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(54) Title: BENZYLOXY PHOSPH(ON)ATE COMPOUNDS

(57) Abstract: Provided herein are 2-substituted benzyloxy phosph(on)ate compounds, their preparation and their uses, such as treating liver diseases or conditions.

BENZYLOXY PHOSPH(ON)ATE COMPOUNDS

FIELD

[0001] The present disclosure relates to the field of chemistry and medicine. More specifically, the present disclosure relates to 2-substituted benzyloxy phosph(on)ate compounds, their preparation and their uses. In some embodiments, such compounds are useful to effectively deliver certain pharmaceutical agents to the target cells or organs.

BACKGROUND

[0002] The following description of the background is provided to aid in understanding the invention, but is not admitted to be, or to describe, prior art.

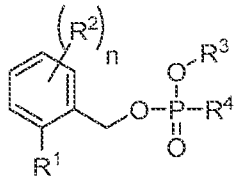
[0003] Phosph(on)ates are important compound class that can be used as medical agents to improve human health. Many types of phosph(on)ate derivative compounds are designed as prodrugs to facilitate oral absorption and delivery of the active to the target cells or organs. Synthetic nucleotides and their derivatives are widely used as antiviral or anticancer agents. Prodrug technologies have been used to improve the nucleotides molecular properties to enable the nucleotides to be more bioavailable, including improving oral bioavailability. Thus, new compounds with bioavailability enhancement may significantly improve the therapeutic benefits of nucleos(t)ide based therapies.

SUMMARY

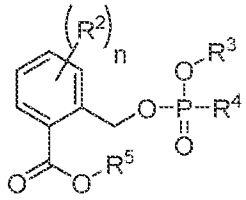
[0004] Novel 2-substituted benzyloxy phosph(on)ate compounds, their preparation and their uses are described. Some embodiments are novel 2-substituted benzyloxy phosph(on)ate compounds that are delivered orally to the liver and other organs where the compounds provide a therapeutic benefit. Additional embodiments include novel 2-substituted benzyloxy phosph(on)ate compounds that treat a disease, disorder or condition including: certain mitochondrial DNA depletion syndromes, hepatitis, cancer, liver fibrosis, fatty liver, malaria, viral infection, parasitic infection, diabetes, hyperlipidemia, atherosclerosis, obesity, dyslipidemia, hyperglycemia, a hormonal condition, HIV, and various types of cancer.

Another aspect includes the use of the 2-substituted benzyloxy phosph(on)ate compounds to treat diseases that benefit from enhanced drug distribution to the target cells or organs. In another aspect, the 2-substituted benzyloxy phosph(on)ate compounds are used to increase the pharmacological or clinical activity of certain classes of pharmaceutical compounds such as nucleotide derived analog compounds. In some embodiments, the 2-substituted benzyloxy phosph(on)ate compounds are useful in the more efficient oral delivery of the nucleotide or its derivative compounds to the liver and/or other target organs. Some additional embodiments relate to a method of making the 2-substituted benzyloxy phosph(on)ate compounds.

[0005] Some embodiments provided herein include a compound of Formula I or Formula Ia:



(I),



(Ia),

or a stereoisomer or a pharmaceutically acceptable salt thereof,

wherein R^1, R^2, R^3, R^4, R^5, and n have any of the values described herein.

[0006] Some embodiments relate to a pharmaceutical composition comprising one of the above compounds and a pharmaceutically acceptable excipient(s).

[0007] Some embodiments relate to a method of treating a disease, disorder or condition comprising administering an effective amount of the above compounds.

[0008] In some embodiments, the disease, disorder or condition is a disease, disorder or condition of the liver.

[0009] In some embodiments, the disease, disorder or condition is a non-liver disease, disorder or condition.

[0010] Some embodiments relate to a method of treating a liver disease comprising administering an effective amount of one of the above compounds to a subject in need thereof.

[0011] Some embodiments relate to a method of treating a non-liver disease comprising administering an effective amount of a combination of one of the above compounds to a subject in need thereof.

[0012] Some embodiments further comprise administering an effective amount of at least one additional therapeutic agent to the subject in need thereof.

[0013] In some embodiments, the subject is a mammal.

[0014] In some embodiments, the subject is human.

[0015] Some embodiments relate to a method of intervening in a molecular pathway or modulating a target in a cell comprising contacting the cell with one of the above compounds.

[0016] In some embodiments, the cell is in vivo.

[0017] In some embodiments, the cell is ex vivo.

[0018] In some embodiments, the cell is a hepatocyte.

[0019] In some embodiments, the cell is a mammalian cell.

[0020] In some embodiments, the cell is a human cell.

[0021] Some embodiments of the compounds, compositions, and methods provided herein include a pharmaceutical composition comprising one of the compounds provided herein and a pharmaceutically acceptable excipient(s).

[0022] Some embodiments of the compounds, compositions, and methods provided herein include a method of treating a disease or condition of the liver in a subject comprising administering an effective amount of one of the compounds provided herein to a subject in need thereof.

[0023] Some embodiments of the compounds, compositions, and methods provided herein include a method of treating a disease or condition in a subject comprising administering an effective amount of one of the compounds provided herein to a subject in need thereof.

[0024] Some embodiments also include administering an effective amount of one or more additional therapeutic agents to the subject in need thereof.

[0025] In some embodiments, the subject is a mammal.

[0026] In some embodiments, the subject is a human.

[0027] Some embodiments also include the use of one of the compounds provided herein in combination with an additional therapeutic agent.

[0028] Some embodiments also include the use of one or more of the compounds provided herein in combination with an additional therapeutic agent.

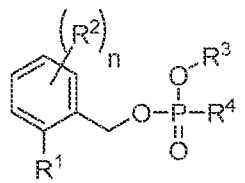
[0029] Some embodiments of the compounds, compositions, and methods provided herein include one or more of the compositions provided herein for use in the preparation of a medicament for treating a disease or condition in the liver or a disease or condition in which the physiological or pathogenic pathways involve the liver.

[0030] Some embodiments of the compounds, compositions, and methods provided herein include one or more of the compositions provided herein for use in the preparation of a medicament for treating a non-liver disease or condition.

DETAILED DESCRIPTION

[0031] The present embodiments are directed to compositions and methods related to novel 2-substituted benzyloxy phosph(on)ate compounds, their preparation and their uses. In some embodiments, the novel 2-substituted benzyloxy phosph(on)ate compounds facilitate delivery into cells of nucleotide or nucleotide derivative or nucleotide analog agents.

[0032] These 2-substituted benzyloxy phosph(on)ate compounds and their stereoisomers and pharmaceutically acceptable salts are represented by Formula I or Formula Ia:



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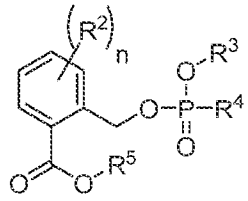
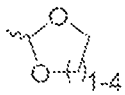
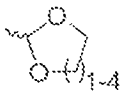


(Ia),

or a stereoisomer or a pharmaceutically acceptable salt thereof,

wherein R^1, R^2, R^3, R^4, R^5, and n have any of the values described herein.

[0033] In some embodiments, R^1 is selected from a group of $-CH(OR^6)_2$, $-C(O)N(R^6)_2$, $-CH_2OR^7$, CH_2SR^7, $-CH_2N(R^7)_2$, $-CH_2OCH_2OR^6$, $-COOR^5$, and .

[0034] In some embodiments, R^1 is selected from a group of $-CH(OR^6)_2$, $-C(O)N(R^6)_2$, and .

[0035] In some embodiments, each R^2 is independently selected from a group of halogen, an optionally substituted alkyl, and an optionally substituted alkyloxy.

[0036] In some embodiments, R^3 is selected from a group of H, an optionally substituted aryl, and therapeutic or diagnostic moiety.

[0037] In some embodiments, R^3 is selected from the group consisting of H and an optionally substituted aryl.

[0038] In some embodiments, R^3 is an unsubstituted aryl.

[0039] In some embodiments, R^3 is phenyl.

[0040] In some embodiments, R^4 is selected from a nucleoside or analog thereof or a nucleoside base or analog thereof, or alternatively, R^4 and R^3 together with the atoms to which they are attached form a monocyclic heterocyclyl substituted with a nucleoside base or analog thereof, or R^4 and R^5 together with the atoms to which they are attached form a heterocyclyl substituted with a nucleoside base or analog thereof.

[0041] In some embodiments, the nucleoside or analog thereof is a therapeutically active fragment of an agent such as abacavir, aciciovir, acyclovir, cytarabine, didanosine, edoxudine, emtricitabine, entecavir, galidesivir, ganciclovir, gemcitabine, ibacitabine, idoxuridine, inosine, lamivudine, maribavir, molnupiravir, penciclovir, remdesivir, ribavirin, stavudine, telbivudine, trifluridine, vidarabine, zalcitabine, and zidovudine; or in some embodiments the nucleoside or analog thereof is a therapeutically active fragment of an agent such as adefovir, brincidofovir, cidofovir, and tenofovir.

[0042] In some embodiments, R^5 is selected from a group of H and an optionally substituted alkyl.

[0043] In some embodiments, R^5 is an unsubstituted C_1-C_6 alkyl.

[0044] In some embodiments, R^5 is ethyl.

[0045] In some embodiments, R^5 is *i*-propyl.

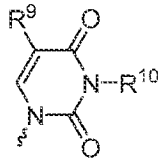
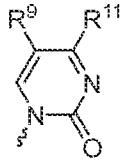
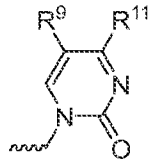
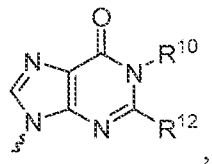
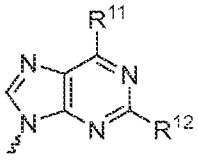
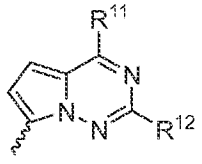
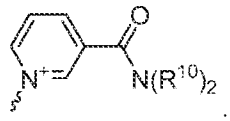
[0046] In some embodiments, R^5 is H.

[0047] In some embodiments, each R^6 is independently an optionally substituted alkyl.

[0048] In some embodiments, R^7 is selected from a group of H, an optionally substituted C_1-C_{10} acyl, an optionally substituted C_1-C_{10} alkyl-OC(O)-, an optionally substituted ($C_{6\text{-}10}$ aryl)-C(O)-, and an optionally substituted ($C_{6\text{-}10}$ aryl)-OC(O)-.

[0049] In some embodiments, n is 0, 1, 2, or 3.

[0050] In some embodiments, n is 1.

[0051] In some embodiments, the nucleoside base or analog thereof is selected from the group consisting of , , , , , , and .

[0052] In some embodiments, R^9 is H, halo, or an optionally substituted C_1-C_{10} alkyl.

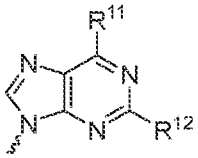
[0053] In some embodiments, R^{10} is selected from the group consisting of H, an optionally substituted C_1-C_{10} alkyl, an optionally substituted C_1-C_{10} alkyl-OCH_2-, an optionally substituted C_1-C_{10} alkyl-$NHCH_2$-, an optionally substituted C_1-C_{10} acyl, an optionally substituted C_1-C_{10} alkyl-OC(O)-, an optionally substituted ($C_{6\text{-}10}$ aryl)-CH_2OCH_2-, an optionally substituted ($C_{6\text{-}10}$ aryl)-OCH_2-, an optionally substituted ($C_{6\text{-}10}$ aryl)-C(O)-, and an optionally substituted ($C_{6\text{-}10}$ aryl)-OC(O)-.

[0054] In some embodiments, R^{11} is selected from the group consisting of OH, NH_2, $NHOR^7$, an optionally substituted C_1-C_{10} alkyloxy, an optionally substituted C_1-C_{10} alkylamino, an optionally substituted C_1-C_{10} acyloxy, an optionally substituted C_1-C_{10} acylamino, an optionally substituted C_1-C_{10} alkyl-OC(O)NH-, an optionally substituted ($C_{6\text{-}10}$

aryl)-C(O)O-, an optionally substituted (C_{6-10} aryl)-C(O)NH-, an optionally substituted (C_{6-10} aryl)-OC(O)NH-, an optionally substituted C_1-C_{10} alkyl-OCH_2NH-, and an optionally substituted C_1-C_{10} alkyl-OCH_2O-.

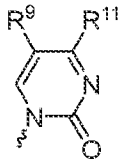
[0055] In some embodiments, R^{12} is selected from a group of H, NH_2, an optionally substituted C_1-C_{10} alkylamino, an optionally substituted C_1-C_{10} acylamino, an optionally substituted C_1-C_{10} alkyl-OC(O)NH-, an optionally substituted (C_{6-10} aryl)-C(O)NH-, an optionally substituted (C_{6-10} aryl)-OC(O)NH-, and an optionally substituted C_1-C_{10} alkyl-OCH_2NH-.

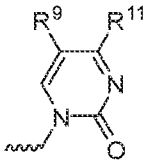
[0056] In some embodiments, the nucleoside base or analog thereof is



[0057] In some embodiments, R^{11} is NH_2.

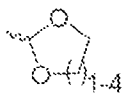
[0058] In some embodiments, R^{12} is H.

[0059] In some embodiments, the nucleoside base or analog thereof is .

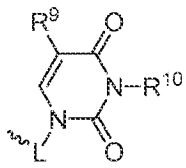
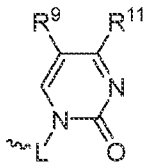
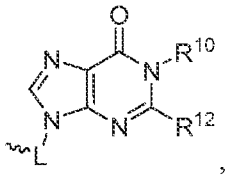
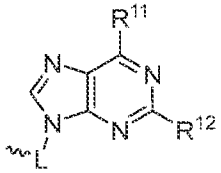
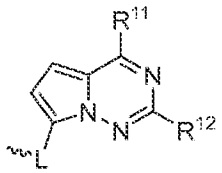
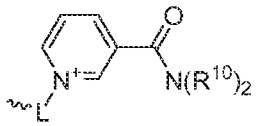
[0060] In some embodiments, the nucleoside base or analog thereof is .

[0061] In some embodiments, R^9 is H.

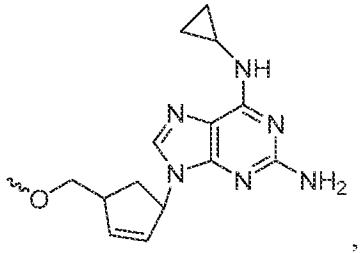
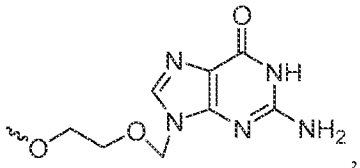
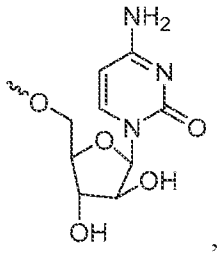
[0062] In some embodiments, R^{11} is NH_2.

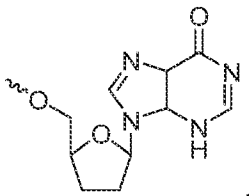
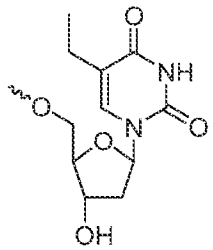
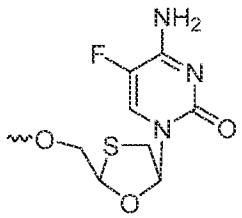
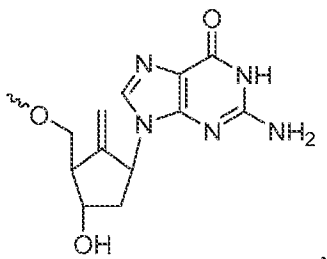
[0063] In some embodiments, R^1 is selected from a group of -$CH(OR^6)_2$, -$C(O)N(R^6)_2$, and .

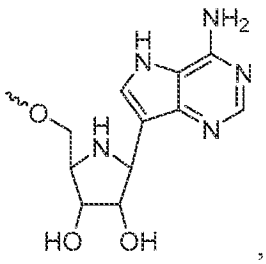
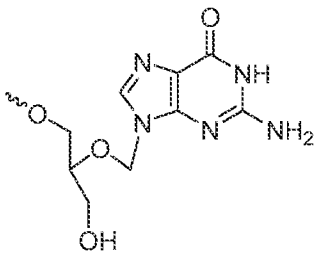
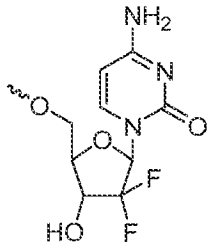
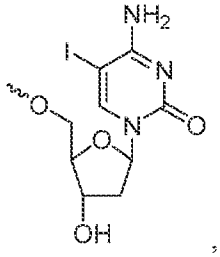
[0064] In some embodiments, R^2 is H.

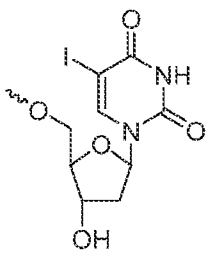
[0065] In some embodiments, the nucleoside base or analog thereof is selected from the group consisting of , , , , , and , wherein L is a sugar or sugar analog.

[0066] In some embodiments, the nucleoside base or analog thereof is selected from the group consisting of:

, , ,

, , , ,

, , , ,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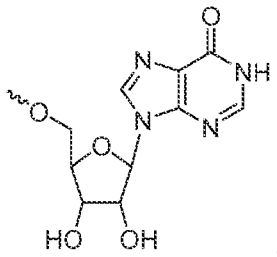
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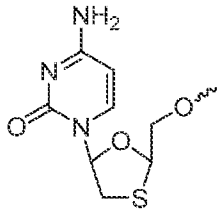
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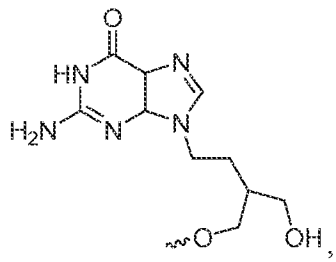
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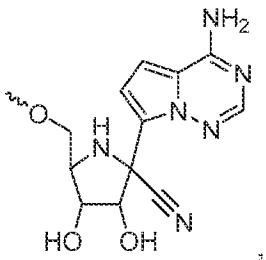
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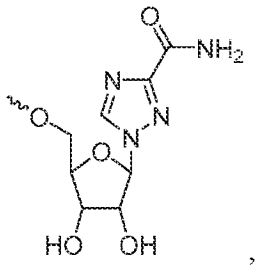
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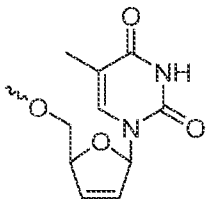
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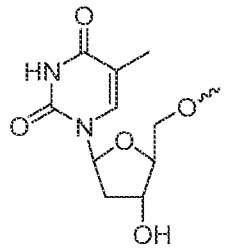
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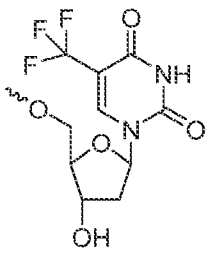
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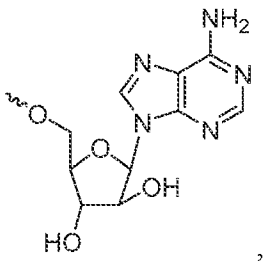
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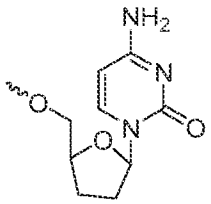
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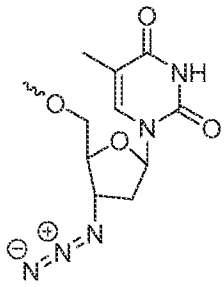
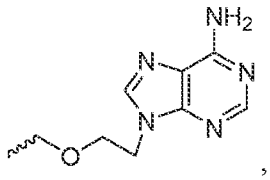


[0067] In some embodiments, the nucleoside base or analog thereof is selected from the group consisting of: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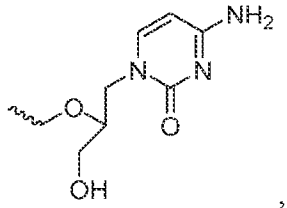
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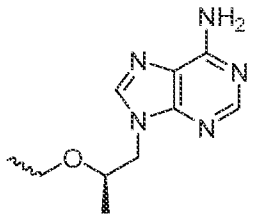
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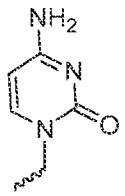
[0068] In some embodiments, the nucleoside base or analog thereof is

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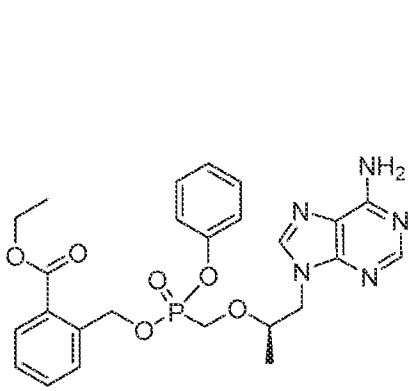
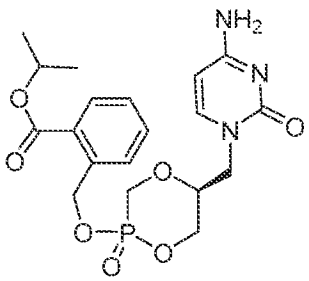
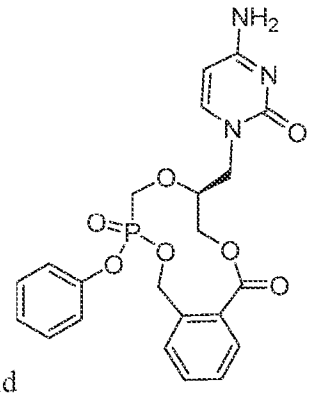
[0069] In some embodiments, the compound is selected from the group consisting of:

, and .

[0070] In some embodiments, the 2-substituted benzyloxy phosph(on)ate compounds of Formula I and Ia are substrates of liver enzymes such as cytochrome p450 isozymes CYP3As (a family of monooxygenase), dehydrogenases, esterases, and amidases.

[0071] In some embodiments, the compound is activated within a cell upon cleavage of the prodrug moieties, releasing an active form of the compound.

[0072] In some embodiments, due to the liver-targeting nature of the 2-substituted benzyloxy phosph(on)ate compounds of Formula I and Ia, the compounds are used to treat diseases that benefit from enhanced drug distribution to the liver and like tissues and cells, including but not limited to diseases of the liver.

[0073] In some embodiments, the disclosed compounds are used to improve pharmacokinetic properties such as prolonging half-life or enhancing absorption of a nucleotide or its analog. In addition, the disclosed methodology can be used to achieve sustained delivery of a biologically relevant nucleotide or its analog. Due to the pharmacokinetic property enhancement of the 2-substituted benzyloxy phosph(on)ate compounds of Formula I and Ia, the compounds are used to treat diseases that benefit from enhanced drug properties. In some embodiments, a method of making these compounds is described.

[0074] Certain compounds of Formula I and Ia have asymmetric centers where the stereochemistry may be unspecified, and the diastereomeric mixtures of these compounds are included, as well as the individual stereoisomers when referring to a compound of Formula I and Ia generally.

[0075] In some embodiments, an effective amount of a disclosed compound is used to treat a disease, disorder, or condition in a subject in need thereof.

[0076] Some embodiments of the compounds, compositions and methods provided herein include a pharmaceutical composition comprising a compound provided herein and a pharmaceutically acceptable carrier.

[0077] Some embodiments also include administering an effective amount of a second or multiple therapeutic agents in combination with a compound provided herein to the subject in need thereof.

[0078] In some embodiments, the subject is a mammal.

[0079] In some embodiments, the subject is human.

[0080] Some embodiments of the compounds, compositions and methods provided herein include a method of testing a compound in a cell comprising contacting the cell with the disclosed compounds.

[0081] Some embodiments of the compounds, compositions and methods provided herein include use of a compound provided herein in the treatment of a disease of the liver.

[0082] Some embodiments include the use of a compound provided herein in combination with additional therapeutic agent(s) for the treatment of a disease of the liver.

[0083] In some embodiments, the compounds provided herein are used in the preparation of a medicament for treating a liver disease.

[0084] In some embodiments, the compounds provided herein are used in a method of treating a liver disease comprising administering an effective amount of the compound to a subject in need thereof.

[0085] Some embodiments of the compounds, compositions and methods provided herein include use of a compound provided herein in the treatment of a non-liver disease.

[0086] Some embodiments include the use of a compound provided herein in combination with additional therapeutic agent(s) for the treatment of a non-liver disease.

[0087] 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.

[0088] 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.

[0089] 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

[0090] In accordance with the present disclosure and as used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the subject matter claimed. In this application, the use of the singular includes the plural unless specifically stated otherwise. In this application, the use of "or" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "includes," and "included" is not limiting.

[0091] As used herein, ranges and amounts can be expressed as "about" a particular value or range. "About" also includes the exact amount. Hence "about 10%" means "about 10%" and also "10%."

[0092] As used herein, "optional" or "optionally" means that the subsequently described event or circumstance does or does not occur, and that the description includes

instances where the event or circumstance occurs and instances where it does not. For example, an optionally substituted group means that the group is unsubstituted or is substituted.

[0093] As used herein, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to a composition comprising "a therapeutic agent" includes compositions with one or a plurality of therapeutic agents.

[0094] 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 "C_1 to C_4 alkyl" or "C_{1-4} alkyl" group refers to all alkyl groups having from 1 to 4 carbons, that is, CH_3-, CH_3CH_2-, $CH_3CH_2CH_2$-, $(CH_3)_2CH$-, $CH_3CH_2CH_2CH_2$-, $CH_3CH_2CH(CH_3)$- and $(CH_3)_3C$-.

[0095] 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 "C_1-C_4 alkyl" or similar designations. By way of example only, "C_1-C_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, iso-propyl, 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.

[0096] 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 C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), C_3-C_7-carbocyclyl-C_1-C_6-alkyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6

haloalkoxy), 3-10 membered heterocycyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), 3-10 membered heterocycyl-C_1-C_6-alkyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), aryl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), aryl(C_1-C_6)alkyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), 5-10 membered heteroaryl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), 5-10 membered heteroaryl(C_1-C_6)alkyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, cyano, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkoxy(C_1-C_6)alkyl (i.e., ether), aryloxy (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), C_3-C_7 carbocyclyloxy (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), 3-10 membered heterocyclyl-oxy (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), 5-10 membered heteroaryl-oxy (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), C_3-C_7-carbocyclyl-C_1-C_6-alkoxy (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), 3-10 membered heterocyclyl-C_1-C_6-alkoxy (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), aryl(C_1-C_6)alkoxy (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), 5-10 membered heteroaryl(C_1-C_6)alkoxy (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), sulfhydryl (mercapto), halo(C_1-C_6)alkyl (e.g., $-CF_3$), halo(C_1-C_6)alkoxy (e.g., $-OCF_3$), C_1-C_6 alkylthio, arylthio (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), C_3-C_7 carbocyclylthio (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), 3-10 membered heterocyclyl-thio (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), 5-10 membered heteroaryl-thio (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), C_3-C_7-carbocyclyl-C_1-C_6-alkylthio (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), 3-10 membered heterocyclyl-C_1-C_6-alkylthio (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), aryl(C_1-C_6)alkylthio (optionally substituted with halo,

C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), 5-10 membered heteroaryl(C_1-C_6)alkylthio (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), amino, amino(C_1-C_6)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.

[0097] As used herein, "acyl" refers to –C(=O)**R**, wherein **R** is 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 heterocycyl, as defined herein. Non-limiting examples include formyl, acetyl, propanoyl, benzoyl, and acryl.

[0098] An "heteroacyl" refers to –C(=O)**R**, wherein **R** is a C_{1-6} heteroalkyl.

[0099] An "alkyloxymethylene" refers to –CH_2O**R**, wherein **R** is a C_{1-6} alkyl, or heteroalkyl, all optionally substituted.

[0100] An "O-carboxy" group refers to a "-OC(=O)**R**" group in which **R** is selected from 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 heterocycyl, as defined herein.

[0101] A "C-carboxy" group refers to a "-C(=O)O**R**" group in which **R** is selected from 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, as defined herein. A non-limiting example includes carboxyl (i.e., -C(=O)OH).

[0102] A "cyano" group refers to a "-CN" group.

[0103] A "cyanato" group refers to an "-OCN" group.

[0104] An "isocyanato" group refers to a "-NCO" group.

[0105] A "thiocyanato" group refers to a "-SCN" group.

[0106] An "isothiocyanato" group refers to an " -NCS" group.

[0107] A "sulfinyl" group refers to an "-S(=O)**R**" group in which **R** is selected from 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 heterocycyl, as defined herein.

[0108] A "sulfonyl" group refers to an "-SO_2**R**" group in which **R** is selected from 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 heterocycyl, as defined herein.

[0109] An "S-sulfonamido" group refers to a "-$SO_2N\mathbf{R_A}\mathbf{R_B}$" group in which $\mathbf{R_A}$ and $\mathbf{R_B}$ are each independently selected from 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 heterocycyl, as defined herein.

[0110] An "N-sulfonamido" group refers to a "-$N(\mathbf{R_A})SO_2\mathbf{R_B}$" group in which $\mathbf{R_A}$ and $\mathbf{R_B}$ are each independently selected from 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 heterocycyl, as defined herein.

[0111] An "O-carbamyl" group refers to a "-$OC(=O)N\mathbf{R_A}\mathbf{R_B}$" group in which $\mathbf{R_A}$ and $\mathbf{R_B}$ are each independently selected from 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 heterocycyl, as defined herein.

[0112] An "N-carbamyl" group refers to an "-$N(\mathbf{R_A})C(=O)O\mathbf{R_B}$" group in which $\mathbf{R_A}$ and $\mathbf{R_B}$ are each independently selected from 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 heterocycyl, as defined herein.

[0113] An "O-thiocarbamyl" group refers to a "-$OC(=S)N\mathbf{R_A}\mathbf{R_B}$" group in which $\mathbf{R_A}$ and $\mathbf{R_B}$ are each independently selected from 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 heterocycyl, as defined herein.

[0114] An "N-thiocarbamyl" group refers to an "-$N(\mathbf{R_A})C(=S)O\mathbf{R_B}$" group in which $\mathbf{R_A}$ and $\mathbf{R_B}$ are each independently selected from 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 heterocycyl, as defined herein.

[0115] A "C-amido" group refers to a "-$C(=O)N\mathbf{R_A}\mathbf{R_B}$" group in which $\mathbf{R_A}$ and $\mathbf{R_B}$ are each independently selected from 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 heterocycyl, as defined herein each optionally substituted with one or more substituents selected from the group

consisting of –OH, C_{1-6} alkyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, 3-10 membered heterocycyl, C_{1-6} alkyl optionally substituted with C_{1-6} alkoxy or –OH and C_{1-6} alkoxy optionally substituted with C_{1-6} alkoxy or –OH.

[0116] An "N-amido" group refers to a "-N($\mathbf{R_A}$)C(=O)$\mathbf{R_B}$" group in which $\mathbf{R_A}$ and $\mathbf{R_B}$ are each independently selected from 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 heterocycyl, as defined herein each optionally substituted with one or more substituents selected from the group consisting of –OH, C_{1-6} alkyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, 3-10 membered heterocycyl, C_{1-6} alkyl optionally substituted with C_{1-6} alkoxy or –OH and C_{1-6} alkoxy optionally substituted with C_{1-6} alkoxy or –OH.

[0117] An "amino" group refers to a "-N$\mathbf{R_A}\mathbf{R_B}$" group in which $\mathbf{R_A}$ and $\mathbf{R_B}$ are each independently selected from 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 heterocycyl, as defined herein. A non-limiting example includes free amino (i.e., $-NH_2$).

[0118] An "aminoalkyl" group refers to an amino group connected via an alkylene group.

[0119] An "alkoxyalkyl" group refers to an alkoxy group connected via an alkylene group, such as a "C_{2-8} alkoxyalkyl" and the like.

[0120] The term "acyloxy" refers to -OC(O)R where R is alkyl.

[0121] The term "alkoxy" or "alkyloxy" refers to OR where R is alkyl, or heteroalkyl, all optionally substituted.

[0122] The term "carboxyl" refers to a C(O)OH.

[0123] The term "oxo" refers to an =O group.

[0124] The term "halogen" or "halo" refers to F (fluoro), Cl (chloro), Br (bromo) and I (iodo).

[0125] The term "haloalkyl" refer to alkyl groups containing at least one halogen, in a further aspect are 1 to 3 haloatoms. Suitable haloatoms include F, Cl, and Br.

[0126] The term "haloacyl" refer to -C(O)-haloalkyl groups.

[0127] The term "alkenyl" refers to unsaturated groups which have 2 to 12 atoms and contain at least one carbon carbon double bond and includes straight chain, branched chain

and cyclic groups. Alkenyl groups may be optionally substituted. Suitable alkenyl groups include allyl.

[0128] The term "alkynyl" refers to unsaturated groups which have 2 to 12 atoms and contain at least one carbon carbon triple bond and includes straight chain, branched chain and cyclic groups. Alkynyl groups may be optionally substituted. Suitable alkynyl groups include ethynyl.

[0129] 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 "C_{6-10} aryl," "C_6 or C_{10} aryl," or similar designations. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, azulenyl, and anthracenyl.

[0130] 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. Heteroaryl groups may be optionally substituted. Examples of heteroaryl groups include, but are not limited to, aromatic C3-8 heterocyclic groups comprising one oxygen or sulfur atom or up to four nitrogen atoms, or a combination of one oxygen or sulfur atom and up to two nitrogen atoms, and their substituted as well as benzo- and pyrido-fused derivatives, for example, connected via one of the ring-forming carbon atoms. In some embodiments, heteroaryl groups are optionally substituted with one or more substituents, independently selected from halo, hydroxy, amino, cyano, nitro, alkylamido, acyl, C_{1-6}-alkoxy, C_{1-6}-alkyl, C_{1-6}-hydroxyalkyl, C1-6-aminoalkyl, C1-6-

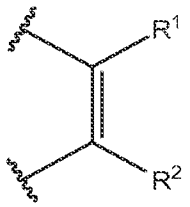
alkylamino, alkylsulfenyl, alkylsulfinyl, alkylsulfonyl, sulfamoyl, or trifluoromethyl. Examples of heteroaryl groups include, but are not limited to, unsubstituted and mono- or di-substituted derivatives of furan, benzofuran, thiophene, benzothiophene, pyrrole, pyridine, indole, oxazole, benzoxazole, isoxazole, benzisoxazole, thiazole, benzothiazole, isothiazole, imidazole, benzimidazole, pyrazole, indazole, tetrazole, quinoline, isoquinoline, pyridazine, pyrimidine, purine and pyrazine, furazan, 1,2,3-oxadiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, triazole, benzotriazole, pteridine, phenoxazole, oxadiazole, benzopyrazole, quinolizine, cinnoline, phthalazine, quinazoline, and quinoxaline. In some embodiments, the substituents are halo, hydroxy, cyano, O-C_{1-6}-alkyl, C_{1-6}-alkyl, hydroxy-C_{1-6}-alkyl, and amino-C_{1-6}-alkyl.

[0131] As used herein, "cycloalkyl" means a fully saturated carbocyclyl ring or ring system. Examples include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. The cycloalkyl group may have 3 to 10 carbon atoms (whenever it appears herein, a numerical range such as "3 to 10" refers to each integer in the given range. The cycloalkyl group may be designated as "C_3-C_8 cycloalkyl" or similar designations. By way of example only, "C_3-C_8 cycloalkyl" indicates that there are three to eight carbon atoms in the carbocyclyl ring or ring system.

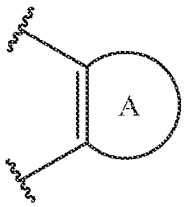
[0132] As used herein, "heterocyclyl" means a non-aromatic cyclic ring or ring structure that is fully saturated or partially saturated and includes at least one heteroatom selected from nitrogen, oxygen, and sulfur in the ring backbone. Heterocyclyls may have any degree of saturation provided that at 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 heterocycloalkyl group may be designated as "3-15-membered heterocycloalkyl," "4-10-membered heterocycloalkyl," "3-15-membered C_{2-14}heterocycloalkyl," "5-9-membered C_{4-8}heterocycloalkyl," "5-10-membered C_{4-9}heterocycloalkyl," "5-membered C_{3-4}heterocycloalkyl," "6-membered

C_{4-5}heterocycloalkyl," "7-membered C_{5-6}heterocycloalkyl," "bicyclic or tricyclic 9-15-membered C_{8-14}heterocycloalkyl," "monocyclic or bicyclic 3-10-membered C_{2-9}heterocycloalkyl," "bicyclic 8-10-membered C_{4-9}heterocycloalkyl," "bicyclic 8-10-membered C_{5-9}heterocycloalkyl," "monocyclic 4-7-membered C_{3-6}-heterocycloalkyl," "monocyclic 5-6-membered C_{3-5}-heterocycloalkyl," or similar designations. The heterocyclyl group could also be a C_2-C_9 heterocyclyl having 3 to 10 ring members with from one up to three of O (oxygen), N (nitrogen) or S (sulfur). The heterocyclyl group may be designated as "3-10 membered C_2-C_9 heterocyclyl" or similar designations. In preferred six membered monocyclic heterocyclyls, the heteroatom(s) are selected from one up to three of O (oxygen), N (nitrogen) or S (sulfur), and in preferred five membered monocyclic heterocyclyls, the heteroatom(s) are selected from one or two heteroatoms selected from O (oxygen), N (nitrogen) or S (sulfur). Examples of heterocyclyl rings include, but are not limited to, azepinyl, acridinyl, carbazolyl, cinnolinyl, dioxolanyl, imidazolinyl, 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, isoxazolinyl, isoxazolidinyl, oxazolinyl, oxazolidinyl, oxazolidinonyl, thiazolinyl, thiazolidinyl, 1,3-oxathiolanyl, indolinyl, isoindolinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydro-1,4-thiazinyl, thiamorpholinyl, dihydrobenzofuranyl, benzimidazolidinyl, and tetrahydroquinoline.

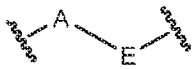
[0133] Similarly, when two "adjacent" R groups are said to form a ring "together with the atom to which they are attached," it is meant that the collective unit of the atoms, intervening bonds, and the two R groups are the recited ring. For example, when the following substructure is present:



and R^1 and R^2 are defined as selected from the group consisting of hydrogen and alkyl, or R^1 and R^2 together with the atoms to which they are attached form an aryl or carbocyclyl, it is meant that R^1 and R^2 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.

[0134] 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.

[0135] The phrase "therapeutically effective amount" means an amount of a compound or a combination of compounds that partially or fully ameliorates, attenuates or eliminates one or more of the symptoms of a particular disease or condition or prevents, modifies, or delays the onset of one or more of the symptoms of a particular disease or condition. Such amount can be administered as a single dosage or can be administered according to a regimen, whereby it is effective. Repeated administration may be needed to achieve a desired result (e.g., treatment of the disease and/or condition).

[0136] The term "pharmaceutically acceptable salt" includes salts of compounds of Formula I derived from the combination of a compound of the present embodiments and an organic or inorganic acid or base. 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, adipic 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, benzenesulfonic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, (+)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-methanesulfonic acid, 1,2-ethanedisulfonic acid, dodecyl sulfonic acid, salicylic acid, glucoheptonic acid, gluconic acid, glucuronic acid, hippuric acid, hydrochloride hemiethanolic acid, 2-hydroxyethanesulfonic acid, lactic acid, lactobionic acid, methylbromide acid, methyl sulfuric acid, 2-naphthalenesulfonic acid, oleic acid, 4,4′-methylenebis-[3-hydroxy-2-naphthalenecarboxylic acid], polygalacturonic acid, stearic acid, sulfosalicylic acid, tannic acid, terphthalic acid and the like. Inorganic bases from which salts can be derived include, for example, bases that contain 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. In some embodiments, treatment of the compounds disclosed herein with an inorganic base results in loss of a labile hydrogen from the compound to afford the salt form including an inorganic cation such as Li^+, Na^+, K^+, Mg^{2+} and Ca^{2+} and the like. 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.

[0137] Where the number of any given substituent is not specified (e.g., "haloalkyl"), there may be one or more substituents present. For example, "haloalkyl" can include one or more of the same or different halogens. For example, "haloalkyl" includes each of the substituents CF_3, CHF_2 and CH_2F.

[0138] The term "patient" refers to an animal being treated including a mammal, such as a dog, a cat, a cow, a horse, a sheep, and a human. In some embodiments, the patient is a mammal, either male or female. In some embodiments, the patient is a male or female human.

[0139] The term "prodrug" as used herein refers to any compound that when administered to a biological system generates a biologically active compound as a result of spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s), and/or metabolic chemical reaction(s), or a combination of each. Standard prodrugs are formed using groups attached to functionality, e.g. HO-, HS-, HOOC-, HOOPR2-, associated with the drug, that

cleave in vivo. Standard prodrugs include but are not limited to carboxylate esters where the group is alkyl, aryl, aralkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl as well as esters of hydroxyl, thiol and amines where the group attached is an acyl group, an alkoxycarbonyl, aminocarbonyl, phosphate or sulfate. The groups illustrated are examples, not exhaustive, and one skilled in the art could prepare other known varieties of prodrugs. Prodrugs must undergo some form of a chemical transformation to produce the compound that is biologically active or is a precursor of the biologically active compound. In some cases, the prodrug is biologically active, usually less than the drug itself, and serves to improve drug efficacy or safety through improved oral bioavailability, pharmacodynamic half-life, etc. Prodrug forms of compounds may be utilized, for example, to improve bioavailability, improve subject acceptability such as by masking or reducing unpleasant characteristics such as bitter taste or gastrointestinal irritability, alter solubility such as for intravenous use, provide for prolonged or sustained release or delivery, improve ease of formulation, or provide site specific delivery of the compound.

[0140] The term "stereoisomer" refers to the relative or absolute spatial relationship of the R group(s) attached to the stereogenic centers either carbon or phosphorus atoms, and refers to individual or any combination of the individual isomers such as a racemic mixture and a diastereomeric mixture. When a compound has two stereogenic centers, there are 4 potential stereoisomers.

[0141] The term "liver" refers to the liver organ.

[0142] The term "liver specificity" refers to the ratio:

[drug or a drug metabolite in liver tissue]/
[drug or a drug metabolite in blood or another tissue]

[0143] as measured in animals treated with the drug or a prodrug. The ratio can be determined by measuring tissue levels at a specific time or may represent an AUC (area under a curve) based on values measured at three or more time points.

[0144] The term "increased or enhanced liver specificity" refers to an increase in liver specificity ratio in animals treated with the prodrug relative to animals treated with the parent drug.

[0145] The term "enhanced oral bioavailability" refers to an increase of at least about 50% of the absorption of the dose of the reference drug. In an additional aspect, the

increase in oral bioavailability of the compound (compared to the reference drug) is at least about 100%, or a doubling of the absorption. Measurement of oral bioavailability usually refers to measurements of the prodrug, drug, or drug metabolite in blood, plasma, tissues, or urine following oral administration compared to measurements following parenteral administration.

[0146] The term "therapeutic index" refers to the ratio of the dose of a drug or prodrug that produces a therapeutically beneficial response relative to the dose that produces an undesired response such as death, an elevation of markers that are indicative of toxicity, and/or pharmacological side effects.

[0147] The term "sustained delivery" refers to an increase in the period in which there is a prolongation of therapeutically-effective drug levels due to the presence of the prodrug.

[0148] The terms "treating" or "treatment" of a disease includes inhibiting the disease (slowing or arresting or partially arresting its development), preventing the disease, providing relief from the symptoms or side effects of the disease (including palliative treatment), and/or relieving the disease (causing regression of the disease).

[0149] The term "therapeutic or diagnostic moiety" refers to a moiety that itself confers a therapeutic or diagnostic property when the compound to which is attached is administered to a subject, or when cleaved from the rest of the molecule to which is attached forms a compound that has therapeutic or diagnosis properties. In some embodiments, the therapeutic or diagnostic moiety contains a radioactive isotope or a heavy atom.

[0150] The terms "molecular pathway" refers to a series of molecular events in tissues such as a receptor modulating sequence, an enzyme modulating sequence, or a biosynthesis sequence that is involved in physiological or pathophysiological functions of a living animal.

[0151] A "nucleoside or analog thereof" refers to a natural nucleoside or an analog or derivative of a natural nucleoside, and includes compounds or moieties containing a nucleobase and a sugar or sugar analog. Nucleosides or analogs thereof can include therapeutically active fragments of known therapeutic nucleoside analogs or nucleotide analogs. The known therapeutic nucleoside analogs can include an agent selected from the group consisting of abacavir, aciciovir, acyclovir, cytarabine, didanosine, edoxudine,

emtricitabine, entecavir, galidesivir, ganciclovir, gemcitabine, ibacitabine, idoxuridine, inosine, lamivudine, penciclovir, remdesivir, ribavirine, stavudine, telbivudine, trifluridine, vidarabine, zalcitabine, and zidovudine. The known therapeutic nucleotide analogs can include an agent selected from the group consisting of adefovir, brincidofovir, cidofovir, and tenofovir. When the nucleoside or analog thereof is a therapeutically active fragment of a therapeutic nucleotide analog, the fragment can include the portion of the nucleotide analog left after cleavage of any phosphate groups from the nucleotide.

[0152] A "therapeutically active fragment" refers to a portion of a molecule that retains therapeutic activity when it is cleaved from the rest of the molecule to which it is attached, including when such cleavage occurs *in vivo*.

Administration and Pharmaceutical Compositions

[0153] The disclosed compounds may be used alone or in combination with other treatments. These compounds, when used in combination with other agents, may be administered as a daily dose or an appropriate fraction of the daily dose (e.g., b.i.d.). The compounds may be administered after a course of treatment by another agent, during a course of therapy with another agent, administered as part of a therapeutic regimen, or may be administered prior to therapy with another agent in a treatment program.

[0154] Examples of pharmaceutically acceptable salts include acetate, adipate, besylate, bromide, camsylate, chloride, citrate, edisylate, estolate, fumarate, gluceptate, gluconate, glucuronate, hippurate, hyclate, hydrobromide, hydrochloride, iodide, isethionate, lactate, lactobionate, maleate, mesylate, methylbromide, methylsulfate, napsylate, nitrate, oleate, palmoate, phosphate, polygalacturonate, stearate, succinate, sulfate, sulfosalicylate, tannate, tartrate, terphthalate, tosylate, and triethiodide.

[0155] Compositions containing the active ingredient may be in any form suitable for the intended method of administration. In some embodiments, the compounds of a method and/or composition described herein can be provided via oral administration, rectal administration, transmucosal administration, intestinal administration, enteral administration, topical administration, transdermal administration, intrathecal administration, intraventricular administration, intraperitoneal administration, intranasal administration, intraocular administration and/or parenteral administration.

[0156] When the compounds are administered via oral administration, for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

[0157] Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient can be mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient can be mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

[0158] Formulations suitable for parenteral administration include aqueous and non-aqueous isotonic sterile injection solutions which may contain, for example, antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

[0159] In some embodiments unit dosage formulations contain a daily dose or unit, daily sub-dose, or an appropriate fraction thereof, of a drug. It will be understood, however,

that the specific dose level for any particular patient will depend on a variety of factors including the activity of the specific compound employed; the age, body weight, general health, sex and diet of the individual being treated; the time and route of administration; the rate of excretion; other drugs which have previously been administered; and the severity of the particular disease undergoing therapy, as is well understood by those skilled in the art.

[0160] The actual dose of the 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. In some embodiments, a daily dose may be from about 0.1 mg/kg to about 100 mg/kg or more of body weight, from about 0.25 mg/kg or less to about 50 mg/kg from about 0.5 mg/kg or less to about 25 mg/kg, from about 1.0 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 7 mg per day to about 7000 mg per day, from about 35 mg per day or less to about 2000 mg per day or more, from about 70 mg per day to about 1000 mg per day.

Methods of Treatment

[0161] Some embodiments of the present invention include methods of treating a disease, disorder or condition is selected from the group consisting of hepatitis, liver cancer, liver fibrosis, fatty liver, malaria, viral infection, parasitic infection, diabetes, hyperlipidemia, atherosclerosis, obesity, dyslipidemia, hyperglycemia, a hormonal condition, HIV, and various types of cancer with the compounds, and compositions comprising compounds described herein. Some methods include administering a compound, composition, pharmaceutical composition described herein to a subject in need thereof. In some embodiments, a subject can be an animal, e.g., a mammal, a human. In some embodiments, the subject is a human.

[0162] Further embodiments include administering a combination of compounds to a subject in need thereof. A combination can include a compound, composition, pharmaceutical composition described herein with an additional medicament.

[0163] Some embodiments include co-administering a compound, composition, and/or pharmaceutical composition described herein, with an additional medicament or additional therapeutic agent(s). 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 i.v.

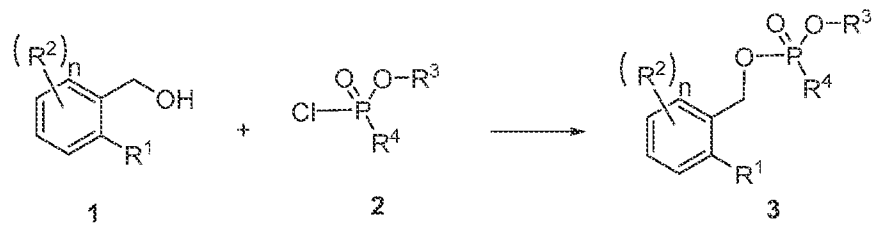
[0164] To further illustrate this invention, the following examples are included. The examples should not, of course, be construed as specifically limiting the invention. Variations of these examples within the scope of the claims are within the purview of one skilled in the art and are considered to 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.

Synthesis of compounds

[0165] The following procedures for the preparation of the new compounds illustrate the general procedures used to prepare the 2-substituted benzyloxy phosph(on)ate compounds.

[0166] Scheme I describes general synthesis of the phosph(on)ate compounds of Formula I. The 2-substituted benzyl alcohol (1) reacts with the phosph(on)ate chloride (2) to give the product of structure 3, the final product of Formula I.

Scheme I



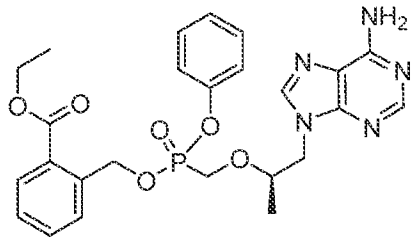
1 2 3

EXAMPLES

[0167] Some compounds of Formula I and Ia are prepared as outlined below.

Example 1

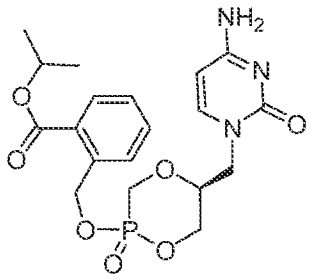
[0168] Ethyl 2-(((((((R)-1-(6-amino-9H-purin-9-yl)propan-2-yl)oxy)methyl)(phenoxy)-phosphoryl)oxy)methyl)benzoate (Compound 101)



[0169] Compound 101 was prepared according to the method described in Scheme I from ethyl 2-(hydroxymethyl)benzoate and phenyl ((((R)-1-(6-amino-9H-purin-9-yl)propan-2-yl)oxy)methyl)phosphonochloridate as a mixture of two isomers. $[M+1]^+$ calculated for $C_{25}H_{28}N_5O_6P$: 526.19. Found: 526.1.

Example 2

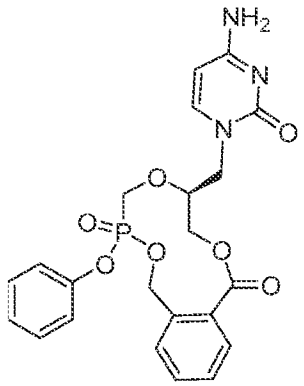
[0170] Isopropyl 2-((((5S)-5-((4-amino-2-oxopyrimidin-1(2H)-yl)methyl)-2-oxido-1,4,2-dioxaphosphinan-2-yl)oxy)methyl)benzoate (Compound 102)



[0171] Compound 102 was be prepared according to the method described in Scheme I from (S)-(((1-(4-amino-2-oxopyrimidin-1(2H)-yl)-3-hydroxypropan-2-yl)oxy)methyl)phosphonic acid as a mixture of two isomers. $[M+1]^+$ calculated for $C_{19}H_{24}N_3O_7P$: 436.13. Found: 436.1.

Example 3

[0172] 4-Amino-1-(((6S)-3-oxido-9-oxo-3-phenoxy-1,4,6,7,9-pentahydrobenzo[i][1,4,7]trioxa[2]phosphacycloundecin-6-yl)methyl)pyrimidin-2(1H)-one (Compound 103)



[0173] Compound 103 can be prepared according to the method described in Scheme I from 2-(chloromethyl)benzoic acid chloride and phenyl hydrogen (S)-(((1-(4-amino-2-oxopyrimidin-1(2H)-yl)-3-hydroxypropan-2-yl)oxy)methyl)phosphonic acid as a mixture of two isomers. $[M+1]^+$ calculated for $C_{22}H_{22}N_3O_7P$: 472.13.

Biological Examples

[0174] Examples of use of the method include the following. It will be understood that the following are examples and that the method is not limited solely to these examples.

Example 4: Tissue Distribution Following Oral Administration of reference compounds and the disclosed compounds

[0175] The prodrug efficiency of the disclosed compounds is compared relative to a corresponding active compound in target organs.

Methods:

[0176] Reference compounds and the compounds disclosed herein are administered at 5-50 mg/kg to fasted rats by oral gavage. Plasma concentrations of the metabolites, and parent compounds in circulation and in the hepatic portal vein are determined by HPLC-UV, and the liver, small intestine, and other organ concentrations are measured by LC-MS using standard chromatography methods.

[0177] All numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth herein are approximations that may vary depending upon the desired properties sought to be obtained. At the very least, and not as an attempt to limit the application of the doctrine of

equivalents to the scope of any claims in any application claiming priority to the present application, each numerical parameter should be construed in light of the number of significant digits and ordinary rounding approaches.

[0178] Language of degree used herein, such as the terms "approximately," "about," "generally," and "substantially" as used herein represent a value, amount, or characteristic close to the stated value, amount, or characteristic that still performs a desired function or achieves a desired result. For example, the terms "approximately", "about", "generally," and "substantially" may refer to an amount that is within less than 10% of, within less than 5% of, within less than 1% of, within less than 0.1% of, and within less than 0.01% of the stated amount. As another example, in certain embodiments, the terms "generally parallel" and "substantially parallel" refer to a value, amount, or characteristic that departs from exactly parallel by less than or equal to 15%, 10%, 5%, 3%, 1%, 0.1%, or otherwise. Similarly, in certain embodiments, the terms "generally perpendicular" and "substantially perpendicular" refer to a value, amount, or characteristic that departs from exactly perpendicular by less than or equal to 15%, 10%, 5%, 3%, 1%, 0.1%, or otherwise.

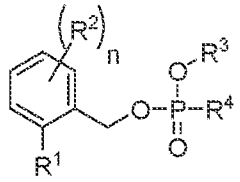
[0179] The above description discloses several methods and materials. This invention is susceptible to modifications in the methods and materials, as well as alterations in the fabrication methods and equipment. Such modifications will become apparent to those skilled in the art from a consideration of this disclosure or practice of the invention disclosed herein. Consequently, it is not intended that this invention be limited to the specific embodiments disclosed herein, but that it cover all modifications and alternatives coming within the true scope and spirit of the invention.

[0180] All references cited herein, including but not limited to published and unpublished applications, patents, and literature references, are incorporated herein by reference in their entirety and are hereby made a part of this specification. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

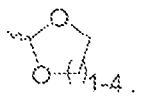
[0181] Although some embodiments and examples have been described, it should be understood that numerous and various modifications can be made without departing from the spirit of the invention.

WHAT IS CLAIMED IS:

1. A compound of Formula I:



(I), wherein:

R^1 is selected from the group consisting of $-CH(OR^6)_2$, $-C(O)N(R^6)_2$, $-CH_2OR^7$, CH_2SR^7, $-CH_2N(R^7)_2$, $-CH_2OCH_2OR^6$, $-COOR^5$, and ;

each R^2 is independently selected from the group consisting of halogen, an optionally substituted alkyl, and an optionally substituted alkyloxy;

R^3 is selected from the group consisting of H, an optionally substituted aryl, and a therapeutic or diagnostic moiety;

R^4 is selected from a nucleoside or analog thereof or a nucleoside base or analog thereof, or alternatively, R^4 and R^3 together with the atoms to which they are attached form a monocyclic heterocyclyl substituted with a nucleoside base or analog thereof, or R^4 and R^5 together with the atoms to which they are attached form a heterocyclyl substituted with a nucleoside base or analog thereof;

R^5 is H or an optionally substituted alkyl;

each R^6 is independently an optionally substituted alkyl;

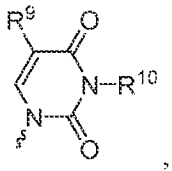
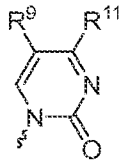
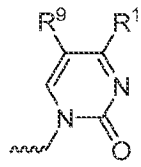
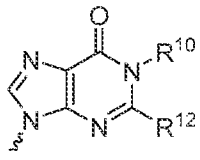
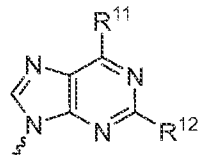
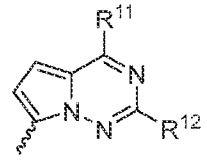
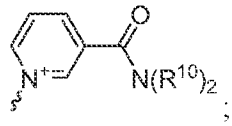
R^7 is selected from the group consisting of H, an optionally substituted C_1-C_{10} acyl, an optionally substituted C_1-C_{10} alkyl-OC(O)-, an optionally substituted (C_{6-10} aryl)-C(O)-, and an optionally substituted (C_{6-10} aryl)-OC(O)-; and

n is 0, 1, 2, or 3;

or a stereoisomer or pharmaceutically acceptable salt thereof.

2. The compound of Claim 1, wherein the nucleoside base or analog thereof is a therapeutically active fragment of an agent selected from the group consisting of abacavir, aciciovir, acyclovir, cytarabine, didanosine, edoxudine, emtricitabine, entecavir, galidesivir, ganciclovir, gemcitabine, ibacitabine, idoxuridine, inosine, lamivudine, maribavir, molnupiravir, penciclovir, remdesivir, ribavirine, stavudine, telbivudine, trifluridine, vidarabine, zalcitabine, and zidovudine.

3. The compound of Claim 1, wherein the nucleoside base or analog thereof is a therapeutically active fragment of an agent selected from the group consisting of adefovir, brincidofovir, cidofovir, and tenofovir.

4. The compound of Claim 1, wherein the nucleoside base or analog thereof is selected from the group consisting of , , , , , , and ; wherein

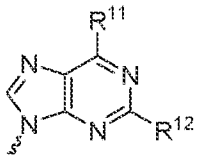
R^9 is H, halo, or an optionally substituted C_1-C_{10} alkyl;

R^{10} is selected from the group consisting of H, an optionally substituted C_1-C_{10} alkyl, an optionally substituted C_1-C_{10} alkyl-OCH_2-, an optionally substituted C_1-C_{10} alkyl-$NHCH_2$-, an optionally substituted C_1-C_{10} acyl, an optionally substituted C_1-C_{10} alkyl-OC(O)-, an optionally substituted ($C_{6\text{-}10}$ aryl)-CH_2OCH_2-, an optionally substituted ($C_{6\text{-}10}$ aryl)-OCH_2-, an optionally substituted ($C_{6\text{-}10}$ aryl)-C(O)-, and an optionally substituted ($C_{6\text{-}10}$ aryl)-OC(O)-;

R^{11} is selected from the group consisting of OH, NH_2, $NHOR^7$, an optionally substituted C_1-C_{10} alkyloxy, an optionally substituted C_1-C_{10} alkylamino, an optionally substituted C_1-C_{10} acyloxy, an optionally substituted C_1-C_{10} acylamino, an optionally substituted C_1-C_{10} alkyl-OC(O)NH-, an optionally substituted ($C_{6\text{-}10}$ aryl)-C(O)O-, an optionally substituted ($C_{6\text{-}10}$ aryl)-C(O)NH-, an optionally substituted ($C_{6\text{-}10}$ aryl)-OC(O)NH-, an optionally substituted C_1-C_{10} alkyl-OCH_2NH-, and an optionally substituted C_1-C_{10} alkyl-OCH_2O-; and

R^{12} is selected from a group of H, NH_2, an optionally substituted C_1-C_{10} alkylamino, an optionally substituted C_1-C_{10} acylamino, an optionally substituted C_1-C_{10} alkyl-OC(O)NH-, an optionally substituted ($C_{6\text{-}10}$ aryl)-C(O)NH-, an optionally substituted ($C_{6\text{-}10}$ aryl)-OC(O)NH-, and an optionally substituted C_1-C_{10} alkyl-OCH_2NH-.

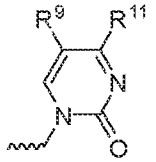
5. The compound of Claim 4, wherein the nucleoside base or analog thereof is



6. The compound of Claim 5, wherein R^{11} is NH_2.

7. The compound of Claim 5 or 6, wherein R^{12} is H.

8. The compound of Claim 4, wherein the nucleoside base or analog thereof is

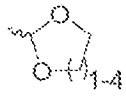


9. The compound of Claim 8, wherein R^9 is H.

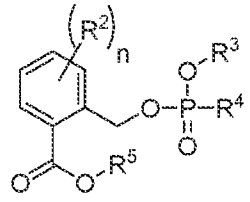
10. The compound of Claim 8 or 9, wherein R^{11} is NH_2.

11. The compound of any one of Claims 1-10, wherein n is 1.

12. The compound of any one of Claims 1-11, wherein R^3 is selected from the group consisting of H and an optionally substituted aryl.

13. The compound of any one of Claims 1-12, wherein R^1 is selected from a group of $-CH(OR^6)_2$, $-C(O)N(R^6)_2$, and .

14. The compound of any one of Claims 1-12, wherein the compound of Formula I is represented by Formula (Ia):



(Ia),

or a stereoisomer or a pharmaceutically acceptable salt thereof.

15. The compound of Claim 14, wherein R^5 is an unsubstituted C_1-C_6 alkyl.

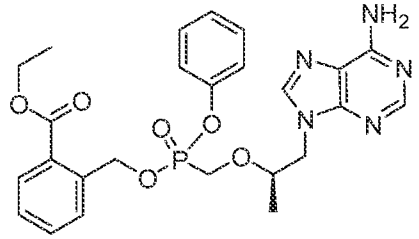
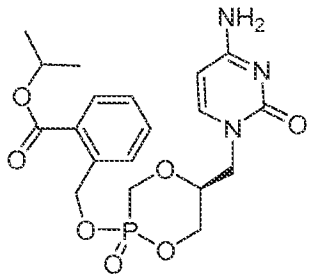
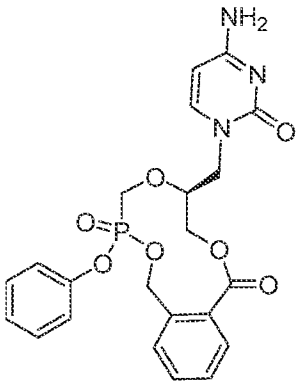
16. The compound of Claim 15, wherein R^5 is ethyl.

17. The compound of Claim 15, wherein R^5 is *i*-propyl.

18. The compound of Claim 14, wherein R^5 is H.

19. The compound of Claim 14, wherein R^3 is an unsubstituted aryl.

20. The compound of Claim 14, wherein R^3 is phenyl.

21. The compound of Claim 1, wherein the compound is selected from the group consisting of: , , and .

22. A compound of any one of Claims 1-21 for use in treating a disease of the liver.

23. The compound of Claim 22, in combination with one or more additional therapeutic agents.

24. Use of a compound of any one of Claims 1-21 in the preparation of a medicament for treating a liver disease.

25. A method of treating a liver disease comprising administering an effective amount of a compound of any one of Claims 1-21 to a subject in need thereof.

26. The method of Claim 25, wherein the subject is a mammal.

27. The method of Claim 26, wherein the mammal is a human.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/027930

A. CLASSIFICATION OF SUBJECT MATTER

C07F 9/40 (2006.01) C07F 9/655 (2006.01) C07F 9/6553 (2006.01) A61P 1/16 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN (Registry/CAPlus): Substructure search based upon formula (I).

Database DOCDB and DWPI: Applicant/Inventor search.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 June 2021	07 June 2021

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INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/US2021/027930**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2020/219464 A1 (LIGAND PHARMACEUTICALS, INC) 29 October 2020 Compounds in claim 51	1-27
A	US 2020/0399227 A1 (NUCORION PHARMACEUTICALS, INC.) 24 December 2020 Page 47 RHS third compound	1-27
A	WO 2016/138026 A1 (LIGAND PHARMACEUTICALS, INC) 01 September 2016 Paragraph 0007 page 3	1-27
A	WO 2014/043380 A1 (LIGAND PHARMACEUTICALS, INC) 20 March 2014 Page 37	1-27

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2021/027930**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
WO 2020/219464 A1	29 October 2020	WO 2020219464 A1	29 Oct 2020
US 2020/0399227 A1	24 December 2020	US 2020399227 A1	24 Dec 2020
		CN 111801339 A	20 Oct 2020
		TW 201936585 A	16 Sep 2019
		WO 2019143860 A1	25 Jul 2019
		WO 2021011692 A1	21 Jan 2021
WO 2016/138026 A1	01 September 2016	WO 2016138026 A1	01 Sep 2016
		CN 107295800 A	24 Oct 2017
		US 2018044368 A1	15 Feb 2018
WO 2014/043380 A1	20 March 2014	WO 2014043380 A1	20 Mar 2014
		US 2015246068 A1	03 Sep 2015
		US 9326991 B2	03 May 2016

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.