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(54) Title: ACETAL COMPOUNDS AND THERAPEUTIC USES THEREOF

(57) **Abrégé/Abstract:**

Disclosed herein are acetal and cyclic acetal compounds, compositions, their preparation, and their uses. Some embodiments relate to their use as liver-targeting compounds.

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(54) Title: ACETAL COMPOUNDS AND THERAPEUTIC USES THEREOF

(57) Abstract: Disclosed herein are acetal and cyclic acetal compounds, compositions, their preparation, and their uses. Some embodiments relate to their use as liver-targeting compounds.

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ACETAL COMPOUNDS AND THERAPEUTIC USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/615,357 filed January 9, 2018 entitled “ACETAL COMPOUNDS AND THERAPEUTIC USES THEREOF”, which is incorporated by reference in its entirety.

BACKGROUND

Field

[0002] The present disclosure relates to the field of chemistry and medicine. More specifically, the present disclosure relates to acetal and cyclic acetal compounds, compositions, their preparation, and their use as therapeutic agents.

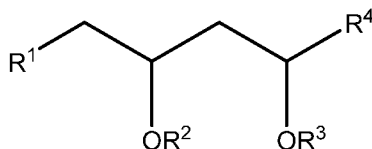
Description of the Related Art

[0003] Statins are a class of liver-targeting compounds that inhibit HMG-CoA reductase, one of the liver enzymes in the cholesterol biosynthetic pathway. Statins are used as lipid-lowering medicines for the prophylactic and therapeutic treatment of coronary heart disease. Despite their ubiquitous use, statins, like other liver-targeting drugs, suffer from poor oral bioavailability and inadequate distribution to the liver. In fact, a significant portion of patients cannot take statins because of side effects from statin biological activity outside of the liver.

[0004] Thus, there is a need for improved liver-targeting compounds and strategies to increase the bioavailability of liver-targeting drugs, to increase drug distribution to the liver, and to reduce drug biological activity outside of the liver.

SUMMARY

[0005] Some embodiments described herein relate to compounds having the structure of Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein R^1 , R^2 , R^3 , and R^4 have any of the values described herein.

[0006] In some embodiments, R^1 is selected from the group consisting of optionally substituted C_{1-8} alkyl, -COOR^5 , optionally substituted C_{2-10} alkoxyalkyl, and optionally substituted 3-12 membered heterocyclyl. Alternatively, in some embodiments, R^1 and R^2 together with the atoms to which they are attached form an optionally substituted 4-10 membered heterocyclyl, or R^1 and R^3 together with the atoms to which they are attached form an optionally substituted 6-10 membered heterocyclyl.

[0007] R^2 in some embodiments is selected from the group consisting of H, -C(O)R^6 , and optionally substituted C_{2-10} alkoxyalkyl. Alternatively, in some embodiments, R^1 and R^2 together with the atoms to which they are attached form an optionally substituted 4-10 membered heterocyclyl, or R^2 and R^3 together with the atoms to which they are attached form a 6-10 membered heterocyclyl, optionally substituted with one or more R^7 .

[0008] In some embodiments, R^3 is selected from the group consisting of H, -C(O)R^8 , and optionally substituted C_{2-10} alkoxyalkyl. Alternatively, in some embodiments, R^1 and R^3 together with the atoms to which they are attached form an optionally substituted 6-10 membered heterocyclyl, or R^2 and R^3 together with the atoms to which they are attached form a 6-10 membered heterocyclyl, optionally substituted with one or more R^7 .

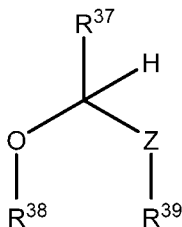
[0009] R^4 in some embodiments is a fragment of a therapeutic agent.

[0010] In some embodiments, each of R^5 , R^6 , and R^8 is independently selected from the group consisting of H, optionally substituted C_{1-6} alkyl, halogen, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{3-7} carbocyclyl, optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, and optionally substituted 3-10 membered heterocyclyl.

[0011] In some embodiments, each R^7 is independently selected from the group consisting of optionally substituted C_{1-8} alkyl, oxo, optionally substituted C_{6-18} aryl, and optionally substituted 5-18 membered heteroaryl.

[0012] In some embodiments, at least one of R^2 and R^3 is not H, or R^1 is not $-\text{COOH}$. Moreover, in some embodiments, if R^1 and R^3 together with the atoms to which they are attached form a 6 membered heterocyclyl, then R^2 is not H.

[0013] Some embodiments described herein relate to compounds having the structure of Formula II:



II

[0014] or a pharmaceutically acceptable salt thereof, wherein R^{37} , R^{38} , R^{39} , and Z have any of the values described herein.

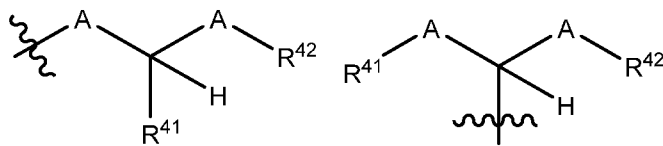
[0015] In some embodiments, Z is O, S, or NR^{40} .

[0016] R^{37} in some embodiments is selected from the group consisting of H, a fragment of a therapeutic agent, optionally substituted C_{1-8} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, optionally substituted C_{3-7} carbocyclyl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{6-18} aryl, 5-10 membered heteroaryl, and optionally substituted C_{2-10} alkoxyalkyl.

[0017] In some embodiments, each of R^{38} and R^{39} is independently selected from the group consisting of a fragment of a therapeutic agent, optionally substituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, optionally substituted C_{3-7} carbocyclyl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{6-18} aryl, optionally substituted C_{2-10} alkoxyalkyl, and optionally substituted 5-10 membered heteroaryl.

[0018] In some embodiments, at least one of R^{37} , R^{38} , and R^{39} is a fragment of a therapeutic agent.

[0019] In some embodiments, the fragment of a therapeutic agent is further optionally substituted with one or more moieties selected from the group consisting of



, C₁₋₆alkyl, halo, and C₆₋₁₈aryl. In some such embodiments, each A is independently selected from O, S, and NR⁴³, provided that at least one A is O. In some such embodiments, each of R⁴¹, R⁴², and R⁴³ is independently selected from the group consisting of H, optionally substituted C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆heteroalkyl, optionally substituted C₃₋₇carbocyclyl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C₆₋₁₈aryl, optionally substituted C₂₋₁₀alkoxyalkyl, and optionally substituted 5-10 membered heteroaryl.

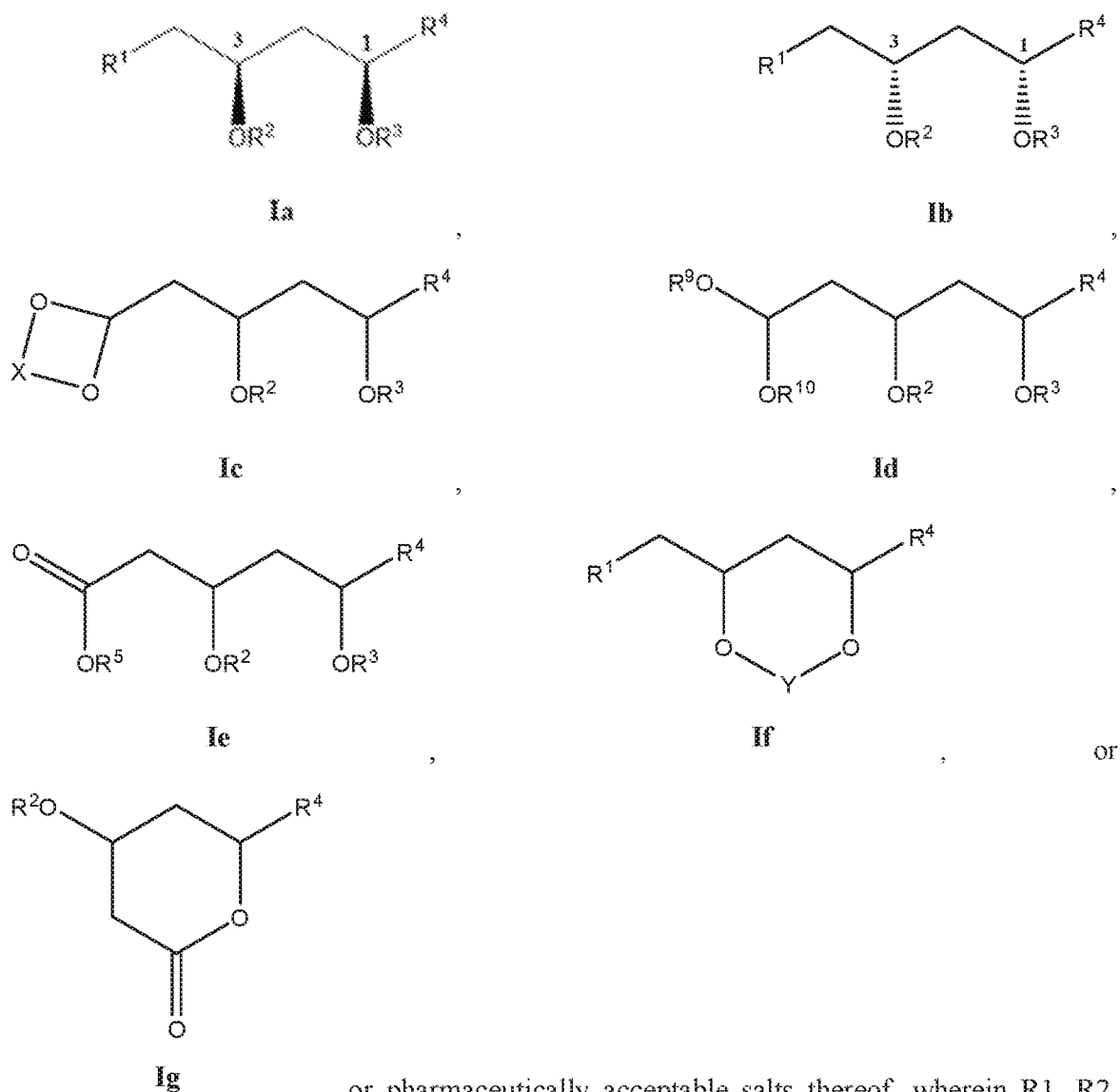
[0020] In some embodiments, R⁴⁰ is independently selected from the group consisting of optionally substituted C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆heteroalkyl, optionally substituted C₃₋₇carbocyclyl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C₆₋₁₈aryl, optionally substituted C₂₋₁₀alkoxyalkyl, and optionally substituted 5-10 membered heteroaryl.

DETAILED DESCRIPTION

[0021] Compounds of Formula I and II

[0022] In some embodiments, liver-targeting compounds containing an acetal moiety are provided that afford increased bioavailability relative to their active drug counterparts, increased drug distribution to the liver relative to their active drug counterparts, and/or reduced biological activity outside of the liver.

[0023] Various embodiments of these compounds include compounds having the structures of Formula I or II as described above or pharmaceutically acceptable salts thereof. In some embodiments, the compounds of Formula I are also represented by the structure of Formula Ia, Ib, Ic, Id, Ie, If, or Ig:



, or pharmaceutically acceptable salts thereof, wherein R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11, R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22, R23, R24, R25, R26, R27, R28, R29, R30, R31, R32, R33, R34, R35, R36, X, and Y have any of the values described herein.

[0024] In some embodiments of the compounds of Formula Ic, X is an optionally substituted C1-7alkylene linker. In some such embodiments, X is a C1-7alkylene linker optionally substituted with one or more R11. In some such embodiments, R11 is selected from the group consisting of C1-6alkyl, C1-6alkenyl, C1-6alkynyl, C1-6heteroalkyl, C3-7carbocyclyl, 3-10 membered heterocyclyl, C6-18aryl, C6-18arylC1-6alkyl, 5-10 membered heteroaryl, 5-10 membered heteroarylC1-6alkyl, halo, cyano, hydroxy, C1-6alkoxy, C2-

10alkoxyalkyl, C6-18aryloxy, sulfhydryl, haloC1-6alkyl, haloC1-6alkoxy, C1-6alkylthio, C6-18arylthio, and nitro. In some such embodiments, R11 is selected from the group consisting of C1-6alkyl, C3-7carbocyclyl, C1-6alkoxy, C6-18aryl, or halo. In some further embodiments, X is a C2alkylene linker. In some particular embodiments, X is -CH₂CH₂-. In some further embodiments, X is a C3alkylene linker. In some particular embodiments, X is -CH₂CH₂CH₂-. In some particular embodiments, X is -CH₂(CH₂CH₃)CH₂-. In other particular embodiments, X is -CH₂(CH₃)CH₂CH₂(CH₃)-.

[0025] In some embodiments of the compounds of Formula Id, each of R9 and R10 is independently an optionally substituted C1-6alkyl. In some such embodiments, each of R9 and R10 is independently a C1-6alkyl optionally substituted with one or more R12. In some such embodiments, R12 is selected from the group consisting of C1-6alkyl, C1-6alkenyl, C1-6alkynyl, C1-6heteroalkyl, C3-7carbocyclyl, C3-7carbocyclylC1-6alkyl, 3-10 membered heterocyclyl, 3-10 membered heterocyclylC1-6alkyl, C6-18aryl, C6-18arylC1-6alkyl, 5-10 membered heteroaryl, 5-10 membered heteroarylC1-6alkyl, and haloC1-6alkyl. In some further embodiments, R9 is a C1-6alkyl. In some particular embodiments, R9 is ethyl. In some further embodiments, R10 is a C1-6alkyl. In some particular embodiments, R10 is ethyl.

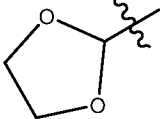
[0026] In some embodiments of the compounds Formula If, Y is a C1-5alkylene linker, optionally substituted with one or more R7. In some such embodiments, R7 is selected from the group consisting of optionally substituted C1-8alkyl, oxo, optionally substituted C6-18aryl, and optionally substituted 5-18 membered heteroaryl. In some further embodiments, Y is a C1alkylene linker.

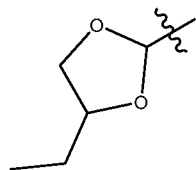
[0027] In some embodiments of the compounds of Formula I, Ia, Ib, or If, R1 is an optionally substituted C1-8alkyl. In some such embodiments, R1 is a C1-8alkyl optionally substituted with one or more R13. In some such embodiments, R13 is selected from the group consisting of halo, cyano, hydroxy, C1-6alkoxy, C6-10aryloxy, sulfhydryl, haloC1-6alkoxy, C1-6alkylthio, C6-10arylthio, and nitro. In some particular embodiments, R1 is -CH₂OH.

[0028] In some embodiments of the compounds of Formula I, Ia, Ib, or If, R1 is -COOR₅. In some such embodiments, R₅ is H. In other such embodiments, R₅ is methyl.

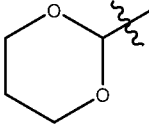
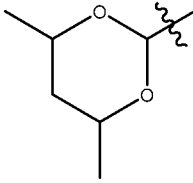
[0029] In some embodiments of the compounds of Formula I, Ia, Ib, or If, R1 is an optionally substituted C2-10alkoxyalkyl. In some such embodiments, R1 is a C2-10alkoxyalkyl optionally substituted with one or more R14. In some such embodiments, R14 is selected from the group consisting of halo, cyano, hydroxy, C1-6alkoxy, C6-10aryloxy, sulfhydryl, haloC1-6alkoxy, C1-6alkylthio, C6-10arylthio, and nitro. In some particular embodiments, R1 is -CH₂OCH₂OCH₂CH₃. In some particular embodiments, R1 is -CH(OCH₂CH₃)₂.

[0030] In some embodiments of the compounds of Formula I, Ia, Ib, or If, R1 is an optionally substituted 3-12 membered heterocyclyl. In some such embodiments, R1 is a 3-12 membered heterocyclyl optionally substituted with one or more R15. In some such embodiments, R15 is selected from the group consisting of C1-6alkyl, C1-6alkenyl, C1-6alkynyl, C1-6heteroalkyl, C3-7carbocyclyl, 3-10 membered heterocyclyl, C6-18aryl, C6-18arylC1-6alkyl, 5-10 membered heteroaryl, 5-10 membered heteroarylC1-6alkyl, halo, cyano, hydroxy, C1-6alkoxy, C2-10alkoxyalkyl, aryloxy, sulfhydryl, haloC1-6alkyl, haloC1-6alkoxy, C1-6alkylthio, C6-18arylthio, and nitro. In some further embodiments, R1 is a 5

membered heterocyclyl. In some particular embodiments, R1 is  or



. In some further embodiments, R1 is a 6 membered heterocyclyl. In some

particular embodiments, R1 is  or .

[0031] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or Ie, R2 is H.

[0032] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, Ie, or Ig, R2 is -C(O)R6. In some such embodiments, R6 is an optionally substituted C1-6alkyl. In some such embodiments, R6 is a C1-6alkyl optionally substituted with one or more R16. In some such embodiments, R16 is selected from the group consisting of halo, cyano, hydroxy,

C1-6alkoxy, C6-10aryl, C6-10aryloxy, sulfhydryl, haloC1-6alkoxy, C1-6alkylthio, C6-10arylthio, and nitro. In some particular embodiments, R6 is -CH(CH₃)₂.

[0033] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, Ie, or Ig, R2 is an optionally substituted C2-10alkoxyalkyl. In some such embodiments, R2 is a C2-10alkoxyalkyl optionally substituted with one or more R17. In some such embodiments, R17 is selected from the group consisting of halo, cyano, hydroxy, C1-6alkoxy, C6-10aryl, C6-10aryloxy, sulfhydryl, haloC1-6alkoxy, C1-6alkylthio, C6-10arylthio, and nitro. In some particular embodiments, R2 is -CH₂OCH₂CH₃.

[0034] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or Ie, R3 is H.

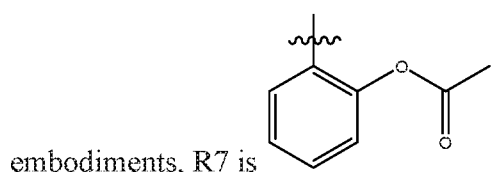
[0035] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or Ie, R3 is -C(O)R8. In some such embodiments, R8 is an optionally substituted C1-6alkyl. In some such embodiments, R8 is a C1-6alkyl optionally substituted with one or more R18. In some such embodiments, R18 is selected from the group consisting of halo, cyano, hydroxy, C1-6alkoxy, C6-10aryl, C6-10aryloxy, sulfhydryl, haloC1-6alkoxy, C1-6alkylthio, C6-10arylthio, and nitro. In some particular embodiments, R8 is -CH(CH₃)₂.

[0036] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, or Ie, R3 is an optionally substituted C2-10alkoxyalkyl. In some such embodiments, R3 is a C2-10alkoxyalkyl optionally substituted with one or more R19. In some such embodiments, R19 is selected from the group consisting of halo, cyano, hydroxy, C1-6alkoxy, C6-10aryl, C6-10aryloxy, sulfhydryl, haloC1-6alkoxy, C1-6alkylthio, C6-10arylthio, and nitro. In some particular embodiments, R3 is -CH₂OCH₂CH₃.

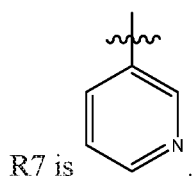
[0037] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, Ie, or If, R7 is an optionally substituted C1-8alkyl. In some such embodiments, R7 is a C1-8alkyl optionally substituted with one or more R20. In some such embodiments, R20 is selected from the group consisting of halo, cyano, hydroxy, C1-6alkoxy, C6-10aryl, C6-10aryloxy, sulfhydryl, haloC1-6alkoxy, C1-6alkylthio, C6-10arylthio, and nitro. In some particular embodiments, R7 is methyl. In some other particular embodiments, R7 is -CH₂CH₂CH₂OH.

[0038] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, Ie, or If, R7 is oxo.

[0039] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, Ie, or If, R7 is an optionally substituted C6-18aryl. In some such embodiments, R7 is a C6-18aryl optionally substituted with one or more R21. In some such embodiments, R21 is selected from the group consisting of C1-6alkyl, halo, cyano, hydroxy, C1-6alkoxy, haloC1-6alkyl, haloC1-6alkoxy, nitro, -C(=O)NR22R23, -N(R24)C(=O)R25, -C(=O)OR26, -OC(=O)R27, and -C(=O)R28. In some such embodiments, each of R22, R23, R24, R25, R26, R27, and R28 is independently selected from the group consisting of hydrogen, C1-6alkyl, C2-6alkenyl, C2-6alkynyl, C3-7carbocyclyl, C6-10aryl, 5-10 membered heteroaryl, and 3-10 membered heterocyclyl. In some further embodiments, R7 is a phenyl. In some particular

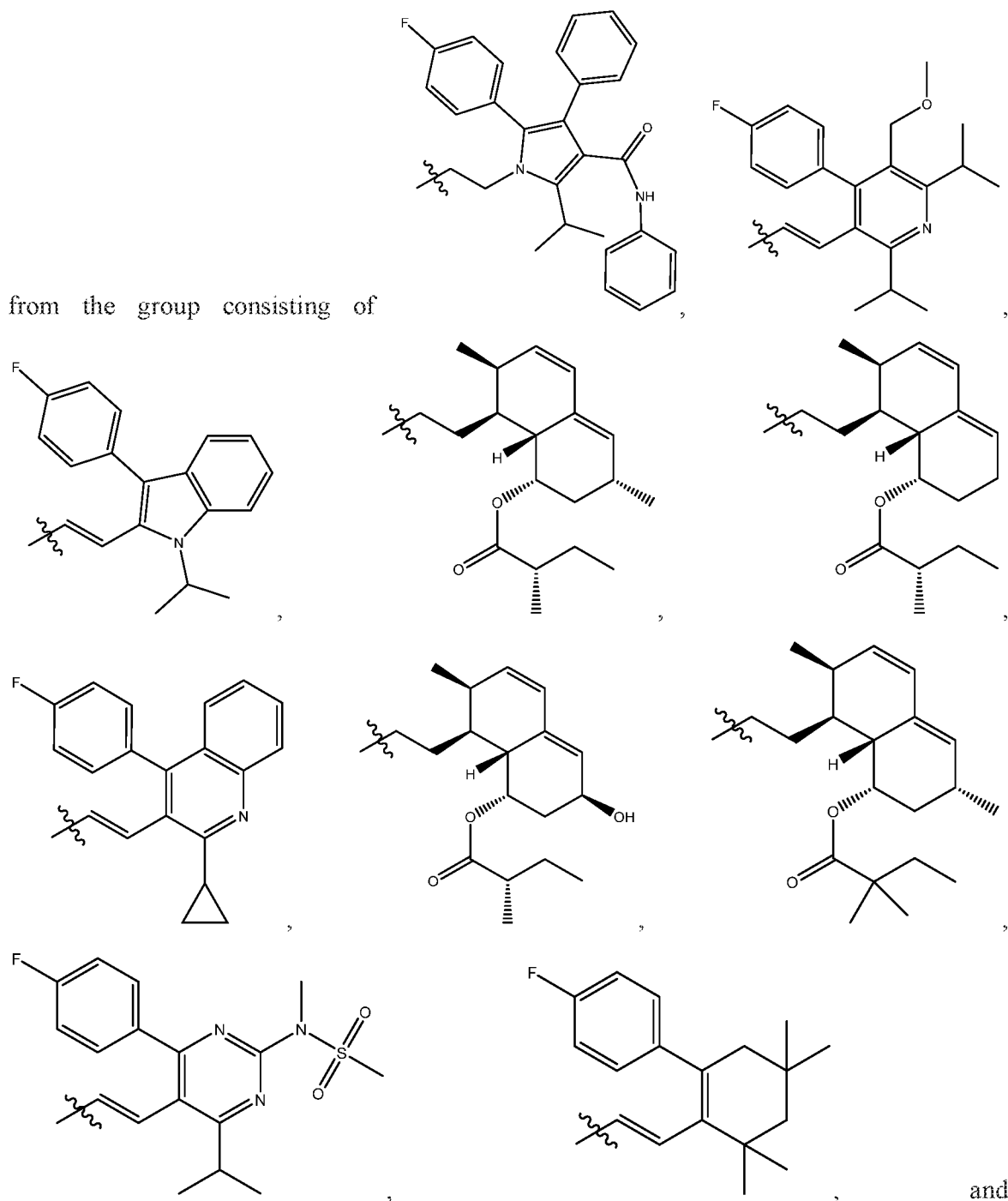


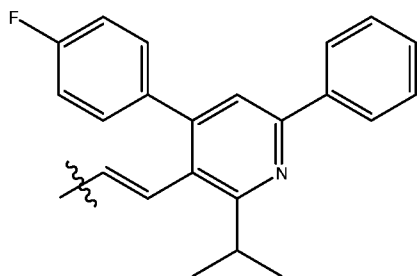
[0040] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, Ie, or If, R7 is an optionally substituted 5-18 membered heteroaryl. In some such embodiments, R7 is a 5-18 membered heteroaryl optionally substituted with one or more R29. In some such embodiments, R29 is selected from the group consisting of C1-6alkyl, halo, cyano, hydroxy, C1-6alkoxy, haloC1-6alkyl, haloC1-6alkoxy, nitro, -C(=O)NR30R31, -N(R32)C(=O)R33, -C(=O)OR34, -OC(=O)R35, and -C(=O)R36. In some such embodiments, each of R30, R31, R32, R33, R34, R35, and R36 is independently selected from the group consisting of hydrogen, C1-6alkyl, C2-6alkenyl, C2-6alkynyl, C3-7carbocyclyl, C6-10aryl, 5-10 membered heteroaryl, and 3-10 membered heterocyclyl. In some further embodiments, R7 is a 6 membered heteroaryl. In some particular embodiments,



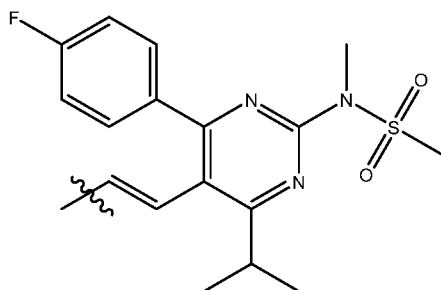
[0041] In some embodiments of the compounds of Formula I, Ia, Ib, Ic, Id, Ie, If, or Ig, R4 is a fragment of a liver-targeting therapeutic agent or a fragment of a liver-activated therapeutic agent. In some such embodiments, R4 is a fragment of a lipid-lowering therapeutic agent or a fragment of a cholesterol-biosynthesis-inhibiting therapeutic agent. In some such embodiments, R4 is a fragment of a HMG-CoA reductase inhibitor. In some such

embodiments, R4 is a fragment of a statin. In some further embodiments, R4 is selected





In some particular embodiments, R4 is

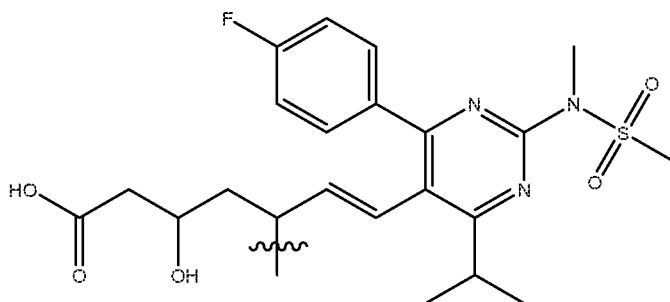


[0042] In some embodiments of the compounds of Formula II, Z is O.

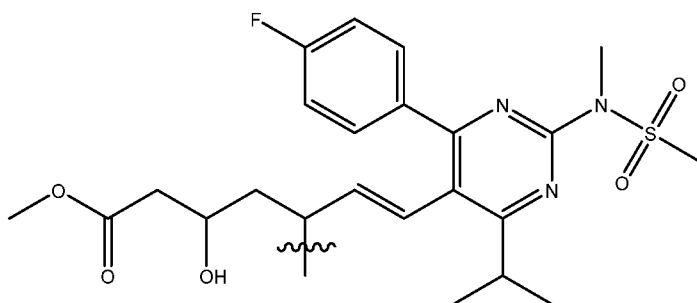
[0043] In some embodiments, R37 is H.

[0044] R39 in some embodiments is ethyl.

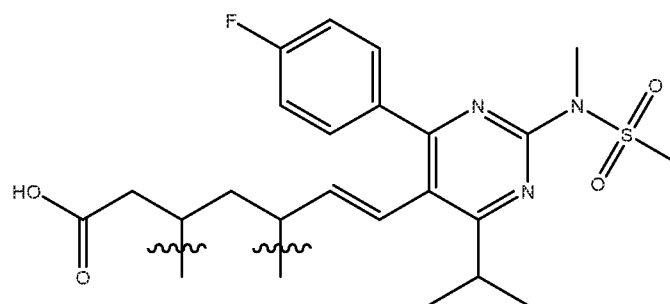
[0045] R38 in some embodiments is the optionally substituted fragment of a therapeutic agent. In some such embodiments, the fragment of a therapeutic agent is



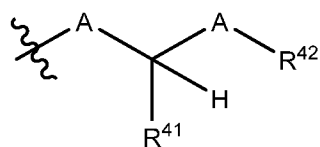
, optionally substituted with one or more moieties C1-6alkyl, halo, and C6-18aryl. In some such embodiments, the substituent is methyl, such that R38 has the structure



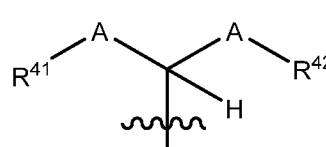
In some embodiments, the



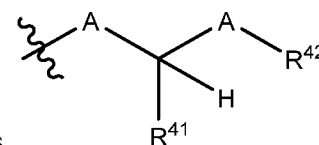
fragment of the therapeutic agent is



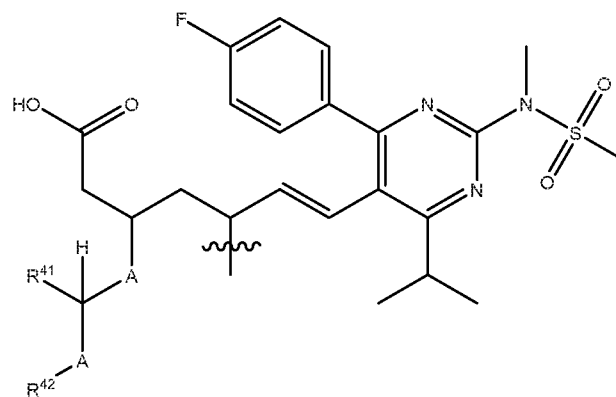
optionally substituted with



, C1-6alkyl,



halo, and C6-18aryl. In some such embodiments, the substituent is



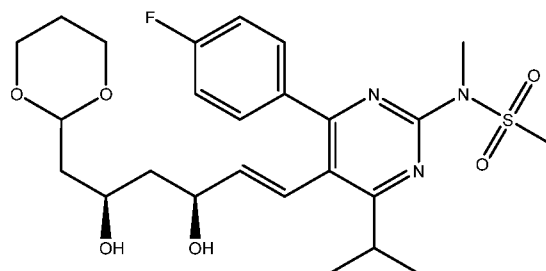
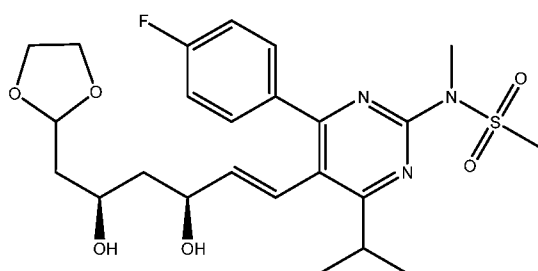
, such that R38 has the structure

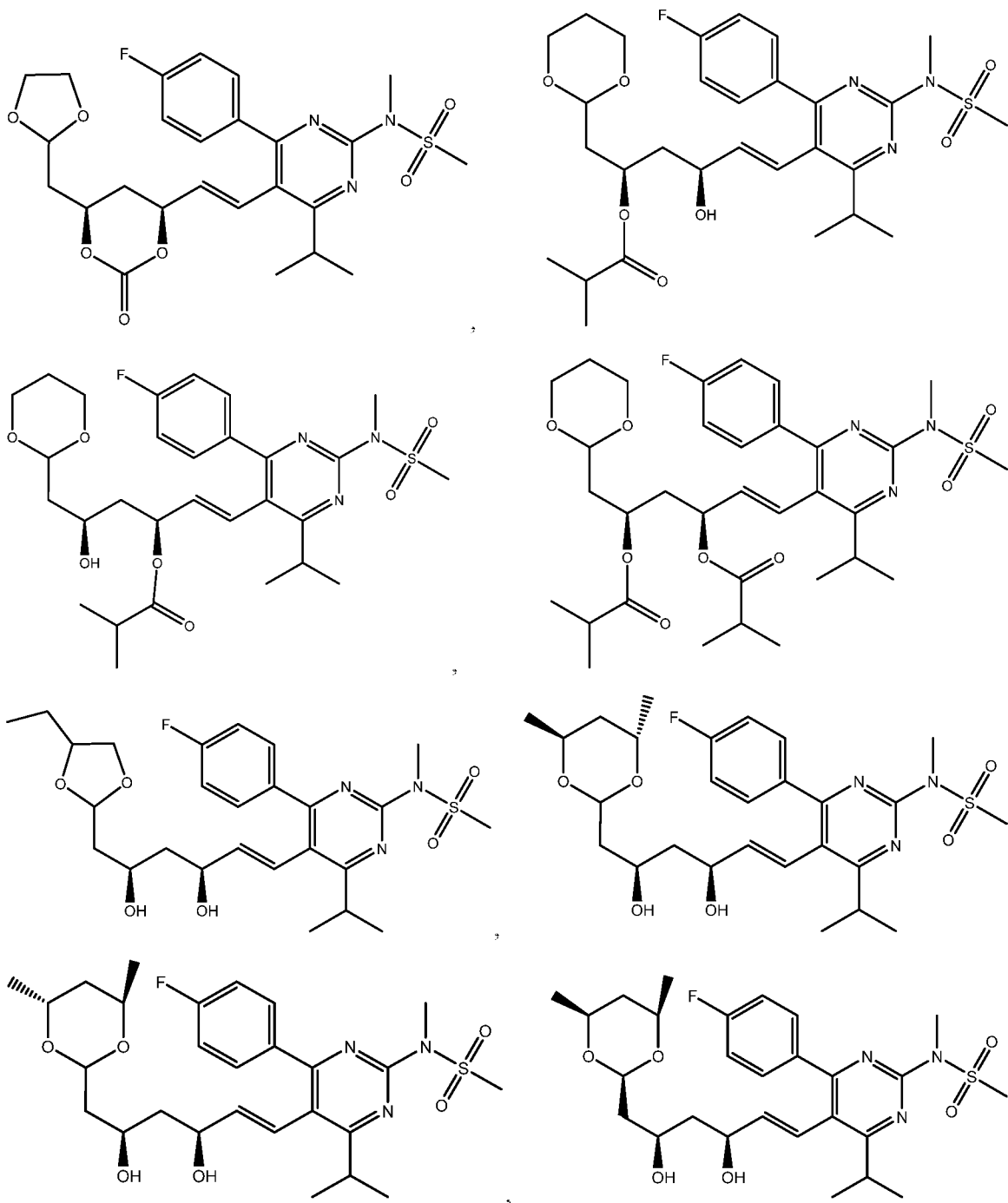
[0046] In some embodiments, A is O.

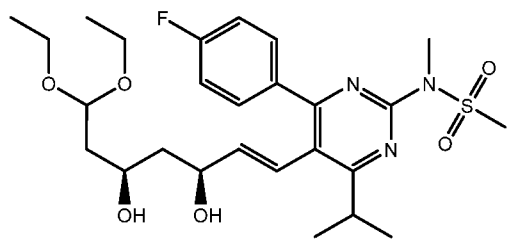
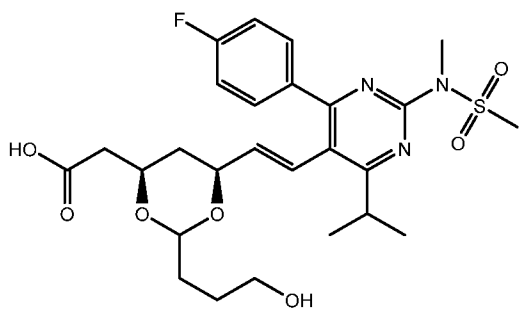
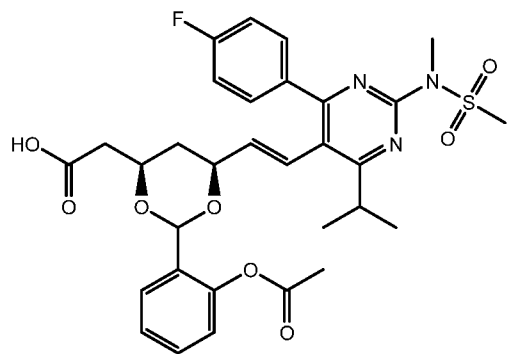
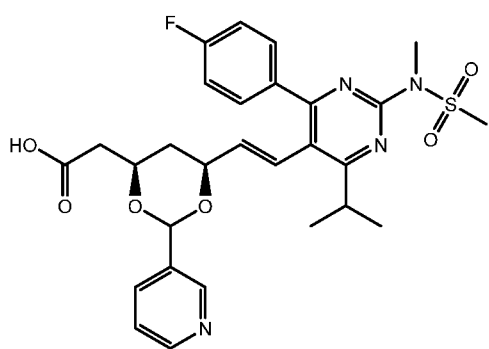
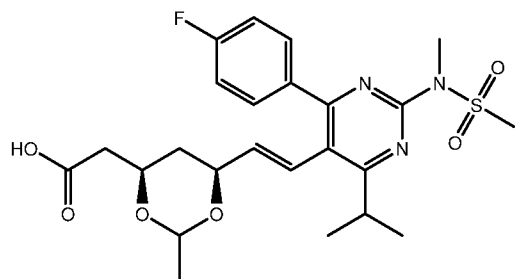
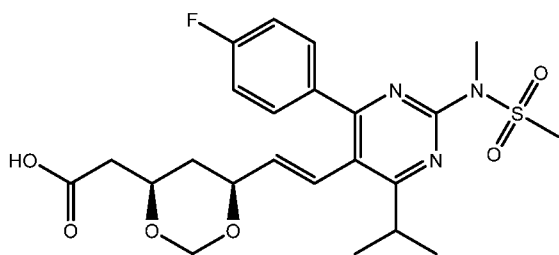
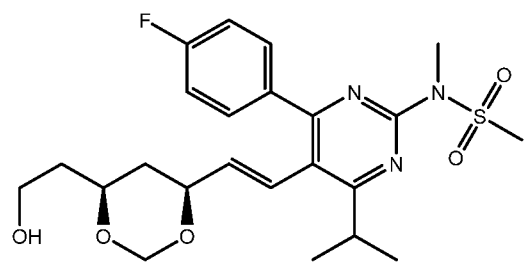
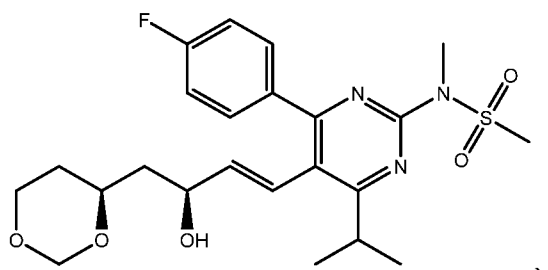
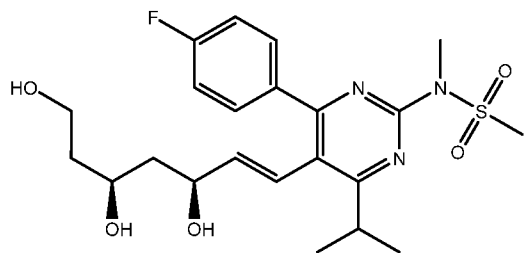
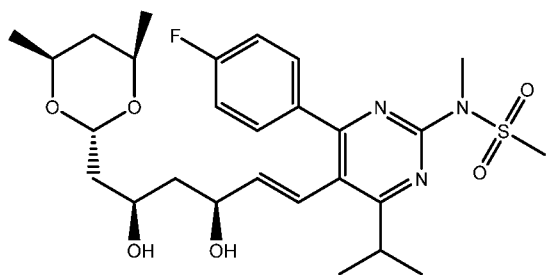
[0047] In some embodiments, R41 is H.

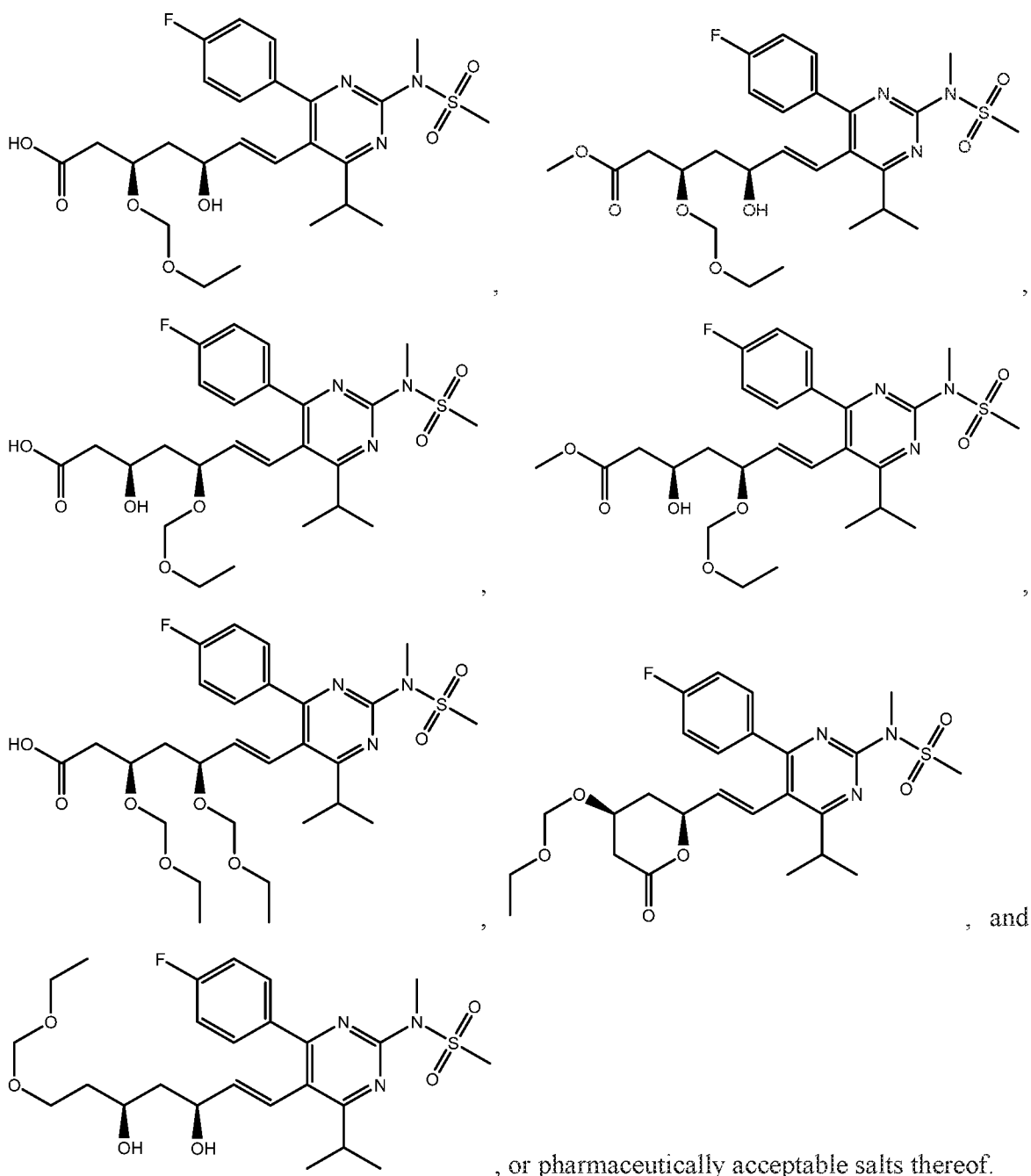
[0048] In some embodiments, R42 is ethyl.

[0049] In some embodiments, the compounds of Formula I, Ia, Ib, Ic, Id, Ie, If, Ig, or II as described herein are selected from the group consisting of









[0050] In some embodiments, the pharmaceutically acceptable salts are selected from alkaline metal salts or ammonium salts. In some embodiments, the pharmaceutically acceptable salts are sodium salts, including disodium salts.

[0051] Where the compounds disclosed herein have at least one chiral center, they may exist as individual enantiomers and diastereomers or as mixtures of such isomers, including racemates. Separation of the individual isomers or selective synthesis of the

individual isomers is accomplished by application of various methods which are well known to practitioners in the art. Unless otherwise indicated, all such isomers and mixtures thereof are included in the scope of the compounds disclosed herein. Furthermore, compounds disclosed herein may exist in one or more crystalline or amorphous forms. Unless otherwise indicated, all such forms are included in the scope of the compounds disclosed herein, including any polymorphic forms. In addition, some of the compounds disclosed herein may form solvates with water (i.e., hydrates) or common organic solvents. Unless otherwise indicated, such solvates are included in the scope of the compounds disclosed herein.

[0052] The skilled artisan will recognize that some structures described herein may be resonance forms or tautomers of compounds that may be fairly represented by other chemical structures, even when kinetically; the artisan recognizes that such structures may only represent a very small portion of a sample of such compound(s). Such compounds are considered within the scope of the structures depicted, though such resonance forms or tautomers are not represented herein.

[0053] Isotopes may be present in the compounds described. Each chemical element as represented in a compound structure may include any isotope of said element. For example, in a compound structure a hydrogen atom may be explicitly disclosed or understood to be present in the compound. At any position of the compound that a hydrogen atom may be present, the hydrogen atom can be any isotope of hydrogen, including but not limited to hydrogen-1 (protium) and hydrogen-2 (deuterium). Thus, reference herein to a compound encompasses all potential isotopic forms unless the context clearly dictates otherwise.

Definitions

[0054] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications, and other publications referenced herein are incorporated by reference in their entirety unless stated otherwise. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise. As used in the specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein

chemistry, biochemistry, recombinant DNA techniques, and pharmacology are employed. The use of “or” or “and” means “and/or” unless stated otherwise. Furthermore, use of the term “including” as well as other forms, such as “include”, “includes,” and “included,” is not limiting. As used in this specification, whether in a transitional phrase or in the body of the claim, the terms “comprise(s)” and “comprising” are to be interpreted as having an open-ended meaning. That is, the terms are to be interpreted synonymously with the phrases “having at least” or “including at least.” When used in the context of a process, the term “comprising” means that the process includes at least the recited steps, but may include additional steps. When used in the context of a compound, composition, or device, the term “comprising” means that the compound, composition, or device includes at least the recited features or components, but may also include additional features or components.

[0055] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[0056] As used herein, common organic abbreviations are defined as follows:

Ac	Acetyl
aq.	Aqueous
Bn	Benzyl
Bz	Benzoyl
BOC or Boc	tert-Butoxycarbonyl
°C	Temperature in degrees Centigrade
DCM	Dichloromethane
DMF	N,N-dimethylformamide
EA	Ethyl acetate
Et	Ethyl
g	Gram(s)
h or hr	Hour(s)
HATU	2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HPLC	High-Performance Liquid Chromatography
iPr	Isopropyl
m or min	Minute(s)

MECN	Acetonitrile
mL	Milliliter(s)
NMR	Nuclear magnetic resonance
PE	Petroleum ether
PG	Protecting group
Ph	Phenyl
rt	Room temperature
TBDMSCl	tert-Butyldimethylsilyl chloride
TBS	tert-Butyldimethylsilyl
TEA	Triethylamine
Tert, t	tertiary
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPDS	Tetraisopropylidisiloxanylidene
TIPDSCl	Tetraisopropylidisiloxanylidene Chloride
TLC	Thin-layer chromatography
TosOH	p-Toluenesulfonic Acid
μL	Microliter(s)

[0057] As used herein, “C_a to C_b” or “C_{a-b}” in which “a” and “b” are integers refer to the number of carbon atoms in the specified group. That is, the group can contain from “a” to “b”, inclusive, carbon atoms. Thus, for example, a “C₁ to C₄ alkyl” or “C₁₋₄ alkyl” group refers to all alkyl groups having from 1 to 4 carbons, that is, CH₃-, CH₃CH₂-, CH₃CH₂CH₂-, (CH₃)₂CH-, CH₃CH₂CH₂CH₂-, CH₃CH₂CH(CH₃)- and (CH₃)₃C-.

[0058] The term “halogen” or “halo,” as used herein, means any one of the radio-stable atoms of column 7 of the Periodic Table of the Elements, e.g., fluorine, chlorine, bromine, or iodine, with fluorine and chlorine being preferred.

[0059] As used herein, “alkyl” refers to a straight or branched hydrocarbon chain that is fully saturated (i.e., contains no double or triple bonds). The alkyl group may have 1 to 20 carbon atoms (whenever it appears herein, a numerical range such as “1 to 20” refers to each integer in the given range; e.g., “1 to 20 carbon atoms” means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 20 carbon

atoms, although the present definition also covers the occurrence of the term “alkyl” where no numerical range is designated). The alkyl group may also be a medium size alkyl having 1 to 9 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 4 carbon atoms. The alkyl group may be designated as “C₁₋₄ alkyl” or similar designations. By way of example only, “C₁₋₄ alkyl” indicates that there are one to four carbon atoms in the alkyl chain, i.e., the alkyl chain is selected from the group consisting of methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, and t-butyl. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl, and the like.

[0060] As used herein, “alkoxy” refers to the formula –OR wherein R is an alkyl as is defined above, such as “C₁₋₉ alkoxy”, including but not limited to methoxy, ethoxy, n-propoxy, 1-methylethoxy (isopropoxy), n-butoxy, iso-butoxy, sec-butoxy, and tert-butoxy, and the like.

[0061] As used herein, “alkylthio” refers to the formula –SR wherein R is an alkyl as is defined above, such as “C₁₋₉ alkylthio” and the like, including but not limited to methylmercapto, ethylmercapto, n-propylmercapto, 1-methylethylmercapto (isopropylmercapto), n-butylmercapto, iso-butylmercapto, sec-butylmercapto, tert-butylmercapto, and the like.

[0062] As used herein, “alkenyl” refers to a straight or branched hydrocarbon chain containing one or more double bonds. The alkenyl group may have 2 to 20 carbon atoms, although the present definition also covers the occurrence of the term “alkenyl” where no numerical range is designated. The alkenyl group may also be a medium size alkenyl having 2 to 9 carbon atoms. The alkenyl group could also be a lower alkenyl having 2 to 4 carbon atoms. The alkenyl group may be designated as “C₂₋₄ alkenyl” or similar designations. By way of example only, “C₂₋₄ alkenyl” indicates that there are two to four carbon atoms in the alkenyl chain, i.e., the alkenyl chain is selected from the group consisting of ethenyl, propen-1-yl, propen-2-yl, propen-3-yl, buten-1-yl, buten-2-yl, buten-3-yl, buten-4-yl, 1-methyl-propen-1-yl, 2-methyl-propen-1-yl, 1-ethyl-ethen-1-yl, 2-methyl-propen-3-yl, buta-1,3-dienyl, buta-1,2,-dienyl, and buta-1,2-dien-4-yl. Typical alkenyl groups include, but are in no way limited to, ethenyl, propenyl, butenyl, pentenyl, and hexenyl, and the like.

[0063] As used herein, “alkynyl” refers to a straight or branched hydrocarbon chain containing one or more triple bonds. The alkynyl group may have 2 to 20 carbon atoms, although the present definition also covers the occurrence of the term “alkynyl” where no numerical range is designated. The alkynyl group may also be a medium size alkynyl having 2 to 9 carbon atoms. The alkynyl group could also be a lower alkynyl having 2 to 4 carbon atoms. The alkynyl group may be designated as “C₂₋₄ alkynyl” or similar designations. By way of example only, “C₂₋₄ alkynyl” indicates that there are two to four carbon atoms in the alkynyl chain, i.e., the alkynyl chain is selected from the group consisting of ethynyl, propyn-1-yl, propyn-2-yl, butyn-1-yl, butyn-3-yl, butyn-4-yl, and 2-butyne-1-yl. Typical alkynyl groups include, but are in no way limited to, ethynyl, propynyl, butynyl, pentynyl, and hexynyl, and the like.

[0064] As used herein, “heteroalkyl” refers to a straight or branched hydrocarbon chain containing one or more heteroatoms, that is, an element other than carbon, including but not limited to, nitrogen, oxygen and sulfur, in the chain backbone. The heteroalkyl group may have 1 to 20 carbon atom, although the present definition also covers the occurrence of the term “heteroalkyl” where no numerical range is designated. The heteroalkyl group may also be a medium size heteroalkyl having 1 to 9 carbon atoms. The heteroalkyl group could also be a lower heteroalkyl having 1 to 4 carbon atoms. The heteroalkyl group may be designated as “C₁₋₄ heteroalkyl” or similar designations. The heteroalkyl group may contain one or more heteroatoms. By way of example only, “C₁₋₄ heteroalkyl” indicates that there are one to four carbon atoms in the heteroalkyl chain and additionally one or more heteroatoms in the backbone of the chain. In various embodiments, a heteroalkyl may contain from 1 to 10 heteroatoms, for example, 1 to 5 heteroatoms, 1 to 3 heteroatoms, 2 heteroatoms, or 1 heteroatom.

[0065] As used herein, “alkylene” means a branched, or straight chain fully saturated di-radical chemical group containing only carbon and hydrogen that is attached to the rest of the molecule via two points of attachment (i.e., an alkanediyl). The alkylene group may have 1 to 20 carbon atoms, although the present definition also covers the occurrence of the term alkylene where no numerical range is designated. The alkylene group may also be a medium size alkylene having 1 to 9 carbon atoms. The alkylene group could also be a lower alkylene having 1 to 4 carbon atoms. The alkylene group may be designated

as “C₁₋₄ alkylene” or similar designations. By way of example only, “C₁₋₄ alkylene” indicates that there are one to four carbon atoms in the alkylene chain, i.e., the alkylene chain is selected from the group consisting of methylene, ethylene, ethan-1,1-diyl, propylene, propan-1,1-diyl, propan-2,2-diyl, 1-methyl-ethylene, butylene, butan-1,1-diyl, butan-2,2-diyl, 2-methyl-propan-1,1-diyl, 1-methyl-propylene, 2-methyl-propylene, 1,1-dimethyl-ethylene, 1,2-dimethyl-ethylene, and 1-ethyl-ethylene.

[0066] As used herein, “alkenylene” means a straight or branched chain di-radical chemical group containing only carbon and hydrogen and containing at least one carbon-carbon double bond that is attached to the rest of the molecule via two points of attachment. The alkenylene group may have 2 to 20 carbon atoms, although the present definition also covers the occurrence of the term alkenylene where no numerical range is designated. The alkenylene group may also be a medium size alkenylene having 2 to 9 carbon atoms. The alkenylene group could also be a lower alkenylene having 2 to 4 carbon atoms. The alkenylene group may be designated as “C₂₋₄ alkenylene” or similar designations. By way of example only, “C₂₋₄ alkenylene” indicates that there are two to four carbon atoms in the alkenylene chain, i.e., the alkenylene chain is selected from the group consisting of ethenylene, ethen-1,1-diyl, propenylene, propen-1,1-diyl, prop-2-en-1,1-diyl, 1-methyl-ethenylene, but-1-enylene, but-2-enylene, but-1,3-dienylene, buten-1,1-diyl, but-1,3-dien-1,1-diyl, but-2-en-1,1-diyl, but-3-en-1,1-diyl, 1-methyl-prop-2-en-1,1-diyl, 2-methyl-prop-2-en-1,1-diyl, 1-ethyl-ethenylene, 1,2-dimethyl-ethenylene, 1-methyl-propenylene, 2-methyl-propenylene, 3-methyl-propenylene, 2-methyl-propen-1,1-diyl, and 2,2-dimethyl-ethen-1,1-diyl.

[0067] The term “aromatic” refers to a ring or ring system having a conjugated pi electron system and includes both carbocyclic aromatic (e.g., phenyl) and heterocyclic aromatic groups (e.g., pyridine). The term includes monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of atoms) groups provided that the entire ring system is aromatic.

[0068] As used herein, “aryl” refers to an aromatic ring or ring system (i.e., two or more fused rings that share two adjacent carbon atoms) containing only carbon in the ring backbone. When the aryl is a ring system, every ring in the system is aromatic. The aryl group may have 6 to 18 carbon atoms, although the present definition also covers the

occurrence of the term “aryl” where no numerical range is designated. In some embodiments, the aryl group has 6 to 10 carbon atoms. The aryl group may be designated as “C₆₋₁₀ aryl,” “C₆ or C₁₀ aryl,” or similar designations. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, azulenyl, and anthracenyl.

[0069] As used herein, “aryloxy” and “arylthio” refers to RO- and RS-, in which R is an aryl as is defined above, such as “C₆₋₁₀ aryloxy” or “C₆₋₁₀ arylthio” and the like, including but not limited to phenyloxy.

[0070] An “aralkyl” or “arylalkyl” is an aryl group connected, as a substituent, via an alkylene group, such as “C₇₋₁₄ aralkyl” and the like, including but not limited to benzyl, 2-phenylethyl, 3-phenylpropyl, and naphthylalkyl. In some cases, the alkylene group is a lower alkylene group (i.e., a C₁₋₄ alkylene group).

[0071] As used herein, “heteroaryl” refers to an aromatic ring or ring system (i.e., two or more fused rings that share two adjacent atoms) that contain(s) one or more heteroatoms, that is, an element other than carbon, including but not limited to, nitrogen, oxygen and sulfur, in the ring backbone. When the heteroaryl is a ring system, every ring in the system is aromatic. The heteroaryl group may have 5-18 ring members (i.e., the number of atoms making up the ring backbone, including carbon atoms and heteroatoms), although the present definition also covers the occurrence of the term “heteroaryl” where no numerical range is designated. In some embodiments, the heteroaryl group has 5 to 10 ring members or 5 to 7 ring members. The heteroaryl group may be designated as “5-7 membered heteroaryl,” “5-10 membered heteroaryl,” or similar designations. In some embodiments, of the ring members, from 1 to 5 are heteroatoms, for example, the heteroaryl may contain from 1 to 4 heteroatoms, from 1 to 3 heteroatoms, two heteroatoms, or one heteroatom. Examples of heteroaryl rings include, but are not limited to, furyl, thienyl, phthalazinyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, quinolinyl, isoquinlinyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, indolyl, isoindolyl, and benzothienyl.

[0072] A “heteroaralkyl” or “heteroarylalkyl” is heteroaryl group connected, as a substituent, via an alkylene group. Examples include but are not limited to 2-thienylmethyl, 3-thienylmethyl, furylmethyl, thienylethyl, pyrrolylalkyl, pyridylalkyl, isoxazolylalkyl, and

imidazolylalkyl. In some cases, the alkylene group is a lower alkylene group (i.e., a C₁₋₄ alkylene group).

[0073] As used herein, “carbocyclyl” means a non-aromatic cyclic ring or ring system containing only carbon atoms in the ring system backbone. When the carbocyclyl is a ring system, two or more rings may be joined together in a fused, bridged or spiro-connected fashion. Carbocyclyls may have any degree of saturation provided that at least one ring in a ring system is not aromatic. Thus, carbocyclyls include cycloalkyls, cycloalkenyls, and cycloalkynyls. The carbocyclyl group may have 3 to 20 carbon atoms, although the present definition also covers the occurrence of the term “carbocyclyl” where no numerical range is designated. The carbocyclyl group may also be a medium size carbocyclyl having 3 to 10 carbon atoms. The carbocyclyl group could also be a carbocyclyl having 3 to 6 carbon atoms. The carbocyclyl group may be designated as “C₃₋₆ carbocyclyl” or similar designations. Examples of carbocyclyl rings include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, 2,3-dihydro-indene, bicycle[2.2.2]octanyl, adamantyl, and spiro[4.4]nonanyl.

[0074] A “(carbocyclyl)alkyl” is a carbocyclyl group connected, as a substituent, via an alkylene group, such as “C₄₋₁₀ (carbocyclyl)alkyl” and the like, including but not limited to, cyclopropylmethyl, cyclobutylmethyl, cyclopropylethyl, cyclopropylbutyl, cyclobutylethyl, cyclopropylisopropyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl, cyclohexylethyl, cycloheptylmethyl, and the like. In some cases, the alkylene group is a lower alkylene group.

[0075] As used herein, “cycloalkyl” means a fully saturated carbocyclyl ring or ring system. Examples include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0076] As used herein, “cycloalkenyl” means a carbocyclyl ring or ring system having at least one double bond, wherein no ring in the ring system is aromatic. An example is cyclohexenyl.

[0077] As used herein, “heterocyclyl” means a non-aromatic cyclic ring or ring system containing at least one heteroatom in the ring backbone. Heterocyclyls may be joined together in a fused, bridged or spiro-connected fashion. Heterocyclyls may have any degree of saturation provided that at least one ring in the ring system is not aromatic. The heteroatom(s) may be present in either a non-aromatic or aromatic ring in the ring system.

The heterocyclyl group may have 3 to 20 ring members (i.e., the number of atoms making up the ring backbone, including carbon atoms and heteroatoms), although the present definition also covers the occurrence of the term “heterocyclyl” where no numerical range is designated. The heterocyclyl group may also be a medium size heterocyclyl having 3 to 10 ring members. The heterocyclyl group could also be a heterocyclyl having 3 to 6 ring members. The heterocyclyl group may be designated as “3-6 membered heterocyclyl” or similar designations. In some embodiments, of the ring members, from 1 to 5 are heteroatoms, for example, the heterocyclyl may contain from 1 to 4 heteroatoms, from 1 to 3 heteroatoms, two heteroatoms, or one heteroatom. In preferred six membered monocyclic heterocyclyls, the heteroatom(s) are selected from one up to three of O, N or S, and in preferred five membered monocyclic heterocyclyls, the heteroatom(s) are selected from one or two heteroatoms selected from O, N, or S. Examples of heterocyclyl rings include, but are not limited to, azepinyl, acridinyl, carbazolyl, cinnolinyl, dioxolanyl, imidazolanyl, imidazolidinyl, morpholinyl, oxiranyl, oxepanyl, thiepanyl, piperidinyl, piperazinyl, dioxopiperazinyl, pyrrolidinyl, pyrrolidonyl, pyrrolidionyl, 4-piperidonyl, pyrazolinyl, pyrazolidinyl, 1,3-dioxinyl, 1,3-dioxanyl, 1,4-dioxinyl, 1,4-dioxanyl, 1,3-oxathianyl, 1,4-oxathiinyl, 1,4-oxathianyl, 2*H*-1,2-oxazinyl, trioxanyl, hexahydro-1,3,5-triazinyl, 1,3-dioxolyl, 1,3-dioxolanyl, 1,3-dithiolyl, 1,3-dithiolanyl, isoxazolanyl, isoxazolidinyl, oxazolanyl, oxazolidinyl, oxazolidinonyl, thiazolanyl, thiazolidinyl, 1,3-oxathiolanyl, indolinyl, isoindolinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydro-1,4-thiazinyl, thiamorpholinyl, dihydrobenzofuranyl, benzimidazolidinyl, and tetrahydroquinoline.

[0078] A “(heterocyclyl)alkyl” is a heterocyclyl group connected, as a substituent, via an alkylene group. Examples include, but are not limited to, imidazolinylmethyl and indolinylethyl.

[0079] As used herein, “acyl” refers to $-C(=O)R$, wherein R is selected from hydrogen, optionally substituted C_{1-6} alkyl, halogen, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{3-7} carbocyclyl, optionally substituted C_{6-10} aryl, optionally substituted 5-10 membered heteroaryl, and optionally substituted 3-10 membered heterocyclyl, as defined herein. Non-limiting examples include formyl, acetyl, propanoyl, benzoyl, and acryl.

[0080] An “O-carboxy” group refers to a “-OC(=O)R” group in which R is selected from hydrogen, optionally substituted C₁₋₆ alkyl, halogen, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, optionally substituted C₃₋₇ carbocyclyl, optionally substituted C₆₋₁₀ aryl, optionally substituted 5-10 membered heteroaryl, and optionally substituted 3-10 membered heterocyclyl, as defined herein.

[0081] A “C-carboxy” group refers to a “-C(=O)OR” group in which R is selected from hydrogen, halogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, optionally substituted C₃₋₇ carbocyclyl, optionally substituted C₆₋₁₀ aryl, optionally substituted 5-10 membered heteroaryl, and optionally substituted 3-10 membered heterocyclyl, as defined herein. A non-limiting example includes carboxyl (i.e., -C(=O)OH).

[0082] A “cyano” group refers to a “-CN” group.

[0083] A “cyanato” group refers to an “-OCN” group.

[0084] An “isocyanato” group refers to a “-NCO” group.

[0085] A “thiocyanato” group refers to a “-SCN” group.

[0086] An “isothiocyanato” group refers to an “-NCS” group.

[0087] A “sulfinyl” group refers to an “-S(=O)R” group in which R is selected from hydrogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, optionally substituted C₃₋₇ carbocyclyl, optionally substituted C₆₋₁₀ aryl, optionally substituted 5-10 membered heteroaryl, and optionally substituted 3-10 membered heterocyclyl, as defined herein.

[0088] A “sulfonyl” group refers to an “-SO₂R” group in which R is selected from hydrogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, optionally substituted C₃₋₇ carbocyclyl, optionally substituted C₆₋₁₀ aryl, optionally substituted 5-10 membered heteroaryl, and optionally substituted 3-10 membered heterocyclyl, as defined herein.

[0089] An “S-sulfonamido” group refers to a “-SO₂NR_AR_B” group in which R_A and R_B are each independently selected from hydrogen, halogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ alkoxy, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, optionally substituted C₃₋₇ carbocyclyl, optionally substituted C₆₋₁₀

aryl, optionally substituted 5-10 membered heteroaryl, and optionally substituted 3-10 membered heterocyclyl, as defined herein.

[0090] An “N-sulfonamido” group refers to a “-N(R_A)SO₂R_B” group in which R_A and R_B are each independently selected from hydrogen, halogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, optionally substituted C₃₋₇ carbocyclyl, optionally substituted C₆₋₁₀ aryl, optionally substituted 5-10 membered heteroaryl, and optionally substituted 3-10 membered heterocyclyl, as defined herein.

[0091] A “C-amido” group refers to a “-C(=O)NR_AR_B” group in which R_A and R_B are each independently selected from hydrogen, halogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ alkoxy, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, optionally substituted C₃₋₇ carbocyclyl, optionally substituted C₆₋₁₀ aryl, optionally substituted 5-10 membered heteroaryl, and optionally substituted 3-10 membered heterocyclyl, as defined herein.

[0092] An “N-amido” group refers to a “-N(R_A)C(=O)R_B” group in which R_A and R_B are each independently selected from hydrogen, halogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ alkoxy, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, optionally substituted C₃₋₇ carbocyclyl, optionally substituted C₆₋₁₀ aryl, optionally substituted 5-10 membered heteroaryl, and optionally substituted 3-10 membered heterocyclyl, as defined herein.

[0093] An “O-carbamyl” group refers to a “-OC(=O)NR_AR_B” group in which R_A and R_B are each independently selected from hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ carbocyclyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0094] An “N-carbamyl” group refers to an “-N(R_A)OC(=O)R_B” group in which R_A and R_B are each independently selected from hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ carbocyclyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0095] An “O-thiocarbamyl” group refers to a “-OC(=S)NR_AR_B” group in which R_A and R_B are each independently selected from hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆

alkynyl, C₃₋₇ carbocyclyl, a C₆₋₁₀ aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0096] An “N-thiocarbamyl” group refers to an “-N(R_A)OC(=S)R_B” group in which R_A and R_B are each independently selected from hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ carbocyclyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0097] An “amino” group refers to a “-NR_AR_B” group in which R_A and R_B are each independently selected from hydrogen, halogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, optionally substituted C₃₋₇ carbocyclyl, optionally substituted C₆₋₁₀ aryl, optionally substituted 5-10 membered heteroaryl, and optionally substituted 3-10 membered heterocyclyl as defined herein. A non-limiting example includes free amino (i.e., -NH₂).

[0098] An “aminoalkyl” group refers to an amino group connected via an alkylene group.

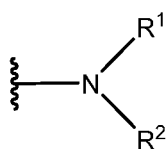
[0099] An “alkoxyalkyl” group refers to an alkoxy group connected via an alkylene group, such as a “C₂₋₈ alkoxyalkyl” and the like.

[0100] As used herein, a substituted group is derived from the unsubstituted parent group in which there has been an exchange of one or more hydrogen atoms for another atom or group. Unless otherwise indicated, when a group is deemed to be “substituted,” it is meant that the group is substituted with one or more substituents independently selected from C₁₋₆ alkyl, C₁₋₆ alkenyl, C₁₋₆ alkynyl, C₁₋₆ heteroalkyl, C₃₋₇ carbocyclyl (optionally substituted with halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, and C₁₋₆ haloalkoxy), C₃₋₇-carbocyclyl-C₁₋₆-alkyl (optionally substituted with halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, and C₁₋₆ haloalkoxy), 3-10 membered heterocyclyl (optionally substituted with halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, and C₁₋₆ haloalkoxy), 3-10 membered heterocyclyl-C₁₋₆-alkyl (optionally substituted with halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, and C₁₋₆ haloalkoxy), aryl (optionally substituted with halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, and C₁₋₆ haloalkoxy), aryl(C₁₋₆)alkyl (optionally substituted with halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, and C₁₋₆ haloalkoxy), 5-10 membered heteroaryl (optionally substituted with halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, and C₁₋₆ haloalkoxy), 5-10 membered heteroaryl(C₁₋₆)alkyl (optionally

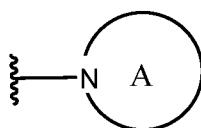
substituted with halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, and C₁-C₆ haloalkoxy), halo, cyano, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkoxy(C₁-C₆)alkyl (i.e., ether), aryloxy, sulfhydryl (mercapto), halo(C₁-C₆)alkyl (e.g., -CF₃), halo(C₁-C₆)alkoxy (e.g., -OCF₃), C₁-C₆ alkylthio, arylthio, amino, amino(C₁-C₆)alkyl, nitro, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, acyl, cyanato, isocyanato, thiocyanato, isothiocyanato, sulfinyl, sulfonyl, and oxo (=O). Wherever a group is described as “optionally substituted” that group can be substituted with the above substituents.

[0101] It is to be understood that certain radical naming conventions can include either a mono-radical or a di-radical, depending on the context. For example, where a substituent requires two points of attachment to the rest of the molecule, it is understood that the substituent is a di-radical. For example, a substituent identified as alkyl that requires two points of attachment includes di-radicals such as -CH₂-, -CH₂CH₂-, -CH₂CH(CH₃)CH₂-, and the like. Other radical naming conventions clearly indicate that the radical is a di-radical such as “alkylene” or “alkenylene.”

[0102] When two R groups are said to form a ring (e.g., a carbocyclyl, heterocyclyl, aryl, or heteroaryl ring) “together with the atom to which they are attached,” it is meant that the collective unit of the atom and the two R groups are the recited ring. The ring is not otherwise limited by the definition of each R group when taken individually. For example, when the following substructure is present:

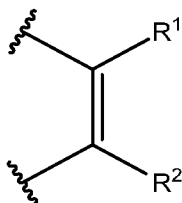


and R¹ and R² are defined as selected from the group consisting of hydrogen and alkyl, or R¹ and R² together with the nitrogen to which they are attached form a heterocyclyl, it is meant that R¹ and R² can be selected from hydrogen or alkyl, or alternatively, the substructure has structure:

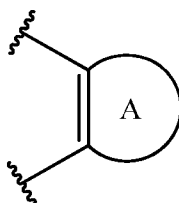


where ring A is a heterocyclyl ring containing the depicted nitrogen.

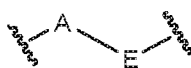
[0103] Similarly, when two “adjacent” R groups are said to form a ring “together with the atom to which they are attached,” it is meant that the collective unit of the atoms, intervening bonds, and the two R groups are the recited ring. For example, when the following substructure is present:



and R¹ and R² are defined as selected from the group consisting of hydrogen and alkyl, or R¹ and R² together with the atoms to which they are attached form an aryl or carbocyclyl, it is meant that R¹ and R² can be selected from hydrogen or alkyl, or alternatively, the substructure has structure:



where A is an aryl ring or a carbocyclyl containing the depicted double bond.

[0104] Wherever a substituent is depicted as a di-radical (i.e., has two points of attachment to the rest of the molecule), it is to be understood that the substituent can be attached in any directional configuration unless otherwise indicated. Thus, for example, a substituent depicted as –AE– or  includes the substituent being oriented such that the A is attached at the leftmost attachment point of the molecule as well as the case in which A is attached at the rightmost attachment point of the molecule.

[0105] “Subject” as used herein, means a human or a non-human mammal, e.g., a dog, a cat, a mouse, a rat, a cow, a sheep, a pig, a goat, a non-human primate or a bird, e.g., a chicken, as well as any other vertebrate or invertebrate.

[0106] The term “mammal” is used in its usual biological sense. Thus, it specifically includes, but is not limited to, primates, including simians (chimpanzees, apes, monkeys) and humans, cattle, horses, sheep, goats, swine, rabbits, dogs, cats, rodents, rats, mice guinea pigs, or the like.

[0107] The term “pharmaceutically acceptable carrier” or “pharmaceutically acceptable excipient” includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. 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 is contemplated. In addition, various adjuvants such as are commonly used in the art may be included. Considerations for the inclusion of various components in pharmaceutical compositions are described, e.g., in Gilman et al. (Eds.) (1990); Goodman and Gilman’s: The Pharmacological Basis of Therapeutics, 8th Ed., Pergamon Press.

[0108] A therapeutic effect relieves, to some extent, one or more of the symptoms of a disease or condition, and includes curing a disease or condition. “Curing” means that the symptoms of a disease or condition are eliminated; however, certain long-term or permanent effects may exist even after a cure is obtained (such as extensive tissue damage).

[0109] “Treat,” “treatment,” or “treating,” as used herein refers to administering a compound or pharmaceutical composition to a subject for prophylactic and/or therapeutic purposes. The term “prophylactic treatment” refers to treating a subject who does not yet exhibit symptoms of a disease or condition, but who is susceptible to, or otherwise at risk of, a particular disease or condition, whereby the treatment reduces the likelihood that the patient will develop the disease or condition. The term “therapeutic treatment” refers to administering treatment to a subject already suffering from a disease or condition.

[0110] “Metabolites” of the compounds disclosed herein include active species that are produced upon introduction of the compounds into the biological milieu.

[0111] “Solvate” refers to the compound formed by the interaction of a solvent and a compound described herein, a metabolite, or salt thereof. Suitable solvates are pharmaceutically acceptable solvates including hydrates.

[0112] The term “pharmaceutically acceptable salt” refers to salts that retain the biological effectiveness and properties of a compound, which are not biologically or otherwise undesirable for use in a pharmaceutical. In many cases, the compounds herein are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto. Pharmaceutically acceptable acid addition salts can be

formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like; particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. Many such salts are known in the art, as described in WO 87/05297, Johnston et al., published September 11, 1987 (incorporated by reference herein in its entirety).

Methods of Preparation

[0113] The compounds disclosed herein may be synthesized by methods described below, or by modification of these methods. Ways of modifying the methodology include, among others, temperature, solvent, reagents, etc., known to those skilled in the art. In general, during any of the processes for preparation of the compounds disclosed herein, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry* (ed. J.F.W. McOmie, Plenum Press, 1973); and P.G.M. Green, T.W. Wutts, *Protecting Groups in Organic Synthesis* (3rd ed.) Wiley, New York (1999), which are both hereby incorporated herein by reference in their entirety. The protecting groups may be removed at a convenient subsequent stage using methods known from the art. Synthetic chemistry transformations useful in synthesizing applicable compounds are known in the art and include, e.g., those

described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers, 1989, or L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, 1995, which are both hereby incorporated herein by reference in their entirety. The routes shown and described herein are illustrative only and are not intended, nor are they to be construed, to limit the scope of the claims in any manner whatsoever. Those skilled in the art will be able to recognize modifications of the disclosed syntheses and to devise alternate routes based on the disclosures herein; all such modifications and alternate routes are within the scope of the claims.

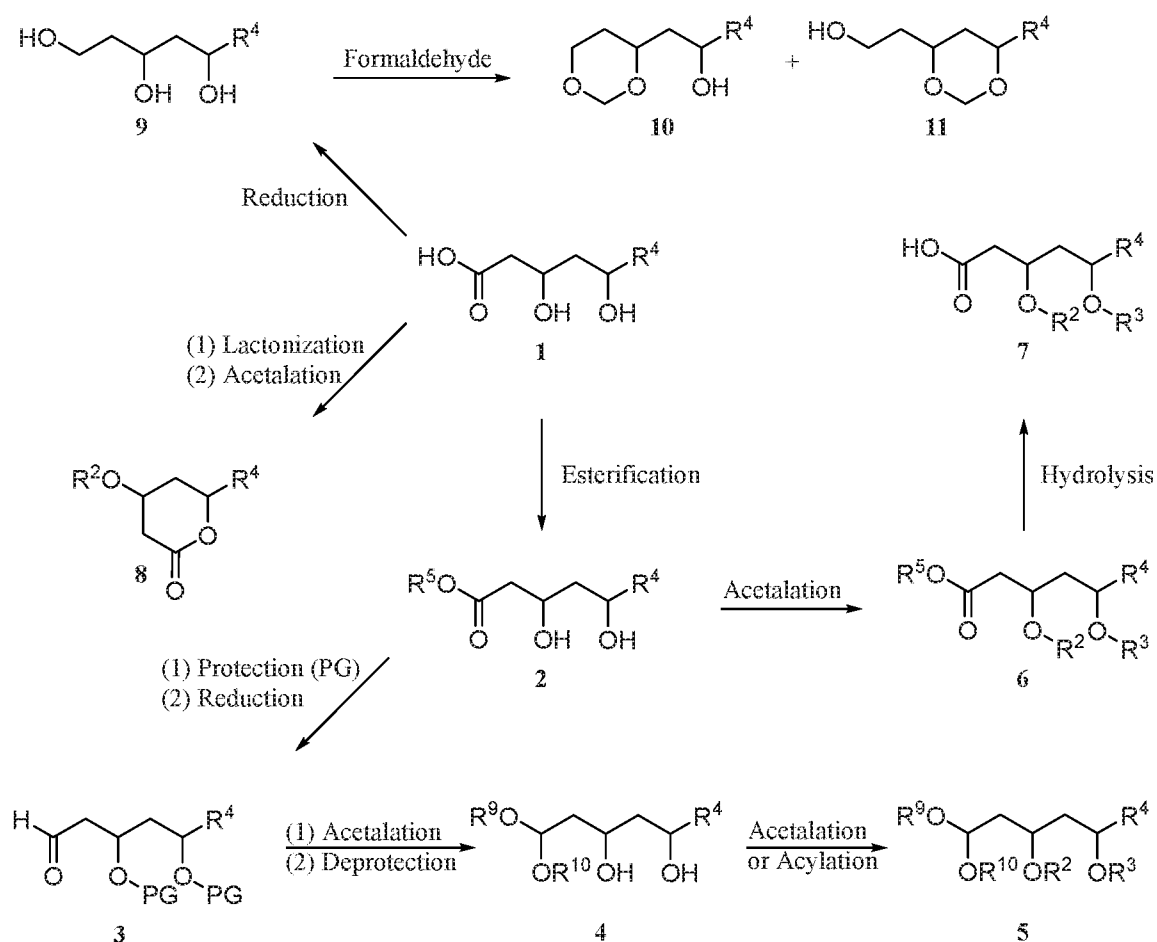
[0114] Scheme I is provided for the guidance of the reader, and represents an example of a general strategy for making the compounds described herein. Other methods for preparing the compounds described herein will be readily apparent to the person of ordinary skill in the art in light of the following reaction schemes and examples.

[0115] Compounds of structure 4 can be prepared from precursors of structure 1 by protection of the diol, reduction of the carboxyl to the corresponding aldehyde (structure 3), acetalation, and then deprotection. Compounds of structure 5 can be obtained by acylation or further acetalation of the compounds of structure 4.

[0116] Compounds of structure 6 can be prepared from precursors of structure 1 by esterification followed by acetalation. Compounds of structure 7 can be prepared by direct acetalation of precursors of structure 1. Compounds of structure 8 can be obtained from precursors of structure 1 by lactonization followed by acetalation.

[0117] Compounds of structure 9 can be obtained by direct reduction of precursors of structure 1. Compounds of structures 10 and 11 can be prepared from compounds of structure 9 by treatment with formaldehyde.

Scheme I



Administration and Pharmaceutical Compositions

[0118] The compounds are administered at a therapeutically effective dosage. While human dosage levels have yet to be optimized for the compounds described herein, generally, a daily dose may be from about 0.25 mg/kg to about 120 mg/kg or more of body weight, from about 0.5 mg/kg or less to about 70 mg/kg, from about 1.0 mg/kg to about 50 mg/kg of body weight, or from about 1.5 mg/kg to about 10 mg/kg of body weight. Thus, for administration to a 70 kg person, the dosage range would be from about 17 mg per day to about 8000 mg per day, from about 35 mg per day or less to about 7000 mg per day or more, from about 70 mg per day to about 6000 mg per day, from about 100 mg per day to about 5000 mg per day, or from about 200 mg to about 3000 mg per day. The amount of active compound administered will, of course, be dependent on the subject and disease state being

treated, the severity of the affliction, the manner and schedule of administration and the judgment of the prescribing physician.

[0119] Administration of the compounds disclosed herein or the pharmaceutically acceptable salts thereof can be via any of the accepted modes of administration for agents that serve similar utilities including, but not limited to, orally, subcutaneously, intravenously, intranasally, topically, transdermally, intraperitoneally, intramuscularly, intrapulmonarily, vaginally, rectally, or intraocularly. Oral and parenteral administrations are customary in treating the indications that are the subject of the preferred embodiments.

[0120] The compounds described above can be formulated into pharmaceutical compositions for use in treatment of these conditions. Standard pharmaceutical formulation techniques are used, such as those disclosed in Remington's The Science and Practice of Pharmacy, 21st Ed., Lippincott Williams & Wilkins (2005), incorporated by reference in its entirety. Accordingly, some embodiments include pharmaceutical compositions comprising: (a) a safe and therapeutically effective amount of a compound described herein (including enantiomers, diastereoisomers, tautomers, polymorphs, and solvates thereof), or pharmaceutically acceptable salts thereof; and (b) a pharmaceutically acceptable carrier, diluent, excipient or combination thereof.

[0121] In addition to the compounds described above, some embodiments include compositions containing a pharmaceutically-acceptable carrier. The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. 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 is contemplated. In addition, various adjuvants such as are commonly used in the art may be included. Considerations for the inclusion of various components in pharmaceutical compositions are described, e.g., in Gilman et al. (Eds.) (1990); Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 8th Ed., Pergamon Press, which is incorporated herein by reference in its entirety.

[0122] Some examples of substances, which can serve as pharmaceutically-acceptable carriers or components thereof, are 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 methyl cellulose; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid and magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; alginic acid; emulsifiers, such as the TWEENS; wetting agents, such sodium lauryl sulfate; coloring agents; flavoring agents; tableting agents, stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

[0123] The choice of a pharmaceutically-acceptable carrier to be used in conjunction with the subject compound is basically determined by the way the compound is to be administered.

[0124] The compositions described herein are preferably provided in unit dosage form. As used herein, a "unit dosage form" is a composition containing an amount of a compound that is suitable for administration to an animal, preferably mammal subject, in a single dose, according to good medical practice. The preparation of a single or unit dosage form however, does not imply that the dosage form is administered once per day or once per course of therapy. Such dosage forms are contemplated to be administered once, twice, thrice or more per day and may be administered as infusion over a period of time (e.g., from about 30 minutes to about 2-6 hours), or administered as a continuous infusion, and may be given more than once during a course of therapy, though a single administration is not specifically excluded. The skilled artisan will recognize that the formulation does not specifically contemplate the entire course of therapy and such decisions are left for those skilled in the art of treatment rather than formulation.

[0125] The compositions described above may be in any of a variety of suitable forms for a variety of routes for administration, for example, for oral, nasal, rectal, topical (including transdermal), ocular, intracerebral, intracranial, intrathecal, intra-arterial, intravenous, intramuscular, or other parental routes of administration. The skilled artisan will appreciate that oral and nasal compositions comprise compositions that are administered by inhalation, and made using available methodologies. Depending upon the particular route of administration desired, a variety of pharmaceutically-acceptable carriers well-known in the art may be used. Pharmaceutically-acceptable carriers include, for example, solid or

liquid fillers, diluents, hydrotropies, surface-active agents, and encapsulating substances. Optional pharmaceutically-active materials may be included, which do not substantially interfere with the inhibitory activity of the compound. The amount of carrier employed in conjunction with the compound is sufficient to provide a practical quantity of material for administration per unit dose of the compound. Techniques and compositions for making dosage forms useful in the methods described herein are described in the following references, all incorporated by reference herein: Modern Pharmaceutics, 4th Ed., Chapters 9 and 10 (Banker & Rhodes, editors, 2002); Lieberman *et al.*, Pharmaceutical Dosage Forms: Tablets (1989); and Ansel, Introduction to Pharmaceutical Dosage Forms 8th Edition (2004).

[0126] Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules and bulk powders. Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules, and effervescent preparations reconstituted from effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring agents and flavoring agents.

[0127] The pharmaceutically-acceptable carrier suitable for the preparation of unit dosage forms for peroral administration is well-known in the art. Tablets typically comprise conventional pharmaceutically-compatible adjuvants as inert diluents, such as calcium carbonate, sodium carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and sucrose; disintegrants such as starch, alginic acid and croscarmellose; lubricants such as magnesium stearate, stearic acid and talc. Glidants such as silicon dioxide can be used to improve flow characteristics of the powder mixture. Coloring agents, such as the FD&C dyes, can be added for appearance. Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors, are useful adjuvants for chewable tablets. Capsules typically comprise one or more solid diluents disclosed above. The selection of carrier components depends on secondary considerations like taste, cost, and shelf stability, which are not critical, and can be readily made by a person skilled in the art.

[0128] Peroral compositions also include liquid solutions, emulsions, suspensions, and the like. The pharmaceutically-acceptable carriers suitable for preparation of such compositions are well known in the art. Typical components of carriers for syrups, elixirs, emulsions and suspensions include ethanol, glycerol, propylene glycol, polyethylene glycol, liquid sucrose, sorbitol and water. For a suspension, typical suspending agents include methyl cellulose, sodium carboxymethyl cellulose, AVICEL RC-591, tragacanth and sodium alginate; typical wetting agents include lecithin and polysorbate 80; and typical preservatives include methyl paraben and sodium benzoate. Peroral liquid compositions may also contain one or more components such as sweeteners, flavoring agents and colorants disclosed above.

[0129] Such compositions may also be coated by conventional methods, typically with pH or time-dependent coatings, such that the subject compound is released in the gastrointestinal tract in the vicinity of the desired topical application, or at various times to extend the desired action. Such dosage forms typically include, but are not limited to, one or more of cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, Eudragit coatings, waxes and shellac.

[0130] Compositions described herein may optionally include other drug actives.

[0131] Other compositions useful for attaining systemic delivery of the subject compounds include sublingual, buccal and nasal dosage forms. Such compositions typically comprise one or more of soluble filler substances such as sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose and hydroxypropyl methyl cellulose. Glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included.

[0132] A liquid composition, which is formulated for topical ophthalmic use, is formulated such that it can be administered topically to the eye. The comfort should be maximized as much as possible, although sometimes formulation considerations (e.g. drug stability) may necessitate less than optimal comfort. In the case that comfort cannot be maximized, the liquid should be formulated such that the liquid is tolerable to the patient for topical ophthalmic use. Additionally, an ophthalmically acceptable liquid should either be packaged for single use, or contain a preservative to prevent contamination over multiple uses.

[0133] For ophthalmic application, solutions or medicaments are often prepared using a physiological saline solution as a major vehicle. Ophthalmic solutions should preferably be maintained at a comfortable pH with an appropriate buffer system. The formulations may also contain conventional, pharmaceutically acceptable preservatives, stabilizers and surfactants.

[0134] Preservatives that may be used in the pharmaceutical compositions disclosed herein include, but are not limited to, benzalkonium chloride, PHMB, chlorobutanol, thimerosal, phenylmercuric acetate and phenylmercuric nitrate. A useful surfactant is, for example, Tween 80. Likewise, various useful vehicles may be used in the ophthalmic preparations disclosed herein. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose and purified water.

[0135] Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

[0136] Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. For many compositions, the pH will be between 4 and 9. Accordingly, buffers include acetate buffers, citrate buffers, phosphate buffers and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

[0137] In a similar vein, an ophthalmically acceptable antioxidant includes, but is not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

[0138] Other excipient components, which may be included in the ophthalmic preparations, are chelating agents. A useful chelating agent is edetate disodium, although other chelating agents may also be used in place or in conjunction with it.

[0139] For topical use, creams, ointments, gels, solutions or suspensions, etc., containing the compound disclosed herein are employed. Topical formulations may generally be comprised of a pharmaceutical carrier, co-solvent, emulsifier, penetration enhancer, preservative system, and emollient.

[0140] For intravenous administration, the compounds and compositions described herein may be dissolved or dispersed in a pharmaceutically acceptable diluent, such as a saline or dextrose solution. Suitable excipients may be included to achieve the desired pH, including but not limited to NaOH, sodium carbonate, sodium acetate, HCl, and citric acid. In various embodiments, the pH of the final composition ranges from 2 to 8, or preferably from 4 to 7. Antioxidant excipients may include sodium bisulfite, acetone sodium bisulfite, sodium formaldehyde, sulfoxylate, thiourea, and EDTA. Other non-limiting examples of suitable excipients found in the final intravenous composition may include sodium or potassium phosphates, citric acid, tartaric acid, gelatin, and carbohydrates such as dextrose, mannitol, and dextran. Further acceptable excipients are described in Powell, et al., *Compendium of Excipients for Parenteral Formulations, PDA J Pharm Sci and Tech* 1998, 52 238-311 and Nema et al., *Excipients and Their Role in Approved Injectable Products: Current Usage and Future Directions, PDA J Pharm Sci and Tech* 2011, 65 287-332, both of which are incorporated herein by reference in their entirety. Antimicrobial agents may also be included to achieve a bacteriostatic or fungistatic solution, including but not limited to phenylmercuric nitrate, thimerosal, benzethonium chloride, benzalkonium chloride, phenol, cresol, and chlorobutanol.

[0141] The compositions for intravenous administration may be provided to caregivers in the form of one more solids that are reconstituted with a suitable diluent such as sterile water, saline or dextrose in water shortly prior to administration. In other embodiments, the compositions are provided in solution ready to administer parenterally. In still other embodiments, the compositions are provided in a solution that is further diluted prior to administration. In embodiments that include administering a combination of a compound described herein and another agent, the combination may be provided to caregivers as a mixture, or the caregivers may mix the two agents prior to administration, or the two agents may be administered separately.

[0142] The actual dose of the active compounds described herein depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

Methods of Treatment

[0143] Some embodiments of the present invention include methods of treating a liver disease, disorder, or condition by administering the compounds or pharmaceutical compositions described herein to a subject in need thereof. In some such embodiments, the liver disease, disorder, or condition involves the metabolism, storage, or homeostatic control of biochemical end products such as cholesterol, fatty acids, bile, triglycerides, plasma proteins, carrier proteins, lipoproteins, acute phase proteins, apolipoproteins, carbohydrates, hemostatic factors, fibrinolysis factors, thrombopoietin, insulin-like growth factor 1, hepcidin, angiotensinogen, vitamin A, vitamin D, vitamin B12, vitamin K, iron, copper, or catalase. In some particular embodiments, the liver disease, disorder, or condition being treated is liver fibrosis, cirrhosis, hepatitis, alcoholic liver disease, fatty liver, liver cancer, hemochromatosis, Wilson's disease, primary sclerosing cholangitis, alpha 1-antitrypsin deficiency, hyperglycemia, hypoglycemia, or diabetes.

[0144] Some embodiments of the present invention include methods of treating a cardiovascular disease, disorder, or condition, by administering the compounds or pharmaceutical compositions described herein to a subject in need thereof. In some particular embodiments, the cardiovascular disease, disorder, or condition is dyslipidemia or atherosclerosis. In other particular embodiments, the cardiovascular disease, disorder, or condition is hyperlipidemia.

[0145] Some embodiments of the present invention include methods of altering blood lipid concentration by administering the compounds or pharmaceutical compositions described herein to a subject in need thereof.

[0146] Some embodiments of the present invention include methods of inhibiting HMG-CoA reductase by administering the compounds or pharmaceutical compositions described herein to a subject in need thereof.

[0147] Some embodiments of the present invention include methods of reducing the side effects of liver-targeting or liver-activated drugs by administering the compounds or pharmaceutical compositions described herein, rather than their corresponding active drug compound, to a subject in need thereof. In some such embodiments, the corresponding active drug compound is a statin. Examples side effects that can be reduced include headache, difficulty sleeping, flushing of the skin, muscle aches, muscle tenderness, muscle weakness,

drowsiness, dizziness, nausea, vomiting, abdominal pain, bloating, gas, diarrhea, constipation, or rash.

[0148] Some embodiments of the present invention include methods of increasing the therapeutic index of liver-targeting or liver-activated therapeutic agents.

[0149] In some embodiments, the subject is a mammal.

[0150] In some embodiments, the subject is a human.

[0151] Further embodiments include administering a combination of compounds to a subject in need thereof. A combination can include a compound or pharmaceutical composition described herein with an additional medicament.

[0152] Some embodiments include co-administering a compound or pharmaceutical composition described herein, with an additional medicament. By “co-administration,” it is meant that the two or more agents may be found in the patient’s bloodstream at the same time, regardless of when or how they are actually administered. In one embodiment, the agents are administered simultaneously. In one such embodiment, administration in combination is accomplished by combining the agents in a single dosage form. In another embodiment, the agents are administered sequentially. In one embodiment, the agents are administered through the same route, such as orally. In another embodiment, the agents are administered through different routes, such as one being administered orally and another being administered intravenously.

[0153] In some embodiments, the additional medicament is a cholesterol absorption inhibitor, a hypertension medicament, niacin, or aspirin. In some such embodiments, the cholesterol absorption inhibitor is ezetimibe. In some such embodiments, the hypertension medicament is a diuretic, a beta-blocker, an angiotensin-converting enzyme inhibitor, an angiotensin receptor blocker, a calcium channel blocker, an alpha blocker, an alpha-2 receptor agonist, a combined alpha and beta-blocker, a central agonist, a peripheral adrenergic inhibitor, or a vasodilator. Examples of hypertension medicaments that can be used as the additional medicament include acebutolol, alpha methyl dopa, amiloride hydrochloride, amlodipine besylate, atenolol, benazepril hydrochloride, betaxolol, bepridil, bisoprolol fumarate, bumetanide, candesartan, captopril, carteolol hydrochloride, carvedilol, chlorthalidone, chlorothiazide, clonidine hydrochloride, diltiazem hydrochloride, doxazosin mesylate, enalapril maleate, eprosartan mesylate, felodipine, fosinopril sodium, furosemide,

hydralazine hydrochloride, hydrochlorothiazide, guanabenz acetate, guanadrel, guanethidine monosulfate, guanfacine hydrochloride, indapamide, irbesarten, isradipine, labetalol hydrochloride, lisinopril, losartan potassium, methyldopa, metolazone, metoprolol succinate, metoprolol tartrate, minoxidil, moexipril, nadolol, nicardipine, nifedipine, nisoldipine, penbutolol sulfate, perindopril, pindolol, prazosin hydrochloride, propranolol hydrochloride, quinapril hydrochloride, ramipril, reserpine, telmisartan, terazosin hydrochloride, trandolapril, triamterene, solotol hydrochloride, spironolactone, timolol maleate, valsartan, and verapamil hydrochloride.

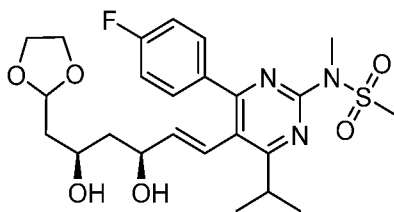
[0154] To further illustrate this invention, the following examples are included. The examples should not, of course, be construed as specifically limiting the invention. Variations of these examples within the scope of the claims are within the purview of one skilled in the art and are considered to fall within the scope of the invention as described, and claimed herein. The reader will recognize that the skilled artisan, armed with the present disclosure, and skill in the art is able to prepare and use the invention without exhaustive examples. The following examples will further describe the present invention, and are used for the purposes of illustration only, and should not be considered as limiting.

EXAMPLES

[0155] Some compounds of Formula I, Ia, Ib, Ic, Id, Ie, If, Ig, and II can be prepared as described below.

Example 1

[0156] N-(5-((3S,5R,E)-6-(1,3-Dioxolan-2-yl)-3,5-dihydroxyhex-1-en-1-yl)-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl)-N-methylmethanesulfonamide (Compound 101)



[0157] To a solution of rosuvastatin (10.0 g, 20.8 mmol) in DMF (75.0 mL) was added 3-bromoprop-1-ene (4.20 g, 34.7 mmol, 1.67 eq). The solution was stirred at 25°C and monitored by TLC. After 16 hours, the reaction mixture was concentrated under reduced

pressure, diluted with H₂O, and extracted with DCM. After drying over Na₂SO₄, the combined organic layers were concentrated under reduced pressure. The concentrate was purified by column chromatography (PE/EA = 1:1) to give rosuvastatin allyl ester (6.41 g, 12.3 mmol, 59% yield) as a light-yellow oil.

[0158] Imidazole (5.56 g, 81.7 mmol, 6.00 eq) was added to a solution of the allyl ester (6.91 g, 13.6 mmol) in DMF (50 mL), and then a solution of TIPDSCl (6.33 g, 27.22 mmol, 2.00 eq) in DMF (25 mL) was added dropwise. The resulting mixture was stirred at 25°C for 16 hours and monitored by TLC. Afterward, the reaction mixture was concentrated under reduced pressure, diluted with H₂O, and extracted with DCM. The combined organic layers were dried over Na₂SO₄ and concentrated to give the crude mixture. Purification by column chromatography (PE/EA = 5:1) afforded TIPDS-protected rosuvastatin allyl ester (10.0 g, 13.1 mmol, 96% yield) as a light-yellow oil.

[0159] To a solution of the TIPDS-protected rosuvastatin allyl ester (12.9 g, 16.8 mmol) in EtOH (200 mL) was added NaBH₄ (1.27 g, 33.7 mmol, 2.00 eq). The resulting mixture was stirred at 40°C and monitored by TLC. After 16 hours, the reaction mixture was filtered, washed with EtOH, and concentrated under reduced pressure. Purification by column chromatography (PE: EA = 5:1) yielded the primary alcohol (6.56 g, 9.24 mmol, 55% yield) as a light-yellow oil.

[0160] To a solution of the primary alcohol (6.38 g, 8.99 mmol) in DCM (120 mL) was added Dess-Martin periodinane (4.58 g, 10.79 mmol, 1.20 eq). The reaction mixture was stirred at 25°C for 16 hours while monitoring by TLC. The reaction mixture was filtered, concentrated under reduced pressure, diluted with DCM, and then washed with water. After drying over Na₂SO₄, the combined organic layers were concentrated under reduced pressure. The concentrate was purified by column chromatography (PE/EA = 10:1) to afford the aldehyde (4.17 g, 5.89 mmol, 65% yield).

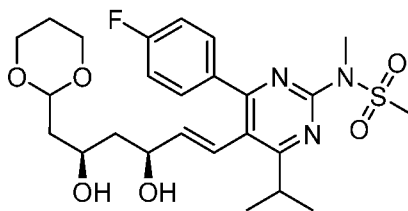
[0161] Ethylene glycol (87.7 mg, 1.41 mmol, 2.00 eq), TosOH (60.8 mg, 0.353 mmol, 0.50 eq) and MgSO₄ (10 g, 83 mmol) were added to a solution of the aldehyde (500 mg, 0.706 mmol) in DCM (50 mL). The resulting mixture was stirred at 60°C for 48 hours and until HPLC (ET12043-33-P1B) indicated that 30% of the aldehyde was consumed. The reaction mixture was filtered and the filtrate washed with DCM. Afterward, the combined organics were concentrated, diluted with DCM, and washed with water. The combined

organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (PE/EA = 25:1) gave the acetal (177 mg, 0.235 mmol, 33% yield) as a light-yellow oil.

[0162] To a solution of the acetal (602 mg, 0.80 mmol) in THF (50.0 mL) was added TEA-3HF (774 mg, 4.80 mmol, 6.00 eq). The resulting mixture was stirred at 30°C for 16 hours and until TLC indicated that most of the acetal was consumed. The reaction mixture was concentrated and purified by column chromatography (PE/EA = 25/1 to 3/1) to afford Compound 101 (328 mg, 0.64 mmol, 80% yield) as light-yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 7.65-7.62 (m, 2H), 7.09-7.05 (m, 2H), 6.63-6.58 (dd, J = 16.0 and 1.65, 1H), 5.47-5.41 (dd, J = 16.0 and 5.07, 1H), 5.00-4.98 (t, 1H), 4.45-4.42 (m, 1H), 4.17-4.12 (m, 1H), 4.02-3.98 (m, 2H), 3.92-3.82 (m, 3H), 3.55 (s, 3H), 3.50 (s, 3H), 3.40-3.31 (m, 1H), 1.89-1.81 (m, 2H), 1.59-1.50 (m, 3H), 1.44-1.40 (m, 1H), 1.24-1.25 (d, J = 6.62, 6H). $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{24}\text{H}_{32}\text{FN}_3\text{O}_6\text{S}$: 510.21; found: 510.2.

Example 2

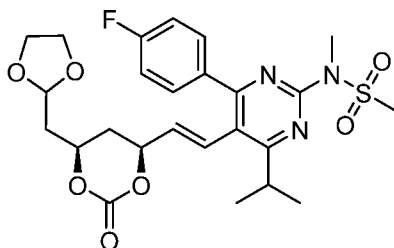
[0163] N-(5-(((3S,5R,E)-6-(1,3-Dioxan-2-yl)-3,5-dihydroxyhex-1-en-1-yl)-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl)-N-methylmethanesulfonamide (Compound 102)



[0164] Compound 102 was prepared according to Scheme I from rosuvastatin and 1,3-dihydroxypropane in a manner similar to that of Compound 101. $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{25}\text{H}_{34}\text{FN}_3\text{O}_6\text{S}$: 524.23; found: 524.3.

Example 3

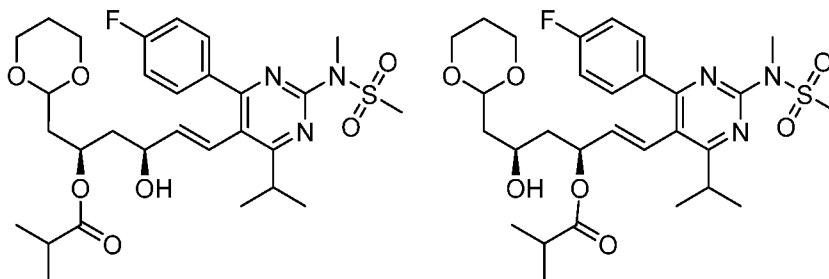
[0165] N-(5-((E)-2-((4S,6R)-6-((1,3-Dioxolan-2-yl)methyl)-2-oxo-1,3-dioxan-4-yl)vinyl)-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl)-N-methylmethanesulfonamide (Compound 103)



[0166] Compound 103 was prepared from treatment of Compound 101 with carbonyldiimidazole. $[M+H]^+$ calculated for $C_{25}H_{30}FN_3O_7S$: 536.19; found: 536.1.

Example 4

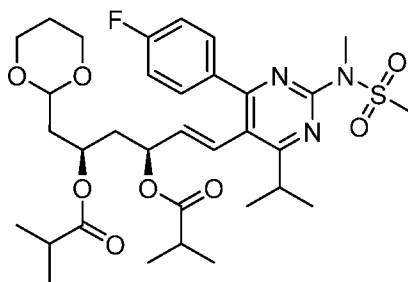
[0167] (2R,4S,E)-1-(1,3-Dioxan-2-yl)-6-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methylmethanesulfonamido)pyrimidin-5-yl)-4-hydroxyhex-5-en-2-yl isobutyrate (Compound 104) and (3S,5R,E)-6-(1,3-dioxan-2-yl)-1-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methylmethanesulfonamido)pyrimidin-5-yl)-5-hydroxyhex-1-en-3-yl isobutyrate (Compound 105)



[0168] Compounds 104 and 105 were prepared as a mixture from treatment of Compound 102 with isobutyryl chloride in the presence of pyridine. $[M+H]^+$ calculated for $C_{29}H_{40}FN_3O_7S$: 594.27; found: 594.3.

Example 5

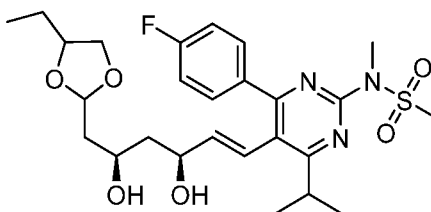
[0169] (2R,4S,E)-1-(1,3-Dioxan-2-yl)-6-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methylmethanesulfonamido)pyrimidin-5-yl)hex-5-ene-2,4-diyl bis(2-methylpropanoate) (Compound 106)



[0170] Compounds 106 were prepared from treatment of Compound 102 with isobutyryl chloride in the presence of pyridine. $[M+H]^+$ calculated for $C_{33}H_{46}FN_3O_8S$: 664.31; found: 664.3.

Example 6

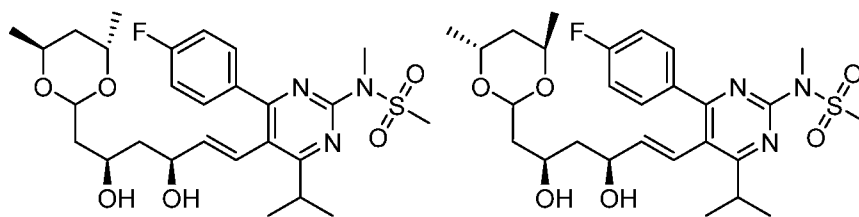
[0171] N-(5-((3S,5R,E)-6-(4-Ethyl-1,3-dioxolan-2-yl)-3,5-dihydroxyhex-1-en-1-yl)-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl)-N-methylmethanesulfonamide (Compound 107)



[0172] Compound 107 was prepared according to Scheme I from rosuvastatin and ($\pm$)-1,2-dihydroxybutane in a manner similar to that of Compound 101. $[M+H]^+$ calculated for $C_{26}H_{36}FN_3O_6S$: 538.24; found: 538.2.

Example 7

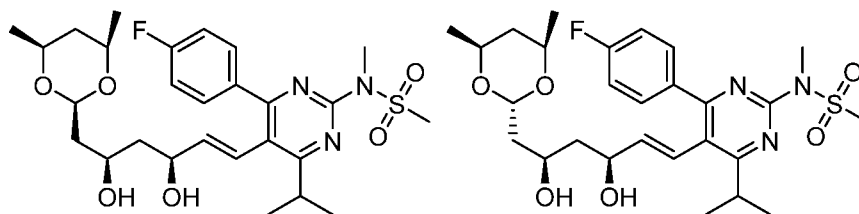
[0173] N-(5-((3S,5R,E)-6-((4S,6S)-4,6-Dimethyl-1,3-dioxan-2-yl)-3,5-dihydroxyhex-1-en-1-yl)-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl)-N-methylmethanesulfonamide (Compound 108) and N-(5-((3S,5R,E)-6-((4R,6R)-4,6-dimethyl-1,3-dioxan-2-yl)-3,5-dihydroxyhex-1-en-1-yl)-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl)-N-methylmethanesulfonamide (Compound 109)



[0174] Compounds 108 and 109 were prepared as a mixture according to Scheme I from rosuvastatin and (±)-2,4-dihydroxypentane in a manner similar to that of Compound 101. $[M+H]^+$ calculated for $C_{27}H_{38}FN_3O_6S$: 552.26; found: 552.2.

Example 8

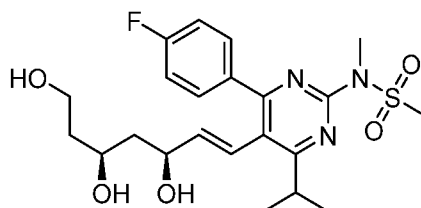
[0175] N-(5-((3S,5R,E)-6-((2S,4S,6R)-4,6-Dimethyl-1,3-dioxan-2-yl)-3,5-dihydroxyhex-1-en-1-yl)-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl)-N-methylmethanesulfonamide (Compound 110) and N-(5-((3S,5R,E)-6-((2R,4R,6R)-4,6-dimethyl-1,3-dioxan-2-yl)-3,5-dihydroxyhex-1-en-1-yl)-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl)-N-methylmethanesulfonamide (Compound 111)



[0176] Compounds 110 and 111 were isolated as a mixture from the reaction in Example 7 operated according to Scheme I from rosuvastatin and (±)-2,4-dihydroxypentane in a manner similar to that of Compound 101. $[M+H]^+$ calculated for $C_{27}H_{38}FN_3O_6S$: 552.26; found: 552.2.

Example 9

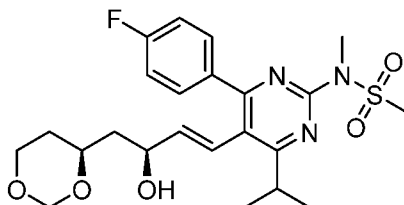
[0177] N-(4-(4-Fluorophenyl)-6-isopropyl-5-((3S,5S,E)-3,5,7-trihydroxyhept-1-en-1-yl)pyrimidin-2-yl)-N-methylmethanesulfonamide (Compound 112)



[0178] Compounds 112 was prepared by directly reduction of rosuvastatin with sodium borohydride. $[M+H]^+$ calculated for $C_{22}H_{30}FN_3O_5S$: 468.20; found: 468.2.

Example 10

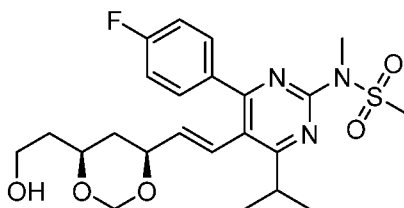
[0179] N-(5-((S,E)-4-((S)-1,3-Dioxan-4-yl)-3-hydroxybut-1-en-1-yl)-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl)-N-methylmethanesulfonamide (Compound 113)



[0180] Compounds 113 was prepared according to a standard acetyl procedure from Compound 112 and formaldehyde. $[M+H]^+$ calculated for $C_{23}H_{30}FN_3O_5S$: 480.20; found: 480.2.

Example 11

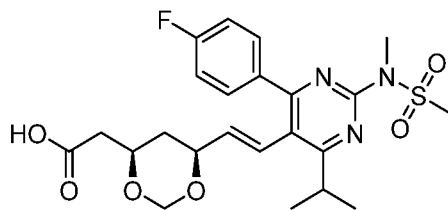
[0181] N-(4-(4-Fluorophenyl)-5-((E)-2-((4S,6S)-6-(2-hydroxyethyl)-1,3-dioxan-4-yl)vinyl)-6-isopropylpyrimidin-2-yl)-N-methylmethanesulfonamide (Compound 114)



[0182] Compounds 114 was isolated from the reaction in Example 10 to prepare Compound 113 according to a standard acetyl procedure from Compound 112 and formaldehyde. $[M+H]^+$ calculated for $C_{23}H_{30}FN_3O_5S$: 480.20; found: 480.2.

Example 12

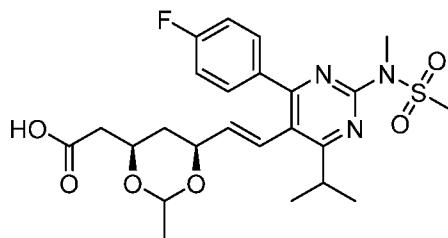
[0183] 2-(((4R,6S)-6-((E)-2-(4-(4-Fluorophenyl)-6-isopropyl-2-(N-methylmethanesulfonamido)pyrimidin-5-yl)vinyl)-1,3-dioxan-4-yl)acetic acid (Compound 115)



[0184] Compounds 115 was prepared according to Scheme I from rosuvastatin and formaldehyde. $[M+H]^+$ calculated for $C_{23}H_{28}FN_3O_6S$: 494.18; found: 494.3.

Example 13

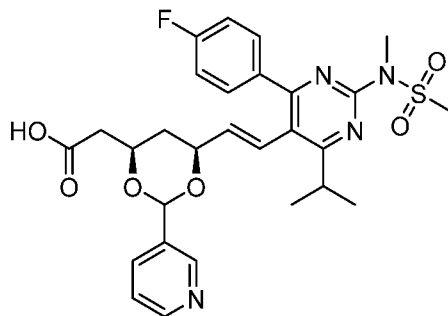
[0185] 2-((4R,6S)-6-((E)-2-(4-(4-Fluorophenyl)-6-isopropyl-2-(N-methylmethylsulfonamido)pyrimidin-5-yl)vinyl)-2-methyl-1,3-dioxan-4-yl)acetic acid (Compound 116)



[0186] Compounds 116 was prepared according to Scheme I from rosuvastatin and acetaldehyde. $[M+H]^+$ calculated for $C_{24}H_{30}FN_3O_6S$: 508.19; found: 508.1.

Example 14

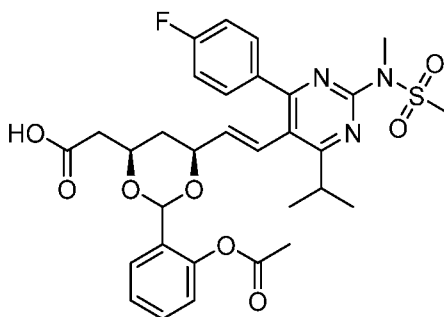
[0187] 2-((4R,6S)-6-((E)-2-(4-(4-Fluorophenyl)-6-isopropyl-2-(N-methylmethylsulfonamido)pyrimidin-5-yl)vinyl)-2-(pyridin-3-yl)-1,3-dioxan-4-yl)acetic acid (Compound 117)



[0188] Compounds 117 was prepared according to Scheme I from rosuvastatin and nicotinaldehyde. $[M+H]^+$ calculated for $C_{28}H_{31}FN_4O_6S$: 571.20; found: 571.1.

Example 15

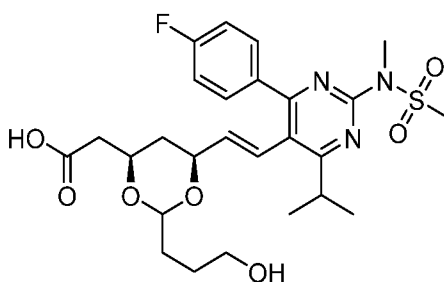
[0189] 2-((4R,6S)-2-(2-Acetoxyphenyl)-6-((E)-2-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methylmethanesulfonamido)pyrimidin-5-yl)vinyl)-1,3-dioxan-4-yl)acetic acid (Compound 118)



[0190] Compounds 118 was prepared according to Scheme I from rosuvastatin and nicotinaldehyde. $[M+H]^+$ calculated for $C_{31}H_{34}FN_3O_8S$: 628.22; found: 628.1.

Example 16

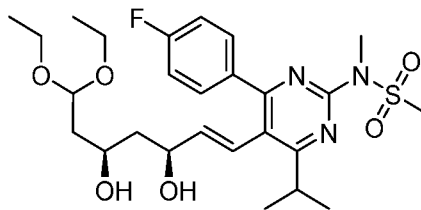
[0191] 2-((4R,6S)-6-((E)-2-(4-(4-Fluorophenyl)-6-isopropyl-2-(N-methylmethanesulfonamido)pyrimidin-5-yl)vinyl)-2-(3-hydroxypropyl)-1,3-dioxan-4-yl)acetic acid (Compound 119)



[0192] Compounds 119 was prepared according to Scheme I from rosuvastatin and 4-hydroxybutanal. $[M+H]^+$ calculated for $C_{26}H_{34}FN_3O_7S$: 552.22; found: 552.5.

Example 17

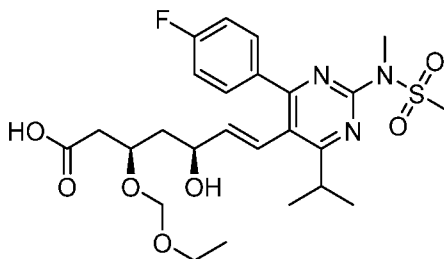
[0193] N-(5-((3S,5R,E)-7,7-Diethoxy-3,5-dihydroxyhept-1-en-1-yl)-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl)-N-methylmethanesulfonamide (Compound 120)



[0194] Compound 120 was prepared according to Scheme I from rosuvastatin and ethanol in a manner similar to that of Compound 101. $[M+H]^+$ calculated for $C_{26}H_{38}FN_3O_6S$: 540.26; found: 540.2.

Example 18

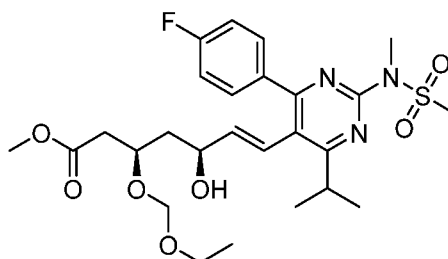
[0195] (3R,5S,E)-3-(Ethoxymethoxy)-7-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methylmethylsulfonamido)pyrimidin-5-yl)-5-hydroxyhept-6-enoic acid (Compound 121)



[0196] Compound 121 was prepared according to a standard procedure from rosuvastatin and chloromethyl ethyl ether. $[M+H]^+$ calculated for $C_{25}H_{34}FN_3O_7S$: 540.22; found: 540.2.

Example 19

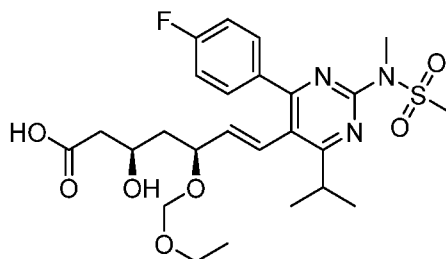
[0197] Methyl (3R,5S,E)-3-(ethoxymethoxy)-7-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methylmethylsulfonamido)pyrimidin-5-yl)-5-hydroxyhept-6-enoate (Compound 122)



[0198] Compounds 122 was prepared according to a standard procedure from rosuvastatin and chloromethyl ethyl ether. $[M+H]^+$ calculated for $C_{26}H_{36}FN_3O_7S$: 554.24; found: 554.2.

Example 20

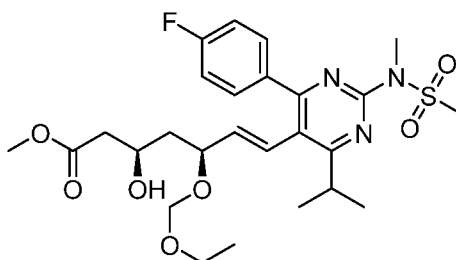
[0199] (3R,5S,E)-5-(Ethoxymethoxy)-7-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methylmethylsulfonamido)pyrimidin-5-yl)-3-hydroxyhept-6-enoic acid (Compound 123)



[0200] Compounds 123 was prepared according to a standard procedure from rosuvastatin and chloromethyl ethyl ether. $[M+H]^+$ calculated for $C_{25}H_{34}FN_3O_7S$: 540.22; found: 540.2.

Example 21

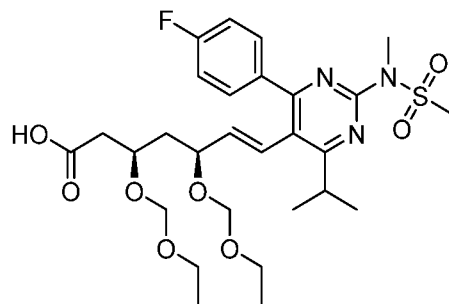
[0201] Methyl (3R,5S,E)-5-(ethoxymethoxy)-7-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methylmethylsulfonamido)pyrimidin-5-yl)-3-hydroxyhept-6-enoate (Compound 124)



[0202] Compounds 124 was prepared according to a standard procedure from rosuvastatin and chloromethyl ethyl ether. $[M+H]^+$ calculated for $C_{26}H_{36}FN_3O_7S$: 554.24; found: 554.2.

Example 22

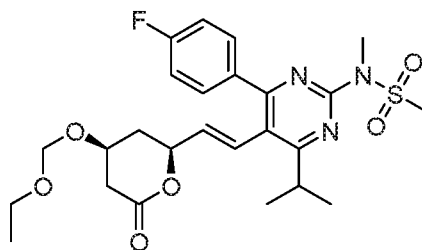
[0203] (3R,5S,E)-3,5-bis(Ethoxymethoxy)-7-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methylmethylsulfonamido)pyrimidin-5-yl)hept-6-enoic acid (Compound 125)



[0204] Compounds 125 can be prepared according to a standard procedure from rosuvastatin and chloromethyl ethyl ether. $[M+H]^+$ calculated for $C_{28}H_{40}FN_3O_8S$: 598.26.

Example 23

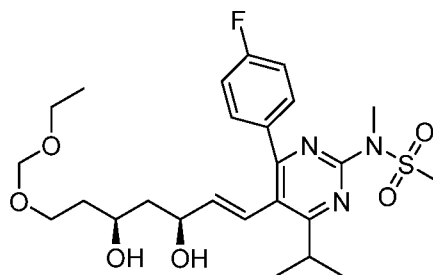
[0205] N-(5-((E)-2-((2S,4S)-4-(Ethoxymethoxy)-6-oxotetrahydro-2H-pyran-2-yl)vinyl)-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl)-N-methylmethanesulfonamide (Compound 126)



[0206] Compound 126 was prepared according to a standard procedure from rosuvastatin and chloromethyl ethyl ether. $[M+H]^+$ calculated for $C_{25}H_{32}FN_3O_6S$: 522.21; found: 522.2.

Example 24

[0207] N-(5-((3S,5S,E)-7-(Ethoxymethoxy)-3,5-dihydroxyhept-1-en-1-yl)-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl)-N-methylmethanesulfonamide (Compound 127)



[0208] Compounds 127 can be prepared according to a standard procedure from rosuvastatin and chloromethyl ethyl ether. $[M+H]^+$ calculated for $C_{25}H_{36}FN_3O_6S$: 526.24.

Example 25

Tissue Distribution Following Oral Administration

[0209] The liver specificity of the disclosed compounds were determined and compared with their corresponding active drug compounds. The disclosed compounds and reference active drug compounds were administered at 5-20 mg/kg to fasted rats by oral gavage. Plasma concentrations of the active, metabolite, and the prodrug compounds in circulation and in the hepatic portal vein were determined by a standard HPLC-UV method. Concentrations of the same in the liver, small intestine, and other organs were measured by the standard LC-MS method.

[0210] Table 1 summarizes the results, which demonstrates improved liver distribution of the disclosed compounds relative to their active drug counterparts.

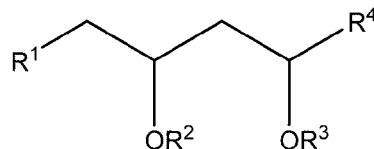
Table 1. Total Rosuvastatin Levels 1 and 5 Hours after 5 mg/kg Administration in Rats

Compound	Total rosuvastatin levels* in the liver (ng/g)	Total rosuvastatin levels* in blood (ng/mL)	Liver/Blood Ratio
Rosuvastatin	1,046	43	24
101	>1,000	< 50	> 24
104/105	> 3,000	< 100	> 24
108/109	> 10,000	< 500	> 24
110/111	> 14,000	< 500	> 24
120	> 10,000	< 500	> 24
121	> 3,000	< 100	> 24
123	> 10,000	< 500	> 24

* Total rosuvastatin level = rosuvastatin level at 1 hour + rosuvastatin level at 5 hours

WHAT IS CLAIMED IS:

1. A compound having the structure of Formula I:

**I**

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of optionally substituted C_{1-8} alkyl, $-\text{COOR}^5$, and optionally substituted C_{2-10} alkoxyalkyl, and 3-12 membered heterocyclyl optionally substituted with one or more R^{15} , or alternatively:

- (i) R^1 and R^2 together with the atoms to which they are attached form an optionally substituted 4-10 membered heterocyclyl, or
- (ii) R^1 and R^3 together with the atoms to which they are attached form an optionally substituted 6-10 membered heterocyclyl;

R^2 is selected from the group consisting of H, $-\text{C}(\text{O})\text{R}^6$, and optionally substituted C_{2-10} alkoxyalkyl, or alternatively:

- (i) R^1 and R^2 together with the atoms to which they are attached form an optionally substituted 4-10 membered heterocyclyl, or
- (ii) R^2 and R^3 together with the atoms to which they are attached form a 6-10 membered heterocyclyl, optionally substituted with one or more R^7 ;

R^3 is selected from the group consisting of H, $-\text{C}(\text{O})\text{R}^8$, and optionally substituted C_{2-10} alkoxyalkyl, or alternatively:

- (i) R^1 and R^3 together with the atoms to which they are attached form an optionally substituted 6-10 membered heterocyclyl, or
- (ii) R^2 and R^3 together with the atoms to which they are attached form a 6-10 membered heterocyclyl, optionally substituted with one or more R^7 ;

R^4 is a fragment of a therapeutic agent;

R^5 is selected from the group consisting of halogen, optionally substituted C_{2-6} alkynyl, optionally substituted C_{6-10} aryl, and optionally substituted 5-10 membered heteroaryl;

R⁶ is selected from the group consisting of H, halogen, optionally substituted C₂₋₆alkenyl, optionally substituted C₂₋₆alkynyl, optionally substituted C₃₋₇carbocyclyl, and optionally substituted 3-10 membered heterocyclyl;

R⁸ is selected from the group consisting of H, optionally substituted C₁₋₆alkyl, halogen, optionally substituted C₂₋₆alkenyl, optionally substituted C₂₋₆alkynyl, optionally substituted C₃₋₇carbocyclyl, optionally substituted C₆₋₁₀aryl, optionally substituted 5-10 membered heteroaryl, and optionally substituted 3-10 membered heterocyclyl; and

each R⁷ is independently selected from the group consisting of optionally substituted C₁₋₈alkyl, oxo, optionally substituted C₆₋₁₈aryl, and optionally substituted 5-18 membered heteroaryl;

each R¹⁵ is selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkenyl, C₁₋₆alkynyl, C₁₋₆heteroalkyl, C₃₋₇carbocyclyl, 3-10 membered heterocyclyl, C₆₋₁₈aryl, C₆₋₁₈arylC₁₋₆alkyl, 5-10 membered heteroaryl, 5-10 membered heteroarylC₁₋₆alkyl, halo, cyano, hydroxyl, C₁₋₆alkoxy, C₂₋₁₀alkoxyalkyl, aryloxy, sulfhydryl, haloC₁₋₆alkyl, haloC₁₋₆alkoxy, C₁₋₆alkylthio, C₆₋₁₈arylthio, and nitro;

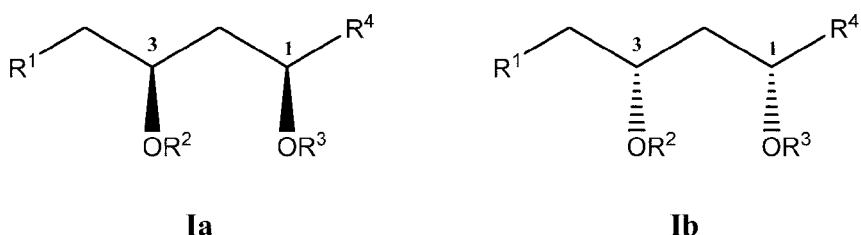
wherein when an alkyl group is substituted, it is substituted with one or more substituents selected from the group consisting of: C_{1-C6} alkyl; C_{1-C6} alkenyl; C_{1-C6} alkynyl; C_{1-C6} heteroalkyl; C_{3-C7} carbocyclyl optionally substituted with halo, C_{1-C6} alkyl, C_{1-C6} alkoxy, C_{1-C6} haloalkyl, and C_{1-C6} haloalkoxy; C_{3-C7}-carbocyclyl-C_{1-C6}-alkyl optionally substituted with halo, C_{1-C6} alkyl, C_{1-C6} alkoxy, C_{1-C6} haloalkyl, and C_{1-C6} haloalkoxy; 3-10 membered heterocyclyl optionally substituted with halo, C_{1-C6} alkyl, C_{1-C6} alkoxy, C_{1-C6} haloalkyl, and C_{1-C6} haloalkoxy; 3-10 membered heterocyclyl-C_{1-C6}-alkyl optionally substituted with halo, C_{1-C6} alkyl, C_{1-C6} alkoxy, C_{1-C6} haloalkyl, and C_{1-C6} haloalkoxy; aryl optionally substituted with halo, C_{1-C6} alkyl, C_{1-C6} alkoxy, C_{1-C6} haloalkyl, and C_{1-C6} haloalkoxy; aryl(C_{1-C6})alkyl optionally substituted with halo, C_{1-C6} alkyl, C_{1-C6} alkoxy, C_{1-C6} haloalkyl, and C_{1-C6} haloalkoxy; 5-10 membered heteroaryl optionally substituted with halo, C_{1-C6} alkyl, C_{1-C6} alkoxy, C_{1-C6} haloalkyl, and C_{1-C6} haloalkoxy; 5-10 membered heteroaryl(C_{1-C6})alkyl optionally substituted with halo, C_{1-C6} alkyl, C_{1-C6} alkoxy, C_{1-C6} haloalkyl, and C_{1-C6} haloalkoxy; halo; cyano; hydroxyl; C_{1-C6} alkoxy; C_{1-C6} alkoxy(C_{1-C6})alkyl; aryloxy; sulfhydryl; halo(C_{1-C6})alkyl; halo(C_{1-C6})alkoxy; C_{1-C6} alkylthio; arylthio; amino; amino(C_{1-C6})alkyl; nitro; O-carbamyl; N-carbamyl; O-thiocarbamyl; N-thiocarbamyl; C-amido; N-amido; S-sulfonamido;

N-sulfonamido; C-carboxy; O-carboxy; acyl; cyanate; isocyanato; thiocyanato; isothiocyanato; sulfinyl; and sulfonyl;

wherein at least one of R^2 and R^3 is not H; and

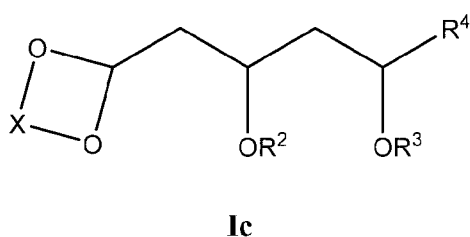
wherein if R^1 and R^3 together with the atoms to which they are attached form a 6 membered heterocyclyl, then R^2 is not H.

2. The compound of claim 1 having the defined 1,3-cis-stereochemistry shown in Formula Ia or Ib:



or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1 having the structure of Formula Ic:



or a pharmaceutically acceptable salt thereof, wherein X is an optionally substituted C_{1-7} alkylene linker.

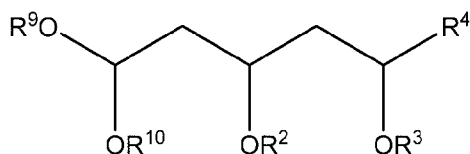
4. The compound of claim 3 wherein X is a C_{1-7} alkylene linker optionally substituted with one or more R^{11} , and wherein R^{11} is selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, C_{1-6} heteroalkyl, C_{3-7} carbocyclyl, 3-10 membered heterocyclyl, C_{6-18} aryl, C_{6-18} aryl C_{1-6} alkyl, 5-10 membered heteroaryl, 5-10 membered heteroaryl C_{1-6} alkyl, halo, cyano, hydroxyl, C_{1-6} alkoxy, C_{2-10} alkoxyalkyl, C_{6-18} aryloxy, sulfhydryl, halo C_{1-6} alkyl, halo C_{1-6} alkoxy, C_{1-6} alkylthio, C_{6-18} arylthio, and nitro.

5. The compound of claim 4, wherein R^{11} is selected from the group consisting of C_{1-6} alkyl, C_{3-7} carbocyclyl, C_{1-6} alkoxy, C_{6-18} aryl, and halo.

6. The compound of any one of claims 4-5, wherein R^{11} is selected from the group consisting of C_{1-6} alkyl and C_{6-18} aryl.

7. The compound of any one of claims 3-6, wherein X is a C_2 alkylene linker.

8. The compound of any one of claims 3-7, wherein X is -CH₂CH₂-.
9. The compound of any one of claims 3-6, wherein X is a C₃alkylene linker.
10. The compound of any one of claims 3-6 or 9, wherein X is -CH₂CH₂CH₂-.
11. The compound of any one of claims 3-6, wherein X is -CH₂(CH₂CH₃)CH₂-.
12. The compound of any one of claims 3-6, wherein X is -CH₂(CH₃)CH₂CH₂(CH₃)-
13. The compound of claim 1 having the structure of Formula Id:

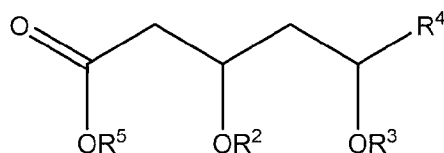
**Id**

or a pharmaceutically acceptable salt thereof, wherein each of R⁹ and R¹⁰ is independently an optionally substituted C₁₋₆alkyl.

14. The compound of claim 13 wherein each of R⁹ and R¹⁰ is independently a C₁₋₆alkyl optionally substituted with one or more R¹², and wherein R¹² is selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkenyl, C₁₋₆alkynyl, C₁₋₆heteroalkyl, C₃₋₇carbocyclyl, C₃₋₇carbocyclylC₁₋₆alkyl, 3-10 membered heterocyclyl, 3-10 membered heterocyclylC₁₋₆alkyl, C₆₋₁₈aryl, C₆₋₁₈arylC₁₋₆alkyl, 5-10 membered heteroaryl, 5-10 membered heteroarylC₁₋₆alkyl, and haloC₁₋₆alkyl.

15. The compound of claim 14 wherein R¹² is selected from the group consisting of C₁₋₆alkyl, C₁₋₆heteroalkyl, C₆₋₁₈aryl, C₆₋₁₈arylC₁₋₆alkyl, and haloC₁₋₆alkyl.

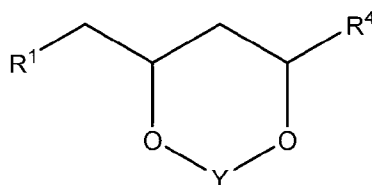
16. The compound of any one of claims 13-15, wherein R⁹ is a C₁₋₆alkyl.
17. The compound of any one of claims 13-16, wherein R⁹ is ethyl.
18. The compound of any one of claims 13-17, wherein R¹⁰ is a C₁₋₆alkyl.
19. The compound of any one of claims 13-18, wherein R¹⁰ is ethyl.
20. The compound of claim 1 having the structure of Formula Ie:

**Ie**

or a pharmaceutically acceptable salt thereof.

21. The compound of claim 1 having the structure of Formula If:

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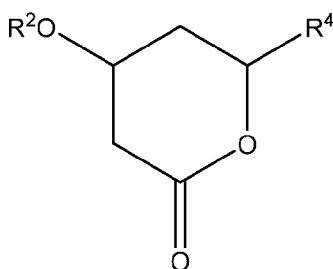
If

or a pharmaceutically acceptable salt thereof, wherein Y is a C₁₋₅alkylene linker, optionally substituted with one or more R⁷.

22. The compound of claim 21 wherein R⁷ is selected from the group consisting of optionally substituted C₆₋₁₈aryl and optionally substituted 5-18 membered heteroaryl.

23. The compound of claim 21 or 22 wherein Y is a C₁alkylene linker.

24. The compound of claim 1 having the structure of Formula Ig:



Ig

or a pharmaceutically acceptable salt thereof.

25. The compound of any one of claims 1-2 or 21-23, wherein R¹ is an optionally substituted C₁₋₈alkyl.

26. The compound of any one of claims 1-2, 21-23, or 25, wherein R¹ is a C₁₋₈alkyl optionally substituted with one or more R¹³, and wherein R¹³ is selected from the group consisting of halo, cyano, hydroxyl, C₁₋₆alkoxy, C₆₋₁₀aryloxy, sulfhydryl, haloC₁₋₆alkoxy, C₁₋₆alkylthio, C₆₋₁₀arylthio, and nitro.

27. The compound of claim 26, wherein R¹³ is selected from the group consisting of halo, hydroxyl, C₁₋₆alkoxy, and C₆₋₁₀aryloxy.

28. The compound of any one of claims 1-2, 21-23, or 25-27, wherein R¹ is -CH₂OH.

29. The compound of any one of claims 1-2 or 21-23, wherein R¹ is -COOR⁵.

30. The compound of any one of claims 1-2 or 21-23, wherein R¹ is an optionally substituted C₂₋₁₀alkoxyalkyl.

31. The compound of any one of claims 1-2, 21-23, or 30, wherein R^1 is a C_{2-10} alkoxyalkyl optionally substituted with one or more R^{14} , and wherein R^{14} is selected from the group consisting of halo, cyano, hydroxyl, C_{1-6} alkoxy, C_{6-10} aryloxy, sulfhydryl, halo C_{1-6} alkoxy, C_{1-6} alkylthio, C_{6-10} arylthio, and nitro.

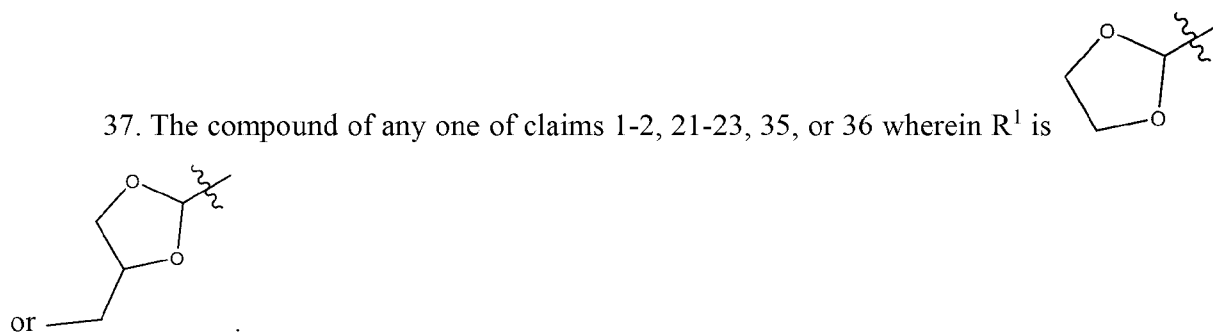
32. The compound of claim 31, wherein R^{14} is selected from the group consisting of halo, hydroxyl, C_{1-6} alkoxy, and C_{6-10} aryloxy.

33. The compound of any one of claims 1-2, 21-23, or 30-32, wherein R^1 is $-CH_2OCH_2OCH_2CH_3$.

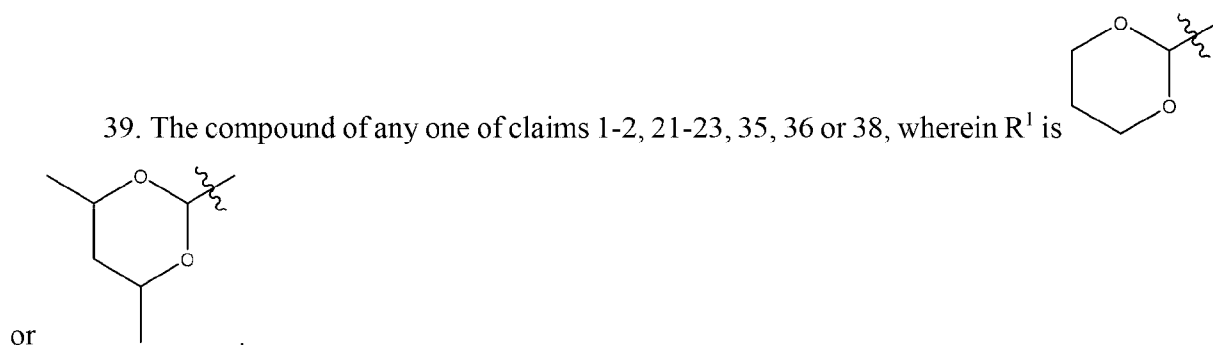
34. The compound of any one of claims 1-2, 21-23, or 30-32, wherein R^1 is $-CH(OCH_2CH_3)_2$.

35. The compound of any one of claims 1-2 or 21-23, wherein R^1 is a 3-12 membered heterocyclyl substituted with one or more R^{15} .

36. The compound of any one of claims 1-2, 21-23, 35, wherein R^{15} is selected from the group consisting of C_{1-6} alkyl, C_{3-7} carbocyclyl, C_{1-6} alkoxy, C_{6-18} aryl, and halo.



38. The compound of any one of claims 1-2, 21-23, 35, or 36 wherein R^1 is a 6 membered heterocyclyl.



40. The compound of any one of claims 1-20, wherein R^2 is H.

41. The compound of any one of claims 1-20 or 24, wherein R^2 is $-C(O)R^6$.

42. The compound of any one of claims 1-20 or 24, wherein R^2 is an optionally substituted C_{2-10} alkoxyalkyl.

43. The compound of any one of claims 1-20, 24, or 42, wherein R^2 is a C_{2-10} alkoxyalkyl optionally substituted with one or more R^{17} , and wherein R^{17} is selected from the group consisting of halo, cyano, hydroxyl, C_{1-6} alkoxy, C_{6-10} aryl, C_{6-10} aryloxy, sulfhydryl, halo C_{1-6} alkoxy, C_{1-6} alkylthio, C_{6-10} arylthio, and nitro.

44. The compound of claim 43, wherein R^{17} is selected from the group consisting of halo, hydroxyl, C_{1-6} alkoxy, C_{6-10} aryl, and C_{6-10} aryloxy.

45. The compound of any one of claims 1-20, 24, or 42-44, wherein R^2 is $-CH_2OCH_2CH_3$.

46. The compound of any one of claims 1-20, wherein R^3 is H.

47. The compound of any one of claims 1-20, wherein R^3 is $-C(O)R^8$.

48. The compound of any one of claims 1-20 or 47, wherein R^8 is an optionally substituted C_{1-6} alkyl.

49. The compound of any one of claims 1-20, 47, or 48 wherein R^8 is a C_{1-6} alkyl optionally substituted with one or more R^{18} , and wherein R^{18} is selected from the group consisting of halo, cyano, hydroxyl, C_{1-6} alkoxy, C_{6-10} aryl, C_{6-10} aryloxy, sulfhydryl, halo C_{1-6} alkoxy, C_{1-6} alkylthio, C_{6-10} arylthio, and nitro.

50. The compound of claim 49, wherein R^{18} is selected from the group consisting of halo, hydroxyl, C_{1-6} alkoxy, C_{6-10} aryl, and C_{6-10} aryloxy.

51. The compound of any one of claims 1-20 or 47-50, wherein R^8 is $-CH(CH_3)_2$.

52. The compound of any one of claims 1-20, wherein R^3 is an optionally substituted C_{2-10} alkoxyalkyl.

53. The compound of any one of claims 1-20 or 52, wherein R^3 is a C_{2-10} alkoxyalkyl optionally substituted with one or more R^{19} , and wherein R^{19} is selected from the group consisting of halo, cyano, hydroxyl, C_{1-6} alkoxy, C_{6-10} aryl, C_{6-10} aryloxy, sulfhydryl, halo C_{1-6} alkoxy, C_{1-6} alkylthio, C_{6-10} arylthio, and nitro.

54. The compound of claim 53, wherein R^{19} is selected from the group consisting of halo, hydroxyl, C_{1-6} alkoxy, C_{6-10} aryl, and C_{6-10} aryloxy.

55. The compound of any one of claims 1-20 or 52-54, wherein R^3 is $-CH_2OCH_2CH_3$.

56. The compound of any one of claims 1-23 or 25-39, wherein R^7 is an optionally substituted C_{1-8} alkyl.

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57. The compound of any one of claims 1-23, 25-39, or 56, wherein R^7 is a C_{1-8} alkyl optionally substituted with one or more R^{20} , and wherein R^{20} is selected from the group consisting of halo, cyano, hydroxyl, C_{1-6} alkoxy, C_{6-10} aryl, C_{6-10} aryloxy, sulfhydryl, halo C_{1-6} alkoxy, C_{1-6} alkylthio, C_{6-10} arylthio, and nitro.

58. The compound of claim 57, wherein R^{20} is selected from the group consisting of halo, hydroxyl, C_{1-6} alkoxy, C_{6-10} aryl, and C_{6-10} aryloxy.

59. The compound of any one of claims 1-23, 25-39, or 56-58, wherein R^7 is methyl.

60. The compound of any one of claims 1-23, 25-39, or 56-58, wherein R^7 is $-CH_2CH_2CH_2OH$.

61. The compound of any one of claims 1-23 or 25-39, wherein R^7 is oxo.

62. The compound of any one of claims 1-23 or 25-39, wherein R^7 is an optionally substituted C_{6-18} aryl.

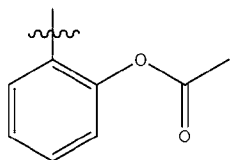
63. The compound of any one of claims 1-23, 25-39, or 62, wherein R^7 is a C_{6-18} aryl optionally substituted with one or more R^{21} .

64. The compound of claim 63, wherein R^{21} is selected from the group consisting of C_{1-6} alkyl, halo, cyano, hydroxyl, C_{1-6} alkoxy, halo C_{1-6} alkyl, halo C_{1-6} alkoxy, nitro, $-C(=O)NR^{22}R^{23}$, $-N(R^{24})C(=O)R^{25}$, $-C(=O)OR^{26}$, $-OC(=O)R^{27}$, and $-C(=O)R^{28}$, and wherein each of R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , and R^{28} is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 3-10 membered heterocyclyl.

65. The compound of claim 64, wherein each of R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , and R^{28} is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{6-10} aryl.

66. The compound of any one of claims 1-23, 25-39, or 62-65, wherein R^7 is a phenyl.

67. The compound of any one of claims 1-23, 25-39, or 62-66, wherein R^7 is



68. The compound of any one of claims 1-23 or 25-39, wherein R^7 is an optionally substituted 5-18 membered heteroaryl.

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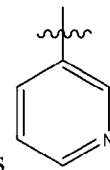
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69. The compound of any one of claims 1-23, 25-39, or 68, wherein R^7 is a 5-18 membered heteroaryl optionally substituted with one or more R^{29} .

70. The compound of claim 69, wherein R^{29} is selected from the group consisting of C_{1-6} alkyl, halo, cyano, hydroxyl, C_{1-6} alkoxy, halo C_{1-6} alkyl, halo C_{1-6} alkoxy, nitro, $-C(=O)NR^{30}R^{31}$, $-N(R^{32})C(=O)R^{33}$, $-C(=O)OR^{34}$, $-OC(=O)R^{35}$, and $-C(=O)R^{36}$, and wherein each of R^{30} , R^{31} , R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 3-10 membered heterocyclyl.

71. The compound of claim 70, wherein each of R^{30} , R^{31} , R^{32} , R^{33} , R^{34} , R^{35} , and R^{36} is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{6-10} aryl.

72. The compound of any one of claims 1-23, 25-39, or 68-71, wherein R^7 is a 6 membered heteroaryl.



73. The compound of any one of claims 1-23, 25-39, or 68-72, wherein R^7 is

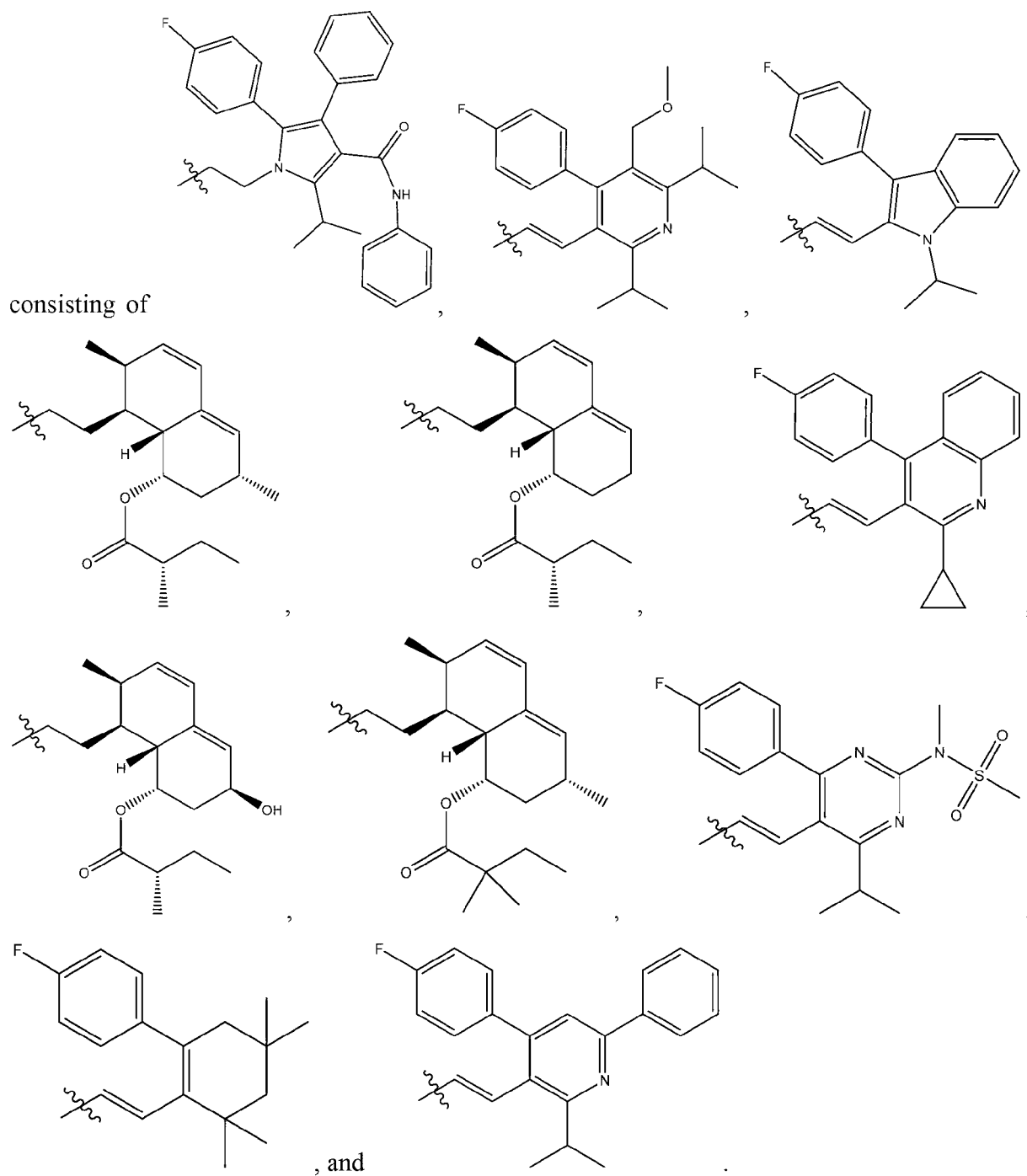
74. The compound of any one of claims 1-73, wherein R^4 is a fragment of a liver-targeting therapeutic agent or a fragment of a liver-activated therapeutic agent.

75. The compound of any one of claims 1-74, wherein R^4 is a fragment of a lipid-lowering therapeutic agent or a fragment of a cholesterol-biosynthesis-inhibiting therapeutic agent.

76. The compound of any one of claims 1-75, wherein R^4 is a fragment of a HMG-CoA reductase inhibitor.

77. The compound of any one of claims 1-76, wherein R^4 is a fragment of a statin.

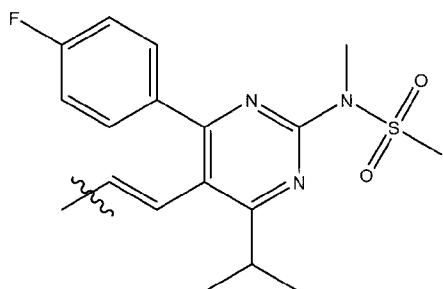
78. The compound of any one of claims 1-77, wherein R^4 is selected from the group



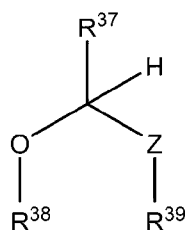
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79. The compound of any one of claims 1-78, wherein R^4 is



80. A compound having the structure of Formula II:



II

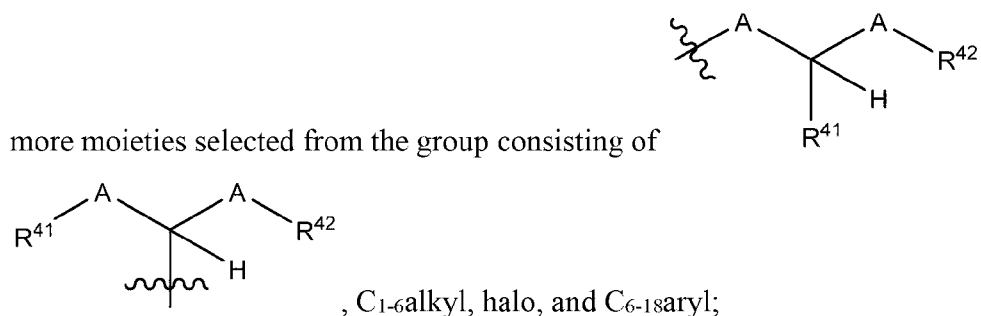
or a pharmaceutically acceptable salt thereof, wherein:

Z is O, S, or NR^{40} ,

R^{37} is selected from the group consisting of H, a fragment of a therapeutic agent, optionally substituted C_{1-8} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, optionally substituted C_{3-7} carbocyclyl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{6-18} aryl, 5-10 membered heteroaryl, and optionally substituted C_{2-10} alkoxyalkyl;

each of R^{38} and R^{39} is independently selected from the group consisting of a fragment of a therapeutic agent, optionally substituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, optionally substituted C_{3-7} carbocyclyl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C_{6-18} aryl, optionally substituted C_{2-10} alkoxyalkyl, and optionally substituted 5-10 membered heteroaryl, wherein at least one of R^{37} , R^{38} , and R^{39} is a fragment of a therapeutic agent,

wherein the fragment of a therapeutic agent is further optionally substituted with one or



each A is independently selected from O, S, and NR⁴³, provided that at least one A is O;

R⁴⁰ is independently selected from the group consisting of optionally substituted C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆heteroalkyl, optionally substituted C₃₋₇carbocyclyl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C₆₋₁₈aryl, optionally substituted C₂₋₁₀alkoxyalkyl, and optionally substituted 5-10 membered heteroaryl; and

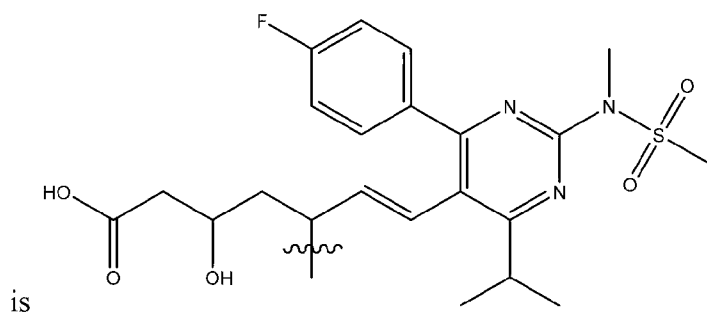
each of R⁴¹, R⁴², and R⁴³ is independently selected from the group consisting of H, optionally substituted C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆heteroalkyl, optionally substituted C₃₋₇carbocyclyl, optionally substituted 3-10 membered heterocyclyl, optionally substituted C₆₋₁₈aryl, optionally substituted C₂₋₁₀alkoxyalkyl, and optionally substituted 5-10 membered heteroaryl.

81. The compound claim 80, wherein Z is O.

82. The compound of claim 80 or 81, wherein R³⁷ is H.

83. The compound of any one of claims 80-82, wherein R³⁸ is the optionally substituted fragment of a therapeutic agent.

84. The compound of any one of claims 80-83, wherein the fragment of a therapeutic agent

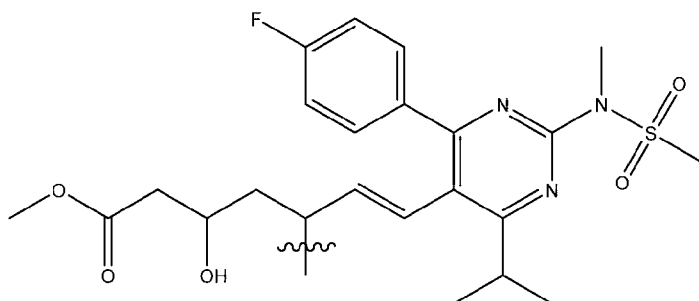


85. The compound of any one of claims 80-84, wherein R³⁹ is ethyl.

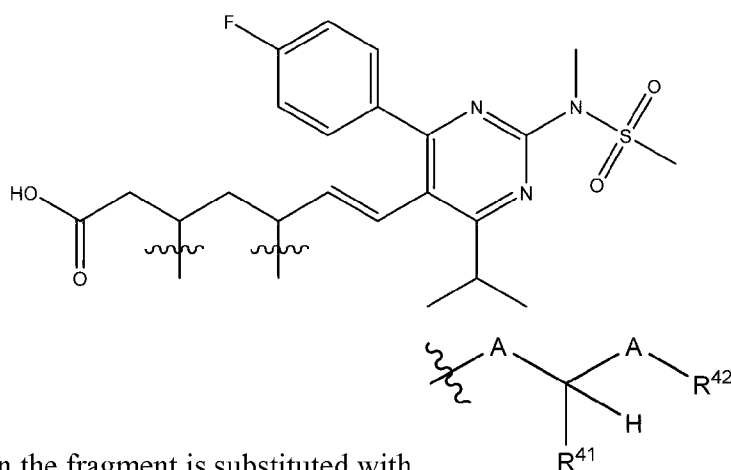
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86. The compound of any one of claims 83-85, wherein the fragment of a therapeutic agent is substituted with methyl, such that R^{38} has the structure

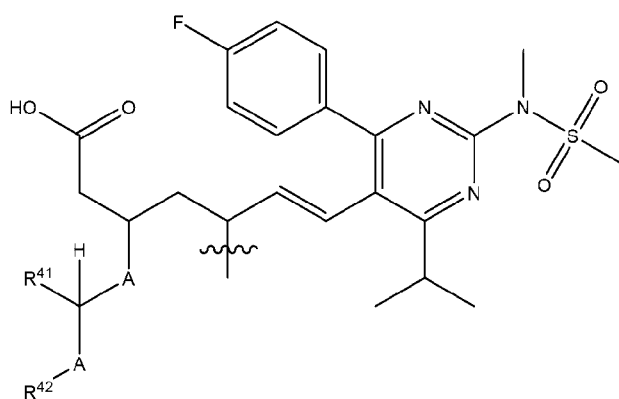


87. The compound of any one of claims 80-83, wherein the fragment of a therapeutic agent is:



wherein the fragment is substituted with

, such that R^{38} has the structure

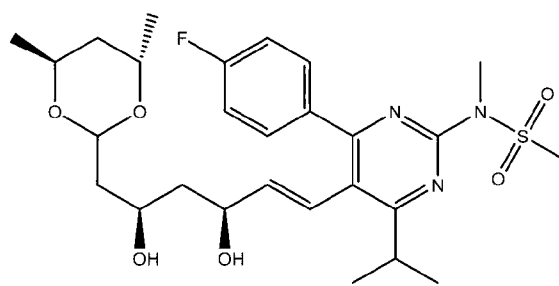
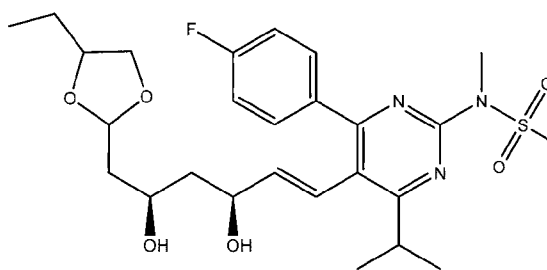
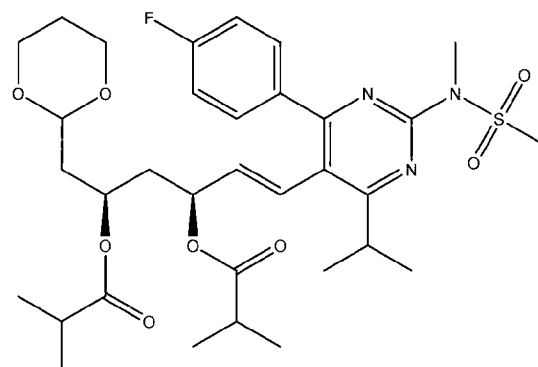
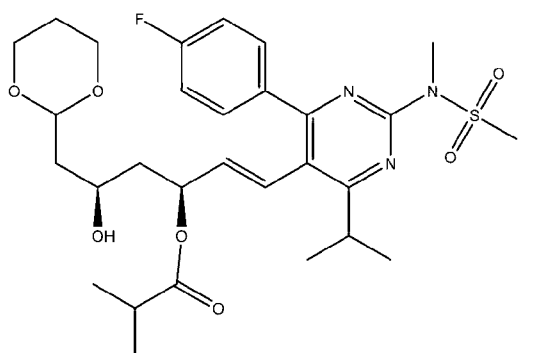
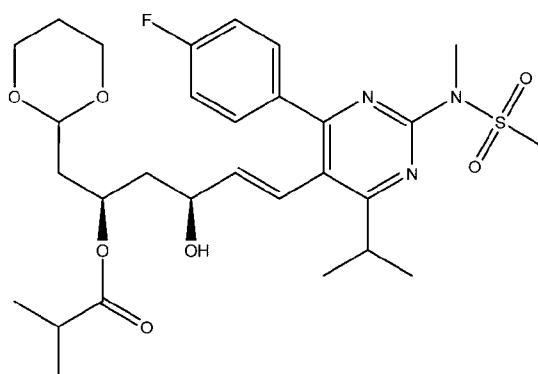
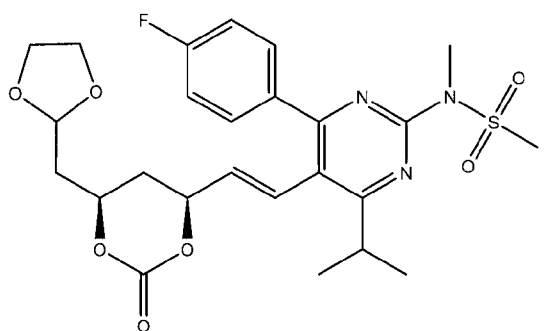
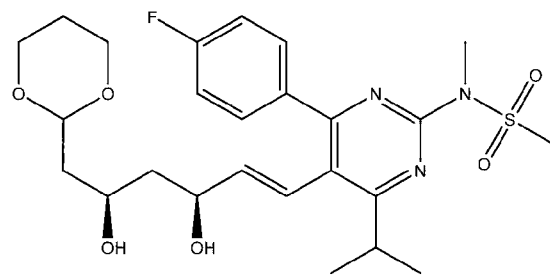
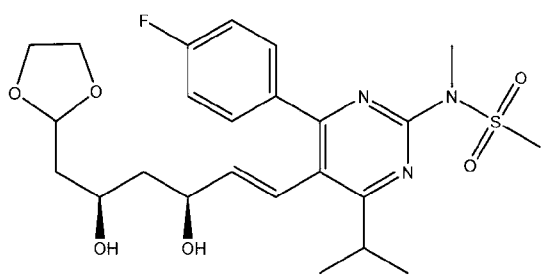


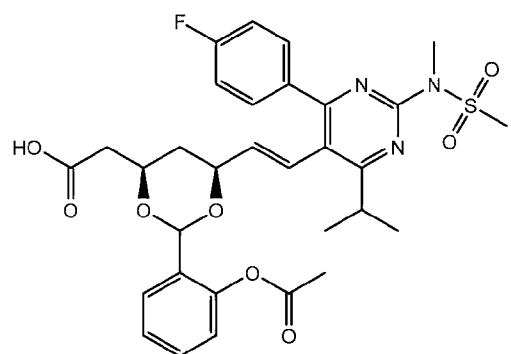
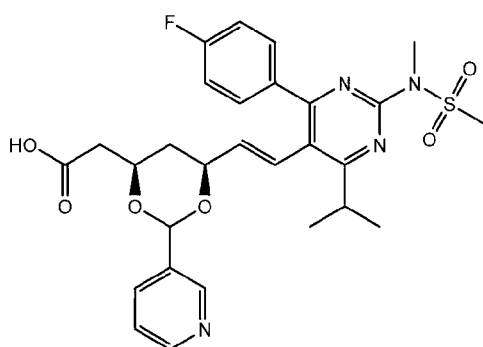
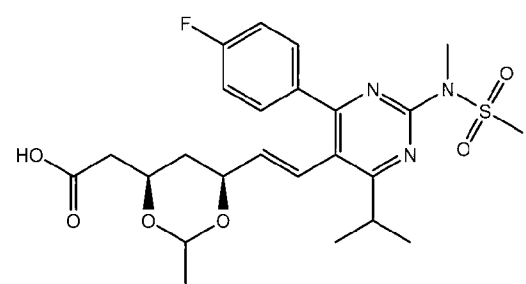
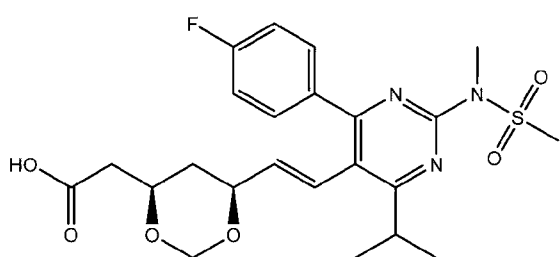
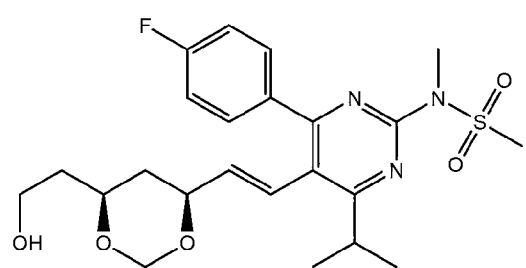
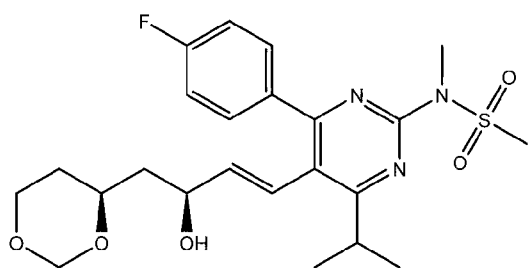
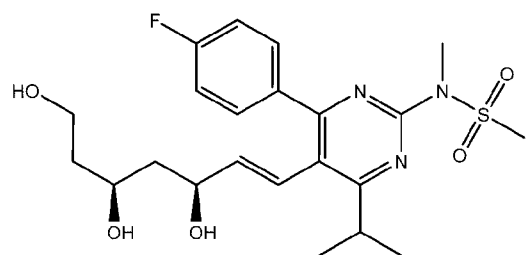
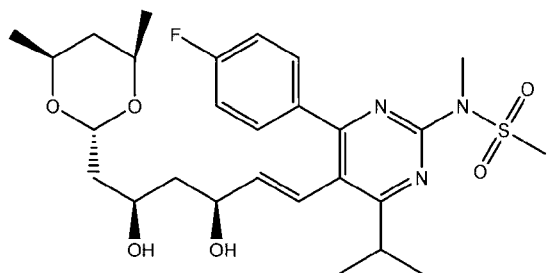
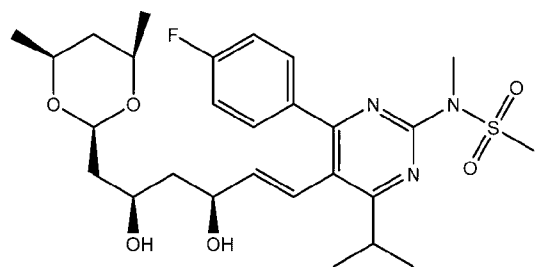
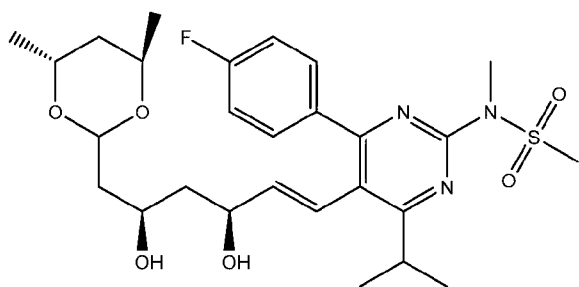
88. The compound of claim 87, wherein each A is O.

89. The compound of claim 87 or 88, wherein R^{41} is H.

90. The compound of any one of claims 87-89, wherein R^{42} is ethyl.

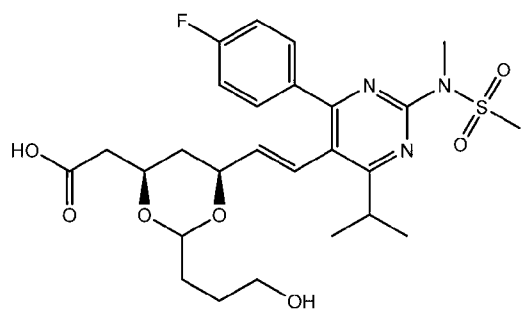
91. A compound selected from the group consisting of



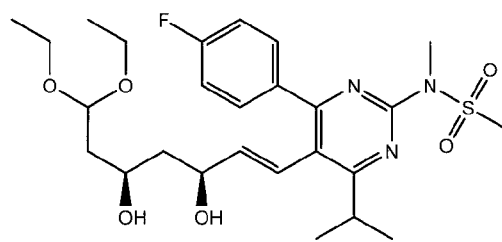


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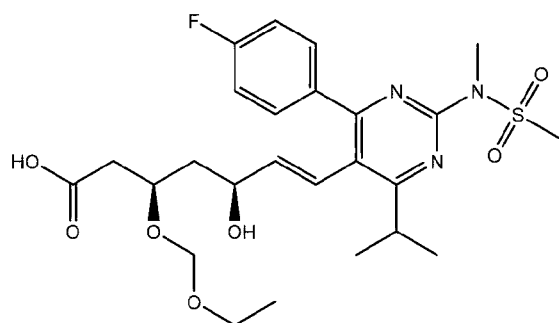
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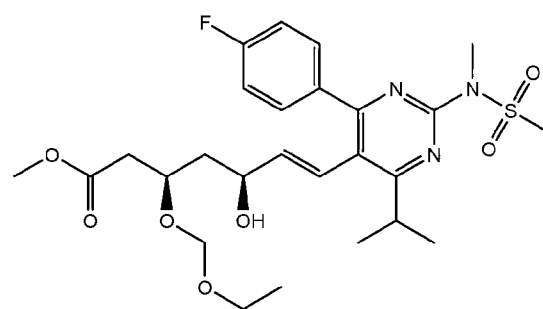
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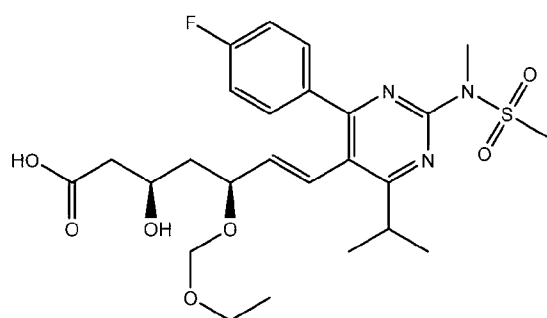
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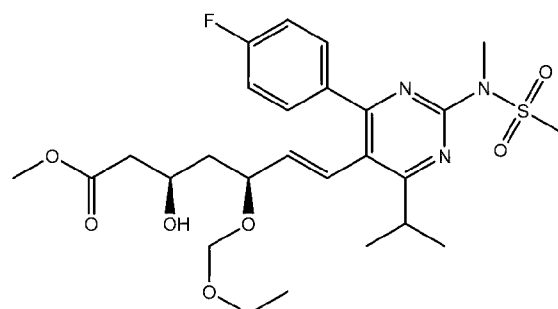
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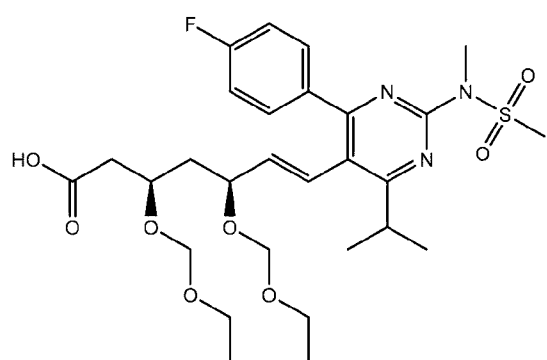
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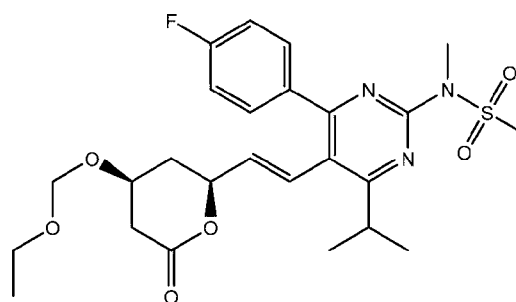
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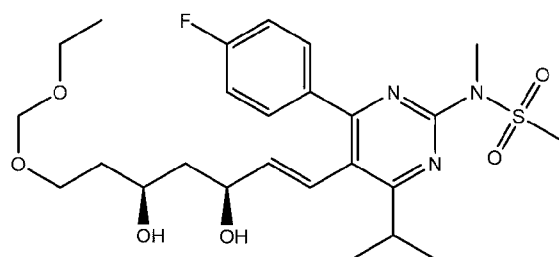
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, and



, or pharmaceutically acceptable salts thereof.

92. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of claims 1-91, and a pharmaceutically acceptable excipient.

93. The pharmaceutical composition of claim 92, further comprising an additional medicament.

94. The pharmaceutical composition of claim 93, wherein the additional medicament is selected from the group consisting of a cholesterol absorption inhibitor, a hypertension medicament, niacin, and aspirin.

95. The pharmaceutical composition of claim 93 or 94, wherein the cholesterol absorption inhibitor is ezetimibe.

96. The pharmaceutical composition of claim 93 or 94, wherein the hypertension medicament is selected from the group consisting of a diuretic, a beta-blocker, an angiotensin-converting enzyme inhibitor, an angiotensin receptor blocker, a calcium channel blocker, an alpha blocker, an alpha-2 receptor agonist, a combined alpha and beta-blocker, a central agonist, a peripheral adrenergic inhibitor, and a vasodilator.

97. The pharmaceutical composition of claim 93, 94, or 96, wherein the hypertension medicament is selected from the group consisting of acebutolol, alpha methyldopa, amiloride hydrochloride, amlodipine besylate, atenolol, benazepril hydrochloride, betaxolol, bepridil, bisoprolol fumarate, bumetanide, candesartan, captopril, carteolol hydrochloride, carvedilol, chlorthalidone, chlorothiazide, clonidine hydrochloride, diltiazem hydrochloride, doxazosin mesylate, enalapril maleate, eprosartan mesylate, felodipine, fosinopril sodium, furosemide, hydralazine hydrochloride, hydrochlorothiazide, guanabenz acetate, guanadrel, guanethidine monosulfate, guanfacine hydrochloride, indapamide, irbesartan, isradipine, labetalol hydrochloride, lisinopril, losartan potassium, methyldopa, metolazone, metoprolol succinate, metoprolol tartrate, minoxidil, moexipril, nadolol, nicardipine, nifedipine, nisoldipine, penbutolol sulfate, perindopril, pindolol, prazosin hydrochloride, propranolol hydrochloride, quinapril hydrochloride, ramipril, reserpine, telmisartan, terazosin hydrochloride, trandolapril, triamterene, solotol hydrochloride, spironolactone, timolol maleate, valsartan, and verapamil hydrochloride.

98. A method of treating a liver disease, disorder, or condition, comprising administering a compound of any one of claims 1-91 or administering a pharmaceutical composition of any one of claims 92-97, to a subject in need thereof.

99. The method of claim 98, wherein the liver disease, disorder, or condition involves the metabolism, storage, or homeostatic control of cholesterol, fatty acids, bile, triglycerides, plasma proteins, carrier proteins, lipoproteins, acute phase proteins, apolipoproteins, carbohydrates, hemostatic factors, fibrinolysis factors, thrombopoietin, insulin-like growth factor 1, hepcidin, angiotensinogen, vitamin A, vitamin D, vitamin B12, vitamin K, iron, copper, or catalase.

100. The method of claim 98 or 99, wherein the liver disease, disorder, or condition is selected from the group consisting of liver fibrosis, cirrhosis, hepatitis, alcoholic liver disease, fatty liver, liver cancer, hemochromatosis, Wilson's disease, primary sclerosing cholangitis, alpha 1-antitrypsin deficiency, hyperglycemia, hypoglycemia, and diabetes.

101. A method of treating a cardiovascular disease, disorder, or condition, comprising administering a compound of any one of claims 1-91 or administering a pharmaceutical composition of any one of claims 100-105, to a subject in need thereof.

102. The method of claim 101, wherein the cardiovascular disease, disorder, or condition is dyslipidemia or atherosclerosis.

103. The method of claim 101 or 102, wherein the cardiovascular disease, disorder, or condition is hyperlipidemia.

104. A method of altering blood lipid concentration, comprising administering a compound of any one of claims 1-91 or administering a pharmaceutical composition of any one of claims 92-97, to a subject in need thereof.

105. A method of inhibiting HMG-CoA reductase, comprising administering a compound of any one of claims 1-91 or administering a pharmaceutical composition of any one of claims 92-97, to a subject in need thereof.

106. The method of any one of claims 98-105, wherein the subject is a mammal.

107. The method of any one of claims 98-105, wherein the subject is a human.