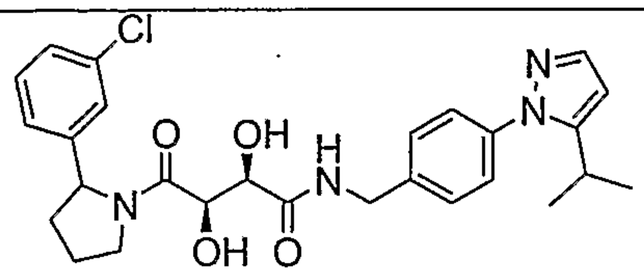
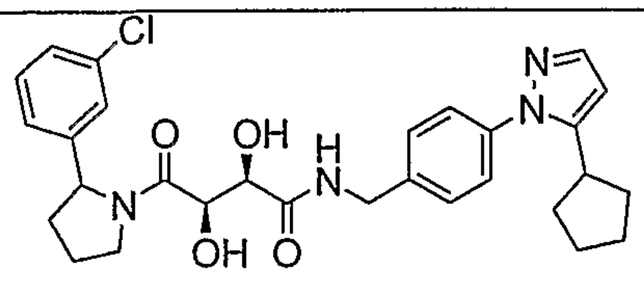
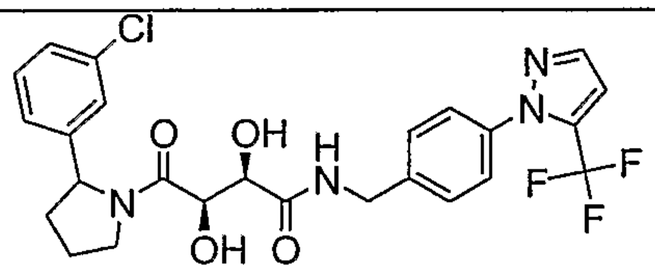
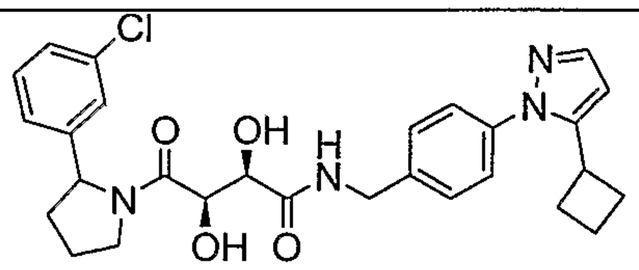
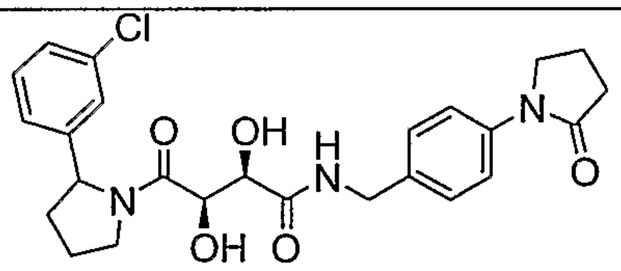
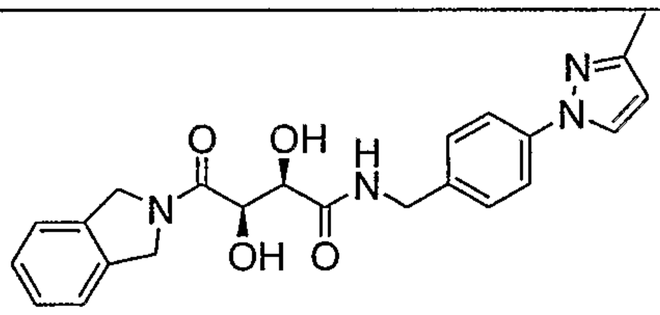
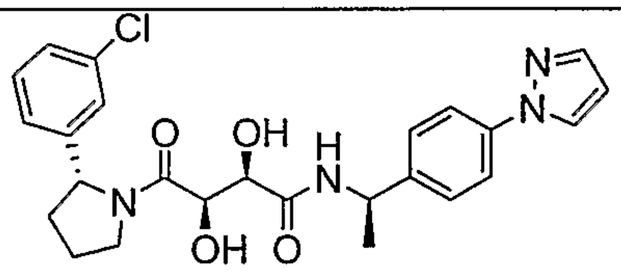
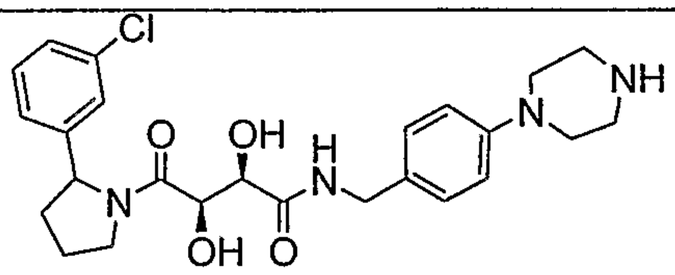
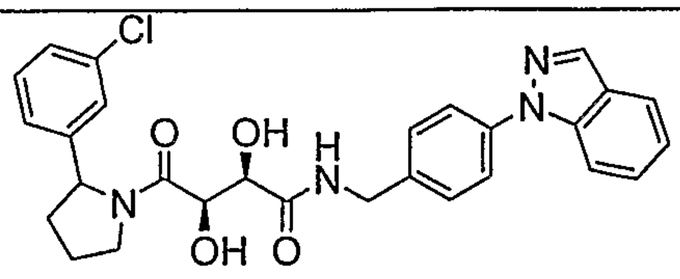
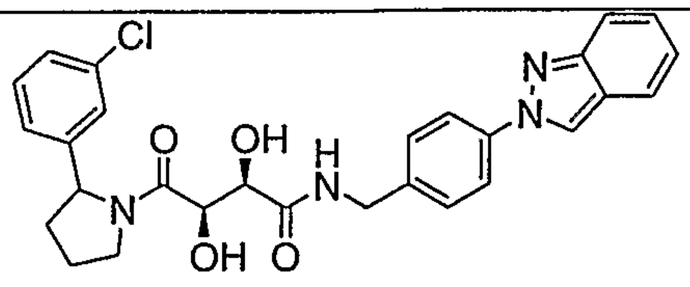
Parts C and D:

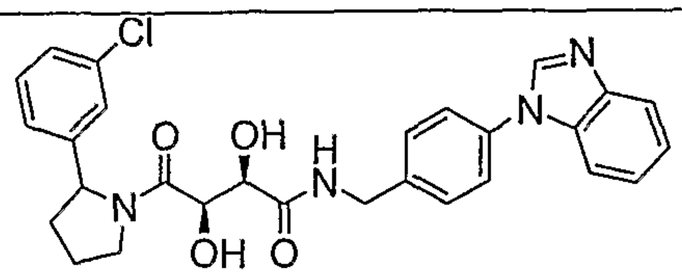
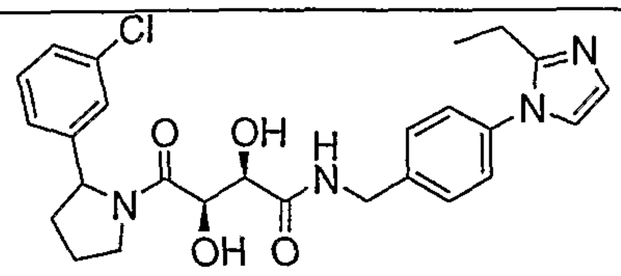
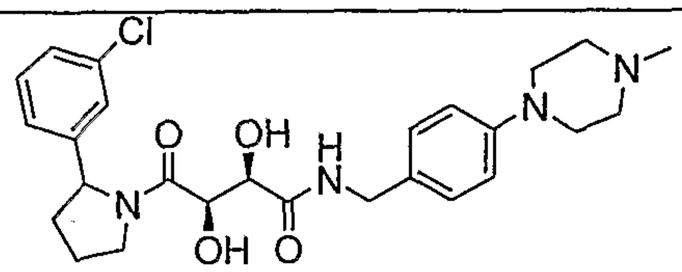
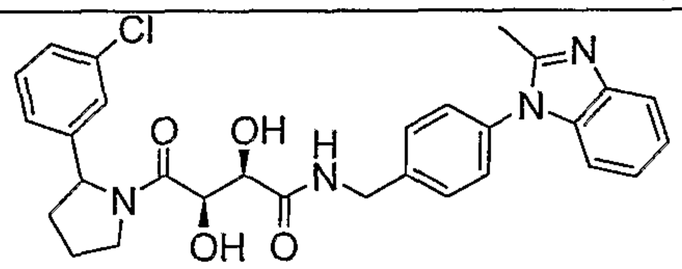
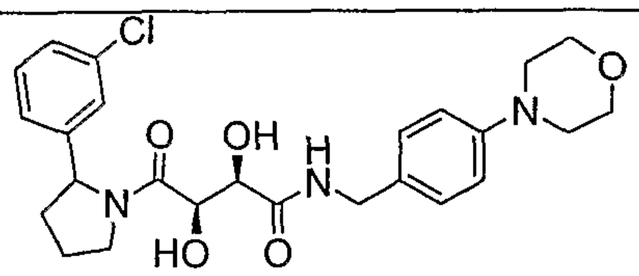
Compounds **917** and **918** were prepared via procedures similar to those described in Example 14 -Parts D and E. Data for **917**: ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.98-7.62 (m, 4H), 7.46-7.13 (m, 8H), 6.68-6.47 (m, 2H), 5.86-5.41 (m, 2H), 5.24-5.10 (m, 2H), 4.05-3.48 (m, 2H), 2.22-1.79 (m, 10H), 1.58-1.55 (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

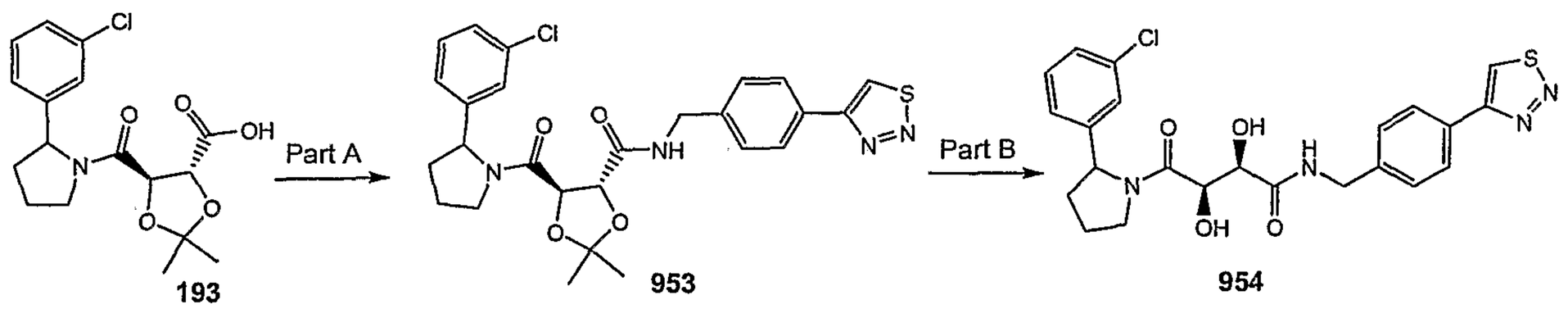
928		448.2	449.1
929		515.2	516.3
930		482.2	483.1
931		469.2	470.0
932		482.2	483.1
933		421.2	422.1
934		434.2	435.1
935		462.2	463.1
936		457.2	458.2
937		550.1	551.0

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:

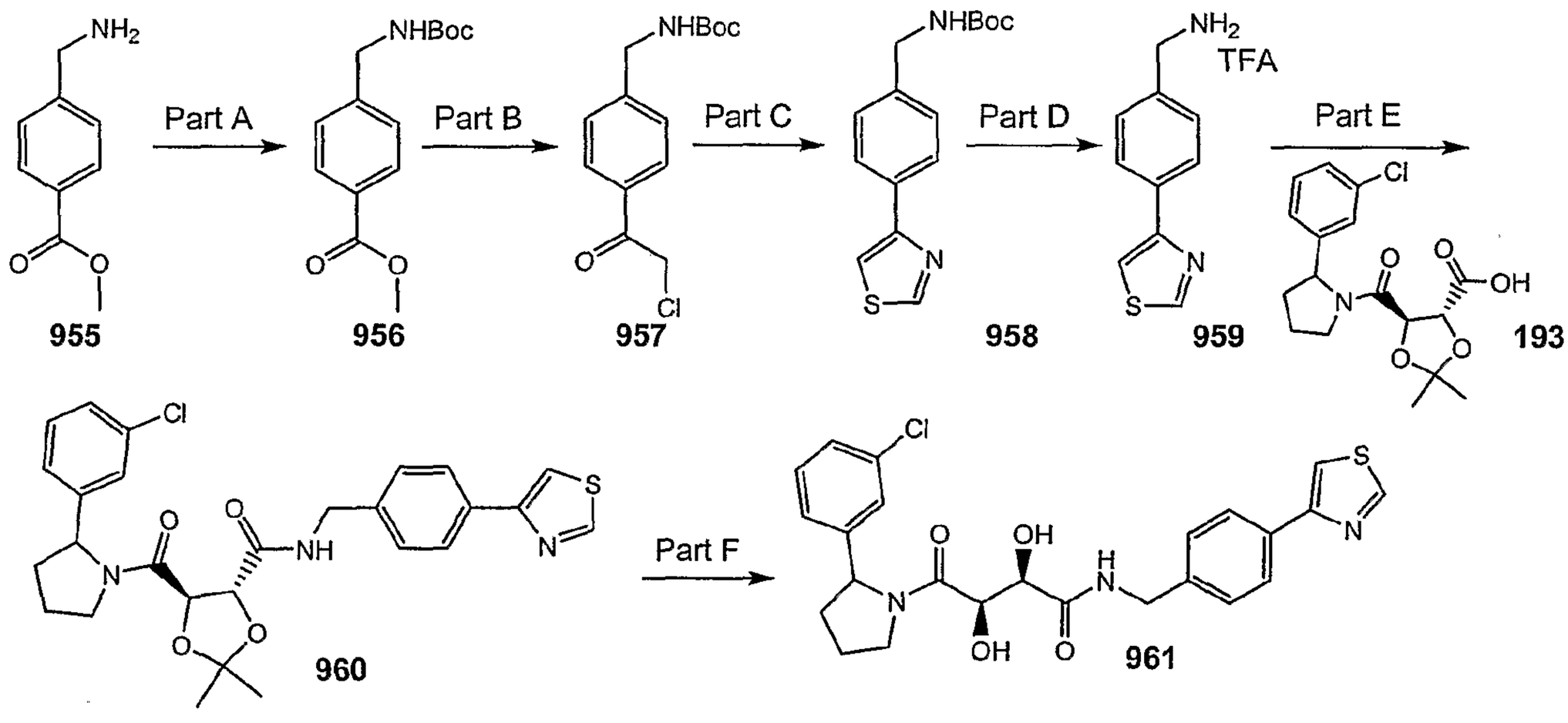
To **193** (42 mg, 0.12 mmol) in DMF (2 mL) was added 4-[1,2,3]thiadiazol-4-yl-benzylamine (25 mg, 0.13 mmol), DIEA (45 µL, 0.26 mmol) and HATU (50 mg, 0.13 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. 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).

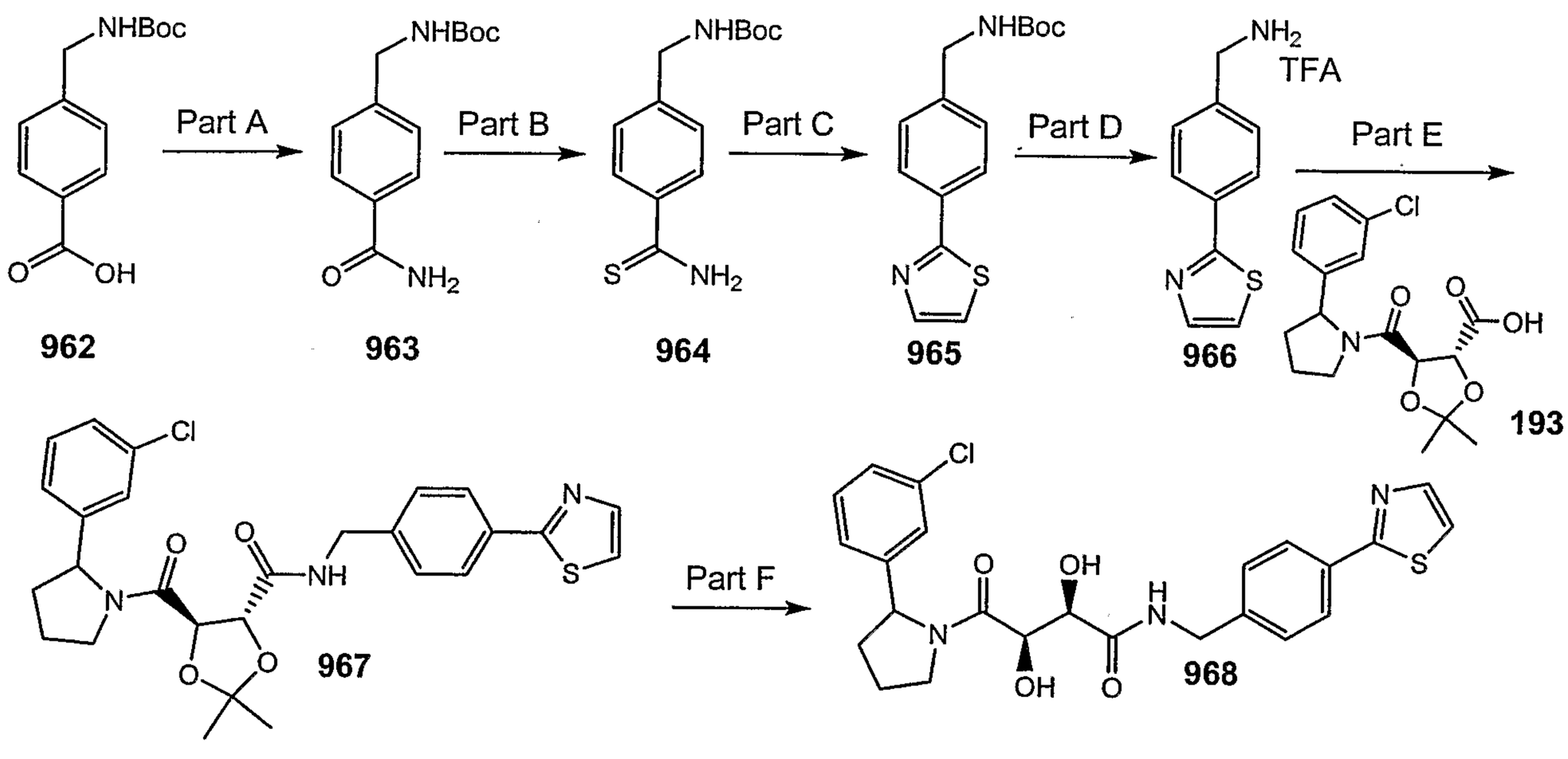
Part E:

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

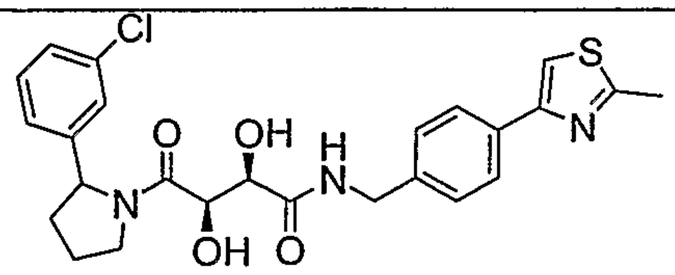
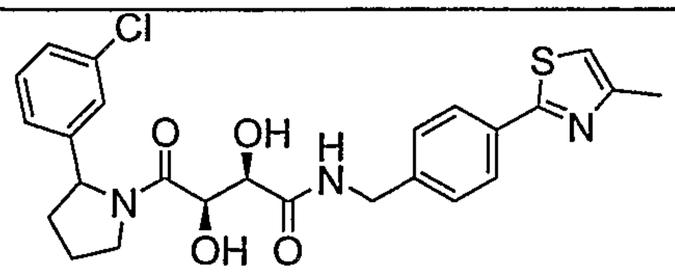
in vacuo to afford **966** as an oil (60 mg). ^{1}H NMR (400 MHz, CD_3OD) δ 8.03 (d, 2H, J = 8.8 Hz), 7.90 (d, 1H, J = 3.2 Hz), 7.65 (d, 1H, J = 3.6 Hz), 7.56 (d, 2H, J = 8.8 Hz), 4.18 (s, 2H).

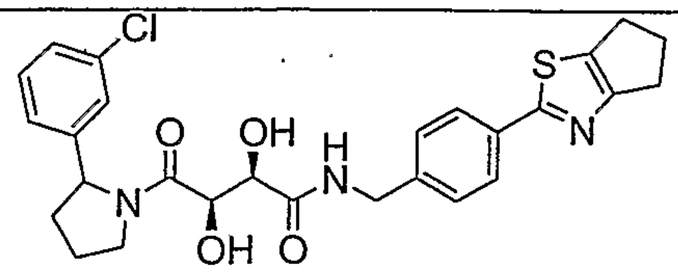
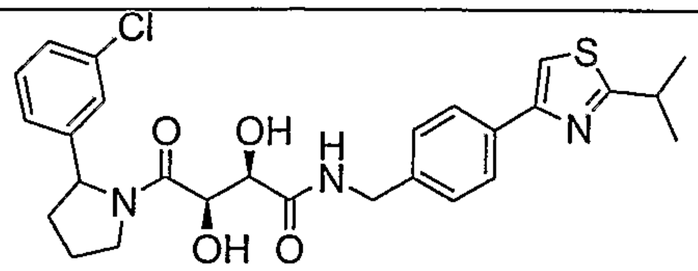
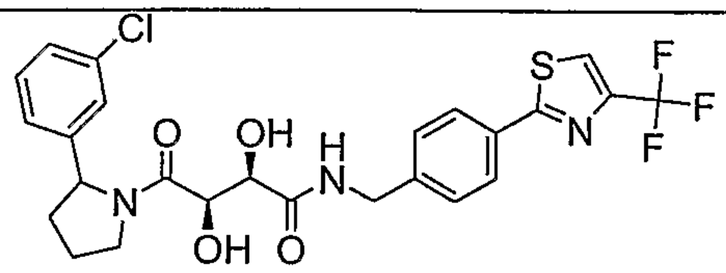
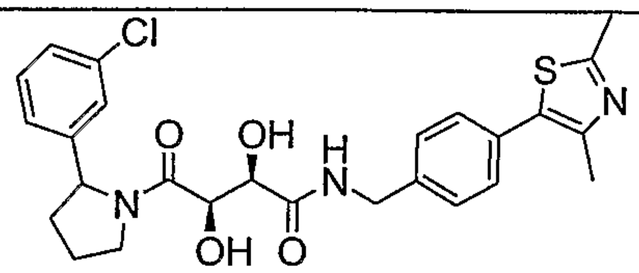
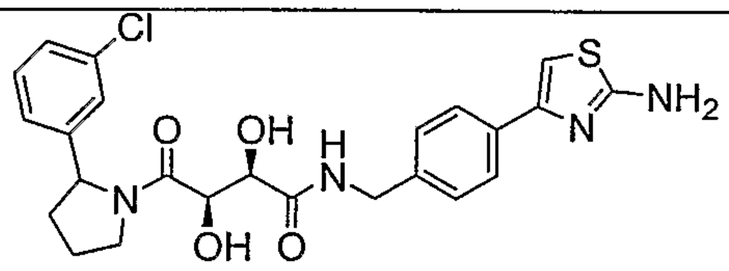
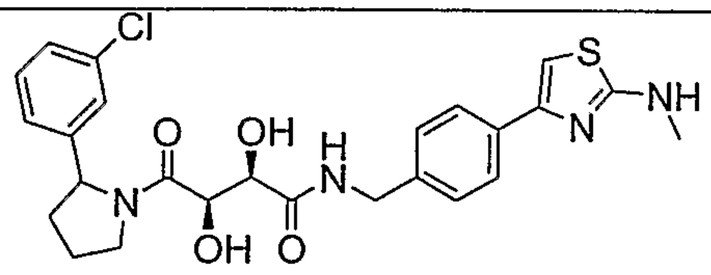
Part E:

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:

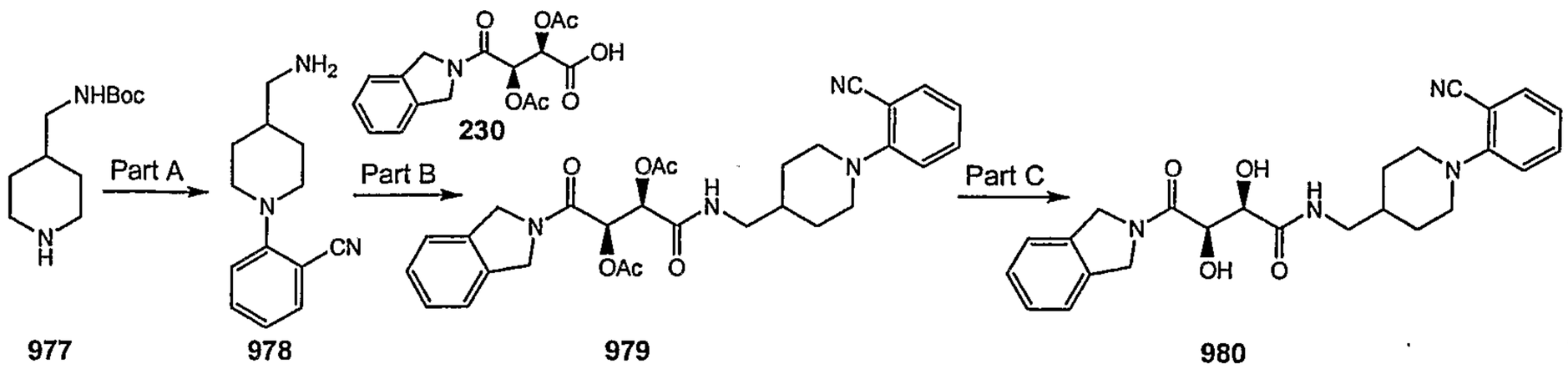
Compound **967** was dissolved in 4:1 TFA:water (2 mL) and stirred at room temperature for 2 hours. The reaction was quenched by the addition of 1:1 acetonitrile:water (4 mL) and the solvents were removed in vacuo. Purification by reverse phase prep-LC afforded **968** as a white solid (15 mg). HPLC-MS 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).

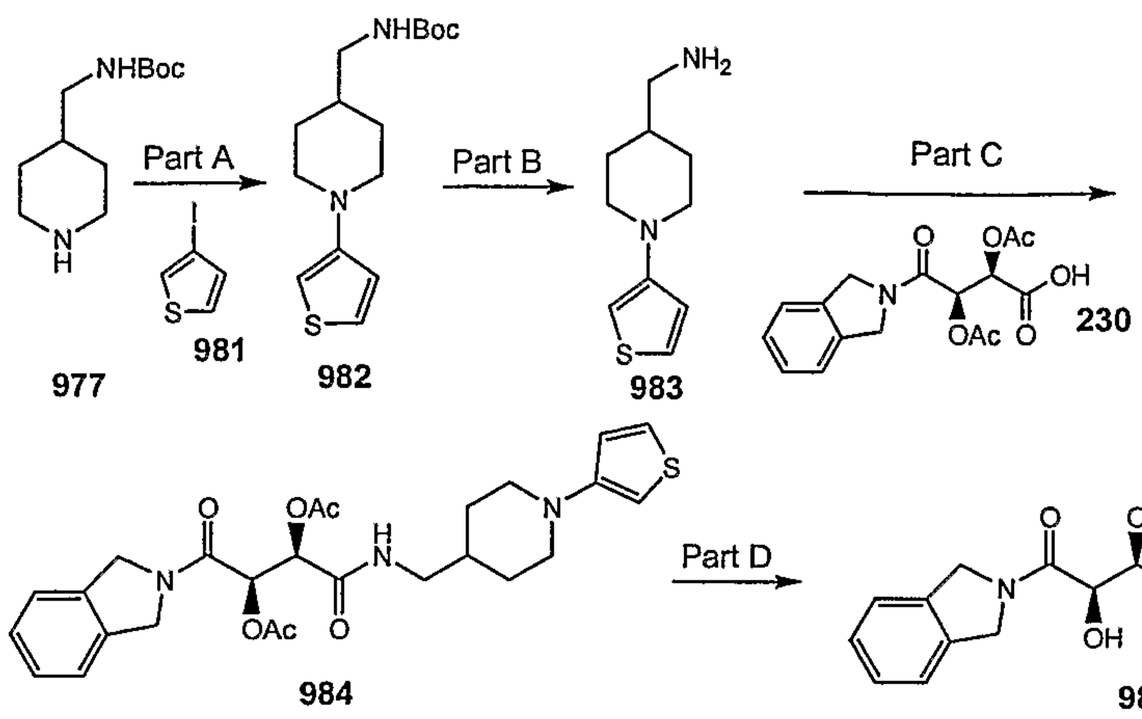
Part B:

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).

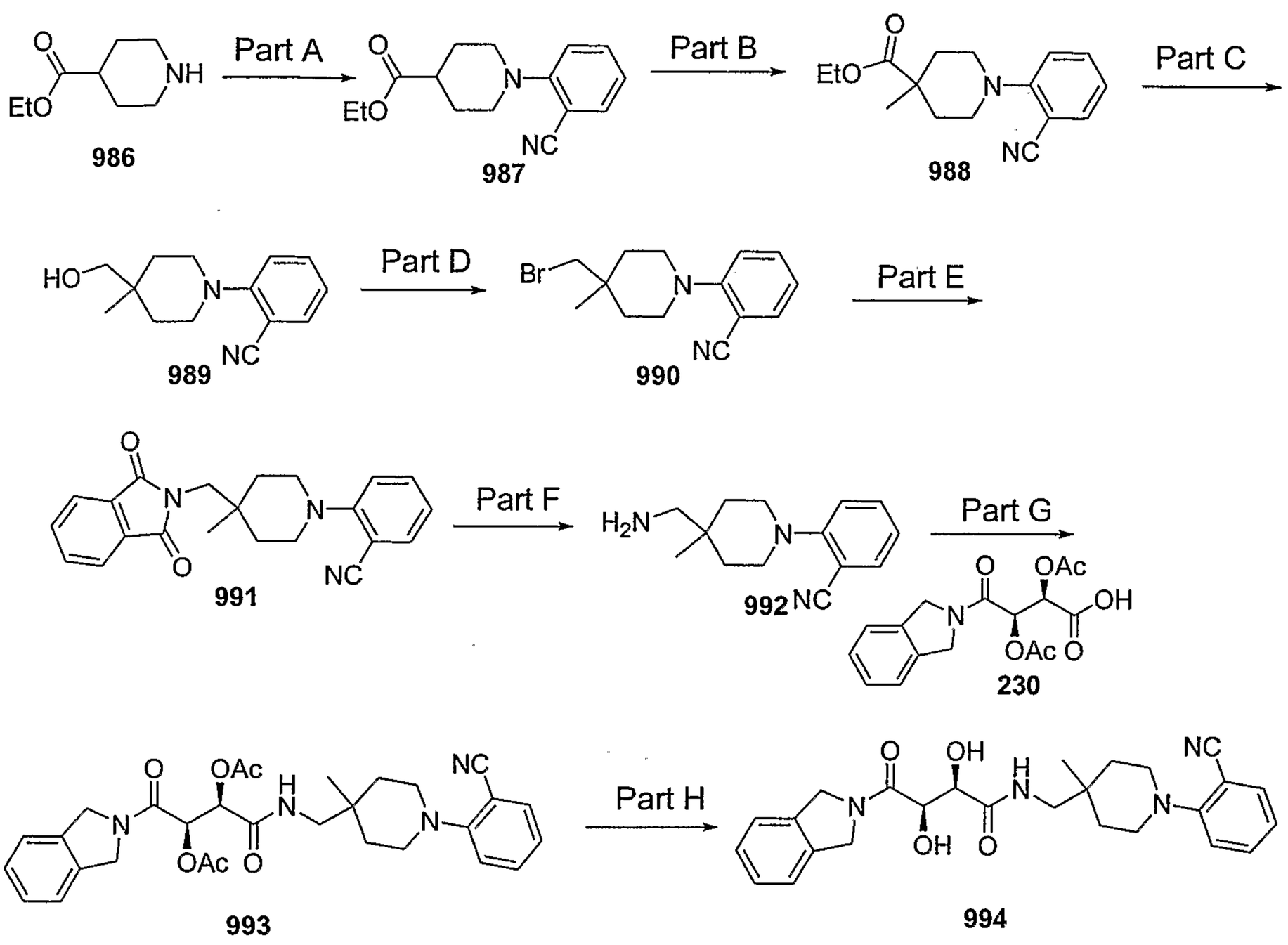
Part C:

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:

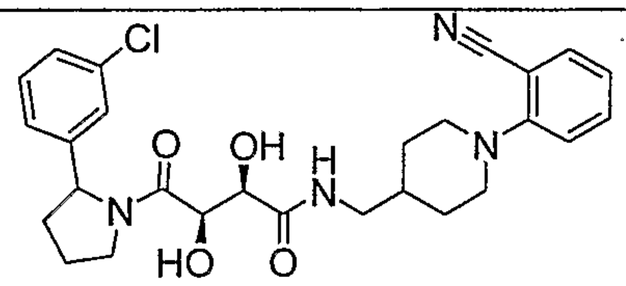
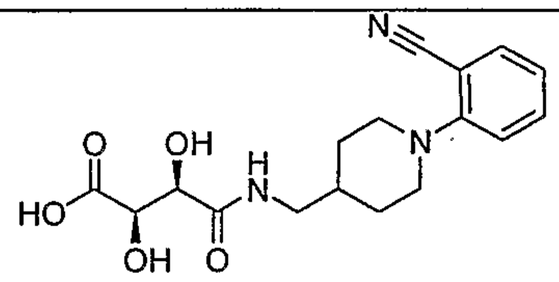
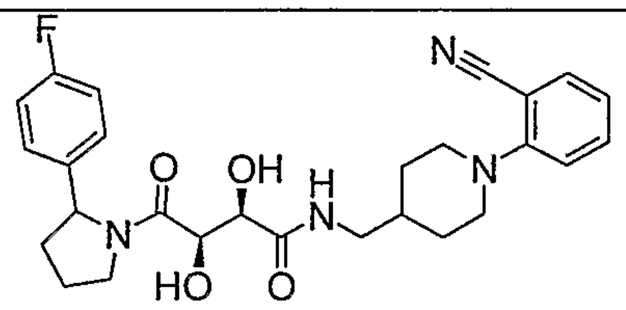
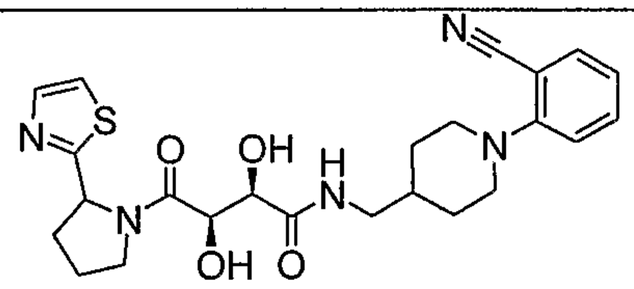
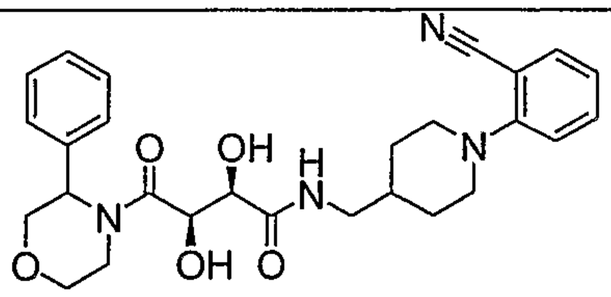
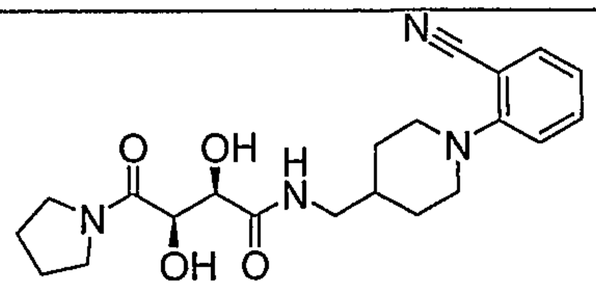
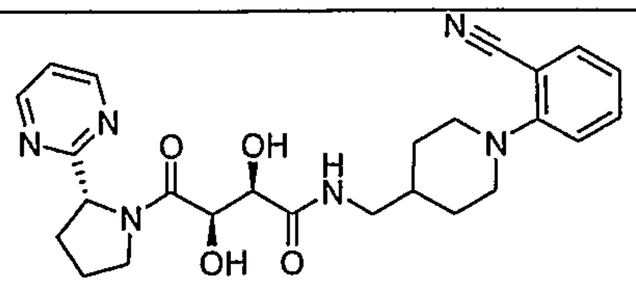
Compound **992** was dissolved in DMF (5 mL) and compound **230** (84 mg, 0.25 mmol) and HATU (114 mg, 0.30 mmol) were added and stirred overnight. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with bicarbonate solution and brine; dried 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.

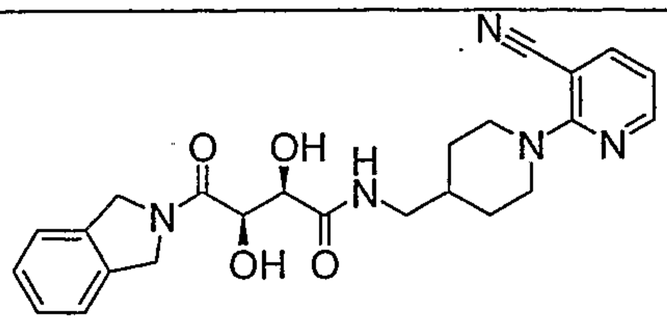
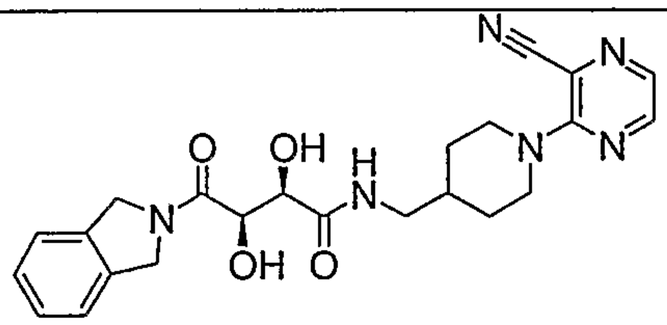
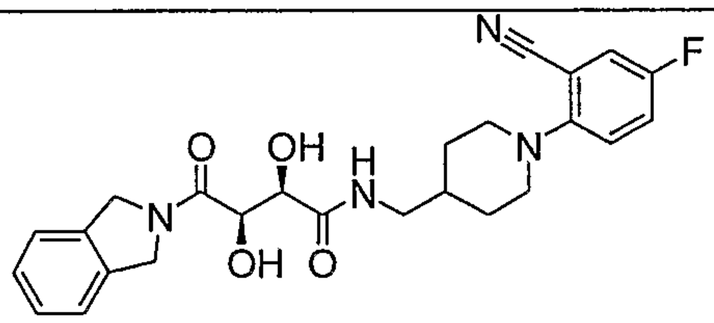
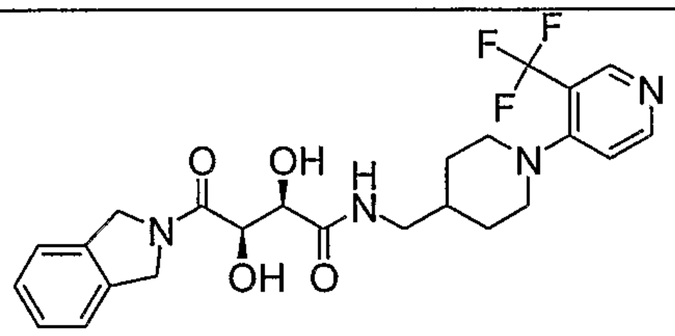
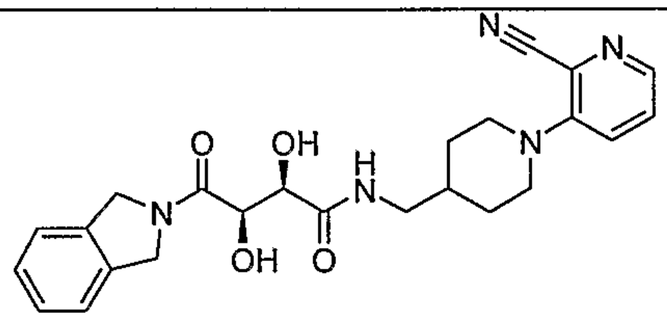
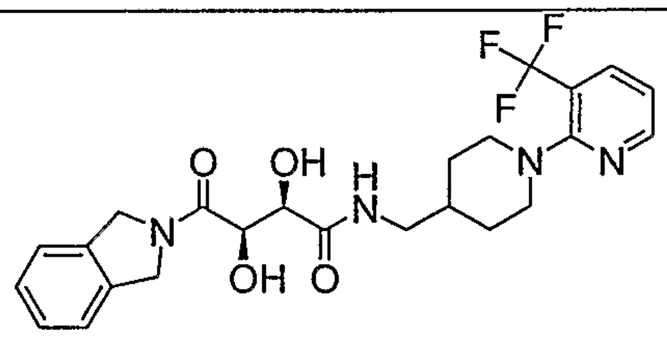
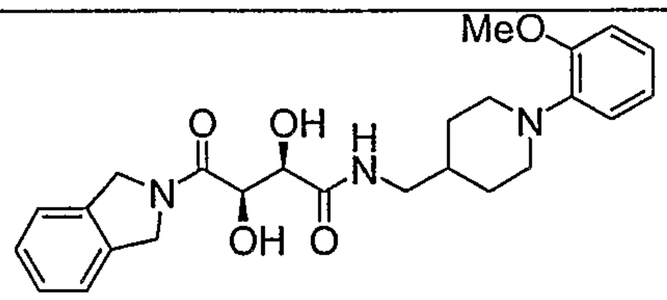
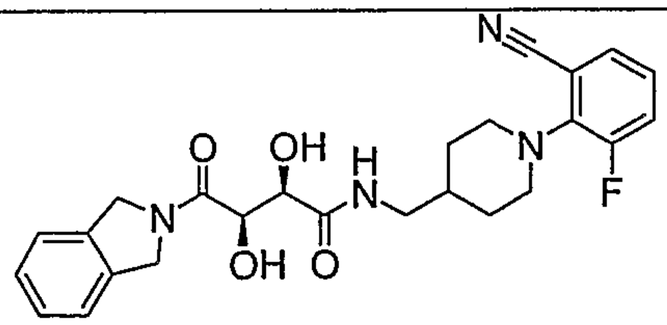
Part H:

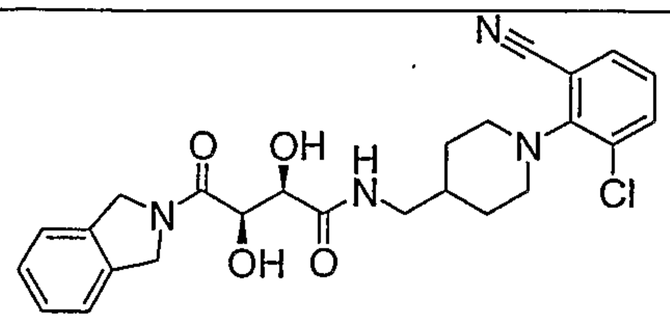
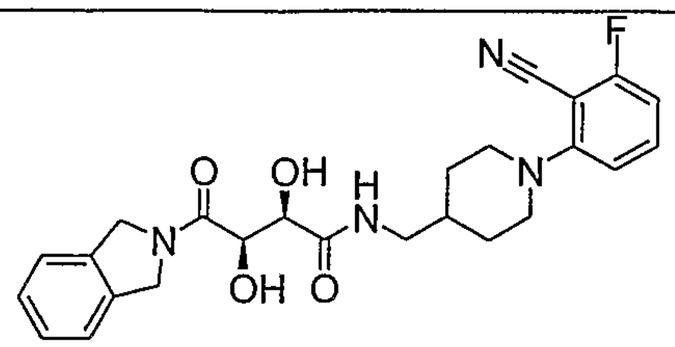
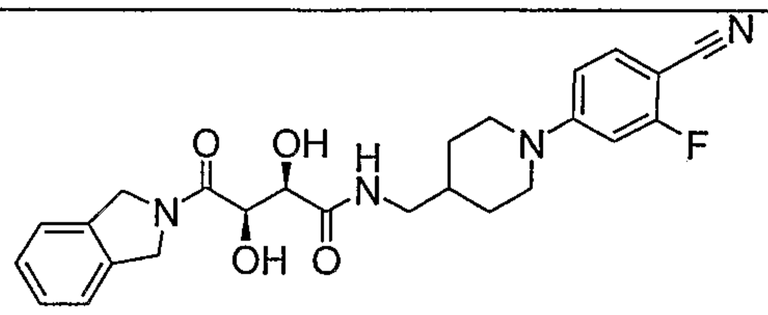
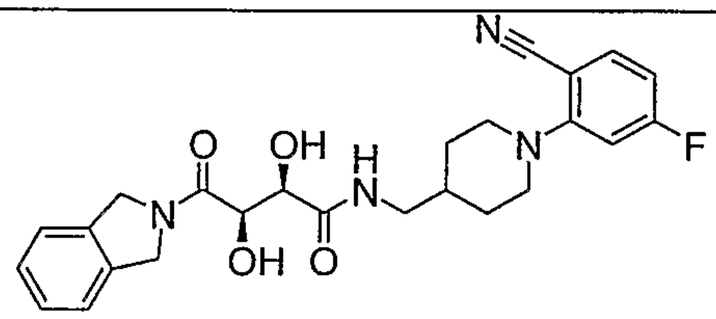
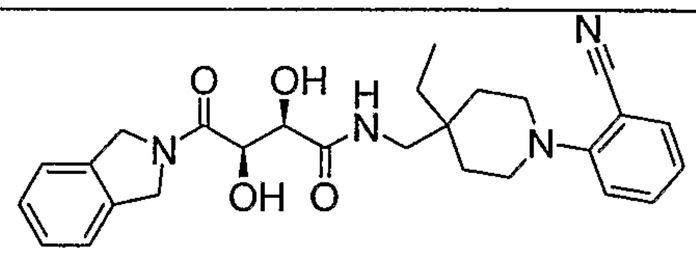
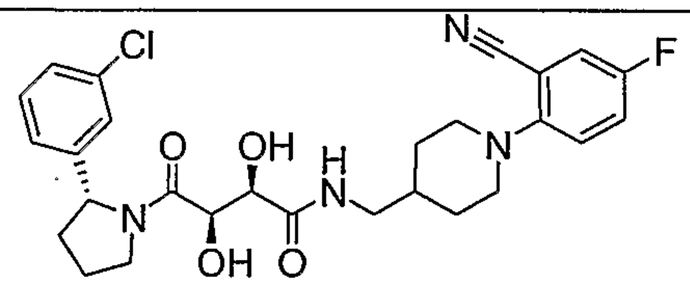
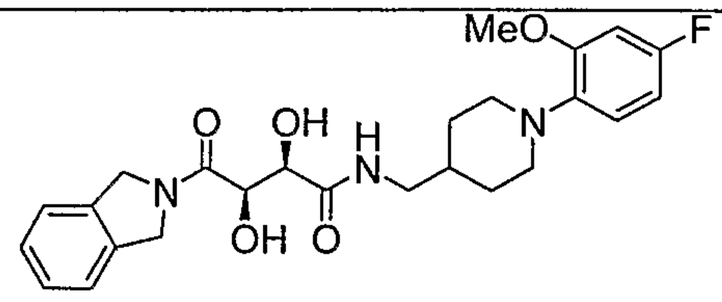
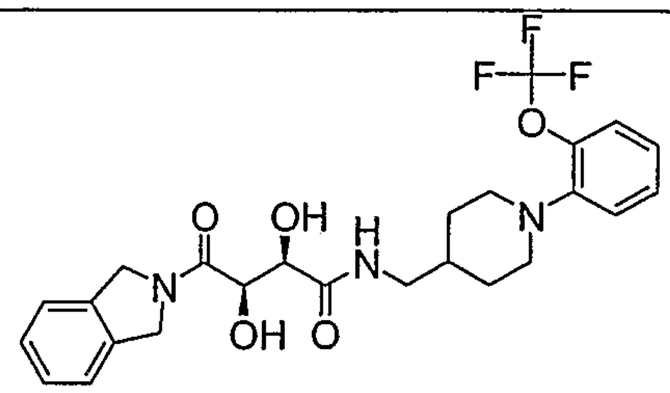
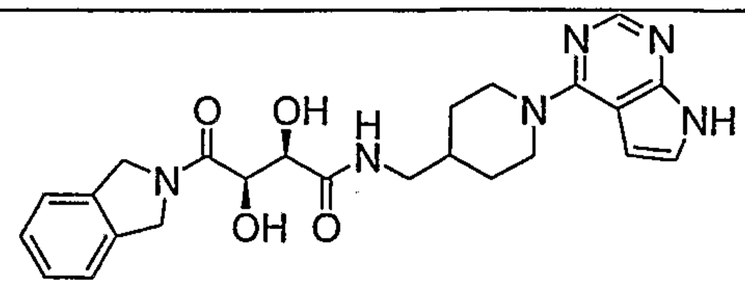
Compound **993** (100 mg, 0.182 mmol) was dissolved in methanol (5 mL) and potassium carbonate (100 mg) was added and stirred for 30 minutes. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with bicarbonate solution and brine; dried over sodium sulfate and concentrated. Purification by reverse phase prep-LC afforded a white solid **994** (7 mg, 8%) after lyophilization. HPLC-MS

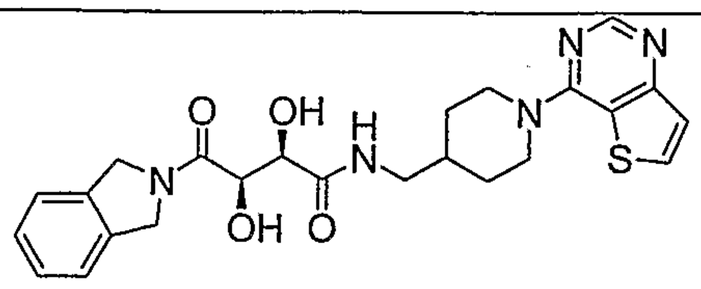
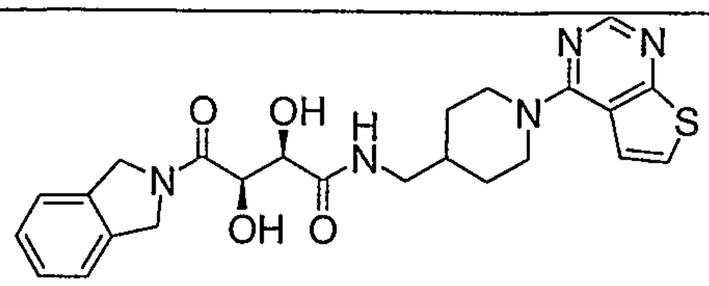
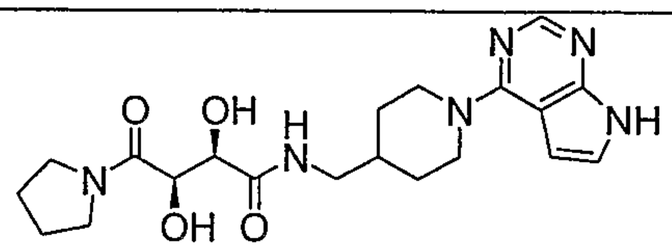
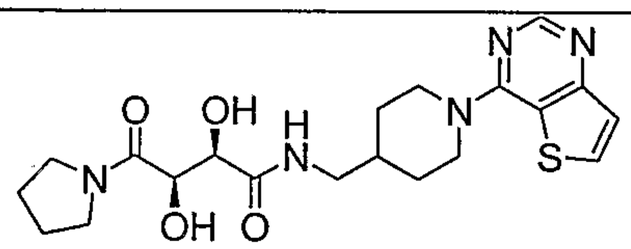
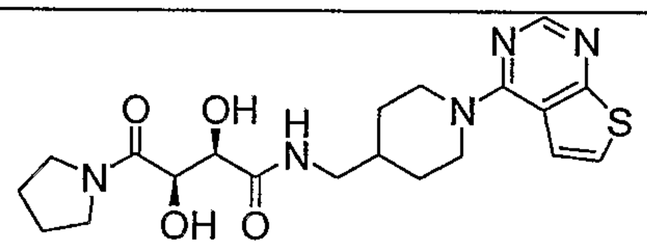
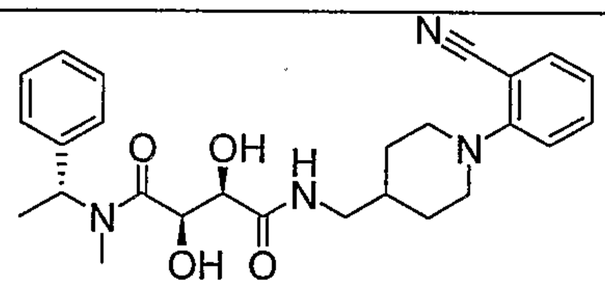
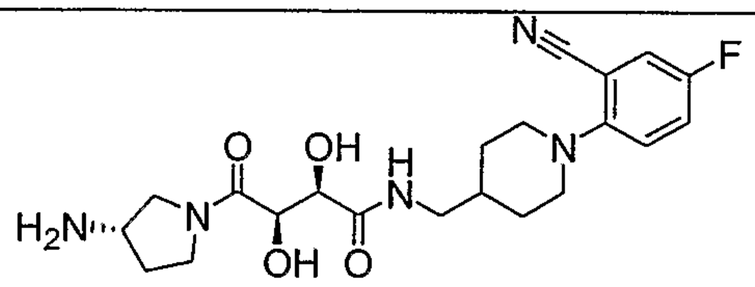
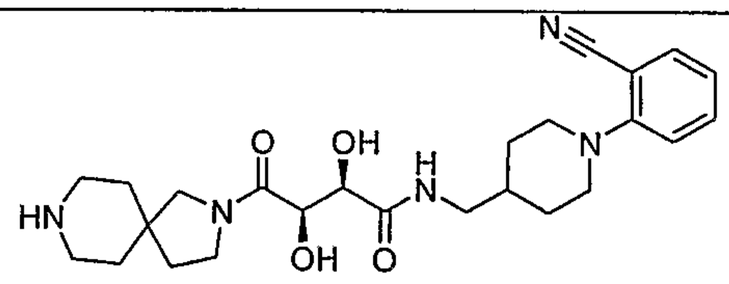
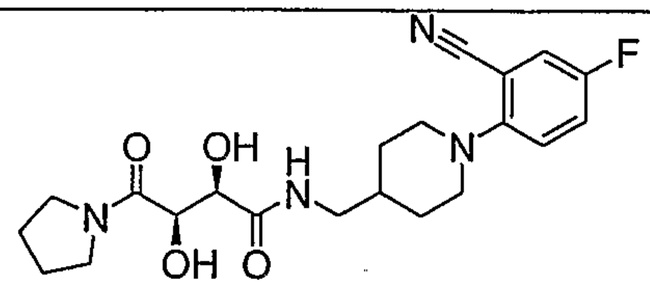
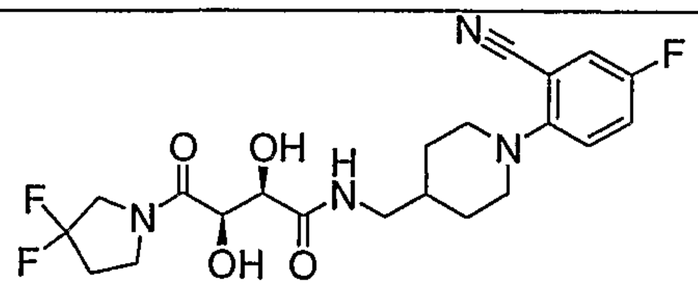
t_R = 4.32 min ($UV_{254\ nm}$, 10 min); mass calculated for formula $C_{26}H_{30}N_4O_4$ 462.23, observed LCMS m/z 463.1 (M+H).

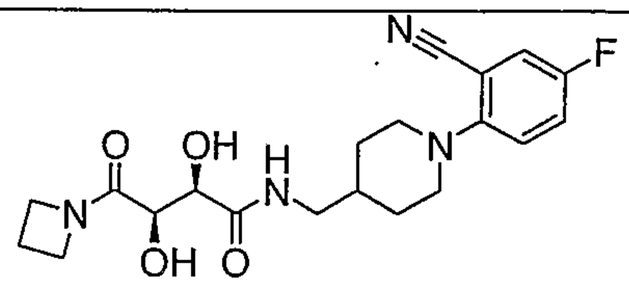
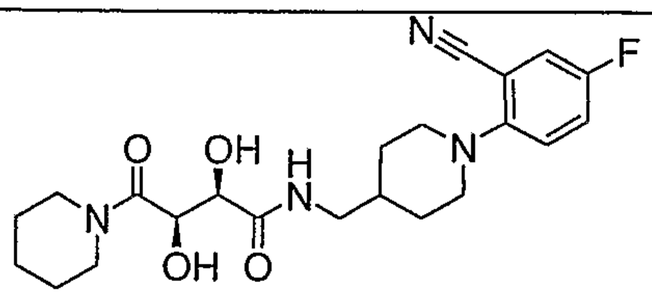
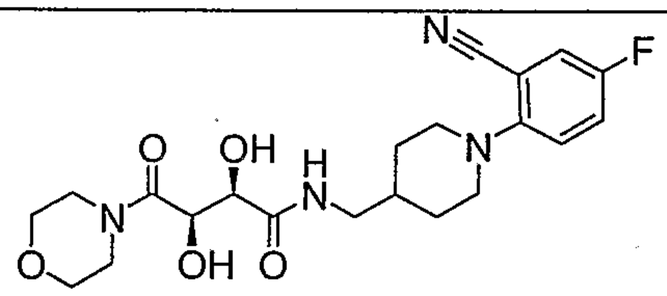
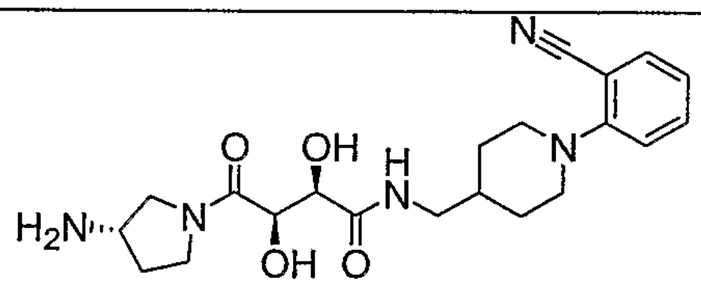
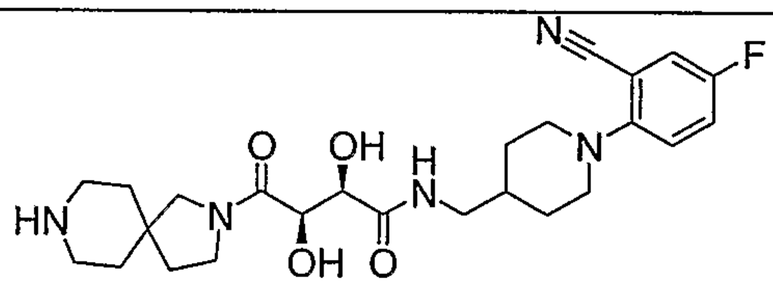
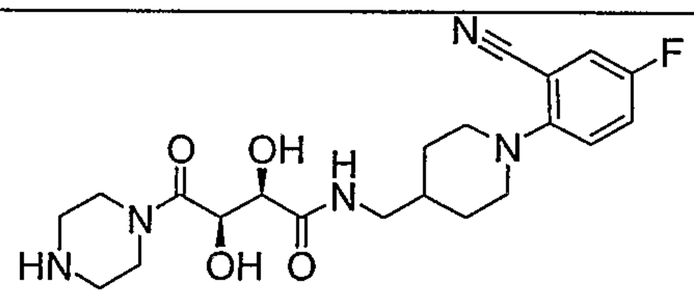
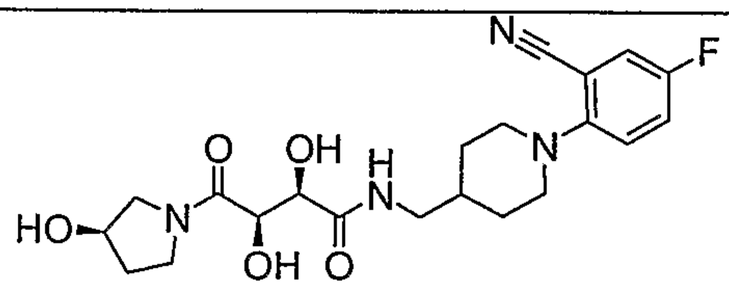
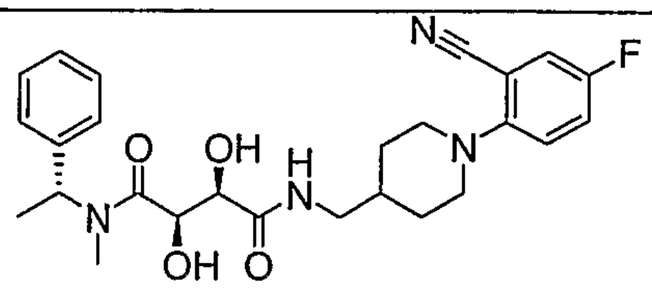
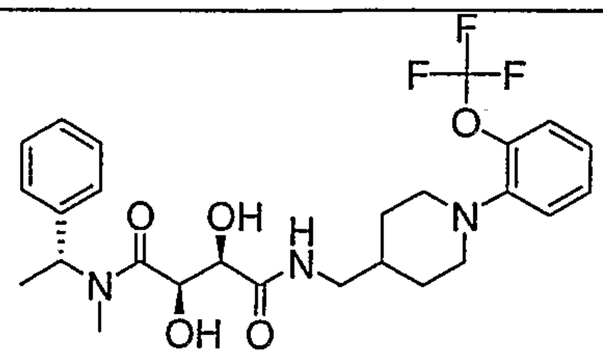
The following table contains compounds that were prepared using the procedures described in Example 27 A – C. Compounds such as **1002** were made from the chloropyridyl precursor using the procedures described in Example 27A Part A.

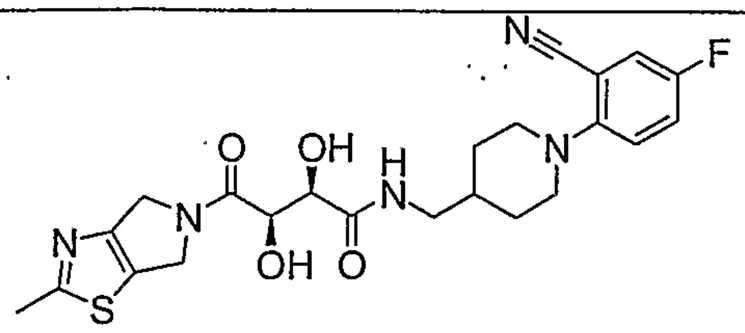
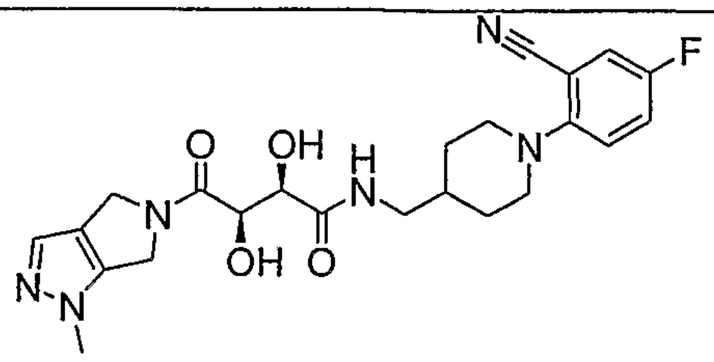
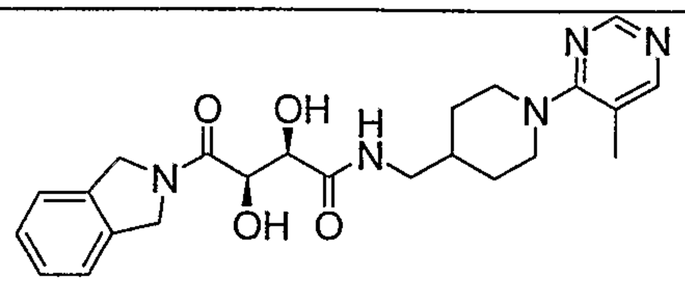
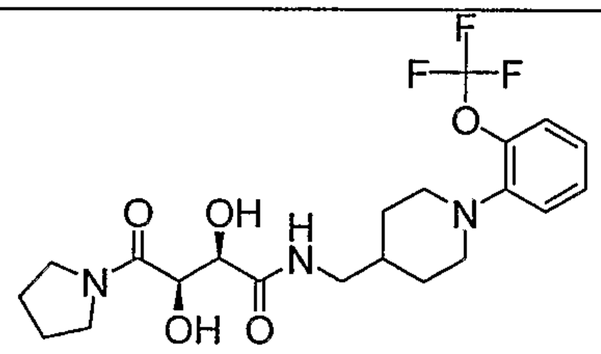
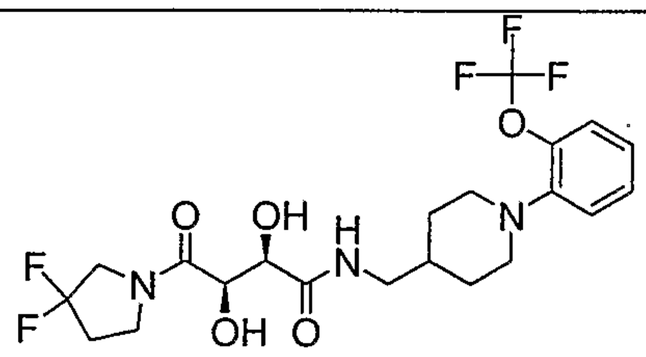
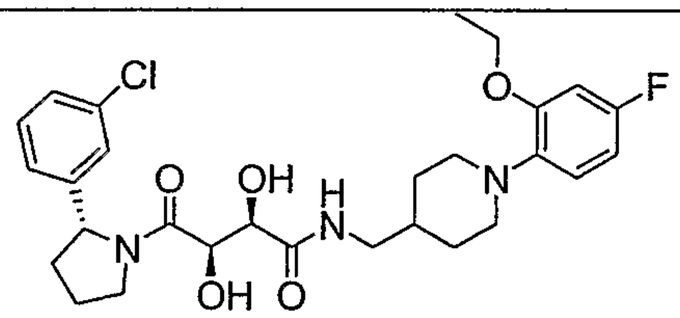
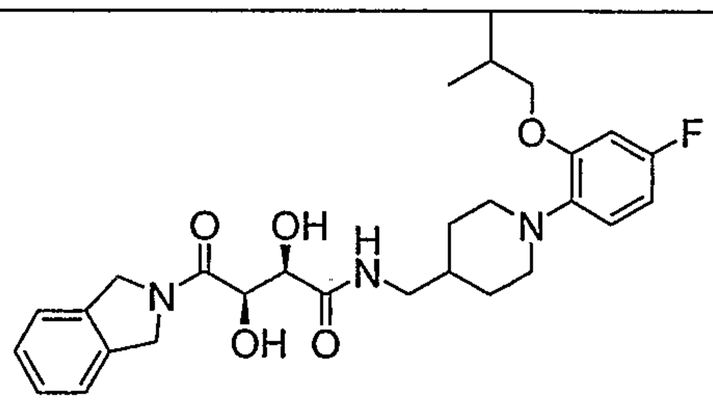
Compound #	Structure	Exact mass	MS m/z (M+H)
995		510.2	511.1
996		347.1	348.3
997		494.2	495.2
998		483.2	484.1
999		492.2	493.1
1000		400.2	401.2
1001		478.2	479.2

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

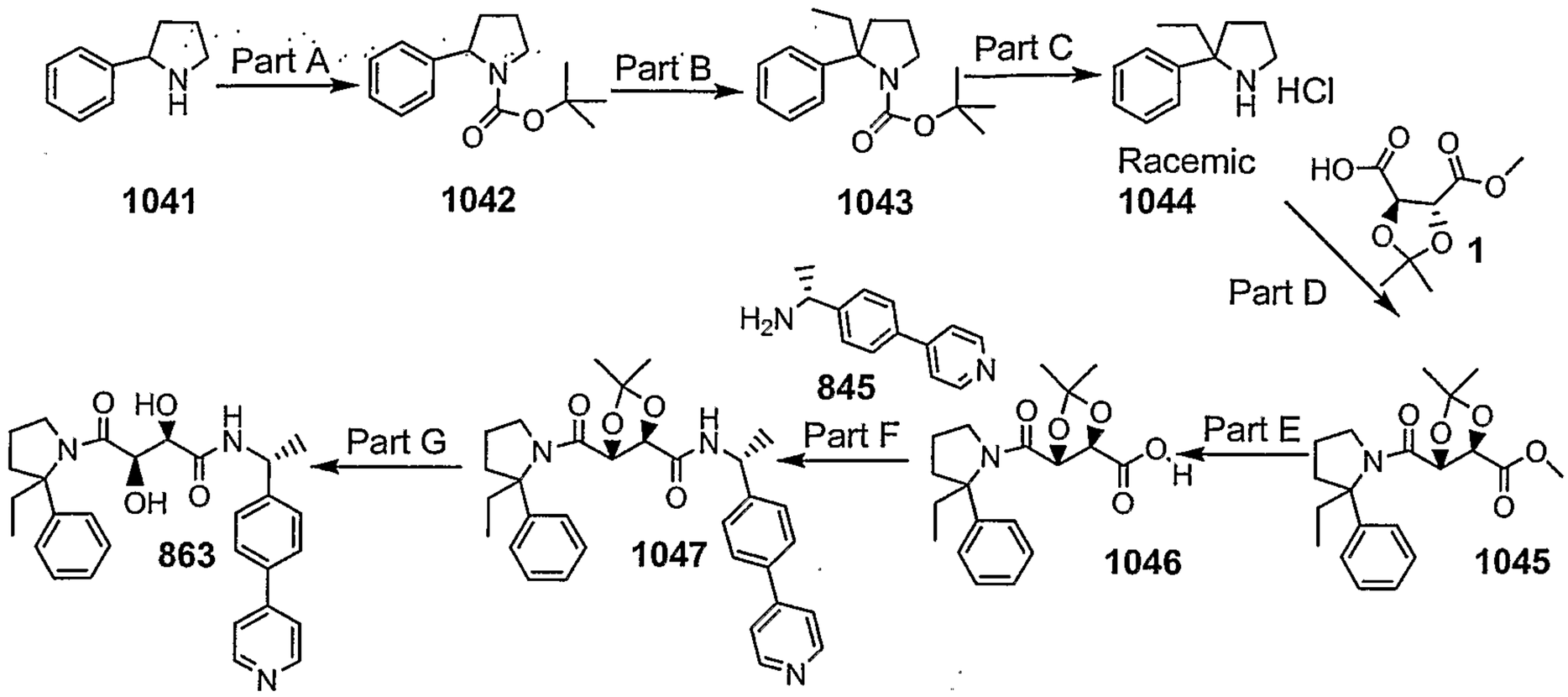
1010		482.2	483.1
1011		466.2	467.2
1012		466.2	467.2
1013		466.2	467.2
1014		476.2	477.1
1015		528.2	529.2
1016		471.2	472.1
1017		507.2	508.2
1018		464.2	465.2

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:

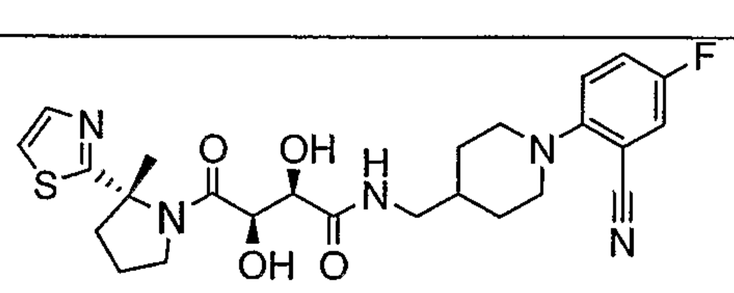
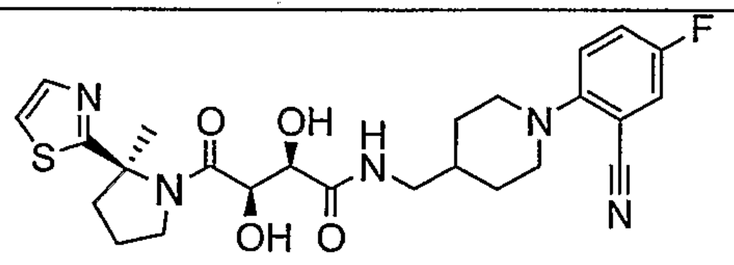
Compound **1046** (69 mg, 0.19 mmol) and **845** (51 mg, 0.22 mmol) were dissolved in DMF (1 mL) and diisopropylamine (100 µL, 0.58 mmol). PyBrop was added (108 mg, 0.338 mmol) and the reaction was stirred overnight at rt. The reaction mixture was diluted with EtOAc and washed with 1.0 M pH 8.0 sodium 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:

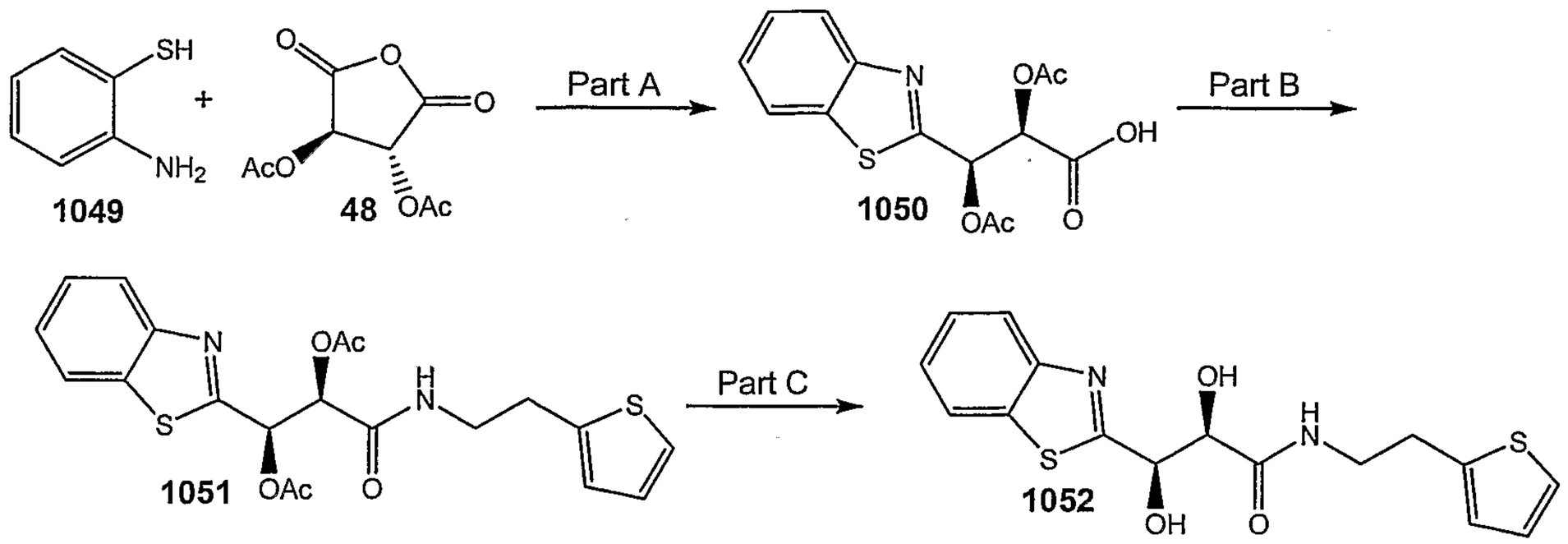
Compound **1047** (74 mg, 0.14 mmol) was dissolved in 5 mL of 9:1 trifluoroacetic acid:water solution. The reaction mixture was stirred at rt for 3 h 10 m, then concentrated to dryness. The crude product was purified purified by column chromatography (SiO_2, 0%-7% MeOH/ CH_2Cl_2) to give 26 mg of compound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

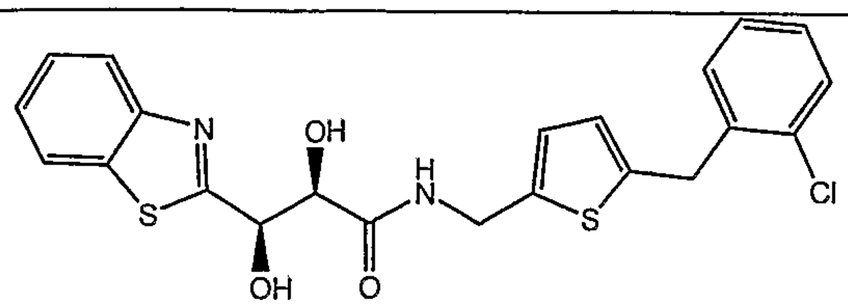
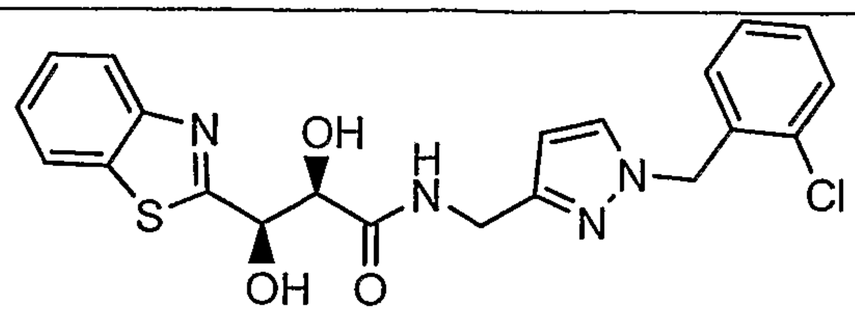
Part B:

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).

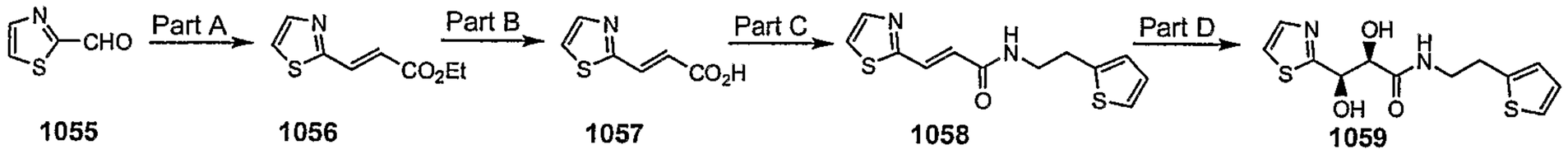
Part C:

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:



1055 **1056** **1057** **1058** **1059**

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

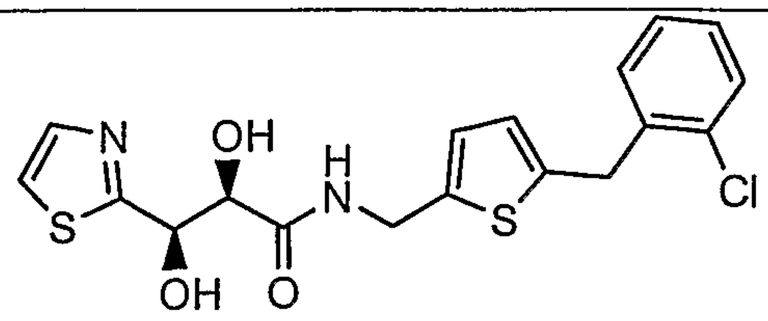
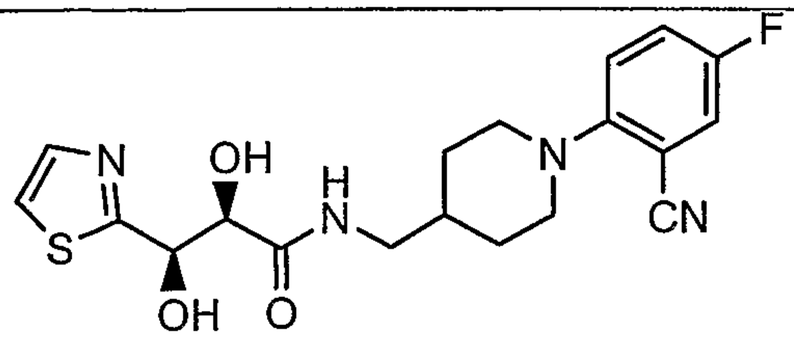
MHz, $CDCl_3$) δ 7.97 (d, 1H, J = 3.0 Hz), 7.89 (d, 1H, J = 15.7 Hz), 7.49 (d, 1H, J = 3.0 Hz), 6.75 (d, 1H, J = 15.7 Hz).

Part C:

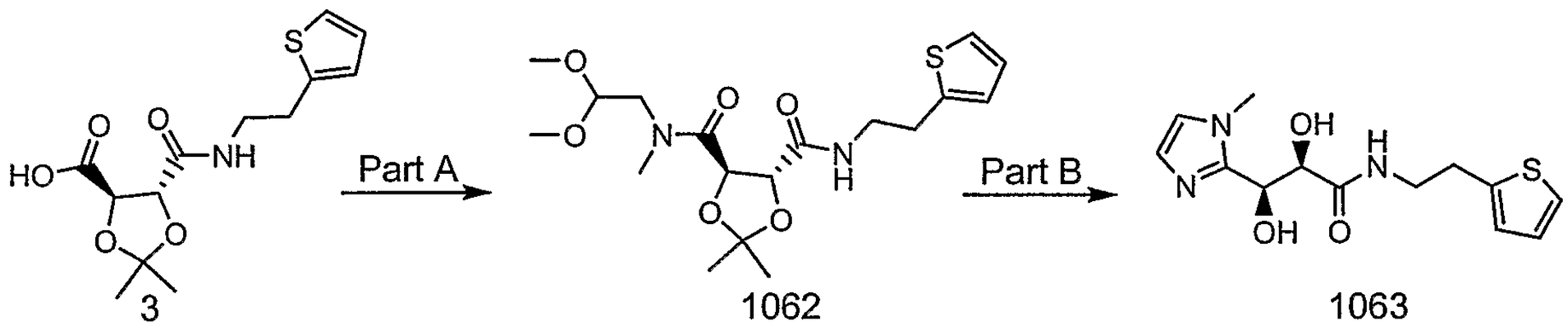
Compound **1058** was prepared from Compound **1057** (32 mg, 0.21 mmol) using the standard HATU coupling strategy described in Example 2 Part A. Purification by column chromatography (SiO_2, 50% ethyl acetate/hexane) afforded the product as a film (35 mg, 63%). HPLC-MS t_R = 1.35 min ($UV_{254\ nm}$); 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.

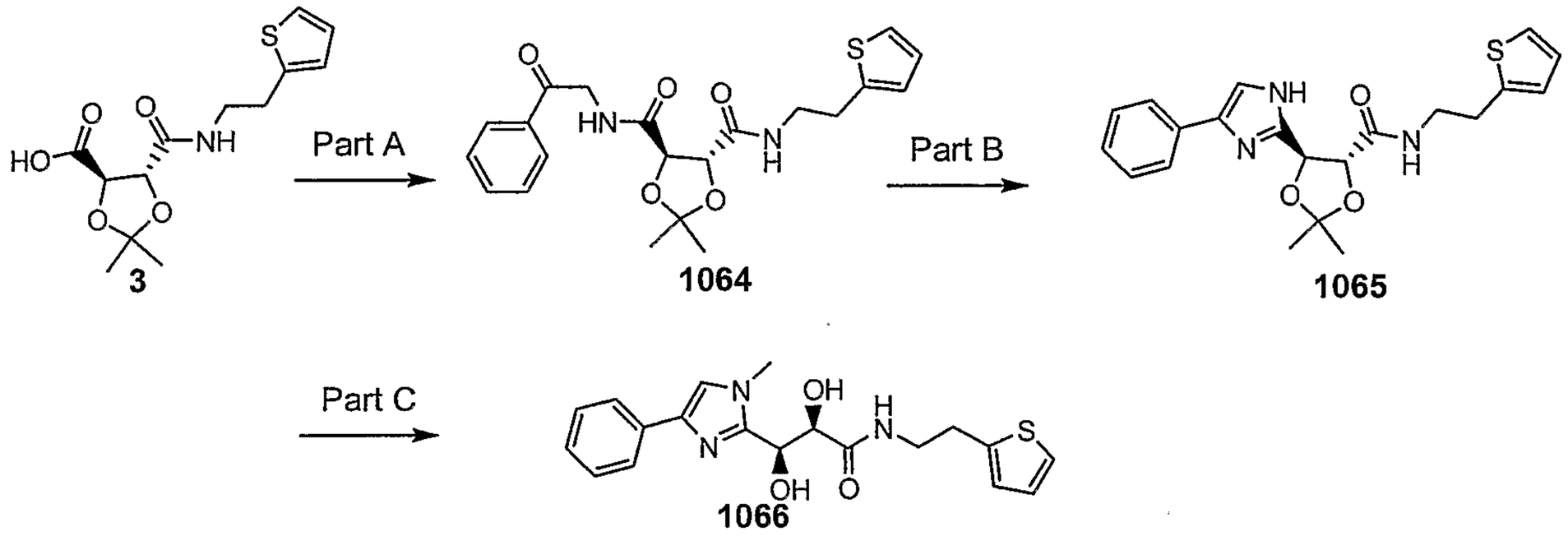
HPLC-MS t_R = 1.69 min ($UV_{254\ nm}$); mass calculated for formula $C_{18}H_{28}N_2O_6S$ 400.2, observed LCMS m/z 401.2 (M+H).

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:

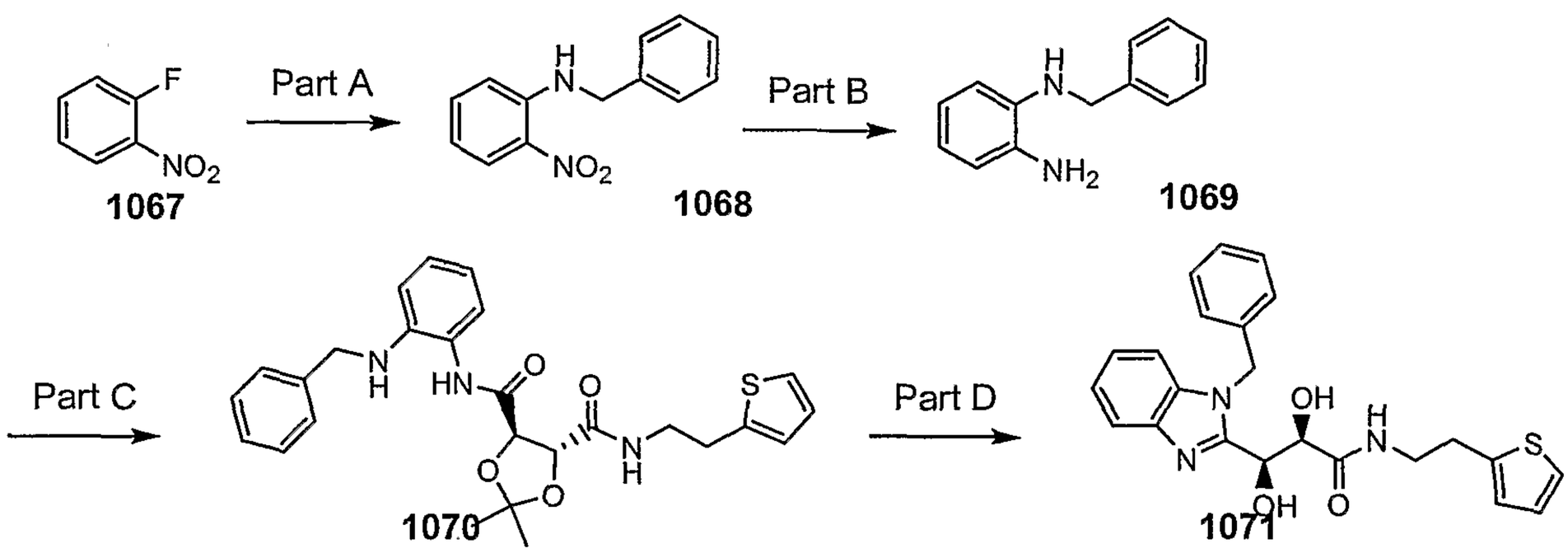
Compound **1064** (216 mg, 0.52 mmol) and ammonium acetate (2 g, 25.9 mmol) in acetic acid (6 ml) were heated overnight at 110 °C. The reaction mixture was concentrated. The residue was suspended in DCM and the solids removed by filtration. The filtrate was concentrated and purified by reverse phase 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:



1067 **1068** **1069** **1070** **1071**

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).

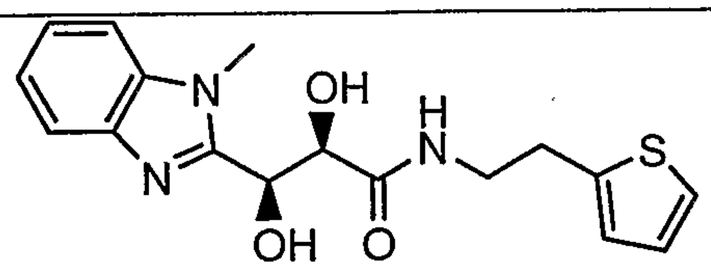
Part C:

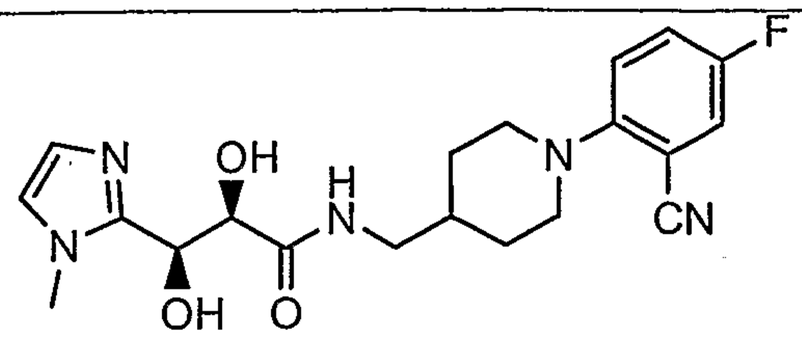
Compound **1070** was prepared following the procedures described in Example 29C Part A. HPLC-MS t_R = 2.13 min ($UV_{254\ nm}$); mass calculated for formula $C_{26}H_{29}N_3O_4S$ 479.2, observed LCMS m/z 480.1 (M+H).

Part D:

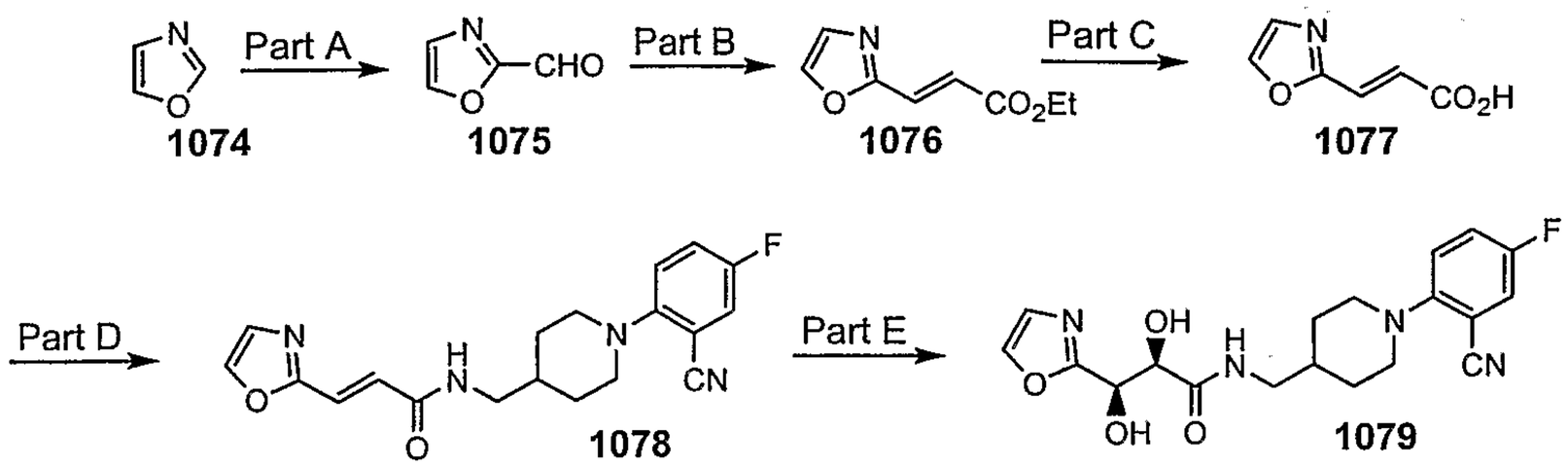
A mixture of compound **1070** (75 mg, 0.156 mmol) and p-toluenesulfonic acid monohydrate (30 mg, 0.156 mmol) in toluene (3 ml) was heated overnight at reflux. The reaction mixture was concentrated to a residue identified as the acetonide deprotected product by LC-MS. Further purification by reverse 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:

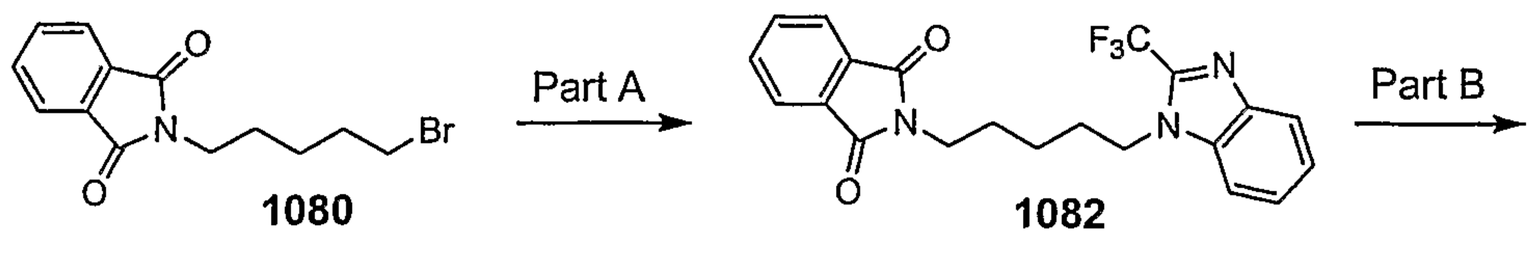
Compound **1078** was prepared from compound **1077** (165 mg, 1.7 mmol) using the procedure described in Example 29B Part C. After standard HATU coupling work-up the solid residue was triturated with 1:1 DCM/hexane, filtered and washed with 1:1 DCM/hexane to give **1078** (123 mg, 70%) as a pale yellow 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%); ^{1}H 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%). ^{1}H 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).

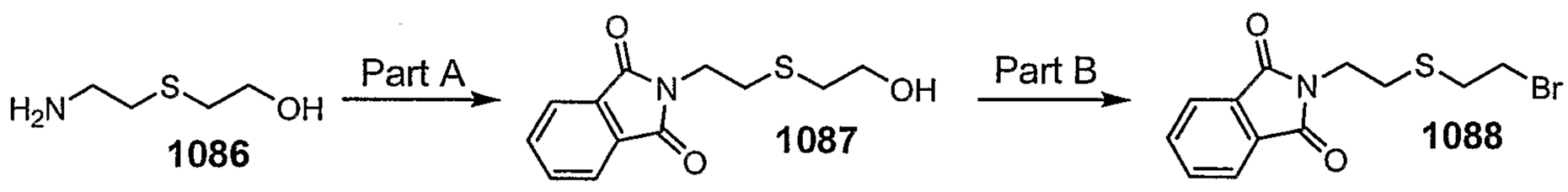
Part C:

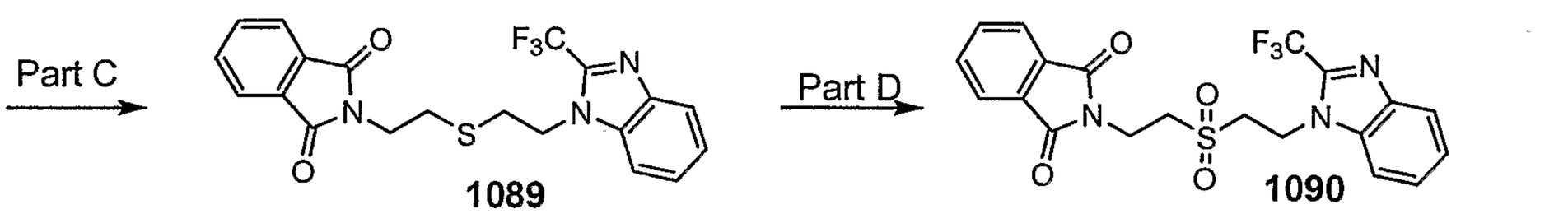
Compound **1084** was prepared from **1083** and **230** following the procedures described in Example 2.

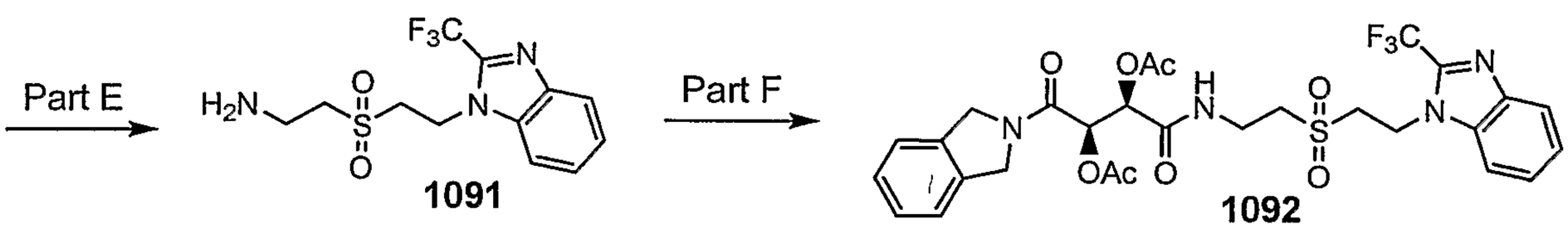
Part D:

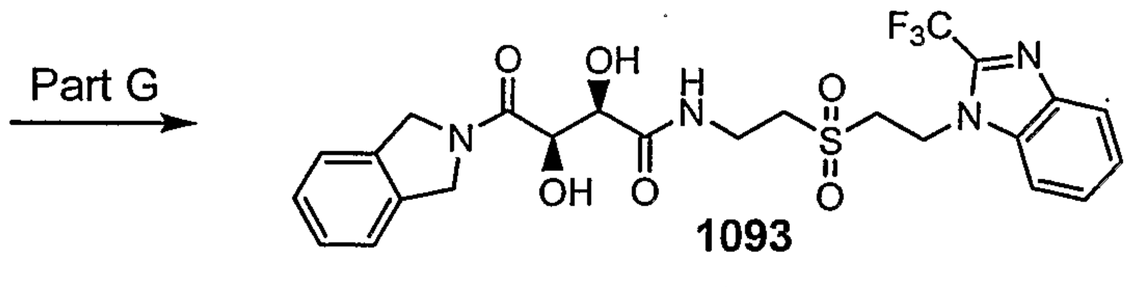
Compound **1085** was prepared following the procedures described in Example 2. HPLC-MS t_R = 4.14 min (10 min; $UV_{254\ nm}$); mass calculated for formula $C_{25}H_{27}F_3N_4O_4$ 504.2, observed LCMS m/z 505.1 (M+H).

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%). ^{1}H 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. ^{1}H 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. ^{1}H 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-

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CONTAINING PAGES 1 TO 535

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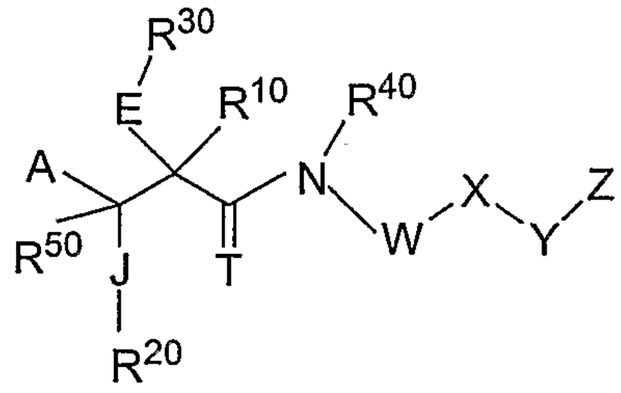
NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

Claims

What is claimed is:

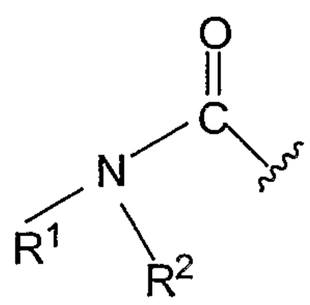
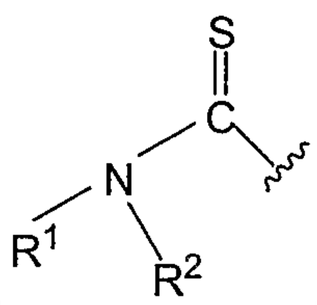
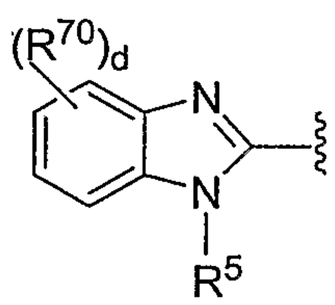
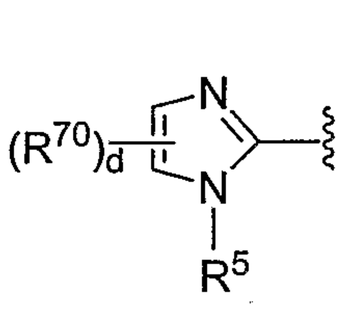
1. A compound of formula (I):



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 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

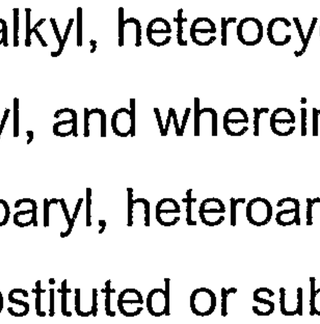
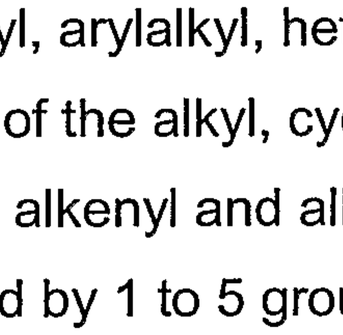
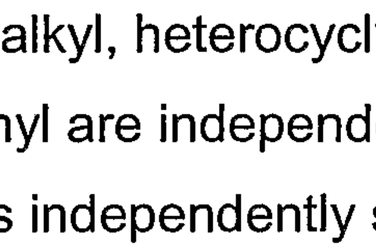
$-S(O)_qR^{15}$ wherein q is 1 to 2; and wherein each of the alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl are independently unsubstituted or substituted by 1 to 5 groups independently selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, 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.

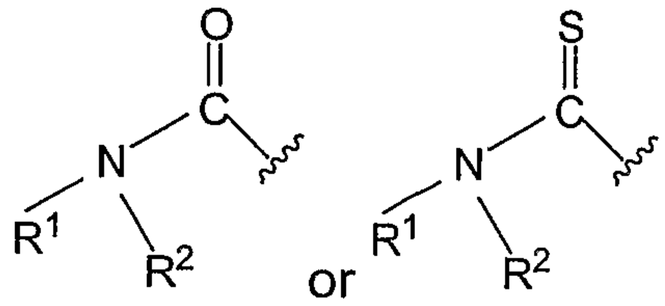
2. The compound of claim 1 wherein A is selected from the group consisting of:



and


wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 4-8 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

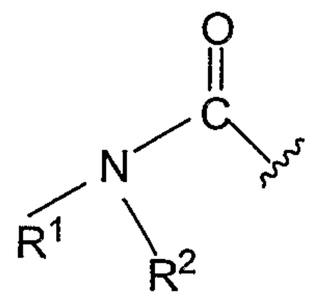
4-8 membered heterocyclic ring can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group of R^{70} moieties.

3. The compound of claim 1 wherein A is

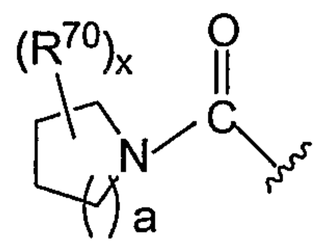


wherein R^1 and R^2 are the same or different, each being independently selected from the group consisting of H, alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl, and heteroaryl; wherein said alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaralkyl and heteroaryl can be unsubstituted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

4. The compound of claim 3 wherein A is



5. The compound of claim 2 wherein A is

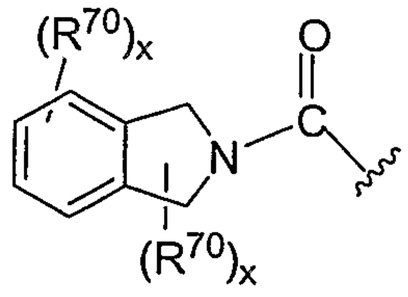


wherein

a is 0 to 4; and

x is 0 to 4.

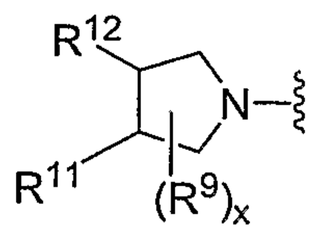
6. The compound of claim 2 wherein A is



wherein

each x idependently is 0 to 4.

7. The compound of claim 2 wherein a ring is formed from $-NR^1R^2$ and said ring is



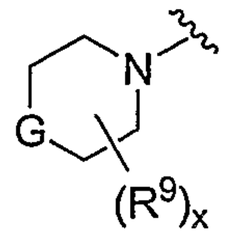
wherein

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.

8. The compound of claim 2 wherein a ring is formed from $-NR^1R^2$ and said ring is



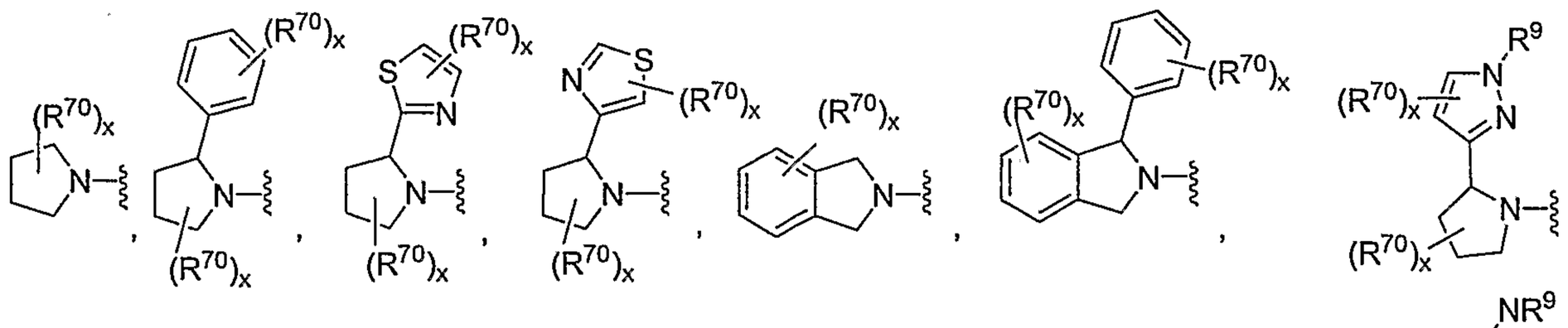
wherein

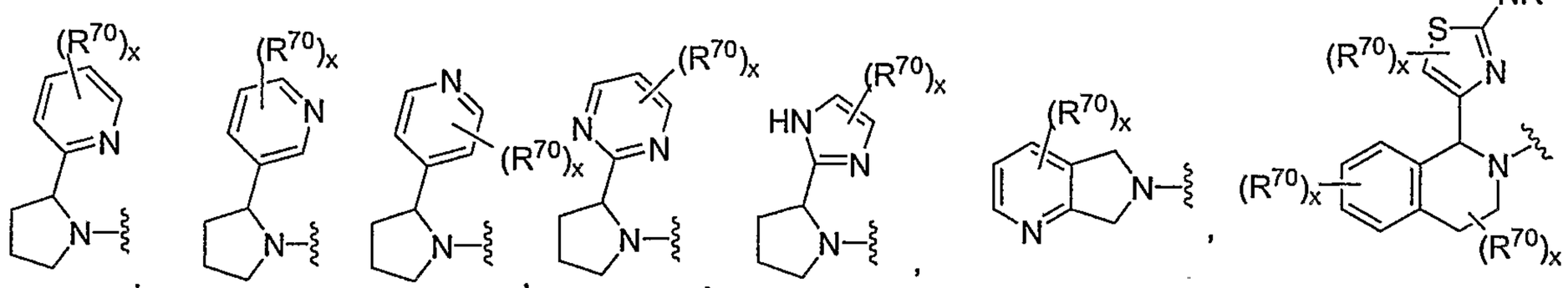
each R^9 is a substituent for H where indicated and can be the same or different, each being independently selected from the group consisting of -OH, $-OR^{14}$, $-C(O)OR^{15}$, $-C(O)N(R^{15})(R^{16})$, alkyl, aryl, heteroaryl, alkenyl, alkynyl, cycloalkyl and heterocyclyl, wherein said alkyl, aryl,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

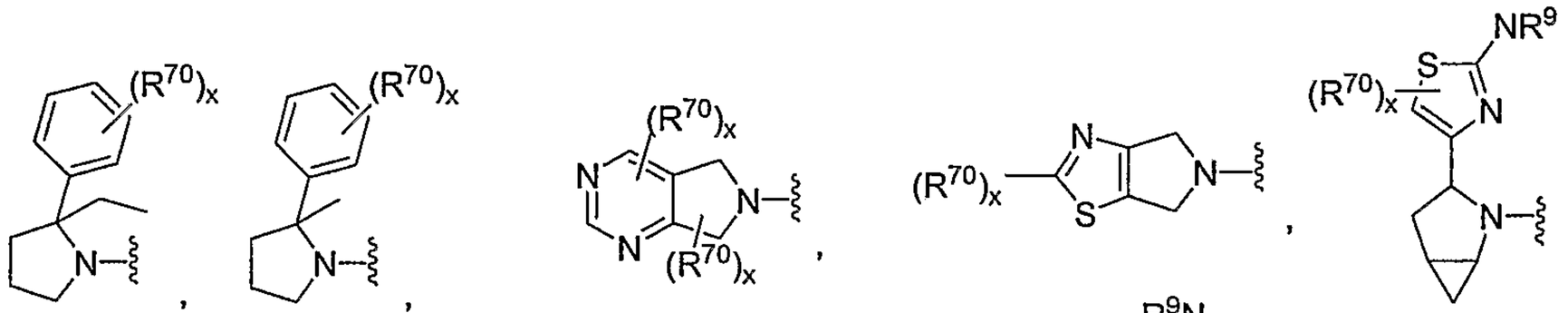
x is 0 to 4, and when x is greater than 1, each R^9 moiety can be the same or different, each moiety being independently selected from the group of R^9 moieties; and

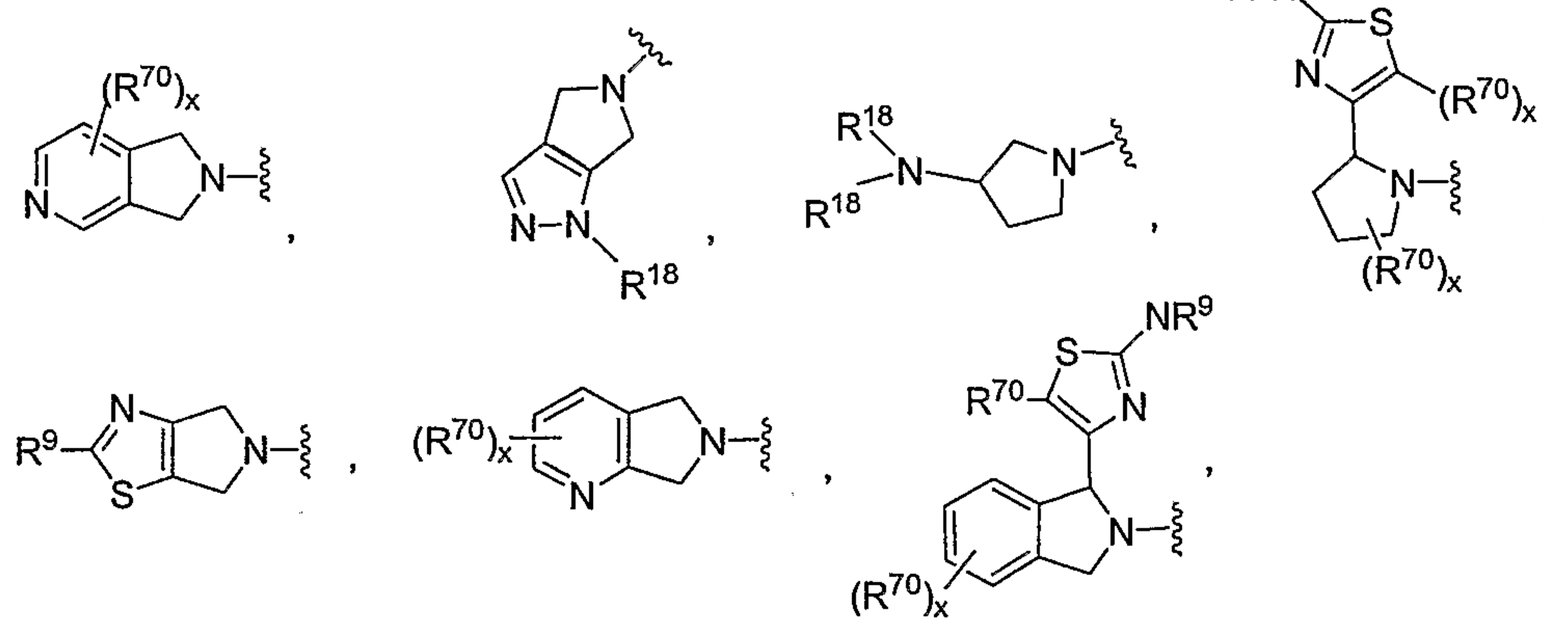
G is selected from the group consisting of CH_2, NR^7, O, S, or SO_2.

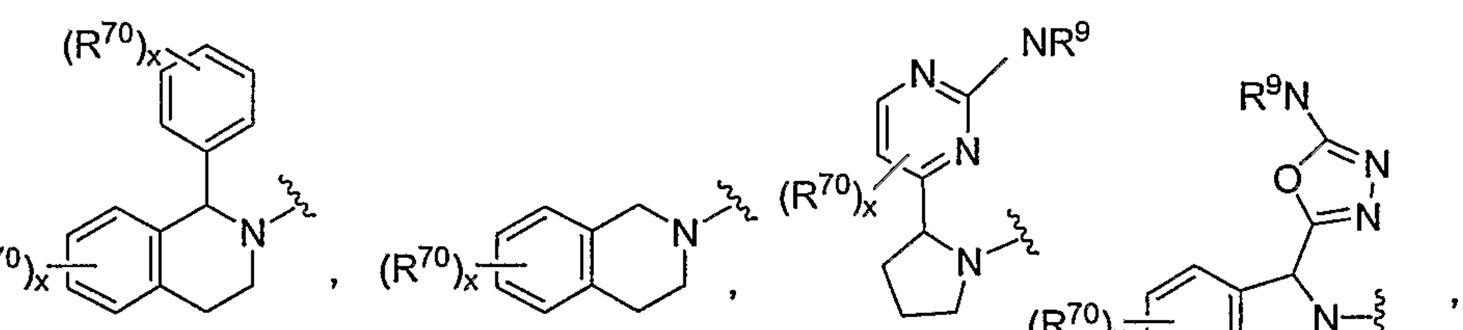
9. The compound of claim 2 wherein a ring is formed from $-NR^1R^2$ and said ring is selected from the group consisting of

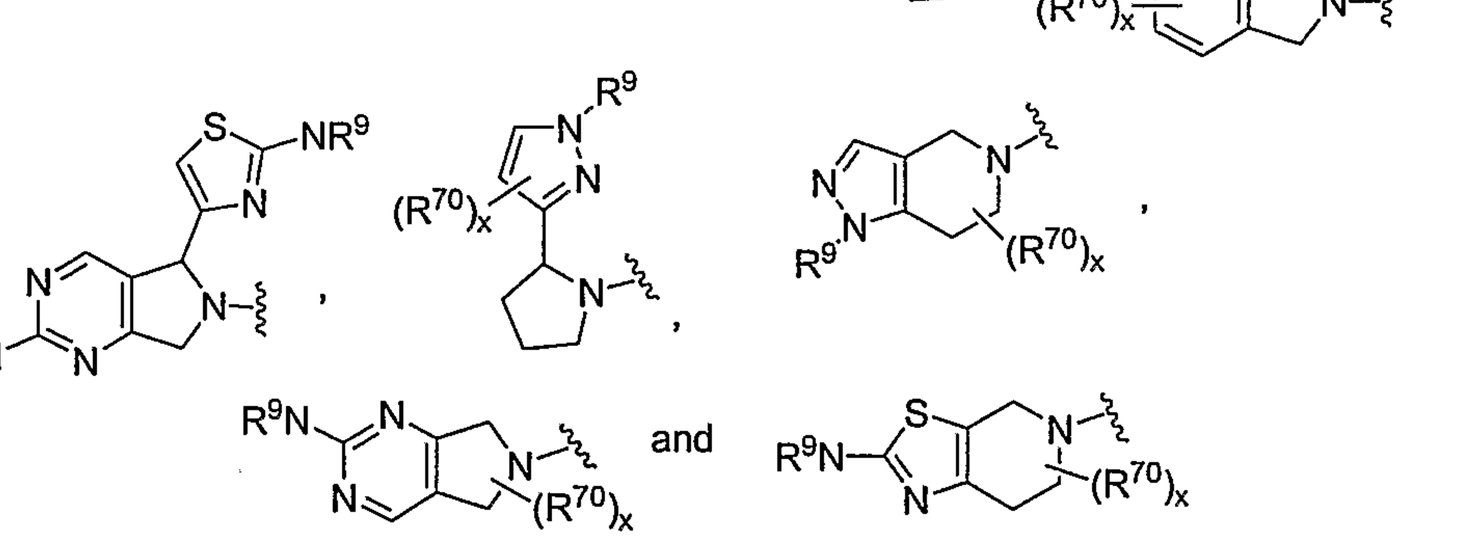












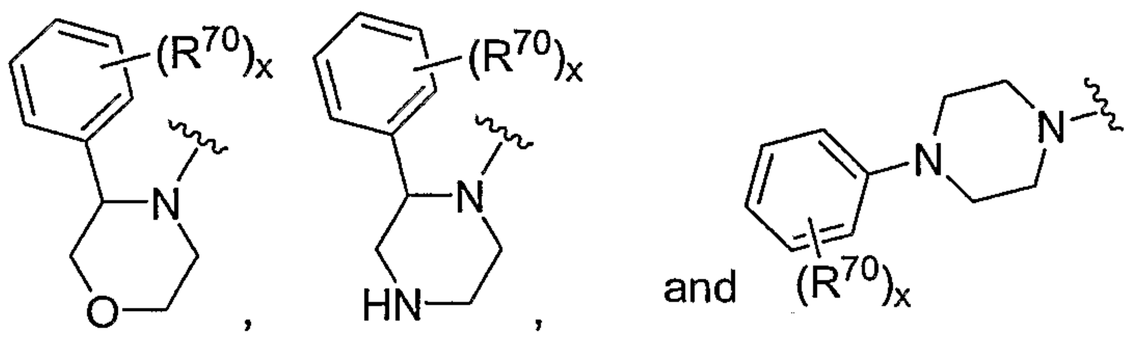
and

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.

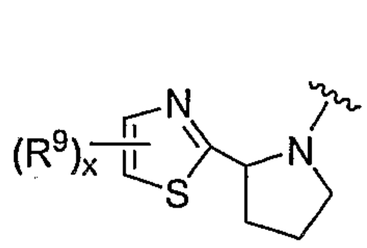
10. The compound of claim 2 wherein a ring is formed from $-NR^1R^2$ and said ring is selected from the group consisting of:



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.

11. The compound of claim 2 wherein a ring is formed from $-NR^1R^2$ and is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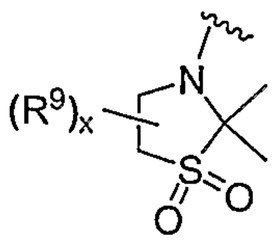
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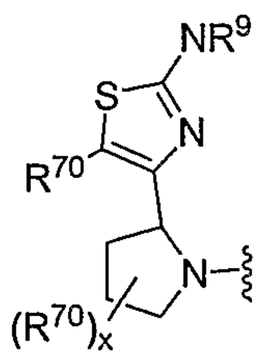
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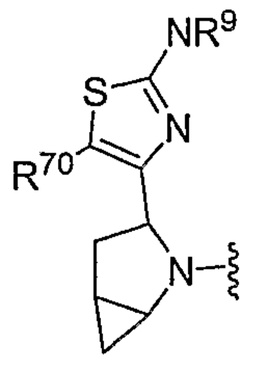

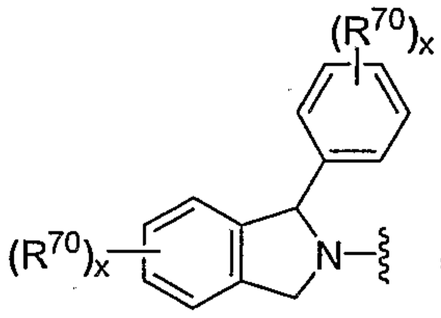
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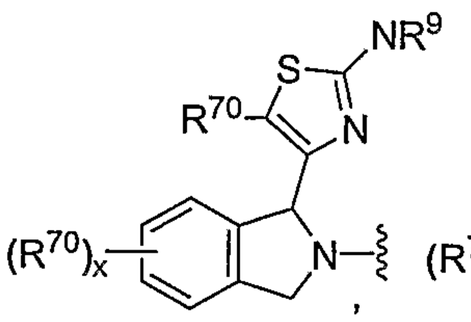
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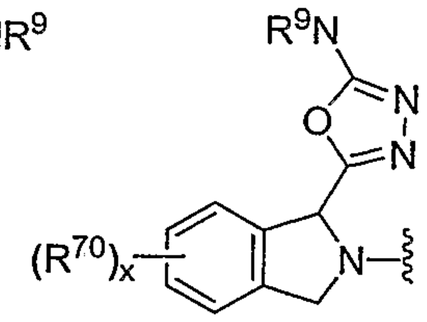
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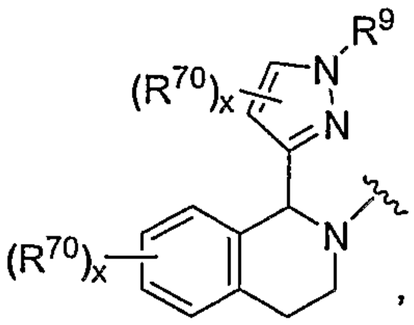

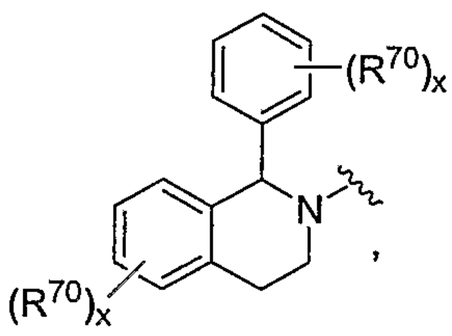
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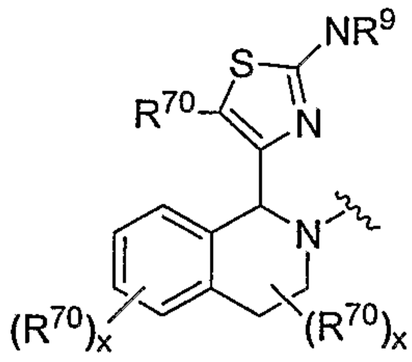
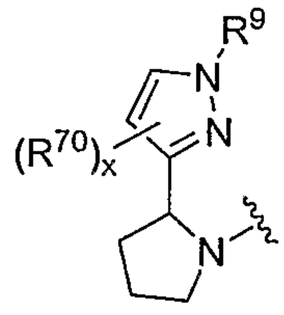
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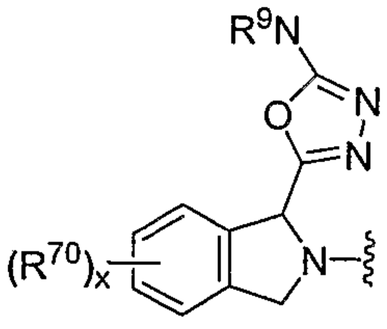
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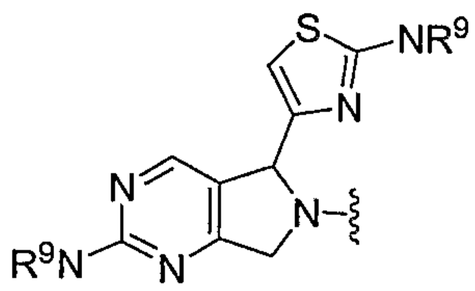


wherein

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.

12. The compound of claim 2 wherein J is O.

13. The compound of claim 2 wherein E is O.

14. The compound of claim 2 wherein R^{10} is H or alkyl.

15. The compound of claim 2 wherein R^{20} is H.

16. The compound of claim 2 wherein R^{30} is H.

17. The compound of claim 2 wherein R^{40} is H.

18. The compound of claim 2 wherein R^{50} is H.

19. The compound of claim 2 wherein R^{13} is H or alkyl.

20. The compound of claim 19 wherein R^{13} is H or $-CH_3$.

21. The compound of claim 2 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.

22. The compound of claim 2 wherein Y is a covalent bond or -$[C(R^6)_2]_n$- wherein n is 1 to 2.

23. The compound of claim 2 wherein Y is selected from the group consisting of a covalent bond, -CH_2-, -C(H)(OH)-, -C(O)- and –O-.

24. The compound of claim 23 wherein Y is a covalent bond or -CH_2-.

25. The compound of claim 24 wherein Y is a covalent bond.

26. The compound of claim 2 wherein W is -$(CR^{13}{}_2)_n$-, in which n is 1-5 and each R^{13} is H, or alkyl.

27. The compound of claim 2 wherein W is selected from the group consisting of -CH_2-, -C(H)(CH_3)-, -$C(CH_3)_2$- and -CH_2CH_2-.

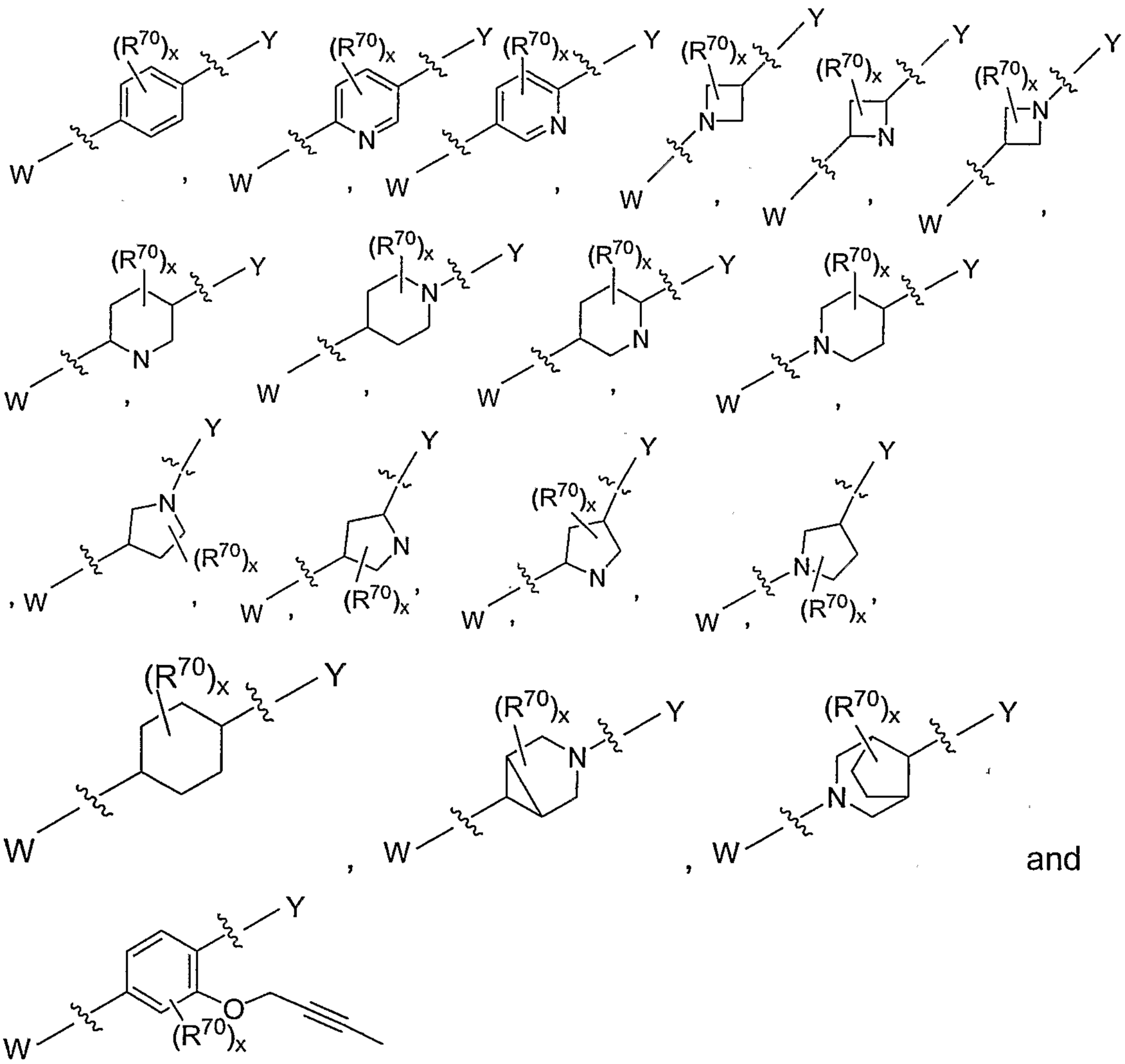
28. The compound of claim 27 wherein W is -CH_2- or –C(H)(CH_3)-.

29. The compound of claim 2 wherein X is selected from the group consisting of alkyl, aryl, heterocyclyl and heteroaryl.

30. The compound of claim 29 wherein X is selected from the group consisting of phenyl, azetidinyl, pyrrolidinyl, piperidinyl, pyridinyl, thienyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl.

31. The compound of claim 30 wherein X is selected from the group consisting of phenyl, piperidinyl and pyridinyl.

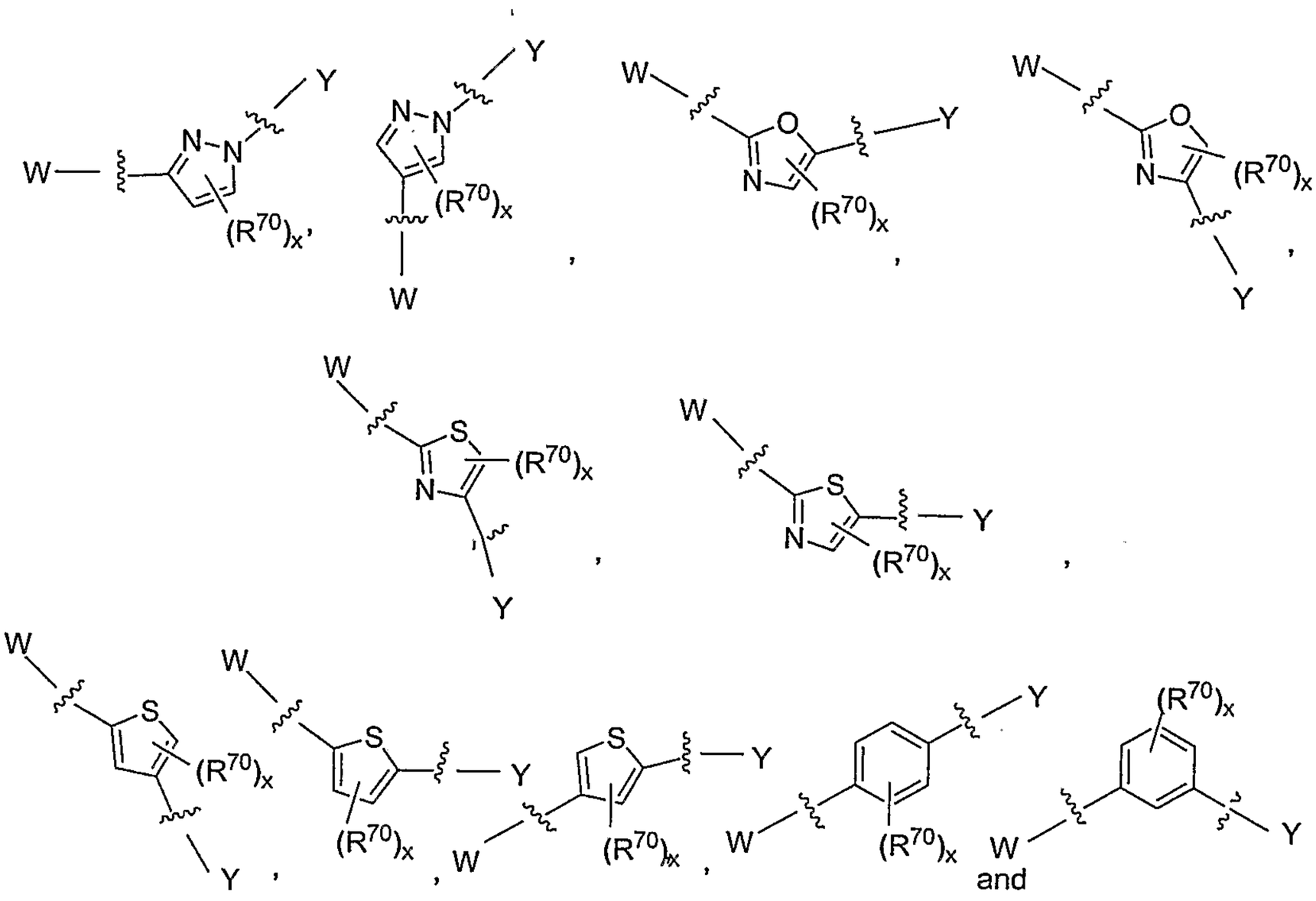
32. The compound of claim 29 wherein X is selected from the group consisting of



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.

33. The compound of claim 29, wherein X is selected from the group consisting of



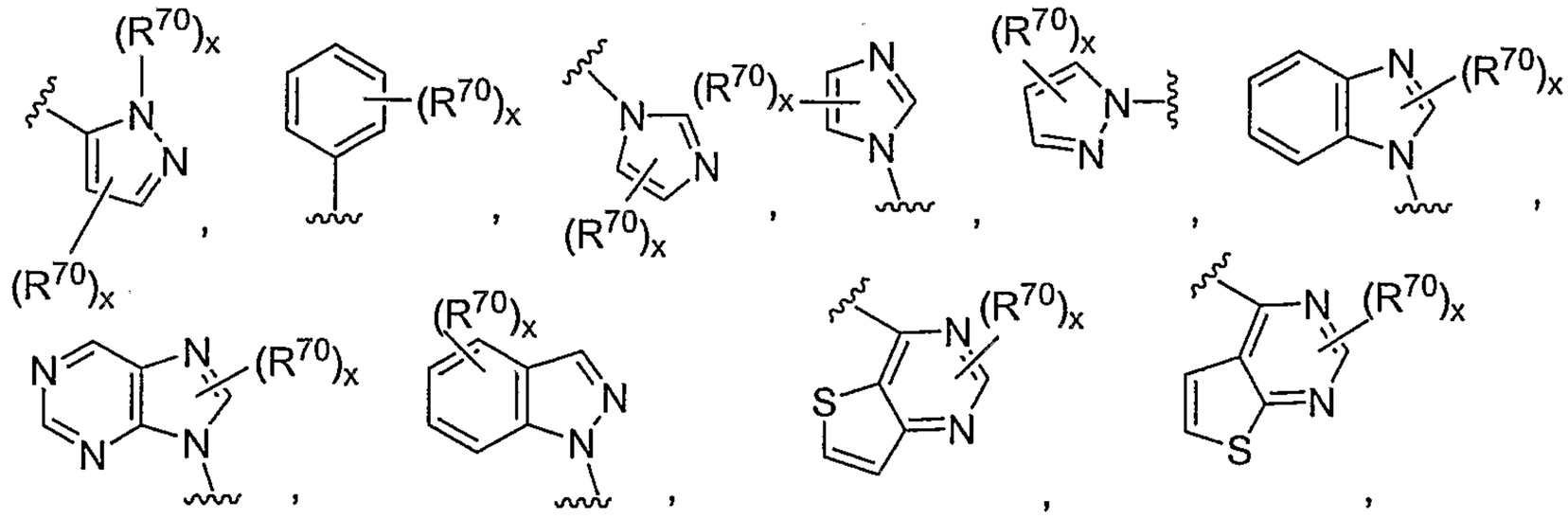
wherein

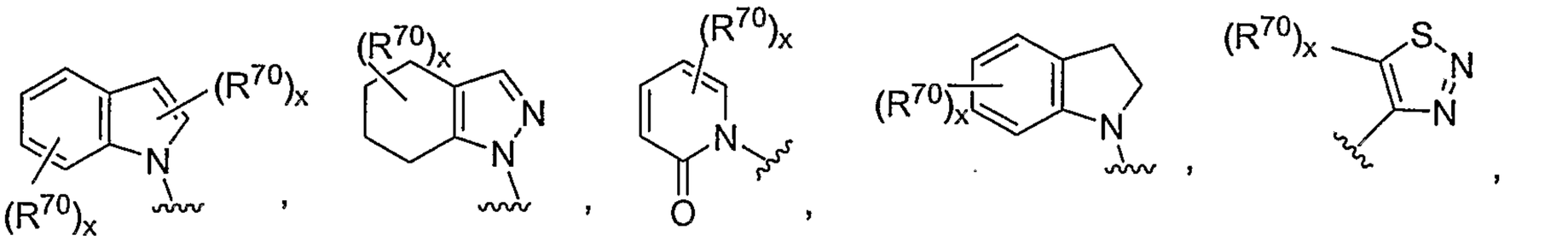
x is 0 to 4, and when x is greater than 1, each R^{70} moiety can be the same or different, each moiety being independently selected from the group of R^{70} moieties.

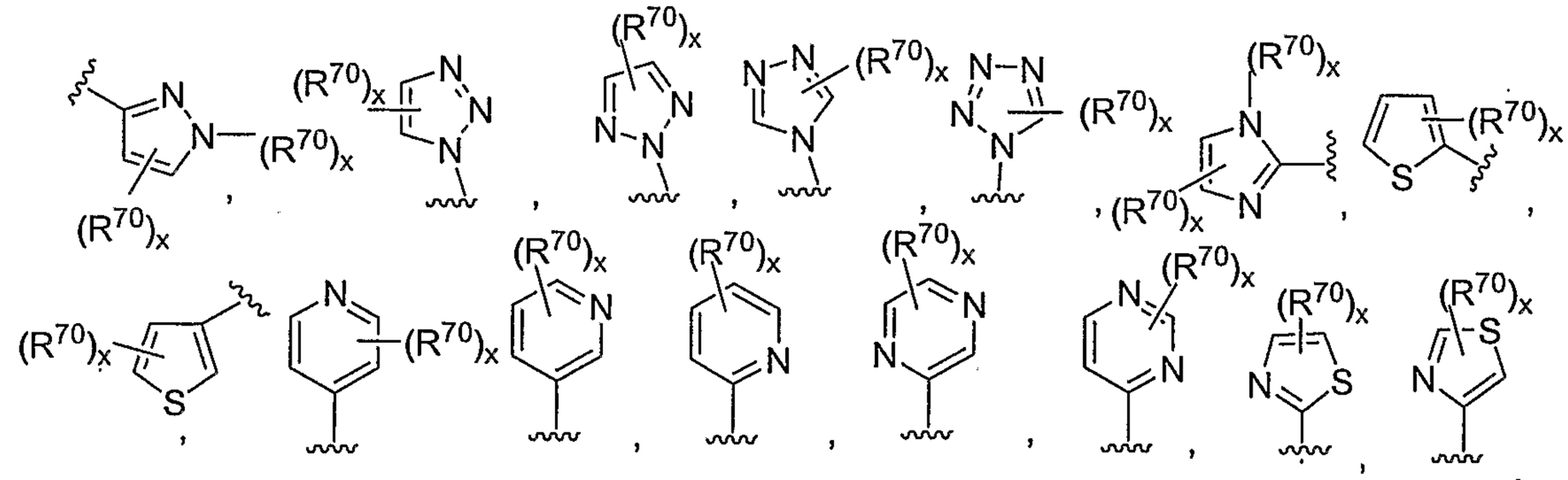
34. The compound of claim 2 wherein Z is selected from the group consisting of H, aryl and heteroaryl.

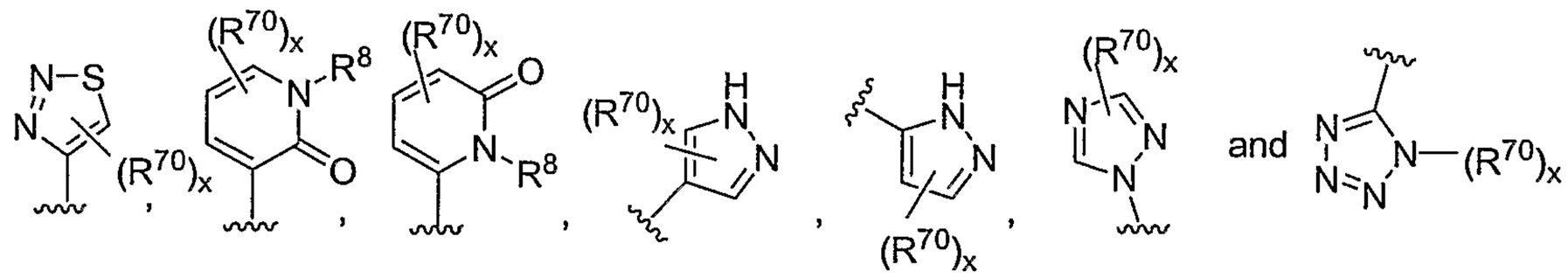
35. The compound of claim 34 wherein Z is selected from the group consisting of H, phenyl, indolyl, benzimidazolyl, pyrazolyl, thienyl, pyridinyl, thiazolyl, thiadiazolyl, imidazolyl, pyrrolidinyl, pyrazinyl, triazolyl, tetrazolyl and tetrazinyl, wherein said phenyl, indolyl, benzimidazolyl, pyrazolyl, 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.

36. The compound of claim 35 wherein 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.

37. The compound of claim 35 wherein Z is phenyl.

38. The compound of claim 37 wherein said phenyl is substituted with at least one substituent selected from the group consisting of cyano, alkoxy, halogen, alkyl, haloalkyl, hydroxy, aryl, heteroaryl, aryloxy, amino and tetrazole.

39. The compound of claim 35 wherein Z is thienyl.

40. The compound of claim 39 wherein said thienyl is substituted with at least one substituent selected from the group consisting of cyano,

alkoxy, halogen, alkyl, haloalkyl, hydroxy, aryl, heteroaryl, aryloxy, amino and tetrazole.

41. The compound of claim 35 wherein Z is pyrazolyl.

42. The compound of claim 41 wherein said pyrazolyl is substituted with at least one substituent selected from the group consisting of cyano, alkoxy, halogen, alkyl, haloalkyl, hydroxy, aryl, heteroaryl, aryloxy, amino and tetrazole.

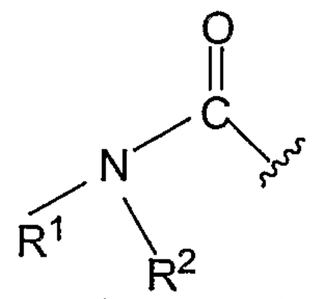
43. The compound of claim 35 wherein Z is pyridinyl.

44. The compound of claim 43 wherein said pyridinyl is substituted with at least one substituent selected from the group consisting of cyano, alkoxy, halogen, alkyl, haloalkyl, hydroxy, aryl, heteroaryl, aryloxy, amino and tetrazole.

45. The compound of claim 35 wherein Z is imidazolyl.

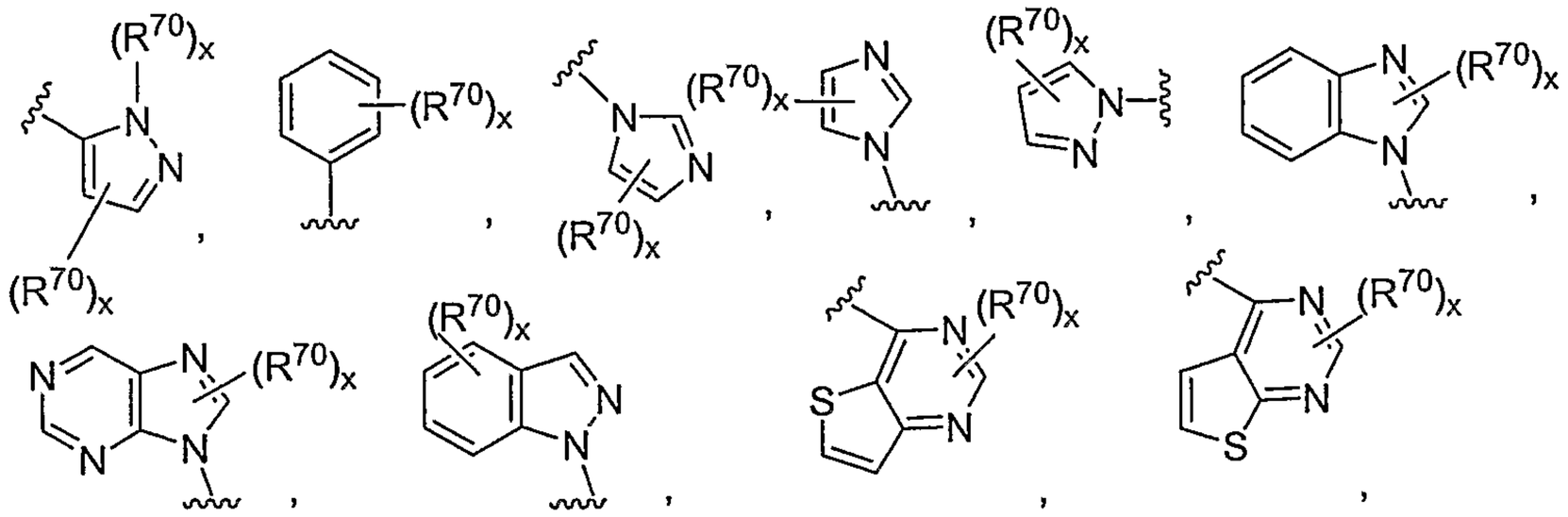
46. The compound of claim 45 wherein said imidazolyl is substituted with at least one substituent selected from the group consisting of cyano, alkoxy, halogen, alkyl, haloalkyl, hydroxy, aryl, heteroaryl, aryloxy, amino and tetrazole.

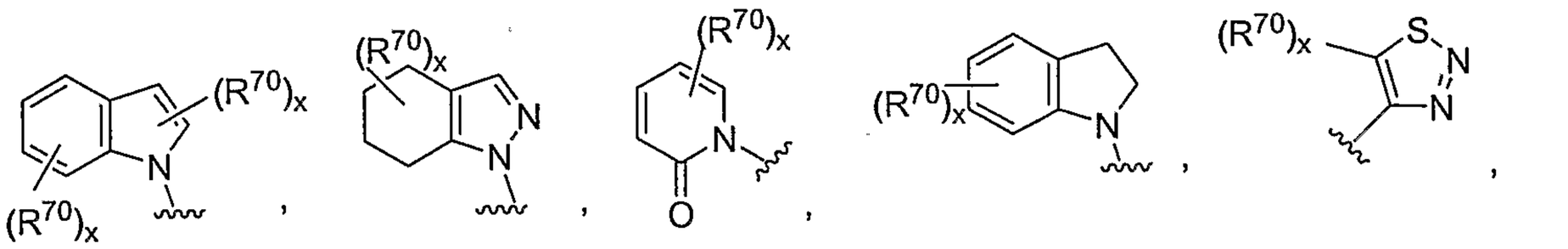
47. The compound of claim 2 wherein A is

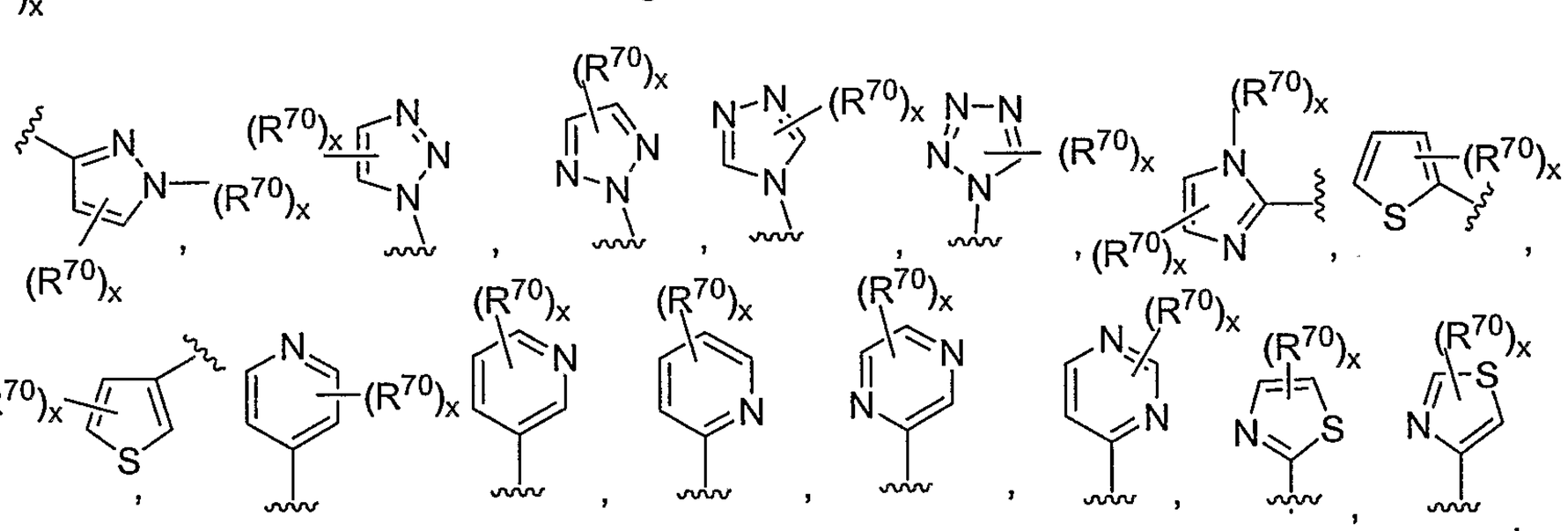


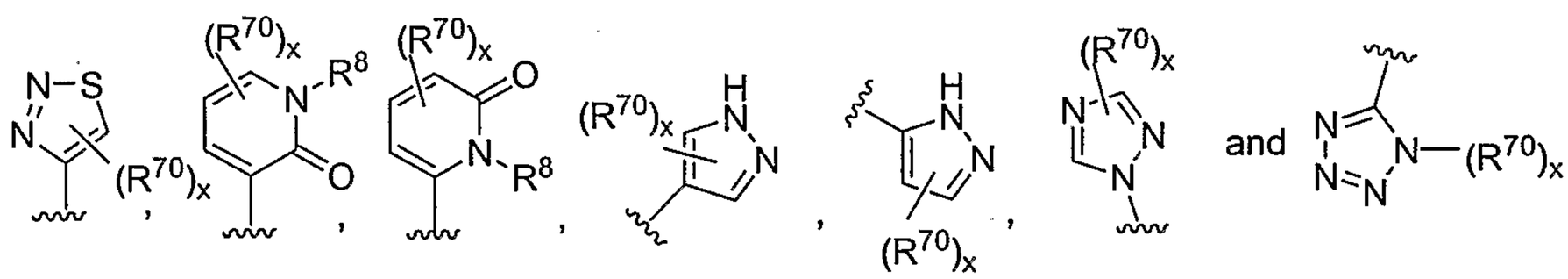
wherein R^1 and R^2, taken together with the N to which R^1 and R^2 are shown attached, represent a 4-8 membered heterocyclic ring having 1-3 heteroatoms including said N, said heterocyclic ring being optionally substituted with one or more R^{70}, or optionally fused with aryl, heteroaryl, cycloalkyl,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









48. The compound of claim 47 wherein the $-NR^1R^2$ of

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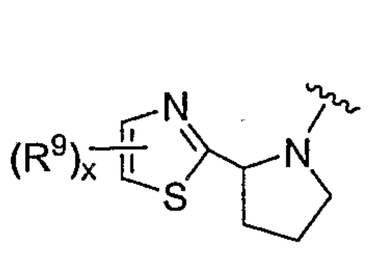
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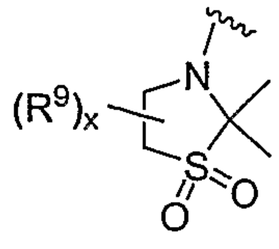
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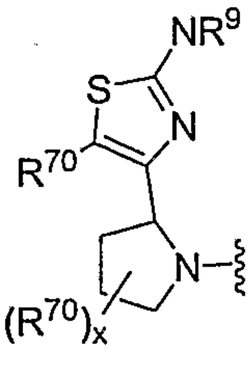
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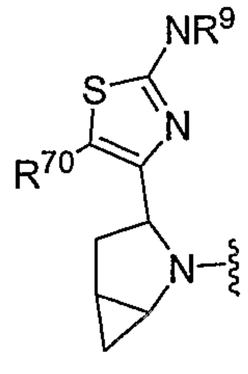
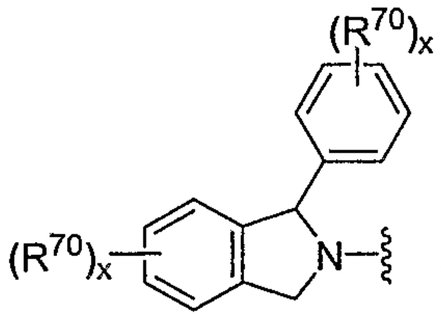
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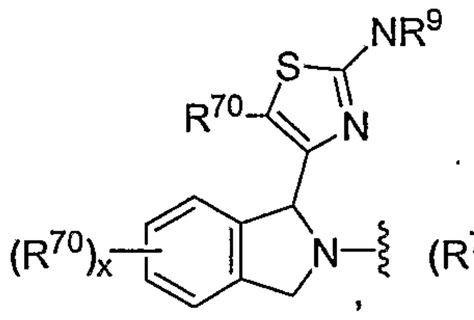
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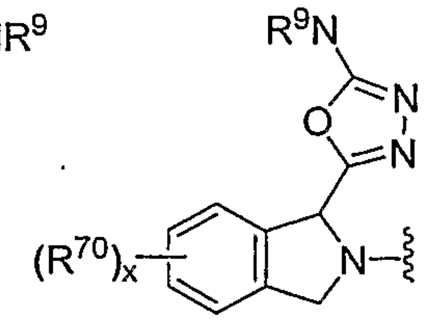
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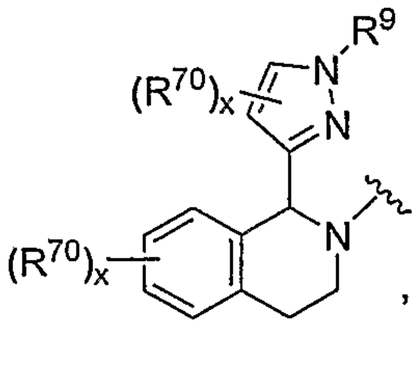
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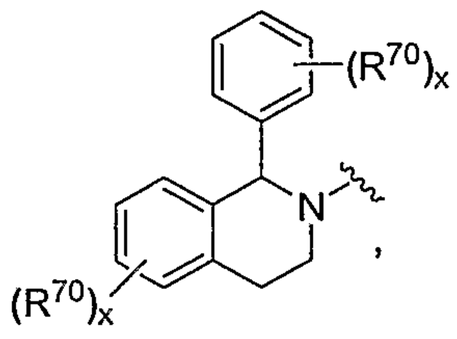
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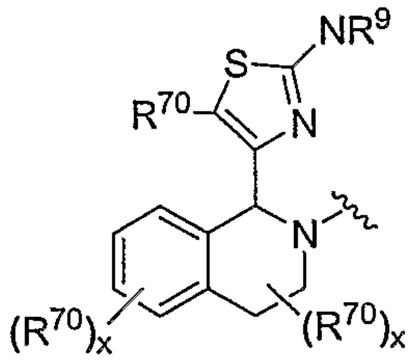
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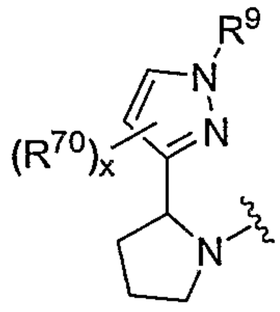
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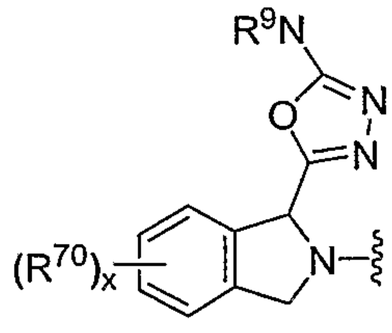
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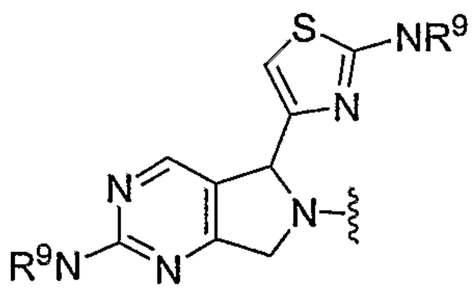


wherein

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.

49. The compound of claim 47 wherein X is selected from the group consisting of phenyl, piperidinyl, pyridinyl, thienyl, thiazolyl, oxazolyl, and pyrazolyl.

50. The compound of claim 48 wherein 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-

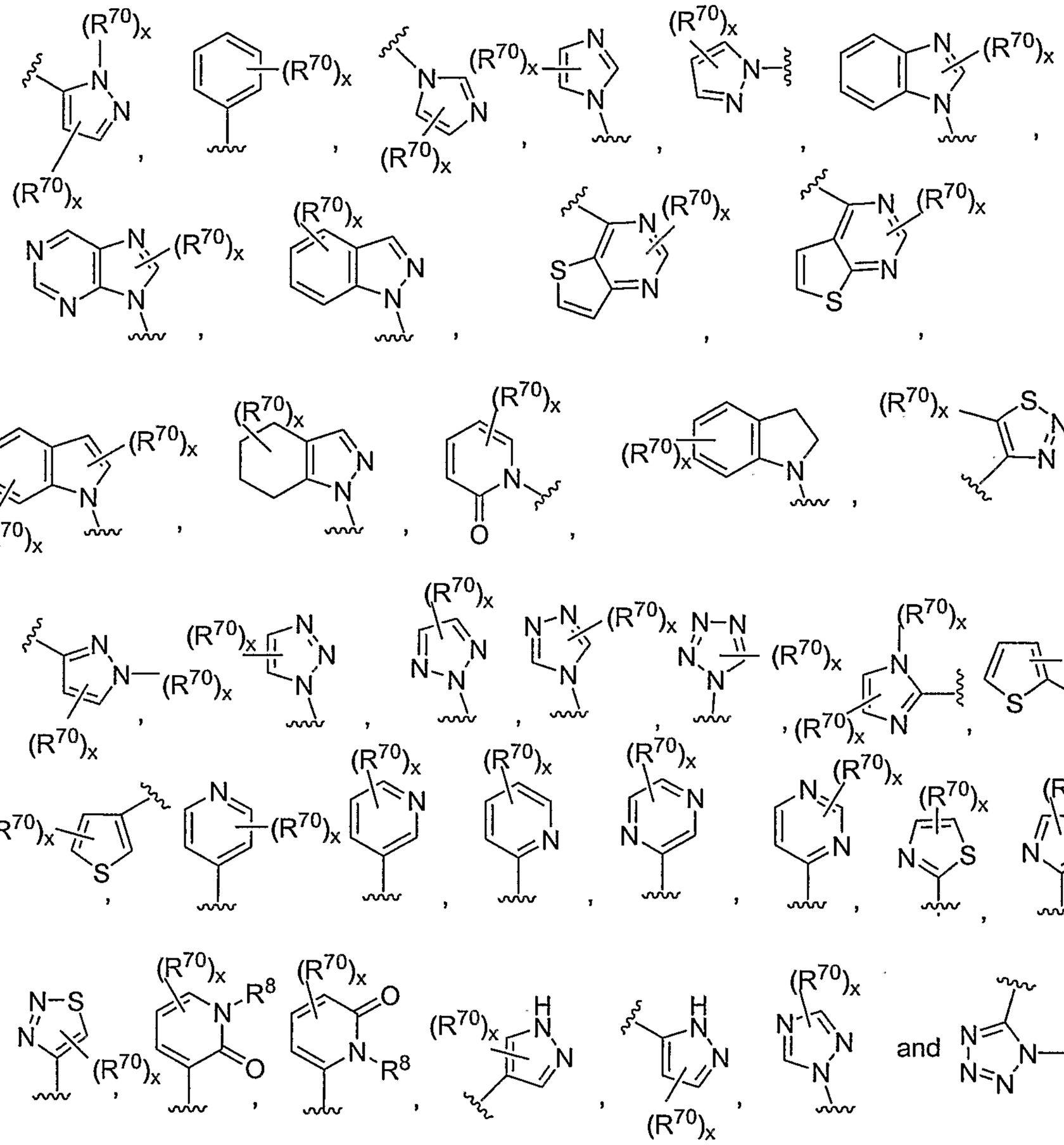
.

51. The compound of claim 48 wherein 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.

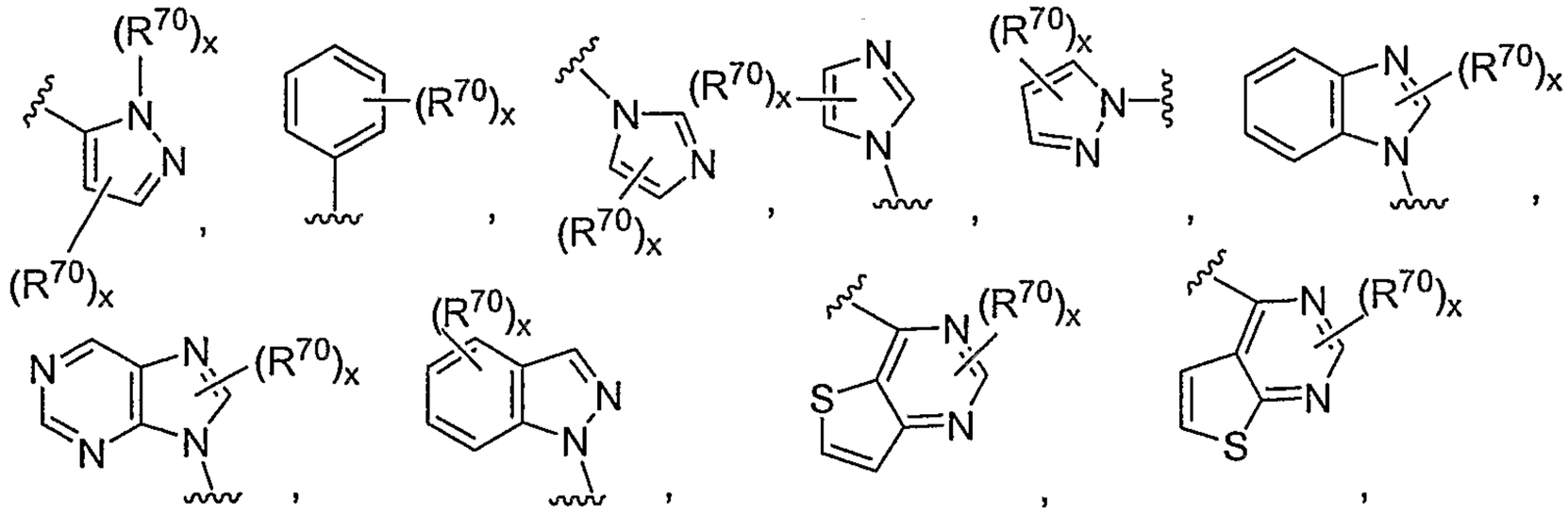
52. The compound of claim 47 wherein W is selected from the group consisting of -CH_2-, –C(H)CH_3-, -$C(CH_3)_2$- and Y is a covalent bond.

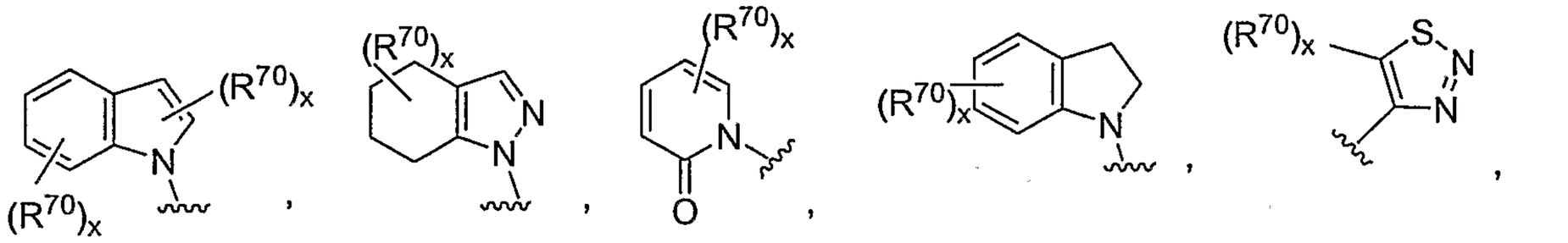
53. The compound of claim 47 wherein W is -CH_2- or –C(H)(CH_3)- and Y is -CH_2-.

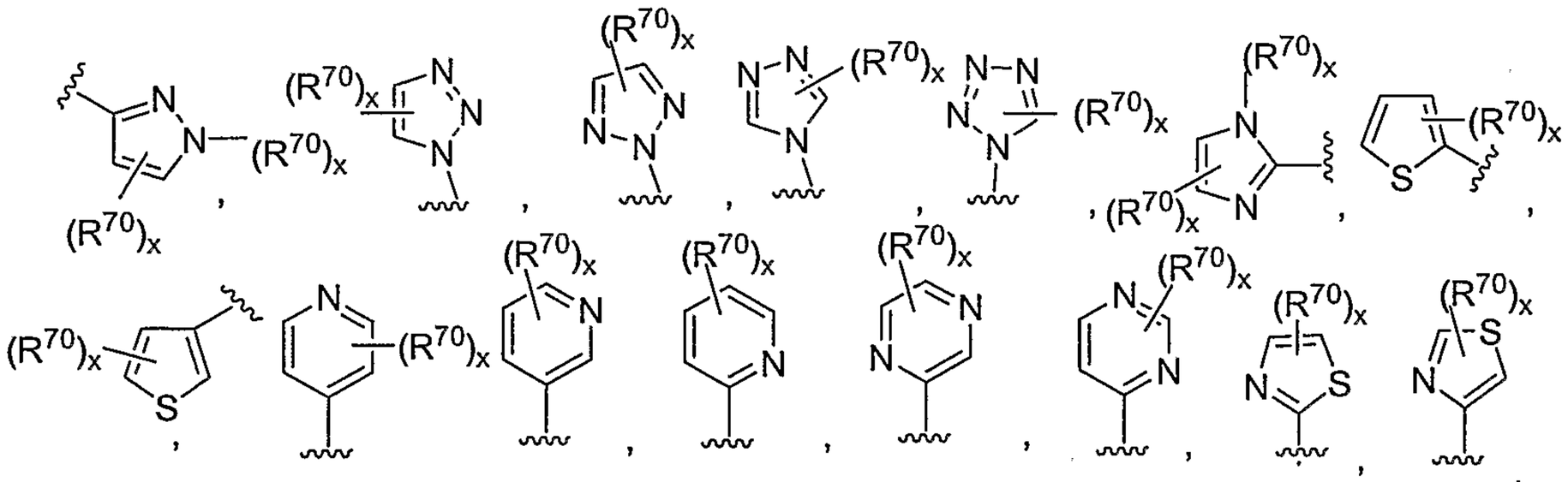
54. The compound of claim 47 wherein X is selected from the group consisting of phenyl, piperidinyl, pyridinyl, thienyl, thiazolyl, oxazolyl and pyrazolyl; Y is -$[C(R^6)_2]_n$- wherein n is 1 to 2; and Z is selected from the group consisting of

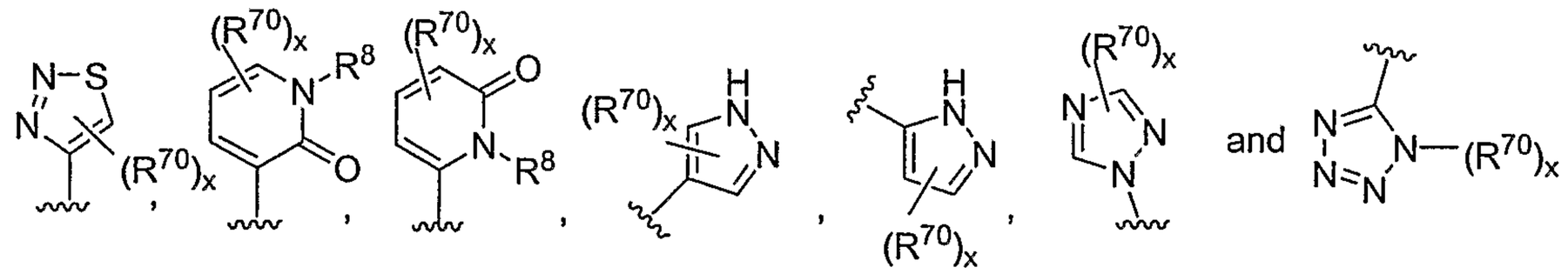


55. The compound of claim 47 wherein X is selected from the group consisting of phenyl, piperidinyl, pyridinyl, thienyl, thiazolyl, oxazolyl and pyrazolyl; Y is selected from the group consisting of O-, -S-, and -NR^1-; and Z is selected from the group consisting of









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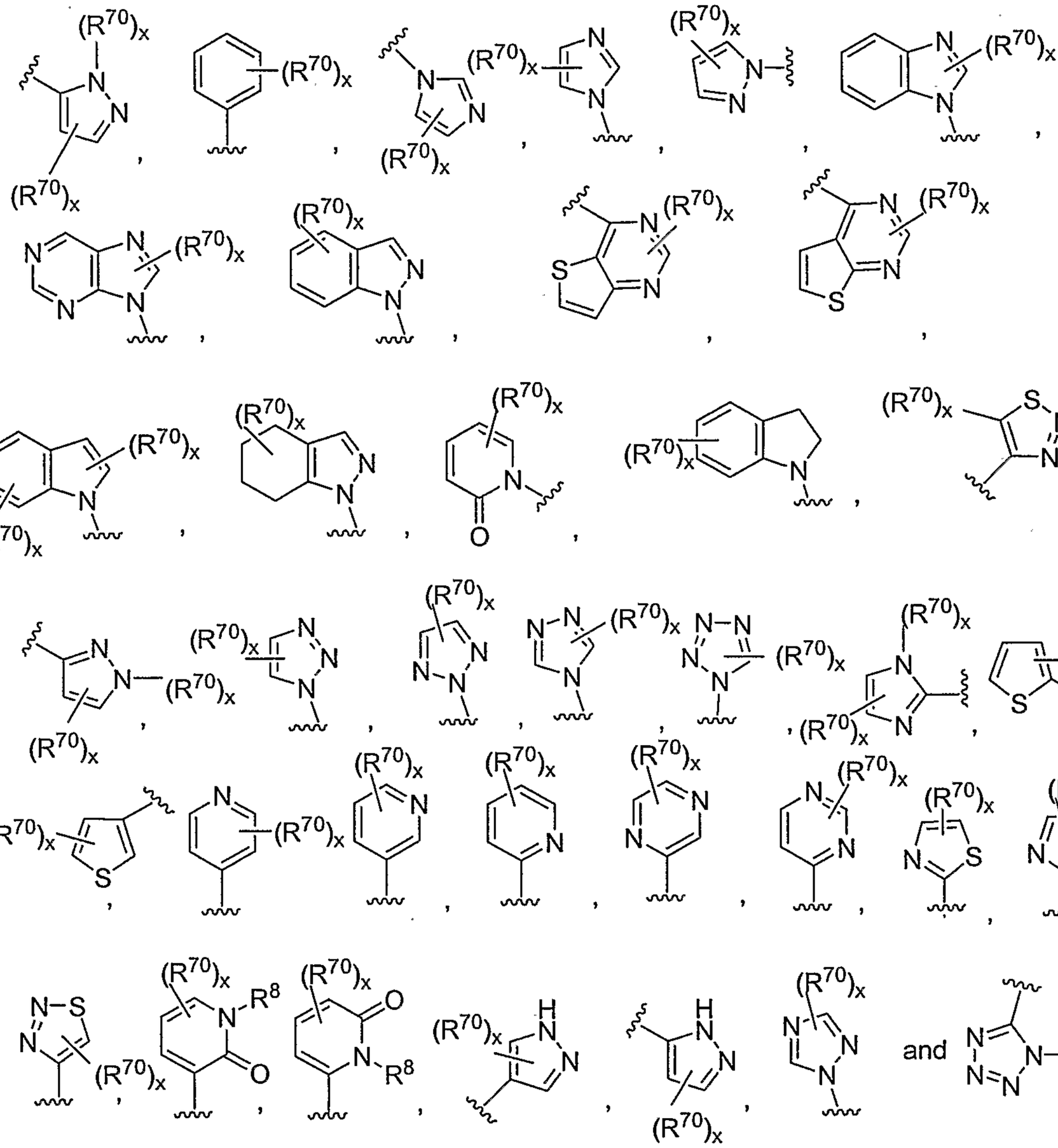
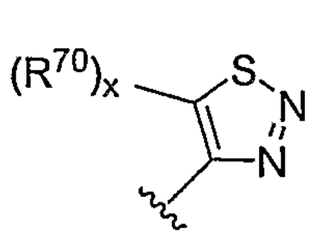
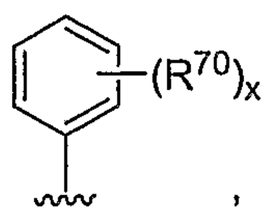
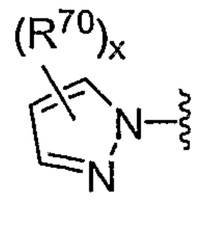
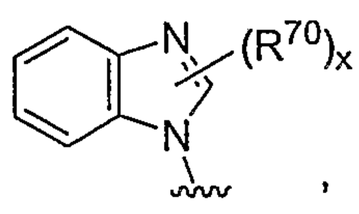
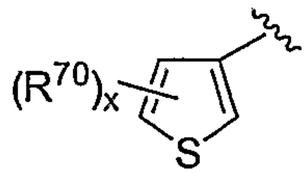
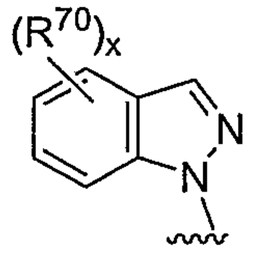
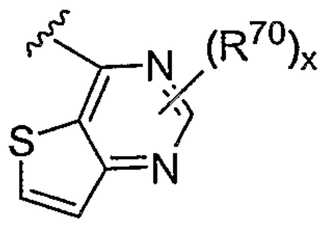
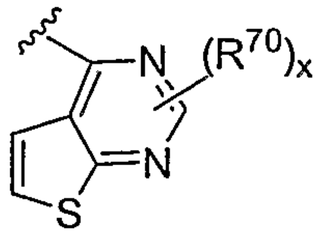
56. The compound of claim 47 wherein W is -$(CR^{13}{}_2)_n$- wherein n is 1 or 2; X is selected from the group consisting of phenyl, piperidinyl, pyridinyl, thienyl, thiazolyl, oxazolyl and pyrazolyl; Y is a covalent bond and Z is selected from the group consisting of

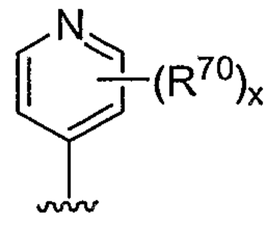
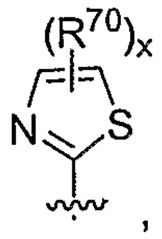
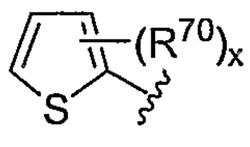


57. The compound of claim 53 wherein Z is selected from the group consisting of

58. The compound of claim 54 wherein Z is selected from the group consisting of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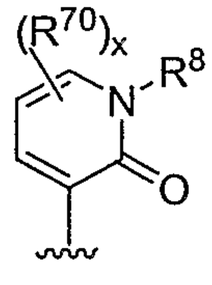
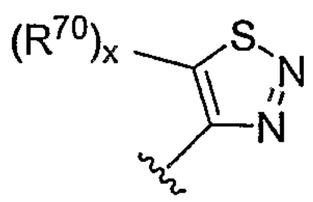
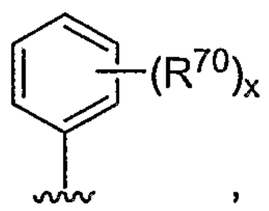
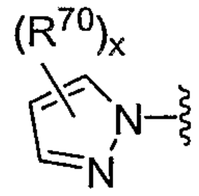
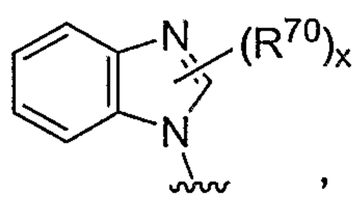
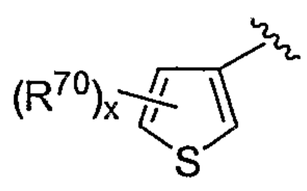
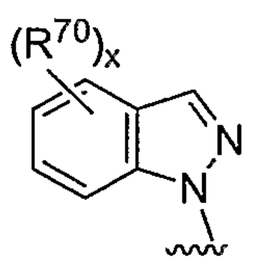
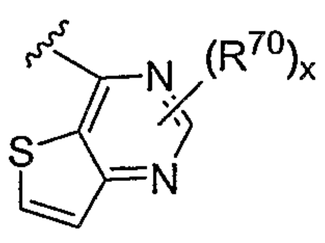
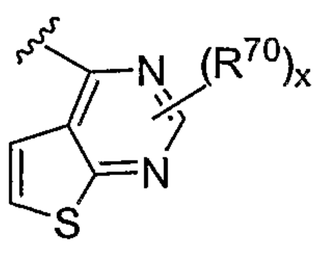
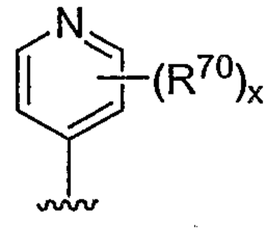
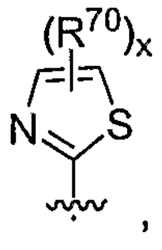
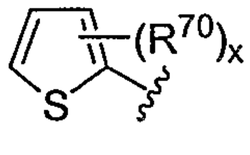


59. The compound of claim 55 wherein Z is selected from the group consisting of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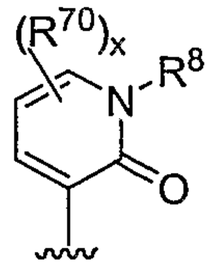
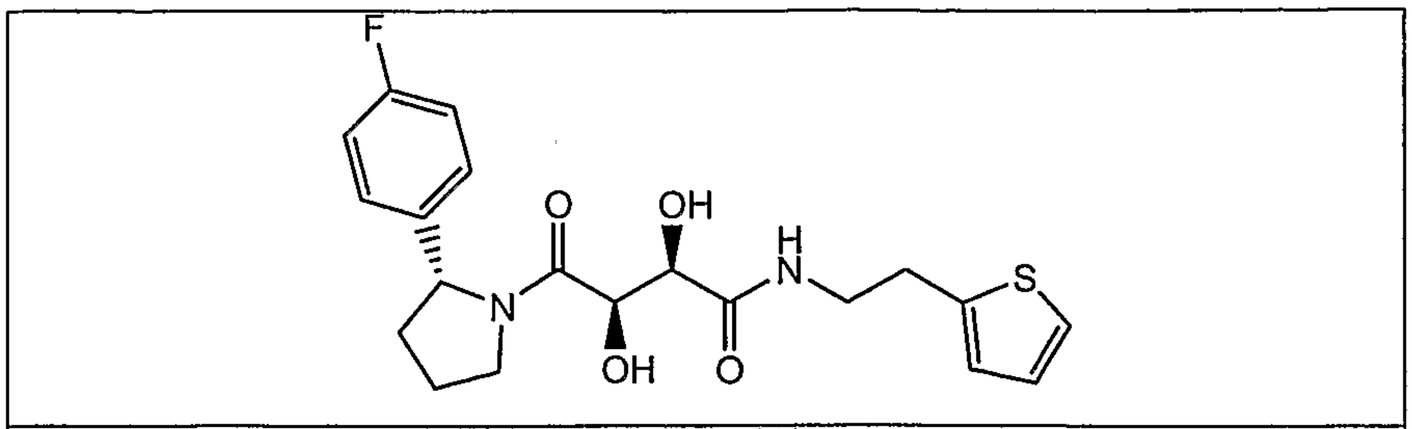
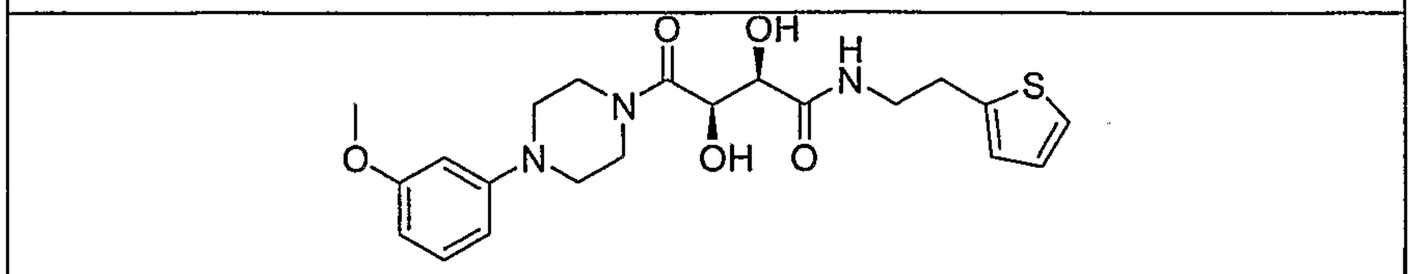
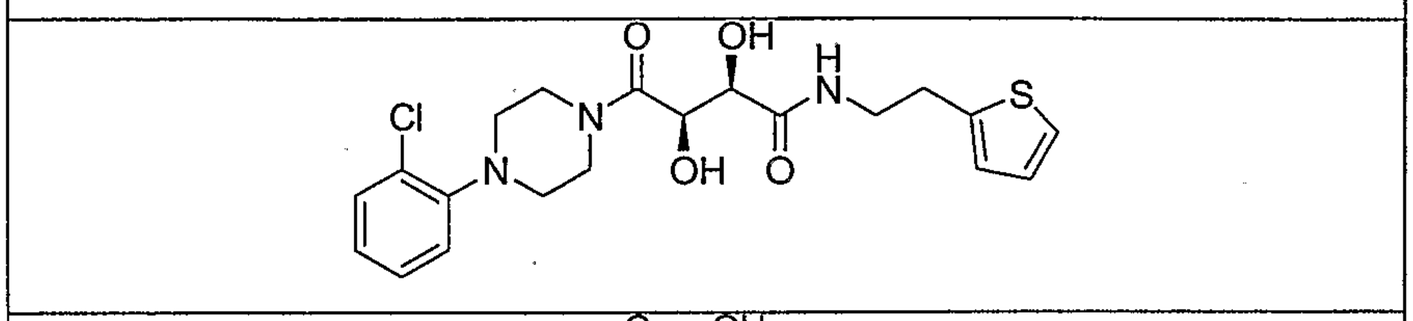
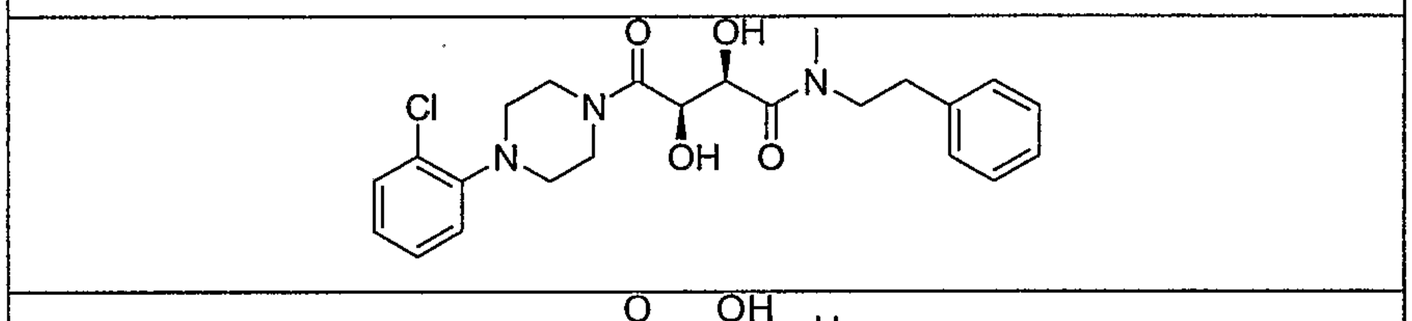


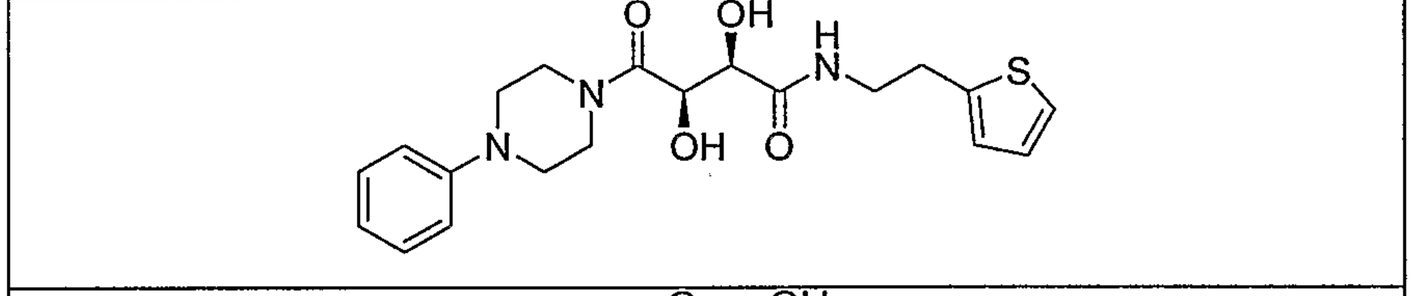
60. A compound exhibiting TACE, TNF-α, MMP or any combination thereof inhibitory activity, including enantiomers, stereoisomers and tautomers of said compound, and pharmaceutically acceptable salts or solvates of said compound, said compound being selected from the compounds of structures listed below:

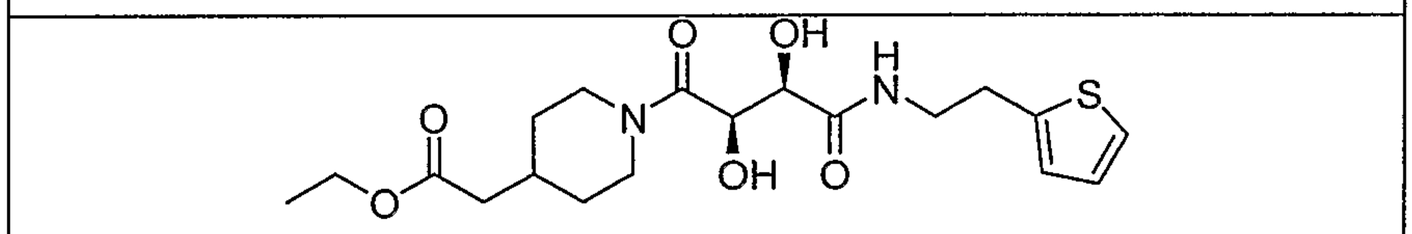


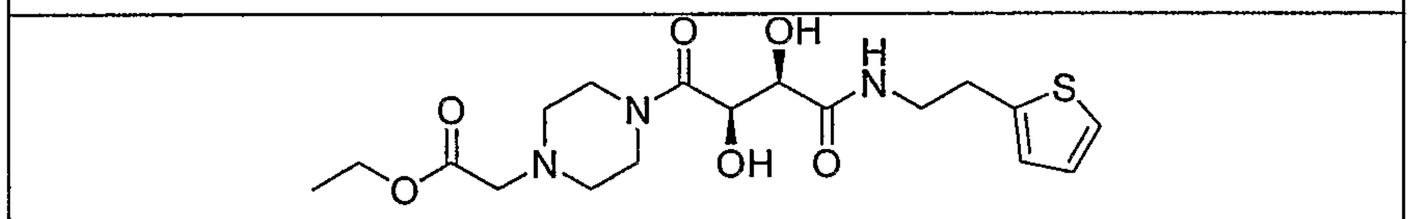


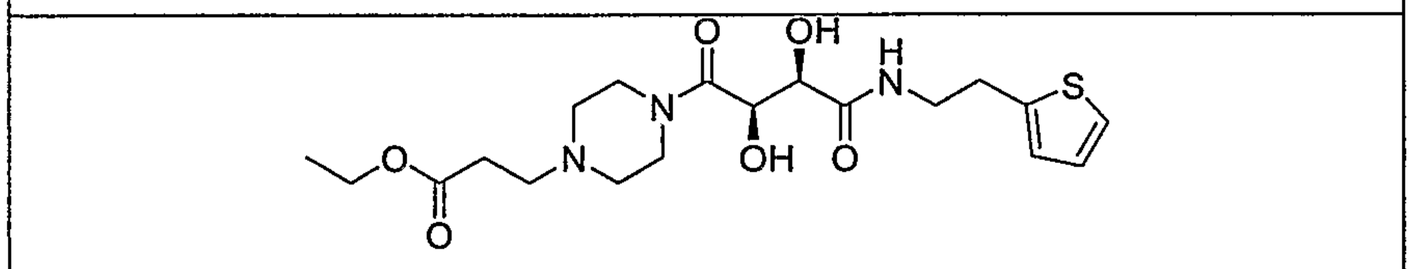


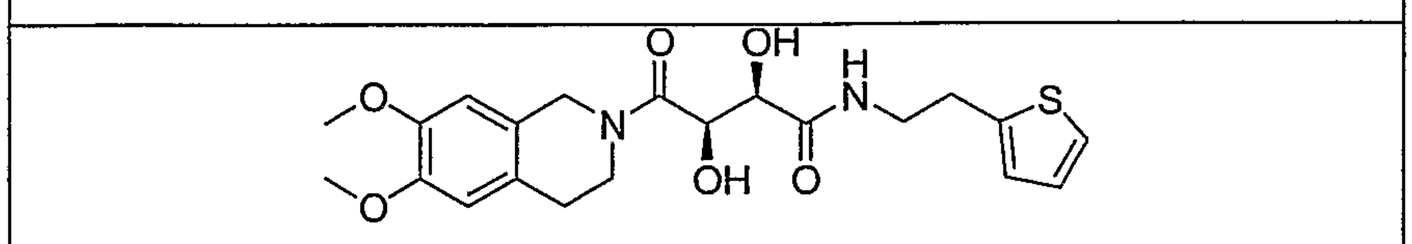


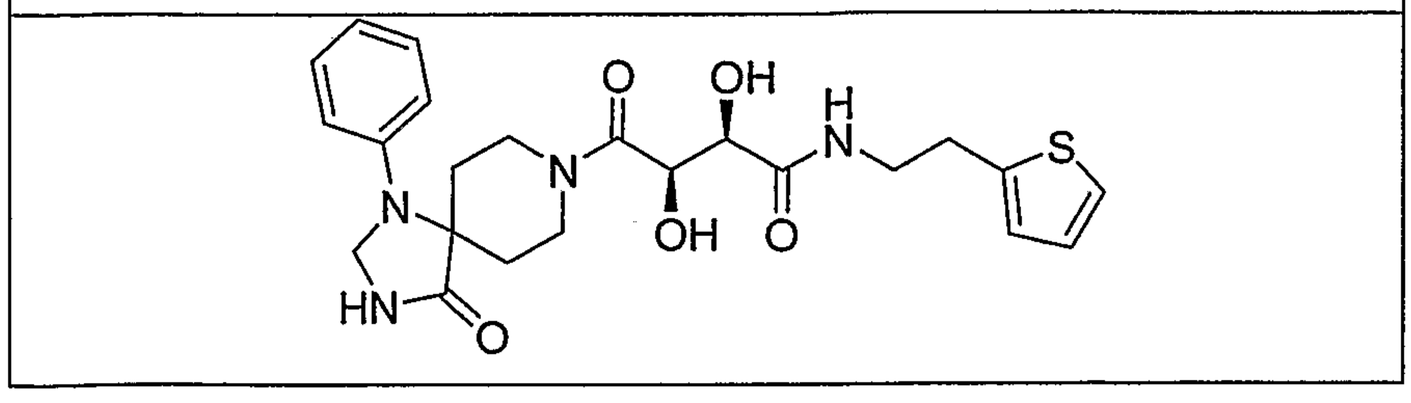


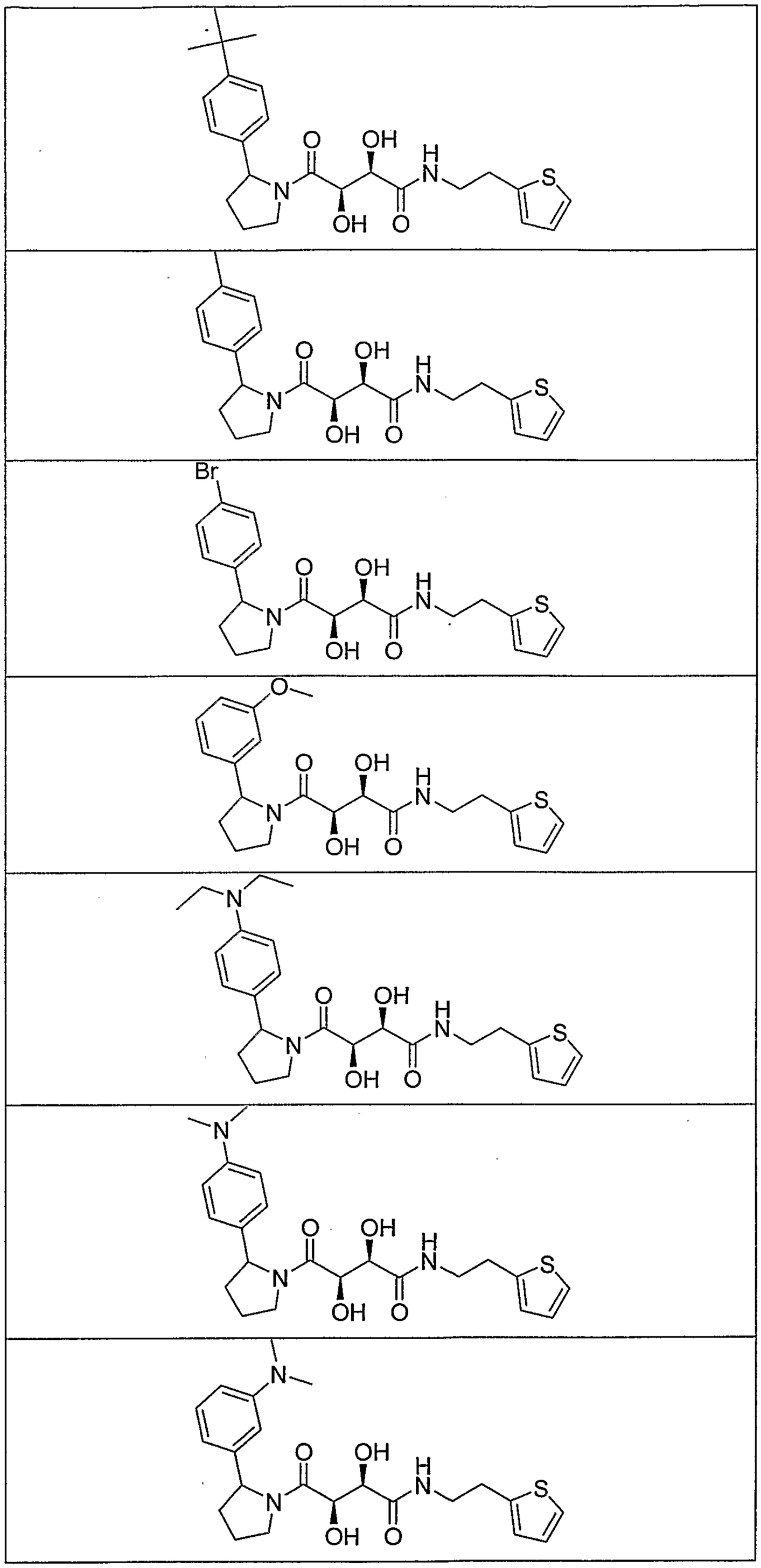


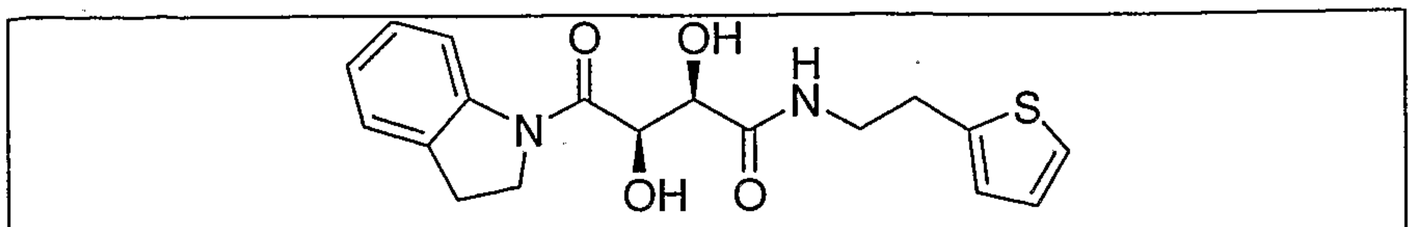


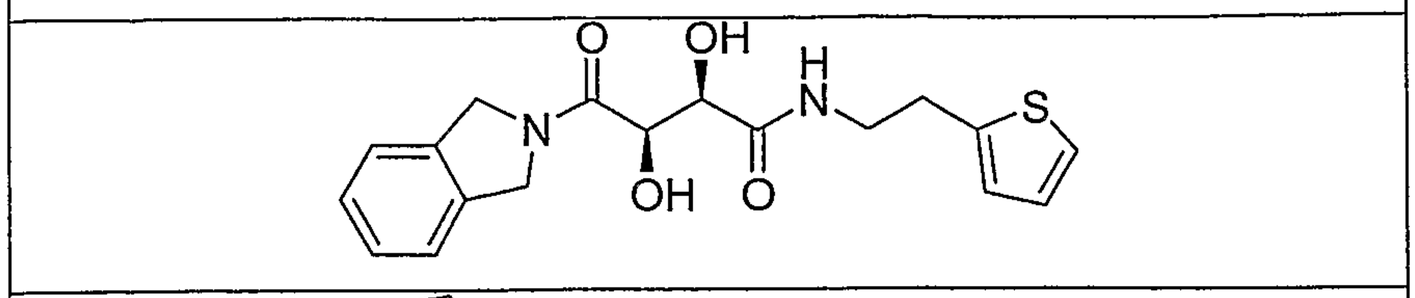


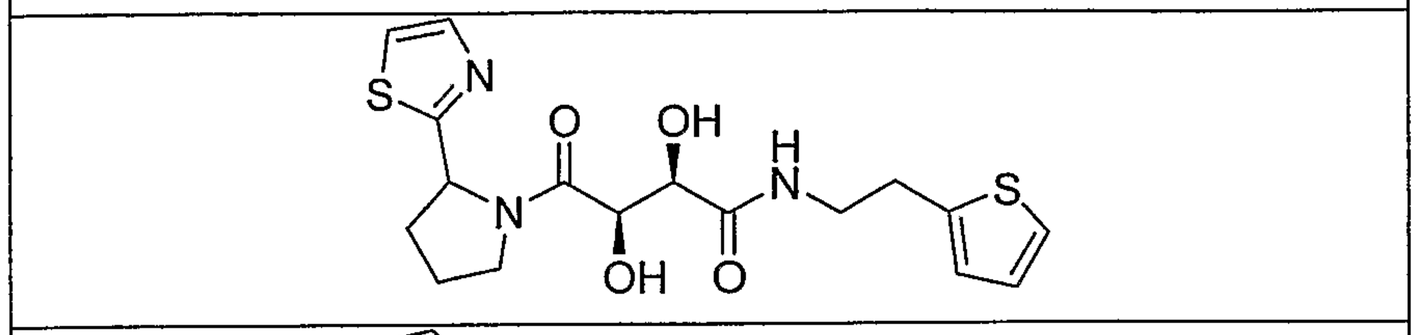


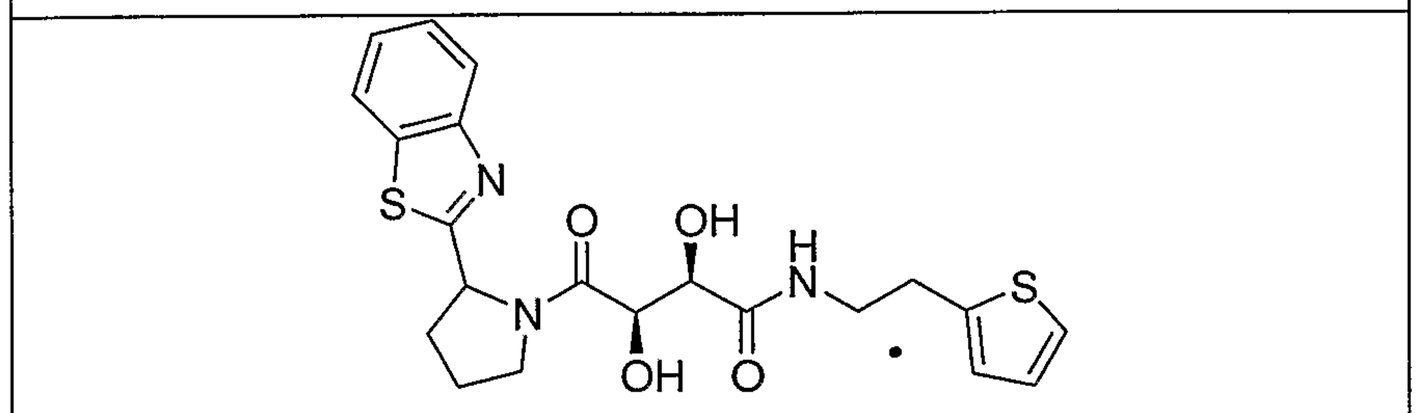


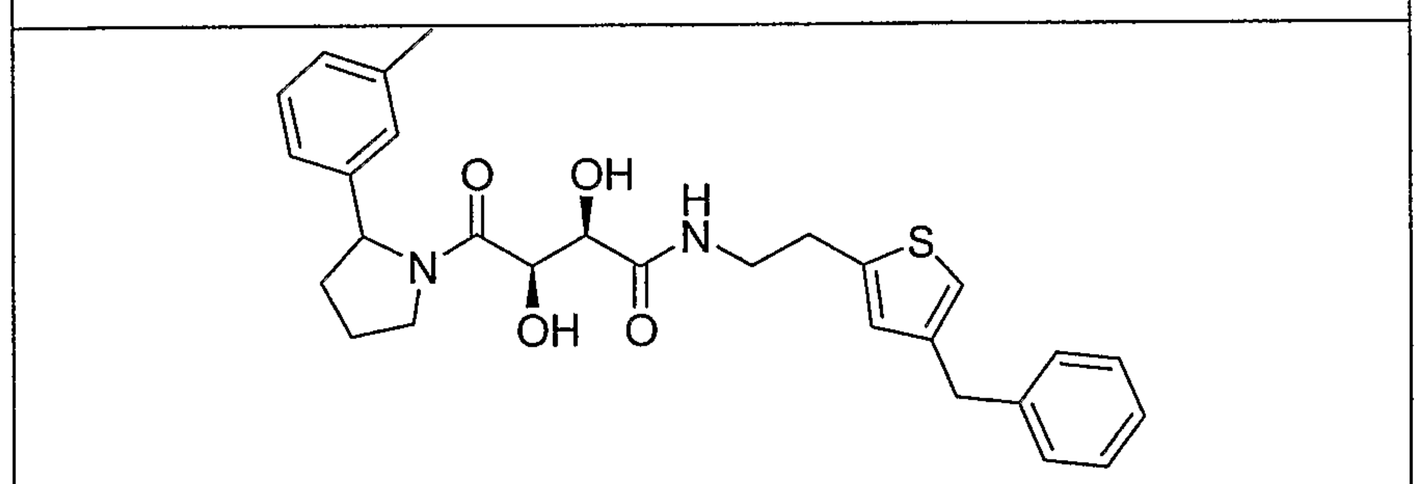


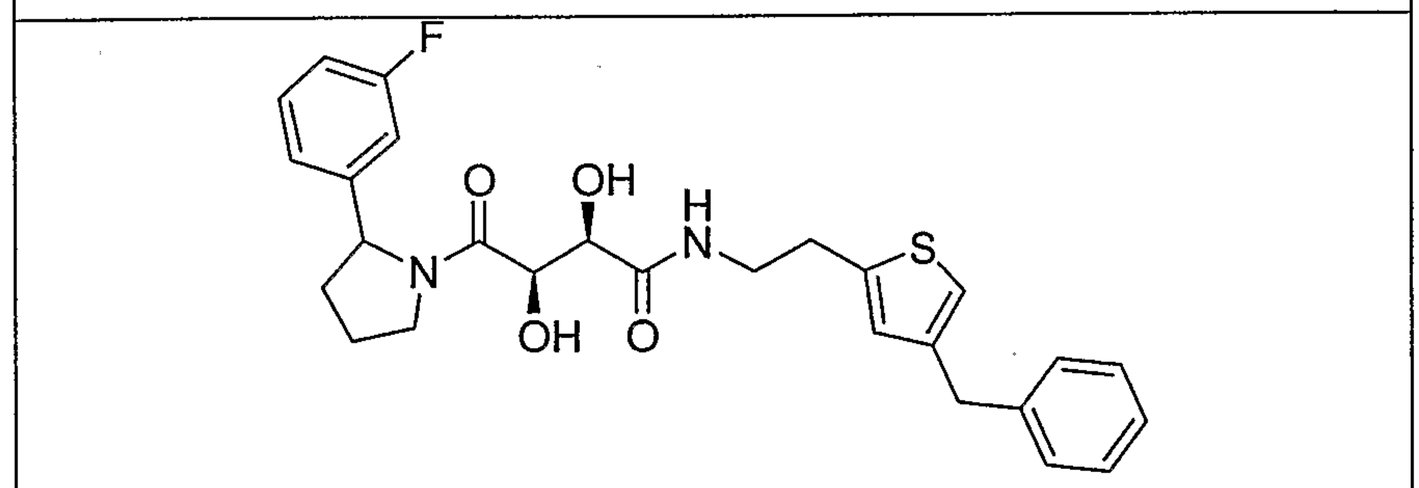


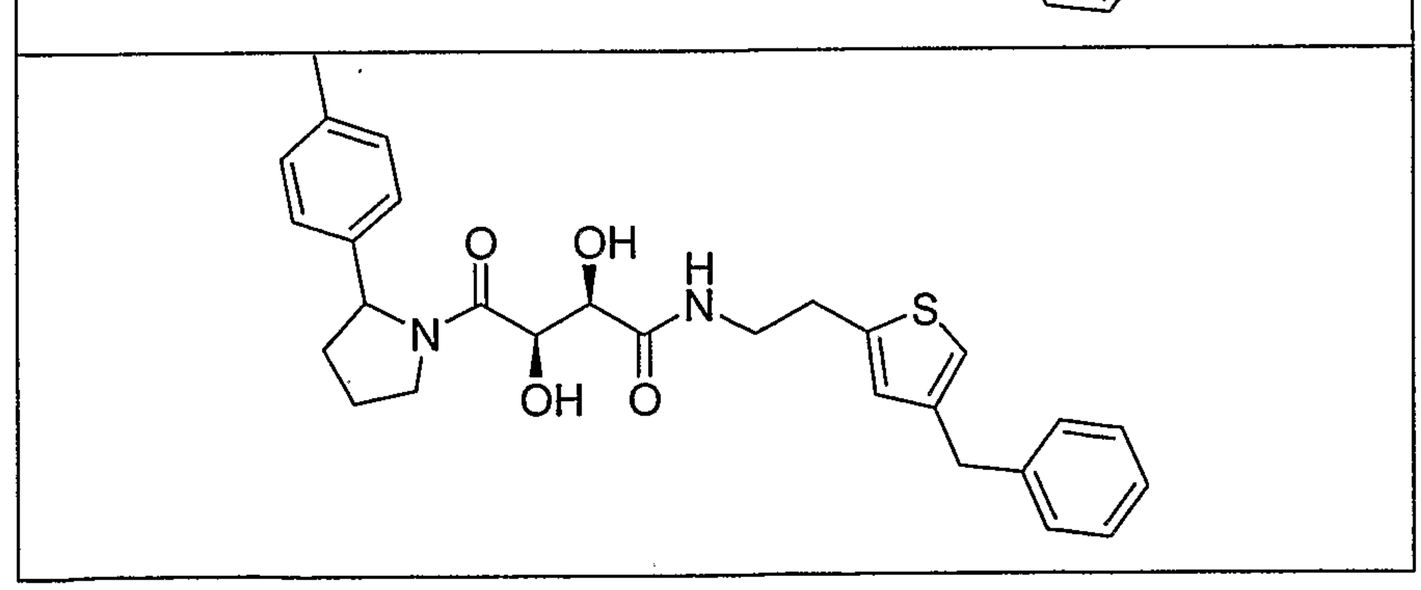


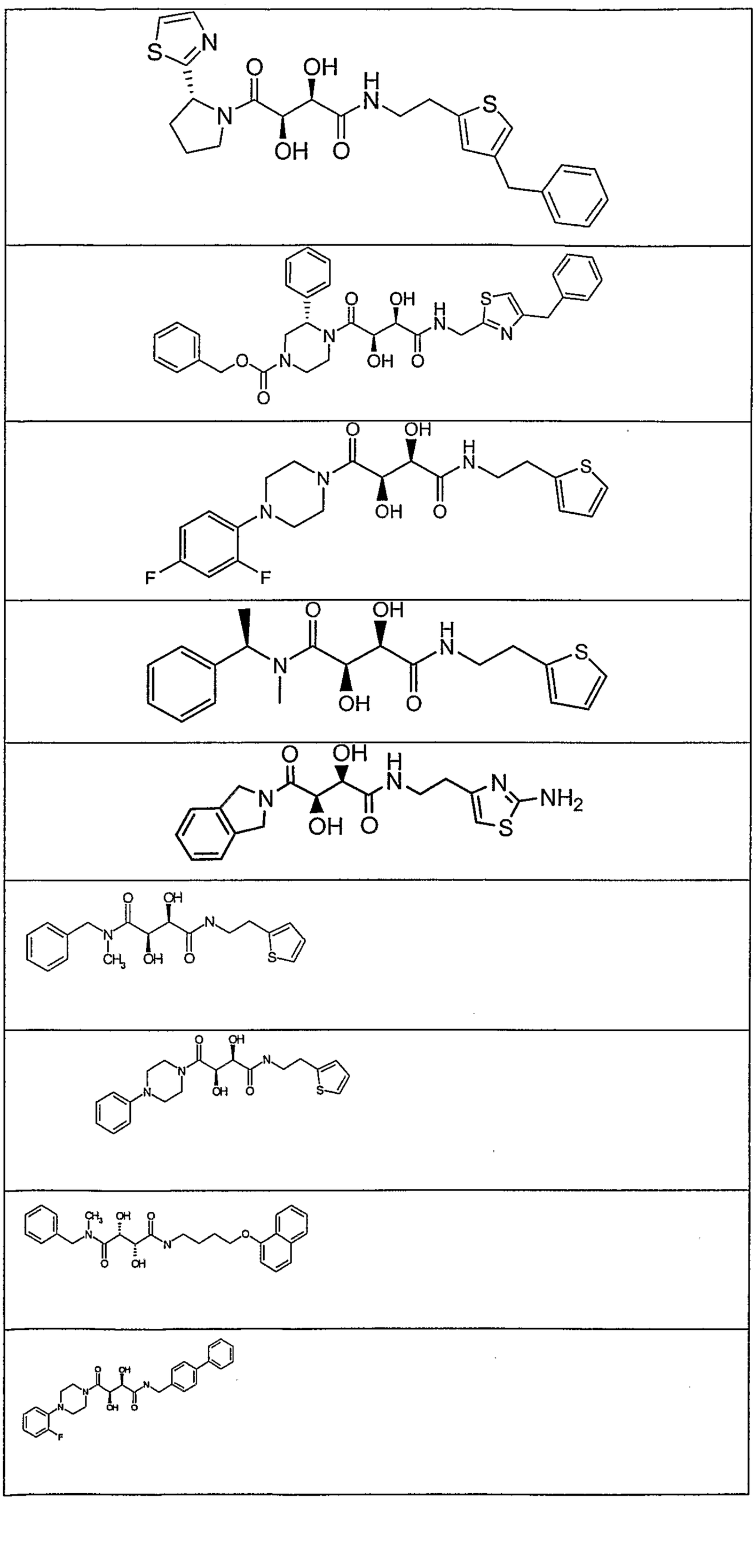


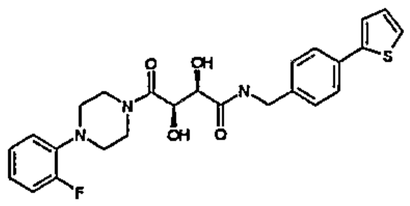


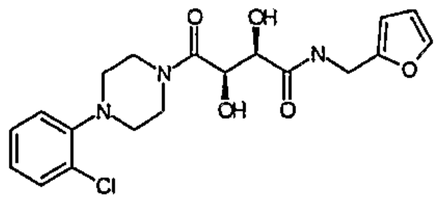


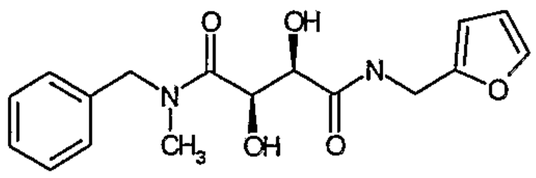


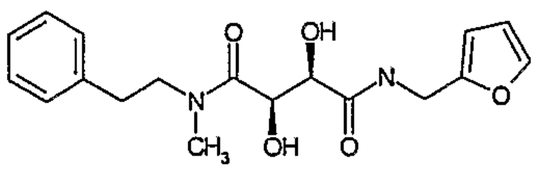


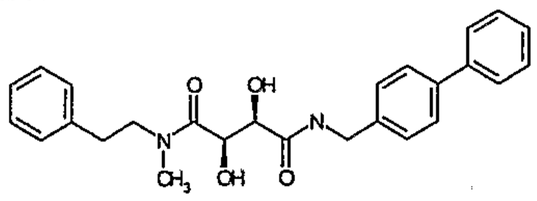


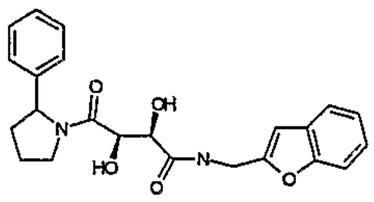


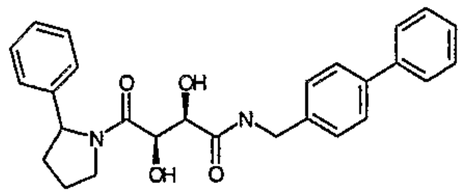


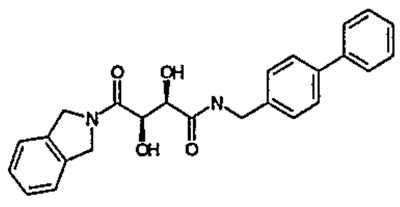


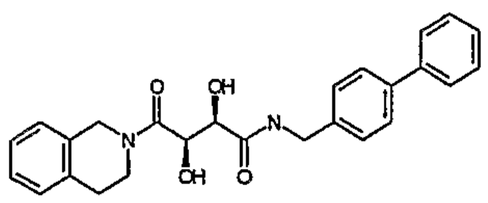


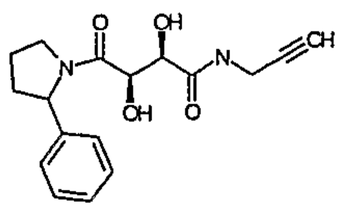


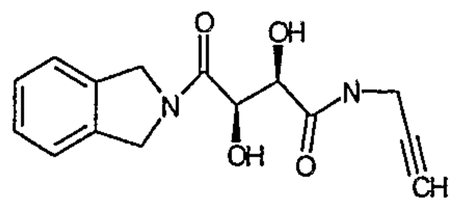


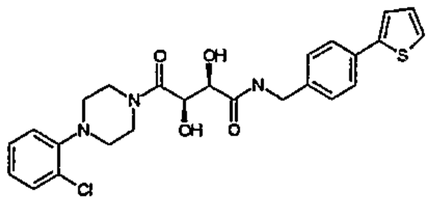


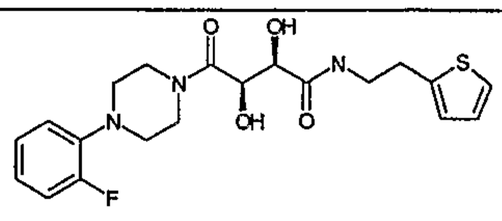


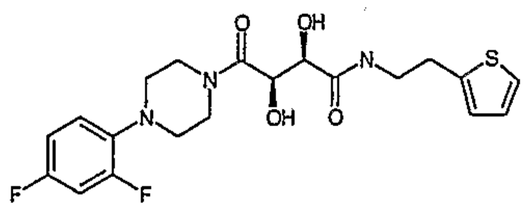


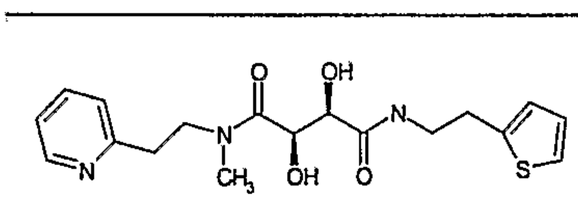


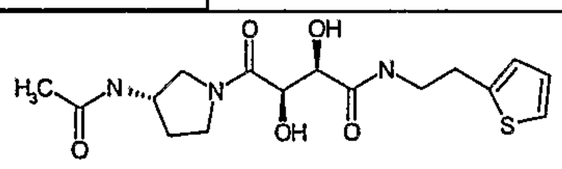


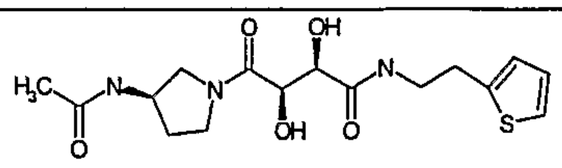


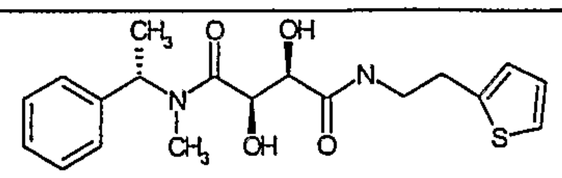


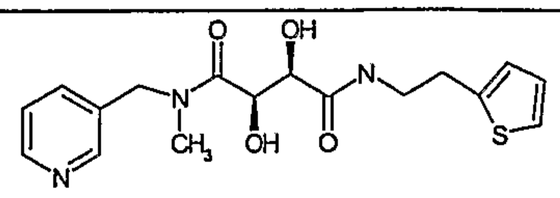


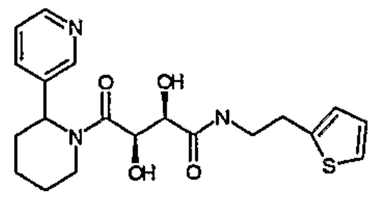


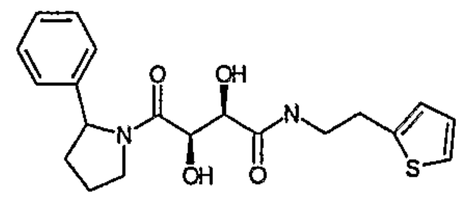


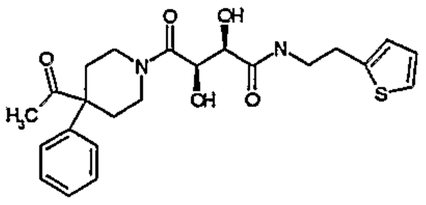


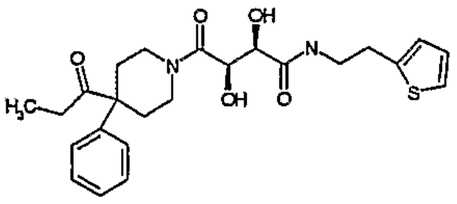


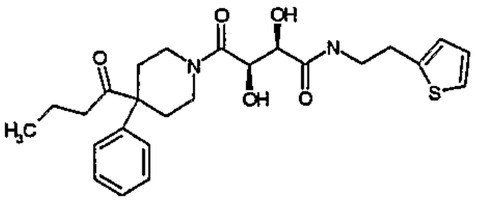


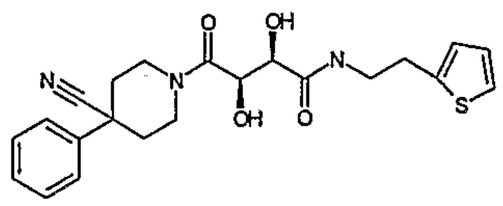


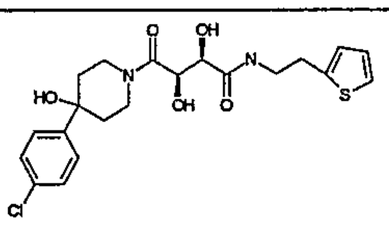


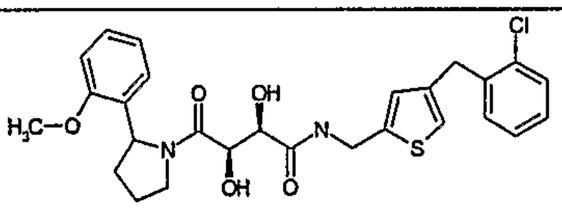


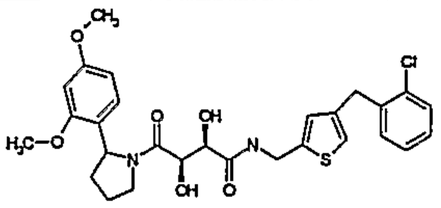


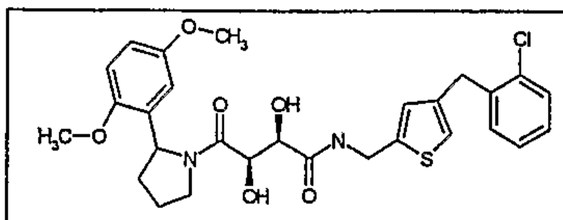
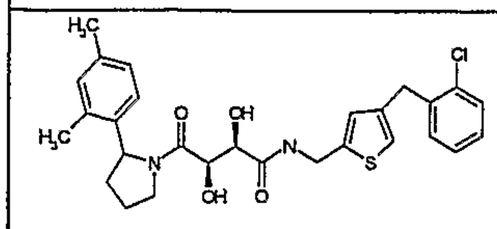
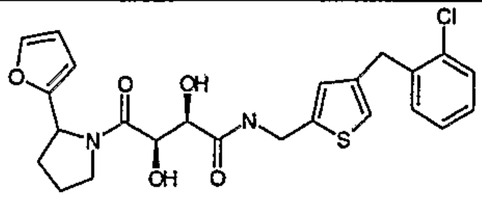
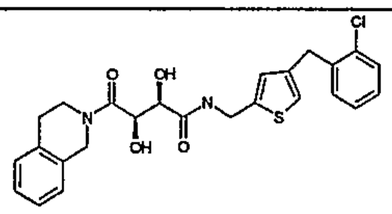
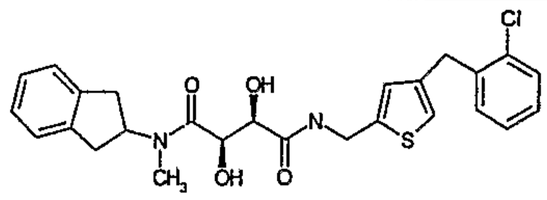
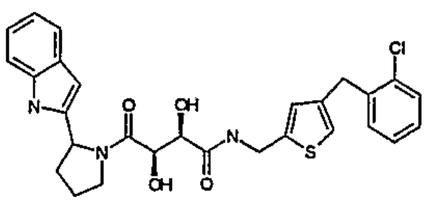
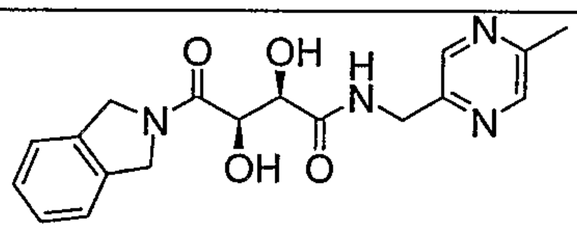
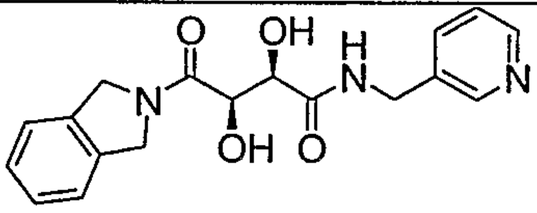
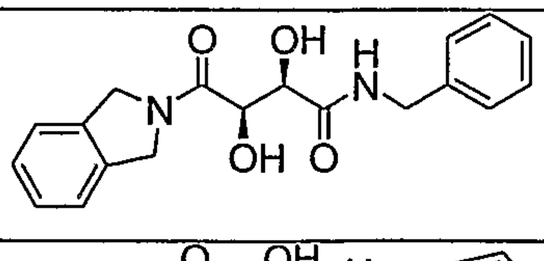
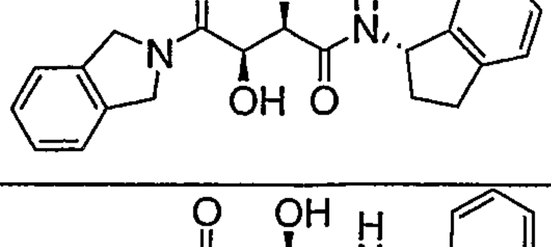
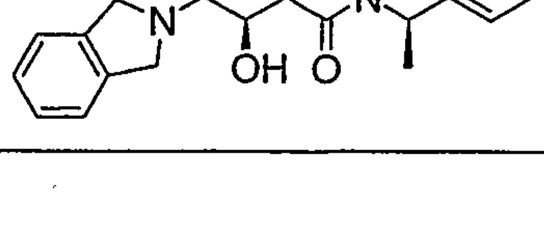


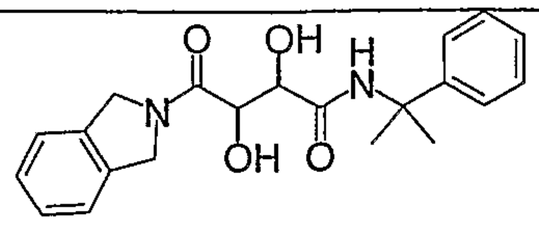
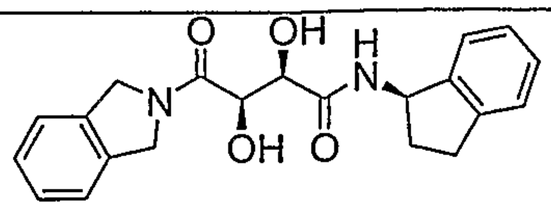
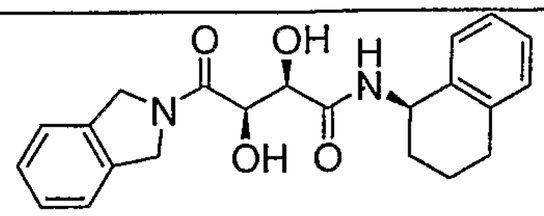
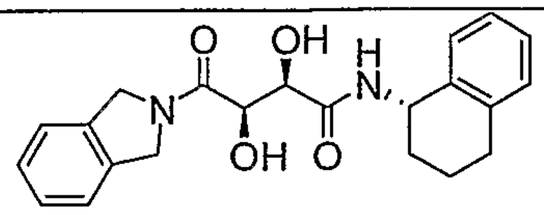
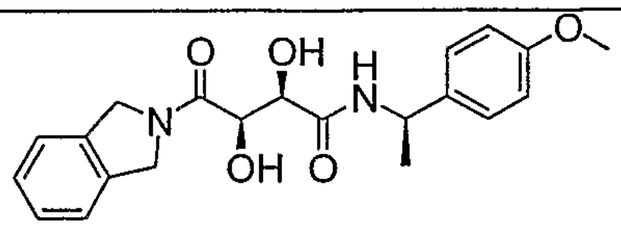
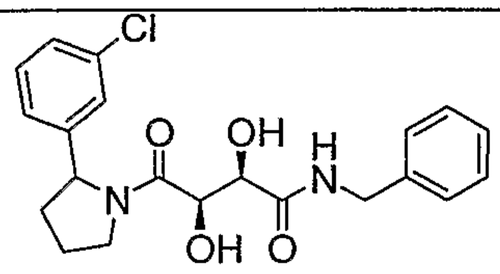
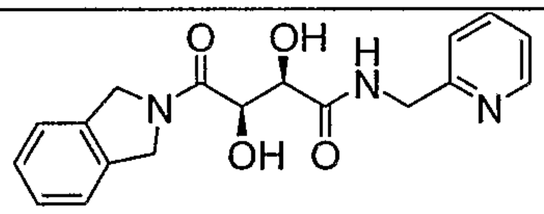
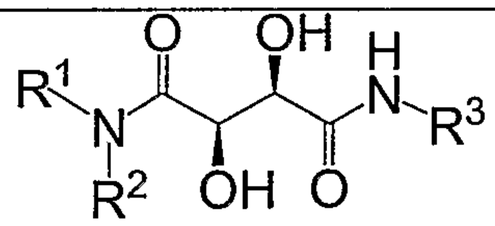
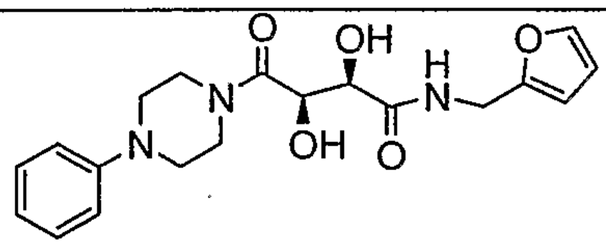
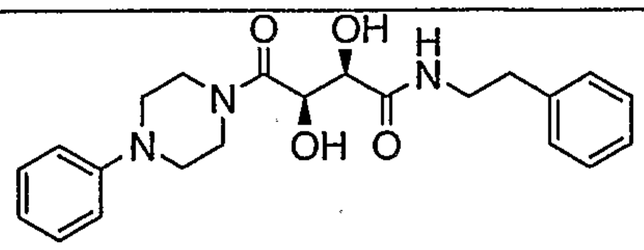
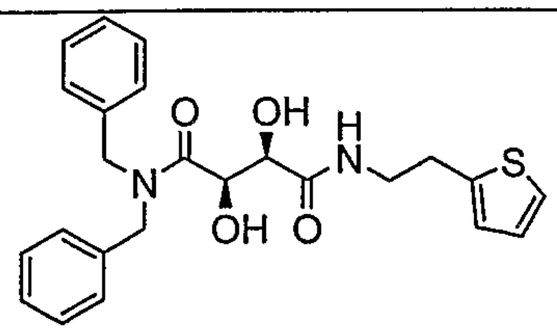


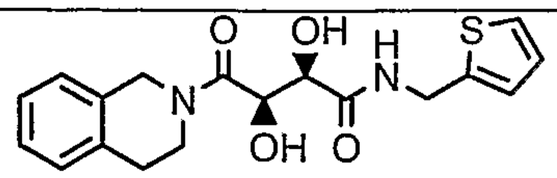
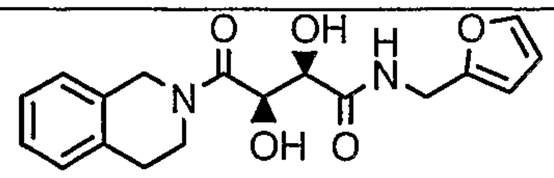
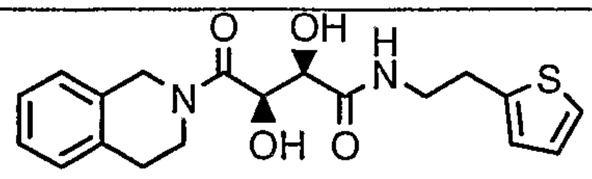
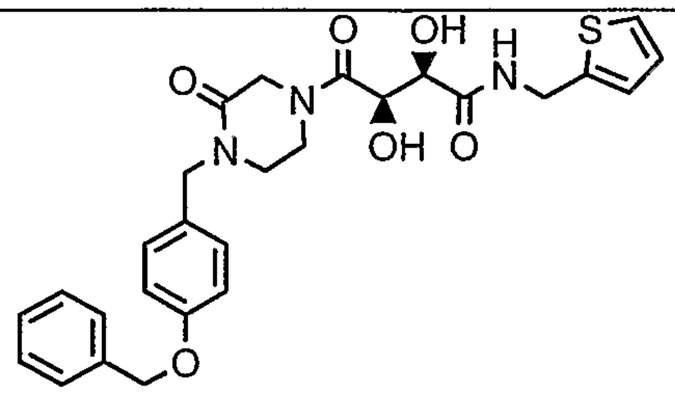
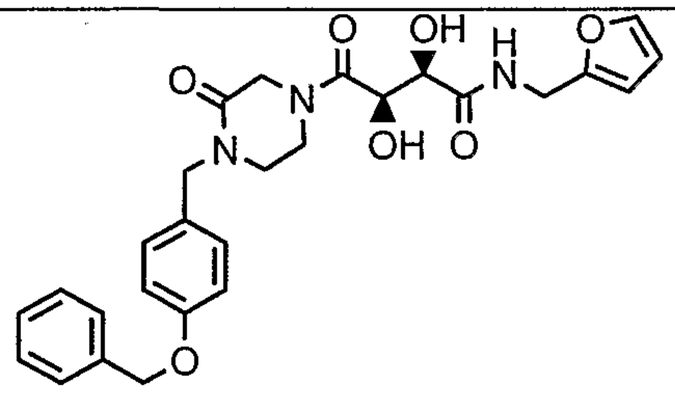
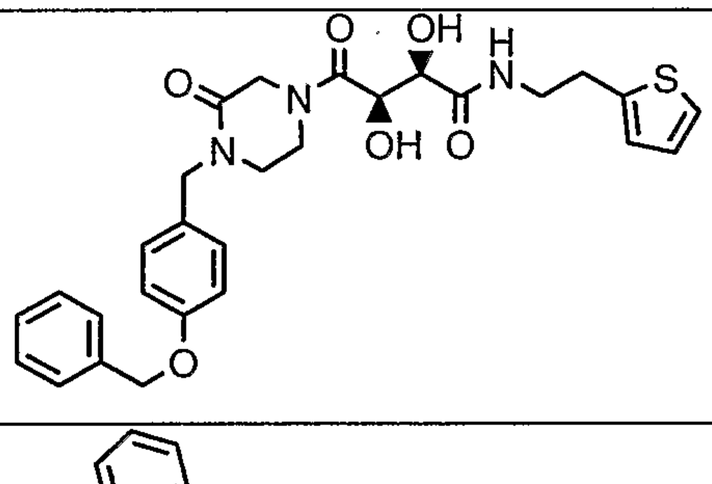
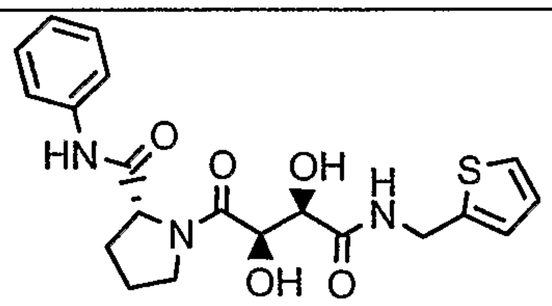
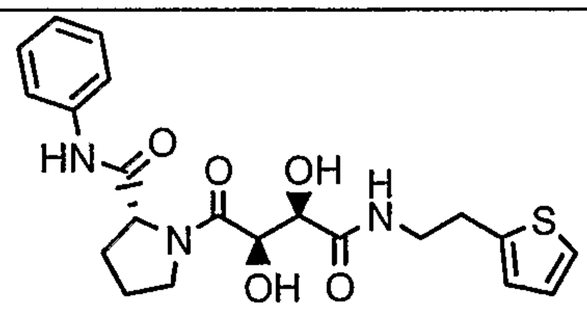
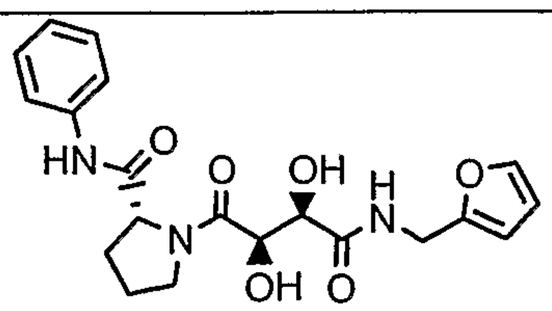


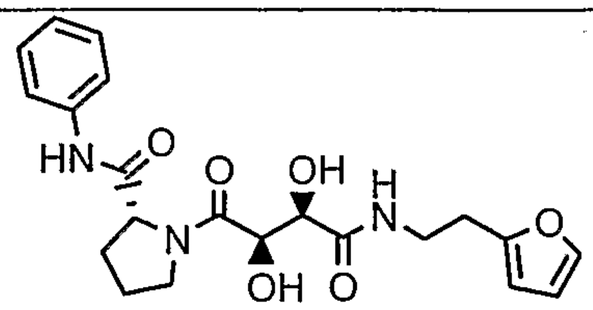
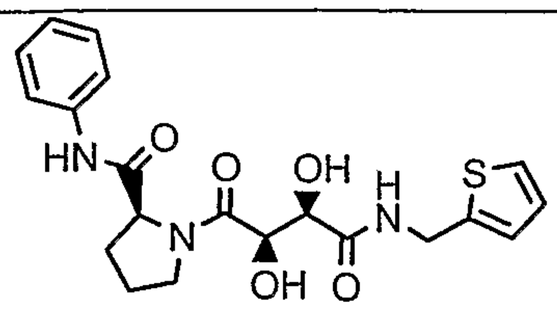
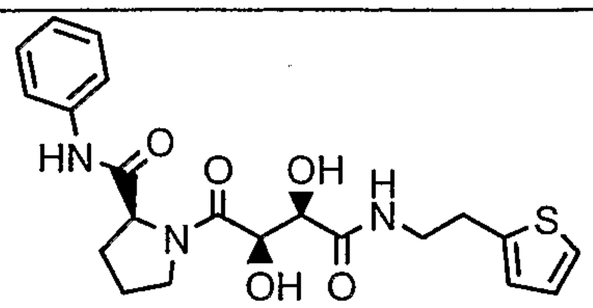
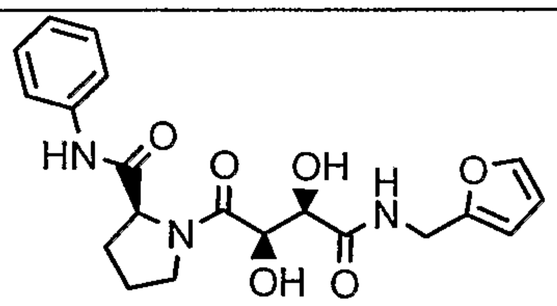
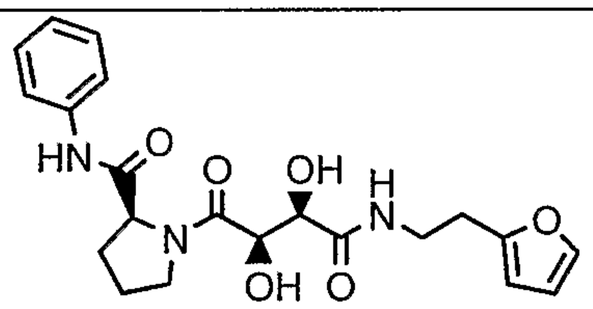
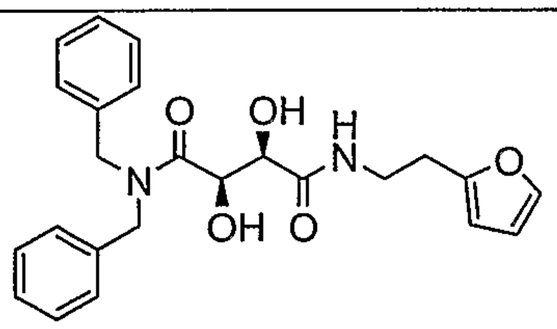
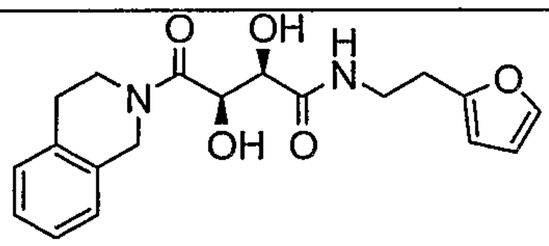
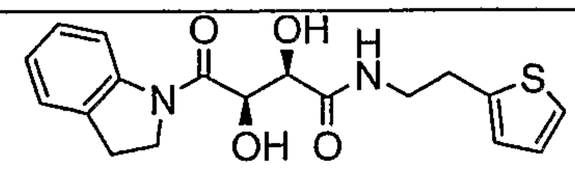
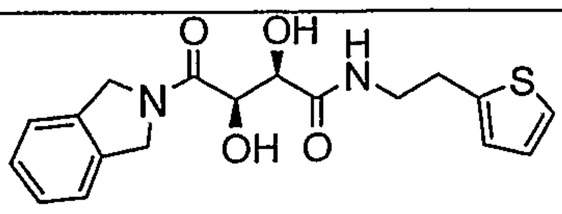
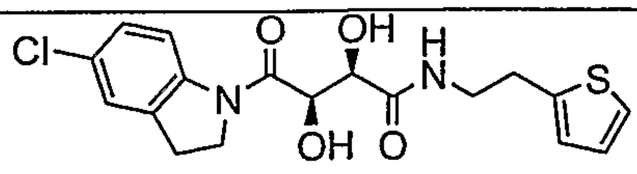
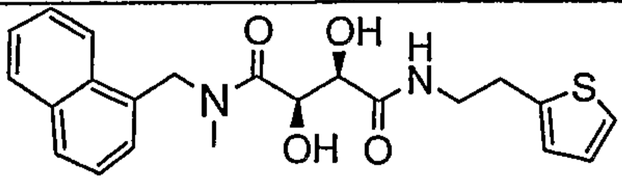


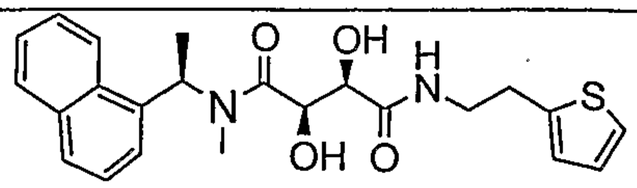
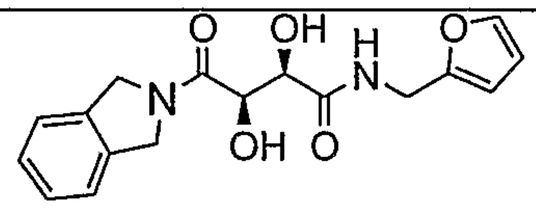
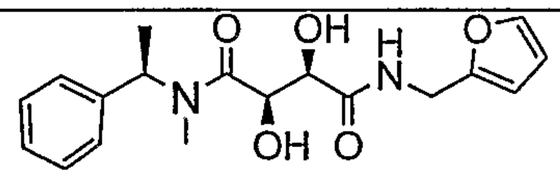
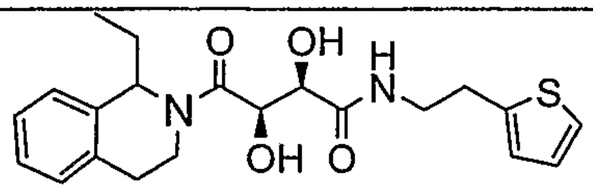
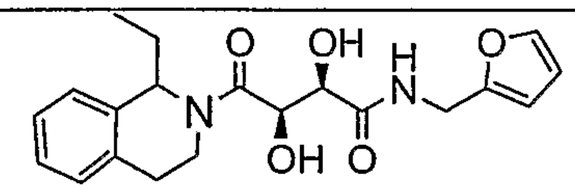
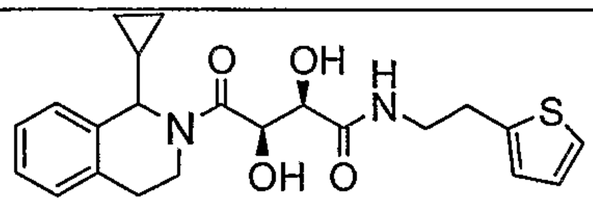
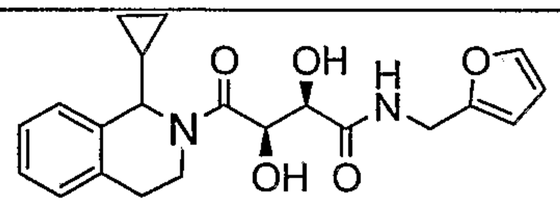
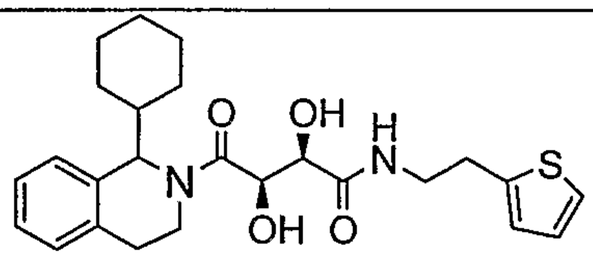
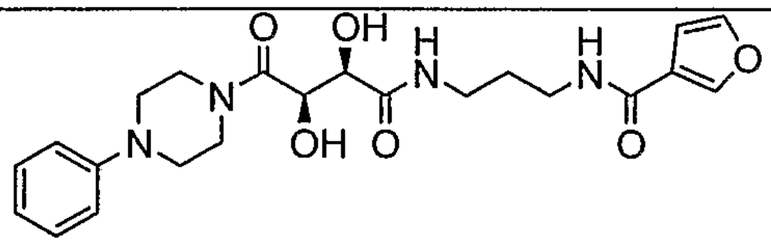
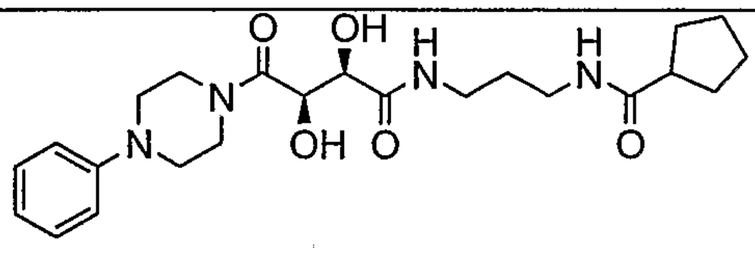
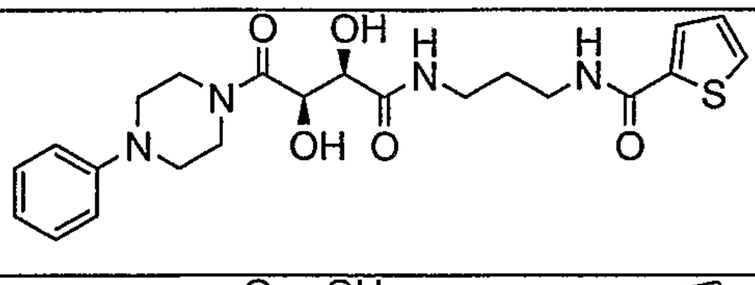
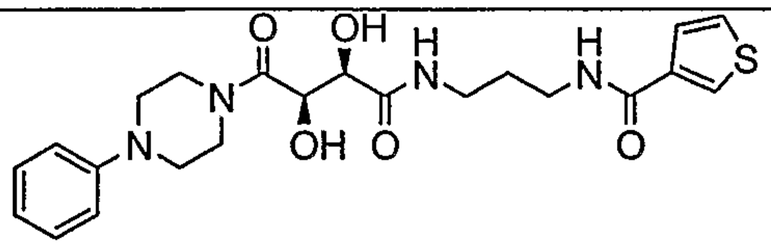
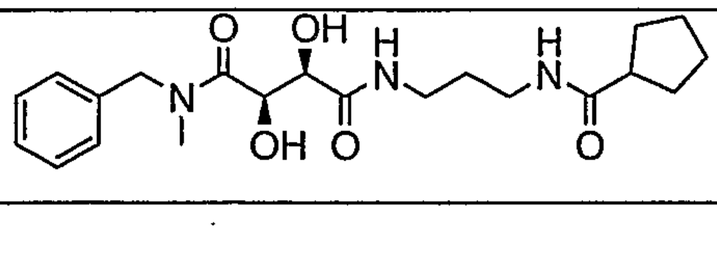


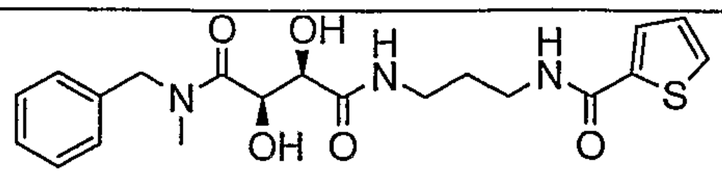
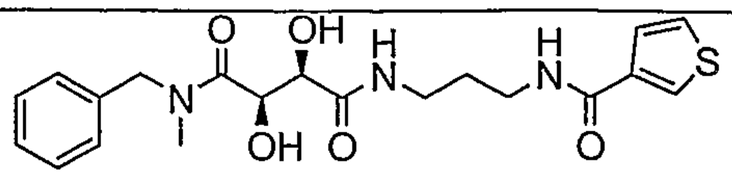
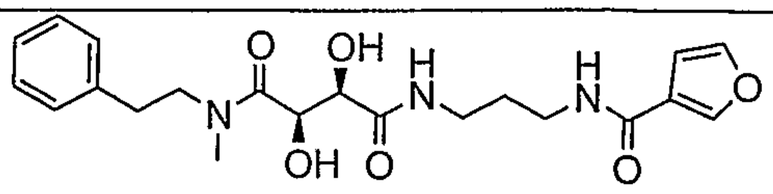
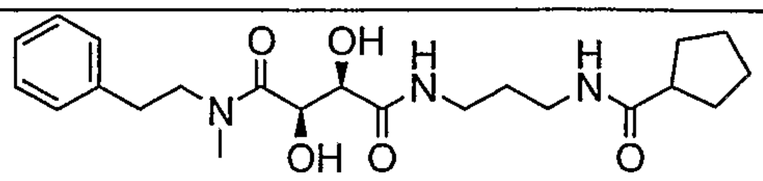
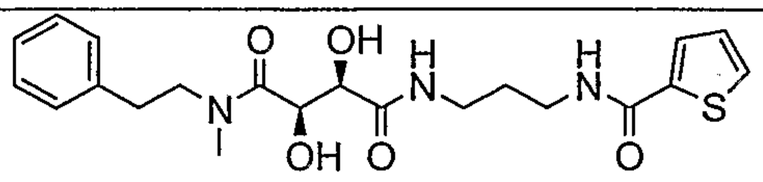
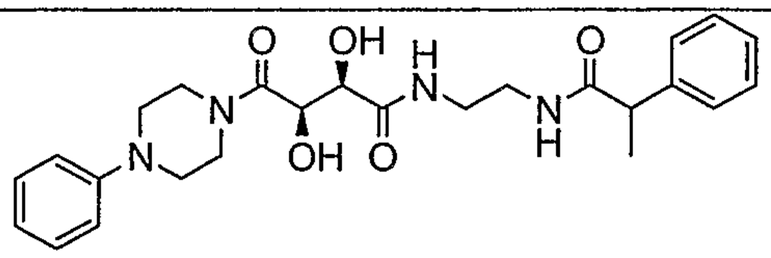
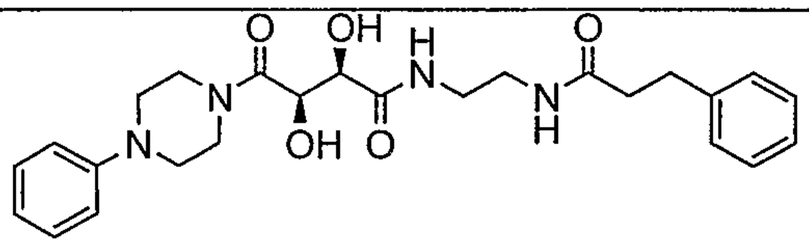
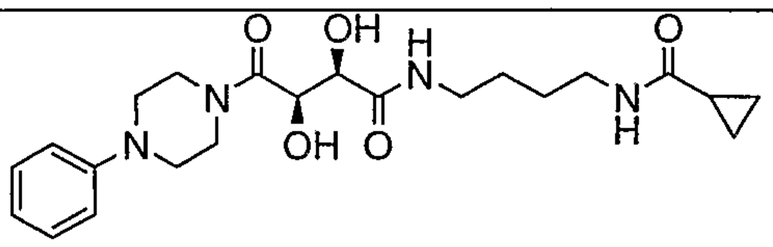
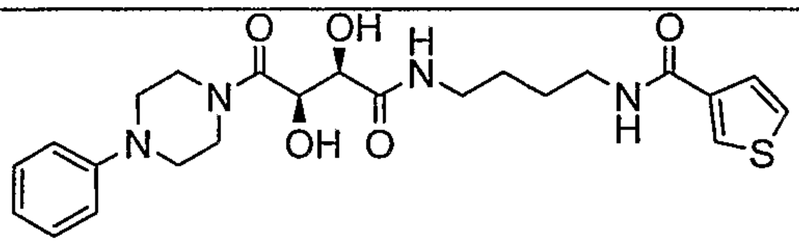
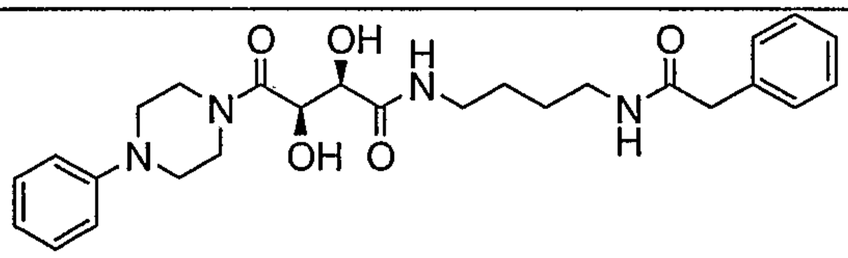
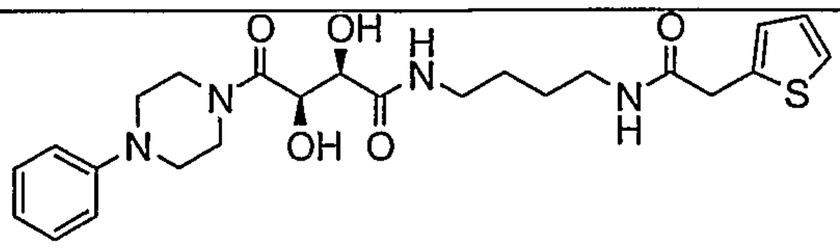
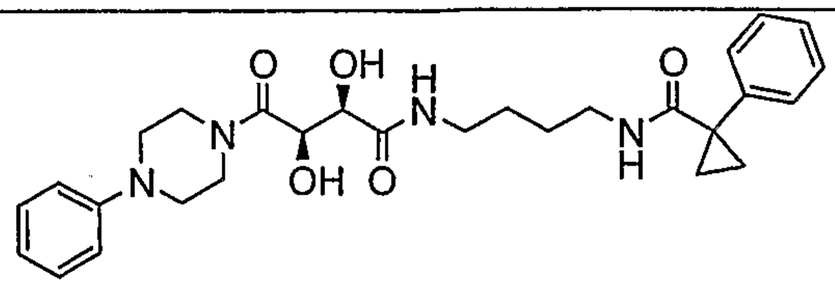












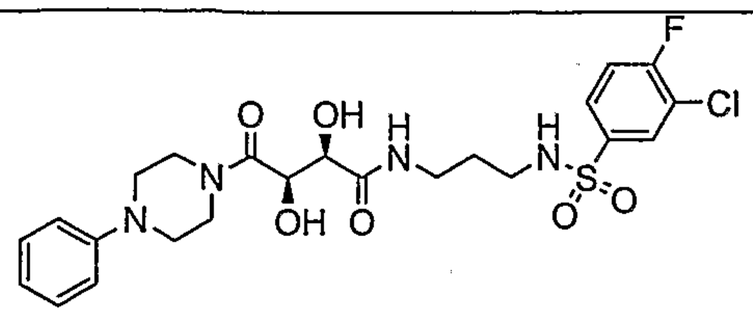
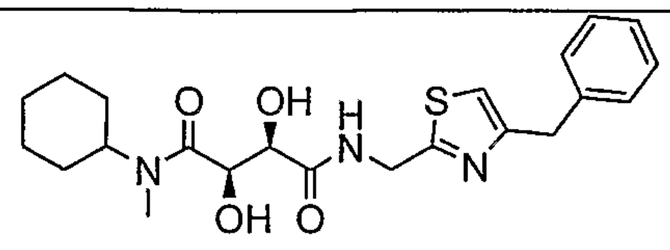
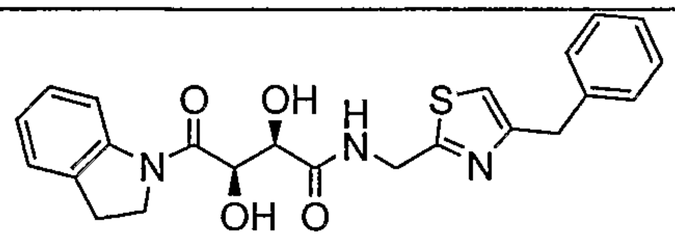
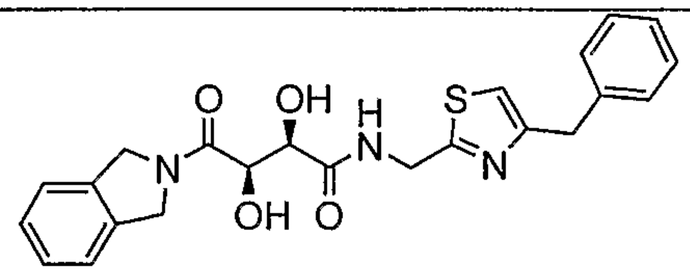
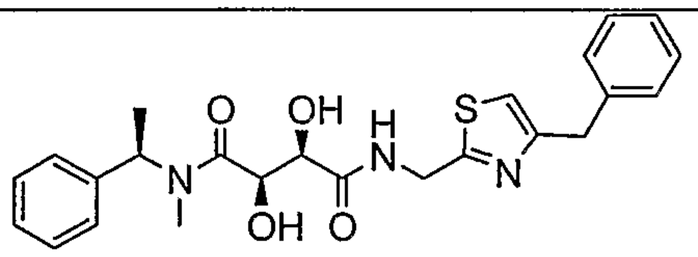
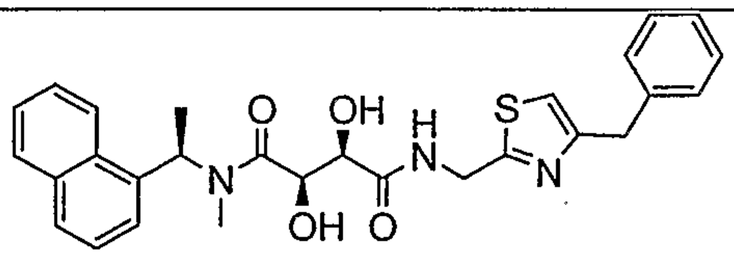
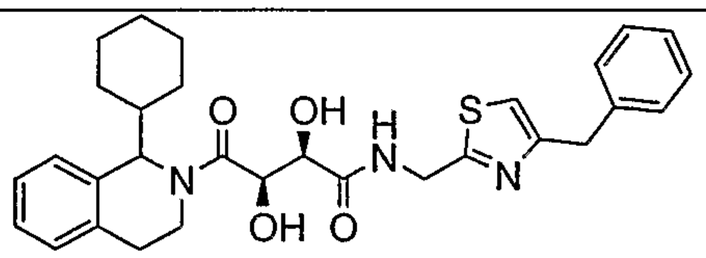
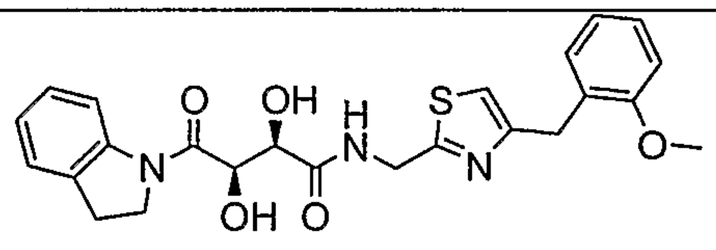
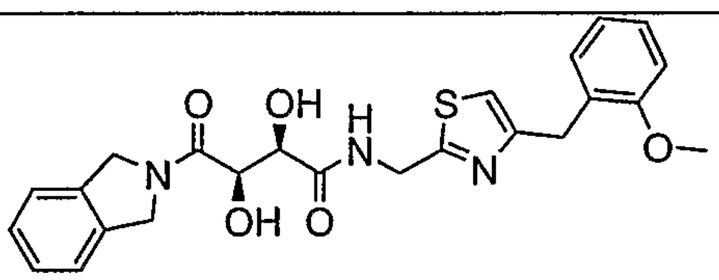
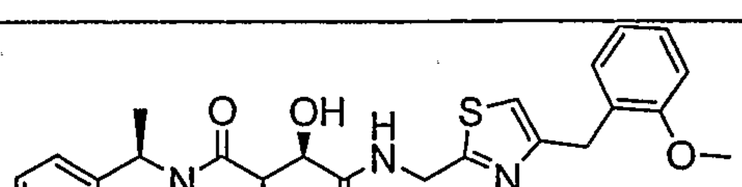
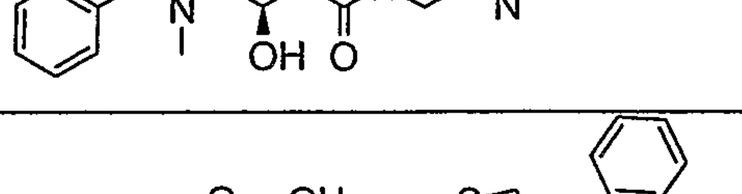







 (R1 = R2 = CH_2Ph, R3 = $CH_2CH_2(C_4H_4O)$




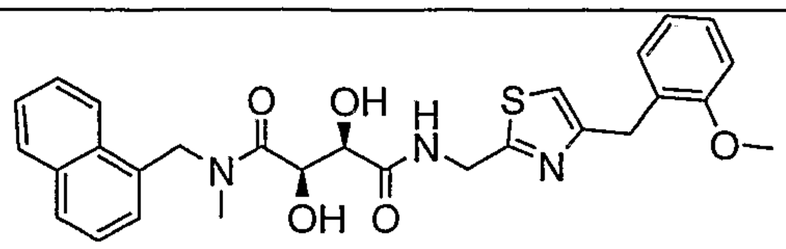










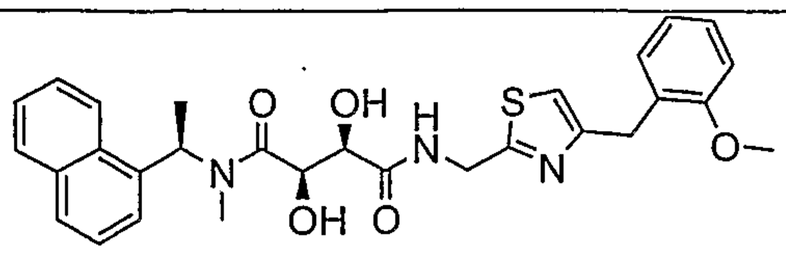












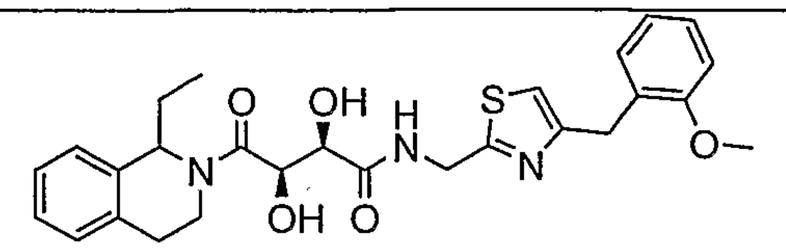














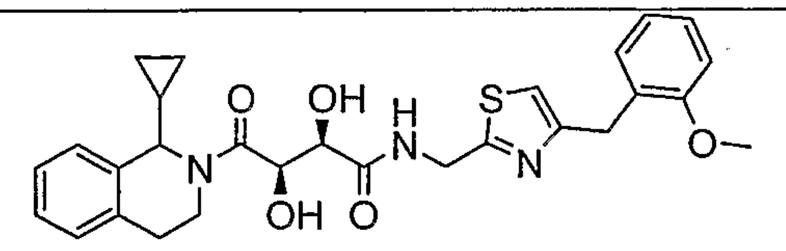













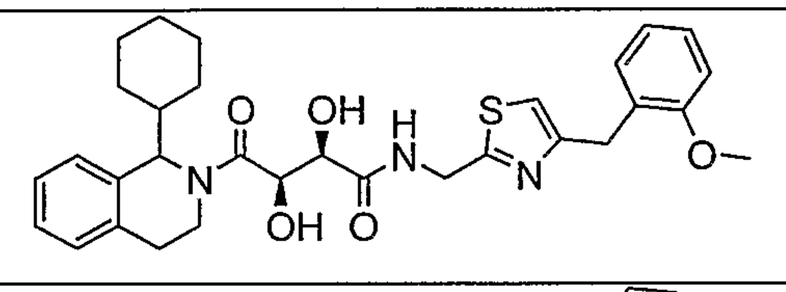












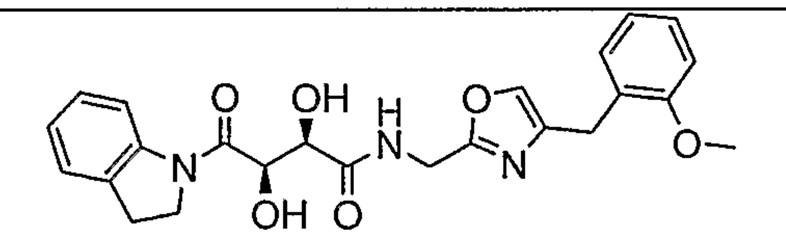


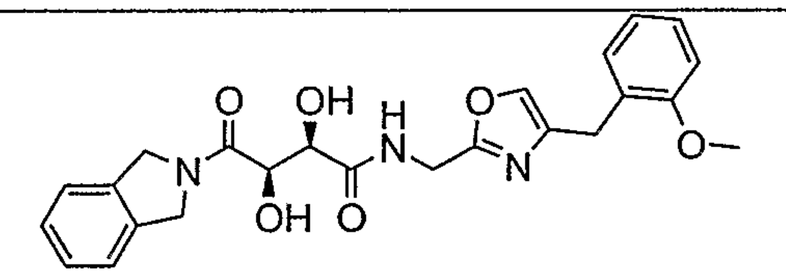


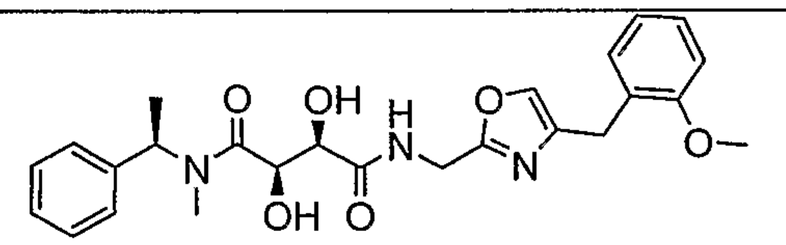


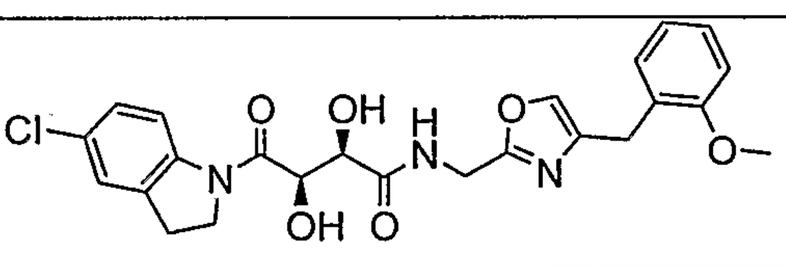


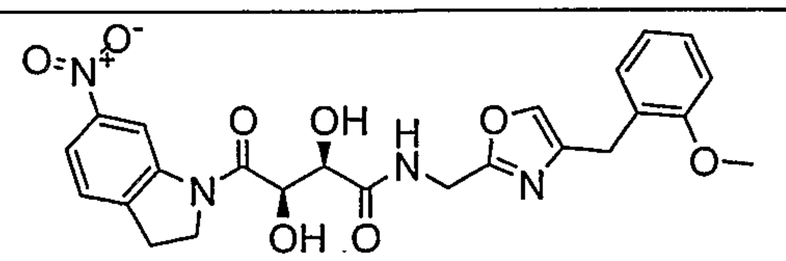


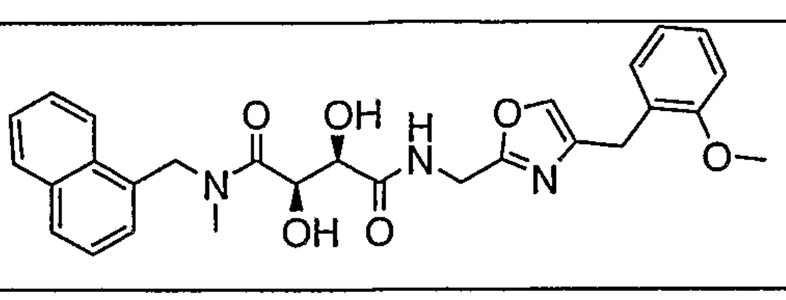


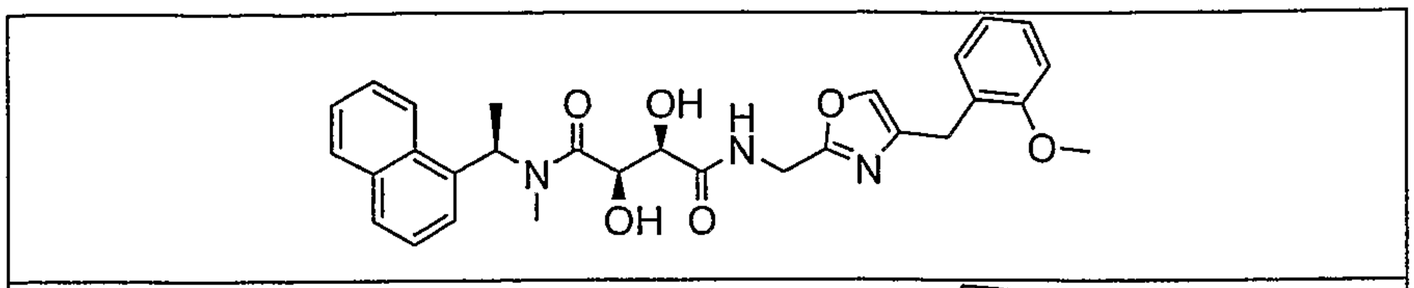


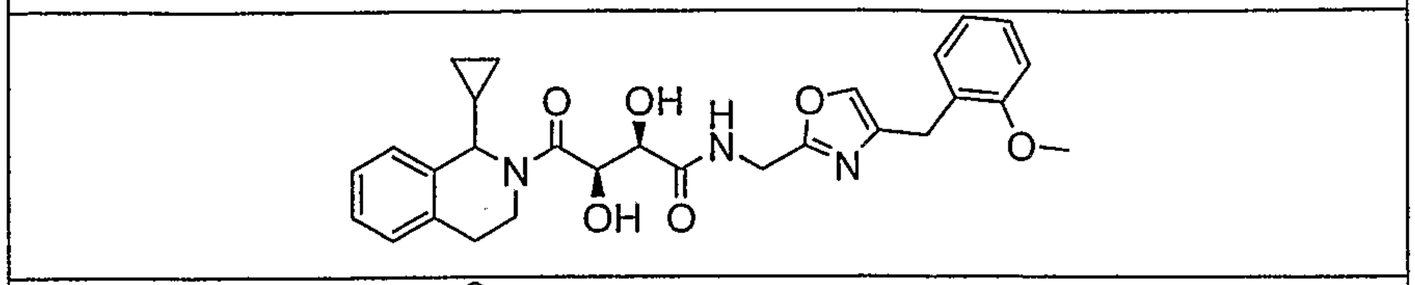


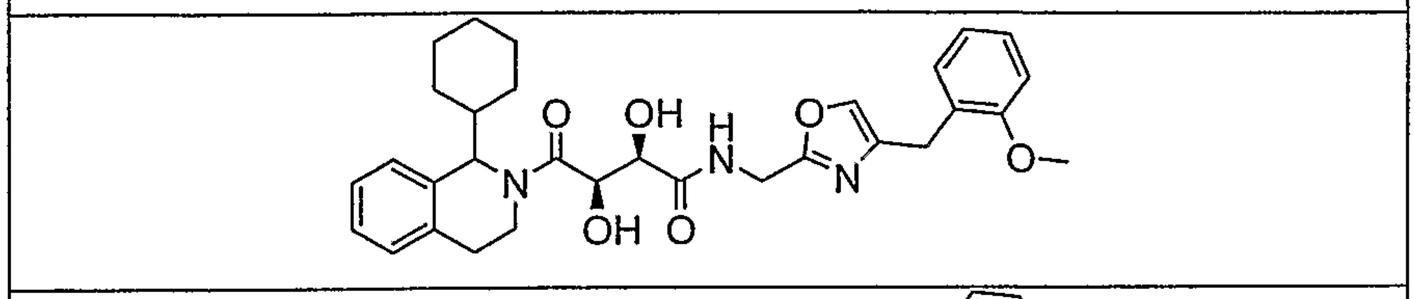


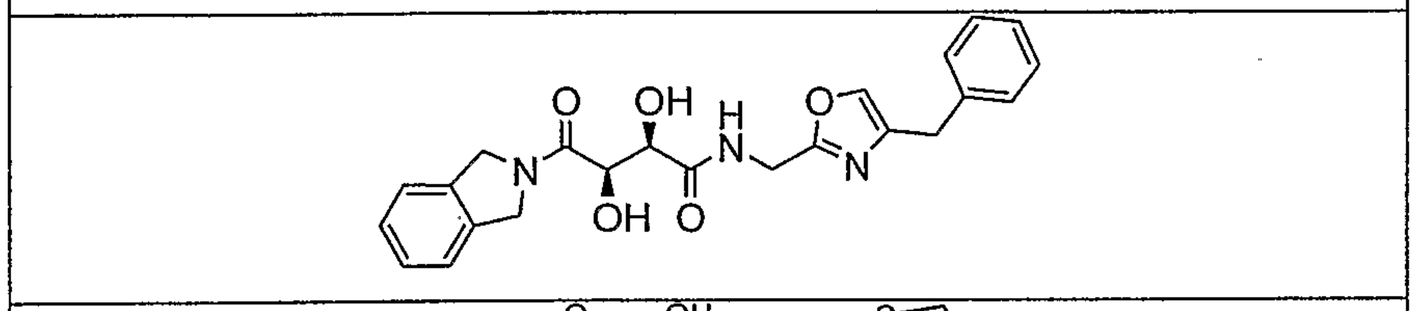


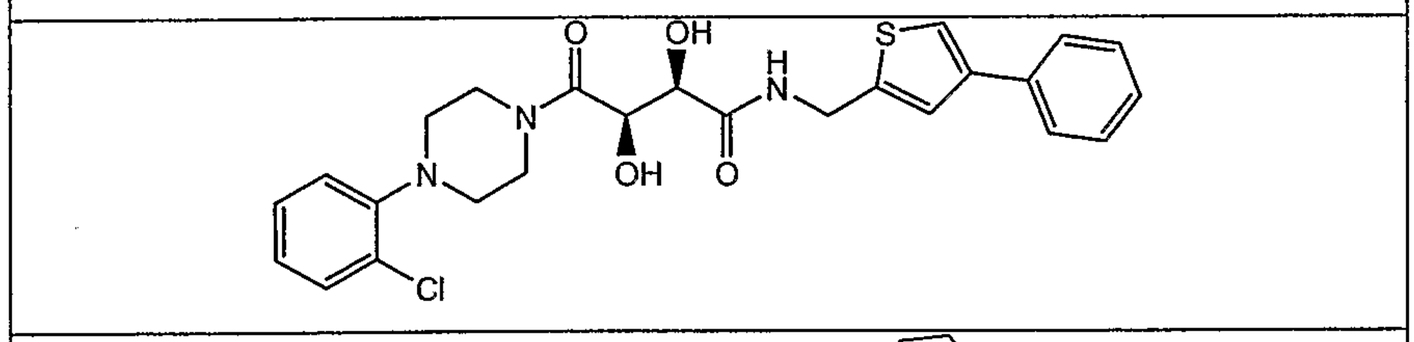


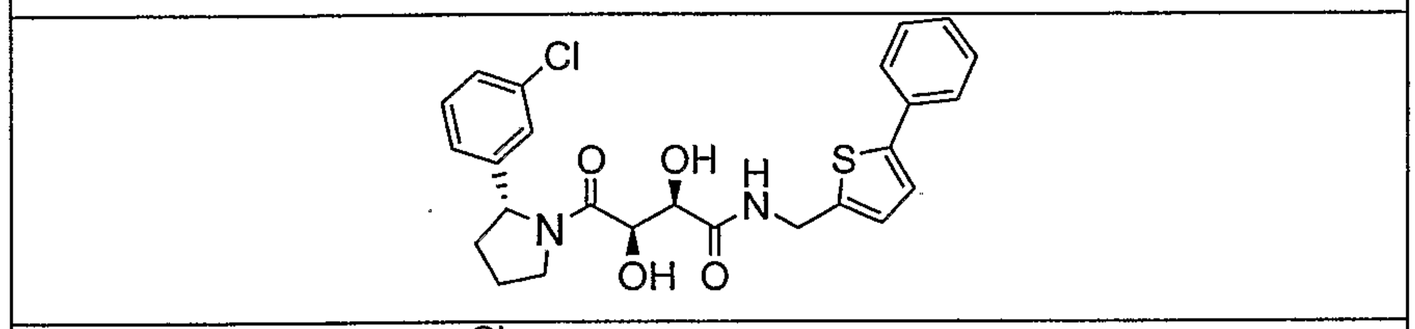


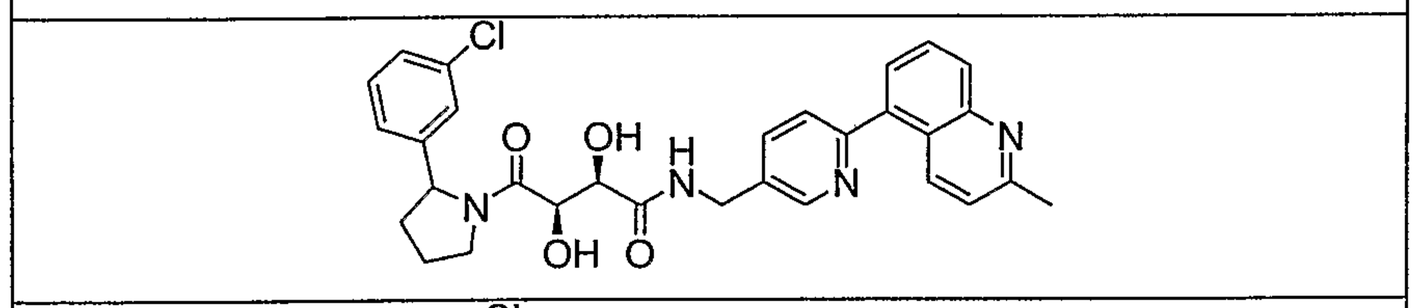


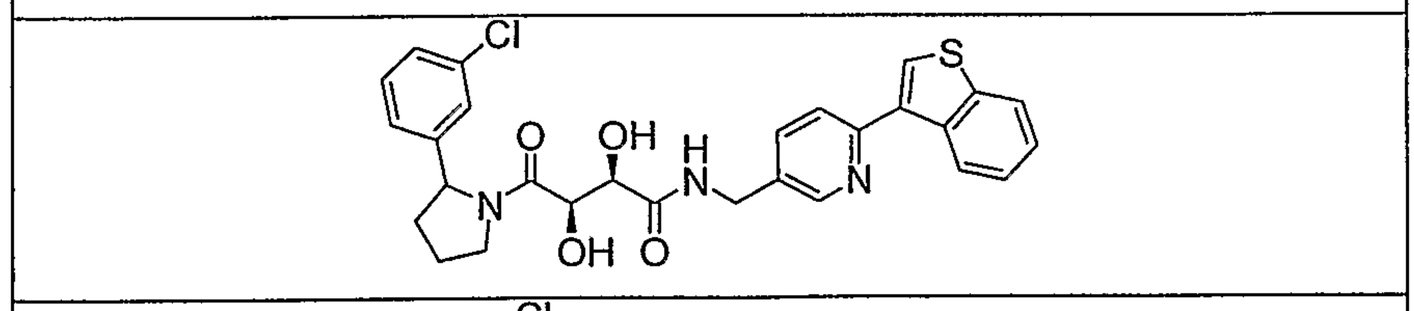


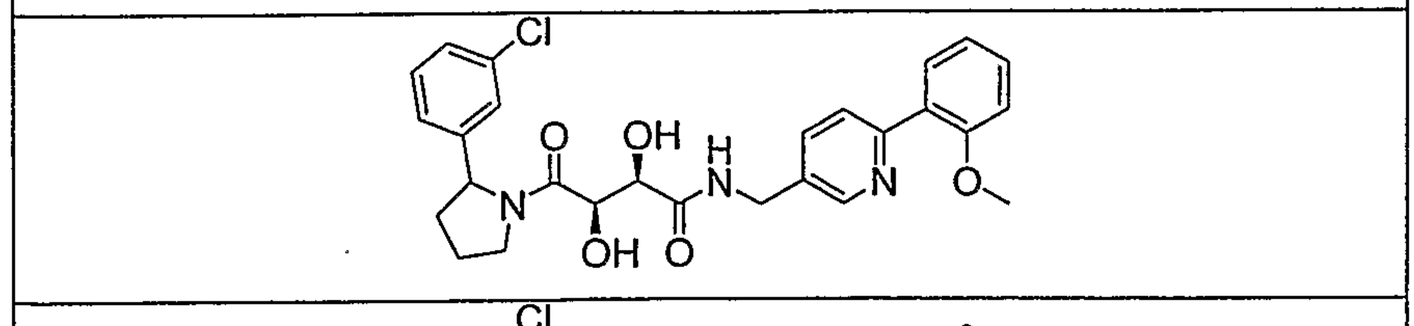


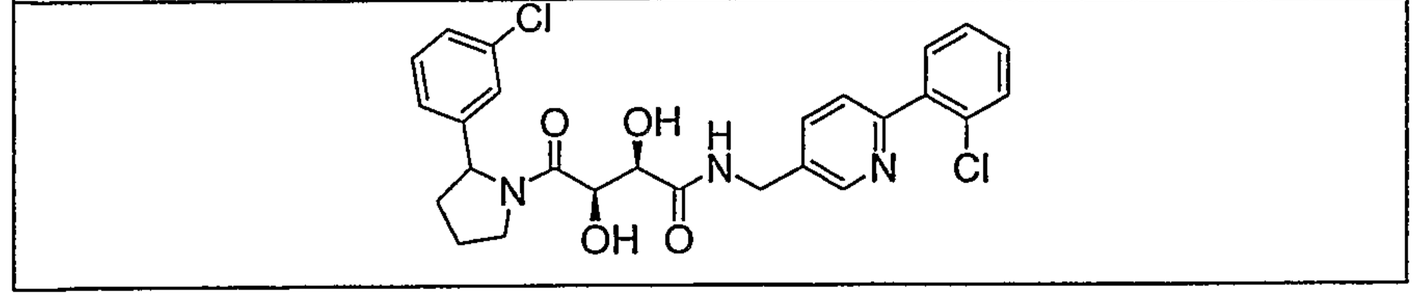


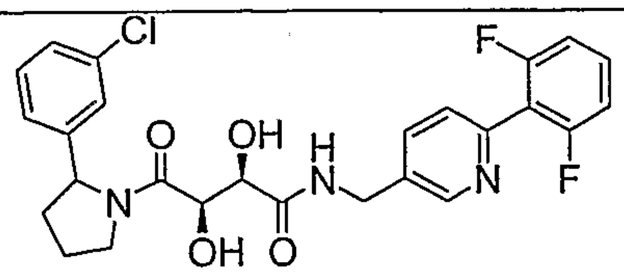


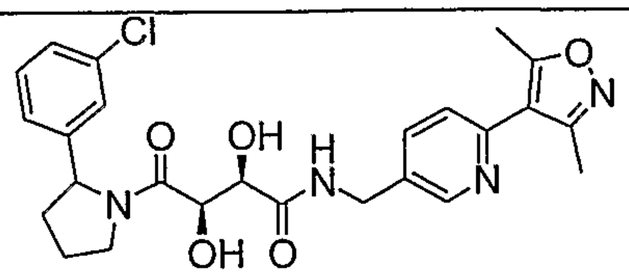


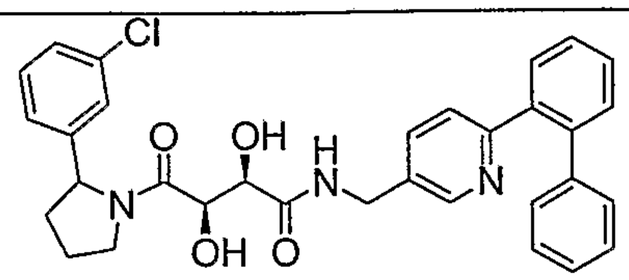


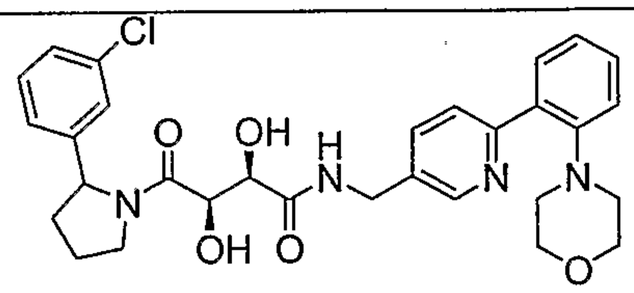


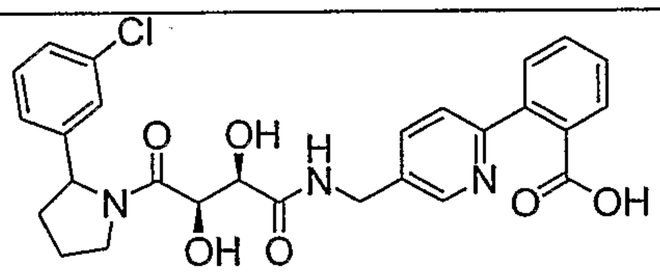


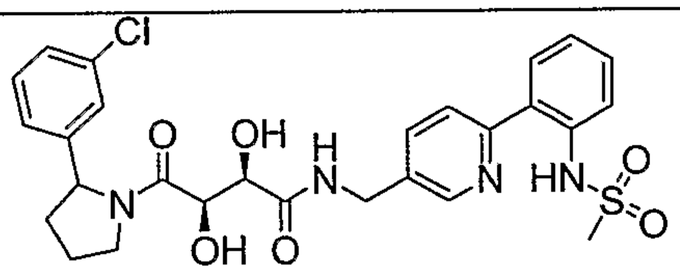


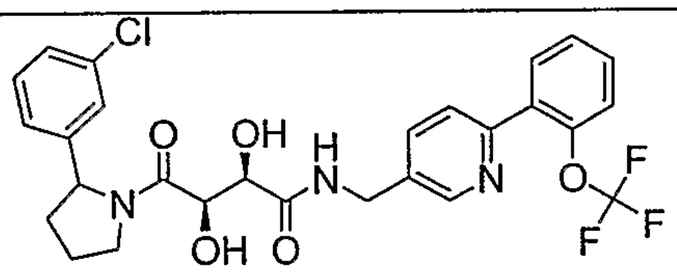


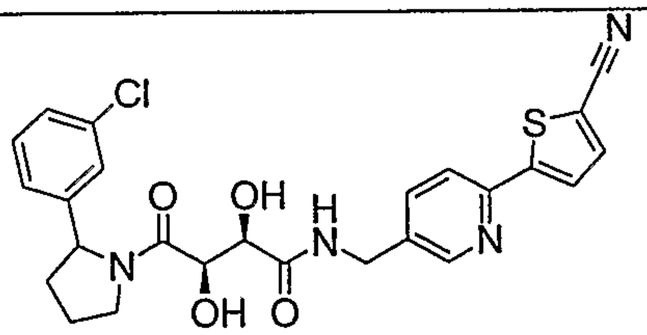


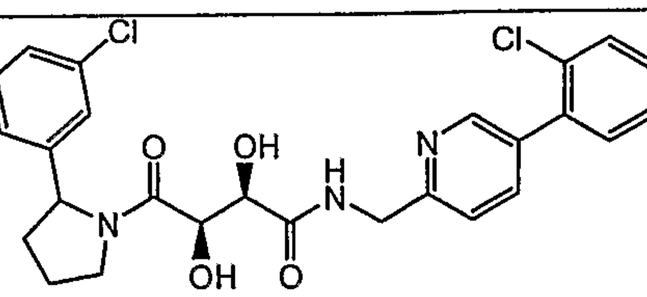


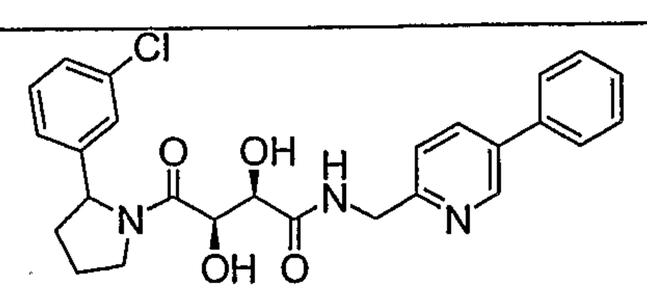


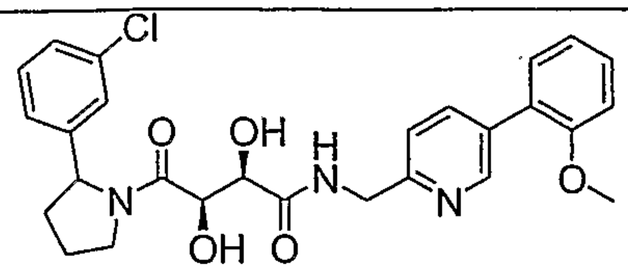
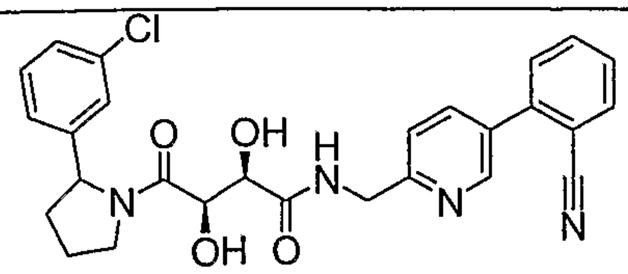
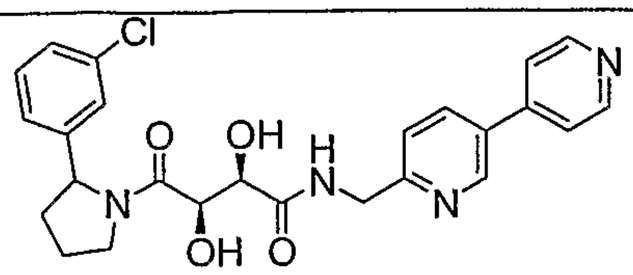
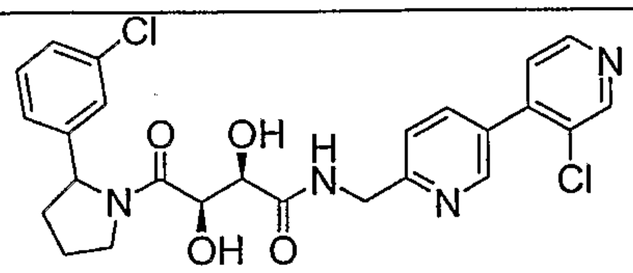
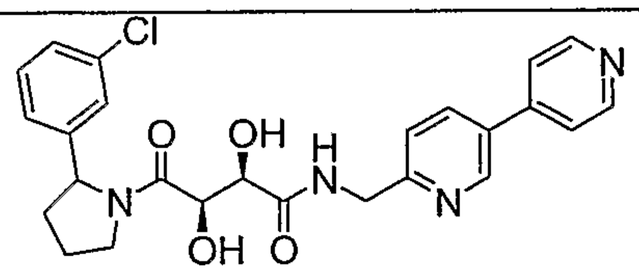
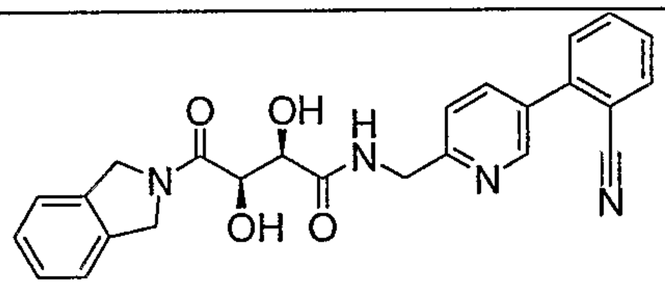
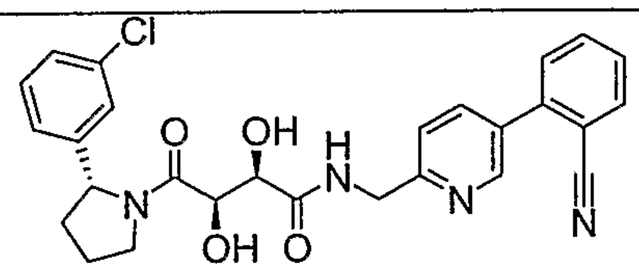
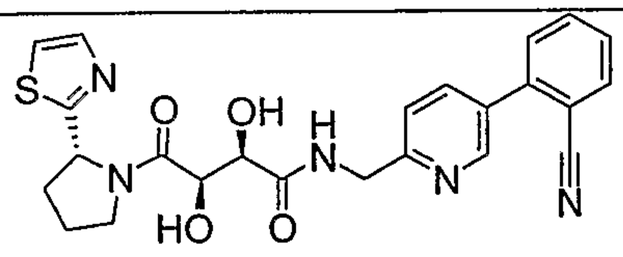
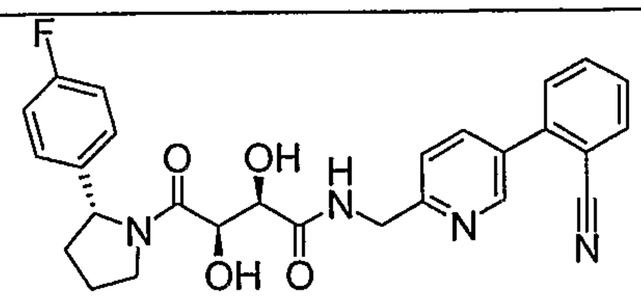
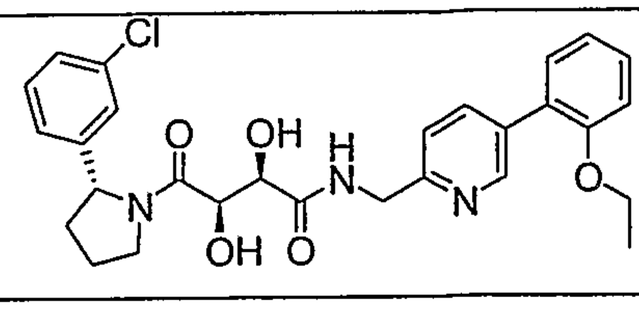










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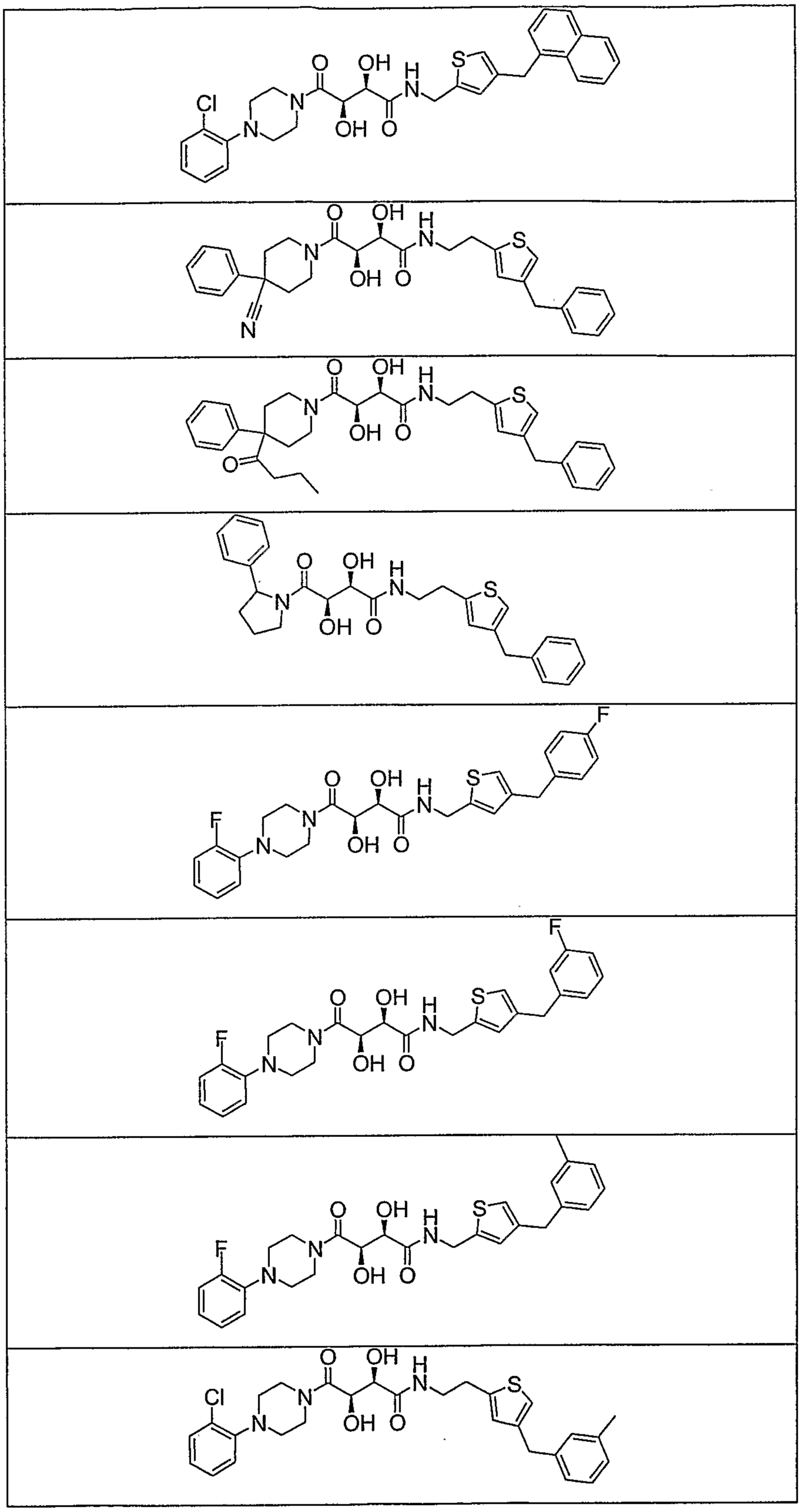

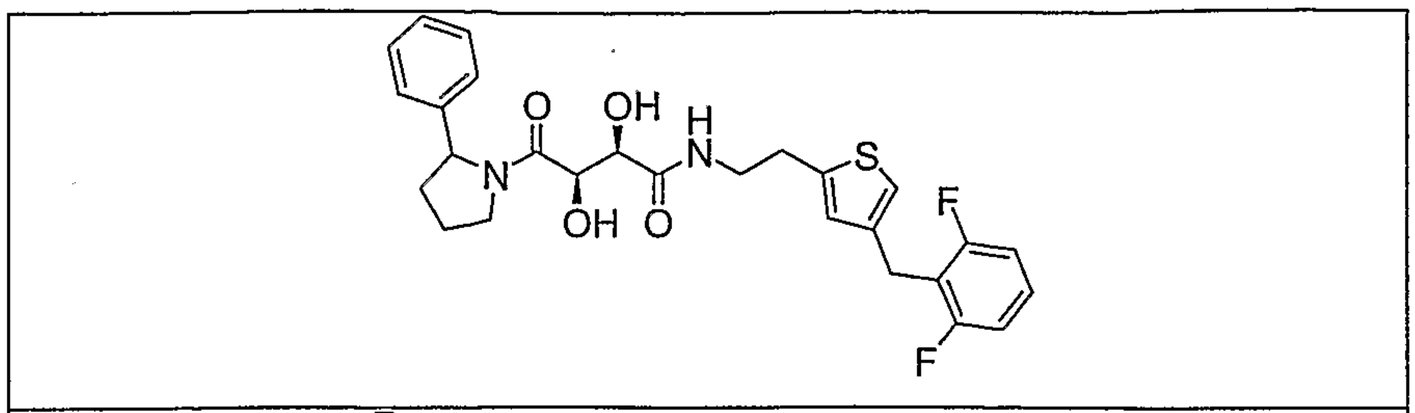

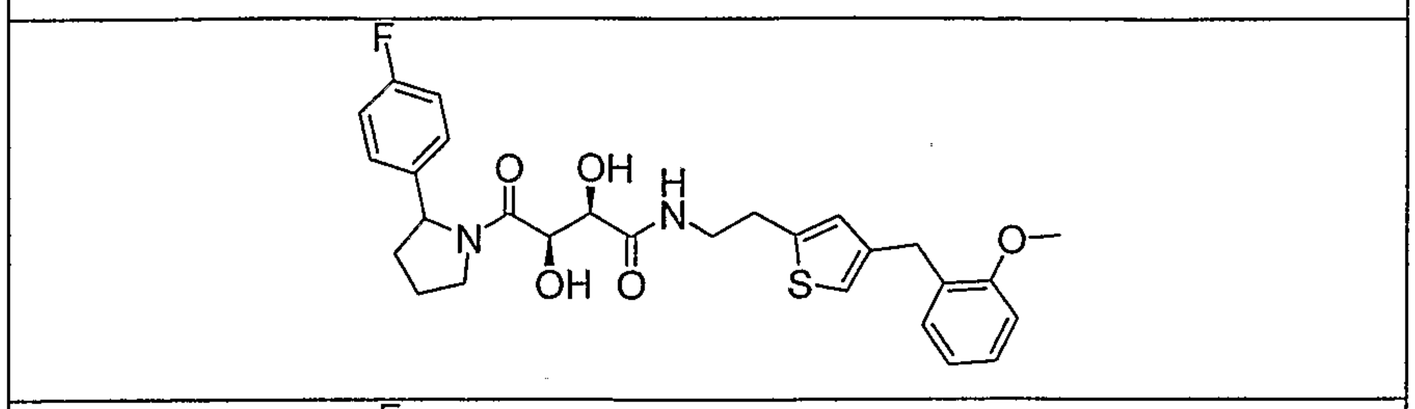

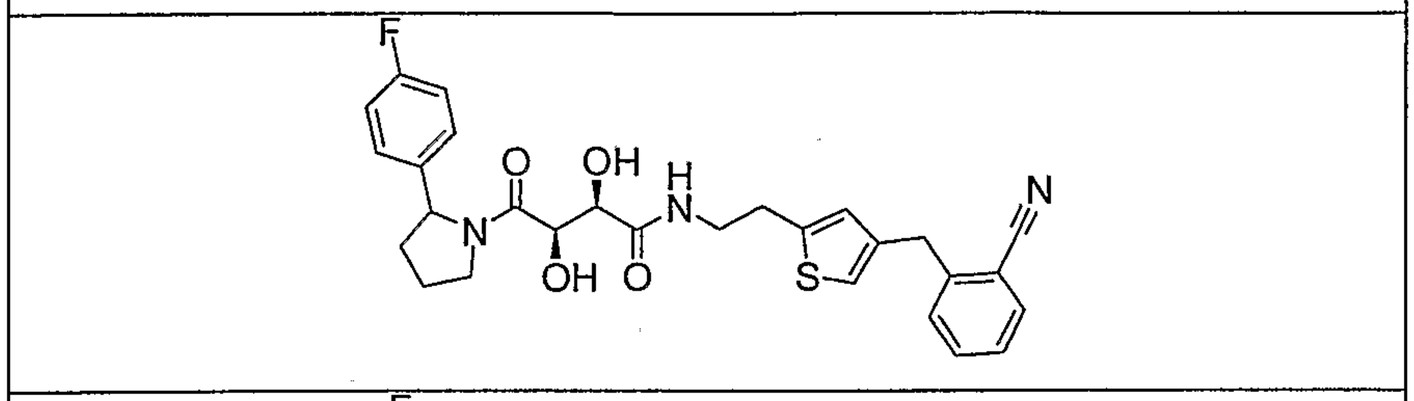

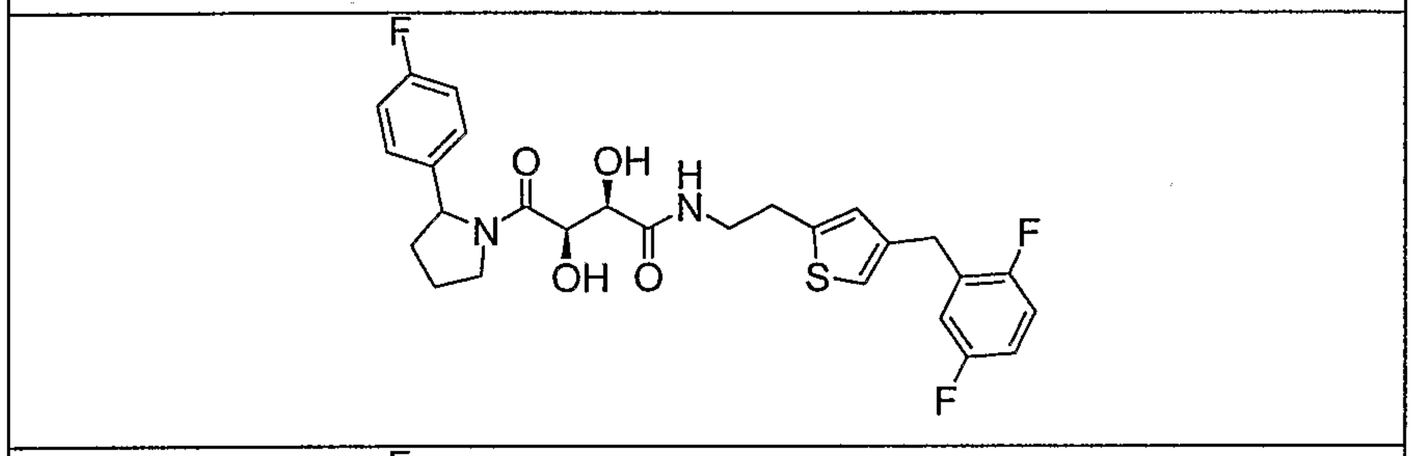

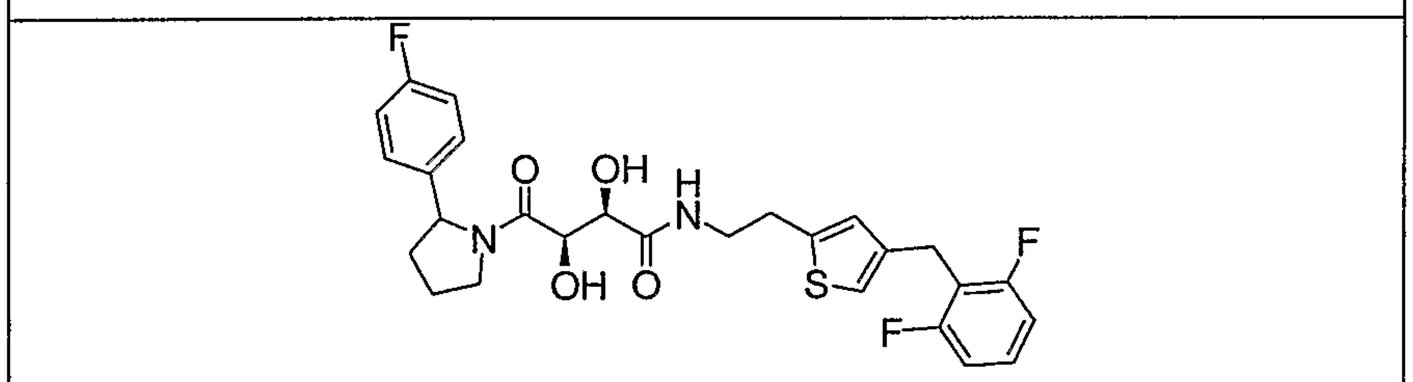

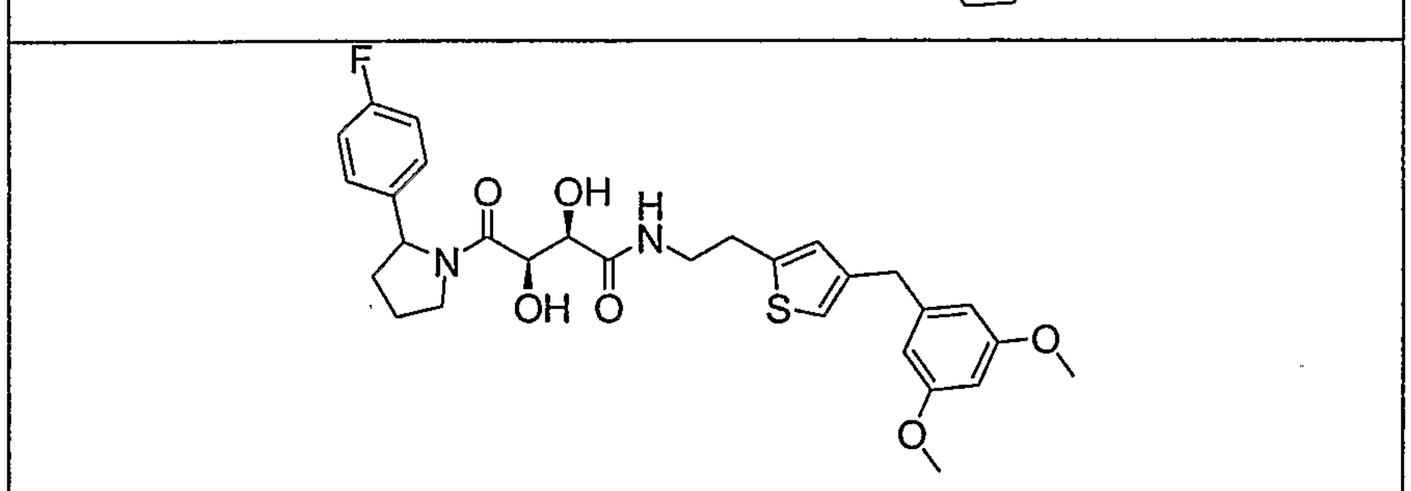

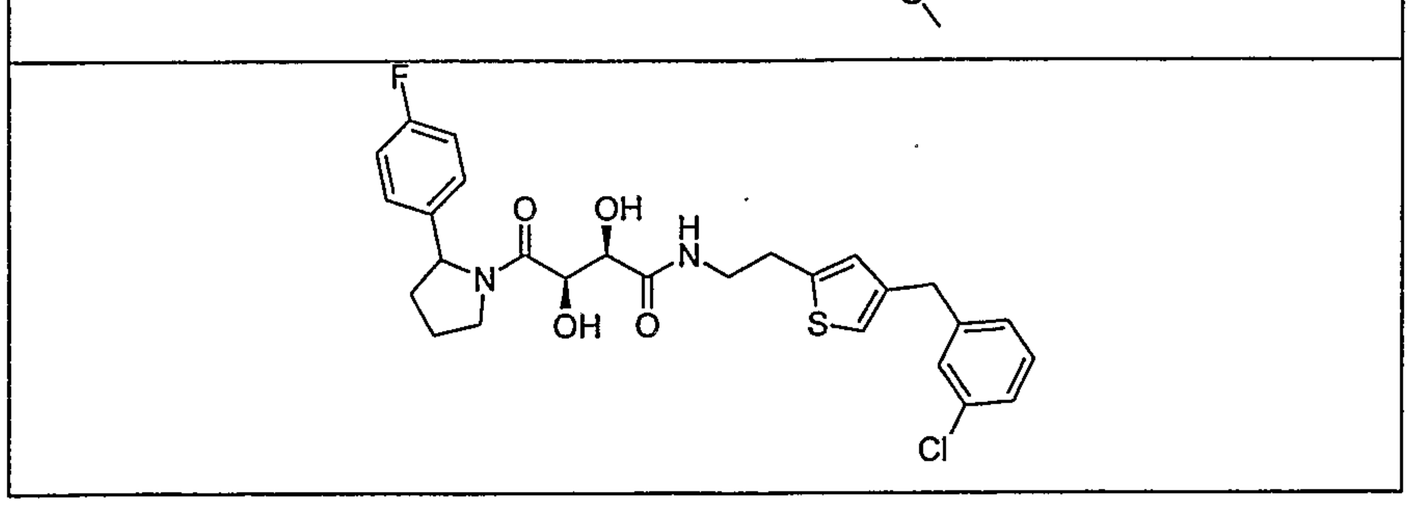

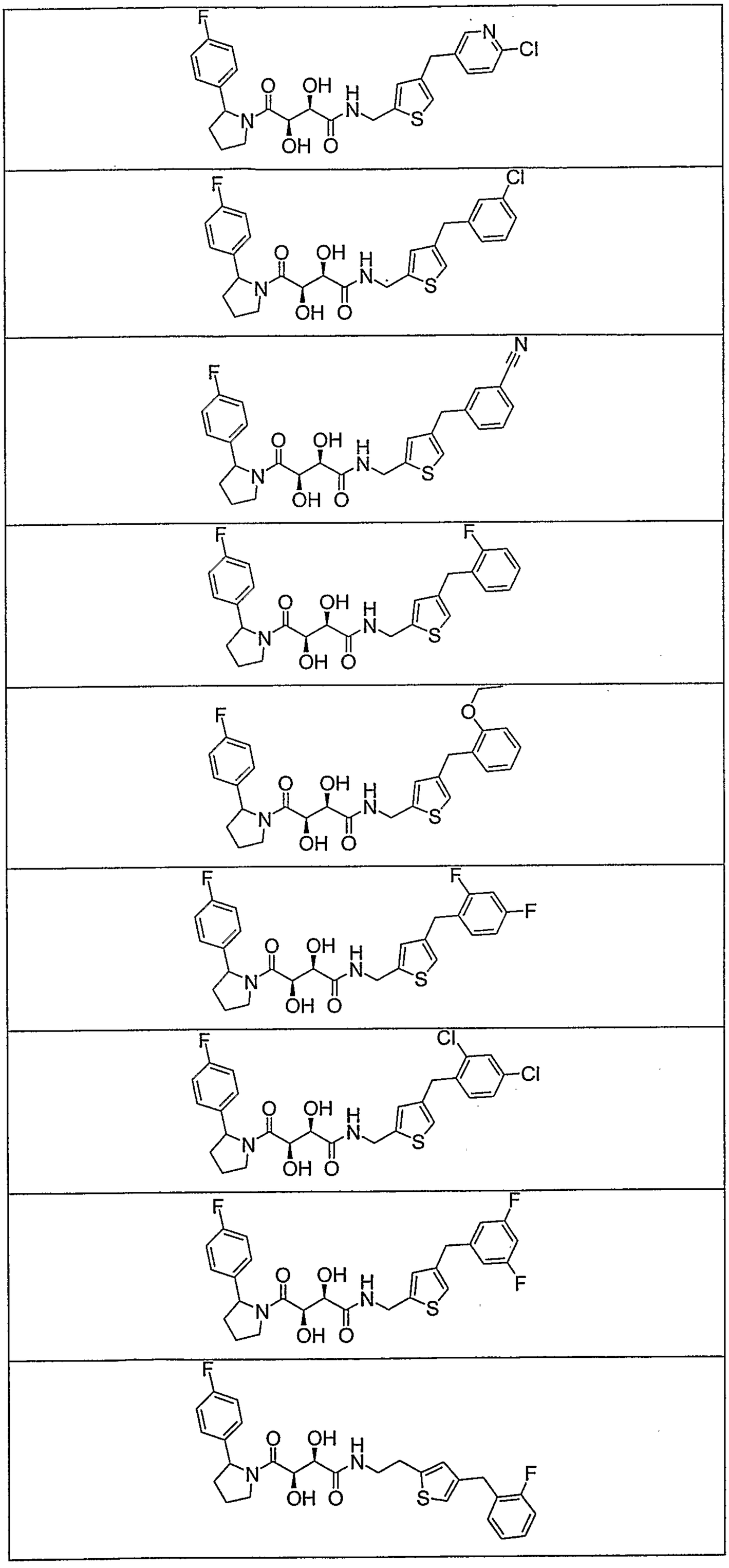

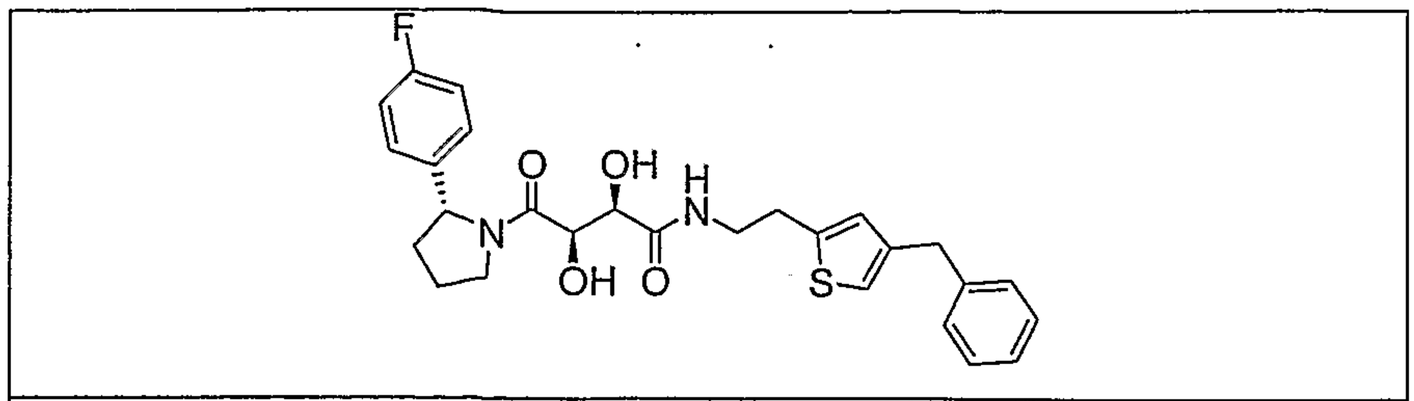
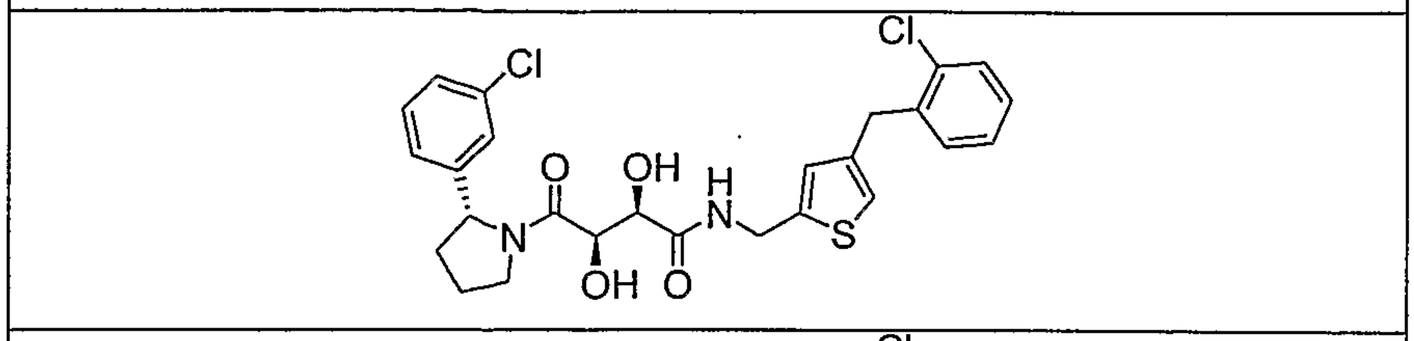
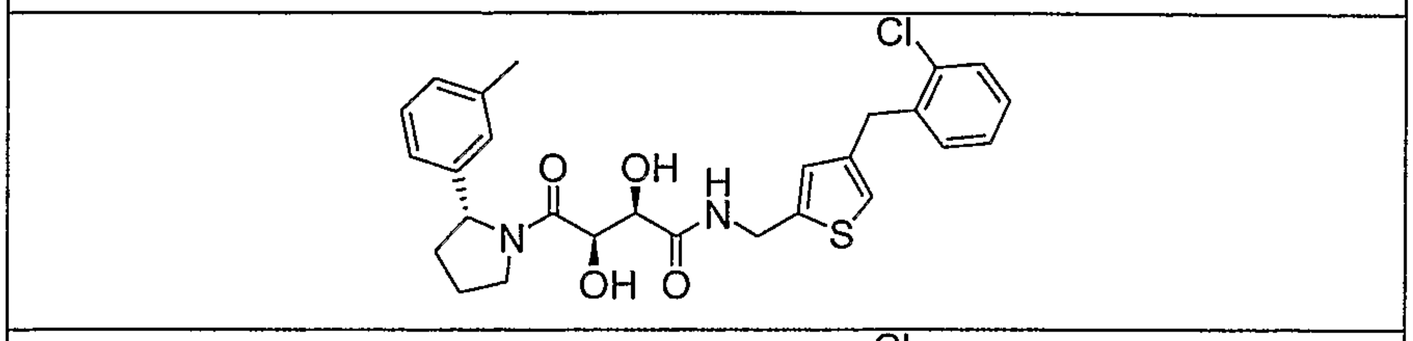
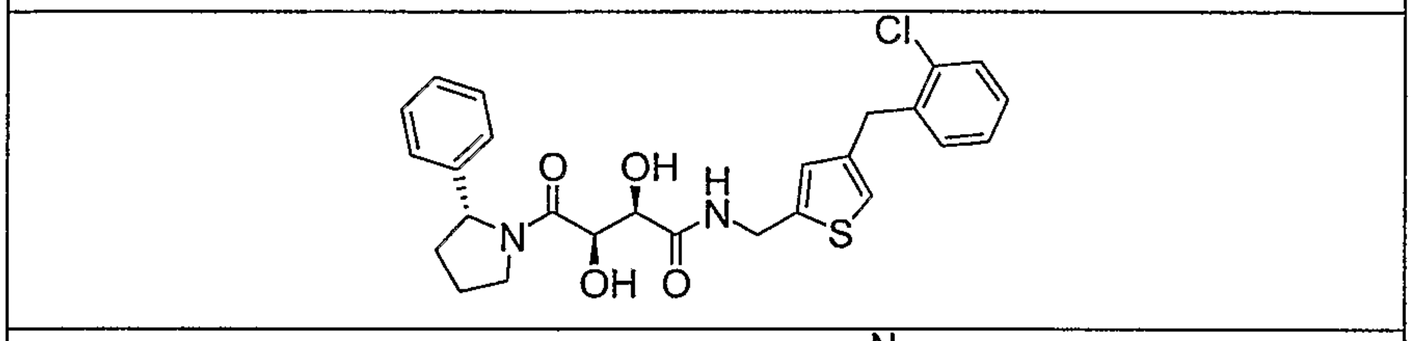
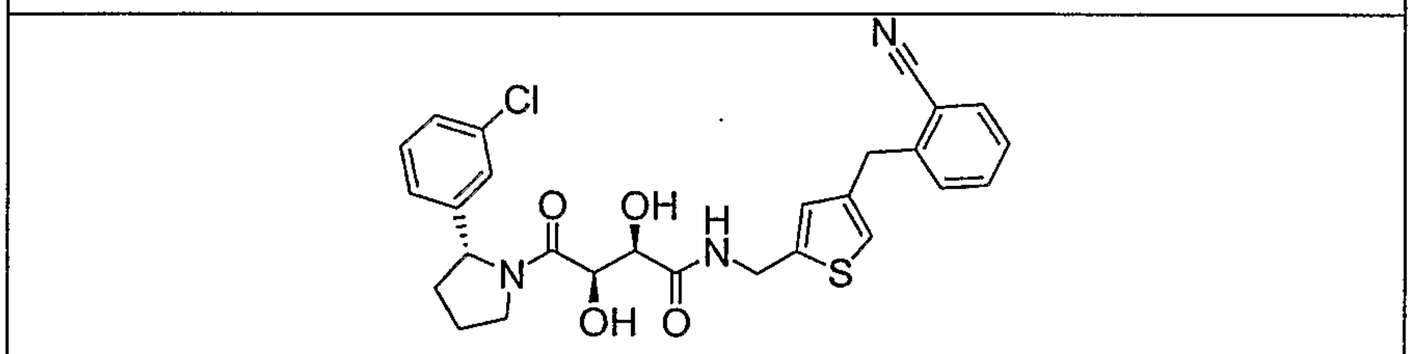
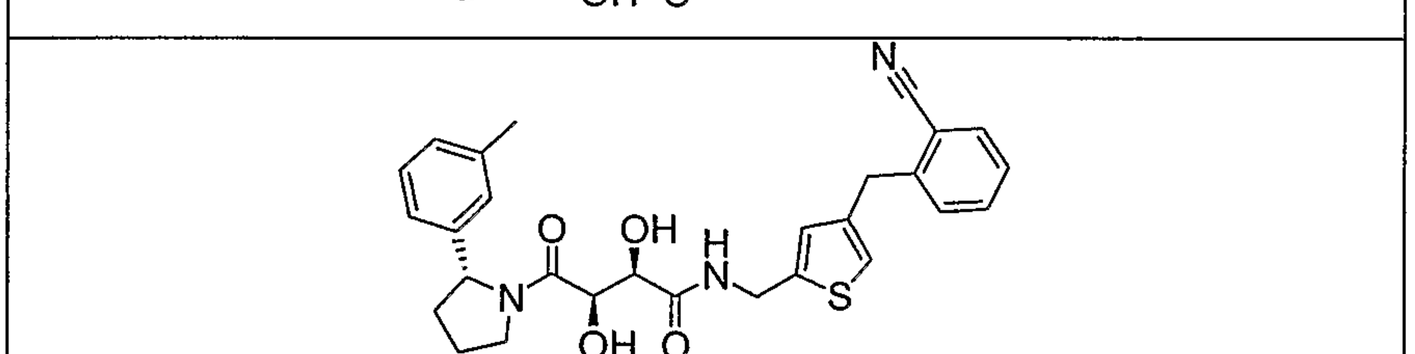
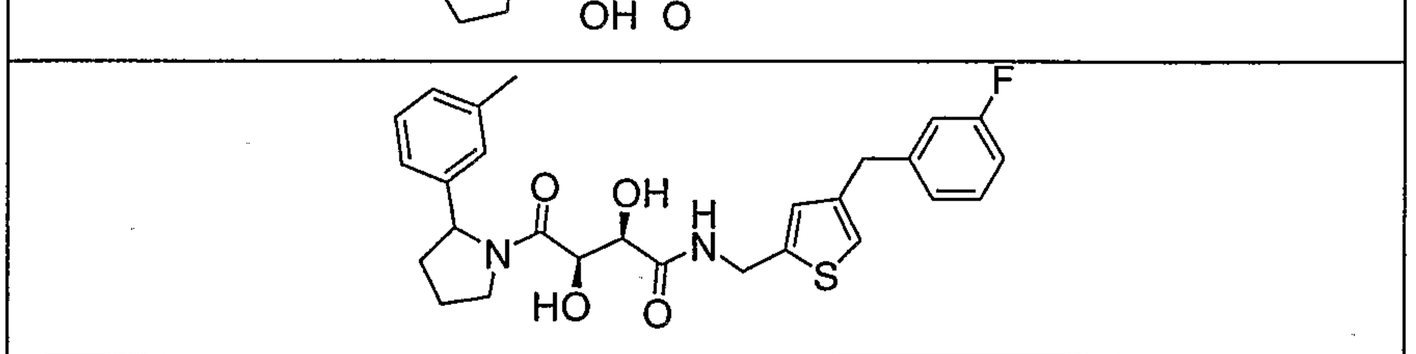
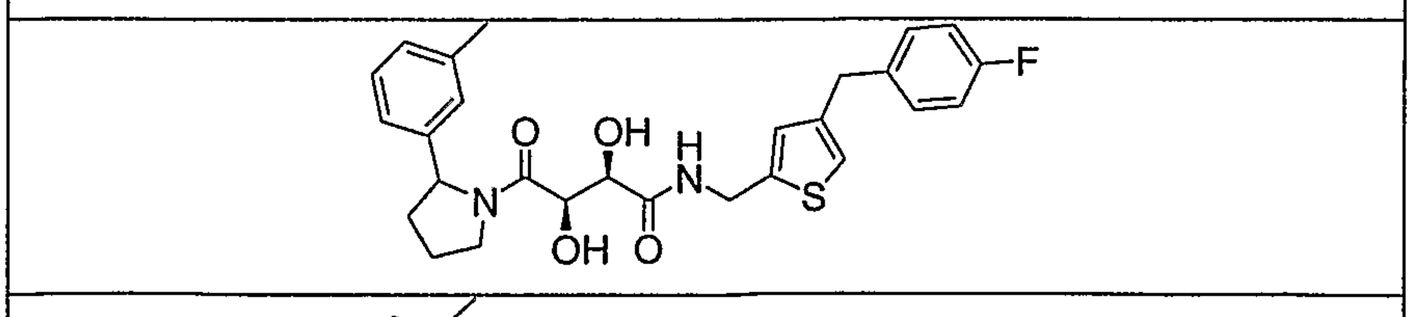
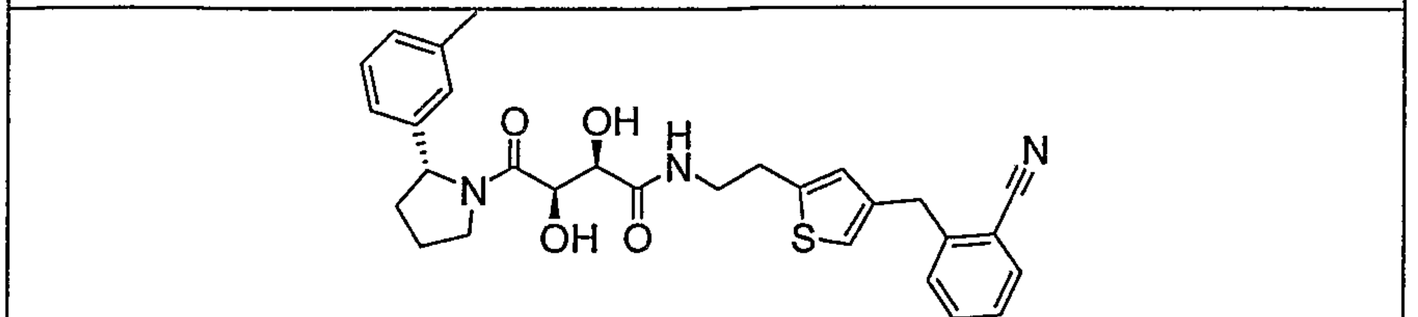

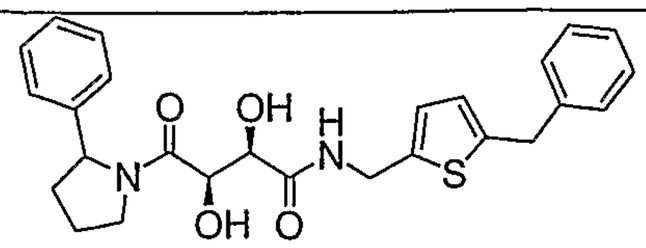
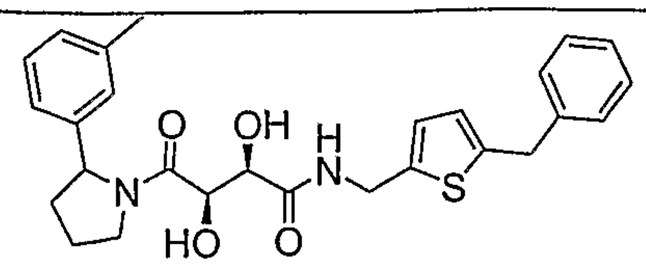
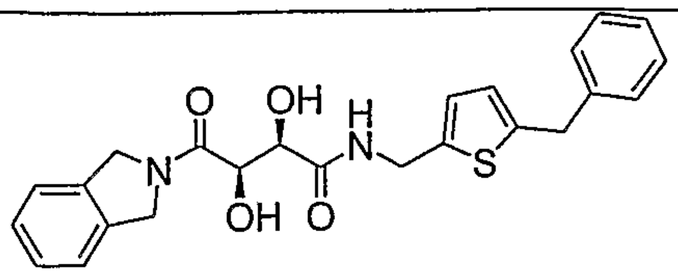
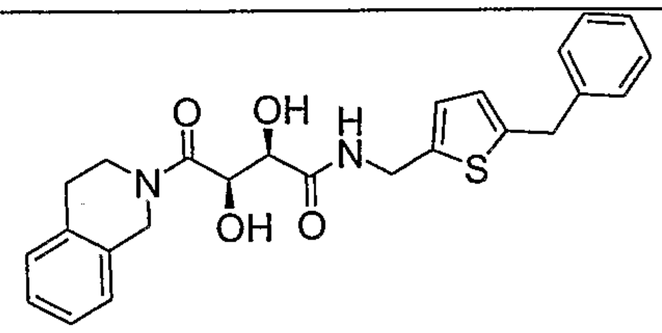
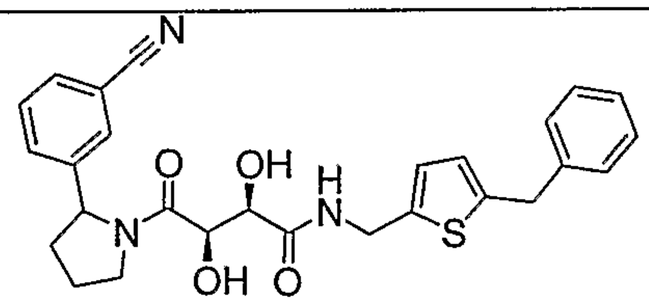
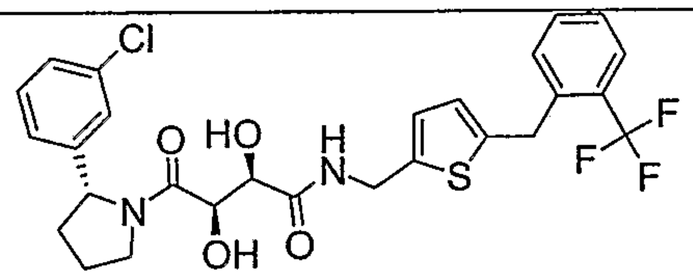
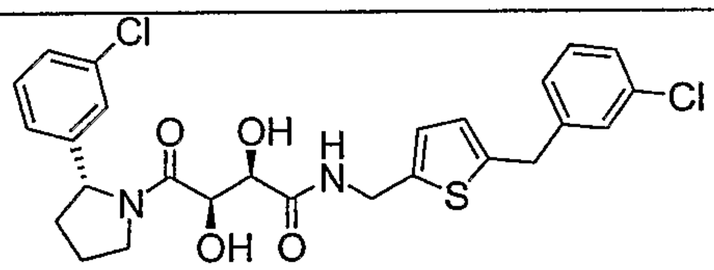
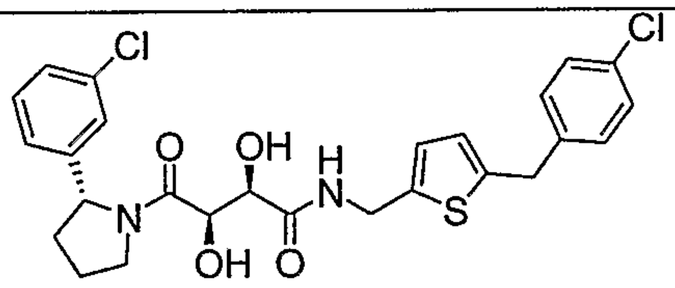
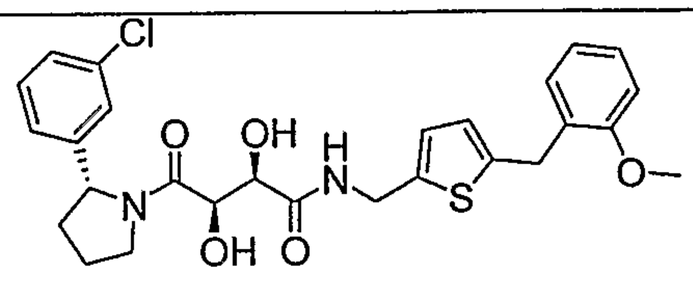
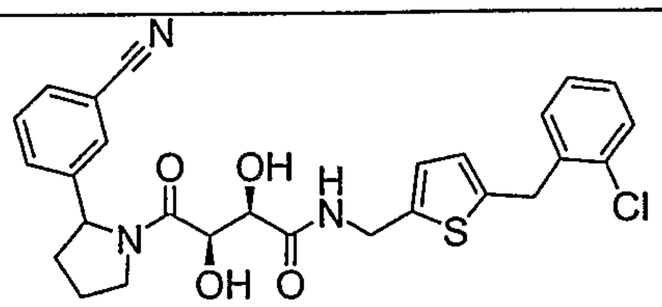

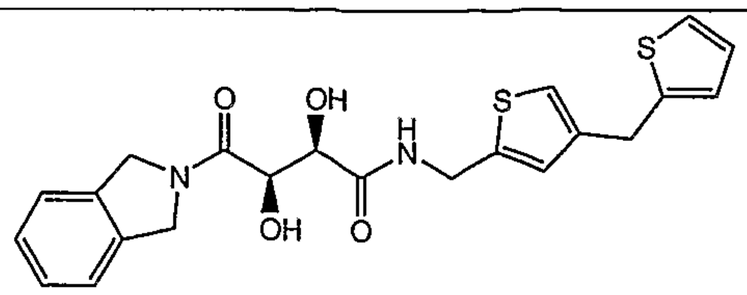
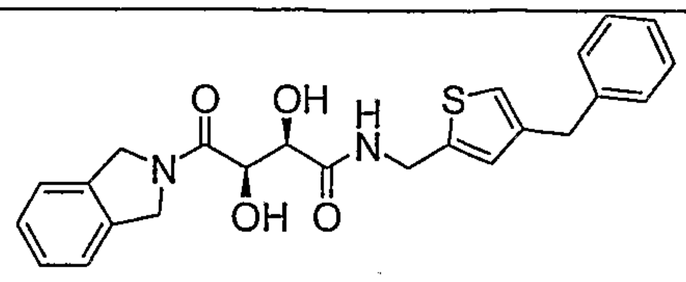
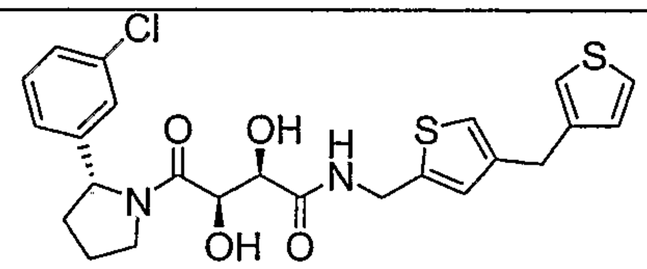
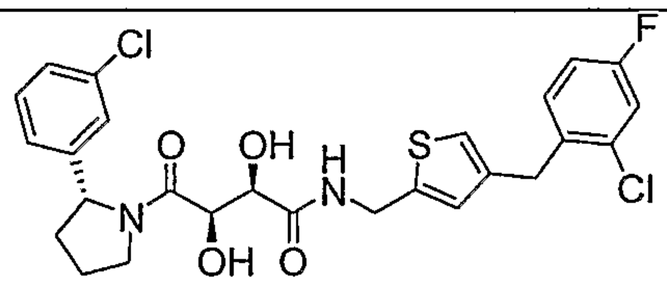
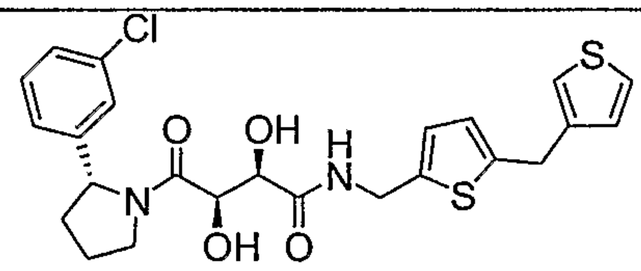
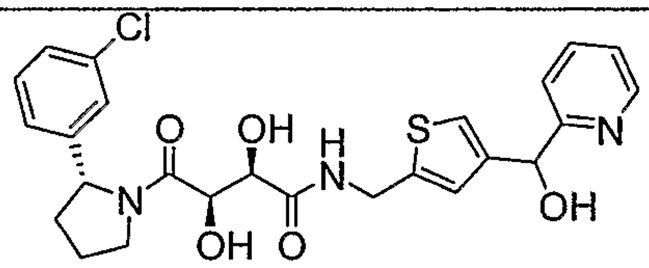
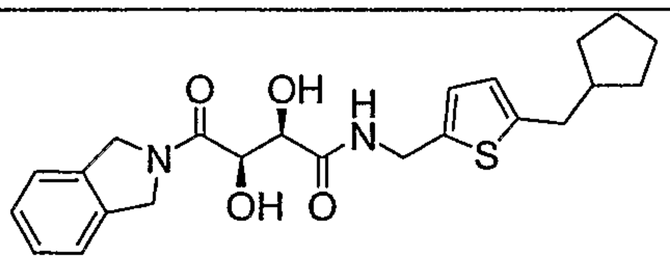
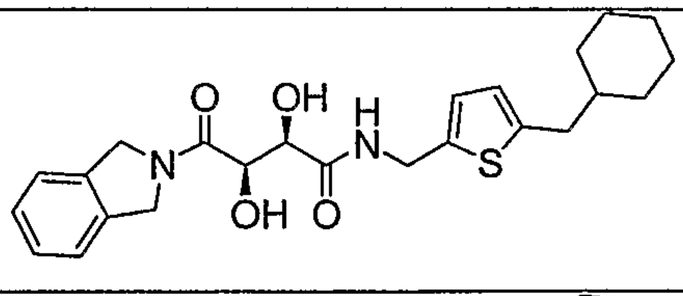
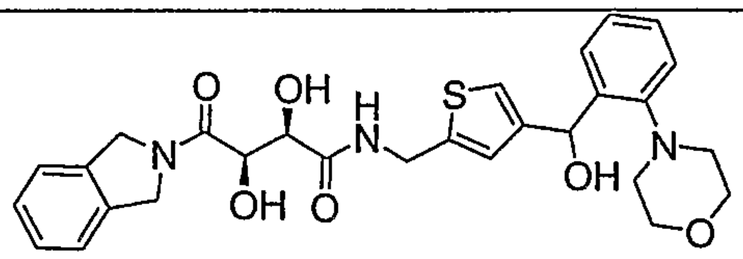
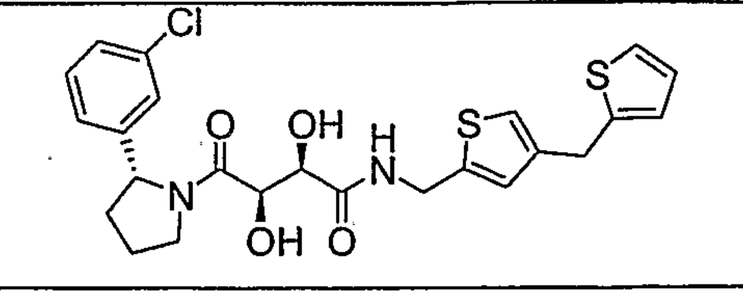

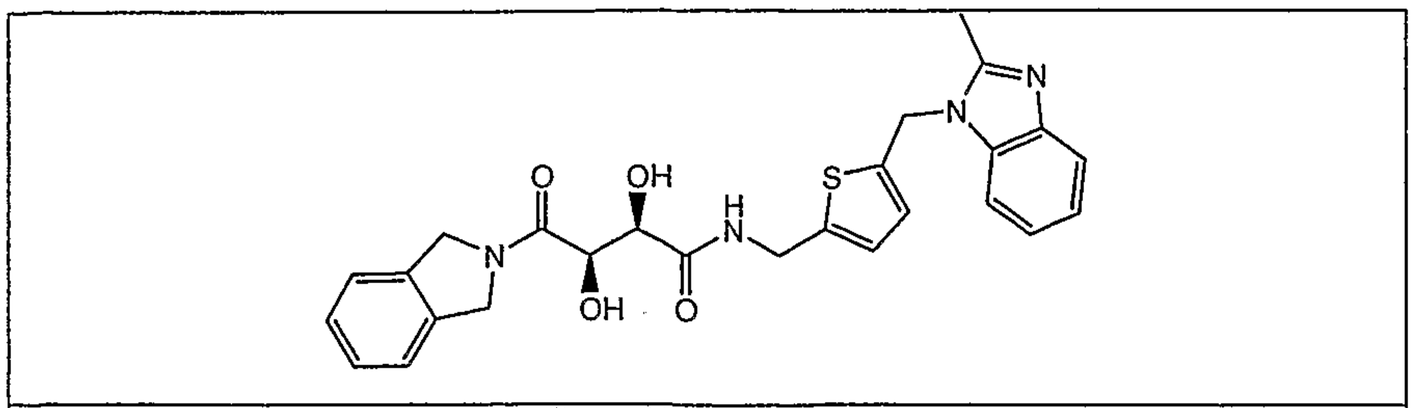

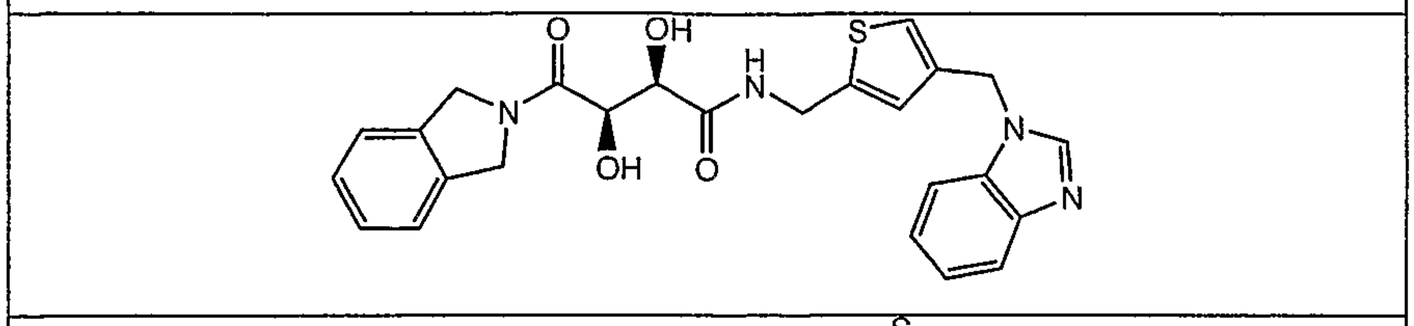

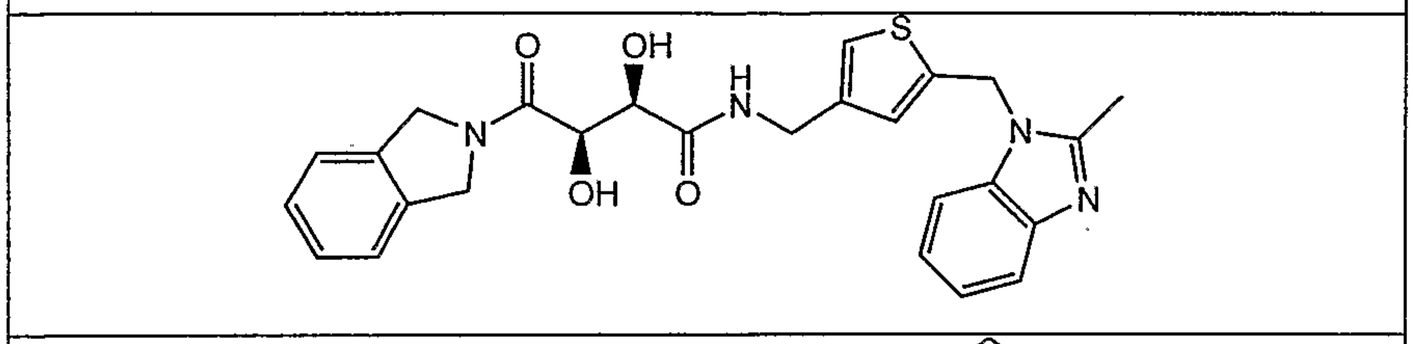

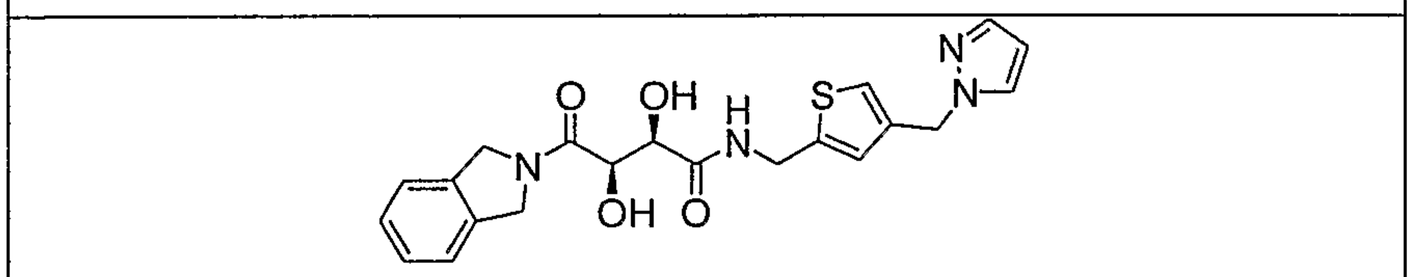

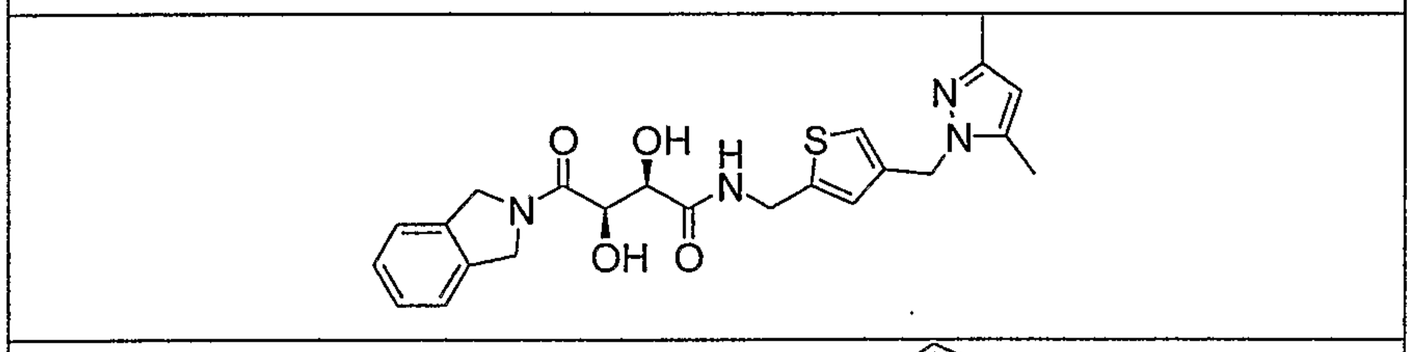

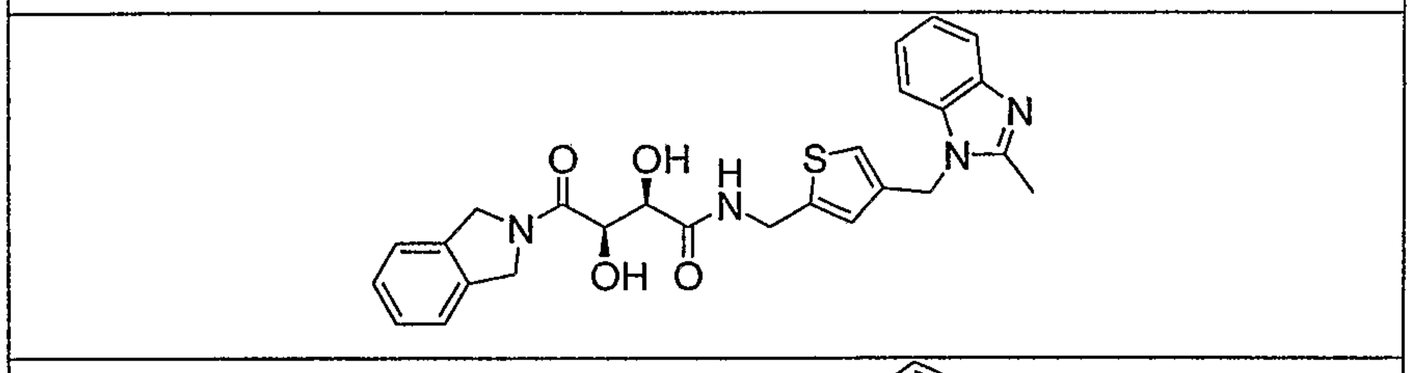

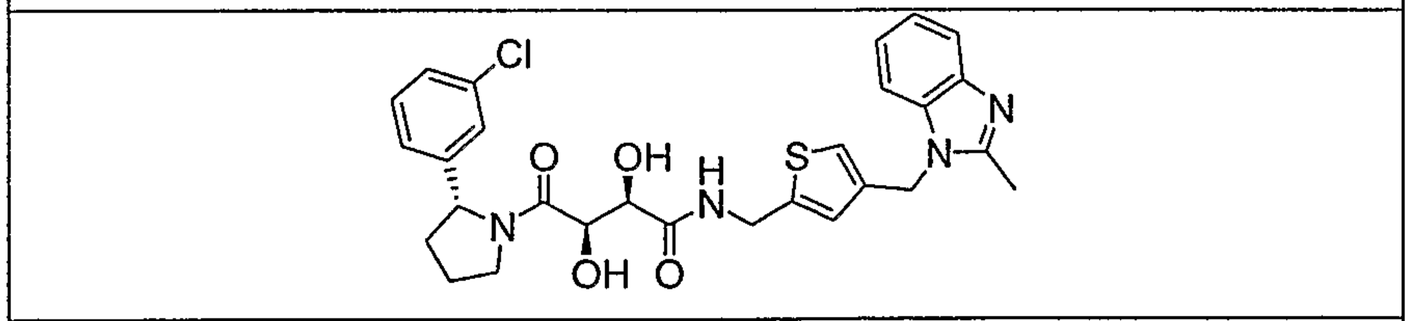

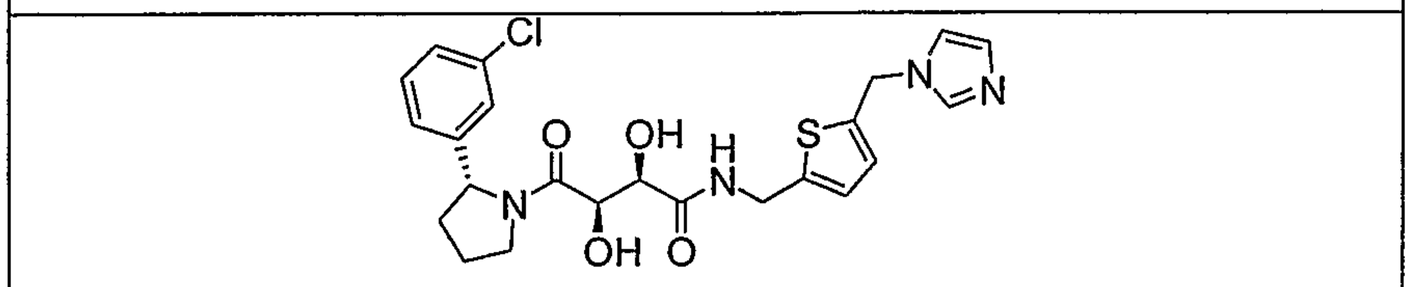

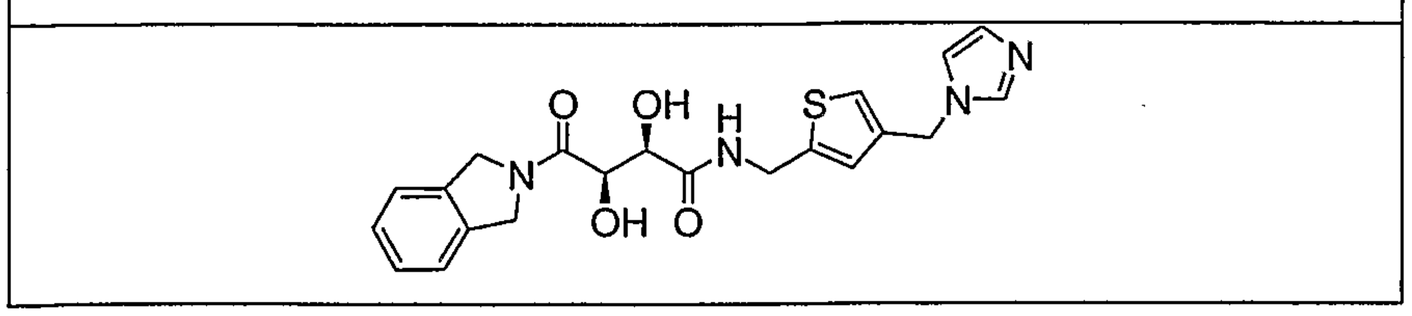

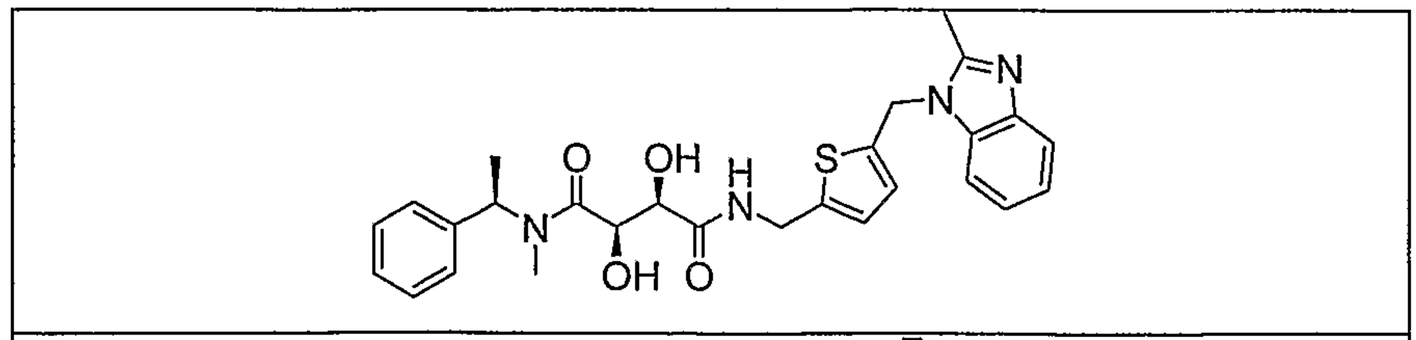

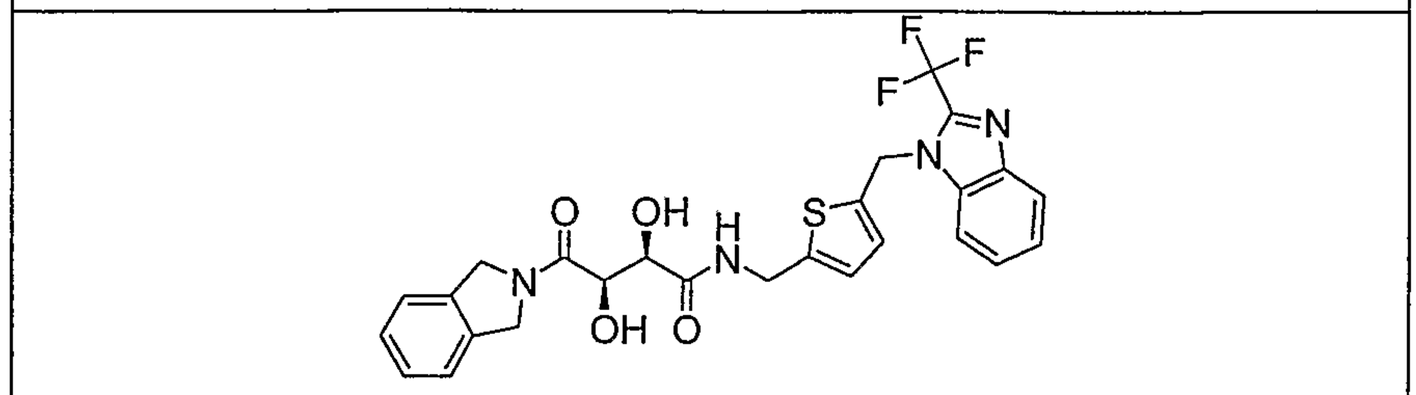

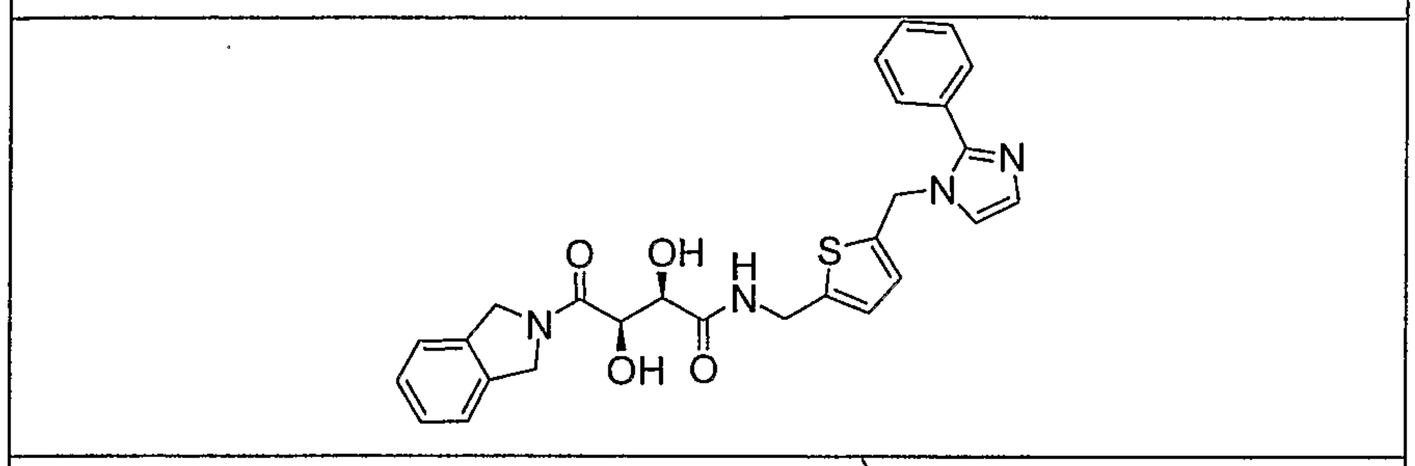

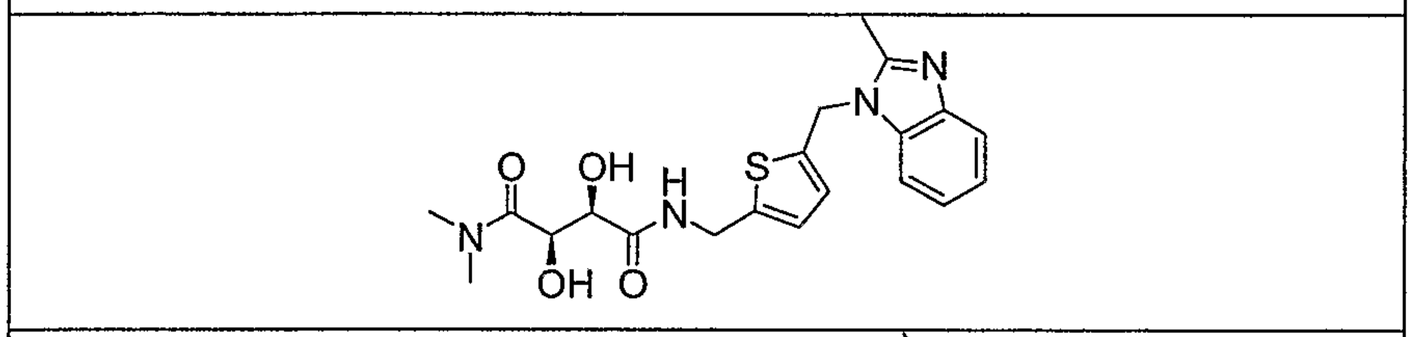

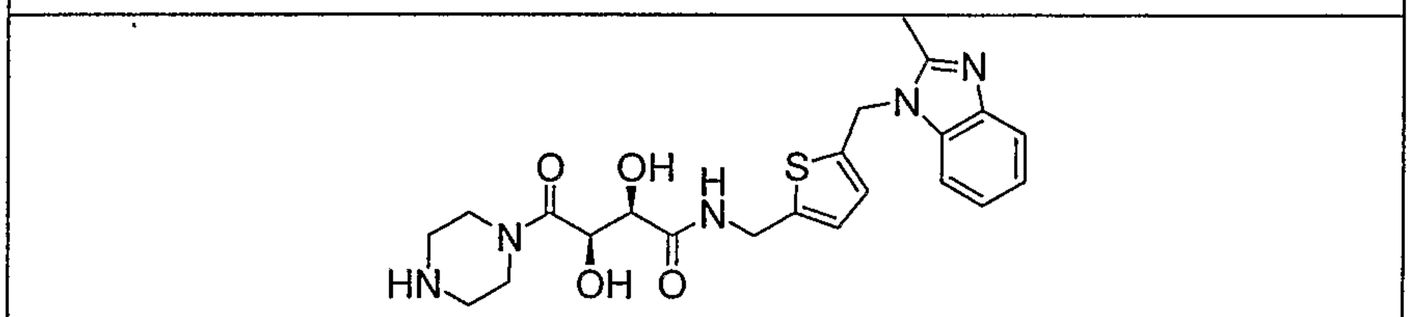

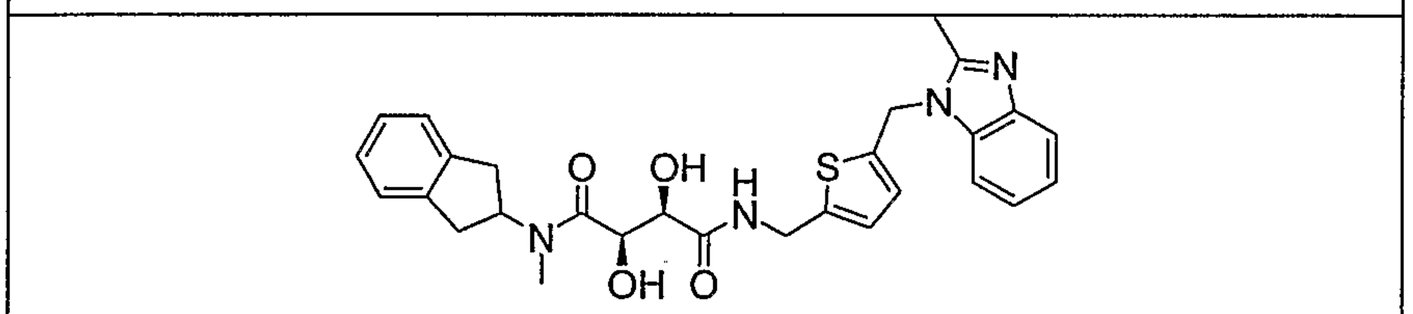

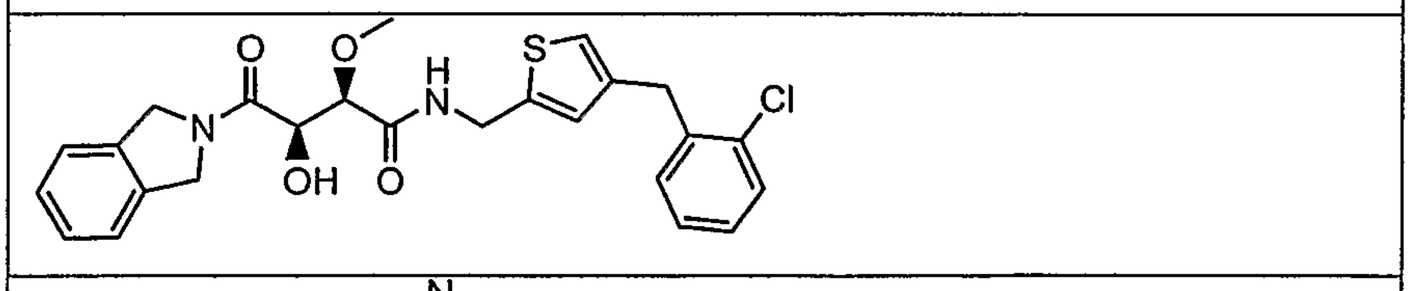

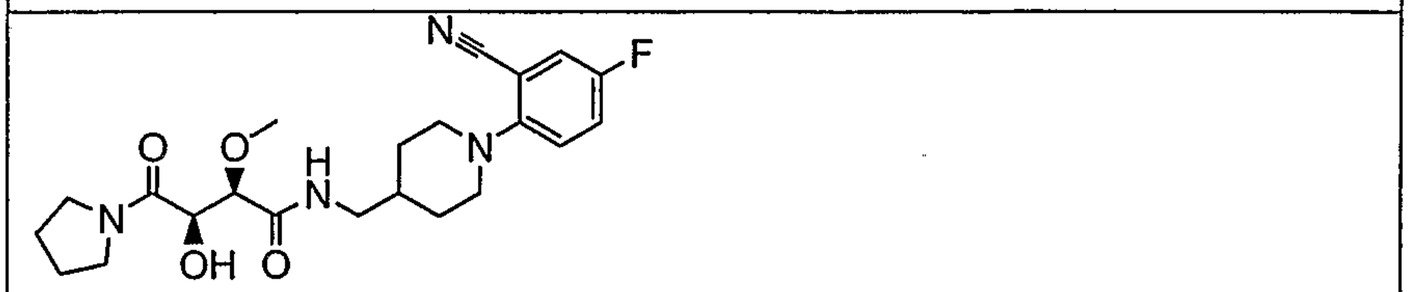

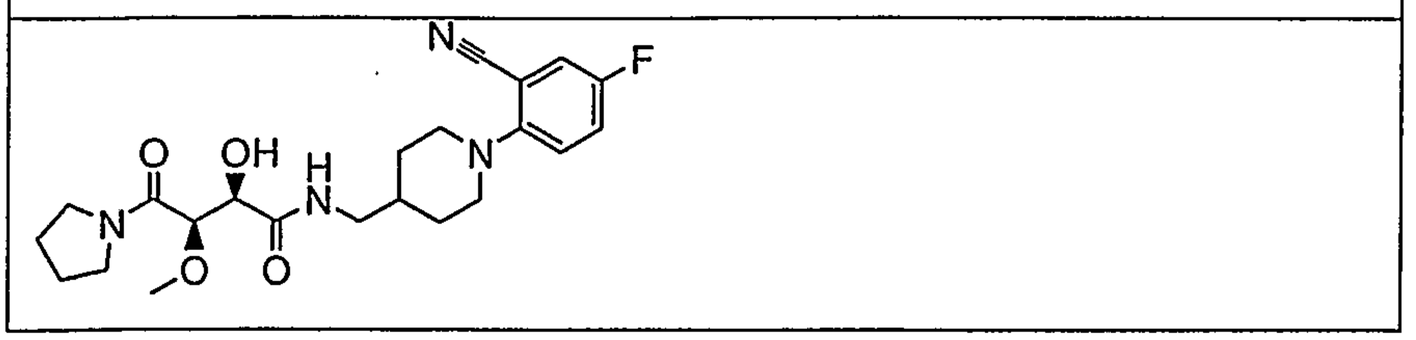

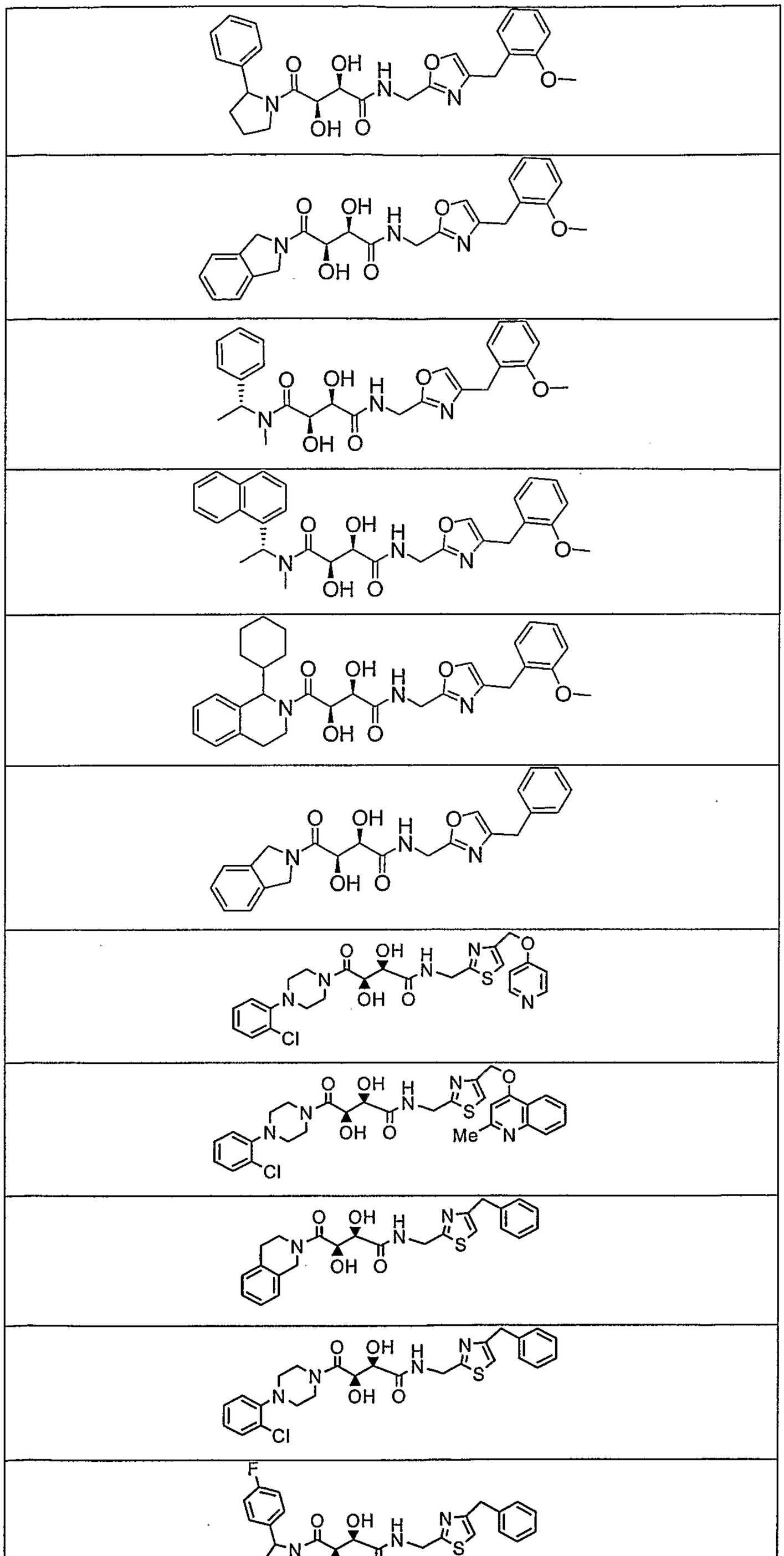

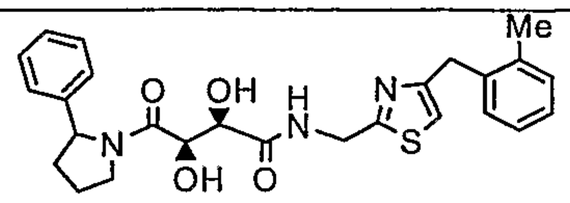
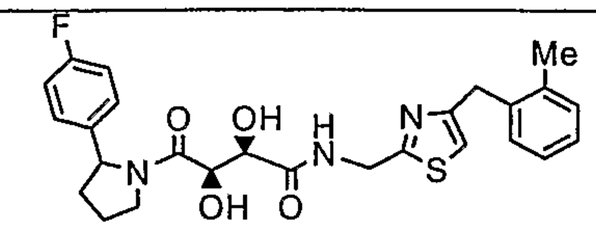
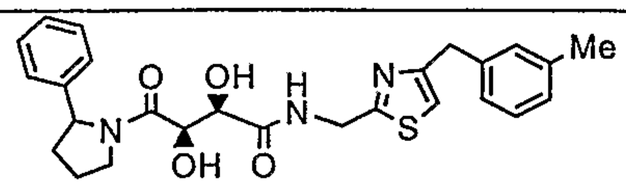
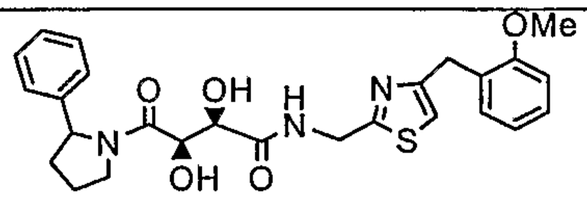
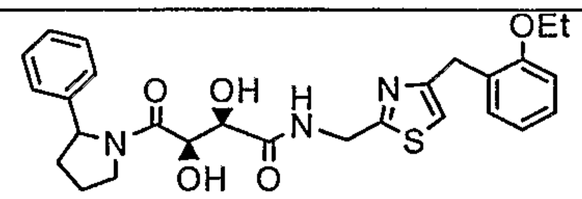
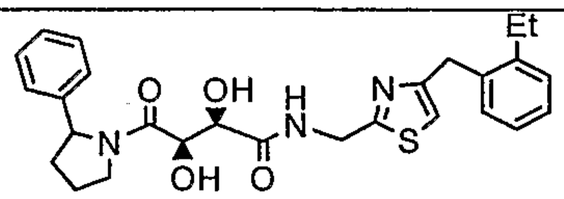
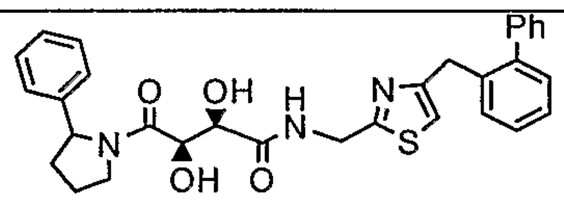
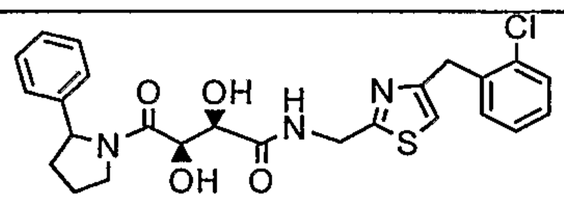
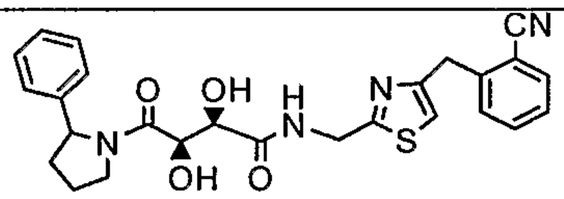
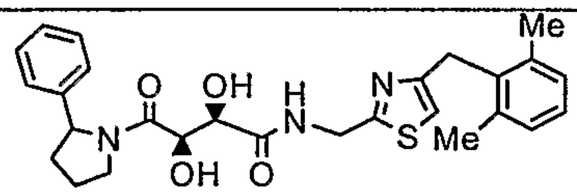
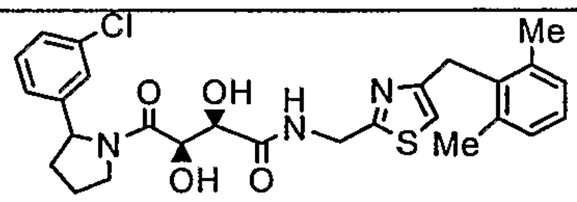
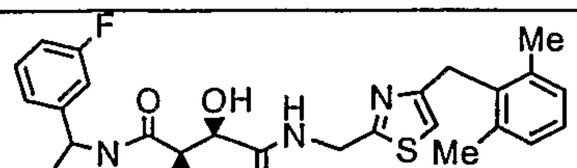
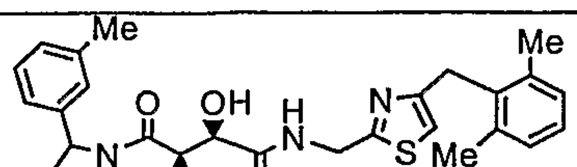

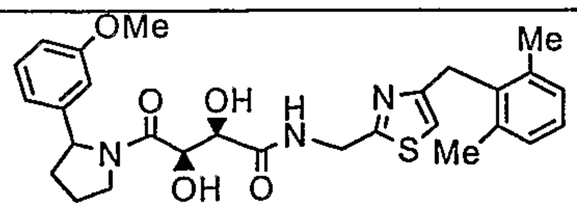
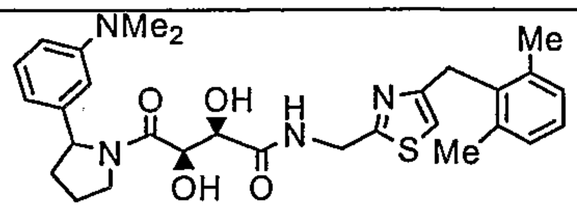
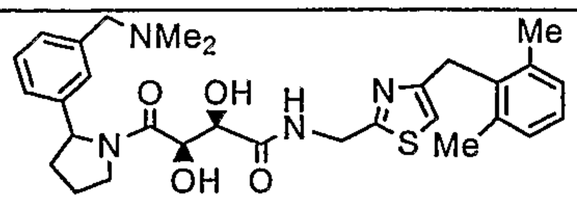
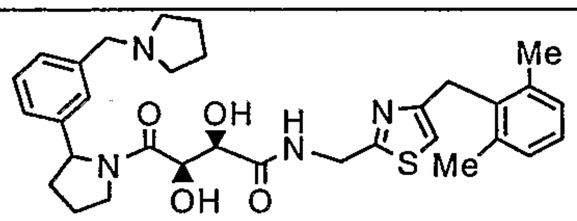
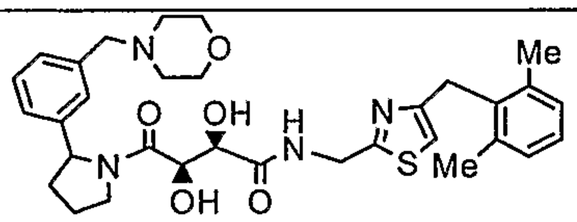
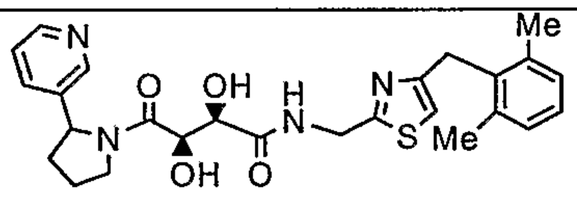
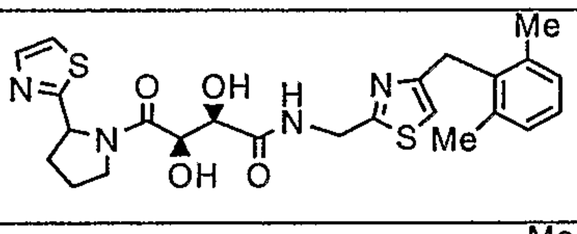
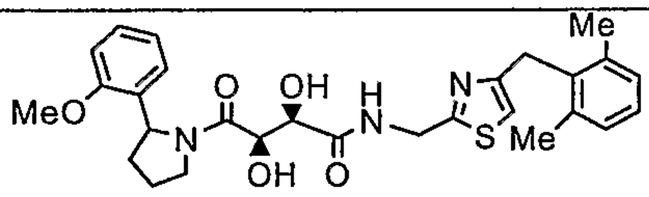
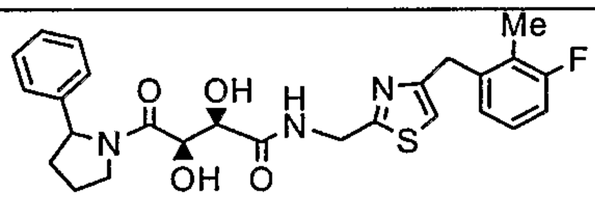
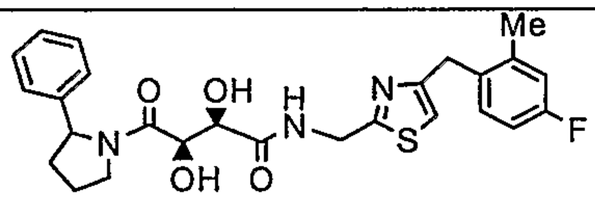
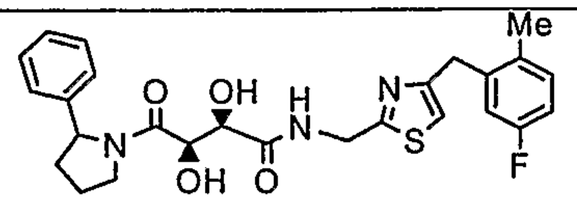
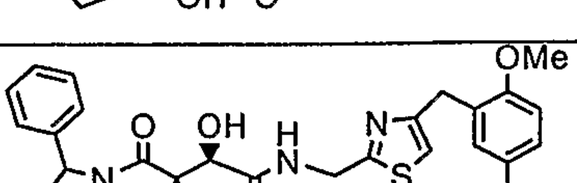
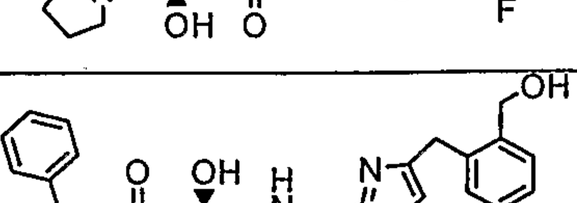
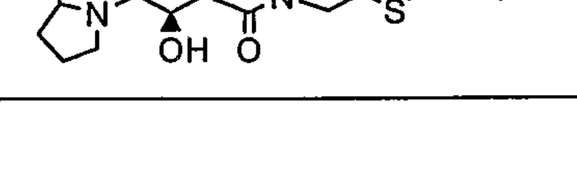

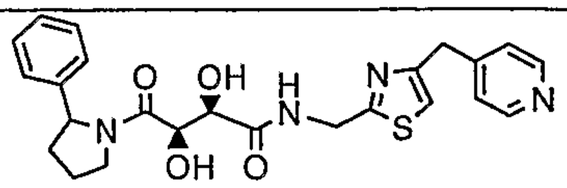
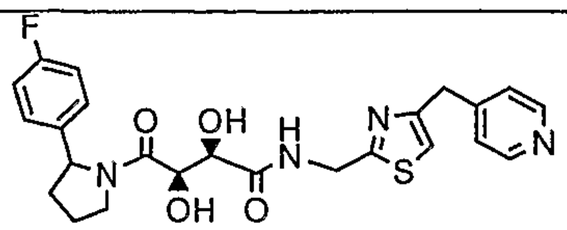
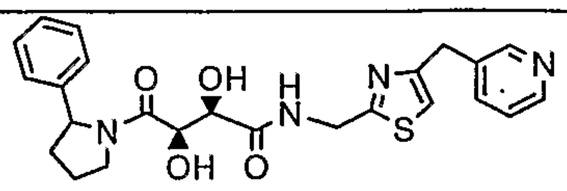
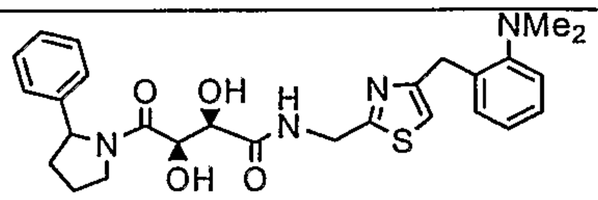
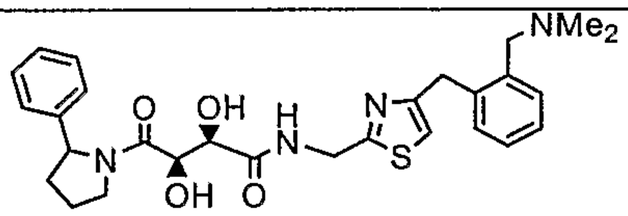
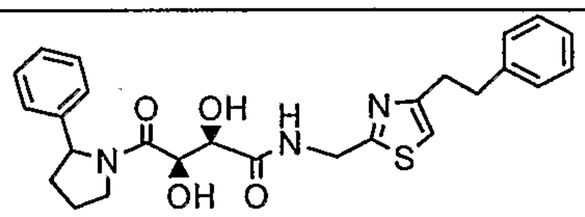
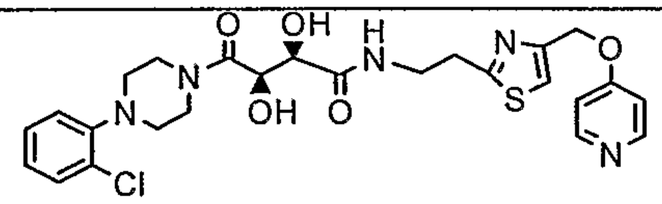
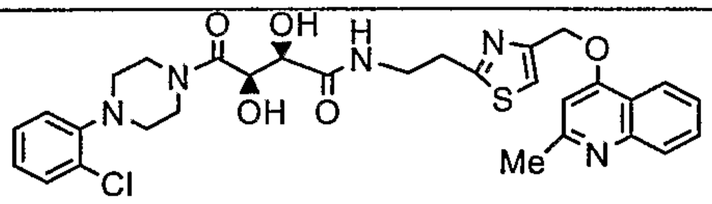
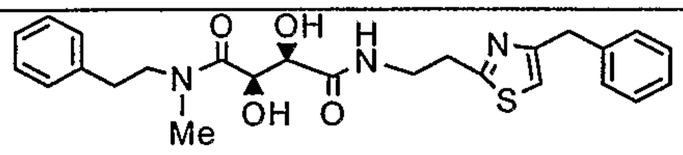
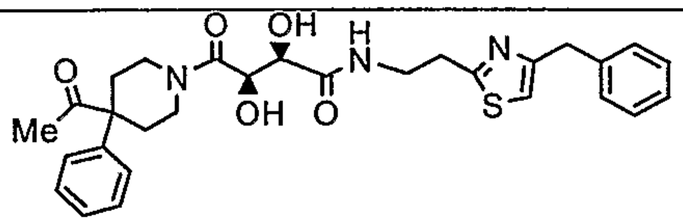
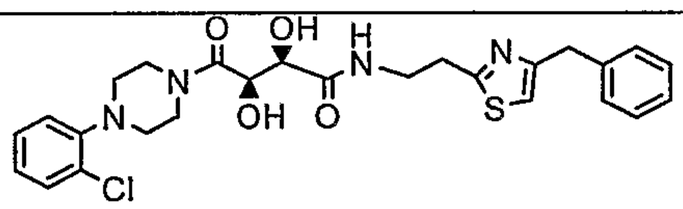
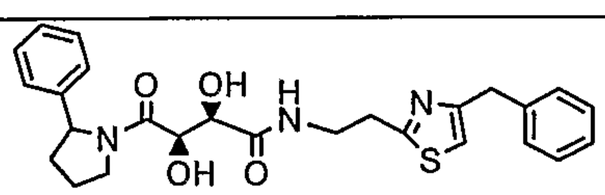
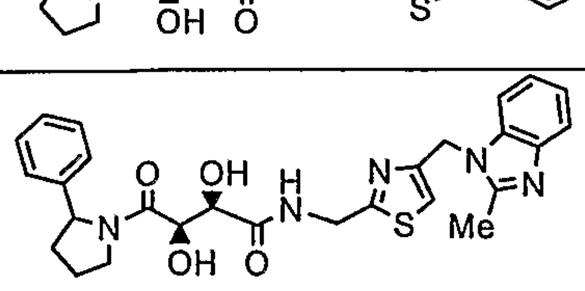

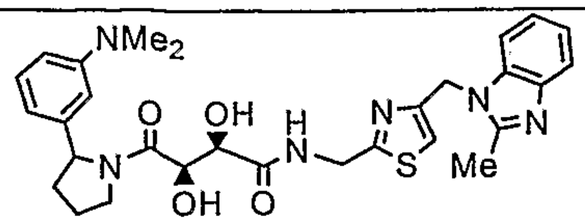
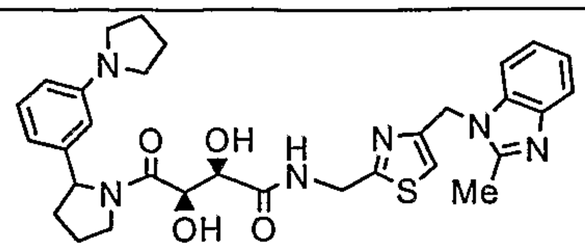
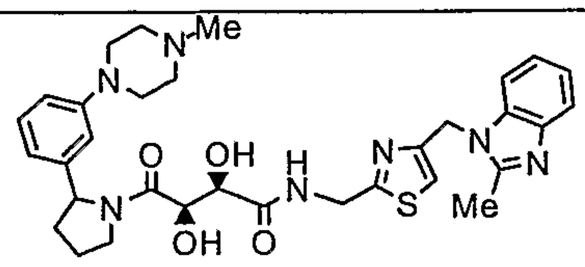
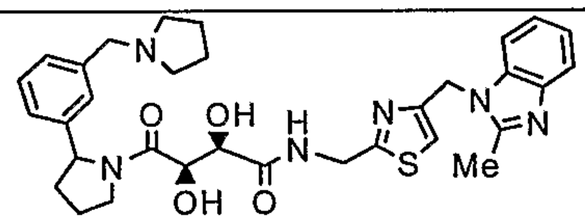
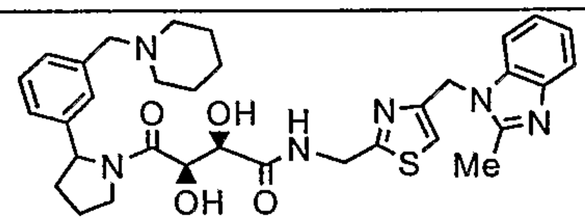
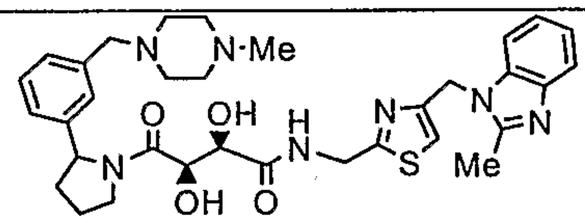
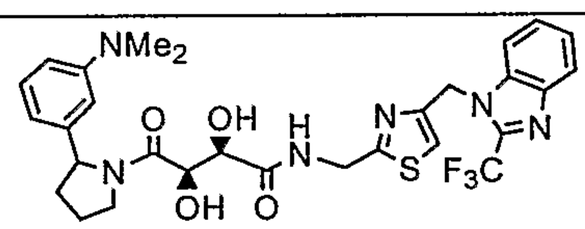
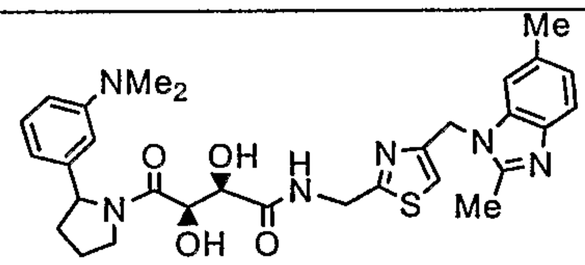 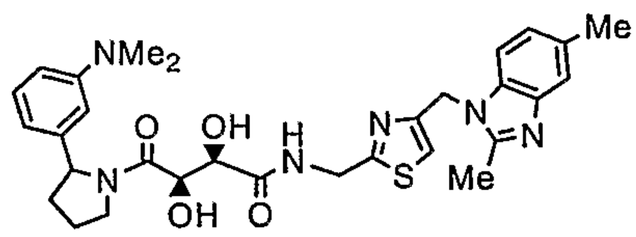
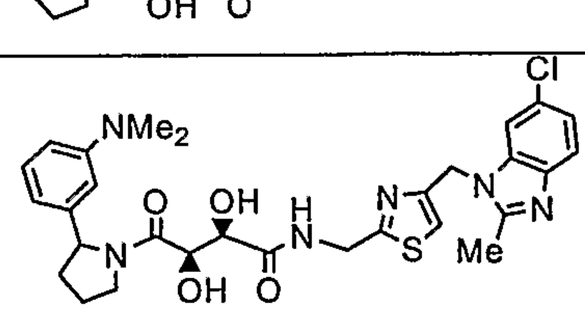 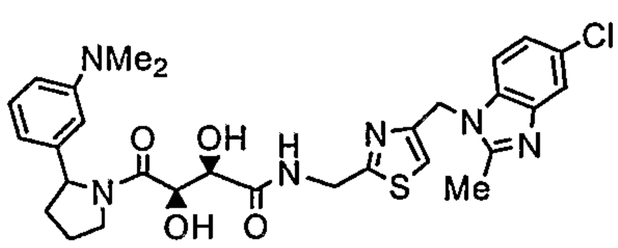

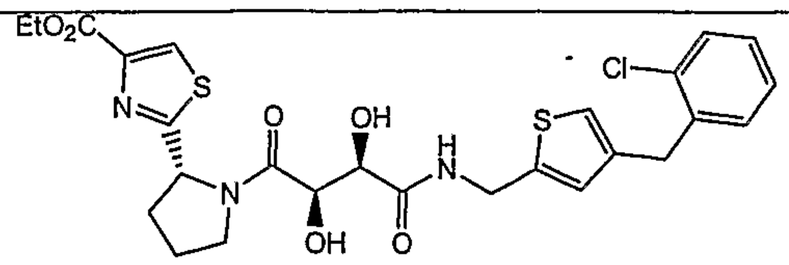
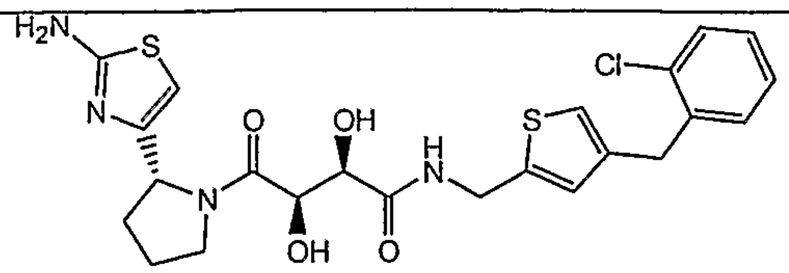
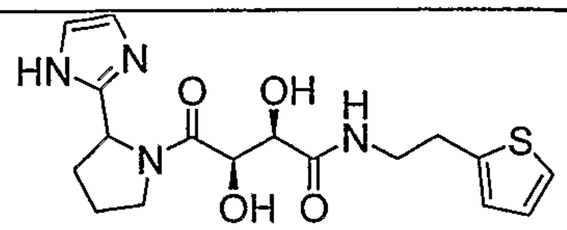
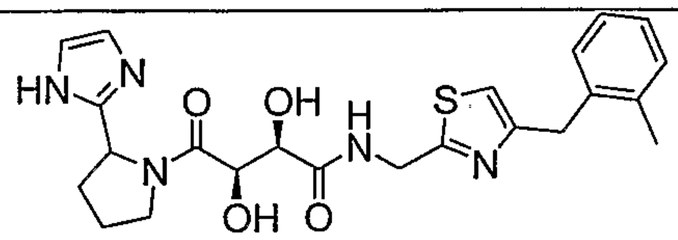
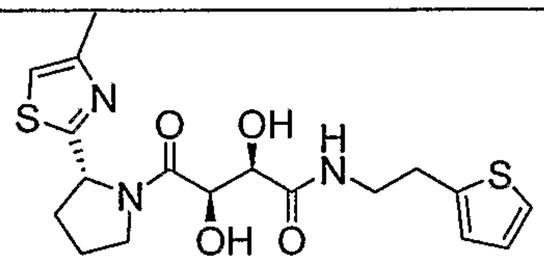
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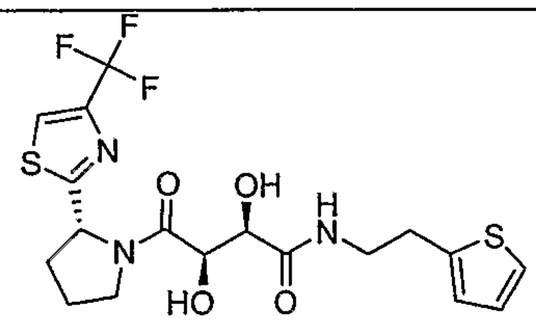
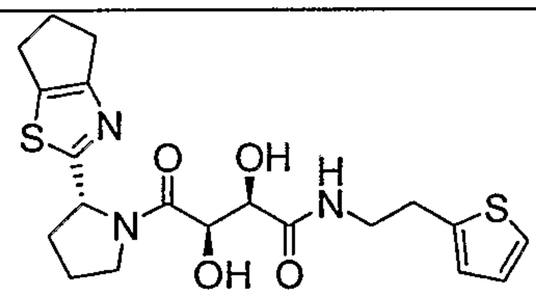
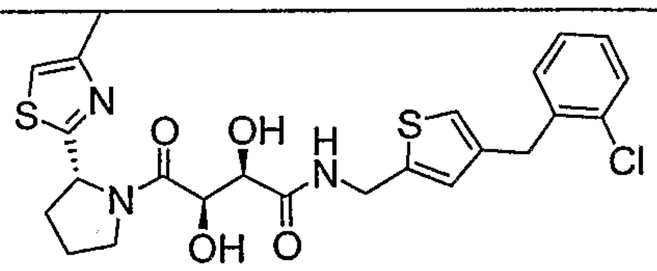
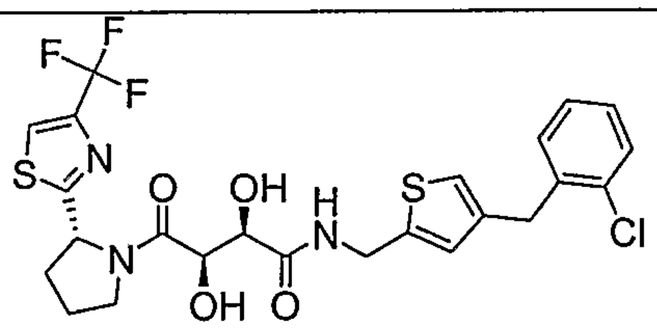
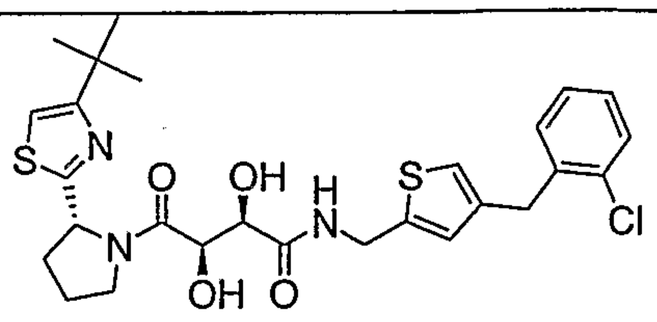

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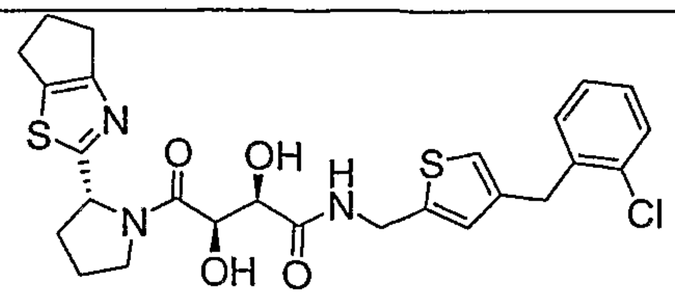
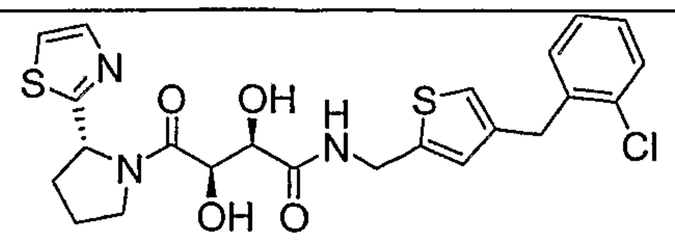
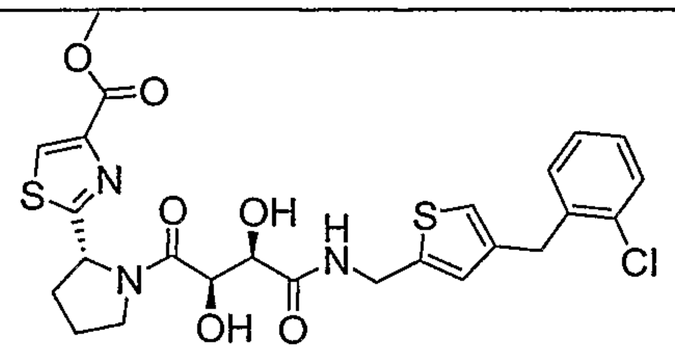
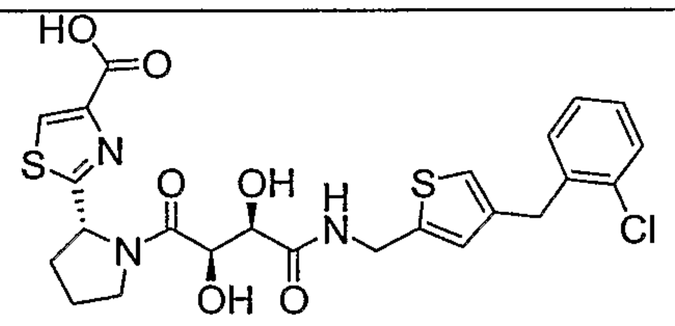
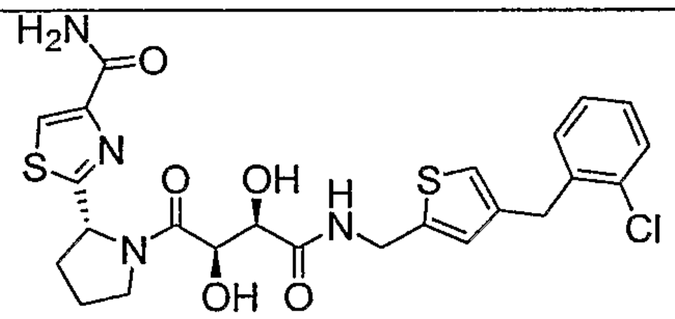
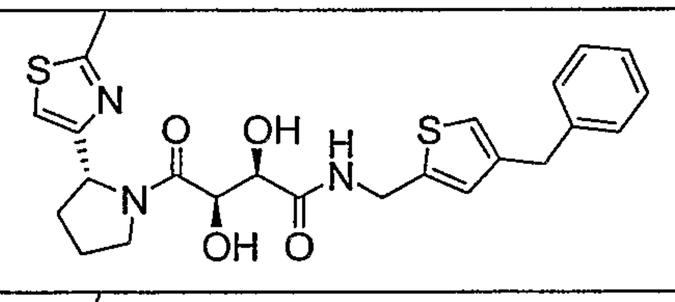
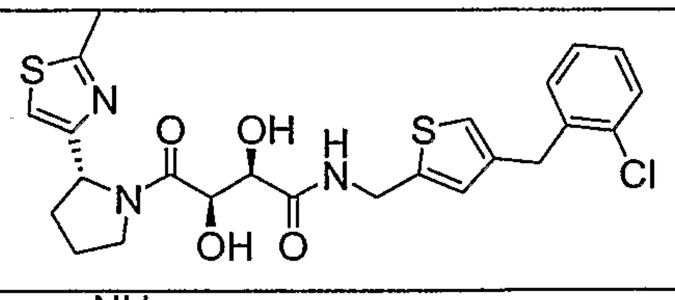
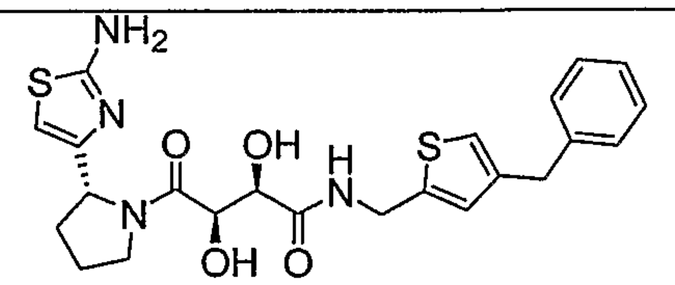
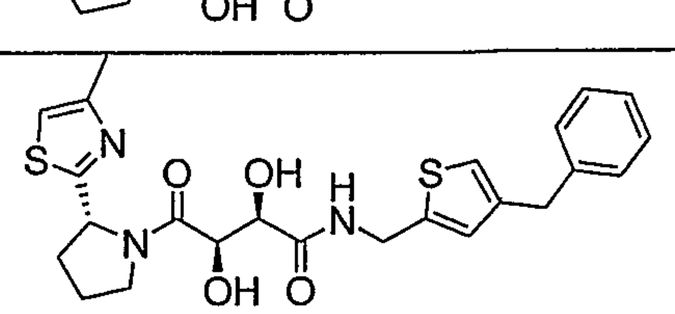
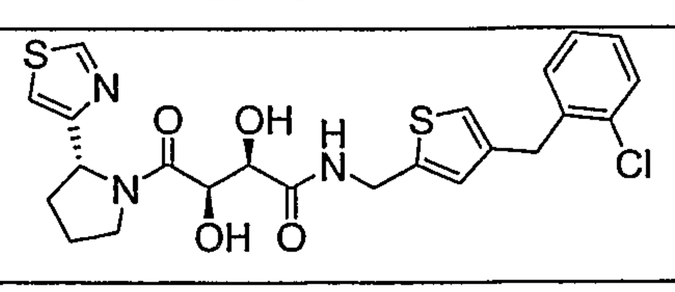

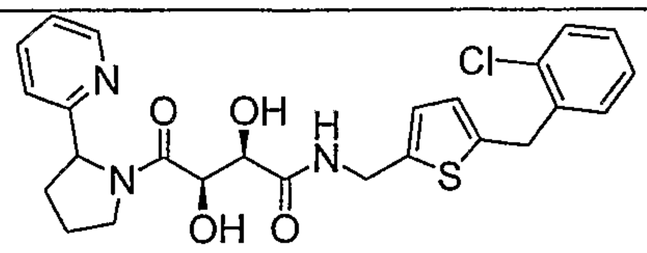
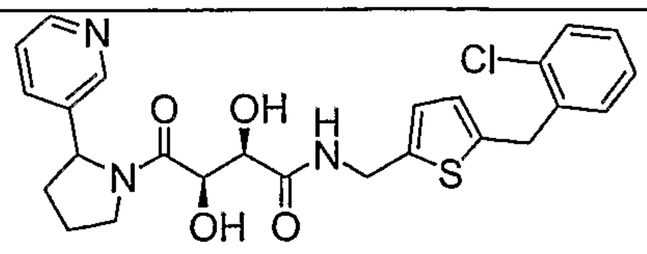
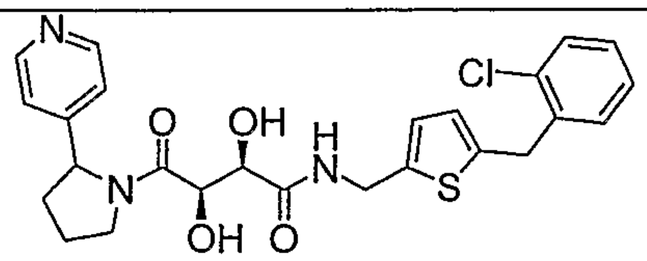
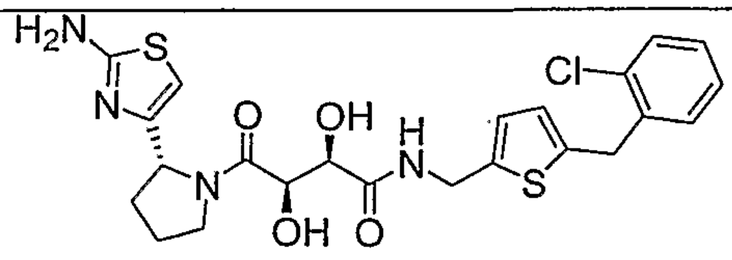
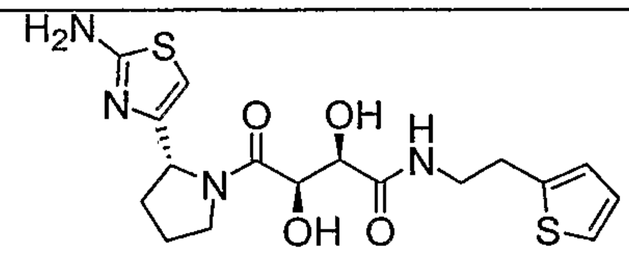
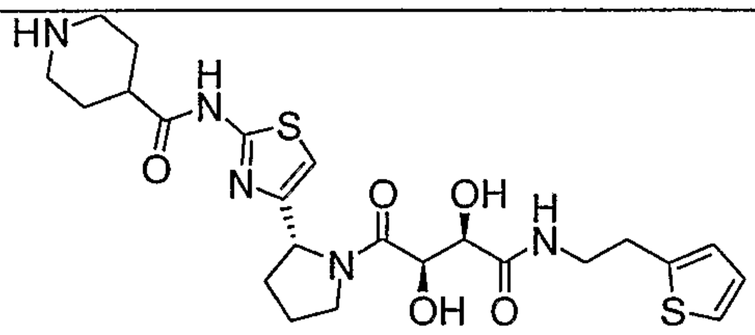
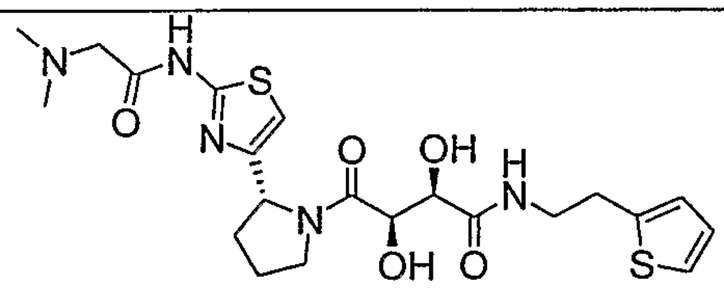
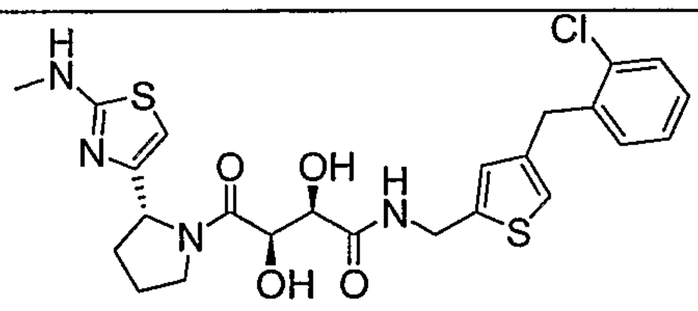
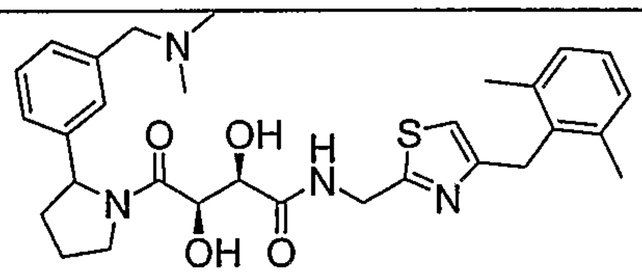
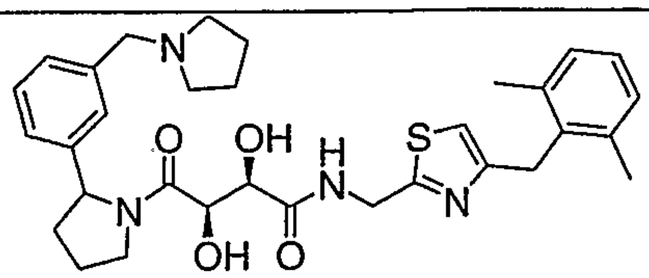

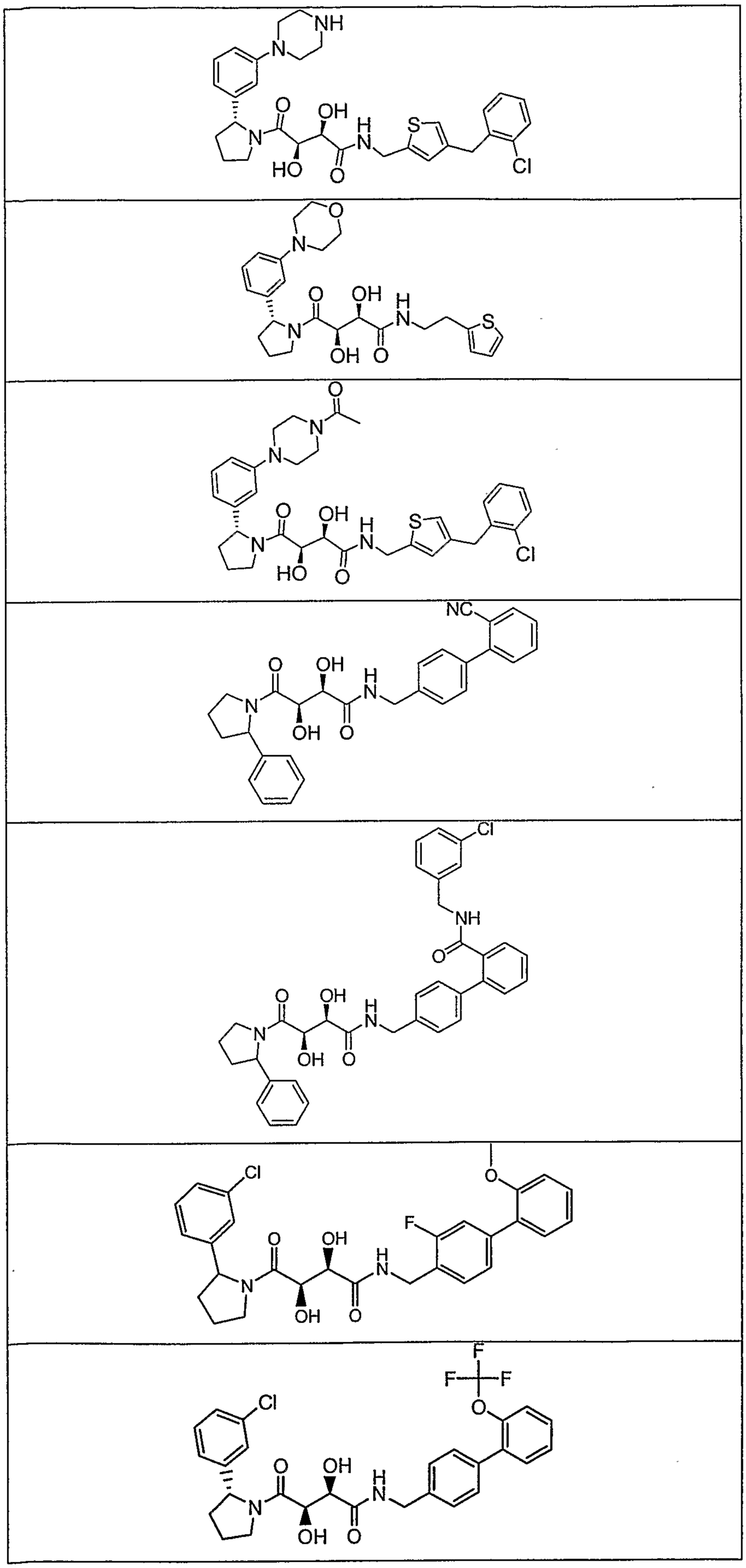

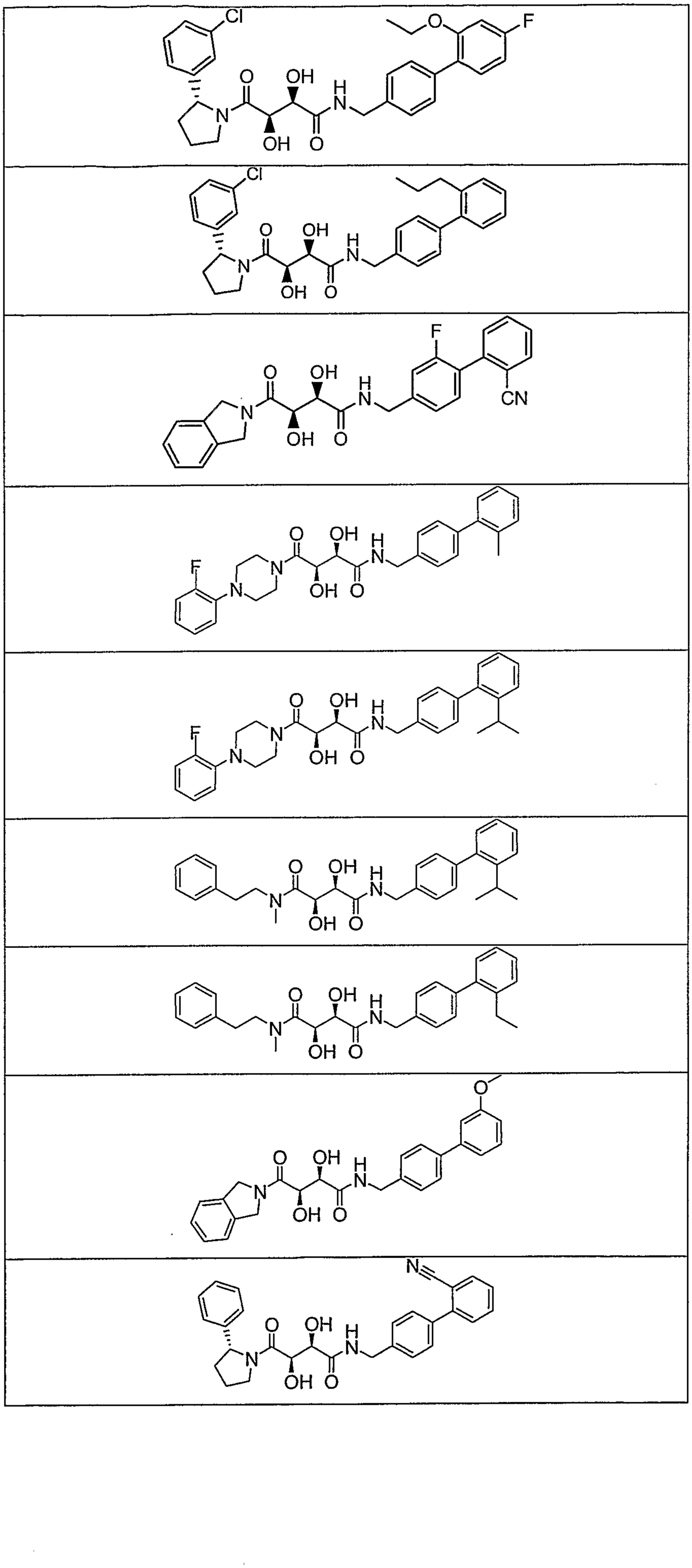

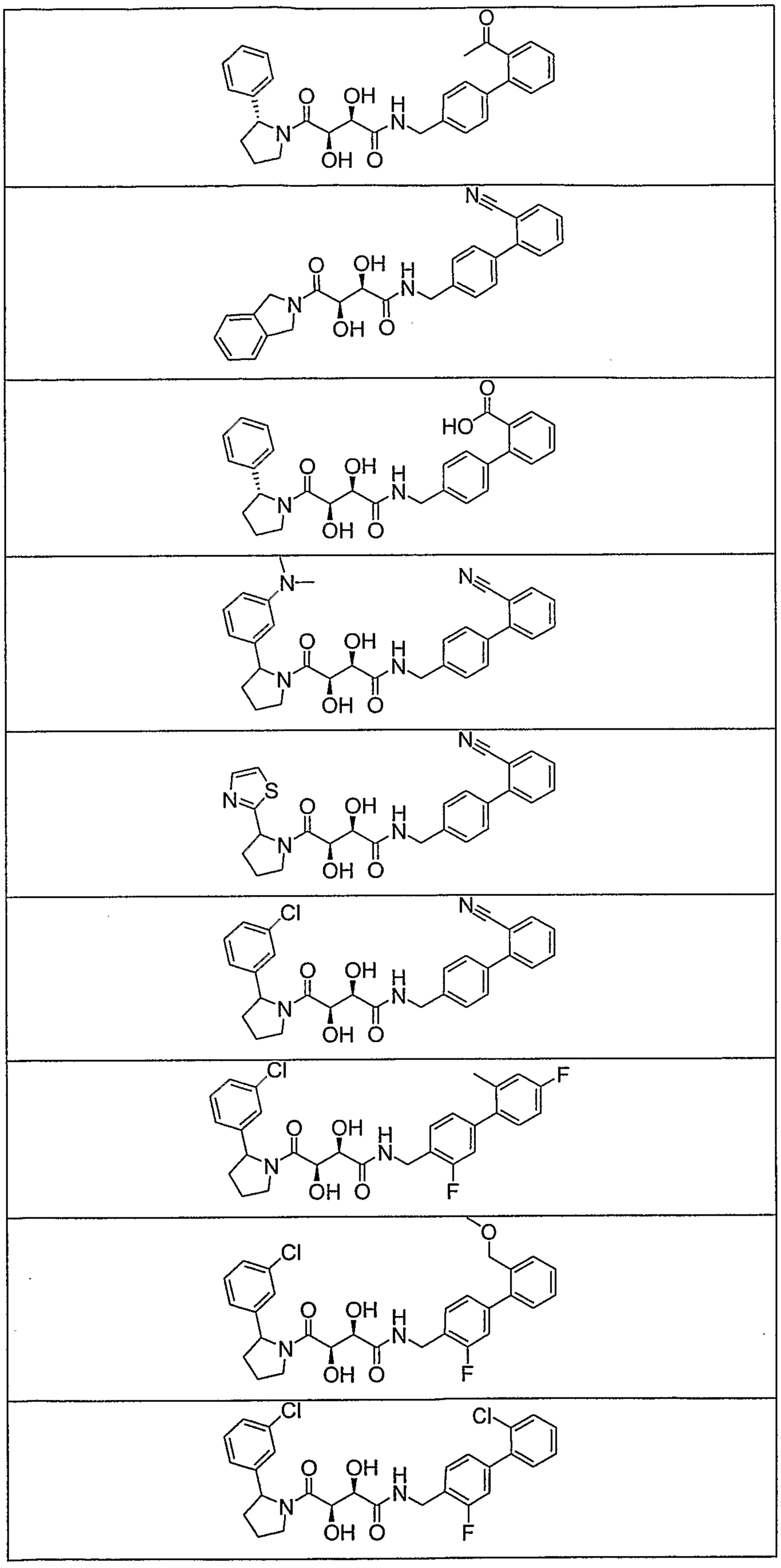

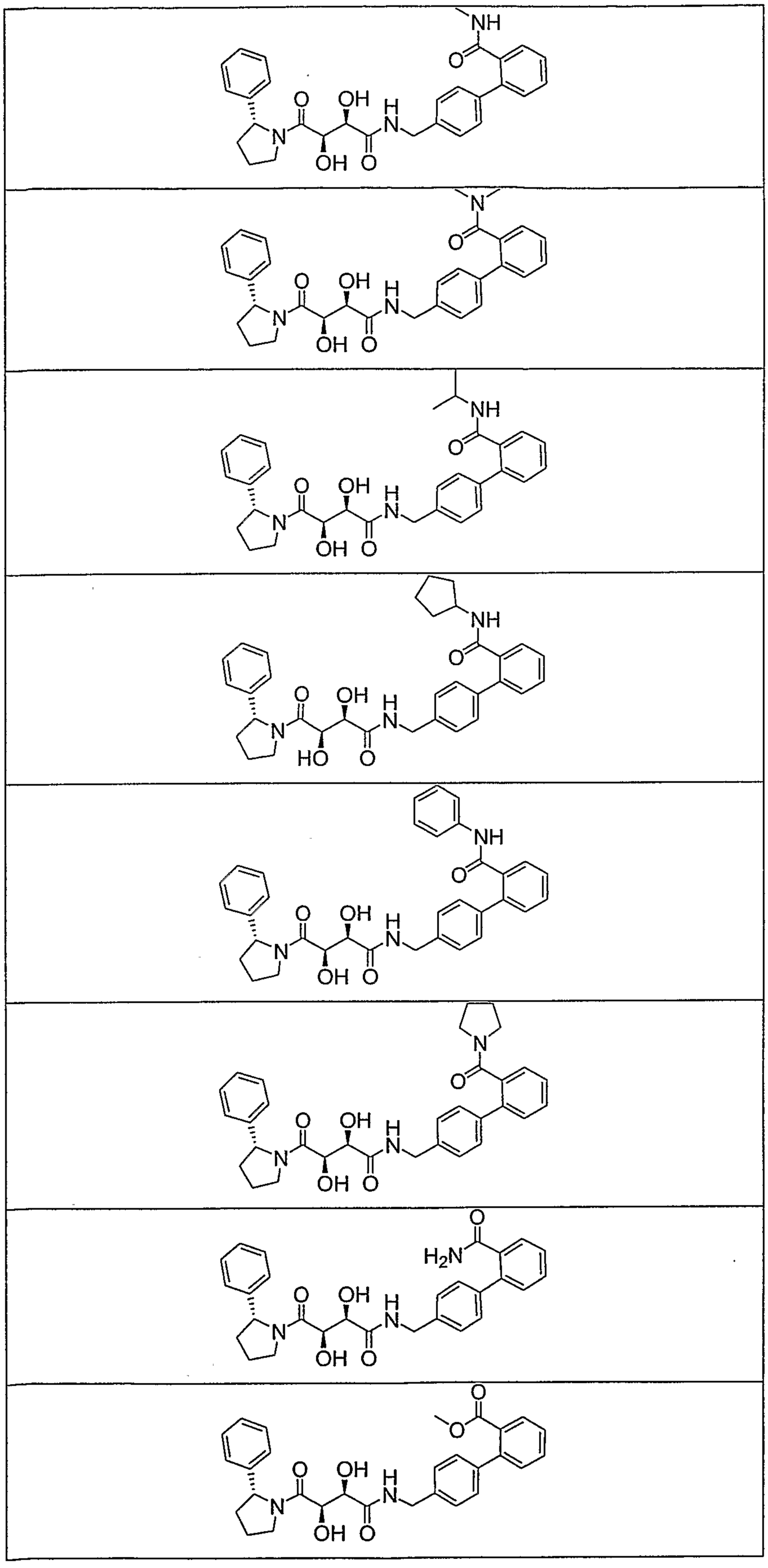

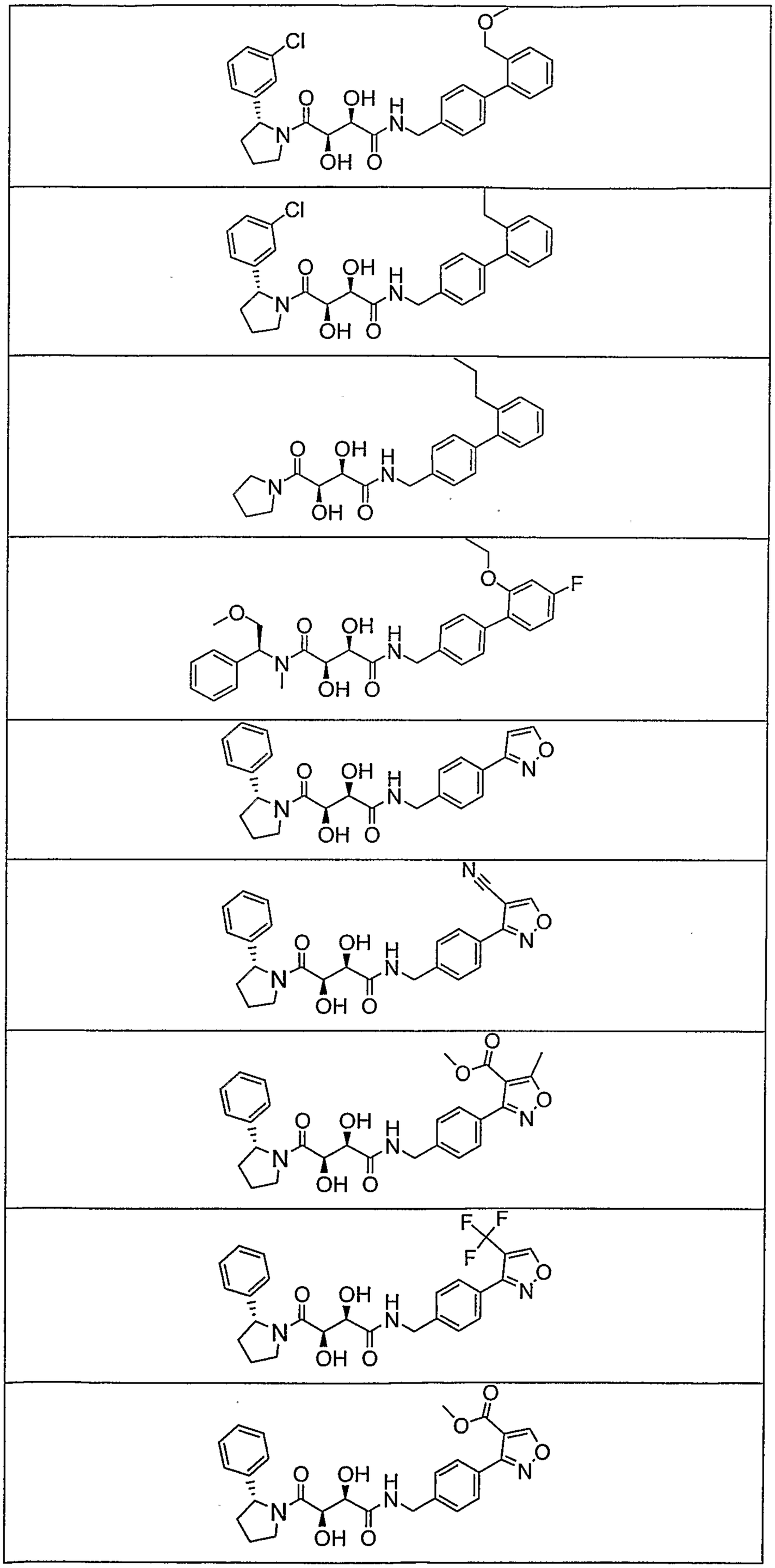

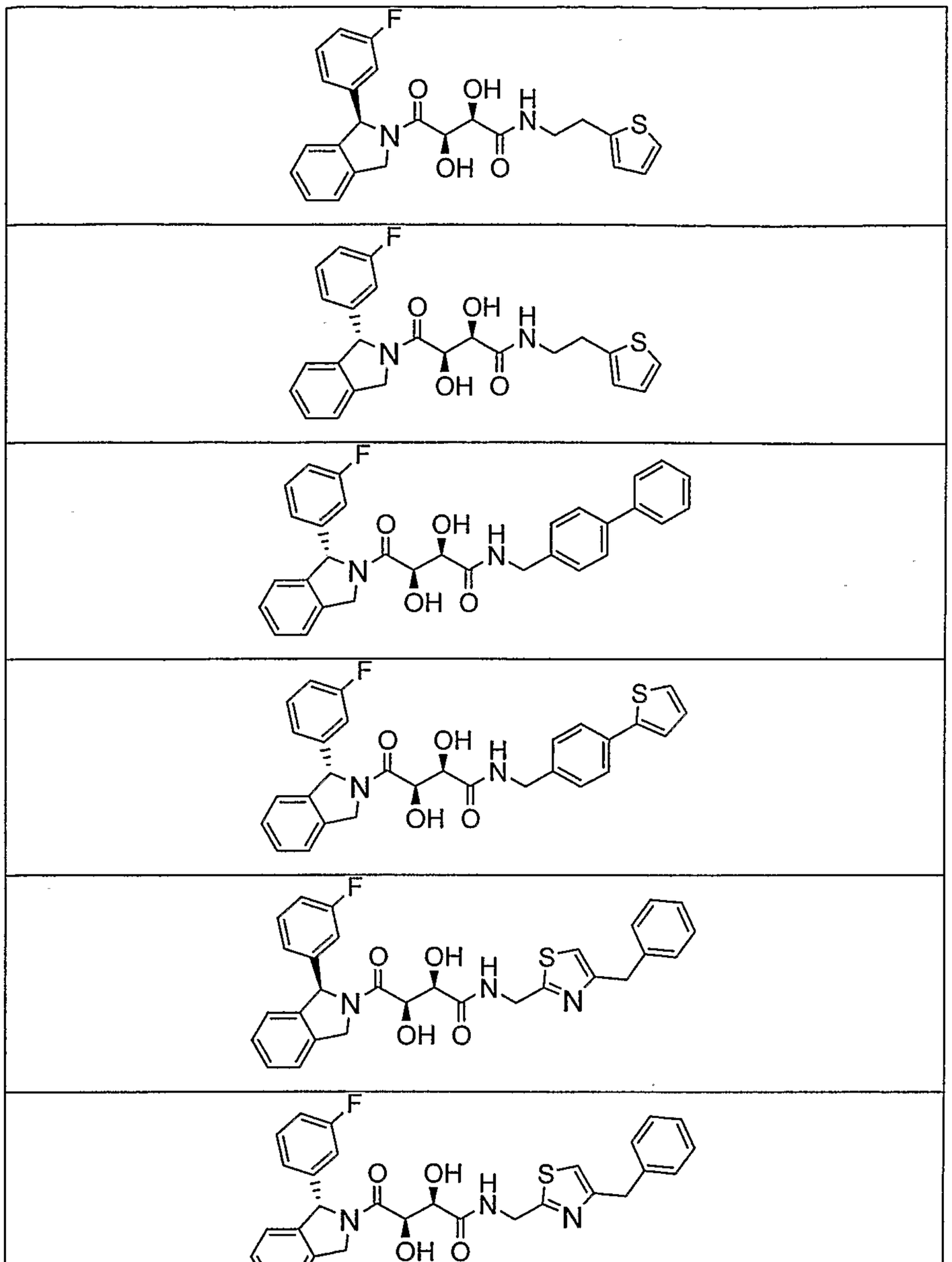

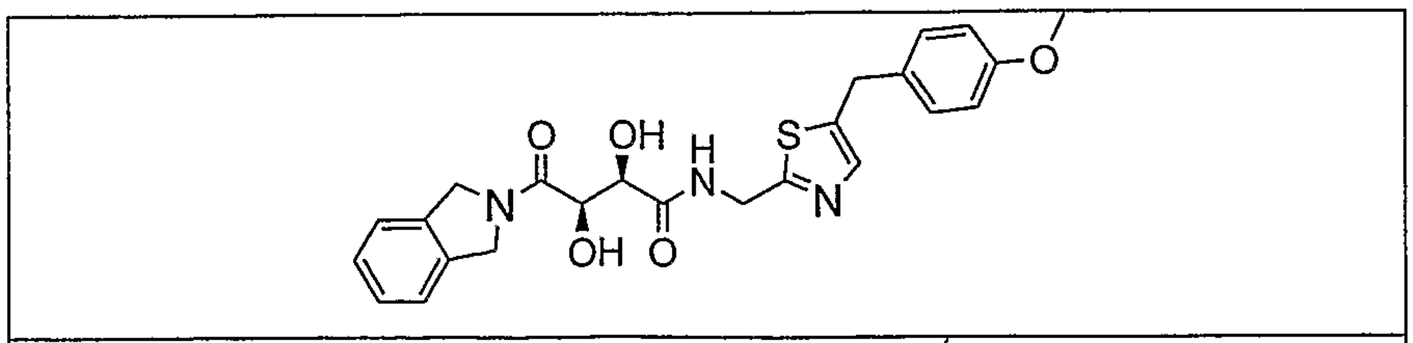

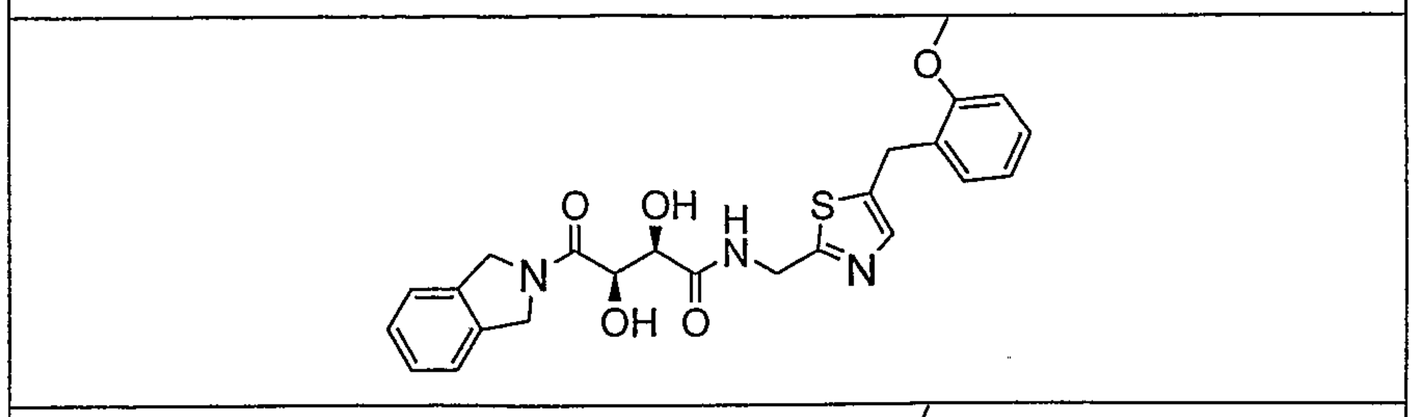

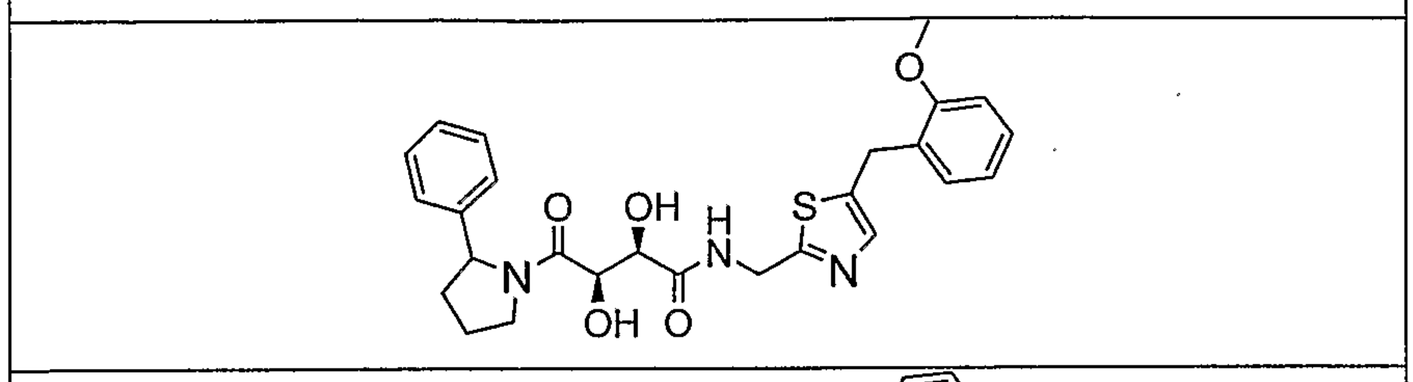

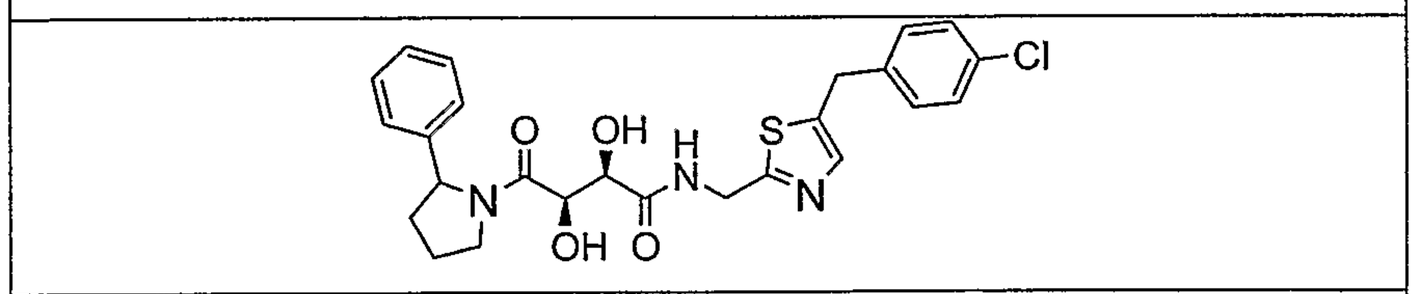

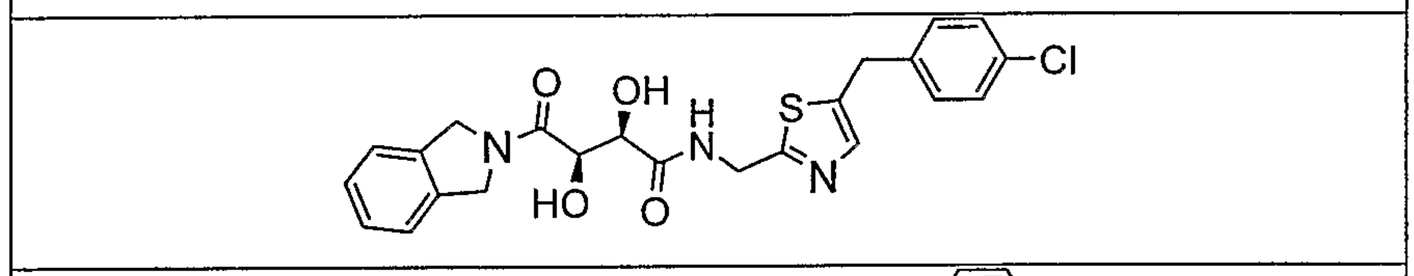

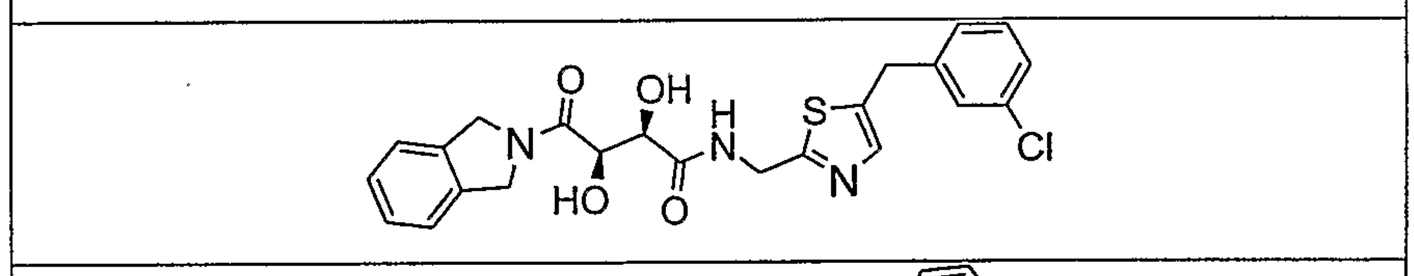

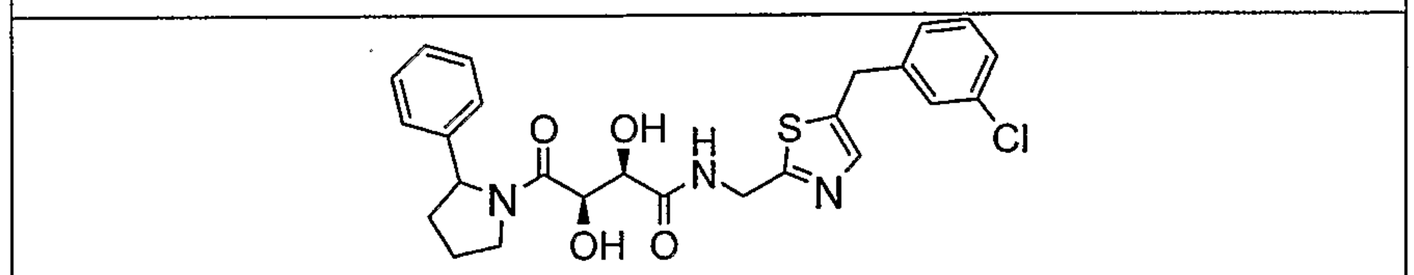

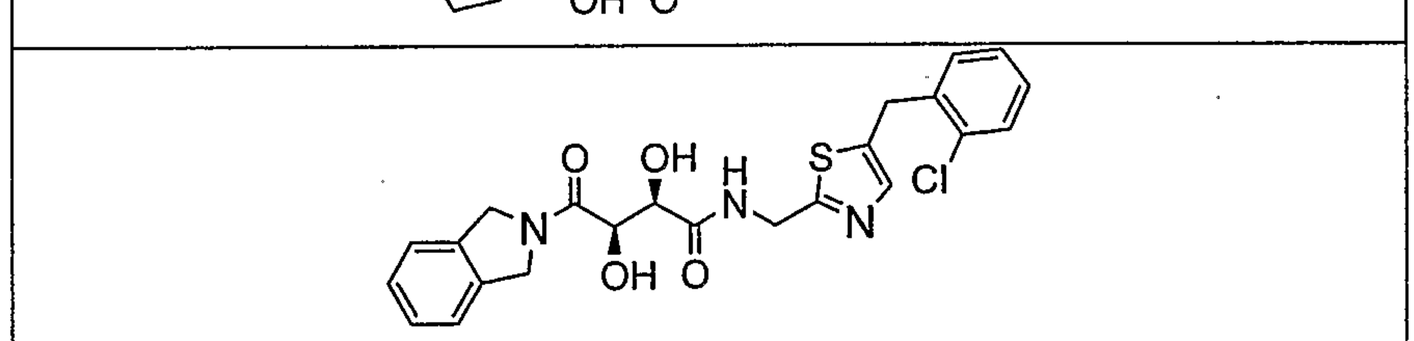

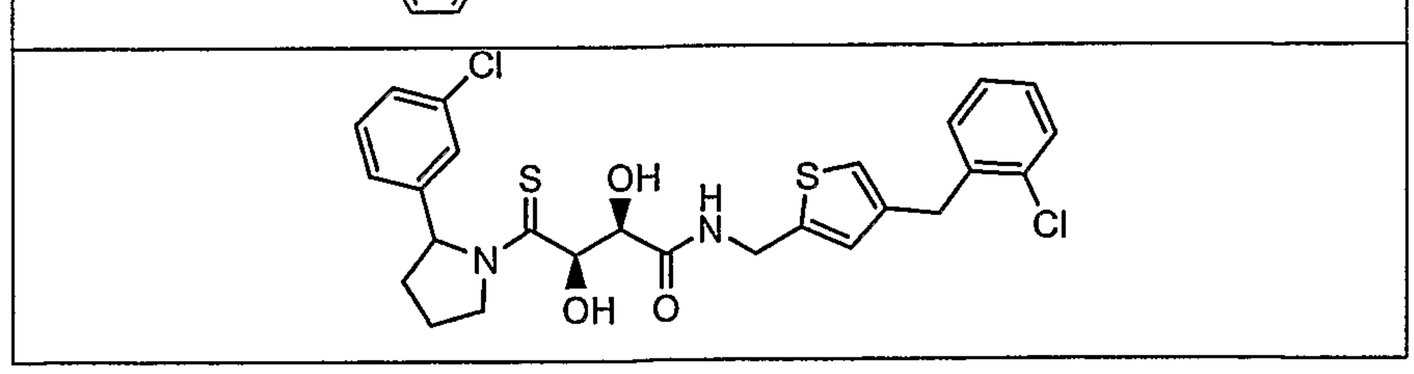

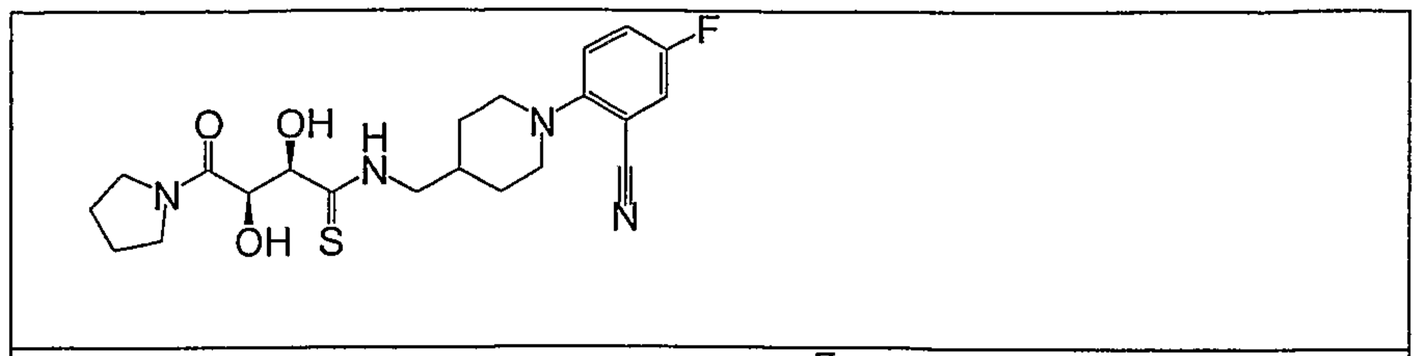

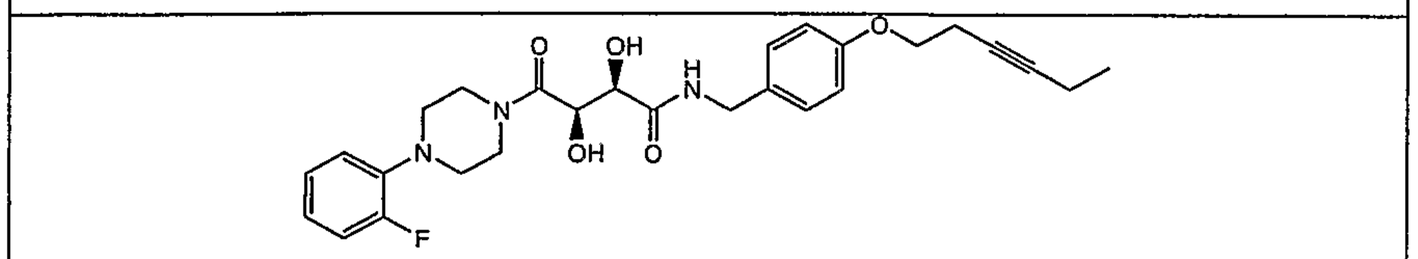

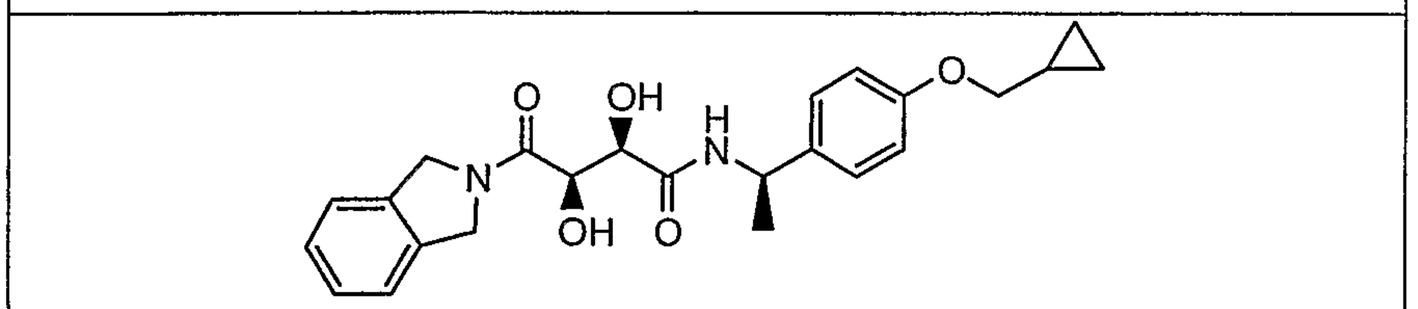

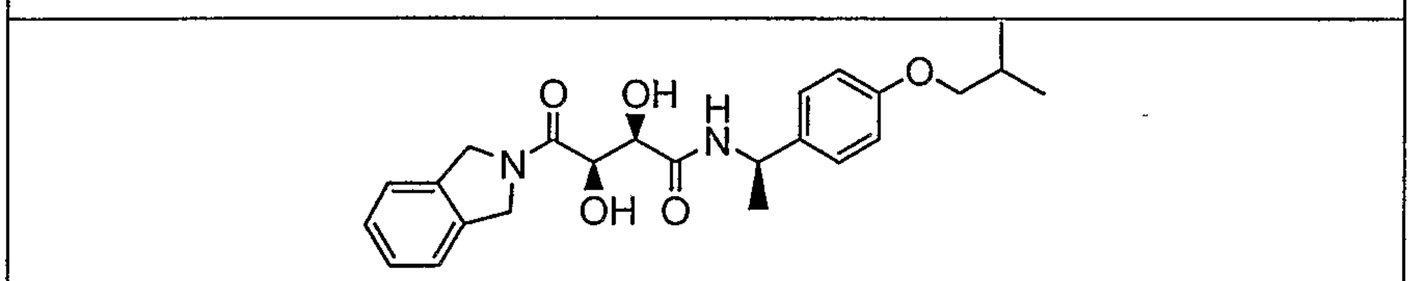

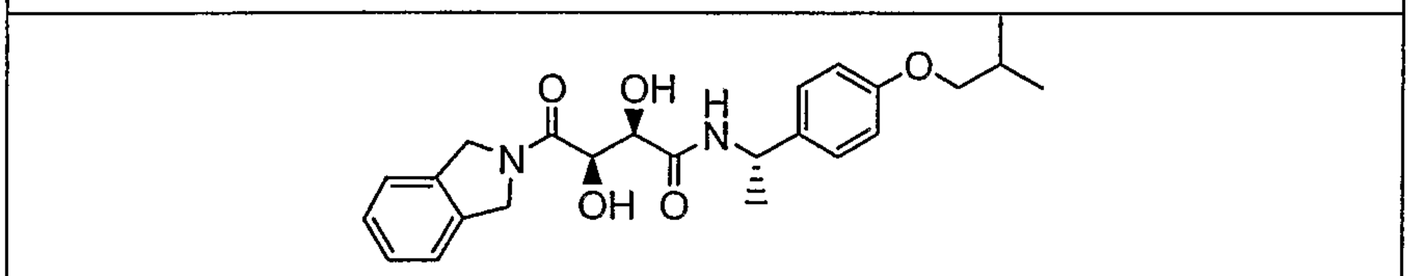

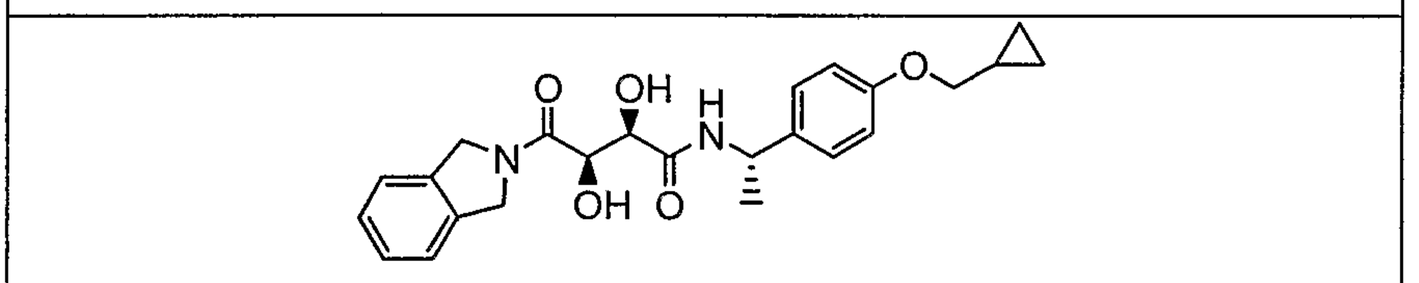

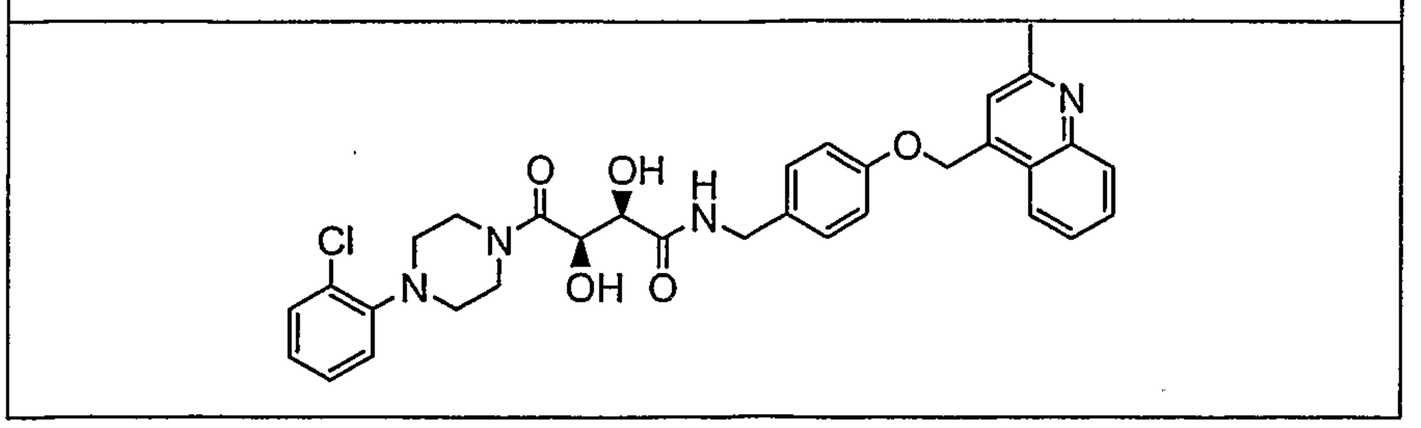

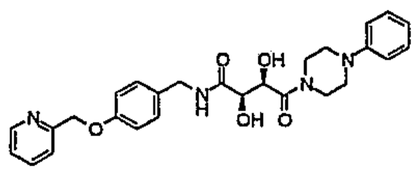
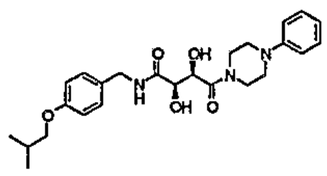
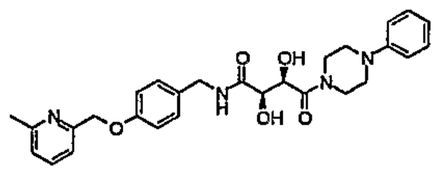
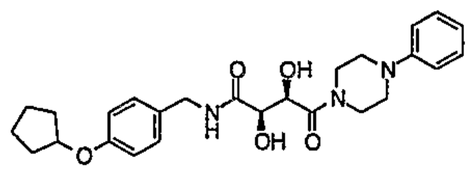
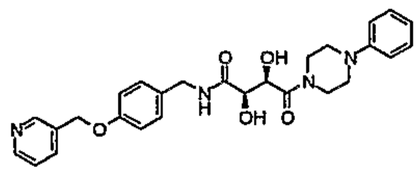
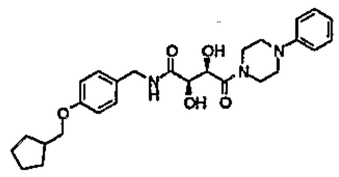
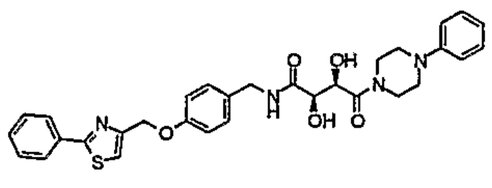
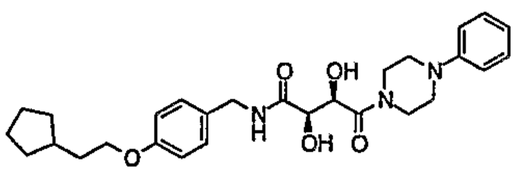
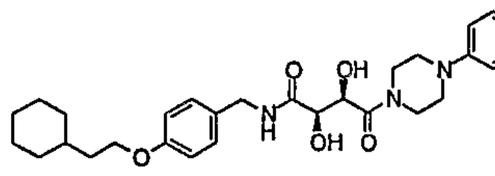
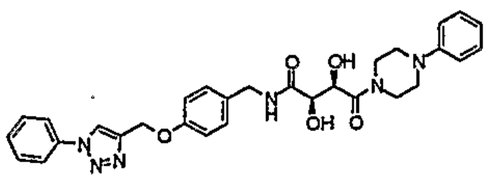

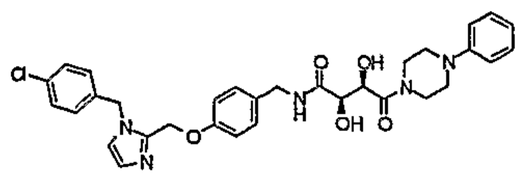
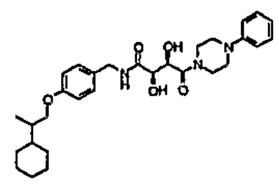
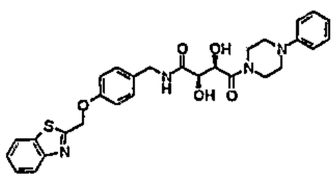
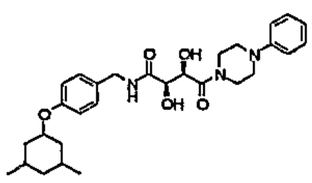
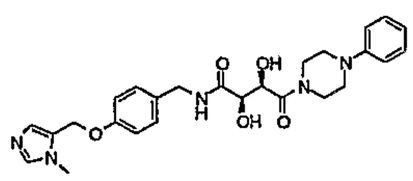
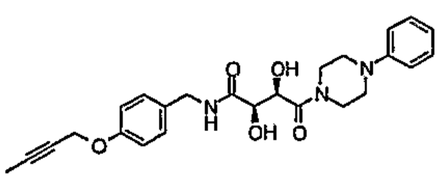
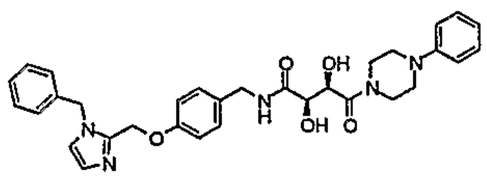
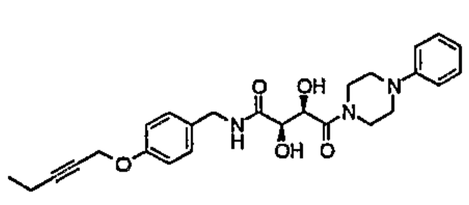
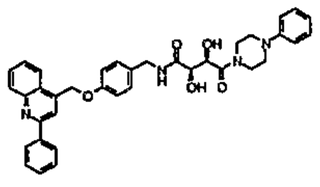

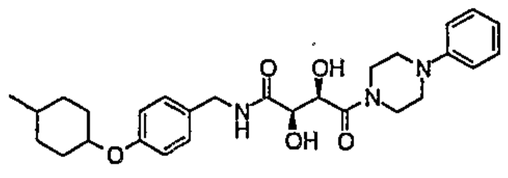
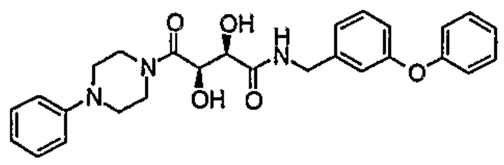
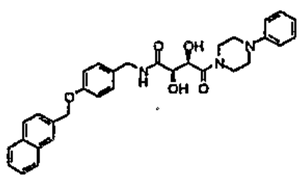
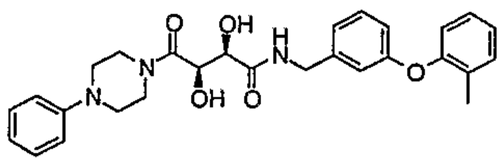
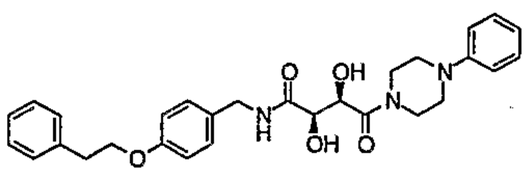
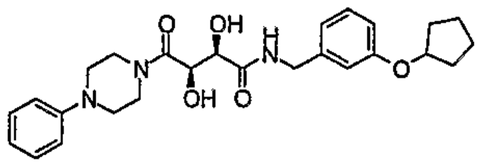
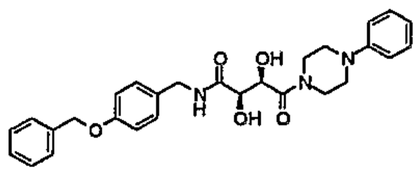

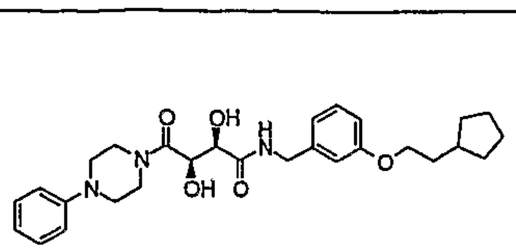

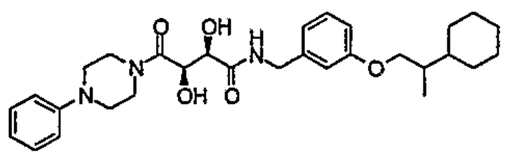

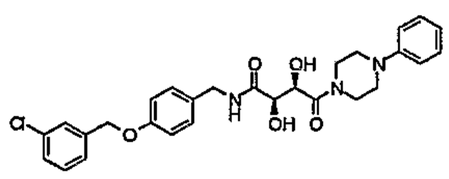

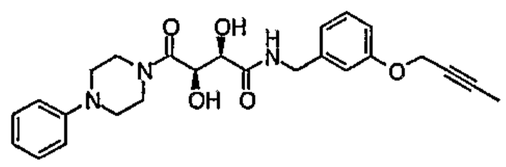

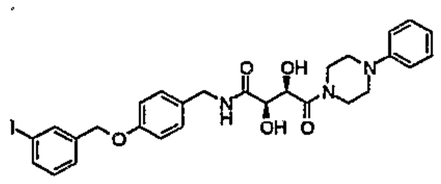

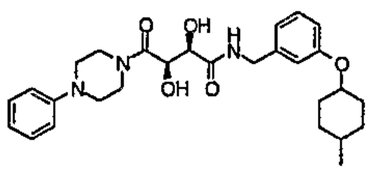

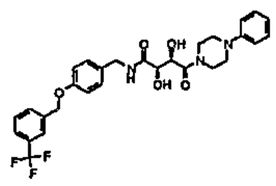

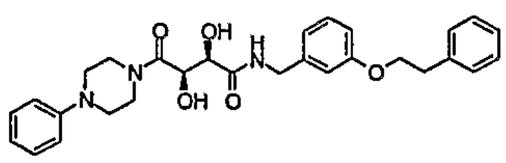

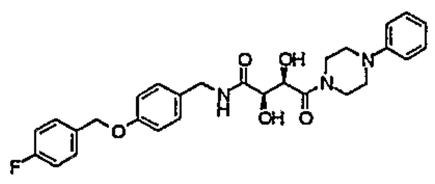

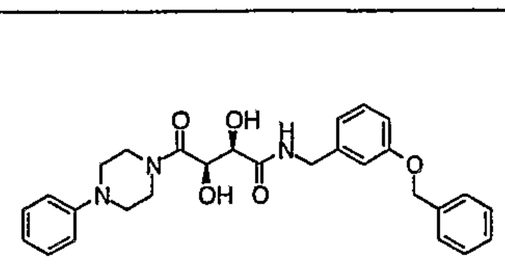

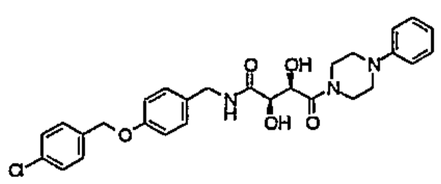

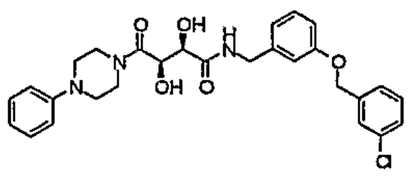

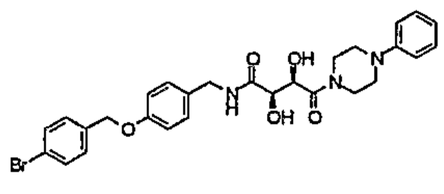

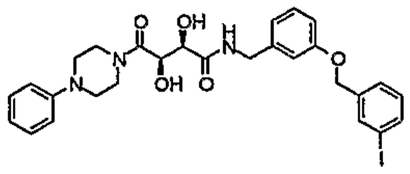

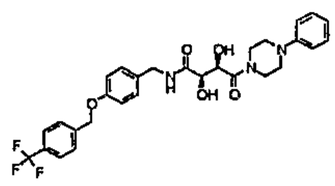

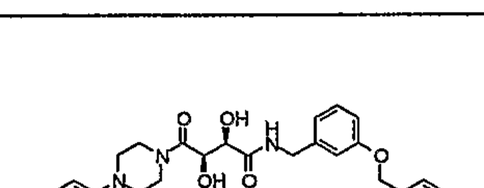

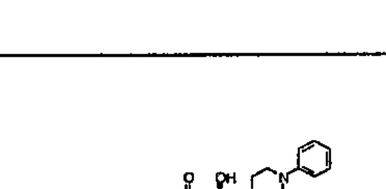

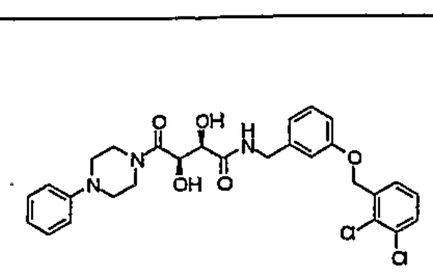

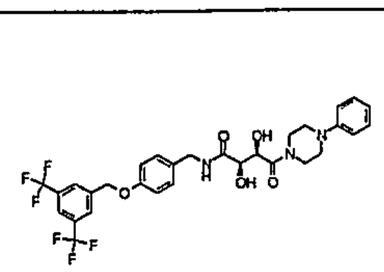

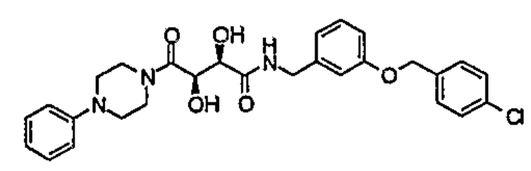

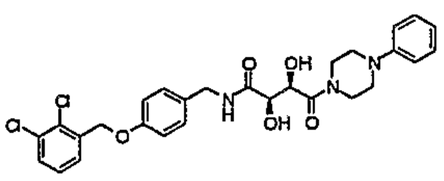

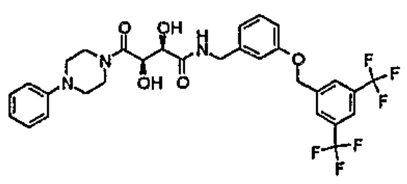

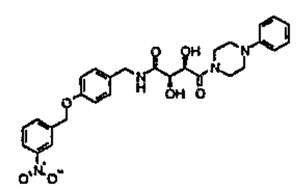

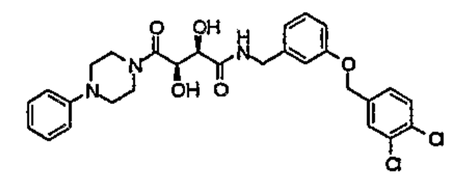

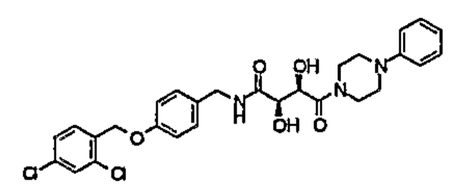

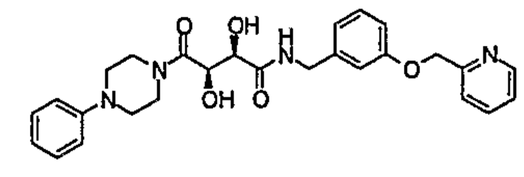

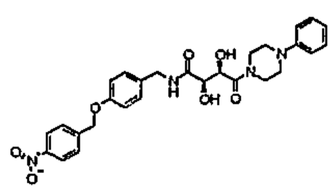

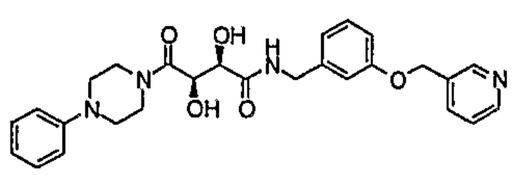

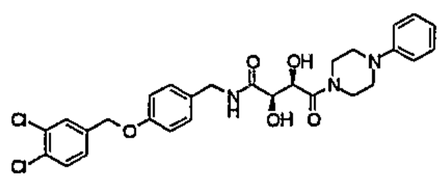

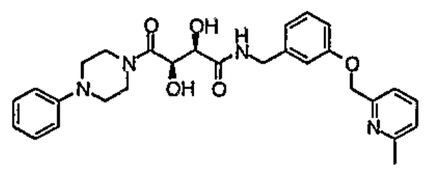

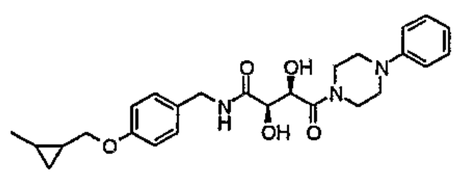

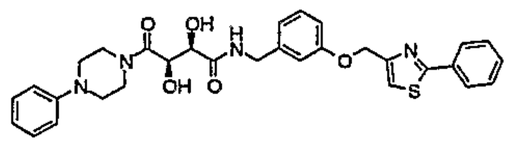

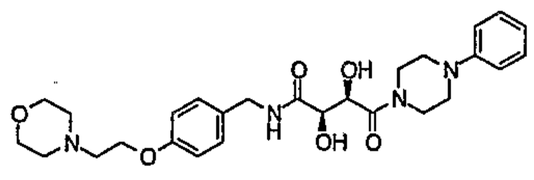

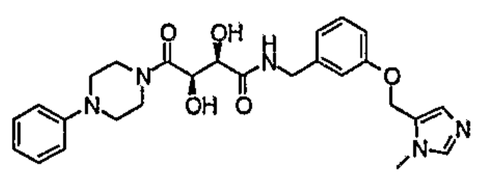

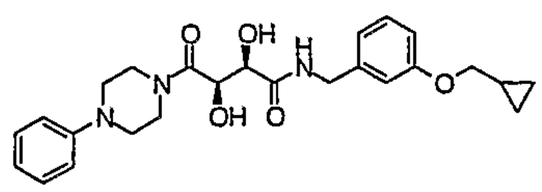

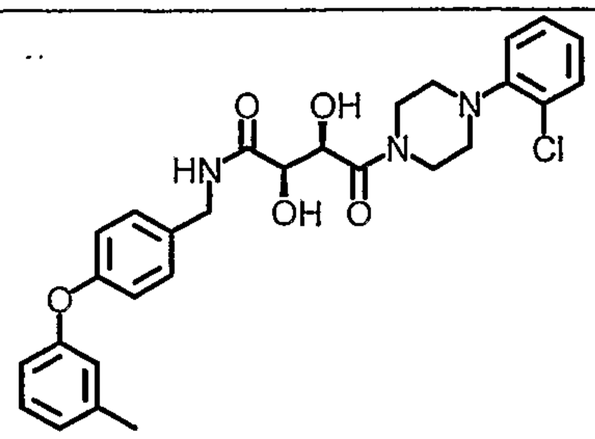

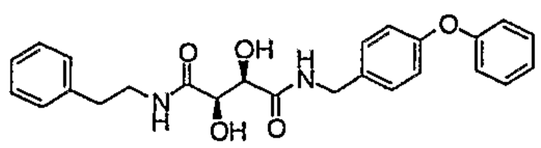

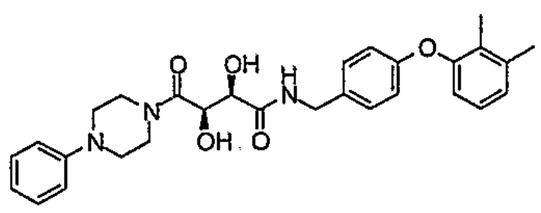

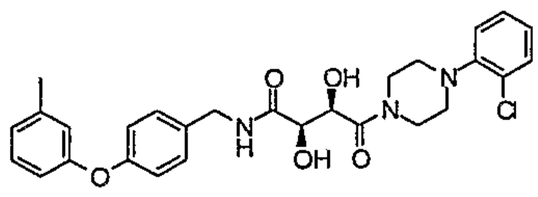

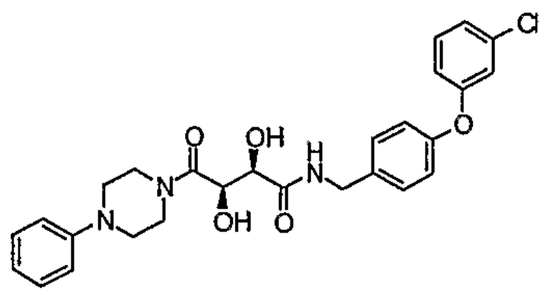

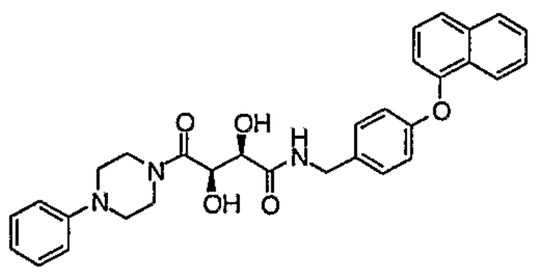

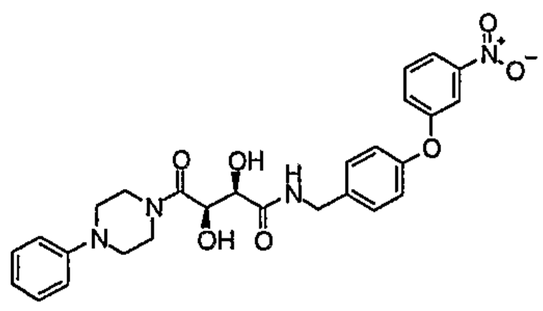

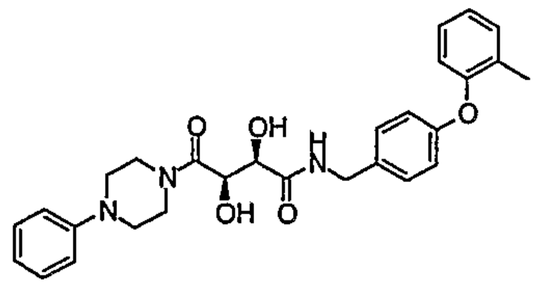

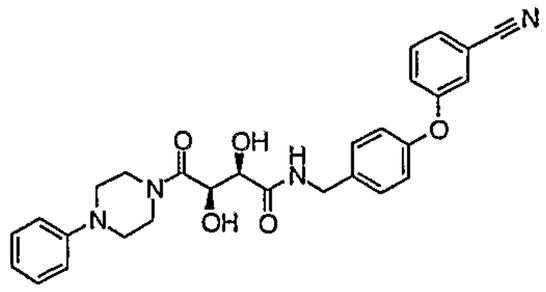

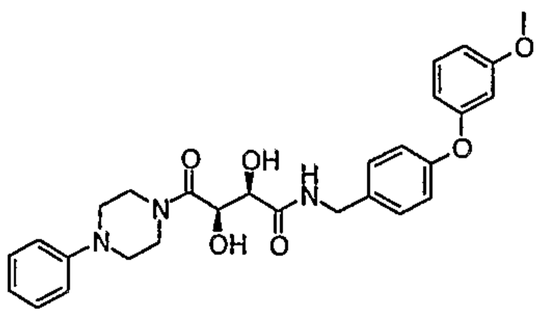

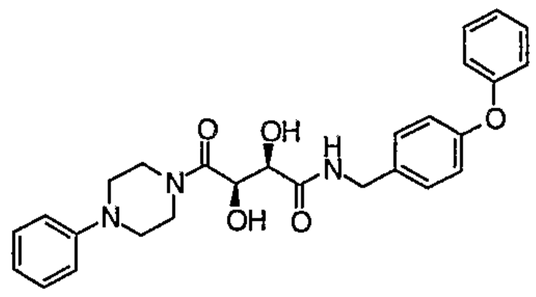

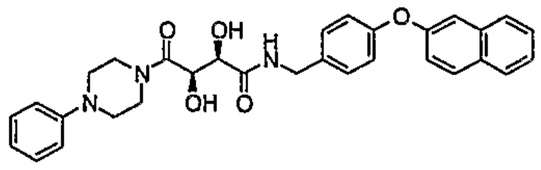

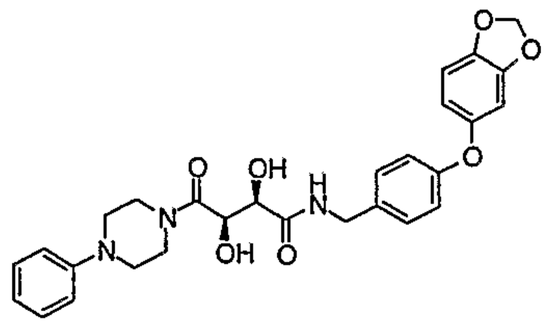

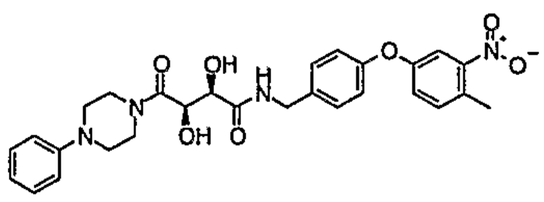

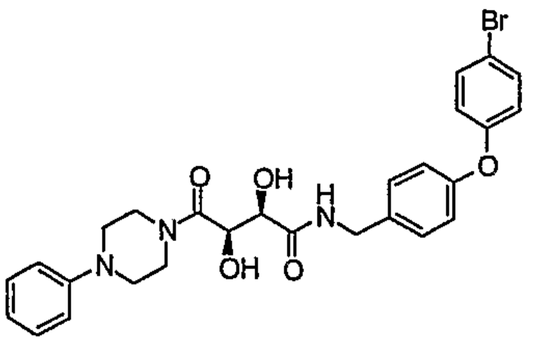

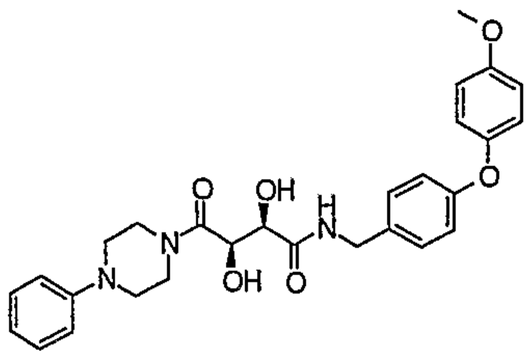

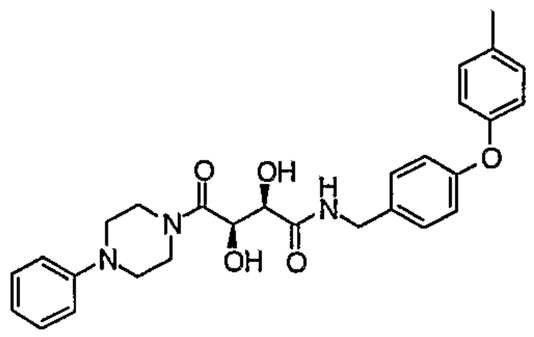

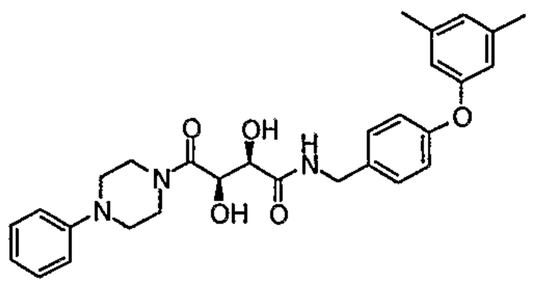

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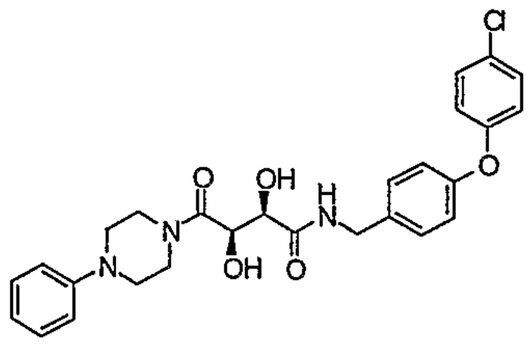

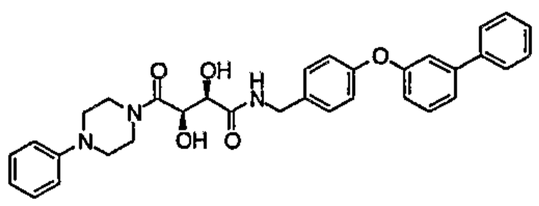

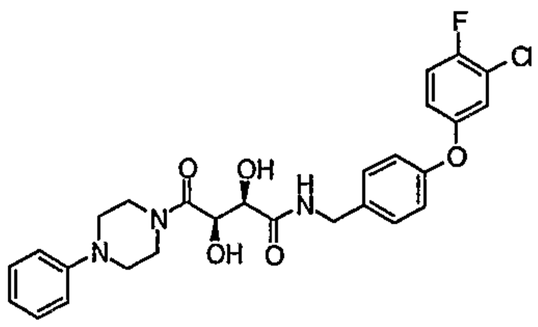

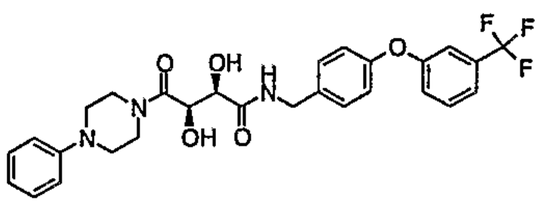

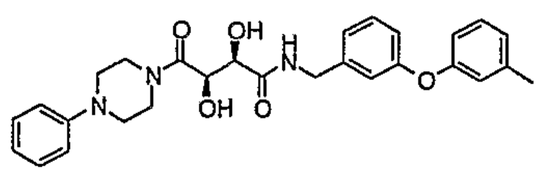
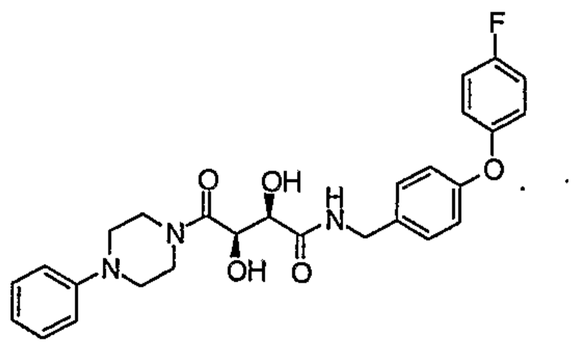
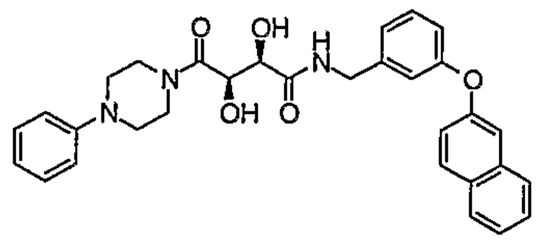
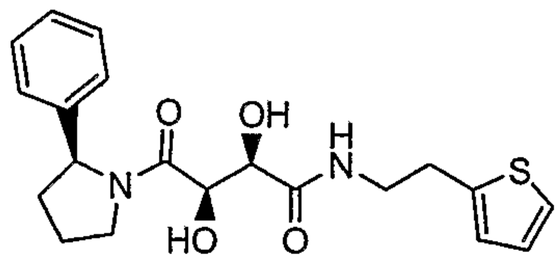
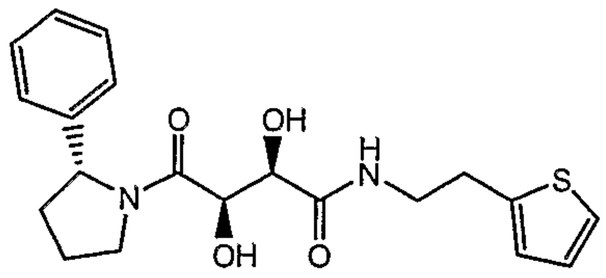
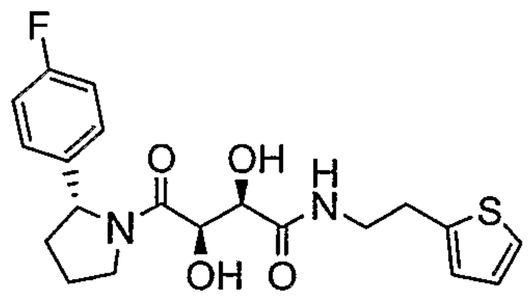
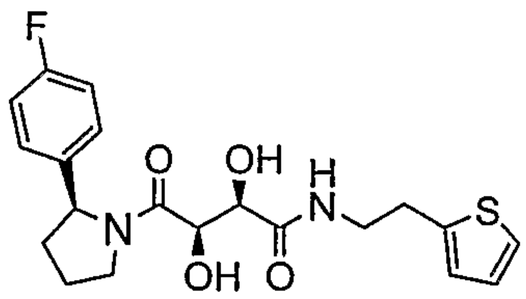
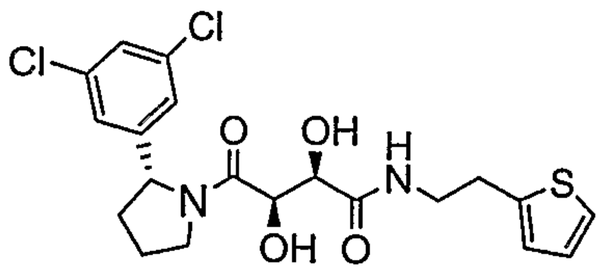

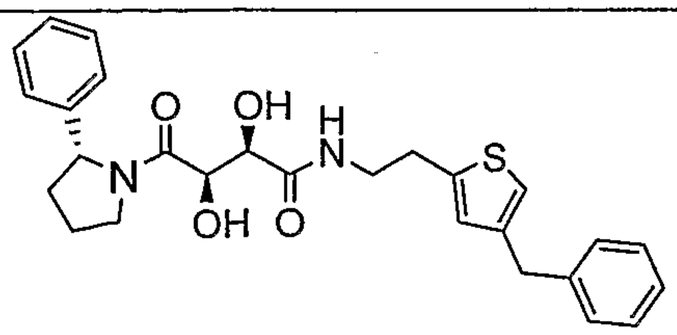
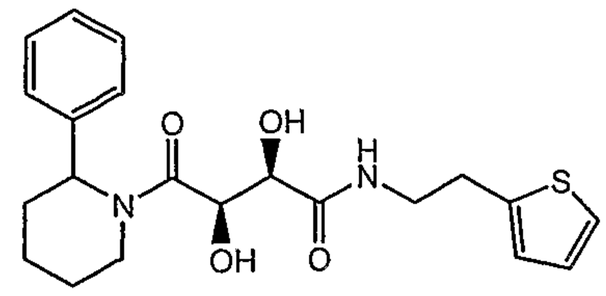
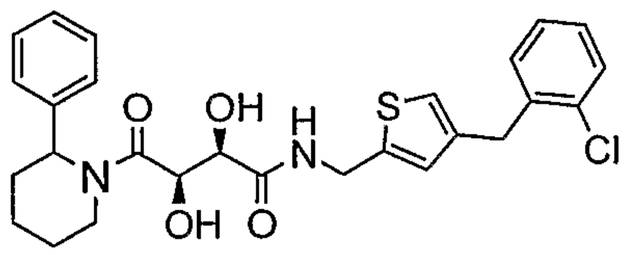
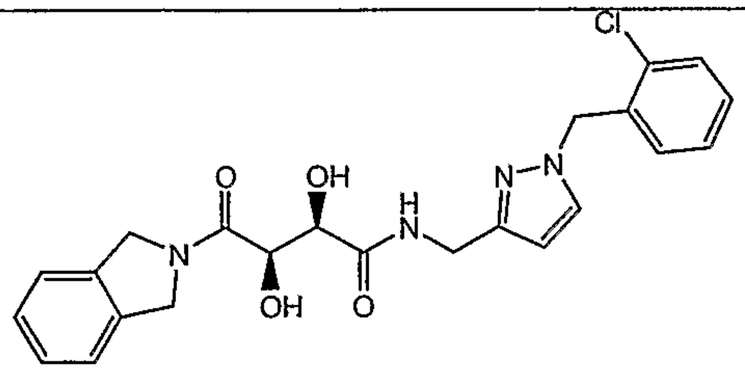
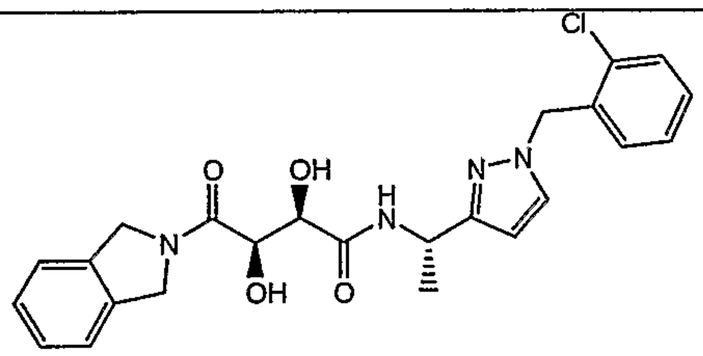
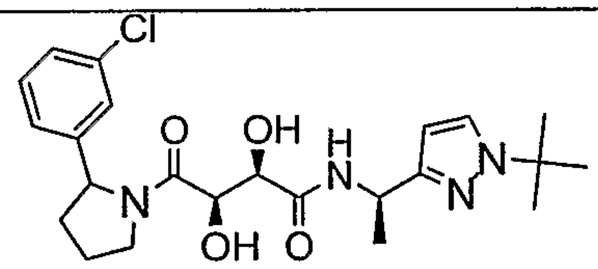
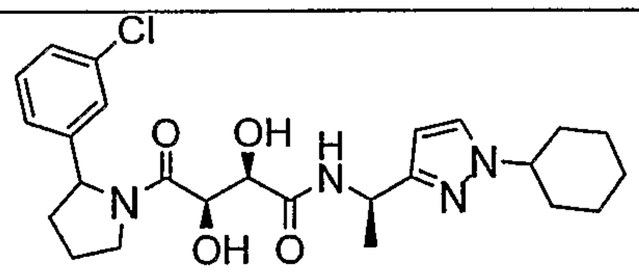
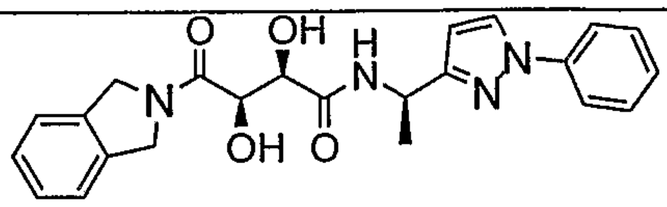
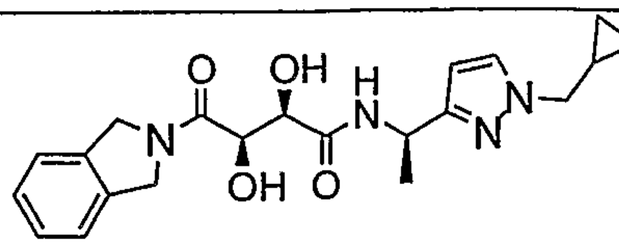

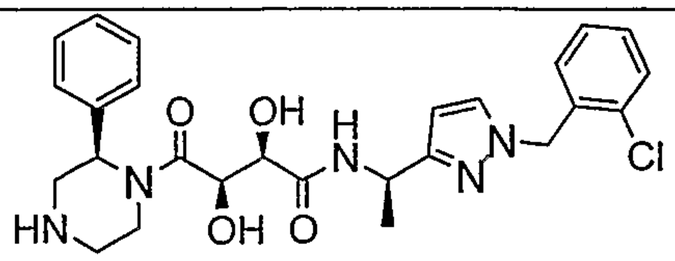

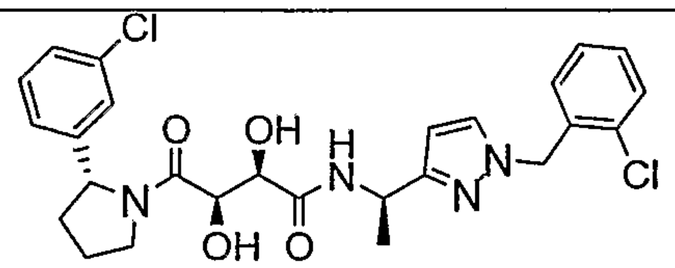

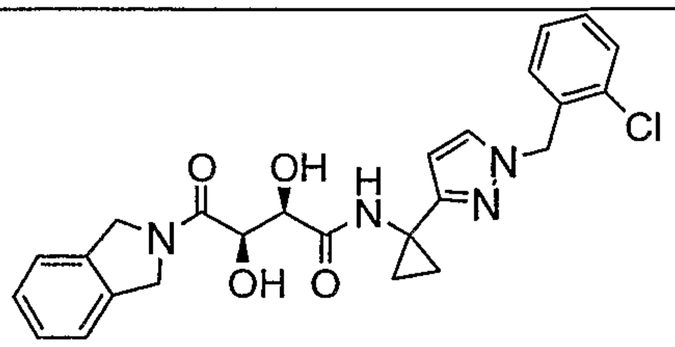

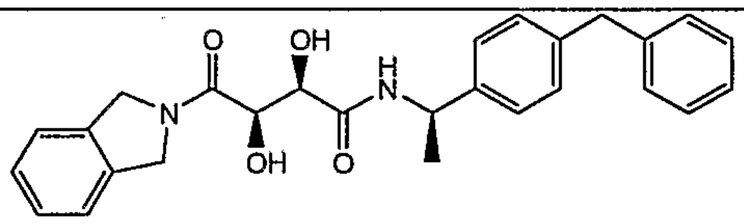

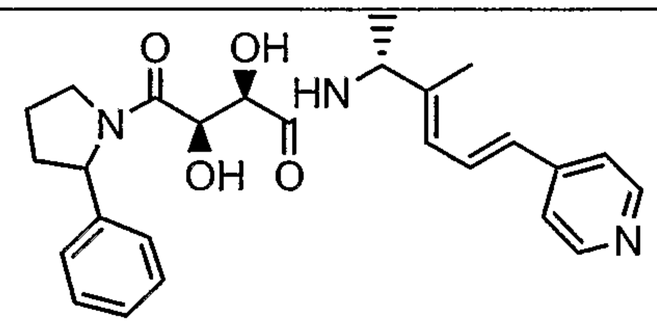

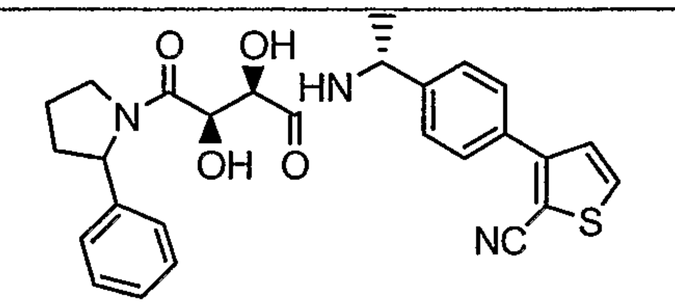

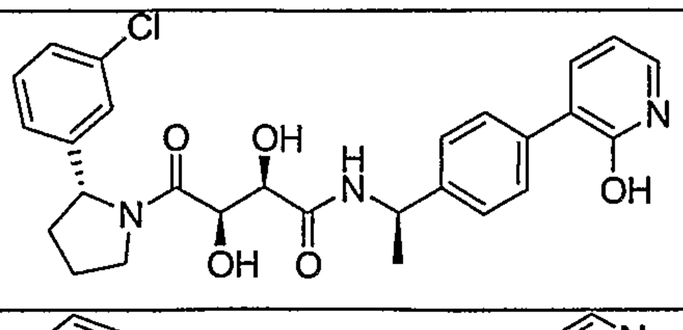

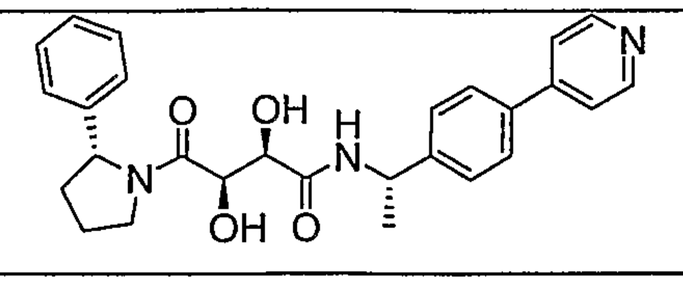

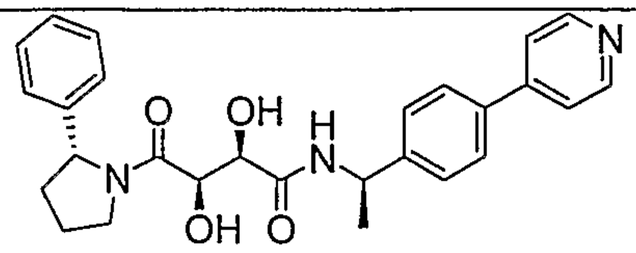
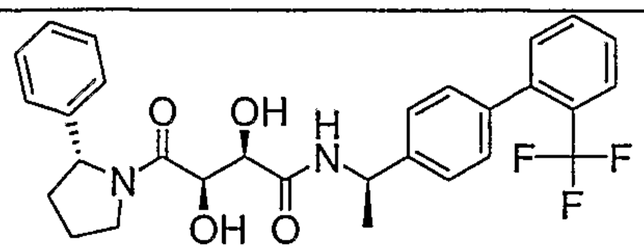
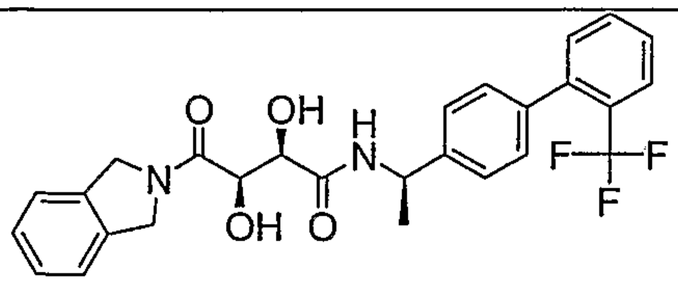
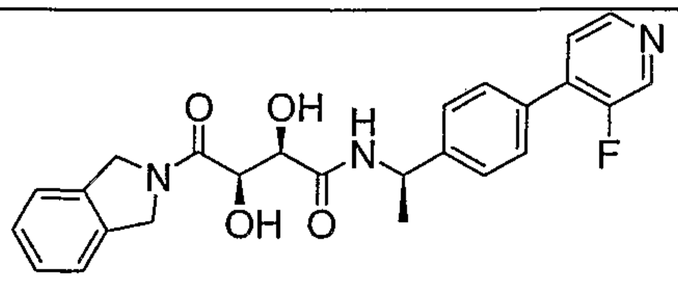
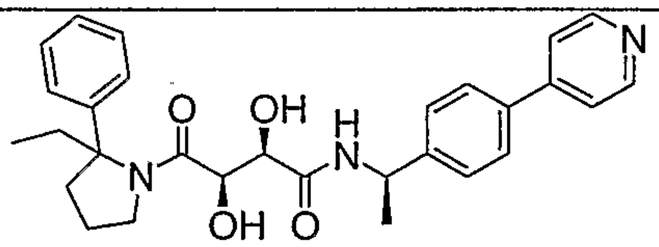
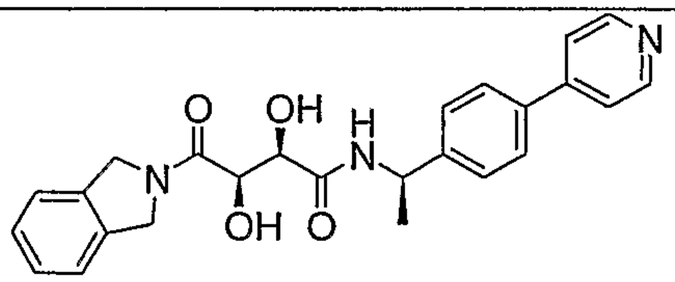
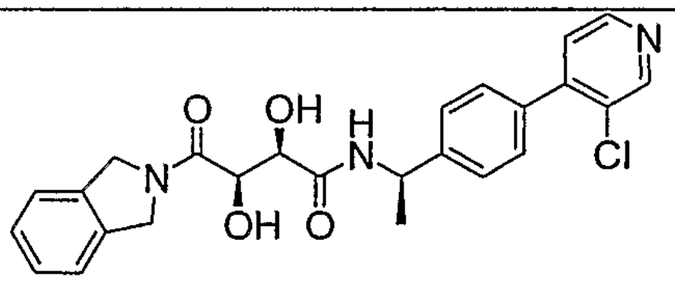
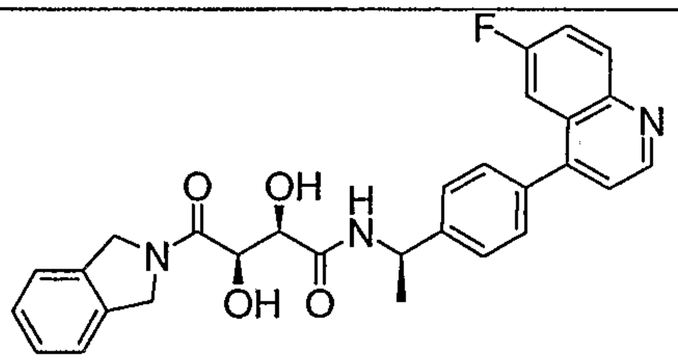
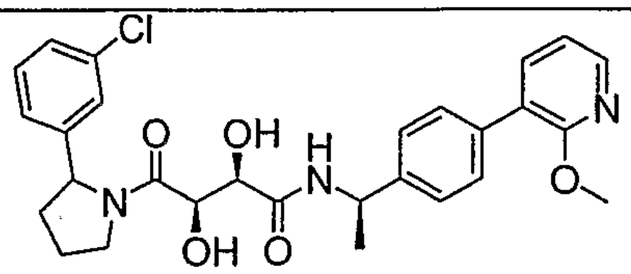
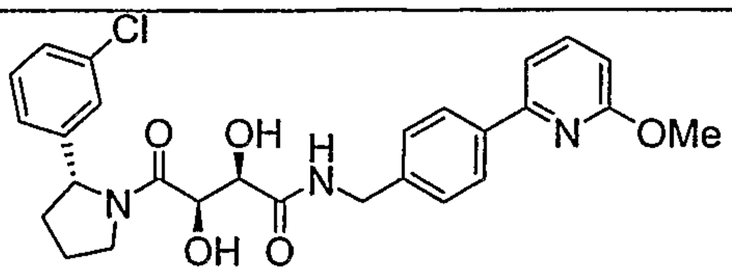

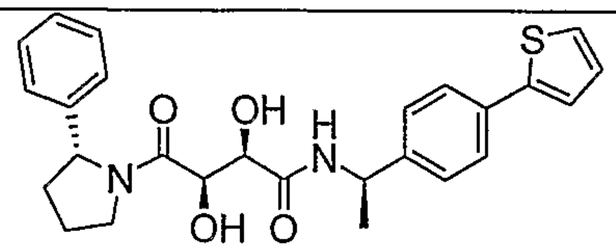
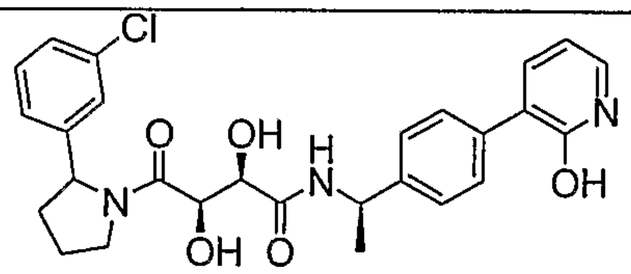
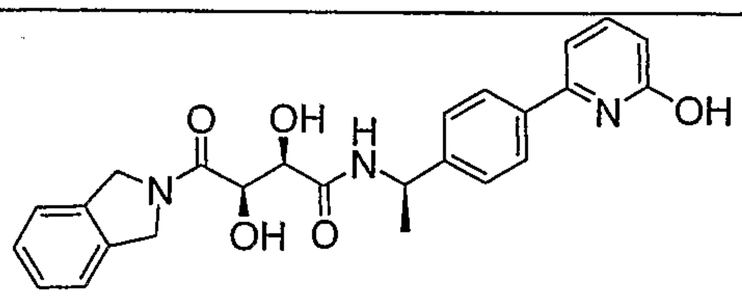
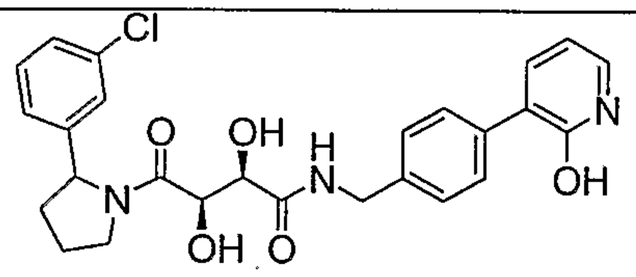
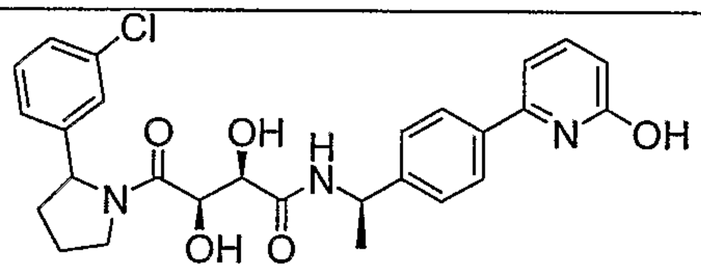
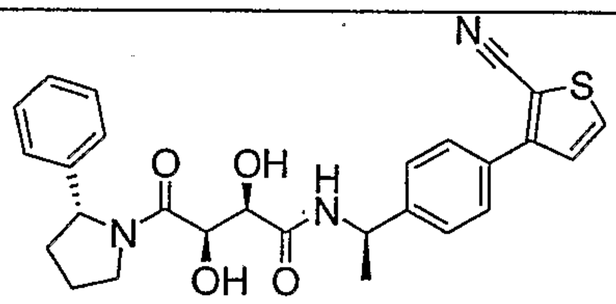
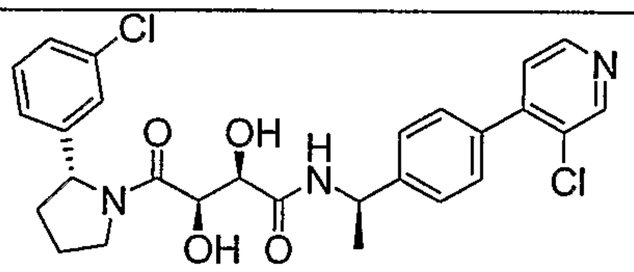
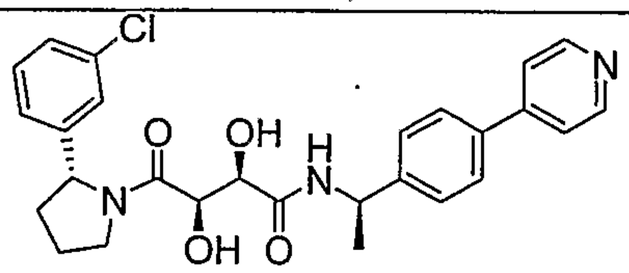
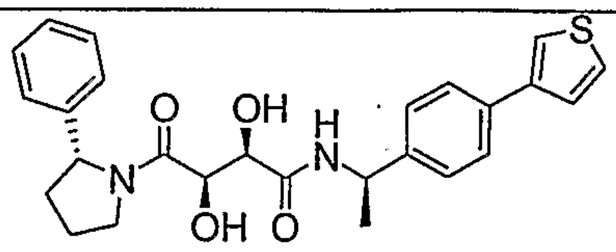
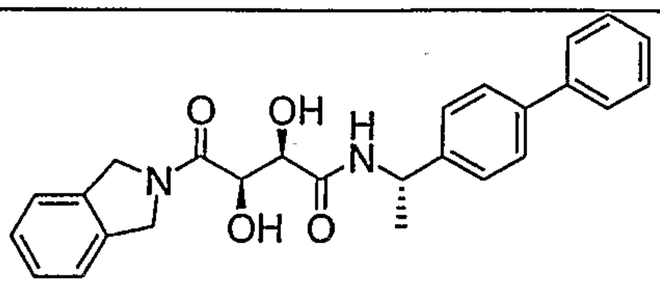

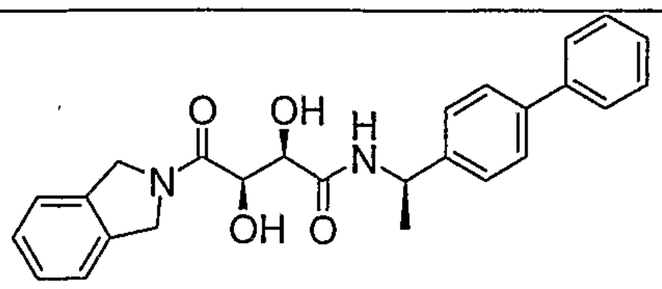

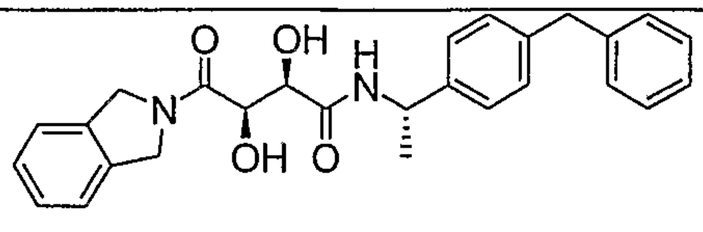

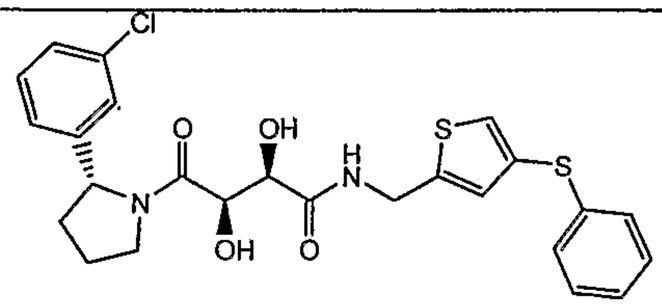

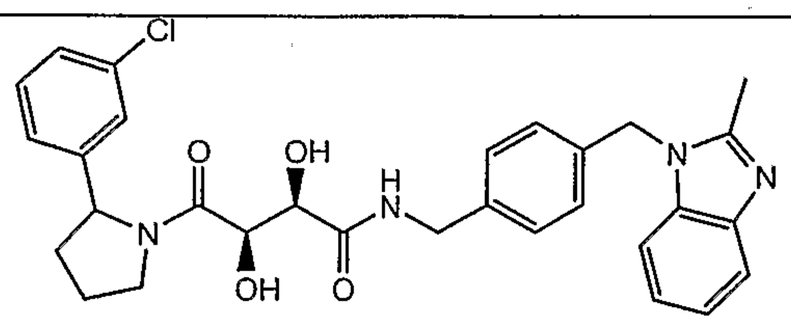

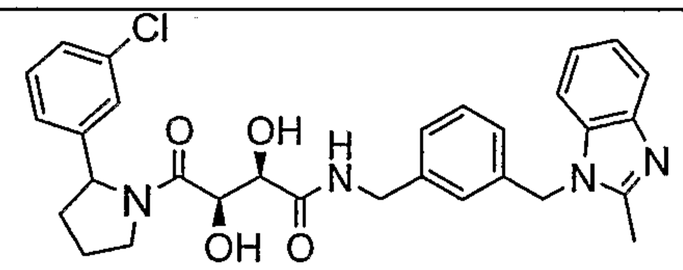

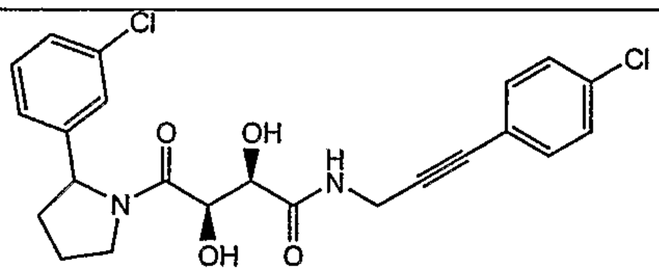

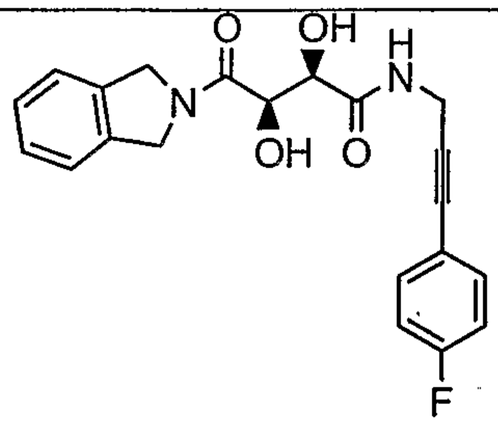

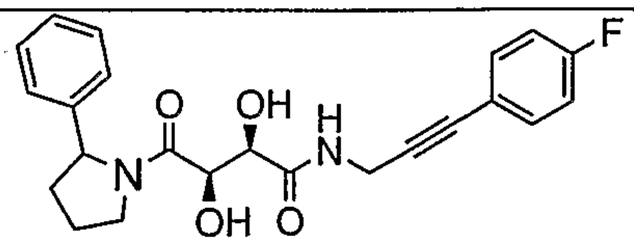

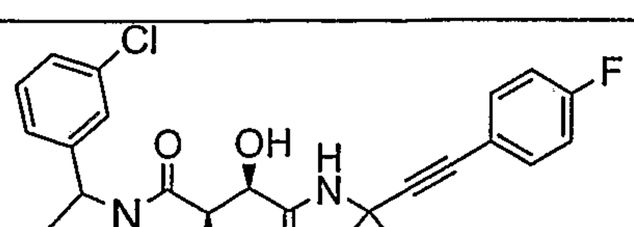

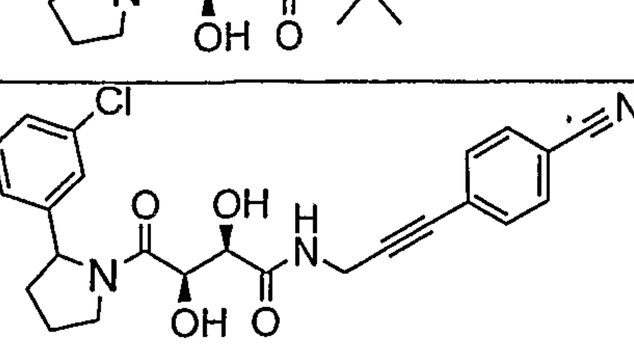

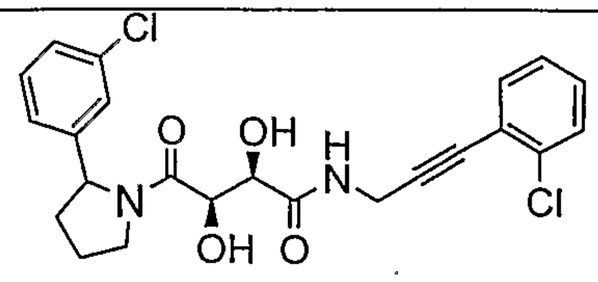
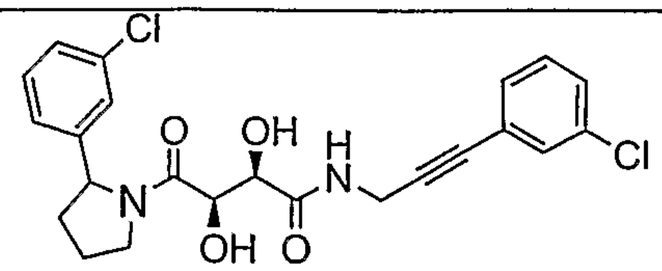
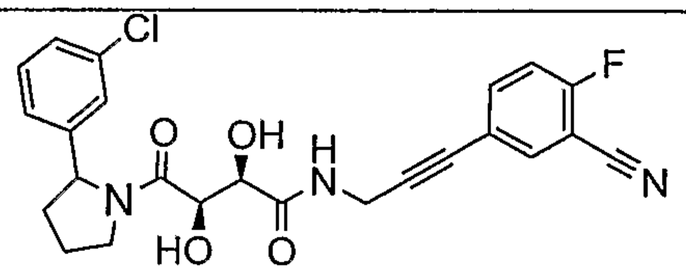
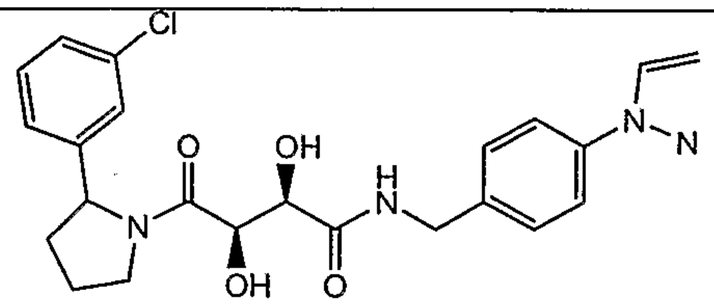
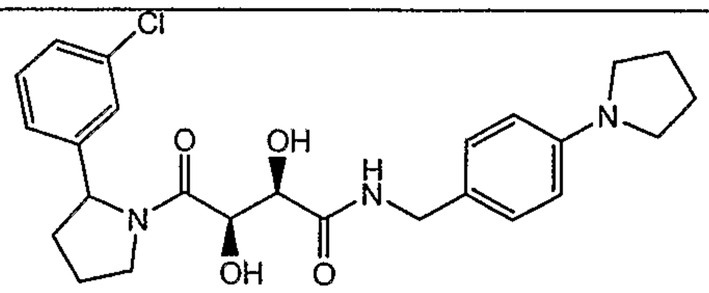
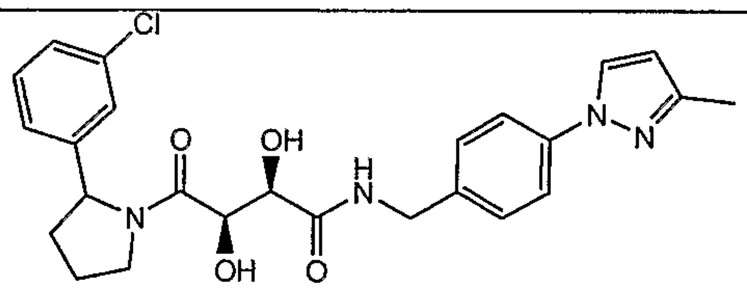
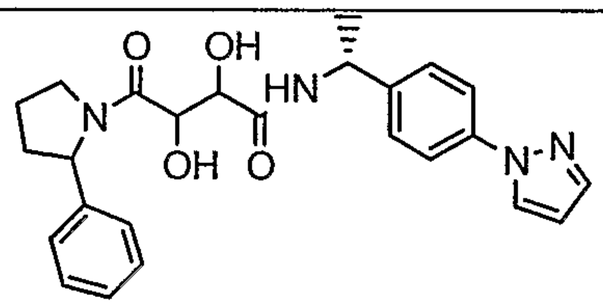
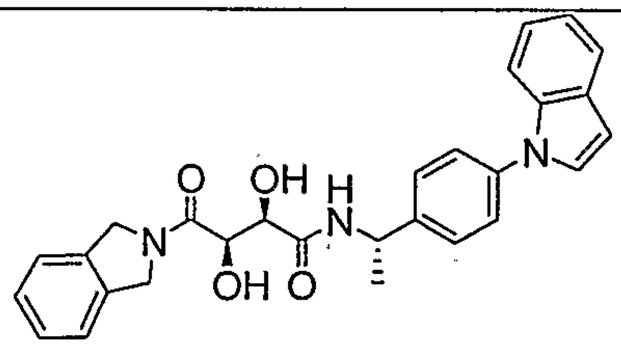
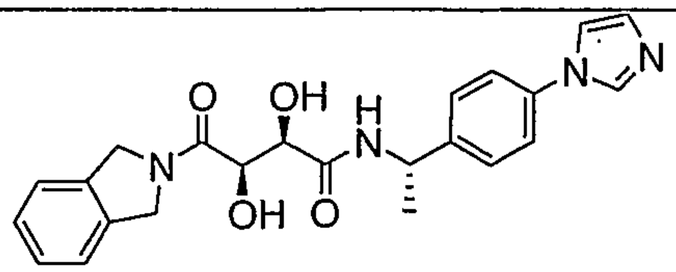
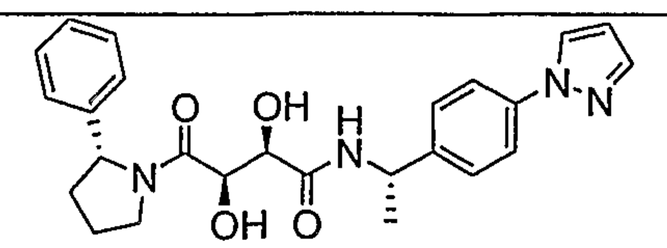

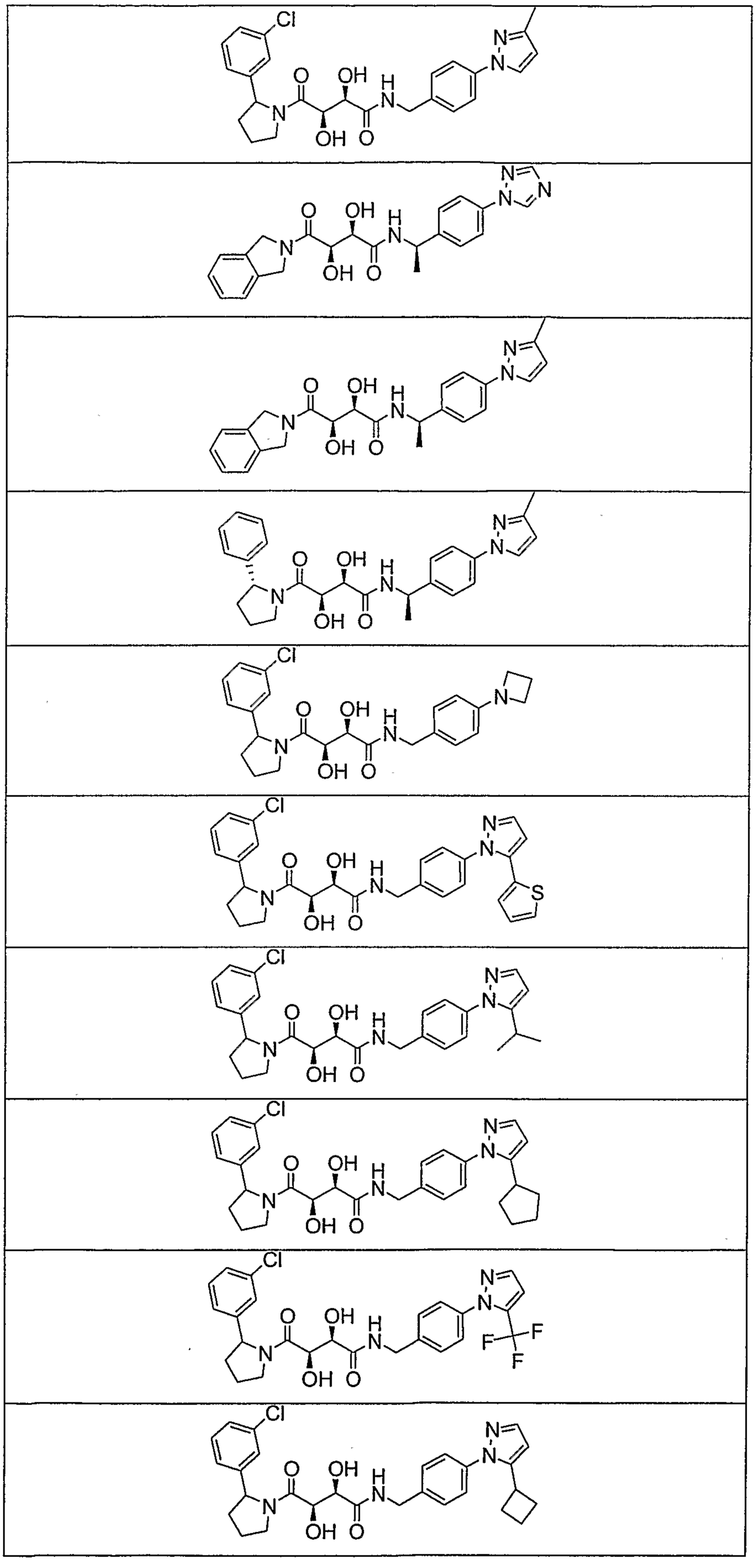

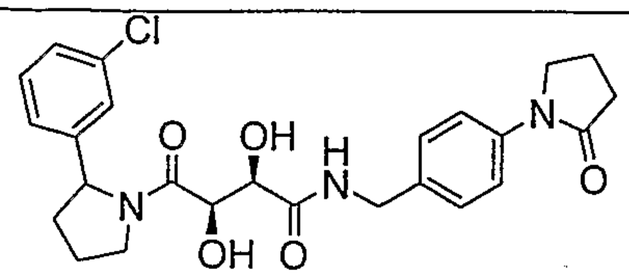
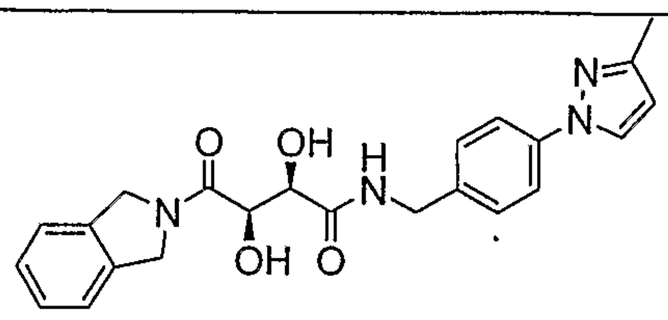
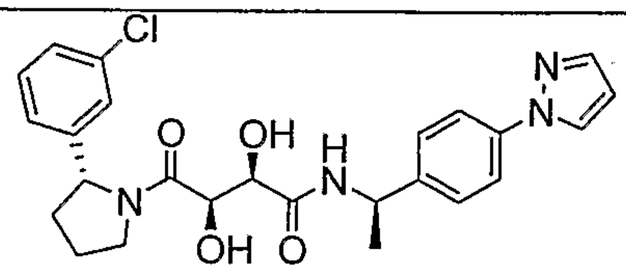
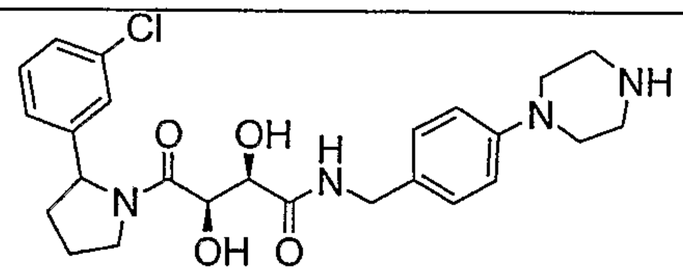
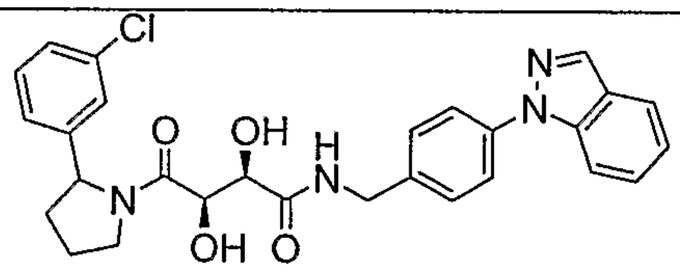
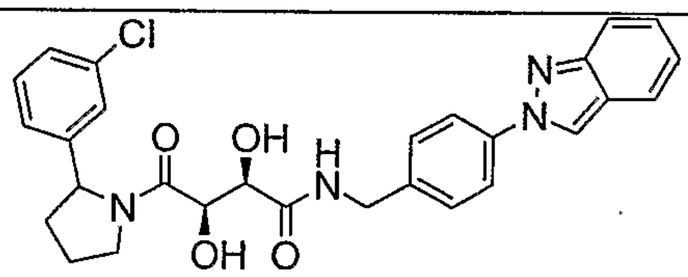
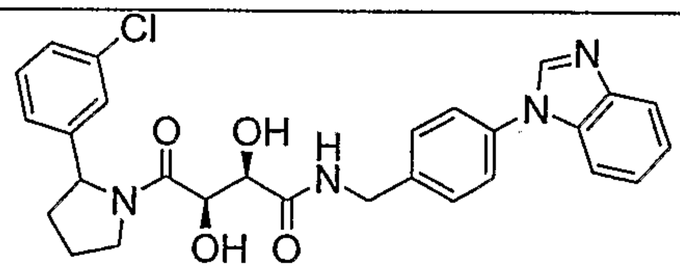
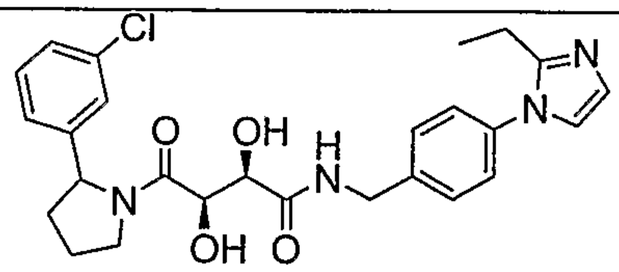
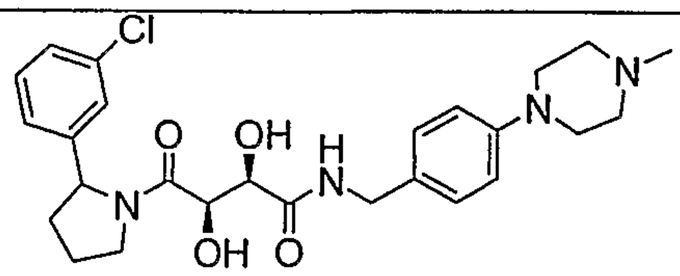
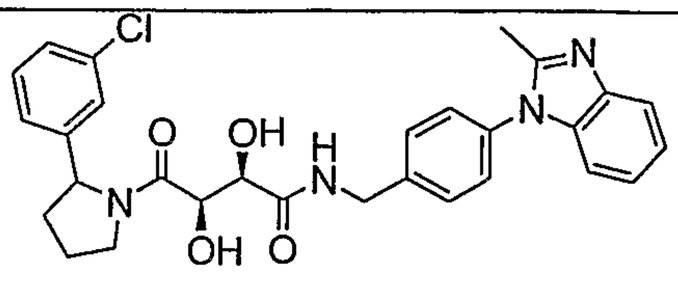

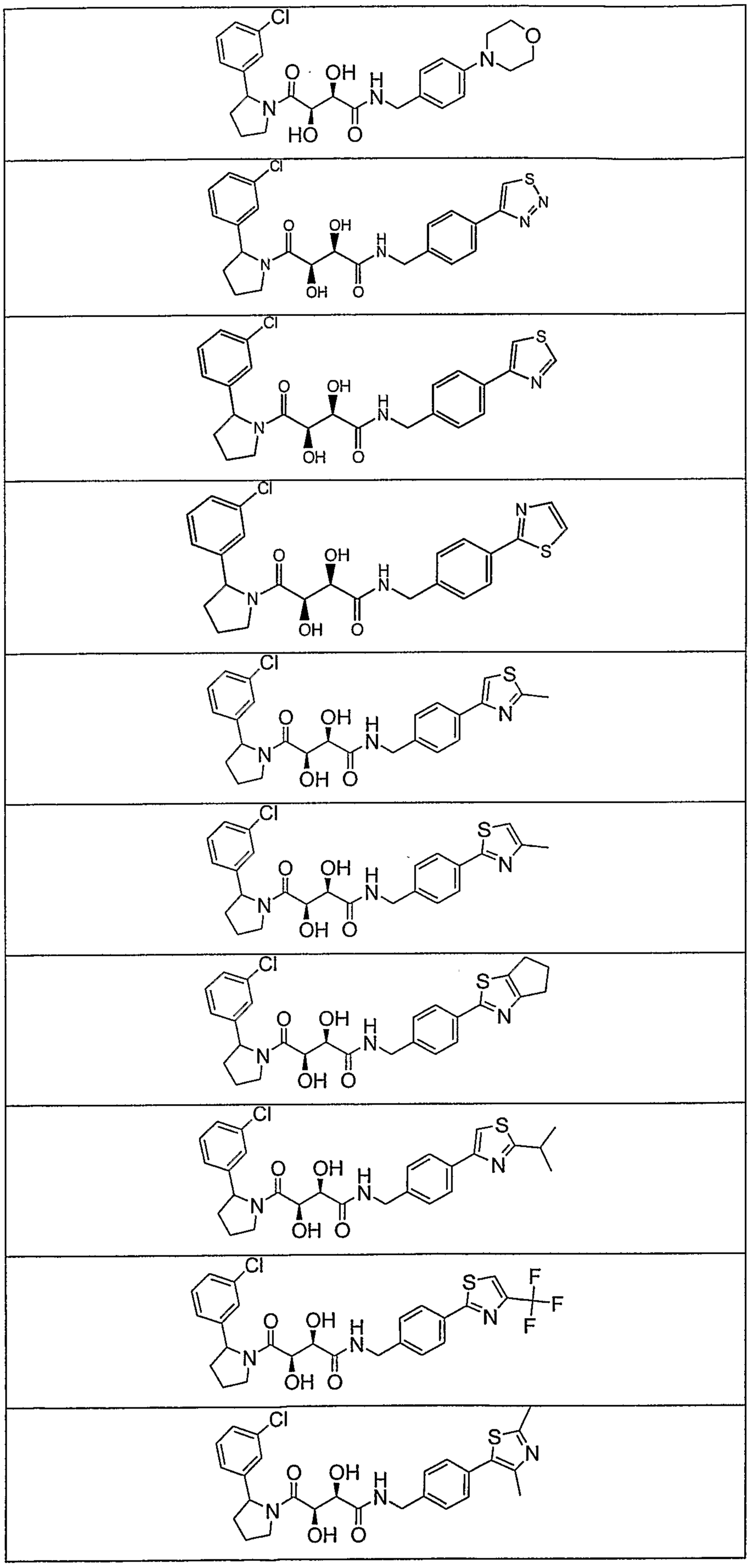

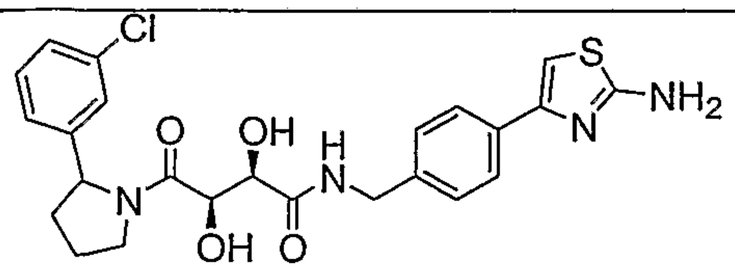
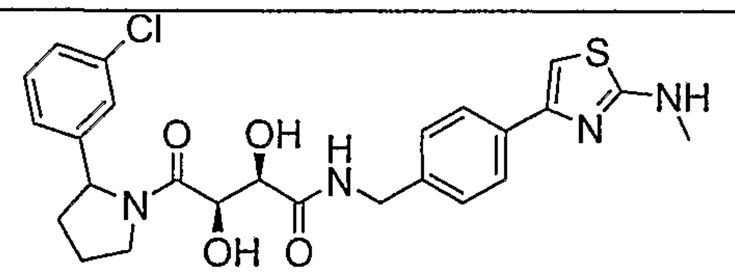
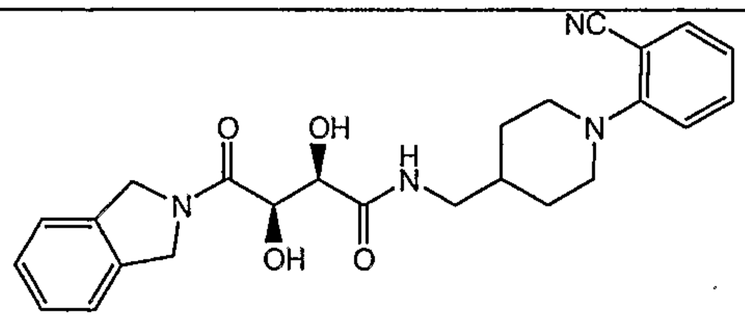
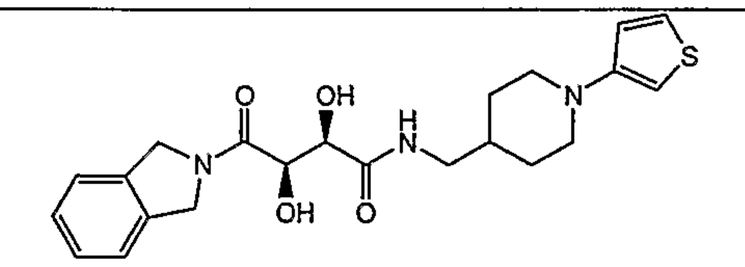
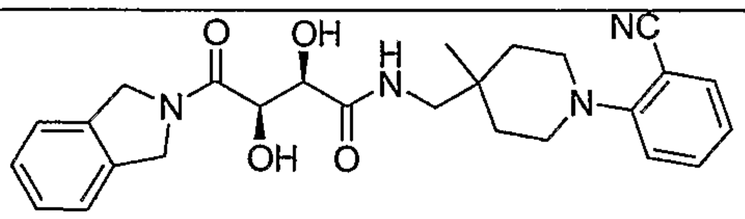
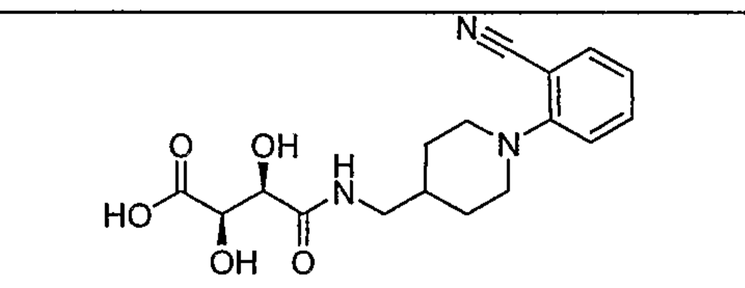
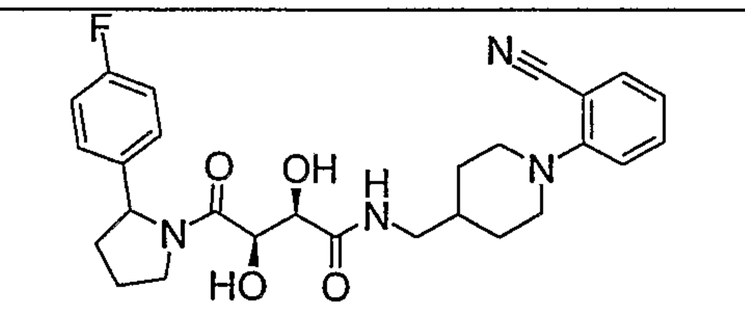
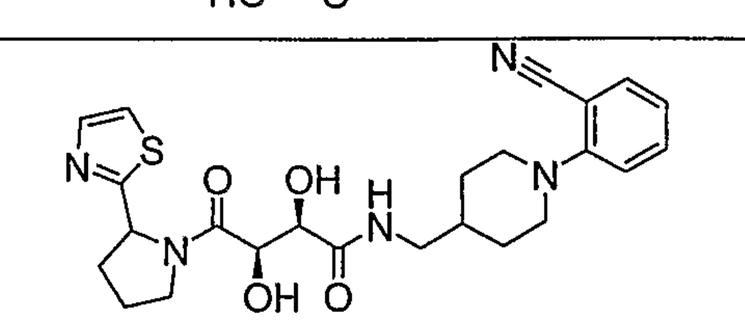
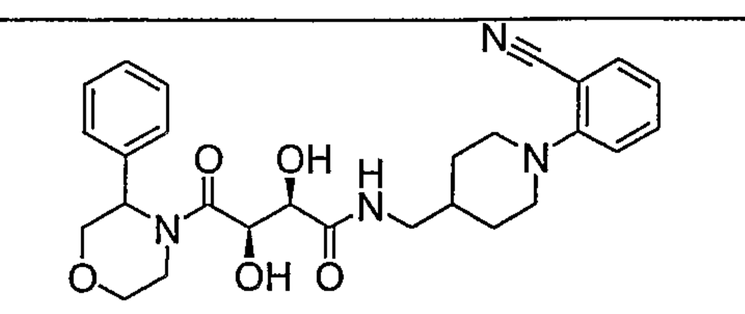

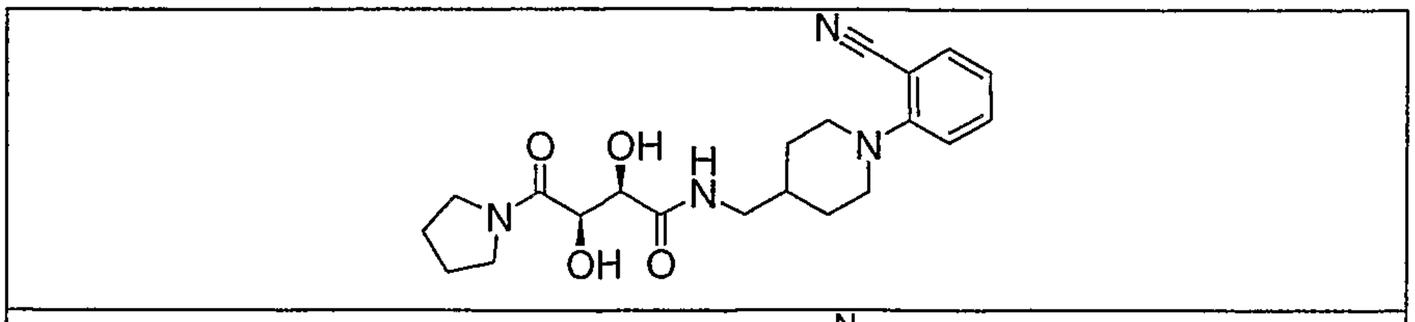

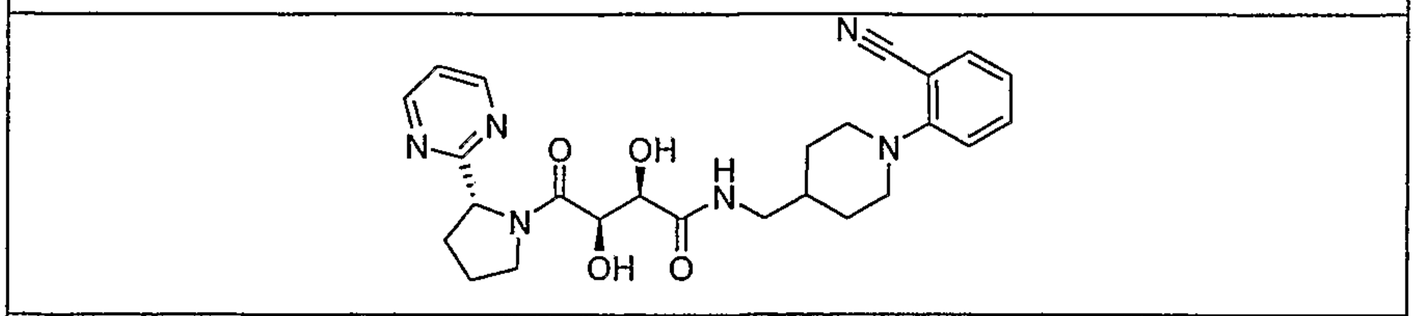

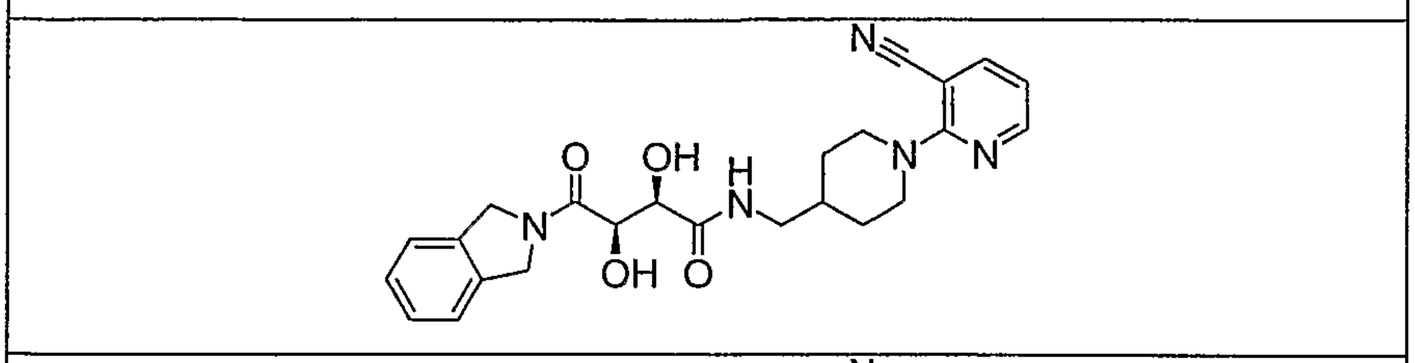

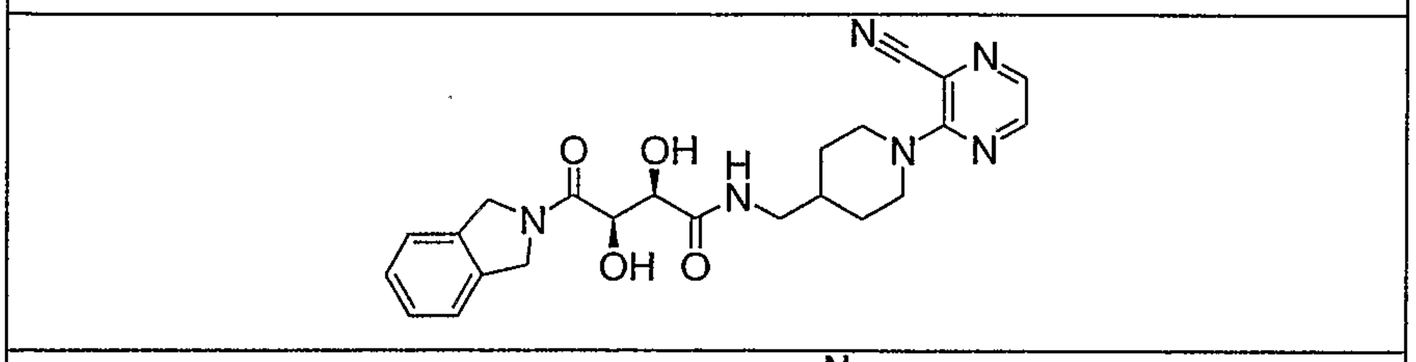

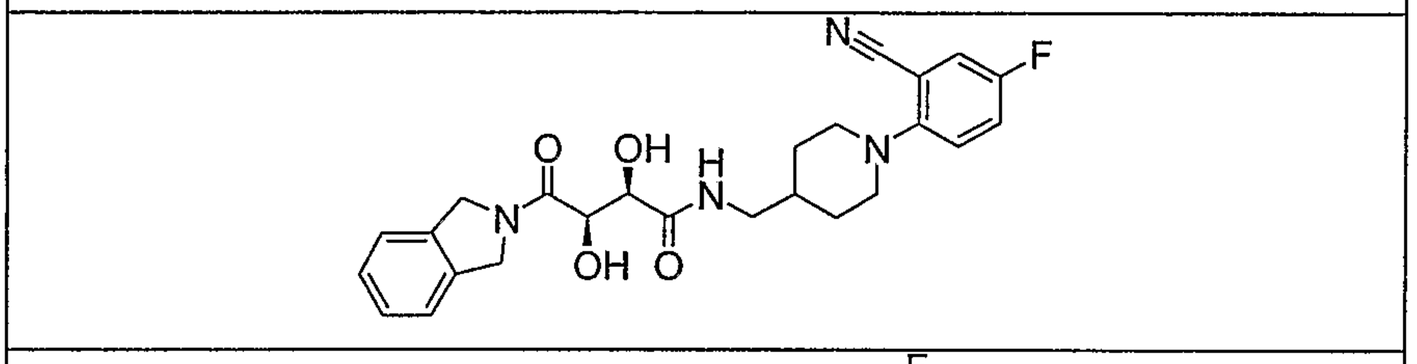

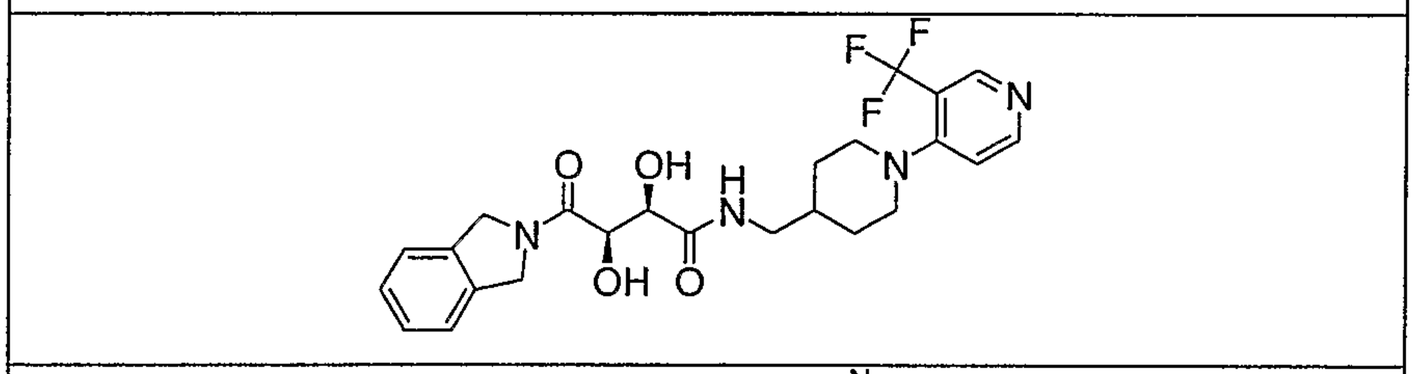

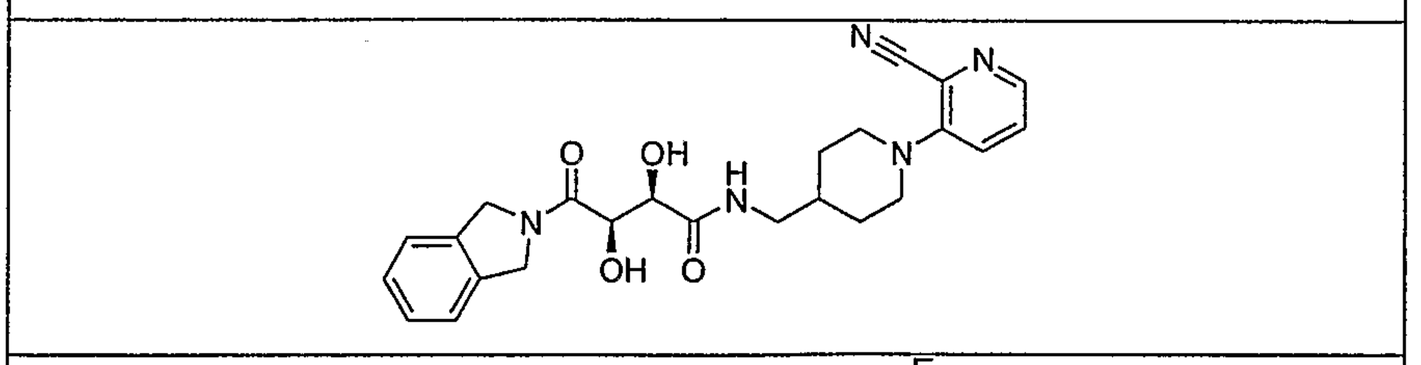

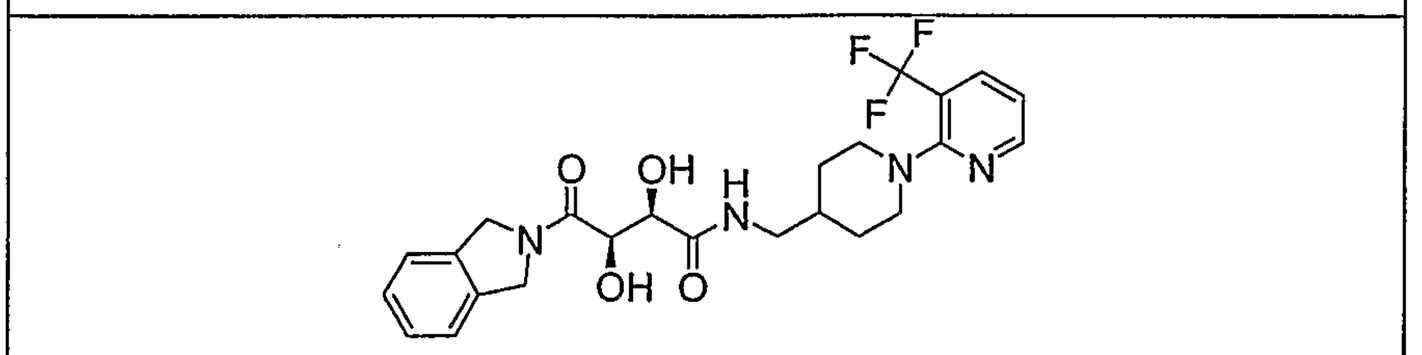

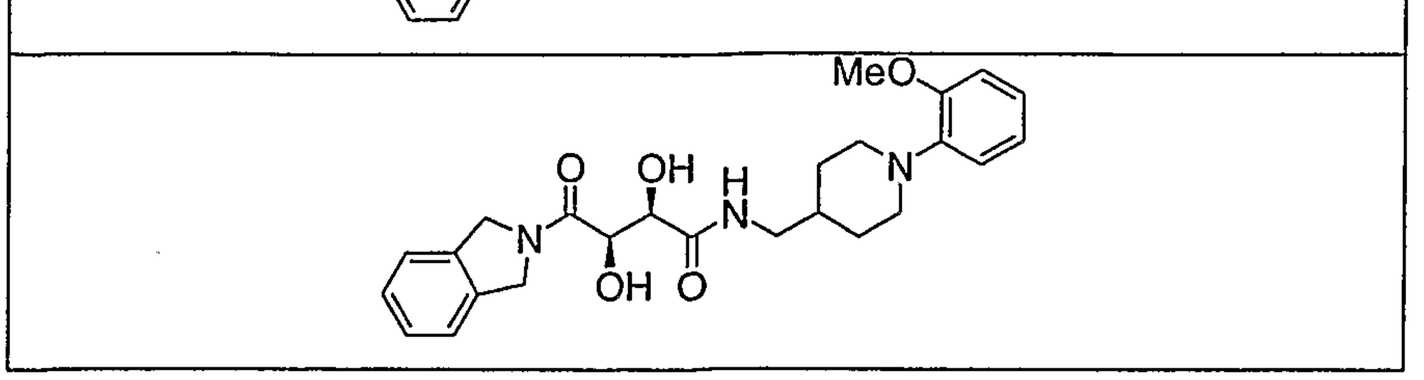

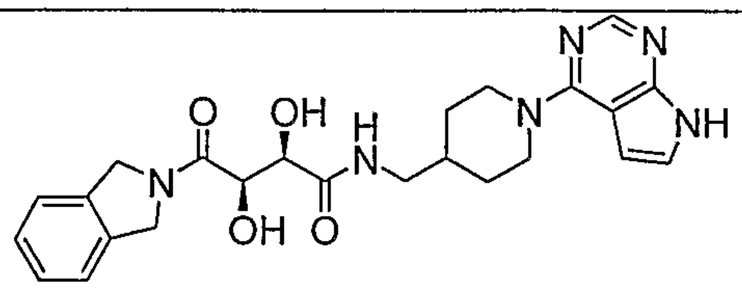

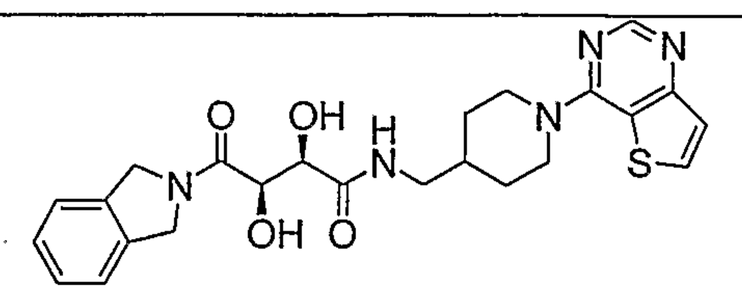

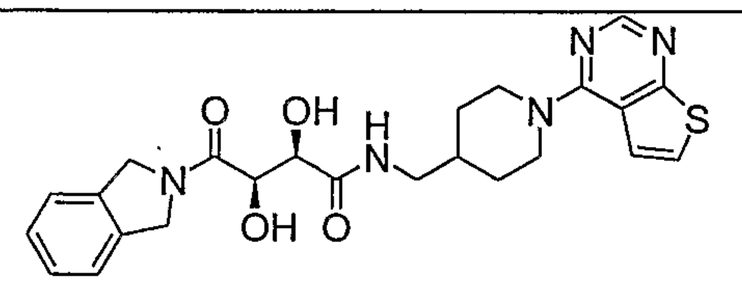

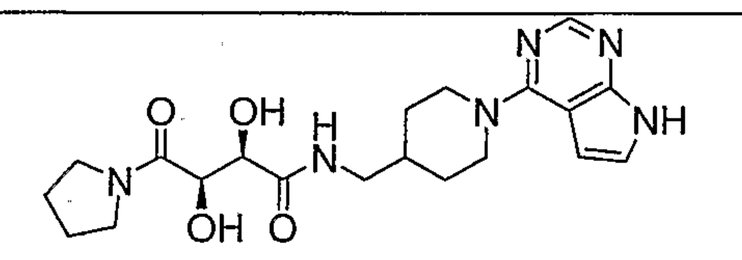

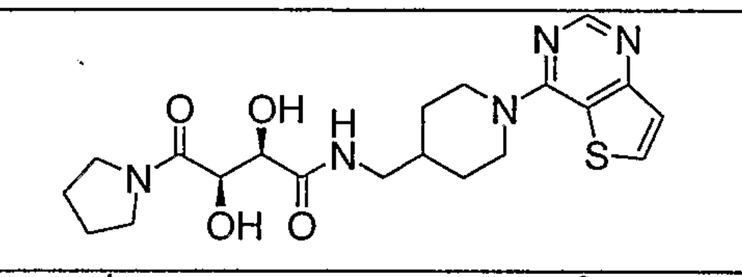

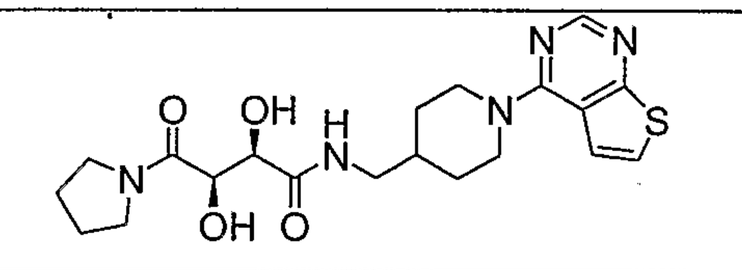

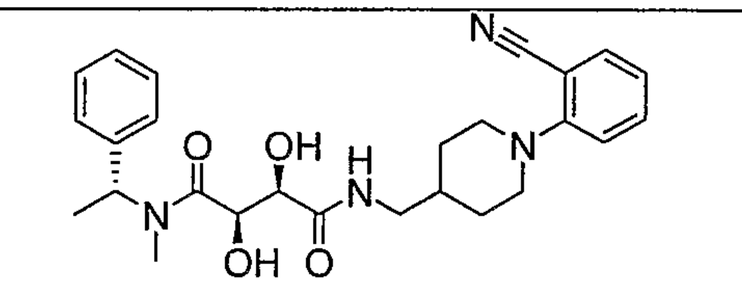

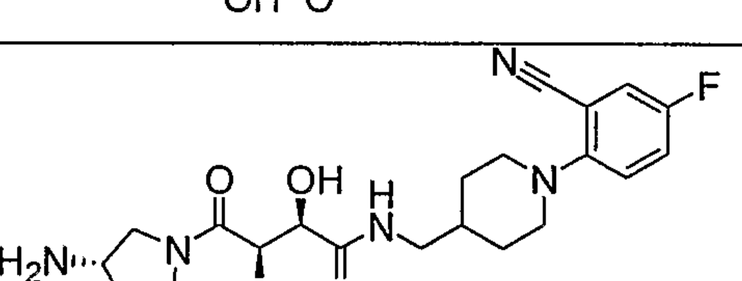

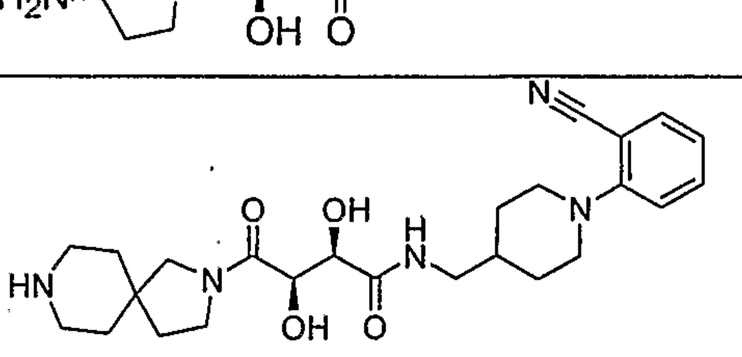

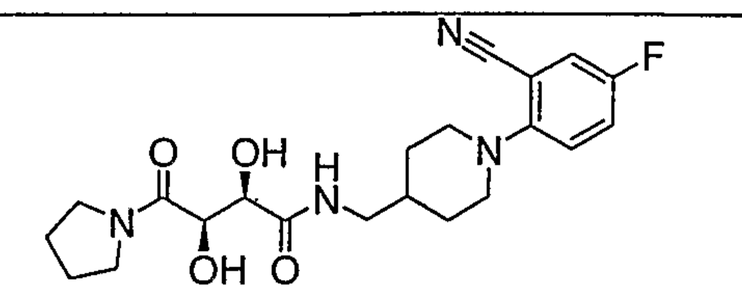

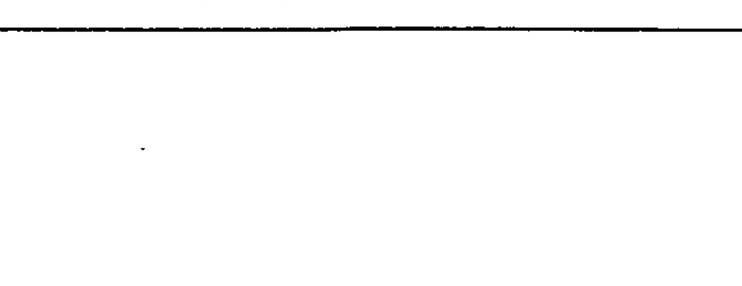

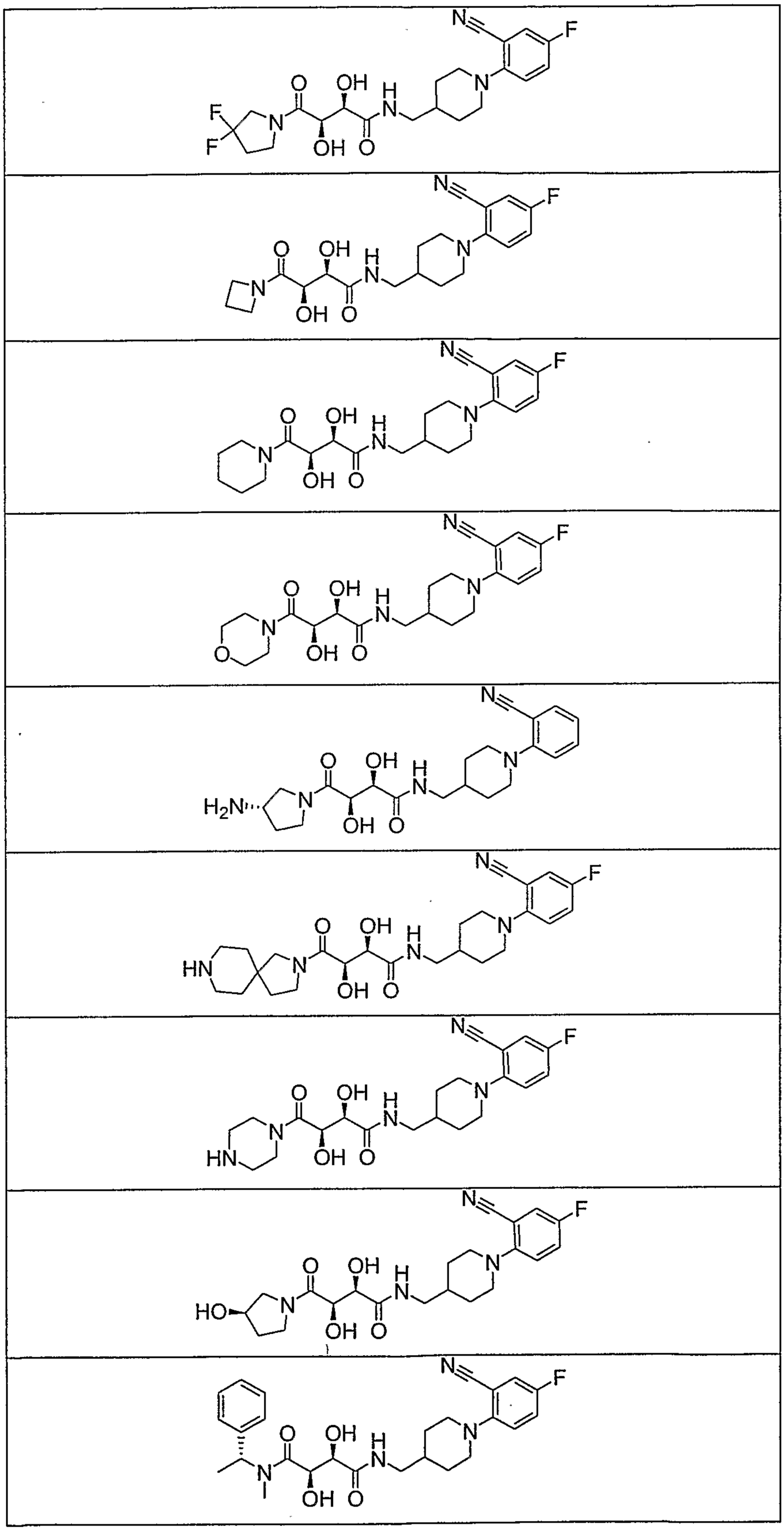

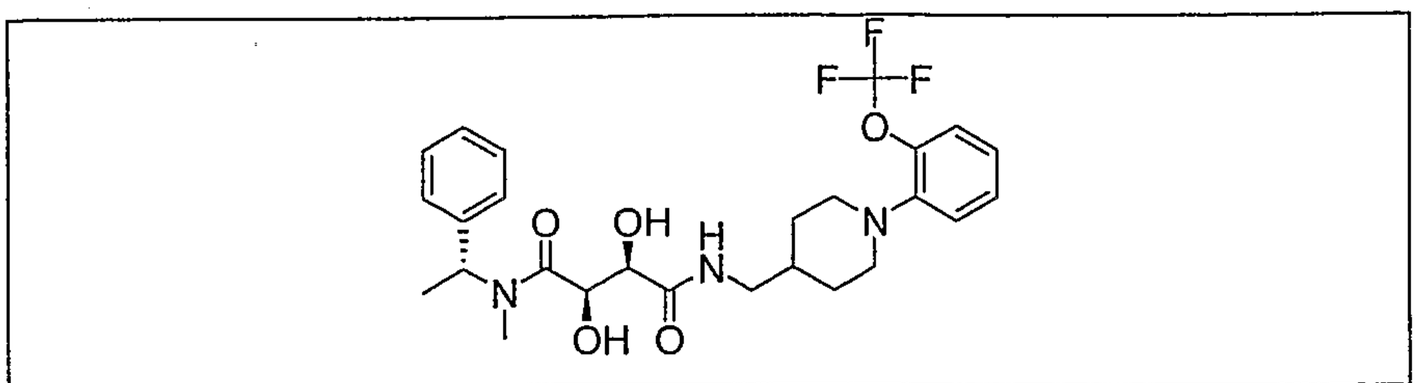

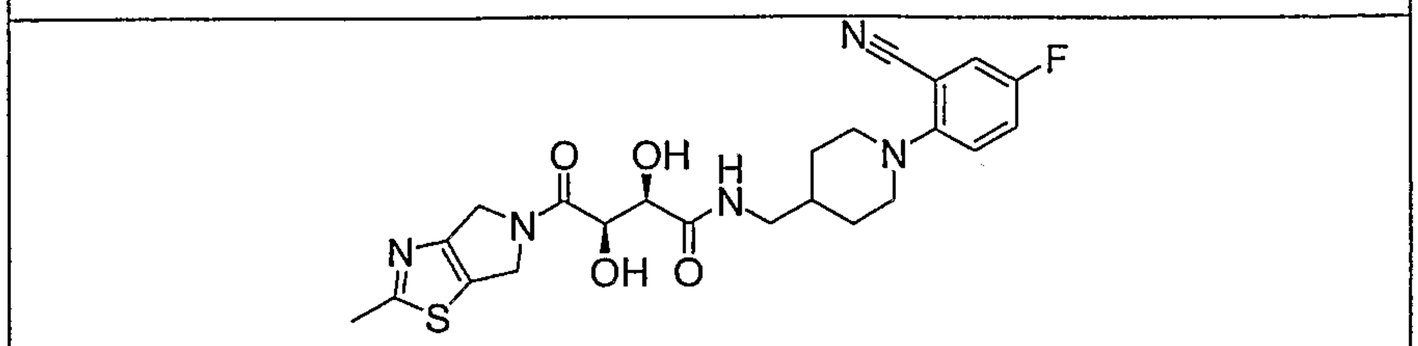

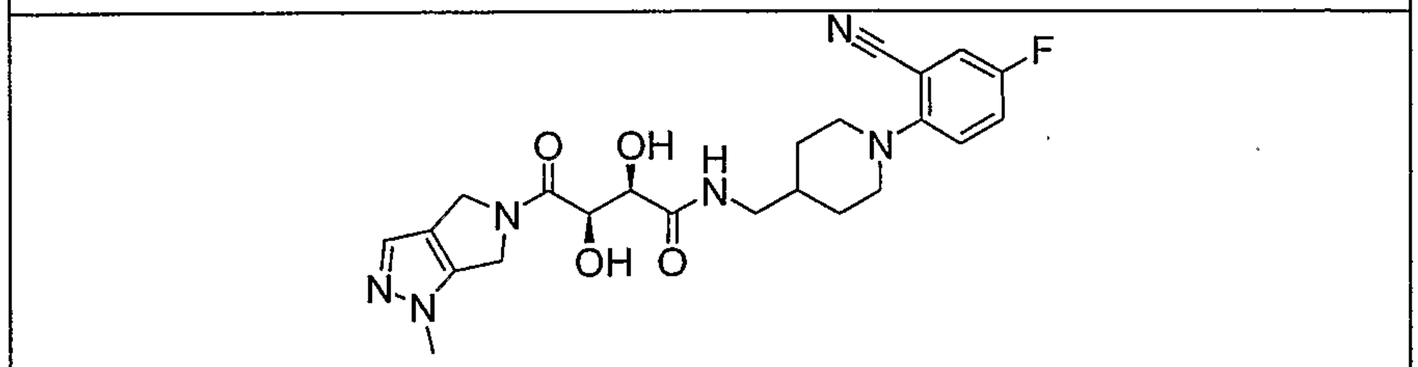

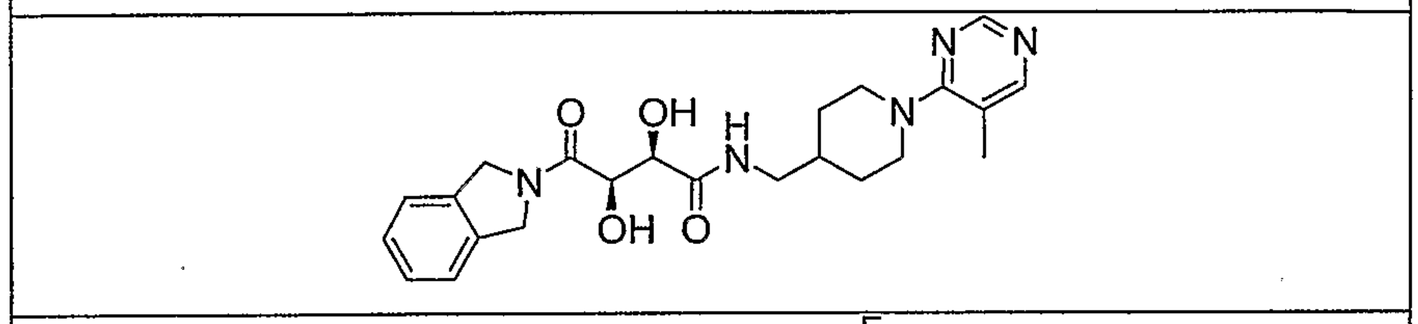

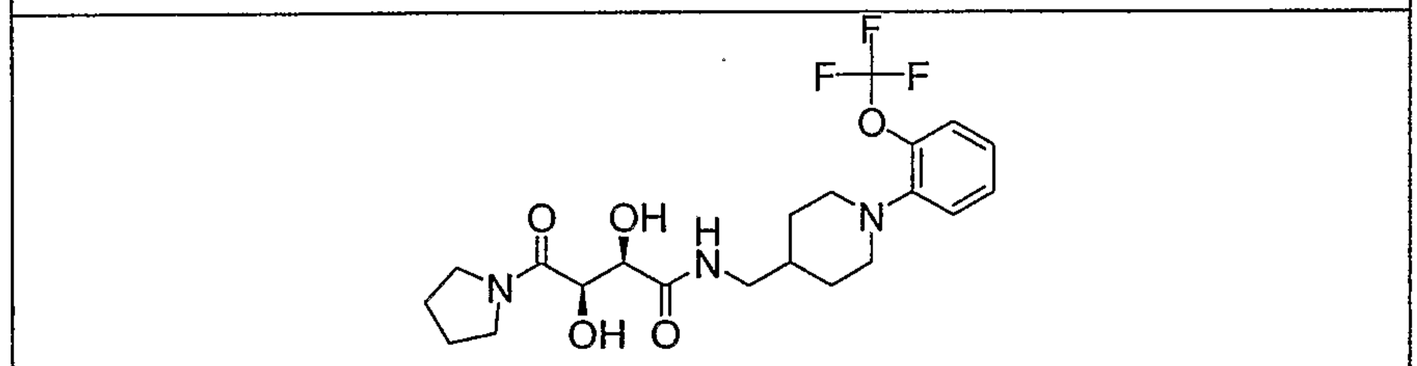

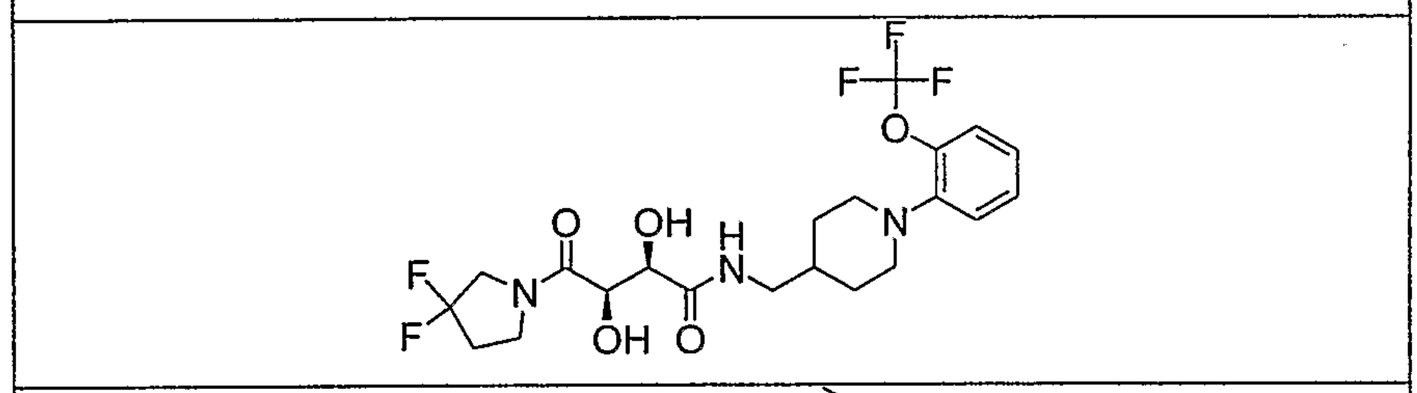

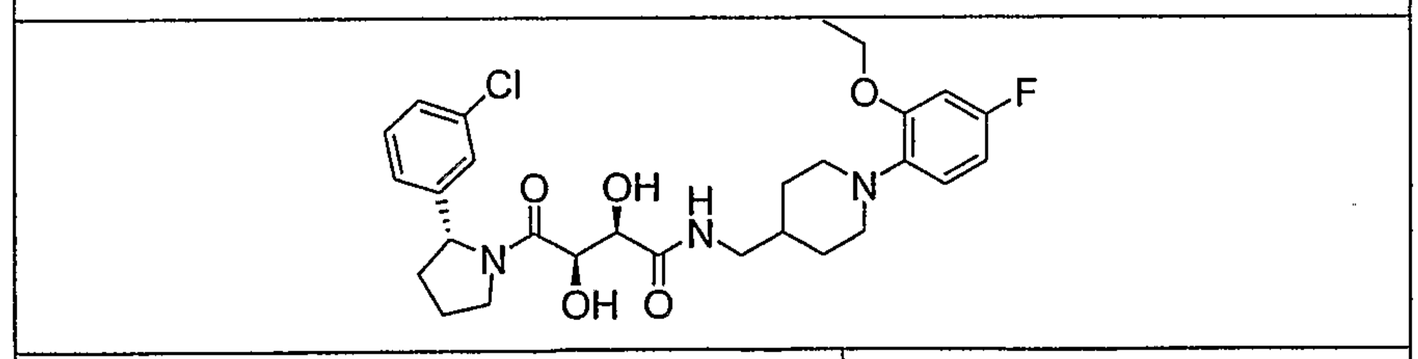

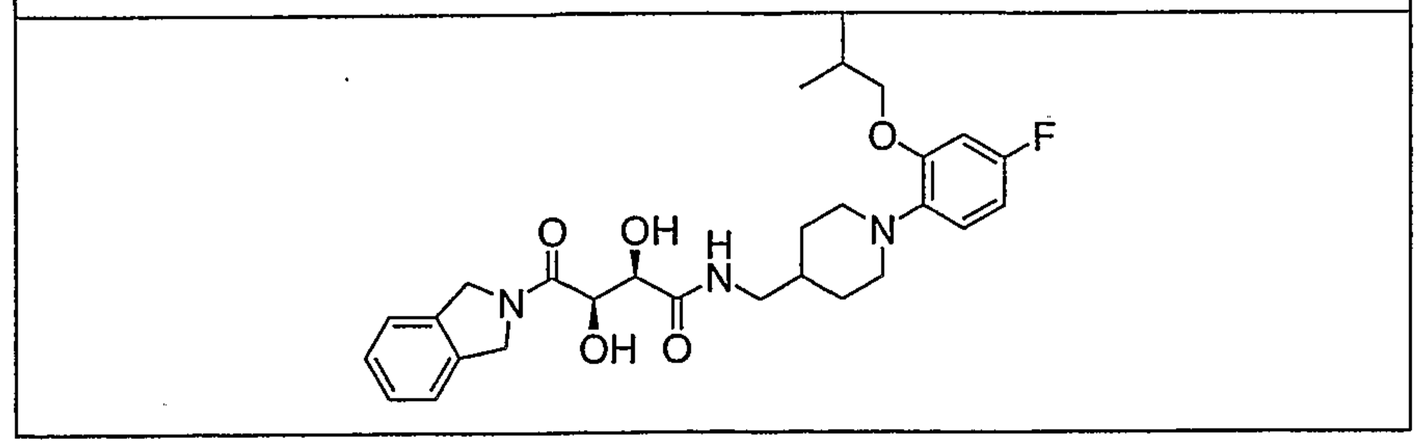

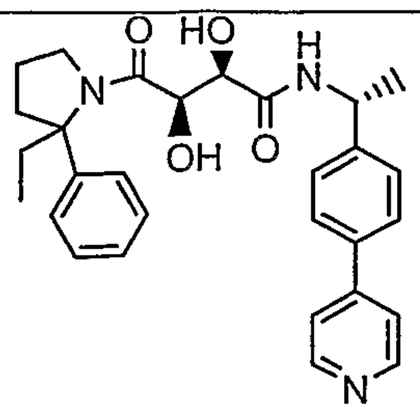

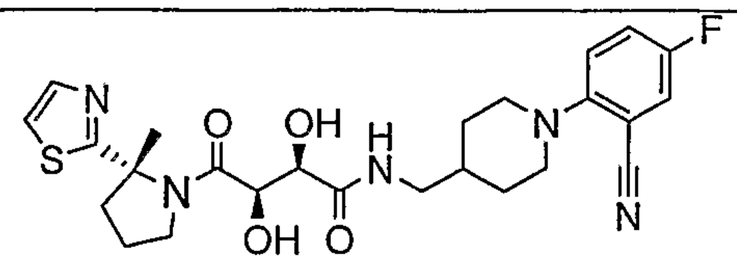

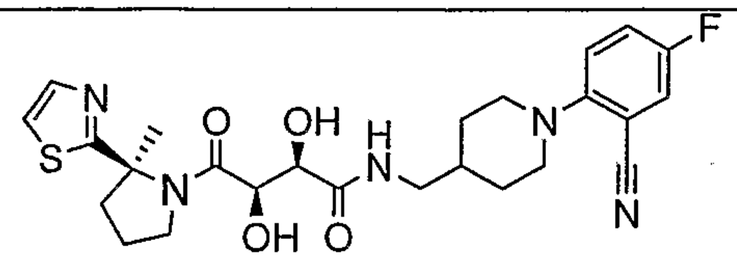

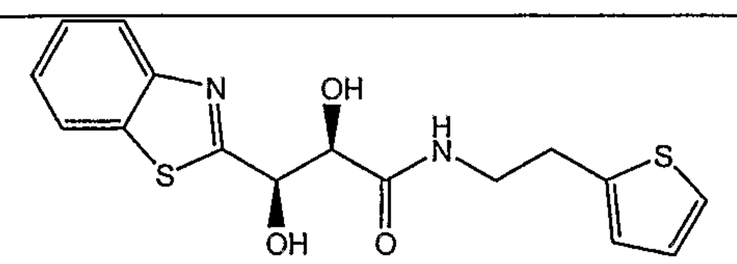

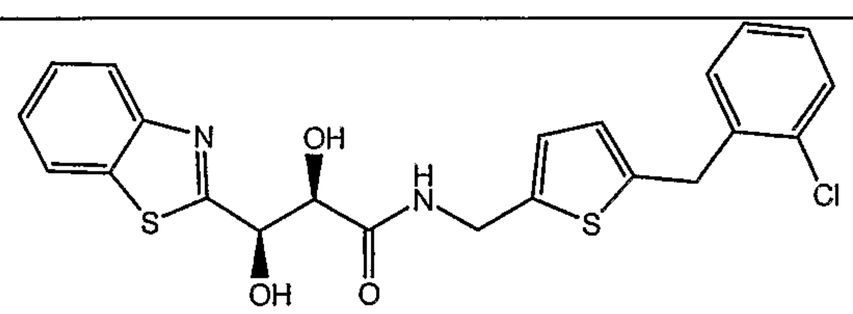

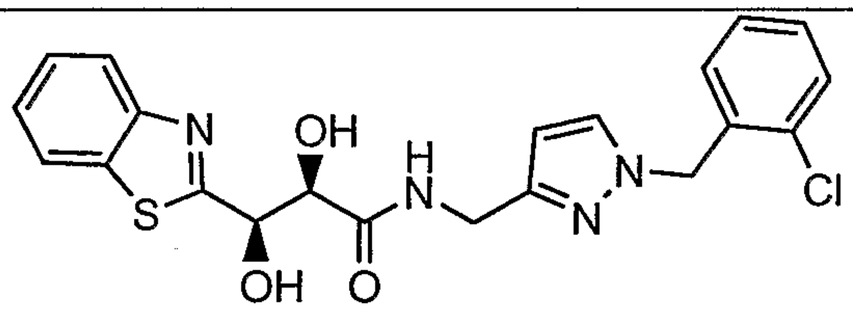

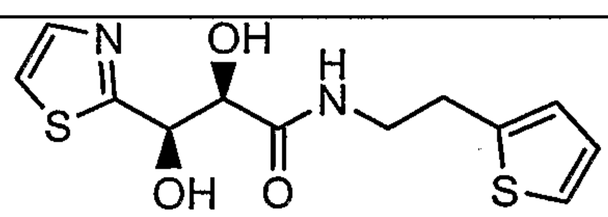

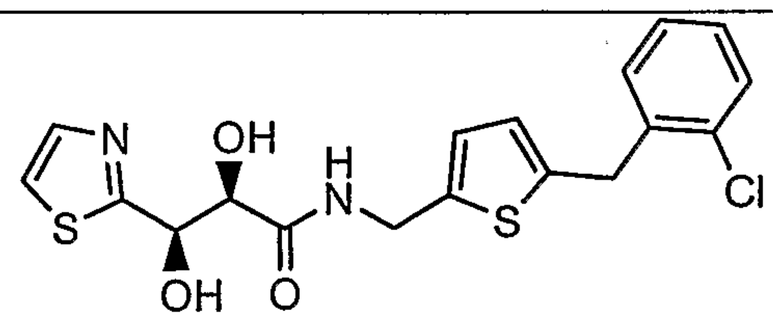

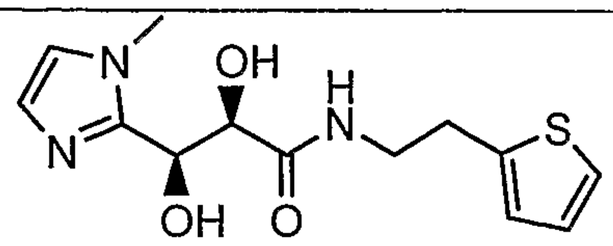

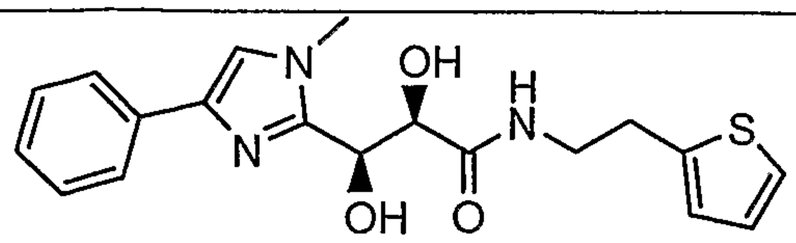

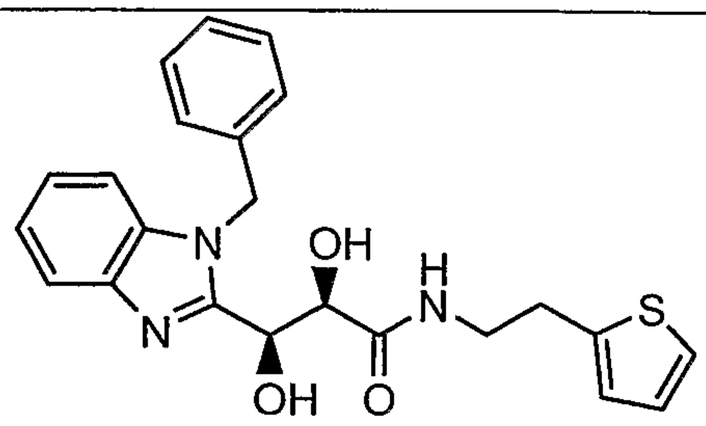

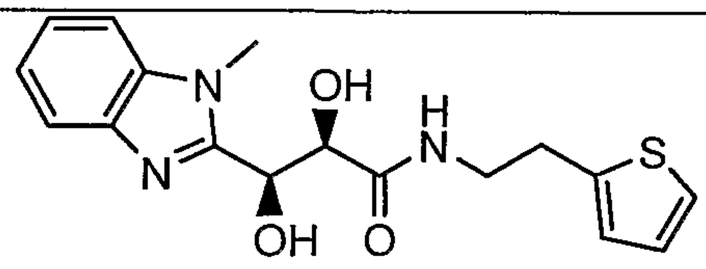

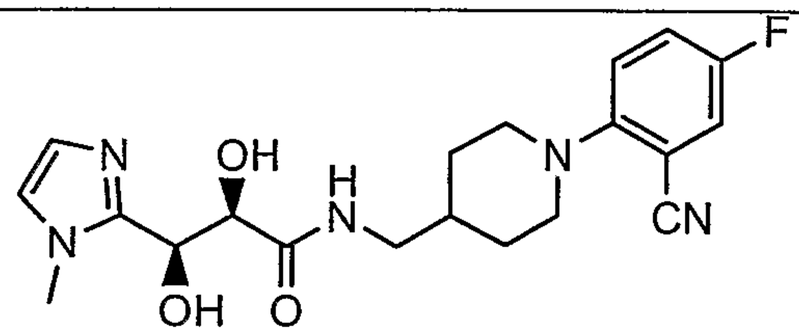

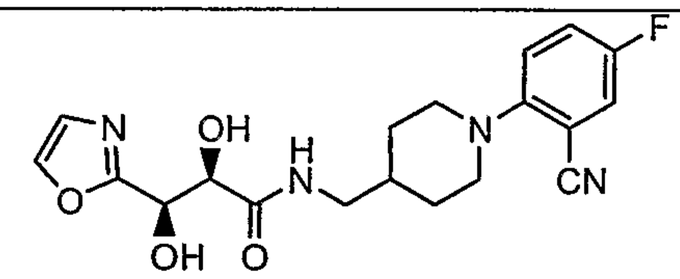

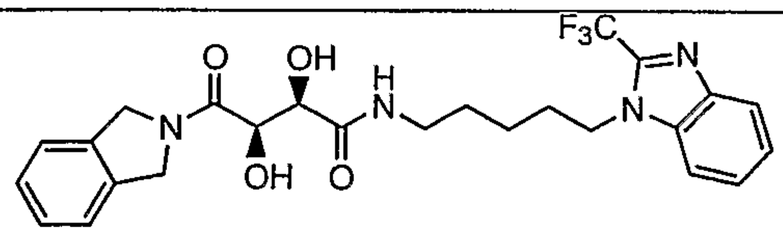

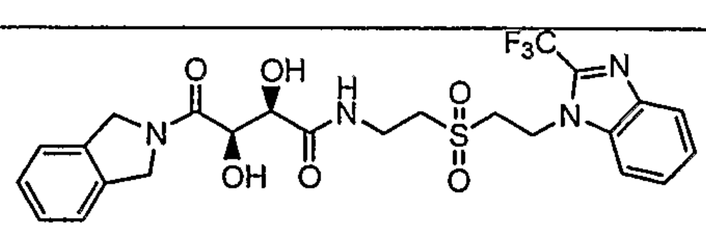

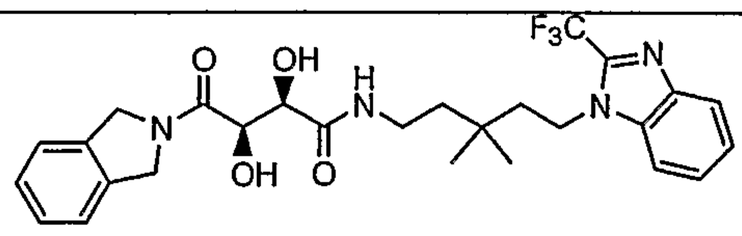

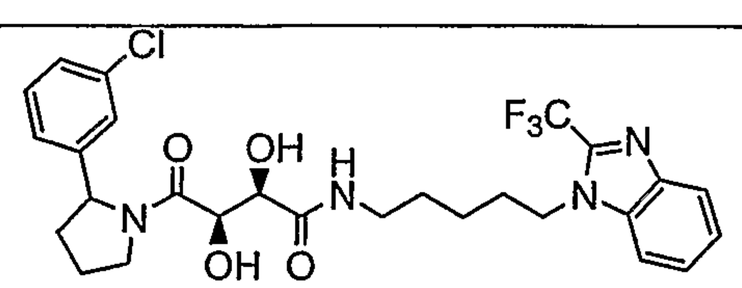

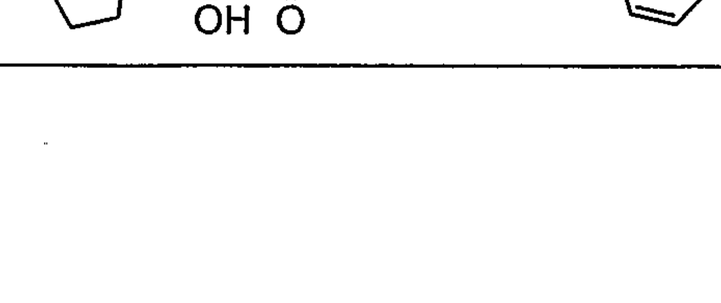

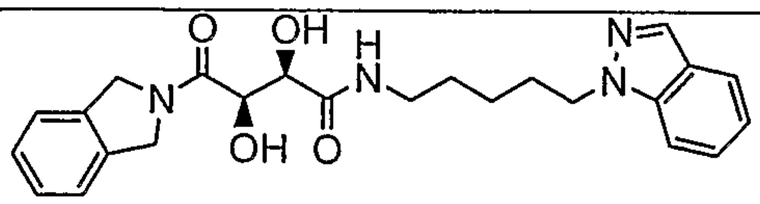

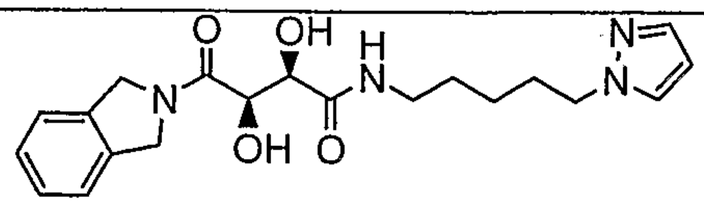

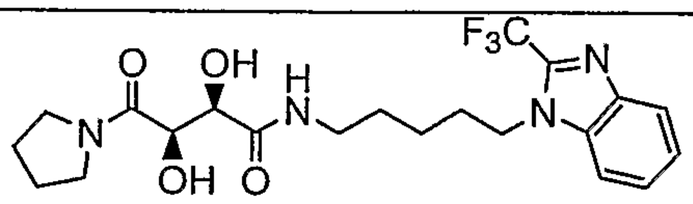

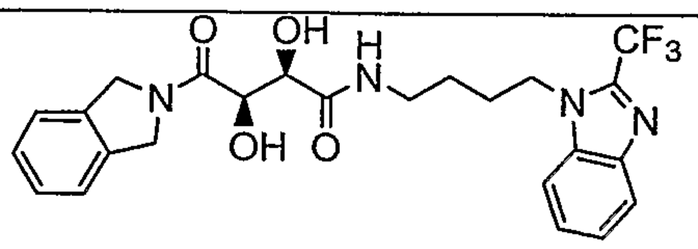

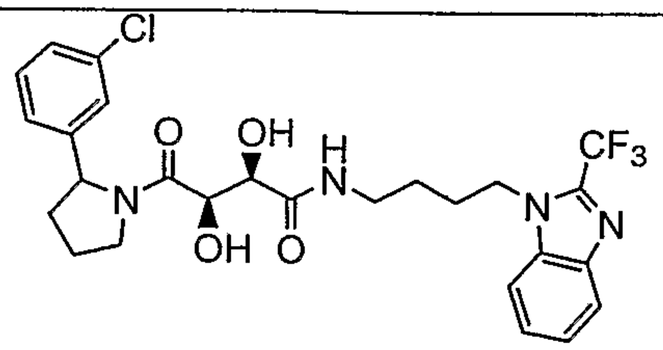

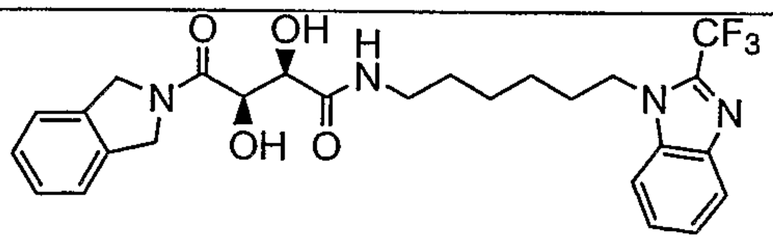

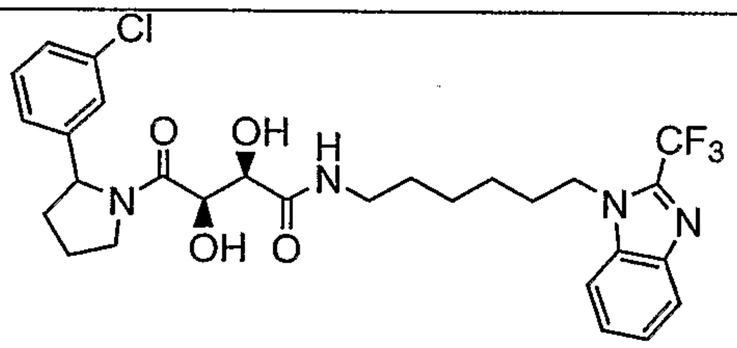

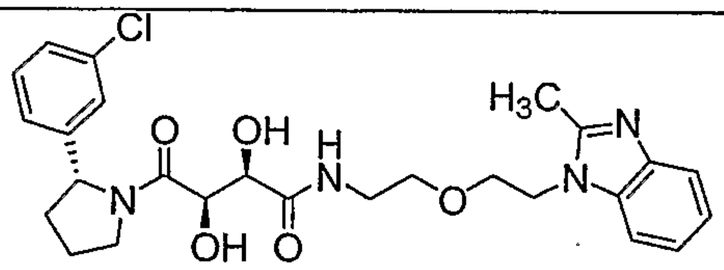

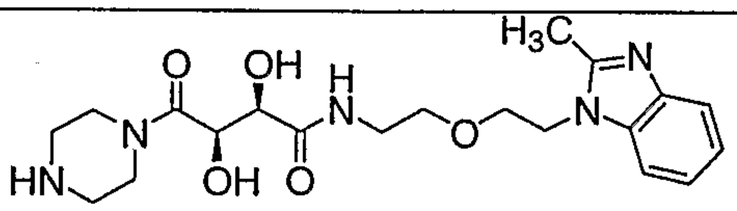

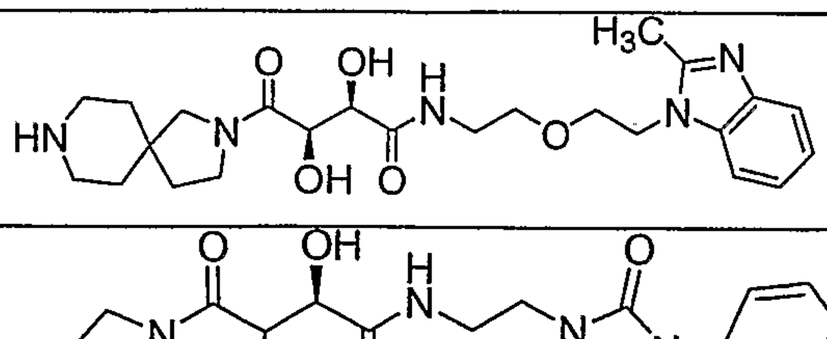

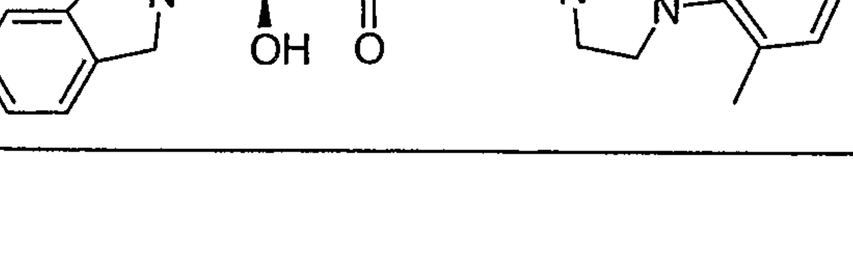

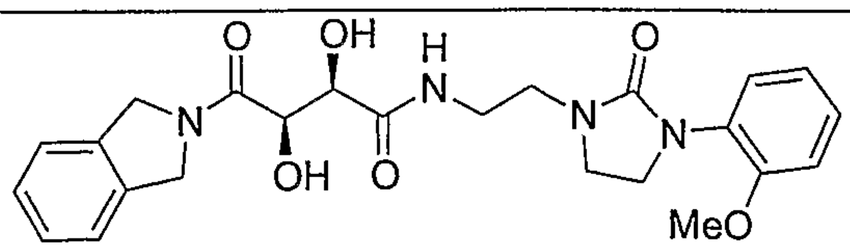
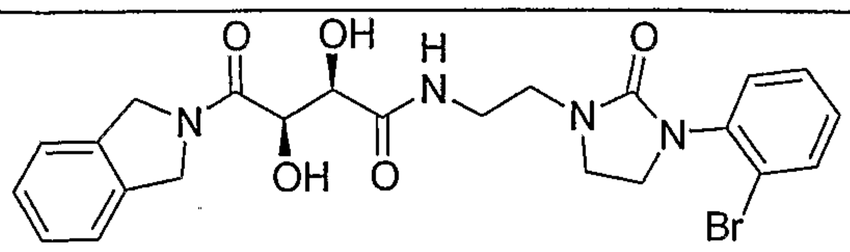
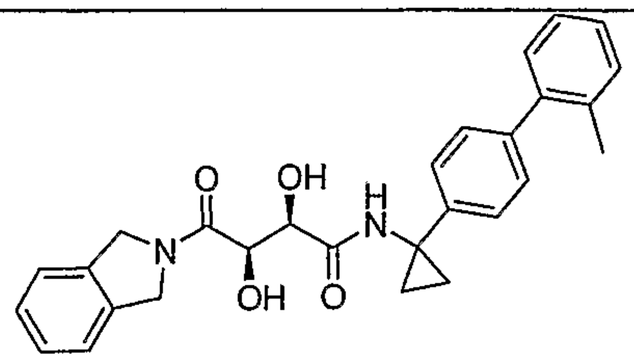
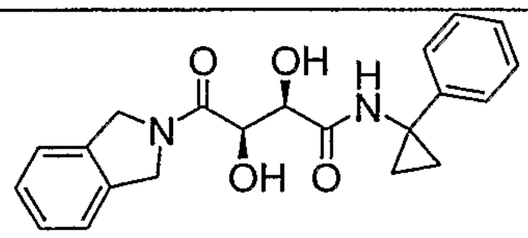
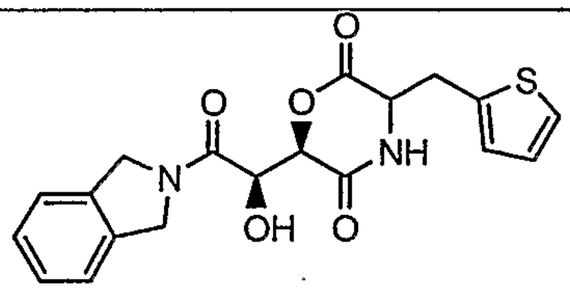
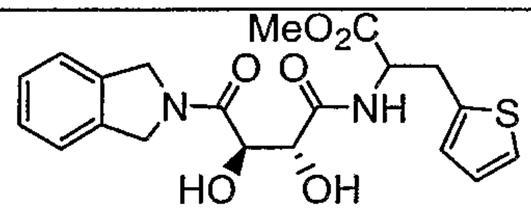
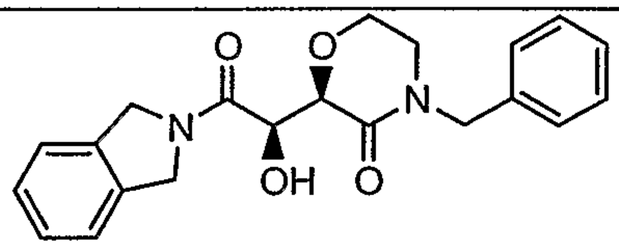
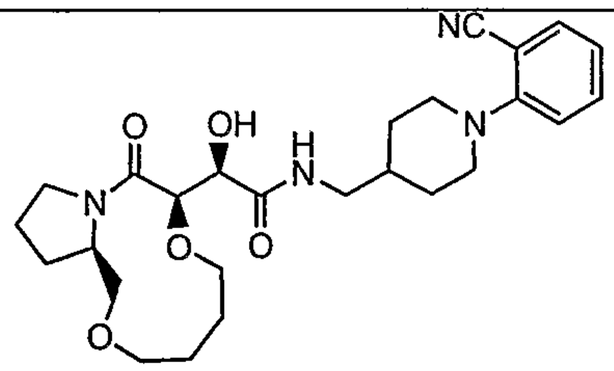
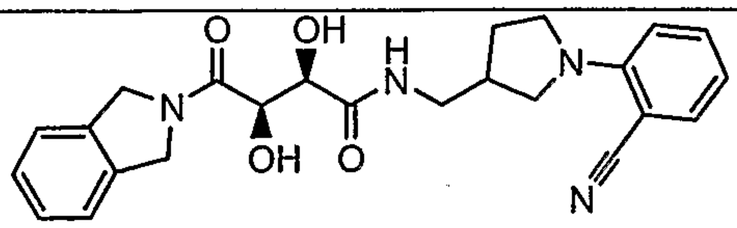
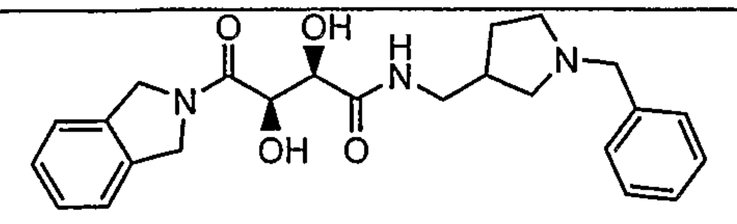

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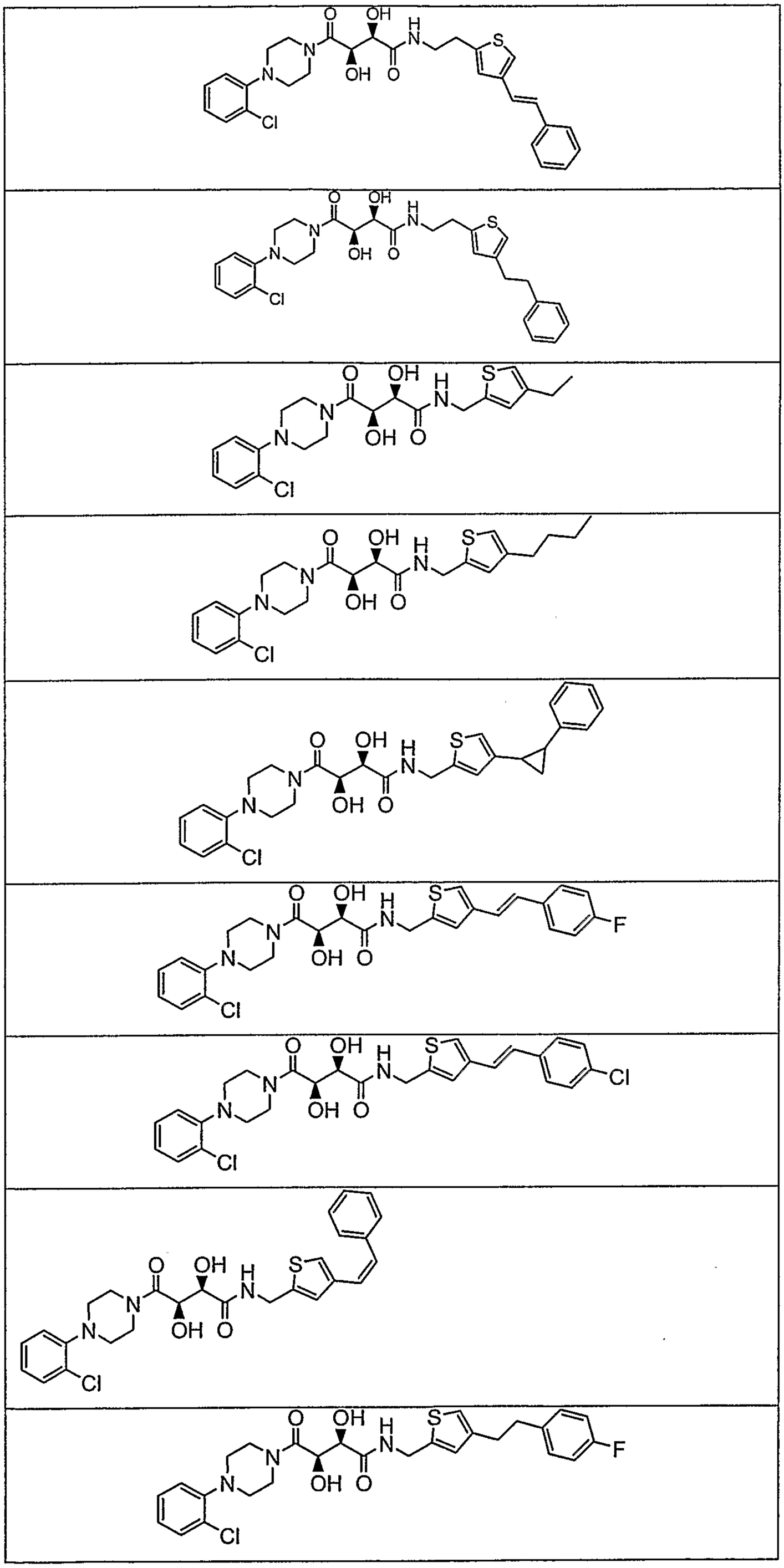
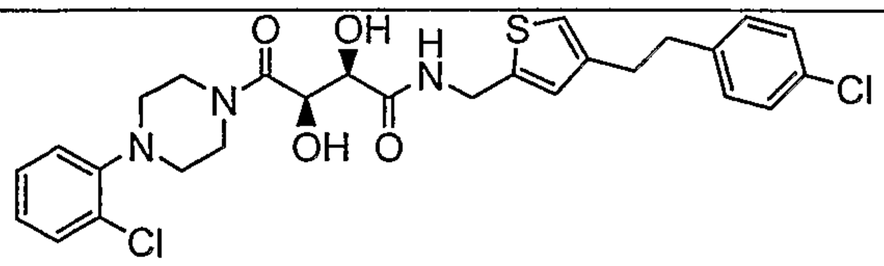
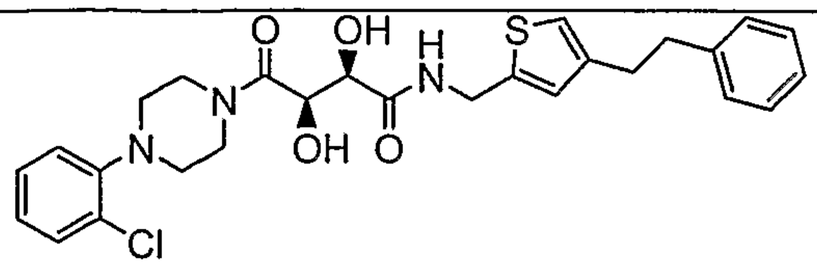
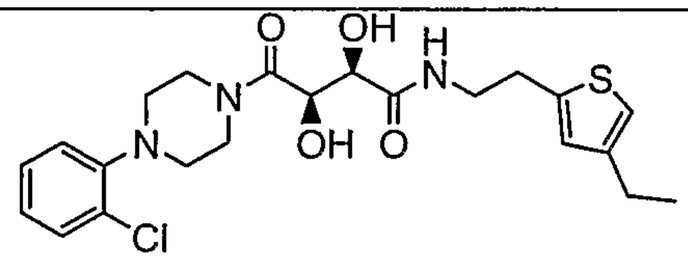
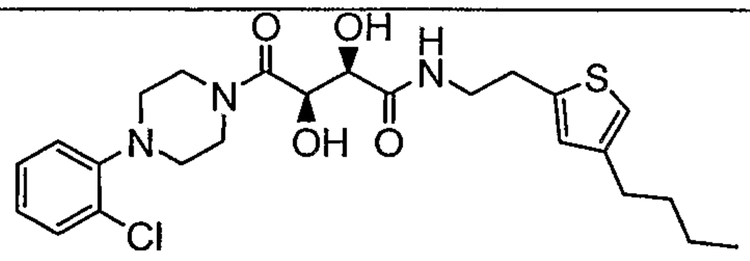
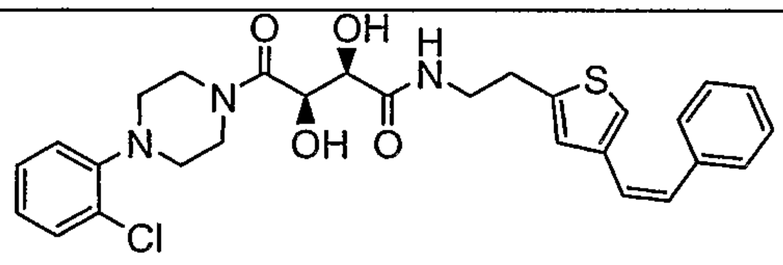
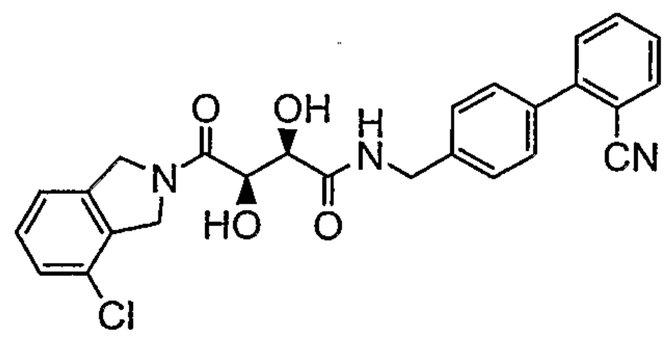
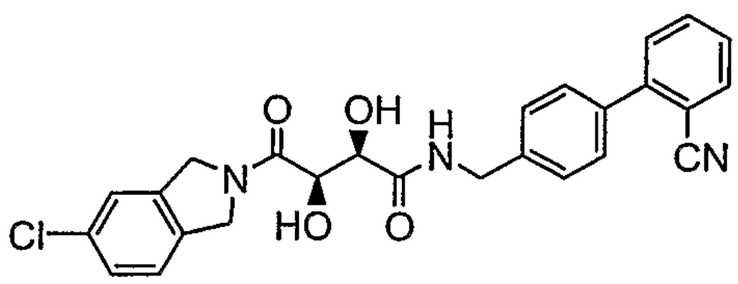
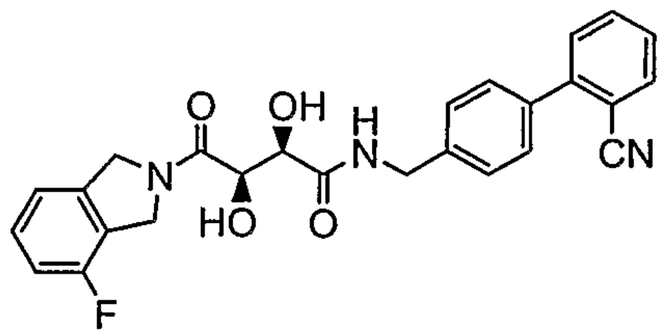
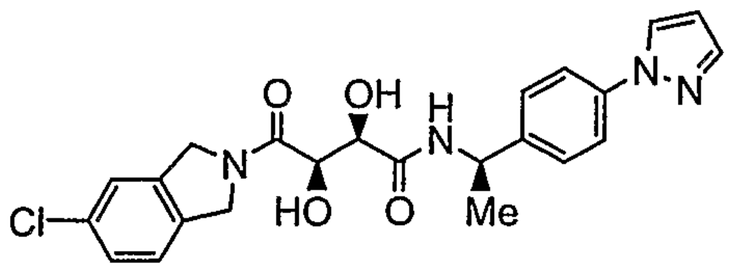
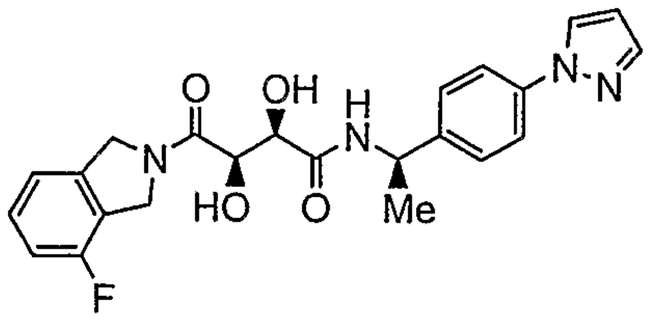
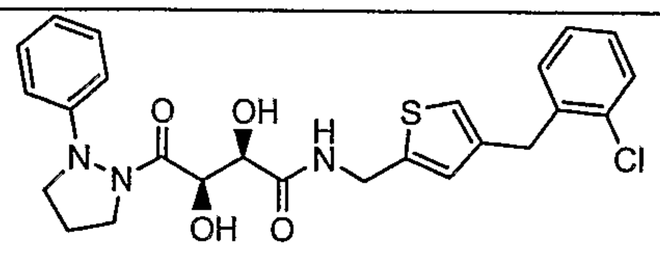
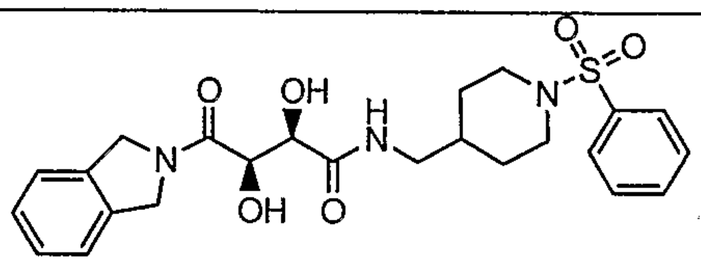
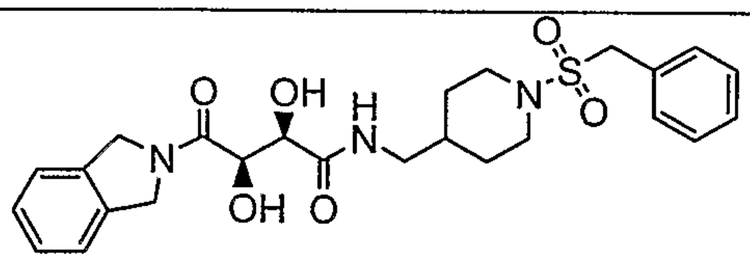


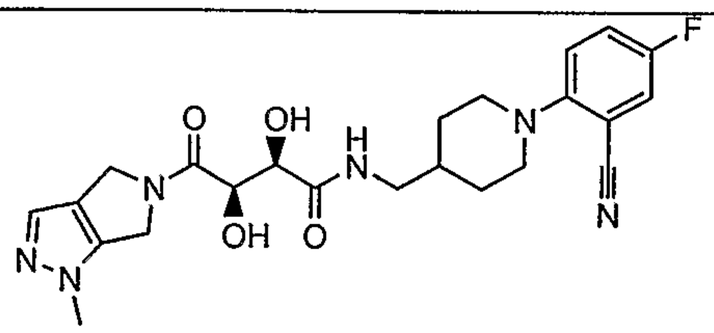










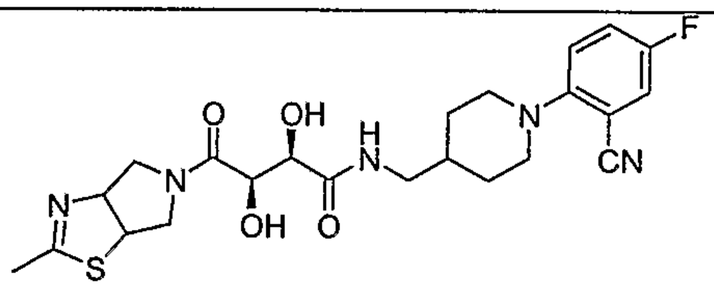


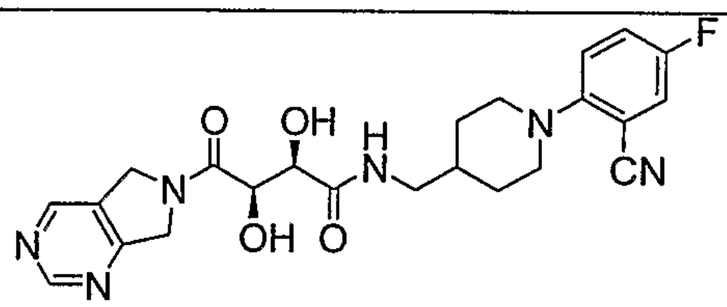


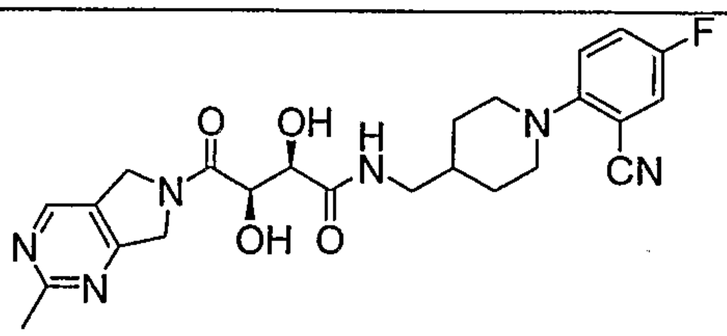


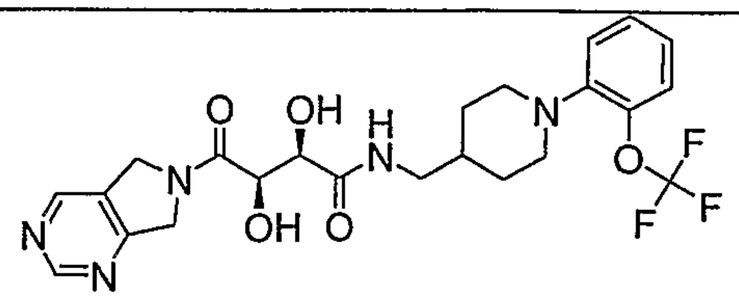


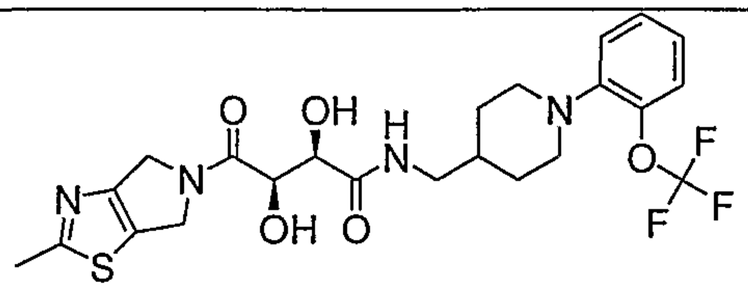
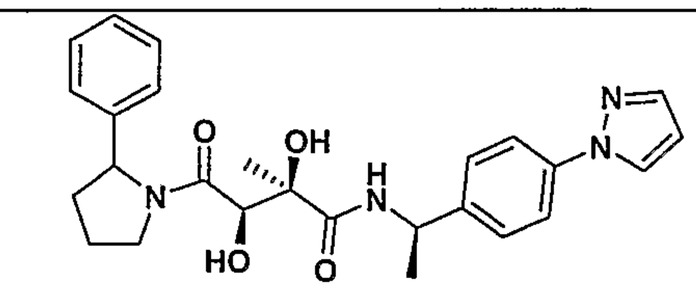
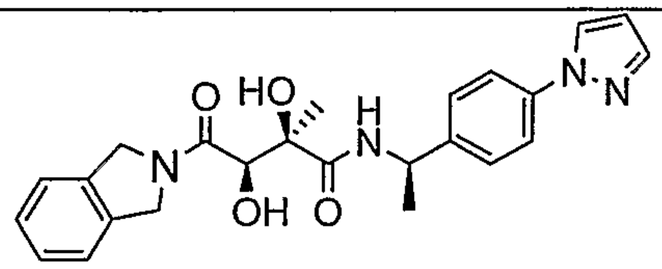
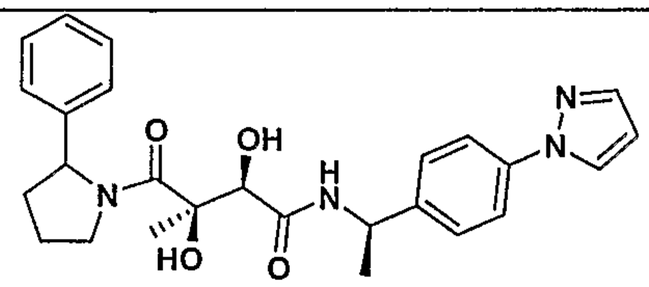
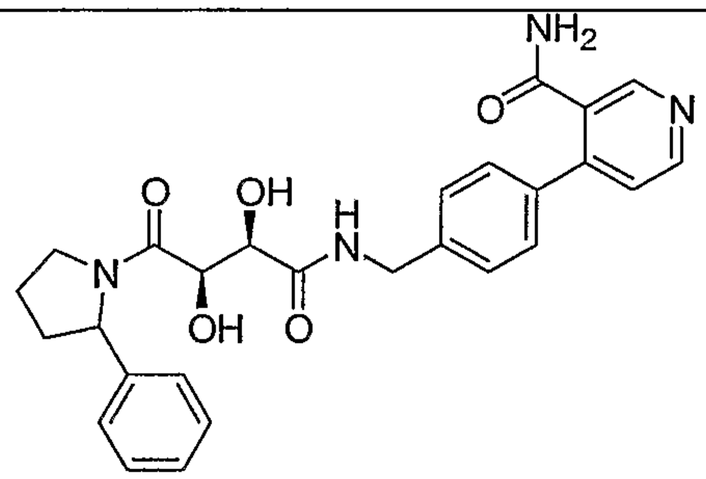
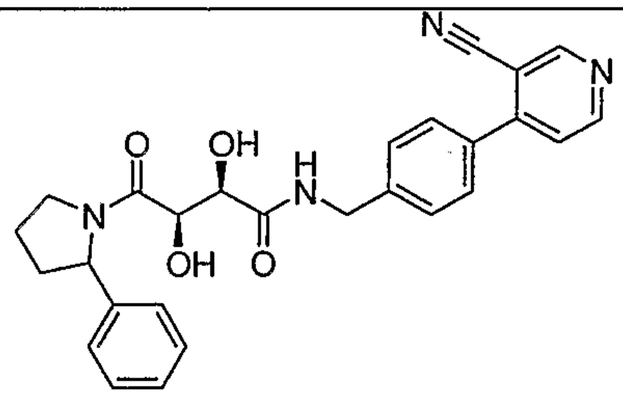
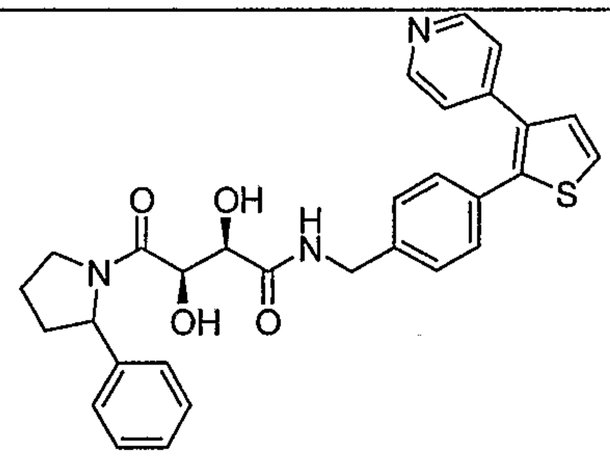
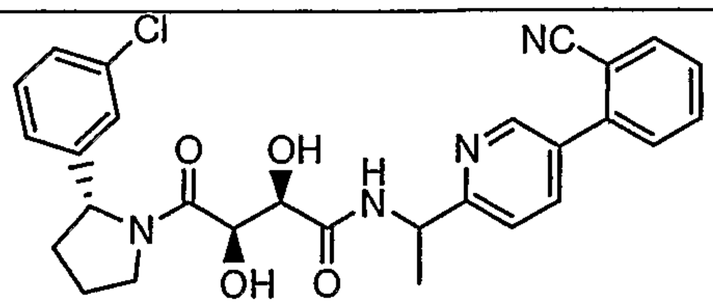


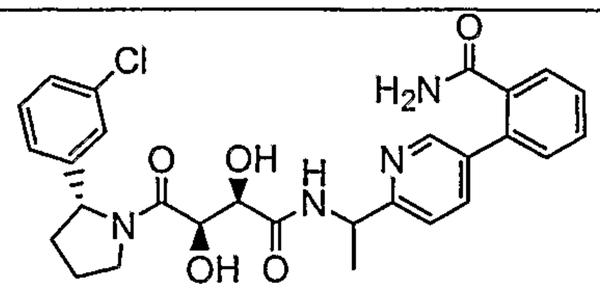


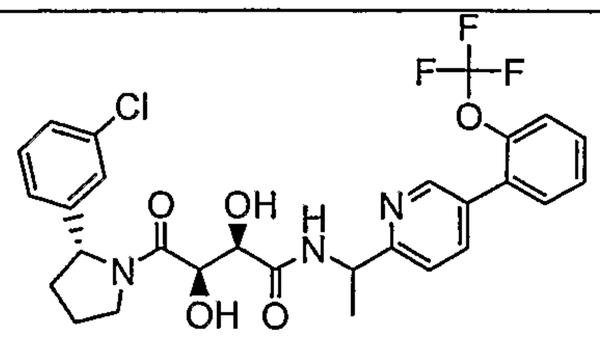


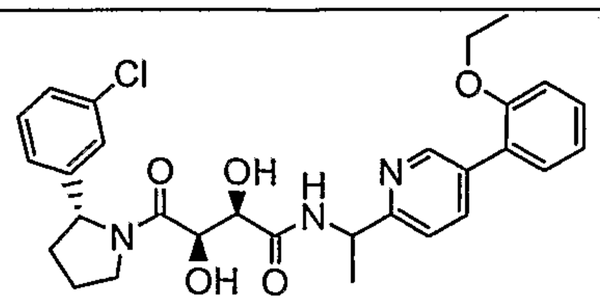


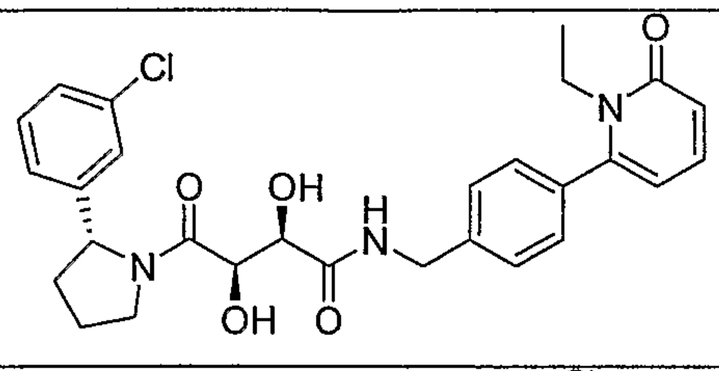


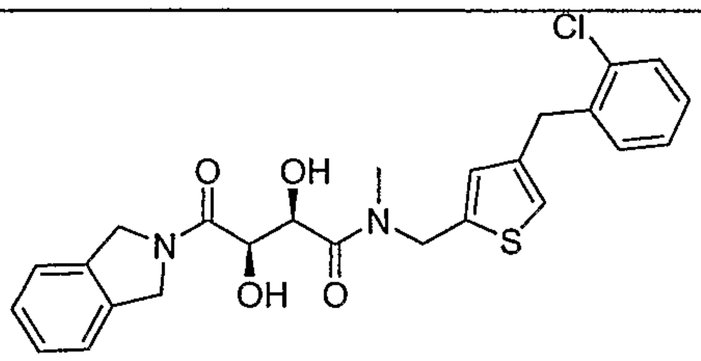









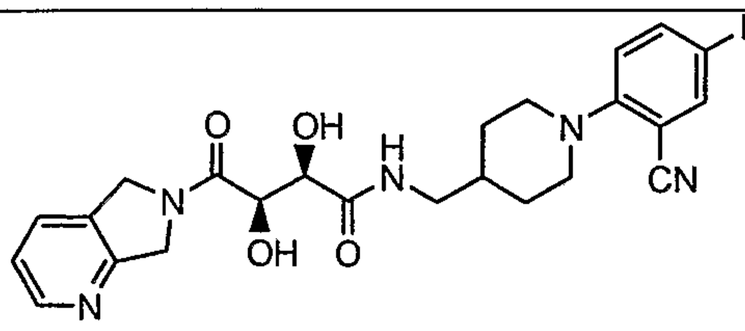


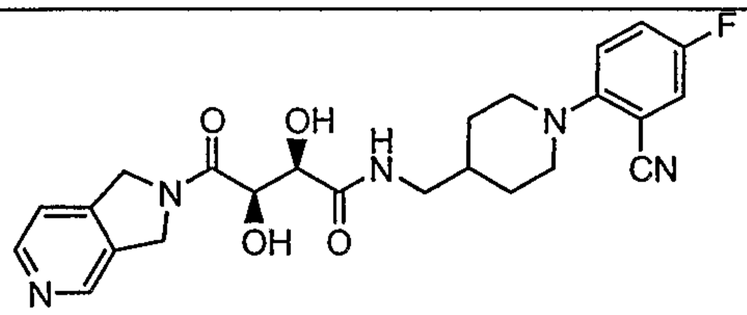


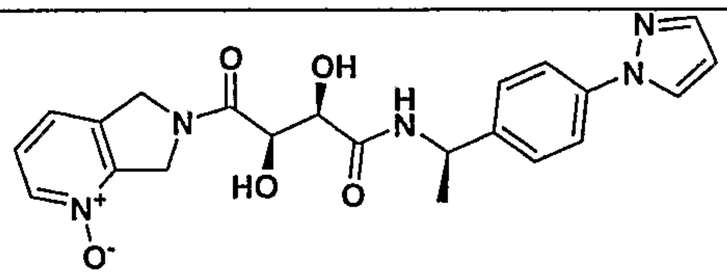


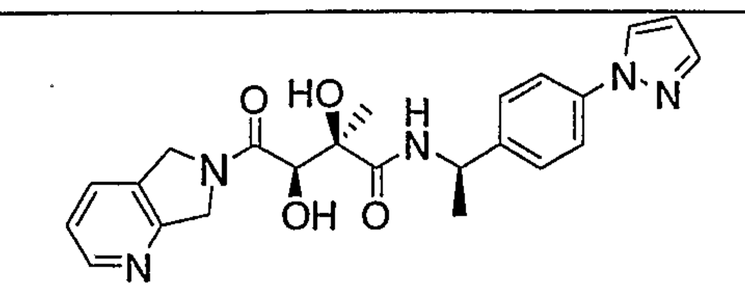


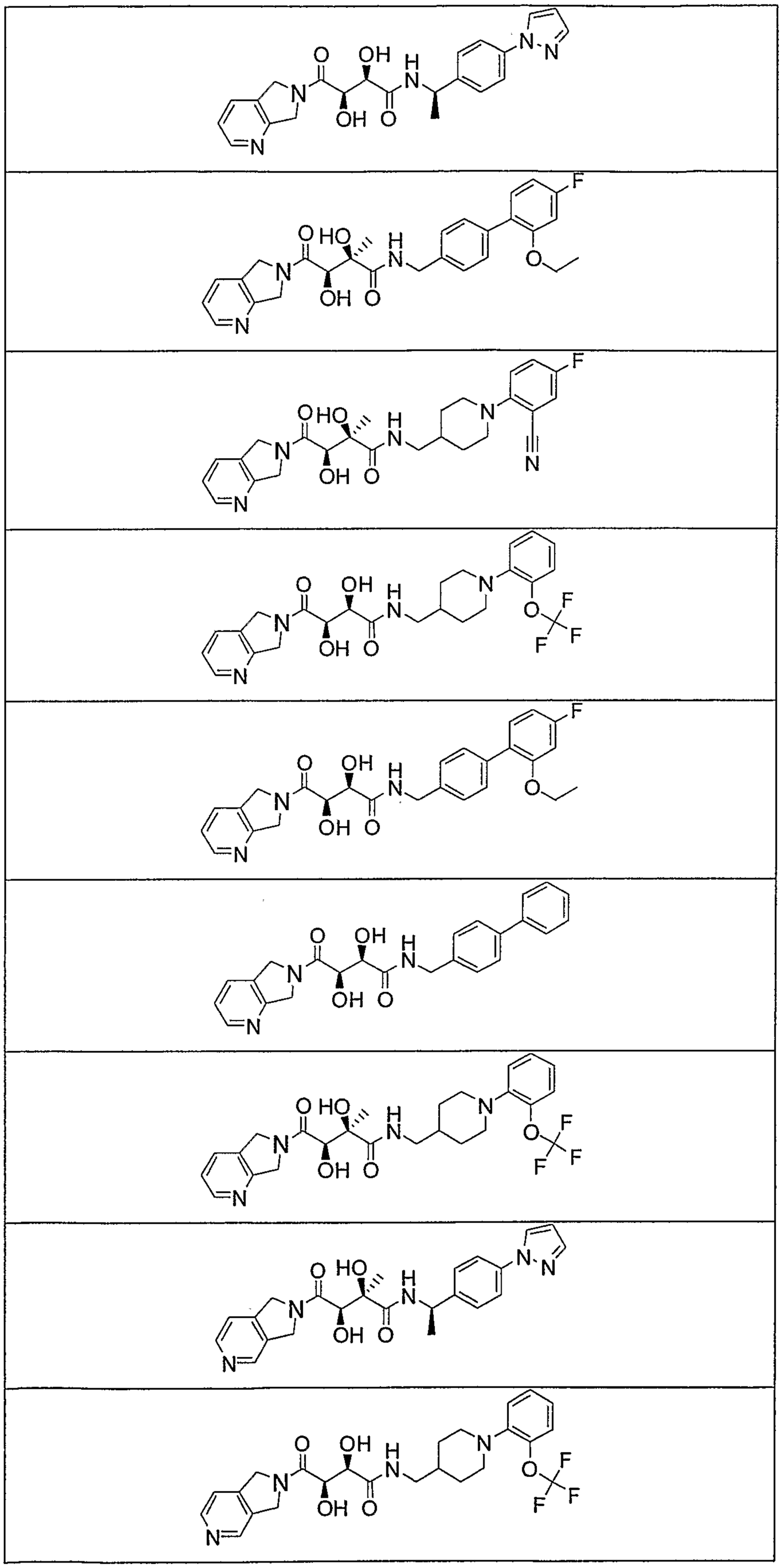


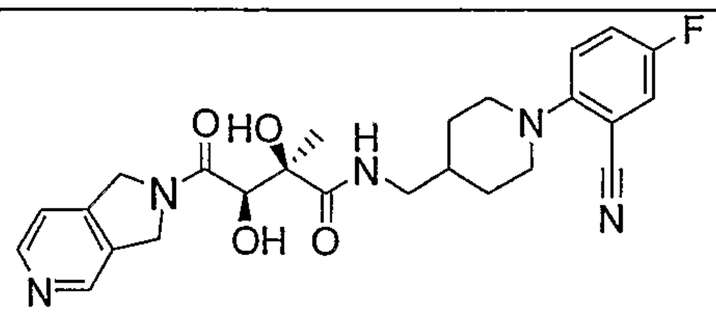
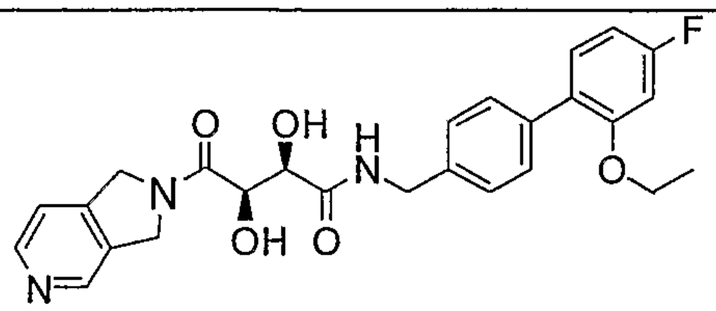
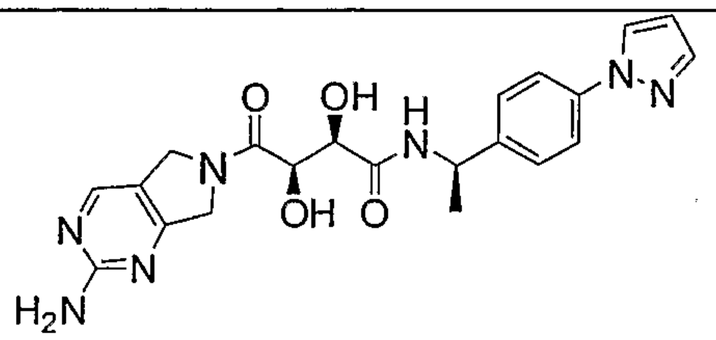
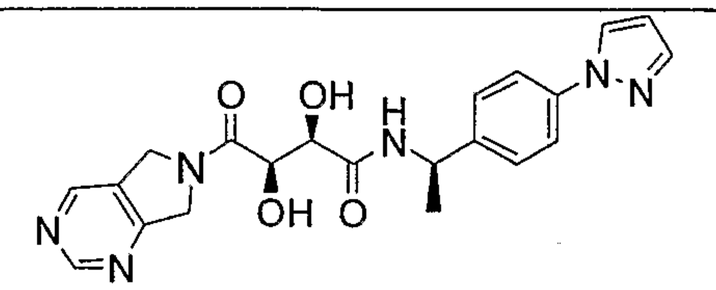
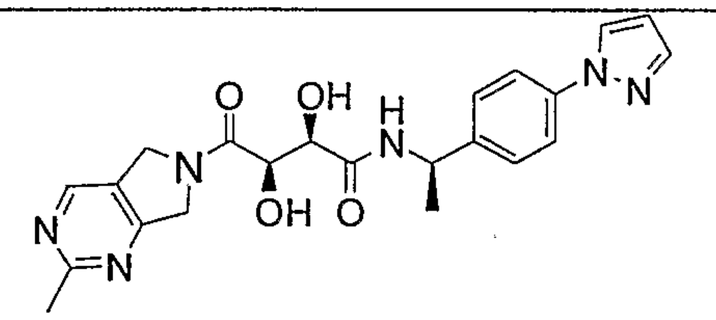
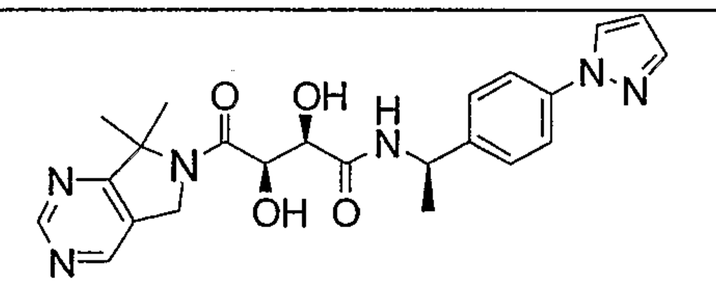
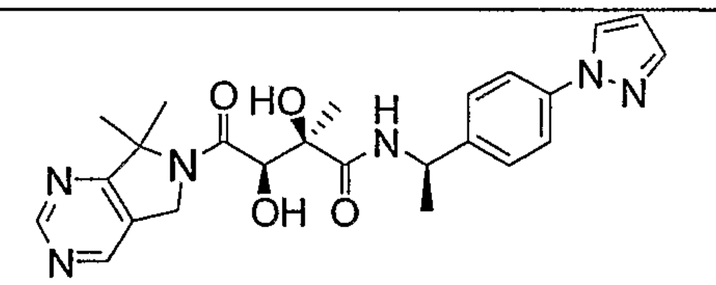
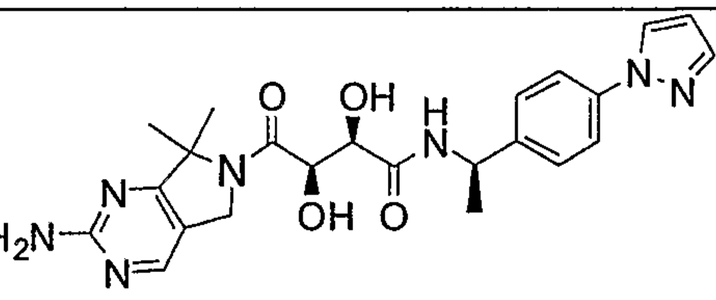
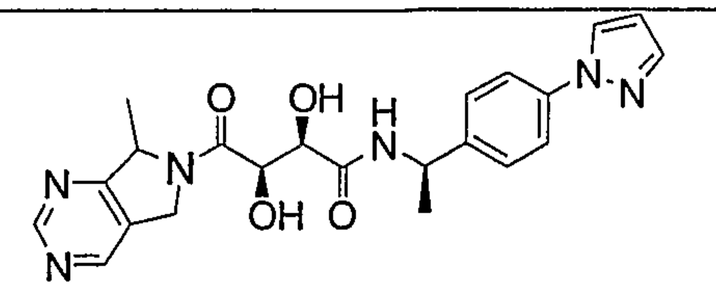


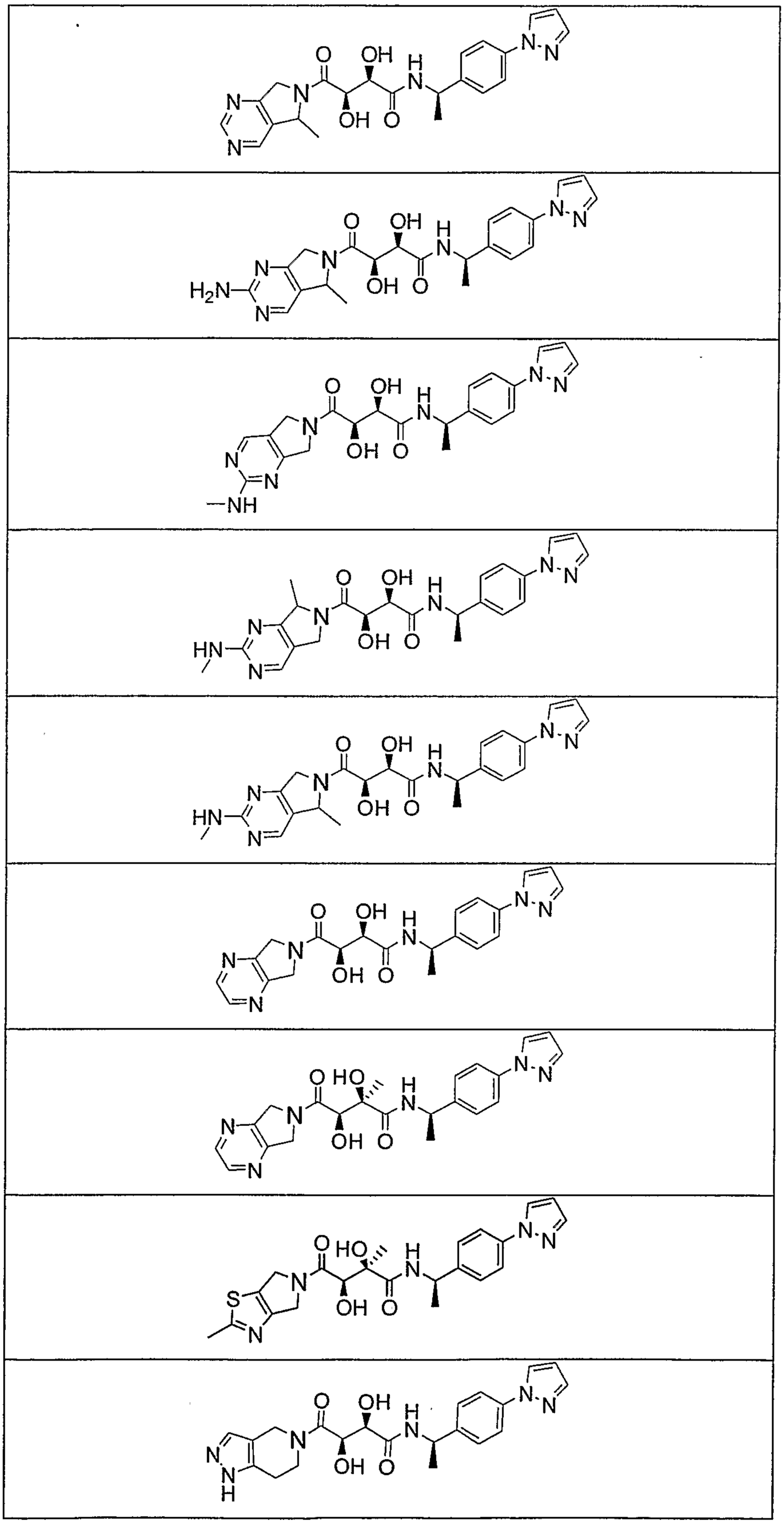


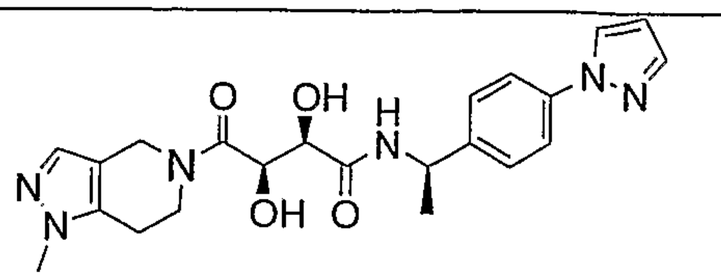


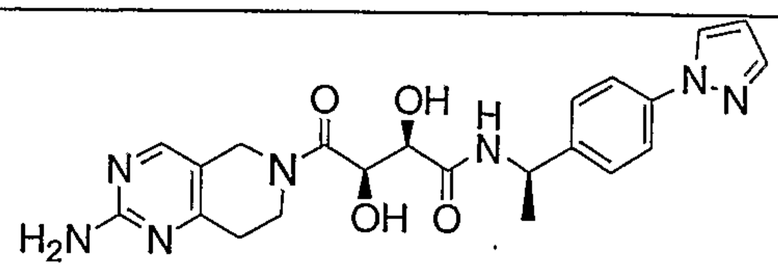


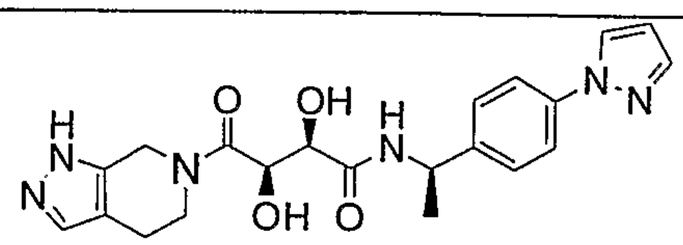


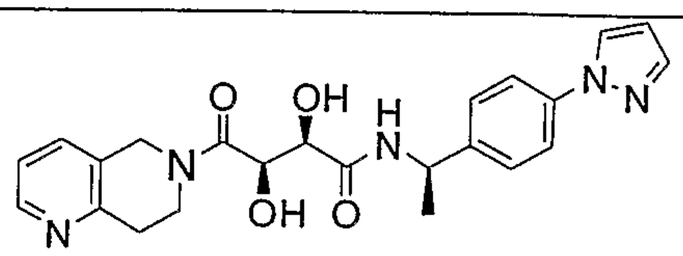










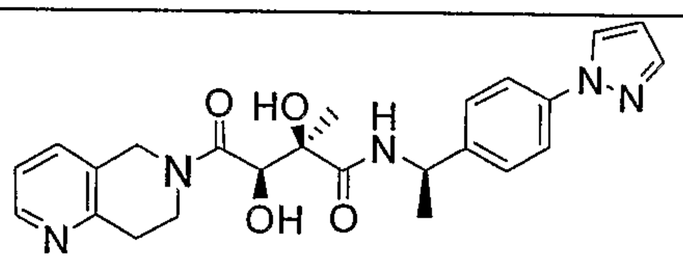


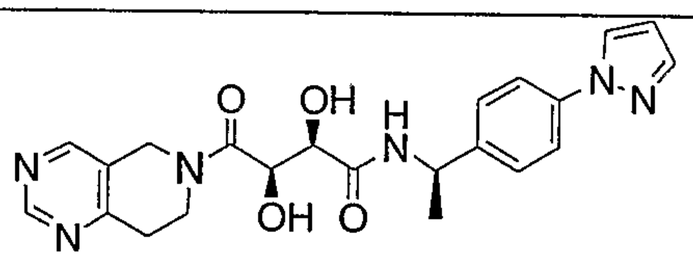


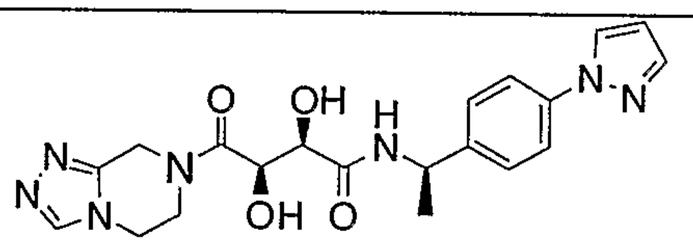


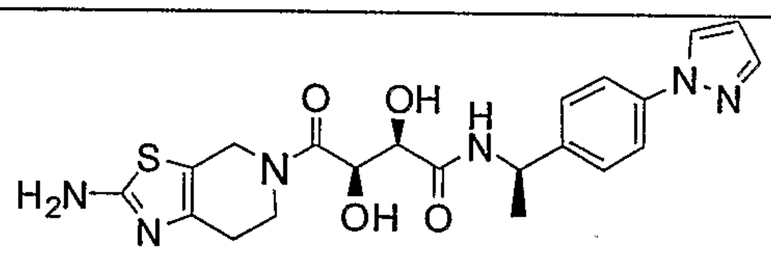


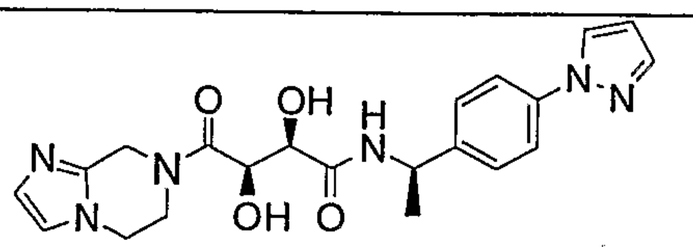


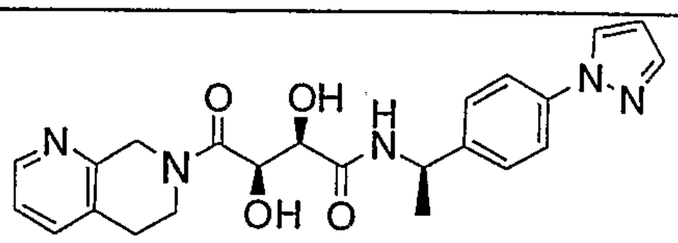


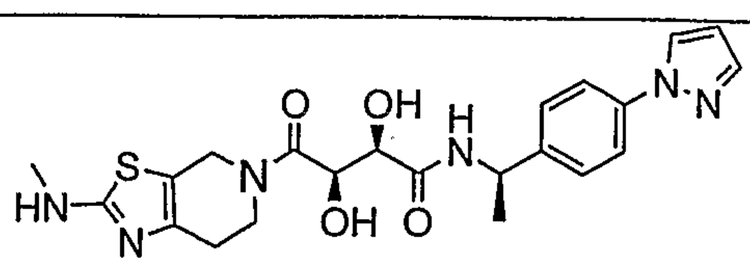


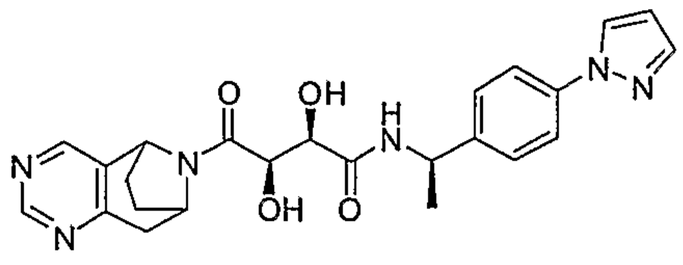


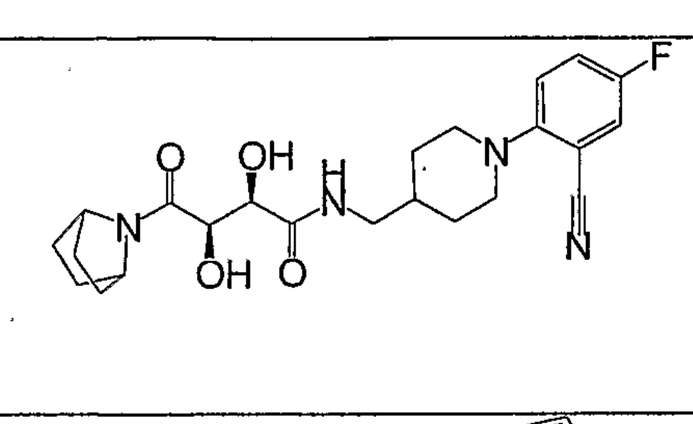


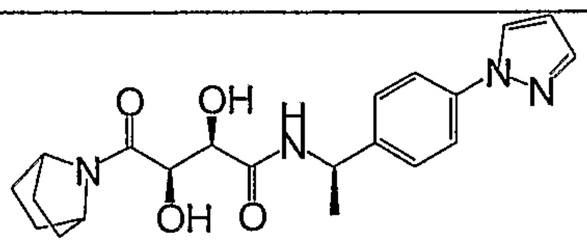


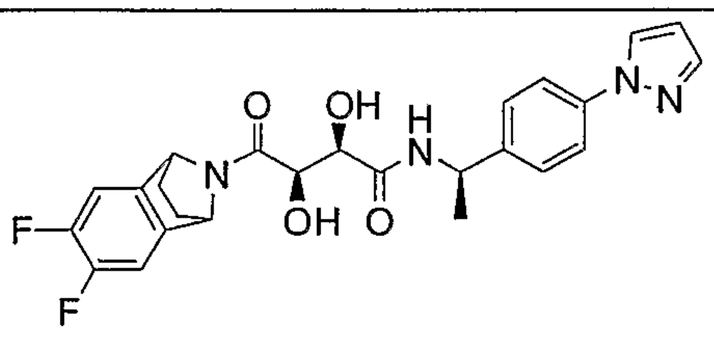


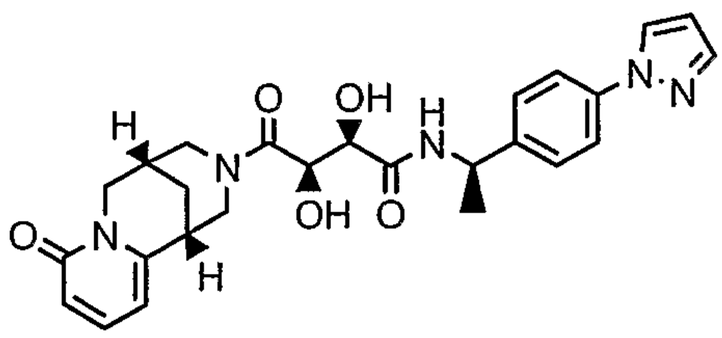


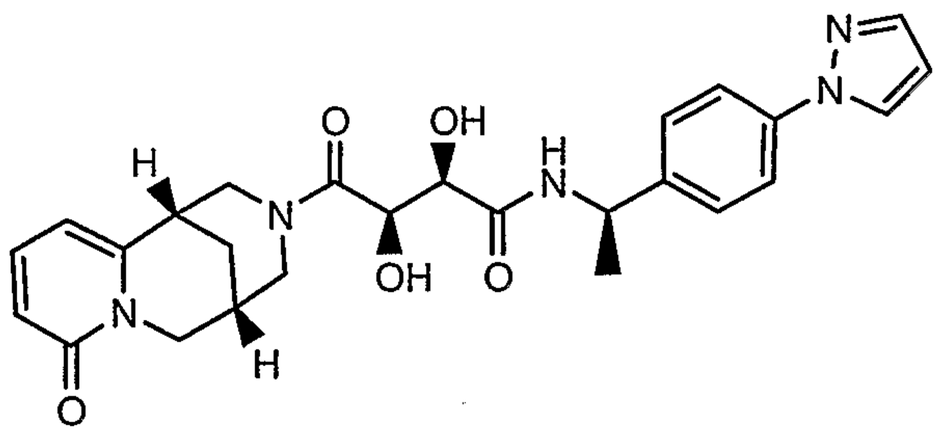


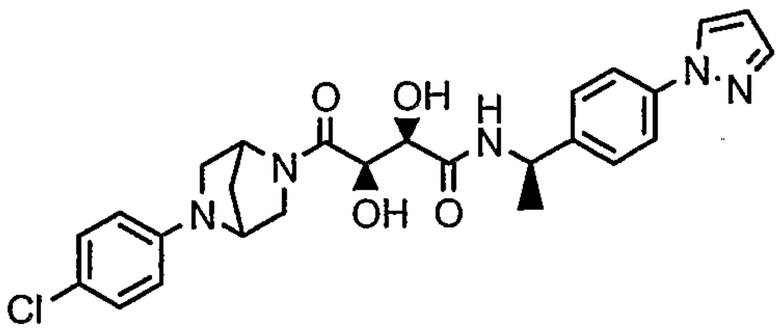


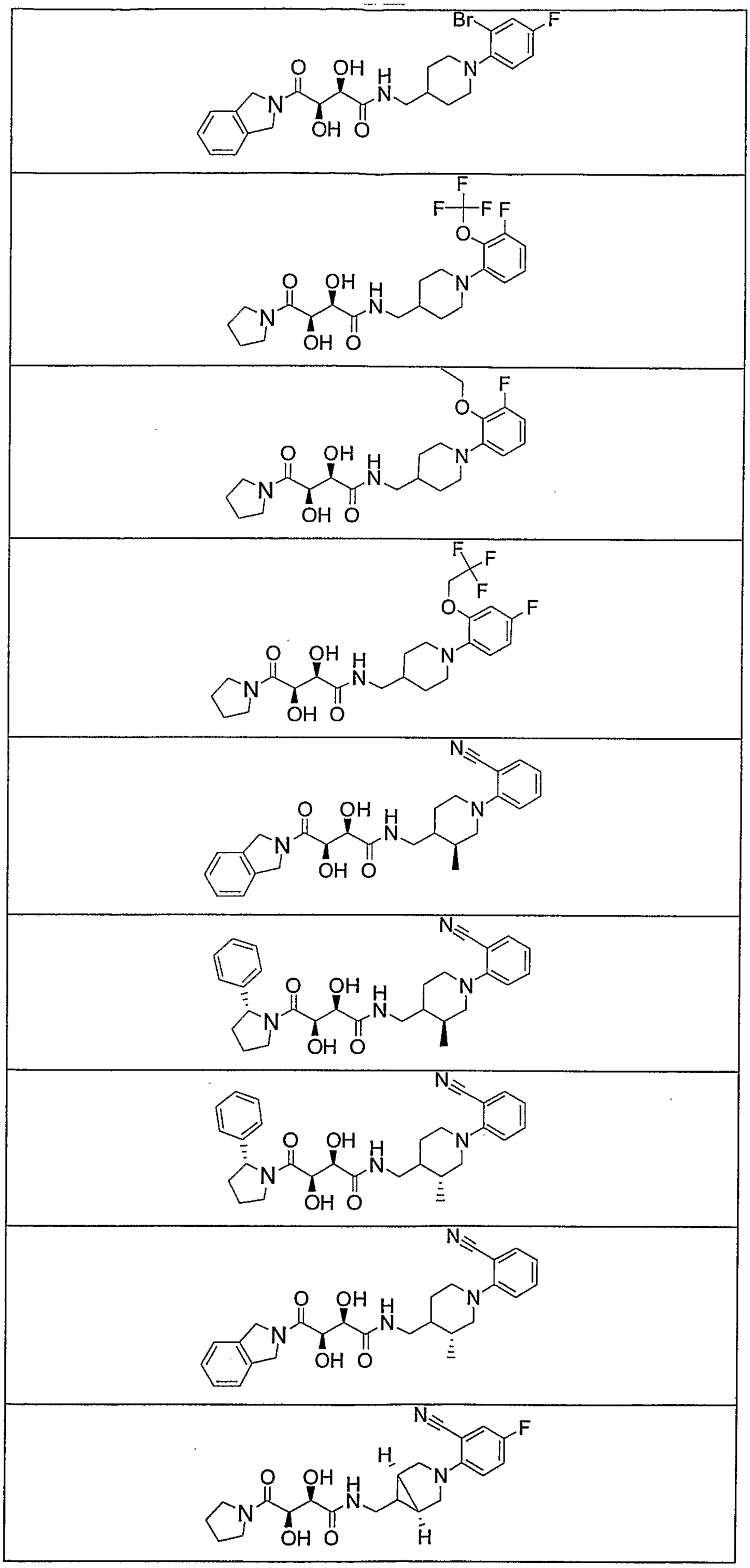


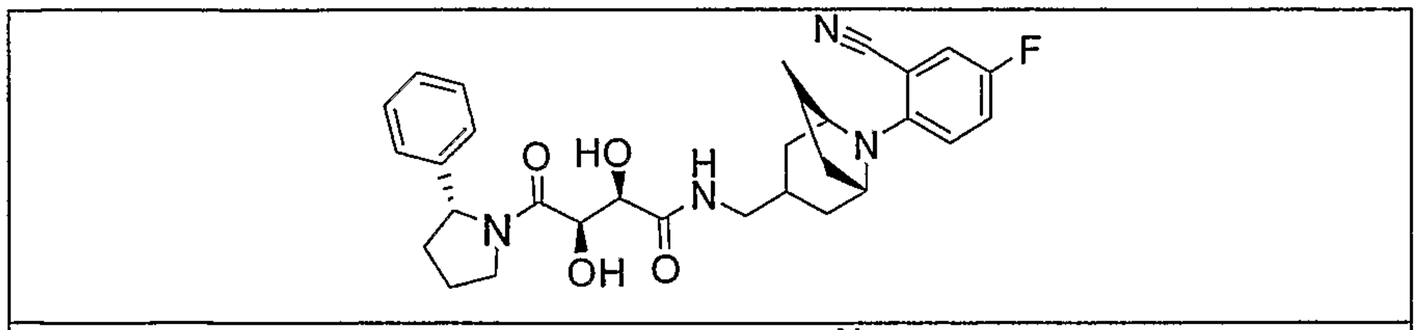


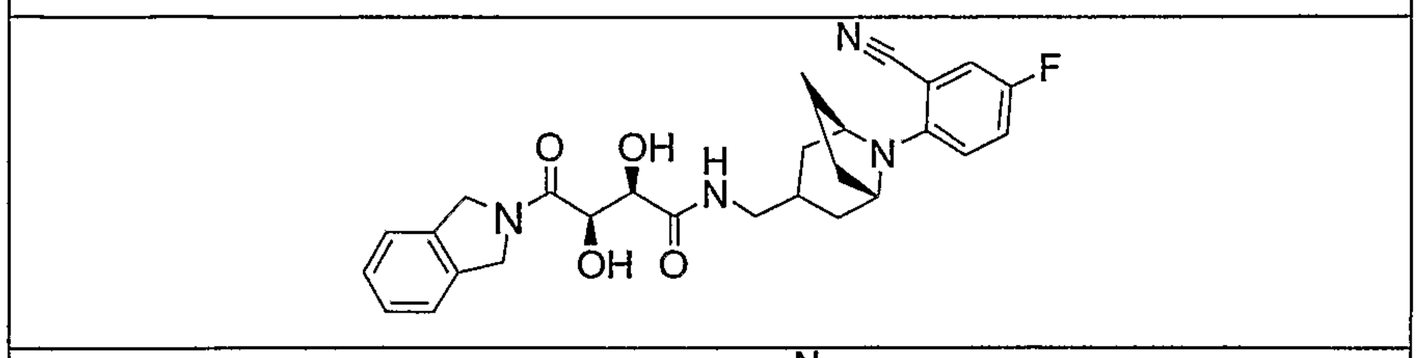


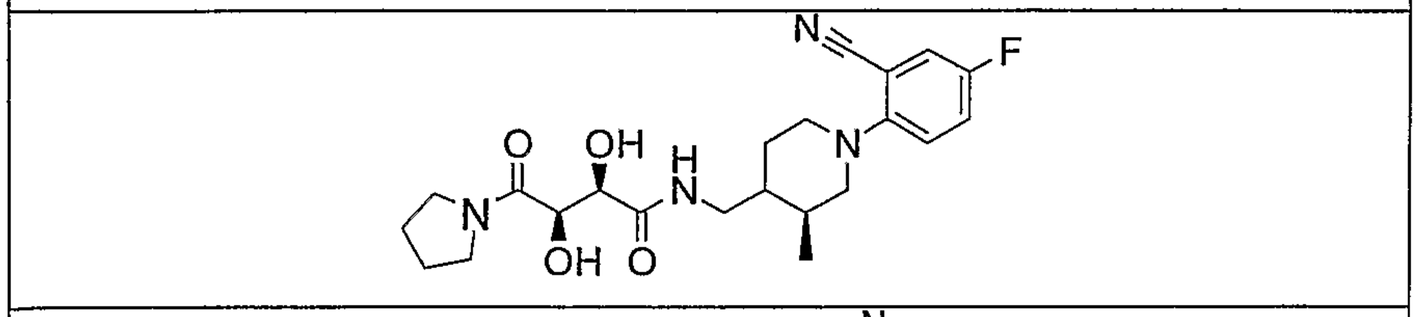


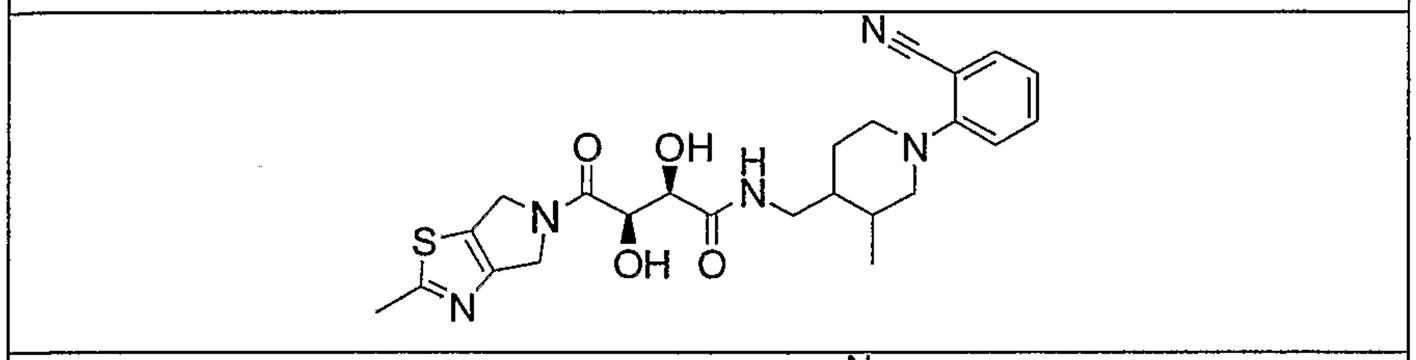


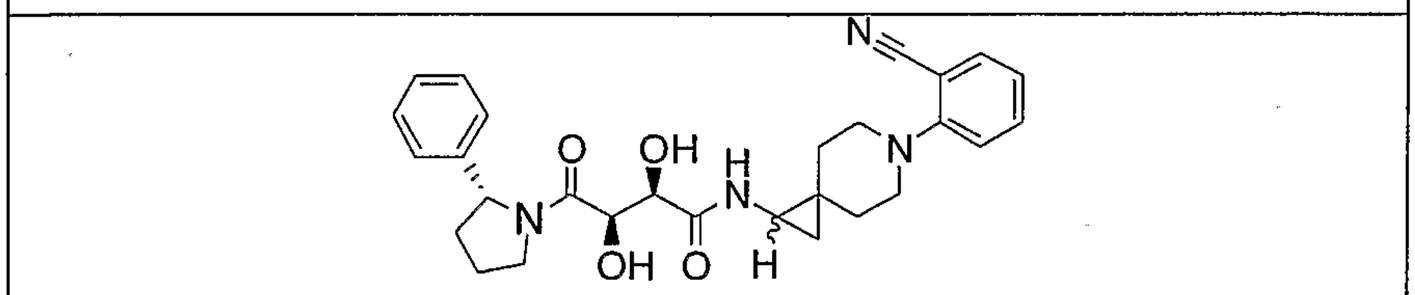


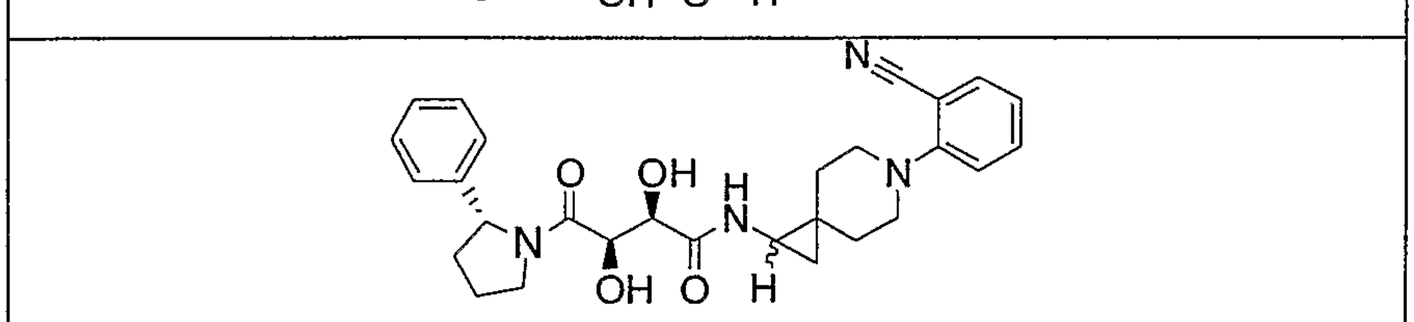


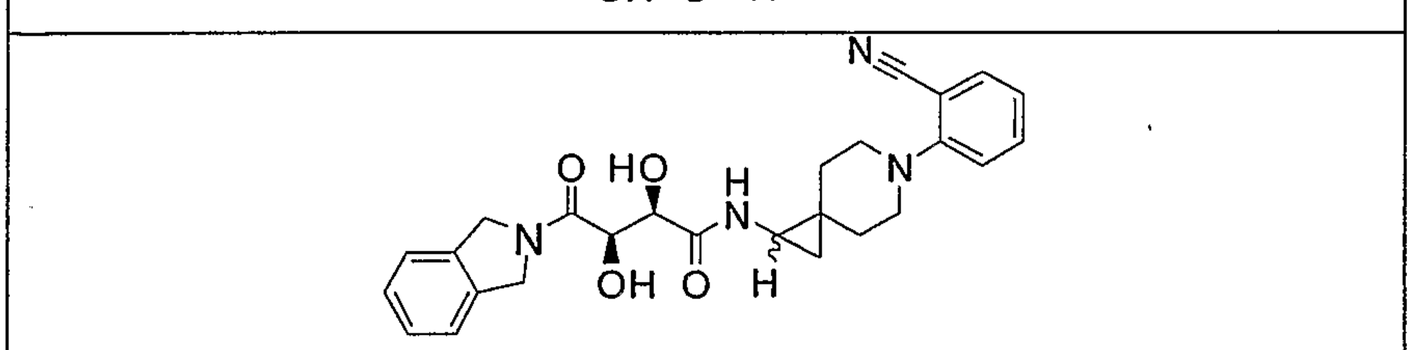


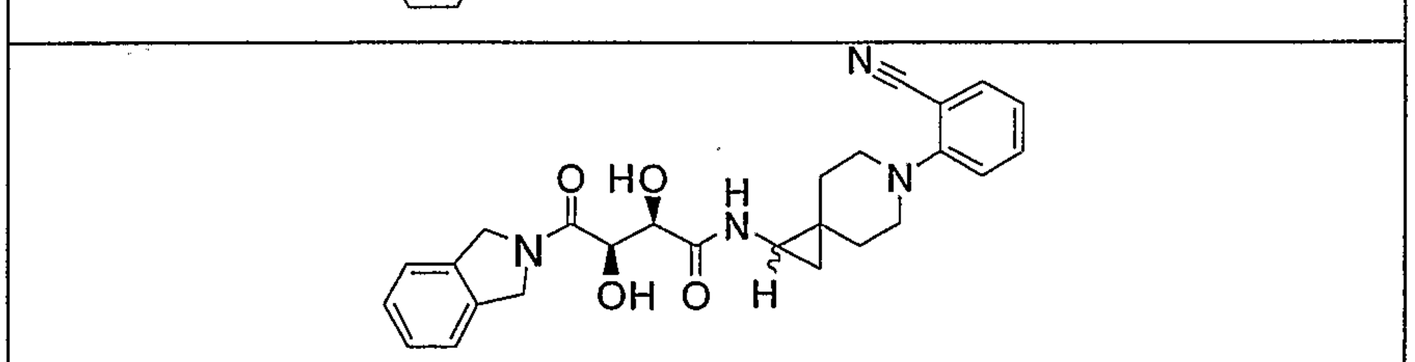


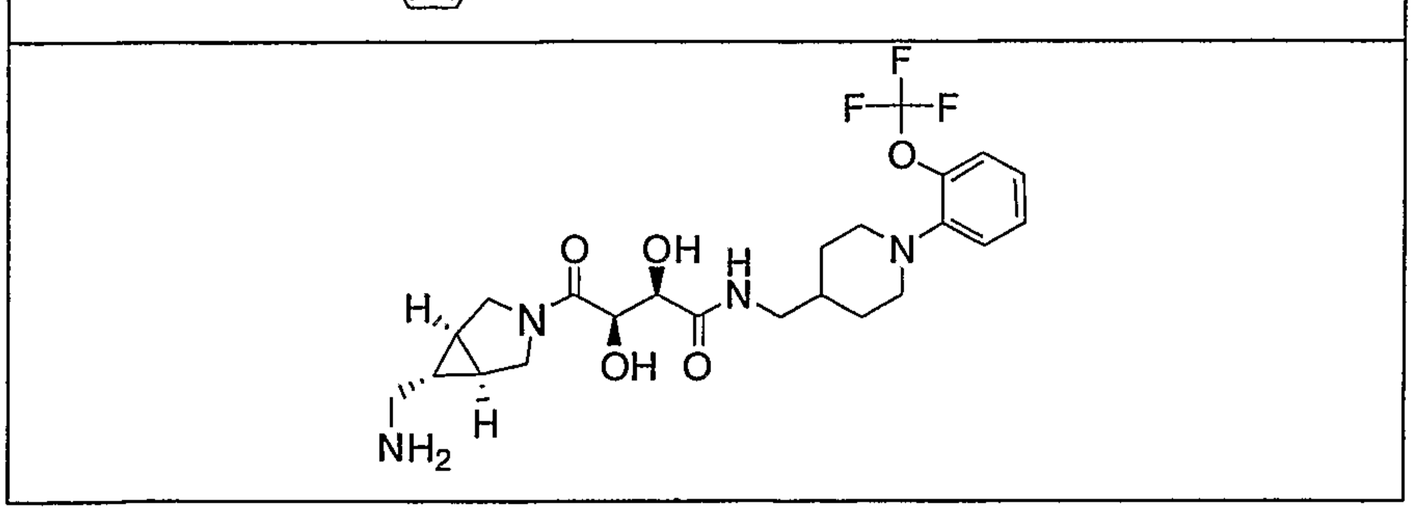


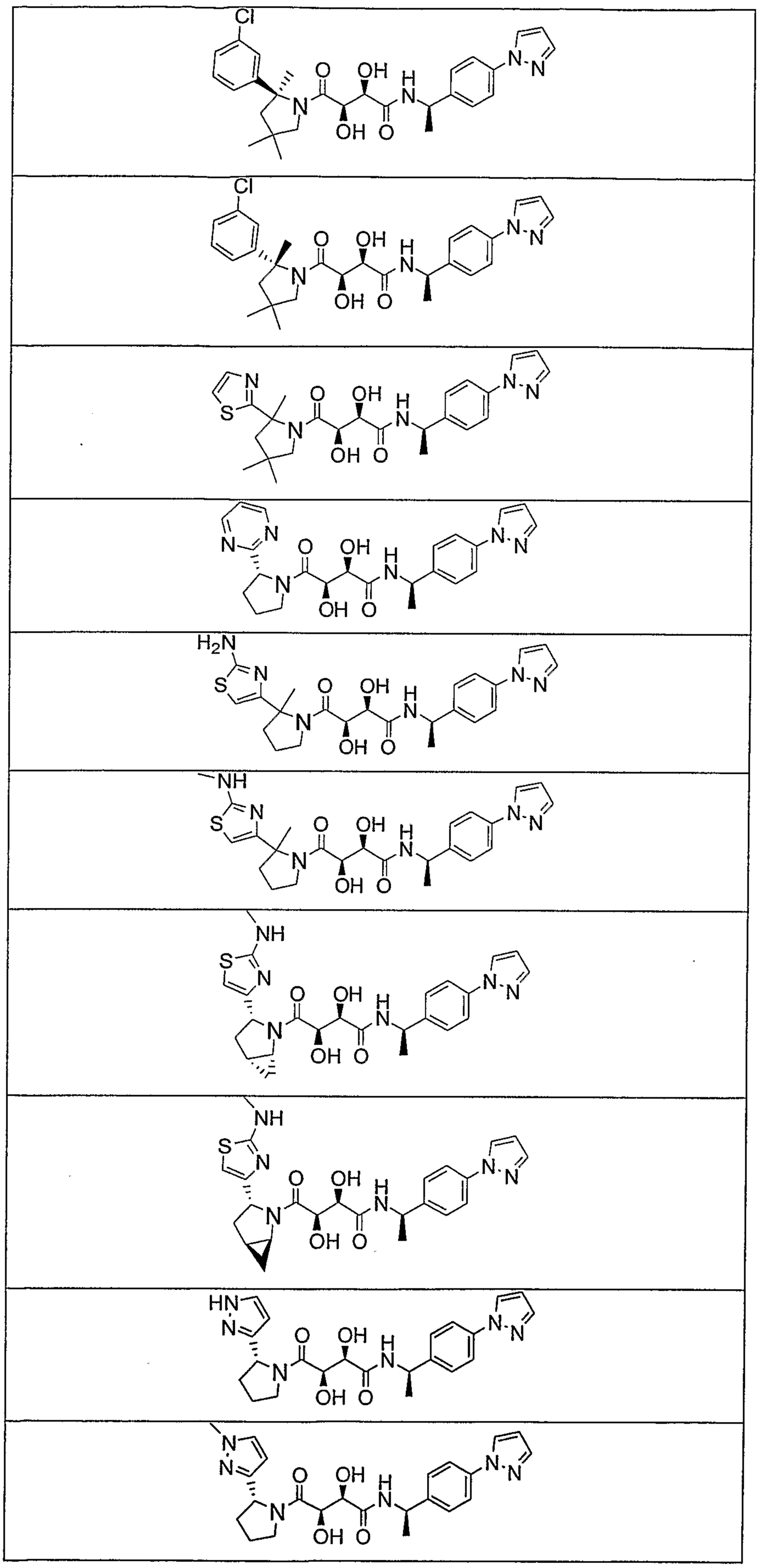


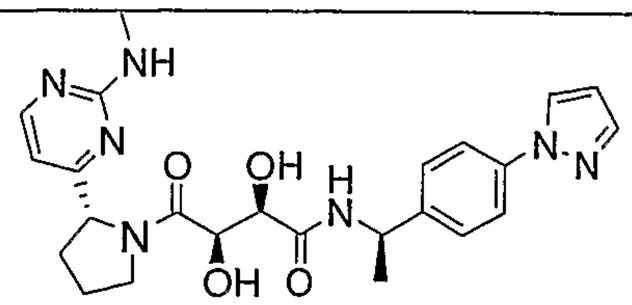
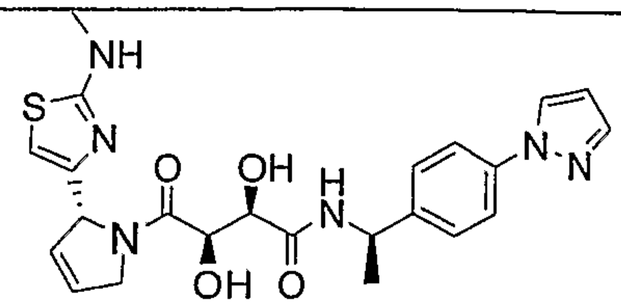
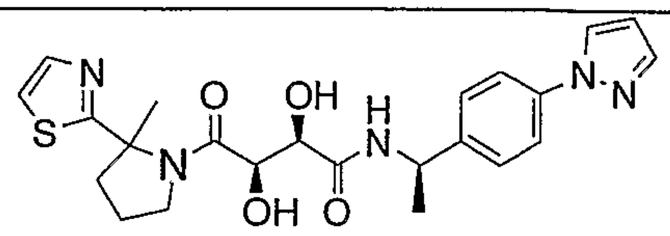
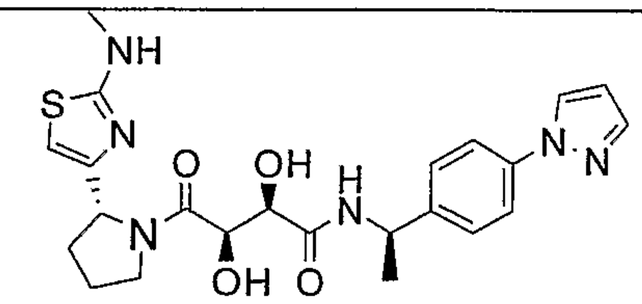
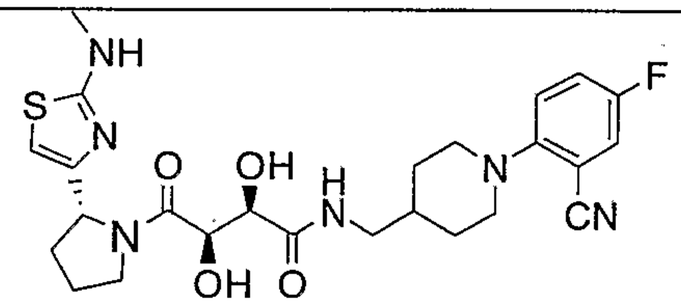
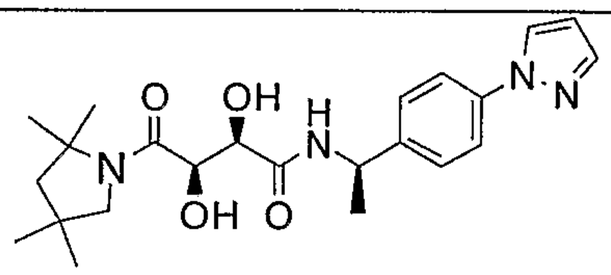
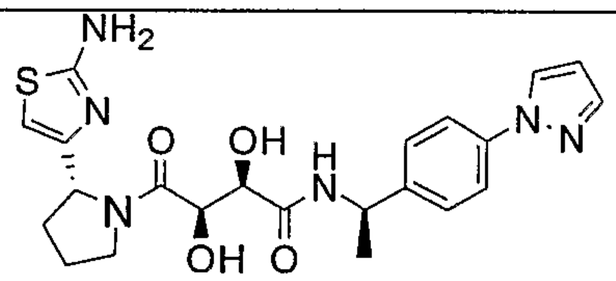
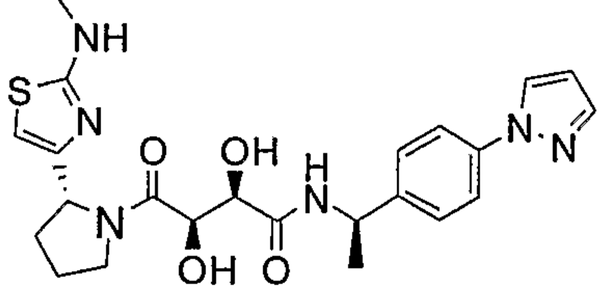
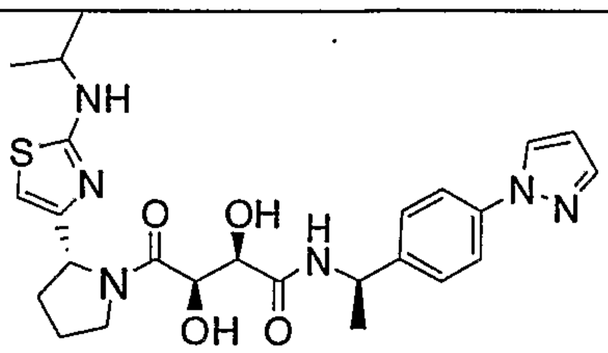


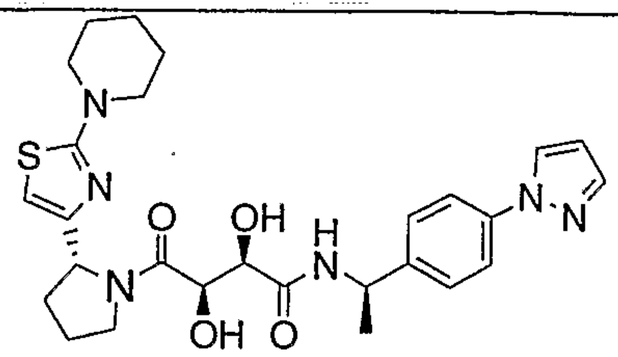
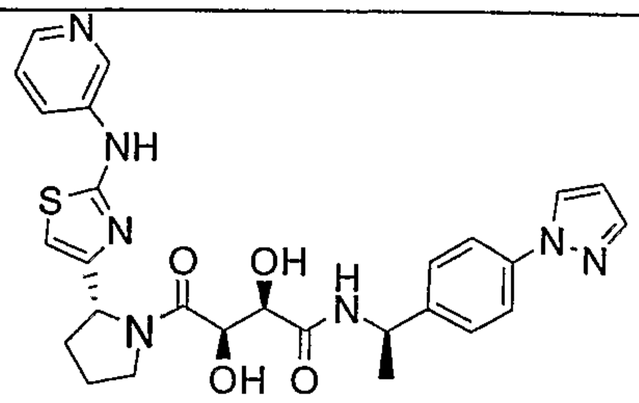
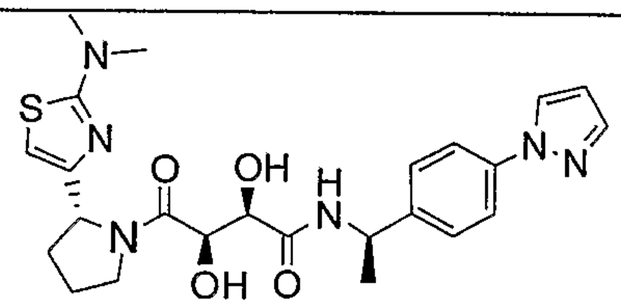
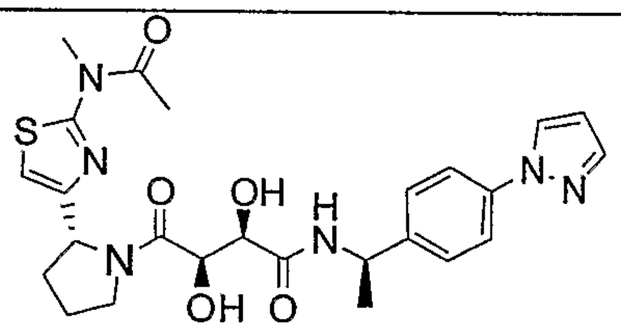
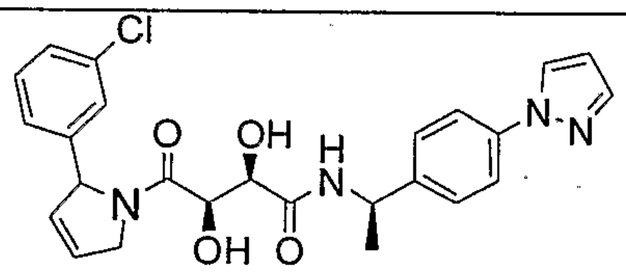
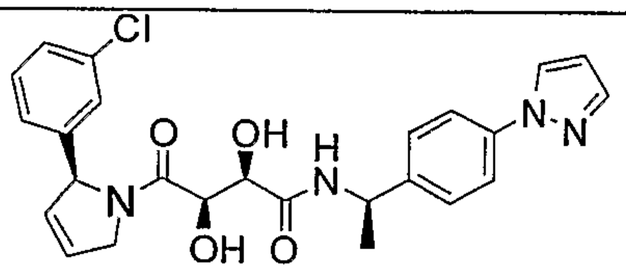
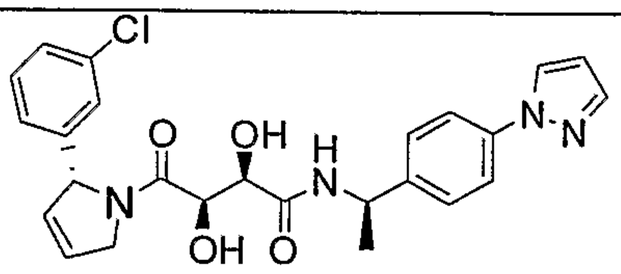
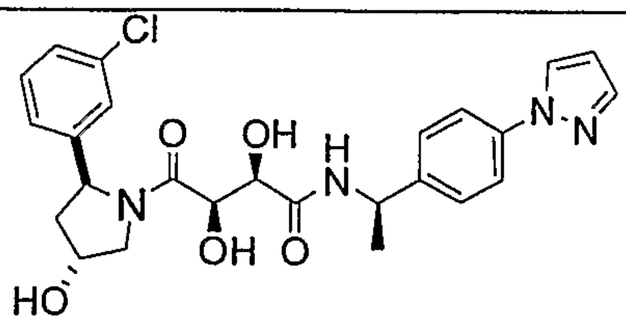
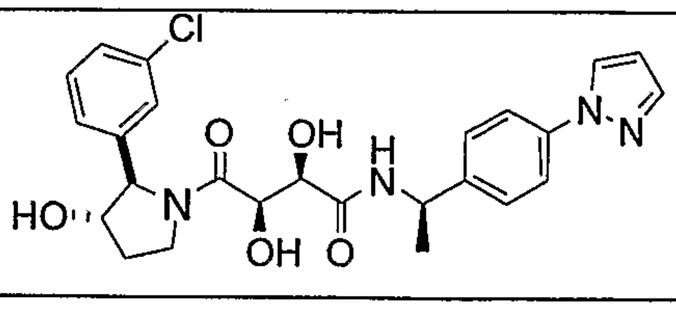


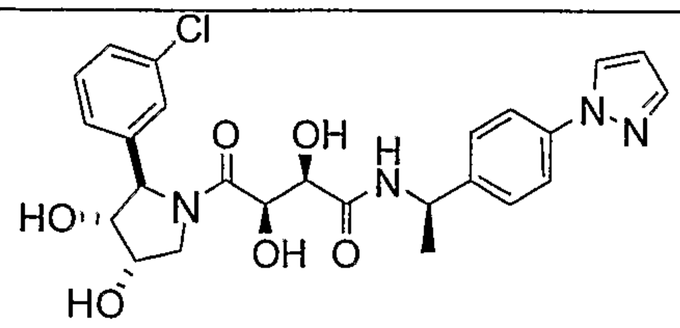
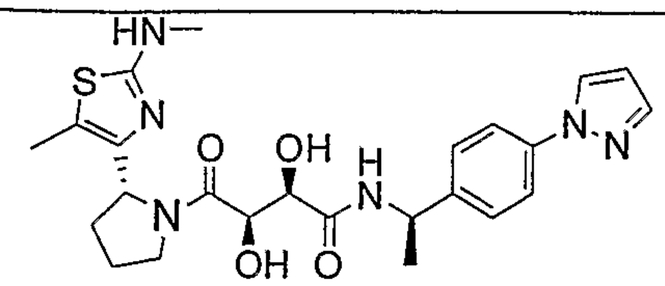
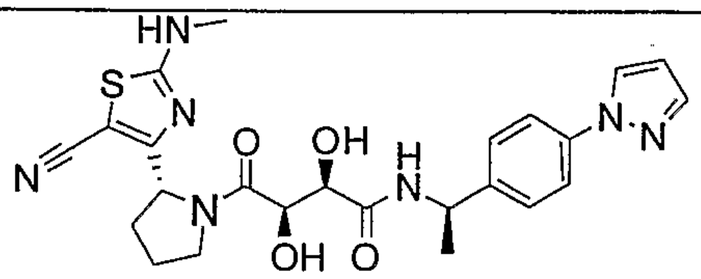
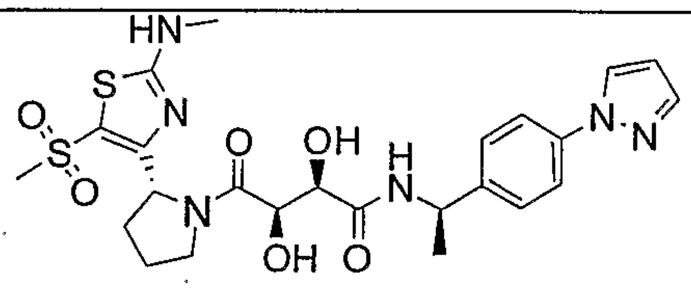
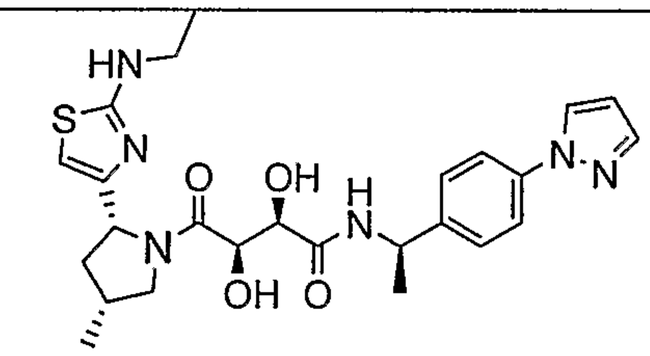
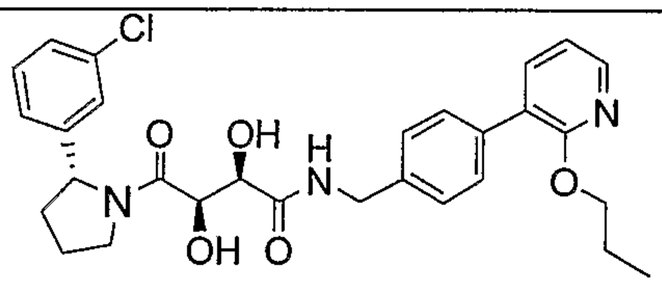
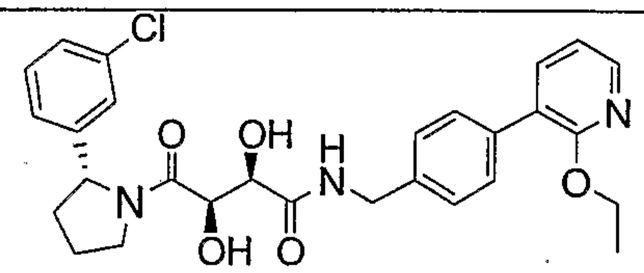
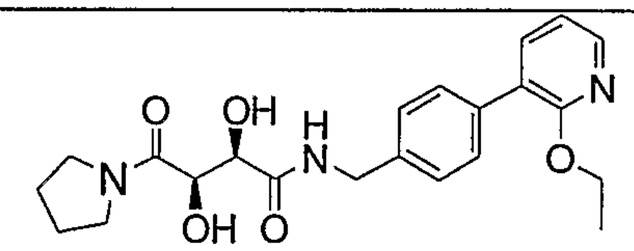
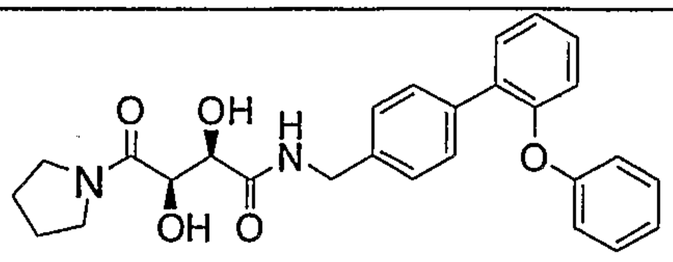
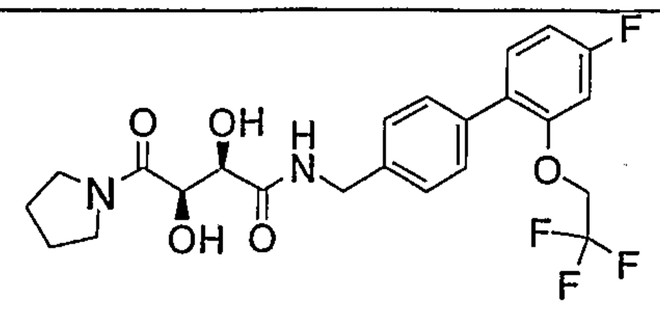


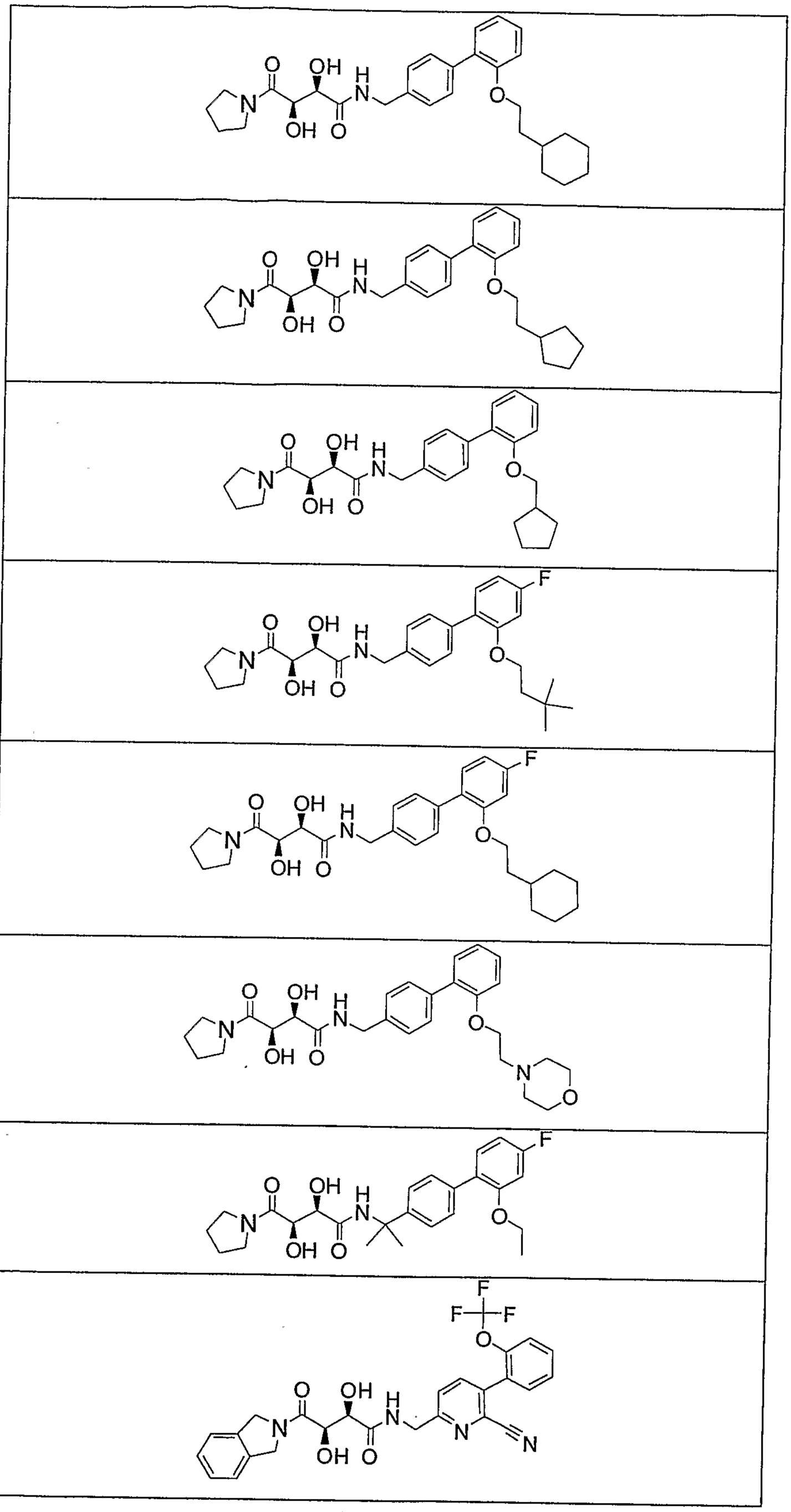


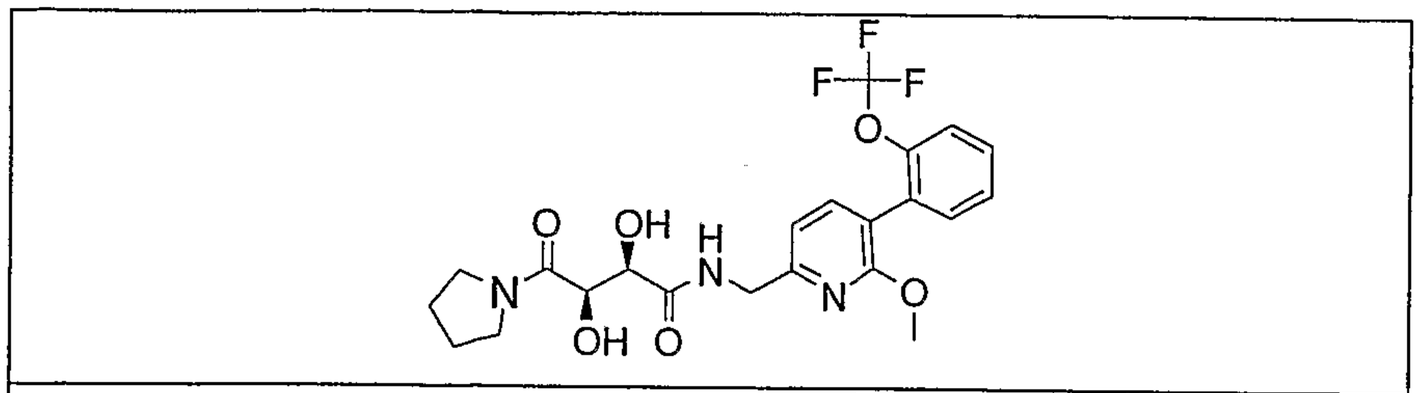


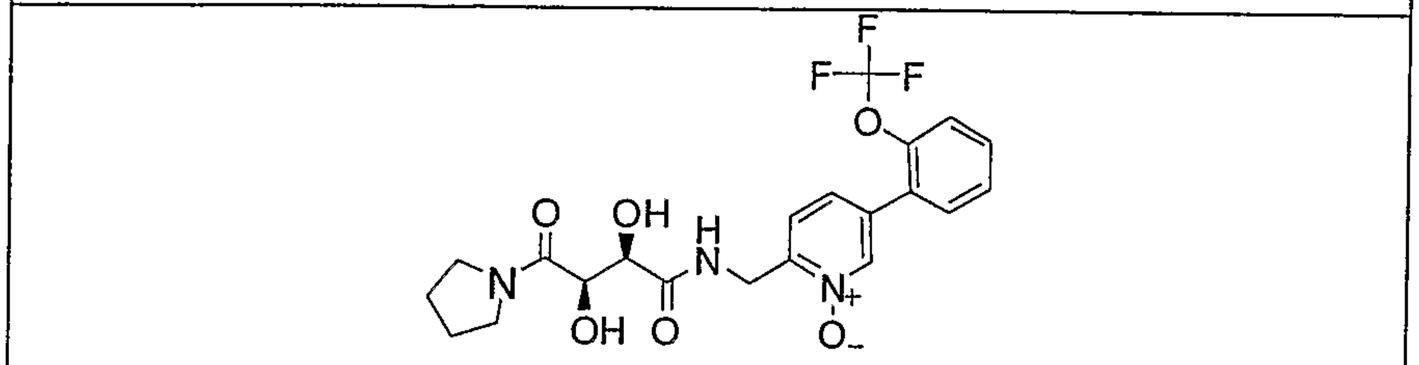










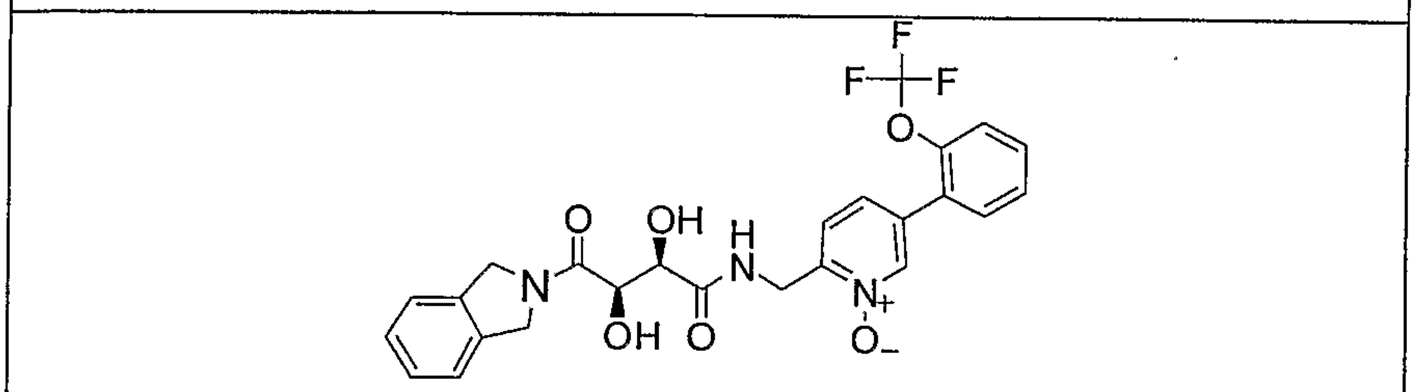










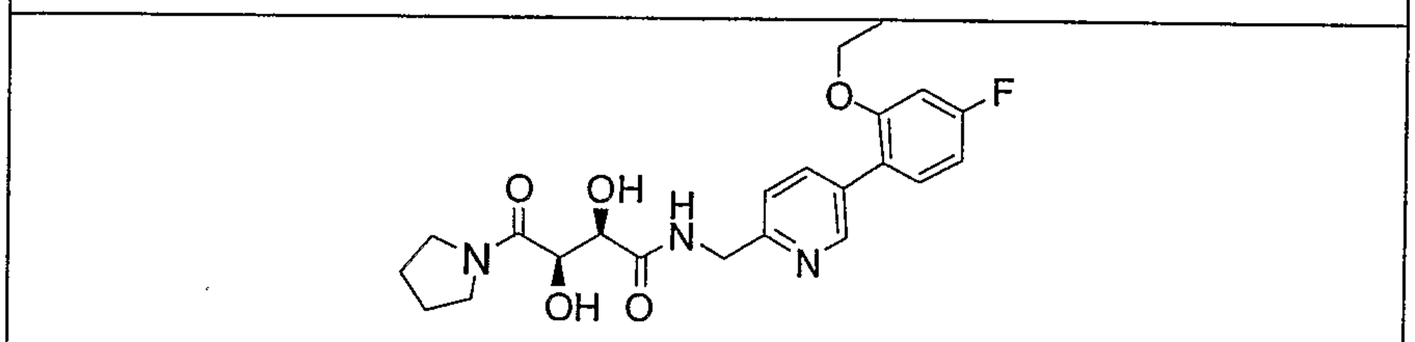











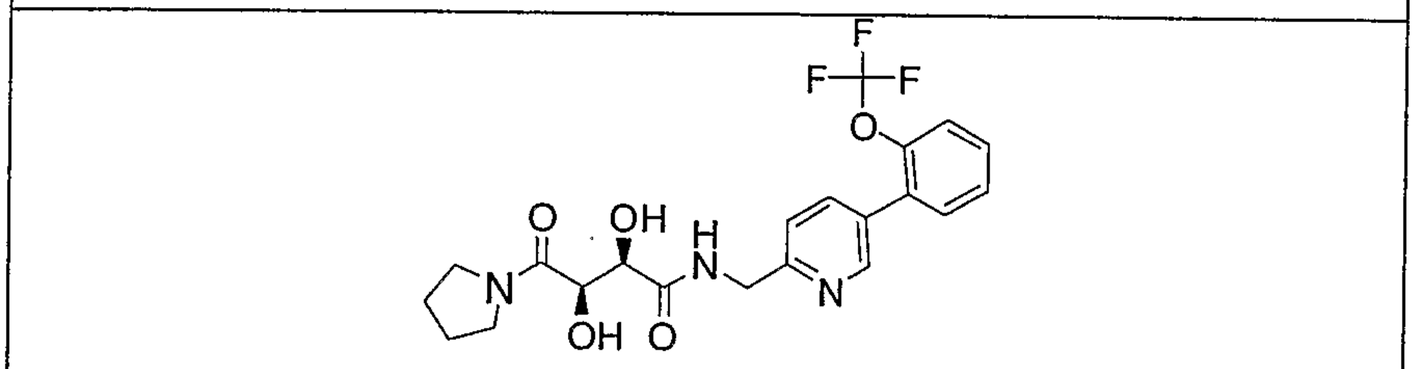


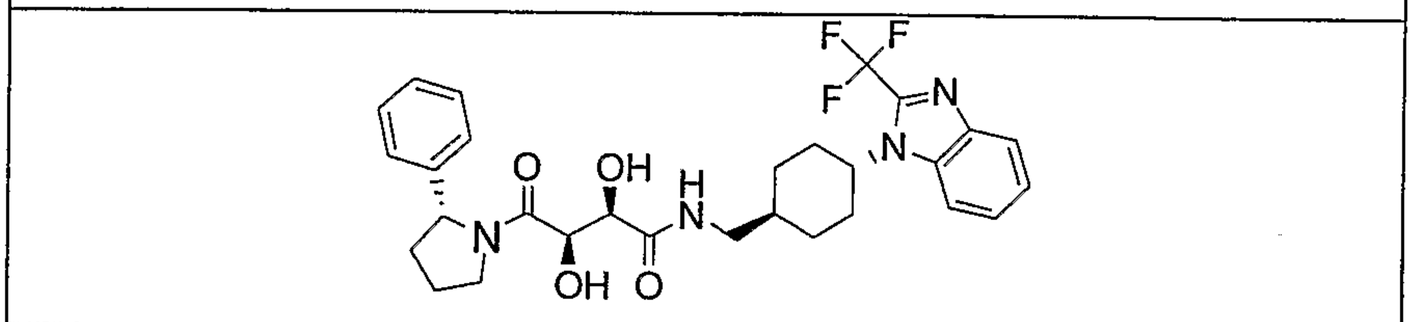


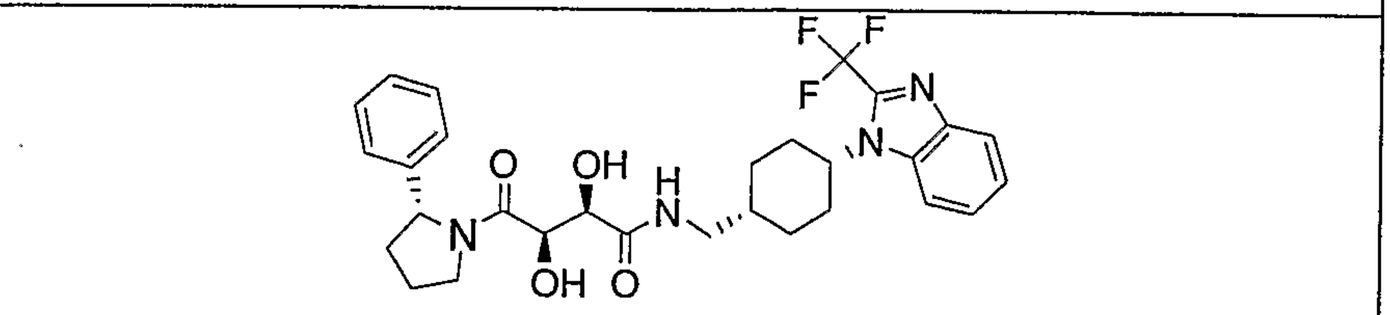


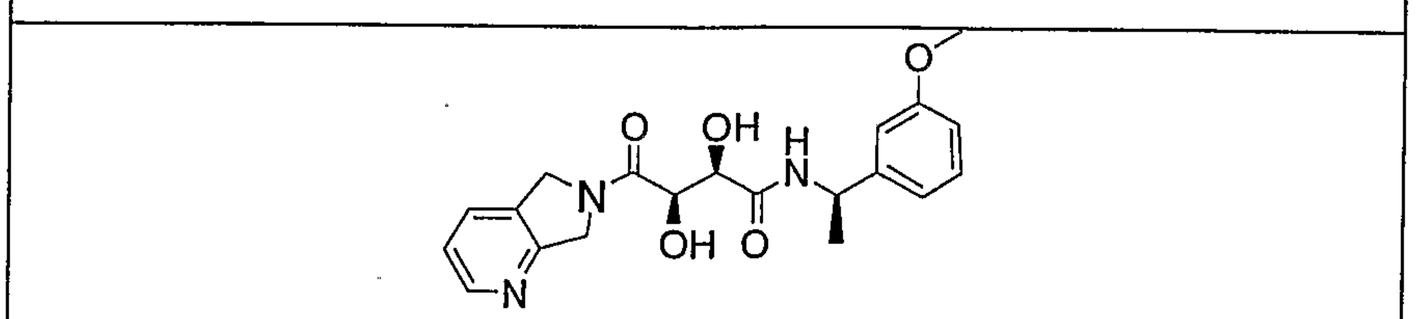


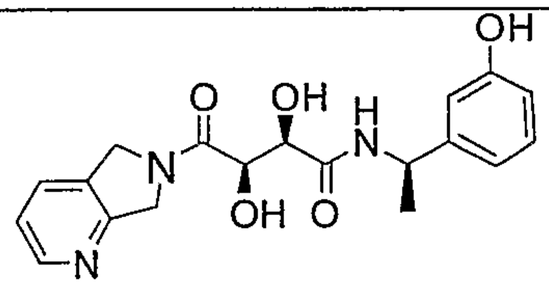
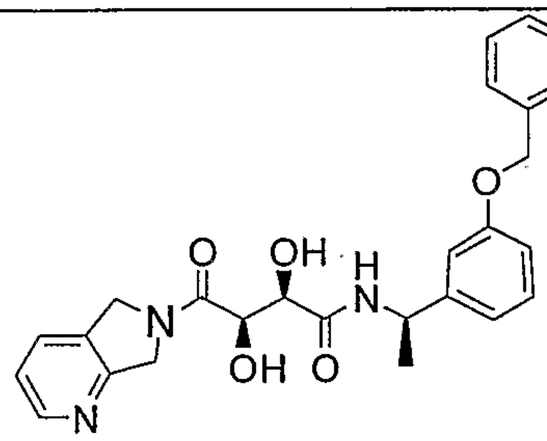
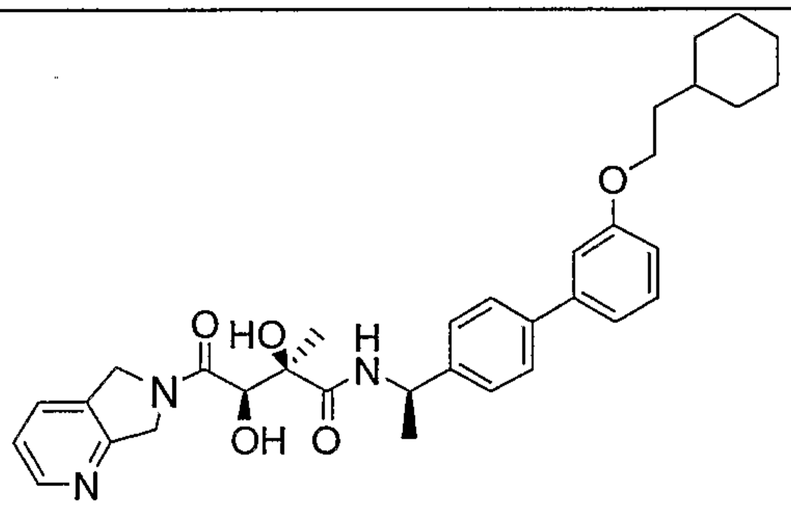
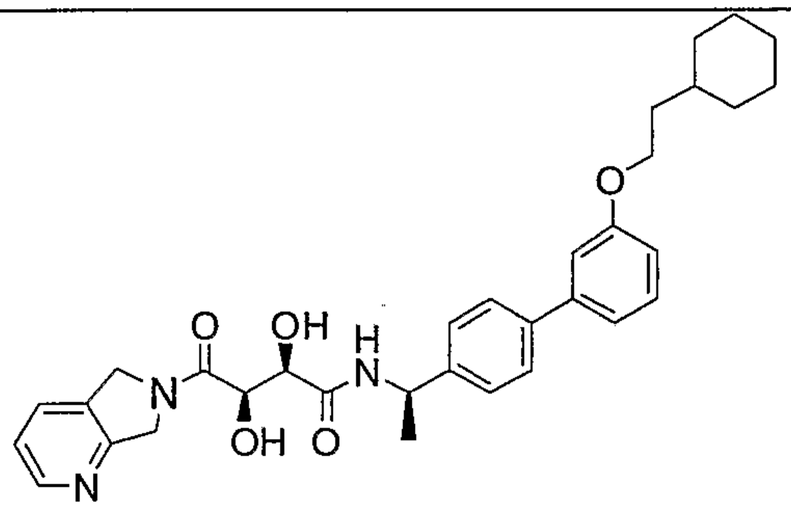
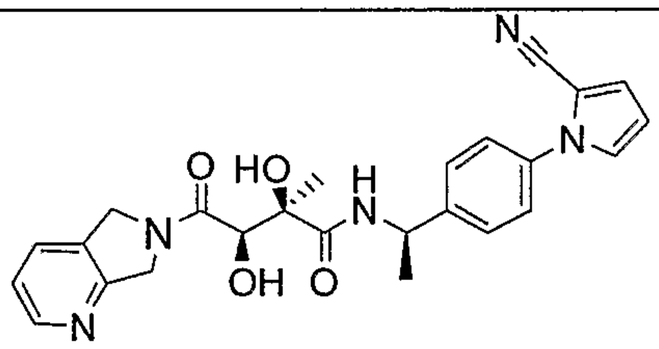
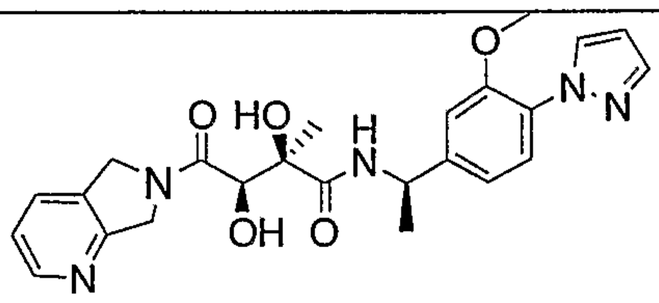
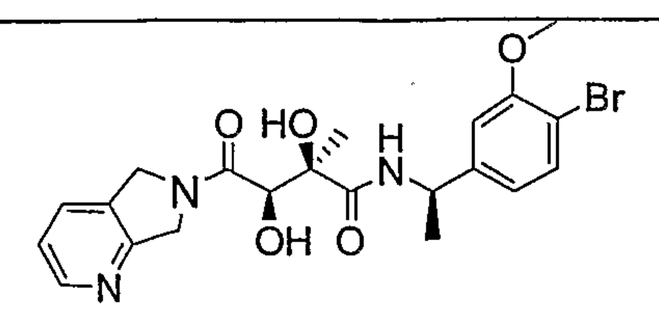


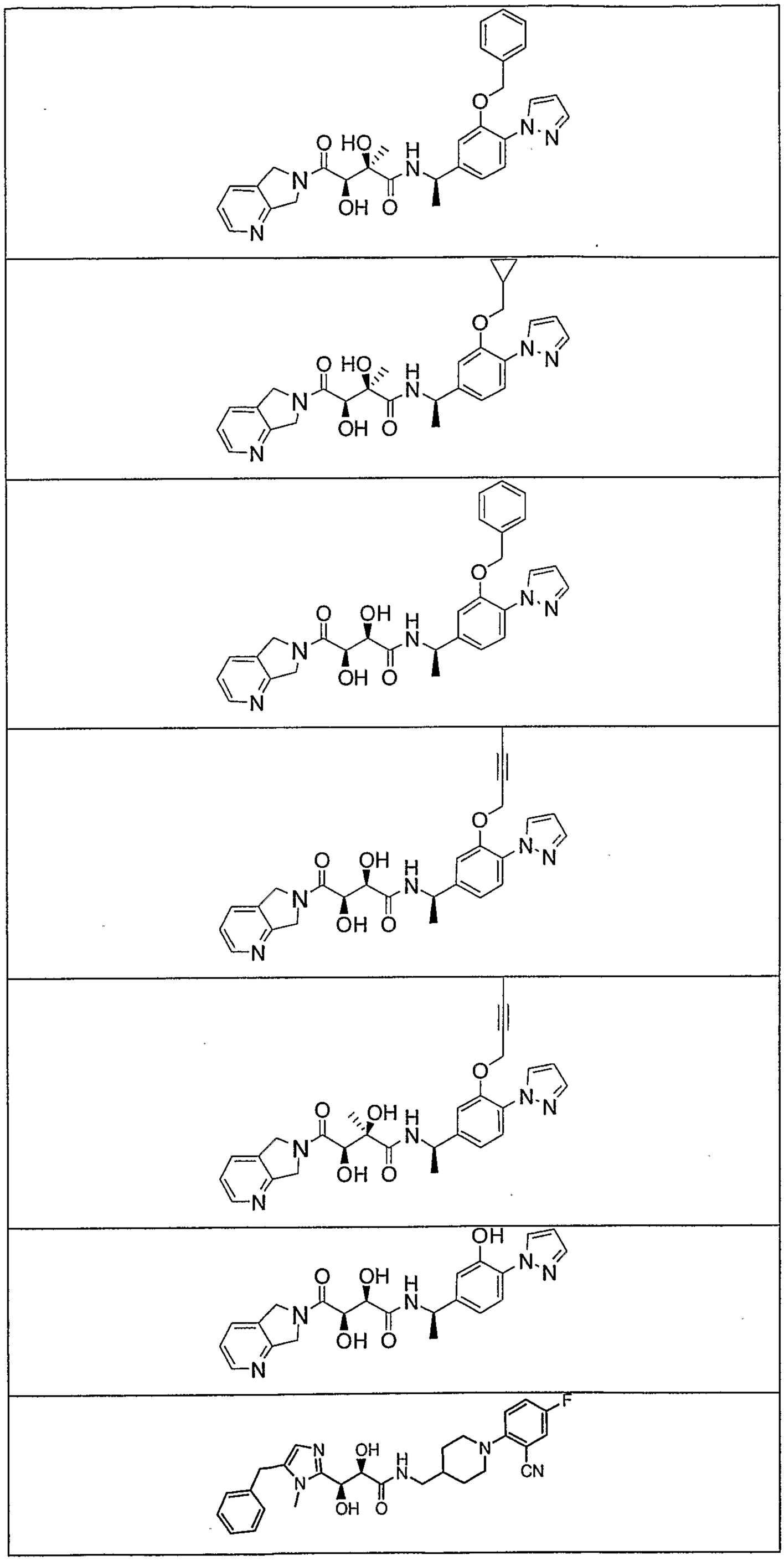


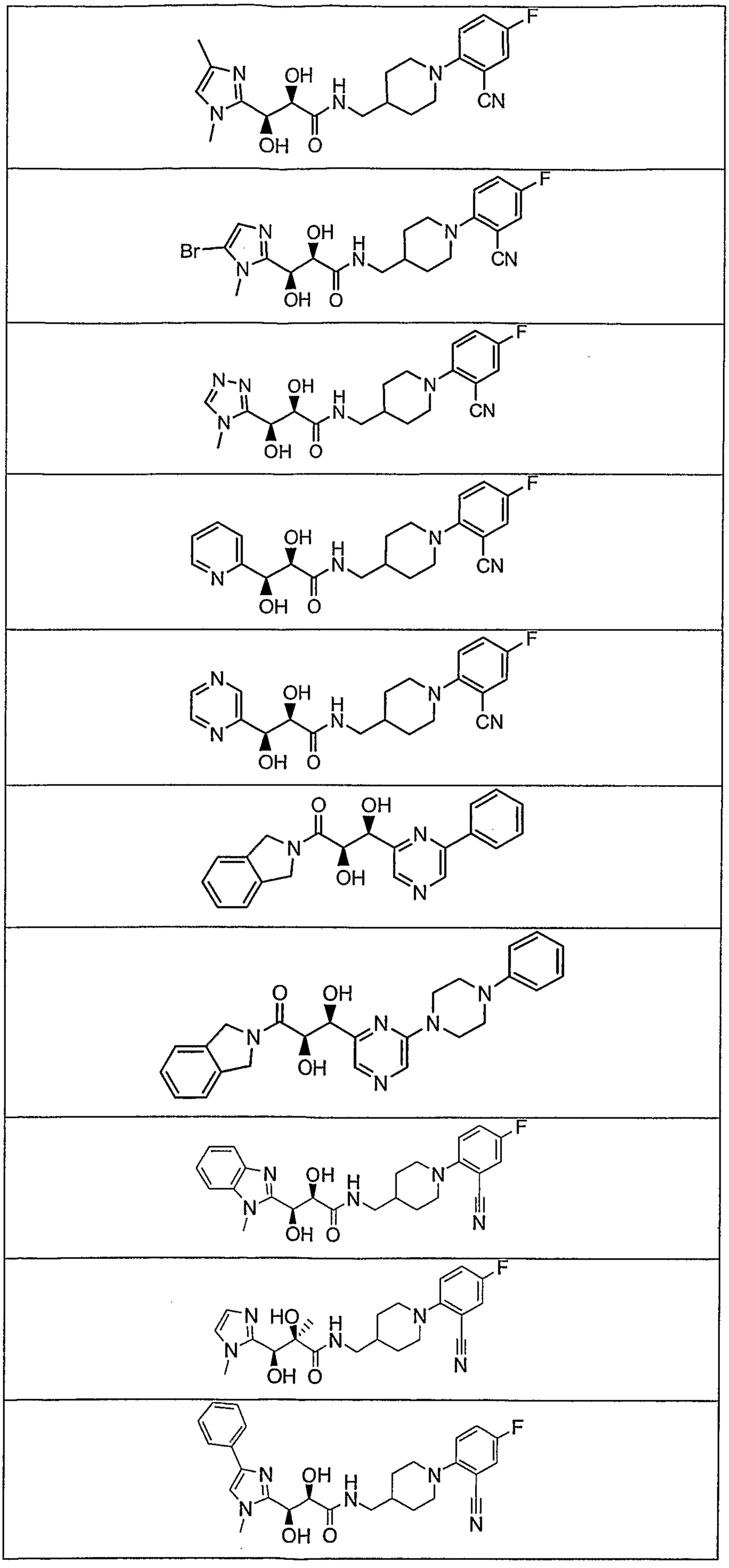


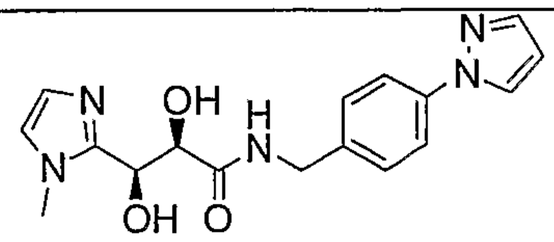
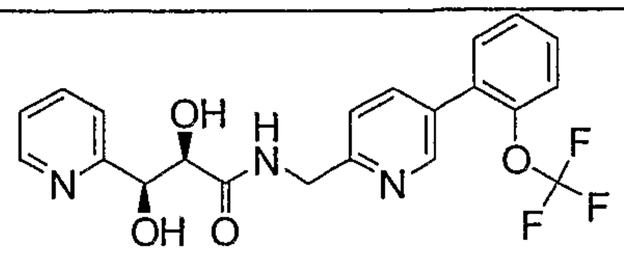
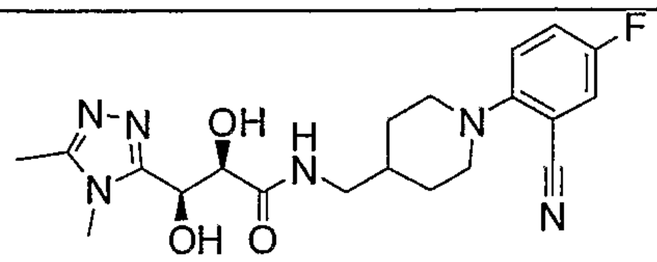
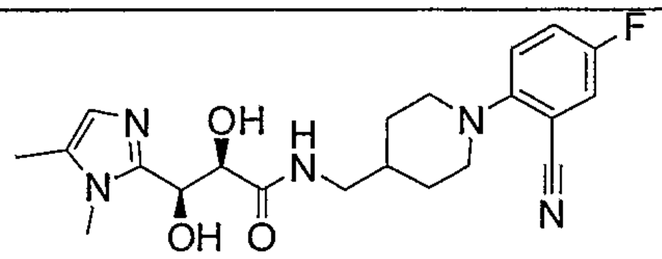
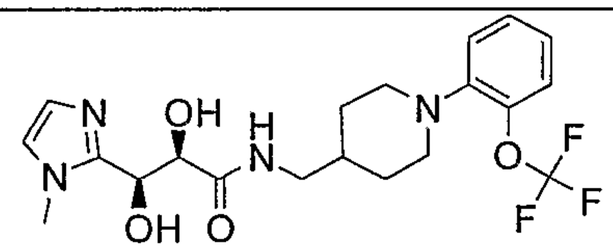
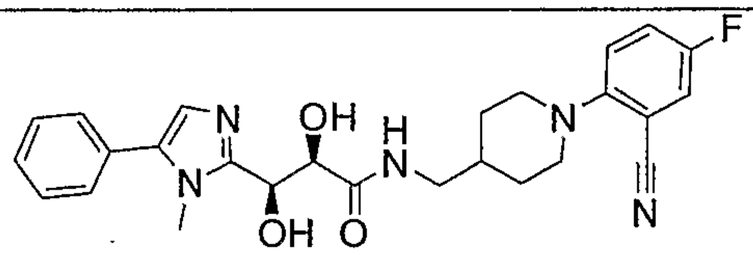
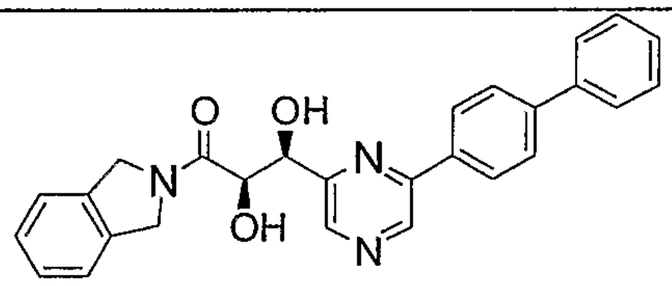
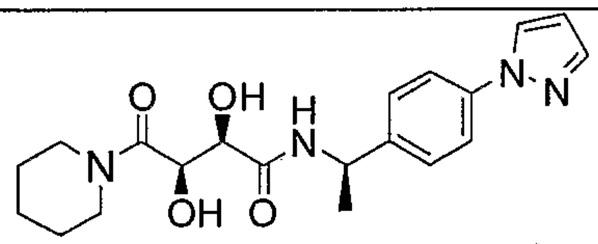
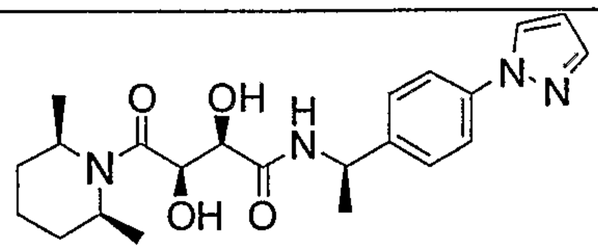
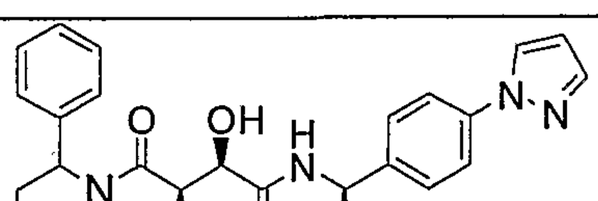
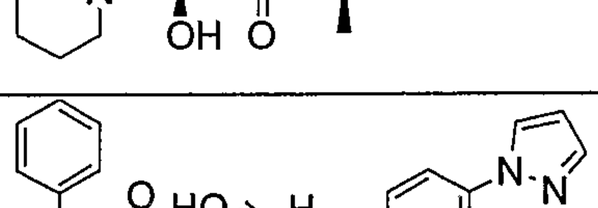


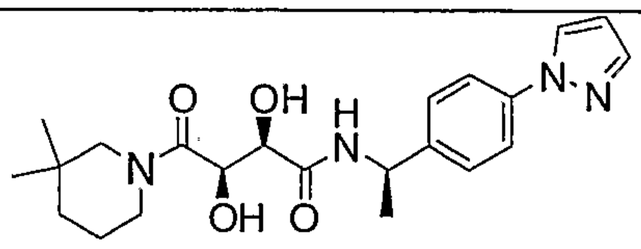


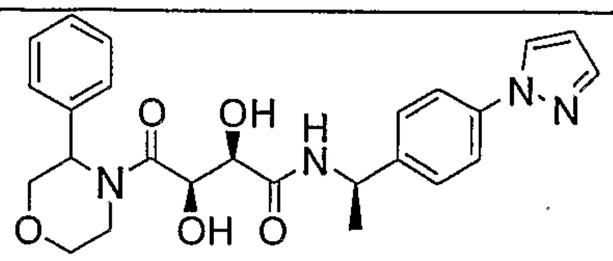








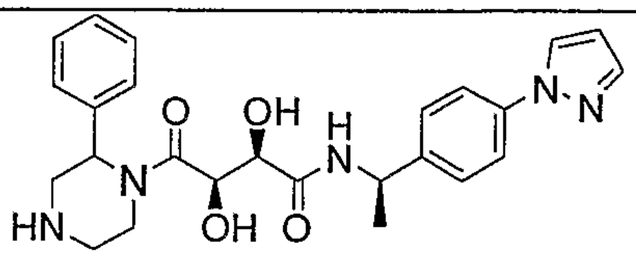


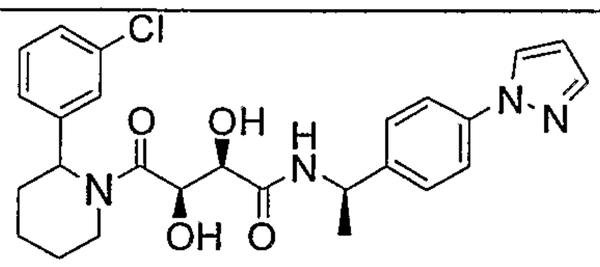


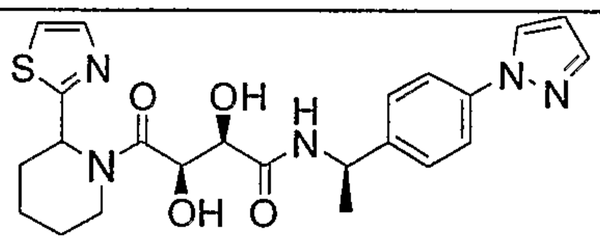












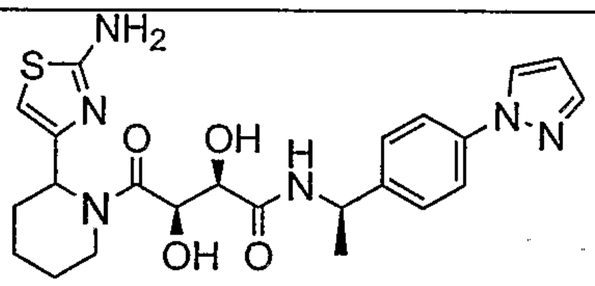


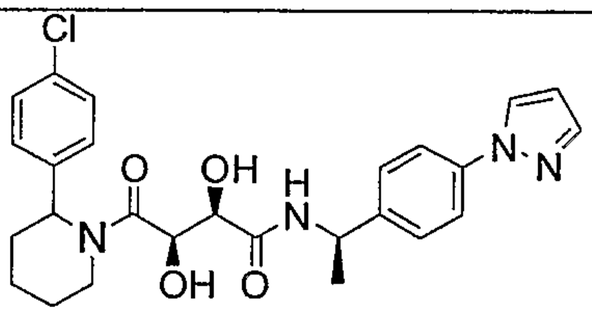


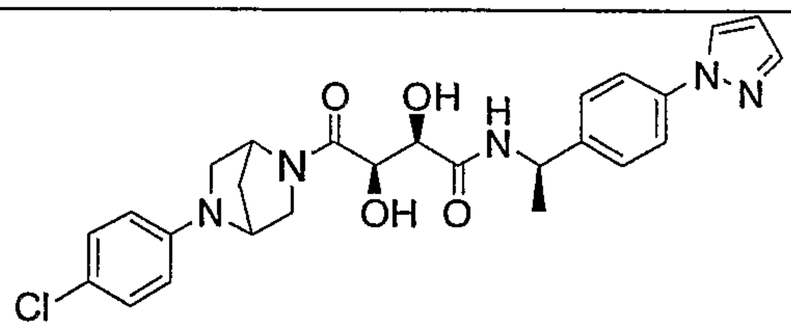


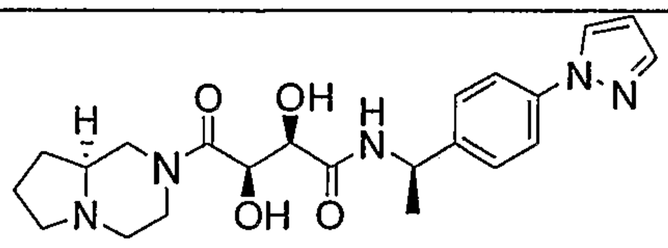


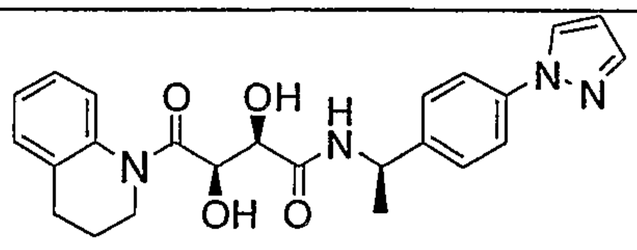


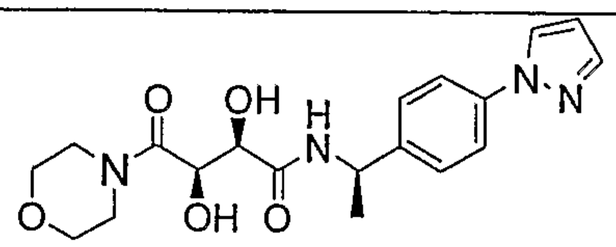


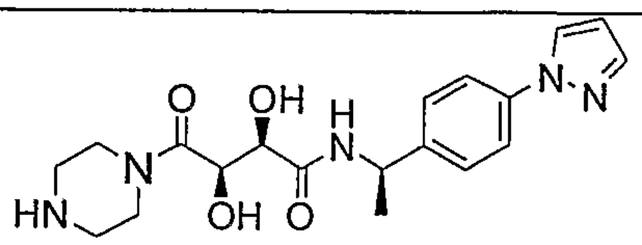


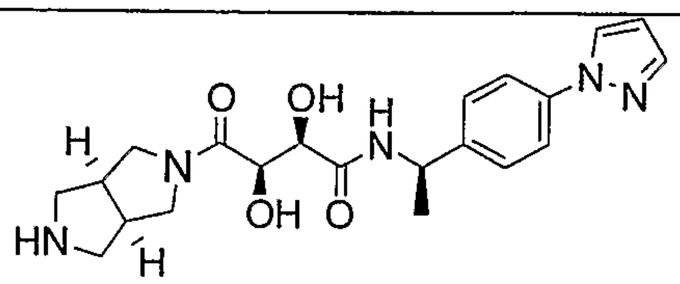


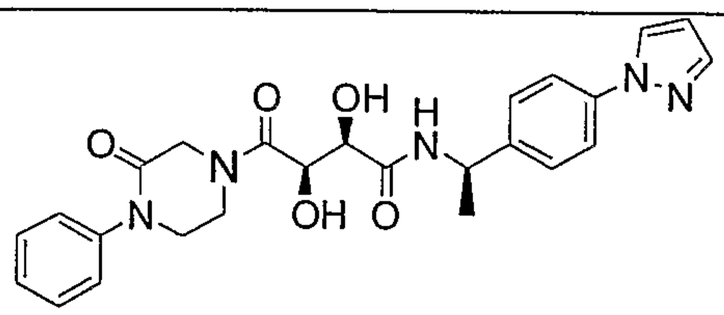


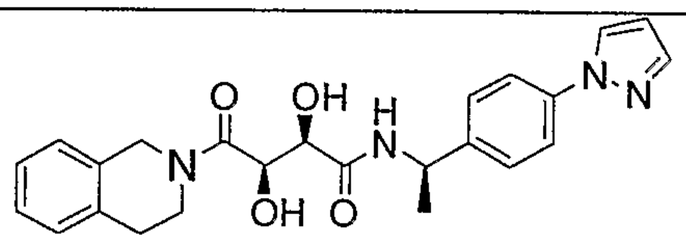


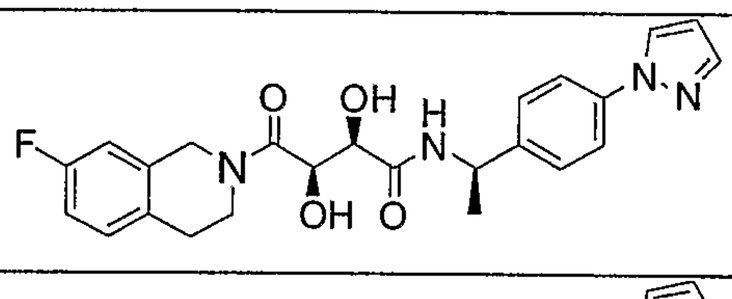


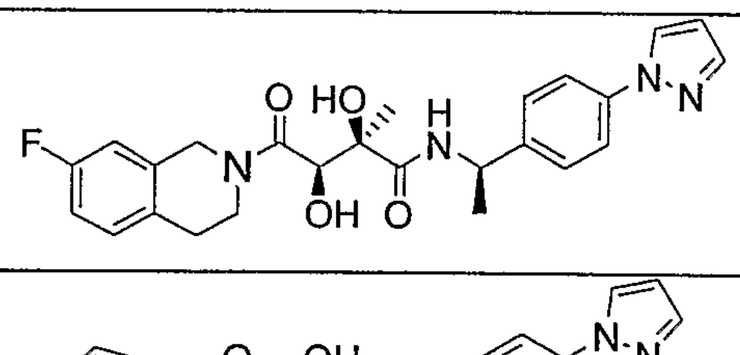


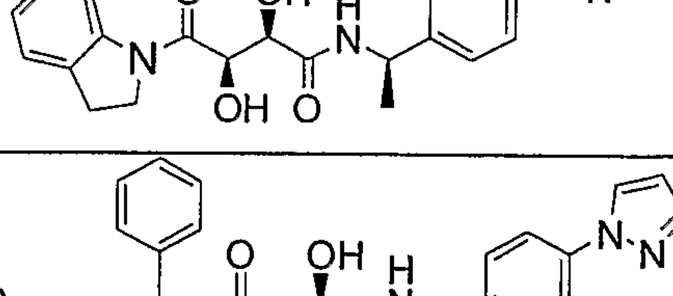


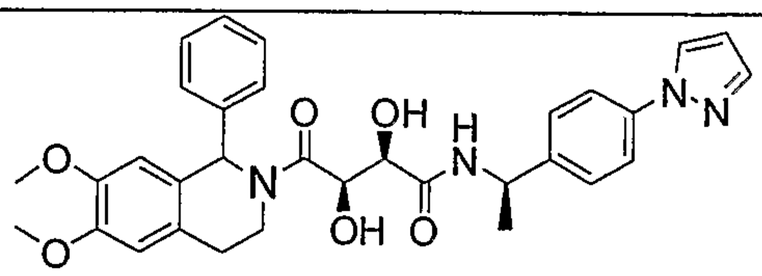


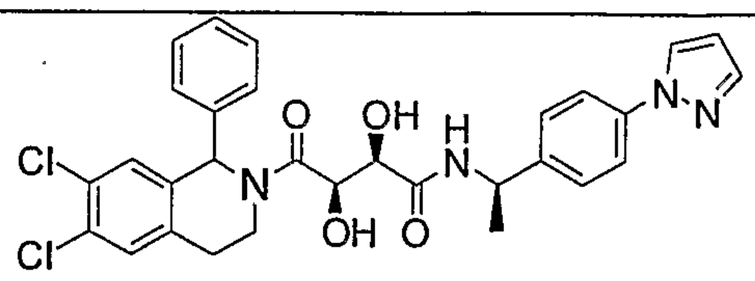


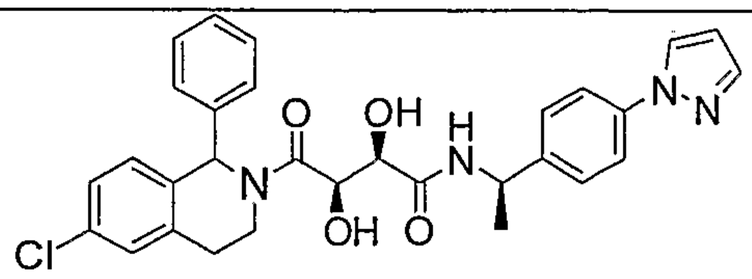


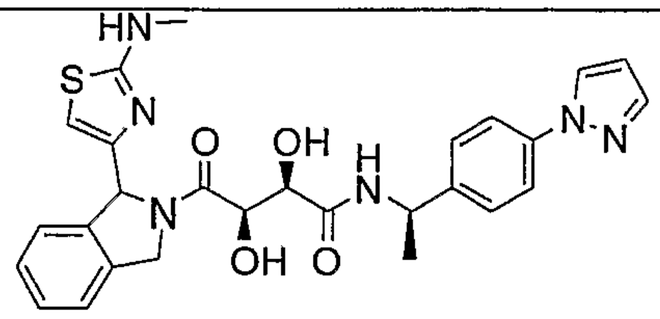


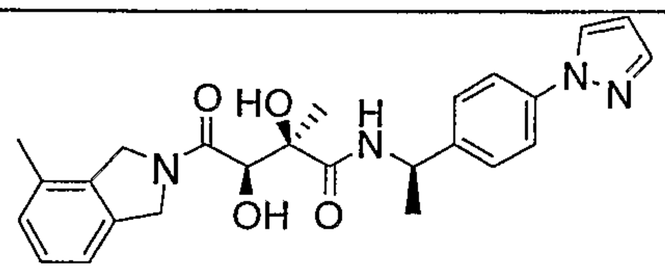


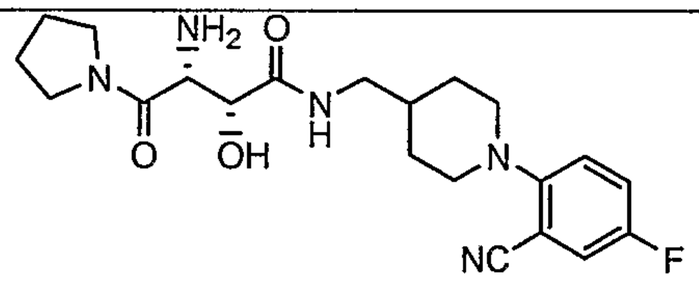


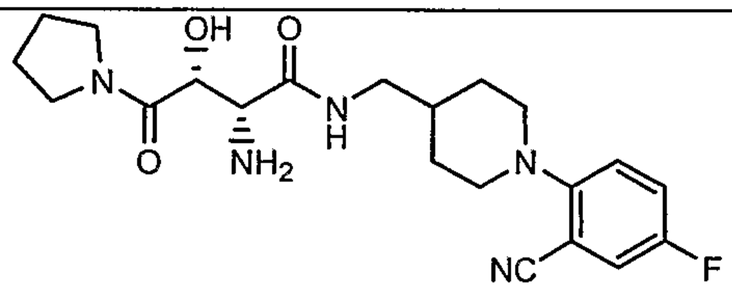


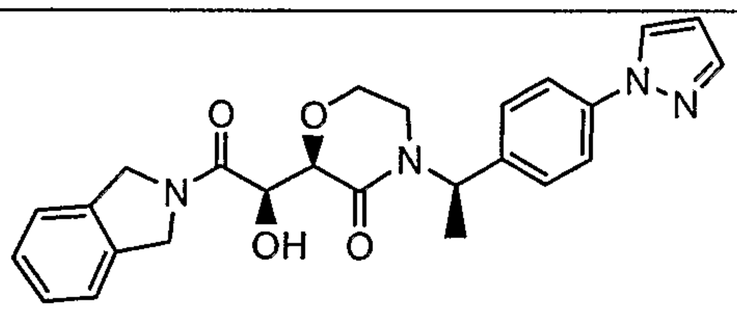


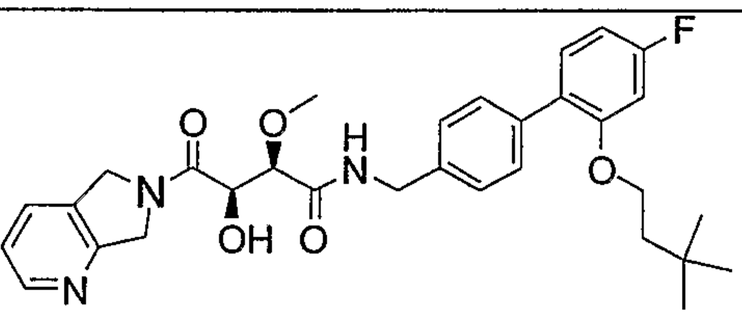


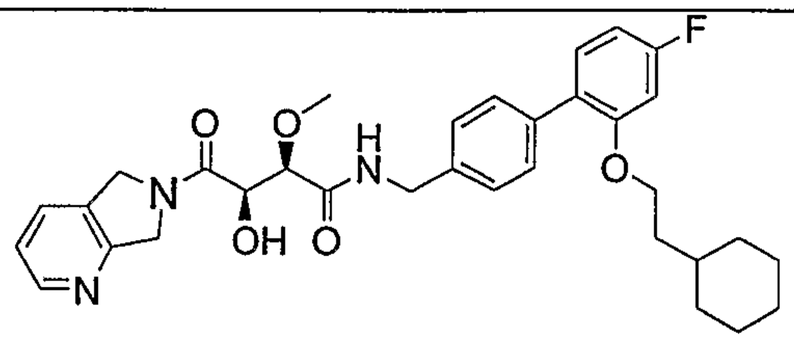


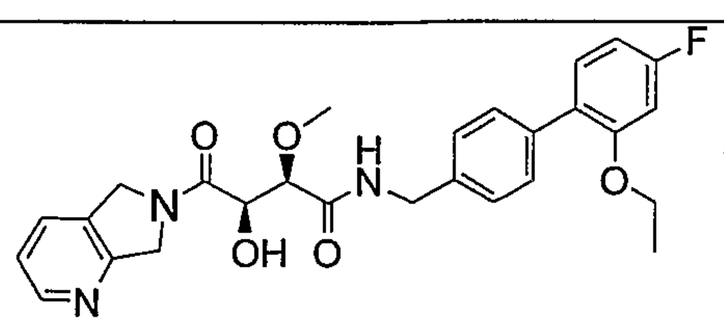


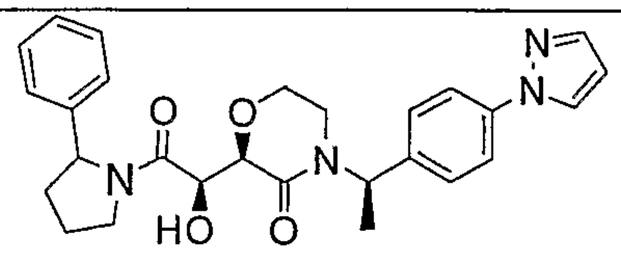
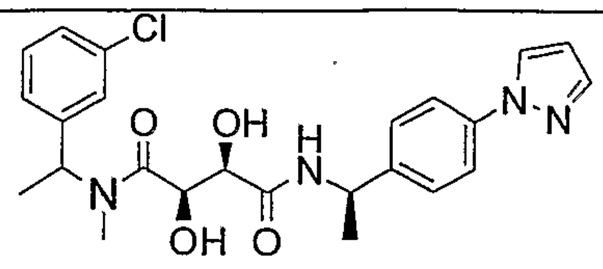
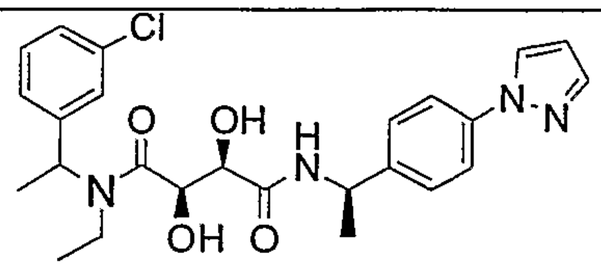
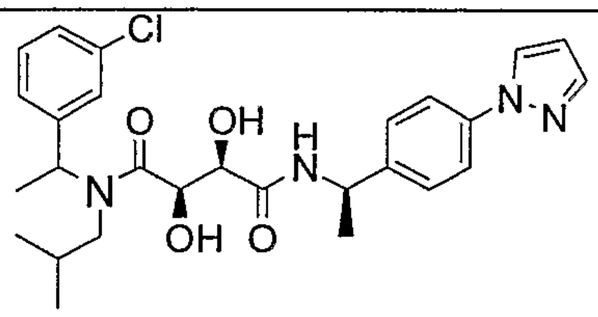
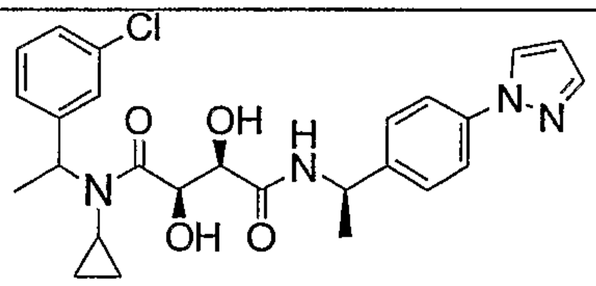
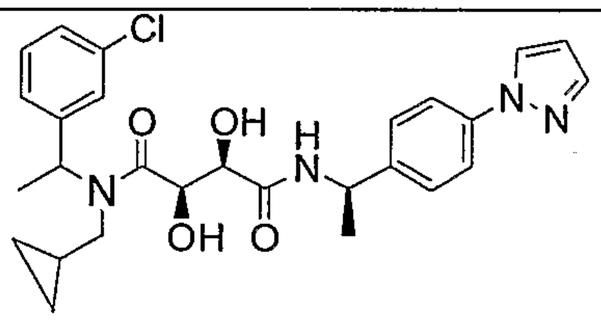
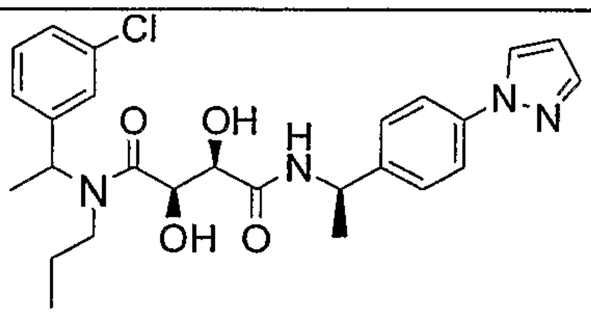
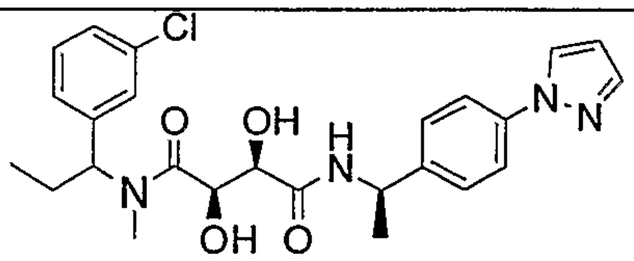
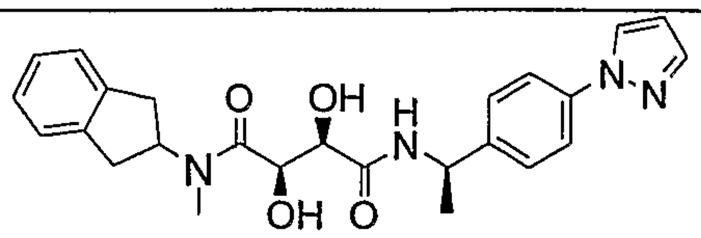
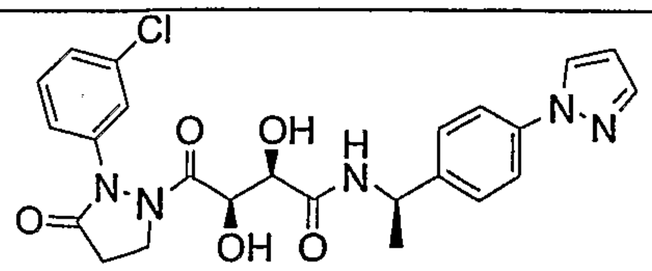


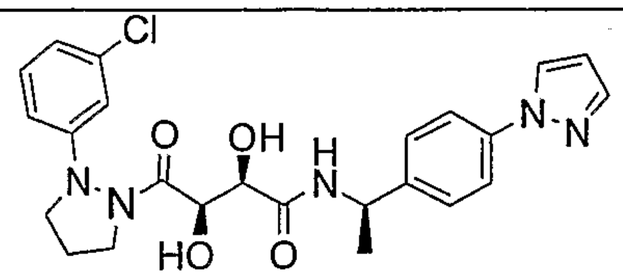


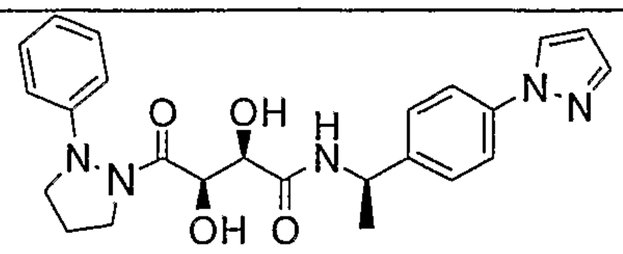


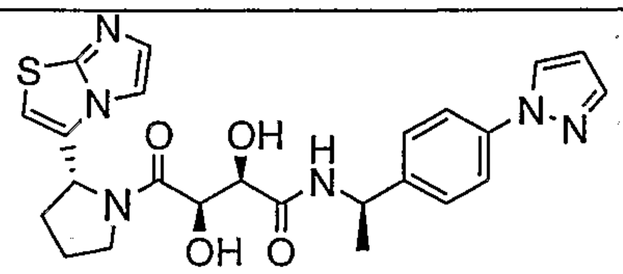


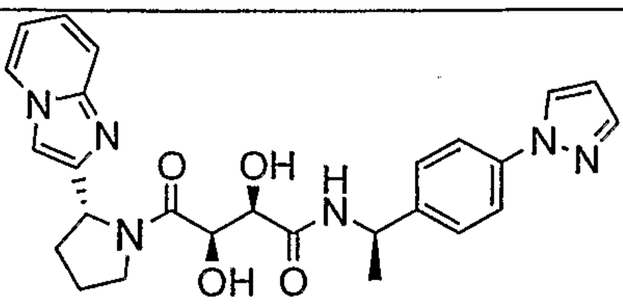


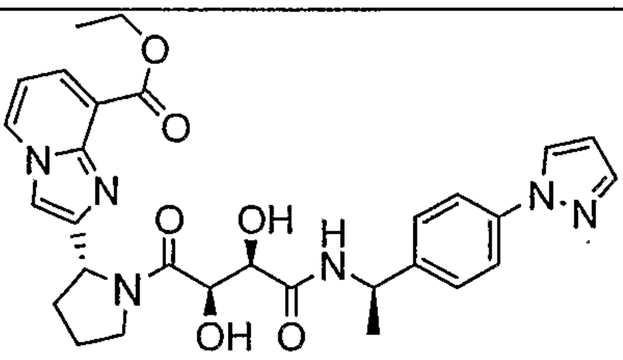











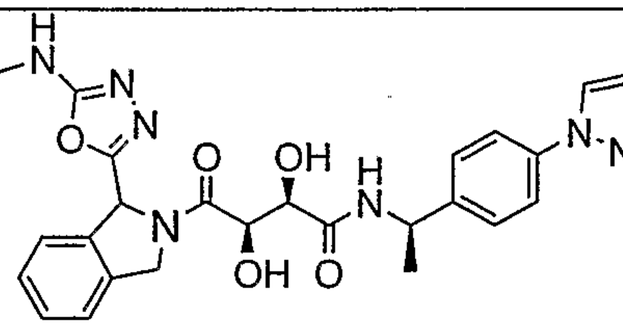


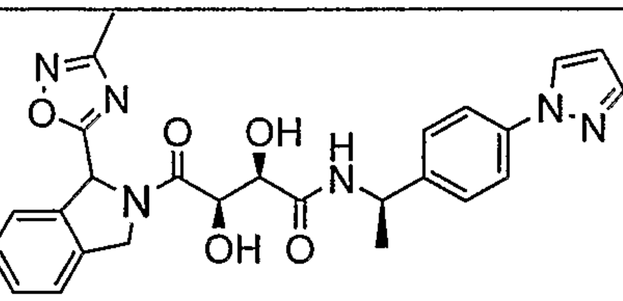


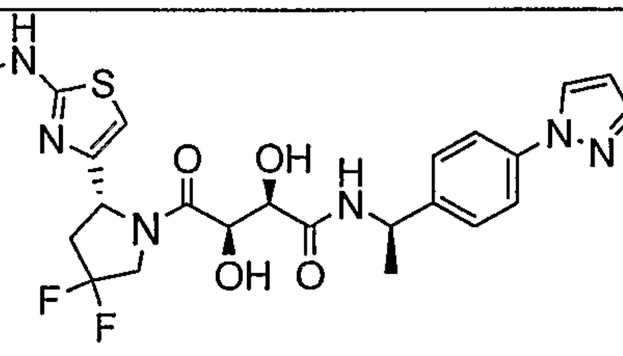


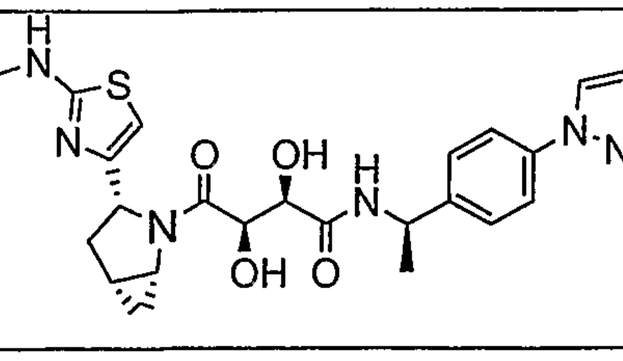


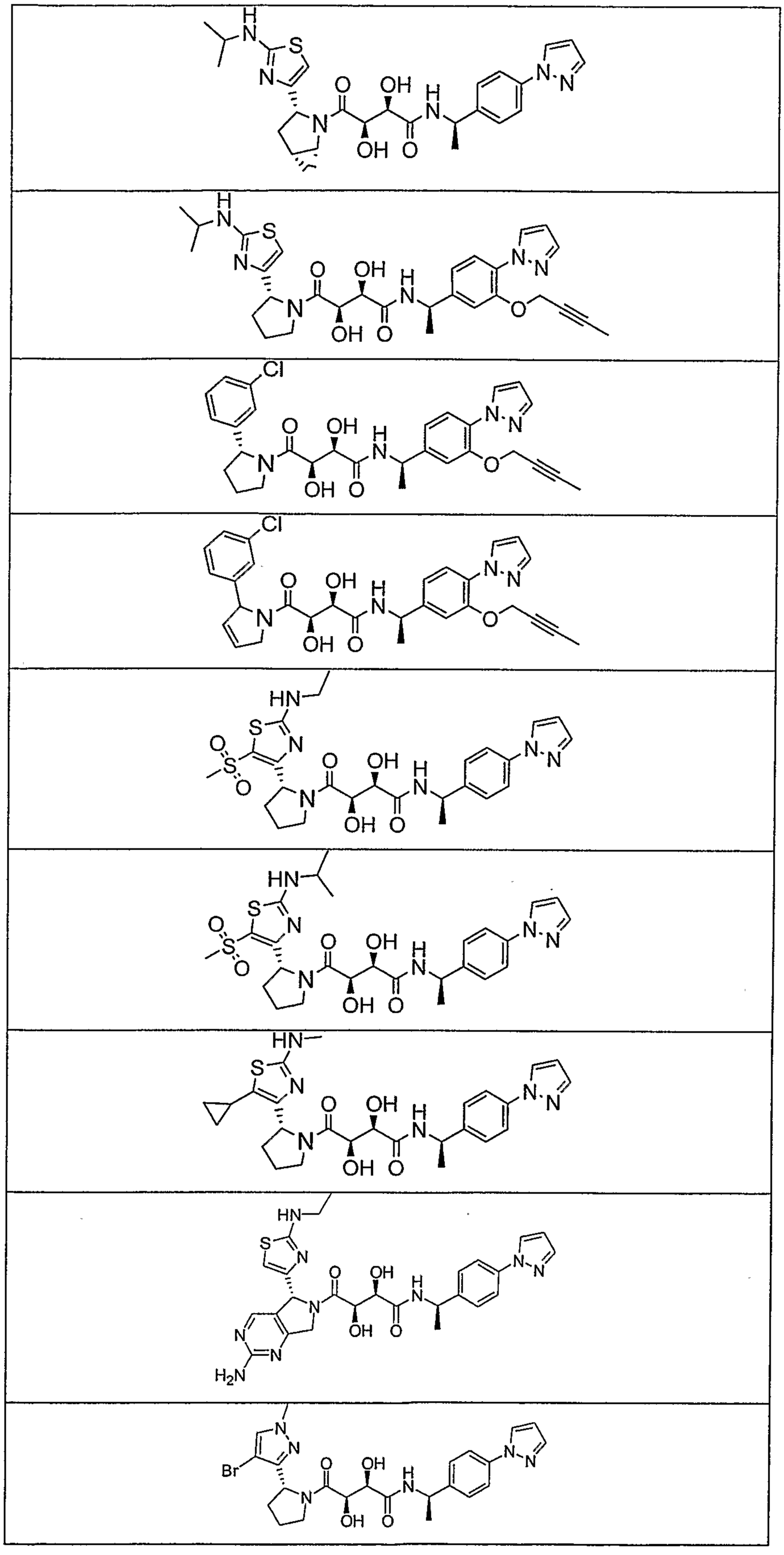


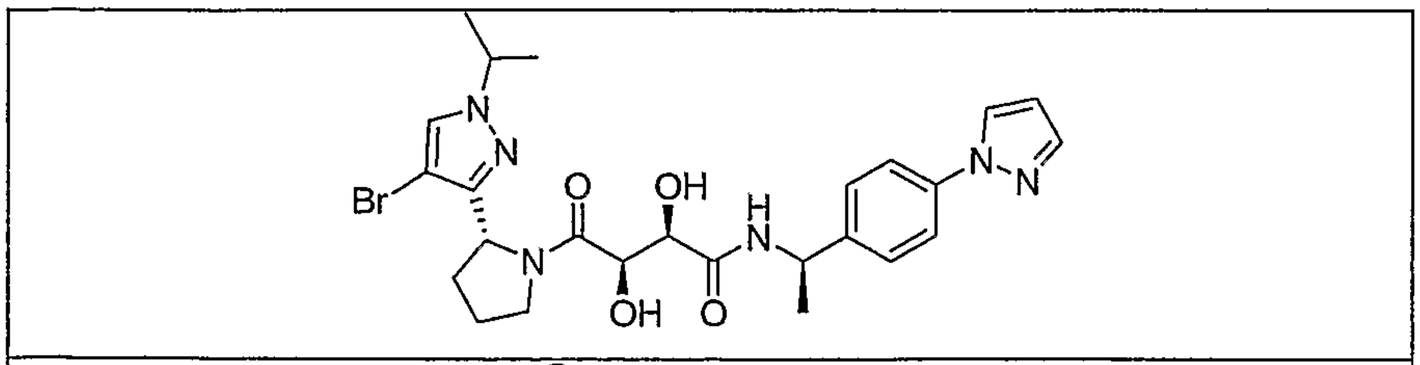


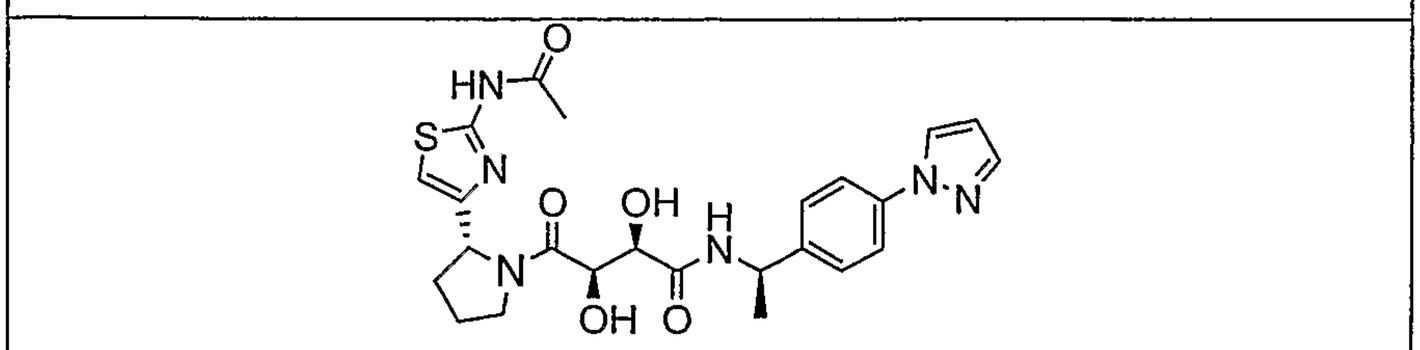


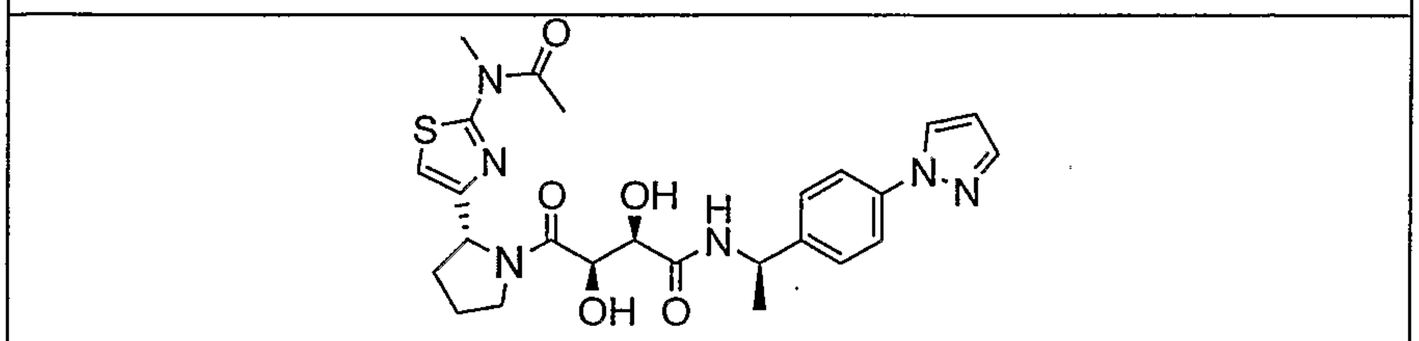


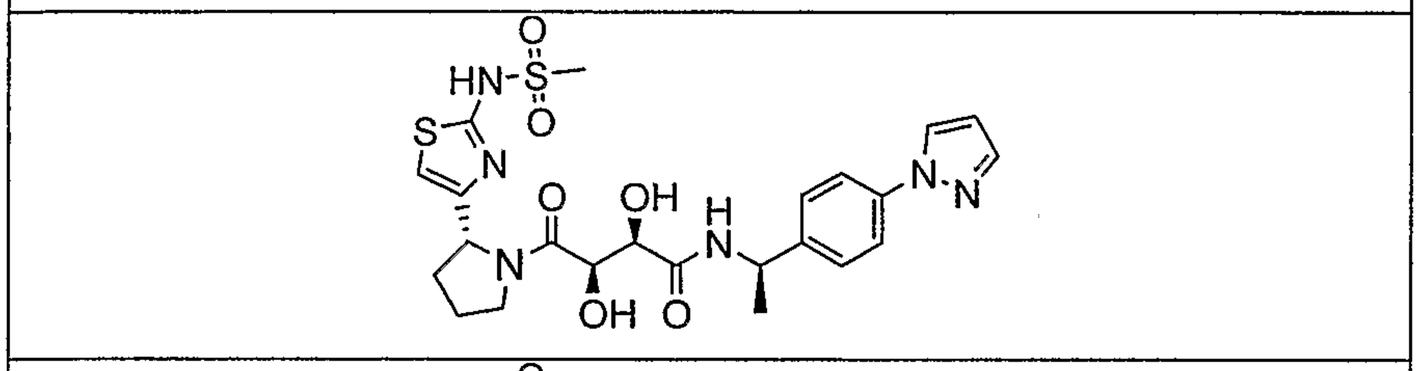


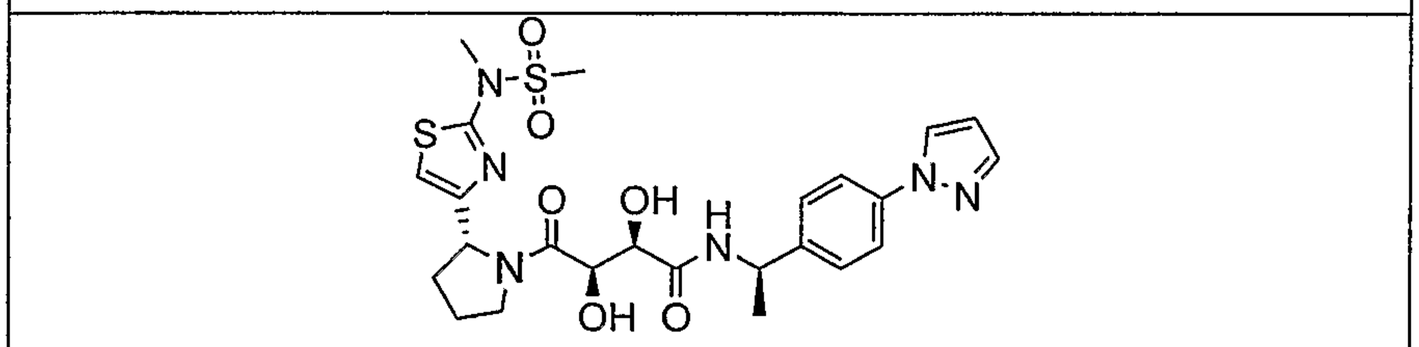


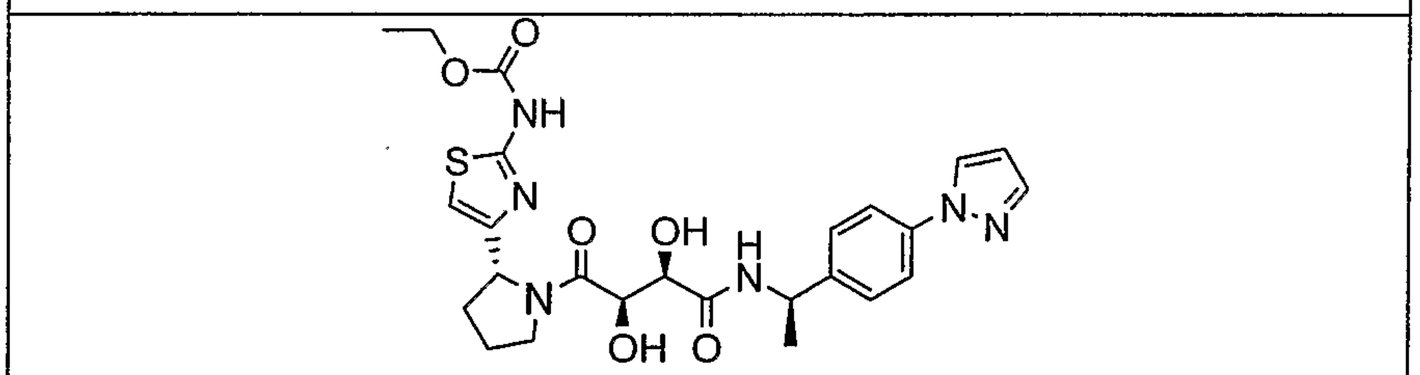


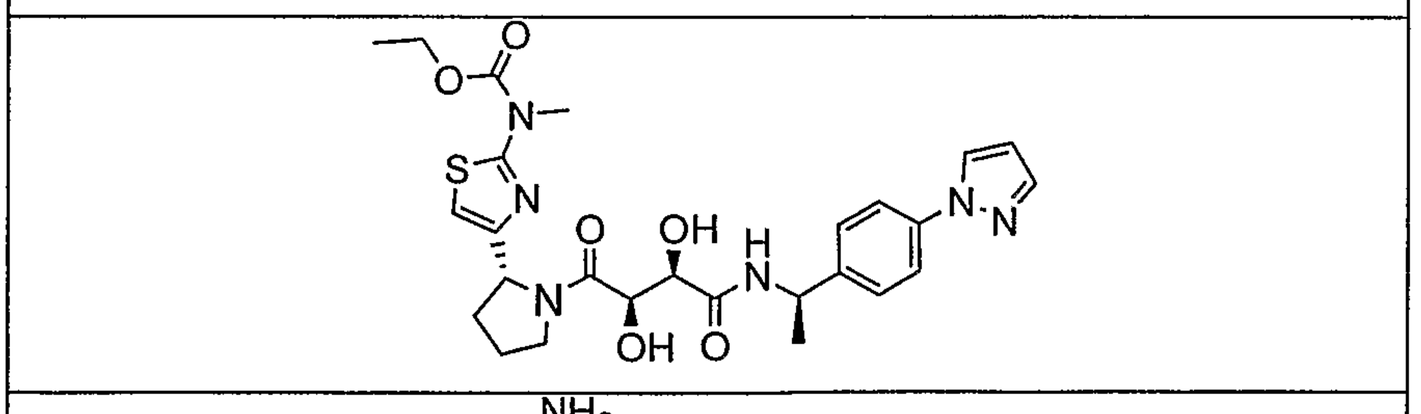


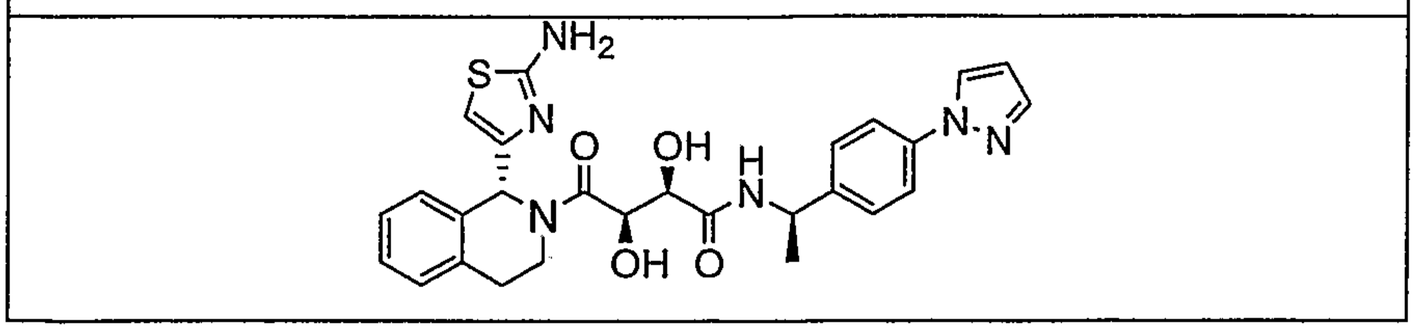


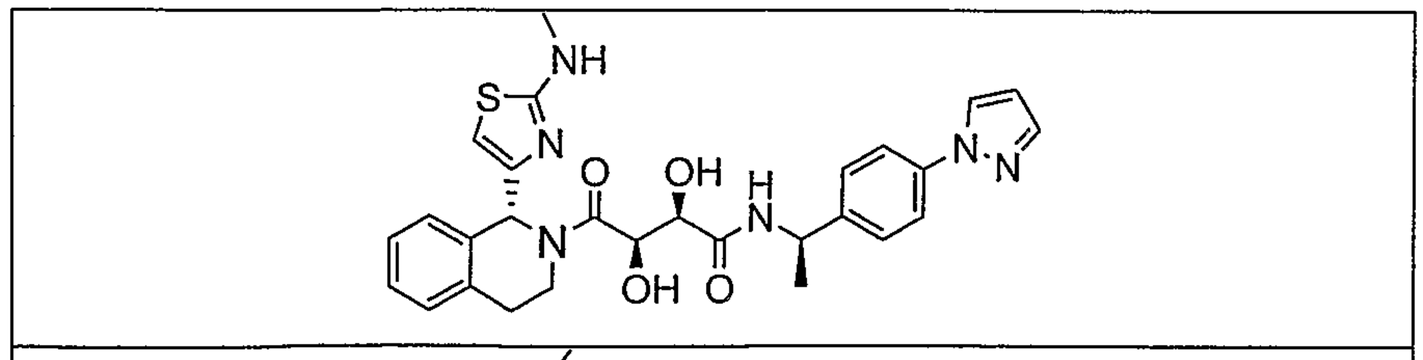


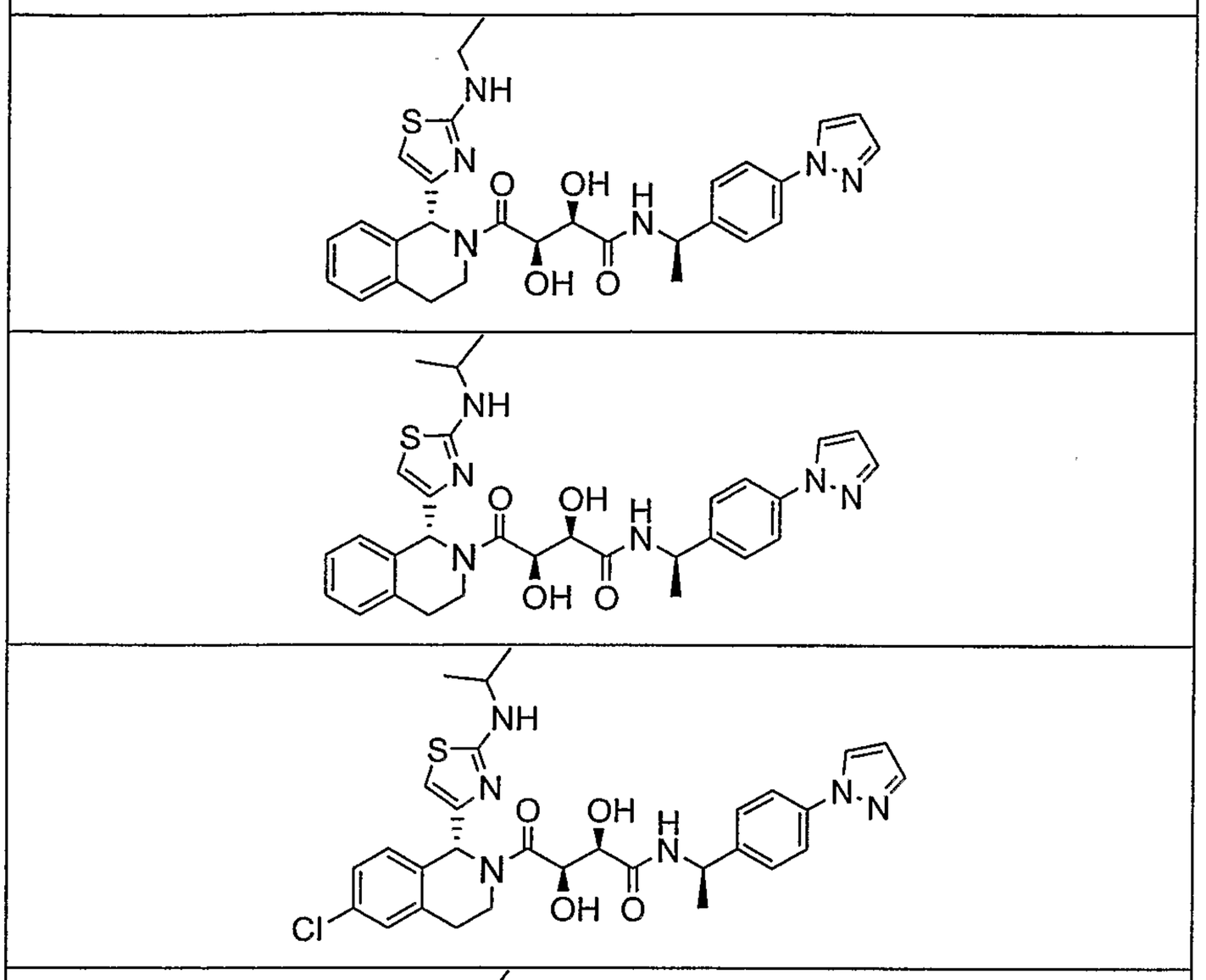


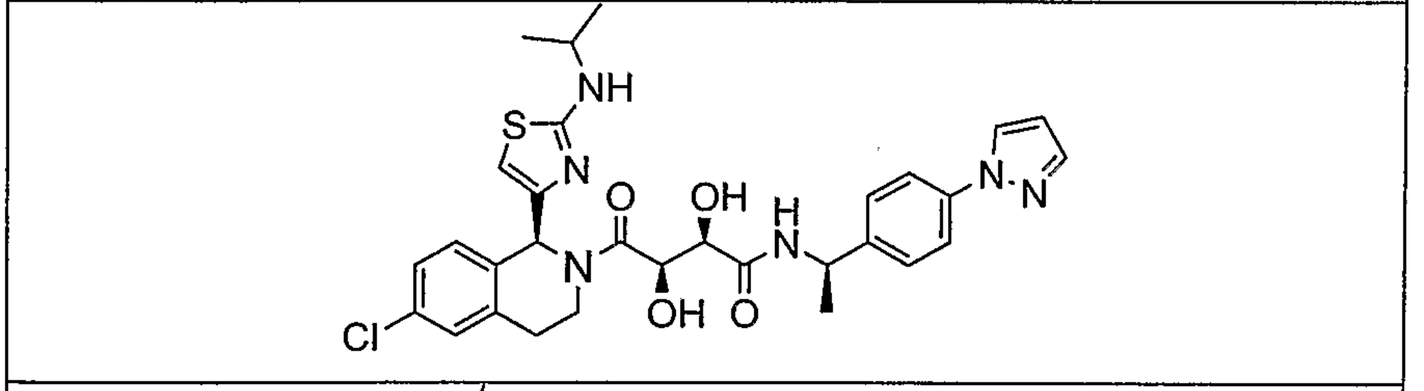


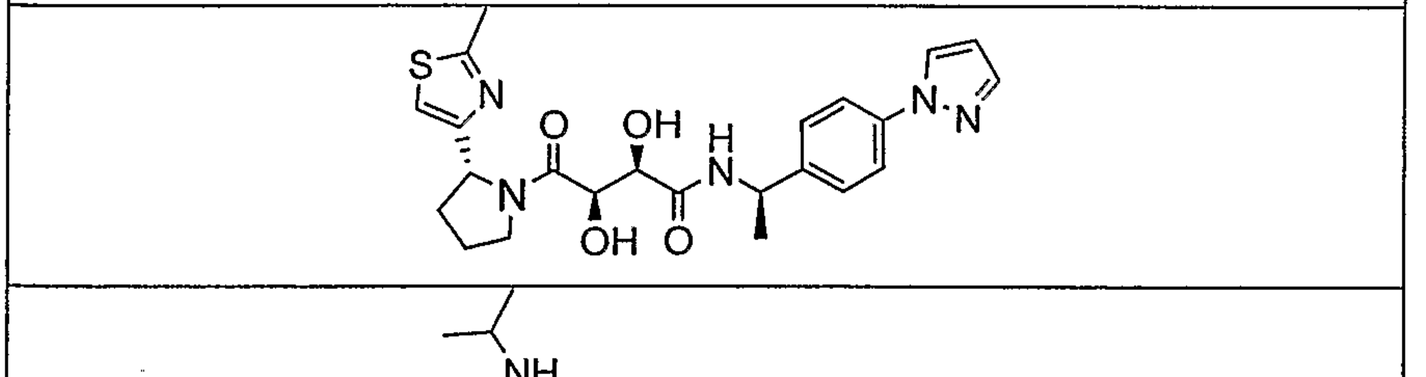


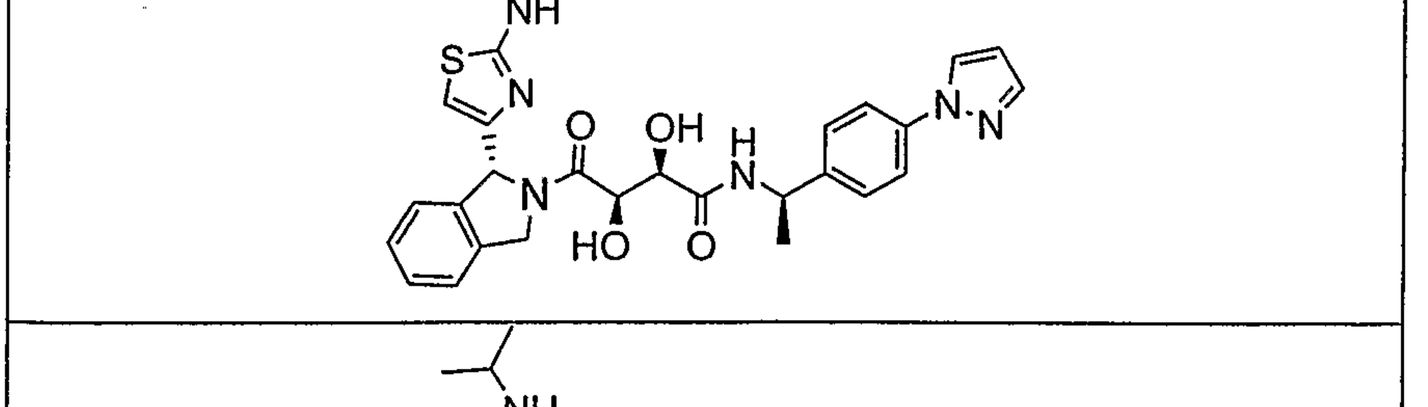


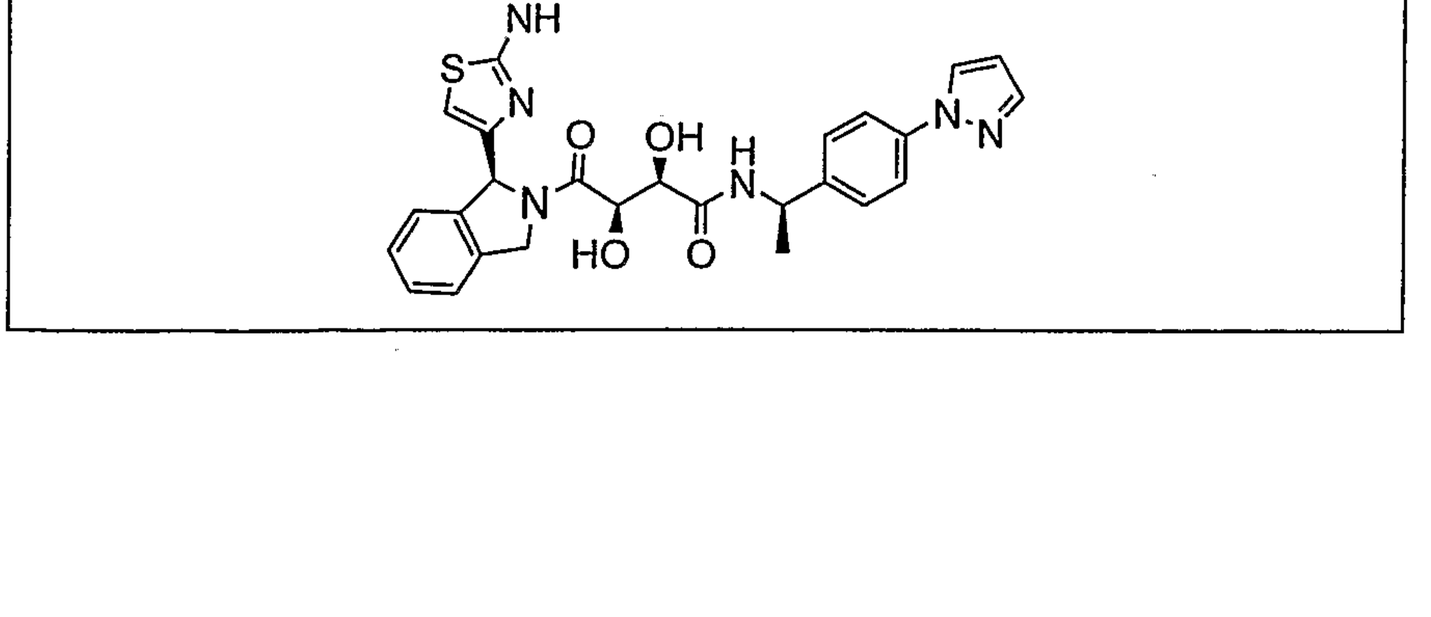


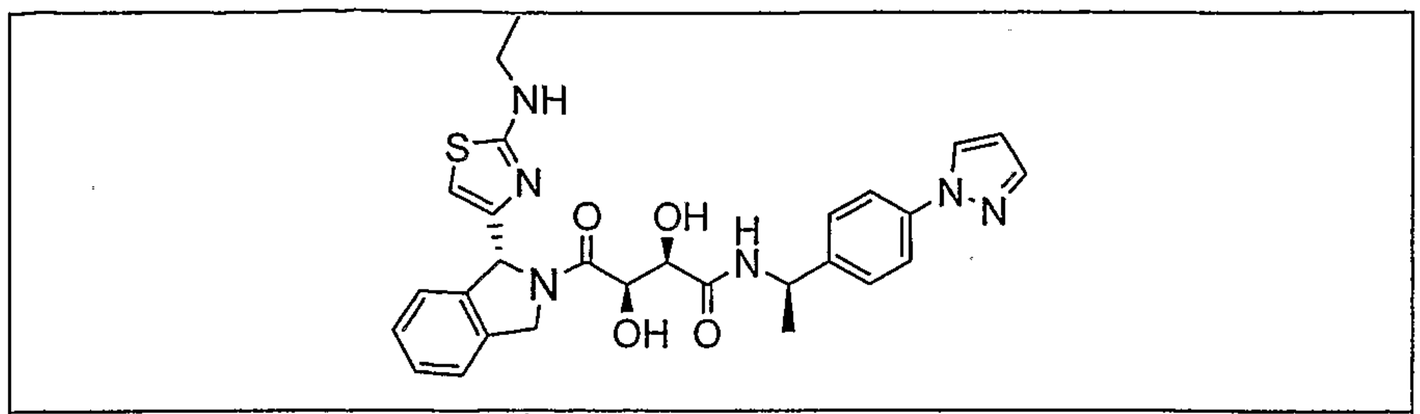


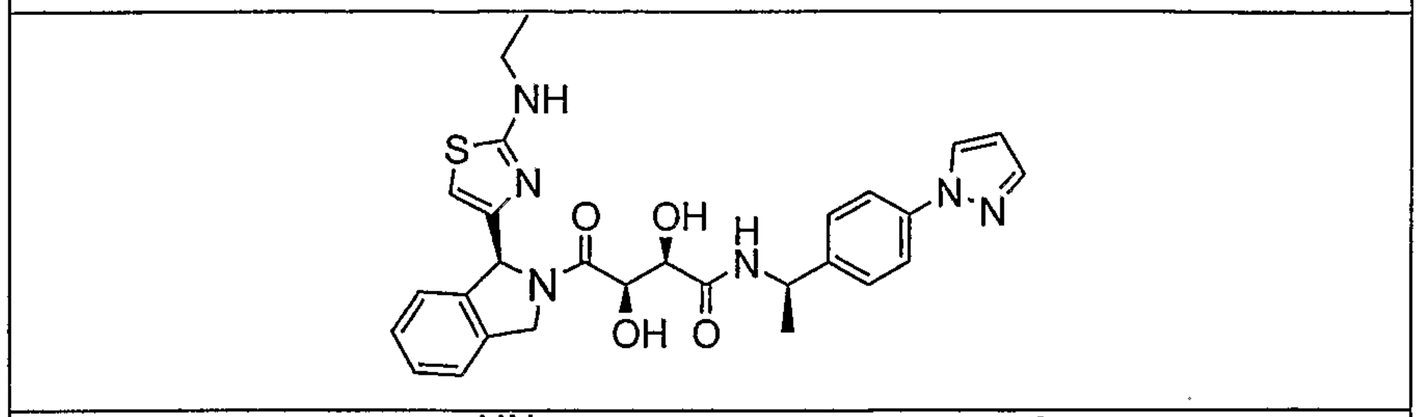


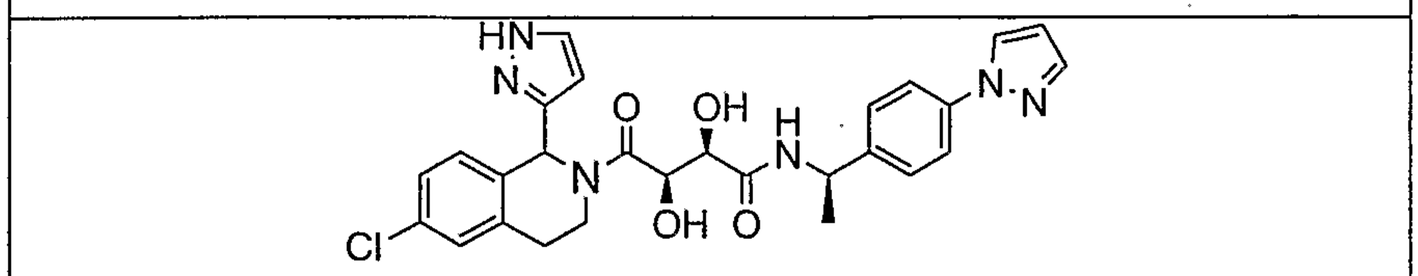


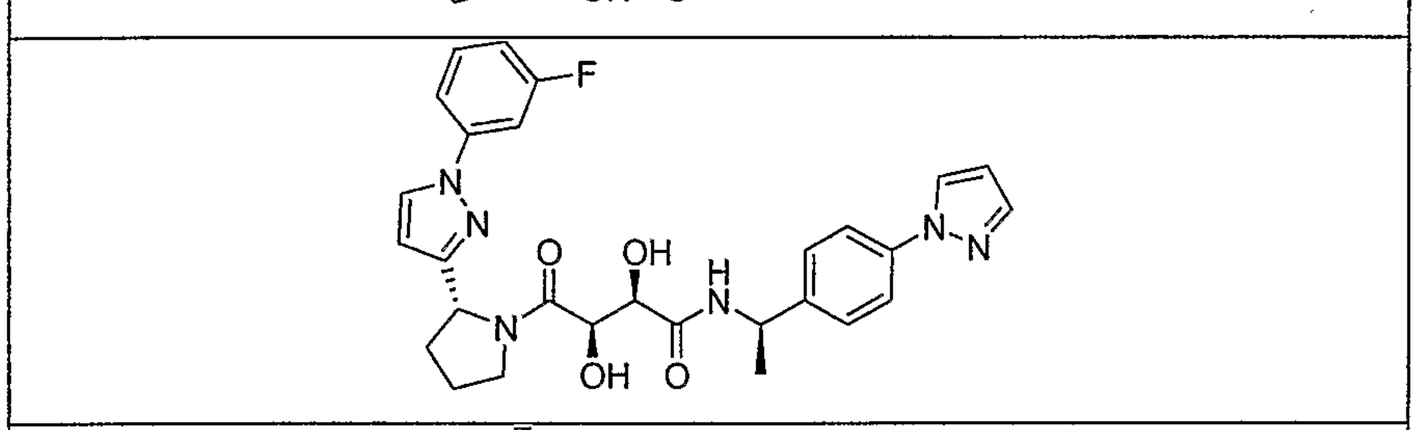


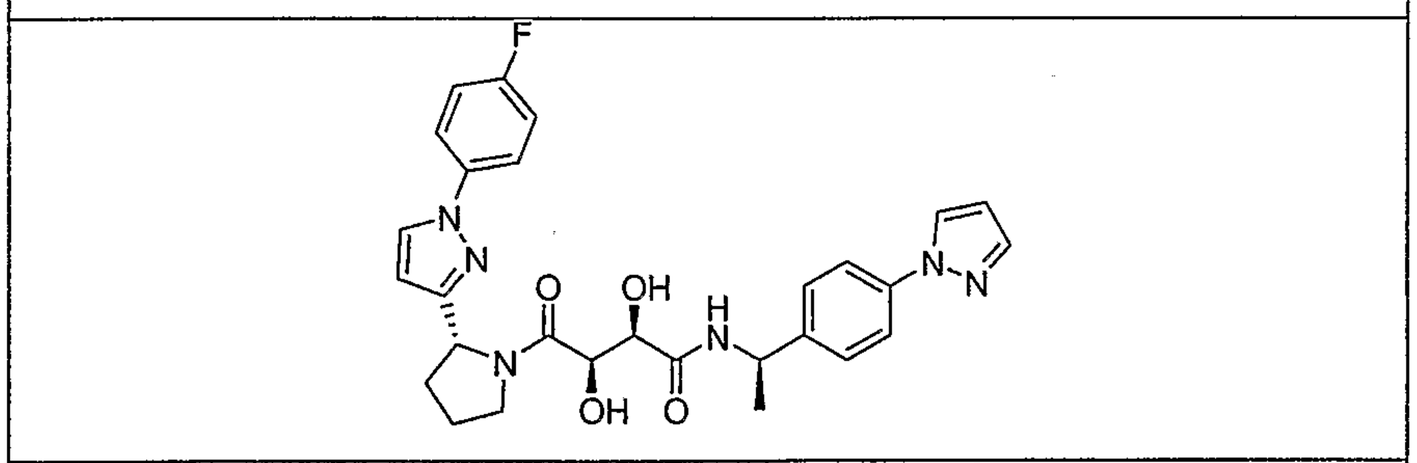


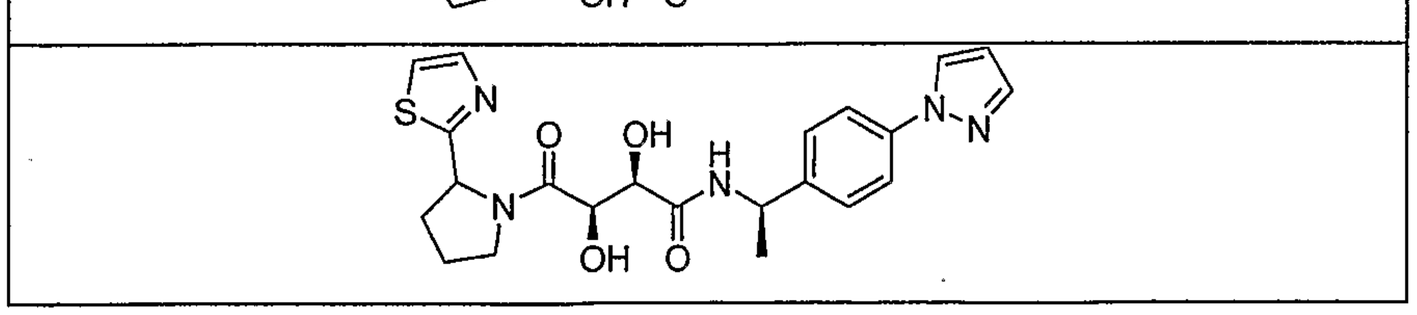




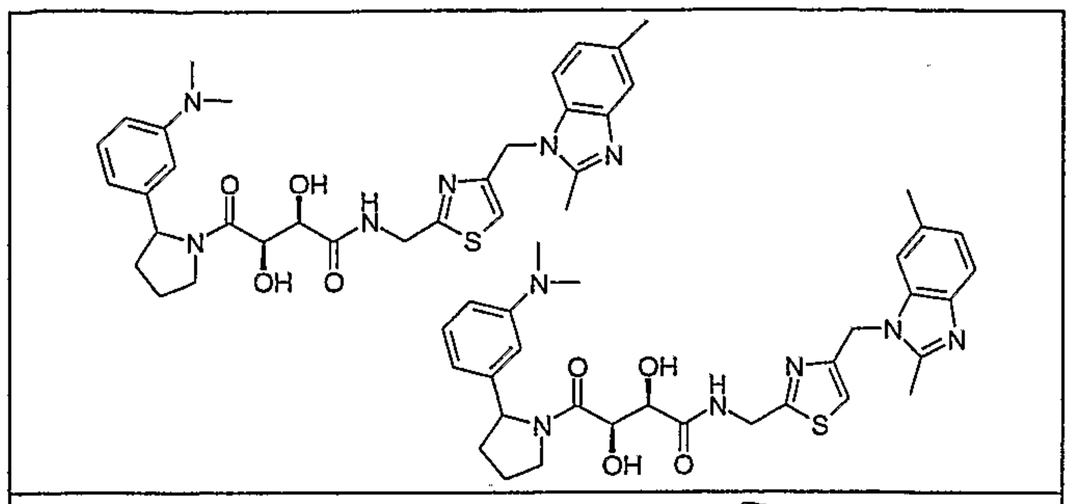


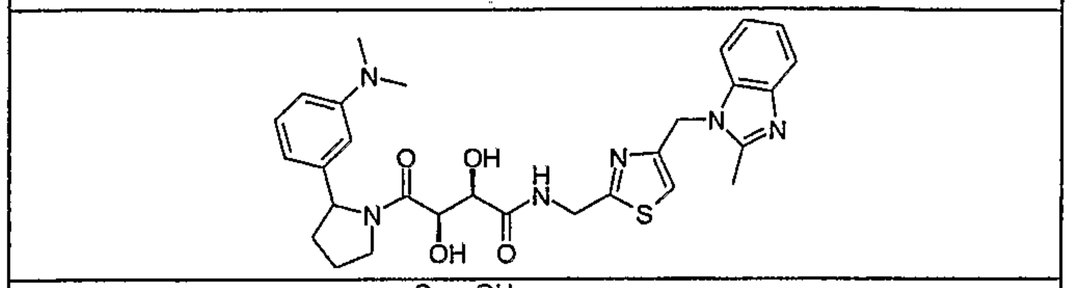


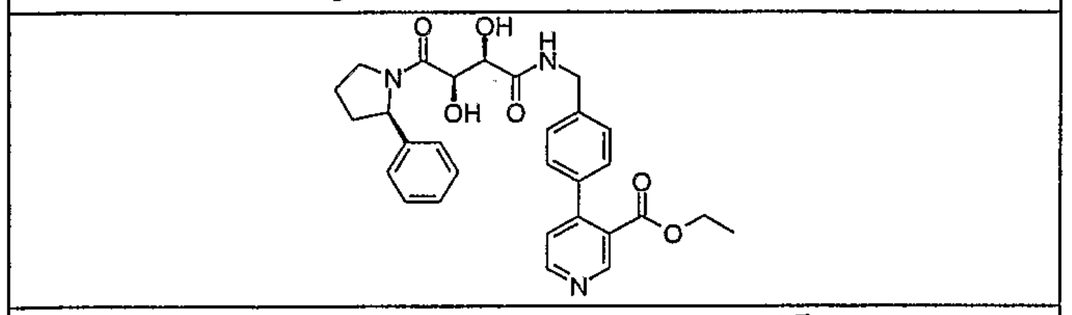


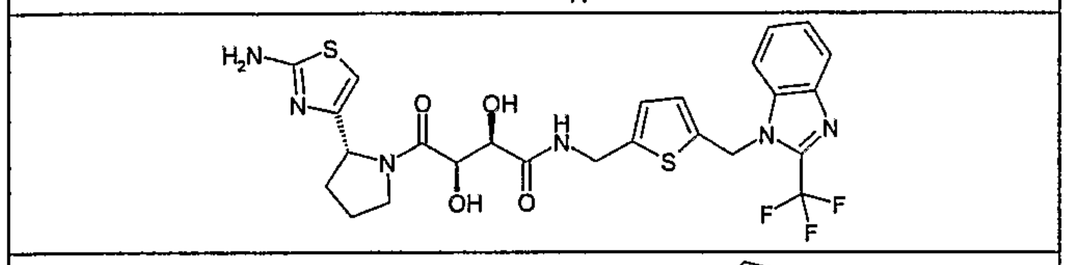


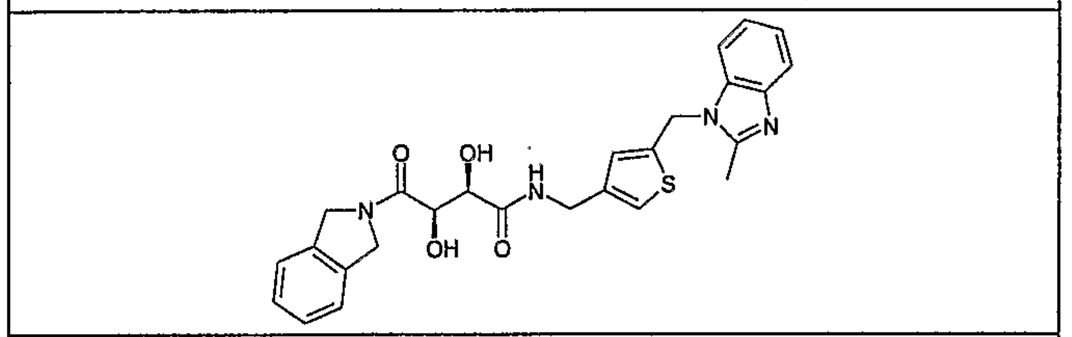
61. The compound of claim 60, said compound being selected from the compounds of structures listed below:

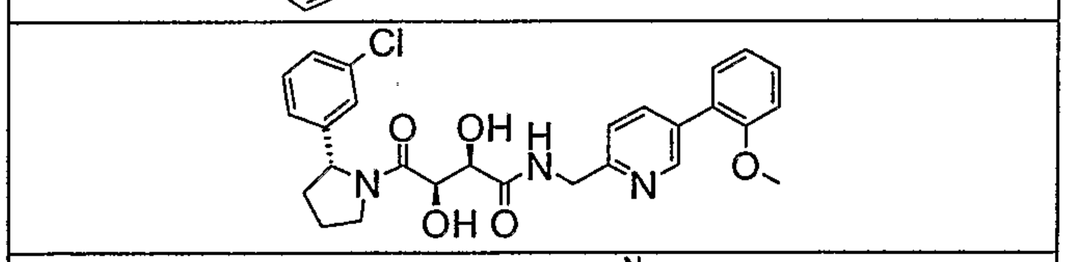


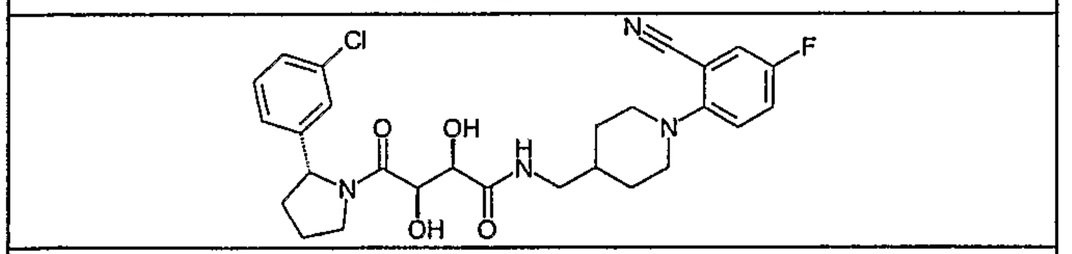


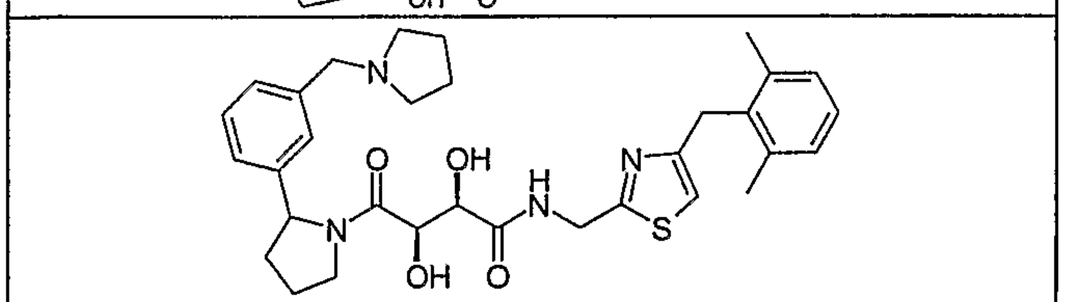


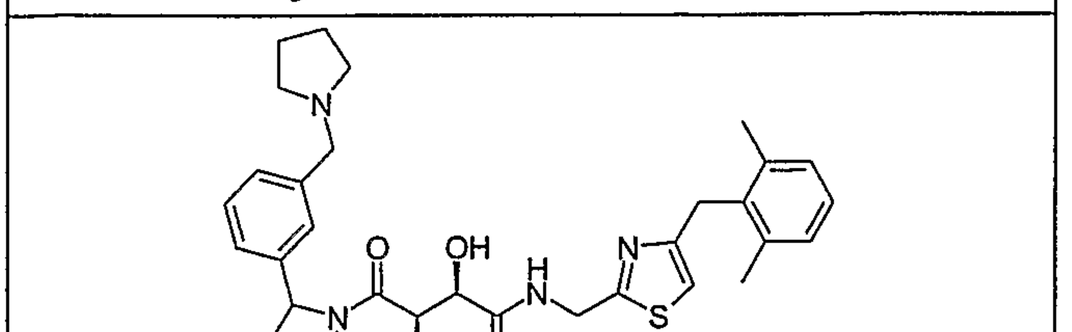


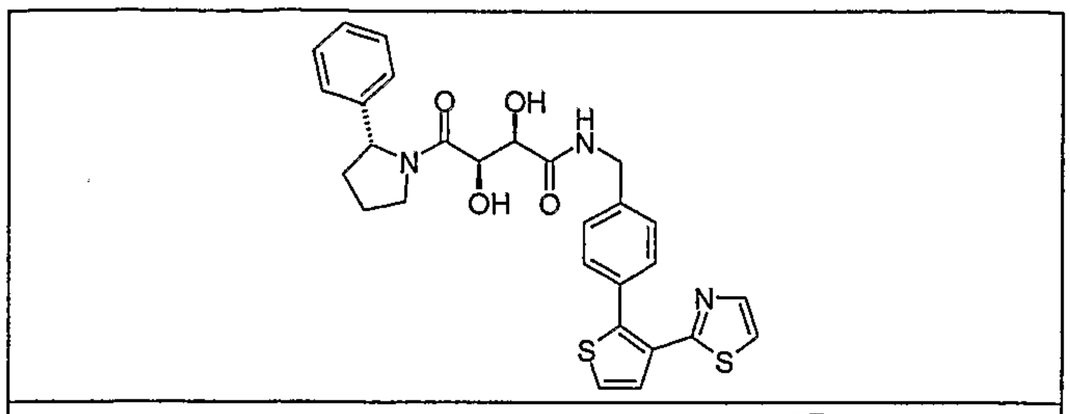


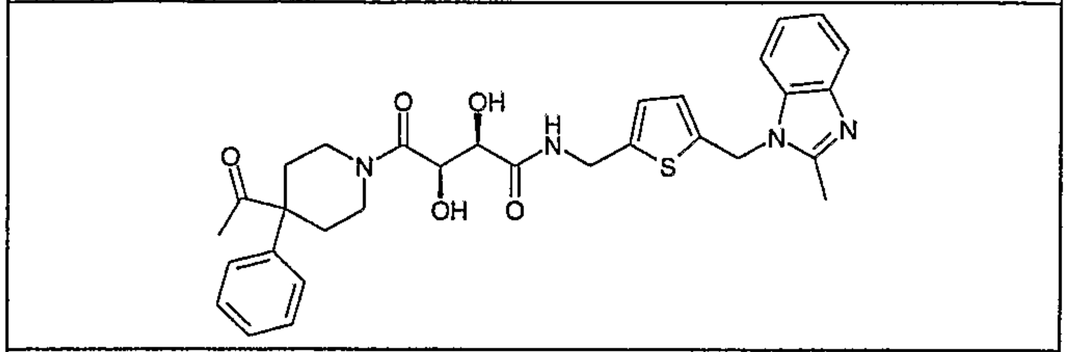


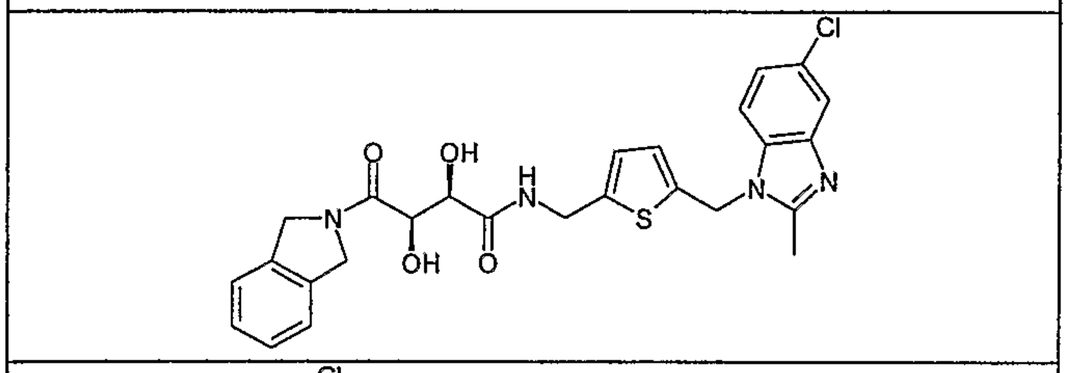


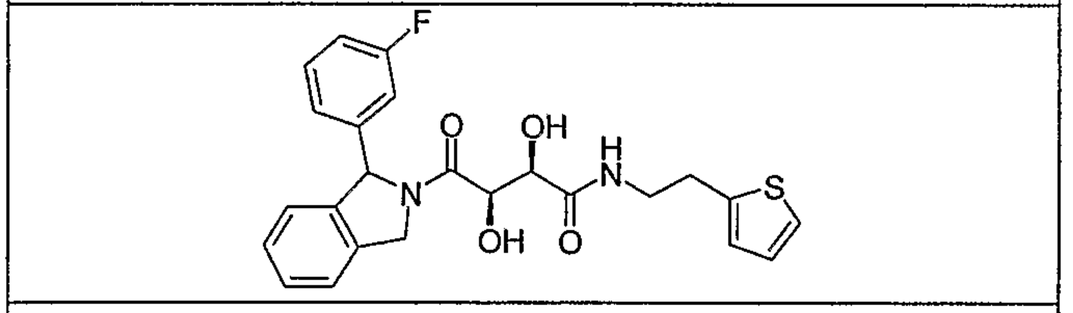


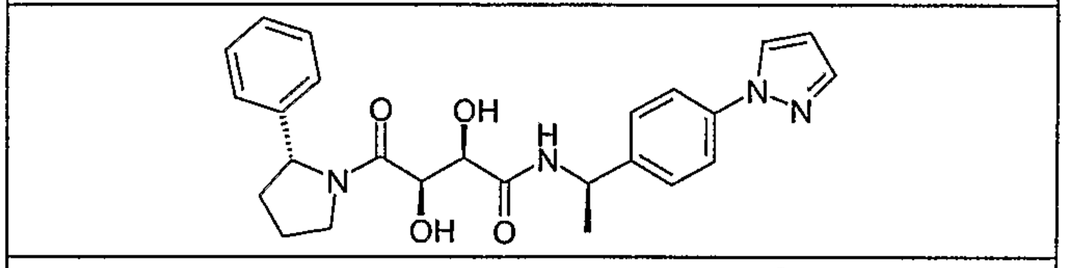


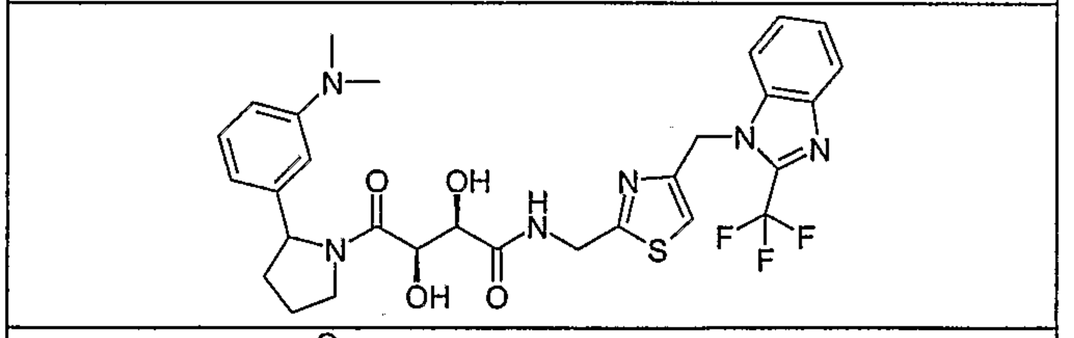


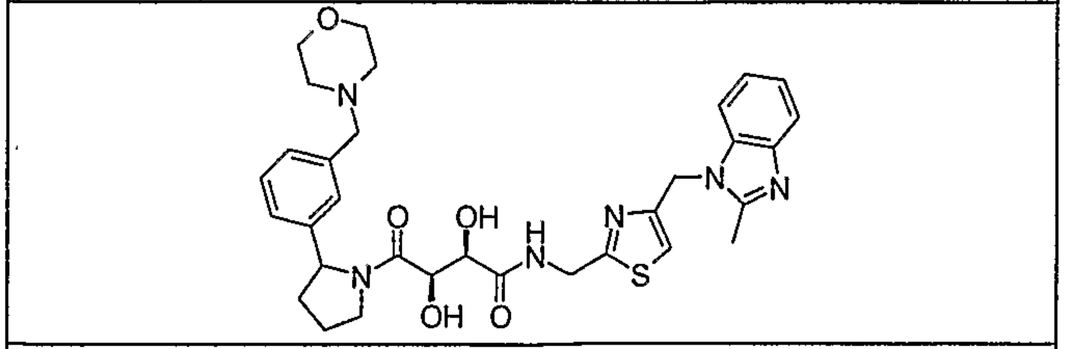


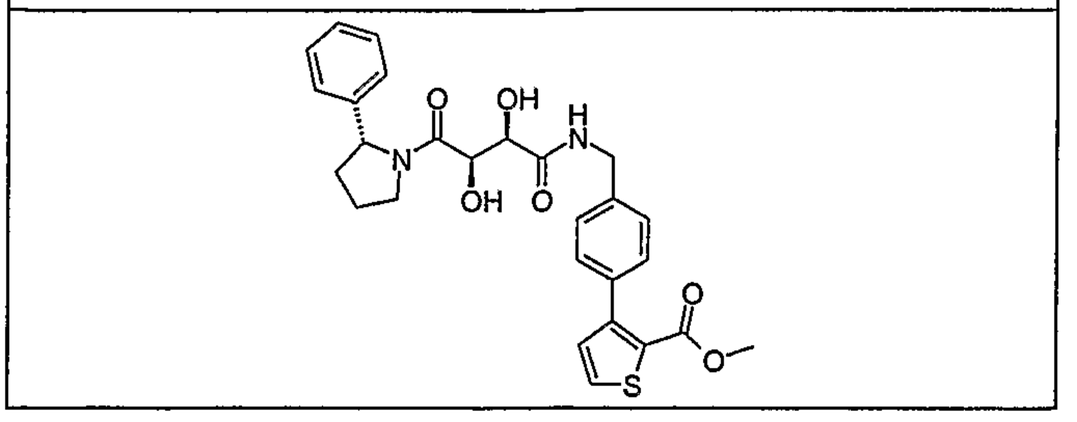


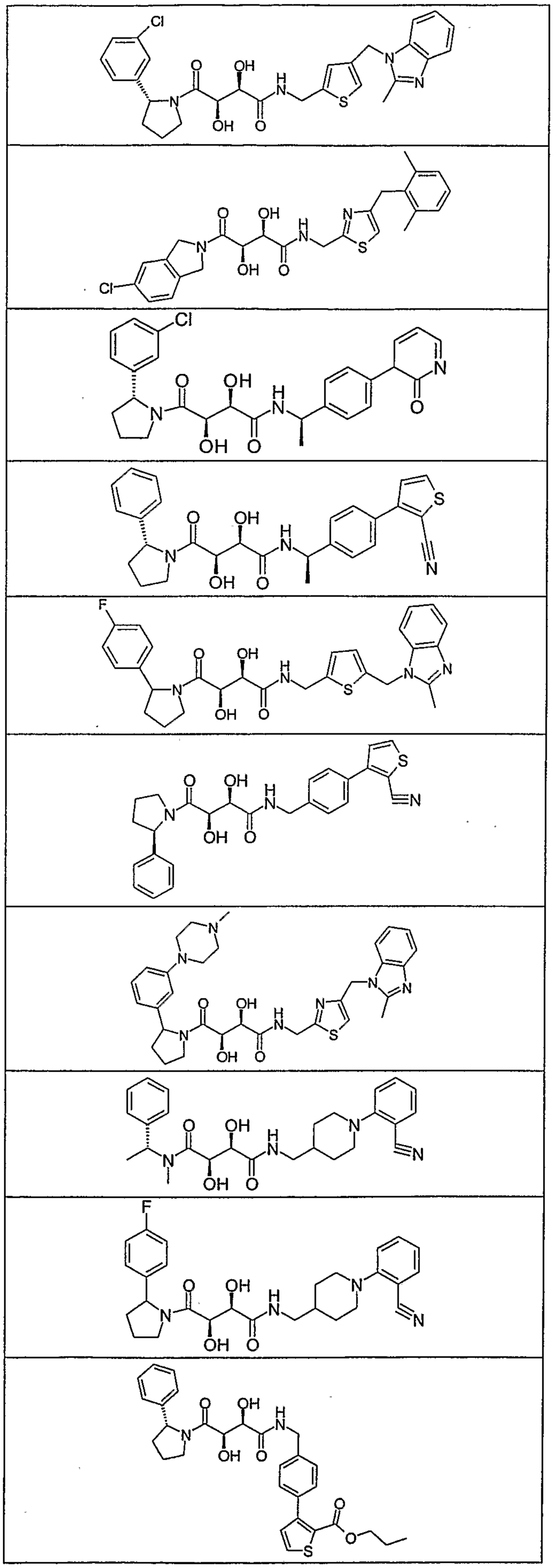


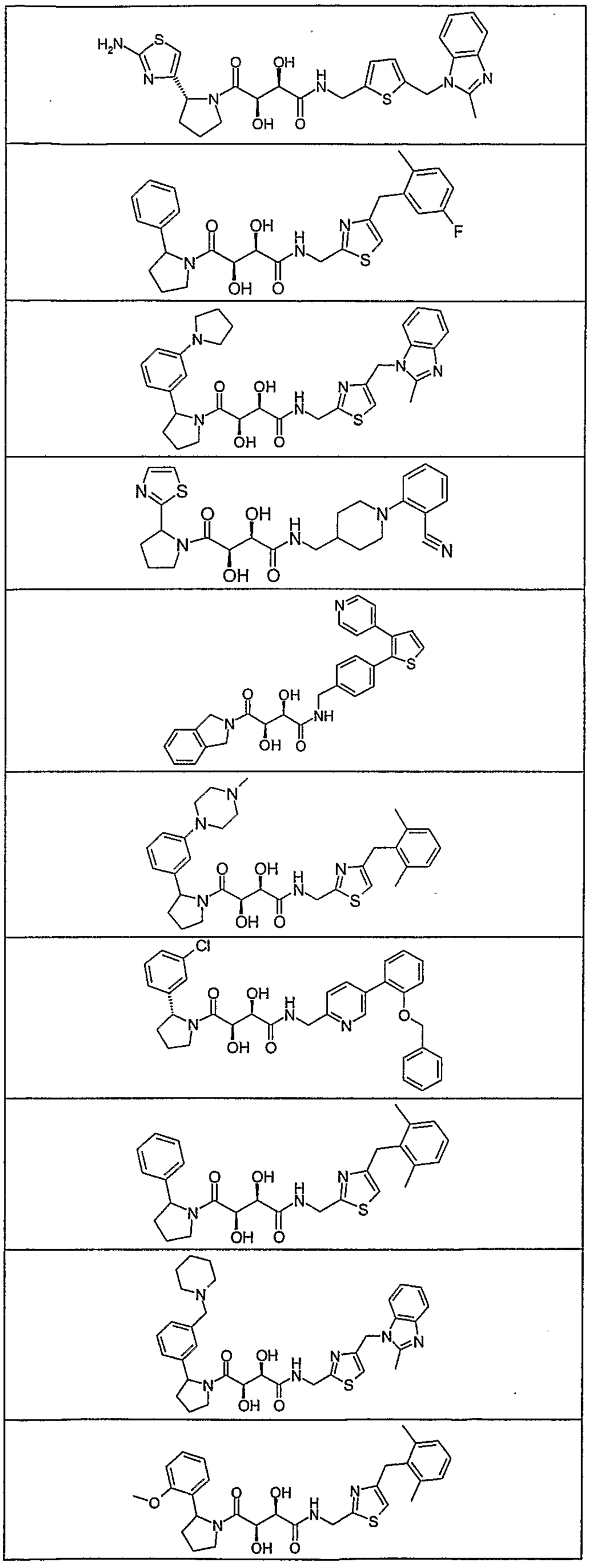


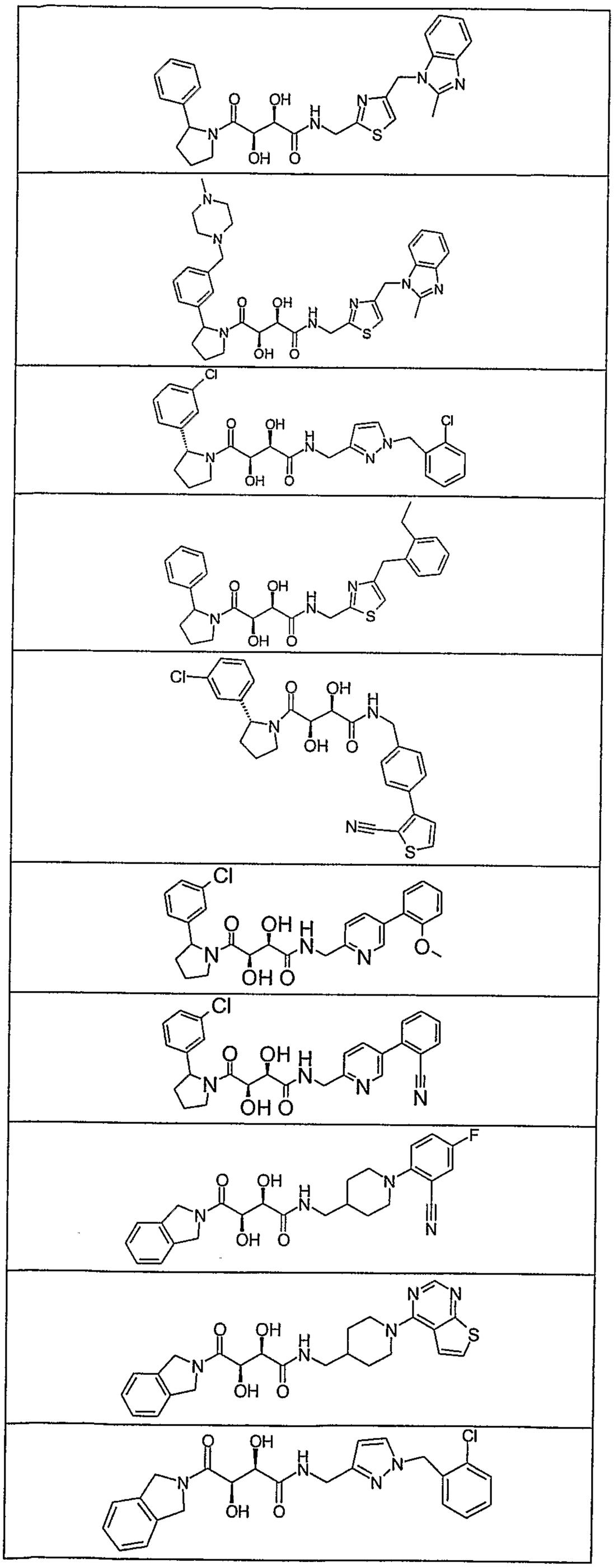


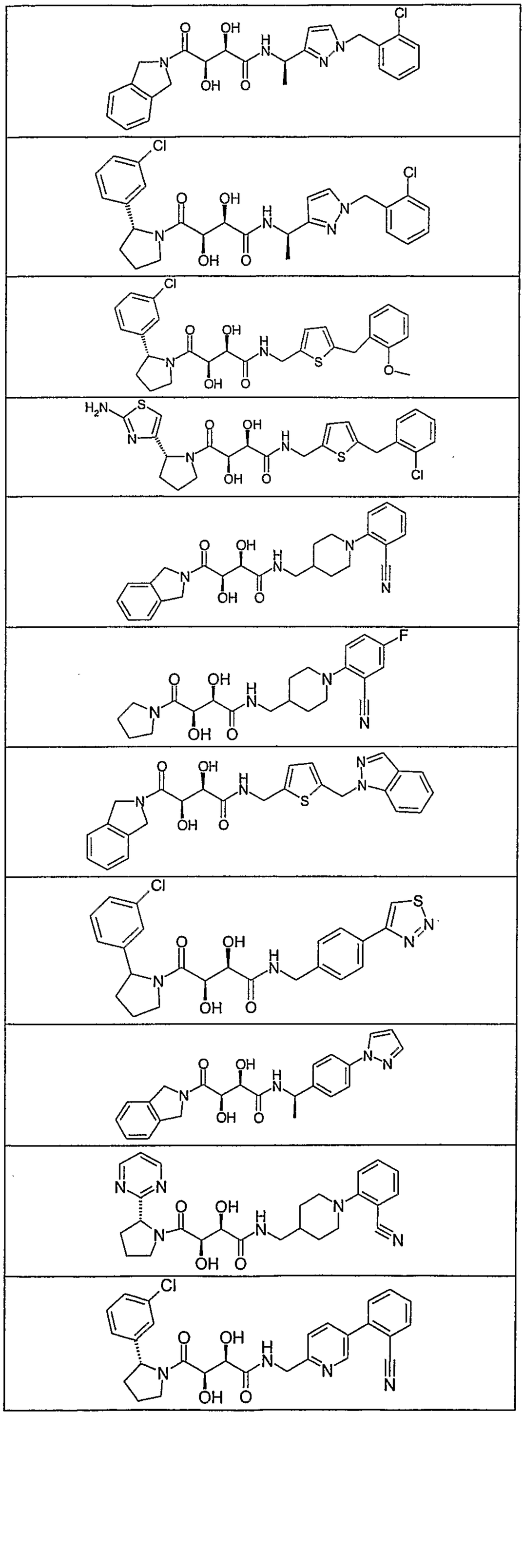


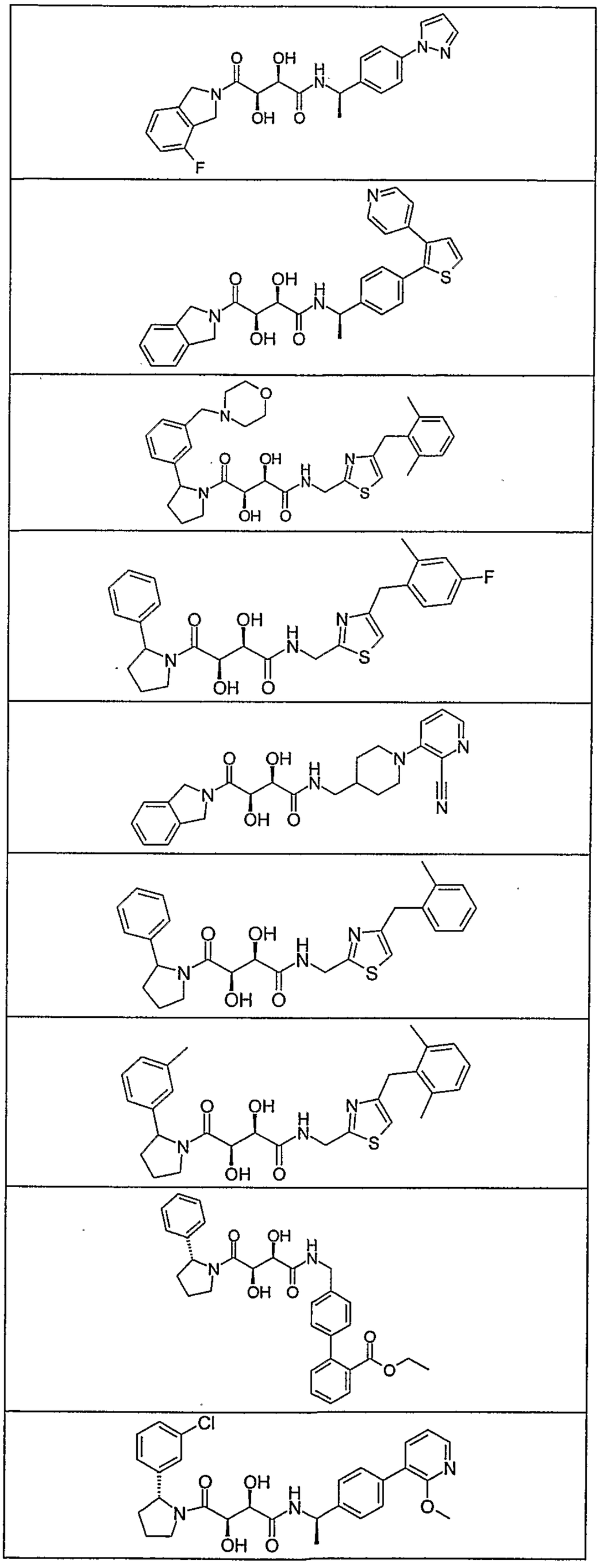


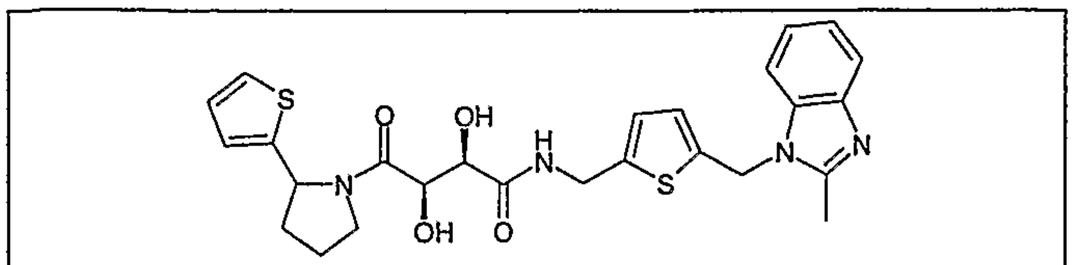


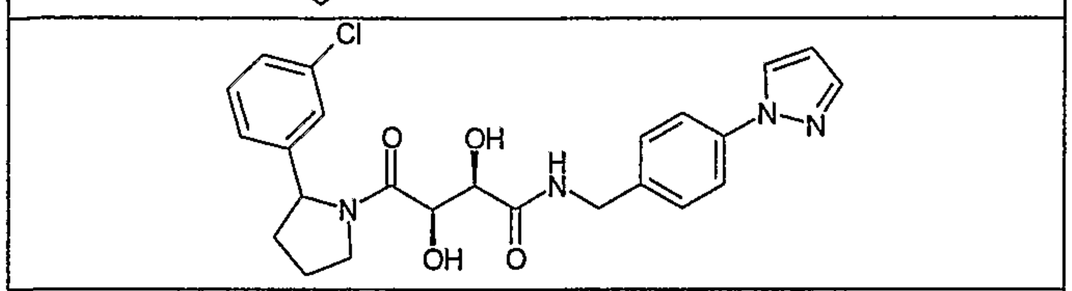


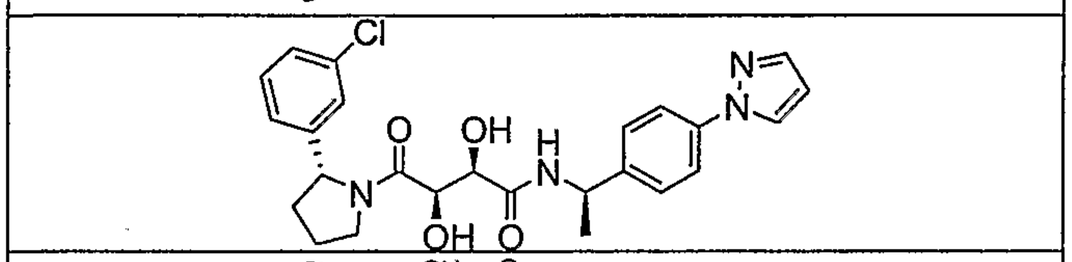


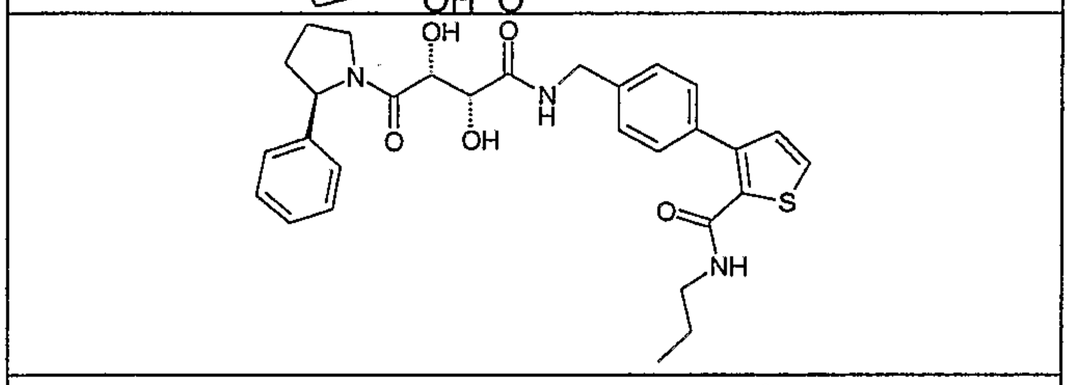


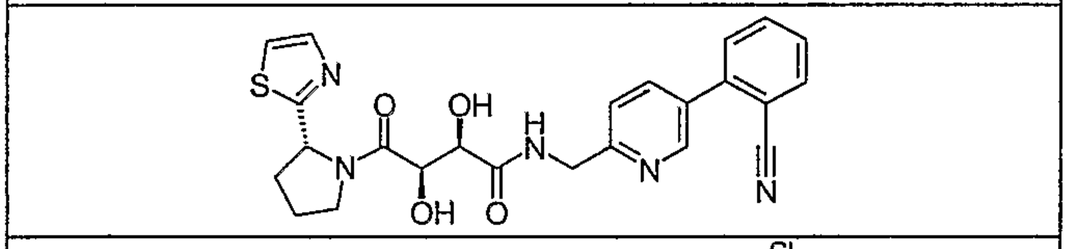


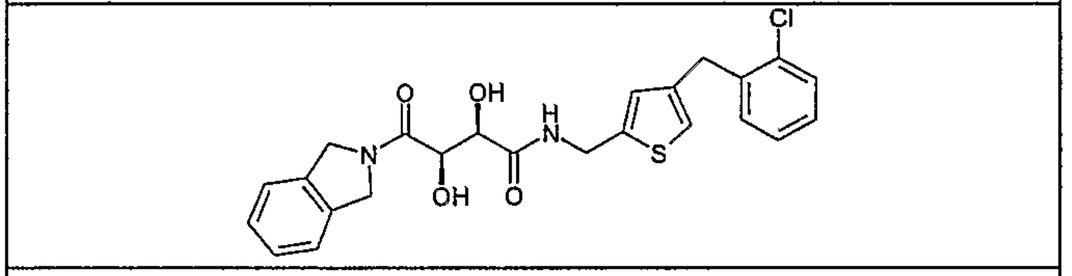


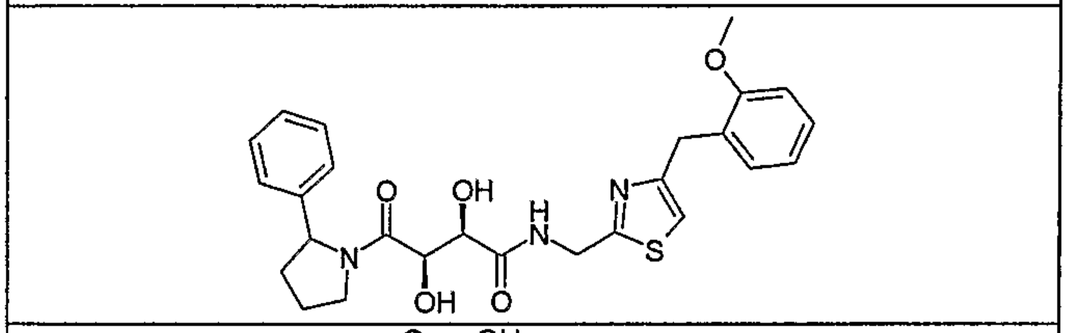


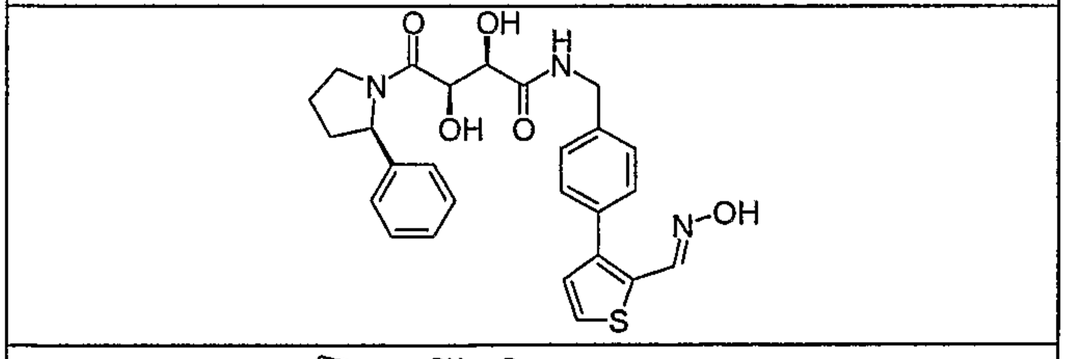


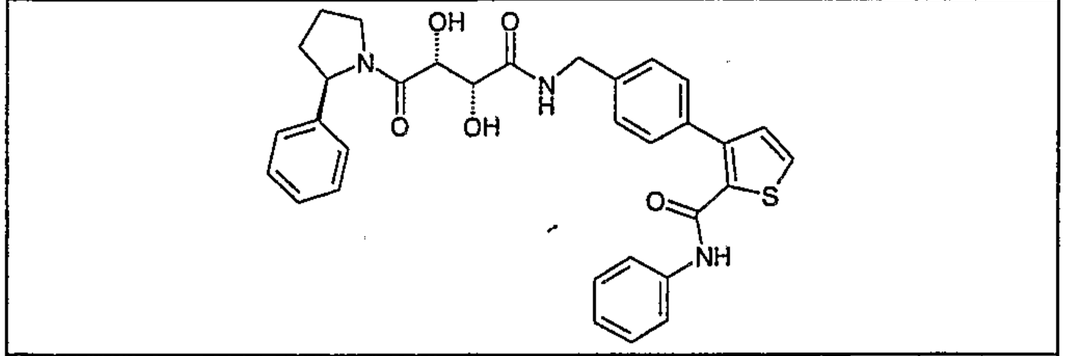


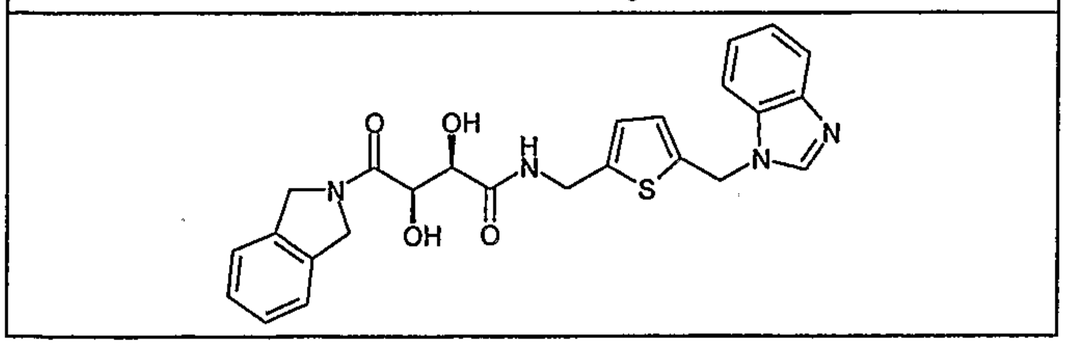


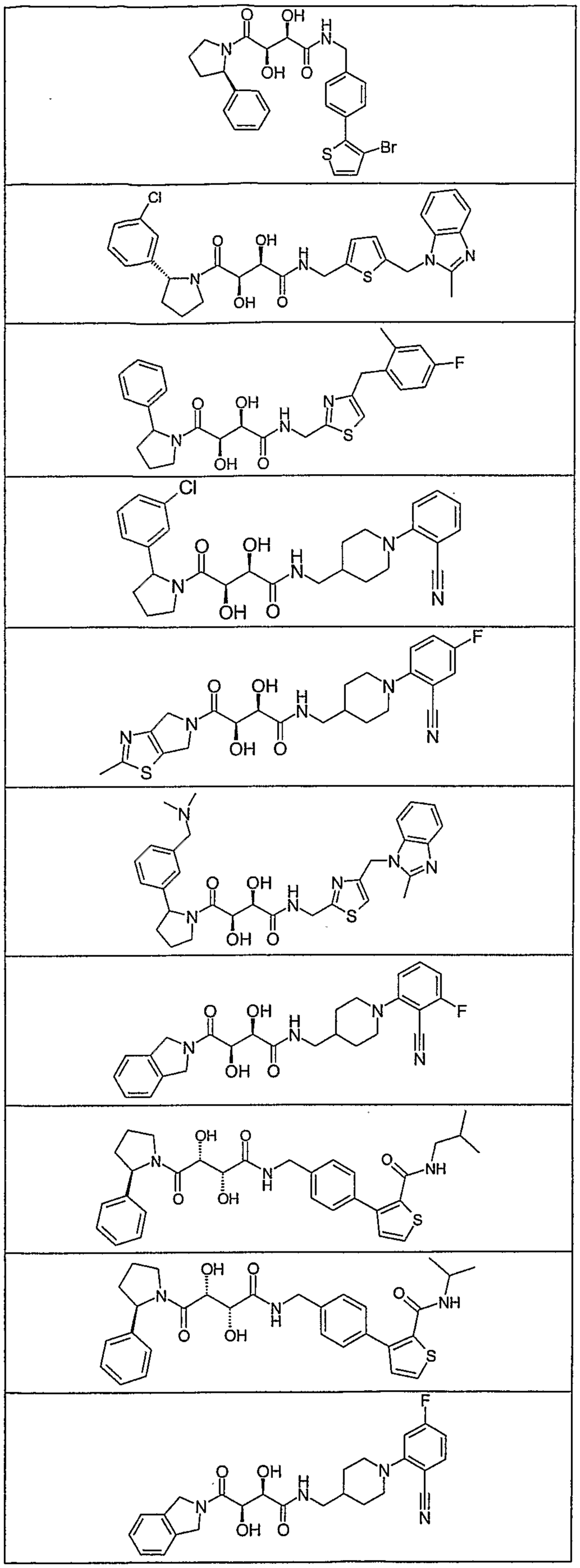


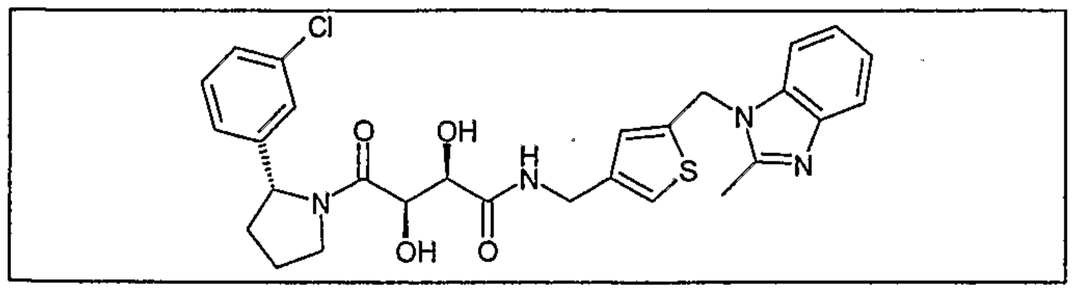


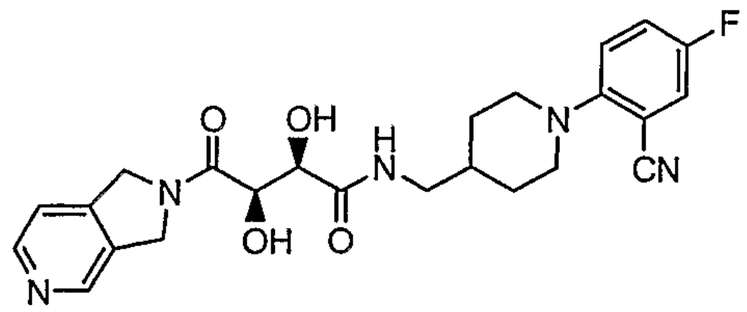


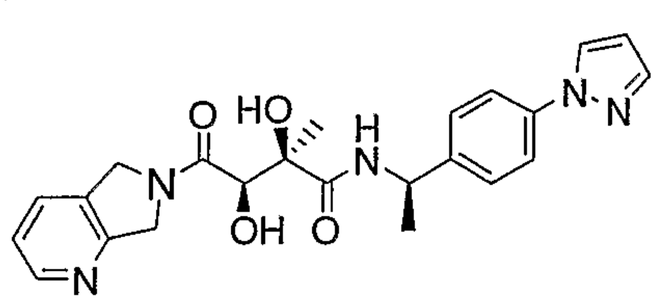


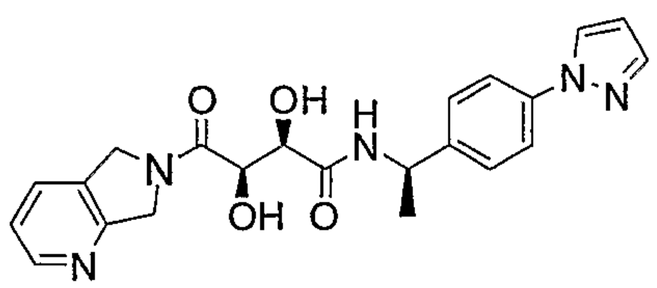


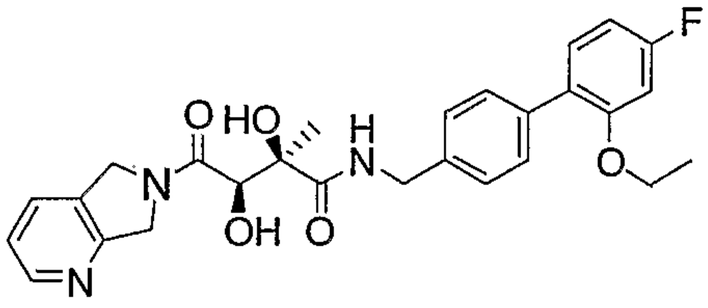


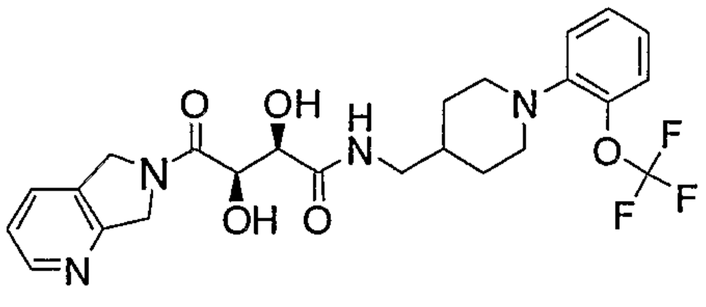


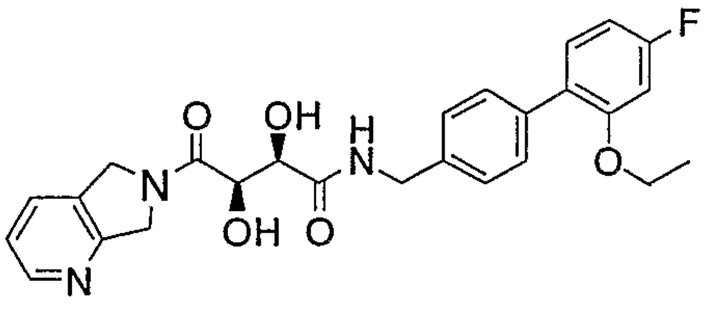


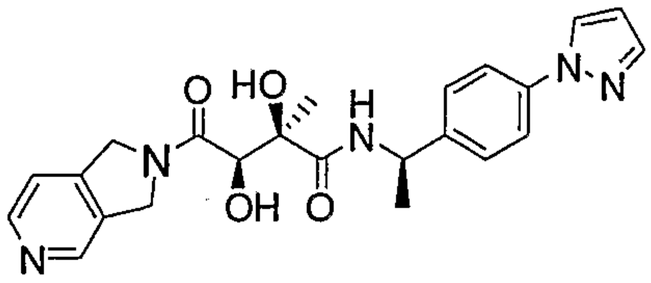


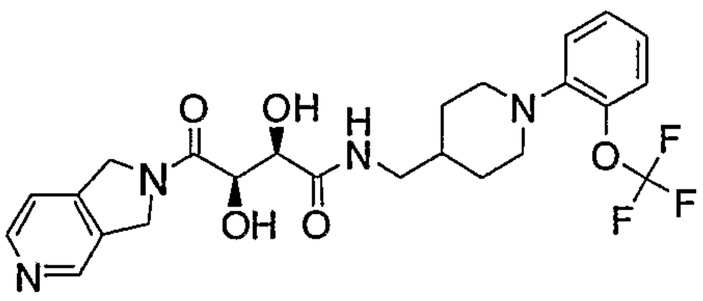


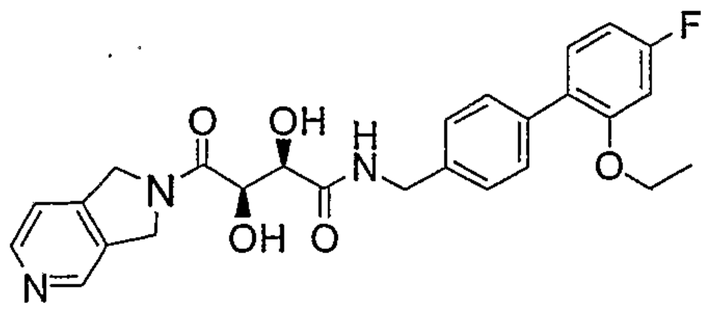


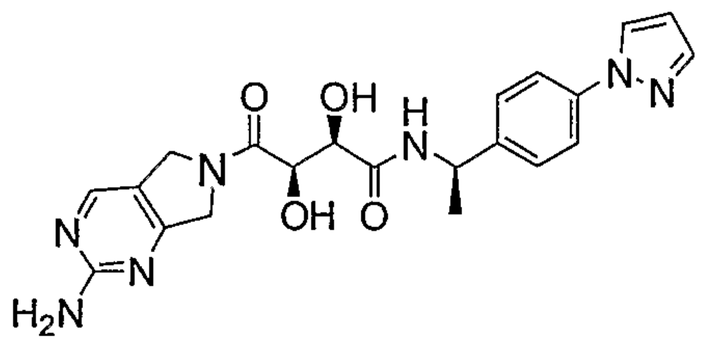


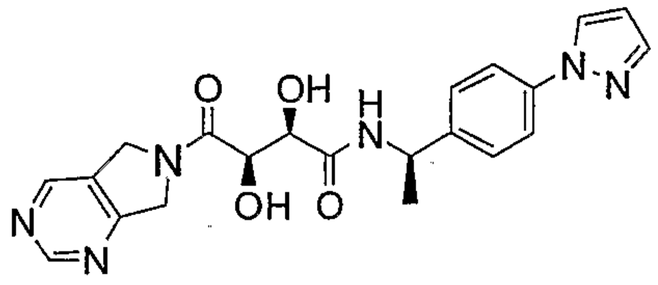


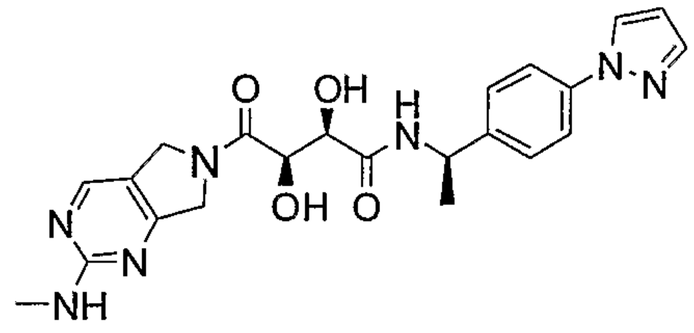


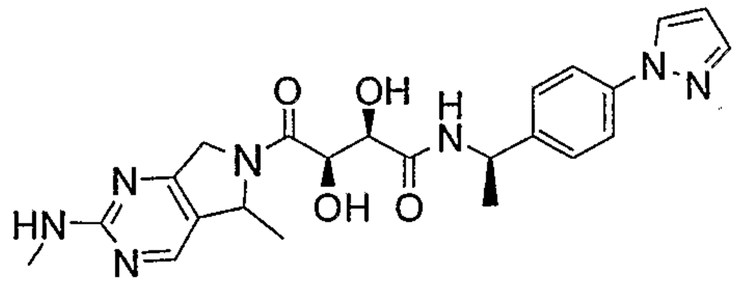


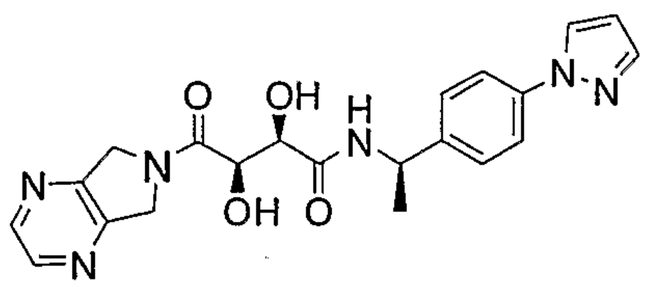


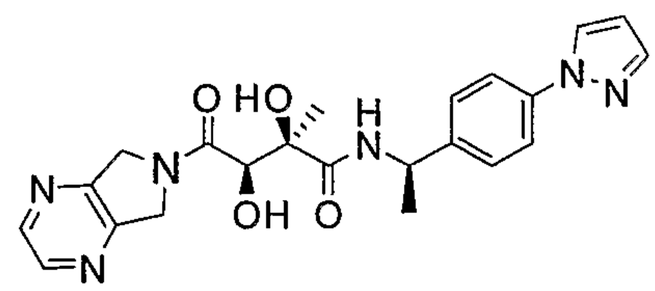


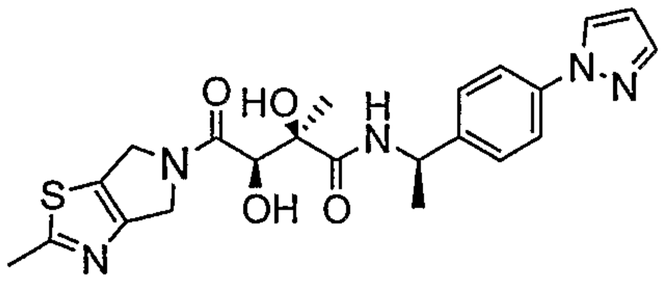


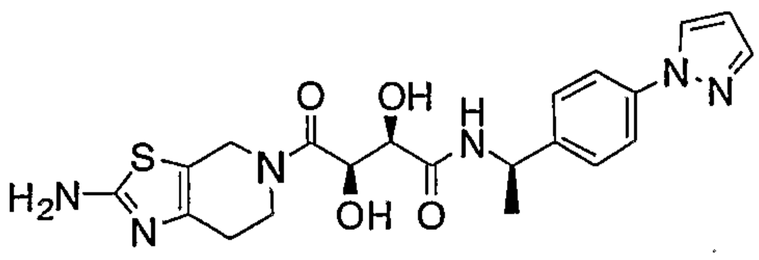


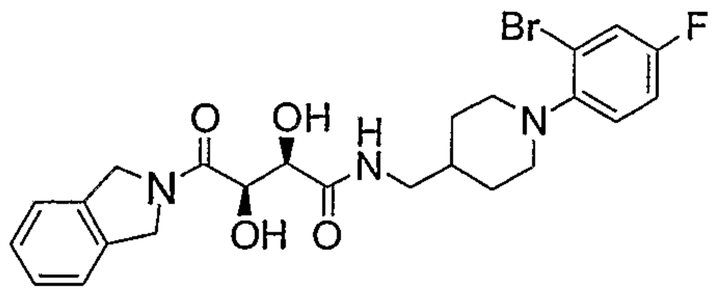


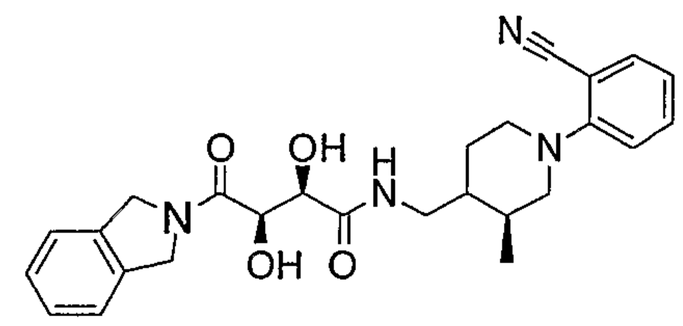


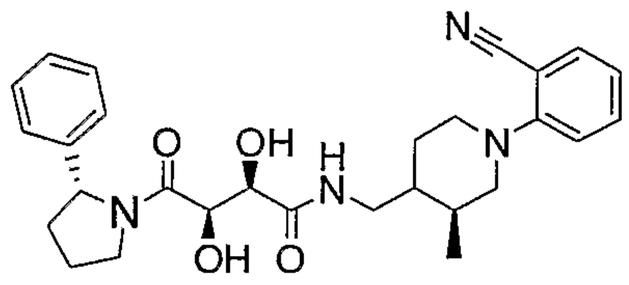


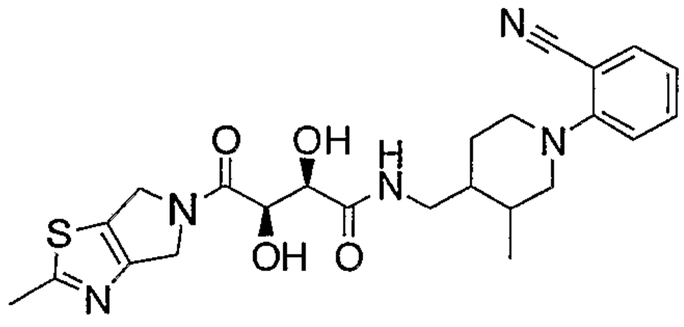


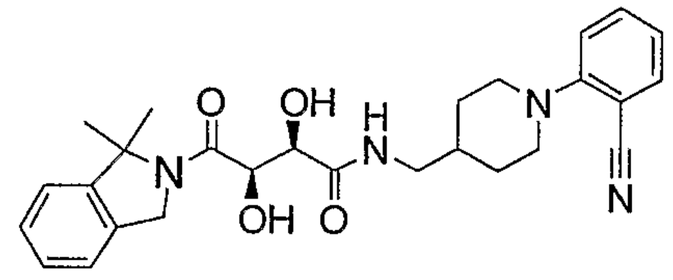


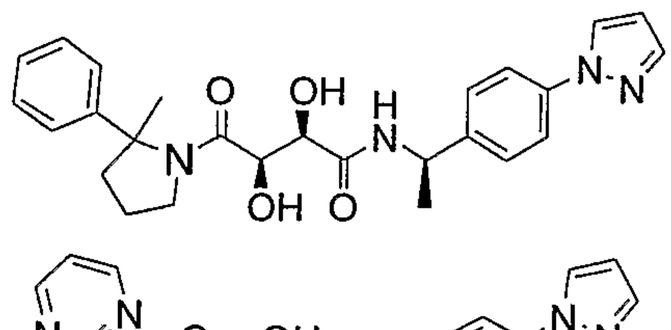


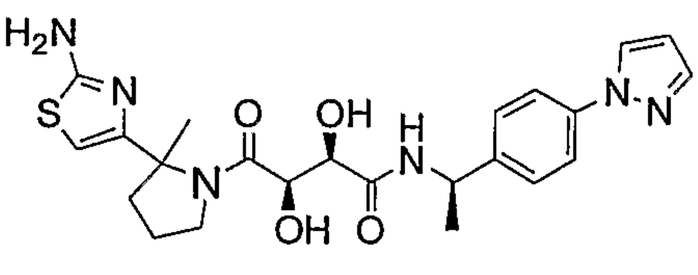


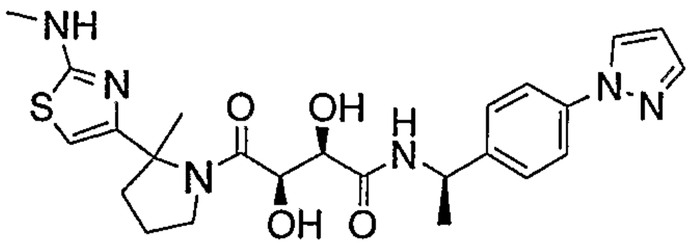


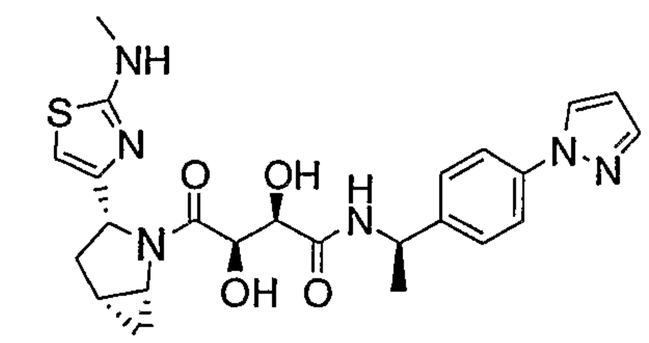


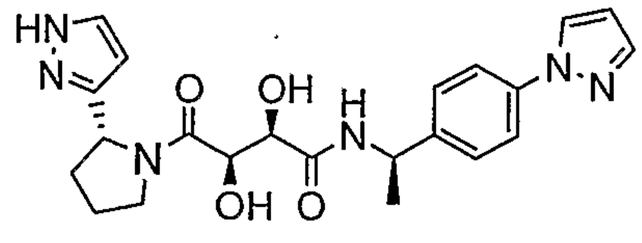


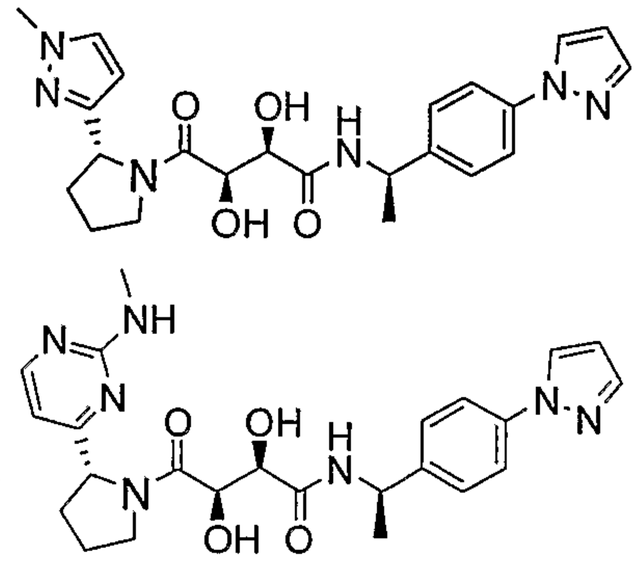


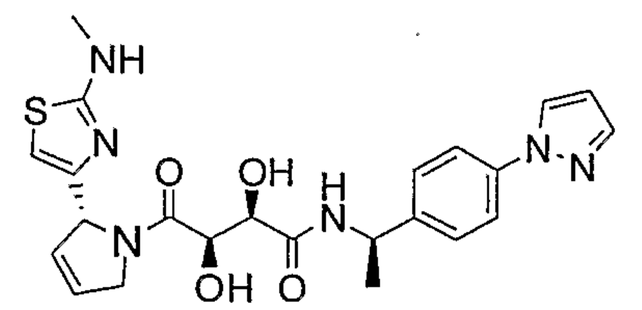


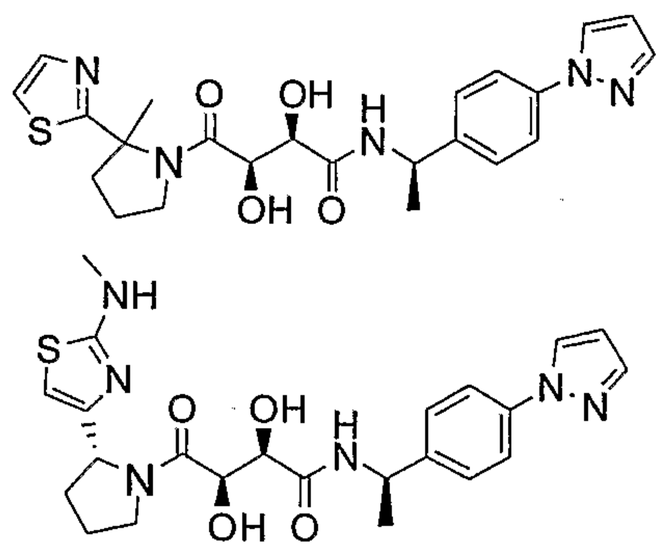


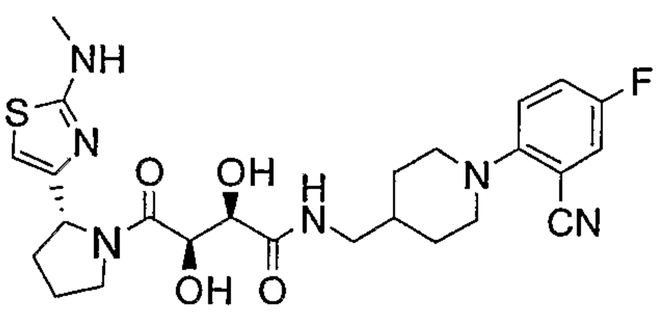


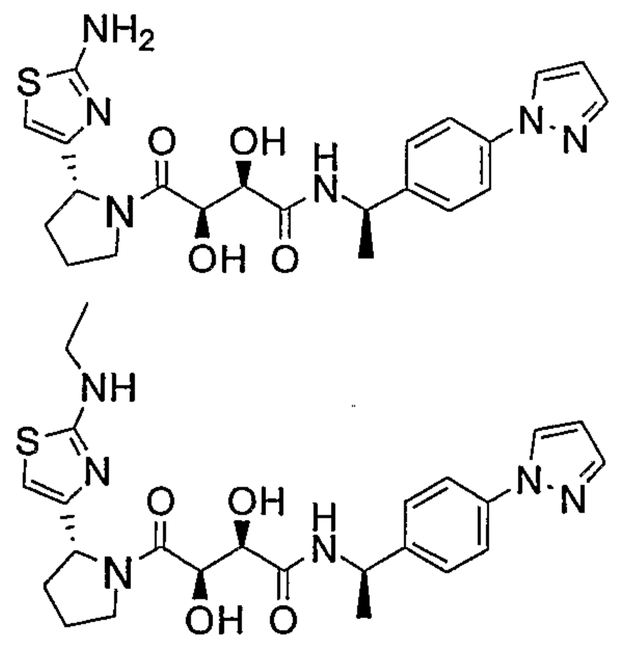


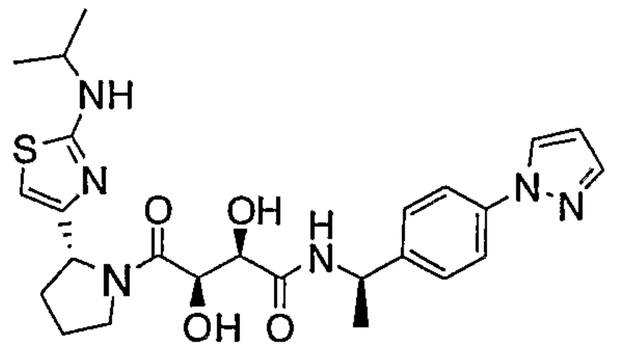


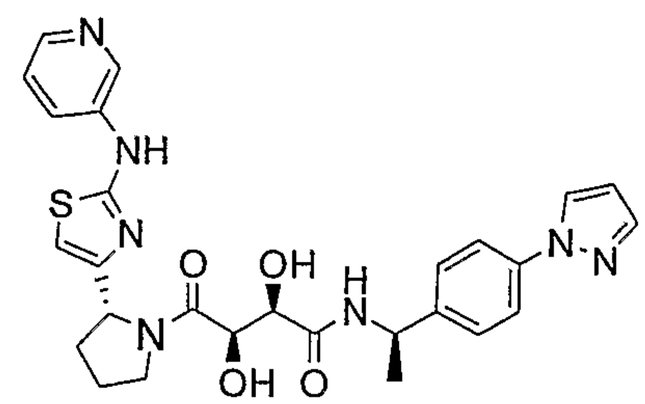


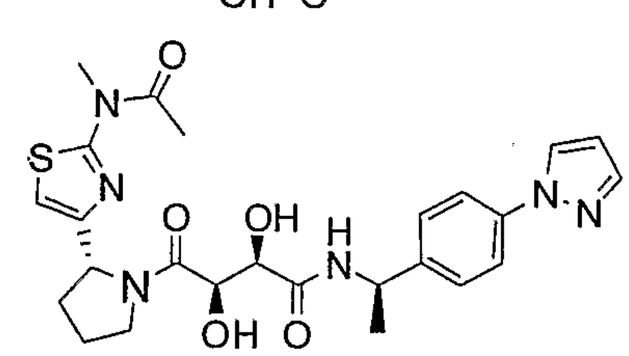


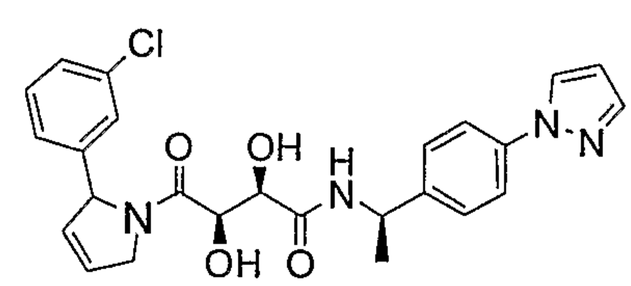


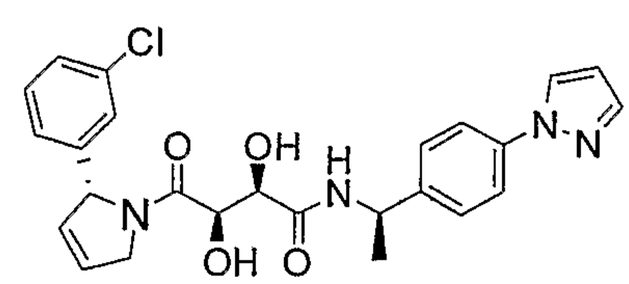


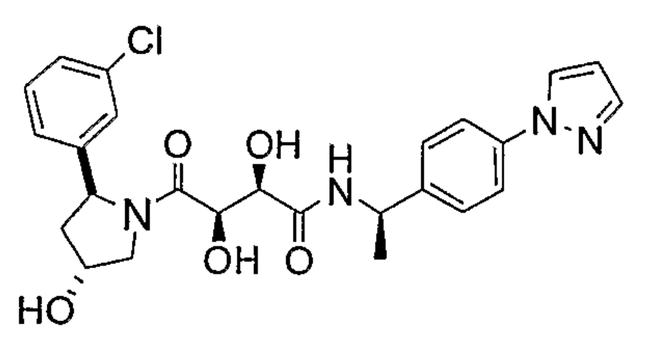


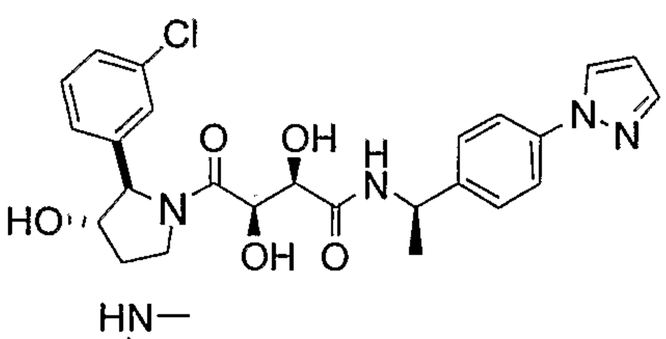


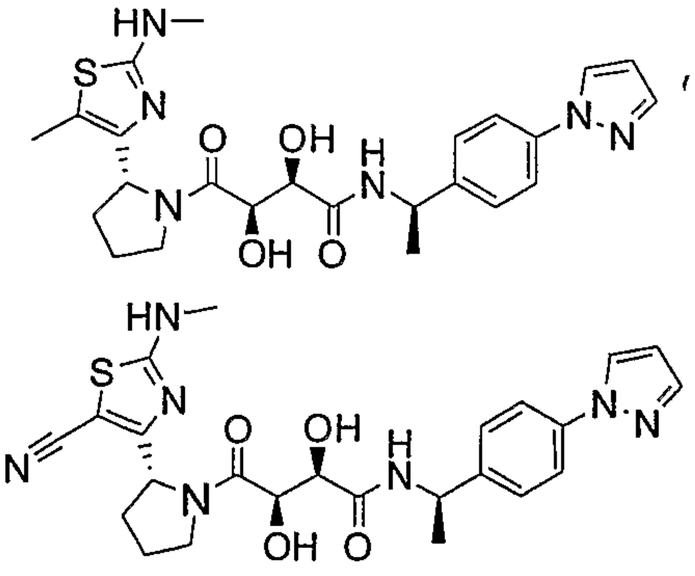


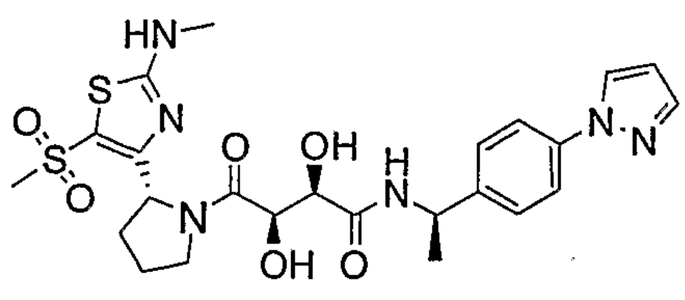


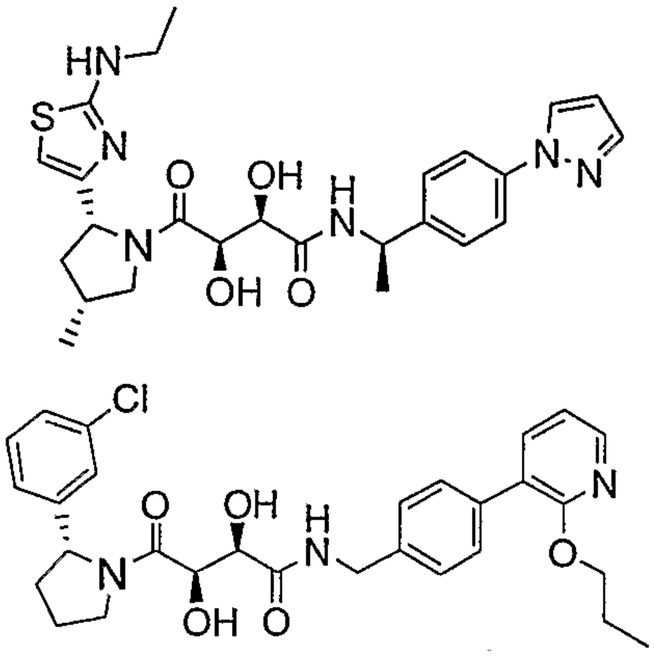


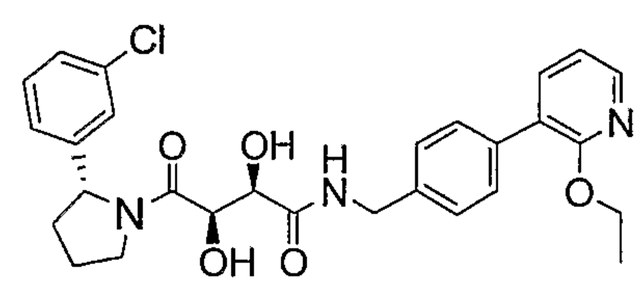


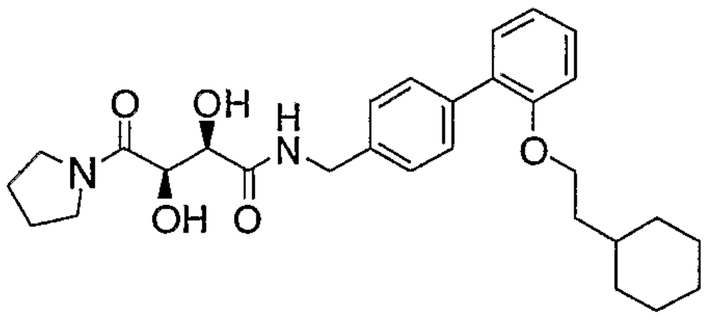


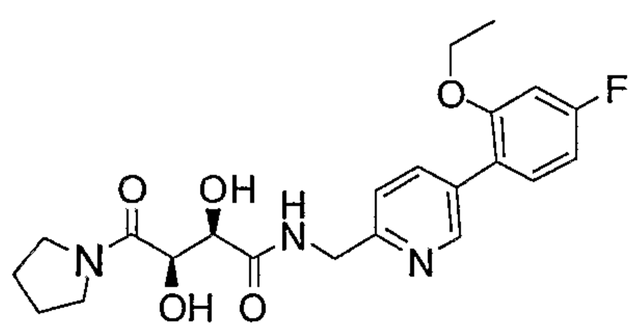


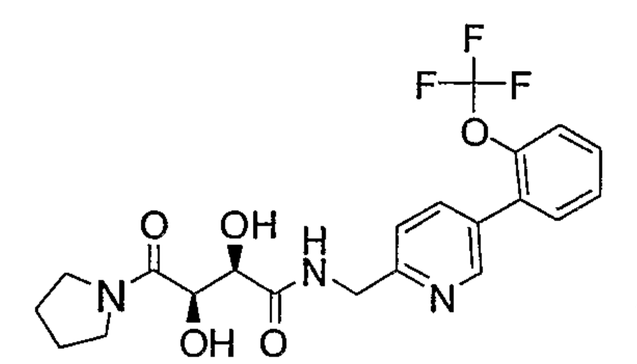


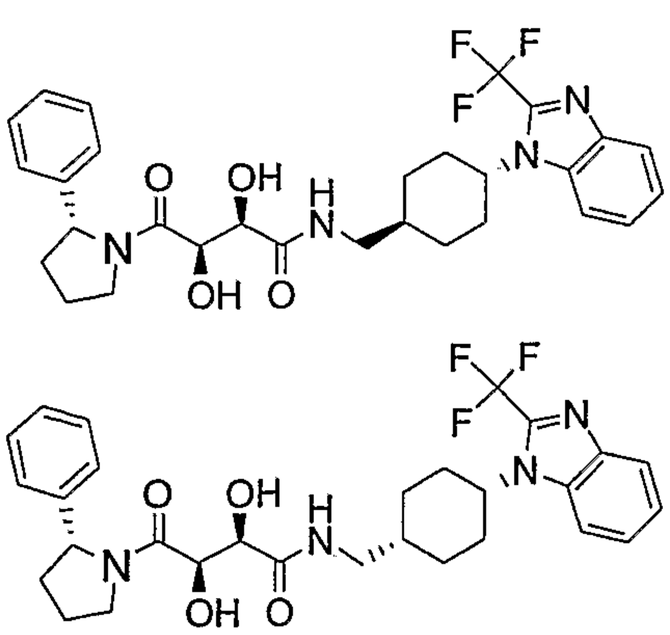


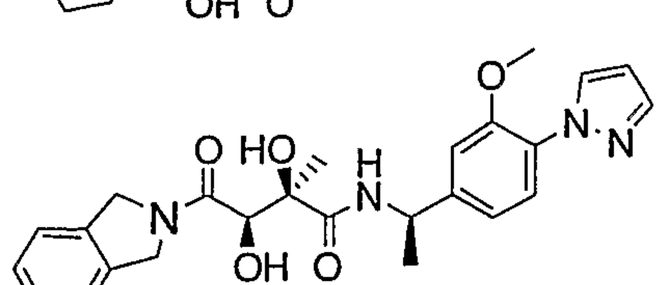


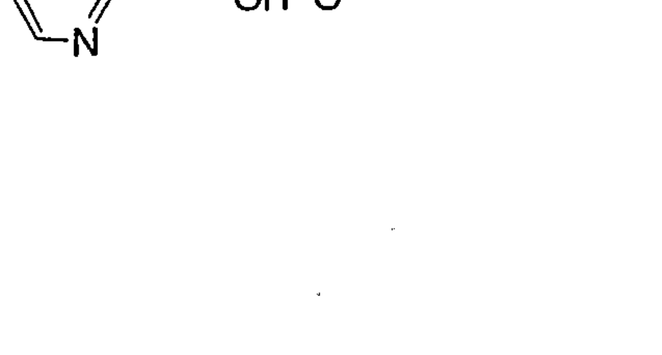


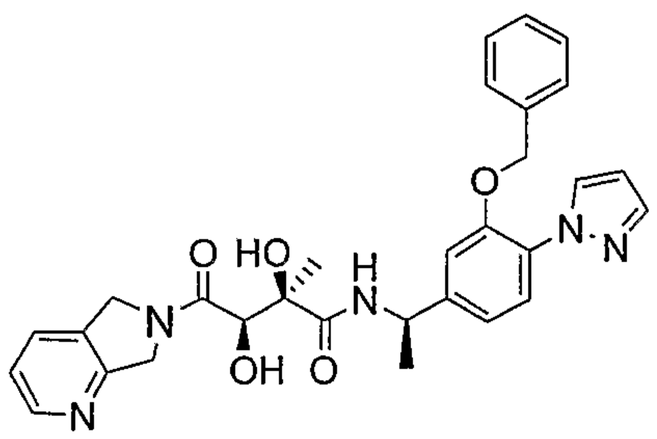


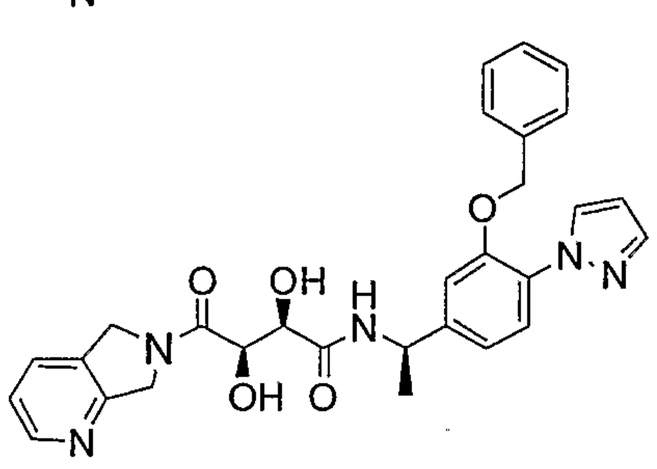


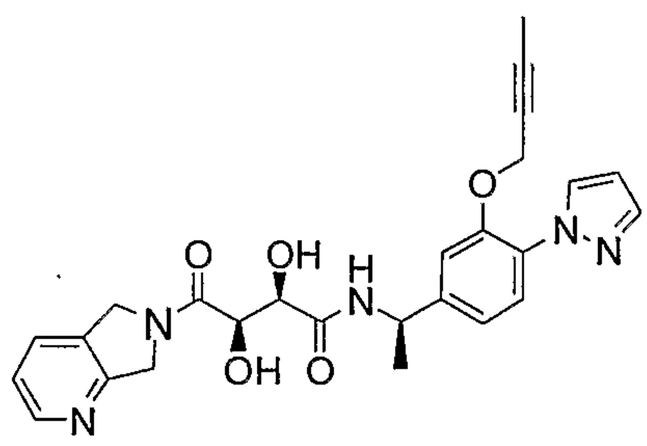


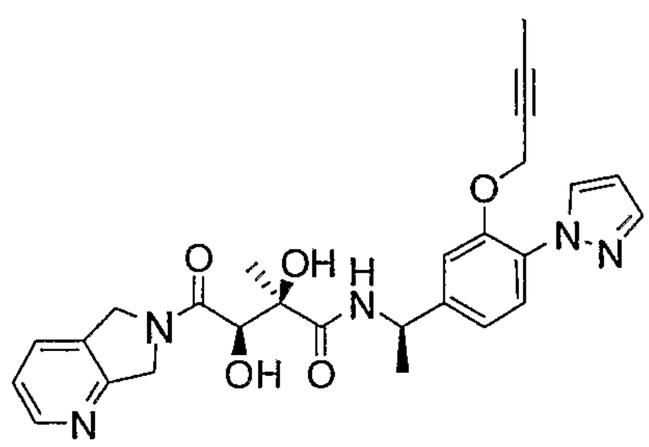


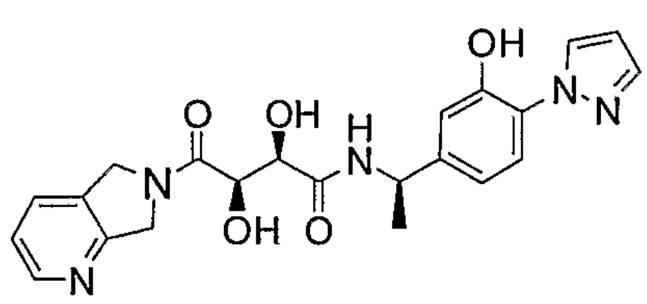


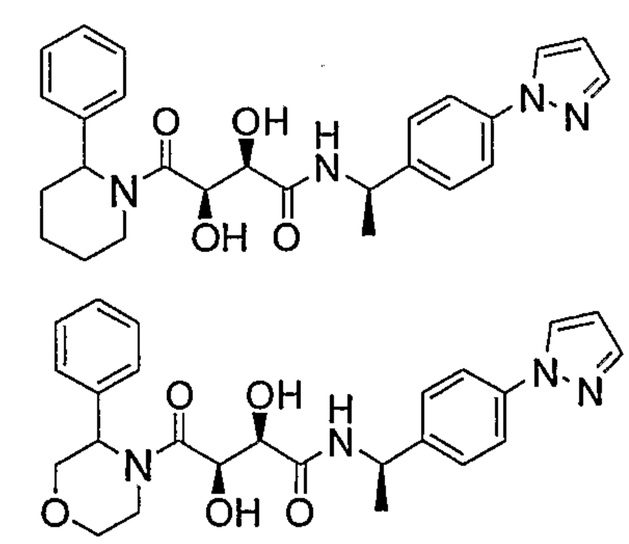


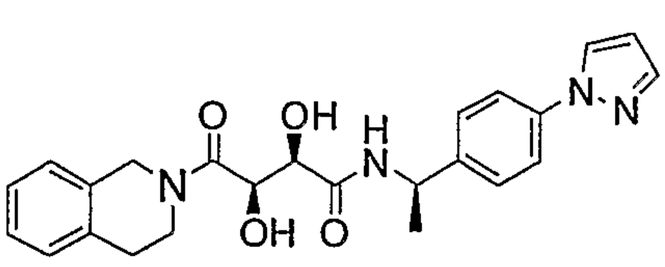


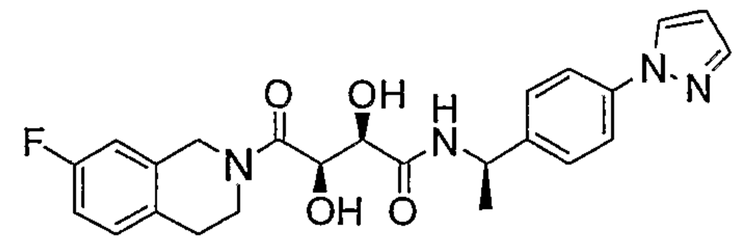


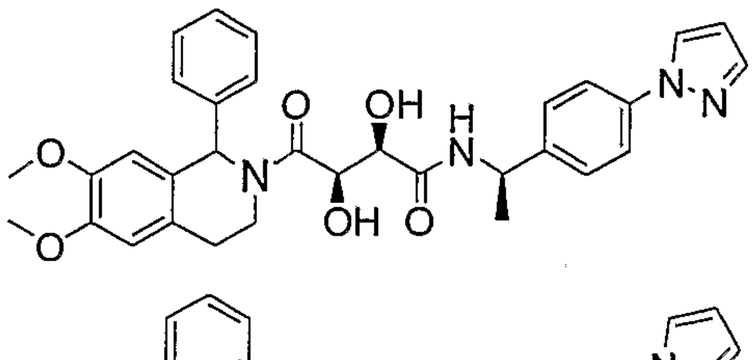


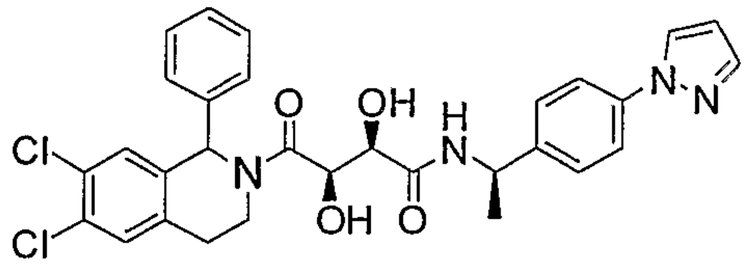


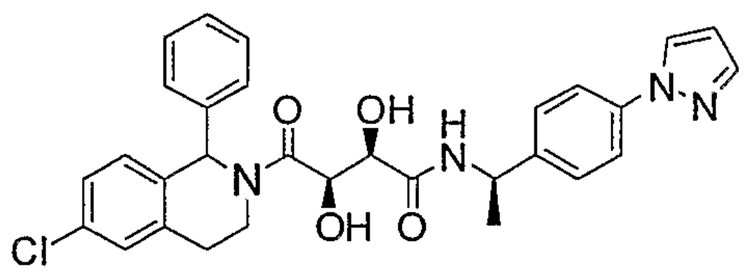


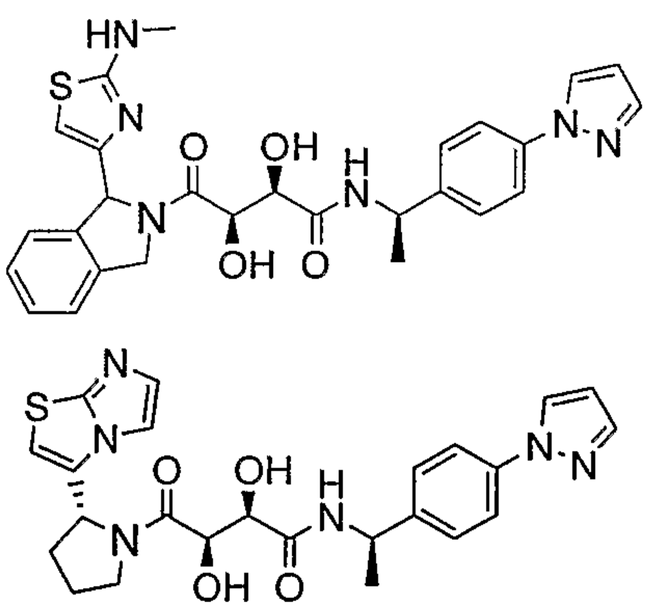


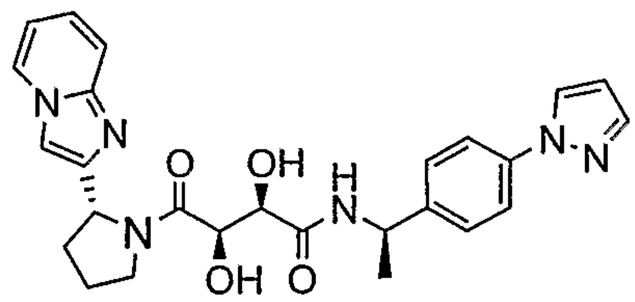


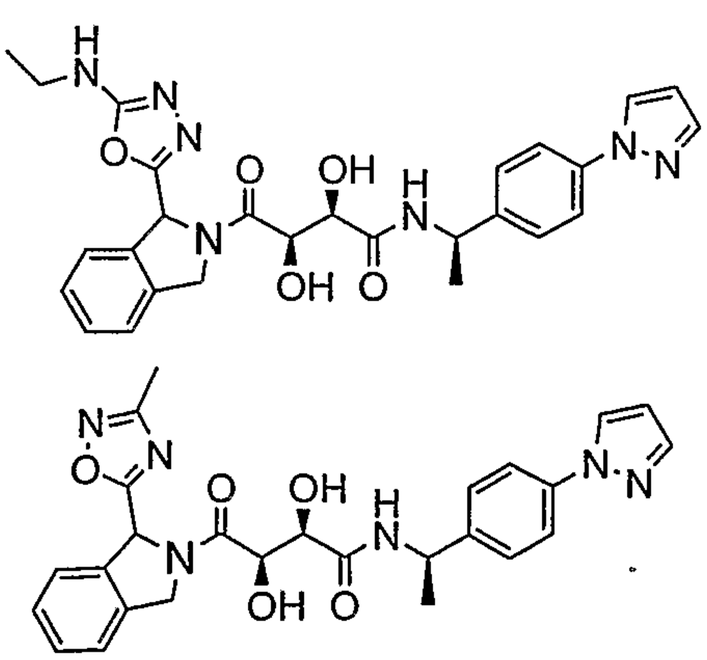


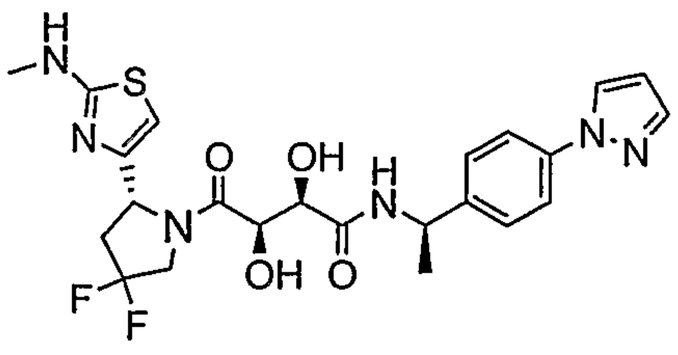


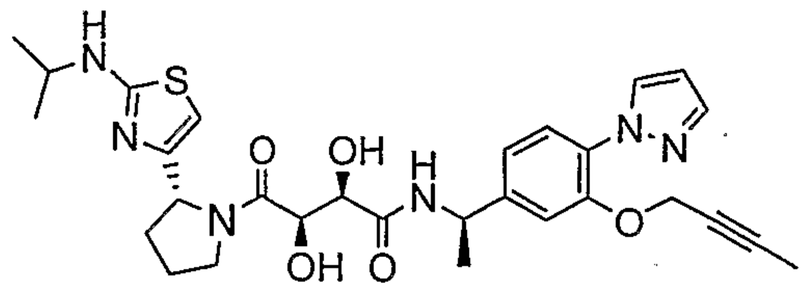


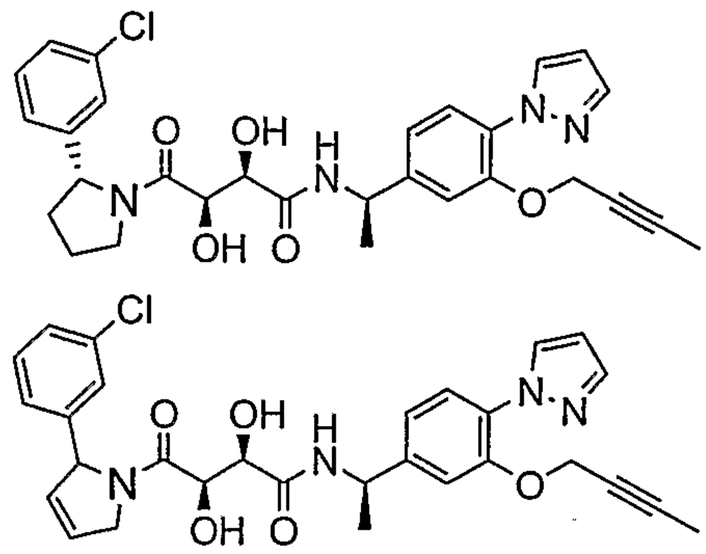


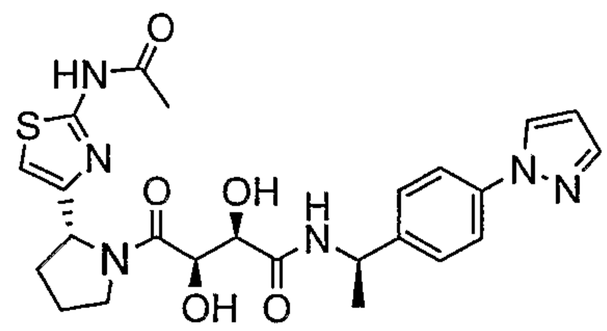


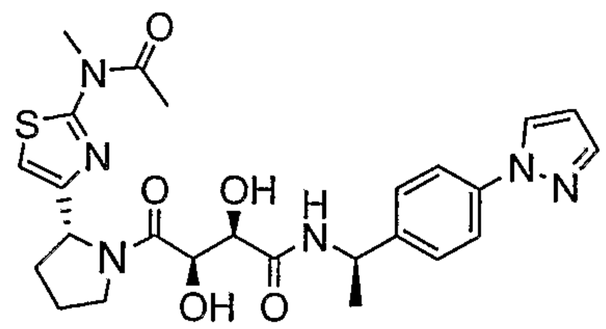


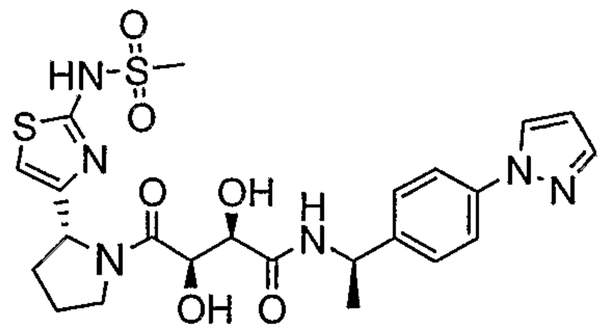


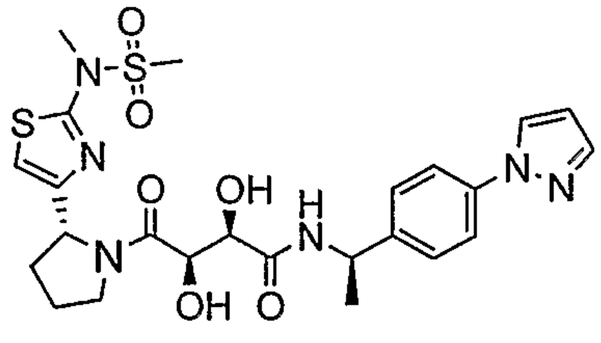


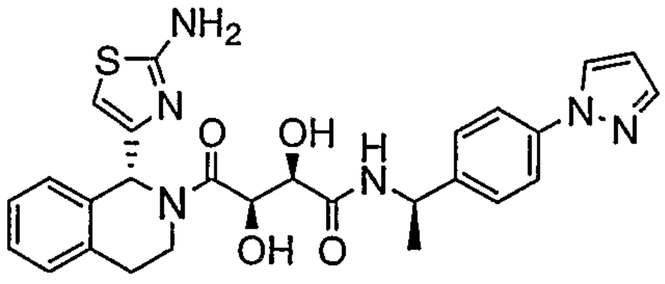


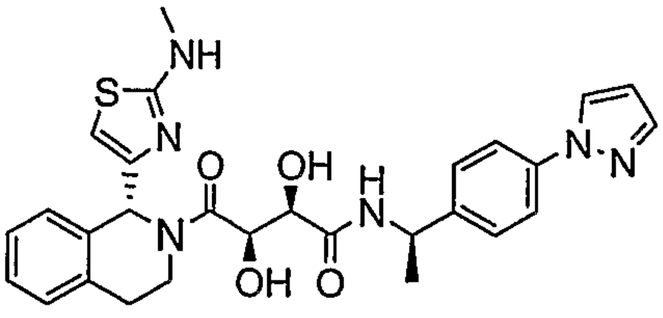


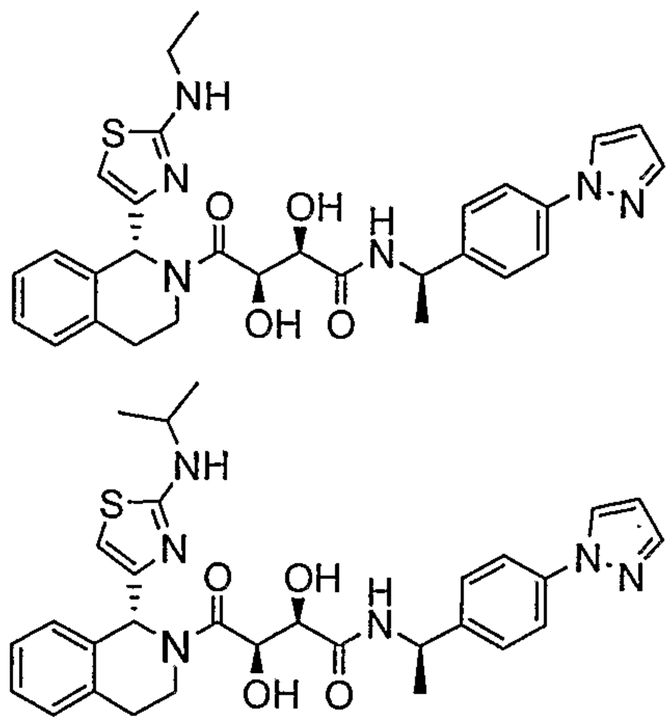


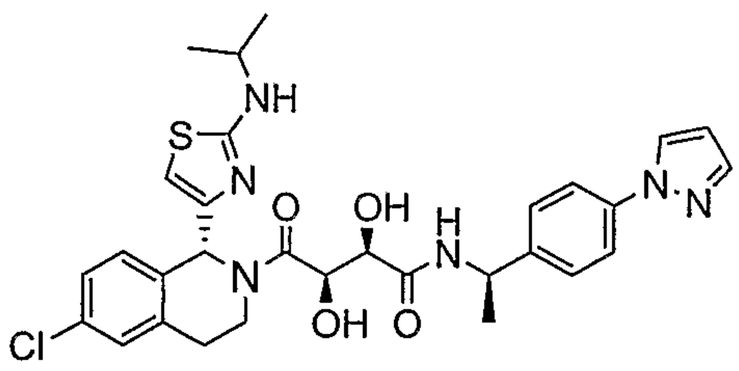


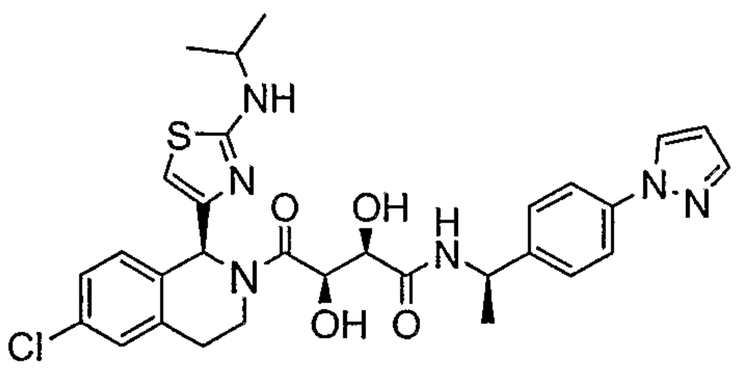


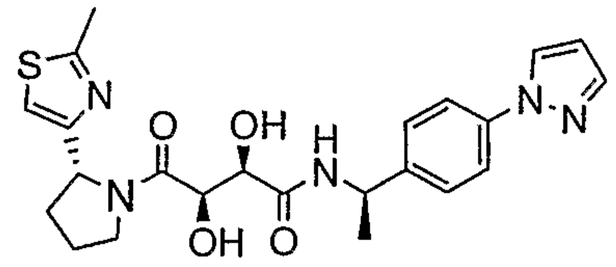


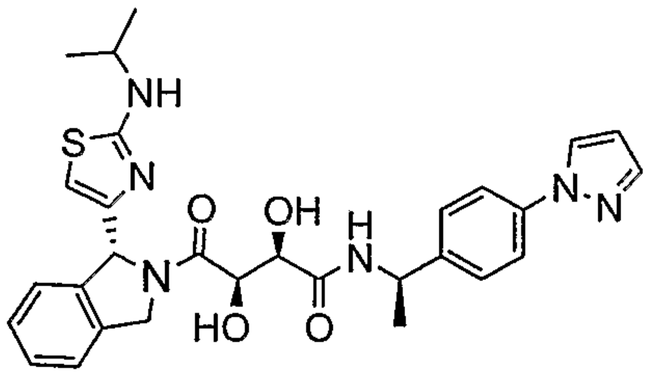


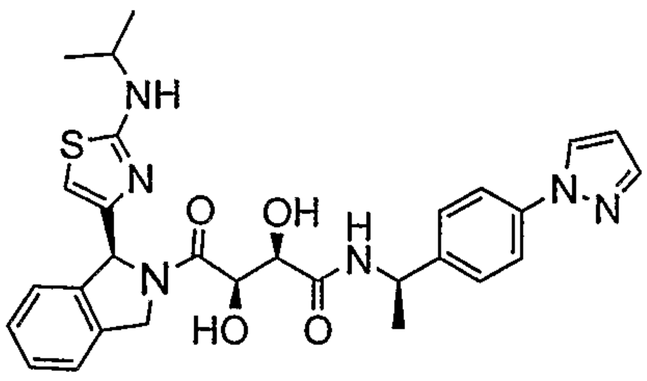


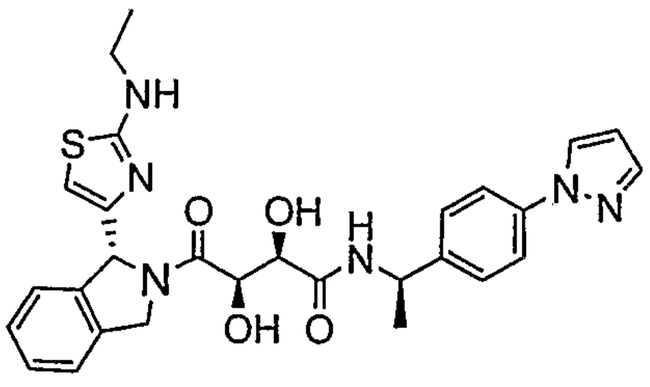


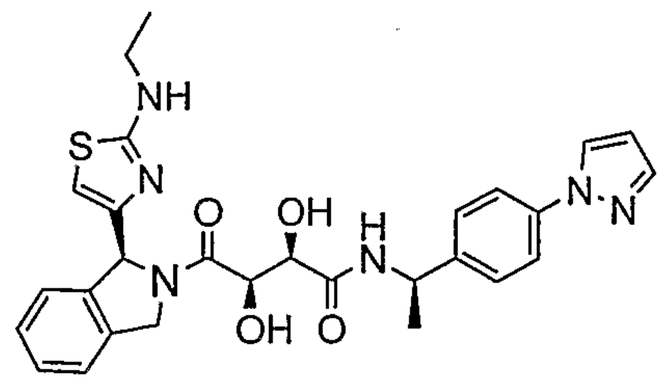


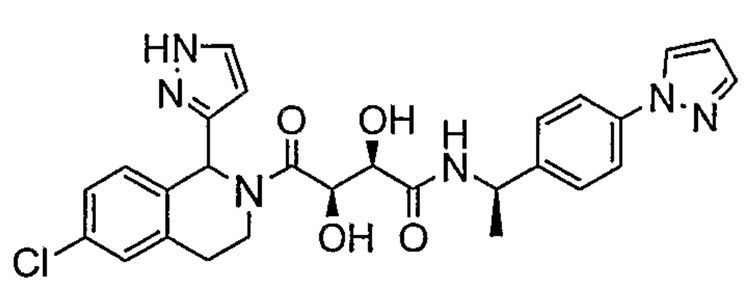


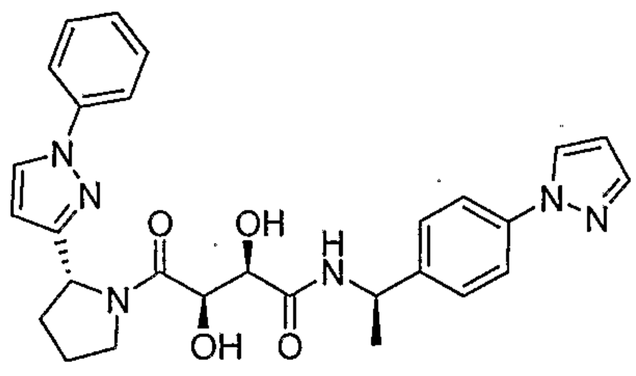


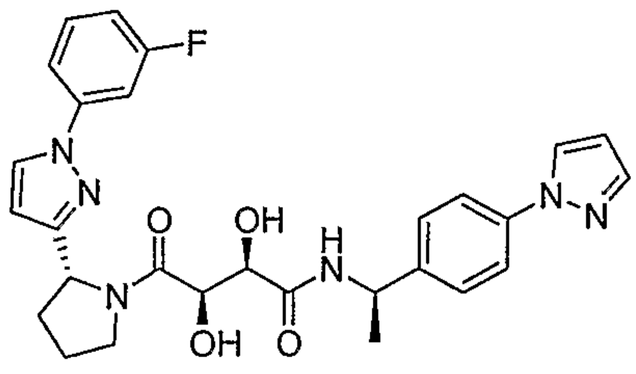


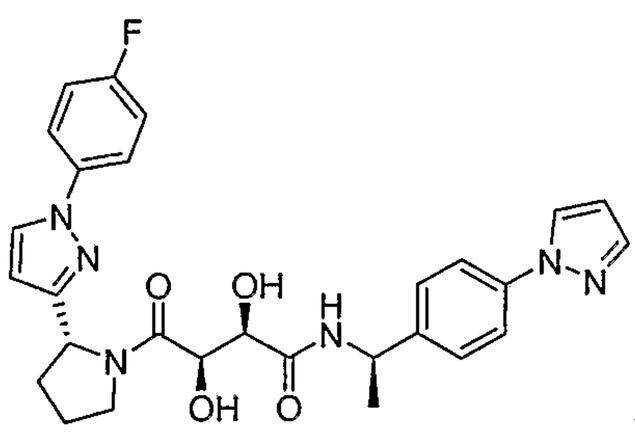




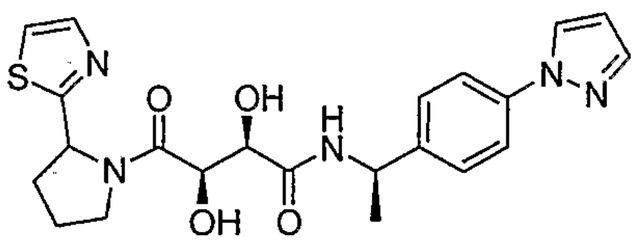




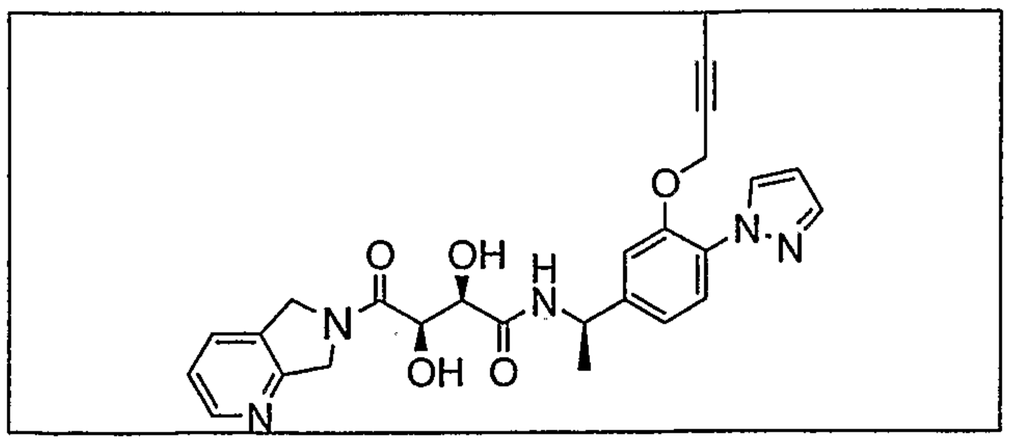


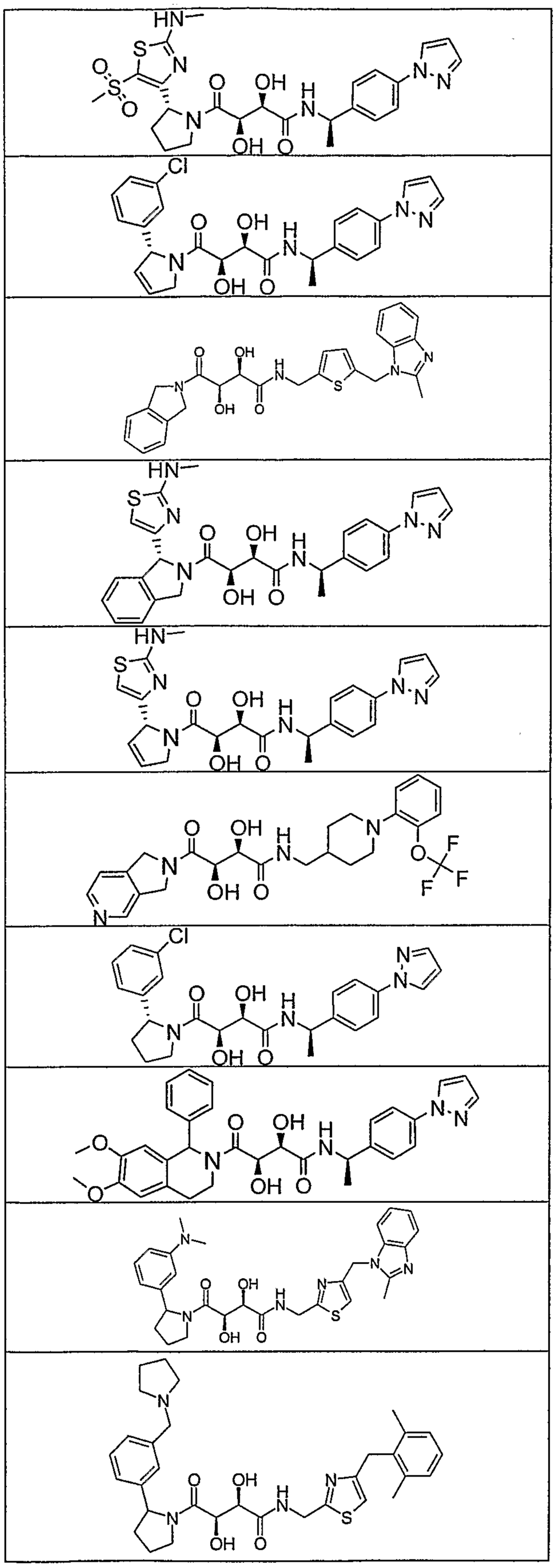


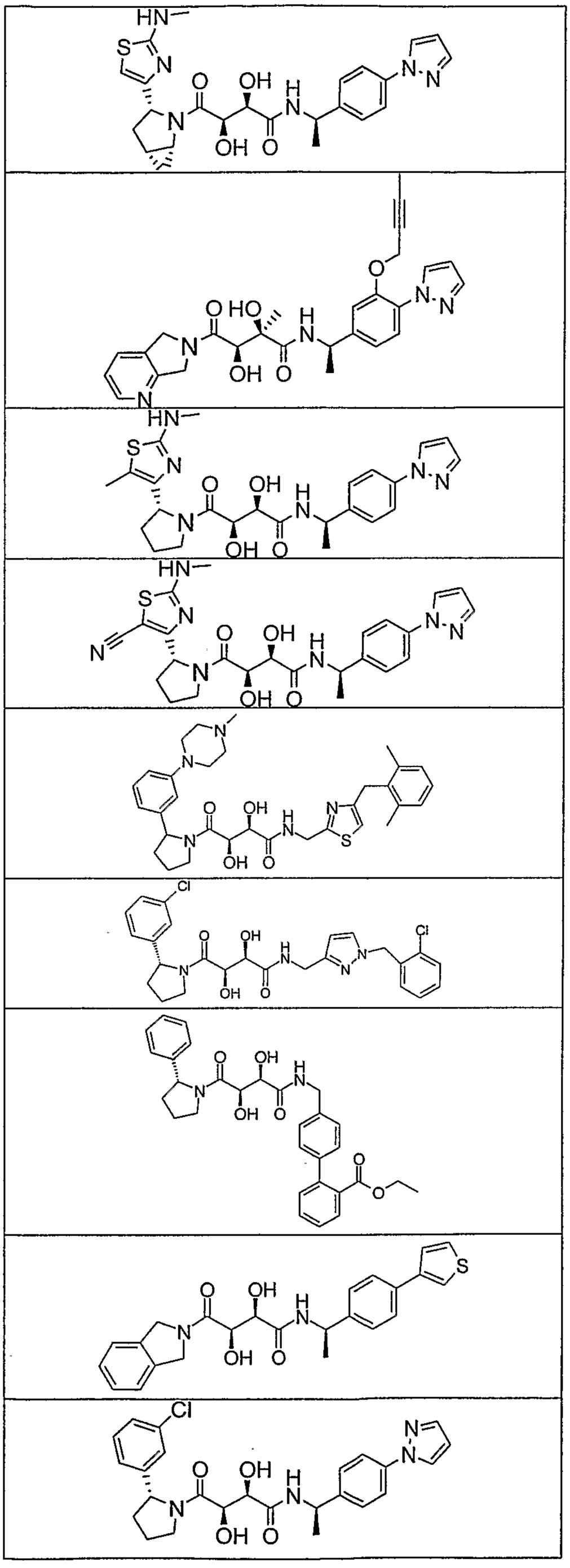
and

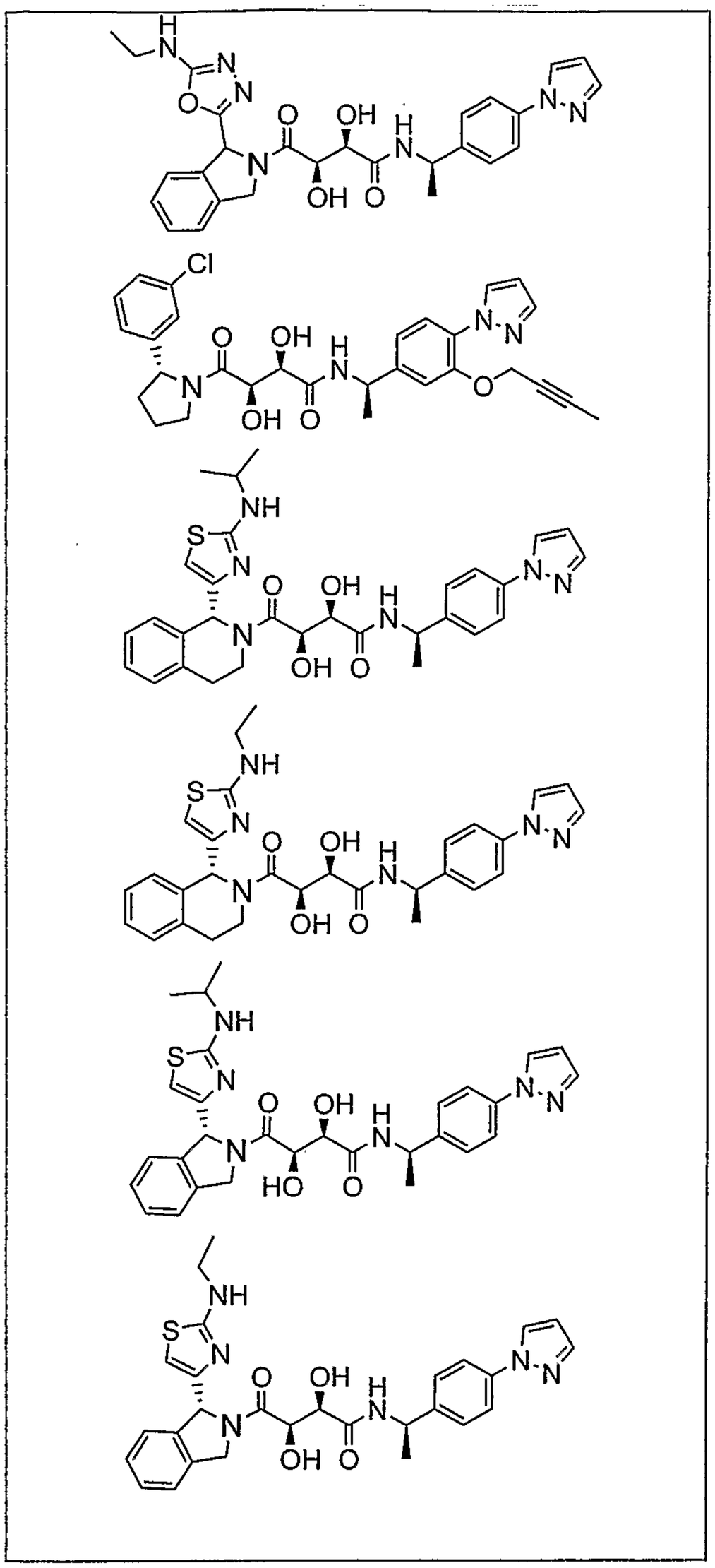


62. The compound of claim 61, said compound being selected from the compounds of structures listed below:









63. A pharmaceutical composition comprising as an active ingredient at least one compound of claim 1.

64. The pharmaceutical composition of claim 1 additionally comprising at least one pharmaceutically acceptable carrier.

65. A method of treating disorders associated with tumor necrosis factor-alpha-converting enzyme (TACE), 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.

66. The use of a compound of claim 1 for the manufacture of a medicament to treat disorders associated with TACE, TNF-α, MMPs, ADAMs or any combination thereof.

67. A method of preparing a pharmaceutical composition for treating the disorders associated with TACE, TNF-α, MMPs, ADAMs or any combination thereof, said method comprising bringing into intimate contact at least one compound of claim 1 and at least one pharmaceutically acceptable carrier.

68. A pharmaceutical composition for treating disorders associated with TACE, 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 isomer thereof.

69. A compound of claim 1 in purified form.

70. A method of treating a condition or disease mediated by TACE, 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 claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

71. The method of claim 70, wherein said aggrecanase is aggrecanase 1 or aggrecanase 2.

72. 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.

73. 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 isomer thereof.

74. 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.

75. 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 isomer thereof.

76. 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 isomer thereof.

77. 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 isomer thereof.

78. 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 isomer thereof.

79. 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 isomer thereof.

80. 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 isomer thereof.

81. 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 isomer thereof.

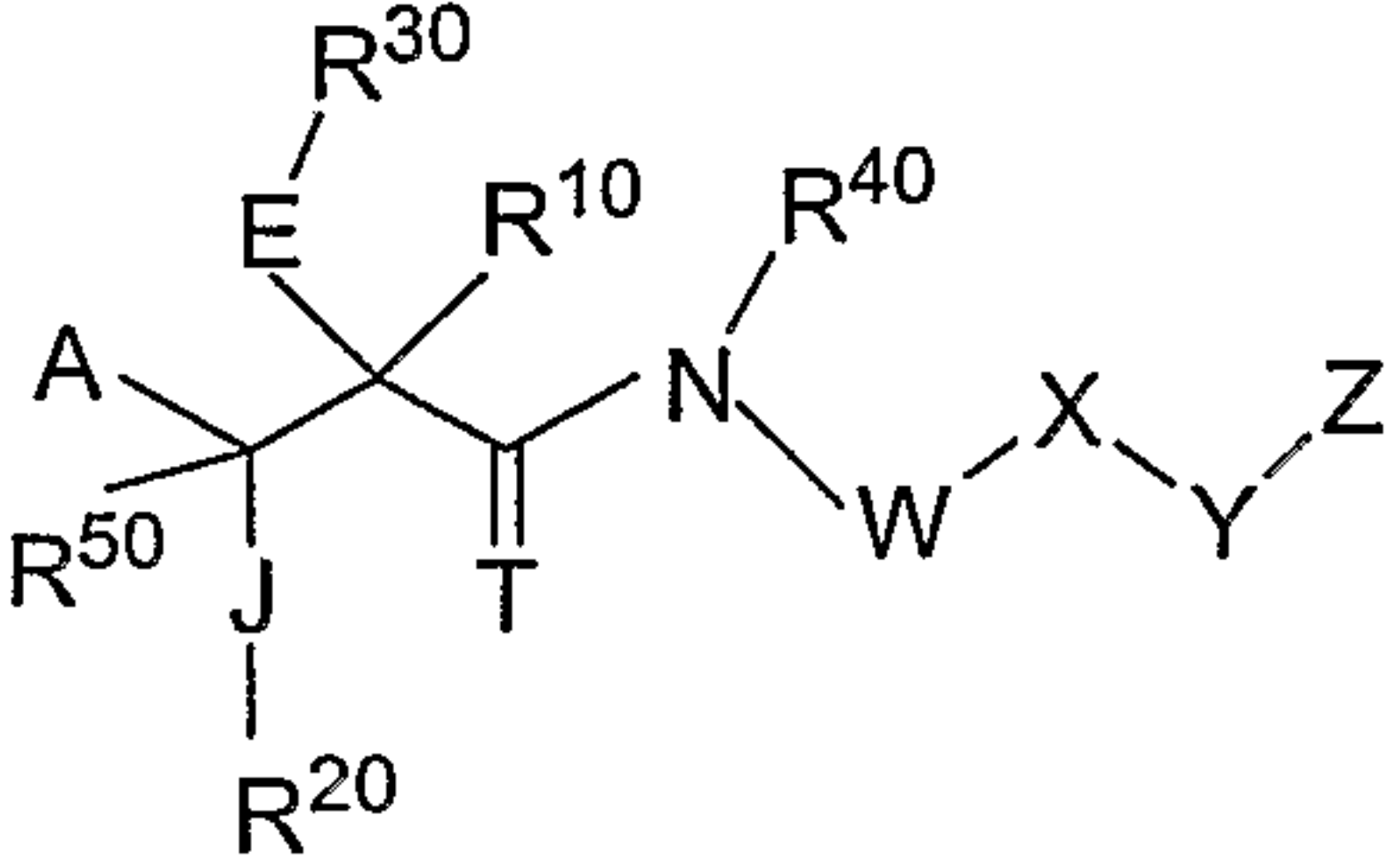
82. A method of treating a condition or disease associated with psoriatic arthritis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

83. 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 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.

84. The method of claim 71 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.

85. A method of claim 73, 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.

86. A method of claim 75, 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.



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