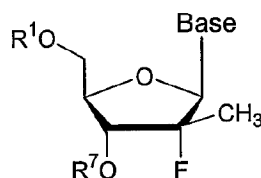
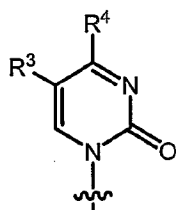


and wherein X is defined as above, R¹ is H, R³ is H, R⁴ is NH₂ or OH, R⁶ is H, and R⁷ is H.

In a twelfth embodiment, a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside or its pharmaceutically acceptable salt or prodrug thereof is provided of the structure:

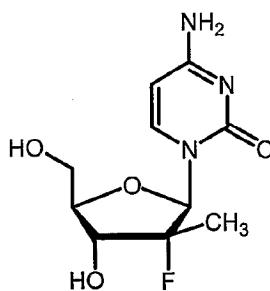


wherein Base is:

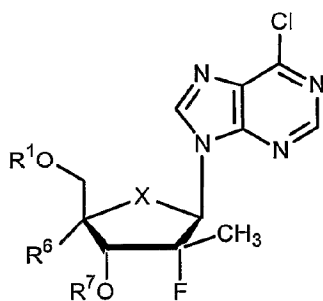


and wherein R¹ is H, R³ is H, R⁴ is NH₂ or OH, and R⁷ is H.

A thirteenth embodiment provides a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside or its pharmaceutically acceptable salt or prodrug thereof of the structure:

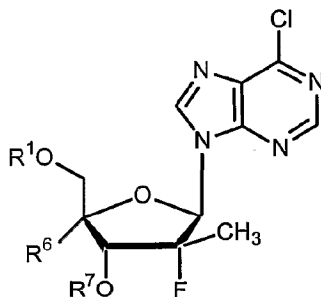


In a fourteenth embodiment, a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside, its pharmaceutically acceptable salt or product thereof is provided by the structure:



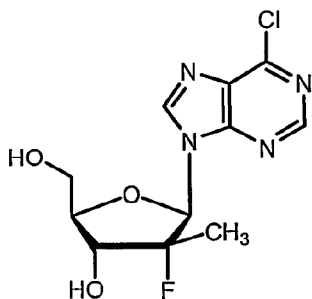
wherein X, R¹, R⁶ and R⁷ are as defined above.

In a fifteenth embodiment, a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside, its pharmaceutically acceptable salt or product thereof is provided by the structure:

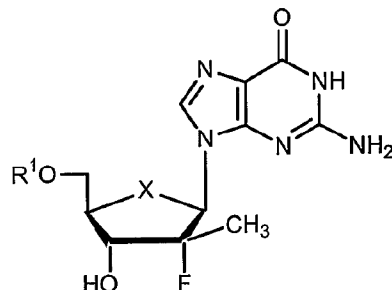


wherein R¹, R⁶ and R⁷ are as defined above.

In a sixteenth embodiment, a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside nucleoside, its pharmaceutically acceptable salt or product thereof is provided by the structure:



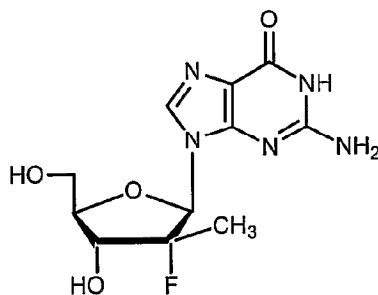
In a seventeenth embodiment, a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside, its pharmaceutically acceptable salt or product thereof is provided by the structure:



5

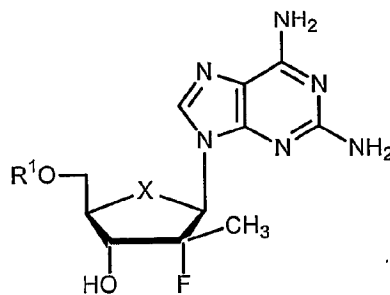
wherein X and R¹ are as defined above.

In an eighteenth embodiment, a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside, its pharmaceutically acceptable salt or product thereof is provided by the structure:



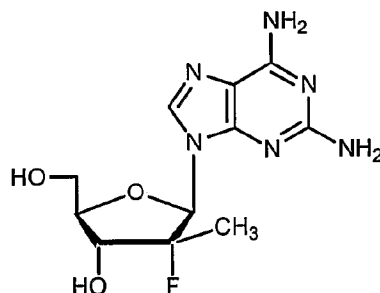
10

In a nineteenth embodiment, a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside, its pharmaceutically acceptable salt or product thereof is provided by the structure:



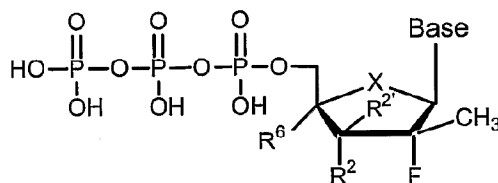
wherein X and R¹ are as defined above.

In a twentieth embodiment, a (2'*R*)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside, its pharmaceutically acceptable salt or product thereof is provided by the structure:



5

The present invention also contemplates 5'-triphosphate triphosphoric acid ester derivatives of the 5'-hydroxyl group of a nucleoside compound of the present invention having the following general structural formula:

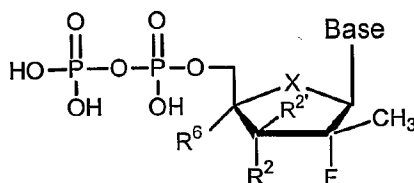


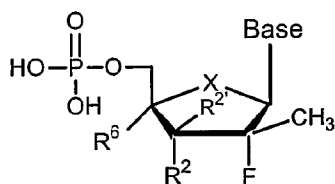
10

wherein Base, X, R², R^{2'}, and R⁶ are as defined as above.

The compounds of the present invention are also intended to include pharmaceutically acceptable salts of the triphosphate ester as well as pharmaceutically acceptable salts of 5'-diphosphate and 5'-monophosphate ester derivatives of the following structural formulas, respectively.

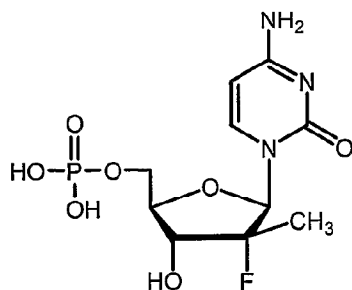
15



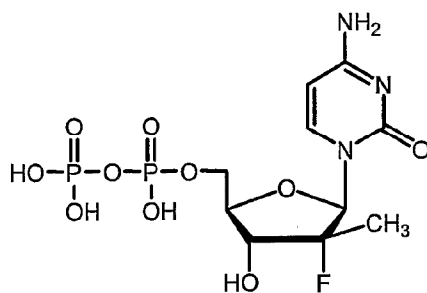
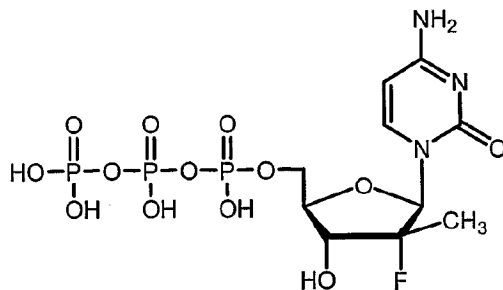


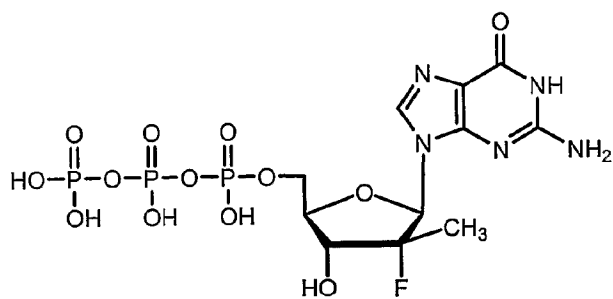
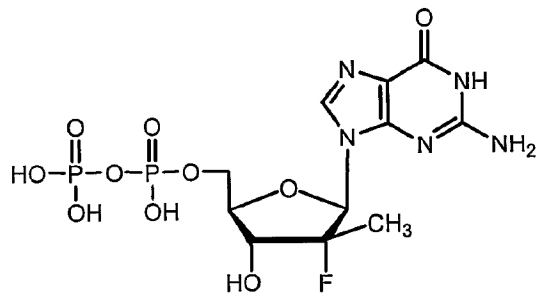
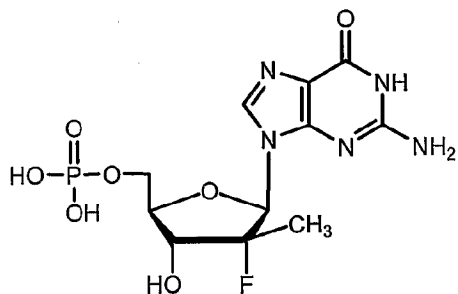
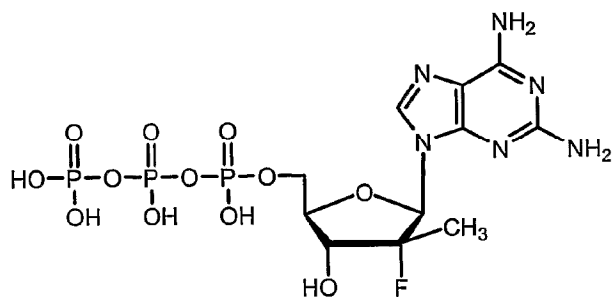
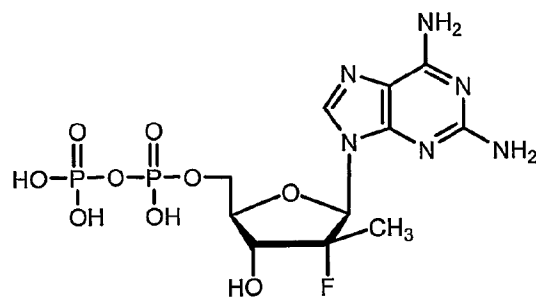
wherein Base, X, R², R^{2'} and R⁶ are as defined above.

Further non-limiting examples of phosphoric acid derivatives are the nucleosides of the present invention are shown below:

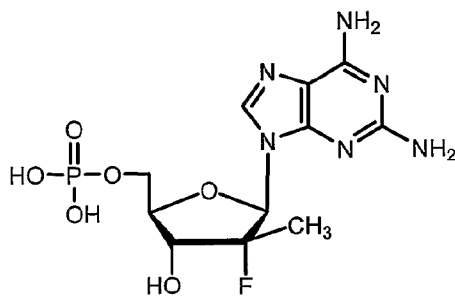


5





44



The present invention also contemplates that any phosphate nucleoside derivative can include a 5'-(*S*-acyl-2-thioethyl)phosphate or "SATE" mono or di-ester derivative of the 5'-monophosphates.

5 Alternative embodiments are also contemplated wherein the N-4 amino group on a phosphate nucleoside derivative can be replaced with H, F, Cl, Br or I.

Additional embodiments include 3' and/or 5' produrgs as described in more detail herein.

10 In the various embodiments, the fluorinated derivatives are preferred. Fluorine is viewed as "isosteric" with hydrogen because of its size (Van der Waals radii for H is 1.20Å and for F 1.35Å). However, the atomic weight (18.998) and electronegativity of fluorine (4.0 [Pauling's scale], 4.000 [Sanderson's scale]) are more similar to oxygen (3.5 [Pauling], 3.654 [Sanderson]) than hydrogen (2.1 [Pauling], 2.592 [Sanderson]) (March, J., "Advances in Organic Chemistry: Reactions, Mechanisms, and Structure" Third edition, 1985, p. 14., Wiley Interscience, New York). Fluorine is known to be capable of forming a hydrogen bond, but unlike a hydroxyl group (which can act both as proton acceptor and proton donor) fluorine acts only as a proton acceptor. On the other hand, 2'-fluoro-*ribonucleosides* can be viewed as analogues of both *ribonucleosides* and *deoxynucleosides*. They may be better recognized by viral RNA polymerase at the triphosphate level than by the host RNA polymerase thus selectively inhibiting the viral enzyme.

15
20

II. Pharmaceutically Acceptable Salts and Prodrugs

25 In cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compound as a pharmaceutically

acceptable salt may be appropriate. Pharmaceutically acceptable salts include those derived from pharmaceutically acceptable inorganic or organic bases and acids. Suitable salts include those derived from alkali metals such as potassium and sodium, alkaline earth metals such as calcium and magnesium, among numerous
5 other acids well known in the pharmaceutical art. In particular, examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids, which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, α -ketoglutarate, and α -glycerophosphate. Suitable inorganic salts may
10 also be formed, including, sulfate, nitrate, bicarbonate, and carbonate salts.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for
15 example calcium) salts of carboxylic acids can also be made.

Any of the nucleosides described herein can be administered as a nucleotide prodrug to increase the activity, bioavailability, stability or otherwise alter the properties of the nucleoside. A number of nucleotide prodrug ligands are known. In general, alkylation, acylation or other lipophilic modification of the mono, di or
20 triphosphate of the nucleoside will increase the stability of the nucleotide. Examples of substituent groups that can replace one or more hydrogens on the phosphate moiety are alkyl, aryl, steroids, carbohydrates, including sugars, 1,2-diacylglycerol and alcohols. Many are described in R. Jones and N. Bischofberger, *Antiviral Research*, 27 (1995) 1-17. Any of these can be used in combination with the
25 disclosed nucleosides to achieve a desired effect.

The active nucleoside can also be provided as a 5'-phosphoether lipid or a 5'-ether lipid, as disclosed in the following references, which are incorporated by reference herein: Kucera, L.S., N. Iyer, E. Leake, A. Raben, Modest E.K., D.L.W., and C. Piantadosi. 1990. "Novel membrane-interactive ether lipid analogs that
30 inhibit infectious HIV-1 production and induce defective virus formation." *AIDS Res. Hum. Retro Viruses*. 6:491-501; Piantadosi, C., J. Marasco C.J., S.L. Morris-

Natschke, K.L. Meyer, F. Gumus, J.R. Surles, K.S. Ishaq, L.S. Kucera, N. Iyer, C.A. Wallen, S. Piantadosi, and E.J. Modest. 1991. "Synthesis and evaluation of novel ether lipid nucleoside conjugates for anti-HIV activity." *J. Med. Chem.* 34:1408.1414; Hosteller, K.Y., D.D. Richman, D.A. Carson, L.M. Stuhmiller, G.M. T. van Wijk, and H. van den Bosch. 1992. "Greatly enhanced inhibition of human immunodeficiency virus type 1 replication in CEM and HT4-6C cells by 3'-deoxythymidine diphosphate dimyristoylglycerol, a lipid prodrug of 3'-deoxythymidine." *Antimicrob. Agents Chemother.* 36:2025.2029; Hosetler, K.Y., L.M. Stuhmiller, H.B. Lenting, H. van den Bosch, and D.D. Richman, 1990. "Synthesis and antiretroviral activity of phospholipid analogs of azidothymidine and other antiviral nucleosides." *J. Biol. Chem.* 265:61127.

Nonlimiting examples of U.S. patents that disclose suitable lipophilic substituents that can be covalently incorporated into the nucleoside, preferably at the 5'-OH position of the nucleoside or lipophilic preparations, include U.S. Patent Nos. 5,149,794; 5,194,654; 5,223,263; 5,256,641; 5,411,947; 5,463,092; 5,543,389; 5,543,390; 5,543,391; and 5,554,728, all of which are incorporated herein by reference. Foreign patent applications that disclose lipophilic substituents that can be attached to the nucleosides of the present invention, or lipophilic preparations, include WO 89/02733, WO 90/00555, WO 91/16920, WO 91/18914, WO 93/00910, WO 94/26273, WO 96/15132, EP 0 350 287, EP 93917054.4, and WO 91/19721.

III. Pharmaceutical Compositions

Pharmaceutical compositions based upon a β -D or β -L compound disclosed herein or its pharmaceutically acceptable salt or prodrug can be prepared in a therapeutically effective amount for treating a *Flaviviridae* infection, including hepatitis C virus, West Nile Virus, yellow fever virus, and a rhinovirus infection, optionally in combination with a pharmaceutically acceptable additive, carrier or excipient. The therapeutically effective amount may vary with the infection or condition to be treated, its severity, the treatment regimen to be employed, the pharmacokinetics of the agent used, as well as the patient treated.

In one aspect according to the present invention, the compound according to the present invention is formulated preferably in a mixture with a pharmaceutically

acceptable carrier. In general, it is preferable to administer the pharmaceutical composition in orally administrable form, but formulations may be administered via parenteral, intravenous, intramuscular, transdermal, buccal, subcutaneous, suppository or other route. Intravenous and intramuscular formulations are preferably administered in sterile saline. One of ordinary skill in the art may modify the formulation within the teachings of the specification to provide numerous formulations for a particular route of administration without rendering the compositions of the present invention unstable or compromising its therapeutic activity. In particular, a modification of a desired compound to render it more soluble in water or other vehicle, for example, may be easily accomplished by routine modification (salt formulation, esterification, etc.).

In certain pharmaceutical dosage forms, the prodrug form of the compound, especially including acylated (acetylated or other) and ether derivatives, phosphate esters and various salt forms of the present compounds, is preferred. One of ordinary skill in the art will recognize how to readily modify the present compound to a prodrug form to facilitate delivery of active compound to a targeted site within the host organism or patient. The artisan also will take advantage of favorable pharmacokinetic parameters of the prodrug form, where applicable, in delivering the desired compound to a targeted site within the host organism or patient to maximize the intended effect of the compound in the treatment of a *Flaviviridae* infection, including hepatitis C virus, West Nile Virus, yellow fever virus, and a rhinovirus infection.

The amount of compound included within therapeutically active formulations, according to the present invention, is an effective amount for treating the infection or condition, in preferred embodiments, a *Flaviviridae* infection, including hepatitis C virus, West Nile Virus, yellow fever virus, and a rhinovirus infection. In general, a therapeutically effective amount of the present compound in pharmaceutical dosage form usually ranges from about 50 mg to about 2,000 mg or more, depending upon the compound used, the condition or infection treated and the route of administration. For purposes of the present invention, a prophylactically or preventively effective amount of the compositions, according to the present invention, falls within the same concentration range as set forth above for

therapeutically effective amount and is usually the same as a therapeutically effective amount.

Administration of the active compound may range from continuous (intravenous drip) to several oral administrations per day (for example, Q.I.D., B.I.D., etc.) and may include oral, topical, parenteral, intramuscular, intravenous, subcutaneous, transdermal (which may include a penetration enhancement agent), buccal and suppository administration, among other routes of administration. Enteric-coated oral tablets may also be used to enhance bioavailability and stability of the compounds from an oral route of administration. The most effective dosage form will depend upon the pharmacokinetics of the particular agent chosen, as well as the severity of disease in the patient. Oral dosage forms are particularly preferred, because of ease of administration and prospective favorable patient compliance.

To prepare the pharmaceutical compositions according to the present invention, a therapeutically effective amount of one or more of the compounds according to the present invention is preferably mixed with a pharmaceutically acceptable carrier according to conventional pharmaceutical compounding techniques to produce a dose. A carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral. In preparing pharmaceutical compositions in oral dosage form, any of the usual pharmaceutical media may be used. Thus, for liquid oral preparations such as suspensions, elixirs and solutions, suitable carriers and additives including water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used. For solid oral preparations such as powders, tablets, capsules, and for solid preparations such as suppositories, suitable carriers and additives including starches, sugar carriers, such as dextrose, mannitol, lactose and related carriers, diluents, granulating agents, lubricants, binders, disintegrating agents and the like may be used. If desired, the tablets or capsules may be enteric-coated for sustained release by standard techniques. The use of these dosage forms may significantly impact the bioavailability of the compounds in the patient.

For parenteral formulations, the carrier will usually comprise sterile water or aqueous sodium chloride solution, though other ingredients, including those that aid dispersion, also may be included. Where sterile water is to be used and maintained as sterile, the compositions and carriers must also be sterilized. Injectable
5 suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed.

Liposomal suspensions (including liposomes targeted to viral antigens) may also be prepared by conventional methods to produce pharmaceutically acceptable carriers. This may be appropriate for the delivery of free nucleosides, acyl
10 nucleosides or phosphate ester prodrug forms of the nucleoside compounds according to the present invention.

In particularly preferred embodiments according to the present invention, the compounds and compositions are used to treat, prevent or delay the onset of a *Flaviviridae* infection, including hepatitis C virus, West Nile Virus, yellow fever
15 virus, and a rhinovirus infection. The present compounds are preferably administered orally, but may be administered parenterally, topically or in suppository form.

The compounds according to the present invention, because of their low toxicity to host cells in certain instances, may be advantageously employed
20 prophylactically to prevent a *Flaviviridae* infection, including hepatitis C virus, West Nile Virus, yellow fever virus, and a rhinovirus infection or to prevent the occurrence of clinical symptoms associated with the viral infection or condition. Thus, the present invention also encompasses methods for the prophylactic treatment of viral infection, and in particular a *Flaviviridae* infection, including
25 hepatitis C virus, West Nile Virus, yellow fever virus, and a rhinovirus infection. In this aspect, according to the present invention, the present compositions are used to prevent or delay the onset of a *Flaviviridae* infection, including hepatitis C virus, West Nile Virus, yellow fever virus, and a rhinovirus infection. This prophylactic method comprises administration to a patient in need of such treatment, or who is at
30 risk for the development of the virus or condition, an amount of a compound according to the present invention effective for alleviating, preventing or delaying

the onset of the viral infection or condition. In the prophylactic treatment according to the present invention, it is preferred that the antiviral compound utilized should be low in toxicity and preferably non-toxic to the patient. It is particularly preferred in this aspect of the present invention that the compound that is used should be maximally effective against the virus or condition and should exhibit a minimum of toxicity to the patient. In the case of a *Flaviviridae* infection, including hepatitis C virus, West Nile Virus, yellow fever virus, and a rhinovirus infection, compounds according to the present invention, which may be used to treat these disease states, may be administered within the same dosage range for therapeutic treatment (i.e., about 250 micrograms up to 1 gram or more from one to four times per day for an oral dosage form) as a prophylactic agent to prevent the proliferation of the viral infection, or alternatively, to prolong the onset of the viral infection, which manifests itself in clinical symptoms.

In addition, compounds according to the present invention can be administered in combination or alternation with one or more antiviral agents, including other compounds of the present invention. Certain compounds according to the present invention may be effective for enhancing the biological activity of certain agents according to the present invention by reducing the metabolism, catabolism or inactivation of other compounds and as such, are co-administered for this intended effect.

IV. Stereoisomerism and Polymorphism

It is appreciated that nucleosides of the present invention have several chiral centers and may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically active, diastereomeric, polymorphic, or stereoisomeric form, or mixtures thereof, of a compound of the invention, which possess the useful properties described herein. It being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase).

Carbons of the nucleoside are chiral, their nonhydrogen substituents (the base and the CHOR groups, respectively) can be either *cis* (on the same side) or *trans* (on opposite sides) with respect to the sugar ring system. The four optical isomers therefore are represented by the following configurations (when orienting the sugar moiety in a horizontal plane such that the oxygen atom is in the back): *cis* (with both groups "up", which corresponds to the configuration of naturally occurring β -D nucleosides), *cis* (with both groups "down", which is a nonnaturally occurring β -L configuration), *trans* (with the C2' substituent "up" and the C4' substituent "down"), and *trans* (with the C2' substituent "down" and the C4' substituent "up"). The "D-nucleosides" are *cis* nucleosides in a natural configuration and the "L-nucleosides" are *cis* nucleosides in the nonnaturally occurring configuration.

Likewise, most amino acids are chiral (designated as L or D, wherein the L enantiomer is the naturally occurring configuration) and can exist as separate enantiomers.

Examples of methods to obtain optically active materials are known in the art, and include at least the following.

- i) physical separation of crystals - a technique whereby macroscopic crystals of the individual enantiomers are manually separated. This technique can be used if crystals of the separate enantiomers exist, i.e., the material is a conglomerate, and the crystals are visually distinct;
- ii) simultaneous crystallization - a technique whereby the individual enantiomers are separately crystallized from a solution of the racemate, possible only if the latter is a conglomerate in the solid state;
- iii) enzymatic resolutions - a technique whereby partial or complete separation of a racemate by virtue of differing rates of reaction for the enantiomers with an enzyme;
- iv) enzymatic asymmetric synthesis - a synthetic technique whereby at least one step of the synthesis uses an enzymatic reaction to obtain an

enantiomerically pure or enriched synthetic precursor of the desired enantiomer;

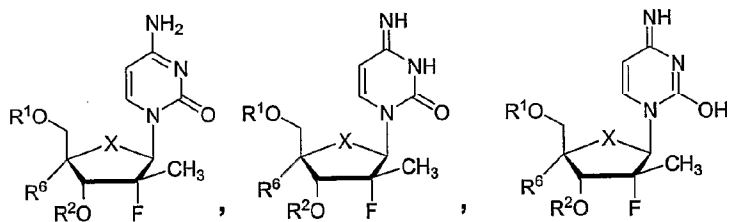
- 5 v) chemical asymmetric synthesis - a synthetic technique whereby the desired enantiomer is synthesized from an achiral precursor under conditions that produce asymmetry (i.e., chirality) in the product, which may be achieved using chiral catalysts or chiral auxiliaries;
- 10 vi) diastereomer separations - a technique whereby a racemic compound is reacted with an enantiomerically pure reagent (the chiral auxiliary) that converts the individual enantiomers to diastereomers. The resulting diastereomers are then separated by chromatography or crystallization by virtue of their now more distinct structural differences and the chiral auxiliary later removed to obtain the desired enantiomer;
- 15 vii) first- and second-order asymmetric transformations - a technique whereby diastereomers from the racemate equilibrate to yield a preponderance in solution of the diastereomer from the desired enantiomer or where preferential crystallization of the diastereomer from the desired enantiomer perturbs the equilibrium such that eventually in principle all the material is converted to the crystalline diastereomer from the desired enantiomer. The desired enantiomer is then released from the diastereomer.
- 20 viii) kinetic resolutions - this technique refers to the achievement of partial or complete resolution of a racemate (or of a further resolution of a partially resolved compound) by virtue of unequal reaction rates of the enantiomers with a chiral, non-racemic reagent or catalyst under kinetic conditions;
- 25 ix) enantiospecific synthesis from non-racemic precursors - a synthetic technique whereby the desired enantiomer is obtained from non-chiral starting materials and where the stereochemical integrity is not or is only minimally compromised over the course of the synthesis;

- 5 x) chiral liquid chromatography - a technique whereby the enantiomers of a racemate are separated in a liquid mobile phase by virtue of their differing interactions with a stationary phase. The stationary phase can be made of chiral material or the mobile phase can contain an additional chiral material to provoke the differing interactions;
- xi) chiral gas chromatography - a technique whereby the racemate is volatilized and enantiomers are separated by virtue of their differing interactions in the gaseous mobile phase with a column containing a fixed non-racemic chiral adsorbent phase;
- 10 xii) extraction with chiral solvents - a technique whereby the enantiomers are separated by virtue of preferential dissolution of one enantiomer into a particular chiral solvent;
- 15 xiii) transport across chiral membranes - a technique whereby a racemate is placed in contact with a thin membrane barrier. The barrier typically separates two miscible fluids, one containing the racemate, and a driving force such as concentration or pressure differential causes preferential transport across the membrane barrier. Separation occurs as a result of the non-racemic chiral nature of the membrane which allows only one enantiomer of the racemate to pass through.
- 20 Chiral chromatography, including simulated moving bed chromatography, is used in one embodiment. A wide variety of chiral stationary phases are commercially available.

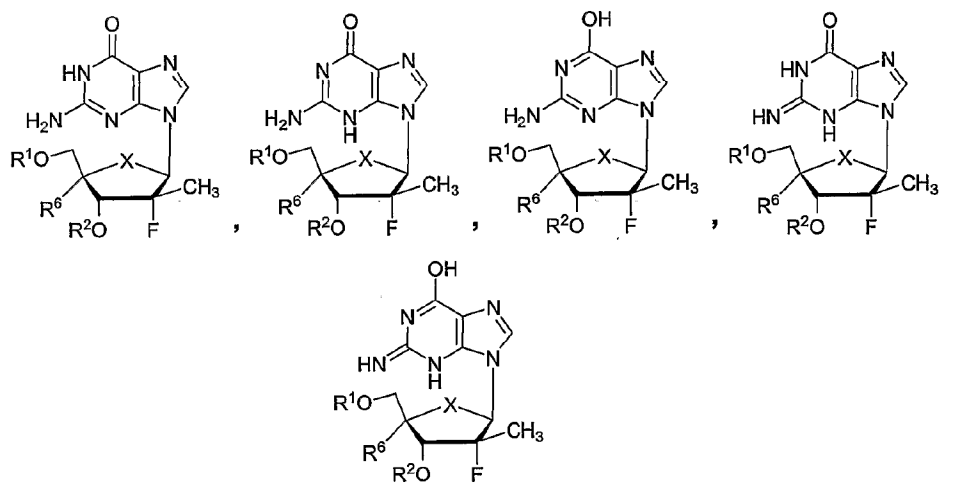
Some of the compounds described herein contain olefinic double bonds and unless otherwise specified, are meant to include both E and Z geometric isomers.

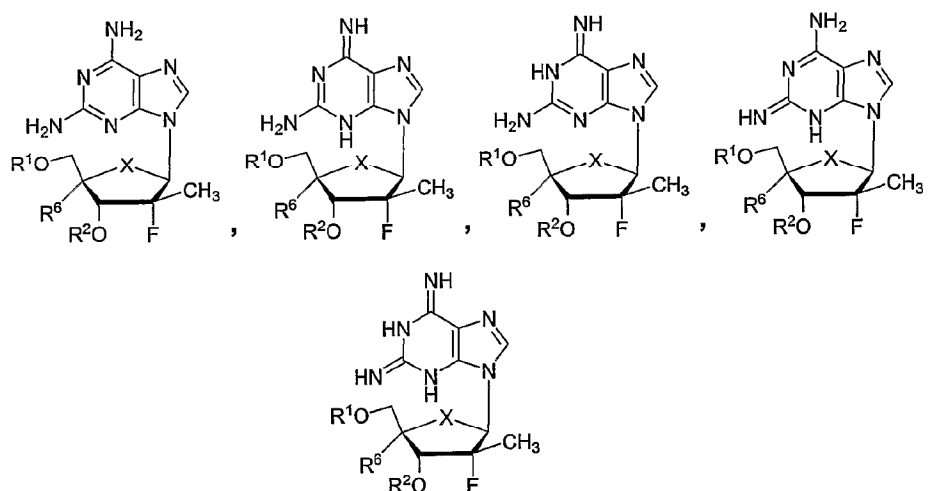
- 25 In addition, some of the nucleosides described herein, may exist as tautomers, such as, keto-enol tautomers. The individual tautomers as well as mixtures thereof are intended to be encompassed within the compounds of the present invention as illustrated below.

A (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine:



5

A (2'*R*)-2'-deoxy-2'-fluoro-2'-C-methylguanosine:A (2'*R*)-2-amino-2'-deoxy-2'-fluoro-2'-C-methyladenosine:



In each example above, the first drawn structure is the preferred form.

V. Prodrugs and Derivatives

The active compound can be administered as any salt or prodrug that upon administration to the recipient is capable of providing directly or indirectly the parent compound, or that exhibits activity itself. Nonlimiting examples are the pharmaceutically acceptable salts (alternatively referred to as "physiologically acceptable salts"), and a compound, which has been alkylated, acylated, or otherwise modified at the 5'-position, or on the purine or pyrimidine base (a type of "pharmaceutically acceptable prodrug"). Further, the modifications can affect the biological activity of the compound, in some cases increasing the activity over the parent compound. This can easily be assessed by preparing the salt or prodrug and testing its antiviral activity according to the methods described herein, or other methods known to those skilled in the art.

15 Pharmaceutically Acceptable Salts

In cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compound as a pharmaceutically acceptable salt may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed by addition of acids, which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorate, a-ketoglutarate, a-

glycerophosphate, formate, fumarate, propionate, glycolate, lactate, pyruvate, oxalate, maleate, and salicylate. Suitable inorganic salts may also be formed, including, sulfate, nitrate, bicarbonate, carbonate salts, hydrobromate and phosphoric acid. In a preferred embodiment, the salt is a mono- or di- hydrochloride salt.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be made. In one embodiment, the salt is a hydrochloride, hydrobromide, or mesylate salt of the compound. In another embodiment, the pharmaceutically acceptable salt is a dihydrochloride, dihydrobromide, or dimesylate salt.

Nucleotide Prodrug Formulations

The nucleosides described herein can be administered as a nucleotide prodrug to increase the activity, bioavailability, stability or otherwise alter the properties of the nucleoside. A number of nucleotide prodrug ligands are known. In general, alkylation, acylation or other lipophilic modification of the mono-, di- or triphosphate of the nucleoside reduces polarity and allows passage into cells. Examples of substituent groups that can replace one or more hydrogens on the phosphate moiety are alkyl, aryl, steroids, carbohydrates, including sugars, 1,2-diacylglycerol and alcohols. Many are described in R. Jones and N. Bisehoferger, Antiviral Research, 1995, 27:1-17. Any of these can be used in combination with the disclosed nucleosides to achieve a desired effect.

In an alternative embodiment, the nucleoside is delivered as a phosphonate or a SATE derivative.

The active nucleoside can also be provided as a 2'-, 3'- and/or 5'-phosphoether lipid or a 2'-, 3'- and/or 5'-ether lipid. Non-limiting examples are described include the following references, which are incorporated by reference herein: Kucera, L.S., N. Iyer, E. Leake, A. Raben, Modest E.K., D.L.W., and C.

Piantadosi. 1990. "Novel membrane-interactive ether lipid analogs that inhibit infectious HIV-1 production and induce defective virus formation." *AIDS Res. Hum. Retro Viruses*. 6:491-501; Piantadosi, C., J. Marasco C.J., S.L. Morris-Natschke, K.L. Meyer, F. Gumus, J.R. Surles, K.S. Ishaq, L.S. Kucera, N. Iyer, CA. Wallen, S. Piantadosi, and E.J. Modest. 1991. "Synthesis and evaluation of novel ether lipid nucleoside conjugates for anti-HIV activity." *J. Med Chem.* 34:1408.1414; Hosteller, K.Y., D.D. Richman, D.A. Carson, L.M. Stuhmiller, G.M. T. van Wijk, and H. van den Bosch. 1992. "Greatly enhanced inhibition of human immunodeficiency virus type 1 replication in CEM and HT4-6C cells by 3'-deoxythymine diphosphate dimyristoylglycerol, a lipid prodrug of 3'-deoxythymine." *Antlnzicrob. Agents Chemother.* 36:2025.2029; Hostetler, K.Y., L.M. Stuhmiller, H.B. Lenting, H. van den Bosch, and D.D. Richman, 1990. "Synthesis and antiretroviral activity of phospholipid analogs of azidothymidine and other antiviral nucleosides." *J. Biol. Chem.* 265:61127.

Nonlimiting examples of U.S. patents that disclose suitable lipophilic substituents that can be covalently incorporated into the nucleoside, preferably at the 2'-, 3'- and/or 5'-OH position of the nucleoside or lipophilic preparations, include U.S. Patent Nos. 5,149,794 (Sep. 22, 1992, Yatvin et al.); 5,194,654 (Mar. 16, 1993, Hostetler et al., 5,223,263 (June 29, 1993, Hostetler et al.); 5,256,641 (Oct. 26, 1993, Yatvin et al.); 5,411,947 (May 2, 1995, Hostetler et al.); 5,463,092 (Oct. 31, 1995, Hostetler et al.); 5,543,389 (Aug. 6, 1996, Yatvin et al.); 5,543,390 (Aug. 6, 1996, Yatvin et al.); 5,543,391 (Aug. 6, 1996, Yatvin et al.); and 5,554,728 (Sep. 10, 1996; Basava et al.), all of which are incorporated herein by reference. Foreign patent applications that disclose lipophilic substituents that can be attached to the nucleosides of the present invention, or lipophilic preparations, include WO 89/02733, WO 90/00555, WO 91/16920, WO 91/18914, WO 93/00910, WO 94/26273, WO 96/15132, EP 0350287, EP 93917054.4, and WO 91/19721.

Aryl esters, especially phenyl esters, are also provided. Nonlimiting examples are disclosed in DeLambert et al., *J. Med. Chem.* 37: 498 (1994). Phenyl esters containing a carboxylic ester ortho to the phosphate are also provided. Khaninei and Torrence, *J. Med. Chem.*; 39:41094115 (1996). In particular, benzyl esters, which generate the parent compound, in some cases using substituents at the

ortho- or para-position to accelerate hydrolysis, are provided. Examples of this class of prodrugs are described by Mitchell et al., *J. Chem. Soc. Perkin Trans. I* 2345 (1992); Brook, et al. WO 91/19721; and Glazier et al. WO 91/1 9721.

5 Cyclic and noncyclic phosphonate esters are also provided. Nonlimiting examples are disclosed in Hunston et al., *J. Med. Chem.* 27: 440-444 (1984) and Starrett et al. *J. Med. Chem.* 37: 1857-1864 (1994). Additionally, cyclic 3',5'-phosphate esters are provided. Nonlimiting examples are disclosed in Meier et al. *J. Med. Chem.* 22: 811-815 (1979). Cyclic 1',3'-propanyl phosphonate and phosphate esters, such as ones containing a fused aryl ring, i.e. the cyclosaligenyl ester, are also
10 provided (Meier et al., *Bioorg. Med. Chem. Lett.* 7: 99-104 (1997)). Unsubstituted cyclic 1',3'-propanyl esters of the monophosphates are also provided (Farquhar et al., *J. Med. Chem.* 26: 1153 (1983); Farquhar et al., *J. Med. Chem.* 28: 1358 (1985)) were prepared. In addition, cyclic 1',3'-propanyl esters substituted with a pivaloyloxy methyloxy group at C-1' are provided (Freed et al., *Biochem. Pharmac.*
15 38: 3193 (1989); Biller et al., U.S. Pat. No. 5,157,027).

 Cyclic phosphoramidates are known to cleave in vivo by an oxidative mechanism. Therefore, in one embodiment of the present invention, a variety of substituted 1',3' propanyl cyclic phosphoramidates are provided. Non-limiting
20 examples are disclosed by Zon, *Progress in Med. Chem.* 19, 1205 (1982). Additionally, a number of 2'- and 3'- substituted proesters are provided. 2'-Substituents include methyl, dimethyl, bromo, trifluoromethyl, chloro, hydroxy, and methoxy; 3'-substituents including phenyl, methyl, trifluoromethyl, ethyl, propyl, i-propyl, and cyclohexyl. A variety of 1'-substituted analogs are also provided.

 Cyclic esters of phosphorus-containing compounds are also provided. Non-
25 limiting examples are described in the following:

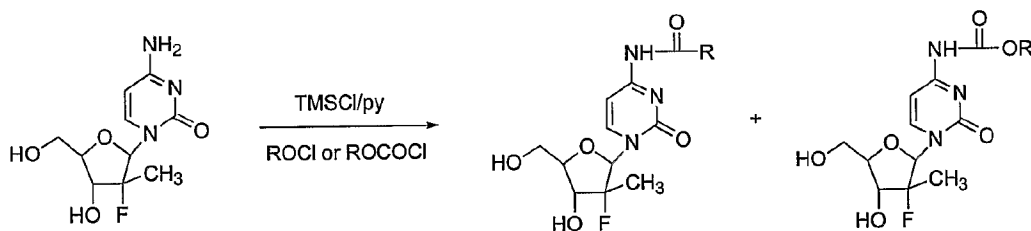
- di and tri esters of phosphoric acids as reported in Nifant'ev et al., *Phosphorus, Sulfur Silicon and Related Elements*, 113: 1 (1996); Wijnberg et al., EP-180276 A1;
- phosphorus (III) acid esters. Kryuchkov et al., *Izv. Akad. Nauk SSSR, Ser. Khim.* 6:1244 (1987). Some of the compounds were claimed to be useful for
30

the asymmetric synthesis of L-Dopa precursors. Sylvain et al., DE3S 12781 A1;

- phosphoramidates. Shili et al., Bull. Inst. Chem. Acad. Sin, 41: 9 (1994); Edmundson et al., J. Chem. Res. Synop. 5:122 (1989); and
- 5 • phosphonates. Neidlein et al., Heterocycles 35: 1185 (1993).

N⁴-acyl Prodrugs

The invention also provides N⁴- acyl prodrugs. A non-limiting example of an N⁴-acyl derivative of (2'*R*)-2'-F-2'-C-methylcytidine is shown below:



10

wherein R can be any acyl group as described herein.

15

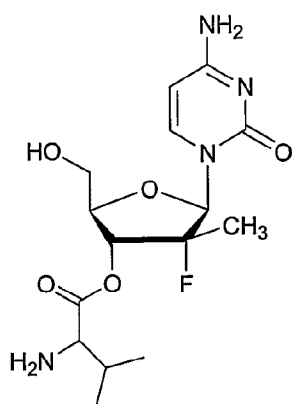
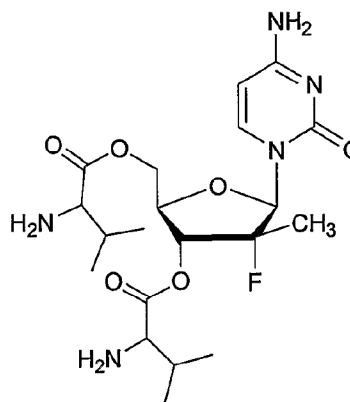
20

25

The invention also contemplates other embodiments, wherein the prodrug of a (2'*R*)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β -D or β -L) includes biologically cleavable moieties at the 3' and/or 5' positions. Preferred moieties are natural or synthetic D or L amino acid esters, including D or L -valyl, though preferably L -amino acids esters, such as L -valyl, and alkyl esters including acetyl. Therefore, this invention specifically includes 3'- L or D - amino acid ester and 3', 5'- L or D - diamino acid ester of (2'*R*)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β -D or β -L) nucleosides, preferably L -amino acid, with any desired purine or pyrimidine base, wherein the parent drug optionally has an EC₅₀ of less than 15 micromolar, and even more preferably less than 10 micromolar; 3'-(alkyl or aryl) ester or 3',5'- L - di(alkyl or aryl) ester of (2'*R*)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β -D or β -L) with any desired purine or pyrimidine base, wherein the parent drug optionally has an EC₅₀ of less than 10 or 15 micromolar; and prodrugs of 3',5'-diesters of (2'*R*)-2'-deoxy-2'-fluoro-2'-C-methyl nucleosides (β -D or β -L) wherein (i) the 3' ester is an amino acid ester and the 5'-ester is an alkyl or aryl ester; (ii) both esters are amino acid esters; (iii) both esters are independently alkyl or aryl esters; and (iv) the 3'

ester is independently an alkyl or aryl ester and the 5'-ester is an amino acid ester, wherein the parent drug optionally has an EC_{50} of less than 10 or 15 micromolar.

Non-limiting examples of prodrugs falling within the invention are:



5

VI. Combination or Alternation Therapy

In another embodiment, for the treatment, inhibition, prevention and/or prophylaxis of any viral infection described herein, the active compound or its derivative or salt can be administered in combination or alternation with another antiviral agent. In general, in combination therapy, effective dosages of two or more agents are administered together, whereas during alternation therapy, an effective dosage of each agent is administered serially. The dosage will depend on absorption, inactivation and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens and schedules should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions.

It has been recognized that drug-resistant variants of flaviviruses, pestiviruses or HCV can emerge after prolonged treatment with an antiviral agent. Drug resistance most typically occurs by mutation of a gene that encodes for an enzyme used in viral replication. The efficacy of a drug against the viral infection can be prolonged, augmented, or restored by administering the compound in

combination or alternation with a second, and perhaps third, antiviral compound that induces a different mutation from that caused by the principle drug. Alternatively, the pharmacokinetics, biodistribution or other parameter of the drug can be altered by such combination or alternation therapy. In general, combination therapy is typically preferred over alternation therapy because it induces multiple simultaneous stresses on the virus.

For example, one skilled in the art will recognize that any antiviral drug or therapy can be used in combination or alternation with any nucleoside of the present invention. Any of the viral treatments described in the Background of the Invention can be used in combination or alternation with the compounds described in this specification. Nonlimiting examples of the types of antiviral agents or their prodrugs that can be used in combination with the compounds disclosed herein include: interferon, including interferon alpha 2a, interferon alpha 2b, a pegylated interferon, interferon beta, interferon gamma, interferon tau and interferon omega; an interleukin, including interleukin 10 and interleukin 12; ribavirin; interferon alpha or pegylated interferon alpha in combination with ribavirin or levovirin; levovirin; a protease inhibitor including an NS3 inhibitor, a NS3-4A inhibitor; a helicase inhibitor; a polymerase inhibitor including HCV RNA polymerase and NS5B polymerase inhibitor; gliotoxin; an IRES inhibitor; and antisense oligonucleotide; a thiazolidine derivative; a benzanilide, a ribozyme; another nucleoside, nucleoside prodrug or nucleoside derivative; a 1-amino-alkylcyclohexane; an antioxidant including vitamin E; squalene; amantadine; a bile acid; N-(phosphonoacetyl)-L-aspartic acid; a benzenedicarboxamide; polyadenylic acid; a benzimidazoles; thymosin; a beta tubulin inhibitor; a prophylactic vaccine; an immune modulator, an IMPDH inhibitor; silybin-phosphatidylcholine phytosome; and mycophenolate.

Further nonlimiting examples of the types of drugs or their prodrugs described above include: acyclovir (ACV), ganciclovir (GCV or DHPG) and its prodrugs (e.g. valyl-ganciclovir), E-5-(2-bromovinyl)-2'-deoxyuridine (BVDU), (E)-5-vinyl-1- β -D-arabonosyluracil (VaraU), (E)-5-(2-bromovinyl)-1- β -D-arabinosyluracil (BV-araU), 1-(2-deoxy-2-fluoro- β -D-arabinosyl)-5-iodocytosine (D-FIAC), 1-(2-deoxy-2-fluoro- β -L-arabinosyl)-5-methyluracil (L-FMAU, or

clevudine), (*S*)-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine [(*S*)-HPMPA], (*S*)-9-(3-hydroxy-2-phosphonylmethoxypropyl)-2,6-diaminopurine [(*S*)-HPMPDAP], (*S*)-1-(3-hydroxy-2-phosphonyl-methoxypropyl)cytosine [(*S*)-HPMPC, or cidofovir], and (2*S*,4*S*)-1-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]-5-iodouracil (L-5-IoddU), entecavir, lamivudine (3TC), LdT, LdC, tenofovir, and adefovir, the (-)-enantiomer of 2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-oxathiolane ((-)-FTC); the (-)-enantiomer of 2-hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane (3TC); carbovir, acyclovir, famciclovir, penciclovir, AZT, DDI, DDC, L-(-)-FMAU, D4T, amdoxovir, Reverset, Racivir, abacavir, L-DDA phosphate prodrugs, and β -D-dioxolanyl-6-chloropurine (ACP), non-nucleoside RT inhibitors such as nevirapine, MKC-442, DMP-226 (sustiva), protease inhibitors such as indinavir, saquinavir, Kaletra, atazanavir; and anti-HIV compounds such as BILN-2061, ISIS 14803; viramidine, NM 283, VX-497, JKT-003, levovirin, isatoribine, albuferon, Peg-infergen, VX-950, R803, HCV-086, R1479 and DMP45.

15 Pharmaceutical Compositions

Hosts, including humans, infected with pestivirus, flavivirus, HCV infection, or any other condition described herein, or another organism replicating through a RNA-dependent RNA viral polymerase, or for treating any other disorder described herein, can be treated by administering to the patient an effective amount of the active compound or a pharmaceutically acceptable prodrug or salt thereof in the presence of a pharmaceutically acceptable carrier or diluent. The active materials can be administered by any appropriate route, for example, orally, parenterally, intravenously, intradermally, subcutaneously, or topically, in liquid or solid form.

A preferred dose of the compound for a *Flaviviridae* infection, including hepatitis C virus, West Nile Virus and yellow fever virus and rhinovirus infection will be in the range from about 50 to about 2000 mg one to four times per day. Lower doses may be useful, and thus ranges can include from 50 – 1,000 mg one to four times per day. The effective dosage range of the pharmaceutically acceptable salts and prodrugs can be calculated based on the weight of the parent nucleoside to be delivered. If the salt or prodrug exhibits activity in itself the effective dosage can

be estimated as above using the weight of the salt or prodrug, or by other means known to those skilled in the art.

5 The compound is conveniently administered in unit any suitable dosage form, including but not limited to one containing 25 to 3000 mg, preferably 50 to 2000 mg of active ingredient per unit dosage form. An oral dosage of 50-1000 mg is usually convenient, including in one or multiple dosage forms of 50, 100, 200, 250, 300, 400, 500, 600, 700, 800, 900 or 1000 mgs. Also contemplated are doses of 0.1-50 mg, or 0.1-20 mg or 0.1-10.0 mg. Furthermore, lower doses may be utilized in the case of administration by a non-oral route, as, for example, by
10 injection or inhalation.

Ideally the active ingredient should be administered to achieve peak plasma concentrations (C_{max}) of the active compound of from about 5.0 to 70 μ M, preferably about 5.0 to 15 μ M. This may be achieved, for example, by the intravenous injection of a 0.1 to 5% solution of the active ingredient, optionally in
15 saline, or administered as a bolus of the active ingredient.

The concentration of active compound in the drug composition will depend on absorption, inactivation and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that
20 for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. The active ingredient may be
25 administered at once, or may be divided into a number of smaller doses to be administered at varying intervals of time.

A preferred mode of administration of the active compound is oral. Oral compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral
30 therapeutic administration, the active compound can be incorporated with excipients

and used in the form of tablets, troches, or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition.

5 The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is
10 a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or other enteric agents.

15 The compound can be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

20 The compound or a pharmaceutically acceptable prodrug or salts thereof can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as antibiotics, antifungals, anti-inflammatories, or other antivirals, including other nucleoside compounds. Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parental preparation can be enclosed in ampoules, disposable syringes
25 or multiple dose vials made of glass or plastic.
30

If administered intravenously, preferred carriers are physiological saline or phosphate buffered saline (PBS).

In a preferred embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation.

Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) are also preferred as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art. For example, liposome formulations may be prepared by dissolving appropriate lipid(s) (such as stearyl phosphatidyl ethanolamine, stearyl phosphatidyl choline, arachadoyl phosphatidyl choline, and cholesterol) in an inorganic solvent that is then evaporated, leaving behind a thin film of dried lipid on the surface of the container. An aqueous solution of the active compound or its monophosphate, diphosphate, and/or triphosphate derivatives is then introduced into the container. The container is then swirled by hand to free lipid material from the sides of the container and to disperse lipid aggregates, thereby forming the liposomal suspension.

VII. Biological Methods

Antiviral Testing Of Candidate Compounds With HCV Replicon System In Huh7 Cells.

Huh7 cells harboring the HCV replicon can be cultivated in DMEM media (high glucose, no pyruvate) containing 10% fetal bovine serum, 1X non-essential Amino Acids, Pen-Strep-Glu (100 units/liter, 100 microgram/liter, and 2.92 mg/liter, respectively) and 500 to 1000 microgram/milliliter G418. Antiviral screening assays can be done in the same media without G418 as follows: in order to keep cells in logarithmic growth phase, cells are seeded in a 96-well plate at low density,

for example 1000 cells per well. The test compound is added immediately after seeding the cells and incubate for a period of 3 to 7 days at 37°C in an incubator. Media is then removed, and the cells are prepared for total nucleic acid extraction (including replicon RNA and host RNA). Replicon RNA can then be amplified in a Q-RT-PCR protocol, and quantified accordingly. The observed differences in replicon HCV RNA levels compared to the untreated control is one way to express the antiviral potency of the test compound.

In another typical setting, a compound might reduce the viral RNA polymerase activity, but not the host RNA polymerase activity. Therefore, quantification of *r*RNA or beta-actin *m*RNA (or any other host RNA fragment) and comparison with RNA levels of the no-drug control is a relative measurement of the inhibitory effect of the test compound on cellular RNA polymerases.

Phosphorylation Assay of Nucleoside to Active Triphosphate

To determine the cellular metabolism of the compounds, Huh-7 cells are obtained from the American Type Culture Collection (Rockville, MD), and are grown in 225 cm² tissue culture flasks in minimal essential medium supplemented with non-essential amino acids, 1% penicillin-streptomycin. The medium is renewed every three days, and the cells are sub cultured once a week. After detachment of the adherent monolayer with a 10 minute exposure to 30 mL of trypsin-EDTA and three consecutive washes with medium, confluent Huh-7 cells are seeded at a density of 2.5 x 10⁶ cells per well in a 6-well plate and exposed to 10 µM of [³H] labeled active compound (500 dpm/pmol) for the specified time periods. The cells are maintained at 37 °C under a 5% CO₂ atmosphere. At the selected time points, the cells are washed three times with ice-cold phosphate-buffered saline (PBS). Intracellular active compound and its respective metabolites are extracted by incubating the cell pellet overnight at -20 °C with 60% methanol followed by extraction with an additional 20 µL of cold methanol for one hour in an ice bath. The extracts are then combined, dried under gentle filtered air flow and stored at -20 °C until HPLC analysis.

Bioavailability Assay in Cynomolgus Monkeys

Within 1 week prior to the study initiation, the cynomolgus monkey is surgically implanted with a chronic venous catheter and subcutaneous venous access port (VAP) to facilitate blood collection and underwent a physical examination including hematology and serum chemistry evaluations and the body weight was recorded. Each monkey (six total) receives approximately 250 μCi of ^3H -labeled compound combined with each dose of active compound at a dose level of 10 mg/kg at a dose concentration of 5 mg/mL, either via an intravenous bolus (3 monkeys, IV), or via oral gavage (3 monkeys, PO). Each dosing syringe is weighed before dosing to gravimetrically determine the quantity of formulation administered. Urine samples are collected via pan catch at the designated intervals (approximately 18-0 hours pre-dose, 0-4, 4-8 and 8-12 hours post-dosage) and processed. Blood samples are collected as well (pre-dose, 0.25, 0.5, 1, 2, 3, 6, 8, 12 and 24 hours post-dosage) via the chronic venous catheter and VAP or from a peripheral vessel if the chronic venous catheter procedure should not be possible. The blood and urine samples are analyzed for the maximum concentration (C_{max}), time when the maximum concentration is achieved (T_{max}), area under the curve (AUC), half life of the dosage concentration ($T_{1/2}$), clearance (CL), steady state volume and distribution (V_{ss}) and bioavailability (F).

Bone Marrow Toxicity Assay

Human bone marrow cells are collected from normal healthy volunteers and the mononuclear population are separated by Ficoll-Hypaque gradient centrifugation as described previously by Sommadossi J-P, Carlisle R. "Toxicity of 3'-azido-3'-deoxythymidine and 9-(1,3-dihydroxy-2-propoxymethyl)guanine for normal human hematopoietic progenitor cells in vitro" Antimicrobial Agents and Chemotherapy 1987; 31:452-454; and Sommadossi J-P, Schinazi RF, Chu CK, Xie M-Y. "Comparison of cytotoxicity of the (-)- and (+)-enantiomer of 2',3'-dideoxy-3'-thiacytidine in normal human bone marrow progenitor cells" Biochemical Pharmacology 1992; 44:1921-1925. The culture assays for CFU-GM and BFU-E are performed using a bilayer soft agar or methylcellulose method. Drugs are diluted in tissue culture medium and filtered. After 14 to 18 days at 37 °C in a humidified atmosphere of 5% CO_2 in air, colonies of greater than 50 cells are counted using an

inverted microscope. The results are presented as the percent inhibition of colony formation in the presence of drug compared to solvent control cultures.

Mitochondria Toxicity Assay

Fifty microliters of 2X drug dilutions were added per well in a 96 well plate. A “no drug” (media only) control was used to determine maximum amount of mitochondrial DNA produced and ribosomal DNA. 3TC @ 10 μ M was used as a negative control, and ddC @ 10 μ M was used as a toxic control. Ribosomal DNA levels were used to determine specific toxicity to mitochondria or generally cytotoxicity. HepG2 cells (5,000 cells/well at 50 μ l) were added to the plate. The plate was incubated at 37°C in a humidified 5% CO₂ atmosphere for 7 days. After incubation, the supernatant was removed and stored for lactic acid quantification, and total DNA was extracted from cells as described in the RNeasy 96 handbook (February 1999), pages 22-23. No DNA digestions were performed, therefore total RNA and DNA were extracted.

The extracted DNA was amplified and the change in mitochondrial DNA and ribosomal DNA for each sample was determined. The fold difference in mitochondrial DNA normalized for ribosomal DNA relative to control was calculated.

Lactic acid quantification was performed by the D-Lactic Acid/ L-Lactic acid test kit (Boehringer Mannheim/ R-Biopharm/ Roche). The total amount of lactic acid produced for each sample was found as well as the fold change in lactic acid production (% of lactic acid / % of rDNA) as described in the manufacturers instructions.

Cytotoxicity Assay

50 μ l of 2X drug dilutions were added per well in a 96 well plate. Final concentrations of drug ranged from 1 to 100 μ M. A “no drug” (media only) control was used to determine the minimum absorbance values and a “cells + media only” control was used for maximum absorbance value. A solvent control was also used. Cells were then added (PBM: 5 x 10⁴ cells/well; CEM : 2.5 x 10³ cells/well; Vero, HepG2, Huh-7, and Clone A: 5 x 10³ cells/well) and incubated at 37°C in a

humidified 5% CO₂ atmosphere for 3-5 days (PBM :5 days; CEM : 3 days, all others :4 days). After incubation, 20 µl of MTS dye was added from Cell Titer Aqueous One Solution Cell Proliferation Assay to each well and the plate was re-incubated for 2-4 hours. The absorbance (490 nm) was then read on an ELISA plate reader using the media only/ no cell wells as blanks. Percent inhibition was found and used to calculate the CC₅₀.

In vivo Toxicity in Mice

In vivo toxicity was also determined following injections into female Swiss mice of the various nucleosides disclosed in the present invention. Intraperitoneal injections were given on days 0, day 1, day 2, day 3, and day 5 of varying doses of the particular nucleoside. Separate animals were injected with vehicle as control groups. In these studies, each dosing group contained 5-10 mice. The average weight change in each of the mice was measured as a sign of toxicity of the compound.

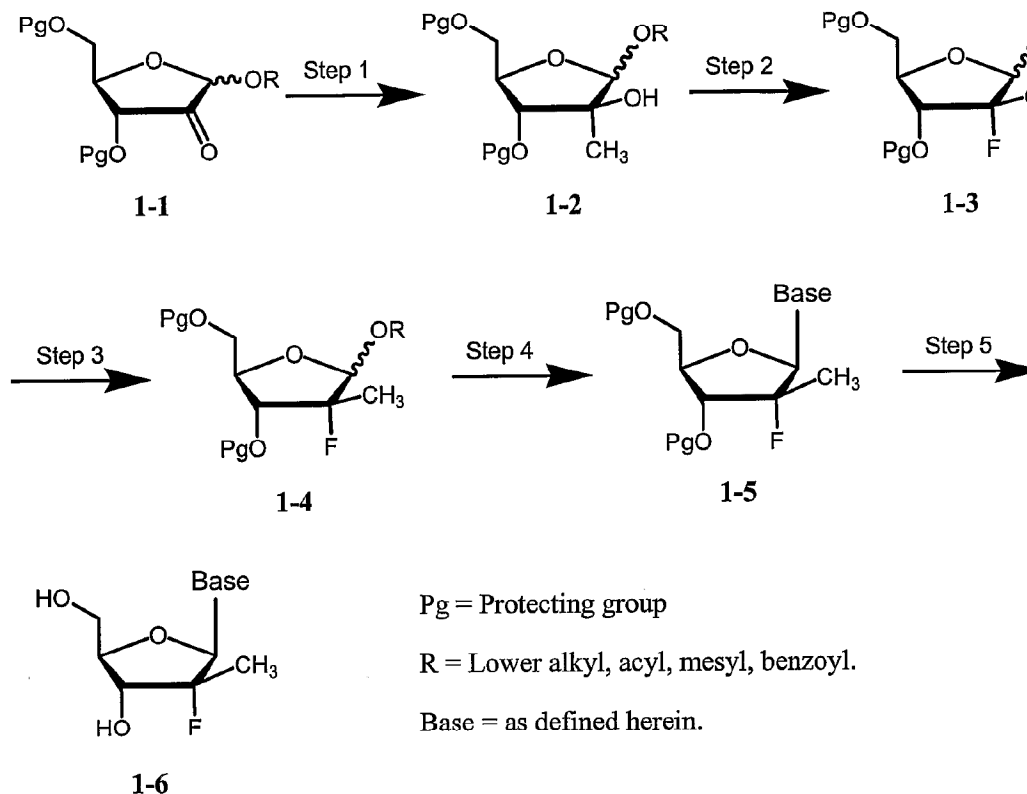
(BVDV) Yield Reduction Assay]

Madin-Darby Bovine Kidney (MDBK) cells were grown in Dulbecco's modified eagle medium supplemented with 10% horse serum and 100µg/ml penicillin-streptomycin. Cells were seeded in a 96-well plate at 5×10^3 cells /well and incubated for 72h at 37°C in a humidified 5% CO₂ atmosphere. Cells were infected with either cytopathic (NADL strain) or noncytopathic (SD-1 strain) BVDV at a virus dilution of 10^{-2} and incubated for 45 min. Cell monolayers were washed three times with medium. Fresh medium-containing test compounds in dose response concentrations or ribavirin, as a positive control, were added to cultures and medium containing no drug was added to the no-drug controls. After 72h incubation, supernatant was collected and viral RNA was extracted using the QIAmp Viral RNA Mini Kit (Qiagen, CA). Viral load was determined by Q-RT-PCR using primers specific for either NADL or SD-1 (1).

VIII. Synthetic Protocol

The following non-limiting embodiments illustrate some general methodologies to obtain the nucleosides of the present invention. Two representative general methods for the preparation of compounds of the present invention are outlined in Schemes 1 and 2 while more specific examples of these
5 general methods are provided in Scheme 3 (Example 1), Scheme 4 (Example 2), Scheme 5 (Example 3), and Scheme 6 (Example 4). Scheme 1 represents a generalized process starting from a (2*R*) 2-deoxy-2-methyl-2-fluoro-carbohydrate and forms the nucleosides of the present invention by condensing with a nucleobase. Scheme 2 starts from a pre-formed, purine or pyrimidine nucleoside, optionally
10 substituted at C-4' and constructs the C-2' (*R*) methyl, fluoro nucleosides of the present invention. While these schemes illustrate the syntheses of compounds of the present invention of general formulas (I) and (II) wherein there is a furanose ring in the β-D-ribo configuration, this is not intended to be a limitation on the scope of the process invention in any way, and they should not be so construed. Those skilled in
15 the art of nucleoside and nucleotide synthesis will readily appreciate that known variations of the conditions and processes of the following preparative procedures and known manipulations of the nucleobase can be used to prepare these and other compounds of the present invention. Additionally, the L-enantiomers corresponding to the compounds of the invention can be prepared following the same methods,
20 beginning with the corresponding L-carbohydrate building block or nucleoside L-enantiomer as the starting material.

1. Glycosylation of the nucleobase with an appropriately modified sugar

Scheme 1

5 Step 1 in Scheme 1 introduces the 2-methyl group by using an appropriate alkylating agent such as methyllithium, trimethylaluminum, or methylmagnesium bromide in an anhydrous solvent such as tetrahydrofuran (THF), chloroform, or diethyl ether. Compounds **1-1** through **1-4** can be purely α or β or they may exist as an anomeric mixture containing both α and β anomers in any ratio. However, the preferred anomeric configuration of structure **1-1** is β .

10

Step 2 introduces the fluorine atom at the 2- position of the alkyl furanoside. This can be achieved by treatment of the tertiary alcohol, **1-2**, with a commercially available fluorinating reagent such as (diethylamino)sulfur trifluoride (DAST) or Deoxofluor in an anhydrous, aprotic solvent such as tetrahydrofuran, chloroform, dichloromethane, or toluene. Preferably the stereochemistry proceeds with inversion of configuration at C-2. That is, starting from a C-2 hydroxyl "up" (or

15

arabinofuranoside) in structure 1-2, the C-2 fluorine is "down" in the intermediate ribofuranoside 1-3.

In step 3, the optional protecting groups (Pg) can be deprotected and reprotected to groups more suitable for the remaining manipulations (T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis," 3rd ed., John Wiley & Sons, 1999). For example, benzyl ethers (Bn) may be difficult to remove in the protected nucleoside, 1-5 and may be deprotected and replaced with a group more facile to remove from the nucleoside of structural type 1-5. Furthermore, the anomeric position (C-1) can also be optionally manipulated to a suitable group for the coupling reaction with the nucleobase (step 4). Several methods for anomeric manipulations are established to those skilled in the art of nucleoside synthesis. Some non-limiting examples by treatment of the alkyl furanoside (1-3, R = alkyl) with a mixture of acetic anhydride, acetic acid, and a catalytic amount of sulfuric acid (acetolysis) to provide structure 1-4 where R = Ac, with optional protecting groups. Also, the alkyl group in 1-3 may be converted to an acetate, benzoate, mesylate, tosylate, triflate, or tosylate, for example, by first hydrolyzing the 1-*Oalkyl* group to a 1-hydroxyl group by using a mineral acid consisting of but not limited to sulfuric acid, hydrochloric acid, and hydrobromic acid or an organic acid consisting of but not limited to trifluoroacetic acid, acetic acid, and formic acid (at ambient temperature or elevated temperature). The reducing sugar could then be converted to the desired carbohydrate by treatment with acetyl chloride, acetic anhydride, benzyol chloride, benzoic anhydride, methanesulfonyl chloride, triflic anhydride, trifyl chloride, or tosyl chloride in the presence of a suitable base such as triethylamine, pyridine, or dimethylaminopyridine.

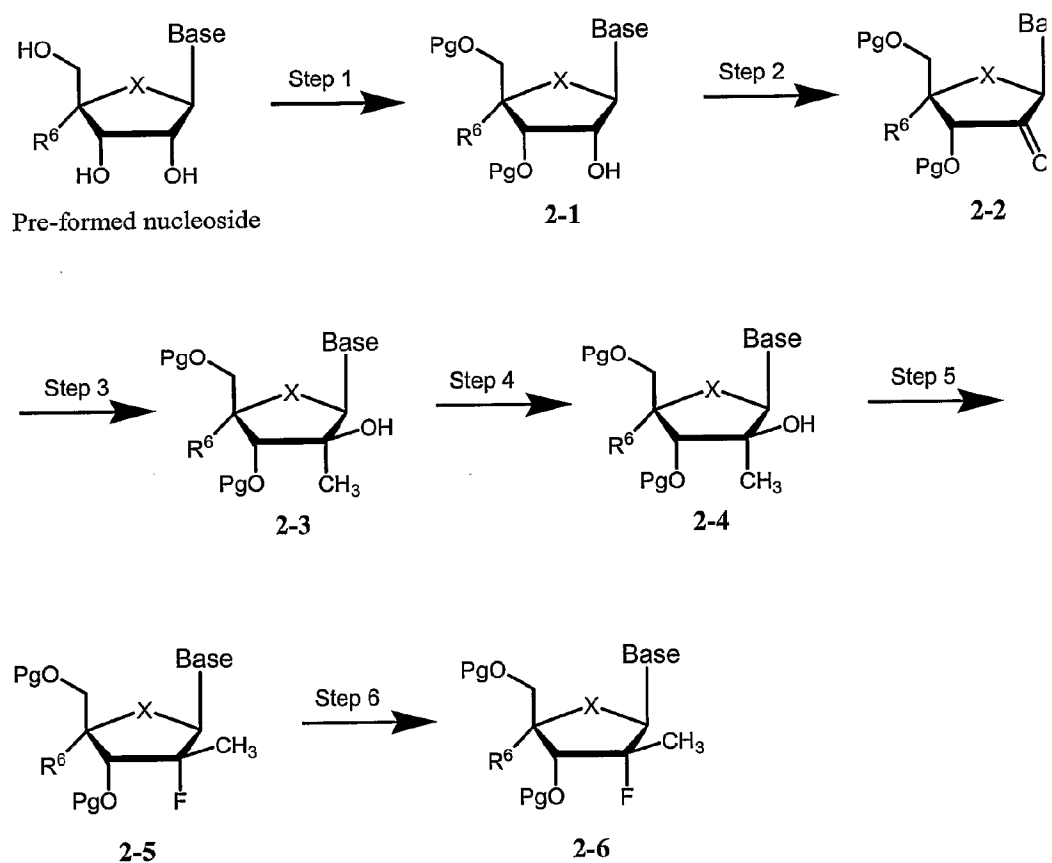
The nucleosidic linkage is constructed by treatment of intermediate 1-3 or 1-4 with the appropriate persilylated nucleobase in the presence of a lewis acid such as tin tetrachloride, titanium tetrachloride, trimethylsilyltriflate, or a mercury (II) reagent (HgO/HgBr₂) usually at an elevated temperature in an aprotic solvent such as toluene, acetonitrile, benzene, or a mixture of any or all of these solvents.

The optional protecting groups in the protected nucleosides or structural formula 1-5 can be cleaved following established deprotection methodologies (T.W.

Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis," 3rd ed., John Wiley & Sons, 1999).

2. Modification of a pre-formed nucleoside

Scheme 2



Pg = Protecting group

Base = as defined herein (optionally protected)

X = as defined herein

R⁶ = as defined herein

The starting material for this process is an appropriately substituted purine or pyrimidine nucleoside with a 2'-OH and 2'-H. The nucleoside can be purchased or

can be prepared by any known means including standard coupling techniques. The nucleoside can be optionally protected with suitable protecting groups, preferably with acyl or silyl groups, by methods well known to those skilled in the art, as taught by T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis," 3rd ed., John Wiley & Sons, 1999.

The purine or pyrimidine nucleoside can then be oxidized at the 2'-position with the appropriate oxidizing agent in a compatible solvent at a suitable temperature to yield the 2'-modified nucleoside. Possible oxidizing agents are a mixture of dimethylsulfoxide, trifluoroacetic anhydride or acetic anhydride (a Swern/Moffat oxidation), chromium trioxide or other chromate reagent, Dess-Martin periodinane, or by ruthenium tetroxide/sodium periodate.

The optionally protected nucleoside 2'-ketone is then alkylated using such alkylating agents methyllithium, trimethylaluminum, methylmagnesium bromide, or similar reagents in an anhydrous solvent such tetrahydrofuran (THF), chloroform, or diethyl ether usually at temperatures below 0 °C. Compounds of the structural formula 2-3 are preferred to have the 2'(S) or 2'-methyl "down", 2'-OH "up" configuration.

The nucleoside of structure 2-3 can be deprotected and reprotected with a number of protecting groups such as an *O*-acyl (alkyl or aryl), *O*-sulfonyl, or an *N*-acyl (alkyl or aryl) for the base. This optional reprotection step need not be limited to protecting groups that function as chemical protecting groups. Other protecting groups such as long chain acyl groups of between 6 and 18 carbon units or amino acids can be introduced independently on the nucleobase or the sugar. The protecting groups can serve as prodrugs of the active substance.

Step 5 introduces the fluorine atom at the 2' position of the pre-formed nucleoside. This can be achieved by treatment of the tertiary alcohol, 2-4, with a commercially available fluorinating reagent such as (diethylamino)sulfur trifluoride (DAST) or Deoxofluor in an anhydrous, aprotic solvent such as tetrahydrofuran, chloroform, dichloromethane, or toluene. Preferably the stereochemistry proceeds with inversion of configuration at the 2' position. That is, starting from a C-2' hydroxyl "up" (or arabinonucleoside) in structure 2-4, the C-2' fluorine is "down" in

the intermediate nucleoside **2-5**. The absolute configuration of a nucleoside of structure **2-4** is (2'*S*) while the absolute configuration of a nucleoside of structure **2-5** is (2'*R*).

5 Subsequently, the nucleosides of structural type **2-5** can be deprotected by methods well known to those skilled in the art, as taught by T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis," 3rd ed., John Wiley & Sons, 1999.

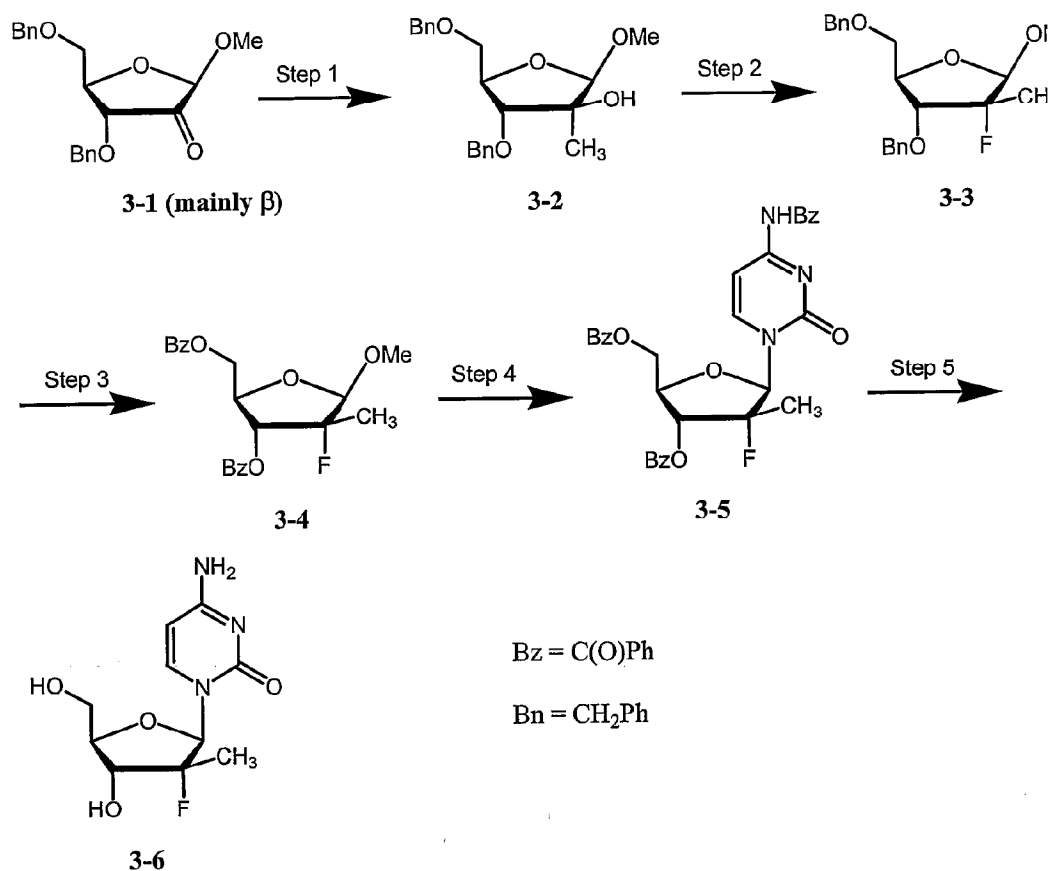
10 The following working examples provide a further understanding of the method of the present invention and further exemplify the general examples in Schemes 1 and 2 above. These examples are of illustrative purposes, and are not meant to limit the scope of the invention. Equivalent, similar or suitable solvents, reagents or reaction conditions may be substituted for those particular solvents, reagents or reaction conditions described without departing from the general scope of the method.

15

EXAMPLES

Example 1

*Synthesis of (2'*R*)-2'-Deoxy-2'-Fluoro-2'-C-Methylcytidine Starting from a Carbohydrate*

Scheme 3

Step 1: Compound **3-1** (7.7 g, 0.022 mmol) was dissolved in anhydrous diethyl ether and cooled to -78 °C. To this solution was added MeLi (30 mL, 1.6 M in diethyl ether). After the reaction was complete, the mixture was treated with ammonium chloride (1 M, 65 mL) and the organic phase was separated, dried (Na₂SO₄), filtered, and concentrated to dryness. Silica gel chromatography followed by crystallization from diethyl ether-hexanes afforded pure compound **3-2** (6.31 g).

¹H NMR (400 MHz, CDCl₃): δ 1.40 (s, 3H), 3.41 (s, 3H), 3.49 (dd, 1H, *J* = 10.3, 6.89 Hz), 3.57 (dd, 1H, *J* = 10.3, 3.88 Hz), 3.84 (d, 1H, *J* = 7.3 Hz), 4.03 (m, 1H), 4.48 (s, 1H), 4.58 (m, 3H), 4.83 (d, 1H, *J* = 11.6 Hz), 7.31–7.36 (m, 10H); ¹³C NMR (100 MHz, CDCl₃): δ 18.4, 55.4, 72.2, 73.4, 79.5, 80.2, 84.7, 107.4, 127.7, 127.8, 127.83, 128.5, 138.2, 138.3.

Step 2: Compound **3-2** was dissolved in CH₂Cl₂ and was treated with DAST (4.0 mL, 30.3 mmol) at room temperature. The solution was stirred at room temp overnight. The so-obtained mixture was poured into sat NaHCO₃ (100 mL) and washed with sat NaHCO₃ (1 x 15 mL). The organic layer was further worked up in the usual manner. Silica gel chromatography (1:5 EtOAc-hexanes) gave crude compound **3-3** (0.671 g) that was sufficiently pure for the next step. ¹H NMR (400 MHz, CDCl₃): δ 1.43 (d, 3H, *J* = 22.8 Hz), 3.35 (s, 3H), 3.49 (dd, 1H, *J* = 10.5, 5.4 Hz), 3.55 (dd, 1H, *J* = 10.5, 4.1 Hz), 3.87 (dd, 1H, *J* = 23.5, 7.5 Hz), 4.26 (m, 1H), 4.56 (d, 2H, *J* = 6.9 Hz), 4.66 (d, 2H, *J* = 8.2 Hz), 4.72 (d, 1H, *J* = 10.8 Hz), 7.29–7.36 (m, 10H); ¹³C NMR (100 MHz, CDCl₃): δ 17.0 (d, *J* = 24.4 Hz), 55.2, 77.1, 73.4, 73.8, 77.3, 80.3, 81.2 (d, *J* = 16 Hz), 99.7 (d, *J* = 178.9 Hz), 106.8 (d, *J* = 32.0 Hz), 127.7, 127.8, 128.1, 128.3, 128.5, 128.6, 137.8, 138.3; ¹⁹F NMR (100 MHz, CDCl₃): δ -8.2 (m, 1F).

Step 3: Compound **3-3** (0.39 g, 1.1 mmol) was dissolved in 1:2 EtOH-EtOAc and treated with Pd/C (~0.1 g) and cyclohexene (~1 mL). The mixture was heated to reflux overnight and then filtered through celite. The solvent was removed *in vacuo* and the residue was dissolved in pyridine (~5 mL). To this solution was added benzoyl chloride (0.22 mL, 1.83 mmol) and the mixture was stirred at room temp overnight. The pyridine was removed *in vacuo* and the residue was partitioned between CH₂Cl₂ and sat NaHCO₃ (10.0 mL). The organic phase was dried (Na₂SO₄), filtered, and the solution was concentrated to dryness. Column chromatography provided 0.350 g of pure compound **3-4**. ¹H NMR (400 MHz, CDCl₃): δ 1.53 (d, 3H, *J* = 22.4 Hz), 3.39 (s, 3H), 4.46 (dd, 1H, *J* = 11.6, 4.7 Hz), 4.58 (m, 1H), 4.65 (dd, 1H, *J* = 11.6, 3.9 Hz), 4.87 (d, 1H, *J* = 9.9 Hz), 5.64 (dd, 2H, *J* = 24.1, 7.8 Hz), 7.29–7.36 (m, 10H); ¹⁹F NMR (100 MHz, CDCl₃): δ -7.5 (m, 1F).

Step 4: A solution of bis(trimethylsilyl)-*N*-benzoylcytosine (0.28 g, 0.77 mmol) and compound **3-4** (0.20 g, 0.5 mmol) in 1,2 dichloroethane (2 mL) and toluene (2 mL) was treated with TMSOTf (0.15 mL, 0.77 mmol). After most of the starting material disappeared as judged by TLC, the solution was cooled to room temp, washed with water (1 x 5 mL), brine (1 x 5 mL), dried (Na₂SO₄), filtered, and concentrated to dryness. Flash chromatography followed by crystallization from CH₂Cl₂-hexanes afforded compound **3-5** (68 mg). mp 241 °C; ¹H NMR (400 MHz,

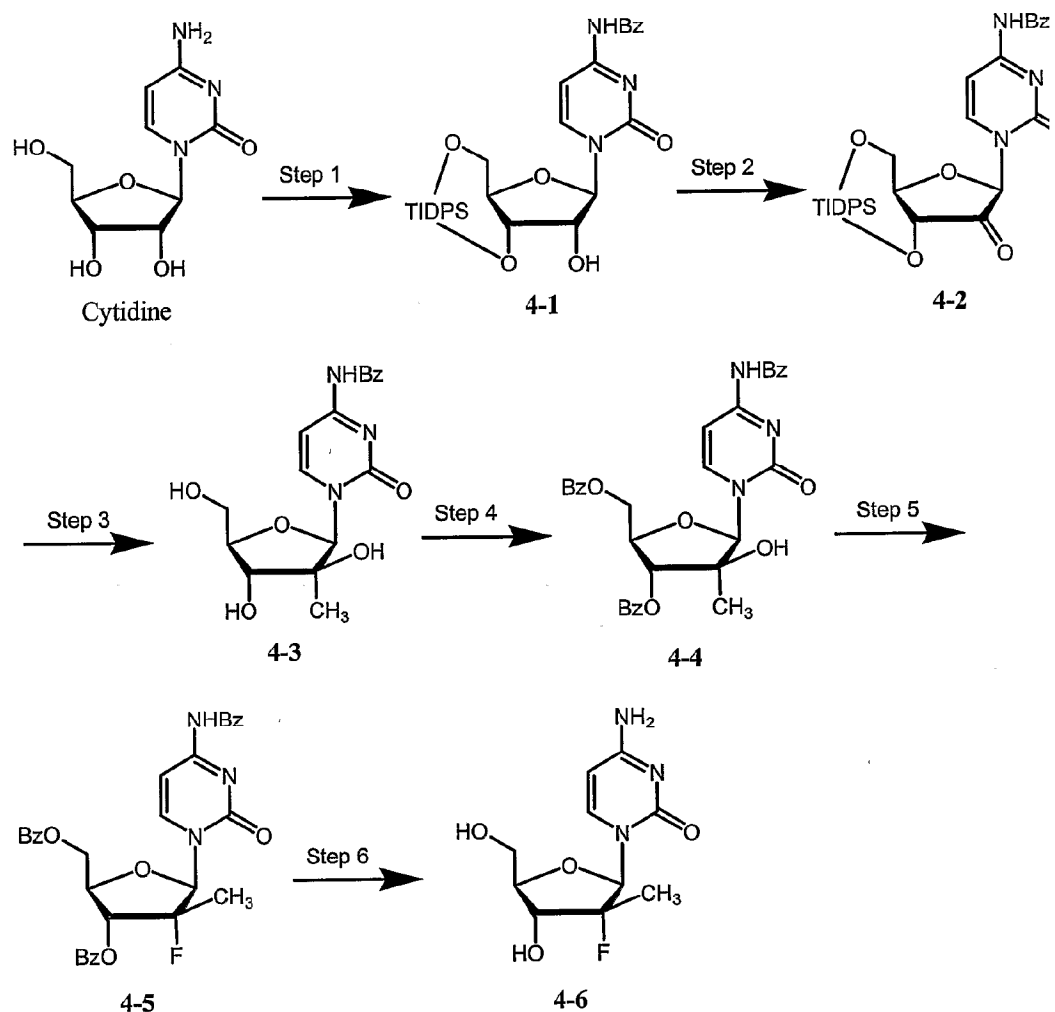
CDCl₃): δ 1.49 (d, 3H, J = 22.4 Hz), 4.64 (dd, 1H, J = 12.9, 3.4 Hz), 4.73 (app d, 1H, J = 9.5 Hz), 4.89 (dd, 1H, J = 12.7, 2.2 Hz), 5.56 (dd, 1H, J = 20.7, 8.6 Hz), 6.52 (d, 1H, J = 15.9 Hz), 7.38–7.67 (m, 10H), 7.89 (d, 2H, J = 6.9 Hz), 8.07–8.11 (m, 5H), 8.67 (s, 1H); ¹⁹F NMR (100 MHz, CDCl₃): δ 2.85 (m, 1F).

5 **Step 5:** Compound **3-5** (40 mg, 0.05 mmol) was dissolved in methanolic ammonia and stirred at room temp for 48 h. The solution was concentrated to dryness and chromatographed (SiO₂) eluting with 1:4 EtOH-CH₂Cl₂. The yield was about 12 mg of pure (2'*R*)-2'-deoxy-2'-fluoro-2'-C-methylcytidine, **3-6**. ¹H NMR (400 MHz, DMSO-d₆): δ 1.16 (d, 3H, J = 22.0 Hz), 3.61 (dd, 1H, J = 11.6, 5.2 Hz),
10 3.60–3.83 (m, 3H, J = 10.5, 5.4 Hz), 5.24 (s, 1H, exchangeable with D₂O), 5.59 (s, 1H, exchangeable with D₂O), 5.71 (d, 1H, J = 7.3 Hz), 6.08 (d, 1H, J = 19.0 Hz), 7.24 (d, 1H, J = 17.7 Hz, exchangeable with D₂O), 7.87 (d, 1H); ¹⁹F NMR (100 MHz, DMSO-d₆): δ 4.13 (m, 1F).

Example 2

15 *Synthesis of (2'*R*)-2'-Deoxy-2'-Fluoro-2'-C-Methylcytidine Starting from Cytidine*

Scheme 4



TIDPS = 1,3-(1,1,3,3-Tetraisopropylidisiloxanylidene)

5 **Step 1:** To a suspension of cytidine (100 g, 0.411 mol) in DMF (2.06 L) is added benzoic anhydride (102.4 g, 0.452 mol). The mixture was stirred at room temperature for 20 h. The DMF was removed *in vacuo* and the residue was triturated with diethyl ether. The resulting solid was collected by suction filtration and washed with diethyl ether (2 x 200 mL). Further drying *in vacuo* at room
10 temperature gave the N⁴ benzamide (140.6 g, 98.3%). A portion of this material

(139.3 g, 0.401 mol) was dissolved in anhydrous pyridine (1.2 L) and was treated with 1,3-dichloro-1,1,3,3-tetraisopropyl-disiloxane (141.4 mL, 0.441 mol) at room temp. The solution was stirred at room temperature overnight. The mixture was concentrated to near dryness *in vacuo* and coevaporated with toluene (3 x 200 mL).
5 The residue was treated with EtOAc (1.8 L) and washed with HCl (2 x 200 mL, 0.05 N), NaHCO₃ (5 %, 2 x 400 mL). The organic layer was washed dried (Na₂SO₄), filtered, and evaporated to dryness. Compound **4-1** (256.5 g, >100%) was isolated as a white foam and used without further purification.

Step 2: Compound **4-1** (236.5 g, 0.40 mol) was dissolved in dry THF (1.22 L). Anhydrous dmso (180.8 mL, 2.1 mol) was added and the resulting solution was cooled to between -20 °C and -15 °C. Trifluoroacetic anhydride (90.6 mL, 0.64 mol) was added dropwise over 45 minutes and the solution was stirred between -20 °C and -15 °C for 2 hrs after which anhydrous triethylamine (223.5 mL, 1.6 mol) was added over 20 min. The crude reaction containing ketone **4-2** was dissolved in
15 EtOAc (500 mL), and the resulting solution was washed with H₂O (3 x 400 mL), dried (Na₂SO₄) and the solvents were removed *in vacuo* to give a yellow solid that was purified on a silica gel column eluting with a stepwise gradient of Et₂O (0–60%) in hexanes followed by a stepwise gradient of EtOAc (50–100%) in hexanes. The crude ketone so-obtained (~192 g) was crystallized from petroleum ether to give
20 ketone **4-2** (138.91 g, 57.5% from cytidine) as a white solid and 22 g of unreacted starting material, **4-1**, as a yellow solid.

Step 3: Compound **4-2** (48.57 g, 8.26 mmol) was dissolved in anhydrous toluene (~400 mL) and the solvent was removed *in vacuo* with exclusion of moisture. The residue was then further dried *in vacuo* (oil pump) for another 2 h.
25 With strict exclusion of moisture, the residual foam was dissolved in anhydrous diethyl ether (1.03 L) under argon. The resulting solution was cooled to -78 °C under argon and MeLi (1.6 M, 258.0 mL, 0.413 mol) was added dropwise *via* additional funnel. After the addition was complete, the mixture was stirred for 2 h at -78 °C. Aqueous 1 M NH₄Cl (500 mL) was added slowly. After warming to room
30 temperature, the mixture was washed with H₂O (2 x 500 mL), dried (Na₂SO₄), and then concentrated to dryness to give a brown foam (~60 g, >100%).

The reaction was performed two more times using 37.62 g and 56.4 g of compound 4-2. The combined crude products (128.0 g, 0.212 mol) were dissolved in THF (1.28 L) and treated with concd HOAc (23 mL, 0.402 mol). To the solution was added TBAF (384.0 mL, 1 M in THF). The solution was stirred at room temp
5 for 0.75 h and the mixture was treated with silica gel (750 g) and concentrated to dryness. The powder was placed on a silica gel column packed in CH₂Cl₂. Elution with 1:7 EtOH-CH₂Cl₂ afforded a dark waxy solid that was pre-adsorbed on silica gel (300 g) and chromatographed as before. Compound 4-3 (46.4 g, 53.0 % from 4-2) was isolated as an off-white solid. ¹H NMR (DMSO-d₆): δ 1.20 (s, 3H, CH₃),
10 3.62–3.69 (m, 2H), 3.73–3.78 (m, 2H), 5.19 (t, 1H, *J* = 5.4 Hz, OH-5'), 5.25 (s, 1H, OH-2'), 5.52 (d, 1H, *J* = 5.0 Hz, OH-3'), 5.99 (s, 1H, H-1'), 7.32 (d, 1H, *J* = 5.8 Hz), 7.50 (Ψt, 2H, *J* = 7.7 Hz), 7.62 (Ψt, 1H, *J* = 7.3 Hz), 8.00 (d, 2H, *J* = 7.3 Hz), 8.14 (d, 1H, *J* = 6.9 Hz), 11.22 (s, 1H, NH). Anal. Calcd for C₁₇H₁₉N₃O₆ • 0.5 H₂O: C, 55.13; H, 5.44; N, 11.35. Found: C, 55.21; H, 5.47; N, 11.33.

15 **Step 4:** Compound 4-3 (46.0 g, 0.13 mol) was dissolved in anhydrous pyridine and concentrated to dryness *in vacuo*. The resulting syrup was dissolved in anhydrous pyridine under argon and cooled to 0 °C with stirring. The brown solution was treated with benzoyl chloride (30 mL, 0.250 mol) dropwise over 10 min. The ice bath was removed and stirring continued for 1.5 h whereby TLC
20 showed no remaining starting material. The mixture was quenched by the addition of water (5 mL) and concentrated to dryness. The residue was dissolved in a minimal amount of CH₂Cl₂ and washed with satd NaHCO₃ (1 x 500 mL) and H₂O (1 x 500 mL). The organic phase was dried (Na₂SO₄) and filtered, concentrated to dryness and chromatographed on silica gel eluting with a stepwise gradient of
25 EtOAc-hexanes (25-60%) to provide compound 4-4 as yellow foam (48.5 g, 67%). ¹H NMR (CDCl₃): δ 1.64 (s, 3H, CH₃), 4.50 (m, 1H, H-4), 4.78–4.85 (m, 2H, H-5', 5a'), 5.50 (d, 1H, *J* = 3.4 Hz, H-3'), 6.42 (s, 1H, H-1'), 7.44–7.54 (m, 7H, Ar), 7.57–7.66 (m, 3H, Ar), 7.94 (d, 2H, *J* = 7.8 Hz), 8.05–8.09 (m, 4H, Ar), 8.21 (d, 1H, *J* = 7.3 Hz). Anal. Calcd for C₃₁H₂₇N₃O₈: C, 65.37; H, 4.78; N, 7.38. Found: C,
30 65.59; H, 4.79; N, 7.16.

Step 5: Compound 4-4 (7.50 g, 0.013 mol) was dissolved in anhydrous toluene (150 mL) under argon and cooled to -20 °C. DAST (2.5 mL, 18.9 mmol)

was added slowly and the cooling bath was removed after the addition was complete. Stirring was continued for 1 h and the mixture was poured into satd NaHCO₃ (100 mL) and washed until gas evolution ceased. The organic phase was dried (Na₂SO₄), concentrated, and purified by silica gel chromatography eluting with 1:1 EtOAc-hexanes. Yield was 1.22 g (16.3%) of pure **4-5** as a white solid. mp 241 °C (CH₂Cl₂-hexanes); ¹H NMR (CDCl₃): δ 1.49 (d, 3H, *J* = 22.4 Hz, CH₃), 4.64 (dd, 1H, *J* = 3.44, 12.9 Hz, H-5'), 4.73 (d, 1H, *J* = 9.5 Hz, H-4'), 4.90 (dd, 1H, *J* = 2.4, 12.7 Hz, H-5a'), 5.56 (dd, 1H, *J* = 8.6, 20.7 Hz, H-3'), 6.52 (d, 1H, *J* = 18.0 Hz, H-1'), 7.47–7.57 (m, 7H, Ar), 7.62–7.71 (m, 3H, Ar), 7.89 (d, 2H, *J* = 6.9 Hz), 8.07–8.11 (m, 5H, Ar), 8.67 (bs, 1H, NH). ¹⁹F NMR (CDCl₃): δ 3.3 (m). Anal. Calcd for C₃₁H₂₆FN₃O₇ • 0.7 H₂O: C, 63.74; H, 4.72; N, 7.20. Found: C, 63.71; H, 4.54; N, 7.20.

Step 6: Compound **4-5** (6.30 g, 0.011 mol) was suspended in methanolic ammonia (*ca* 7 N, 150 mL) and stirred at room temperature overnight. The solvent was removed *in vacuo*, co-evaporated with methanol (1 x 20 mL), and pre-adsorbed onto silica gel. The white powder was placed onto a silica gel column (packed in CHCl₃) and the column was eluted with 9% EtOH in CHCl₃, then 17% EtOH and finally 25% EtOH in CHCl₃. Concentration of the fractions containing the product, filtration through a 0.4 μm disk, and lyophilization from water afforded compound **4-6**, 2.18 g (76%). ¹H NMR (DMSO-d₆): δ 1.17 (d, 3H, *J* = 22.3 Hz, CH₃), 3.63 (dd, 1H, *J* = 2.7, 13.7 Hz, H-5'), 3.70–3.84 (m, 3H, H-3', H-4', H-5a'), 5.24 (app s, 1H, OH-3'), 5.60 (d, 1H, *J* = 5.4 Hz, H-5'), 5.74 (d, 1H, *J* = 7.71 Hz, H-5), 6.07 (d, 1H, *J* = 18.9 Hz, H-1'), 7.31 (s, 1H, NH₂), 7.42 (s, 1H, NH₂), 7.90 (d, 1H, *J* = 7.3 Hz, H-6). ¹⁹F NMR (DMSO-d₆): δ 2.60 (m). Anal. Calcd for C₁₀H₁₄FN₃O₄ • 1.4 H₂O: C, 44.22; H, 5.95; N, 14.77. Found: C, 42.24; H, 5.63; N, 14.54. Compound **4-6** (0.10 g, 0.386 mmol) was converted to the hydrochloride salt by dissolving in water (2 mL) and adjusting the pH to approximately 3.0 with 1 M HCl. The water was removed *in vacuo* and the residue was crystallized from aqueous EtOH to give **4-6** as the hydrochloride salt (71.0 mg). mp 243 °C (dec); ¹H NMR (DMSO-d₆): δ 1.29 (d, 3H, *J* = 22.6 Hz, CH₃), 3.65 (dd, 1H, *J* = 2.3, 12.7 Hz, H-5'), 3.76–3.90 (m, 3H, H-3', H-4', H-5a'), 5.96 (d, 1H, *J* = 17.3 Hz, H-1'), 6.15 (d, 1H, *J* = 7.9 Hz, H-5), 8.33 (d, 1H, *J* = 7.9 Hz, H-6), 8.69 (s, 1.5H, NH), 9.78 (s, 1.5H, NH). ¹⁹F

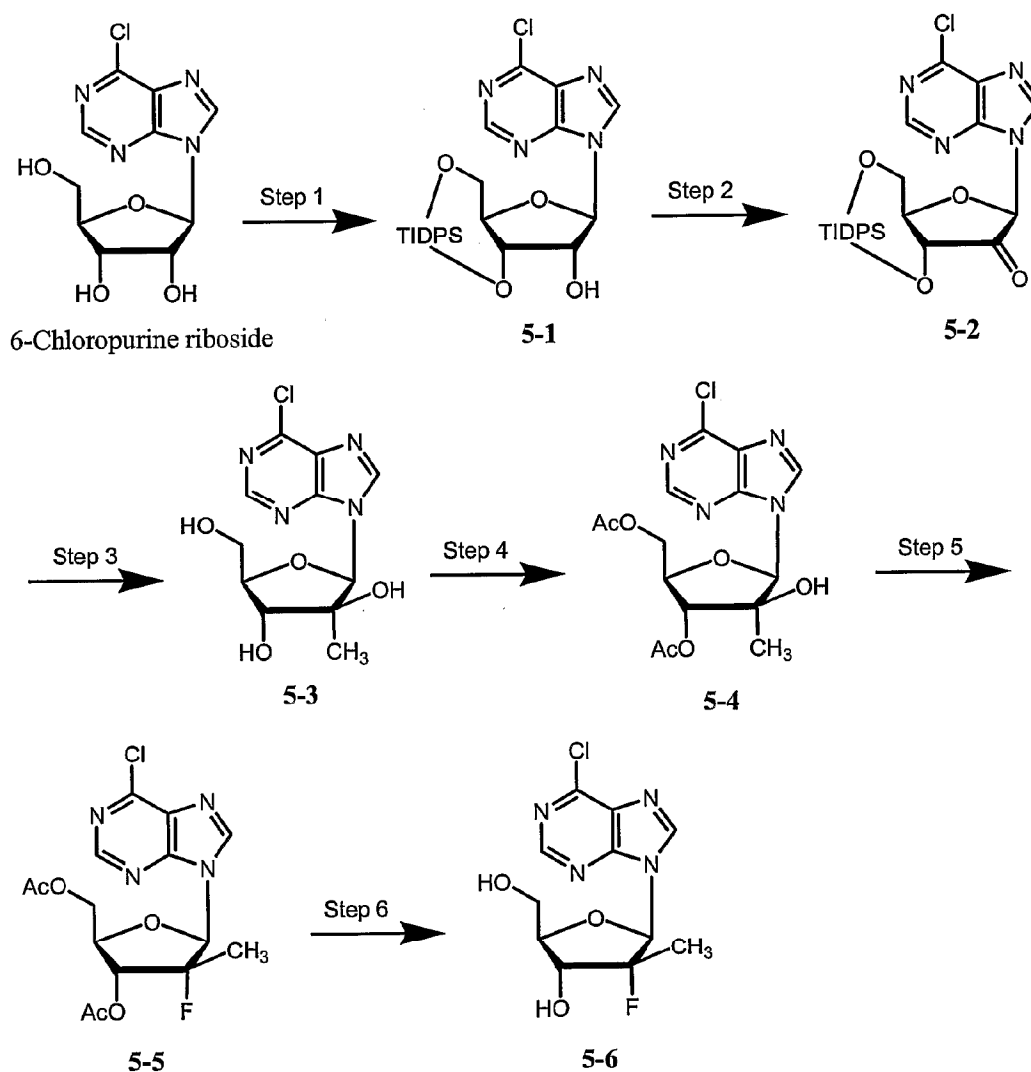
NMR (DMSO- d_6): δ 1.69 (m). Anal. Calcd for $C_{10}H_{14}FN_3O_4 \cdot HCl$: C, 40.62; H, 5.11; N, 14.21. Found: C, 40.80; H, 5.09; N, 14.23.

Example 3

Synthesis of (2'R)-6-Chloro-2'-Deoxy-2'-Fluoro-2'-C-Methylpurine Starting from 6-Chloropurine Riboside.

5

Scheme 5



TIDPS = 1,3-(1,1,3,3-Tetraisopropylidisiloxanylidene)

Step 1: The nucleoside, 6-chloropurine riboside, (3.18 g, 11.09 mmol) was dissolved in anhydrous pyridine (300 mL) and was treated dropwise with 1,3-dichloro-1,1,3,3-tetraisopropyl-disiloxane (4.08 mL, 12.75 mmol) at 0 °C under an argon atmosphere. The solution was brought to room temp and stirred overnight.

5 The mixture was concentrated to near dryness *in vacuo*, dissolved in a minimal amount of chloroform, and washed with HCl (100 mL, 0.05 N) and NaHCO₃ (5%, 100 mL). The organic layer was dried (Na₂SO₄), filtered, and evaporated to dryness to afford compound **5-1** as an amber glass (6.10 g, >100%) that was used without further purification. ¹H NMR (CDCl₃): δ 1.01–1.13 (m, 24H), 4.03–4.18 (m, 3H),

10 4.58 (d, 1H, *J* = 5.2 Hz), 5.01 (m, 1H), 6.07 (s, 1H), 8.31 (s, 1H), 8.71 (s, 1H).

Step 2: Compound **5-1** (7.13 g, 13.47 mmol) was dissolved in dry THF (35 mL). Anhydrous DMSO (5.11 mL, 72.06 mmol) was added and the resulting solution was cooled to between -20°C and -15°C. Trifluoroacetic anhydride (3.06 mL, 21.69 mmol) was added dropwise over 45 minutes and the solution was stirred

15 between -20 °C and -15 °C for 2 hrs after which anhydrous triethylamine (8.08 mL, 57.92 mmol) was added over 20 min. The crude reaction containing ketone **5-2** was dissolved in Et₂O (25 mL), and the resulting solution was washed with H₂O (2 x 50 mL), dried (Na₂SO₄) and the solvents were removed *in vacuo* to give a yellow solid that was purified on a silica gel column eluting with a stepwise stepwise gradient of

20 0–50% petroleum ether-diethyl ether afforded compound **5-2** as a mixture with the corresponding geminal diol. The glass was dissolved in CH₂Cl₂ and stirred over an excess of MgSO₄ for 36 h. The mixture, free from the geminal diol, was filtered, and evaporated to dryness to afford compound **5-2** as an amber glass (7.0 g, 97%). ¹H NMR (CDCl₃): δ 1.01–1.13 (m, 24H), 4.09–4.22 (m, 3H), 5.55 (d, 1H, *J* = 9.6

25 Hz), 5.80 (s, 1H), 8.19 (s, 1H), 8.61 (s, 1H).

Step 3: A solution of compound **5-2** (7.0 g, 13.26 mmol) in anhydrous tetrahydrofuran (45 mL) was cooled to -78 °C with stirring under an argon atmosphere. To the solution was added methylmagnesium bromide (15.85 mL, 3.0 M in ethyl ether) dropwise over a 30 min period. After stirring for an additional 3 h

30 at -78 °C, the reaction was quenched by the careful addition of aqueous 1 M NH₄Cl (50.0 mL). After warming to room temperature, the mixture was washed with H₂O

(2 x 500 mL), dried (Na_2SO_4), and concentrated to dryness to give a brown foam (3.8 g) that was dissolved in tetrahydrofuran (50 mL) and treated with a solution of TBAF (18.9 mL, 1 M solution in THF) and glacial acetic acid (0.85 mL) at room temp. The solution was stirred at room temp for 2h, concentrated to dryness, and
5 purified by silica gel chromatography to give compound **5-3** (2.0 g, 50%).

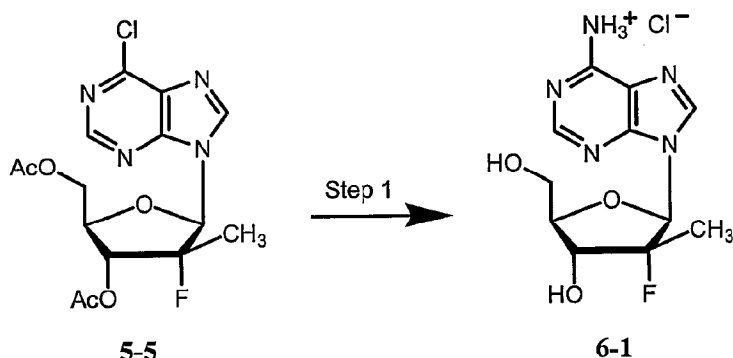
Step 4: Compound **5-3** (0.491 g, 1.63 mmol) was dissolved in pyridine (3 mL) and treated with acetic anhydride (0.38 mL, 4.08 mL) at room temp. The solution was stirred at room temp for 2 h after which time, the solution was concentrated to dryness and treated with diethyl ether (10 mL) and water (5 mL).
10 The organic layer was further washed with water (2 x 10 mL), dried (Na_2SO_4), filtered, and evaporated to dryness to give compound **5-4** as a foam (0.450 g, 91.0%). ^1H NMR (CDCl_3): δ 1.39 (s, 3H), 2.15 (s, 3H), 2.21 (s, 3H), 4.27 (m, 1H), 4.49 (dd, 1H, $J = 4.2, 11.9$ Hz), 4.57 (dd, 1H, $J = 6.16, 11.9$ Hz), 5.14 (d, 1H, $J = 3.1$ Hz), 6.25 (s, 1H), 8.54 (s, 1H), 8.75 (s, 1H).

Step 5: Compound **5-4** (0.100 g, 0.259 mmol) was dissolved in anhydrous toluene (3.0 mL) under argon and cooled to -20°C . DAST (0.2 mL, 1.55 mmol) was added slowly and the cooling bath was removed after the addition was complete. Stirring was continued for 1 h and the mixture was poured into satd NaHCO_3 (100 mL) and washed until gas evolution ceased. The organic phase was
20 dried (Na_2SO_4), concentrated, and purified by silica gel chromatography eluting with 30% Et_2O -petroleum ether gave pure **5-5** (0.028 g, 27.9%). ^1H NMR (CDCl_3): δ 1.24 (d, 3H, $J = 22.8$ Hz), 2.20 (s, 3H), 2.22 (s, 3H), 4.41–4.55 (m, 3H), 4.47 (dd, 1H, $J = 9.2, 22.0$ Hz), 6.37 (d, 1H, $J = 17.6$ Hz), 8.45 (s, 1H), 8.82 (s, 1H).

Step 6: Compound **5-5** (0.018 g, 0.047 mmol) was dissolved in methanol (5 mL) and treated with a solution of sodium methoxide (3.6 mg, 0.67 mmol) in methanol (5 mL). The solution was stirred at room temp for 1 h, neutralized with concd acetic acid and chromatographed on silica gel eluting with a stepwise gradient of Et_2O /methanol (0-5%) to afford compound **5-6** (0.010 g, 70.9%). ^1H NMR (CDCl_3): δ 1.23 (d, 3H, $J = 22.4$ Hz), 4.04 (dd, 1H, $J = 2.11, 12.5$ Hz), 4.17 (dd,
25 1H, $J = 1.5, 9.2$ Hz), 4.25 (dd, 1H, $J = 1.9, 12.3$ Hz), 4.61 (dd, 1H, $J = 9.2, 22.3$ Hz),
30 6.37 (d, 1H, $J = 17.3$ Hz), 8.70 (s, 1H), 8.78 (s, 1H).

Example 4

Synthesis of (2'R)-2'-Deoxy-2'-Fluoro-2'-C-Methyladenosine Starting from (2'R)-6-Chloro-2'-Deoxy-2'-Fluoro-2'-C-Methylpurine

Scheme 6

5

Step 1: Compound **5-5** (0.100 g, 0.26 mmol) was heated in a pressure tube with methanolic ammonia (ca. 7 N, 25 mL) at 80 °C for 12 h. The crude reaction was pre-adsorbed onto silica gel and purified by column chromatography eluting with a stepwise gradient of Et₂O-MeOH (0-5%). The impure product was converted to the hydrochloride salt by dissolving the compound in a minimal amount of ethanol and treating the solution with 0.5 mL of a 0.6 M HCl solution.

Concentration to near dryness gave compound **6-1** as off-white crystals (0.020g, 24.2%). ¹H NMR (CD₃OD): δ 1.19 (d, 3H, *J* = 22.3 Hz), 3.88 (dd, 1H, *J* = 2.7, 12.7 Hz), 4.06 (dd, 1H, *J* = 2.1, 12.5 Hz), 4.11 (app d, 1H, *J* = 9.2 Hz), 4.35 (dd, 1H, *J* = 9.4, 24.5 Hz), 6.35 (d, 1H, *J* = 16.5 Hz), 8.43 (s, 1H), 8.85 (s, 1H).

15

Example 5

Antiviral Activity of (2'R)-2'-Deoxy-2'-Fluoro-2'-C-Methylcytidine

HCV Replicon Assay

The anti-flavivirus activity of the compounds was determined as described by Stuyver, et al. ("Ribonucleoside analogue that blocks replication of bovine viral diarrhea and hepatitis C viruses in culture", *Antimicrobial Agents and Chemotherapy* 47:244-254 (2003)). The compound was dissolved in DMSO and

20

added to the culture media at final concentrations ranging from 3 to 100 μM . A 4-days incubation resulted in dose-dependant reduction of the replicon HCV RNA (Figure 1A). A 1-log reduction of replicon RNA (or EC_{90} value) was reached at approximately 2.5 μM . Measurement of the reduction of rRNA gave an indication of the inhibitory effect on cellular polymerases. Subtraction of this cellular toxicity value from the antiviral values resulted in the therapeutic index line and EC_{90} value. Based on these calculations, an average EC_{90} value, corrected for cellular toxicity, of approximately 2.5 μM was obtained. Figure 1A shows the dose-dependant reduction of the replicon HCV RNA based on the treatment with (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine. The viral reduction was compared to the reduction of cellular RNA levels (ribosomal RNA) to obtain therapeutic index values. EC_{90} represents the effective concentration 90% at 96 hours following the dose dependant administration of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine. Figure 1B shows the prolonged reduction in replicon HCV RNA up to 7 days following treatment with 5 and 25 μM .

The activity of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine in the replicon system is summarized in Table 1. The EC_{90} values for (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine as well as 2'-C-methylcytidine and 2'-C-methyladenosine are shown for three separate replicon clones (HCV-WT (Wild Type), 9-13 and 21-5) as well as two other clones (S282T and rRNA). The EC_{90} values for (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine were in the range of 1.6 to 4.6 μM for the replicon clones. In contrast the EC_{90} values for 2'-C-methylcytidine were in the range of 6.6-37.4 μM . Interestingly, the EC_{90} values for 2'-C-methyladenosine were comparable to those of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine. The activity of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine and 2'-C-methylcytidine in other replicons tested is shown in Table 2.

Polymerase Assay

Table 3 shows the potency of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine-5'-triphosphate (TP) in the NS5B polymerase assay. The inhibitory concentration 50% was determined to be in the range of 1.7 to 7.7 μM .

Toxicity

A summary of the toxicity data for (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine using the mitochondrial toxicity assay is shown in Tables 6 and 7. Table 7 shows the lack of effects of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine and 2'-*C*-methylcytidine on mitochondrial DNA synthesis and lack of effects on lactic acid increase in this assay. Results shows the relative lack of toxicity of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine. Table 6 shows a cytotoxicity analysis in various cell lines (Clone A, Huh7, HepG2, MDBK, PBM, CEM, Vero, MRC-5). Cytotoxic concentration 50% (CC₅₀) was greater than 75-100 μM in all clones tested for (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine as well as 2'-*C*-methylcytidine. In contrast is the relative toxicity of 2'-*C*-methyladenosine.

The effects the nucleoside analogs tested on human bone marrow cells is depicted in Table 9. As shown, the IC₅₀ values for 2'-methyl-2'-fluorocytidine were significantly higher (98.2, BFU-E) and 93.9 (CFU-GM) as compared to 2'-methylcytidine or AZT. Results show that 2'-methyl-2'-fluorocytidine was significantly less toxic than compared to the other nucleoside compounds.

Animal Studies

Figure 2 depicts the average weight change (%) of female Swiss mice in vivo the toxicity analysis of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine at various doses. Intraperitoneal injections were given on days 0 to day 5 of the 0, 3.3, 10, 33, 100 mg/kg. Each dosing group contained 5 mice and no mice died during the 30-day study. No significant toxicity was observed in the mice.

Figure 3 and Table 6 summarize the pharmacokinetic parameters of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine in Rhesus monkeys given a single dose (33.3 mg/kg) oral (Table 6, Figure 3) or intravenous dose (Figure 3) of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine.

Other Antiviral Activity

Summary of the range of antiviral activity of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine is shown in Table 4. Table shows that in addition to HCV virus (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine shows activity against Rhinovirus, West Nile virus, Yellow Fever virus, and Dengue virus.

5 Table 5 shows the lack of activity of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine on HCV surrogate models BVDV as well as other viruses including HIV, HBV and Corona virus. In contrast, 2'-*C*-methylcytidine and 2'-*C*-methyladenosine show greater activity in the HCV surrogate model, BVDV. These results show the necessity for screening this series of compounds against the HCV
10 replicon system versus surrogate HCV systems.

Table 1: Summary of the Anti-HCV Replicon Activity of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine*

Replicon	(2' <i>R</i>)-2'-deoxy-2'-fluoro-2'- <i>C</i> -methylcytidine	2'- <i>C</i> -methylcytidine	2'- <i>C</i> -methyladenosine
HCV-WT 1b	4.6 ± 2.0	21.9 ± 4.3	2.1 ± 0.27
S282T mut. 1b	30.7 ± 11.7	37.4 ± 12.1	>100
9-13 (subgenomic)	4.6 ± 2.3	13.0	0.7
21-5 (full-length)	1.6 ± 0.7	6.6	0.6

* Values represent EC₉₀ (μM)

Table 2: Activity of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine and 2'-C-methylcytidine in other Replicons

Replicon	(2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine			2'-C-methylcytidine		
	EC ₉₀	IC ₉₀		EC ₉₀	IC ₉₀	
	(μ M)	(μM)		(μM)	(μM)	
		GAPDH	MTT		GAPDH	MTT
1b (Ntat)	3.8	>100	>100	27.2	>100	>100
1b (Btat)	11.5	>100	>100	31.1	>100	>100
1a (pp1aSI-7)	34.7	>100	>100	35.0	>100	>100

Table 3: HCV 1b NS5B Polymerase Assay (IC₅₀, μ M)

	(2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine TP	2'-C-methylcytidine TP	2'-C-methyladenosine TP
Wild-Type NS5B	1.7 $\pm$ 0.4 ^a	6.0 $\pm$ 0.5	20.6 $\pm$ 5.2
	7.7 $\pm$ 1.2 ^b		
S282T	2.0 ^a	26.9 $\pm$ 5.5	>100
	8.3 $\pm$ 2.4 ^c		

5 ^a Values determined using batch 1; ^b Value determined using batch 2 and 3; and ^c Value determined using batch 2.

Table 4: Summary of Antiviral Activity of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylecytidine

Virus	Cell	EC ₅₀ , CPE (μ M)	EC ₅₀ , NR ^a (μ M)	CC ₅₀ , CPE (μ M)	CC ₅₀ , NR ^a (μ M)
West Nile	Vero	32	12	>100	32
Dengue Type 2	Vero	32/55	>100/>100	>100	>100
Yellow Fever	Vero	19/3.2	32/12	>100	>100
Influenza A (H1N1)	MDCK	>100	>100	>100	>100
Influenza A (H3N2)	MDCK	>100	>100	>100	>100
Influenza B	MDCK	>100	>100	>100	>100
Rhinovirus Type 2	KB	25	20	>100	>100
VEE	Vero	>100	>100	>100	>100
SARSCoV	Vero	>100	>100	>100	>100

^aNR = Neutral Red.

Table 5: Summary of Antiviral Activity of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylecytidine

Virus	(2'R)-2'-deoxy-2'-fluoro-2'-C-methylecytidine (EC ₉₀ , μ M)	2'-C-methylecytidine (EC ₉₀ , μ M)	2'-C-methyladenosine (EC ₉₀ , μ M)
BVDVncp	>22	0.5	1.2
BVDVcp	>100	2	1.5
RSV	>100	>100	>100
HIV ^a	>100	ND	ND
HBV	>10	>10	ND
Coronavirus 229E	>100	ND	ND

ND = Not determined.

Table 6: Cytotoxicity Studies^a

Cell Line	(2' <i>R</i>)-2'-deoxy-2'-fluoro-2'- <i>C</i> -methylcytidine CC ₅₀ , μ M	2'- <i>C</i> -methylcytidine CC ₅₀ , μ M	2'- <i>C</i> -methyladenosine CC ₅₀ , μ M
CloneA	>100	>100	37
Huh7	>100	>100	30
HepG2	75	>100	58
MDBK	>100	>100	
PBM	>100		
CEM	>100		
Vero	>100		
MRC-5	>100		

^aResults determined using MTS assay.

5

Table 7: Mitochondrial Toxicity Study

Compound	mtDNA Synthesis (IC ₅₀ , μ M)	Lactic Acid Increase
(2' <i>R</i>)-2'-deoxy-2'-fluoro-2'- <i>C</i> -methylcytidine	>25	No effect $\geq 33\mu$ M
2'- <i>C</i> -methylcytidine	>25	No effect $\geq 33\mu$ M

10

Table 8: Preliminary PK Parameters in Rhesus Monkeys Following a Single Oral Dose of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine at 33.3 mg/kg

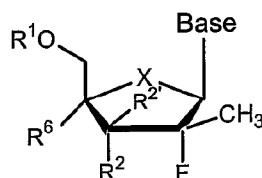
Parameter	Units	Mean $\pm$ SD
C _{max}	μ M	9.6 $\pm$ 2.7
T _{max}	hours	2 $\pm$ 1
AUC _{0-last}	μ Mxh	44.2 $\pm$ 22.2
T 1/2	hours	3.9 $\pm$ 0.1
Bioavailability	F%	21 $\pm$ 11

Table 9: Effect of Nucleoside Analogs on Human Bone Marrow Cells

Compound (β -D-analog)	BFU-E	CFU-GM
	IC ₅₀ (μ M)	
2'-fluoro-2'-C-methylcytidine	98.2	93.9
2'-C-methylcytidine	20.1	13.2
AZT	0.08	0.95

WE CLAIM:

1. A (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D or β -L) of the formula:



5 wherein

Base is a purine or pyrimidine base;

X is O, S, CH₂, Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), C(W)₂,
wherein W is F, Cl, Br, or I;

10 R¹ and R⁷ are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or
15 arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid (or racemic mixture), a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when
20 administered *in vivo* is capable of providing a compound wherein R¹ is H or phosphate; R² is H or phosphate; R¹ and R² or R⁷ can also be linked with cyclic phosphate group;

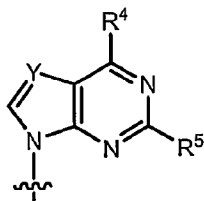
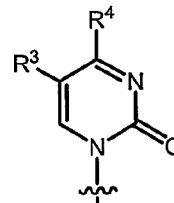
25 R² and R^{2'} are independently H, C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl, vinyl, N₃, CN, Cl, Br, F, I, NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄

alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl),
 SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄
 4 acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkenyl), NH₂, NH(C₁₋₄
 alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl),
 5 N(C₁₋₄ alkyl)₂, N(C₁₋₁₈ acyl)₂, wherein alkyl, alkynyl, alkenyl
 and vinyl are optionally substituted by N₃, CN, one to three
 halogen (Cl, Br, F, I), NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄
 alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄
 acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄
 10 alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄
 alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl),
 SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄
 4 acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkenyl), NH₂, NH(C₁₋₄
 alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl),
 15 N(C₁₋₄ alkyl)₂, N(C₁₋₄ acyl)₂, OR⁷; R² and R^{2'} can be linked
 together to form a vinyl optionally substituted by one or two
 of N₃, CN, Cl, Br, F, I, NO₂; and

R⁶ is an optionally substituted alkyl (including lower alkyl), cyano
 (CN), CH₃, OCH₃, OCH₂CH₃, hydroxy methyl (CH₂OH),
 20 fluoromethyl (CH₂F), azido (N₃), CHCN, CH₂N₃, CH₂NH₂,
 CH₂NHCH₃, CH₂N(CH₃)₂, alkyne (optionally substituted), or
 fluoro;

or its pharmaceutically acceptable salt or prodrug thereof.

2. The (2'*R*)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D or β-L) of
 25 claim 1 or its pharmaceutically acceptable salt or prodrug thereof, wherein Base
 is selected from the group consisting of:



(a)

(b)

wherein

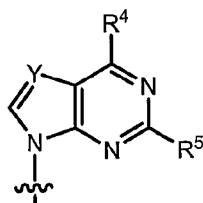
Y is N or CH.

5 R^3 , R^4 and R^5 are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH_2 , NHR' , NR'_2 , lower alkyl of C_1-C_6 , halogenated (F, Cl, Br, I) lower alkyl of C_1-C_6 such as CF_3 and CH_2CH_2F , lower alkenyl of C_2-C_6 such as $CH=CH_2$, halogenated (F, Cl, Br, I) lower alkenyl of C_2-C_6 such as $CH=CHCl$, $CH=CHBr$ and $CH=CHI$, lower alkynyl of C_2-C_6 such as $C\equiv CH$, halogenated (F, Cl, Br, I) lower alkynyl of C_2-C_6 , lower alkoxy of C_1-C_6 such as CH_2OH and CH_2CH_2OH , halogenated (F, Cl, Br, I) lower alkoxy of C_1-C_6 , CO_2H , CO_2R' , $CONH_2$, $CONHR'$, $CONR'_2$, $CH=CHCO_2H$, $CH=CHCO_2R'$; and,

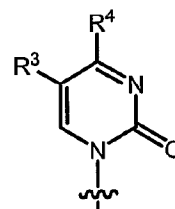
15 R' is an optionally substituted alkyl of C_1-C_{12} (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C_2-C_6 , optionally substituted lower alkenyl of C_2-C_6 , or optionally substituted acyl.

20 3. The (2'*R*)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β -D) of claim 1 or its pharmaceutically acceptable salt or prodrug thereof,

wherein Base is selected from the group consisting of (a) or (b):



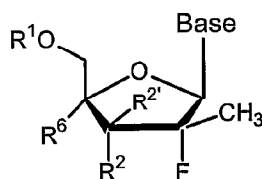
(a)



(b)

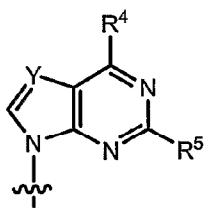
and wherein R^1 is H, R^2 is OH, $R^{2'}$ is H, R^3 is H, and R^4 is NH_2 or OH, and R^5 is NH_2 .

4. A (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D or β -L) of the
5 formula:

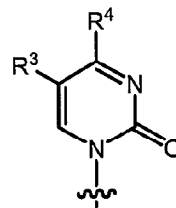


wherein

Base is selected from the group consisting of



(a)



(b)

Y is N or CH;

R^1 and R^7 are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid (or racemic mixture), a carbohydrate, a peptide, a cholesterol, or other

pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R¹ is H or phosphate; R² is H or phosphate; R¹ and R² or R⁷ can also be linked with cyclic phosphate group;

5 R² and R^{2'} are independently H, C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl, vinyl, N₃, CN, Cl, Br, F, I, NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkynyl), NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₁₈ acyl)₂, wherein alkyl, alkynyl, alkenyl and vinyl are optionally substituted by N₃, CN, one to three halogen (Cl, Br, F, I), NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkynyl), NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₄ acyl)₂, OR⁷; R² and R^{2'} can be linked together to form a vinyl optionally substituted by one or two of N₃, CN, Cl, Br, F, I, NO₂;

30 R³, R⁴ and R⁵ are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃ and CH₂CH₂F, lower alkenyl of C₂-C₆ such as CH=CH₂, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆ such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C₂-C₆

5

such as $C\equiv CH$, halogenated (F, Cl, Br, I) lower alkynyl of C_2-C_6 , lower alkoxy of C_1-C_6 such as CH_2OH and CH_2CH_2OH , halogenated (F, Cl, Br, I) lower alkoxy of C_1-C_6 , CO_2H , CO_2R' , $CONH_2$, $CONHR'$, $CONR'_2$, $CH=CHCO_2H$, $CH=CHCO_2R'$;

10

R' is an optionally substituted alkyl of C_1-C_{12} (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C_2-C_6 , optionally substituted lower alkenyl of C_2-C_6 , or optionally substituted acyl;

R^6 is an optionally substituted alkyl (including lower alkyl), cyano (CN), CH_3 , OCH_3 , OCH_2CH_3 , hydroxy methyl (CH_2OH), fluoromethyl (CH_2F), azido (N_3), $CHCN$, CH_2N_3 , CH_2NH_2 , CH_2NHCH_3 , $CH_2N(CH_3)_2$, alkyne (optionally substituted), or fluoro;

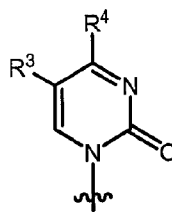
15

or its pharmaceutically acceptable salt or prodrug thereof.

5. The (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D) of claim 4 or its pharmaceutically acceptable salt or prodrug thereof, wherein

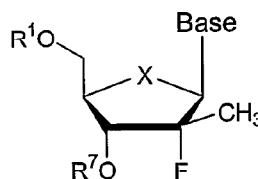
Base is

20



and R^1 is H, R^2 is OH, $R^{2'}$ is H, R^3 is H, R^4 is NH_2 or OH, and R^6 is H.

6. A (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D or β -L) or its pharmaceutically acceptable salt or prodrug thereof of the structure:



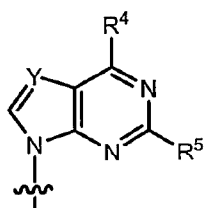
wherein Base is a purine or pyrimidine base;

5 X is O, S, CH₂, Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), C(W)₂, wherein W is F, Cl, Br, or I; and,

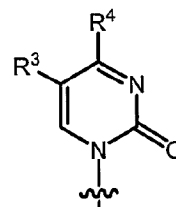
R¹ and R⁷ are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid, a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R¹ or R⁷ is independently H or phosphate; R¹ and R⁷ can also be linked with cyclic phosphate group.

7. The (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D or β -L) of claim 6 or its pharmaceutically acceptable salt or prodrug thereof,

wherein Base is selected from the group consisting of:



(a)



(b)

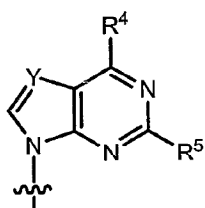
Y is N or CH;

R³, R⁴ and R⁵ are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃ and CH₂CH₂F, lower alkenyl of C₂-C₆ such as CH=CH₂, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆ such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C₂-C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆ such as CH₂OH and CH₂CH₂OH, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, CH=CHCO₂R'; and,

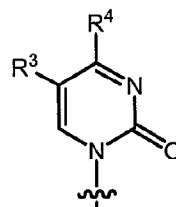
R' is an optionally substituted alkyl of C₁-C₁₂ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C₂-C₆, optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl.

8. The (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β-D) of claim 6 or its pharmaceutically acceptable salt or prodrug thereof,

wherein Base is selected from the group consisting of (a) or (b):



(a)



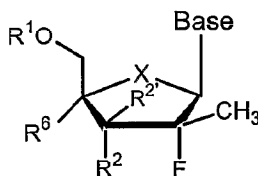
(b)

and wherein R^1 and R^7 are H, R^3 is H, and R^4 is NH_2 or OH , and R^5 is NH_2 .

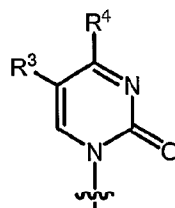
5

9. A (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D or β -L) of the formula:

10



wherein Base is



X is O, S, CH_2 , Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), C(W)_2 ,

15

wherein W is F, Cl, Br, or I;

R^1 and R^7 are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl,

including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid (or racemic mixture), a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R¹ is H or phosphate; R² is H or phosphate; R¹ and R² or R⁷ can also be linked with cyclic phosphate group;

R² and R^{2'} are independently H, C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl, vinyl, N₃, CN, Cl, Br, F, I, NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkenyl), NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₁₈ acyl)₂, wherein alkyl, alkynyl, alkenyl and vinyl are optionally substituted by N₃, CN, one to three halogen (Cl, Br, F, I), NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkenyl), NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₄ acyl)₂, OR⁷; R² and R^{2'} can be linked

together to form a vinyl optionally substituted by one or two of N₃, CN, Cl, Br, F, I, NO₂;

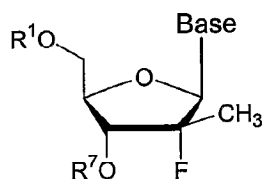
5 R³ and R⁴ are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃ and CH₂CH₂F, lower alkenyl of C₂-C₆ such as CH=CH₂, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆ such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C₂-C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆ such as CH₂OH and CH₂CH₂OH, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, CH=CHCO₂R'; and,

15 R' is an optionally substituted alkyl of C₁-C₁₂ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C₂-C₆, optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl.

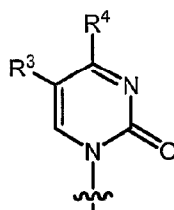
20 R⁶ is an optionally substituted alkyl (including lower alkyl), cyano (CN), CH₃, OCH₃, OCH₂CH₃, hydroxy methyl (CH₂OH), fluoromethyl (CH₂F), azido (N₃), CHCN, CH₂N₃, CH₂NH₂, CH₂NHCH₃, CH₂N(CH₃)₂, alkyne (optionally substituted), or fluoro;

or its pharmaceutically acceptable salt or prodrug thereof.

25 10. A (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D or β-L) of the formula



wherein Base is



- 5 R^1 and R^7 are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its
- 10 peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid (or racemic mixture), a carbohydrate, a peptide, a cholesterol, or other
- 15 pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is H or phosphate; R^2 is H or phosphate; R^1 and R^2 or R^7 can also be linked with cyclic phosphate group;
- 20 R^3 and R^4 are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃ and CH₂CH₂F, lower alkenyl of C₂-C₆ such as CH=CH₂, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆ such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C₂-C₆

such as $C\equiv CH$, halogenated (F, Cl, Br, I) lower alkynyl of C_2 - C_6 , lower alkoxy of C_1 - C_6 such as CH_2OH and CH_2CH_2OH , halogenated (F, Cl, Br, I) lower alkoxy of C_1 - C_6 , CO_2H , CO_2R' , $CONH_2$, $CONHR'$, $CONR'_2$, $CH=CHCO_2H$, $CH=CHCO_2R'$;

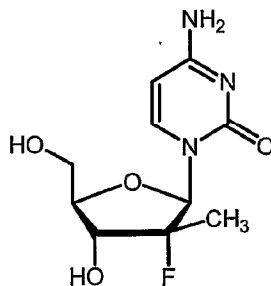
5

R' is an optionally substituted alkyl of C_1 - C_{12} (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C_2 - C_6 , optionally substituted lower alkenyl of C_2 - C_6 , or optionally substituted acyl;

10

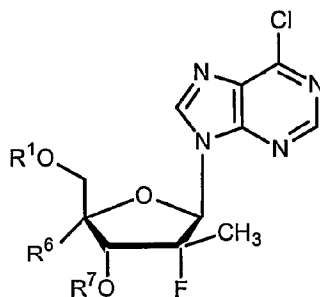
or its pharmaceutically acceptable salt or prodrug thereof.

11. A (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D) or its pharmaceutically acceptable salt or prodrug thereof of the formula:



15

12. A (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D) or its pharmaceutically acceptable salt or prodrug thereof of the formula:



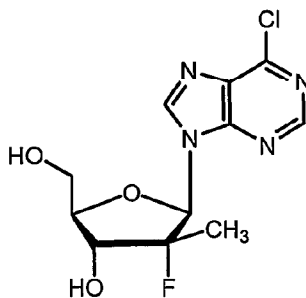
107

wherein

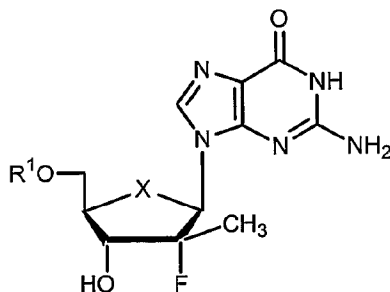
R^1 and R^7 are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid, a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 or R^7 is independently H or phosphate; R^1 and R^7 can also be linked with cyclic phosphate group; and,

R^6 is an optionally substituted alkyl (including lower alkyl), cyano (CN), CH_3 , OCH_3 , OCH_2CH_3 , hydroxy methyl (CH_2OH), fluoromethyl (CH_2F), azido (N_3), $CHCN$, CH_2N_3 , CH_2NH_2 , CH_2NHCH_3 , $CH_2N(CH_3)_2$, alkyne (optionally substituted), or fluoro.

13. A (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D) or its pharmaceutically acceptable salt or prodrug thereof of the formula:



14. A (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D) or its pharmaceutically acceptable salt or prodrug thereof of the formula:



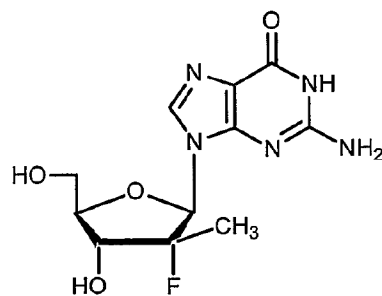
wherein

5 X is O, S, CH₂, Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), C(W)₂, wherein W is F, Cl, Br, or I; and

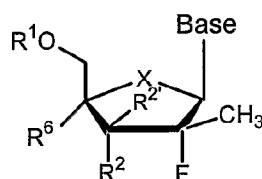
10 R¹ is H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid, a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R¹ is H or phosphate.

20

15. A (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D) or its pharmaceutically acceptable salt or prodrug thereof of the formula:



16. A pharmaceutical composition comprising a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D or β -L) of the formula:



5

wherein

Base is a purine or pyrimidine base;

X is O, S, CH₂, Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), C(W)₂, wherein W is F, Cl, Br, or I;

10

R¹ and R⁷ are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid (or racemic mixture), a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound

15

20

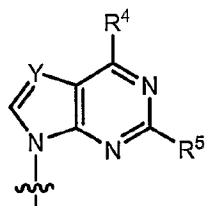
wherein R^1 is H or phosphate; R^2 is H or phosphate; R^1 and R^2 or R^7 can also be linked with cyclic phosphate group;

R^2 and $R^{2'}$ are independently H, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkynyl, vinyl, N_3 , CN, Cl, Br, F, I, NO_2 , $C(O)O(C_{1-4}$ alkyl), $C(O)O(C_{1-4}$ alkyl), $C(O)O(C_{1-4}$ alkynyl), $C(O)O(C_{1-4}$ alkenyl), $O(C_{1-4}$ acyl), $O(C_{1-4}$ alkyl), $O(C_{1-4}$ alkenyl), $S(C_{1-4}$ acyl), $S(C_{1-4}$ alkyl), $S(C_{1-4}$ alkynyl), $S(C_{1-4}$ alkenyl), $SO(C_{1-4}$ acyl), $SO(C_{1-4}$ alkyl), $SO(C_{1-4}$ alkynyl), $SO(C_{1-4}$ alkenyl), $SO_2(C_{1-4}$ acyl), $SO_2(C_{1-4}$ alkyl), $SO_2(C_{1-4}$ alkynyl), $SO_2(C_{1-4}$ alkenyl), $O_3S(C_{1-4}$ acyl), $O_3S(C_{1-4}$ alkyl), $O_3S(C_{1-4}$ alkynyl), NH_2 , $NH(C_{1-4}$ alkyl), $NH(C_{1-4}$ alkenyl), $NH(C_{1-4}$ alkynyl), $NH(C_{1-4}$ acyl), $N(C_{1-4}$ alkyl)₂, $N(C_{1-18}$ acyl)₂, wherein alkyl, alkynyl, alkenyl and vinyl are optionally substituted by N_3 , CN, one to three halogen (Cl, Br, F, I), NO_2 , $C(O)O(C_{1-4}$ alkyl), $C(O)O(C_{1-4}$ alkyl), $C(O)O(C_{1-4}$ alkynyl), $C(O)O(C_{1-4}$ alkenyl), $O(C_{1-4}$ acyl), $O(C_{1-4}$ alkyl), $O(C_{1-4}$ alkenyl), $S(C_{1-4}$ acyl), $S(C_{1-4}$ alkyl), $S(C_{1-4}$ alkynyl), $S(C_{1-4}$ alkenyl), $SO(C_{1-4}$ acyl), $SO(C_{1-4}$ alkyl), $SO(C_{1-4}$ alkynyl), $SO(C_{1-4}$ alkenyl), $SO_2(C_{1-4}$ acyl), $SO_2(C_{1-4}$ alkyl), $SO_2(C_{1-4}$ alkynyl), $SO_2(C_{1-4}$ alkenyl), $O_3S(C_{1-4}$ acyl), $O_3S(C_{1-4}$ alkyl), $O_3S(C_{1-4}$ alkynyl), NH_2 , $NH(C_{1-4}$ alkyl), $NH(C_{1-4}$ alkenyl), $NH(C_{1-4}$ alkynyl), $NH(C_{1-4}$ acyl), $N(C_{1-4}$ alkyl)₂, $N(C_{1-4}$ acyl)₂, OR^7 ; R^2 and $R^{2'}$ can be linked together to form a vinyl optionally substituted by one or two of N_3 , CN, Cl, Br, F, I, NO_2 ;

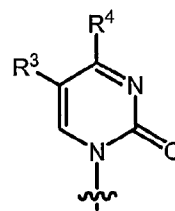
R^6 is an optionally substituted alkyl (including lower alkyl), cyano (CN), CH_3 , OCH_3 , OCH_2CH_3 , hydroxy methyl (CH_2OH), fluoromethyl (CH_2F), azido (N_3), $CHCN$, CH_2N_3 , CH_2NH_2 , CH_2NHCH_3 , $CH_2N(CH_3)_2$, alkyne (optionally substituted), or fluoro;

or its pharmaceutically acceptable salt or prodrug thereof, a pharmaceutically acceptable carrier.

17. The composition of claim 16, wherein Base is selected from the group consisting of:



(a)



(b)

5

wherein

Y is N or CH.

10

R^3 , R^4 and R^5 are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃ and CH₂CH₂F, lower alkenyl of C₂-C₆ such as CH=CH₂, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆ such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C₂-C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆ such as CH₂OH and CH₂CH₂OH, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, CH=CHCO₂R'; and,

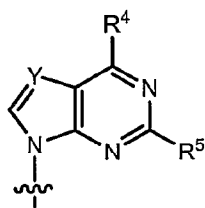
15

20

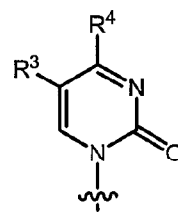
R' is an optionally substituted alkyl of C₁-C₁₂ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C₂-C₆, optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl.

18. The composition of claim 16, wherein

Base is selected from the group consisting of (a) or (b):



(a)

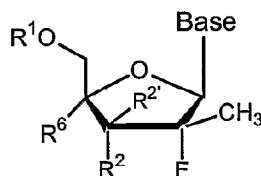


(b)

and wherein R^1 is H, R^2 is OH, $R^{2'}$ is H, R^3 is H, and R^4 is NH_2 or OH, and R^5 is NH_2 .

5

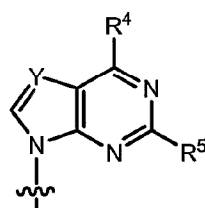
19. A pharmaceutical composition comprising a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D or β -L) of the formula:



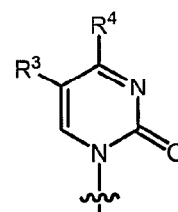
10

wherein

Base is selected from the group consisting of



(a)



(b)

Y is N or CH;

15

R^1 and R^7 are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl,

including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid (or racemic mixture), a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R¹ is H or phosphate; R² is H or phosphate; R¹ and R² or R⁷ can also be linked with cyclic phosphate group;

R² and R^{2'} are independently H, C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl, vinyl, N₃, CN, Cl, Br, F, I, NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkynyl), NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₁₈ acyl)₂, wherein alkyl, alkynyl, alkenyl and vinyl are optionally substituted by N₃, CN, one to three halogen (Cl, Br, F, I), NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkynyl), NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₄ acyl)₂, OR⁷; R² and R^{2'} can be linked together to form a vinyl optionally substituted by one or two of N₃, CN, Cl, Br, F, I, NO₂;

R^3 , R^4 and R^5 are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃ and CH₂CH₂F, lower alkenyl of C₂-C₆ such as CH=CH₂, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆ such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C₂-C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆ such as CH₂OH and CH₂CH₂OH, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, CH=CHCO₂R';

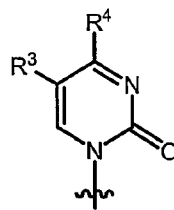
R' is an optionally substituted alkyl of C₁-C₁₂ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C₂-C₆, optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl;

R^6 is an optionally substituted alkyl (including lower alkyl), cyano (CN), CH₃, OCH₃, OCH₂CH₃, hydroxy methyl (CH₂OH), fluoromethyl (CH₂F), azido (N₃), CHCN, CH₂N₃, CH₂NH₂, CH₂NHCH₃, CH₂N(CH₃)₂, alkyne (optionally substituted), or fluoro;

or its pharmaceutically acceptable salt or prodrug thereof in a pharmaceutically acceptable carrier.

20. The composition of claim 19, wherein

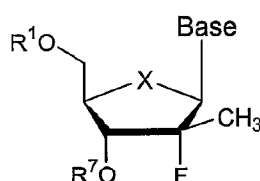
Base is



115

and R¹ is H, R² is OH, R^{2'} is H, R³ is H, R⁴ is NH₂ or OH, and R⁶ is H.

- 5 21. A pharmaceutical composition comprising a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β-D or β-L) or its pharmaceutically acceptable salt or prodrug thereof, in a pharmaceutically acceptable carrier, of the structure:



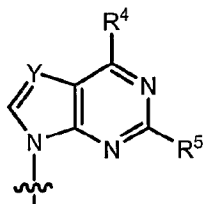
wherein Base is a purine or pyrimidine base;

- 10 X is O, S, CH₂, Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), C(W)₂, wherein W is F, Cl, Br, or I; and,

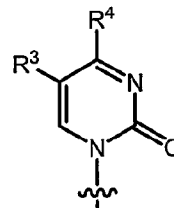
- 15 R¹ and R⁷ are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, 20 including a phospholipid, an L or D-amino acid, a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R¹ or R⁷ is independently H or phosphate; R¹ and R⁷ 25 can also be linked with cyclic phosphate group.

22. The composition of claim 21, wherein

Base is selected from the group consisting of:



(a)



(b)

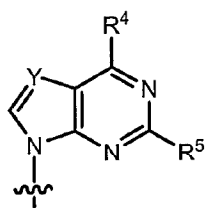
5 Y is N or CH;

10 R^3 , R^4 and R^5 are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃ and CH₂CH₂F, lower alkenyl of C₂-C₆ such as CH=CH₂, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆ such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C₂-C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆ such as CH₂OH and CH₂CH₂OH, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, CH=CHCO₂R'; and,

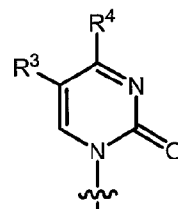
20 R' is an optionally substituted alkyl of C₁-C₁₂ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C₂-C₆, optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl.

23. The composition of claim 21, wherein

Base is selected from the group consisting of (a) or (b):



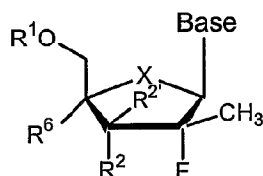
(a)



(b)

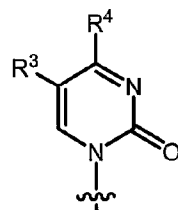
and wherein R^1 and R^7 are H, R^3 is H, and R^4 is NH_2 or OH, and R^5 is NH_2 .

24. A pharmaceutical composition comprising a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D or β -L) of the formula:



wherein

Base is



10

X is O, S, CH_2 , Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), $C(W)_2$, wherein W is F, Cl, Br, or I;

15

R^1 and R^7 are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl,

wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid (or racemic mixture), a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R¹ is H or phosphate; R² is H or phosphate; R¹ and R² or R⁷ can also be linked with cyclic phosphate group;

R² and R^{2'} are independently H, C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl, vinyl, N₃, CN, Cl, Br, F, I, NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkynyl), NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₁₈ acyl)₂, wherein alkyl, alkynyl, alkenyl and vinyl are optionally substituted by N₃, CN, one to three halogen (Cl, Br, F, I), NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkynyl), NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₄ acyl)₂, OR⁷; R² and R^{2'} can be linked together to form a vinyl optionally substituted by one or two of N₃, CN, Cl, Br, F, I, NO₂;

R³ and R⁴ are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃

5 and $\text{CH}_2\text{CH}_2\text{F}$, lower alkenyl of $\text{C}_2\text{-C}_6$ such as $\text{CH}=\text{CH}_2$, halogenated (F, Cl, Br, I) lower alkenyl of $\text{C}_2\text{-C}_6$ such as $\text{CH}=\text{CHCl}$, $\text{CH}=\text{CHBr}$ and $\text{CH}=\text{CHI}$, lower alkynyl of $\text{C}_2\text{-C}_6$ such as $\text{C}\equiv\text{CH}$, halogenated (F, Cl, Br, I) lower alkynyl of $\text{C}_2\text{-C}_6$, lower alkoxy of $\text{C}_1\text{-C}_6$ such as CH_2OH and $\text{CH}_2\text{CH}_2\text{OH}$, halogenated (F, Cl, Br, I) lower alkoxy of $\text{C}_1\text{-C}_6$, CO_2H , $\text{CO}_2\text{R}'$, CONH_2 , CONHR' , CONR'_2 , $\text{CH}=\text{CHCO}_2\text{H}$, $\text{CH}=\text{CHCO}_2\text{R}'$;

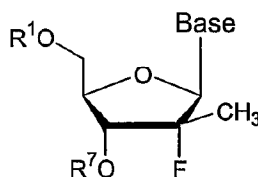
10 R' is an optionally substituted alkyl of $\text{C}_1\text{-C}_{12}$ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of $\text{C}_2\text{-C}_6$, optionally substituted lower alkenyl of $\text{C}_2\text{-C}_6$, or optionally substituted acyl; and

15 R^6 is an optionally substituted alkyl (including lower alkyl), cyano (CN), CH_3 , OCH_3 , OCH_2CH_3 , hydroxy methyl (CH_2OH), fluoromethyl (CH_2F), azido (N_3), CHCN , CH_2N_3 , CH_2NH_2 , CH_2NHCH_3 , $\text{CH}_2\text{N}(\text{CH}_3)_2$, alkyne (optionally substituted), or fluoro;

or its pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable carrier.

20

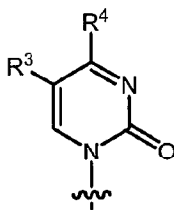
25. A pharmaceutical composition comprising a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside ($\beta\text{-D}$ or $\beta\text{-L}$) of the formula:



25

wherein

Base is



5 R^1 and R^7 are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid,
 10 including a phospholipid, an L or D-amino acid, a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 or R^7 is independently H or phosphate; R^1 and R^7
 15 can also be linked with cyclic phosphate group;

20 R^3 and R^4 are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃ and CH₂CH₂F, lower alkenyl of C₂-C₆ such as CH=CH₂, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆ such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C₂-C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆ such as CH₂OH and CH₂CH₂OH, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H,
 25 CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, CH=CHCO₂R';

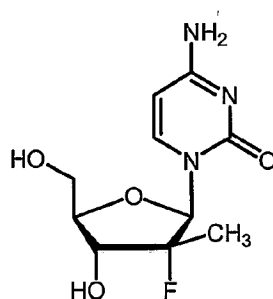
R^2 is an optionally substituted alkyl of C₁-C₁₂ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally

substituted alkynyl of C₂-C₆, optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl;

or its pharmaceutically acceptable salt or prodrug thereof, in a pharmaceutically acceptable carrier.

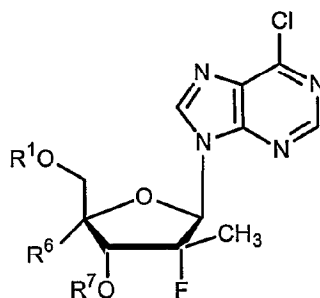
5

26. A pharmaceutical composition comprising a a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D) or its pharmaceutically acceptable salt or prodrug thereof, in a pharmaceutically acceptable carrier of the formula:



10

27. A pharmaceutical composition comprising a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D or β -L), or its pharmaceutically acceptable salt or prodrug thereof, in a pharmaceutically acceptable carrier, of the formula:



15

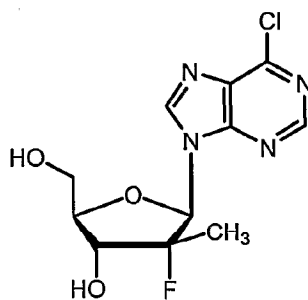
wherein

R¹ and R⁷ are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl,

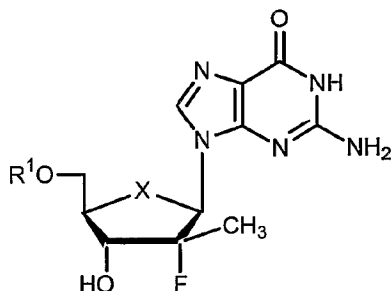
including optionally substituted phenyl and lower acyl, alkyl,
including lower alkyl, O-substituted carboxyalkylamino or its
peptide derivatives, sulfonate ester, including alkyl or
arylalkyl sulfonyl, including methanesulfonyl and benzyl,
5 wherein the phenyl group is optionally substituted, a lipid,
including a phospholipid, an L or D-amino acid, a
carbohydrate, a peptide, a cholesterol, or other
pharmaceutically acceptable leaving group which when
administered *in vivo* is capable of providing a compound
10 wherein R^1 or R^7 is independently H or phosphate; R^1 and R^7
can also be linked with cyclic phosphate group; and,

R^6 is an optionally substituted alkyl (including lower alkyl), cyano
(CN), CH_3 , OCH_3 , OCH_2CH_3 , hydroxy methyl (CH_2OH),
fluoromethyl (CH_2F), azido (N_3), $CHCN$, CH_2N_3 , CH_2NH_2 ,
15 CH_2NHCH_3 , $CH_2N(CH_3)_2$, alkyne (optionally substituted), or
fluoro.

28. A pharmaceutical composition comprising a (2'*R*)-2'-deoxy-2'-fluoro-
2'-C-methyl nucleoside (β -D) or its pharmaceutically acceptable salt or prodrug
20 thereof, in a pharmaceutically acceptable carrier, of the formula:



29. A pharmaceutical composition comprising a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D) or its pharmaceutically acceptable salt or prodrug thereof in a pharmaceutically acceptable carrier of the formula:



5 wherein

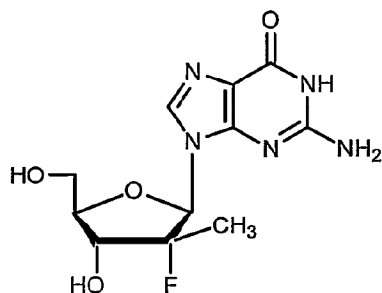
X is O, S, CH₂, Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), C(W)₂, wherein W is F, Cl, Br, or I; and

10 R¹ is H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid, a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound

15

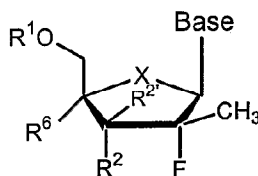
20 wherein R¹ is H or phosphate;

30. A pharmaceutical composition comprising a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D) or its pharmaceutically acceptable salt or prodrug thereof, in a pharmaceutically acceptable carrier, of the structure:



5

31. Use of an an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D or β -L) of the formula:



10

wherein

Base is a purine or pyrimidine base;

X is O, S, CH₂, Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), C(W)₂, wherein W is F, Cl, Br, or I;

15

R¹ and R⁷ are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid,

20

including a phospholipid, an L or D-amino acid (or racemic mixture), a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R¹ is H or phosphate; R² is H or phosphate; R¹ and R² or R⁷ can also be linked with cyclic phosphate group;

R² and R^{2'} are independently H, C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl, vinyl, N₃, CN, Cl, Br, F, I, NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkenyl), NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₁₈ acyl)₂, wherein alkyl, alkynyl, alkenyl and vinyl are optionally substituted by N₃, CN, one to three halogen (Cl, Br, F, I), NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkenyl), NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₄ acyl)₂, OR⁷; R² and R^{2'} can be linked together to form a vinyl optionally substituted by one or two of N₃, CN, Cl, Br, F, I, NO₂;

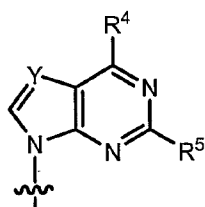
R⁶ is an optionally substituted alkyl (including lower alkyl), cyano (CN), CH₃, OCH₃, OCH₂CH₃, hydroxy methyl (CH₂OH), fluoromethyl (CH₂F), azido (N₃), CHCN, CH₂N₃, CH₂NH₂,

CH_2NHCH_3 , $\text{CH}_2\text{N}(\text{CH}_3)_2$, alkyne (optionally substituted), or fluoro;

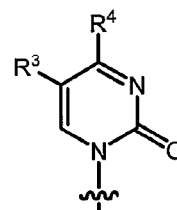
or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of hepatitis C infection in a host.

32. The use of claim 31,

wherein Base is selected from the group consisting of:



(a)



(b)

Y is N or CH.

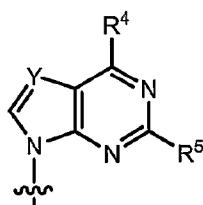
R^3 , R^4 and R^5 are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH_2 , NHR' , NR'_2 , lower alkyl of $\text{C}_1\text{-C}_6$, halogenated (F, Cl, Br, I) lower alkyl of $\text{C}_1\text{-C}_6$ such as CF_3 and $\text{CH}_2\text{CH}_2\text{F}$, lower alkenyl of $\text{C}_2\text{-C}_6$ such as $\text{CH}=\text{CH}_2$, halogenated (F, Cl, Br, I) lower alkenyl of $\text{C}_2\text{-C}_6$ such as $\text{CH}=\text{CHCl}$, $\text{CH}=\text{CHBr}$ and $\text{CH}=\text{CHI}$, lower alkynyl of $\text{C}_2\text{-C}_6$ such as $\text{C}\equiv\text{CH}$, halogenated (F, Cl, Br, I) lower alkynyl of $\text{C}_2\text{-C}_6$, lower alkoxy of $\text{C}_1\text{-C}_6$ such as CH_2OH and $\text{CH}_2\text{CH}_2\text{OH}$, halogenated (F, Cl, Br, I) lower alkoxy of $\text{C}_1\text{-C}_6$, CO_2H , $\text{CO}_2\text{R}'$, CONH_2 , CONHR' , CONR'_2 , $\text{CH}=\text{CHCO}_2\text{H}$, $\text{CH}=\text{CHCO}_2\text{R}'$; and,

R' is an optionally substituted alkyl of C₁-C₁₂ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C₂-C₆, optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl.

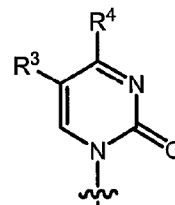
5

33. The use of claim 31, wherein

Base is selected from the group consisting of (a) or (b):



(a)



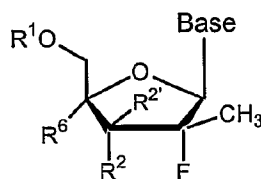
(b)

10

and wherein R¹ is H, R² is OH, R^{2'} is H, R³ is H, and R⁴ is NH₂ or OH, and R⁵ is NH₂.

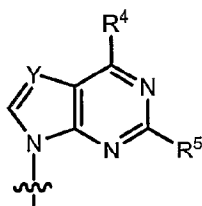
34. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D or β-L) of the formula:

15

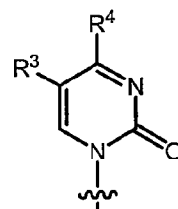


wherein

Base is selected from the group consisting of



(a)



(b)

and wherein Y is N or CH;

R¹ and R⁷ are independently H, phosphate, including monophosphate,
 5 diphosphate, triphosphate, or a stabilized phosphate prodrug,
 H-phosphonate, including stabilized H-phosphonates, acyl,
 including optionally substituted phenyl and lower acyl, alkyl,
 including lower alkyl, O-substituted carboxyalkylamino or its
 10 peptide derivatives, sulfonate ester, including alkyl or
 arylalkyl sulfonyl, including methanesulfonyl and benzyl,
 wherein the phenyl group is optionally substituted, a lipid,
 including a phospholipid, an L or D-amino acid (or racemic
 mixture), a carbohydrate, a peptide, a cholesterol, or other
 pharmaceutically acceptable leaving group which when
 15 administered *in vivo* is capable of providing a compound
 wherein R¹ is H or phosphate; R² is H or phosphate; R¹ and
 R² or R⁷ can also be linked with cyclic phosphate group;

R² and R²¹ are independently H, C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl,
 vinyl, N₃, CN, Cl, Br, F, I, NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄
 20 alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄
 acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄
 alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄
 alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl),
 SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄
 25 acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkenyl), NH₂, NH(C₁₋₄
 alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl),
 N(C₁₋₄ alkyl)₂, N(C₁₋₁₈ acyl)₂, wherein alkyl, alkynyl, alkenyl
 and vinyl are optionally substituted by N₃, CN, one to three

5 halogen (Cl, Br, F, I), NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkynyl), NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₄ acyl)₂, OR⁷; R² and R^{2'} can be linked together to form a vinyl optionally substituted by one or two of N₃, CN, Cl, Br, F, I, NO₂;

15 R³, R⁴ and R⁵ are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃ and CH₂CH₂F, lower alkenyl of C₂-C₆ such as CH=CH₂, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆ such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C₂-C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆ such as CH₂OH and CH₂CH₂OH, 20 halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, CH=CHCO₂R';

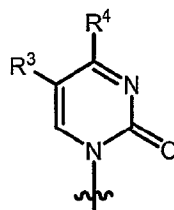
25 R' is an optionally substituted alkyl of C₁-C₁₂ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C₂-C₆, optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl;

30 R⁶ is an optionally substituted alkyl (including lower alkyl), cyano (CN), CH₃, OCH₃, OCH₂CH₃, hydroxy methyl (CH₂OH), fluoromethyl (CH₂F), azido (N₃), CHCN, CH₂N₃, CH₂NH₂, CH₂NHCH₃, CH₂N(CH₃)₂, alkyne (optionally substituted), or fluoro;

or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of hepatitis C infection in a host.

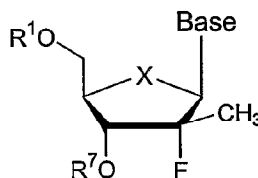
5 35. The use of claim 34, wherein

Base is



10 and R¹ is H, R² is OH, R^{2'} is H, R³ is H, R⁴ is
NH₂ or OH, and R⁶ is H.

36. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β-D or β-L) of the structure:



15 wherein Base is a purine or pyrimidine base;

X is O, S, CH₂, Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), C(W)₂,
wherein W is F, Cl, Br, or I; and,

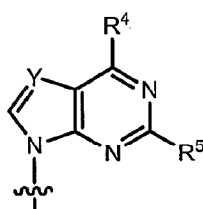
20 R¹ and R⁷ are independently H, phosphate, including monophosphate,
diphosphate, triphosphate, or a stabilized phosphate prodrug,
H-phosphonate, including stabilized H-phosphonates, acyl,
including optionally substituted phenyl and lower acyl, alkyl,

including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid, a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 or R^7 is independently H or phosphate; R^1 and R^7 can also be linked with cyclic phosphate group; and

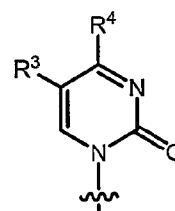
or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of hepatitis C infection in a host.

37. The use of claim 36, wherein

Base is selected from the group consisting of:



(a)



(b)

Y is N or CH;

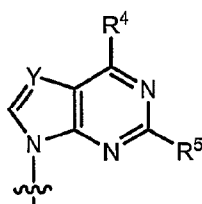
R^3 , R^4 and R^5 are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃ and CH₂CH₂F, lower alkenyl of C₂-C₆ such as CH=CH₂, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆ such as

CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C₂-C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆ such as CH₂OH and CH₂CH₂OH, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, CH=CHCO₂R'; and,

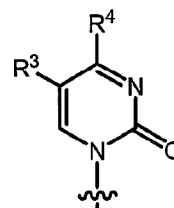
R' is an optionally substituted alkyl of C₁-C₁₂ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C₂-C₆, optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl.

38. The use of claim 36, wherein

Base is selected from the group consisting of (a) or (b):



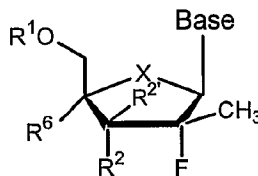
(a)



(b)

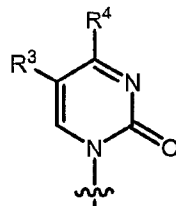
and wherein R¹ and R⁷ are H, R³ is H, and R⁴ is NH₂ or OH, and R⁵ is NH₂.

39. Use of an antivirally effective amount of a (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D or β-L) of the formula:



wherein

Base is



5 X is O, S, CH₂, Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), C(W)₂,
wherein W is F, Cl, Br, or I;

10 R¹ and R⁷ are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid (or racemic mixture), a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R¹ is H or phosphate; R² is H or phosphate; R¹ and R² or R⁷ can also be linked with cyclic phosphate group;

20 R² and R²¹ are independently H, C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl, vinyl, N₃, CN, Cl, Br, F, I, NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkenyl), NH₂, NH(C₁₋₄

alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl),
 N(C₁₋₄ alkyl)₂, N(C₁₋₁₈ acyl)₂, wherein alkyl, alkynyl, alkenyl
 and vinyl are optionally substituted by N₃, CN, one to three
 halogen (Cl, Br, F, I), NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄
 5 alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄
 acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄
 alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄
 alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl),
 SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄
 10 acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkenyl), NH₂, NH(C₁₋₄
 alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl),
 N(C₁₋₄ alkyl)₂, N(C₁₋₄ acyl)₂, OR⁷; R² and R^{2'} can be linked
 together to form a vinyl optionally substituted by one or two
 of N₃, CN, Cl, Br, F, I, NO₂;

15 R³ and R⁴ are independently H, halogen including F, Cl, Br, I, OH,
 OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆,
 halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃
 and CH₂CH₂F, lower alkenyl of C₂-C₆ such as CH=CH₂,
 halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆ such as
 20 CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C₂-C₆
 such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-
 C₆, lower alkoxy of C₁-C₆ such as CH₂OH and CH₂CH₂OH,
 halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H,
 CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H,
 25 CH=CHCO₂R';

R' is an optionally substituted alkyl of C₁-C₁₂ (particularly when the
 alkyl is an amino acid residue), cycloalkyl, optionally
 substituted alkynyl of C₂-C₆, optionally substituted lower
 alkenyl of C₂-C₆, or optionally substituted acyl;

30 R⁶ is an optionally substituted alkyl (including lower alkyl), cyano
 (CN), CH₃, OCH₃, OCH₂CH₃, hydroxy methyl (CH₂OH),

fluoromethyl (CH_2F), azido (N_3), CHCN , CH_2N_3 , CH_2NH_2 , CH_2NHCH_3 , $\text{CH}_2\text{N}(\text{CH}_3)_2$, alkyne (optionally substituted), or fluoro;

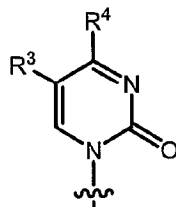
5 or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier for the treatment or prophylaxis of hepatitis C infection in a host

40. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D or β -L) of the formula:



wherein

Base is



15 R^1 and R^7 are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or

20 arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid, a

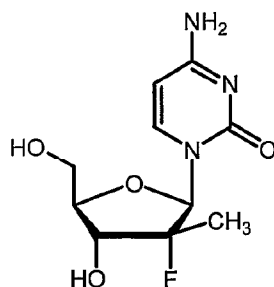
carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R¹ or R⁷ is independently H or phosphate; R¹ and R⁷ can also be linked with cyclic phosphate group;

R³ and R⁴ are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃ and CH₂CH₂F, lower alkenyl of C₂-C₆ such as CH=CH₂, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆ such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C₂-C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆ such as CH₂OH and CH₂CH₂OH, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, CH=CHCO₂R';

R' is an optionally substituted alkyl of C₁-C₁₂ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C₂-C₆, optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl.

or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of hepatitis C infection in a host

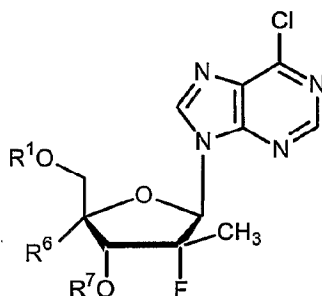
41. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β-D) of the formula:



or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier for the treatment or prophylaxis of hepatitis C infection in a host.

5

42. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D) of the formula:



wherein

10

R^1 and R^7 are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid, a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when

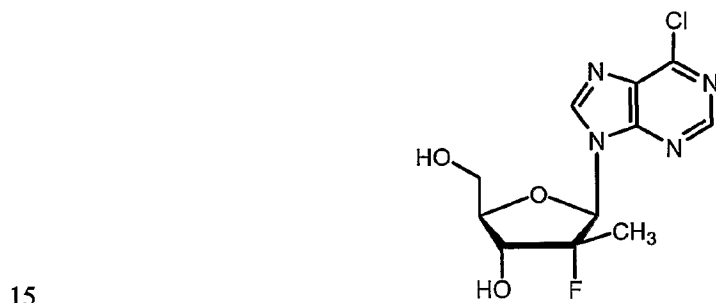
20

administered *in vivo* is capable of providing a compound wherein R¹ or R⁷ is independently H or phosphate; R¹ and R⁷ can also be linked with cyclic phosphate group; and,

5 R⁶ is an optionally substituted alkyl (including lower alkyl), cyano (CN), CH₃, OCH₃, OCH₂CH₃, hydroxy methyl (CH₂OH), fluoromethyl (CH₂F), azido (N₃), CHCN, CH₂N₃, CH₂NH₂, CH₂NHCH₃, CH₂N(CH₃)₂, alkyne (optionally substituted), or fluoro;

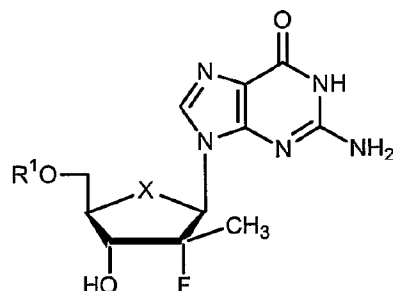
10 or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier for the treatment or prophylaxis of hepatitis C infection in a host

43. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D) of the formula:



or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of hepatitis C infection in a host

20 44. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D) of the formula:



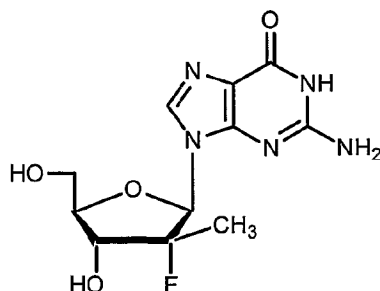
wherein

X is O, S, CH₂, Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), C(W)₂,
wherein W is F, Cl, Br, or I; and

5 R¹ is H, phosphate, including monophosphate, diphosphate,
triphosphate, or a stabilized phosphate prodrug, H-
phosphonate, including stabilized H-phosphonates, acyl,
including optionally substituted phenyl and lower acyl, alkyl,
including lower alkyl, O-substituted carboxyalkylamino or its
10 peptide derivatives, sulfonate ester, including alkyl or
arylalkyl sulfonyl, including methanesulfonyl and benzyl,
wherein the phenyl group is optionally substituted, a lipid,
including a phospholipid, an L or D-amino acid, a
carbohydrate, a peptide, a cholesterol, or other
15 pharmaceutically acceptable leaving group which when
administered *in vivo* is capable of providing a compound
wherein R¹ is H or phosphate;

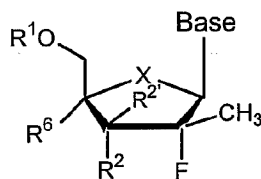
or its pharmaceutically acceptable salt or prodrug thereof, optionally in a
pharmaceutically acceptable carrier, for the treatment or prophylaxis of hepatitis C
20 infection in a host

45. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-
2'-C-methyl nucleoside (β-D) of the formula:



or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of hepatitis C infection in a host.

- 5 46. A method for the treatment or prophylaxis of a rhinovirus infection comprising administering to a host an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D or β -L) of the formula:



wherein

- 10 Base is a purine or pyrimidine base;

X is O, S, CH₂, Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), C(W)₂,
wherein W is F, Cl, Br, or I;

- 15 R¹ and R⁷ are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid (or racemic mixture), a carbohydrate, a peptide, a cholesterol, or other
- 20

pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R¹ is H or phosphate; R² is H or phosphate; R¹ and R² or R⁷ can also be linked with cyclic phosphate group;

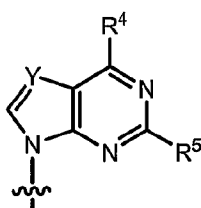
5 R² and R^{2'} are independently H, C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl, vinyl, N₃, CN, Cl, Br, F, I, NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkenyl), NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₁₈ acyl)₂, wherein alkyl, alkynyl, alkenyl and vinyl are optionally substituted by N₃, CN, one to three halogen (Cl, Br, F, I), NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkenyl), NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₄ acyl)₂, OR⁷; R² and R^{2'} can be linked together to form a vinyl optionally substituted by one or two of N₃, CN, Cl, Br, F, I, NO₂;

15 R⁶ is an optionally substituted alkyl (including lower alkyl), cyano (CN), CH₃, OCH₃, OCH₂CH₃, hydroxy methyl (CH₂OH), fluoromethyl (CH₂F), azido (N₃), CHCN, CH₂N₃, CH₂NH₂, CH₂NHCH₃, CH₂N(CH₃)₂, alkyne (optionally substituted), or fluoro;

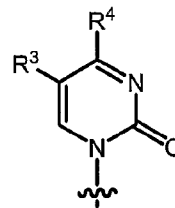
or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier.

47. The method of claim 46,

5 wherein Base is selected from the group consisting of:



(a)



(b)

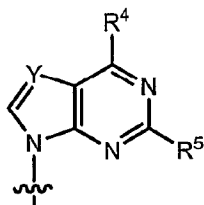
Y is N or CH.

10 R³, R⁴ and R⁵ are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃ and CH₂CH₂F, lower alkenyl of C₂-C₆ such as CH=CH₂, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆ such as
15 CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C₂-C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆ such as CH₂OH and CH₂CH₂OH, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H,
20 CH=CHCO₂R'; and,

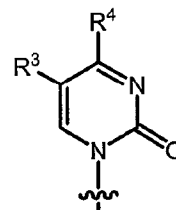
wherein R' is an optionally substituted alkyl of C₁-C₁₂ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C₂-C₆, optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl.

48. The method of claim 46, wherein

Base is selected from the group consisting of (a) or (b):



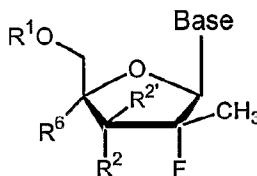
(a)



(b)

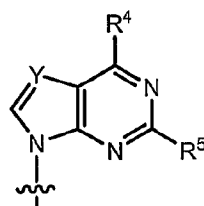
and wherein R^1 is H, R^2 is OH, $R^{2'}$ is H, R^3 is H,
and R^4 is NH_2 or OH, and R^5 is NH_2 .

49. A method for the treatment or prophylaxis of a rhinovirus infection
comprising administering to a host an antivirally effective amount of a (2'R)-2'-
deoxy-2'-fluoro-2'-C-methyl nucleoside (β -D or β -L) of the formula:

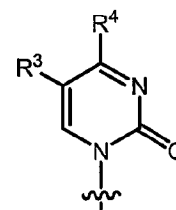


wherein

Base is selected from the group consisting of



(a)



(b)

and wherein Y is N or CH;

R¹ and R⁷ are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid (or racemic mixture), a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R¹ is H or phosphate; R² is H or phosphate; R¹ and R² or R⁷ can also be linked with cyclic phosphate group;

R² and R^{2'} are independently H, C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl, vinyl, N₃, CN, Cl, Br, F, I, NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkenyl), NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₁₈ acyl)₂, wherein alkyl, alkynyl, alkenyl and vinyl are optionally substituted by N₃, CN, one to three halogen (Cl, Br, F, I), NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋

4 acyl), $O_3S(C_{1-4} \text{ alkyl})$, $O_3S(C_{1-4} \text{ alkenyl})$, NH_2 , $NH(C_{1-4} \text{ alkyl})$, $NH(C_{1-4} \text{ alkenyl})$, $NH(C_{1-4} \text{ alkynyl})$, $NH(C_{1-4} \text{ acyl})$, $N(C_{1-4} \text{ alkyl})_2$, $N(C_{1-4} \text{ acyl})_2$, OR^7 ; R^2 and $R^{2'}$ can be linked together to form a vinyl optionally substituted by one or two of N_3 , CN , Cl , Br , F , I , NO_2 ;

R^3 , R^4 and R^5 are independently H , halogen including F , Cl , Br , I , OH , OR' , SH , SR' , NH_2 , NHR' , NR'_2 , lower alkyl of C_1-C_6 , halogenated (F , Cl , Br , I) lower alkyl of C_1-C_6 such as CF_3 and CH_2CH_2F , lower alkenyl of C_2-C_6 such as $CH=CH_2$, halogenated (F , Cl , Br , I) lower alkenyl of C_2-C_6 such as $CH=CHCl$, $CH=CHBr$ and $CH=CHI$, lower alkynyl of C_2-C_6 such as $C\equiv CH$, halogenated (F , Cl , Br , I) lower alkynyl of C_2-C_6 , lower alkoxy of C_1-C_6 such as CH_2OH and CH_2CH_2OH , halogenated (F , Cl , Br , I) lower alkoxy of C_1-C_6 , CO_2H , CO_2R' , $CONH_2$, $CONHR'$, $CONR'_2$, $CH=CHCO_2H$, $CH=CHCO_2R'$;

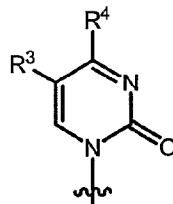
R' is an optionally substituted alkyl of C_1-C_{12} (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C_2-C_6 , optionally substituted lower alkenyl of C_2-C_6 , or optionally substituted acyl;

R^6 is an optionally substituted alkyl (including lower alkyl), cyano (CN), CH_3 , OCH_3 , OCH_2CH_3 , hydroxy methyl (CH_2OH), fluoromethyl (CH_2F), azido (N_3), $CHCN$, CH_2N_3 , CH_2NH_2 , CH_2NHCH_3 , $CH_2N(CH_3)_2$, alkyne (optionally substituted), or fluoro;

or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier.

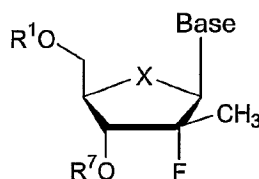
50. The method of claim 49, wherein

Base is



5 and R¹ is H, R² is OH, R^{2'} is H, R³ is H, R⁴ is NH₂ or OH, and R⁶ is H.

51. A method for the treatment or prophylaxis of a rhinovirus infection comprising administering to a host an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D or β -L) or its pharmaceutically acceptable salt or prodrug thereof of the structure:



wherein Base is a purine or pyrimidine base;

X is O, S, CH₂, Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), C(W)₂, wherein W is F, Cl, Br, or I; and,

15 R¹ and R⁷ are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its
20 peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid,

pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R¹ is H or phosphate; R² is H or phosphate; R¹ and R² or R⁷ can also be linked with cyclic phosphate group;

5 R² and R^{2'} are independently H, C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl, vinyl, N₃, CN, Cl, Br, F, I, NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkynyl), O₃S(C₁₋₄ alkenyl), NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₁₈ acyl)₂, wherein alkyl, alkynyl, alkenyl and vinyl are optionally substituted by N₃, CN, one to three halogen (Cl, Br, F, I), NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkynyl), O₃S(C₁₋₄ alkenyl), NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₄ acyl)₂, OR⁷; R² and R^{2'} can be linked together to form a vinyl optionally substituted by one or two of N₃, CN, Cl, Br, F, I, NO₂;

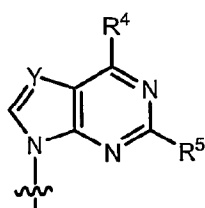
30 R⁶ is an optionally substituted alkyl (including lower alkyl), cyano (CN), CH₃, OCH₃, OCH₂CH₃, hydroxy methyl (CH₂OH), fluoromethyl (CH₂F), azido (N₃), CHCN, CH₂N₃, CH₂NH₂, CH₂NHCH₃, CH₂N(CH₃)₂, alkyne (optionally substituted), or fluoro;

or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier.

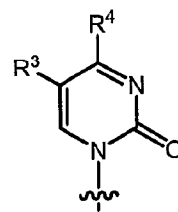
47. The method of claim 46,

5

wherein Base is selected from the group consisting of:



(a)



(b)

Y is N or CH.

10

R^3 , R^4 and R^5 are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃ and CH₂CH₂F, lower alkenyl of C₂-C₆ such as CH=CH₂, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆ such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C₂-C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆ such as CH₂OH and CH₂CH₂OH, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, CH=CHCO₂R'; and,

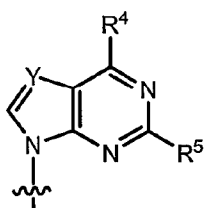
15

20

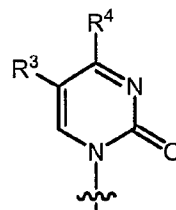
wherein R' is an optionally substituted alkyl of C₁-C₁₂ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C₂-C₆, optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl.

48. The method of claim 46, wherein

Base is selected from the group consisting of (a) or (b):



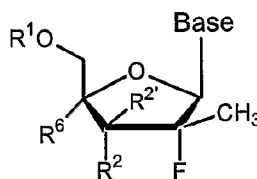
(a)



(b)

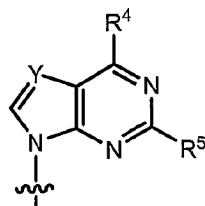
and wherein R^1 is H, R^2 is OH, $R^{2'}$ is H, R^3 is H,
and R^4 is NH_2 or OH, and R^5 is NH_2 .

49. A method for the treatment or prophylaxis of a rhinovirus infection
comprising administering to a host an antivirally effective amount of a (2'*R*)-2'-
deoxy-2'-fluoro-2'-C-methyl nucleoside (β -D or β -L) of the formula:

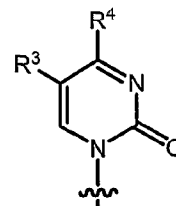


wherein

Base is selected from the group consisting of



(a)



(b)

and wherein Y is N or CH;

R¹ and R⁷ are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid (or racemic mixture), a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R¹ is H or phosphate; R² is H or phosphate; R¹ and R² or R⁷ can also be linked with cyclic phosphate group;

R² and R^{2'} are independently H, C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl, vinyl, N₃, CN, Cl, Br, F, I, NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkynyl), O₃S(C₁₋₄ alkenyl), NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₁₈ acyl)₂, wherein alkyl, alkynyl, alkenyl and vinyl are optionally substituted by N₃, CN, one to three halogen (Cl, Br, F, I), NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋

4 acyl), $O_3S(C_{1-4} \text{ alkyl})$, $O_3S(C_{1-4} \text{ alkenyl})$, NH_2 , $NH(C_{1-4} \text{ alkyl})$, $NH(C_{1-4} \text{ alkenyl})$, $NH(C_{1-4} \text{ alkynyl})$, $NH(C_{1-4} \text{ acyl})$, $N(C_{1-4} \text{ alkyl})_2$, $N(C_{1-4} \text{ acyl})_2$, OR^7 ; R^2 and $R^{2'}$ can be linked together to form a vinyl optionally substituted by one or two
 5 of N_3 , CN , Cl , Br , F , I , NO_2 ;

R^3 , R^4 and R^5 are independently H , halogen including F , Cl , Br , I , OH , OR' , SH , SR' , NH_2 , NHR' , NR'_2 , lower alkyl of C_1-C_6 , halogenated (F , Cl , Br , I) lower alkyl of C_1-C_6 such as CF_3 and CH_2CH_2F , lower alkenyl of C_2-C_6 such as $CH=CH_2$,
 10 halogenated (F , Cl , Br , I) lower alkenyl of C_2-C_6 such as $CH=CHCl$, $CH=CHBr$ and $CH=CHI$, lower alkynyl of C_2-C_6 such as $C\equiv CH$, halogenated (F , Cl , Br , I) lower alkynyl of C_2-C_6 , lower alkoxy of C_1-C_6 such as CH_2OH and CH_2CH_2OH , halogenated (F , Cl , Br , I) lower alkoxy of C_1-C_6 , CO_2H ,
 15 CO_2R' , $CONH_2$, $CONHR'$, $CONR'_2$, $CH=CHCO_2H$, $CH=CHCO_2R'$;

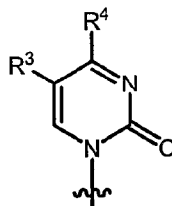
R' is an optionally substituted alkyl of C_1-C_{12} (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C_2-C_6 , optionally substituted lower
 20 alkenyl of C_2-C_6 , or optionally substituted acyl;

R^6 is an optionally substituted alkyl (including lower alkyl), cyano (CN), CH_3 , OCH_3 , OCH_2CH_3 , hydroxy methyl (CH_2OH), fluoromethyl (CH_2F), azido (N_3), $CHCN$, CH_2N_3 , CH_2NH_2 , CH_2NHCH_3 , $CH_2N(CH_3)_2$, alkyne (optionally substituted), or
 25 fluoro;

or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier.

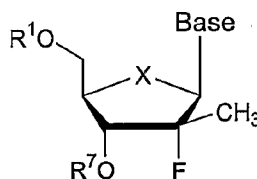
50. The method of claim 49, wherein

Base is



5 and R¹ is H, R² is OH, R^{2'} is H, R³ is H, R⁴ is NH₂ or OH, and R⁶ is H.

51. A method for the treatment or prophylaxis of a rhinovirus infection comprising administering to a host an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β-D or β-L) or its pharmaceutically acceptable salt or prodrug thereof of the structure:



wherein Base is a purine or pyrimidine base;

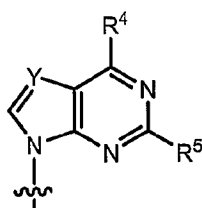
X is O, S, CH₂, Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), C(W)₂, wherein W is F, Cl, Br, or I; and,

15 R¹ and R⁷ are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its
20 peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid,

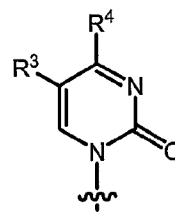
including a phospholipid, an L or D-amino acid, a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R¹ or R⁷ is independently H or phosphate; R¹ and R⁷ can also be linked with cyclic phosphate group; optionally in a pharmaceutically acceptable carrier.

52. The method of claim 51, wherein

Base is selected from the group consisting of:



(a)



(b)

Y is N or CH;

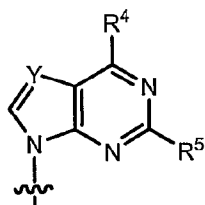
R³, R⁴ and R⁵ are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃ and CH₂CH₂F, lower alkenyl of C₂-C₆ such as CH=CH₂, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆ such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C₂-C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆ such as CH₂OH and CH₂CH₂OH, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, CH=CHCO₂R'; and,

R' is an optionally substituted alkyl of C₁-C₁₂ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C₂-C₆, optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl.

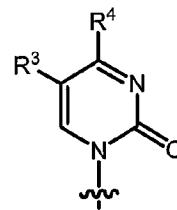
5

53. The method of claim 51, wherein

Base is selected from the group consisting of (a) or (b):



(a)

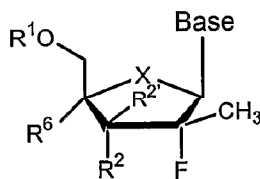


(b)

10

and wherein R¹ and R⁷ are H, R³ is H, and R⁴ is NH₂ or OH, and R⁵ is NH₂.

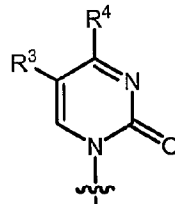
54. A method for the treatment or prophylaxis of a rhinovirus infection comprising administering to a host an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D or β-L) of the formula:



15

wherein

Base is



149

X is O, S, CH₂, Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), C(W)₂,
wherein W is F, Cl, Br, or I;

R¹ and R⁷ are independently H, phosphate, including monophosphate,
diphosphate, triphosphate, or a stabilized phosphate prodrug,
5 H-phosphonate, including stabilized H-phosphonates, acyl,
including optionally substituted phenyl and lower acyl, alkyl,
including lower alkyl, O-substituted carboxyalkylamino or its
peptide derivatives, sulfonate ester, including alkyl or
arylalkyl sulfonyl, including methanesulfonyl and benzyl,
10 wherein the phenyl group is optionally substituted, a lipid,
including a phospholipid, an L or D-amino acid (or racemic
mixture), a carbohydrate, a peptide, a cholesterol, or other
pharmaceutically acceptable leaving group which when
administered *in vivo* is capable of providing a compound
15 wherein R¹ is H or phosphate; R² is H or phosphate; R¹ and
R² or R⁷ can also be linked with cyclic phosphate group;

R² and R^{2'} are independently H, C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl,
vinyl, N₃, CN, Cl, Br, F, I, NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄
4 alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄
acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄
alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄
alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl),
SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄
4 acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkenyl), NH₂, NH(C₁₋₄
25 alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl),
N(C₁₋₄ alkyl)₂, N(C₁₋₁₈ acyl)₂, wherein alkyl, alkynyl, alkenyl
and vinyl are optionally substituted by N₃, CN, one to three
halogen (Cl, Br, F, I), NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄
alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄
30 acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄
alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄
alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl),

5 SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkenyl), NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₄ acyl)₂, OR⁷; R² and R^{2'} can be linked together to form a vinyl optionally substituted by one or two of N₃, CN, Cl, Br, F, I, NO₂;

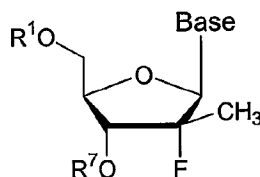
10 R³ and R⁴ are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃ and CH₂CH₂F, lower alkenyl of C₂-C₆ such as CH=CH₂, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆ such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C₂-C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆ such as CH₂OH and CH₂CH₂OH, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, CH=CHCO₂R';

20 R' is an optionally substituted alkyl of C₁-C₁₂ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C₂-C₆, optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl;

25 R⁶ is an optionally substituted alkyl (including lower alkyl), cyano (CN), CH₃, OCH₃, OCH₂CH₃, hydroxy methyl (CH₂OH), fluoromethyl (CH₂F), azido (N₃), CHCN, CH₂N₃, CH₂NH₂, CH₂NHCH₃, CH₂N(CH₃)₂, alkyne (optionally substituted), or fluoro;

or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier.

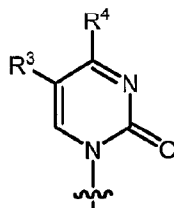
55. A method for the treatment or prophylaxis of a rhinovirus infection comprising administering to a host an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D or β -L) of the formula:



5

wherein

Base is



10

15

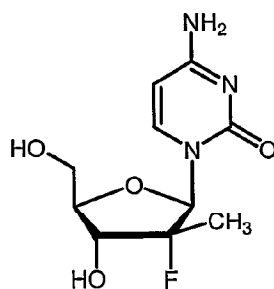
20

R^1 and R^7 are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid, a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 or R^7 is independently H or phosphate; R^1 and R^7 can also be linked with cyclic phosphate group;

R^3 and R^4 are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆,

- 5 halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃ and CH₂CH₂F, lower alkenyl of C₂-C₆ such as CH=CH₂, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆ such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C₂-C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆ such as CH₂OH and CH₂CH₂OH, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, CH=CHCO₂R';
- 10 R' is an optionally substituted alkyl of C₁-C₁₂ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C₂-C₆, optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl;
- or its pharmaceutically acceptable salt or prodrug thereof, optionally in a
- 15 pharmaceutically acceptable carrier.

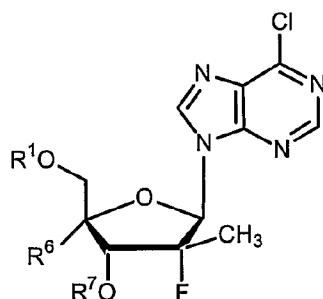
56. A method for the treatment or prophylaxis of a rhinovirus infection comprising administering to a host an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β-D) or its pharmaceutically acceptable salt or prodrug thereof of the formula:
- 20



optionally in a pharmaceutically acceptable carrier.

57. A method for the treatment or prophylaxis of a rhinovirus infection comprising administering to a host an antivirally effective amount of a (2'*R*)-2'-

deoxy-2'-fluoro-2'-C-methyl nucleoside (β -D) or its pharmaceutically acceptable salt or prodrug thereof of the formula:



wherein

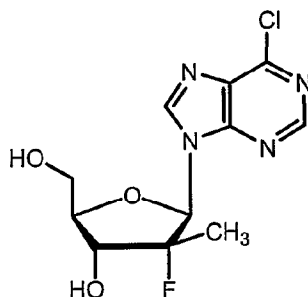
5 R^1 and R^7 are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its
10 peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid, a carbohydrate, a peptide, a cholesterol, or other
15 pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 or R^7 is independently H or phosphate; R^1 and R^7 can also be linked with cyclic phosphate group; and,

20 R^6 is an optionally substituted alkyl (including lower alkyl), cyano (CN), CH_3 , OCH_3 , OCH_2CH_3 , hydroxy methyl (CH_2OH), fluoromethyl (CH_2F), azido (N_3), $CHCN$, CH_2N_3 , CH_2NH_2 , CH_2NHCH_3 , $CH_2N(CH_3)_2$, alkyne (optionally substituted), or fluoro; and

optionally in a pharmaceutically acceptable carrier.

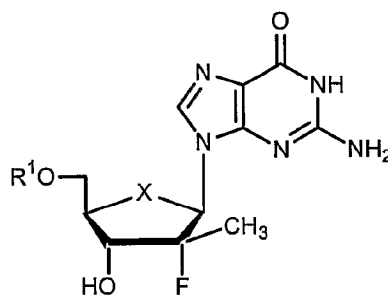
25

58. A method for the treatment or prophylaxis of a rhinovirus infection comprising administering to a host an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D) or its pharmaceutically acceptable salt or prodrug thereof of the formula:



optionally in a pharmaceutically acceptable carrier.

59. A method for the treatment or prophylaxis of a rhinovirus infection comprising administering to a host an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D) or its pharmaceutically acceptable salt or prodrug thereof of the formula:



wherein

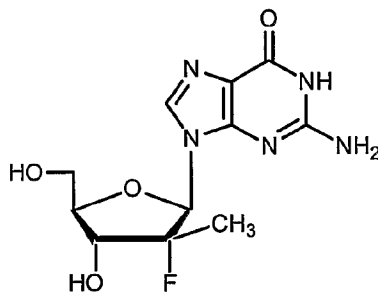
X is O, S, CH₂, Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), C(W)₂,

wherein W is F, Cl, Br, or I; and

R¹ is H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl,

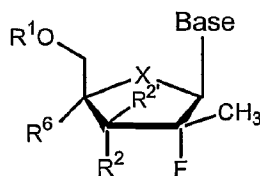
- 5 including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid, a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R¹ is H or phosphate;
- 10 optionally in a pharmaceutically acceptable carrier.

60. A method for the treatment or prophylaxis of a rhinovirus infection comprising administering to a host an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β-D) or its pharmaceutically acceptable salt or prodrug thereof of the formula:
- 15



optionally in a pharmaceutically acceptable carrier.

61. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β-D or β-L) of the formula:
- 20



wherein

Base is a purine or pyrimidine base;

X is O, S, CH₂, Sc, NH, N-alkyl, CHW (*R*, *S*, or racemic), C(W)₂,
wherein W is F, Cl, Br, or I;

5 R¹ and R⁷ are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its
10 peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid (or racemic mixture), a carbohydrate, a peptide, a cholesterol, or other
15 pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R¹ is H or phosphate; R² is H or phosphate; R¹ and R² or R⁷ can also be linked with cyclic phosphate group;

R² and R^{2'} are independently H, C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl,
20 vinyl, N₃, CN, Cl, Br, F, I, NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl),
25 SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkenyl), NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₁₈ acyl)₂, wherein alkyl, alkynyl, alkenyl and vinyl are optionally substituted by N₃, CN, one to three
30 halogen (Cl, Br, F, I), NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄

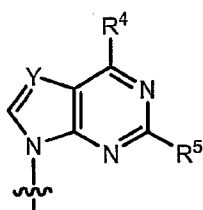
5 acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkynyl), NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₄ acyl)₂, OR⁷; R² and R^{2'} can be linked together to form a vinyl optionally substituted by one or two of N₃, CN, Cl, Br, F, I, NO₂;

10 R⁶ is an optionally substituted alkyl (including lower alkyl), cyano (CN), CH₃, OCH₃, OCH₂CH₃, hydroxy methyl (CH₂OH), fluoromethyl (CH₂F), azido (N₃), CHCN, CH₂N₃, CH₂NH₂, CH₂NHCH₃, CH₂N(CH₃)₂, alkyne (optionally substituted), or fluoro;

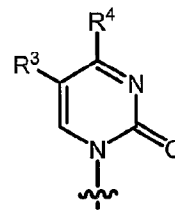
15 or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of a yellow fever virus infection in a host.

62. The use of claim 61,

wherein Base is selected from the group consisting of:



(a)



(b)

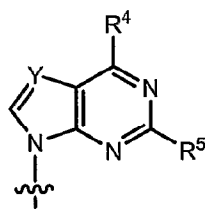
Y is N or CH.

R^3 , R^4 and R^5 are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃ and CH₂CH₂F, lower alkenyl of C₂-C₆ such as CH=CH₂, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆ such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C₂-C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆ such as CH₂OH and CH₂CH₂OH, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, CH=CHCO₂R'; and,

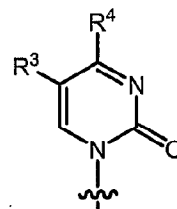
R' is an optionally substituted alkyl of C₁-C₁₂ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C₂-C₆, optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl.

63. The use of claim 61, wherein

Base is selected from the group consisting of (a) or (b):



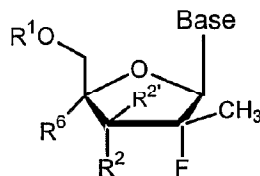
(a)



(b)

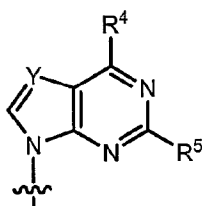
and wherein R^1 is H, R^2 is OH, $R^{2'}$ is H, R^3 is H, and R^4 is NH₂ or OH, and R^5 is NH₂.

64. Use of an antivirally effective amount of a (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β -D or β -L) of the formula:

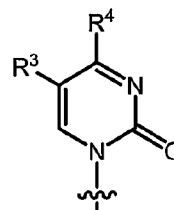


wherein

Base is selected from the group consisting of



(a)



(b)

Y is N or CH;

R^1 and R^7 are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid (or racemic mixture), a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is H or phosphate; R^2 is H or phosphate; R^1 and R^2 or R^7 can also be linked with cyclic phosphate group;

R^2 and $R^{2'}$ are independently H, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkynyl, vinyl, N_3 , CN, Cl, Br, F, I, NO_2 , $C(O)O(C_{1-4}$ alkyl), $C(O)O(C_{1-4}$

4 alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄
 acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄
 alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄
 alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl),
 5 SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄
 acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkenyl), NH₂, NH(C₁₋₄
 alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl),
 N(C₁₋₄ alkyl)₂, N(C₁₋₁₈ acyl)₂, wherein alkyl, alkynyl, alkenyl
 and vinyl are optionally substituted by N₃, CN, one to three
 10 halogen (Cl, Br, F, I), NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄
 alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄
 acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄
 alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄
 alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl),
 15 SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄
 acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkenyl), NH₂, NH(C₁₋₄
 alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl),
 N(C₁₋₄ alkyl)₂, N(C₁₋₄ acyl)₂, OR⁷; R² and R^{2'} can be linked
 together to form a vinyl optionally substituted by one or two
 20 of N₃, CN, Cl, Br, F, I, NO₂;

R³, R⁴ and R⁵ are independently H, halogen including F, Cl, Br, I,
 OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆,
 halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃
 and CH₂CH₂F, lower alkenyl of C₂-C₆ such as CH=CH₂,
 25 halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆ such as
 CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C₂-C₆
 such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-
 C₆, lower alkoxy of C₁-C₆ such as CH₂OH and CH₂CH₂OH,
 halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H,
 30 CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H,
 CH=CHCO₂R';

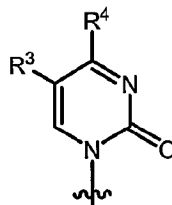
R' is an optionally substituted alkyl of C₁-C₁₂ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C₂-C₆, optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl;

5 R⁶ is an optionally substituted alkyl (including lower alkyl), cyano (CN), CH₃, OCH₃, OCH₂CH₃, hydroxy methyl (CH₂OH), fluoromethyl (CH₂F), azido (N₃), CHCN, CH₂N₃, CH₂NH₂, CH₂NHCH₃, CH₂N(CH₃)₂, alkyne (optionally substituted), or fluoro;

10 or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of a yellow fever virus infection in a host.

65. The use of claim 64, wherein

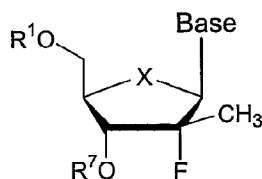
15 Base is



and R¹ is H, R² is OH, R^{2'} is H, R³ is H, R⁴ is NH₂ or OH, and R⁶ is H.

20

66. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D or β-L) of the structure:



wherein Base is a purine or pyrimidine base;

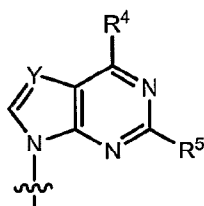
X is O, S, CH₂, Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), C(W)₂,
wherein W is F, Cl, Br, or I; and,

5 R¹ and R⁷ are independently H, phosphate, including monophosphate,
diphosphate, triphosphate, or a stabilized phosphate prodrug,
H-phosphonate, including stabilized H-phosphonates, acyl,
including optionally substituted phenyl and lower acyl, alkyl,
including lower alkyl, O-substituted carboxyalkylamino or its
10 peptide derivatives, sulfonate ester, including alkyl or
arylalkyl sulfonyl, including methanesulfonyl and benzyl,
wherein the phenyl group is optionally substituted, a lipid,
including a phospholipid, an L or D-amino acid, a
carbohydrate, a peptide, a cholesterol, or other
15 pharmaceutically acceptable leaving group which when
administered *in vivo* is capable of providing a compound
wherein R¹ or R⁷ is independently H or phosphate; R¹ and R⁷
can also be linked with cyclic phosphate group and

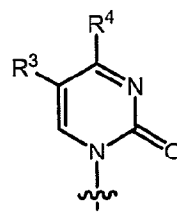
20 or its pharmaceutically acceptable salt or prodrug thereof, optionally in a
pharmaceutically acceptable carrier, for the treatment or prophylaxis of a yellow
fever virus infection in a host

67. The use of claim 66, wherein

Base is selected from the group consisting of:



(a)



(b)

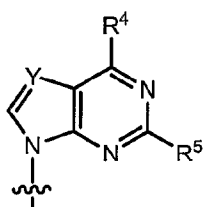
Y is N or CH;

R³, R⁴ and R⁵ are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃ and CH₂CH₂F, lower alkenyl of C₂-C₆ such as CH=CH₂, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆ such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C₂-C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆ such as CH₂OH and CH₂CH₂OH, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, CH=CHCO₂R'; and,

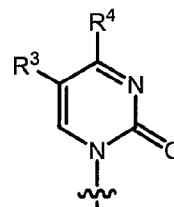
R' is an optionally substituted alkyl of C₁-C₁₂ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C₂-C₆, optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl.

68. The use of claim 66, wherein

Base is selected from the group consisting of (a) or (b):



(a)

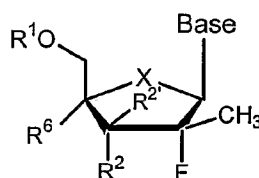


(b)

and wherein R^1 and R^7 are H, R^3 is H, and R^4 is NH_2 or OH, and R^5 is NH_2 .

5

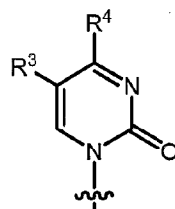
69. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D or β -L) of the formula:



wherein

10

Base is



X is O, S, CH_2 , Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), $C(W)_2$, wherein W is F, Cl, Br, or I;

15

R^1 and R^7 are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or

165

5 arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid (or racemic mixture), a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R¹ is H or phosphate; R² is H or phosphate; R¹ and R² or R⁷ can also be linked with cyclic phosphate group;

10 R² and R^{2'} are independently H, C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl, vinyl, N₃, CN, Cl, Br, F, I, NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl);
 15 SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkenyl), NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₁₈ acyl)₂, wherein alkyl, alkynyl, alkenyl and vinyl are optionally substituted by N₃, CN, one to three
 20 halogen (Cl, Br, F, I), NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl),
 25 SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkenyl), NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₄ acyl)₂, OR⁷; R² and R^{2'} can be linked together to form a vinyl optionally substituted by one or two
 30 of N₃, CN, Cl, Br, F, I, NO₂;

R³ and R⁴ are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆,

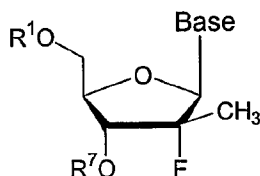
5 halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃ and CH₂CH₂F, lower alkenyl of C₂-C₆ such as CH=CH₂, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆ such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C₂-C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆ such as CH₂OH and CH₂CH₂OH, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, CH=CHCO₂R';

10 R' is an optionally substituted alkyl of C₁-C₁₂ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C₂-C₆, optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl;

15 R⁶ is an optionally substituted alkyl (including lower alkyl), cyano (CN), CH₃, OCH₃, OCH₂CH₃, hydroxy methyl (CH₂OH), fluoromethyl (CH₂F), azido (N₃), CHCN, CH₂N₃, CH₂NH₂, CH₂NHCH₃, CH₂N(CH₃)₂, alkyne (optionally substituted), or fluoro;

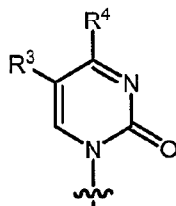
20 or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of a yellow fever virus infection in a host

70. Use of antivirally effective amount of a (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D or β-L) of the formula:



wherein

Base is



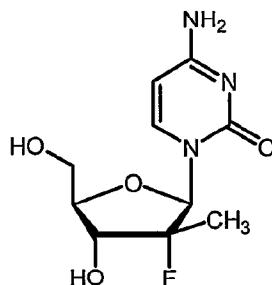
5 R^1 and R^7 are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or
 10 arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid, a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when
 15 administered *in vivo* is capable of providing a compound wherein R^1 or R^7 is independently H or phosphate; R^1 and R^7 can also be linked with cyclic phosphate group;

20 R^3 and R^4 are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃ and CH₂CH₂F, lower alkenyl of C₂-C₆ such as CH=CH₂, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆ such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C₂-C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-
 25 C₆, lower alkoxy of C₁-C₆ such as CH₂OH and CH₂CH₂OH, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, CH=CHCO₂R';

R' is an optionally substituted alkyl of C₁-C₁₂ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C₂-C₆, optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl.

- 5 or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of a yellow fever virus infection in a host.

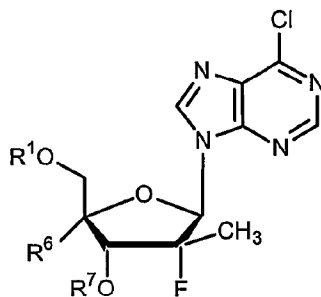
- 10 71. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β-D) of the formula:



or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of a yellow fever virus infection in a host.

15

72. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β-D) of the formula:



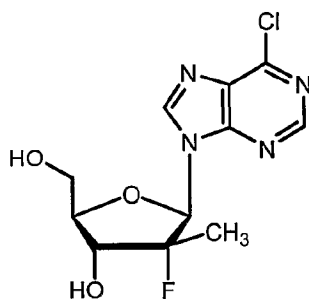
wherein

5 R¹ and R⁷ are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, 10 including a phospholipid, an L or D-amino acid, a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R¹ or R⁷ is independently H or phosphate; R¹ and R⁷ 15 can also be linked with cyclic phosphate group; and,

 R⁶ is an optionally substituted alkyl (including lower alkyl), cyano (CN), CH₃, OCH₃, OCH₂CH₃, hydroxy methyl (CH₂OH), fluoromethyl (CH₂F), azido (N₃), CHCN, CH₂N₃, CH₂NH₂, CH₂NHCH₃, CH₂N(CH₃)₂, alkyne (optionally substituted), or 20 fluoro, and

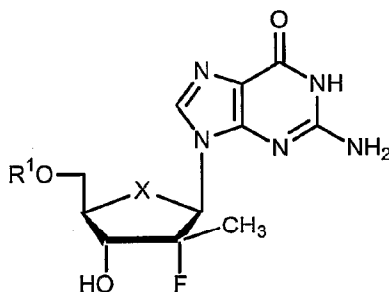
or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of a yellow fever virus infection in a host.

25 73. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D) of the formula:



or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of a yellow fever virus infection in a host.

- 5 74. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D) of the formula:



wherein

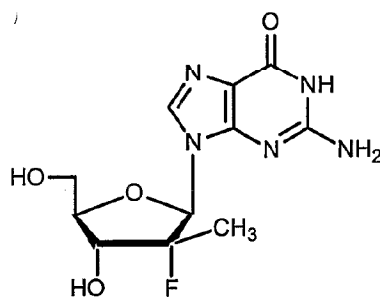
- 10 X is O, S, CH₂, Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), C(W)₂,
wherein W is F, Cl, Br, or I; and

- 15 R¹ and R² are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid, a carbohydrate, a peptide, a cholesterol, or other

pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R¹ is H or phosphate;

- 5 or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of a yellow fever virus infection in a host.

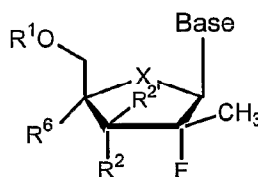
75. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β-*D*) of the formula:



10

or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of a yellow fever virus infection in a host.

- 15 76. Use an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β-*D* or β-*L*) of the formula:



wherein

Base is a purine or pyrimidine base;

X is O, S, CH₂, Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), C(W)₂,
wherein W is F, Cl, Br, or I;

R¹ and R⁷ are independently H, phosphate, including monophosphate,
diphosphate, triphosphate, or a stabilized phosphate prodrug,
5 H-phosphonate, including stabilized H-phosphonates, acyl,
including optionally substituted phenyl and lower acyl, alkyl,
including lower alkyl, O-substituted carboxyalkylamino or its
peptide derivatives, sulfonate ester, including alkyl or
arylalkyl sulfonyl, including methanesulfonyl and benzyl,
10 wherein the phenyl group is optionally substituted, a lipid,
including a phospholipid, an L or D-amino acid (or racemic
mixture), a carbohydrate, a peptide, a cholesterol, or other
pharmaceutically acceptable leaving group which when
administered *in vivo* is capable of providing a compound
15 wherein R¹ is H or phosphate; R² is H or phosphate; R¹ and
R² or R⁷ can also be linked with cyclic phosphate group;

R² and R^{2'} are independently H, C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl,
vinyl, N₃, CN, Cl, Br, F, I, NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄
4 alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄
acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄
20 alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄
alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl),
SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄
4 acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkenyl), NH₂, NH(C₁₋₄
25 alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl),
N(C₁₋₄ alkyl)₂, N(C₁₋₁₈ acyl)₂, wherein alkyl, alkynyl, alkenyl
and vinyl are optionally substituted by N₃, CN, one to three
halogen (Cl, Br, F, I), NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄
alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄
30 acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄
alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄
alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl),

5

SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkenyl), NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₄ acyl)₂, OR⁷; R² and R²¹ can be linked together to form a vinyl optionally substituted by one or two of N₃, CN, Cl, Br, F, I, NO₂;

10

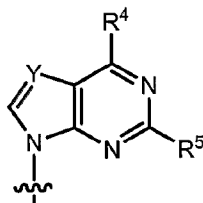
R⁶ is an optionally substituted alkyl (including lower alkyl), cyano (CN), CH₃, OCH₃, OCH₂CH₃, hydroxy methyl (CH₂OH), fluoromethyl (CH₂F), azido (N₃), CHCN, CH₂N₃, CH₂NH₂, CH₂NHCH₃, CH₂N(CH₃)₂, alkyne (optionally substituted), or fluoro;

or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of a West Nile virus infection in a host.

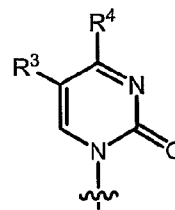
15

77. The use of claim 76,

wherein Base is selected from the group consisting of:



(a)



(b)

20

Y is N or CH.

R³, R⁴ and R⁵ are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃ and CH₂CH₂F, lower alkenyl of C₂-C₆ such as CH=CH₂,

5

halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆ such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C₂-C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆ such as CH₂OH and CH₂CH₂OH, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, CH=CHCO₂R'; and,

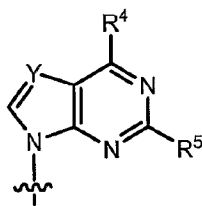
10

R' is an optionally substituted alkyl of C₁-C₁₂ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C₂-C₆, optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl.

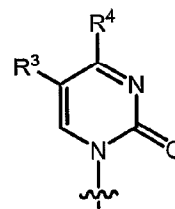
78. The use of claim 76, wherein

Base is selected from the group consisting of (a) or (b):

15



(a)

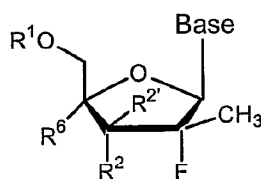


(b)

and wherein R¹ is H, R² is OH, R^{2'} is H, R³ is H, and R⁴ is NH₂ or OH, and R⁵ is NH₂.

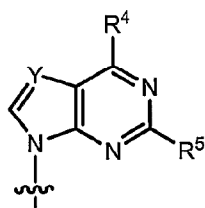
20

79. Use of an antivirally effective amount of a (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D) of the formula:

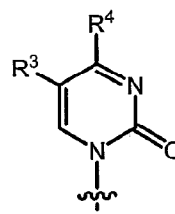


wherein

Base is selected from the group consisting of



(a)



(b)

5

Y is N or CH;

R¹ and R⁷ are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid (or racemic mixture), a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R¹ is H or phosphate; R² is H or phosphate; R¹ and R² or R⁷ can also be linked with cyclic phosphate group;

10

15

20

R² and R²¹ are independently H, C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl, vinyl, N₃, CN, Cl, Br, F, I, NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄

acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkynyl), NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₁₈ acyl)₂, wherein alkyl, alkynyl, alkenyl and vinyl are optionally substituted by N₃, CN, one to three halogen (Cl, Br, F, I), NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkynyl), NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₄ acyl)₂, OR⁷; R² and R^{2'} can be linked together to form a vinyl optionally substituted by one or two of N₃, CN, Cl, Br, F, I, NO₂;

R³, R⁴ and R⁵ are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃ and CH₂CH₂F, lower alkenyl of C₂-C₆ such as CH=CH₂, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆ such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C₂-C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆ such as CH₂OH and CH₂CH₂OH, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, CH=CHCO₂R';

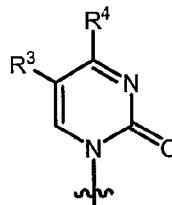
R' is an optionally substituted alkyl of C₁-C₁₂ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C₂-C₆, optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl;

5 R⁶ is an optionally substituted alkyl (including lower alkyl), cyano (CN), CH₃, OCH₃, OCH₂CH₃, hydroxy methyl (CH₂OH), fluoromethyl (CH₂F), azido (N₃), CHCN, CH₂N₃, CH₂NH₂, CH₂NHCH₃, CH₂N(CH₃)₂, alkyne (optionally substituted), or fluoro;

10 or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of a West Nile virus infection in a host.

80. The use of claim 79, wherein

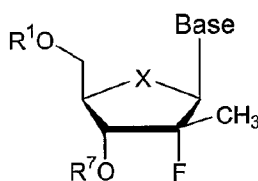
15 Base is



and R¹ is H, R² is OH, R^{2'} is H, R³ is H, R⁴ is NH₂ or OH, and R⁶ is H.

20

81. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D or β-L) of the structure:



wherein Base is a purine or pyrimidine base;

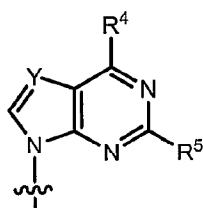
X is O, S, CH₂, Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), C(W)₂,
wherein W is F, Cl, Br, or I; and,

5 R¹ and R⁷ are independently H, phosphate, including monophosphate,
diphosphate, triphosphate, or a stabilized phosphate prodrug,
H-phosphonate, including stabilized H-phosphonates, acyl,
including optionally substituted phenyl and lower acyl, alkyl,
including lower alkyl, O-substituted carboxyalkylamino or its
10 peptide derivatives, sulfonate ester, including alkyl or
arylalkyl sulfonyl, including methanesulfonyl and benzyl,
wherein the phenyl group is optionally substituted, a lipid,
including a phospholipid, an L or D-amino acid, a
carbohydrate, a peptide, a cholesterol, or other
15 pharmaceutically acceptable leaving group which when
administered *in vivo* is capable of providing a compound
wherein R¹ or R⁷ is independently H or phosphate; R¹ and R⁷
can also be linked with cyclic phosphate group;

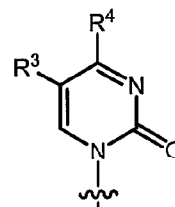
20 or its pharmaceutically acceptable salt or prodrug thereof, optionally in a
pharmaceutically acceptable carrier, for the treatment or prophylaxis of a West Nile
virus infection in a host.

82. The use of claim 81, wherein

Base is selected from the group consisting of:



(a)



(b)

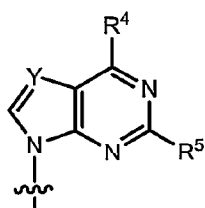
Y is N or CH;

R³, R⁴ and R⁵ are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃ and CH₂CH₂F, lower alkenyl of C₂-C₆ such as CH=CH₂, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆ such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C₂-C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆ such as CH₂OH and CH₂CH₂OH, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, CH=CHCO₂R'; and,

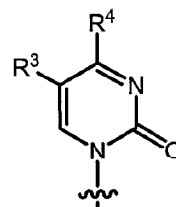
R' is an optionally substituted alkyl of C₁-C₁₂ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C₂-C₆, optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl.

83. The use of claim 81, wherein

Base is selected from the group consisting of (a) or (b):



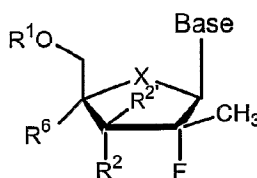
(a)



(b)

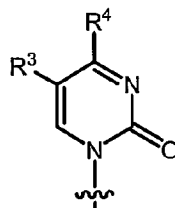
and wherein R^1 and R^7 are H, R^3 is H, and R^4 is NH_2 or OH, and R^5 is NH_2 .

- 5 84. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D or β -L) of the formula:



wherein

Base is



10

X is O, S, CH_2 , Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), $C(W)_2$, wherein W is F, Cl, Br, or I;

15

R^1 and R^7 are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl,

wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid (or racemic mixture), a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R¹ is H or phosphate; R² is H or phosphate; R¹ and R² or R⁷ can also be linked with cyclic phosphate group;

R² and R^{2'} are independently H, C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl, vinyl, N₃, CN, Cl, Br, F, I, NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkenyl), NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₁₈ acyl)₂, wherein alkyl, alkynyl, alkenyl and vinyl are optionally substituted by N₃, CN, one to three halogen (Cl, Br, F, I), NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkenyl), NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₄ acyl)₂, OR⁷; R² and R^{2'} can be linked together to form a vinyl optionally substituted by one or two of N₃, CN, Cl, Br, F, I, NO₂;

R³ and R⁴ are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃

5 and $\text{CH}_2\text{CH}_2\text{F}$, lower alkenyl of $\text{C}_2\text{-C}_6$ such as $\text{CH}=\text{CH}_2$, halogenated (F, Cl, Br, I) lower alkenyl of $\text{C}_2\text{-C}_6$ such as $\text{CH}=\text{CHCl}$, $\text{CH}=\text{CHBr}$ and $\text{CH}=\text{CHI}$, lower alkynyl of $\text{C}_2\text{-C}_6$ such as $\text{C}\equiv\text{CH}$, halogenated (F, Cl, Br, I) lower alkynyl of $\text{C}_2\text{-C}_6$, lower alkoxy of $\text{C}_1\text{-C}_6$ such as CH_2OH and $\text{CH}_2\text{CH}_2\text{OH}$, halogenated (F, Cl, Br, I) lower alkoxy of $\text{C}_1\text{-C}_6$, CO_2H , $\text{CO}_2\text{R}'$, CONH_2 , CONHR' , CONR'_2 , $\text{CH}=\text{CHCO}_2\text{H}$, $\text{CH}=\text{CHCO}_2\text{R}'$;

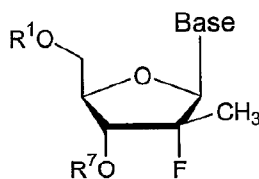
10 R' is an optionally substituted alkyl of $\text{C}_1\text{-C}_{12}$ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of $\text{C}_2\text{-C}_6$, optionally substituted lower alkenyl of $\text{C}_2\text{-C}_6$, or optionally substituted acyl;

15 R^6 is an optionally substituted alkyl (including lower alkyl), cyano (CN), CH_3 , OCH_3 , OCH_2CH_3 , hydroxy methyl (CH_2OH), fluoromethyl (CH_2F), azido (N_3), CHCN , CH_2N_3 , CH_2NH_2 , CH_2NHCH_3 , $\text{CH}_2\text{N}(\text{CH}_3)_2$, alkyne (optionally substituted), or fluoro;

20 or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of a West Nile virus infection in a host.

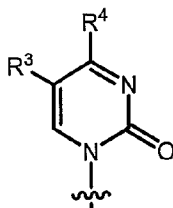
25

85. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside ($\beta\text{-D}$ or $\beta\text{-L}$) of the formula:



wherein

Base is



5

R^1 and R^7 are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid, a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 or R^7 is independently H or phosphate; R^1 and R^7 can also be linked with cyclic phosphate group;

10

15

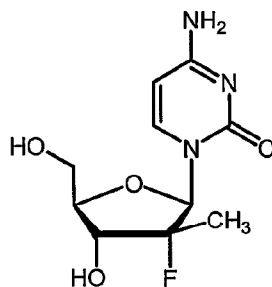
R^3 and R^4 are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃ and CH₂CH₂F, lower alkenyl of C₂-C₆ such as CH=CH₂, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆ such as

5 CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C₂-C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆ such as CH₂OH and CH₂CH₂OH, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, CH=CHCO₂R';

10 R' is an optionally substituted alkyl of C₁-C₁₂ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C₂-C₆, optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl;

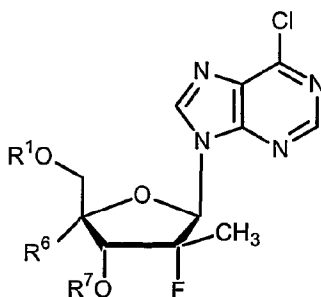
or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of a West Nile virus infection in a host.

15 86. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D) of the formula:



20 or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of a West Nile virus infection in a host.

87. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D) of the formula:



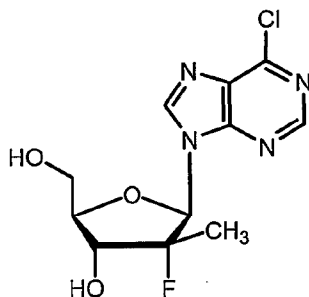
wherein

5 R^1 and R^7 are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its
10 peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid, a carbohydrate, a peptide, a cholesterol, or other
15 pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 or R^7 is independently H or phosphate; R^1 and R^7 can also be linked with cyclic phosphate group; and,

20 R^6 is an optionally substituted alkyl (including lower alkyl), cyano (CN), CH_3 , OCH_3 , OCH_2CH_3 , hydroxy methyl (CH_2OH), fluoromethyl (CH_2F), azido (N_3), $CHCN$, CH_2N_3 , CH_2NH_2 , CH_2NHCH_3 , $CH_2N(CH_3)_2$, alkyne (optionally substituted), or fluoro and,

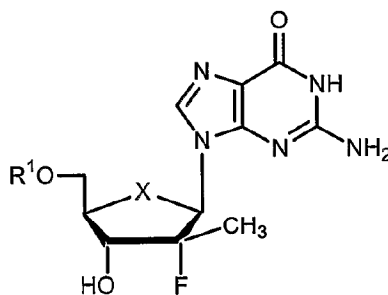
25 or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of a West Nile virus infection in a host.

88. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D) of the formula:



5 or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of a West Nile virus infection in a host.

89. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D) of the formula:



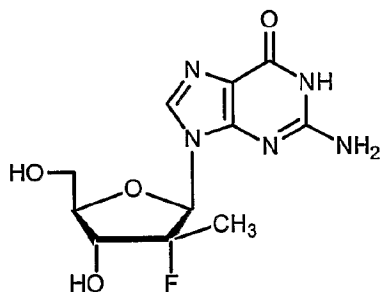
wherein

X is O, S, CH₂, Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), C(W)₂, wherein W is F, Cl, Br, or I; and

15 R¹ is H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl,

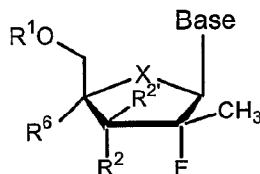
- 5 including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid, a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R¹ is H or phosphate;
- 10 or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of a West Nile virus infection in a host.

90. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D) of the formula:
- 15



or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of a West Nile virus infection in a host.

91. Use an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β -D or β -L) of the formula:



wherein

Base is a purine or pyrimidine base;

X is O, S, CH₂, Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), C(W)₂,
wherein W is F, Cl, Br, or I;

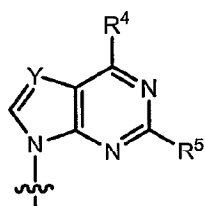
R¹ and R⁷ are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid (or racemic mixture), a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R¹ is H or phosphate; R² is H or phosphate; R¹ and R² or R⁷ can also be linked with cyclic phosphate group;

R² and R^{2'} are independently H, C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl, vinyl, N₃, CN, Cl, Br, F, I, NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄

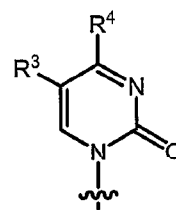
- 5 acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkenyl), NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₁₈ acyl)₂, wherein alkyl, alkynyl, alkenyl and vinyl are optionally substituted by N₃, CN, one to three halogen (Cl, Br, F, I), NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkenyl), NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₄ acyl)₂, OR⁷; R² and R^{2'} can be linked together to form a vinyl optionally substituted by one or two of N₃, CN, Cl, Br, F, I, NO₂;
- 10
- 15
- 20 R⁶ is an optionally substituted alkyl (including lower alkyl), cyano (CN), CH₃, OCH₃, OCH₂CH₃, hydroxy methyl (CH₂OH), fluoromethyl (CH₂F), azido (N₃), CHCN, CH₂N₃, CH₂NH₂, CH₂NHCH₃, CH₂N(CH₃)₂, alkyne (optionally substituted), or fluoro;
- 25 or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of a Dengue virus infection in a host.

92. The use of claim 91,

wherein Base is selected from the group consisting of:



(a)



(b)

Y is N or CH.

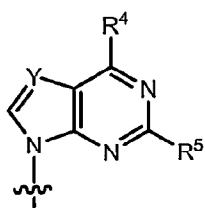
5 R^3 , R^4 and R^5 are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃ and CH₂CH₂F, lower alkenyl of C₂-C₆ such as CH=CH₂, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆ such as
 10 CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C₂-C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆ such as CH₂OH and CH₂CH₂OH, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H,
 15 CH=CHCO₂R'; and,

R' is an optionally substituted alkyl of C₁-C₁₂ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C₂-C₆, optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl.

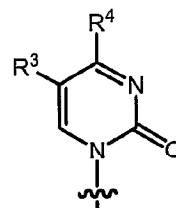
20

93. The use of claim 91, wherein

Base is selected from the group consisting of (a) or (b):



(a)

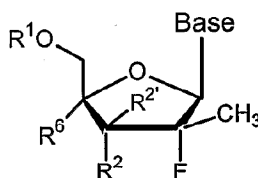


(b)

and wherein R^1 is H, R^2 is OH, $R^{2'}$ is H, R^3 is H, and R^4 is NH_2 or OH, and R^5 is NH_2 .

5

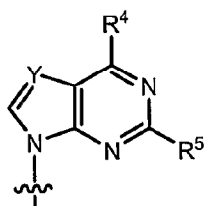
94. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β -D) of the formula:



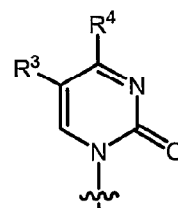
10

wherein

Base is selected from the group consisting of



(a)



(b)

Y is N or CH;

15

R^1 and R^7 are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl,

including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid (or racemic mixture), a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R¹ is H or phosphate; R² is H or phosphate; R¹ and R² or R⁷ can also be linked with cyclic phosphate group;

R² and R^{2'} are independently H, C₁₋₄ alkyl, C₁₋₄ alkenyl, C₁₋₄ alkynyl, vinyl, N₃, CN, Cl, Br, F, I, NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkenyl), NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₁₈ acyl)₂, wherein alkyl, alkynyl, alkenyl and vinyl are optionally substituted by N₃, CN, one to three halogen (Cl, Br, F, I), NO₂, C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkyl), C(O)O(C₁₋₄ alkynyl), C(O)O(C₁₋₄ alkenyl), O(C₁₋₄ acyl), O(C₁₋₄ alkyl), O(C₁₋₄ alkenyl), S(C₁₋₄ acyl), S(C₁₋₄ alkyl), S(C₁₋₄ alkynyl), S(C₁₋₄ alkenyl), SO(C₁₋₄ acyl), SO(C₁₋₄ alkyl), SO(C₁₋₄ alkynyl), SO(C₁₋₄ alkenyl), SO₂(C₁₋₄ acyl), SO₂(C₁₋₄ alkyl), SO₂(C₁₋₄ alkynyl), SO₂(C₁₋₄ alkenyl), O₃S(C₁₋₄ acyl), O₃S(C₁₋₄ alkyl), O₃S(C₁₋₄ alkenyl), NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkenyl), NH(C₁₋₄ alkynyl), NH(C₁₋₄ acyl), N(C₁₋₄ alkyl)₂, N(C₁₋₄ acyl)₂, OR⁷; R² and R^{2'} can be linked together to form a vinyl optionally substituted by one or two of N₃, CN, Cl, Br, F, I, NO₂;

5 R³, R⁴ and R⁵ are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃ and CH₂CH₂F, lower alkenyl of C₂-C₆ such as CH=CH₂, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆ such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C₂-C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆ such as CH₂OH and CH₂CH₂OH, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, CH=CHCO₂R';

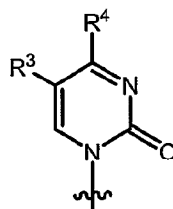
15 R' is an optionally substituted alkyl of C₁-C₁₂ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C₂-C₆, optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl;

20 R⁶ is an optionally substituted alkyl (including lower alkyl), cyano (CN), CH₃, OCH₃, OCH₂CH₃, hydroxy methyl (CH₂OH), fluoromethyl (CH₂F), azido (N₃), CHCN, CH₂N₃, CH₂NH₂, CH₂NHCH₃, CH₂N(CH₃)₂, alkyne (optionally substituted), or fluoro;

or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of a Dengue virus infection in a host.

25 95. The use of claim 94, wherein

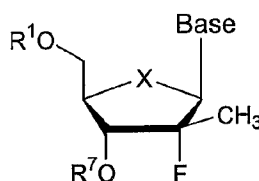
Base is



and R^1 is H, R^2 is OH, $R^{2'}$ is H, R^3 is H, R^4 is NH_2 or OH, and R^6 is H.

5

96. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D or β -L) of the structure:



wherein Base is a purine or pyrimidine base;

10

X is O, S, CH_2 , Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), C(W)_2 , wherein W is F, Cl, Br, or I; and,

15

R^1 and R^7 are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid, a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound

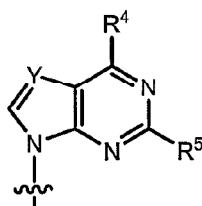
20

wherein R^1 or R^7 is independently H or phosphate; R^1 and R^7 can also be linked with cyclic phosphate group;

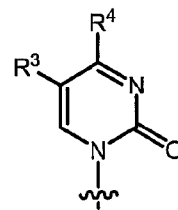
or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of a Dengue virus infection in a host.

97. The use of claim 96, wherein

Base is selected from the group consisting of:



(a)



(b)

Y is N or CH;

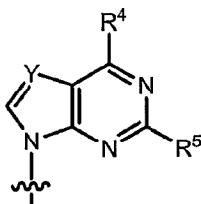
R^3 , R^4 and R^5 are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃ and CH₂CH₂F, lower alkenyl of C₂-C₆ such as CH=CH₂, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆ such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C₂-C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆ such as CH₂OH and CH₂CH₂OH, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, CH=CHCO₂R'; and,

R' is an optionally substituted alkyl of C₁-C₁₂ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally

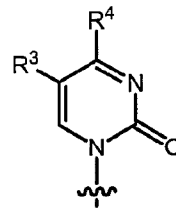
substituted alkynyl of C₂-C₆, optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl.

98. The use of claim 96, wherein

5 Base is selected from the group consisting of (a) or (b):



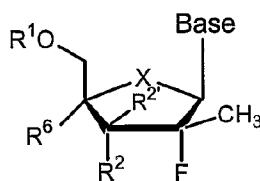
(a)



(b)

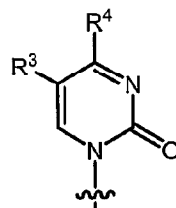
and wherein R¹ and R⁷ are H, R³ is H, and R⁴ is NH₂ or OH, and R⁵ is NH₂.

10 99. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D or β-L) of the formula:



wherein

Base is



15

X is O, S, CH₂, Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), C(W)₂, wherein W is F, Cl, Br, or I;

5 R^1 and R^7 are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid (or racemic mixture), a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is H or phosphate; R^2 is H or phosphate; R^1 and R^2 or R^7 can also be linked with cyclic phosphate group;

15 R^2 and $R^{2'}$ are independently H, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkynyl, vinyl, N_3 , CN, Cl, Br, F, I, NO_2 , $C(O)O(C_{1-4}$ alkyl), $C(O)O(C_{1-4}$ alkyl), $C(O)O(C_{1-4}$ alkynyl), $C(O)O(C_{1-4}$ alkenyl), $O(C_{1-4}$ acyl), $O(C_{1-4}$ alkyl), $O(C_{1-4}$ alkenyl), $S(C_{1-4}$ acyl), $S(C_{1-4}$ alkyl), $S(C_{1-4}$ alkynyl), $S(C_{1-4}$ alkenyl), $SO(C_{1-4}$ acyl), $SO(C_{1-4}$ alkyl), $SO(C_{1-4}$ alkynyl), $SO(C_{1-4}$ alkenyl), $SO_2(C_{1-4}$ acyl), $SO_2(C_{1-4}$ alkyl), $SO_2(C_{1-4}$ alkynyl), $SO_2(C_{1-4}$ alkenyl), $O_3S(C_{1-4}$ acyl), $O_3S(C_{1-4}$ alkyl), $O_3S(C_{1-4}$ alkenyl), NH_2 , $NH(C_{1-4}$ alkyl), $NH(C_{1-4}$ alkenyl), $NH(C_{1-4}$ alkynyl), $NH(C_{1-4}$ acyl), $N(C_{1-4}$ alkyl)₂, $N(C_{1-18}$ acyl)₂, wherein alkyl, alkynyl, alkenyl and vinyl are optionally substituted by N_3 , CN, one to three halogen (Cl, Br, F, I), NO_2 , $C(O)O(C_{1-4}$ alkyl), $C(O)O(C_{1-4}$ alkyl), $C(O)O(C_{1-4}$ alkynyl), $C(O)O(C_{1-4}$ alkenyl), $O(C_{1-4}$ acyl), $O(C_{1-4}$ alkyl), $O(C_{1-4}$ alkenyl), $S(C_{1-4}$ acyl), $S(C_{1-4}$ alkyl), $S(C_{1-4}$ alkynyl), $S(C_{1-4}$ alkenyl), $SO(C_{1-4}$ acyl), $SO(C_{1-4}$ alkyl), $SO(C_{1-4}$ alkynyl), $SO(C_{1-4}$ alkenyl), $SO_2(C_{1-4}$ acyl), $SO_2(C_{1-4}$ alkyl), $SO_2(C_{1-4}$ alkynyl), $SO_2(C_{1-4}$ alkenyl), $O_3S(C_{1-4}$ acyl), $O_3S(C_{1-4}$ alkyl), $O_3S(C_{1-4}$ alkenyl), NH_2 , $NH(C_{1-4}$ alkyl), $NH(C_{1-4}$ alkenyl), $NH(C_{1-4}$ alkynyl), $NH(C_{1-4}$ acyl),

$N(C_{1-4} \text{ alkyl})_2$, $N(C_{1-4} \text{ acyl})_2$, OR^7 ; R^2 and $R^{2'}$ can be linked together to form a vinyl optionally substituted by one or two of N_3 , CN , Cl , Br , F , I , NO_2 ;

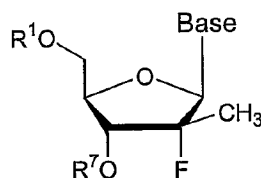
5 R^3 and R^4 are independently H , halogen including F , Cl , Br , I , OH , OR' , SH , SR' , NH_2 , NHR' , NR'_2 , lower alkyl of C_1-C_6 , halogenated (F , Cl , Br , I) lower alkyl of C_1-C_6 such as CF_3 and CH_2CH_2F , lower alkenyl of C_2-C_6 such as $CH=CH_2$, halogenated (F , Cl , Br , I) lower alkenyl of C_2-C_6 such as $CH=CHCl$, $CH=CHBr$ and $CH=CHI$, lower alkynyl of C_2-C_6
10 such as $C\equiv CH$, halogenated (F , Cl , Br , I) lower alkynyl of C_2-C_6 , lower alkoxy of C_1-C_6 such as CH_2OH and CH_2CH_2OH , halogenated (F , Cl , Br , I) lower alkoxy of C_1-C_6 , CO_2H , CO_2R' , $CONH_2$, $CONHR'$, $CONR'_2$, $CH=CHCO_2H$, $CH=CHCO_2R'$;

15 R' is an optionally substituted alkyl of C_1-C_{12} (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C_2-C_6 , optionally substituted lower alkenyl of C_2-C_6 , or optionally substituted acyl;

20 R^6 is an optionally substituted alkyl (including lower alkyl), cyano (CN), CH_3 , OCH_3 , OCH_2CH_3 , hydroxy methyl (CH_2OH), fluoromethyl (CH_2F), azido (N_3), $CHCN$, CH_2N_3 , CH_2NH_2 , CH_2NHCH_3 , $CH_2N(CH_3)_2$, alkyne (optionally substituted), or fluoro;

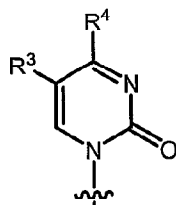
25 or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of a Dengue virus infection in a host.

100. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D or β -L) of the formula:



wherein

Base is



5

10

15

R^1 and R^7 are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, including a phospholipid, an L or D-amino acid, a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 or R^7 is independently H or phosphate; R^1 and R^7 can also be linked with cyclic phosphate group;

20

25

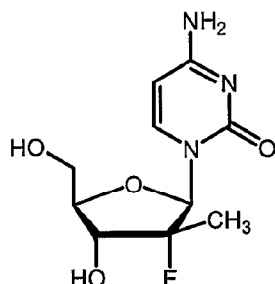
R^3 and R^4 are independently H, halogen including F, Cl, Br, I, OH, OR', SH, SR', NH₂, NHR', NR'₂, lower alkyl of C₁-C₆, halogenated (F, Cl, Br, I) lower alkyl of C₁-C₆ such as CF₃ and CH₂CH₂F, lower alkenyl of C₂-C₆ such as CH=CH₂, halogenated (F, Cl, Br, I) lower alkenyl of C₂-C₆ such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C₂-C₆ such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C₂-C₆, lower alkoxy of C₁-C₆ such as

CH₂OH and CH₂CH₂OH, halogenated (F, Cl, Br, I) lower alkoxy of C₁-C₆, CO₂H, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H, CH=CHCO₂R';

5 R' is an optionally substituted alkyl of C₁-C₁₂ (particularly when the alkyl is an amino acid residue), cycloalkyl, optionally substituted alkynyl of C₂-C₆, optionally substituted lower alkenyl of C₂-C₆, or optionally substituted acyl.

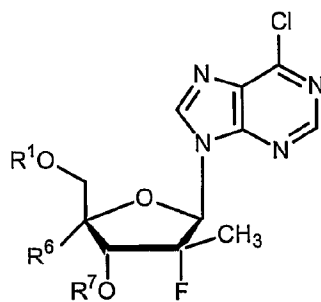
or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of a Dengue virus
10 infection in a host.

101. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β-D) of the formula:



15 or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of a Dengue virus infection in a host.

20 102. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β-D) of the formula:



201

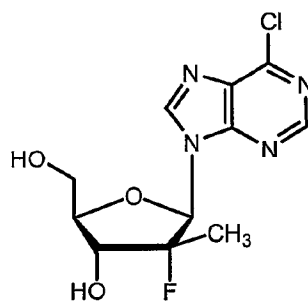
wherein

5 R¹ and R⁷ are independently H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid, 10 including a phospholipid, an L or D-amino acid, a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R¹ or R⁷ is independently H or phosphate; R¹ and R⁷ 15 can also be linked with cyclic phosphate group; and,

R⁶ is an optionally substituted alkyl (including lower alkyl), cyano (CN), CH₃, OCH₃, OCH₂CH₃, hydroxy methyl (CH₂OH), fluoromethyl (CH₂F), azido (N₃), CHCN, CH₂N₃, CH₂NH₂, CH₂NHCH₃, CH₂N(CH₃)₂, alkyne (optionally substituted), or 20 fluoro and,

or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of a Dengue virus infection in a host.

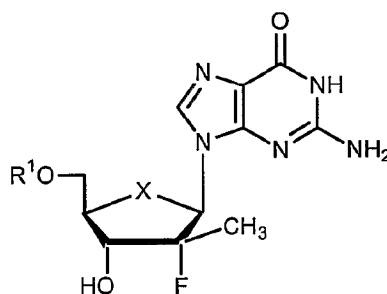
103. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro- 25 2'-*C*-methyl nucleoside (β-D) of the formula:



or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of a Dengue virus infection in a host.

5

104. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D) of the formula:



wherein

10

X is O, S, CH₂, Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), C(W)₂, wherein W is F, Cl, Br, or I; and

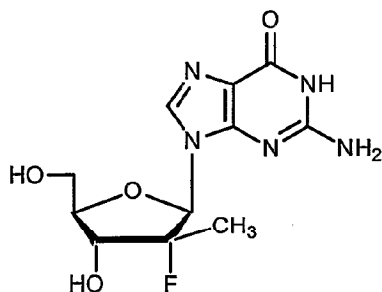
15

R¹ is H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, H-phosphonate, including stabilized H-phosphonates, acyl, including optionally substituted phenyl and lower acyl, alkyl, including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives, sulfonate ester, including alkyl or arylalkyl sulfonyl, including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted, a lipid,

including a phospholipid, an L or D-amino acid, a carbohydrate, a peptide, a cholesterol, or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R¹ is H or phosphate;

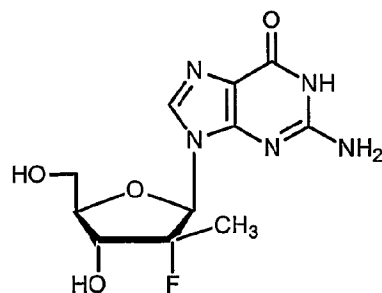
or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of a Dengue virus infection in a host.

105. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β-D) of the formula:



or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of a Dengue virus infection in a host.

106. Use of an antivirally effective amount of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β-D) of the formula:



or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of a West Nile virus infection in a host.

5 107. The use claim 31, wherein the antivirally effective amount of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside is administered in combination or alternation with at least one treatment selected from the group consisting of: interferon, including interferon alpha 2a, interferon alpha 2b, a pegylated interferon, interferon beta, interferon gamma, interferon tau and interferon omega; an
10 interleukin, including interleukin 10 and interleukin 12; ribavirin; interferon alpha or pegylated interferon alpha in combination with ribavirin or levovirin; levovirin; a protease inhibitor including an NS3 inhibitor, a NS3-4A inhibitor; a helicase inhibitor; a polymerase inhibitor including HCV RNA polymerase and NS5B
15 polymerase inhibitor; gliotoxin; an IRES inhibitor; and antisense oligonucleotide; a thiazolidine derivative; a benzanilide, a ribozyme; another nucleoside, nucleoside prodrug or nucleoside derivative; a 1-amino-alkylcyclohexane; an antioxidant including vitamin E; squalene; amantadine; a bile acid; N-(phosphonoacetyl)-L-aspartic acid; a benzenedicarboxamide; polyadenylic acid; a benzimidazoles; thymosin; a beta tubulin inhibitor; a prophylactic vaccine; an immune modulator, an
20 IMPDH inhibitor; silybin-phosphatidylcholine phytosome; and mycophenolate.

 108. The use claim 41, wherein the antivirally effective amount of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside is administered in combination or alternation with at least one treatment selected from the group consisting of:
25 interferon, including interferon alpha 2a, interferon alpha 2b, a pegylated interferon, interferon beta, interferon gamma, interferon tau and interferon omega; an interleukin, including interleukin 10 and interleukin 12; ribavirin; interferon alpha or pegylated interferon alpha in combination with ribavirin or levovirin; levovirin; a protease inhibitor including an NS3 inhibitor, a NS3-4A inhibitor; a helicase
30 inhibitor; a polymerase inhibitor including HCV RNA polymerase and NS5B polymerase inhibitor; gliotoxin; an IRES inhibitor; and antisense oligonucleotide; a

thiazolidine derivative; a benzanilide, a ribozyme; another nucleoside, nucleoside prodrug or nucleoside derivative; a 1-amino-alkylcyclohexane; an antioxidant including vitamin E; squalene; amantadine; a bile acid; N-(phosphonoacetyl)-L-aspartic acid; a benzenedicarboxamide; polyadenylic acid; a benzimidazoles;
5 thymosin; a beta tubulin inhibitor; a prophylactic vaccine; an immune modulator, an IMPDH inhibitor; silybin-phosphatidylcholine phytosome; and mycophenolate.

109. The use of claim 43, wherein the antivirally effective amount of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside is administered in combination or
10 alternation with at least one treatment selected from the group consisting of: interferon, including interferon alpha 2a, interferon alpha 2b, a pegylated interferon, interferon beta, interferon gamma, interferon tau and interferon omega; an interleukin, including interleukin 10 and interleukin 12; ribavirin; interferon alpha or pegylated interferon alpha in combination with ribavirin or levovirin; levovirin; a
15 protease inhibitor including an NS3 inhibitor, a NS3-4A inhibitor; a helicase inhibitor; a polymerase inhibitor including HCV RNA polymerase and NS5B polymerase inhibitor; gliotoxin; an IRES inhibitor; and antisense oligonucleotide; a thiazolidine derivative; a benzanilide, a ribozyme; another nucleoside, nucleoside prodrug or nucleoside derivative; a 1-amino-alkylcyclohexane; an antioxidant
20 including vitamin E; squalene; amantadine; a bile acid; N-(phosphonoacetyl)-L-aspartic acid; a benzenedicarboxamide; polyadenylic acid; a benzimidazoles; thymosin; a beta tubulin inhibitor; a prophylactic vaccine; an immune modulator, an IMPDH inhibitor; silybin-phosphatidylcholine phytosome; and mycophenolate.

25 110. The use of claim 45, wherein the antivirally effective amount of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside is administered in combination or alternation with at least one treatment selected from the group consisting of: interferon, including interferon alpha 2a, interferon alpha 2b, a pegylated interferon, interferon beta, interferon gamma, interferon tau and interferon omega; an
30 interleukin, including interleukin 10 and interleukin 12; ribavirin; interferon alpha or pegylated interferon alpha in combination with ribavirin or levovirin; levovirin; a

protease inhibitor including an NS3 inhibitor, a NS3-4A inhibitor; a helicase inhibitor; a polymerase inhibitor including HCV RNA polymerase and NS5B polymerase inhibitor; gliotoxin; an IRES inhibitor; and antisense oligonucleotide; a thiazolidine derivative; a benzanilide, a ribozyme; another nucleoside, nucleoside
5 prodrug or nucleoside derivative; a 1-amino-alkylcyclohexane; an antioxidant including vitamin E; squalene; amantadine; a bile acid; N-(phosphonoacetyl)-L-aspartic acid; a benzenedicarboxamide; polyadenylic acid; a benzimidazoles; thymosin; a beta tubulin inhibitor; a prophylactic vaccine; an immune modulator, an IMPDH inhibitor; silybin-phosphatidylcholine phytosome; and mycophenolate.

10

111. The use of claim 46, wherein the antivirally effective amount of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside is administered in combination or alternation with at least one treatment selected from the group consisting of: interferon, including interferon alpha 2a, interferon alpha 2b, a pegylated interferon,
15 interferon beta, interferon gamma, interferon tau and interferon omega; an interleukin, including interleukin 10 and interleukin 12; ribavirin; interferon alpha or pegylated interferon alpha in combination with ribavirin or levovirin; levovirin; a protease inhibitor including an NS3 inhibitor, a NS3-4A inhibitor; a helicase inhibitor; a polymerase inhibitor including HCV RNA polymerase and NS5B
20 polymerase inhibitor; gliotoxin; an IRES inhibitor; and antisense oligonucleotide; a thiazolidine derivative; a benzanilide, a ribozyme; another nucleoside, nucleoside prodrug or nucleoside derivative; a 1-amino-alkylcyclohexane; an antioxidant including vitamin E; squalene; amantadine; a bile acid; N-(phosphonoacetyl)-L-aspartic acid; a benzenedicarboxamide; polyadenylic acid; a benzimidazoles;
25 thymosin; a beta tubulin inhibitor; a prophylactic vaccine; an immune modulator, an IMPDH inhibitor; silybin-phosphatidylcholine phytosome; and mycophenolate.

112. The use of claim 56, wherein the antivirally effective amount of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside is administered in combination or
30 alternation with at least one treatment selected from the group consisting of: interferon, including interferon alpha 2a, interferon alpha 2b, a pegylated interferon,

interferon beta, interferon gamma, interferon tau and interferon omega; an interleukin, including interleukin 10 and interleukin 12; ribavirin; interferon alpha or pegylated interferon alpha in combination with ribavirin or levovirin; levovirin; a protease inhibitor including an NS3 inhibitor, a NS3-4A inhibitor; a helicase inhibitor; a polymerase inhibitor including HCV RNA polymerase and NS5B polymerase inhibitor; gliotoxin; an IRES inhibitor; and antisense oligonucleotide; a thiazolidine derivative; a benzanilide, a ribozyme; another nucleoside, nucleoside prodrug or nucleoside derivative; a 1-amino-alkylcyclohexane; an antioxidant including vitamin E; squalene; amantadine; a bile acid; N-(phosphonoacetyl)-L-aspartic acid; a benzenedicarboxamide; polyadenylic acid; a benzimidazoles; thymosin; a beta tubulin inhibitor; a prophylactic vaccine; an immune modulator, an IMPDH inhibitor; silybin-phosphatidylcholine phytosome; and mycophenolate.

113. The use of claim 58, wherein the antivirally effective amount of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside is administered in combination or alternation with at least one treatment selected from the group consisting of: interferon, including interferon alpha 2a, interferon alpha 2b, a pegylated interferon, interferon beta, interferon gamma, interferon tau and interferon omega; an interleukin, including interleukin 10 and interleukin 12; ribavirin; interferon alpha or pegylated interferon alpha in combination with ribavirin or levovirin; levovirin; a protease inhibitor including an NS3 inhibitor, a NS3-4A inhibitor; a helicase inhibitor; a polymerase inhibitor including HCV RNA polymerase and NS5B polymerase inhibitor; gliotoxin; an IRES inhibitor; and antisense oligonucleotide; a thiazolidine derivative; a benzanilide, a ribozyme; another nucleoside, nucleoside prodrug or nucleoside derivative; a 1-amino-alkylcyclohexane; an antioxidant including vitamin E; squalene; amantadine; a bile acid; N-(phosphonoacetyl)-L-aspartic acid; a benzenedicarboxamide; polyadenylic acid; a benzimidazoles; thymosin; a beta tubulin inhibitor; a prophylactic vaccine; an immune modulator, an IMPDH inhibitor; silybin-phosphatidylcholine phytosome; and mycophenolate.

114. The use of claim 60, wherein the antivirally effective amount of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside is administered in combination or alternation with at least one treatment selected from the group consisting of: interferon, including interferon alpha 2a, interferon alpha 2b, a pegylated interferon, interferon beta, interferon gamma, interferon tau and interferon omega; an interleukin, including interleukin 10 and interleukin 12; ribavirin; interferon alpha or pegylated interferon alpha in combination with ribavirin or levovirin; levovirin; a protease inhibitor including an NS3 inhibitor, a NS3-4A inhibitor; a helicase inhibitor; a polymerase inhibitor including HCV RNA polymerase and NS5B polymerase inhibitor; gliotoxin; an IRES inhibitor; and antisense oligonucleotide; a thiazolidine derivative; a benzanilide, a ribozyme; another nucleoside, nucleoside prodrug or nucleoside derivative; a 1-amino-alkylcyclohexane; an antioxidant including vitamin E; squalene; amantadine; a bile acid; N-(phosphonoacetyl)-L-aspartic acid; a benzenedicarboxamide; polyadenylic acid; a benzimidazoles; thymosin; a beta tubulin inhibitor; a prophylactic vaccine; an immune modulator, an IMPDH inhibitor; silybin-phosphatidylcholine phytosome; and mycophenolate.

115. The use of claim 61, wherein the antivirally effective amount of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside is administered in combination or alternation with at least one treatment selected from the group consisting of: interferon, including interferon alpha 2a, interferon alpha 2b, a pegylated interferon, interferon beta, interferon gamma, interferon tau and interferon omega; an interleukin, including interleukin 10 and interleukin 12; ribavirin; interferon alpha or pegylated interferon alpha in combination with ribavirin or levovirin; levovirin; a protease inhibitor including an NS3 inhibitor, a NS3-4A inhibitor; a helicase inhibitor; a polymerase inhibitor including HCV RNA polymerase and NS5B polymerase inhibitor; gliotoxin; an IRES inhibitor; and antisense oligonucleotide; a thiazolidine derivative; a benzanilide, a ribozyme; another nucleoside, nucleoside prodrug or nucleoside derivative; a 1-amino-alkylcyclohexane; an antioxidant including vitamin E; squalene; amantadine; a bile acid; N-(phosphonoacetyl)-L-aspartic acid; a benzenedicarboxamide; polyadenylic acid; a benzimidazoles;

thymosin; a beta tubulin inhibitor; a prophylactic vaccine; an immune modulator, an IMPDH inhibitor; silybin-phosphatidylcholine phytosome; and mycophenolate.

116. The use of claim 71, wherein the antivirally effective amount of
5 (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside is administered in combination or alternation with at least one treatment selected from the group consisting of: interferon, including interferon alpha 2a, interferon alpha 2b, a pegylated interferon, interferon beta, interferon gamma, interferon tau and interferon omega; an interleukin, including interleukin 10 and interleukin 12; ribavirin; interferon alpha
10 or pegylated interferon alpha in combination with ribavirin or levovirin; levovirin; a protease inhibitor including an NS3 inhibitor, a NS3-4A inhibitor; a helicase inhibitor; a polymerase inhibitor including HCV RNA polymerase and NS5B polymerase inhibitor; gliotoxin; an IRES inhibitor; and antisense oligonucleotide; a thiazolidine derivative; a benzanilide, a ribozyme; another nucleoside, nucleoside
15 prodrug or nucleoside derivative; a 1-amino-alkylcyclohexane; an antioxidant including vitamin E; squalene; amantadine; a bile acid; N-(phosphonoacetyl)-L-aspartic acid; a benzenedicarboxamide; polyadenylic acid; a benzimidazoles; thymosin; a beta tubulin inhibitor; a prophylactic vaccine; an immune modulator, an IMPDH inhibitor; silybin-phosphatidylcholine phytosome; and mycophenolate.

20

117. The use of claim 73, wherein the antivirally effective amount of
(2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside is administered in combination or alternation with at least one treatment selected from the group consisting of: interferon, including interferon alpha 2a, interferon alpha 2b, a pegylated interferon,
25 interferon beta, interferon gamma, interferon tau and interferon omega; an interleukin, including interleukin 10 and interleukin 12; ribavirin; interferon alpha or pegylated interferon alpha in combination with ribavirin or levovirin; levovirin; a protease inhibitor including an NS3 inhibitor, a NS3-4A inhibitor; a helicase inhibitor; a polymerase inhibitor including HCV RNA polymerase and NS5B
30 polymerase inhibitor; gliotoxin; an IRES inhibitor; and antisense oligonucleotide; a thiazolidine derivative; a benzanilide, a ribozyme; another nucleoside, nucleoside

prodrug or nucleoside derivative; a 1-amino-alkylcyclohexane; an antioxidant including vitamin E; squalene; amantadine; a bile acid; N-(phosphonoacetyl)-L-aspartic acid; a benzenedicarboxamide; polyadenylic acid; a benzimidazoles; thymosin; a beta tubulin inhibitor; a prophylactic vaccine; an immune modulator, an
5 IMPDH inhibitor; silybin-phosphatidylcholine phytosome; and mycophenolate.

118. The use of claim 75, wherein the antivirally effective amount of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside is administered in combination or alternation with at least one treatment selected from the group consisting of:
10 interferon, including interferon alpha 2a, interferon alpha 2b, a pegylated interferon, interferon beta, interferon gamma, interferon tau and interferon omega; an interleukin, including interleukin 10 and interleukin 12; ribavirin; interferon alpha or pegylated interferon alpha in combination with ribavirin or levovirin; levovirin; a protease inhibitor including an NS3 inhibitor, a NS3-4A inhibitor; a helicase
15 inhibitor; a polymerase inhibitor including HCV RNA polymerase and NS5B polymerase inhibitor; gliotoxin; an IRES inhibitor; and antisense oligonucleotide; a thiazolidine derivative; a benzanilide, a ribozyme; another nucleoside, nucleoside prodrug or nucleoside derivative; a 1-amino-alkylcyclohexane; an antioxidant including vitamin E; squalene; amantadine; a bile acid; N-(phosphonoacetyl)-L-aspartic acid; a benzenedicarboxamide; polyadenylic acid; a benzimidazoles;
20 thymosin; a beta tubulin inhibitor; a prophylactic vaccine; an immune modulator, an IMPDH inhibitor; silybin-phosphatidylcholine phytosome; and mycophenolate.

119. The use of claim 76, wherein the antivirally effective amount of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside is administered in combination or alternation with at least one treatment selected from the group consisting of:
25 interferon, including interferon alpha 2a, interferon alpha 2b, a pegylated interferon, interferon beta, interferon gamma, interferon tau and interferon omega; an interleukin, including interleukin 10 and interleukin 12; ribavirin; interferon alpha or pegylated interferon alpha in combination with ribavirin or levovirin; levovirin; a
30 protease inhibitor including an NS3 inhibitor, a NS3-4A inhibitor; a helicase

inhibitor; a polymerase inhibitor including HCV RNA polymerase and NS5B polymerase inhibitor; gliotoxin; an IRES inhibitor; and antisense oligonucleotide; a thiazolidine derivative; a benzanilide, a ribozyme; another nucleoside, nucleoside prodrug or nucleoside derivative; a 1-amino-alkylcyclohexane; an antioxidant
5 including vitamin E; squalene; amantadine; a bile acid; N-(phosphonoacetyl)-L-aspartic acid; a benzenedicarboxamide; polyadenylic acid; a benzimidazoles; thymosin; a beta tubulin inhibitor; a prophylactic vaccine; an immune modulator, an IMPDH inhibitor; silybin-phosphatidylcholine phytosome; and mycophenolate.

10 120. The use of claim 86, wherein the antivirally effective amount of (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside is administered in combination or alternation with at least one treatment selected from the group consisting of: interferon, including interferon alpha 2a, interferon alpha 2b, a pegylated interferon, interferon beta, interferon gamma, interferon tau and interferon omega; an
15 interleukin, including interleukin 10 and interleukin 12; ribavirin; interferon alpha or pegylated interferon alpha in combination with ribavirin or levovirin; levovirin; a protease inhibitor including an NS3 inhibitor, a NS3-4A inhibitor; a helicase inhibitor; a polymerase inhibitor including HCV RNA polymerase and NS5B polymerase inhibitor; gliotoxin; an IRES inhibitor; and antisense oligonucleotide; a
20 thiazolidine derivative; a benzanilide, a ribozyme; another nucleoside, nucleoside prodrug or nucleoside derivative; a 1-amino-alkylcyclohexane; an antioxidant including vitamin E; squalene; amantadine; a bile acid; N-(phosphonoacetyl)-L-aspartic acid; a benzenedicarboxamide; polyadenylic acid; a benzimidazoles; thymosin; a beta tubulin inhibitor; a prophylactic vaccine; an immune modulator, an
25 IMPDH inhibitor; silybin-phosphatidylcholine phytosome; and mycophenolate.

121. The use of claim 88, wherein the antivirally effective amount of (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside is administered in combination or alternation with at least one treatment selected from the group consisting of:
30 interferon, including interferon alpha 2a, interferon alpha 2b, a pegylated interferon, interferon beta, interferon gamma, interferon tau and interferon omega; an

interleukin, including interleukin 10 and interleukin 12; ribavirin; interferon alpha or pegylated interferon alpha in combination with ribavirin or levovirin; levovirin; a protease inhibitor including an NS3 inhibitor, a NS3-4A inhibitor; a helicase inhibitor; a polymerase inhibitor including HCV RNA polymerase and NS5B
5 polymerase inhibitor; gliotoxin; an IRES inhibitor; and antisense oligonucleotide; a thiazolidine derivative; a benzanilide, a ribozyme; another nucleoside, nucleoside prodrug or nucleoside derivative; a 1-amino-alkylcyclohexane; an antioxidant including vitamin E; squalene; amantadine; a bile acid; N-(phosphonoacetyl)-L-aspartic acid; a benzenedicarboxamide; polyadenylic acid; a benzimidazoles;
10 thymosin; a beta tubulin inhibitor; a prophylactic vaccine; an immune modulator, an IMPDH inhibitor; silybin-phosphatidylcholine phytosome; and mycophenolate.

122. The use of claim 90, wherein the antivirally effective amount of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside is administered in combination or
15 alternation with at least one treatment selected from the group consisting of: interferon, including interferon alpha 2a, interferon alpha 2b, a pegylated interferon, interferon beta, interferon gamma, interferon tau and interferon omega; an interleukin, including interleukin 10 and interleukin 12; ribavirin; interferon alpha or pegylated interferon alpha in combination with ribavirin or levovirin; levovirin; a
20 protease inhibitor including an NS3 inhibitor, a NS3-4A inhibitor; a helicase inhibitor; a polymerase inhibitor including HCV RNA polymerase and NS5B polymerase inhibitor; gliotoxin; an IRES inhibitor; and antisense oligonucleotide; a thiazolidine derivative; a benzanilide, a ribozyme; another nucleoside, nucleoside prodrug or nucleoside derivative; a 1-amino-alkylcyclohexane; an antioxidant
25 including vitamin E; squalene; amantadine; a bile acid; N-(phosphonoacetyl)-L-aspartic acid; a benzenedicarboxamide; polyadenylic acid; a benzimidazoles; thymosin; a beta tubulin inhibitor; a prophylactic vaccine; an immune modulator, an IMPDH inhibitor; silybin-phosphatidylcholine phytosome; and mycophenolate.

30 123. The use of claim 91, wherein the antivirally effective amount of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside is administered in combination or

alternation with at least one treatment selected from the group consisting of:
interferon, including interferon alpha 2a, interferon alpha 2b, a pegylated interferon,
interferon beta, interferon gamma, interferon tau and interferon omega; an
interleukin, including interleukin 10 and interleukin 12; ribavirin; interferon alpha
5 or pegylated interferon alpha in combination with ribavirin or levovirin; levovirin; a
protease inhibitor including an NS3 inhibitor, a NS3-4A inhibitor; a helicase
inhibitor; a polymerase inhibitor including HCV RNA polymerase and NS5B
polymerase inhibitor; gliotoxin; an IRES inhibitor; and antisense oligonucleotide; a
thiazolidine derivative; a benzanilide, a ribozyme; another nucleoside, nucleoside
10 prodrug or nucleoside derivative; a 1-amino-alkylcyclohexane; an antioxidant
including vitamin E; squalene; amantadine; a bile acid; N-(phosphonoacetyl)-L-
aspartic acid; a benzenedicarboxamide; polyadenylic acid; a benzimidazoles;
thymosin; a beta tubulin inhibitor; a prophylactic vaccine; an immune modulator, an
IMPDH inhibitor; silybin-phosphatidylcholine phytosome; and mycophenolate.

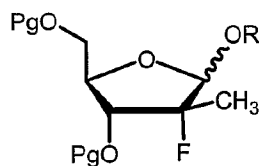
15 124. The use of claim 101, wherein the antivirally effective amount of
(2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside is administered in combination or
alternation with at least one treatment selected from the group consisting of:
interferon, including interferon alpha 2a, interferon alpha 2b, a pegylated interferon,
interferon beta, interferon gamma, interferon tau and interferon omega; an
20 interleukin, including interleukin 10 and interleukin 12; ribavirin; interferon alpha
or pegylated interferon alpha in combination with ribavirin or levovirin; levovirin; a
protease inhibitor including an NS3 inhibitor, a NS3-4A inhibitor; a helicase
inhibitor; a polymerase inhibitor including HCV RNA polymerase and NS5B
polymerase inhibitor; gliotoxin; an IRES inhibitor; and antisense oligonucleotide; a
25 thiazolidine derivative; a benzanilide, a ribozyme; another nucleoside, nucleoside
prodrug or nucleoside derivative; a 1-amino-alkylcyclohexane; an antioxidant
including vitamin E; squalene; amantadine; a bile acid; N-(phosphonoacetyl)-L-
aspartic acid; a benzenedicarboxamide; polyadenylic acid; a benzimidazoles;
thymosin; a beta tubulin inhibitor; a prophylactic vaccine; an immune modulator, an
30 IMPDH inhibitor; silybin-phosphatidylcholine phytosome; and mycophenolate.

125. The use of claim 103, wherein the antivirally effective amount of
(2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside is administered in combination or

alternation with at least one treatment selected from the group consisting of:
interferon, including interferon alpha 2a, interferon alpha 2b, a pegylated interferon,
interferon beta, interferon gamma, interferon tau and interferon omega; an
interleukin, including interleukin 10 and interleukin 12; ribavirin; interferon alpha
5 or pegylated interferon alpha in combination with ribavirin or levovirin; levovirin; a
protease inhibitor including an NS3 inhibitor, a NS3-4A inhibitor; a helicase
inhibitor; a polymerase inhibitor including HCV RNA polymerase and NS5B
polymerase inhibitor; gliotoxin; an IRES inhibitor; and antisense oligonucleotide; a
thiazolidine derivative; a benzanilide, a ribozyme; another nucleoside, nucleoside
10 prodrug or nucleoside derivative; a 1-amino-alkylcyclohexane; an antioxidant
including vitamin E; squalene; amantadine; a bile acid; N-(phosphonoacetyl)-L-
aspartic acid; a benzenedicarboxamide; polyadenylic acid; a benzimidazoles;
thymosin; a beta tubulin inhibitor; a prophylactic vaccine; an immune modulator, an
IMPDH inhibitor; silybin-phosphatidylcholine phytosome; and mycophenolate.

15 126. The use of claim 105, wherein the antivirally effective amount of
(2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside is administered in combination or
alternation with at least one treatment selected from the group consisting of:
interferon, including interferon alpha 2a, interferon alpha 2b, a pegylated interferon,
interferon beta, interferon gamma, interferon tau and interferon omega; an
20 interleukin, including interleukin 10 and interleukin 12; ribavirin; interferon alpha
or pegylated interferon alpha in combination with ribavirin or levovirin; levovirin; a
protease inhibitor including an NS3 inhibitor, a NS3-4A inhibitor; a helicase
inhibitor; a polymerase inhibitor including HCV RNA polymerase and NS5B
polymerase inhibitor; gliotoxin; an IRES inhibitor; and antisense oligonucleotide; a
25 thiazolidine derivative; a benzanilide, a ribozyme; another nucleoside, nucleoside
prodrug or nucleoside derivative; a 1-amino-alkylcyclohexane; an antioxidant
including vitamin E; squalene; amantadine; a bile acid; N-(phosphonoacetyl)-L-
aspartic acid; a benzenedicarboxamide; polyadenylic acid; a benzimidazoles;
thymosin; a beta tubulin inhibitor; a prophylactic vaccine; an immune modulator, an
30 IMPDH inhibitor; silybin-phosphatidylcholine phytosome; and mycophenolate.

127. A method of synthesizing a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D or β -L) comprising glycosylation of a nucleobase with an intermediate structure:

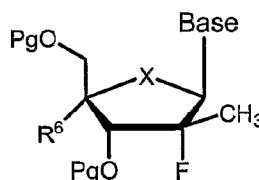


1-4

5 wherein R is lower alkyl, acyl, benzoyl, or mesyl; and Pg is any acceptable protecting group consisting of but not limited to C(O)-alkyl, C(O)Ph, C(O)aryl, CH₃, CH₂-alkyl, CH₂-alkenyl, CH₂Ph, CH₂-aryl, CH₂O-alkyl, CH₂O-aryl, SO₂-alkyl, SO₂-aryl, *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, or both Pg's may come together to form a 1,3-(1,1,3,3-tetraisopropylidisiloxanylidene).

10

128. A method of synthesizing a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D or β -L) comprising selective deprotection of either Pg in an intermediate of the structure:



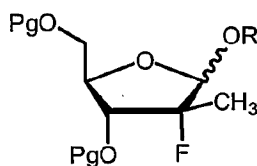
2-5

15

wherein, X is O, S, CH₂, Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), C(W)₂, wherein W is F, Cl, Br, or I; and Pg is independently any pharmaceutically acceptable protecting group selected from the group consisting of C(O)-alkyl, C(O)Ph, C(O)aryl, CH₃, CH₂-alkyl, CH₂-alkenyl, CH₂Ph, CH₂-aryl, CH₂O-alkyl, CH₂O-aryl, SO₂-alkyl, SO₂-aryl, *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, or both Pg's may come together to form a 1,3-(1,1,3,3-tetraisopropylidisiloxanylidene).

20

129. An intermediate in the synthesis of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D or β -L), wherein the intermediate is of the structure:

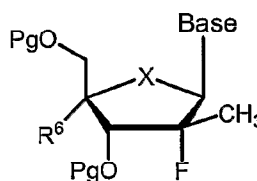


1-4

5 wherein R is lower alkyl, acyl, benzoyl, or mesyl; and Pg is any acceptable protecting group consisting of but not limited to C(O)-alkyl, C(O)Ph, C(O)aryl, CH₃, CH₂-alkyl, CH₂-alkenyl, CH₂Ph, CH₂-aryl, CH₂O-alkyl, CH₂O-aryl, SO₂-alkyl, SO₂-aryl, *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, or both Pg's may come together to for a 1,3-(1,1,3,3-tetraisopropylidisiloxanylidene).

10

130. An intermediate in the synthesis of a (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside (β -D or β -L), wherein the intermediate is of the structure:



2-5

15 wherein, X is O, S, CH₂, Se, NH, N-alkyl, CHW (*R*, *S*, or racemic), C(W)₂, wherein W is F, Cl, Br, or I; and Pg is independently any pharmaceutically acceptable protecting group selected from the group consisting of C(O)-alkyl, C(O)Ph, C(O)aryl, CH₃, CH₂-alkyl, CH₂-alkenyl, CH₂Ph, CH₂-aryl, CH₂O-alkyl, CH₂O-aryl, SO₂-alkyl, SO₂-aryl, *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, or both Pg's may
20 come together to for a 1,3-(1,1,3,3-tetraisopropylidisiloxanylidene).

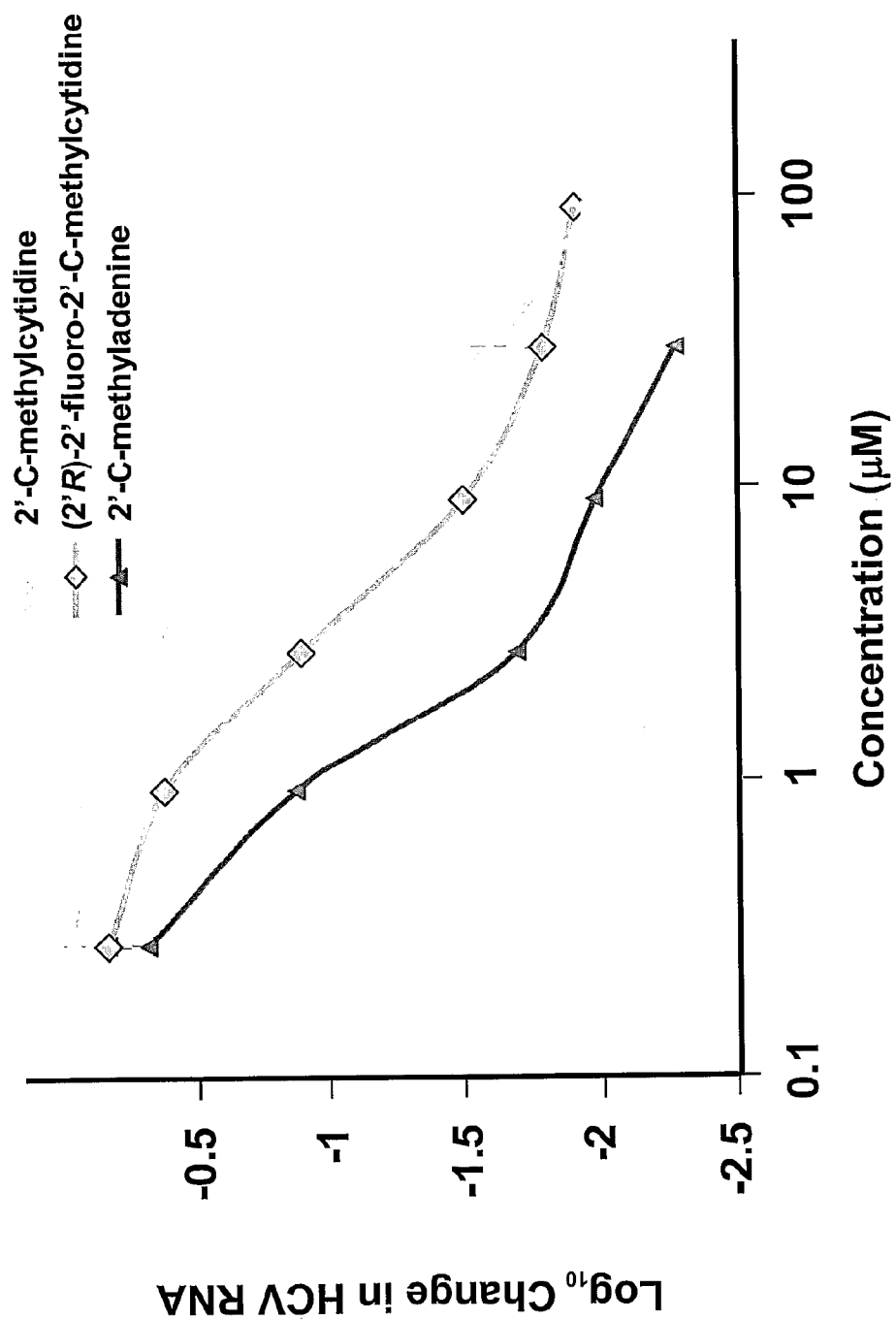


Figure 1A

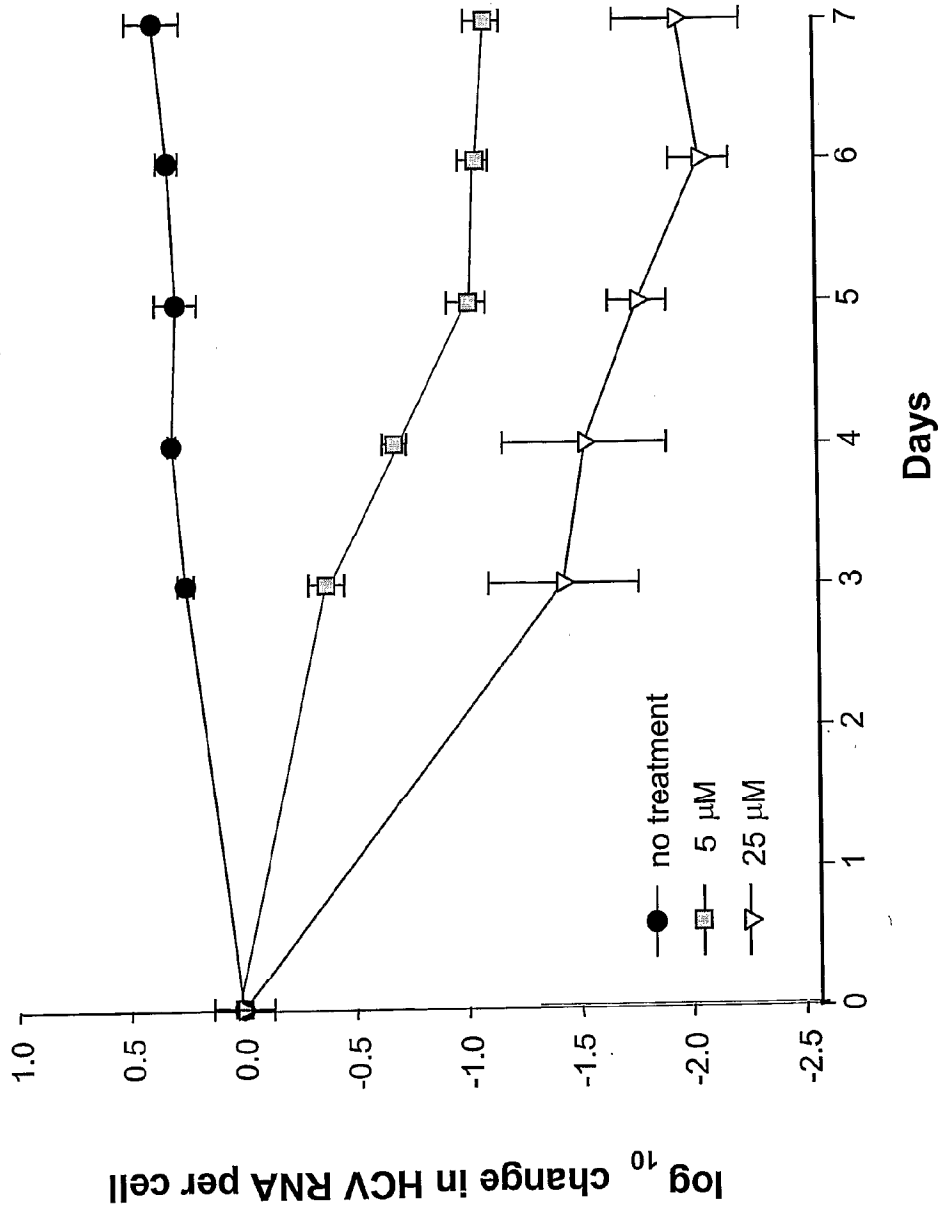


Figure 1B

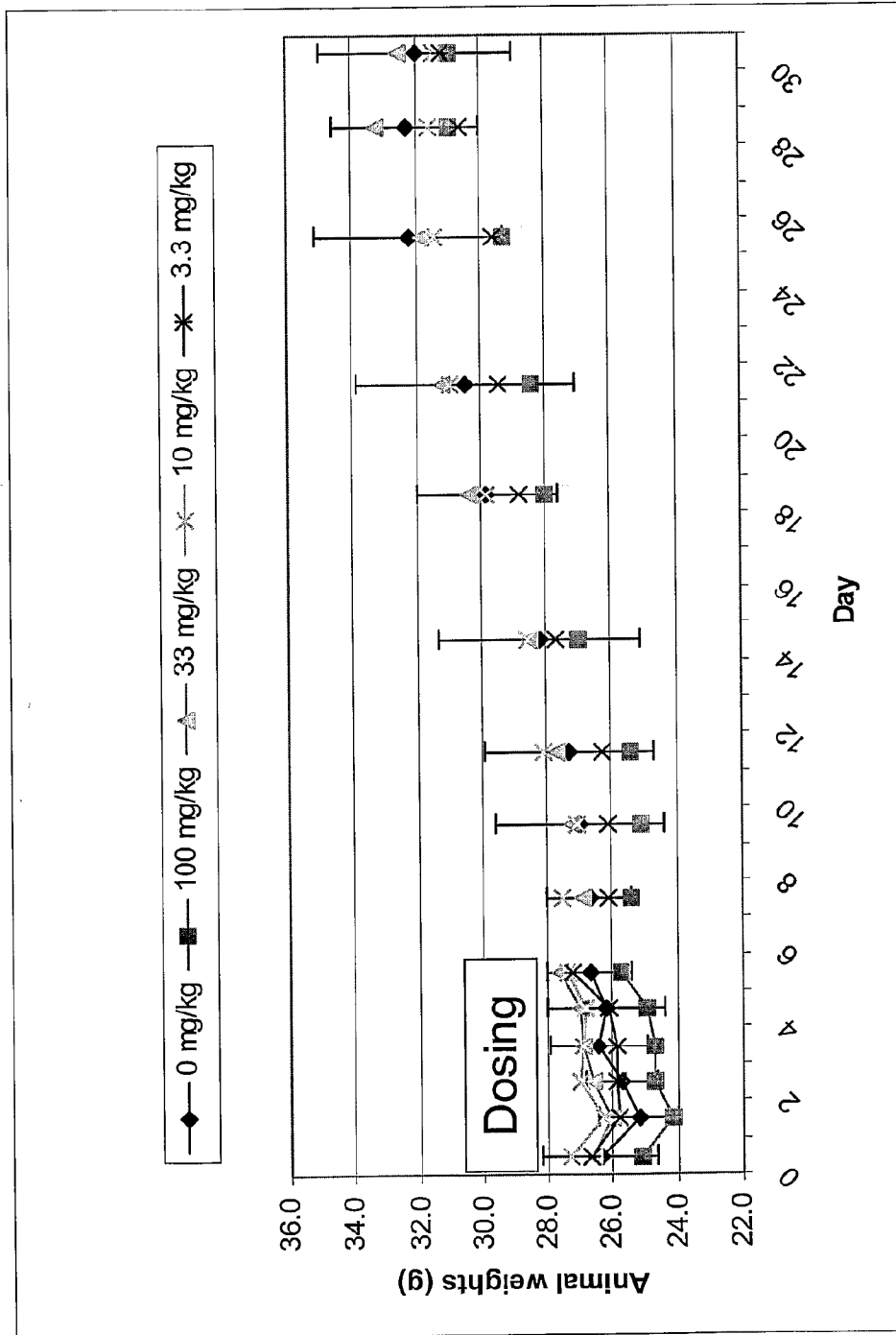


Figure 2

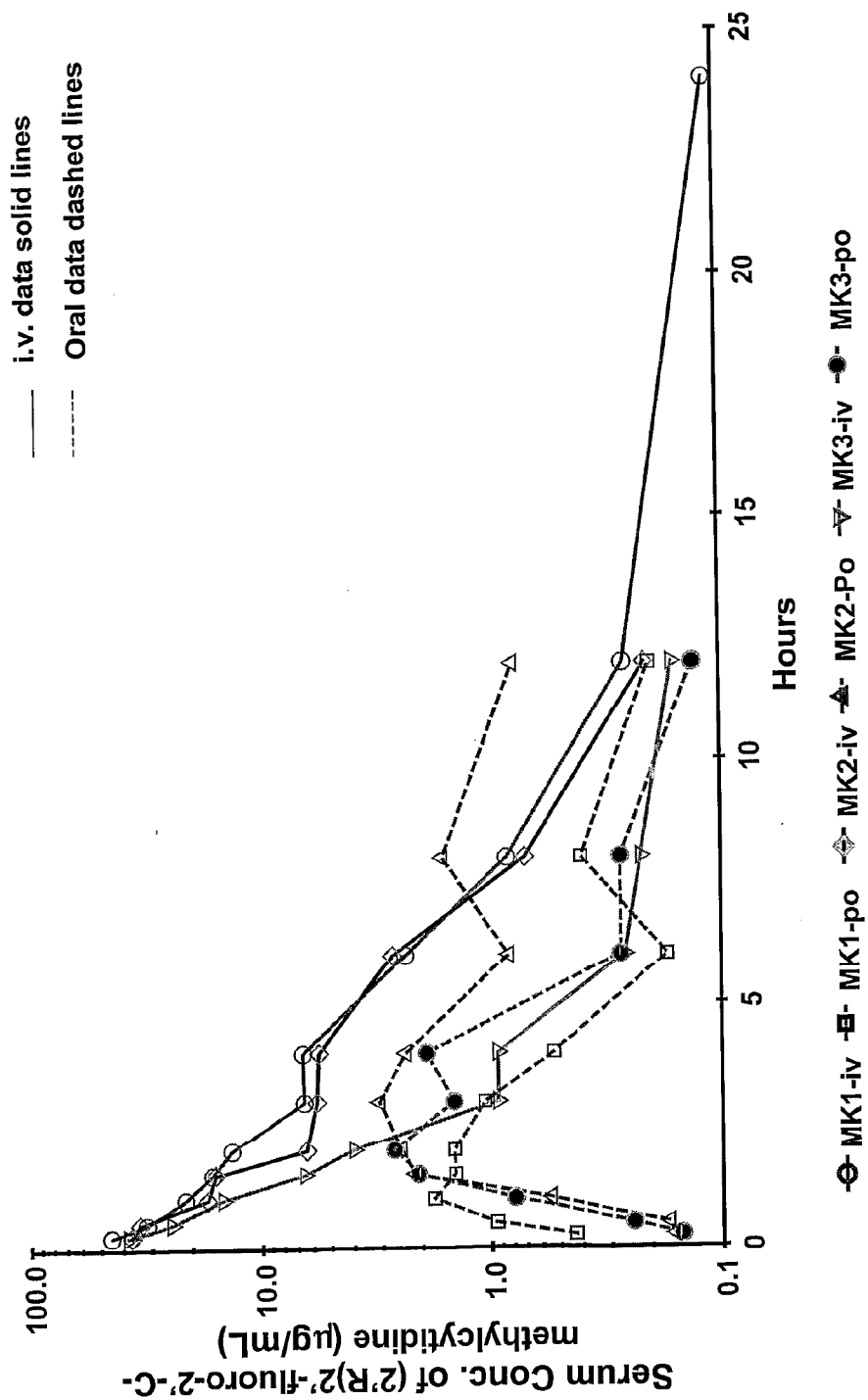


Figure 3

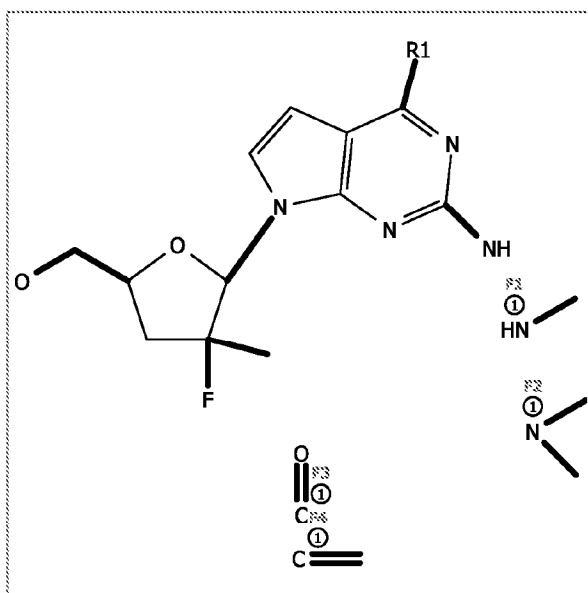
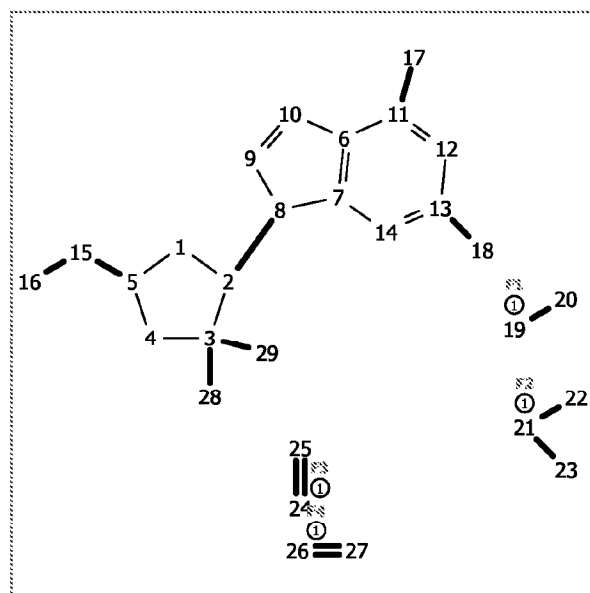
Structure Details (17077267-str2)

Chain Bonds

-  Chain Only
-  Ring or Chain
-  Ring Only

Ring Bonds

-  Closed to ring formation
-  Open to ring formation



R-group Definitions

R-group	Values
R1	H, X, OH, NH2, F1, F2, F3, F4

Node Attributes

Only nodes with attributes changed from the default value of 'Any' are included in this table.

Nodes which do not support these attributes (R-groups, shortcuts and VAP center points) are not included in this table.

Node	Type	H Count	Non H Count	Mass	Valency
1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14	Ring				
15, 16, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29	Chain				

Bond Attributes

Bond	Type	Value
6-7, 6-11, 11-12, 12-13, 13-14, 14-7	Ring	Normalized
1-2, 2-3, 3-4, 4-5, 5-1, 7-8, 8-9, 9-10, 10-6	Ring	Exact/Normalized
26-27	Chain	Exact
3-28, 3-29, 5-15, 8-2, 11-17, 13-18, 15-16, 19-20, 21-22, 21-23, 24-25	Chain	Exact/Normalized

Markush Attributes

Nodes which do not support these attributes (R-groups and VAP center points) are not included in this table.

Node	Match Level	Element Count Level
1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14	Atom	Limited
15, 16, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29	Class	Limited



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
 United States Patent and Trademark Office
 Address: COMMISSIONER FOR PATENTS
 P.O. Box 1450
 Alexandria, Virginia 22313-1450
 www.uspto.gov

BIB DATA SHEET

CONFIRMATION NO. 4237

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.		
17/077,267	10/22/2020	514	1623	37JD-199059-US13		
APPLICANTS GILEAD PHARMASSET LLC, FOSTER CITY, CA; INVENTORS Jinfa Du, Redwood City, CA; Dhanapalan Nagarathnam, Bethany, CT; Michael Joseph Sofia, Doylestown, PA; Peiyuan Wang, San Mateo, CA;						
** CONTINUING DATA ***** This application is a CON of 16/817,318 03/12/2020 ABN which is a CON of 16/516,192 07/18/2019 ABN which is a CON of 16/169,878 10/24/2018 ABN which is a CON of 15/411,506 01/20/2017 PAT 10183037 which is a CON of 14/656,546 03/12/2015 PAT 9585906 which is a CON of 14/013,237 08/29/2013 PAT 9085573 which is a CON of 13/609,614 09/11/2012 PAT 8580765 which is a CON of 13/099,671 05/03/2011 PAT 8334270 which is a CON of 12/053,015 03/21/2008 PAT 7964580 which claims benefit of 60/982,309 10/24/2007 and claims benefit of 60/909,315 03/30/2007						
** FOREIGN APPLICATIONS ***** ** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** 12/01/2020						
Foreign Priority claimed ☐ Yes ☒ No 35 USC 119(a-d) conditions met ☐ Yes ☒ No Verified and Acknowledged <u>/PATRICK T LEWIS/</u> Examiner's Signature		☐ Met after Allowance Initials	STATE OR COUNTRY CA	SHEETS DRAWINGS 0	TOTAL CLAIMS 7	INDEPENDENT CLAIMS 1
ADDRESS Gilead Sciences, Inc. c/o Sheppard Mullin Richter & Hampton LLP 650 Town Center Drive, 10th Floor Costa Mesa, CA 92626 UNITED STATES						
TITLE NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS						
FILING FEE RECEIVED 6180	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:			☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue)		

	☐ Other _____
	☐ Credit

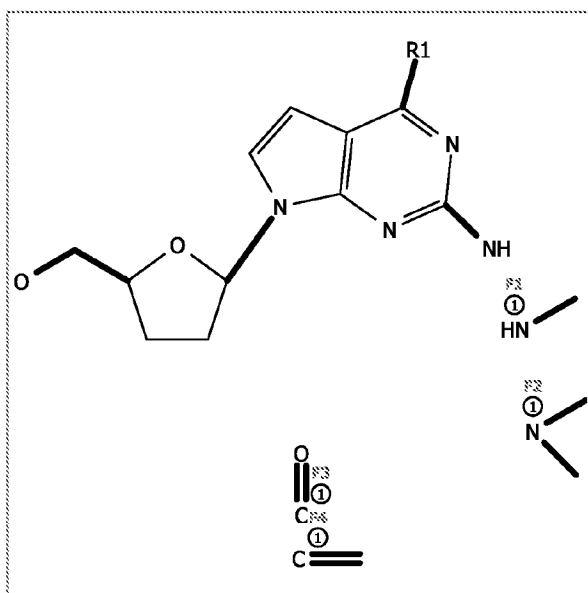
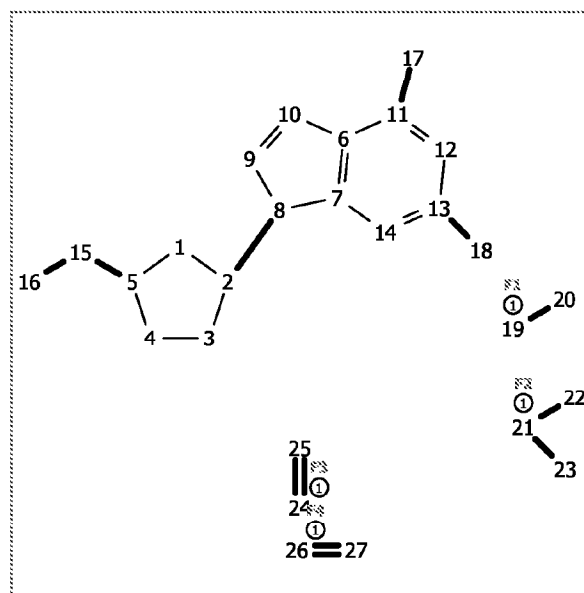
Structure Details (17077267-str1)

Chain Bonds

-  Chain Only
-  Ring or Chain
-  Ring Only

Ring Bonds

-  Closed to ring formation
-  Open to ring formation



R-group Definitions

R-group	Values
R1	H, X, OH, NH2, F1, F2, F3, F4

Node Attributes

Only nodes with attributes changed from the default value of 'Any' are included in this table.

Nodes which do not support these attributes (R-groups, shortcuts and VAP center points) are not included in this table.

Node	Type	H Count	Non H Count	Mass	Valency
1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14	Ring				
15, 16, 20, 21, 22, 23, 24, 25, 26, 27	Chain				

Bond Attributes

Bond	Type	Value
6-7, 6-11, 11-12, 12-13, 13-14, 14-7	Ring	Normalized
1-2, 2-3, 3-4, 4-5, 5-1, 7-8, 8-9, 9-10, 10-6	Ring	Exact/Normalized
26-27	Chain	Exact
5-15, 8-2, 11-17, 13-18, 15-16, 19-20, 21-22, 21-23, 24-25	Chain	Exact/Normalized

Markush Attributes

Nodes which do not support these attributes (R-groups and VAP center points) are not included in this table.

Node	Match Level	Element Count Level
1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14	Atom	Limited
15, 16, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27	Class	Limited

(FILE 'HOME' ENTERED AT 08:31:08 ON 07 APR 2022)

FILE 'REGISTRY' ENTERED AT 08:31:20 ON 07 APR 2022
L1 STRUCTURE UPLOADED
L2 50 S L1 SSS SAM
L3 12573 S L1 SSS FULL

FILE 'CAPLUS, MEDLINE, USPATFULL, USPAT2' ENTERED AT 08:36:46 ON 07
APR 2022

L4 10079 S L3
L5 4245 S L4 AND "HCV"
L6 785 S L5 AND PRODRUG
L7 372 S L6 AND PURINE
L8 0 S L7 AND ADENOSIEN
L9 111 S L7 AND ADENOSINE

FILE 'REGISTRY' ENTERED AT 08:39:12 ON 07 APR 2022
L10 STRUCTURE UPLOADED
L11 6 S L10 SSS SAM
L12 131 S L10 SSS FULL

FILE 'CAPLUS, MEDLINE, USPATFULL, USPAT2' ENTERED AT 08:41:36 ON 07
APR 2022

L13 83 S L12
L14 82 S L13 AND ("HCV" OR "HEPATITIS C")

FILE 'REGISTRY' ENTERED AT 08:57:29 ON 07 APR 2022
L15 STRUCTURE UPLOADED
L16 40 S L15 SSS SAM
L17 871 S L15 SSS FULL

FILE 'CAPLUS, MEDLINE, USPATFULL, USPAT2' ENTERED AT 08:58:43 ON 07
APR 2022

L18 518 S L17
L19 228 S L18 AND HCV

=>

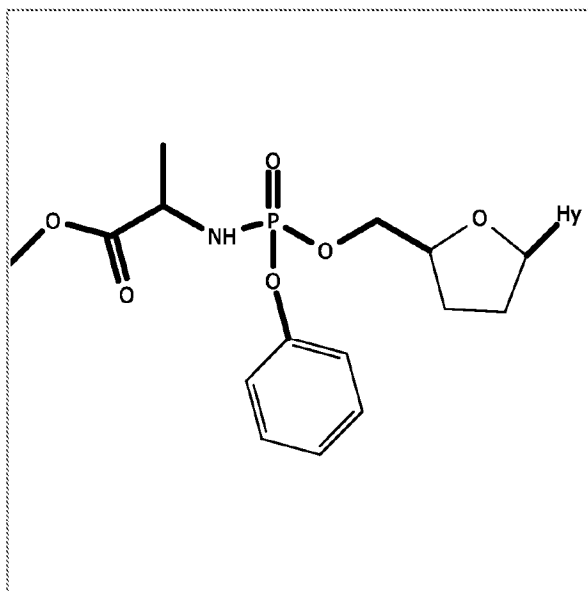
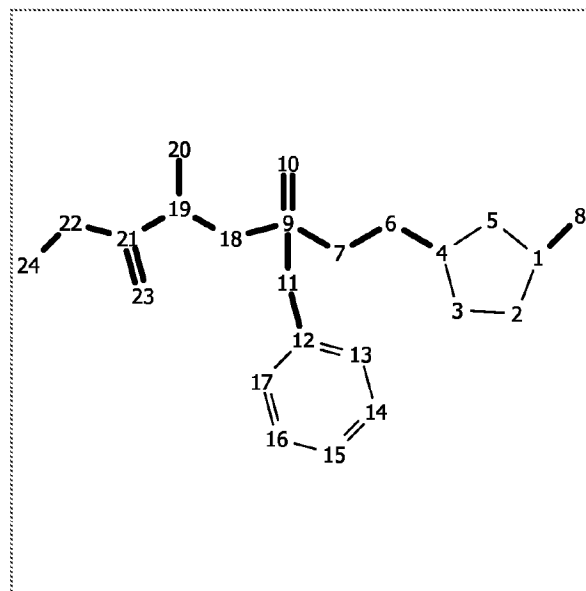
Structure Details

Chain Bonds

-  Chain Only
-  Ring or Chain
-  Ring Only

Ring Bonds

-  Closed to ring formation
-  Open to ring formation



Node Attributes

Only nodes with attributes changed from the default value of 'Any' are included in this table.

Nodes which do not support these attributes (R-groups, shortcuts and VAP center points) are not included in this table.

Node	Type	H Count	Non H Count	Mass	Valency
1, 2, 3, 4, 5, 12, 13, 14, 15, 16, 17	Ring				
6, 7, 9, 10, 11, 19, 20, 21, 22, 23, 24	Chain				

Bond Attributes

Bond	Type	Value
12-13, 13-14, 14-15, 15-16, 16-17, 17-12	Ring	Normalized
1-2, 2-3, 3-4, 4-5, 5-1	Ring	Exact/Normalized
4-6, 19-21, 19-20	Chain	Exact
1-8, 6-7, 7-9, 9-18, 9-10, 9-11, 11-12, 18-19, 21-22, 21-23, 22-24	Chain	Exact/Normalized

Markush Attributes

Nodes which do not support these attributes (R-groups and VAP center points) are not included in this table.

Node	Match Level	Element Count Level
1, 2, 3, 4, 5, 8, 12, 13, 14, 15, 16, 17	Atom	Limited
6, 7, 9, 10, 11, 18, 19, 20, 21, 22, 23, 24	Class	Limited

<i>Search Notes</i> 	Application/Control No. 17/077,267	Applicant(s)/Patent Under Reexamination Du et al.
	Examiner PATRICK T LEWIS	Art Unit 1623

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Inventor, REGISTRY, CAPLUS, MEDLINE, USPATFULL, USPAT2 (see attached)	04/07/2022	/PL/

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/PATRICK T LEWIS/ Primary Examiner, Art Unit 1623	
--	--

<i>Notice of References Cited</i>	Application/Control No. 17/077,267		Applicant(s)/Patent Under Reexamination Du et al.	
	Examiner PATRICK T LEWIS		Art Unit 1623	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
	A					
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N	WO-2005003147-A2	01-2005	WO	CLARK J	A61K31/7068
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Perrone et al. J. Med. Chem. (2007), Vol. 50, pages 1840-1849.
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

U.S. Patent and Trademark Office
PTO-892 (Rev. 01-2001)

Notice of References Cited

Part of Paper No. 20220407

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	1	of	51	Attorney Docket Number	37JD-199059-US13

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
		US-20010034440	10-25-2001	Shepard et al.	
		US-20020058635	05-16-2002	Averett	
		US-20020198173	12-26-2002	Schinazi et al.	
		US-20030050229	03-13-2003	Sommadossi et al.	
		US-20030060400	03-27-2003	LaColla et al.	
		US-20030109697	06-12-2003	Shepard et al.	
		US-20030120071	06-26-2003	McGuigan et al.	
		US-20030144502	07-31-2003	Pietrzkowski et al.	
		US-20030153744	08-14-2003	Mekouar et al.	
		US-20030187018	10-02-2003	Llinas-Brunet et al.	
		US-20040006007	01-08-2004	Gosselin et al.	
		US-20040014108	01-22-2004	Eldrup et al.	
		US-20040023240	02-05-2004	Marliere et al.	
		US-20040023901	02-05-2004	Cook et al.	
		US-20040059104	03-25-2004	Cook et al.	
		US-20040063622	04-01-2004	Sommadossi et al.	
		US-20040067901	04-08-2004	Bhat et al.	
		US-20040072788	04-15-2004	Bhat et al.	
		US-20040097461	05-20-2004	Sommadossi et al.	

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁶
		Country Code ³ -Number ⁴ -Kind Code ⁵ (if known)				
		CN-101108870	01-23-2008	YIXIN, LENG		
		DE-19914474	10-07-1999	F. HOFFMANN-LA ROCHE AG		
		EP-0180276	05-07-1986	OCE ANDENO BV		
		EP-0350287	01-10-1990	VICAL, INC		
		EP-1828217	09-05-2007	FEBIT BIOTECH GMBH		
		EP-1881001	01-23-2008	TIBOTEC PHARM LTD		
		EP-2097430	09-09-2009	CT BADAN MOLEKULAR I MAKRO		
		EP-2124555	12-02-2009	MERCK & CO., INC		
		EP-2207786	07-21-2010	EISAI INC		

Examiner Signature		Date Considered	
-----------------------	--	--------------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L./

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	2	of	51	Attorney Docket Number	37JD-199059-US13

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
		US-20040097462	05-20-2004	Sommadossi et al.	
		US-20040101535	05-27-2004	Sommadossi et al.	
		US-20040102414	05-27-2004	Sommadossi et al.	
		US-20040110717	06-10-2004	Carroll et al.	
		US-20040167140	08-26-2004	Schinazi et al.	
		US-20040191824	09-30-2004	Dempcy et al.	
		US-20040214844	10-28-2004	Otto et al.	
		US-20040229839	11-18-2004	Babu et al.	
		US-20040229840	11-18-2004	Bhat et al.	
		US-20040248892	12-09-2004	Wang	
		US-20040254141	12-16-2004	Schinazi et al.	
		US-20040259934	12-23-2004	Olsen et al.	
		US-20040265969	12-30-2004	Li et al.	
		US-20040266996	12-30-2004	Rabi	
		US-20050009737	01-13-2005	Clark	
		US-20050020825	01-27-2005	Storer et al.	
		US-20050026853	02-03-2005	Mekouar et al.	
		US-20050031588	02-10-2005	Sommadossi et al.	
		US-20050059632	03-17-2005	Storer et al.	
		US-20050075309	04-07-2005	Storer et al.	

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁶
		Country Code ³ Number ⁴ Kind Code ⁵ (if known)				
		JP-2007505742	03-15-2007	E.I. DUPONT DE NEMOURS AND COMPANY		
		JP-5238939	07-17-2013	MITSUBISHI CHEMICALS CORP		
		WO-8902733	04-06-1989	THE REGENTS OF THE UNIVERSITY OF CALIFORNIA		
		WO-9000555	01-25-1990	VICAL, INC.		
		WO-9116920	11-14-1991	VICAL, INC.		
		WO-9118914	12-12-1991	VICAL, INC.		

Examiner Signature		Date Considered	
-----------------------	--	--------------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L./

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	3	of	51	Attorney Docket Number	37JD-199059-US13

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
		US-20050080034	04-14-2005	Standring et al.	
		US-20050090660	04-28-2005	Watanabe et al.	
		US-20050124532	06-09-2005	Sommadossi et al.	
		US-20050130931	06-16-2005	Boyer et al.	
		US-20050137161	06-23-2005	Sommadossi et al.	
		US-20050148534	07-07-2005	Castellino et al.	
		US-20050154056	07-14-2005	Yang et al.	
		US-20050164960	07-28-2005	Olsen et al.	
		US-20050215513	09-29-2005	Boojamra et al.	
		US-20050227947	10-13-2005	Chen et al.	
		US-20050261237	11-24-2005	Boojamra et al.	
		US-20050267018	12-01-2005	Blatt et al.	
		US-20060003951	01-05-2006	Mekouar et al.	
		US-20060014943	01-19-2006	Dempcy et al.	
		US-20060035866	02-16-2006	Cannizzaro et al.	
		US-20060040890	02-23-2006	Martin et al.	
		US-20060040927	02-23-2006	Blake et al.	
		US-20060040944	02-23-2006	Gosselin et al.	
		US-20060079478	04-13-2006	Boojamra et al.	

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁶
		Country Code ³ -Number ⁴ -Kind Code ⁵ (if known)				
		WO-9119721	12-26-1991	GLAZIER, ARNOLD		
		WO-9300910	01-21-1993	VICAL, INC.		
		WO-9426273	11-24-1994	HOSTETLER, KARL		
		WO-9513090	05-18-1995	ENZON, INC.		
		WO-9524185	09-14-1995	ISIS PHARMACEUTICALS, INC.		
		WO-9615132	05-23-1996	THE REGENTS OF THE UNIVERSITY OF CALIFORNIA		
		WO-9629336	09-26-1996	MEDICAL RESEARCH COUNCIL		

Examiner Signature		Date Considered	
-----------------------	--	--------------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L./

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
				Attorney Docket Number	37JD-199059-US13
Sheet	4	of	51		

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
		US-20060110727	05-25-2006	McGall et al.	
		US-20060116557	06-01-2006	Moore et al.	
		US-20060122146	06-08-2006	Chun et al.	
		US-20060122154	06-08-2006	Olsen et al.	
		US-20060142238	06-29-2006	McGuigan	
		US-20060166964	07-27-2006	Hudyma et al.	
		US-20060194749	08-31-2006	Keicher et al.	
		US-20060199783	09-07-2006	Wang et al.	
		US-20060241064	10-26-2006	Roberts et al.	
		US-20060276511	12-07-2006	Serrano-Wu et al.	
		US-20060293306	12-28-2006	Beaulieu et al.	
		US-20070015905	01-18-2007	LaColla et al.	
		US-20070037735	02-15-2007	Gosselin et al.	
		US-20070037773	02-15-2007	Sommadossi et al.	
		US-20070042939	02-22-2007	LaColla et al.	
		US-20070042988	02-22-2007	Klumpp et al.	
		US-20070042990	02-22-2007	Gosselin et al.	
		US-20070049754	03-01-2007	BooJamra et al.	
		US-20070060498	03-15-2007	Gosselin et al.	

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁶
		Country Code ³ Number ⁴ Kind Code ⁵ (if known)				
		WO-9632403	10-17-1996	SCHERING AKTIENGESELLSCHAFT		
		WO-9712033	04-03-1997	EMORY UNIVERSITY		
		WO-9736554	10-09-1997	VIROPHARMA INCORPORATED		
		WO-9816184	04-23-1998	ICN PHARMACEUTICALS, INC.		
		WO-9817679	04-30-1998	VERTEX PHARMACEUTICALS INCORPORATED		
		WO-9822496	05-28-1998	F. HOFFMANN-LA ROCHE AG		

Examiner Signature		Date Considered	
-----------------------	--	--------------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L./

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	5	of	51	Attorney Docket Number	37JD-199059-US13

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
		US-20070060541	03-15-2007	Gosselin et al.	
		US-20070087960	04-19-2007	Storer et al.	
		US-20070197463	08-23-2007	Chun et al.	
		US-20070225249	09-27-2007	Shi	
		US-20070265222	11-15-2007	MacCoss et al.	
		US-20070275912	11-29-2007	Bhat et al.	
		US-20070275947	11-29-2007	Bergstrom	
		US-20080070861	03-20-2008	CLARK	
		US-20080253995	10-16-2008	CLARK	
		US-20090004135	01-01-2009	Clark	
		US-20090036666	02-05-2009	CLARK	
		US-20090137521	05-28-2009	Hamilton et al.	
		US-20090176732	07-09-2009	Beigelman et al.	
		US-20090233879	09-17-2009	REDDY et al.	
		US-20090280084	11-12-2009	Schinazi et al.	
		US-20090306007	12-10-2009	Wagner	
		US-20100022468	01-28-2010	Meppen et al.	
		US-20100029008	02-04-2010	Rojas Stutz et al.	
		US-20100035835	02-11-2010	Narjes et al.	

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁶
		Country Code ³ -Number ⁴ -Kind Code ⁵ (if known)				
		WO-9907734	02-18-1999	BOEHRINGER INGELHEIM (CANADA) LTD.		
		WO-9915194	04-01-1999	SCHERING CORPORATION		
		WO-9932139	07-01-1999	ENZON, INC.		
		WO-9932140	07-01-1999	ENZON, INC.		
		WO-9937753	07-29-1999	NEWBIOTICS, INC.		
		WO-9943691	09-02-1999	EMORY UNIVERSITY		

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L./

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	6	of	51	Attorney Docket Number	37JD-199059-US13

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
		US-20100048917	02-25-2010	Wang et al.	
		US-20100081628	04-01-2010	DU et al.	
		US-20100137576	06-03-2010	Stec et al.	
		US-20100152128	06-17-2010	Attenni et al.	
		US-20100173863	07-08-2010	Schinazi et al.	
		US-20100227801	09-09-2010	HOPKINS	
		US-20100279973	11-04-2010	CHUN et al.	
		US-20100286083	11-11-2010	BAO et al.	
		US-20100298257	11-25-2010	ROSS et al.	
		US-20100316594	12-16-2010	Sommadossi et al.	
		US-20110015146	01-20-2011	SOFIA et al.	
		US-20110124592	05-26-2011	McGuigan et al.	
		US-20110245484	10-06-2011	ROSS et al.	
		US-20110251152	10-13-2011	Ross et al.	
		US-20110257122	10-20-2011	Sofia et al.	
		US-20120107278	05-03-2012	BERREY et al.	
		US-20120245335	09-27-2012	Clark	
		US-20130029929	01-31-2013	Sofia et al.	
		US-20130109647	05-02-2013	Berrey et al.	

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁶
		Country Code ³ -Number ⁴ -Kind Code ⁵ (if known)				
		WO-9959621	11-25-1999	SCHERING CORPORATION		
		WO-9964016	12-16-1999	F. HOFFMANN-LA ROCHE AG		
		WO-0006529	02-10-2000	ISTITUTO DI RICERCHE DI BIOLOGIA MOLECOLARE P ANGELETTI S.P.A.		
		WO-0009531	02-24-2000	NOVIRIO PHARMACEUTICALS LIMITED		
		WO-0037110	06-29-2000	SCHERING CORPORATION		
		WO-0107454	02-01-2001	NEWBIOTICS, INC.		

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L./

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	7	of	51	Attorney Docket Number	37JD-199059-US13

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
		US-20130136776	05-30-2013	Cleary et al.	
		US-20130137654	05-30-2013	Ross et al.	
		US-20130165401	06-27-2013	Ross et al.	
		US-20130165644	06-27-2013	Ross et al.	
		US-20130288997	10-31-2013	Ross et al.	
		US-20130310551	11-21-2013	Ross et al.	
		US-20180000855	01-04-2018	Du et al.	
		US-60/392,350	06-28-2002	Storer	
		US-60/392,351	06-28-2002	Gosselin	
		US-60/909,315	03-30-2007	Sofia et al.	
		US-60/982,309	10-24-2007	Sofia et al.	
		US-RE29,835	11-14-1978	Witkowski et al.	
		US-3,798,209	03-19-1974	Witkowski et al.	
		US-3,852,267	12-03-1974	Meyer, Jr. et al.	
		US-4,814,477	03-21-1989	Wijnberg et al.	
		US-4,957,924	09-18-1990	Beauchamp	
		US-5,026,687	06-25-1991	Yarchoan et al.	
		US-5,118,820	06-02-1992	Hertel	

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁶
		Country Code ³ Number ⁴ Kind Code ⁵ (if known)				
		WO-0132153	05-10-2001	BIOCHEM PHARMA INC.		
		WO-0160315	08-23-2001	BIOCHEM PHARMA INC.		
		WO-0179246	10-25-2001	PHARMASSET, LTD.		
		WO-0181359	11-01-2001	SCHERING CORPORATION		
		WO-0190121	11-29-2001	NOVIRIO PHARMACEUTICALS LIMITED		
		WO-0191737	12-06-2001	NOVIRIO PHARMACEUTICALS LIMITED		

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L./

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	8	of	51	Attorney Docket Number	37JD-199059-US13

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
		US-5,149,794	09-22-1992	Yatvin et al.	
		US-5,157,027	10-20-1992	Biller et al.	
		US-5,192,549	03-09-1993	Barenolz et al.	
		US-5,194,654	03-16-1993	Hostetler et al.	
		US-5,223,263	06-29-1993	Hostetler et al.	
		US-5,256,641	10-26-1993	Yatvin et al.	
		US-5,256,798	10-26-1993	Chou et al.	
		US-5,372,808	12-13-1994	Blatt et al.	
		US-5,376,380	12-27-1994	Kikuchi et al.	
		US-5,405,598	04-11-1995	Schinazi et al.	
		US-5,411,947	05-02-1995	Hostetler et al.	
		US-5,420,266	05-30-1995	Britton et al.	
		US-5,426,183	06-20-1995	Kjell	
		US-5,453,499	09-26-1995	Chou et al.	
		US-5,462,724	10-31-1995	Schinazi et al.	
		US-5,463,092	10-31-1995	Hostetler et al.	
		US-5,496,546	03-05-1996	Wang et al.	
		US-5,538,865	07-23-1996	Reyes et al.	

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁶
		Country Code ² Number ³ Kind Code ⁵ (if known)				
		WO-0192282	12-06-2001	NOVIRIO PHARMACEUTICALS LIMITED		
		WO-0196353	12-20-2001	NOVIRIO PHARMACEUTICALS LIMITED		
		WO-02057287	07-25-2002	MERCK & CO., INC.		
		WO-02057425	07-25-2002	MERCK & CO., INC.		
		WO-02060926	08-08-2002	BRISTOL-MYERS SQUIBB COMPANY		
		WO-0208187	01-31-2002	SCHERING CORPORATION		
		WO-0208198	01-31-2002	SCHERING CORPORATION		

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L./

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	9	of	51	Attorney Docket Number	37JD-199059-US13

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
		US-5,543,389	08-06-1996	Yatvin et al.	
		US-5,543,390	08-06-1996	Yatvin et al.	
		US-5,543,391	08-06-1996	Yatvin et al.	
		US-5,554,728	09-10-1996	Basava et al.	
		US-5,610,054	03-11-1997	Draper	
		US-5,633,358	05-27-1997	Gruetzke et al.	
		US-5,633,388	05-27-1997	Diana et al.	
		US-5,676,942	10-14-1997	Testa et al.	
		US-5,703,058	12-30-1997	Schinazi et al.	
		US-5,711,944	01-27-1998	Gilbert et al.	
		US-5,725,859	03-10-1998	Omer	
		US-5,738,845	04-14-1998	Imakawa	
		US-5,738,846	04-14-1998	Greenwald et al.	
		US-5,747,646	05-05-1998	Hakimi et al.	
		US-5,767,097	06-16-1998	Tam	
		US-5,792,834	08-11-1998	Hakimi et al.	
		US-5,830,455	11-03-1998	Valtuna et al.	
		US-5,830,905	11-03-1998	Diana et al.	

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁶
		Country Code ³ Number ⁴ Kind Code ⁵ (if known)				
		WO-0208241	01-31-2002	GILEAD SCIENCES, INC.		
		WO-0208251	01-31-2002	CORVAS INTERNATIONAL, INC.		
		WO-0208256	01-31-2002	SCHERING CORPORATION		
		WO-02100415	12-19-2002	F. HOFFMANN-LA ROCHE AG		
		WO-0218404	03-07-2002	F. HOFFMANN-LA ROCHE AG		
		WO-0232414	04-25-2002	SCHERING CORPORATION		
		WO-0232920	04-25-2002	PHARMASSET LIMITED		

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.I./

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	10	of	51	Attorney Docket Number	37JD-199059-US13

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
		US-5,834,594	11-10-1998	Hakimi et al.	
		US-5,837,257	11-17-1998	Tsai et al.	
		US-5,846,964	12-08-1998	Ozeki	
		US-5,849,696	12-15-1998	Chretien et al.	
		US-5,869,253	02-09-1999	Draper	
		US-5,891,874	04-06-1999	Colacino et al.	
		US-5,905,070	05-18-1999	Schinazi et al.	
		US-5,908,621	06-01-1999	Glue et al.	
		US-5,922,757	07-13-1999	Chojkier	
		US-5,928,636	07-27-1999	Alber et al.	
		US-5,942,223	08-24-1999	Bazer et al.	
		US-5,980,884	11-09-1999	Blatt et al.	
		US-5,990,276	11-23-1999	Zhang et al.	
		US-6,004,933	12-21-1999	Spruce et al.	
		US-6,034,134	03-07-2000	Gold et al.	
		US-6,043,077	03-28-2000	Barber et al.	
		US-6,056,961	05-02-2000	Lavie et al.	
		US-6,060,080	05-09-2000	Kikuchi et al.	
		US-6,090,932	07-18-2000	McGee et al.	

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁶
		Country Code ³ -Number ⁴ -Kind Code ⁵ (if known)				
		WO-0248116	06-20-2002	BRISTOL-MYERS SQUIBB PHARMA COMPANY		
		WO-0248157	06-20-2002	BRISTOL-MYERS SQUIBB PHARMA COMPANY		
		WO-0248165	06-20-2002	PHARMASSET LTD.		
		WO-0248172	06-20-2002	SCHERING CORPORATION		
		WO-03000713	01-03-2003	GLAXO GROUP LIMITED		
		WO-03006490	01-23-2003	VERTEX PHARMACEUTICALS INCORPORATED		

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L./

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	11	of	51	Attorney Docket Number	37JD-199059-US13

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
		US-6,130,326	10-10-2000	Ramasamy et al.	
		US-6,132,763	10-17-2000	Fisher	
		US-6,156,501	12-05-2000	McGall et al.	
		US-6,180,134	01-30-2001	Zalipsky et al.	
		US-6,232,300	05-15-2001	Schinazi et al.	
		US-6,239,159	05-29-2001	Brown et al.	
		US-6,348,587	02-19-2002	Schinazi et al.	
		US-6,372,883	04-16-2002	Attwood et al.	
		US-6,391,859	05-21-2002	Schinazi et al.	
		US-6,410,531	06-25-2002	Llinas-Brunet et al.	
		US-6,420,380	07-16-2002	Llinas-Brunet et al.	
		US-6,455,513	09-24-2002	McGuigan et al.	
		US-6,455,690	09-24-2002	Tam et al.	
		US-6,475,985	11-05-2002	Wagner et al.	
		US-6,479,463	11-12-2002	Wang et al.	
		US-6,495,677	12-17-2002	Ramasamy et al.	
		US-6,509,320	01-21-2003	Wang et al.	
		US-6,534,523	03-18-2003	Llinas-Brunet et al.	
		US-6,552,183	04-22-2003	Ramasamy et al.	

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁶
		Country Code ³ Number ⁴ Kind Code ⁵ (if known)				
		WO-03010141	02-06-2003	BOEHRINGER INGELHEIM (CANADA) LTD.		
		WO-03024461	03-27-2003	SCHERING CORPORATION		
		WO-03026589	04-03-2003	IDENIX (CAYMAN) LIMITED		
		WO-03037895	05-08-2003	GLAXO GROUP LIMITED		
		WO-03051899	06-26-2003	RIBAPHARM INC.		
		WO-03053989	07-03-2003	MRC TECHNOLOGY LIMITED		
		WO-03061576	07-31-2003	RIBAPHARM INC.		
		WO-03062256	07-31-2003	RIBAPHARM INC.		

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L./

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	12	of	51	Attorney Docket Number	37JD-199059-US13

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
		US-6,555,677	04-29-2003	Petrillo et al.	
		US-6,573,248	06-03-2003	Ramasamy et al.	
		US-6,589,941	07-08-2003	Fahrig et al.	
		US-6,642,206	11-04-2003	Ramasamy et al.	
		US-6,660,721	12-09-2003	Devos et al.	
		US-6,677,314	01-13-2004	Klecker et al.	
		US-6,677,315	01-13-2004	Klecker et al.	
		US-6,680,303	01-20-2004	Schinazi et al.	
		US-6,682,715	01-27-2004	Klecker et al.	
		US-6,683,045	01-27-2004	Klecker et al.	
		US-6,703,374	03-09-2004	Klecker et al.	
		US-6,753,309	06-22-2004	Klecker et al.	
		US-6,777,395	08-17-2004	Bhat et al.	
		US-6,784,166	08-31-2004	Devos et al.	
		US-6,787,305	09-07-2004	Li et al.	
		US-6,787,526	09-07-2004	Bryant et al.	
		US-6,812,219	11-02-2004	LaColla et al.	

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁶
		Country Code ³ -Number ⁴ -Kind Code ⁵ (if known)				
		WO-03064456	08-07-2003	BOEHRINGER INGELHEIM INT		
		WO-03068244	08-21-2003	MERCK & CO., INC.		
		WO-03101993	12-11-2003	NEOGENESIS PHARMACEUTICALS, INC.		
		WO-03104250	12-18-2003	KYLIX, B. V.		
		WO-03105770	12-24-2003	MERCK & CO., INC.		
		WO-03106477	12-24-2003	ISIS PHARMACEUTICALS, INC.		
		WO-2004000858	12-31-2003	MERCK & CO., INC.		
		WO-2004002422	01-08-2004	IDENIX (CAYMAN) LIMITED		

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L./

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	13	of	51	Attorney Docket Number	37JD-199059-US13

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
		US-6,815,542	11-09-2004	Hong et al.	
		US-6,846,810	01-25-2005	Martin et al.	
		US-6,897,201	05-24-2005	Boyer et al.	
		US-6,908,924	06-21-2005	Watanabe et al.	
		US-6,911,424	06-28-2005	Schinazi et al.	
		US-6,914,054	07-05-2005	Sommadossi et al.	
		US-6,962,991	11-08-2005	Dempcy et al.	
		US-7,018,985	03-28-2006	Boyer et al.	
		US-7,018,989	03-28-2006	McGuigan et al.	
		US-7,081,449	07-25-2006	Pietrzkowski et al.	
		US-7,105,493	09-12-2006	Sommadossi et al.	
		US-7,105,499	09-12-2006	Carroll et al.	
		US-7,125,855	10-24-2006	Bhat et al.	
		US-7,148,206	12-12-2006	Sommadossi et al.	
		US-7,163,929	01-16-2007	Sommadossi et al.	
		US-7,202,224	04-10-2007	Eldrup et al.	
		US-7,217,523	05-15-2007	Wagner	
		US-7,268,119	09-11-2007	Cook et al.	
		US-7,307,065	12-11-2007	Schinazi et al.	
		US-7,323,453	01-29-2008	Olsen et al.	
		US-7,365,057	04-29-2008	LaColla et al.	
		US-7,390,791	06-24-2008	Becker et al.	

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁶
		Country Code ³ -Number ⁴ -Kind Code ⁵ (if known)				
		WO-2004002940	01-08-2004	PHARMACIA & UPJOHN COMPANY		
		WO-2004002944	01-08-2004	PHARMACIA & UPJOHN COMPANY		
		WO-2004002977	01-08-2004	PHARMACIA & UPJOHN COMPANY LLC		

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L./

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	14	of	51	Attorney Docket Number	37JD-199059-US13

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
		US-7,429,572	09-30-2008	Clark	
		US-7,601,820	10-13-2009	Wang et al.	
		US-7,608,597	10-27-2009	Sommadossi et al.	
		US-7,608,600	10-27-2009	Storer et al.	
		US-7,635,689	12-22-2009	LaColla et al.	
		US-7,754,699	07-13-2010	Chun et al.	
		US-7,879,815	02-01-2011	MacCoss et al.	
		US-7,964,580	06-21-2011	Sofia et al.	
		US-8,148,349	04-03-2012	Meppen et al.	
		US-8,173,621	05-08-2012	Du et al.	
		US-8,334,270	12-18-2012	Sofia et al.	
		US-8,415,322	04-09-2013	Clark	
		US-8,551,973	10-08-2013	Bao et al.	
		US-8,580,765	11-12-2013	Sofia et al.	
		US-8,735,372	05-27-2014	Du et al.	
		US-8,906,880	12-09-2014	Du et al.	
		US-8,957,046	02-17-2015	Du et al.	
		US-9,085,573	07-21-2015	Du et al.	
		US-9,585,906	03-07-2017	Du et al.	

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁶
		Country Code ³ -Number ⁴ -Kind Code ⁵ (if known)				
		WO-2004002999	01-08-2004	IDENIX (CAYMAN) LIMITED		
		WO-2004003000	01-08-2004	IDENIX (CAYMAN) LIMITED		
		WO-2004003138	01-08-2004	MERCK & CO., INC.		
		WO-2004007512	01-22-2004	MERCK & CO., INC.		
		WO-2004009020	01-29-2004	MERCK & CO., INC.		
		WO-2004009610	01-29-2004	PTC THERAPEUTICS, INC.		
		WO-2004011478	02-05-2004	MICROLOGIX BIOTECH INC.		

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L./

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	15	of	51	Attorney Docket Number	37JD-199059-US13

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁶
		Country Code ² Number ³ Kind Code ⁴ (if known)				
		WO-2004014313	02-19-2004	BRISTOL-MYERS SQUIBB COMPANY		
		WO-2004014852	02-19-2004	BRISTOL-MYERS SQUIBB COMPANY		
		WO-2004035571	04-29-2004	RIGEL PHARMACEUTICALS, INC.		
		WO-2004041201	05-21-2004	VIOPHARMA INCORPORATED		
		WO-2004046331	06-03-2004	IDENIX (CAYMAN) LIMITED		
		WO-2004065367	08-05-2004	BOEHRINGER INGELHEIM INTERNATIONAL GMBH		
		WO-2004080466	09-23-2004	RIBAPHARM INC.		
		WO-2004094452	11-04-2004	BRISTOL-MYERS SQUIBB COMPANY		
		WO-2004096210	11-11-2004	GLAXO GROUP LIMITED		
		WO-2004096234	11-11-2004	GILEAD SCIENCES, INC.		
		WO-2004096235	11-11-2004	GILEAD SCIENCES, INC.		
		WO-2004096286	11-11-2004	GILEAD SCIENCES, INC.		
		WO-2004106356	12-09-2004	SYDDANSK UNIVERSITET		
		WO-2005002626	01-13-2005	GILEAD SCIENCES, INC.		
		WO-2005003147	01-13-2005	PHARMASSET, LTD.		
		WO-2005007810	01-27-2005	GRINSTAFF		
		WO-2005009418	02-03-2005	IDENIX (CAYMAN) LIMITED		
		WO-2005012327	02-10-2005	UNIVERSITY COLLEGE CARDIFF CONSULTANTS LIMITED		
		WO-2005020884	03-10-2005	IDENIX (CAYMAN) LIMITED		
		WO-2005021568	03-10-2005	BIOTA, INC.		
		WO-2005028502	03-31-2005	VERTEX PHARMACEUTICALS, INCORPORATED		

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L./

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	16	of	51	Attorney Docket Number	37JD-199059-US13

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ²
		Country Code ³ Number ⁴ Kind Code ⁵ (if known)				
		WO-2005030891	04-07-2005	E.I. DUPONT DE NEMOURS AND COMPANY		
		WO-2005037214	04-28-2005	INTERMUNE, INC.		
		WO-2005067900	07-28-2005	ACHILLION PHARMACEUTICALS, INC.		
		WO-2005072361	08-11-2005	MERCK & CO., INC.		
		WO-2005082144	09-09-2005	GOVERNMENT OF THE UNITED STATES OF AMERICA		
		WO-2005087788	09-22-2005	THE REGENTS OF THE UNIVERSITY OF CALIFORNIA		
		WO-2005095403	10-13-2005	INTERMUNE, INC.		
		WO-2005103045	11-03-2005	GLAXO GROUP LIMITED		
		WO-2005123087	12-29-2005	MERCK & CO., INC.		
		WO-2006000922	01-05-2006	IDENIX (CAYMAN) LIMITED		
		WO-2006012078	02-02-2006	MERCK & CO., INC.		
		WO-2006012440	02-02-2006	PHARMASSET, INC.		
		WO-2006020082	02-23-2006	BRISTOL-MYERS SQUIBB COMPANY		
		WO-2006029081	03-16-2006	NEOPHARM, INC.		
		WO-2006031725	03-23-2006	PHARMASSET, INC.		
		WO-2006035061	04-06-2006	TIBOTEC PHARMACEUTICALS LTD.		
		WO-2006037028	04-06-2006	IDENIX (CAYMAN) LIMITED		
		WO-2006050161	05-11-2006	BIOCRIST PHARMACEUTICALS, INC.		
		WO-2006063149	06-15-2006	REGENTS OF THE UNIVERSITY OF MINNESOTA		

Examiner Signature		Date Considered	
-----------------------	--	--------------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L./

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	17	of	51	Attorney Docket Number	37JD-199059-US13

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ²
		Country Code ³ Number ⁴ Kind Code ⁵ (if known)				
		WO-2006063717	06-22-2006	UNIVERSITAT KARLSRUHE		
		WO-2006065335	06-22-2006	MERCK & CO., INC.		
		WO-2006065590	06-22-2006	XTL BIOPHARMACEUTICALS INC.		
		WO-2006067606	06-29-2006	INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM)		
		WO-2006093801	09-08-2006	ABBOTT LABORATORIES		
		WO-2006100310	09-28-2006	TIBOTEC PHARMACEUTICALS LTD.		
		WO-2006116557	11-02-2006	GENELABS TECHNOLOGIES, INC.		
		WO-2006120251	11-16-2006	TIBOTEC PHARMACEUTICALS LTD.		
		WO-2006120252	11-16-2006	TIBOTEC PHARMACEUTICALS LTD.		
		WO-2006121820	11-16-2006	VALEANT RESEARCH & DEVELOPMENT		
		WO-2007002602	01-04-2007	DEPUY SPINE, INC.		
		WO-2007014920	02-08-2007	TIBOTEC PHARMACEUTICALS LTD.		
		WO-2007014921	02-08-2007	TIBOTEC PHARMACEUTICALS LTD.		
		WO-2007014922	02-08-2007	TIBOTEC PHARMACEUTICALS LTD.		
		WO-2007014925	02-08-2007	TIBOTEC PHARMACEUTICALS LTD.		
		WO-2007014926	02-08-2007	TIBOTEC PHARMACEUTICALS LTD.		
		WO-2007015824	02-08-2007	INTERMUNE, INC.		
		WO-2007020193	02-22-2007	F. HOFFMANN-LA ROCHE AG		
		WO-2007027248	03-08-2007	VALEANT RESEARCH & DEVELOPMENT		

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 809. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.I./

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	18	of	51	Attorney Docket Number	37JD-199059-US13

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁵
		Country Code ² Number ³ Kind Code ⁴ (if known)				
		WO-2007039142	04-12-2007	GLAXO GROUP LIMITED		
		WO-2007039145	04-12-2007	GLAXO GROUP LIMITED		
		WO-2007065829	06-14-2007	F. HOFFMANN-LA ROCHE AG		
		WO-2007070556	06-21-2007	GENELABS TECHNOLOGIES, INC.		
		WO-2007076034	07-05-2007	ABBOTT LABORATORIES		
		WO-2007088148	08-09-2007	SMITHKLINE BEECHAM CORPORATION		
		WO-2007092000	08-16-2007	BRISTOL-MYERS SQUIBB COMPANY		
		WO-2007093901	08-23-2007	PFIZER LIMITED		
		WO-2007095269	08-23-2007	MERCK & CO., INC.		
		WO-2008010921	01-24-2008	GILEAD SCIENCES, INC.		
		WO-2008045419	04-17-2008	PHARMASSET, INC.		
		WO-2008048128	04-24-2008	CENTRUM BADAN MOLEKULARNYCH I MAKROMOLEKULARNYCH, POLSKIEJ AKADEMII NAUK		
		WO-2008062206	05-29-2008	UNIVERSITY COLLEGE CARDIFF CONSULTANTS LIMITED		
		WO-2008079206	07-03-2008	MERCK & CO., INC.		
		WO-2008082601	07-10-2008	IDENIX PHARMACEUTICALS, INC.		
		WO-2008085508	07-17-2008	MERCK & CO., INC.		
		WO-2008121634	10-09-2008	PHARMASSET, INC.		
		WO-2008142055	11-27-2008	ISTITUTO DI RICERCHE DI BIOLOGIA MOLECOLARE P. ANGELETTI SPA		

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L./

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	19	of	51	Attorney Docket Number	37JD-199059-US13

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁵
		Country Code ² Number ³ Kind Code ⁴ (if known)				
		WO-2009052287	04-23-2009	EISAL CORPORATION OF NORTH AMERICA		
		WO-2009115893	09-24-2009	HETERO RESEARCH FOUNDATION		
		WO-2009120878	10-01-2009	ALNYLAM PHARMACEUTICALS, INC.		
		WO-2009129120	10-22-2009	RFS PHARMA, LLC		
		WO-2009152095	12-17-2009	PHARMASSET, INC.		
		WO-2010009121	01-21-2010	UNIVERSITY OF FLORIDA RESEARCH FOUNDATION, INC.		
		WO-2010042834	04-15-2010	ANADYS PHARMACEUTICALS, INC.		
		WO-2010075554	07-01-2010	PHARMASSET, INC.		
		WO-2010080878	07-15-2010	SCYNEXIS, INC.		
		WO-2011123645	10-06-2011	PHARMASSET, INC.		

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L./

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	20	of	51	Attorney Docket Number	37JD-199059-US13

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		ABRAHAM et al., "Synthesis and Biological Activity of Aromatic Amino Acid Phosphoramidates of 5-fluoro-2'-deoxyuridine and 1-beta-Arabinofuranosylcytosine: Evidence of Phosphoramidase Activity," J. Med. Chem., vol. 39, No. 23, pp. 4569-4575, (1996).	
		ABRAHAM et al., "Synthesis, Biological Activity and Decomposition Studies of Amino Acid Phosphomonoester Amidates of Acyclovir," Nucleosides, Nucleotides and Nucleic Acids, vol. 16, No. 10, pp. 2079-2092 (1997).	
		Abstract, 100, presented at the 19th International Conference of Antiviral Research, May 7-11, 2006.	
		AQUARO et al., "Activities of Masked 2',3'-Dideoxynucleoside Monophosphate Derivatives Against Human Immunodeficiency Virus in Resting Macrophages," Antimicrobial Agents and Chemotherapy, vol. 44, no. 1, pp. 173-177 (2000).	
		ARNOLD, et al. Sensitivity of mitochondrial transcription and resistance of RNA polymerase II dependent nuclear transcription to antiviral ribonucleosides. PLoS Pathog. 2012; 8(11): e1003030. doi: 10.1371/journal.ppat.1003030. Epub 2012 Nov 15.	
		ASIF et al., "Pharmacokinetics of the Antiviral Agent B-D-2'-Deoxy-2'-Fluoro-2'-C-Methylcytidine in Rhesus Monkeys," Antimicrobial Agents and Chemotherapy, vol. 51, no. 8, pp. 2877-2882 (2007).	
		Balzarini et al., Mechanism of anti-HIV action of masked alaninyl d4T-MP derivatives, Proc. Natl. Acad. Sci., vol. 93, pp. 7295-7299 (1996).	
		BANKER et al., "Prodrugs," Modern Pharmaceutics, Third Edition, Revised and Expanded, pp. 451 and 596 (1996).	
		BARTENSCHLAGER et al., "Kinetic and Structural Analyses of Hepatitis C Virus Polyprotein Processing," J. Virol., vol. 68, no. 8, pp. 5045-5055 (1994).	
		BARTENSCHLAGER et al., "Nonstructural Protein 3 of the Hepatitis C Virus Encodes a Serine-Type Proteinase Required for Cleavage at the NS3/4 and NS4/5 Junctions," J. Virol., vol. 67, no. 7, pp. 3835-3844 (1993).	

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L./

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	21	of	51	Attorney Docket Number	37JD-199059-US13

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		BASCHANG et al., "Neue Derivate von Thymidin-3',5'-cyclophosphat," Angew. Chem., vol. 85, no. 1, pp. 44-45 (1973).	
		BATTAGLIA et al., "Combination Therapy with Interferon and Ribavirin in the Treatment of Chronic Hepatitis C Infection," The Annals of Pharmacotherapy, vol. 34, no. 4, pp. 487-494 (2000).	
		BAZAN et al., "Detection of a Trypsin-like Serine Protease Domain in Flaviviruses and Pestiviruses," Virology, vol. 171, pp. 637-639 (1989).	
		BEAULIEU et al., "Inhibitors of the HCV NS5B polymerase: New hope for the treatment of hepatitis C infections," Current Opinion in Investigational Drugs, vol. 5, no. 8, pp. 838-850 (2004).	
		BEHRENS et al., "Identification and properties of the RNA-dependent RNA polymerase of hepatitis C virus," The EMBO Journal, vol. 15, no. 1, pp. 12-22 (1996).	
		BERENGUER, M., "Hepatitis C virus in the transplant setting," Antiviral Therapy, vol. 3, Supplement 3, pp. 125-136 (1998).	
		BHAT et al., "Synthesis and Pharmacokinetic Properties of Nucleoside Analogues as Possible Inhibitors of HCV RNA Replication," (Oral Session V: Hepatitis C Virus, Flaviviruses), 16th International Conference on Antiviral Research, Abstract No. 120, p. A75 (Apr. 27-May 1, 2003).	
		Board Opinion dated 2017-01-12 for Chinese Application No. 200880018024.2.	
		BROEDERS et al., "A 400-and 600-Mhz ¹ H NMR Conformational Study on Nucleoside Cyclic 3', 5' PV-TBP Systems. Conformational Transmission Induces Diequatorial Orientation of the 3', 5'-Dioxaphosphorinane Ring in a Nonchair Confirmation," J. Am. Chem. Soc., vol. 112, no. 21, pp. 7475-7482 (1990).	
		CAHARD, DOMINIQUE, et al., Aryloxy Phosphoramidate Triesters as Pro-Tides, Mini-Reviews in Medicinal Chemistry (2004), 4, 371-381.	

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L/

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	22	of	51	Attorney Docket Number	37JD-199059-US13

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		CALISHER et al., "Antigenic Relationships between Flaviviruses as Determined by Cross-neutralization Tests with Polyclonal Antisera," J. Gen. Virol., vol. 70, pp. 37-43 (1989).	
		CARROLL et al., "Nucleoside Analog Inhibitors of Hepatitis C Virus Replication," Infectious Disorders--Drug Targets, vol. 6, no. 1, pp. 17-29 (2006).	
		CHANG et al., "Amino Acid Phosphoramidate Monoesters of 3'-Azido-3'-deoxythymidine: Relationship between Antiviral Potency and Intracellular Metabolism," J. Med. Chem., vol. 44, no. 2, pp. 223-231 (2001).	
		Chang et al., "Deoxycytidine-resistant Stereoisomer Is the Active Form of (±)-2',3'-Dideoxy-3'-thiacytidine in the Inhibition of Hepatitis B Virus Replication," J. Bio. Chem., (1992), 267(20):13938-13942.	
		CHAPMAN et al., "Practical Synthesis, Separation, and Stereochemical Assignment of the PMPA Pro-Drug GS-7340," Nucleosides, Nucleotides & Nucleic Acids, vol. 20, no. 4-7, pp. 621-628 (2001).	
		CHAPMAN et al., "Purification of PMPA Amidate Prodrugs by SMB Chromatography and X-Ray Crystallography of the Diastereomerically Pure GS-7340," Nucleosides, Nucleotides & Nucleic Acids, vol. 20, no. 4-7, pp. 1085-1090 (2001).	
		CHEN et al., "In Vivo Pharmacokinetics and Metabolism of Anti-Human Immunodeficiency Virus Agent D4t-5'-[P-Bromophenyl Methoxyalaninyl Phosphate] (Sampidine) in Mice," Drug Metabolism and Disposition, vol. 29, no. 7, pp. 1035-1041 (2001).	
		CHEN et al., "Metabolism of Stavudine-5'-[P-Bromophenyl Methoxyalaninyl Phosphate], Stampidine, in Mice, Dogs, and Cats," Drug Metabolism and Disposition, vol. 30, no. 12, pp. 1523-1531 (2002).	
		CHOU et al., "Evidence that Human Histidine Triad Nucleotide Binding Protein 3 (Hint3) is a Distinct Branch of the Histidine Triad (HIT) Superfamily," J. Mol. Biol., vol. 373, pp. 978-989 (2007).	
		CHOU et al., "Phosphoramidate Pronucleotides: A Comparison of the Phosphoramidase Substrate Specificity of Human and Escherichia coli Histidine Triad Nucleotide Binding Proteins," Molecular Pharmaceutics, vol. 4, no. 2, pp. 208-217 (2006).	

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L./

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	23	of	51	Attorney Docket Number	37JD-199059-US13

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		CHU et al., "Isolation and Structure of SCH 351633: A Novel Hepatitis C Virus (HCV) NS3 Protease Inhibitor from the Fungus <i>Penicillium griseofulvum</i> ," <i>Bioorg. & Med. Chem. Lett.</i> , vol. 9, pp. 1949-1952 (1999).	
		CHU et al., "Structure of Sch 68631: A New Hepatitis C Virus Proteinase Inhibitor from <i>Streptomyces</i> sp." <i>Tet. Lett.</i> , vol. 37, no. 40, pp. 7229-7232 (1996).	
		CIHLAR et al., "Design and Profiling of GS-9148, a Novel Nucleotide Analog Active against Nucleoside-Resistant Variants of Human Immunodeficiency Virus Type 1, and Its Orally Bioavailable Phosphonoamidate Prodrug, GS-9131," <i>Antimicrobial Agents and Chemotherapy</i> , vol. 52, no. 2, pp. 655-665 (2008).	
		CLARK et al., "Design, Synthesis, and Antiviral Activity of 2'-Deoxy-2'-fluoro-2'-C-methylcytidine, a Potent Inhibitor of Hepatitis C Virus Replication," <i>J. Med. Chem.</i> , vol. 48, no. 17, pp. 5504-5508 (2005). XP002415215.	
		CLARK et al., "Synthesis and antiviral activity of 2'-deoxy-2'-fluoro-2'-C-methyl purine nucleosides as inhibitors of hepatitis C virus RNA replication", <i>BIOORGANIC & MEDICINAL CHEMISTRY LETTERS</i> , PERGAMON, AMSTERDAM, NL, vol. 16, no. 6, 15 March 2006 (2006-03-15), pages 1712-1715, XP027966449, ISSN: 0960-894X.	
		CLAYDEN et al., <i>Organic Chemistry</i> , OUP, 2005, cover page and pages 48-49.	
		CODINGTON, et al., "Nucleoside-s. XVIII. Synthesis of 2'-Fluorothymidine, 2'-FluoroDE-oxyuridine, and Other 2'-Halogeno-2'-DE-oxy Nucleoside-s 1'2", <i>The Division of Nucleoprotein Chemistry, Sloan-Kettering Institute for Cancer Research, Sloan-Kettering Division of Cornell University Medical College, New York 21, New York</i> , vol. 29, pages 558-564, (1963).	
		Cole et al., R-7128: RNA-directed RNA polymerase (NS5B) inhibitor treatment of hepatitis C virus infection, <i>Drugs of the Future</i> 2009, 34(4):282-290.	
		Communication pursuant to Rules 70(2) and 70a(2) EPC and reference to Rule 39(1) EPC for European Application No. 14179593.0 dated 01/19/2015.	
		CONGIATU et al. "Molecular Modeling Studies on the Binding of Some Protides to the Putative Human Phosphoramidase Hint1," <i>Nucleosides, Nucleotides and Nucleic Acids</i> , vol. 26, pp. 1121-1124 (2007).	

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L./

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	24	of	51	Attorney Docket Number	37JD-199059-US13

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		CONGIATU et al., "Naphthyl Phosphoramidate Derivatives of BVdU as Potential Anticancer Agents: Design, Synthesis and Biological Evaluation," Nucleosides, Nucleotides, and Nucleic Acids, vol. 24, no. 5-7, pp. 485-489 (2005).	
		Congiatu et al., Novel potential anticancer naphthyl phosphoramidates of BVdU: separation of diastereoisomers and assignment of the absolute configuration of the phosphorus center. Journal of Medicinal Chemistry 2006, 49(2):452-455.	
		CURLEY et al., "Synthesis and anti-HIV evaluation of some phosphoramidate derivatives of AZT: studies on the effect of chain elongation on biological activity," Antiviral Research, vol. 14, pp. 345-356 (1990).	
		D'CRUZ et al., "Stampidine: a selective oculo-genital microbicide," Journal of Antimicrobial Chemotherapy, vol. 56, pp. 10-19 (2005).	
		DAVIS, G. L., "Current Therapy for Chronic Hepatitis C," Gastroenterology, vol. 118, no. 2, pp. S104-S114 (2000).	
		De Francesco et al., Challenges and successes in developing new therapies for hepatitis C. Nature 2005; 436(7053):953-960.	
		DE LOMBAERT et al., "N-Phosphonomethyl Dipeptides and Their Phosphonate Prodrugs, a New Generation of Neutral Endopeptidase (NEP, EC 3.4.24.11) Inhibitors," J. Med. Chem., vol. 37, no. 4, pp. 498-511 (1994).	
		DRONTLE et al., "Designing a Pronucleotide Stratagem: Lessons from Amino Acid Phosphoramidates of Anticancer and Antiviral Pyrimidines," MiniReviews in Medicinal Chemistry, vol. 4, no. 4, pp. 409-419 (2004).	
		DUMEZ, DARIN, et al., "Large-Scale Synthesis and Formulation of GMP-Grade Stampidine, a New Anti-HIV Agent," Arzneimittel.-Forsch./Drug Res. (2006); 56(2a):136-151.	
		Dyken et al., Strategies to reduce late-stage drug attrition due to mitochondrial toxicity. Expert Rev Mol Diagn. 2007; 7(2):161-175.	

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L./

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	25	of	51	Attorney Docket Number	37JD-199059-US13

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		ECKART et al., "The Hepatitis C Virus Encodes a Serine Protease Involved in Processing of the Putative Nonstructural Proteins from the Viral Polyprotein Precursor," Biochemical and Biophysical Research Communications, vol. 192, No. 2, pp. 399-406 (1993).	
		EDMUNDSON et al., "Cyclic Organophosphorus Compounds. Part 23. Configurational Assignments in the 4-Phenyl-1,3,2-dioxaphosphorinane Series. X-Ray Molecular Structure of cis-2-Benzylamino-4-phenyl-1,3,2-dioxaphosphorinane 2-oxide," J. Chem. Research (S), pp. 122-123 (1989).	
		EGRON et al., "S-Acyl-2-thioethyl Phosphoramidate Diester Derivatives as Mononucleotide Prodrugs" J. Med. Chem., vol. 46, no. 21, pp. 4564-4571 (2003).	
		EISENBERG et al., "Metabolism of GS-7340, a Novel Phenyl Monophosphoramidate Intracellular Prodrug of PMPA, in Blood," Nucleosides, Nucleotides & Nucleic Acids, vol. 20, no. 4-7, pp. 1091-1098 (2001).	
		ELDRUP et al., "Oral Session V: Hepatitis C Virus, Flaviviruses," Program and Abstracts, The Sixteenth International Conference on Antiviral Research, p. A75, Abstract 119 (Apr. 27 to May 1, 2003).	
		ELDRUP et al., "Structure-Activity Relationship of Purine Ribonucleosides for Inhibition of Hepatitis C Virus RNA-Dependent RNA Polymerase," J. Med. Chem., vol. 47, no. 9, pp. 2283-2295 (2004).	
		EMA Press Release. European Medicines Agency recommends approval of sofosbuvir for the treatment of chronic hepatitis C dated November 22, 2013.	
		ENGELS et al., "Cyclophosphate, III. Synthese und Eigenschaften von Uridin-3',5'-cyclophosphat-estern," Chemische Berichte, vol. 110, no. 6, pp. 2019-2027 (1977).	
		English Translation of Office Action for Israeli Application No. 222810 dated 01/04/2015.	
		English Translation of Office Action for Korean Application No. 10-2009-7022652 dated 12/19/2013.	

Examiner Signature		Date Considered	
-----------------------	--	--------------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L./

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	26	of	51	Attorney Docket Number	37JD-199059-US13

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		English Translation of Office Action in Mexican Application No. MX/A/2012/000289 dated 01/22/2015.	
		English Translation of Office Action in Mexican Application No. MX/A/2012/000289 dated 10/30/2014.	
		Examination Report for Australian Patent Application No. 2019203002 dated April 20, 2020. 5 pages	
		Extended European Search Report for European Patent Application No. 14169060.2 dated October 10, 2014. 9 pages	
		Extended European Search Report for European Patent Application No. 14179593.0 dated December 17, 2014. 7 pages	
		Extended Search Report for European Application No. 14151876.1 dated 09/18/2014.	
		FAILLA et al., "Both NS3 and NS4A are Required for Proteolytic Processing of Hepatitis C Virus Nonstructural Proteins," J. Virol., vol. 68, no. 6, pp. 3753-3760 (1994).	
		FARQUHAR et al., "Synthesis and Biological Evaluation of Neutral Derivatives of 5-Fluoro-2'-deoxyuridine 5'-Phosphate," J. Med. Chem., vol. 26, no. 8, pp. 1153-1158 (1983).	
		FARQUHAR et al., "Synthesis of Biological Evaluation of 9[5'-(2-Oxo-1,3,2-oxazaphosphorinan-2-yl)-beta-D-arabinosyl] adenine and 9[5'-(2-Oxo-1,3,2-dioxaphosphorinan-2-yl)-beta-D-arabinosyl]adenine: Potential Neutral Precursors of 9-[beta-D-Arabinofuranosyl]adenine 5'-Monophosphate," J. Med. Chem., vol. 28, no. 9, pp. 1358-1361 (1985).	
		FDA Consumer Health Information leaflet, "Faster Easier Cures for Hepatitis C", July 2014.	

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L/

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	27	of	51	Attorney Docket Number	37JD-199059-US13

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		FDA Guidance for Industry Antiviral Product Development--Conducting and Submitting Virology Studies to the Agency, June 2006.	
		Feng et al., Role of Mitochondrial RNA Polymerase in the Toxicity of Nucleotide Inhibitors of Hepatitis C Virus. Antimicrob Agents Chemother. Accepted: 23 November 2015; Printed February 2016; 60(2): pp. 806-817.	
		Final Rejection for Brazilian Patent Application No. PI0809654-6 dated December 28, 2020. 2 pages.	
		FREED et al., "Evidence for acyloxymethyl esters of pyrimidine 5'-deoxyribonucleotides as extracellular sources of active 5'-deoxyribonucleotides in cultured cells," Biochemical Pharmacology, vol. 38, no. 19, pp. 3193-3198 (1989).	
		Furman et al., "PSI-7851: A Novel Liver-Targeting Nucleotide Prodrug for the Treatment of Hepatitis C. Poster Presented at 59th Annual Meeting of the American Association for the Study of Liver Diseases, Oct. 31 to Nov. 4, 2008.	
		Furman et al., "The Anti-Hepatitis B Virus Activities, Cytotoxicities, and Anabolic Profiles of the (-) and (+) Enantiomers of cis-5-Fluoro-1-[2-(Hydroxymethyl)-1,3-Ozathiolan-5-yl]Cytosine," Antimicrobial Agents and Chemotherapy, (1992), 36(2):2686-2692.	
		Furman et al., Discovery and Development of PSI-6130/RG7128, Antiviral Drugs: From Basic Discovery through Clinical Trials, Edited by Wieslaw M. Kazmierski. Published 2011; pp. 305-315.	
		Ghany et al., Diagnosis, management, and treatment of hepatitis C: An update. Hepatology, April 2009, 49(4), pp. 1335-1374. doi/10.1002/hep.22759.	
		GILLESPIE, S., et al., "Stereoselective Inhibition of Cholesterol Esterase by Enantiomeric Phosphonates," Phosphorous, Sulfur and Silicon, 1997, 122: 205-208.	
		GOEKJIAN et al., "Synthesis of Fluorinated Marcocyclic Bis(indolyl)maleimides as Potential 19F NMR Probes for Protein Kinase C," J. Org. Chem. vol., 64., no. 12, pp. 4238-4246 (1999).	

Examiner Signature		Date Considered	
-----------------------	--	--------------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L./

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	28	of	51	Attorney Docket Number	37JD-199059-US13

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		GORBALENYA et al., "A conserved NTP-motif in putative helicases," Nature, vol. 333, p. 22 (1988).	
		GORBALENYA et al., "N-terminal domains of putative helicases of flavi-and pestiviruses may be serine proteases," Nucleic Acids Research, vol. 17, no. 10, pp. 3889-3897 (1989).	
		GRAKOU I et al., "A second hepatitis C virus-encoded proteinase," Proc. Natl. Acad. Sci., vol. 90, pp. 10583-10587 (1993).	
		GRAKOU I et al., "Characterization of the Hepatitis C Virus-Encoded Serine Proteinase: Determination of Proteinase-Dependent Polyprotein Cleavage Sites," J. Virol., vol. 67, no. 5, pp. 2832-2843 (1993).	
		GRIFFITH et al., "HCV Anti-viral Agents," Annual Reports in Medicinal Chemistry, vol. 39, pp. 223-237 (2004).	
		GROMOVA et al., "Optical Rotatory Dispersion and Circular Dichroism of Mono- and Oligonucleotide-Amino Acids (Amidates)," Biochim. Biophys. Acta., vol. 240, no. 1, pp. 1-11 (1971).	
		Gudmundsson et al., Phosphoramidate protides of 2',3'-dideoxy-3'-fluoroadenosine and related nucleosides with potent activity against HIV and HBV. Nucleosides Nucleotides Nucleic Acids. 2003, 22(10):1953-1961.	
		GUDMUNDSSON, KRISTJAN S., et al., "Phosphoramidate Protides of Carbocyclic 2',3'-Dideoxy-2',3'-Didehydro-7-Deazaadenosine with Potent Activity Against HIV and HBV," Nucleosides, Nucleotides & Nucleic Acids (2004), 23(12): 1929-1937.	
		Guinic et al., " Cyclic monophosphate prodrugs of base=modified 2'-C-methyl ribonucleosides as potent inhibitors of hepatitis C virus RNA replicaion," Bioorg Med Chem Lett., (2007), 17(9):2456-2458.	
		GUNIC et al., "6-Hydrazinopurine 2'-methyl ribonucleosides and their 5'-monophosphate prodrugs as potent hepatitis C virus inhibitors," Bioorg. & Med. Chem. Lett., vol. 17, pp. 2456-2458 (2007).	

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L./

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	29	of	51	Attorney Docket Number	37JD-199059-US13

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		HALSTEAD, S. B., "Pathogenesis of Dengue: Challenges to Molecular Biology," Science, vol. 239, pp. 476-481 (1988).	
		HALSTEAD, S. B., "Selective Primary Health Care: Strategies for Control of Disease in the Developing World. XI. Dengue," Review of Infectious Diseases, vol. 6, no. 2, pp. 251-263 (1984).	
		HARRIS et al., "Synthesis and antiviral evaluation of phosphoramidate derivatives of (E)-5-(2-bromovinyl)-2'-deoxyuridine," Antiviral Chemistry & Chemotherapy, vol. 12, no. 5, pp. 293-300 (2001).	
		HERNANDEZ et al., "Synthesis of Highly Functionalized Chiral Nitriles by Radical Fragmentation of beta-Hydroxy Azides. Convenient Transformation of Aldononitriles into 1,4- and 1,5-Iminoalditols," J. Org. Chem., vol. 69, no. 24, pp. 8437-8444 (2004).	
		HERTEL et al., "Synthesis of 2-Deoxy-2,2-difluoro-D-ribose and 2-Deoxy-2,2-difluoro-D-ribofuranosyl Nucleosides," J. Org. Chem., vol. 53, no. 11, pp. 2406-2409 (1988).	
		HIJIKATA et al., "Two Distinct Proteinase Activities required for the Processing of a Putative Nonstructural Precursor Protein of Hepatitis C Virus," J. Virol., vol. 67, no. 8, pp. 4665-4675 (1993).	
		HOSTETLER et al., "Greatly Enhanced Inhibition of Human Immunodeficiency Virus Type 1 Replication in CEM and HT4-6C Cells by 3'-Deoxythymidine Diphosphate Dimyristoylglycerol, a Lipid Prodrug of 3'-Deoxythymidine," Antimicrobial Agents and Chemotherapy, vol. 36, no. 9, pp. 2025-2029 (1992).	
		HOSTETLER et al., "Synthesis and Antiretroviral Activity of Phospholipid Analogs of Azidothymidine and Other Antiviral Nucleosides," J. Biol. Chem., vol. 265, no. 11, pp. 6112-6117 (1990).	
		HOWES et al., "The Regiospecific One-Pot Phosphorylation of Either the 5'-or 2'-Hydroxyl in 3'-Deoxycytidines Without Protection: Critical Role of the Base," Nucleosides, Nucleotides, and Nucleic Acids, vol. 22, no. 5-8, pp. 687-689 (2003).	
		HREBAECKY et al., "1-(3,5-O-alkylidene-2-DE-oxy-4-C-hydroxymethyl-alpha-L-threo-pentofuranosyl) uracils," Collect. Czech. Chem. Commun., vol. 62, pp. 957-970, (1997).	

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L./

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	30	of	51	Attorney Docket Number	37JD-199059-US13

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		Hrebabecky, et al., "Synthesis of 1-(3-azido-2,3-dideoxy-4-C-hydroxymethyl-alpha-L-threopentofuranosyl)thymine, 1-(2,3-dideoxy-4-C-hydroxy-methyl-alpha-L-glycero-pentofuranosyl)thymine and 1-(2,3-dideoxy-4-C-hydroxymethyl-alpha-L-glycero-pent-2-enofuranosyl)thymine," Collect. Czech. Chem. Commun., vol. 58, pp. 409-420, (1992).	
		Hrebabecky, et al., "Synthesis of 1-(3-azido-2,3-dideoxy-beta-D-allofuranosyl)thymine, 1-(2,3-dideoxy-beta-D-allofuranosyl)thymine, and 1-(2,3-dideoxy-beta-D-erythro-hex-2-enofuranosyl)thymine," Carbohydrate Research, 1991, vol. 216, pp. 179-186.	
		Hrebabecky et al., Synthesis of 1-(3-Azido-2,3-dideoxy-beta-D-ribo-hexofuranosyl)-, 1-(2,3-Dideoxy-beta-D-erythro-hexofuranosyl)- and 1-(2,3-Dideoxy-beta-D-erythro-hex-2-enofuranosyl)pyrimidine Nucleosides. Collect. Czech. Chem. Commun. 1994, vol. 59, pp. 412-420.	
		Huheey et al., Inorganic Chemistry: Principles of Structure and Reactivity. Fourth Edition. HarperCollins College Publishers 1993, cover page and pages 233-234.	
		HUNSTON et al., "Synthesis and Biological Properties of Some Cyclic Phosphotriesters Derived from 2'-Deoxy-5-fluorouridine," J. Med. Chem., vol. 27, no. 4, pp. 440-444 (1984).	
		International Preliminary Report on Patentability and Written Opinion of the International Searching Authority issued in International Application No. PCT/US2008/058183 issued April 7, 2010. (17 pages)	
		International Search Report and Written Opinion of the International Searching Authority issued in International Application No. PCT/US2008/058183 mailed March 31, 2010.	
		IYER et al., "Synthesis, in Vitro Anti-Breast Cancer Activity, and Intracellular Decomposition of Amino Acid Methyl Ester and Alkyl Amide Phosphoramidate Monoesters of 3'-Azido-3'-deoxythymidine (AZT)," J. Med. Chem., vol. 43, no. 11, pp. 2266-2274 (2000).	
		JIN et al., "Expression, Isolation, and characterization of the Hepatitis C Virus ATPase/RNA Helicase," Archives of Biochemistry and Biophysics, vol. 323, no. 1, pp. 47-53 (1995).	
		JONES et al., "Minireview: Nucleotide Prodrugs," Antiviral Research, vol. 27, no. 1-2, pp. 1-17 (1995).	

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L./

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	31	of	51	Attorney Docket Number	37JD-199059-US13

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		JUODKA et al., "Oligonucleotides and Nucleotide-Peptides. XXXIV. Synthesis and Some Properties of Complex Nucleotidyl (Oligonucleotidyl)-P-N-Amino Acids (Peptides) and Their Ethyl Esters," J. Carbohydrates Nucleosides Nucleotides, vol. 6, no. 4, pp. 333-357 (1979).	
		JUODKA et al., "Oligonucleotides and Nucleotide-Peptides. XXXV. Some Properties of Nucleotidyl-(5'-N)-Amino Acid Esters Differing in Amino Acid and Nucleotide Components," J. Carbohydrates Nucleosides Nucleotides, vol. 8, no. 1, pp. 19-39 (1981).	
		JUODKA et al., "Oligonucleotides and Nucleotide-Peptides. XXXVII. On the Mechanism of Hydrolysis of Uridylyl-(5'-N)-Amino Acids. Intramolecular Catalysis by the alpha-Carboxyl Group of Amino Acids," J. Carbohydrates Nucleosides Nucleotides, vol. 8, no. 6, pp. 519-535 (1981).	
		Kaplan. Propagation of hepatitis C virus infection: Elucidating targets for therapeutic intervention. Drug Discovery Today: Disease Mechanisms 2006, 3(4), pp. 471-477.	
		Karen Weinstock at the FDA Communication. Dated July 15, 2015.	
		KHAMNEI et al., "Neighboring Group Catalysis in the Design of Nucleotide Prodrugs," J. Med. Chem., vol. 39, no. 20, pp. 4109-4115 (1996).	
		KIM et al., "C-Terminal Domain of the Hepatitis C Virus NS3 Protein Contains an RNA Helicase Activity," Biochemical and Biophysical Research Communications, vol. 215, no. 1, pp. 160-166 (1995).	
		Kim et al., "Direct Measurement of Nucleoside Monophosphate Delivery from a Phosphoramidate Pronucleotide by Stable Isotope Labeling and LC-ESI-MS/MS," Molecular Pharmaceutics, 2004, 1(2), pp. 102-111.	
		KIM et al., "Monitoring the Intracellular Metabolism of Nucleoside Phosphoramidate Pronucleotides by 31P NMR," Nucleosides, Nucleotides and Nucleic Acid, vol. 23, no. 1 & 2, pp. 483-493 (2004).	
		Klebl et al., Host Cell Targets in HCV Therapy: Novel Strategy or Proven Practice?, Antiviral Chemistry and Chemotherapy 2005, 16, pp. 69-90.	

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L/

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	32	of	51	Attorney Docket Number	37JD-199059-US13

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		Klump, et al., "The Novel Nucleoside Analog R1479(4'-Azidocytidine) Is a Potent Inhibitor of NS5B-dependent RCA Synthesis and Hepatitis C Virus Replication in Cell Culture," J. Bio. Chem., (2006), 281:3793-3799.	
		KOONIN et al., "Evolution and Taxonomy of Positive-Strand RNA Viruses: Implications of Comparative Analysis of Amino Acid Sequences," Critical Reviews in Biochemistry and Molecular Biology, vol. 28, no. 5, pp. 375-430 (1993).	
		KOTRA et al., "Structure-Activity Relationships of 2'-Deoxy-2',2'-difluoro-L-erythro-pentofuranosyl Nucleosides," J. Med. Chem., vol. 40, no. 22, pp. 3635-3644 (1997).	
		Kowdley et al., Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naive patients with hepatitis C genotype-1 infection (ATOMIC): an open-label, randomised, multicentre phase 2 trial. Lancet. 2013 Jun 15;381(9883):2100-2107.	
		KRYUCHKOV et al., "Influence of Solvent on the Strength of Cyclic Oxygen-Containing Phosphorus Acids," Bulletin of the Academy of Sciences of the USSR. Division of Chemical Science, vol. 36, no. 6, Part 1, pp. 1145-1148 (1987) Translated from Russian.	
		KUCERA et al., "Novel Membrane-Interactive Ether Lipid Analogs That Inhibit Infectious HIV-1 Production and Induce Defective Virus Formation," Aids Research and Human Retroviruses, vol. 6, no. 4, pp. 491-501 (1990).	
		LACKEY et al., "Enzyme-catalyzed therapeutic agent (ECTA) design: activation of the antitumor ECTA compound NB1011 by thymidylate synthase," Biochemical Pharmacology, vol. 61, No. 2, pp. 179-189 (2001).	
		LALEZARI et al., ONCE DAILY PSI-7977 PLUS PEGIFN/RBV IN A PHASE 2B TRIAL: RAPID VIROLOGIC SUPPRESSION IN TREATMENT-NAIVE PATIENTS WITH HCV GT2/GT3. Journal of Hepatology 2011, vol. 54, S25-S44. Abstract 61.	
		Lam et al., Sofosbuvir (Sovaldi) for the treatment of hepatitis C. Expert Review of Clinical Pharmacology 2014, 7(5), pp. 555-566.	
		Landowski et al., "Targeted delivery to PEPT1-overexpressing cells: Acidic, basic, and secondary floxuridine amino acid ester prodrugs," MCT, (2005), 4(4):659-667.	

Examiner Signature		Date Considered	
-----------------------	--	--------------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L/

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	33	of	51	Attorney Docket Number	37JD-199059-US13

NON PATENT LITERATURE DOCUMENTS				
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²	
		Lawitz et al., Pharmacokinetics, Pharmacodynamics, and Tolerability of GS-9851, a Nucleotide Analog Polymerase Inhibitor, following Multiple Ascending Doses in Patients with Chronic Hepatitis C Infection. Antimicrobial Agents and Chemotherapy 2013, 57(3), pp. 1209-1217; doi: 10.1128/AAC.01263-12. Epub 2012 Dec 21.		
		Lawitz et al., Sofosbuvir for Previously Untreated Chronic Hepatitis C Infection. N Engl J Med 2013; 368(20), pp. 1878-1887. doi: 10.1056/NEJMoa1214853. Epub 2013 Apr 23.		
		LEE et al., "Selective Intracellular Activation of a Novel Prodrug of the Human Immunodeficiency Virus reverse Transcriptase Inhibitor Tenofovir Leads to Preferential Distribution and Accumulation in Lymphatic Tissue," Antimicrobial Agents and Chemotherapy, vol. 49, no. 5, pp. 1898-1906 (2005).		
		LEHSTEN et al., "An Improved Procedure for the Synthesis of Nucleoside Phosphoramidates," Organic Process Research and Development, vol. 6, pp. 819-822 (2002).		
		Letter from British Library dated June 8, 2015 confirming publication date of DYKENS, et al. Strategies to reduce late-stage drug attrition due to mitochondrial toxicity. Expert Rev Mol Diagn. 2007 Mar;7(2): 161-175.		
		Li et al., Synthesis of the Phosphoramidite Derivative of 2'-Deoxy-2'-C-beta-methylcytidine. J. Org. Chem. 2003, vol. 68, no. 17, pp. 6799-6802.		
		Lima et al., Bioisosterism: a useful strategy for molecular modification and drug design. Current Medicinal Chemistry 2005, vol. 12, pp. 23-49.		
		Lin et al., A stereospecific synthesis of 2',3'-dideoxy-β-L-cytidine (β-L-ddC), a potent inhibitor against human hep-atitis B virus (HBV) and human immunodeficiency virus (HIV). Tetrahedron Letters 1994, vol. 35, no. 21, pp. 3477-3480.		
		LOHMANN et al., "Biochemical Properties of Hepatitis C Virus NS5B RNA-Dependent RNA Polymerase and Identification of Amino Acid Sequence Motifs Essential for Enzymatic Activity," J. Virol., vol. 71, no. 11, pp. 8416-8428 (1997).		
		LOPEZ APARICIO et al., "Synthesis of Saccharinic Acid Derivatives," Carbohydrate Research, vol. 129, pp. 99-109 (1984).		

Examiner Signature		Date Considered	
-----------------------	--	--------------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 809. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L./

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	34	of	51	Attorney Docket Number	37JD-199059-US13

NON PATENT LITERATURE DOCUMENTS				
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²	
		Ma et al., "Characterization of the Intracellular Metabolism of β -d-2'-Deoxy-2'-Fluoro-2'-C-Methyl-Cytidine and the Inhibition of HCV Polymerase NS5B by its 5'-Triphosphate Species," Antiviral Research, (2007), 74(3): A36; Abstract 23.		
		MA et al., "Characterization of the Metabolic Activation of Hepatitis C Virus Nucleoside Inhibitor B-D-2'-Deoxy-2'-Fluoro-2'-C-Methylcytidine (PSI-6130) and Identification of a Novel Active 5'-Triphosphate Species," J. Biol. Chem., vol. 282, No. 41, pp. 29812-29820 (2007).		
		McGuigan et al., "Sub Micromolar Inhibitors of HCV Generated from Inactive Nucleosides by Application of ProTide Technology," Antiviral Research, (2007), 74(3): A36; Abstract 24.		
		MCGUIGAN et al., "Application of Phosphoramidate Pronucleotides Technology to Abacavir Leads to a Significant Enhancement of Antiviral Potency," J. Med. Chem., vol. 48, no. 10, pp. 3504-3515 (2005).		
		MCGUIGAN et al., "Application of Phosphoramidate ProTide Technology Significantly Improves Antiviral Potency of Carbocyclic Adenosine Derivatives," J. Med. Chem., vol. 49, no. 24, pp. 7215-7226 (2006).		
		MCGUIGAN et al., "Aryl phosphate derivatives of AZT retain activity against HIV1 in cell lines which are resistant to the action of AZT," Antiviral Research, vol. 17, pp. 311-321 (1992).		
		MCGUIGAN et al., "Aryl Phosphoramidate Derivatives of d4T Have Improved Anti-HIV Efficacy in Tissue Culture and May Act by the Generation of a Novel Intracellular Metabolite," J. Med. Chem., vol. 39, no. 8, pp. 1748-1753 (1996).		
		MCGUIGAN et al., "Synthesis and anti-HIV activity of some novel chain-extended phosphoramidate derivatives of d4T (stavudine): esterase hydrolysis as a rapid predictive test for antiviral potency," Antiviral Chemistry and Chemotherapy, vol. 9, pp. 109-115 (1998).		
		MCGUIGAN et al., "Synthesis and evaluation of some novel phosphoramidate derivatives of 3'-azido-3'-deoxythymidine (AZT) as anti-HIV compounds," Antiviral Chemistry and Chemotherapy, vol. 1, no. 2, pp. 107-113 (1990).		

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L./

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	35	of	51	Attorney Docket Number	37JD-199059-US13

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		MCGUIGAN et al., Certain Phosphoramidate Derivatives of Dideoxy Uridine (ddU) Are Active Against HIV and Successfully By-pass Thymidine Kinase, FEBS Letters (1994), 351, 11-14.	
		McGuigan et al., Synthesis, anti-human immunodeficiency virus activity and esterase lability of some novel carboxylic ester-modified phosphoramidate derivatives of stavudine (d4T). Antiviral Chemistry & Chemotherapy 1998, vol. 9, pp. 473-479.	
		McGulgan, "Phosphoramidate derivatives of stavudine as inhibitors of HIV: unnatural amino acids may substitute for alanine," Antiviral Chemistry & Chemotherapy, (2000), 11:111-116.	
		MCINTEE et al., "Amino Acid Phosphoramidate Nucleosides: Potential ADEPT/GDEPT Substrates," Bioorganic & Medicinal Chemistry Letters, vol. 11, no. 21, pp. 2803-2805 (2001).	
		MCINTEE et al., "Probing the Mechanism of Action and Decomposition of Amino Acid Phosphomonoester Amides of Antiviral Nucleoside Prodrugs," J. Med. Chem., vol. 40, no. 21, pp. 3323-3331 (1997).	
		MEIER et al., "Cyclic Saligenyl Phosphotriesters of 2',3' -Dideoxy-2',3'-didehydrothymidine (d4T) - A New Pro-Nucleotide Approach," Bioorg. & Med. Chem. Lett., vol. 7, no. 2, pp. 99-104, (1997).	
		MEYERS et al., "Molecular Characterization of Pestiviruses," Advance in Virus Research, vol. 47, pp. 53-119 (1996).	
		MITCHELL et al., "Bioreversible Protection for the Phospho Group: Bioactivation of the Di(4-acyloxybenzyl) and Mono(4-acyloxybenzyl) Phosphoesters of Methylphosphonate and Phosphonoacetate," J. Chem. Soc. Perkin. Trans. 1, pp. 2345-2353 (1992).	
		MOENNIG et al., "The Pestiviruses," Advances in Virus Research, vol. 41, pp. 53-99 (1992).	
		MONATH, T. P., M.D., "Japanese Encephalitis-A Plague of the Orient," N. Engl. J. Med., vol. 319, no. 10, pp. 641-643 (Sep. 8, 1988).	

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

SMRH:4831-9482-4419.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L./