NUCLEOSIDE PHOSPHORAMIDATES

This application is being filed on 23 December 2009, as a PCT International Patent application in the name of Pharmasset, Inc., a U.S. national corporation, applicant for the designation of all countries except the US, and Michael Joseph Sofia and Jinfa Du, both citizens of the U.S., Peiyuan Wang, a citizen of China, and Dhanapalan Nagarathnam, a citizen of the U.S., applicants for the designation of the US only.

PRIORITY CLAIM

The present application claims priority to U.S. Provisional Patent Application No. 61/140,423, filed December 23, 2008, the contents of which are incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention pertains to nucleoside phosphoramidates and their use as agents for treating viral diseases. These compounds are inhibitors of RNA-dependent RNA viral replication and are useful as inhibitors of HCV NS5B polymerase, as inhibitors of HCV replication and for treatment of hepatitis C infection in mammals.

BACKGROUND

Hepatitis C virus (HCV) infection is a major health problem that leads to chronic liver disease, such as cirrhosis and hepatocellular carcinoma, in a substantial number of infected individuals, estimated to be 2-15% of the world's population. There are an estimated 4.5 million infected people in the United States alone, according to the U.S. Center for Disease Control. According to the World Health Organization, there are more than 200 million infected individuals worldwide, with at least 3 to 4 million people being infected each year. Once infected, about 20% of people clear the virus, but the rest can harbor HCV the rest of their lives. Ten to twenty percent of chronically infected individuals eventually develop liver-destroying cirrhosis or cancer. The viral disease is transmitted parenterally by contaminated blood and blood products, contaminated needles, or sexually and vertically from infected mothers or carrier mothers to their offspring. Current treatments for HCV infection, which are restricted to immunotherapy with recombinant interferon-α alone or in combination with the nucleoside analog

ribavirin, are of limited clinical benefit. Moreover, there is no established vaccine for HCV. Consequently, there is an urgent need for improved therapeutic agents that effectively combat chronic HCV infection.

The HCV virion is an enveloped positive-strand RNA virus with a single oligoribonucleotide genomic sequence of about 9600 bases which encodes a polyprotein of about 3,010 amino acids. The protein products of the HCV gene consist of the structural proteins C, E1, and E2, and the non-structural proteins NS2, NS3, NS4A and NS4B, and NS5A and NS5B. The nonstructural (NS) proteins are believed to provide the catalytic machinery for viral replication. The NS3 protease releases NS5B, the RNA-dependent RNA polymerase from the polyprotein chain. HCV NS5B polymerase is required for the synthesis of a double-stranded RNA from a single-stranded viral RNA that serves as a template in the replication cycle of HCV. Therefore, NS5B polymerase is considered to be an essential component in the HCV replication complex (K. Ishi, et al, *Heptology*, 1999, 29: 1227-1235; V. Lohmann, et al., *Virology*, 1998, 249: 108-118). Inhibition of HCV NS5B polymerase prevents formation of the double-stranded HCV RNA and therefore constitutes an attractive approach to the development of HCV-specific antiviral therapies.

HCV belongs to a much larger family of viruses that share many common features.

Flaviviridae Viruses

The Flaviviridae family of viruses comprises at least three distinct genera: *pestiviruses*, which cause disease in cattle and pigs; *flavivruses*, which are the primary cause of diseases such as dengue fever and yellow fever; and *hepaciviruses*, whose sole member is HCV. The flavivirus genus includes more than 68 members separated into groups on the basis of serological relatedness (Calisher et al., *J. Gen. Virol*, 1993,70,37-43). Clinical symptoms vary and include fever, encephalitis and hemorrhagic fever (*Fields Virology*, Editors: Fields, B. N., Knipe, D. M., and Howley, P. M., Lippincott-Raven Publishers, Philadelphia, PA, 1996, Chapter 31, 931-959). Flaviviruses of global concern that are associated with human disease include the Dengue Hemorrhagic Fever viruses (DHF), yellow fever virus, shock

syndrome and Japanese encephalitis virus (Halstead, S. B., *Rev. Infect. Dis.*, 1984, 6, 251-264; Halstead, S. B., *Science*, 239:476-481, 1988; Monath, T. P., *New Eng. J. Med*, 1988, 319, 64 1-643).

The pestivirus genus includes bovine viral diarrhea virus (BVDV), classical swine fever virus (CSFV, also called hog cholera virus) and border disease virus (BDV) of sheep (Moennig, V. et al. *Adv. Vir. Res.* 1992, 41, 53-98). Pestivirus infections of domesticated livestock (cattle, pigs and sheep) cause significant economic losses worldwide. BVDV causes mucosal disease in cattle and is of significant economic importance to the livestock industry (Meyers, G. and Thiel, H.J., Advances in Virus Research, 1996, 47, 53-118; Moennig V., et al, Adv. Vir. Res. 1992, 41, 53-98). Human pestiviruses have not been as extensively characterized as the animal pestiviruses. However, serological surveys indicate considerable pestivirus exposure in humans.

Pestiviruses and hepaciviruses are closely related virus groups within the Flaviviridae family. Other closely related viruses in this family include the GB virus A, GB virus A-like agents, GB virus-B and GB virus-C (also called hepatitis G virus, HGV). The hepacivirus group (hepatitis C virus; HCV) consists of a number of closely related but genotypically distinguishable viruses that infect humans. There are at least 6 HCV genotypes and more than 50 subtypes. Due to the similarities between pestiviruses and hepaciviruses, combined with the poor ability of hepaciviruses to grow efficiently in cell culture, bovine viral diarrhea virus (BVDV) is often used as a surrogate to study the HCV virus.

The genetic organization of pestiviruses and hepaciviruses is very similar. These positive stranded RNA viruses possess a single large open reading frame (ORF) encoding all the viral proteins necessary for virus replication. These proteins are expressed as a polyprotein that is co- and post-translationally processed by both cellular and virus-encoded proteinases to yield the mature viral proteins. The viral proteins responsible for the replication of the viral genome RNA are located within approximately the carboxy-terminal. Two-thirds of the ORF are termed nonstructural (NS) proteins. The genetic organization and polyprotein processing of the nonstructural protein portion of the ORF for pestiviruses and hepaciviruses is very similar. For both the pestiviruses and hepaciviruses, the mature nonstructural

(NS) proteins, in sequential order from the amino-terminus of the nonstructural protein coding region to the carboxy-terminus of the ORF, consist of p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B.

The NS proteins of pestiviruses and hepaciviruses share sequence domains that are characteristic of specific protein functions. For example, the NS3 proteins of viruses in both groups possess amino acid sequence motifs characteristic of serine proteinases and of helicases (Gorbalenya et al., *Nature,* 1988, 333, 22; Bazan and Fletterick *Virology* , 1989,171,637-639; Gorbalenya et al., *Nucleic Acid Res.,*1989, 17, 3889-3897). Similarly, the NS5B proteins of pestiviruses and hepaciviruses have the motifs characteristic of RNA-directed RNA polymerases (Koonin, E.V. and Dolja, V.V., *Crir. Rev. Biochem. Molec. Biol.* 1993, 28, 375-430).

The actual roles and functions of the NS proteins of pestiviruses and hepaciviruses in the lifecycle of the viruses are directly analogous. In both cases, the NS3 serine proteinase is responsible for all proteolytic processing of polyprotein precursors downstream of its position in the ORF (Wiskerchen and Collett, *Virology*, 1991, 184, 341-350; Bartenschlager et al., *J. Virol.* 1993, 67, 3835-3844; Eckart et al. *Biochem. Biophys. Res. Comm.* 1993,192, 399-406; Grakoui et al., *J. Virol.* 1993, 67, 2832-2843; Grakoui et al., *Proc. Natl. Acad Sci. USA* 1993, 90, 10583-10587; Hijikata et al., *J. Virol.* 1993, 67, 4665-4675; Tome et al., *J. Virol.*, 1993, 67, 4017-4026). The NS4A protein, in both cases, acts as a cofactor with the NS3 serine protease (Bartenschlager et al., *J. Virol.* 1994, 68, 5045-5055; Failla et al., *J. Virol.* 1994, 68, 3753-3760; Xu et al., *J. Virol.*, 1997, 71:53 12-5322). The NS3 protein of both viruses also functions as a helicase (Kim et al., *Biochem. Biophys. Res. Comm.*, 1995, 215, 160-166; Jin and Peterson, *Arch. Biochem. Biophys.*, 1995, 323, 47-53; Warrener and Collett, *J. Virol.* 1995, 69,1720-1726). Finally, the NS5B proteins of pestiviruses and hepaciviruses have the predicted RNA-directed RNA polymerases activity (Behrens et al., EMBO, 1996, 15, 12-22; Lechmann et al., *J. Virol.*, 1997, 71, 8416-8428; Yuan et al., *Biochem. Biophys. Res. Comm.* 1997, 232, 231-235; Hagedorn, PCT WO 97/12033; Zhong et al, *J. Virol.,* 1998, 72, 9365-9369).

Currently, there are limited treatment options for individuals infected with hepatitis C virus. The current approved therapeutic option is the use of

immunotherapy with recombinant interferon-α alone or in combination with the nucleoside analog ribavirin. This therapy is limited in its clinical effectiveness and only 50% of treated patients respond to therapy. Therefore, there is significant need for more effective and novel therapies to address the unmet medical need posed by HCV infection.

A number of potential molecular targets for drug development of direct acting antivirals as anti -HCV therapeutics have now been identified including, but not limited to, the NS2-NS3 autoprotease, the N3 protease, the N3 helicase and the NS5B polymerase. The RNA-dependent RNA polymerase is absolutely essential for replication of the single-stranded, positive sense, RNA genome and this enzyme has elicited significant interest among medicinal chemists.

Inhibitors of HCV NS5B as potential therapies for HCV infection have been reviewed: Tan, S.-L., et al., *Nature Rev. Drug Discov.*, 2002, 1, 867-881; Walker, M.P. et al., *Exp. Opin. Investigational Drugs*, 2003, 12, 1269-1280; Ni, Z-J., et al., *Current Opinion in Drug Discovery and Development*, 2004, 7, 446-459; Beaulieu, P. L., et al., *Current Opinion in Investigational Drugs*, 2004, 5, 838-850; Wu, J., et al., *Current Drug Targets-Infectious Disorders*, 2003, 3, 207-219; Griffith, R.C., et al, *Annual Reports in Medicinal Chemistry*, 2004, 39, 223-237; Carrol, S., et al., *Infectious Disorders-Drug Targets*, 2006, 6, 17-29. The potential for the emergence of resistant HCV strains and the need to identify agents with broad genotype coverage supports the need for continuing efforts to identify novel and more effective nucleosides as HCV NS5B inhibitors.

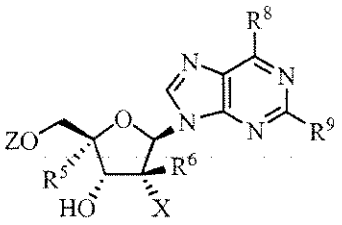
Nucleoside inhibitors of NS5B polymerase can act either as a non-natural substrate that results in chain termination or as a competitive inhibitor which competes with nucleotide binding to the polymerase. To function as a chain terminator the nucleoside analog must be taken up by the cell and converted *in vivo* to a triphosphate to compete for the polymerase nucleotide binding site. This conversion to the triphosphate is commonly mediated by cellular kinases which imparts additional structural requirements on a potential nucleoside polymerase inhibitor. Unfortunately, this limits the direct evaluation of nucleosides as inhibitors of HCV replication to cell-based assays capable of *in situ* phosphorylation.

In some cases, the biological activity of a nucleoside is hampered by its poor substrate characteristics for one or more of the kinases needed to convert it to the active triphosphate form. Formation of the monophosphate by a nucleoside kinase is generally viewed as the rate limiting step of the three phosphorylation events. To circumvent the need for the initial phosphorylation step in the metabolism of a nucleoside to the active triphosphate analog, the preparation of stable phosphate prodrugs has been reported. Nucleoside phosphoramidate prodrugs have been shown to be precursors of the active nucleoside triphosphate and to inhibit viral replication when administered to viral infected whole cells (McGuigan, C., et al., *J. Med. Chem.*, 1996, 39, 1748-1753; Valette, G., et al., *J. Med. Chem.*, 1996, 39, 1981-1990; Balzarini, J., et al., *Proc. National Acad Sci USA*, 1996, 93, 7295-7299; Siddiqui, A. Q., et al., *J. Med. Chem.*, 1999, 42, 4122-4128; Eisenberg, E. J., et al., *Nucleosides, Nucleotides and Nucleic Acids*, 2001, 20, 1091-1098; Lee, W.A., et al., *Antimicrobial Agents and Chemotherapy*, 2005, 49, 1898); US 2006/0241064; and WO 2007/095269.

Also limiting the utility of nucleosides as viable therapeutic agents is their sometimes poor physicochemical and pharmacokinetic properties. These poor properties can limit the intestinal absorption of an agent and limit uptake into the target tissue or cell. To improve on their properties prodrugs of nucleosides have been employed. It has been demonstrated that preparation of nucleoside phosphoramidates improves the systemic absorption of a nucleoside and furthermore, the phosphoramidate moiety of these "pronucleotides" is masked with neutral lipophilic groups to obtain a suitable partition coefficient to optimize uptake and transport into the cell dramatically enhancing the intracellular concentration of the nucleoside monophosphate analog relative to administering the parent nucleoside alone. Enzyme-mediated hydrolysis of the phosphate ester moiety produces a nucleoside monophosphate wherein the rate limiting initial phosphorylation is unnecessary.

SUMMARY OF THE INVENTION

The present invention is directed to a phosphoramidate nucleoside represented by formula **I**, or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



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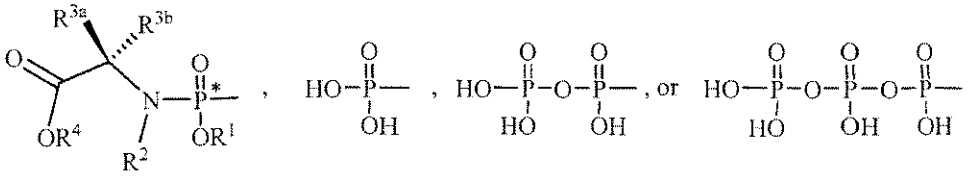
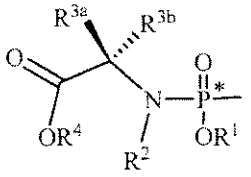
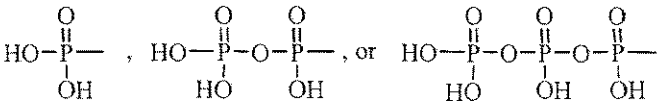
Z is  ,

wherein when

Z is 

R^1 is hydrogen or phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is hydrogen, methyl, ^{i}Pr, or cyclopentyl; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OMe, –N(-$CH_2CH_2CH_2$-) (azetidin-1-yl), OBn, or OH; and R^9 is NH_2;

and wherein when

Z is 

R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OMe, –N(-$CH_2CH_2CH_2$-) (azetidin-1-yl), OBn, or OH; and R^9 is NH_2.

DEFINITIONS

The phrase "a" or "an" entity as used herein refers to one or more of that entity; for example, a compound refers to one or more compounds or at least one compound. As such, the terms "a" (or "an"), "one or more", and "at least one" can be used interchangeably herein.

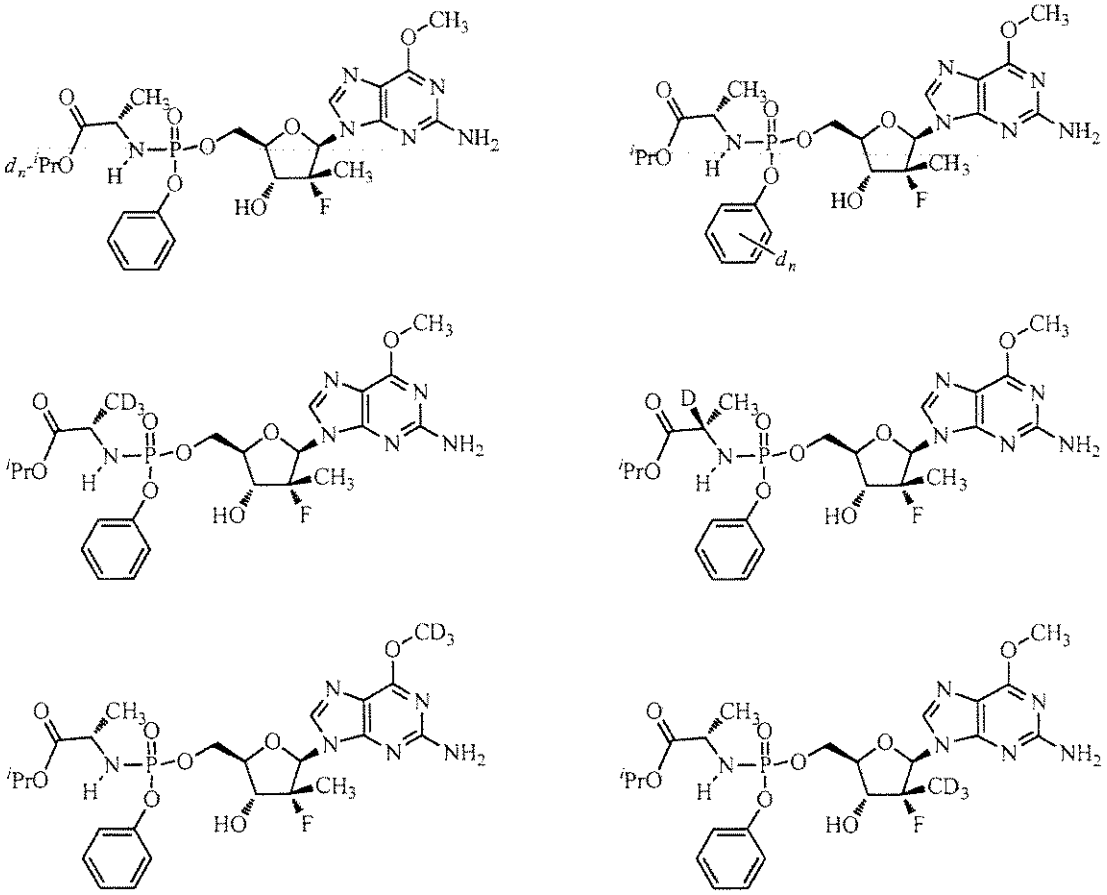
The phrase "as defined herein above" or "as defined herein" refers to the first definition provided in the Summary of the Invention.

The terms "optional" or "optionally" as used herein means that a subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "optional bond" means that the bond may or may not be present, and that the description includes single, double, or triple bonds.

The term "independently" is used herein to indicate that a variable is applied in any one instance without regard to the presence or absence of a variable having that same or a different definition within the same compound. Thus, in a compound in which R appears twice and is defined as "independently carbon or nitrogen", both R's can be carbon, both R's can be nitrogen, or one R' can be carbon and the other nitrogen.

The term "purified," as described herein, refers to the purity of a given compound. For example, a compound is "purified" when the given compound is a major component of the composition, i.e., at least 50% w/w pure. Thus, "purified" embraces at least 50% w/w purity, at least 60% w/w purity, at least 70% purity, at least 80% purity, at least 85% purity, at least 90% purity, at least 92% purity, at least 94% purity, at least 96% purity, at least 97% purity, at least 98% purity, and at least 99% purity.

It is also contemplated that the compound represented by formula **I** embraces deuterated analogs. The term "deuterated analogs" means a compound described herein or its salts thereof, whereby a ^{1}H-isotope, i.e., hydrogen (H), is substituted by a ^{2}H-isotope, i.e., deuterium (D). Deuterium substitution can be partial or complete. Partial deuterium substitution means that at least one hydrogen is substituted by at least one deuterium. For instance, for a compound represented by formula **11**, one of ordinary skill can contemplate at least the following partial deuterated analogs (where "d_n" represents n-number of deuterium atoms, such as, for an isopropyl group n = 1-7, while for a phenyl group, n = 1-5). Although the methyl groups depicted below are shown as being completely deuterated, one will recognize that partial-deuterated variations are also possible, such as, $-CDH_2$ and $-CD_2H$.



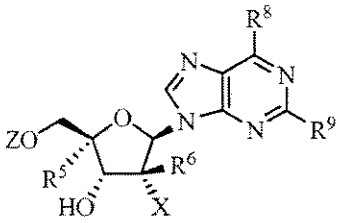
These are but a few deuterated analogs that are synthetically accessible by procedures and reagents that are known to one of ordinary skill.

The term "metabolite," as described herein, refers to a compound produced in vivo after administration to a subject in need thereof.

The term "salts," as described herein, refers to a compound produced by the protonation of a proton-accepting moiety and/or deprotonation of a proton-donating moiety. It should be noted that protonation of the proton-accepting moiety results in the formation of a cationic species in which the charge is balanced by the presence of a physiological anion, whereas deprotonation of the proton-donating moiety results in the formation of an anionic species in which the charge is balanced by the presence of a physiological cation.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a phosphoramidate nucleoside represented by formula **I,** or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



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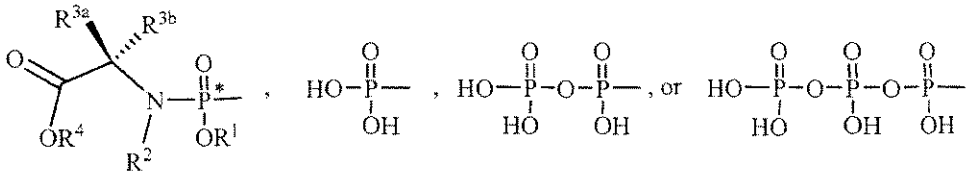
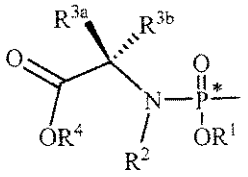
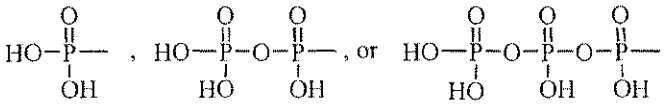
Z is 

wherein when

Z is 

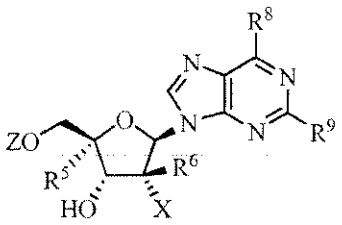
R^1 is hydrogen or phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is hydrogen, methyl, ^{i}Pr, or cyclopentyl; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OMe, –N(-$CH_2CH_2CH_2$-) (azetidin-1-yl), OBn, or OH; and R^9 is NH_2;

and wherein when

Z is 

R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OMe, –N(-$CH_2CH_2CH_2$-) (azetidin-1-yl), OBn, or OH; and R^9 is NH_2.

A first embodiment of the present invention is directed to a phosphoramidate nucleoside represented by formula **I,** or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



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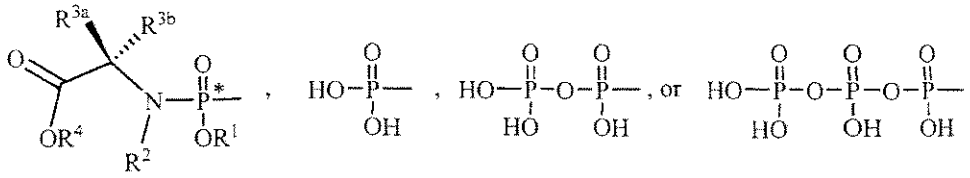
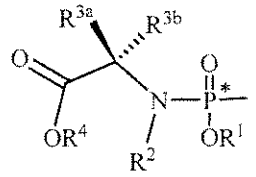
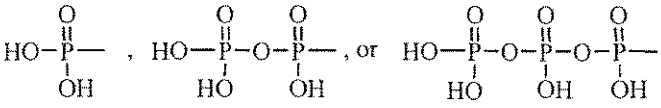
Z is 

wherein when

Z is 

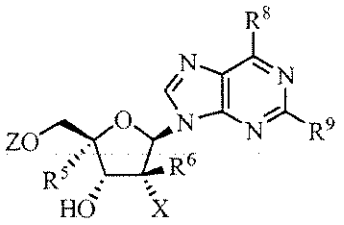
R^1 is hydrogen or phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is hydrogen, methyl, ^{i}Pr, or cyclopentyl; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OMe; and R^9 is NH_2;

and wherein when

Z is 

R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OMe; and R^9 is NH_2.

A first aspect of the first embodiment is directed to a phosphoramidate nucleoside represented by formula **I**, or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



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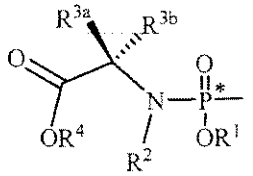

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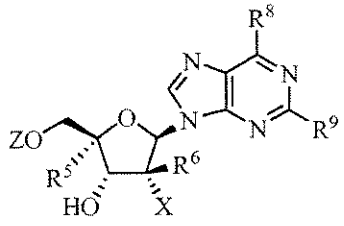
R^1 is hydrogen or phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is hydrogen, methyl, ^{i}Pr, or cyclopentyl; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OMe; and R^9 is NH_2.

A second aspect of the first embodiment is directed to a phosphoramidate nucleoside represented by formula **I,** or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



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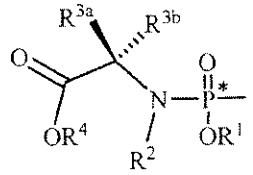

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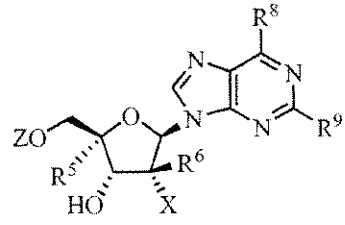
R^1 is phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is methyl, ^{i}Pr, or cyclopentyl; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OMe; and R^9 is NH_2.

A third aspect of the first embodiment is directed to a phosphoramidate nucleoside represented by formula **I,** or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



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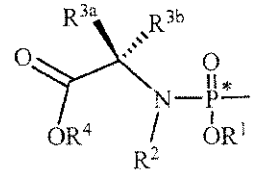

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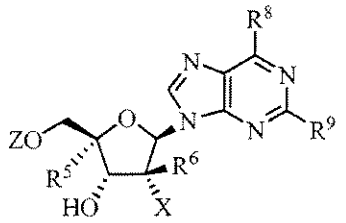
R^1 is phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is methyl; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OMe; and R^9 is NH_2.

A fourth aspect of the first embodiment is directed to a phosphoramidate nucleoside represented by formula **I**, or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



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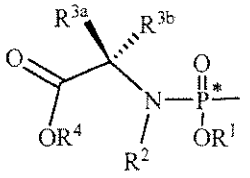
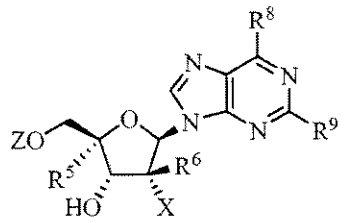


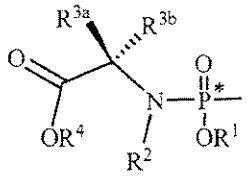
I

R^1 is phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is ^{i}Pr; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OMe; and R^9 is NH_2.

A fifth aspect of the first embodiment is directed to a phosphoramidate nucleoside represented by formula **I**, or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



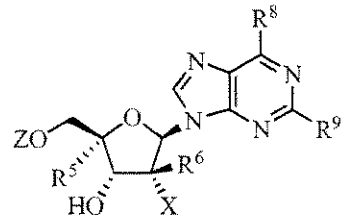
Z is



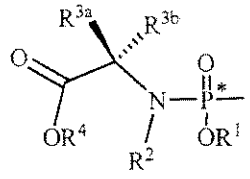
I

R^1 is phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is cyclopentyl; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OMe; and R^9 is NH_2.

A sixth aspect of the first embodiment is directed to a phosphoramidate nucleoside represented by formula **I**, or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



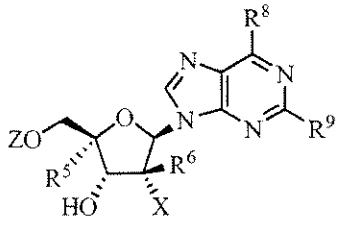
Z is



I

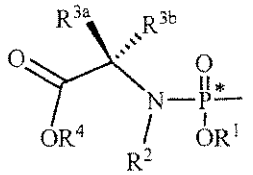
R^1 is phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is hydrogen; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OMe; and R^9 is NH_2.

A seventh aspect of the first embodiment is directed to a phosphoramidate nucleoside represented by formula **I**, or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



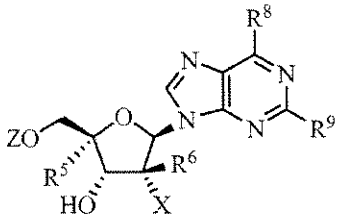
I

Z is



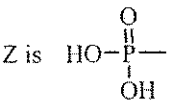
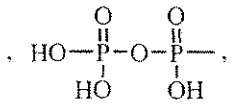
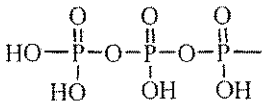
R^1 is hydrogen; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is hydrogen; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OMe; and R^9 is NH_2.

An eighth aspect of the first embodiment is directed to a phosphoramidate nucleoside represented by formula **I**, or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



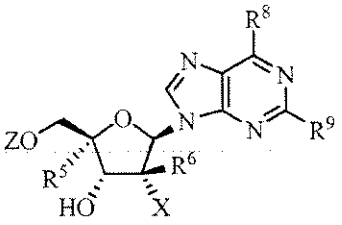
I

wherein

Z is  , , or 

and wherein R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OMe; and R^9 is NH_2.

A second embodiment of the present invention is directed to a phosphoramidate nucleoside represented by formula **I**, or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



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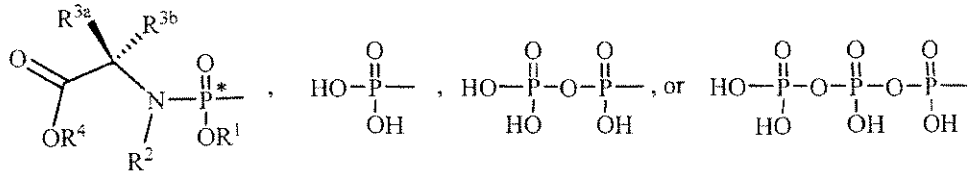
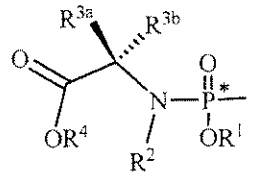
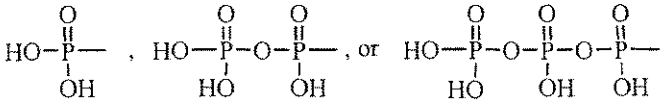
Z is  ,

wherein when

Z is 

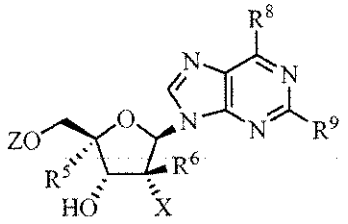
R^1 is hydrogen or phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is hydrogen, methyl, ^{i}Pr, or cyclopentyl; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is –N(-$CH_2CH_2CH_2$-) (azetidin-1-yl); and R^9 is NH_2;

and wherein when

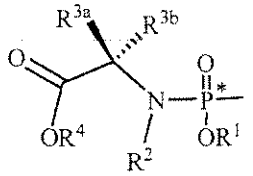
Z is 

R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is –N(-$CH_2CH_2CH_2$-) (azetidin-1-yl); and R^9 is NH_2.

A first aspect of the second embodiment is directed to a phosphoramidate nucleoside represented by formula **I,** or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



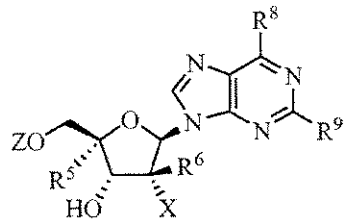
Z is



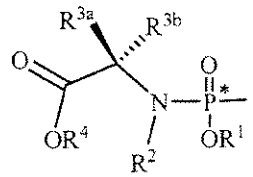
I

R^1 is hydrogen or phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is hydrogen, methyl, ^{i}Pr, or cyclopentyl; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is –N(-$CH_2CH_2CH_2$-) (azetidin-1-yl); and R^9 is NH_2.

A second aspect of the second embodiment is directed to a phosphoramidate nucleoside represented by formula **I**, or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



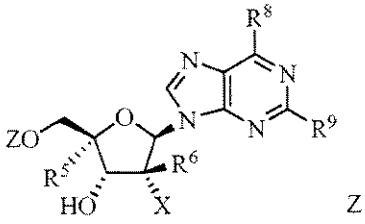
Z is



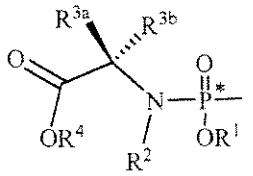
I

R^1 is phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is methyl, ^{i}Pr, or cyclopentyl; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is –N(-$CH_2CH_2CH_2$-) (azetidin-1-yl); and R^9 is NH_2.

A third aspect of the second embodiment is directed to a phosphoramidate nucleoside represented by formula **I**, or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



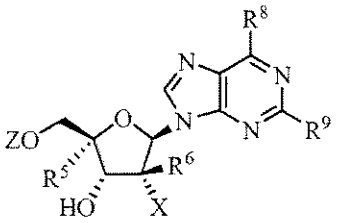
Z is



I

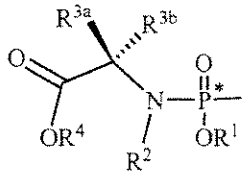
R^1 is phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is methyl; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is –N(-$CH_2CH_2CH_2$-) (azetidin-1-yl); and R^9 is NH_2.

A fourth aspect of the second embodiment is directed to a phosphoramidate nucleoside represented by formula **I,** or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



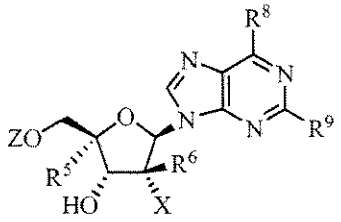
I

Z is



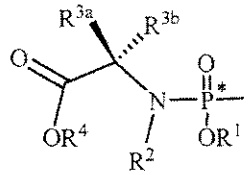
R^1 is phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is ^{i}Pr; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is –N(-$CH_2CH_2CH_2$-) (azetidin-1-yl); and R^9 is NH_2.

A fifth aspect of the second embodiment is directed to a phosphoramidate nucleoside represented by formula **I,** or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



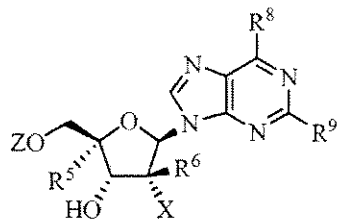
I

Z is



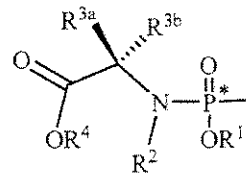
R^1 is phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is cyclopentyl; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is –N(-$CH_2CH_2CH_2$-) (azetidin-1-yl); and R^9 is NH_2.

A sixth aspect of the second embodiment is directed to a phosphoramidate nucleoside represented by formula **I,** or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



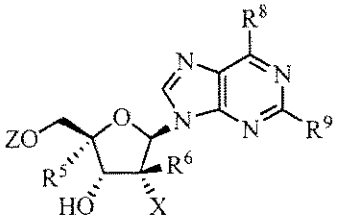
I

Z is



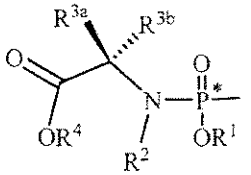
R^1 is phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is hydrogen; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is –N(-$CH_2CH_2CH_2$-) (azetidin-1-yl); and R^9 is NH_2.

A seventh aspect of the second embodiment is directed to a phosphoramidate nucleoside represented by formula **I**, or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



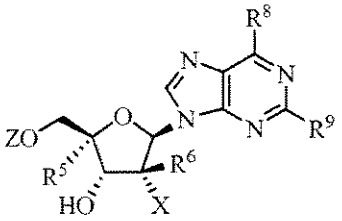
I

Z is



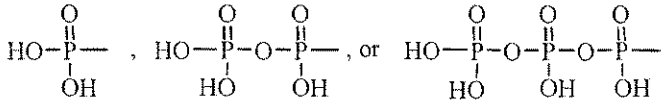
R^1 is hydrogen; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is hydrogen; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is –N(-$CH_2CH_2CH_2$-) (azetidin-1-yl); and R^9 is NH_2.

An eighth aspect of the second embodiment is directed to a phosphoramidate nucleoside represented by formula **I**, or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



I

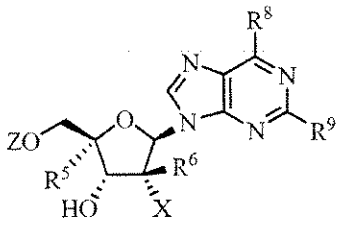
wherein

Z is 

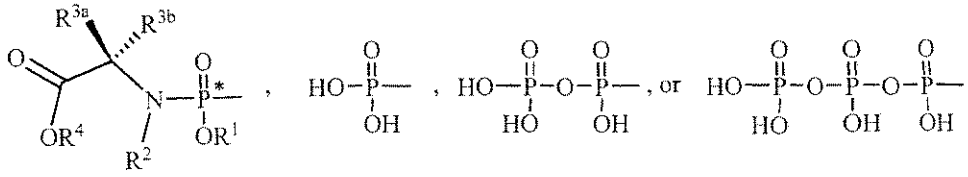
and wherein R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is –N(-$CH_2CH_2CH_2$-) (azetidin-1-yl); and R^9 is NH_2.

A third embodiment of the present invention is directed to a phosphoramidate nucleoside represented by formula **I**, or its stereoisomers, salts,

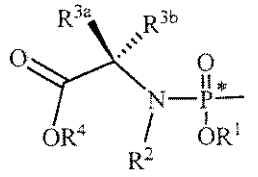
pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



I

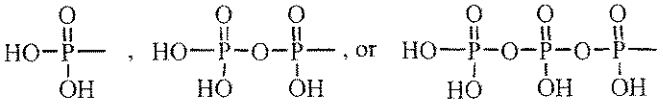
Z is 

wherein when

Z is 

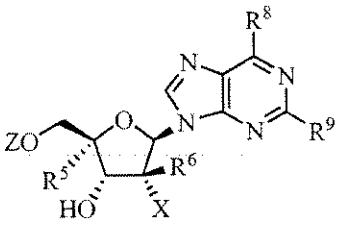
R^1 is hydrogen or phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is hydrogen, methyl, ^{i}Pr, or cyclopentyl; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OBn; and R^9 is NH_2;

and wherein when

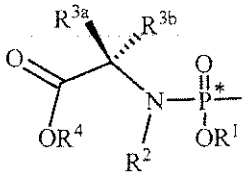
Z is 

R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OBn; and R^9 is NH_2.

A first aspect of the third embodiment is directed to a phosphoramidate nucleoside represented by formula **I**, or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



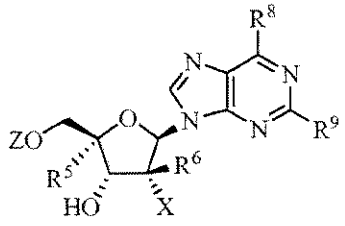
Z is



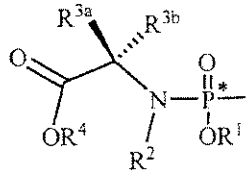
I

R^1 is hydrogen or phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is hydrogen, methyl, ^{i}Pr, or cyclopentyl; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OBn; and R^9 is NH_2.

A second aspect of the third embodiment is directed to a phosphoramidate nucleoside represented by formula **I,** or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



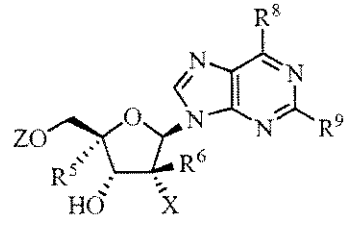
Z is



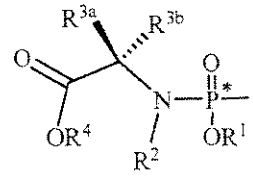
I

R^1 is phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is methyl, ^{i}Pr, or cyclopentyl; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OBn; and R^9 is NH_2.

A third aspect of the third embodiment is directed to a phosphoramidate nucleoside represented by formula **I,** or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



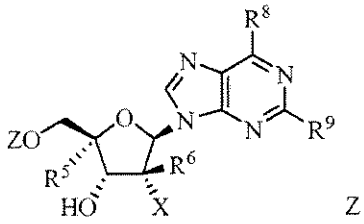
Z is



I

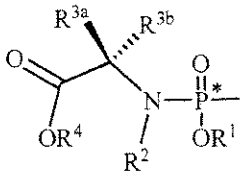
R^1 is phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is methyl; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OBn; and R^9 is NH_2.

A fourth aspect of the third embodiment is directed to a phosphoramidate nucleoside represented by formula **I**, or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



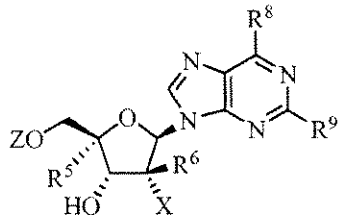
I

Z is



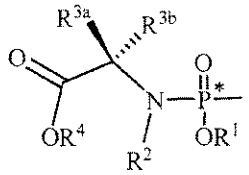
R^1 is phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is ^{i}Pr; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OBn; and R^9 is NH_2.

A fifth aspect of the third embodiment is directed to a phosphoramidate nucleoside represented by formula **I**, or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



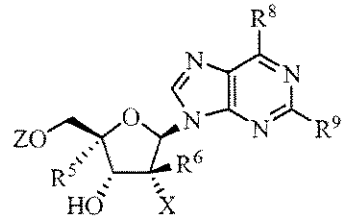
I

Z is



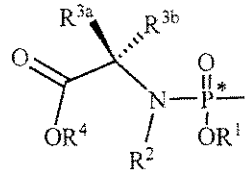
R^1 is phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is cyclopentyl; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OBn; and R^9 is NH_2.

A sixth aspect of the third embodiment is directed to a phosphoramidate nucleoside represented by formula **I**, or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



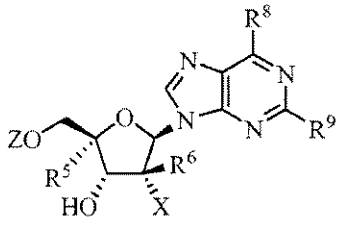
I

Z is

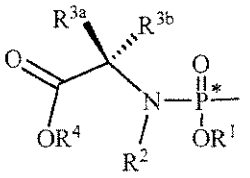


R^1 is phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is hydrogen; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OBn; and R^9 is NH_2.

A seventh aspect of the third embodiment is directed to a phosphoramidate nucleoside represented by formula **I,** or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



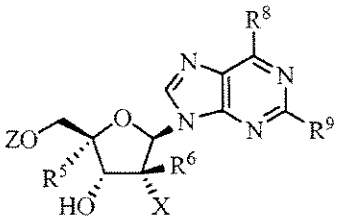
Z is



I

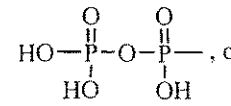
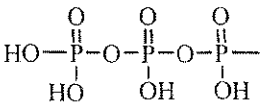
R^1 is hydrogen; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is hydrogen; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OBn; and R^9 is NH_2.

An eighth aspect of the third embodiment is directed to a phosphoramidate nucleoside represented by formula **I,** or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



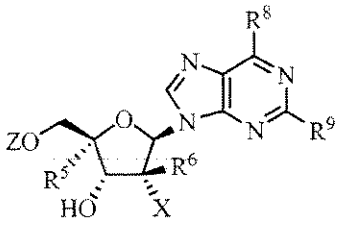
I

wherein

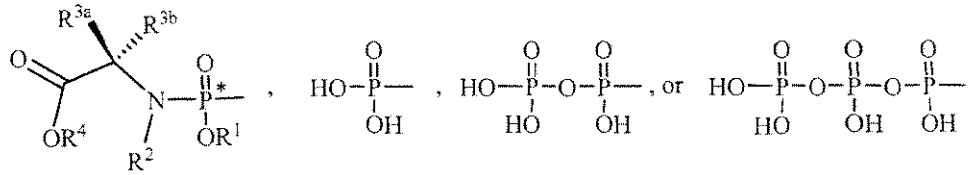
Z is , , or 

and wherein R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OBn; and R^9 is NH_2.

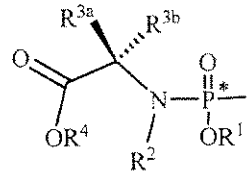
A fourth embodiment of the present invention is directed to a phosphoramidate nucleoside represented by formula **I,** or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



I

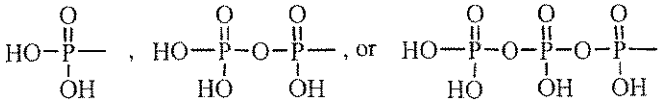
Z is 

wherein when

Z is 

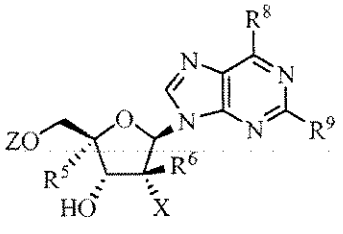
R^1 is hydrogen or phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is hydrogen, methyl, ^{i}Pr, or cyclopentyl; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OH; and R^9 is NH_2;

and wherein when

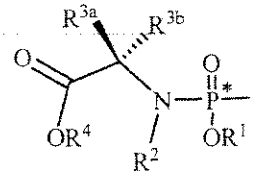
Z is 

R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OH; and R^9 is NH_2.

A first aspect of the fourth embodiment is directed to a phosphoramidate nucleoside represented by formula **I,** or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



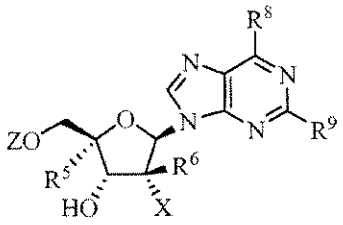
Z is



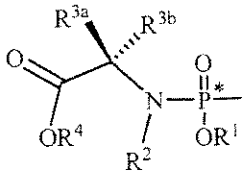
I

R^1 is hydrogen or phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is hydrogen, methyl, ^{i}Pr, or cyclopentyl; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OH; and R^9 is NH_2.

A second aspect of the fourth embodiment is directed to a phosphoramidate nucleoside represented by formula **I,** or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



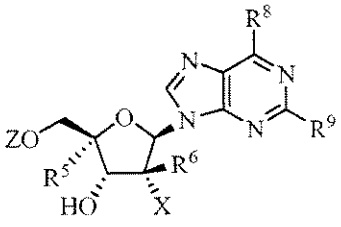
Z is



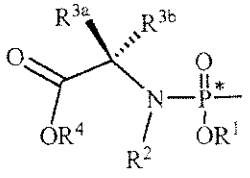
I

R^1 is phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is methyl, ^{i}Pr, or cyclopentyl; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OH; and R^9 is NH_2.

A third aspect of the fourth embodiment is directed to a phosphoramidate nucleoside represented by formula **I,** or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



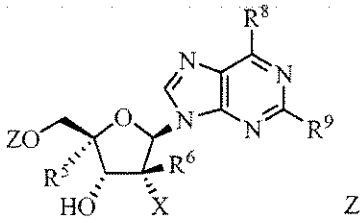
Z is



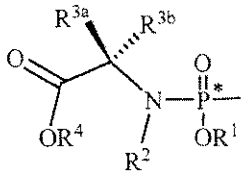
I

R^1 is phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is methyl; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OH; and R^9 is NH_2.

A fourth aspect of the fourth embodiment is directed to a phosphoramidate nucleoside represented by formula **I,** or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



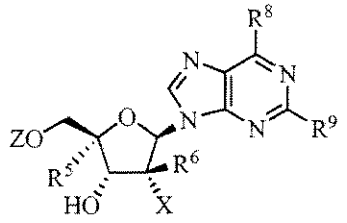
Z is



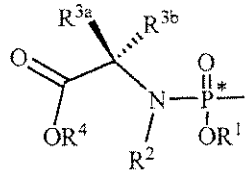
I

R^1 is phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is ^{i}Pr; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OH; and R^9 is NH_2.

A fifth aspect of the fourth embodiment is directed to a phosphoramidate nucleoside represented by formula **I,** or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



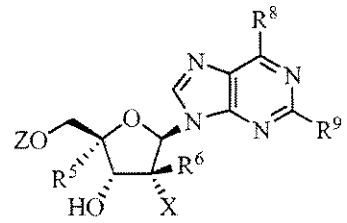
Z is



I

R^1 is phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is cyclopentyl; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OH; and R^9 is NH_2.

A sixth aspect of the fourth embodiment is directed to a phosphoramidate nucleoside represented by formula **I,** or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



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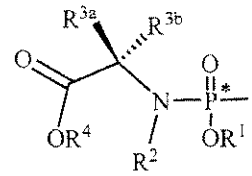
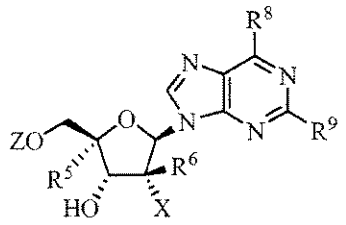


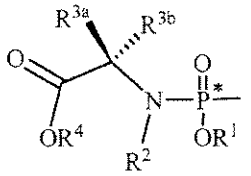
I

R^1 is phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is hydrogen; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OH; and R^9 is NH_2.

A seventh aspect of the fourth embodiment is directed to a phosphoramidate nucleoside represented by formula **I,** or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



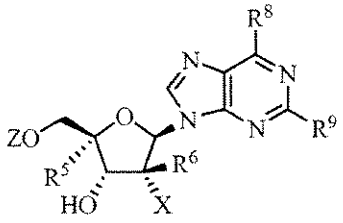
Z is



I

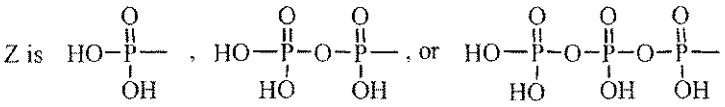
R^1 is hydrogen; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is hydrogen; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OH; and R^9 is NH_2.

An eighth aspect of the fourth embodiment is directed to a phosphoramidate nucleoside represented by formula **I,** or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



I

wherein

Z is 

and wherein R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OH; and R^9 is NH_2.

DOSAGE, ADMINISTRATION, AND USE

A fifth embodiment of the present invention is directed to a composition for the treatment of any of the viral agents disclosed herein said composition comprising a pharmaceutically acceptable medium selected from among an excipient, carrier, diluent, or equivalent medium and a compound, that is intended to include its salts (acid or basic addition salts), hydrates, solvates, and crystalline forms can be obtained, represented by formula **I**.

It is contemplated that the formulation of the fifth embodiment can contain any of the compounds contemplated in the present invention either alone or in combination with another compound of the present invention.

The compounds of the present invention may be formulated in a wide variety of oral administration dosage forms and carriers. Oral administration can be in the form of tablets, coated tablets, hard and soft gelatin capsules, solutions, emulsions, syrups, or suspensions. Compounds of the present invention are efficacious when administered by suppository administration, among other routes of administration. The most convenient manner of administration is generally oral using a convenient daily dosing regimen which can be adjusted according to the severity of the disease and the patient's response to the antiviral medication.

A compound or compounds of the present invention, as well as their pharmaceutically acceptable salts, together with one or more conventional excipients, carriers, or diluents, may be placed into the form of pharmaceutical compositions and unit dosages. The pharmaceutical compositions and unit dosage forms may be comprised of conventional ingredients in conventional proportions, with or without additional active compounds and the unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. The pharmaceutical compositions may be employed as solids, such as tablets or filled capsules, semisolids, powders, sustained release formulations, or liquids such as suspensions, emulsions, or filled capsules for oral use; or in the form of suppositories for rectal or vaginal administration. A typical preparation will contain from about 5% to about 95% active compound or compounds (w/w). The term "preparation" or "dosage form" is intended to include both solid and liquid formulations of the active compound and one skilled in the art will appreciate that an active ingredient can exist in different preparations depending on the desired dose and pharmacokinetic parameters.

The term "excipient" as used herein refers to a compound that is used to prepare a pharmaceutical composition, and is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipients that are acceptable for veterinary use as well as human pharmaceutical use. The compounds of this invention can be administered alone but will generally be administered in admixture

with one or more suitable pharmaceutical excipients, diluents or carriers selected with regard to the intended route of administration and standard pharmaceutical practice.

A "pharmaceutically acceptable salt" form of an active ingredient may also initially confer a desirable pharmacokinetic property on the active ingredient which were absent in the non-salt form, and may even positively affect the pharmacodynamics of the active ingredient with respect to its therapeutic activity in the body. The phrase "pharmaceutically acceptable salt" of a compound as used herein means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as glycolic acid, pyruvic acid, lactic acid, malonic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, salicylic acid, muconic acid, and the like or (2) basic addition salts formed with the conjugate bases of any of the inorganic acids listed above, wherein the conjugate bases comprise a cationic component selected from among Na^{+}, K^{+}, Mg^{2+}, Ca^{2+}, $NH_gR'''_{4-g}{}^{+}$, in which R''' is a C_{1-3} alkyl and g is a number selected from among 0, 1, 2, 3, or 4. It should be understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) as defined herein, of the same acid addition salt.

Solid form preparations include, for example, powders, tablets, pills, capsules, suppositories, and dispersible granules. A solid carrier may be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. In powders, the carrier generally is a finely divided solid which is a mixture with the finely divided active component. In tablets, the active component generally is mixed with the carrier having the necessary binding capacity

in suitable proportions and compacted in the shape and size desired. Suitable carriers include but are not limited to magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. Solid form preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like. Examples of solid formulations are exemplified in EP 0524579; US 6,635,278; US 2007/0099902; US 7,060,294; US 2006/0188570; US 2007/0077295; US 2004/0224917; US 7,462,608; US 2006/0057196; US 6,267,985; US 6,294,192; US 6,569,463; US 6,923,988; US 2006/0034937; US 6,383,471; US 6,395,300; US 6,645,528; US 6,932,983; US 2002/0142050; US 2005/0048116; US 2005/0058710; US 2007/0026073; US 2007/0059360; and US 2008/0014228, each of which is incorporated by reference.

Liquid formulations also are suitable for oral administration include liquid formulation including emulsions, syrups, elixirs and aqueous suspensions. These include solid form preparations which are intended to be converted to liquid form preparations shortly before use. Emulsions may be prepared in solutions, for example, in aqueous propylene glycol solutions or may contain emulsifying agents such as lecithin, sorbitan monooleate, or acacia. Aqueous suspensions can be prepared by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well known suspending agents.

The compounds of the present invention may be formulated for administration as suppositories. A low melting wax, such as a mixture of fatty acid glycerides or cocoa butter is first melted and the active component is dispersed homogeneously, for example, by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and to solidify.

The compounds of the present invention may be formulated for vaginal administration. Pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Suitable formulations along with pharmaceutical carriers, diluents and excipients are described in *Remington: The Science and Practice of Pharmacy* **1995,** edited by E. W. Martin, Mack Publishing Company, 19th edition, Easton, Pennsylvania, which is hereby incorporated by reference. A skilled formulation scientist may modify the formulations 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 their therapeutic activity.

The modification of the present compounds to render them more soluble in water or other vehicle, for example, may be easily accomplished by minor modifications (e.g., salt formulation), which are well within the ordinary skill in the art. It is also well within the ordinary skill of the art to modify the route of administration and dosage regimen of a particular compound in order to manage the pharmacokinetics of the present compounds for maximum beneficial effect in patients.

Additionally, the purified compounds of the present invention may be formulated in conjunction with liposomes or micelles. As to liposomes, it is contemplated that the purified compounds can be formulated in a manner as disclosed in U.S. Patent Nos. 5,013,556; U.S. 5,213,804; 5,225,212; 5,891,468;6,224,903; 6,180,134; 5,192,549; 5,316,771; 4,797,285; 5,376,380; 6,060,080; 6,132,763; 6,653,455; 6,680,068; 7,060,689; 7,070,801; 5,077,057; 5,277,914; 5,549,910; 5,567,434; 5,077,056; 5,154,930; 5,736,155; 5,827,533; 5,882,679; 6,143,321; 6,200,598; 6,296,870; 6,726,925; and 6,214,375, each of which is incorporated by reference. As to micelles, it is contemplated that the purified compounds can be formulated in a manner as disclosed in U.S. Patent Nos. 5,145,684 and 5,091,188, both of which are incorporated by reference.

A sixth embodiment of the present invention is directed to a use of the compound represented by formula **I** in the manufacture of a medicament for the treatment of any condition the result of an infection by any one of the following viral agents: hepatitis C virus, West Nile virus, yellow fever virus, degue virus, rhinovirus, polio virus, hepatitis A virus, bovine viral diarrhea virus and Japanese encephalitis virus.

The term "medicament" means a substance used in a method of treatment and/or prophylaxis of a subject in need thereof, wherein the substance includes, but is not limited to, a composition, a formulation, a dosage form, and the like, comprising the compound of formula **I**. It is contemplated that the use of the compound represented by formula **I** in the manufacture of a medicament, for the treatment of any of the antiviral conditions disclosed herein, either alone or in combination with another compound of the present invention. A medicament includes, but is not limited to, any one of the compositions contemplated by the seventh embodiment of the present invention.

A seventh embodiment of the present invention is directed to a method of treatment and/or prophylaxis in a subject in need thereof said method comprises administering a therapeutically effective amount of the compound represented by formula **I** to the subject.

A first aspect of the seventh embodiment is directed to a method of treatment and/or prophylaxis in a subject in need thereof said method comprises administering a therapeutically effective of at least two compounds falling within the scope of the compound represented by formula **I** to the subject.

A second aspect of the seventh embodiment is directed to a method of treatment and/or prophylaxis in a subject in need thereof said method comprises alternatively or concurrently administering a therapeutically effective of at least two compounds falling within the scope of the compound represented by formula **I** to the subject.

It is intended that a subject in need thereof is one that has any condition the result of an infection by any of the viral agents disclosed herein, which includes, but is not limited to, hepatitis C virus, West Nile virus, yellow fever virus, degue virus, rhinovirus, polio virus, hepatitis A virus, bovine viral diarrhea virus or Japanese encephalitis virus, flaviviridae viruses or pestiviruses or hepaciviruses or a viral agent causing symptoms equivalent or comparable to any of the above-listed viruses.

The term "subject" means a mammal, which includes, but is not limited to, cattle, pigs, sheep, chicken, turkey, buffalo, llama, ostrich, dogs, cats, and humans, preferably the subject is a human. It is contemplated that in the method of treating a

subject thereof of the ninth embodiment can be any of the compounds contemplated herein, either alone or in combination with another compound of the present invention.

The term "therapeutically effective amount" as used herein means an amount required to reduce symptoms of the disease in an individual. The dose will be adjusted to the individual requirements in each particular case. That dosage can vary within wide limits depending upon numerous factors such as the severity of the disease to be treated, the age and general health condition of the patient, other medicaments with which the patient is being treated, the route and form of administration and the preferences and experience of the medical practitioner involved. For oral administration, a daily dosage of between about 0.001 and about 10 g, including all values in between, such as 0.001, 0.0025, 0.005, 0.0075, 0.01, 0.025, 0.050, 0.075, 0.1, 0.125, 0.150, 0.175, 0.2, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, and 9.5, per day should be appropriate in monotherapy and/or in combination therapy. A particular daily dosage is between about 0.01 and about 1 g per day, including all incremental values of 0.01 g (i.e., 10 mg) in between, a preferred daily dosage about 0.01 and about 0.8 g per day, more preferably about 0.01 and about 0.6 g per day, and most preferably about 0.01 and about 0.25 g per day, each of which including all incremental values of 0.01 g in between. Generally, treatment is initiated with a large initial "loading dose" to rapidly reduce or eliminate the virus following by a decreasing the dose to a level sufficient to prevent resurgence of the infection. One of ordinary skill in treating diseases described herein will be able, without undue experimentation and in reliance on personal knowledge, experience and the disclosures of this application, to ascertain a therapeutically effective amount of the compounds of the present invention for a given disease and patient.

Therapeutic efficacy can be ascertained from tests of liver function including, but not limited to protein levels such as serum proteins (e.g., albumin, clotting factors, alkaline phosphatase, aminotransferases (e.g., alanine transaminase, aspartate transaminase), 5'-nucleosidase, γ-glutaminyltranspeptidase, etc.), synthesis of bilirubin, synthesis of cholesterol, and synthesis of bile acids; a liver metabolic function, including, but not limited to, carbohydrate metabolism, amino acid and

ammonia metabolism. Alternatively the therapeutic effectiveness may be monitored by measuring HCV-RNA. The results of these tests will allow the dose to be optimized.

A third aspect of the seventh embodiment, is directed to a method of treatment and/or prophylaxis in a subject in need thereof said method comprises administering to the subject a therapeutically effective amount of a compound represented by formula **I** and a therapeutically effective amount of another antiviral agent; wherein the administration is concurrent or alternative. It is understood that the time between alternative administration can range between 1-24 hours, which includes any sub-range in between including, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, and 23 hours. Examples of "another antiviral agent" include, but are not limited to: HCV NS3 protease inhibitors (see WO 2008010921, WO 2008010921, EP 1881001, WO 2007015824, WO 2007014925, WO 2007014926, WO 2007014921, WO 2007014920, WO 2007014922, US 2005267018, WO 2005095403, WO 2005037214, WO 2004094452, US 2003187018, WO 200364456, WO 2005028502, and WO 2003006490); HCV NS5B Inhibitors (see US 2007275947, US20072759300, WO2007095269, WO 2007092000, WO 2007076034, WO 200702602, US 2005-98125, WO 2006093801, US 2006166964, WO 2006065590, WO 2006065335, US 2006040927, US 2006040890, WO 2006020082, WO 2006012078, WO 2005123087, US 2005154056, US 2004229840, WO 2004065367, WO 2004003138, WO 2004002977, WO 2004002944, WO 2004002940, WO 2004000858, WO 2003105770, WO 2003010141, WO 2002057425, WO 2002057287, WO 2005021568, WO 2004041201, US 20060293306, US 20060194749, US 20060241064, US 6784166, WO 2007088148, WO 2007039142, WO 2005103045, WO 2007039145, WO 2004096210, and WO 2003037895); HCV NS4 Inhibitors (see WO 2007070556 and WO 2005067900); HCV NS5a Inhibitors (see US 2006276511, WO 2006120252, WO 2006120251, WO 2006100310, WO 2006035061); Toll-like receptor agonists (seeWO 2007093901); and other inhibitors (see WO 2004035571, WO 2004014852, WO 2004014313, WO 2004009020, WO 2003101993, WO 2000006529); and compounds disclosed in U.S. Patent Application No. 12/053,015, filed March 21, 2008 (the contents of which are incorporated by reference).

A fourth aspect of the seventh embodiment, is directed to a method of treatment and/or prophylaxis in a subject in need thereof said method comprises alternatively or concurrently administering a therapeutically effective amount of a compound represented by formula **I** and another antiviral agent to the subject. It is understood that the time between alternative administration can range between 1-24 hours, which includes any sub-range in between including, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, and 23 hours.

It is contemplated that the another antiviral agent such as interferon-α, interferon-β, pegylated interferon-α, ribavirin, levovirin, viramidine, another nucleoside HCV polymerase inhibitor, a HCV non-nucleoside polymerase inhibitor, a HCV protease inhibitor, a HCV helicase inhibitor or a HCV fusion inhibitor. When the active compound or its derivative or salt are administered in combination with another antiviral agent the activity may be increased over the parent compound. When the treatment is combination therapy, such administration may be concurrent or sequential with respect to that of the nucleoside derivatives. "Concurrent administration" as used herein thus includes administration of the agents at the same time or at different times. Administration of two or more agents at the same time can be achieved by a single formulation containing two or more active ingredients or by substantially simultaneous administration of two or more dosage forms with a single active agent.

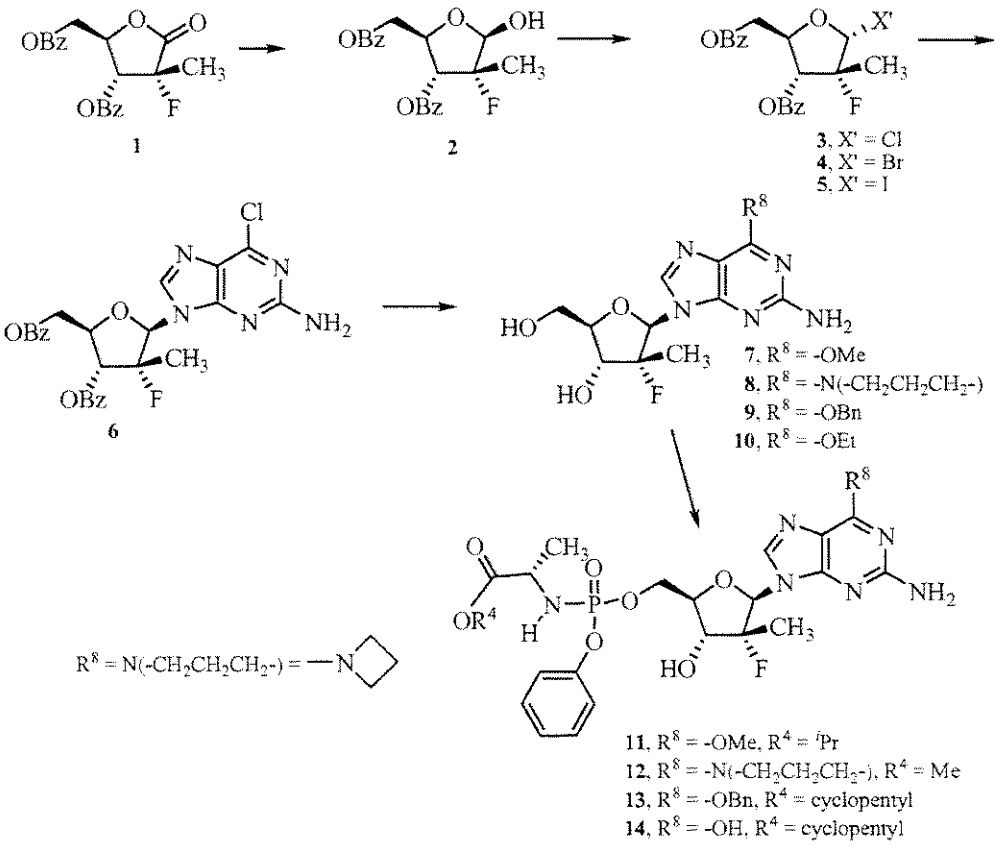
It should be noted that for the compounds disclosed herein metabolites may be produced upon administration to a subject in need thereof. For instance for a compound represented by formula **I**, it is contemplated that hydrolysis of phosphate ester ($-OR^1$) or the carbonyl ester ($-OR^4$) may occur; and that the resultant hydrolyzed product can itself undergo in vivo hydrolysis to form a monophosphate, which can be converted to a diphosphate and/or triphosphate. It is contemplated that the claims provided below embrace both synthetic compounds and compounds produced in vivo. The metabolite compounds of the compounds represented by structures **11-14** (see below) can be obtained by administering said compounds to a patient in need thereof. Alternatively, the metabolite compounds can be prepared by selective hydrolysis of the carbonyl ester ($-OR^4$) or the phosphate ester ($-OR^1$) for compounds represented by structures **11-**

14 (see below). As metabolites or metabolite salts are contemplated herein, it is also contemplated as an alternative embodiment a method of treatment in a patient in need thereof contacting at least one compound represented by formula **I** with at least one hepatitis C virus infected cell.

It will be understood that references herein to treatment extend to prophylaxis as well as to the treatment of existing conditions. Furthermore, the term "treatment" of a HCV infection, as used herein, also includes treatment or prophylaxis of a disease or a condition associated with or mediated by HCV infection, or the clinical symptoms thereof.

EXAMPLES

A further understanding of the disclosed embodiments will be appreciated by consideration of the following examples, which are only meant to be illustrative, and not limit the disclosed invention.



The use of the convergent glycosylation route to prepare 2'-deoxy-2'-fluoro-2'-C-methyl purine nucleosides and their corresponding nucleotide

phosphoramidates came about with the development of the synthesis of 3,5-di-O-benzoyl-2-deoxy-2-fluoro-2-*C*-methylribonolactone (Chun, K.; Wang, P. Intl. Pat. Appl. WO 2006/031725).

After several attempts using Vorbrueggen-type Lewis acid mediated coupling and the ribonolactol 1-*O*-acetate of 3,5-di-O-benzoyl-2-deoxy-2-fluoro-2-*C*-methylribonolactone, we observed very low coupling yields and the undesired α-anomer was the major product. Mitsunobu coupling with the ribonolactol (**2**) did give the desired product but with no stereoselectivity and very difficult chromatographic separation resulting in isolated yields of 6-10% for this step alone and the method was not scaleable.

The preferred approach became the S_N2 type reaction using a halo-sugar and a salt of the purine base. Again, the challenge of this approach was how to obtain a α halo-sugar stereospecifically in high yield to take advantage the inversion of configuration expected with S_N2 type reactions. A typical method treats an anomeric mixture of the 1-*O*-acetate of a sugar with HCl or HBr in acetic acid. However, this method resulted in production of unfavorable anomeric mixtures. Reducing the lactone (e.g., with $LiAlH(t\text{-}BuO)_3$ or Red-Al) initially generates at 2:1 ratio of β/α anomers but after initial purification through a silica gel filtration column, the resulting oil slowly anomerizes to form pure crystalline β-anomer of the lactol (**2**). This can be accelerated from several days at ambient temperature to 5-17 h at 50°C with seeding β-crystals. We observed that once the lactol is in solution, it slowly anomerizes back towards the 2:1 equilibrium in solvents such as dichloromethane or chloroform at ambient temperature. This process can be slowed considerable by chilling the solution (e.g. -20°C).

Chlorination through an S_N2 mechanism with N-chlorosuccinimide (NCS) produced an α-chlorosugar (**3**) in a stereospecific manner in almost quantitative yield.

To obtain an α-bromosugar (**4**), many bromination conditions were tried including N-bromosuccinimide (NBS) and HBr in acetic acid. Among them, we followed a general bromination reaction using a combination of triphenylphosphine (PPh_3) and carbon tetrabromide (CBr_4) (e.g. Hooz et al, *Can. J. Chem.*, **1968**, *46*, 86-87). Under the conditions of using methylene chloride as the solvent and

maintaining a low temperature (-10 to -20°C) we obtained the best result where the desired α/β isomer ratio was greater than 10:1, in a yield of greater than 80%. Applicants believe that there are no literature precedents describing this level of stereoselectivity for this reaction type. Another practical observation was that by conducting the bromination under sub-ambient temperature conditions, such as, most preferably about -20°C) and exposing the cold reaction solution to silica gel as soon as possible after the completion of the reaction minimizes anomerization of the bromosugar. The bromosugar can be purified through a silica gel filtration column. Once treated with silica gel, the bromosugar it is practically stable even at elevated temperatures.

The iodosugar (**5**) was prepared in a similar manner, which can be coupled with the purine to produce the key intermediate (**6**).

Following the general purine coupling method of Bauta et al (Intl. Pat. Appl. WO 2003/011877), we coupled the α-bromosugar (**4**) with the potassium salt of 6-chloro-2-amino-purine in t-butanol in acetonitrile. The reaction took over a week at ambient temperatures. The reaction was optimized to go to completion in 24 h at 50°C. After partial purification through a silica gel filtration column, the anomeric mixture was isolated in 63% yield in a ratio of 14:1 β/α. The β-anomer (**6**) could be selectively crystallized out from a methanolic solution to give the pure desired β-anomer (**6**) in 55% yield from the bromosugar (**4**).

With the key intermediate **6** in hand, conversion to unprotected 2-amino-6-substituted purines (e.g., **7-10**) was accomplished. Further conversion to the phosphoramidate derivatives (e.g., **11-14**) proceeded by an adaptation of the method of Lehsten et al., Org. *Proc. Res. Dev.*, **2002**, *6*, 819-822 or as disclosed in U.S. Patent Application No. 12/053,015, filed March 21, 2008, pp. 651-675. As the phosphoramidate group can also react to a minor extent on the secondary 3' hydroxyl, the potential exists for 3' monophosphoramidate and 3', 5' bis-phosphoramidate impurities. The 3' isomer would be expected to have similar physical properties to the desired 5' isomer making purification by chromatography difficult. This is ameliorated by further reacting the crude product mixture with sub-stoichiometric amounts of protecting groups which are selective for primary hydroxyls over secondary hydroxyls such as t-butyldimethylsilyl chloride, t-butyldiphenylsilyl chloride or 4,4'-dimethoxytrityl chloride in the presence of

pyridine or similar base to generate 5' protected 3' phosphoramidate. The resulting product and the bis substituted phosphoramidate are less polar than the desired 5' phosphoramidate and can be separated readily by chromatography.

Compound (**1**) can be obtained by a process disclosed at page 5 in U.S. Published Application No. 2008/0139802 (which corresponds to WO 2008/045419), at pages 11-13 in WO 2006/012440, and at pages 20-22 and 30-31 in WO 2006/031725, each of which is hereby incorporated by reference.

Synthesis of ((2R,3R,4R,5R)-3-(benzoyloxy)-4-fluoro-5-hydroxy-4-methyltetrahydrofuran-2-yl)methyl benzoate (2)

To a 5 L of dry three-neck round-bottomed flask fit with a mechanical stirrer, addition funnel and thermometer was charged the lactone ((2R,3R,4R)-3-(benzoyloxy)-4-fluoro-4-methyl-5-oxotetrahydrofuran-2-yl)methyl benzoate) (**1**, 379 g, 1.018 mol). The solid was dissolved in anhydrous THF (1.75 L) and cooled to -30°C under a nitrogen atmosphere. A solution of lithium tri-tert-butoxyaluminohydride (1.0 M in THF, 1.527 L) was added to the lactone solution while stirring over 1 h and maintaining the -30°C temperature. After finishing the addition, the temperature was slowly increased and the reaction was followed by TLC (lactol R_f 0.4, 30% EtOAc in hexanes). The reaction was complete after 1h 15 min (temperature reached -10°C). The reaction was quenched by addition of Ethyl acetate (900 mL) via addition funnel. Sat. NH_4Cl (40 mL) was added at 0°C. The cloudy mixture was decanted into a 10 L round-bottomed flask. The solid residue left behind was filtered and washed with ethyl acetate (2x200 mL). The filtrate was combined with the decanted solution and the combined solution was concentrated under reduced pressure. The oily residue was dissolved in ethyl acetate (2 L) and washed with 3 *N* HCl (600 mL). The aqueous layer was back-extracted with ethyl acetate (3x400 mL). The combined organic layer was washed with water (3x800 mL), sat. $NaHCO_3$ (400 mL) and brine (400 mL). The organic solution was dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a light brown oily residue. The residue was purified by plug column (2.2 kg of 40-63 micron silica gel, packed in a 6 L sintered glass funnel, 22 cm length of silica gel, diameter 15 cm) using suction and a step-gradient of 5%, 10%, 20%, and 30% ethyl

acetate in hexanes –ca 5 L of each). The product containing fractions were combined and concentrated under reduced pressure to a colorless, very thick liquid (310.4 g).

The liquid slowly solidified after adding crystalline beta product as seeds (ca 100 mg spread out) under vacuum (0.2 mmHg) at 50°C. The process of solidification was complete in 20 hours at 50°C with or without vacuum. The white solid thus collected (293.8 g, 77%) has a mp of 79-80°C and ratio of β/α is 20:1 based on NMR.

^{1}H-NMR (DMSO-d_6) β-isomer, δ = 5.20 (dd, 1 H, OH); α-isomer, δ = 5.40 (dd, 1 H, OH). (β-lactol) .(DMSO-d_6): δ 7.99 (m, 2 H, arom.), 7.93 (m, 2 H, arom.), 7.70 (m, 1 H, arom.), 7.61 (m, 1 H, arom.), 7.55 (m, 2 H, arom.), 7.42 (m, 2 H, arom.), 7.32 (dd, 1 H, C1-H), 5.54 (dd, 1 H, C3-H), 5.20 (dd, 1 H, OH), 4.55-4.50 (m, 1 H, C5-Ha), 4.46-4.40 (m, 2 H, C5-Hb and C4-H), 1.42 (d, 3 H, CH_3).

Synthesis of ((2R,3R,4R,5R)-3-(benzoyloxy)-5-chloro-4-fluoro-4-methyltetrahydrofuran-2-yl)methyl benzoate (3)

To a solution of mixture of compound **2** (1.0 g, 2.67 mmol) and PPh_3 (1.4 g, 5.34 mmol) in CH_2Cl_2 (15 mL) was added NCS (1.07 g, 8.01 mmol) portionwise at 0°C. Then the resulting mixture was stirred at rt for 1h and poured into a silica gel column and eluted with EtOAc-hexanes (1:4) using pressure. The collected right fractions were combined, concentrated, and co-evaporated with CH_2Cl_2 several times and used next step (1.0 g, 95%).

^{1}H-NMR ($CDCl_3$) δ = 8.13-8.02 (m, 4H, aromatic), 7.78-7.50 (m, aromatic, 2H), 7.53-7.43 (m, 4H, aromatic), 6.01 (s, 1H, H-1), 5.28 (dd, 1H, J = 3.2, 5.6 Hz, H-3), 4.88 (m, 1H, H-H-4), 4.77 (dd, 1H, J = 3.2, 12.4 Hz, H-5), 4.61 (dd, 1H, J = 4.0, 12.4 Hz, H-5'), 1.73 (d, 3H, J = 21.6 Hz, CH_3).

Synthesis of ((2R,3R,4R,5R)-3-(benzoyloxy)-5-bromo-4-fluoro-4-methyltetrahydrofuran-2-yl)methyl benzoate (4)

Anhydrous dichloromethane (5.6 L) was charged into a reactor and cooled to -22°C or below. Triphenylphosphine (205.4 g, 0.783 mol) was added to the cold solvent and the suspension was stirred to form a solution. The lactol (**2**, 209.4 g, 0.559 mol) in solid form was added to the cold solution and stirred for 15 mins. Carbon tetrabromide (278.2 g, 0.839 mol) was added portion-wise while maintaining

the temperature of the solution between -22°C to -20 °C under a flow of nitrogen gas (approx. 30 min). After finishing the addition of CBr_4, the temperature was slowly raised to -17°C over 20 mins. The reaction was judged to be >95% complete by TLC (R_fs 0.61 (α), 0.72 (β), 0.36 lactol; 20% EtOAc in hexanes). The reaction solution was immediately transferred to a vessel containing 230 g of flash chromatography grade silica gel (40-63 microns). The stirred mixture was immediately passed through a pad of silica gel (680 g) in a 2.5 L sintered glass Buchner funnel. The filtrate was concentrated under reduced pressure to about 800 mL and the ratio of α/β isomers of the crude product was 10:1 as determined by ^{1}H-NMR. ($CDCl_3$) δ = 6.35, (s, α C1-H), 6.43, (d, β C1-H). The residue was purified by plug column chromatography using 2.1 kg of silica gel in a 6 L sintered glass Buchner funnel and eluted (via suction) with a stepwise gradient elution of 1%, 5%, 8% 12% EtOAc in hexane (ca 4 L each) to remove non-polar impurities followed by 12%, 25% EtOAc in hexane (6 L total) to elute the product. The product containing fractions were combined into two fractions, concentrated under reduced pressure, dried under vacuum (0.1 mmHg, ambient temp., 20 h) to colorless oils. Main fraction (197 g, 89% α/β = 20:1). The alpha isomer crystallized from a small portion of the oil upon standing at 0°C for several weeks to give large, thin plates, mp 59-61°C. The pure beta isomer crystallized from a mixture of alpha and beta product oil from an earlier less selective run to give needles, mp 77-79°C.

^{1}H-NMR (β-bromide) ($CDCl_3$): δ = 8.08 (m, 2 H, arom.), 8.04 (m, 2 H, arom.), 7.62 (m, 1 H, arom.), 7.54-7.45 (m, 3 H, arom.), 7.35 (m, 2 H, arom.), 6.43 (d, 1 H, C1-H), 6.04 (dd, 1 H, C3-H), 4.78-4.73 (m, 2 H, C4-H and C5-Ha), 4.63-4.58 (m, 1 H, C5-Hb), 1.76 (d, 3 H, CH_3). α-bromide, α/β = 20:1) ($CDCl_3$): δ 8.13 (m, 2 H, arom.), 8.02 (m, 2 H, arom.), 7.63-7.56 (m, 2 H, arom.), 7.50-7.42 (m, 4 H, arom.), 6.34 (s, 1 H, C1-H), 5.29 (dd, 1 H, C3-H), 4.88 (m, 1 H, C4-H), 4.78 (dd, 1 H, C5-Ha), 4.63 (dd, 1 H, C5-Hb), 1.72 (d, 3 H, CH_3).

Synthesis of ((2R,3R,4R,5R)-3-(benzoyloxy)-4-fluoro-5-iodo -4-methyltetrahydrofuran-2-yl)methyl benzoate (5)

To a solution of compound **2** (1 g, 2.67 mmol), triphenylphosphine (700 mg, 2.67 mmol), and imidazole (180 mg, 2.67 mmol) in anhydrous CH_2Cl_2 (10 mL) iodine (680 mg, 2.68 mmol) was added. The resulting mixture was stirred for 30 min and poured into a silica gel column and eluted with EtOAc-hexanes (1:4) to

give a syrupy product (1.3 g, quantitative) and used in next reaction without further characterization.

Synthesis of (2R,3R,4R,5R)-5-(2-amino-6-chloro-9H-purin-9-yl)-2-(benzoyloxymethyl)-4-fluoro-4-methyltetrahydrofuran-3-yl benzoate (6)

To a 12 L of three-neck round-bottomed flask was charged 6-chloro-2-aminopurine (225.4 g, 1.329 mol). Anhydrous tert-BuOH (4.5 L) was added and the solution was stirred with a mechanical stirrer at ambient temperature. Potassium tert-butoxide (solid, 151.6 g, 1.35 mol) was added portion-wise under a flow of nitrogen gas while stirring. The mixture was stirred at RT for an additional 30 min. To a 5 L round-bottomed flask was loaded the α-bromide (**4**, 197 g, 0.451 mol) and 3 L of anhydrous acetonitrile at ambient temperature. The bromide solution was added to the purine base suspension over 1 min at ambient temperature. The 5L flask was rinsed with acetonitrile (2x1L) to transfer bromide completely to the reaction mixture. The mixture was heated gradually to 50°C over 2 h with a heating mantle and controller, and stirred for 20 h. The reaction was almost complete as shown by TLC beta (R_f 0.28, 30% EtOAc in hexanes). The reaction was quenched by the addition of sat. NH_4Cl (200 mL) to form a suspension. The suspended solid[1] was removed by filtration through a 3 cm pad of Celite in a 2.5 L porcelain Buchner funnel. The solid was washed with toluene (3x100 mL). The combined filtrate was neutralized by adding 6 N HCl solution until pH 7 (approx 220 mL). The mixture was concentrated under reduced pressure. When the volume of mixture was reduced to about one-third volume, additional precipitated solid was removed by filtration in a similar manner. The filtrate was further concentrated to a volume of about 800 mL. The residue was loaded onto a plug column (1.6 kg flash grade silica gel in a 6 L sintered glass Buchner funnel) and eluted (via suction) with a gradient of 10% ethyl acetate in hexanes (6 L) to remove non-polar impurities, 30% ethyl acetate in hexanes to afford a small amount of lactol (6 L), and then 40%~45% ethyl acetate in hexanes (4 L) to elute the main amount of product. The product containing fractions were combined, concentrated under reduced pressure and dried under vacuum (0.2 mmHg, 24 h, ambient temp.) to a white foam solid (150.7 g, β/α = 14:1 by NMR.

^{1}H-NMR. ($CDCl_3$) beta: δ = 1.33 (d, 22.4 Hz, 2'-*C*-CH_3), alpha: 1.55 (d, 22 Hz, 2'-*C*-CH_3).

The product mixture foam was dissolved in methanol (700 mL) at ambient temperature. Upon standing, a solid slowly formed over 2 h. The suspension was cooled in a freezer to -5°C for 17 h. The resulting white solid was collected by filtration and washed with cold MeOH (-5°C, 3x60 mL) and ethyl ether (3x100 mL). The solid was dried under vacuum (0.2 mmHg, 24 h, ambient temp.) to afford 110.5 g of β-product with excellent de (β/α 99.8:1 by HPLC). The filtrate was partially concentrated (ca. 400 mL) and then diluted with more MeOH (400 mL) while heating to 60°C. The solution was cooled down to ambient temperature, seeded and the cooled to -5°C. The second crop was collected, washed and dried in a similar manner to give more product as a white solid (12.26 g) with similar diastereomeric purity. The mother liquor was concentrated to dryness under reduced pressure (ca. 25 g). The residue was a mixture of β and α-isomers. It was subjected to automated silica gel column chromatography (Analogix, 240 g cartridge, 40% to 50% ethyl acetate in hexanes) to afford 14.52 g of product foam which was recrystallized from MeOH, washed and dried in a similar manner to afford an additional 8.46 g of product in high purity.

The three solids were judged to be of similar purity and they were combined to give 131.2 g of white crystalline product **6**, (55% from bromosugar, 49% from lactol). Mp 160.5-162.0°C. HPLC purity 99.5% including 0.20 % alpha.

^{1}H-NMR (pure β-anomer, $CDCl_3$): δ = 8.03 (m, 2 H, arom.), 7.93 (m, 2 H, arom.), 7.88 (s, 1 H, C8-H), 7.60 (m, 1 H, arom.), 7.50 (m, 1 H, arom.), 7.44 (m, 2 H, arom.), 7.33 (m, 2 H, arom.), 6.44 (dd, 1 H, C1'-H), 6.12 (d, 1 H, C3'-H), 5.35 (s, 2 H, NH_2), 5.00 (dd, 1 H, C5'-Ha), 4.76 (m, 1 H, C4'-H), 4.59 (dd, 1 H, C5'-Hb), 1.33 (d, 3 H, CH_3).

^{1}H-NMR (α-isomer, $CDCl_3$): δ = 8.11-8.09 (m, 3 H, arom. and C8-H), 8.01 (m, 2 H, arom.), 7.63 (m, 1 H, arom.), 7.55 (m, 1 H, arom.), 7.48 (m, 2 H, arom.), 7.39 (m, 2 H, arom.), 6.35 (d, 1 H, C1'-H), 5.76 (dd, 1 H, C3'-H), 5.18 (s, 2 H, NH_2), 4.93-4.89 (m, 1 H, C4'-H), 4.75-4.71 (m, 1 H, C5'-Ha), 4.58-4.54 (m, 1 H, C5'-Hb), 1.55 (d, 3 H, CH_3).

Synthesis of (2R,3R,4R,5R)-5-(2-amino-6-chloro-9H-purin-9-yl)-2-(benzoyloxymethyl)-4-fluoro-4-methyltetrahydrofuran-3-yl benzoate (6) from compound 3

To a solution of compound **3** (450 mg, 2.68 mmol) in chlorobenzene (1.5 mL) were added potassium salt of the base (1.37 g, 8.05 mmol) in t-butanol (5 mL) and subsequently anhydrous acetonitrile (5 mL) at rt. The resulting mixture was stirred at 80-140°C in a sealed tube for 7 days and concentrated *in vacuo* after neutralization with HCl. The residue was purified by silica gel column chromatography (hexanes:EtOAc = 2:1) to give compound **6** (90 mg, 15%) as a white foam.

Synthesis of (2R,3R,4R,5R)-5-(2-amino-6-chloro-9H-purin-9-yl)-2-(benzoyloxymethyl)-4-fluoro-4-methyltetrahydrofuran-3-yl benzoate (6) from compound 5

To a solution of compound **5** (1.3 g, 2.68 mmol) in t-butanol (10 mL) was added sodium salt of the base (1.37 g, 8.05 mmol) in DMF (10 mL) at ambient temperature. The resulting mixture was stirred for 15h and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexanes:EtOAc = 2:1) to give compound **6** (220 mg, 16%) as a white foam.

Synthesis of (2R,3R,4R,5R)-5-(2-amino-6-methoxy-9H-purin-9-yl)-4-fluoro-2-(hydroxymethyl)-4-methyltetrahydrofuran-3-ol (7)

To a 250 mL dry round-bottomed flask was charged (2R,3R,4R,5R)-5-(2-amino-6-chloro-9H-purin-9-yl)-2-(benzoyloxymethyl)-4-fluoro-4-methyltetrahydrofuran-3-yl benzoate (**6**, 7.50 g, 14.26 mmol). Anhydrous methanol (30 mL) was added and a white suspension was formed. At 50°C, a solution of sodium methoxide in methanol (25%, 19.7 mL, 64.17 mmol) was added via a dry syringe under a nitrogen atmosphere. A white cloudy reaction mixture was formed. After 3.5 h at 50°C, the reaction was complete with no starting material left as shown by TLC test. The mixture was cooled down to room temperature and neutralized by addition of glacial acetic acid (3 mL). A white solid was filtered out and washed with methanol (3x5 mL). The filtrate was mixed with 20 g of silica gel and concentrated to dryness. The mixture was loaded in line with a silica gel cartridge and separated via column chromatography using a gradient of methanol in

dichloromethane 0 to 15% MeOH. The product eluted out at 12% methanol in dichloromethane. The product containing fractions were combined, concentrated under reduced pressure and dried under vacuum (0.2 mmHg, 50°C, 24 h) to a white powder solid (4.45 g, 98% yield), mp 199-202°C.

^{1}H-NMR (DMSO-d_6): δ = 8.18 (1 H, s, C8-H), 6.61 (2 H, s, NH_2), 6.05 (1 H, d, C1'-H), 5.68 (1 H, d, 3'-OH), 5.26 (1 H, m, 5'-OH), 4.23-4.13 (1 H, m, C3'-H), 3.96 (3 H, s, OCH_3), 3.92-3.83 (2 H, m, C4'-H and C5'-H_a), 3.70-3.67 (1 H, m, C5'-H_b), 1.06 (3 H, d, C2'-CH_3).

Synthesis of (2S)-isopropyl 2-((((2R,3R,4R,5R)-5-(2-amino-6-methoxy-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy) (phenoxy) phosphorylamino)propanoate (11)

To a 250 mL dry round-bottomed flask were loaded phenyl dichlorophosphate (2.66 g, 12.61 mmol) and anhydrous dichloromethane (40 mL). The amino ester salt (2.60 g, 15.53 mmol) was added to the solution and the mixture was cooled to -5°C. *N*-Methyl imidazole (7.7 mL, 97 mmol) was then added quickly via a dry syringe at -5°C and the solution was stirred at -5°C for 1 h. The nucleoside (7, 3.04 g, 9.7 mmol) was added from a vial in one portion at -5°C and the solid was slowly dissolved in 20 minutes. The reaction temperature was allowed to rise to ambient temperature over 2 h. After 17 h, the reaction was not complete. More reagents were made (as described above from phosphate (2.66g), aminoester (2.60g), and NMI (3.8 mL, 48 mmol)) and added to the reaction mixture at -5°C. The reaction was stirred at room temperature for 2 more hours. The reaction was almost complete as shown by TLC result and diluted with 70 mL of dichloromethane. HCl solution (1 *N*, 70 mL) was added. The aqueous layer was separated and extracted with dichloromethane. The organic layer was washed with saturated $NaHCO_3$, water, brine and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the sticky residue was purified through automated column chromatography using a 240 g cartridge and a gradient of 0-8% 2-PrOH in dichloromethane to afford product as a foam solid (4.16 g, 7.14 mmol, 73% yield). HPLC purity 97.4%. NMR spectra of product showed it is a mixture of two diastereoisomers with a ratio of 1.2 : 1.

^{1}H-NMR (DMSO-d_6): δ = 7.98 (1 H, s, 8-H of one isomer), 7.95 (1 H, s, 8-H of another isomer), 7.37-7.32 (2 H, m, arom-H), 7.22-7.15 (3 H, m, arom-H), 6.6 (2

H, s, NH_2), 6.11 (1 H, d, C1'-H of one isomer), 6.09 (1 H, d, C1'-H of another isomer), 6.09-5.98 (1 H, m, amide NH), 5.88 (1 H, d, 3'-OH of one isomer), 5.81 (1 H, d, 3'-H of another isomer), 4.85-4.75 (1 H, hepta, methine H of *iso*-propyl), 4.46-4.27 (2 H, m, C4'-H, α-H of amino ester), 4.15-4.07 (1 H, m, C3'-H), 3.96 (3 H, s, OCH_3), 3.82-3.72 (2 H, m, C5'-H_a and C5'-H_b), 1.23-1.06 (9 H, m, CH_3's of amino ester), 1.03 (3 H, d, C2'-CH_3).

^{31}P-NMR (DMSO-d_6): δ = 4.91 (one isomer), 4.72 (another isomer).

An alternate purification method is to chemically alter the minor 3' phosphoramidate by-product in order to simplify the chromatographic separation. The crude phosphoramidate product is dissolved in anhydrous pyridine (5 mL/g), and is treated with 0.5 molar equivalents of t-butyldimethylsilyl chloride at ambient temperature to react selectively with the free 5' primary hydroxyl of the 3' isomer impurity. Reaction progress can be monitored by LC/MS. Once the 3' isomer is converted to a 5'-tBDMS-3'-phosphoramidate derivative, the reaction is quenched with methanol (3 eq), concentrated under reduced pressure, partitioned between ethyl acetate and 5% citric acid and then the organic layer is concentrated. The residue is then subjected to chromatography which can now be done with a higher loading and a faster gradient and achieve a higher purity.

Synthesis of (2R,3R,4R,5R)-5-(2-amino-6-(azetidin-1-yl)-9H-purin-9-yl)-4-fluoro-2-(hydroxymethyl)-4-methyltetrahydrofuran-3-ol (8)

To a 350 mL of dry seal pressure flask (Chemglass) were added (2R,3R,4R,5R)-5-(2-amino-6-chloro-9H-purin-9-yl)-2-(benzoyloxymethyl)-4-fluoro-4-methyltetrahydrofuran-3-yl benzoate (**6**, 3.6 g, 6.85 mmol) and 150 mL of absolute ethanol. Azetidine hydrochloride (2.56 g, 27.4 mmol) was added and then followed by triethylamine (4.16 g, 41.1 mmol). The suspension was stirred and heated to 70°C while sealed for 5 hours. All the starting material was consumed but the benzoyl groups remained as shown by TLC. Sodium methoxide (7.8 mL, 34.3 mmol, 25% solution in methanol) was added to the mixture and heated at 50°C. The reaction was complete after 3.5 h. The reaction mixture was allowed to cool to room temperature and neutralized by addition of glacial acetic acid (0.41 g, 6.85 mmol). The mixture was concentrated under reduced pressure and then the residue was triturated with ethyl acetate. The resulting solid was removed by filtration and the solid was washed with EtOAc (2x 15 mL). The filtrate was concentrated under

reduced pressure and the residue was purified via column chromatography (Analogix, 120 g cartridge, gradient of 0 to15% MeOH in DCM). The pure product containing fractions were combined, concentrated under reduced pressure and dried (50°C, 0.2 mmHg, 17 h) to a light pink colored foam solid (2.15 g, 6.35 mmol, 93%).

^{1}H-NMR (DMSO-d_6) δ = 8.00 (s, 1 H, C8-H), 6.03 (s, 2 H, NH_2), 6.00 (d, 1 H, C1'-H), 5.64 (d, 1 H, 3'-OH), 5.24 (t, 1 H, 5'-OH), 4.24-4.10 (m, 5 H, N-CH_2 of azetidine, C3'-H), 3.90-3.81 (m, 2 H, C4'-H and C5'-H_a), 3.69-3.64 (m, 1 H, C5'-H_b), 2.37 (penta, 2 H, center CH_2 of azetidine), 1.05 (d, 3 H, C2'-CH_3).

Synthesis of (2S)-methyl 2-((((2R,3R,4R,5R)-5-(2-amino-6-(azetidin-1-yl)-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate (12)

To a 100 mL dry round-bottomed flask were added phenyl dichlorophosphate (1.72 g, 8.15 mmol) and anhydrous dichloromethane (17 mL). The amino ester (1.42 g, 10.2 mmol) was added and the suspension was cooled to -5°C. *N*-Methylimidazole (3.34 g, 40.7 mmol) was added via a syringe in one portion and the solution was stirred at -5°C for 1 h under a nitrogen atmosphere. The nucleoside (**8**, 1.38 g, 4.07 mmol) (foam solid) was then added in one portion and the solution was allowed to warm up over 1 h to ambient temperature. After 4 h at ambient temperature, TLC (5% MeOH in DCM) indicated an incomplete reaction (about 30% SM remained) but also a growing less polar impurity. The reaction was quenched by the addition of sat NH_4Cl (20 mL) and diluted with dichloromethane (20 mL). The organic layer was separated and washed with water (5x 30 mL), brine (20 mL) and dried over Na_2SO_4. The product containing solution was filtered and concentrated under reduced pressure to a crude oily residue, 3.26 g. This was purified by column chromatography (Analogix, 40 g cartridge, gradient of MeOH in DCM from 0% to 10%). The product eluted at 4% MeOH in DCM. The pure product containing fractions were combined, concentrated under reduced pressure and dried (50°C, 0.2 mmHg, 17 h) to a white foam solid (1.322 g, 2.28 mmol, 56%). HPLC purity 99.25%. NMR spectra of product showed it is a mixture of two diastereoisomers with a ratio of 55:45.

^{1}H-NMR (DMSO-d_6) δ = 7.80 (s, 1 H, 8-H of one isomer), 7.80 (s, 1 H, 8-H of another isomer), 7.38-7.33 (m, 2 H, arom-H), 7.22-7.14 (m, 3 H, arom-H), 6.09

(s, 2 H, NH_2), 6.12-6.02 (m, 2 H, C1'-H and NH), 5.83 (d, 1 H, 3'-OH of one isomer), 5.77 (d, 1 H, 3'-OH of another isomer), 4.46-4.05 (m, 8 H, NCH_2 of azetidine, α-H of aminoester, C3'-H, C4'-H, C5'-H_a), 3.89-3.79 (m, 1 H, C5'-H_b), 3.56 (s, 3 H, OCH_3 of aminoester in one isomer), 3.54 (s, 3 H, OCH_3 of aminoester in another isomer), 2.37 (penta, 2 H, center CH_2 of azetidine), 1.21 (d, 3 H, α-CH_3 of aminoester in one isomer), 1.19 (d, 3 H, α-CH_3 of aminoester in another isomer), 1.08 (d, 3 H, C2'-CH_3).

^{31}P NMR (DMSO-d_6): δ 4.85 (one isomer), 4.77 (other isomer).

Synthesis of (2R,3R,4R,5R)-5-(2-amino-6-(benzyloxy)-9H-purin-9-yl)-4-fluoro-2-(hydroxymethyl)-4-methyltetrahydrofuran-3-ol (9)

To a 500 mL of dry round-bottomed flask were added (2R,3R,4R,5R)-5-(2-amino-6-chloro-9H-purin-9-yl)-2-(benzoyloxymethyl)-4-fluoro-4-methyltetrahydrofuran-3-yl benzoate (**6**, 8.0 g, 15.2 mmol) and anhydrous benzyl alcohol (128 mL). To another 250 mL of dry round-bottomed flask were charged NaH (60% in mineral oil, 2.44 g, 60.8 mmol) and anhydrous DMF (40 mL). The suspension was stirred at 0°C in an ice-water bath. Benzyl alcohol (27 mL) was added drop-wise via a syringe. A solution was slowly formed and it was transferred to the nucleoside suspension quickly under a nitrogen atmosphere at room temperature. The mixture was heated to 50°C and stirred. The reaction was complete after 3 h and cooled to ambient temperature. It was neutralized by the addition of 4 *N* HCl to *ca.* pH=7 (12 mL). The solution was concentrated under reduced pressure (4 mbar, 90°C bath). The cloudy residue was diluted with dichloromethane (100 mL) and washed with water (3x 30 mL), brine (30 mL) and dried over Na_2SO_4. The suspension was filtered and the filtrate was concentrated under reduced pressure to an oily residue. This was purified by column chromatography (Analogix, 0 to 8% gradient of MeOH in DCM). The product eluted at 4% MeOH in DCM. The product containing fractions were combined, concentrated under reduced pressure and dried (50°C, 0.2 mmHg, 17 h) to a white foam solid (4.57 g, 11.7 mmol, 77.2%).

^{1}H-NMR (DMSO-d_6) δ = 8.18 (s, 1 H, 8-H), 7.53-7.51 (m, 2 H, arom-H), 7.43-7.34 (m, 3 H, arom-H), 6.66 (s, 2 H, NH_2), 6.05 (d, 1 H, C1'-H), 5.67 (d, 1 H, 3'-OH), 5.48 (dd, 2 H, CH_2 of Benzyl), 5.25 (t, 1 H, 5'-OH), 4.18 (dt, 1 H, C3'-H),

3.92-3.82 (m, 2 H, C4'-H and C5'-H_a), 3.71-3.66 (m, 1 H, C5'- H_b), 1.07 (d, 3 H, C2'-CH_3).

Synthesis of (2S)-cyclopentyl 2-((((2R,3R,4R,5R)-5-(2-amino-6-(benzyloxy)-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate (13)

To a 100 mL of dry round-bottomed flask were charged phenyl dichlorophosphate (3.29 g, 15.58 mmol) and anhydrous dichloromethane (24 mL). The aminoester tosylate (white powder) was added and the solution was cooled to -5°C under nitrogen. *N*-Methylimidazole (4.92 g, 59.94 mmol) was added via a dry syringe in one portion and the resulted colorless clear solution was stirred at -5°C for one hour. Then the nucleoside (**9**) solid was added (2.334 g, 5.99 mmol) to the solution under nitrogen in one portion and the mixture was allowed to warm to ambient temperature to give a colorless solution. Reaction progress was monitored by TLC (5% methanol in dichloromethane). TLC indicated an incomplete reaction after 20 h (about 30% starting material left). The reaction was still quenched by the addition of dichloromethane (30 mL) and 1 *N* HCl (60 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2x20 mL). The combined organic layer was washed with water (2x40 mL), sat $NaHCO_3$ (30 mL), water, and brine. The organic layer was dried over Na_2SO_4. After removal of solid by filtration, the filtrate was concentrated under reduced pressure to a gummy residue (7.28 g). The residue was purified via column chromatography (Analogix, 80 g cartridge, gradient of 0 to 10% MeOH in DCM). The product eluted at 2% MeOH in DCM. The product containing fractions were combined, concentrated under reduced pressure and dried (50°C, 0.2 mmHg, 17 h) to a white foam solid (2.249 g, a mixture of two isomers, 60:40). A portion of the starting nucleoside (0.257 g) was also recovered. Yield is 62% based on consumed starting material.

^{1}H-NMR (DMSO-d_6): δ = 7.98 (s, 1 H, 8-H of one isomer), 7.96 (s, 1 H, 8-H of another isomer), 7.52-7.50 (m, 2 H, arom-H), 7.42-7.31 (m, 5 H, arom-H), 7.21-7.12 (m, 3 H, arom-H), 6.68 (s, 2 H, NH_2), 6.12 (d, 1 H, C1'-H of one isomer), 6.10 (d, 1 H, C1'-H of another isomer), 6.04-5.96 (m, 1 H, NH), 5.87 (d, 1 H, 3'-OH of one isomer), 5.81 (d, 1 H, 3'-OH of another isomer), 5.48 (dd, 2 H, CH_2 of Benzyl), 4.99-4.93 (m, 1 H, α-H of aminoester), 4.46-4.27 (m, 3 H, C3'-H, C4'-H, OCH of aminoester), 4.15-4.06 (m, 1 H, C5'-H_a), 3.81-3.71 (m, 1 H, C5'- H_b), 1.74-

1.43 (m, 8 H, methylene CH_2 of *c*-pentyl), 1.18 (d, 3 H, α-CH_3 of aminoester), 1.09 (d, 3 H, C2'-CH_3 of one isomer), 1.08 (d, 3 H, C2'-CH_3 of another isomer).

^{31}P NMR (DMSO-d_6): δ = 4.91 (one isomer), 4.73 (other isomer).

Synthesis of (2S)-cyclopentyl 2-((((2R,3R,4R,5R)-5-(2-amino-6-hydroxy-9H-purin-9-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate (14)

To a 250 mL of dry round-bottomed flask with starting material (**13,** 1.92 g, 2.8 mmol) was added anhydrous absolute ethanol (50 mL). Palladium on charcoal (10%, 120 mg) was added. The atmosphere in the flask was exchanged with hydrogen and the mixture was stirred under 1 atm of hydrogen gas for 3.5 h at room temperature. The reaction was judged complete by TLC and the Pd on charcoal was removed by filtration and washed with ethanol (2x 10 mL). The filtrate was concentrated under reduced pressure to a solid residue. The solid was mixed with silica gel (10 g) and purified by column chromatography (Analogix, 40 g cartridge, gradient of 1% to 16% MeOH in DCM). The product containing fractions were combined, concentrated under reduced pressure and dried (50°C, 0.2 mmHg, 17 h) to a white powder (1.43 g, 86%). HPLC purity 99.55%. NMR spectra of product showed it is a mixture of two diastereoisomers with a ratio of 60:40.

Mp=133~150°C.

^{1}H-NMR (DMSO-d_6): δ = 10.70 (s, 1 H, NH of imide), 7.81 (s, 1 H, 8-H of one isomer), 7.79 (s, 1 H, 8-H of another isomer), 7.38-7.33 (m, 2 H, arom-H), 7.22-7.14 (m, 3 H, arom-H), 6.62 (s, 2 H, NH_2), 6.08-5.97 (m, 2 H, C1'-H and NH of aminoester), 5.88 (b, 1 H, 3'-OH of one isomer), 5.82 (b, 1 H, 3'-OH of another isomer), 5.01-4.94 (m, 1 H, α-H of aminoester), 4.44-4.25 (m, 3 H, C3'-H, C4'-H, OCH of aminoester), 4.12-4.04 (m, 1 H, C5'-H_a), 3.82-3.72 (m, 1 H, C5'- H_b), 1.77-1.46 (m, 8 H, methylene CH_2 of *c*-pentyl), 1.21-1.19 (m, 3 H, α-CH_3 of aminoester), 1.09 (d, 3 H, C2'-CH_3 of one isomer), 1.08 (d, 3 H, C2'-CH_3 of another isomer).

^{31}P-NMR (DMSO-d_6): δ = 4.95 (one isomer), 4.72 (another isomer).

Synthesis of (2R,3R,4R,5R)-5-(2-amino-6-ethoxy-9H-purin-9-yl)-4-fluoro-2-(hydroxymethyl)-4-methyltetrahydrofuran-3-ol (10)

To a 500 mL of dry round-bottomed flask was loaded (**6**, 11 g, 20.92 mmol). Anhydrous absolute ethanol (210 mL) was added and followed by anhydrous K_2CO_3

(28.91 g, 209.2 mmol). The suspension was stirred and heated at 75°C under nitrogen for 5.5 h. All the starting material was consumed at that time by TLC test. The mixture was cooled to room temperature and solid was filtered out. The filtrate was neutralized by addition of glacial acetic acid (2.52 g) to pH~7 and concentrated under reduced pressure. The residue was dissolved in methanol and mixed with silica gel (15 g). The dried mixture of crude product and silica gel was transferred to an empty cartridge and separated through column chromatography (Analogix 220 g, gradient of 0 to 15% MeOH in DCM) to afford product (5% MeOH in DCM) as a white foam solid (3.73 g, 54.5%). A second white solid was isolated from column (10% MeOH in DCM, 1.44 g) and it is a mixture of two dimers of nucleoside. A more polar, third white solid was collected from column (15% MeOH in DCM, 0.47 g) and it is a mixture of trimers of nucleoside. HPLC purity of product 99.94%.

^{1}H-NMR (DMSO-d_6): δ 8.16 (s, 1 H, 8-H), 6.55 (s, 2 H, NH_2), 6.04 (d, 1 H, C1'-H), 5.66 (d, 1 H, 3'-OH), 5.24 (m, 1 H, 5'-OH), 4.44 (q, 2 H, 6-OCH_2), 4.23-4.08 (m, 1 H, C3'-H), 3.91-3.82 (m, 2 H, C4'-H and C5'-H_a), 3.71-3.66 (m, 1 H, C5'- H_b), 1.36 (t, 3 H, CH_3 of ethyl), 1.06 (d, 3 H, C2'-CH_3).

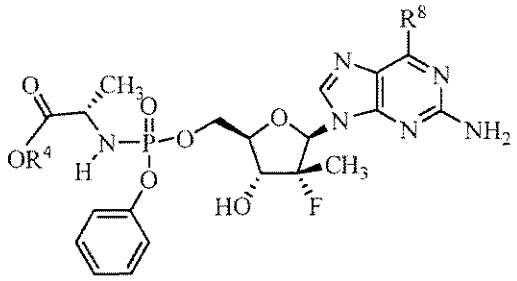
Biological Data

HCV replicon assay. HCV replicon RNA-containing Huh7 cells (clone A cells; Apath, LLC, St. Louis, Mo.) were kept at exponential growth in Dulbecco's modified Eagle's medium (high glucose) containing 10% fetal bovine serum, 4 mM L-glutamine and 1 mM sodium pyruvate, 1× nonessential amino acids, and G418 (1,000 μg/ml). Antiviral assays were performed in the same medium without G418. Cells were seeded in a 96-well plate at 1,500 cells per well, and test compounds were added immediately after seeding. Incubation time 4 days. At the end of the incubation step, total cellular RNA was isolated (RNeasy 96 kit; Qiagen). Replicon RNA and an internal control (TaqMan rRNA control reagents; Applied Biosystems) were amplified in a single-step multiplex RT-PCR protocol as recommended by the manufacturer. The HCV primers and probe were designed with Primer Express software (Applied Biosystems) and covered highly conserved 5′-untranslated region (UTR) sequences (sense, 5′-AGCCATGGCGTTAGTA(T)GAGTGT-3′, and

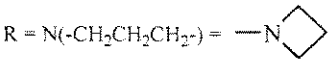
antisense, 5′-TTCCGCAGACCACTATGG-3′; probe, 5′-FAM-CCTCCAGGACCCCCCCTCCC-TAMRA-3′).

To express the antiviral effectiveness of a compound, the threshold RT-PCR cycle of the test compound was subtracted from the average threshold RT-PCR cycle of the no-drug control (ΔCt_{HCV}). A ΔCt of 3.3 equals a 1-log 10 reduction (equal to the 90% effective concentration [EC_{90}]) in replicon RNA levels. The cytotoxicity of the test compound could also be expressed by calculating the ΔCt_{rRNA} values. The ΔΔCt specificity parameter could then be introduced ($\Delta Ct_{HCV} - \Delta Ct_{rRNA}$), in which the levels of HCV RNA are normalized for the rRNA levels and calibrated against the no-drug control.

Compounds **11**, **12**, and **14**, are represented by the following structure(s),



11, R^8 = -OMe, R^4 = ^{i}Pr
12, R^8 = -N(-$CH_2CH_2CH_2$-), R^4 = Me
14, R^8 = -OH, R^4 = cyclopentyl



were tested for their biological properties based on the preceding assay. The results of these tests are disclosed in the Table 1.

Table 1. Activity of Selected Compounds

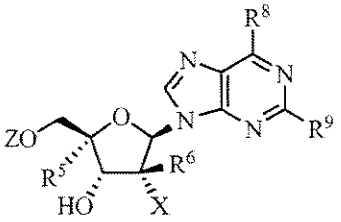
Compd. No.	CloneA EC_{90} (μM)
11	0.02
12	0.07
14	0.13

The contents of U.S. Patent Application No. 12/053,015, filed March 21, 2008 (see also WO 2008/121634), U.S. Patent Application No. 12/479,075, filed

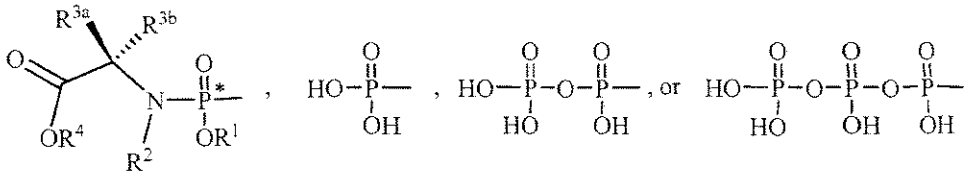
June 5, 2009, and U.S. Provisional Patent Application Nos. 61/060,683, filed June 11, 2008, 61/140,441, 61/140,317, and 61/140,369, each of which being filed December 23, 2008 are hereby incorporated by reference in their entirety. Moreover, the patent and non-patent references disclosed herein are incorporated by reference. In the event that the incorporated subject matter contains a term that conflicts with a term disclosed in the present application text, the meaning of the term contained in the present application controls provided that the overall meaning of the incorporated subject matter is not lost.

CLAIMS

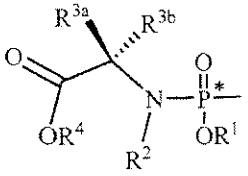
1. A compound represented by formula **I**, or its stereoisomers, salts, pharmaceutically acceptable salts, hydrates, solvates, crystalline, or metabolite forms thereof:



I

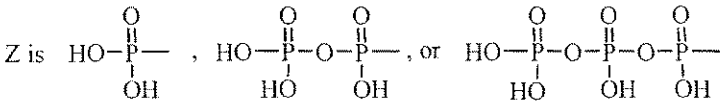
Z is 

wherein when

Z is 

R^1 is hydrogen or phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is hydrogen, ^{i}Pr, or cyclopentyl; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OMe, –N(-$CH_2CH_2CH_2$-) (azetidin-1-yl), OBn, or OH; and R^9 is NH_2;

and wherein when

Z is 

R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OMe, –N(-$CH_2CH_2CH_2$-) (azetidin-1-yl), OBn, or OH; and R^9 is NH_2.

2. A composition for the treatment and/or prophylaxis of any of the viral agents disclosed herein said composition comprising a pharmaceutically acceptable

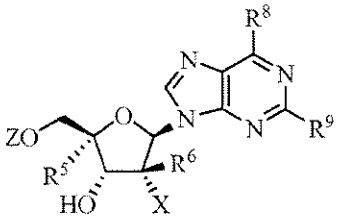
medium selected from among an excipient, carrier, diluent, and equivalent medium and the compound as claimed in claim 1.

3. A use of the compound as claimed in claim 1 in the manufacture of a medicament for the treatment of any condition the result of an infection by hepatitis C virus, West Nile virus, yellow fever virus, dengue virus, rhinovirus, polio virus, hepatitis A virus, bovine viral diarrhea virus or Japanese encephalitis virus.

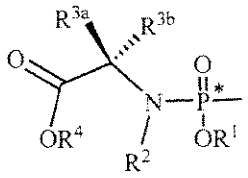
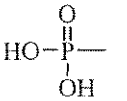
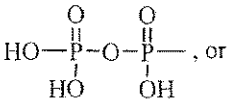
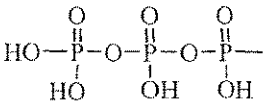
4. A method of treatment in a subject in need thereof, which comprises administering a therapeutically effective amount of the compound as claimed in claim 1.

5. A method of treatment in a subject in need thereof, which comprises contacting at least one compound as claimed in claim 1 with at least one hepatitis C virus infected cell.

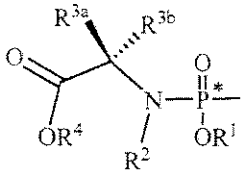
6. A compound represented by formula **I**, or a metabolite or salt or metabolite salt thereof:



I

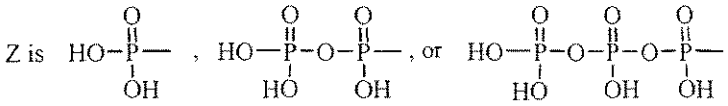
Z is  ,  ,  , or 

wherein when

Z is 

R^1 is hydrogen or phenyl; R^2 is hydrogen; R^{3a} is hydrogen; R^{3b} is CH_3; R^4 is hydrogen, ^{i}Pr, or cyclopentyl; R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OMe, –N(-$CH_2CH_2CH_2$-) (azetidin-1-yl), OBn, or OH; and R^9 is NH_2;

and wherein when

Z is  , or

R^5 is hydrogen; R^6 is CH_3; X is F; and R^8 is OMe, –N(-$CH_2CH_2CH_2$-) (azetidin-1-yl), OBn, or OH; and R^9 is NH_2.

7. A composition for the treatment and/or prophylaxis of any of the viral agents disclosed herein said composition comprising a pharmaceutically acceptable medium selected from among an excipient, carrier, diluent, and equivalent medium and the compound as claimed in claim 6.

8. A use of the compound as claimed in claim 6 in the manufacture of a medicament for the treatment of any condition the result of an infection by hepatitis C virus, West Nile virus, yellow fever virus, dengue virus, rhinovirus, polio virus, hepatitis A virus, bovine viral diarrhea virus or Japanese encephalitis virus.

9. A method of treatment in a subject in need thereof, which comprises administering a therapeutically effective amount of the compound as claimed in claim 6.

10. A method of treatment in a subject in need thereof, which comprises contacting at least one compound as claimed in claim 6 with at least one hepatitis C virus infected cell.