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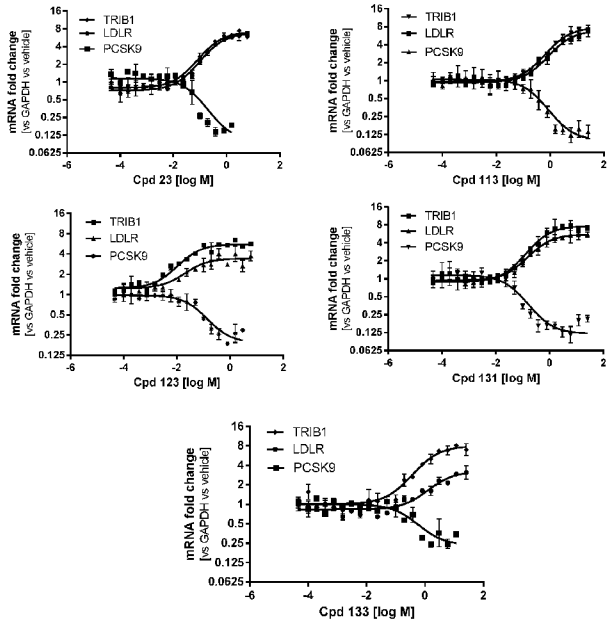
(54) **Title**: MODULATORS OF HEPATIC LIPOPROTEIN METABOLISM

FIG. 1



(57) **Abstract**: The invention relates to compounds for modulating hepatic cholesterol metabolism. The invention includes methods of making and using the compounds. These compounds or pharmaceutically acceptable salts thereof are useful for treating, preventing, and/or alleviating a cholesterol related disorder, a cardiovascular disease and/or liver disease in a human or animal.

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MODULATORS OF HEPATIC LIPOPROTEIN METABOLISM

GOVERNMENT INTEREST

This invention was made with government support under 3U54HG005032-05S1 awarded by the National Institute of Health. The government has certain rights in the invention.

BACKGROUND OF THE INVENTION

Cardiovascular disease is one of the leading causes of death worldwide. It is estimated that over 70 million people in the United States alone suffer from a cardiovascular disease, such as hypercholesterolemia, myocardial infarction, and coronary artery disease. Heterozygous familial hypocholesterolemia is a common genetic disorder, with a prevalence of 1/500 that leads to elevated low-density lipoprotein cholesterol (LDL-C) in circulation, and is associated with increased risk of coronary artery disease and myocardial infarction.

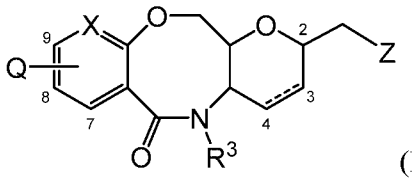
Population-based data and clinical trials have shown that LDL-C reduction is an effective strategy for preventing coronary artery disease, slowing its progression or reducing damage. Statins are efficacious LDL-C lowering agents that represent the current therapy of choice. Despite the widespread use of statins, almost half a million people die from myocardial infarction each year in the United States alone. Patients who are at the highest cardiovascular risk can also be the ones that fail more often to achieve their therapeutic goal, in particular diabetics. Some patients also require larger reductions of LDL-C due to their high baseline levels, like those with familial hypercholesterolemia. A substantial proportion of patients are also intolerant to statin therapy. Therefore, there is a critical need for additive or replacement therapy to statins for improved treatments for cardiovascular diseases and related disorders.

SUMMARY OF THE INVENTION

The invention relates generally to the field of compounds for modulating cardiovascular disease and/or liver disease and to methods of making and using them. These compounds or pharmaceutically acceptable salts thereof are useful for treating, preventing, and/or alleviating a cardiovascular disease or disorder and/or liver disease or disorder in a human or animal. In some aspects, these compounds or pharmaceutically acceptable salts thereof are useful for treating a cardiovascular disease or disorder and/or liver disease or

disorder in a human or animal. In some aspects, these compounds or pharmaceutically acceptable salts thereof are useful for preventing a cardiovascular disease and/or liver disease in a human or animal. In some aspects, these compounds or pharmaceutically acceptable salts thereof are useful for alleviating a cardiovascular disease or disorder and/or liver disease or disorder in a human or animal.

More specifically, the invention relates to a compound of formula I:



(I),

or a pharmaceutically acceptable salt thereof, wherein Q, X, R^3, and Z can be selected from the respective groups of chemical moieties defined herein.

In addition, the invention provides pharmaceutical compositions comprising an effective amount of a compound of the invention, or a pharmaceutically acceptable salt, and a pharmaceutical carrier, diluent, or excipient.

In one aspect, the invention provides a method of treating or preventing a cardiovascular disease or disorder in a subject in need thereof, comprising administering to the subject an effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof. In one aspect, the invention provides a method of treating a cardiovascular disease or disorder in a subject in need thereof, comprising administering to the subject an effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof. In one aspect, the cardiovascular disease is myocardial infarction, coronary heart disease, atherosclerosis or hypercholesterolemia. In one aspect, the cardiovascular disease is any cardiovascular disease that can be treated by increasing expression levels of *TRIB1*. In one aspect, the cardiovascular disease is any cardiovascular disease that can be prevented by increasing expression levels of *TRIB1*.

In one aspect, the invention provides a method of treating or preventing a liver disease or disorder in a subject in need thereof, comprising administering to the subject an effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof. In one aspect, the invention provides a method of treating a liver disease or disorder in a subject in need thereof, comprising administering to the subject an effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof. In one aspect, the liver disease or disorder is liver cirrhosis, hepatocellular carcinoma, liver injury or abnormal liver function.

In one aspect, the invention provides a method of treating or preventing a disease or disorder in a subject in need thereof, comprising administering to the subject an effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof, wherein said compound downregulates the expression level of *PCSK9* and upregulates the expression level of *TRIB1*. In one aspect, the invention provides a method of treating a disease or disorder in a subject in need thereof, comprising administering to the subject an effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof, wherein said compound downregulates the expression level of *PCSK9* and upregulates the expression level of *TRIB1* In one aspect, the disease is a cardiovascular disease or disorder, or a liver disease or disorder. In one aspect, the subject is at an elevated risk for cardiovascular disease or disorder.

In one aspect, the invention provides methods of downregulating the expression level of *PCSK9*. In one aspect, the invention provides methods of upregulating the expression level of *TRIB1*. In one aspect, the invention provides methods of downregulating the expression level of *PCSK9* and upregulating the expression level of *TRIB1*. In one aspect, the expression level of *PCSK9* is downregulated by at least about 30% in relation to a vehicle placebo. In one aspect, the expression level of *TRIB1* is upregulated by at least about 50% in relation to a vehicle placebo.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent for treating a disease in a subject comprising: (a) determining the expression level of *TRIB1* in a sample from the subject; and (b) comparing the expression level of *TRIB1* to a reference profile, wherein an increase in *TRIB1* expression compared to the reference profile indicates that the therapeutic agent is effective for treating the disease.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent for treating a disease in a subject comprising: (a) determining the expression level of *PCSK9* in a sample from the subject; and (b) comparing the expression level of *PCSK9* to a reference profile, wherein a decrease in *PCSK9* expression compared to the reference profile indicates that the therapeutic agent is effective for treating the disease.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent for treating a disease in a subject comprising: (a) determining the expression levels of *TRIB1* and *PCSK9* in a sample from the subject; and (b) comparing the expression levels of *TRIB1* and *PCSK9* to a reference profile; wherein an increase in *TRIB1* expression and a decrease in *PCKS9* expression compared to the reference profile indicates that the therapeutic agent is effective for treating the disease. In one aspect, the disease is any

disease that is associated with decreased expression of *TRIB1*. In one aspect, the disease is any disease that is treated or prevented by increasing *TRIB1*. In one aspect, the disease is any disease that is associated with decreased expression of *PCKS9*. In one aspect, the disease is any disease that is treated or prevented by increasing *PCKS9*.

In one aspect, the invention provides a method, wherein the disease is any cardiovascular disease/disorder or lipoprotein related disease/disorder (e.g., cholesterol related disorder) that is associated with decreased expression of *TRIB1*. In one aspect, the disease is any cardiovascular disease or lipoprotein related disorder (e.g., cholesterol related disorder) that is treated or prevented by increasing *TRIB1*. In one aspect, the disease is any cardiovascular disease or lipoprotein related disorder (e.g., cholesterol related disorder) that is treated by increasing *TRIB1*.

In one aspect, the invention provides a method, wherein determining the expression level is determining the level of protein or RNA transcripts.

In one aspect, the invention provides a method, wherein the reference profile is obtained from a subject that does not have the disease or disorder.

In one aspect, the invention provides a method of upregulating *TRIB1* expression, wherein said expression level of *TRIB1* in the subject is upregulated by at least about 50% in relation to a vehicle placebo.

In one aspect, the invention provides a method of downregulating *PCSK9* expression, wherein said expression level of *PCSK9* is downregulated by at least about 50% in relation to a vehicle placebo.

In one aspect, the invention provides a method, wherein the therapeutic agent is a compound of the invention or a pharmaceutically acceptable salt thereof.

In one aspect, the invention provides a method, wherein the disease or disorder is a cardiovascular disease. In one aspect, the invention provides a method, wherein the disease is a cholesterol related disorder. In one aspect, the disease is a lipoprotein related disorder.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent for treating a disease or disorder in a subject comprising: (a) determining the protein expression level of ApoB in a sample from the subject; and (b) comparing the protein expression level of ApoB to a reference profile, wherein a decrease in expression compared to the reference profile indicates that the therapeutic agent is effective for treating the disease. In one aspect, the protein expression level of ApoB in the sample from the subject is downregulated by at least about 50%. In one aspect, the protein expression level of

ApoB decreased by at least about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 10-fold, about 15-fold, or about 20-fold.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent for treating a disease or disorder in a subject comprising: (a) determining the protein expression level of LDLR in a sample from the subject; and (b) comparing the protein expression level of LDLR to a reference profile, wherein an increase in expression compared to the reference profile indicates that the therapeutic agent is effective for treating the disease. In one aspect, the protein expression level of LDLR in the sample from the subject is upregulated by at least about 50%. In one aspect, the protein expression level of LDLR is increased by at least about 1.5-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 10-fold, about 15-fold, or about 20-fold.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent for treating a disease or disorder in a subject comprising: (a) determining the protein expression level of PCSK9 in a sample from the subject; and (b) comparing the protein expression level of PCSK9 to a reference profile; wherein a decrease in expression as compared to the reference profile indicates that the therapeutic agent is effective for treating the disease. In one aspect, the protein expression level of PCSK9 in the sample from the subject is downregulated by at least about 50%. In one aspect, the protein expression level of PCSK9 is decreased by at least about 1.5-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 10-fold, about 15-fold, or about 20-fold.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent for treating a disease or disorder in a subject comprising: (a) determining the RNA transcript level of *MTTP* in a sample from the subject; and (b) comparing the RNA transcript level of *MTTP* to a reference profile, wherein a decrease in expression compared to the reference profile indicates that the therapeutic agent is effective for treating the disease. In one aspect, the RNA transcript level of *MTTP* in the sample from the subject is downregulated by at least about 50%. In one aspect, the RNA transcript level of *MTTP* is decreased by at least about 1.5-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 10-fold, about 15-fold, or about 20-fold.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent for treating a disease or disorder in a subject comprising: (a) determining the RNA transcript level of *APOC3* in a sample from the subject; and (b) comparing the RNA transcript level of *APOC3* to a reference profile, wherein a decrease in expression compared to the reference profile indicates that the therapeutic agent is effective for treating the disease.

In one aspect, the RNA transcript level of *APOC3* in the sample from the subject is downregulated by at least about 50%. In one aspect, the RNA transcript level of *APOC3* is decreased by at least about 1.5-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 10-fold, about 15-fold, or about 20-fold.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent for treating a disease or disorder in a subject comprising: (a) determining the RNA transcript level of *SREBF1* in a sample from the subject; and (b) comparing the RNA transcript level of *SREBF1* to a reference profile, wherein a decrease in expression compared to the reference profile indicates that the therapeutic agent is effective for treating the disease. In one aspect, the RNA transcript level of *SREBF1* in the sample from the subject is downregulated by about 1-2 fold.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent for treating a disease or disorder in a subject comprising: (a) determining the RNA transcript level of *HMGCR* in a sample from the subject; and (b) comparing the RNA transcript level of *HMGCR* to a reference profile, wherein a decrease in expression compared to the reference profile indicates that the therapeutic agent is effective for treating the disease. In one aspect, the RNA transcript level of *HMGCR* in the sample from the subject is downregulated by at least about 50%. In one aspect, the RNA transcript level of *HMGCR* is decreased by about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 10-fold, about 15-fold, or about 20-fold.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent for treating a disease or disorder in a subject comprising: (a) determining the RNA transcript level of *HMGCS* in a sample from the subject; and (b) comparing the RNA transcript level of *HMGCS* to a reference profile, wherein a decrease in expression compared to the reference profile indicates that the therapeutic agent is effective for treating the disease. In one aspect, the RNA transcript level of *HMGCS* in the sample from the subject is downregulated by at least about 2-fold.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent for treating a disease or disorder in a subject comprising: (a) determining the RNA transcript level of *FASN* in a sample from the subject, and (b) comparing the RNA transcript level of *FASN* to a reference profile; wherein a decrease in expression compared to the reference profile indicates that the therapeutic agent is effective for treating the disease. In one aspect, the RNA transcript level of *FASN* in the sample from the subject is down regulated by at least about 2-fold.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent for treating a disease or disorder in a subject comprising: (a) determining the RNA transcript level of *SCD1* in a sample from the subject, and (b) comparing the RNA transcript level of *SCD1* to a reference profile; wherein a decrease in expression compared to the reference profile indicates that the therapeutic agent is effective for treating the disease. In one aspect, the RNA transcript level of *SCD1* in the sample from the subject is down regulated by at least about 2-fold.

For example, in any of the foregoing methods, the reference profile can be obtained from a subject that does not have the disease.

For example, in any of the foregoing methods, the therapeutic agent can be a compound of the invention or a pharmaceutically acceptable salt thereof.

For example, in any of the foregoing methods, the disease can be a cardiovascular disease or disorder. For example, in any of the foregoing methods, the disease can be a lipoprotein related disorder (e.g., cholesterol related disorder).

In one aspect, the invention provides a method of synthesizing a compound of the invention or a pharmaceutically acceptable salt thereof.

In one aspect, the invention provides a medical device containing a compound of the invention or a pharmaceutically acceptable salt thereof.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. In the specification, the singular forms also include the plural unless the context clearly dictates otherwise. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. The references cited herein are not admitted to be prior art to the claimed invention. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be limiting.

Other features and advantages of the invention will be apparent from the following detailed description and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a series of five graphs showing responses of HepG2 cells to treatment with compounds 23, 113, 123, 131, and 133. Relative changes (vs. *GAPDH* expression) in expression levels for *TRIB1* and *LDLR* were measured by qPCR after 6 hours of treatment and for *PCSK9* after 24 hrs of treatment with indicated concentrations of compounds.

FIGS. 2A and 2B displays responses of mouse primary hepatocytes to indicated concentrations of Compound 23. Fold inductions (vs. *Gapdh* expression) of expressions of *Trib1* (shown in **FIG. 2A)** and *Ldlr* (shown in **FIG. 2B**) were measured by qPCR 24 hours after compound addition.

FIG. 3 is a graph that displays the pharmacokinetic results of intraperitoneal administration of a single dose (10 mg/kg) of Compounds 23, 113, 123, 131, and 133 in C57BL/6 mice. The plasma concentrations of Compounds 23 (–♦–), 113 (–x–), 123 (–■–), 131 (–▲–), and 133 (–>|<–) were measured at different time points after administration.

FIG. 4 is a graph that displays the pharmacokinetic results of intraperitoneal administration of a single dose (10 mg/kg) of Compounds 23, 113, 123, 131, and 133 in C57BL/6 mice. The liver concentrations of Compounds 23 (–♦–), 113 (–x–), 123 (–■–), 131 (–▲–), and 133 (–>|<–) were measured at different time points after administration.

FIG. 5A is a graph that shows the pharmacokinetic results of intraperitoneal administration of a single dose of Compound 123 in C57BL/6 mice at 10 mg/kg (–♦–), 15 mg/kg (–■–), 30 mg/kg (–▲–), and 45 mg/kg (–x–). The liver concentrations of Compound 123 were measured at different time points after administration.

FIG. 5B is a bar graph that shows relative expression of *TRIB1* after intraperitoneal administration of a single dose of Compound 123 in C57BL/6 mice at 15 mg/kg and 30 mg/kg. Expressions of *TRIB1* were measured by qPCR at different time points after administration.

DESCRIPTION OF THE INVENTION

Despite widespread use of statins, cardiovascular disease remains one of the leading causes of death worldwide. Epidemiological studies have repeatedly demonstrated that elevated levels of circulating LDL-C have a strong association with the development of coronary artery disease (CAD) and myocardial infarction (MI). Because in humans 70% of LDL is removed from circulation by LDL receptor mediated uptake in the liver, therapeutic strategies that lead to elevated hepatic expression of the LDL receptor gene (*LDLR*) have

proven to be efficacious in lowering LDL-C and provide protection from cardiovascular disease. Statins, through the inhibition of HMG CoA reductase, deplete cholesterol in the endoplasmic reticulum (ER) of hepatic cells leading to activation of the SREBF2 dependent transcriptional program, which includes increased expression of *LDLR*. Paradoxically, clinical efficacy of statin therapy is limited by the fact that activation of SREBF2 also leads to increased expression of *PCSK9*, which acts as a negative regulator of LDL uptake by promoting degradation of LDL receptor. Recent results from clinical trials with anti-PCSK9 mAbs suggest that PCSK9 blockade may indeed provide a more efficacious mechanism for elevating LDL receptor levels than traditional inhibition of HMG CoA reductase. Alternative strategies of lowering circulating LDL-C include treatments that lower hepatic secretion of very-low-density lipoprotein (VLDL) particles – the precursor of LDL particles – into the bloodstream. Recently approved examples of such treatments include inhibitors of microsomal triglyceride transfer protein (MTP) and antisense DNA directed against apoB.

Limited efficacy as well as dose limiting toxicities of statins prevent the majority of patients from reaching their cholesterol treatment goals. Limitations and the side effects of statins, including recent concerns about cognitive impairment and the link to diabetes, as well the side effects - such as hepatic fat accumulation and liver toxicity - described for other treatments underscore the need for development of new therapeutic strategies to lower LDL-C and to prevent MI.

Disclosed herein is the identification of compounds for the treatment or prevention of a lipoprotein related disease or disorder (e.g., cholesterol related disorder), including cardiovascular disease. In one aspect, the present invention provides compounds with an activity profile that favorably differs from profiles produced by statins or other lipoprotein-active therapies. *TRIB1* is a locus strongly associated with decreased risk of coronary artery disease (CAD) and myocardial infarction (MI) as well as with decreased levels of low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG) in blood. The present invention provides compounds that induce *TRIB1* gene expression and modifies expression of cholesterol and triglyceride metabolic genes, leading to decreased secretion of apolipoprotein B (apoB) and increased uptake of LDL by hepatic cells. In one aspect, the present invention provides compounds that inhibit the expression of *PCSK9* mRNA and secretion of PCSK9 protein. This activity profile can provide advantages over current therapies.

For purposes of the present invention, the following definitions will be used (unless expressly stated otherwise):

As used herein, the articles "a" and "an" refer to one or to more than one (*i.e.*, to at least one) of the grammatical object of the article.

As used herein, the term "about" will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. As used herein when referring to a measurable value such as an amount, a temporal duration, and the like, the term "about" is meant to encompass variations of ±20% or ±10%, such as ±5%, such as ±1%, and such as ±0.1% from the specified value, as such variations are appropriate to the amounts disclosed herein.

The general chemical terms used throughout have their usual meanings. For example, the term "alkyl" refers to a branched or unbranched saturated hydrocarbon group. The term "*n*-alkyl" refers to an unbranched alkyl group. The term "C_x-C_y alkyl" refers to an alkyl group having between x and y carbon atoms, inclusively, in the branched or unbranched hydrocarbon group. By way of illustration, but without limitation, the term "C_1-C_8 alkyl" refers to a straight chain or branched hydrocarbon moiety having from 1, 2, 3, 4, 5, 6, 7, or 8 carbon atoms. "C_1-C_6" refers to a straight chain or branched hydrocarbon moiety having from 1, 2, 3, 4, 5, or 6 carbon atoms. "C_1-C_4 alkyl" refers to a straight chain or branched hydrocarbon moiety having from 1, 2, 3, or 4 carbon atoms, including methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, and *tert*-butyl. The term "C_1-C_4 *n*-alkyl" refers to straight chain hydrocarbon moieties that have 1, 2, 3, or 4 carbon atoms including methyl, ethyl, *n*-propyl, and *n*-butyl. An alkyl group can be optionally substituted with one or more substituents selected from halogen, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl.

As used herein, the term "alkenyl" employed alone or in combination with other terms means, unless otherwise stated, a stable containing at least one double bond, and having from two to ten carbon atoms (i.e., $C_{2\text{-}10}$ alkenyl). Whenever it appears herein, a numerical range such as "2 to 10" refers to each integer in the given range; e.g., "2 to 10 carbon atoms" means that the alkenyl group can consist of 2 carbon atoms, 3 carbon atoms, etc., up to and including 10 carbon atoms. In certain embodiments, an alkenyl comprises two to eight carbon atoms. In other embodiments, an alkenyl comprises two to six carbon atoms (e.g., $C_{2\text{-}6}$ alkenyl). The alkenyl is attached to the parent molecular structure by a single bond, for example, ethenyl (i.e., vinyl), prop-1-enyl (i.e., allyl), but- 1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like. The one or more carbon-carbon double bonds can be internal (such as in 2-butenyl) or terminal (such as in 1-butenyl). Examples of $C_{2\text{-}4}$ alkenyl groups include

ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), 2-methylprop-2-enyl (C_4), butadienyl (C_4) and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkenyl groups as well as pentenyl (C_5), pentadienyl (C_5), hexenyl (C_6), 2,3-dimethyl-2-butenyl (C_6) and the like. Additional examples of alkenyl include heptenyl (C_7), octenyl (C_8), octatrienyl (C_8) and the like. Further examples include vinyl, propenyl (or allyl), crotyl, isopentenyl, butadienyl, 1,3-pentadienyl, 1,4-pentadienyl, and the higher homologs and isomers. A functional group representing an alkene is exemplified by $-CH_2-CH=CH_2$. An alkenylgroup can be optionally substituted with one or more substituents selected from halogen, alkyl, aralkyl, heteroalkyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl.

As used herein, the term “alkynyl” employed alone or in combination with other terms means, unless otherwise stated, a stable straight chain or branched chain hydrocarbon group with containing at least one triple bond, having from two to ten carbon atoms (i.e., C_{2-10} alkynyl). Whenever it appears herein, a numerical range such as "2 to 10" refers to each integer in the given range; e.g., "2 to 10 carbon atoms" means that the alkynyl group can consist of 2 carbon atoms, 3 carbon atoms, etc., up to and including 10 carbon atoms. In certain embodiments, an alkynyl comprises two to eight carbon atoms. In other embodiments, an alkynyl has two to six carbon atoms (e.g., C_{2-6} alkynyl). The alkynyl is attached to the parent molecular structure by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl, 3-methyl-4-pentenyl, hexynyl, and the like. Non-limiting examples include ethynyl and propynyl, and the higher homologs and isomers. The term “propargylic” refers to a group exemplified by $-CH_2-C\equiv CH$. The term “homopropargylic” refers to a group exemplified by $-CH_2CH_2-C\equiv CH$. The term “substituted propargylic” refers to a group exemplified by $-CR_2-C\equiv CR$, wherein each occurrence of R is independently H, alkyl, substituted alkyl, alkenyl or substituted alkenyl, with the proviso that at least one R group is not hydrogen. The term “substituted homopropargylic” refers to a group exemplified by $-CR_2CR_2-C\equiv CR$, wherein each occurrence of R is independently H, alkyl, substituted alkyl, alkenyl or substituted alkenyl, with the proviso that at least one R group is not hydrogen. An alkynyl group can be optionally substituted with one or more substituents selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, cycloalkyl, hydroxyl, alkoxy, amino, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl.

As used herein, the term "alkoxy" employed alone or in combination with other terms means, unless otherwise stated, an alkyl group having the designated number of carbon atoms, as defined above, connected to the rest of the molecule via an oxygen atom, such as, for example, methoxy, ethoxy, 1-propoxy, 2-propoxy (isopropoxy) and the higher homologs and isomers. In some aspects, the (C_1-C_3)alkoxy, is ethoxy or methoxy. The terms "alkoxy", "phenyloxy", "benzoxy" and "pyrimidinyloxy" refer to an alkyl group, phenyl group, benzyl group, or pyrimidinyl group, respectively, each optionally substituted, that is bonded through an oxygen atom. An alkoxy group can be optionally substituted with one or more substituents selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl.

The term "amino" refers to $-NH_2$. "Monoalkylamino" refers to an –NH(alkyl) group, "Dialkylamino" refers to an –N(alkyl)(alkyl) group where each alkyl moiety may be the same or different. An "alkyl" on an amino group can be optionally substituted with one or more substituents selected from halogen, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy amino, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl.

The terms "aminocarbonyl", "acylamino", "amide" or "amido" each refer to a chemical moiety with formula $-C(O)N(R^b)_2$, $-C(O)N(R^b)-$, $-NR_bC(O)-$ or $-NR_bC(O)R_b$, where R_b is independently selected from hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon) or heteroarylalkyl. An amido group can be optionally substituted with one or more substituents selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl.

The term "C_3-C_6 cycloalkyl" or "C_3-C_6 cycloalkyl ring" refers to cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. The term "C_3-C_7 cycloalkyl" or "C_3-C_7 cycloalkyl ring" also includes cycloheptyl. The term "C_3-C_8 cycloalkyl" or "C_3-C_8 cycloalkyl ring" also includes cyclooctyl. The terms "cycloalkyl" and "carbocyclyl" are interchangeable. Cycloalkylalkyl refers to cycloalkyl moieties linked through an alkyl linker chain, as for example, but without limitation, cyclopropylmethyl, cyclopropylethyl, cyclopropylpropyl, cyclopropylbutyl, cyclobutylmethyl, cyclobutylethyl, cyclobutylpropyl, cyclopentylmethyl, cyclopentylethyl, cyclopentylpropyl, cyclohexylmethyl, cyclohexylethyl, and

cyclohexylpropyl. The term "cycloalkyl" also includes bridged and spiro-fused cyclic structures containing no heteroatoms. A cycloalkyl group can be optionally substituted with one or more substituents selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, hydroxyl, alkoxy, amino, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl.

The term "C_4-C_8 cycloalkenyl" refers cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl rings having one or more sites of unsaturation e.g., one or more double bonds. These rings may be optionally substituted as specified herein for "cycloalkyl".

The term "3 to 8 membered ring" includes a 3, 4, 5, 6, 7, and 8-membered ring.

The term "halogen" refers to fluoro, chloro, bromo, or iodo.

The term "hydroxyl" or "hydroxy" means -OH.

The term "aryl" or "aromatic ring", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. In a multi-ring group, only one ring is required to be aromatic, so groups such as indanyl are encompassed by the aryl definition. The ring or ring system can have 6 to 14 ring atoms (e.g., C_{6-14} aromatic or C_{6-14} aryl). Whenever it appears herein, a numerical range such as "6 to 14 aryl" refers to each integer in the given range; e.g., "6 to 14 ring atoms" means that the aryl group can consist of 6 ring atoms, 7 ring atoms, etc., up to and including 14 ring atoms. The term "aryl" or "aromatic ring" embraces aromatic radicals such as phenyl (C_6H_6), naphthyl, tetrahydronaphthyl, indane and biphenyl, and includes carbocyclic aryl, heterocyclic aryl and biaryl groups, all of which may be optionally substituted. Non-limiting examples of aryl groups include phenyl, phenalenyl, naphthalenyl, tetrahydronaphthyl, phenanthrenyl, anthracenyl, fluorenyl, indolyl, indanyl, and the like. An aryl group can be optionally substituted with one or more substituents selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl.

The term "heteroaryl" or "heteroaromatic ring" as used herein includes 5-, 6- and 7-membered monocyclic or polycyclic (e.g., bicyclic or tricyclic) aromatic ring system having ring carbon atoms and 1, 2, 3, or 4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous and sulfur. For example, a heteroaryl can have one or two 5- or 6-membered ring and 1 to 4 heteroatoms selected from N, O, and S. Heteroaryl polycyclic ring systems can include one or

more heteroatoms in one or both rings. Exemplary heteroaryls include, but are not limited to, pyrrole, furan, thiophene, imidazole, oxazole, oxadiazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine, azepine, oxepine, oxazine, triazine, pyrimidine, indole, and benzoimidazole, and the like. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles" or "heteroaromatics." The aromatic ring can be substituted at one or more ring positions with such substituents as described above, for example, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, $-CF_3$, -CN, or the like. IN some aspects, the optional substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl.

"Heteroaryl" also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment to the parent molecular structure is either on the aryl or on the heteroaryl ring, or wherein the heteroaryl ring, as defined above, is fused with one or more cycloalkyl or heterocyclyl groups wherein the point of attachment to the parent molecular structure is on the heteroaryl ring. For polycyclic heteroaryl groups wherein one ring does not contain a heteroatom (e.g., indolyl, quinolinyl, carbazolyl and the like), the point of attachment to the parent molecular structure can be on either ring, i.e., either the ring bearing a heteroatom (e.g., 2-indolyl) or the ring that does not contain a heteroatom (e.g., 5-indolyl). In some embodiments, a heteroaryl group is a 5-6 membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous, and sulfur ("5-6 membered heteroaryl"). In some embodiments, the 5-6 membered heteroaryl has 1-3 ring heteroatoms selected from nitrogen, oxygen, phosphorous, and sulfur. In some embodiments, the 5-6 membered heteroaryl has 1-2 ring heteroatoms selected from nitrogen, oxygen, phosphorous, and sulfur. In some embodiments, the 5-6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, phosphorous, and sulfur. A heteroaryl group can be optionally substituted with one or more substituents selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl.

Examples of heteroaryls include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzindolyl, 1,3-benzodioxolyl, benzofuranyl, benzooxazolyl, benzo[d]thiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, benzo[b][1,4] oxazinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzoxazolyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzopyranonyl, benzofurazanyl, benzothiazolyl, benzothienyl (benzothiophenyl), benzothieno[3,2-d]pyrimidinyl, benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, cyclopenta[d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[4,5]thieno [2,3-d]pyrimidinyl, 5,6-dihydrobenzo[h]quinazolinyl, 5,6-dihydrobenzo[h]cinnolinyl, 6,7-dihydro-5H benzo[6,7]cyclohepta[1,2-c]pyridazinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furazanyl, furanonyl, furo [3,2 -c]pyridinyl, 5,6,7,8,9,10-hexahydrocycloocta[d] pyrimidinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridazinyl, 5,6,7,8,9,10 hexahydrocycloocta[d]pyridinyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazolinyl, naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 5,6,6a,7,8,9,10,10a-octahydrobenzo[h]quinazolinyl, 1-phenyl-lH-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyranyl, pyrrolyl, pyrazolyl, pyrazolo[3,4-d]pyrimidinyl, pyridinyl, pyrido[3,2-d]pyrimidinyl, pyrido[3,4-d]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, 5,6,7,8-tetrahydroquinazolinyl, 5,6,7,8- tetrahydrobenzo [4,5] thieno [2,3 -d]pyrimdinyl, 6,7,8,9-tetrahydro-5H-cyclohepta[4,5]thieno [2,3-d]pyrimidinyl, 5,6,7,8-tetrahydropyrido[4,5-c]pyridazinyl, thiazolyl, thiadiazolyl, thiapyranyl, triazolyl, tetrazolyl, triazinyl, thieno[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, thieno [2,3-c]pyridinyl, and thiophenyl (i.e., thienyl).

The terms "heterocyclic ring", “heterocycle”, and “heterocyclyl” are taken to mean a saturated, unsaturated, or partially unsaturated ring containing from 1, 2, 3, or 4 heteroatoms selected from nitrogen, oxygen and sulfur, said ring optionally being benzofused. A heterocyclic ring can be multicyclic e.g., bicyclic or tricyclic. Polycyclic ring systems can be a fused, bridged or spiro ring system. A heterocycle may have from 3 to 8 ring atoms. The term “3- to 8-membered heterocyclic ring” refers to a ring having from 3, 4, 5, 6, 7 or 8 atoms. The term “3- to 6-membered heterocyclic ring” refers to a ring having from 3, 4, 5, or 6 atoms. The term “5- to 6-membered heterocyclic ring” refers to a ring having 5 or 6 atoms. In some aspects, a heterocyclyl can have one or two 5- or 6-membered rings and 1 to 4 heteroatoms selected from N, O, and S. Exemplary mono-heterocyclic rings, for the purposes

of the present invention, include furanyl, thiophenyl (thienyl or thiophenyl), pyrrolyl, pyrrolidinyl, pyridinyl, N-methylpyrrolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, triazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, thiazolidinyl, N-acetylthiazolidinyl, pyrimidinyl, pyrazinyl, pyridazinyl, and the like. A heterocyclyl group can be optionally substituted with one or more substituents selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl.

"Heterocyclyl" also includes ring systems wherein the heterocycyl ring, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment to the parent molecular structure is on the heterocyclyl ring. Heterocyclic rings include bicyclic rings for example, 3-azabicyclo[3.1.0]hexane, 8-oxa-3-azabicyclo[3.2.1]octane. Benzofused heterocyclic rings include isoquinolinyl, benzoxazolyl, benzodioxolyl, benzothiazolyl, quinolinyl, benzofuranyl, benzothiophenyl, indolyl, and the like, all of which may be optionally substituted, which also of course includes optionally substituted on the benzo ring when the heterocycle is benzofused.

As may be specified herein, "heterocyclic ring" or “heterocycle” refers to saturated ring containing from 1, 2, 3, or 4 heteroatoms selected from nitrogen, oxygen and sulfur, and can be multicyclic e.g., bicyclic or tricyclic. Exemplary heterocyclic rings, for the purposes of the present invention, include azetidinyl, pyrrolidinyl, pyrrolidinonyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, piperazinyl, morpholinyl, oxetanyl, and oxathianyl-dioxide.

Exemplary 3-membered heterocyclyls containing 1 heteroatom include, without limitation, azirdinyl, oxiranyl, and thiorenyl. Exemplary 4-membered heterocyclyls containing 1 heteroatom include, without limitation, azetidinyl, oxetanyl and thietanyl. Exemplary 5-membered heterocyclyls containing 1 heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyls containing 2 heteroatoms include, without limitation, dioxolanyl, oxathiolanyl, thiazolidinyl, and dithiolanyl. Exemplary 5-membered heterocyclyls containing 3 heteroatoms include, without limitation, triazolinyl, diazolonyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6-membered heterocyclyl groups containing 1 heteroatom include, without limitation, piperidinyl,

tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6 membered heterocyclyl groups containing 2 heteroatoms include, without limitation, piperazinyl, morpholinyl, thiomorpholinyl, dithianyl, dioxanyl, and triazinanyl. Exemplary 7-membered heterocyclyl groups containing 1 heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8-membered heterocyclyl groups containing 1 heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary bicyclic heterocyclyl groups include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, tetrahydrobenzothienyl, tetrahydrobenzofuranyl, benzoxanyl, benzopyrrolidinyl, benzopiperidinyl, benzoxolanyl, benzothiolanyl, benzothianyl, tetrahydroindolyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, decahydroisoquinolinyl, 3-1H-benzimidazol-2-one, (1-substituted)-2-oxo-benzimidazol-3-yl, octahydrochromenyl, octahydroisochromenyl, decahydronaphthyridinyl, decahydro-1,8-naphthyridinyl, octahydropyrrolo[3,2 -b]pyrrole, phenanthridinyl, indolinyl, phthalimidyl, naphthalimidyl, chromanyl, chromenyl, 1H-benzo[e] [1,4]diazepinyl, 1,4,5,7-tetrahydropyrano[3,4-b]pyrrolyl, 5,6-dihydro-4H-furo[3,2-b]pyrrolyl, 6,7-dihydro-5H-furo [3,2-b]pyranyl, 5,7-dihydro-4H-thieno [2,3-c]pyranyl, 2,3-dihydro-lH-pyrrolo[2,3-b]pyridinyl, hydrofuro[2,3-b]pyridinyl, 4,5,6,7 tetrahydro- 1H-pyrrolo[2,3-b]pyridinyl, 4,5,6,7-tetrahydrofuro[3,2-c]pyridinyl, 4,5,6,7-tetrahydrothieno[3,2-b]pyridinyl, 1,2,3,4-tetrahydro-1,6-naphthyridinyl, and the like.

It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Non-limiting examples of optional substituents as referred to herein include halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl.

The terms "pharmaceutical" or “pharmaceutically acceptable”, when used herein as an adjective, mean substantially non-toxic and substantially non-deleterious to the subject.

By "pharmaceutical formulation" it is further meant that the carrier, solvent, excipient(s) and/or salt must be compatible with the active ingredient of the formulation (e.g. a compound of the invention). It is understood by those of ordinary skill in this art that the terms “pharmaceutical formulation” and “pharmaceutical composition” are generally interchangeable, and they are so used for the purposes of this application.

The term “acid addition salt” refers to a salt of a compound of the invention prepared by reaction of a compound of the invention with a mineral or organic acid. For exemplification of pharmaceutically acceptable acid addition salts, see, *e.g.*, Berge, S.M., Bighley, L.D., and Monkhouse, D.C., *J. Pharm. Sci.*, 66:1, 1977. For example, compounds of this invention which are an amine compound are basic in nature and accordingly react with any of a number of inorganic and organic acids to form pharmaceutically acceptable acid addition salts.

Pharmaceutically acceptable acid addition salts of the invention can be formed by the reaction of a compound of the invention with an equimolar or excess amount of acid. Alternatively, hemi-salts can be formed by the reaction of a compound of the invention with the desired acid in a 2:1 ratio, compound to acid. The reactants are generally combined in a mutual solvent such as diethyl ether, tetrahydrofuran, methanol, ethanol, *iso*-propanol, benzene, or the like. The salts normally precipitate out of solution within, e.g., about one hour to about ten days and can be isolated by filtration or other conventional methods.

Inorganic acids commonly employed to form such salts include hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like. Organic acids commonly employed to form such salts include p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid and the like. Examples of such pharmaceutically acceptable salts thus are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, *iso*-butyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, hemisuccinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β-hydroxybutyrate,

glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandalate and the like.

Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc.), the compounds of the present invention can be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the compounds of the invention, methods of delivering the same and compositions containing the same. "Prodrugs" are intended to include any covalently bonded carriers that release an active parent drug (compound) of the present invention *in vivo* when such prodrug is administered to a subject. Prodrugs are prepared, for example, by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of the invention wherein a hydroxyl or amino group is bonded to any group that, when the prodrug of the present invention is administered to a subject, it cleaves to form a free hydroxyl or free amino group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention. Examples of prodrugs include, but are not limited to, benzamide derivatives of an amine functional group in the active compound and the like. Other examples of prodrugs include compounds that comprise –NO, $-NO_2$, -ONO, or $–ONO_2$ moieties.

For example, if a disclosed compound or a pharmaceutically acceptable form of the compound contains a carboxylic acid functional group, a prodrug can comprise a pharmaceutically acceptable ester formed by the replacement of the hydrogen atom of the acid group with a group such as (C_{1-8})alkyl, (C_{1-12})alkanoyloxymethyl, 1- (alkanoyloxy) ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 10 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_{1-2})alkylamino(C_{2-3})alkyl (such as [3-dimethylaminoethyl), carbamoyl-(C_{1-2})alkyl, N,N-di(C_{1-2})alkylcarbamoyl-(C_{1-2})alkyl and piperidino-, pyrrolidino- or morpholino(C_{2-3})alkyl.

Similarly, if a disclosed compound or a pharmaceutically acceptable form of the compound contains an alcohol functional group, a prodrug can be formed by the replacement

of the hydrogen atom of the alcohol group with a group such as (C_{1-6})alkanoyloxymethyl, 1-((C_{1-6})alkanoyloxy)ethyl, 1-methyl-1-((C_{1-6})alkanoyloxy)ethyl, (C_{1-6})alkoxycarbonyloxymethyl, N-(C_{1-6})alkoxycarbonylaminomethyl, succinoyl, (C_{1-6})alkanoyl, α-amino(C_{1-4})alkanoyl, arylacyl, and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, -P(O)(OH)$_2$, -P(O)(O(C_{1-6})alkyl)$_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

If a disclosed compound or a pharmaceutically acceptable form of the compound incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently (C_{1-10})alkyl, (C_{3-7})cycloalkyl, benzyl, a natural α-aminoacyl or natural α-aminoacyl-natural-α-aminoacyl, -C(OH)C(O)OY^1 wherein Y^1 is H, (C_{1-6})alkyl or benzyl, C(OY^2)Y^3 wherein Y^2 is (C_{1-4})alkyl and Y^3 is (C_{1-6})alkyl, carboxy(C_{1-6})alkyl, amino(C_{1-4})alkyl or mono-N- or di-N,N-(C_{1-6})alkylaminoalkyl, -C(Y^4)Y^5 wherein Y^4 is H or methyl and Y^5 is mono-N- or di-N,-(C_{1-6})alkylamino, morpholino, piperidin-1-yl or pyrrolidin-1-yl.

In certain cases, a prodrug has improved physical and/or delivery properties over the parent compound. Prodrugs can increase the bioavailability of the compound when administered to a subject (e.g., by permitting enhanced absorption into the blood following oral administration) or which enhance delivery to a biological compartment of interest (e.g., the brain or lymphatic system) relative to the parent compound. Exemplary prodrugs include derivatives of a disclosed compound with enhanced aqueous solubility or active transport through the gut membrane, relative to the parent compound.

The term "solvate" means a solvent addition form that contains either a stoichiometric or non- stoichiometric amount of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in a solid state, thus forming a solvate. If the solvent is water, the solvate formed is a hydrate; when the solvent is alcohol, the solvate formed is an alcoholate. Hydrates are formed by the combination of one or more molecules of water with one of the substances in which the water retains its molecular state as H_2O, such combination being able to form one or more hydrates.

The term "suitable solvent" refers to any solvent, or mixture of solvents, that may be inert to the ongoing reaction that sufficiently solubilizes the reactants to afford a medium within which to effect the desired reaction.

In some aspects, the compound is an isomer. "Isomers" are different compounds that have the same molecular formula. "Stereoisomers" are isomers that differ only in the way the atoms are arranged in space. As used herein, the term "isomer" includes any and all geometric isomers and stereoisomers. For example, "isomers" include geometric double bond cis- and trans-isomers, also termed E- and Z-isomers; R- and S-enantiomers; diastereomers, (d)-isomers and (l)-isomers, racemic mixtures thereof; and other mixtures thereof, as falling within the scope of this disclosure.

Geometric isomers can be represented by the symbol ----- which denotes a bond that can be a single, double or triple bond as described herein. Provided herein are various geometric isomers and mixtures thereof resulting from the arrangement of substituents around a carbon-carbon double bond or arrangement of substituents around a carbocyclic ring. Substituents around a carbon-carbon double bond are designated as being in the "Z" or "E" configuration wherein the terms "Z" and "E" are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting double bonds encompass both the "E" and "Z" isomers.

Substituents around a carbon-carbon double bond alternatively can be referred to as "cis" or "trans," where "cis" represents substituents on the same side of the double bond and "trans" represents substituents on opposite sides of the double bond. The arrangement of substituents around a carbocyclic ring can also be designated as "cis" or "trans." The term "cis" represents substituents on the same side of the plane of the ring, and the term "trans" represents substituents on opposite sides of the plane of the ring. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of plane of the ring are designated "cis/trans."

The term "enantiomers" refers to a pair of stereoisomers that are non-superimposable mirror images of each other. An atom having an asymmetric set of substituents can give rise to an enantiomer. A mixture of a pair of enantiomers in any proportion can be known as 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 an enantiomer, the stereochemistry at each chiral carbon can 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 and can

thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that can be defined, in terms of absolute stereochemistry at each asymmetric atom, as (R)- or (S)-. The present chemical entities, pharmaceutical compositions and methods are meant to include all such possible isomers, including racemic mixtures, optically substantially pure forms and intermediate mixtures.

Optically active (R)- and (S)-isomers can be prepared, for example, using chiral synthons or chiral reagents, or resolved using conventional techniques. Enantiomers can be isolated from racemic mixtures by any method known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC), the formation and crystallization of chiral salts, or prepared by asymmetric syntheses.

Optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, e.g., by formation of diastereoisomeric salts, by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric, and camphorsulfonic acid. The separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts affords separation of the isomers. Another method involves synthesis of covalent diastereoisomeric molecules by reacting disclosed compounds with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically enriched compound. Optically active compounds can also be obtained by using active starting materials. In some embodiments, these isomers can be in the form of a free acid, a free base, an ester or a salt.

In certain embodiments, the compound of the invention can be a tautomer. As used herein, the term "tautomer" is a type of isomer that includes two or more interconvertible compounds resulting from at least one formal migration of a hydrogen atom and at least one change in valency (e.g., a single bond to a double bond, a triple bond to a single bond, or vice versa). "Tautomerization" includes prototropic or proton-shift tautomerization, which is considered a subset of acid-base chemistry. "Prototropic tautomerization" or "proton-shift tautomerization" involves the migration of a proton accompanied by changes in bond order. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. Where tautomerization is possible (e.g., in solution), a chemical equilibrium of tautomers can be reached. Tautomerizations (i.e., the reaction providing a tautomeric pair) can be catalyzed by acid or base, or can occur without the action or presence of an external agent. Exemplary tautomerizations include, but are not limited to, keto-to-enol; amide-to-

imide; lactam-to-lactim; enamine-to-imine; and enamine-to-(a different) enamine tautomerizations. A specific example of keto-enol tautomerization is the interconversion of pentane-2,4-dione and 4-hydroxypent-3-en-2-one tautomers. Another example of tautomerization is phenol-keto tautomerization. A specific example of phenol-keto tautomerization is the interconversion of pyridin-4-ol and pyridin-4(1H)-one tautomers.

All chiral, diastereomeric, racemic, and geometric isomeric forms of a structure are intended, unless specific stereochemistry or isomeric form is specifically indicated. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention. All tautomers of shown or described compounds are also considered to be part of the present invention.

The invention also comprehends isotopically-labeled compounds, which are identical to those recited in the formulae of the invention, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number most commonly found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, fluorine, such as ^{2}H, ^{3}H, ^{13}C ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl,.

Compounds of the invention and salts, or prodrugs of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Isotopically-labeled compounds of the invention, for example those into which radioactive isotopes such as ^{3}H, ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes can be used for their ease of preparation and detectability. ^{11}C and ^{18}F isotopes are useful in PET (positron emission tomography). PET is useful in brain imaging. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be advantageous in some circumstances. Isotopically labeled compounds of this invention can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent. In one embodiment, the compounds of the invention, salts or prodrugs thereof are not isotopically labelled.

When any variable (*e.g.*, R^{h}) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with one or more

R^h moieties, then R^h at each occurrence is selected independently from the Markush group recited for R^h. Also, combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds within a designated atom's normal valency.

As used herein, the term "treat," "treatment" or "treating" herein, is meant decreasing the symptoms, markers, and/or any negative effects of a disease, disorder, and/or condition in any appreciable degree in a patient who currently has the a disease, disorder, and/or condition. Treatment can include a decrease in the severity of symptoms in acute or chronic disease as well as a decrease in the relapse or exacerbation rate in relapsing-remitting disease. In one aspect, treating a disease means reversing or stopping the disease's progression. Ameliorating a disease and alleviating a disease are equivalent to treating a disease.

As used herein, the term "prevent," "prevention," or "preventing" refers to any method to partially or completely prevent or delay the onset of one or more symptoms or features of a disease, disorder, and/or condition. Prevention is causing the clinical symptoms of the disease state not to develop, i.e., inhibiting the onset of disease, in a subject that may be exposed to or predisposed to the disease state, but does not yet experience or display symptoms of the disease state. Prevention may be administered to a subject who does not exhibit signs of a disease, disorder, and/or condition.

As used herein, the term "reducing the risk of" refers to any method of reducing the risk of developing a disease, disorder, and/or condition in a subject who exhibits only early signs of the condition.

As used herein, an "effective amount" of a therapeutic agent, e.g. a compound of the invention, refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic, biologic or prophylactic effect. For example, an effective amount of a compound of the invention is that amount sufficient to treat a disease, disorder, or condition. In another aspect, an effective amount of a compound is that amount sufficient to prevent a disease, disorder, or condition. Combined with the teachings provided herein, by choosing among the various active compounds and weighing factors such as potency, relative bioavailability, patient body weight, severity of adverse side- effects and mode of administration, an effective prophylactic or therapeutic treatment regimen can be planned which does not cause substantial toxicity and yet is entirely effective to treat the subject. The effective amount for any particular application can vary depending on such factors as the condition being treated, the particular compounds being administered the size of the subject, or the severity of the condition.

As used herein, "subject" to which administration is contemplated includes, but is not limited to, humans (i.e., a male or female of any age group, e.g., a pediatric subject (e.g., infant, child, adolescent) or adult subject (e.g., young adult, middle-aged adult or senior adult)) and/or other primates (e.g., cynomolgus monkeys, rhesus monkeys); mammals, including commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs; and/or birds, including commercially relevant birds such as chickens, ducks, geese, quail, and/or turkeys.

As used herein, the term "sample" in the context of the present invention is any biological sample isolated from a subject. In one aspect, the sample is a tissue from a biopsy, including a liver biopsy sample. In one aspect, the sample is a blood sample, such as whole blood or peripheral blood mononuclear cells (PBMCs).

As used herein, "therapeutic agent" refers to any agent or compound that can be used to treat, prevent, ameliorate, lessen, or reduce at least one symptom of a disease or disorder, such as a lipoprotein related disorder (e.g., cholesterol related disorder), cardiovascular disease or disorder, or liver disease or disorder. The term "therapeutic agent" as used herein includes a compound of the invention. In one aspect, the term "therapeutic agent" means any compound or pharmaceutically acceptable salt that can be used to treat a disease or disorder described herein. In one aspect, the term "therapeutic agent" means only a compound of the invention.

As used herein, the term "lipoprotein" refers to an assembly that contains both protein and lipid. Lipoprotein includes, e.g., cholesterol, triglycerides, and ApoB (all relevant members to this set).

For the avoidance of doubt, the term "a compound of the invention" refers to a compound disclosed herein, e.g., a compound of the invention includes a compound of any of the formulae described herein or a compound in Table A. Whenever the term is used in the context of the present invention, it is to be understood that the reference is being made to both the free base and the corresponding salts, solvates (hydrates) and prodrugs, provided that such is possible and/or appropriate under the circumstances.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The pharmaceutically acceptable carrier or excipient does not destroy the pharmacological activity of the disclosed compound and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the compound. The use of such media and agents for pharmaceutically active substances is well known in the art.

Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions as disclosed herein is contemplated. Non-limiting examples of pharmaceutically acceptable carriers and excipients include sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as polyethylene glycol and propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate; coloring agents; releasing agents; coating agents; sweetening, flavoring and perfuming agents; preservatives; antioxidants; ion exchangers; alumina; aluminum stearate; lecithin; self-emulsifying drug delivery systems (SEDDS) such as d-atocopherol polyethyleneglycol 1000 succinate; surfactants used in pharmaceutical dosage forms such as Tweens or other similar polymeric delivery matrices; serum proteins such as human serum albumin; glycine; sorbic acid; potassium sorbate; partial glyceride mixtures of saturated vegetable fatty acids; water, salts or electrolytes such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, and zinc salts; colloidal silica; magnesium trisilicate; polyvinyl pyrrolidone; cellulose-based substances; polyacrylates; waxes; and polyethylene-polyoxypropylene-block polymers. Cyclodextrins such as α-, β-, and γ-cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl-cyclodextrins, or other solubilized derivatives can also be used to enhance delivery of compounds described herein.

As used herein, “a method of the invention” refers to any method described herein.

As used herein, “unsaturated” refers to compounds or structures having at least one degree of unsaturation (e.g., at least one double or triple bond).

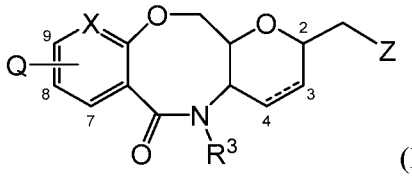
The term "modulating" as used herein means increasing or decreasing, e.g. activity, by a measurable amount.

As used herein, the term “reference profile” means an expression profile measured in samples obtained from subjects treated with vehicle and/or placebo.

As used herein, the term “metabolism” means catabolism and anabolism.

Compounds of the Invention

The invention relates to a compound of formula I:



(I),

or a pharmaceutically acceptable salt thereof, wherein:

X is CH or N;

Q is H, cyano, nitro, amino, $NR^QC(O)R^1$, $C(O)NR^QR^1$, $NR^QC(O)NR^{Q'}R^1$, or $NR^{1a}R^{1b}$;

R^1 is CH_3, unsubstituted or substituted phenyl, or unsubstituted or substituted pyridyl, wherein the substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

R^{1a} is H or unsubstituted C_1-C_3 alkyl;

R^{1b} is unsubstituted C_1-C_3 alkyl or $(CR^{1c}R^{1d})_{0-3}$-R^{1e};

R^{1e} is cyano, unsubstituted or substituted phenyl, unsubstituted or substituted pyridyl, or unsubstituted or substituted C_3-C_6 carbocyclyl, wherein the substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryll;

R^3 is H, CH_3, C_1-C_3 alkyl substituted with amino, methylamino, dimethylamino, or azido, or $(CR^{3a}R^{3b})_{1-3}$-O-$(CR^{3c}R^{3d})_{0-3}$-R^{3e};

R^{3e} is H or unsubstituted phenyl;

----- is a single or double bond;

Z is unsubstituted or substituted heteroaryl comprising one 5- or 6-membered ring and 1 to 4 heteroatoms selected from N, O, and S, $C(O)NR^ZR^{2'}$, $C(O)OR^2$, $NR^ZC(O)R^2$, $NR^ZC(O)OR^2$, $NR^ZS(O)_2R^2$, or $NR^{2a}R^{2b}$, wherein the substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido,

nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

R^2 is H, unsubstituted C_1-C_6 alkyl, C_1-C_6 alkyl substituted with halogen, $(CR^{2e}R^{2f})_{0-3}$-R^{2c}, or $(CR^{2e}R^{2f})_{1-3}$-R^{2g};

R^{2c} is unsubstituted phenyl, unsubstituted 2,3-dihydroindenyl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-membered rings and 1 to 4 heteroatoms selected from N, O, and S, unsubstituted or substituted C_3-C_6 carbocyclyl, or unsubstituted or substituted heterocyclyl comprising one or two 5- or 6-membered rings and 1 to 4 heteroatoms selected from N, O, and S, wherein the substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

R^{2g} is unsubstituted C_1-C_6 alkoxy or di-C_1-C_3 alkylamino;

$R^{2'}$ is unsubstituted C_1-C_3 alkyl or $(CR^{2e}R^{2f})_{0-3}$-R^{2d};

R^{2d} is unsubstituted phenyl, unsubstituted 2,3-dihydroindenyl, unsubstituted heteroaryl comprising one or two 5- or 6-membered rings and 1 to 4 heteroatoms selected from N, O, and S, or unsubstituted C_3-C_6 carbocyclyl;

R^{2a} and R^{2b} are each independently H, unsubstituted or substituted C_1-C_3 alkyl, or $(CR^{2e}R^{2f})_{1-3}$-R^{2c}, or R^{2a} and R^{2b}, together with the nitrogen atom to which they are attached, form a 5- to 7-membered ring, which is optionally substituted and optionally comprises 1 to 3 additional heteroatoms selected from N, O, and S, wherein the substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

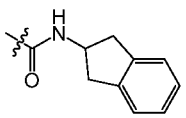
each R^{2e} and each R^{2f} are independently H, OH, methoxy, or unsubstituted C_1-C_3 alkyl;

each R^{1c}, each R^{1d}, each R^{3a}, each R^{3b}, each R^{3c}, and each R^{3d} are each independently H or unsubstituted C_1-C_3 alkyl; and

R^Q, $R^{Q'}$, and R^Z are each independently H or unsubstituted C_1-C_3 alkyl;

provided that:

when X is CH; Q is $NHC(O)R^1$; R^1 is 4-trifluoromethyl-phenyl; and R^3 is CH_3;

then Z is not  , or

when X is CH; Q is amino or nitro; and R^3 is CH_3; then Z is not $C(O)OCH_3$.

In one aspect, X is CH. In another aspect, X is N.

In one aspect, Q is bonded to the carbon atom at position 8 in formula I. In another aspect, Q is bonded to the carbon atom at position 9 in formula I.

In one aspect, Q is H.

In another aspect, Q is cyano, nitro, amino, $NR^QC(O)R^1$, $C(O)NR^QR^1$, $NR^QC(O)NR^{Q'}R^1$, or $NR^{1a}R^{1b}$.

In a further aspect, Q is cyano, nitro, or amino.

In another further aspect, Q is $NR^QC(O)R^1$, $C(O)NR^QR^1$, $NR^QC(O)NR^{Q'}R^1$, or $NR^{1a}R^{1b}$.

In a further aspect, Q is $NR^QC(O)R^1$ or $C(O)NR^QR^1$.

In a further aspect, Q is $NR^QC(O)R^1$. In a further aspect Q is $NHC(O)R^1$. In another further aspect, Q is $NCH_3C(O)R^1$.

In another further aspect, Q is $C(O)NR^QR^1$. In a further aspect Q is $C(O)NHR^1$. In another further aspect, Q is $C(O)NCH_3R^1$.

In another further aspect, Q is $NR^{1a}R^{1b}$. In a further aspect, Q is NHR^{1b}. In another further aspect, Q is NCH_3R^{1b}.

In another further aspect, Q is $NR^QC(O)NR^{Q'}R^1$. In a further aspect, Q is $NHC(O)NHR^1$.

In one aspect, R^Q is H. In another aspect R^Q is unsubstituted C_1-C_3 alkyl (*e.g.*, methyl, ethyl, propyl, and *iso*-propyl). In a further aspect, R^Q is methyl.

In one aspect, $R^{Q'}$ is H. In another aspect $R^{Q'}$ is unsubstituted C_1-C_3 alkyl (*e.g.*, methyl, ethyl, propyl, and *iso*-propyl). In a further aspect, $R^{Q'}$ is methyl.

In one aspect, R^1 is CH_3.

In another aspect, R^1 is unsubstituted phenyl. In another aspect, R^1 is phenyl substituted with one or more substituents, each of which is independently selected from unsubstituted C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, and hexyl), C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, and hexyl) substituted with halogen (*e.g.*, F, Cl, Br, and I), halogen (*e.g.*, F, Cl, Br, and I), cyano, unsubstituted C_1-C_6 alkoxy (*e.g.*, methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy, and *tert*-butoxy), and C_1-C_6 alkoxy (*e.g.*, methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy, and *tert*-butoxy) substituted with halogen (*e.g.*, F, Cl, Br, and I). In a further aspect, R^1 is phenyl substituted with one or more substituents, each of which is independently selected from methyl, trifluoromethyl, *iso*-propyl, methoxy, F, Cl, and cyano.

In a further aspect, R^1 is phenyl substituted with trifluoromethyl. In a further aspect, R^1 is phenyl substituted with 4-trifluoromethyl.

In another aspect, R^1 is unsubstituted pyridyl. In another aspect, R^1 is pyridyl substituted with one or more substituents, each of which is independently selected from unsubstituted C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, and hexyl), C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, and hexyl) substituted with halogen (*e.g.*, F, Cl, Br, and I), halogen (*e.g.*, F, Cl, Br, and I), cyano, unsubstituted C_1-C_6 alkoxy (*e.g.*, methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy, and *tert*-butoxy), and C_1-C_6 alkoxy (*e.g.*, methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy, and *tert*-butoxy) substituted with halogen (*e.g.*, F, Cl, Br, and I). In a further aspect, R^1 is pyridyl substituted with trifluoromethyl.

In one aspect, R^{1a} is H. In another aspect R^{1a} is unsubstituted C_1-C_3 alkyl (*e.g.*, methyl, ethyl, propyl, and *iso*-propyl). In a further aspect, R^{1a} is methyl.

In one aspect, R^{1b} unsubstituted C_1-C_3 alkyl (*e.g.*, methyl, ethyl, propyl, and *iso*-propyl). In a further aspect, R^{1b} is methyl.

In another aspect, R^{1b} is $(CR^{1c}R^{1d})_{0-3}$-R^{1e}. In a further aspect, R^{1b} is R^{1e}. In another further aspect, R^{1b} is $(CR^{1c}R^{1d})_1$-R^{1e}. In another further aspect, R^{1b} is $(CR^{1c}R^{1d})_2$-R^{1e}. In another further aspect, R^{1b} is $(CR^{1c}R^{1d})_3$-R^{1e}.

In one aspect, each R^{1c} and each R^{1d} are H. In another aspect, each R^{1c} is H, and at least one R^{1d} is unsubstituted C_1-C_3 alkyl (*e.g.*, methyl, ethyl, propyl, and *iso*-propyl). In another aspect, at least one R^{1c} and at least one R^{1d} are independently unsubstituted C_1-C_3 alkyl (*e.g.*, methyl, ethyl, propyl, and *iso*-propyl).

In one aspect, R^{1e} is cyano.

In another aspect, R^{1e} is unsubstituted phenyl. In another aspect, R^{1e} is phenyl substituted with one or more substituents, each of which is independently selected from unsubstituted C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, and hexyl), C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, and hexyl) substituted with halogen (*e.g.*, F, Cl, Br, and I), halogen (*e.g.*, F, Cl, Br, and I), cyano, unsubstituted C_1-C_6 alkoxy (*e.g.*, methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy, and *tert*-butoxy), and C_1-C_6 alkoxy (*e.g.*, methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy, and *tert*-butoxy) substituted with halogen (*e.g.*, F, Cl, Br, and I). In a further aspect, R^{1e} is phenyl substituted with one or more substituents, each of which is independently selected from methyl, trifluoromethyl, *iso*-propyl, methoxy, F, Cl, and cyano.

In another aspect, R^{1e} is unsubstituted pyridyl. In another aspect, R^{1e} is pyridyl substituted with one or more substituents, each of which is independently selected from unsubstituted C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, and hexyl), C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, and hexyl) substituted with halogen (*e.g.*, F, Cl, Br, and I), halogen (*e.g.*, F, Cl, Br, and I), cyano, unsubstituted C_1-C_6 alkoxy (*e.g.*, methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy, and *tert*-butoxy), and C_1-C_6 alkoxy (*e.g.*, methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy, and *tert*-butoxy) substituted with halogen (*e.g.*, F, Cl, Br, and I).

In another aspect, R^{1e} is unsubstituted C_3-C_6 carbocyclyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl). In a further aspect, R^{1e} is unsubstituted cyclohexyl.

In another aspect, R^{1e} is C_3-C_6 carbocyclyl substituted with one or more substituents, each of which is independently selected from unsubstituted C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, and hexyl), C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, and hexyl) substituted with halogen (*e.g.*, F, Cl, Br, and I), halogen (*e.g.*, F, Cl, Br, and I), cyano, unsubstituted C_1-C_6 alkoxy (*e.g.*, methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy, and *tert*-butoxy), and C_1-C_6 alkoxy (*e.g.*, methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy, and *tert*-butoxy) substituted with halogen (*e.g.*, F, Cl, Br, and I).

In one aspect, R^3 is H.

In another aspect, R^3 is CH_3, C_1-C_3 alkyl substituted with amino, methylamino, dimethylamino, or azido, or $(CR^{3a}R^{3b})_{1-3}$-O-$(CR^{3c}R^{3d})_{0-3}$-R^{3e}.

In a further aspect, R^3 is CH_3.

In another further aspect, R^3 is C_1-C_3 alkyl (*e.g.*, methyl, ethyl, propyl, and *iso*-propyl) substituted with amino, methylamino, dimethylamino, or azido. In a further embodiment, R^3 is ethyl substituted with amino, methylamino, dimethylamino, or azido.

In another further aspect, R^3 is $(CR^{3a}R^{3b})_{1-3}$-O-$(CR^{3c}R^{3d})_{0-3}$-R^{3e}. In a further aspect, R^3 is $(CR^{3a}R^{3b})$-O-$(CR^{3c}R^{3d})_{0-3}$-R^{3e}. In another further aspect, R^3 is $(CR^{3a}R^{3b})_2$-O-$(CR^{3c}R^{3d})_{0-3}$-R^{3e}. In another further aspect, R^3 is $(CR^{3a}R^{3b})_3$-O-$(CR^{3c}R^{3d})_{0-3}$-R^{3e}. In another further aspect, R^3 is $(CR^{3a}R^{3b})_{1-3}$-O-R^{3e}. In another further aspect, R^3 is $(CR^{3a}R^{3b})_{1-3}$-O-$(CR^{3c}R^{3d})$-R^{3e}. In another further aspect, R^3 is $(CR^{3a}R^{3b})_{1-3}$-O-$(CR^{3c}R^{3d})_2$-R^{3e}. In another further aspect, R^3 is $(CR^{3a}R^{3b})_{1-3}$-O-$(CR^{3c}R^{3d})_3$-R^{3e}. In another further aspect, R^3 is $(CR^{3a}R^{3b})$-O-$(CR^{3c}R^{3d})$-R^{3e}. In another further aspect, R^3 is $(CR^{3a}R^{3b})_2$-O-$(CR^{3c}R^{3d})$-R^{3e}.

In one aspect, each R^{3a}, each R^{3b}, each R^{3c}, and each R^{3d} are H. In another aspect, each R^{3a}, each R^{3b}, and each R^{3c} are H, and at least one R^{3d} is unsubstituted C_1-C_3 alkyl (*e.g.*,

methyl, ethyl, propyl, and *iso*-propyl). In another aspect, each R^{3a}, each R^{3c}, and each R^{3d} are H, and at least one R^{3b} is unsubstituted C_1-C_3 alkyl (*e.g.*, methyl, ethyl, propyl, and *iso*-propyl). In another aspect, each R^{3a} and each R^{3b} are H, and at least one R^{3c} and at least one R^{3d} are independently unsubstituted C_1-C_3 alkyl (*e.g.*, methyl, ethyl, propyl, and *iso*-propyl). In another aspect, each R^{3c} and each R^{3d} are H, and at least one R^{3a} and at least one R^{3b} are independently unsubstituted C_1-C_3 alkyl (*e.g.*, methyl, ethyl, propyl, and *iso*-propyl).

In one aspect, R^{3e} is H. In another aspect, R^{3e} is unsubstituted phenyl.

In one aspect, ----- is a single bond. In another aspect, ----- is a double bond.

In one aspect, Z is unsubstituted heteroaryl. In another aspect, Z is heteroaryl substituted with one or more substituents, each of which is independently selected from unsubstituted C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, and hexyl), C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, and hexyl) substituted with halogen (*e.g.*, F, Cl, Br, and I), halogen (*e.g.*, F, Cl, Br, and I), cyano, unsubstituted C_1-C_6 alkoxy (*e.g.*, methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy, and *tert*-butoxy), C_1-C_6 alkoxy (*e.g.*, methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy, and *tert*-butoxy) substituted with halogen (*e.g.*, F, Cl, Br, and I), amino, and $NR^tR^{t'}$, wherein R^t is unsubstituted C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, and hexyl) or unsubstituted C_3-C_6 carbocyclyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl) and $R^{t'}$ is H or unsubstituted C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, and hexyl).

In a further aspect, Z is heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, pyridyl, and pyrimidinyl. In a further aspect, Z is oxadiazolyl.

In another aspect, Z is $C(O)NR^ZR^{2'}$, $C(O)OR^2$, $NR^ZC(O)R^2$, $NR^ZC(O)OR^2$, $NR^ZS(O)_2R^2$, or $NR^{2a}R^{2b}$.

In a further aspect, Z is $NR^ZC(O)OR^2$ or $NR^ZS(O)_2R^2$.

In a further aspect, Z is $NR^ZC(O)OR^2$.

In another further aspect, Z is $C(O)NR^ZR^{2'}$, $C(O)OR^2$, $NR^ZC(O)R^2$, or $NR^{2a}R^{2b}$.

In a further aspect, Z is $C(O)NR^ZR^{2'}$ or $NR^ZC(O)R^2$. In a further aspect, Z is $C(O)NR^ZR^{2'}$. In another further aspect, Z is $NR^ZC(O)R^2$.

In another further aspect, Z is $C(O)OR^2$.

In another further aspect, Z is $NR^{2a}R^{2b}$.

In one aspect, R^Z is H. In another aspect R^Z is unsubstituted C_1-C_3 alkyl (*e.g.*, methyl, ethyl, propyl, and *iso*-propyl). In a further aspect, R^Z is methyl.

In one aspect, R^2 is H.

In another aspect, R^2 is unsubstituted C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, and hexyl). In a further aspect, R^2 is unsubstituted methyl, *iso*-butyl, or *tert*-butyl. In another aspect, R^2 is C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, and hexyl) substituted with halogen (*e.g.*, F, Cl, Br, and I).

In another aspect, R^2 is $(CR^{2e}R^{2f})_{0-3}$-R^{2c}. In a further aspect, R^2 is R^{2c}. In a further aspect, R^2 is $(CR^{2e}R^{2f})$-R^{2c}. In another further aspect, R^2 is $(CR^{2e}R^{2f})_2$-R^{2c}. In a further aspect, R^2 is $(CR^{2e}R^{2f})_3$-R^{2c}.

In another aspect, R^2 is $(CR^{2e}R^{2f})_{1-3}$-R^{2g}. In a further aspect, R^2 is $(CR^{2e}R^{2f})$-R^{2g}. In another further aspect, R^2 is $(CR^{2e}R^{2f})_2$-R^{2g}. In a further aspect, R^2 is $(CR^{2e}R^{2f})_3$-R^{2g}.

In one aspect, $R^{2'}$ is unsubstituted C_1-C_3 alkyl (*e.g.*, methyl, ethyl, propyl, and *iso*-propyl). In a further aspect, $R^{2'}$ is *iso*-propyl.

In another aspect, $R^{2'}$ is $(CR^{2e}R^{2f})_{0-3}$-R^{2d}. In a further aspect, $R^{2'}$ is R^{2d}. In another further aspect, $R^{2'}$ is $(CR^{2e}R^{2f})$-R^{2d}. In another further aspect, $R^{2'}$ is $(CR^{2e}R^{2f})_2$-R^{2d}. In another further aspect, $R^{2'}$ is $(CR^{2e}R^{2f})_3$-R^{2d}.

In one aspect, R^{2c} is unsubstituted C_1-C_6 alkoxy (*e.g.*, methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy, and *tert*-butoxy), or di-C_1-C_3 alkylamino (*e.g.*, dimethylamino, diethylamino, and dipropylamino). In a further aspect, R^{2c} is methoxy, *iso*-propoxy, or *tert*-butoxy. In another further aspect, R^{2c} is diethylamino.

In another aspect, R^{2c} is unsubstituted phenyl.

In another aspect, R^{2c} is unsubstituted 2,3-dihydroindenyl.

In another aspect, R^{2c} is unsubstituted heteroaryl. In another aspect, R^{2c} is heteroaryl substituted with one or more substituents, each of which is independently selected from unsubstituted C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, and hexyl), C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, and hexyl) substituted with halogen (*e.g.*, F, Cl, Br, and I), halogen (*e.g.*, F, Cl, Br, and I), cyano, unsubstituted C_1-C_6 alkoxy (*e.g.*, methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy, and *tert*-butoxy), C_1-C_6 alkoxy (*e.g.*, methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy, and *tert*-butoxy) substituted with halogen (*e.g.*, F, Cl, Br, and I), C(O)-C_1-C_6 alkyl, C(O)O-C_1-C_6 alkyl, and C_3-C_6 carbocyclyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl).

In a further aspect, R^{2c} is heteroaryl selected from pyrrolyl, furanyl, thienyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyrazolyl, oxazolyl, oxadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinolinyl, isoquinolinyl, naphthrydinyl, indolyl, and purinyl. In a further aspect, R^{2c} is oxazolyl or oxadiazolyl.

In another aspect, R^{2c} is unsubstituted C_3-C_6 carbocyclyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl). In another aspect, R^{2c} is C_3-C_6 carbocyclyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl) substituted with one or more substituents, each of which is independently selected from unsubstituted C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, and hexyl), C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, and hexyl) substituted with halogen (*e.g.*, F, Cl, Br, and I), halogen (*e.g.*, F, Cl, Br, and I), cyano, unsubstituted C_1-C_6 alkoxy (*e.g.*, methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy, and *tert*-butoxy), C_1-C_6 alkoxy (*e.g.*, methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy, and *tert*-butoxy) substituted with halogen (*e.g.*, F, Cl, Br, and I), C(O)-C_1-C_6 alkyl, and C(O)O-C_1-C_6 alkyl. In a further aspect, R^{2c} is cyclopropyl or cyclopentyl.

In another aspect, R^{2c} is unsubstituted heterocyclyl. In another aspect, R^{2c} is heterocyclyl substituted with one or more substituents, each of which is independently selected from unsubstituted C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, and hexyl), C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, and hexyl) substituted with halogen (*e.g.*, F, Cl, Br, and I), halogen (*e.g.*, F, Cl, Br, and I), cyano, unsubstituted C_1-C_6 alkoxy (*e.g.*, methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy, and *tert*-butoxy), C_1-C_6 alkoxy (*e.g.*, methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy, and tert-butoxy) substituted with halogen (*e.g.*, F, Cl, Br, and I), C(O)-C_1-C_6 alkyl, and C(O)O-C_1-C_6 alkyl.

In a further aspect, R^{2c} is heterocyclyl selected from azetidinyl, pyrrolidinyl, pyrrolidinonyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahyrofuranyl, piperidinyl, piperazinyl, morpholinyl, oxetanyl, and oxathianyl-dioxide. In a further aspect, R^{2c} is heterocyclyl selected from azetidinyl, pyrrolidinyl, pyrrolidinonyl, tetrahydrofuranyl, oxetanyl, and oxathianyl-dioxide.

In one aspect, R^{2d} is unsubstituted phenyl.

In another aspect, R^{2d} is unsubstituted 2,3-dihydroindenyl.

In another aspect, R^{2d} is unsubstituted heteroaryl selected from pyrrolyl, furanyl, thienyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyrazolyl, oxazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinolinyl, isoquinolinyl, naphthrydinyl, indolyl, purinyl, and

benzoimidazolyl. In a further aspect, R^{2d} is unsubstituted heteroaryl selected from pyridyl, indolyl, benzoimidazolyl.

In another aspect, R^{2d} is unsubstituted C_3-C_6 carbocyclyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl). In a further aspect, R^{2d} is unsubstituted cyclopentyl.

In one aspect, each R^{2e} and each R^{2f} are H. In another aspect, each R^{2e} is H, and at least one R^{2f} is OH, methxoxy, or unsubstituted C_1-C_3 alkyl (*e.g.*, methyl, ethyl, propyl, and *iso*-propyl). In a further aspect, each R^{2e} is H, and at least one R^{2f} is OH. In another further aspect, each R^{2e} is H, and at least one R^{2f} is methoxy. In another further aspect, each R^{2e} is H, and at least one R^{2f} is unsubstituted C_1-C_3 alkyl (*e.g.*, methyl, ethyl, propyl, and *iso*-propyl). In another aspect, at least one R^{2e} is OH or methoxy, and at least one R^{2f} is unsubstituted C_1-C_3 alkyl (*e.g.*, methyl, ethyl, propyl, and *iso*-propyl). In a further aspect, at least one R^{2e} is OH or methoxy, and at least one R^{2f} is methyl.

In one aspect, R^{2a} and R^{2b} are each H.

In another aspect, one of R^{2a} and R^{2b} is H, and the other is unsubstituted or substituted C_1-C_3 alkyl or $(CR^{2e}R^{2f})_{1\text{-}3}$-$R^{2c}$. Optional substituents can be selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl. In a further aspect, one of R^{2a} and R^{2b} is H, and the other is unsubstituted or substituted C_1-C_3 alkyl. In a further aspect, one of R^{2a} and R^{2b} is H, and the other is $(CR^{2e}R^{2f})$-R^{2c}. In another further aspect, one of R^{2a} and R^{2b} is H, and the other is $(CR^{2e}R^{2f})_2$-R^{2c}. In another further aspect, one of R^{2a} and R^{2b} is H, and the other is $(CR^{2e}R^{2f})_3$-R^{2c}.

In another aspect, one of R^{2a} and R^{2b} is unsubstituted or substituted C_1-C_3 alkyl, and the other is $(CR^{2e}R^{2f})_{1\text{-}3}$-$R^{2c}$. In a further aspect, one of R^{2a} and R^{2b} is unsubstituted or substituted C_1-C_3 alkyl, and the other is $(CR^{2e}R^{2f})$-R^{2c}. In another further aspect, one of R^{2a} and R^{2b} is unsubstituted or substituted C_1-C_3 alkyl, and the other is $(CR^{2e}R^{2f})_2$-R^{2c}. In another further aspect, one of R^{2a} and R^{2b} is unsubstituted or substituted C_1-C_3 alkyl, and the other is $(CR^{2e}R^{2f})_3$-R^{2c}.

In one aspect, Q is bonded to the carbon atom at position 8 in formula I, and is $NR^QC(O)R^1$; R^Q is H; and Z is $C(O)NR^ZR^{2'}$. In a further aspect, R^1 is substituted phenyl. In a further aspect, R^1 is phenyl substituted with trifluoromethyl. In a further aspect, R^1 is phenyl substituted with 4-trifluoromethyl. In another further aspect, R^1 is substituted pyridyl. In a further aspect, R^1 is pyridyl substituted with trifluoromethyl.

In one aspect, Q is bonded to the carbon atom at position 8 in formula I, and is $NR^QC(O)R^1$; R^Q is H; and Z is $C(O)NR^ZR^{2'}$. In a further aspect, $R^{2'}$ is R^{2d}. In a further aspect, R^{2d} is unsubstituted 2,3-dihydroindenyl, unsubstituted heteroaryl, or unsubstituted C_3-C_6 carbocyclyl. In a further aspect, R^Z is H.

In one aspect, Q is bonded to the carbon atom at position 8 in formula I, and is $NR^QC(O)R^1$; R^Q is H; Z is $C(O)NR^ZR^{2'}$; X is CH; and R^3 is CH_3.

In one aspect, Q is bonded to the carbon atom at position 8 in formula I, and is $NR^QC(O)R^1$; R^Q is H; Z is $C(O)NR^ZR^{2'}$; X is N; and R^3 is CH_3.

In one aspect, Q is bonded to the carbon atom at position 8 in formula I, and is $NR^{1a}R^{1b}$; R^{1b} is $(CR^{1c}R^{1d})$-R^{1e}; and Z is $C(O)NR^ZR^{2'}$. In a further aspect, R^{1e} is substituted phenyl. In a further aspect, R^{1e} is phenyl substituted with trifluoromethyl. In a further aspect, R^{1e} is phenyl substituted with 4-trifluoromethyl.

In one aspect, Q is bonded to the carbon atom at position 8 in formula I, and is $NR^{1a}R^{1b}$; R^{1b} is $(CR^{1c}R^{1d})$-R^{1e}; and Z is $C(O)NR^ZR^{2'}$. In a further aspect, $R^{2'}$ is R^{2d}. In a further aspect, R^{2d} is unsubstituted 2,3-dihydroindenyl.

In one aspect, Q is bonded to the carbon atom at position 8 in formula I, and is $NR^{1a}R^{1b}$; R^{1b} is $(CR^{1c}R^{1d})$-R^{1e}; Z is $C(O)NR^ZR^{2'}$; X is CH; and R^3 is CH_3.

In one aspect, Q is bonded to the carbon atom at position 8 in formula I, and is $NR^QC(O)R^1$; R^Q is H; and Z is $NR^ZC(O)R^2$. In a further aspect, R^1 is substituted phenyl. In a further aspect, R^1 is phenyl substituted with trifluoromethyl. In a further aspect, R^1 is phenyl substituted with 4-trifluoromethyl.

In one aspect, Q is bonded to the carbon atom at position 8 in formula I, and is $NR^QC(O)R^1$; R^Q is H; and Z is $NR^ZC(O)R^2$. In a further aspect, R^2 is unsubstituted or substituted C_1-C_6 alkyl or $(CR^{2e}R^{2f})_{1\text{-}3}$-$R^{2c}$. In a further aspect, R^2 is unsubstituted or substituted C_1-C_6 alkyl. In a further aspect, R^2 is $(CR^{2e}R^{2f})$-R^{2c}; and R^{2c} is unsubstituted 2,3-dihydroindenyl, or unsubstituted or substituted C_3-C_6 carbocyclyl. In a further aspect, R^Z is H. Optional substituents can be selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl. In one aspect, Q is bonded to the carbon atom at position 8 in formula I, and is $NR^QC(O)R^1$; R^Q is H; Z is $NR^ZC(O)R^2$; X is CH; and R^3 is CH_3.

In one aspect, Q is bonded to the carbon atom at position 8 in formula I, and is $NR^{1a}R^{1b}$; R^{1b} is $(CR^{1c}R^{1d})$-R^{1e}; and Z is $NR^ZC(O)R^2$. In a further aspect, R^{1e} is substituted

phenyl. In a further aspect, R^{1e} is phenyl substituted with trifluoromethyl. In a further aspect, R^{1e} is phenyl substituted with 4-trifluoromethyl.

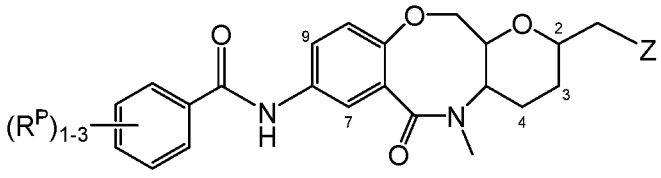
In one aspect, Q is bonded to the carbon atom at position 8 in formula I, and is $NR^{1a}R^{1b}$; R^{1b} is $(CR^{1c}R^{1d})$-R^{1e}; and Z is $NR^ZC(O)R^2$. In a further aspect, R^2 is unsubstituted or substituted C_1-C_6 alkyl or $(CR^{2e}R^{2f})_{1-3}$-R^{2c}. In a further aspect, R^2 is unsubstituted or substituted C_1-C_6 alkyl. In a further aspect, R^2 is $(CR^{2e}R^{2f})$-R^{2c}; and R^{2c} is unsubstituted 2,3-dihydroindenyl, or unsubstituted or substituted C_3-C_6 carbocyclyl. In a further aspect, R^Z is H. Optional substituents can be selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl.

In one aspect, Q is bonded to the carbon atom at position 8 in formula I, and is $NR^{1a}R^{1b}$; R^{1b} is $(CR^{1c}R^{1d})$-R^{1e}; Z is $NR^ZC(O)R^2$; X is CH; and R^3 is CH_3.

In one aspect, Q is bonded to the carbon atom at position 8 in formula I, and is $NR^QC(O)R^1$; R^Q is H; and Z is $NR^ZC(O)OR^2$. In a further aspect, R^1 is substituted phenyl. In a further aspect, R^1 is phenyl substituted with trifluoromethyl. In a further aspect, R^1 is phenyl substituted with 4-trifluoromethyl.

In one aspect, Q is bonded to the carbon atom at position 8 in formula I, and is $NR^QC(O)R^1$; R^Q is H; and Z is $NR^ZC(O)OR^2$. In a further aspect, R^2 is unsubstituted or substituted C_1-C_6 alkyl or $(CR^{2e}R^{2f})_{1-3}$-R^{2c}. In a further aspect, R^2 is unsubstituted or substituted C_1-C_6 alkyl. In a further aspect, R^2 is $(CR^{2e}R^{2f})$-R^{2c}; and R^{2c} is unsubstituted 2,3-dihydroindenyl, or unsubstituted or substituted C_3-C_6 carbocyclyl. In a further aspect, R^Z is H. Optional substituents can be selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl. In one aspect, Q is bonded to the carbon atom at position 8 in formula I, and is $NR^QC(O)R^1$; R^Q is H; Z is $NR^ZC(O)OR^2$; X is CH; and R^3 is CH_3.

In one aspect, the invention provides a compound of formula II:



(II),

or pharmaceutically acceptable salt thereof, wherein:

each R^P is independently unsubstituted or substituted C_1-C_3 alkyl, unsubstituted or substituted C_1-C_3 alkoxy, halogen, or cyano, where optional substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

Z is unsubstituted or substituted heteroaryl comprising one 5- or 6-membered ring and 1 to 4 heteroatoms selected from N, O, and S, $C(O)NR^ZR^{2'}$, $C(O)OR^2$, $NR^ZC(O)R^2$, $NR^ZC(O)OR^2$, $NR^ZS(O)_2R^2$, or $NR^{2a}R^{2b}$, where optional substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

R^2 is H, unsubstituted C_1-C_6 alkyl, C_1-C_6 alkyl substituted with halogen, $(CR^{2e}R^{2f})_{0-3}$-R^{2c}, or $(CR^{2e}R^{2f})_{1-3}$-R^{2g};

R^{2c} is unsubstituted phenyl, unsubstituted 2,3-dihydroindenyl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-membered rings and 1 to 4 heteroatoms selected from N, O, and S, unsubstituted or substituted C_3-C_6 carbocyclyl, or unsubstituted or substituted heterocyclyl comprising one or two 5- or 6-membered rings and 1 to 4 heteroatoms selected from N, O, and S, where optional substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

R^{2g} is unsubstituted C_1-C_6 alkoxy or di-C_1-C_3 alkylamino;

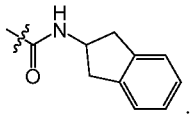
$R^{2'}$ is unsubstituted C_1-C_3 alkyl or $(CR^{2e}R^{2f})_{0-3}$-R^{2d};

R^{2d} is unsubstituted phenyl, unsubstituted 2,3-dihydroindenyl, unsubstituted heteroaryl comprising one or two 5- or 6-membered rings and 1 to 4 heteroatoms selected from N, O, and S, or unsubstituted C_3-C_6 carbocyclyl;

R^{2a} and R^{2b} are each independently H, unsubstituted or substituted C_1-C_3 alkyl, or $(CR^{2e}R^{2f})_{1-3}$-R^{2c}, or R^{2a} and R^{2b}, together with the nitrogen atom to which they are attached, form a 5- to 7-membered ring, which is optionally substituted and optionally comprises 1 to 3 additional heteroatoms selected from N, O, and S, where optional substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

each R^{2e} and each R^{2f} are independently H, OH, methoxy, or unsubstituted C_1-C_3 alkyl; and

R^Z is H or unsubstituted C_1-C_3 alkyl;

provided that when R^P is 4-trifluoromethyl, then Z is not  .

Each of the variables in formula II can be selected from any of the substituents or chemical moieties defined or illustrated for the corresponding variables in formula I, provided that these substituents or chemical moieties do not go beyond the definition of each of the variables in formula II.

In one aspect, each R^P is independently halogen, cyano, or unsubstituted C_1-C_3 alkyl (*e.g.*, methyl, ethyl, propyl, and *iso*-propyl). In another aspect, each R^P is halogen, cyano, or C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, and *iso*-propyl) substituted with halogen (*e.g.*, F, Cl, Br, and I).

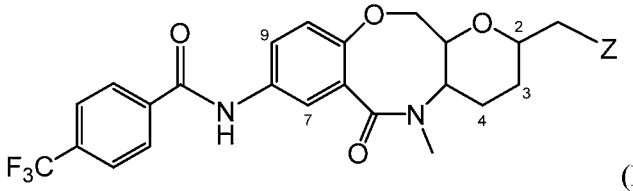
In one aspect, at least one R^P is trifluoromethyl.

In another aspect, each R^P is independently halogen, cyano, or unsubstituted C_1-C_3 alkoxy (*e.g.*, methoxy, ethoxy, propoxy, and *iso*-propoxy). In another aspect, each R^P is halogen, cyano, or C_1-C_6 alkyl (*e.g.*, methoxy, ethoxy, propoxy, and *iso*-propoxy) substituted with halogen (*e.g.*, F, Cl, Br, and I).

In one aspect, at least one R^P is methoxy.

In one aspect, at least one R^P is at the para-position of the phenyl ring.

In one aspect, the invention provides a compound of formula IIa:



(IIa),

or pharmaceutically acceptable salt thereof, wherein:

Z is unsubstituted or substituted heteroaryl comprising one 5- or 6-membered ring and 1 to 4 heteroatoms selected from N, O, and S, $C(O)NR^ZR^{2'}$, $C(O)OR^2$, $NR^ZC(O)R^2$, $NR^ZC(O)OR^2$, $NR^ZS(O)_2R^2$, or $NR^{2a}R^{2b}$where optional substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

R^2 is H, unsubstituted C_1-C_6 alkyl, C_1-C_6 alkyl substituted with halogen, $(CR^{2e}R^{2f})_{0-3}$-R^{2c}, or $(CR^{2e}R^{2f})_{1-3}$-R^{2g};

R^{2c} is unsubstituted phenyl, unsubstituted 2,3-dihydroindenyl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-membered rings and 1 to 4 heteroatoms selected from N, O, and S, unsubstituted or substituted C_3-C_6 carbocyclyl, or unsubstituted or substituted heterocyclyl comprising one or two 5- or 6-membered rings and 1 to 4 heteroatoms selected from N, O, and S, where optional substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

R^{2g} is unsubstituted C_1-C_6 alkoxy or di-C_1-C_3 alkylamino;

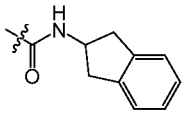
$R^{2'}$ is unsubstituted C_1-C_3 alkyl or $(CR^{2e}R^{2f})_{0-3}$-R^{2d};

R^{2d} is unsubstituted phenyl, unsubstituted 2,3-dihydroindenyl, unsubstituted heteroaryl comprising one or two 5- or 6-membered rings and 1 to 4 heteroatoms selected from N, O, and S, or unsubstituted C_3-C_6 carbocyclyl;

R^{2a} and R^{2b} are each independently H, unsubstituted or substituted C_1-C_3 alkyl, or $(CR^{2e}R^{2f})_{1-3}$-R^{2c}, or R^{2a} and R^{2b}, together with the nitrogen atom to which they are attached, form a 5- to 7-membered ring, which is optionally substituted and optionally comprises 1 to 3 additional heteroatoms selected from N, O, and S, where optional substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

each R^{2e} and each R^{2f} are each independently H, OH, methoxy, or unsubstituted C_1-C_3 alkyl; and

R^Z is H or unsubstituted C_1-C_3 alkyl;

provided that Z is not 

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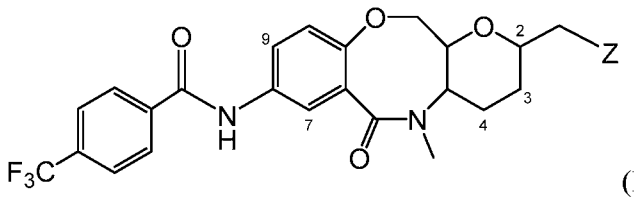
Each of the variables in formula IIa can be selected from any of the substituents or chemical moieties defined or illustrated for the corresponding variables in formula I, provided that these substituents or chemical moieties do not go beyond the definition of each of the variables in formula IIa.

In one aspect, the invention provides a compound of formula IIb:



(IIb),

or pharmaceutically acceptable salt thereof, wherein:

Z is $NR^ZC(O)R^2$, $NR^ZC(O)OR^2$, or $NR^{2a}R^{2b}$;

R^2 is H, unsubstituted C_1-C_6 alkyl, C_1-C_6 alkyl substituted with halogen, $(CR^{2e}R^{2f})_{0-3}$-R^{2c}, or $(CR^{2e}R^{2f})_{1-3}$-R^{2g};

R^{2c} is unsubstituted phenyl, unsubstituted 2,3-dihydroindenyl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-membered rings and 1 to 4 heteroatoms selected from N, O, and S, unsubstituted or substituted C_3-C_6 carbocyclyl, or unsubstituted or substituted heterocyclyl comprising one or two 5- or 6-membered rings and 1 to 4 heteroatoms selected from N, O, and S, where optional substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

R^{2g} is unsubstituted C_1-C_6 alkoxy or di-C_1-C_3 alkylamino;

R^{2a} and R^{2b} are each independently H, unsubstituted or substituted C_1-C_3 alkyl, or $(CR^{2e}R^{2f})_{1-3}$-R^{2c}, or R^{2a} and R^{2b}, together with the nitrogen atom to which they are attached, form a 5- to 7-membered ring, which is optionally substituted and optionally comprises 1 to 3 additional heteroatoms selected from N, O, and S, where optional substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

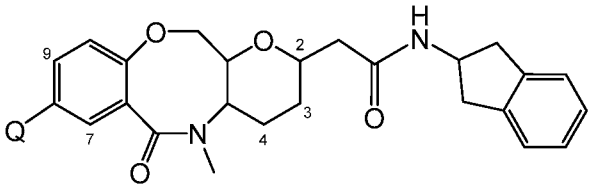
R^{2e} and R^{2f} are each independently H, OH, methoxy, or unsubstituted C_1-C_3 alkyl; and

R^Z is H or unsubstituted C_1-C_3 alkyl.

Each of the variables in formula IIb can be selected from any of the substituents or chemical moieties defined or illustrated for the corresponding variables in formula I, provided that these substituents or chemical moieties do not go beyond the definition of each of the variables in formula IIb.

In one aspect, Z is $NR^ZC(O)R^2$ or $NR^ZC(O)OR^2$. In a further aspect, Z is $NR^ZC(O)R^2$.

In one aspect, the invention provides a compound of formula III:



(III),

or pharmaceutically acceptable salt thereof, wherein:

Q is $NR^QC(O)R^1$, $C(O)NR^QR^1$, $NR^QC(O)NR^{Q'}R^1$, or $NR^{1a}R^{1b}$;

R^1 is CH_3, unsubstituted or substituted phenyl, or unsubstituted or substituted pyridyl, where optional substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

R^{1a} is H or unsubstituted C_1-C_3 alkyl;

R^{1b} is unsubstituted C_1-C_3 alkyl or $(CR^{1c}R^{1d})_{0-3}$-R^{1e};

R^{1e} is cyano, unsubstituted or substituted phenyl, unsubstituted or substituted pyridyl, or unsubstituted or substituted C_3-C_6 carbocyclyl, where optional substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

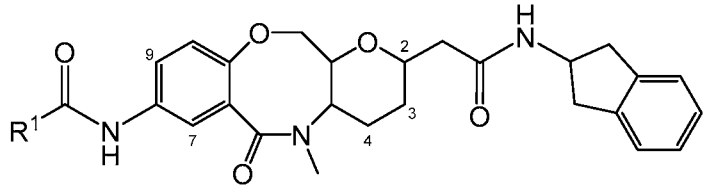
each R^{1c} and each R^{1d} are independently H or unsubstituted C_1-C_3 alkyl; and

R^Q and $R^{Q'}$ are each independently H or unsubstituted C_1-C_3 alkyl;

provided that when Q is $NHC(O)R^1$, then R^1 is not 4-trifluoromethyl-phenyl.

Each of the variables in formula III can be selected from any of the substituents or chemical moieties defined or illustrated for the corresponding variables in formula I, provided that these substituents or chemical moieties do not go beyond the definition of each of the variables in formula III.

In one aspect, the invention provides a compound of formula IIIa:



(IIIa),

or pharmaceutically acceptable salt thereof, wherein:

R^1 is CH_3, unsubstituted or substituted phenyl, or unsubstituted or substituted pyridyl, where optional substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl,

alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

provided that R^1 is not 4-trifluoromethyl-phenyl.

Each of the variables in formula IIIa can be selected from any of the substituents or chemical moieties defined or illustrated for the corresponding variables in formula I, provided that these substituents or chemical moieties do not go beyond the definition of each of the variables in formula IIIa.

The invention relates to a compound in Table A or a pharmaceutically acceptable salt thereof.

Table A.

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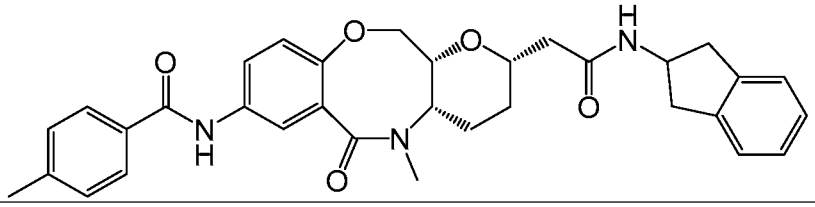
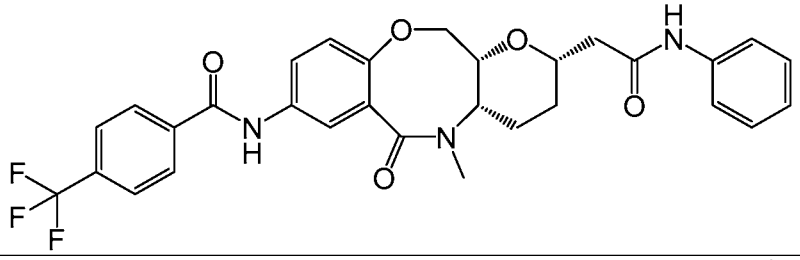
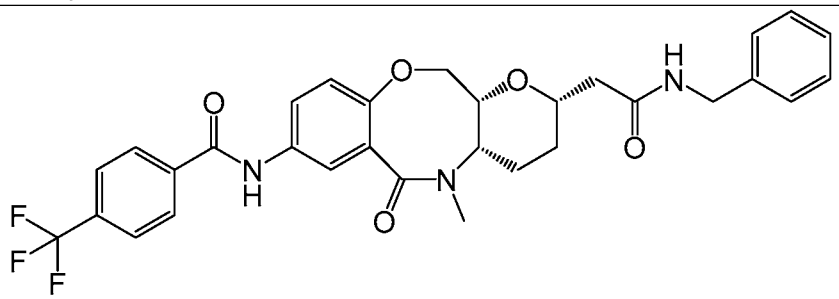
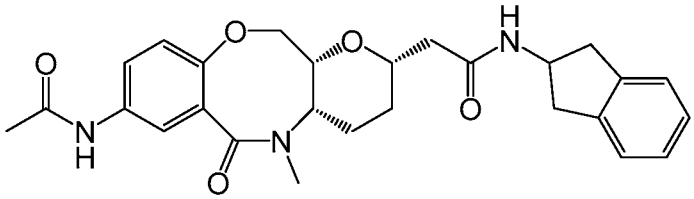
1	
2	
4	
5	

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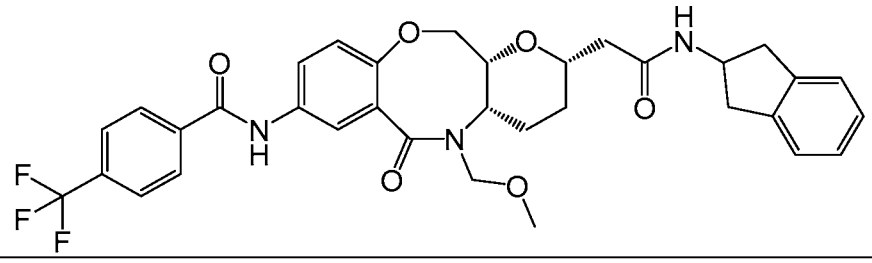
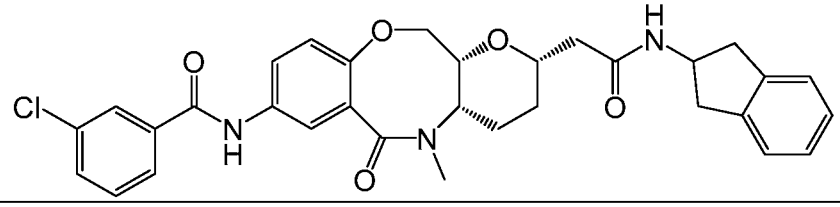
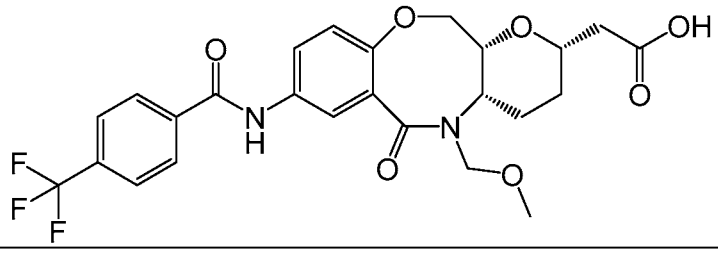
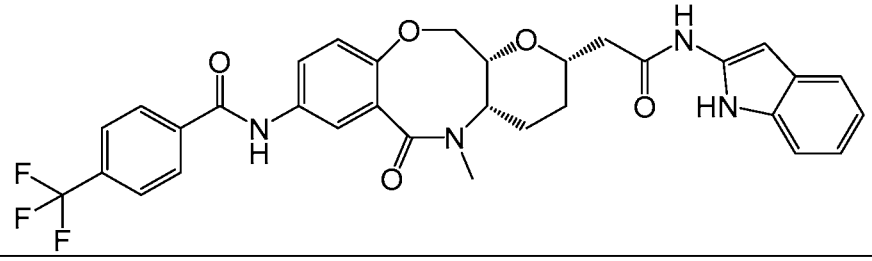
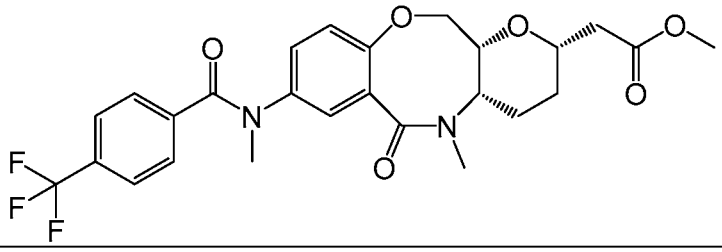
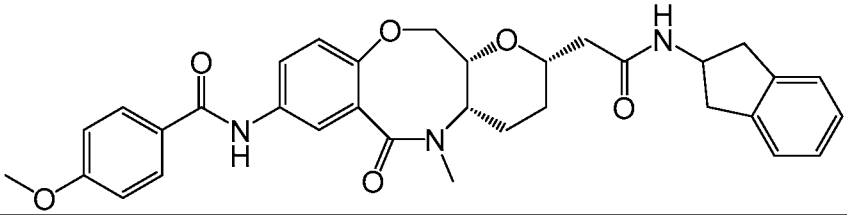
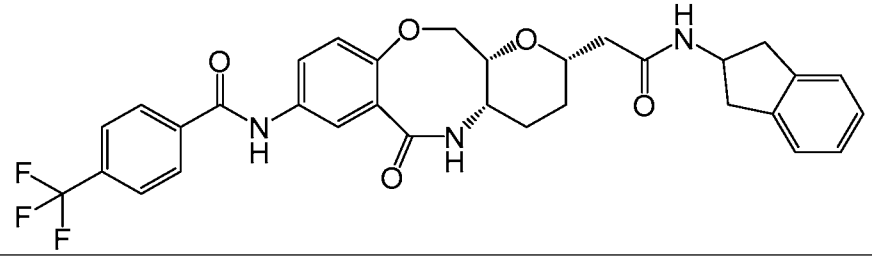
7	
8	
9	
10	
11	
12	
13	

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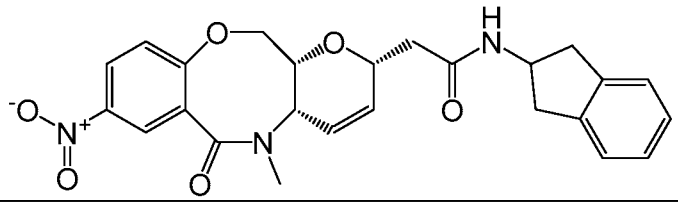
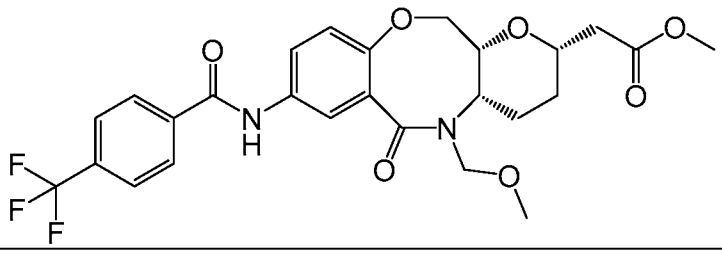
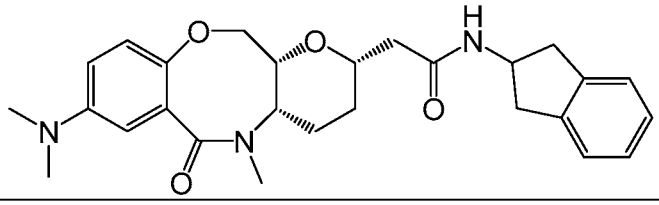
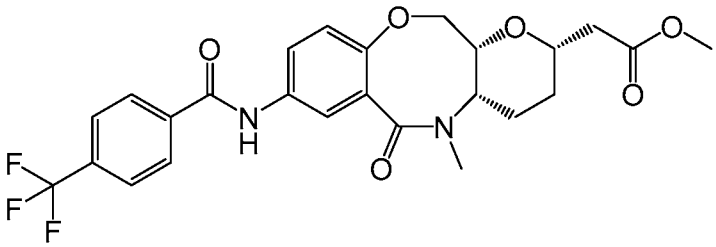
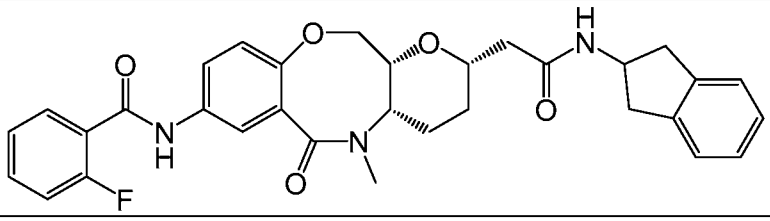
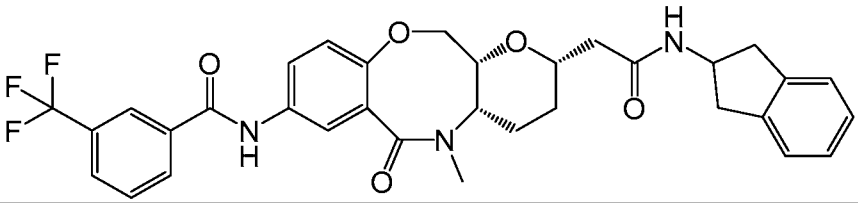
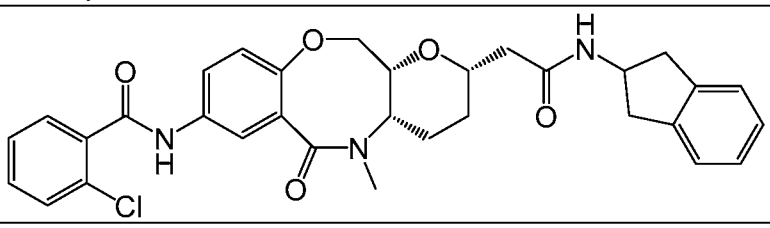
14	
15	
16	
17	
18	
19	
21	

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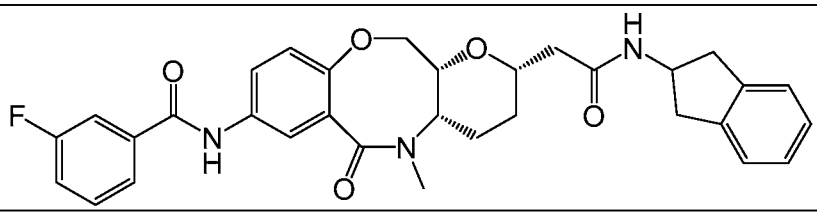
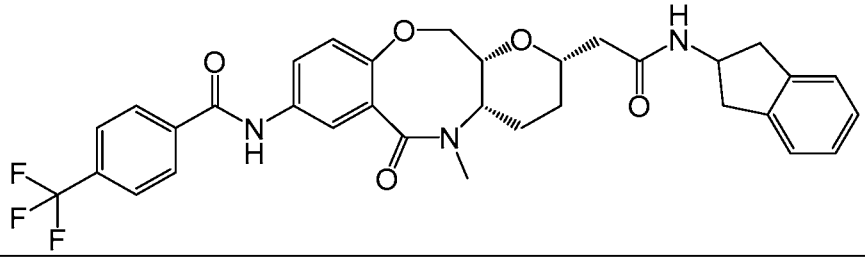
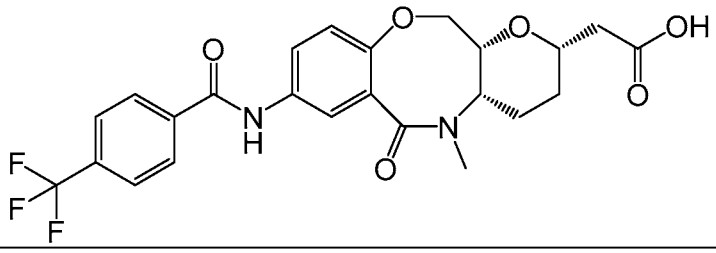
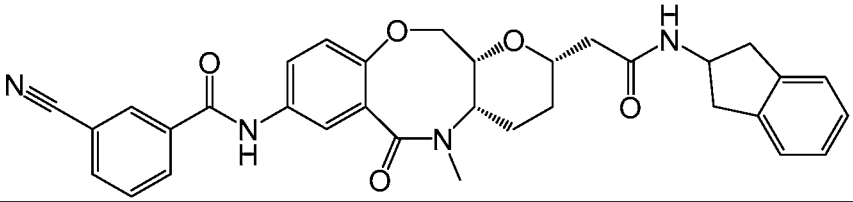
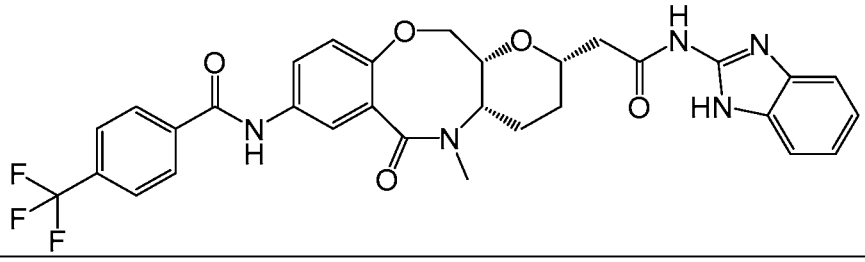
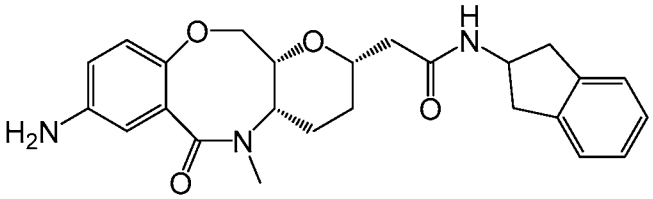
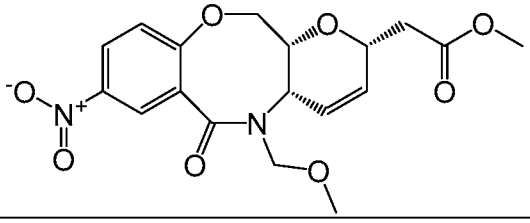
22	
23	
25	
26	
27	
28	
29	

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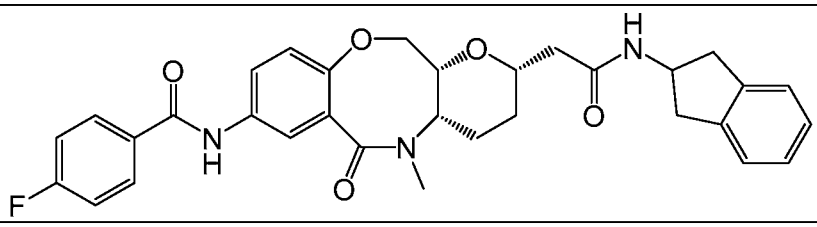
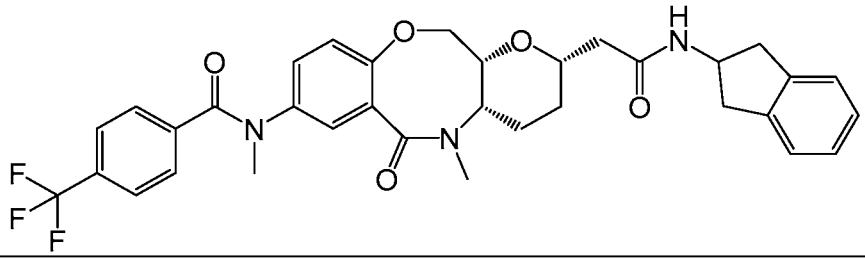
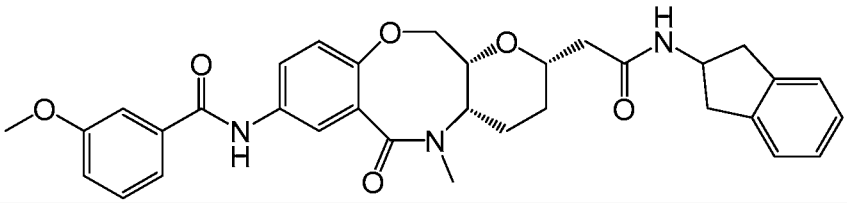
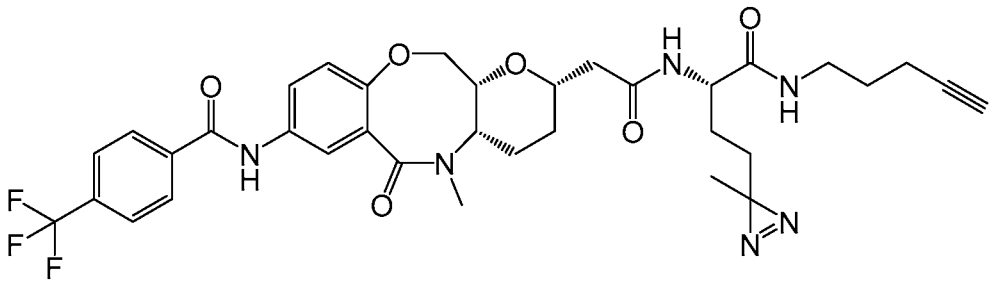
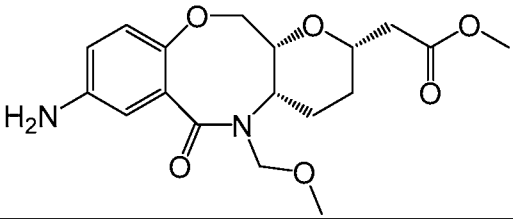
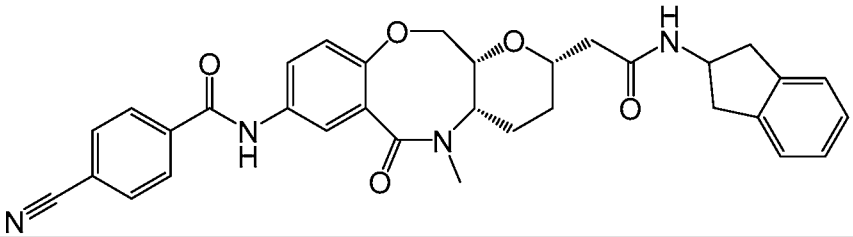
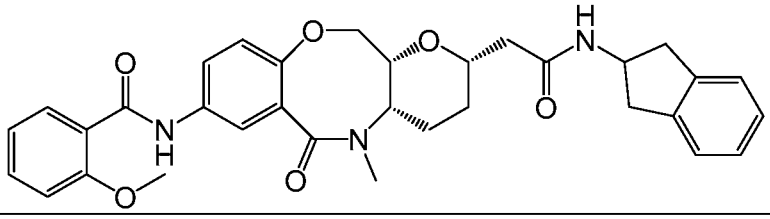
30	
31	
32	
33	
34	
35	
36	

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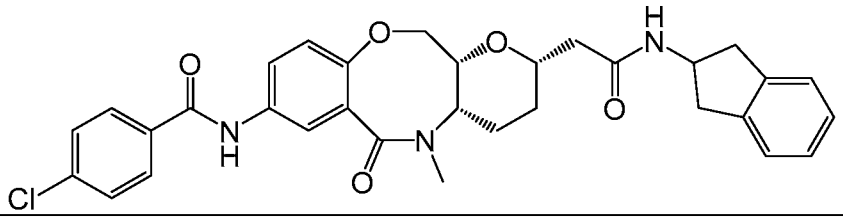
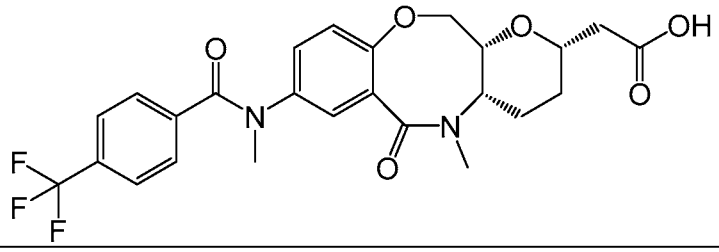
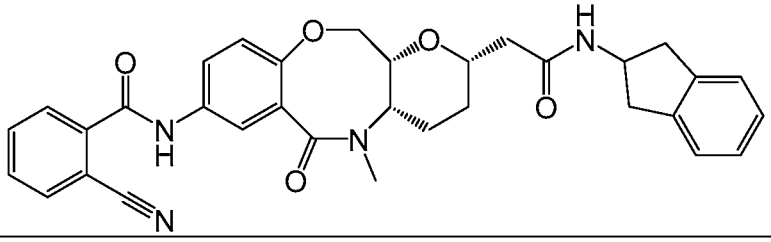
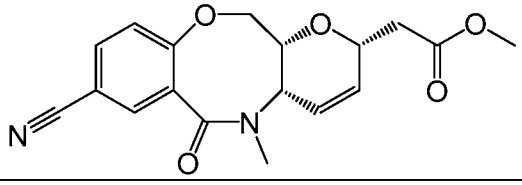
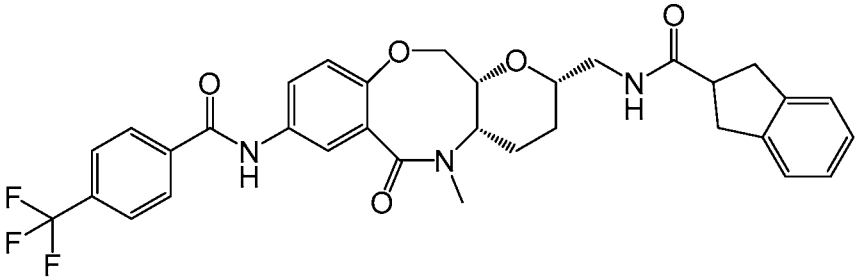
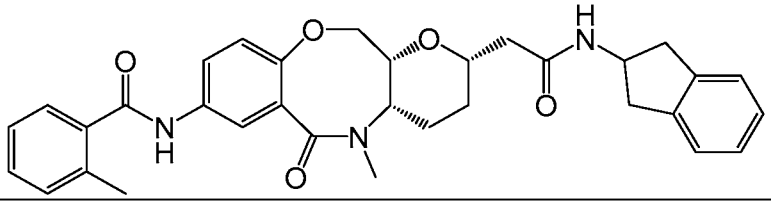
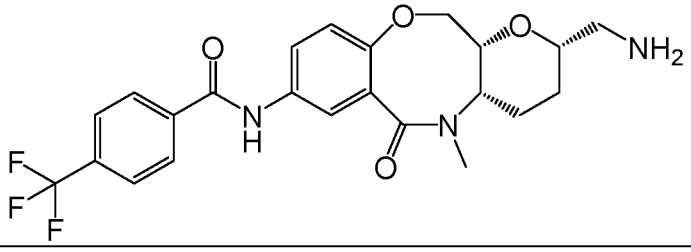
37	
38	
39	
40	
41	
42	
43	

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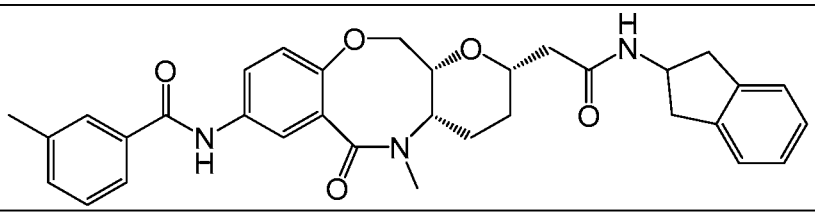
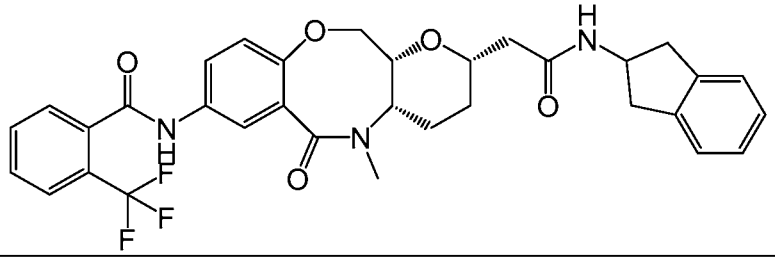
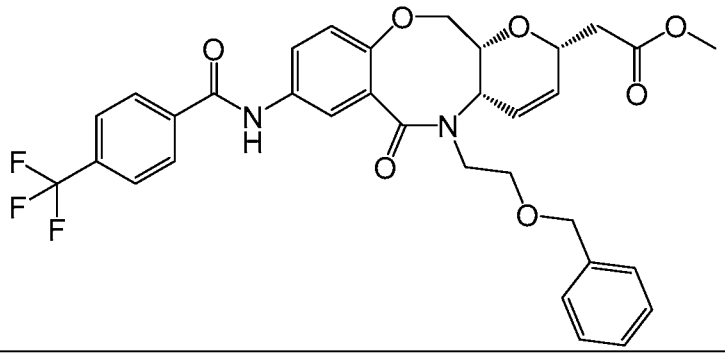
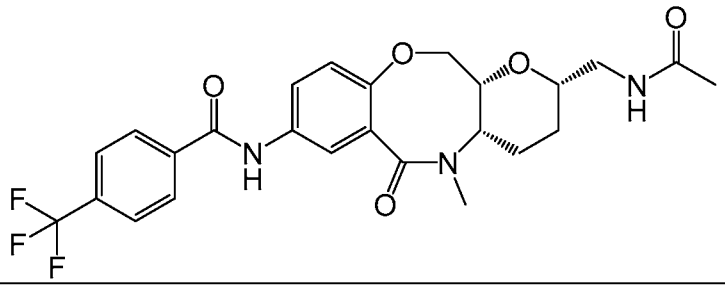
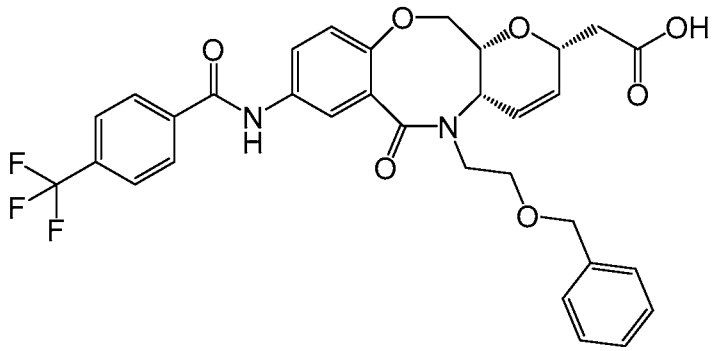
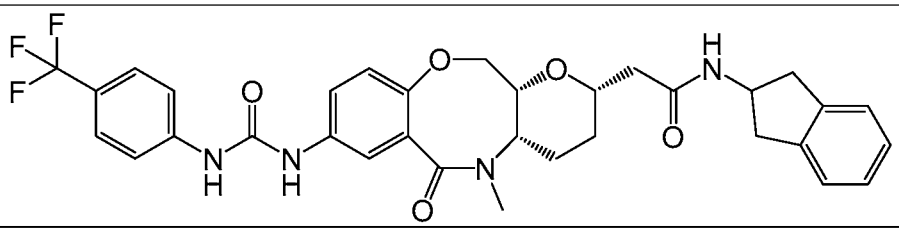
44	
45	
46	
48	
49	
50	

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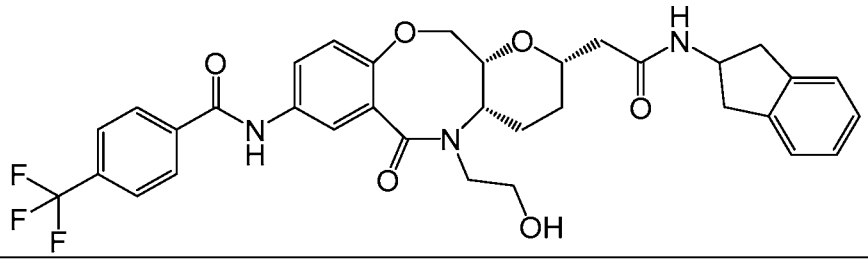
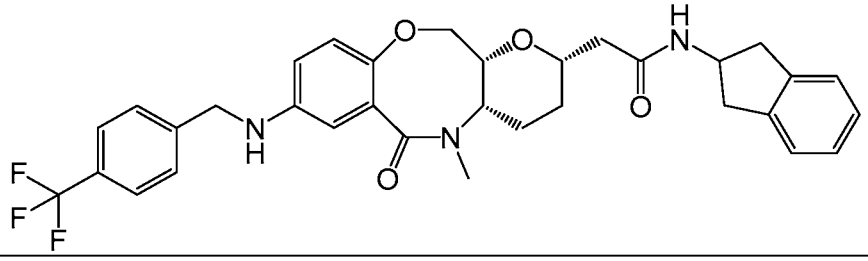
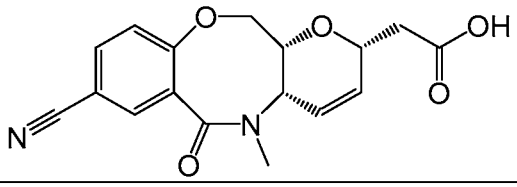
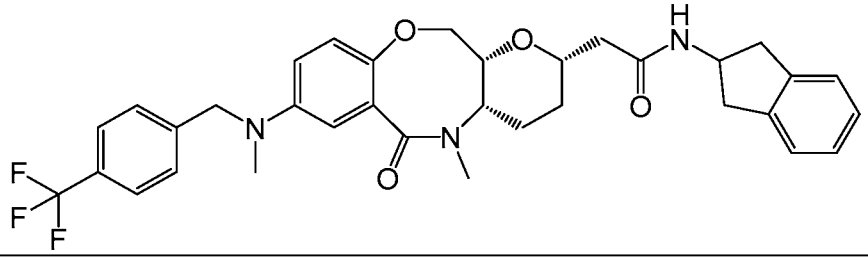
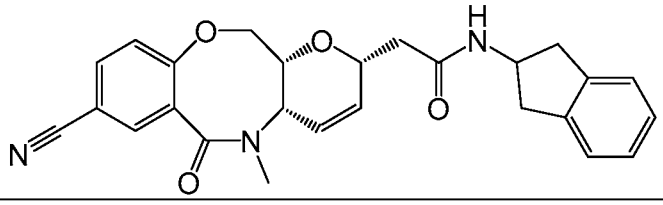
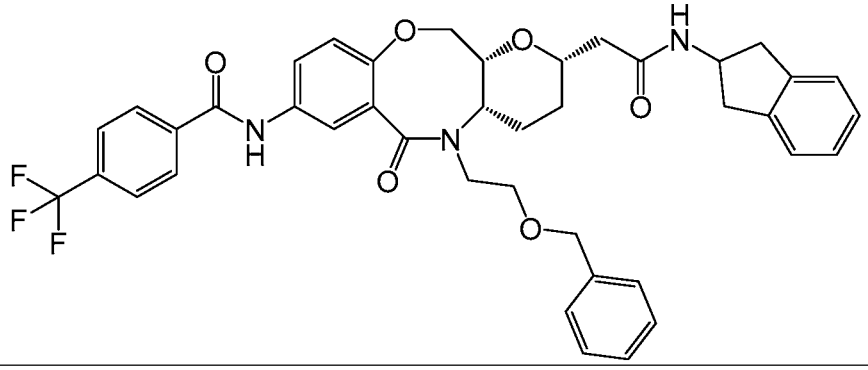
51	
52	
53	
54	
55	
56	

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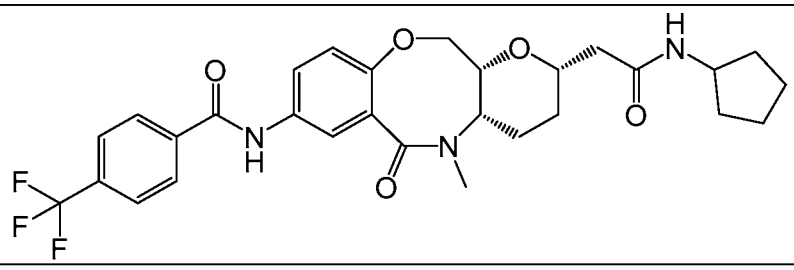
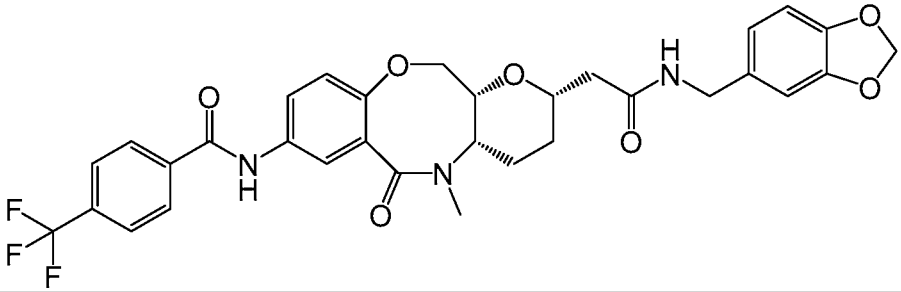
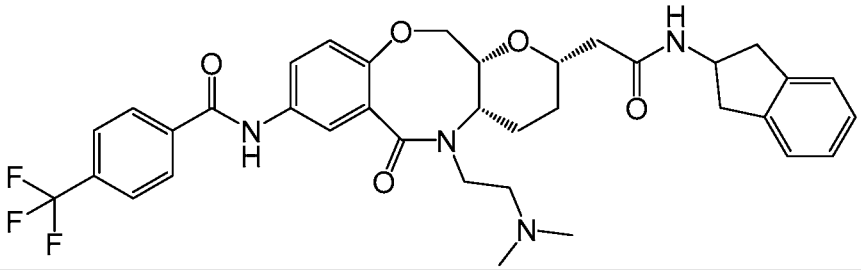
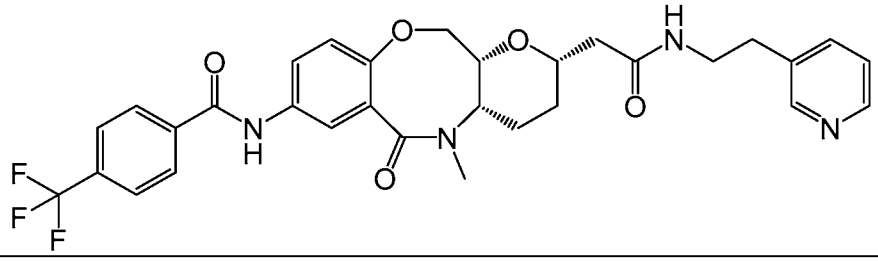
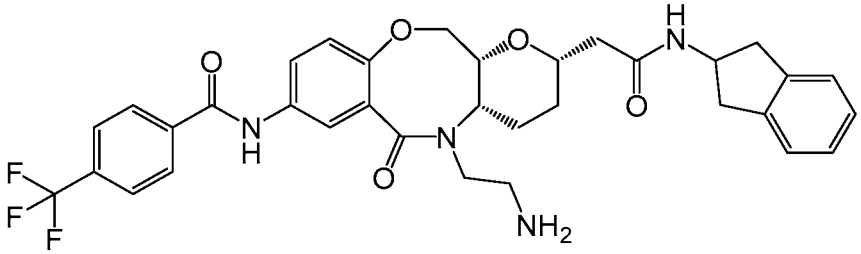
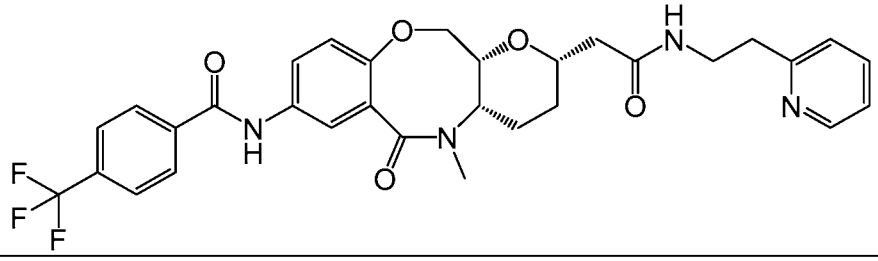
57	
58	
59	
60	
61	
62	

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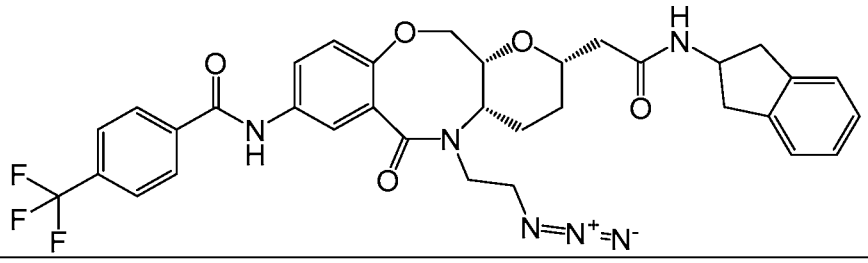
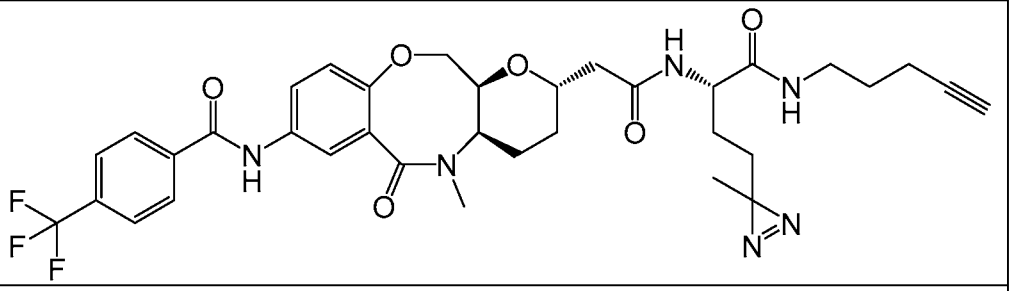
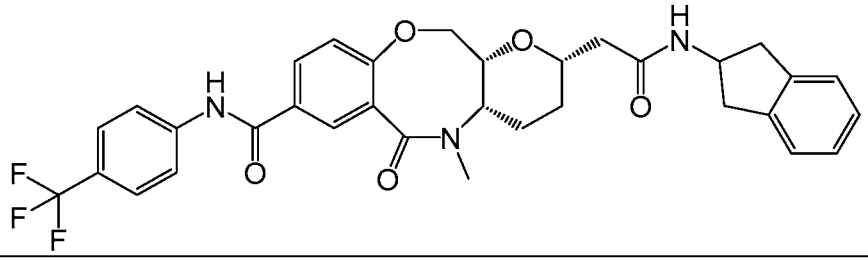
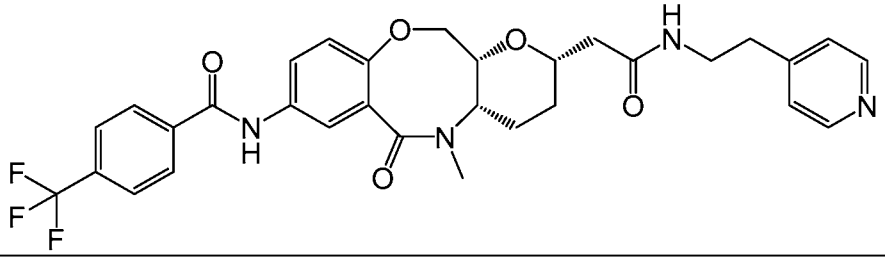
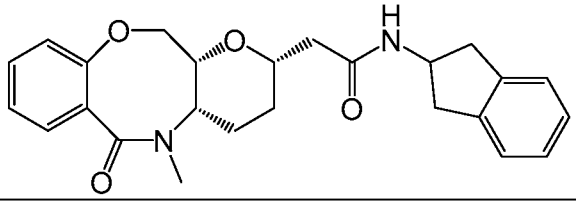
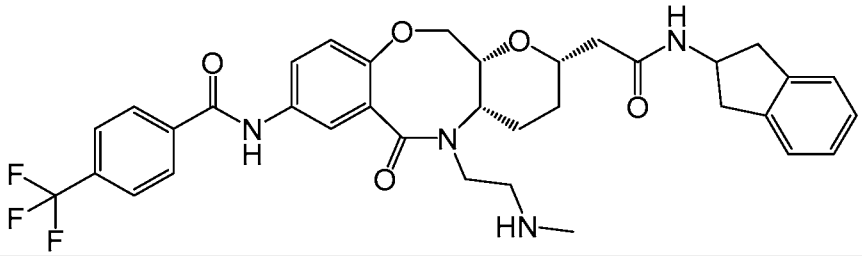
63	
64	
66	
67	
68	
69	

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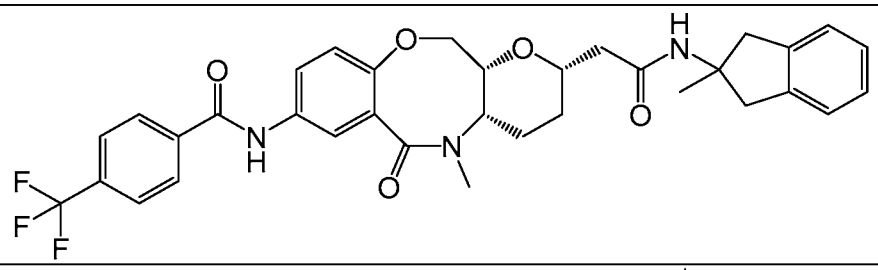
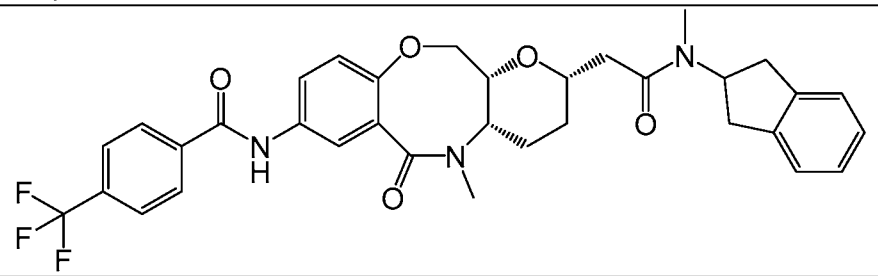
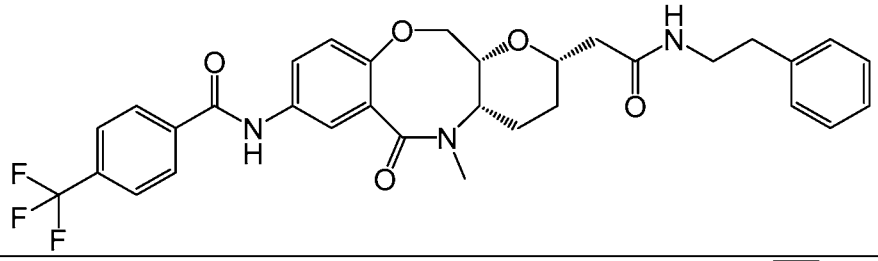
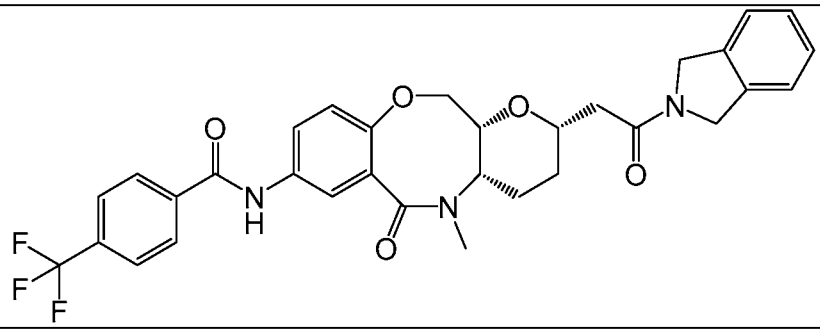
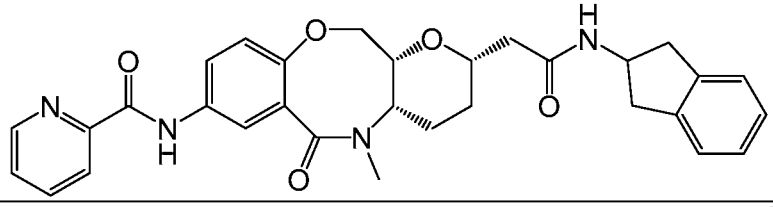
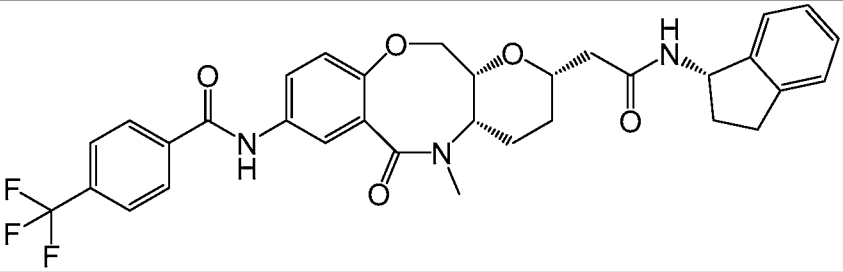
70	
71	
72	
73	
74	
75	

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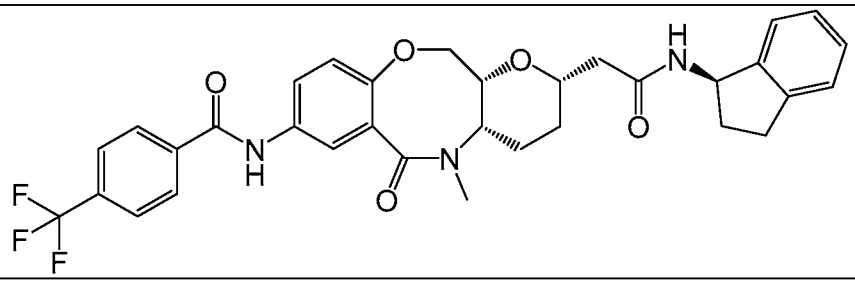
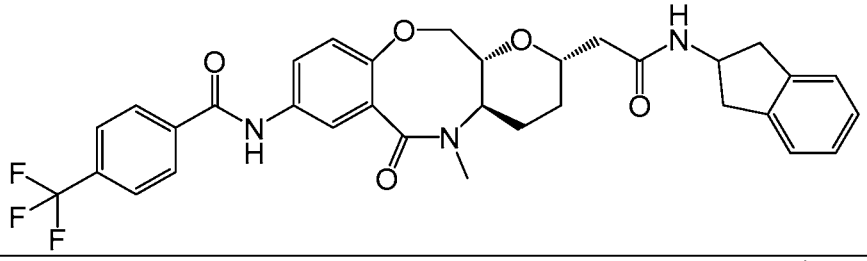
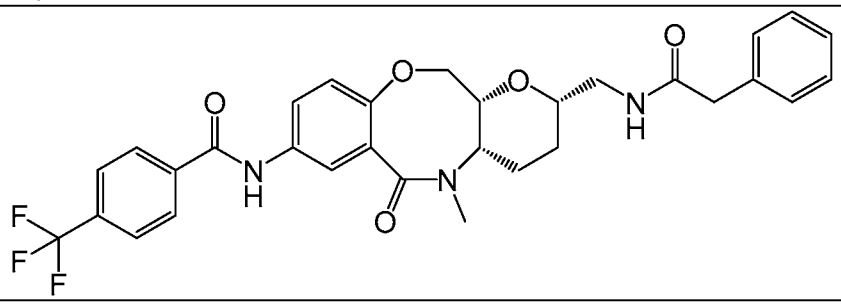
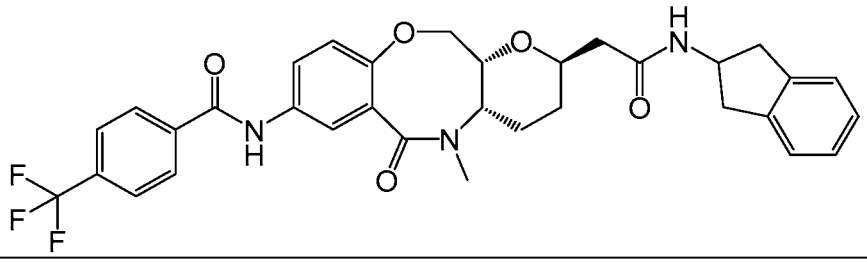
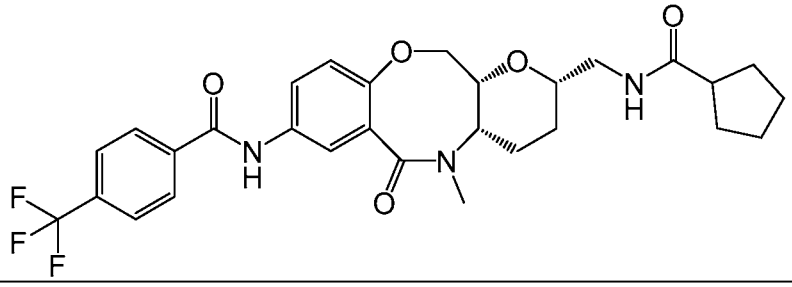
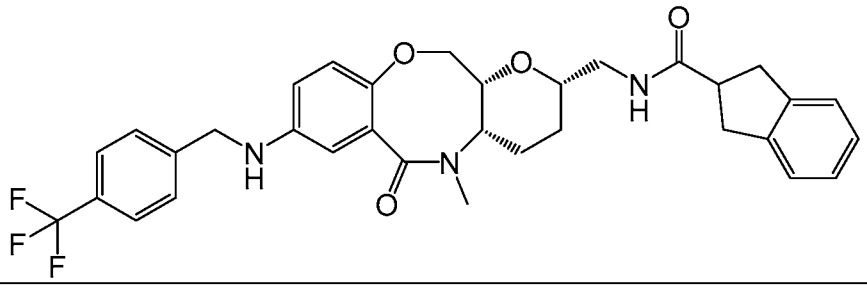
76	
77	
78	
79	
80	
81	

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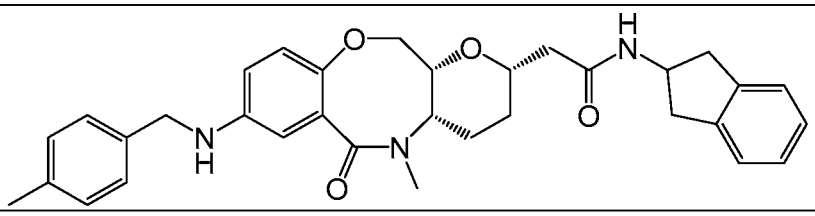
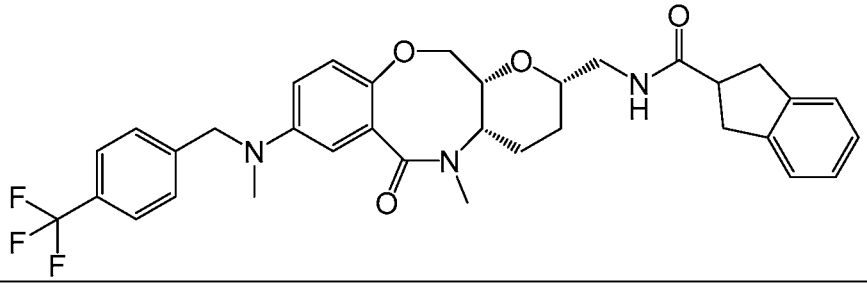
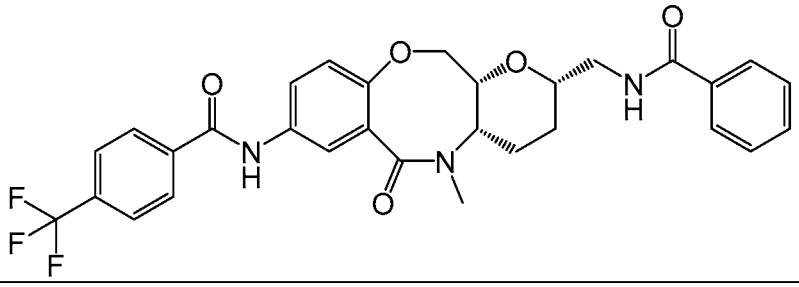
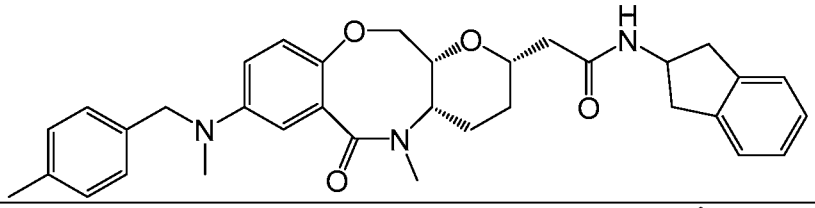
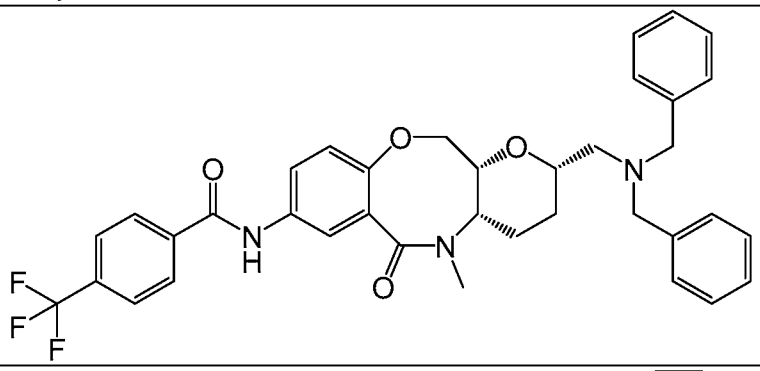
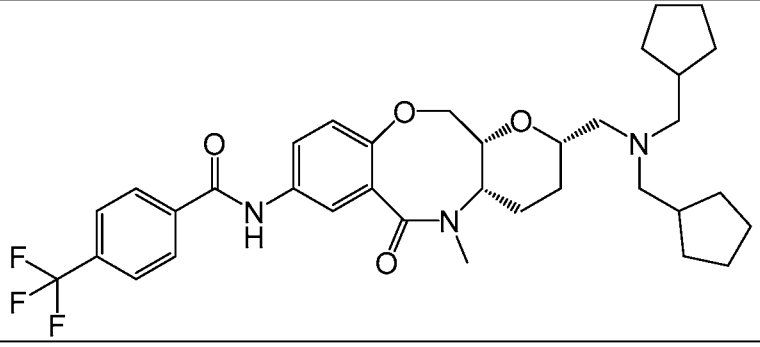
82	
83	
84	
85	
86	
87	

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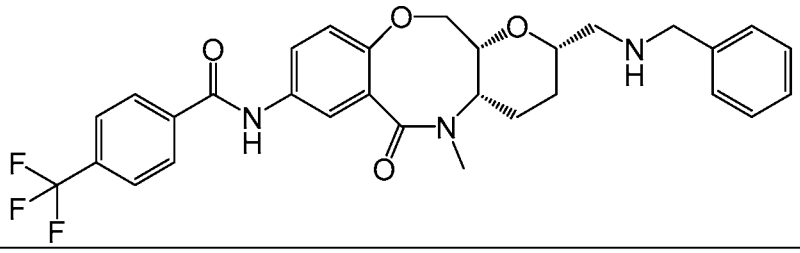
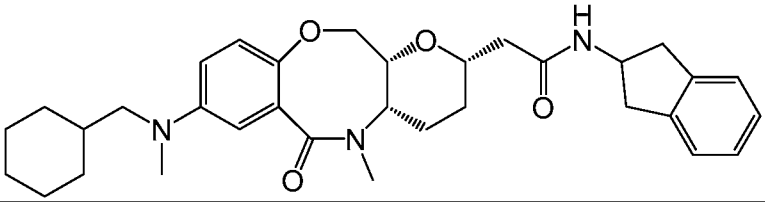
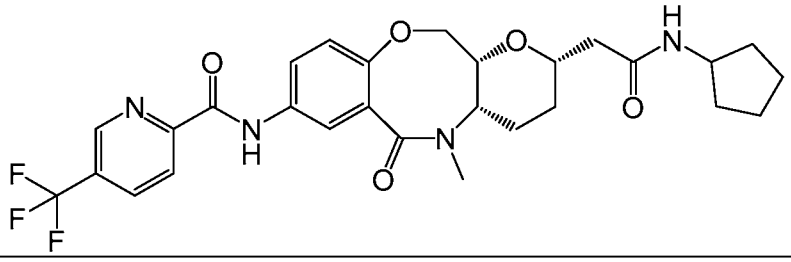
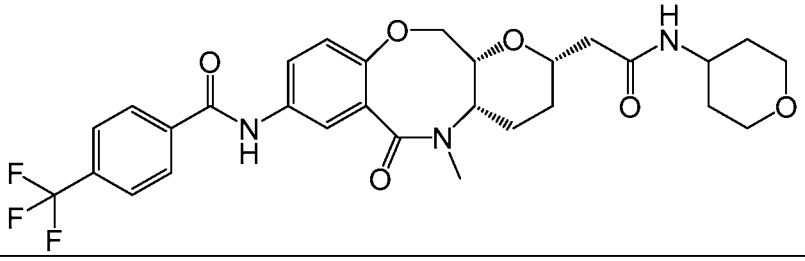
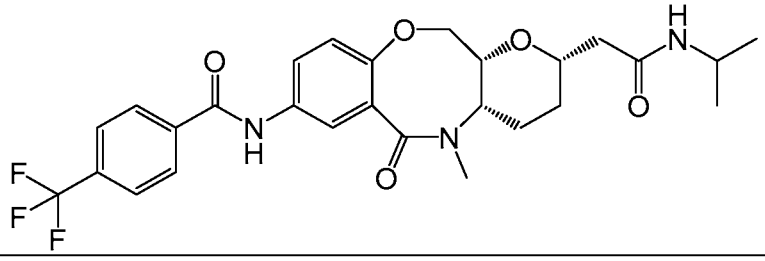
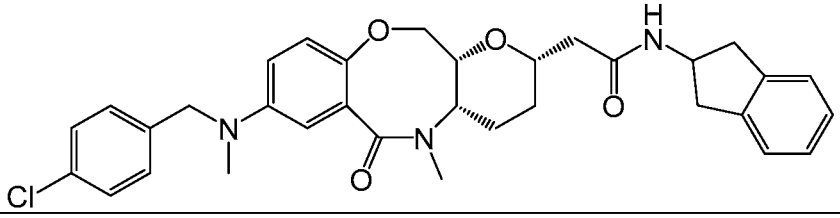
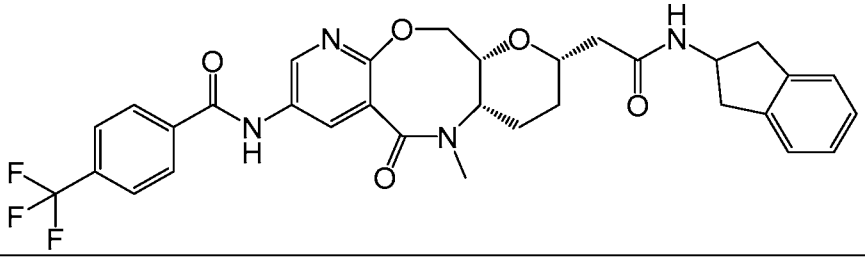
88	
89	
90	
91	
92	
93	
94	

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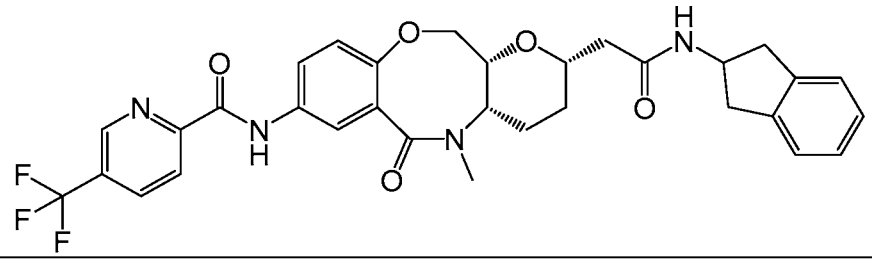
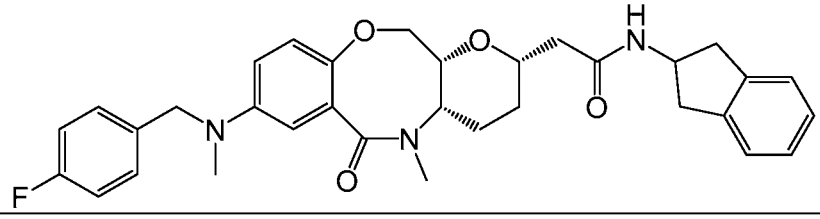
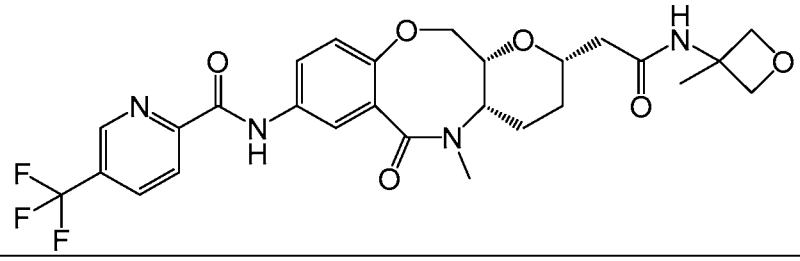
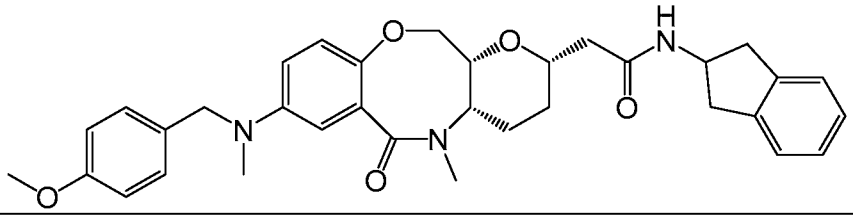
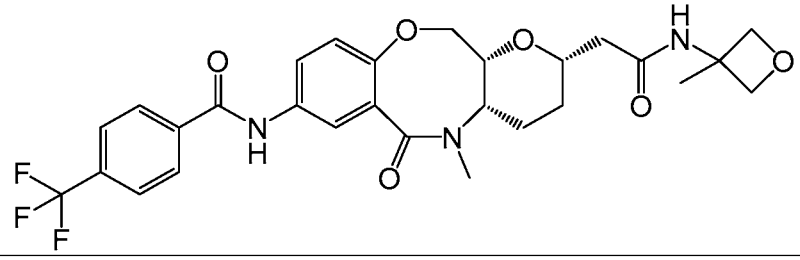
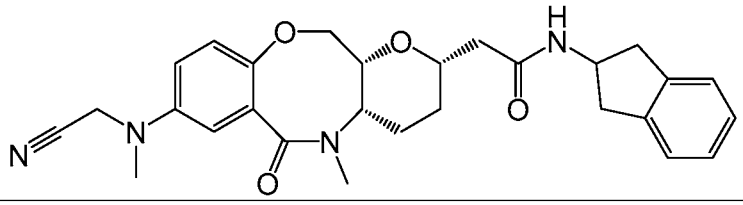
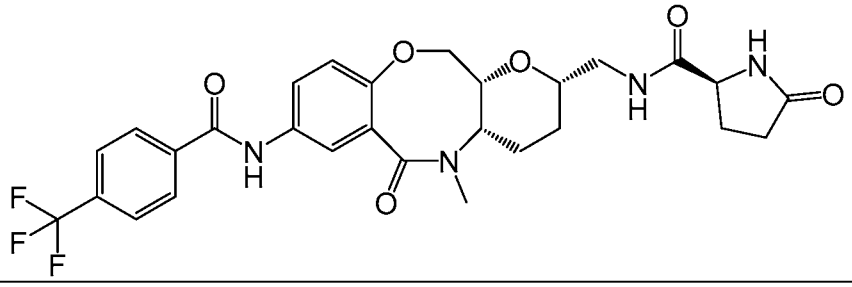
95	
96	
97	
99	
100	
101	
102	

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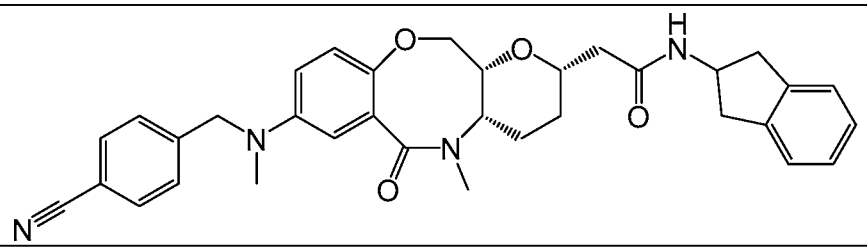
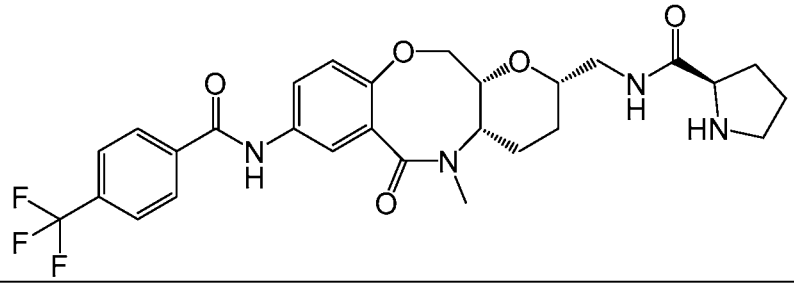
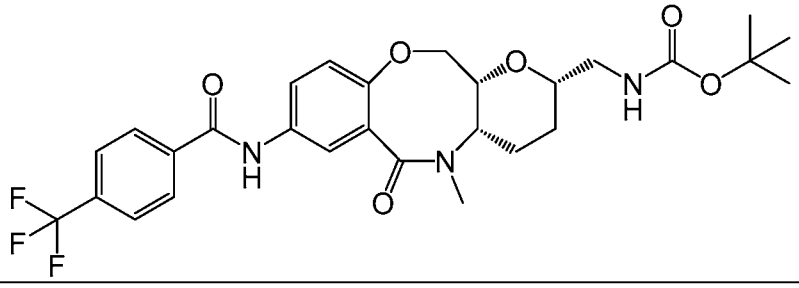
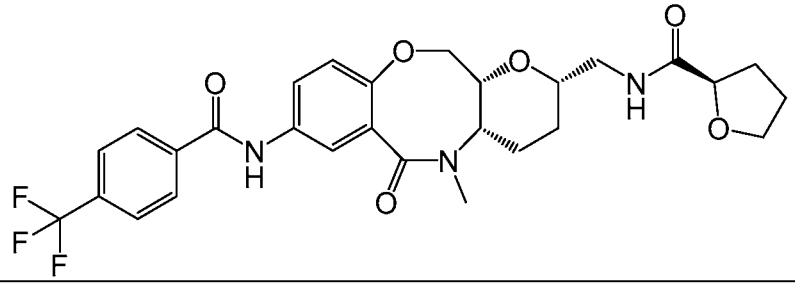
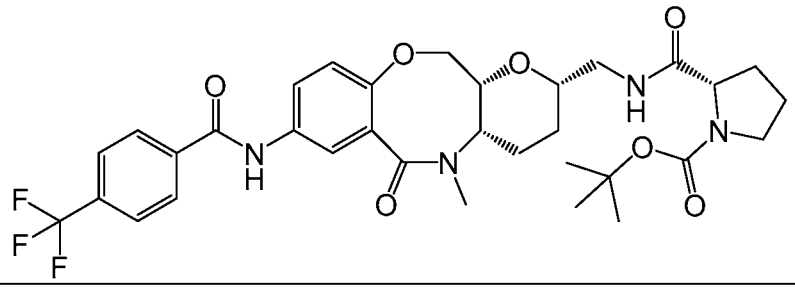
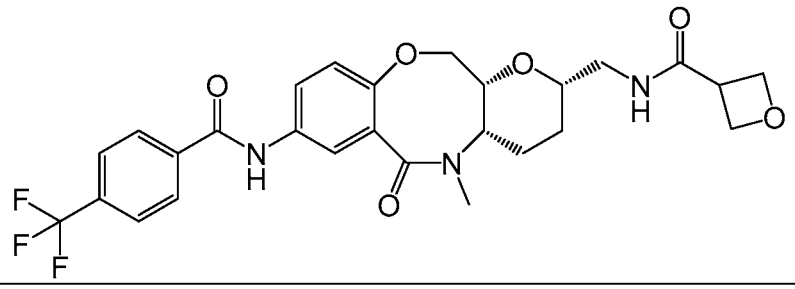
103	
104	
106	
108	
109	
110	

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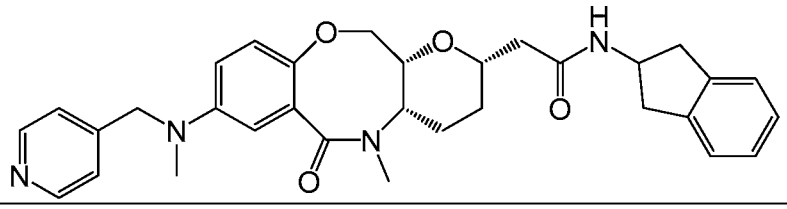
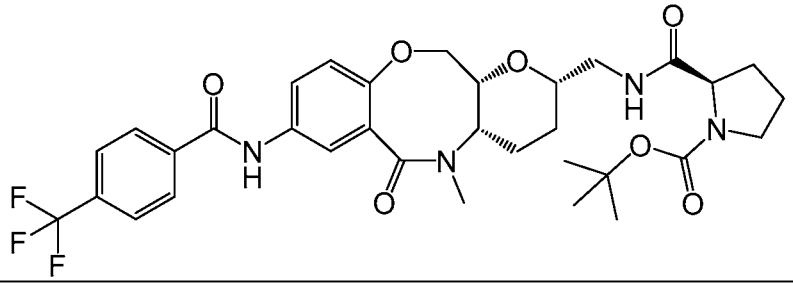
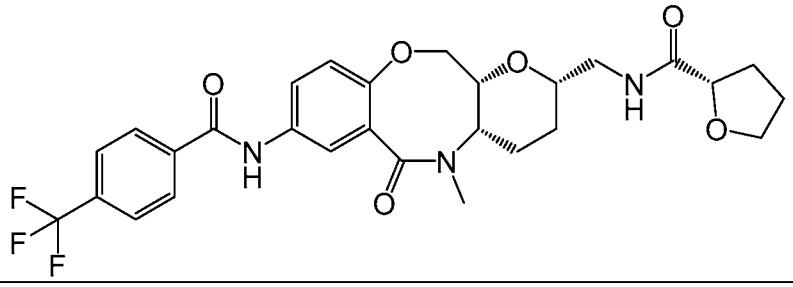
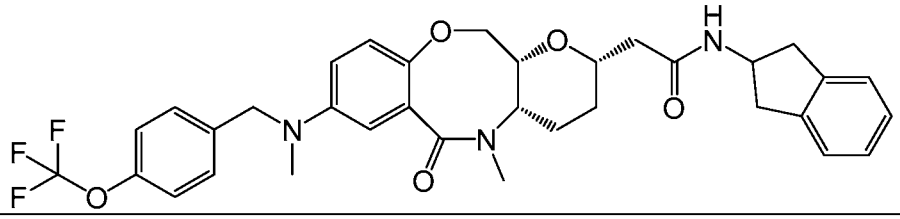
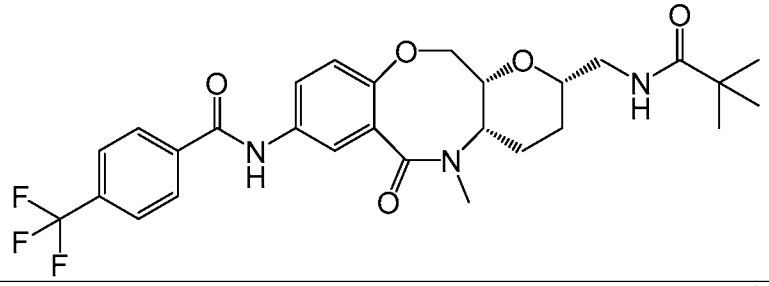
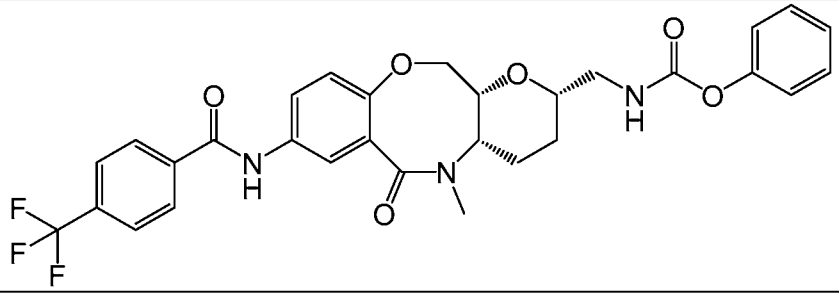
111	
112	
113	
115	
116	
117	

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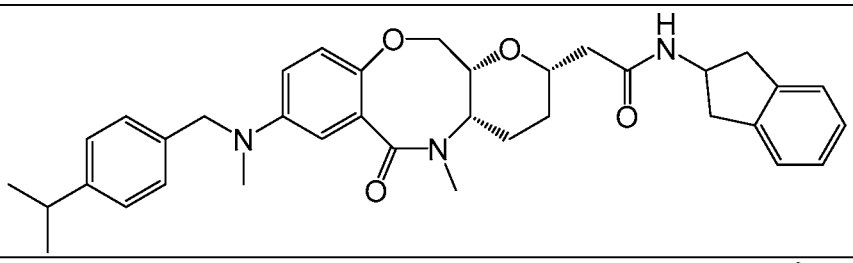
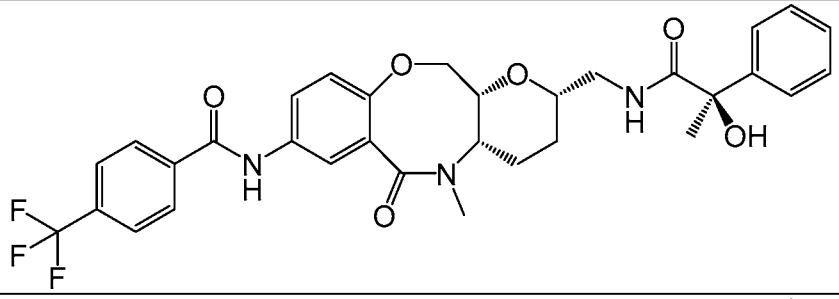
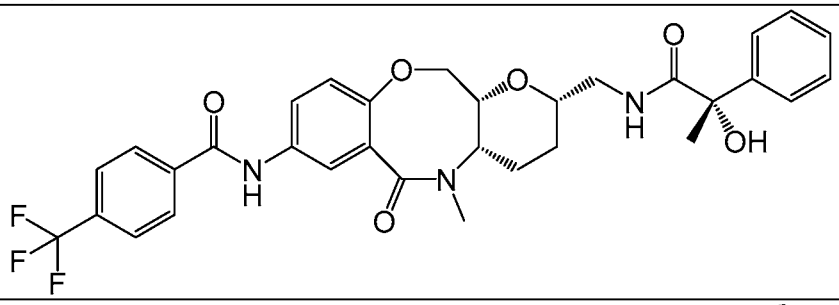
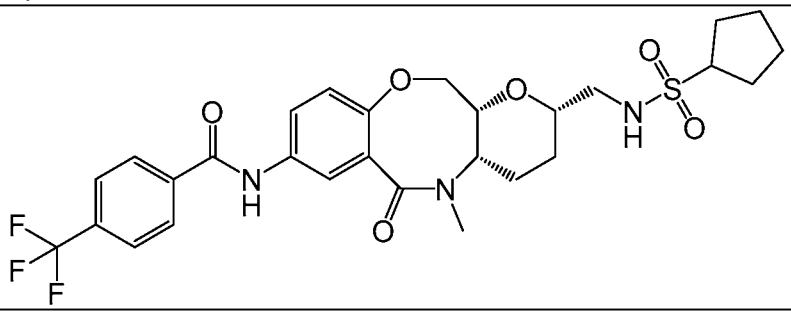
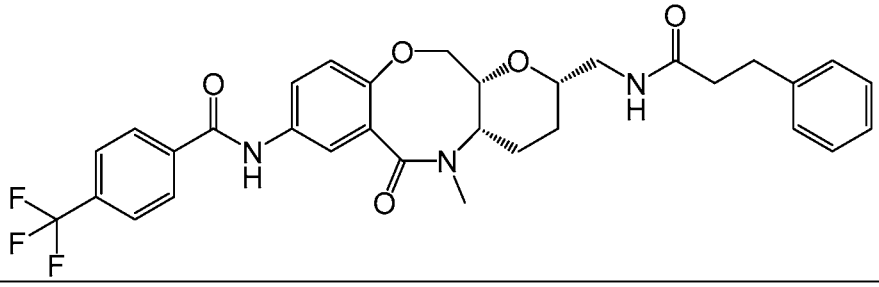
118	
119	
120	
121	
122	

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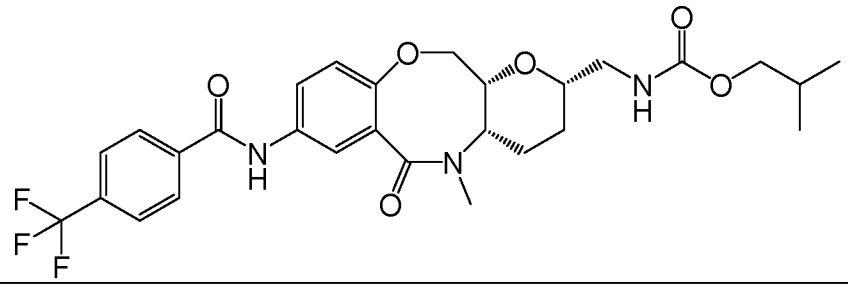
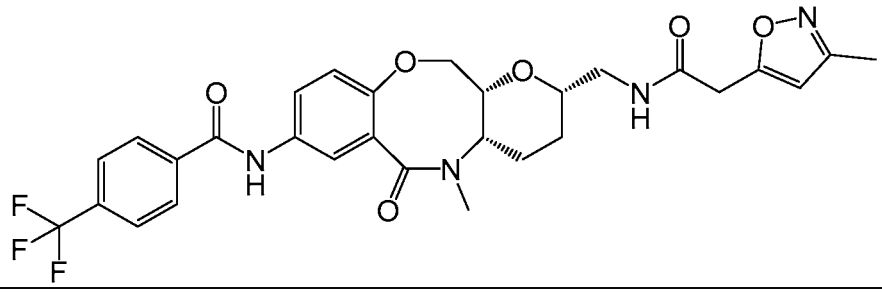
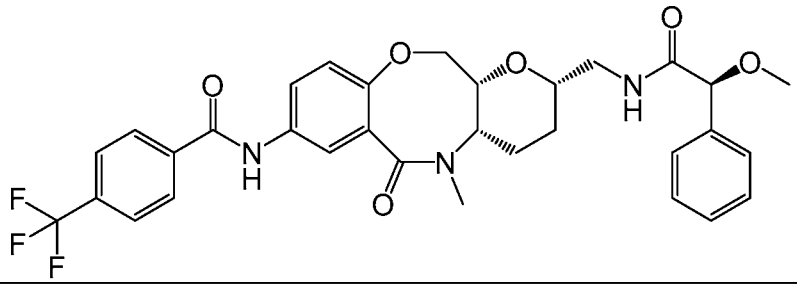
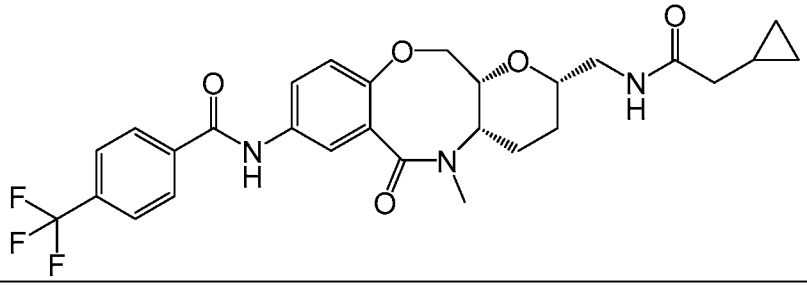
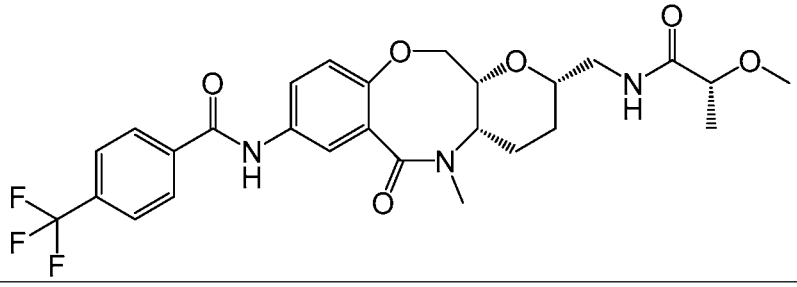
123	
124	
125	
126	
127	

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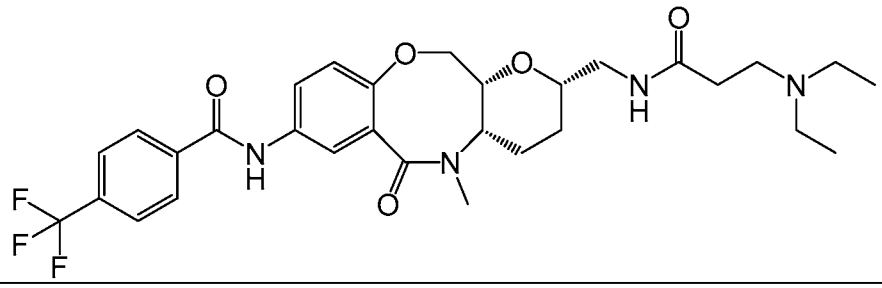
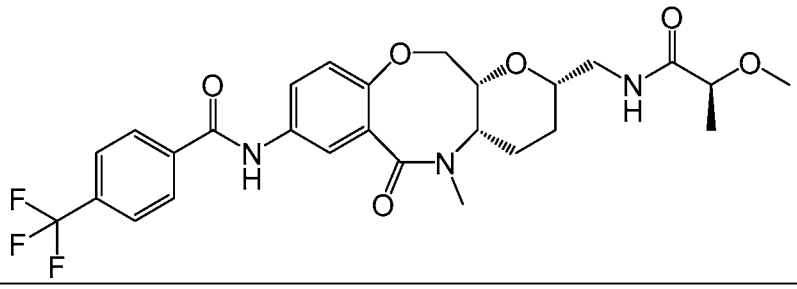
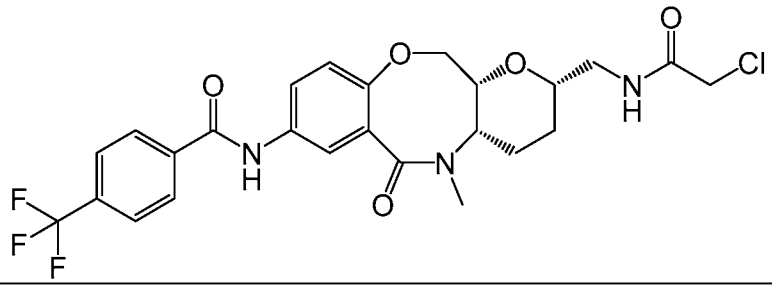
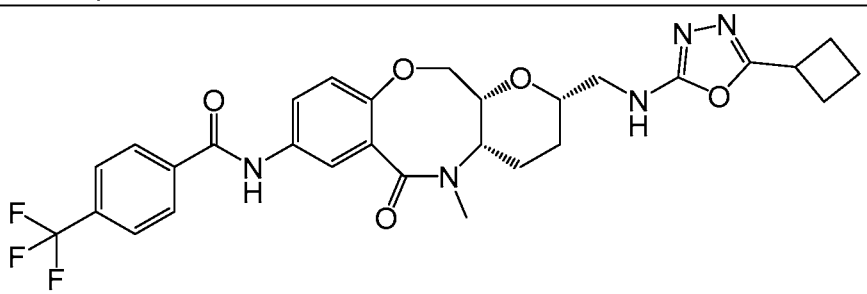
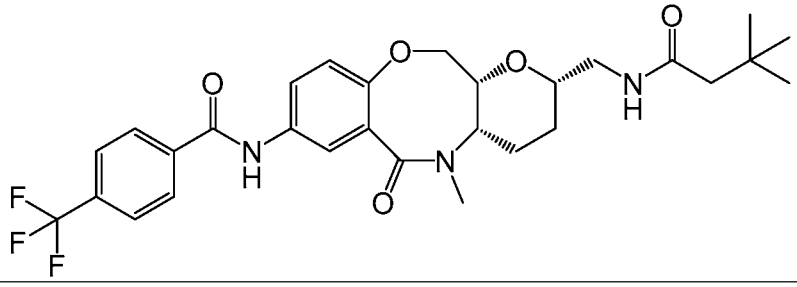
128	
129	
130	
131	
133	

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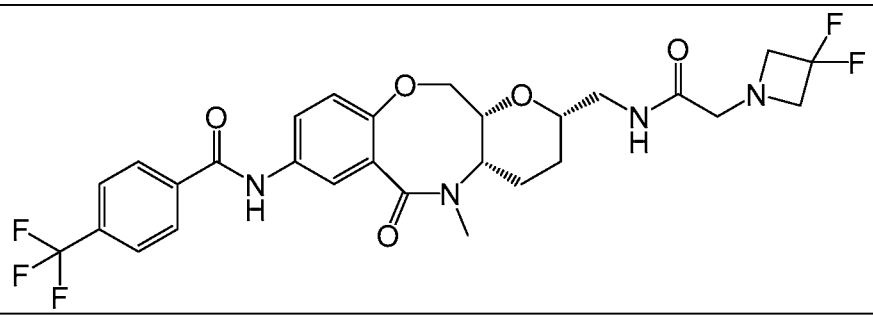
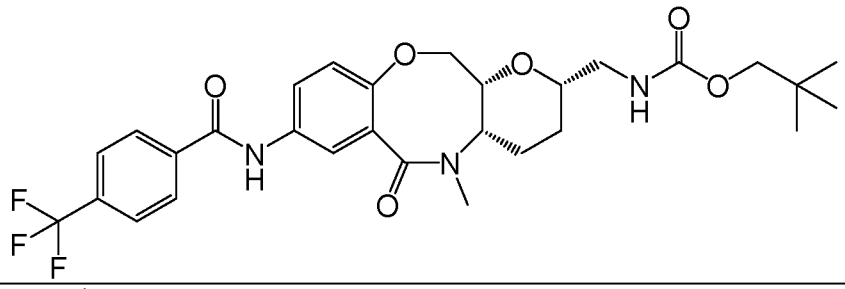
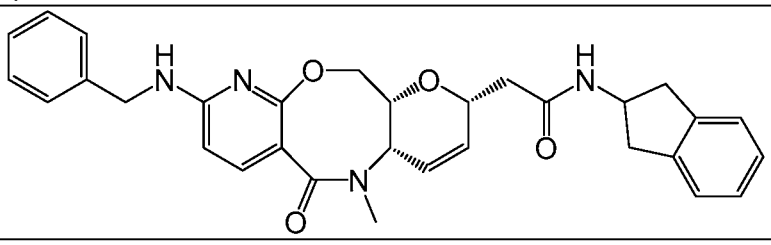
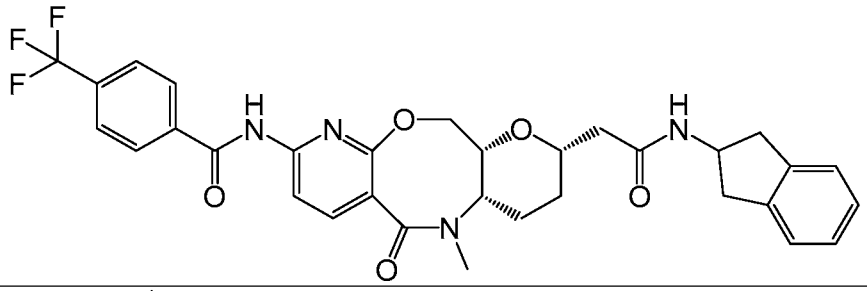
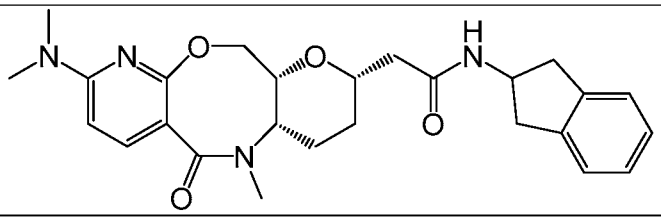
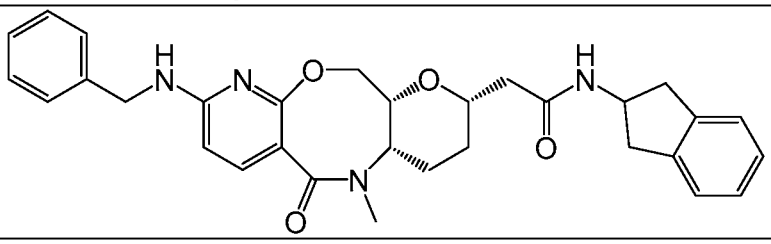
134	
135	
136	
137	
138	
139	

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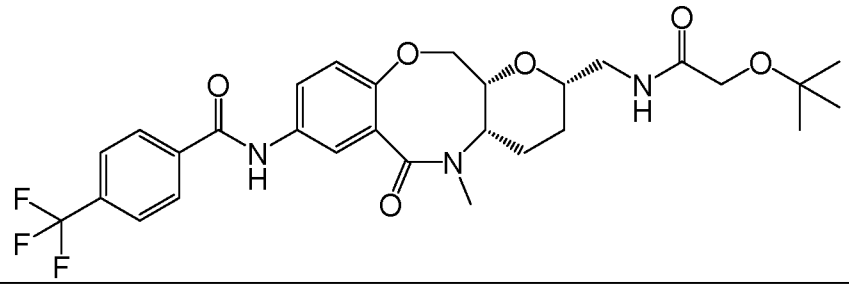
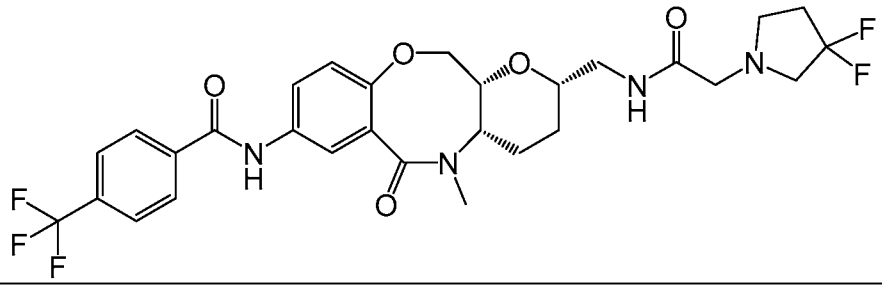
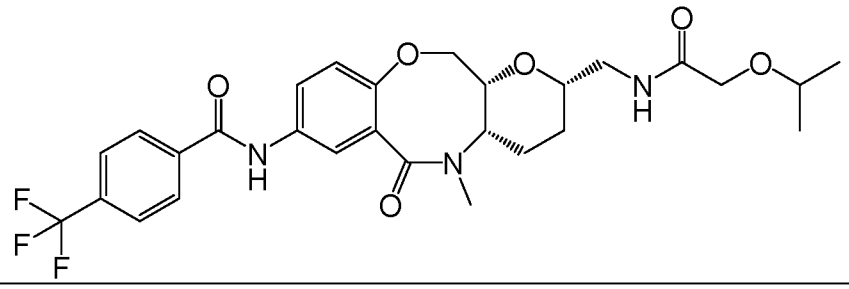
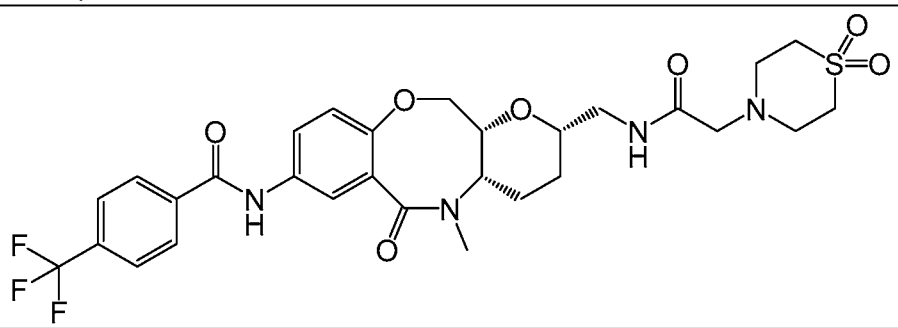
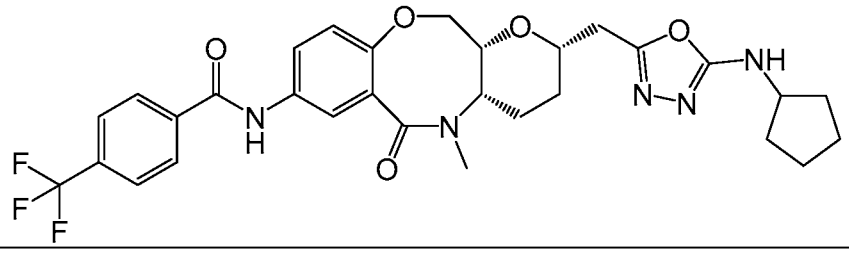
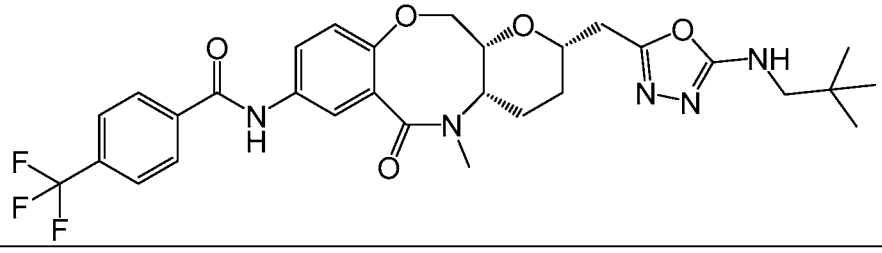
140	
141	
142	
143	
144	
145	

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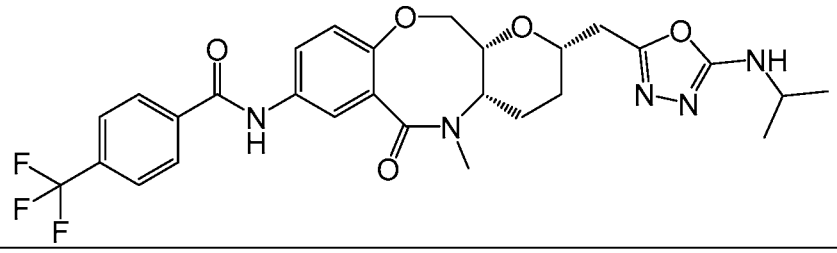
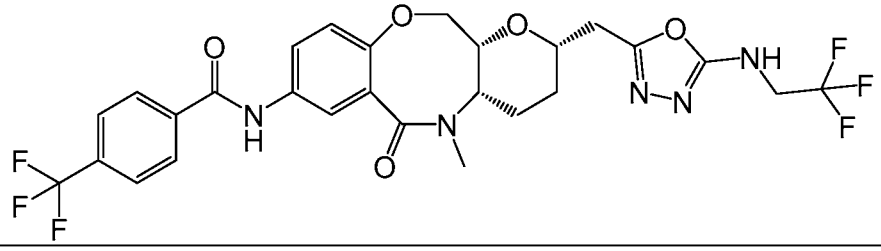
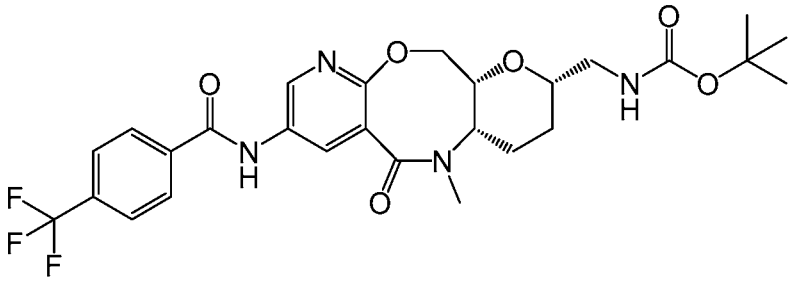
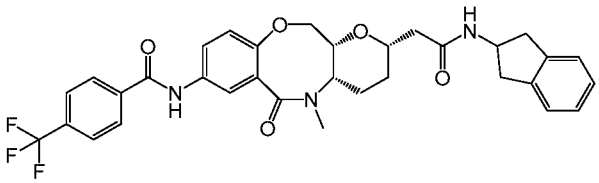
146	
147	
148	

Compounds of the invention show improved pharmacokinetic profiles as compared to reference compounds.

For example, the reference compound is:



For example, compounds of the invention have a plasma C_{max} that is at least about 1.5 fold, at least about 2 fold, at least about 3 fold, at least about 4 fold, at least about 5 fold, at least about 6 fold, at least about 8 fold, or at least about 10 fold higher than the plasma C_{max} of reference compounds. For example, compounds of the invention have a plasma C_{max} that is at least about 4 fold, at least about 5 fold, at least about 6 fold, at least about 8 fold, or at least about 10 fold higher than the plasma C_{max} of reference compounds. For example, compounds of the invention have a plasma C_{max} that is at least about 500 μg/L, at least about 750 μg/L, at least about 1,000 μg/L, at least about 1,500 μg/L, at least about 2,000 μg/L, at least about 2,500 μg/L, or at least about 3,000 μg/L. For example, compounds of the

invention have a plasma C_{max} that is at least 1,500 μg/L, at least about 2,000 μg/L, at least about 2,500 μg/L, or at least about 3,000 μg/L.

For example, compounds of the invention have a plasma AUC that is at least about 1.5 fold, at least about 2 fold, at least about 3 fold, at least about 4 fold, at least about 5 fold, at least about 6 fold, at least about 8 fold, or at least about 10 fold higher than the plasma AUC of references compounds. For example, compounds of the invention have a plasma AUC that is at least about 3 fold, at least about 4 fold, at least about 5 fold, at least about 6 fold, at least about 8 fold, or at least about 10 fold higher than the plasma AUC of reference compounds. For example, compounds of the invention have a plasma AUC that is at least about 1,200 μg/L*hr, at least about 1,500 μg/L*hr, at least about 2,000 μg/L*hr, at least about 2,500 μg/L*hr, at least about 3,000 μg/L*hr, at least about 4,000 μg/L*hr, at least about 5,000 μg/L*hr, or at least about 6,000 μg/L*hr. For example, compounds of the invention have a plasma AUC that is at least about 3,000 μg/L*hr, at least about 4,000 μg/L*hr, at least about 5,000 μg/L*hr, or at least about 6,000 μg/L*hr.

For example, compounds of the invention have a plasma clearance (CL) that is at least about 1.5 fold, at least about 2 fold, at least about 3 fold, at least about 4 fold, at least about 5 fold, at least about 6 fold, at least about 8 fold, or at least about 10 fold lower than the CL of reference compounds. For example, compounds of the invention have a CL that is at least about 3 fold, at least about 4 fold, at least about 5 fold, at least about 6 fold, at least about 8 fold, or at least about 10 fold lower than the CL of reference compounds. For example, compounds of the invention have a CL that is at most about 9.5 L/hr/kg, at most about 9 L/hr/kg, at most about 8 L/hr/kg, at most about 7 L/hr/kg, at most about 6 L/hr/kg, at most about 5 L/hr/kg, at most about 4 L/hr/kg, at most about 3 L/hr/kg, or at most about 2 L/hr/kg. For example, compounds of the invention have a CL that is at most about 4 L/hr/kg, at most about 3 L/hr/kg, or at most about 2 L/hr/kg.

For example, compounds of the invention have a V_z (*i.e.*, volume of distribution associated with the terminal phase) that is at least about 1.5 fold, at least about 2 fold, at least about 3 fold, at least about 4 fold, at least about 5 fold, at least about 6 fold, at least about 8 fold, or at least about 10 fold lower than the V_z of reference compounds. For example, compounds of the invention have a V_z that is at least about 5 fold, at least about 6 fold, at least about 8 fold, or at least about 10 fold lower than the CL of reference compounds. For example, compounds of the invention have a V_z that is at most about 20 L/kg, at most about 18 L/kg, at most about 16 L/kg, at most about 14 L/kg, at most about 12 L/kg, at most about 10 L/kg, at most about 8 L/kg, at most about 6 L/kg, at most about 5 L/kg, at most about 4

L/kg, at most about 3 L/kg, at most about 2 L/kg, or at most about 1 L/kg. For example, compounds of the invention have a V_z that is at most about 6 L/kg, at most about 5 L/kg, at most about 4 L/kg, at most about 3 L/kg, at most about 2 L/kg, or at most about 1 L/kg.

Compounds of the invention show improved potency (*e.g.*, abilities to modulate expression of *TRIB1* and other key regulators in lipoprotein metabolism). For example, compounds of the invention have an EC_{50} of upregulating *TRIB1* that is at least about 1.5 fold, at least about 2 fold, at least about 3 fold, at least about 4 fold, at least about 5 fold, at least about 6 fold, at least about 8 fold, or at least about 10 fold lower than the EC_{50} of upregulating *TRIB1* of reference compounds. For example, compounds of the invention have an EC_{50} of upregulating *TRIB1* that is at most about 0.8 μM, at most about 0.7 μM, at most about 0.6 μM, at most about 0.5 μM, at most about 0.4 μM, at most about 0.3 μM, at most about 0.2 μM, at most about 0.1 μM, at most about 0.09 μM, at most about 0.08 μM, at most about 0.07 μM, at most about 0.06 μM, at most about 0.05 μM, at most about 0.04 μM, at most about 0.03 μM, at most about 0.02 μM, or at most about 0.01 μM.

For example, compounds of the invention have an EC_{50} of upregulating *LDLR* that is at least about 1.5 fold, at least about 2 fold, at least about 3 fold, at least about 4 fold, at least about 5 fold, at least about 6 fold, at least about 8 fold, or at least about 10 fold lower than the EC_{50} of upregulating *LDLR* of reference compounds. For example, compounds of the invention have an EC_{50} of upregulating *LDLR* that is at most about 0.8 μM, at most about 0.7 μM, at most about 0.6 μM, at most about 0.5 μM, at most about 0.4 μM, at most about 0.3 μM, at most about 0.2 μM, at most about 0.1 μM, at most about 0.09 μM, at most about 0.08 μM, at most about 0.07 μM, at most about 0.06 μM, at most about 0.05 μM, at most about 0.04 μM, at most about 0.03 μM, at most about 0.02 μM, or at most about 0.01 μM.

For example, compounds of the invention have an EC_{50} of downregulating *PCSK9* that is at least about 1.5 fold, at least about 2 fold, at least about 3 fold, at least about 4 fold, at least about 5 fold, at least about 6 fold, at least about 8 fold, or at least about 10 fold lower than the EC_{50} of downregulating *PCSK9* of reference compounds. For example, compounds of the invention have an EC_{50} of downregulating *PCSK9* that is at most about 0.06 μM, at most about 0.05 μM, at most about 0.04 μM, at most about 0.03 μM, at most about 0.02 μM, at most about 0.01 μM, at most about 0.009 μM, at most about 0.008 μM, at most about 0.007 μM, at most about 0.006 μM, at most about 0.005 μM, at most about 0.004 μM, at most about 0.003 μM, at most about 0.002 μM, or at most about 0.001 μM.

Compounds of the invention show improved microsomal stability. Microsomal stability was determined by incubating compounds at 37°C for 60 minutes with both human

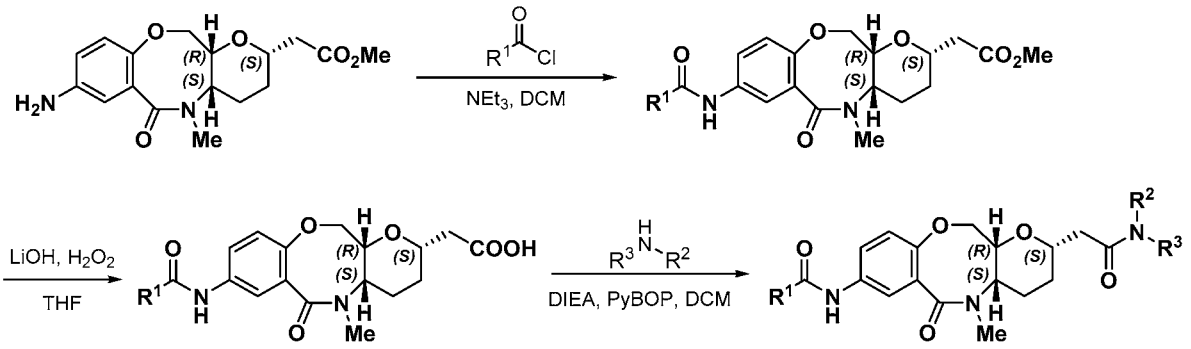
and mouse microsomes. Each compound was prepared in duplicate at 1 μM with 0.3 mg/mL microsomes in PBS pH 7.4 (1% DMSO). Compounds were incubated at 37°C for 60 minutes with a 350-rpm orbital shaking with time points taken at 0 minutes and 60 minutes. Samples were analyzed by UPLC-MS (Waters, Milford, MA) with compounds detected by SIR detection on a single quadrupole mass spectrometer.

Compounds of the invention show improved water solubility. For example, compounds of the invention have at least about 1.5 fold, at least about 2 fold, at least about 3 fold, at least about 4 fold, at least about 5 fold, at least about 6 fold, at least about 8 fold, at least about 10 fold, at least about 50 fold, at least about 100 fold, at least about 500 fold, or at least about 1,000 fold increase in water solubility as compared to reference compounds. For example, compounds of the invention have a water solubility of at least about 2 μM, at least about 4 μM, at least about 6 μM, at least about 8 μM, at least about 10 μM, at least about 20 μM, at least about 30 μM, at least about 40 μM, at least about 50 μM, at least about 60 μM, at least about 70 μM, at least about 80 μM, at least about 90 μM, or at least about 100 μM. For example, compounds of the invention have a water solubility of at least about 6 μM, at least about 8 μM, at least about 10 μM, 20 μM, 30 μM, 40 μM, 50 μM, 60 μM, 70 μM, 80 μM, 90 μM, or 100 μM.

The invention relates to a compound of the invention or a pharmaceutically acceptable salt, solvate, or prodrug thereof. In one aspect, the invention relates to a compound of the invention or a pharmaceutically acceptable salt. In one aspect, the invention relates to a compound of the invention or a pharmaceutically acceptable salt or solvate thereof. In one aspect, the invention relates to a pharmaceutically acceptable salt of a compound of the invention. In one aspect, the invention relates to a solvate of a compound of the invention. In one aspect, the invention relates to a hydrate of a compound of the invention. In one aspect, the invention relates to a prodrug of a compound of the invention.

The invention relates to methods of synthesizing a compound of the invention. A compound of the invention can be synthesized using a variety of methods known in the art. The schemes and description below depict general routes for the preparation of a compound of the invention.

General Synthetic Scheme 1



General protocol for amine capping

At 0 °C, the appropriate acid chloride (1.1 equiv) was added dropwise to a solution of methyl 2-((2*S*,4a*S*,12a*R*)-8-amino-5-methyl-6-oxo-2,3,4,4a,5,6,12,12a-octahydrobenzo[*b*]pyrano[3,2-*f*][1,5]oxazocin-2-yl)acetate (1.0 equiv) and triethylamine (1.5 equiv) in CH_2Cl_2 (0.05 M). After complete conversion of the starting material, the reaction was quenched with a saturated solution of ammonium chloride, and the crude mixture was partially concentrated. The aqueous phase was extracted with EtOAc and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography to give the desired product.

General protocol for ester hydrolysis

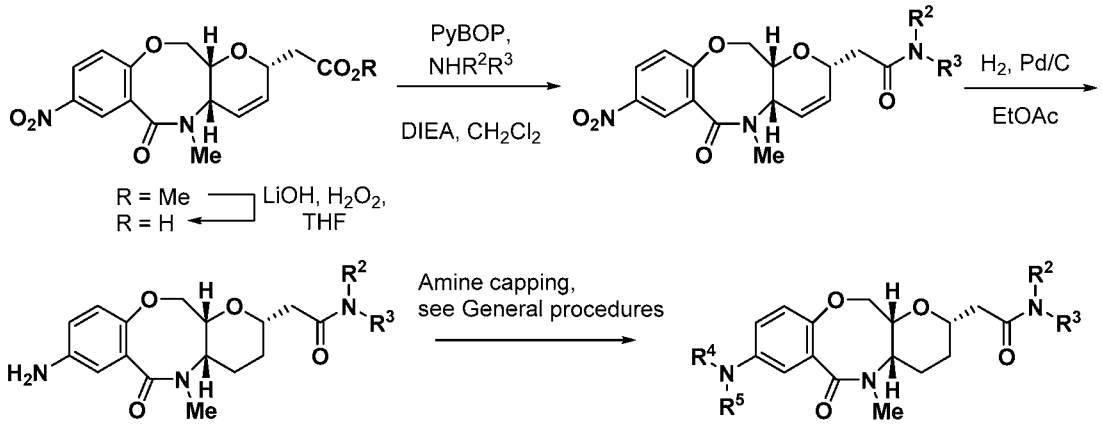
A THF solution (0.05 M) of the appropriate methyl ester (1.0 equiv) was cooled in an ice bath (0 °C), and hydrogen peroxide (30 % by weight, 12.0 equiv) was added to the mixture, followed by lithium hydroxide (1.0 M in water, 6.0 equiv). The reaction was stirred overnight, reaching r.t. progressively, upon which LCMS analysis showed complete disappearance of the starting material. At 0 °C, the reaction mixture was acidified with 1N HCl solution until pH ~3, diluted with brine (75 mL) and extracted with EtOAc (3x40 mL). Combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the desired product, which is used in the next step without further purification.

General protocol for amidation of the carboxylic acid

At 0 °C, the appropriate amine (1.3 equiv) was added to a solution of the appropriate carboxylic acid (1.0 equiv) and DIEA (3.0 equiv) in CH_2Cl_2 (0.05 M), followed by PyBOP (1.6 equiv). The reaction mixture was stirred overnight, reaching r.t. progressively. The reaction mixture was diluted with CH_2Cl_2 and washed with a saturated solution of ammonium chloride. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers

were dried over Na_2SO_4, filtered and concentrated to yield a crude material which was purified by chromatography on silica gel.

General Synthetic Scheme 2



Hydrolysis and amidation were carried out using the general protocol described above.

General protocol for reduction of the nitro and alkene motifs

The appropriate starting material (1.0 equiv) was dissolved in EtOAc (0.1 M) and the mixture was degassed with an argon sparge for 15 minutes. Activated palladium on carbon (Pd/C, 10% by weight, 0.025 equiv) was added at r.t., and hydrogen was sparged through the suspension for 30 min. The reaction was stirred overnight under hydrogen atmosphere and the mixture was filtered through a plug of celite. Removal of the solvents *in vacuo* afforded the desired product, which was used directly without further purification.

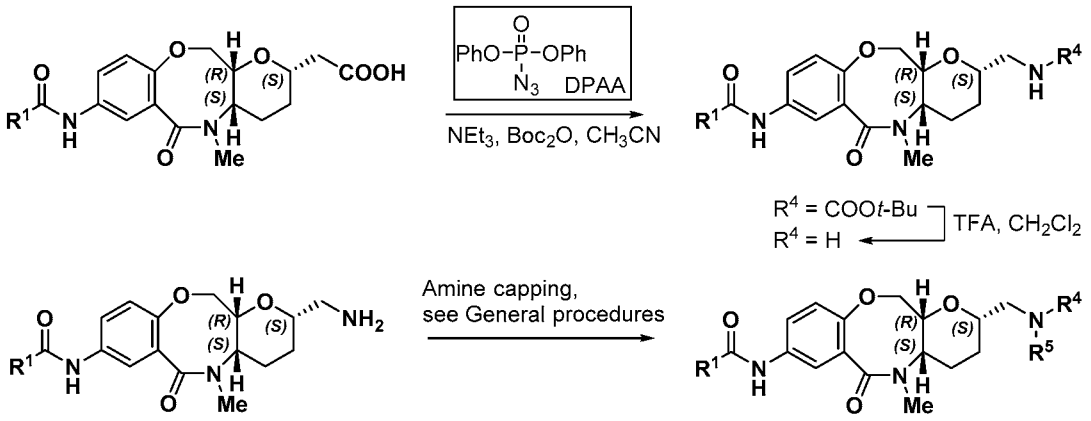
General protocol for aniline capping

Amidation: carried out using the general protocol above.

Reductive alkylation: At r.t., sodium cyanoborohydride (3.0 equiv) was added in one portion to a solution of the appropriate amine (1.0 equiv) and the appropriate aldehyde (1.0 equiv) in THF (0.05 M). Acetic acid (AcOH, 0.5 equiv) was added and the reaction mixture was stirred overnight at r.t., diluted with EtOAc and quenched with a saturated solution of sodium bicarbonate. The aqueous layer was extracted with EtOAc and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The resulting crude material was purified by column chromatography on silica gel.

For analogs in which R^5 is Me, the appropriate SM ($R^4 \neq H$ and $R^5 = H$) is treated with formaldehyde using the general protocol for reductive alkylation.

General Synthetic Scheme 3



General protocol for Curtius reaction

At r.t. and under argon atmosphere, DPPA (2.0 equiv) was added dropwise to a solution of the appropriate carboxylic acid (1.0 equiv) and triethylamine (3.0 equiv) in dry acetonitrile (0.01 M). The reaction mixture was heated at 50 °C for two hours, cooled to r.t. for 15 min and transferred dropwise *via* Pasteur pipet to an aqueous solution of 1M NaOH, under vigorous stirring and cooled at 0 °C. After 30 min, Boc_2O (10 equiv) was quickly added to the solution and the reaction mixture was stirred overnight, gradually warming to r.t.. Solvents were partially removed *in vacuo* and the mixture was extracted with CH_2Cl_2. Combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated and the residue was purified by silica gel chromatography.

General protocol for Boc deprotection

At 0 °C, trifluoroacetic acid (TFA, 20.0 equiv) was added dropwise to a solution of the appropriate Boc protected amine (1.0 equiv) in CH_2Cl_2 (0.05 M). After 10 min, the reaction mixture was warmed to r.t. and stirred until complete disappearance of the starting material (LCMS). The crude was then concentrated to dryness, redissolved in EtOAc and washed with a saturated solution of sodium bicarbonate until pH ~ 7. The combined aqueous phases were extracted with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to give the desired product, which was used without further purification.

General protocol for amine capping

Formation of carbomate: At 0 °C, the appropriate chloroformate (1.1 equiv) was added to a solution of the appropriate amine (1.0 equiv) and triethylamine (5.0 equiv) in CH_2Cl_2 (0.05 M). After 15 min, the ice bath was removed and the reaction mixture was stirred at rt overnight. Silica gel was then added and the crude was concentrated to dryness. Purification was done *via* silica gel chromatography affording the desired product.

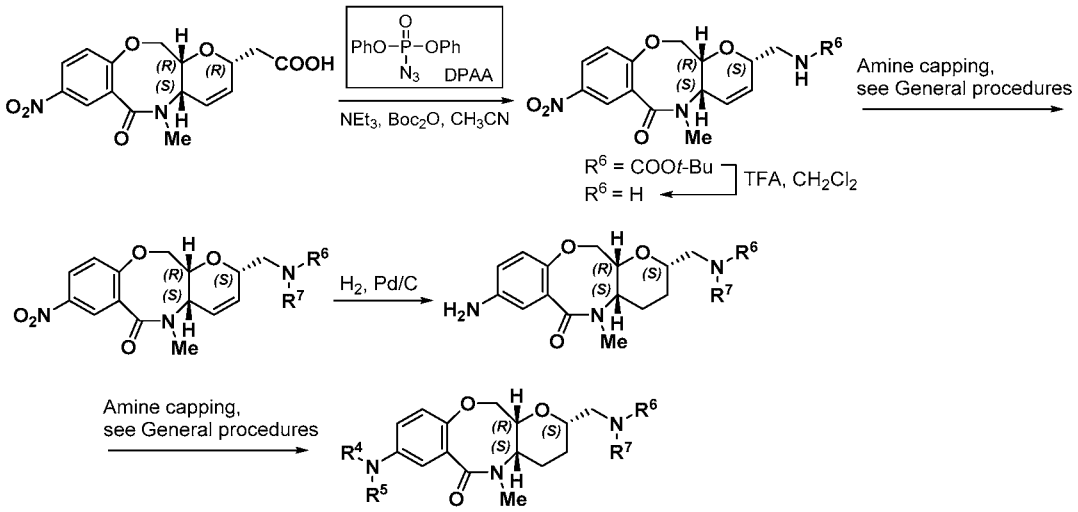
Alternative protocol for the formation of carbomate: At 0 °C, the appropriate chloroformate (1.1 equiv) was added to a solution of the appropriate amine (1.0 equiv) in a mixture of 1,4-dioxane and saturated aqueous sodium bicarbonate solution (dioxane:sat. $NaHCO_3$=2:1, 0.05M concentration). Upon completion of the reaction (LCMS), extraction of the mixture with EtOAc followed by evaporation of the solvents afforded a crude residue which was purified via silica gel chromatography.

Formation of amide: At 0 °C, the appropriate carboxylic acid (2.0 equiv) was added to a solution of the amine (1.0 equiv) and TEA (6.0 equiv) in CH_2Cl_2/DMF (40:1 ratio, 0.05 M), followed by PyBOP (2.2 equiv). The reaction mixture was stirred overnight, reaching r.t. progressively. The reaction mixture was diluted with CH_2Cl_2 and washed with a saturated solution of sodium bicarbonate. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4, filtered and concentrated to yield a crude material which was purified by chromatography on silica gel.

Formation of amino oxadiazole: The appropriate oxadiazolone (1.3 equiv) was added to the appropriate amine (1.0 equiv) in DMF (0.05M), followed by DIPEA (4 equiv) and BOP (1.5 equiv). The reaction was stirred at room temperature until complete conversion was observed. The mixture was partially concentrated, taken up in EtOAc and washed with a saturated solution of sodium bicarbonate. The layers separated and the aqueous layer extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated to yield a crude material which was purified by chromatography on silica gel.

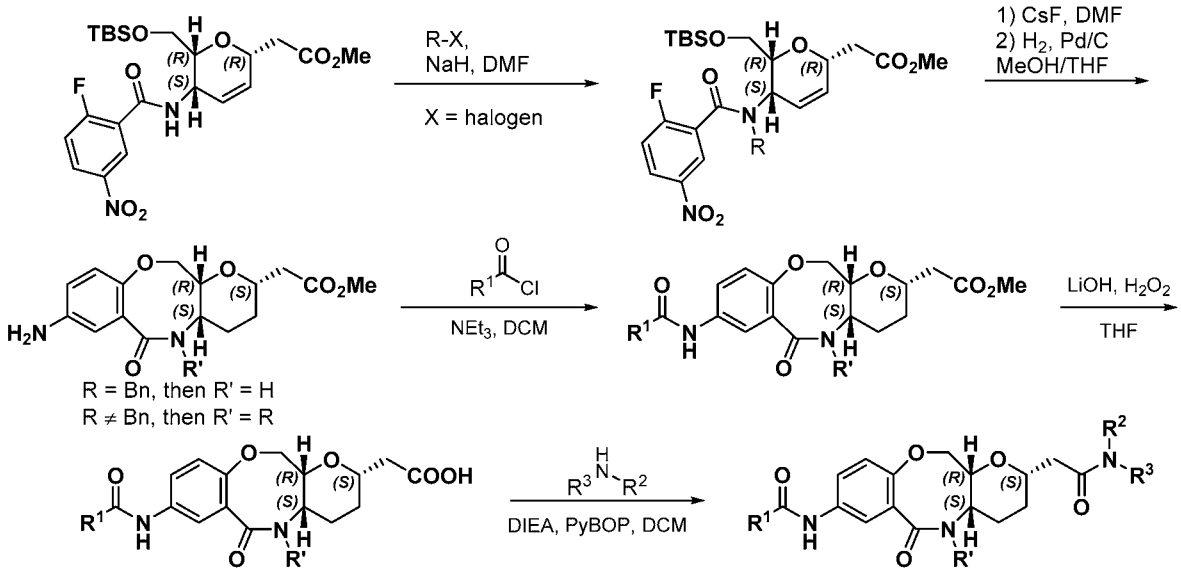
Formation of sulfonamide: At 0 °C, the appropriate sulfonyl chloride (1.1 equiv) was added to a solution of the appropriate amine (1.0 equiv) and triethylamine (5.0 equiv) in CH2Cl2 (0.05 M). After 15 min, the ice bath was removed and the reaction mixture was stirred at rt overnight. Silica gel was then added and the crude was concentrated to dryness. Purification was done via silica gel chromatography affording the desired product.

General Synthetic Scheme 4



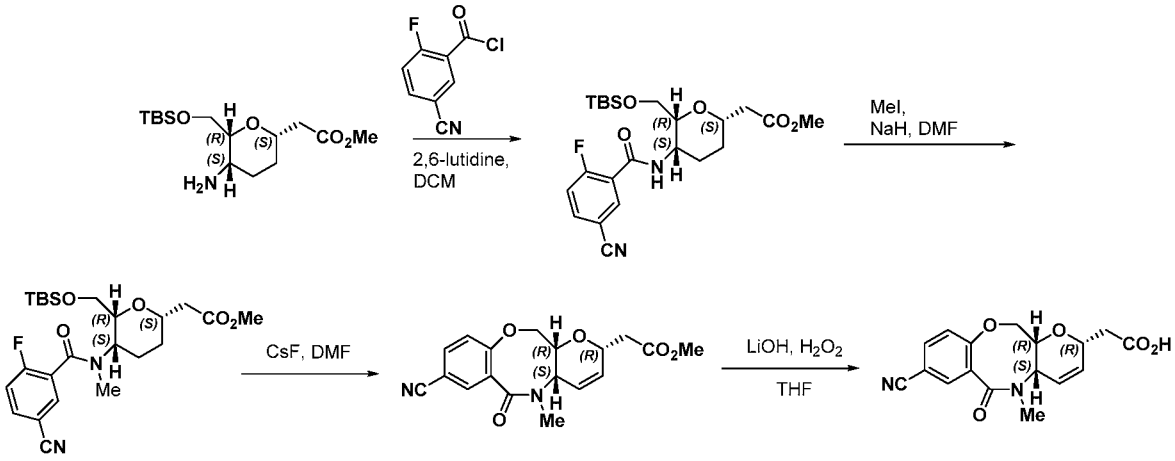
The Curtius reaction, Boc deprotection, amine capping, reduction of the nitro and alkene, and subsequent aniline (amine) capping were carried out using the general protocol described above.

General Synthetic Scheme 5



The starting material for this synthesis is Compound 12, which is described in J. Org. Chem., 2013, 78, 5160-5171.

General Synthetic Scheme 6



Synthesis of the starting material has been previously reported in J. Org. Chem., 2013, 78, 5160-5171.

Modulation of *TRIB1* and other key regulators in lipoprotein metabolism

Recent genome-wide association (GWAS) studies have uncovered novel genes associated with CAD and MI. *TRIB1* emerged in several GWAS studies as a novel cardiovascular locus where the protective allele is strongly associated with decreased levels of circulating LDL-C and triglycerides (TG), increased levels of high-density lipoprotein (HDL) as well as with reduced incidence of CAD and MI (T. M. Teslovich et al., Nature 466, 707 (Aug 5, 2010)). Additional studies in mice confirmed the link between *TRIB1* and lipid levels and demonstrated that increased expression of *TRIB1* is protective against the disease (R. Burkhardt *et al.*, *J Clin Invest* **120**, 4410 (Dec, 2010)). Hepatic overexpression of *TRIB1* in mice reduces the secretion of VLDL particles from the liver into the bloodstream and consistently, overexpression of *TRIB1* in human hepatoma cells reduces apoB secretion. Studies have shown that hepatic overexpression of *TRIB1* in mice correlates with decreased expression of TG biosynthetic genes (Fasn, Scd1, Dgat2) and decreased rate of TG formation suggesting that reduced availability of TG's leads to insufficient apoB lipidation targeting nascent apoB to ER-associated degradation (R. Burkhardt *et al.*, 2010)). *TRIB1*, as other members of the tribbles family, is a pseudokinase and it may act as an adaptor protein in the MEK/ERK signaling pathway. It has been reported to be involved in inflammation (T. Yokoyama, T. Nakamura, Cancer Sci 102, 1115 (Jun, 2011)), however prior to cardiovascular GWAS studies it was not generally known to modulate hepatic lipoprotein metabolism (E. Kiss-Toth, Biochem Soc Trans 39, 684 (Apr, 2011)). Compounds of the invention are inducers or upregulators of *TRIB1* expression. As a result, these compounds are

useful in treating and/or preventing various diseases, disorders and conditions of the cardiovascular system, including e.g., myocardial infarction, coronary heart disease, atherosclerosis and dyslipidemia. The compounds of the invention are useful in treating and/or preventing various diseases, disorders and conditions of the liver, including e.g., cirrhosis and liver cancer. The compounds of the invention are useful in treating and/or preventing various diseases, disorders and conditions that would benefit from higher expression of *TRIB1* and/or higher expression levels of *LDLR* and/or lower expression levels of *PCSK9* and/or lower expression levels of *MTTP* and/or lower expression levels of *APOC3*.

In one aspect, the invention provides a method of increasing the uptake of LDL in a cell, the method comprising contacting a cell or a population of cells with a compound of the invention or a pharmaceutically acceptable salt thereof with an amount sufficient to increase the uptake of LDL as compared to the LDL of the cell or population of cells in the absence of the compound or pharmaceutically acceptable salt thereof. In one aspect, the uptake of LDL is increased by at least about 1.5-fold, about 2-fold, about 3-fold, about 5-fold, about 10-fold, about 15-fold, about 20-fold or about 30-fold. In one aspect, the type of cell or population of cells is selected from heptic, skin, adrenal gland, muscle, or kidney cell. In one aspect, the type of cell is HepG2 cell. In one aspect, compounds of the invention modulate the expression of one or more genes or one or more products of one or more genes selected from *TRIB1*, *SCAP*, *SREBF1*, *SREBF2*, *PCSK9*, *LDLR*, *HMGCR*, *HMGCS*, *FASN*, *SCD1*, *MTTP and APOC3*. The number of genes or products of genes modulated is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12.

In one aspect, the compounds of the invention increase the expression of *TRIB1*. In one aspect, the compounds of the invention increase the expression of *TRIB1* and decrease the expression of *PCSK9*. In one aspect, the compounds of the invention increase the expression of *TRIB1* and *LDLR* and decrease the expression of *PCSK9, MTTP and APOC3*. In one aspect, the compounds of the invention decrease expression of one or more genes selected from *HMGCR*, *HMGCS*, *FASN*, *SREBF1*, and *SCD1*. The number of genes is 1, 2, 3, 4, or 5. In one aspect, the compounds of the invention do not change the expression of one or more genes selected from *SCAP* or *SREBF2*. The number of genes is 1 or 2. In one aspect, the compounds of the invention modulate the protein expression level of a protein selected from ApoB and LDLR.

In one aspect, the invention provides a method of increasing the LDL receptor level on a cell, the method comprising contacting a cell or a population cells with a compound of the invention with an amount sufficient to increase LDL receptor level as compared to the

LDL receptor level of the cell or population of cells in the absence of the compound. In one aspect, the uptake of LDL is increased by at least about 1.5-fold, at least about 2-fold, at least about 3-fold, at least about 5-fold, at least about 10-fold, at least about 15-fold, at least about 20-fold or at least about 30-fold. In one aspect, the type of cell or population of cells is selected from heptic, skin, adrenal gland, muscle, or kidney cell. In one aspect, the type of cell is HepG2 cell. In aspect, the compounds of the invention modulate the expression of one or more genes or one or more products of one or more genes selected from *TRIB1*, *SCAP*, *SREBF1*, *SREBF2*, *PCSK9*, *LDLR*, *HMGCR*, *HMGCS*, *FASN*, *SCD1, MTTP and APOC3*. The number of genes or products of genes is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12.

In one aspect, the compounds of the invention increase the expression of *TRIB1*. In one aspect, the compounds of the invention increase the expression of *TRIB1* and decrease the expression of *PCSK9*. In one aspect, the compounds of the invention increase the expression of *TRIB1* and *LDLR* and decrease the expression *PCSK9, MTTP and APOC3*. In one aspect, the compounds of the invention decrease expression of one or more genes selected from *HMGCR*, *HMGCS*, *FASN*, *SREBF1* and *SCD1*. The number of genes is 1, 2, 3, 4, or 5. In one aspect, the compounds of the invention do not change the expression of one or more genes selected from *SCAP* or *SREBF2*. The number of genes is 1 or 2. In one aspect, the compounds of the invention modulate the protein expression level of a protein selected from ApoB and LDLR.

The invention provides methods of treating or preventing a disease, disorder, or condition. In one aspect, the invention provides a method of treating a disease, disorder, or condition. In one aspect, the invention provides a method of preventing a disease, disorder, or condition.

In one aspect, the invention provides a method of treating or preventing a disease, disorder, or condition associated with elevated LDL-cholesterol in a subject in need thereof comprising administering to the subject an effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof. In one aspect, the invention provides a method of treating disease, disorder, or condition associated with elevated LDL-cholesterol in a subject in need thereof comprising administering to the subject an effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof.

In one aspect, the invention provides a method of treating or preventing a lipoprotein related disorder (e.g., cholesterol related disorder) in a subject in need thereof comprising administering to the subject an effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof. In one aspect, the invention provides a method of

treating a lipoprotein related disorder (e.g., cholesterol related disorder) in a subject in need thereof comprising administering to the subject an effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof. In one aspect, the lipoprotein related disorder (e.g., cholesterol related disorder) is any disorder that is characterized by decreased levels of *TRIB1* in the subject. In one aspect, the lipoprotein related disorder (e.g., cholesterol related disorder) is any disorder that can be treated by increasing expression levels of *TRIB1* in a subject in need of treatment. In one aspect, the lipoprotein related disorder (e.g., cholesterol related disorder) is any disorder that can be prevented by increasing expression levels of *TRIB1* in a subject in need of prevention.

In one aspect, the invention provides a method of increasing availability of LDLR in a subject comprising administering to the subject an effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof.

In one aspect, the invention provides a method of reducing LDL-cholesterol level in a subject comprising administering to the subject an effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof.

In one aspect, the invention provides a method of lowering serum LDL-cholesterol level in a subject comprising administering to the subject an effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof.

In one aspect, the invention provides a method of treating or preventing a disease in a subject in need thereof comprising administering to the subject an effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof, wherein said compound increases LDL uptake. In one aspect, the invention provides a method of treating a disease in a subject in need thereof comprising administering to the subject an effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof, wherein said compound increases LDL uptake.

In one aspect, the invention provides a method of treating or preventing diseases, conditions, or disorders in a subject in need thereof, where said diseases, conditions, or disorders are generally addressable through the use of statins. In one aspect, the invention provides a method of treating diseases, conditions, or disorders in a subject in need thereof, where said diseases, conditions, or disorders are generally addressable through the use of statins.

In one aspect, the invention provides a method of treating or preventing cardiovascular disease in a subject in need thereof comprising administering to the subject an effective amount of a compound of the invention or a pharmaceutically acceptable salt

thereof. In one aspect, the invention provides a method of treating cardiovascular disease in a subject in need thereof comprising administering to the subject an effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof. In one aspect, the cardiovascular disease is myocardial infarction, coronary heart disease, atherosclerosis or hypocholesterolemia. In one aspect, the cardiovascular disease is any cardiovascular disease that is characterized by decreased levels of *TRIB1* in the subject. In one aspect, the cardiovascular disease is any cardiovascular disease that can be treated by increasing expression levels of *TRIB1* in a subject in need of treatment. In one aspect, the cardiovascular disease is any cardiovascular disease that can be prevented by increasing expression levels of *TRIB1* in a subject in need of prevention.

In one aspect, the invention provides a method of treating hypercholesterolemia in a subject, comprising administering to the subject an effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof.

In one aspect, the invention provides a method of treating or preventing a liver disease or disorder in a subject in need thereof comprising administering to the subject an effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof. In one aspect, the invention provides a method of treating a liver disease or disorder in a subject in need thereof comprising administering to the subject an effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof. In one aspect, the liver disease or disorder is liver cirrhosis, hepatocellular carcinoma, liver injury or abnormal liver function.

In one aspect, the invention provides a method of treating or preventing a disease in a subject in need thereof comprising administering to the subject an effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof, wherein said compound down regulates the expression level of *PCSK9, MTTP and APOC3* and up regulates expression level of *TRIB1 and LDLR*. In one aspect, the invention provides a method of treating a disease in a subject in need thereof comprising administering to the subject an effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof, wherein said compound down regulates the expression level of *PCSK9, MTTP and APOC3* and up regulates expression level of *TRIB1 and LDLR*. In one aspect, the disease is a lipoprotein related disorder (e.g., cholesterol related disorder). In one aspect, the disease is a cardiovascular disease or a liver disease or disorder. In one aspect, the subject is at an elevated risk for cardiovascular disease. In one aspect, the expression level of *PCSK9* is

down regulated by at least about 50%. In one aspect, the expression level of *TRIB1* is up regulated by at least about 50%.

TRIB1 (tribbles homolog 1, TRB1) is a regulator of lipoprotein metabolism. Recent genome-wide association studies identified *TRIB1* as having minor alleles associated with lower levels of plasma triglyceride and LDL-C (low density lipoprotein cholesterol), higher levels of HDL-C (high density lipoprotein-C), as well as significantly decreased risk for myocardial infarction and coronary heart disease (T. M. Teslovich *et al.*, *Nature* **466**, 707 (Aug 5, 2010)). *TRIB1* is highly expressed in the liver, which is the major site for the formation, secretion, and clearance of circulating lipoproteins. Overexpression of *TRIB1* in mouse models causes significant reduction of VLDL (very low density lipoprotein), LDL, and HDL cholesterol and triglycerides (R. Burkhardt et al., J Clin Invest 120, 4410 (Dec, 2010)). In one aspect, a compound of the invention modulates or upregulates *TRIB1* for treating and/or a preventing cardiovascular disease (e.g., myocardial infarction, coronary heart disease, atherosclerosis, or dyslipidemia).

TRIB1 alleles have also been shown to be associated with concentrations of liver enzymes (J. C. Chambers et al., Nat Genet 43, 1131 (Nov, 2011)). High liver enzyme concentrations are associated with increased risk of cirrhosis, hepatocellular carcinoma, liver injury (e.g., alcohol misuse, viral and other infections, metabolic disorders, obesity, autoimmune disease, and drug toxicity), and abnormal liver function (D. S. Pratt, M. M. Kaplan, N Engl J Med 342, 1266 (Apr 27, 2000)). In one aspect, a compound of the invention is useful for treating and/or preventing liver diseases (e.g., cirrhosis or liver cancer).

In one aspect, compounds of the present invention increase the expression levels of *TRIB1*. In one aspect, the protein expression level of *TRIB1* is increased. In one aspect, the RNA transcript level is increased. In one aspect, compounds of the invention increase *TRIB1* expression by at least about 50%. In one aspect, compounds of the invention increase *TRIB1* expression by at least about 1.5-fold, at least about 2-fold, at least about 3-fold, at least about 4-fold, at least about 5-fold, at least about 10-fold, at least about 15-fold, or at least about 20-fold.

In one aspect, compounds of the invention are useful for diseases that are associated with decreased levels of *TRIB1* in a subject. In one aspect, compounds of the invention are useful for diseases that are treated or prevented by increasing levels of *TRIB1* in a subject. In

one aspect, a compound of the invention is useful for diseases that are treated by increasing levels of *TRIB1* in a subject.

In one aspect, compounds of the invention also decrease the expression of *PCSK9*. In one aspect, compounds of the invention also increase the expression of *LDLR* (low density lipoprotein receptor). In one aspect, expression or expression levels refers to protein expression and/or gene expression (e.g., RNA).

In one aspect, compounds of the invention stimulate a unique signature of cellular responses, without affecting cellular ATP levels or cell viability. This unique signature of cellular responses comprises: 1) upregulation of transcript levels for *TRIB1*; 2) downregulation of transcript levels for *PCSK9*; or 3) up regulation of transcript levels for *LDLR*. The unique signature of cellular responses may further comprise any one or more of the following: 1) downregulation of transcript levels for genes in the cholesterol biosynthetic pathway (e.g., *HMGCS*, *HMGCR*); 2) downregulation of transcript levels for genes in the triglyceride biosynthetic pathway (e.g., *FASN, SCD1*); 3) down regulation of transcript levels of a gene for microsomal triglyceride transfer protein (*MTTP*) important for the lipidation of the ApoB 4) down regulation of transcript levels of a gene for apolipoprotein C3 that up regulates triglyceride levels (*APOC3*) 5) decreased level of secreted ApoB100 protein; 6) decreased level of secreted PCSK9 protein; or 7) increased level of LDLR in cells. Each of the responses listed above has individually been linked to the reduction of LDL-C and/or TG in circulation.

The transcriptional profile produced by compounds of the invention is markedly different from the transcriptional profile produced by statin treatment. In addition to *TRIB1* upregulation, treatment with compounds of the invention also modulates the expression of one or more genes involved in sterol regulatory pathways. In one aspect, compounds of the invention upregulate the expression of *LDLR* and downregulate the expression of *PCKS9, HMGCS, HMGCR, FASN, SCD1, MTTP and APOC3*. In contrast, treatment with a statin, such as atorvastatin, upregulates the expression of *PCSK9*, as well as *LDLR, HMGCS* and *HMGCR*. In one aspect, downregulation of *PCKS9* is indicative or confers additional therapeutic benefits of treatment with compounds of the invention. Differences in pharmacological mode of action between compounds of the invention and statins suggest different efficacies in treating and preventing cardiovascular diseases and related disorders. Downregulation of *PSCK9* expression with compounds of the invention may provide therapeutic benefit similar to treatments with anti-PCSK9 monoclonal antibodies or other biologic PSCK9 blockers but can differ from anti-PCSK9 biologics in the route of

administration and offer a convenience and the ease of use of an oral drug versus intravenous therapy.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent for treating a disease in a subject comprising: (a) administering the therapeutic agent to the subject; (b) determining a first level of expression of one or more signature genes or one or more products of one or more signature genes in a sample from the subject at a first time point; and (c) comparing the first level of expression of one or more signature genes or one or more products of one or more signature genes at the first time point to a reference profile; wherein the difference in the level of expression at the first time point as compared to the level of expression of the reference profile indicates that the therapeutic agent is effective for treating the disease. In one aspect, the one or more signature genes are selected from *TRIB1*, *SCAP*, *SREBF1*, *SREBF2*, *PCSK9*, *LDLR*, *HMGCR*, *HMGCS*, *FASN*, *SCD1*, *MTTP and APOC3*. In one aspect, the number of signature genes is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12. In one aspect, the disease is associated with decreased expression of *TRIB1*. In one aspect, determining the expression level is determining the level of protein or RNA transcripts. In one aspect, the reference profile is obtained from a subject that does not have the disease. In one aspect, the reference profile is obtained from the subject at a time point prior to administering the therapeutic agent. In one aspect, the disease is a lipoprotein (e.g., cholesterol) related disorder. In one aspect, the disease is a cardiovascular disease. In one aspect, the therapeutic agent is a compound of the invention.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent for treating a disease in a subject comprising: (a) administering the therapeutic agent to the subject; (b) determining the expression level of *TRIB1* in a sample from the subject at a first time point; and (c) comparing the expression level of *TRIB1* at the first time point to a reference profile, wherein an increase in *TRIB1* expression compared to the reference profile indicates that the therapeutic agent is effective for treating the disease.

In one aspect, the invention provides a method of accessing the efficacy of a therapeutic agent for treating a disease in a subject comprising: (a) administering the therapeutic agent to the subject; (b) determining the expression level of *PCKS9* in a sample from the subject at a first time point; and (c) comparing the expression level of *PCKS9* at a first time point to a reference profile, wherein a decrease in the level of *PCKS9* expression at the first time point as compared to the reference profile indicates that the therapeutic agent is effective for treating the disease.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent for treating a disease in a subject comprising: (a) administering the therapeutic agent to the subject; (b) determining the expression level of *TRIB1* and *PCSK9* in a sample from the subject at a first time point; and (c) comparing the expression level of *TRIB1* and *PCSK9* at a first time point to a reference profile; wherein an increase in *TRIB1* expression and a decrease in *PCKS9* expression compared to the reference profile indicates that the therapeutic agent is effective for treating the disease. In one aspect, the disease is associated with decreased expression of *TRIB1*. In one aspect, the invention provides a method, wherein determining the expression level is determining the level of protein or RNA transcripts.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent related to determining the expression level of *TRIB1* and/or *PCSK9*, wherein the reference profile is obtained from a subject that does not have the disease. In one aspect, the reference profile is obtained from the subject a time point prior to administering the therapeutic agent.

In one aspect, the expression level of *TRIB 1* at the first time point is up regulated by at least about 50%. In one aspect, the expression level of *TRIB1* at the first time point is increased by at least about 1.5-fold, at least about 2-fold, at least about 3-fold, at least about 4-fold, at least about 5-fold, at least about 10-fold, at least about 15-fold, or at least about 20-fold. In one aspect, the invention provides a method, wherein said expression level of *PCSK9* is downregulated by at least about 50%. In one aspect, the expression level of *PCSK9* is decreased by at least about 2-fold, at least about 3-fold, at least about 4-fold, at least about 5-fold, at least about 10-fold, at least about 15-fold, or at least about 20-fold. In one aspect, the therapeutic agent is a compound of the invention. In one aspect, the disease is a lipoprotein related disorder (e.g., cholesterol related disorder). In one aspect, the disease is a cardiovascular disease.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent for treating a disease in a subject comprising: (a) administering a therapeutic agent to the subject; (b) determining the protein expression level of ApoB in a sample from the subject at a first time point; and (c) comparing the protein expression level of ApoB at the first time point to a reference profile; wherein a decrease in expression of ApoB at the first time point compared to the reference profile indicates that the therapeutic agent is effective for treating the disease. In one aspect, the reference profile is obtained from a subject that does not have the disease. In one aspect, the reference profile is obtained from

the subject a time point prior to administering the therapeutic agent. In one aspect, the protein expression level of ApoB at the first time point is downregulated by at least about 50%. In one aspect, the expression of ApoB is increased by at least about 1.5-fold, at least about 2-fold, at least about 3-fold, at least about 4-fold, at least about 5-fold, at least about 10-fold, at least about 15-fold, or at least about 20-fold. In one aspect, the therapeutic agent is a compound of the invention. In one aspect, the disease is a lipoprotein related disorder (e.g., cholesterol related disorder). In one aspect, the disease is a cardiovascular disease.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent for treating a disease in a subject comprising: (a) administering a therapeutic agent to the subject; (b) determining the protein expression level of LDLR in a sample from the subject at a first time point; and (c) comparing the protein expression level of LDLR at the first time point to a reference profile; wherein an increase in expression of LDLR at the first time point compared to the reference profile indicates that the therapeutic agent is effective for treating the disease. In one aspect, the reference profile is obtained from the subject prior to administering the therapeutic agent. In one aspect, the protein expression level of LDLR at the first time point is up regulated by at least about 50%. In one aspect, the expression of LDLR is increased by at least about 1.5-fold, at least about 2-fold, at least about 3-fold, at least about 4-fold, at least about 5-fold, at least about 10-fold, at least about 15-fold, or at least about 20-fold. In one aspect, the therapeutic agent is a compound of the invention. In one aspect, the disease is a lipoprotein related disorder (e.g., cholesterol related disorder). In one aspect, the disease is a cardiovascular disease.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent for treating a disease in a subject comprising: (a) administering the therapeutic agent to the subject; (b) determining the RNA transcript level of *SREBF1* in a sample from the subject at a first time point; and (c) comparing the RNA transcript level of *SREBF1*at the first time point to a reference profile; wherein a decrease in expression of *SREBF1* at the first time point compared to the reference profile indicates that the therapeutic agent is effective for treating the disease. In one aspect, the RNA transcript level of *SREBF1* in the sample from the subject is down regulated by about 1-2 fold. In one aspect, the reference profile is obtained from the subject prior to administering the therapeutic agent. In one aspect, the therapeutic agent is a compound of the invention. In one aspect, the disease is a lipoprotein (e.g., cholesterol related disorder). In one aspect, the disease is a cardiovascular disease.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent for treating a disease in a subject comprising: (a) administering the therapeutic agent to the subject; (b) determining the RNA transcript level of *HMGCR* in a sample from the subject at a first time point; and (c) comparing the RNA transcript level of *HMGCR* at the first time point to a reference profile; wherein a decrease in expression of *HMGCR* at the first time point compared to the reference profile indicates that the therapeutic agent is effective for treating the disease. In one aspect, the RNA transcript level of *HMGCR* in the sample from the subject is down regulated by at least about 50%. In one aspect, the expression of *HMGCR* is decreased by at least about 2-fold, at least about 3-fold, at least about 4-fold, at least about 5-fold, at least about 10-fold, at least about 15-fold, or at least about 20-fold. In one aspect, the reference profile is obtained from the subject prior to administering the therapeutic agent. In one aspect, the therapeutic agent is a compound of the invention. In one aspect, the disease is a lipoprotein related disorder (e.g., cholesterol related disorder). In one aspect, the disease is a cardiovascular disease.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent for treating a disease in a subject comprising: (a) administering a therapeutic agent to the subject; (b) determining the RNA transcript level of *HMGCS* in a sample from the subject at a first time point; and (c) comparing the RNA transcript level of *HMGCS* at the first time point to a reference profile; wherein a decrease in the RNA transcript level of *HMGCS* at the first time point compared to the reference profile indicates that the therapeutic agent is effective for treating the disease. In one aspect, the RNA transcript level of *HMGCS* in the sample from the subject is down regulated by at least about 50%. In one aspect, the RNA transcript level of *HMGCS* is decreased by at least about 2-fold, at least about 3-fold, at least about 4-fold, at least about 5-fold, at least about 10-fold, at least about 15-fold, or at least about 20-fold. In one aspect, the reference profile is obtained from the subject prior to administering the therapeutic agent. In one aspect, the therapeutic agent is a compound of the invention. In one aspect, the disease is a lipoprotein related disorder. In one aspect, the disease is a cholesterol related disorder. In one aspect, the disease is a cardiovascular disease.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent for treating a disease in a subject comprising: (a) administering the therapeutic agent to the subject; (b) determining the RNA transcript level of *FASN* in a sample from the subject at a first time point; and (c) comparing the RNA transcript level of *FASN* at the first time point to a reference profile; wherein a decrease in RNA transcript level

at the first time point compared to the reference profile indicates that the therapeutic agent is effective for treating the disease. In one aspect, the RNA transcript level of *FASN* in the sample from the subject is down regulated by at least about 50%. In one aspect, the RNA transcript level of *FASN* is decreased by at least about 2-fold, at least about 3-fold, at least about 4-fold, at least about 5-fold, at least about 10-fold, at least about 15-fold, or at least about 20-fold. In one aspect, the reference profile is obtained from the subject prior to administering the therapeutic agent. In one aspect, the therapeutic agent is a compound of the invention. In one aspect, the disease is a lipoprotein related disorder. In one aspect, the disease is a cholesterol related disorder. In one aspect, the disease is a cardiovascular disease.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent for treating a disease in a subject comprising: (a) administering the therapeutic agent to the subject; (b) determining the RNA transcript level of *SCD1* in a sample from the subject at a first time point; and (c) comparing the RNA transcript level of *SCD1* at the first time point to a reference profile; wherein a decrease in the RNA transcript level at the first time point compared to the reference profile indicates that the therapeutic agent is effective for treating the disease. In one aspect, the RNA transcript level of *SCD1* in the sample from the subject is down regulated by at least about 50%. In one aspect, the RNA transcript level of *SCD1* is decreased by at least about 2-fold, at least about 3-fold, at least about 4-fold, at least about 5-fold, at least about 10-fold, at least about 15-fold, or at least about 20-fold. In one aspect, the reference profile is obtained from the subject prior to administering the therapeutic agent. In one aspect, the therapeutic agent is a compound of the invention. In one aspect, the disease is a lipoprotein related disorder. In one aspect, the disease is a cholesterol related disorder. In one aspect, the disease is a cardiovascular disease.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent for treating a disease in a subject comprising: (a) administering the therapeutic agent to the subject; (b) determining the RNA transcript level of *MTTP* in a sample from the subject at a first time point; and (c) comparing the RNA transcript level of *MTTP* at the first time point to a reference profile; wherein a decrease in the RNA transcript level at the first time point compared to the reference profile indicates that the therapeutic agent is effective for treating the disease. In one aspect, the RNA transcript level of *MTTP* in the sample from the subject is down regulated by any detectable amount. For example, the RNA transcript level of *MTTP* is down regulated by at least about 50%. In one aspect, the RNA transcript level of *MTTP* is decreased by at least about at least about 2-fold, at least about 3-fold, at least about 4-fold, at least about 5-fold, at least about 10-fold, at least about

15-fold, or at least about 20-fold. In one aspect, the reference profile is obtained from the subject prior to administering the therapeutic agent. In one aspect, the therapeutic agent is a compound of the invention. In one aspect, the disease is a lipoprotein related disorder. In one aspect, the disease is a cholesterol related disorder. In one aspect, the disease is a cardiovascular disease.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent for treating a disease in a subject comprising: (a) administering the therapeutic agent to the subject; (b) determining the RNA transcript level of *APOC3* in a sample from the subject at a first time point; and (c) comparing the RNA transcript level of *APOC3* at the first time point to a reference profile; wherein a decrease in the RNA transcript level at the first time point compared to the reference profile indicates that the therapeutic agent is effective for treating the disease. In one aspect, the RNA transcript level of *APOC3* in the sample from the subject is down regulated by any detectable amount. For example, the RNA transcript level of *APOC3* is down regulated by at least about 50%. n one aspect, the RNA transcript level of *APOC3* is decreased by at least about 2-fold, at least about 3-fold, at least about 4-fold, at least about 5-fold, at least about 10-fold, at least about 15-fold, or at least about 20-fold. In one aspect, the reference profile is obtained from the subject prior to administering the therapeutic agent. In one aspect, the therapeutic agent is a compound of the invention. In one aspect, the disease is a lipoprotein related disorder. In one aspect, the disease is a cholesterol related disorder. In one aspect, the disease is a cardiovascular disease. The invention provides a method of reducing the level of circulating LDL-cholesterol in a subject comprising administering to the subject a compound of the invention. In one aspect, the invention provides a method of monitoring a reduction in the level of circulating LDL-cholesterol in a subject, comprising: (a) determining a first level of expression of one or more signature genes or one or more products of one or more signature genes in a sample from the subject at a first time point; (b) administering to the subject a compound of the invention; (c) determining a second level of expression of the one or more signature genes or one or more products of one or more signature genes in a sample from the subject at a second time point; and (d) comparing the first level of expression with the second level of expression, wherein a change in the first level as compared to the second level indicates a reduction in the level of circulating LDL-cholesterol. In one aspect, the level of circulating LDL-cholesterol is reduced by at least about 2-fold, at least about 3-fold, at least about 5-fold, at least about 10-fold, at least about 15-fold, or at least about 20-fold. In one aspect, the one or more signature genes selected from *TRIB1*, *SCAP*, *SREBF1*, *SREBF2*, *PCSK9*, *LDLR*, *HMGCR*, *HMGCS*,

FASN, *SCD1*, *MTTP and APOC3*. The number of signature genes is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12.

In one aspect, invention provides a method of monitoring a reduction in the level of circulating LDL-cholesterol in a subject, comprising: (a) determining the level of LDL-cholesterol in a sample from the subject at a first time point; (b) administering to the subject a compound of the invention; (c) determining the level of LDL-cholesterol in a sample from the subject at a second time point after administration of the compound; and (d) comparing the level of LDL-cholesterol at the first and second time points. In one aspect, the level of circulating LDL-cholesterol is reduced by at least about 2-fold, at least about 3-fold, at least about 5-fold, at least about 10-fold, at least about 15-fold, or at least about 20-fold.

The invention provides a method of reducing the level of circulating triglycerides in a subject comprising administering to the subject a compound of the invention. In one aspect, the invention provides a method of monitoring a reduction in the level of circulating triglycerides in a subject, comprising: (a) determining a first level of expression of one or more signature genes or one or more products of one or more signature genes in a sample from the subject at a first time point; (b) administering to the subject a compound of the invention; (c) determining a second level of expression of the one or more signature genes or one or more products of one or more signature genes in a sample from the subject at a second time point; and (d) comparing the first level of expression with the second level of expression, wherein a change in the first level as compared to the second level indicates a reduction in the level of circulating triglycerides. In one aspect, the level of circulating triglycerides is reduced by at least about 2-fold, at least about 3-fold, at least about 5-fold, at least about 10-fold, at least about 15-fold, or at least about 20-fold. In one aspect, the one or more signature genes are selected from *TRIB1*, *SCAP*, *SREBF1*, *SREBF2*, *PCSK9*, *LDLR*, *HMGCR*, *HMGCS*, *FASN*, *SCD1*, *MTTP and APOC3*. The number of signature genes is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12.

In one aspect, the invention provides a method of monitoring a reduction in the level of circulating triglycerides in a subject, comprising: (a) determining the level of triglycerides in a sample from the subject at a first time point; (b) administering to the subject a compound of the invention; (c) determining the level of triglycerides in a sample from the subject at a second time point after administration of the compound; (d) comparing the levels of triglycerides obtained at the first and second time points. In one aspect, the level of circulating triglycerides is reduced by at least about 2-fold, at least about 3-fold, at least about 5-fold, at least about 10-fold, at least about 15-fold, or at least about 20-fold.

The invention provides a method of reducing the secretion of VLDL particles from the liver into the bloodstream in a subject comprising administering to the subject a compound of the invention. In one aspect, the invention provides a method of monitoring a reduction in the secretion of VLDL particles in a subject, comprising: (a) determining a first level of expression of one or more signature genes or one or more products of one or more signature genes at a first time point; (b) administering to the subject a compound of the invention; (c) determining a second level of expression of the one or more signature genes or one or more products of one or more signature genes at a second time point; and (d) comparing the first level of expression with the second level of expression, wherein a change in the first level as compared to the second level indicates a reduction in the level of secretion of VLDL particles. In one aspect, the level of secretion of VLDL particles is reduced by at least about 2-fold, at least about 3-fold, at least about 5-fold, at least about 10-fold, at least about 15-fold, or at least about 20-fold. In one aspect, the one or more signature genes selected from *TRIB1*, *SCAP*, *SREBF1*, *SREBF2*, *PCSK9*, *LDLR*, *HMGCR*, *HMGCS*, *FASN*, *SCD1*, *MTTP and APOC3*. The number of signature genes is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12.

In one aspect, the invention provides a method of monitoring a reduction in the secretion of VLDL particles from the liver into the bloodstream in a subject, comprising: (a) determining a first level of VLDL particles in a sample from the subject at a first time point; (b) administering to the subject a compound the invention; (c) determining the second level of VLDL particles in a sample from the subject at a second time point after administration of the compound; and (d) comparing the first level with the second level of VLDL particles. In one aspect, the level of VLDL particles is reduced by at least about 2-fold, at least about 3-fold, at least about 5-fold, at least about 10-fold, at least about 15-fold, or at least about 20-fold.

The invention provides a method of reducing ApoB secretion in a subject comprising administering to the subject a compound the invention. In one aspect, the invention provides a method of monitoring a reduction in ApoB secretion in a subject, comprising: (a) determining a first level of expression of one or more signature genes or one or more products of one or more signature genes in a sample from the subject at a first time point; (b) administering to the subject a compound of the invention; (c) determining a second level of expression of the one or more signature genes or one or more products of one or more signature genes in a sample from the subject at a second time point; and (d) comparing the first level of expression with the second level of expression, wherein a change in the first

level as compared to the second level indicates a reduction in the level of secretion of ApoB. In one aspect, the level of secretion of ApoB is reduced by at least about 2-fold, at least about 3-fold, at least about 5-fold, at least about 10-fold, at least about 15-fold, or at least about 20-fold. In one aspect, the one or more signature genes selected from *TRIB1*, *SCAP*, *SREBF1*, *SREBF2*, *PCSK9*, *LDLR*, *HMGCR*, *HMGCS*, *FASN*, *SCD, MTTP and APOC3.* The number of signature genes is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12.

In one aspect, the invention provides a method of monitoring a reduction in ApoB secretion in a subject, comprising: (a) determining the level of ApoB in a sample from the subject at a first time point; (b) administering to the subject a compound of the invention; (c) determining the level of ApoB in a sample from the subject at a second time point after administration of the compound; and (d) comparing the levels of ApoB at the first and second time points. In one aspect, the level of ApoB is reduced by at least about 2-fold, at least about 3-fold, at least about 5-fold, at least about 10-fold, at least about 15-fold, or at least about 20-fold.

The invention provides a method of reducing total serum cholesterol in a subject comprising administering to the subject a compound of the invention. In one aspect, the invention provides a method of monitoring a reduction in total serum cholesterol in a subject, comprising: (a) determining a first level of expression of one or more signature genes or one or more products of one or more signature genes in a sample from the subject at a first time point; (b) administering to the subject a compound of the invention; (c) determining a second level of expression of the one or more signature genes or one or more products of one or more signature genes in a sample from the subject at a second time point; and (d) comparing the first level of expression with the second level of expression, wherein a change in the first level as compared to the second level indicates a reduction in the level of total serum cholesterol. In one aspect, the level of total serum cholesterol is reduced by at least about 2-fold, at least about 3-fold, at least about 5-fold, at least about 10-fold, at least about 15-fold, or at least about 20-fold. In one aspect, the one or more signature genes selected from *TRIB1*, *SCAP*, *SREBF1*, *SREBF2*, *PCSK9*, *LDLR*, *HMGCR*, *HMGCS*, *FASN*, *SCD, MTTP and APOC3.* The number of signature genes is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12.

In one aspect, the invention provides a method of monitoring a reduction in the total serum cholesterol level in a subject, comprising: (a) determining the level of total serum cholesterol in a sample from the subject at a first time point; (b) administering to the subject a compound of the invention; (c) determining the level of total serum cholesterol in a sample from the subject at a second time point after administration of the compound; and (d)

comparing the levels of total serum cholesterol at the first and second time points. In one aspect, the level of total serum cholesterol is reduced by at least about 2-fold, at least about 3-fold, at least about 5-fold, at least about 10-fold, at least about 15-fold, or at least about 20-fold.

In one aspect, the invention provides a method of downregulating the expression level of *PCSK9* in a subject in need thereof, comprising administering to the subject an effective amount of a compound of the invention.

In one aspect, the invention provides a method of upregulating the expression level of *TRIB1* in a subject in need thereof, comprising administering to the subject an effective amount of a compound of the invention.

In one aspect, the invention provides a method of downregulating the expression level of *PCSK9* and upregulating the expression level of *TRIB1,* in a subject in need thereof, comprising administering to the subject an effective amount of a compound of the invention.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent, comprising: (a) administering the therapeutic agent to a subject; (b) determining the expression level of *TRIB1* in a sample from the subject at a first time point; and (c) comparing the expression level of *TRIB1* at the first time point to a reference profile, wherein an increase in *TRIB1* expression compared to the reference profile indicates the efficacy of the therapeutic agent.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent, comprising: (a) administering the therapeutic agent to a subject; (b) determining the expression level of *PCKS9* in a sample from the subject at a first time point; and (c) comparing the expression level of *PCKS9* at the first time point to a reference profile, wherein a decrease in *PCKS9* expression compared to the reference profile indicates the efficacy of the therapeutic agent.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent, comprising: (a) administering the therapeutic agent to a subject; (b) determining the expression level of *TRIB1* and *PCSK9* in a sample from the subject at a first time point; and (c) comparing the expression level of *TRIB1* and *PCSK9* at a first time point to a reference profile; wherein an increase in *TRIB1* expression and a decrease in *PCKS9* expression compared to the reference profile indicates the efficacy of the therapeutic agent.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent, comprising: (a) administering the therapeutic agent to a subject; (b) determining the expression level of ApoB in a sample from the subject at a first time point;

and (c) comparing the expression level of ApoB at the first time point to a reference profile, wherein a decrease in ApoB expression compared to the reference profile indicates the efficacy of the therapeutic agent.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent, comprising: (a) administering the therapeutic agent to a subject; (b) determining the expression level of LRDR in a sample from the subject at a first time point; and (c) comparing the expression level of LRDR at the first time point to a reference profile, wherein an increase in LRDR expression compared to the reference profile indicates the efficacy of the therapeutic agent.

In one aspect, the invention provides a method of assessing the efficacy of a therapeutic agent, comprising: (a) administering the therapeutic agent to a subject; (b) determining the expression level of an RNA transcript of a gene selected from *SREBF1, SREBF2, SCAP, HMGCR, HMGCS, FASN, SCD1, MTTP,* and *APOC3* in a sample from the subject at a first time point; and (c) comparing the expression level of the RNA transcript at the first time point to a reference profile, wherein either an increase or decrease in the expression level of the RNA transcript compared to the reference profile indicates the efficacy of the therapeutic agent.

In one aspect, the invention provides a method of reducing LDL-C in circulation, comprising administering to the subject an effective amount of a compound of the invention.

In some aspects, the reference profile is obtained from the subject prior to administering the therapeutic agent. In other aspects, the therapeutic agent is a compound of the invention.

Cholesterol Related Disorders

In one aspect, "a cholesterol related disorder" includes any one or more of the following: hypercholesterolemia, heart disease, metabolic syndrome, diabetes, coronary heart disease, stroke, cardiovascular diseases, Alzheimer's disease and generally dyslipidemias, which can be manifested, for example, by an elevated total serum cholesterol, elevated LDL, elevated triglycerides, elevated VLDL, and/or low HDL. Some non-limiting examples of primary and secondary dyslipidemias that can be treated using a compound of the invention, either alone, or in combination with one or more other agents, include the metabolic syndrome, diabetes mellitus, familial combined hyperlipidemia, familial hypertriglyceridemia, familial hypercholesterolemias, including heterozygous hypercholesterolemia, homozygous hypercholesterolemia, familial defective apoplipoprotein

B-100; polygenic hypercholesterolemia; remnant removal disease, hepatic lipase deficiency; dyslipidemia secondary to any of the following: dietary indiscretion, hypothyroidism, drugs including estrogen and progestin therapy, beta-blockers, and thiazide diuretics; nephrotic syndrome, chronic renal failure, Cushing's syndrome, primary biliary cirrhosis, glycogen storage diseases, hepatoma, cholestasis, acromegaly, insulinoma, isolated growth hormone deficiency, and alcohol-induced hypertriglyceridemia. Compounds of the invention can also be useful in preventing or treating atherosclerotic diseases, such as, for example, coronary heart disease, coronary artery disease, peripheral arterial disease, stroke (ischaemic and hemorrhagic), angina pectoris, or cerebrovascular disease and acute coronary syndrome, myocardial infarction. In certain embodiments, the compounds of the invention are useful in reducing the risk of: nonfatal heart attacks, fatal and non-fatal strokes, certain types of heart surgery, hospitalization for heart failure, chest pain in patients with heart disease, and/or cardiovascular events because of established heart disease such as prior heart attack, prior heart surgery, and/or chest pain with evidence of clogged arteries. In certain embodiments, the compounds of the invention and methods described herein can be used to reduce the risk of recurrent cardiovascular events.

In one aspect, the invention provides methods and compositions for treating and/or preventing cardiovascular diseases and related disorders. Cardiovascular diseases and related disorders referred to herein are diseases and disorders that involve the heart or blood vessels (e.g., arteries and veins). Cardiovascular diseases and related disorders include atherosclerosis, cardiac dysrhythmia, cardiomyopathy, coronary heart disease, hypertension, dyslipidemia, myocardial infarction, myocarditis, congestive heart failure, valvular heart disease, and vascular disease.

In one aspect, the invention provides a method and/or composition for treating and/or preventing myocardial infarction, coronary heart disease, atherosclerosis or dyslipidemia. In one aspect, the invention provides a method and/or composition for treating myocardial infarction, coronary heart disease, atherosclerosis or dyslipidemia.

Myocardial infarction (MI) or acute myocardial infarction (AMI), commonly known as a heart attack, is the interruption of blood supply to part of the heart, causing myocardial cellular death. Classical symptoms of acute myocardial infarction include sudden chest pain, shortness of breath, nausea, vomiting, palpitations, sweating, anxiety, weakness, a feeling of indigestion, and fatigue. Myocardial infarctions are commonly a result of atherosclerosis, but are also associated with severe infections, intense psychological stress or physical exertion, coronary heart disease, and diabetes.

Coronary heart disease refers to any condition in which there is the narrowing or blockage of the coronary arteries, usually caused by atherosclerosis. Examples of coronary heart disease include, but are not limited to, coronary artery disease.

Atherosclerosis is the buildup of cholesterol and fatty deposits, called plaques, on the inner walls of the arteries. Plaque formation causes thickening of the blood vessel walls, which obstructs blood flow and leads to diminished amounts of oxygen and nutrients reaching the target organ. Atherosclerosis can lead to ischemia, myocardial infarction, coronary heart disease, and/or congestive heart failure. Examples of atherosclerosis include, but are not limited to arteriosclerosis and ateriolosclerosis.

Dyslipidemia or dyslipidaemia is an abnormal amount of lipids in the blood. Examples of dyslipidemia include, but are not limited to hyperlipidemia, hypercholesterolemia, hyperglyceridemia, hyperlipoproteinemia, hyperchylomicronemia, and combined hyperlipidemia.

Cardiac dysrhythmia (also known as cardiac arrhythmia or irregular heartbeat) is a term for any of a large and heterogeneous group of conditions in which there is abnormal electrical activity in the heart. The most common symptom is palpitations, or abnormal heartbeats, which can be frequent, infrequent, or continuous. Arrhythmias can be associated with higher risk of blood clotting within the heart, embolism, stroke, heart failure and sudden cardiac death. Examples of cardiac dysrhythmias include, but are not limited to proarrhythmia, sinus arrhythmia, premature atrial contractions, wandering atrial pacemaker, atrial flutter, premature ventricular contractions, accelerated idioventricular rhythm, atrioventricular blocks, sudden arrthythmic death syndrome, tachycardias (e.g., multifocal atrial tachycardia, supraventricular tachycardia, atrioventricular nodal reentrant tachycardia, junctional tachycardia, monomorphic ventricular tachycardia, polymorphic ventricular tachycardia), fibrillations (e.g., atrial fibrillation, ventricular fibrillation), and bradycardias.

Vascular disease includes diseases affecting the arteries, veins, lymph vessels, and blood disorders that affect circulation. Most commonly, vascular disease is associated atherosclerosis. Examples of vascular disease include, but are not limited to, cerebrovascular disease, peripheral artery disease, aneurysm, renal artery disease, Raynaud's Phenomenon, Buerger's Disease, peripheral venous disease, varicose veins, blood clotting disorders, blood clots in the veins, and lymphedema.

Cardiomyopathy is the deterioration of the function of the myocardium (the heart muscle), usually leading to heart failure. Examples of cardiomyopathies include, but are not limited to, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy,

isolated ventricular non-compaction, mitochondrial myopathy, dilated cardiomypoathy, restrictive cardiomyopathy, Takotsubo cardiomyopathy, Loeffler endocarditis, amyloidosis, hemochromatosis, Chagas disease, diabetic cardiomyopathy, alcoholic cardiomyopathy, obesity-associated cardiomyopathy, ischemic cardiomyopathy, and congestive heart failure.

Congestive heart failure (CHF), or heart failure, is a condition in which the heart is restricted from pumping enough blood to the body's other organs. This can result from narrowed arteries that supply blood to the heart muscle (e.g., coronary artery disease), past myocardial infarction having scar tissue that interferes with the heart muscle's normal work, high blood pressure, heart valve disease due to past rheumatic fever or other causes, cardiomyopathy, congenital heart defects, endocarditis and/or myocarditis.

Hypertension, or high blood pressure, is a chronic medical condition in which the blood pressure in the arteries is elevated. Hypertension increases the risk for ischemic heart disease, strokes, peripheral vascular disease, heart failure, aortic aneurysm, diffuse atherosclerosis, pulmonary embolism, hypertensive retinopathy, and hypertensive nephropathy.

Valvular heart disease refers to any disease process involving one or more of the valves of the heart (e.g., the aortic valve, the mitral valve, the pulmonary valve, and the tricuspid valve). Valvular heart diseases include, but are not limited to, rheumatic heart disease, mitral valve prolapse, heart valve dysplasia, Ebstein's anomaly, tetralogy of Fallot, aortic stenosis, mitral stenosis, pulmonary stenosis, tricuspid stenosis, aortic regurgitation or incompetence, mitral regurgitation or incompetence, pulmonary regurgitation or incompetence, tricuspid regurgitation or incompetence and restenosis.

Myocarditis is inflammation of heart muscle (myocardium) often resulting in damage to the heart. The most common cause is infection. Endocarditis is inflammation of the inside lining of the heart chambers and heart valves (endocardium). Associated conditions include chest pain, congestive heart failure, dilated cardiomyopathy, cardiac arrhythmias and heart blocks.

Other cardiovascular related disorders include stroke, diabetes, inflammation-related heart conditions, aneurysm and ischemia.

Liver Disease and Related Disorders

In one aspect, the invention relates to a method for treating and/or preventing liver disease, liver cancer, liver injury (e.g., alcohol misuse, viral and other infections, metabolic disorders, obesity, autoimmune disease, and drug toxicity), or abnormal liver function. In

one aspect, the invention relates to a method for treating liver disease, liver cancer, liver injury (e.g., alcohol misuse, viral and other infections, metabolic disorders, obesity, autoimmune disease, and drug toxicity), or abnormal liver function.

The term "liver disease" applies to a disease or disorder that causes the liver to function improperly or stop functioning. Examples include, but are not limited to, steatosis, nonalcoholic steatohepatitis (NASH), cirrhosis, amebic liver abscess, autoimmune hepatitis, biliary atresia, coccidioidomycosis, delta agent (Hepatitis D), drug-induced cholestasis, hemochromatosis, Hepatitis A, Hepatitis B, Hepatitis C, alcohol-induced liver disease, primary biliary cirrhosis, pyogenic liver abscess, Reye syndrome, sclerosing cholangitis, and Wilson's disease.

As used herein, liver cancer includes a disorder and/or a stage of progression associated with liver cancer. Examples of liver cancer include, but are not limited to, liver cell dysplasia, hepatic microvasculary dysplasia, portal atresia, primary liver cancer, hepatoma, hepatocellular carcinoma, or metastatic liver cancer (in which the cancer has spread to the liver, but originated from a different organ).

Combination Therapies

The invention includes combination therapies including the methods of treating and/or preventing conditions described herein. Combination therapy includes administering one or more compounds of the invention, or one or more compounds of the invention in combination with at least one or more additional medicaments. In one aspect, the other medicament may be a pharmaceutically active agent or a non-pharmaceutically active ingredient (e.g., surgery).

The invention provides a pharmaceutical composition comprising a compound of the invention and one or more additional medicaments. In one aspect, the invention provides a combination therapy for use in any of the methods described herein. In one aspect, the invention provides a method of treating or preventing a disease in a subject in need thereof comprising administering to the subject an effective amount of a first medicament and one or more additional medicaments. In one aspect, a compound of the invention is the first medicament of the combination therapy. In one aspect, one or more additional medicaments are the second medicament of the combination therapy. In one aspect, there is one additional medicament. In one aspect, there are two additional medicaments. In one aspect, there are three additional medicaments.

In one aspect, the invention provides a combination therapy for use in a method of the invention, wherein administration of the one or more additional medicaments of the combination therapy reduces the level of Low Density Lipoprotein-cholesterol (LDL-C) in the blood, and in the serum, of the subject. In some aspects, the one or more additional medicaments decrease LDL-C levels by at least about 2-fold, at least about 3-fold, at least about 5-fold, at least about 10-fold, at least about 15-fold, or at least about 20-fold as compared to pre-treatment levels. In one aspect, administration of the one or more additional medicaments decreases LDL-C levels such that the level LDL-C is less than the level of LDL-C obtained through administration of the one or more additional medicaments alone.

In one aspect, the invention provides a combination therapy for use in a method of the invention, wherein administration of one or more additional medicaments of the combination therapy elevates the level of HDL-cholesterol in the blood, and in one aspect, in the serum, of the subject. In some aspects, the one or more additional medicaments increase the HDL-cholesterol levels by at least about 2-fold, at least about 3-fold, at least about 5-fold, at least about 10-fold, at least about 15-fold, or at least about 20-fold as compared to pre-treatment levels. In one aspect, administration of the one or more additional medicaments increases the level of HDL-cholesterol such that the level HDL-cholesterol is greater than the level of HDL-cholesterol obtained through administration of the one or more additional medicaments alone.

In one aspect, the invention provides a combination therapy for use in a method of the invention, wherein the one or more additional medicaments of the combination therapy upregulate the expression level of *LDLR*. In one aspect, administration of the one or more additional medicaments increases *LDLR* expression levels in the subject by about 5% to about 60%. In some aspects, *LDLR* expression levels are increased by at least about 1, at least about 2, at least about 3, at least about 4, at least about 5, at least about 6, at least about 7, at least about 8, at least about 9, at least about 10, at least about 11, at least about 12, at least about 13, at least about 14, at least about 15, at least about 16, at least about 17, at least about 18, at least about 19, at least about 20, at least about 25, at least about 30, at least about 35, at least about 40, at least about 45, at least about 50, at least about 55, or by at least about 60%. In one aspect, administration of the one or more additional medicaments increases *LDLR* expression levels for at least about 1, at least about 2, at least about 3, at least about 4, at least about 5, at least about 7, at least about 10, at least about 14, at least about 21, at least about 25, at least about 30 or at least about 40 or more days. In one aspect, administration of the one or more additional medicaments increases *LDLR* expression levels such that the level

of *LDLR* expression is greater than the level of *LDLR* obtained through administration of the one or more additional medicaments alone.

In one aspect, the invention provides a combination therapy for use in a method of the invention, wherein administration of the one or more additional medicaments upregulate the expression level of *PCSK9*. In one aspect, the additional medicament is a statin. In one aspect, the additional medicament is atorvastatin.

In one aspect, administration of the one or more additional medicaments reduces *PCSK9* expression. In one aspect, the one or more additional medicaments reduces the levels by at least about 2-fold, at least about 3-fold, at least about 5-fold, at least about 10-fold, at least about 15-fold, or at least about 20-fold as compared to pre-treatment levels. In one aspect, the expression level of *PCSK9* is lower than the expression level of *PCSK9* obtained through administration of the first medicament or one or more additional medicaments alone.

In one aspect, the invention provides a combination therapy for use in any of the methods described herein, wherein the combination therapy comprises a compound of the invention and one or more additional medicaments selected from a small molecule, an antibody, or a small interfering RNA (siRNA) or a combination thereof.

In one aspect, the invention provides a combination therapy for use in any of the methods described herein, wherein the additional medicament is a small molecule. In one aspect, the small molecule is a HMG-CoA reductase inhibitor. Exemplary HMG-CoA reductase inhibitors include atorvastatin (Pfizer's Lipitor®/Tahor/Sortis/Torvast/Cardyl), pravastatin (Bristol-Myers Squibb's Pravachol, Sankyo's Mevalotin/Sanaprav), simvastatin (Merck's Zocor®/Sinvacor, Boehringer Ingelheim's Denan, Banyu's Lipovas), lovastatin (Merck's Mevacor/Mevinacor, Bexal's Lovastatina, Cepa; Schwarz Pharma's Liposcler), fluvastatin (Novartis' Lescol®/Locol/Lochol, Fujisawa's Cranoc, Solvay's Digaril), cerivastatin (Bayer's Lipobay/GlaxoSmithKline's Baycol), rosuvastatin (AstraZeneca's Crestor ®), and pitivastatin (itavastatin/risivastatin) (Nissan Chemical, Kowa Kogyo, Sankyo, and Novartis). In one aspect, the HMG-CoA reductase is a statin. In one aspect, the statin is selected from atorvastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, cerivastatin, and any combination thereof. In one aspect, the statin is simvastatin. In one aspect, the statin is atorvastatin.

In one aspect, the invention provides a combination therapy for use in any of the methods described herein, wherein the additional medicament is an antibody. In one aspect, the antibody is a PCSK9 antibody (See e.g., US 2012/0195910). In one aspect, the anti-

PCSK9 antibody inhibits binding of human PCSK9 to LDLR by at least about 20-40%, at least about 40-60%, at least about 60-80%, at least about 80-85%, or more.

In one aspect, the invention provides a combination therapy for use in any of the methods described herein, wherein the additional medicament is a siRNA (See e.g., US 2012/0244207). In one aspect, the siRNA targets a VSP, TTR, PCSK-9, SCAP, S14, MIG12, APOC3, APOB, PNPLA3, Hepcidin, or a PCSK5 gene. In one aspect, siRNA targeted gene is suppressed by at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, or at least about 50% by administration of a siRNA. In one aspect, the siRNA targeted gene is suppressed by at least about 60%, at least about 70%, or at least about 80% by administration of the siRNA. In one aspect, the siRNA targeted gene is suppressed by at least about 85%, at least about 90%, or at least about 95% by administration of the siRNA.

In one aspect, the siRNA is a *PCSK9* targeted siRNA. In one aspect, the siRNA targeted to the *PCSK9* gene and administration results in a decrease in LDLc (low density lipoprotein cholesterol) levels in the blood, and in the serum, of the mammal. In one aspect, LDLc levels are decreased by at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 40%, at least about 50%, or at least about 60%, or more, as compared to pretreatment levels.

In one aspect, the *PCSK9* targeted siRNA comprises AD-10792 or AD-9680.

In one aspect, the invention provides a method, wherein administration of the first medicament and one or more additional medicaments of the combination therapy upregulates the expression level of *LDLR*.

In one aspect, the invention provides a method, wherein the expression level of *LDLR* is greater than the expression level of *LDLR* obtained through administration of the first medicament or one or more additional medicaments alone.

In one aspect, the invention provides a method, wherein the expression level of *PCSK9* is lower than the expression level of *PCSK9* obtained through administration of one or more additional medicaments alone.

In one aspect, the additional medicament of the combination therapy is for preventing and/or treating atherosclerosis and/or cardiovascular disease. In one aspect, the additional medicament is for use in a method of reducing the risk of recurrent cardiovascular events. In one aspect, the additional medicament is for elevating the level of HDL-cholesterol in a subject.

In one aspect, the additional medicament of the combination therapy is an inhibitor of PCSK9 expression, e.g., a PCSK9 antibody or a PCSK9 targeted siRNA.

Examples of other medicaments for use in the combination therapy with a compound of the invention include: antibiotics; anti-histamines; aspirin; antiarrthythmic agents (e.g., quinidine, procainadmide, disopyramide, lidocaine, phenytoin, mexiletine, flecainid), anticoagulants (e.g., warfarin and heparins); antiplatelet drug therapy (e.g., aspirin and clopidogrel); angiotensin-converting enzyme (ACE) inhibitors (e.g., captopril, zofenopril, enalapril, ramipril, quinapril, perindopril, lisinopril, benazepril, fosinopril, casokinins and lactokinins); aldosterone antogonis agents (e.g., eplerenone and spironolactone); antianginal drugs; antihypertensive drugs; angiotensin antagonists; antiviral drugs; antifungal drugs; immunosuppressants; inotropes (e.g., Milrinone), estradiol, berberine, statins (e.g., atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, mevastatin, pravastatin, rosuvastatin, and simvastatin), growth factors; hormones; steroids; thrombolytic drugs; cardioplegic solutions; cariotonic agents; fibrinolytic agents; nitric oxide donors; nitroglycerin; potassium channel blockers; sodium channel blockers; vasoconstrictors; vasodilators; beta blockers; cholesterol-lowering medications; calcium channel blockers; digitalis; diuretics; dietary supplements (e.g., folic acid, niacin, omega 3 fatty acids, and Vitamin C); receptor kinase inhibitors; and chemotherapeutic reagents.

In one aspect, the one or more additional medicaments for use in the combination therapy is selected from an HMG-CoA reductase inhibitor, a fibrate, a bile acid sequestrant, niacin, an antiplatelet agent, an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, an acyl-CoA cholesterol acetyltransferase (ACAT) inhibitor, a cholesterol absorption inhibitor, a cholesterol ester transfer protein (CETP) inhibitor, a microsomal triglyceride transfer protein (MTTP) inhibitor, a cholesterol modulator, a bile acid modulator, a peroxisome proliferation activated receptor (PPAR) agonist, a gene-based therapy, a composite vascular protestant, a glycoprotein IIb/IIIa inhibitor, aspirin or an aspirin-like compound, an IBAT inhibitor, a squalene synthase inhibitor, and a monocyte chemoattractant protein (MCP)-I inhibitor.

In another aspect, the one or more additional medicaments for use in the combination therapy with a compound of the invention is selected from an HMG-CoA reductase inhibitor (e.g., a statin), a fibrate, a bile acid sequestrant, niacin, an antiplatelet agent, an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist (e.g., losartan potassium, such as Merck & Co.'s Cozaar®, an acylCoA cholesterol acetyltransferase (ACAT) inhibitor, a cholesterol absorption inhibitor, a cholesterol ester transfer protein (CETP) inhibitor, a

microsomal triglyceride transfer protein (MTTP) inhibitor, a cholesterol modulator, a bile acid modulator, a peroxisome proliferation activated receptor (PPAR) agonist, a gene-based therapy, a composite vascular protectant (e.g., AGI-1067, from Atherogenics), a glycoprotein IIb/IIIa inhibitor, aspirin or an aspirin-like compound, an IBAT inhibitor (e.g., S-8921, from Shionogi), a squalene synthase inhibitor, or a monocyte chemoattractant protein (MCP)-I inhibitor. Exemplary HMG-CoA reductase inhibitors are described herein. Exemplary fibrates include, e.g., bezafibrate (e.g., Roche's Befizal®/Cedur®/Bezalip®, Kissei's Bezatol), clofibrate (e.g., Wyeth's Atromid-S®), fenofibrate (e.g., Fournier's Lipidil/Lipantil, Abbott's Tricor®, Takeda's Lipantil, generics), gemfibrozil (e.g., Pfizer's Lopid/Lipur) and ciprofibrate (Sanofi-Synthelabo's Modalim®). Exemplary bile acid sequestrants include, e.g., cholestyramine (Bristol-Myers Squibb's Questran® and Questran Light™), colestipol (e.g., Pharmacia's Colestid), and colesevelam (Genzyme/Sankyo's WelChol™). Exemplary niacin therapies include, e.g., immediate release formulations, such as Aventis' Nicobid, Upsher-Smith's Niacor, Aventis' Nicolar, and Sanwakagaku's Perycit. Niacin extended release formulations include, e.g., Kos Pharmaceuticals' Niaspan and Upsher-Smith's SIo-Niacin. Exemplary antiplatelet agents include, e.g., aspirin (e.g., Bayer's aspirin), clopidogrel (Sanofi-Synthelabo/Bristol-Myers Squibb's Plavix), and ticlopidine (e.g., Sanofi-Synthelabo's Ticlid and Daiichi's Panaldine). Other aspirin-like compounds useful in combination with a dsRNA include, e.g., Asacard (slow-release aspirin, by Pharmacia) and Pamicogrel (Kanebo/Angelini Ricerche/CEPA). Exemplary angiotensin-converting enzyme inhibitors include, e.g., ramipril (e.g., Aventis' Altace) and enalapril (e.g., Merck & Co.'s Vasotec). Exemplary acyl CoA cholesterol acetyltransferase (ACAT) inhibitors include, e.g., avasimibe (Pfizer), eflucimibe (BioMerieux Pierre Fabre/Eli Lilly), CS-505 (Sankyo and Kyoto), and SMP-797 (Sumito). Exemplary cholesterol absorption inhibitors include, e.g., ezetimibe (Merck/Schering-Plough Pharmaceuticals Zetia®) and Pamaqueside (Pfizer). Exemplary CETP inhibitors include, e.g., Torcetrapib (also called CP-529414, Pfizer), JTT-705 (Japan Tobacco), and CETi-I (Avant Immunotherapeutics). Exemplary microsomal triglyceride transfer protein (MTTP) inhibitors include, e.g., implitapide (Bayer), R-103757 (Janssen), and CP-346086 (Pfizer). Other exemplary cholesterol modulators include, e.g., NO-1886 (Otsuka/TAP Pharmaceutical), CI-1027 (Pfizer), and WAY-135433 (Wyeth-Ayerst). Exemplary bile acid modulators include, e.g., HBS-107 (Hisamitsu/Banyu), Btg-511 (British Technology Group), BARI-1453 (Aventis), S-8921 (Shionogi), SD-5613 (Pfizer), and AZD-7806 (AstraZeneca). Exemplary peroxisome proliferation activated receptor (PPAR) agonists include, e.g., tesaglitazar (AZ-242) (AstraZeneca), Netoglitazone (MCC-555) (Mitsubishi/Johnson & Johnson), GW-

409544 (Ligand Pharmaceuticals/GlaxoSmithKline), GW-501516 (Ligand Pharmaceuticals/GlaxoSmithKline), LY-929 (Ligand Pharmaceuticals and Eli Lilly), LY-465608 (Ligand Pharmaceuticals and Eli Lilly), LY-518674 (Ligand Pharmaceuticals and Eli Lilly), and MK-767 (Merck and Kyorin). Exemplary gene-based therapies include, e.g., AdGWEGF121.10 (GenVec), ApoAl (UCB Pharma/Groupe Fournier), EG-004 (Trinam) (Ark Therapeutics), and ATP-binding cassette transporter-Al (ABCAl) (CV Therapeutics/Incyte, Aventis, Xenon). Exemplary Glycoprotein IIb/IIIa inhibitors include, e.g., roxifiban (also called DMP754, Bristol-Myers Squibb), Gantofiban (Merck KGaA/Yamanouchi), and Cromafiban (Millennium Pharmaceuticals). Exemplary squalene synthase inhibitors include, e.g., BMS-1884941 (Bristol-Myers Squibb), CP-210172 (Pfizer), CP-295697 (Pfizer), CP-294838 (Pfizer), and TAK-475 (Takeda). An exemplary MCP-I inhibitor is, e.g., RS-504393 (Roche Bioscience). The anti-atherosclerotic agent BO-653 (Chugai Pharmaceuticals), and the nicotinic acid derivative Nyclin (Yamanouchi Pharmaceuticals) are also appropriate for administering in combination with a compound of the invention. Exemplary combination therapies suitable for administration with a compound of the invention, e.g., advicor (Niacin/lovastatin from Kos Pharmaceuticals), amlodipine/atorvastatin (Pfizer), and ezetimibe/simvastatin (e.g., Vytorin®10/10, 10/20, 10/40, and 10/80 tablets by Merck/Schering-Plough Pharmaceuticals). Agents for treating hypercholesterolemia, and suitable for administration in combination with a compound of the invention include, e.g., lovastatin, niacin Altoprev®Extended-Release Tablets (Andrx Labs), lovastatin Caduet™. Tablets (Pfizer), amlodipine besylate, atorvastatin calcium Crestor®Tablets (AstraZeneca), rosuvastatin calcium Lescol® Capsules (Novartis), fluvastatin sodium Lescol® (Reliant, Novartis), fluvastatin sodium Lipitor® Tablets (Parke-Davis), atorvastatin calcium Lofibra® Capsules (Gate), Niaspan Extended-Release Tablets (Kos), niacin Pravachol Tablets (Bristol-Myers Squibb), pravastatin sodium TriCor® Tablets (Abbott), fenofibrate Vytorin® 10/10 Tablets (Merck/Schering-Plough Pharmaceuticals), ezetimibe, simvastatin WelChol™ Tablets (Sankyo), colesevelam hydrochloride Zetia® Tablets (Schering), ezetimibe Zetia® Tablets (Merck/Schering-Plough Pharmaceuticals), and ezetimibe Zocor® Tablets (Merck).

Other therapies or medicaments known in the art for treating cholesterol disorders, cardiovascular diseases and related conditions which may be combined with one or more compound of the invention include: angioplasty; brachytherapy; surgery; coronary artery bypass; stents; pacemakers; ventricular assist devices (LVADs); defibrillators; heart

transplant; liver transplant; intracoronary radiation; exercise; weight control; smoking cessation; and dietary restriction.

It is understood that the combination therapies described herein can be used in any of the methods of the invention, including but not limited to, a method of treating a disease, including a cholesterol disorder or cardiovascular disease. It is understood that any of the methods of assessing the efficacy of a therapeutic agent can be applied to assess the efficacy of a combination therapy e.g., the therapeutic agent is a compound of the invention and one or more additional agents as described herein. The methods of monitoring the effects of a compound of the invention described herein are also applicable for monitoring the effects of combination therapies described herein e.g., methods of monitoring a reduction in the level of circulating LDL-cholesterol, a reduction in the level of circulating triglycerides, a reduction in the secretion of VLDL particles, etc.

In one aspect, the invention provides a combination therapy for use in a method of the invention, wherein the first medicament and one or more additional medicaments are administered simultaneously or in parallel by combination of the first and one or more additional medicaments in a co-formulation or separate formulations or by alternation.

In one aspect, the invention provides a combination therapy for use in method of the invention, wherein administration of the first medicament and one or more additional medicaments by alteration consists of delivering the first medicament and the one or more additional medicaments serially, sequentially, or alternating in separate pharmaceutical formulations.

In one aspect, the invention provides a combination therapy for use in a method of the invention, wherein the one or more additional medicaments are administered before the first medicament.

In one aspect, the invention provides a combination therapy for use in a method of the invention, comprising administration of the first medicament and one additional medicament.

In one aspect, the invention provides a combination therapy for use in a method of the invention, wherein the first medicament being administered after the one or more additional medicaments reduces the expression level of PCSK9.

In some aspects, the invention provides a medical device containing a compound of the invention.The invention further provides a medical device containing a combination therapy e.g., compound of the invention and one or more additional medicaments. The one or more additional medicaments can be any of the medicaments described above. In one aspect, the additional medicament is a statin. In one aspect, the medical device is a stent.

Formulations

The compounds of the invention may be administered alone (e.g., in saline or buffer) or using any delivery vehicles known in the art. For instance the following delivery vehicles have been described: Cochleates; Emulsomes, ISCOMs; Liposomes; Live bacterial vectors (e.g., Salmonella, Escherichia coli, Bacillus calmatte-guerin, Shigella, Lactobacillus); Live viral vectors (e.g., Vaccinia, adenovirus, Herpes Simplex); Microspheres; Nucleic acid vaccines; Polymers; Polymer rings; Proteosomes; Sodium Fluoride; Transgenic plants; Virosomes; Virus-like particles. Other delivery vehicles are known in the art and some additional examples are provided below.

The compounds of the invention may be administered by any route known, such as, for example, orally, transdermally, intravenously, cutaneously, subcutaneously, nasally, intramuscularly, intraperitoneally, intracranially, and intracerebroventricularly.

In certain embodiments, compounds of the invention are administered at dosage levels greater than about 0.001mg/kg, such as greater than about 0.01 mg/kg or greater than about 0.1 mg/kg. For example, the dosage level may be from about 0.001 mg/kg to about 50 mg/kg such as from about 0.01 mg/kg to about 25 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, or from about 1 mg/kg to about 5 mg/kg of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect. It will also be appreciated that dosages smaller than about 0.001 mg/kg or greater than about 50 mg/kg (for example about 50-100 mg/kg) can also be administered to a subject.

In one embodiment, the compound of the invention is administered once-daily, twice-daily, or three-times daily. In one embodiment, the compound of the invention is administered continuously (i.e., every day) or intermittently (e.g., 3-5 days a week). In another embodiment, administration could be on an intermittent schedule.

Further, administration less frequently than daily, such as, for example, every other day may be chosen. In additional embodiments, administration with at least 2 days between doses may be chosen. By way of example only, dosing may be every third day, bi-weekly or weekly. As another example, a single, acute dose may be administered. Alternatively, compounds of the invention can be administered on a non-regular basis e.g., whenever symptoms begin. For any compound described herein the effective amount can be initially determined from animal models.

Toxicity and efficacy of the compounds of the invention can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose

therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Compounds that exhibit large therapeutic indices may have a greater effect when practicing the methods of the invention. While compounds that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such compounds to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

Data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage of the compounds of the invention for use in humans. The dosage of such agents lies within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC50 (i.e., the concentration of the test compound that achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography. In certain embodiments, pharmaceutical compositions may comprise, for example, at least about 0.1% of an active compound. In other embodiments, the active compound may comprise between about 2% to about 75% of the weight of the unit, or between about 25% to about 60%, for example, and any range derivable therein. Multiple doses of the compounds of the invention are also contemplated.

The formulations of the invention are administered in pharmaceutically acceptable solutions, which may routinely contain pharmaceutically acceptable concentrations of salt, buffering agents, preservatives, compatible carriers, and optionally other therapeutic ingredients.

For use in therapy, an effective amount of one or more compounds of the invention can be administered to a subject by any mode that delivers the compound(s) to the desired surface, e.g., mucosal, systemic. Administering the pharmaceutical composition of the present invention may be accomplished by any means known to the skilled artisan. Compounds of the invention may be administered orally, transdermally, intravenously, cutaneously, subcutaneously, nasally, intramuscularly, intraperitoneally, intracranially, or intracerebroventricularly.

For oral administration, one or more compounds of the invention can be formulated readily by combining the active compound(s) with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a subject to be treated.

Pharmaceutical preparations for oral use can be obtained as solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. Optionally the oral formulations may also be formulated in saline or buffers, i.e. EDTA for neutralizing internal acid conditions or may be administered without any carriers.

Also specifically contemplated are oral dosage forms of one or more compounds of the invention. The compound(s) may be chemically modified so that oral delivery of the derivative is efficacious. Generally, the chemical modification contemplated is the attachment of at least one moiety to the compound itself, where said moiety permits (a) inhibition of proteolysis; and (b) uptake into the blood stream from the stomach or intestine. Also desired is the increase in overall stability of the compound(s) and increase in circulation time in the body. Examples of such moieties include: polyethylene glycol, copolymers of ethylene glycol and propylene glycol, carboxymethyl cellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone and polyproline. Other polymers that could be used are poly-1,3-dioxolane and poly-l,3,6-tioxocane. In some aspects for pharmaceutical usage, as indicated above, are polyethylene glycol moieties.

The location of release may be the stomach, the small intestine (the duodenum, the jejunum, or the ileum), or the large intestine. One skilled in the art has available formulations which will not dissolve in the stomach, yet will release the material in the duodenum or elsewhere in the intestine. In some aspects, the release will avoid the deleterious effects of the stomach environment, either by protection of the compound or by release of the biologically active material beyond the stomach environment, such as in the intestine.

To ensure full gastric resistance a coating impermeable to at least pH 5.0 is important. Examples of the more common inert ingredients that are used as enteric coatings are cellulose acetate trimellitate (CAT), hydroxypropylmethylcellulose phthalate (HPMCP), HPMCP 50, HPMCP 55, polyvinyl acetate phthalate (PVAP), Eudragit L30D, Aquateric, cellulose acetate phthalate (CAP), Eudragit L, Eudragit S, and Shellac. These coatings may be used as mixed films.

A coating or mixture of coatings can also be used on tablets, which are not intended for protection against the stomach. This can include sugar coatings, or coatings which make the tablet easier to swallow. Capsules may consist of a hard shell (such as gelatin) for delivery of dry therapeutic i.e. powder; for liquid forms, a soft gelatin shell may be used. The shell material of cachets could be thick starch or other edible paper. For pills, lozenges, molded tablets or tablet triturates, moist massing techniques can be used.

The compound of the invention can be included in the formulation as fine multiparticulates in the form of granules or pellets of particle size about 1 mm. The formulation of the material for capsule administration could also be as a powder, lightly compressed plugs or even as tablets. The compound of the invention could be prepared by compression.

Colorants and flavoring agents may all be included. For example, the compound of the invention may be formulated (such as by liposome or microsphere encapsulation) and then further contained within an edible product, such as a refrigerated beverage containing colorants and flavoring agents.

One may dilute or increase the volume of compound delivered with an inert material. These diluents could include carbohydrates, especially mannitol, α-lactose, anhydrous lactose, cellulose, sucrose, modified dextrans and starch. Certain inorganic salts may be also be used as fillers including calcium triphosphate, magnesium carbonate and sodium chloride. Some commercially available diluents are Fast-Flo, Emdex, STA-Rx 1500, Emcompress and Avicell. Disintegrants may be included in the formulation of the therapeutic into a solid dosage form. Materials used as disintegrates include but are not limited to starch, including the commercial disintegrant based on starch, Explotab. Sodium starch glycolate, Amberlite, sodium carboxymethylcellulose, ultramylopectin, sodium alginate, gelatin, orange peel, acid carboxymethyl cellulose, natural sponge and bentonite may all be used. Another form of the disintegrants is the insoluble cationic exchange resins. Powdered gums may be used as disintegrants and as binders and these can include powdered gums such as agar, Karaya or tragacanth. Alginic acid and its sodium salt are also useful as disintegrants.

Binders may be used to hold the therapeutic together to form a hard tablet and include materials from natural products such as acacia, tragacanth, starch and gelatin. Others include methyl cellulose (MC), ethyl cellulose (EC) and carboxymethyl cellulose (CMC). Polyvinyl pyrrolidone (PVP) and hydroxypropylmethyl cellulose (HPMC) could both be used in alcoholic solutions to granulate the therapeutic.

An anti-frictional agent may be included in the formulation of the compound of the invention to prevent sticking during the formulation process. Lubricants may be used as a layer between the compound and the die wall, and these can include but are not limited to; stearic acid including its magnesium and calcium salts, polytetrafluoroethylene (PTFE), liquid paraffin, vegetable oils and waxes. Soluble lubricants may also be used such as sodium lauryl sulfate, magnesium lauryl sulfate, polyethylene glycol of various molecular weights, Carbowax 4000 and 6000. Glidants that might improve the flow properties of the drug during formulation and to aid rearrangement during compression might be added. The glidants may include starch, talc, pyrogenic silica and hydrated silicoaluminate.

To aid dissolution of the compound into the aqueous environment a surfactant might be added as a wetting agent. Surfactants may include anionic detergents such as sodium lauryl sulfate, dioctyl sodium sulfosuccinate and dioctyl sodium sulfonate. Cationic detergents might be used and could include benzalkonium chloride or benzethomium chloride. The list of potential non-ionic detergents that could be included in the formulation as surfactants are lauromacrogol 400, polyoxyl 40 stearate, polyoxyethylene hydrogenated castor oil 10, 50 and 60, glycerol monostearate, polysorbate 40, 60, 65 and 80, sucrose fatty acid ester, methyl cellulose and carboxymethyl cellulose. These surfactants could be present in the formulation of the compound either alone or as a mixture in different ratios.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. Microspheres formulated for oral administration may also be used. Such microspheres have been well defined in the art. All formulations for oral administration should be in dosages suitable for such administration.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present invention may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

Also contemplated herein is pulmonary delivery of the compounds of the invention. The compound is delivered to the lungs of a mammal while inhaling and traverses across the lung epithelial lining to the blood stream using methods well known in the art.

Contemplated for use in the practice of this invention are a wide range of mechanical devices designed for pulmonary delivery of therapeutic products, including but not limited to nebulizers, metered dose inhalers, and powder inhalers, all of which are familiar to those skilled in the art. Some specific examples of commercially available devices suitable for the practice of this invention are the Ultravent nebulizer, manufactured by Mallinckrodt, Inc., St. Louis, Missouri; the Acorn II nebulizer, manufactured by Marquest Medical Products, Englewood, Colorado; the Ventolin metered dose inhaler, manufactured by Glaxo Inc., Research Triangle Park, North Carolina; and the Spinhaler powder inhaler, manufactured by Fisons Corp., Bedford, Massachusetts.

All such devices require the use of formulations suitable for the dispensing of compound. Typically, each formulation is specific to the type of device employed and may involve the use of an appropriate propellant material, in addition to the usual diluents, and/or carriers useful in therapy. Also, the use of liposomes, microcapsules or microspheres, inclusion complexes, or other types of carriers is contemplated. Chemically modified compound may also be prepared in different formulations depending on the type of chemical modification or the type of device employed. Formulations suitable for use with a nebulizer, either jet or ultrasonic, will typically comprise compound dissolved in water at a concentration of about 0.1 to about 25 mg of biologically active compound per mL of solution. The formulation may also include a buffer and a simple sugar (e.g., for stabilization and regulation of osmotic pressure). The nebulizer formulation may also contain a surfactant, to reduce or prevent surface induced aggregation of the compound caused by atomization of the solution in forming the aerosol.

Formulations for use with a metered-dose inhaler device will generally comprise a finely divided powder containing the compound suspended in a propellant with the aid of a surfactant. The propellant may be any conventional material employed for this purpose, such as a chlorofluorocarbon, a hydrochlorofluorocarbon, a hydrofluorocarbon, or a hydrocarbon, including trichlorofluoromethane, dichlorodifiuoromethane, dichlorotetrafluoroethanol, and 1,1,1,2-tetrafluoroethane, or combinations thereof. Suitable surfactants include sorbitan trioleate and soya lecithin. Oleic acid may also be useful as a surfactant.

Formulations for dispensing from a powder inhaler device will comprise a finely divided dry powder containing compound and may also include a bulking agent, such as lactose, sorbitol, sucrose, or mannitol in amounts which facilitate dispersal of the powder from the device, e.g., about 50 to about 90% by weight of the formulation. The compound should most advantageously be prepared in particulate form with an average particle size of less than 10 mm (or microns), such as about 0.5 to about 5 mm, for an effective delivery to the distal lung.

Nasal delivery of a compound of the invention is also contemplated. Nasal delivery allows the passage of a compound of the present invention to the blood stream directly after administering the therapeutic product to the nose, without the necessity for deposition of the product in the lung. Formulations for nasal delivery include those with dextran or cyclodextran.

For nasal administration, a useful device is a small, hard bottle to which a metered dose sprayer is attached. In one embodiment, the metered dose is delivered by drawing the pharmaceutical composition of the present invention solution into a chamber of defined volume, which chamber has an aperture dimensioned to aerosolize and aerosol formulation by forming a spray when a liquid in the chamber is compressed. The chamber is compressed to administer the pharmaceutical composition of the present invention. In a specific embodiment, the chamber is a piston arrangement. Such devices are commercially available.

Alternatively, a plastic squeeze bottle with an aperture or opening dimensioned to aerosolize an aerosol formulation by forming a spray when squeezed is used. The opening is usually found in the top of the bottle, and the top is generally tapered to partially fit in the nasal passages for efficient administration of the aerosol formulation. In some aspects, the nasal inhaler will provide a metered amount of the aerosol formulation, for administration of a measured dose of the drug.

The compound, when it is desirable to deliver them systemically, may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions.

Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Alternatively, the active compounds may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The compounds may also be formulated in rectal or vaginal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

Suitable liquid or solid pharmaceutical preparation forms are, for example, aqueous or saline solutions for inhalation, microencapsulated, encochleated, coated onto microscopic gold particles, contained in liposomes, nebulized, aerosols, pellets for implantation into the skin, or dried onto a sharp object to be scratched into the skin. The pharmaceutical compositions also include granules, powders, tablets, coated tablets,

(micro)capsules, suppositories, syrups, emulsions, suspensions, creams, drops or preparations with protracted release of active compounds, in whose preparation excipients and additives and/or auxiliaries such as disintegrants, binders, coating agents, swelling agents, lubricants, flavorings, sweeteners or solubilizers are customarily used as described above. The pharmaceutical compositions are suitable for use in a variety of drug delivery systems.

The compounds of the invention may be administered per se (neat) or in the form of a pharmaceutically acceptable salt. When used in medicine the salts should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts may conveniently be used to prepare pharmaceutically acceptable salts thereof. Such salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, maleic, acetic, salicylic, p-toluene sulphonic, tartaric, citric, methane sulphonic, formic, malonic, succinic, naphthalene-2-sulphonic, and benzene sulphonic. Also, such salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts of the carboxylic acid group.

Suitable buffering agents include: acetic acid and a salt (about 1-2% w/v); citric acid and a salt (about 1 -3% w/v); boric acid and a salt (about 0.5-2.5% w/v); and phosphoric acid and a salt (about 0.8-2% w/v). Suitable preservatives include benzalkonium chloride (about 0.003-0.03% w/v); chlorobutanol (about 0.3-0.9% w/v); parabens (about 0.01-0.25% w/v) and thimerosal (about 0.004- 0.02% w/v).

The pharmaceutical compositions of the invention contain an effective amount of a compound of the invention optionally included in a pharmaceutically acceptable carrier. The term pharmaceutically acceptable carrier means one or more compatible solid or liquid filler, diluents or encapsulating substances which are suitable for administration to a human or other vertebrate animal. The term carrier denotes an organic or inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate the application. The components of the pharmaceutical compositions also are capable of being commingled with the compounds of the invention, and with each other, in a manner such that there is no interaction which would substantially impair the desired pharmaceutical efficiency.

The dsRNA molecules of the combination therapy described herein may be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration of the dsRNA may be topical, pulmonary, e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal, intranasal, epidermal and transdermal, and subdermal, oral or parenteral, e.g., subcutaneous. For example, when treating a subject with hyperlipidemia, the dsRNA may be

administered systemically via parental means. Parenteral administration includes intravenous, intra-arterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; or intracranial, e.g., intraparenchymal, intrathecal or intraventricular, administration. For example, dsRNAs, conjugated or unconjugated or formulated with or without liposomes, can be administered intravenously to a subject. For such, a dsRNA can be formulated into compositions such as sterile and non-sterile aqueous solutions, non-aqueous solutions in common solvents such as alcohols, or solutions in liquid or solid oil bases. Such solutions also can contain buffers, diluents, and other suitable additives. For parenteral, intrathecal, or intraventricular administration, a dsRNA can be formulated into compositions such as sterile aqueous solutions, which also can contain buffers, diluents, and other suitable additives (e.g., penetration enhancers, carrier compounds, and other pharmaceutically acceptable carriers). Formulations are described in more detail herein. The dsRNA can be delivered in a manner to target a particular tissue, such as the liver (e.g., the hepatocytes of the liver).

The dsRNA (siRNA) of the combination therapy described herein may be formulated into any of many possible dosage forms such as, but not limited to, tablets, capsules, gel capsules, liquid syrups, soft gels, suppositories, and enemas. The dsRNA may also be formulated as suspensions in aqueous, non-aqueous or mixed media. Aqueous suspensions may further contain substances which increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol and/or dextran. The suspension may also contain stabilizers.

The dsRNA in the combination therapy described herein include, but are not limited to, solutions, emulsions, and liposome-containing formulations. These dsRNA formulations may be generated from a variety of components that include, but are not limited to, preformed liquids, self-emulsifying solids and self-emulsifying semisolids. In one aspect, they are formulations that target the liver when treating hepatic disorders such as hyperlipidemia.

In addition, dsRNA that target the target gene can be formulated into compositions containing the dsRNA admixed, encapsulated, conjugated, or otherwise associated with other molecules, molecular structures, or mixtures of nucleic acids in addition to a compound of the invention. For example, a composition containing one or more dsRNA agents that target the target gene can contain other therapeutic agents, such as one or more dsRNA compounds that target other target genes.

dsRNA compositions and formulations for oral administration include powders or

granules, microparticulates, nanoparticulates, suspensions or solutions in water or non-aqueous media, capsules, gel capsules, sachets, tablets or minitablets. Thickeners, flavoring agents, diluents, emulsifiers, dispersing aids or binders may be desirable. In some embodiments, oral formulations are those in which dsRNAs featured in the combination therapy described herein are administered in conjunction with one or more penetration enhancers surfactants and chelators. Suitable surfactants include fatty acids and/or esters or salts thereof, bile acids and/or salts thereof. Suitable bile acids/salts include chenodeoxycholic acid (CDCA) and ursodeoxychenodeoxycholic acid (UDCA), cholic acid, dehydrocholic acid, deoxycholic acid, glucholic acid, glycholic acid, glycodeoxycholic acid, taurocholic acid, taurodeoxycholic acid, sodium tauro-24,25-dihydro-fusidate and sodium glycodihydrofusidate. Suitable fatty acids include arachidonic acid, undecanoic acid, oleic acid, lauric acid, caprylic acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, monoolein, dilaurin, glyceryl 1-monocaprate, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, or a monoglyceride, a diglyceride or a pharmaceutically acceptable salt thereof (e.g., sodium). In some aspects, combinations of penetration enhancers are used, for example, fatty acids/salts in combination with bile acids/salts. One exemplary combination is the sodium salt of lauric acid, capric acid and UDCA. Further penetration enhancers include polyoxyethylene-9-lauryl ether, polyoxyethylene-20-cetyl ether. dsRNAs featured in the combination therapy of the invention may be delivered orally, in granular form including sprayed dried particles, or complexed to form micro or nanoparticles. dsRNA complexing agents include poly-amino acids; polyimines; polyacrylates; polyalkylacrylates, polyoxethanes, polyalkylcyanoacrylates; cationized gelatins, albumins, starches, acrylates, polyethyleneglycols (PEG) and starches; polyalkylcyanoacrylates; DEAE-derivatized polyimines, pollulans, celluloses and starches. Suitable complexing agents include chitosan, N-trimethylchitosan, poly-L-lysine, polyhistidine, polyornithine, polyspermines, protamine, polyvinylpyridine, polythiodiethylaminomethylethylene P(TDAE), polyaminostyrene (e.g., p-amino), poly(methylcyanoacrylate), poly(ethylcyanoacrylate), poly(butylcyanoacrylate), poly(isobutylcyanoacrylate), poly(isohexylcynaoacrylate), DEAE-methacrylate, DEAE-hexylacrylate, DEAE-acrylamide, DEAE-albumin and DEAE-dextran, polymethylacrylate, polyhexylacrylate, poly(D,L-lactic acid), poly(DL-lactic-co-glycolic acid (PLGA), alginate, and polyethyleneglycol (PEG).

dsRNA compositions and formulations for parenteral, intraparenchymal (into the brain), intrathecal, intraventricular or intrahepatic administration may include sterile aqueous

solutions which may also contain buffers, diluents and other suitable additives such as, but not limited to, penetration enhancers, carrier compounds and other pharmaceutically acceptable carriers or excipients.

dsRNA pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Suitable topical formulations include those in which the dsRNAs featured in the invention are in admixture with a topical delivery agent such as lipids, liposomes, fatty acids, fatty acid esters, steroids, chelating agents and surfactants. Suitable lipids and liposomes include neutral (e.g., dioleoylphosphatidyl DOPE ethanolamine, dimyristoylphosphatidyl choline DMPC, distearolyphosphatidyl choline) negative (e.g., dimyristoylphosphatidyl glycerol DMPG) and cationic (e.g., dioleoyltetramethylaminopropyl DOTAP and dioleoylphosphatidyl ethanolamine DOTMA). dsRNAs featured in the invention may be encapsulated within liposomes or may form complexes thereto. Alternatively, dsRNAs may be complexed to lipids. Suitable fatty acids and esters include but are not limited to arachidonic acid, oleic acid, eicosanoic acid, lauric acid, caprylic acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, monoolein, dilaurin, glyceryl 1-monocaprate, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, or a C_{1-10} alkyl ester (e.g., isopropylmyristate IPM), monoglyceride, diglyceride or pharmaceutically acceptable salt thereof. In addition, dsRNA molecules can be administered to a mammal using biologic or abiologic means Abiologic delivery can be accomplished by a variety of methods including, without limitation, (1) loading liposomes with a dsRNA acid molecule provided herein and (2) complexing a dsRNA molecule with lipids or liposomes to form nucleic acid-lipid or nucleic acid-liposome complexes. The liposome can be composed of cationic and neutral lipids commonly used to transfect cells in vitro. Cationic lipids can complex (e.g., charge-associate) with negatively charged nucleic acids to form liposomes. Examples of cationic liposomes include, without limitation, lipofectin, lipofectamine, lipofectace, and DOTAP. Procedures for forming liposomes are well known in the art. Liposome compositions can be formed, for example, from phosphatidylcholine, dimyristoyl phosphatidylcholine, dipalmitoyl phosphatidylcholine, dimyristoyl phosphatidylglycerol, or dioleoyl phosphatidylethanolamine. Numerous lipophilic agents are commercially available, including Lipofectin.TM. (Invitrogen/Life Technologies, Carlsbad, Calif.) and Effectene.TM. (Qiagen, Valencia, Calif.). In addition, systemic delivery methods can be optimized using

commercially available cationic lipids such as DDAB or DOTAP, each of which can be mixed with a neutral lipid such as DOPE or cholesterol. In some cases, liposomes such as those described by Templeton et al. (Nature Biotechnology, 15: 647-652 (1997)) can be used. In other embodiments, polycations such as polyethyleneimine can be used to achieve delivery in vivo and ex vivo (Boletta et al., J. Am. Soc. Nephrol. 7: 1728 (1996)). Biologic delivery of dsRNA can be accomplished by a variety of methods including, without limitation, the use of viral vectors. For example, viral vectors (e.g., adenovirus and herpes virus vectors) can be used to deliver dsRNA to liver cells. Standard molecular biology techniques can be used to introduce one or more of the dsRNAs provided herein into one of the many different viral vectors previously developed to deliver nucleic acid to cells. These resulting viral vectors can be used to deliver the one or more dsRNAs to cells by, for example, infection. The dsRNA of the combination therapy described herein can be formulated according to the liposomal formulations described in US2012/0244207.

The dsRNA of the combination therapy described herein are administered in dosages sufficient to inhibit expression of target genes. In one aspect, the dosage of the dsRNA of the combination therapy described herein is lower than the dosage of the dsRNA when administered alone. In general, a suitable dose of dsRNA will be in the range of about 0.01 to about 200.0 milligrams per kilogram body weight of the recipient per day, generally in the range of about 1 to about 50 mg per kilogram body weight per day. For example, the dsRNA can be administered at about 0.01 mg/kg, about 0.05 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 1.5 mg/kg, about 2.0 mg/kg, about 3.0 mg/kg, about 5.0 mg/kg, about 10 mg/kg, about 20 mg/kg, about 30 mg/kg, about 40 mg/kg, or about 50 mg/kg per single dose.

In another aspect, the dosage is between about 0.01 and about 0.2 mg/kg. For example, the dsRNA can be administered at a dose of about 0.01 mg/kg, about 0.02 mg/kg, about 0.03 mg/kg, about 0.04 mg/kg, about 0.05 mg/kg, about 0.06 mg/kg, about 0.07 mg/kg, about 0.08 mg/kg, about 0.09 mg/kg, about 0.10 mg/kg, about 0.11 mg/kg, about 0.12 mg/kg, about 0.13 mg/kg, about 0.14 mg/kg, about 0.15 mg/kg, about 0.16 mg/kg, about 0.17 mg/kg, about 0.18 mg/kg, about 0.19 mg/kg, or about 0.20 mg/kg.

In one aspect, the dosage is between about 0.2 mg/kg and about 1.5 mg/kg. For example, the dsRNA can be administered at a dose of about 0.2 mg/kg, about 0.3 mg/kg, about 0.4 mg/kg, about 0.5 mg/kg, about 0.6 mg/kg, about 0.7 mg/kg, about 0.8 mg/kg, about 0.9 mg/kg, about 1 mg/kg, about 1.1 mg/kg, about 1.2 mg/kg, about 1.3 mg/kg, about 1.4 mg/kg, or about 1.5 mg/kg. In one aspect, the dsRNA can be administered at a dose of about 0.03, about 0.1, about 0.3, about 1.3, or about 3.0 mg/kg.

In one aspect, the dsRNA can be administered once daily, or the dsRNA may be administered as two, three, or more sub-doses at appropriate intervals throughout the day. The effect of a single dose on target mRNA levels is long lasting, such that subsequent doses are administered at not more than 7 day intervals, or at not more than 1, 2, 3, or 4 week intervals.

In one aspect, the lipid formulated mRNA targeted dsRNA is administered at a first dose followed by administering at least one subsequent dose once a week, wherein the subsequent dose is lower than the first dose. The subsequent dose can be administered, e.g., once a week for four weeks. In some embodiments the dsRNA is administered using continuous infusion or delivery through a controlled release formulation. In that case, the dsRNA contained in each sub-dose must be correspondingly smaller in order to achieve the total daily dosage. The dosage unit can also be compounded for delivery over several days, e.g., using a conventional sustained release formulation which provides sustained release of the dsRNA over a several day period. Sustained release formulations are well known in the art and are particularly useful for delivery of agents at a particular site, such as could be used with the agents of the present invention. In this embodiment, the dosage unit contains a corresponding multiple of the daily dose.

The antibodies of the combination therapy described herein can be administered by any suitable means, including parenteral, intrapulmonary, and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. Dosing can be by any suitable route, e.g., by injections, such as intravenous or subcutaneous injections, depending in part on whether the administration is brief or chronic. Various dosing schedules including but not limited to single or multiple administrations over various time-points, bolus administration, and pulse infusion are contemplated herein.

The anti-PCSK9 antibodies of the combination therapy described herein are formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular subject being treated, the clinical condition of the individual subject, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners.

For the prevention or treatment of disease using a combination therapy described herein, the appropriate dosage of an antibody will depend on the type of disease to be treated, the type of antibody, the severity and course of the disease, whether the antibody is

administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the antibody, and the discretion of the attending physician. The antibody is suitably administered to the patient at one time or over a series of treatments. Depending on the type and severity of the disease, about 1 μg/kg to about 15 mg/kg (e.g. about 0.1 mg/kg-10 mg/kg) of antibody can be an initial candidate dosage for administration to the subject, whether, for example, by one or more separate administrations, or by continuous infusion. One typical daily dosage might range from about 1 μg/kg to about 100 mg/kg or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition, the treatment would generally be sustained until a desired suppression of disease symptoms occurs. One exemplary dosage of the antibody would be in the range from about 0.05 mg/kg to about 10 mg/kg. Thus, one or more doses of about 0.5 mg/kg, about 2.0 mg/kg, about 4.0 mg/kg or about 10 mg/kg (or any combination thereof) may be administered to the subject. Such doses may be administered intermittently, e.g. every week or every three weeks (e.g. such that the patient receives from about two to about twenty, or e.g. about six doses of the antibody). An initial higher loading dose, followed by one or more lower doses may be administered.

In certain aspects, a flat-fixed dosing regimen is used to administer anti-PCSK9 antibody to an individual. Depending on the type and severity of the disease an exemplary flat-fixed dosage might range from about 10 to about 1000 mg of anti-PCSK9 antibody. One exemplary dosage of the antibody would be in the range from about 10 mg to about 600 mg. Another exemplary dosage of the antibody would be in the range from about 100 mg to about 600 mg. In certain embodiments, about 150 mg, about 300 mg, or about 600 mg of anti-PCSK9 antibody is administered to an individual. However, other dosage regimens may be useful. It is understood that any of the above formulations or may be carried out using an immunoconjugate in place of or in addition to an anti-PCSK9 antibody.

Compounds of the invention and combination therapies described herein can be evaluated using a variety of methods known in the art. For example, the following methods can be used to evaluate compounds and combination therapies of the invention. Methods to evaluate compound efficacy or efficacy of combination therapy include measurement of cholesterol (including HDL and LDL cholesterol) and triglycerides in a patient. In specific cases, a fasting lipoprotein profile is performed, such as by standard means in the art.

Screening

The invention provides a method of identifying a compound for treating or preventing a disease comprising: a) contacting a first population of cells with a small molecule; b) determining the expression level of one or more signature genes or one or more products of the signature genes of the first population of cells at a first time point; c) comparing the expression level at the first time point to the expression level of the one or more signature genes or one or more products of the signature genes of a reference sample. In one aspect, the cell type of the population of cells is selected from hepatic, skin, adrenal gland, muscle, and kidney cell. In one aspect, the cell type is hepatic. In one aspect, the cell type is HepG2. In one aspect, the reference sample comprises a second population of cells comprising the same cell type as the first population of cells except that the second population of cells is not contacted with the small molecule. In one aspect, the one or more signature genes is selected from *TRIB1*, *SCAP*, *SREBF1*, *SREBF2*, *PCSK9*, *LDLR*, *HMGCR*, *HMGCS*, *FASN*, *SCD1*, *MTTP and APOC3*. The number of signature genes is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12. In one aspect, the compound identified increases the expression of *TRIB1*. In one aspect, the compound identified increases the expression of *TRIB1* and decreases the expression of *PCSK9*. In one aspect, the compound identified decreases expression of one or more genes selected from *HMGCR*, *HMGCS*, *FASN*, *SREBF1*, *SCD1*, *MTTP and APOC3*. The number of genes is 1, 2, 3, 4, 5, 6, or 7. In one aspect, the compound identified does not change one or more genes selected from *SCAP* and *SREBF2*. The number of genes is 1 or 2.

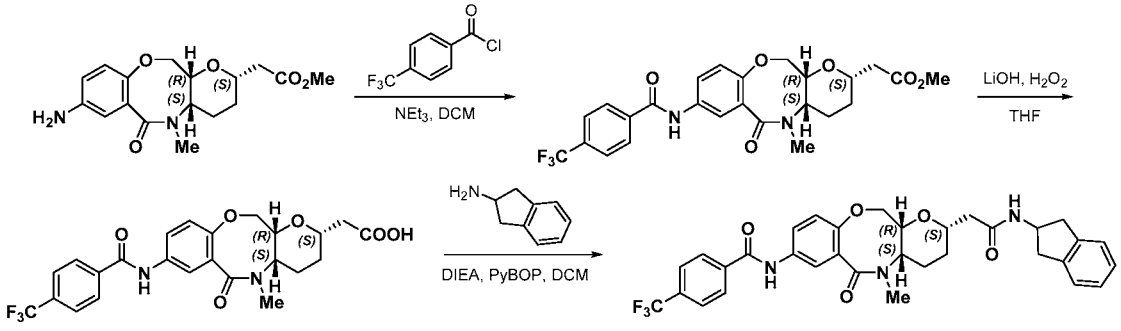
The following Examples are illustrative and should not be interpreted in any way so as to limit the scope of the invention

EXAMPLES

Example 1: Preparation of compounds of the invention

Compounds of the invention were prepared according to synthetic methods described herein and/or techniques known in the art.

Example 1-1:



Step 1: synthesis of methyl 2-((2*S*,4a*S*,12a*R*)-5-methyl-6-oxo-8-(4-(trifluoromethyl)benzamido)-2,3,4,4a,5,6,12,12a-octahydrobenzo[*b*]pyrano[3,2-*f*][1,5]oxazocin-2-yl)acetate

At 0 °C, 4-trifluoromethylbenzoyl chloride (0.49 mL, 3.3 mmol, 1.1 equiv) was added dropwise to a solution of methyl 2-((2*S*,4a*S*,12a*R*)-8-amino-5-methyl-6-oxo-2,3,4,4a,5,6,12,12a-octahydrobenzo[*b*]pyrano[3,2-*f*][1,5]oxazocin-2-yl)acetate (1.0 g, 3.0 mmol, 1.0 equiv) and triethylamine (0.63 mL, 4.49 m\mol, 1.5 equiv) in CH_2Cl_2 (60 mL). After complete conversion of the starting material (LCMS, 30 min), the reaction was quenched with a saturated solution of ammonium chloride (30 mL), and the crude mixture was partially concentrated. The aqueous phase was extracted with EtOAc (3x50 mL) and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (gradient: 0–80% EtOAc in hexanes), which yielded 1.2 g (2.36 mmol, 79 % yield) of methyl 2-((2*S*,4a*S*,12a*R*)-5-methyl-6-oxo-8-(4-(trifluoromethyl)benzamido)-2,3,4,4a,5,6,12,12a-octahydrobenzo[*b*]pyrano[3,2-*f*][1,5]oxazocin-2-yl)acetate, as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.98 (d, *J* = 8.1 Hz, 2H), 7.87 (d, *J* = 9.3 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 2H), 7.45 (d, *J* = 2.7 Hz, 1H), 6.82 (d, *J* = 9.0 Hz, 1H), 4.07 (dd, *J* = 12.2, 3.2 Hz, 1H), 4.02 – 3.76 (m, 4H), 3.72 (s, 3H), 3.26 (s, 3H), 2.61 (dd, *J* = 15.7, 7.3 Hz, 1H), 2.48 (dd, *J* = 15.7, 5.3 Hz, 1H), 2.21 – 2.08 (m, 2H), 1.98 – 1.80 (m, 1H), 1.80 – 1.69 (m, 1H). LRMS (ESI) calcd for $C_{25}H_{26}F_3N_2O_6$ $[M + H]^+$ 507.17, found 507.22.

Step 2: synthesis of 2-((2*S*,4a*S*,12a*R*)-5-methyl-6-oxo-8-(4-(trifluoromethyl)benzamido)-2,3,4,4a,5,6,12,12a-octahydrobenzo[*b*]pyrano[3,2-*f*][1,5]oxazocin-2-yl)acetic acid

A THF solution (43 mL) of methyl 2-((2*S*,4a*S*,12a*R*)-5-methyl-6-oxo-8-(4-(trifluoromethyl)benzamido)-2,3,4,4a,5,6,12,12a-octahydrobenzo[*b*]pyrano[3,2-*f*][1,5]oxazocin-2-yl)acetate (1.1 g, 2.2 mmol, 1.0 equiv) was cooled in an ice bath (0 °C), and hydrogen peroxide (30 % by weight, 2.7 mL, 26.0 mmol, 12.0 equiv) was added to the mixture, followed by lithium hydroxide (1.0 M in water, 13.0 mL, 13.0 mmol, 6.0 equiv). The reaction was stirred overnight, reaching r.t. progressively upon which LCMS analysis showed complete disappearance of the starting material. At 0 °C, the reaction mixture was acidified with 1N HCl solution until pH ~3, diluted with brine (75 mL) and extracted with EtOAc (3x40 mL). Combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give 2-((2*S*,4a*S*,12a*R*)-5-methyl-6-oxo-8-(4-

(trifluoromethyl)benzamido)-2,3,4,4a,5,6,12,12a-octahydrobenzo[*b*]pyrano[3,2-*f*][1,5]oxazocin-2-yl)acetic acid as a white solid (1.1 g, 2.2 mmol), which was used in the next step without further purification.

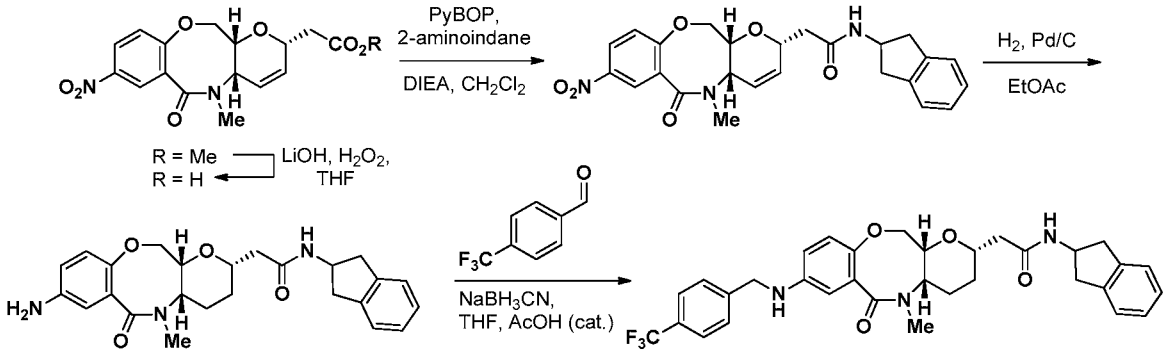
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.21 (s, 1H), 7.99 (d, *J* = 8.1 Hz, 2H), 7.91 (d, *J* = 9.8 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.47 (d, *J* = 2.7 Hz, 1H), 6.77 (d, *J* = 9.0 Hz, 1H), 4.10 – 3.88 (m, 2H), 3.87 – 3.70 (m, 3H), 3.23 (s, 3H), 2.63 (dd, *J* = 15.9, 7.2 Hz, 1H), 2.52 (dd, *J* = 15.9, 5.2 Hz, 1H), 2.19 – 2.06 (m, 2H), 1.97 – 1.82 (m, 1H), 1.82 – 1.69 (m, 1H). LRMS (ESI) calcd for $C_{24}H_{24}F_3N_2O_6$ $[M + H]^+$ 493.16, found 493.42.

Step 3: synthesis of *N*-((2*S*,4a*S*,12a*R*)-2-(2-((2,3-dihydro-1*H*-inden-2-yl)amino)-2-oxoethyl)-5-methyl-6-oxo-2,3,4,4a,5,6,12,12a-octahydrobenzo[*b*]pyrano[3,2-*f*][1,5]oxazocin-8-yl)-4-(trifluoromethyl)benzamide

At 0 °C, 2-aminoindane (13.7 µ, 0.1 mmol, 1.3 equiv) was added to a solution of crude 2-((2*S*,4a*S*,12a*R*)-5-methyl-6-oxo-8-(4-(trifluoromethyl)benzamido)-2,3,4,4a,5,6,12,12a-octahydrobenzo[*b*]pyrano[3,2-*f*][1,5]oxazocin-2-yl)acetic acid (40 mg, 0.08 mmol, 1.0 equiv) and DIEA (42.6 µL, 0.24 mmol, 3.0 equiv) in CH_2Cl_2 (0.16 mL), followed by PyBOP (67.6 mg, 0.13 mmol, 1.6 equiv). The reaction mixture was stirred overnight, reaching rt progressively. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with a saturated solution of ammonium chloride (2x10 mL). The aqueous phase was extracted with CH_2Cl_2 (3x10 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated to yield a crude material which was purified by chromatography on silica gel (gradient: 10–100% EtOAc in Hexanes). *N*-((2*S*,4a*S*,12a*R*)-2-(2-((2,3-dihydro-1*H*-inden-2-yl)amino)-2-oxoethyl)-5-methyl-6-oxo-2,3,4,4a,5,6,12,12a-octahydrobenzo[*b*]pyrano[3,2-*f*][1,5]oxazocin-8-yl)-4-(trifluoromethyl)benzamide was isolated as an off-white solid (42 mg, 0.07 mmol, 85 % yield over two steps).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.96 (d, *J* = 8.1 Hz, 2H), 7.89 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 2.8 Hz, 1H), 7.30 – 7.17 (m, 4H), 6.82 (d, *J* = 9.0 Hz, 1H), 6.17 (d, *J* = 7.9 Hz, 1H), 4.81 – 4.69 (m, 1H), 3.94 – 3.81 (m, 1H), 3.79 – 3.66 (m, 4H), 3.36 (dd, *J* = 7.0, 4.3 Hz, 1H), 3.31 (dd, *J* = 6.7, 4.2 Hz, 1H), 3.16 (s, 3H), 2.83 (dd, *J* = 4.1, 4.1 Hz, 1H), 2.78 (dd, *J* = 4.0, 4.0 Hz, 1H), 2.33 (d, *J* = 5.9 Hz, 2H), 2.13 – 2.06 (m, 2H), 1.88 – 1.76 (m, 1H), 1.76 – 1.65 (m, 1H). LRMS (ESI) calcd for $C_{33}H_{33}F_3N_3O_5$ $[M + H]^+$ 608.24, found 608.28.

Example 1-2:



Step 1: synthesis of *N*-(2,3-dihydro-1*H*-inden-2-yl)-2-((2*R*,4a*S*,12a*R*)-5-methyl-8-nitro-6-oxo-2,4a,5,6,12,12a-hexahydrobenzo[*b*]pyrano[3,2-*f*][1,5]oxazocin-2-yl)acetamide

At 0 °C, an aqueous solution of lithium hydroxide (1.0 M, 5.8 mL, 5.8 mmol, 3.0 equiv) was quickly added to a solution of methyl 2-((2*R*,4a*S*,12a*R*)-5-methyl-8-nitro-6-oxo-2,4a,5,6,12,12a-hexahydrobenzo[*b*]pyrano[3,2-*f*][1,5]oxazocin-2-yl)acetate (700 mg, 1.93 mmol, 1.0 equiv) and hydrogen peroxide (30% by weight, 1.2 mL, 11.6 mmol, 6.0 equiv) in THF (38 mL). The reaction mixture was stirred overnight at r.t., quenched with aqueous HCl (2.0 M) until pH ~3 and partitioned between brine and EtOAc. The aqueous layer was extracted with EtOAc and the combined organic phases were dried over MgSO4, filtered and concentrated to afford 2-((2*R*,4a*S*,12a*R*)-5-methyl-8-nitro-6-oxo-2,4a,5,6,12,12a-hexahydrobenzo[*b*]pyrano[3,2-*f*][1,5]oxazocin-2-yl)acetic acid (670 mg, 1.93 mmol, 99%) as a white solid. The carboxylic acid was directly coupled with 2-aminoindane (1.2 equiv) using PyBOP (1.5 equiv) conditions in the presence of DIEA (3.0 equiv) in CH_2Cl_2 (0.05 M), following the experimental conditions described herein to yield *N*-(2,3-dihydro-1*H*-inden-2-yl)-2-((2*R*,4a*S*,12a*R*)-5-methyl-8-nitro-6-oxo-2,4a,5,6,12,12a-hexahydrobenzo[*b*]pyrano[3,2-*f*][1,5]oxazocin-2-yl)acetamide (785 mg, 1.7 mmol, 88% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, *J* = 2.8 Hz, 1H), 8.10 (dd, *J* = 9.2, 2.9 Hz, 1H), 7.27 – 7.16 (m, 4H), 6.94 (d, *J* = 9.2 Hz, 1H), 6.27 – 6.13 (m, 2H), 5.97 – 5.86 (m, 1H), 4.82 – 4.62 (m, 2H), 4.19 (d, *J* = 6.8 Hz, 2H), 4.05 – 3.98 (m, 1H), 3.94 (ddd, *J* = 6.8, 6.8, 2.4 Hz, 1H), 3.35 (dd, *J* = 7.0, 2.4 Hz, 1H), 3.30 (dd, *J* = 7.0, 2.7 Hz, 1H), 3.05 (s, 3H), 2.83 (d, *J* = 4.2 Hz, 1H), 2.78 (d, *J* = 4.2 Hz, 1H), 2.45 – 2.38 (m, 2H). LRMS (ESI) calcd for $C_{25}H_{26}N_3O_6$ $[M + H]^+$ 464.18, found 464.19.

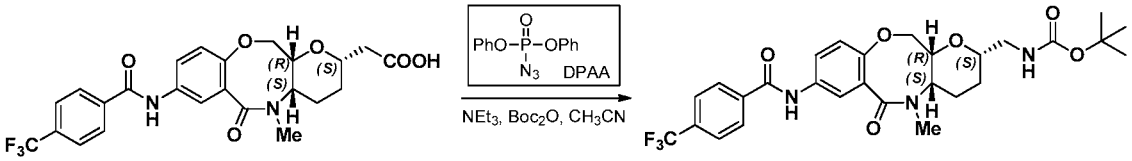
Steps 2 and 3: synthesis of *N*-(2,3-dihydro-1*H*-inden-2-yl)-2-((2*S*,4a*S*,12a*R*)-5-methyl-6-oxo-8-((4-(trifluoromethyl)benzyl)amino)-2,3,4,4a,5,6,12,12a-octahydrobenzo[*b*]pyrano[3,2-*f*][1,5]oxazocin-2-yl)acetamide

N-(2,3-dihydro-1*H*-inden-2-yl)-2-((2*R*,4a*S*,12a*R*)-5-methyl-8-nitro-6-oxo-2,4a,5,6,12,12a-hexahydrobenzo[*b*]pyrano[3,2-*f*][1,5]oxazocin-2-yl)acetamide (785 mg, 1.7 mmol, 1.0 equiv) was dissolved in EtOAc (17 mL) and the mixture was degassed with an argon sparge for 15 minutes. Activated palladium on carbon (Pd/C, 10% by weight, 45.0 mg, 0.025 equiv) was added at r.t., and hydrogen was sparged through the suspension for 30 min. The reaction was stirred overnight under hydrogen atmosphere and the mixture was filtered through a plug of celite. Removal of the solvents *in vacuo* afforded 2-((2*S*,4a*S*,12a*R*)-8-amino-5-methyl-6-oxo-2,3,4,4a,5,6,12,12a-octahydrobenzo[*b*]pyrano[3,2-*f*][1,5]oxazocin-2-yl)-*N*-(2,3-dihydro-1*H*-inden-2-yl)acetamide (679 mg, 1.56 mmol, 92% yield) as a colorless oil which was used directly without further purification.

At r.t., sodium cyanoborohydride (17.3 mg, 0.3 mmol, 3.0 equiv) was added in one portion to a solution of 2-((2*S*,4a*S*,12a*R*)-8-amino-5-methyl-6-oxo-2,3,4,4a,5,6,12,12a-octahydrobenzo[*b*]pyrano[3,2-*f*][1,5]oxazocin-2-yl)-*N*-(2,3-dihydro-1*H*-inden-2-yl)acetamide (40.0 mg, 0.1 mmol, 1.0 equiv) and 4-(trifluoromethyl)benzaldehyde (14.0 μL, 0.101 mmol) in THF (1.5 mL). Acetic acid (AcOH, 2.6 μL, 0.05 mmol, 0.5 equiv) was added and the reaction mixture was stirred overnight at rt, diluted with EtOAc (10 mL) and quenched with a saturated solution of sodium bicarbonate (10 mL). The aqueous layer was extracted with EtOAc and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The resulting crude material was purified by column chromatography on silica gel (gradient: 0–7% MeOH in CH_2Cl_2) to afford *N*-(2,3-dihydro-1*H*-inden-2-yl)-2-((2*S*,4a*S*,12a*R*)-5-methyl-6-oxo-8-((4-(trifluoromethyl)benzyl)amino)-2,3,4,4a,5,6,12,12a-octahydrobenzo[*b*]pyrano[3,2-*f*][1,5]oxazocin-2-yl)acetamide (28.2 mg, 48.0 μmol, 52% yield) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 7.9 Hz, 2H), 7.28 – 7.15 (m, 4H), 6.72 – 6.57 (m, 3H), 6.20 (d, *J* = 7.9 Hz, 1H), 4.80 – 4.67 (m, 1H), 4.34 (s, 2H), 3.99 (dd, *J* = 12.3, 9.3 Hz, 1H), 3.91 – 3.80 (m, 1H), 3.80 – 3.65 (m, 3H), 3.34 (dd, *J* = 6.9, 4.0 Hz, 1H), 3.29 (dd, *J* = 6.8, 4.1 Hz, 1H), 3.22 (s, 3H), 2.81 (dd, *J* = 4.2, 4.2 Hz, 1H), 2.76 (dd, *J* = 4.3, 4.3 Hz, 1H), 2.33 (d, *J* = 6.0 Hz, 2H), 2.16 – 1.99 (m, 2H), 1.92 – 1.74 (m, 1H), 1.74 – 1.60 (m, 1H). LRMS (ESI) calcd for $C_{33}H_{35}F_3N_3O_4$ $[M + H]^+$ 594.26, found 594.31.

Example 1-3:

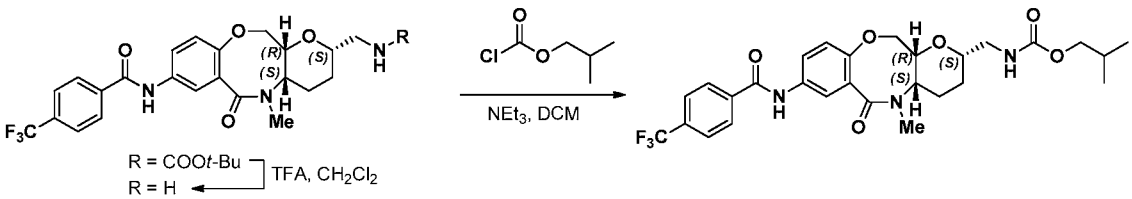


Synthesis of *tert*-butyl (((2*S*,4a*S*,12a*R*)-5-methyl-6-oxo-8-(4-(trifluoromethyl)benzamido)-2,3,4,4a,5,6,12,12a-octahydrobenzo[*b*]pyrano[3,2-*f*][1,5]oxazocin-2-yl)methyl)carbamate

At r.t. and under argon atmosphere, DPPA (0.43 mL, 2.0 mmol, 2.0 equiv) was added dropwise to a solution of 2-((2*S*,4a*S*,12a*R*)-5-methyl-6-oxo-8-(4-(trifluoromethyl)benzamido)-2,3,4,4a,5,6,12,12a-octahydrobenzo[*b*]pyrano[3,2-*f*][1,5]oxazocin-2-yl)acetic acid (490 mg, 1.0 mmol, 1.0 equiv) and triethylamine (0.42 mL, 3.0 mmol, 3.0 equiv) in dry acetonitrile (100 mL). The reaction mixture was heated at 50 °C for two hours, cooled to r.t. for 15 min and transferred dropwise *via* Pasteur pipet to an aqueous solution of 1M NaOH (100 mL), under vigorous stirring and cooled at 0 °C. After 30 min, Boc_2O (2.17 g, 9.95 mmol, 10 equiv) was quickly added to the solution and the reaction mixture was stirred overnight, gradually warming to r.t.. Solvents were partially removed *in vacuo* and the mixture was extracted with CH_2Cl_2 (3x45 mL). Combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated and the residue was purified by silica gel chromatography (gradient: 0–70% EtOAc in Hexanes) to yield *tert*-butyl (((2*S*,4a*S*,12a*R*)-5-methyl-6-oxo-8-(4-(trifluoromethyl)benzamido)-2,3,4,4a,5,6,12,12a-octahydrobenzo[*b*]pyrano[3,2-*f*][1,5]oxazocin-2-yl)methyl)carbamate as a white powder (394 mg, 0.70 mmol, 70 % yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (s, 1H), 7.98 (d, *J* = 8.2 Hz, 2H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 2H), 7.45 (d, *J* = 2.8 Hz, 1H), 6.82 (d, *J* = 9.1 Hz, 1H), 4.89 (s, 1H), 4.09 (dd, *J* = 12.1, 3.5 Hz, 1H), 3.92 – 3.71 (m, 3H), 3.66 – 3.52 (m, 1H), 3.50 – 3.35 (m, 1H), 3.24 (s, 3H), 3.10 – 2.97 (m, 1H), 2.16 – 2.04 (m, 1H), 1.92 – 1.76 (m, 1H), 1.71 – 1.57 (m, 2H), 1.47 (s, 9H). LRMS (ESI) calcd for $C_{28}H_{31}F_3N_3O_6$ $[M - H]^+$ 562.22, found 562.42.

Example 1-4:



Synthesis of *iso*-butyl (((2*S*,4a*S*,12a*R*)-5-methyl-6-oxo-8-(4-(trifluoromethyl)benzamido)-2,3,4,4a,5,6,12,12a-octahydrobenzo-[*b*]pyrano[3,2-*f*][1,5]oxazocin-2-yl)methyl)carbamate

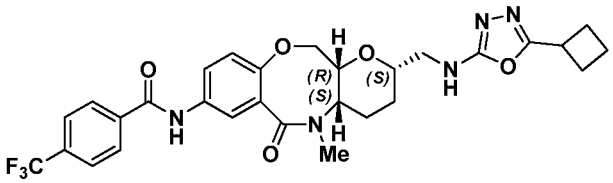
At 0 °C, trifluoroacetic acid (TFA, 0.60 mL, 7.81 mmol, 20.0 equiv) was added dropwise to a solution of *tert*-butyl (((2*S*,4a*S*,12a*R*)-5-methyl-6-oxo-8-(4-(trifluoromethyl)benzamido)-2,3,4,4a,5,6,12,12a-octahydrobenzo[*b*]pyrano[3,2-*f*][1,5]oxazocin-2-yl)methyl)carbamate (220 mg, 0.39 mmol, 1.0 equiv) in CH_2Cl_2 (8 mL). After 10 min, the reaction mixture was warmed to r.t. and stirred until complete disappearance of the starting material (LCMS, 1h 40min). The crude was then concentrated to dryness, redissolved in EtOAc (20 mL) and washed with a saturated solution of sodium bicarbonate until pH ~ 7. The combined aqueous phases were extracted with EtOAc (3x50 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to give *N*-((2*S*,4a*S*,12a*R*)-2-(aminomethyl)-5-methyl-6-oxo-2,3,4,4a,5,6,12,12a-octahydrobenzo[*b*]pyrano[3,2-*f*][1,5]oxazocin-8-yl)-4-(trifluoromethyl)benzamide as a white solid (166 mg, 0.36 mmol, 92% yield) which was used without further purification.

At 0 °C, *iso*-butylchloroformate (9.3 µL, 71 µmol, 1.1 equiv) was added to a solution of crude *N*-((2*S*,4a*S*,12a*R*)-2-(aminomethyl)-5-methyl-6-oxo-2,3,4,4a,5,6,12,12a-octahydrobenzo[*b*]pyrano[3,2-*f*][1,5]oxazocin-8-yl)-4-(trifluoromethyl)benzamide (30 mg, 65 µmol, 1.0 equiv) and triethylamine (45.1 µL, 0.32 mmol, 5.0 equiv) in CH_2Cl_2 (1.2 mL). After 15 min, the ice bath was removed and the reaction mixture was stirred at rt overnight. Silica gel was then added and the crude was concentrated to dryness. Purification was done *via* silica gel chromatography (gradient: 5–65% EtOAc in Hexanes) affording *iso*-butyl (((2*S*,4a*S*,12a*R*)-5-methyl-6-oxo-8-(4-(trifluoromethyl)benzamido)-2,3,4,4a,5,6,12,12a-octahydro-benzo-[*b*]pyrano[3,2-*f*][1,5]oxazocin-2-yl)methyl)carbamate (16.6 mg, 29 µmol, 46 % yield) as a white powder. Alternatively, the title compound was also prepared from *N*-((2*S*,4a*S*,12a*R*)-2-(aminomethyl)-5-methyl-6-oxo-2,3,4,4a,5,6,12,12a-octahydrobenzo[*b*]pyrano[3,2-*f*][1,5]oxazocin-8-yl)-4-(trifluoromethyl)benzamide and *iso*-butylchloroformate (1.1 equiv), in a mixture of 1,4-dioxane and saturated aqueous sodium bicarbonate solution (dioxane:sat. $NaHCO_3$=2:1, 0.05M concentration), at 0 °C. Upon completion of the reaction (LCMS, 2h), extraction of the mixture with EtOAc followed by evaporation of the solvents afforded a crude residue which was purified on silica using the same conditions as described above.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (br s, 1H), 8.04 (br d, *J* = 8.0 Hz, 1H), 7.99 (d, *J* = 8.1 Hz, 2H), 7.67 (d, *J* = 7.9 Hz, 2H), 7.47 (s, 1H), 6.74 (d, *J* = 9.0 Hz, 1H), 5.08 – 4.99 (m,

1H), 3.93 (d, J = 14.7 Hz, 1H), 3.90 – 3.79 (m, 2H), 3.79 – 3.66 (m, 2H), 3.59 (br s, 1H), 3.55 – 3.40 (m, 2H), 3.19 (s, 3H), 3.12 – 3.00 (m, 1H), 2.15 – 2.00 (m, 2H), 1.93 (ddd, J = 13.7, 6.9, 6.9 Hz, 1H), 1.86 – 1.74 (m, 1H), 1.63 (br d, J = 13.7 Hz, 1H), 0.95 (s, 3H), 0.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 165.1, 157.1, 150.9, 138.9, 133.0 (q, J_{C-F} = 32.9 Hz), 132.3, 128.3, 125.4 (q, J_{C-F} = 3.6 Hz), 124.8, 123.9 (q, J_{C-F} = 272.6 Hz), 123.4, 119.8, 119.3, 77.8, 71.4, 64.9, 51.0, 45.6, 32.2, 28.2, 24.5, 23.6, 19.1. LRMS (ESI) calcd for $C_{28}H_{33}F_3N_3O_6$ $[M + H]^+$ 564.23, found 564.13.

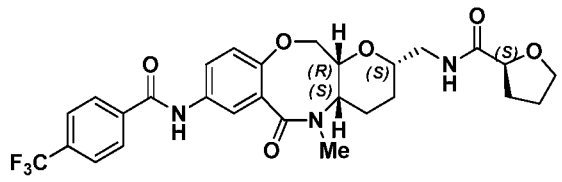
Example 1-5:



N-((2*S*,4a*S*,12a*R*)-2-(((5-cyclobutyl-1,3,4-oxadiazol-2-yl)amino)methyl)-5-methyl-6-oxo-2,3,4,4a,5,6,12,12a-octahydrobenzo[*b*]pyrano[3,2-*f*][1,5]oxazocin-8-yl)-4-(trifluoromethyl)benzamide was synthesized according to the synthetic protocols described herein.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.01 (d, J = 7.8 Hz, 2H), 7.93 (br d, J = 9.0 Hz, 1H), 7.72 (d, J = 8.0 Hz, 2H), 7.49 (s, 1H), 6.80 (d, J = 9.0 Hz, 1H), 5.97 (br s, 1H), 4.14 – 4.00 (m, 1H), 3.88 – 3.72 (m, 4H), 3.70 – 3.54 (m, 1H), 3.37 – 3.25 (m, 1H), 3.23 (s, 3H), 2.47 – 2.33 (m, 4H), 2.22 – 2.06 (m, 3H), 2.06 – 1.95 (m, 1H), 1.94 – 1.79 (m, 1H), 1.78 – 1.67 (m, 1H). LRMS (ESI) calcd for $C_{29}H_{31}F_3N_5O_5$ $[M + H]^+$ 586.23, found 586.25.

Example 1-6:



(*S*)-*N*-(((2*S*,4a*S*,12a*R*)-5-methyl-6-oxo-8-(4-(trifluoromethyl)benzamido)-2,3,4,4a,5,6,12,12a-octahydrobenzo[*b*]pyrano[3,2-*f*][1,5]oxazocin-2-yl)methyl)tetrahydrofuran-2-carboxamide was synthesized according to the synthetic protocols described herein.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1H), 8.06 (d, J = 8.7 Hz, 1H), 8.00 (d, J = 7.8 Hz, 2H), 7.68 (d, J = 7.9 Hz, 2H), 7.49 (s, 1H), 7.04 (br s, 1H), 6.73 (d, J = 9.0 Hz, 1H), 4.36 (dd, J = 7.0 Hz, 1H), 4.01 – 3.83 (m, 3H), 3.79 – 3.66 (m, 2H), 3.65 – 3.42 (m, 3H), 3.23 (s, 4H), 2.37 – 2.24 (m, 1H), 2.15 – 1.99 (m, 3H), 1.99 – 1.71 (m, 3H), 1.68 – 1.57 (m, 1H). LRMS (ESI) calcd for $C_{28}H_{31}F_3N_3O_6$ $[M + H]^+$ 562.22, found 562.44.

Example 2: Evaluation of activity of compounds of the invention

Compounds of the invention were tested in HepG2 cells to further characterize the cellular response to treatment with compounds of the invention. The results of the ELISA, Cell Titer Glo (CTG) assay (Invitrogen) and qPCR assays are summarized in Tables 1A-1F and 2. For all assays, the experiments were performed using powders of freshly purified compounds.

To further characterize the consequences of *TRIB1* and *LDLR* mRNA induction and *PCSK9* mRNA reduction, ELISAs were performed to measure the levels of secreted ApoB and PCSK9. *TRIB1* overexpression has previously been shown to reduce ApoB production. As observed, treatment with compounds of the invention caused a decrease in ApoB levels detected by ELISA (Tables 1A-1F). ELISA analysis confirmed that treatment with compounds of the invention reduced the PCSK9 protein levels (Tables 1A-1F). Functional effects of increased expression of *LDLR* were analyzed by LDL uptake assays to determine whether compounds that modulate *TRIB1, LDLR* and *PCSK9* had any effect on LDL uptake. Results indicate that generally, LDL uptake rates were increased (Tables 1B, 1D, and 1E).

Cell viability was determined using a CTG assay (Invitrogen) after treatment with compounds of the invention. In this assay, the number of viable cells in culture is based on quantitation of ATP, which indicates metabolically active cells. Addition of the reagent results in cell lysis and generation of a luminescent signal proportional to the amount of ATP present, which is directly proportional to the number of viable, metabolically active cells present in culture. Most compounds of the invention had no significant effect on cell viability as compared to the reference compounds (*e.g.*, Compound 23) (Tables 1A-1F and 2).

Modulation of gene expression of *TRIB1* and other key regulators in lipoprotein metabolism, including *LDLR* and *PCSK9*, after treatment by compounds of the invention was monitored by qPCR analysis (**FIGS. 1, 2A, 2B**, and **5B**). Expression levels were calculated as the fold change, as normalized to *GADPH* control and vehicle controls. Many compounds of the invention induce these gene expression changes at much lower concentrations than the reference compound (*e.g.*, Compound 23) (Tables 1A-1F and 2). This increased potency indicates the potential therapeutic efficacy of such compounds for treatment of cardiovascular diseases, particularly hypercholesterolemia and related conditions. In addition, Compound 23, which is the reference compound representing the series, was found to induce *TRIB1* and

LDLR expression in primary mouse hepatocutes (**FIGs. 2A** and **2B**) indicating that the effects produced by compound treatment are preserved across species.

Based on the results of these assays, compounds of the invention were found to stimulate a signature pattern of cellular responses in HepG2 cells without affecting cellular ATP levels or cell viability. This pattern of cellular responses includes: 1) upregulation of transcript levels for *TRIB1*; 2) downregulation of transcript levels for *PCSK9*; 3) upregulation of transcript levels for *LDLR*; 4) downregulation of transcript levels for genes in the cholesterol biosynthetic pathway (e.g., *HMGCS, HMGCR*); 5) downregulation of transcript levels for genes in the triglyceride biosynthetic pathway (e.g., *FASN, SCD1*); 6) downregulation of transcript levels of *MTTP*; 7) down regulation of transcript levels of *APOC3*; 8) decreased level of secreted ApoB100 protein; 9) decreased level of secreted PCSK9 protein; or 10) increased level of functional LDLR in cells. Each of the responses listed above has individually been linked to the reduction of LDL-C in circulation, therefore, indicating the efficacy and use for treating, preventing, and/or alleviating one or more symptoms of a cardiovascular disease or related disorder.

Tables 1A-1E and 2 provide results of the assays described herein. Blank spaces in the table indicate that value was either not measured or not disclosed herein.

Table 1A

Cmpd #	MW	Trib1			LDLR			PCSK9		ApoB IC_{50} (μM) ELISA	PCSK9 IC_{50} (μM) ELISA	Solubility (μM)	Microsomal Stab. (%) H/M	PS (H/M), PB (H/M) (% bd)	CTG	
		Up. Reg. EC_{50} (μM)	[Max Induc.]	*(% Resp. of Ref. Cmpd.)*	Up. Reg. EC_{50} (μM)	[Max Induc.]	*(% Resp. of Ref. Cmpd.)*	Down Reg. IC_{50} (μM)	*(% Inhib. (DMSO))*						(% Inhib.)	30% effect [μM]
23	607	0.17-0.69, 0.7	[2.12-7.20]	-	0.12-0.86, 0.5	[2.98-6.60]	-	0.06-0.42, 0.36	*(60-93%)*	0.97	0.68	0	0/0	84/68, 99/99	(25-33, 28)	[2-3]
19	607	6.8	[5.6-6.2]	*(89-97%)*	6.0	[6.3-7.9]	*(126-132%)*	1.20	*(60%)*						(31)	[12]
45	607	9.85	[3.53]	*(59%)*	14.36	[6.21]	*(179%)*	NA							(10)	[-]
	540	9.3	[5.96]	*(85%)*	7.87	[6.00]	*(112%)*									
30	558	3.63	[2.40]	*(113%)*	3.51	[3.80]	*(128%)*	1.54	*(45%)*						(35)	[6]
22	558	8.78	[2.34]	*(110%)*	8.77	[3.60]	*(121%)*	13.41	*(8%)*						(33)	[12]
18	558	4.39	[2.36]	*(111%)*	3.52	[4.50]	*(130%)*	NA							(20)	[-]
37	573	1.44	[2.97]	*(140%)*	2.16	[3.14]	*(105%)*	0.67	*(44%)*			0.2	0/-		(27)	[-]
8	573	5.53	[2.46]	*(116%)*	5.61	[3.90]	*(131%)*	6.08	*(38%)*						(21)	[-]
21	573	17.51	[2.02]	*(95%)*	3.77	[3.90]	*(131%)*	Induced							(23)	[-]
35	565	6.95	[2.04]	*(96%)*	8.07	[3.40]	*(114%)*	2.1	*(31%)*						(23)	[-]
26	565	13.58	[2.18]	*(103%)*	10.41	[2.78]	*(93%)*	6.4	*(46%)*						(20)	[-]
39	565	12.32	[2.46]	*(116%)*	15.78	[2.80]	*(94%)*	9.49	*(68%)*						(15)	[-]
12	570	2.3-3.0	[5.4-6.3]	*(90-93%)*	2.1-2.8	[5.3-6.7]	*(106-112%)*	1.3	*96%*						(24)	[-]
32	570	8.00-9.00	[5.1-5.6]	*(80-88%)*	7.00-8.00	[5.0-6.6]	*(100-110%)*	3	*50%*						(25)	[-]
36	570	10-17	[4.9-5.8]	*(83-84%)*	5.5-8.6	[6.0-8.2]	*(120-137%)*	NA							(18)	[-]
1	554	5.29	[2.44]	*(115%)*	4.92	[3.49]	*(117%)*	NA*							(28)	[-]
44	554	11.90	[7.21]	*(120%)*	7.43	[6.73]	*(194%)*	NA							(30)	[25]
42	554	17.85	[7.99]	*(133%)*	7.25	[6.00]	*(173%)*	6.36	*(induced)*						(31)	[25]
74	540	4.6-5.2	[4.6-7]	*(92-112%)*	3.5-4.7	[5.2-6]	*(107-112%)*	2.3	*(24%)*			84.6	0/-			
68	420	> 25	[2.5]	*(35%)*	> 25	[2.7]	*(41%)*	4.1	*(42%)*						(24)	[-]
5	477	NA			> 25	[1.70]	*(57%)*	NA							(11)	[-]

Cmpd #	MW	Trib1			LDLR			PCSK9		ApoB IC_{50} (μM) ELISA	PCSK9 IC_{50} (μM) ELISA	Solubility (μM)	Microsomal Stab. (%) H/M	PS (H/M), PB (H/M) (% bd)	CTG	
		Up. Reg. EC_{50} (μM)	[Max Induc.]	*(% Resp. of Ref. Cmpd.)*	Up. Reg. EC_{50} (μM)	[Max Induc.]	*(% Resp. of Ref. Cmpd.)*	Down Reg. IC_{50} (μM)	*(% Inhib. (DMSO))*						(% Inhib.)	30% effect [μM]
50	622	2.5->25	[3.90, 2.80]	*(48-56%)*	1.9-2.5	[3.00, 3.80]	*(60-63%)*	NA							(15)	[-]
31	621	11->25	[3.4-3.8]	*(54-59%)*	8.0-10	[4.60-4.90]	*(82-92%)*	9.20	*(57%)*							NA
66	607	0.05-0.3	[5.5-6.8]	*(94-135%)*	0.06-0.4	[4.5-7.3]	*(94-130%)*	0.04, 0.3	*(56-75%)*	0.001 *(73% inhib)*		6.7	0/0 (NADPH)	91/81, 100/100	(17)	[-]

Table 1B

Cmpd #	MW	Trib1			LDLR			PCSK9		ApoB IC_{50} (μM) ELISA *(% Inhib.)*	PCSK9 IC_{50} (μM) ELISA *(% Inhib.)*	LDL Uptake EC_{50} (μM) [Fold Induc.]	Solubility (μM)	Microsomal Stab. (%) H/M	PS (H/M), PB (H/M) (% bd)	CTG	
		Up. Reg. EC_{50} (μM)	[Max Induc.]	*(% Resp. of Ref. Cmpd.)*	Up. Reg. EC_{50} (μM)	[Max Induc.]	*(% Resp. of Ref. Cmpd.)*	Down Reg. IC_{50} (μM)	*(% Inhib. (DMSO))*							(% Inhib.)	30% effect [μM]
23	607	0.17-0.69, 0.7	[2.12-7.20]	-	0.12-0.86, 0.5	[2.98-6.60]	-	0.06-0.42, 0.36	*(60-93%)*	0.04 *(91%)*	0.02-0.05 *(94-99%)*	0.07-0.34 [2.4-7.5]	0	0/0	84/68, 99/99	(25-33, 28)	[2-3]
28	435	NA			NA			NA								NA	
16/98	463	18.14, 14.5, >25	[2-3.5]	*(49-100%)*	24.67, >25	[2.32, 2.6]	*(46-78%)*	0.12 – 0.36	*(73-75%)*				> 100	0/-	-/60, -/83	(30)	[25]
89	545	22	[3]	*(73%)*	6.9	[4.9]	*(88%)*						1.2	-/0	-/96, -/>99		
101	488	IA, >25	[1.6]	*(30%)*	IA, >25	[2.5]	*(40%)*	1.6	*(37%)*				192, 97	-/0-0**	-/2, -/96, -/99, -/94	(19)	
82	539	2.2	[2.6]	*(77%)*	2.6	[5.2]	*(98%)*	9.5	*(69%)*				11.2	0/0		(48)	IC_{50}= 23 μM

Cmpd #	MW	Trib1			LDLR			PCSK9		ApoB IC_{50} (μM) ELISA (% *Inhib.)*	PCSK9 IC_{50} (μM) ELISA (% *Inhib.)*	LDL Uptake EC_{50} (μM) [Fold Induc.]	Solubility (μM)	Microsomal Stab. (%) H/M	PS (H/M), PB (H/M) (% bd)	CTG	
		Up. Reg. EC_{50} (μM)	[Max Induc.]	*(% Resp. of Ref. Cmpd.)*	Up. Reg. EC_{50} (μM)	[Max Induc.]	*(% Resp. of Ref. Cmpd.)*	Down Reg. IC_{50} (μM)	*(% Inhib. (DMSO))*							(% Inhib.)	30% effect [μM]
85	553	1.9	[3.3]	*(95%)*	1	[4.9]	*(146%)*	> 25	(Induced)				1.1	0/0		(40)	12.5
52	593	0.2 – 0.7	[4.8-7]	*(89-118%)*	0.15 – 0.43	[4.6-6.6]	*(92-117%)*	0.25 – 0.4	*(69-84, 71%)*	0.07 *(37%)*	0.13-0.3 *(96-99%)*	0.8-1.03 [3.2-5.4]	5.1	0.5/-	-/81, ->99	(38, 28)	[25,-]
54	607	0.07 – 0.4	[4.1 – 6.7]	*(82-103%)*	0.5 - 0.8	[5.2-6.9]	*(101-115%)*	0.2 – 0.4	*(59-80%)*	0.008 *(95%)*	0.02-0.03 *(96-99%)*	0.01-0.05 [1.9-5.3]	1.7	2.0/-	-/68, -/100	(39, 29)	[3,-]
93	573	2	[3.7]	*(90%)*	2.4	[6.4]	*(115%)*						2.6	-/0	-/100, -/99		
96	557	1-1.9	[4.7-5.5]	*(124-133%)*	1.2-1.3	[6.1-6.8]	*(99-122%)*	1	*(89%)*				0.6, 15.6	-/0, -/0**	-/86, -/99, ->100, -100	(34)	[25]
99	569	0.5	[4.5]	*(110%)*	0.78	[7]	*(126%)*						12.4	-/0	-/100, -/97		
103	564	0.8	[3.7]	*(76%)*	0.6	[5.9]	*(95%)*	0.17	*(90%)*				16	-/0**	->100, -/99**	(23)	
111	540	15	[3.1]	*(63%)*	4.2	[3.8]	*(62%)*	0.8	*(73%)*				> 100	-/0**	->100, -/98	(22)	
115	623	6		*(51%)*	1.9		*(127%)*	0.2	*(84%)*				0.7	-/0**	-/99,-/100**	(24)	
118	581	0.9		*(127%)*	1.2		*(101%)*	0.3	*(84%)*				0.5	-/26**	-/99,-/100*	(21)	

Table 1C

Cmpd. #	MW	Trib1			LDLR			PCSK9		ApoB IC_{50} (μM) ELISA	PCSK9 IC_{50} (μM) ELISA	Solubility (μM)	Microsomal Stab. (%) H/M	PS (H/M), PB (H/M) (% bd)	CTG	
		Up. Reg. EC_{50} (μM)	[Max Induc.]	*(% Resp. of Ref. Cmpd.)*	Up. Reg. EC_{50} (μM)	[Max Induc.]	*(% Resp. of Ref. Cmpd.)*	Down Reg. IC_{50} (μM)	*(% Inhib. (DMSO))*						(% Inhib.)	30% effect [μM]
23	607	0.17-0.69, 0.7	[2.12-7.20]	-	0.12-0.86, 0.5	[2.98-6.60]	-	0.06-0.42, 0.36	*(60-93%)*	0.97	0.68	0	0/0	84/68, 99/99	(25-33, 28)	[2-3]
31	621	11->25	[3.4-3.8]	*(54-59%)*	8.0-11.0	[4.60-4.90]	*(82-92%)*	9.20	*(192%)*							
38	506	NA			NA			NA							NA	
11/65	520	> 25	[1.5]	*(21%)*	> 25	[1.5]	*(23%)*	> 25	*(26%)*			12 - >25			(11)	[-]
17	506	15->25	[4.3-4.6]	*(66-74%)*	23->25	[3.10-4.20]	-	9.60	*(70%)*						(25)	[-]
25	492	NA			NA			NA							NA	
71	621	1.15, 1	[4.8-6.93]	*(81-99%)*	1.19, 1.2	[3.7-4.31]	*(80%)*	0.8	*(65%)*							
70	621	~ 0.25, 0.3	[5.4-7.8]	*(90-111%)*	~ 1.00, 0.3	[5.3-9.7]	*(111-181%)*	NA								
75	607	0.81, 1.5	[5.4-6.48]	*(89-93%)*	0.99, 1.7	[4-4.50]	*(84-86%)*	0.5	*(77%)*							
76	607	1.71, 2.6	[6.5-7.0]	*(100-108%)*	1.62, 2.3	[4.8-5.64]	*(101-105%)*	1.3	*(53%)*							
73	593	5.28, 4.4	[5.2-7.0]	*(87-100%)*	1.34, 2.4	[4.79-5]	*(89-105%)*	NA								

Table 1D

Cmpd. #	MW	Trib1			LDLR			PCSK9		ApoB IC_{50} (μM) ELISA *(% Inhib.)*	PCSK9 IC_{50} (μM) ELISA *(% Inhib.)*	LDL Uptake EC_{50} (μM) [Fold Induc.]	Solubi-lity (μM)	Micro-somal Stab. (%) H/M	PS (H/M), PB (H/M) (% bd)	CTG	
		Up. Reg. EC_{50} (μM)	[Max Induc.]	*(% Resp. of Ref. Cmpd.)*	Up. Reg. EC_{50} (μM)	[Max Induc.]	*(% Resp. of Ref. Cmpd.)*	Down Reg. IC_{50} (μM)	*(% Inhib. (DMSO))*							(% Inhib.)	30% effect [μM]
23	607	0.17-0.69, 0.7	[2.12-7.20]	-	0.12-0.86, 0.5	[2.98-6.60]	-	0.06-0.42, 0.36	*(60-93%)*	0.04 *(91%)*	0.02-0.05 *(94-99%)*	0.07-0.34 [2.4-7.5]	0	0/0	84/68, 99/99	(25-33, 28)	[2-3]
2	568	3.76	[2.56]	*(121%)*	2.47	[2.61]	*(88%)*	7.88	*(64%)*							(31)	[6]
4	582	4.20-4.80	[5.70-6.30]	*(81-109%)*	4.00-7.00	[4.10-6.60]	*(81-109%)*	3.00	*(80%)*							NA	
58	625	1.9	[6.9]	*(96%)*	2.6	[7.6]	*(115%)*	1.6	*(46%)*							(29)	[-]
72	595	0.85, 1.8	[6.1-7.0]	*(100-101%)*	1.55, 2.3	[5.0-5.74]	*(107%)*	0.4	*(69%)*								
27	607	NA			NA			1.74	*(23%)*							(17)	[-]
10	606	3.0-6.0	[5.7-7.9]	*(98-113%)*	1.8-2.0	[3.00-3.90]	*(60-65%)*	1.2	*(88%)*							(20)	[-]
62	596	4.9	[7.3]	*(103%)*	7	[7.6]	*(114%)*	7.6	*(81%)*							(35)	[6]
60	596	15	[7.3]	*(102%)*	14	[7.6]	*(103%)*	1.2	*(89%)*							(30)	[25]
67	596	8.6	[7.4]	*(103%)*	9.3	[7.3]	*(110%)*	2.2	*(83%)*							(33)	[4]

Cmpd. #	MW	Trib1			LDLR			PCSK9		ApoB IC_{50} (μM) ELISA *(% Inhib.)*	PCSK9 IC_{50} (μM) ELISA *(% Inhib.)*	LDL Uptake EC_{50} (μM) [Fold Induc.]	Solubility (μM)	Microsomal Stab. (%) H/M	PS (H/M), PB (H/M) (% bd)	CTG	
		Up. Reg. EC_{50} (μM)	[Max Induc.]	*(% Resp. of Ref. Cmpd.)*	Up. Reg. EC_{50} (μM)	[Max Induc.]	*(% Resp. of Ref. Cmpd.)*	Down Reg. IC_{50} (μM)	*(% Inhib. (DMSO))*							(% Inhib.)	30% effect [μM]
57	559	0.16 - 0.97	[5-8.4]	*(114-123%)*	0.14 - 0.75	[3.9-5.9]	*(82-105%)*	0.26	*(80-87%)*	0.01 *(89%)*	0.02-0.32 *(88-98%)*	0.13-0.19 [2-4.1]	0.1, 0.25	4.3/0.6 -17*	93/85, 96/95, -/77 (87), -/97 (91)*	(34)	[2]
91	575	6	[1.5]	*(35%)*	12	[5.2]	*(93%)*						1.5	-/66.2	-/76, -/93		
92	533	12-15	[4.8-5]	*(89-122%)*	10-17	[4.8-7]	*(86-111%)*	3.9	*(82%)*				11.3, 1.7	-/69.2, 75, 81*	-/>100, -/93, -/88, -/91**	(24)	
100	561	10	[3.1]	*(74%)*	10	[5.3]	*(94%)*						197	-/92.1	-/88, -/96		
41	607	0.03 - 0.1	[3.4-7.5]	*(82-124%)*	0.04-0.1	[4.8-7.2]	*(89-120%)*	0.02 - 0.07	*(76-81%)*	0.004 *(78%)*	0.002-0.008 *(94-99%)*	0.001-0.07 [2.6-5.3]	9.2	0.2/-	-/45, -/99		
80	559	0.05 - 0.1	[4.6-7.9]	*(107-112%)*	0.1 - 1	[4.5-6]	*(80-107%)*	0.03	*(90%)*		0.02 *(93%)*		0.4, 0.9	0/0-10**	-/89, -/89**	(25-27)	
84	567	2	[2.7]	*(79%)*	2	[5.5]	*(106%)*	9	(Induced)				15.3	100/35		(29)	
78	581	0.5 - 0.67		*(72%)*	0.6 - 3	[4.4]	*(84-159%)*	0.15 - 0.2	*(77-86%)*	0.1 *(56%)*	0.3-0.3 *(96-99%)*	0.7-1.32 [2.9-3.6]	13.3, 20.8	0/0	-/61, -/99	(34)	[12.5]

Cmpd. #	MW	Trib1			LDLR			PCSK9		ApoB IC_{50} (μM) ELISA (% Inhib.)	PCSK9 IC_{50} (μM) ELISA (% Inhib.)	LDL Uptake EC_{50} (μM) [Fold Induc.]	Solubility (μM)	Microsomal Stab. (%) H/M	PS (H/M), PB (H/M) (% bd)	CTG	
		Up. Reg. EC_{50} (μM)	[Max Induc.]	(% Resp. of Ref. Cmpd.)	Up. Reg. EC_{50} (μM)	[Max Induc.]	(% Resp. of Ref. Cmpd.)	Down Reg. IC_{50} (μM)	(% Inhib. (DMSO))							(% Inhib.)	30% effect [μM]
122	595	2.2		(115%)	5.1		(87%)	0.2	(83%)				32	-/0**	-/74, -/94**	(19)	
116	547	0.9		(106%)	2.8		(102%)	0.1	(89%)				0.6	-/64*	-/74, -/94**	(21)	
126	545	2.4	[5.4]	(100%)	5.8	[5.9]	(94%)	0.07	(76%)				7.1	-/46*	-/85, -/95**	(28)	
48	505	> 25	[2.60-2.80]	(37-48%)	> 25	[2.40-2.60]	(43-48%)	23.00	(60%)							(16)	
121	595	11		(69%)	3.7		(112%)	1	(72%)				9.0	-/11**	-/83, -/80**	(23)	
110	547	>25	[2]	(41%)	>25	[3]	(48%)	1.8	(86%)				100	-/67**	-/80, -/86**	(20)	
113/ 114	561	1-1.2	[3.6-3.7]	(58-76%)	1.9-3	[3.8-4.8]	(78-79%)	0.03-0.2	(73-97%)				>100, 79	-/54*, 25	-/85, -/87**, -/80, -/89	(30-32)	[10-25]
108	561	22	[2.5]	(51%)	>25	[2.6]	(42%)	0.9	(94%)				3.8	-/41*	-/69, -/87**	(30)	[25]
124	586	11	[3.4]	(63%)	>25	[2.9]	(46%)	0.28	(80%)				6.7	-/65*	-/78, -/92**	(28)	
104/ 105	560	13	[3.7]	(76%)	7.2	[4.9]	(79%)	0.86	(81%)				98	-/73	-/89, -/89*	(17)	
109	660	>25	[1.8]	(37%)	10	[3.5]	(57%)	0.57	(62%)							(15)	

Cmpd. #	MW	Trib1			LDLR			PCSK9		ApoB IC_{50} (μM) ELISA (% Inhib.)	PCSK9 IC_{50} (μM) ELISA (% Inhib.)	LDL Uptake EC_{50} (μM) [Fold Induc.]	Solubility (μM)	Microsomal Stab. (%) H/M	PS (H/M), PB (H/M) (% bd)	CTG	
		Up. Reg. EC_{50} (μM)	[Max Induc.]	(% Resp. of Ref. Cmpd.)	Up. Reg. EC_{50} (μM)	[Max Induc.]	(% Resp. of Ref. Cmpd.)	Down Reg. IC_{50} (μM)	(% Inhib. (DMSO))							(% Inhib.)	30% effect [μM]
112	660	IA			>25	[1.6]	(26%)	IA								IA	
102	574	IA			IA			IA					> 100	/94*	-/85, -/79**	IA	
120	611	12		(56%)	8.4		(97%)	0.5	(70%)				0.8	-/50*	-/79, -/96**	(27)	
119	611	5		(49%)	8.5		(100%)	0.05	(71%)				40	-/46**	-/64, -/95**	(22)	
125	611	8.6	[4.6]	(86%)	3.5	[6.9]	(110%)	0.08	(80%)				0	-/14**	-/82, -/98*	(27)	
127	549	5.2	[5]	(94%)	16	[4.8]	(77%)	0.32	(70%)				65	-/38*	-/85, -/85**	(29)	
129	549	19	[3.9]	(73%)	>25	[3.4]	(54%)	2.8	(83%)				56	-/50*	-/86, -/85**	(27)	
121	595	11		(69%)	3.7		(112%)	1	(72%)				9		-/83, -/80**	(23)	
130	539	4.3	[1.2]	(18%)	3.8	[1.8]	(32%)	IA					62	-/1.3	-/68, -/87**	(8)	
134	596	1.5-3	[4.2-6.7]	(67-106%)	2.8-3.6	[2.5-3.3]	(43-69%)	0.39-0.5	(72-82%)				73, 75	-/0, 2	-/78, -/92, -/80, -/93	(16-27)	
133	561	0.72	[6.6]	(106%)	0.5	[1.9]	(34%)	0.1	(80%)				6.4	-/0	-/85, -/96**	(18)	

Cmpd. #	MW	Trib1			LDLR			PCSK9		ApoB IC_{50} (μM) ELISA *(% Inhib.)*	PCSK9 IC_{50} (μM) ELISA *(% Inhib.)*	LDL Uptake EC_{50} (μM) [Fold Induc.]	Solubility (μM)	Microsomal Stab. (%) H/M	PS (H/M), PB (H/M) (% bd)	CTG	
		Up. Reg. EC_{50} (μM)	[Max Induc.]	*(% Resp. of Ref. Cmpd.)*	Up. Reg. EC_{50} (μM)	[Max Induc.]	*(% Resp. of Ref. Cmpd.)*	Down Reg. IC_{50} (μM)	*(% Inhib. (DMSO))*							(% Inhib.)	30% effect [μM]
131/ 132	585	0.2-0.43	[4.4-4.8]	*(70-76%)*	1.3-1.6	[2.5-5]	*(44-105%)*	0.03-0.16	*(74-89%)*				33, 22	-/18, 26	-/66, -/98, -/74, -/98	(20-39)	[3]
140	577	2.6	[5.5]	(89%)	4.7	[3.9]	*(81%)*	0.9	*(75%)*				<1	-/0	-/76, -/97	(28)	
143	638	IA			19	[1.7]	*(36%)*	IA					86	-/15.1	-/76, -/79	IA	
141	610	1	[6]	*(96%)*	1.4	[3.9]	*(82%)*	0.07	*(75%)*				7	-/0	-/79, -/95	(30)	[10]
106/ 107	563	0.03, 1.2, 0.8	[4-5.2, 4.2]	*(82-83, 67%)*	0.05, 0.28, 0.9	[6.5-6.6, 4.7]	*(105-115, 99%)*	0.002, 0.23, 0.03	*(72-93, 74%)*				31, 9	-/36**, 40	-/78, -/100**, -/83, -/98	(21-29, 35)	[3]
117	583	0.1-1	[6.5]	*(75-104%)*	0.6-1.8	[6.5]	*(137-149%)*	0.06-0.5	*(69-79%)*				20, 9	-/23**, 20	-/0, -/NA**, -/3, -/NA	(28-35)	[2]
123	563	0.01-0.03	[5.5-6]	*(96-102%)*	0.04-0.3	[3.4-4]	*(64-72%)*	0.001 - 0.003	*(68-86%)*				8, 6	-/3, 28**	-/76, -/100**, -/80, -/99	(29-39)	[0.5]

Cmpd. #	MW	Trib1			LDLR			PCSK9		ApoB IC_{50} (μM) ELISA (% Inhib.)	PCSK9 IC_{50} (μM) ELISA (% Inhib.)	LDL Uptake EC_{50} (μM) [Fold Induc.]	Solubility (μM)	Microsomal Stab. (%) H/M	PS (H/M), PB (H/M) (% bd)	CTG	
		Up. Reg. EC_{50} (μM)	[Max Induc.]	(% Resp. of Ref. Cmpd.)	Up. Reg. EC_{50} (μM)	[Max Induc.]	(% Resp. of Ref. Cmpd.)	Down Reg. IC_{50} (μM)	(% Inhib. (DMSO))							(% Inhib.)	30% effect [μM]
135	577	0.3-0.38	[5.8-6.3]	(93-101%)	0.3-0.5	[1.6-3.5]	(28-74%)	0.01-0.06	(73-83%)				2, 5	-/0, 0	-/73, -/100** , -/75, -/100	(19-32)	[3]
142	563	2.7	[5.2]	(84%)	3.6	[3]	(63%)	1.3	(74%)				2	-/0	-/77, -/96	(24)	
43	463	3.98	[4.38]	(73%)	12.39	[6.50]	(187%)	2.02	(63%)				> 100	76.5/-		(19)	[-]
87	627	IA			IA			Increase					0.2, 0	-/1.4, 16.8, 17	-/65, -/>99	(17)	
88	553	9	[0.7]	(10%)	2.8	[2]	(36%)	Increase					14, 108.6	-/13.7, 14.8	-/100, -/99	(27)	
86	643	IA			IA			IA					0, 0	-/0, 16.1	-/64, -/>99	(10)	
144		0.5-0.98	[3.1-6.6]		1.2	[5.4]		0.018-0.18	(77%)								
146		2.9	[2.8]					0.7	(80%)								
147		5.4	[3.2]					1.3	(72%)								
41	607	0.03-0.1	[6.1-7.5]	(97-124%)	0.04-0.1	[4.8-7.2]	(102-120%)	0.02-0.07	(76-81%)				9.2	0.2/-			

Cmpd. #	MW	Trib1			LDLR			PCSK9		ApoB IC_{50} (μM) ELISA *(% Inhib.)*	PCSK9 IC_{50} (μM) ELISA *(% Inhib.)*	LDL Uptake EC_{50} (μM) [Fold Induc.]	Solubi-lity (μM)	Micro-somal Stab. (%) H/M	PS (H/M), PB (H/M) (% bd)	CTG	
		Up. Reg. EC_{50} (μM)	[Max Induc.]	*(% Resp. of Ref. Cmpd.)*	Up. Reg. EC_{50} (μM)	[Max Induc.]	*(% Resp. of Ref. Cmpd.)*	Down Reg. IC_{50} (μM)	*(% Inhib. (DMSO))*							(% Inhib.)	30% effect [μM]
81	593	0.2-0.25	[5.5-8.5]	*(115-133%)*	0.2-0.9	[4.1-5.6]	*(73-101%)*	0.05	*(91%)*				2.4, 2.1	0/0	-/86, -/100	(32)	[12.5]
83	607	0.01-0.02	[5.3-8.6]	*(116-128%)*	0.02-0.05	[5.5-6.3]	*(98-113%)*	0.01	*(91%)*				0.1	0/0		(32, 45)	[15, 6]

Table 1E

Cmpd. #	MW	Trib1			LDLR			PCSK9		ApoB IC_{50} (μM) ELISA *(% Inhib.)*	PCSK9 IC_{50} (μM) ELISA *(% Inhib.)*	LDL Uptake EC_{50} (μM) [Fold Induc.]	Solubi-lity (μM)	Micro-somal Stab. (%) H/M	PS (H/M), PB (H/M) (% bd)	CTG	
		Up. Reg. EC_{50} (μM)	[Max Induc.]	*(% Resp. of Ref. Cmpd.)*	Up. Reg. EC_{50} (μM)	[Max Induc.]	*(% Resp. of Ref. Cmpd.)*	Down Reg. IC_{50} (μM)	*(% Inhib. (DMSO))*							(% Inhib.)	30% effect [μM]
23	607	0.17-0.69, 0.7	[2.12-7.20]	-	0.12-0.86, 0.5	[2.98-6.60]	-	0.06-0.42, 0.36	*(60-93%)*	0.04 *(91%)*	0.02-0.05 *(94-99%)*	0.07-0.34 [2.4-7.5]	0	0/0	84/68, 99/99	(25-33, 28)	[2-3]
95	608	2.1	[4.8]	*(117%)*	2.2	[7.4]	*(133%)*						16.8	-/0	-/3, -/98		
90	560	4.6	[3.4]	*(83%)*	3.6	[5.1]	*(91%)*						2.5	0/10.9	-/28, -/98		
97	562	IA			IA								200	-/93.1	-/39, -/78		
94	608	0.53	[4.9]	*(119%)*	0.34	[6.7]	*(120%)*	0.8	*(73%)*		0.13 *(94%)*		29.4	-/0	-/84, -/97		
148		0.26	[7.1]		0.29	[5.8]		0.064	*(90%)*								
137	608	1.9	[4.6]	*(74%)*	4.5	[6.5]	*(135%)*	0.4	*(62%)*				15	-/0	-/89, -/100	(22)	
139	526	12	[1.4]	*(22%)*	17	[3]	*(62%)*	IA					55	-/9.2	-/>100, -/96	IA	

Table 1F

Cmpd. #	MW	Trib1			LDLR			PCSK9		ApoB IC_{50} (μM) ELISA	PCSK9 IC_{50} (μM) ELISA	Solubility (μM)	Microsomal Stab. (%) H/M	PS (H/M), PB (H/M) (% bd)	CTG	
		Up. Reg. EC_{50} (μM)	[Max Induc.]	*(% Resp. of Ref. Cmpd.)*	Up. Reg. EC_{50} (μM)	[Max Induc.]	*(% Resp. of Ref. Cmpd.)*	Down Reg. IC_{50} (μM)	*(% Inhib. (DMSO))*						(% Inhib.)	30% effect [μM]
23	607	0.17-0.69, 0.7	[2.12-7.20]	-	0.12-0.86, 0.5	[2.98-6.60]	-	0.06-0.42, 0.36	*(60-93%)*	0.97	0.68	0	0/0	84/68, 99/99	(25-33, 28)	[2-3]
13	593	6.89	[2.50]	*(118%)*	2.95	[4.50]	*(151%)*	NA*							(63)	[6]
7	637	NA			3.71	[3.09]	*(104%)*	Induced							(20)	[-]
56	727	NA			NA			NA							NA	
51	637	19-25	[4.40-4.60]	*(63-79%)*	16.00, 6.80	[3.40-5.30]	*(68-88%)*	NA							(22)	[-]
61	636	> 25	[1.01]	*(14%)*	0.66	[2.5]	*(38%)*	NA	(induced)						(8)	[-]
69	650	NA			0.01	[2.5]	*(37%)*	NA							(5)	[-]
59	664	> 25	[1.5]	*(21%)*	25	[5.4]	*(81%)*	NA	(induced)						(68)	[15]
63		5.1	[1.3]	*(19%)*	3	[2.8]	*(42%)*	4.8	(Induced)						(7)	[-]

Trib1 Up Reg. (EC_{50}, 6h, qPCR, HepG2, μM)
LDLR Up Reg. (EC_{50}, 6h, qPCR, HepG2, μM)
PCSK9 Down Reg (IC_{50}, 24h, qPCR, μM)
NA: Not Active
* GAPDH Ct values increased probably due to toxicity

Solubility 1% DMSO in PBS
Microsomal Stability (% remaining after one hour Human/Mouse)

Table 2

Cmpd #	23	133	123	113	131
MW	607	561	563	561	585
Trib1 Up Reg. EC_{50} (μM) [max Induction]	0.17-0.69, 0.7 [2.12-7.20]	0.72 [6.6]	0.01-0.03 [5.5-6]	1-1.2 [3.6-3.7]	0.2-0.43 [4.4-4.8]
LDLR Up Reg. EC_{50} (μM) [max Induction]	0.12-0.86, 0.5 [2.98-6.60]	0.5 [1.9]	0.04-0.3 [3.4-4]	1.9-3 [3.8-4.8]	1.3-1.6 [2.5-5]
PCSK9 Down Reg. IC_{50} (μM) *(% Inhibition (DMSO)*	0.06-0.42, 0.36 *(60-93%)*	0.1 *(80%)*	0.001-0.003 *(68-86%)*	0.03-0.2 *(73-97%)*	0.03-0.16 *(74-89%)*
Solubility (μM)	0	6	8, 6	>100, 79	33, 22
Microsomal Stab. (%) H/M	0/0	-/0	-/28**	-/54*	-/18
PS (H/M), PB (H/M) (% bd)	84/68, 99/99	-/85, -/96**	-/76, -/100** -/80, -/99	-/85, -/87** -/80, -/89	-/66, -/98 -/74, -/98
CTG (% Inhibition) 30% effect [μM]	(25-33, 28) [2-3]	(18)	(29-39) [0.5]	(30-32) [10-25]	(20-39) [3]

Trib1 Up Reg. (EC_{50}, 6h, qPCR, HepG2, μM)
LDLR Up Reg. (EC_{50}, 6h, qPCR, HepG2, μM)
PCSK9 Down Reg (IC_{50}, 24h, qPCR, μM)
NA: Not Active
* GAPDH Ct values increased probably due to toxicity
Solubility 1% DMSO in PBS
Microsomal Stability (% remaining after one hour Human/Mouse)

Example 3: Determination of half maximal effective concentration

Compounds of the invention were found to induce *TRIB1* and *LDLR* transcript levels with improved potency as compared to the reference compounds (*e.g.*, Compound 23). Many compounds of the invention have a half maximal effective concentration (EC_{50}) less than the EC_{50} of the reference compounds (*e.g.*, Compound 23) (Tables 1A-1F and 2).

Example 4: Determination of solubility

Many compounds of the invention were found to have with improved solubility as compared to the reference compounds (*e.g.*, Compound 23). Many compounds of the invention have a solubility greater than 0.2 μM. Further, a substantial number of compounds of the invention have a solubility greater than 1 μM (Tables 1A-1F and 2).

Example 5: Rodent models

Rodent models of hypercholesterolemia and cardiovascular disease are utilized to determine the efficacy of the selected *TRIB1* inducers for treating, preventing, and/or alleviating one or more symptoms of hypercholesterolemia or cardiovascular disease. Selected *TRIB1* inducers are administered to rodents with hypercholesterolemia over a period of time. Levels of *TRIB1*, *PCSK9*, *LDL*, *FASN* and other transcripts and/or protein are measured throughout the treatment to monitor response to the *TRIB1* inducers. Testing the levels of blood lipids, particularly triglycerides and LDL cholesterol, provides the measure of efficacy of selected compounds.

Example 6: Pharmacokinetic studies

A group of twelve male mice were administered intraperitoneally with the defined compound solution formulation prepared in 10 % DMSO, 55% PEG-400 in Normal Saline at 10 mg/kg dose. The blood samples were collected from a set of two mice under light isoflurane anesthesia at each time point in labeled micro centrifuge tube containing K2EDTA as anticoagulant. Immediately after blood collection, plasma was harvested by centrifugation and stored at -70°C until analysis. Following blood collection, animals were euthanized by CO2 asphyxiation. Liver was collected at 0.08, 0.5, 1, 2, 4 and 8 hr. Collected liver was dipped in 20 mL fresh phosphate buffer saline (pH 7.4) thrice, dried on blotted paper and weighed. Liver samples were homogenized using ice-cold phosphate buffer saline (pH 7.4) and homogenates were stored below -70°C until analysis. Total homogenate volume was ten

times the liver weight. All samples were processed for analysis by protein precipitation using acetonitrile and analyzed with fit-for-purpose LC-MS/MS method (LLOQ = 1.02 ng/mL in plasma and liver). The mean levels of each tested compound measured in plasma and in liver at six time points after administration are graphed at **FIG. 3** and **FIG. 4**, respectively. Pharmacokinetic parameters were calculated using the non-compartmental analysis tool of Phoenix WinNonlin® (Version 6.3) and are shown in Table 3.

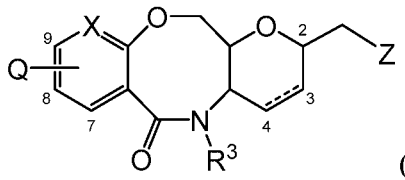
In a separate study distribution of Compound 123 was measured in plasma and in livers of C57BL/6 mice at eight time points after single IP administration at four different doses. The liver exposure to Compound 123 is shown in **FIG. 5A**. Fragments of liver tissue from the same animals were used for RNA extraction and qRT-PCR analysis of changes in the expression of *Trib1* (**FIG. 5B**). Significant increase in the level of *Trib1* expression was measured after 12 hours at 15 mpk dose and at 12 and 24 hours at the 30 mpk dose.

Table 3

Cmpd #	T_{max} (hr)	C_{max} (µg/L)	AUC_{inf} (µg/L*hr)	$T_{1/2}$ (hr)	CL (L/hr/kg)	Vz (L/kg)
23	1.00	436.70	1010.92	1.63	9.89	23.30
123	0.50	2307.67	3616.20	1.12	2.77	4.48
131	1.00	3047.75	6464.61	1.46	1.55	3.26

CLAIMS

1. A compound having the structure of formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein:

X is CH or N;

Q is H, cyano, nitro, amino, $NR^QC(O)R^1$, $C(O)NR^QR^1$, $NR^QC(O)NR^{Q'}R^1$, or $NR^{1a}R^{1b}$;

R^1 is CH_3, unsubstituted or substituted phenyl, or unsubstituted or substituted pyridyl, wherein the substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

R^{1a} is H or unsubstituted C_1-C_3 alkyl;

R^{1b} is unsubstituted C_1-C_3 alkyl or $(CR^{1c}R^{1d})_{0-3}$-R^{1e};

R^{1e} is cyano, unsubstituted or substituted phenyl, unsubstituted or substituted pyridyl, or unsubstituted or substituted C_3-C_6 carbocyclyl, wherein the substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryll;

R^3 is H, CH_3, C_1-C_3 alkyl substituted with amino, methylamino, dimethylamino, or azido, or $(CR^{3a}R^{3b})_{1-3}$-O-$(CR^{3c}R^{3d})_{0-3}$-R^{3e};

R^{3e} is H or unsubstituted phenyl;

----- is a single or double bond;

Z is unsubstituted or substituted heteroaryl comprising one 5- or 6-membered ring and 1 to 4 heteroatoms selected from N, O, and S, $C(O)NR^ZR^{2'}$, $C(O)OR^2$, $NR^ZC(O)R^2$, $NR^ZC(O)OR^2$, $NR^ZS(O)_2R^2$, or $NR^{2a}R^{2b}$, wherein the substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

R^2 is H, unsubstituted C_1-C_6 alkyl, C_1-C_6 alkyl substituted with halogen, $(CR^{2e}R^{2f})_{0-3}$-R^{2c}, or $(CR^{2e}R^{2f})_{1-3}$-R^{2g};

R^{2c} is unsubstituted phenyl, unsubstituted 2,3-dihydroindenyl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-membered rings and 1 to 4 heteroatoms selected from N, O, and S, unsubstituted or substituted C_3-C_6 carbocyclyl, or unsubstituted or substituted heterocyclyl comprising one or two 5- or 6-membered rings and 1 to 4 heteroatoms selected from N, O, and S, wherein the substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

R^{2g} is unsubstituted C_1-C_6 alkoxy or di-C_1-C_3 alkylamino;

$R^{2'}$ is unsubstituted C_1-C_3 alkyl or $(CR^{2e}R^{2f})_{0-3}$-R^{2d};

R^{2d} is unsubstituted phenyl, unsubstituted 2,3-dihydroindenyl, unsubstituted heteroaryl comprising one or two 5- or 6-membered rings and 1 to 4 heteroatoms selected from N, O, and S, or unsubstituted C_3-C_6 carbocyclyl;

R^{2a} and R^{2b} are each independently H, unsubstituted or substituted C_1-C_3 alkyl, or $(CR^{2e}R^{2f})_{1-3}$-R^{2c}, or R^{2a} and R^{2b}, together with the nitrogen atom to which they are attached, form a 5- to 7-membered ring, which is optionally substituted and optionally comprises 1 to 3 additional heteroatoms selected from N, O, and S, wherein the substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

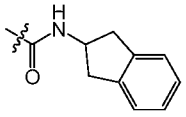
each R^{2e} and each R^{2f} are independently H, OH, methoxy, or unsubstituted C_1-C_3 alkyl;

each R^{1c}, each R^{1d}, each R^{3a}, each R^{3b}, each R^{3c}, and each R^{3d} are each independently H or unsubstituted C_1-C_3 alkyl; and

R^Q, $R^{Q'}$, and R^Z are each independently H or unsubstituted C_1-C_3 alkyl;

provided that:

when X is CH; Q is $NHC(O)R^1$; R^1 is 4-trifluoromethyl-phenyl; and R^3 is CH_3;

then Z is not  , or

when X is CH; Q is amino or nitro; and R^3 is CH_3; then Z is not $C(O)OCH_3$.

2. The compound of claim 1, wherein X is CH.

3. The compound of claim 1, wherein Q is $NR^QC(O)R^1$.

4. The compound of claim 3, wherein R^Q is H.

5. The compound of claim 3, wherein R^1 is unsubstituted phenyl or unsubstituted pyridyl.

6. The compound of claim 3, wherein R^1 is substituted phenyl or substituted pyridyl.

7. The compound of claim 6, wherein the substituted phenyl is substituted with C_1-C_6 alkyl substituted with one or more halogens.

8. The compound of claim 7, wherein the substituted phenyl is substituted with 4-trifluoromethyl.

9. The compound of claim 1, wherein ----- is a single bond.

10. The compound of claim 1, wherein R^3 is CH_3.

11. The compound of claim 1, wherein Z is $C(O)NR^ZR^{2'}$.

12. The compound of claim 11, wherein R^Z is H and $R^{2'}$ is R^{2d}.

13. The compound of claim 12, R^{2d} is unsubstituted 2,3-dihydroindenyl.

13. The compound of claim 1, wherein Z is $NR^ZC(O)R^2$.

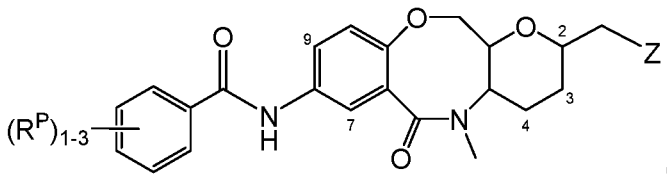
14. The compound of claim 13, wherein R^Z is H and R^2 is R^{2c}.

15. The compound of claim 14, wherein R^{2c} is unsubstituted 2,3-dihydroindenyl.

16. The compound of claim 1, wherein Z is $NR^ZC(O)OR^2$.

17. The compound claim 16, wherein R^Z is H and R^2 is C_1-C_6 alkyl.

18. The compound of claim 1, having the structure of formula (II):



(II),

or a pharmaceutically acceptable salt thereof, wherein:

each R^P is independently unsubstituted or substituted C_1-C_3 alkyl, unsubstituted or substituted C_1-C_3 alkoxy, halogen, or cyano, where optional substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

Z is unsubstituted or substituted heteroaryl comprising one 5- or 6-membered ring and 1 to 4 heteroatoms selected from N, O, and S, $C(O)NR^ZR^{2'}$, $C(O)OR^2$, $NR^ZC(O)R^2$, $NR^ZC(O)OR^2$, $NR^ZS(O)_2R^2$, or $NR^{2a}R^{2b}$, where optional substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

R^2 is H, unsubstituted C_1-C_6 alkyl, C_1-C_6 alkyl substituted with halogen, $(CR^{2e}R^{2f})_{0-3}$-R^{2c}, or $(CR^{2e}R^{2f})_{1-3}$-R^{2g};

R^{2c} is unsubstituted phenyl, unsubstituted 2,3-dihydroindenyl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-membered rings and 1 to 4 heteroatoms selected from N, O, and S, unsubstituted or substituted C_3-C_6 carbocyclyl, or unsubstituted or substituted heterocyclyl comprising one or two 5- or 6-membered rings and 1 to 4 heteroatoms selected from N, O, and S, where optional substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

R^{2g} is unsubstituted C_1-C_6 alkoxy or di-C_1-C_3 alkylamino;

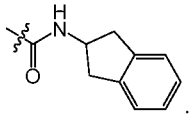
$R^{2'}$ is unsubstituted C_1-C_3 alkyl or $(CR^{2e}R^{2f})_{0-3}$-R^{2d};

R^{2d} is unsubstituted phenyl, unsubstituted 2,3-dihydroindenyl, unsubstituted heteroaryl comprising one or two 5- or 6-membered rings and 1 to 4 heteroatoms selected from N, O, and S, or unsubstituted C_3-C_6 carbocyclyl;

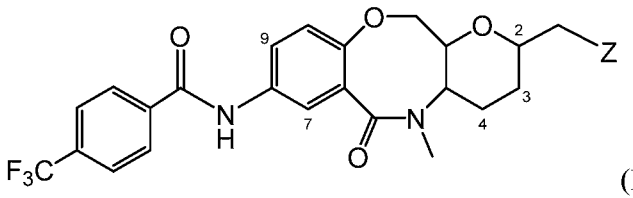
R^{2a} and R^{2b} are each independently H, unsubstituted or substituted C_1-C_3 alkyl, or $(CR^{2e}R^{2f})_{1-3}$-R^{2c}, or R^{2a} and R^{2b}, together with the nitrogen atom to which they are attached, form a 5- to 7-membered ring, which is optionally substituted and optionally comprises 1 to 3 additional heteroatoms selected from N, O, and S, where optional substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

each R^{2e} and each R^{2f} are independently H, OH, methoxy, or unsubstituted C_1-C_3 alkyl; and

R^Z is H or unsubstituted C_1-C_3 alkyl;

provided that when R^P is 4-trifluoromethyl, then Z is not  .

19. The compound of claim 18, having the structure of formula (IIa):



(IIa),

or pharmaceutically acceptable salt thereof, wherein:

Z is unsubstituted or substituted heteroaryl comprising one 5- or 6-membered ring and 1 to 4 heteroatoms selected from N, O, and S, $C(O)NR^ZR^{2'}$, $C(O)OR^2$, $NR^ZC(O)R^2$, $NR^ZC(O)OR^2$, $NR^ZS(O)_2R^2$, or $NR^{2a}R^{2b}$where optional substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

R^2 is H, unsubstituted C_1-C_6 alkyl, C_1-C_6 alkyl substituted with halogen, $(CR^{2e}R^{2f})_{0-3}$-R^{2c}, or $(CR^{2e}R^{2f})_{1-3}$-R^{2g};

R^{2c} is unsubstituted phenyl, unsubstituted 2,3-dihydroindenyl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-membered rings and 1 to 4 heteroatoms selected from N, O, and S, unsubstituted or substituted C_3-C_6 carbocyclyl, or unsubstituted or

substituted heterocyclyl comprising one or two 5- or 6-membered rings and 1 to 4 heteroatoms selected from N, O, and S, where optional substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

R^{2g} is unsubstituted C_1-C_6 alkoxy or di-C_1-C_3 alkylamino;

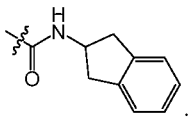
$R^{2,}$ is unsubstituted C_1-C_3 alkyl or $(CR^{2e}R^{2f})_{0-3}$-R^{2d};

R^{2d} is unsubstituted phenyl, unsubstituted 2,3-dihydroindenyl, unsubstituted heteroaryl comprising one or two 5- or 6-membered rings and 1 to 4 heteroatoms selected from N, O, and S, or unsubstituted C_3-C_6 carbocyclyl;

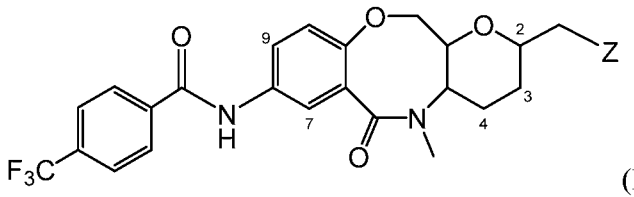
R^{2a} and R^{2b} are each independently H, unsubstituted or substituted C_1-C_3 alkyl, or $(CR^{2e}R^{2f})_{1-3}$-R^{2c}, or R^{2a} and R^{2b}, together with the nitrogen atom to which they are attached, form a 5- to 7-membered ring, which is optionally substituted and optionally comprises 1 to 3 additional heteroatoms selected from N, O, and S, where optional substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

each R^{2e} and each R^{2f} are each independently H, OH, methoxy, or unsubstituted C_1-C_3 alkyl; and

R^Z is H or unsubstituted C_1-C_3 alkyl;

provided that Z is not  .

20. The compound of claim 18, having the structure of formula (IIb):



(IIb),

or pharmaceutically acceptable salt thereof, wherein:

Z is $NR^ZC(O)R^2$, $NR^ZC(O)OR^2$, or $NR^{2a}R^{2b}$;

R^2 is H, unsubstituted C_1-C_6 alkyl, C_1-C_6 alkyl substituted with halogen, $(CR^{2e}R^{2f})_{0-3}$-R^{2c}, or $(CR^{2e}R^{2f})_{1-3}$-R^{2g};

R^{2c} is unsubstituted phenyl, unsubstituted 2,3-dihydroindenyl, unsubstituted or substituted heteroaryl comprising one or two 5- or 6-membered rings and 1 to 4 heteroatoms selected from N, O, and S, unsubstituted or substituted C_3-C_6 carbocyclyl, or unsubstituted or substituted heterocyclyl comprising one or two 5- or 6-membered rings and 1 to 4 heteroatoms selected from N, O, and S, where optional substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

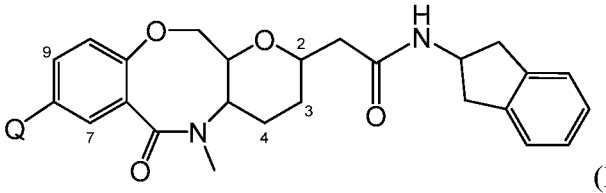
R^{2g} is unsubstituted C_1-C_6 alkoxy or di-C_1-C_3 alkylamino;

R^{2a} and R^{2b} are each independently H, unsubstituted or substituted C_1-C_3 alkyl, or $(CR^{2e}R^{2f})_{1-3}$-R^{2c}, or R^{2a} and R^{2b}, together with the nitrogen atom to which they are attached, form a 5- to 7-membered ring, which is optionally substituted and optionally comprises 1 to 3 additional heteroatoms selected from N, O, and S, where optional substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

R^{2e} and R^{2f} are each independently H, OH, methoxy, or unsubstituted C_1-C_3 alkyl; and

R^{Z} is H or unsubstituted C_1-C_3 alkyl.

21. The compound of claim 1, having the structure of formula (III):



(III),

or pharmaceutically acceptable salt thereof, wherein:

Q is $NR^{Q}C(O)R^{1}$, $C(O)NR^{Q}R^{1}$, $NR^{Q}C(O)NR^{Q}R^{1}$, or $NR^{1a}R^{1b}$;

R^{1} is CH_3, unsubstituted or substituted phenyl, or unsubstituted or substituted pyridyl, where optional substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

R^{1a} is H or unsubstituted C_1-C_3 alkyl;

R^{1b} is unsubstituted C_1-C_3 alkyl or $(CR^{1c}R^{1d})_{0-3}$-R^{1e};

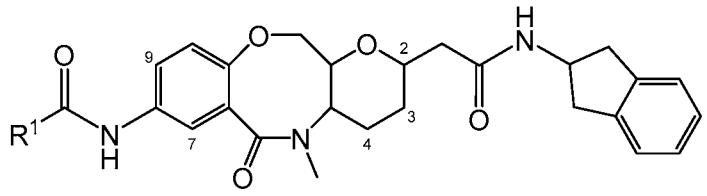
R^{1e} is cyano, unsubstituted or substituted phenyl, unsubstituted or substituted pyridyl, or unsubstituted or substituted C_3-C_6 carbocyclyl, where optional substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

each R^{1c} and each R^{1d} are independently H or unsubstituted C_1-C_3 alkyl; and

R^Q and $R^{Q'}$ are each independently H or unsubstituted C_1-C_3 alkyl;

provided that when Q is $NHC(O)R^1$, then R^1 is not 4-trifluoromethyl-phenyl.

22. The compound of claim 21, having the structure of formula (IIIa):



(IIIa),

or pharmaceutically acceptable salt thereof, wherein:

R^1 is CH_3, unsubstituted or substituted phenyl, or unsubstituted or substituted pyridyl where optional substituents are selected from halogen, alkyl, aralkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, amido, nitro, cyano, amido, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aryl, and heteroaryl;

provided that R^1 is not 4-trifluoromethyl-phenyl.

23. A compound selected from:

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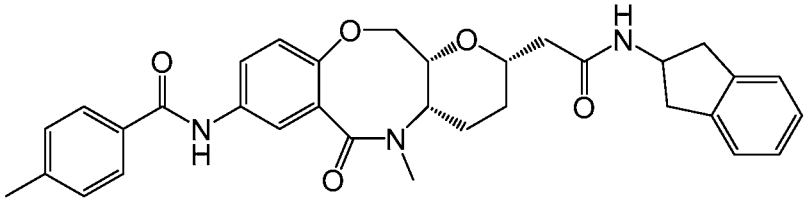
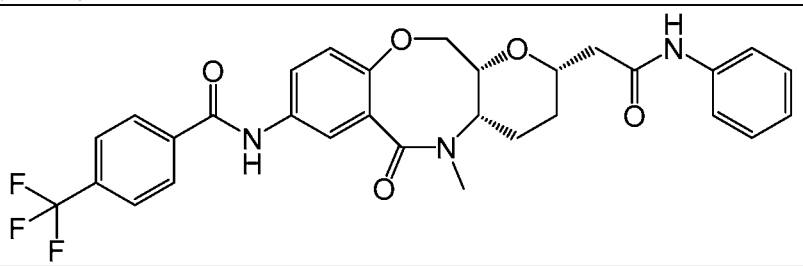
1	
2	

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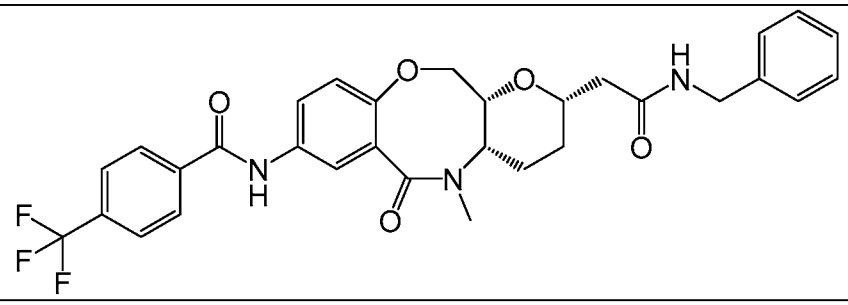
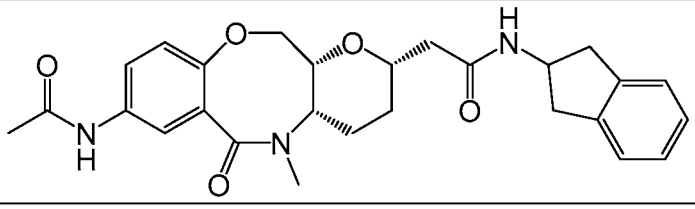
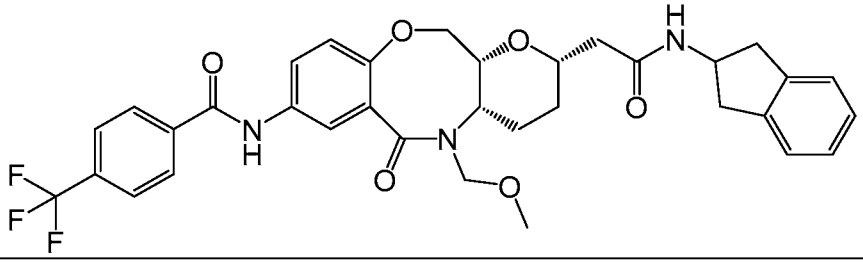
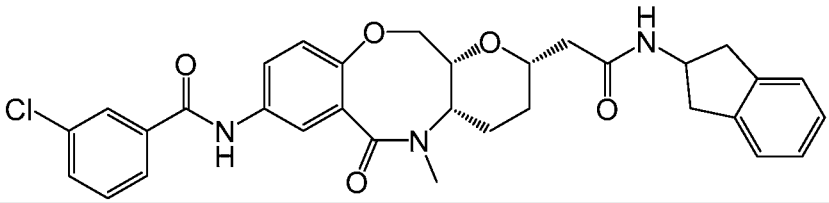
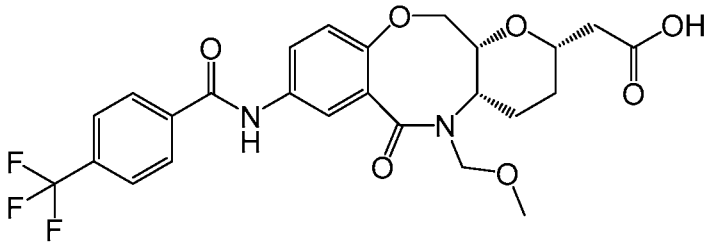
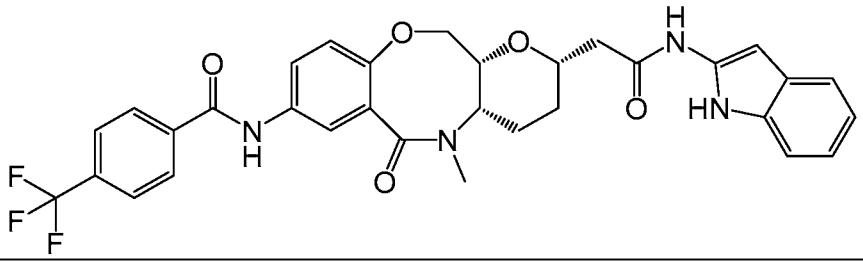
4	
5	
7	
8	
9	
10	

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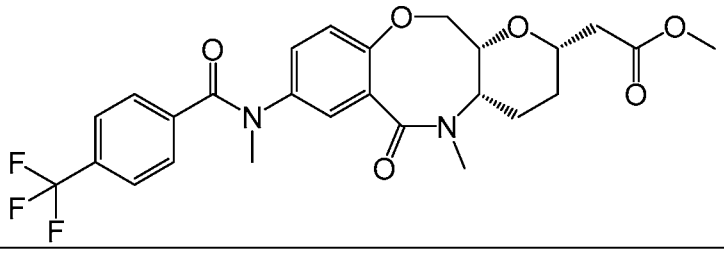
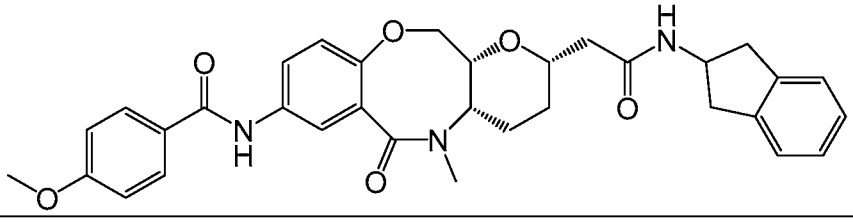
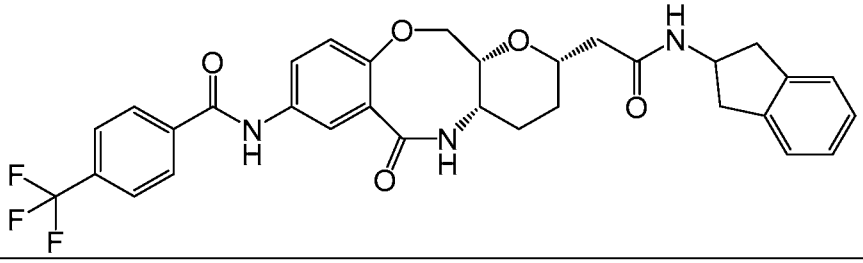
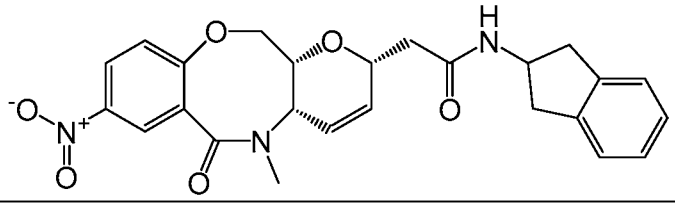
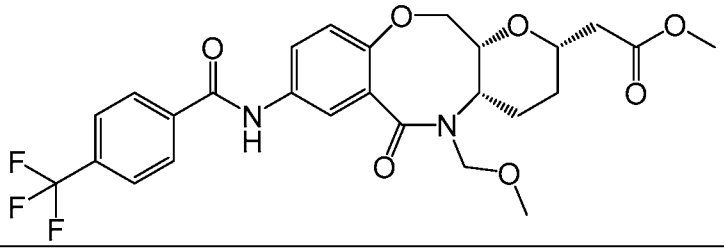
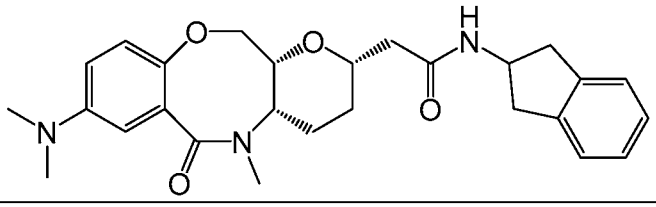
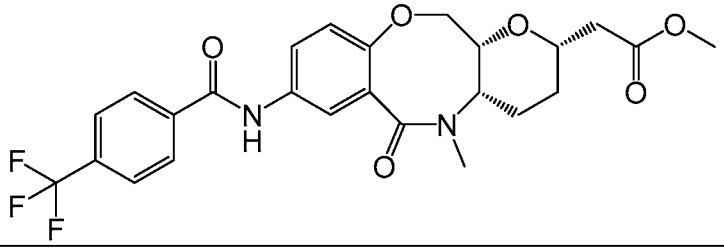
11	
12	
13	
14	
15	
16	
17	

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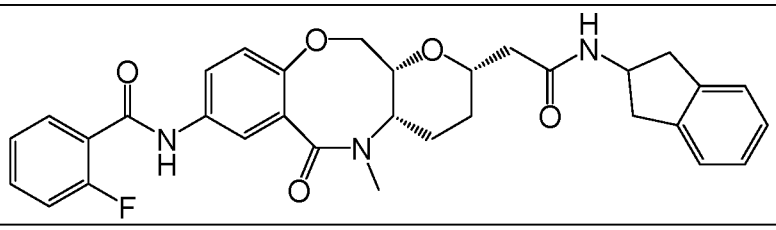
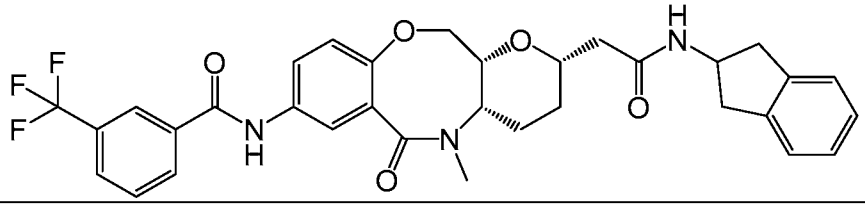
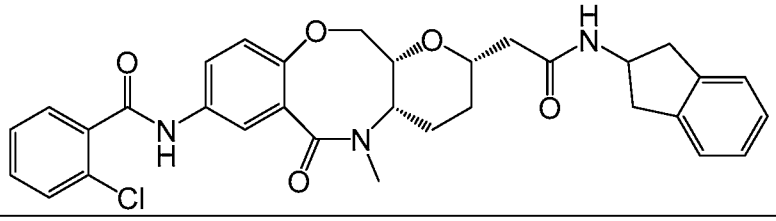
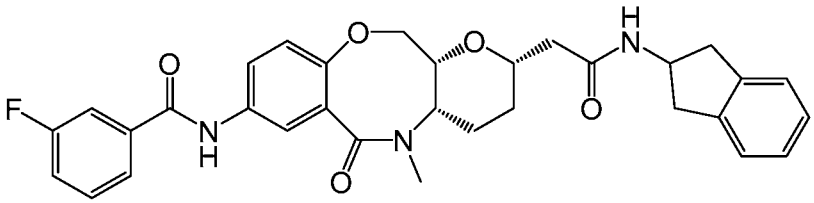
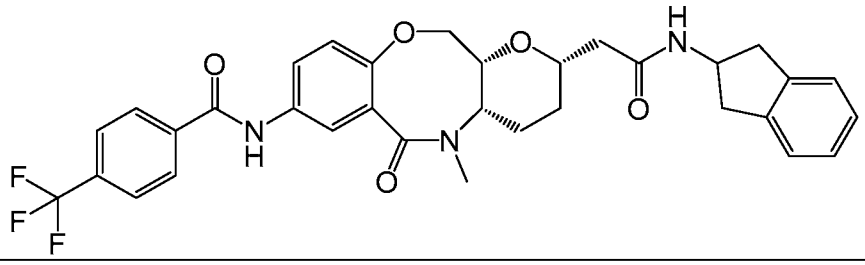
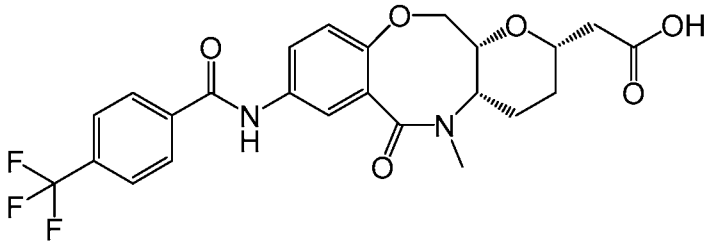
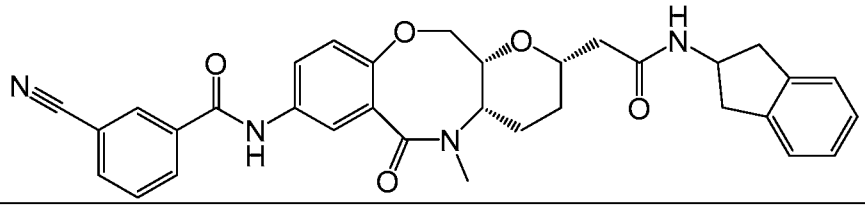
18	
19	
21	
22	
23	
25	
26	

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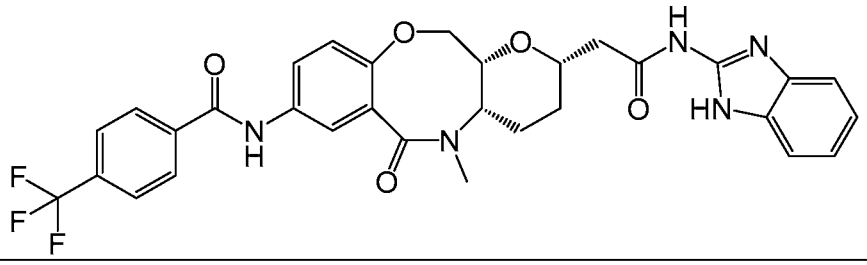
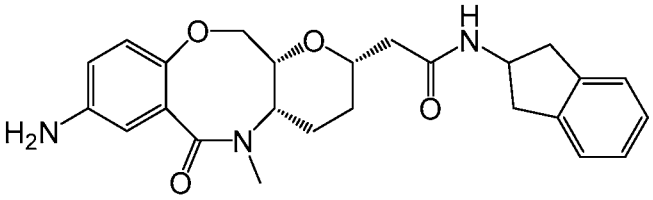
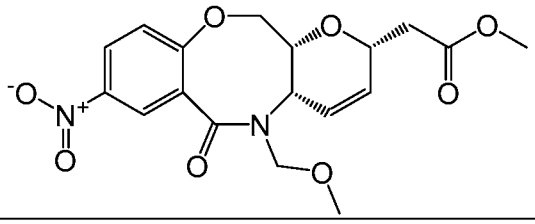
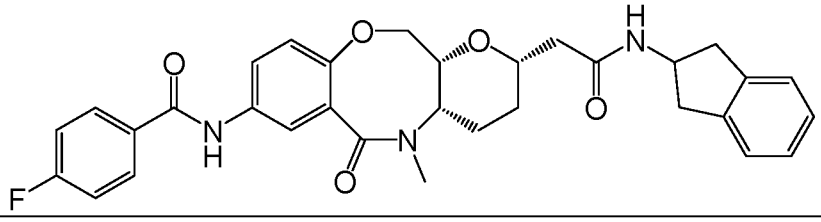
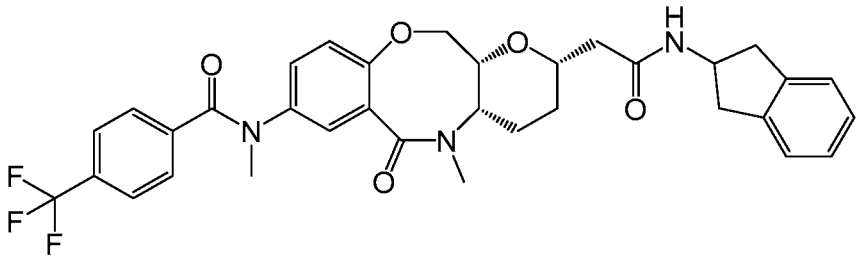
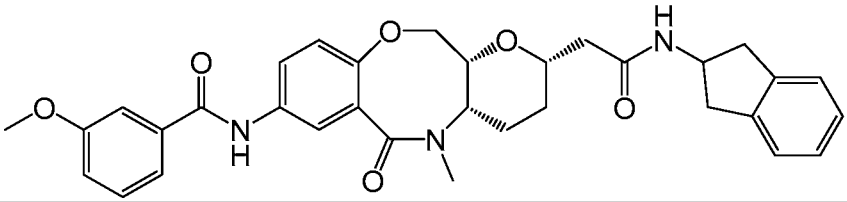
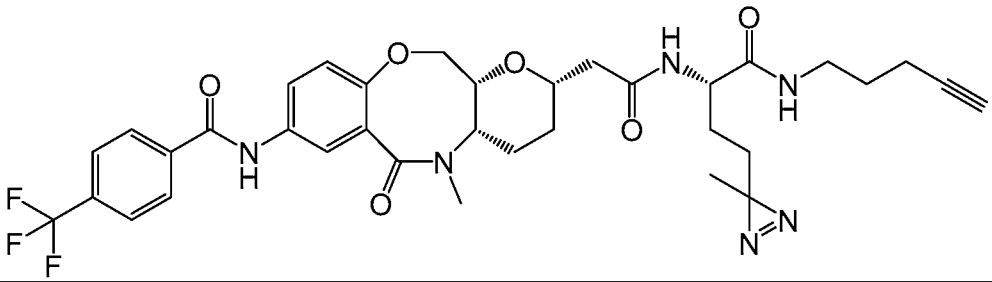
27	
28	
29	
30	
31	
32	
33	

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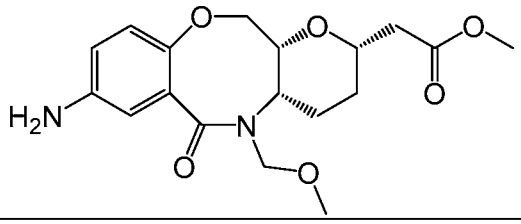
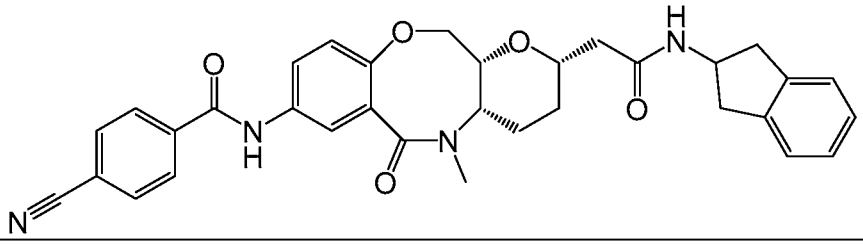
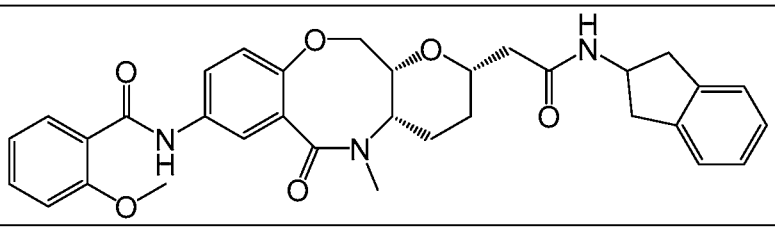
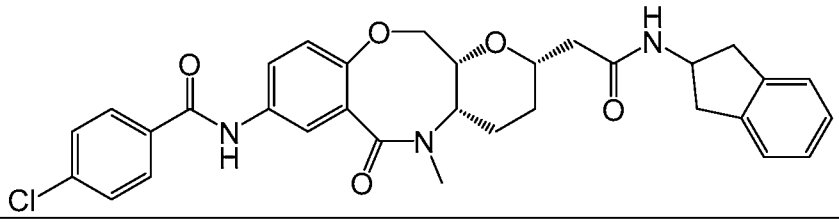
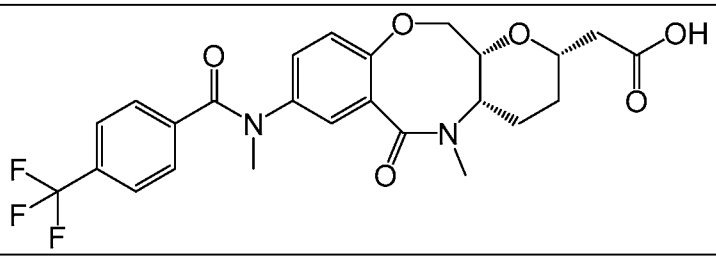
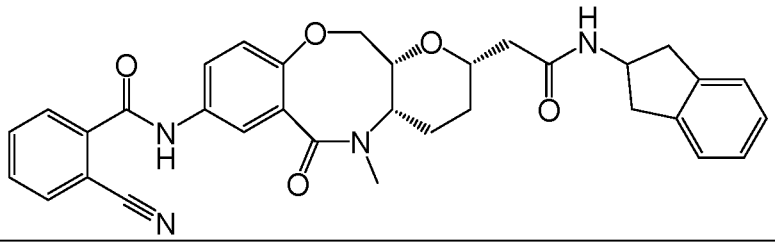
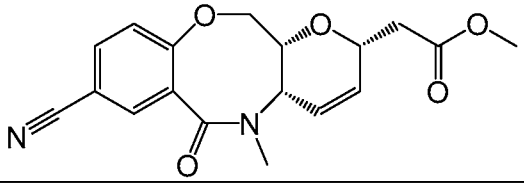
34	
35	
36	
37	
38	
39	
40	

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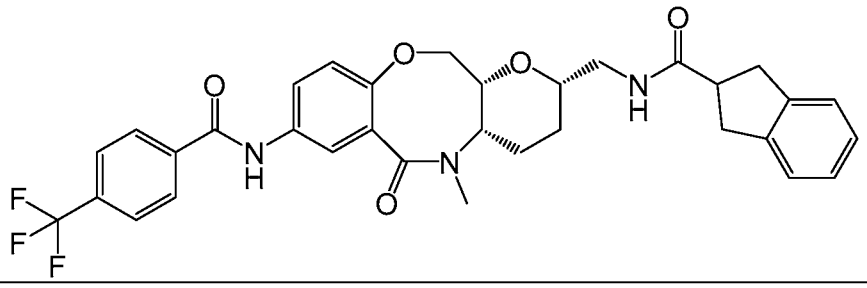
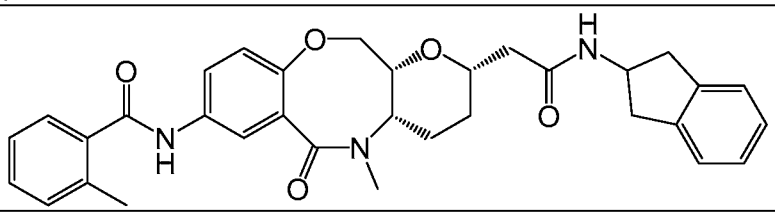
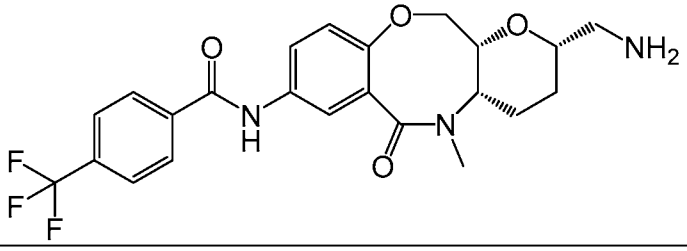
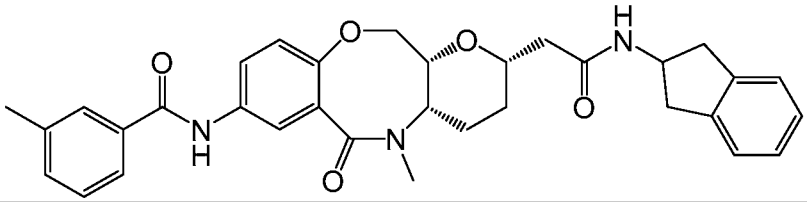
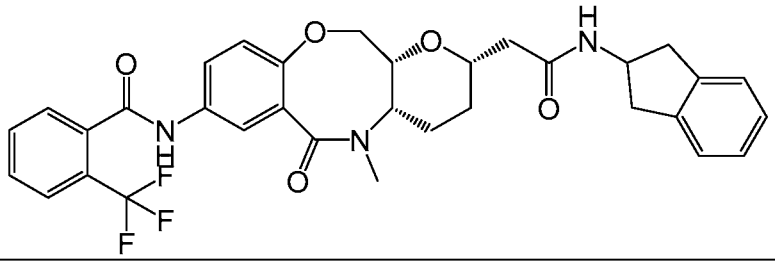
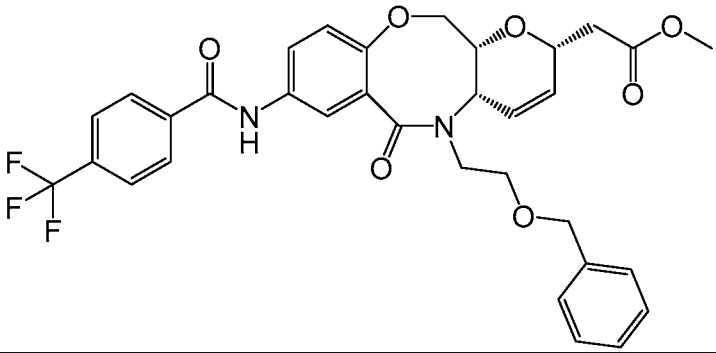
41	
42	
43	
44	
45	
46	

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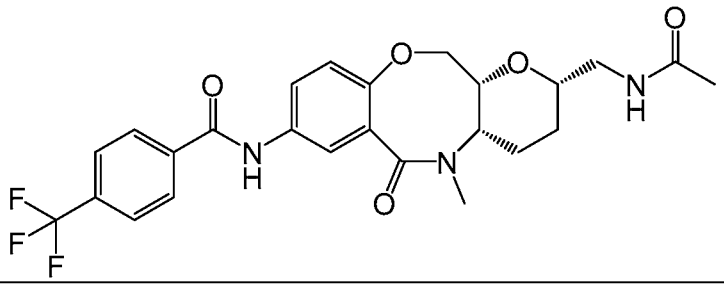
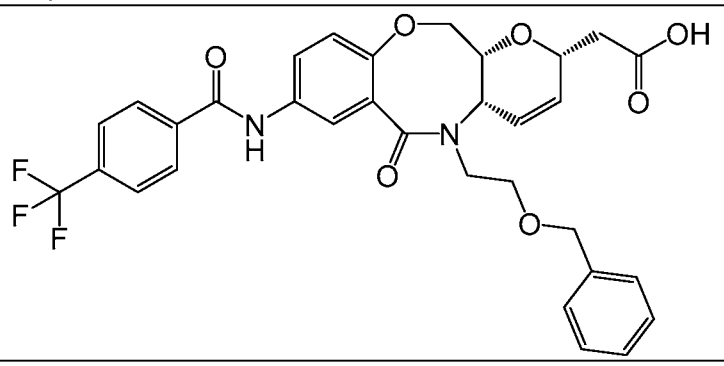
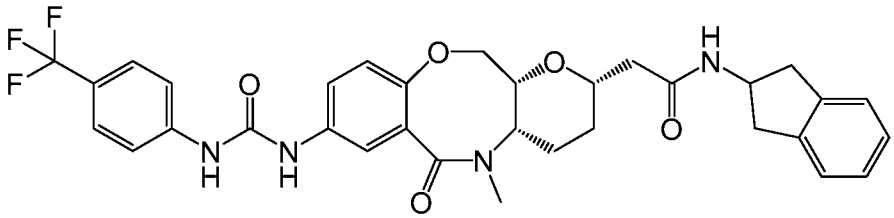
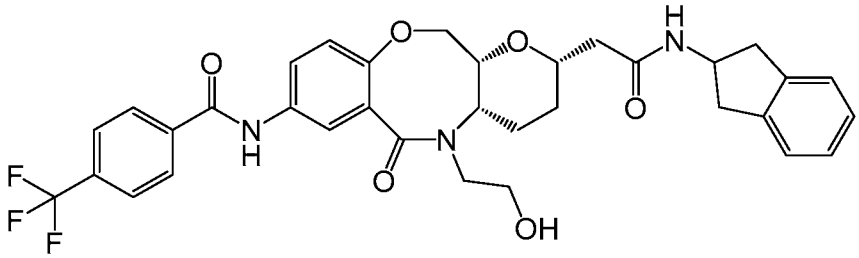
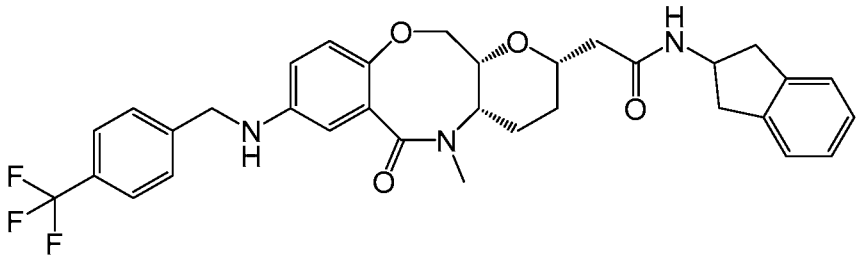
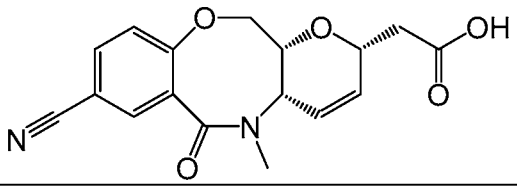
48	
49	
50	
51	
52	
53	

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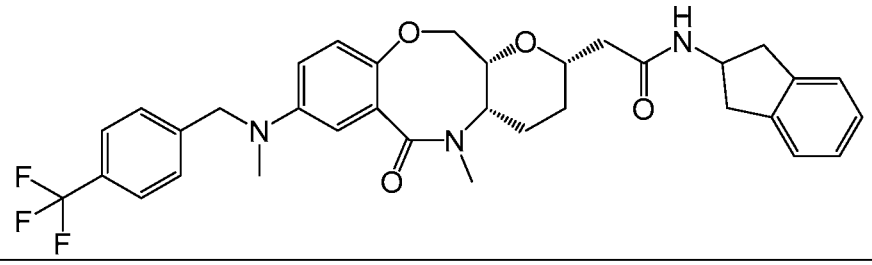
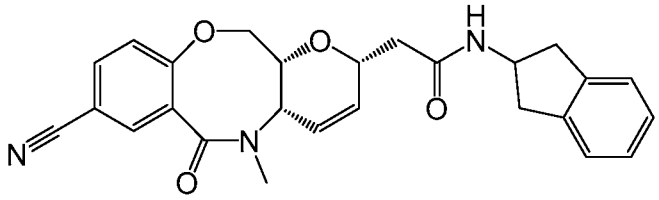
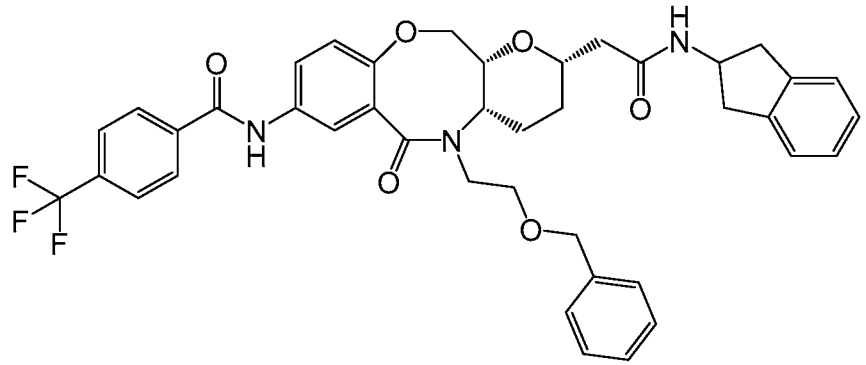
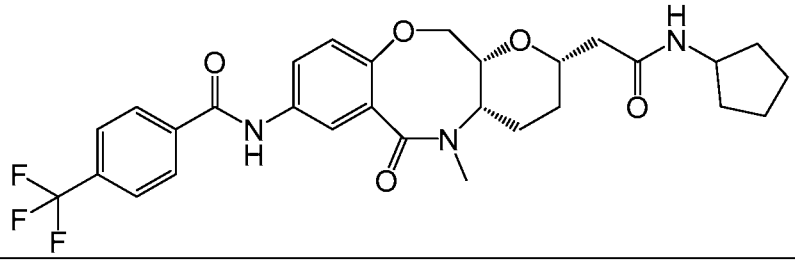
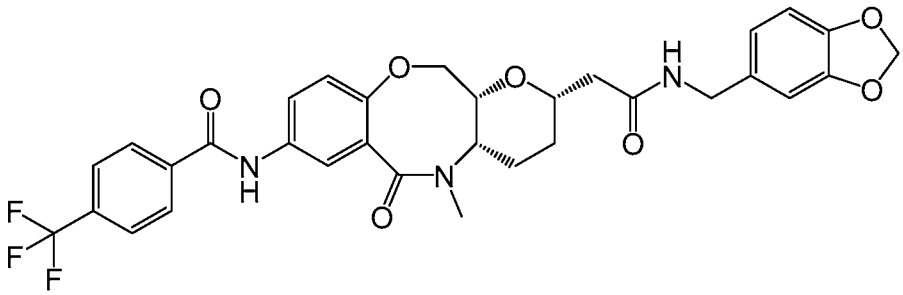
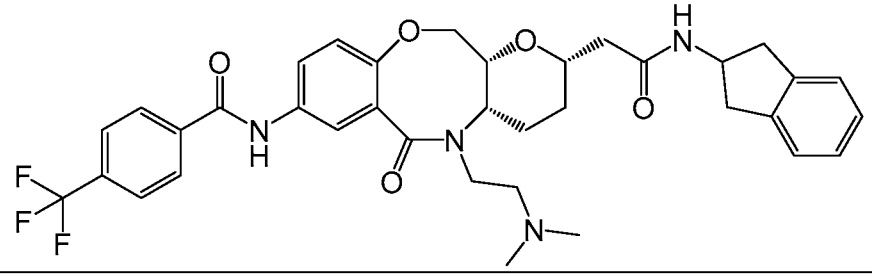
54	
55	
56	
57	
58	
59	

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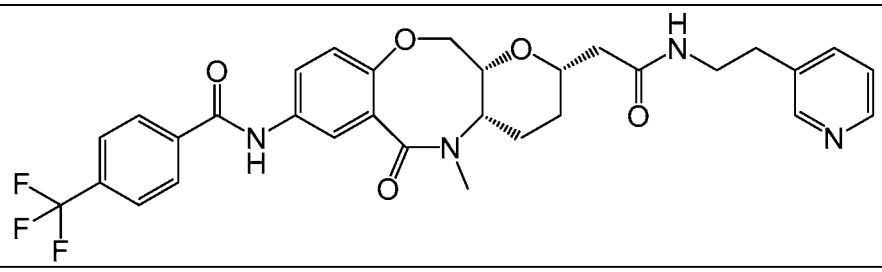
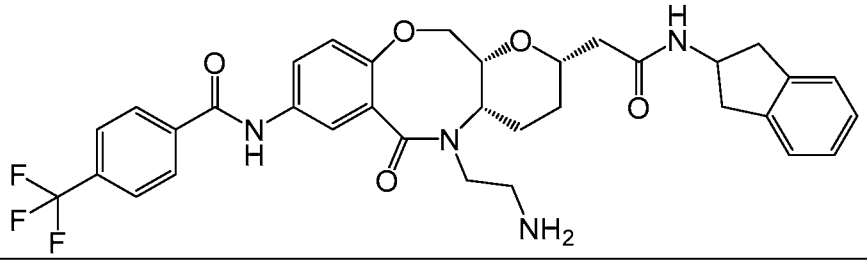
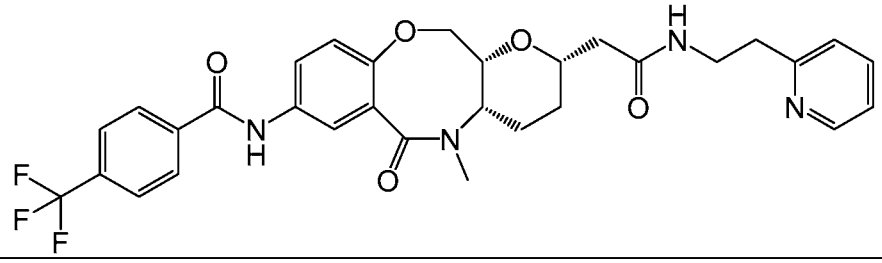
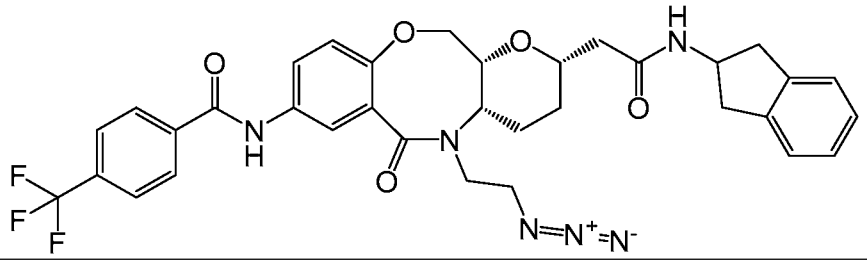
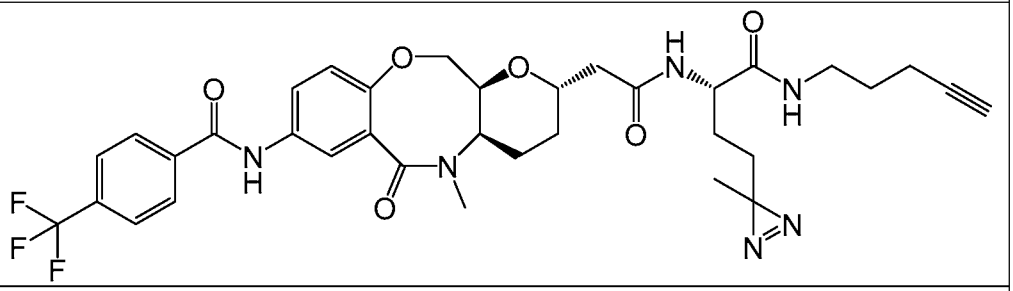
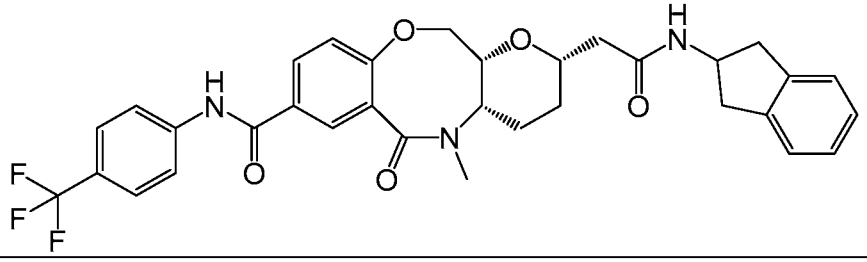
60	
61	
62	
63	
64	
66	

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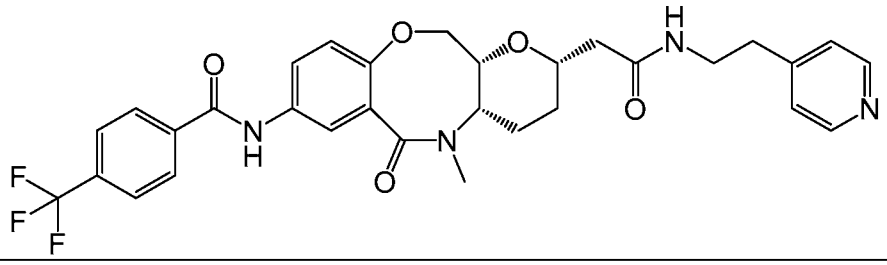
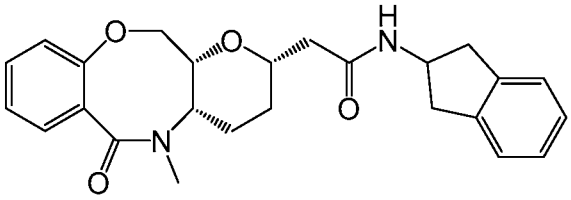
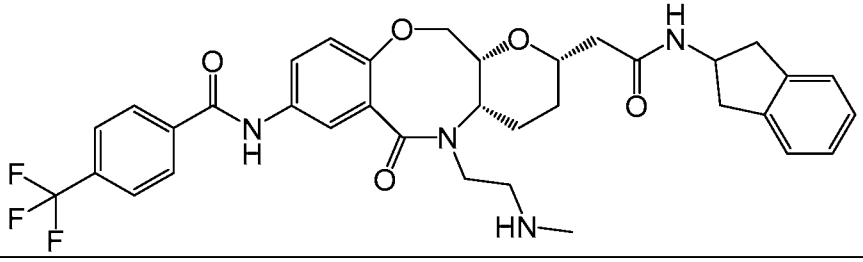
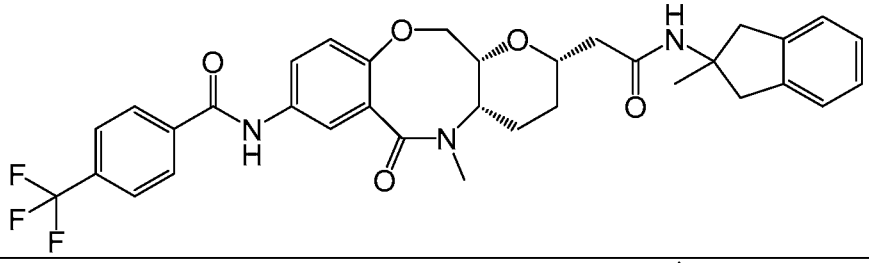
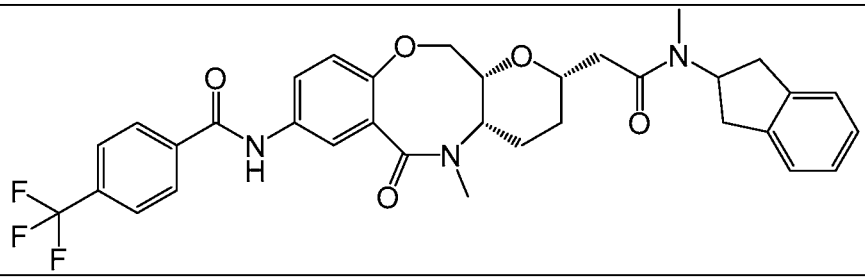
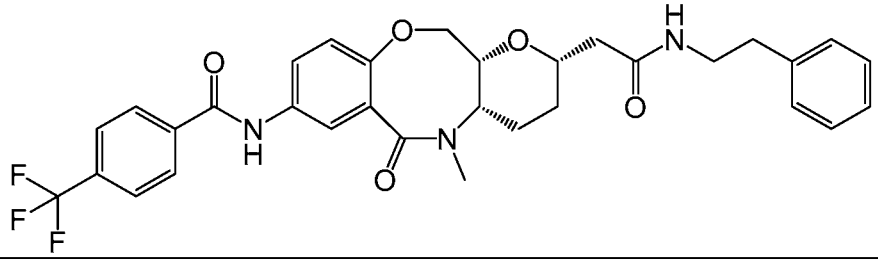
67	
68	
69	
70	
71	
72	

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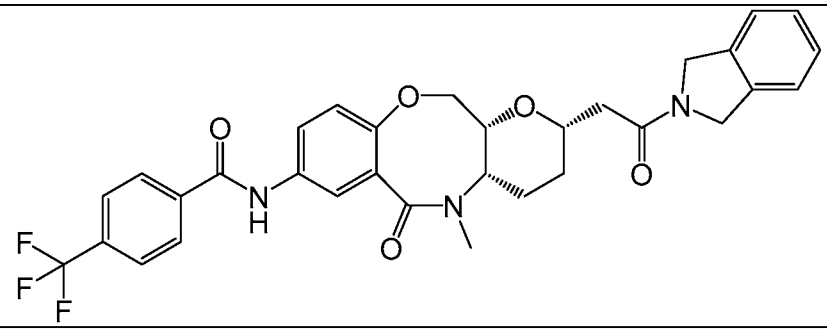
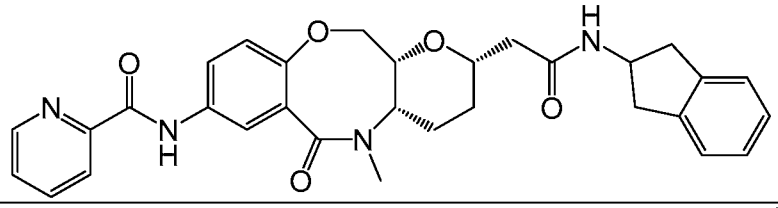
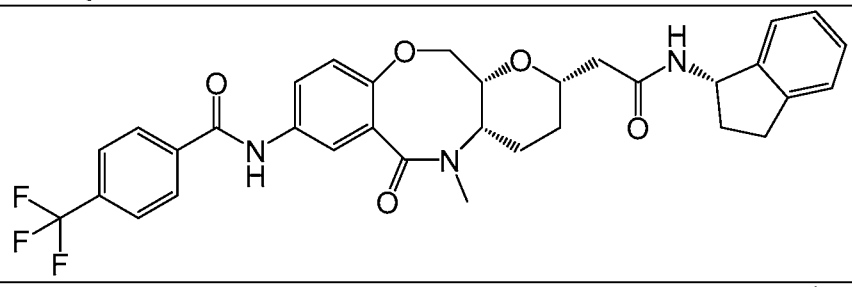
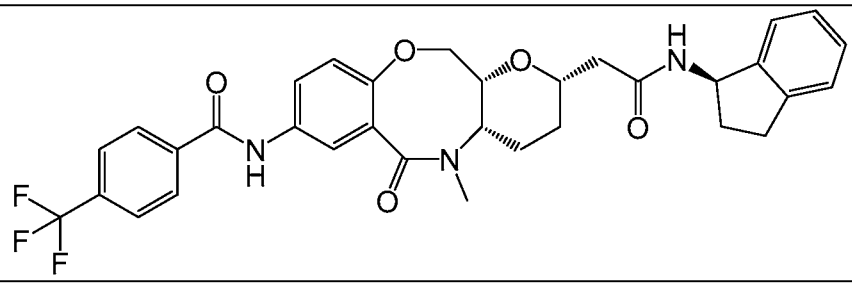
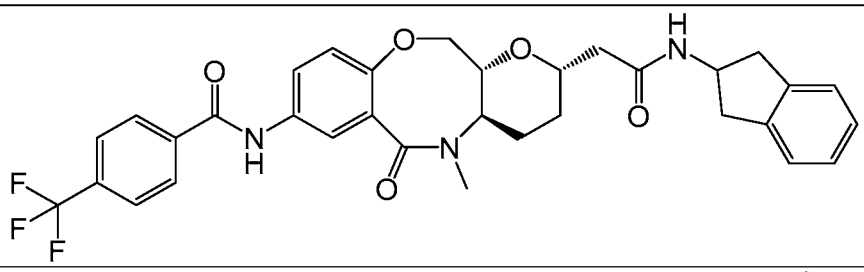
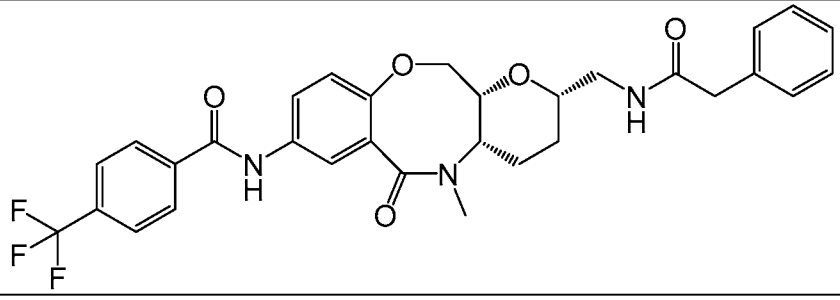
73	
74	
75	
76	
77	
78	

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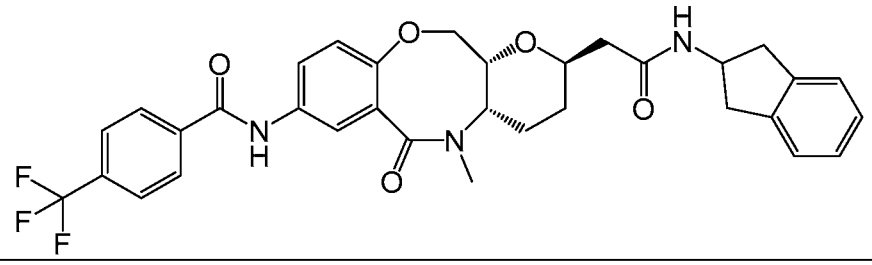
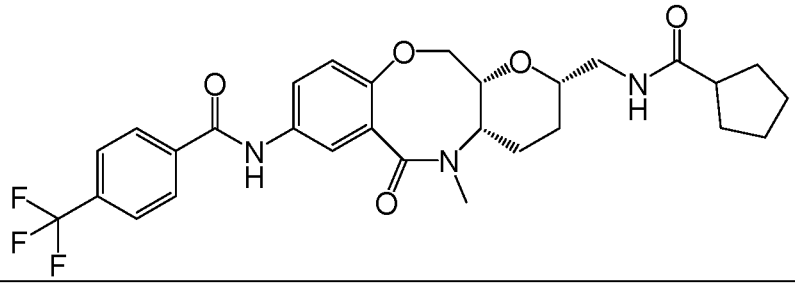
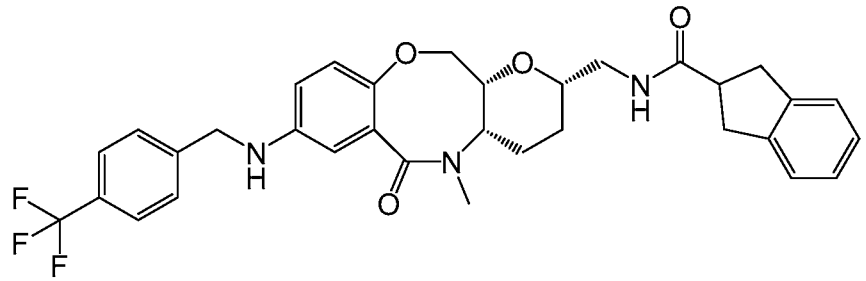
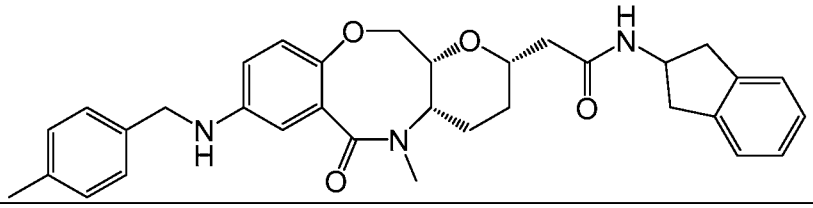
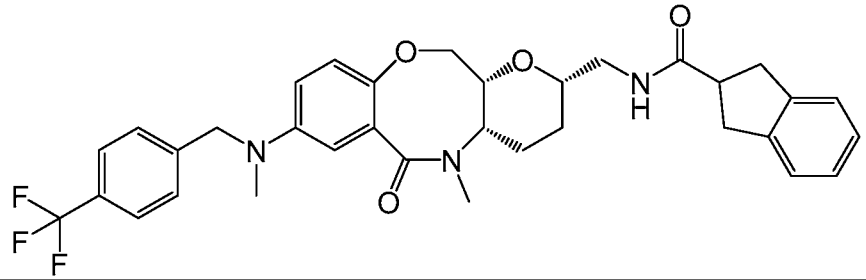
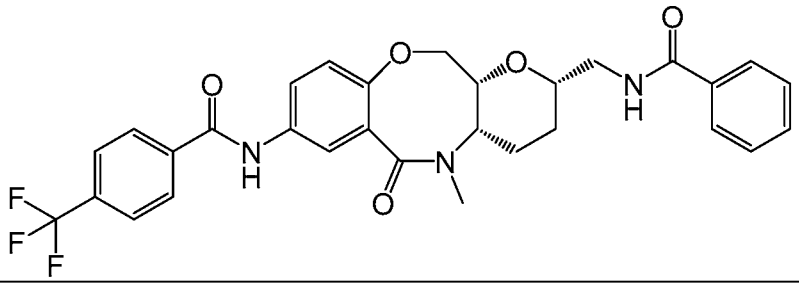
79	
80	
81	
82	
83	
84	

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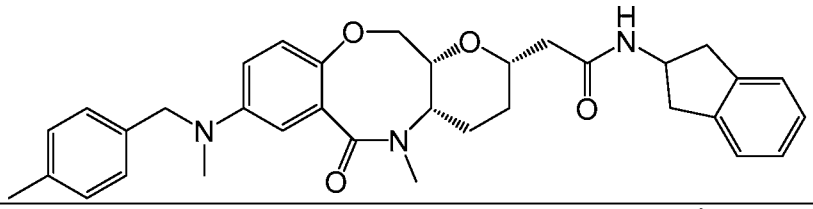
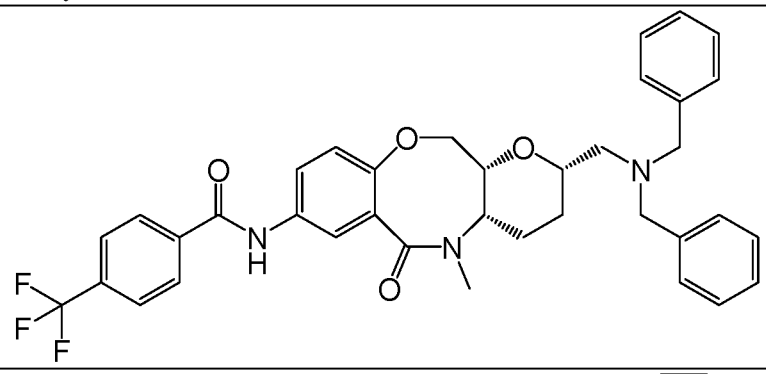
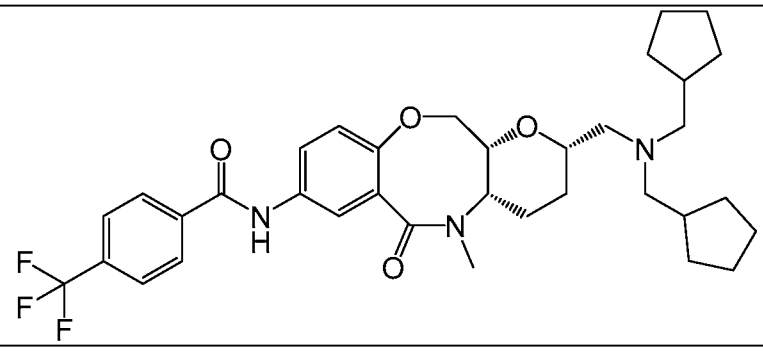
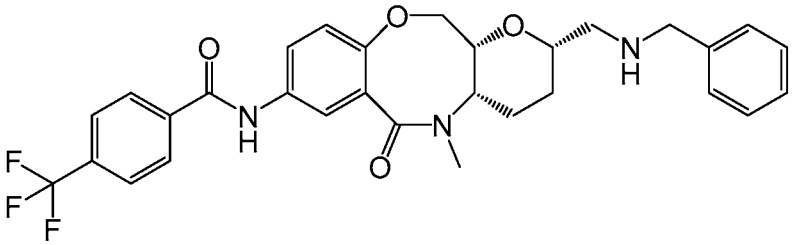
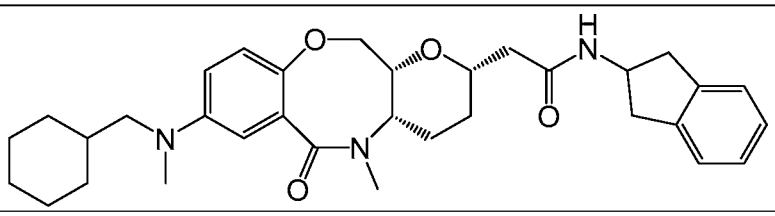
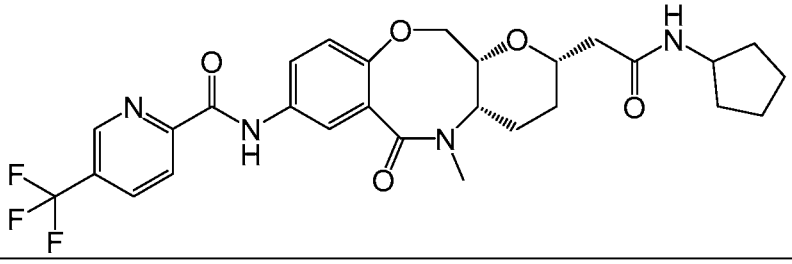
85	
86	
87	
88	
89	
90	

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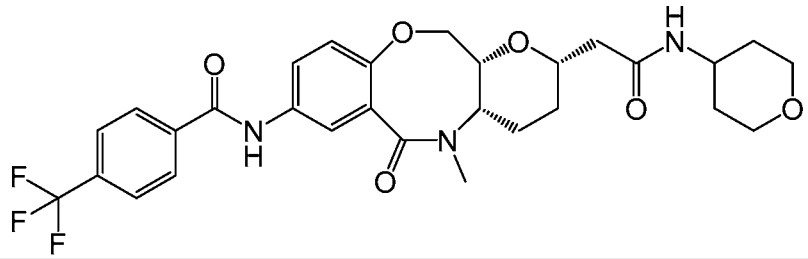
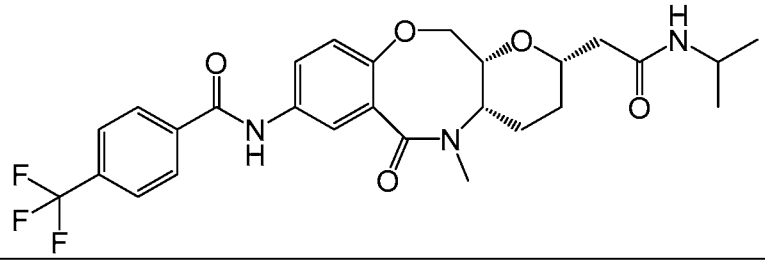
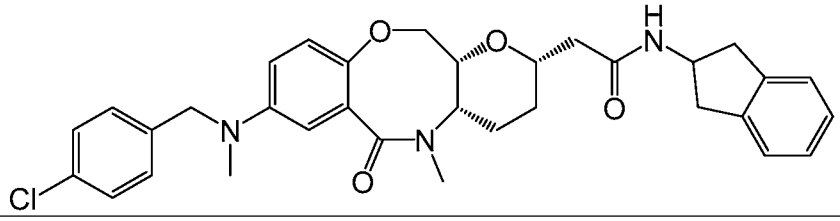
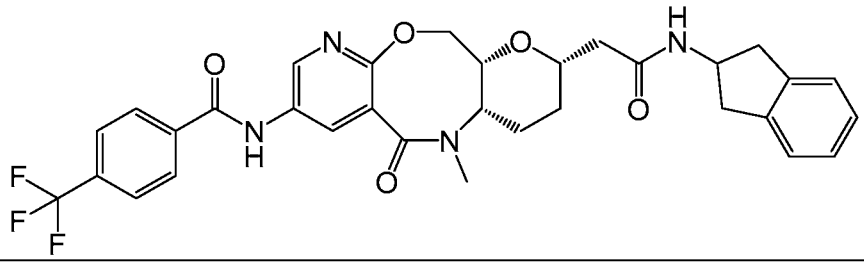
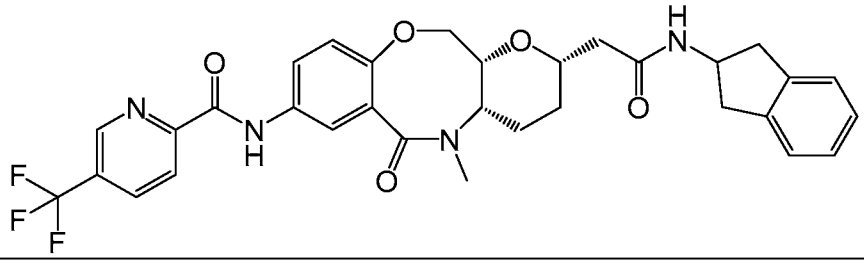
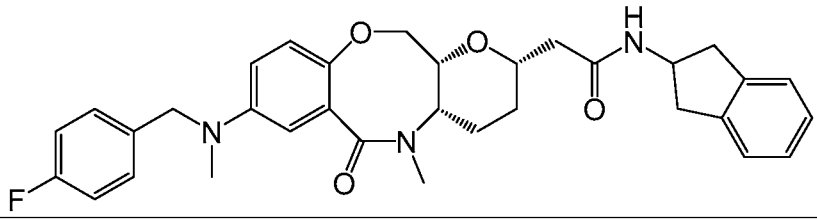
91	
92	
93	
94	
95	
96	

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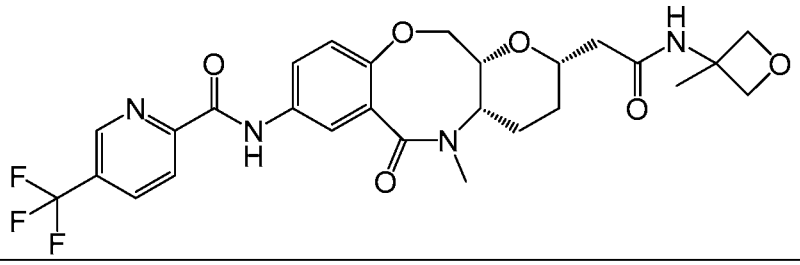
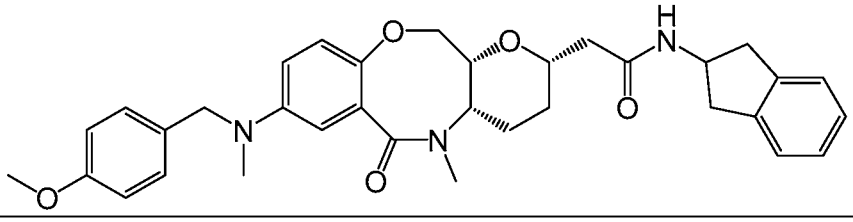
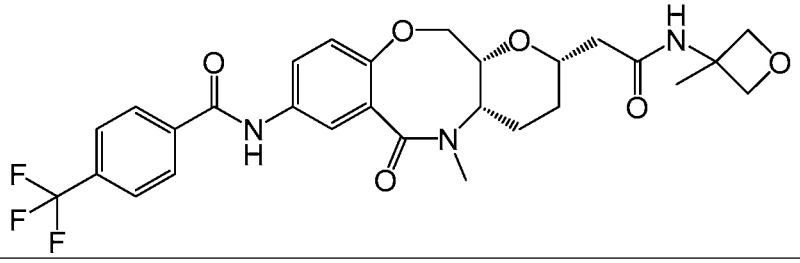
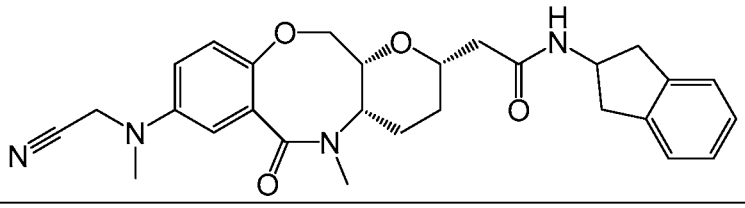
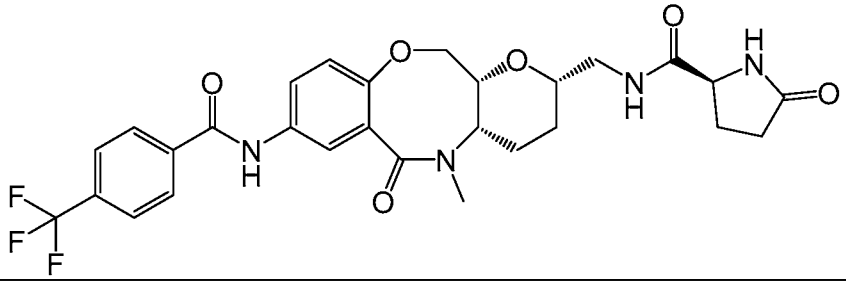
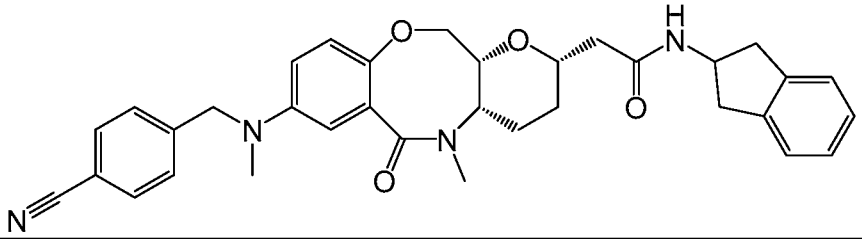
97	
99	
100	
101	
102	
103	

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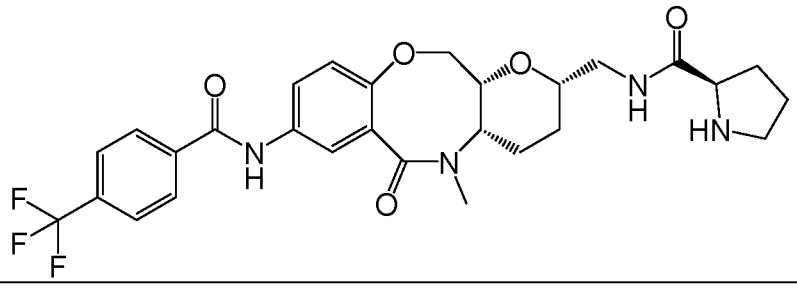
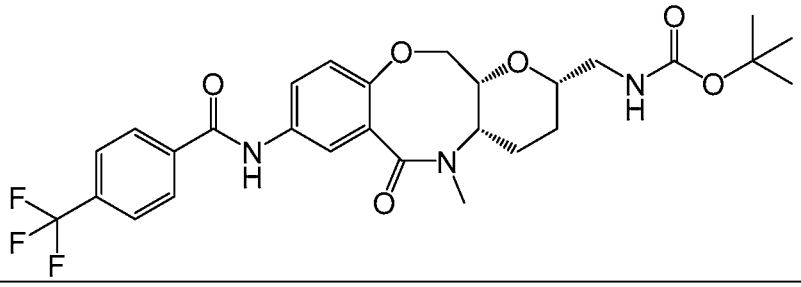
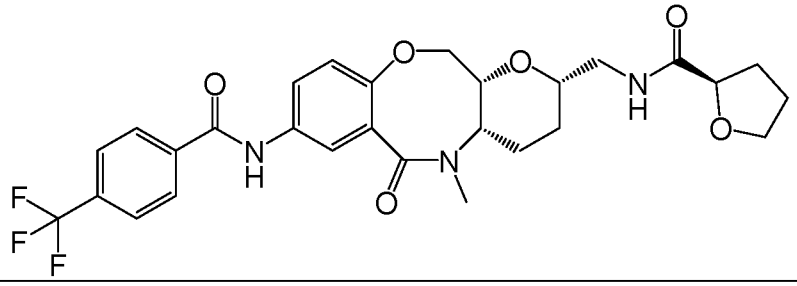
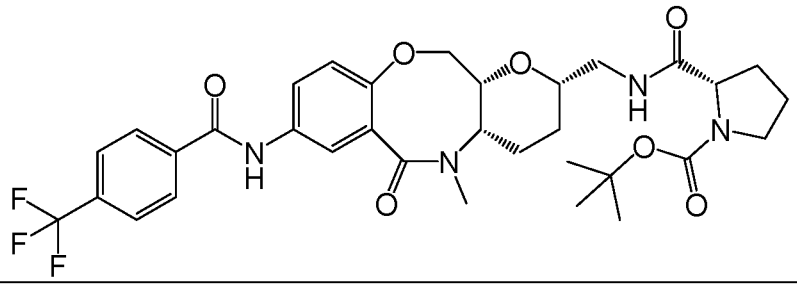
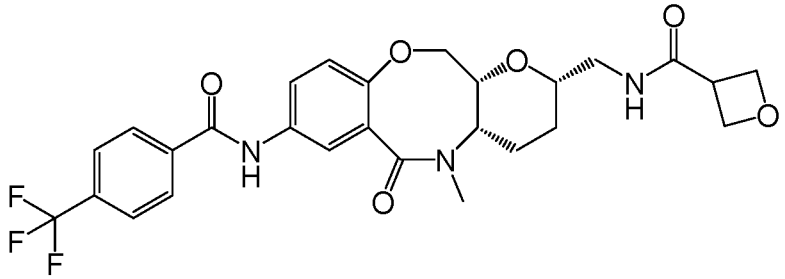
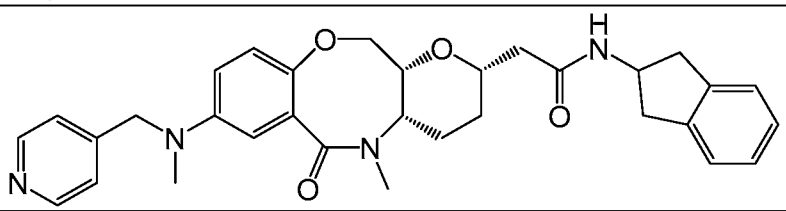
104	
106	
108	
109	
110	
111	

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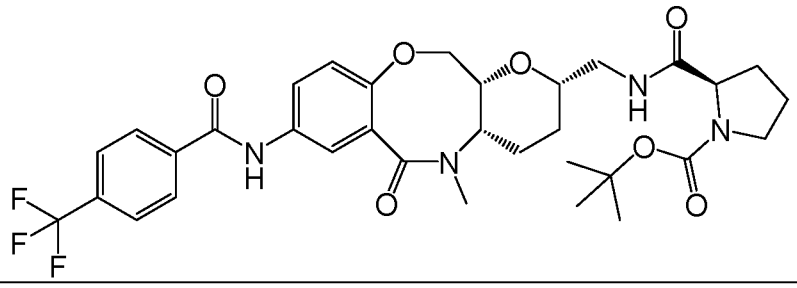
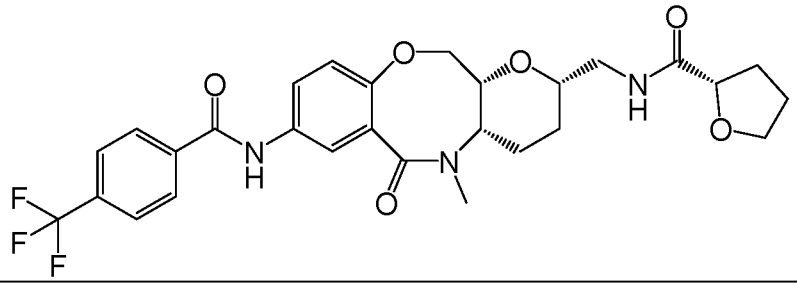
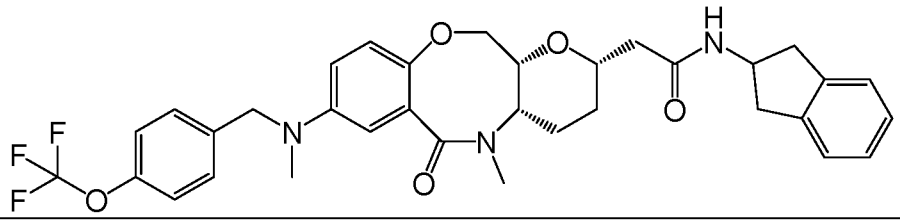
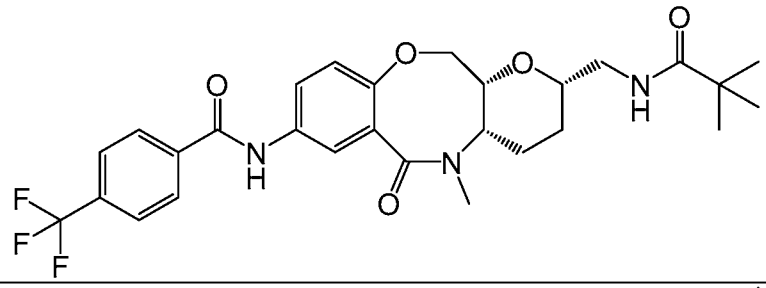
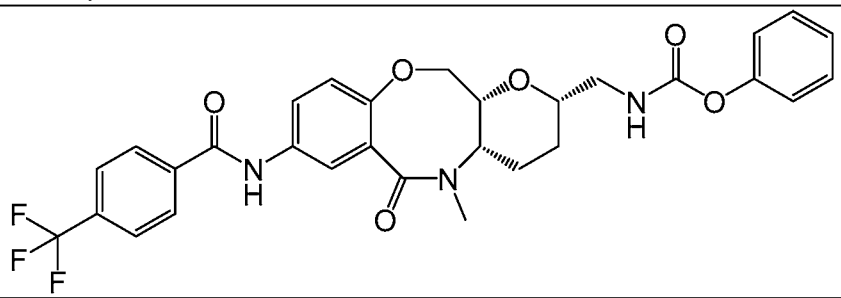
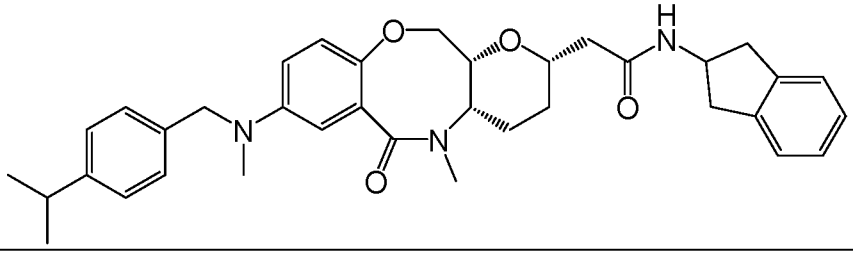
112	
113	
115	
116	
117	
118	

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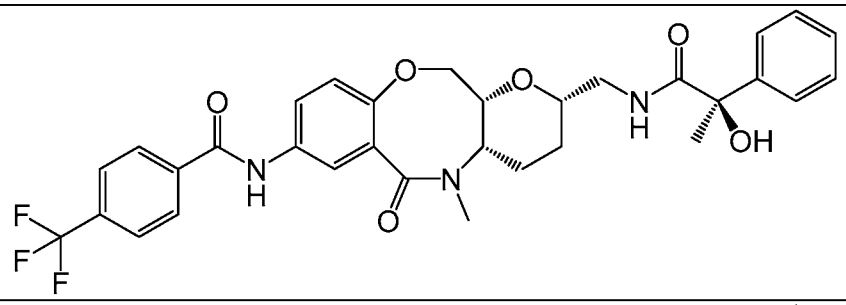
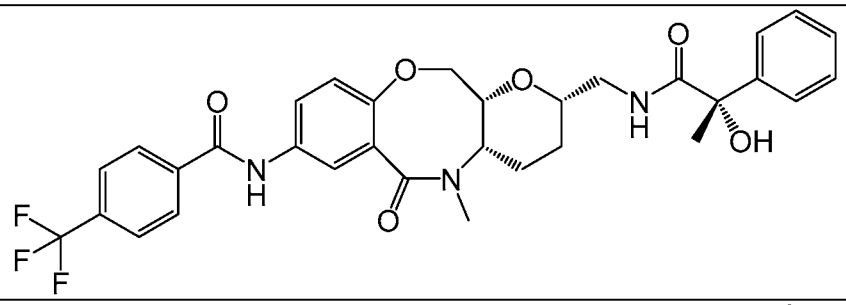
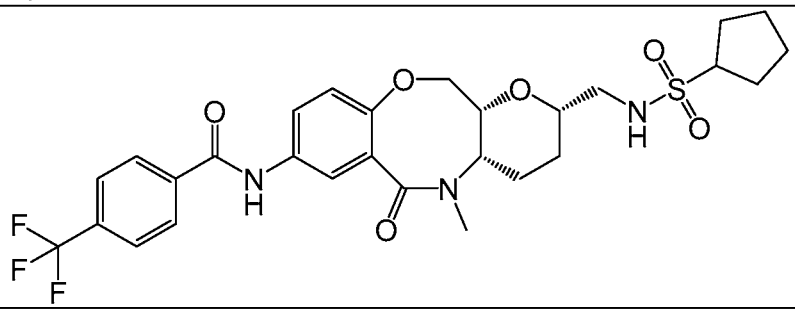
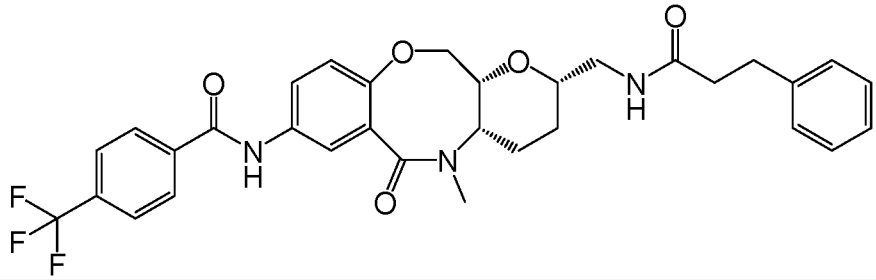
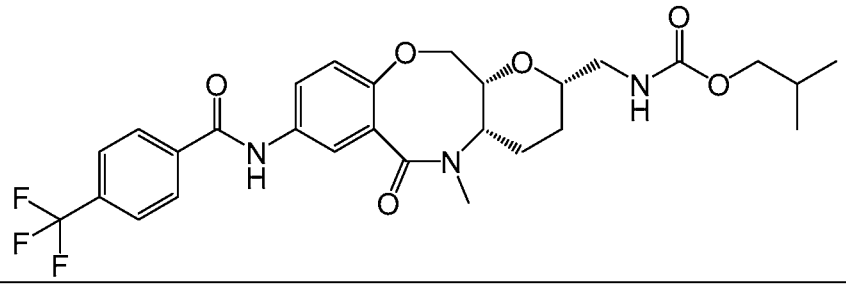
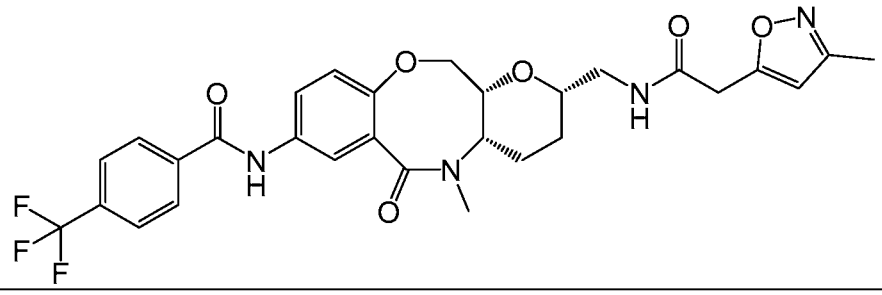
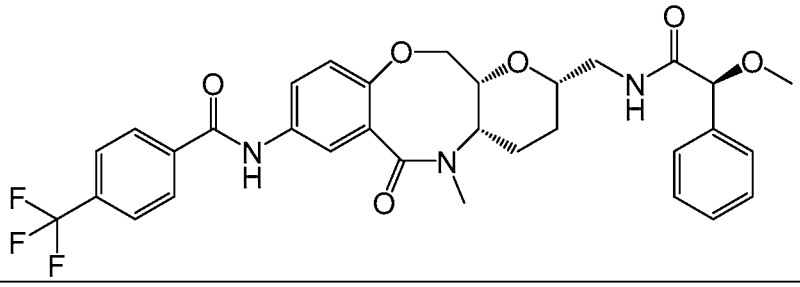
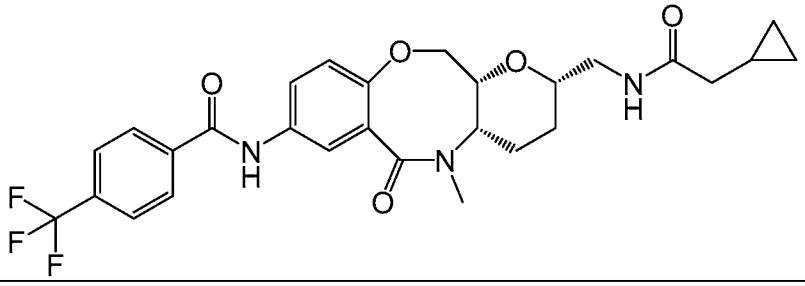
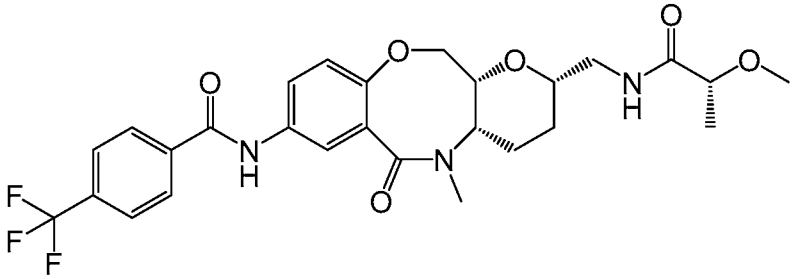
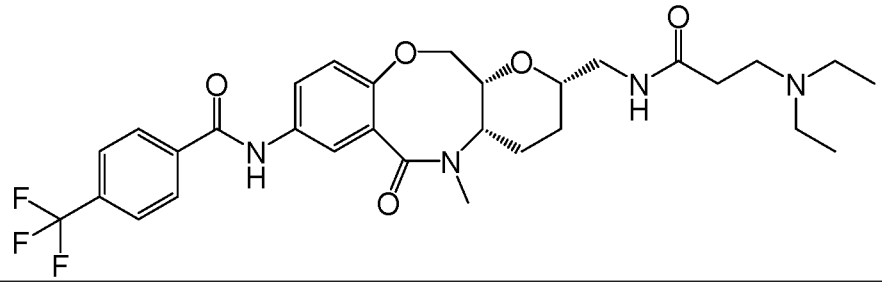
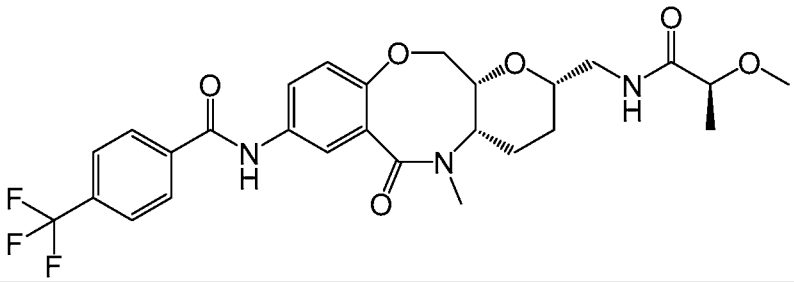
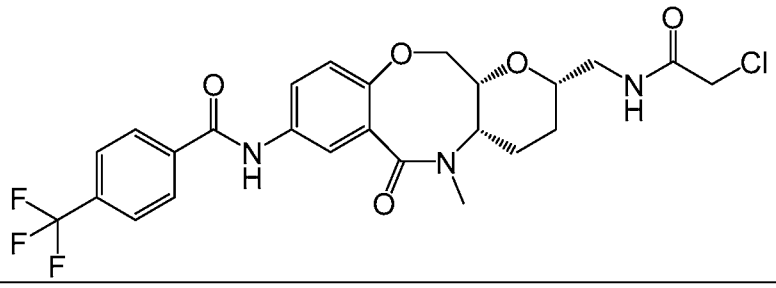
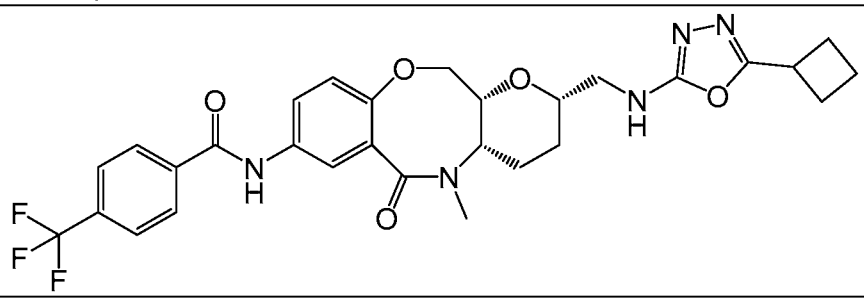
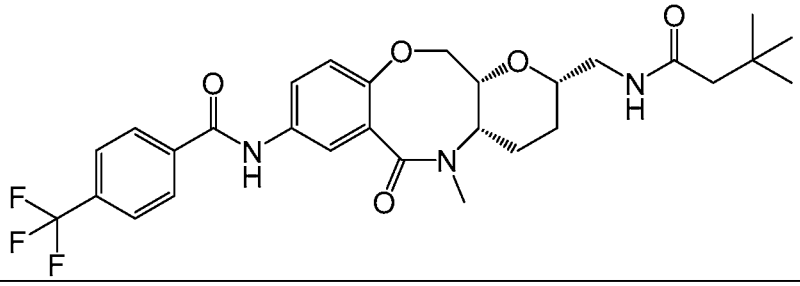
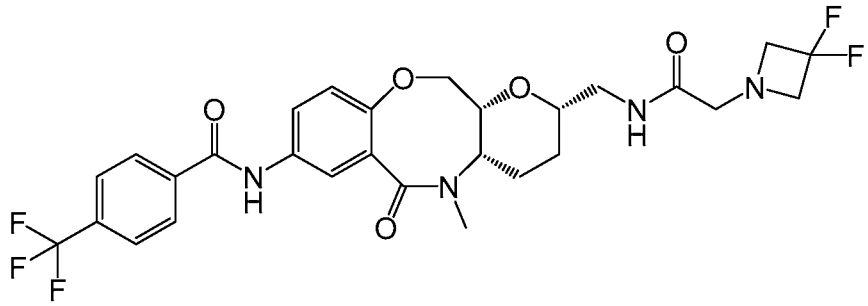
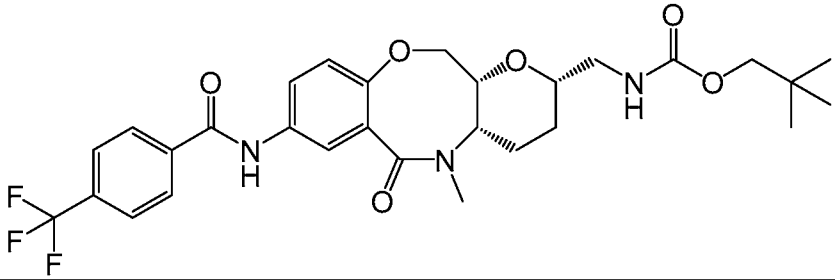
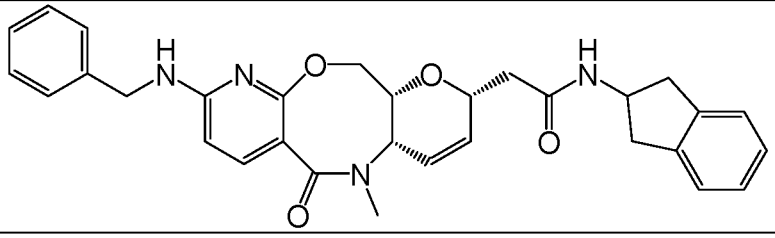
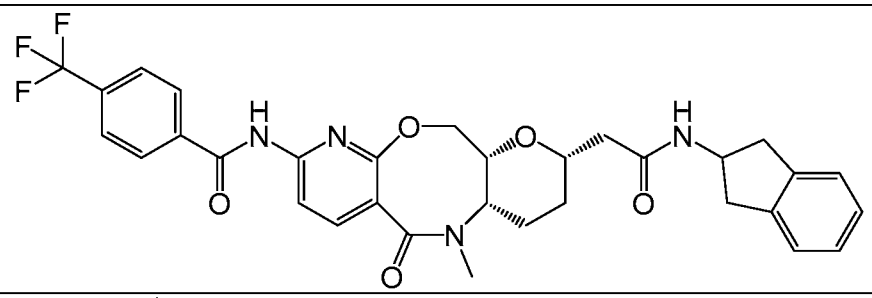
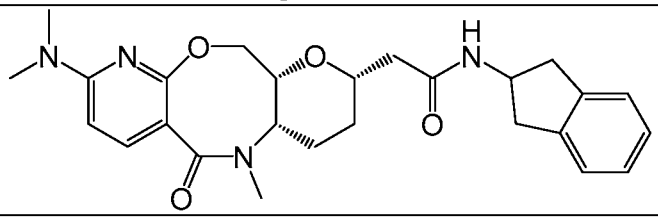
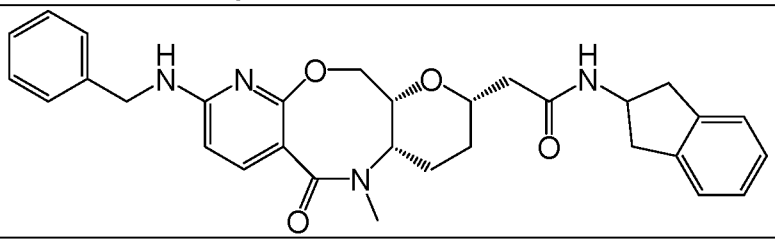
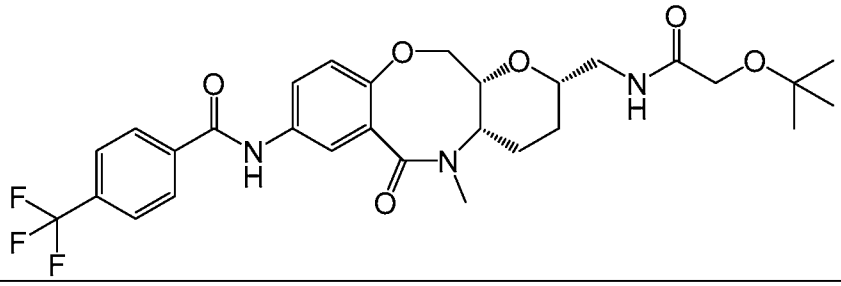
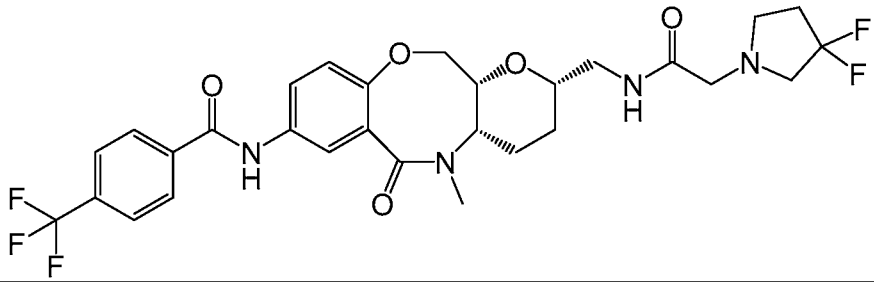
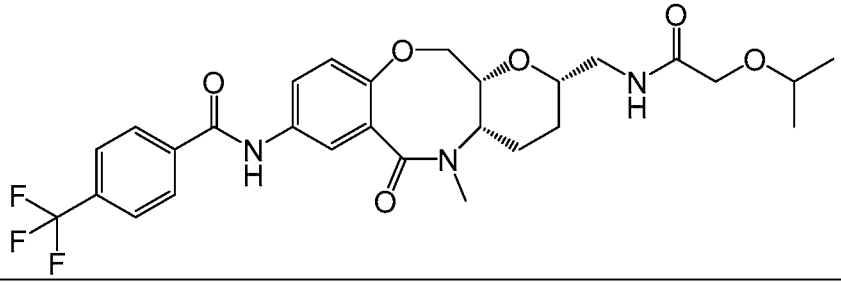
119	
120	
121	
122	
123	

ID #	STRUCTURE
124	
125	
126	
127	
128	
129	

ID #	STRUCTURE
130	
131	
133	
134	
135	
136	

ID #	STRUCTURE
137	
138	
139	
140	
141	
142	

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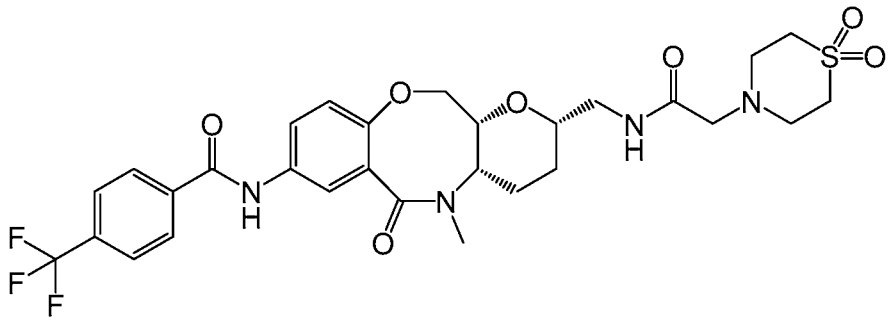
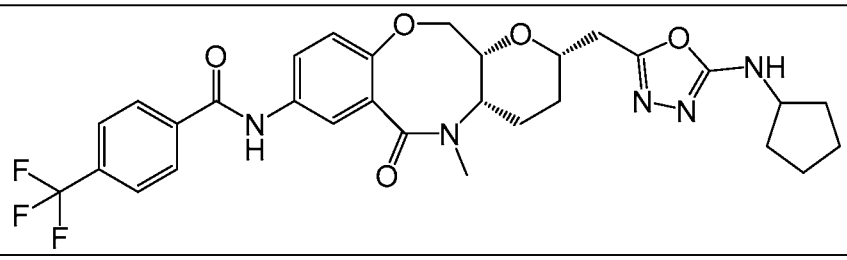
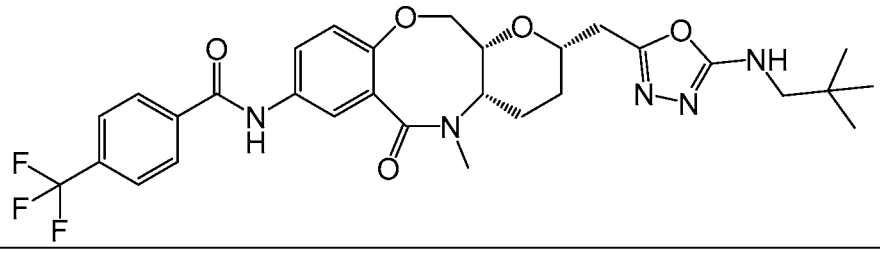
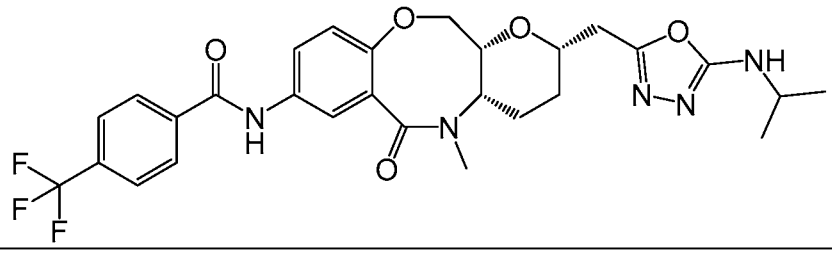
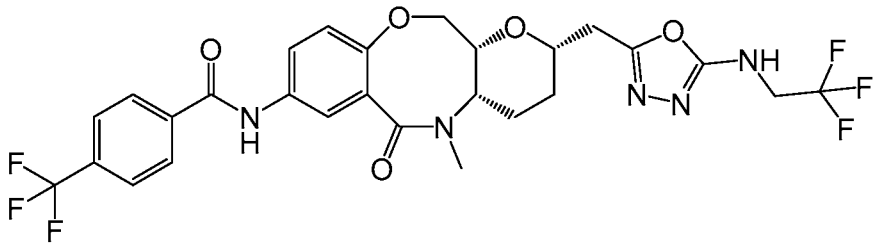
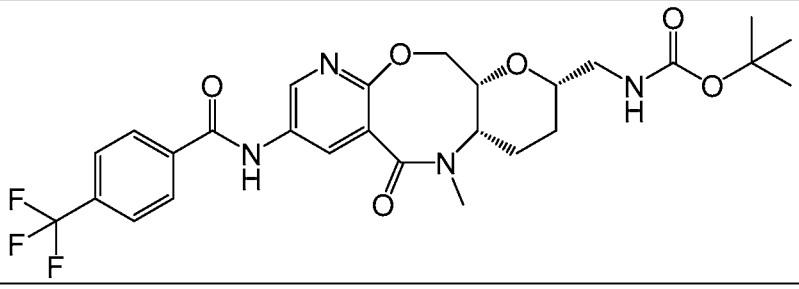
143	
144	
145	
146	
147	
148	

or a pharmaceutically acceptable salt thereof.

24. A pharmaceutical composition comprising an effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutical carrier, diluent, or excipient.

25. A method of treating a cardiovascular disease in a subject in need thereof, comprising administering to the subject an effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof.

26. The method of claim 25, wherein the cardiovascular disease is selected from the group consisting of myocardial infarction, coronary heart disease, atherosclerosis, and hypercholesterolemia.

27. The method of claim 25, wherein the cardiovascular disease is any cardiovascular disease that can be treated by increasing expression levels of *TRIB1*.

28. The method of claim 25, wherein the cardiovascular disease is any cardiovascular disease that can be prevented by increasing expression levels of *TRIB1*.

29. A method of treating a liver disease or disorder in a subject in need thereof, comprising administering to the subject an effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof.

30. The method of claim 27, wherein the liver disease or disorder is selected from the group consisting of liver cirrhosis, hepatocellular carcinoma, liver injury, and abnormal liver function.

31. A method of treating a disease in a subject in need thereof, comprising administering to the subject an effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound downregulates the expression level of *PCSK9* and upregulates the expression level of *TRIB1*.

32. A method of downregulating the expression level of *PCSK9* in a subject in need thereof, comprising administering to the subject an effective amount of a compound of claim 1.

33. A method of upregulating the expression level of *TRIB1* in a subject in need thereof, comprising administering to the subject an effective amount of a compound of claim 1.

34. A method of downregulating the expression level of *PCSK9* and upregulating the expression level of *TRIB1,* in a subject in need thereof, comprising administering to the subject an effective amount of a compound of claim 1.

35. A method of assessing the efficacy of a therapeutic agent, comprising: (a) administering the therapeutic agent to a subject; (b) determining the expression level of *TRIB1* in a sample from the subject at a first time point; and (c) comparing the expression level of *TRIB1* at the first time point to a reference profile, wherein an increase in *TRIB1* expression compared to the reference profile indicates the efficacy of the therapeutic agent.

36. A method of assessing the efficacy of a therapeutic agent, comprising: (a) administering the therapeutic agent to a subject; (b) determining the expression level of *PCKS9* in a sample from the subject at a first time point; and (c) comparing the expression level of *PCKS9* at the first time point to a reference profile, wherein a decrease in *PCKS9* expression compared to the reference profile indicates the efficacy of the therapeutic agent.

37. A method of assessing the efficacy of a therapeutic agent, comprising: (a) administering the therapeutic agent to a subject; (b) determining the expression level of *TRIB1* and *PCSK9* in a sample from the subject at a first time point; and (c) comparing the expression level of *TRIB1* and *PCSK9* at a first time point to a reference profile; wherein an increase in *TRIB1* expression and a decrease in *PCKS9* expression compared to the reference profile indicates the efficacy of the therapeutic agent.

38. A method of assessing the efficacy of a therapeutic agent, comprising: (a) administering the therapeutic agent to a subject; (b) determining the expression level of ApoB in a sample from the subject at a first time point; and (c) comparing the expression level of ApoB at the first time point to a reference profile, wherein a decrease in ApoB expression compared to the reference profile indicates the efficacy of the therapeutic agent.

39. A method of assessing the efficacy of a therapeutic agent, comprising: (a) administering the therapeutic agent to a subject; (b) determining the expression level of LRDR in a sample from the subject at a first time point; and (c) comparing the expression level of LRDR at the first time point to a reference profile, wherein an increase in LRDR expression compared to the reference profile indicates the efficacy of the therapeutic agent.

40. A method of assessing the efficacy of a therapeutic agent, comprising: (a) administering the therapeutic agent to a subject; (b) determining the expression level of an RNA transcript of a gene selected from *SREBF1, SREBF2, SCAP, HMGCR, HMGCS, FASN, SCD1, MTTP,* and *APOC3* in a sample from the subject at a first time point; and (c) comparing the expression level of the RNA transcript at the first time point to a reference profile, wherein either an increase or decrease in the expression level of the RNA transcript compared to the reference profile indicates the efficacy of the therapeutic agent.

41. A method of reducing LDL-C in circulation, comprising administering to the subject an effective amount of a compound of claim 1.

42. The method of any one of claims 35-40, wherein the reference profile is obtained from the subject prior to administering the therapeutic agent.

43. The method of any one of claims 35-40, wherein the therapeutic agent is a compound of claim 1.

FIG. 1

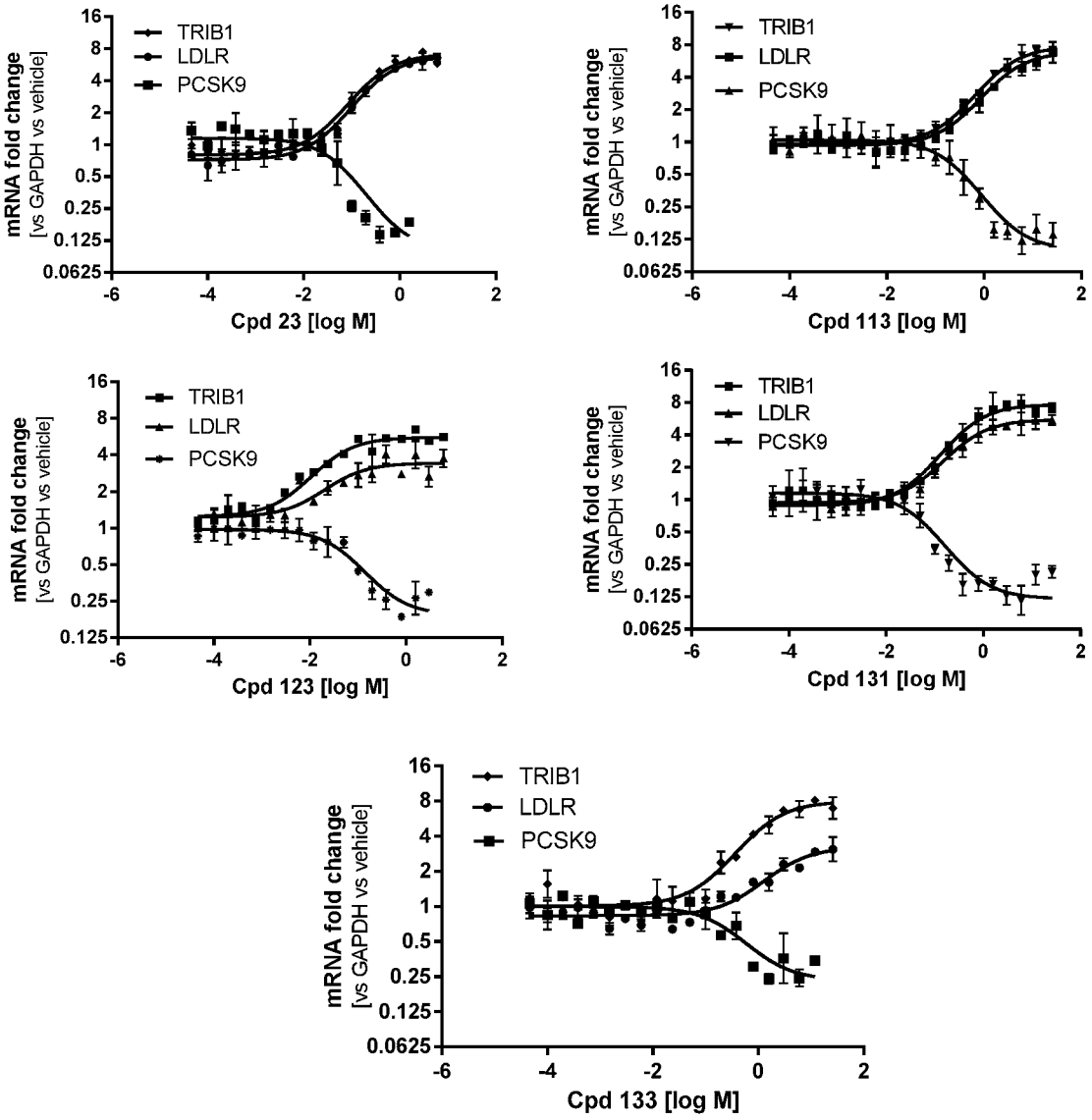

TRIB1
LDLR
PCSK9
mRNA fold change
[vs GAPDH vs vehicle]
16
8
4
2
1
0.5
0.25
0.125
0.0625
-6
-4
-2
0
2
Cpd 23 [log M]
Cpd 113 [log M]
Cpd 123 [log M]
Cpd 131 [log M]
Cpd 133 [log M]

FIG. 2A

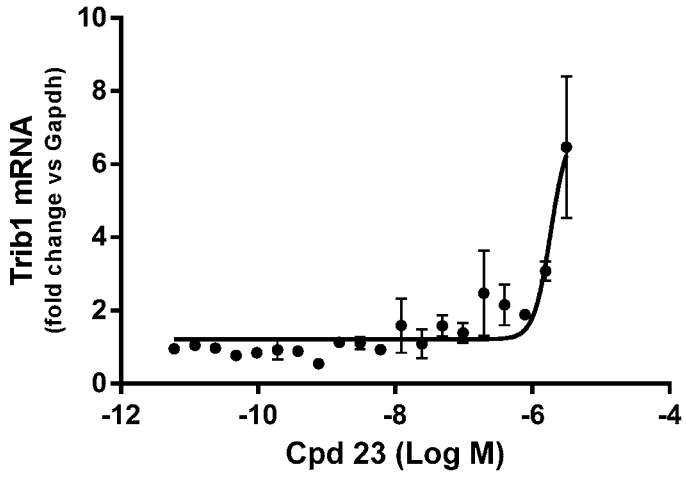

Trib1 mRNA
(fold change vs Gapdh)
10
8
6
4
2
0
-12
-10
-8
-6
-4
Cpd 23 (Log M)

FIG. 2B

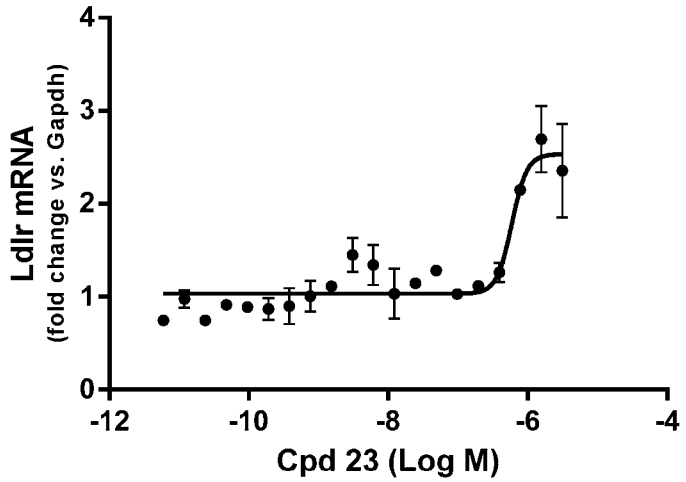

Ldlr mRNA
(fold change vs. Gapdh)
4
3
2
1
0
-12
-10
-8
-6
-4
Cpd 23 (Log M)

FIG. 3

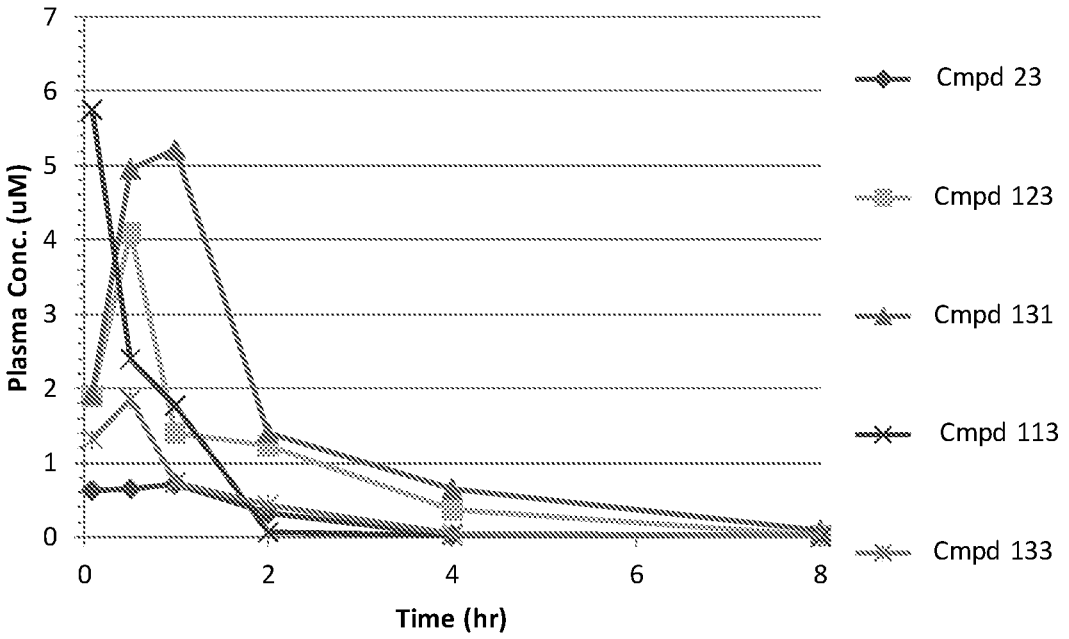

Plasma Conc. (uM)
7
6
5
4
3
2
1
0
0
2
4
6
8
Time (hr)
Cmpd 23
Cmpd 123
Cmpd 131
Cmpd 113
Cmpd 133

FIG. 4

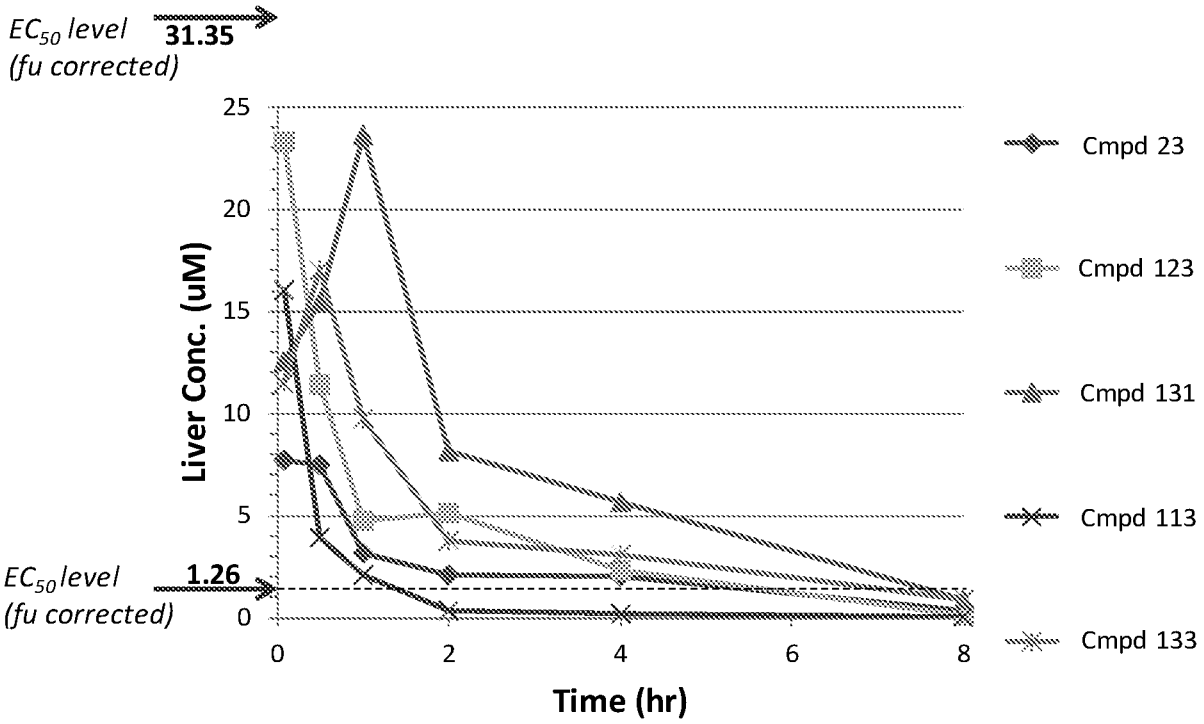

EC50 level
(fu corrected)
31.35
25
20
15
10
5
EC50 level
(fu corrected)
1.26
0
Liver Conc. (uM)
0
2
4
6
8
Time (hr)
Cmpd 23
Cmpd 123
Cmpd 131
Cmpd 113
Cmpd 133

FIG. 5A

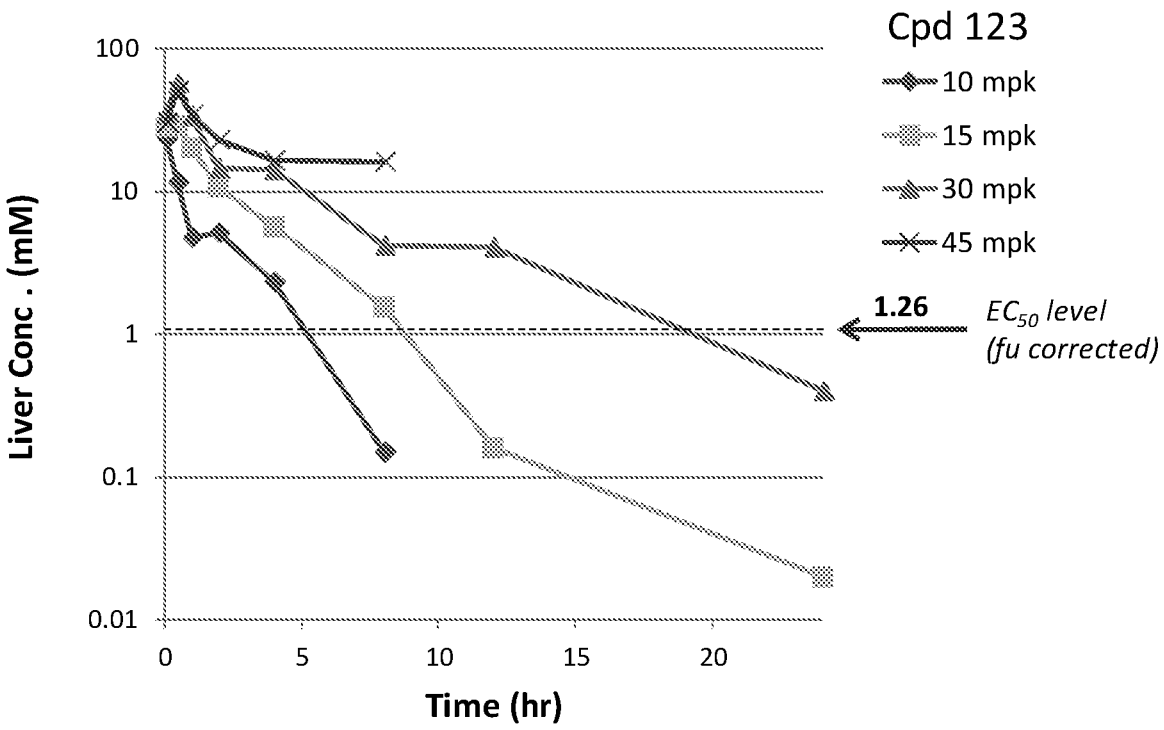
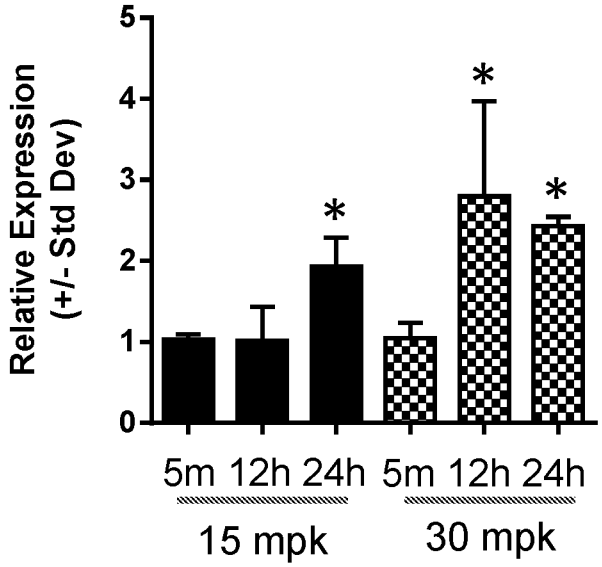

Cpd 123
10 mpk
15 mpk
30 mpk
45 mpk
1.26
EC_{50} level
(fu corrected)
Liver Conc . (mM)
100
10
1
0.1
0.01
0
5
10
15
20
Time (hr)

FIG. 5B


Relative Expression
(+/- Std Dev)
5
4
3
2
1
0
*
*
*
5m 12h 24h 5m 12h 24h
15 mpk
30 mpk