2,3,5-Trisubstituted Thiophene Compounds and Uses Thereof

Field of the Invention

Compounds and compositions, methods for their preparation, and methods for their use in treating viral infections in patients mediated, at least in part, by a virus in the *Flaviviridae* family of viruses are disclosed.

State of the Art

Chronic infection with HCV is a major health problem associated with liver cirrhosis, hepatocellular carcinoma, and liver failure. An estimated 170 million chronic carriers worldwide are at risk of developing liver disease (Szabo, E. *et al.*, *Pathol.Oncol.Res.* 2003, 9:215-221; Hoofnagle J.H., *Hepatology* 1997, 26:15S-20S). In the United States alone 2.7 million are chronically infected with HCV, and the number of HCV-related deaths in 2000 was estimated between 8,000 and 10,000, a number that is expected to increase significantly over the next years. Infection by HCV is insidious in a high proportion of chronically infected (and infectious) carriers who may not experience clinical symptoms for many years. Liver cirrhosis can ultimately lead to liver failure. Liver failure resulting from chronic HCV infection is now recognized as a leading cause of liver transplantation.

HCV is a member of the *Flaviviridae* family of RNA viruses that affect animals and humans. The genome is a single ~9.6-kilobase strand of RNA, and consists of one open reading frame that encodes for a polyprotein of ~3000 amino acids flanked by untranslated regions at both 5' and 3' ends (5'- and 3'-UTR). The polyprotein serves as the precursor to at least 10 separate viral proteins critical for replication and assembly of progeny viral particles. The organization of structural and non-structural proteins in the HCV polyprotein is as follows: C-E1-E2-p7-NS2-NS3-NS4a-NS4b-NS5a-NS5b. Because the replicative cycle of HCV does not involve any DNA intermediate and the virus is not integrated into the host genome, HCV infection can theoretically be cured.

At present, the standard treatment for chronic HCV is pegylated interferon alpha (IFN-alpha) in combination with ribavirin and this requires at least six (6) months of treatment. IFN-alpha belongs to a family of naturally occurring small proteins with characteristic biological effects such as antiviral, immunoregulatory, and antitumoral activities that are produced and secreted by most animal nucleated cells in response to several diseases, in particular viral infections. IFN-alpha is an important regulator of growth and differentiation affecting cellular communication and immunological control. Treatment of HCV with interferon has frequently

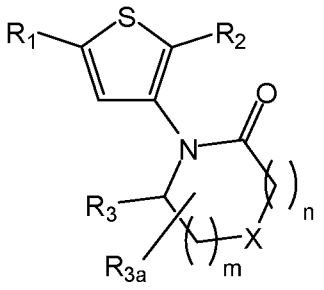
been associated with adverse side effects such as fatigue, fever, chills, headache, myalgias, arthralgias, mild alopecia, psychiatric effects and associated disorders, autoimmune phenomena and associated disorders and thyroid dysfunction. Ribavirin, an inhibitor of inosine 5'-monophosphate dehydrogenase (IMPDH), enhances the efficacy of IFN-alpha in the treatment of HCV. Despite the introduction of ribavirin, more than 50% of the patients do not eliminate the virus with the current standard therapy of interferon-alpha (IFN) and ribavirin. By now, standard therapy of chronic hepatitis C has been changed to the combination of pegylated IFN-alpha plus ribavirin. However, a number of patients still have significant side effects, primarily related to ribavirin. Ribavirin causes significant hemolysis in 10-20% of patients treated at currently recommended doses, and the drug is both teratogenic and embryotoxic. Even with recent improvements, a substantial fraction of patients do not respond with a sustained reduction in viral load and there is a clear need for more effective antiviral therapy of HCV infection (Fried, M.W., *et al. N. Engl. J Med* 2002, 347:975-982).

A number of approaches are being pursued to combat the virus. These include, for example, application of antisense oligonucleotides or ribozymes for inhibiting HCV replication. Furthermore, low-molecular weight compounds that directly inhibit HCV proteins and interfere with viral replication are considered as attractive strategies to control HCV infection. Among the viral targets, the NS3/4a protease and the NS5b RNA-dependent RNA polymerase are considered the most promising viral targets for new drugs (see Ni, Z. J. and Wagman, A. S. *Curr. Opin. Drug Discov. Devel.* 2004, *7*, 446-459; Beaulieu, P. L. and Tsantrizos, Y. S. *Curr. Opin. Investig. Drugs* 2004, *5*, 838-850; and Griffith, R. C. *et al.*, *Ann. Rep. Med. Chem 39*, 223-237, 2004). However, none of these compounds have progressed beyond clinical trials.

In view of the worldwide epidemic level of HCV and other members of the *Flaviviridae* family of viruses, and further in view of the limited treatment options, there is a strong need for new effective drugs for treating infections cause by these viruses.

Summary Of The Invention

In a first embodiment, the invention provides compounds of Formula (I), compositions thereof and methods of using same to treat viral infection. In particular, the compounds of the invention as defined by Formula (I) are useful for the treatment or prevention of hepatitis C virus infection and diseases assocated with or caused by HCV infection. The structure of compounds of Formula (I) is as follows:



(I)

Compounds of Formula (I) includes salts thereof. Definitions for variables present in Formula (I) are defined *infra*.

Unless specified otherwise, the term "compounds of the present invention" refers to compounds of Formula (I) and subformulae thereof (add other additional genus structures as necessary), prodrugs thereof, salts of the compound and/or prodrugs, hydrates or solvates of the compounds, salts and/or prodrugs, as well as all stereoisomers (including diastereoisomers and enantiomers), tautomers and isotopically labeled compounds (including deuterium substitutions), as well as inherently formed moieties (e.g., polymorphs, solvates and/or hydrates).

In one embodiment provided is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Formula (I).

In other embodiments provided are methods for preparing the compounds of Formula (I) and compositions thereof and for their therapeutic uses. In one embodiment provided is a method for treating a viral infection in a patient mediated at least in part by a virus in the *Flaviviridae* family of viruses, comprising administering to said patient a composition comprising a compound or a salt of Formula (I). In some aspects, the viral infection is mediated by hepatitis C virus.

These and other embodiments of the invention are further described in the text that follows.

Detailed Description Of The Invention

Throughout this application, references are made to various embodiments relating to compounds, compositions, and methods. The various embodiments described are meant to provide a variety of illustrative examples and should not be construed as descriptions of alternative species. Rather it should be noted that the descriptions of various embodiments

provided herein may be of overlapping scope. The embodiments discussed herein are merely illustrative and are not meant to limit the scope of the present invention.

For purposes of interpreting this specification, the following definitions will apply and whenever appropriate, terms used in the singular will also include the plural and vice versa.

As used herein, the term “alkyl” refers to a fully saturated branched or unbranched hydrocarbon moiety having up to 20 carbon atoms. Unless otherwise provided, alkyl refers to hydrocarbon moieties having 1 to 16 carbon atoms, 1 to 10 carbon atoms, 1 to 7 carbon atoms, or 1 to 4 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, *n*-hexyl, 3-methylhexyl, 2,2- dimethylpentyl, 2,3-dimethylpentyl, *n*-heptyl, *n*-octyl, *n*-nonyl, *n*-decyl and the like.

As used herein, the term “alkylene” refers to divalent alkyl group as defined herein above having 1 to 20 carbon atoms. It comprises 1 to 20 carbon atoms, Unless otherwise provided, alkylene refers to moieties having 1 to 16 carbon atoms, 1 to 10 carbon atoms, 1 to 7 carbon atoms, or 1 to 4 carbon atoms. Representative examples of alkylene include, but are not limited to, methylene, ethylene, *n*-propylene, *iso*-propylene, *n*-butylene, *sec*-butylene, *iso*-butylene, *tert*-butylene, *n*-pentylene, isopentylene, neopentylene, *n*-hexylene, 3-methylhexylene, 2,2-dimethylpentylene, 2,3-dimethylpentylene, *n*-heptylene, *n*-octylene, *n*-nonylene, *n*-decylene and the like.

As used herein, the term “haloalkyl” refers to an alkyl as defined herein, that is substituted by one or more halo groups as defined herein. The haloalkyl can be monohaloalkyl, dihaloalkyl or polyhaloalkyl including perhaloalkyl. A monohaloalkyl can have one iodo, bromo, chloro or fluoro within the alkyl group. Dihaloalky and polyhaloalkyl groups can have two or more of the same halo atoms or a combination of different halo groups within the alkyl. Typically the polyhaloalkyl contains up to 12, or 10, or 8, or 6, or 4, or 3, or 2 halo groups. Non-limiting examples of haloalkyl include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. A perhaloalkyl refers to an alkyl having all hydrogen atoms replaced with halo atoms.

The term "aryl" refers to an aromatic hydrocarbon group having 6-20 carbon atoms in the ring portion. Typically, aryl is monocyclic, bicyclic or tricyclic aryl having 6-20 carbon atoms.

Furthermore, the term "aryl" as used herein, refers to an aromatic substituent which can be a single aromatic ring, or multiple aromatic rings that are fused together.

Non-limiting examples include phenyl, naphthyl or tetrahydronaphthyl, each of which may optionally be substituted by 1-4 substituents, such as alkyl, trifluoromethyl, cycloalkyl, halogen, hydroxy, alkoxy, acyl, alkyl-C(O)-O-, aryl-O-, heteroaryl-O-, amino, thiol, alkyl-S-, aryl-S-, nitro, cyano, carboxy, alkyl-O-C(O)-, carbamoyl, alkyl-S(O)-, sulfonyl, sulfonamido, phenyl, and heterocyclyl.

As used herein, the term "alkoxy" refers to alkyl-O-, wherein alkyl is defined herein above. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, *tert*-butoxy, pentyloxy, hexyloxy, cyclopropyloxy-, cyclohexyloxy- and the like. Typically, alkoxy groups have about 1-7, more preferably about 1-4 carbons.

As used herein, the term "heterocyclyl" or "heterocyclo" refers to a saturated or unsaturated non-aromatic ring or ring system, *e.g.*, which is a 4-, 5-, 6-, or 7-membered monocyclic, 6-, 7-, 8-, 9-, 10-, 11-, or 12-membered bicyclic or 10-, 11-, 12-, 13-, 14- or 15-membered tricyclic ring system and contains at least one heteroatom selected from O, S and N, where the N and S can also optionally be oxidized to various oxidation states. The heterocyclic group can be attached at a heteroatom or a carbon atom. The heterocyclyl can include fused or bridged rings as well as spirocyclic rings. Examples of heterocycles include tetrahydrofuran (THF), dihydrofuran, 1,4-dioxane, morpholine, 1,4-dithiane, piperazine, piperidine, 1,3-dioxolane, imidazolidine, imidazoline, pyrroline, pyrrolidine, tetrahydropyran, dihydropyran, oxathiolane, dithiolane, 1,3-dioxane, 1,3-dithiane, oxathiane,and thiomorpholine.

The term "heterocyclyl" further refers to heterocyclic groups as defined herein substituted with 1 to 5 substituents independently selected from the groups consisting of the following:

(a) alkyl;
(b) hydroxy (or protected hydroxy);
(c) halo;
(d) oxo, i.e., =O;
(e) amino, alkylamino or dialkylamino;

(f) alkoxy;

(g) cycloalkyl;

(h) carboxyl;

(i) heterocyclooxy, wherein heterocyclooxy denotes a heterocyclic group bonded through an oxygen bridge;

(j) alkyl-O-C(O)-;

(k) mercapto;

(l) amido or carboxamido

(m) cyano;

(n) sulfamoyl, sulfamido or sulfonamido;

(o) aryl;

(p) alkyl-C(O)-O-;

(q) aryl-C(O)-O-;

(r) aryl-S-;

(s) aryloxy;

(t) alkyl-S-;

(u) formyl, i.e., HC(O)-;

(v) carbamoyl;

(w) aryl-alkyl-; and

(x) aryl substituted with alkyl, cycloalkyl, alkoxy, hydroxy, amino, alkyl-C(O)-NH-, alkylamino, dialkylamino or halogen.

(y) alkyl substituted with cycloalkyl, alkoxy, hydroxy, amino, alkyl-C(O)-NH-, alkylamino, dialkylamino or halogen.

As used herein, the term "cycloalkyl" refers to saturated or unsaturated monocyclic, bicyclic or tricyclic hydrocarbon groups of 3-12 carbon atoms. Unless otherwise provided, cycloalkyl refers to cyclic hydrocarbon groups having between 3 and 9 ring carbon atoms or between 3 and 7 ring carbon atoms, each of which can be optionally substituted by one, or two, or three, or more substituents independently selected from the group consisting of alkyl, halo, oxo, hydroxy, alkoxy, alkyl-C(O)-, acylamino, carbamoyl, alkyl-NH-, $(alkyl)_2N$-, thiol, alkyl-S-, nitro, cyano, carboxy, alkyl-O-C(O)-, sulfonyl, sulfonamido, sulfamoyl, sulfamido, and heterocyclyl. Exemplary monocyclic hydrocarbon groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl and cyclohexenyl and the like. Exemplary bicyclic hydrocarbon groups include bornyl, indyl, hexahydroindyl,

tetrahydronaphthyl, decahydronaphthyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.1]heptenyl, 6,6-dimethylbicyclo[3.1.1]heptyl, 2,6,6-trimethylbicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl and the like. Exemplary tricyclic hydrocarbon groups include adamantyl and the like.

As used herein, the term “aryloxy” refers to both an --O-aryl and an --O-heteroaryl group, wherein aryl and heteroaryl are defined herein.

As used herein, the term "heteroaryl" refers to a 5-14 membered monocyclic- or bicyclic- or tricyclic-aromatic ring system, having 1 to 8 heteroatoms selected from N, O or S. Typically, the heteroaryl is a 5-10 membered ring system (e.g., 5-7 membered monocycle or an 8-10 memberred bicycle) or a 5-7 membered ring system. Typical heteroaryl groups include 2- or 3-thienyl, 2- or 3-furyl, 2- or 3-pyrrolyl, 2-, 4-, or 5-imidazolyl, 3-, 4-, or 5- pyrazolyl, 2-, 4-, or 5-thiazolyl, 3-, 4-, or 5-isothiazolyl, 2-, 4-, or 5-oxazolyl, 3-, 4-, or 5-isoxazolyl, 3- or 5-1,2,4-triazolyl, 4- or 5-1,2, 3-triazolyl, tetrazolyl, 2-, 3-, or 4-pyridyl, 3- or 4-pyridazinyl, 3-, 4-, or 5-pyrazinyl, 2-pyrazinyl, and 2-, 4-, or 5-pyrimidinyl.

The term “heteroaryl” also refers to a group in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring. Nonlimiting examples include 1-, 2-, 3-, 5-, 6-, 7-, or 8- indolizinyl, 1-, 3-, 4-, 5-, 6-, or 7-isoindolyl, 2-, 3-, 4-, 5-, 6-, or 7-indolyl, 2-, 3-, 4-, 5-, 6-, or 7-indazolyl, 2-, 4-, 5-, 6-, 7-, or 8- purinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8-, or 9-quinolizinyl, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinoliyl, 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinoliyl, 1-, 4-, 5-, 6-, 7-, or 8-phthalazinyl, 2-, 3-, 4-, 5-, or 6-naphthyridinyl, 2-, 3- , 5-, 6-, 7-, or 8-quinazolinyl, 3-, 4-, 5-, 6-, 7-, or 8-cinnolinyl, 2-, 4-, 6-, or 7-pteridinyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, or 8-4aH carbazolyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, or 8-carbzaolyl, 1-, 3-, 4-, 5-, 6-, 7-, 8-, or 9-carbolinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, or 10-phenanthridinyl, 1- , 2-, 3-, 4-, 5-, 6-, 7-, 8-, or 9-acridinyl, 1-, 2-, 4-, 5-, 6-, 7-, 8-, or 9-perimidinyl, 2-, 3-, 4-, 5-, 6-, 8-, 9-, or 10-phenathrolinyl, 1-, 2- , 3-, 4-, 6-, 7-, 8-, or 9-phenazinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, or 10-phenothiazinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, or 10-phenoxazinyl, 2-, 3-, 4-, 5-, 6-, or l-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, or 10- benzisoqinolinyl, 2-, 3-, 4-, or thieno[2,3-b]furanyl, 2-, 3-, 5-, 6-, 7-, 8-, 9-, 10 -, or 11-7H-pyrazino[2,3-c]carbazolyl,2-, 3-, 5-, 6-, or 7-2H- furo[3,2-b]-pyranyl, 2-, 3-, 4-, 5-, 7-, or 8-5H-pyrido[2,3-d]-o-oxazinyl, 1-, 3-, or 5-1H-pyrazolo[4,3-d]-oxazolyl, 2-, 4-, or 54H-imidazo[4,5-d] thiazolyl, 3-, 5-, or 8-pyrazino[2,3-d]pyridazinyl, 2-, 3-, 5-, or 6- imidazo[2,1-b] thiazolyl, 1-, 3-, 6-, 7-, 8-, or 9-furo[3,4-c]cinnolinyl, 1-, 2-, 3-, 4-, 5-, 6-, 8-, 9-, 10, or 11-4H-pyrido[2,3-c]carbazolyl, 2-, 3-, 6-, or 7-imidazo[1,2-b][1,2,4]triazinyl, 7-benzo[b]thienyl, 2-, 4-, 5- ,

6-, or 7-benzoxazolyl, 2-, 4-, 5-, 6-, or 7-benzimidazolyl, 2-, 4-, 4-, 5-, 6-, or 7-benzothiazolyl, 1-, 2-, 4-, 5-, 6-, 7-, 8-, or 9- benzoxapinyl, 2-, 4-, 5-, 6-, 7-, or 8-benzoxazinyl, 1-, 2-, 3-, 5-, 6-, 7-, 8-, 9-, 10-, or 11-1H-pyrrolo[1,2-b][2]benzazapinyl. Typical fused heteroary groups include, but are not limited to 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl, 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolinyl, 2-, 3-, 4-, 5-, 6-, or 7-indolyl, 2-, 3-, 4-, 5-, 6-, or 7-benzo[b]thienyl, 2-, 4-, 5- , 6-, or 7-benzoxazolyl, 2-, 4-, 5-, 6-, or 7-benzimidazolyl, and 2-, 4-, 5-, 6-, or 7-benzothiazolyl.

A heteroaryl group may be substituted with 1 to 5 substituents independently selected from the groups consisting of the following:

(a) alkyl;

(b) hydroxy (or protected hydroxy);

(c) halo;

(d) oxo, i.e., =O;

(e) amino, alkylamino or dialkylamino;

(f) alkoxy;

(g) cycloalkyl;

(h) carboxyl;

(i) heterocyclooxy, wherein heterocyclooxy denotes a heterocyclic group bonded through an oxygen bridge;

(j) alkyl-O-C(O)-;

(k) mercapto;

(l) amido or carboxamido

(m) cyano;

(n) sulfamoyl, sulfamido or sulfonamido;

(o) aryl;

(p) alkyl-C(O)-O-;

(q) aryl-C(O)-O-;

(r) aryl-S-;

(s) aryloxy;

(t) alkyl-S-;

(u) formyl, i.e., HC(O)-;

(v) carbamoyl;

(w) aryl-alkyl-; and

(x) aryl substituted with alkyl, cycloalkyl, alkoxy, hydroxy, amino, alkyl-C(O)-NH-, alkylamino, dialkylamino or halogen.

(y) alkyl substituted with cycloalkyl, alkoxy, hydroxy, amino, alkyl-C(O)-NH-, alkylamino, dialkylamino or halogen.

As used herein, the term “halogen” or “halo” refers to fluoro, chloro, bromo, and iodo.

As used herein, the term “optionally substituted” unless otherwise specified refers to a group that is unsubstituted or is substituted by one or more, typically 1, 2, 3 or 4, suitable non-hydrogen substituents, each of which is independently selected from the group consisting of:

(a) alkyl;
(b) hydroxy (or protected hydroxy);
(c) halo;
(d) oxo, i.e., =O;
(e) amino, alkylamino or dialkylamino;
(f) alkoxy;
(g) cycloalkyl;
(h) carboxyl;
(i) heterocyclooxy, wherein heterocyclooxy denotes a heterocyclic group bonded through an oxygen bridge;
(j) alkyl-O-C(O)-;
(k) mercapto;
(l) amido or carboxamido
(m) cyano;
(n) sulfamoyl, sulfamido or sulfonamido;
(o) aryl;
(p) alkyl-C(O)-O-;
(q) aryl-C(O)-O-;
(r) aryl-S-;
(s) aryloxy;
(t) alkyl-S-;
(u) formyl, i.e., HC(O)-;
(v) carbamoyl;

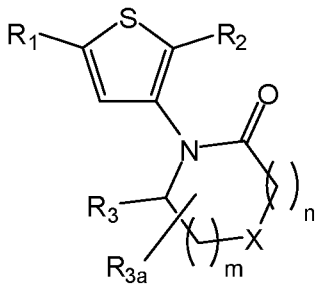
(w) aryl-alkyl-; and

(x) aryl substituted with alkyl, cycloalkyl, alkoxy, hydroxy, amino, alkyl-C(O)-NH-, alkylamino, dialkylamino or halogen.

(y) alkyl substituted with cycloalkyl, alkoxy, hydroxy, amino, alkyl-C(O)-NH-, alkylamino, dialkylamino or halogen.

In one aspect, compounds of Formula (I) are provided:

1. A compound of formula (I):



(I)

or a salt thereof, wherein

m is 0, 1 or 2;

n is 0 or 1, wherein m + n is 1, 2 or 3;

R_1 is C_3-C_{10}alkynyl or phenyl, which phenyl is substituted with 0, 1, 2, or 3 substituents which are independently selected from the group consisting of halogen, hydroxy, cyano, C_1-C_4alkyl, haloC_1-C_4alkyl and C_1-C_4alkoxy, and which alkynyl is optionally substituted with a C_3-C_7cycloalkyl substituent, which cycloalkyl is optionlly substituted with 1 or 2 independently selected C_1-C_4alkyl groups;

R_2 is CO_2H, tetrazole, $C(O)N(H)S(O)_2CH_3$ or a carboxylic acid isostere;

R_3 is C_3-C_7cycloalkyl which is substituted with 0, 1, 2 or 3 halogen atoms;

R_{3a} represents 0, 1, 2, 3 or 4 residues independently selected at each occurrence from the group consisting of hydroxy, amino, cyano, halogen, C_1-C_6alkyl, C_1-C_6alkoxy, wherein each alkyl or alkoxy substituent is substituted with 0,1 or 2 substituents independently selected from hydroxy, cyano, C_1-C_4alkoxy, C_1-C_4alkylsulfone, $N(R_{3b})_2$, $C(O)$ $N(R_{3b})$, heterocycle having 4 to 7 ring atoms and 1 or 2 ring heteroatoms selected from N, O or S and 5 or 6 member heteroaryl; or two geminal R_{3a} substituents, taken in combination form a spirocyclic 3 to 6 member cycloalkyl or heterocycle;

R_{3b} is independently selected at each occurrence from hydrogen, C_1-C_4alkyl, C_1-C_4alkoxyC_1-C_4alkyl and C_1-C_4alkanoyl ; or $N(R_{3b})_2$, taken in combination, form a 4 to 6 member heterocycle having 0 or 1 additional ring heteroatoms selected from N, O or S;

X is O, N-L-R_4 or CR_5R_6;

L is a bond, $S(O)_2$, C(O) or C(O)O;

R_4 is C_1-C_6alkyl, C_3-C_7cycloalkyl or C_3-C_7cycloalkylC_1-C_4alkyl each of which is substituted with 0, 1, or 2 hydroxy and 0 or 1 substituents selected from cyano, $S(O)_2$-C_1-C_4alkyl, CO_2H, $NR_{4a}R_{4b}$, phenyl or pyridyl, wherein the phenyl or pyridyl substituent is substituted with 0, 1, or 2 substituents selected from C_1-C_4alkyl, halogen, $NR_{4a}R_{4b}$ or 5 or 6 member heteroaryl having 1 or 2 ring nitrogen atoms ;

R_4 is naphthyl or phenyl, which phenyl is substituted with 0, 1, 2, or 3 substituents independently selected form the group consisting of halogen, cyano, C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxy, haloC_1-C_6alkoxy, hydroxy, , hydroxyC_1-C_4alkyl, aminoC_1-C_4alkyl, C_1-C_6alkyl-OC(O)NH-, C_1-C_4alkyl-C(O)NH-, $NR_{4a}R_{4b}$. CO_2H, -C(O)$NR_{4a}R_{4b}$, phenyl, phenoxy, heteroaryl having one or two ring nitrogen atoms and having 0, 1, or 2 C_1-C_4alkyl substituents, or two substituents combine to form a fused heterocyclic or heteroary ring, which fused heterocycle has 5, 6 or 7 ring atoms, has 1 or 2 ring heteroatoms selected from N, O or S, and which fused heterocycle is substituted with 0, 1 or 2 substituents independently selected from C_1-C_6alkyl or oxo and which fused heteroaryl has 5 or 6 ring atoms, has 1 or 2 ring heteroatoms selected from N, O or S and which fused heteroaryl is substituted with 0, 1, or 2 independently selected C_1-C_4alkyl substituents; or

R_4 is a 5 or 6 member heteroaryl having 1 to 3 heteroatoms selected from N, O or S, which heteroaryl is substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxy, haloC_1-C_6alkoxy, hydroxy, $NR_{4a}R_{4b}$, hydroxyC_1-C_4alkyl, aminoC_1-C_4alkyl, C_1-C_6alkyl-OC(O)NH-, CO_2H, C_3-C_7cycloalkyl, C_5-C_7cycloalkenyl, phenyl, 5 or 6 membered heteroaryl having 1 or 2 ring heteroatoms selected from N, O or S, saturated or partially unsaturated monocyclic or bicyclic heterocycle or two substituents, taken in combiantion form a saturated heterocyclic ring having 5 or 6 ring atoms, 1 or 2 ring heteroatoms selected from N, O or S and wherein the fused heterocyle is substituted with 0, 1, or 2 independently selected C_1-C_4alkyl substituents; and wherein the monocyclic or bicyclic heterocycle has 1 or 2 ring N, O or S atoms, 5 to 7 ring atoms in each ring and is substituted with 0, 1 or 2 substituents independently selected from the group consisting of halogen, C_1-C_6alkyl, C_1-C_6alkanoyl, C_1-C_6alkoxycarbonyl, C_1-C_6alkoxyC(O)N(H)-, C_1-C_6alkoxyC(O)N(H)CH_2-, aminoC_1-C_4alkyl, C_1-C_4alkoxyC_1-C_4alkyl and

$NR_{4a}R_{4b}$, and wherein the phenyl or heteroaryl substituent is substituted with 0, 1 or 2 independently selected substituents selected from halogen, CO_2H, cyano, C_1-C_4alkyl, C_1-C_4alkoxy, $NR_{4a}R_{4b}$, $CH_2NR_{4a}R_{4b}$, $C(O)NR_{4a}R_{4b}$, or two phenyl substituents combine to form a divalent $–O-(CH_2)_q-O–$ substituent in which q is 1, 2, or 3; or

R_4 is a saturated heterocycle 1 ring nitrogen and 0 or 1 additional ring heteroatom selected from N, O or S, which heterocyclic ring is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_1-C_6alkyl, CO_2C_1-C_6alkyl or CO_2benzyl;

R_{4a} is independently selected at each occurrence from the group consisting of hydrogen and C_1-C_6alkyl, wherein the alkyl substituent is unsubstituted or substituted with hydroxy, C_1-C_4alkoxy, amino or mono- and di-C_1-C_4alkylamino;

R_{4b} is independently selected at each occurrence from the group consisting of hydrogen, C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_4alkanoyl, and heterocycle having 4 to 7 ring atoms and 1 or 2 ring heteroatoms indpendently selected at each occurrence from N, O or S, wherein the alkyl substituent is unsubstituted or substituted with hydroxy, C_1-C_4alkoxy, amino or mono- and di-C_1-C_4alkylamino; or

$NR_{4a}R_{4b}$, taken in combination, form a heterocyclic ring having one ring nitrogen atom and 0 or 1 additional ring heteroatom selected from N, O and S, which heterocyclic ring is substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of halogen, hydroxy, oxo, amino, C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, aminoC_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4alkanoyl, C_1-C_4alkoxyC_1-C_4alkyl, and mono- and di- C_1-C_4alkylamino;

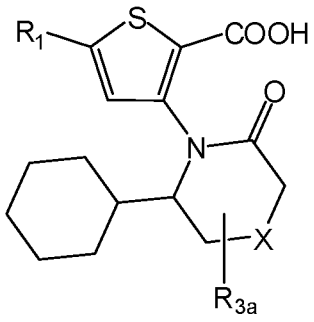
R_5 is absent or is selected from the group consisting of hydrogen and C_1-C_6alkyl;

R_6 is oxo, hydrogen, hydroxy, amino, N(H)-J-R_7;

J is absent, C(O) or $S(O)_2$; and

R_7 is C_1-C_6alkyl, phenyl or benzyl, each of is optionally substituted with C_1-C_6alkyl, C_1-C_6alkoxy, halogen, phenyl or phenoxy.

Certain compounds of formula (I) provided by the invention include compounds of formula (Ia) and salts thereof:



(Ia)

wherein

R_1 is C_3-C_8alkynyl or phenyl, which phenyl is substituted with 0, 1, 2, or 3 substituents which are independently selected from the group consisting of halogen, hydroxy, cyano, C_1-C_4alkyl and C_1-C_4alkoxy, and which alkynyl is optionally substituted with a C_3-C_7cycloalkyl substituent, which cycloalkyl is optionlly substituted with 1 or 2 independently selected C_1-C_4alkyl groups;

R_{3a} represents 0, 1, 2, 3 or 4 residues independently selected at each occurrence from the group consisting of hydroxy, amino, C_1-C_6alkyl, C_1-C_6alkoxy, wherein each alkyl or alkoxy substituent is substituted with 0,1 or 2 substituents independently selected from hydroxy, C_1-C_4alkoxy, C_1-C_4alkylsulfoxide and $N(R_{3b})$; or two geminal R_{3a} substituents, taken in combination form a spirocyclic 3 to 6 member cycloalkyl or heterocycle;

R_{3b} is independently selected at each occurrence from hydrogen, C_1-C_4alkyl, C_1-C_4alkoxyC_1-C_4alkyl, or $N(R_{3b})_2$, taken in combination, form a 4 to 6 member heterocycle having 0 or 1 additional ring heteroatoms selected from N, O or S;

X is O, N-L-R_4 or CR_5R_6;

L is a bond, $S(O)_2$ or C(O);

R_4 is C_1-C_6alkyl or C_3-C_7cycloalkyl each of which is substituted with 0 or 1 substituents selected from CO_2H or $NR_{4a}R_{4b}$ or C1-C4 alkylphenyl,or

R_4 is naphthyl or phenyl, which phenyl is substituted with 0, 1, 2, or 3 substituents independently selected form the group consisting of halogen, cyano, C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxy, haloC_1-C_6alkoxy, amino, hydroxy, mono- and di-C_1-C_6alkylamino, hydroxyC_1-C_4alkyl, aminoC_1-C_4alkyl, C_1-C_6alkyl-OC(O)NH-, C1-C4alkyl-C(O)NH-, -$C(O)NR_{4a}R_{4b}$, phenyl, phenoxy, heteroaryl having one or two ring nitrogen atoms and having 0, 1, or 2 C_1-C_4alkyl substituents, or two substituents combine to form a fused heterocyclic ring, which heterocycle has 5, 6 or 7 ring atoms, 1 or 2 ring heteroatoms selected from N, O or S and which heterocycle is substituted with 0, 1 or 2 substituents independently selected from C_1-C_6alkyl; or

R_4 is a 5 or 6 member heteroaryl having 1 to 3 heteroatoms selected from N, O or S, which heteroaryl is substituted with 0, 1, or 2 substituents independently selected from the

group consisting of halogen, cyano, C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxy, haloC_1-C_6alkoxy, hydroxy, $NR_{4a}R_{4b}$, hydroxyC_1-C_4alkyl, aminoC_1-C_4alkyl, C_1-C_6alkyl-OC(O)NH-, C_3-C_7cycloalkyl, C_5-C_7cycloalkenyl, phenyl, thienyl optionally substituted with CO_2H, or saturated or partially unsaturated monocyclic or bicyclic heterocycle which heterocycle has 1 or 2 ring N, O or S atoms, 5 to 7 ring atoms in each ring and is substituted with 0, 1 or 2 substituents independently selected from the group consisting of C_1-C_6alkyl, C_1-C_6alkanoyl, -N(H)C(O)C_1-C_6alkoxy, -CH_2N(H)C(O)C_1-C_6alkoxy, aminoC_1-C_4alkyl, C_1-C_4alkoxyC_1-C_4alkyl and $NR_{4a}R_{4b}$, or two substituents on the heteroaryl ring combine to form a fused heterocyclic ring, which heterocycle has 5, 6 or 7 ring atoms, 1 or 2 ring heteroatoms selected from N, O or S and which heterocycle is substituted with 0, 1 or 2 substituents independently selected from C_1-C_6alky, and wherein the phenyl substituent is unsubstituted or substituted with halogen, C_1-C_4alkyl, or C(O)$NR_{4a}R_{4b}$; or

R_4 is a saturated heterocycle 1 ring nitrogen and 1 or 1 additional ring heteroatom selected from N, O or S, which heterocyclic ring is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_1-C_6alkyl, CO_2C_1-C_6alkyl or CO_2benzyl;

R_{4a} is independently selected at each occurrence from the group consisting of hydrogen and C_1-C_6alkyl, wherein the alkyl substituent is unsubstituted or substituted with hydroxy, C_1-C_4alkoxy, amino or mono- and di-C_1-C_4alkylamino;

R_{4b} is independently selected at each occurrence from the group consisting of hydrogen, C_1-C_6alkyl and C_1-C_4alkanoyl, wherein the alkyl substituent is unsubstituted or substituted with hydroxy, C_1-C_4alkoxy, amino or mono- and di-C_1-C_4alkylamino; or

$NR_{4a}R_{4b}$, taken in combination, form a heterocyclic ring having one ring nitrogen atom and 0 or 1 additional ring heteroatom selected from N, O and S, which heterocyclic ring is substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of halogen, hydroxy, amino, C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, aminoC_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4alkoxyC_1-C_4alkyl, and mono- and di- C_1-C_4alkylamino;

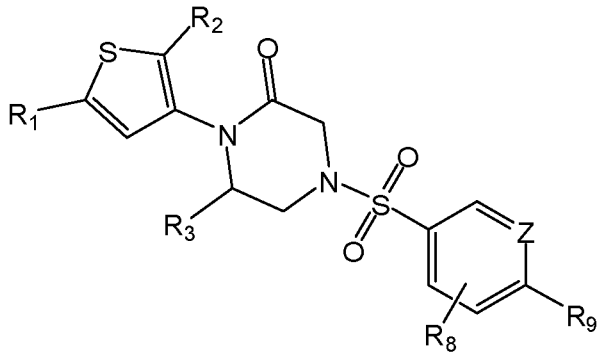
R_5 is absent or is selected from the group consisting of hydrogen and C_1-C_6alkyl;

R_6 is oxo, hydrogen, hydroxy, amino, N(H)-J-R_7;

J is absent, C(O) or $S(O)_2$; and

R_7 is C_1-C_6alkyl, phenyl or benzyl, each of is optionally substituted with C_1-C_6alkyl, C_1-C_6alkoxy, halogen, phenyl or phenoxy.

In one aspect, compounds of formula (I) include compounds of formula (II) and salts thereof:



(II)

wherein

Z is CH or N;

R_8 is selected from hydrogen, CO_2H, C_1-C_4alkyl, C-C_4alkoxy, cyano or halogen;

R_9 is selected from C_1-C_6alkyl, C_1-C_6alkoxy, phenyl, $NR_{9a}R_{9b}$, N(H)-C(O)-O-C_1-C_4alkyl, and heterocycle, wherein the heterocycle has one or two rings, each ring having 5, 6, or 7 ring atoms, one ring nitrogen atom and 0 or 1 additional ring heteroatom selected from N, O or S, and wherein the heterocycle is unsubstituted or substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, hydroxy, amino, C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, aminoC_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4alkoxyC_1-C_4alkyl, and mono- and di- C_1-C_4alkylamino; or

R_8 and R_9, taken in combination form a divalent residue selected from $-O(CH_2)_pO-$, $-O(CH_2)_2NH-$, or $-O(CH_2)_2N(CH_3)-$;

R_{9a} is selected from the group consisting of hydrogen and C_1-C_6alkyl, wherein the alkyl substituent is unsubstituted or substituted with hydroxy, C_1-C_4alkoxy, amino or mono- and di-C_1-C_4alkylamino; and

R_{9b} is selected from the group consisting of hydrogen, C_1-C_6alkyl and C_1-C_4alkanoyl, wherein the alkyl substituent is unsubstituted or substituted with hydroxy, C_1-C_4alkoxy, amino or mono- and di-C_1-C_4alkylamino.

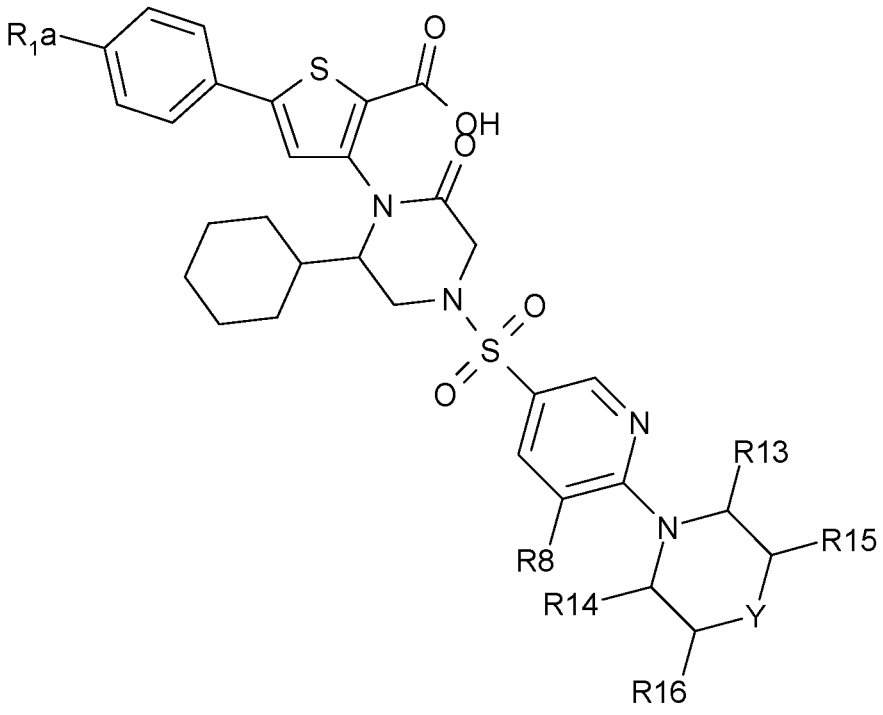
In certain aspects, compounds of formula (II) include those compounds in which R_8 is selected from hydrogen, CO_2H, methyl, methoxy or hydroxymethyl.

Certain other compounds of formula (II) include those compounds in which R_9 is selected from the group consisting of morpholino, piperidinyl, piperazinyl, and pyrrolidinyl, each of which is unsubstituted or substituted with one or two substituents selected from the group consisting of C_1-C_4alkyl, hydroxyC_1-C_4alkyl, aminoC_1-C_4alkyl, C_1-C_4alkoxy, mono- and di-C_1-C_4alkylamino, and C_1-C_4alkoxycarbonyl.

Still other compounds of formula (II) include those compounds in which Z is N.

In yet other aspects, compounds of formula (II) include those compounds in which
R_8 is selected from hydrogen, CO_2H, methyl, methoxy or hydroxymethyl;
R_9 is selected from the group consisting of morpholino, piperidinyl, piperazinyl, and pyrrolidinyl, each of which is unsubstituted or substituted with one or two substituents selected from the group consisting of C_1-C_4alkyl, hydroxyC_1-C_4alkyl, aminoC_1-C_4alkyl, C_1-C_4alkoxy, mono- and di-C_1-C_4alkylamino, and C_1-C_4alkoxycarbonyl; and Z is N.

In certain aspects, compounds of formula (I), (Ia) or (II) include compounds of formula (IIa) and salts thereof

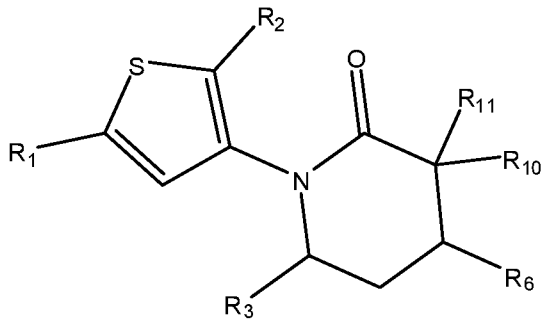


(IIa)

Wherein
Y is a bond, O, NR_{17}, or $CR_{17}R_{18}$;
R_{1a} is H, F, Cl or CH_3
R_8 is hydrogen, methyl, CO_2H, or methoxy;
R_{13} and R_{14}, are each independently selected from hydrogen or C_1-C_4alkyl;

R_{15} and R_{16}, are each independently selected from hydrogen, C_1-C_4alkyl, hydroxyC_1-C_4alkyl, amino, or mono- and di C_1-C_4alkylamino;
R_{17} is selected from hydrogen, C_1-C_4alkyl, or C_1-C_4alkoxycarbonyl; and
R_{18} is selected from hydrogen, C_1-C_4alkyl, C_1-C_4alkoxy, amino, or amino C_1-C_4alkyl.

In another aspect, compounds of formula (I) include compounds of formula (III) and salts thereof:

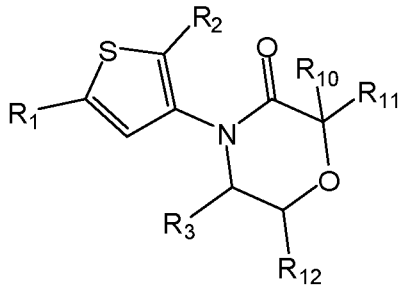


(III)

wherein
R_6 is hydrogen, hydroxy, amino or N(H)-J-R_7;
J is C(O) or $S(O)_2$;
R_7 is (a) C_1-C_4alkyl optionally substituted with phenyl or phenoxy, or
(b) phenyl optionally substituted with C_1-C_4alkyl, halogen or C_1-C_4alkoxy;
R_{10} is selected from hydrogen and C_1-C_6alkyl which alkyl is unsubstituted or substituted with one or two substituents selected from OH, cyano, SO_2CH_3, methoxy, ethoxy, $N(R_{10a})_2$ and $C(O)(NR_{10a})_2$;
R_{10a} is selected at each occurence from the group consisting of hydrogen and C_1-C_4alkyl which is substituted with 0 or 1 substituents selected from hydroxy, methoxy or ethoxy;
R_{11} is selected from the group consisting of hydrogen, fluoro, hydroxy and C_1-C_4alkyl.

In another aspect, compounds of formula (III) include those compounds in which R_{10} is hydrogen or C_1-C_6alkyl substituted with one or two hydroxy substituents or one substitutent independently selected from the group consisting of cyano, SO_2CH_3, methoxy, ethoxy, amino, mono- and di-C_1-C_2alkylamino, $C(O)NH_2$, C(O)N(H)Me and $C(O)NMe_2$. In certain other compounds of formula (III), R_{10} is C_1-C_6alkyl substituted with one or two hydroxy substituents or one substitutent independently selected from the group consisting of cyano, SO_2CH_3, methoxy, ethoxy, amino, or mono- and di-C_1-C_2alkylamino.

In yet another aspect, compounds of formula (I) include compounds of formula (IV) and salts thereof:



(IV)

wherein

R_{10} , R_{11} is independently selected from hydrogen and C_1-C_6alkyl which alkyl is unsubstituted or substituted with one or two substituents selected from OH, SO_2CH_3, cyano, methoxy, ethoxy, $N(R_{10a})_2$ and $C(O)N(R_{10a})_2$;

R_{10a} is selected at each occurence from the group consisting of hydrogen and C_1-C_4alkyl which is substituted with 0 or 1 substituents selected from hydroxy, methoxy or ethoxy;

Or $N(R_{10a})_2$ could form a 3-6 member cycloakyl or heterocycle

R_{12} is selected from the group consisting of hydrogen and C_1-C_4alkyl.

In another aspect, compounds of formula (IV) include those compounds in which R_{10} is hydrogen or C_1-C_6alkyl substituted with one or two hydroxy substituents or one substitutent independently selected from the group consisting of cyano, SO_2CH_3, methoxy, ethoxy, amino, mono- and di-C_1-C_2alkylamino, $C(O)NH_2$, C(O)N(H)Me and $C(O)NMe_2$. In certain other compounds of formula (IV), R_{10} is C_1-C_6alkyl substituted with one or two hydroxy substituents or one substitutent independently selected from the group consisting of cyano, SO_2CH_3, methoxy, ethoxy, amino, or mono- and di-C_1-C_2alkylamino.

In one aspect, compounds of formula (I), (Ia), (II), (IIa), (III) or (IV) include those compounds in which R_1 is *tert*-butylethynyl, phenyl, or phenyl para-substituted with F, Cl, or methyl. In certain instances, compounds of the identified formulae include those compounds in which R_1 is phenyl or *tert*-butylethynyl. In certain other compounds of formula (I), (Ia), (II), (IIa), (III), and/or (IV), R_1 is phenyl. In still other compounds of formula (I), (Ia), (II), (IIa), (III), and/or (IV), R_1 is *tert*-butylethynyl.

In another aspect, compounds of formula (I), (II), (IIa), (III) or (IV) include those compounds in which R_2 is CO_2H.

In one aspect, compounds of formula (I), (Ia), (II), (IIa), (III) or (IV) include those compounds in which R_3 is cyclohexyl.

In yet another aspect, compounds of (III) include those compounds in which R_6 is hydrogen;
R_{10} is hydrogen or hydoxyC_1-C_6alkyl; and
R_{11} is hydrogen, methyl, hydroxy or fluoro.

In yet another aspect, compounds of (III) include those compounds in which R_6 is hydrogen;
R_{10} is hydoxyC_1-C_6alkyl; and
R_{11} is hydrogen, methyl, hydroxy or fluoro.

In yet another aspect, compounds of (IV) include those compounds in which R_{10} is hydoxyC_1-C_6alkyl;
R_{11} is hydrogen or methyl; and
R_{12} is hydrogen or methyl.

In certain aspects, compounds of formula (III) are provided in which R_1 is *tert*-butylethynyl, phenyl, or phenyl para-substituted with F, Cl, or methyl;
R_2 is CO_2H;
R_3 is cyclohexyl;
R_6 is hydrogen;
R_{10} is hydroxyC_1-C_6alkyl; and
R_{11} is hydrogen, hydroxy, methyl or fluoro.

In certain aspects, compounds of formula (III) are provided in which R_1 is *tert*-butylethynyl;
R_2 is CO_2H;
R_3 is cyclohexyl;
R_6 is hydrogen;
R_{10} is hydroxyC_1-C_6alkyl; and

R_{11} is hydrogen, hydroxy, methyl or fluoro.

In certain aspects, compounds of formula (IV) are provided in which R_1 is *tert*-butylethynyl;

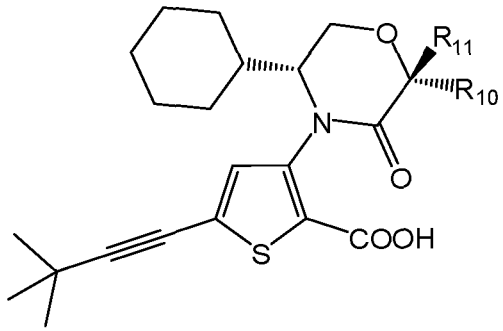
R_2 is CO_2H;

R_3 is cyclohexyl;

R_{10} is hydroxyC_1-C_6alkyl; and

R_{11} and R_{12} are independently selected from the group consisting of is hydrogen and methyl.

In certain other aspects, the invention provides compounds of Formula (V)



(V)

or a salt thereof, wherein

R_{11} is hydrogen or methyl;

R_{10} is C_2-C_6hydroxyalkyl wherein the hydroxyl group is a primary, secondary or tertiary alcohol. For example R_{10} is selected from $-(CH_2)_aOH$, $-(CH_2)_bCH(CH_3)OH$ or $-(CH_2)_bC(CH_3)_2OH$, wherein a is 2, 3, or 4 and b is 1, 2, or 3. In certain compounds of Formula (V) a is 2 or 3 and b is 1 or 2.

As used herein, the term "isomers" refers to different compounds that have the same molecular formula but differ in arrangement and configuration of the atoms. Also as used herein, the term "an optical isomer" or "a stereoisomer" refers to any of the various stereo isomeric configurations which may exist for a given compound of the present invention and includes geometric isomers. It is understood that a substituent may be attached at a chiral center of a carbon atom. Therefore, the invention includes enantiomers, diastereomers or racemates of the compound. "Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a

"racemic" mixture. The term is used to designate a racemic mixture where appropriate. "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn- Ingold- Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon may be specified by either *R* or *S*. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers or axes and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)-. The present invention is meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (*R*)- and (*S*)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. If the compound contains a double bond, the substituent may be E or Z configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans-configuration. All tautomeric forms are also intended to be included.

As used herein, the terms "salt" or "salts" refers to an acid addition or base addition salt of a compound of the invention. "Salts" include in particular "pharmaceutical acceptable salts". The term "pharmaceutically acceptable salts" refers to salts that retain the biological effectiveness and properties of the compounds of this invention and, which typically are not biologically or otherwise undesirable. In many cases, the compounds of the present invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids, e.g., acetate, aspartate, benzoate, besylate, bromide/hydrobromide, bicarbonate/carbonate, bisulfate/sulfate, camphorsulfornate, chloride/hydrochloride, chlortheophyllonate, citrate, ethandisulfonate, fumarate, gluceptate, gluconate, glucuronate, hippurate, , hydroiodide/iodide, isethionate, lactate, lactobionate, laurylsulfate, malate, maleate, malonate, mandelate, mesylate, methylsulphate, naphthoate, napsylate, nicotinate, nitrate, octadecanoate, oleate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, propionate, stearate, succinate, sulfosalicylate, tartrate, tosylate and trifluoroacetate salts.

Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like.

Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, sulfosalicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases.

Inorganic bases from which salts can be derived include, for example, ammonium salts and metals from columns I to XII of the periodic table. In certain embodiments, the salts are derived from sodium, potassium, ammonium, calcium, magnesium, iron, silver, zinc, and copper; particularly suitable salts include ammonium, potassium, sodium, calcium and magnesium salts.

Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like. Certain organic amines include isopropylamine, benzathine, cholinate, diethanolamine, diethylamine, lysine, meglumine, piperazine and tromethamine.

The pharmaceutically acceptable salts of the present invention can be synthesized from a parent compound, a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, use of non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile is desirable, where practicable. Lists of additional suitable salts can be found, e.g., in “Remington's Pharmaceutical Sciences”, 20th ed., Mack Publishing Company, Easton, Pa., (1985); and in “Handbook of Pharmaceutical Salts: Properties, Selection, and Use” by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F ^{31}P, ^{32}P, ^{35}S, ^{36}Cl, ^{125}I respectively. The invention includes various isotopically labeled compounds as defined herein, for example those into which radioactive isotopes, such as ^{3}H, ^{13}C, and ^{14}C , are present. Such isotopically labelled compounds are useful in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^{2}H or ^{3}H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or labeled compound may be particularly desirable for PET or SPECT studies. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

Further, substitution with heavier isotopes, particularly deuterium (i.e., ^{2}H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent of a compound of the formula (I). The concentration of such a heavier isotope, specifically deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this invention is denoted deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, *e.g.* D_2O, d_6-acetone, d_6-DMSO.

Compounds of the invention, i.e. compounds of formula (I) that contain groups capable of acting as donors and/or acceptors for hydrogen bonds may be capable of forming co-crystals with suitable co-crystal formers. These co-crystals may be prepared from compounds of formula (I) by known co-crystal forming procedures. Such procedures include grinding, heating, co-subliming, co-melting, or contacting in solution compounds of formula (I) with the co-crystal former under crystallization conditions and isolating co-crystals thereby formed. Suitable co-crystal formers include those described in WO 2004/078163. Hence the invention further provides co-crystals comprising a compound of formula (I).

As used herein, the term "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (*e.g.*, antibacterial agents, antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drugs, drug stabilizers, binders, excipients, disintegration agents, lubricants, sweetening agents, flavoring agents, dyes, and the like and combinations thereof, as would be known to those skilled in the art (see, for example, Remington's Pharmaceutical Sciences, 18th Ed. Mack Printing Company, 1990, pp. 1289- 1329). Except insofar as any conventional carrier is incompatible with the active ingredient, its use in the therapeutic or pharmaceutical compositions is contemplated.

The term "a therapeutically effective amount" of a compound of the present invention refers to an amount of the compound of the present invention that will elicit the biological or medical response of a subject, for example, reduction or inhibition of an enzyme or a protein activity, or ameliorate symptoms, alleviate conditions, slow or delay disease progression, or prevent a disease, etc. In one non-limiting embodiment, the term “a therapeutically effective amount” refers to the amount of the compound of the present invention that, when administered to a subject, is effective to (1) at least partially alleviating, inhibiting, preventing and/or ameliorating a condition, or a disorder or a disease (i) mediated by HCV infection, or (ii) associated with HCV

infection; or (2) reducing or inhibiting the viral replication or viral load of HCV. In another non-limiting embodiment, the term “a therapeutically effective amount” refers to the amount of the compound of the present invention that, when administered to a cell, or a tissue, or a non-cellular biological material, or a medium, is effective to at least partially reducing or inhibiting the activity of NS5b; or at least partially reducing or inhibiting the replication of HCV.

As used herein, the term “subject” refers to an animal. Typically the animal is a mammal. A subject also refers to for example, primates (*e.g.*, humans, male or female), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like. In certain embodiments, the subject is a primate. In yet other embodiments, the subject is a human.

As used herein, the term “inhibit”, "inhibition" or “inhibiting” refers to the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.

As used herein, the term “treat”, “treating" or "treatment" of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment “treat”, "treating" or "treatment" refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another embodiment, “treat”, "treating" or "treatment" refers to modulating the disease or disorder, either physically, (*e.g.*, stabilization of a discernible symptom), physiologically, (*e.g.*, stabilization of a physical parameter), or both. In yet another embodiment, “treat”, "treating" or "treatment" refers to preventing or delaying the onset or development or progression of the disease or disorder.

As used herein, a subject is “in need of” a treatment if such subject would benefit biologically, medically or in quality of life from such treatment.

As used herein, the term "a," "an," "the” and similar terms used in the context of the present invention (especially in the context of the claims) are to be construed to cover both the singular and plural unless otherwise indicated herein or clearly contradicted by the context.

All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (*e.g.* "such as”) provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention otherwise claimed.

Any asymmetric atom (e.g., carbon or the like) of the compound(s) of the present invention can be present in racemic or enantiomerically enriched, for example the (*R*)-, (*S*)- or (*R,S*)-configuration. In certain embodiments, each asymmetric atom has at least 50 % enantiomeric excess, at least 60 % enantiomeric excess, at least 70 % enantiomeric excess, at least 80 % enantiomeric excess, at least 90 % enantiomeric excess, at least 95 % enantiomeric excess, or at least 99 % enantiomeric excess in the (*R*)- or (*S*)- configuration. Substituents at atoms with unsaturated bonds may, if possible, be present in *cis*- (*Z*)- or *trans*- (*E*)- form.

Accordingly, as used herein a compound of the present invention can be in the form of one of the possible isomers, rotamers, atropisomers, tautomers or mixtures thereof, for example, as substantially pure geometric (*cis* or *trans*) isomers, diastereomers, optical isomers (antipodes), racemates or mixtures thereof.

Any resulting mixtures of isomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.

Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by known methods, *e.g.*, by separation of the diastereomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. In particular, a basic moiety may thus be employed to resolve the compounds of the present invention into their optical antipodes, *e.g.*, by fractional crystallization of a salt formed with an optically active acid, *e.g.*, tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, di-*O,O'-p*-toluoyl tartaric acid, mandelic acid, malic acid or camphor-10-sulfonic acid. Racemic products can also be resolved by chiral chromatography, *e.g.*, high pressure liquid chromatography (HPLC) using a chiral adsorbent.

Compounds of the present invention are either obtained in the free form, as a salt thereof, or as prodrug derivatives thereof.

When both a basic group and an acid group are present in the same molecule, the compounds of the present invention may also form internal salts, e.g., zwitterionic molecules.

The present invention also provides pro-drugs of the compounds of the present invention that converts *in vivo* to the compounds of the present invention. A pro-drug is an active or inactive compound that is modified chemically through *in vivo* physiological action, such as hydrolysis,

metabolism and the like, into a compound of this invention following administration of the prodrug to a subject. The suitability and techniques involved in making and using pro-drugs are well known by those skilled in the art. Prodrugs can be conceptually divided into two non-exclusive categories, bioprecursor prodrugs and carrier prodrugs. See *The Practice of Medicinal Chemistry*, Ch. 31-32 (Ed. Wermuth, Academic Press, San Diego, Calif., 2001). Generally, bioprecursor prodrugs are compounds, which are inactive or have low activity compared to the corresponding active drug compound, that contain one or more protective groups and are converted to an active form by metabolism or solvolysis. Both the active drug form and any released metabolic products should have acceptably low toxicity.

Carrier prodrugs are drug compounds that contain a transport moiety, *e.g.*, that improve uptake and/or localized delivery to a site(s) of action. Desirably for such a carrier prodrug, the linkage between the drug moiety and the transport moiety is a covalent bond, the prodrug is inactive or less active than the drug compound, and any released transport moiety is acceptably non-toxic. For prodrugs where the transport moiety is intended to enhance uptake, typically the release of the transport moiety should be rapid. In other cases, it is desirable to utilize a moiety that provides slow release, *e.g.*, certain polymers or other moieties, such as cyclodextrins. Carrier prodrugs can, for example, be used to improve one or more of the following properties: increased lipophilicity, increased duration of pharmacological effects, increased site-specificity, decreased toxicity and adverse reactions, and/or improvement in drug formulation (*e.g.*, stability, water solubility, suppression of an undesirable organoleptic or physiochemical property). For example, lipophilicity can be increased by esterification of (a) hydroxyl groups with lipophilic carboxylic acids (e.g., a carboxylic acid having at least one lipophilic moiety), or (b) carboxylic acid groups with lipophilic alcohols (e.g., an alcohol having at least one lipophilic moiety, for example aliphatic alcohols).

Exemplary prodrugs are, *e.g.*, esters of free carboxylic acids and *S*-acyl derivatives of thiols and *O*-acyl derivatives of alcohols or phenols, wherein acyl has a meaning as defined herein. Suitable prodrugs are often pharmaceutically acceptable ester derivatives convertible by solvolysis under physiological conditions to the parent carboxylic acid, *e.g.*, lower alkyl esters, cycloalkyl esters, lower alkenyl esters, benzyl esters, mono- or di-substituted lower alkyl esters, such as the -(amino, mono- or di-lower alkylamino, carboxy, lower alkoxycarbonyl)-lower alkyl esters, the -(lower alkanoyloxy, lower alkoxycarbonyl or di-lower alkylaminocarbonyl)-lower alkyl esters, such as the pivaloyloxymethyl ester and the like conventionally used in the art. In addition, amines have been masked as arylcarbonyloxymethyl substituted derivatives which are

cleaved by esterases *in vivo* releasing the free drug and formaldehyde (Bundgaard, *J. Med. Chem*. 2503 (1989)). Moreover, drugs containing an acidic NH group, such as imidazole, imide, indole and the like, have been masked with N-acyloxymethyl groups (Bundgaard, *Design of Prodrugs*, Elsevier (1985)). Hydroxy groups have been masked as esters and ethers. EP 039,051 (Sloan and Little) discloses Mannich-base hydroxamic acid prodrugs, their preparation and use.

Furthermore, the compounds of the present invention, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization. The compounds of the present invention may inherently or by design form solvates with pharmaceutically acceptable solvents (including water); therefore, it is intended that the invention embrace both solvated and unsolvated forms. The term "solvate" refers to a molecular complex of a compound of the present invention (including pharmaceutically acceptable salts thereof) with one or more solvent molecules. Such solvent molecules are those commonly used in the pharmaceutical art, which are known to be innocuous to the recipient, e.g., water, ethanol, and the like. The term "hydrate" refers to the complex where the solvent molecule is water.

The compounds of the present invention, including salts, hydrates and solvates thereof, may inherently or by design form polymorphs.

In another aspect, the present invention provides a pharmaceutical composition comprising a compound of the present invention and a pharmaceutically acceptable carrier. The pharmaceutical composition can be formulated for particular routes of administration such as oral administration, parenteral administration, and rectal administration, etc. In addition, the pharmaceutical compositions of the present invention can be made up in a solid form (including without limitation capsules, tablets, pills, granules, powders or suppositories), or in a liquid form (including without limitation solutions, suspensions or emulsions). The pharmaceutical compositions can be subjected to conventional pharmaceutical operations such as sterilization and/or can contain conventional inert diluents, lubricating agents, or buffering agents, as well as adjuvants, such as preservatives, stabilizers, wetting agents, emulsifers and buffers, etc.

Typically, the pharmaceutical compositions are tablets or gelatin capsules comprising the active ingredient together with

a) diluents, *e.g.*, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine;

b) lubricants, *e.g.*, silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also

c) binders, *e.g.*, magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone; if desired

d) disintegrants, *e.g.*, starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or

e) absorbents, colorants, flavors and sweeteners.

Tablets may be either film coated or enteric coated according to methods known in the art.

Suitable compositions for oral administration include an effective amount of a compound of the invention in the form of tablets, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use are prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions can 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 may contain the active ingredient in admixture with nontoxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients are, 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 are uncoated or 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 can be employed. Formulations for oral use can be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

Certain injectable compositions are aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. Said

compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1-75%, or contain about 1-50%, of the active ingredient.

Suitable compositions for transdermal application include an effective amount of a compound of the invention with a suitable carrier. Carriers suitable for transdermal delivery include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

Suitable compositions for topical application, *e.g.*, to the skin and eyes, include aqueous solutions, suspensions, ointments, creams, gels or sprayable formulations, *e.g.*, for delivery by aerosol or the like. Such topical delivery systems will in particular be appropriate for dermal application, *e.g.*, for the treatment of skin cancer, *e.g.*, for prophylactic use in sun creams, lotions, sprays and the like. They are thus particularly suited for use in topical, including cosmetic, formulations well-known in the art. Such may contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

As used herein a topical application may also pertain to an inhalation or to an intranasal application. They may be conveniently delivered in the form of a dry powder (either alone, as a mixture, for example a dry blend with lactose, or a mixed component particle, for example with phospholipids) from a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray, atomizer or nebuliser, with or without the use of a suitable propellant.

The present invention further provides anhydrous pharmaceutical compositions and dosage forms comprising the compounds of the present invention as active ingredients, since water may facilitate the degradation of certain compounds.

Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. An anhydrous pharmaceutical composition may be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are packaged using

materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (*e. g.*, vials), blister packs, and strip packs.

The invention further provides pharmaceutical compositions and dosage forms that comprise one or more agents that reduce the rate by which the compound of the present invention as an active ingredient will decompose. Such agents, which are referred to herein as "stabilizers," include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers, etc.

The compounds of formula I in free form or in salt form, exhibit valuable pharmacological properties, e.g NS5b inhibitory properties, e.g. as indicated in in vitro and in vivo tests as provided in the next sections and are therefore indicated for therapy.
In one embodiment, the invention provides a method of treating an HCV-associated disorder comprising administering to a subject in need thereof a pharmaceutically acceptable amount of a compound of the invention, such that the HCV-associated disorder is treated.

In another embodiment, the invention provides a method of treating an HIV infection comprising administering to a subject in need thereof a pharmaceutically acceptable amount of a compound of the invention.

In still another embodiment, the invention provides a method of treating, inhibiting or preventing the activity of HCV in a subject in need thereof, comprising administering to the subject a pharmaceutically acceptable amount of a compound of the invention. In one embodiment, the compounds of the invention inhibit the activity of the NS2 protease, the NS3 protease, the NS3 helicase, the NS5a protein, and/or the NS5b polymerase. In another embodiment, the interaction between the NS3 protease and NS4A cofactor is disrupted. In yet another embodiment, the compounds of the invention prevent or alter the severing of one or more of the NS4A-NS4B, NS4B-NS5A and NS5A-NS5B junctions of the HCV. In another embodiment, the invention provides a method of inhibiting the activity of a serine protease, comprising the step of contacting said serine protease with a compound of the invention. In another embodiment, the invention provides a method of treating, inhibiting or preventing the activity of HCV in a subject in need thereof, comprising administering to the subject a pharmaceutically acceptable amount of a compound of the invention, wherein the compound interacts with any target in the HCV life cycle. In one embodiment, the target of the HCV life cycle is selected from the group consisting of NS2 protease, NS3 protease, NS3 helicase, NS5a protein and NS5b polymerase.

In another embodiment, the invention provides a method of decreasing the HCV RNA load in a

subject in need thereof comprising administering to the subject a pharmaceutically acceptable amount of a compound of the invention.

In another embodiment, the compounds of the invention exhibit HCV protease activity. In one embodiment, the compounds are an HCV NS3-4A protease inhibitor.

In another embodiment, the invention provides a method of treating an HCV-associated disorder in a subject, comprising administering to a subject in need thereof a pharmaceutically acceptable amount of a compound of the invention, and a pharmaceutically acceptable carrier, such that the HCV-associated disorder is treated.

In still another embodiment, the invention provides a method of treating an HCV-associated disorder comprising administering to a subject in need thereof a pharmaceutically effective amount of a compound of the invention, in combination with a pharmaceutically effective amount of an additional HCV-modulating compound, such as interferon or derivatized interferon, or a cytochrome P450 monooxygenase inhibitor, such that the HCV-associated disorder is treated. In one embodiment, the additional HCV-modulating compound is selected from the group consisting of NIM811, ITMN191, MK-7009, TMC 435350, Sch 503034 and VX-950.

In another embodiment, the invention provides a method of inhibiting hepatitis C virus replication in a cell, comprising contacting said cell with a compound of the invention.

In yet another embodiment, the invention provides a packaged HCV-associated disorder treatment, comprising an HCV-modulating compound of the invention, packaged with instructions for using an effective amount of the HCV-modulating compound to treat an HCV-associated disorder.

In certain embodiments, the HCV-associated disorder is selected from the group consisting of HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin's lymphoma, liver fibrosis and a suppressed innate intracellular immune response.

In another embodiment, the invention provides a method of treating HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin's lymphoma, liver fibrosis and/or a suppressed innate intracellular immune response in subject in need thereof comprising administering to the subject a pharmaceutically acceptable amount of a compound of the invention.

In one embodiment, the HCV to be treated is selected of any HCV genotype. In another embodiment, the HCV is selected from HCV genotype 1, 2 and/or 3.

The pharmaceutical composition or combination of the present invention can be in unit dosage of about 1-1000 mg of active ingredient(s) for a subject of about 50-70 kg, or about 1-500 mg or about 1-250 mg or about 1-150 mg or about 0.5-100 mg, or about 1-50 mg of active ingredients. The therapeutically effective dosage of a compound, the pharmaceutical composition, or the combinations thereof, is dependent on the species of the subject, the body weight, age and individual condition, the disorder or disease or the severity thereof being treated. A physician, clinician or veterinarian of ordinary skill can readily determine the effective amount of each of the active ingredients necessary to prevent, treat or inhibit the progress of the disorder or disease.

The above-cited dosage properties are demonstrable *in vitro* and *in vivo* tests using advantageously mammals, *e.g.*, mice, rats, dogs, monkeys or isolated organs, tissues and preparations thereof. The compounds of the present invention can be applied *in vitro* in the form of solutions, *e.g.*, aqueous solutions, and *in vivo* either enterally, parenterally, advantageously intravenously, *e.g.*, as a suspension or in aqueous solution. The dosage *in vitro* may range between about 10^{-3} molar and 10^{-9} molar concentrations. A therapeutically effective amount *in vivo* may range depending on the route of administration, between about 0.1-500 mg/kg, or between about 1-100 mg/kg.

The activity of a compound according to the present invention can be assessed by the *in vitro* & *in vivo* methods provided *infra*.

The compound of the present invention may be administered either simultaneously with, or before or after, one or more other therapeutic agent. The compound of the present invention may be administered separately, by the same or different route of administration, or together in the same pharmaceutical composition as the other agents.

In one embodiment, the invention provides a product comprising a compound of formula (I) and at least one other therapeutic agent as a combined preparation for simultaneous, separate or sequential use in therapy. In one embodiment, the therapy is the treatment of a viral infection or disease associated with viral infection or condition mediated by hepatitis C virus. Products

provided as a combined preparation include a composition comprising the compound of formula (I) and the other therapeutic agent(s) together in the same pharmaceutical composition, or the compound of formula (I) and the other therapeutic agent(s) in separate form, *e.g.* in the form of a kit.

In one embodiment, the invention provides a pharmaceutical composition comprising a compound of formula (I) and another therapeutic agent(s). Optionally, the pharmaceutical composition may comprise a pharmaceutically acceptable excipient, as described above.

In one embodiment, the invention provides a kit comprising two or more separate pharmaceutical compositions, at least one of which contains a compound of formula (I). In one embodiment, the kit comprises means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is a blister pack, as typically used for the packaging of tablets, capsules and the like.

The kit of the invention may be used for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit of the invention typically comprises directions for administration.

In the combination therapies of the invention, the compound of the invention and the other therapeutic agent may be manufactured and/or formulated by the same or different manufacturers. Moreover, the compound of the invention and the other therapeutic may be brought together into a combination therapy: (i) prior to release of the combination product to physicians (*e.g.* in the case of a kit comprising the compound of the invention and the other therapeutic agent); (ii) by the physician themselves (or under the guidance of the physician) shortly before administration; (iii) in the patient themselves, *e.g.* during sequential administration of the compound of the invention and the other therapeutic agent.
Accordingly, the invention provides the use of a compound of formula (I) for treating a disease or condition caused by or associated with HCV infection, wherein the medicament is prepared for administration with another therapeutic agent. The invention also provides the use of another therapeutic agent for treating a disease or condition caused by or associated with HCV infection, wherein the medicament is administered with a compound of formula (I).

The invention also provides a compound of formula (I) for use in a method of treating a disease or condition caused by or associated with HCV infection, wherein the compound of formula (I) is prepared for administration with another therapeutic agent. The invention also provides another therapeutic agent for use in a method of treating a disease or condition caused by or associated with HCV infection, wherein the other therapeutic agent is prepared for administration with a compound of formula (I). The invention also provides a compound of formula (I) for use in a method of treating a disease or condition caused by or associated with HCV infection, wherein the compound of formula (I) is administered with another therapeutic agent. The invention also provides another therapeutic agent for use in a method of treating a disease or condition caused by or associated with HCV infection, wherein the other therapeutic agent is administered with a compound of formula (I).

The invention also provides the use of a compound of formula (I) for treating a disease or condition caused by or associated with HCV infection, wherein the patient has previously (*e.g.* within 24 hours) been treated with another therapeutic agent. The invention also provides the use of another therapeutic agent for treating a disease or condition caused by or associated with HCV infection, wherein the patient has previously (*e.g.* within 24 hours) been treated with a compound of formula (I).

In one embodiment, the other therapeutic agent is selected from second therapeutic agents which are active against viruses and, in particular, against HCV. The compound and agent may be administered in a single or separate formulations. Agents active against HCV include, but are not limited to, interferon-α, pegylated interferon-α (peginterferon-α), albinterferon-α2b (albIFN, Novartis/Human Genome Science), PEG-Interferon lambda (BMS/ZymoGenetics), ribavirin, levovirin, viramidine, a combination of interferon-α and ribavirin, a combination of peginterferon-α and ribavirin, a combination of albIFN and ribavirin, a combination of interferon-α and levovirin, a combination of peginterferon-α and levovirin, and a combination of albIFN and levovirin. Interferon-α includes, but is not limited to, recombinant interferon-α2a (such as ROFERON interferon available from Hoffman-LaRoche, Nutley, NJ), interferon-α2b (such as Intron-A interferon available from Schering Corp., Kenilworth, New Jersey, USA), a consensus interferon, and a purified interferon-α product. Pegylated interferon-α includes, but is not limited to, PEG IFN-α2a (such as Pegsys available from Hoffman-LaRoche, Nutley, NJ), PEG IFN-α2b (such as PegIntron available from Schering Corp., Kenilworth, New Jersey, USA), For a discussion of ribavirin and its activity against HCV, see J.O. Saunders and S.A. Raybuck,

"Inosine Monophosphate Dehydrogenase: Consideration of Structure, Kinetics and Therapeutic Potential," *Ann. Rep. Med. Chem.*, 35:201-210 (2000).

The agents active against hepatitis C virus also include agents that inhibit HCV NS2 or NS3 proteases, HCV NS5B polymerase, HCV NS5A protein, HCV NS3 helicase, HCV NS4B protein, HCV p7 protein, HCV NS4A protein, HCV IRES and protein translation, HCV entry, HCV assembly, HCV egress, and inosine 5'-monophosphate dehydrogenase, cyclophilins or other host factors that are required for HCV replication. Still other compounds include those disclosed in WO 2004/014313 and WO 2004/014852 and in the references cited therein.

Specific antiviral agents include BI-201335 (Boehringer Ingelheim), telaprevir (Vertex), VX-813 (Vertex), VX-500 (Vertex), boceprevir (Schering-Plough), Sch 900518 (Schering-Plough), ITMN-191/R7227 (Intermune/Roche), ITMN-5489 (Intermune), MK-7009 (Merck), TMC435 (Tibotec), BMS-650032 (Bristol-Myers-Squibb), PHX1766 (Phenomix), GS-9256 (Gilead), VCH-916 (Vertex), VCH-759 (Vertex), VCH-222/VX-222 (Vertex), ABT-333 (Abbott), ANA-598 (Anadys), PF-868,554 (Pfizer), MK-3281 (Merck), PSI-7851 (Pharmasset), R7128 (Pharmasset/Roche), R1626 (Roche), GS9190 (Gilead), BI-207127 (Boehringer Ingelheim), JTK-652 (Japan Tobacco Inc.), IDX375 (Idenix), Valopicitabine/NM283 (Idenix), IDX-184 (Idenix), AZD2836/A-831 (Arrow/AstraZeneca), AZD7295/A-689 (Arrow/AstraZeneca), BMS-790052 (Bristol-Myers-Squibb), PPI-461 (Presidio), EDP-239 (Enanta), Ceplene (Maxim Pharmaceuticals), Civacir (Nabi Biopharmaceuticals Inc, VX-497 (Vertex Pharmaceuticals Inc.), XTL-002 (XTL Biopharmaceuticals), isatoribine and its prodrugs ANA971,ANA975 and ANA773 (Anadys), NIM811 (Novartis), DEBIO-025 (DebioPharm/Novartis), SCY-635 (Scynexis), and nitazoxanide (Romark), IDN-6556 (Idun Pharmaceuticals), IP-501 (Indevus Pharmaceuticals), ISIS 14803 (ISIS Pharmaceuticals Inc.),

In some embodiments, the compositions and methods of the present invention contain a compound of the invention and interferon. In some aspects, the interferon is selected from the group consisting of interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastoid interferon tau.

In other embodiments the compositions and methods of the present invention contain a compound of the invention and a compound having anti-HCV activity is selected from the group consisting of interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiquimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

In still other embodiments, the compound having anti-HCV activity is Ribavirin, levovirin, viramidine, thymosin alpha-1, an inhibitor of NS3 serine protease, and inhibitor of inosine monophosphate dehydrogenase, interferon-alpha, or pegylated interferon-alpha alone or in combination with Ribavirin or viramidine.

In another embodiments, the compound having anti-HCV activity is said agent active against HCV is interferon-alpha or pegylated interferon-alpha alone or in combination with Ribavirin or viramidine.

General Synthetic Methods

The compounds disclosed herein can be prepared by following the general procedures and examples set forth below. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional groups as well as suitable conditions for protecting and deprotecting particular functional groups are well known in the art. For example, numerous protecting groups are described in T. W. Greene and P. G. M. Wuts, Protecting Groups in Organic Synthesis, Third Edition, Wiley, New York, 1999, and references cited therein.

If the compounds of this invention contain one or more chiral centers, such compounds can be prepared or isolated as pure stereoisomers, i.e., as individual enantiomers or diastereomers, or as stereoisomer-enriched mixtures. All such stereoisomers (and enriched mixtures) are included within the scope of this invention, unless otherwise indicated. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents and the like.

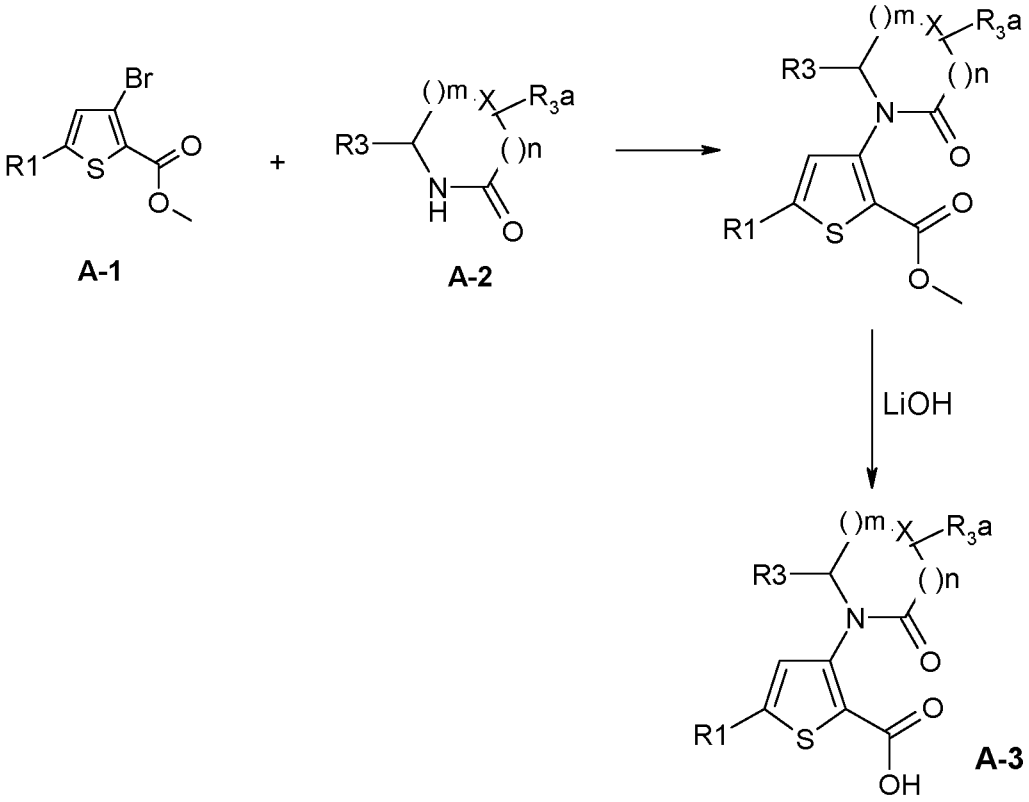
Typically, the compounds of formula (I) can be prepared according to the Schemes provided *infra*

General Procedures

Example A

Compound according to general structure **A-3** could be synthesized by coupling reaction between fragment **A-1** and fragment **A-2** with CuI and *trans*-cyclohexane diamine as promoters followed by hydrolysis of the methyl ester under basic condition.

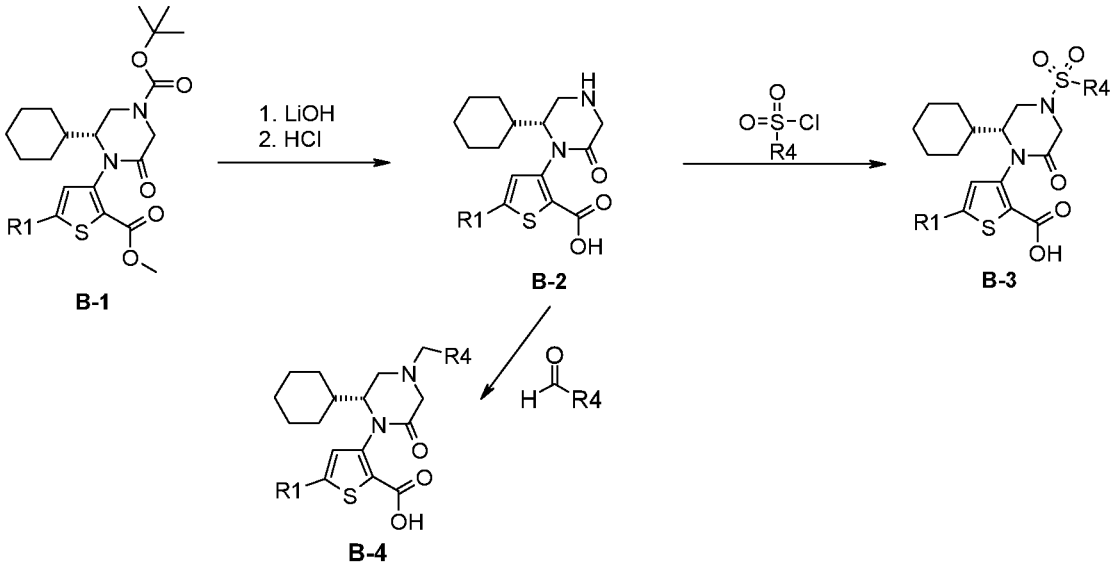
Scheme I



Example B

Compound according to general structure **B-3** could be synthesized by following method (**Scheme II**). **B-1** could be converted to **B-2** by hydrolyzing the methyl ester under basic condition followed by cleaving Boc with HCl. **B-2** could react with sulfonyl chloride to give sulfonamide **B-3**. Or **B-2** could undergo reductive amination with aldehyde to give amine **B-4**.

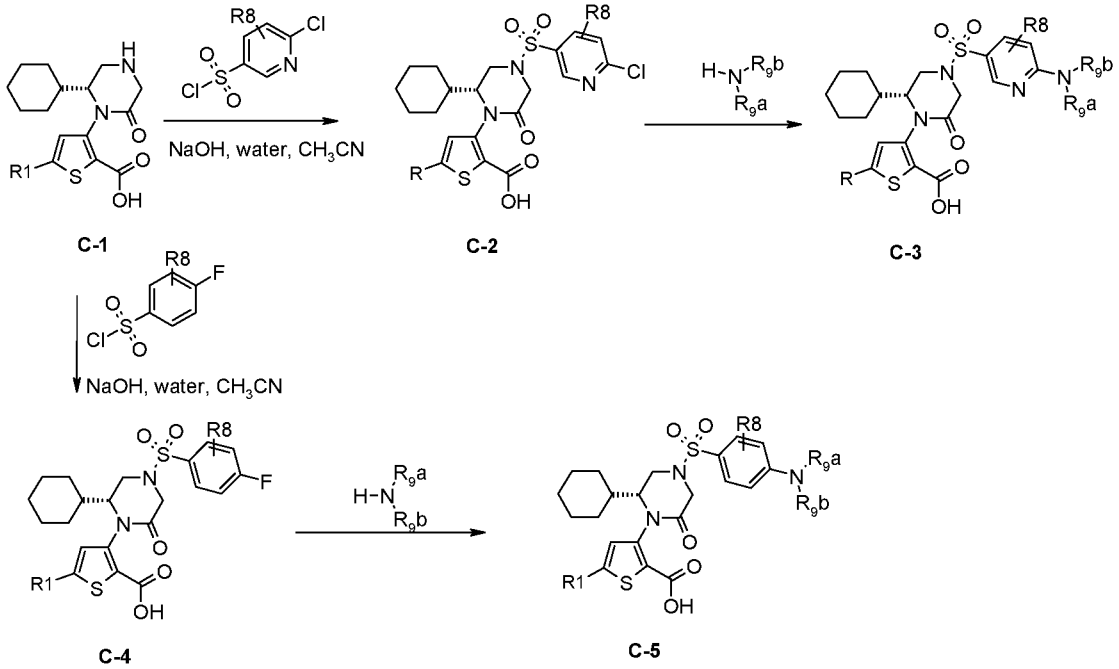
Scheme II



Example C

Compounds according to general structure **C-3** and **C-5** could be synthesized by followed method. Amine **C-1** could be converted to pyridyl sulfonamide **C-2** by reacting with pyridine sulfonyl chloride. Displacement of chloride with amine would provide **C-3**. **C-1** could react with 4-fluro phenylsulfonyl chloride to give **C-4**. Displacement of fluoride with amine would give **C-5**.

Scheme III



The invention further includes any variant of the present processes, in which an intermediate product obtainable at any stage thereof is used as starting material and the remaining steps are carried out, or in which the starting materials are formed *in situ* under the reaction conditions, or in which the reaction components are used in the form of their salts or optically pure antipodes.

Compounds of the invention and intermediates can also be converted into each other according to methods generally known *to those skilled in the art*.

Within the scope of this text, only a readily removable group that is not a constituent of the particular desired end product of the compounds of the present invention is designated a "protecting group", unless the context indicates otherwise. The protection of functional groups by such protecting groups, the protecting groups themselves, and their cleavage reactions are described for example in standard reference works, such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981, in "Methoden der organischen Chemie" (Methods of Organic Chemistry), Houben Weyl, 4th edition, Volume 15/I, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jeschkeit, "Aminosäuren, Peptide, Proteine" (Amino acids, Peptides, Proteins), Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982, and in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (Chemistry of Carbohydrates: Monosaccharides and Derivatives), Georg Thieme Verlag, Stuttgart 1974. A characteristic of protecting groups is that they can be removed readily (i.e. without the occurrence of undesired secondary reactions) for example by solvolysis, reduction, photolysis or alternatively under physiological conditions (*e.g.* by enzymatic cleavage).

Salts of compounds of the present invention having at least one salt-forming group may be prepared in a manner known to those skilled in the art. For example, salts of compounds of the present invention having acid groups may be formed, for example, by treating the compounds with metal compounds, such as alkali metal salts of suitable organic carboxylic acids, *e.g.* the sodium salt of 2-ethylhexanoic acid, with organic alkali metal or alkaline earth metal compounds, such as the corresponding hydroxides, carbonates or hydrogen carbonates, such as sodium or potassium hydroxide, carbonate or hydrogen carbonate, with corresponding calcium compounds or with ammonia or a suitable organic amine, stoichiometric amounts or

only a small excess of the salt-forming agent preferably being used. Acid addition salts of compounds of the present invention are obtained in customary manner, *e.g.* by treating the compounds with an acid or a suitable anion exchange reagent. Internal salts of compounds of the present invention containing acid and basic salt-forming groups, *e.g.* a free carboxy group and a free amino group, may be formed, *e.g.* by the neutralisation of salts, such as acid addition salts, to the isoelectric point, *e.g.* with weak bases, or by treatment with ion exchangers.

Salts can be converted into the free compounds in accordance with methods known to those skilled in the art. Metal and ammonium salts can be converted, for example, by treatment with suitable acids, and acid addition salts, for example, by treatment with a suitable basic agent.

Mixtures of isomers obtainable according to the invention can be separated in a manner known to those skilled in the art into the individual isomers; diastereoisomers can be separated, for example, by partitioning between polyphasic solvent mixtures, recrystallisation and/or chromatographic separation, for example over silica gel or by *e.g.* medium pressure liquid chromatography over a reversed phase column, and racemates can be separated, for example, by the formation of salts with optically pure salt-forming reagents and separation of the mixture of diastereoisomers so obtainable, for example by means of fractional crystallisation, or by chromatography over optically active column materials.

Intermediates and final products can be worked up and/or purified according to standard methods, *e.g.* using chromatographic methods, distribution methods, (re-) crystallization, and the like.

The following applies in general to all processes mentioned herein before and hereinafter.

All the above-mentioned process steps can be carried out under reaction conditions that are known to those skilled in the art, including those mentioned specifically, in the absence or, customarily, in the presence of solvents or diluents, including, for example, solvents or diluents that are inert towards the reagents used and dissolve them, in the absence or presence of catalysts, condensation or neutralizing agents, for example ion exchangers, such as cation exchangers, *e.g.* in the H+ form, depending on the nature of the reaction and/or of the reactants at reduced, normal or elevated temperature, for example in a temperature range of from about -100 ºC to about 190 ºC, including, for example, from approximately -80 ºC to approximately 150

ºC, for example at from -80 to -60 ºC, at room temperature, at from -20 to 40 ºC or at reflux temperature, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under an argon or nitrogen atmosphere.

At all stages of the reactions, mixtures of isomers that are formed can be separated into the individual isomers, for example diastereoisomers or enantiomers, or into any desired mixtures of isomers, for example racemates or mixtures of diastereoisomers, for example analogously to the methods described under "Additional process steps".

The solvents from which those solvents that are suitable for any particular reaction may be selected include those mentioned specifically or, for example, water, esters, such as lower alkyl-lower alkanoates, for example ethyl acetate, ethers, such as aliphatic ethers, for example diethyl ether, or cyclic ethers, for example tetrahydrofuran or dioxane, liquid aromatic hydrocarbons, such as benzene or toluene, alcohols, such as methanol, ethanol or 1- or 2-propanol, nitriles, such as acetonitrile, halogenated hydrocarbons, such as methylene chloride or chloroform, acid amides, such as dimethylformamide or dimethyl acetamide, bases, such as heterocyclic nitrogen bases, for example pyridine or *N*-methylpyrrolidin-2-one, carboxylic acid anhydrides, such as lower alkanoic acid anhydrides, for example acetic anhydride, cyclic, linear or branched hydrocarbons, such as cyclohexane, hexane or isopentane, methycyclohexane, or mixtures of those solvents, for example aqueous solutions, unless otherwise indicated in the description of the processes. Such solvent mixtures may also be used in working up, for example by chromatography or partitioning.

The compounds, including their salts, may also be obtained in the form of hydrates, or their crystals may, for example, include the solvent used for crystallization. Different crystalline forms may be present.

The invention relates also to those forms of the process in which a compound obtainable as an intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example in a protected form or in the form of a salt, or a compound obtainable by the process according to the invention is produced under the process conditions and processed further in situ.

All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents and catalysts utilized to synthesize the compounds of the present invention are either

commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art (Houben-Weyl 4th Ed. 1952, Methods of Organic Synthesis, Thieme, Volume 21).

In one embodiment, the invention provides a method of modulating viral activity in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of the compound according to the definition of formula (I). Methods of inhibiting viral replication or inhibiting viral load in a subject are provided, wherein the virus is a member of the *Flaviviridae* family of viruses such as hepatitis C virus.

In one embodiment, the invention provides a method of treating a disorder or a disease in a subject caused by or associated with HCV infection, wherein the method comprises administering to the subject a therapeutically effective amount of the compound according to the definition of formula (I).

In one embodiment, the invention provides a method of treating a disorder or a disease in a subject caused by or associated with HCV infection, wherein the disorder or the disease is selected from of HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin's lymphoma, liver fibrosis and a suppressed innate intracellular immune response.

In one embodiment, the invention provides a compound according to the definition of formula (I), for use as a medicament.

In one embodiment, the invention provides the use of a compound according to the definition of formula (I), for the treatment of a disorder or disease in a subject caused by or associated with HCV infection.

In one embodiment, the invention provides the use of a compound according to the definition of formula (I), in the manufacture of a medicament for the treatment of a disorder or disease in a subject caused by or associated with HCV infection, wherein said disorder or disease is in particular selected from HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin's lymphoma, liver fibrosis and a suppressed innate intracellular immune response.

In one embodiment, the invention provides the use of a compound according to the definition of formula (I), for the treatment of a disorder or disease in a subject caused by or

associated with HCV infection, wherein the disorder or disease is selected from HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin's lymphoma, liver fibrosis and a suppressed innate intracellular immune response.

In another embodiment, the invention provides compounds according to the definition of formula (I), which compounds include the exemplified compounds provided *infra*. Certain compounds of Formula (I) provided by the invention include compounds selected from the group consisting of:

1. 3-((S)-2-Cyclohexyl-5-oxo-pyrrolidin-1-yl)-5-phenyl-thiophene-2-carboxylic acid
2. 3-(2-Cyclohexyl-6-oxo-piperidin-1-yl)-5-phenyl-thiophene-2-carboxylic acid
3. 3-(3-Cyclohexyl-5-oxo-morpholin-4-yl)-5-phenyl-thiophene-2-carboxylic acid
4. 3-[(R)-2-Cyclohexyl-6-oxo-4-(toluene-4-sulfonyl)-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid
5. 3-(2-Cyclohexyl-6-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
6. 3-((S)-2-Cyclohexyl-6-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
7. 3-(2-Cyclohexyl-6-oxo-piperidin-1-yl)-5-(4-fluoro-phenyl)-thiophene-2-carboxylic acid
8. 3-(2-Cyclohexyl-6-oxo-piperidin-1-yl)-5-p-tolyl-thiophene-2-carboxylic acid
9. 5-(4-Chloro-phenyl)-3-(2-cyclohexyl-6-oxo-piperidin-1-yl)-thiophene-2-carboxylic acid
10. 3-[2-Cyclohexyl-4-(6-dipropylamino-pyridine-3-sulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid
11. 3-{(R)-2-Cyclohexyl-4-[6-((R)-2-methyl-pyrrolidin-1-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid
12. 3-[(R)-2-Cyclohexyl-6-oxo-4-(6-pyrrolidin-1-yl-pyridine-3-sulfonyl)-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid
13. 3-{(R)-2-Cyclohexyl-4-[6-((2S,5R)-2,5-dimethyl-pyrrolidin-1-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid
14. 3-[2-Cyclohexyl-6-oxo-4-(toluene-4-sulfonyl)-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
15. 3-{(R)-2-Cyclohexyl-4-[6-((2R,6S)-2,6-dimethyl-morpholin-4-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid
16. 3-[2-Cyclohexyl-4-(6-morpholin-4-yl-pyridine-3-sulfonyl)-6-oxo-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid

17. 3-[(R)-2-Cyclohexyl-4-(6-diethylamino-pyridine-3-sulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid
18. 3-[(R)-2-Cyclohexyl-6-oxo-4-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-sulfonyl)-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid
19. 3-((R)-4-Cyclohexyl-2-oxo-oxazolidin-3-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
20. 3-[(R)-2-Cyclohexyl-4-(6-morpholin-4-yl-pyridine-3-sulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid
21. 3-[(R)-2-Cyclohexyl-4-(4-methoxy-benzenesulfonyl)-6-oxo-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
22. 3-[(R)-2-Cyclohexyl-4-(6-methoxy-pyridine-3-sulfonyl)-6-oxo-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
23. 3-[(R)-2-Cyclohexyl-4-(1-methyl-1H-pyrazole-3-sulfonyl)-6-oxo-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
24. 3-{(R)-2-Cyclohexyl-4-[6-(8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-p-tolyl-thiophene-2-carboxylic acid
25. 3-(2-Cyclohexyl-5-oxo-pyrrolidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
26. 3-((R)-3-Cyclohexyl-5-oxo-morpholin-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
27. 3-((4S,5R)-5-Cyclohexyl-3,4-dimethyl-2-oxo-imidazolidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
28. 5-(4-Chloro-phenyl)-3-((R)-3-cyclohexyl-5-oxo-morpholin-4-yl)-thiophene-2-carboxylic acid
29. 3-[(R)-5-Cyclohexyl-2-(2-morpholin-4-yl-2-oxo-ethyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
30. 3-[(R)-5-Cyclohexyl-2-(3-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
31. 3-[(R)-5-Cyclohexyl-2-(3-methanesulfonyl-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
32. 3-{(R)-5-Cyclohexyl-2-[(2-methoxy-ethylamino)-methyl]-3-oxo-morpholin-4-yl}-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
33. 3-(4-Cyclohexyl-2-oxo-[1,3]oxazinan-3-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid

34. 3-((R)-5-Cyclohexyl-2-morpholin-4-ylmethyl-3-oxo-morpholin-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
35. 3-[(2R,5R)-5-Cyclohexyl-2-(3-hydroxy-propyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
36. 3-((2S,5R)-2-Cyanomethyl-5-cyclohexyl-2-methyl-3-oxo-morpholin-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
37. 3-(6-Cyclohexyl-3-hydroxy-2-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
38. 3-((R)-5-Cyclohexyl-2,2-dimethyl-3-oxo-morpholin-4-yl)-5-p-tolyl-thiophene-2-carboxylic acid
39. 3-(6-Cyclohexyl-3-hydroxy-2-oxo-piperidin-1-yl)-5-p-tolyl-thiophene-2-carboxylic acid
40. 3-[(2S,5R)-5-Cyclohexyl-2-(3-hydroxy-3-methyl-butyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
41. 3-[(2R,5R)-5-Cyclohexyl-2-(3-hydroxy-3-methyl-butyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
42. 3-[(2S,5R)-5-Cyclohexyl-2-((R)-3-hydroxy-butyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
43. 3-[(2R,5R)-5-Cyclohexyl-2-((R)-3-hydroxy-butyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
44. 3-((S)-6-Cyclohexyl-3-hydroxy-2-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
45. 3-[(2R,5R)-5-Cyclohexyl-2-(2-hydroxy-ethyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
46. 3-(6-Cyclohexyl-3-hydroxy-3-methyl-2-oxo-piperidin-1-yl)-5-p-tolyl-thiophene-2-carboxylic acid
47. 3-((R)-3-Cyclohexyl-5-oxo-1,9-dioxa-4-aza-spiro[5.5]undec-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
48. 3-[6-Cyclohexyl-3-(3-hydroxy-propyl)-2-oxo-piperidin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
49. 3-[(2S,5R)-5-Cyclohexyl-2-(2,3-dihydroxy-propyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
50. 3-[(2S,5R)-5-Cyclohexyl-2-(2-hydroxy-ethyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid

51. 3-((R)-5-Cyclohexyl-2-hydroxymethyl-3-oxo-morpholin-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
52. 3-[(2R,5R)-5-Cyclohexyl-2-(2,3-dihydroxy-propyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
53. 3-[(2S,5R)-5-Cyclohexyl-2-(2,3-dihydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
54. 3-[(2S,5R)-5-Cyclohexyl-2-(2-hydroxy-ethyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
55. 3-[6-Cyclohexyl-3-hydroxy-3-(3-hydroxy-propyl)-2-oxo-piperidin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
56. 3-[(2R,5R)-5-Cyclohexyl-2-(2,3-dihydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
57. 3-[(2R,5R)-5-Cyclohexyl-2-(2-hydroxy-ethyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
58. 3-[(2S,5R)-5-Cyclohexyl-2-(3-hydroxy-propyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
59. 3-((S)-6-Cyclohexyl-3-hydroxy-2-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
60. 3-[(2R,5R)-5-Cyclohexyl-2-(3-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
61. 3-[(2S,5R)-5-Cyclohexyl-2-(3-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
62. 3-[(2R,5R)-5-Cyclohexyl-2-((R)-2-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
63. 3-[(2R,5R)-5-Cyclohexyl-2-((S)-2-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
64. 3-[(S)-6-Cyclohexyl-3-(3-hydroxy-propyl)-2-oxo-piperidin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
65. 3-((S)-3-Amino-6-cyclohexyl-2-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid
66. 3-[(S)-6-Cyclohexyl-3-(2-hydroxy-ethyl)-2-oxo-piperidin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees centrigrade. If not

mentioned otherwise, all evaporations are performed under reduced pressure, typically between about 15 mm Hg and 100 mm Hg (= 20-133 mbar). The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, *e.g.*, microanalysis and spectroscopic characteristics, *e.g.*, MS, IR, NMR. Abbreviations used are those conventional in the art.

All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents, and catalysts utilized to synthesis the compounds of the present invention are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art (Houben-Weyl 4th Ed. 1952, Methods of Organic Synthesis, Thieme, Volume 21). Further, the compounds of the present invention can be produced by organic synthesis methods known to one of ordinary skill in the art as shown in the following examples.

LIST OF ABBREVIATIONS

Ac	acetyl
ACN	Acetonitrile
AcOEt / EtOAc	Ethyl acetate
AcOH	acetic acid
aq	aqueous
Ar	aryl
Bn	benzyl
Bu	butyl (nBu = n-butyl, tBu = tert-butyl)
CDI	Carbonyldiimidazole
CH_3CN	Acetonitrile
DBU	1,8-Diazabicyclo[5.4.0]-undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DIPEA	N-Ethyldiisopropylamine
DMAP	Dimethylaminopyridine
DMF	N,N'-Dimethylformamide
DMSO	Dimethylsulfoxide
EI	Electrospray ionisation
Et_2O	Diethylether
Et_3N	Triethylamine
Ether	Diethylether

EtOH	Ethanol
FC	Flash Chromatography
h	hour(s)
HATU	O-(7-Azabenzotriazole-1-yl)-N,N,N'N'-tetramethyluronium hexafluorophosphate
HBTU	O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HCl	Hydrochloric acid
HOBt	1-Hydroxybenzotriazole
HPLC	High Performance Liquid Chromatography
H_2O	Water
L	liter(s)
LC-MS	Liquid Chromatography Mass Spectrometry
Me	methyl
MeI	Iodomethane
MeOH	Methanol
mg	milligram
min	minute(s)
mL	milliliter
MS	Mass Spectrometry
Pd/C	palladium on charcoal
PG	protecting group
Ph	phenyl
Prep	Preparative
Rf	ratio of fronts
RP	reverse phase
Rt	Retention time
rt	Room temperature
SiO_2	Silica gel
TBAF	Tetrabutylammonium fluoride
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofurane
TLC	Thin Layer Chromatography

HPLC methods:

A. 4.6 mm x 150 mm C18 reverse phase column, 5.0 um particle size running a gradient of 5-95% MeCN/water (0.1% formic acid) over a period of 20 min at a flow rate of 1.5 mL/min at 30 °C. DAD-UV detection, 220-600 nm

B. 3 mm x 100 mm C18 reverse phase column, 3.0 um particle size running a gradient of 5-95% MeCN/water (0.1% formic acid) over a period of 7.45 min at a flow rate of 1 mL/min at 40 °C. DAD-UV detection, 220-600 nm.

C. 4.6 mm x 50 mm C18 reverse phase column, 5.0 um particle size running a gradient of 5-95% MeCN/water (0.1% formic acid) over a period of 3.4 min at a flow rate of 2 mL/min at 40 °C. DAD-UV detection, 220-600 nm.

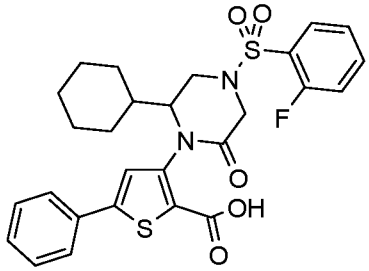
D. 4.6 mm x 50 mm C18 reverse phase column, 5.0 um particle size running a gradient of 5-95% MeCN/water (0.1% ammonium formate) over a period of 3.4 min at a flow rate of 2 mL/min at 40 °C. DAD-UV detection, 220-600 nm.

E. 3.0 mm x 33 mm C8 reverse phase column, 3.0 um particle size running a gradient of 5-95% MeCN/water (0.1% ammonium formate) over a period of 2.0 min at a flow rate of 2 mL/min at 50 °C. DAD-UV detection, 220-600 nm.

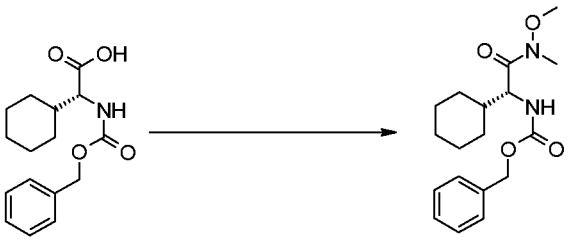
Procedures

Example 1

Synthesis of 3-[-2-Cyclohexyl-4-(2-fluoro-benzenesulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid [Compound 40]

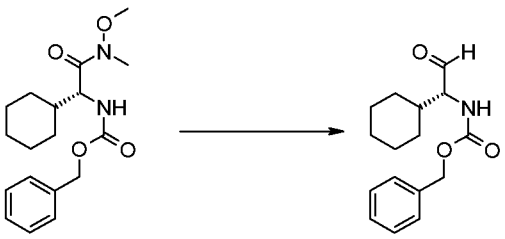


Step 1. Synthesis of [(R)-Cyclohexyl-(methoxy-methyl-carbamoyl)-methyl]-carbamic acid benzyl ester



To a solution of (R)-benzyloxycarbonylamino-cyclohexyl-acetic acid (25 g, 88 mmol) in DMF (100 mL) at -10 °C was added HATU (36.7 g, 96 mmol, 1.0 equiv) followed by N,O-dimethyl hydroxyamine HCl salt (10.3 g, 105 mmol, 1.2 equiv). To this solution was then slowly added N-methyl morpholine (28.9 mL, 263 mmol, 3.0 equiv). The internal temperature was carefully monitored. During the addition, the internal temperature rose to 0 °C. The solution was stirred at 0 °C for 2 hours after which the solution was diluted with EtOAc (500 mL) and washed with sat. aq. $NaHCO_3$ solution, water, 1.0 N aq. HCl solution and brine. The organic layer was dried over Na_2SO_4 and the solvent including DMF was removed under vacuum. The residue was diluted with EtOAc and the solution was washed with water, brine, dried ($MgSO_4$) and concentrated to give product [(R)-Cyclohexyl-(methoxy-methyl-carbamoyl)-methyl]-carbamic acid benzyl ester 26 g (yield 90 %).

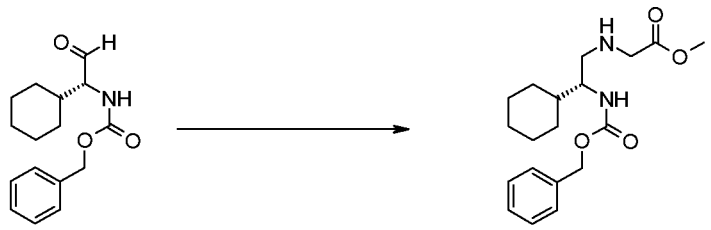
Step 2. Synthesis of ((R)-1-Cyclohexyl-2-oxo-ethyl)-carbamic acid benzyl ester



To a solution of [(R)-Cyclohexyl-(methoxy-methyl-carbamoyl)-methyl]-carbamic acid benzyl ester (27 g, 82 mmol) in THF (400 mL) at -20 °C was slowly added $LiAlH_4$ (4.06 g, 106 mmol, 1.3 equiv). $LiAlH_4$ was freshly ground from pellet purchased from Aldrich. During addition, the internal temperature was carefully monitored and did not rise above 0 °C. After addition the mixture was stirred at 0 °C and the reaction was monitored by TLC and LCMS. After 1 hour, the reaction solution was cooled at -10 °C and quenched by slow addition of sat. aq. $KHSO_4$ solution until pH=5. The mixture was partitioned between water and EtOAc. The phases were separated and the organic layer was concentrated. The residue was dissolved in EtOAc and the solution was washed with water, brine, dried over Na_2SO_4 and concentrated to

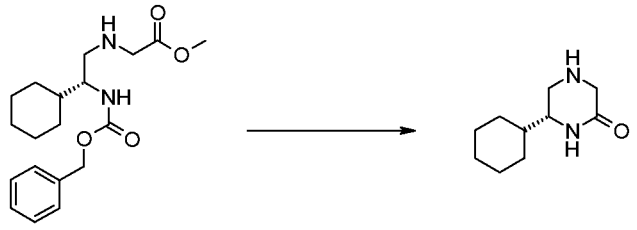
give product ((R)-1-Cyclohexyl-2-oxo-ethyl)-carbamic acid benzyl ester 22 g (99 %). The material was continued to next step with no further purification.

Step 3. Synthesis of ((R)-2-Benzyloxycarbonylamino-2-cyclohexyl-ethylamino)-acetic acid methyl ester



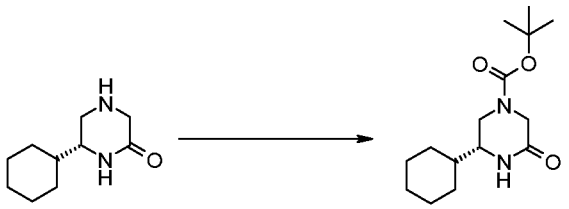
A solution of aldehyde (25 g, 91 mmol) in CH_2Cl_2 (350 mL) at 0 ^oC was added methyl glycine hydrochloride salt (22.8 g, 182 mmol, 2.0 equiv) followed by DIPEA (23.8 mL, 136 mmol, 1.5 equiv). To the solution was then added sodium triacetoxyborohydride (28.9 g, 136 mmol, 1.5 equiv). The mixture was stirred at room temperature for 3 hours. The reaction was quenched by addition of sat. aq. $NaHCO_3$ solution until pH=8. The phases were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with water, brine, dried ($MgSO_4$) and concentrated to give product ((R)-2-Benzyloxycarbonylamino-2-cyclohexyl-ethylamino)-acetic acid methyl ester (34 g, 107 % yield). The crude product which contained impurity and solvent was continued to the next step with no further purification.

Step 4. Synthesis of (R)-6-Cyclohexyl-piperazin-2-one



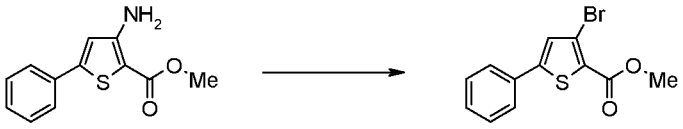
To a 2.0 L round bottom flask containing a solution of ((R)-2-Benzyloxycarbonylamino-2-cyclohexyl-ethylamino)-acetic acid methyl ester (27 g, 77 mmol) in MeOH (300 mL) under a stream of N_2 was added Pd (10% on carbon, 4.1 g , 0.05 equiv). The mixture was stirred under 1.0 atm of H_2 for 18 hours. The mixture was diluted with 100 mL of CH_2Cl_2 and filtered through Celite. The filtrate was concentrated to give crude product (R)-6-Cyclohexyl-piperazin-2-one 18 g (127 %). The product, which contained impurity and solvent, was continued to the next step with no further purification.

Step 5. Synthesis of (R)-3-Cyclohexyl-5-oxo-piperazine-1-carboxylic acid tert-butyl ester



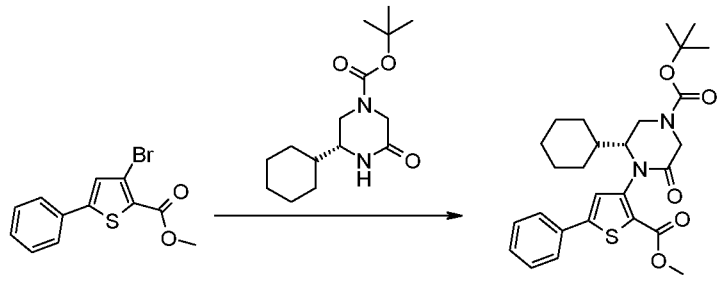
To a solution of (R)-6-Cyclohexyl-piperazin-2-one (7.3 g, 40 mmol) in CH_2Cl_2 (200 mL) was added $(Boc)_2O$ (10.5 g, 11.1 mmol, 1.2 equiv). The solution was stirred at room temperature for 1 hour, after which the solvent was removed under vacuum. The residue was purified by silica gel column chromatography (acetone/heptane, 40%). The collected fraction was concentrated until ~100 mL solvent left. The solid was filtered and dried to give product (R)-3-Cyclohexyl-5-oxo-piperazine-1-carboxylic acid tert-butyl ester 6.7 g (59 %). The ee of product was determined to be >98% by chiral SFC.

Step 6. Synthesis of 3-bromo-5-phenyl-thiophene-2-carboxylic acid methyl ester



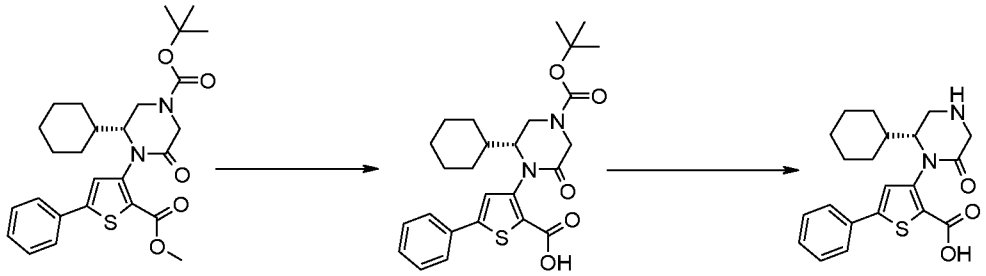
To a 250 round bottom flask equipped with refluxing condenser was added $CuBr_2$ (11.5 g, 51 mmol, 1.2 equiv), CH_3CN (250 mL) and t-butyl nitrite (6.63 g, 64.3 mmol, 1.5 equiv). The solution was heated at 65 ^oC and to this solution was added a solution of 3-amino-5-phenyl-thiophene-2-carboxylic acid methyl ester (10.0 g, 42.0 mmol) in CH_3CN (50 mL). The resulting mixture was heated at 65 ^oC for 1 hour. The reaction mixture was then cooled at room temperature and added to 1.0 N HCl aq. solution. EtOAc was added and the phases were separated. The aqueous layer was extracted with EtOAc. The organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel to give product 3-bromo-5-phenyl-thiophene-2-carboxylic acid methyl ester 7.5 g.

Step 7. Synthesis of (R)-3-Cyclohexyl-4-(2-methoxycarbonyl-5-phenyl-thiophen-3-yl)-5-oxo-piperazine-1-carboxylic acid tert-butyl ester



A tube was charged with *trans*-cyclohexanediamine (162 mg, 1.42 mmol, 0.5 equiv), K_2CO_3 (783 mg, 5.67 mmol, 2.0 equiv), 3-bromo-5-phenyl-thiophene-2-carboxylic acid methyl ester (1.01 g, 3.40 mmol, 1.2 equiv), CuI (270 mg, 1.42 mmol, 0.5 equiv), (R)-3-Cyclohexyl-5-oxo-piperazine-1-carboxylic acid tert-butyl ester (800 mg, 2.83 mmol, 1.0 equiv) and 1,4-dioxane (3.0 mL). The tube was then flushed with N_2 and sealed. The reaction mixtures were heated at 110 °C for 72 hours after which it was diluted with EtOAc and filtered. The filtrate was washed with 1.0 N HCl aq. solution, brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (EtOAc/heptane, 50 %) to give product (R)-3-Cyclohexyl-4-(2-methoxycarbonyl-5-phenyl-thiophen-3-yl)-5-oxo-piperazine-1-carboxylic acid tert-butyl ester 415 mg.

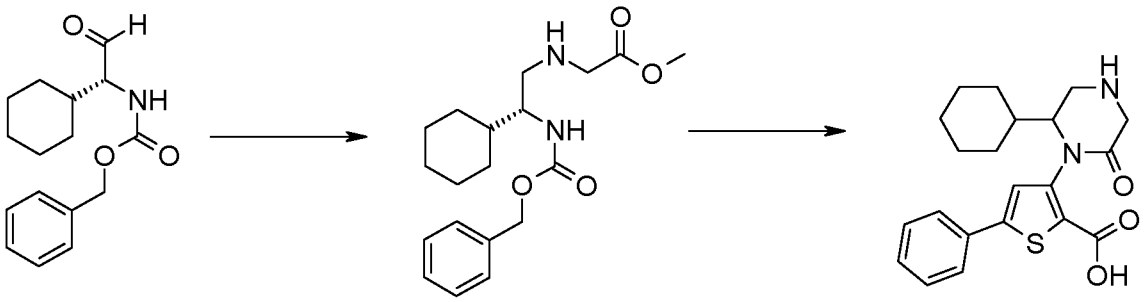
Step 8. Synthesis of 3-((R)-2-Cyclohexyl-6-oxo-piperazin-1-yl)-5-phenyl-thiophene-2-carboxylic acid



To a solution of (R)-3-Cyclohexyl-4-(2-methoxycarbonyl-5-phenyl-thiophen-3-yl)-5-oxo-piperazine-1-carboxylic acid tert-butyl ester (1.8 g, 3.6 mmol) in THF/water/MeOH (1/1/1, 30 mL) was added lithium hydroxide monohydrate (0.45 g, 10.8 mmol, 3.0 equiv) and the resulting solution was heated at 55 °C for 1 hour. The reaction was quenched by addition of 1.0 N HCl aq. solution until pH=5. The solution was then extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated to give (R)-4-(2-Carboxy-5-phenyl-thiophen-3-yl)-3-cyclohexyl-5-oxo-piperazine-1-carboxylic acid tert-butyl ester 3-((R)-2-Cyclohexyl-6-oxo-piperazin-1-yl)-5-phenyl-thiophene-2-carboxylic acid (1.7 g, 97 %). The material was continued to the next step with no further purification.

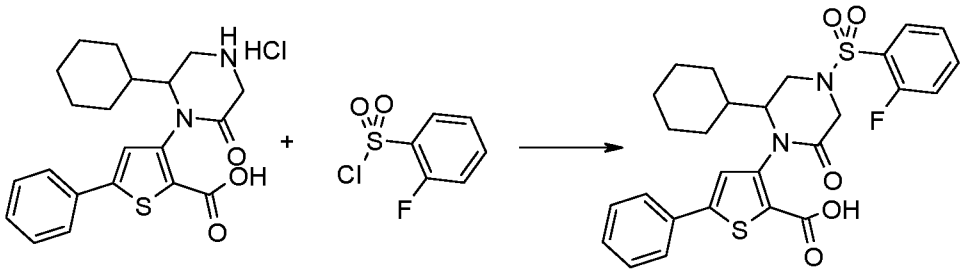
To a solution of (R)-4-(2-Carboxy-5-phenyl-thiophen-3-yl)-3-cyclohexyl-5-oxo-piperazine-1-carboxylic acid tert-butyl ester (1.7 g) in 1,4-dioxane (5.0 mL) was added a solution of 4.0 N HCl in dioxane (20 mL) and the resulting mixture was stirred at room temperature of 2 hours. The solvent was then removed under vacuum to give product as HCl salt (1.4 g, 95 %).

Step 9. Synthesis of racemic 3-(2-cyclohexyl-6-oxo-piperazin-1-yl)-5-phenyl-thiophene-2-carboxylic acid



To a solution of (R)-benzyloxycarbonylamino-cyclohexyl-acetic acid (15 g, 51.5 mmol) in CH_2Cl_2 (60 mL) at 0 °C was added N-methylmorpholine (12.5 mL, 113 mmol, 2.2 equiv) and at -25 °C isobutyl chloroformate (6.76 mL, 51.5 mmol, 1.0 equiv) was added. The resulting solution was stirred at –10 °C for 1 hour, after which to this solution was added a suspension N,O-dimethyl hydroxyamine HCl salt (5.52 g, 56.5 mmol, 1.1 equiv) in CH_2Cl_2 (60 mL). The mixture was then stirred at room temperature for 3 hours, after which the solution was diluted with EtOAc (500 mL) and washed with 1.0 N aq. HCl solution and brine. The organic layer was dried over Na_2SO_4 and concentrated. Racemic 3-(2-cyclohexyl-6-oxo-piperazin-1-yl)-5-phenyl-thiophene-2-carboxylic acid was synthesized from this material following step 2-8 described above.

Step 10. Synthesis of 3-[-2-Cyclohexyl-4-(2-fluoro-benzenesulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid

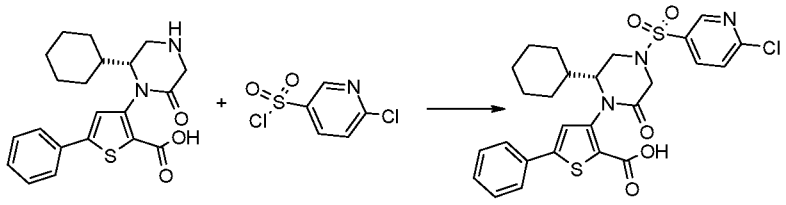


To a solution of 3-(2-cyclohexyl-6-oxo-piperazin-1-yl)-5-phenyl-thiophene-2-carboxylic acid (15.0 mg, 0.036 mmol, 1.0 equiv) in MeCN (0.2 mL) at room temperature, was added NaOH (0.40 mL, 1.5 N solution, 0.60 mmol, 16.7 equiv) and 2-fluoro-benzenesulfonyl chloride (11.4 mg, 0.059 mmol, 1.64 equiv). The mixture was stirred at room temperature for 30 minutes. The mixture was acidified with 3 N HCl (0.3 mL), and then diluted with EtOAc (10 mL). The mixture was washed with water (5 mL), brine (5 mL), then dried (over Na_2SO_4), filtered and the filtrate was concentrated under reduced pressure. The residue was purified by HPLC (0.1% NH_4OH) to give product (5.0 mg, 24 %) as white solid. MS: 543 [M-H$^+$]. ^{1}H-NMR (400 MH_Z,

$CDCl_3$): δ 1.12 (m, 3H), 1.34 (m, 1H), 1.45-1.90 (m, 7H), 2.70-2.87 (m, 2H), 3.34 (d, 1H), 3.60-3.70 (m, 2H), 3.95 (d, 1H), 4.18 (d, 1H), 7.13 (s, 1H), 7.21 (t, 1H), 7.27 (t, 1H), 7.30-7.40 (m, 3H), 7.51-7.61 (m, 3H), 7.83 (t, 1H).

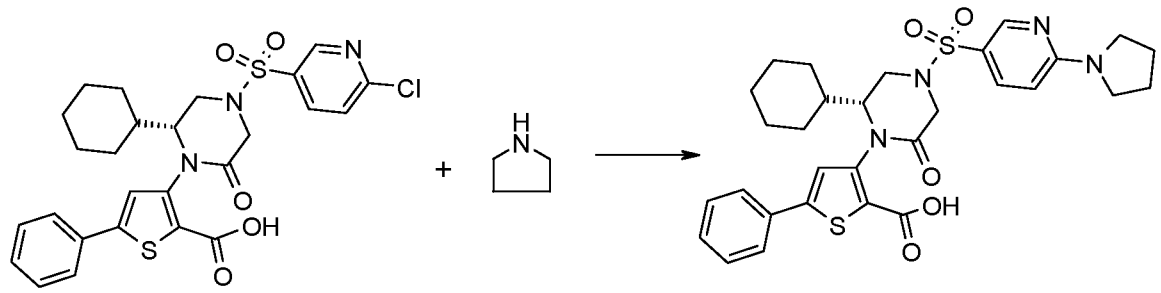
Example 2. Synthesis of 3-[(R)-2-Cyclohexyl-6-oxo-4-(6-pyrrolidin-1-yl-pyridine-3-sulfonyl)-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid [Compound 135]

Step 1. Synthesis of 3-[(R)-4-(6-Chloro-pyridine-3-sulfonyl)-2-cyclohexyl-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid



To a solution of 3-(2-cyclohexyl-6-oxo-piperazin-1-yl)-5-phenyl-thiophene-2-carboxylic acid (0.80 g, 1.90 mmol, 1.0 equiv) in MeCN (20 mL) at room temperature, was added 6-chloro-pyridine-3-sulfonyl chloride (1.10 g, 5.20 mmol, 2.7 equiv) and followed by NaOH (6.94 mL, 1.5 N solution, 10.4 mmol, 5.5 equiv) dropwise. The mixture was stirred at room temperature for 10 minutes. The mixture was acidified with 3 N HCl (2.5 mL), and then diluted with EtOAc (50 mL). The mixture was washed water (25 mL), brine (25 mL), dried (over Na_2SO_4), filtered and concentrated to give crude product (1.0 g, 94 %) as yellow-green solid. MS: 560 [M-H^+].

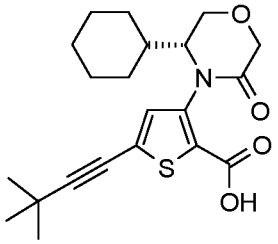
Step 2. Synthesis of 3-[(R)-2-Cyclohexyl-6-oxo-4-(6-pyrrolidin-1-yl-pyridine-3-sulfonyl)-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid



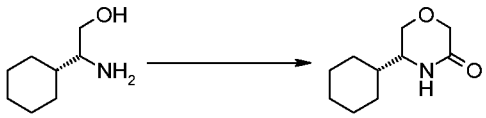
To a solution of 3-[(R)-4-(6-chloro-pyridine-3-sulfonyl)-2-cyclohexyl-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid (100 mg, 0.18 mmol, 1.0 equiv) in DMF (0.8 mL) at room temperature was added pyrrolidine (127 mg, 1.79 mmol, 10.0 equiv) and Et_3N (0.37 mL, 2.68 mmol, 15.0 equiv). The mixture was stirred at 70 °C for 2 hours. The mixture was then cooled

to room temperature and filtered. The filtrate was concentrated and purified by HPLC (0.1% NH_4OH) to give product (35 mg, 33 %) as white solid. MS: 595 [M-H^+]. ^{1}H-NMR (400 MH_Z, MeOD): δ 1.10-1.23 (m, 5H), 1.40-2.00 (m, 10H), 3.04-3.12 (m, 2H), 3.20 (t, 2H), 3.42 (d, 2H), 3.88 (d, 1H), 3.97 (br, 1H), 4.07 (d, 1H), 6.62 (s, 1H), 7.19 (s, 1H), 7.32 (t, 1H), 7.40 (t, 2H), 7.63 (d, 2H), 7.83 (m, 1H), 8.44 (d, 1H).

Example 3. Synthesis of 3-((R)-3-Cyclohexyl-5-oxo-morpholin-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid [Compound 236]

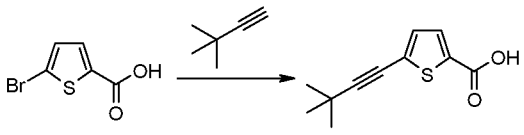


Step 1. Synthesis of (R)-5-Cyclohexyl-morpholin-3-one



To a solution containing 3.8 g (26.5 mmol, 1.0 equiv) of (R)-2-amino-2-cyclohexyl-ethanol in 100 mL of THF was added sodium hydride (1.4 g, 58.4 mmol, 60% in mineral oil, 2.2 equiv). The reaction mixture was stirred at 25 °C for 30 minutes, at which time hydrogen evolution had ceased. The mixture was cooled at 0 °C and was added ethyl chloroacetate (3.3 g, 26.5 mmol, 1.0 equiv), dropwise, over 5 minutes. The reaction mixture was stirred for 1 hour at 25 °C and then 2 hours at reflux. The solvent was removed under vacuum and to the residue was added 1.0 N HCl aq. solution until pH=6. The mixture was extracted with ethyl acetate. The resulting organic extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was recrystallized from EtOAc/heptane to give product 2.8 g. The mother liquid was concentrated and the residue was purified by silica gel column chromatography (acetone/heptane 50%) to give product 1.3 g. Combined yield 4.1 g (84%)

Step 2. Synthesis of 5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid



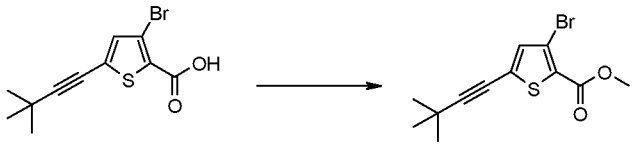
A 350 mL heavy wall round bottom flask was charged with TEA (33.7 mL, 24 mmol, 5.0 equiv), BINAP (3.0 g, 4.83 mmol, 0.1 equiv), 5-bromo-thiophene-2-carboxylic acid (48.3 mmol, 1.0 equiv), CuI (0.184 g, 0.97 mmol, 0.02 equiv), Pd_2dba_3 (2.2 g, 2.4 mmol, 0.05 equiv) and DMF (40.0 mL). The flask was flushed with N_2 and to the mixture was added t-butyl acetylene (15.8 g, 193 mmol, 4.0 equiv). The mixture was sealed and stirred at 70 °C for 48 hours. After cooled at room temperature, the reaction mixture was filtered and the filtrate was concentrated under vacuum. The residue was acidified with 3.0 N HCl until pH=4. The aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silical gel, EtOAc/heptane 5% to EtOAc/heptane 30% with 2% of AcOH to give product 6.5 g (yield 65%).

Step 3. Synthesis of 3-Bromo-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid



To a of solution of 5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid (6.5 g, 31.3 mmol, 1.0 equiv) in THF (150 mL) at -78 °C was added n-BuLi (44.9 mL, 1.6 M in heptane, 71.9 mmol, 2.3 equiv) and the resulting solution was stirred at -78 °C for 1 hour. To the solution was then added 1,2-dibromo-1,1,2,2-tetrafluoro-ethane (16.2 g, 62.5 mmol, 2.0 equiv) and the solution was allowed to warm to room temperature over 2 hours. The reaction was quenched by addition of sat. aq. NH_4Cl solution and the mixture was extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated. The crude material was continued to the next step with no further purification.

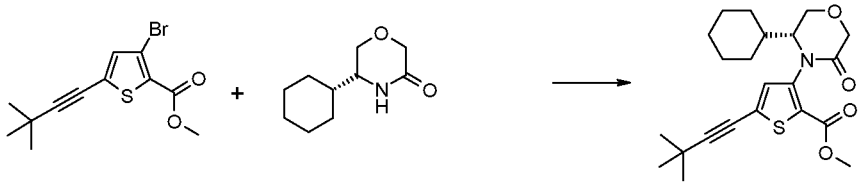
Step 4. Synthesis of 3-Bromo-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester



The product from previous step was dissolved in DMF (15.0 mL) and to the solution was added K_2CO_3 (8.6 g, 62.6 mmol, 2.0 equiv) and MeI (8.9 g, 62.6 mmol, 2.0 equiv). The resulting mixture was stirred at room temperature for 18 hours. The mixture was filtered and the filtrate

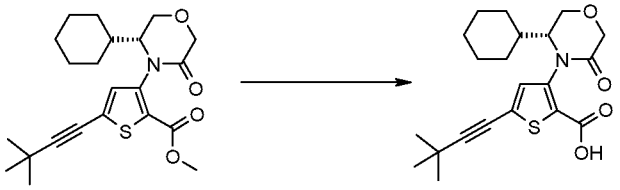
was concentrated under vacuum. The residue was purified by silica gel column chromatography, heptane/EtOAc 15% to give product 7.0 g (74% yield for 2 steps).

Step 5. Synthesis of 3-((R)-3-Cyclohexyl-5-oxo-morpholin-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester



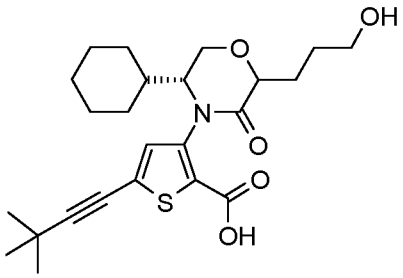
A heavy wall flask was charged with *trans*-cyclohexane diamine (623 mg, 5.5 mmol, 0.5 equiv), 3-bromo-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester (4.27 g, 14.2 mmol, 1.3 equiv), K_2CO_3 (3.02 g, 21.8 mmol, 2.0 equiv), CuI (1.04 g, 5.5 mmol, 0.5 equiv), 5-cyclohexyl-morpholin-3-one (2.0 g, 10.9 mmol, 1.0 equiv) and 1,4-dioxane (10.0 mL). The mixture was flushed with N_2 and stirred at 110 °C for 48 hours. The mixture was filtered through celite and the filtrate was concentrated under vacuum. The residue was purified by silica gel, EtOAc/heptane 50% to give product 2.8 g (yield 50%).

Step 6. Synthesis of 3-((R)-3-Cyclohexyl-5-oxo-morpholin-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid

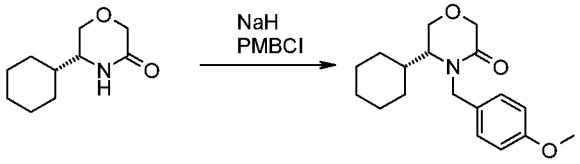


To a solution of methyl ester (35 mg, 0.087 mmol, 1.0 equiv) in THF (0.5 mL), MeOH (0.5 mL), water (0.5 mL) was added lithium hydroxide monohydrate (10.9 mg, 0.26 mmol, 3.0 equiv). The resulting mixture was stirred at 50 °C for 1 hour, after which the reaction was neutralized by addition of 1.0 N HCl aq. solution to pH=6. The mixture was extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by reverse phase HPLC to give product 18 mg (yield 53%). MS: 390.1 [$M+H^+$]. ^{1}H-NMR (400MHz, CD_3OD): 6.87(s, 1H), 4.19(s, 2H), 4.05(m, 2H), 3.82(s, 1H), 1.43-1.90(m, 6H), 1.06-1.39(m, 14H)

Example 4. Synthesis of 3-[(R)-5-Cyclohexyl-2-(3-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid [Compound 299]

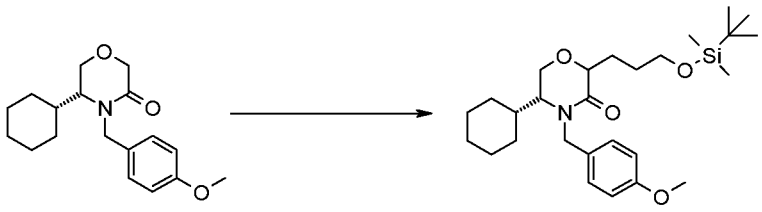


Step 1. Synthesis of cyclohexyl-4-(4-methoxy-benzyl)-morpholin-3-one



To a solution of 5-Cyclohexyl-morpholin-3-one (1.0 g, 5.5 mmol, 1.0 equiv) in DMF (15.0 mL) at 0°C was added NaH (0.26 g, 60% in oil, 6.5 mmol, 1.2 equiv) slowly. The mixture was stirred at room temperature for 30 minutes, then it was added PMBCl (0.94 g, 6.0 mmol, 1.1 equiv). After stirred at room temperature for 2 hours, the reaction mixture was quenched by added to sat. aq. NH_4Cl solution. The mixtures were extracted with EtOAc. The organic layers were combined and washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel, acetone/heptane 30% to give 1.5 g (91%) of 5-Cyclohexyl-4-(4-methoxy-benzyl)-morpholin-3-one.

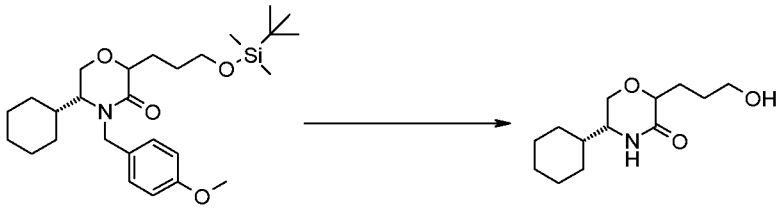
Step 2. Synthesis of 2-[3-(tert-Butyl-dimethyl-silanyloxy)-propyl]-5-cyclohexyl-4-(4-methoxy-benzyl)-morpholin-3-one



To a solution of 5-cyclohexyl-4-(4-methoxy-benzyl)-morpholin-3-one (700 mg, 2.3 mmol, 1.0 equiv) in THF (10.0 mL) at -78 °C was added n-BuLi (1.58 mL, 1.6 M in heptane, 2.54 mmol, 1.1 equiv). The resulting solution was stirred at -78 °C for 30 minutes, after which it was added a solution of tert-Butyl-(3-iodo-propoxy)-dimethyl-silane (693 mg, 2.3 mmol, 1.0 equiv) in THF (1.0 mL). The solution was stirred at -78 °C for 30 minutes and 2 hours at room temperature after which it was quenched by addition of sat. aq. NH_4Cl solution. The mixture was extracted with EtOAc. The organic layer was combined, dried over $MgSO_4$ and concentrated. The

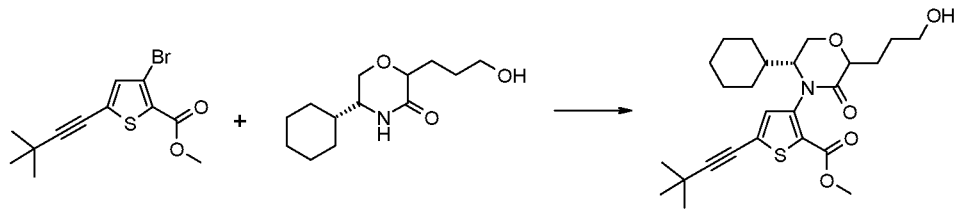
residue was purified by silica gel column chromatography, EtOAc/heptane 30% to give product 480 mg (yield 44%).

Step 3. Synthesis of 5-Cyclohexyl-2-(3-hydroxy-propyl)-morpholin-3-one



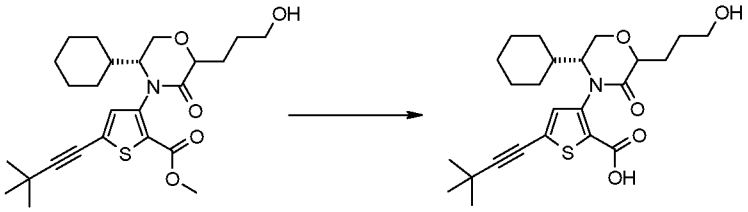
To a solution of 2-[3-(tert-Butyl-dimethyl-silanyloxy)-propyl]-5-cyclohexyl-4-(4-methoxy-benzyl)-morpholin-3-one (400 mg, 0.84 mmol, 1.0 equiv) in CH_3CN (0.3 mL) and water (0.3 mL) was added CAN (922 mg, 1.68 mmol, 2.0 equiv). The mixture was stirred at room temperature for 1 hour then second portion of CAN (900 mg) was added. After stirred at room temperature for 1 hour, the reaction mixture was diluted with EtOAc and the phases were separated. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography, EtOAc/heptane 50% to 100% EtOAc to give 5-cyclohexyl-2-(3-hydroxy-propyl)-morpholin-3-one 134 mg.

Step 4. Synthesis of 3-[(R)-5-Cyclohexyl-2-(3-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester



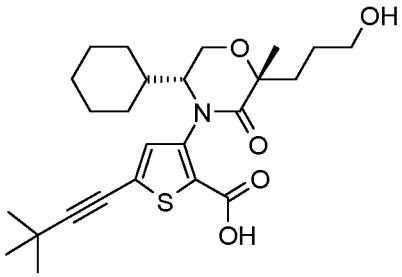
A 10 mL heavy wall vial was charged with *trans*-cyclohexane diamine (11.8 mg, 0.10 mmol, 0.5 equiv), 3-bromo-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester (125 mg, 0.41 mmol, 2.0 equiv), K_2CO_3 (57 mg, 0.41 mmol, 2.0 equiv), CuI (19.7 mg, 0.10 mmol, 0.5 equiv), 5-cyclohexyl-2-(3-hydroxy-propyl)-morpholin-3-one (50 mg, 0.21 mmol, 1.0 equiv) and 1,4-dioxane (0.5 mL). The mixture was flushed with N_2 and stirred at 110 ^oC for 24 hours. The mixture was filterd through celite and the filtrate was concentrated under vacuum. The residue was purified by silica gel, EtOAc/heptane 30% to give product 10 mg (yield 10%).

Step 5. Synthesis of 3-[(R)-5-Cyclohexyl-2-(3-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid

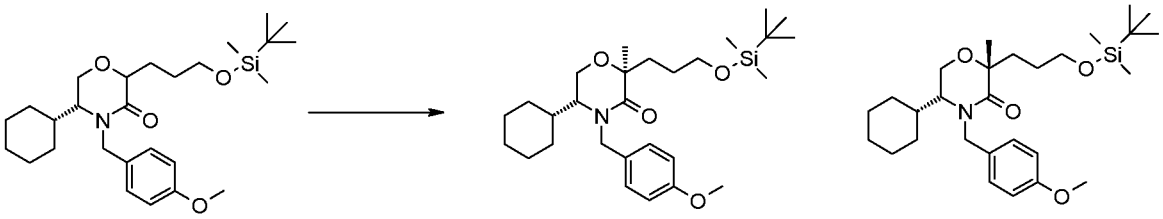


To a solution of methyl ester (10 mg, 0.022 mmol, 1.0 equiv) in THF (0.2 mL), MeOH (0.2 mL), water (0.2 mL) was added lithium hydroxide hydrate (4.5 mg, 0.11 mmol, 5.0 equiv). The resulting mixture was stirred at 50 °C for 30 minutes, after which the reaction was neutralized by addition of 1.0 N HCl aq. solution to pH=6. The mixture was extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by reverse phase HPLC to give product 2.6 mg. MS: 448.5 [$M+H^+$]

Example 5. Synthesis of 3-[(2R,5R)-5-Cyclohexyl-2-(3-hydroxy-propyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid [Compound 311]



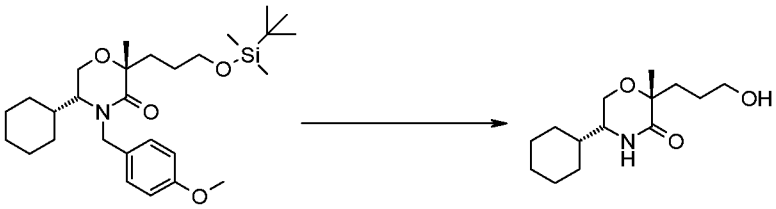
Step 1. (R)-2-[3-(tert-Butyl-dimethyl-silanyloxy)-propyl]-5-cyclohexyl-4-(4-methoxy-benzyl)-2-methyl-morpholin-3-one



To a solution of diisopropyl amine (138 mg, 1.36 mmol, 1.3 equiv) in THF (6.0 mL) at -78 °C was added n-BuLi (0.79 mL, 1.6 mL in heptane, 1.26 mmol, 1.2 equiv) and the resulting solution was stirred at -78 °C for 10 minutes. To the solution was added a solution of 2-[3-(tert-Butyl-dimethyl-silanyloxy)-propyl]-5-cyclohexyl-4-(4-methoxy-benzyl)-morpholin-3-one (500 mg, 1.05 mmol, 1.0 equiv) in THF (2 mL) and the solution was stirred at -78 °C for 30 mins. MeI was added and the solution was stirred at -78 °C for 1 hour then slowly warmed to room temperature

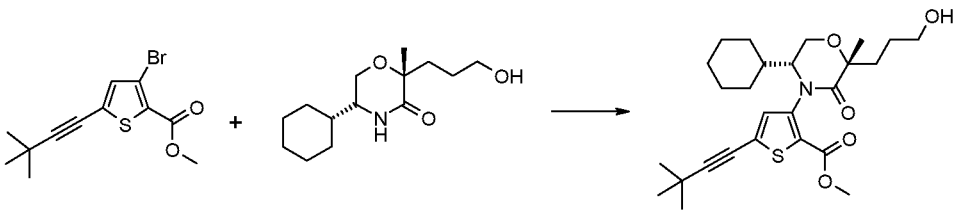
over 2 hours. The reaction was quenched by addition of sat. aq. NH_4Cl solution. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography, EtOAc/heptane 20% to give product (S)-2-[3-(tert-Butyl-dimethyl-silanyloxy)-propyl]-5-cyclohexyl-4-(4-methoxy-benzyl)-2-methyl-morpholin-3-one 110 mg and product (R)-2-[3-(tert-butyl-dimethyl-silanyloxy)-propyl]-5-cyclohexyl-4-(4-methoxy-benzyl)-2-methyl-morpholin-3-one 205 mg.

Step 2. Synthesis of (R)-5-cyclohexyl-2-(3-hydroxy-propyl)-2-methyl-morpholin-3-one



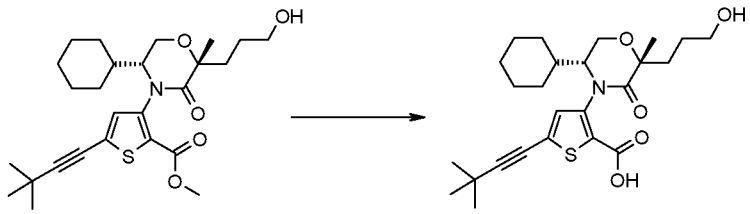
To a solution of TBS ether (200 mg, 0.41 mmol, 1.0 equiv) in CH_3CN (1.0 mL) and water (1.0 mL) was added CAN (461 mg, 0.82 mmol, 2.0 equiv). The mixture was stirred at room temperature for 1 hour then second portion of CAN (400 mg) was added. After stirred at room temperature for 1 hour, the reaction mixture was diluted with EtOAc and the phases were separated. The organic layer was washed with brine and dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography, EtOAc/heptane 50% to 100% EtOAc to give product 45 mg (43% yield).

Step 3. Synthesis of 3-[(2R,5R)-5-Cyclohexyl-2-(3-hydroxy-propyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester



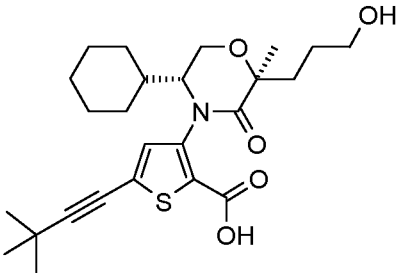
To a 10 mL vial was added *trans*-cyclohexane diamine (13.4 mg, 0.12 mmol, 1.0 equiv), 3-bromo-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester (70.8 mg, 0.24 mmol, 2.0 equiv), K_2CO_3 (32.5 mg, 0.24 mmol, 2.0 equiv), CuI (22 mg, 0.12 mmol, 1.0 equiv), (R)-5-cyclohexyl-2-(3-hydroxy-propyl)-2-methyl-morpholin-3-one (30 mg, 0.12 mmol, 1.0 equiv) and 1,4-dioxane (0.4 mL). The mixture was flushed with N_2 and stirred at 120 ^oC for 18 hours. The mixture was filterd through celite and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography, EtOAc/heptane 80% to give product 15 mg (yield 26%).

Step 4. Synthesis of 3-[(2R,5R)-5-Cyclohexyl-2-(3-hydroxy-propyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid



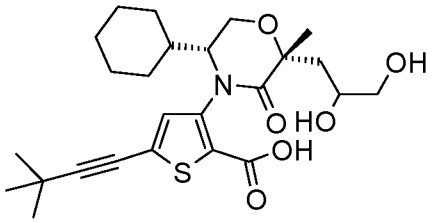
To a solution of methyl ester (15 mg, 0.032 mmol, 1.0 equiv) in THF (0.5 mL), MeOH (0.5 mL), water (0.5 mL) was added lithium hydroxide (3.8 mg, 0.16 mmol, 5.0 equiv). The resulting mixture was stirred at 50 ^{o}C for 30 minutes, after which the reaction was neutralized by addition of 1.0 N HCl aq. solution to pH=6. The mixture was extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by reverse phase HPLC to give product 4.3 mg (yield 29%). MW: 462.2 [M+H]. ^{1}H-NMR (400MHz, MeOD): δ 6.91(s, 1H), 4.23(d, 1H), 3.94(d, 1H), 3.62(m, 1H), 3.55(m, 2H), 1.96-1.52(m, 10H), 1.45(s, 3H), 1.32(s, 9H), 1.21 (m, 4H), 1.05 (m, 1H).

Example 6. Synthesis of 3-[(2S,5R)-5-Cyclohexyl-2-(3-hydroxy-propyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid [Compound 7]

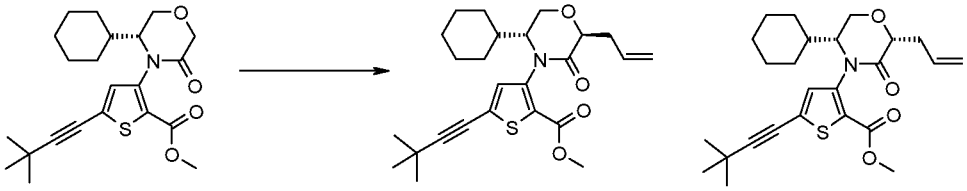


(S)-2-[3-(tert-Butyl-dimethyl-silanyloxy)-propyl]-5-cyclohexyl-4-(4-methoxy-benzyl)-2-methyl-morpholin-3-one from **Example 5 step 1** was carried on according to procedure in **Example 5 step 2-step 4** to provide 3-[(2S,5R)-5-Cyclohexyl-2-(3-hydroxy-propyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid. MS: 462.2[M+H$^+$]. ^{1}H-NMR (400MHz, CD_3OD): δ 6.93(s, 1H), 4.12(d, 1H), 3.91(d, 1H), 3.66(s, 1H), 3.54(t, 2H), 2.14(m, 1H), 1.91(m, 1H), 1.44-1.85(m, 8H), 1.41(s, 3H), 1.06-1.37(m, 14H).

Example 7. Synthesis of 3-[(2R,5R)-5-Cyclohexyl-2-(2,3-dihydroxy-propyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid [Compound 330]

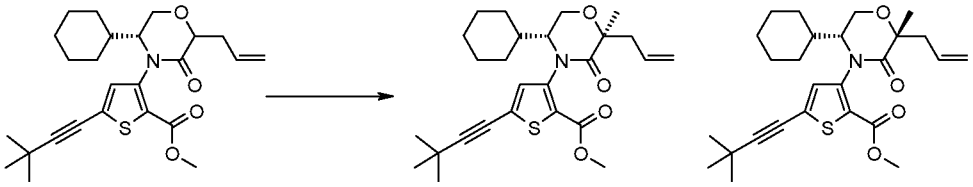


Step 1. Synthesis of 3-((R)-2-Allyl-5-cyclohexyl-3-oxo-morpholin-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester



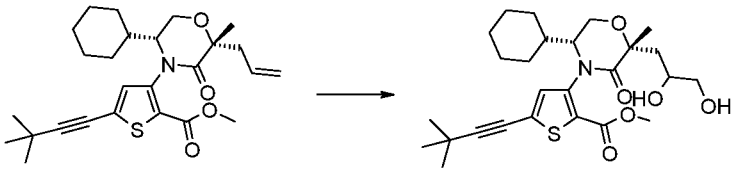
To a solution of 3-((R)-3-Cyclohexyl-5-oxo-morpholin-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester (600 mg, 1.49 mmol, 1.0 equiv) in THF (5.0 mL) at -78 ^{o}C was added LDA (0.82 mL, 2.0 M in THF, 1.64 mmol, 1.1 equiv) and the resulting solution was stirred at -78 ^{o}C for 20 minutes. To the solution was then added allyliodide (300 mg, 1.78 mmol, 1.2 equiv). The solution was warmed to room temperature and stirred at this temperature for 30 minutes. The reaction was quenched by addition of sat. aq. NH_4Cl solution. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography, EtOAc/heptane 25% to give 3-((2S,5R)-2-Allyl-5-cyclohexyl-3-oxo-morpholin-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl 140 mg, 3-((2R,5R)-2-Allyl-5-cyclohexyl-3-oxo-morpholin-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester 60 mg and mixed fraction 200 mg.

Step 2. Synthesis of 3-((2S,5R)-2-Allyl-5-cyclohexyl-2-methyl-3-oxo-morpholin-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester and product 3-((2R,5R)-2-Allyl-5-cyclohexyl-2-methyl-3-oxo-morpholin-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester



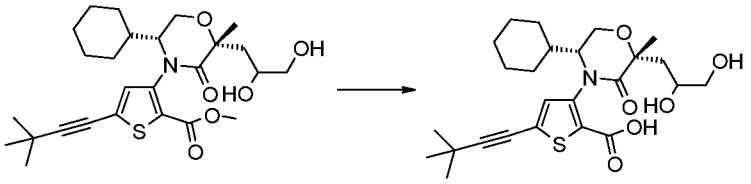
To a solution of 3-((R)-2-Allyl-5-cyclohexyl-3-oxo-morpholin-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester (120 mg, 0.27 mmol, 1.0 equiv) in THF (1.0 mL) at -78 °C was added LDA (0.16 mL, 2.0 M in THF, 0.32 mmol, 1.2 equiv) and the resulting solution was stirred at -78 °C for 20 minutes. To the solution was then added methyliodide (192 mg, 1.35 mmol, 5.0 equiv). The solution was warmed to room temperature and the stirred at this temperature for 30 minutes. The reaction was quenched by addition of sat. aq. NH_4Cl solution. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography, EtOAc/heptane 25% to give product 3-((2S,5R)-2-Allyl-5-cyclohexyl-2-methyl-3-oxo-morpholin-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester 18 mg and product 3-((2R,5R)-2-Allyl-5-cyclohexyl-2-methyl-3-oxo-morpholin-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester 50 mg.

Step 3. Synthesis of 3-[(2R,5R)-5-Cyclohexyl-2-(2,3-dihydroxy-propyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester



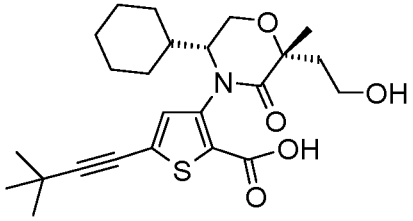
To a solution of 3-((2R,5R)-2-Allyl-5-cyclohexyl-2-methyl-3-oxo-morpholin-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester (0.40 g, 0.87 mmol, 1.0 equiv) in acetone (6.0 mL) was sequentially added N-methylmorpholine oxide (0.31 g, 2.63 mmol, 3.0 equiv), water (2.0 mL) and OsO_4 (0.44 g, 0.044 mmol, 0.05 equiv, 2.5wt% in t-butanol) at 0 °C. The mixture was stirred at room temperature for 60 minutes, after which the reaction was quenched by adding brine solution (0.5 mL) and EtOAc (10 mL). The organic layer was separated, dried (over Na_2SO_4) and concentrated. The crude material was continued to the next step with no further purification.

Step 4. Synthesis of 3-[(2R,5R)-5-Cyclohexyl-2-(2,3-dihydroxy-propyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid

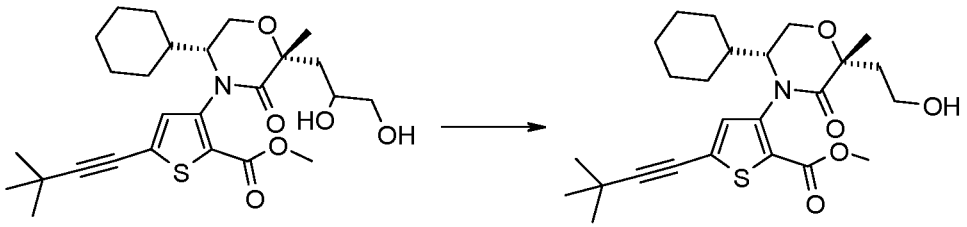


3-[(2R,5R)-5-Cyclohexyl-2-(2,3-dihydroxy-propyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester from the previous step was dissolved in 4.0 ml of THF and 0.3 mL of solution was taken out for the reaction. To the stirred solution was added THF (0.3 mL), MeOH (0.3 mL), water (0.3 mL), and $LiOH \bullet H_2O$ (25.6 mg, 0.61 mmol, 10.0 equiv) and the resulting solution was stirred at room temperature for 30 minutes. The reaction was quenched by addition of 3.0 N HCl aqueous solution until pH=5. To the solution was then added EtOAc and the phases were separated. The aqueous layer was extracted by EtOAc. The organic layers were combined, dried (over Na_2SO_4) and concentrated. The residue was purified by HPLC (0.1% NH_4OH, MeCN/H_2O, 10%-90%) to give product (11 mg, 37.7% yield) as white solid. MS: 478 [$M-H^+$].

Example 8. Synthesis of 3-[(2R,5R)-5-Cyclohexyl-2-(2-hydroxy-ethyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid [Compound 323]

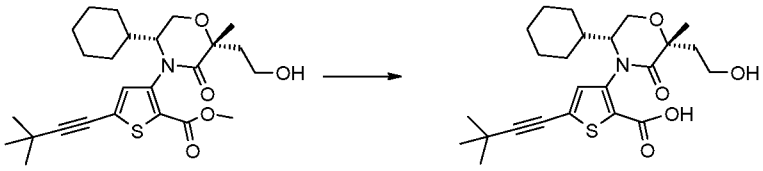


Step 1. Synthesis of 3-[(2R,5R)-5-Cyclohexyl-2-(2-hydroxy-ethyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester



3-[(2R,5R)-5-Cyclohexyl-2-(2,3-dihydroxy-propyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester from Example 7 Step 3 was dissolved in 4 ml THF, and 3.7 mL solution was taken out for the reaction. To the stirred solution was added THF (2.3 mL), water (2.0 mL), and then sodium periodate (0.28 g, 1.31 mmol, 1.6 equiv) at 0 °C. The resulting solution was stirred at room temperature for 30 minutes. And then at 0 °C another portion of sodium periodate (0.09 g, 0.44 mmol, 0.5 equiv) was added to the mixture and stirred for another 30 minutes at room temperature. The reaction was quenched by adding brine solution (0.5 mL) and EtOAc (10 mL). The organic layer was separated, dried (over Na_2SO_4) and concentrated. The residue was dissolved in ethanol (6.0 mL) and to the resulting solution at 0 °C was added sodium borohydride (0.27 g, 7.0 mmol, 8.8 equiv). The mixture was stirred at 0 °C for 15 minutes after which the reaction was quenched by adding water (2.0 mL) and EtOAc (10 mL). The organic layer was separated, dried (over Na_2SO_4) and concentrated to give product 128 mg (yield 35%). The crude product was continued to the next step with no further purification. MS: 462 [M-H^+].

Step 2. Synthesis of 3-[(2R,5R)-5-Cyclohexyl-2-(2-hydroxy-ethyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid

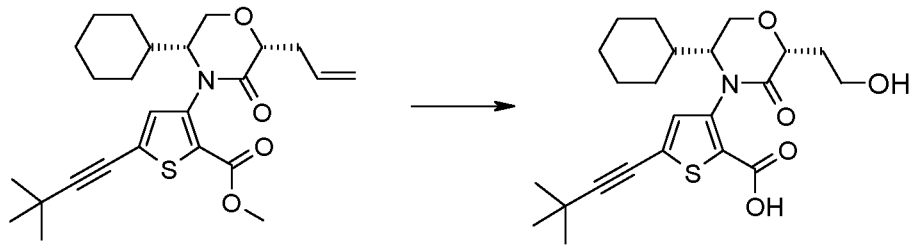


To a solution of methyl ester (128 mg, 0.28 mmol, 1.0 equiv) in THF (2.0 mL), MeOH (1.0 mL) and water (1.0 mL) was added $LiOH \bullet H_2O$ (93 mg, 2.22 mmol, 8.0 equiv) and the resulting solution was stirred at room temperature for 30 minutes. The reaction was quenched by addition of 3.0 N HCl aqueous solution until pH=5. To the solution was then added EtOAc and the phases were separated. The aqueous layer was extracted by EtOAc. The organic layers were combined and dried (over Na_2SO_4) and then concentrated. The residue was

purified by HPLC (0.1% NH_4OH, MeCN/H_2O, 10%-90%) to give product (87 mg, 78.2% yield) as white solid. MS: 448.3 [M+H$^+$]. ^{1}H-NMR (400MHz, CD_3OD): 6.87(s, 1H), 4.24(tert, 1H), 3.93(d, 1H), 3.62-3.82(m, 3H), 2.08-2.21(m, 1H), 1.88-2.04(m, 2H), 1.56-1.87(m, 4H), 1.43-1.56(m, 4H), 0.98-1.35(m, 14H)

Example 9. Synthesis of 3-[(2R,5R)-5-Cyclohexyl-2-(2-hydroxy-ethyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid [Compound 8]

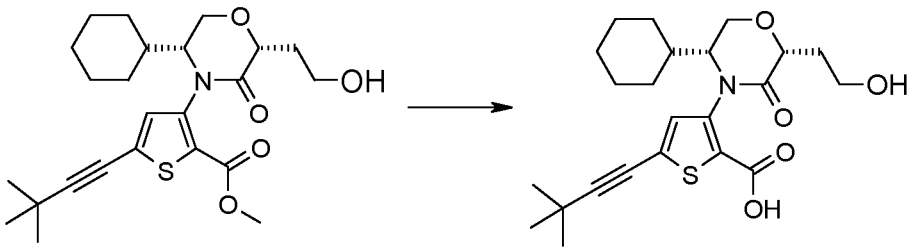
Step 1. Synthesis of 3-[(2R,5R)-5-Cyclohexyl-2-(2-hydroxy-ethyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester



To a solution of 3-((2R,5R)-2-Allyl-5-cyclohexyl-3-oxo-morpholin-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester (0.20 g, 0.45 mmol, 1.0 equiv) in acetone (3.0 mL) was sequentially added N-methylmorpholine oxide (0.160 g, 1.35 mmol, 3.0 equiv), water (1.0 mL) and OsO_4 (0.22 g, 0.023 mmol, 0.05 equiv, 2.5wt% in t-butanol) at 0 °C. The mixture was stirred at room temperature for 60 minutes, after which the reaction was quenched by adding brine solution and EtOAc. The organic layer was separated, dried (over Na_2SO_4) and concentrated. The crude material was continued to the next step with no further purification.

The crude material from previous step was dissolved in 3.0 ml THF and water (1.0 mL) and to the solution was added sodium periodate (0.19 g, 0.92 mmol, 2.0 equiv) at 0 °C. The resulting solution was stirred at room temperature for 30 minutes after which brine solution and EtOAc was added. The organic layer was separated, dried (over Na_2SO_4) and concentrated. The residue was dissolved in ethanol (3.0 mL) and to the resulting solution at 0 °C was added sodium borohydride (0.136 g, 3.6 mmol, 8.0 equiv). The mixture was stirred at 0 °C for 15 minutes after which the reaction was quenched by adding water (2.0 mL) and EtOAc (10 mL). The organic layer was separated, dried (over Na_2SO_4) and concentrated to give product 45 mg (yield 22%). The crude product was continued to the next step with no further purification.

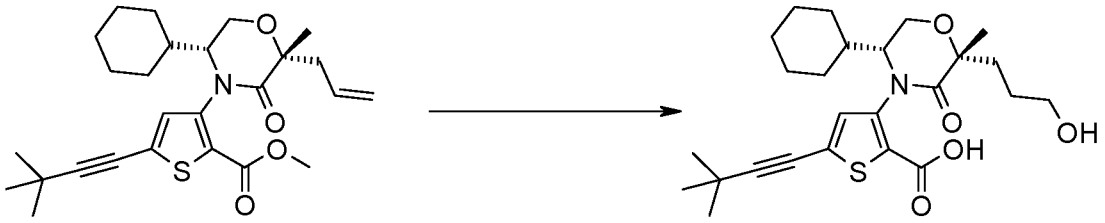
Step 2. Synthesis of 3-[(2R,5R)-5-Cyclohexyl-2-(2-hydroxy-ethyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid



To a solution of methyl ester (45 mg, 0.10 mmol, 1.0 equiv) in THF (2.0 mL), MeOH (1.0 mL) and water (1.0 mL) was added LiOH•H_2O (33 mg, 0.8 mmol, 8.0 equiv) and the resulting solution was stirred at room temperature for 30 minutes. The reaction was quenched by addition of 3.0 N HCl aqueous solution until pH=5. To the solution was then added EtOAc and the phases were separated. The aqueous layer was extracted by EtOAc. The organic layers were combined and dried (over Na_2SO_4) and then concentrated. The residue was purified by reverse phase HPLC to give product (25 mg, 57% yield) as white solid.

MS: 434.2 [M+H^+]. ^{1}H-NMR (400MHz, CD_3OD): δ 6.90(s, 1H), 4.24(tert, 1H), 4.13(d, 1H), 4.01(tert, 1H), 3.73(d, 1H), 3.71(d, 1H), 3.66(t, 1H), 2.21(m,1H), 1.41-1.98(m, 8H), 1.05-1.37(m, 15H).

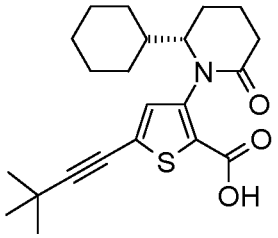
Example 10. Synthesis of 3-[(2R,5R)-5-Cyclohexyl-2-(3-hydroxy-propyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid [Compound 311]



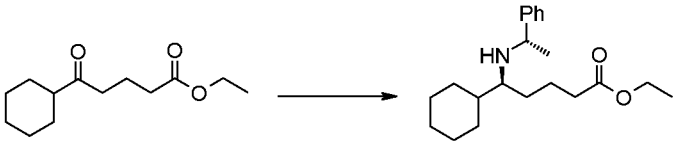
To a solution of 3-((2R,5R)-2-allyl-5-cyclohexyl-2-methyl-3-oxo-morpholin-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester (50 mg, 0.11 mmol, 1.0 equiv) in THF (1.0 mL) was added 9-BBN (0.5 M solution in THF, 0.55 ml, 0.27 mmol, 2.5 equiv) at 0 °C. The reaction mixture was then stirred at room temperature for 2 hours. To the solution was then cooled in an ice water bath and was added EtOH, followed by aq. NaOH solution and H_2O_2 aq. solution. During addition the reaction internal temperature was kept between 5 °C and 10 °C. The reaction mixture was then heated to reflux for 90 minutes. After cooled at room temperature, the reaction mixture was extracted with EtOAc. The organic layer was dried over

Na_2SO_4 and concentrated *in vacuo*. The residue was purified by prep-HPLC to give the product 26 mg. MW: 462.2 $[M+H]^+$. ^{1}H-NMR (400MHz, MeOD): δ 6.91(s, 1H), 4.23(d, 1H), 3.94(d, 1H), 3.62(m, 1H), 3.55(m, 2H), 1.96- 1.52(m, 10H), 1.45(s, 3H), 1.32(s, 9H), 1.21 (m, 4H), 1.05(m, 1H).

Example 11. Synthesis of 3-((S)-2-Cyclohexyl-6-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid [Compound 35]



Step 1. Synthesis of (S)-5-Cyclohexyl-5-((S)-1-phenyl-ethylamino)-pentanoic acid ethyl ester



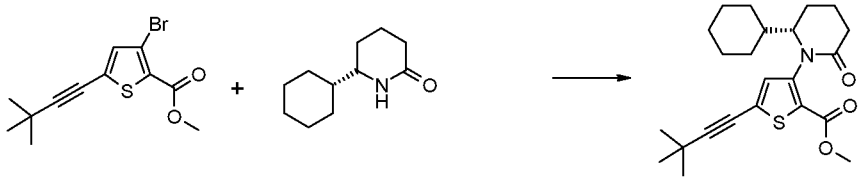
A solution of $TiCl_4$ in DCM (8.8 mL, 1.0 M solution in DCM, 8.8 mmol, 0.5 equiv) was added dropwisely to a vigorously stirred ice cooled solution of s-methyl benzyl amine (2.78 g, 23.0 mmol, 1.3 equiv) and TEA (10.7 g, 106 mmol, 6.0 equiv) in DCM (50 mL). The solution was heated to reflux and 5-Cyclohexyl-5-oxo-pentanoic acid ethyl ester (4.0 g, 17.6 mmol, 1.0 equiv) was added over 1 minute. The solution was then heated at reflux for 2 hours, after which, it was cooled to room temperature and diluted with ether, filtered through Celite. The cloudy solution was washed with sat. aq. $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated. The residue was dissolved in EtOH (40.0 mL) and at -78 °C was added $NaBH_4$. After stirred at 30 minutes, the reaction mixture was warmed to 0 °C and stirred at 0 °C for 30 minutes. To the solution was then added 6.0 N aq. HCl solution until pH=3. The organic solvent was removed under vacuum and the residue was basified with sat. aq. $NaHCO_3$ until pH=9. The mixture was extracted with EtOAc and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel, EtOAc/heptane 0-15% to give product 2.3 g (yield 39%) as the major product which eluted from the column first.

Step 2. Synthesis of (S)-6-Cyclohexyl-piperidin-2-one



To a solution of (S)-5-Cyclohexyl-5-((S)-1-phenyl-ethylamino)-pentanoic acid ethyl ester (2.0 g, 6.0 mmol, 1.0 equiv) in MeOH (60 mL) was added Pd (1.6 g, 10% on carbon, 1.51 mmol, 0.25 equiv) and ammonium formate (3.8 g, 60.3 mmol, 10.0 equiv). The mixture was heated to reflux for 2 hours. The solution was then cooled at room temperature and filtered through Celite. The filtrate was concentrated and the residue was purified by silica gel column chromatography, acetone/heptane 50% to give product 1.05 g (96% yield).

Step 3. Synthesis of 3-((S)-2-Cyclohexyl-6-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester



To a 10 mL vial was added *trans*-cyclohexane diamine (283 mg, 2.5 mmol, 0.5 equiv), 3-Bromo-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester (2.24 g, 7.4 mmol, 1.5 equiv), K_2CO_3 (1.37 g, 9.9 mmol, 2.0 equiv), CuI (473 mg, 2.5 mmol, 0.5 equiv), (S)-6-Cyclohexyl-piperidin-2-one (900 mg, 5.0 mmol, 1.0 equiv) and 1,4-dioxane (5.0 mL). The mixture was flushed with N_2 and stirred at 110 °C for 48 hours. The mixture was filtered through Celite and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography, EtOAc/heptane 30% to give product 800 mg (yield 40%).

Step 4. Synthesis of 3-((S)-2-Cyclohexyl-6-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid

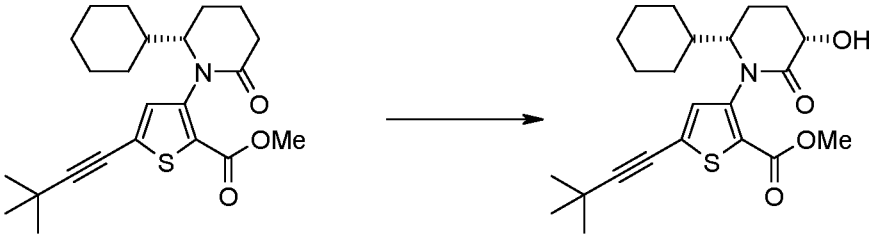


To a solution of methyl ester (10 mg, 0.025 mmol, 1.0 equiv) in THF (0.3 mL), MeOH (0.3 mL), water (0.3 mL) was added lithium hydroxide monohydrate (5.2 mg, 0.12 mmol, 5.0 equiv). The resulting mixture was stirred at 50 °C for 1 hour, after which the reaction was neutralized by addition of 1.0 N HCl aq. solution to pH=6. The mixture was extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated. The residue

was purified by reverse phase HPLC to give product 6.0 mg (yield 62%). MW: 388.4 $[M+H]^+$. ^{1}H-NMR (400MHz, MeOD): δ 7.03(s, 1H), 3.81(m, 1H), 2.25(m, 1H), 1.88-1.38(m, 6H), 1.29(s, 9H), 1.18(m, 4H), 1.06 (m, 4H).

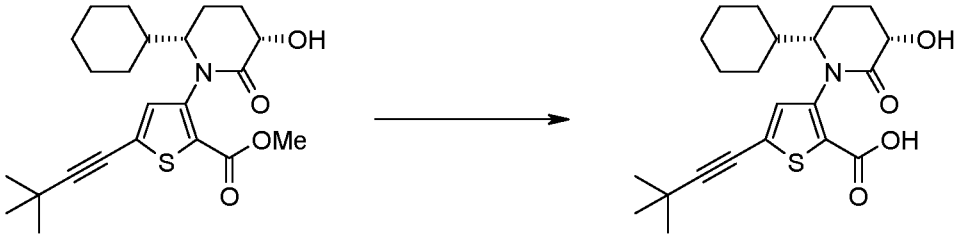
Example 12. Synthesis of 3-((S)-Amino-6-cyclohexyl-2-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid: [Compound 322]

Step1. Synthesis of 3-((3S,6S)-6-Cyclohexyl-3-hydroxy-2-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester



To a solution of 3-((S)-2-cyclohexyl-6-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester (3.2 g, 7.97 mmol, 1,0 equiv) in THF (15.0 ml) was added NaHMDS (1.0 M in THF) at -78°C and the resulting solution was stirred at -78°C for 1.5 hours. To this solution was then added a solution of (S)-(+)-(camphorsulfonyl)oxaziridine (3.65 g, 15.94 mmol, 2.0 equiv) in THF (10 ml) and the reaction mixture was stirred at -78°C for 3 hours. The reaction was quenched by addition of sat. NH_4Cl aq. solution. The mixture was extracted with EtOAc and the combined organic layer was dried over Na_2SO_4, and concentrate. The residue was purified by silica gel column chromatography, (Et_2O/DCM 5%~40%) to give 1.5 g of the desired product (yield 45%). MS: 418 $[M+H^+]$

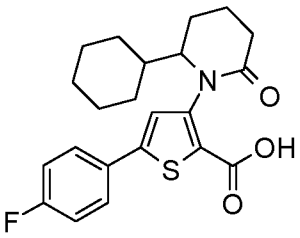
Step 2. Synthesis of 5-(3,3-Dimethyl-but-1-ynyl)-3-[(3S,6S)-6-(1-ethyl-pentyl)-3-hydroxy-2-oxo-piperidin-1-yl]-thiophene-2-carboxylic acid



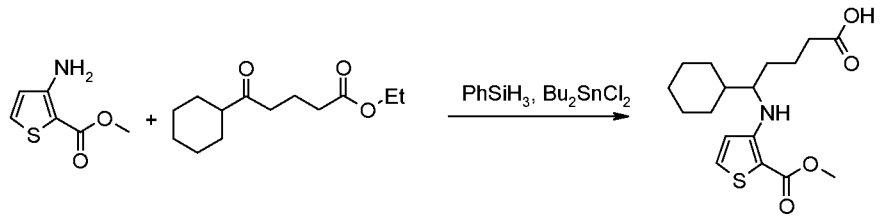
To a solution of 3-((3S,6S)-6-Cyclohexyl-3-hydroxy-2-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester (1.5 g, 3.59 mmol, 1 equiv.) in THF/H_2O/MeOH (5.0 mL/5.0 mL/1.0 mL) was added $LiOH \cdot H_2O$ (0.79 g, 17.56 mmol, 5.0 equiv.)

at room temperature. The reaction mixture was stirred at 50 °C for 20 minutes. The reaction was then acidified to pH=5 by addition of 3.0 N HCl aq. solution and the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4, and concentrated. The residue was purified by prep-HPLC(XBridge Prep C 18 5 um, 30×50 mm) in basic condition (0.1% NH_4OH, 10%~45% CH_3CN/H_2O, 10 min run, 40 ml/min) to give 850 mg of product (yield 57%). MS: 404 [M+H$^+$]. ^{1}H-NMR (400MHz, MeOD): δ 6.95(s, 1H), 4.09(m, 1H), 3.74(m, 1H), 2.09(m, 1H), 1.94-1.67(m, 8H), 1.38(m, 1H), 1.33(s, 9H), 1.17(m, 5H).

Example 13. Synthesis of 3-(2-Cyclohexyl-6-oxo-piperidin-1-yl)-5-(4-fluoro-phenyl)-thiophene-2-carboxylic acid [Compound 70]

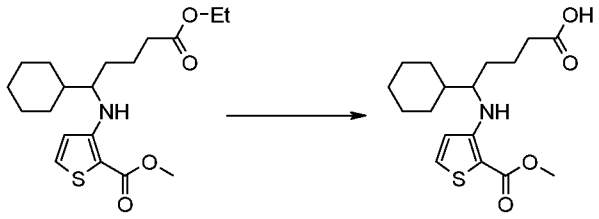


Step 1. Synthesis of 3-(1-Cyclohexyl-4-ethoxycarbonyl-butylamino)-thiophene-2-carboxylic acid methyl ester



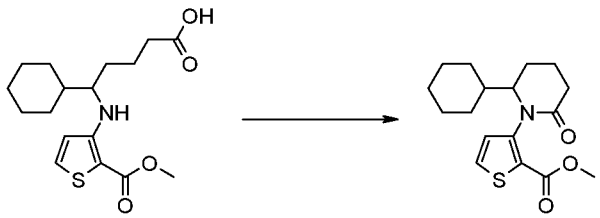
A flask was charged with 3-amino-thiophene-2-carboxylic acid methyl ester (600 mg, 3.82 mmol, 1.0 equiv), 5-cyclohexyl-5-oxo-pentanoic acid ethyl ester (864 mg, 3.82 mmol, 1.0 equiv), phenyl silane (496 mg, 4.58 mmol, 1.2 equiv), dibutyltin dichloride (116 mg, 0.38 mmol, 0.1 equiv) and dioxane (3.0 mL). The resulting solution was heated at 60 °C for 18 hours. The solution was then concentrated and the residue was purified by silica gel column chromatography, CH_2Cl_2/heptane 30% to 100%, to give 3-(1-Cyclohexyl-4-ethoxycarbonyl-butylamino)-thiophene-2-carboxylic acid methyl ester 810 mg (yield 57%).

Step 2. Synthesis of 3-(4-Carboxy-1-cyclohexyl-butylamino)-thiophene-2-carboxylic acid methyl ester



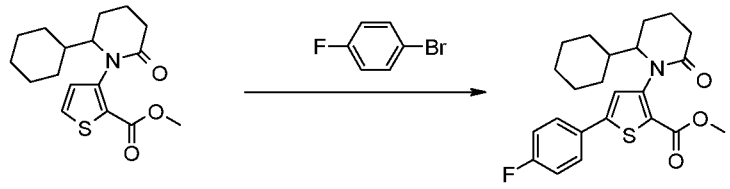
To a solution of methyl ester (300 mg, 0.82 mmol, 1.0 equiv) in THF (1.0 mL), MeOH (1.0 mL), water (1.0 mL) was added lithium hydroxide (58.6 mg, 2.45 mmol, 3.0 equiv). The resulting mixture was stirred at room temperature for 4 hours, after which the organic solvent was removed under vacuum. The resulted solution was neutralized by addition of 1.0 N HCl aq. solution until pH=6. The mixture was extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4 and concentrated to give desired carboxylic acid.

Step 3. Synthesis of 3-(2-Cyclohexyl-6-oxo-piperidin-1-yl)-thiophene-2-carboxylic acid methyl ester



To a solution of carboxylic acid (700 mg, 2.06 mmol, 1.0 equiv) in toluene (30 .0 mL) was added pyridine (816 mg, 10.3 mmol, 5.0 equiv) at 0 °C followed by thionyl chloride (245 mg, 2.06 mmol, 1.0 equiv). The solution was stirred at 0 °C for 1 hour. The reaction was quenched by addition of sat. aq. NH_4Cl solution. The mixture was extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel, heptane/EtOAc 1/1 to give product 350 mg (yield 53%).

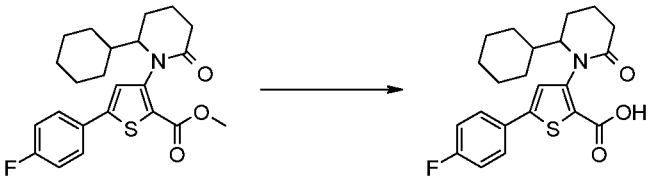
Step 4. Synthesis of 3-(2-Cyclohexyl-6-oxo-piperidin-1-yl)-5-(4-fluoro-phenyl)-thiophene-2-carboxylic acid methyl ester



A 5 mL vial was charged with 3-(2-cyclohexyl-6-oxo-piperidin-1-yl)-thiophene-2-carboxylic acid methyl ester (32 mg, 0.10 mmol, 1.0 equiv), 1-bromo-4-fluoro benzene (17 mg, 0.10 mmol, 1.0 equiv), potassium carbonate (20.6 mg, 0.15 mmol, 1.5 equiv), tricyclophenylphosphine tetrafluroborate (8.7 mg, 0.024 mmol, 0.24 equiv), $Pd(OAc)_2$ (2.7 mg, 0.012 mmol, 0.12 equiv),

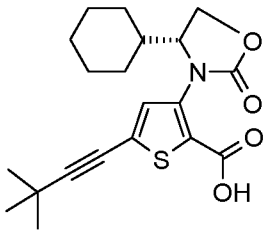
pivalic acid (6.1 mg, 0.060 mmol, 0.6 equiv) and DMA (0.3 mL). The resulted mixture was flushed with nitrogen and stirred at 100 °C for 18 hours. The mixture was loaded to silica gel column and flushed with EtOAc/heptane 67% to give product 27 mg (yield 65%).

Step 5. Synthesis of 3-(2-Cyclohexyl-6-oxo-piperidin-1-yl)-5-(4-fluoro-phenyl)-thiophene-2-carboxylic acid

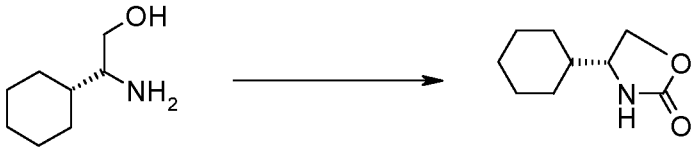


To a solution of methyl ester (20 mg, 0.048 mmol, 1.0 equiv) in THF (0.5 mL), EtOH (0.2 mL), water (0.5 mL) was added lithium hydroxide monohydrate (19 mg, 0.48 mmol, 10.0 equiv). The resulting mixture was stirred at 55 °C for 3 hours, after which the mixture was concentrated under vacuum. The residue was purified by reverse phase HPLC to give product 15.0 mg (yield 78%).

Example 14: Synthesis of 3-((R)-4-Cyclohexyl-2-oxo-oxazolidin-3-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid [Compound 181]

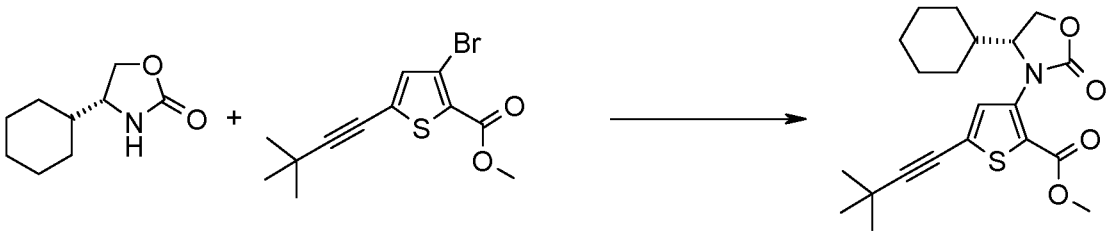


Step 1. Synthesis of (R)-4-Cyclohexyl-oxazolidin-2-one



To a solution of (R)-2-Amino-2-cyclohexyl-ethanol·HCl salt (1.0 g, 5.57 mmol, 1.0 equiv) in CH_2Cl_2 (30.0 mL) at 0 °C was added DIPEA (1.94 mL, 11.1 mmol, 2.0 equiv) followed by triphosgene (4.95 g, 16.7 mmol, 3.0 equiv) and the resulting solution was stirred at room temperature for 12 hours. The solution was then concentrated and the residue was diluted with EtOAc. The solution was washed with water, brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography, (EtOAc 100%) to give product 520 mg.

Step 2. Synthesis of 3-((R)-4-Cyclohexyl-2-oxo-oxazolidin-3-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester



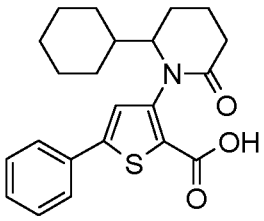
A heavy wall flask was charged with *trans*-cyclohexane diamine (18.9 mg, 0.17 mmol, 0.5 equiv), 3-bromo-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester (100 mg, 0.332 mmol, 1.0 equiv), K_2CO_3 (92m g, 0.664 mmol, 2.0 equiv), CuI (31.6 mg, 0.166 mmol, 0.5 equiv), (R)-4-cyclohexyl-oxazolidin-2-one (56.2 mg, 0.332 mmol, 1.0 equiv) and 1,4-dioxane (0.5 mL). The mixture was flushed with N_2 and stirred at 110 °C for 18 hours, after which the mixture was filtered through celite and the filtrate was concentrated under vacuum. The residue was purified by silica gel, EtOAc/heptane 30% to give product 54 mg (yield 42%).

Step 3. Synthesis of 3-((R)-4-Cyclohexyl-2-oxo-oxazolidin-3-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid

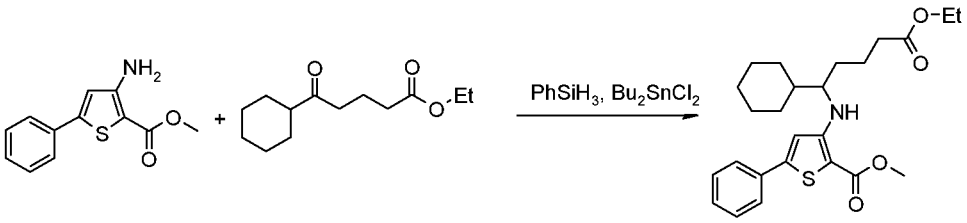


To a solution of methyl ester (50 mg, 0.128 mmol, 1.0 equiv) in THF (0.5 mL), MeOH (0.5 mL), water (0.5 mL) was added lithium hydroxide monohydrate (16.2 mg, 0.38 mmol, 3.0 equiv). The resulting mixture was stirred at 50 °C for 1 hour, after which the reaction was neutralized by addition of 1.0 N HCl aq. solution to pH=6. The mixture purified directly by reverse phase HPLC to give product 28 mg (yield 58%). MS: 376.4 [$M+H^+$].

Example 15. Synthesis of 3-(2-Cyclohexyl-6-oxo-piperidin-1-yl)-5-phenyl-thiophene-2-carboxylic acid [Compound 4]

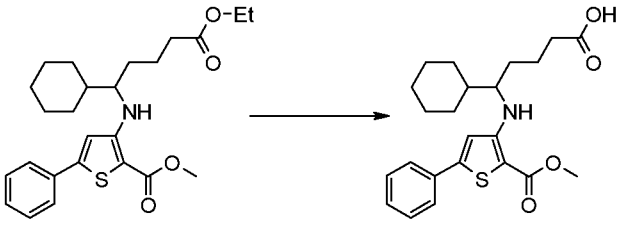


Step 1. Synthesis of 3-(1-Cyclohexyl-4-ethoxycarbonyl-butylamino)-5-phenyl-thiophene-2-carboxylic acid methyl ester



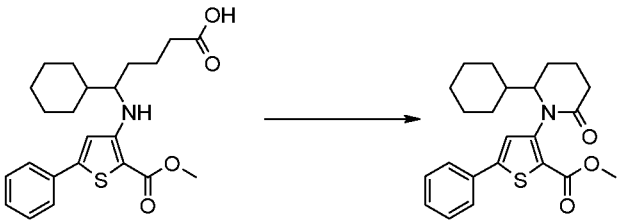
A flask was charged with 3-amino-5-phenyl-thiophene-2-carboxylic acid methyl ester (515 mg, 2.2 mmol, 1.0 equiv), 5-cyclohexyl-5-oxo-pentanoic acid ethyl ester (500 mg, 2.2 mmol, 1.0 equiv), phenyl silane (240 mg, 2.2 mmol, 1.0 equiv), dibutyltin dichloride (67 mg, 0.22 mmol, 0.1 equiv) and dioxane (2.0 mL). The resulting solution was heated at 120 °C with microwave for 2 hours. The solution was then concentrated and the residue was purified by silica gel column chromatography, EtOAc/heptane 5% to 40%, to give oil that contained starting material. The material was further purified with silica gel column chromotography, EtOH/DCM 2%to 10% to give product 150 mg (yield 15%).

Step 2. Synthesis of 3-(4-Carboxy-1-cyclohexyl-butylamino)-5-phenyl-thiophene-2-carboxylic acid methyl ester



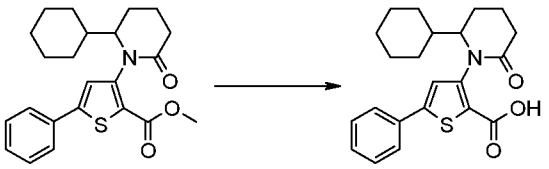
To a solution of 3-(1-Cyclohexyl-4-ethoxycarbonyl-butylamino)-5-phenyl-thiophene-2-carboxylic acid methyl ester (40 mg, 0.09 mmol, 1.0 equiv) in THF (0.4 mL), EtOH (0.2 mL), water (0.4 mL) was added lithium hydroxide (18.9 mg, 0.45 mmol, 5.0 equiv). The resulting mixture was stirred at 50 °C for 2 hours, after which the organic solvent was removed under vacuum. The resulted solution was neutralized by addition of 1.0 N HCl aq. solution until pH=6. The mixture was extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4 and concentrated to product 30 mg (yield 83%).

Step 3. Synthesis of 3-(2-Cyclohexyl-6-oxo-piperidin-1-yl)-5-phenyl-thiophene-2-carboxylic acid methyl ester



To a vial containing a solution of 3-(4-Carboxy-1-cyclohexyl-butylamino)-5-phenyl-thiophene-2-carboxylic acid methyl ester (40 mg, 0.096 mmol, 1.0 equiv) in 1,2-dioxane (1.0 mL) was added pyridine (3.8 mg, 0.048 mmol, 0.5 equiv) and Boc_2O (25 mg, 0.166 mmol, 1.2 equiv). The vial was then sealed and heated at 65 °C for 18 hours. The solution was concentrated and the residue was purified by silica gel column chromatography, EtOAc/Heptane 5% to 100% to give product 15 mg (yield 39%).

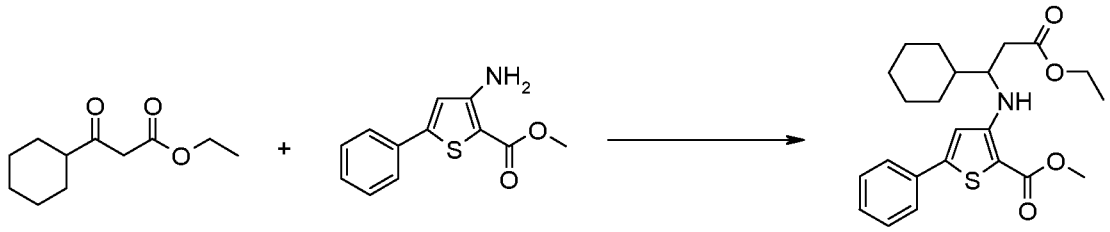
Step 4. Synthesis of 3-(2-Cyclohexyl-6-oxo-piperidin-1-yl)-5-phenyl-thiophene-2-carboxylic acid



To a solution of methyl ester (15 mg, 0.038 mmol, 1.0 equiv) in THF (0.2 mL), EtOH (0.2 mL), water (0.1 mL) was added lithium hydroxide monohydrate (7.9 mg, 0.19 mmol, 5.0 equiv). The resulting mixture was stirred at 50 °C for 2 hours, after which the mixture was concentrated under vacuum. The residue was purified by reverse phase HPLC to give product 5.0 mg (yield 35%). MW: 384.1 $[M+H]^+$. ^{1}H-NMR (400MHz, $CDCl_3$): δ 7.43(m, 2H), 7.21(m, 3H), 6.94(m, 1H), 3.68(m, 1H), 2.45(m, 2H), 2.21(m, 1H), 1.83-1.51 (m, 12H), 1.32(m, 2H).

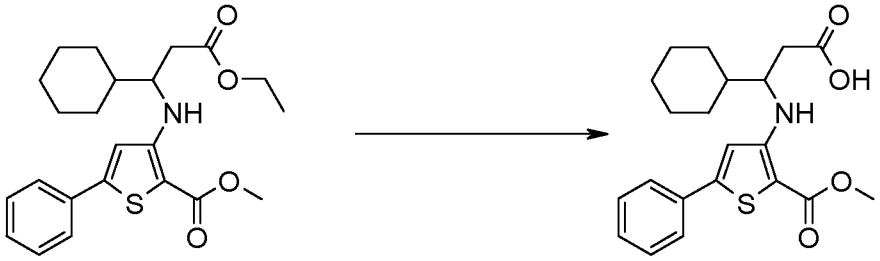
Example 16. Synthesis of 3-(2-Cyclohexyl-4-hydroxy-6-oxo-piperidin-1-yl)-5-phenyl-thiophene-2-carboxylic acid methyl ester [Compound 12]

Step 1. 3-(1-Cyclohexyl-2-ethoxycarbonyl-ethylamino)-5-phenyl-thiophene-2-carboxylic acid methyl ester



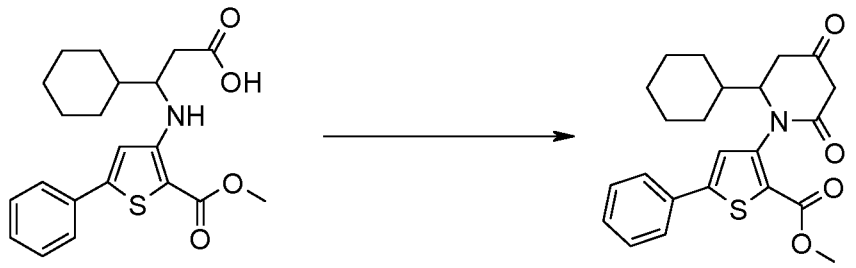
To a solution of 3-Cyclohexyl-3-oxo-propionic acid ethyl ester (1.0 g, 5.0 mmol, 1.0 equiv) in THF (5.0 mL) was added 3-Amino-5-phenyl-thiophene-2-carboxylic acid methyl ester (1.17 g, 5.0 mmol, 1.0 equiv) and $SnBu_2Cl_2$ (0.15 g, 0.50 mmol, 0.1 equiv) at room temperature. After stirred at room temperature for 5 minutes, the solution was added $PhSiH_3$. The resulting reaction mixture was stirred at 65 °C under N_2 for 18 hours, after which the solution was concentrated under vacuum and the residue was purified by silica gel column chromatography EtOAc/heptane, 10-60% to give product (0.7 g). MS: 416 [$M+H^+$].

Step 2. 3-(2-Carboxy-1-cyclohexyl-ethylamino)-5-phenyl-thiophene-2-carboxylic acid methyl ester



To a solution of 3-(1-cyclohexyl-2-ethoxycarbonyl-ethylamino)-5-phenyl-thiophene-2-carboxylic acid methyl ester (300 mg, 0.72 mmol, 1.0 equiv) in THF (2.0 mL), EtOH (1.0 mL) and water (2.0 mL) was added $LiOH\bullet H_2O$ (152 mg, 3.6 mmol, 5.0 equiv). The mixture was stirred at 55 °C for 20 minutes. The organic solvent was then evaporated. To the resulting solution was added 3.0 N HCl aq. solution until pH=5~6. The solid was then collected by filtration and washed with water. The filtrate was extracted with EtOAc and the organic layer was washed with sat. $NaHCO_3$ aq. solution, brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude material was continued to the next step with no further purification.

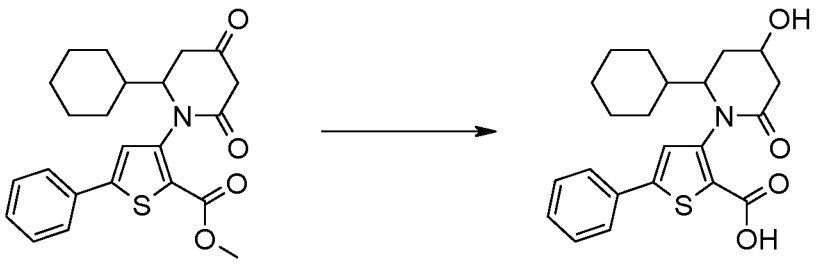
Step 3. Synthesis of 3-(2-Cyclohexyl-4,6-dioxo-piperidin-1-yl)-5-phenyl-thiophene-2-carboxylic acid methyl ester



To a solution of 3-(2-carboxy-1-cyclohexyl-ethylamino)-5-phenyl-thiophene-2-carboxylic acid methyl ester (200 mg, 0.52 mmol, 1.0 equiv) in DCM (1.0 mL) was added EDC (148 mg, 0.77 mmol, 1.5 equiv), DMAP (95 mg, 0.77 mmol, 1.5 equiv), and Meldrum's acid (75 mg, 0.52 mmol, 1.0 equiv) at 0 °C. The mixture was then warmed to room temperature and stirred at this temperature for 3 hours. To the reaction mixture was then added sat. $NaHSO_4$ aq. solution. The mixture was extracted with DCM and the organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was continued to the next step with no further purification.

The crude product from previous step (240 mg 0.47 mmol, 1.0 equiv) was dissolved in EtOAc (5.0 mL) and the resulting solution was heated to reflux for 2 hours. To the mixture was then added sat. aq. $NaHSO_4$ solution at room temperature. The mixture was extracted with DCM and the organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/Heptane 10%~60%) to give product (160 mg). MS: 412 [$M+H^+$]

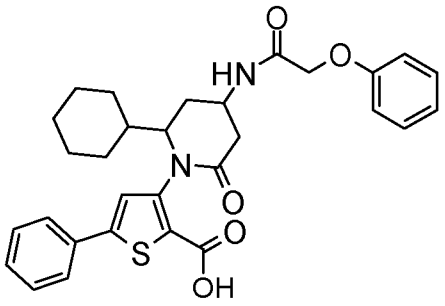
Step 4. Synthesis of 3-(2-Cyclohexyl-4-hydroxy-6-oxo-piperidin-1-yl)-5-phenyl-thiophene-2-carboxylic acid methyl ester



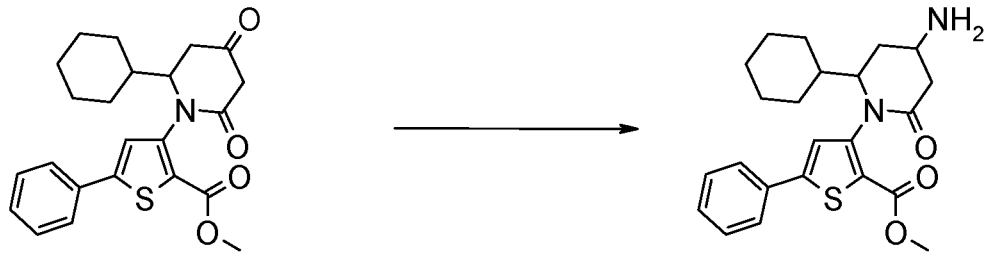
To a stirred solution of 3-(2-Cyclohexyl-4,6-dioxo-piperidin-1-yl)-5-phenyl-thiophene-2-carboxylic acid methyl ester (60 mg, 0.15 mmol, 1.0 equiv.) in anhydrous DCM (1.0 mL) was added $NaBH_4$ (11 mg, 0.29 mmol, 2 equiv) and AcOH (0.8 mg, 0.01 mmol, 0.1 equiv) at 0 °C. The reaction mixture was then stirred at room temperature for 4 hours after which the reaction was quenched by addition of water. The mixture was extracted with DCM. The organic layer was washed with

sat. aq. $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/heptane, 10%~60%) to give product 15 mg. The product was dissolved in THF (0.2 mL), EtOH (0.1 mL) and water (0.2 mL). To the solution was added $LiOH\bullet H_2O$ (7.6 mg, 0.18 mmol, 5 equiv) and the resulting mixture was stirred at 55 ^oC for 1 hour. The organic solvent was then evaporated and to the resulting solution was added 1.0 N HCl aq. solution until pH=4. The solution was extracted with EtOAc, and the organic layer was washed with sat. $NaHCO_3$ aqueous solution, brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by HPLC to give product 4 8 mg. MS: 400 [$M+H^+$].

Example 17. Synthesis of 3-(4-Benzoylamino-2-cyclohexyl-6-oxo-piperidin-1-yl)-5-phenyl-thiophene-2-carboxylic acid [Compound 21]



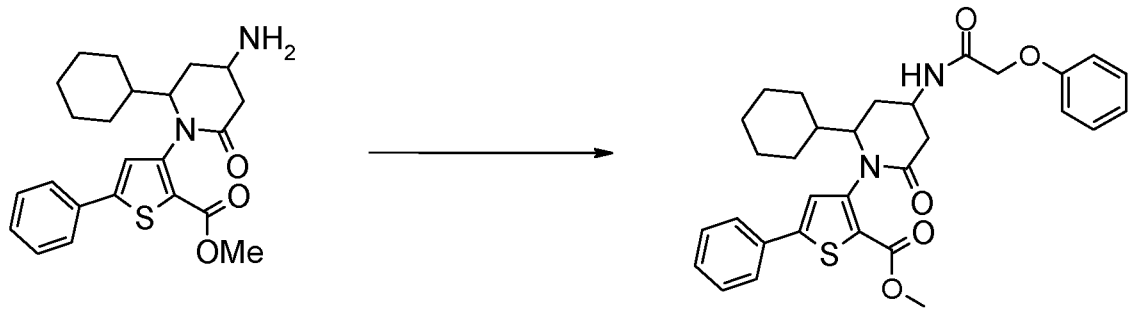
Step 1. Synthesis of 3-(4-Amino-2-cyclohexyl-6-oxo-piperidin-1-yl)-5-phenyl-thiophene-2-carboxylic acid methyl ester



To a solution of 3-(2-cyclohexyl-4,6-dioxo-piperidin-1-yl)-5-phenyl-thiophene-2-carboxylic acid methyl ester (400 mg, 0.98 mmol, 1.0 equiv) in MeOH (2.0 mL) was added NH_4OAc (375 mg, 4.86 mmol, 5 equiv) and the resulting solution was stirred at room temperature for 18 hours. The reaction mixture was concentrated *in vacuo* and the residue was dissolved MeOH. To the solution was added $NaCNBH_3$ (247 mg, 1.16 mmol, 1.2 equiv) and HOAc (56 mg, 0.97 mmol, 1 equiv). The resulting mixture was stirred at room temperature for 18 hours. The solvent was then removed *in vacuo*. To the residue was added sat. aq. $NaHCO_3$ solution until pH>8. The

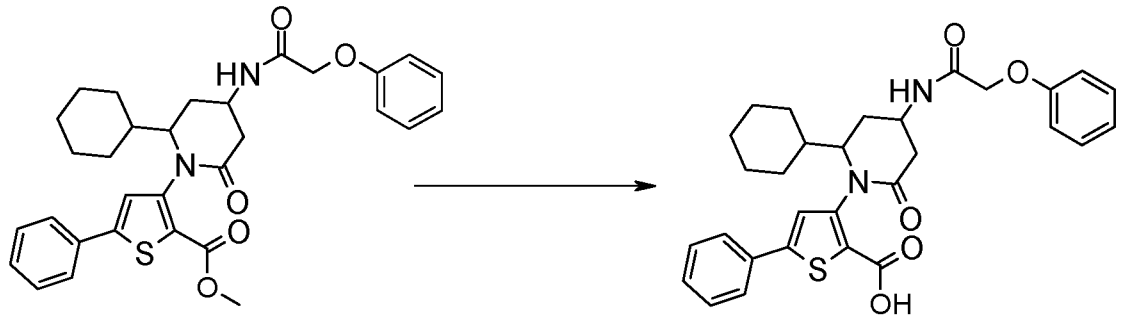
mixture was extracted with DCM. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was continued to the next step with no further purification.

Step 2. Synthesis of 3-[2-Cyclohexyl-6-oxo-4-(2-phenoxy-acetylamino)-piperidin-1-yl]-5-phenyl-thiophene-2-carboxylic acid methyl ester



To a solution of 3-(4-amino-2-cyclohexyl-6-oxo-piperidin-1-yl)-5-phenyl-thiophene-2-carboxylic acid methyl ester (30 mg, 0.073 mmol, 1.0 equiv) in DCM (1.0 mL) at 0 °C was added phenoxyacetyl chloride (0.02 ml, 0.145 mmol, 2.0 equiv) and TEA (0.02 mL). The resulting mixture was then stirred at 0 °C for 20 minutes after which the solvent was removed under vacuum. The residue was purified by silica gel column chromatography (EtOAc/hepatane 10% ~ 80%) to give product (20 mg). MS: 547 [M+H$^+$].)

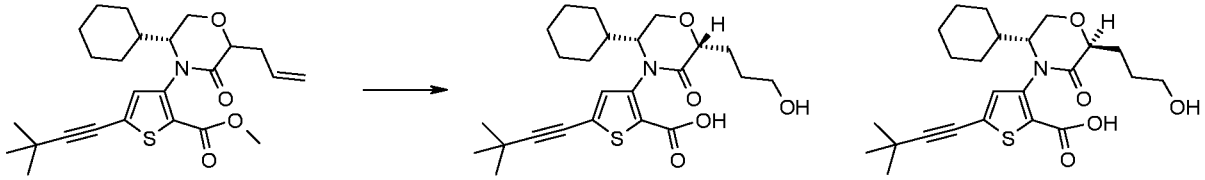
Step 3. Synthesis of 3-[2-Cyclohexyl-6-oxo-4-(2-phenoxy-acetylamino)-piperidin-1-yl]-5-phenyl-thiophene-2-carboxylic acid



To a solution of methyl ester (10 mg, 0.018 mmol, 1.0 equiv) in THF (0.2 mL), EtOH (0.1 mL) and water (0.2 mL) was added LiOH•H_2O (8 mg, 0.18 mmol, 10 equiv). The mixture was stirred at 55 °C for 30 minutes, after which, the organic solvent was evaporated. To the resulting solution was added 3.0 N HCl aq. solution until pH=5. The solution was extracted with EtOAc, and the organic layer was washed with sat. $NaHCO_3$ aqueous solution, brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by prep-HPLC to give the product 6 mg. MS: 533[M+H$^+$]. ^{1}H-NMR (400MHz, DMSO): δ 10.31(d, 1H), 7.63(d, 2H), 7.42(t,

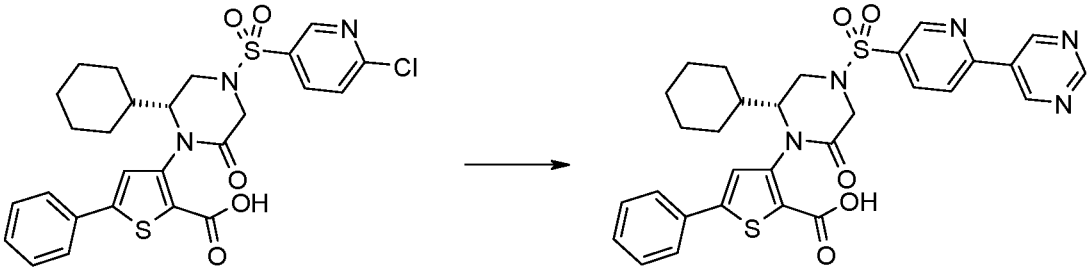
2H), 7.31(t, 2H), 7.23(m, 2H), 7.14(s, 1H), 6.98(m, 3H), 4.61(m, 2H), 4.45(m, 1H), 4.10(m, 1H), 3.32(s, 2H), 2.20(m, 1H), 1.88-1.76(m, 4H), 1.65-1.58(m, 2H), 1.41-1.05(m, 6H).

Example 18. Synthesis of 3-[(2R,5R)-5-Cyclohexyl-2-(3-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid and 3-[(2S,5R)-5-Cyclohexyl-2-(3-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid [Compound 2] [Compound 3]



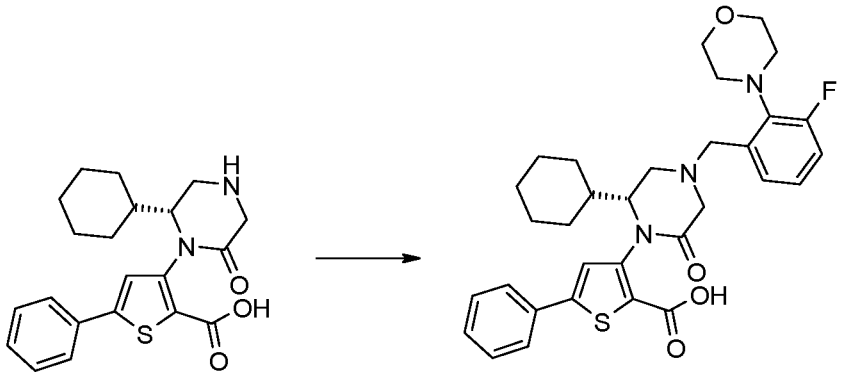
To a solution of 3-((R)-2-Allyl-5-cyclohexyl-3-oxo-morpholin-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester (200 mg, 0.45 mmol, 1.0 equiv) in THF (4.0 mL) at 0 °C was added 9-BBN (2.2 mL, 0.5 M in THF, 1.1 mmol, 2.5 equiv) over 10 minutes and the resulting solution was stirred at room temperature for 18 hours. The solution was then cooled to 0 °C and to the solution was added EtOH, aq. NaOH. solution, aq. H_2O_2 solution. The reaction mixture was heated to reflux for 90 minutes. After cooled to room temperature, the reaction mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and the residue was was purified by prep-HPLC to give product 3-[(2R,5R)-5-Cyclohexyl-2-(3-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid (20 mg) and 3-[(2S,5R)-5-Cyclohexyl-2-(3-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid (20 mg). The stereochemistry at 2 position of morpholinone has not been established. Product 1: MW: 448.3 $[M+H]^+$. ^{1}H-NMR (400MHz, CD_3OD): δ 6.93(s, 1H), 4.14(m, 1H), 4.0(m, 1H), 3.62(m, 1H), 3.58(m, 2H), 2.02- 1.48(m, 10H), 1.32(s, 9H), 1.25-1.17(m, 6H). Product 2: MW: 448.3 $[M+H]^+$. ^{1}H-NMR (400MHz, CD_3OD): δ 6.97(s, 1H), 4.13(m, 1H), 3.90(m, 1H), 3,82(m, 1H), 3.57(m, 2H), 1.97- 1.48(m, 10H), 1.32(s, 9H), 1.26-1.09(m, 6H).

Example 19: Synthesis of 3-[(R)-2-Cyclohexyl-6-oxo-4-(6-pyrimidin-5-yl-pyridine-3-sulfonyl)-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid [Compound 206]



To a solution of 3-[(R)-4-(6-chloro-pyridine-3-sulfonyl)-2-cyclohexyl-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid (1.20 g, 2.14 mmol, 1.0 equiv) in acetonitrile (15.0 mL) was added potassium phosphate (8.58 ml, 1.0 M aqueous solution, 4.0 equiv) and chloro(2-dicyclohexyl phosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl)[2-(2-amino ethyl) phenyl] Pd(II) Me-t-butyl ether adduct (0.32 g, 0.43 mmol, 0.2 equiv) at room temperature. The mixture was stirred at room temperature for 10 minutes to form a stock solution. To 0.8 mL of above solution was added 5-pyrimidinyl boronic acid (17.7 mg, 0.143 mmol, 2.0 equiv) and acetonitrile (0.5 mL) at room temperature. The mixture was stirred at 80 °C for 4 hours. The mixture was purified by HPLC (0.1% NH_4OH) to afford the product (15.9 mg, 36.9%). MS: 603.2 [M-H^+].

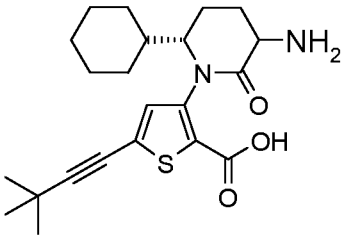
Example 20:3-[(R)-2-Cyclohexyl-4-(3-fluoro-2-morpholin-4-yl-benzyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid [Compound 266]



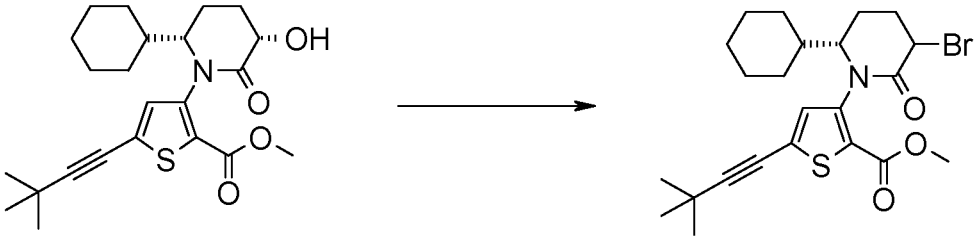
A solution of 3-((R)-2-cyclohexyl-6-oxo-piperazin-1-yl)-5-phenyl-thiophene-2-carboxylic acid (50.0 mg, 0.13 mmol, 1.0 equiv) and 3-fluoro-2-morpholinobenzaldehyde (108.8 mg, 0.52 mmol, 4.0 equiv) in acetic acid (0.2 mL) and methanol (0.5 mL) was stirred at room temperature for 60 minutes. Then sodium triacetoxyborohydride (110.2 mg, 0.52 mmol, 4.0 equiv) was added to the mixture and the resulting mixture was stirred at 75 °C for 3 hours. The solvent was removed by Genevac and the residue was dissolved in EtOAc (6 mL). The organic phase was

washed by brine (3 mL), dried over Na_2SO_4 and concentrated. The residue was purified by HPLC (0.1% NH_4OH) to afford the product (9 mg, 12%). MS: 577.2 [$M-H^+$].

Example 21. Synthesis of 3-((S)-3-Amino-6-cyclohexyl-2-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid [Compound 340]

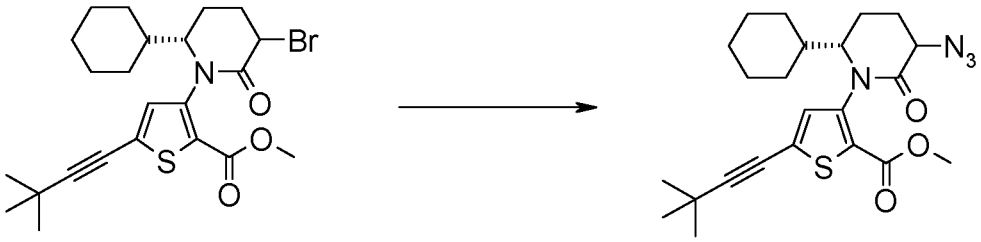


Step 1. Synthesis of 3-((S)-3-Bromo-6-cyclohexyl-2-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester



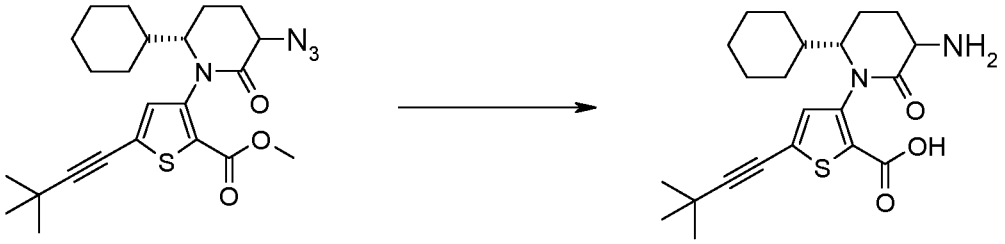
To a solution of 3-((3S,6S)-6-cyclohexyl-3-hydroxy-2-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester (200 mg, 0.75 mmol, 1 equiv) in CH_2Cl_2 (1.0 mL) was added PBr_3 (1.0 M in CH_2Cl_2, 0.09 ml, 0.38 mmol, 0.8 equiv.) at room temperature and the resulting solution was stirred at room temperature for 18 hours. The reaction solution was then concentrated under vacuum and the residue was purified by silica gel column chromatography, (EtOAc/Heptane, 10%~60%) to give product 166 mg (yield 76%). MS: 481 [$M+H^+$].

Step 2. Synthesis of 3-((S)-3-Azido-6-cyclohexyl-2-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester



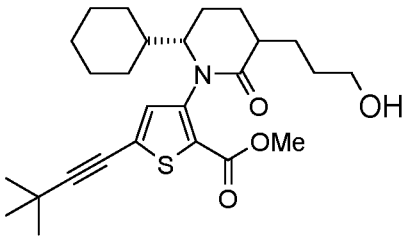
To the solution of 3-((S)-3-bromo-6-cyclohexyl-2-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester (78 mg, 0.16 mmol, 1 equiv.) in DMF (1.0 mL) was added NaN_3 (12 mg, 0.19 mmol, 1.2 equiv) and the resulting mixture was stirred at 65°C for 18 hours. The solvent was then removed under vacuum. The residue was purified by silica gel column chromatography (EtOAc/Heptane, 10%~60%) to give product 42 mg (yield 56%). MS: 442 [M+H$^+$].

Step 3. Synthesis of 3-((S)-3-Amino-6-cyclohexyl-2-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid



To the solution of 3-((S)-3-azido-6-cyclohexyl-2-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester (40 mg, 0.09 mmol, 1 equiv) in MeOH (0.5 mL) was added $SnCl_2$ (17 mg, 0.09 mmol, 1 equiv) and the resulting solution was stirred at room temperature for 18 hours. The solvent was then removed under vacuum. The residue was dissolved in THF/H_2O/MeOH (0.5 mL/0.5 mL/1.0 mL) and to the solution was added $LiOH \cdot H_2O$ (21 mg, 0.48 mmol, 5 equiv). The reaction mixture was stirred at 50 °C for 20 minutes. The organic solvents were removed under vacuum and the residue was acidified to pH=5 by addition of 3.0 N HCl aq. solution. The mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by prep-HPLC (XBridge Prep C 18 5 um, 30×50 mm) in basic condition (0.1% NH_4OH, 10%~45% CH_3CN/H_2O, 10 min run, 40 ml/min) to give product 12 mg. MS: 403 [M+H$^+$]. ^{1}H-NMR (400 MH_Z, CD_3OD): δ 6.81 (s, 1H), 3.96 (br, 1H), 3.48 (m, 1H), 2.06(m, 3H), 1.84(m, 3H), 1.70(br, 2H), 1.46 (m, 1H), 1.37(m, 1H), 1.31(s, 9H), 1.16(m, 5H).

Example 22. Synthesis of 3-((S)-6-cyclohexyl-3-(3-hydroxy-propyl)-2-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid [Compound 341]

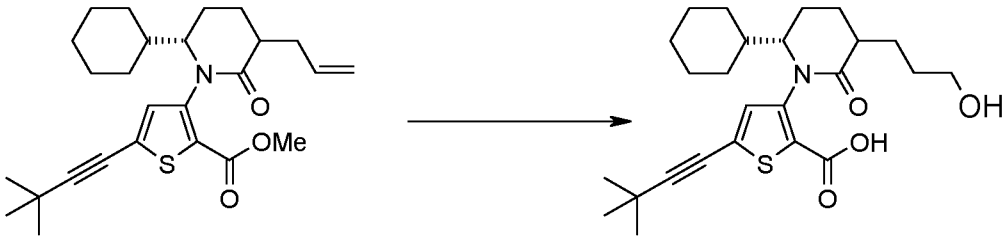


Step 1. Synthesis of 3-((S)-3-Allyl-6-cyclohexyl-2-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester



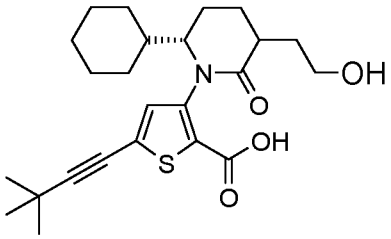
To a solution of 3-((S)-2-cyclohexyl-6-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester (200 mg, 0.5 mmol, 1,0 equiv) in THF (2.0 mL) was added LDA (2.0 M in THF, 0.3 mL, 0.6 mmol, 1.2 equiv) at −78°C and the resulting solution was stirred at −78°C for 10 minutes. To the solution was then added 3-iodo-propene (250 mg, 1.5 mmol, 3.0 equiv) and the reaction mixture was stirred at room temperature for 15 minutes. The reaction was quenched by addition of water. The mixture was extracted with EtOAc. The organic layer was washed with sat. $NaHCO_3$ aq. solution and brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by silica gel column chromatography, Heptane/DCM (contained 3% EtOAc) to give 60 mg of less polar diastereomer and 100 mg of more polar diastereomer. MS: 442 [$M+H^+$].

Step 2. Synthesis of 3-((S)-6-cyclohexyl-3-(3-hydroxy-propyl)-2-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid

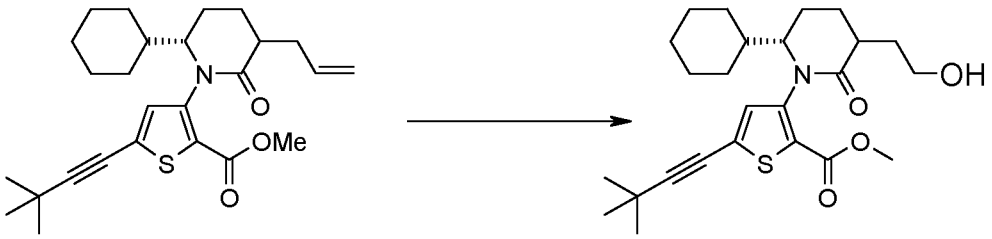


To a solution of 3-((S)-3-allyl-6-cyclohexyl-2-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester (less polar diastereomer from previous step) (60 mg, 0.14 mmol, 1.0 equiv) in anhydrous THF (2.0 ml) was added 9-BBN (0.5 M in THF, 0.68 ml, 0.34 mmol, 2.5 equiv) at 0 °C and the resulting solution was stirred at room temperature for 2 hours. The solution was then cooled at 0 °C and to the solution was added EtOH, 1.0 M aq. NaOH solution and aqueous H_2O_2 solution. The reaction mixture was heated to reflux for 90 minutes and then cooled at room temperature. The mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by prep-HPLC (0.1% NH_4OH) to give 20 mg of the desired product (yield 33%). MS: 446 [$M+H^+$]. ^{1}H-NMR (400 MH_Z, CD_3OD): 6.81 (s, 1H), 4.00 (br, 1H), 3.53 (t, 2H), 2.27(br, 1H), 1.97(m, 3H), 1.82~1.64(m, 7H), 1.58 (m, 2H), 1.37(m, 2H), 1.31(s, 9H), 1.14(m, 5H).

Example 23. Synthesis of 3-((S)-6-cyclohexyl-3-(2-hydroxy-ethyl)-2-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid [Compound 343]



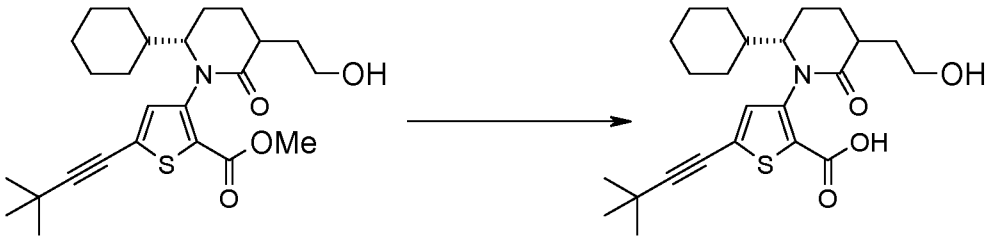
Step 1. Synthesis of 3-[(S)-6-Cyclohexyl-3-(2-hydroxy-ethyl)-2-oxo-piperidin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester



To a solution of 3-((S)-3-allyl-6-cyclohexyl-2-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester (less polar diastereomer from previous step) (200 mg, 0.45 mmol, 1.0 equiv) in acetone (3.0 mL) at 0 °C was added N-methylmorpholine oxide (160 mg, 1.36 mmol, 3 equiv), water (1.0 mL) and OsO_4 (230 mg, 0.02 mmol, 0.05 equiv). The reaction mixture was stirred at room temperature for 1 hour. The solution was partitioned between brine and EtOAc. The phases were separated and the organic layer was dried over Na_2SO_4, and concentrated under vacuum. The residue was dissolved in THF/water(3.0 mL/1.0

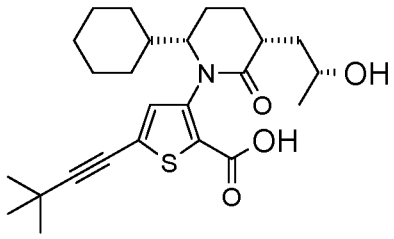
mL). To the solution was added $NaIO_4$ (194 mg, 0.9 mmol, 2 equiv), and the resulting mixture was stirred at room temperature for 30 minutes, after which another portion of $NaIO_4$ (0.5 equiv) was added. After stirred at room temperature for 30 minutes, the mixture was partitioned between brine and EtOAc. The organic layer was separated, dried over Na_2SO_4, and concentrated. The residue was dissolved in EtOH (3.0 ml) and the solution was cooled at 0 °C. To the solution was added $NaBH_4$ and the mixture was stirred at 0 °C for 15 minutes. The reaction was quenched by addition of water (2.0 mL) and EtOAc (10.0 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography, Heptane/EtOAc 1/1 to give 123 mg of the product (yield 60%). MS: 446 [$M+H^+$]

Step 2. Synthesis of 3-((S)-6-cyclohexyl-3-(2-hydroxy-ethyl)-2-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid

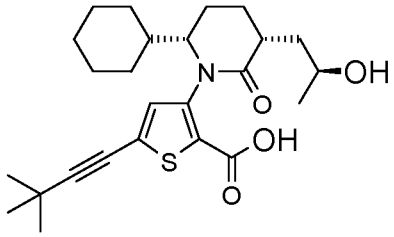


To a solution of 3-[(S)-6-cyclohexyl-3-(2-hydroxy-ethyl)-2-oxo-piperidin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester (123 mg, 0.28 mmol, 1 equiv.) in THF/H_2O/MeOH (1.0 mL/1.0 mL/0.5 mL) was added $LiOH \cdot H_2O$ (60 mg, 1.38 mmol, 5 equiv) and the resulting solution was stirred at 50 °C for 20 minutes. The solution was then acidified to pH=5 by addition of 3.0 N HCl aq. solution. The solution was extracted with EtOAc. The organic layer was dried over Na_2SO_4, and concentrated. The residue was purified by prep-HPLC(XBridge Prep C 18 5 um, 30×50 mm) in basic condition (0.1% NH_4OH, 10%~45% CH_3CN/H_2O, 10 min run, 40 ml/min) to give product 28 mg (yield 23%). MS: 432 [$M+H^+$]. ^{1}H-NMR (400 MH_Z, CD_3OD): 6.85(s, 1H), 3.92 (br, 1H), 3.67 (m, 2H), 2.41(br, 1H), 2.15(m, 1H), 1.97(m, 2H), 1.78 (m, 7H), 1.37(m, 2H), 1.31(s, 9H), 1.14(m, 5H).

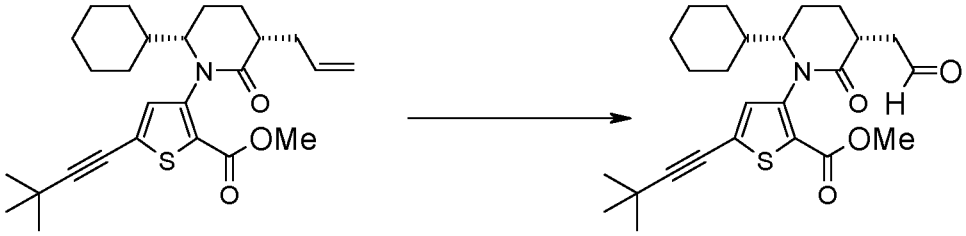
Example 24. Synthesis of 3-[(2R,5R)-5-Cyclohexyl-2-((R)-2-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid [Compound 336]



and 3-[(2R,5R)-5-Cyclohexyl-2-((S)-2-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid [Compound 337]



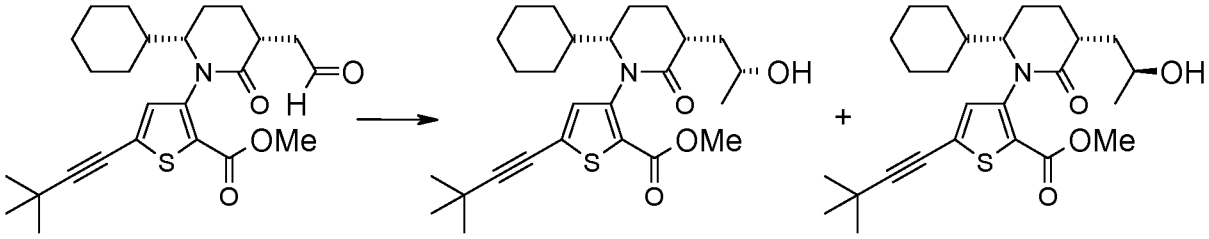
Step 1. Synthesis of 3-[(2R,5R)-5-Cyclohexyl-3-oxo-2-(2-oxo-ethyl)-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester



To a solution of 3-((2R, 5R)-2-allyl-5-cyclohexyl-3-oxo-morpholin-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester (3.15 g, 7.10 mmol, 1.0 equiv) in acetone (40 mL) at 0 °C was added N-methylmorpholine oxide (2.51 g, 21.30 mmol, 3.0 equiv), water (14 mL) and osmium tetroxide (3.60 g, 2.5%wt in THF, 0.36 mmol, 0.05 equiv). The mixture was stirred at room temperature for 60 minutes. Acetone was removed under vacuum and the residue was partitioned between EtOAc (80 mL) and brine (15 mL). The phases were separated and the organic layer was dried (over Na_2SO_4) and concentrated. To the residue was added THF (40 mL) and water (14 mL). At 0 °C, sodium periodate (2.28 g, 10.65 mmol, 1.5 equiv) was added to the mixture and the mixture was stirred at room temperature for 30 minutes. After cooled at 0 °C, another portion of sodium periodate (0.76 g, 3.55 mmol, 0.5 equiv) was added. The mixture was stirred at room temperature for another 30 minutes. Volatile solvent was removed under vacuum and the residue was partitioned between EtOAc (100 mL) and brine (10

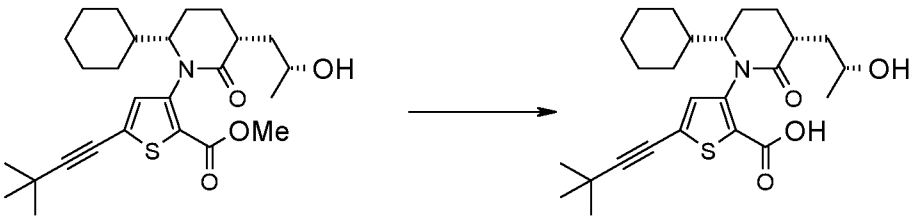
mL). The organic layer was separated, dried (over Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (EtOAc/Heptane, 25% to 50%) to give product (2.1 g, 66%). MS: 446.3 [M-H^+].

Step 2. Synthesis of 3-[(2R,5R)-5-Cyclohexyl-2-((R)-2-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester and 3-[(2R,5R)-5-Cyclohexyl-2-((S)-2-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester



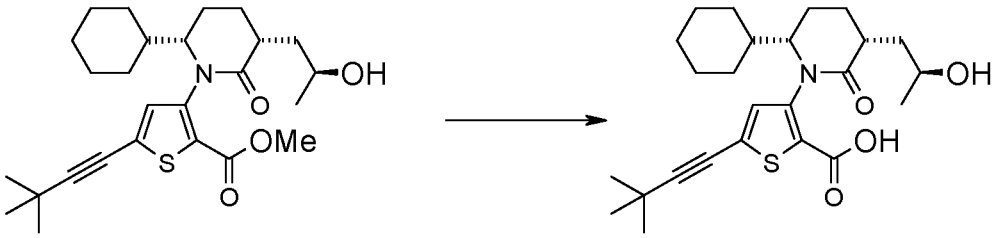
To a solution of 3-[(2R,5R)-5-cyclohexyl-3-oxo-2-(2-oxo-ethyl)-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester (1.9 g, 4.26 mmol, 1.0 equiv) in THF (200 mL) at -10 °C, was added MeMgBr (1.85 mL, 3.0 M solution in THF, 5.54 mmol, 1.3 equiv). The resulting solution was stirred at -10 °C for 20 minutes. The reaction was quenched by addition of 3.0 N HCl aqueous solution until pH=1. The volatile solvent was removed under vacuum and the residue was partitioned between EtOAc (100 mL) and brine (5 mL). The separated organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography [Et_2O(2% EtOAc)/Heptane, 25% to 50%] to give 3-[(2R,5R)-5-Cyclohexyl-2-((R)-2-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester (0.57 g, 29.0%) and 3-[(2R,5R)-5-Cyclohexyl-2-((S)-2-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester (0.80 g,.40.7%). MS: 462.4 [M-H^+].

Step 3. Synthesis of 3-[(2R,5R)-5-cyclohexyl-2-((R)-2-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid



To a solution of 3-[(2R,5R)-5-cyclohexyl-2-((R)-2-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester (650 mg, 1.41 mmol, 1.0 equiv) in THF (10 mL), MeOH (5 mL) and water (5 mL) was added LiOH•H_2O (177 mg, 4.22 mmol, 3.0 equiv). The resulting solution was stirred at room temperature for 2 hours. The volatile solvent was removed under vacuum and to the residue was added water (15 mL). The mixture was cooled to 0 ^oC and acidified by addition of 3.0 N HCl aqueous solution until pH=1. The precipitate was isolated by filtration to give product (586 mg, 93%) as white solid. MS: 448.3 [M-H^+]. ^1H NMR (400 MHz, CD_3OD): 1.09 - 1.31 (m, 8 H) 1.32 (s, 9 H) 1.45 - 1.85 (m, 5 H) 1.89 - 2.10 (m, 3 H) 3.56 - 3.61 (m, 1 H) 3.93 - 4.00 (m, 1 H) 4.00 - 4.10 (m, 1 H) 4.12 - 4.22 (m, 2 H) 6.99 (s, 1 H).

Step 4. Synthesis of 3-[(2R,5R)-5-Cyclohexyl-2-((S)-2-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid

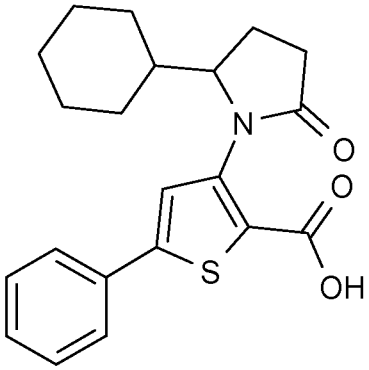
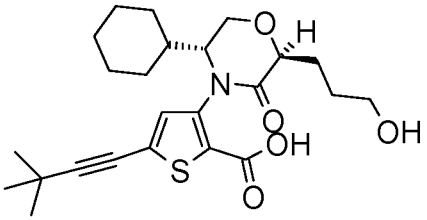
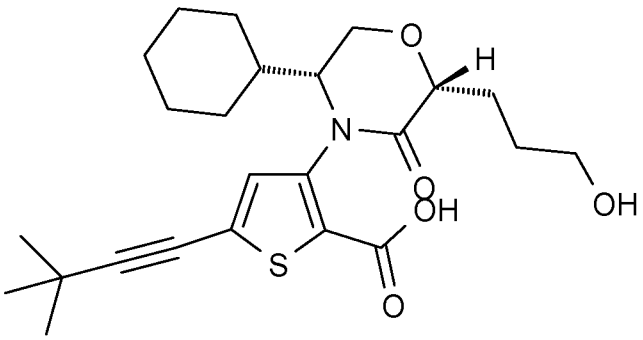


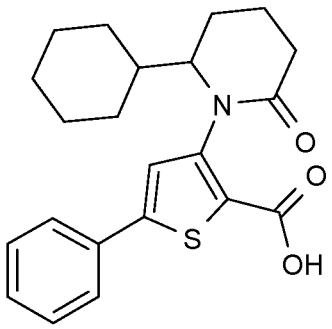
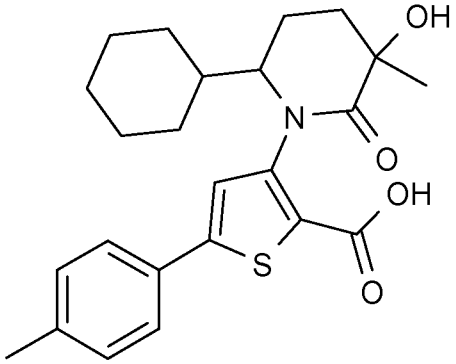
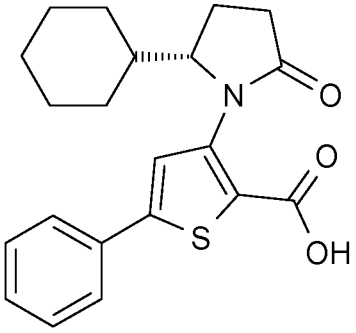
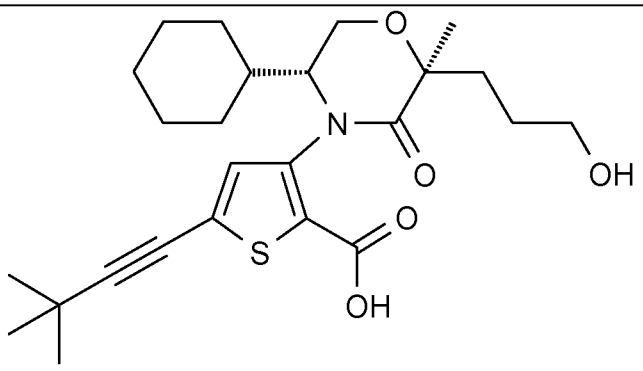
To a solution of 3-[(2R,5R)-5-cyclohexyl-2-(2-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester (420 mg, 0.91 mmol, 1.0 equiv) in THF (8 mL), MeOH (4 mL) and water (4 mL) was added LiOH•H_2O (115 mg, 2.73 mmol, 3.0 equiv). The resulting solution was stirred at room temperature for one hour. The volatile solvent was removed under vacuum and the residue was acidified by addition of 3.0 N HCl aqueous solution until pH=1. The mixture was extracted with EtOAc (50 mL). The separated organic layer was washed with brine (10 mL), dried (over Na_2SO_4) and concentrated. The residue was purified by HPLC(0.1% NH_4OH) to give product (68 mg, 16.7%). MS: 448.2 [M-H^+]. ^1H NMR (400 MHz, CD_3OD) δ 1.07 - 1.31 (m, 8 H) 1.32 (s, 9 H) 1.45 - 1.60 (m, 2 H) 1.63 -

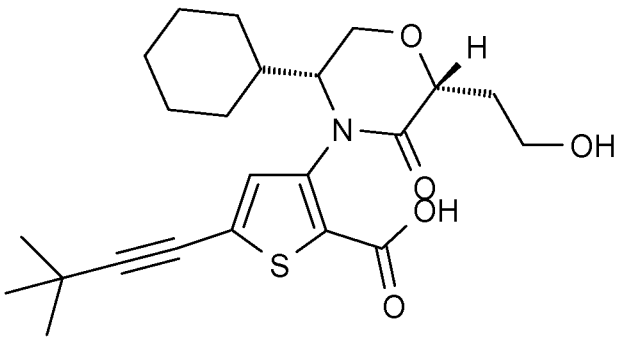
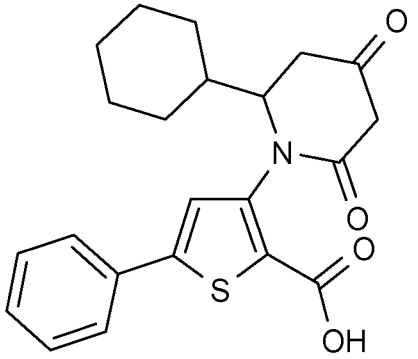
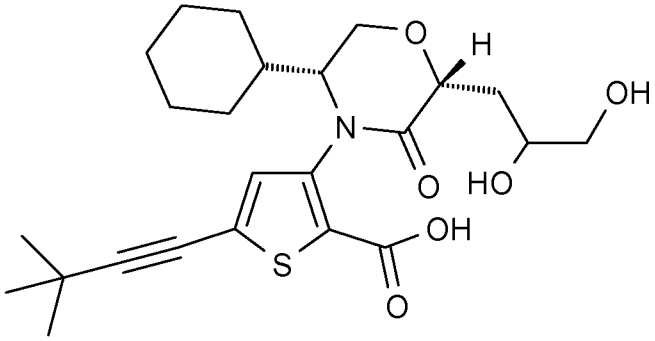
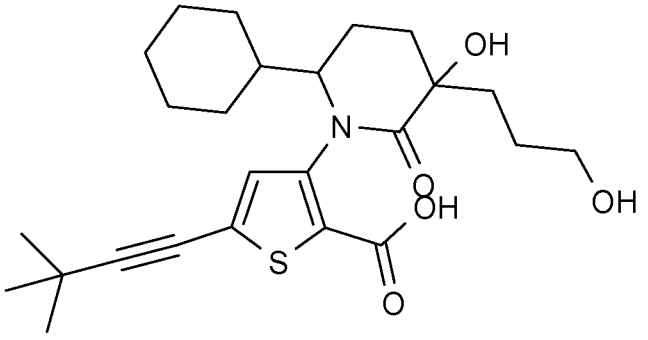
1.85 (m, 4 H) 1.87 - 1.98 (m, 1 H) 2.02 - 2.11 (m, 1 H) 3.60 - 3.66 (m, 1 H) 3.93 - 4.03 (m, 2 H) 4.15 (d, 1 H) 4.26 - 4.35 (m, 1 H) 6.94 (s, 1 H).

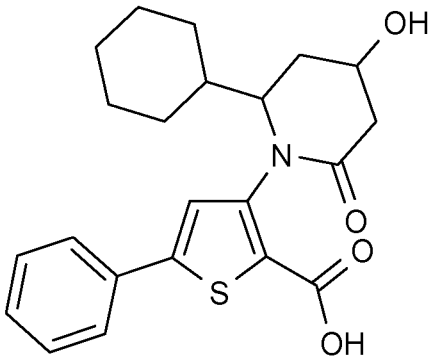
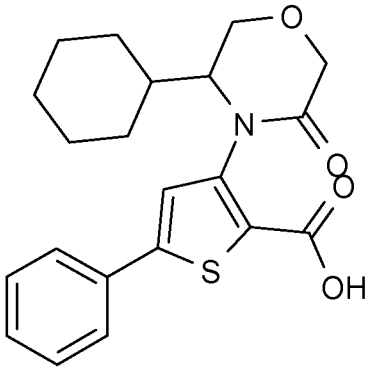
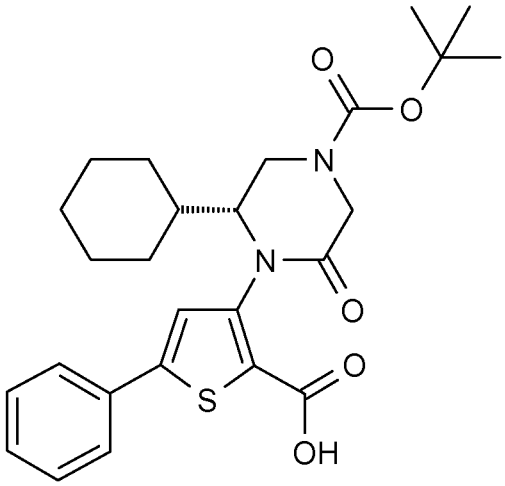
Additional non-limiting exemplary compounds of the invention are provided in Table 1. The compounds of Table 1 may be prepared by analogy to the synthetic procedures provided in the general synthetic description, the procedures of Examples 1-20 and/or by synthetic methodology known to the skilled medicinal chemist.

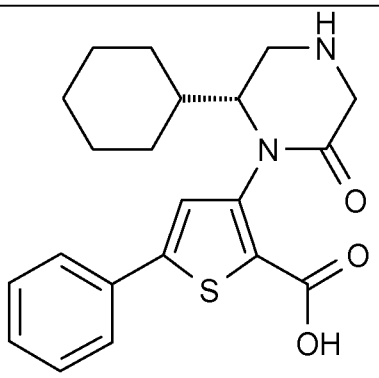
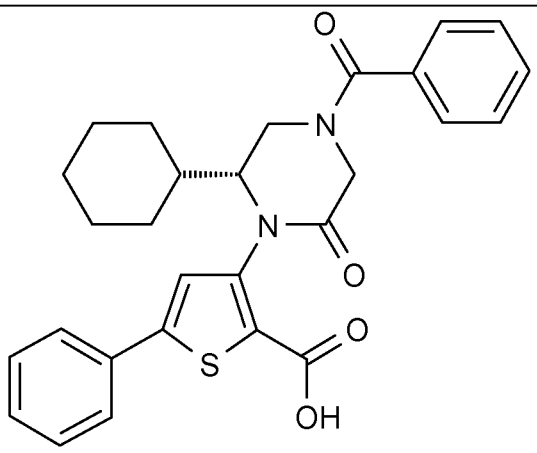
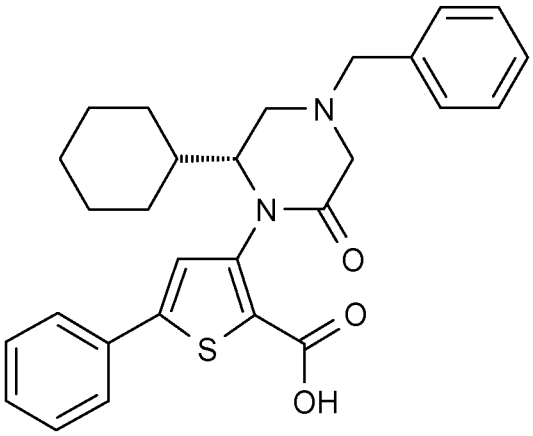
Table 1

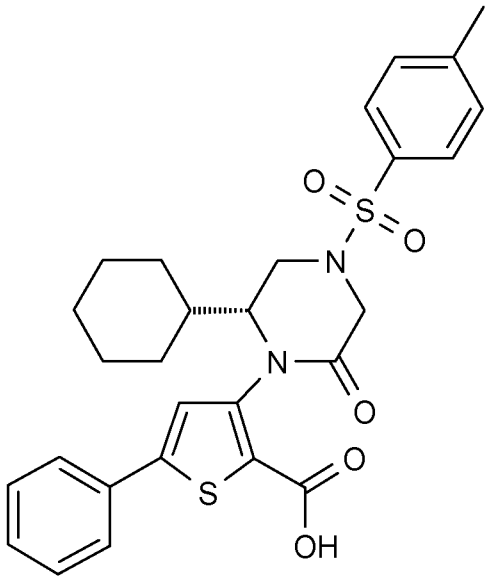
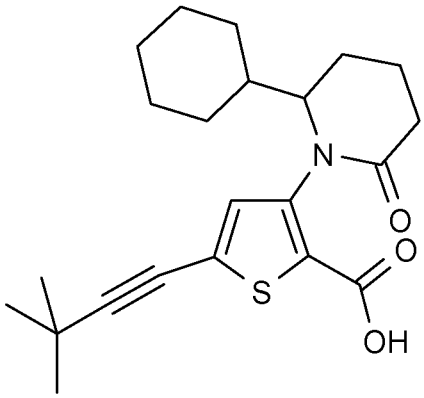
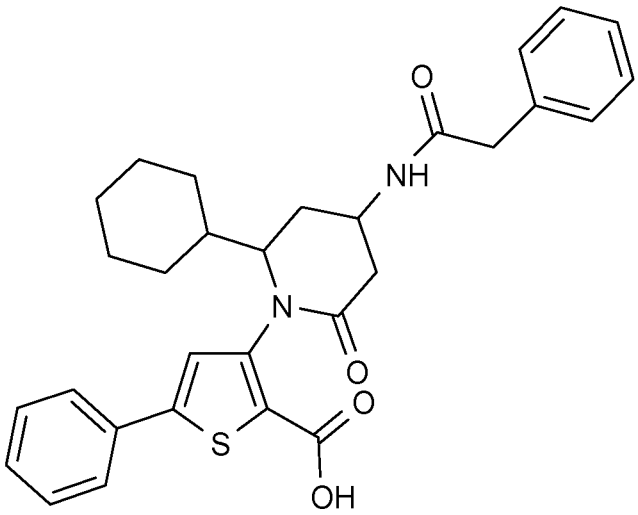
Compound number	Name	Structure
1	3-(2-Cyclohexyl-5-oxo-pyrrolidin-1-yl)-5-phenyl-thiophene-2-carboxylic acid	
2	3-[(2S,5R)-5-Cyclohexyl-2-(3-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
3	3-[(2R,5R)-5-Cyclohexyl-2-(3-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	

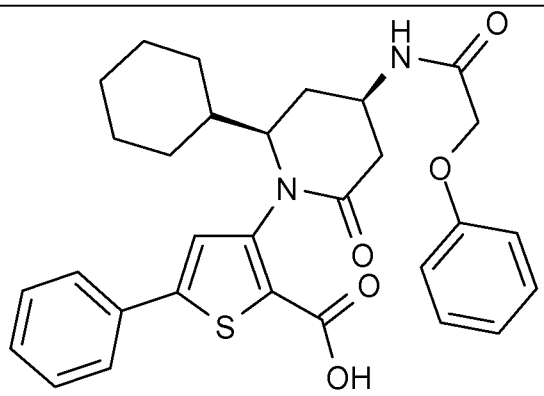
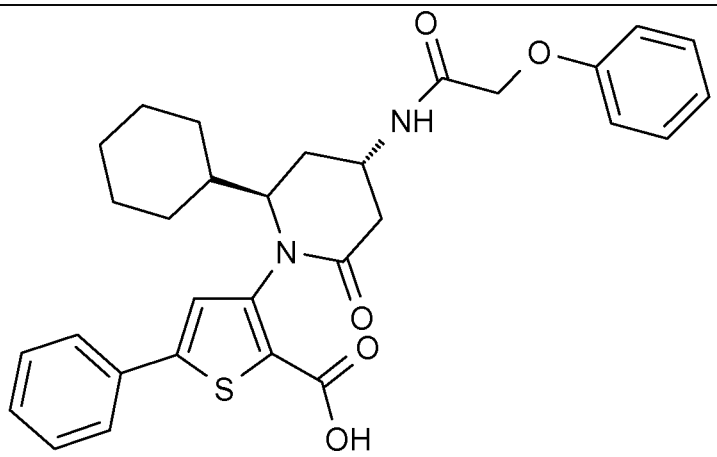
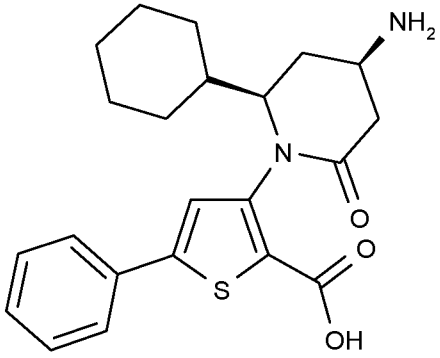
4	3-(2-Cyclohexyl-6-oxo-piperidin-1-yl)-5-phenyl-thiophene-2-carboxylic acid	
5	3-(6-Cyclohexyl-3-hydroxy-3-methyl-2-oxo-piperidin-1-yl)-5-p-tolyl-thiophene-2-carboxylic acid	
6	3-((S)-2-Cyclohexyl-5-oxo-pyrrolidin-1-yl)-5-phenyl-thiophene-2-carboxylic acid	
7	3-[(2S,5R)-5-Cyclohexyl-2-(3-hydroxy-propyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	

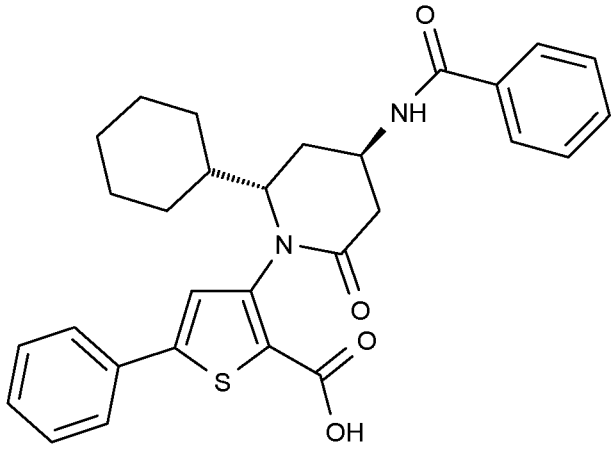
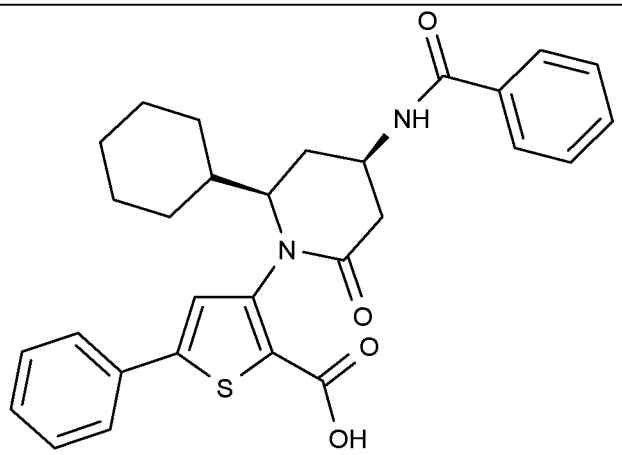
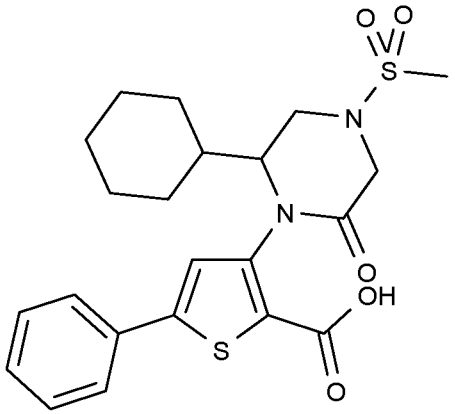
8	3-[(2R,5R)-5-Cyclohexyl-2-(2-hydroxy-ethyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
9	3-(2-Cyclohexyl-4,6-dioxo-piperidin-1-yl)-5-phenyl-thiophene-2-carboxylic acid	
10	3-[(2R,5R)-5-Cyclohexyl-2-(2,3-dihydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
11	3-[6-Cyclohexyl-3-hydroxy-3-(3-hydroxy-propyl)-2-oxo-piperidin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	

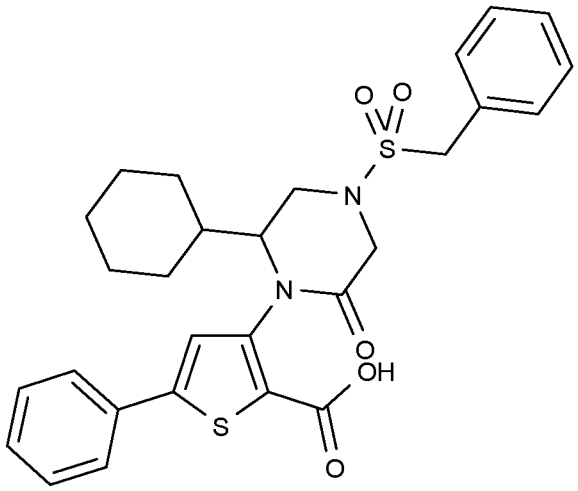
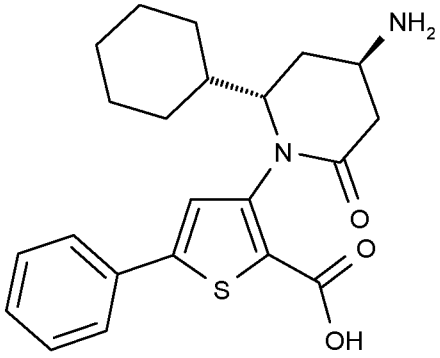
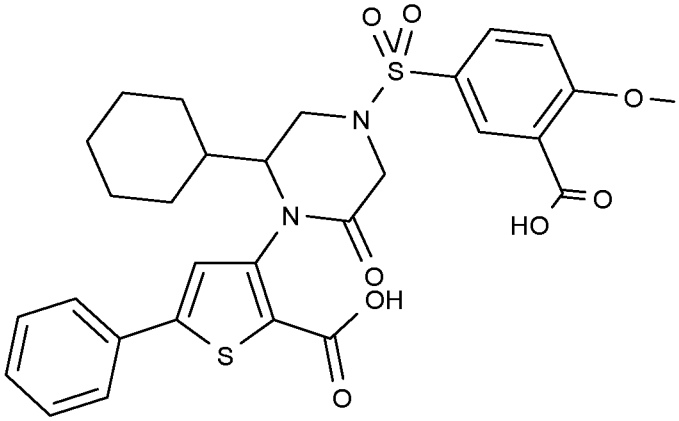
12	3-(2-Cyclohexyl-4-hydroxy-6-oxo-piperidin-1-yl)-5-phenyl-thiophene-2-carboxylic acid	
13	3-(3-Cyclohexyl-5-oxo-morpholin-4-yl)-5-phenyl-thiophene-2-carboxylic acid	
14	(R)-4-(2-Carboxy-5-phenyl-thiophen-3-yl)-3-cyclohexyl-5-oxo-piperazine-1-carboxylic acid tert-butyl ester	

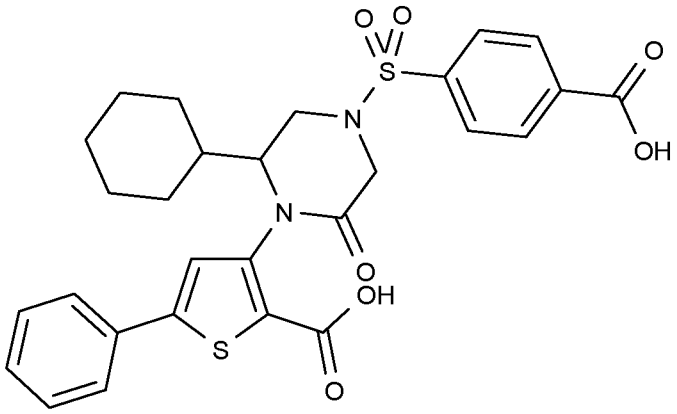
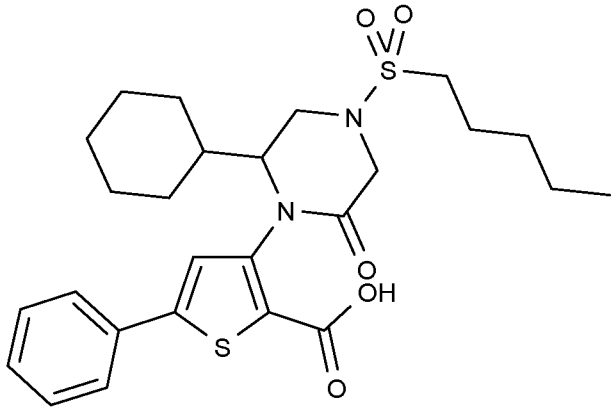
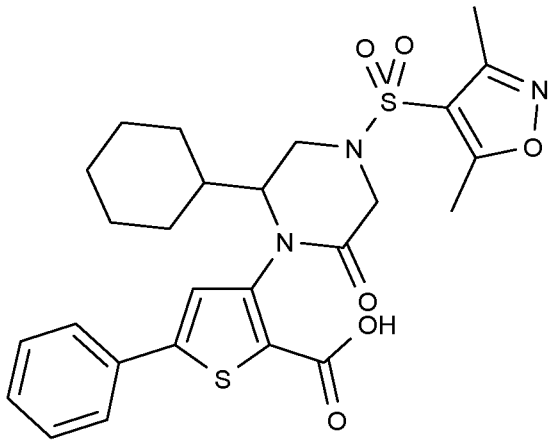
15	3-((R)-2-Cyclohexyl-6-oxo-piperazin-1-yl)-5-phenyl-thiophene-2-carboxylic acid	
16	3-((R)-4-Benzoyl-2-cyclohexyl-6-oxo-piperazin-1-yl)-5-phenyl-thiophene-2-carboxylic acid	
17	3-((R)-4-Benzyl-2-cyclohexyl-6-oxo-piperazin-1-yl)-5-phenyl-thiophene-2-carboxylic acid	

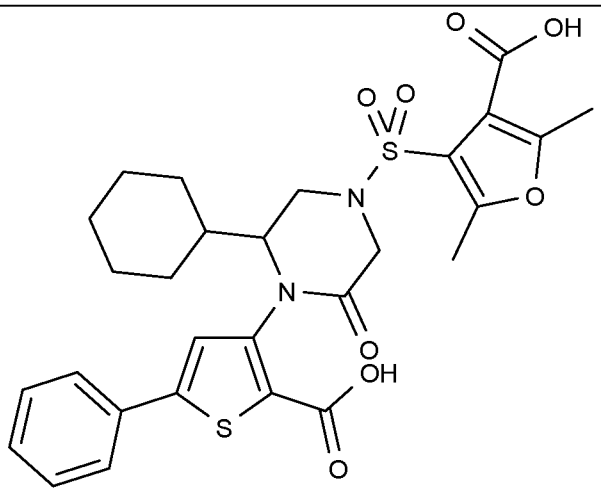
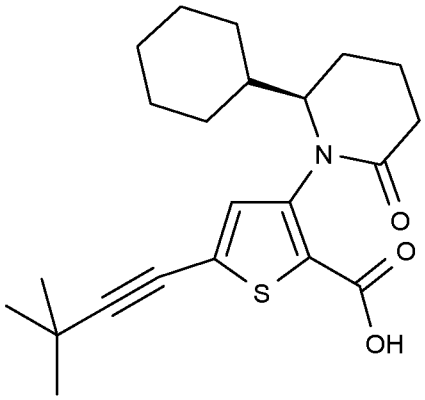
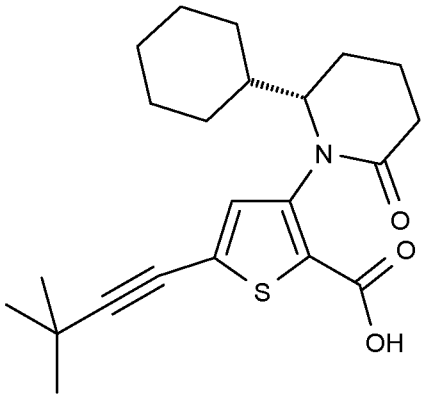
18	3-[(R)-2-Cyclohexyl-6-oxo-4-(toluene-4-sulfonyl)-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
19	3-(2-Cyclohexyl-6-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
20	3-(2-Cyclohexyl-6-oxo-4-phenylacetylamino-piperidin-1-yl)-5-phenyl-thiophene-2-carboxylic acid	

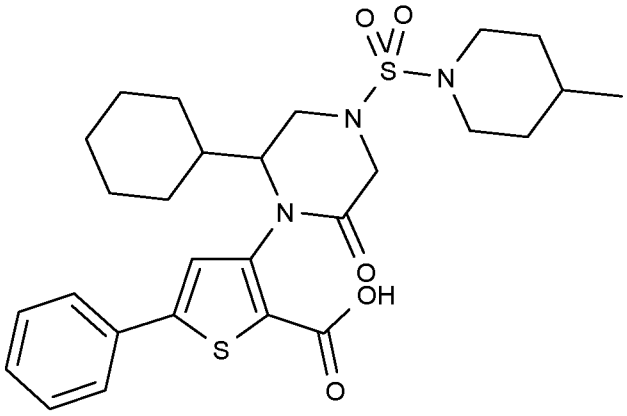
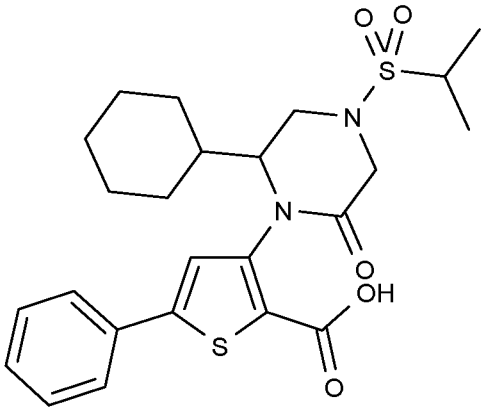
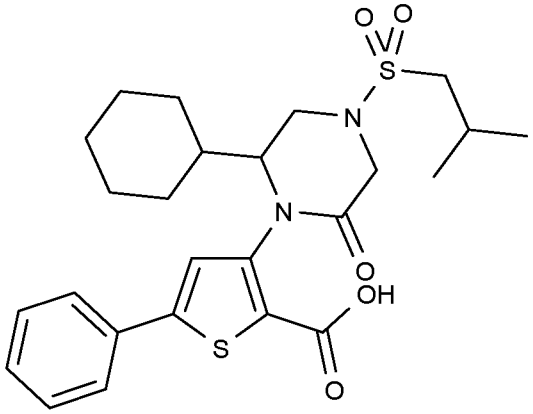
21	3-[2-Cyclohexyl-6-oxo-4-(2-phenoxy-acetylamino)-piperidin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
22	3-[(2R,4S)-2-Cyclohexyl-6-oxo-4-(2-phenoxy-acetylamino)-piperidin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
23	3-((2R,4R)-4-Amino-2-cyclohexyl-6-oxo-piperidin-1-yl)-5-phenyl-thiophene-2-carboxylic acid	

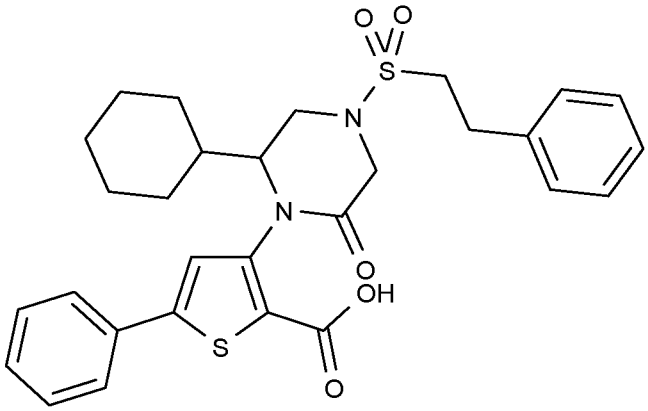
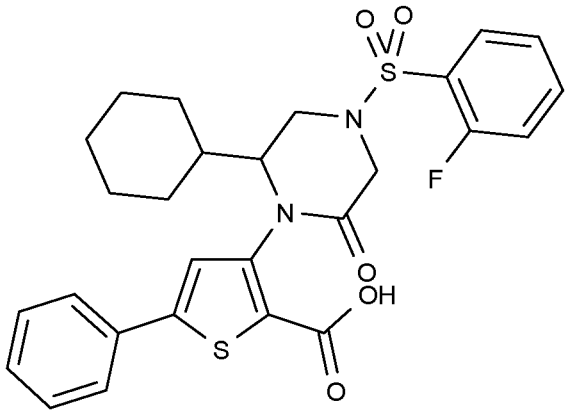
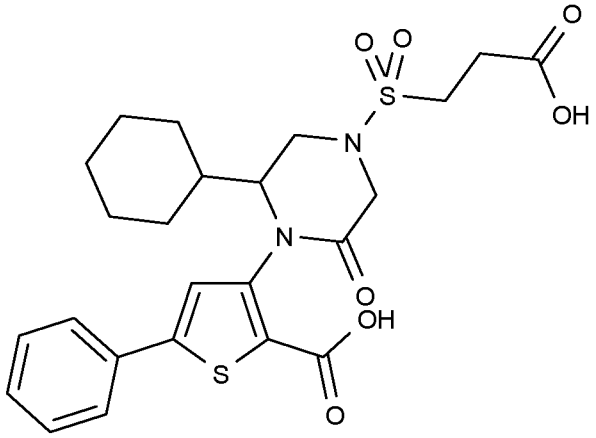
24	3-((2S,4R)-4-Benzoylamino-2-cyclohexyl-6-oxo-piperidin-1-yl)-5-phenyl-thiophene-2-carboxylic acid	
25	3-((2R,4R)-4-Benzoylamino-2-cyclohexyl-6-oxo-piperidin-1-yl)-5-phenyl-thiophene-2-carboxylic acid	
26	3-(2-Cyclohexyl-4-methanesulfonyl-6-oxo-piperazin-1-yl)-5-phenyl-thiophene-2-carboxylic acid	

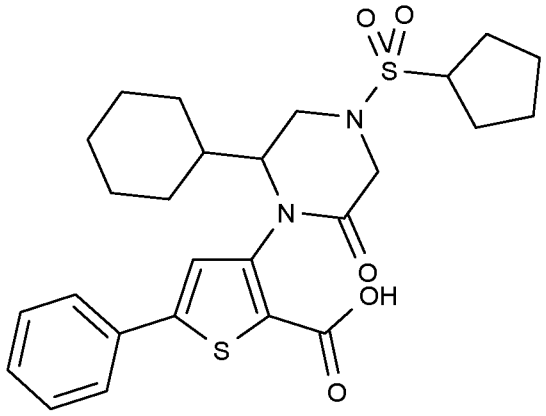
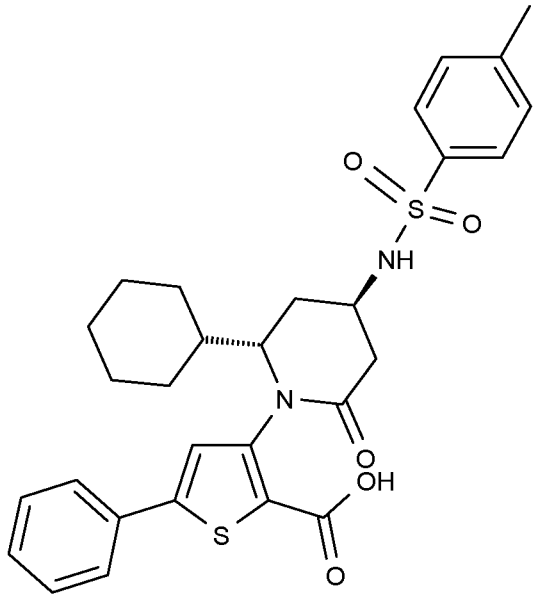
27	3-(2-Cyclohexyl-6-oxo-4-phenylmethanesulfonyl-piperazin-1-yl)-5-phenyl-thiophene-2-carboxylic acid	
28	3-((2S,4R)-4-Amino-2-cyclohexyl-6-oxo-piperidin-1-yl)-5-phenyl-thiophene-2-carboxylic acid	
29	3-[4-(3-Carboxy-4-methoxy-benzenesulfonyl)-2-cyclohexyl-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	

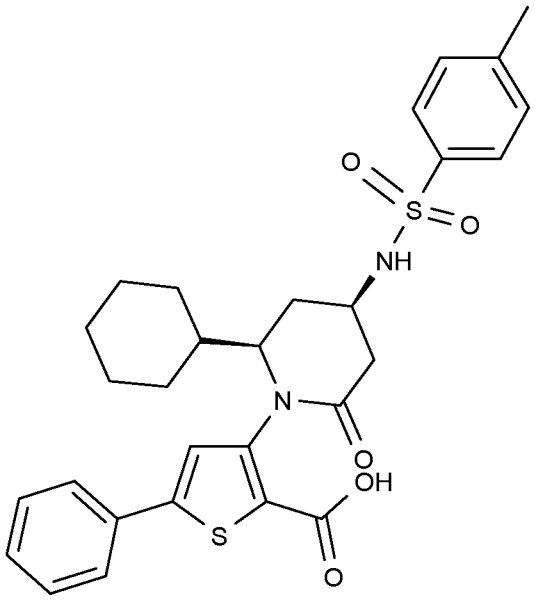
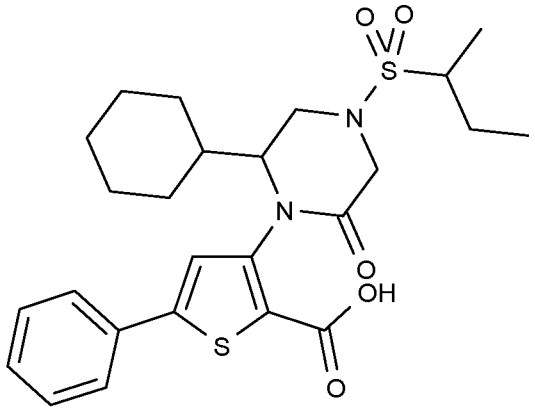
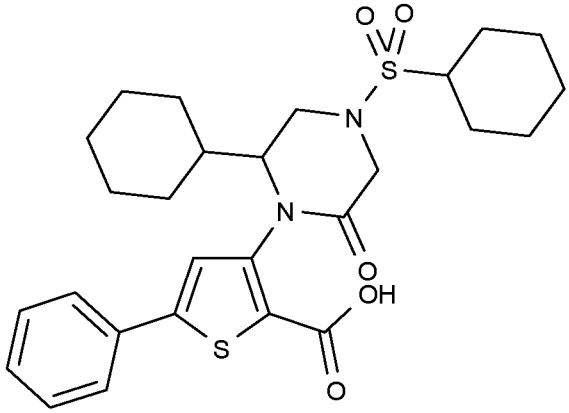
30	3-[4-(4-Carboxy-benzenesulfonyl)-2-cyclohexyl-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	Chiral 
31	3-[2-Cyclohexyl-6-oxo-4-(pentane-1-sulfonyl)-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
32	3-[2-Cyclohexyl-4-(3,5-dimethyl-isoxazole-4-sulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	

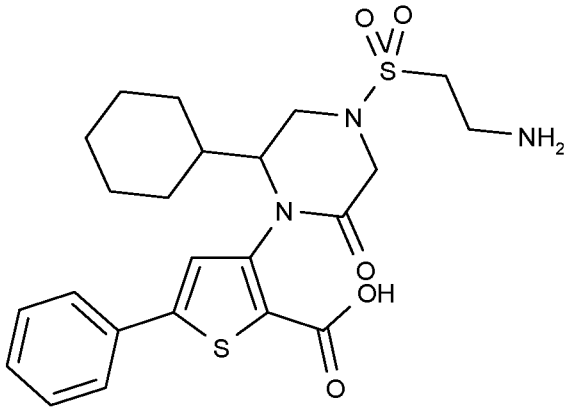
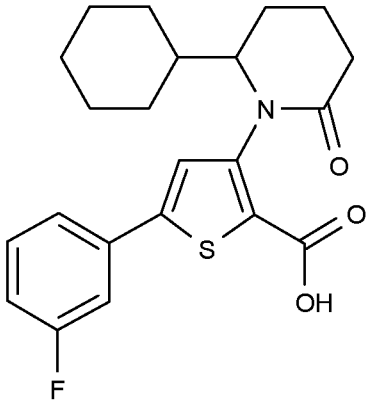
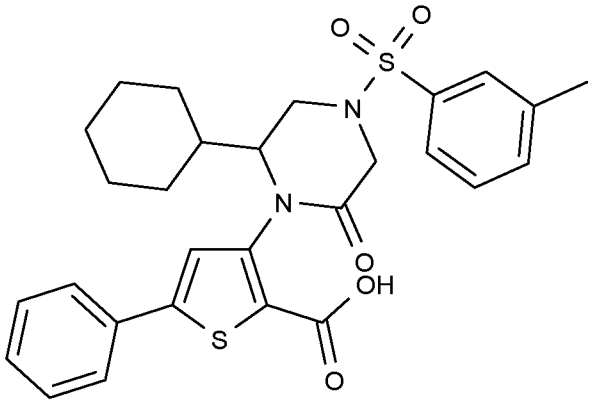
33	4-[4-(2-Carboxy-5-phenyl-thiophen-3-yl)-3-cyclohexyl-5-oxo-piperazine-1-sulfonyl]-2,5-dimethyl-furan-3-carboxylic acid	
34	3-((R)-2-Cyclohexyl-6-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
35	3-((S)-2-Cyclohexyl-6-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	

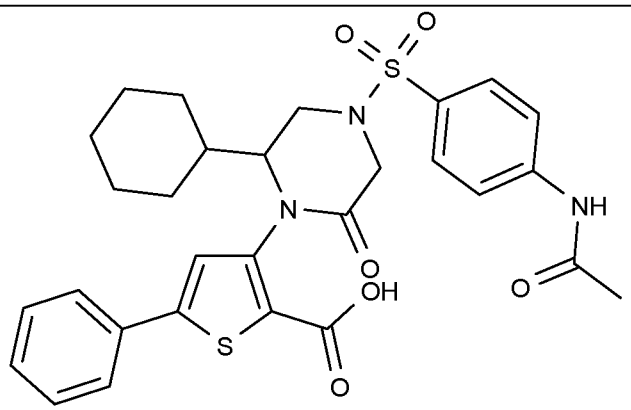
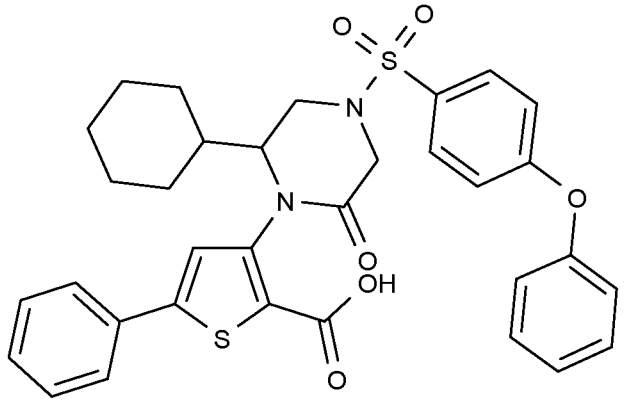
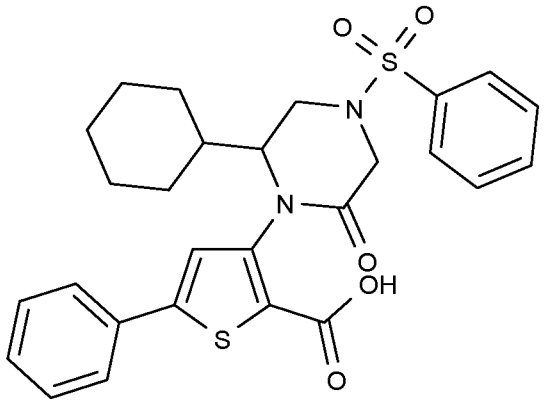
36	3-[2-Cyclohexyl-4-(4-methyl-piperidine-1-sulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
37	3-[2-Cyclohexyl-6-oxo-4-(propane-2-sulfonyl)-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
38	3-[2-Cyclohexyl-4-(2-methyl-propane-1-sulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	

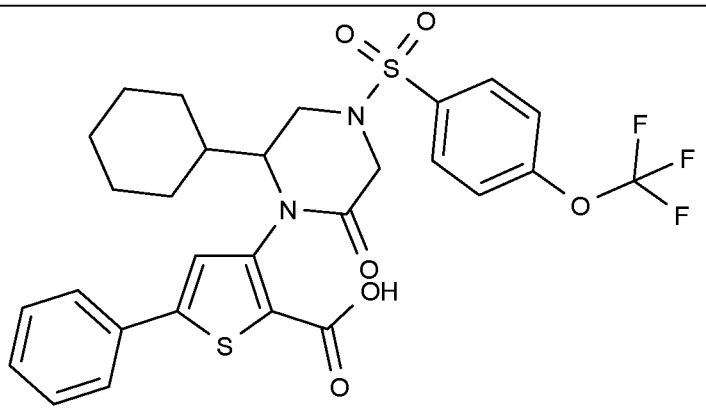
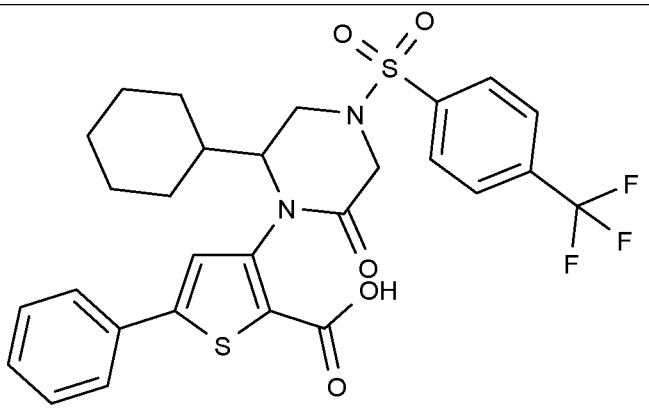
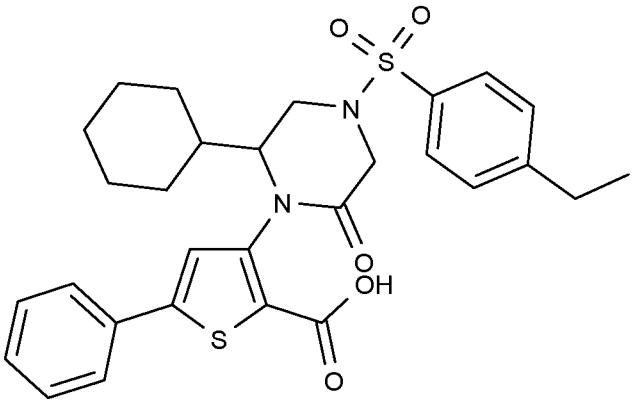
39	3-[2-Cyclohexyl-6-oxo-4-(2-phenyl-ethanesulfonyl)-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
40	3-[2-Cyclohexyl-4-(2-fluoro-benzenesulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	Chiral 
41	3-[4-(2-Carboxy-ethanesulfonyl)-2-cyclohexyl-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	

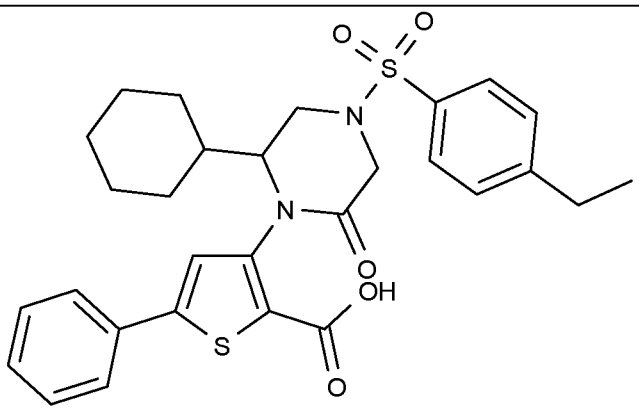
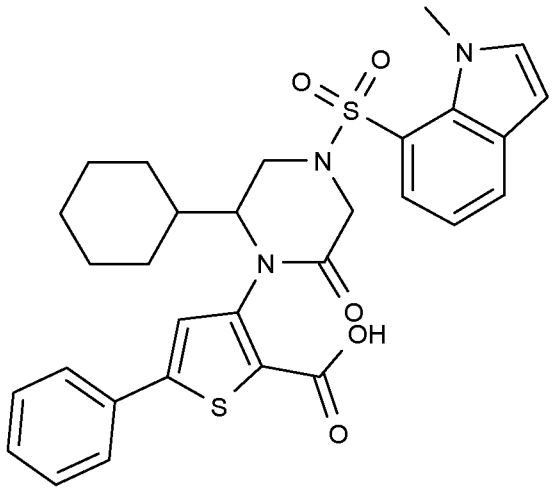
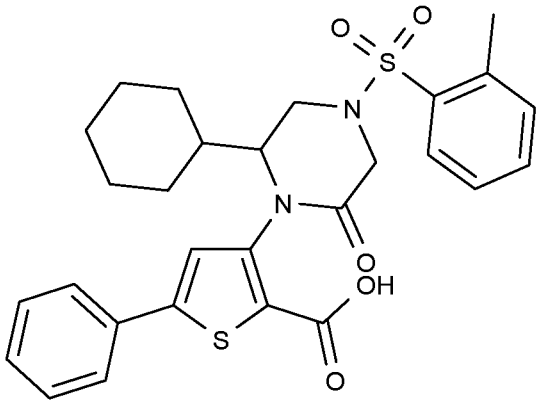
42	3-(2-Cyclohexyl-4-cyclopentanesulfonyl-6-oxo-piperazin-1-yl)-5-phenyl-thiophene-2-carboxylic acid	
43	3-[(2S,4R)-2-Cyclohexyl-6-oxo-4-(toluene-4-sulfonylamino)-piperidin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	

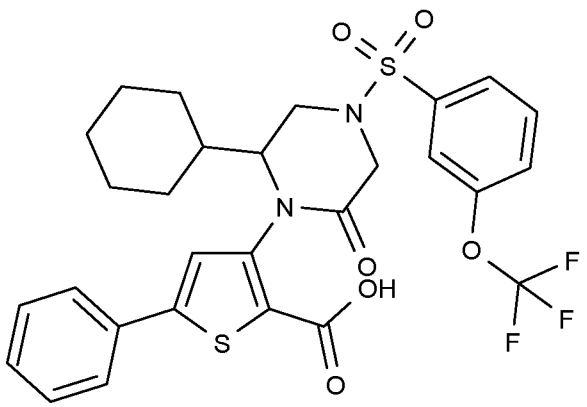
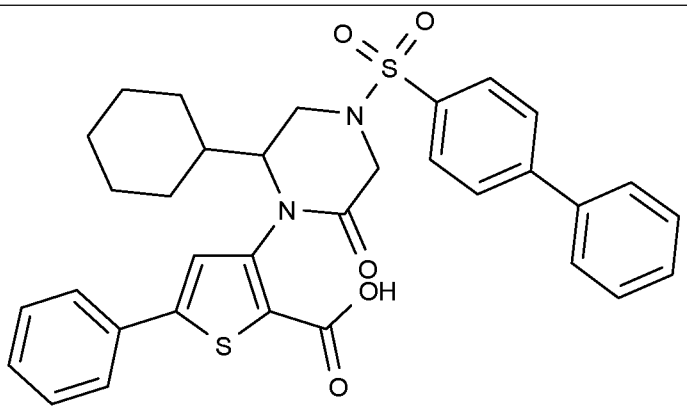
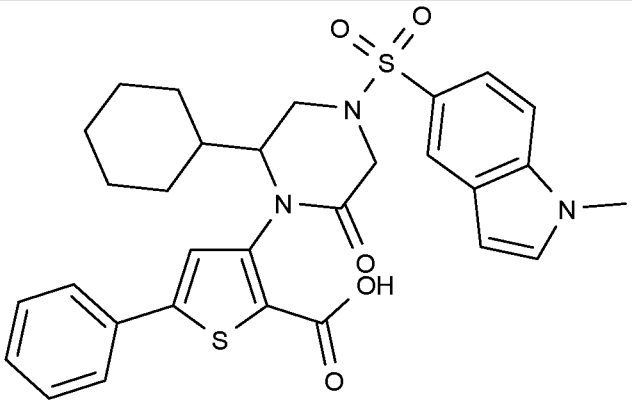
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45	3-[4-(Butane-2-sulfonyl)-2-cyclohexyl-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
46	3-(4-Cyclohexanesulfonyl-2-cyclohexyl-6-oxo-piperazin-1-yl)-5-phenyl-thiophene-2-carboxylic acid	

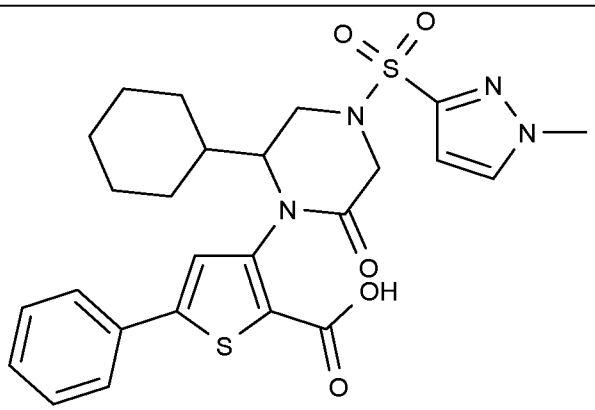
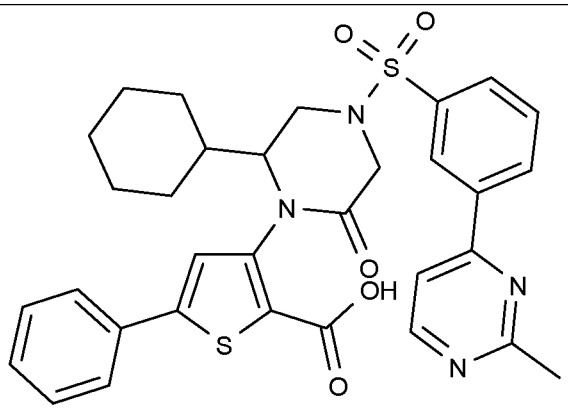
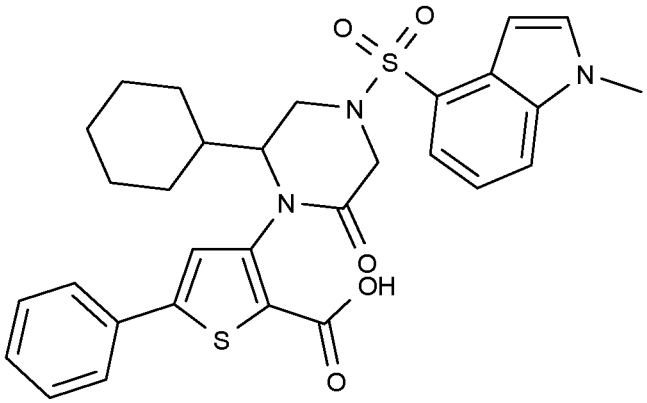
47	3-[4-(2-Amino-ethanesulfonyl)-2-cyclohexyl-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
48	3-(2-Cyclohexyl-6-oxo-piperidin-1-yl)-5-(3-fluoro-phenyl)-thiophene-2-carboxylic acid	
49	3-[2-Cyclohexyl-6-oxo-4-(toluene-3-sulfonyl)-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	

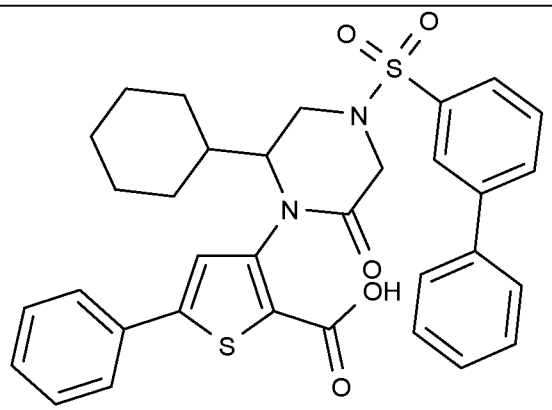
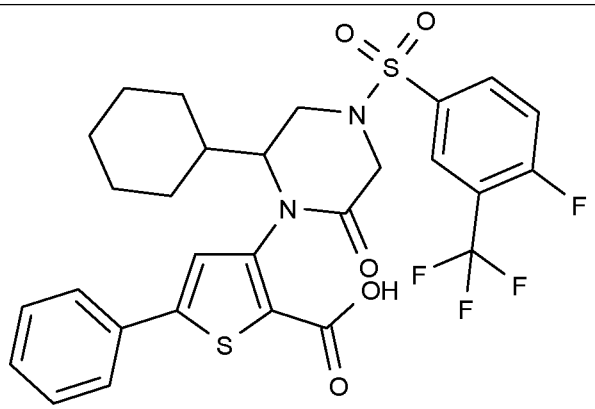
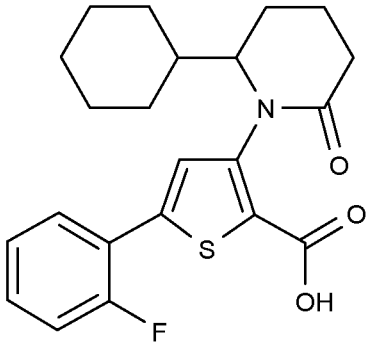
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51	3-[2-Cyclohexyl-6-oxo-4-(4-phenoxy-benzenesulfonyl)-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
52	3-(4-Benzenesulfonyl-2-cyclohexyl-6-oxo-piperazin-1-yl)-5-phenyl-thiophene-2-carboxylic acid	

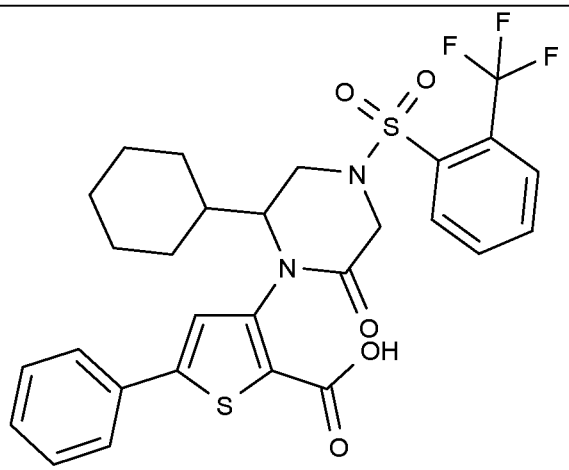
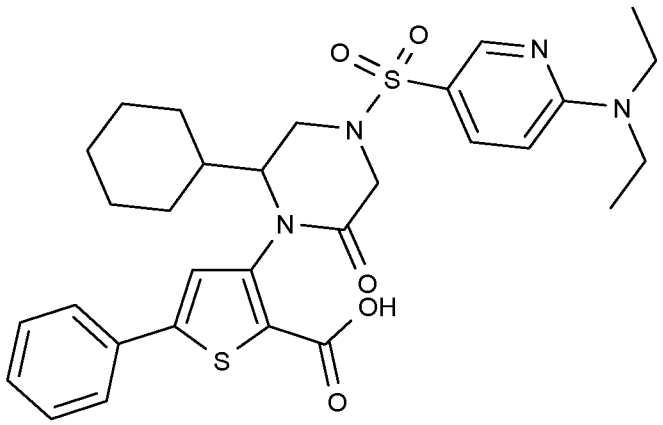
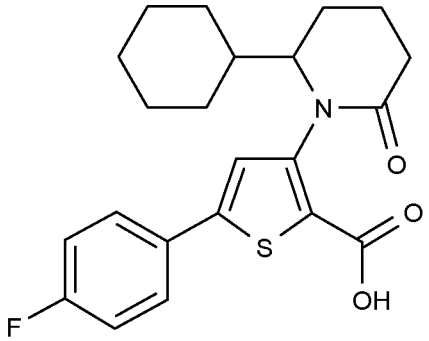
53	3-[2-Cyclohexyl-6-oxo-4-(4-trifluoromethoxy-benzenesulfonyl)-piperazin-1-yl]-5-[(Z)-1-eth-(E)-ylidene-but-2-enyl]-thiophene-2-carboxylic acid	
54	3-[2-Cyclohexyl-6-oxo-4-(4-trifluoromethyl-benzenesulfonyl)-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
55	3-[2-Cyclohexyl-4-(4-ethyl-benzenesulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	

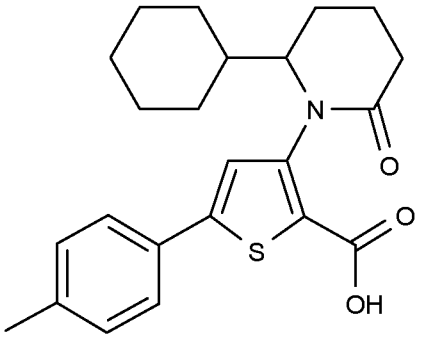
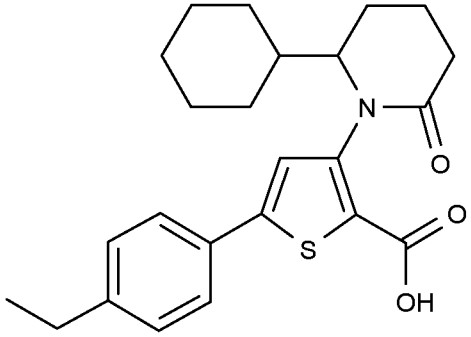
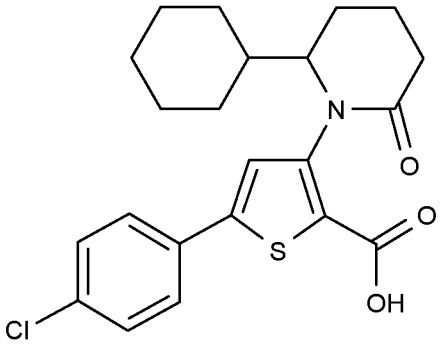
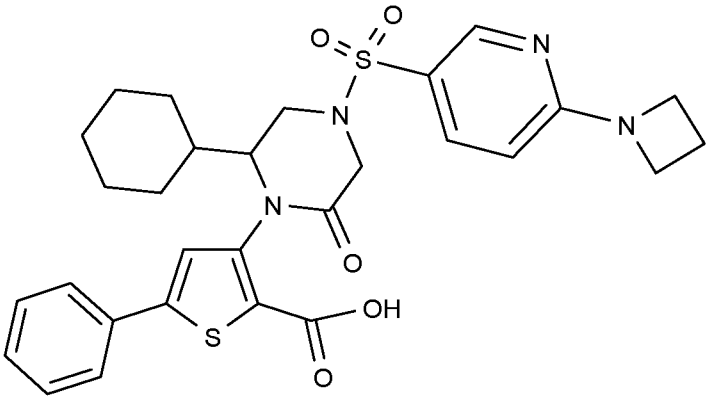
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57	3-[2-Cyclohexyl-4-(1-methyl-1H-indole-7-sulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
58	3-[2-Cyclohexyl-6-oxo-4-(toluene-2-sulfonyl)-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	

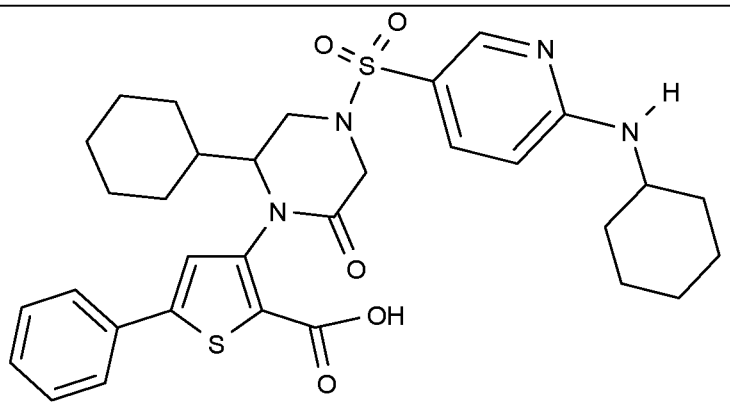
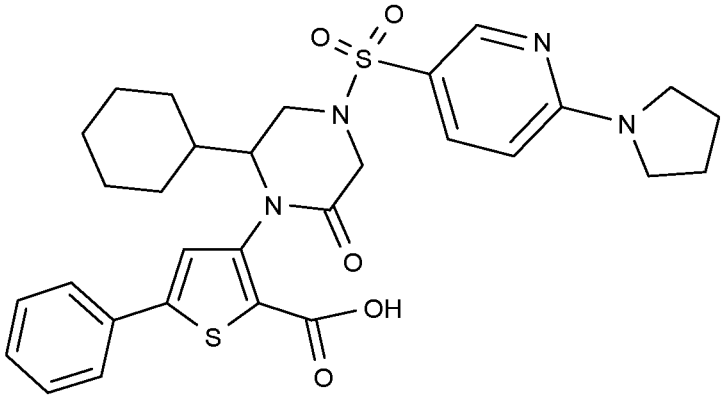
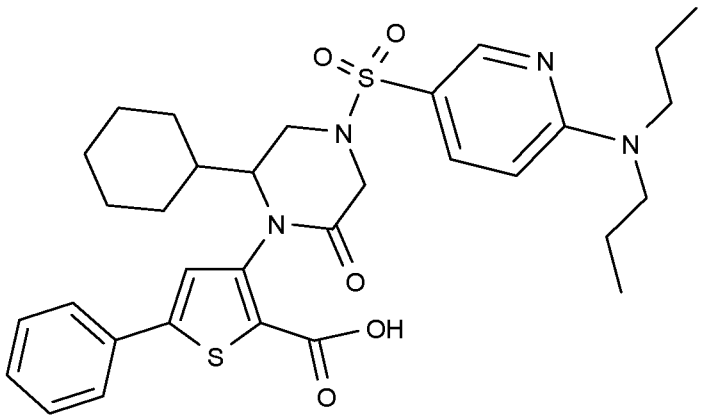
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60	3-[4-(Biphenyl-4-sulfonyl)-2-cyclohexyl-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
61	3-[2-Cyclohexyl-4-(1-methyl-1H-indole-5-sulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	

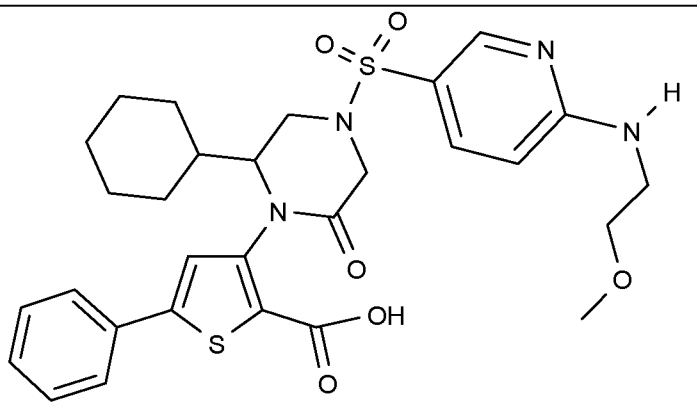
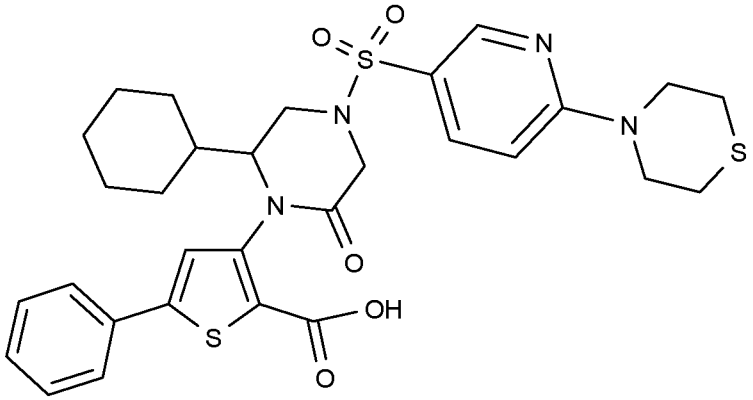
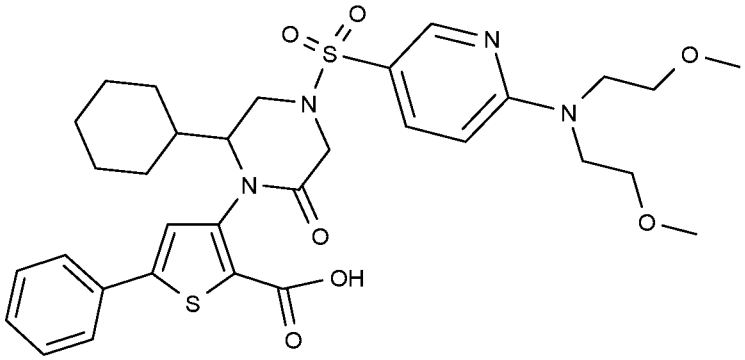
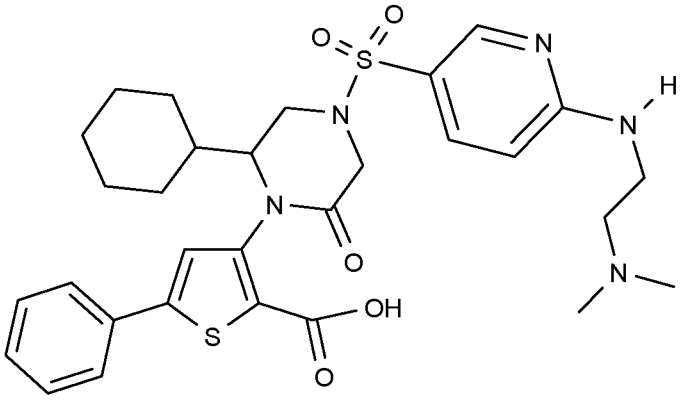
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63	3-{2-Cyclohexyl-4-[3-(2-methyl-pyrimidin-4-yl)-benzenesulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
64	3-[2-Cyclohexyl-4-(1-methyl-1H-indole-4-sulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	

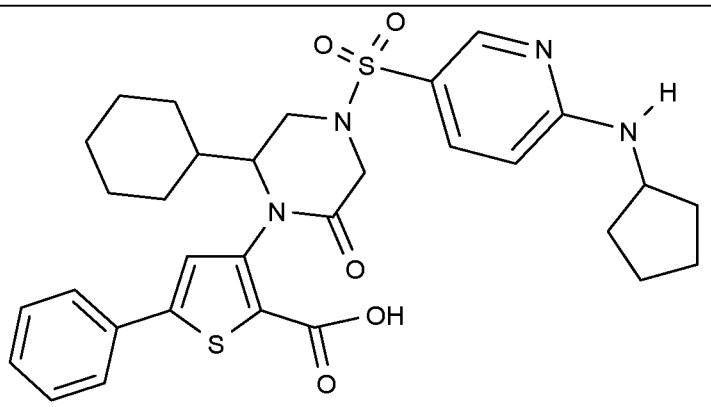
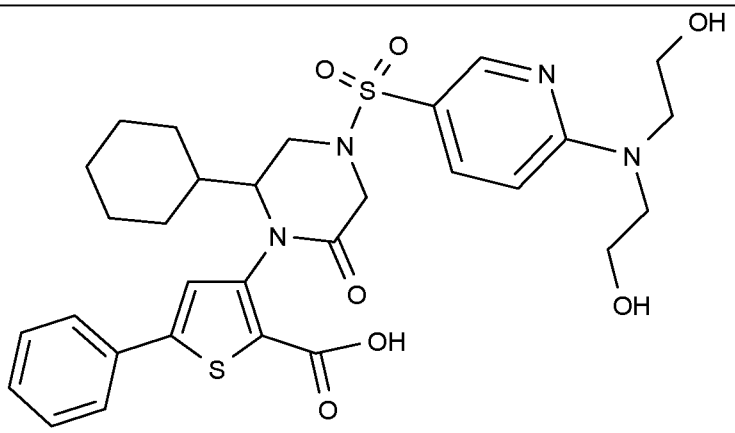
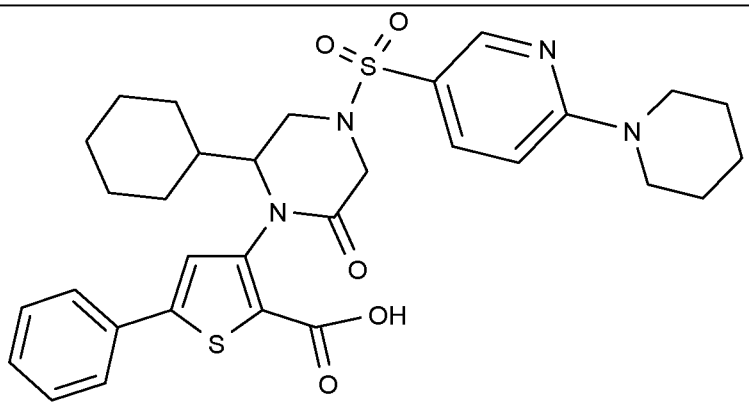
65	3-[4-(Biphenyl-3-sulfonyl)-2-cyclohexyl-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
66	3-[2-Cyclohexyl-4-(4-fluoro-3-trifluoromethyl-benzenesulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
67	3-(2-Cyclohexyl-6-oxo-piperidin-1-yl)-5-(2-fluoro-phenyl)-thiophene-2-carboxylic acid	

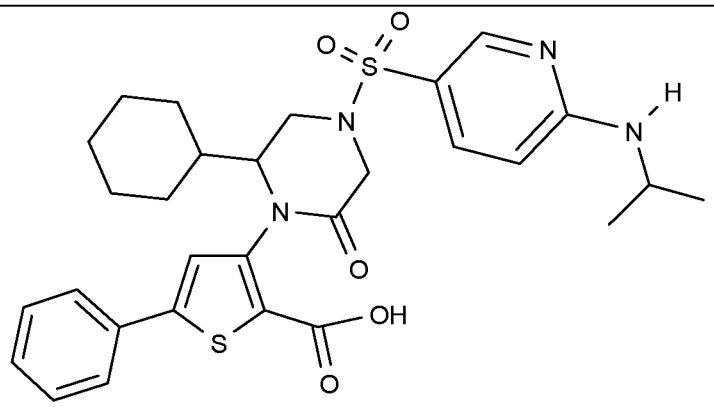
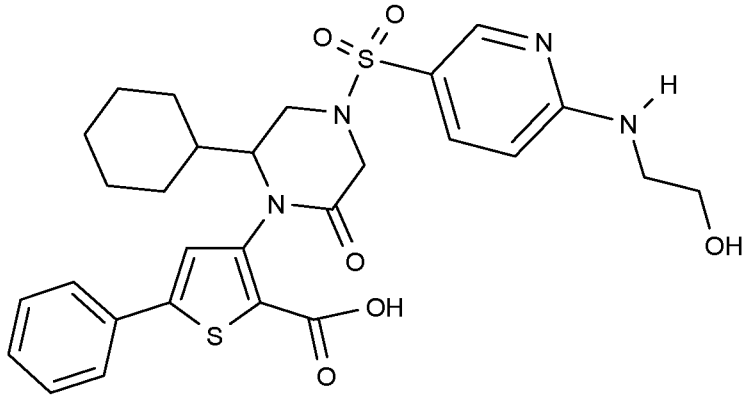
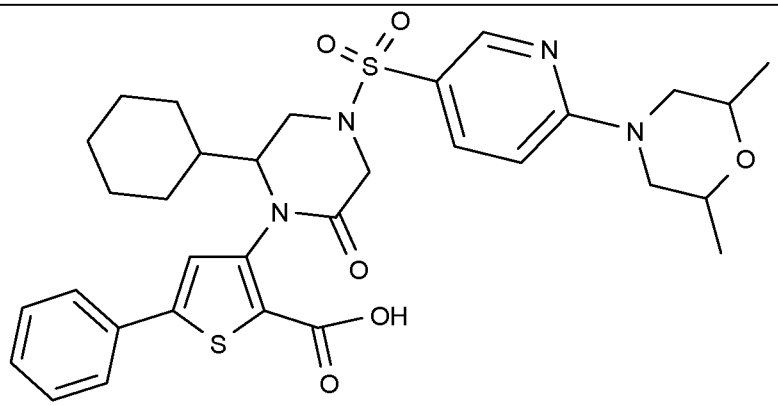
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69	3-[2-Cyclohexyl-4-(6-diethylamino-pyridine-3-sulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
70	3-(2-Cyclohexyl-6-oxo-piperidin-1-yl)-5-(4-fluoro-phenyl)-thiophene-2-carboxylic acid	

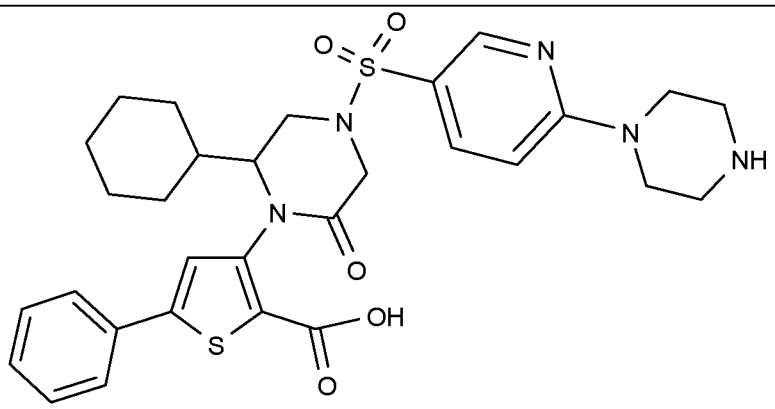
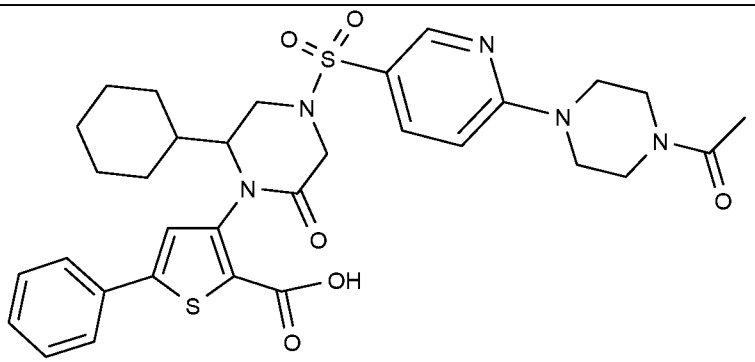
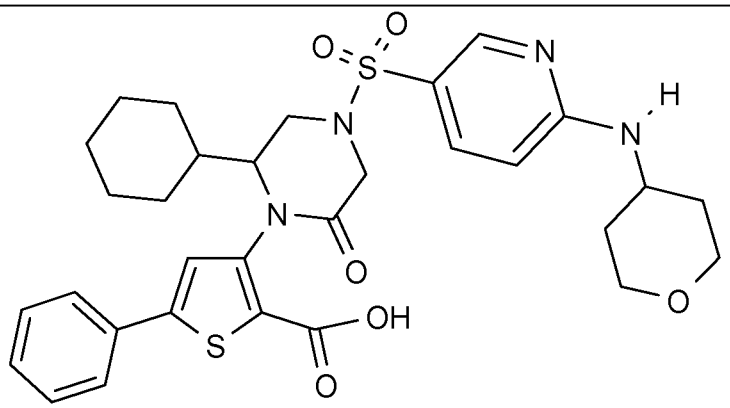
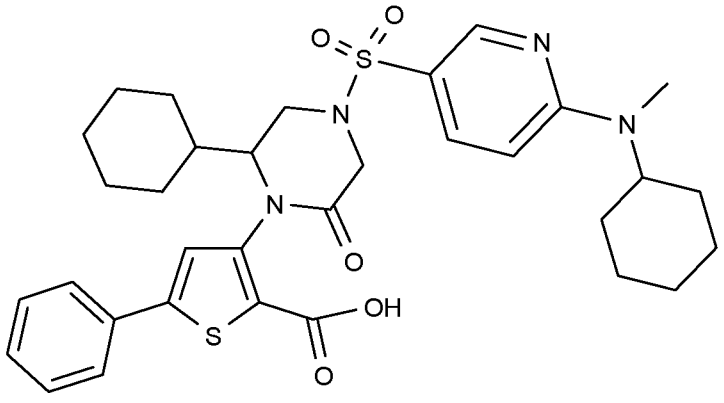
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72	3-(2-Cyclohexyl-6-oxo-piperidin-1-yl)-5-(4-ethyl-phenyl)-thiophene-2-carboxylic acid	
73	5-(4-Chloro-phenyl)-3-(2-cyclohexyl-6-oxo-piperidin-1-yl)-thiophene-2-carboxylic acid	
74	3-[4-(6-Azetidin-1-yl-pyridine-3-sulfonyl)-2-cyclohexyl-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	

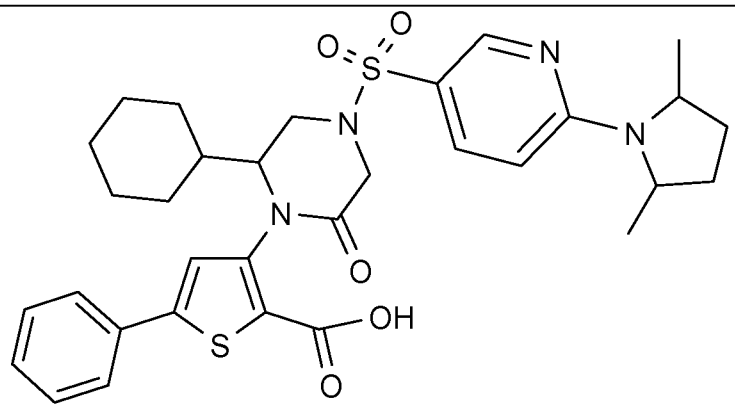
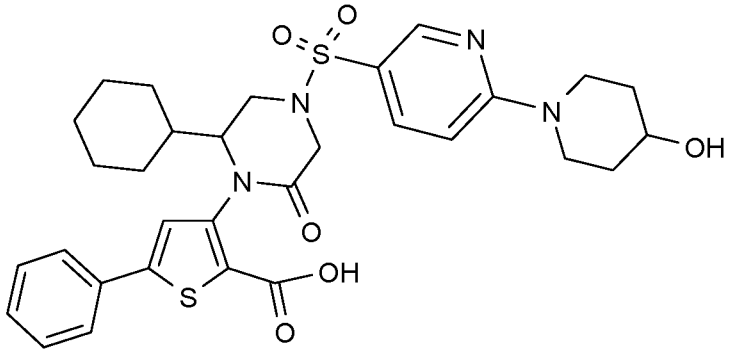
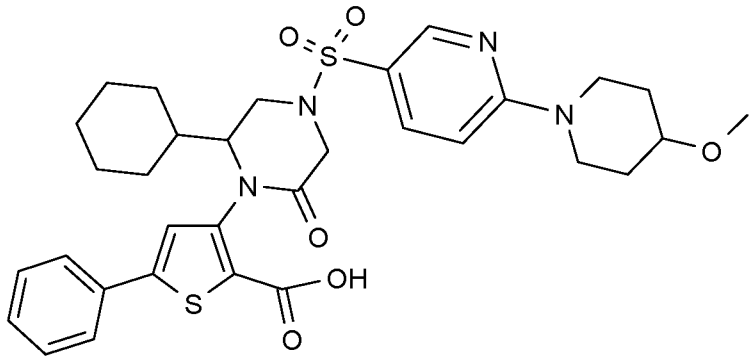
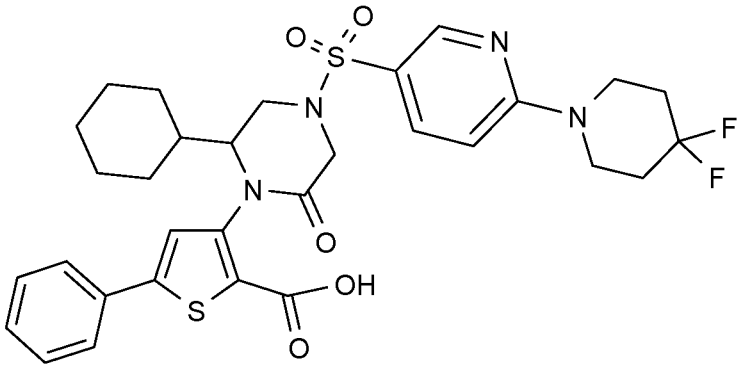
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76	3-[2-Cyclohexyl-6-oxo-4-(6-pyrrolidin-1-yl-pyridine-3-sulfonyl)-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
77	3-[2-Cyclohexyl-4-(6-dipropylamino-pyridine-3-sulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	

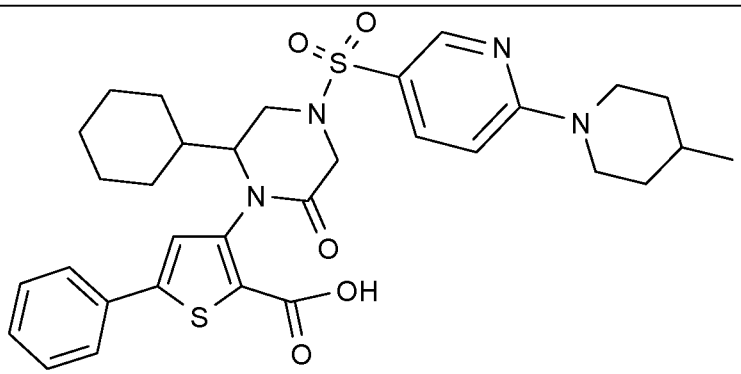
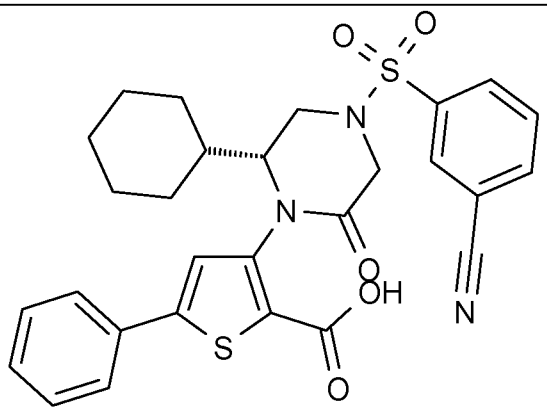
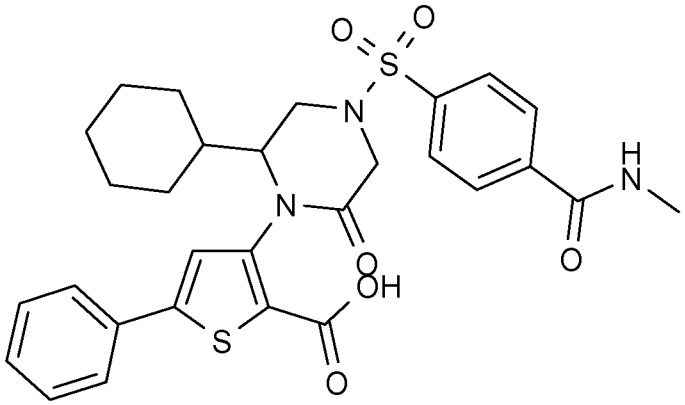
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80	3-(4-{6-[Bis-(2-methoxy-ethyl)-amino]-pyridine-3-sulfonyl}-2-cyclohexyl-6-oxo-piperazin-1-yl)-5-phenyl-thiophene-2-carboxylic acid	
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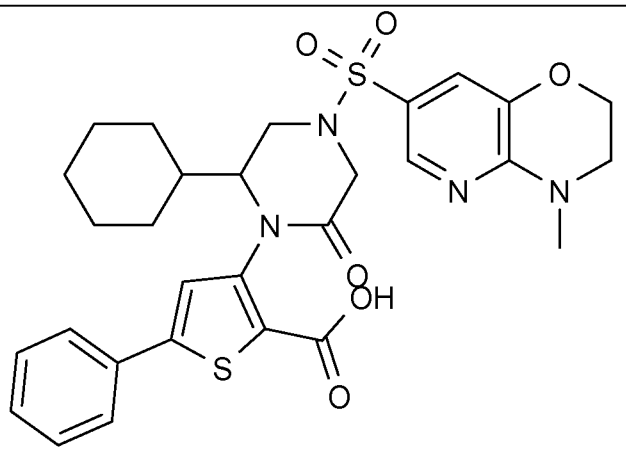
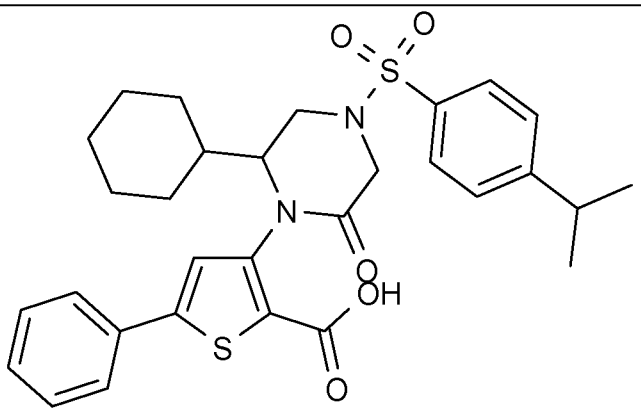
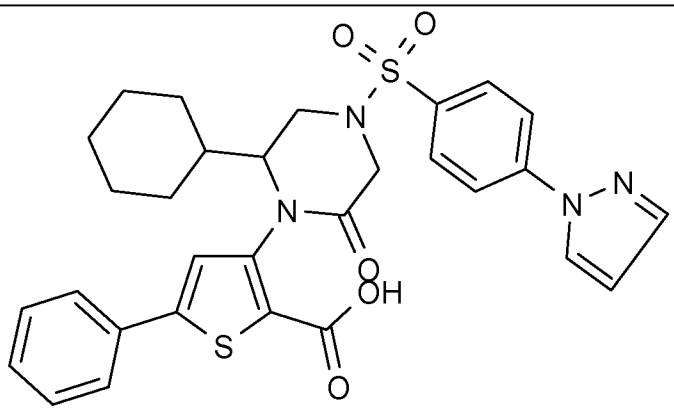
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83	3-(4-{6-[Bis-(2-hydroxy-ethyl)-amino]-pyridine-3-sulfonyl}-2-cyclohexyl-6-oxo-piperazin-1-yl)-5-phenyl-thiophene-2-carboxylic acid	
84	3-[2-Cyclohexyl-6-oxo-4-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-sulfonyl)-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	

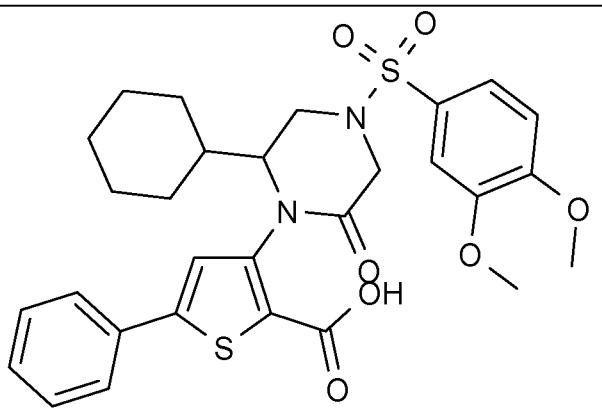
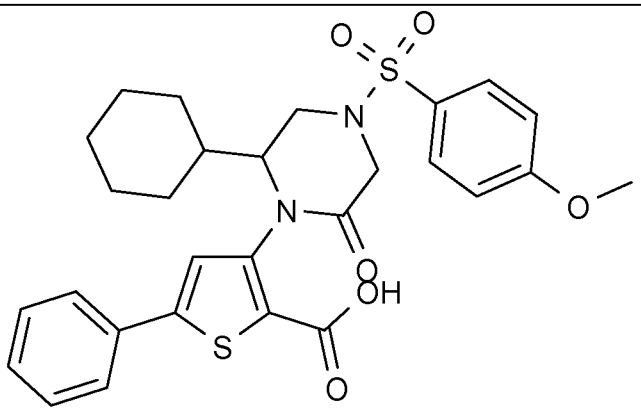
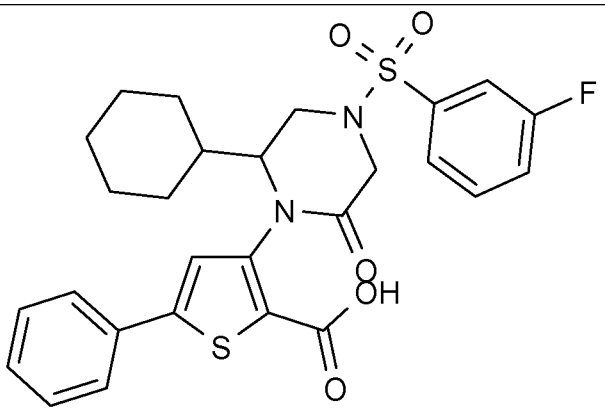
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86	3-{2-Cyclohexyl-4-[6-(2-hydroxy-ethylamino)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
87	3-{2-Cyclohexyl-4-[6-(2,6-dimethyl-morpholin-4-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	

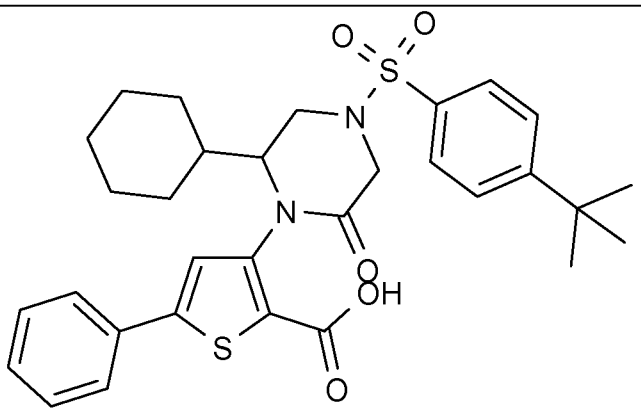
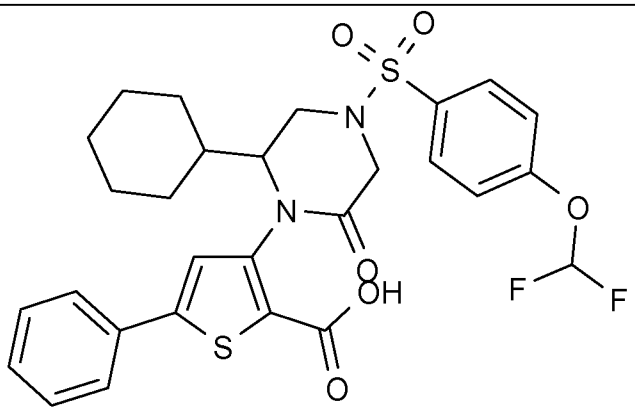
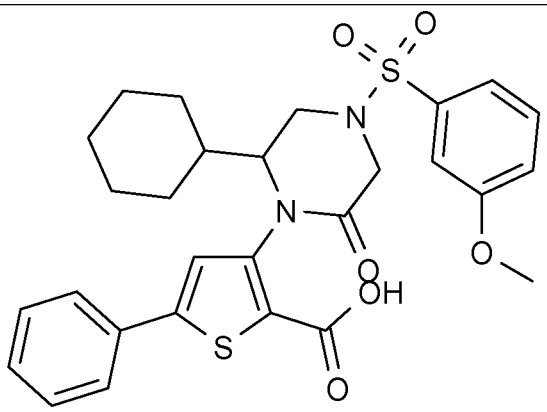
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89	3-{4-[6-(4-Acetyl-piperazin-1-yl)-pyridine-3-sulfonyl]-2-cyclohexyl-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
90	3-{2-Cyclohexyl-6-oxo-4-[6-(tetrahydro-pyran-4-ylamino)-pyridine-3-sulfonyl]-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
91	3-{2-Cyclohexyl-4-[6-(cyclohexyl-methyl-amino)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	

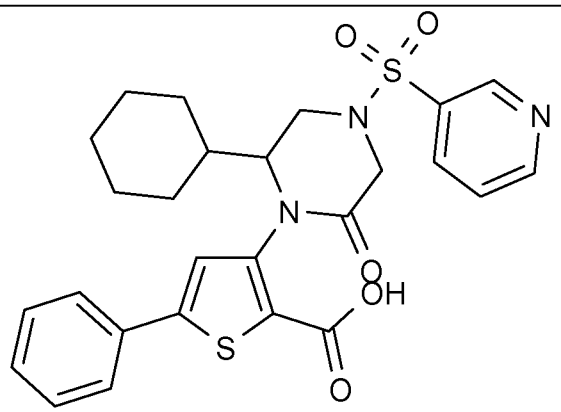
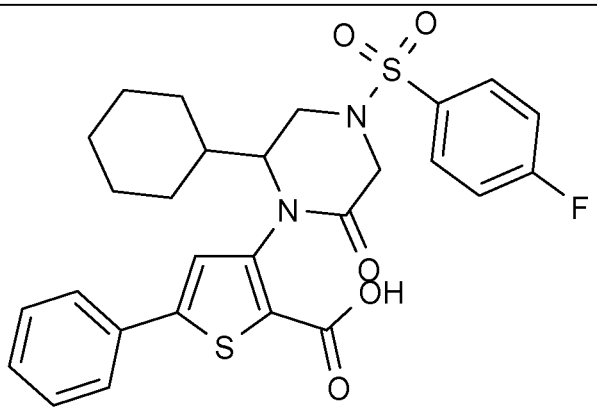
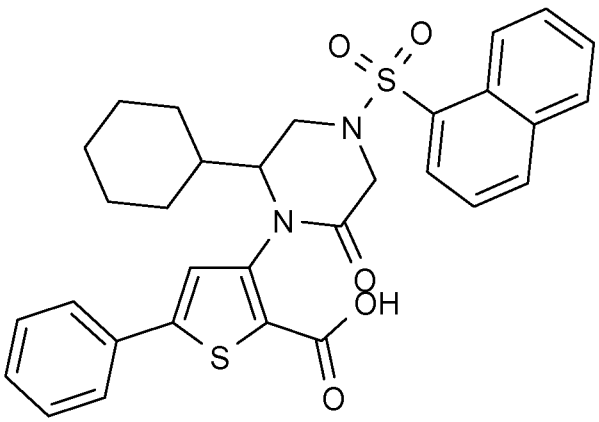
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93	3-[2-Cyclohexyl-4-(4-hydroxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-sulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
94	3-[2-Cyclohexyl-4-(4-methoxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-sulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
95	3-[2-Cyclohexyl-4-(4,4-difluoro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-sulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	

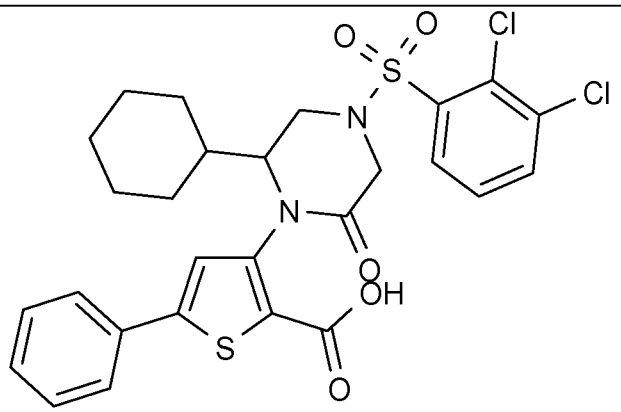
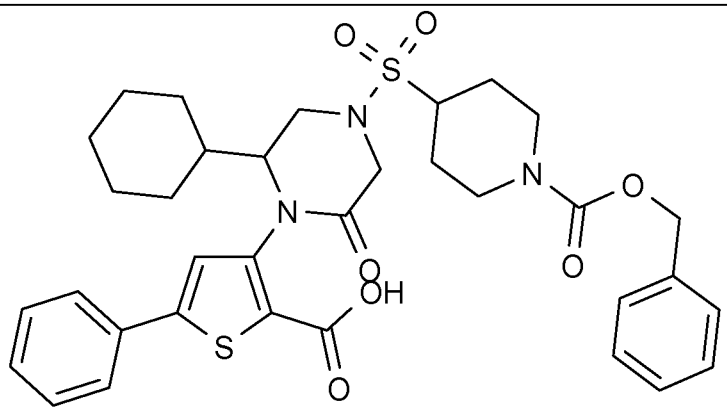
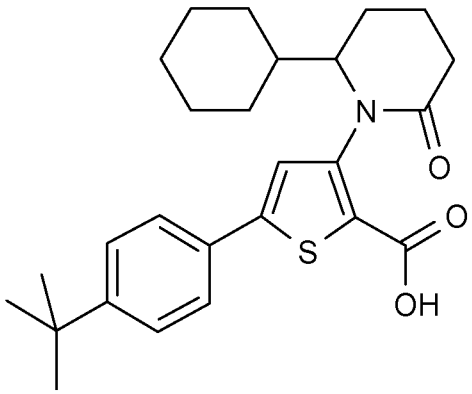
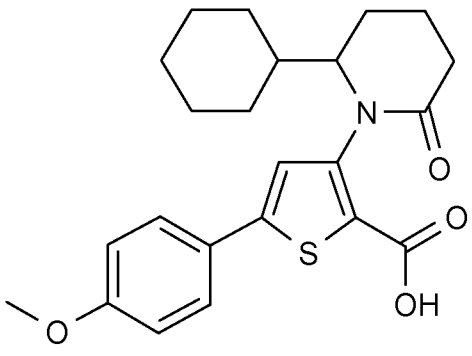
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97	3-[(R)-4-(3-Cyano-benzenesulfonyl)-2-cyclohexyl-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
98	3-[2-Cyclohexyl-4-(4-methylcarbamoyl-benzenesulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	

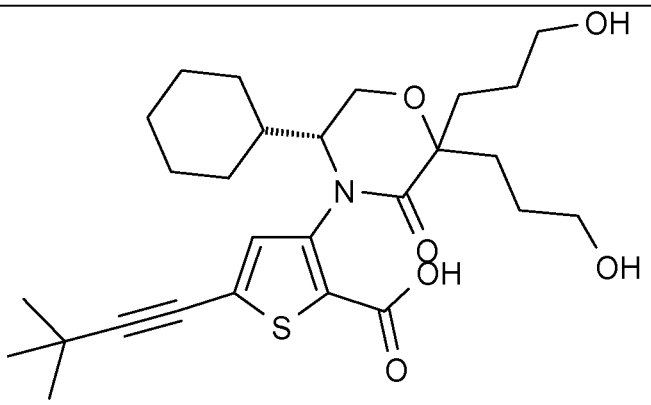
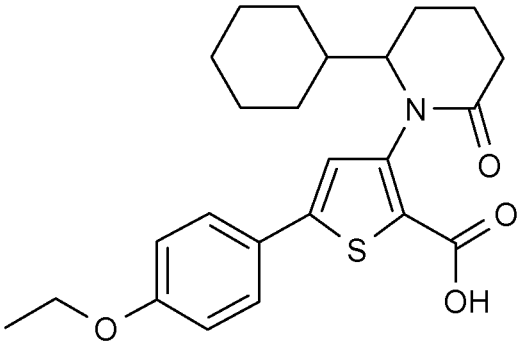
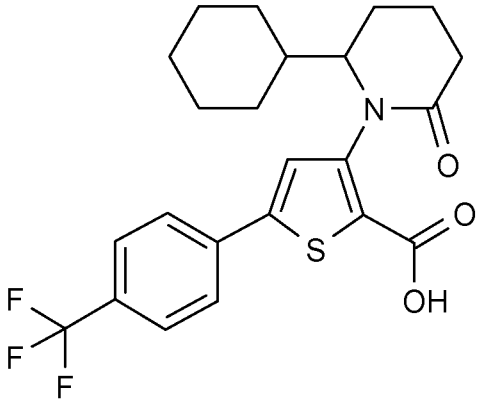
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100	3-[2-Cyclohexyl-4-(4-isopropyl-benzenesulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
101	3-[2-Cyclohexyl-6-oxo-4-(4-pyrazol-1-yl-benzenesulfonyl)-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	

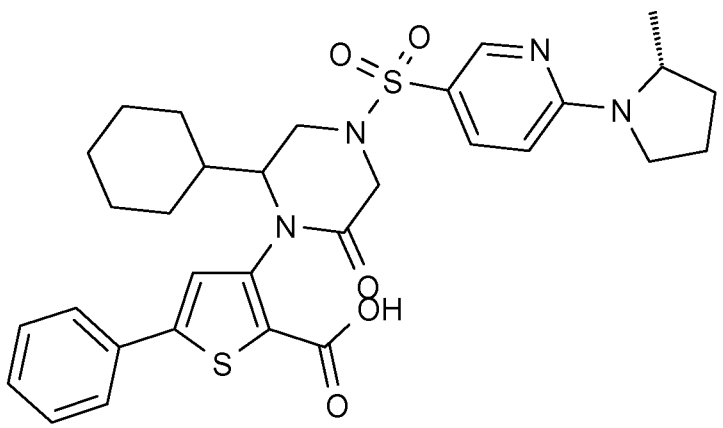
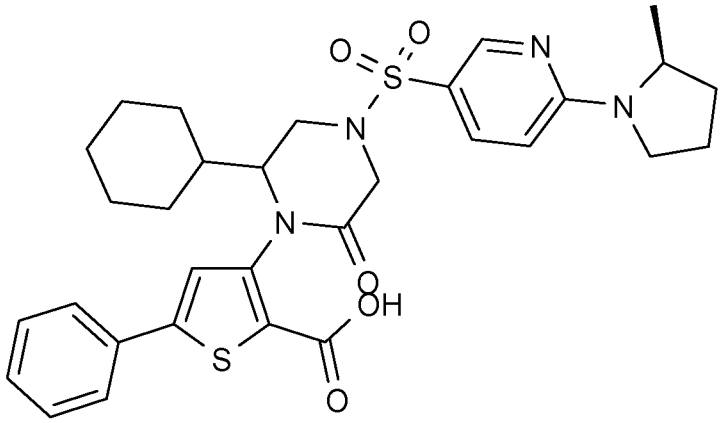
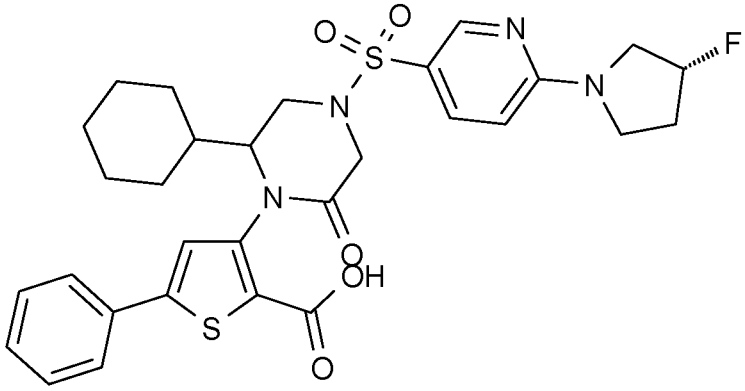
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103	3-[2-Cyclohexyl-4-(4-methoxy-benzenesulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
104	3-[2-Cyclohexyl-4-(3-fluoro-benzenesulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	

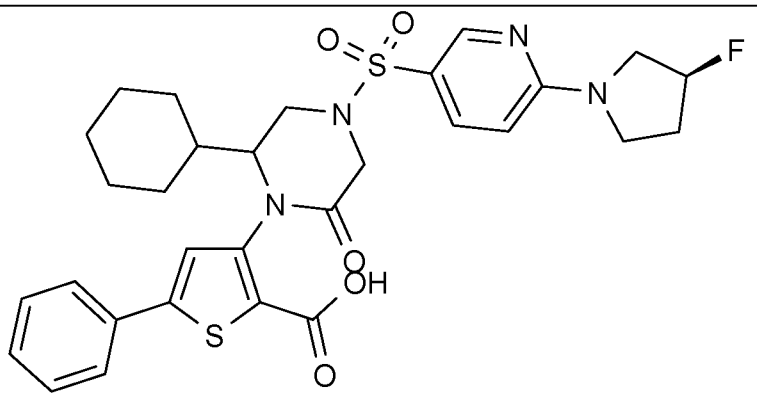
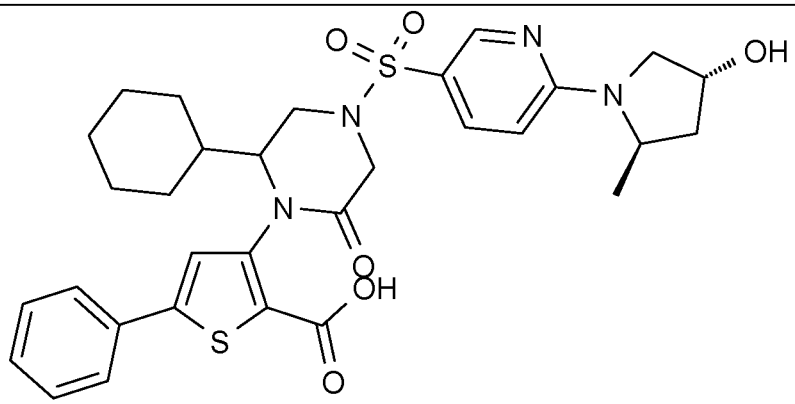
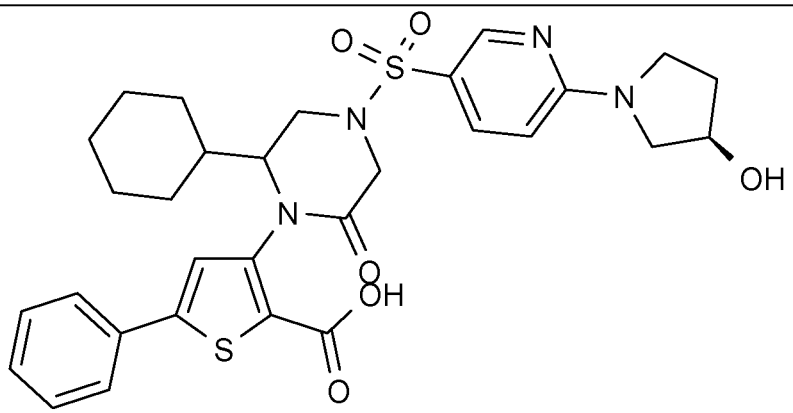
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106	3-[2-Cyclohexyl-4-(4-difluoromethoxy-benzenesulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
107	3-[(R)-2-Cyclohexyl-4-(3-methoxy-benzenesulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	

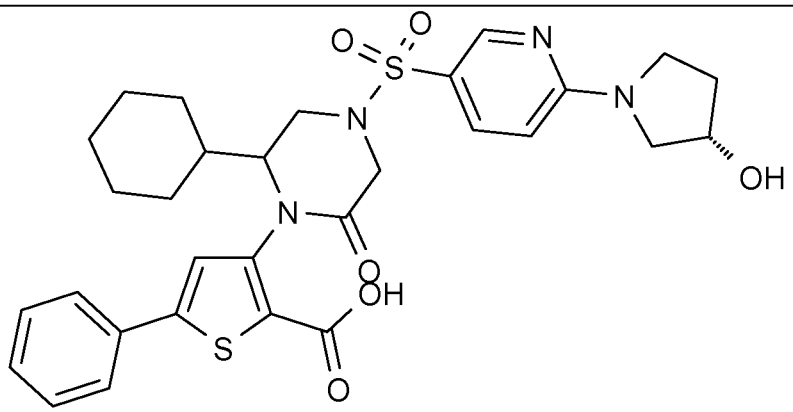
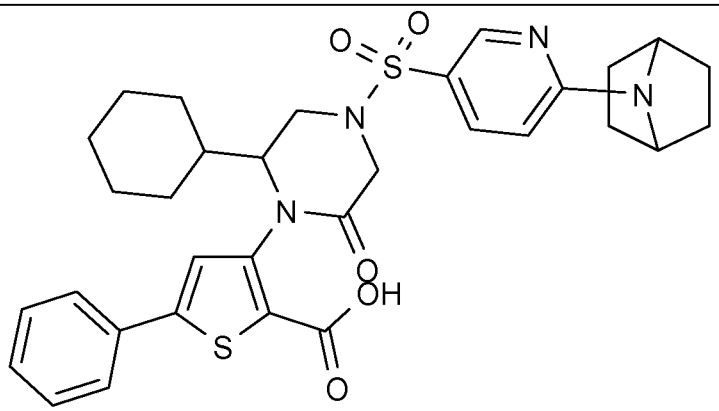
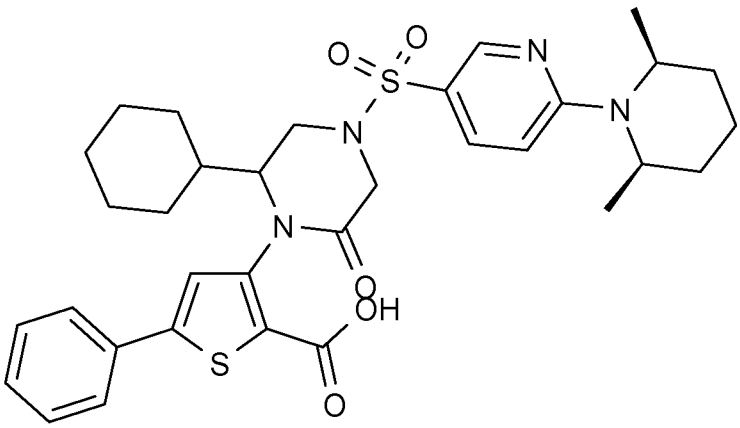
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109	3-[2-Cyclohexyl-4-(4-fluoro-benzenesulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
110	3-[2-Cyclohexyl-4-(naphthalene-1-sulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	

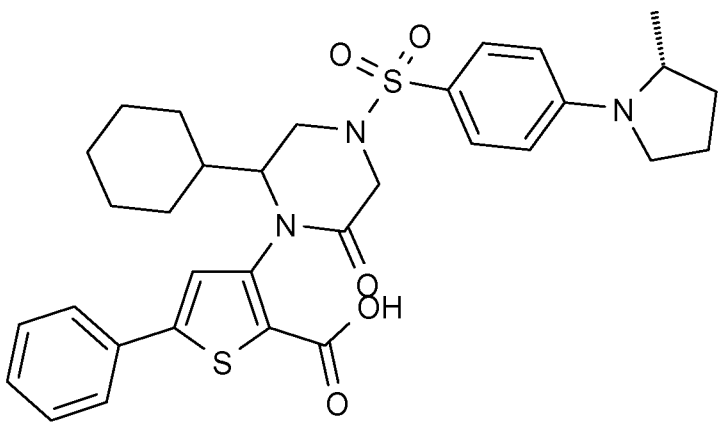
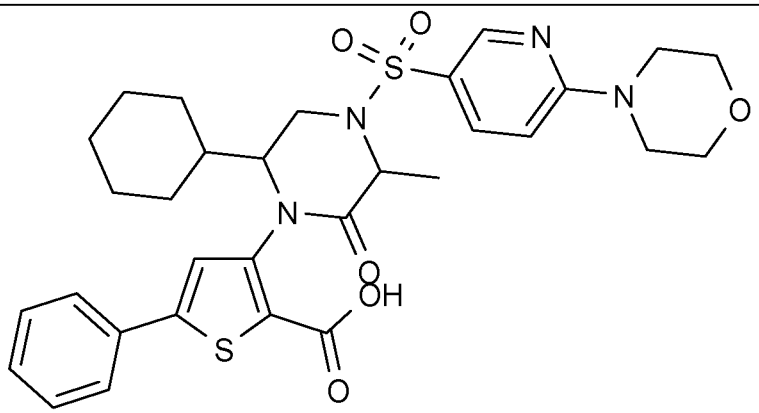
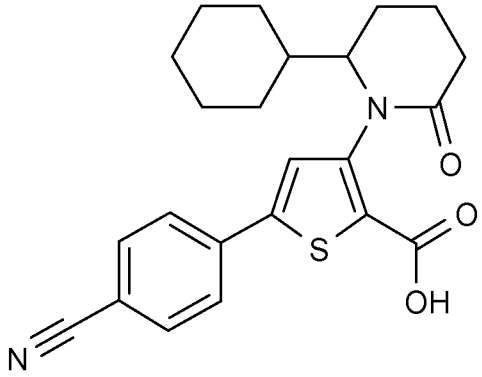
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112	4-[4-(2-Carboxy-5-phenyl-thiophen-3-yl)-3-cyclohexyl-5-oxo-piperazine-1-sulfonyl]-piperidine-1-carboxylic acid benzyl ester	
113	5-(4-tert-Butyl-phenyl)-3-(2-cyclohexyl-6-oxo-piperidin-1-yl)-thiophene-2-carboxylic acid	
114	3-(2-Cyclohexyl-6-oxo-piperidin-1-yl)-5-(4-methoxy-phenyl)-thiophene-2-carboxylic acid	

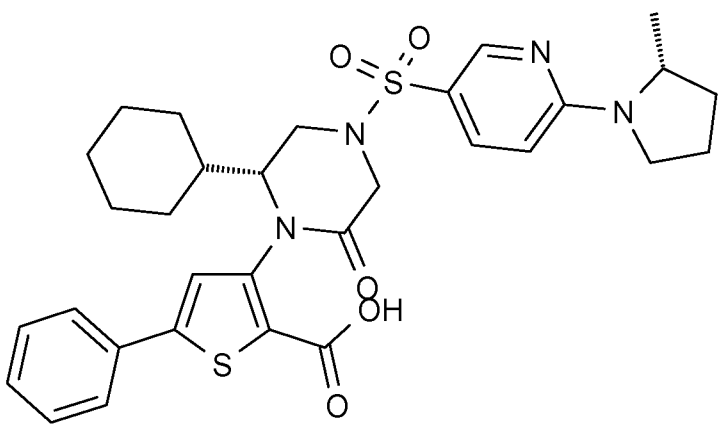
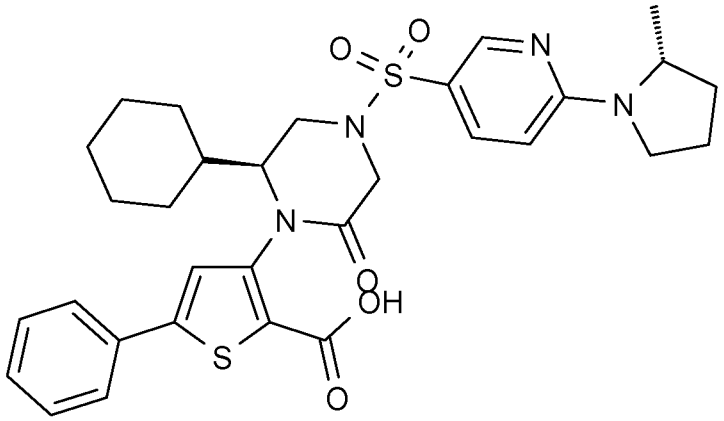
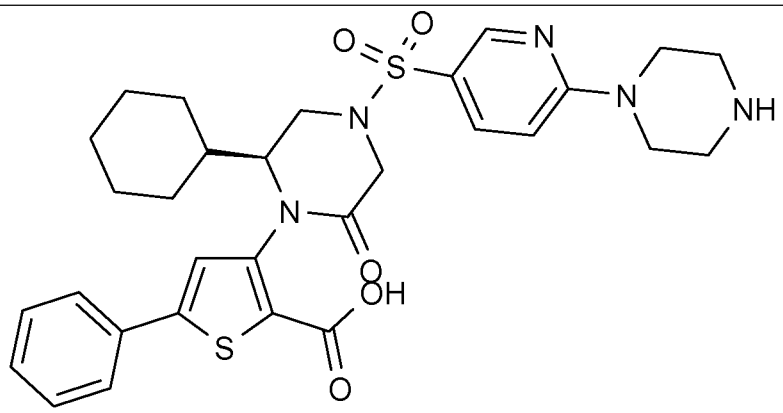
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116	3-(2-Cyclohexyl-6-oxo-piperidin-1-yl)-5-(4-ethoxy-phenyl)-thiophene-2-carboxylic acid	
117	3-(2-Cyclohexyl-6-oxo-piperidin-1-yl)-5-(4-trifluoromethyl-phenyl)-thiophene-2-carboxylic acid	

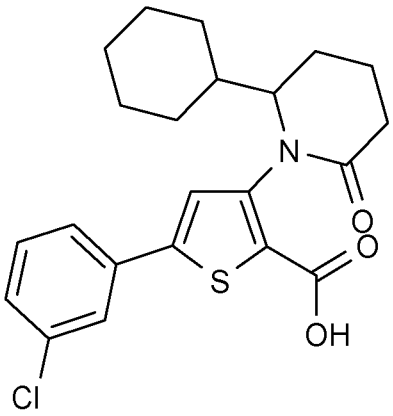
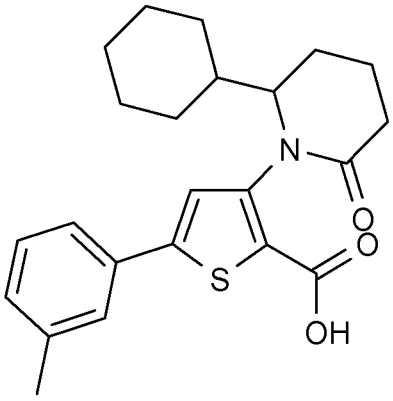
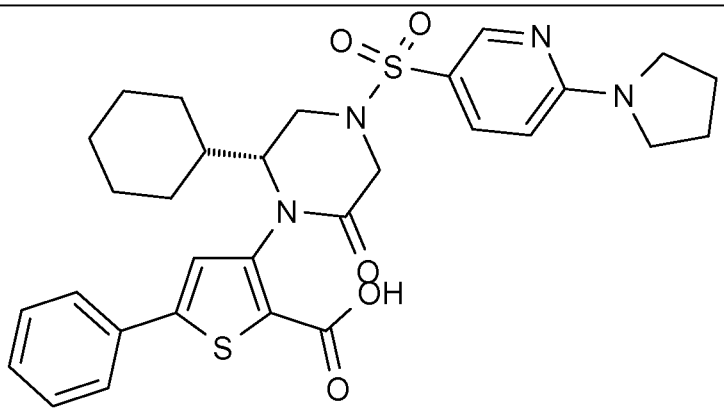
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120	3-{2-Cyclohexyl-4-[6-((R)-3-fluoro-pyrrolidin-1-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	

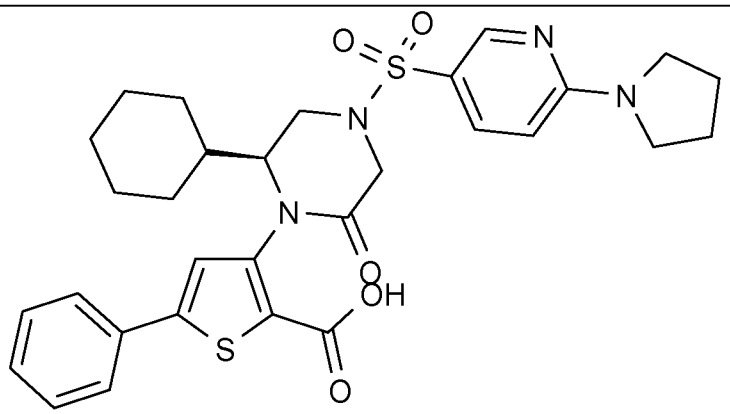
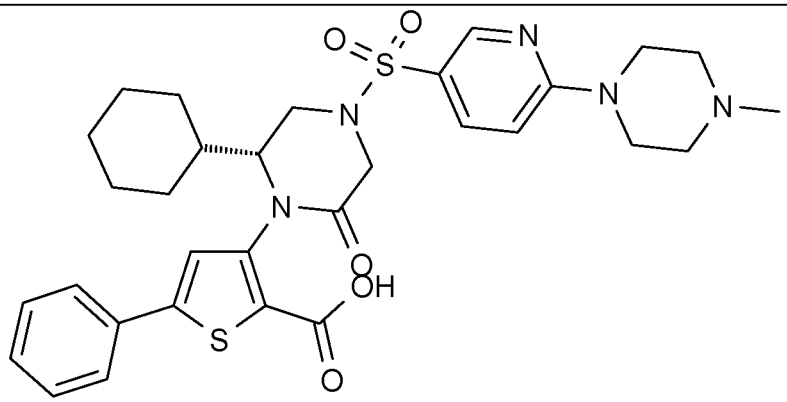
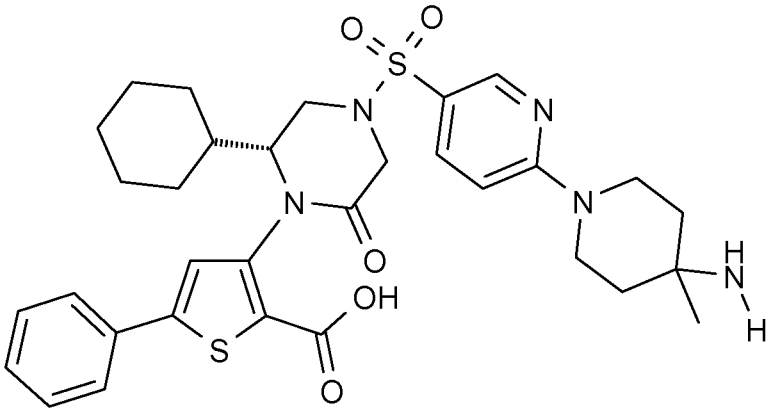
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122	3-{2-Cyclohexyl-4-[6-((2R,4R)-4-hydroxy-2-methyl-pyrrolidin-1-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
123	3-{2-Cyclohexyl-4-[6-((R)-3-hydroxy-pyrrolidin-1-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	

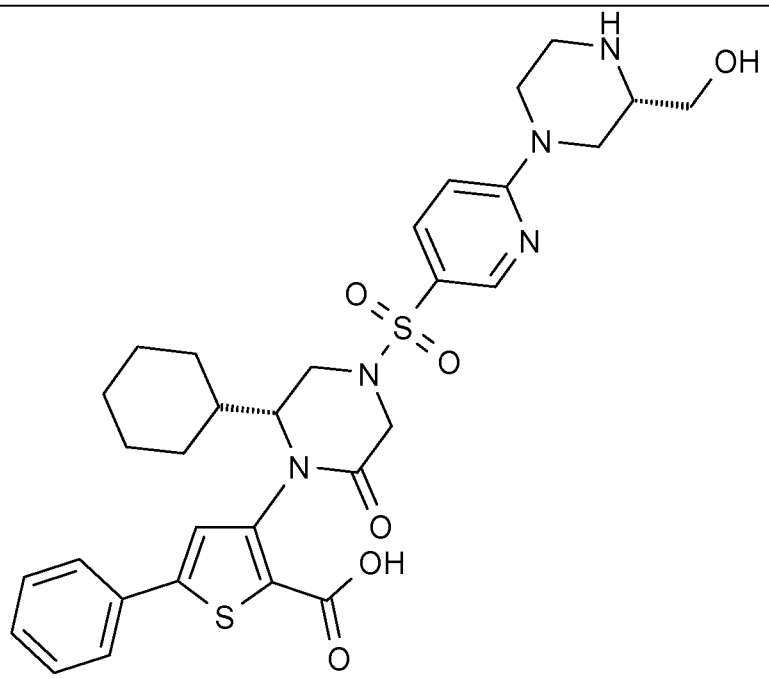
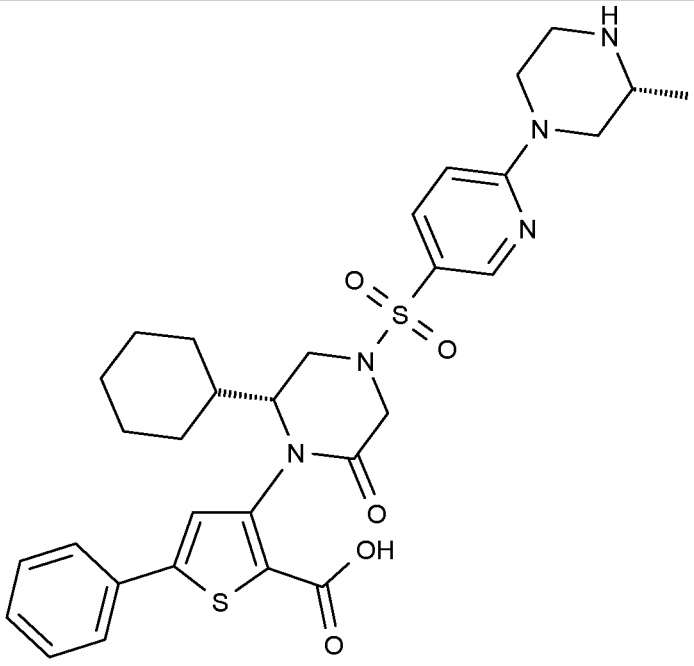
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125	3-{4-[6-(7-Aza-bicyclo[2.2.1]hept-7-yl)-pyridine-3-sulfonyl]-2-cyclohexyl-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
126	3-[2-Cyclohexyl-4-((2S,6R)-2,6-dimethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-sulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	

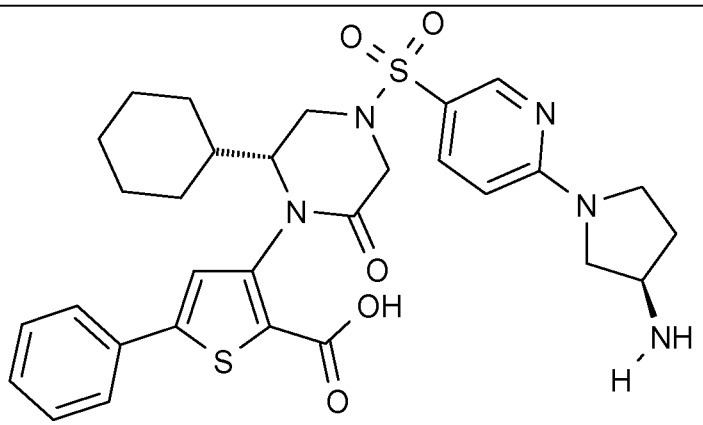
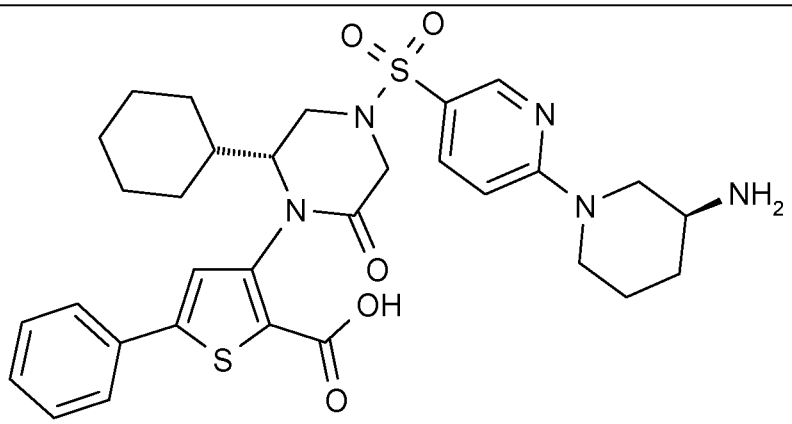
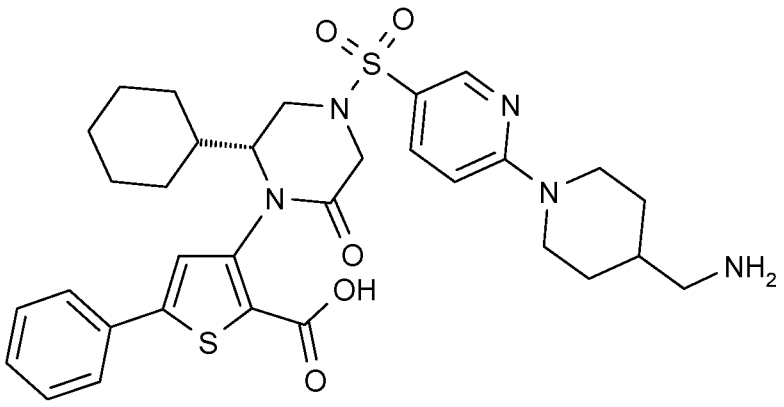
127	3-{2-Cyclohexyl-4-[4-((R)-2-methyl-pyrrolidin-1-yl)-benzenesulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
128	3-[6-Cyclohexyl-3-methyl-4-(6-morpholin-4-yl-pyridine-3-sulfonyl)-2-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
129	5-(4-Cyano-phenyl)-3-(2-cyclohexyl-6-oxo-piperidin-1-yl)-thiophene-2-carboxylic acid	

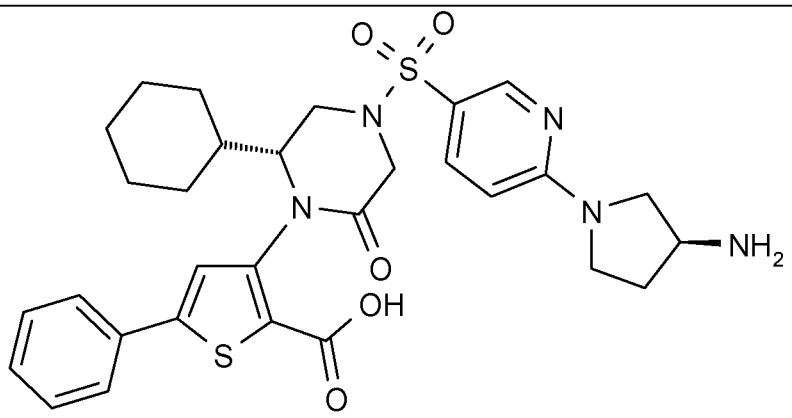
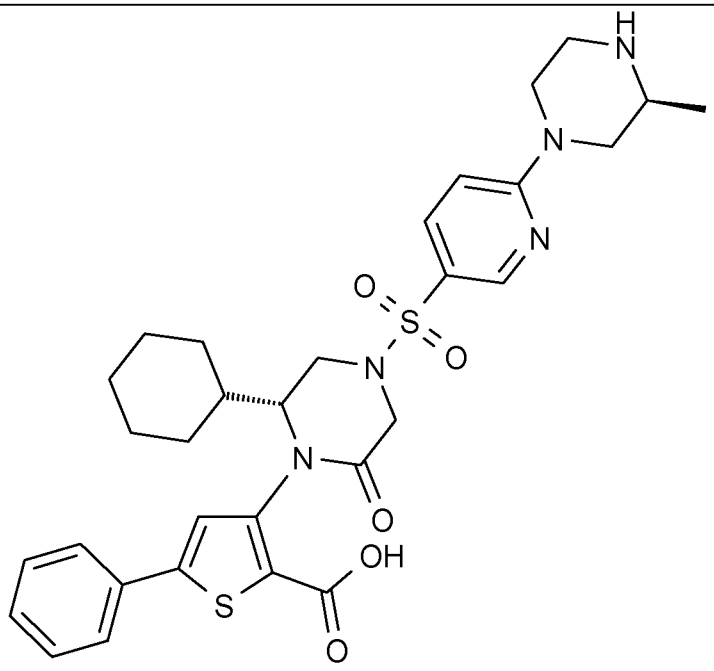
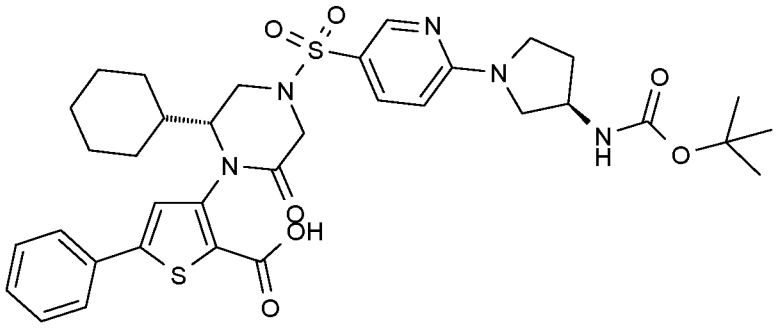
130	3-{(R)-2-Cyclohexyl-4-[6-((R)-2-methyl-pyrrolidin-1-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
131	3-{(S)-2-Cyclohexyl-4-[6-((R)-2-methyl-pyrrolidin-1-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
132	3-[(S)-2-Cyclohexyl-6-oxo-4-(6-piperazin-1-yl-pyridine-3-sulfonyl)-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	

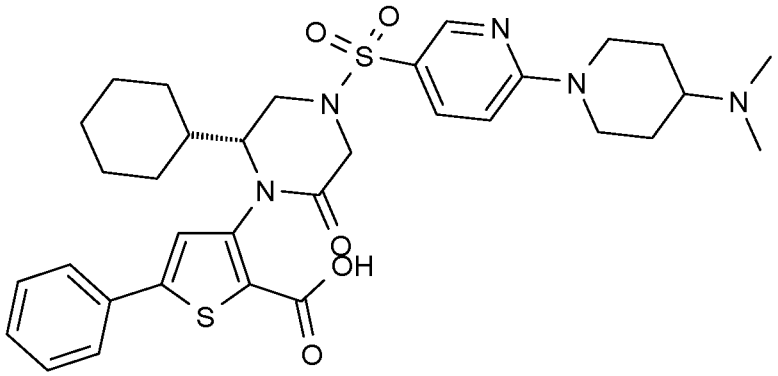
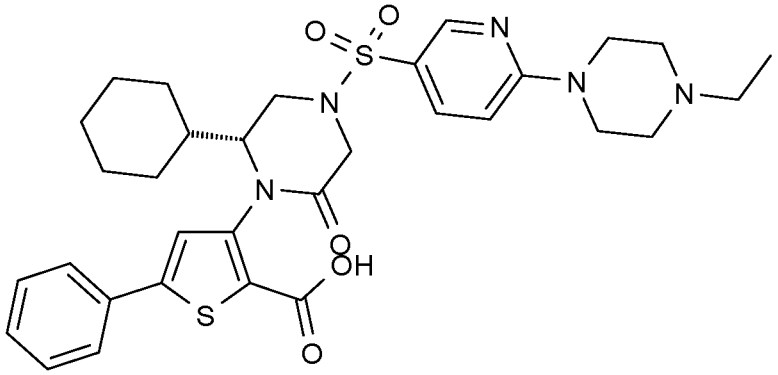
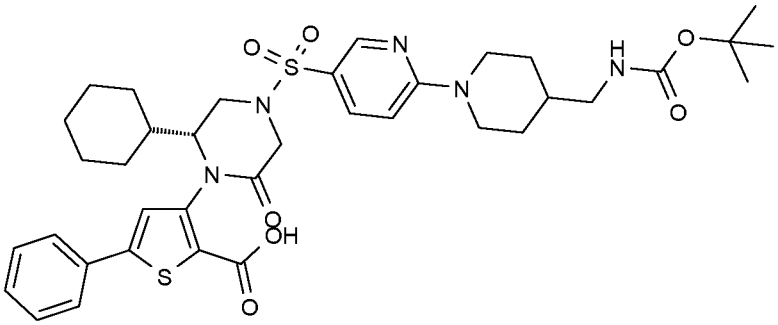
133	5-(3-Chloro-phenyl)-3-(2-cyclohexyl-6-oxo-piperidin-1-yl)-thiophene-2-carboxylic acid	
134	3-(2-Cyclohexyl-6-oxo-piperidin-1-yl)-5-m-tolyl-thiophene-2-carboxylic acid	
135	3-[(R)-2-Cyclohexyl-6-oxo-4-(6-pyrrolidin-1-yl-pyridine-3-sulfonyl)-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	

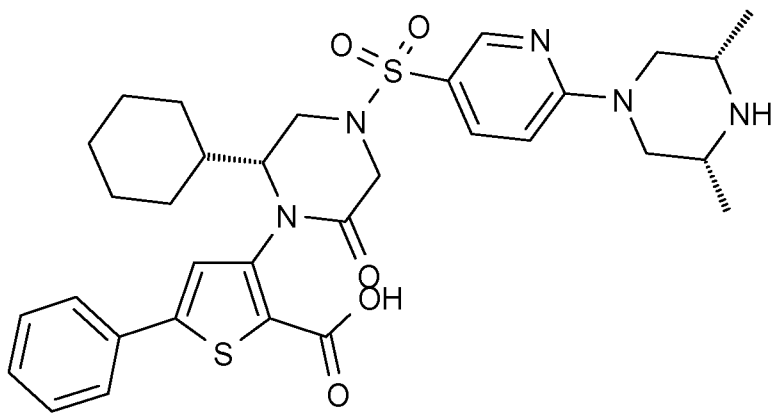
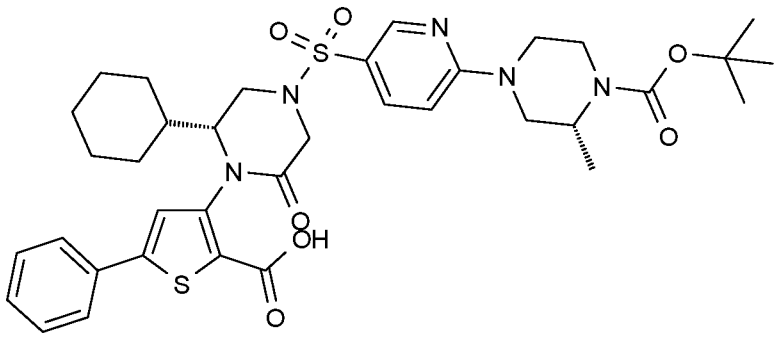
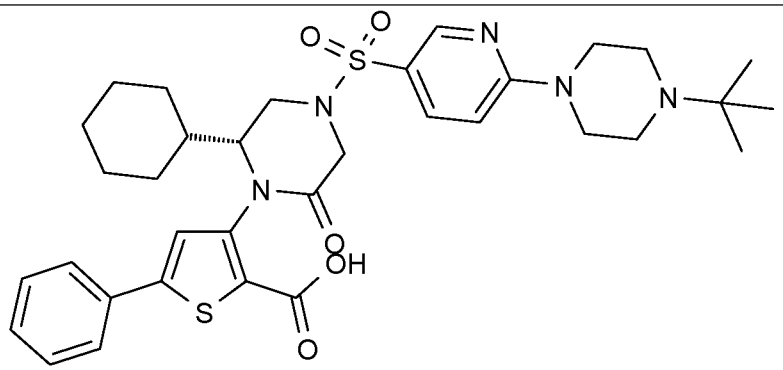
136	3-[(S)-2-Cyclohexyl-6-oxo-4-(6-pyrrolidin-1-yl-pyridine-3-sulfonyl)-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
137	3-{(R)-2-Cyclohexyl-4-[6-(4-methyl-piperazin-1-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
138	3-[(R)-4-(4-Amino-4-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-sulfonyl)-2-cyclohexyl-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	

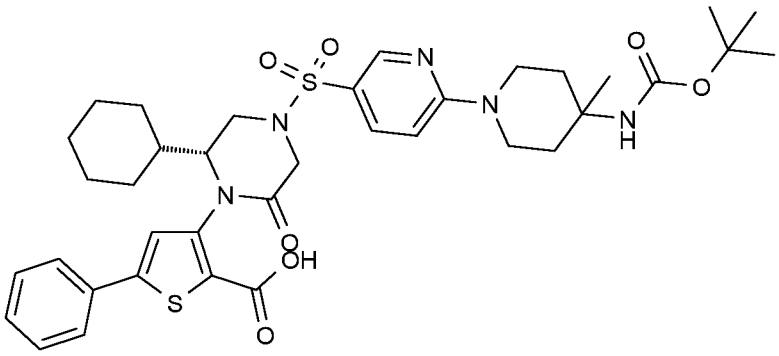
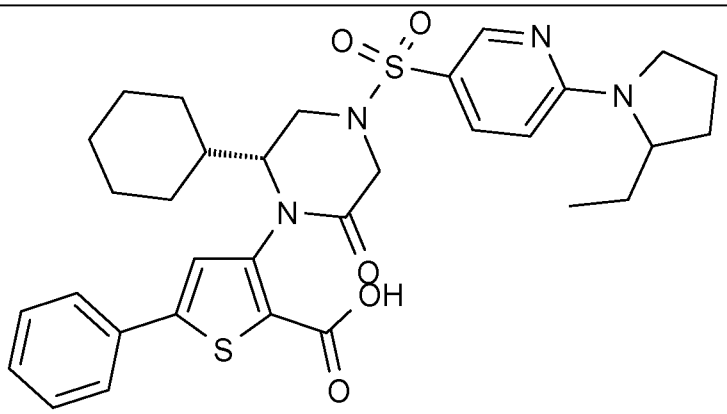
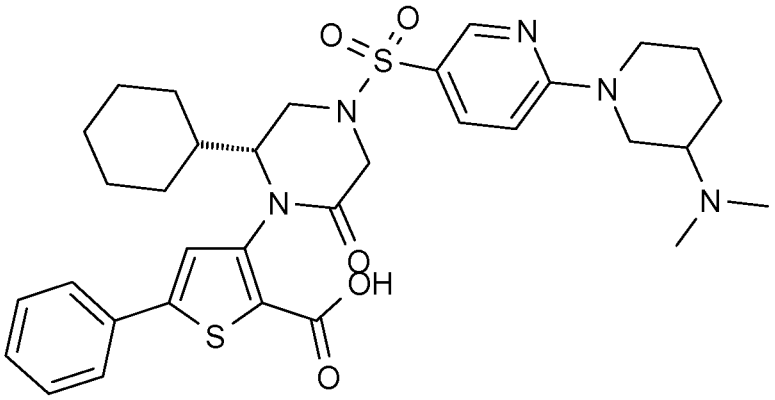
139	3-{(R)-2-Cyclohexyl-4-[6-((S)-3-hydroxymethyl-piperazin-1-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
140	3-{(R)-2-Cyclohexyl-4-[6-((R)-3-methyl-piperazin-1-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	

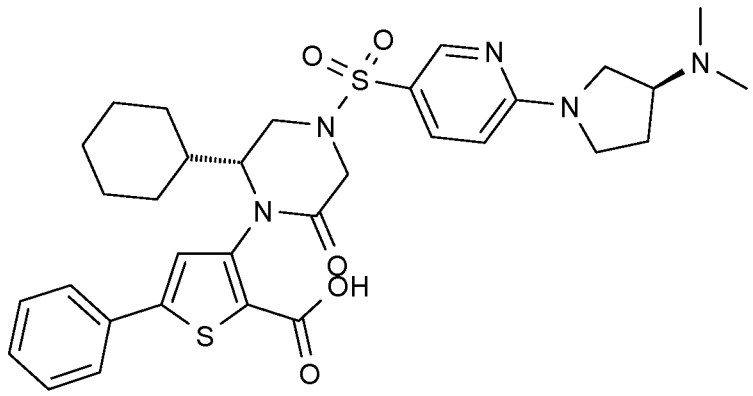
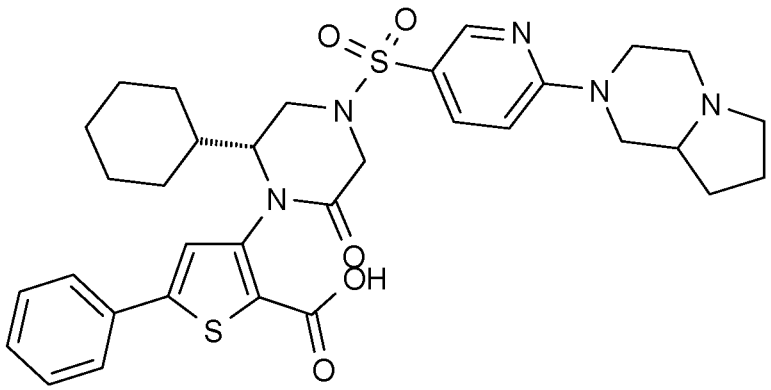
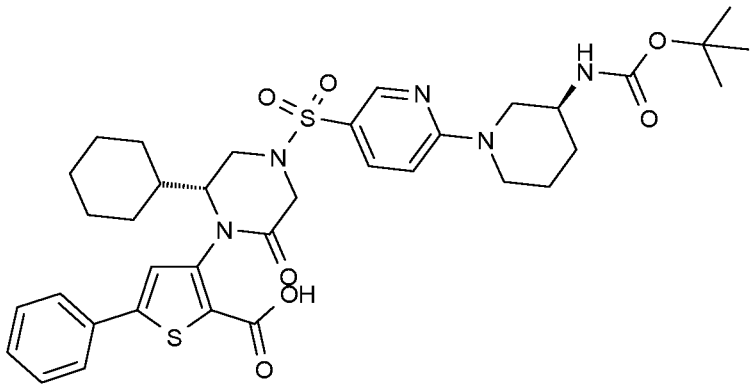
141	3-{(R)-4-[6-((R)-3-Amino-pyrrolidin-1-yl)-pyridine-3-sulfonyl]-2-cyclohexyl-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
142	3-[(R)-4-((S)-3-Amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-sulfonyl)-2-cyclohexyl-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
143	3-[(R)-4-(4-Aminomethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-sulfonyl)-2-cyclohexyl-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	

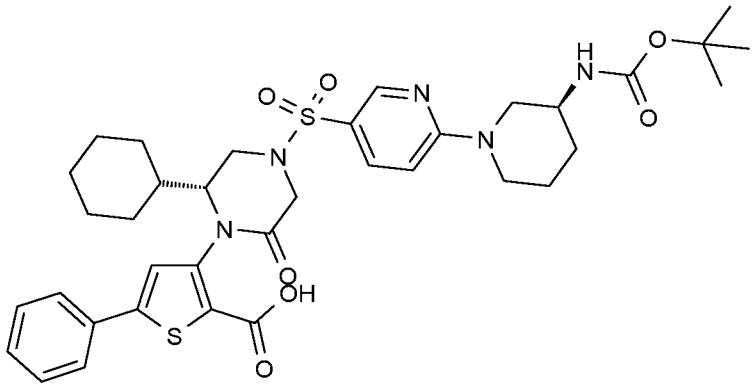
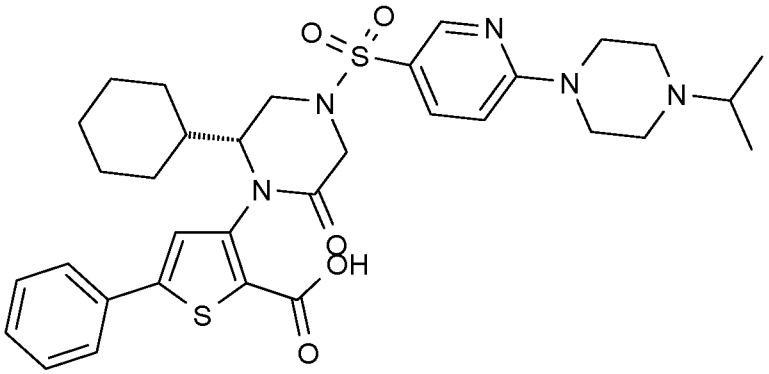
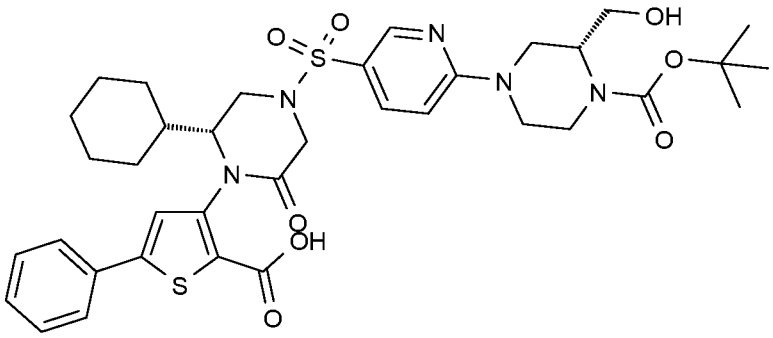
144	3-{(R)-4-[6-((S)-3-Amino-pyrrolidin-1-yl)-pyridine-3-sulfonyl]-2-cyclohexyl-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
145	3-{(R)-2-Cyclohexyl-4-[6-((S)-3-methyl-piperazin-1-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
146	3-{(R)-4-[6-((R)-3-tert-Butoxycarbonylamino-pyrrolidin-1-yl)-pyridine-3-sulfonyl]-2-cyclohexyl-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	

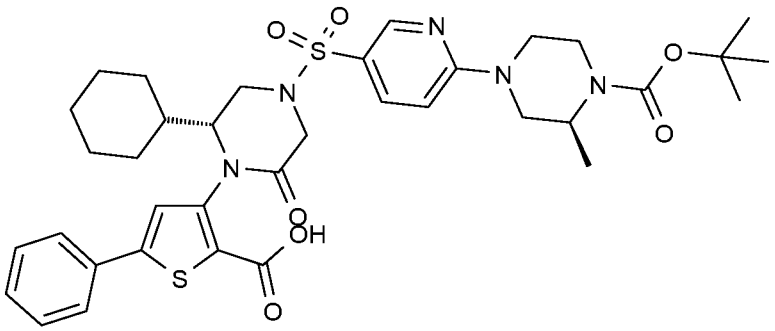
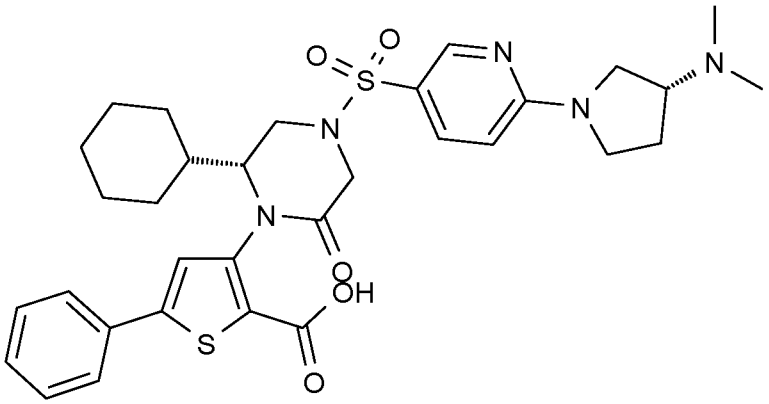
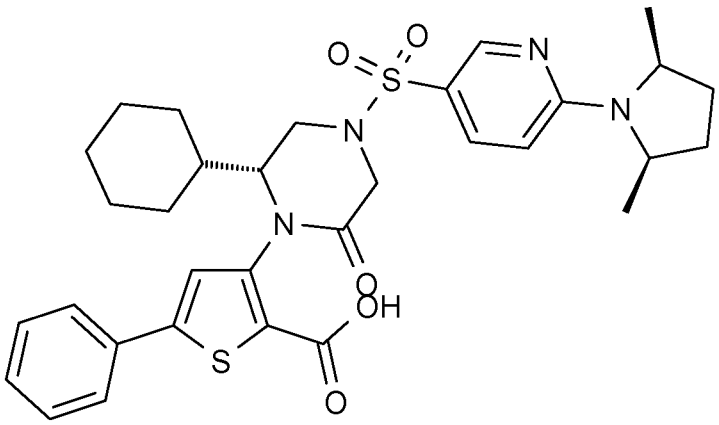
147	3-[(R)-2-Cyclohexyl-4-(4-dimethylamino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-sulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
148	3-{(R)-2-Cyclohexyl-4-[6-(4-ethyl-piperazin-1-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
149	3-{(R)-4-[4-(tert-Butoxycarbonylamino-methyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-sulfonyl]-2-cyclohexyl-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	

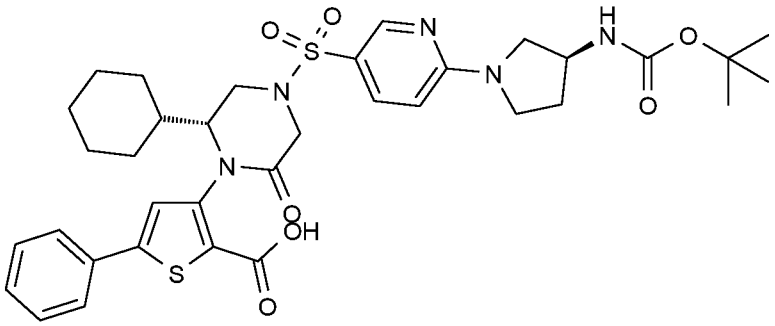
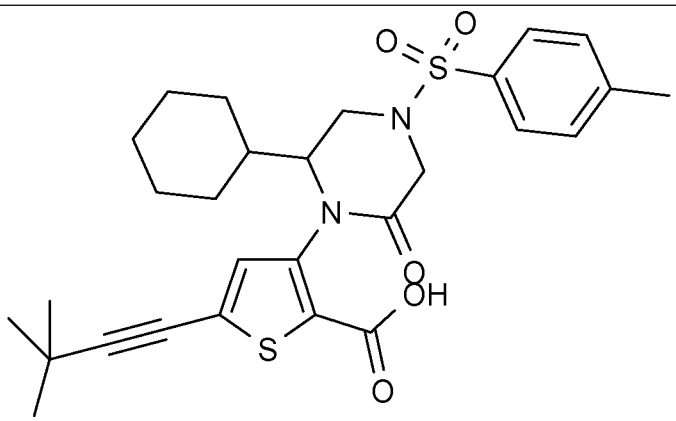
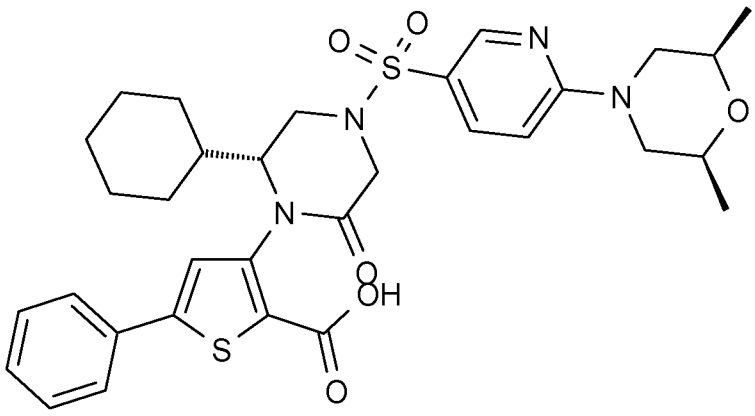
150	3-{(R)-2-Cyclohexyl-4-[6-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
151	(R)-4-{5-[(R)-4-(2-Carboxy-5-phenyl-thiophen-3-yl)-3-cyclohexyl-5-oxo-piperazine-1-sulfonyl]-pyridin-2-yl}-2-methyl-piperazine-1-carboxylic acid tert-butyl ester	
152	3-{(R)-4-[6-(4-tert-Butyl-piperazin-1-yl)-pyridine-3-sulfonyl]-2-cyclohexyl-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	

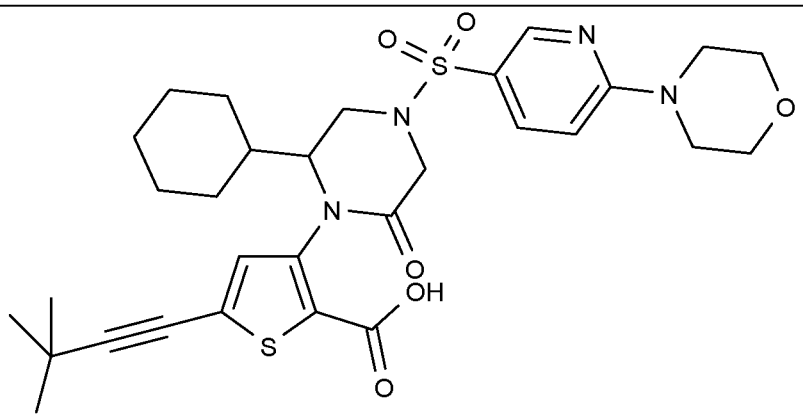
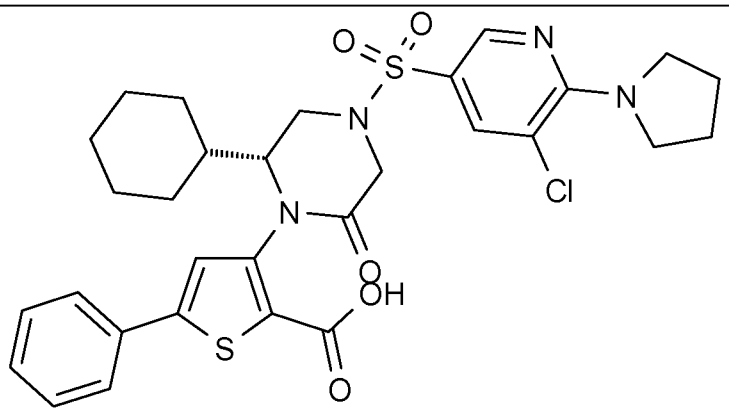
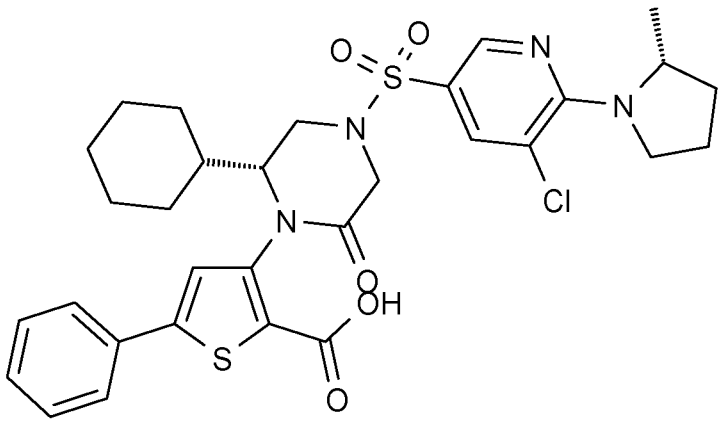
153	3-[(R)-4-(4-tert-Butoxycarbonylamino-4-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-sulfonyl)-2-cyclohexyl-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
154	3-{(R)-2-Cyclohexyl-4-[6-(2-ethyl-pyrrolidin-1-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
155	3-[(R)-2-Cyclohexyl-4-(3-dimethylamino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-sulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	

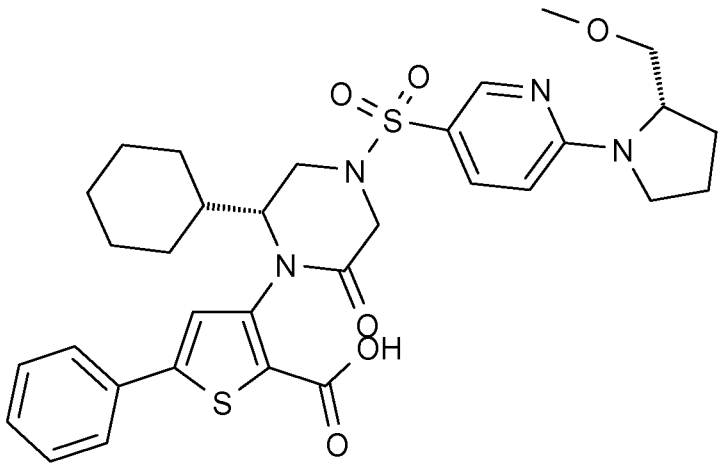
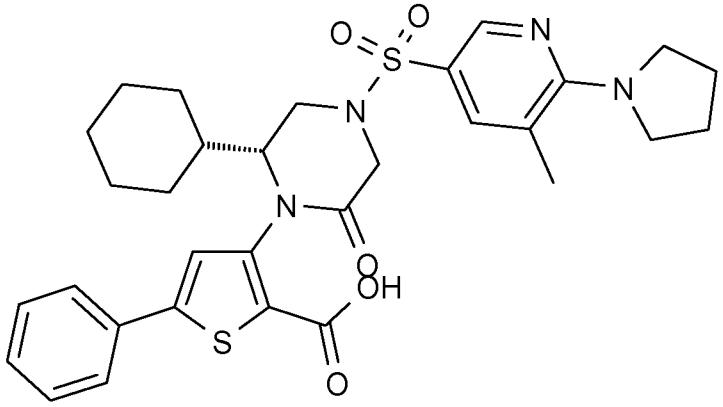
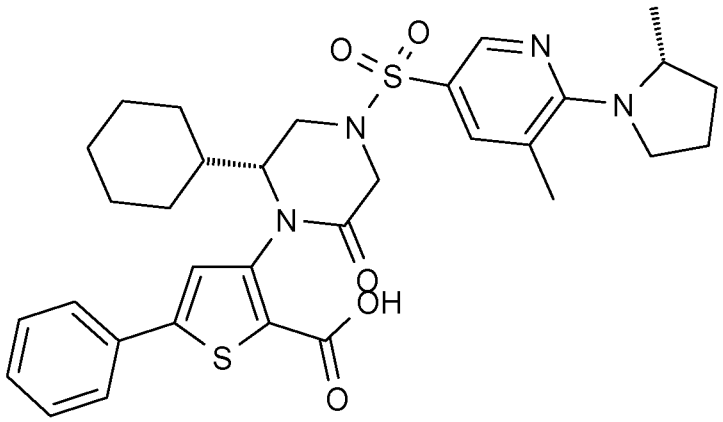
156	3-{(R)-2-Cyclohexyl-4-[6-((S)-3-dimethylamino-pyrrolidin-1-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
157	3-{(R)-2-Cyclohexyl-4-[6-(hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
158	3-[(R)-4-((S)-3-tert-Butoxycarbonylamino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-sulfonyl)-2-cyclohexyl-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	

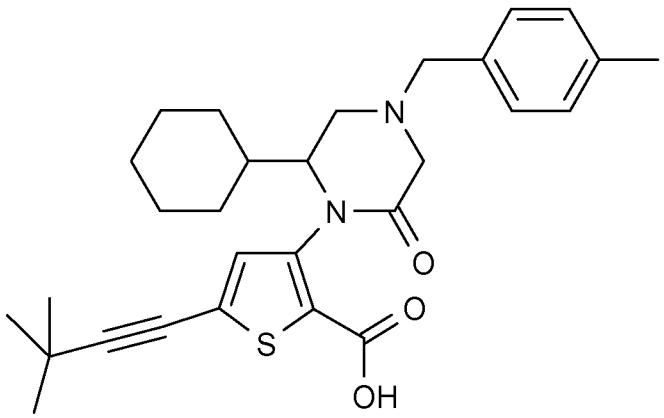
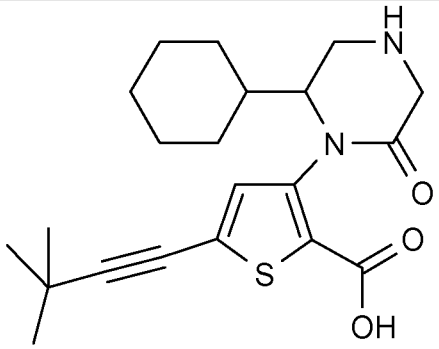
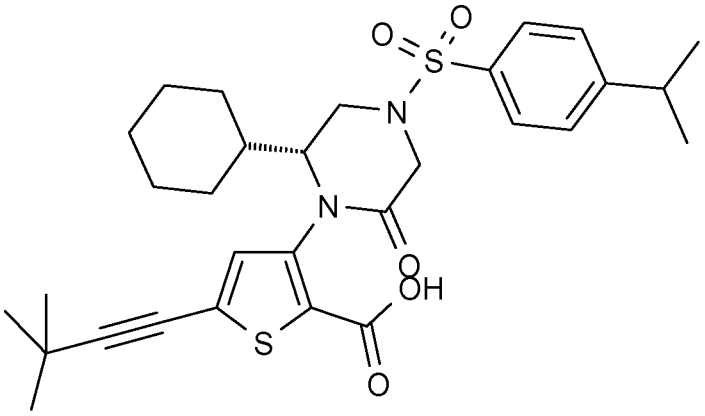
159	3-[(R)-4-((S)-3-tert-Butoxycarbonylamino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-sulfonyl)-2-cyclohexyl-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
160	3-{(R)-2-Cyclohexyl-4-[6-(4-isopropyl-piperazin-1-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
161	(R)-4-{5-[(R)-4-(2-Carboxy-5-phenyl-thiophen-3-yl)-3-cyclohexyl-5-oxo-piperazine-1-sulfonyl]-pyridin-2-yl}-2-hydroxymethyl-piperazine-1-carboxylic acid tert-butyl ester	

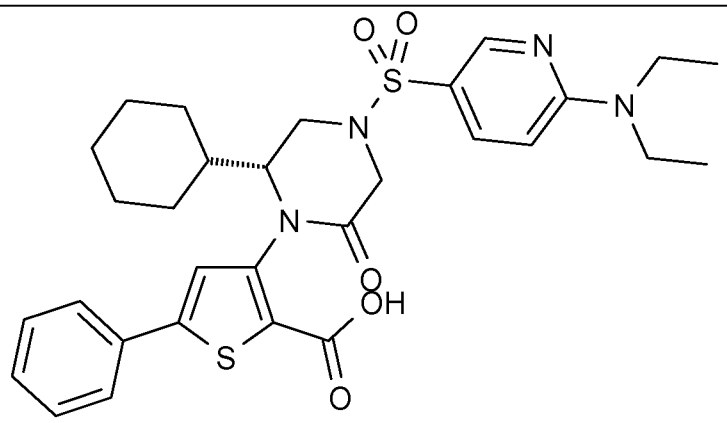
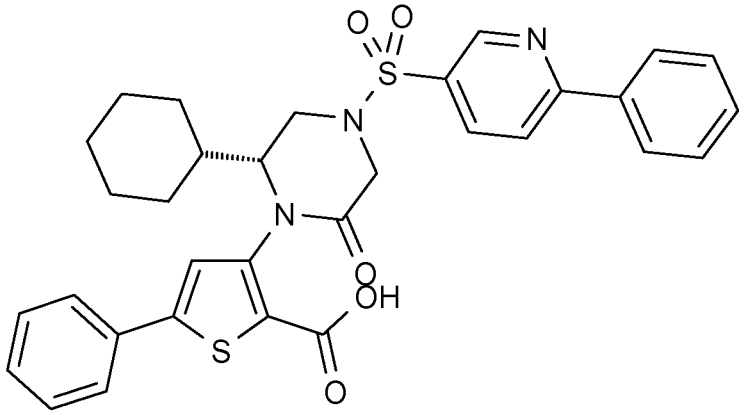
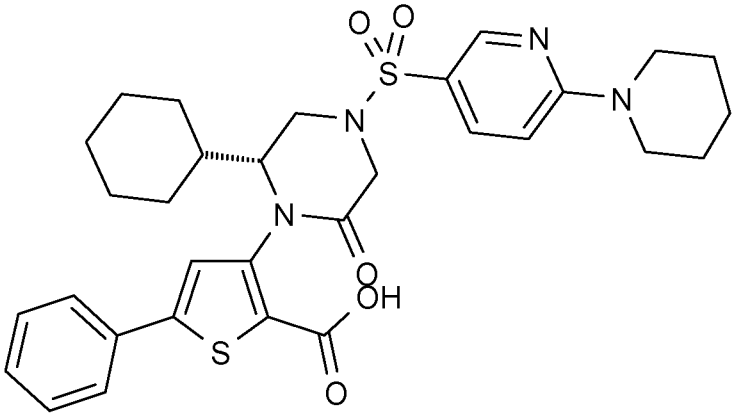
162	(S)-4-{5-[(R)-4-(2-Carboxy-5-phenyl-thiophen-3-yl)-3-cyclohexyl-5-oxo-piperazine-1-sulfonyl]-pyridin-2-yl}-2-methyl-piperazine-1-carboxylic acid tert-butyl ester	
163	3-{(R)-2-Cyclohexyl-4-[6-((R)-3-dimethylamino-pyrrolidin-1-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
164	3-{(R)-2-Cyclohexyl-4-[6-((2S,5R)-2,5-dimethyl-pyrrolidin-1-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	

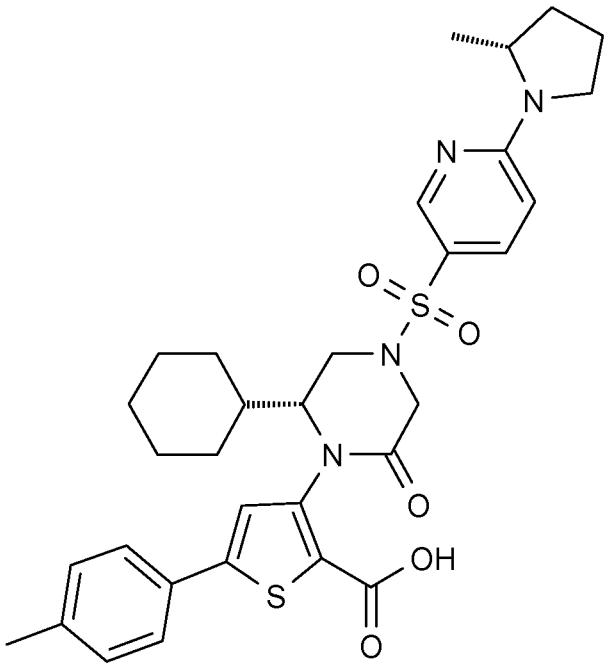
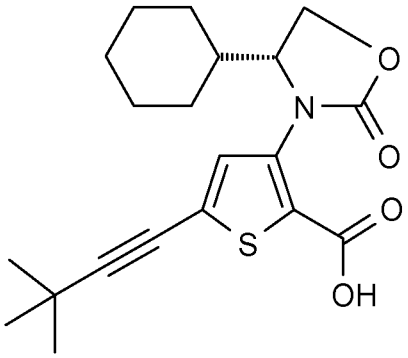
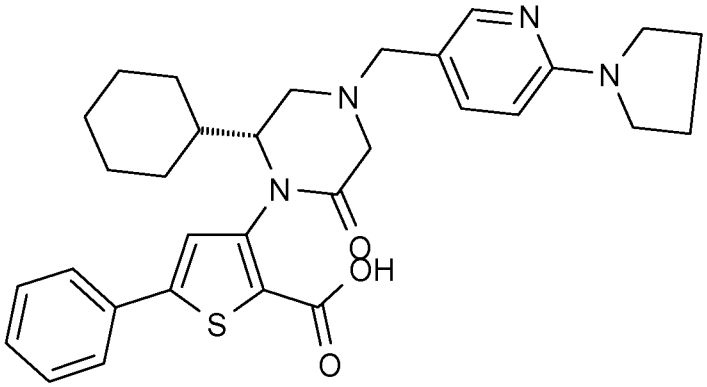
165	3-{(R)-4-[6-((S)-3-tert-Butoxycarbonylamino-pyrrolidin-1-yl)-pyridine-3-sulfonyl]-2-cyclohexyl-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
166	3-[2-Cyclohexyl-6-oxo-4-(toluene-4-sulfonyl)-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
167	3-{(R)-2-Cyclohexyl-4-[6-((2R,6S)-2,6-dimethyl-morpholin-4-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	

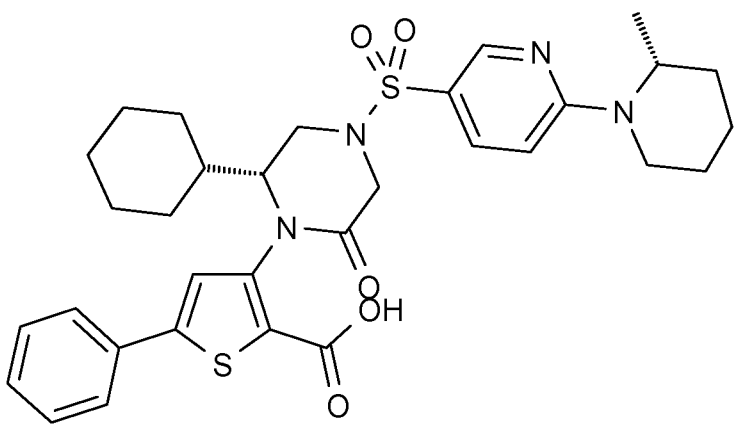
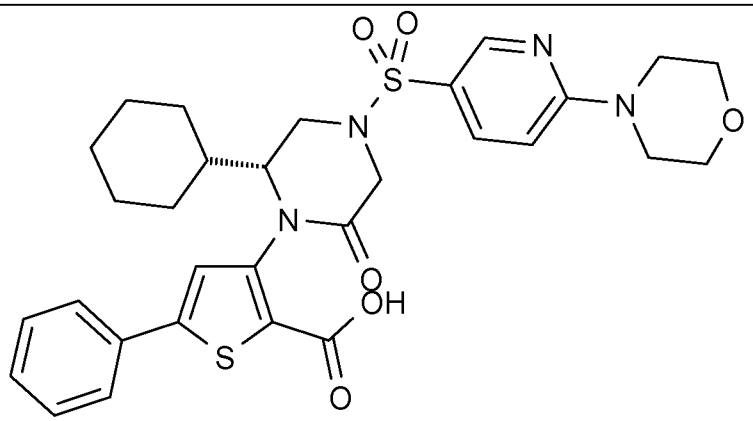
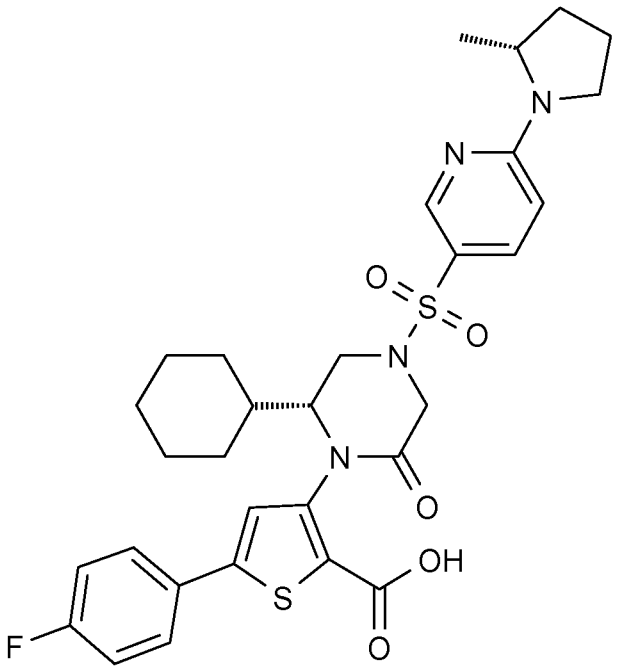
168	3-[2-Cyclohexyl-4-(6-morpholin-4-yl-pyridine-3-sulfonyl)-6-oxo-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
169		
170	3-{(R)-4-[5-Chloro-6-((R)-2-methyl-pyrrolidin-1-yl)-pyridine-3-sulfonyl]-2-cyclohexyl-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	

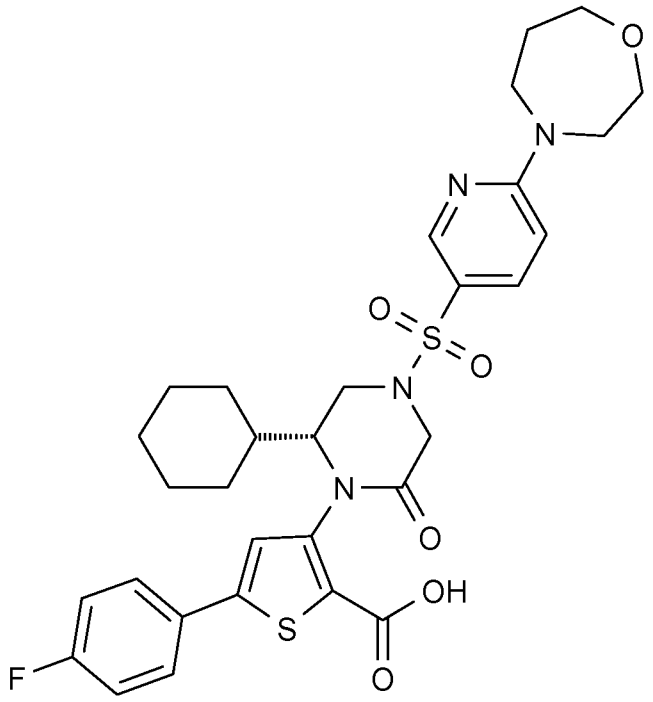
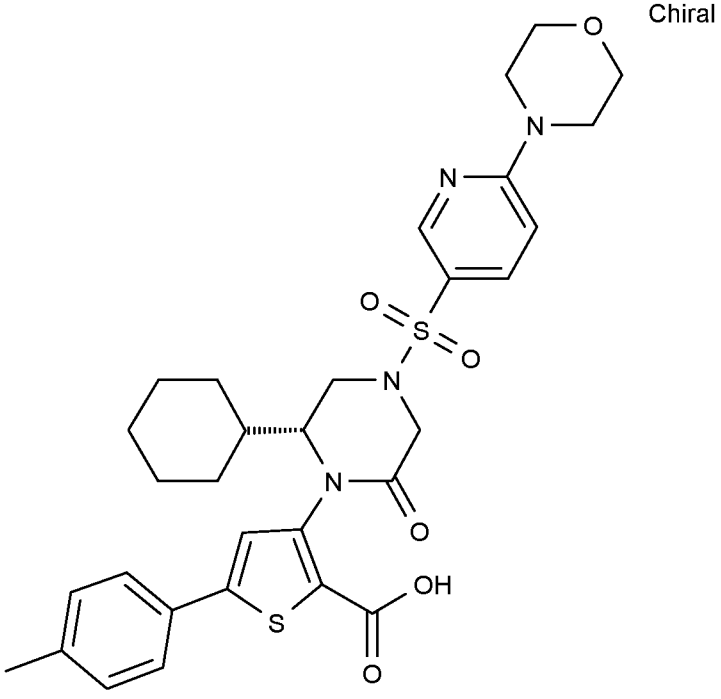
171	3-{(R)-2-Cyclohexyl-4-[6-((S)-2-methoxymethyl-pyrrolidin-1-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
172	3-[(R)-2-Cyclohexyl-4-(5-methyl-6-pyrrolidin-1-yl-pyridine-3-sulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
173	3-{(R)-2-Cyclohexyl-4-[5-methyl-6-((R)-2-methyl-pyrrolidin-1-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	

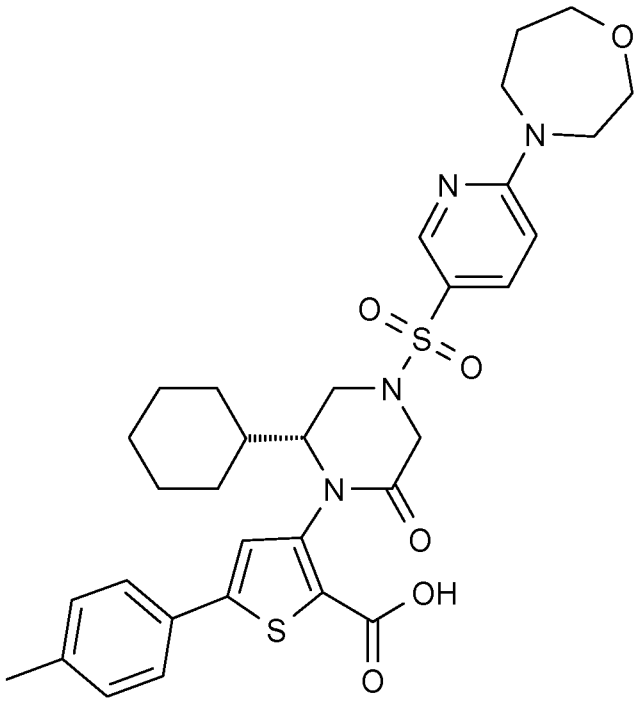
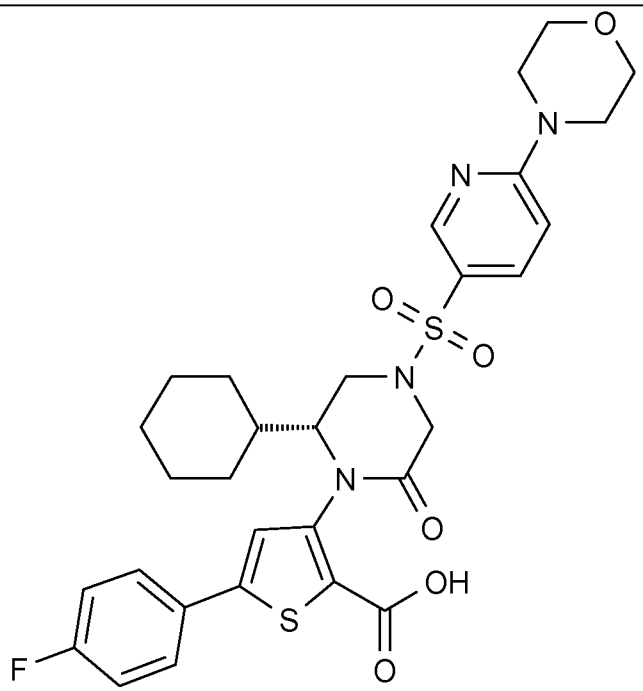
174	3-[2-Cyclohexyl-4-(4-methyl-benzyl)-6-oxo-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
175	3-(2-Cyclohexyl-6-oxo-piperazin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
176	3-[(R)-2-Cyclohexyl-4-(4-isopropyl-benzenesulfonyl)-6-oxo-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	

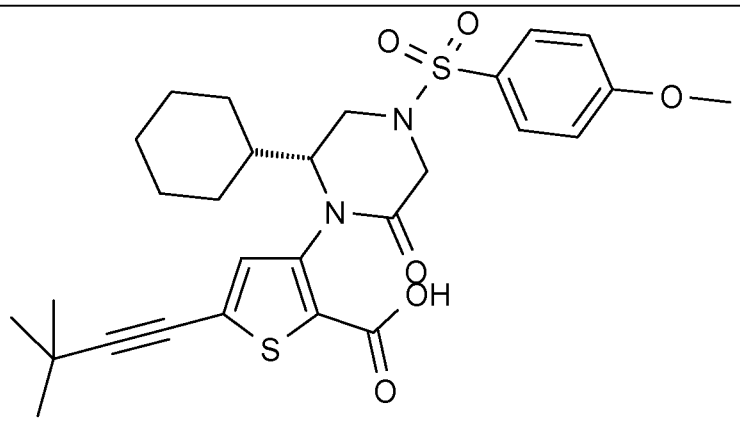
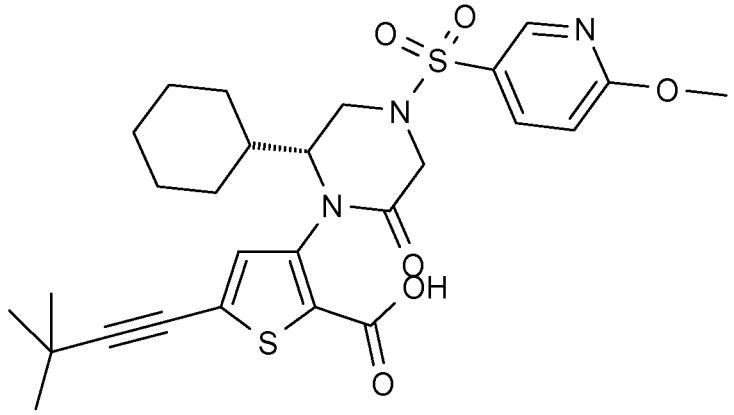
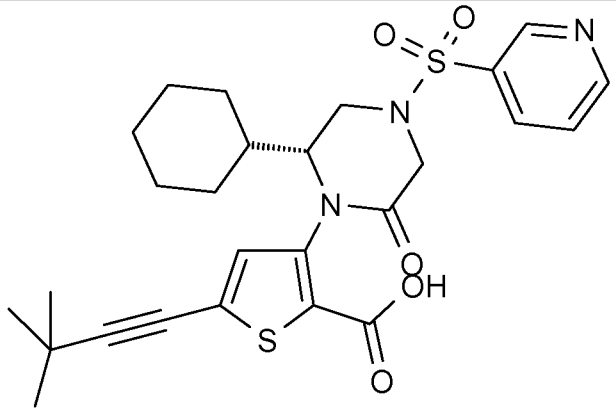
177	3-[(R)-2-Cyclohexyl-4-(6-diethylamino-pyridine-3-sulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
178	3-[(R)-2-Cyclohexyl-6-oxo-4-(6-phenyl-pyridine-3-sulfonyl)-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
179	3-[(R)-2-Cyclohexyl-6-oxo-4-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-sulfonyl)-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	

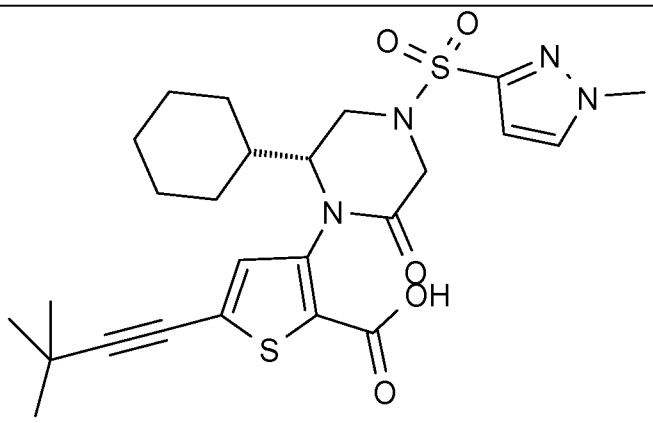
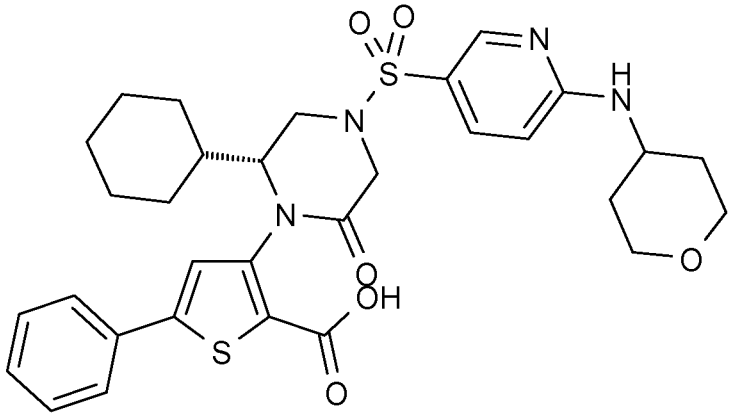
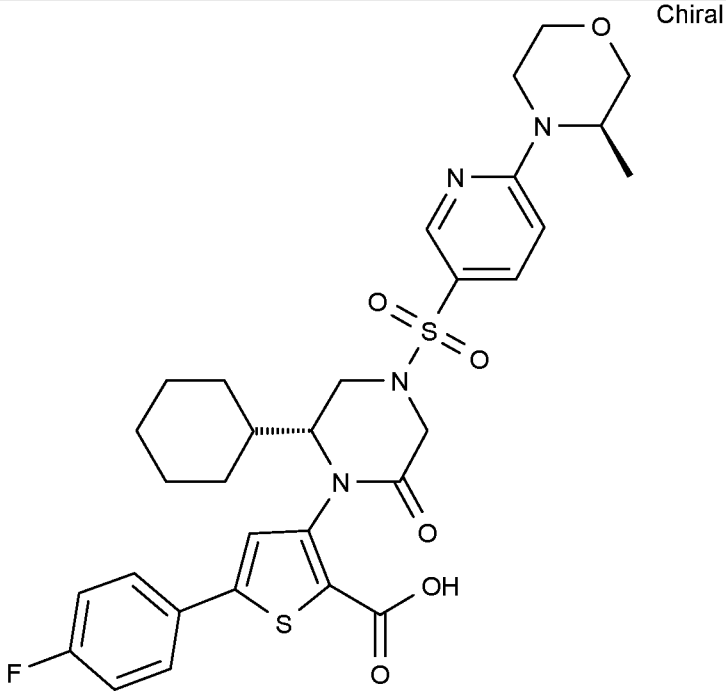
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181	3-((R)-4-Cyclohexyl-2-oxo-oxazolidin-3-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
182	3-[(R)-2-Cyclohexyl-6-oxo-4-(6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	

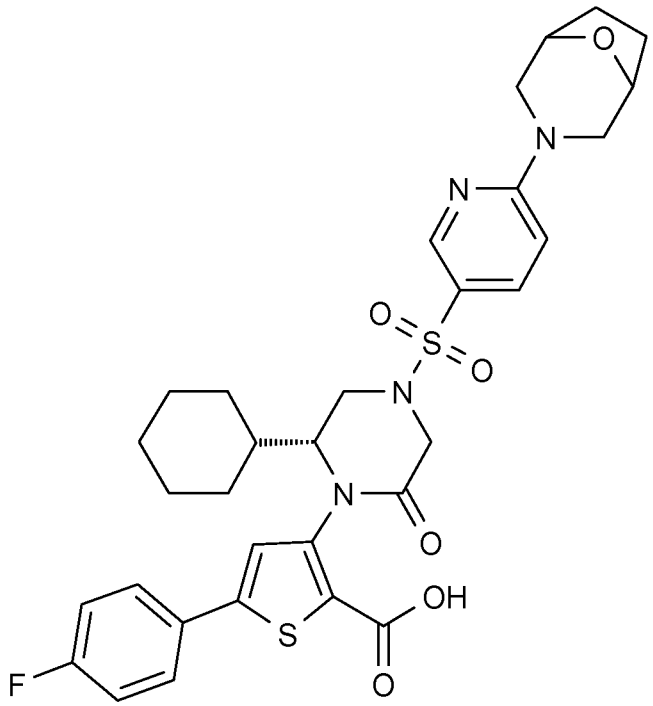
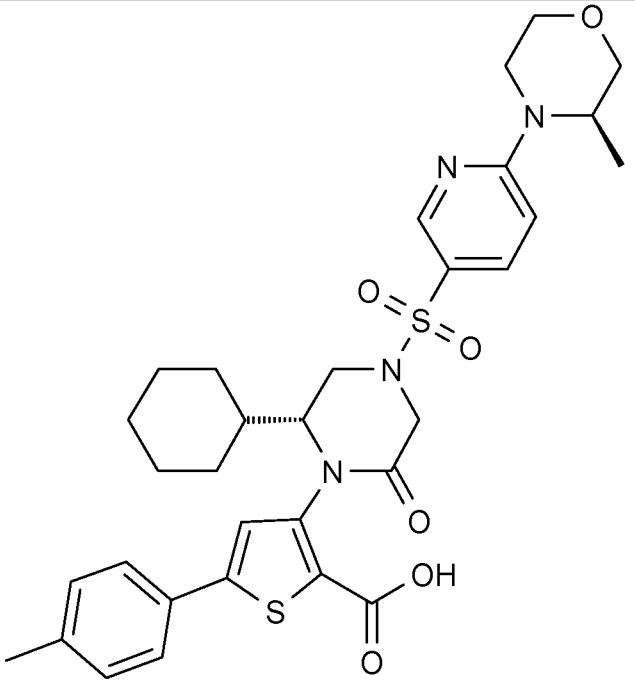
183	3-[(R)-2-Cyclohexyl-4-((R)-2-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-sulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
184	3-[(R)-2-Cyclohexyl-4-(6-morpholin-4-yl-pyridine-3-sulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
185	3-{(R)-2-Cyclohexyl-4-[6-((R)-2-methyl-pyrrolidin-1-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-(4-fluoro-phenyl)-thiophene-2-carboxylic acid	

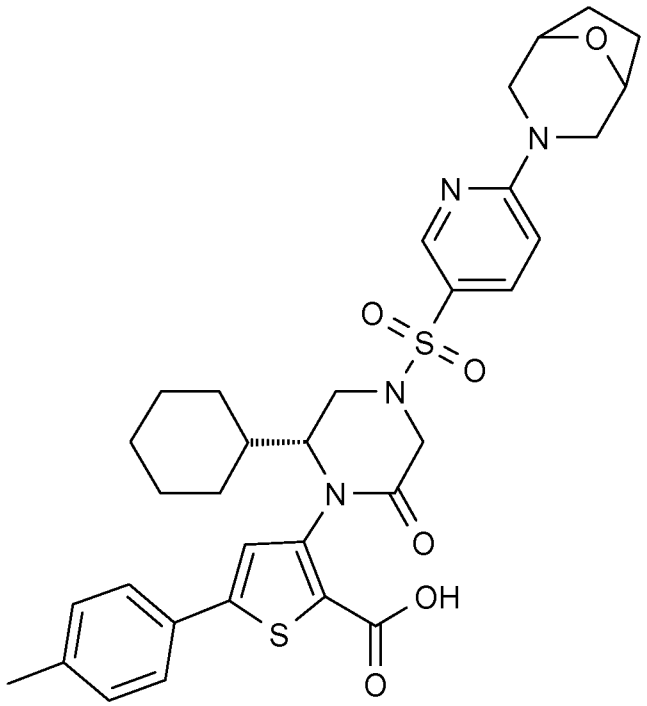
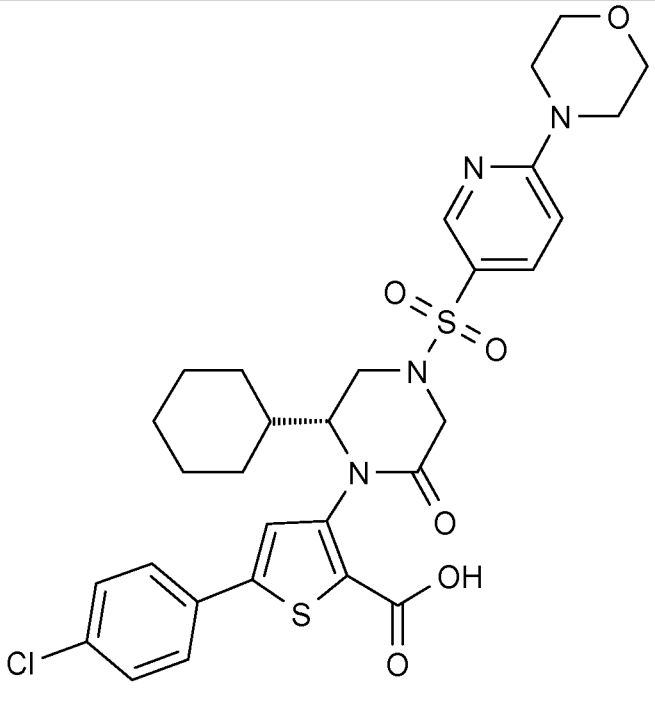
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187	3-[(R)-2-Cyclohexyl-4-(6-morpholin-4-yl-pyridine-3-sulfonyl)-6-oxo-piperazin-1-yl]-5-p-tolyl-thiophene-2-carboxylic acid	Chiral 

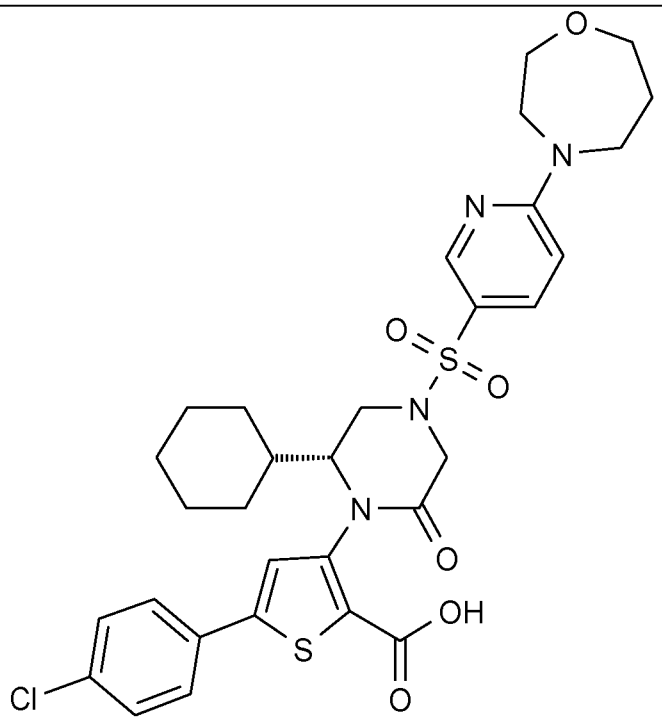
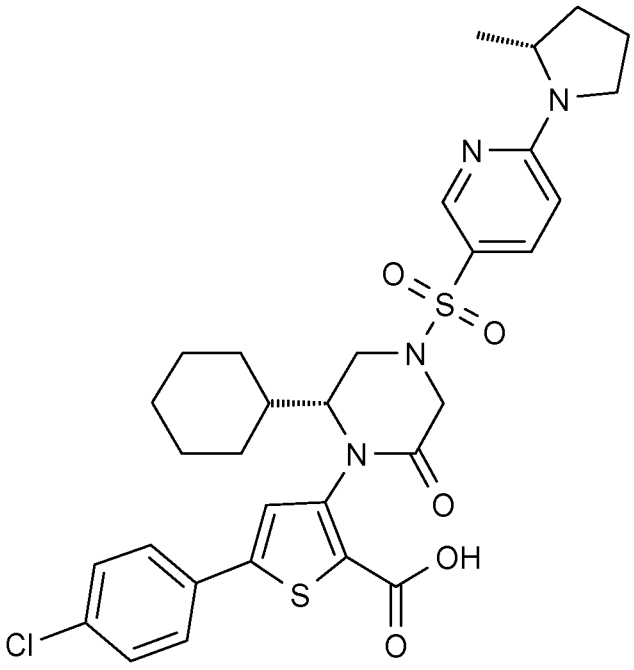
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189	3-[(R)-2-Cyclohexyl-4-(6-morpholin-4-yl-pyridine-3-sulfonyl)-6-oxo-piperazin-1-yl]-5-(4-fluoro-phenyl)-thiophene-2-carboxylic acid	

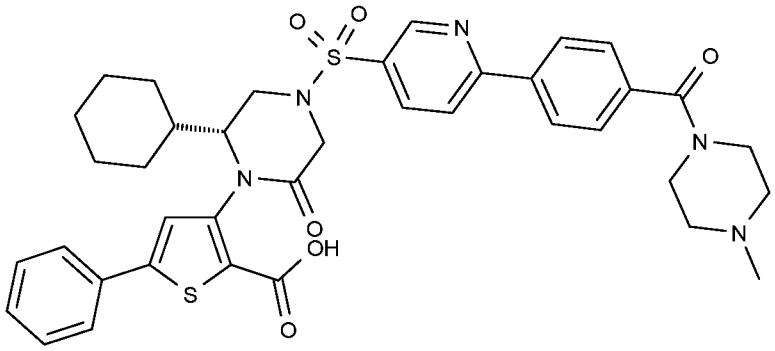
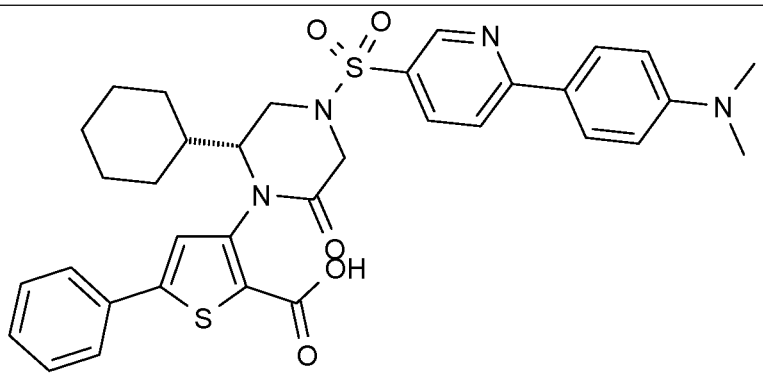
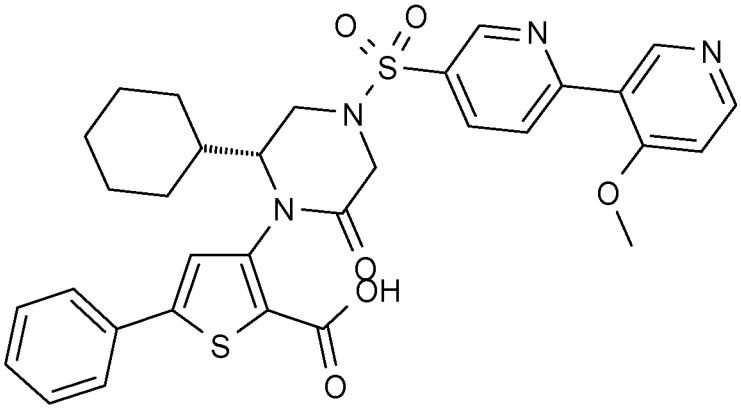
190	3-[(R)-2-Cyclohexyl-4-(4-methoxy-benzenesulfonyl)-6-oxo-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
191	3-[(R)-2-Cyclohexyl-4-(6-methoxy-pyridine-3-sulfonyl)-6-oxo-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
192	3-[(R)-2-Cyclohexyl-6-oxo-4-(pyridine-3-sulfonyl)-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	

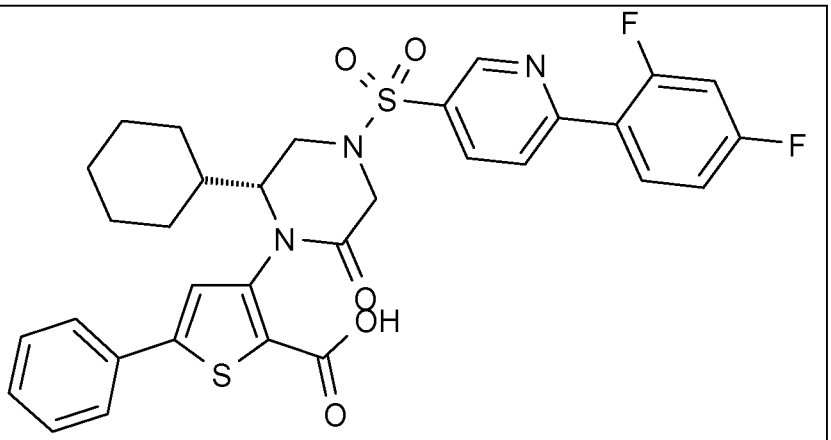
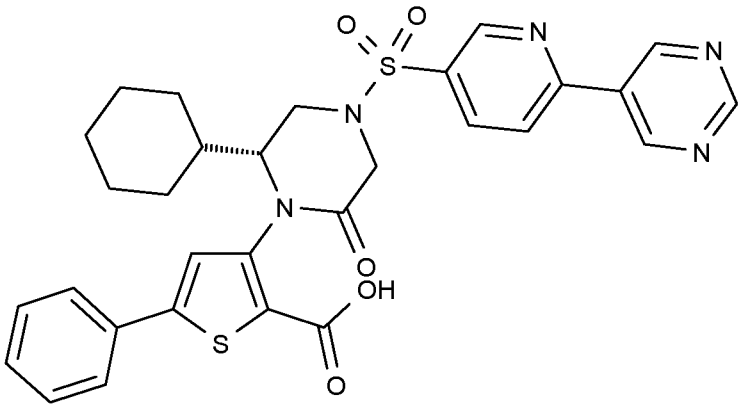
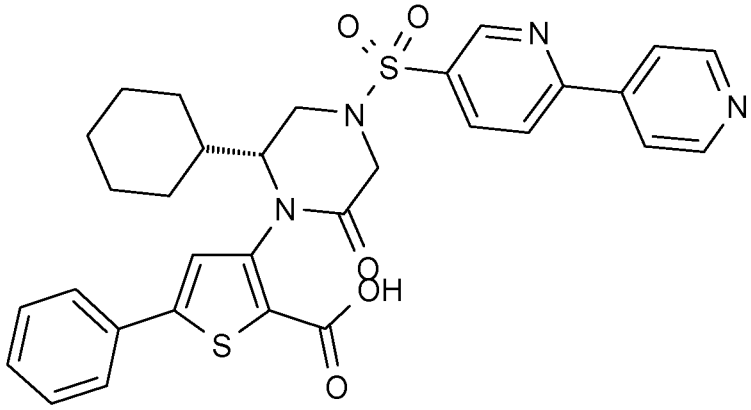
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194	3-{(R)-2-Cyclohexyl-6-oxo-4-[6-(tetrahydro-pyran-4-ylamino)-pyridine-3-sulfonyl]-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
195	3-{(R)-2-Cyclohexyl-4-[6-((R)-3-methyl-morpholin-4-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-(4-fluoro-phenyl)-thiophene-2-carboxylic acid	Chiral 

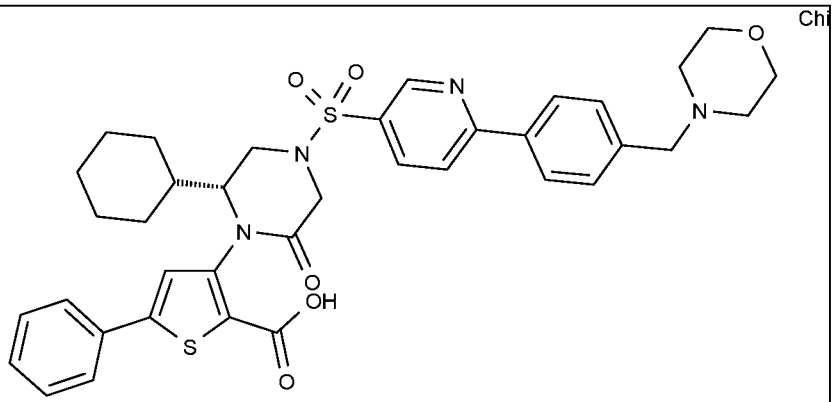
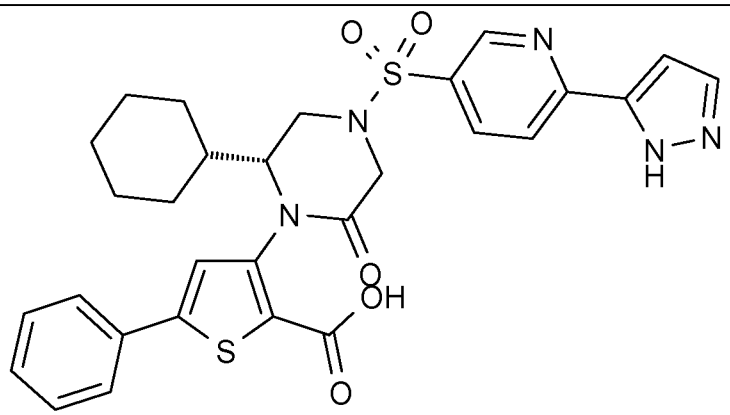
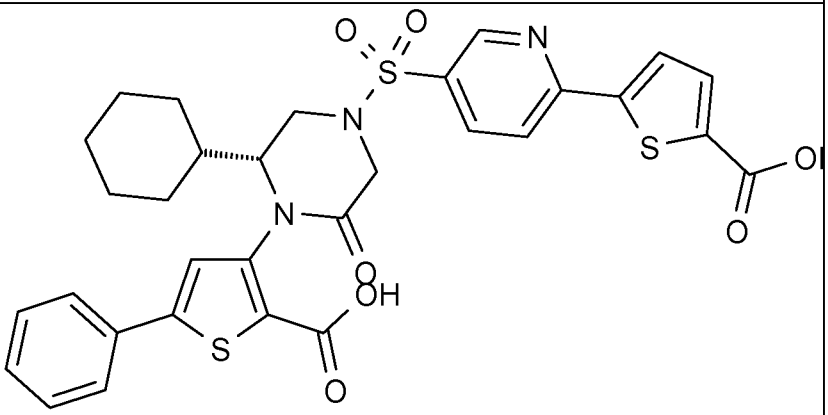
196	3-{(R)-2-Cyclohexyl-4-[6-(8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-(4-fluoro-phenyl)-thiophene-2-carboxylic acid	
197	3-{(R)-2-Cyclohexyl-4-[6-((R)-3-methyl-morpholin-4-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-p-tolyl-thiophene-2-carboxylic acid	

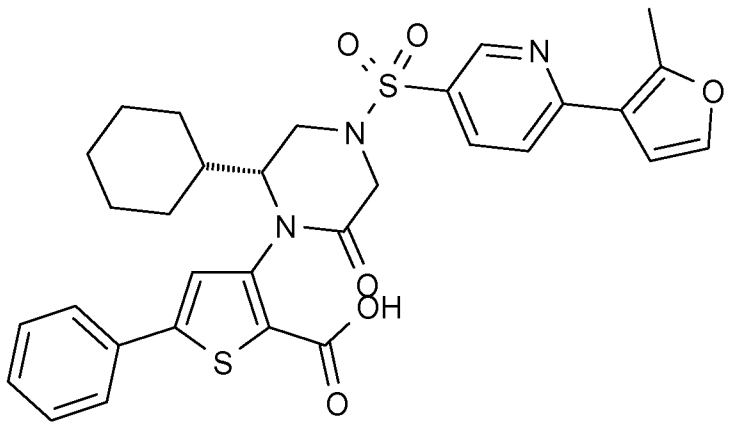
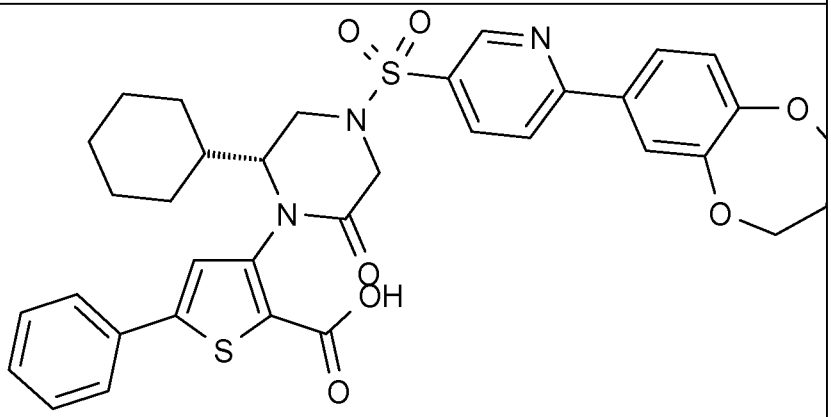
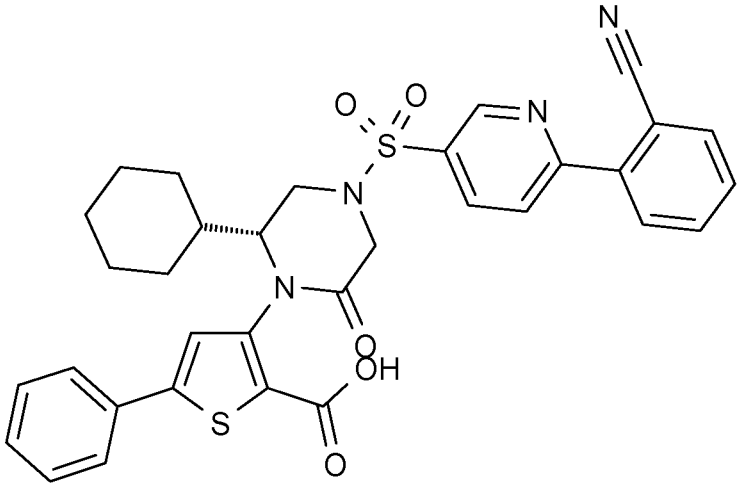
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199	5-(4-Chloro-phenyl)-3-[(R)-2-cyclohexyl-4-(6-morpholin-4-yl-pyridine-3-sulfonyl)-6-oxo-piperazin-1-yl]-thiophene-2-carboxylic acid	

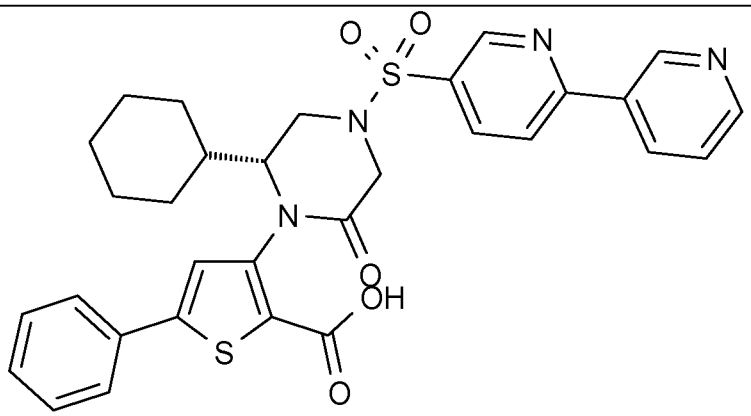
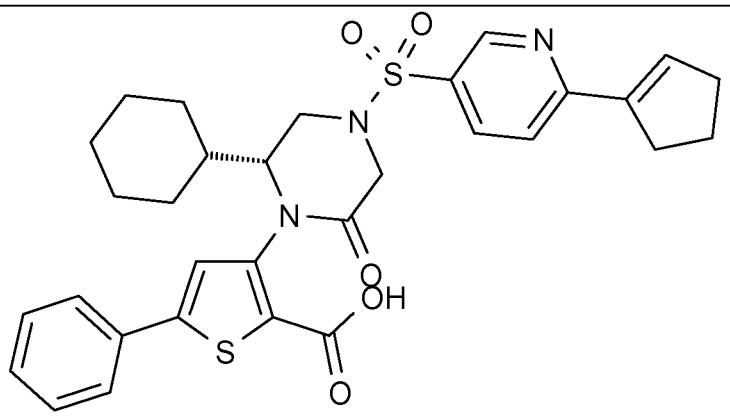
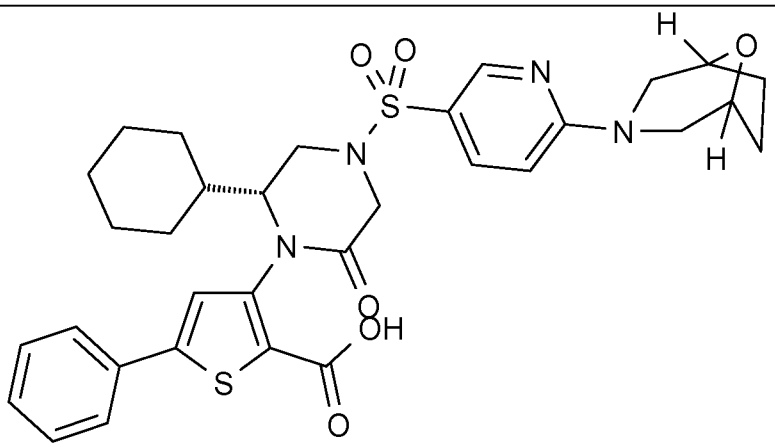
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201	5-(4-Chloro-phenyl)-3-{(R)-2-cyclohexyl-4-[6-((R)-2-methyl-pyrrolidin-1-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-thiophene-2-carboxylic acid	

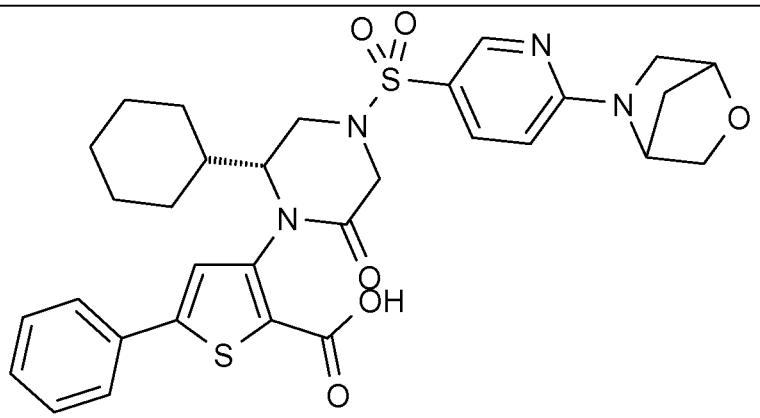
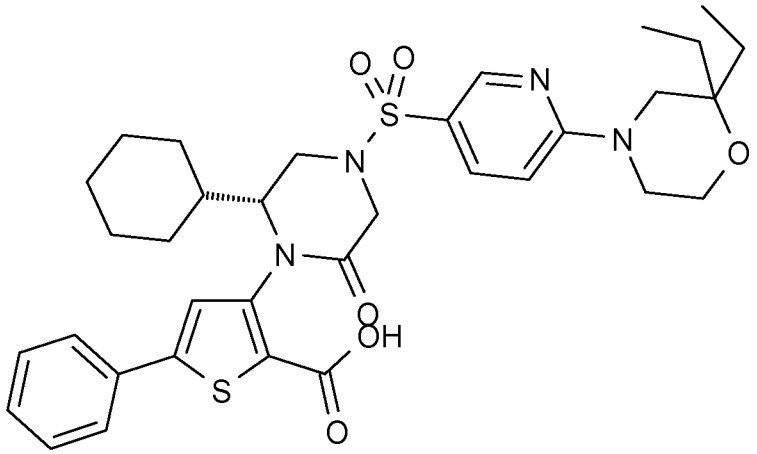
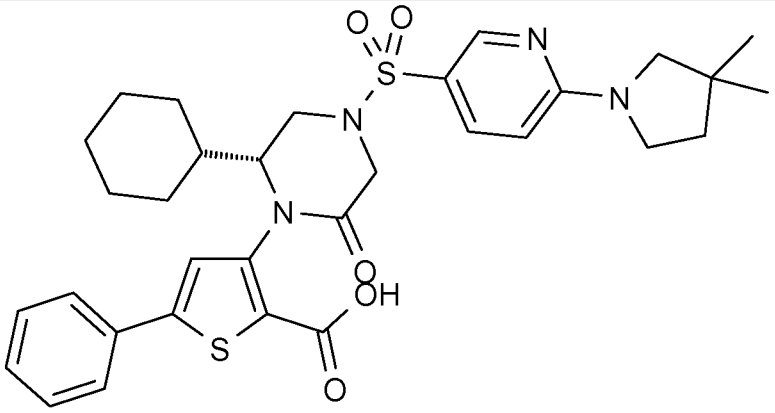
202	3-((R)-2-Cyclohexyl-4-{6-[4-(4-methyl-piperazine-1-carbonyl)-phenyl]-pyridine-3-sulfonyl}-6-oxo-piperazin-1-yl)-5-phenyl-thiophene-2-carboxylic acid	 Chi
203	3-{(R)-2-Cyclohexyl-4-[6-(4-dimethylamino-phenyl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
204	3-[(R)-2-Cyclohexyl-4-(4'-methoxy-[2,3']bipyridinyl-5-sulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	

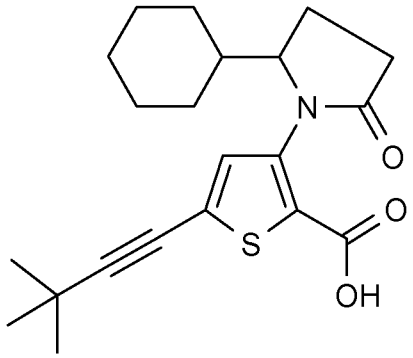
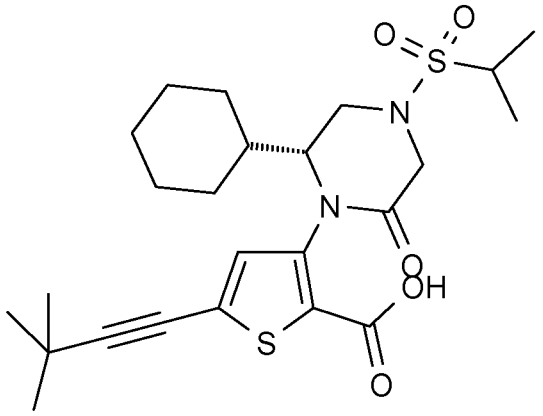
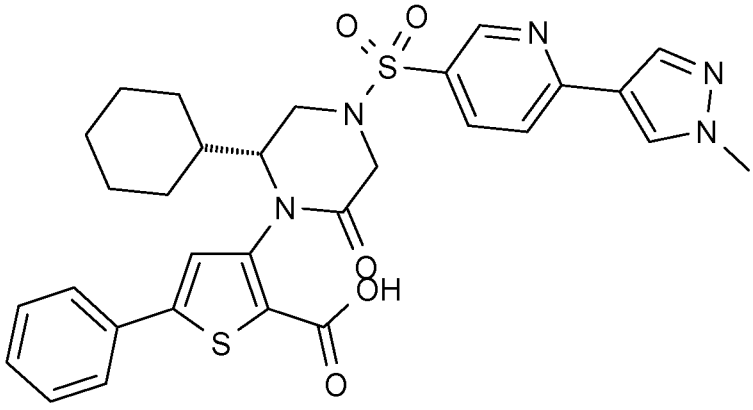
205	3-{(R)-2-Cyclohexyl-4-[6-(2,4-difluoro-phenyl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
206	3-[(R)-2-Cyclohexyl-6-oxo-4-(6-pyrimidin-5-yl-pyridine-3-sulfonyl)-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	Chira 
207	3-[(R)-4-([2,4']Bipyridinyl-5-sulfonyl)-2-cyclohexyl-6-oxo-piperazin-1-yl]-5-[(E)-((Z)-1-propenyl)-buta-1,3-dienyl]-thiophene-2-carboxylic acid	

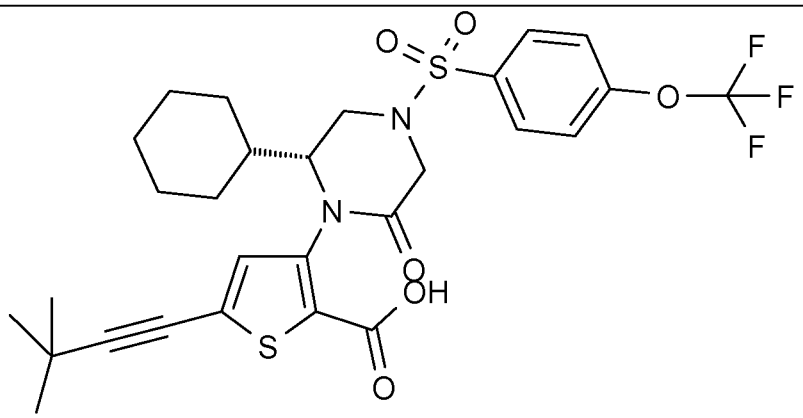
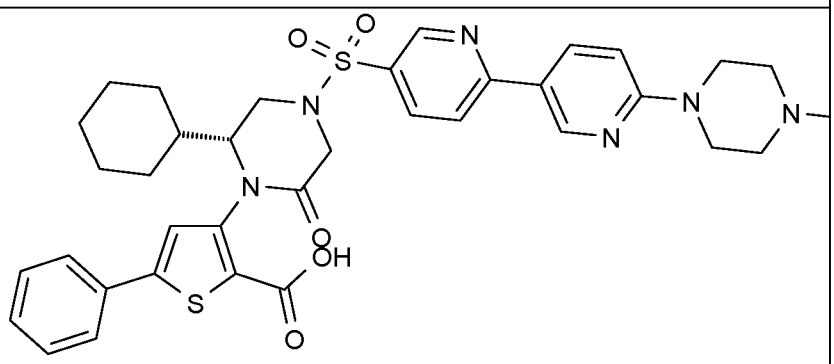
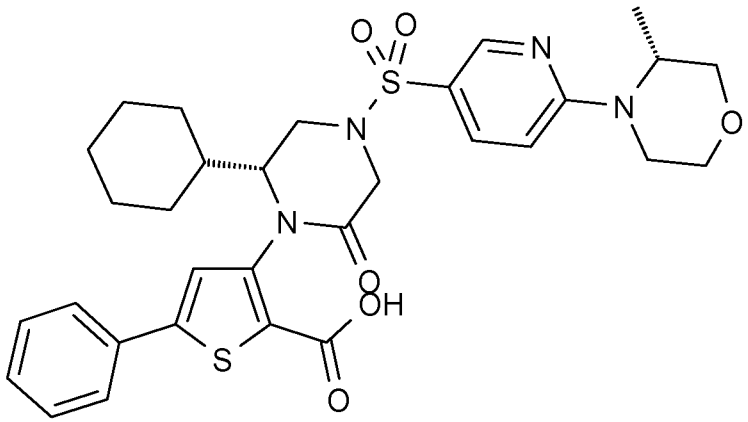
208	3-{(R)-2-Cyclohexyl-4-[6-(4-morpholin-4-ylmethyl-phenyl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
209	3-{(R)-2-Cyclohexyl-6-oxo-4-[6-(2H-pyrazol-3-yl)-pyridine-3-sulfonyl]-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
210	3-{(R)-4-[6-(5-Carboxy-thiophen-2-yl)-pyridine-3-sulfonyl]-2-cyclohexyl-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	

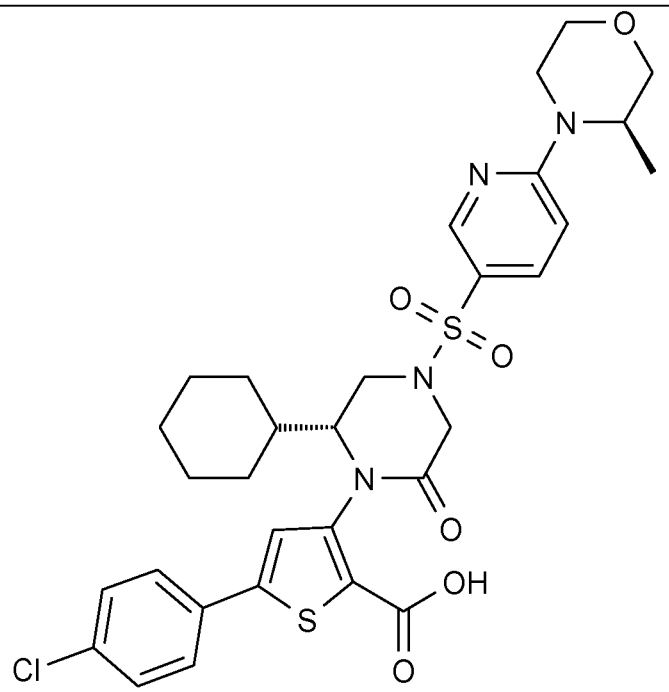
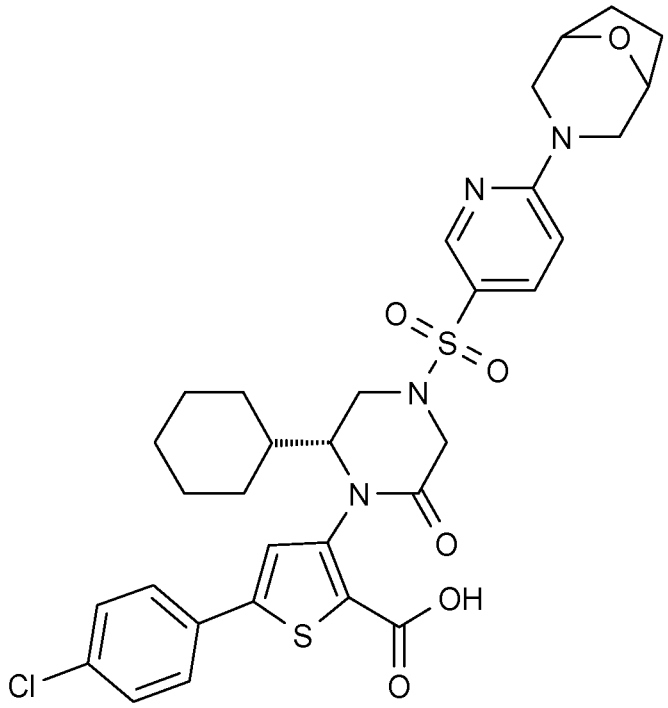
211	3-{(R)-2-Cyclohexyl-4-[6-(2-methyl-furan-3-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
212	3-{(R)-2-Cyclohexyl-4-[6-(3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
213	3-{(R)-4-[6-(2-Cyano-phenyl)-pyridine-3-sulfonyl]-2-cyclohexyl-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	

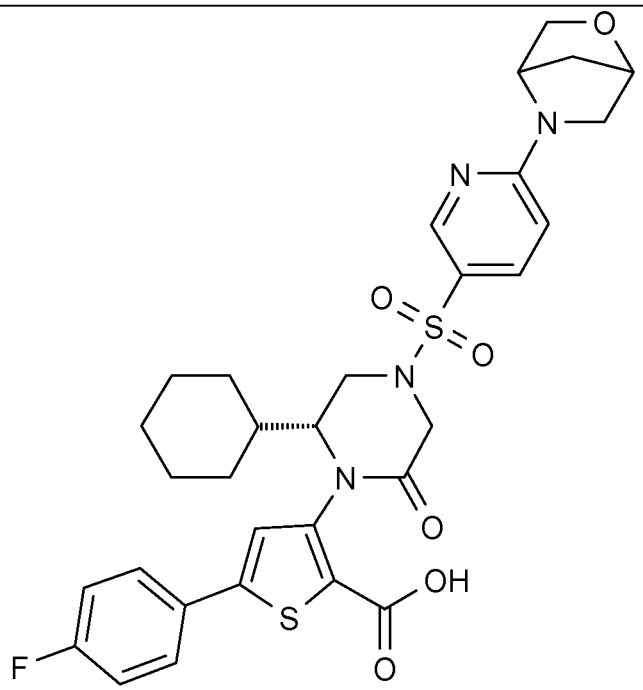
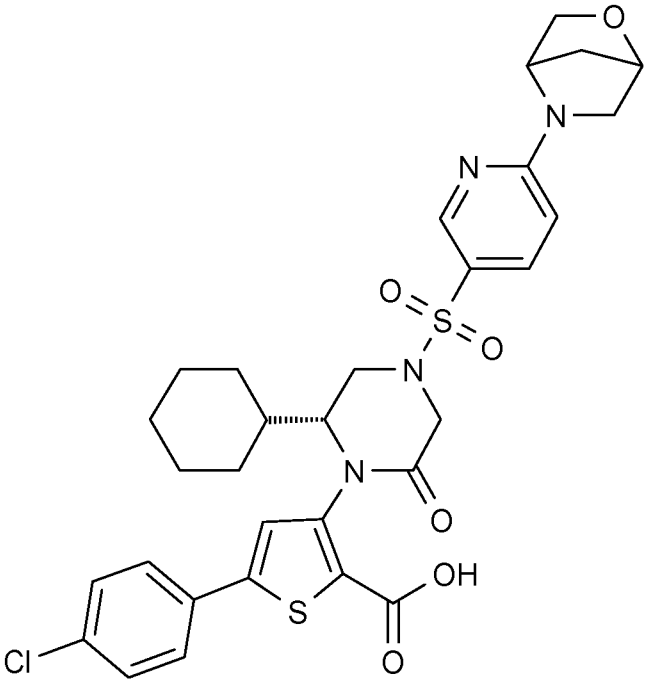
214	3-[(R)-4-([2,3']Bipyridinyl-5-sulfonyl)-2-cyclohexyl-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
215	3-[(R)-2-Cyclohexyl-4-(6-cyclopent-1-enyl-pyridine-3-sulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
216	3-{(R)-2-Cyclohexyl-4-[6-(8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	

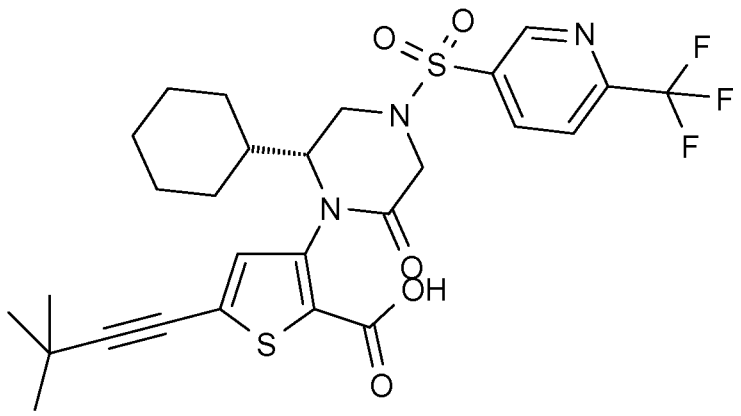
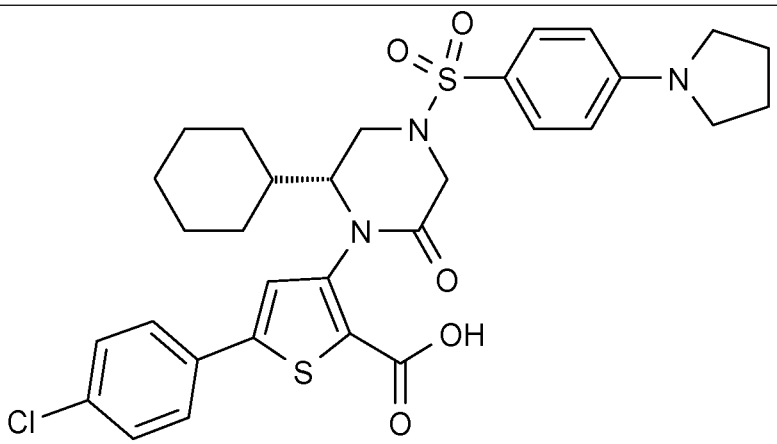
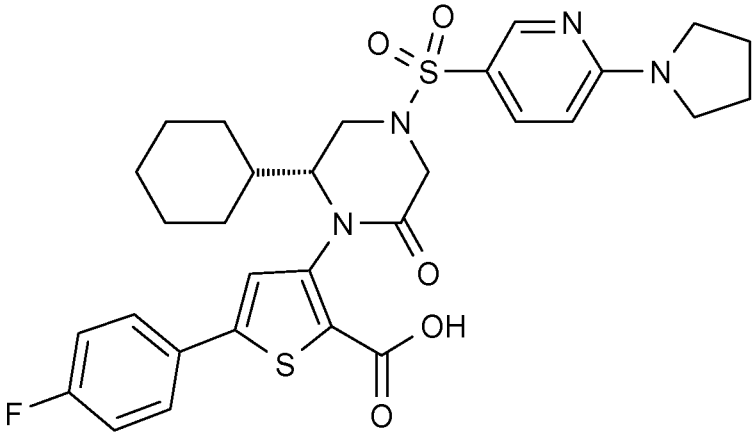
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218	3-{(R)-2-Cyclohexyl-4-[6-(2,2-diethyl-morpholin-4-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
219	3-{(R)-2-Cyclohexyl-4-[6-(3,3-dimethyl-pyrrolidin-1-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	

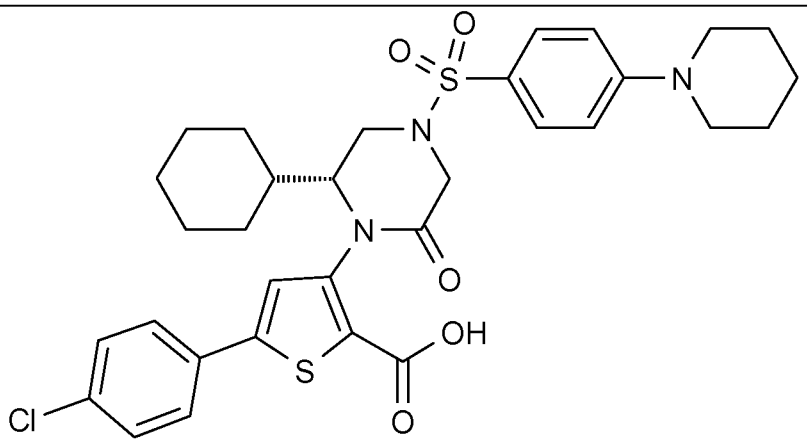
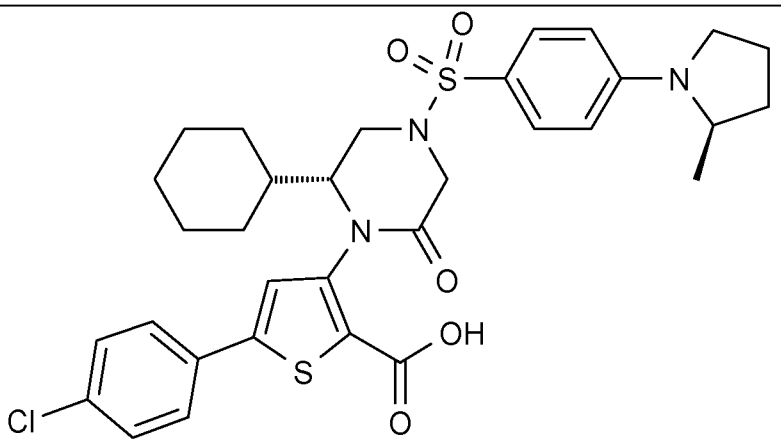
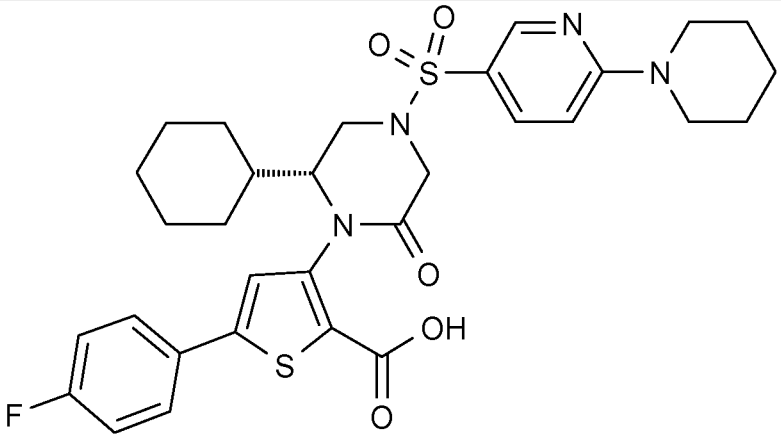
220	3-(2-Cyclohexyl-5-oxo-pyrrolidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
221	3-[(R)-2-Cyclohexyl-6-oxo-4-(propane-2-sulfonyl)-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
222	3-{(R)-2-Cyclohexyl-4-[6-(1-methyl-1H-pyrazol-4-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	

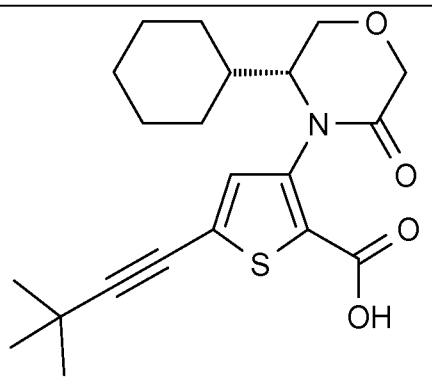
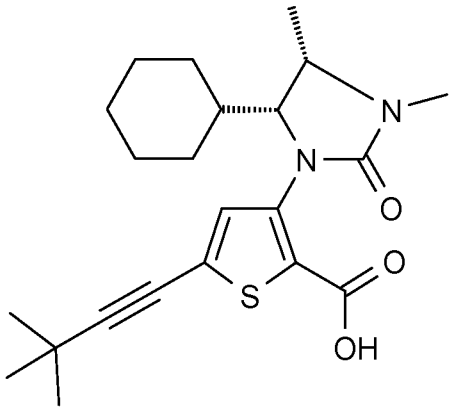
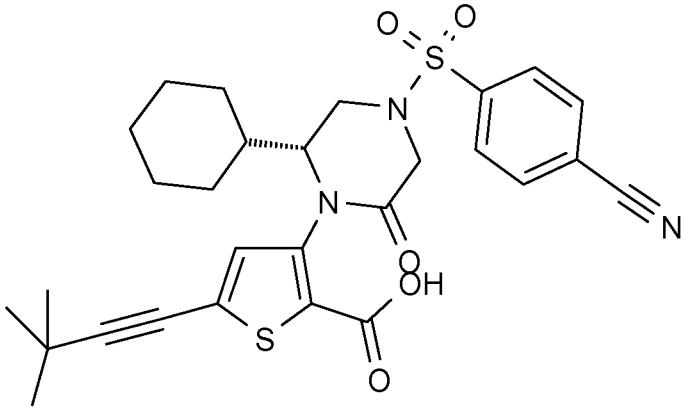
223	3-[(R)-2-Cyclohexyl-6-oxo-4-(4-trifluoromethoxy-benzenesulfonyl)-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
224	3-{(R)-2-Cyclohexyl-4-[6'-(4-methyl-piperazin-1-yl)-[2,3']bipyridinyl-5-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	
225	3-{(R)-2-Cyclohexyl-4-[6-((R)-3-methyl-morpholin-4-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	

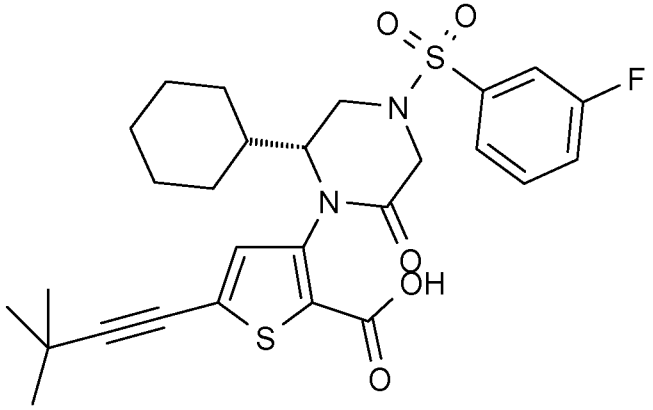
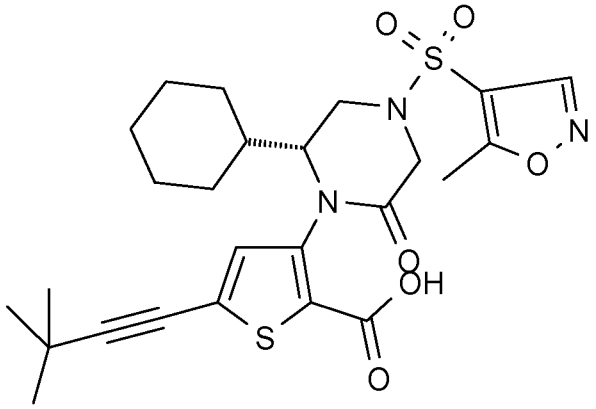
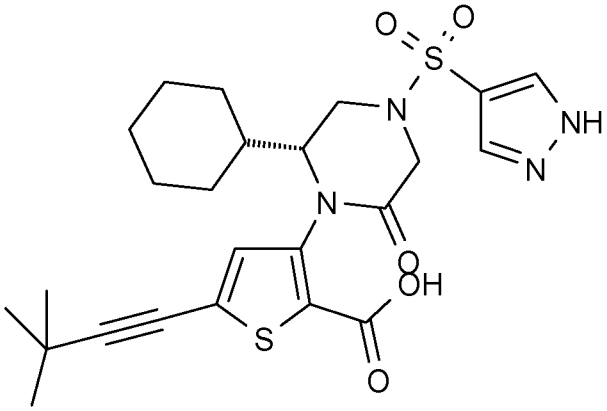
226	5-(4-Chloro-phenyl)-3-{(R)-2-cyclohexyl-4-[6-((R)-3-methyl-morpholin-4-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-thiophene-2-carboxylic acid	
227	5-(4-Chloro-phenyl)-3-{(R)-2-cyclohexyl-4-[6-(8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-thiophene-2-carboxylic acid	

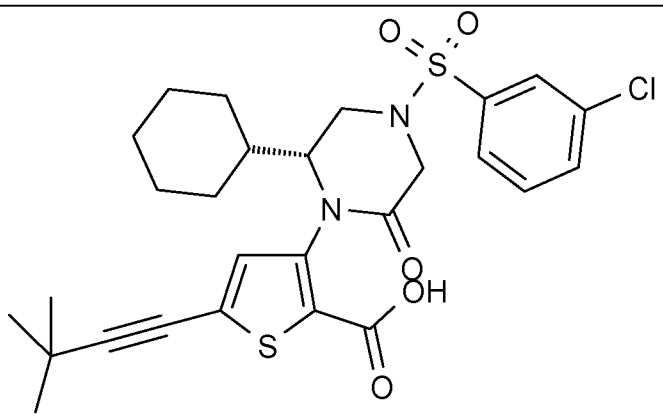
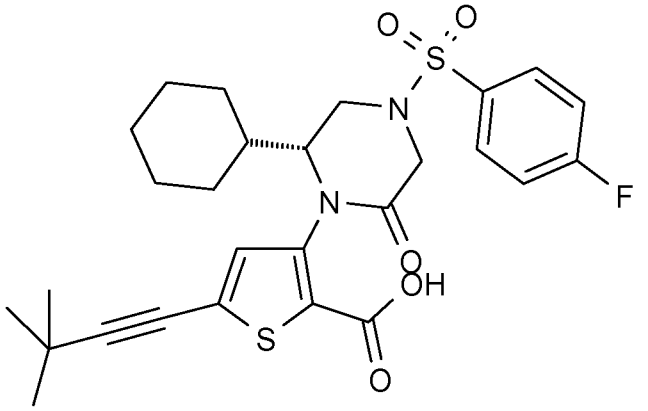
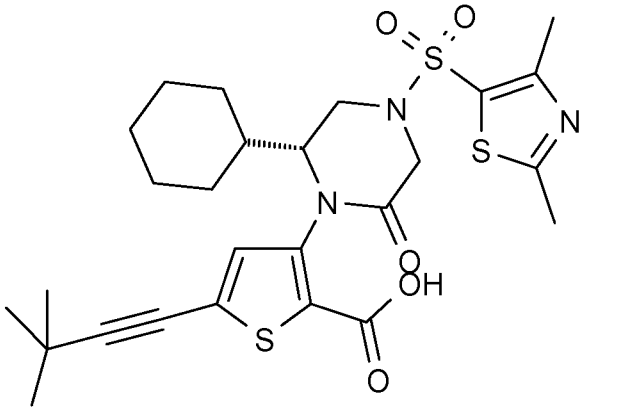
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229	5-(4-Chloro-phenyl)-3-{(R)-2-cyclohexyl-4-[6-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-thiophene-2-carboxylic acid	

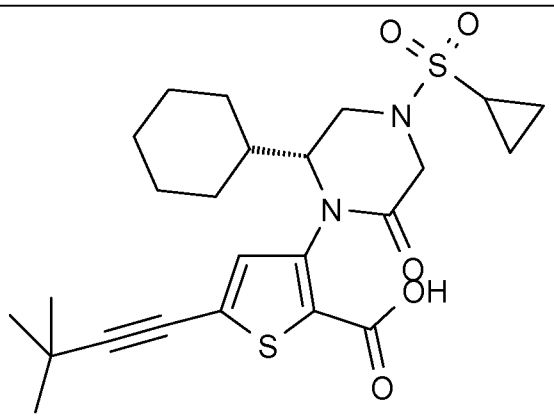
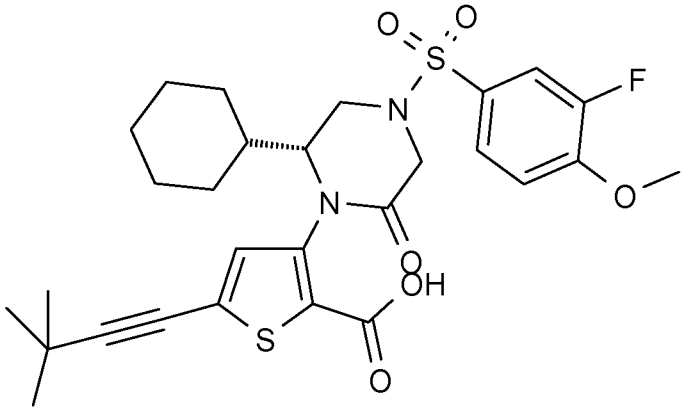
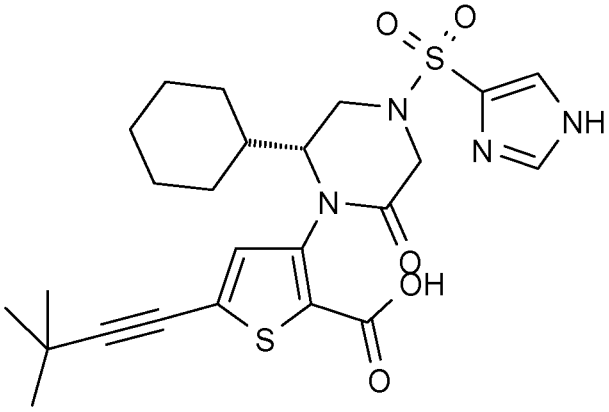
230	3-[(R)-2-Cyclohexyl-6-oxo-4-(6-trifluoromethyl-pyridine-3-sulfonyl)-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
231	5-(4-Chloro-phenyl)-3-[(R)-2-cyclohexyl-6-oxo-4-(4-pyrrolidin-1-yl-benzenesulfonyl)-piperazin-1-yl]-thiophene-2-carboxylic acid	
232	3-[(R)-2-Cyclohexyl-6-oxo-4-(6-pyrrolidin-1-yl-pyridine-3-sulfonyl)-piperazin-1-yl]-5-(4-fluoro-phenyl)-thiophene-2-carboxylic acid	

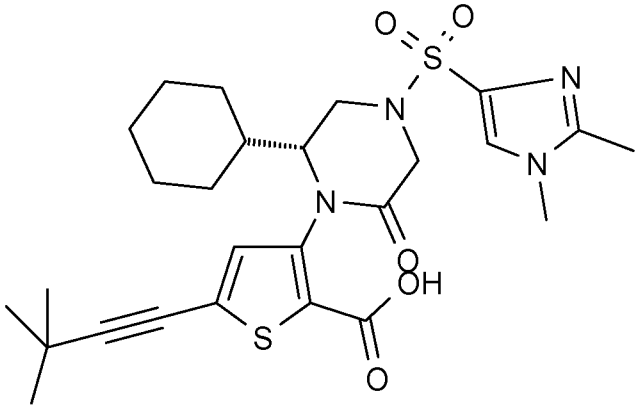
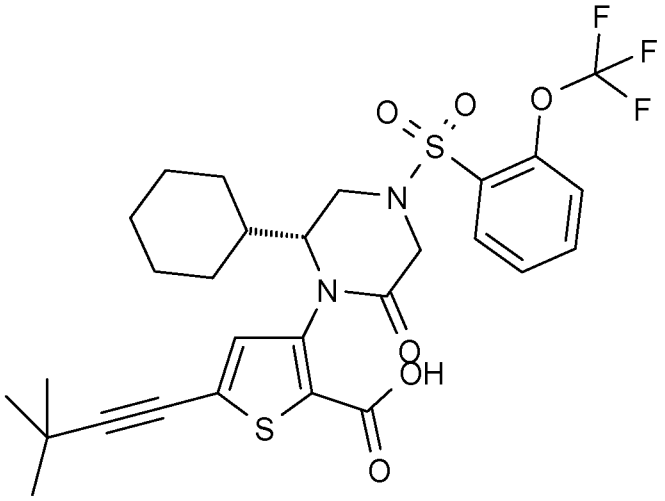
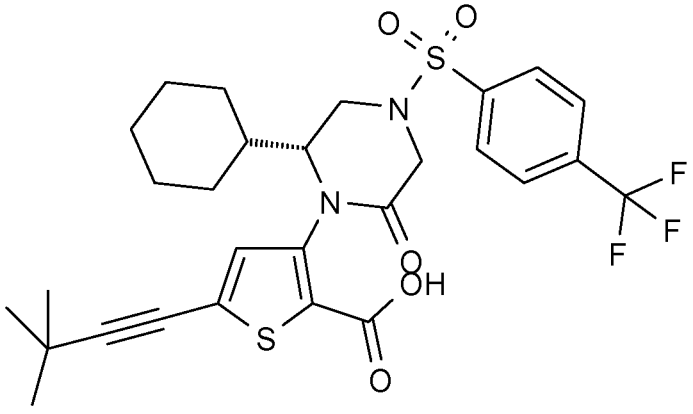
233	5-(4-Chloro-phenyl)-3-[(R)-2-cyclohexyl-6-oxo-4-(4-piperidin-1-yl-benzenesulfonyl)-piperazin-1-yl]-thiophene-2-carboxylic acid	
234	5-(4-Chloro-phenyl)-3-{(R)-2-cyclohexyl-4-[4-((R)-2-methyl-pyrrolidin-1-yl)-benzenesulfonyl]-6-oxo-piperazin-1-yl}-thiophene-2-carboxylic acid	
235	3-[(R)-2-Cyclohexyl-6-oxo-4-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-sulfonyl)-piperazin-1-yl]-5-(4-fluoro-phenyl)-thiophene-2-carboxylic acid	

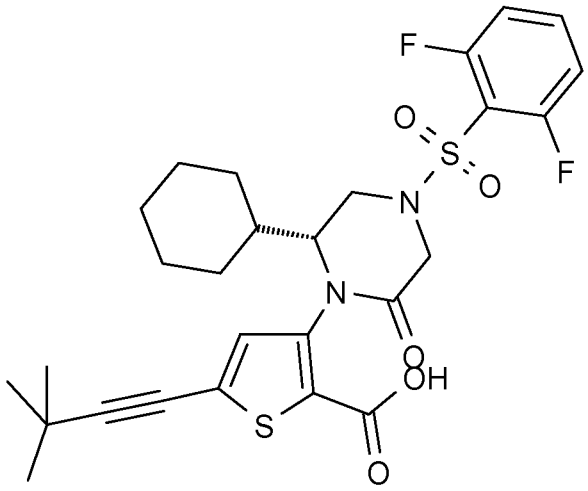
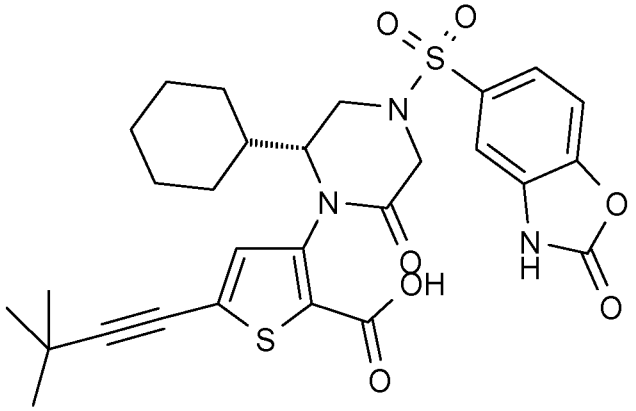
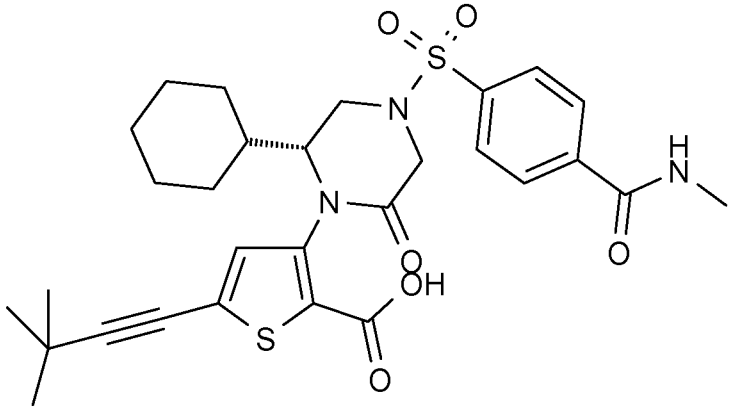
236	3-((R)-3-Cyclohexyl-5-oxo-morpholin-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
237	3-((4S,5R)-5-Cyclohexyl-3,4-dimethyl-2-oxo-imidazolidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
238	3-[(R)-4-(4-Cyano-benzenesulfonyl)-2-cyclohexyl-6-oxo-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	

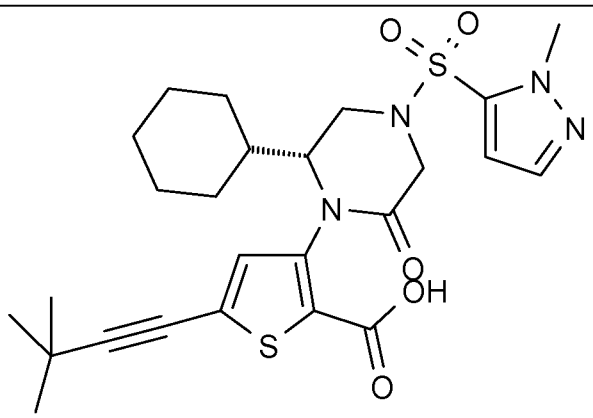
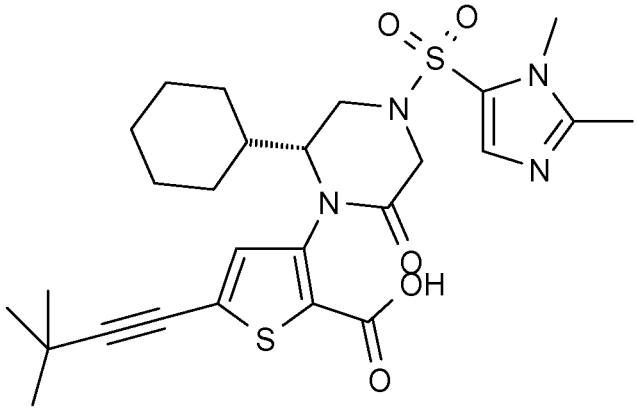
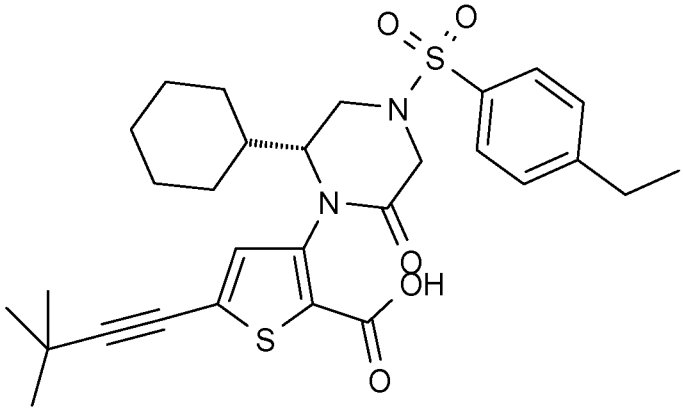
239	3-[(R)-2-Cyclohexyl-4-(3-fluoro-benzenesulfonyl)-6-oxo-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
240	3-[(R)-2-Cyclohexyl-4-(5-methyl-isoxazole-4-sulfonyl)-6-oxo-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
241	3-[(R)-2-Cyclohexyl-6-oxo-4-(1H-pyrazole-4-sulfonyl)-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	

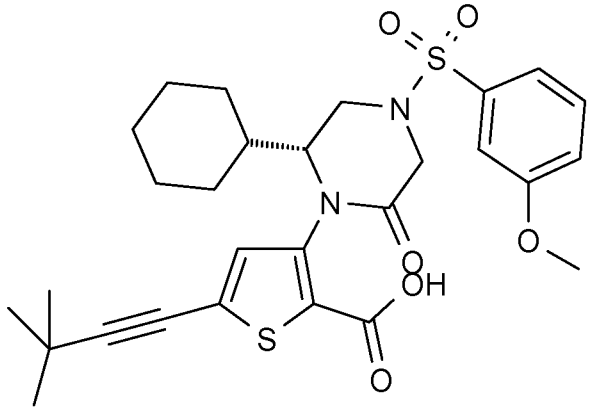
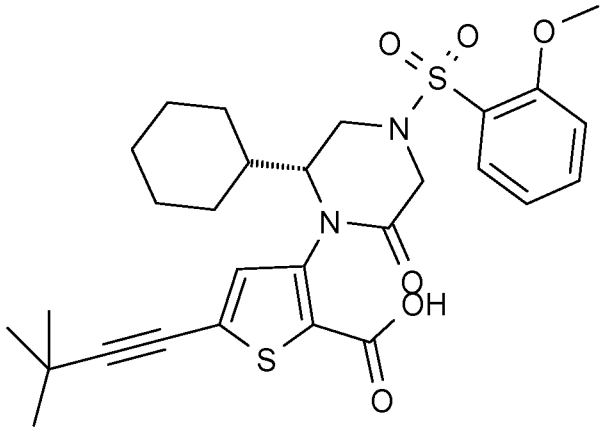
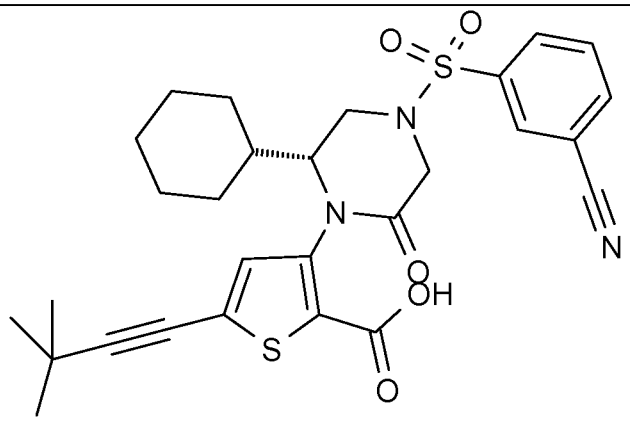
242	3-[(R)-4-(3-Chloro-benzenesulfonyl)-2-cyclohexyl-6-oxo-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
243	3-[(R)-2-Cyclohexyl-4-(4-fluoro-benzenesulfonyl)-6-oxo-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
244	3-[(R)-2-Cyclohexyl-4-(2,4-dimethyl-thiazole-5-sulfonyl)-6-oxo-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	

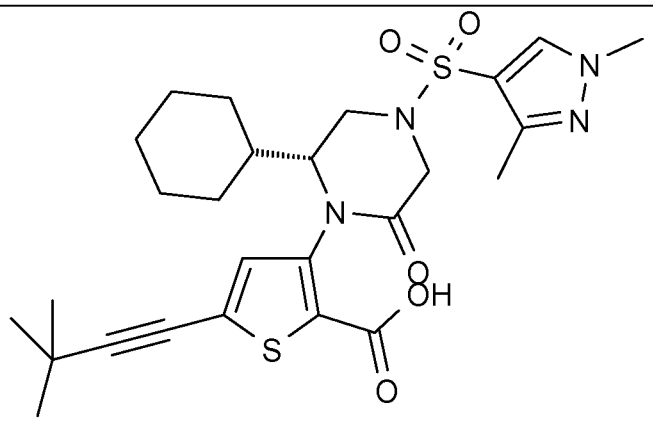
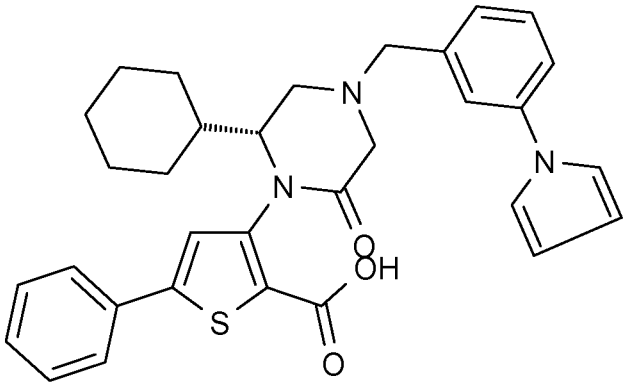
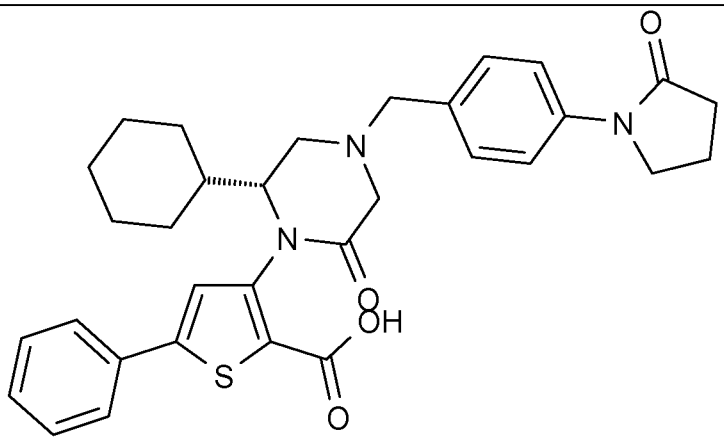
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246	3-[(R)-2-Cyclohexyl-4-(3-fluoro-4-methoxy-benzenesulfonyl)-6-oxo-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
247	3-[(R)-2-Cyclohexyl-4-(1H-imidazole-4-sulfonyl)-6-oxo-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	

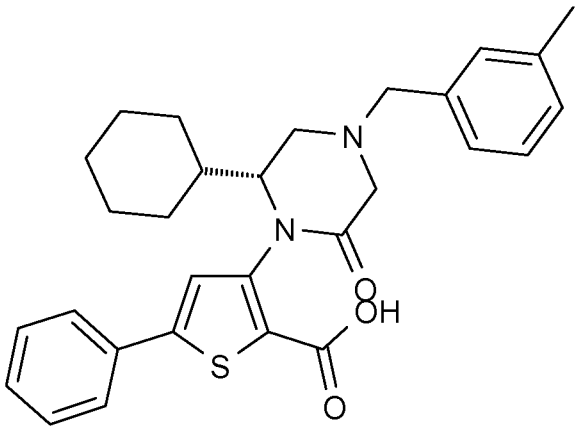
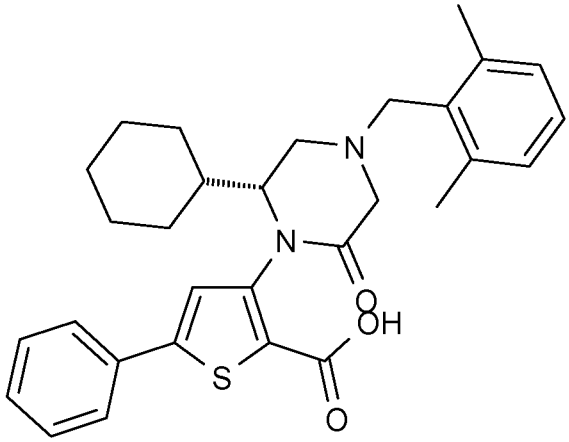
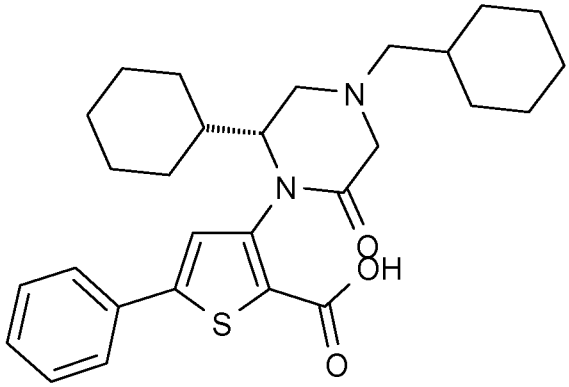
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249	3-[(R)-2-Cyclohexyl-6-oxo-4-(2-trifluoromethoxy-benzenesulfonyl)-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
250	3-[(R)-2-Cyclohexyl-6-oxo-4-(4-trifluoromethyl-benzenesulfonyl)-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	

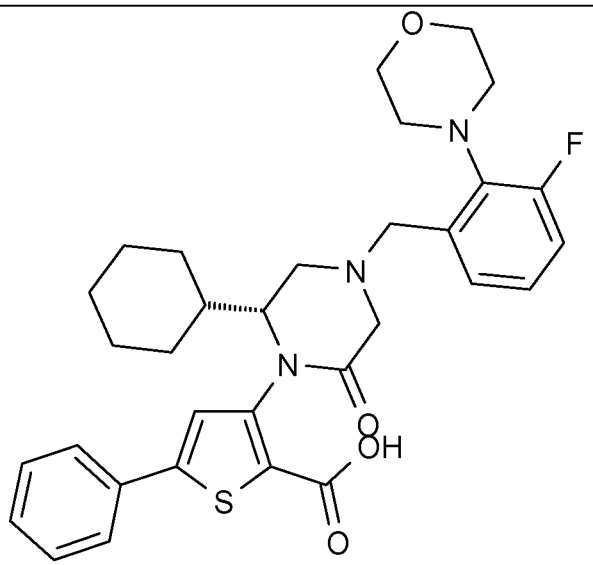
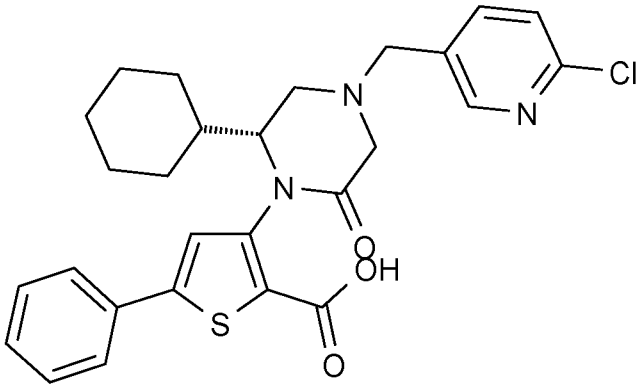
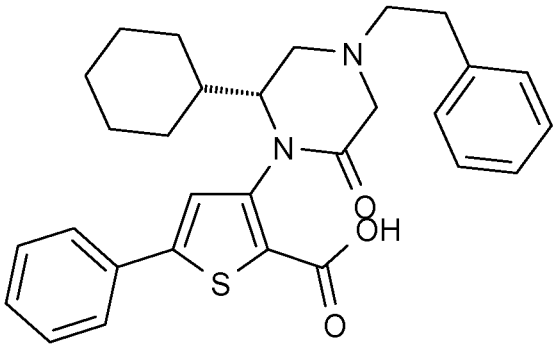
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252	3-[(R)-2-Cyclohexyl-6-oxo-4-(2-oxo-2,3-dihydro-benzooxazole-5-sulfonyl)-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
253	3-[(R)-2-Cyclohexyl-4-(4-methylcarbamoyl-benzenesulfonyl)-6-oxo-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	

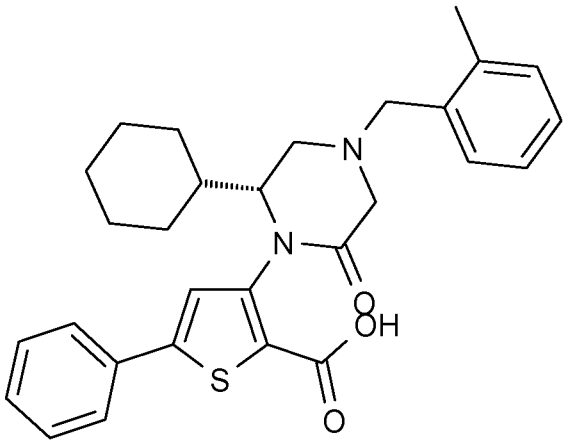
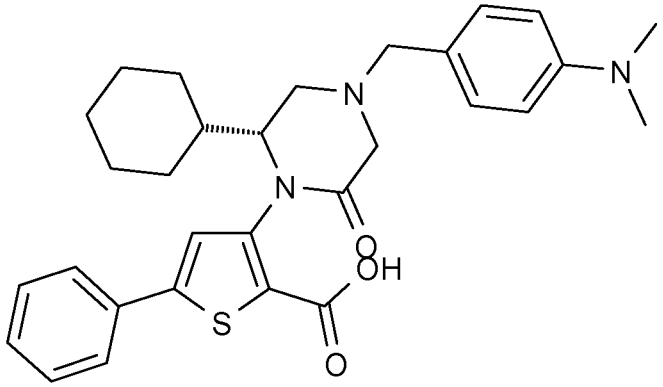
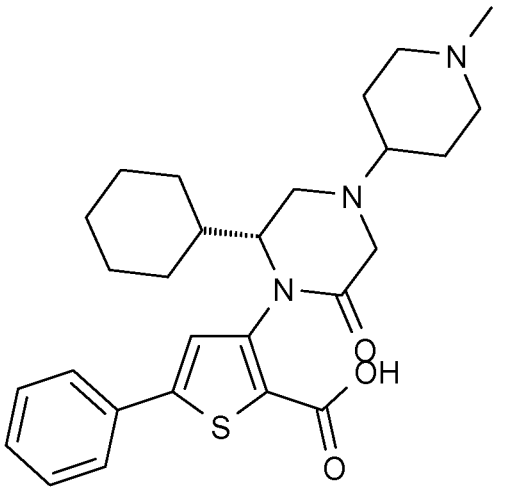
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255	3-[(R)-2-Cyclohexyl-4-(2,3-dimethyl-3H-imidazole-4-sulfonyl)-6-oxo-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
256	3-[(R)-2-Cyclohexyl-4-(4-ethyl-benzenesulfonyl)-6-oxo-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	

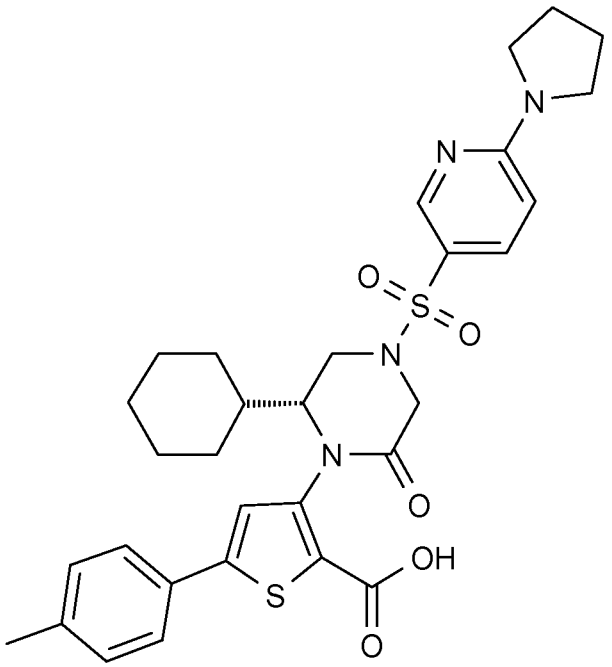
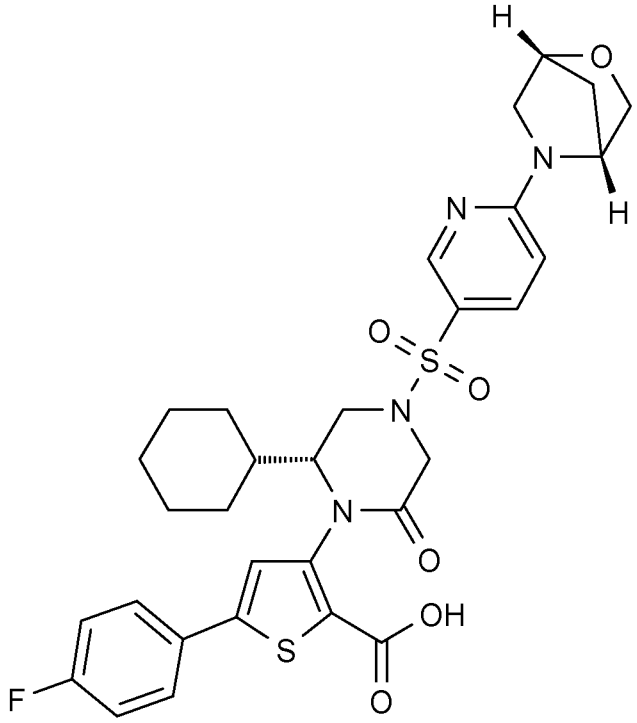
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258	3-[(R)-2-Cyclohexyl-4-(2-methoxy-benzenesulfonyl)-6-oxo-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
259	3-[(R)-4-(3-Cyano-benzenesulfonyl)-2-cyclohexyl-6-oxo-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	

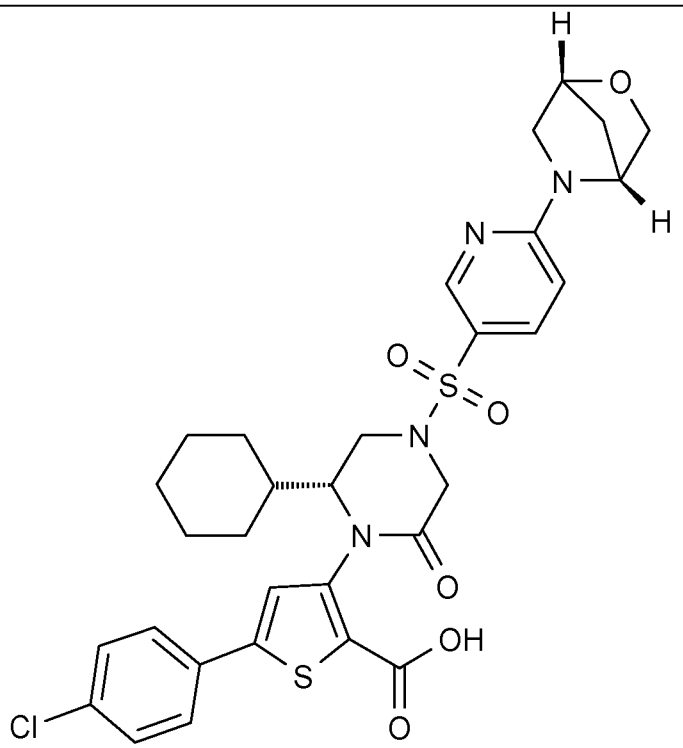
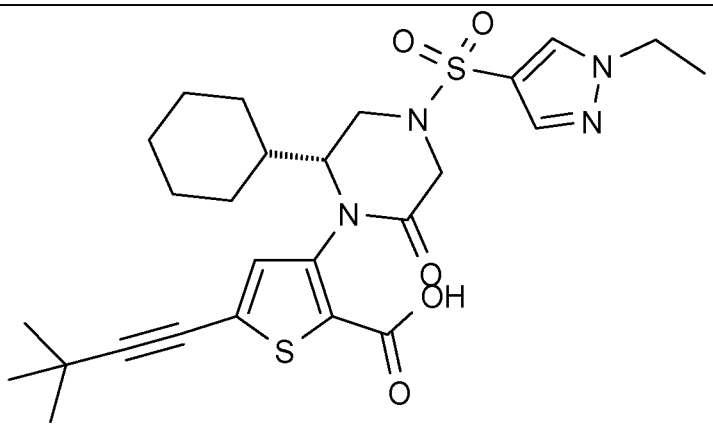
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261	3-[(R)-2-Cyclohexyl-6-oxo-4-(3-pyrrol-1-yl-benzyl)-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
262	3-{(R)-2-Cyclohexyl-6-oxo-4-[4-(2-oxo-pyrrolidin-1-yl)-benzyl]-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid	

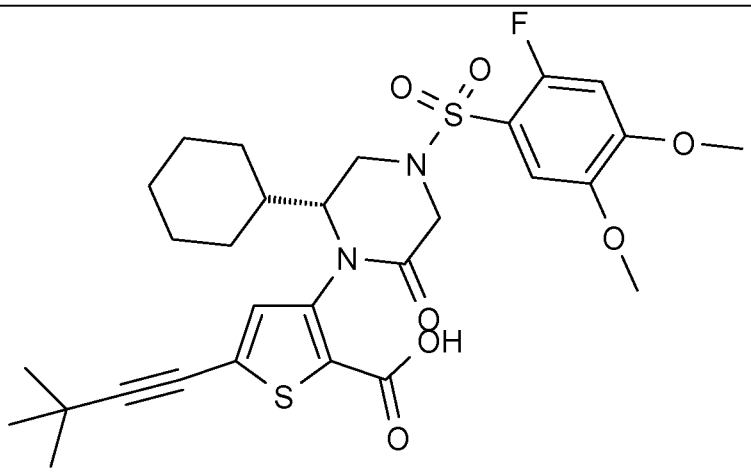
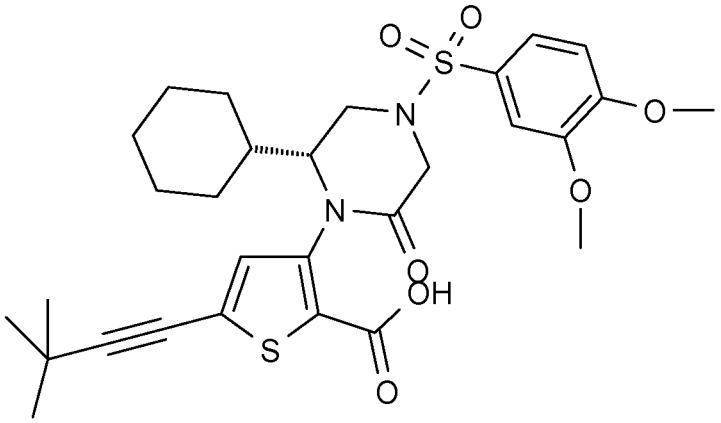
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264	3-[(R)-2-Cyclohexyl-4-(2,6-dimethyl-benzyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
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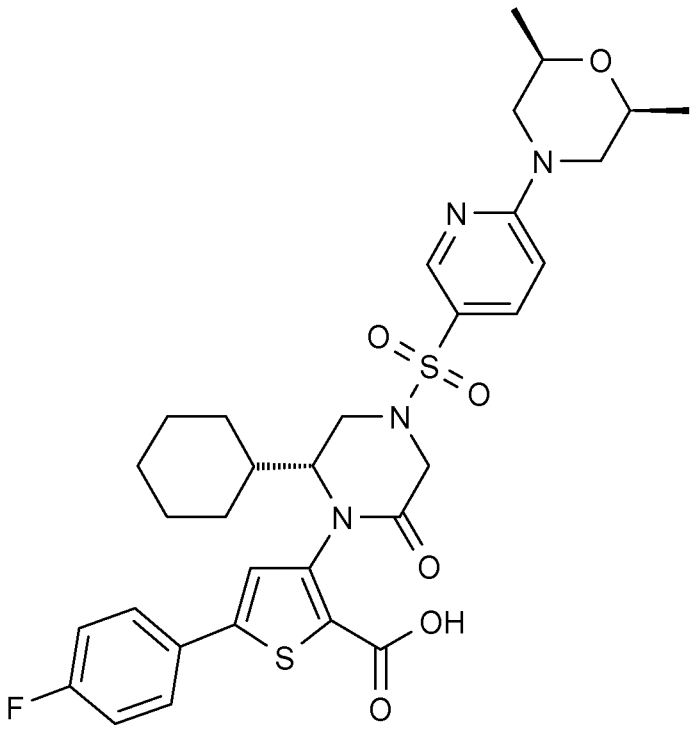
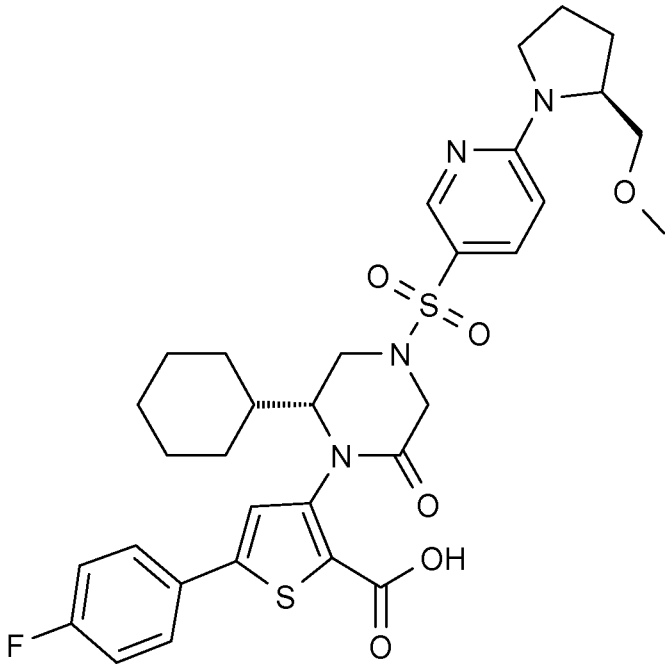
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267	3-[(R)-4-(6-Chloro-pyridin-3-ylmethyl)-2-cyclohexyl-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
268	3-((R)-2-Cyclohexyl-6-oxo-4-phenethyl-piperazin-1-yl)-5-phenyl-thiophene-2-carboxylic acid	

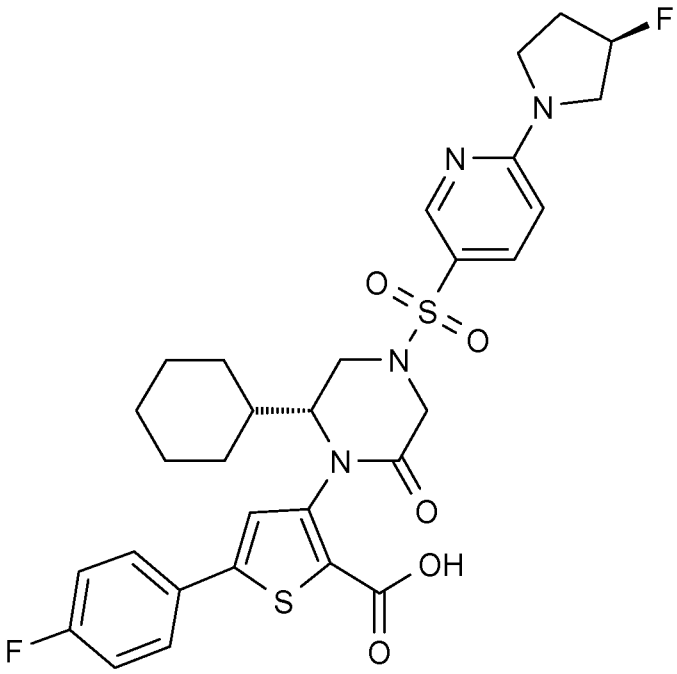
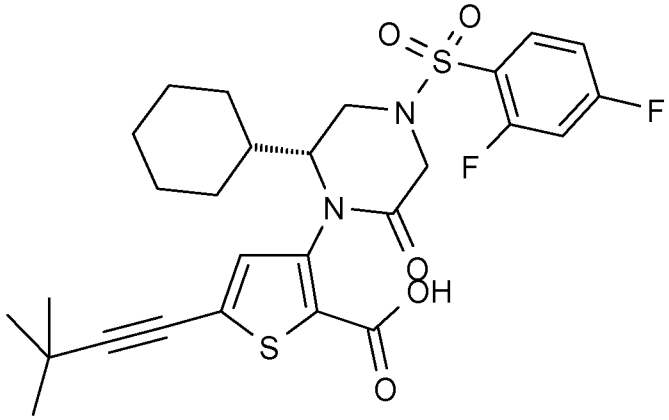
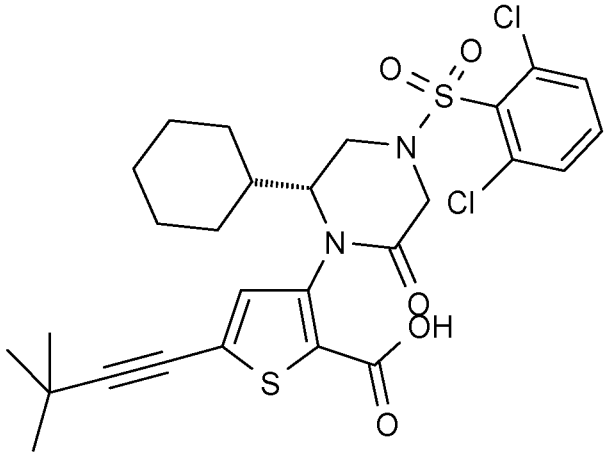
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270	3-[(R)-2-Cyclohexyl-4-(4-dimethylamino-benzyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid	
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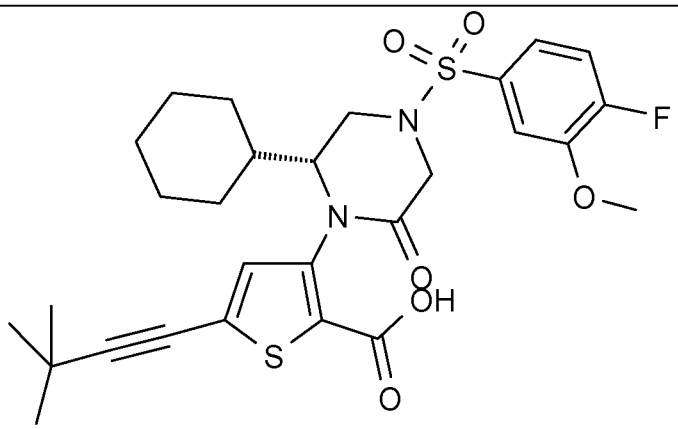
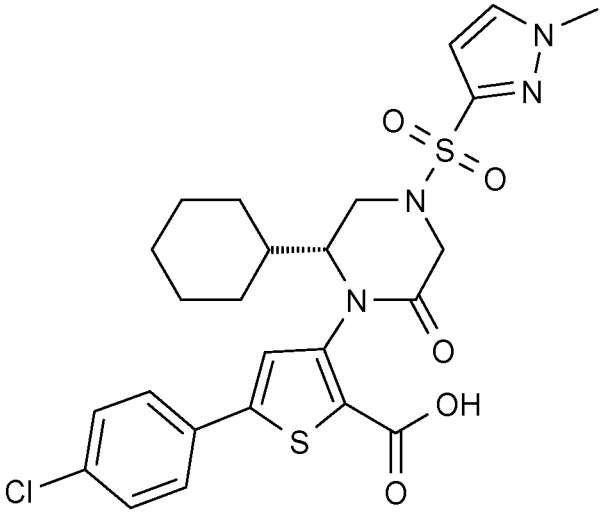
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273	3-{(R)-2-Cyclohexyl-4-[(1R,4R)-6-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-(4-fluoro-phenyl)-thiophene-2-carboxylic acid	

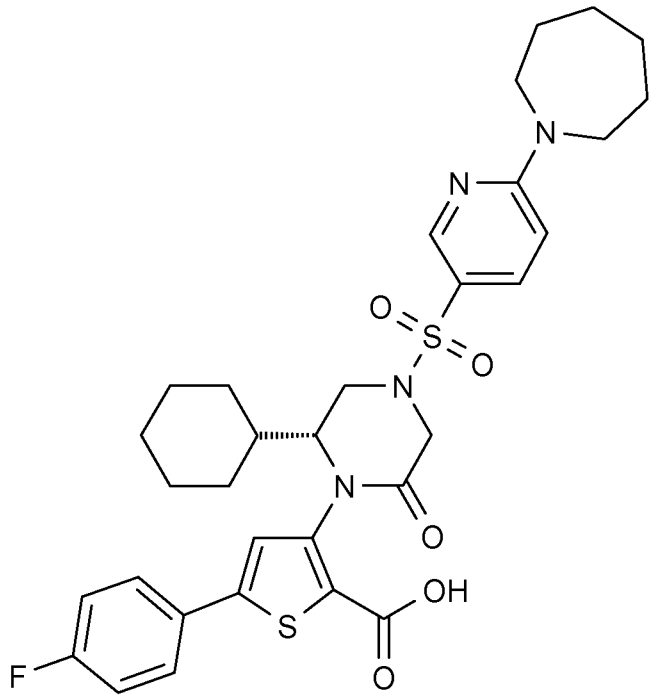
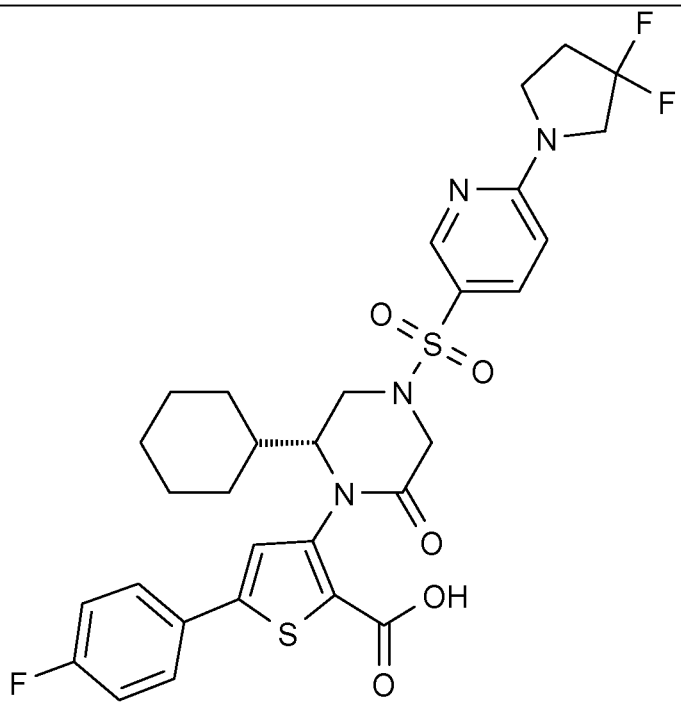
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275	3-[(R)-2-Cyclohexyl-4-(1-ethyl-1H-pyrazole-4-sulfonyl)-6-oxo-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	

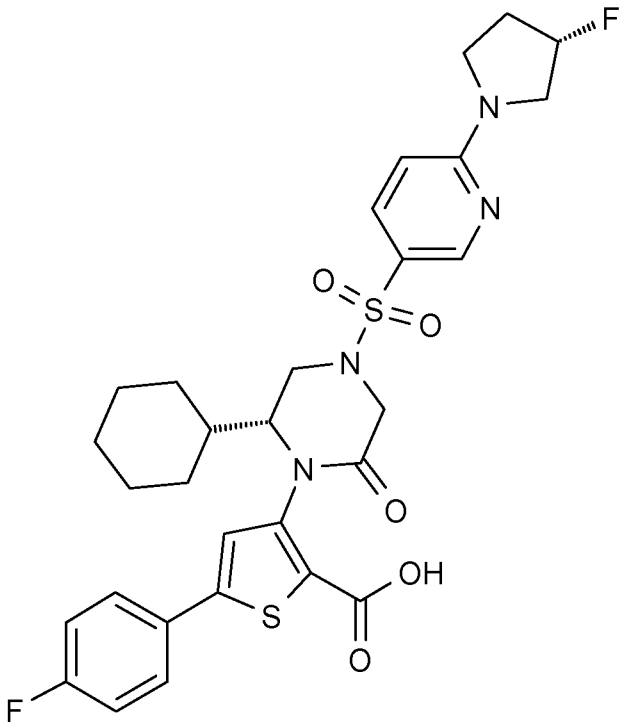
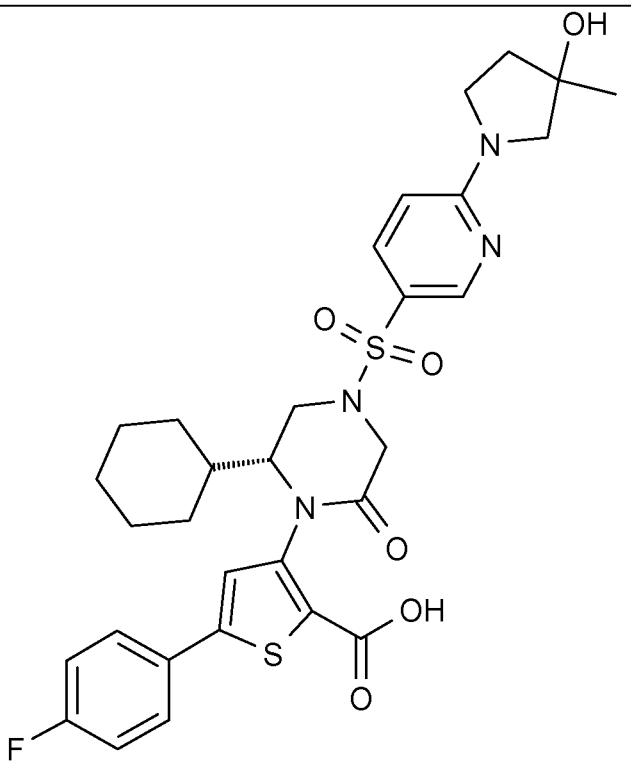
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277	3-[(R)-2-Cyclohexyl-4-(3,4-dimethoxy-benzenesulfonyl)-6-oxo-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	

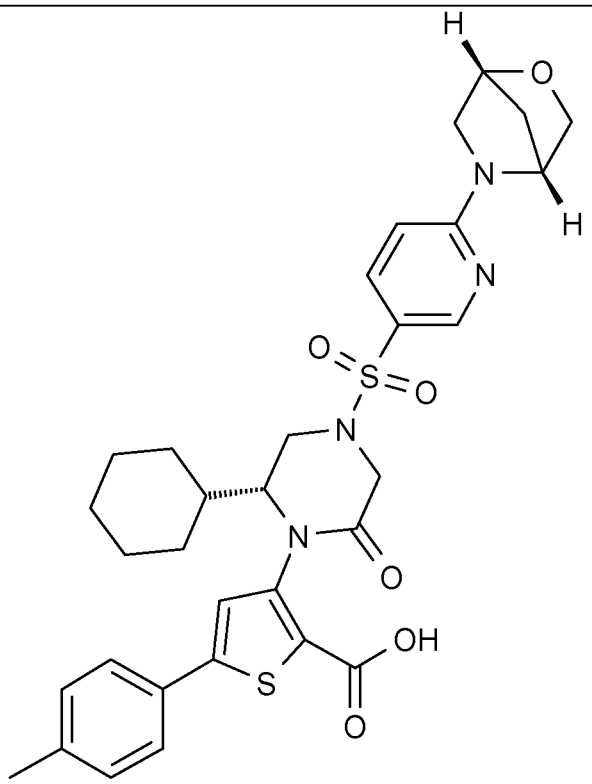
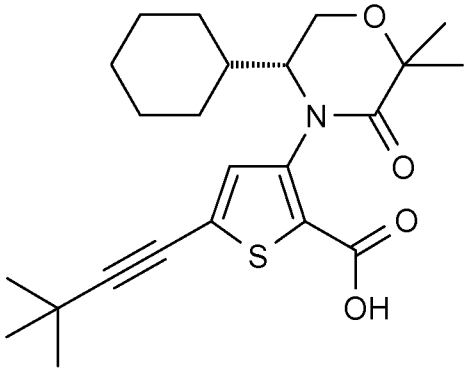
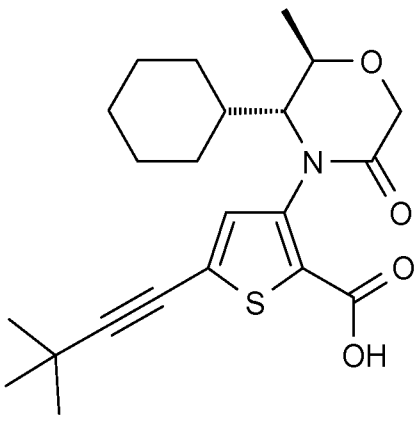
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279	3-{(R)-2-Cyclohexyl-4-[6-((S)-2-methoxymethyl-pyrrolidin-1-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-(4-fluoro-phenyl)-thiophene-2-carboxylic acid	

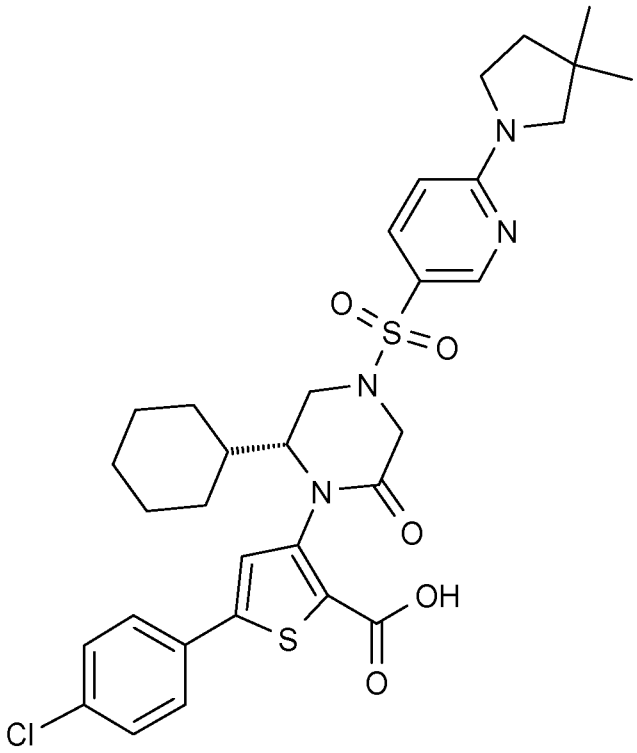
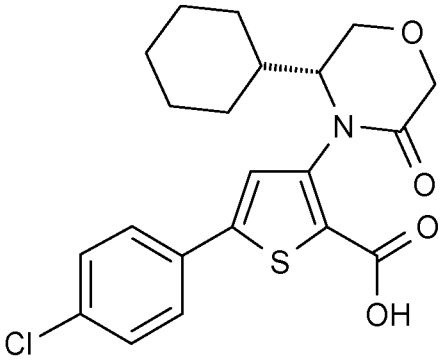
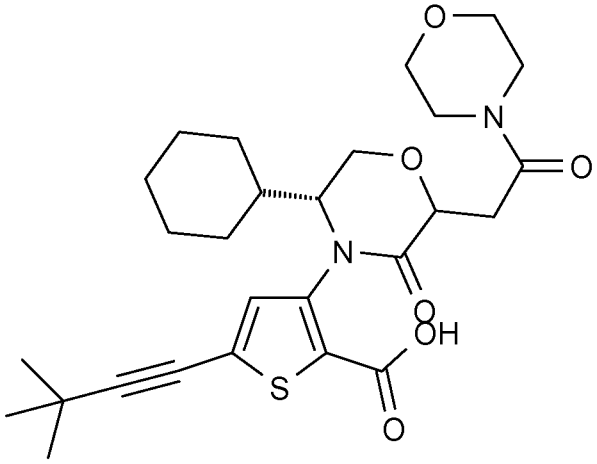
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281	3-[(R)-2-Cyclohexyl-4-(2,4-difluoro-benzenesulfonyl)-6-oxo-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
282	3-[(R)-2-Cyclohexyl-4-(2,6-dichloro-benzenesulfonyl)-6-oxo-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	

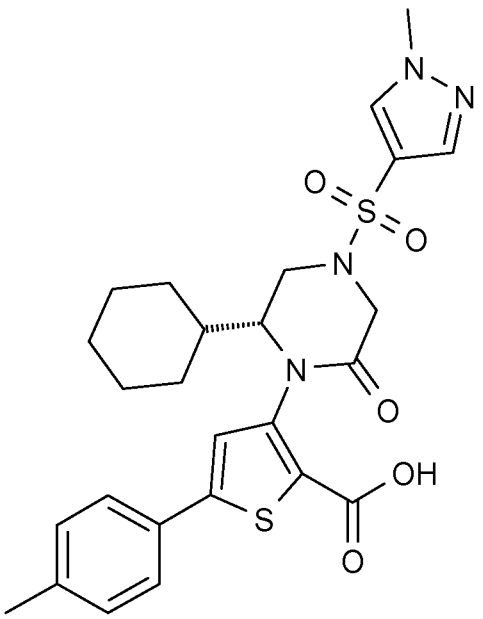
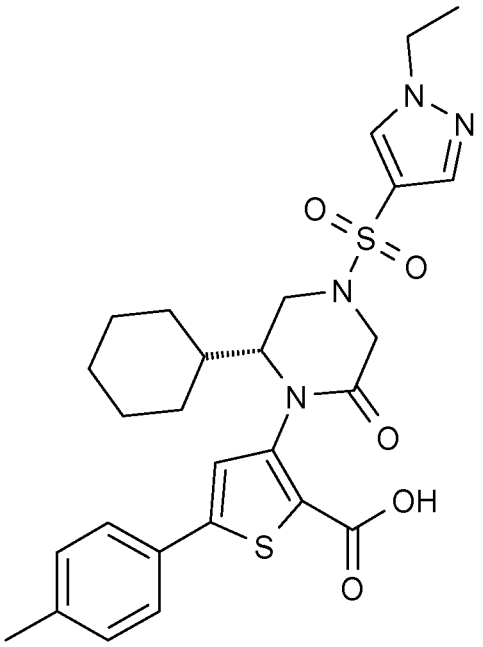
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284	5-(4-Chloro-phenyl)-3-[(R)-2-cyclohexyl-4-(1-methyl-1H-pyrazole-3-sulfonyl)-6-oxo-piperazin-1-yl]-thiophene-2-carboxylic acid	

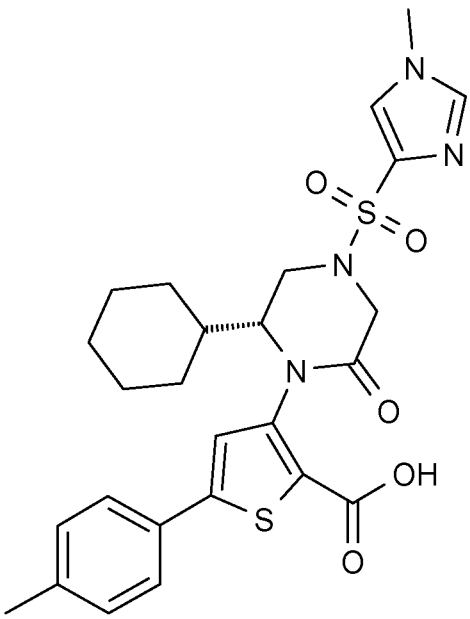
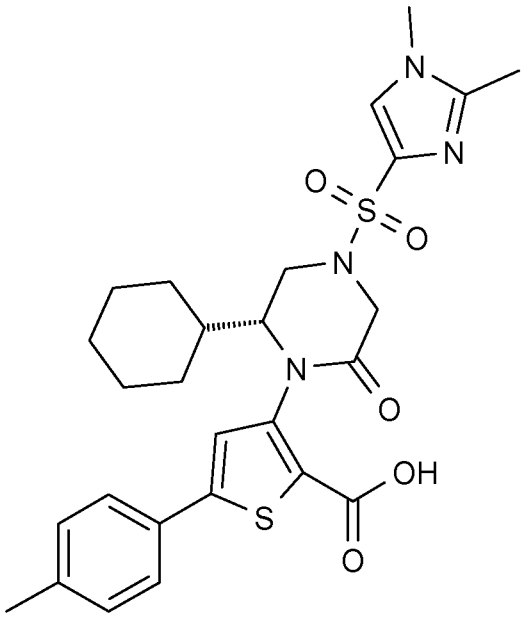
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286	3-{(R)-2-Cyclohexyl-4-[6-(3,3-difluoro-pyrrolidin-1-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-(4-fluoro-phenyl)-thiophene-2-carboxylic acid	

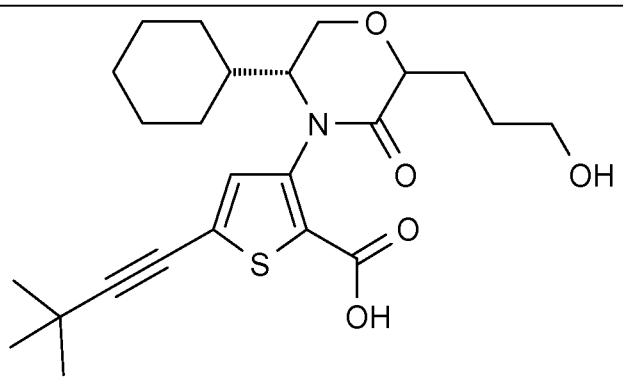
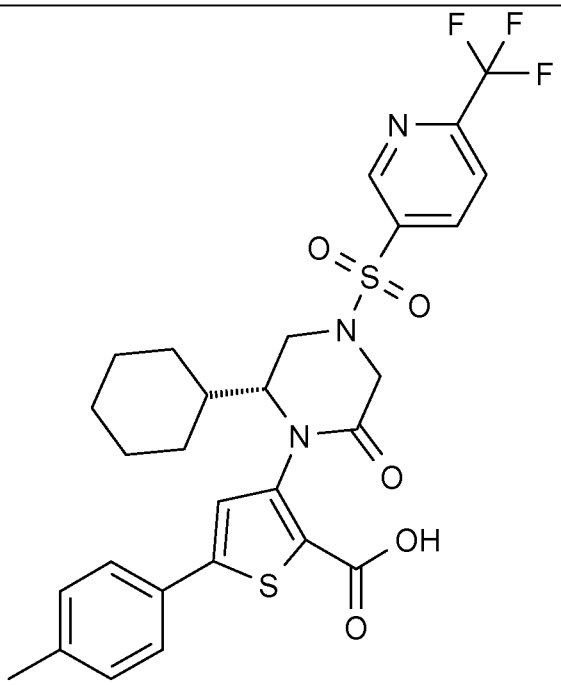
287	3-{(R)-2-Cyclohexyl-4-[6-((S)-3-fluoro-pyrrolidin-1-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-(4-fluoro-phenyl)-thiophene-2-carboxylic acid	
288	3-{(R)-2-Cyclohexyl-4-[6-(3-hydroxy-3-methyl-pyrrolidin-1-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-(4-fluoro-phenyl)-thiophene-2-carboxylic acid	

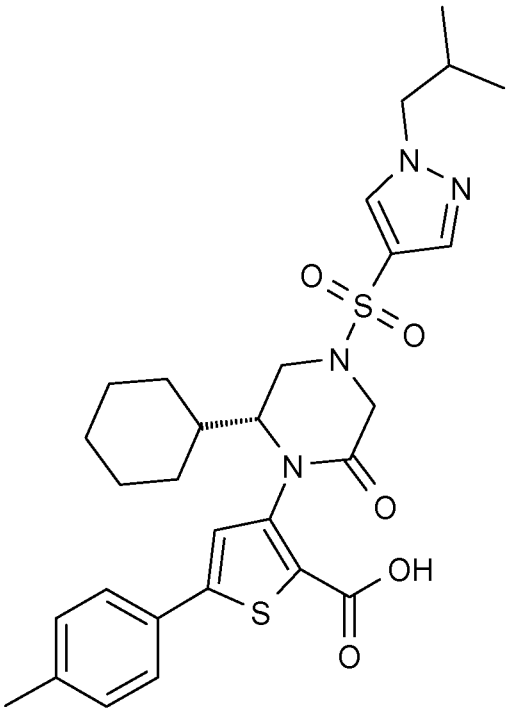
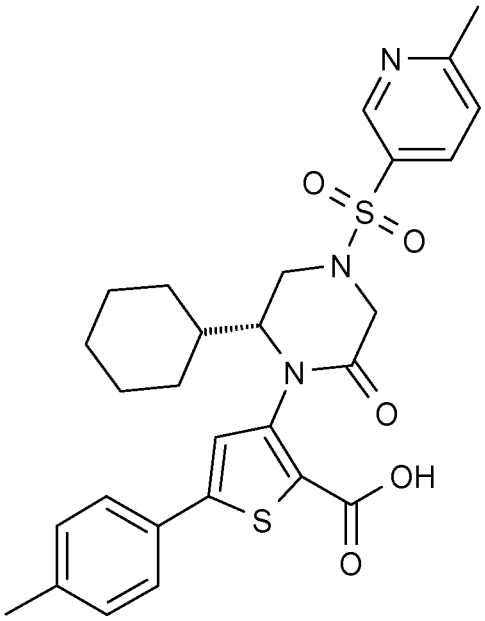
289	3-{(R)-2-Cyclohexyl-4-[(1R,4R)-6-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-p-tolyl-thiophene-2-carboxylic acid	
290	3-((R)-5-Cyclohexyl-2,2-dimethyl-3-oxo-morpholin-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
291	3-((2R,3R)-3-Cyclohexyl-2-methyl-5-oxo-morpholin-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	

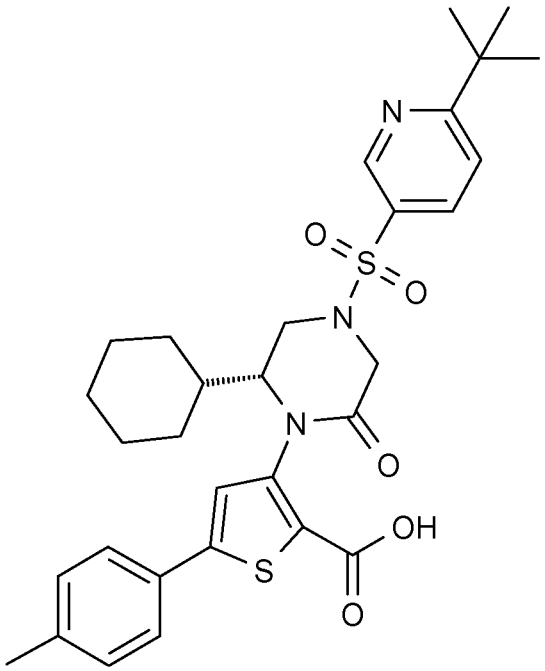
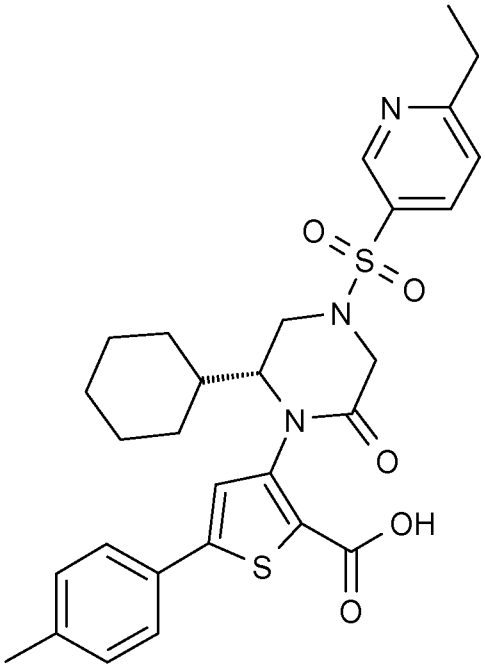
292	5-(4-Chloro-phenyl)-3-{(R)-2-cyclohexyl-4-[6-(3,3-dimethyl-pyrrolidin-1-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-thiophene-2-carboxylic acid	
293	5-(4-Chloro-phenyl)-3-((R)-3-cyclohexyl-5-oxo-morpholin-4-yl)-thiophene-2-carboxylic acid	
294	3-[(R)-5-Cyclohexyl-2-(2-morpholin-4-yl-2-oxo-ethyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	

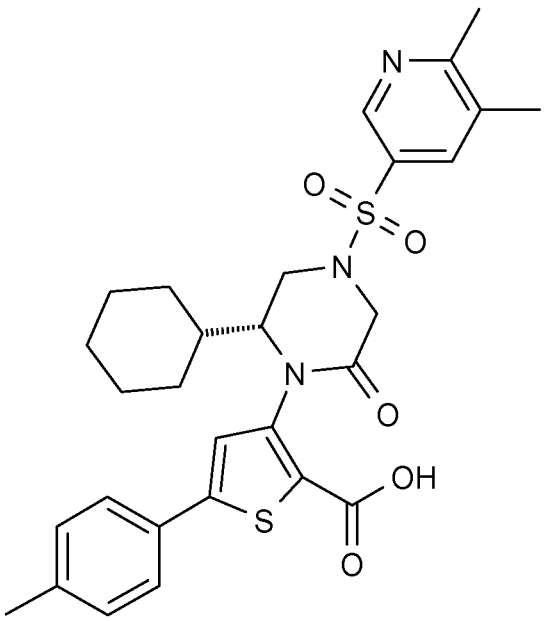
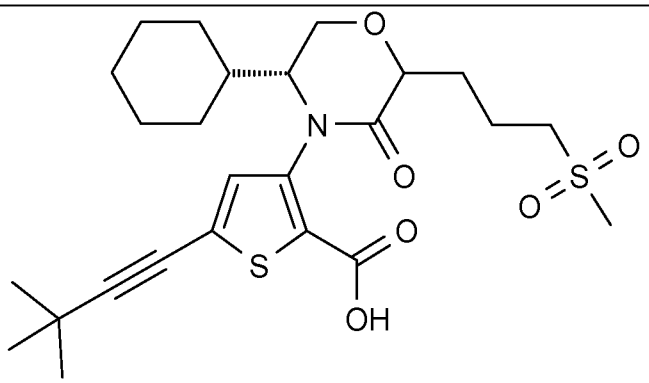
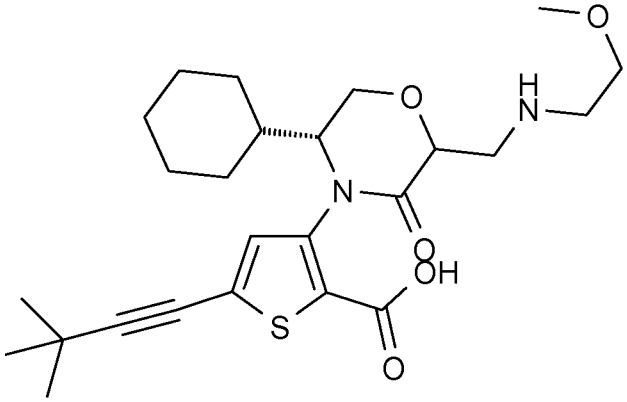
295	3-[(R)-2-Cyclohexyl-4-(1-methyl-1H-pyrazole-4-sulfonyl)-6-oxo-piperazin-1-yl]-5-p-tolyl-thiophene-2-carboxylic acid	
296	3-[(R)-2-Cyclohexyl-4-(1-ethyl-1H-pyrazole-4-sulfonyl)-6-oxo-piperazin-1-yl]-5-p-tolyl-thiophene-2-carboxylic acid	

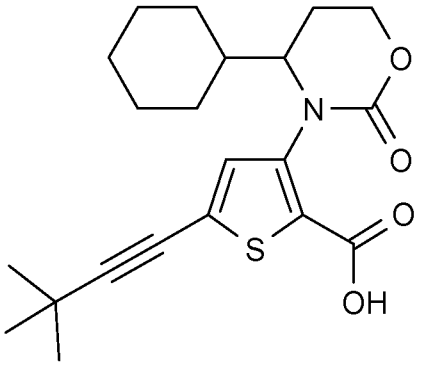
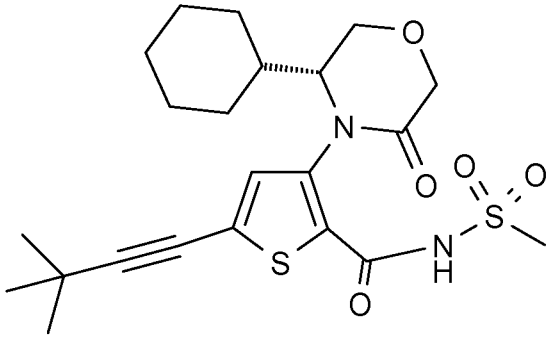
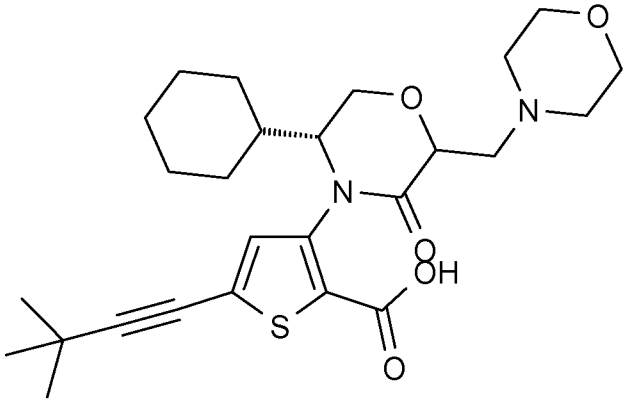
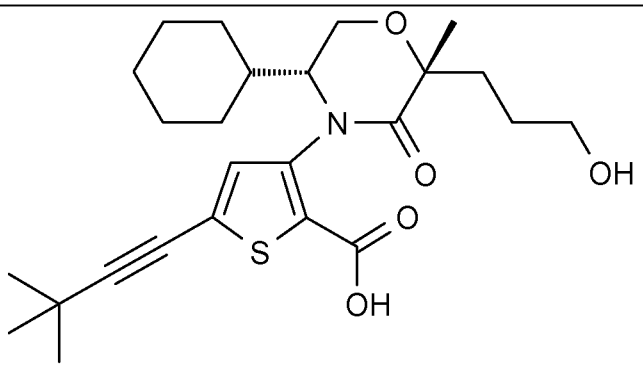
297	3-[(R)-2-Cyclohexyl-4-(1-methyl-1H-imidazole-4-sulfonyl)-6-oxo-piperazin-1-yl]-5-p-tolyl-thiophene-2-carboxylic acid	
298	3-[(R)-2-Cyclohexyl-4-(1,2-dimethyl-1H-imidazole-4-sulfonyl)-6-oxo-piperazin-1-yl]-5-p-tolyl-thiophene-2-carboxylic acid	

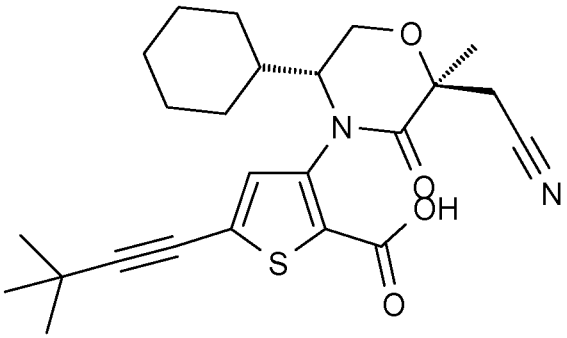
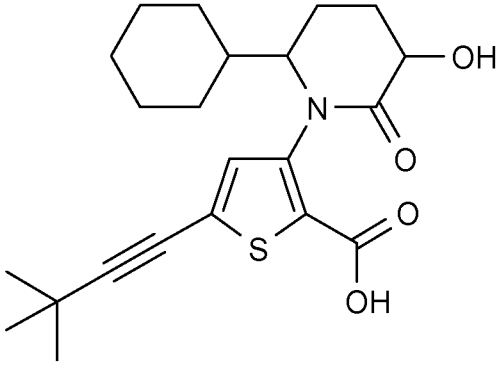
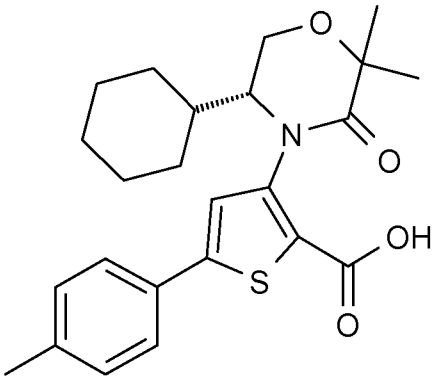
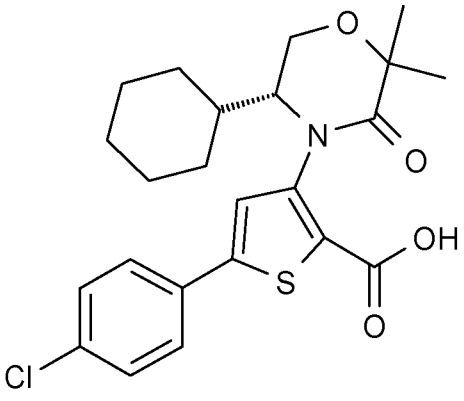
299	3-[(R)-5-Cyclohexyl-2-(3-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
300	3-[(R)-2-Cyclohexyl-6-oxo-4-(6-trifluoromethyl-pyridine-3-sulfonyl)-piperazin-1-yl]-5-p-tolyl-thiophene-2-carboxylic acid	

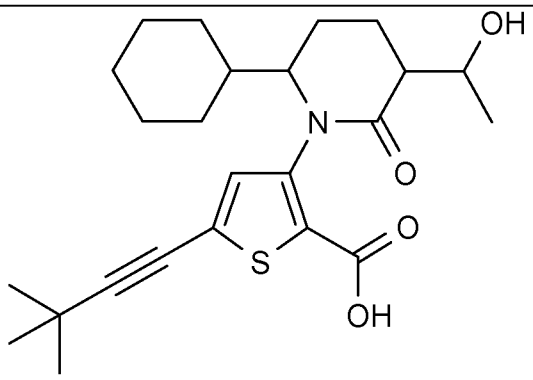
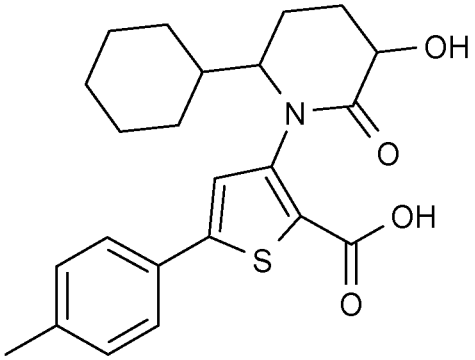
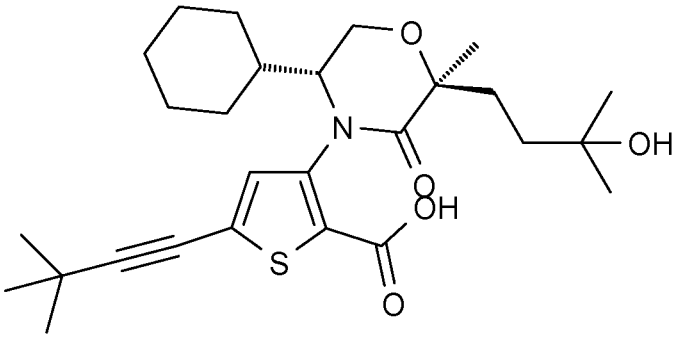
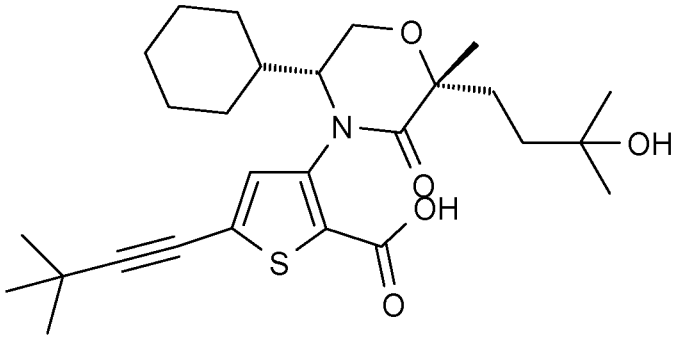
301	3-[(R)-2-Cyclohexyl-4-(1-isobutyl-1H-pyrazole-4-sulfonyl)-6-oxo-piperazin-1-yl]-5-p-tolyl-thiophene-2-carboxylic acid	
302	3-[(R)-2-Cyclohexyl-4-(6-methyl-pyridine-3-sulfonyl)-6-oxo-piperazin-1-yl]-5-p-tolyl-thiophene-2-carboxylic acid	

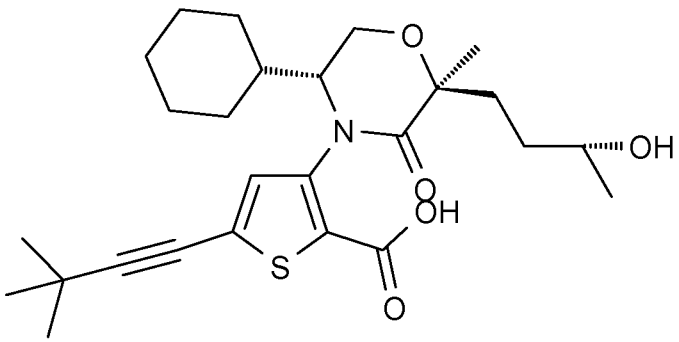
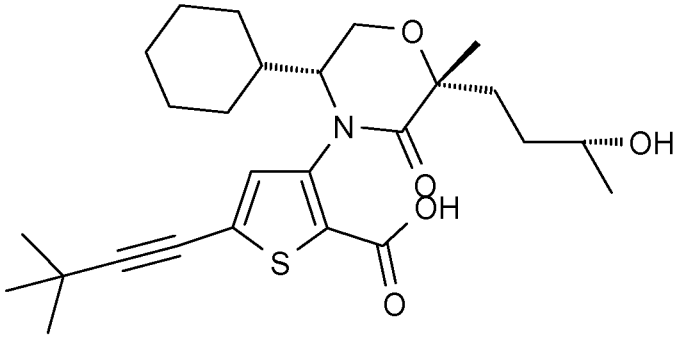
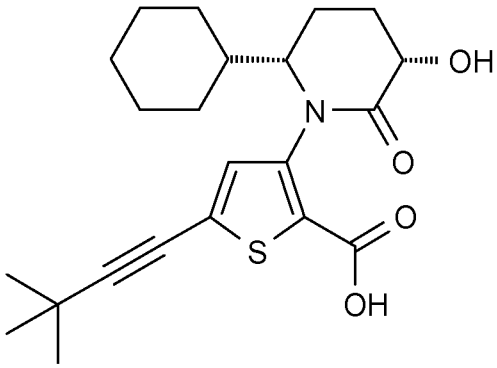
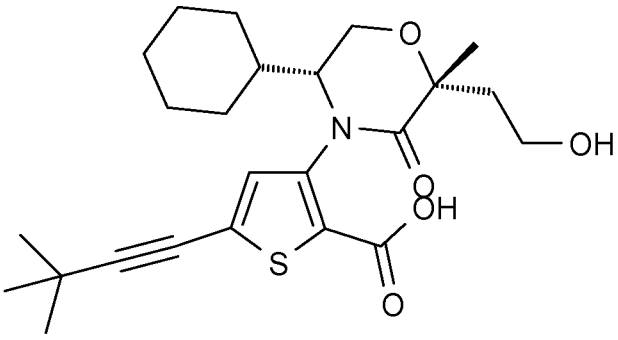
303	3-[(R)-4-(6-tert-Butyl-pyridine-3-sulfonyl)-2-cyclohexyl-6-oxo-piperazin-1-yl]-5-p-tolyl-thiophene-2-carboxylic acid	
304	3-[(R)-2-Cyclohexyl-4-(6-ethyl-pyridine-3-sulfonyl)-6-oxo-piperazin-1-yl]-5-p-tolyl-thiophene-2-carboxylic acid	

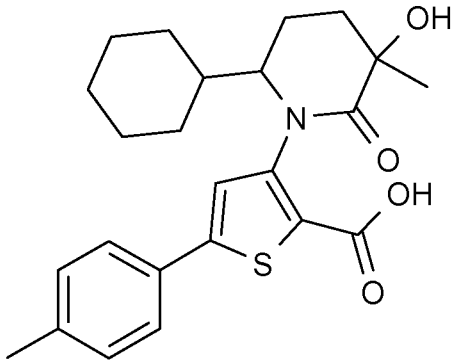
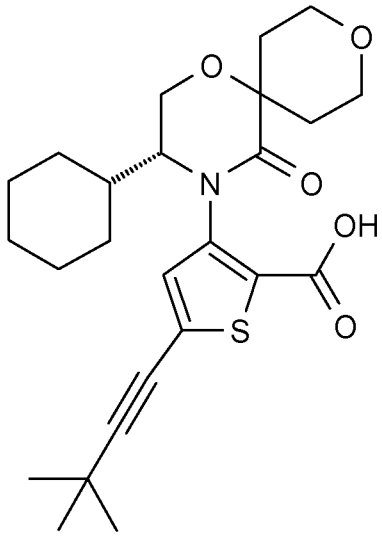
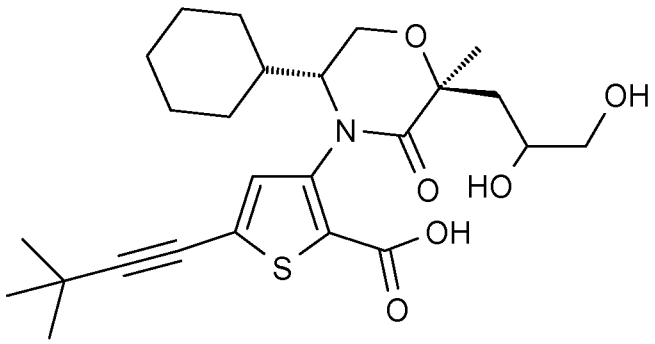
305	3-[(R)-2-Cyclohexyl-4-(5,6-dimethyl-pyridine-3-sulfonyl)-6-oxo-piperazin-1-yl]-5-p-tolyl-thiophene-2-carboxylic acid	
306	3-[(R)-5-Cyclohexyl-2-(3-methanesulfonyl-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
307	3-{(R)-5-Cyclohexyl-2-[(2-methoxy-ethylamino)-methyl]-3-oxo-morpholin-4-yl}-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	

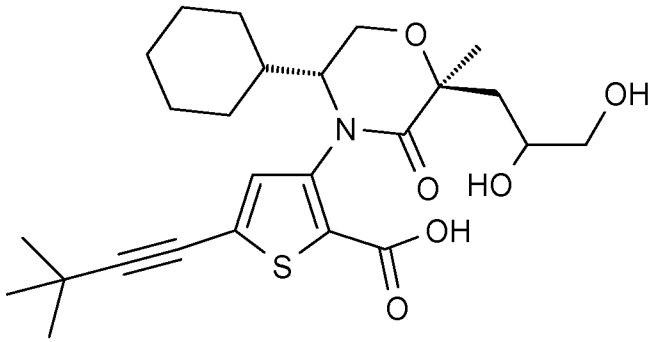
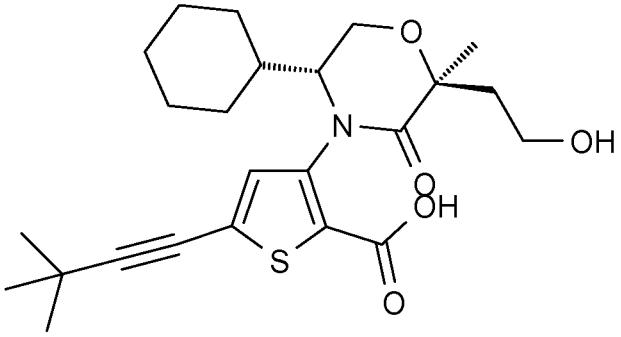
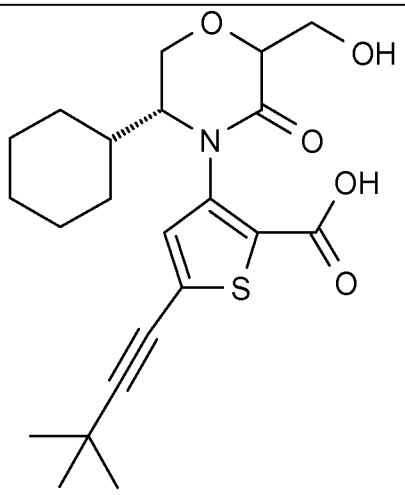
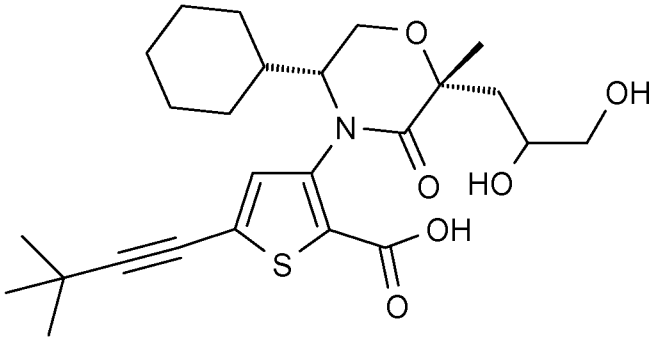
308	3-(4-Cyclohexyl-2-oxo-[1,3]oxazinan-3-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
309	N-[3-((R)-3-Cyclohexyl-5-oxo-morpholin-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carbonyl]-methanesulfonamide	
310	3-((R)-5-Cyclohexyl-2-morpholin-4-ylmethyl-3-oxo-morpholin-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
311	3-[(2R,5R)-5-Cyclohexyl-2-(3-hydroxy-propyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	

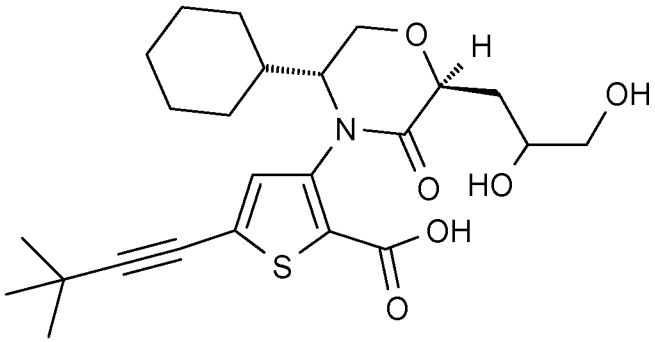
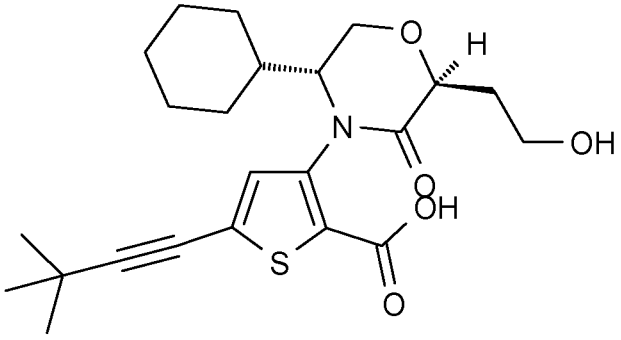
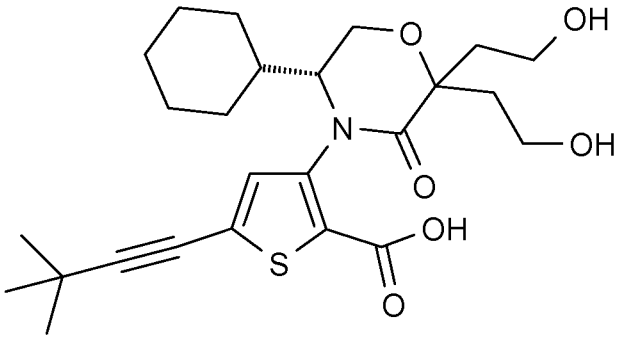
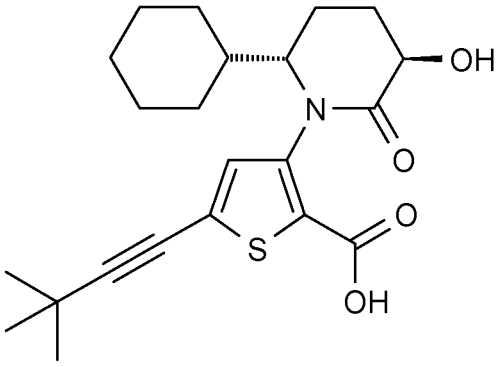
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313	3-(6-Cyclohexyl-3-hydroxy-2-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
314	3-((R)-5-Cyclohexyl-2,2-dimethyl-3-oxo-morpholin-4-yl)-5-p-tolyl-thiophene-2-carboxylic acid	
315	5-(4-Chloro-phenyl)-3-((R)-5-cyclohexyl-2,2-dimethyl-3-oxo-morpholin-4-yl)-thiophene-2-carboxylic acid	

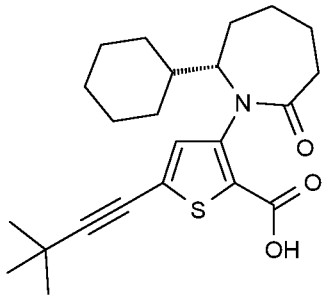
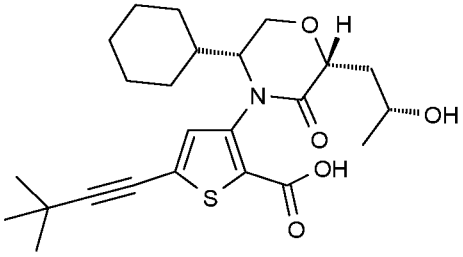
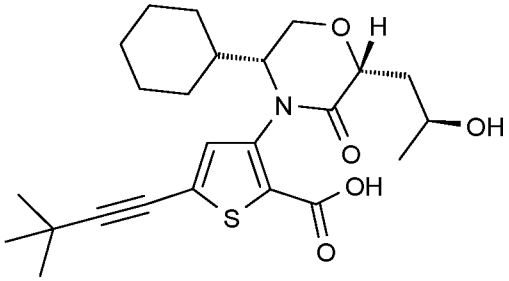
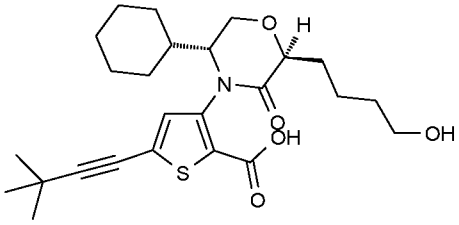
316	3-[6-Cyclohexyl-3-(1-hydroxy-ethyl)-2-oxo-piperidin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
317	3-(6-Cyclohexyl-3-hydroxy-2-oxo-piperidin-1-yl)-5-p-tolyl-thiophene-2-carboxylic acid	
318	3-[(2S,5R)-5-Cyclohexyl-2-(3-hydroxy-3-methyl-butyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
319	3-[(2R,5R)-5-Cyclohexyl-2-(3-hydroxy-3-methyl-butyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	

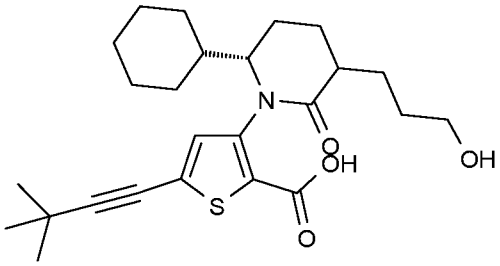
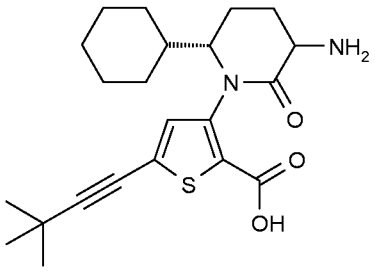
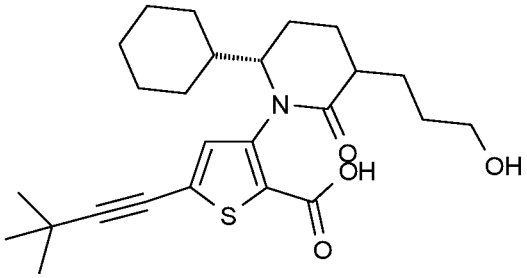
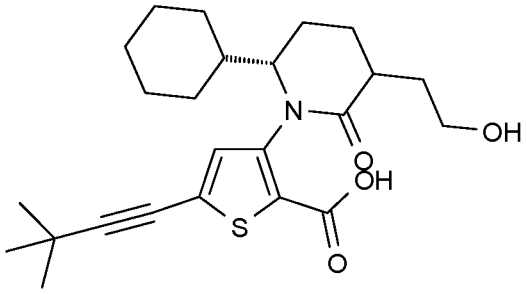
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321	3-[(2R,5R)-5-Cyclohexyl-2-((R)-3-hydroxy-butyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
322	3-((3S,6S)-6-Cyclohexyl-3-hydroxy-2-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
323	3-[(2R,5R)-5-Cyclohexyl-2-(2-hydroxy-ethyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	

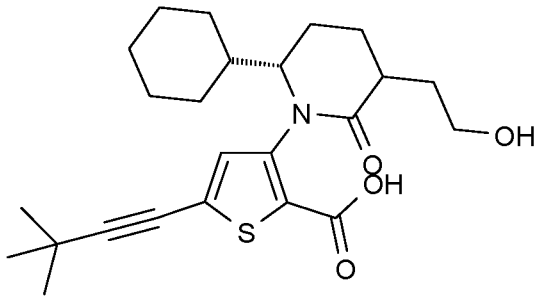
324	3-(6-Cyclohexyl-3-hydroxy-3-methyl-2-oxo-piperidin-1-yl)-5-p-tolyl-thiophene-2-carboxylic acid	
325	3-((R)-3-Cyclohexyl-5-oxo-1,9-dioxa-4-aza-spiro[5.5]undec-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
326	3-[(2S,5R)-5-Cyclohexyl-2-(2,3-dihydroxy-propyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	

327	3-[(2S,5R)-5-Cyclohexyl-2-(2,3-dihydroxy-propyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
328	3-[(2S,5R)-5-Cyclohexyl-2-(2-hydroxy-ethyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
329	3-((R)-5-Cyclohexyl-2-hydroxymethyl-3-oxo-morpholin-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
330	3-[(2R,5R)-5-Cyclohexyl-2-(2,3-dihydroxy-propyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	

331	3-[(2S,5R)-5-Cyclohexyl-2-(2,3-dihydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
332	3-[(2S,5R)-5-Cyclohexyl-2-(2-hydroxy-ethyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
333	3-[(R)-5-Cyclohexyl-2,2-bis-(2-hydroxy-ethyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
334	3-((3R,6S)-6-Cyclohexyl-3-hydroxy-2-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	

335	3-((S)-2-Cyclohexyl-7-oxo-azepan-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
336	3-[(2R,5R)-5-Cyclohexyl-2-((R)-2-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
337	3-[(2R,5R)-5-Cyclohexyl-2-((S)-2-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
338	3-[(2S,5R)-5-Cyclohexyl-2-(4-hydroxy-butyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	

339	3-[(S)-6-Cyclohexyl-3-(3-hydroxy-propyl)-2-oxo-piperidin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
340	3-((S)-3-Amino-6-cyclohexyl-2-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
341	3-[(S)-6-Cyclohexyl-3-(3-hydroxy-propyl)-2-oxo-piperidin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	
342	3-[(S)-6-Cyclohexyl-3-(2-hydroxy-ethyl)-2-oxo-piperidin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	

343	3-[(S)-6-Cyclohexyl-3-(2-hydroxy-ethyl)-2-oxo-piperidin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid	

NMR data for certain compounds of the invention are provided in Table 2.

Table 2

Compound number	NMR data
1	^{1}H-NMR (400MHz, CD_3OD): 7.80(d, 2H), 7.40(t, 2H), 7.29(t, 1H), 7.18(s, 1H), 4.62(m, 1H), 2.30(m, 2H), 2.03(m, 1H), 1.80-1.10 (m, 12H)
2	^{1}H-NMR (400MHz, CD_3OD): δ 6.97(s, 1H), 4.13(m, 1H), 3.90(m, 1H), 3,82(m, 1H), 3.57(m, 2H), 1.97- 1.48(m, 10H), 1.32(s, 9H), 1.26-1.09(m, 6H).
3	^{1}H-NMR (400MHz, CD_3OD): δ 6.93(s, 1H), 4.14(m, 1H), 4.0(m, 1H), 3.62(m, 1H), 3.58(m, 2H), 2.02- 1.48(m, 10H), 1.32(s, 9H), 1.25-1.17(m, 6H).
4	^{1}H-NMR (400MHz, $CDCl_3$): δ 7.43(m, 2H), 7.21(m, 3H), 6.94(m, 1H), 3.68(m, 1H), 2.45(m, 2H), 2.21(m, 1H), 1.83-1.51 (m, 12H), 1.32(m, 2H).
5	1H NMR (400 MHz, $CDCl_3$): δ 0.88-1.12(m, 5H), 1.29(m, 2H), 1.37(s, 3H), 1.48-1.60(m, 2H), 1.71(m, 2H), 1.84(m, 2H), 1.96(m, 1H), 2.12(m, 1H), 2.29(s, 3H), 3.72(m, 1H), 6.93(s, 1H), 7.11(d, 2H), 7.39(d, 2H)
6	^{1}H-NMR (400MHz, DMSO-d_6): δ 13.1(s, 1H), 7.75(d, 2H), 7.58(s, 1H), 7.37-7.52(m, 3H), 4.21(m, 1H), 2.34(m, 2H), 2.09(m, 1H), 1.91(m, 1H), 1.36-1.79(m, 5H), 0.91-1.31(m, 6H).

Compound number	NMR data
7	^{1}H-NMR (400MHz, CD_3OD): δ 6.93(s, 1H), 4.12(d, 1H), 3.91(d, 1H), 3.66(s, 1H), 3.54(t, 2H), 2.14(m, 1H), 1.91(m, 1H), 1.44-1.85(m, 8H), 1.41(s, 3H), 1.06-1.37(m, 14H)
8	^{1}H-NMR (400MHz, CD_3OD): δ 6.90(s, 1H), 4.24(tert, 1H), 4.13(d, 1H), 4.01(tert, 1H), 3.73(d, 1H), 3.71(d, 1H), 3.66(t, 1H), 2.21(m,1H), 1.41-1.98(m, 8H), 1.05-1.37(m, 15H).
10	^{1}H-NMR (400MHz, DMSO-d_6): δ 7.57(s, 1H), 7.32-7.45(m, 6H), 7.28(t, 3H), 7.20(t, 1H), 5.45(m, 1H), 2.52-2.63(m, 3H), 1.89(m, 1H).
11	^{1}H-NMR (400MHz, CD_3OD): δ 6.89(s, 1H), 3.94(m, 1H), 3.58(m, 2H), 2.05(m, 1H), 1.92-1.39(m, 13H), 1.32(s, 9H), 1.25-1.13 (m, 5H)
13	^{1}H-NMR (400MHz, $CDCl_3$): δ 7.56(d, 2H), 7.35(m, 3H), 7.12(s, 1H), 4.26(tert, 2H), 3.98(m, 2H), 3.60(s, 1H), 0.94-1.93(m, 11H)
18	^{1}H-NMR (400MHz, CD_3OD): δ 7.74(d, 2H), 7.65(d, 2H), 7.49(d, 2H), 7.41(t, 2H), 7.33(t, 1H), 7.21(s, 1H), 4.12(d, 1H), 3.95(d, 1H), 3.93(s, 1H), 3.37(d, 1H), 3.02(tert, 1H), 2.47(s, 3H), 1.41-1.99(m, 7H), 1.05-1.32(m, 4H)
22	^{1}H-NMR (400MHz, DMSO): δ 10.31(d, 1H), 7.63(d, 2H), 7.42(t, 2H), 7.31(t, 2H), 7.23(m, 2H), 7.14(s, 1H), 6.98(m, 3H), 4.61(m, 2H), 4.45(m, 1H), 4.10(m, 1H), 3.32(s, 2H), 2.20(m, 1H), 1.88-1.76(m, 4H), 1.65-1.58(m, 2H), 1.41-1.05(m, 6H)
23	^{1}H-NMR (400MHz, DMSO): δ 8.55(m, 2H), 7.63(d, 2H), 7.48(t, 2H), 7.32(t, 2H), 7.15(s, 1H), 5.76(s, 1H), 3.98(m, 1H), 3.82(m, 1H), 2.33(m, 2H), 2.07(m, 1H), 1.80(m, 2H), 1.61(m, 3H), 1.38(m, 2H), 1.03(m, 5H)
35	^{1}H-NMR (400MHz, CD_3OD): δ 7.03(s, 1H), 3.81(m, 1H), 2.25(m, 1H), 1.88-1.38(m, 6H), 1.29(s, 9H), 1.18(m, 4H), 1.06 (m, 4H)

Compound number	NMR data
62	^{1}H-NMR (400MHz, CD_3OD): δ 7.82(d, 1H), 7.68(d, 2H), 7.44(m, 3H), 7.36(s, 1H), 6.78(d, 1H), 4.16(d, 1H), 4.02(s, 3H), 3.94(d, 1H), 3.81(s, 1H), 3.65(d, 1H), 3.18(tert, 1H), 2.00(d, 1H), 1.36-1.87(m, 6H), 1.05-1.29(m, 4H)
135	^{1}H-NMR (400MHz, CD_3OD): δ 8.47(d, 1H), 7.85(tert, 1H), 7.64(d, 2H), 7.43(t, 2H), 7.30(m, 2H), 6.61(d, 1H), 3.94(s, 1H), 3.88(d, 1H), 3.74(d, 1H), 2.81-3.24(m, 6H), 1.49-2.06(m, 8H), 0.98-1.35(m, 7H)
184	^{1}H-NMR (400MHz, CD_3OD): δ 8.51(d, 1H), 7.86(tert, 1H), 7.64(d, 2H), 7.41(t, 2H), 7.32(t, 1H), 7.19(s, 1H), 7.91(d, 1H), 4.10(d, 1H), 3.96(s, 1H), 3.89(d, 1H), 3.65-3.81(m, 8H), 3.41(d, 1H), 3.06(d, 1H), 1.37-1.98(m, 8H), 1.03-1.26(m, 3H)
185	1H NMR (400 MHz, $CDCl_3$): δ 1.03(m, 3H), 1.15(d, 3H), 1.30(m, 1H), 1.43(m, 2H), 1.58(m, 2H), 1.63(m, 1H), 1.7-1.8(m, 2H), 1.9(d, 1H), 1.95-2.10(m, 3H), 2.96(d, 1H), 3.33(d, 2H), 3.60(s, 1H), 3.75(s, 1H), 3.81(d, 1H), 4.05(s, 1H), 4.20(d, 1H), 6.37(d, 1H), 7.02-7.05(m, 3H), 7.50-7.54(m, 2H), 7.66(m, 1H), 8.38(s, 1H)
193	^{1}H-NMR (400MHz, CD_3OD): δ 7.80(d, 1H), 6.95(s, 1H), 6.75(d, 1H), 4.14(d, 1H), 3.93(d, 1H), 3.64(d, 1H), 3.16(m, 1H), 2.30(m, 2H), 1.90(m, 1H), 1.83(m, 3H), 1.69 (m, 2H), 1.58(t, 3H), 1.47 (m, 2H), 1.31(s, 9H), 1.18 (m, 4H)
196	1H NMR (400 MHz, $CDCl_3$): δ 0.95-1.15(m, 4H), 1.20(m, 1H), 1.30-1.40(m, 1H), 1.47(m, 1H), 1.57(m, 2H), 1.66(s, 1H), 1.70-1.85(m, 3H), 1.85-1.95(m, 2H), 3.03(m, 1H), 3.18(d, 2H), 3.43(d, 1H), 3.69(s, 1H), 3.75-3.90(m, 3H), 4.10(d, 1H), 4.45(s, 2H), 6.51(d, 1H), 7.00-7.10(m, 3H), 7.49(m, 2H), 7.70(m, 1H), 8.46(s, 1H)
200	1H NMR (400 MHz, $CDCl_3$): δ 0.90-1.15(m, 5H), 1.40-1.60(m, 3H), 1.60-1.85(m, 3H), 1.95(m, 2H), 3.20(d, 1H), 3.55(d, 2H), 3.68(m, 2H), 3.70-3.85(m, 6H), 3.85-3.95(m, 2H), 6.48(d, 1H), 7.02(s, 1H), 7.27(d, 2H), 7.42(d, 2H), 7.67(d,1H), 8.43(d, 1H)
236	^{1}H-NMR (400MHz, CD_3OD): δ 6.87(s, 1H), 4.19(s, 2H), 4.05(m, 2H), 3.82(s, 1H), 1.43-1.90(m, 6H), 1.06-1.39(m, 14H)

Compound number	NMR data
279	1H NMR (400 MHz, $CDCl_3$): δ 0.93-1.15(m, 4H), 1.29-1.39(m, 1H), 1.45(m, 1H), 1.50-1.60(m, 2H), 1.65(m, 1H), 1.70-1.80(d, 1H), 1.80-1.90(d, 1H), 1.90-2.10(m, 4H), 3.05(d, 1H), 3.20(m, 1H), 3.27(s, 3H), 3.30(m, 1H), 3.36-3.53(m, 3H), 3.61-3.74(m, 2H), 4.06(d, 1H), 6.42(s, 1H), 6.99-7.07(m, 3H), 7.48(m, 2H), 7.64(d, 1H), 8.42(s, 1H)
295	1H NMR (400 MHz, $CDCl_3$): δ 0.96-1.14(m, 4H), 1.32-1.44(m, 1H), 1.48(m, 1H), 1.57(m, 2H), 1.67(m, 1H), 1.76(d, 1H), 1.83(d, 1H), 2.30(s, 3H), 2.98(d, 1H), 3.40(d, 1H), 3.67(m, 1H), 3.79(d, 1H), 3.91(s, 3H), 4.10(d, 1H), 7.06(s, 1H), 7.15(d, 2H), 7.42(d, 2H), 7.71(s, 1H), 7.75(s, 1H)
302	1H NMR (400 MHz, $CDCl_3$): δ 0.97-1.15(m, 4H), 1.27(m, 1H), 1.47-1.64(m, 3H), 1.68(m, 1H), 1.76(d, 1H), 1.84(d, 1H), 2.28(s, 3H), 2.73(s, 3H), 3.31(d, 1H), 3.52(d, 1H), 3.71(m, 1H), 3.85(d, 1H), 4.14(d, 1H), 7.06(s, 1H), 7.12(d, 1H), 7.40(d, 2H), 7.45(d, 1H), 8.13(d, 1H), 8.98(s, 1H)
311	^{1}H-NMR (400MHz, CD_3OD): δ 6.91(s, 1H), 4.23(d, 1H), 3.94(d, 1H), 3.62(m, 1H), 3.55(m, 2H), 1.96- 1.52(m, 10H), 1.45(s, 3H), 1.32(s, 9H), 1.21 (m, 4H), 1.05(m, 1H)
314	1H NMR (400 MHz, $CDCl_3$): δ 0.94-1.13(m, 4H), 1.26(m, 1H), 1.38(m, 1H), 1.43(s, 3H), 1.45(s, 3H), 1.47-1.59(m, 2H), 1.62(m, 1H), 1.74(d, 1H), 1.87(d, 1H), 2.29(s, 3H), 3.45(m, 1H), 3.84(d, 1H), 4.09(d, 1H), 7.02(s, 1H), 7.12(d, 2H), 7.42(d, 2H)
316	^{1}H-NMR (400MHz, CD_3OD): δ 6.93(s, 1H), 4.23(m, 1H), 3.80(m, 1H), 2.49(m, 1H), 2.06-1.42(m, 10H), 1.32(s, 9H), 1.22(d, 3H), 1.12 (m, 5H).
318	^{1}H-NMR (400MHz, CD_3OD): δ 6.97(s, 1H), 4.11(d, 1H), 3.92(d, 1H), 3.62(m, 1H), 2.17(m, 1H), 1.93(m,1H), 1.62-1.85(m, 4H), 1.45-1.62(m, 4H), 1.37-1.44(m, 3H), 1.27-1.37(m, 10H), 1.11-1.27(m, 10H)
319	^{1}H-NMR (400MHz, CD_3OD): δ 6.97(s, 1H), 4.18(d, 1H), 3.94(d, 1H), 3.53(m, 1H), 2.17(t, 1H), 1.95(m,2H), 1.70-1.86(m, 4H), 1.58-1.69(m, 2H), 1.46-1.58(m, 2H), 1.39-1.46(m, 3H), 1.29-1.39(m, 10H), 1.10-1.29(m, 10H)

Compound number	NMR data
322	^{1}H-NMR (400MHz, CD_3OD): δ 6.95(s, 1H), 4.09(m, 1H), 3.74(m, 1H), 2.09(m, 1H), 1.94-1.67(m, 8H), 1.38(m, 1H), 1.33(s, 9H), 1.17(m, 5H)
323	^{1}H-NMR (400MHz, CD_3OD): δ 6.87(s, 1H), 4.24(tert, 1H), 3.93(d, 1H), 3.62-3.82(m, 3H), 2.08-2.21(m, 1H), 1.88-2.04(m, 2H), 1.56-1.87(m, 4H), 1.43-1.56(m, 4H), 0.98-1.35(m, 14H)
324	1H NMR (400 MHz, $CDCl_3$): δ 0.88-1.13(m, 4H), 1.32(m, 2H), 1.43(s, 3H), 1.48-1.67(m, 3H), 1.69-1.87(m, 4H), 1.96(m, 1H), 2.06(m, 1H), 2.31(s, 3H), 3.67(m, 1H), 7.08(s, 1H), 7.15(d, 2H), 7.44(d, 2H)
325	1H NMR (400 MHz, $CDCl_3$): δ 0.96-1.19(m, 5H), 1.23(s, 9H), 1.37(m, 1H), 1.45(m, 1H), 1.61(m, 2H), 1.64-1.81(m, 4H), 1.83(m, 1H), 2.22(m, 1H), 3.37(m,1H), 3.57-3.78(m, 4H), 3.89(d, 1H), 3.98(d, 1H), 6.79(s, 1H)
326	^{1}H-NMR (400MHz, CD_3OD): δ 6.78(s, 1H), 4.07(m, 1H), 3.53(m, 2H), 2.26(m, 1H), 1.96-1.38(m, 14H), 1.30(s, 9H), 1.14 (m, 5H).
328	^{1}H-NMR (400MHz, CD_3OD): δ 6.87(s, 1H), 4.14(tert, 1H), 3.92(tert, 1H), 3.77(d, 1H), 3.70(t, 2H), 2.32(m, 1H), 1.82-1.99(m, 2H), 1.71-1.82(m, 2H), 1.66(m, 1H), 1.41-1.59(m, 5H), 1.03-1.34(m, 14H)
334	^{1}H-NMR (400MHz, CD_3OD): δ 6.95(s, 1H), 4.08(m, 1H), 3.74(m, 1H), 2.18(m, 1H), 1.94-1.67(m, 8H), 1.42(m, 1H), 1.33(s, 9H), 1.17(m, 5H)
336	^{1}H NMR (400 MHz, CD_3OD): δ 1.09-1.31 (m, 8 H), 1.32 (s, 9 H), 1.45-1.85 (m, 5 H), 1.89-2.10 (m, 3 H), 3.56-3.61 (m, 1 H), 3.93-4.00 (m, 1 H), 4.00-4.10 (m, 1 H), 4.12-4.22 (m, 2 H), 6.99 (s, 1 H)
337	^{1}H NMR (400 MHz, CD_3OD): δ 1.07-1.31 (m, 8 H), 1.32 (s, 9 H), 1.45-1.60 (m, 2 H), 1.63-1.85 (m, 4 H), 1.87-1.98 (m, 1 H), 2.02-2.11 (m, 1 H), 3.60-3.66 (m, 1 H), 3.93-4.03 (m, 2 H), 4.15 (d, 1 H), 4.26-4.35 (m, 1 H), 6.94 (s, 1 H)

Compound number	NMR data
340	^{1}H-NMR (400 MH$_Z$, CD$_3$OD): δ 6.81 (s, 1H), 3.96 (br, 1H), 3.48 (m, 1H), 2.06(m, 3H), 1.84(m, 3H), 1.70(br, 2H), 1.46 (m, 1H), 1.37(m, 1H), 1.31(s, 9H), 1.16(m, 5H)
341	^{1}H-NMR (400 MH$_Z$, CD$_3$OD): δ 6.81 (s, 1H), 4.00 (br, 1H), 3.53 (t, 2H), 2.27(br, 1H), 1.97(m, 3H), 1.82-1.64(m, 7H), 1.58 (m, 2H), 1.37(m, 2H), 1.31(s, 9H), 1.14(m, 5H)
343	^{1}H-NMR (400 MH$_Z$, CD$_3$OD): δ 6.85(s, 1H), 3.92 (br, 1H), 3.67 (m, 2H), 2.41(br, 1H), 2.15(m, 1H), 1.97(m, 2H), 1.78 (m, 7H), 1.37(m, 2H), 1.31(s, 9H), 1.14(m, 5H).

Biological Examples

Biological Example 1. Anti-Hepatitis C Activity

Compounds can exhibit anti-hepatitis C activity by inhibiting HCV polymerase, by inhibiting other enzymes needed in the replication cycle, or by other pathways. A number of assays have been published to assess these activities. A general method that assesses the gross increase of HCV virus in culture was disclosed in U.S. Patent No. 5,738,985 to Miles *et al.* *In vitro* assays have been reported in Ferrari *et al. Jnl. of Vir.,* 73:1649-1654, 1999; Ishii *et al., Hepatology,* 29:1227-1235, 1999; Lohmann *et al., Jnl of Bio. Chem.,* 274:10807-10815, 1999; and Yamashita *et al., Jnl. of Bio. Chem.,* 273:15479-15486, 1998.

WO 97/12033, filed on September 27, 1996, by Emory University, listing C. Hagedorn and A. Reinoldus as inventors, which claims priority to United States Provisional Patent Application Serial No. 60/004,383, filed on September 1995, described an HCV polymerase assay that can be used to evaluate the activity of the of the compounds described herein. Another HCV polymerase assay has been reported by Bartholomeusz, *et al.,* Hepatitis C Virus (HCV) RNA polymerase assay using cloned HCV non-structural proteins; Antiviral Therapy 1996:1(Supp 4) 18-24.

Screens that measure reductions in kinase activity from HCV drugs were disclosed in U.S. Patent No. 6,030,785, to Katze *et al.,* U.S. Patent No. 6,228,576, Delvecchio, and U.S. Patent No. 5,759,795 to Jubin *et al.* Screens that measure the protease inhibiting activity of proposed HCV drugs were disclosed in U.S. Patent No. 5,861,267 to Su *et al.,* U.S. Patent No. 5,739,002 to De Francesco *et al.,* and U.S. Patent No. 5,597,691 to Houghton *et al.*

Biological Example 2. Replicon Assay

A cell line, ET (Huh-lucubineo-ET) was used for screening of compounds for inhibiting HCV RNA dependent RNA polymerase. The ET cell line was stably transfected with RNA transcripts harboring a I_{389}luc-ubi-neo/NS3-3'/ET; replicon with firefly luciferase-ubiquitin-neomycin phosphotransferase fusion protein and EMCV-IRES driven NS3-5B polyprotein containing the cell culture adaptive mutations (E1202G; T1280I; K1846T) (Krieger at al, 2001 and unpublished). The ET cells were grown in DMEM (Dulbeco's Modified Eagle's Medium), supplemented with 10% fetal calf serum, 2 mM Glutamine, Penicillin (100 IU/mL)/Streptomycin (100 µg/mL), 1x nonessential amino acids, and 250 µg/mL G418 ("Geneticin"). Reagents were all available through Life Technologies (Bethesda, MD). The cells were plated at 0.5-1.0 $x10^4$ cells/well in the 96 well plates and incubated for 24 hrs before

adding test compound. The compounds were added to the cells to achieve a final concentration of 0.1 nM to 50 μM and a final DMSO (dimethylsulfoxide) concentration of 0.5%. Luciferase activity was measured 48 hours later by adding a lysis buffer and the substrate (Catalog number Glo-lysis buffer E2661 and Bright-Glo luciferase system E2620 Promega, Madison, WI). Cells should not be too confluent during the assay. Percent inhibition of replication data was plotted relative to no compound control. To determine the EC_{50} (effective concentration at which 50% of the maximum inhibition was observed), a 10 point, 3-fold serial dilution for each compound was used, which spans a concentration range of 1000 fold. EC_{50} values were calculated by fitting %inhibition at each concentration to the following equation:

$$\% \text{ inhibition} = 100\%/[(EC_{50}/[I])^b + 1]$$

where b was Hill's coefficient.

In some aspects, certain compounds of Formula (I), exhibited EC_{50} of equal to or less than 50 μM when tested according to the assay of Example 2. In other aspects the EC_{50} was equal to or less than 10 μM. In still other aspects the EC_{50} was equal to or less than 1 μM.

Biological Example 3. Cloning and expression of recombinant HCV-NS5b

The coding sequence of NS5b protein was cloned by PCR from $pFKI_{389}luc/NS3\text{-}3'/ET$ as described by Lohmann, V., *et al.* (1999) *Science* 285, 110-113 using the primers shown on page 266 of WO 2005/012288.

The cloned fragment was missing the C terminus 21 amino acid substituents. The cloned fragment was inserted into an IPTG-inducible (isopropyl-β-D-thiogalactopyranoside) expression plasmid that provides an epitope tag (His)6 at the carboxy terminus of the protein.

The recombinant enzyme was expressed in XL-1 cells and after induction of expression, the protein was purified using affinity chromatography on a nickel-NTA (nitrilotriacetic acid) column. Storage conditions were 10 mM Tris-HCl pH 7.5, 50 mM NaCl, 0.1 mM EDTA (ethylenediaminetetraacetic acid), 1 mM DTT (dithiothreotol), and 20% glycerol at -20 °C.

Biological Example 4. HCV-NS5b Enzyme Assay using heteropolymer substrate

The polymerase activity was assayed by measuring incorporation of radiolabeled UTP into a RNA product using a biotinylated, heteropolymeric template, which included a portion of the HCV genome. Typically, the assay mixture (50 μL) contained 10 mM Tris-HCl (pH 7.5), 5 mM $MgCl_2$, 0.2 mM EDTA, 10 mM KCl, 1 unit/μL RNAsin, 1 mM DTT, 10 μM each of NTP (nucleoside triphosphate), including [^{3}H]-UTP (uridine triphosphate), and 10 ng/μL

heteropolymeric template. Test compounds were initially dissolved in 100% DMSO and further diluted in aqueous buffer containing 5% DMSO. Typically, compounds were tested at concentrations between 1 nM and 100 μM. Reactions were started with addition of enzyme and allowed to continue at 37°C for 2 hours. Reactions were quenched with 8 μL of 100 mM EDTA and reaction mixtures (30 μL) were transferred to streptavidin-coated scintillation proximity microtiter plates (FlashPlates) and incubated at room temperature overnight. Incorporation of radioactivity was determined by scintillation counting.

Biological Example 5. HCV-NS5b Enzyme Assay using homopolymer substrate

The polymerase activity was assayed by measuring incorporation of radiolabeled UTP into a RNA product using a biotinylated, homopolymeric template. The template was formed by annealing adenosine homopolymer to uridine 20-mer capped with a 5'-biotin group (biotin-U^{20}) in the ratio of 1:4. Typically, the assay mixture (50 μL) contained 25 mM Tris-HCl (pH 7.5), 40 mM KCl, 0.3 mM $MgCl_2$, 0.05 mM EDTA, 0.2 unit/μL Superase RNAse Inhibitor, 5 mM DTT, 30 μM UTP (Uridine triphosphate), including [^{3}H]-UTP (uridine triphosphate) at 0.4 μCi/μL with final concentration of 1 μM, and 50 nM of homopolymeric template. Test compounds were initially dissolved in 100% DMSO and further diluted in aqueous buffer containing 5% DMSO. Typically, compounds were tested at concentrations between 2 nM and 50 μM. Reactions were started with addition of enzyme and allowed to continue at 30°C for 90 minutes. Reactions were quenched with 8 μL of 100 mM EDTA and reaction mixtures (30 μL) were transferred to streptavidin-coated scintillation proximity microtiter plates (FlashPlates) and incubated at room temperature overnight. Incorporation of radioactivity was determined by scintillation counting.

Inhibitor IC_{50} values were determined by adding test compound as ten point, two-fold serial dilutions in 100% DMSO with a final reaction concentration of 5%. IC_{50} values were calculated by plotting the % inhibition against compound concentration and fitting the data to a constrained four parameter sigmoidal curve, equivalent to the "four parameter logistic equation", where Bottom was the minimum Y value, Top was the maximum Y value, and Hillslope was the slope of the linear portion of the semi-log curve. Top and Bottom were constrained to values of 0% and 100%, respectively. These analyses were performed using Graphpad Prism v.4.0 (Graphpad Software, Inc.) in conjunction with DS Accord for EXCEL 6.0 (Accelrys, Microsoft Corp.).

Biological Example 6.

The polymerase activity was also assayed by measuring incorporation of radiolabeled GTP into an RNA product using a biotinylated oligoG13 primer with a polycytidylic acid RNA

template. Typically, the assay mixture (40 µL) contains 50 mM HEPES (pH 7.3), 2.5 mM magnesium acetate, 2 mM sodium chloride, 37.5 mM potassium acetate, 5 mM DTT, 0.4 U/mL RNasin, 2.5% glycerol, 3 nM NS5B, 20 nM polyC RNA template, 20 nM biotin-oligoG13 primer, and 0.2 µM tritiated guanosine triphosphate. Test compounds were initially dissolved and diluted in 100% DMSO and further diluted into aqueous buffer, producing a final concentration of 5% DMSO. Typically, compounds were tested at concentrations between 0.2 nM and 10 µM. Reactions were started with addition of tritiated guanosine triphosphate and allowed to continue at 30°C for 2 hours. Reactions were quenched with 100 µL stop buffer containing 10 mM EDTA and 1 µg/mL streptavidin-coated scintillation proximity beads. Reaction plates were incubated at 4°C for 10 hours and then incorporation of radioactivity was determined by scintillation counting.

Compounds in Table 1 *supra* have been tested in the polymerase assay of Biological Example 1 and the IC_{50} values for each compound were provided in Table 3 *infra*. Most of the compounds of Table 1 exhibit an IC_{50} of 1 µM or less or an IC_{50} of 500 nM or less in the replicon assay of Biological Example 2 provided herein. For example, the compounds of Example numbers 2, 3, 5, 7, 8, 10, 11, 19, 35, 69, 74, 75, 76, 77, 78, 79, 80, 81, 82, 84, 85, 86, 87, 88, 89, 90, 91, 91, 92, 93, 94, 95, 96, 99, 118, 119, 120, 121, 122, 123, 125, 126, 127, 130, 135, 137, 138, 140, 141, 143, 145, 146, 147, 148, 149, 150, 151, 152, 154, 155, 156, 157, 158, 160, 161, 162, 163, 164, 165, 167, 168, 169, 170, 171, 172, 173, 176, 177, 179, 180, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 208, 212, 213, 216, 217, 218, 219, 222, 224, 225, 226, 227, 228, 229, 231, 232, 233, 234, 235, 236, 238, 239, 240, 241, 243, 244, 246, 247, 248, 250, 251, 253, 256, 257, 258, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 295, 296, 297, 298, 299, 301, 302, 303, 304, 305, 307, 308, 310, 311, 312, 313, 314, 315, 316, 318, 319, 320, 321, 322, 323, 325, 327, 328, 329, 330, 332, 334, 336, 337, 339, 340, 341, 342, 343 exhibit an IC_{50} of 100 nM or less in the replicon assay of Biological Example 2. The compounds of Example numbers 1, 4, 6, 12, 13, 17, 18, 24, 26, 27, 29, 31, 36, 37, 38, 39, 40, 42, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 70, 71, 72, 73, 83, 97, 98, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 113, 114, 115, 116, 124, 128, 129, 131, 136, 139, 142, 144, 153, 159, 178, 181, 204, 205, 206, 207, 209, 211, 214, 215, 220, 221, 223, 230, 237, 242, 245, 249, 252, 254, 255, 259, 260, 262, 267, 282, 293, 294, 300, 206, 309, 317, 324, 326, 331, 333, 335, 338 exhibit an IC_{50} between 100 nM and 5.0 uM in the replicon assay of Biological Example 2. The compounds of Example numbers 9, 15, 16, 20, 21, 22, 23, 25, 28, 30, 32, 33, 34, 41, 47, 57, 110, 111, 112, 117, 132, 166, 174, 175, 210 , 271 exhibit an IC_{50} of 5.0 µM or more in the replicon assay of Biological Example 2.

Table 3

	NS5B-enzyme3 (uM)	MS [M+H$^+$]	Retention time (min)	HPLC method
1	0.1815	370.4	12.36	A
2	0.035	448.3	13.02	A
3	0.004	448.3	13.03	A
4	0.073	384.4	12.76	A
5	0.052	427.5	13.06	A
6	-	370.1	12.4	A
7	0.006	462.2	13.72	A
8	0.001	434.3	8.45	A
9	0.08	398.2	11.64	A
10	0.003	464.3	7.96	A
11	0.008	461.9	12.25	A
12	0.045	400.5	10.48/11.76	A
13	0.079	386.1	12.14	A
14	3.651	485.6	14.11	A
15	0.0735	385.3	6.12	A
16	0.4205	489.3	12.73	A
17	0.024	475.2	12.48	A
18	0.002	539.6	14.19	A
19	0.015	388.6	14.3	A
20	0.128	517.6	12.55/13.80	A
21	0.97	533.6	13.11	A
22	0.02	533.6	13.45	A
23	0.245	399.5	5.89	A
24	0.0445	503.6	13.46	A
25	0.173	503.4	12.66	A
26	0.067	463.3	12.13	A
27	0.022	539.3	13.7	A
28	0.226	399.5	7.01	A
29	0.001	599.3	12.76	A
30	0.003	569.3	13.09	A
31	0.047	519.6	14.34	A
32	0.241	544.6	13.79	A
33	0.038	587.3	12.8	A
34	1.05	388.6	14.34	A
35	0.0095	388.4	14.35	A
36	0.058	546.6	14.69	A
37	0.072	492.6	12.8	A
38	0.065	505.6	13.75	A
39	0.051	553.4	14.19	A

40	0.013	543.3	13.87	A
41	0.218	521.3	11.71	A
42	0.148	517.6	13.73	A
43		553.6	15.49	A
44		553.6	12.91	A
45	4.9	505.6	13.55	A
46	0.063	531.6	14.33	A
47	0.088	492.3	6.52	A
48	0.187	402.3	13.73	A
49	0.015	539.17	4.16	C
50	0.007	582.17	3.69	C
51	0.011	617.18	4.57	C
52	0.015	525.15	4.1	C
53	0.024	609.13	7.56	B
54	0.018	593.14	6.97	B
55	0.071	609.14	4.22	C
56	0.0071	553.18	4.4	C
57	0.26	578.18	8.23	B
58	0.088	539.17	6	B
59	0.039	609.13	6.75	B
60	0.009	601.18	4.73	C
61	0.003	578.18	8.98	B
62	0.011	529.16	7.84	B
63	0.042	617.19	9.78	B
64	0.031	578.17	9.18	B
65	0.045	601.18	7.23	B
66	0.049	611.13	4.39	C
67	0.1835	402.3	13.48	A
68		593.14	6.77	B
69	0.002	597.4	16.51	A
70	0.067	402.5	15.7	A
71	0.052	398.5	16.1	A
72	0.064	412.6	16.77	A
73	0.021	418.5	16.91	A
74	0.012	581.19	8.44	B
75	0.008	623.24	2.28	D
76	0.004	595.6	17.16	A
77	0.003	625.6	17.66	A
78	0.005	599.2	7.91	B
79	0.004	627.18	17.35	A
80	0.006	657.24	9.57	B
81	0.009	612.23	4.74	B
82	0.006	609.22	7.11	B
83	0.003	629.21	7.16	B

84	0.004	609.22	16.76	A
85	0.002	583.5	16.78	A
86	0.006	585.18	7.1	B
87	0.005	639.23	17.73	A
88	0.002133	610.3	7.08	A
89	0.003	652.23	7.62	B
90	0.004	625.22	7.95	B
91	0.012	637.25	17.92	A
92	0.004	623.5	8.17	B
93	0.004	625.22	7.65	B
94	0.002	639.5	17.13	A
95	0.005	645.4	17.27	A
96		623.4	17.53	A
97	0.027	550.3	11.24	A
98	0.003	582.3	9.34	A
99	0.002	597.3	10.73	A
100	0.004	567.3	13.4	A
101	0.011	591.3	11.52	A
102	0.0045	585.3	10.83	A
103	0.002	555.3	11.42	A
104	0.021	543.3	11.85	A
105	0.002	581.3	14.04	A
106	0.014	591.3	11.98	A
107	< 0.001	555.3	11.66	A
108	0.037	526.3	9.94	A
109	0.03	543.3	11.57	A
110	0.183	573.2]	12.89	A
111	0.243	593.2	13.18	A
112	0.173	666.4	12.61	A
113	0.044	440.6	16.03	A
114	0.09	414.5	12.96	A
115	0.004	506.3	11.8	A
116	0.064	428.6	13.88	A
117	0.739	452.5	13.93	A
118	0.002	609.4	12.09	A
119	0.009	609.4	12.12	A
120	0.006	613.3	10.87	A
121	0.007	613.3	10.87	A
122	0.002	625.4	9.33	A
123	0.002	611.3	8.46	A
124	0.004	611.3	8.46	A
125	0.018	621.4	12.74	A
126	0.011	637.3	13.87	A
127	0.003	608.3	12.96	A

128	0.009	625.3	9.86, 10.06	A
129	0.096	409.2	12.3	A
130	0.001	609.3	14.24	A
131	0.261	609.3	14.27	A
132	0.108	610.3	7.09	A
133		418.2	14.01	A
134		398.5	13.56	A
135	0.002333	595.3	13.58	A
136	0.26	595.3	13.61	A
137	0.0015	624.3	7.15	A
138	0.001	638.3	7.21	A
139	0.001	640.3	7.05	A
140	0.001	624.3	7.2	A
141	0.002	610.3	7.02	A
142	0.002	624.3	7.21	A
143	0.0019	638.3	7.14	A
144	0.002	610.3	6.98	A
145	0.001	624.3	7.19	A
146	0.002	710.4	2.23	D
147	0.001	652.4	2.34	D
148	0.002	638.3	2.17/	D
149	0.003	738.4	2.40/	D
150	0.004	638.3	2.21/	D
151	0.003	724.4	2.40/	D
152	0.003	666.4	2.31/	D
153	0.004	738.4	2.43/	D
154	0.003	623.3	2.28/	D
155	0.003	652.4	2.15	D
156	0.001	638.3	2.15	D
157	0.001	650.4	2.13	D
158	0.002	623.3	2.35	D
159	0.003	724.4	2.22	D
160	0.001	652.4	2.16	D
161	0.001	740.4	2.18	D
162	0.002	724.4	2.38	D
163	0.001	638.3	2.12	D
164	0.001	623.3	2.27	D
165	0.002	710.4	2.2	D
166	0.982	543.5	15.74	A
167	0.0035	639.3	14.32	A
168	3.8165	615.5	14.95	A
169	0.003	629.2	15.57	A
170	0.004	643.2	16.03	A
171	0.002	639.3	14.02	A

172	0.0012	609.6	13.8	A
173	0.001	623.6	15	A
174	5.113	493.2	15.41	A
175	> 10	389.2	6.89	A
176	1.41285	571.5	16.35	A
177	0.002	597.2	14.33	A
178	0.001	602.2	14.89	A
179	0.001	609.2	14.81	A
180	< 0.0002	623.2	14.74	A
181	0.003	376.4	14.22	
182	0.002	545.3	6.78	A
183	0.0018	623.5	15.31	A
184	0.0017	611.2	13.24	A
185	0.001	627.2	14.41	A
186	0.001	643.2	13.57	A
187	0.001	625.2	13.96	A
188	0.001	638.8	14.04	A
189	0.001	628.8	13.5	A
190	0.001	559.4	15.28	A
191	0.001	560.4	15.33	A
192	0.003	530.1	14.74	A
193	0.001	533.4	14.21	A
194	0.002	625.2	13.26	A
195	0.003	643.2	14.24	A
196	0.001	655.3	13.87	A
197	0.0046	639.2	14.58	A
198	0.001	651.3	14.21	A
199	0.002	645.2	14.63	A
200	0.001	659.3	14.75	A
201		643.3	15.55	A
202	0.001	728.3	2.21	D
203	0.001	645.2	2.43	D
204	0.002	633.2	2.32	D
205	0.004	638.1	2.38	D
206	0.001	604.1	2.13	D
207		603.1	2.21	D
208	0.0014	701.2	2.29	D
209	0.001	592.1	2.14	D
210	0.003	652.1	1.79	D
211	0.002	606.1	2.36	D
212	0.002	674.2	2.38	D
213	0.001	627.1	2.25	D
214	0.001	603.1	2.16	D
215	0.002	592.2	2.34	D

216	0.001	637.3	13.63	A
217	0.001	623.2	12.73	A
218	0.001	667.3	15.39	A
219		623.2	14.75	A
220	0.015	374.2	14.17	
221	0.019	495.1	14.79	A
222	0.002	606.2	2.14	D
223	0.009	613.2	16.14	A
224		701.3	7.4	A
225	0.001	625.2	13.72	A
226	0.009	659.1	15.15	A
227	0.001	671.2	14.94	A
228		641.3	12.97	A
229	0.001	657.2	14.1	A
230	0.006	598.1	15.77	A
231	0.001	628.2	15.91	A
232	0.001	613.2	13.77	A
233	0.002	642.2	16.26	A
234	0.001	642.1	16.2	A
235		627.2	14.99	A
236	0.003	390.1	13.86	A
237	0.042	403.2	1.16	E
238	0.002	554.2	7.65	B
239	0.002	547.2	7.8	B
240		534.2	7.62	B
241	0.001	519.2	6.88	B
242	0.005	563.1	8.07	B
243	0.002	547.2	7.75	B
244	0.002	564.2	7.75	B
245	0.005	493.2	7.3	B
246	0.004	577.2	7.75	B
247	0.002	519.2	6.57	B
248	0.002	547.2	6.82	B
249	0.019	613.2	8.03	B
250	0.0055	597.2	8.06	B
251	0.004	565.2	7.73	B
252	0.002	586.2	7.22	B
253	0.002	586.2	7.13	B
254	0.015	533.2	7.49	B
255	0.005	547.2	6.57	B
256	0.001	557.2	8.07	B
257	0.002	559.2	7.74	B
258	0.007	559.2	7.54	B
259	0.007	554.2	15.23	A

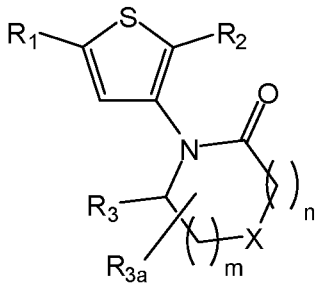
260	0.008	547.1	14.54	A
261	0.199	540.1	2.44	D
262	0.025	558.1	2.14	D
263	0.108	489.2	2.39	D
264	0.538	503.2	2.43	D
265	0.601	481.2	2.49	D
266	0.142	578.2	2.39	D
267	0.064	510.1	2.2	D
268	0.62	489.2	2.36	D
269	0.33	489.2	2.37	D
270	0.019	518.2	2.34	D
271	2.47	482.2	2.12	D
272	0.001	609.2	14.15	A
273	0.001	641.4	12.87	A
274	0.001	657.2	14	A
275	0.002	547.4	14.31	A
276	0.002	607.5	15.04	A
277	0.002	589.2	14.81	A
278	0.001	657.3	14.46	A
279	0.0011	657.2	13.52	A
280	0.001	631.2	13.51	A
281	0.003	565.1	15.58	A
282	0.031	597.1	16.45	A
283	0.004	577.2	15.44	A
284	0.003	563.4	13.81	A
285	0.002	641.3	15.2	A
286	0.001	649.2	14.09	A
287	0.001	631.2	13.53	A
288	0.002	643.3	12.21	A
289	0.001	637.5	13.42	A
290	0.002	418.2	14.92	A
291	0.008	404.5	14.02	
292	0.0023	656.8	15.79	A
293	0.005	420.1	13.56	A
294	0.007	517.3	13.08	A
295	0.004	543.2	13.03	A
296	0.005	557.3	13.45	A
297	0.001	543.2	12.33	A
298	0.001	557.2	12.33	A
299	0.005	448.5	13.07	
300	0.031	564.1	14.79	A
301	0.004	585.2	14.32	A
302	0.003	554.2	13.74	A
303	0.004	596.2	15.55	A

304	0.005	568.2	14.3	A
305	0.004	568.2	14.05	A
306	0.0053	510.1	13.32	
307	0.006	477.2	7.32, 7.64	A
308	0.014	390.5	13.82	
309	0.054	467.1	17.57	A
310	0.004	489.2	7.35, 7.85	A
311	0.002	461.8	12.88	A
312	0.002	443.2	14.94	A
313	0.0315	404.2	13.55	A
314	0.006	427.8	13.88	A
315	0.006	448.1	14.44	A
316	0.003	432.3	14.19	A
317	0.0241	414.2	12.27	A
318	0.014	490.3	14.7	A
319	0.004	490.2	14.04	A
320	0.006	476.2	14.29	A
321	0.002	476.2	13.52	A
322	0.006	404.2	13.07	A
323	0.003	448.3	12.86	A
324	0.085	427.9	12.45	A
325	0.006	459.8	14.87	A
326	0.8815	446.3	13.68	A
327	0.004	478.6	12.57, 12.72	A
328	0.006	448.3	13.51	A
329	0.005	420.5	12.66	A
330	0.003	478.3	11.66, 11.93	A
331	0.008	464.3	7.92	A
332	0.012	434.2	8.32	A
333	0.01	478.3	11.7	A
334	0.003	403.8	13.5	A
335	0.024	402.1		A
336	0.003	448.3	10.28	A
337	0.002	448.2	10.89	A
338	0.031	462.3 [M-H^+]	9.95	A
339	0.008	446	13.67	A
340	0.008	403.0	7.21	A
341	0.005	446	13.17	A
342	0.018	432	13.51	A
343	0.001	432	13.29	A

CLAIMS

What is claimed is:

1. A compound of formula (I):



(I)

or a salt thereof, wherein

m is 0, 1 or 2;

n is 0 or 1, wherein m + n is 1, 2 or 3;

R_1 is C_3-C_{10}alkynyl or phenyl, which phenyl is substituted with 0, 1, 2, or 3 substituents which are independently selected from the group consisting of halogen, hydroxy, cyano, C_1-C_4alkyl, haloC_1-C_4alkyl and C_1-C_4alkoxy, and which alkynyl is optionally substituted with a C_3-C_7cycloalkyl substituent, which cycloalkyl is optionlly substituted with 1 or 2 independently selected C_1-C_4alkyl groups;

R_2 is CO_2H, tetrazole or a carboxylic acid isostere;

R_3 is C_3-C_7cycloalkyl which is substituted with 0, 1, 2 or 3 halogen atoms;

R_{3a} represents 0, 1, 2, 3 or 4 residues independently selected at each occurrence from the group consisting of hydroxy, amino, cyano, halogen, C_1-C_6alkyl, C_1-C_6alkoxy, wherein each alkyl or alkoxy substituent is substituted with 0,1 or 2 substituents independently selected from hydroxy, cyano, C_1-C_4alkoxy, C_1-C_4alkylsulfone, $N(R_{3b})_2$, C(O) $N(R_{3b})$, heterocycle having 4 to 7 ring atoms and 1 or 2 ring heteroatoms selected from N, O or S and 5 or 6 member heteroaryl; or two geminal R_{3a} substituents, taken in combination form a spirocyclic 3 to 6 member cycloalkyl or heterocycle;

R_{3b} is independently selected at each occurrence from hydrogen, C_1-C_4alkyl, C_1-C_4alkoxyC_1-C_4alkyl and C_1-C_4alkanoyl ; or $N(R_{3b})_2$, taken in combination, form a 4 to 6 member heterocycle having 0 or 1 additional ring heteroatoms selected from N, O or S;

X is O, N-L-R_4 or CR_5R_6;

L is a bond, $S(O)_2$ or C(O);

R_4 is C_1-C_6alkyl or C_3-C_7cycloalkyl each of which is substituted with 0, 1, or 2 hydroxy and 0 or 1 substituents selected from cyano, $S(O)_2$-C_1-C_4alkyl, CO_2H or $NR_{4a}R_{4b}$ or phenyl;

R_4 is naphthyl or phenyl, which phenyl is substituted with 0, 1, 2, or 3 substituents independently selected form the group consisting of halogen, cyano, C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxy, haloC_1-C_6alkoxy, amino, hydroxy, mono- and di-C_1-C_6alkylamino, hydroxyC_1-C_4alkyl, aminoC_1-C_4alkyl, C_1-C_6alkyl-OC(O)NH-, C_1-C_4alkyl-C(O)NH-, -C(O)$NR_{4a}R_{4b}$, phenyl, phenoxy, heteroaryl having one or two ring nitrogen atoms and having 0, 1, or 2 C_1-C_4alkyl substituents, or two substituents combine to form a fused heterocyclic ring, which heterocycle has 5, 6 or 7 ring atoms, 1 or 2 ring heteroatoms selected from N, O or S and which heterocycle is substituted with 0, 1 or 2 substituents independently selected from C_1-C_6alkyl; or

R_4 is a 5 or 6 member heteroaryl having 1 to 3 heteroatoms selected from N, O or S, which heteroaryl is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halogen, cyano, C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxy, haloC_1-C_6alkoxy, hydroxy, $NR_{4a}R_{4b}$, hydroxyC_1-C_4alkyl, aminoC_1-C_4alkyl, C_1-C_6alkyl-OC(O)NH-, C_3-C_7cycloalkyl, C_5-C_7cycloalkenyl, phenyl, 55 or 6 membered heteroaryl having 1 or 2 ring heteroatoms selected from N, O or S, or saturated or partially unsaturated monocyclic or bicyclic heterocycle which heterocycle has 1 or 2 ring N, O or S atoms, 5 to 7 ring atoms in each ring and is substituted with 0, 1 or 2 substituents independently selected from the group consisting of halogen, C_1-C_6alkyl, C_1-C_6alkanoyl, C_1-C_6alkoxyC(O)N(H)-, - C_1-C_6alkoxyC(O)N(H)CH_2-,, aminoC_1-C_4alkyl, C_1-C_4alkoxyC_1-C_4alkyl and $NR_{4a}R_{4b}$, , and wherein the phenyl or heteroaryl substituent is unsubstituted or substituted with 1 or 2 independently selected substituents selected from halogen, CO_2H, cyano, C_1-C_4alkyl, C_1-C_4alkoxy, $CH_2NR_{4a}R_{4b}$ or C(O)$NR_{4a}R_{4b}$; or

R_4 is a saturated heterocycle 1 ring nitrogen and 0 or 1 additional ring heteroatom selected from N, O or S, which heterocyclic ring is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_1-C_6alkyl, CO_2C_1-C_6alkyl or CO_2benzyl;

R_{4a} is independently selected at each occurrence from the group consisting of hydrogen and C_1-C_6alkyl, wherein the alkyl substituent is unsubstituted or substituted with hydroxy, C_1-C_4alkoxy, amino or mono- and di-C_1-C_4alkylamino;

R_{4b} is independently selected at each occurrence from the group consisting of hydrogen, C_1-C_6alkyl and C_1-C_4alkanoyl, wherein the alkyl substituent is unsubstituted or substituted with hydroxy, C_1-C_4alkoxy, amino or mono- and di-C_1-C_4alkylamino; or

$NR_{4a}R_{4b}$, taken in combination, form a heterocyclic ring having one ring nitrogen atom and 0 or 1 additional ring heteroatom selected from N, O and S, which heterocyclic ring is

substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of halogen, hydroxy, amino, C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, aminoC_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4alkoxyC_1-C_4alkyl, and mono- and di- C_1-C_4alkylamino;

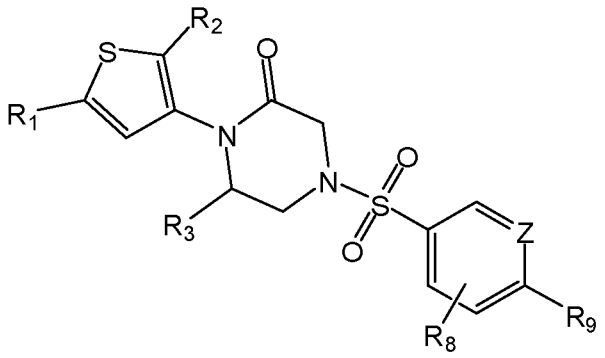
R_5 is absent or is selected from the group consisting of hydrogen and C_1-C_6alkyl;

R_6 is oxo, hydrogen, hydroxy, amino, N(H)-J-R_7;

J is absent, C(O) or $S(O)_2$; and

R_7 is C_1-C_6alkyl, phenyl or benzyl, each of is optionally substituted with C_1-C_6alkyl, C_1-C_6alkoxy, halogen, phenyl or phenoxy.

2. The compound of claim 1, wherein the compound is a compound of formula II, or a salt thereof:



(II)

wherein

Z is CH or N;

R_8 is selected from hydrogen, CO_2H, C_1-C_4alkyl, C-C_4alkoxy, cyano or halogen;

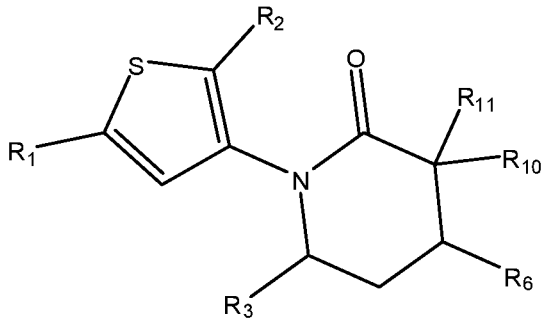
R_9 is selected from C_1-C_6alkyl, C_1-C_6alkoxy, phenyl, $NR_{9a}R_{9b}$, N(H)-C(O)-O-C_1-C_4alkyl, and heterocycle, wherein the heterocycle has one or two rings, each ring having 5, 6, or 7 ring atoms, one ring nitrogen atom and 0 or 1 additional ring heteroatom selected from N, O or S, and wherein the heterocycle is unsubstituted or substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, hydroxy, amino, C_1-C_4alkyl, haloC_1-C_4alkyl, hydroxyC_1-C_4alkyl, aminoC_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4alkoxyC_1-C_4alkyl, and mono- and di- C_1-C_4alkylamino; or

R_8 and R_9, taken in combination form a divalent residue selected from -$O(CH_2)_pO$-, -$O(CH_2)_2NH$-, or -$O(CH_2)_2N(CH_3)$-

R_{9a} is selected from the group consisting of hydrogen and C_1-C_6alkyl, wherein the alkyl substituent is unsubstituted or substituted with hydroxy, C_1-C_4alkoxy, amino or mono- and di-C_1-C_4alkylamino; and

R_{9b} is selected from the group consisting of hydrogen, C_1-C_6alkyl and C_1-C_4alkanoyl, wherein the alkyl substituent is unsubstituted or substituted with hydroxy, C_1-C_4alkoxy, amino or mono- and di-C_1-C_4alkylamino.

3. The compound of claim 1, wherein the compound is a compound of formula III, or a salt thereof:



(III)

wherein

R_6 is hydrogen, hydroxy, amino or N(H)-J-R_7;

J is C(O) or $S(O)_2$;

R_7 is (a) C_1-C_4alkyl optionally substituted with phenyl or phenoxy, or

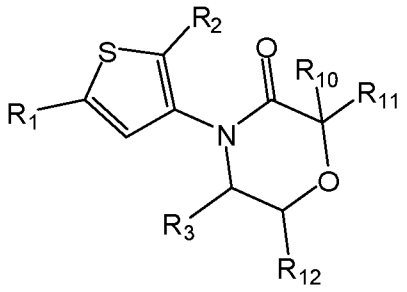
(b) phenyl optionally substituted with C_1-C_4alkyl, halogen or C_1-C_4alkoxy;

R_{10} is selected from hydrogen and C_1-C_6alkyl which alkyl is substituted with 0, 1, or 2 hydroxy and 0 or 1 substituents selected from cyano, SO_2CH_3, methoxy, ethoxy, $N(R_{10a})_2$ and $C(O)(NR_{10a})_2$;

R_{10a} is selected at each occurence from the group consisting of hydrogen and C_1-C_4alkyl which is substituted with 0 or 1 substituents selected from hydroxy, methoxy or ethoxy;

R_{11} is selected from the group consisting of hydrogen, fluoro, cyano, hydroxy and C_1-C_4alkyl.

4. The compound of claim 1, wherein the compound is a compound of formula IV, or a salt thereof:



(IV)

wherein

R_{10} and R_{11} are independently selected from hydrogen and C_1-C_6alkyl which alkyl is substituted with 0, 1, or 2 hydroxy and 0 or 1 substituents selected from SO_2CH_3, cyano, methoxy, ethoxy, $N(R_{10a})_2$ and $C(O)N(R_{10a})_2$;

R_{10a} is selected at each occurence from the group consisting of hydrogen and C_1-C_4alkyl which is substituted with 0 or 1 substituents selected from hydroxy, methoxy or ethoxy, or $N(R_{10a})_2$, taken in combination forms a 4 to 6 member heterocyclic ring;

R_{12} is selected from the group consisting of hydrogen and C_1-C_4alkyl.

5. The compound of any one of claims 1 to 4, wherein R_1 is *tert*-butylethynyl, phenyl, or phenyl para-substituted with F, Cl, Me.

6. The compound of any one of claims 1 to 5, wherein R_1 is *tert*-butylethynyl.

7. The compound of any one of claims 1 to 6, wherein R_2 is CO_2H.

8. The compound of any one of claims 1 to 7, wherein R_3 is cyclohexyl.

9. The compound of claim 3, wherein R_6 is hydrogen;

R_{10} is hydrogen or hydroxyC_1-C_6alkyl; and

R_{11} is hydrogen, methyl, hydroxy or fluoro.

10. The compound of claim 4, wherein R_{10} is hydoxyC_1-C_6alkyl;

R_{11} is hydrogen or methyl; and

R_{12} is hydrogen or methyl.

11. A compound of claim 1, or a pharmaceutically acceptable salt thereof, selected from the group consisting of:

3-((S)-2-Cyclohexyl-5-oxo-pyrrolidin-1-yl)-5-phenyl-thiophene-2-carboxylic acid;

3-(2-Cyclohexyl-6-oxo-piperidin-1-yl)-5-phenyl-thiophene-2-carboxylic acid;

3-(3-Cyclohexyl-5-oxo-morpholin-4-yl)-5-phenyl-thiophene-2-carboxylic acid;

3-[(R)-2-Cyclohexyl-6-oxo-4-(toluene-4-sulfonyl)-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid;

3-(2-Cyclohexyl-6-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-((S)-2-Cyclohexyl-6-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-(2-Cyclohexyl-6-oxo-piperidin-1-yl)-5-(4-fluoro-phenyl)-thiophene-2-carboxylic acid;

3-(2-Cyclohexyl-6-oxo-piperidin-1-yl)-5-p-tolyl-thiophene-2-carboxylic acid;

5-(4-Chloro-phenyl)-3-(2-cyclohexyl-6-oxo-piperidin-1-yl)-thiophene-2-carboxylic acid;

3-[2-Cyclohexyl-4-(6-dipropylamino-pyridine-3-sulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid;

3-{(R)-2-Cyclohexyl-4-[6-((R)-2-methyl-pyrrolidin-1-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid;

3-[(R)-2-Cyclohexyl-6-oxo-4-(6-pyrrolidin-1-yl-pyridine-3-sulfonyl)-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid;

3-{(R)-2-Cyclohexyl-4-[6-((2S,5R)-2,5-dimethyl-pyrrolidin-1-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid;

3-[2-Cyclohexyl-6-oxo-4-(toluene-4-sulfonyl)-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-{(R)-2-Cyclohexyl-4-[6-((2R,6S)-2,6-dimethyl-morpholin-4-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-phenyl-thiophene-2-carboxylic acid;

3-[2-Cyclohexyl-4-(6-morpholin-4-yl-pyridine-3-sulfonyl)-6-oxo-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-[(R)-2-Cyclohexyl-4-(6-diethylamino-pyridine-3-sulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid;

3-[(R)-2-Cyclohexyl-6-oxo-4-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-sulfonyl)-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid;

3-((R)-4-Cyclohexyl-2-oxo-oxazolidin-3-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-[(R)-2-Cyclohexyl-4-(6-morpholin-4-yl-pyridine-3-sulfonyl)-6-oxo-piperazin-1-yl]-5-phenyl-thiophene-2-carboxylic acid;

3-[(R)-2-Cyclohexyl-4-(4-methoxy-benzenesulfonyl)-6-oxo-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-[(R)-2-Cyclohexyl-4-(6-methoxy-pyridine-3-sulfonyl)-6-oxo-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-[(R)-2-Cyclohexyl-4-(1-methyl-1H-pyrazole-3-sulfonyl)-6-oxo-piperazin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-{(R)-2-Cyclohexyl-4-[6-(8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl)-pyridine-3-sulfonyl]-6-oxo-piperazin-1-yl}-5-p-tolyl-thiophene-2-carboxylic acid;

3-(2-Cyclohexyl-5-oxo-pyrrolidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-((R)-3-Cyclohexyl-5-oxo-morpholin-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-((4S,5R)-5-Cyclohexyl-3,4-dimethyl-2-oxo-imidazolidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

5-(4-Chloro-phenyl)-3-((R)-3-cyclohexyl-5-oxo-morpholin-4-yl)-thiophene-2-carboxylic acid;

3-[(R)-5-Cyclohexyl-2-(2-morpholin-4-yl-2-oxo-ethyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-[(R)-5-Cyclohexyl-2-(3-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-[(R)-5-Cyclohexyl-2-(3-methanesulfonyl-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-{(R)-5-Cyclohexyl-2-[(2-methoxy-ethylamino)-methyl]-3-oxo-morpholin-4-yl}-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-(4-Cyclohexyl-2-oxo-[1,3]oxazinan-3-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-((R)-5-Cyclohexyl-2-morpholin-4-ylmethyl-3-oxo-morpholin-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-[(2R,5R)-5-Cyclohexyl-2-(3-hydroxy-propyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-((2S,5R)-2-Cyanomethyl-5-cyclohexyl-2-methyl-3-oxo-morpholin-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-(6-Cyclohexyl-3-hydroxy-2-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-((R)-5-Cyclohexyl-2,2-dimethyl-3-oxo-morpholin-4-yl)-5-p-tolyl-thiophene-2-carboxylic acid;

3-(6-Cyclohexyl-3-hydroxy-2-oxo-piperidin-1-yl)-5-p-tolyl-thiophene-2-carboxylic acid;

3-[(2S,5R)-5-Cyclohexyl-2-(3-hydroxy-3-methyl-butyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-[(2R,5R)-5-Cyclohexyl-2-(3-hydroxy-3-methyl-butyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-[(2S,5R)-5-Cyclohexyl-2-((R)-3-hydroxy-butyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-[(2R,5R)-5-Cyclohexyl-2-((R)-3-hydroxy-butyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-((S)-6-Cyclohexyl-3-hydroxy-2-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-[(2R,5R)-5-Cyclohexyl-2-(2-hydroxy-ethyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-(6-Cyclohexyl-3-hydroxy-3-methyl-2-oxo-piperidin-1-yl)-5-p-tolyl-thiophene-2-carboxylic acid;

3-((R)-3-Cyclohexyl-5-oxo-1,9-dioxa-4-aza-spiro[5.5]undec-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-[6-Cyclohexyl-3-(3-hydroxy-propyl)-2-oxo-piperidin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-[(2S,5R)-5-Cyclohexyl-2-(2,3-dihydroxy-propyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-[(2S,5R)-5-Cyclohexyl-2-(2-hydroxy-ethyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-((R)-5-Cyclohexyl-2-hydroxymethyl-3-oxo-morpholin-4-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-[(2R,5R)-5-Cyclohexyl-2-(2,3-dihydroxy-propyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-[(2S,5R)-5-Cyclohexyl-2-(2,3-dihydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-[(2S,5R)-5-Cyclohexyl-2-(2-hydroxy-ethyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-[6-Cyclohexyl-3-hydroxy-3-(3-hydroxy-propyl)-2-oxo-piperidin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-[(2R,5R)-5-Cyclohexyl-2-(2,3-dihydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-[(2R,5R)-5-Cyclohexyl-2-(2-hydroxy-ethyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-[(2S,5R)-5-Cyclohexyl-2-(3-hydroxy-propyl)-2-methyl-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-((S)-6-Cyclohexyl-3-hydroxy-2-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-[(2R,5R)-5-Cyclohexyl-2-(3-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-[(2S,5R)-5-Cyclohexyl-2-(3-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-[(2R,5R)-5-Cyclohexyl-2-((R)-2-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-[(2R,5R)-5-Cyclohexyl-2-((S)-2-hydroxy-propyl)-3-oxo-morpholin-4-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-[(S)-6-Cyclohexyl-3-(3-hydroxy-propyl)-2-oxo-piperidin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid;

3-((S)-3-Amino-6-cyclohexyl-2-oxo-piperidin-1-yl)-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid; and

3-[(S)-6-Cyclohexyl-3-(2-hydroxy-ethyl)-2-oxo-piperidin-1-yl]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid.

12. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1 to 11 and one or more pharmaceutically acceptable carriers.

13. A combination, in particular a pharmaceutical combination, comprising a therapeutically effective amount of the compound according to any one of claims 1 to 11 and one or more therapeutically active agents.

14. A method of reducing viral load in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of the compound according to any one of claims 1 to 11.

15. A method of treating a disorder or a disease in a subject caused by or associated with HCV infection, wherein the method comprises administering to the subject a therapeutically effective amount of the compound according to any one of claims 1 to 11.

16. A method according to claim 15, wherein the disorder or the disease is selected from HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin's lymphoma, liver fibrosis and a suppressed innate intracellular immune response.

17. A compound according to any one of claims 1 to 11, for use as a medicament.

18 Use of a compound according to any one of claims 1 to 11 in the manufacture of a medicament for the treatment of a disorder or disease in a subject caused by or associated with HCV infection.

19. Use of a compound according to any one of claims 1 to 11, for the treatment of a disorder or disease in a subject caused by or associated with HCV infection.

20. The use of claim 19, wherein the disorder or disease is selected from HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin's lymphoma, liver fibrosis and a suppressed innate intracellular immune response.