[0016] An essential step in the mode of action of purine and pyrimidine nucleosides against viral diseases, and in particular, HBV and HCV is their metabolic activation by cellular kinases, to yield the mono-, di- and triphosphate derivatives. The biologically active species of many nucleosides is the triphosphate form, which inhibits viral DNA polymerase, RNA polymerase, or reverse transcriptase, or causes chain termination.

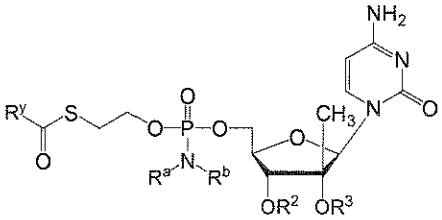
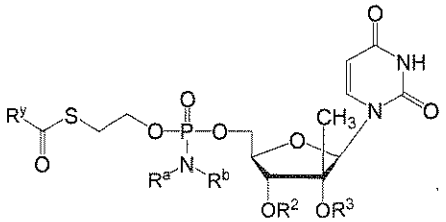
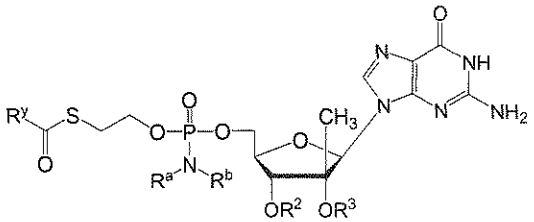
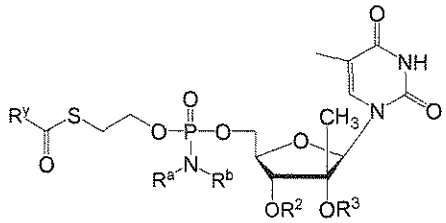
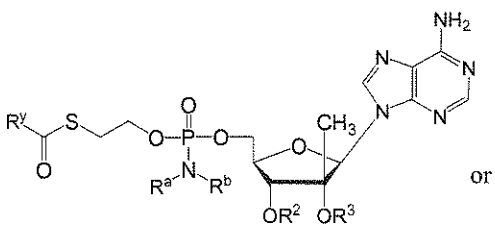
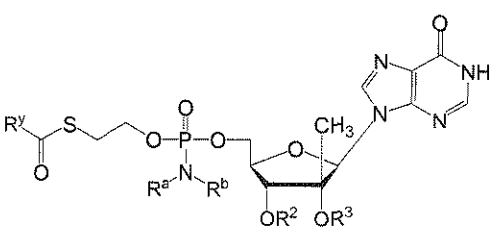
[0017] In light of the fact that hepatitis B and C viruses have reached epidemic levels worldwide, and has severe and often tragic effects on the infected patient, there remains a strong need to provide new effective pharmaceutical agents to treat humans infected with the virus that have low toxicity to the host.

[0018] Therefore, there is a continuing need for effective treatments of HCV and HBV infections.

SUMMARY

[0019] Phosphoramidate and phosphonoamidate compounds of a variety of therapeutic agents are provided, as well as methods for their manufacture and use in the treatment of a variety of disorders including liver disorders.

[0019a] In a first aspect, the present invention refers to a compound of the formula:






or


or a pharmaceutically acceptable salt, a tautomeric or polymorphic form thereof, wherein:

R^y is optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkenyl, hydroxyalkyl, amino, heterocyclyl or heteroaryl;

R^a and R^b are selected as follows:

i) R^a and R^b are each independently hydrogen or alkyl, substituted alkyl, carboxyalkyl, hydroxyalkyl, hydroxyarylalkyl, acyloxyalkyl, aminocarbonylalkyl, alkoxycarbonylalkyl, aryl, substituted benzyl, cycloalkyl, heteroaryl or heterocyclyl; or

ii) R^a and R^b together with the nitrogen atom on which they are substituted form a 3-7 membered heterocyclic or heteroaryl ring; and

R^2 and R^3 are each independently H, or R^2 and R^3 are linked to form a cyclic group by an alkyl, ester or carbamate linkage.

[0019b] In a second aspect, the present invention refers to a pharmaceutical composition comprising a compound of the present invention and a pharmaceutically acceptable excipient, carrier or diluent.

[0019c] In a third aspect, the present invention refers to a use of a compound of the present invention in the manufacture of a medicament for the treatment of a host infected with a *Flaviviridae* virus or hepatitis B virus.

[0019d] C~~Such c~~ompounds disclosed herein can therefore be used in some ~~embodiments~~examples to permit concentration of the therapeutic agent in the liver. In one ~~embodiment~~example, the compound is a *S*-pivaloyl-2-thioethyl phosphoramidate, *S*-pivaloyl-2-thioethyl phosphonoamidate, *S*-hydroxypivaloyl-2-thioethyl phosphoramidate or *S*-hydroxypivaloyl-2-thioethyl phosphonoamidate.

[0020] Phosphoramidate or phosphonoamidate compounds of a variety of therapeutic agents are provided. As used herein, a "phosphoramidate or phosphonoamidate compound of a therapeutic agent" includes a therapeutic agent derivatized to include a phosphoramidate or phosphonoamidate group. The therapeutic agent is, for example, an anti-viral agent that includes, or has been derivatized to include, a reactive group, such as a hydroxyl, for attachment of the phosphoramidate or phosphonoamidate moiety. Such therapeutic agents include, but are not limited to nucleosides and nucleoside analogs including acyclic nucleosides. In some ~~embodiments~~examples, phosphoramidates of nucleotides and nucleotide analogs are also provided, such as phosphoramidates of 1', 2', 3'-branched and 4'-branched nucleosides. Such compounds can be administered in an effective amount for the

treatment of liver disorders, including infectious diseases, such as hepatitis B and hepatitis C infection, including resistant strains thereof.

[0021] In certain ~~embodiments~~examples, while not being limited to any theory, it is possible that the parent drug is obtained from selective metabolism of the phosphoramidate or phosphonoamidate compound in the liver, and thus the parent drug is capable of accumulating in the liver of a host. By selectively targeting and activating compounds in the liver, potentially undesired distribution of active compound in the gastrointestinal tract can be reduced. Moreover, therapeutic amounts of active compound at the site of infection in the liver can be increased.

[0022] In certain ~~embodiments~~examples, a 5'-monophosphate or phosphonate of a parent nucleoside (or nucleoside derivative) drug is formed from metabolism of the phosphoramidate or phosphonoamidate compound in the liver, allowing the monophosphate or phosphonate to form and accumulate in the liver of a host. Thus, in certain ~~embodiments~~examples, the phosphoramidate in effect provides a stabilized phosphate on the nucleoside or nucleoside analogue. In certain ~~embodiments~~examples, where the compound needs to be triphosphorylated to be active, this advantageously can eliminate the requirement for the initial phosphorylation step, and promote more ready formation of the active triphosphate, which inhibits the target enzyme, and can enhance the overall activity of the nucleoside or nucleoside analog.

[0023] Without being limited to any theory, in one ~~embodiment~~example, a phosphoramidate of a nucleoside, such as a 2'-C-methyl-ribonucleoside, is provided, that is selectively concentrated in the liver after oral administration, and metabolized in the liver cell to yield a 5'-monophosphate that can be enzymatically converted to the active form of the 5'-triphosphate, which inhibits the HCV polymerase. Thus potentially therapeutic doses can be reduced in comparison to administering the nucleoside parent molecule.

[0024] Thus, in some ~~embodiments~~examples, after oral administration of the phosphoramidate and phosphonamidate compounds described herein, the compounds can advantageously concentrate in the liver cells at the site of infection and convert to the phosphate or phosphonate in the liver cell, which then is optionally further phosphorylated to implement its therapeutic effect.

[0025] Since these methods allow accumulation of the phosphoramidate or phosphonoamidate compounds disclosed herein in the liver of a host, the methods described herein can be useful, for example, for the treatment and/or prophylaxis of diseases or disorders of the liver, such as hepatitis B or C.

[0026] In certain ~~embodiments~~examples, the compounds provided herein are useful in the prevention and treatment of *Flaviviridae* infections and other related conditions such as anti-*Flaviviridae* antibody positive and *Flaviviridae*-positive conditions, chronic liver inflammation caused by HCV, cirrhosis, fibrosis, acute hepatitis, fulminant hepatitis, chronic persistent hepatitis, and fatigue. These compounds or formulations can also be used prophylactically to prevent or retard the progression of clinical illness in individuals who are anti-*Flaviviridae* antibody or *Flaviviridae*-antigen positive or who have been exposed to a *Flaviviridae*. In one specific ~~embodiment~~example, the *Flaviviridae* is hepatitis C. In certain ~~embodiments~~examples, the compound is used to treat any virus that replicates through an RNA-dependent RNA polymerase.

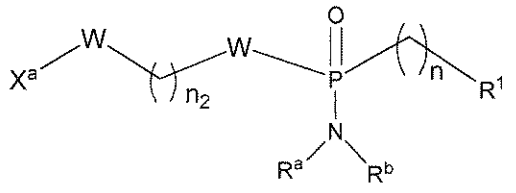
[0027] A method for the treatment of a *Flaviviridae* infection in a host, including a human, is also provided that includes administering an effective amount of a compound provided herein, administered either alone or in combination or alternation with another anti-*Flaviviridae* agent, optionally in a pharmaceutically acceptable carrier.

[0028] In certain ~~embodiments~~examples, a method for treatment and/or prophylaxis of hepatitis B infections and other related conditions such as anti-HBV antibody positive and HBV-positive conditions, chronic liver inflammation caused by HBV, fibrosis, cirrhosis, acute hepatitis, fulminant hepatitis, chronic persistent hepatitis, and fatigue are provided herein.

[0029] In certain ~~embodiments~~examples, phosphoramidate or phosphonoamidate compounds of a variety of pharmaceutical agents can be made and used therapeutically as described herein, to enhance delivery of the drug to the liver. In one ~~embodiment~~example, the compound is an *S*-acyl-2-thioethyl phosphoramidate or an *S*-acyl-2-thioethyl phosphonoamidate derivative, *e.g.*, a *S*-pivaloyl-2-thioethyl phosphoramidate or a *S*-hydroxypivaloyl-2-thioethyl phosphonoamidate derivative.

[0030] The phosphoramidate or phosphonoamidate compounds, as well as salts thereof, and compositions comprising the compounds, provided herein are useful for

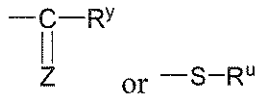
treatment of disorders of the liver, such as HBV and/or HCV infections. In one ~~embodiment~~example, the compound provided herein is a compound of Formula I:



I

or a pharmaceutically acceptable salt, solvate, a stereoisomeric, tautomeric or polymorphic form thereof, wherein

X^a is



Z is O or S;

each W is independently O or S;

R^y and R^u each independently represent alkyl, alkenyl, alkynyl, aryl, aryl alkyl, cycloalkyl, cycloalkenyl, amino, aminoalkyl, hydroxyalkyl, alkoxy, heterocyclyl, or heteroaryl, all optionally substituted;

R^a and R^b are selected as follows:

i) R^a and R^b are each independently hydrogen, alkyl, carboxyalkyl, hydroxyalkyl, hydroxyarylalkyl, acyloxyalkyl, aminocarbonylalkyl, alkoxycarbonylalkyl, aryl, aryl alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl, all optionally substituted; or

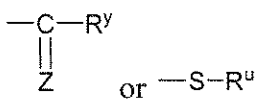
ii) R^a and R^b together with the nitrogen atom on which they are substituted form a 3-7 membered heterocyclic or heteroaryl ring;

n is 0-3; n_2 is 1-4; and

R^1 is a moiety derivable by removal of a hydrogen from a hydroxy group of an anti-viral drug.

[0031] In another ~~embodiment~~example,

X^a is



Z is O, S, NH or NR^w, where R^w is, e.g., alkyl, alkyl, alkenyl, alkynyl, aryl, aryl alkyl, cycloalkyl, cycloalkenyl, amino, aminoalkyl, alkoxy, heterocyclyl, or heteroaryl, all optionally substituted;

each W is O, S, NH or NR^w, where R^w is, e.g., alkyl, alkyl, alkenyl, alkynyl, aryl, aryl alkyl, cycloalkyl, cycloalkenyl, amino, aminoalkyl, alkoxy, heterocyclyl, or heteroaryl, all optionally substituted;

R^y and R^u each independently represent alkyl, alkenyl, alkynyl, aryl, aryl alkyl, cycloalkyl, cycloalkenyl, amino, aminoalkyl, alkoxy, heterocyclyl, or heteroaryl, all optionally substituted;

R^a and R^b are selected as follows:

i) R^a and R^b are each independently hydrogen, alkyl, carboxyalkyl, hydroxyalkyl, hydroxyarylalkyl, acyloxyalkyl, aminocarbonylalkyl, alkoxycarbonylalkyl, aryl, aryl alkyl, cycloalkyl, heteroaryl or heterocyclyl, all optionally substituted; or

ii) R^a and R^b together with the nitrogen atom on which they are substituted form a 3-7 membered heterocyclic or heteroaryl ring;

n is 0-3; n_2 is 1-4; and

R^1 is as decribed herein.

[0032] Those of skill in the art will recognize that compounds of Formula I can be designed or prepared by reaction, e.g., at a hydroxy group of said anti-viral drug, for example, via condensation or dehydration. For convenience, in the description herein when substituents, such as exemplary R^1 groups are identified as a drug, those of skill in the art will recognize that the compound e.g. of Formula I comprises a derivative, *e.g.* a radical of the anti-viral drug. Those derivatives can for example be prepared by elimination of a hydrogen radical from a hydroxy group of the drug, for instance in a dehydration reaction. Where appropriate, certain derivatives can be prepared by modification of a phosphate or phosphonate of an anti-viral drug to yield a compound of formula I.

[0033] In certain ~~embodiments~~examples of Formula I, R^1 is a nucleoside comprising a cyclic or acyclic sugar or an analog thereof.

[0034] In certain ~~embodiments~~examples, R^1 is an anti-viral nucleoside analog useful for treatment of HCV virus infection selected from ribavirin, viramidine, 2'-C-methylcytidine, 2'-C-methylguanosine, valopicitabine (NM 283), MK-0608 and PSI-6130.

[0035] In certain ~~embodiments~~examples, R^1 is an anti-viral nucleoside analog useful for treatment of HBV virus infection selected from lamivudine (Epivir-HBV, Zeffix, or

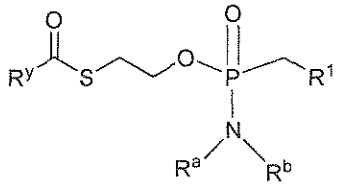
Heptodin), adefovir, entecavir (Baraclude), telbivudine (Tyzeka, Sebivo), emtricitabine (FTC), clevudine (L-FMAU), viread (Tenofovir), torcitabine, valtorcitabine (monoval LdC), amdoxovir (DAPD) and RCV (Racivir).

[0036] In certain ~~embodiments~~examples, R^1 is a non-nucleoside anti-viral useful for treatment of HBV virus infection selected from resiquimod or celgosivir.

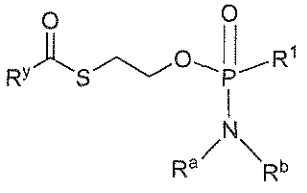
[0037] In certain ~~embodiments~~examples according to Formula I, R^y is substituted alkyl, *e.g.* hydroxyalkyl or aminoalkyl; and R^a and R^b are each independently hydrogen, alkyl, substituted alkyl, benzyl or substituted benzyl, for instance hydroxy- or amino-substituted alkyl or benzyl. In another ~~embodiment~~example, R^y is $-OR^c$, $-C(R^c)_3$ or $-NHR^c$ where each R^c is independently alkyl, substituted alkyl, aryl or substituted aryl, for instance hydroxy- or amino-substituted alkyl or aryl; and R^a and R^b are independently hydrogen, alkyl, substituted alkyl, benzyl or substituted benzyl, for instance hydroxy- or amino-substituted alkyl or benzyl. In a further ~~embodiment~~example, R^a and R^b are independently benzyl or substituted alkyl. In a further ~~embodiment~~example, R^y is selected from the group consisting of alkyl and hydroxyalkyl. In certain ~~embodiments~~examples, R^y is $-C(CH_3)_2CH_2OH$.

[0038] In certain ~~embodiments~~examples, the compounds provided herein are selected such that R^1 is not 3'-azido-2',3'-dideoxythymidine.

[0039] In another ~~embodiment~~example, the compound provided herein is a compound of Formula IIa or IIb:



IIa or



IIb

or a pharmaceutically acceptable salt, solvate, a stereoisomeric, tautomeric or polymorphic form thereof, wherein

R^y is alkyl, alkenyl, alkynyl, aryl, aryl alkyl, cycloalkyl, cycloalkenyl, amino, aminoalkyl, hydroxyalkyl, heterocyclyl or heteroaryl, all optionally substituted;

R^a and R^b are selected as follows:

i) R^a and R^b are each independently hydrogen, alkyl, carboxyalkyl, hydroxyalkyl, hydroxyarylalkyl, acyloxyalkyl, aminocarbonylalkyl,

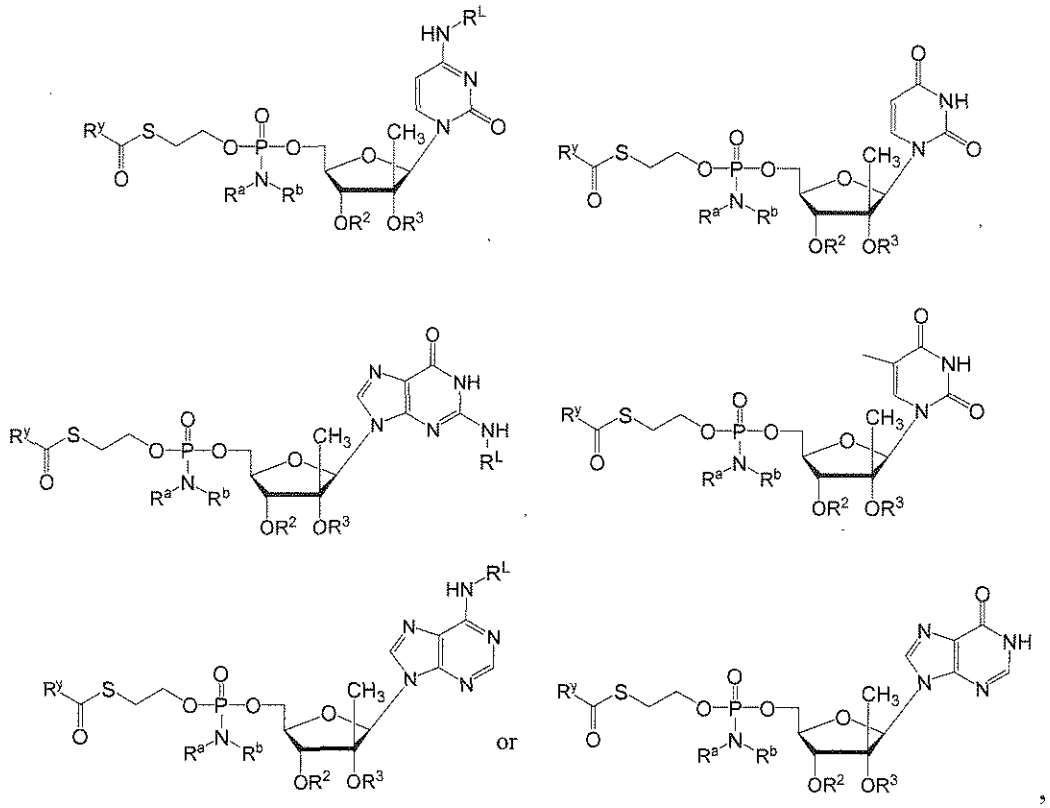
alkoxycarbonylalkyl, aryl, aryl alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl, all optionally substituted; or

ii) R^a and R^b together with the nitrogen atom on which they are substituted form a 3-7 membered heterocyclic or heteroaryl ring; and

R^1 is an antiviral drug (as used herein where R^1 is an antiviral drug, that ~~embodiment~~example includes a moiety derivable by removal of a hydrogen from a hydroxy group of an anti-viral drug), such as a nucleoside or nucleoside analog.

[0040] In certain ~~embodiments~~examples according to Formula IIa or IIb, R^y is substituted alkyl, *e.g.* hydroxyalkyl or aminoalkyl; and R^a and R^b are independently hydrogen, alkyl, substituted alkyl, benzyl or substituted benzyl, for instance hydroxy- or amino-substituted alkyl or benzyl. In another ~~embodiment~~example, R^y is $-OR^c$, $-C(R^c)_3$ or $-NHR^c$ where each R^c is independently alkyl, substituted alkyl, aryl or substituted aryl, for instance hydroxy- or amino-substituted alkyl or aryl; and R^a and R^b are independently hydrogen, alkyl, substituted alkyl, benzyl or substituted benzyl, for instance hydroxy- or amino-substituted alkyl or benzyl. In a further ~~embodiment~~example, R^a and R^b are independently benzyl or substituted alkyl. In a further ~~embodiment~~example, R^y is selected from the group consisting of alkyl and hydroxyalkyl. In certain ~~embodiments~~examples, R^y is $-C(CH_3)_2CH_2OH$.

[0041] In another ~~embodiment~~example, the compound provided herein is a compound of Formula:



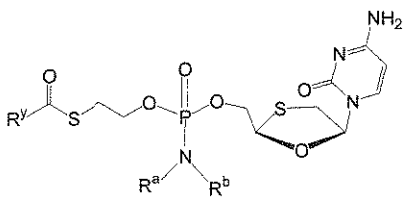
or

wherein R^a, R^b and R^y are as described in Formula I and

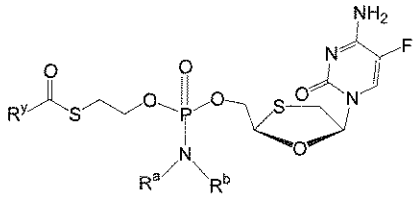
wherein R^2 and R^3 are each independently H, straight chained, branched or cyclic alkyl; acyl (including lower acyl); CO-alkyl, CO-aryl, CO-alkoxyalkyl, CO-aryloxyalkyl, CO-substituted aryl, sulfonate ester such as alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted; alkylsulfonyl, arylsulfonyl, aryl alkylsulfonyl, a lipid, such as a phospholipid; an amino acid; and amino acid residue, a carbohydrate; a peptide; cholesterol; or other pharmaceutically acceptable leaving group which is capable of providing a compound wherein R^2 and/or R^3 is independently H, for example when administered *in vivo*; or R^2 and R^3 are linked to form a cyclic group by an alkyl, ester or carbamate linkage; and wherein each R^L is independently H, carbamyl, straight chained, branched or cyclic alkyl; acyl (including lower acyl); CO-alkyl, CO-aryl, CO-alkoxyalkyl, CO-aryloxyalkyl, CO-substituted aryl, sulfonate ester such as alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted; alkylsulfonyl, arylsulfonyl, aryl alkylsulfonyl, a lipid, such as a phospholipid; an amino acid; an amino acid residue; or a carbohydrate. In certain ~~embodiments~~examples according to this paragraph, R^2 and R^3 are each H; R^y is substituted alkyl, *e.g.* hydroxyalkyl or aminoalkyl; and R^a and R^b are independently hydrogen,

alkyl, substituted alkyl, benzyl or substituted benzyl, for instance hydroxy- or amino-substituted alkyl or benzyl. In another ~~embodiment~~example, R^2 and R^3 are each H; R^y is $-OR^c$, $-C(R^c)_3$ or $-NHR^c$ where each R^c is independently alkyl, substituted alkyl, aryl or substituted aryl, for instance hydroxy- or amino-substituted alkyl or aryl; and R^a and R^b are independently hydrogen, alkyl, substituted alkyl, benzyl or substituted benzyl, for instance hydroxy- or amino-substituted alkyl or benzyl. In a further ~~embodiment~~example, R^2 and R^3 are each H; R^a and R^b are independently benzyl or substituted alkyl. In a further ~~embodiment~~example, R^2 and R^3 are each H; R^y is selected from the group consisting of alkyl and hydroxyalkyl. In certain ~~embodiments~~examples, R^2 and R^3 are each H; R^y is $-C(CH_3)_2CH_2OH$. In certain ~~embodiments~~examples according to this paragraph, R^2 and R^3 are each hydrogen, R^a is hydrogen, R^b is $-CH_2-C_6H_5$ and R^y is $-C(CH_3)_2CH_2OH$.

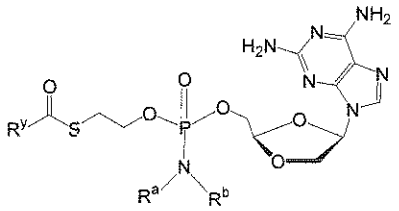
[0042] In another ~~embodiment~~example, the compound provided herein is a compound of formula:



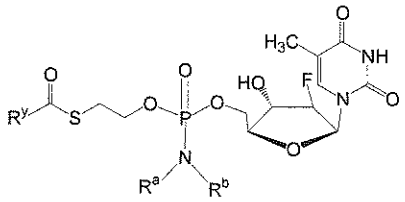
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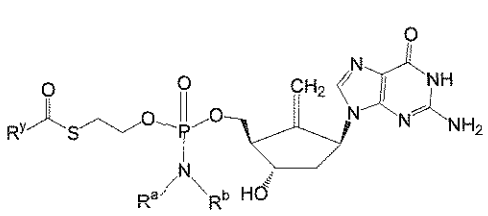
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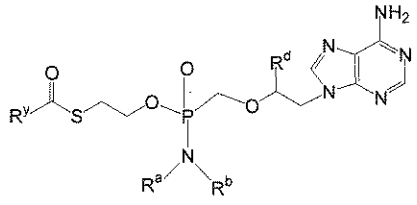
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or

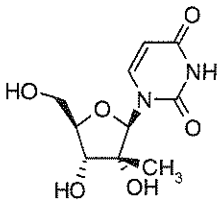
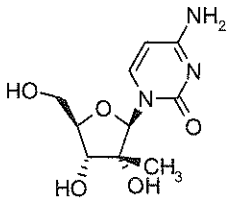
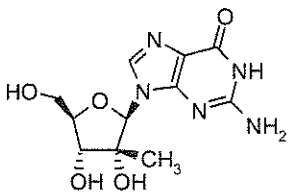
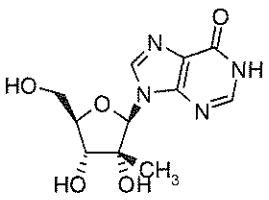


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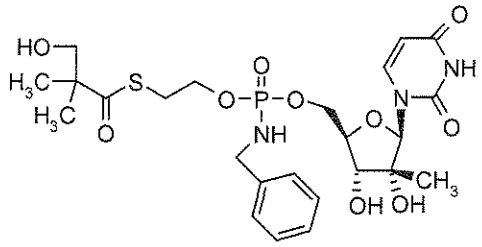
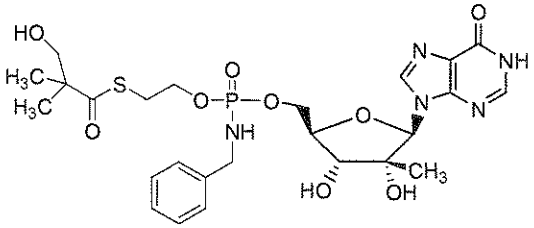
wherein R^a, R^b and R^y are as described in Formula I. R^d is selected from the group consisting of hydrogen, alkyl and alkoxy. In certain ~~embodiments~~examples, R^d is hydrogen, methyl or methoxy. In certain ~~embodiments~~examples according to this paragraph, R^y is substituted alkyl, *e.g.* hydroxyalkyl or aminoalkyl; and R^a and R^b are independently hydrogen, alkyl, substituted alkyl, benzyl or substituted benzyl, for instance hydroxy- or amino-substituted alkyl or benzyl. In another ~~embodiment~~example, R^y is $-OR^c$, $-C(R^c)_3$ or

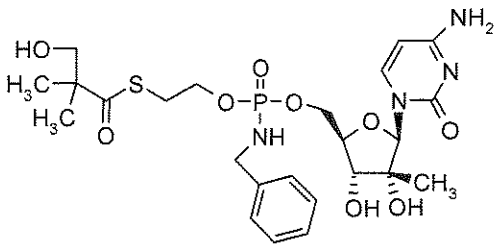
–NHR^c where each R^c is independently alkyl, substituted alkyl, aryl or substituted aryl, for instance hydroxy- or amino-substituted alkyl or aryl; and R^a and R^b are independently hydrogen, alkyl, substituted alkyl, benzyl or substituted benzyl, for instance hydroxy- or amino-substituted alkyl or benzyl. In a further ~~embodiment~~example, R^a and R^b are independently benzyl or substituted alkyl. In a further ~~embodiment~~example, R^y is selected from the group consisting of alkyl and hydroxyalkyl. In certain ~~embodiments~~examples, R^y is $–C(CH_3)_2CH_2OH$. In certain ~~embodiments~~examples according to this paragraph, R^2 and R^3 are each hydrogen, R^a is hydrogen, R^b is $–CH_2-C_6H_5$ and R^y is $–C(CH_3)_2CH_2OH$ In certain ~~embodiments~~examples according to this paragraph, R^a is hydrogen, R^b is $–CH_2-C_6H_5$ and R^y is $–C(CH_3)_2CH_2OH$.

[0043] In one ~~embodiment~~example, the nucleosides that can be derivatized to include a phosphoramidate or phosphonoamidate, *e.g.* at the 5' position include:

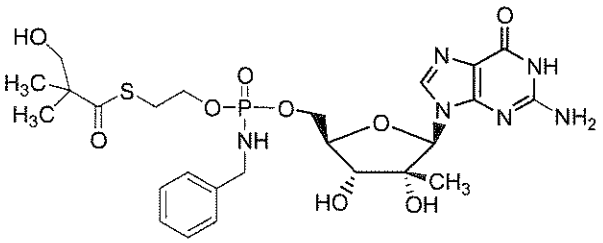





[0044] Examples of phosphoramidate or phosphonoamidate nucleoside compounds include:

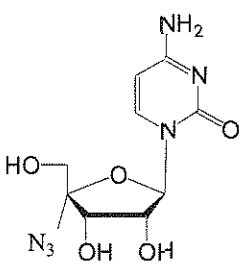

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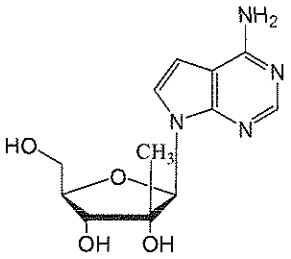
and



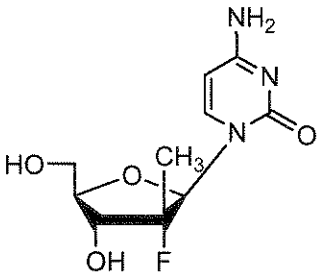
[0045] In one ~~embodiment~~example, the nucleosides that can be derivatized to include a phosphoramidate or phosphonoamidate, *e.g.* at the 5' position include:



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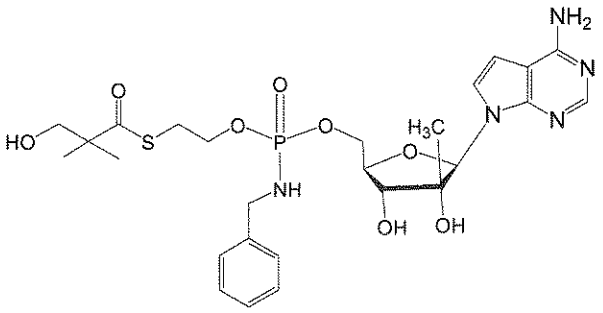


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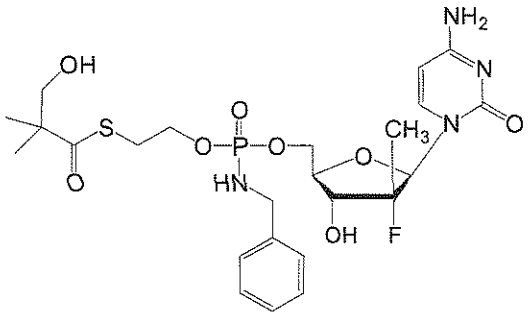


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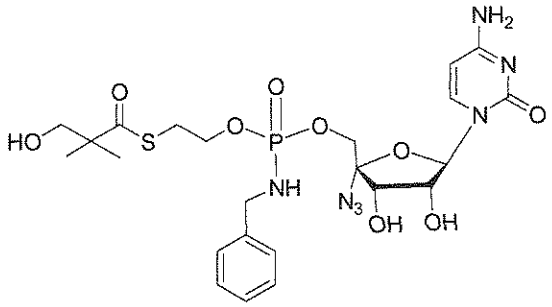
[0046] In one ~~embodiment~~example, phosphoramidate or phosphonoamidate nucleoside compounds include:



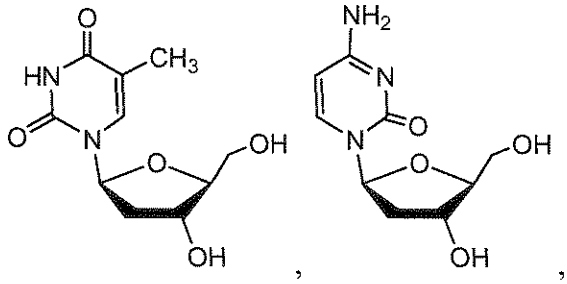
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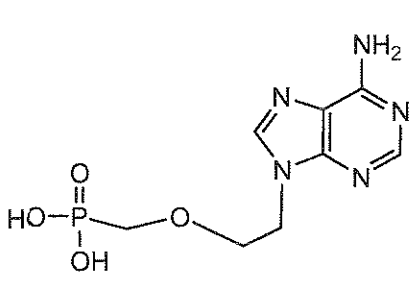


[0047] In one ~~embodiment~~example, the nucleosides that can be derivatized to include a phosphoramidate or phosphonoamidate, *e.g.* at the 5' position include:

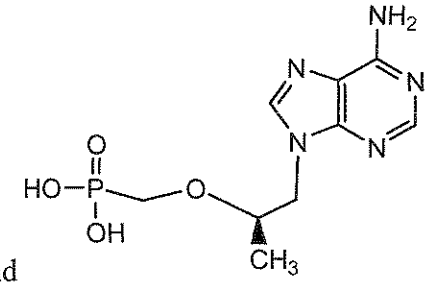


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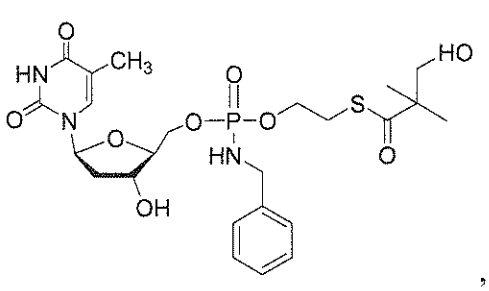


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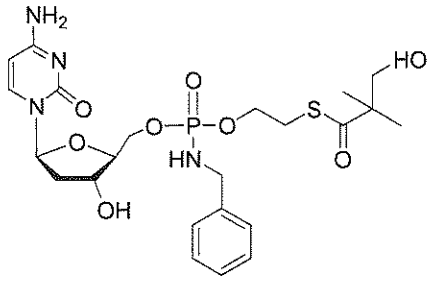


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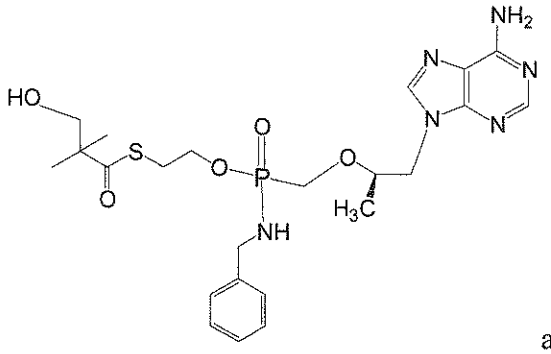
[0048] In one ~~embodiment~~example, phosphoramidate or phosphonoamidate nucleoside compounds include:



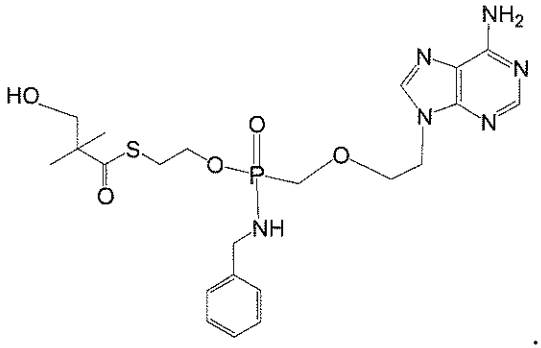
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and



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[0049] In one ~~aspect~~example, the compounds described herein are provided or administered in combination with a second therapeutic agent, such as one useful for the treatment or prevention of HBV and/or HCV infections. Exemplary therapeutic agents are described in detail in the sections below.

[0050] In another ~~aspect~~example, provided are pharmaceutical compositions, single unit dosage forms, and kits suitable for use in treating or preventing disorders such as HBV and/or HCV infections which comprise a therapeutically or prophylactically effective amount of a compound described herein, e.g. of Formula I, IIa or IIb, and a therapeutically or prophylactically effective amount of a second therapeutic such as one useful for the treatment or prevention of HBV and/or HCV infections.

[0051] In certain ~~embodiments~~examples, a method of treatment of a liver disorder is provided comprising administering to an individual in need thereof a treatment

effective amount of a phosphoramidate or phosphonoamidate derivative of a nucleoside or nucleoside analogue, wherein optionally the derivative is a *S*-pivaloyl-2-thioethyl phosphoramidate or *S*-pivaloyl-2-thioethyl phosphonoamidate derivative. The derivative is optionally selected from the compounds disclosed herein.

[0052] In some ~~embodiments~~examples, provided herein are:

(a) compounds as described herein, *e.g.* of Formula I, IIa or IIb, and pharmaceutically acceptable salts and compositions thereof;

(b) compounds as described herein, *e.g.* of Formula I, IIa or IIb, and pharmaceutically acceptable salts and compositions thereof for use in the treatment and/or prophylaxis of a liver disorder including *Flaviviridae* infection, especially in individuals diagnosed as having a *Flaviviridae* infection or being at risk of becoming infected by hepatitis C;

(c) processes for the preparation of compounds as described herein, *e.g.* of Formula I, IIa or IIb, as described in more detail below;

(d) pharmaceutical formulations comprising a compound as described herein, *e.g.* of Formula I, IIa or IIb, or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent;

(e) pharmaceutical formulations comprising a compound as described herein, *e.g.* of Formula I, IIa or IIb, or a pharmaceutically acceptable salt thereof together with one or more other effective anti-HCV agents, optionally in a pharmaceutically acceptable carrier or diluent;

(f) a method for the treatment and/or prophylaxis of a host infected with *Flaviviridae* that includes the administration of an effective amount of a compound as described herein, *e.g.* of Formula I, IIa or IIb, its pharmaceutically acceptable salt or composition;

(g) a method for the treatment and/or prophylaxis of a host infected with *Flaviviridae* that includes the administration of an effective amount of a compounds as described herein, *e.g.* of Formula I, IIa or IIb, its pharmaceutically acceptable salt or composition in combination and/or alternation with one or more effective anti-HCV agent;

(h) compounds as described herein, *e.g.* of Formula I, IIa or IIb, and pharmaceutically acceptable salts and compositions thereof for use in the treatment and/or prophylaxis of a HBV infection, especially in individuals diagnosed as having an HBV infection or being at risk of becoming infected by hepatitis B;

(i) pharmaceutical formulations comprising a compound as described herein, *e.g.* of Formula I, IIa or IIb, or a pharmaceutically acceptable salt thereof together with one or more other effective anti-HBV agents, optionally in a pharmaceutically acceptable carrier or diluent;

(j) a method for the treatment and/or prophylaxis of hepatitis B infections and other related conditions such as anti-HBV antibody positive and HBV-positive conditions, chronic liver inflammation caused by HBV, cirrhosis, acute hepatitis, fulminant hepatitis, chronic persistent hepatitis, and fatigue that includes administering an effective amount of a compound as described herein, *e.g.* of Formula I, IIa or IIb, or its pharmaceutically acceptable salt or composition.

(k) a prophylactic method to prevent or retard the progression of clinical illness in individuals who are anti-HBV antibody or HBV-antigen positive or who have been exposed to HBV.

[0053] *Flaviviridae* which can be treated are, e.g., discussed generally in *Fields Virology*, Editors: Fields, B. N., Knipe, D. M., and Howley, P. M., Lippincott-Raven Publishers, Philadelphia, PA, Chapter 31, 1996. In a particular ~~embodiment~~example of the invention, the *Flaviviridae* is HCV. In an alternate ~~embodiment~~example, the *Flaviviridae* is a flavivirus or pestivirus. Specific flaviviruses include, without limitation: Absettarov, Alfuy, Apoi, Aroa, Bagaza, Banzi, Bouboui, Bussuquara, Cacipacore, Carey Island, Dakar bat, Dengue 1, Dengue 2, Dengue 3, Dengue 4, Edge Hill, Entebbe bat, Gadgets Gully, Hanzalova, Hypr, Ilheus, Israel turkey meningoencephalitis, Japanese encephalitis, Jugra, Jutiapa, Kadam, Karshi, Kedougou, Kokobera, Koutango, Kumlinge, Kunjin, Kyasanur Forest disease, Langat, Louping ill, Meaban, Modoc, Montana myotis leukoencephalitis, Murray valley encephalitis, Naranjal, Negishi, Ntaya, Omsk hemorrhagic fever, Phnom-Penh bat, Powassan, Rio Bravo, Rocio, Royal Farm, Russian spring-summer encephalitis, Saboya, St. Louis encephalitis, Sal