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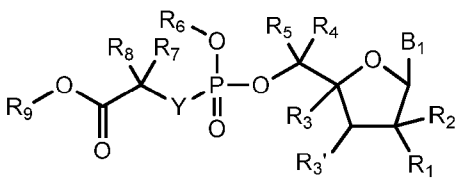
(54) Title: DEUTERATED NUCLEOSIDE PRODRUGS USEFUL FOR TREATING HCV



Formula (I)

(57) Abstract: Deuterated nucleoside analogs of Formula (I) and the pharmaceutically acceptable salts thereof are provided by this disclosure Formula (I) The variables, e.g., B_1, Y, R_1, R_2, R_3, $R_{3'}$, R_4, R_5, R_6, R_7, R_8, and R_9 carry definitions set forth in the disclosure. Compounds of Formula (I) are deuterated at one or more positions and the deuterium enrichment at each deuterated positions is at least 50%. Compounds and salts of Formula (I) are useful for treating viral infections, including HCV infections.

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PATENT APPLICATION IN THE UNITED STATES PATENT OFFICE

DEUTERATED NUCLEOSIDE PRODRUGS USEFUL FOR TREATING HCV

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 61/811,464, filed April 12, 2013, which is hereby incorporated by reference in its entirety.

BACKGROUND

[0002] An estimated 3% of the world's population is infected with the hepatitis C virus. Of those exposed to HCV, 80% to 85% become chronically infected, at least 30 % develop cirrhosis of the liver and 1-4% develop hepatocellular carcinoma. Hepatitis C Virus (HCV) is one of the most prevalent causes of chronic liver disease in the United States, reportedly accounting for about 15 percent of acute viral hepatitis, 60 to 70 percent of chronic hepatitis, and up to 50 percent of cirrhosis, end-stage liver disease, and liver cancer. Chronic HCV infection is the most common cause of liver transplantation in the U.S., Australia, and most of Europe. Hepatitis C causes an estimated 10,000 to 12,000 deaths annually in the United States. While the acute phase of HCV infection is usually associated with mild symptoms, some evidence suggests that only about 15% to 20% of infected people will spontaneously clear HCV.

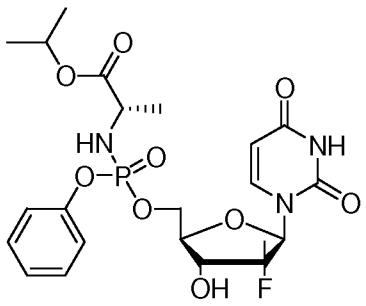
[0003] HCV is an enveloped, single-stranded RNA virus that contains a positive-stranded genome of about 9.6 kb. HCV is classified as a member of the Hepacivirus genus of the family Flaviviridae. At least 4 strains of HCV, GT-1 – GT-4, have been characterized.

[0004] The HCV lifecycle includes entry into host cells; translation of the HCV genome, polyprotein processing, and replicase complex assembly; RNA replication, and virion assembly and release. In the RNA replication process, a complementary negative strand copy of the genomic RNA is produced. The negative strand copy is used as a template to synthesize additional positive strand genomic RNAs that may participate in translation, replication, packaging, or any combination thereof to produce progeny virus.

[0005] There are several proteins in hepatitis C that have been targeted for drug therapy. NS5A is a zinc-binding proline rich hydrophilic phospho-protein with no inherent enzymatic activity, which can be inhibited with certain non-nucleotide compounds. NS5B is a key enzyme which plays the major role in replicating HCV's viral RNA using a viral positive RNA strand as a template, which has been inhibited with synthetic nucleoside derivatives. NS2-3 protease is an enzyme responsible for proteolytic cleavage

between NS2 and NS3, which are non-structural proteins. NS3 protease is responsible for the cleavage of the non-structural protein downstream. RNA helicase uses ATP hydrolysis to unwind RNA.

[0006] Sofosbuvir (Sovaldi, see structure below) is a nucleoside phosphoramidate NS5B inhibitor approved in December 2013 for the treatment of HCV. The approved labeling recommends the following regimens: (i) for genotypes 2 and 3 a 400 mg once a day oral tablet in combination with ribavirin and (ii) for genotypes 1 and 4 a 400 mg once a day oral tablet (triple combination therapy) with ribavirin and pegylated interferon. The Sofosbuvir treatment lasts 12 weeks for genotypes 1, 2 and 4 and 24 weeks for genotype 3. Sofosbuvir can also be used with ribavirin for the treatment of chronic hepatitis C patients with hepatocellular carcinoma awaiting liver transplantation for up to 48 weeks or until liver transplantation to prevent post-transplant HCV infection. The FDA granted Sovaldi Priority Review and Breakthrough Therapy designation based on data from several large clinical trials that indicated a sustained viral response (SVR) of twelve weeks in 50-90 percent of the trial participants. Patients who achieve "SVR12" are often considered cured.



(Sofosbuvir)

[0007] Alios BioPharma, Inc. licensed ALS-2200 to Vertex Pharmaceuticals Inc. for hepatitis C treatment development in June 2011. ALS-2200 is a mixture of diastereomers at a chiral phosphorus stereocenter. Vertex changed the name to VX-135, which is currently in Phase II clinical trials. While the companies have not disclosed the chemical structure of VX-135, they have said that it is a nucleotide analog prodrug, and an NS5B inhibitor. In 2013, the FDA placed VX-135 on partial clinical hold after three patients receiving high dosages of the medicine showed liver toxicity. Lowering the dose of a nucleoside inhibitor to avoid toxicity can sometimes also compromise or lower efficacy. Vertex announced in January 2014 that VX-135 in combination with daclastavir (Bristol-Myers Squibb NS5A inhibitor) had completed a Phase 2a trial. In an intent-to-treat analysis, the sustained viral response rate four weeks after the completion of treatment (SVR4) was 83% (10 of 12) in treatment-naïve genotype 1 infected individuals who received 200 mg VX-135 in combination with daclatasvir. One patient exhibited a serious adverse event of vomiting/nausea. The eleven remaining patients completed 12 weeks of treatment, for a completion of treatment rate (SVR4) of 91% .

[0008] Idenix Pharmaceuticals Inc. is developing IDX21437 for the treatment of hepatitis C, which is a uridine nucleoside prodrug NS5B inhibitor. The details of the chemical structure have not been released to date. In April 2014, Idenix announced that once-daily 300 mg IDX21437 for seven days led to a mean maximum reduction in viral load of 4.2-4.3 log10 IU/mL in 18 treatment naïve patients with genotype 1, 2 or 3.

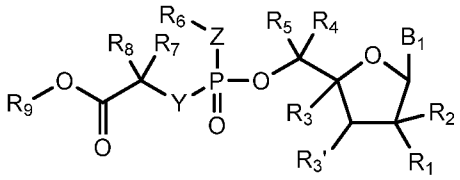
[0009] Despite progress in the area of hepatitis C treatment, there have also been a number of difficult setbacks. BMS-986094, a guanine-based phosphoramidate for hepatitis C was pulled from clinical trials after the death of a patient due to heart failure. BMS thereafter announced in 2013 that it was exiting the hepatitis C research area. Following the BMS drug withdrawal, Idenix Pharmaceuticals's similar phosphoramidate NS5B inhibitor, IDX 19368, was placed on clinical hold and ultimately discontinued. This followed the previous clinical hold and discontinuation of development of the phosphoramidate IDX184 for the same indication.

[0010] It is known that effective treatment against hepatitis C includes combination therapy, due to the onset of viral resistance during monotherapy. Given the documented challenges of developing optimal hepatitis C agents, and the fact that multiple optimal agents are required for effective therapy, there is a strong need for additional hepatitis C agents.

SUMMARY

[0011] Nucleoside analogs are a class of compounds that have known anti-viral activity, including, in some instances, anti-HCV activity. Nucleoside analogs are particularly useful in combination with other direct-acting anti-HCV compounds.

[0012] The present disclosure provides a novel class of deuterated nucleoside analogs of Formula (I) and the pharmaceutically acceptable salts thereof.



Formula (I)

[0013] Within Formula (I) the variables, e.g., B_1, Y, A, R_1, R_2, R_3, R_3', R_4, R_5, R_6, R_7, R_8, and R_9 carry the following definitions.

[0014] Y is NH or O and Z is CH_2 or O.

[0015] R_1 is hydroxyl, fluoro, or $-OCD_3$ and R_2 is hydrogen or deuterium or R_2 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, or C_2-C_6alkynyl; each of which is optionally deuterated and optionally substituted.

[0016] Or, R_1 and R_2 are joined to form a 3- to 6-membered cycloalkyl ring or a 3- to 6-membered heterocycloalkyl ring containing one heteroatom selected from N, O, and S, each of which is optionally substituted.

[0017] R_3 is hydrogen, deuterium, halogen, or–N_3; or R_3 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl, (C_3-C_6cycloalkyl)C_0-C_4carbhydryl, (4- to 6-membered heterocycloalkyl)C_0-C_4carbhydryl, (aryl)C_0-C_4carbhydryl, or (heteroaryl)C_0-C_4carbhydryl, each of which is optionally deuterated and optionally substituted; and R_3' is hydroxyl.

[0018] Or, R_3 and R_3' are taken together to form a 3- to 6- membered ring optionally containing one heteroatom selected from N, O, and S, which ring is optionally substituted with one or more substituents independently selected from halogen, hydroxyl, C_1-C_2alkyl, and C_1-C_2alkoxy.

[0019] R_4 is hydrogen, deuterium, halogen, C_1-C_2haloalkyl, or C_1-C_2haloalkoxy; or R_4 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl, or C_1-C_6alkoxy, each of which is optionally deuterated and optionally substituted; and R_5 is hydrogen, deuterium, or halogen; or R_5 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl, or C_1-C_6alkoxy, each of which is optionally deuterated and optionally substituted.

[0020] Or, R_4 and R_5 are taken together to form a 3- to 6- membered ring optionally containing one heteroatom selected from N, O, and S, which ring is optionally substituted with one or more substituents independently selected from halogen, hydroxyl, C_1-C_2alkyl, and C_1-C_2alkoxy.

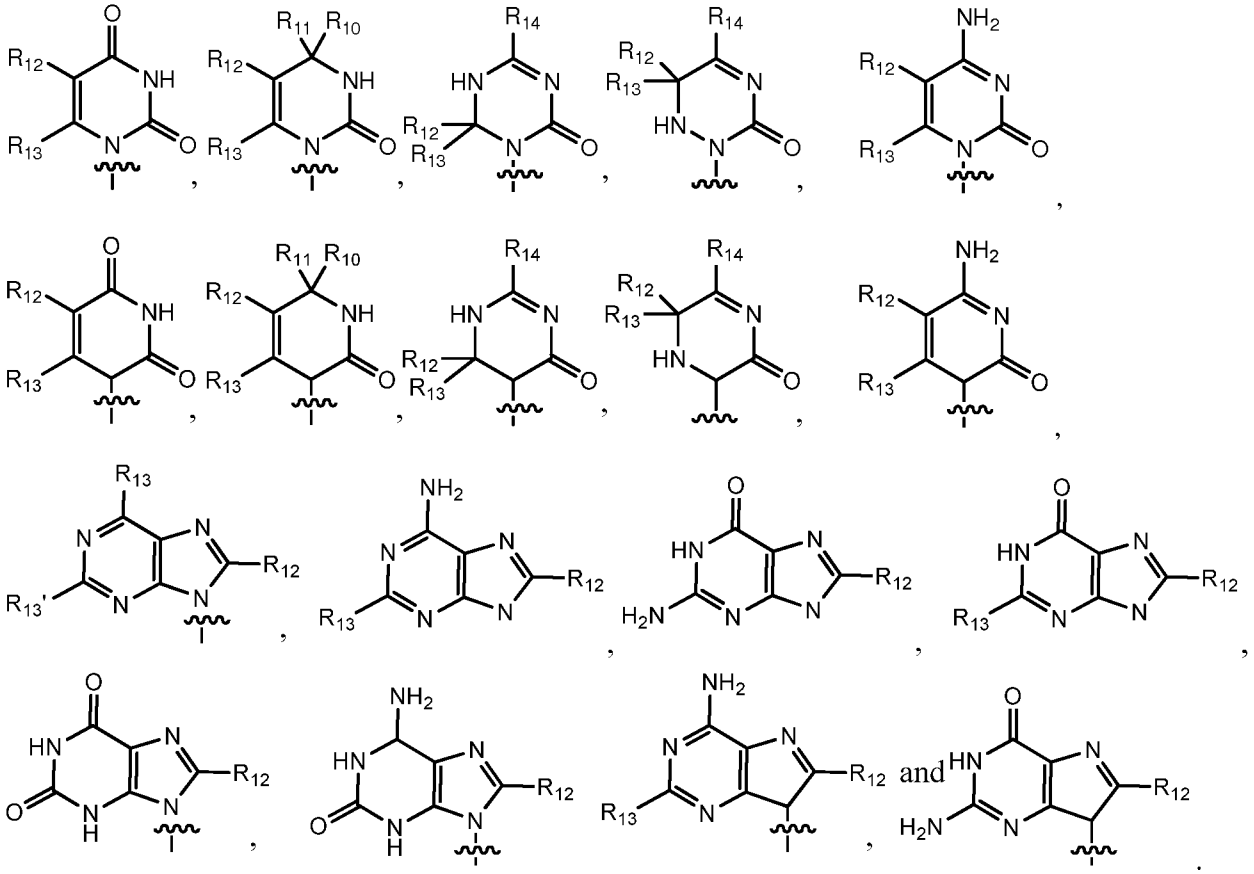
[0021] R_6 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl, (aryl)C_0-C_2alkyl, or 5- to 6-membered monocyclic heteroaryl containing 1 to 3 heteroatoms independently chosen from N, O, and S, or 8- to 10- membered bicyclic heteroaryl containing 1 to 4 heteroatoms independently chosen from N, O, and S; each of which R_6 is optionally substituted.

[0022] R_7 is hydrogen, halogen, C_1-C_2haloalkyl, or C_1-C_2haloalkoxy; or R_7 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, (C_3-C_6cycloalkyl)C_0-C_4alkyl, or (aryl)C_0-C_2alkyl; each of which is optionally substituted; and R_8 is hydrogen, halogen, C_1-C_2haloalkyl, or C_1-C_2haloalkoxy; or R_8 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl,or C_1-C_6alkoxy, each of which is optionally substituted.

[0023] Or, R_7 and R_8 are taken together to form a 3-to 6-membered cycloalkyl ring or 3- to 6-membered heterocycloalkyl ring containing one heteroatom chosen from N, O, and S; each of which is optionally substituted.

[0024] R_9 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl, (C_3-C_7cycloalkyl)C_0-C_4carbhydryl, (aryl)C_0-C_4carbhydryl, (3- to 6-membered heterocycloalkyl)C_0-C_4carbhydryl, or (heteroaryl)C_0-C_4carbhydryl, each of which is optionally substituted.

[0025] B_1 is a base selected from



[0026] R_{10} and R_{11} are independently hydrogen and deuterium.

[0027] R_{12}, R_{13}, and R_{13}' are independently hydrogen, deuterium, methyl, and $-CD_3$.

[0028] R_{14} is hydrogen, deuterium, hydroxyl, amino; C_1-C_4alkoxy, deuterated C_1-C_4alkoxy, C_1-C_4alkylester, or mono- or di-C_1-C_4alkylcarbamate.

[0029] Wherein each position represented by D has a deuterium enrichment of at least 50%; and one or more of R_1, R_2, R_4, R_5, R_{10}, R_{11}, R_{12}, R_{13}, R_{13}', and R_{14} is deuterium with a deuterium enrichment of at least 50% or a deuterated group with at least one position having a deuterium enrichment of at least 50%. The disclosure also includes a pharmaceutical composition comprising a compound or salt of Formula (I) together with a pharmaceutically acceptable carrier. The pharmaceutical composition may contain a compound or salt of Formula (I) as the only active agent or may contain one or more additional active agents, such as an HCV HS3 protease inhibitor and an HCV NS5a inhibitor.

[0030] The disclosure also includes a method of treating hepatitis C infection, comprising providing a therapeutically effective amount of a compound of Formula (I) or a pharmaceutical composition containing a compound of Formula (I) to a patient in need thereof.

DETAILED DESCRIPTION

CHEMICAL DESCRIPTION AND TERMINOLOGY

[0031] Compounds are described using standard nomenclature. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. Unless clearly contraindicated by the context each compound name includes the free acid or free base form of the compound as well as all pharmaceutically acceptable salts of the compound.

[0032] The term "Formula (I)" encompasses all compounds that satisfy Formula (I), including any enantiomers, racemates and stereoisomers, as well as all pharmaceutically acceptable salts of such compounds. "Formula (I)" includes all subgeneric groups of Formula (I), such as Formula (II). Formula (III), and Formula (IV) and also includes pharmaceutically acceptable salts of a compound of Formula (I), unless clearly contraindicated by the context in which this phrase is used.

[0033] The terms "a" and "an" do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced item. The term "or" means "and/or". The open-ended transitional phrase "comprising" encompasses the intermediate transitional phrase "consisting essentially of" and the close-ended phrase "consisting of." Claims reciting one of these three transitional phrases, or with an alternate transitional phrase such as "containing" or "including" can be written with any other transitional phrase unless clearly precluded by the context or art. Recitation of ranges of values are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The endpoints of all ranges are included within the range and independently combinable. All methods described herein can be performed in a suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as"), is intended merely to better illustrate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention as used herein. Unless defined otherwise, technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

[0034] Compounds of Formula (I) include compounds of the formula having isotopic substitutions at any position. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example, and without limitation, isotopes of hydrogen include tritium and deuterium and isotopes of carbon include ^{11}C, ^{13}C, and ^{14}C. While the compounds of Formula (I) require a moderate or high enrichment of deuteration (substitution of a hydrogen with deuterium) at identified positions, Formula (I) includes embodiments in which other positions are isotopically enriched.

[0035] An "active agent" means a compound (including a compound disclosed herein), element, or mixture that when administered to a patient, alone or in combination with another compound, element, or mixture, confers, directly or indirectly, a physiological effect on the patient. The indirect physiological effect may occur via a metabolite or other indirect mechanism.

[0036] A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, $-(C=O)NH_2$ is attached through carbon of the keto (C=O) group.

[0037] "Alkyl" is a branched or straight chain saturated aliphatic hydrocarbon group, having the specified number of carbon atoms, generally from 1 to about 12 carbon atoms. The term C_1-C_6alkyl as used herein indicates an alkyl group having from 1, 2, 3, 4, 5, or 6 carbon atoms. Other embodiments include alkyl groups having from 1 to 8 carbon atoms, 1 to 4 carbon atoms or 1 or 2 carbon atoms, e.g. C_1-C_8alkyl, C_1-C_4alkyl, and C_1-C_2alkyl. When C_0-C_n alkyl is used herein in conjunction with another group, for example, (C_3-C_7cycloalkyl)C_0-C_4 alkyl, the indicated group, in this case cycloalkyl, is either directly bound by a single covalent bond (C_0alkyl), or attached by an alkyl chain having the specified number of carbon atoms, in this case 1, 2, 3, or 4 carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, 3-methylbutyl, t-butyl, n-pentyl, and sec-pentyl.

[0038] "Alkenyl" is a branched or straight chain aliphatic hydrocarbon group having one or more double carbon-carbon bonds that may occur at any stable point along the chain, having the specified number of carbon atoms. Examples of alkenyl include, but are not limited to, ethenyl and propenyl.

[0039] "Alkynyl" is a branched or straight chain aliphatic hydrocarbon group having one or more triple carbon-carbon bonds that may occur at any stable point along the chain, having the specified number of carbon atoms. Examples of alkynyl include, but are not limited to, ethynyl and propynyl.

[0040] "Allenyl" is an alkenyl group having two consecutive double bonds, i.e., a group of formula $-C=C=CH_2$.

[0041] "Alkoxy" is an alkyl group as defined above with the indicated number of carbon atoms covalently bound to the group it substitutes by an oxygen bridge (-O-). Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, 2-butoxy, t-butoxy, n-pentoxy, 2-pentoxy, 3- pentoxy, isopentoxy, neopentoxy, n-hexoxy, 2-hexoxy, 3-hexoxy, and 3- methylpentoxy.

[0042] "Alkanoyl" is an alkyl group as defined above with the indicated number of carbon atoms covalently bound to the group is substitutes through a carbonyl (C=O) bridge. The carbonyl carbon is included in the number of carbons, that is C_2alkanoyl is a $CH_3(C=O)$- group.

[0043] "Alkylester" is an alkyl group as defined herein covalently bound to the group it substitutes by an ester linkage. The ester linkage may be in either orientation, e.g., a group of the formula –O(C=O)alkyl or a group of the formula –(C=O)Oalkyl.

[0044] "Cycloalkyl" is a saturated hydrocarbon ring group, having the specified number of carbon atoms. Monocyclic cycloalkyl groups typically have from 3 to about 8 carbon ring atoms or from 3 to 7 (3, 4, 5, 6, or 7) carbon ring atoms. Cycloalkyl substituents may be pendant from a substituted nitrogen or carbon atom, or a substituted carbon atom that may have two substituents may have a cycloalkyl group, which is attached as a spiro group. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0045] "Haloalkyl" indicates both branched and straight-chain alkyl groups having the specified number of carbon atoms, substituted with 1 or more halogen atoms, up to the maximum allowable number of halogen atoms. Examples of haloalkyl include, but are not limited to, trifluoromethyl, difluoromethyl, 2-fluoroethyl, and penta-fluoroethyl.

[0046] "Haloalkoxy" indicates a haloalkyl group as defined herein attached through an oxygen bridge (oxygen of an alcohol radical).

[0047] "Halo" or "halogen" indicates any of fluoro, chloro, bromo, and iodo.

[0048] "Aryl" indicates aromatic groups containing only carbon in the aromatic ring or rings. Typical aryl groups contain 1 to 3 separate, fused, or pendant rings and from 6 to about 18 ring atoms, without heteroatoms as ring members. When indicated, such aryl groups may be further substituted with carbon or non-carbon atoms or groups. Such substitution may include fusion to a 5 to 7-membered saturated cyclic group that optionally contains 1 or 2 heteroatoms independently chosen from N, O, and S, to form, for example, a 3,4-methylenedioxy-phenyl group. Aryl groups include, for example, phenyl, naphthyl, including 1- naphthyl and 2-naphthyl, and bi-phenyl.

[0049] "Heteroaryl" indicates a stable monocyclic aromatic ring having the indicated number of ring atoms which contains from 1 to 3, or in some embodiments from 1 to 2, heteroatoms chosen from N, O, and S, with remaining ring atoms being carbon, or a stable bicyclic or tricyclic system containing at least one 5- to 7-membered aromatic ring which contains from 1 to 3, or in some embodiments from 1 to 2, heteroatoms chosen from N, O, and S, with remaining ring atoms being carbon. Monocyclic heteroaryl groups typically have from 5 to 7 ring atoms. In some embodiments bicyclic heteroaryl groups are 9- to 10-membered heteroaryl groups, that is, groups containing 9 or 10 ring atoms in which one 5- to 7-member aromatic ring is fused to a second aromatic or non-aromatic ring. When the total number of S and O atoms in the heteroaryl group exceeds 1, these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heteroaryl group is not more than 2. It is particularly preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1. Examples of heteroaryl groups include, but are not limited to, oxazolyl, pyranyl, pyrazinyl, pyrazolopyrimidinyl, pyrazolyl, pyridizinyl, pyridyl, pyrimidinyl, pyrrolyl, quinolinyl, tetrazolyl, thiazolyl, thienylpyrazolyl, thiophenyl, triazolyl, benzo[*d*]oxazolyl, benzofuranyl, benzothiazolyl,

benzothiophenyl, benzoxadiazolyl, dihydrobenzodioxynyl, furanyl, imidazolyl, indolyl, and isoxazolyl. "Heteroaryloxy" is a heteroaryl group as described bound to the group it substituted via an oxygen bridge.

[0050] "Heterocycloalkyl" is a saturated ring group, having 1, 2, 3, or 4 heteroatoms independently chosen from N, S, and O, with remaining ring atoms being carbon. Monocyclic heterocycloalkyl groups typically have from 3 to about 8 ring atoms or from 4 to 6 ring atoms. Examples of heterocycloalkyl groups include morpholinyl, piperazinyl, piperidinyl, and pyrrolinyl.

[0051] "Carbhydryl" is a saturated or unsaturated aliphatic group containing the indicated number of carbon atoms. "carbhydryl" may be used in conjunction with other groups, such as aryl, as in "(aryl)carbhydryl."

[0052] The term "mono- and/ or di-alkylamino" indicates secondary or tertiary alkyl amino groups, wherein the alkyl groups are independently chosen alkyl groups, as defined herein, having the indicated number of carbon atoms. The point of attachment of the alkylamino group is on the nitrogen. Examples of mono- and di-alkylamino groups include ethylamino, dimethylamino, and methyl-propyl-amino.

[0053] "Mono- and/or di-alkylcarbamate" includes mono-alkylcarbamate groups of formula $(alkyl_1)O(C=O)NH$- or a dialkylcarboxamide groups of the formula $(alkyl_1)O(C=O)N(alkyl_2)$- in which the point of attachment of the mono- or dialkylcarboxamide substituent to the molecule it substitutes is on the nitrogen of the carbamate amino. The term "mono and/ or di-alkylcarbamate" also includes groups of the formula $(alkyl_1)NH(C=O)O$- and $(alkyl_1)N(alkyl_2)(C=O)O$- in which the carbamate is covalently bound to the group it substitutes by its non-keto oxygen atom. The groups $alkyl_1$ and $alkyl_2$ are independently chosen alkyl groups, carrying the alkyl definition set forth in this disclosure and having the indicated number of carbon atoms.

[0054] The term "substituted", as used herein, means that any one or more hydrogens on the designated atom or group is replaced with a selection from the indicated group, provided that the designated atom's normal valence is not exceeded. When the substituent is oxo (i.e., =O) then 2 hydrogens on the atom are replaced. When an oxo group substitutes aromatic moieties, the corresponding partially unsaturated ring replaces the aromatic ring. For example a pyridyl group substituted by oxo is a pyridone. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds or useful synthetic intermediates. A stable compound or stable structure is meant to imply a compound that is sufficiently robust to survive isolation from a reaction mixture, and subsequent formulation into an effective therapeutic agent. Unless otherwise specified substituents are named into the core structure. For example, it is to be understood that when aminoalkyl is listed as a possible substituent the point of attachment of this substituent to the core structure is in the alkyl portion.

[0055] Suitable groups that may be present on a "substituted" or "optionally substituted" position include, but are not limited to, e.g., halogen; cyano; hydroxyl; nitro; azido; alkanoyl (such as a C_2-C_6 alkanoyl group); carboxamide; alkyl groups (including cycloalkyl groups) having 1 to about 8 carbon atoms, or 1 to about 6 carbon atoms; alkenyl and alkynyl groups including groups having one or more unsaturated linkages and from 2 to about 8, or 2 to about 6 carbon atoms; alkoxy groups having one or more oxygen linkages and from 1 to about 8, or from 1 to about 6 carbon atoms; aryloxy such as phenoxy; alkylthio groups including those having one or more thioether linkages and from 1 to about 8 carbon atoms, or from 1 to about 6 carbon atoms; alkylsulfinyl groups including those having one or more sulfinyl linkages and from 1 to about 8 carbon atoms, or from 1 to about 6 carbon atoms; alkylsulfonyl groups including those having one or more sulfonyl linkages and from 1 to about 8 carbon atoms, or from 1 to about 6 carbon atoms; aminoalkyl groups including groups having one or more N atoms and from 1 to about 8, or from 1 to about 6 carbon atoms; aryl having 6 or more carbons and one or more rings, (e.g., phenyl, biphenyl, naphthyl, or the like, each ring either substituted or unsubstituted aromatic); arylalkyl having 1 to 3 separate or fused rings and from 6 to about 18 ring carbon atoms, with benzyl being an exemplary arylalkyl group; arylalkoxy having 1 to 3 separate or fused rings and from 6 to about 18 ring carbon atoms, with benzyloxy being an exemplary arylalkoxy group; or a saturated, unsaturated, or aromatic heterocyclic group having 1 to 3 separate or fused rings with 3 to about 8 members per ring and one or more N, O or S atoms, e.g. coumarinyl, quinolinyl, isoquinolinyl, quinazolinyl, pyridyl, pyrazinyl, pyrimidinyl, furanyl, pyrrolyl, thienyl, thiazolyl, triazinyl, oxazolyl, isoxazolyl, imidazolyl, indolyl, benzofuranyl, benzothiazolyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholinyl, piperazinyl, and pyrrolidinyl. Such heterocyclic groups may be further substituted, e.g. with hydroxy, alkyl, alkoxy, halogen and amino. In certain embodiments "optionally substituted" includes one or more substituents independently chosen from halogen, hydroxyl, amino, cyano,
-CHO, -COOH, -$CONH_2$, C_1-C_6alkyl, C_2-C_6alkenyl, C_1-C_6alkoxy, C_2-C_6alkanoyl, C_1-C_6alkylester,
(mono- and di-C_1-C_6alkylamino)C_0-C_2alkyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0056] Deuteration" and "deuterated" mean that a hydrogen at the specified position is replaced by deuterium. In any sample of a compound of Formula I in which a position is deuterated some discrete molecules of the compound of Formula I will likely have hydrogen, rather than deuterium, at the specified position. However the percent of molecules of the compound of Formula I in the sample which have deuterium at the specified position will be much greater than would naturally occur. The deuterium at the deuterated position is enriched. The term "enriched" as used herein, refers to the percentage of deuterium versus other hydrogen species at that location. As an example, if it is said that a position in the compound of Formula I contains 50% deuterium enrichment, that means that rather than hydrogen at the specified position the deuterium content is 50%. For clarity, it is confirmed that the term "enriched" as used herein

does not mean percentage enriched over natural abundance. In one embodiment, deuterated compounds of Formula I will have at least 10% deuterium enrichment at any deuterated position. In other embodiments, there will be at least 50%, at least 90%, or at least 95% deuterium enrichment at the specified deuterated position or positions. A "deuterated substituent" is a substituent in which at least one hydrogen is replaced by deuterium at the specified percent enrichment.-"Optionally deuterated" means that the position may be either hydrogen and the amount of deuterium at the position is only the naturally occurring level of deuterium or the position is enriched with deuterium above the naturally occurring deuterium level.

[0057] A "dosage form" means a unit of administration of an active agent. Examples of dosage forms include tablets, capsules, injections, suspensions, liquids, emulsions, creams, ointments, suppositories, inhalable forms, transdermal forms, and the like.

[0058] "Pharmaceutical compositions" are compositions comprising at least one active agent, such as a compound or salt of Formula (I), and at least one other substance, such as a carrier. Pharmaceutical compositions optional contain one or more additional active agents. When specified, pharmaceutical compositions meet the U.S. FDA's GMP (good manufacturing practice) standards for human or non-human drugs. "Pharmaceutical combinations" are combinations of at least two active agents which may be combined in a single dosage form or provided together in separate dosage forms with instructions that the active agents are to be used together to treat a disorder, such as hepatitis C.

[0059] "Pharmaceutically acceptable salts" includes derivatives of the disclosed compounds in which the parent compound is modified by making inorganic and organic, non-toxic, acid or base addition salts thereof. The salts of the present compounds can be synthesized from a parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate, or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred, where practicable. Salts of the present compounds further include solvates of the compounds and of the compound salts.

[0060] Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts and the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, conventional non-toxic acid salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and

the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, mesylic, esylic, besylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, HOOC-$(CH_2)_n$-COOH where n is 0-4, and the like. Lists of additional suitable salts may be found, e.g., in *Remington's Pharmaceutical Sciences,* 17th ed., Mack Publishing Company, Easton, Pa., p. 1418 (1985).

[0061] The term "carrier" applied to pharmaceutical compositions/ combinations of the invention refers to a diluent, excipient, or vehicle with which an active compound is provided.

[0062] A "pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition/ combination that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes an excipient that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable excipient" as used in the present application includes both one and more than one such excipient.

[0063] A "patient" is a human or non-human animal in need of medical treatment. Medical treatment can include treatment of an existing condition, such as a disease or disorder, prophylactic or preventative treatment, or diagnostic treatment. In some embodiments the patient is a human patient.

[0064] "Providing" means giving, administering, selling, distributing, transferring (for profit or not), manufacturing, compounding, or dispensing.

[0065] "Providing a compound of Formula (I) with at least one additional active agent" means the compound of Formula (I) and the additional active agent(s) are provided simultaneously in a single dosage form, provided concomitantly in separate dosage forms, or provided in separate dosage forms for administration separated by some amount of time that is within the time in which both the compound of Formula (I) and the at least one additional active agent are within the blood stream of a patient. In certain embodiments the compound of Formula (I) and the additional active agent need not be prescribed for a patient by the same medical care worker. In certain embodiments the additional active agent or agents need not require a prescription. Administration of the compound of Formula (I) or the at least one additional active agent can occur via any appropriate route, for example, oral tablets, oral capsules, oral liquids, inhalation, injection, suppositories or topical contact.

[0066] "Treatment," as used herein includes providing a compound of Formula (I), either as the only active agent or together with at least one additional active agent sufficient to: (a) prevent a disease or a symptom of a disease from occurring in a patient who may be predisposed to the disease but has not yet been diagnosed as having it (e.g. including diseases that may be associated with or caused by a primary disease (as in liver fibrosis that can result in the context of chronic HCV infection); (b) inhibiting the disease, i.e. arresting its development; and (c) relieving the disease, i.e., causing regression of the disease.

"Treating" and "treatment" also means providing a therapeutically effective amount of a compound of Formula (I), as the only active agent or together with at least one additional active agent to a patient having or susceptible to a hepatitis C infection.

[0067] A "therapeutically effective amount" of a pharmaceutical composition/ combination of this invention means an amount effective, when administered to a patient, to provide a therapeutic benefit such as an amelioration of symptoms, e.g., an amount effective to decrease the symptoms of a hepatitis C infection. For example a patient infected with a hepatitis C virus may present elevated levels of certain liver enzymes, including AST and ALT. A therapeutically effect amount is thus an amount sufficient to provide a significant reduction in elevated AST and ALT levels or an amount sufficient to provide a return of AST and ALT levels to the normal range. A therapeutically effective amount is also an amount sufficient to prevent a significant increase or significantly reduce the detectable level of virus or viral antibodies in the patient's blood, serum, or tissues. One method of determining treatment efficacy includes measuring HCV RNA levels by a conventional method for determining viral RNA levels such as the Roche TaqMan assay. In certain preferred embodiments treatment reduces HCV RNA levels below the limit of quantitation (30 IU/mL, as measured by the Roche TaqMan(R) assay) or more preferably below the limit of detection (10 IU/mL, Roche TaqMan).

[0068] A significant increase or reduction in the detectable level of virus or viral antibodies is any detectable change that is statistically significant in a standard parametric test of statistical significance such as Student's T-test, where $p < 0.05$.

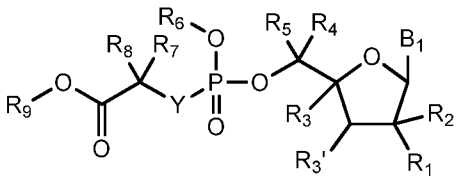
CHEMICAL DESCRIPTION

[0069] Formula (I) includes all subformulae thereof. In certain situations, the compounds of Formula (I) may contain one or more asymmetric elements such as stereogenic centers, stereogenic axes and the like, e.g. asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates or optically active forms. For compounds with two or more asymmetric elements, these compounds can additionally be mixtures of diastereomers. For compounds having asymmetric centers, it should be understood that all of the optical isomers and mixtures thereof are encompassed, unless the stereochemistry is explicitly stated. In addition, compounds with carbon-carbon double bonds may occur in Z- and E-forms, with all isomeric forms of the compounds being included in the present disclosure. In these situations, single enantiomers, i.e., optically active forms, can be obtained by asymmetric synthesis, synthesis from optically pure precursors, or by resolution of the racemates. Resolution of the racemates can also be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example using a chiral HPLC column.

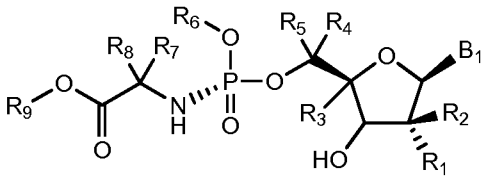
[0070] Where a compound exists in various tautomeric forms, the invention is not limited to any one of the specific tautomers, but rather includes all tautomeric forms.

[0071] Certain compounds are described herein using a general formula that includes variables, e.g. B_1, R_1- R_9. Unless otherwise specified, each variable within such a Formula (I) is defined independently of other variables. Thus, if a group is said to be substituted, e.g. with 0-2 R*, then the group may be substituted with up to two R* groups and R* at each occurrence is selected independently from the definition of R*. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[0072] In addition the compounds and salts of Formula (I) discussed in the SUMMARY section, the disclosure includes compounds and salt of Formula (I), (II) and (III)



(I)



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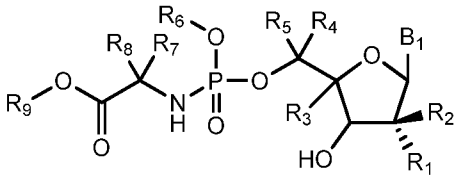


(III)

[0073] In another embodiment, the nucleoside derivative of Formula (I), (II) or (III) is administered as a phosphorus R or S stereoisomer, which is at least in 90% pure form, and typically, 95, 98 or 99% pure form. In another embodiment the compounds or salt of Formula (I), (II), or (III) is supplied as a 50/50 mixture of stereoisomers at the phosphorus chiral center.

Deuteration

[0074] The Each position represented by D in Formula (I)-(III) has a deuterium enrichment of at least 50%. One or more of R_1, R_2, R_4, R_5, R_{10}, R_{11}, R_{12}, R_{13}, R_{13}', and R_{14} in the compound of Formula (I) – (III) is deuterium with a deuterium enrichment of at least 50% or a deuterated substituent with at least one position in the deuterated substituent having a deuterium enrichment of at least 50%.

[0075] Each position represented by D in Formula (I)-(III) has a deuterium enrichment of at least 90%. One or more of R_1, R_2, R_4, R_5, R_{10}, R_{11}, R_{12}, R_{13}, R_{13}', and R_{14} in the compound of Formula (I) – (III)) is deuterium with a deuterium enrichment of at least 90% or a deuterated substituent with at least one position in the deuterated substituent having a deuterium enrichment of at least 90%.

[0076] Each position represented by D in Formula (I)-(III) has a deuterium enrichment of at least 90%. At least 2 of R_1, R_2, R_4, R_5, R_{10}, R_{11}, R_{12}, R_{13}, R_{13}', and R_{14} are deuterium with a deuterium enrichment of at least 90% or a deuterated substituent with at least one position in the deuterated substituent having a deuterium enrichment of at least 90%.Each position represented by D in Formula (I)-(III) has a deuterium enrichment of at least 95%. 2 or 3 of R_1, R_2, R_4, R_5, R_{10}, R_{11}, R_{12}, R_{13}, R_{13}', and R_{14} are deuterium with a deuterium enrichment of at least 95% or a deuterated substituent with at least one position in the deuterated substituent having a deuterium enrichment of at least 95%.

[0077] Each position represented by D in Formula (I)-(III) has a deuterium enrichment of at least 90%. 3 of R1, R_2, R_4, R_5, R_{10}, R_{11}, R_{12}, R_{13}, R_{13}', and R_{14} are deuterium with a deuterium enrichment of at least 90% or a deuterated substituent with at least one position in the deuterated substituent having a deuterium enrichment of at least 90%.

[0078] Each position represented by D in Formula (I)-(III) has a deuterium enrichment of at least 90%. At least R_4, R_5 and one of R_{12} and R_{13} are deuterium with a deuterium enrichment of at least 90% or a deuterated substituent with at least one position in the deuterated substituent having a deuterium enrichment of at least 90%.

[0079] It has been surprisingly discovered that compounds of Formula (I)-(III) in which R_4 and R_5 are both deuterium with a deuterium enrichment of at least 90% are particularly effective NS5B inhibitors and thus useful for the treatment of hepatitis C. In certain embodiments it is also preferred that R_2 is methyl and R_1 is hydroxyl.

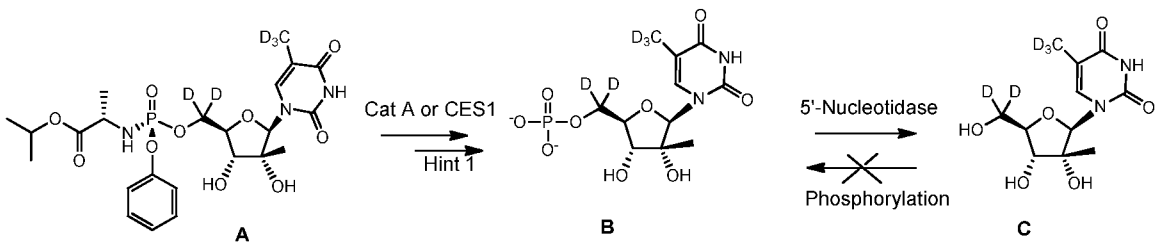
[0080] Upon administration to a patient a compound of Formula (I), (II), or (III) is first converted to the nucleoside monophosphate which is then further phosphorylated to the nucleoside triphosphate, which is the active species. Alternatively the nucleoside monophosphate may be dephosphorylated to the free nucleoside. The free nucleoside is inactive as a NS5B inhibitor. Nucleoside triphosphate (NTP) is the active species that inhibits viral replication in hepatocytes and its levels and intrinsic potency drive the effectiveness of the treatment.

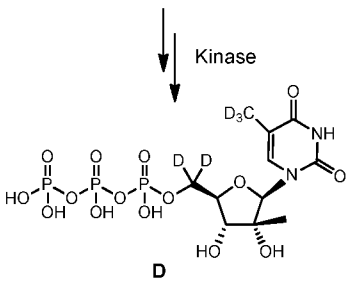
[0081] It has surprisingly been discovered that deuteration of the 5'-position of the nucleoside stabilizes the nucleoside derivative from dephosphorylation to the undesired 5'-OH, 5'-deuterated-nucleoside. This is surprising because the deuterium atom(s) are not cleaved during dephosphorylation and are not bound to an atom that is cleaved during dephosphorylation. The disclosure includes the use 5'-deuterium to produce a significant effect on metabolism and efficacy through a remote and

unexpectedly important secondary deuterium isotope effect. Such an important secondary deuterium isotope effect on de-monophosphorylation at the 5'-position has not been previously reported. By increasing the stability of the 5'-monophosphate of the nucleoside against dephosphorylation, an increase in the active 5'-triphosphate pool of the nucleoside is achieved, which can result in increased efficacy at a given oral dosage or equal efficacy using a lower dose of the nucleoside. It may also have a significant effect on the half-life, and thus pharmacokinetics, of the drug.

[0082] Therefore, in another embodiment, the present disclosure includes a method for treating a host afflicted with a disorder that is treatable with a nucleoside or nucleotide, the improvement comprising substituting one or both of the hydrogens at the 5'-position of the nucleoside or nucleotide with a deuterium with at least 90% enrichment over protium (i.e., less than 10% ^{1}H hydrogen) (and in other embodiments, 50, 95, 98 or 99% enrichment). The therapeutic effect of any nucleotide or nucleoside can be enhanced if the active metabolite is the mono, di or triphosphate of the nucleoside by 5'deuteration of the nucleoside, because 5'-deuteration increases the pool of the nucleoside monophosphate. Nucleoside monophosphate is metabolized to the diphosphate and/or triphosphate with the corresponding nucleoside diphosphate kinase and then nucleoside triphosphate kinase. This method is especially useful for nucleosides which are not easily monophosphorylated, and thus lose substantial activity in the presence of nucleotidases, that cannot be easily recovered by the action of nucleoside monophosphate kinase, such as a branched or highly derivatized nucleoside.

[0083] The conversion of nucleoside derivative (A) to nucleoside monophosphate (B) which can then be converted either to inactive nucleoside (C) or active triphosphate (D) follows.





Cat A: Cathepsin A
CES1: Carboxlyesterase 1

[0084] The efficacy of deuteration can be found indirectly by determining the level of nucleoside monophosphate and dephosphorylated nucleoside provided by a deuterated compound of Formula (I),

(II), or (III) as compared to the level of nucleoside monophosphate and dephosphorylated nucleoside provided by an undeuterated nucleoside monophosphate. A larger ratio of nucleoside monophosphate to dephosphorylated nucleoside is favorable as a higher percentage of nucleoside monophosphate remains and can be converted to the active nucleoside triphosphate. Levels of free nucleoside and nucleoside monophosphate in human hepatocytes can be determined by an LC/MS assay such as the human hepatocyte LCMS assay of Example 16.

[0085] The efficacy of deuteration can be determined directly by determining the level of triphosphorylated nucleoside as compared to the level of triphosphorylated nucleoside provided by an undeuterated nucleoside prodrug. The hepatocyte LCMS assay of Example 16 can also be used to determine nucleoside triphosphate levels.

[0086] The disclosure includes compounds and salts thereof of Formula (I), (II), and (III) and in which the variables meet any of the following conditions. Any combination of variables is within the scope of the disclosure as long as a stable compound results.

The Variable Y

[0087] Y is NH.

[0088] Y is O.

The Variables R_1 and R_2

[0089] R_1 is hydroxyl, fluoro, or $-OCD_3$; R_2 is hydrogen or deuterium; or R_2 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, or C_2-C_6alkynyl; each of which is optionally deuterated and optionally substituted.

[0090] R_1 is hydroxyl or fluoro; and R_2 is C_1-C_4alkyl, allenyl, C_2-C_4alkenyl, or C_2-C_4alkynyl; each of which is optionally deuterated.

[0091] R_1 is hydroxyl or fluoro; and R_2 is methyl or $-CD_3$.

[0092] R_1 and R_2 are joined to form a 3- to 6-membered cycloalkyl ring or a 3- to 6-membered heterocycloalkyl ring containing one heteroatom selected from N, O, and S, each of which is optionally substituted.

[0093] R_1 and R_2 are joined to form a 3- to 6-membered cycloalkyl ring or a 3- to 6-membered heterocycloalkyl ring containing one heteroatom selected from N, O, and S, each of which is optionally substituted with one or more substituents independently chosen from halogen, hydroxyl, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0094] R_1 and R_2 are joined to form a cyclopropyl group.

[0095] R_1 is hydroxyl and R_2 is methyl.

[0096] R_1 is fluoro and R_2 is methyl.

The R_3 Variable

[0097] R_3 is hydrogen, deuterium, halogen, or $-N_3$ and R_3' is hydroxyl.

[0098] R_3 is C_1-C_4alkyl, allenyl, C_2-C_4alkenyl, C_2-C_4alkynyl, (C_3-C_6cycloalkyl)C_0-C_2alkyl, or (phenyl)ethynyl; and R_3' is hydroxyl.

[0099] R_3 and R_3' are taken together to form a 3- to 6- membered ring optionally containing one heteroatom selected from N, O, and S, which ring is optionally substituted with one or more substituents independently selected from halogen, hydroxyl, C_1-C_2alkyl, and C_1-C_2alkoxy.

[0100] R_3 and R_3'are both hydrogen.

[0101] R_3 is $-N_3$ and R_3' is hydrogen.

The R_4 and R_5 Variables

[0102] R_4 is hydrogen, deuterium, C_1-C_2haloalkyl, or C_1-C_2haloalkoxy; or R_4 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl, or C_1-C_6alkoxy, each of which is optionally deuterated and optionally substituted; and R_5 is hydrogen or deuterium; or R_5 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl, or C_1-C_6alkoxy, each of which is optionally deuterated and optionally substituted.

[0103] R_4 is hydrogen, or deuterium or R_4 is C_1-C_4alkyl, allenyl,C_2-C_4alkenyl, C_2-C_4alkynyl, or C_1-C_4alkoxy, each of which is optionally deuterated; and R_5 is hydrogen or deuterium; or R_5 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl, or C_1-C_6alkoxy, each of which is optionally deuterated.

[0104] R_4 and R_5 are both deuterium.

[0105] R_4 and R_5 are taken together to form a 3- to 6- membered ring optionally containing one heteroatom selected from N, O, and S, which ring is optionally substituted with one or more substituents independently selected from halogen, hydroxyl, C_1-C_2alkyl, and C_1-C_2alkoxy.

The R_6 Variable

[0106] R_6 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl, each of which optionally substituted.

[0107] R_6 is (aryl)C_0-C_2alkyl, a 5- to 6-membered monocyclic heteroaryl containing 1 to 3 heteroatoms independently chosen from N, O, and S, or 8- to 10- membered bicyclic heteroaryl containing 1 to 4 heteroatoms independently chosen from N, O, and S; each of which R_6 is optionally substituted.

[0108] R_6 is phenyl, pyridyl, naphthyl, or indolyl, each of which is optionally substituted with one or more substituents independently chosen from halogen, hydroxyl, C_1-C_4alkyl, C_1-C_4alkoxy, (mono- and di-C_1-C_4alkylamino)C_0-C_2alkyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0109] R_6 is phenyl substituted with one or more substituents independently chosen from halogen, hydroxyl, amino, cyano, -CHO, -COOH, $-CONH_2$, C_1-C_6alkyl, C_2-C_6alkenyl, C_1-C_6alkoxy, C_2-

C_6alkanoyl, C_1-C_6alkylester, (mono- and di-C_1-C_6alkylamino)C_0-C_2alkyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0110] R_6 is unsubstituted phenyl.

[0111] R_6 is unsubstituted naphthyl.

The R_7 and R_8 Variables

[0112] R_7 is hydrogen, halogen, C_1-C_2haloalkyl, or C_1-C_2haloalkoxy; or R_7 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, (C_3-C_6cycloalkyl)C_0-C_4alkyl, or (aryl)C_0-C_2alkyl; each of which is optionally substituted; and R_8 is hydrogen, halogen, C_1-C_2haloalkyl, or C_1-C_2haloalkoxy; or R_8 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl,or C_1-C_6alkoxy, each of which is optionally substituted.

[0113] R_7 and R_8 are independently chosen from hydrogen, halogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0114] R_7 and R_8 are taken together to form a 3-to 6-membered cycloalkyl ring or 3- to 6-membered heterocycloalkyl ring containing one heteroatom chosen from N, O, and S; each of which is optionally substituted.

[0115] R_7 is C_1-C_6alkyl and R_8 is hydrogen, halogen, or C_1-C_6alkyl.

[0116] R_7 is methyl and R_8 is hydrogen.

The R_9 Variable

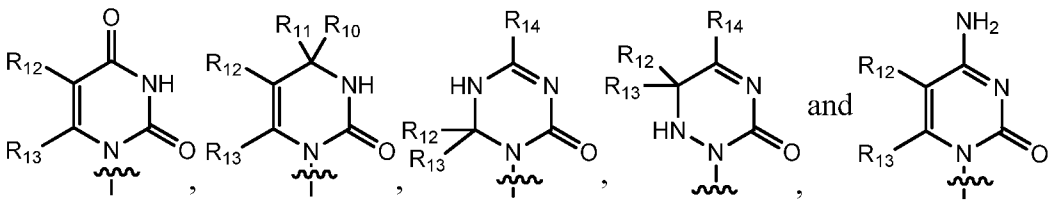
[0117] R_9 is C_1-C_6alkyl, (C_3-C_7cycloalkyl)C_0-C_4alkyl, or (phenyl)C_0-C_4alkyl, each of which is optionally substituted.

[0118] R_9 is C_1-C_6alkyl.

[0119] R_9 is (C_3-C_7cycloalkyl)C_0-C_2alkyl or (phenyl)C_0-C_2alkyl, each of which is optionally substituted with one or more substituents independently chosen from halogen, hydroxyl, C_1-C_4alkyl, C_1-C_4alkoxy, (mono- and di-C_1-C_6alkylamino)C_0-C_2alkyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

The B_1 Variable

[0120] B_1 is a pyrimidine base chosen from group



[0121] The disclosure includes compounds of Formula (I), (II), or (III) in which B_1 is selected from the above group and any of the following conditions are met.

[0122] R_{12} is hydrogen and R_{13} is deuterium.

[0123] R_{12} is deuterium and R_{12} is hydrogen.

[0124] R_{12} and R_{13} are both hydrogen.

[0125] R_{12} and R_{13} are both deuterium.

[0126] R_{12} is CD_3 and R_{13} is deuterium.

[0127] R_{12} is CD_3 and R_{12} is hydrogen.

[0128] R_{12} is hydrogen, R_{13} is deuterium, and R_{14} is amino.

[0129] R_{12} is hydrogen, R_{13} is deuterium, and R_{14} is hydroxyl.

[0130] R_{12} and R_{13} are both deuterium and R_{14} is hydroxyl.

[0131] R_{12} and R_{13} are both hydrogen and R_{14} is hydroxyl.

[0132] R_{12} and R_{13} are both hydrogen and R_{14} is amino.

[0133] R_{12} and R_{13} are both deuterium and R_{14} is amino.

[0134] R_{12} is hydrogen, R_{13} is deuterium, and R_{14} is hydroxyl.

Other embodiments

[0135] The disclosure includes compounds of Formula (I), (II), or (III) in which the following conditions are met.

[0136] R_1 is hydroxyl, fluoro, or $–OCD_3$; and R_2 is hydrogen, $-CH_3$, or $–CD_3$.

[0137] Or, R_1 and R_2 are joined to form a cyclopropyl.

[0138] R_3 is hydrogen or $–N_3$.

[0139] R_4 and R_5 are independently hydrogen, deuterium, methyl, or $–CD_3$.

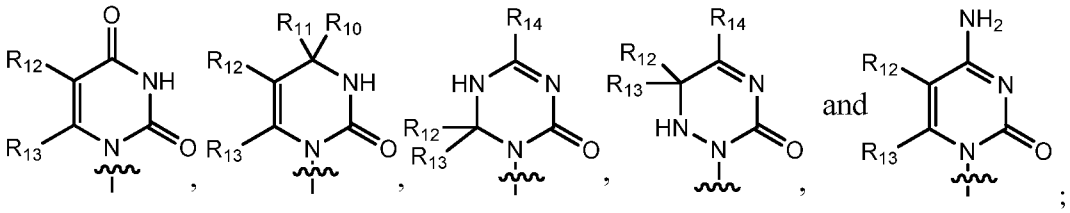
[0140] R_6 is phenyl, pyridyl, naphthyl, or indolyl, each of which is optionally substituted with one or more substituents independently chosen from halogen, hydroxyl, amino, cyano, -CHO, -COOH, $-CONH_2$, C_1-C_6alkyl, C_2-C_6alkenyl, C_1-C_6alkoxy, C_2-C_6alkanoyl, C_1-C_6alkylester, (mono- and di-C_1-C_6alkylamino)C_0-C_2alkyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0141] R_7 is hydrogen, halogen, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, (C_3-C_6cycloalkyl)C_0-C_4alkyl, or (aryl)C_0-C_2alkyl; and R_8 is hydrogen, halogen, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_2haloalkyl, or C_1-C_2haloalkoxy.

[0142] Or, R_7 and R_8 are taken together to form a 3-to 6-membered cycloalkyl ring.

[0143] R_9 is C_1-C_6alkyl, (C_3-C_7cycloalkyl)C_0-C_4alkyl, or (aryl)C_0-C_4alkyl, each of which is optionally substituted with one or more substituents independently chosen from halogen, hydroxyl, amino, cyano, -CHO, -COOH, $-CONH_2$, C_1-C_6alkyl, C_2-C_6alkenyl, C_1-C_6alkoxy, C_2-C_6alkanoyl, C_1-C_6alkylester, (mono- and di-C_1-C_6alkylamino)C_0-C_2alkyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0144] B_1 is a base selected from



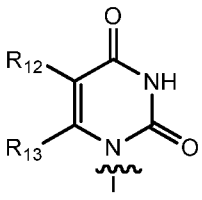
[0145] For B_1 the following conditions are met:

[0146] R_{12} and R_{13} are independently hydrogen and deuterium.

[0147] R_{12} and R_{13} are independently hydrogen, deuterium, and methyl.

[0148] R_{14} is hydroxyl, amino; C_1-C_4alkoxy, C_1-C_4alkylester, or mono- or di-C_1-C_4alkylcarbamate; and in the compound of Formula (I), (II), or (III) each position represented by D has a deuterium enrichment of at least 50%. One or more of R_1, R_2, R_4, R_5, R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} is deuterium with a deuterium enrichment of at least 50% % or a deuterated substituent with at least one position having a deuterium enrichment of at least 50%.

[0149] The disclosure also includes compounds and salts of Formula (I), (II), or (III), in which: B_1 is uridine or cytosine:



. In certain embodiments in which B_1 is uridine, R_{12} and R_{13} are both deuterium; R_{12} is deuterium and R_{13} is hydrogen; R_{12} is hydrogen and R_{13} is deuterium; or R_{12} and R_{13} are both hydrogen. In certain embodiment in which B_1 is cytosine R_{12} is CD_3 and R_{13} is deuterium.

[0150] R_{12} and R_{13} are both deuterium and R_{14} is hydroxyl.

[0151] R_1 is hydroxyl, fluoro, or $-OCD_3$; and R_2 is hydrogen, $-CH_3$, or $-CD_3$.

[0152] Or, R_1 and R_2 are joined to form a cyclopropyl.

[0153] R_3 is hydrogen or $-N_3$.

[0154] R_4 and R_5 are independently hydrogen, deuterium, methyl, or $-CD_3$.

[0155] R_6 is phenyl, pyridyl, naphthyl, or indolyl, each of which is optionally substituted with one or more substituents independently chosen from halogen, hydroxyl, C_1-C_4alkyl, C_1-C_4alkoxy, (mono- and di-C_1-C_4alkylamino)C_0-C_2alkyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0156] R_7 is hydrogen, halogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, (C_3-C_6cycloalkyl)C_0-C_2alkyl, or (phenyl)C_0-C_2alkyl;R_8 is hydrogen, halogen, C_1-C_2alkyl, or C_1-C_2alkoxy.

[0157] R_7 and R_8 are taken together to form a 3-to 6-membered cycloalkyl ring; and

[0158] R_9 is C_1-C_6alkyl, (C_3-C_7cycloalkyl)C_0-C_2alkyl, or (aryl)C_0-C_2alkyl, each of which is optionally substituted with one or more substituents independently chosen from halogen, hydroxyl, C_1-C_4alkyl, C_1-C_4alkoxy, (mono- and di-C_1-C_6alkylamino)C_0-C_2alkyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0159] The disclosure includes compounds and salts of Formula (I), (II), and (III) in which:

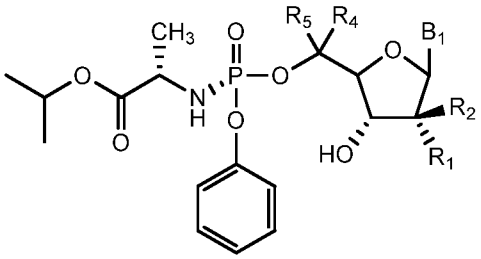
[0160] R_6 is phenyl, naphthyl, or indolyl;

[0161] R_7 is hydrogen, halogen, or C_1-C_4alkyl;

[0162] R_8 is hydrogen, halogen, C_1-C_2alkyl, or C_1-C_2alkoxy; and

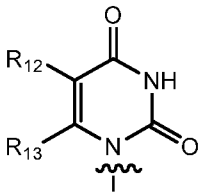
[0163] R_9 is C_1-C_6alkyl.

[0164] This disclosures include compounds, and the pharmaceutically acceptable salts thereof of Formula (IV)



(IV).

[0165] In certain compounds and salts of Formula (IV) B_1 is



.

[0166] In certain compounds and salts of Formula (IV) the following conditions are met.

[0167] R_4 and R_5 are both deuterium; one of R_{12} and R_{13} is deuterium and the other is hydrogen, or R_{12} is CD_3 and R_{13} is hydrogen or deuterium.

[0168] R_1 is hydroxyl and R_2 is methyl.

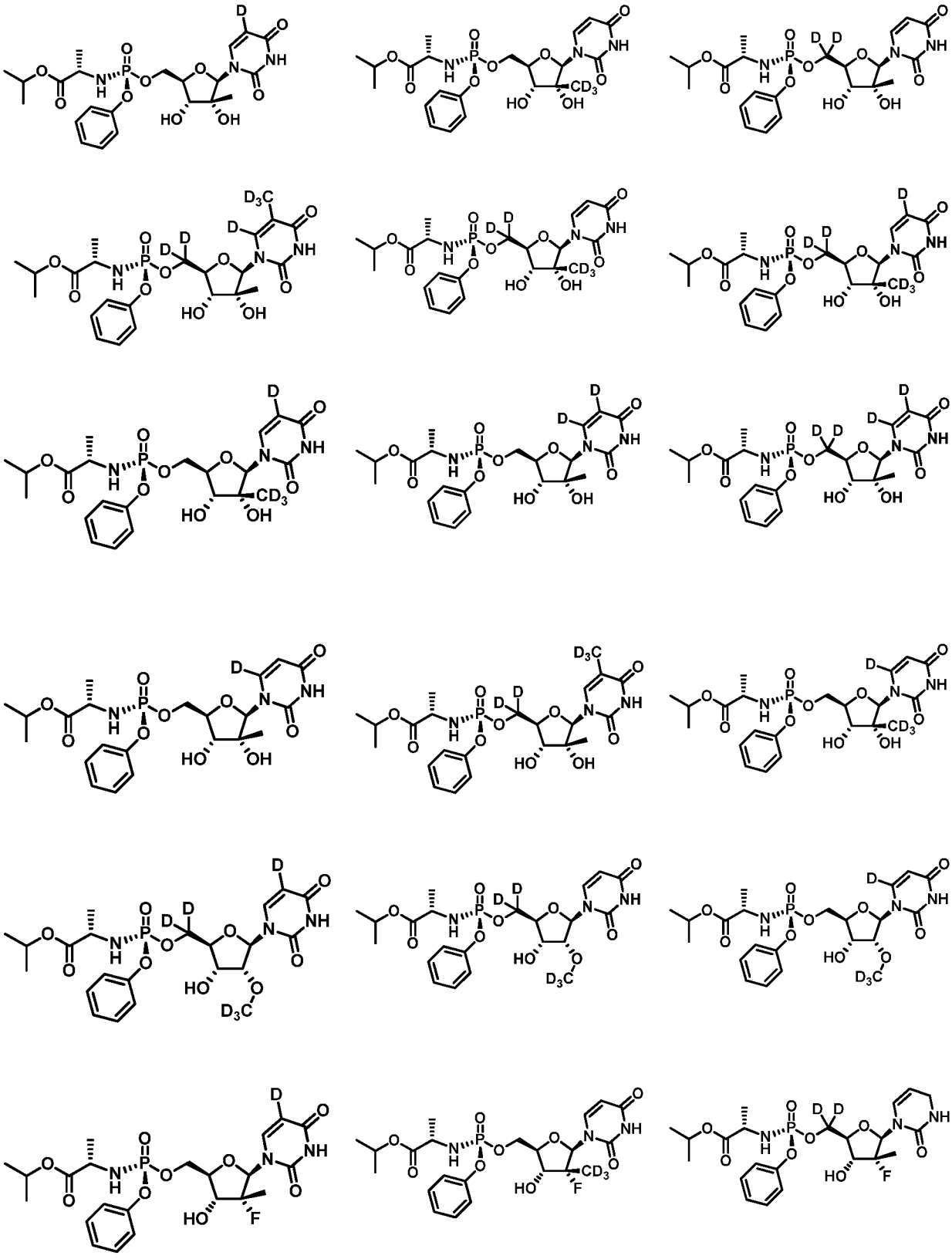
[0169] R_1 is hydroxyl and R_2 is -CD_3.

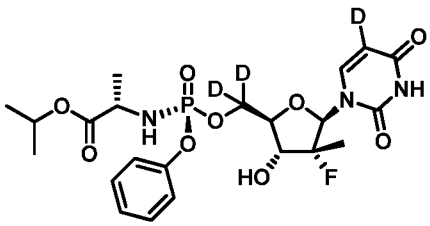
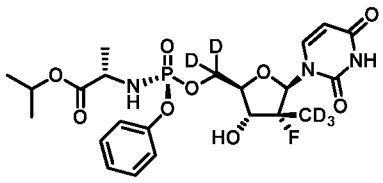
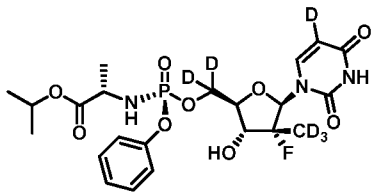
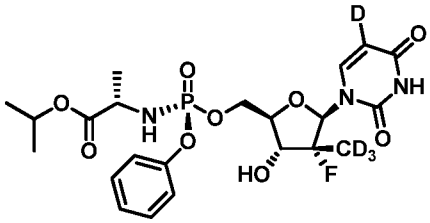
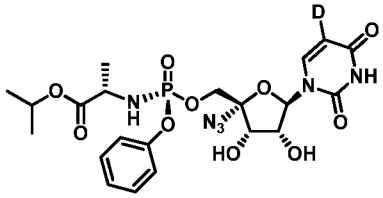
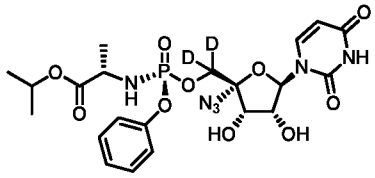
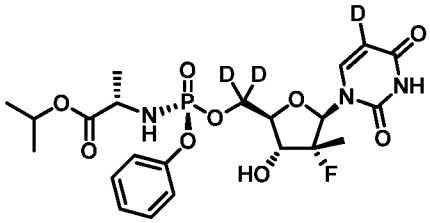
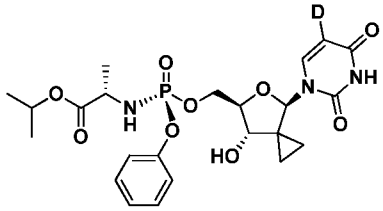
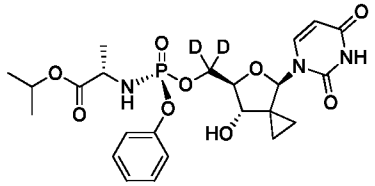
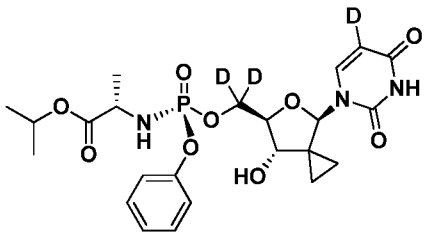
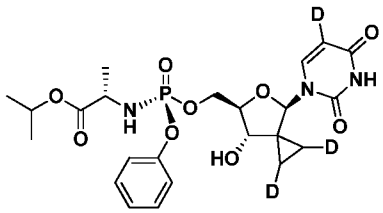
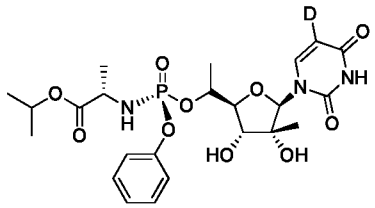
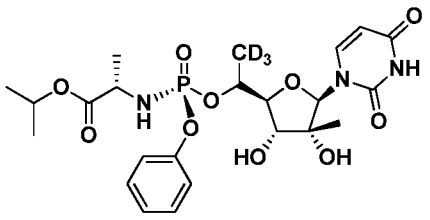
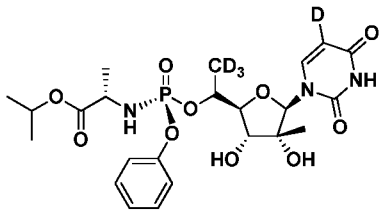
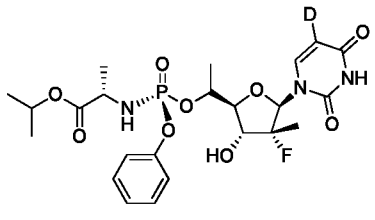
[0170] R_1 and R_2 are joined to form a cyclopropyl group.

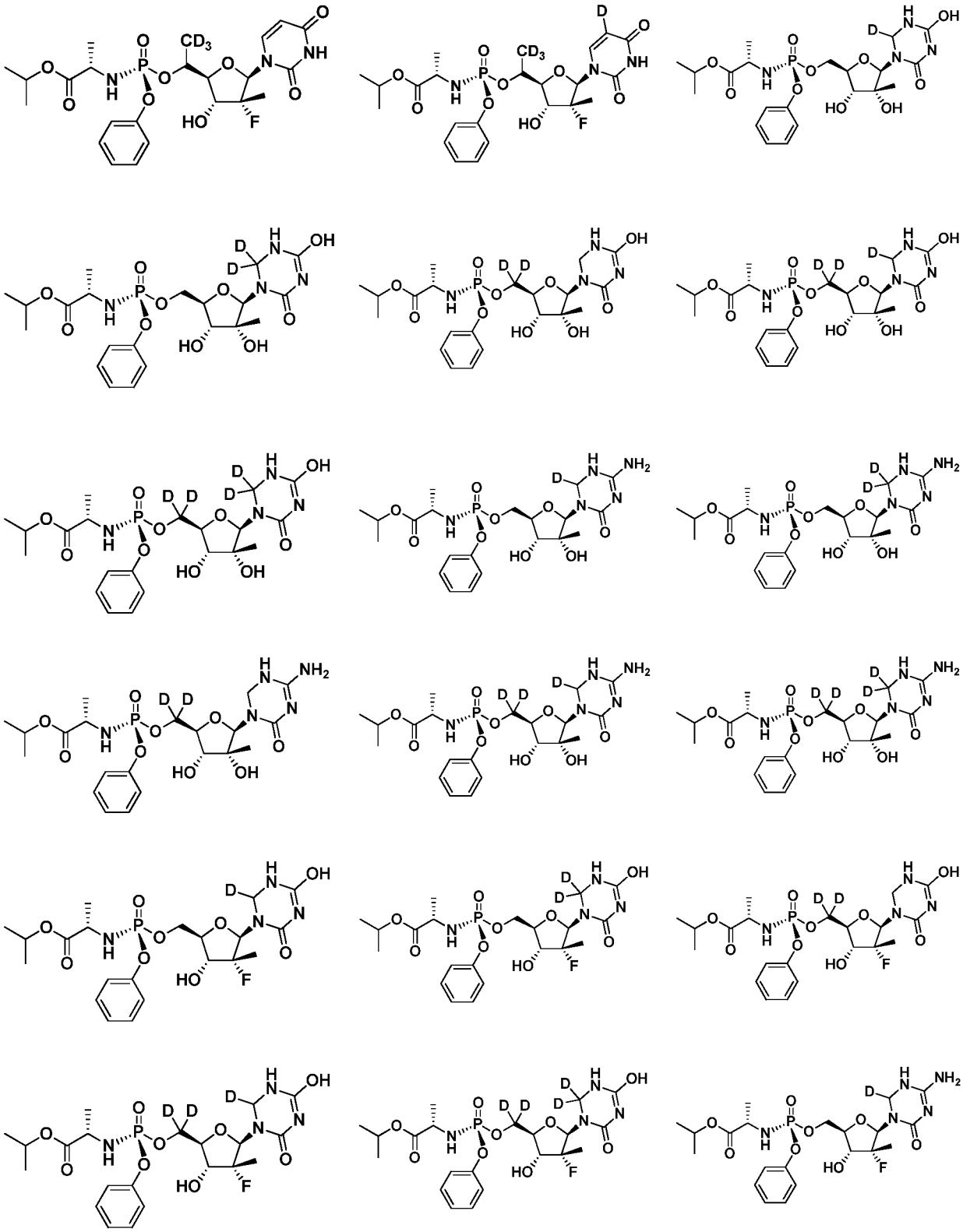
[0171] R_1 is fluoro and R_2 is methyl or –CD_3.

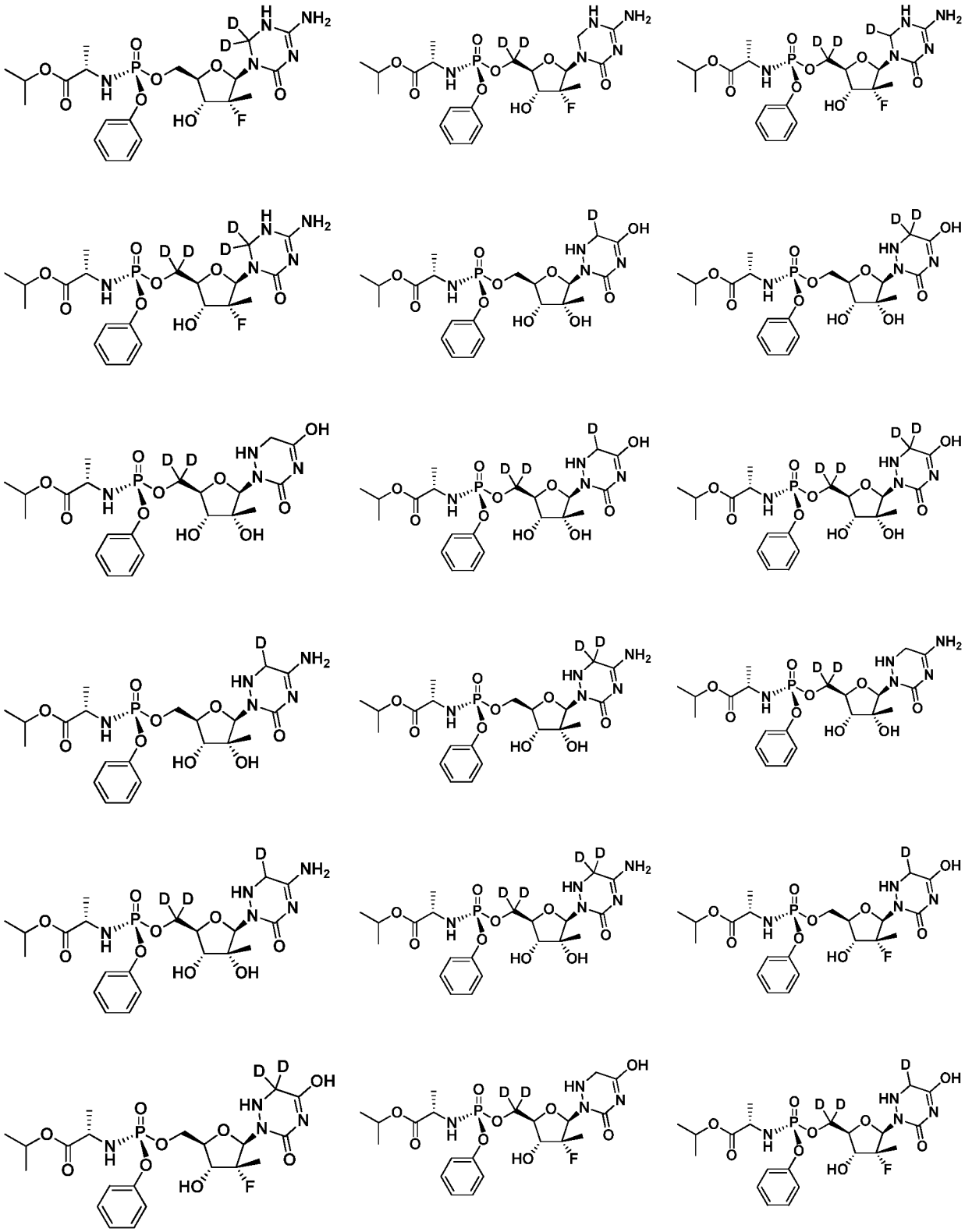
[0172] The disclosure includes the following compounds

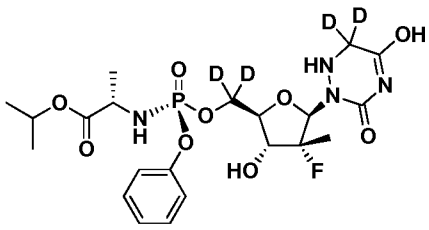
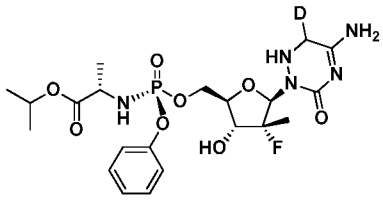
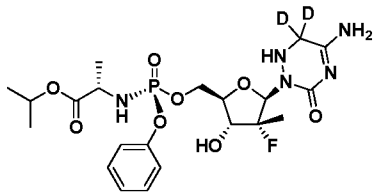
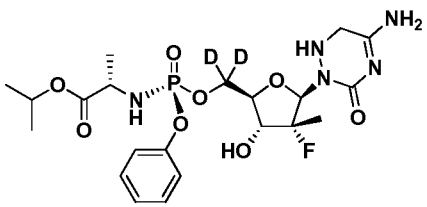
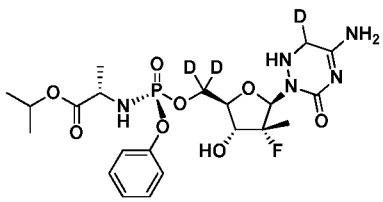
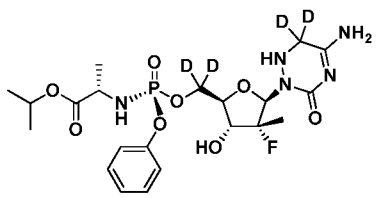
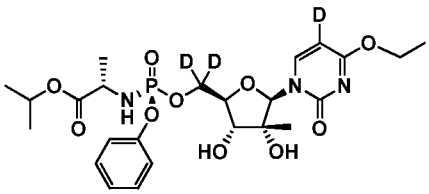
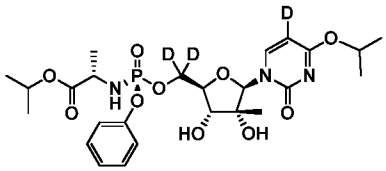
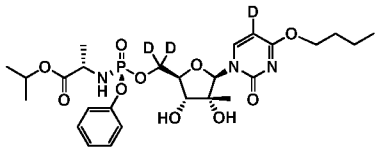
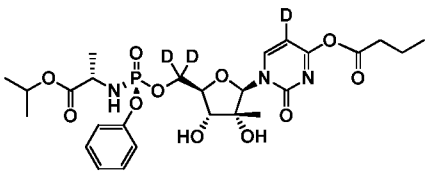
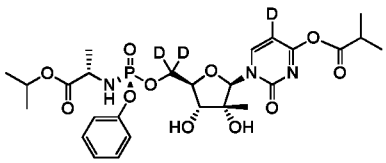
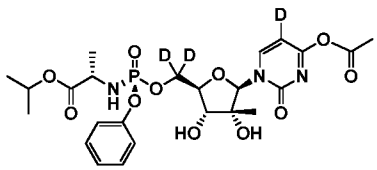
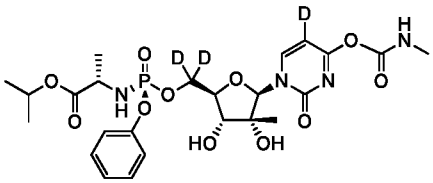
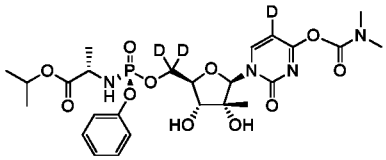
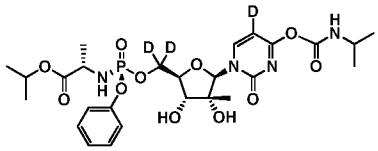
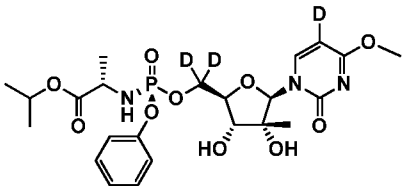
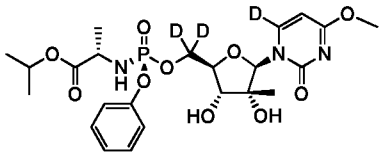
[0173] A compound or salt thereof of Claim 1, wherein the compound is chosen from:







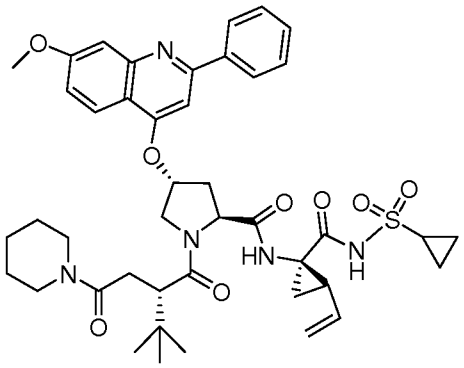


















PHARMACEUTICAL COMPOSITIONS

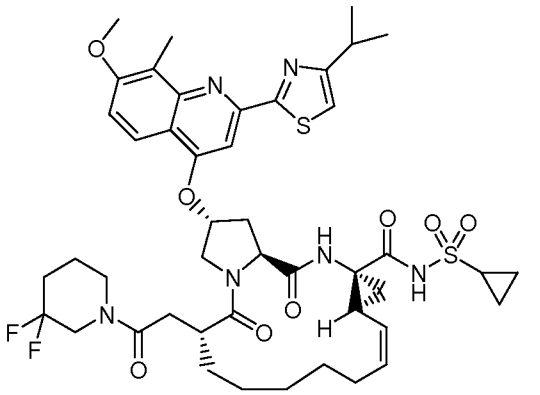
[0174] This disclosure also includes pharmaceutical compositions and combinations comprising a compound of Formula (I) and at least one additional active agent, as well as methods of treatment comprising administering such compositions to a patient infected with hepatitis C. In certain embodiments the additional active agent is an HCV HS3 protease inhibitor or an HCV NS5a inhibitor.

[0175] For example, in some embodiments, the additional active agent is sovaprevir or ACH-2684 (HCV NS3 protease inhibitors) and/ or an (NS5a inhibitor).

[0176] The disclosure includes compositions in which the additional active agent is a NS3 inhibitor such as Sovaprevir or ACH-2684



or



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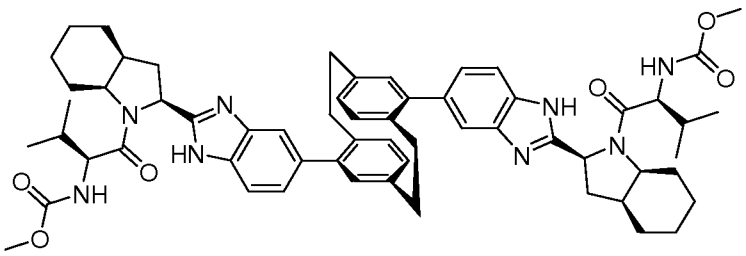
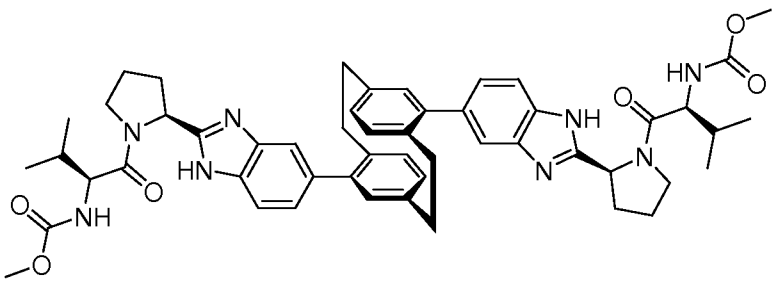
[0177] The disclosure also includes compositions which contain an additional active agent, such as a NS5A inhibitor chosen from:





[0178] NS3 protease inhibitors, useful in the pharmaceutical compositions and combinations described here have been disclosed previously, for example in US Pat. No. 7,906,619, issued March 15, 2011, is hereby incorporated by reference in its entirety for its teachings regarding 4-amino-4-oxobutanoyl peptides. The '619 patent is particularly incorporated by reference at the Examples section beginning in column 50 and extending to column 85 which discloses compounds useful in compositions/ combination with Compounds of Formula (I) described here.

[0179] US Pat. Appl. No. 2010-0216725, published August 26, 2010, is hereby incorporated by reference in its entirety for its teachings regarding 4-amino-4-oxobutanoyl peptides. The '725 application is particularly incorporated by reference at the Examples section beginning at page 22 and extending to page 100 which discloses compounds useful in compositions/ combination with Compounds of Formula (I) described here.

[0180] US Pat. Appl. No. 2010-0152103, published June 17, 2010, hereby incorporated by reference in its entirety for its teachings regarding 4-amino-4-oxobutanoyl peptide cyclic analogues. The '103 application is particularly incorporated by reference at the Examples section beginning at page 19 and extending to page 60 which discloses compounds useful in compositions/ combination with Compounds of Formula (I) described here. Particularly the compounds of Formula (I) disclosed herein may be used in combination with an NS3 protease inhibitor.

[0181] NS5a inhibitors, useful in the pharmaceutical compositions and combinations described here have been disclosed previously. U.S. Pat. Pub. No. US-2012-0302528, published November 29, 2012, is hereby incorporated by reference in its entirety for its teachings regarding Ns5a Inhibitors. Particular NS5a inhibitors that may be used combination with the compound of this disclosure include compounds of the formula T-R-J^1-W-A-W-J^1-R-T; T-R-J^1-A-J^1-R-T; T-R-J^2-A-J^2-R-T; or T-R-J^1-W-A-J^1-R-T.

[0182] In the above formulae, T is independently chosen at each occurrence and is T^k where k is an integer from 1 to 2.

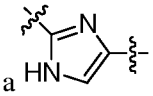
[0183] T^1 is -Y-Z, where Y is covalently bound to R and Y is a bond or C_1-C_4alkylene optionally substituted with oxo; and Z is a 5 or 6-membered heterocyclic group, each of which T^1 is substituted with (i) at least one substituent selected from -(C=O)OH, -(C=O)NH_2, -(C=O)H, -C_1-C_4alkoxy, C_2-C_4alkanoyl, C_1-C_4alkylester, C_1-C_4alkenylester, and mono- and di-C_1-C_4alkylcarboxamide and (ii) optionally substituted with one or more substituents independently chosen from halogen, hydroxyl, C_1-C_2alkyl, and C_1-C_2alkoxy.

[0184] T^2 is independently chosen at each occurrence from C_2-C_6alkanoyl, C_1-C_6alkylester, C_1-C_6alkenylester, C_1-C_6alkylsulfonamide, C_1-C_6alkylsulfonyl, C_2-C_6alkanoyl substituted with mono- or di-C_1-C_6hydrocarbylcarbamate, C_2-C_6alkanoyl substituted with urea or mono- or di-C_1-C_6alkylurea, and C_2-

C_6alkanoyl substituted with mono- or di-C_1-C_6alkylcarboxamide, each of which T^2 is optionally substituted with 1 or more substituents independently chosen from amino, cyano, hydroxyl, halogen, (C_1-C_4alkoxy)C_0-C_4alkyl, (mono- and di-C_1-C_4alkylamino)C_0-C_4alkyl, C_1-C_6alkyl, (C_1-C_4thioalkyl)C_0-C_4alkyl, C_3-C_7cycloalkyl, phenyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0185] R is independently chosen at each occurrence from 4- to 6-membered rings containing one or two nitrogen atoms with remaining ring atoms being carbon, which R is saturated or contains 1 unsaturated bond and is optionally bridged with an methylene or ethylene bridge, or fused to a phenyl or 5- to 6-membered heteroaryl ring; and 6- to 10-membered fused or spiro bicyclic ring systems containing one or two nitrogen atoms with remaining ring atoms being carbon, which 6- to 10-membered bicyclic ring is saturated or contains 1 unsaturated bond.

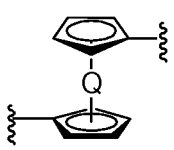
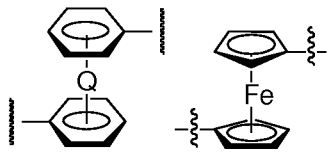
[0186] Each R is optionally substituted with one or more substituents independently chosen from cyano, hydroxyl, halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2haloalkyl, C_1-C_2haloalkyl, C_1-C_2haloalkylene, and C_1-C_2alkylsulfonyl;

[0187] J^1 is phenyl or a 5- to 6- membered heteroaryl group, such as a  group, where each J^1 is optionally substituted with one or more substituents independently chosen from amino, cyano, hydroxyl, halogen, C_1-C_4alkyl, C_1-C_4alkoxy, mono- and di-C_1-C_4alkylamino, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0188] J^2 is a 8- to 10 –membered bicyclic heteroaryl group containing 1 to 4 heteroatoms independently chosen from N, O, and S, such as a benzimidazole group, wherein J^2 is optionally substituted with one or more substituents independently chosen from amino, cyano, hydroxyl, halogen, C_1-C_4alkyl, C_1-C_4alkoxy, mono- and di-C_1-C_4alkylamino, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0189] W is independently chosen at each occurrence and is a phenyl, pyridyl or alkynyl group, optionally substituted with one or more substituents independently chosen from amino, cyano, hydroxyl, halogen, C_1-C_4alkyl, C_1-C_4alkoxy, mono- and di-C_1-C_4alkylamino, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

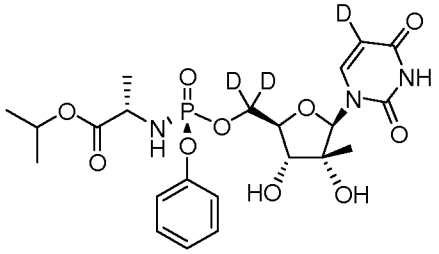
[0190] A is a [2.2]-cyclophane, where each 2 atom linker of the [2.2]-cyclophane optionally contains a heteroatom selected from N, O, or S and is optionally substituted with 1 oxo group, and one or more substituents independently chosen from halogen, hydroxy, amino, C_1-C_2alkyl, and C_1-C_2alkoxy; or

A is a group of the formula  or  , wherein Q is a neutral or cationic metal, each of which A is optionally substituted with one or more substituents independently chosen from halogen, C_1-C_2alkyl, and C_1-C_2alkoxy; or

[0191] A is a group of the formula  , which A is optionally substituted with one or more substituents independently chosen from halogen, C_1-C_2alkyl, and C_1-C_2alkoxy.

[0192] The disclosure particularly includes pharmaceutical compositions containing one deuterated nucleoside prodrug of Formula (I), one NS3 protease inhibitor, and one NS5a inhibitor.

[0193] In certain embodiments the deuterated nucleoside prodrug is



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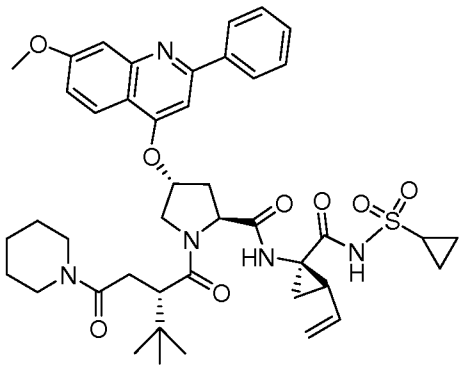
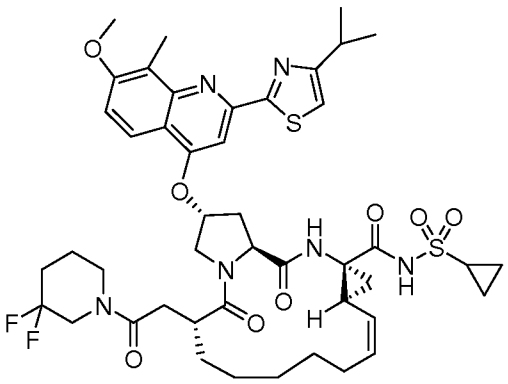
[0194] The NS3 protease inhibitor is chosen from



and



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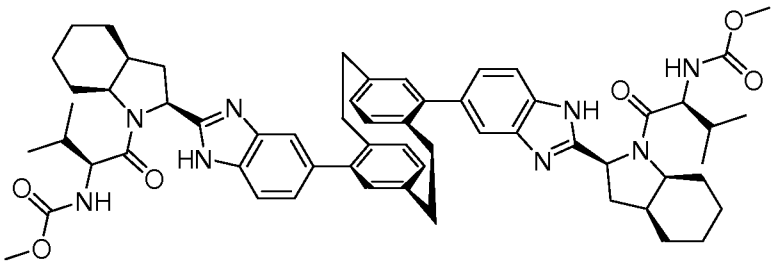
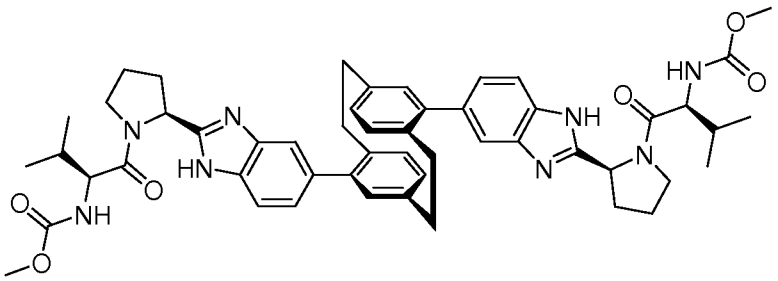
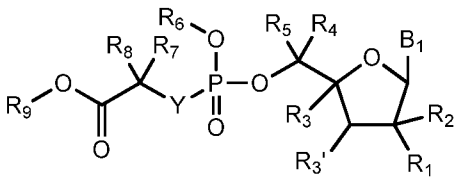
[0195] The NS5a inhibitor is chosen from





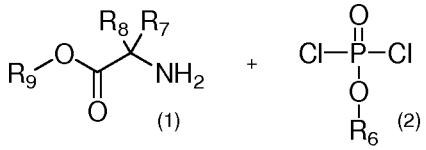
SYNTHETIC METHODS AND INTERMEDIATES

[0196] The disclosure includes methods of preparing compounds of Formula (I).

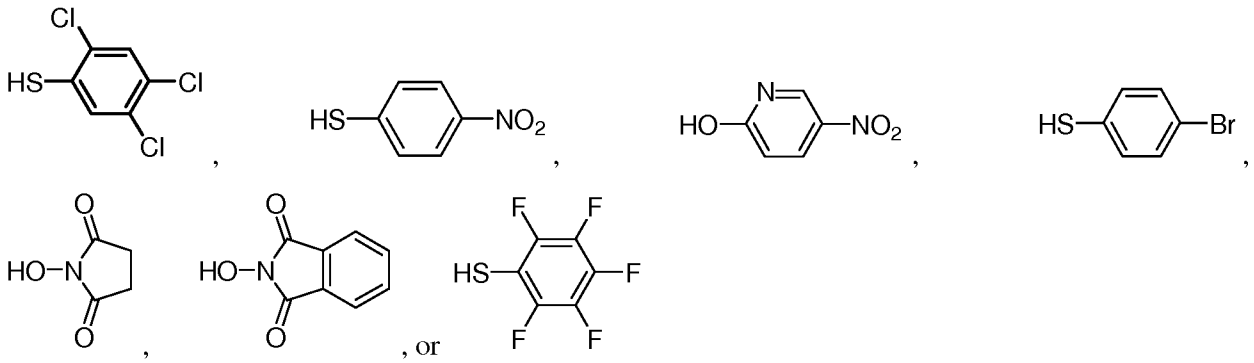
 Formula (I)

comprising

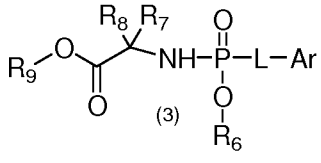
(i) reacting an amino ester (1) with a dichlorophosphate (2) to form a reaction mixture;



(ii) adding to the reaction mixture of (i) an aryl hydroxyl, aryl sulfhydryl, or hydroxylimide, Ar –LH, where L is S or O, and Ar-LH is

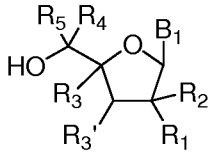


to form an intermediate (3)



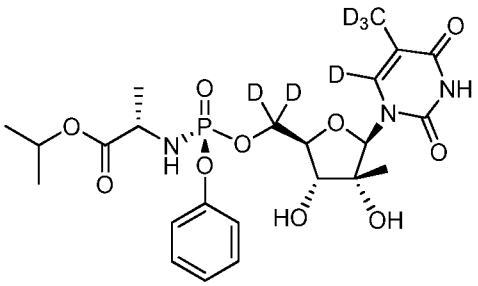
; and

(iii) reacting the intermediate (3) with a nucleoside



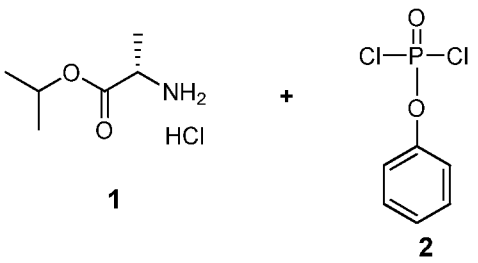
to form the compound of Formula (I). The variables B_1, R_1, R_2, R_3, R_3', R_4, R_5, R_6, R_7, R_8, and R_9 may carry the definitions set forth in the SUMMARY section or for any of the embodiments of Formula (I) described herein.

[0197] In one embodiment the disclosure provides a method for making a compound of Formula (I), in which the compound of Formula (I) is



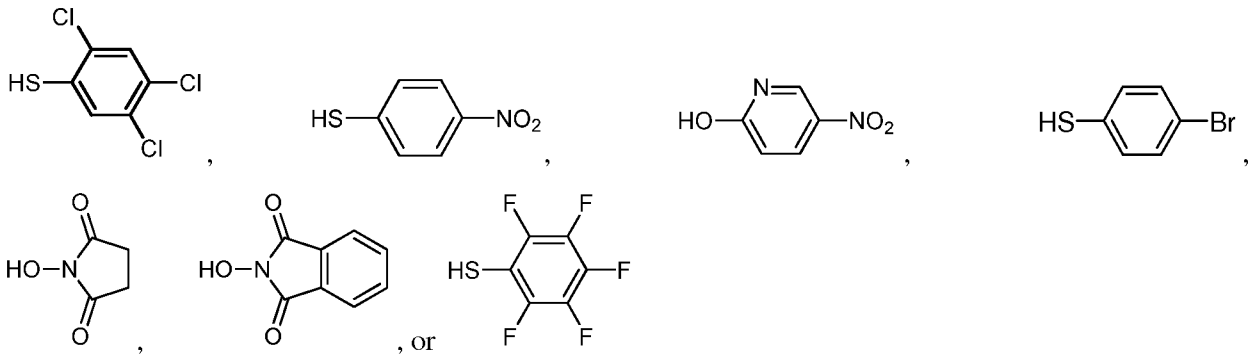
comprising

(i) reacting an amino ester (1), wherein the amino ester is L-alanine isopropyl ester, with a dichlorophosphate (2), wherein the dichlorophosphate is phenoxydichlorophosphate, to form a reaction mixture;

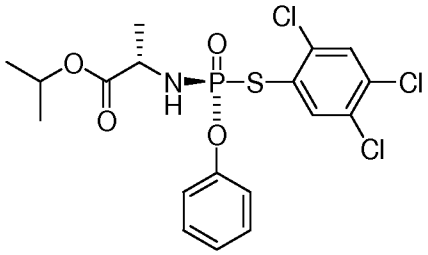


1 2

(ii) adding to the reaction mixture of (i) an aryl hydroxyl,aryl sulfhydryl, or hydroxylimide, Ar –LH, where L is S or O, and aryl is an optionally substituted aryl, heteroaryl, or heterocycloalkyl group such as phenyl, pyrrole, pyridyl, or indole, and in certain embodiments Ar-LH is

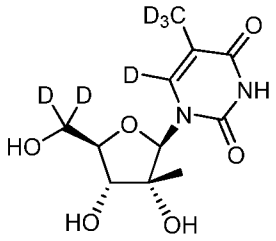


to form an intermediate (**3**)

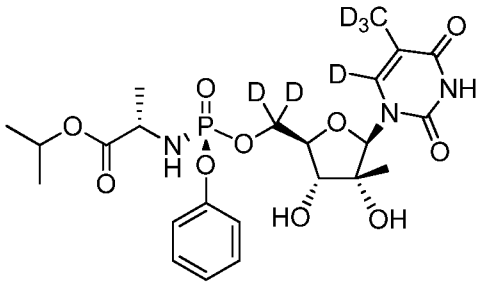


; and

(iii) reacting the intermediate (**3**) with a nucleoside (**14**)



(**14**) to form



.

[0198] In certain embodiments the amino ester (**1**) and the dichlorophosphate (**2**) are combined at a temperature less than -20 °C, more preferably at a temperature of about -40 °C to about -60 °C.

[0199] In certain embodiments triethylamine or other base is added to the mixture of amino ester (1) and the dichlorophosphate (**2**). In certain embodiments the addition occurs in an organic solvent, such as dichloromethane, or other organic solvent such as 1-propanol, 2-methyltetrahydrofuran, or tetrahydrofuran.

[0200] Aryl hydroxyl or aryl sulfhydryl is added to the reaction mixture formed by the combination of amino ester (**1**) and dichlorophosphate (**2**). In certain embodiments the aryl hydroxyl or aryl sulfhydryl is trichlorothiophenol, but may also be replaced by other groups such as nitrothiophenol, bromothiophenol, N-hyddoxysuccinamide, N-hydroxyphthalimide, or nitrohydroxypyridine. In certain embodiments the aryl hydroxyl or aryl sulfhydryl is added as a solution in dichloromethane or other organic solvent such as 1-propanol, 2-methyltetrahydrofuran, or tetrahydrofuran. In certain embodiments the solution containing the aryl hydroxyl or aryl sulfhydryl also contains triethylamine or other base. After the aryl hydroxyl or aryl sulfhydryl is added to the reaction mixture formed by the combination of amino ester (**1**) and dichlorophosphate (**2**) the resulting solution can be warmed to a temperature above 0

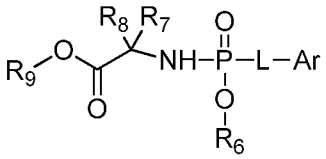
°C, above 15 °C, and preferably to about 20 °C to about 35 °C and may be stirred at this temperature for a period of from about 5 hours to about 30 hours and more preferably from about 10 hours to about 20 hours or about 15 hours.

[0201] The reaction mixture formed by the addition of aryl hydroxyl or aryl sulfhydryl to amino ester (**1**) and dichlorophosphate (**2**) may be extracted with water, which is optionally saturated with salt such as sodium bicarbonate or ammonium sulfate. The crude intermediate (**3**) obtained by drying the organic fraction may be purified by column chromatography, recrystallization, or other suitable purification method. The desired isomer of the intermediate (**3**) may be obtained by dissolving the intermediate, preferably after purification, in ethyl acetate/ heptane or other mixture of other non-polar/polar aprotic solvent such as a mixture of heptane, cyclohexane, benzene (non-polar solvents) and THF, DMF, or DCM (polar aprotic solvents) and seeding the solution with a small amount of the desired isomer of intermediate (**3**). (This seed amount of (**3**) may have been obtained by another method.)

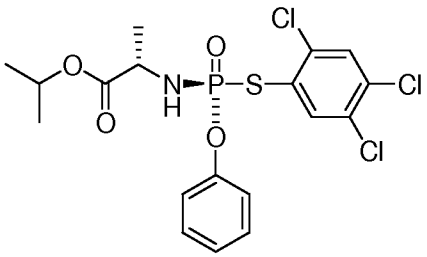
[0202] The nucleoside (**14**) may be suspended in a solvent, preferably a nonpolar aprotic solvent such as THF, DCM, or DMF. The suspension of nucleoside (**14**) in solvent may cooled below 0 °C, preferably below -10 °C to about -40 °C, and preferably to about -20 °C.

[0203] The suspension of nucleoside (**14**) in solvent may be added to an alkylating agent such as a Grignard reagent, for example tert-butyl MgCl, or other alkylmetal halide, at a temperature below 0 °C , preferably below -10 °C to about -40 °C, and preferably to about -20 °C. The reaction mixture of nucleoside (**14**) in solvent and alkylating agent is warmed to above 0 °C, and preferably to about 20 °C to about 30 °C, and stirred for about 1 to about 5 hours, or for preferably from about 2 to about 3 hours. The reaction mixture may then be cooled again to below 0 °C, preferably below -5 °C to about -20 °C, and preferably to about -10 °C. Intermediate (**3**), which may optionally be optically pure, is added to the reaction mixture containing the nucleoside (**14**). The reaction mixture of intermediate (**3**) and nucleoside (**14**) is warmed to above 0 °C, and preferably to about 20 °C to about 30 °C, and stirred for at least 5 hours, preferably about 10 to about 20 hours, or preferably about 15 hours. The reaction may be cooled to about 0 °C and quenched with acid, such as HCl or other acid capable of providing a pH of approximately 1 to 3 or preferably about 2. The resulting product, a compound of Formula (I), may then be purified by organic phase extraction, column chromatography, HPLC, crystallization or any other suitable purification method.

[0204] In addition to a method of making a compound of Formula (**I**) the disclosure provides an intermediate useful for making a compound of Formula (**I**) of the formula



where the variables Ar, L, R_6, R_7, R_8, and R_9 carry the definitions set for these variables earlier in this section, or R_6, R_7, R_8, and R_9 may carry any of the values set for forth in this disclosure for R_6, R_7, R_8, and R_9. In certain embodiments the intermediate is



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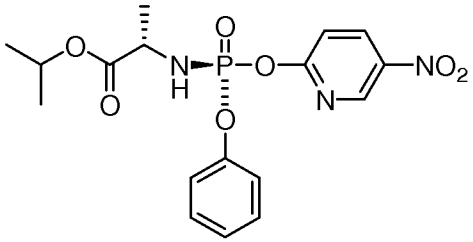
[0205] In other embodiments the intermediate is



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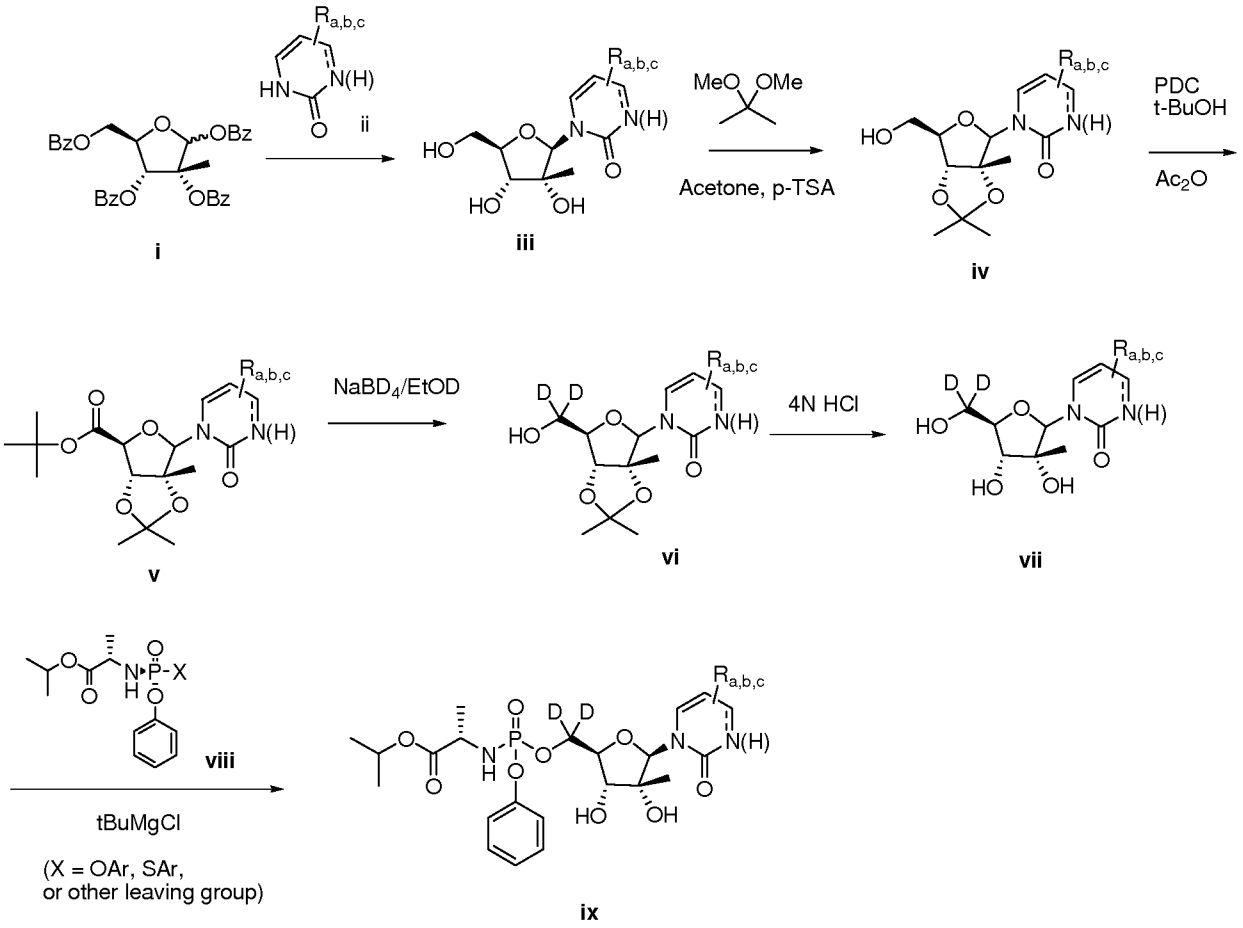
[0206] Compounds of the disclosure can also be made by the method shown in reaction Scheme I.

Scheme I



[0207] In reaction Scheme I a pyrimidine base **ii**, which has up to three substituents and may or may not contain deuterium, is reacted with tetrabenzoyl sugar **i** to give nucleoside **iii**. Nucleoside **iii** is then treated with 2,2-dimethoxypropane and *p*-toluene sulfonic acid (p-TSA) to give acetonide **iv**. Acetonide **iv** is treated with pyridinium dichromate (PDC) in *t*-butanol to effect oxidation and esterification to *t*-butyl ester **v**. Compound **v** is reacted with sodium borodeuteride in deuteroethanol to provide the dideuterated compound **vi**, which is then treated with hydrochloric acid to remove the acetonide and provide triol **vii**. Compound **vii** is treated with a base such as *t*-butyl magnesium halide, followed by addition of an activated phosphate derivative **viii** to afford deuterated nucleoside phosphoramidate **ix** as a final product.

PHARMACEUTICAL PREPARATIONS

[0208] Compounds disclosed herein can be administered as the neat chemical, but are preferably administered as a pharmaceutical composition. Accordingly, the disclosure provides pharmaceutical

compositions comprising a compound or pharmaceutically acceptable salt of Formula (I), together with at least one pharmaceutically acceptable carrier. The pharmaceutical composition/ combination may contain a compound or salt of Formula (I) as the only active agent, but is preferably contains at least one additional active agent. In certain embodiments it is preferred that the additional active agent is an NS3 protease inhibitor or NS5a inhibitor. In certain embodiments the pharmaceutical composition is in a dosage form that contains from about 0.1 mg to about 2000 mg, from about 10 mg to about 1000 mg, from about 100 mg to about 800 mg, or from about 200 mg to about 600 mg of a compound of Formula (I) and optionally from about 0.1 mg to about 2000 mg, from about 10 mg to about 1000 mg, from about 100 mg to about 800 mg, or from about 200 mg to about 600 mg of an additional active agent in a unit dosage form. The pharmaceutical composition may also include a molar ratio of a compound of Formula (I) and an additional active agent. For example the pharmaceutical composition may contain a molar ratio of about 0.5:1, about 1:1, about 2:1, about 3:1 or from about 1.5:1 to about 4:1 of an NS3 protease inhibitor.

[0209] Compounds disclosed herein may be administered orally, topically, parenterally, by inhalation or spray, sublingually, transdermally, via buccal administration, rectally, as an ophthalmic solution, or by other means, in dosage unit formulations containing conventional pharmaceutically acceptable carriers. The pharmaceutical composition may be formulated as any pharmaceutically useful form, e.g., as an aerosol, a cream, a gel, a pill, a capsule, a tablet, a syrup, a transdermal patch, or an ophthalmic solution. Some dosage forms, such as tablets and capsules, are subdivided into suitably sized unit doses containing appropriate quantities of the active components, e.g., an effective amount to achieve the desired purpose.

[0210] Carriers include excipients and diluents and must be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the patient being treated. The carrier can be inert or it can possess pharmaceutical benefits of its own. The amount of carrier employed in conjunction with the compound is sufficient to provide a practical quantity of material for administration per unit dose of the compound.

[0211] Classes of carriers include, but are not limited to binders, buffering agents, coloring agents, diluents, disintegrants, emulsifiers, flavorants, glidents, lubricants, preservatives, stabilizers, surfactants, tableting agents, and wetting agents. Some carriers may be listed in more than one class, for example vegetable oil may be used as a lubricant in some formulations and a diluent in others. Exemplary pharmaceutically acceptable carriers include sugars, starches, celluloses, powdered tragacanth, malt, gelatin; talc, and vegetable oils. Optional active agents may be included in a pharmaceutical composition, which do not substantially interfere with the activity of the compound of the present invention.

[0212] The pharmaceutical compositions/ combinations can be formulated for oral administration. These compositions contain between 0.1 and 99 weight % (wt.%) of a compound of Formula (I) and usually at least about 5 wt.% of a compound of Formula. Some embodiments contain from about 25 wt.% to about 50 wt. % or from about 5 wt.% to about 75 wt.% of the compound of Formula.

METHODS OF TREATMENT

[0213] The pharmaceutical compositions/ combinations disclosed herein are useful for treating viral infections in patients. In one embodiment the viral infection is a hepatitis C infection but the infection may also be an RNA viral infection, a such as a Togaviridae, Picornaviridae, Coronaviridae, or Flaviviridae viral infection. The disclosure includes a method of treating a Togaviridae, Picornaviridae, Coronaviridae, or Flaviviridae viral infection by administering a compound of Formula (I), to a subject infected with a togavirus, picornavirus, coronavirus, or flavivirus. Flaviviridae viral infections include infections with viruses of the genera *Flavivirus, Pestivirus, and Hepacivirus. Flavivirus* infections include yellow fever, Dengue fever, West Nile virus, encephalitis, including St. Louis encephalitis, Japanese B encephalitis, California encephalitis, central European encephalitis, Russian spring-summer encephalitis, and Murray Valley encephalitis, Wesselsbron disease, and Powassan disease. Pestivirus infections include primarily livestock diseases, including swine fever in pigs, BVDV (bovine viral diarrhea virus) in cattle, and Border Disease virus infections. *Hepacivirus* infections includes Hepatitis C and canine Hepacivirus. Togavirus infections include *Sindbis* virus, Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, Ross River virus, O'nyong'nyong virus, Chikungunya virus, Semliki Forest virus, and *Rubella* virus. Picornavirus infections include infections with viruses of the genuses *Aphthovirus, Aquamavirus, Avihepatovirus, Cardiovirus, Cosavirus, Dicipivirus, Enterovirus, Erbovirus, Hepatovirus, Kobuvirus, Megrivirus, Parechovirus, Salivirus, Sapelovirus, Senecavirus, Teschovirus,* and *Tremovirus*. Coronavirus infections include infections with virus of the genuses *Alphacoronavirus*, *Betacoronavirus* (which includes Severe acute respiratory coronavirus (SARS)), *Gammacoronavirus*, and *Deltacoronavirus*. The disclosure particularly includes compositions comprising a compound of Formula (I) useful for treating Dengue fever, West Nile fever, yellow fever, or BVDV (bovine viral diarrhea virus) and methods of treating these infections by administering a compound of Formula (I) to a patient infected with the virus.

[0214] This disclosure provides methods of treating viral infections, including hepatitis C infections, by providing an effective amount of a compound or pharmaceutically acceptable salt of Formula (I) to patient infected with a hepatitis C virus. A compound or salt of Formula (I) may be provided as the only active agent or may be provided together with one or more additional active agents.

In certain embodiments the compound or salt of Formula (I) is administered together with a NS3 protease inhibitor and/ or NS5a inhibitor.

[0215] An effective amount of a pharmaceutical composition/ combination of the invention may be an amount sufficient to (a) inhibit the progression of hepatitis C; (b) cause a regression of the hepatitis C infection; or (c) cause a cure of a hepatitis C infection such that HCV virus or HCV antibodies can no longer be detected in a previously infected patient's blood or plasma. An amount of a pharmaceutical composition/ combination effective to inhibit the progress or cause a regression of hepatitis C includes an amount effective to stop the worsening of symptoms of hepatitis C or reduce the symptoms experienced by a patient infected with the hepatitis C virus. Alternatively a halt in progression or regression of hepatitis C may be indicated by any of several markers for the disease. For example, a lack of increase or reduction in the hepatitis C viral load or a lack of increase or reduction in the number of circulating HCV antibodies in a patient's blood are markers of a halt in progression or regression of hepatitis C infection. Other hepatitis C disease markers include aminotransferase levels, particularly levels of the liver enzymes AST and ALT. These levels will typically be elevated in a HCV infected patient. Disease regression is usually marked by the return of AST and ALT levels to the normal range.

[0216] Symptoms of hepatitis C that may be affected by an effective amount of a pharmaceutical composition/ combination of the invention include decreased liver function, fatigue, flu-like symptoms: fever, chills, muscle aches, joint pain, and headaches, nausea, aversion to certain foods, unexplained weight loss, psychological disorders including depression, tenderness in the abdomen, and jaundice.

[0217] "Liver function" refers to a normal function of the liver, including, but not limited to, a synthetic function including synthesis of proteins such as serum proteins (e.g., albumin, clotting factors, alkaline phosphatase, aminotransferases (e.g., alanine transaminase, aspartate transaminase), 5'-nucleosidase, glutaminyl transpeptidase, etc.), synthesis of bilirubin, synthesis of cholesterol, and synthesis of bile acids; a liver metabolic function, including carbohydrate metabolism, amino acid and ammonia metabolism, hormone metabolism, and lipid metabolism; detoxification of exogenous drugs; and a hemodynamic function, including splanchnic and portal hemodynamics.

[0218] An effective amount of a pharmaceutical composition/ combination described herein will also provide a sufficient concentration of the active agents in the concentration when administered to a patient. A sufficient concentration of an active agent is a concentration of the agent in the patient's body necessary to prevent or combat the infection. Such an amount may be ascertained experimentally, for example by assaying blood concentration of the agent, or theoretically, by calculating bioavailability. The amount of an active agent sufficient to inhibit viral infection in vitro may be determined with a conventional assay for viral infectivity such as a replicon based assay, which has been described in the literature.

[0219] Pharmaceutical compositions/ combinations and methods of treatment in which a compound or salt of Formula (I) is provided together with one or more additional active agents are included herein. In preferred embodiments a compound of Formula (I) is provided together with an NS3 protease inhibitor, and/ or NS5a protease inhibitor, either in a single pharmaceutical composition or a in separate dosage forms with instructions to the patient to use the compound of Formula (I) and additional active agent together. Compounds disclosed in US Pat. No. 7,906,619, US Pat. Pub. No. 2010-0216725, and US Pat. Pub. No. 2010-0152103 are suitable NS3 protease inhibitors for use in combination with compounds and salts of Formula (I). Compounds disclosed in US Pat. Appl. No. 2012-0302538 are suitable NS5a inhibitors for use in combination with compounds of Formula (I). In certain embodiments the active agent (or agents) is an HCV protease inhibitor or HCV polymerase inhibitor. For example the protease inhibitor may be telaprevir (VX-950) and the polymerase inhibitor may be valopicitabine, or NM 107, the active agent which valopicitabine is converted into in vivo. In certain embodiments the at least one additional active agent is ribavirin, interferon, or Peg-interferon alpha conjugate. In certain embodiments the at least one additional active agent is sovaprevir, ACH-2684, or ACH-3102.

[0220] The compound or pharmaceutically acceptable salt of Formula (I) and at least one additional active agent may be: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by any other combination therapy regimen known in the art. When delivered in alternation therapy, the methods of the invention may comprise administering or delivering the compound or salt of Formula (I) and an additional active agent sequentially, e.g., in separate solution, emulsion, suspension, tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, i.e., serially, whereas in simultaneous therapy, effective dosages of two or more active ingredients are administered together. Various sequences of intermittent combination therapy may also be used.

[0221] Methods of treatment and pharmaceutical combinations including compounds or pharmaceutically acceptable salts of Formula (I) described herein together with any one or combination of the following compounds and substances as an additional active agent are provided by the disclosure:

[0222] Caspase Inhibitors: IDN-6556 (Idun Pharmaceuticals) and GS-9450 (Gilead)

[0223] Cyclophilin Inhibitors: for example, NIM811 (Novartis), SCY-635 (Scynexis), and DEBIO-025 (Debiopharm);

[0224] Cytochrome P450 monooxygenase inhibitors: ritonavir, ketoconazole, troleandomycin, 4-methyl pyrazole, cyclosporin, clomethiazole, cimetidine, itraconazole, fluconazole, miconazole, fluvoxamine, fluoxetine, nefazodone, sertraline, indinavir, nelfinavir, amprenavir, fosamprenavir,

saquinavir, lopinavir, delavirdine, erythromycin, and VX-497 (Merimebodib). Preferred CYP inhibitors include ritonavir, ketoconazole, troleandomycin, 4-methyl pyrazole, cyclosporin, and clomethiazole;

[0225] Entry Inhibitors: ITX-5061 (iTherX)

[0226] Glucocorticoids: hydrocortisone, cortisone, prednisone, prednisolone, methylprednisolone, triamcinolone, paramethasone, betamethasone, and dexamethasone.

[0227] HCV Protease Inhibitors: for example Sovaprevir and ACH-2684. ABT-450 (Abbott), ACL-181 and AVL-192 (Avila), BI-335 (Boehringer Ingelheim), BMS-032 (Bristol Myers Squibb), Boceprevir (Merck), danoprevir (Hoffman-La Roche and Genentech), TMC435 (Merck), GS-9256 (Gilead), GS-9451 (Gilead), R7227 (Intermune), Telaprevir (VX-950, Vertex), VX-985 (Vertex), Simeprevir (TMC435, Tibotec), Fosamprenavir (prodrug of Amprenavir, Glaxo/ Vertex), indinavir (CRIXIVAN, Merck), TMC435350 (Tibotec/Medivir), Faldaprevir (BI 201335. Boehringer Ingelheim), PHX-1766 (Phenomix), Vaniprevir (, MK-7009, Merck), narlaprevir (SCH900518, Schering), MK-5172 (Merck)

[0228] Hematopoietins: hematopoietin-1 and hematopoietin-2. Other members of the hematopoietin superfamily such as the various colony stimulating factors (e.g.. G-CSF, GM-CSF, M-CSF), Epo, and SCF (stem cell factor)

[0229] Homeopathic Therapies: Milk Thistle, silymarin, ginseng, glycyrrhizin, licorice root, schisandra, vitamin C, vitamin E, beta carotene, and selenium

[0230] Immunomodulatory compounds: thalidomide, IL-2, hematopoietins, IMPDH inhibitors, for example Merimepodib (Vertex Pharmaceuticals Inc.), interferon, including natural interferon (such as OMNIFERON, Viragen and SUMIFERON, Sumitomo, a blend of natural interferons), natural interferon alpha (ALFERON, Hemispherx Biopharma, Inc.), interferon alpha-nl from lymphblastoid cells (WELLFERON, Glaxo Wellcome), oral alpha interferon, Peg-interferon, Peg-interferon alfa 2a (PEGASYS, Roche), recombinant interferon alfa 2a (ROFERON, Roche), inhaled interferon alpha 2b (AERX, Aradigm), Peg-interferon alpha 2b (ALBUFERON, Human Genome Sciences/ Novartis, PEGINTRON, Schering), recombinant interferon alfa 2b (INTRON A, Schering), pegylated interferon alfa 2b (PEG-INTRON, Schering, VIRAFERONPEG, Schering) ,interferon beta-1a (REBIF, Ares-Serono, Inc. and Pfizer), consensus interferon alpha (INFERGEN, Intermune), interferon gamma-1b (ACTIMMUNE, Intermune, Inc.), un-pegylated interferon alpha, alpha interferon, and its analogs, and synthetic thymosin alpha 1 (ZADAXIN, SciClone Pharmaceuticals Inc.), and lamdba interferon (BMS)

[0231] Immunosupressants: sirolimus (RAPAMUNE, Wyeth)

[0232] Interleukins: (IL-1, IL-3, IL-4, IL-5, IL-6, IL-10, IL-11, IL-12), LIF, TGF-beta, TNF-alpha) and other low molecular weight factors (e.g. AcSDKP, pEEDCK, thymic hormones, and minicytokines)

[0233] Interferon Enhancers: EMZ702 (Transition Therapeutics)

[0234] IRES inhibitors: VGX-410C (VGX Pharma)

[0235] Monoclonal and Polyclonal antibodies: XTL-6865 (HEPX-C, XTL), HuMax-HepC (Genmab), Hepatitis C Immune Globin (human) (CIVACIR, Nabi Biopharmceuticals), XTL-002 (XTL), Rituximab (RITUXAN, Genentech/ IDEC), GS-6624 (Gilead)

[0236] Nucleoside analogues: IDX-184 (Idenix), Sofosbuvier (PSI-7977, Pharmasset and Gilead), PSI-938 (Pharmasset), R7128 (Roche), R7348 (Roche), GS-6620 (Gilead), TMC-649 (Tibotec), Lamivudine (EPIVIR, 3TC, GlaxoSmithKline), MK-0608 (Merck), zalcitabine (HIVID, Roche US Pharmaceuticals), ribavirin (including COPEGUS (Roche), REBETOL (Schering), VILONA (ICN Pharmaceuticals, and VIRAZOLE (ICN Pharmaceuticals), isatoribine (Anadys Pharmaceuticals), ANA971(Anadys Pharmaceuticals), ANA245 (Anadys Pharmaceuticals), and viramidine (ICN), an amidine prodrug of ribavirin. Combinations of nucleoside analogues may also be employed.

[0237] Non-nucleoside inhibitors: PSI-6130 (Roche/ Pharmasset), ABT-333 and ABT-072 (Abbott), delaviridine (RESCRIPTOR, Pfizer), PF-868554 (Pfizer), GSK-852 (GlaxoSmithKline), IDX-325 (Idenix), Setrobuvir (ANA-598, Anadys), VX-222 (Vertex), MK-3281 (Merck), BI-127 (Boehringer Ingelheim), BMS-325 (Bristol Myers), and HCV-796 (Viropharm)

[0238] NS4b inhibitors: clemizole (Eiger BioPharmaceuticals, Inc.)

[0239] NS5a inhibitors: A-382 (Arrow Therapeutics), Daclatasvir (BMS-790052, BMS), AZD-7295 (Astra Zeneca); PPI-461 (Presidio), PPI-688 (Presidio), IDX719 (Idenix), IDX184 (Idenix)

[0240] NS5b inhibitors: INX-181, MBX-700 (Microbotix/ Merck), MK-3281, PSI-7977, PSI-7851, PSI-938, RG-9190, VX-222 (Vertex), and BMS-791325 (Bristol Myers Squibb).

[0241] P7 protein inhibitor: amantadine (SYMMETREL, Endo Pharmaceuticals, Inc.)

[0242] Polymerase inhibitors: NM283 (valopicitabine) (Idenix), JTK 003 (AKROS Pharma), HCV-796 (ViroPharma/ Wyeth), RG7128 (Mericitabine, Genentech), R1626 (Roche), PSI-7851 (Pharmasset), ANA598 (Anadys), BI207127 (Boehringer-Ingelheim), Tegobuvir (GS 9190, Gilead), VX-135 (Vertex, Alios).

[0243] RNA interference: SIRNA-034 RNAi (Sirna Therapeutics) and ISI 14803 (Isis Pharmaceutical/ Elan)

[0244] Therapeutic Vaccines: IC41 (Intercell), IMN-0101 (Imnogenetics), GI 5005 (Globeimmune), Chronvac-C (Tripep/ Inovio), ED-002 (Imnogenetics), Hepavaxx C (ViRex Medical)

[0245] TNF agonists: adalimumab (HUMIRA, Abbott), entanercept (ENBREL, Amgen and Wyeth), infliximab (REMICADE, Centocor, Inc.)

[0246] Tubulin inhibitors: Colchicine

[0247] Sphingosine-1-phosphate receptor modulators: FTY720 (Novartis)

[0248] TLR agonists: ANA-975 (Anadys Pharmaceuticals), TLR7 agonist (Anadys Pharmaceuticals), CPG10101(Coley), andTLR9 agonists including CPG 7909 (Coley).

[0249] Vaccines: HCV/MF59 (Chiron), IC41 (Intercell), E-1 (Innogenetics)

[0250] Patients receiving hepatitis C medications are typically given interferon together with another active agent. Thus methods of treatment and pharmaceutical combinations in which a compound of the invention is provided together with an interferon, such as pegylated interferon alfa 2a, as the additional active agents are included as embodiments. Similarly methods and pharmaceutical combinations in which ribavirin is an additional active agent are provided herein.

[0251] Methods of inhibiting HCV replication *in vivo* comprising providing a compound or pharmaceutically acceptable salt of Formula (I) to a patient infected with HCV, a concentration of the compound or salt of Formula (I) sufficient to inhibit HCV replicon replication *in vitro* are included herein. In this instance the concentration includes an *in vivo* concentration, such as a blood or plasma concentration. The concentration of compound sufficient to inhibit HCV replicon replication *in vitro* may be determined from an assay of replicon replication such as the assay provided in Example 11, herein.

[0252] Methods of treatment include providing certain dosage amounts of a compound or pharmaceutically acceptable salt of Formula (I) to a patient. Dosage levels of each active agent of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single unit dosage form will vary depending upon the patient treated and the particular mode of administration. In certain embodiments about 0.1 mg to about 2000 mg, from about 10 mg to about 1500 mg, from about 100 mg to about 1000 mg, from about 200 mg to about 800 mg, or from about 300 to about 600 mg of a compound of Formula (I) and optionally from about 0.1 mg to about 2000 mg, from about 10 mg to about 1500 mg, from about 100mg to about 1000 mg, from about 200 mg to about 800 mg, or from about 300 to about 600 mg of a compound of an additional active agent, for example an NS3 protease inhibitor are provided daily to a patient. It is preferred that each unit dosage form contains less than 1200 mg of active agent in total. Frequency of dosage may also vary depending on the compound used and the particular disease treated. However, for treatment of most infectious disorders, a dosage regimen of 4 times daily or less is preferred and a dosage regimen of 1 or 2 times daily is particularly preferred.

[0253] It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease in the patient undergoing therapy.

PACKAGED FORMULATIONS

[0254] Methods comprising providing a compound or salt of Formula (I) in a container together with instructions for using the compound to treat a patient suffering from Hepatitis C infection are included herein.

[0255] Packaged pharmaceutical compositions/ combinations are also included herein. Such packaged combinations include a compound of Formula (I) in a container together with instructions for using the combination to treat or prevent a viral infection, such as a hepatitis C infection, in a patient.

[0256] The packaged pharmaceutical composition/ combination may include one or more additional active agents. In certain embodiments the additional active agent is an NS3 protease inhibitor or NS5a inhibitor.

[0257] The packaged pharmaceutical combination may include a compound or pharmaceutically acceptable salt of Formula (I) and the additional active agent provided simultaneously in a single dosage form, concomitantly in separate dosage forms, or provided in separate dosage forms for administration separated by some amount of time that is within the time in which both the compound of Formula (I) and the additional active agent are within the bloodstream of the patient.

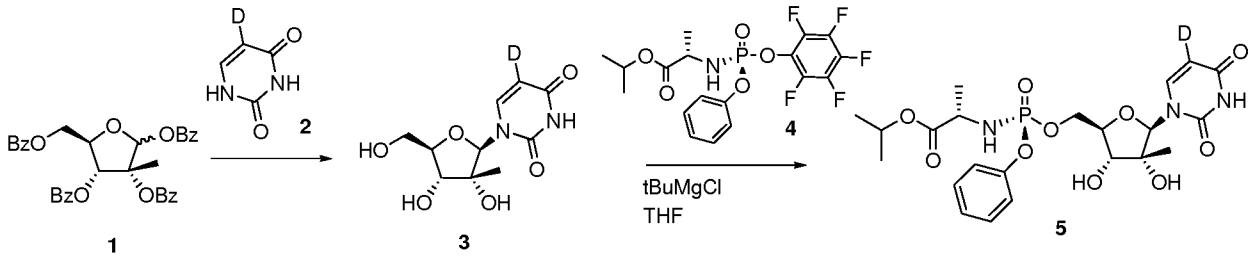
[0258] The packaged pharmaceutical combination may include a compound or pharmaceutically acceptable salt of Formula (I) provided in a container with an additional active agent provided in the same or separate container, with instructions for using the combination to treat an HCV infection in a patient.

EXAMPLES

ABBREVIATIONS

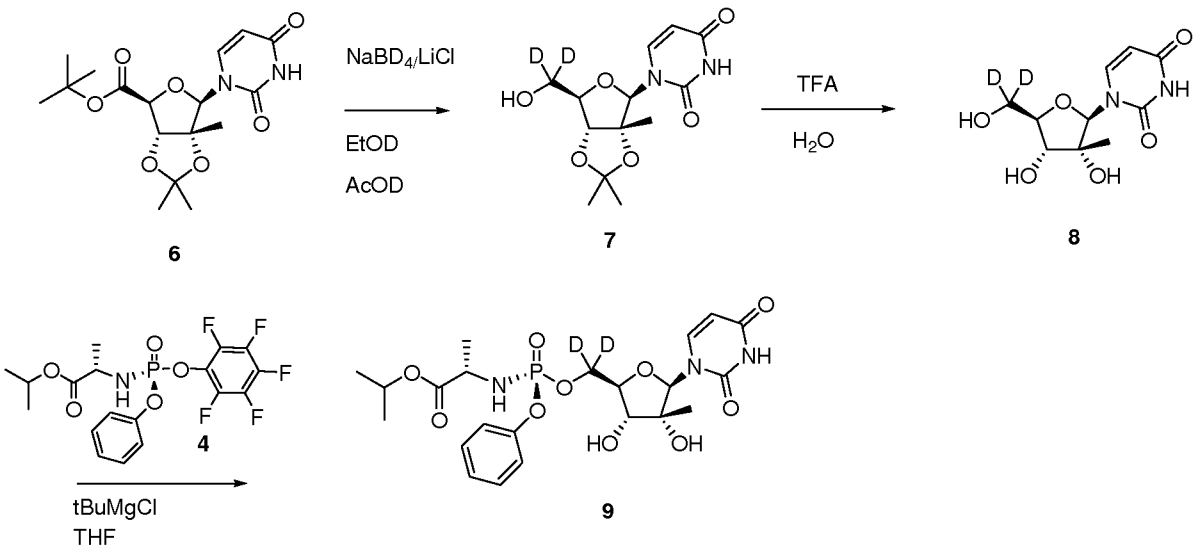
[0259]	Ac_2O	Acetic anhydride
[0260]	AcOD	Acetic Acid, deuterated
[0261]	BuOH	Butanol
[0262]	DCM	Dichloromethane
[0263]	EtOAc	Ethyl Acetate
[0264]	MTBE	Methyl tert-butyl ether
[0265]	PDC	Pyridinium Dichromate
[0266]	THF	Tetrahydrofuran
[0267]	^{t}BuMgCl	tert-Butyl Magnesium Chloride

EXAMPLE 1. PREPARATION OF (S)-ISOPROPYL 2-(((S)-(((2R,3R,4R,5R)-5-(5-DEUTERO-2,4-DIOXO-3,4-DIHYDROPYRIMIDIN-1(2H)-YL)-3,4-DIHYDROXY-4-METHYLTETRAHYDROFURAN-2-YL)METHOXY)(PHENOXY)PHOSPHORYL)AMINO)PROPANOATE (PRODRUG OF 2'-METHYL – 5-DEUTERO–URIDINE)



[0268] Tetrabenzoylsugar (**1,** 2.44g) and 5-Deutero-Uracil (**2,** 1.0g) were reacted following the literature procedure described in Harry-Okuru et al. (*J. Org. Chem.* (1997) 62: 1754), followed by debenzylation using NaOMe/MeOH to give 2'-Methyl-5-D-Uridine (**3,** 0.8g). Compound **3** (0.7g) was converted to its phosphoramidate derivative **5** (0.63g) following literature procedure described by Ross et al.

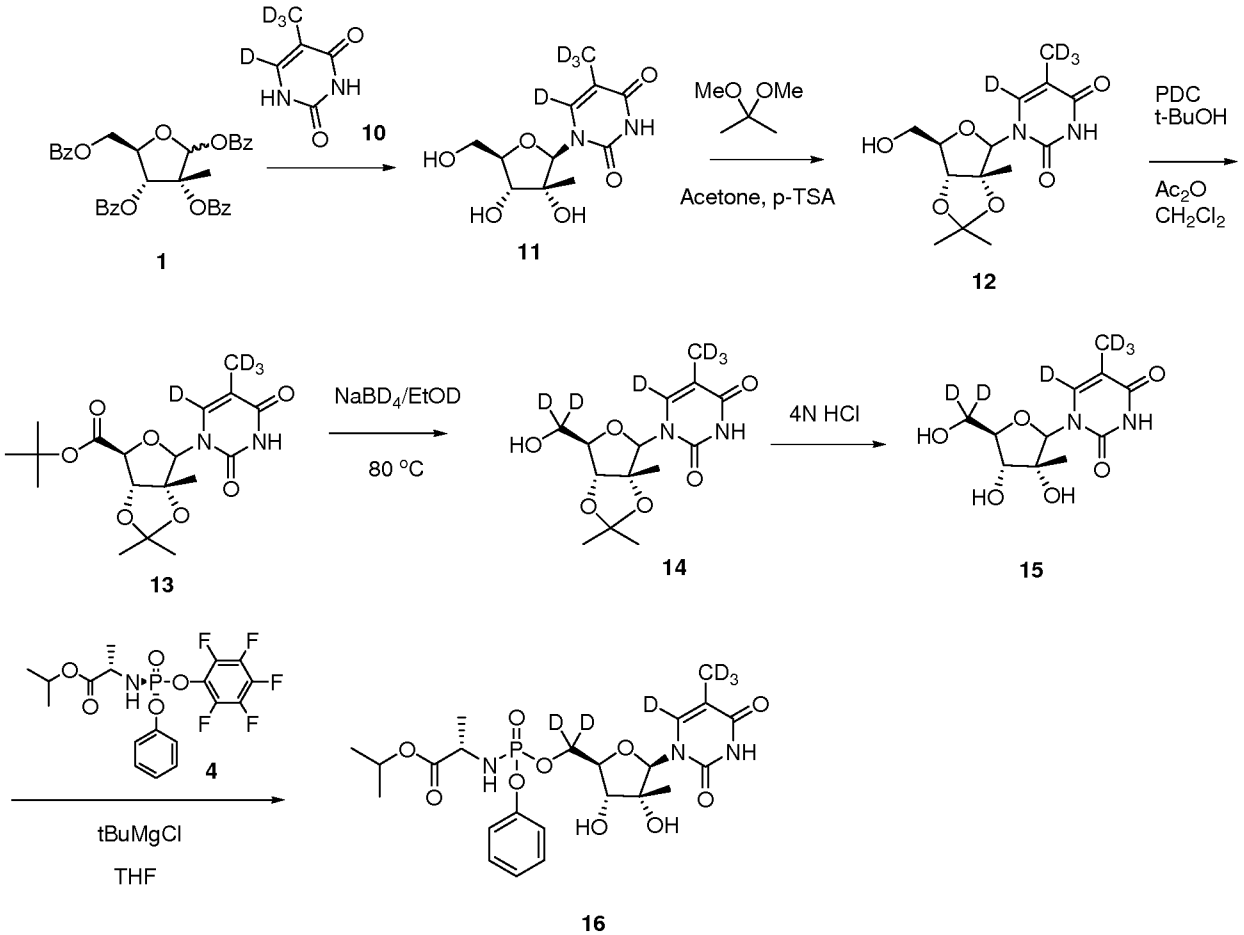
EXAMPLE 2. PREPARATION OF (S)-ISOPROPYL 2-(((R)-(((2S,3R,4R,5R)-5-(2,4-DIOXO-3,4-DIHYDROPYRIMIDIN-1(2H)-YL)-3,4-DIHYDROXY-4-METHYLTETRAHYDROFURAN-2-YL)DIDEUTEROMETHOXY)(PHENOXY)PHOSPHORYL)AMINO) PROPANOATE (PRODRUG OF 2'-METHYL-5', 5'-DIDEUTERO-URIDINE)



[0269] Compound **6** was prepared from 2'-Me-Uridine (**A**) following procedure reported by Corey et al (*J. Org. Chem.* (**1984**) 49: 47350 with some modifications.

[0270] Lithium chloride (1.76 g) was stirred with $NaBD_4$ (1.58g) in EtOD for 1 h. Compound **6** (2.97 g) was added to this solution and stirred at room temperature for 3h and quenched with acetic acid-*d*, diluted with ethyl acetate, washed with brine and evaporated to dryness. The residue was purified by chromatography over silica gel to give 5'-dideuterated compound **7** (2.1g). Compound **7** (2.1g) was treated with trifluoroacetic acid in presence of water to give the dideuterated nucleoside **8** (1.52 g). Compound **8** (1.0g) was converted to its phosphoramidate derivative **9** (0.78 g) following literature procedure described in Ross et al. (*J. Org. Chem.* (2011) 76: 8311).

EXAMPLE 3. PREPARATION OF (2S)-ISOPROPYL 2-(((((2S,3R,4R,5R)-1-(6-DEUTERO-5-(TRIDEUTEROMETHYL)PYRIMIDINE-2,4-DIOXO-3,4-DIHYDROPYRIMIDIN-1(2*H*)-YL)3,4-DIHYDROXY-4-METHYLTETRAHYDROFURAN-2-YL)DIDEUTEROMETHOXY)(PHENOXY)PHOSPHORYL)AMINO)PROPANOATE (Compound **16**)



[0271] Tetrabenzoyl sugar **1** and tetradeutero thymine **10** (2.1 equivalents; prepared according to the procedure in *Heterocycles* (2005) 66:361) were reacted following the literature procedure described in

Harry-Okuru et al. (*J. Org. Chem.* (1997) 62: 1754), followed by debenzylation using NaOMe/MeOH to give compound **11**.

[0272] Excess 2, 2-Dimethyl propane is added to compound **11** in acetone. The resulting mixture was cooled in an ice bath for 30 min, then p-Toluenesulfonic acid (1.3 equivalents) was added and the reaction mixture was stirred at room temperature for 24 hrs. After completion of the reaction (monitored by HPLC), the reaction mixture is cooled in an ice bath for 30 minutes and neutralized using cold aqueous potassium carbonate. The solvent is removed under reduced pressure until dryness. THF is added to the residue and solids are removed by filtration. The filtrate is co-evaporated with silica gel and purified by chromatography over silica to give compound **12**.

[0273] To acetonide **12** in CH_2Cl_2 is added PDC (2.0 equivalents) at room temperature followed by Ac_2O (10 equivalents) and *t*BuOH (20 equivalents). The reaction temperature is maintained below 35 °C during addition of reagents and then stirred at room temperature for 5h.

[0274] The reaction mixture is poured in to aqueous and the organic layer is washed with aqueous $CuSO_4$. Activated charcoal and silica gel are added to the organic layer and stirred for 30 min and filtered. The filtrate is evaporated and residue purified by chromatography over silica gel to give compound **13**.

[0275] $NaBD_4$ (2 equivalents) is added in portions (3-4 portions) to cold (~5°C) EtOD (99% D) in a flask. Acetonide ester **13** (35 g, 90.10 mmol) was added in portions and the resulting reaction mixture was stirred at RT for 3hrs, and then heated at 80^0C for 2 days (NMR used to check greater than 95% Uridine-5D incorporation). Additional EtOD or D_2O can be added to increase the deuterium incorporation.

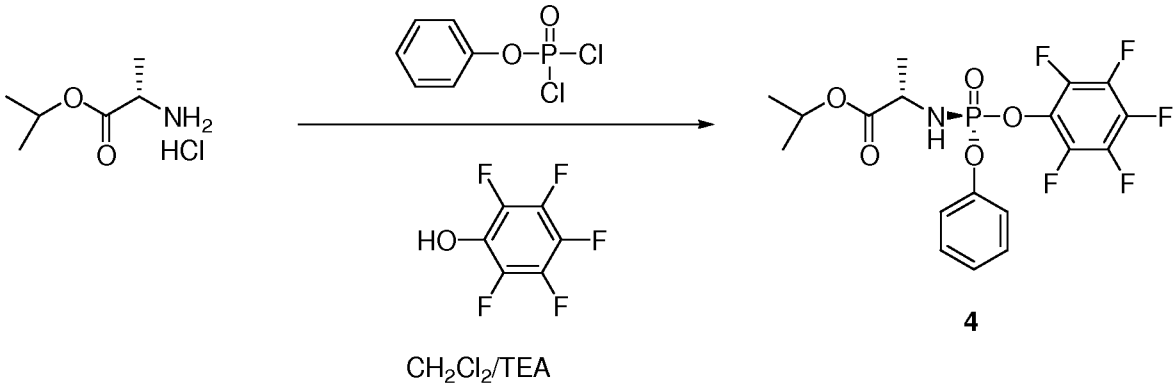
[0276] After completion of the reaction, half the solvent is removed under reduced pressure, reaction mixture was cooled in ice bath, AcOD (10 equivalents) is added and resulting mixture is stirred for 15-20 min. EtOAc and brine are added, organic layer is separated and the aqueous layer was again extracted with EtOAc followed by THF. The combined organic layer was concentrated, residue dissolved in 10% MeOH and $CHCl_3$, filtered, concentrated and purified by chromatography over silica gel to give deuterated acetonide **14.**

[0277] Deuterated acetonide **14** is added to cold (~5 °C) 4N HCl and stirred at room temperature for 3h. The solvent was evaporated to dryness and to the residue was added water and stirred. The suspension was cooled to 5 °C, stirred for 1h and the precipitate was collected by filtration. The solid was washed with cold water and dried to afford the deuterated nucleoside **15**.

[0278] Nucleoside **15** in THF was cooled to -5°C. *t*BuMgCl (3 equivalents) is added and stirred for 30 minutes at the same temperature. The reaction mixture is stirred for another 30 minutes at r.t. then cooled again to -5 °C and a solution of **4** in THF (2 equivalents) was added slowly and then the reaction

mixture was stirred at r.t. for 24 h. The reaction mixture was cooled to -5°C and cold 2N HCl was added, stirred for 10 min, and then saturated aqueous $NaHCO_3$solution was added followed by addition of solid NaCl. The mixture was stirred for 1h and the organic layer was separated. The aqueous layer was extracted with THF. All organic layers are combined and evaporated to dryness. The residue was purified by chromatography over silica gel to afford the title compound (**16**).

EXAMPLE 4. PREPARATION OF (S)-ISOPROPYL 2-(((S)-(PERFLUOROPHENOXY)(PHENOXY) PHOSPHORYL)AMINO)PROPANOATE (Reactant **4**)



4

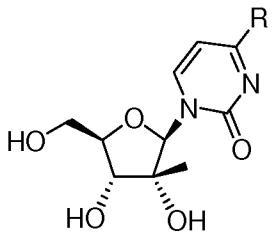
[0279] The preparation of **4** has previously been reported.

[0280] L-analine isopropyl ester HCl salt (160 g, 0.95mol) is charged in a 5L four-necked flask equipped with mechanical stirrer, thermometer and dropping funnel. To the flask, dichloromethane (1L) is added and the suspension is cooled to -70°C, followed by addition of triethylamine (200 g, 276 mL, 1.98 mol) over 45 minutes. To the mixture is added a solution of phenyl dichlorophosphate (200 g, 0.95 mol) in dichloromethane (1L) over 2.5 hours. The reaction mixture is stirred at this temperature for additional 90 minutes and then allowed to warm up to 0°C over a period of 2hr and stirred for 2 hr at 0°C. To the mixture a solution of 2,3,5,6-pentafluoro phenol (174.4 g, 0.95 mol) in 400 mL dichloromethane and a solution of triethylamine (105.4 g, 1.04mol) in 200 mL dichloromethane are added dropwise simultaneously over a period of 1.2hr. The mixture is warmed to room temperature and stirred overnight.

[0281] The solid, triethylamine HCl salt, is filtered off and the cake is washed with dichloromethane (3×150 mL). The filtrate is concentrated under reduced pressure and the residue triturated with MTBE (3.0 Liter). The white solid is removed by filtration. The cake is washed with MTBE (3×150 mL). The filtrate is concentrated and the resulting crude solid triturated with 20% ethyl acetate in hexane (2.0 L). The solid is collected by filtration and washed with 10% $NaHCO_3$ until aqueous phase reached pH=7, the solid is then washed with water and dried in a vacuum oven (55°C) for 28 hr. The dried solid was mixed with 500 mL Hexane-Toluene (5:1) and stirred for 1hr. The solid was collected

by filtration and washed with hexane-toluene (5:1, 2x80 mL) to afford pure one isomer. The solid was dried to give compound **4**.

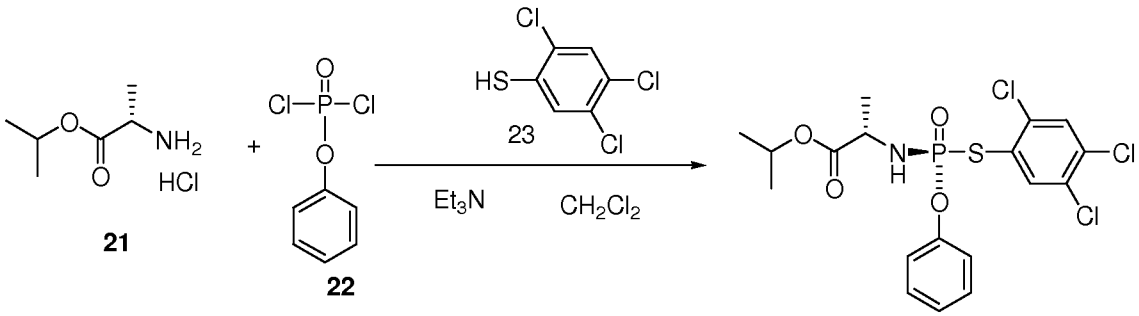
EXAMPLE 5. PREPARATION OF 1-((2R,3R,4R,5R)-3,4-DIHYDROXY-5-(HYDROXYMETHYL)-3-METHYLTETRAHYDROFURAN-2-YL)-4-ALKOXYPYRIMIDIN-2(1H)-ONE



[0282] R = OMe, compound **17**. Compounds **17** and **18** are prepared by methods well-known in the chemical literature.17(9): 1236) ^{1}H NMR (CD_3OD): δ 1.00 (s, 3H), 3.66 (m, 2H), 3.88 (s, 3H), 3.91 (m, 2H), 5.96 (s, 1H), 5.97 (d, 1H, J=7.2 Hz), 8.36 (d, 1H, J=7.2Hz), LCMS: $[M + H]^+$ 273.

[0283] R = OEt, compound **18**. ^{1}H NMR (CD_3OD): δ 1.00 (s, 3H), 1.38 (t, 3H, J=7.1Hz), 3.84 (m, 2H), 3.87 (m, 2H), 4.39 (q, 2H, J=7.1Hz), 6.06 (d, 1H, J=7.4 Hz), 6.08 (s, 1H),, 8.47 (d, 1H, J=7.1Hz), LCMS: $[M + H]^+$ 287

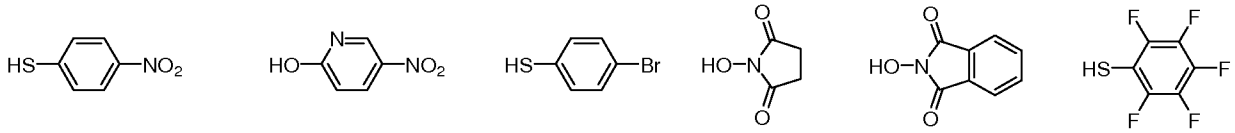
EXAMPLE 6. SYNTHESIS OF (S)-ISOPROPYL 2-(((S)-PHENOXY((2,4,5-TRICHLOROPHENYL)THIO)PHOSPHORYL)AMINO)PROPANOATE (Compound **24**)



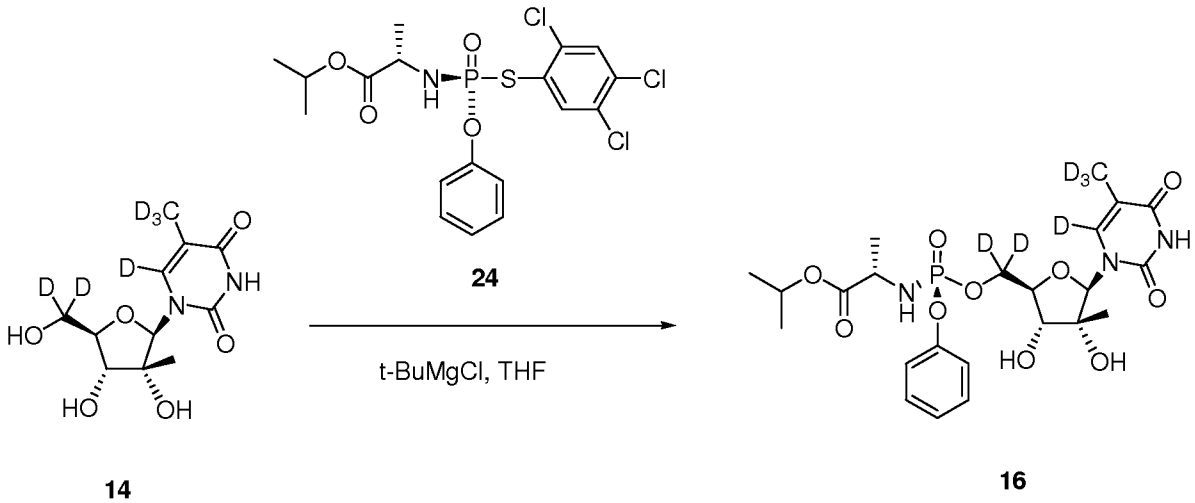
[0284] Phenoxydichlorophosphate (**22**, 12.58g) is added to a cold (- 50 °C) solution of L-Alanine isopropyl ester (**21**, 10 g) in dichloromethane (DCM, 100 mL), followed by the addition of triethylamine (18.3 mL) in DCM (36 mL) maintained at a temperature below – 40 °C. The reaction was warmed to room temperature slowly and stirred for 2h and again cooled to – 50 °C. A solution of trichlorothiophenol (**23**, 12.74g) in DCM (20 mL) containing triethylamine (9.1 mL). The reaction was warmed to room temperature and stirred for 15h.

[0285] The reaction mixture was washed with water (~300 mL) followed by saturated $NaHCO_3$ aq (~300 mL) and the organic layer was collected, dried over Na_2SO_4 and evaporated to dryness. The crude material was passed short SiO_2 column (CH_2Cl_2/EtOAc=0/1~1/4) and product collected after evaporation. The product was dissolved in 100 mL of 2.5% EtOAc in heptane mixture and the solution seeded with compound **24** (~10 mg) and stirred for 1 h at r.t. The precipitate was collected by filtration and solid was washed with a small amount of above solvent and dried to afford single isomer **24**, 5.2 g (18%).

[0286] Trichlorothiophenol (**3**) may be replaced by other groups such as nitrothiophenol, bromothiophenol, N-hyrdoxysuccinamide, N-hydroxyphthalimide, nitrohydroxypyridine.



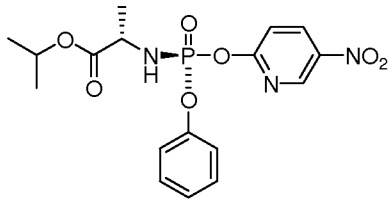
EXAMPLE 7. ALTERNATE METHOD FOR PREPARING (2S)-ISOPROPYL 2-(((((2S,3R,4R,5R)-1-(6-DEUTERO-5-(TRIDEUTEROMETHYL)PYRIMIDINE-2,4-DIOXO-3,4-DIHYDROPYRIMIDIN-1(2*H*)-YL)3,4-DIHYDROXY-4-METHYLTETRAHYDROFURAN-2-YL)DIDEUTEROMETHOXY)(PHENOXY)PHOSPHORYL)AMINO)PROPANOATE (COMPOUND **16**)



14 **16**

[0287] A suspension of **14** in THF is cooled to -20 °C and ^{t}BuMgCl (3.2 equivalents) is added slowly below -20 °C. The reaction mixture is warmed to room temperature slowly (~2 h) and stirred for 2h and then cooled again to -10 °C. Phosphorous reagent, compound **24** (2.1 equivalents), is added and the reaction mixture is warmed to room temperature and stirred for 15 h. The reaction mixture is cooled to 0 °C and 2N aq, HCl is added (solution pH ~2) and stirred for 30 min at 0 °C. Then aq $NaHCO_3$ is added (pH ~8) followed by NaCl and stirred for 30 min. The organic layer is separated, dried and evaporated. Crude material is purified by SiO_2 column to afford **16**.

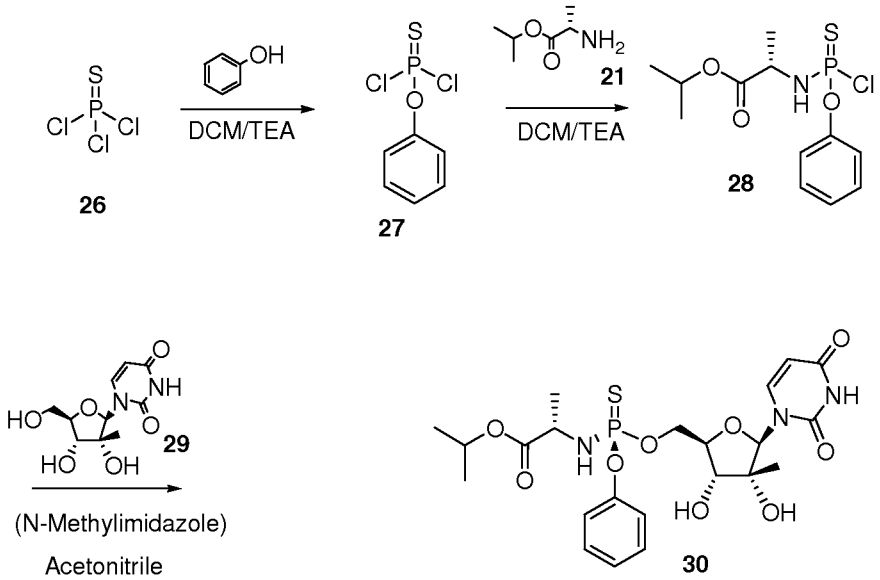
EXAMPLE 8. ALTERNATE METHOD FOR PREPARING COMPOUND **16**



25

[0288] Compound **25** is prepared by the method described in Example 6 for compound **24**. Compound **25** is then reacted with nucleoside **14** by the method described in Example 6 to give compound **16**.

EXAMPLE 9. SYNTHESIS OF (S)-ISOPROPYL 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-DIOXO-3,4-DIHYDROPYRIMIDIN-1(2H)-YL)-3,4-DIHYDROXY-4-METHYLTETRAHYDROFURAN-2-YL)METHOXY)(PHENOXY)PHOSPHOROTHIOYL)AMINO)PROPANOATE **30** (Comparative Example)



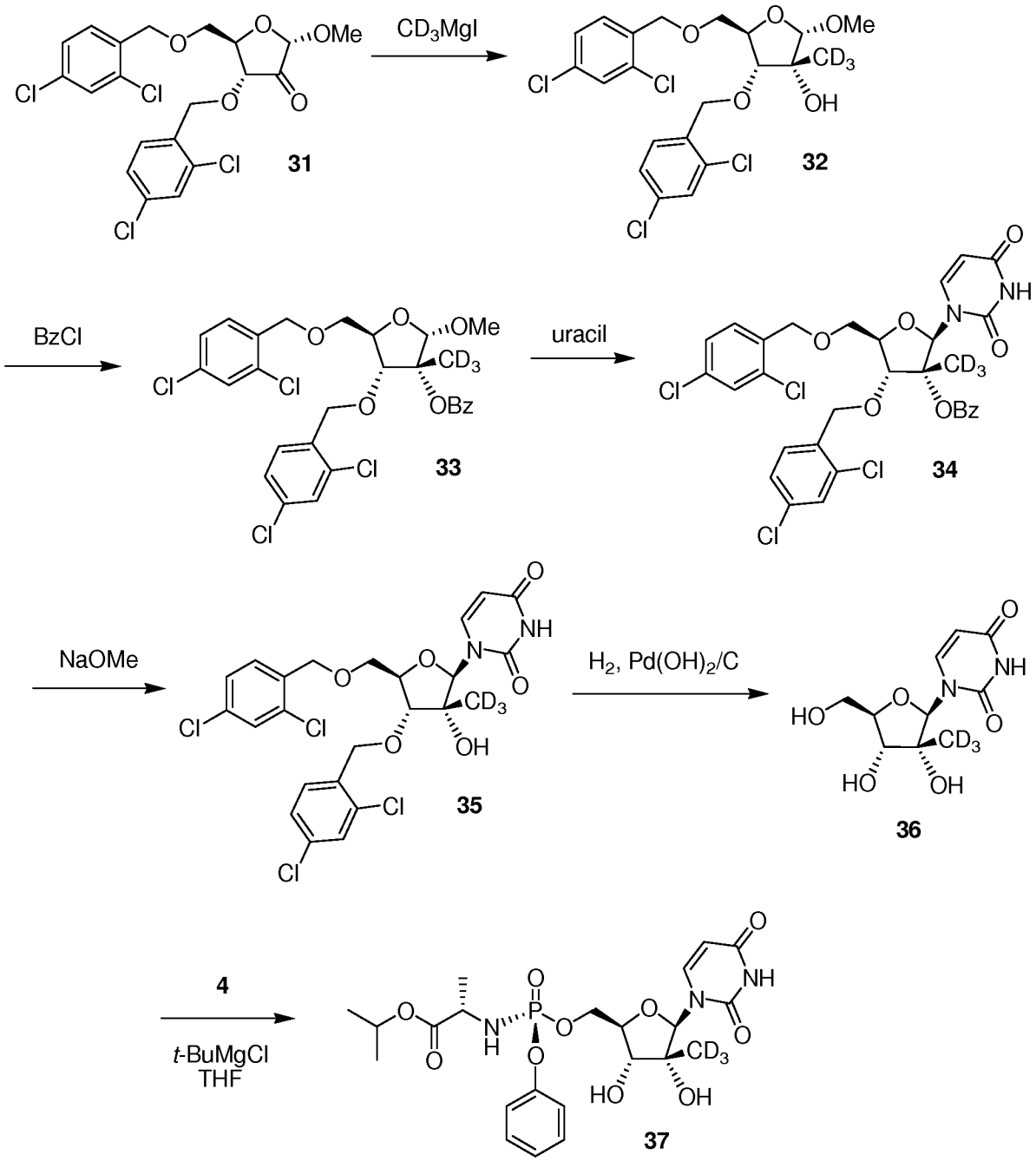
[0289] A solution of phenol (15g) in dichloromethane (DCM) was added to a cold (-78°C) solution of phosphorothioyl trichloride **26** (16.13 mL) in DCM followed by addition of triethylamine (TEA, 22 mL). After the addition was complete the solution was warmed to room temperature and stirred overnight (~16h). DCM was evaporated and the residue triturated by methyl *tert*-butylether (MTBE). The solid (triethylamine hydrochloride) was filtered off and the filtrate evaporated to dryness. The residue, O-phenylphosphorodichloridothioate **27**, was used without purification in the next step.

[0290] O-Phenylphosphorodichloridothioate **27** from above step was dissolved in DCM, cooled to -78 °C, TEA (40 mL) was added followed by a solution of L-alanine isopropyl ester (28 g) in DCM while maintaining the reaction temperature below -60 °C. The reaction was stirred or 30 min and then warmed to room temperature and stirred overnight (~16h). The solvent was evaporated and residue triturated with MTBE and solid triethylamine hydrochloride removed by filtration. The filtrate was evaporated to dryness and the residue purified by chromatography over silica gel (eluted with 0-1.5% ethylacetate/ hexane). The pure fraction were collected and evaporated to obtain 20 g of thiophosphoryl chloride **28**.

[0291] N-Methylimidazole (12 mL) was added to a solution of 2'-C-methyluridine **29** (6.34 g) in acetonitrile and cooled to -10 °C. A solution of compound **28** (7.9g) in acetonitrile was then added. The reaction mixture was stirred at 0 °C for 1h and then at room temperature overnight (~16h). The solvent was evaporated and the residue purified by chromatography over silica gel (eluted with 0-2.5% methanol/DCM). The pure fractions were mixed and evaporated to dryness and the residue crystallized from MTBE. The solid obtained was suspended in MTBE and refluxed for 2h cooled and filtered. The solid was washed with MTBE and dried to give 0.850g of compound **30** (3b(ii)-Sp from application WO 2012/040127). About 3.5% of the other isomer Rp is present.

[0292] 3b(ii)-Sp: ^{1}H-NMR (CD_3OD, 400 MHz): δ 7.76 (d, J=8.4Hz,1H), 7.34 (t, J=8.4 Hz, 2H), 7.27 (d, J=8.8 Hz, 2H), 7.18 (t,J=7.6 Hz, 1H), 5.96 (s, 1H), 5.57 (d, J=8.4 Hz, 1H), 4.98(m, 1H), 4.5 (m, 1H), 4.3 (m,1H), 4.1 (m,2H), 3.81 (d, J=9.2 Hz, 1H), 1.37 (d, J=6.8 Hz, 3H), 1.23, 1.22 (2d,J=6.8 Hz and 6Hz , 6H), 1.15 (s, 3H); ^{31}P-NMR (CD_3OD, 162 MHz): δ 68.42 (96.5%) and 68.21 (3.5%); ESI-LCMS: m/z=544 [M+1].

EXAMPLE 10. PREPARATION OF (*S*)-ISOPROPYL 2-(((*S*)-(((2*R*,3*R*,4*R*,5*R*)-5-(2,4-DIOXO-3,4-DIHYDROPYRIMIDIN-1(2*H*)-YL)-3,4-DIHYDROXY-4-TRIDEUTEROMETHYLTETRAHYDROFURAN-2-YL)METHOXY)(PHENOXY)PHOSPHORYL)AMINO)PROPANOATE.



[0293] Into a flask charged with magnesium turnings (0.25 g) and THF (1 mL) is added CD_3I (0.65 mL) dropwise over 30 min at rt under Ar with gentle stirring. The reaction mixture is stirred at rt for an additional 1 h. The resulting cloudy mixture is cooled to −78 °C, and then **31** (1.0 g) in THF (1.5 mL)

is added. The reaction mixture is allowed to warm to rt over 2 h and then aq NH_4Cl (10 mL) is added to quench the reaction. The mixture is extracted with EtOAc (50 mL). After washing the organic layer with brine (10 mL) and drying over anhydrous Na_2SO_4, the solvent is removed under reduced pressure to give compound **32** as a yellow syrup.

[0294] Compound **32** (0.878 g) is dissolved in CH_2Cl_2 (25 mL) and treated with BzCl (0.51 mL) in the presence of triethylamine (3.1 mL) and DMAP (53 mg) overnight. Volatiles are removed by under reduced pressure, the residue is treated with water, and the product is extracted with EtOAc. After washing the organic layer with aq $NaHCO_3$ and brine, followed by drying over anhydrous Na_2SO_4, the solvent is removed under reduced pressure to give the crude product. This material is purified by column chromatography on silica gel (hexanes/EtOAc 4:1 v/v as eluent) to give **33** as yellow syrup.

[0295] Uracil (0.394 g) in acetonitrile (15 mL) is treated with BSA (*N*,*O*-bis(trimethylsilyl)acetamide, 1.72 mL) at 70 °C under Ar for 1 h. The clear solution is cooled to 0 °C, then compound **33** (0.53 g) in acetonitrile (5 mL) followed by $SnCl_4$ (0.413 mL) is added. The reaction mixture is stirred at 70 °C under Ar for 3 d and quenched by addition of a saturated aq solution of $NaHCO_3$ at 0 °C. CH_2Cl_2 is added and then the mixture is filtered through a Celite pad to remove solids. The filtrate is dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give **34** as a foam.

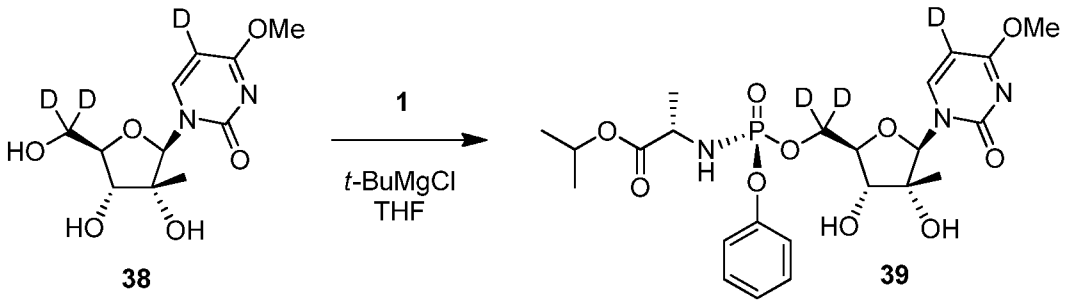
[0296] Compound **34** (0.58 g) is dissolved in MeOH/THF (5 mL/2 mL) and treated with NaOMe/MeOH (30%, 0.2 mL) at rt overnight. Volatiles are removed under reduced pressure. The remaining residue is treated with HCl (10% aq, 0.4 mL) and then purified by column chromatography on silica gel (5% MeOH in CH_2Cl_2 as eluent) to give **35** as a syrup.

[0297] Compound **35** (0.418 g) is dissolved in MeOH (15 mL) and treated with H_2 (~1 atm, balloon) in the presence of $Pd(OH)_2$ on carbon (20% wet, 50 mg) overnight. After filtration and evaporation of the filtrate, the remaining residue was purified by column chromatography on silica gel (15% MeOH in CH_2Cl_2 as eluent) to give nucleoside **36** as a colorless solid. ^{1}H NMR (400 MHz, CD_3OD, 300 K): δ3.78 (dd, J = 12.5 Hz, 2.6 Hz, 1H), 3.84 (d, J = 9.2 Hz, 1H), 3.92 (d of app t, J = 9.2 Hz, 2.4 Hz, 1H), 3.98 (dd, J = 12.5 Hz, 2.2 Hz, 1H), 5.67 (d, J = 8.1 Hz, 1H), 5.96 (s, 1H), 8.14 (d, J = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD, 300 K): δ60.5, 73.4, 79.9, 83.9, 93.1, 102.3, 142.5, 152.5, 166.0 (CD_3 not observed); LC–MS: 262 amu (M + 1).

[0298] Nucleoside **36** was converted to the phosphoramidate derivative **37** in a manner analogous to that described in Example 1. ^{1}H NMR (400 MHz, CD_3OD, 300 K): δ1.21 (2 × d, J = 6.3 Hz, 6H), 1.35 (dd, J = 7.2 Hz, $J_{H,P}$ = 0.9 Hz, 3H), 3.79 (d, J = 9.2 Hz, 1H), 3.91 (dq, $J_{H,P}$ = 10.0 Hz, J = 7.2 Hz, 1H), 4.08 (m, 1H), 4.37 (ddd, J = 11.8 Hz, $J_{H,P}$ = 5.9 Hz, J = 3.7 Hz, 1H), 4.50 (ddd, J = 11.8 Hz, $J_{H,P}$ = 5.9 Hz, J = 2.0 Hz, 1H), 4.96 (septet, J = 6.3 Hz, 1H), 5.60 (d, J = 8.1 Hz, 1H), 5.96 (s, 1H), 7.20

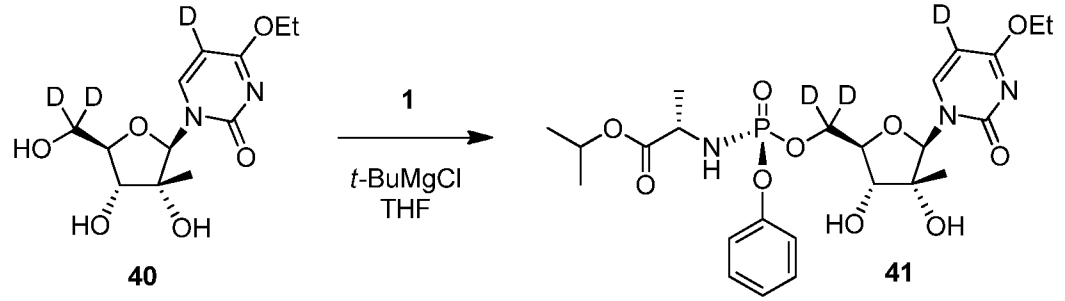
(m, 1H), 7.26 (m, 2H), 7.37 (m, 2H), 7.67 (d, J = 8.1 Hz, 1H); ^{31}P NMR (162 MHz, CD_3OD, 300 K): δ 3.8; LC–MS: 531 amu (M + 1).

EXAMPLE 11. PREPARATION OF (S)-ISOPROPYL 2-(((S)-(((2R,3R,4R,5R)-3,4-DIHYDROXY-5-(5-DEUTERO-4-METHOXY-2-OXOPYRIMIDIN-1(2H)-YL)-4-METHYLTETRAHYDROFURAN-2-YL)DIDEUTEROMETHOXY)(PHENOXY)PHOSPHORYL)AMINO)PROPANOATE (Compound **39**)



[0299] Compound **38** is prepared in a manner analogous to that described in Kang *et al.* (*Chem. Res. Toxicol.* (2004) 17: 1236). Nucleoside **38** is converted to the phosphoramidate derivative **39** in a manner analogous to that described in Example 2. ^{1}H NMR (400 MHz, CD_3OD, 300 K): δ1.11 (s, 3H), 1.23 (d, J = 6.3 Hz, 6H), 1.37 (dd, J = 7.1 Hz, 0.8 Hz, 3H), 3.79 (d, J = 9.3 Hz, 1H), 3.90–3.99 (overlapping s and m, 4H), 4.14 (dd, J = 9.3 Hz, 2.3 Hz, 1H), 4.97 (septet, J = 6.3 Hz, 1H), 6.09 (s, 1H), 7.22 (m, 1H), 7.29 (m, 2H), 7.39 (m, 2H), 8.00 (s, 1H); ^{31}P NMR (162 MHz, CD_3OD, 300 K): δ3.8; LC–MS: 545 amu (M + 1).

EXAMPLE 12. PREPARATION OF (S)-ISOPROPYL 2-(((S)-(((2R,3R,4R,5R)-5-(5-DEUTERO-4-ETHOXY-2-OXOPYRIMIDIN-1(2H)-YL)-3,4-DIHYDROXY-4-METHYLTETRAHYDROFURAN-2-YL)DIDEUTEROMETHOXY)(PHENOXY)PHOSPHORYL)AMINO)PROPANOATE (Compound **41**)

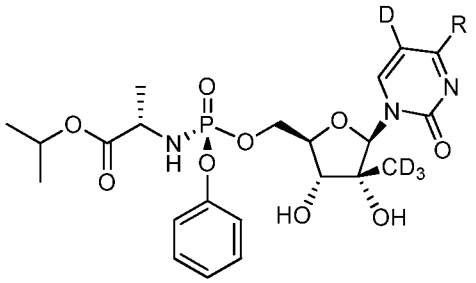


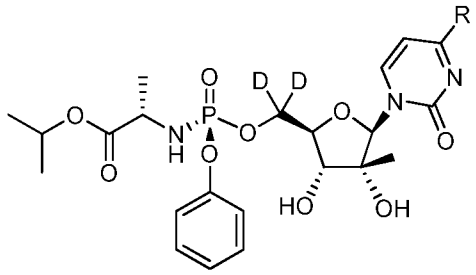
[0300] Compounds **40** and **41** are prepared using methods analogous to those described in Example 11. Spectroscopic data for **41**: ^{1}H NMR (400 MHz, CD_3OD, 300 K): δ1.11 (s, 3H), 1.23 (d, J = 6.3 Hz, 6H), 1.38 (overlapping d and t, 6H), 3.79 (d, J = 9.3 Hz, 1H), 3.94 (m, 1H), 4.14 (dd, J = 9.3 Hz,

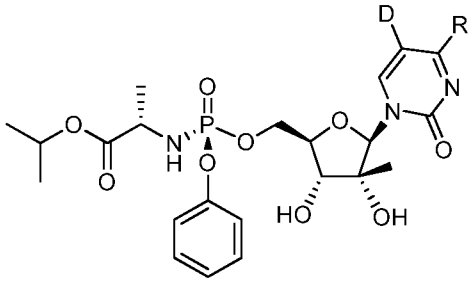
2.3 Hz, 1H), 4.41 (q, J = 7.0 Hz, 2H), 4.97 (septet, J = 6.3 Hz, 1H), 6.08 (s, 1H), 7.22 (m, 1H), 7.29 (m, 2H), 7.39 (m, 2H), 7.99 (s, 1H); ^{31}P NMR (162 MHz, CD_3OD, 300 K): δ 3.8; LC–MS: 559 amu (M + 1).

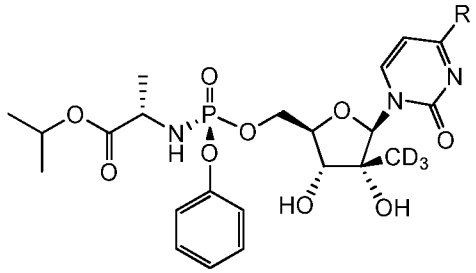
EXAMPLE 13. ADDITIONAL COMPOUNDS

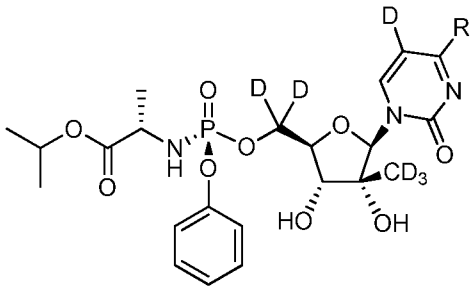
[0301] The following compounds are prepared by the methods given in Examples 1 – 9. In each example R = methoxy or ethoxy.











EXAMPLE 14. DETERMINATION OF ANTI-HCV ACTIVITY AND CYTOTOXICITY

[0302] Compounds claimed herein are tested for the ability to inhibit viral replication of the Hepatitis C replicon in cultured cells in which the HCV replicon construct has been incorporated. The replicon system is predictive of in vivo anti-HCV activity; compounds that are active in humans uniformly evidence activity in the replicon assay. In this assay HCV replicon containing cells are treated with different concentrations of the test compound to ascertain the ability of the test compound to suppress replication of the HCV replicon.

The Cell Line

[0303] The Huh-luc/neo cell line was obtained from ReBLikon GmbH (Mainz, Germany) [**Error! Reference source not found.**]. This cell line harbors a bicistronic genotype-1b/strain Con-1 HCV subgenomic replicon: the first cistron encodes both luciferase and neomycin phosphotransferase II (NPTII) and the second cistron encodes HCV non-structural proteins NS3 through NS5B. Hence, the luciferase activity in the cultured cells was used as a surrogate marker for the level of HCV replicon RNA. The replicon cells were maintained in complete medium [DMEM (Life Technologies, Carlsbad, CA), 10% fetal bovine serum (FBS), 1× non-essential amino acids (Life Technologies, Carlsbad, CA), and penicillin (100 IU/mL), and streptomycin (100 µg/mL)], with addition of 0.25 mg/mL G418 (Life Technologies, Carlsbad, CA) and were passaged twice a week.

[0304] Huh-Lunet cells were derived from Huh-luc/neo cells (Vrolijik, J.M, et al. "J. Virol. Methods (2003) 110(2): 201-209) by eliminating HCV replicons with a selective HCV inhibitor. Huh-Lunet cells were maintained in a complete medium consisting of DMEM, 10% FBS, non-essential amino acids, penicillin, and streptomycin at 37°C in an atmosphere of 5% CO_2.

Determination of Anti-HCV Activity and Cytotoxicity

[0305] Huh-luc/neo cells were seeded in 96-well plates at a density of 8×10^3 cells per well in 200 µL DMEM supplemented with 10% FBS. One day after seeding, compounds were prepared as six half-log dilution series in 100% DMSO and added to cells at a 1:200 ratio, achieving DMSO final concentration of 0.5% in a total volume of 200 µL. Cell plates were incubated at 37°C for 3 days. The anti-HCV activity of ACH-0143422 was determined by quantifying luciferase activity in each well with a Bright-Glo Luciferase Assay kit (Promega, Madison, WI). Due to the wide dynamic range offered by the luciferase activity, anti-HCV activity could be expressed as the concentration that caused a reduction of luciferase activity (relative luminescence units, RLU) by 50% (EC_{50}) in comparison to the untreated controls. EC_{50} values were calculated with a Microsoft Excel-based program. Cellular toxicity of the compound was determined by measuring the cell viability in each well with a CellTiter 96 AQ_{ueous} One Solution kit (Promega, Madison, WI). The concentration of compound that caused a reduction of the cell viability by 50% (CC_{50}) relative to untreated cells was obtained with a Microsoft Excel-based program.

EXAMPLE 15. DETERMINATION OF ANTI HCV ACTIVITY USING TRANSIENT HCV REPLICONS

Plasmids encoding transiently replicating chimeric replicons

[0306] This assay utilizes plasmids encoding transiently replicating chimeric replicons carrying the coding region of NS5B from HCV genotype 3a or 4a. The plasmid pFK-I341PI-luc/NS3-3'/ET (ReBLikon GmbH, Germany) (Lohmann, V., et al, (J. Virol. (2003) 77(5): 3007-3019) was used as backbone for the chimeric replicon constructions. This plasmid encodes a replicon that carries a

luciferase reporter gene driven by the poliovirus IRES and the HCV NS3 to NS5B nonstructural genes from genotype-1b/strain-Con1 HCV driven by the EMCV IRES. Three adaptive mutations, E1202G and T1280I in NS3 and K1846T in NS4B, were introduced into this construct for efficient replicon replication. The NS5B sequences of HCV genotypes 3a and 4a were synthesized by Integrated DNA Technologies, Inc (Coralville, IA). NS5B DNA fragments were inserted in-frame into pFK-I_{341}PI-luc/NS3-3'/ET.

Synthesis of HCV Replicon RNA

[0307] To generate run-off transcripts of HCV replicons, the plasmids encoding various HCV replicons were linearized by digestion with ScaI. After extraction with phenol-chloroform and ethanol precipitation, the plasmids were used as templates for in vitro T7 transcription reactions (Megascript T7 kit, Ambion, Austin, TX). Transcripts were extracted once with acidic phenol and chloroform. After isopropanol precipitation, RNA was dissolved in RNase-free water and concentrations were determined by measurement of the optical density at 260 nm.

Transient HCV replicon assay

[0308] Replicon RNAs were transfected into Huh-Lunet cells by electroporation. In brief, single-cell suspensions of Huh-Lunet cells were prepared at a density of 10^7 cells per mL in Cytomix solution supplemented with 2 mM ATP and 5 mM glutathione. After mixing 5 µg RNA with 400 µL of the cell suspension in a Gene Pulser cuvette (0.4 cm gap), electroporation was immediately performed at 270V and 950 µF with a Gene Pulser system (Bio-Rad, Hercules, CA). Electroporated cells were immediately diluted into 10 mL DMEM supplemented with 10% FBS and seeded into 96-well plates at a density of 8×10^3 cells per well in a final volume of 200 µL DMEM supplemented with 10% FBS. One day after seeding, compounds were prepared as six half-log dilution series in 100% DMSO and added to cells at a 1:200 ratio, achieving DMSO final concentration of 0.5% in a total volume of 200 µL. Cell plates were incubated at 37°C for 3 days. The inhibition of HCV replicon replication was quantified by measurement of firefly or *Renilla* luciferase activity using commercial kits (Bright-Glo Luciferase Assay or *Renilla*-Glo Luciferase Assay, Promega, Madison, WI). Anti-HCV activity was expressed as the concentration that reduced luciferase activity by 50% (EC_{50}) compared to the untreated controls. EC_{50} values were calculated with a Microsoft Excel-based program.

[0309] Certain compounds of Formula (I) exhibit an EC_{50} of less than 0.1 micromolar when evaluated in the replicon assay using the genotype-1b/strain Con-1 HCV subgenomic replicon. Furthermore certain compounds of Formula (I) exhibit a selectivity index (CC_{50}/EC_{50} of greater than 100 and in some instances greater than 500. Furthermore certain compounds of Formula (I) exhibit an EC_{50} that is significantly less than the EC_{50} exhibited by comparative compound **30** (3b(ii)-Sp) when evaluated in the replicon assay using the genotype-1b/strain Con-1 HCV subgenomic replicon. In some instances a

compound of Formula (I) exhibits and EC_{50} that is at least 5-fold less than the EC_{50} of comparative compound **30**. Furthermore certain compounds of Formula (I) exhibit an improved CC_{50}/EC_{50} selectivity index relative to comparative compound **30.** In some instances the selectivity index for a compound of Formula (I) is more than 5-fold greater than the selectivity index for comparative compound **30**. Furthermore certain compounds of Formula (I) exhibit improved potency (lower EC_{50}) over comparative compound **30** when evaluated in the replicon assay against genotypes 3a and 4a replicons.

EXAMPLE 16. DETERMINATION OF NUCLEOSIDE CONCENTRATIONS IN HUMAN HEPATOCYTES\

[0310] This assay is used to determine the concentration free nucleoside in media and hepatocyte cell extract for nucleoside prodrugs incubated with fresh liver hepatocytes. LC MS can also be used to detect the level of nucleoside monophosphate. A higher concentration of free nucleoside is directly related to a decrease in nucleoside prodrug and the loss of drug activity.

Cells

[0311] Fresh human liver hepatocytes were received plated in a 12-well and 6-well format. Upon receipt, shipping media was removed immediately and replaced with 1 mL or 2 mL pre-warmed culture medium. Cells were plated ate a density of 0.67 million cells per well in the 12 well format and 1.7 million cells per well in the 6 well format. Supplemented modified Chee's media (Xenotec, LLC, catalogue no. K2300) was used as the culture media. Cells were acclimated overnight at 37°C with 5% CO_2 atmosphere.

Assay

[0312] Media was aspirated from 12- and 6- well plates and replaced with 1 mL or 2 mL respectively of fresh media containing either 20μM deuterated prodrug or 20μM ACH-undeuterated prodrug or solvent control (0.05% DMSO). Samples incubated at 37°C in 5% CO_2 atmosphere were in duplicate for deuterated prodrug and in singlet undeuterated prodrug in each well format. Stability of compound in absence of cells was also conducted

[0313] At 24 hrs, media was removed and frozen. Cells were washed twice with cold PBS. 70% cold Methanol (0.75 mL or 1.5mL for 12- and 6- well respectively) containing internal standard, an non-deuterated prodrug with known anti-HCV efficacy was added to each well and cells were gently removed from the plate by scraping. The recovered cells suspended in the organic solution were aspirated into a vial and frozen at -80°C.

Extraction and LC-MS/MS Analysis of Hepatocyte Cells

[0314] Cell solutions extracted overnight at -80°C in 70% Methanol were removed from the freezer, defrosted and vortexed. Tubes were centrifuged at 3000 rpm for 15 minutes at 4°C. Supernatants were removed and analyzed by LC-MS/MS.

[0315] Six concentrations of deuterated prodrug, non-deuterated prodrug, free nucleoside of the deuterated prodrug, or free nucleoside on the non-deuterated prodrug were prepared by 3-fold serial dilution in DMSO. Aliquots of the compounds at the specified concentrations were spiked into 70% methanol containing internal standard. 2 concentrations were also spiked into cells solutions from the experiment incubated in the absence of compound. Samples were frozen at -80°C overnight, then defrosted and vortexed. Samples were centrifuged at 3000 rpm for 15 minutes. Supernatants were removed and analyzed by LC-MS/MS. The calibration concentrations were 5, 1.67, 0.556, 0.185, 0.0617 and 0.0206μM.

[0316] The analytes were quantified using linear regression of calibration standard values with instrument response. The acceptance criteria used and calibration standard concentrations was ± 30% of nominal concentration. Calibration standards that did not meet the specified criteria were not used in the calibration curve. Sample values were accepted when at least 66% of the standard concentrations during the run were within 30% of nominal. The "r" value required for acceptance of the run was > 0.98. Cell samples were analyzed without internal standard due to only 81% extraction efficiency of internal standard from cells while calibration was conducted without cells, this gave more accurate determination of concentrations.

Extraction and LC-MS/MS Analysis of Hepatocyte Media

[0317] Hepatocyte media incubates were removed from the freezer, defrosted and vortexed. 2 parts hepatocyte media incubate to 1 part Acetonitrile containing internal standard were mixed and then centrifuged at 3000 rpm for 15 minutes at 4°C. Supernatants were removed and analyzed by LC-MS/MS.

[0318] Six concentrations of deuterated prodrug, non-deuterated prodrug, free nucleoside of the deuterated prodrug, or free nucleoside of the non-deuterated prodrug were prepared by 3-fold serial dilution in DMSO. Aliquots of the compounds were spiked into fresh hepatocyte media to afford 5, 1.67, 0.556, 0.185, 0.0617 and 0.0206μM concentrations. 2 parts calibration media were mixed with 1 part Acetonitrile containing internal standard samples were centrifuged at 3000 rpm for 15 minutes at 4°C. Supernatants were removed and analyzed by LC-MS/MS.

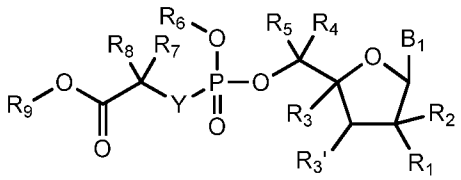
[0319] Analyte concentrations in the samples were quantified using linear regression of calibration standard values with instrument response. The acceptance criteria used and calibration standard concentrations was ± 30% of nominal concentration. Calibration standards that did not meet the specified criteria were not used in the calibration curve. Sample values were accepted when at least 66% of the standard concentrations during the run were within 30% of nominal. The "r" value required for acceptance of the run was > 0.98.

[0320] Certain compounds of this disclosure had increased concentrations (more that 1.5-fold) in the media and hepatocyte cell extract of the free nucleoside for the non-deuterated prodrug relative to the concentration of the free nucleoside for the otherwise identical deuterated nucleoside prodrug.

CLAIMS

What is claimed is:

1. A compound of the Formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein:

Y is NH or O;

R_1 is hydroxyl, fluoro, or $–OCD_3$;

R_2 is hydrogen or deuterium; or

R_2 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, or C_2-C_6alkynyl; each of which is optionally deuterated and optionally substituted; or

R_1 and R_2 are joined to form a 3- to 6-membered cycloalkyl ring or a 3- to 6-membered heterocycloalkyl ring containing one heteroatom selected from N, O, and S, each of which is optionally substituted;

R_3 is hydrogen, deuterium, halogen, or $–N_3$; or

R_3 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl, (C_3-C_6cycloalkyl)C_0-C_4carbhydryl, (4- to 6-membered heterocycloalkyl)C_0-C_4carbhydryl, (aryl)C_0-C_4carbhydryl, or (heteroaryl)C_0-C_4carbhydryl, each or which is optionally deuterated and optionally substituted; and

R_3' is hydroxyl; or

R_3 and R_3' are taken together to form a 3- to 6- membered ring optionally containing one heteroatom selected from N, O, and S, which is optionally substituted with one or more substituents independently selected from halogen, hydroxyl, C_1-C_2alkyl, and C_1-C_2alkoxy;

R_4 is hydrogen, deuterium, halogen, C_1-C_2haloalkyl, or C_1-C_2haloalkoxy; or R_4 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl, or C_1-C_6alkoxy, each of which is optionally deuterated and optionally substituted;

R_5 is hydrogen, deuterium, or halogen; or R_5 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl, or C_1-C_6alkoxy, each of which is optionally deuterated and optionally substituted; or

R_4 and R_5 are taken together to form a 3- to 6- membered ring optionally containing one heteroatom selected from N, O, and S, which ring is optionally substituted with one or more substituents independently selected from halogen, hydroxyl, C_1-C_2alkyl, and C_1-C_2alkoxy;

R_6 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl, (aryl)C_0-C_2alkyl, or 5- to 6-membered monocyclic heteroaryl containing 1 to 3 heteroatoms independently chosen from N, O, and S, or 8- to 10-membered bicyclic heteroaryl containing 1 to 4 heteroatoms independently chosen from N, O, and S; each of which R_6 is optionally substituted;

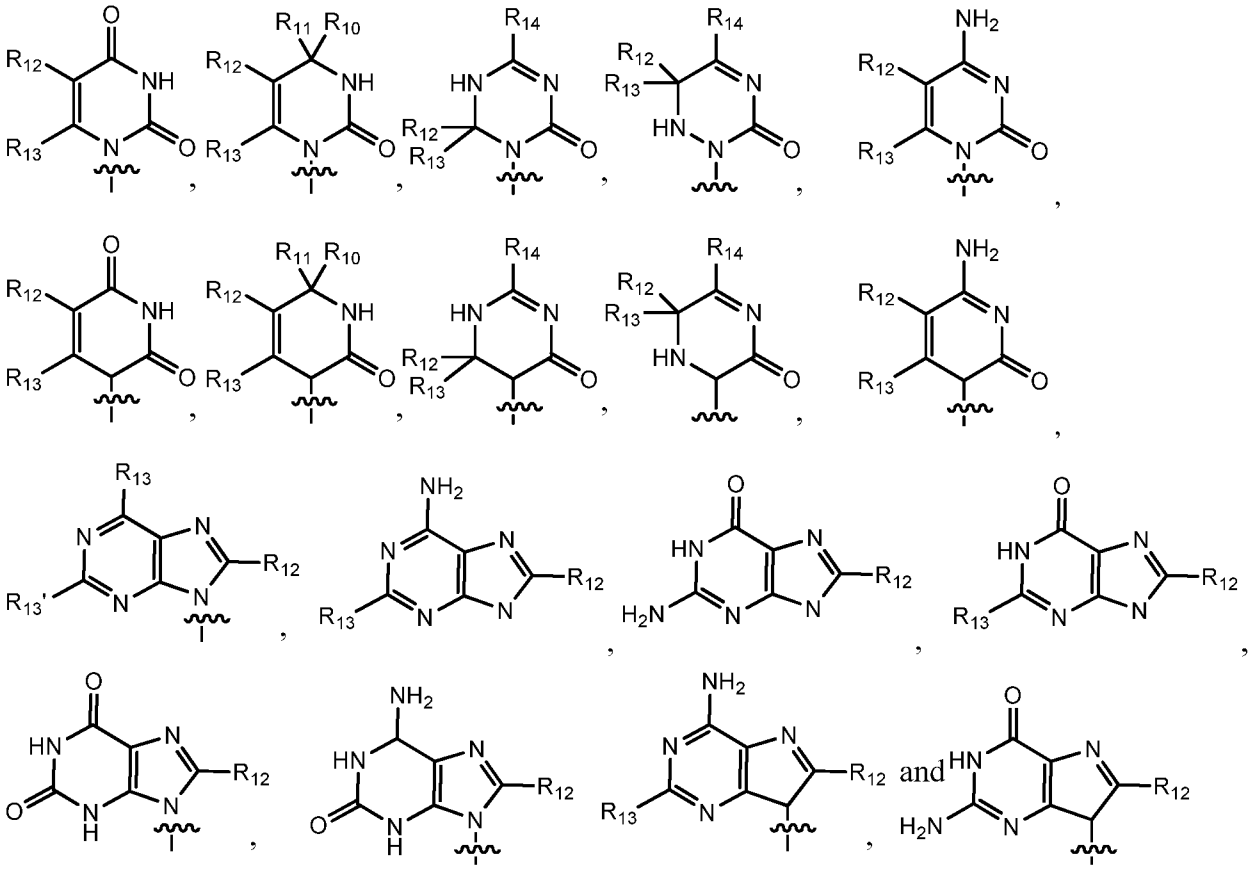
R_7 is hydrogen, halogen, C_1-C_2haloalkyl, or C_1-C_2haloalkoxy; or R_7 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, (C_3-C_6cycloalkyl)C_0-C_4alkyl, or (aryl)C_0-C_2alkyl; each of which is optionally substituted;

R_8 is hydrogen, halogen, C_1-C_2haloalkyl, or C_1-C_2haloalkoxy; or R_8 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl,or C_1-C_6alkoxy, each of which is optionally substituted; or

R_7 and R_8 are taken together to form a 3-to 6-membered cycloalkyl ring or 3- to 6-membered heterocycloalkyl ring containing one heteroatom chosen from N, O, and S; each of which is optionally substituted;

R_9 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl, (C_3-C_7cycloalkyl)C_0-C_4carbhydryl, (aryl)C_0-C_4carbhydryl, (3- to 6-membered heterocycloalkyl)C_0-C_4carbhydryl, or (heteroaryl)C_0-C_4carbhydryl, each of which is optionally substituted;

B_1 is a base selected from



and

R_{10} and R_{11} are independently hydrogen and deuterium;

R_{12}, R_{13}, and R_{13}' are independently hydrogen, deuterium, methyl, and $-CD_3$;

R_{14} is hydrogen, deuterium, hydroxyl, amino, C_1-C_4alkoxy, deuterated C_1-C_4alkoxy, C_1-C_4alkylester, or mono- or di-C_1-C_4alkylcarbamate;

wherein each position represented by D has a deuterium enrichment of at least 50%; and

one or both of R_4 and R_5 is deuterium with a deuterium enrichment of at least 50%; and one or more of R_1, R_2, R_{10}, R_{11}, R_{12}, R_{13}, R_{13}', and R_{14} is optionally deuterium with a deuterium enrichment of at least 50% or a deuterated substituent with at least one position of the substituent having a deuterium enrichment of at least 50%.

2. The compound or salt of Claim 1, wherein

each position represented by D has a deuterium enrichment of at least 90%; and

one or more of R_1, R_2, R_4, R_5, R_{10}, R_{11}, R_{12}, R_{13}, R_{13}', and R_{14} is deuterium with a deuterium enrichment of at least 90% or a deuterated substituent with at least one position of the substituent having a deuterium enrichment of at least 90%.

3. The compound or salt of Claim 1, wherein

each position represented by D has a deuterium enrichment of at least 90%; and

at least two of R_1, R_2, R_4, R_5, R_{10}, R_{11}, R_{12}, R_{13}, R_{13}', and R_{14} is deuterium with a deuterium enrichment of at least 90% or a deuterated substituent with at least one position of the substituent having a deuterium enrichment of at least 90%.

4. The compound or salt of Claim 1, wherein

each position represented by D has a deuterium enrichment of at least 95%; and

2 or 3 of R_1, R_2, R_4, R_5, R_{10}, R_{11}, R_{12}, R_{13}, R_{13}', and R_{14} are deuterium with a deuterium enrichment of at least 95% or a deuterated substituent with at least one position of the substituent having a deuterium enrichment of at least 95%.

5. The compound or salt of Claim 1, wherein

each position represented by D has a deuterium enrichment of at least 90%; and

3 of R_1, R_2, R_4, R_5, R_{10}, R_{11}, R_{12}, R_{13}, R_{13}', and R_{14} are deuterium with a deuterium enrichment of at least 90% or a deuterated substituent with at least one position if the substituent having a deuterium enrichment of at least 90%.

6. The compound or salt of Claim 1, wherein

each position represented by D has a deuterium enrichment of at least 90%; and

at least R_4, R_5 and one of R_{12} and R_{13} are deuterium with a deuterium enrichment of at least 90% or a deuterated substituent with at least one position of the substituent having a deuterium enrichment of at least 90%.

7. A compound or salt of any one of Claims 1 to 6, where Y is NH.

8. A compound or salt of any one of Claim 1 to 7, where

R_1 is hydroxyl, fluoro, or $-OCD_3$;

R_2 is hydrogen or deuterium; or

R_2 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, or C_2-C_6alkynyl; each of which is optionally deuterated and optionally substituted.

9. A compound or salt of Claim 8, wherein

R_1 is hydroxyl or fluoro; and R_2 is C_1-C_4alkyl, allenyl, C_2-C_4alkenyl, or C_2-C_4alkynyl; each of which is optionally deuterated.

10. A compound or salt of Claim 8, wherein

R_1 is hydroxyl or fluoro; and R_2 is methyl or $-CD_3$.

11. A compound or salt of any one of Claims 1 to 7, wherein

R_1 and R_2 are joined to form a 3- to 6-membered cycloalkyl ring or a 3- to 6-membered heterocycloalkyl ring containing one heteroatom selected from N, O, and S, each of which is optionally substituted.

12. A compound or salt of Claim 11, wherein

R_1 and R_2 are joined to form a 3- to 6-membered cycloalkyl ring or a 3- to 6-membered heterocycloalkyl ring containing one heteroatom selected from N, O, and S, each of which is optionally substituted with one or more substituents independently chosen from halogen, hydroxyl, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

13. A compound or salt of Claim 11, wherein R_1 and R_2 are joined to form a cyclopropyl group.

14. A compound or salt of any one of Claims 1 to 13, wherein R_3 is hydrogen, deuterium, halogen, or $-N_3$ and R_3' is hydroxyl.

15. A compound or salt of any one of Claims 1 to 13, wherein

R_3 is C_1-C_4alkyl, allenyl, C_2-C_4alkenyl, C_2-C_4alkynyl, (C_3-C_6cycloalkyl)C_0-C_2alkyl, or (phenyl)ethynyl; and R_3' is hydroxyl.

16. A compound or salt of any one of Claims 1 to 13, wherein

R_3 and R_3' are taken together to form a 3- to 6- membered ring optionally containing one heteroatom selected from N, O, and S, which ring is optionally substituted with one or more substituents independently selected from halogen, hydroxyl, C_1-C_2alkyl, and C_1-C_2alkoxy.

17. A compound or salt of any one of Claims 1 to 16, wherein

R_4 is hydrogen, deuterium, C_1-C_2haloalkyl, or C_1-C_2haloalkoxy; or R_4 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl, or C_1-C_6alkoxy, each of which is optionally deuterated and optionally substituted;

R_5 is hydrogen or deuterium; or R_5 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl, or C_1-C_6alkoxy, each of which is optionally deuterated and optionally substituted.

18. A compound or salt of Claim 17, wherein

R_4 is hydrogen, or deuterium or R_4 is C_1-C_4alkyl, allenyl,C_2-C_4alkenyl, C_2-C_4alkynyl, or C_1-C_4alkoxy, each of which is optionally deuterated; and

R_5 is hydrogen or deuterium; or R_5 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl, or C_1-C_6alkoxy, each of which is optionally deuterated.

19. A compound or salt of Claim 18, wherein both R_4 and R_5 are both deuterium.

20. A compound or salt of any one of Claims 1 to 16, wherein

R_4 and R_5 are taken together to form a 3- to 6- membered ring optionally containing one heteroatom selected from N, O, and S, which ring is optionally substituted with one or more substituents independently selected from halogen, hydroxyl, C_1-C_2alkyl, and C_1-C_2alkoxy.

21. A compound or salt of any one of Claims 1 to 20, wherein

R_6 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl, each of which optionally substituted.

22. A compound or salt of any one of Claims 1 to 20, wherein

R_6 is (aryl)C_0-C_2alkyl, a 5- to 6-membered monocyclic heteroaryl containing 1 to 3 heteroatoms independently chosen from N, O, and S, or 8- to 10- membered bicyclic heteroaryl containing 1 to 4 heteroatoms independently chosen from N, O, and S; each of which R_6 is optionally substituted.

23. A compound or salt of Claim 22, wherein

R_6 is phenyl, pyridyl, naphthyl, or indolyl, each of which is optionally substituted with one or more substituents independently chosen from halogen, hydroxyl, C_1-C_4alkyl, C_1-C_4alkoxy, (mono- and di-C_1-C_4alkylamino)C_0-C_2alkyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

24. A compound or salt of any one of Claim 1 to 23, wherein

R_7 is hydrogen, halogen, C_1-C_2haloalkyl, or C_1-C_2haloalkoxy; or R_7 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, (C_3-C_6cycloalkyl)C_0-C_4alkyl, or (aryl)C_0-C_2alkyl; each of which is optionally substituted; and

R_8 is hydrogen, halogen, C_1-C_2haloalkyl, or C_1-C_2haloalkoxy; or R_8 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl,or C_1-C_6alkoxy, each of which is optionally substituted.

25. A compound or salt of Claim 24, wherein

R_7 and R_8 are independently chosen from hydrogen, halogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

26. A compound or salt of any one of Claims 1 to 23, wherein

R_7 and R_8 are taken together to form a 3-to 6-membered cycloalkyl ring or 3- to 6-membered heterocycloalkyl ring containing one heteroatom chosen from N, O, and S; each of which is optionally substituted.

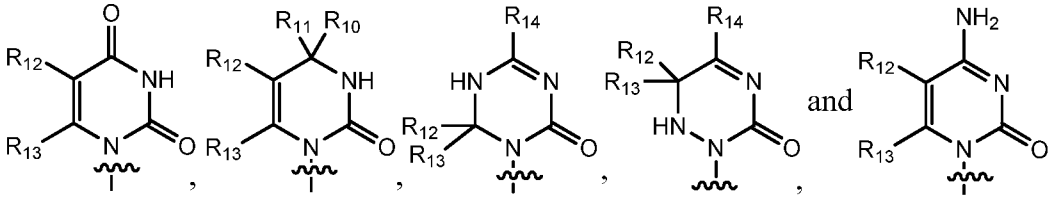
27. A compound or salt of any one of Claims 1 to 26, wherein

R_9 is C_1-C_6alkyl, (C_3-C_7cycloalkyl)C_0-C_4alkyl, or (phenyl)C_0-C_4alkyl, each of which is optionally substituted.

28. A compound or salt of Claim 27, wherein R_9 is C_1-C_6alkyl.

29. A compound or salt of any one of Claims 1 to 28, wherein

B_1 is a pyrimidine base chosen from



and

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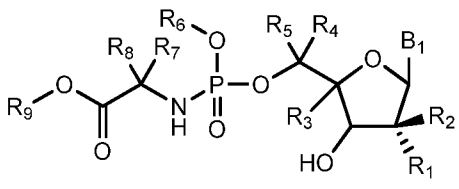
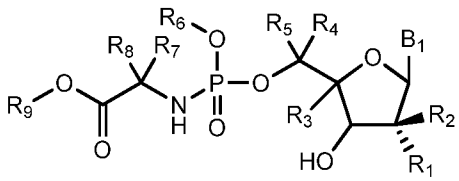
30. A compound or salt of Claim 1 of Formula (II)



(II).

31. A compound or salt of any one of Claims 1 to 6, of Formula (II)



(II)

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is hydroxyl, fluoro, or $–OCD_3$;

R_2 is hydrogen, $-CH_3$, or $–CD_3$; or

R_1 and R_2 are joined to form a cyclopropyl;

R_3 is hydrogen or $–N_3$;

R_4 and R_5 are independently hydrogen, deuterium, methyl, or $–CD_3$;

R_6 is phenyl, pyridyl, naphthyl, or indolyl, each of which is optionally substituted with one or more substituents independently chosen from halogen, hydroxyl, amino, cyano, -CHO, -COOH, $-CONH_2$, C_1-C_6alkyl, C_2-C_6alkenyl, C_1-C_6alkoxy, C_2-C_6alkanoyl, C_1-C_6alkylester, (mono- and di-C_1-C_6alkylamino)C_0-C_2alkyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy;

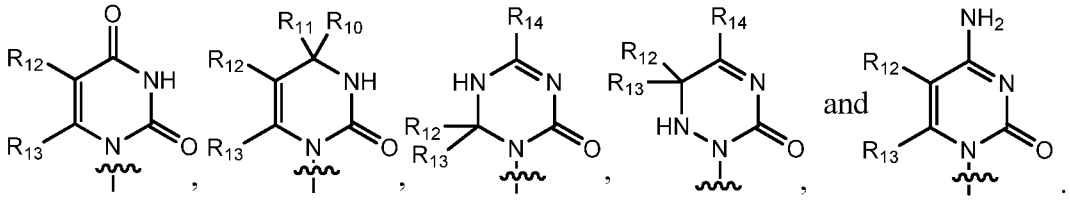
R_7 is hydrogen, halogen, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, (C_3-C_6cycloalkyl)C_0-C_4alkyl, or (aryl)C_0-C_2alkyl;

R_8 is hydrogen, halogen, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_2haloalkyl, or C_1-C_2haloalkoxy; or

R_7 and R_8 are taken together to form a 3-to 6-membered cycloalkyl ring; and

R_9 is C_1-C_6alkyl, (C_3-C_7cycloalkyl)C_0-C_4alkyl, or (aryl)C_0-C_4alkyl, each of which is optionally substituted with one or more substituents independently chosen from halogen, hydroxyl, amino, cyano, -CHO, -COOH, -$CONH_2$, C_1-C_6alkyl, C_2-C_6alkenyl, C_1-C_6alkoxy, C_2-C_6alkanoyl, C_1-C_6alkylester, (mono- and di-C_1-C_6alkylamino)C_0-C_2alkyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy;

B_1 is a base selected from



;

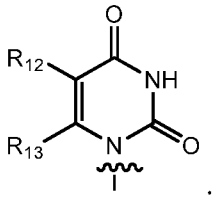
where

R_{10} and R_{11} are independently hydrogen and deuterium;

R_{12} and R_{13} are independently hydrogen, deuterium, and methyl;

R_{14} is hydrogen, deuterium, hydroxyl, amino, C_1-C_4alkoxy, deuterated C_1-C_4alkoxy, C_1-C_4alkylester, or mono- or di-C_1-C_4alkylcarbamate.

32. A compound or salt of Claim 31, wherein B_1 is



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33. A compound or salt of Claim 32, wherein

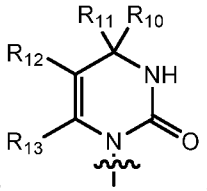
R_{12} is deuterium and R_{13} is hydrogen.

34. A compound or salt of Claim 32, wherein

R_{12} is hydrogen and R_{13} is deuterium.

35. A compound or salt of Claim 32, wherein R_{12} and R_{13} are both hydrogen.

36. A compound or salt of Claim 31, wherein

B_1 is 

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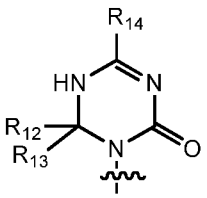
37. A compound or salt of Claim 31 wherein

B_1 is 

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38. A compound or salt of Claim 37, wherein

R_{12} and R_{13} are both deuterium and R_{14} is hydroxyl.

39. A compound or salt of Claim 37, wherein

R_{12} and R_{13} are both hydrogen and R_{14} is hydroxyl.

40. A compound or salt of Claim 37, wherein

R_{12} is hydrogen, R_{13} is deuterium, and R_{14} is hydroxyl.

41. A compound or salt of Claim 37, wherein

R_{12} and R_{13} are both deuterium and R_{14} is amino.

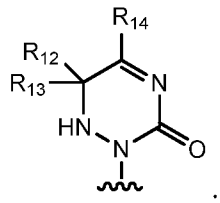
42. A compound or salt of Claim 37, wherein

R_{12} and R_{13} are both hydrogen and R_{14} is amino.

43. A compound or salt of Claim 37, wherein

R_{12} is hydrogen, R_{13} is deuterium, and R_{14} is amino.

44. A compound or salt of Claim 31, wherein



45. A compound or salt of Claim 44, wherein R_{12} and R_{13} are both deuterium and R_{14} is hydroxyl.

46. A compound or salt of Claim 44, wherein R_{12} and R_{13} are both hydrogen and R_{14} is hydroxyl.

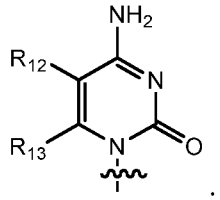
47. A compound or salt of Claim 44, wherein R_{12} is hydrogen, R_{13} is deuterium, and R_{14} is hydroxyl.

48. A compound or salt of Claim 44, wherein R_{12} and R_{13} are both deuterium and R_{14} is amino.

49. A compound or salt of Claim 44, wherein R_{12} and R_{13} are both hydrogen and R_{14} is amino.

50. A compound or salt of Claim 44, wherein R_{12} is hydrogen, R_{13} is deuterium, and R_{14} is amino.

51. A compound or salt of Claim 31, wherein



52. A compound or salt of Claim 51, wherein R_{12} is hydrogen and R_{13} is deuterium.

53. A compound or salt of Claim 51, wherein

R_{12} is deuterium and R_{13} is hydrogen.

54. A compound or salt of any one of Claims 31 to 53 wherein R_3 is hydrogen.

55. A compound or salt of any one of Claims 31 to 53 wherein R_3 is $-N_3$.

56. A compound or salt of any one of Claims 31 to 55, wherein R_6 is phenyl substituted with one or more substituents independently chosen from halogen, hydroxyl, amino, cyano, -CHO, -COOH, $-CONH_2$, C_1-C_6alkyl, C_2-C_6alkenyl, C_1-C_6alkoxy, C_2-C_6alkanoyl, C_1-C_6alkylester, (mono- and di-C_1-C_6alkylamino)C_0-C_2alkyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

57. A compound or salt of any one of Claims 31 to 55, wherein R_6 is unsubstituted phenyl.

58. A compound or salt of any one of Claims 31 to 55, wherein R_6 is unsubstituted naphthyl.

59. A compound or salt of any one of Claims 31 to 58, wherein
R_7 is C_1-C_6alkyl and R_8 is hydrogen, halogen, or C_1-C_6alkyl.

60. A compound or salt of any one of Claims 31 to 58, wherein
R_7 is methyl and R_8 is hydrogen.

61. A compound or salt of any one of Claims 31 to 60, wherein R_9 is C_1-C_6alkyl.

62. A compound or salt of any one of Claims 31 to 60, wherein R_9 is (C_3-C_7cycloalkyl)C_0-C_2alkyl or (phenyl)C_0-C_2alkyl, each of which is optionally substituted with one or more substituents independently chosen from halogen, hydroxyl, C_1-C_4alkyl, C_1-C_4alkoxy, (mono- and di-C_1-C_6alkylamino)C_0-C_2alkyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

63. A compound or salt of Claim 31, wherein
R_1 is hydroxyl, fluoro, or $-OCD_3$;
R_2 is hydrogen, $-CH_3$, or $-CD_3$; or
R_1 and R_2 are joined to form a cyclopropyl;
R_3 is hydrogen or $-N_3$;
R_4 and R_5 are independently hydrogen, deuterium, methyl, or $-CD_3$;

R_6 is phenyl, pyridyl, naphthyl, or indolyl, each of which is optionally substituted with one or more substituents independently chosen from halogen, hydroxyl, C_1-C_4alkyl, C_1-C_4alkoxy, (mono- and di-C_1-C_4alkylamino)C_0-C_2alkyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy;

R_7 is hydrogen, halogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, (C_3-C_6cycloalkyl)C_0-C_2alkyl, or (phenyl)C_0-C_2alkyl;

R_8 is hydrogen, halogen, C_1-C_2alkyl, or C_1-C_2alkoxy; or

R_7 and R_8 are taken together to form a 3-to 6-membered cycloalkyl ring; and

R_9 is C_1-C_6alkyl, (C_3-C_7cycloalkyl)C_0-C_2alkyl, or (aryl)C_0-C_2alkyl, each of which is optionally substituted with one or more substituents independently chosen from halogen, hydroxyl, C_1-C_4alkyl, C_1-C_4alkoxy, (mono- and di-C_1-C_6alkylamino)C_0-C_2alkyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

64. A compound or salt of Claim 63, wherein

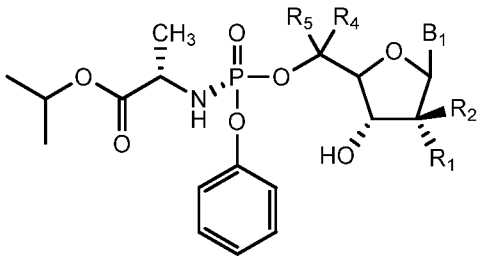
R_6 is phenyl, naphthyl, or indolyl;

R_7 is hydrogen, halogen, or C_1-C_4alkyl;

R_8 is hydrogen, halogen, C_1-C_2alkyl, or C_1-C_2alkoxy; and

R_9 is C_1-C_6alkyl.

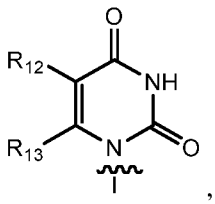
65. A compound or salt of Claim 1, of Formula (IV)



(IV).

66. A compound or salt of any one of Claims 63 to 65, wherein

B_1 is



,

R_4 and R_5 are both deuterium; one of R_{12} and R_{13} is deuterium and the other is hydrogen.

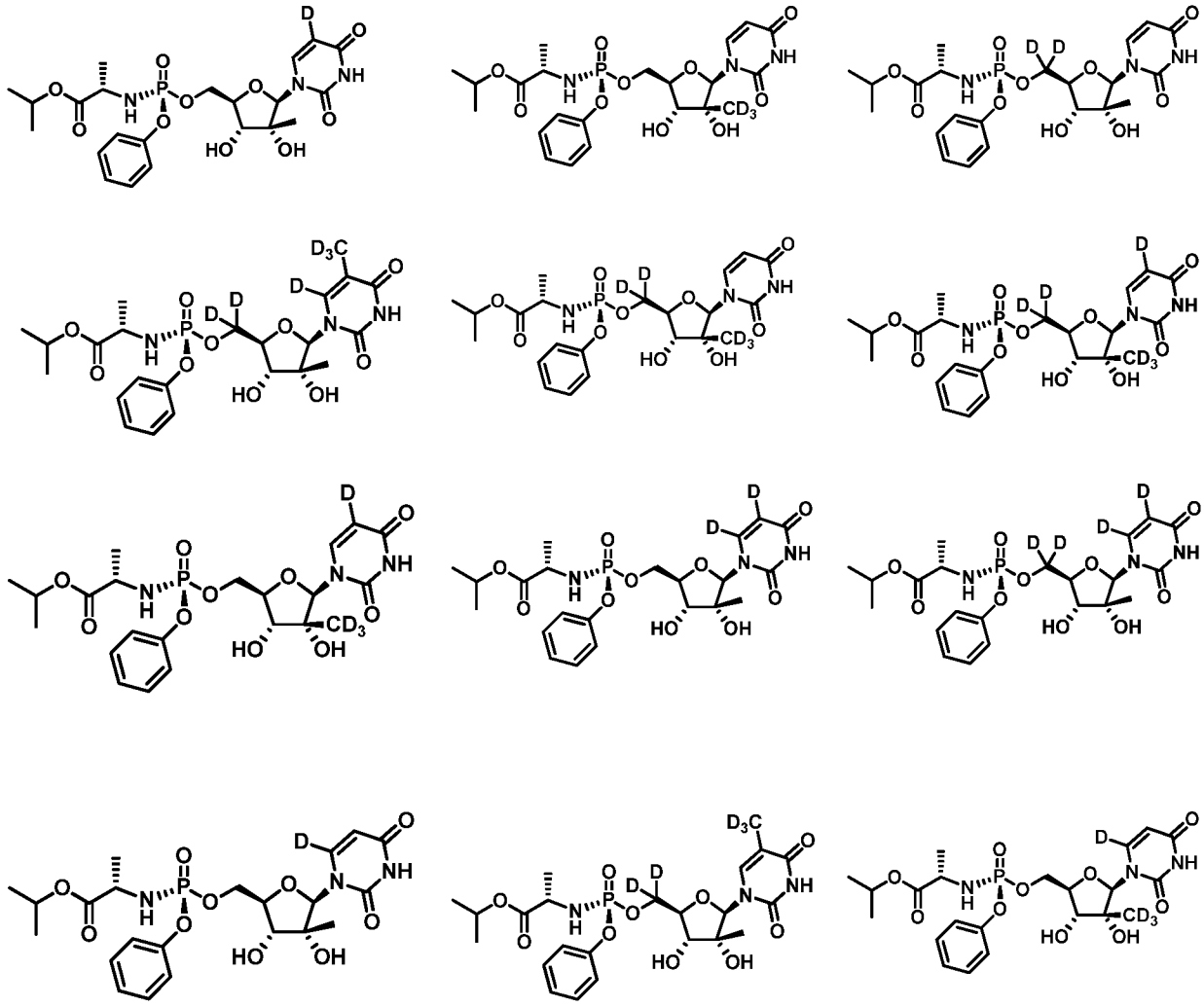
67. A compound or salt of Claim 66, wherein R_1 is hydroxyl and R_2 is methyl.

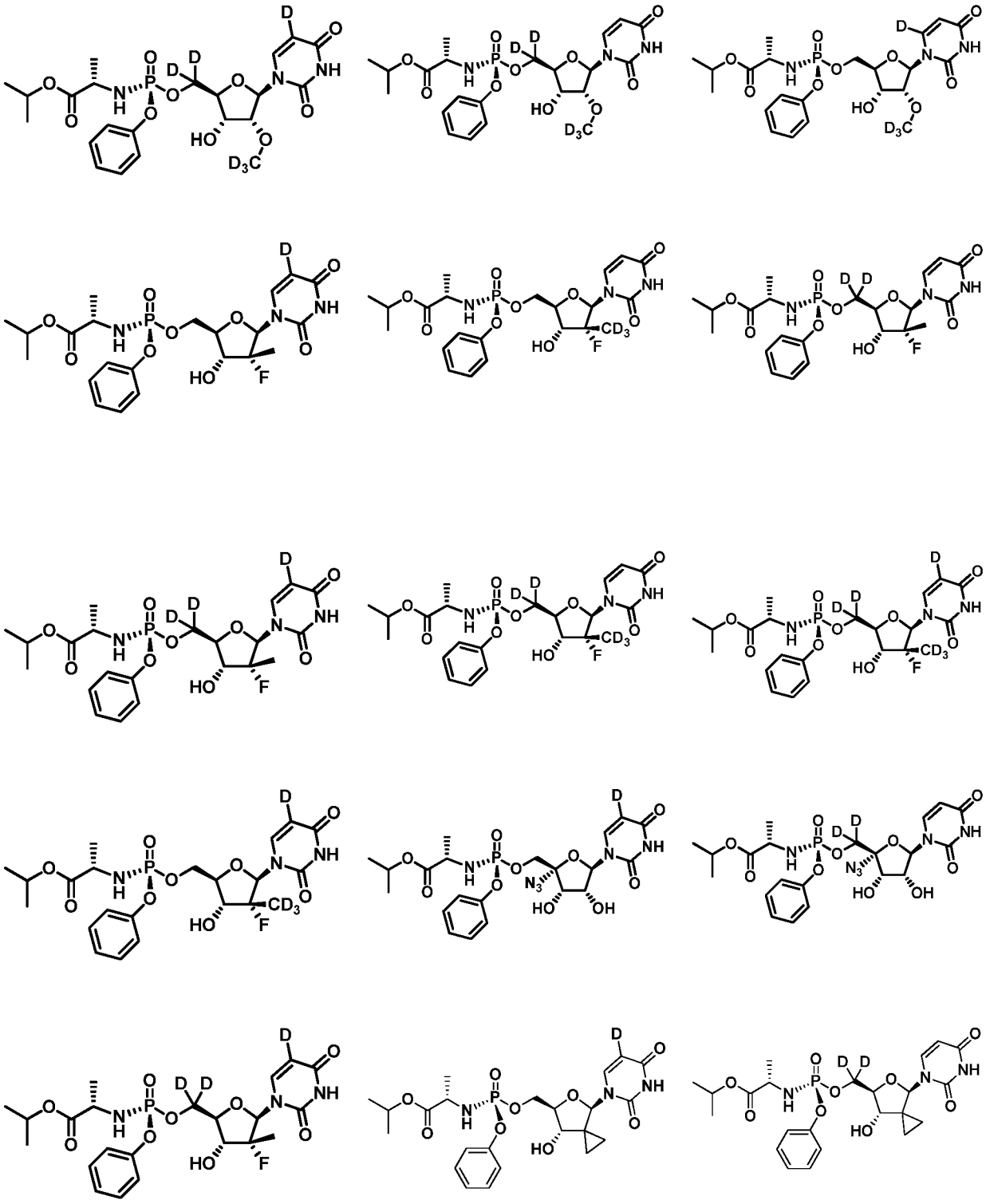
68. A compound or salt of Claim 66, wherein R_1 is hydroxyl and R_2 is -CD_3.

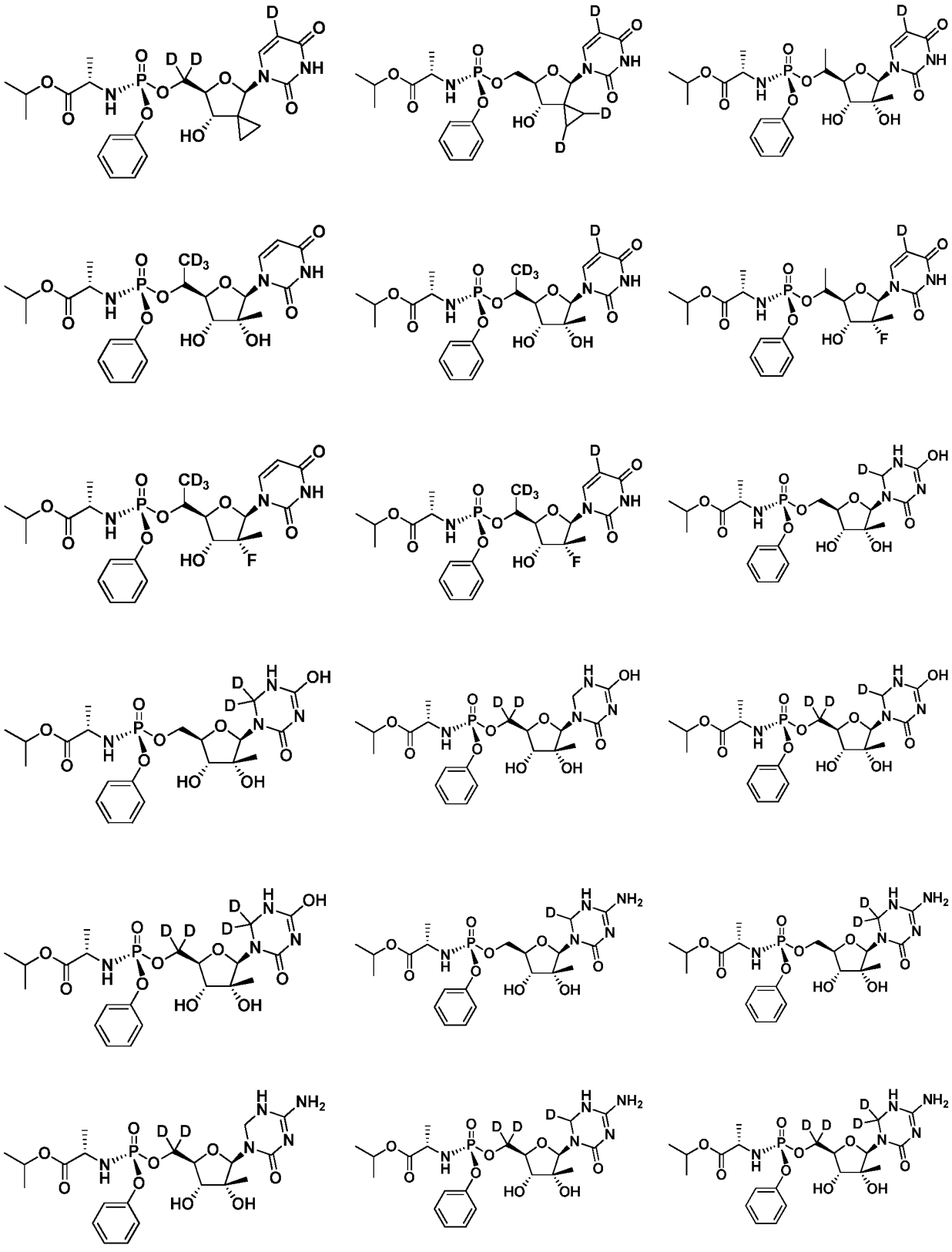
69. A compound or salt of Claim 66, wherein R_1 and R_2 are joined to form a cyclopropyl group.

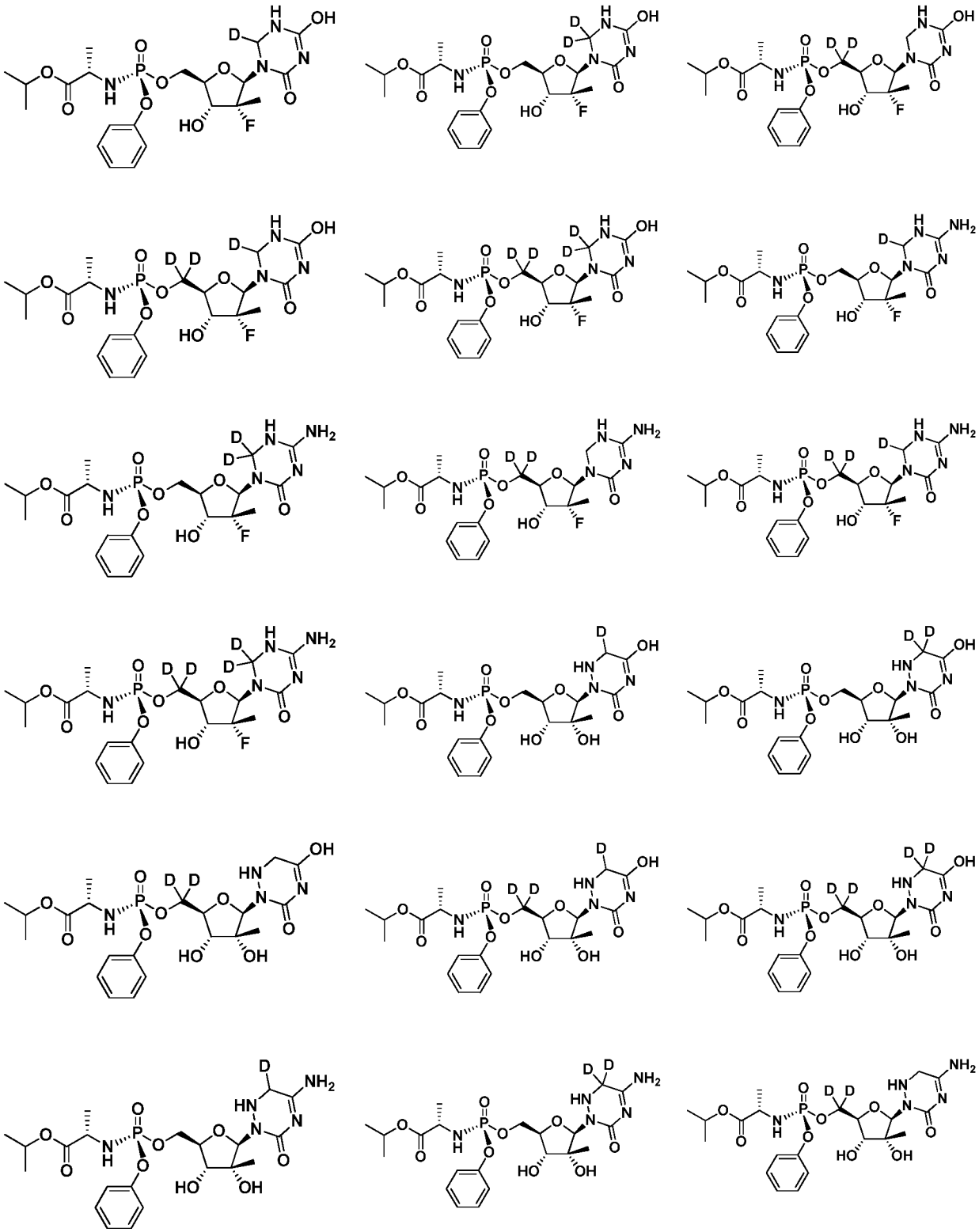
70. A compound or salt of Claim 66, wherein R_1 is fluoro and R_2 is methyl or –CD_3.

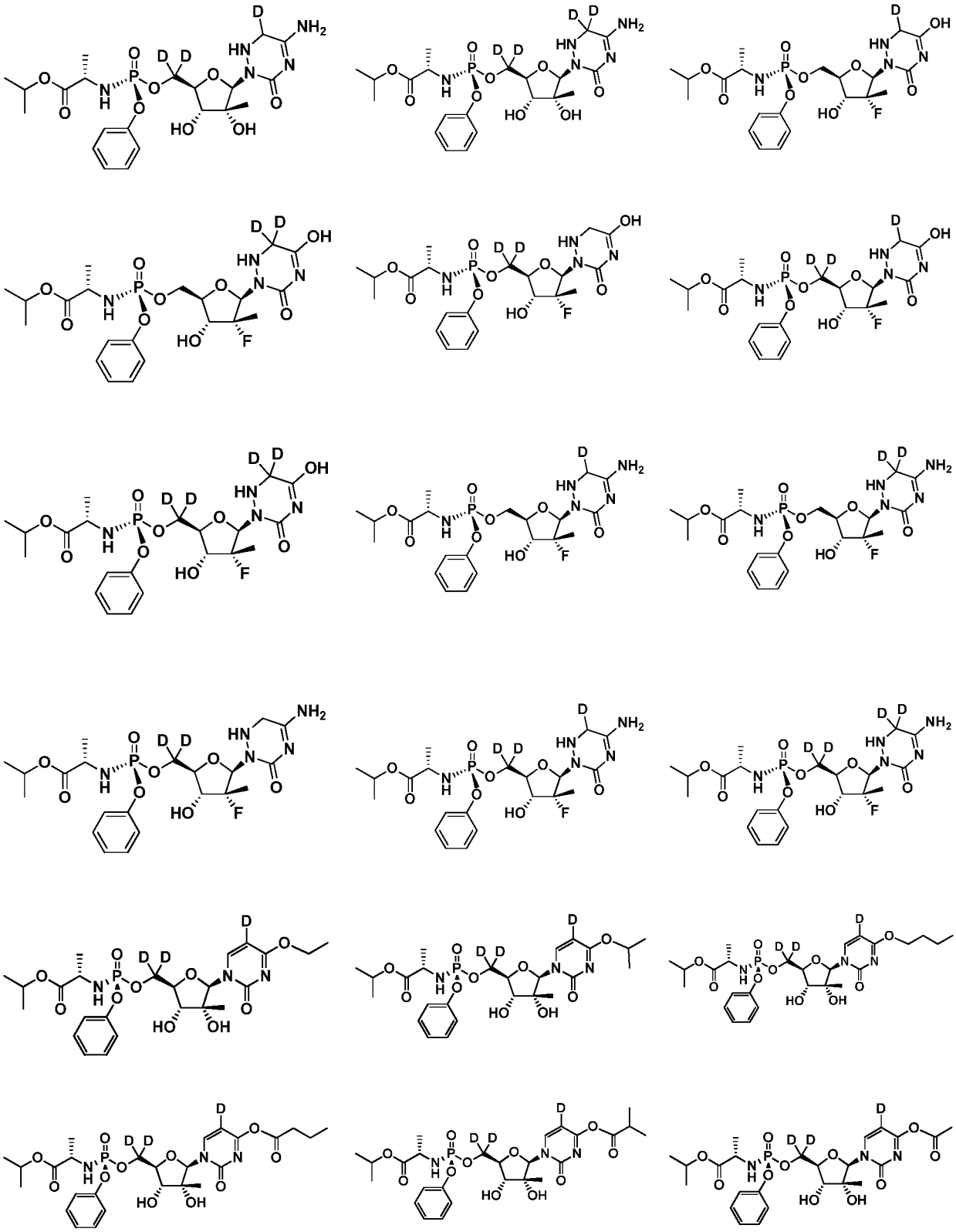
71. A compound or salt thereof of Claim 1, wherein the compound is chosen from:

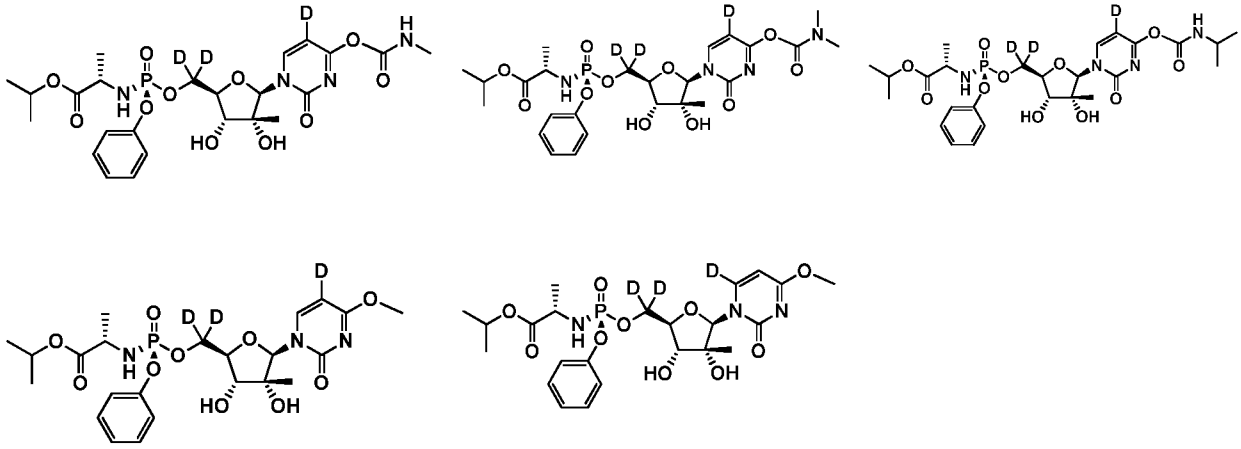












72. A pharmaceutical composition comprising a compound or salt of any one of Claims 1 to 71 together with a pharmaceutically acceptable carrier.

73. The pharmaceutical composition of Claim 72, comprising one or more additional compounds, wherein the additional compound(s) are therapeutic active agents.

74. The pharmaceutical composition of Claim 72, additionally comprising at least one of an HCV HS3 protease inhibitor and an HCV NS5a inhibitor.

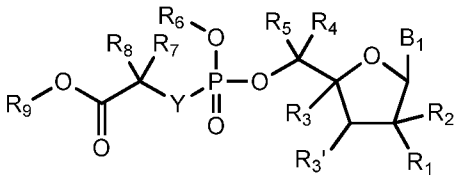
75. The pharmaceutical composition of Claim 72, additionally comprising an NS5a inhibitor and at least one of sovaprevir and ACH-2684.

76. A method of treating hepatitis C infection in a patient, comprising administering an effective amount of a compound of any one of Claims 1 to 71 or a pharmaceutical composition of any one of Claim 72 to 75 to the patient.

77. A method of treating a *Flaviviridae* viral infection in a patient, comprising administering an effective amount of a compound of any one of Claims 1 to 71 or a pharmaceutical composition of any one of Claims 72 to 75 to the patient.

78. The method of Claim 77, wherein the *Flaviviridae* viral infection is Dengue fever, West Nile virus infection, yellow fever, or bovine viral diarrhea virus infection.

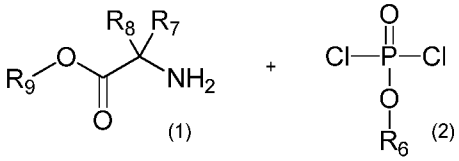
79. A method of preparing a compound of Formula (I).



Formula (I)

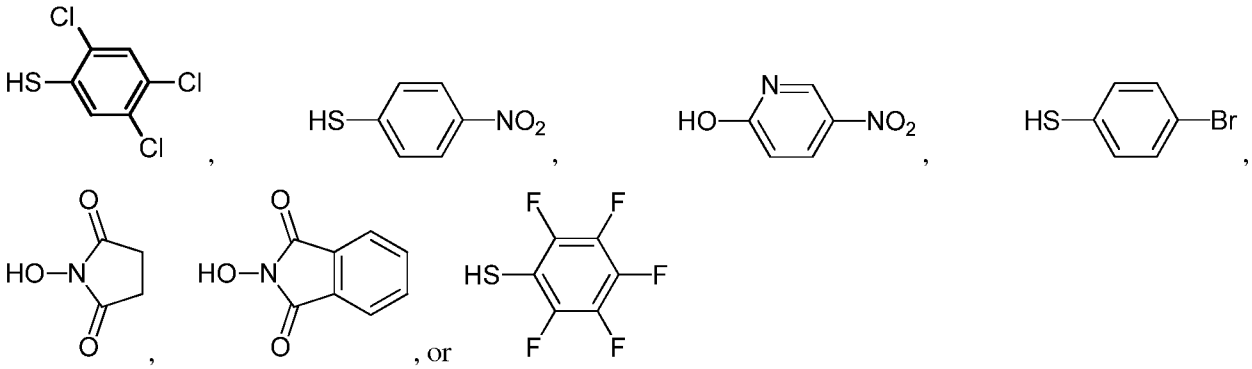
comprising

(i) reacting an amino ester (1) with a dichlorophosphate (2) to form a reaction mixture;

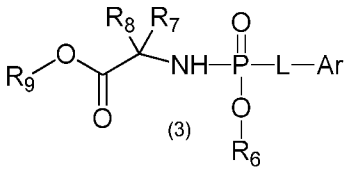


(1) (2)

(ii) adding to the reaction mixture of (i) Ar –LH where L is S or O, and Ar-LH is

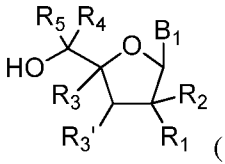


to form an intermediate (3)



(3) ; and

(iii) reacting the intermediate (3) with a nucleoside (**13**)



(**13**)

to form the compound of Formula (I), wherein

Y is NH or O;

R_1 is hydroxyl, fluoro, or $–OCD_3$;

R_2 is hydrogen or deuterium; or

R_2 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, or C_2-C_6alkynyl; each of which is optionally deuterated and optionally substituted; or

R_1 and R_2 are joined to form a 3- to 6-membered cycloalkyl ring or a 3- to 6-membered heterocycloalkyl ring containing one heteroatom selected from N, O, and S, each of which is optionally substituted;

R_3 is hydrogen, deuterium, halogen, or–N_3; or

R_3 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl, (C_3-C_6cycloalkyl) C_0-C_4carbhydryl, (4- to 6-membered heterocycloalkyl)C_0-C_4carbhydryl, (aryl)C_0-C_4carbhydryl, or (heteroaryl)C_0-C_4carbhydryl, each or which is optionally deuterated and optionally substituted; and

R_3' is hydroxyl; or

R_3 and R_3' are taken together to form a 3- to 6- membered ring optionally containing one heteroatom selected from N, O, and S, which is optionally substituted with one or more substituents independently selected from halogen, hydroxyl, C_1-C_2alkyl, and C_1-C_2alkoxy;

R_4 is hydrogen, deuterium, halogen, C_1-C_2haloalkyl, or C_1-C_2haloalkoxy; or R_4 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl, or C_1-C_6alkoxy, each of which is optionally deuterated and optionally substituted;

R_5 is hydrogen, deuterium, or halogen; or R_5 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl, or C_1-C_6alkoxy, each of which is optionally deuterated and optionally substituted; or

R_4 and R_5 are taken together to form a 3- to 6- membered ring optionally containing one heteroatom selected from N, O, and S, which ring is optionally substituted with one or more substituents independently selected from halogen, hydroxyl, C_1-C_2alkyl, and C_1-C_2alkoxy;

R_6 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl, (aryl)C_0-C_2alkyl, or 5- to 6-membered monocyclic heteroaryl containing 1 to 3 heteroatoms independently chosen from N, O, and S, or 8- to 10-membered bicyclic heteroaryl containing 1 to 4 heteroatoms independently chosen from N, O, and S; each of which R_6 is optionally substituted;

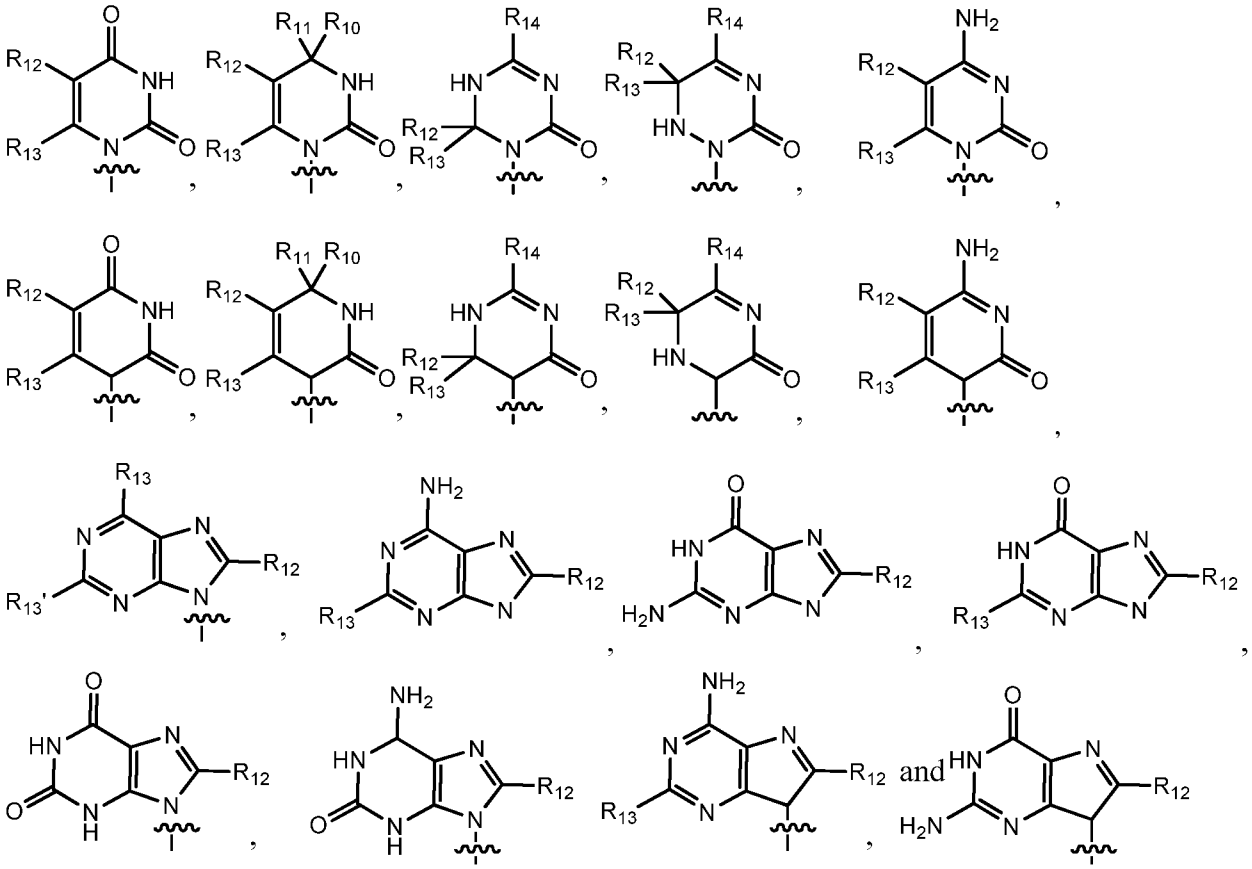
R_7 is hydrogen, halogen, C_1-C_2haloalkyl, or C_1-C_2haloalkoxy; or R_7 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, (C_3-C_6cycloalkyl)C_0-C_4alkyl, or (aryl)C_0-C_2alkyl; each of which is optionally substituted;

R_8 is hydrogen, halogen, C_1-C_2haloalkyl, or C_1-C_2haloalkoxy; or R_8 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl,or C_1-C_6alkoxy, each of which is optionally substituted; or

R_7 and R_8 are taken together to form a 3-to 6-membered cycloalkyl ring or 3- to 6-membered heterocycloalkyl ring containing one heteroatom chosen from N, O, and S; each of which is optionally substituted;

R_9 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl, (C_3-C_7cycloalkyl)C_0-C_4carbhydryl, (aryl)C_0-C_4carbhydryl, (3- to 6-membered heterocycloalkyl)C_0-C_4carbhydryl, or (heteroaryl)C_0-C_4carbhydryl, each of which is optionally substituted;

B_1 is a base selected from



R_{10} and R_{11} are independently hydrogen and deuterium;

R_{12}, R_{13}, and R_{13}' are independently hydrogen, deuterium, methyl, and $-CD_3$;

R_{14} is hydrogen, deuterium, hydroxyl, amino, C_1-C_4alkoxy, deuterated C_1-C_4alkoxy, C_1-C_4alkylester, or mono- or di-C_1-C_4alkylcarbamate;

wherein each position represented by D has a deuterium enrichment of at least 50%; and

one or more of R_1, R_2, R_4, R_5, R_{10}, R_{11}, R_{12}, R_{13}, R_{13}', and R_{14} is deuterium with a deuterium enrichment of at least 50% or deuterated with at least one position having a deuterium enrichment of at least 50%.

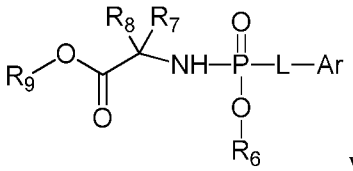
80. The method of Claim 79 wherein the amino ester (**1**) and the dichlorophosphate (**2**) are combined at a temperature less than -20 °C.

81. The method of Claim 80, wherein the amino ester (**1**) and the dichlorophosphate (**2**) are combined at a temperature of -40 °C to about -60 °C.

82. The method of Claim 79 wherein base is added to the mixture of amino ester (1) and the dichlorophosphate (**2**).

83. The method of Claim 82 wherein the base is triethylamine and the addition of base to the mixture occurs in an organic solvent is selected from dichloromethane, 1-propanol, 2-methyltetrahydrofuran, or tetrahydrofuran.

84. An intermediate of the formula



where

Ar is an optionally substituted aryl, heteroaryl, or heterocycloalkyl group;

L is O or S;

R_6 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl, (aryl)C_0-C_2alkyl, or 5- to 6-membered monocyclic heteroaryl containing 1 to 3 heteroatoms independently chosen from N, O, and S, or 8- to 10-membered bicyclic heteroaryl containing 1 to 4 heteroatoms independently chosen from N, O, and S; each of which R_6 is optionally substituted;

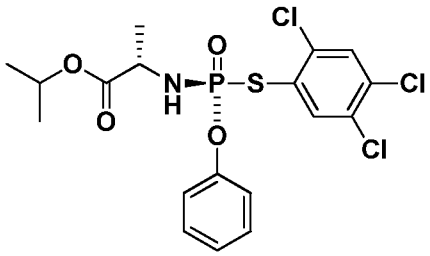
R_7 is hydrogen, halogen, C_1-C_2haloalkyl, or C_1-C_2haloalkoxy; or R_7 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, (C_3-C_6cycloalkyl)C_0-C_4alkyl, or (aryl)C_0-C_2alkyl; each of which is optionally substituted;

R_8 is hydrogen, halogen, C_1-C_2haloalkyl, or C_1-C_2haloalkoxy; or R_8 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl,or C_1-C_6alkoxy, each of which is optionally substituted; or

R_7 and R_8 are taken together to form a 3-to 6-membered cycloalkyl ring or 3- to 6-membered heterocycloalkyl ring containing one heteroatom chosen from N, O, and S; each of which is optionally substituted;

R_9 is C_1-C_6alkyl, allenyl, C_2-C_6alkenyl, C_2-C_6alkynyl, (C_3-C_7cycloalkyl)C_0-C_4carbhydryl, (aryl)C_0-C_4carbhydryl, (3- to 6-membered heterocycloalkyl)C_0-C_4carbhydryl, or (heteroaryl)C_0-C_4carbhydryl, each of which is optionally substituted.

85. An intermediate of Claim 84, of the formula



86. An intermediate of Claim 84, of the formula