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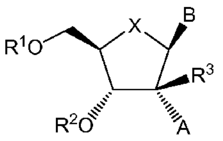
(54) **Title**: 2'-SUBSTITUTED NUCLEOSIDE DERIVATIVES AND METHODS OF USE THEREOF FOR THE TREATMENT OF VIRAL DISEASES



(I)

(57) **Abstract**: The present invention relates to 2'-Substituted Nucleoside Derivatives of Formula (I): and pharmaceutically acceptable salts thereof, wherein A, B, X, R^1, R^2 and R^3 are as defined herein. The present invention also relates to compositions comprising at least one 2'-Substituted Nucleoside Derivative, and methods of using the 2'-Substituted Nucleoside Derivatives for treating or preventing HCV infection in a patient.

2'-SUBSTITUTED NUCLEOSIDE DERIVATIVES AND METHODS OF USE THEREOF FOR THE TREATMENT OF VIRAL DISEASES

FIELD OF THE INVENTION

The present invention relates to 2'-Substituted Nucleoside Derivatives, compositions comprising at least one 2'-Substituted Nucleoside Derivative, and methods of using the 2'-Substituted Nucleoside Derivatives for treating or preventing HCV infection in a patient.

BACKGROUND OF THE INVENTION

Hepatitis C virus (HCV) is a major human pathogen. A substantial fraction of these HCV-infected individuals develop serious progressive liver disease, including cirrhosis and hepatocellular carcinoma, which are often fatal. HCV is a (+)-sense single-stranded enveloped RNA virus that has been implicated as the major causative agent in non-A, non-B hepatitis (NANBH), particularly in blood-associated NANBH (BB-NANBH) (see, International Publication No. WO 89/04669 and European Patent Publication No. EP 381 216). NANBH is to be distinguished from other types of viral-induced liver disease, such as hepatitis A virus (HAV), hepatitis B virus (HBV), delta hepatitis virus (HDV), cytomegalovirus (CMV) and Epstein-Barr virus (EBV), as well as from other forms of liver disease such as alcoholism and primary biliar cirrhosis.

It is well-established that persistent infection of HCV is related to chronic hepatitis, and as such, inhibition of HCV replication is a viable strategy for the prevention of hepatocellular carcinoma. Current therapies for HCV infection include α-interferon monotherapy and combination therapy comprising α-interferon and ribavirin. These therapies have been shown to be effective in some patients with chronic HCV infection, but suffer from poor efficacy and unfavorable side-effects and there are currently efforts directed to the discovery of HCV replication inhibitors that are useful for the treatment and prevention of HCV related disorders.

Current research efforts directed toward the treatment of HCV includes the use of antisense oligonucleotides, free bile acids (such as ursodeoxycholic acid and chenodeoxycholic acid) and conjugated bile acids (such as tauroursodeoxycholic acid). Phosphonoformic acid esters have also been proposed as potentially useful for the treatment of various viral infections, including HCV. Vaccine development, however, has been hampered by the high degree of viral strain heterogeneity and immune evasion and the lack of protection against reinfection, even with the same inoculum.

In light of these treatment hurdles, the development of small-molecule inhibitors directed against specific viral targets has become a major focus of anti-HCV research. The determination of crystal structures for NS3 protease, NS3 RNA helicase, NS5A, and NS5B polymerase, with and without bound ligands, has provided important structural insights useful for the rational design of specific inhibitors. Accoridingly, different approaches to HCV therapy have been taken, which include the inhibition of viral serine proteinase (NS3 protease), helicase, and RNA-dependent RNA polymerase (NS5B), and the development of a vaccine.

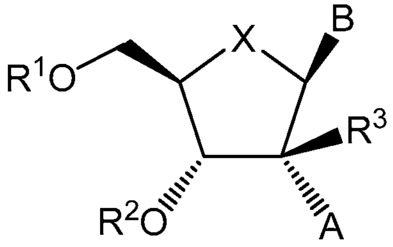
The HCV virion is an enveloped positive-strand RNA virus with a single oligoribonucleotide genomic sequence of about 9600 bases which encodes a polyprotein of about 3,010 amino acids. The protein products of the HCV gene consist of the structural proteins C, E1, and E2, and the non-structural proteins 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. NS5B polymerase is therefore considered to be an essential component in the HCV replication complex [see K. Ishi, *et al.*, "Expression of Hepatitis C Virus NS5B Protein: Characterization of Its RNA Polymerase Activity and RNA Binding," *Hepatology*, 29:1227-1235 (1999) and V. Lohmann, *et al.*, "Biochemical and Kinetic Analyses of NS5B RNA-Dependent RNA Polymerase of the Hepatitis C Virus," *Virology,* 249:108-118 (1998)]. 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.

The development of inhibitors of HCV NS5B polymerase with potential for the treatment of HCV infection has been reviewed in M.P. Walker *et al.*, "Promising candidates for the treatment of chronic hepatitis C," *Expert Opin. Invest. Drugs*, 12:1269-1280 (2003) and in P. Hoffmann *et al.*, "Recent patents on experimental therapy for hepatitis C virus infection (1999-2002)," *Expert Opin. Ther. Patents*," 13:1707-1723 (2003). The activity of purine ribonucleosides against HCV polymerase was reported by A.E. Eldrup *et al.*, "Structure-Activity Relationship of Purine Ribonucleosides for Inhibition of HCV RNA-Dependent RNA Polymerase," *J. Med. Chem.*, 47:2283-2295 (2004).

There is a continuing need for structurally diverse nucleoside derivatives as inhibitors of HCV polymerase as therapeutic approaches for HCV therapy. This invention responds to that need.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides Compounds of Formula (I):



(I)

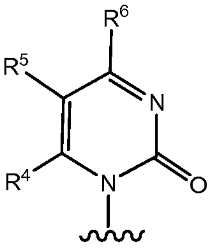
and pharmaceutically acceptable salts thereof,

wherein:

X is O, S or CH_2;

A is C_2-C_6 alkenyl, C_2-C_6 alkynyl, 5- or 6-membered monocyclic heteroaryl, Cl, $-N(R^{20})_2$, -S-(C_1-C_6 alkyl), -S(O)-(C_1-C_6 alkyl), $-S(O)_2$-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-OH, -(C_1-C_6 alkylene)-$N(R^{20})_2$, $-NHSO_2$-(C_1-C_6 alkyl), $-NHC(O)N(R^{20})_2$, -NHOH, $-C(O)OR^{20}$, $-C(O)N(R^{20})_2$, $-NHC(O)R^{20}$ or $-NHC(O)OR^{20}$, or group A and the $-OR^2$ group of formula (I) can join to form -OC(O)-NH-;

B is a natural or non-natural purine or pyrimidine base, or B is selected from one of the following groups:



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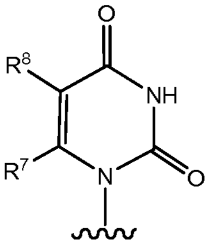

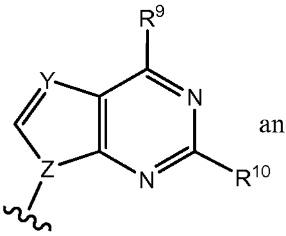

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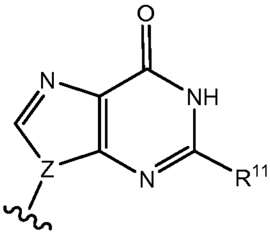

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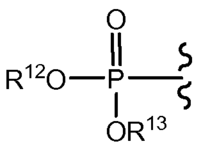
Y is N or $-C(R^{19})$-;

Z is N or -CH-;

R^1 is H,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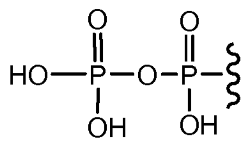
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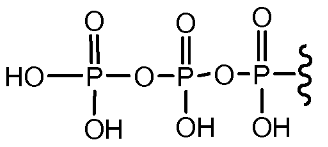
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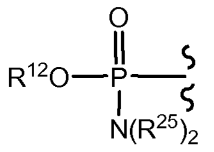
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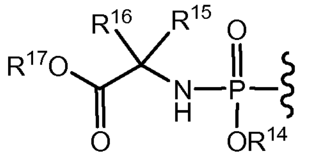
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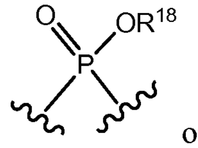
R^2 is H, or R^1 and R^2 join to form a group having the formula: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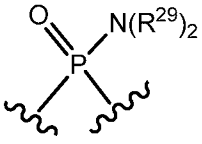
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R^3 is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_7 cycloalkyl;

R^4, R^5, R^7 and R^8 are each independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, halo, -OR^{20}, -SR^{20} or -$N(R^{20})_2$;

R^6, R^9, R^{10}, R^{11} are each independently selected from H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, 4- to 7-membered heterocycloalkyl, 5- or 6-membered monocyclic heteroaryl, 9- or 10-membered bicyclic heteroaryl, halo, -OR^{20}, -SR^{20}, -$S(O)R^{20}$, -$S(O)_2R^{20}$, –$S(O)_2N(R^{20})_2$, -$NHC(O)OR^{20}$, -$NHC(O)N(R^{20})_2$, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, -O-(C_1-C_6 haloalkyl), -CN, -NO_2, -$N(R^{20})_2$, -NH(C_1-C_6 alkylene)-(5- or 6-membered monocyclic heteroaryl), -NH(C_1-C_6 alkylene)-(9- or 10-membered bicyclic heteroaryl), -$C(O)R^{20}$, -$C(O)OR^{20}$, -$C(O)N(R^{20})_2$ and -$NHC(O)R^{20}$, wherein said C_2-C_6 alkenyl group and said C_2-C_6 alkynyl group can be optionally substituted a halo group;

R^{12} is H or –(C_1-C_6 alkylene)-T-R^{21};

R^{13} is H or –(C_1-C_6 alkylene)-T-R^{21}, or R^{12} and R^{13} can join to form a C_2-C_4 alkylene group between the oxygen atoms that R^{12} and R^{13} are attached to, wherein said C_2-C_4 alkylene group is substituted with at least one C_6-C_{10} aryl group;

R^{14} is H, C_6-C_{10} aryl, 5- or 6-membered monocyclic heteroaryl or 9- or 10-membered bicyclic heteroaryl, wherein said C_6-C_{10} aryl group, said 5- or 6-membered monocyclic heteroaryl group and said 9- or 10-membered bicyclic heteroaryl group can be optionally substituted with R^{22};

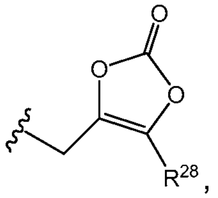
R^{15} is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl or benzyl, wherein said C_1-C_6 alkyl can be optionally substituted with a group selected from halo, -OR^{20}, -SR^{20}, guanidino, -

$N(R^{20})_2$, $-C(O)OR^{20}$, $-C(O)N(R^{20})_2$, $-NHC(O)R^{20}$, 5- or 6-membered monocyclic heteroaryl and 9- or 10-membered bicyclic heteroaryl, and wherein said phenyl group and said benzyl group can be optionally substituted with up to 2 groups, each independently selected from C_1-C_6 alkyl, halo and $-OR^{20}$;

R^{16} is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl or benzyl, wherein said C_1-C_6 alkyl can be optionally substituted with a group selected from halo, $-OR^{20}$, $-SR^{20}$, guanidino, $-N(R^{20})_2$, $-C(O)OR^{20}$, $-C(O)N(R^{20})_2$, $-NHC(O)R^{20}$, 5- or 6-membered monocyclic heteroaryl and 9- or 10-membered bicyclic heteroaryl, and wherein said phenyl group and said benzyl group can be optionally substituted with up to 2 groups, each independently selected from C_1-C_6 alkyl, halo and $-OR^{20}$;

R^{17} is H, C_1-C_{20} alkyl, C_2-C_{20} alkenyl, $-(C_1$-C_3 alkylene$)_m$-C_3-C_7 cycloalkyl, $-(C_1$-C_3 alkylene$)_m$-C_6-C_{10} aryl or adamantyl, wherein said C_1-C_{20} alkyl group, said C_2-C_{20} alkenyl group, said C_6-C_{10} aryl group and said adamantyl group can be optionally substituted with up to three groups, each independently selected from halo, $-OR^{20}$, $-C(O)OR^{20}$, CN, NO_2, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_3-C_7 cycloalkyl, C_6-C_{10} aryl, 5- or 6-membered monocyclic heteroaryl, 9- or 10-membered bicyclic heteroaryl, $-N(R^{20})_2$, $-C(O)N(R^{20})_2$ $-SR^{20}$, $-S(O)R^{20}$, $-S(O)_2R^{20}$, $-S(O)_2N(R^{20})_2$, $-NHC(O)R^{20}$, $-NHC(O)OR^{20}$ and $-NHC(O)N(R^{20})_2$ and;

R^{18} is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, $-(C_1$-C_3 alkylene$)_m$-C_6-C_{10} aryl, 5- or 6-membered monocyclic heteroaryl, 9- or 10-membered bicyclic heteroaryl or:



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wherein said C_6-C_{10} aryl group, said 5- or 6-membered monocyclic heteroaryl group and said 9- or 10-membered bicyclic heteroaryl group can be optionally substituted with up to five groups, each independently selected from C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halo, $-OR^{20}$, $-SR^{20}$, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, $-O-(C_1$-C_6 haloalkyl), -CN, $-NO_2$, $-N(R^{20})_2$, $-C(O)OR^{20}$, $-C(O)N(R^{20})_2$ and $-NHC(O)R^{20}$;

R^{19} is H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, halo, $-OR^{20}$, $-SR^{20}$, $N(R^{20})_2$, C_3-C_7 cycloalkyl, C_6-C_{10} aryl, 5- or 6-membered monocyclic heteroaryl or 9- or 10-membered bicyclic heteroaryl;

each occurrence of R^{20} is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, $-(C_1$-C_3 alkylene$)_m$-(C_3-C_7 cycloalkyl), $-(C_1$-C_3 alkylene$)_m$-(C_6-C_{10} aryl), $-(C_1$-C_3

alkylene)$_m$-(4 to 7-membered heterocycloalkyl), -(C_1-C_3 alkylene)$_m$-(5- or 6-membered monocyclic heteroaryl) or -(C_1-C_3 alkylene)$_m$-(9- or 10-membered bicyclic heteroaryl), wherein said C_3-C_7 cycloalkyl group, said C_6-C_{10} aryl group, said 4 to 7-membered heterocycloalkyl group, said -(5- or 6-membered monocyclic heteroaryl group or said 9- or 10-membered bicyclic heteroaryl group can be optionally substituted with R^{26};

each occurrence of R^{21} is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkenyl, 5- or 6-membered monocyclic heteroaryl, 9- or 10-membered bicyclic heteroaryl, -OR^{20}, -O-(C_1-C_6 haloalkyl) or -$N(R^{20})_2$, wherein said C_2-C_6 alkenyl group, said C_2-C_6 alkynyl group, said C_3-C_7 cycloalkyl group, said C_3-C_7 cycloalkenyl group, said C_6-C_{10} aryl group, said 5- or 6-membered monocyclic heteroaryl group and said 9- or 10-membered bicyclic heteroaryl group can be optionally substituted with up to five groups, each independently selected from C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halo, -OR^{20}, -SR^{20}, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, -O-(C_1-C_6 haloalkyl), -CN, -NO_2, -$N(R^{20})_2$, -$C(O)R^{20}$, -$C(O)OR^{20}$, -$C(O)N(R^{20})_2$ and -$NHC(O)R^{20}$;

R^{22} represents from one to five substituent groups, each independently selected from C_1-C_6 alkyl, halo, -OR^{20}, -SR^{20}, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, -O-(C_1-C_6 haloalkyl), -CN, -NO_2, -$N(R^{20})_2$, -$C(O)OR^{20}$, -$C(O)N(R^{20})_2$ and -$NHC(O)R^{20}$, or any two R^{22} groups on adjacent ring carbon atoms can combine to form –O-R^{23}-O-;

R^{23} is –$[C(R^{24})_2]_n$-;

each occurrence of R^{24} is independently H or C_1-C_6 alkyl;

each occurrence of R^{25} is independently H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, -(C_1-C_3 alkylene)$_m$-(C_6-C_{10} aryl), 4 to 7-membered heterocycloalkyl, 5- or 6-membered monocyclic heteroaryl or 9- or 10-membered bicyclic heteroaryl, wherein said C_1-C_6 alkyl group, said C_2-C_6 alkenyl group, said C_2-C_6 alkynyl group, said C_3-C_7 cycloalkyl group, said C_6-C_{10} aryl group, said 4 to 7-membered heterocycloalkyl group, said -(5- or 6-membered monocyclic heteroaryl group or said 9- or 10-membered bicyclic heteroaryl group can be optionally substituted with R^{26}; or two R^{25} groups, together with the common nitrogen atom to which they are attached, join to form a 4- to 7-membered heterocycloalkyl group;

R^{26} represents from one to five substituent groups, each independently selected from C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halo, -OR^{27}, -SR^{27}, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, -O-(C_1-C_6 haloalkyl), -CN, -NO_2, -$N(R^{27})_2$, -$C(O)OR^{27}$, -$C(O)N(R^{27})_2$ and -$NHC(O)R^{27}$;

each occurrence of R^{27} is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, -(C_1-C_3 alkylene)$_m$-(C_3-C_7 cycloalkyl), -(C_1-C_3 alkylene)$_m$-(C_6-C_{10} aryl), -(C_1-C_3 alkylene)$_m$-(4 to 7-membered heterocycloalkyl), -(C_1-C_3 alkylene)$_m$-(5- or 6-membered monocyclic heteroaryl) or -(C_1-C_3 alkylene)$_m$-(9- or 10-membered bicyclic heteroaryl);

R^{28} is H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkenyl, 5- or 6-membered monocyclic heteroaryl, 9- or 10-membered bicyclic heteroaryl, -OR^{20}, -O-(C_1-C_6 haloalkyl) or -$N(R^{20})_2$, wherein said C_2-C_6 alkenyl group, said C_2-C_6 alkynyl group, said C_3-C_7 cycloalkyl group, said C_3-C_7 cycloalkenyl group, said C_6-C_{10} aryl group, said 5- or 6-membered monocyclic heteroaryl group and said 9- or 10-membered bicyclic heteroaryl group can be optionally substituted with up to five groups, each independently selected from C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halo, -OR^{20}, -SR^{20}, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, -O-(C_1-C_6 haloalkyl), -CN, -NO_2, -$N(R^{20})_2$, -$C(O)R^{20}$, -$C(O)OR^{20}$, -$C(O)N(R^{20})_2$ and -$NHC(O)R^{20}$;

each occurrence of R^{29} is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, -(C_1-C_3 alkylene)$_m$-(C_3-C_7 cycloalkyl), -(C_1-C_3 alkylene)$_m$-(C_6-C_{10} aryl), -(C_1-C_3 alkylene)$_m$-(4 to 7-membered heterocycloalkyl), -(C_1-C_3 alkylene)$_m$-(5- or 6-membered monocyclic heteroaryl) or -(C_1-C_3 alkylene)$_m$-(9- or 10-membered bicyclic heteroaryl), wherein said C_3-C_7 cycloalkyl group, said C_6-C_{10} aryl group, said 4 to 7-membered heterocycloalkyl group, said -(5- or 6-membered monocyclic heteroaryl group or said 9- or 10-membered bicyclic heteroaryl group can be optionally substituted with R^{26};

each occurrence of T is independently –S-, -O-, -SC(O)-, -SC(S)-, -OC(O)- and –OC(S)-;

each occurrence of m is independently 0 or 1; and

each occurrence of n is independently 1 or 2.

The Compounds of Formula (I) (also referred to herein as the “2'-Substituted Nucleoside Derivatives”) and pharmaceutically acceptable salts thereof can be useful, for example, for inhibiting HCV viral replication or replicon activity, and for treating or preventing HCV infection in a patient. Without being bound by any specific theory, it is believed that the 2'-Substituted Nucleoside Derivatives inhibit HCV viral replication by inhibiting HCV NS5B

Accordingly, the present invention provides methods for treating or preventing HCV infection in a patient, comprising administering to the patient an effective amount of at least one 2'-Substituted Nucleoside Derivative.

The details of the invention are set forth in the accompanying detailed description below.

Although any methods and materials similar to those described herein can be used in the practice or testing of the present invention, illustrative methods and materials are now described. Other embodiments, aspects and features of the present invention are either further described in or will be apparent from the ensuing description, examples and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to 2'-Substituted Nucleoside Derivatives, compositions comprising at least one 2'-Substituted Nucleoside Derivative, and methods of using the 2'-Substituted Nucleoside Derivatives for treating or preventing HCV infection in a patient.

Definitions and Abbreviations

The terms used herein have their ordinary meaning and the meaning of such terms is independent at each occurrence thereof. That notwithstanding and except where stated otherwise, the following definitions apply throughout the specification and claims. Chemical names, common names, and chemical structures may be used interchangeably to describe the same structure. If a chemical compound is referred to using both a chemical structure and a chemical name and an ambiguity exists between the structure and the name, the structure predominates. These definitions apply regardless of whether a term is used by itself or in combination with other terms, unless otherwise indicated. Hence, the definition of "alkyl" applies to "alkyl" as well as the "alkyl" portions of "hydroxyalkyl," "haloalkyl," "-O-alkyl," etc...

As used herein, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

A “patient” is a human or non-human mammal. In one embodiment, a patient is a human. In another embodiment, a patient is a chimpanzee.

The term "effective amount" as used herein, refers to an amount of 2'-Substituted Nucleoside Derivative and/or an additional therapeutic agent, or a composition thereof that is effective in producing the desired therapeutic, ameliorative, inhibitory or preventative effect when administered to a patient suffering from a viral infection or virus-related disorder. In the combination therapies of the present invention, an effective amount can refer to each individual agent or to the combination as a whole, wherein the amounts of all agents administered are together effective, but wherein the component agent of the combination may not be present individually in an effective amount.

The term “preventing,” as used herein with respect to an HCV viral infection or HCV-virus related disorder, refers to reducing the likelihood or severity of HCV infection.

The term "alkyl,” as used herein, refers to an aliphatic hydrocarbon group having one of its hydrogen atoms replaced with a bond. An alkyl group may be straight or branched and contain from about 1 to about 20 carbon atoms. In one embodiment, an alkyl group contains from about 1 to about 12 carbon atoms. In different embodiments, an alkyl group contains from 1 to 6 carbon atoms (C_1-C_6 alkyl) or from about 1 to about 4 carbon atoms (C_1-C_4 alkyl). Non-limiting examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, neopentyl, isopentyl, n-hexyl, isohexyl and neohexyl. An alkyl group may be unsubstituted or substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkenyl, alkynyl, aryl, cycloalkyl, cyano, hydroxy, -O-alkyl, -O-aryl, -alkylene-O-alkyl, alkylthio, -NH_2, -NH(alkyl), -N$(alkyl)_2$, -NH(cycloalkyl), -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, -C(O)OH and –C(O)O-alkyl. In one embodiment, an alkyl group is linear. In another embodiment, an alkyl group is branched. Unless otherwise indicated, an alkyl group is unsubstituted.

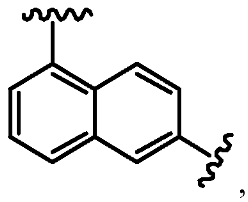
The term "alkenyl,” as used herein, refers to an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and having one of its hydrogen atoms replaced with a bond. An alkenyl group may be straight or branched and contain from about 2 to about 15 carbon atoms. In one embodiment, an alkenyl group contains from about 2 to about 12 carbon atoms. In another embodiment, an alkenyl group contains from about 2 to about 6 carbon atoms. Non-limiting examples of alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl. An alkenyl group may be unsubstituted or substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkenyl, alkynyl, aryl, cycloalkyl, cyano, hydroxy, -O-alkyl, -O-aryl, -alkylene-O-alkyl, alkylthio, -NH_2, -NH(alkyl), -N$(alkyl)_2$, -NH(cycloalkyl), -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, -C(O)OH and –C(O)O-alkyl. The term “C_2-C_6 alkenyl” refers to an alkenyl group having from 2 to 6 carbon atoms. Unless otherwise indicated, an alkenyl group is unsubstituted.

The term "alkynyl,” as used herein, refers to an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and having one of its hydrogen atoms replaced with a bond. An alkynyl group may be straight or branched and contain from about 2 to about 15 carbon atoms. In one embodiment, an alkynyl group contains from about 2 to about 12 carbon atoms. In another embodiment, an alkynyl group contains from about 2 to about 6 carbon atoms. Non-limiting examples of alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl. An alkynyl group may be unsubstituted or substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkenyl, alkynyl, aryl, cycloalkyl, cyano, hydroxy, -O-alkyl, -O-aryl, -alkylene-O-alkyl, alkylthio, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, -NH(cycloalkyl), -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, -C(O)OH and –C(O)O-alkyl. The term "C_2-C_6 alkynyl" refers to an alkynyl group having from 2 to 6 carbon atoms. Unless otherwise indicated, an alkynyl group is unsubstituted.

The term "alkylene," as used herein, refers to an alkyl group, as defined above, wherein one of the alkyl group's hydrogen atoms has been replaced with a bond. Non-limiting examples of alkylene groups include $–CH_2–$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH(CH_3)CH_2CH_2-$, $-CH(CH_3)-$ and $-CH_2CH(CH_3)CH_2-$. In one embodiment, an alkylene group has from 1 to about 6 carbon atoms. In another embodiment, an alkylene group is branched. In another embodiment, an alkylene group is linear. In one embodiment, an alkylene group is $-CH_2-$. The term "C_1-C_6 alkylene" refers to an alkylene group having from 1 to 6 carbon atoms.

The term "aryl," as used herein, refers to an aromatic monocyclic or multicyclic ring system comprising from about 6 to about 14 carbon atoms. In one embodiment, an aryl group contains from about 6 to about 10 carbon atoms. An aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein below. In one embodiment, an aryl group can be optionally fused to a cycloalkyl or cycloalkanoyl group. Non-limiting examples of aryl groups include phenyl and naphthyl. In one embodiment, an aryl group is phenyl. Unless otherwise indicated, an aryl group is unsubstituted.

The term "arylene," as used herein, refers to a bivalent group derived from an aryl group, as defined above, by removal of a hydrogen atom from a ring carbon of an aryl group. An arylene group can be derived from a monocyclic or multicyclic ring system comprising from about 6 to about 14 carbon atoms. In one embodiment, an arylene group contains from about 6 to about 10 carbon atoms. In another embodiment, an arylene group is a naphthylene group. In another embodiment, an arylene group is a phenylene group. An arylene group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein below. An arylene group is divalent and either available bond on an arylene group can connect to either group flanking the arylene group. For example, the group “A-arylene-B,” wherein the arylene group is: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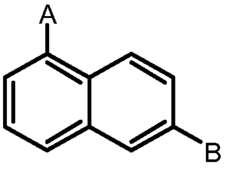
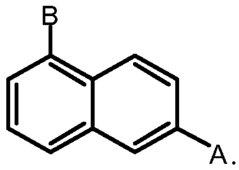
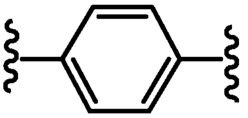
is understood to represent both:



and



In one embodiment, an arylene group can be optionally fused to a cycloalkyl or cycloalkanoyl group. Non-limiting examples of arylene groups include phenylene and naphthalene. In one embodiment, an arylene group is unsubstituted. In another embodiment, an arylene group is: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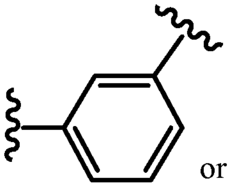
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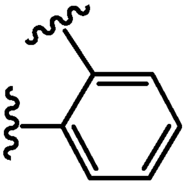
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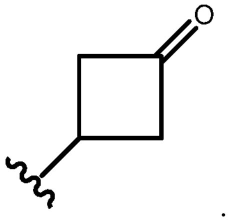
Unless otherwise indicated, an arylene group is unsubstituted.

The term "cycloalkyl," as used herein, refers to a non-aromatic mono- or multicyclic ring system comprising from 3 to about 10 ring carbon atoms. In one embodiment, a cycloalkyl contains from about 5 to about 10 ring carbon atoms. In another embodiment, a cycloalkyl contains from 3 to about 7 ring atoms. In another embodiment, a cycloalkyl contains from about 5 to about 6 ring atoms. The term “cycloalkyl” also encompasses a cycloalkyl group, as defined above, which is fused to an aryl (*e.g.*, benzene) or heteroaryl ring. Non-limiting examples of monocyclic cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. Non-limiting examples of multicyclic cycloalkyls include 1-decalinyl, norbornyl and adamantyl. A cycloalkyl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein below. In one embodiment, a cycloalkyl group is unsubstituted. The term “3 to 6-membered cycloalkyl” refers to a cycloalkyl group having from 3 to 6 ring carbon atoms. Unless otherwise indicated, a cycloalkyl group is unsubstituted. A ring carbon atom of a cycloalkyl group may be functionalized as a carbonyl group. An illustrative example of such a cycloalkyl group (also referred to herein as a "cycloalkanoyl" group) includes, but is not limited to, cyclobutanoyl:



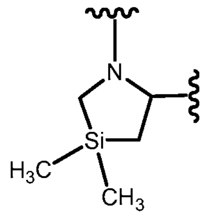
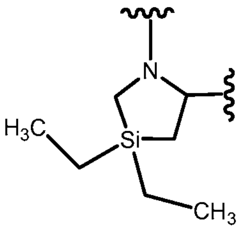
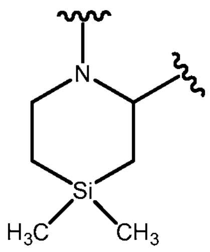
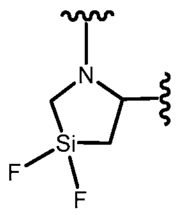
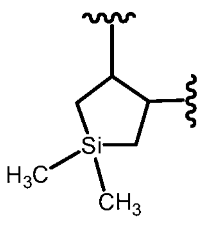
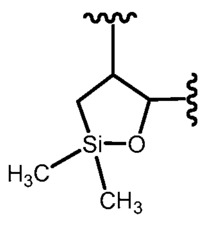
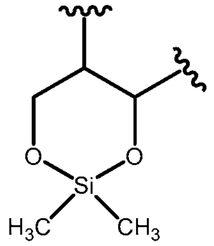
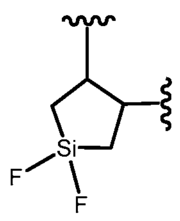
The term "halo," as used herein, means –F, -Cl, -Br or -I.

The term "haloalkyl," as used herein, refers to an alkyl group as defined above, wherein one or more of the alkyl group's hydrogen atoms has been replaced with a halogen. In one embodiment, a haloalkyl group has from 1 to 6 carbon atoms. In another embodiment, a haloalkyl group is substituted with from 1 to 3 F atoms. Non-limiting examples of haloalkyl groups include $–CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2Cl$ and $-CCl_3$. The term "C_1-C_6 haloalkyl" refers to a haloalkyl group having from 1 to 6 carbon atoms.

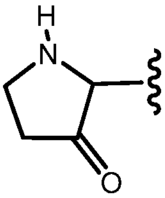
The term "hydroxyalkyl," as used herein, refers to an alkyl group as defined above, wherein one or more of the alkyl group's hydrogen atoms have been replaced with an –OH group. In one embodiment, a hydroxyalkyl group has from 1 to 6 carbon atoms. Non-limiting examples of hydroxyalkyl groups include $–CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$ and $-CH_2CH(OH)CH_3$. The term "C_1-C_6 hydroxyalkyl" refers to a hydroxyalkyl group having from 1 to 6 carbon atoms.

The term "heteroaryl," as used herein, refers to an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, wherein from 1 to 4 of the ring atoms is independently O, N or S and the remaining ring atoms are carbon atoms. In one embodiment, a heteroaryl group has 5 to 10 ring atoms. In another embodiment, a heteroaryl group is monocyclic and has 5 or 6 ring atoms. In another embodiment, a heteroaryl group is bicyclic. A heteroaryl group can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein below. A heteroaryl group is joined via a ring carbon atom, and any nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. The term "heteroaryl" also encompasses a heteroaryl group, as defined above, which is fused to a benzene ring. Non-limiting examples of heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, benzimidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like, and all isomeric forms thereof. The term "heteroaryl" also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like. In one embodiment, a heteroaryl group is a 5-membered heteroaryl. In another embodiment, a heteroaryl group is a 6-membered heteroaryl. In another embodiment, a heteroaryl group comprises a 5- to 6-membered heteroaryl group fused to a benzene ring. Unless otherwise indicated, a heteroaryl group is unsubstituted.

The term "heterocycloalkyl," as used herein, refers to a non-aromatic saturated monocyclic or multicyclic ring system comprising 3 to about 11 ring atoms, wherein from 1 to 4 of the ring atoms are independently O, S, N or Si, and the remainder of the ring atoms are carbon atoms. A heterocycloalkyl group can be joined via a ring carbon, ring silicon atom or ring nitrogen atom. In one embodiment, a heterocycloalkyl group is monocyclic and has from 3 to about 7 ring atoms. In another embodiment, a heterocycloalkyl group is monocyclic has from about 4 to about 7 ring atoms. In another embodiment, a heterocycloalkyl group is bicyclic and has from about 7 to about 11 ring atoms. In still another embodiment, a heterocycloalkyl group is monocyclic and has 5 or 6 ring atoms. In one embodiment, a heterocycloalkyl group is monocyclic. In another embodiment, a heterocycloalkyl group is bicyclic. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Any –NH group in a heterocycloalkyl ring may exist protected such as, for example, as an -N(BOC), -N(Cbz), -N(Tos) group and the like; such protected heterocycloalkyl groups are considered part of this invention. The term "heterocycloalkyl" also encompasses a heterocycloalkyl group, as defined above, which is fused to an aryl (*e.g.*, benzene) or heteroaryl ring. A heterocycloalkyl group can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein below. The nitrogen or sulfur atom of the heterocycloalkyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of monocyclic heterocycloalkyl rings include oxetanyl, piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, delta-lactam, delta-lactone, silacyclopentane, silapyrrolidine and the like, and all isomers thereof. Non-limiting illustrative examples of a silyl-containing heterocycloalkyl group include:

A ring carbon atom of a heterocycloalkyl group may be functionalized as a carbonyl group. An illustrative example of such a heterocycloalkyl group is:

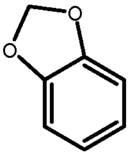


In one embodiment, a heterocycloalkyl group is a 5-membered monocyclic heterocycloalkyl. In another embodiment, a heterocycloalkyl group is a 6-membered monocyclic heterocycloalkyl. The term “3 to 6-membered monocyclic cycloalkyl” refers to a monocyclic heterocycloalkyl group having from 3 to 6 ring atoms. The term “4 to 6-membered monocyclic cycloalkyl” refers to a monocyclic heterocycloalkyl group having from 4 to 6 ring atoms. The term “7 to 11-membered bicyclic heterocycloalkyl” refers to a bicyclic heterocycloalkyl group having from 7 to 11 ring atoms. Unless otherwise indicated, an heterocycloalkyl group is unsubstituted.

The term "natural or non-natural purine or pyrimidine base" includes, but is not limited to, adenine, N$^{6\text{-alkylpurines}}$, N$^{6\text{-acylpurines}}$ (wherein acyl is C(O)(alkyl, aryl, alkylaryl, or arylalkyl), N$^{6\text{-benzylpurine}}$, N$^{6\text{-halopurine}}$, N$^{6\text{-vinylpurine}}$,N$^{6\text{-acetylenic}}$ purine, N$^{6\text{-acyl}}$ purine, N$^{6\text{-hydroxyalkyl}}$ purine, N$^{6\text{-thioalkyl}}$ purine, N$^{2\text{-alkylpurines}}$, N$^{2\text{-alkyl-6-thiopurines}}$, thymine, cytosine, 5-fluorocytosine, 5-methylcytosine, 6-azapyrimidine, including 6-azacytosine, 2-and/or 4-mercaptopyrmidine, uracil, 5-halouracil, including 5-fluorouracil, C$^{5\text{-alkylpyrimidines}}$, C$^{5\text{-benzylpyrimidines}}$, C$^{5\text{-halopyrimidines}}$, C$^{5\text{-vinylpyrimidine}}$, C$^{5\text{-acetylenic}}$ pyrimidine, C$^{5\text{-acyl}}$ pyrimidine,C$^{5\text{-hydroxyalkyl}}$ purine, C$^{5\text{-amidopyrimidine}}$, C$^{5\text{-cyanopyrimidine}}$, C$^{5\text{-nitropyrimidine}}$, C$^{5\text{-aminopyrimidine}}$, N$^{2\text{-alkylpurines}}$, N$^{2\text{-alkyl-6-thiopurines}}$, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl,pyrrolopyrimidinyl, and pyrazolopyrimidinyl.

Purine bases include, but are not limited to, guanine, adenine, hypoxanthine, 2,6-diaminopurine, and 6-chloropurine. Functional oxygen and nitrogen groups on the base can be protected as necessary or desired. Suitable protecting groups are well known to those skilled in the art, and include trimethylsilyl, dimethylhexylsilyl, t-butyldimethylsilyl, and t-butyldiphenylsilyl, trityl, alkyl groups, acyl groups such as acetyl and propionyl, methanesulfonyl, and p-toluenesulfonyl.

The term "ring system substituent," as used herein, refers to a substituent group attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, -alkylene-aryl, -arylene-alkyl, -alkylene-heteroaryl, -alkenylene-heteroaryl, -alkynylene-heteroaryl, -OH, hydroxyalkyl, haloalkyl, -O-alkyl, -O-haloalkyl, -alkylene-O-alkyl, -O-aryl, -O-alkylene-aryl, acyl, -C(O)-aryl, halo, -NO$_2$, -CN, -SF$_5$, -C(O)OH, -C(O)O-alkyl, -C(O)O-aryl, -C(O)O-alkylene-aryl, -S(O)-alkyl, -S(O)$_2$-alkyl, -S(O)-aryl, -S(O)$_2$-aryl, -S(O)-heteroaryl, -S(O)$_2$-heteroaryl, -S-alkyl, -S-aryl, -S-heteroaryl, -S-alkylene-aryl, -S-alkylene-heteroaryl, -S(O)$_2$-alkylene-aryl, -S(O)$_2$-alkylene-heteroaryl, -Si(alkyl)$_2$, -Si(aryl)$_2$, -Si(heteroaryl)$_2$, -Si(alkyl)(aryl), -Si(alkyl)(cycloalkyl), - Si(alkyl)(heteroaryl), cycloalkyl, heterocycloalkyl, -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, -C(=N-CN)-NH$_2$, -C(=NH)-NH$_2$, -C(=NH)-NH(alkyl), -N(Y$_1$)(Y$_2$), -alkylene-N(Y$_1$)(Y$_2$), -C(O)N(Y$_1$)(Y$_2$) and -S(O)$_2$N(Y$_1$)(Y$_2$), wherein Y$_1$ and Y$_2$ can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, and –alkylene-aryl. “Ring system substituent” may also mean a single moiety which simultaneously replaces two available hydrogens on two adjacent carbon atoms (one H on each carbon) on a ring system. Examples of such moiety are methylenedioxy, ethylenedioxy, -C(CH$_3$)$_2$- and the like which form moieties such as, for example: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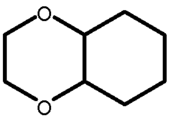
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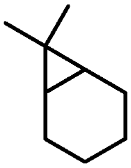
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The term “substituted” means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom’s normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By “stable compound’ or “stable structure” is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "in substantially purified form," as used herein, refers to the physical state of a compound after the compound is isolated from a synthetic process (*e.g.*, from a reaction mixture), a natural source, or a combination thereof. The term "in substantially purified form," also refers to the physical state of a compound after the compound is obtained from a purification process or processes described herein or well-known to the skilled artisan (*e.g.*, chromatography, recrystallization and the like), in sufficient purity to be characterizable by standard analytical techniques described herein or well-known to the skilled artisan.

It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

When a functional group in a compound is termed “protected”, this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in Organic Synthesis* (1991), Wiley, New York.

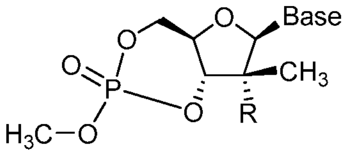
When any substituent or variable (*e.g.*, alkyl, R^6, R^a, etc.) occurs more than one time in any constituent or in Formula (I), its definition on each occurrence is independent of its definition at every other occurrence, unless otherwise indicated.

As used herein, the term “composition” is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design,* (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press. The term “prodrug” means a compound (*e.g.*, a drug precursor) that is transformed *in vivo* to provide a 2'-Substituted Nucleoside Derivative or a pharmaceutically acceptable salt of the compound. The transformation may occur by various mechanisms (*e.g.*, by metabolic or chemical processes), such as, for example, through hydrolysis in blood.

For example, if a 2'-Substituted Nucleoside Derivative or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as, for example, $(C_1–C_8)$alkyl, $(C_2$-$C_{12})$alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-$(C_1$-$C_2)$alkylamino$(C_2$-$C_3)$alkyl (such as β-dimethylaminoethyl), carbamoyl-$(C_1$-$C_2)$alkyl, N,N-di $(C_1$-$C_2)$alkylcarbamoyl-$(C_1$-$C_2)$alkyl and piperidino-, pyrrolidino- or morpholino$(C_2$-$C_3)$alkyl, and the like.

Similarly, if a 2'-Substituted Nucleoside Derivative contains an alcohol functional group, a prodrug can be formed by the replacement of one or more of the hydrogen atoms of the alcohol groups with a group such as, for example, $(C_1$-$C_6)$alkanoyloxymethyl, 1-($(C_1$-$C_6)$alkanoyloxy)ethyl, 1-methyl-1-($(C_1$-$C_6)$alkanoyloxy)ethyl, $(C_1$-$C_6)$alkoxycarbonyloxymethyl, N-$(C_1$-$C_6)$alkoxycarbonylaminomethyl, succinoyl, $(C_1$-$C_6)$alkanoyl, α-amino$(C_1$-$C_4)$alkyl, α-amino$(C_1$-$C_4)$alkylene-aryl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate). Other non-limiting example of alcohol-derived prodrugs include $-P(O)(OH)_2$; $-P(O)(-O-C_1-C_6alkyl)_2$; -P(O)(-NH-(α-aminoacyl group))(-O-aryl); -P(O)(-O-$(C_1$-C_6 alkylene)-S–acyl)(-NH-arylalkyl); any cyclic phosphate ester that forms a bridge between two ribose hydroxyl groups, such as:



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wherein the cyclic phosphate ester forms a bridge between the 3'-OH group and 5'-OH groups; and those described in US Patent No. 7,879,815; International Publication Nos. WO2005/003047, WO2008/082602, WO2010/0081628, WO2010/075517 and WO2010/075549; Mehellou, *Chem. Med. Chem.*, 5:1841-1842 (2005); Bobeck *et al.*, *Antiviral Therapy* 15:935-950 (2010); Furman *et al.*, Future Medicinal Chemistry, 1:1429-1452 (2009); and Erion, *Microsomes and Drug Oxidations, Proceedings of the International Symposium*, 17th, Saratoga Springs, NY, United States, July 6-10, 2008, 7-12 (2008).

If a 2'-Substituted Nucleoside Derivative incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R-carbonyl-, RO-carbonyl-, NRR'-carbonyl- wherein R and R' are each independently $(C_1\text{-}C_{10})$alkyl, $(C_3\text{-}C_7)$ cycloalkyl, benzyl, a natural α-aminoacyl, -C(OH)C(O)OY^1 wherein Y^1 is H, $(C_1\text{-}C_6)$alkyl or benzyl, -C(OY^2)Y^3 wherein Y^2 is $(C_1\text{-}C_4)$ alkyl and Y^3 is $(C_1\text{-}C_6)$alkyl; carboxy $(C_1\text{-}C_6)$alkyl; amino$(C_1\text{-}C_4)$alkyl or mono-N- or di-N,N-$(C_1\text{-}C_6)$alkylaminoalkyl; -C(Y^4)Y^5 wherein Y^4 is H or methyl and Y^5 is mono-N- or di-N,N-$(C_1\text{-}C_6)$alkylamino morpholino; piperidin-1-yl or pyrrolidin-1-yl, and the like.

Pharmaceutically acceptable esters of the present compounds include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy group of a hydroxyl compound, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (*e.g.,* methyl, ethyl, n-propyl, isopropyl, t-butyl, sec-butyl or n-butyl), alkoxyalkyl (*e.g.,* methoxymethyl), aralkyl (*e.g.,* benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (*e.g.,* phenyl optionally substituted with, for example, halogen, $C_{1\text{-}4}$alkyl, -O-($C_{1\text{-}4}$alkyl) or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (*e.g.,* L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a $C_{1\text{-}20}$ alcohol or reactive derivative thereof, or by a 2,3-di $(C_{6\text{-}24})$acyl glycerol.

One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of solvates include ethanolates, methanolates, and the like. A "hydrate" is a solvate wherein the solvent molecule is water.

One or more compounds of the invention may optionally be converted to a solvate. Preparation of solvates is generally known. Thus, for example, M. Caira *et al*, *J.*

Pharmaceutical Sci., 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder *et al*, *AAPS PharmSciTechours.* , 5(1), article 12 (2004); and A. L. Bingham *et al*, *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than room temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example IR spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

The 2'-Substituted Nucleoside Derivatives can form salts which are also within the scope of this invention. Reference to a 2'-Substituted Nucleoside Derivative herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a 2'-Substituted Nucleoside Derivative contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. In one embodiment, the salt is a pharmaceutically acceptable (*i.e.*, non-toxic, physiologically acceptable) salt. In another embodiment, the salt is other than a pharmaceutically acceptable salt. Salts of the Compounds of Formula (I) may be formed, for example, by reacting a 2'-Substituted Nucleoside Derivative with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of*

Medicinal Chemistry (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamine, t-butyl amine, choline, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (*e.g.*, methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (*e.g.*, dimethyl, diethyl, and dibutyl sulfates), long chain halides (*e.g.*, decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (*e.g.*, benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well-known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (*e.g.*, chiral auxiliary such as a chiral alcohol or Mosher’s acid chloride), separating the diastereomers and converting (*e.g.*, hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Sterochemically pure compounds may also be prepared by using chiral starting materials or by employing salt resolution techniques. Also, some of the 2'-Substituted Nucleoside Derivatives may be atropisomers (*e.g.*, substituted biaryls) and are considered as part of this invention. Enantiomers can also be directly separated using chiral chromatographic techniques.

It is also possible that the 2'-Substituted Nucleoside Derivatives may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. For example, all keto-enol and imine-enamine forms of the compounds are included in the invention.

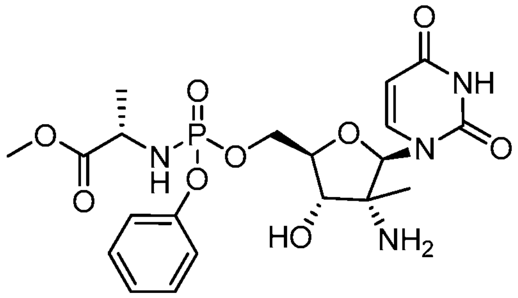
All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, hydrates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention. If a 2'-Substituted Nucleoside Derivative incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention.

Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate", “ester”, "prodrug" and the like, is intended to apply equally to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

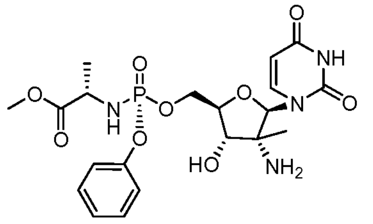
In the Compounds of Formula (I), the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of generic Formula I. For example, different isotopic forms of hydrogen (H) include protium (^1H) and deuterium (^2H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched Compounds of Formula (I) can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates. In one embodiment, a Compound of Formula (I) has one or more of its hydrogen atoms replaced with deuterium.

Polymorphic forms of the 2'-Substituted Nucleoside Derivatives, and of the salts, solvates, hydrates, esters and prodrugs of the 2'-Substituted Nucleoside Derivatives, are intended to be included in the present invention.

In some instances, the compounds of the present invention are designated as "isomer 1" and "isomer 2." This designation refers to stereoisomers at the chiral phosphorus atom of the 5'-prodrug moiety as illustrated below for cyclic and non-cyclic prodrugs, wherein, for example, the structure:



is understood to represent the following two phosphorus stereoisomers:



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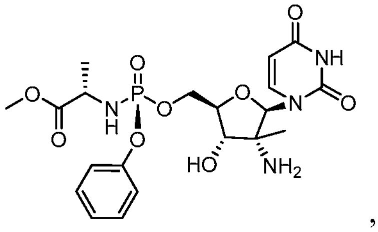

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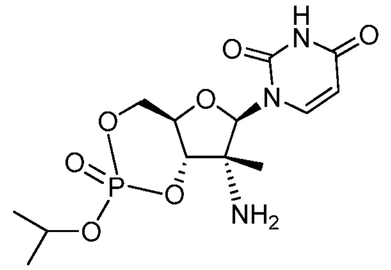
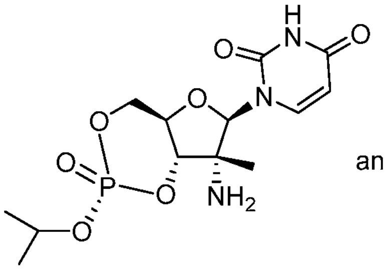
and the structure:



is understood to represent the following two phosphorus stereoisomers:



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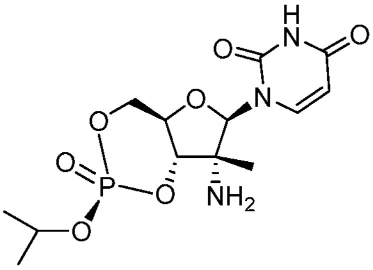

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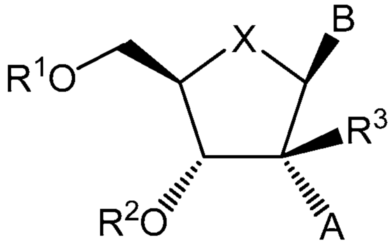
The terms "isomer 1" and "isomer 2" can be assigned to isomers of known absolute configuration or can be used to describe stereoisomers of unknown absolute configuration. Thus, the use of the terms "isomer 1" and "isomer 2" is not to be interpreted as indicating that the absolute configuration of both isomers is known.

The following abbreviations are used below and have the following meanings: Ac is acetyl or -C(O)CH_3, Ac_2O is acetic anhydride; t-BuMgCl is tert-butyl magnesium chloride; DCM is dichloromethane; Dess-Martin Periodinane is 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol- 3(1H)-one; DIBAL-H is diisobutylaluminum hydride; DMAP is N,N-dimethylamino pyridine; EtOAc is ethyl acetate; EtOH is ethanol; HPLC is high performance liquid chromatography; KHMDS is potassium hexamethyldisilazide; KOBut is potassium tert-butoxide; LCMS is liquid chromatography/mass spectrometry; MeOH is methanol; NMI is *N*-methylimidazole; $Pd(OH)_2$ is palladium hydroxide; TBAF is tetra n-butylammonium fluoride; TEMPO is (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl; THF is tetrahydrofuran; $TIPDSiCl_2$ is 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane; and TLC is thin-layer chromatography.

The Compounds of Formula (I)

The present invention provides 2'-Substituted Nucleoside Derivatives of Formula (I):



(I)

and pharmaceutically acceptable salts thereof, wherein A, B, X, R^1, R^2 and R^3 are defined above for the Compounds of Formula (I).

In one embodiment, X is O.

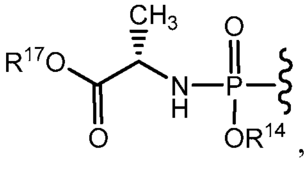
In another embodiment, X is S.

In another embodiment, X is CH_2.

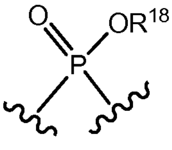
In one embodiment, R^3 is C_1-C_6 alkyl.

In another embodiment, R^3 is methyl.

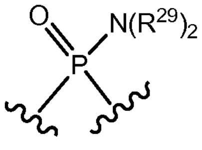
In one embodiment, for the Compounds of Formula (I), R^1 is H or



, or R^1 and R^2 join to form a group having the formula:

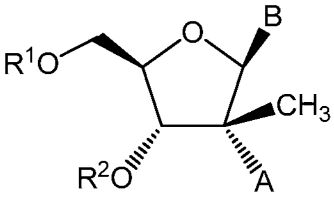


or



, wherein R^{14} is C_6-C_{10} aryl, which can be optionally substituted as set forth above for the Compounds of Formula (I); R^{17} is C_1-C_6 alkyl; R^{18} is C_1-C_6 alkyl; and R^{29} is as defined for the compounds of Formula (I).

In one embodiment, the compounds of formula (I) have the formula (Ia):



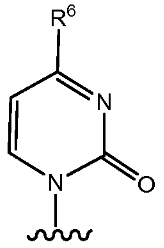
(Ia)

or a pharmaceutically acceptable salt thereof,

wherein:

A is 5- or 6-membered monocyclic heteroaryl, C_2-C_6 alkynyl, $-CH_2NH_2$, $-N(R^{20})_2$, $-S-(C_1-C_6$ alkyl), $-S(O)_2-(C_1-C_6$ alkyl), $-NHC(O)N(R^{20})_2$, $-C(O)N(R^{20})_2$, $-NHC(O)R^{20}$ or group A and the $-OR^2$ group of formula (I) can join to form -OC(O)-NH-;

B is:



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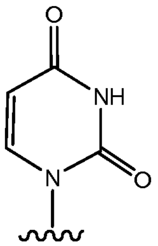
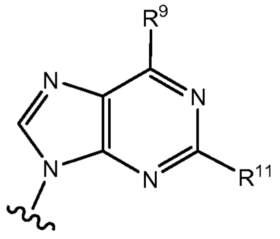
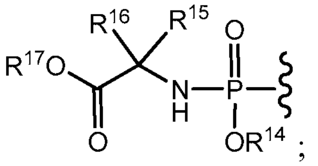


or



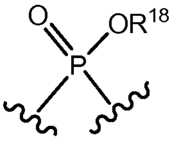
;

R^1 is H or:



;

R^2 is H, or R^1 and R^2 join to form a group having the formula:



;

R^6 and R^{11} are each independently $-N(R^{20})_2$;

R^9 is –OH or $-O-(C_1-C_6$ alkyl);

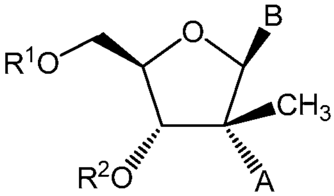
R^{14} is C_6-C_{10} aryl;

R^{15} and R^{16} are each independently H or C_1-C_6 alkyl;

R^{17} and R^{18} are each independently C_1-C_6 alkyl; and

each occurrence of R^{20} is independently H or $-C(O)-(C_1-C_6$ alkyl).

In one embodiment, the compounds of formula (I) have the formula (Ia'):



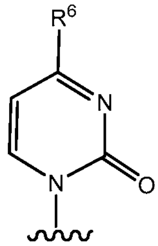
(Ia')

or a pharmaceutically acceptable salt thereof,

wherein:

A is 5- or 6-membered monocyclic heteroaryl, C_2-C_6 alkynyl, -CH_2NH_2, -$N(R^{20})_2$, -S-(C_1-C_6 alkyl), -$S(O)_2$-(C_1-C_6 alkyl), -$NHC(O)N(R^{20})_2$, -$C(O)N(R^{20})_2$, -$NHC(O)R^{20}$ or group A and the –OR^2 group of formula (I) can join to form -OC(O)-NH-;

B is:



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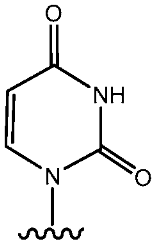
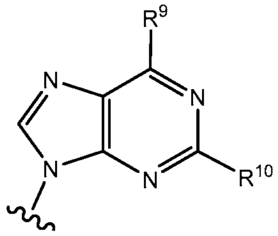
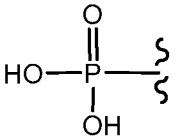


or



;

R^1 is:



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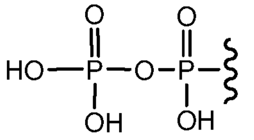
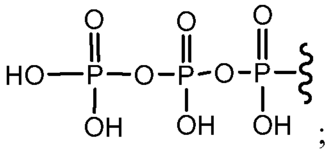


or



;

R^6 and R^{10} are each independently -$N(R^{20})_2$;

R^9 is –OH or -O-(C_1-C_6 alkyl); and

each occurrence of R^{20} is independently H or -C(O)-(C_1-C_6 alkyl).

In one embodiment, for the Compounds of Formula (I), (Ia) or (Ia'), A is 5- or 6-membered monocyclic heteroaryl, C_2-C_6 alkynyl, -CH_2NH_2, -$N(R^{20})_2$, -S-(C_1-C_6 alkyl), -$S(O)_2$-(C_1-C_6 alkyl), -$NHC(O)N(R^{20})_2$, -$C(O)N(R^{20})_2$, -$NHC(O)R^{20}$ or group A and the –OR^2 group of formula (I) can join to form -OC(O)-NH-.

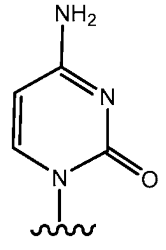
In another embodiment, for the Compounds of Formula (I), (Ia) or (Ia'), A is triazolyl, Cl, -C≡CH, -NH_2, -SCH_3, -$S(O)_2CH_3$, -$NHC(O)NH_2$, -$NHC(O)CH_3$ or group A and the –OR^2 group of formula (I) join to form -OC(O)-NH-.

In another embodiment, for the Compounds of Formula (I), (Ia) or (Ia'), A is –NH_2.

In still another embodiment, for the Compounds of Formula (I), (Ia) or (Ia'), A is C_2-C_6 alkynyl.

In another embodiment, for the Compounds of Formula (I), (Ia) or (Ia'), A is -C≡CH.

In one embodiment, for the Compounds of Formula (I), (Ia) or (Ia'), B is: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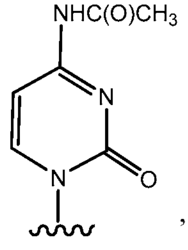
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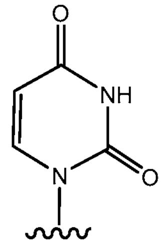
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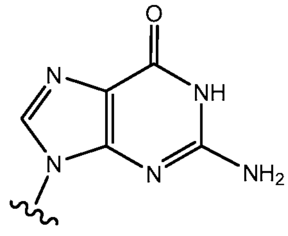
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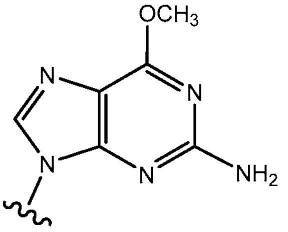
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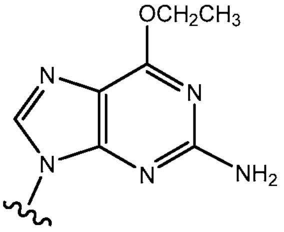
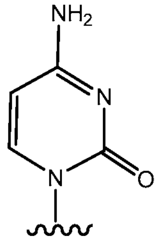

.

In another embodiment, for the Compounds of Formula (I), (Ia) or (Ia'), B is: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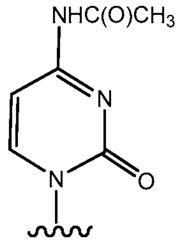
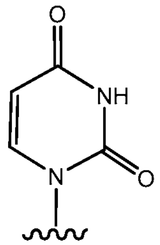
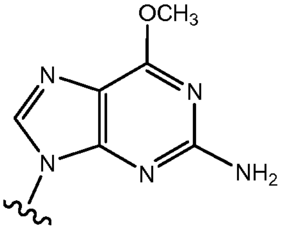

.

In still another embodiment, for the Compounds of Formula (I), (Ia) or (Ia'), B is:


.

In another embodiment, for the Compounds of Formula (I), (Ia) or (Ia'), B is: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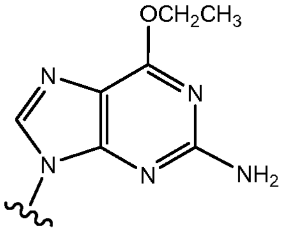
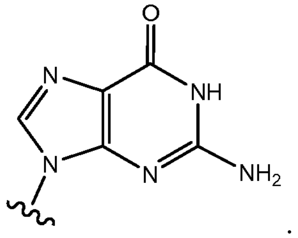
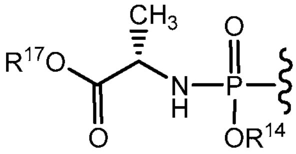

.

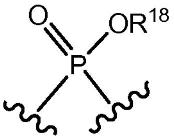
In another embodiment, for the Compounds of Formula (I), (Ia) or (Ia'), B is:



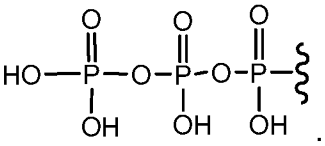
In one embodiment, for the Compounds of Formula (I), (Ia) or (Ia'), R^1 is H.

In another embodiment, for the Compounds of Formula (I), (Ia) or (Ia'), R^1 is H or

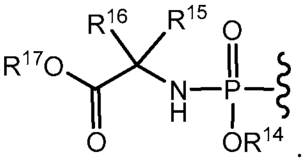
 or R^1 and R^2 join to form a group having the formula:

, wherein R^{14} is C_6-C_{10} aryl, which can be optionally substituted; R^{17} is C_1-C_6 alkyl, C_3-C_7 cycloalkyl or $-C_1$-C_3 alkylene-(C_6-C_{10} aryl); and R^{18} is C_1-C_6 alkyl, C_3-C_7 cycloalkyl or C_6-C_{10} aryl.

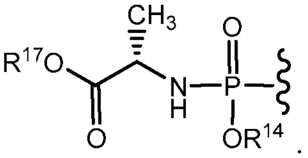
In another embodiment, for the Compounds of Formula (I), (Ia) or (Ia'), R^1 is:



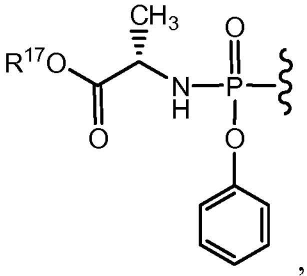
In still another embodiment, for the Compounds of Formula (I), (Ia) or (Ia'), R^1 is:



In another embodiment, for the Compounds of Formula (I), (Ia) or (Ia'), R^1 is:



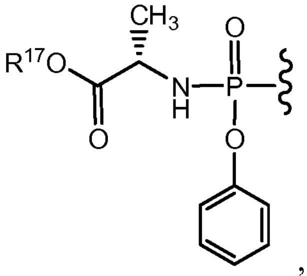
In another embodiment, for the Compounds of Formula (I), (Ia) or (Ia'), R^1 is:



, and R^{17} is C_1-C_6 alkyl,

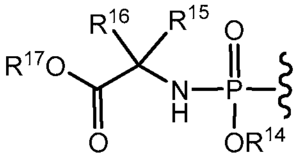
wherein the phenyl moiety can be optionally substituted with up to 2 halo groups, which can be the same or different.

In another embodiment, for the Compounds of Formula (I), (Ia) or (Ia'), R^1 is:



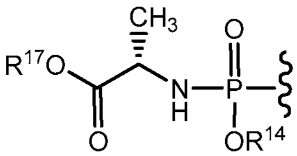
, and R^{17} is C_1-C_6 alkyl.

In yet another embodiment, for the Compounds of Formula (I), (Ia) or (Ia'), R^1 is:



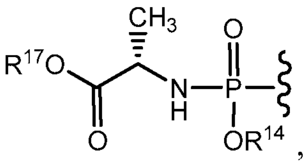
, wherein R^{14} is C_6-C_{10} aryl, which can be optionally substituted as set forth in claim 1; one of R^{15} and R^{16} is H and the other is C_1-C_6 alkyl; and R^{17} is C_1-C_6 alkyl.

In another embodiment, for the Compounds of Formula (I), (Ia) or (Ia'), R^1 is:



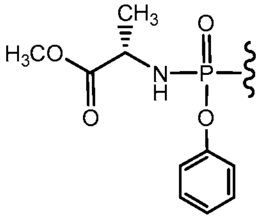
, wherein R^{14} is C_6-C_{10} aryl, which can be optionally substituted as set forth in claim 1; and R^{17} is C_1-C_6 alkyl.

In a further embodiment, for the Compounds of Formula (I), (Ia) or (Ia'), R^1 is:



, R^{14} is naphthyl or phenyl, wherein said phenyl group can be optionally substituted with up to 2 groups, each independently selected from Cl and F, or two groups on adjacent ring carbon atoms of said phenyl group can be joined by a group having the formula -O-CH_2-O-; and R^{17} is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, neopentyl, cyclobutyl, cyclopentyl, cyclohexyl or benzyl.

In another embodiment, for the Compounds of Formula (I), (Ia) or (Ia'), R^1 is: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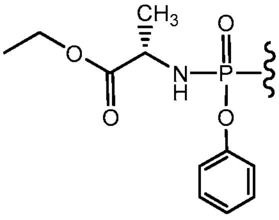
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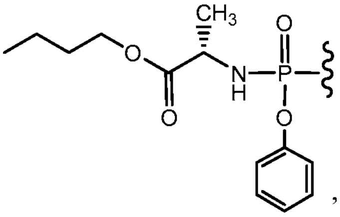
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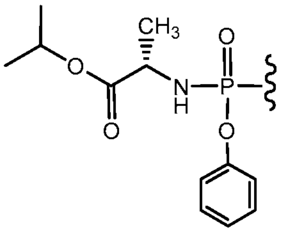
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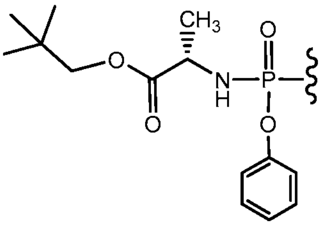
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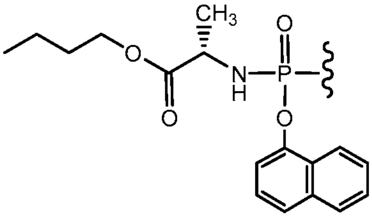
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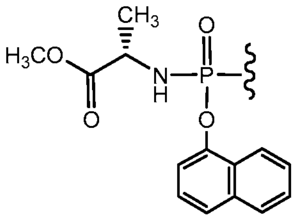
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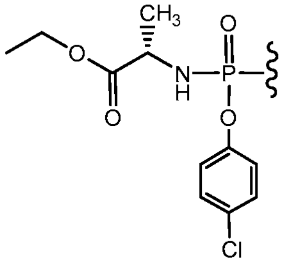
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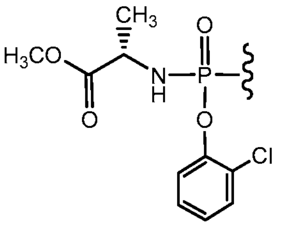

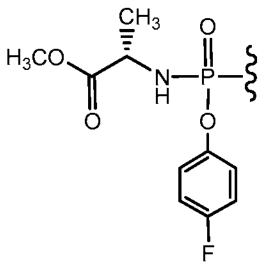

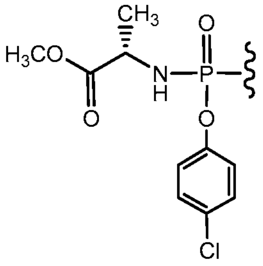
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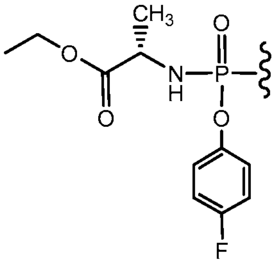
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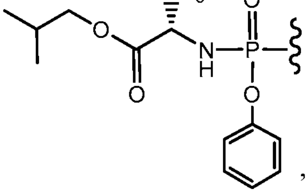
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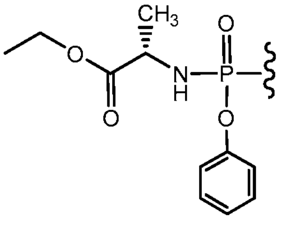
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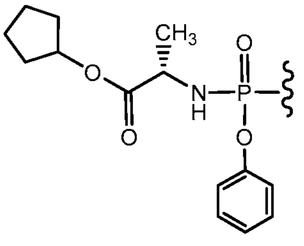
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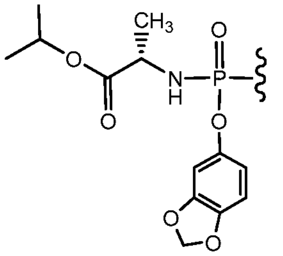
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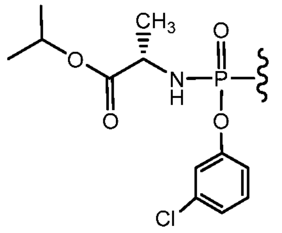
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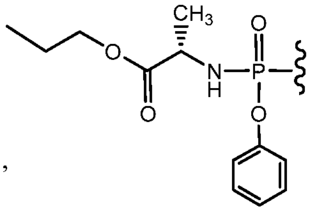
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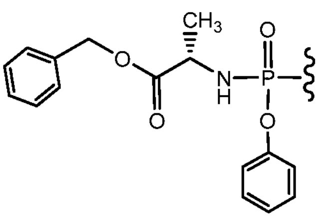
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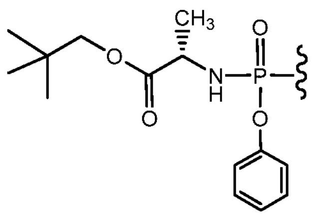
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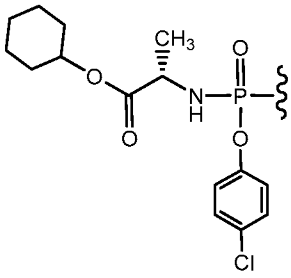
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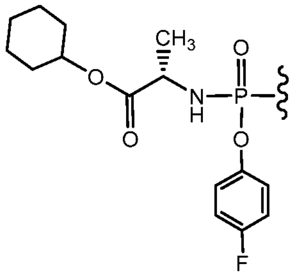
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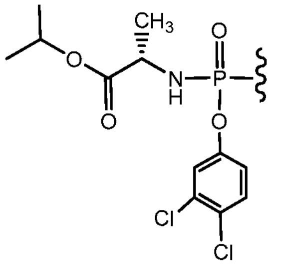
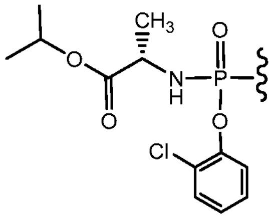
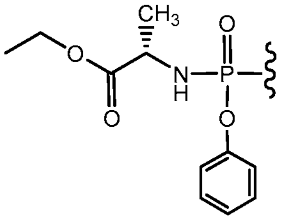
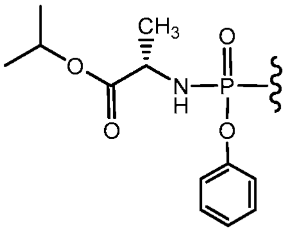

or

.

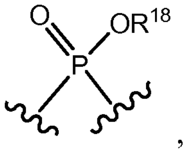
In another embodiment, for the Compounds of Formula (I), (Ia) or (Ia'), R^1 is:


or

.

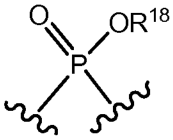
In one embodiment, for the Compounds of Formula (I), (Ia) or (Ia'), R^2 is H.

In one embodiment, for the Compounds of Formula (I), (Ia) or (Ia'), each of R^1 and R^2 is H.

In another embodiment, for the Compounds of Formula (I), (Ia) or (Ia'), R^1 and R^2 join to form a group having the formula:

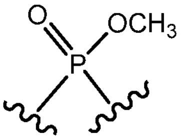

, wherein R^{18} is C_1-C_6 alkyl, C_3-C_7 cycloalkyl or C_6-C_{10} aryl.

In another embodiment, for the Compounds of Formula (I), (Ia) or (Ia'), R^1 and R^2 join to form a group having the formula:

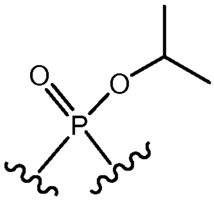
,

wherein R^{18} is methyl, n-propyl, isopropyl, cyclobutyl, cyclopentyl or phenyl.

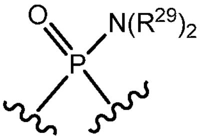
In still another embodiment, for the Compounds of Formula (I), (Ia) or (Ia'), R^1 and R^2 join to form a group having the formula:

.

In still another embodiment, for the Compounds of Formula (I), (Ia) or (Ia'), R^1 and R^2 join to form a group having the formula:

.

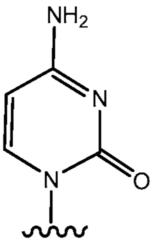
In one embodiment, for the Compounds of Formula (I), (Ia) or (Ia'), R^1 and R^2 join to form a group having the formula:

.

In one embodiment, for the Compounds of Formula (I), (Ia) or (Ia'),

R^2 is H;

B is: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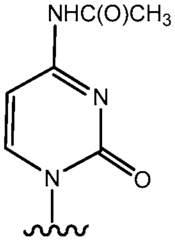
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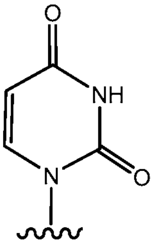
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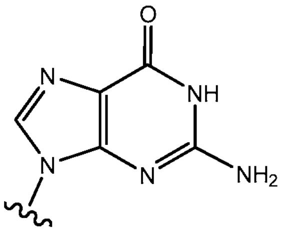
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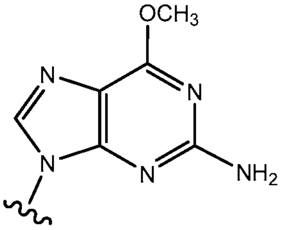
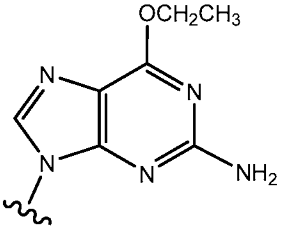
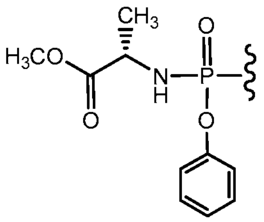

or

; and

R^1 is:



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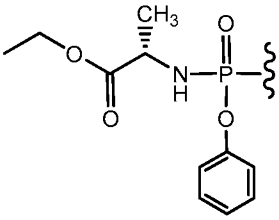

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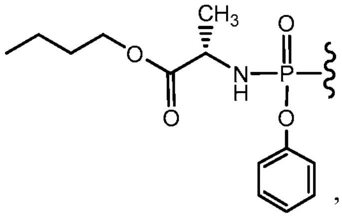

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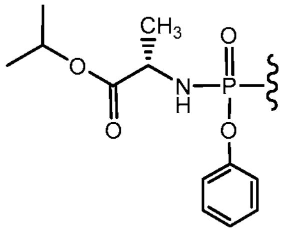

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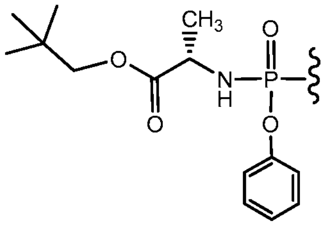

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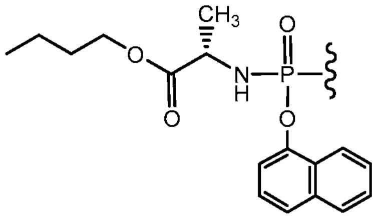

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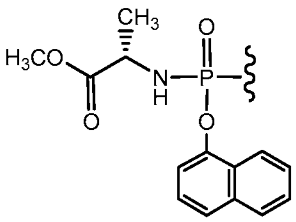

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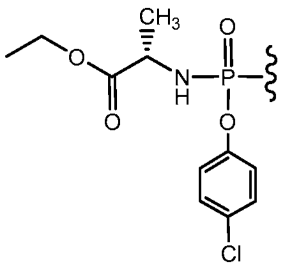

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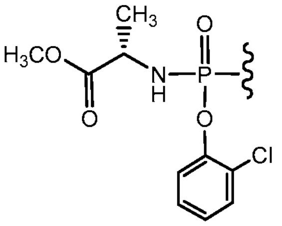

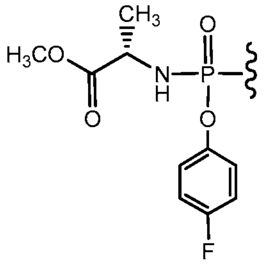

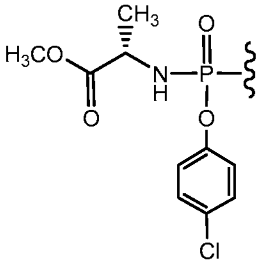

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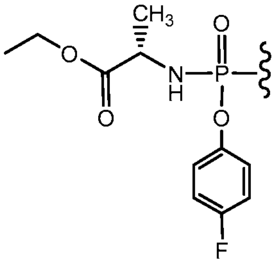

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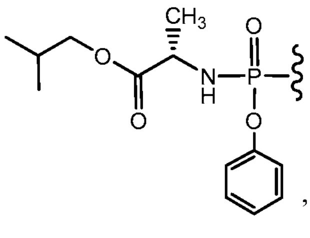

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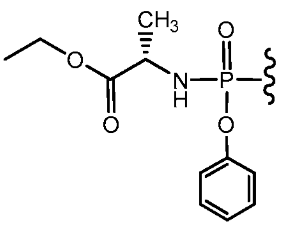

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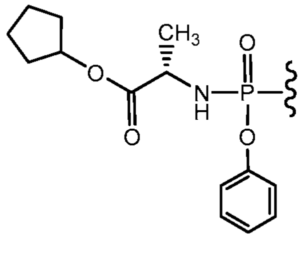

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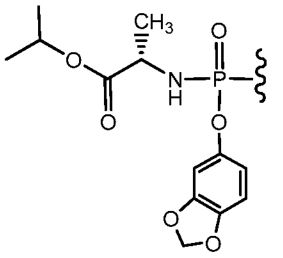
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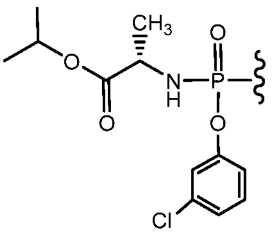
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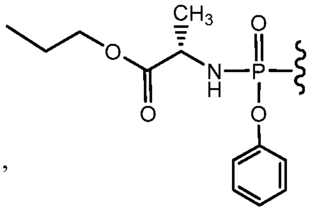
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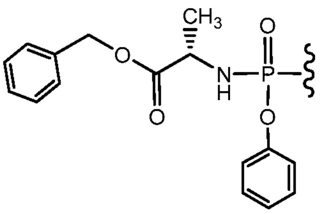
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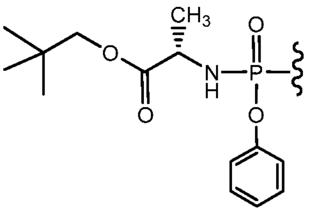
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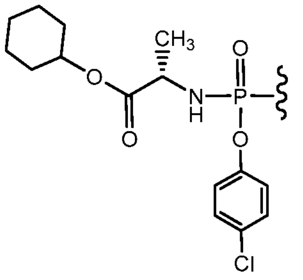
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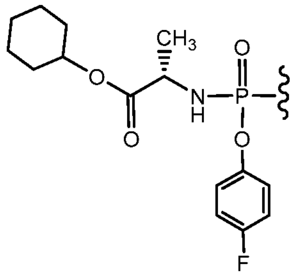
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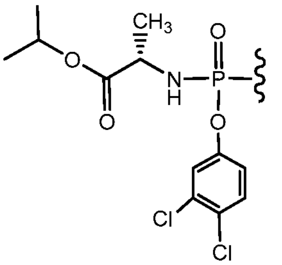
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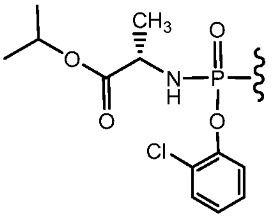
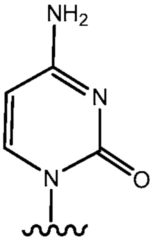

.

In another embodiment, for the Compounds of Formula (I), (Ia) or (Ia'),

R^2 is H;

B is: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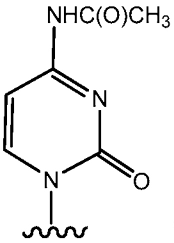
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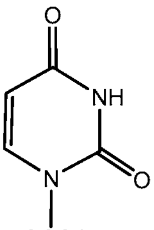
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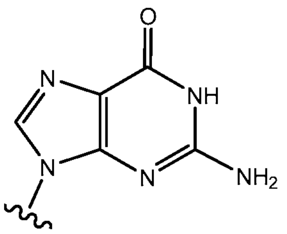
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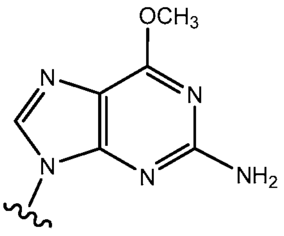
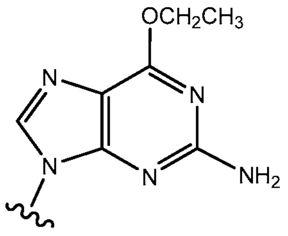
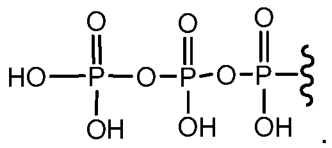
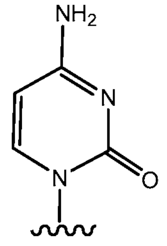

or

; and

R^1 is:



$HO-P(=O)(OH)-O-P(=O)(OH)-O-P(=O)(OH)-$.

In another embodiment, for the Compounds of Formula (I), (Ia) or (Ia'), B is:



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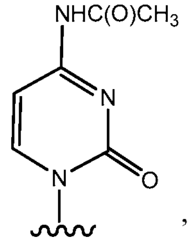

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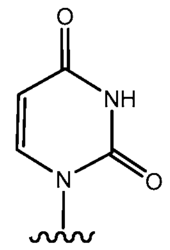

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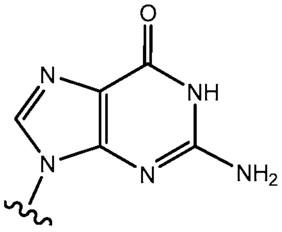

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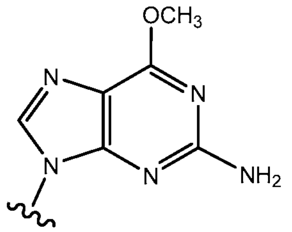

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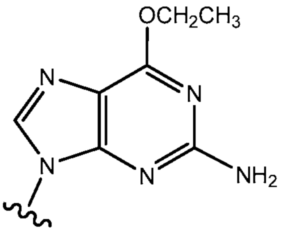
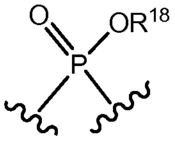


; and

R^1 and R^2 join to form a group having the formula:



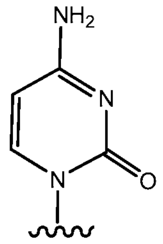
,

wherein R^{18} is methyl, n-propyl, isopropyl, cyclobutyl, cyclopentyl or phenyl.

.

In still another embodiment, for the Compounds of Formula (I), (Ia) or (Ia'), R^1 and R^2 are each H; and

B is:



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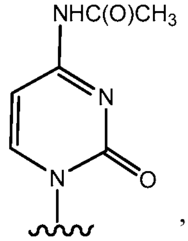

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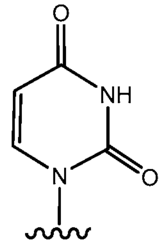

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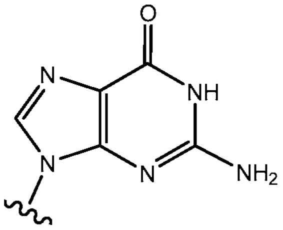

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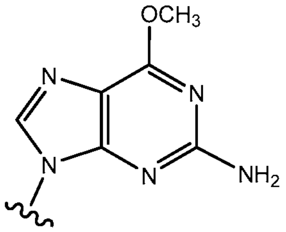
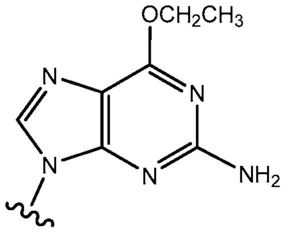
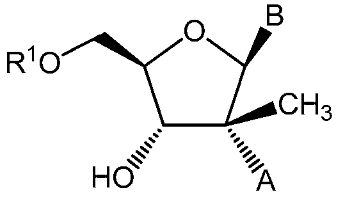


or



.

In one embodiment, the Compounds of Formula (I) have the formula (Ib):



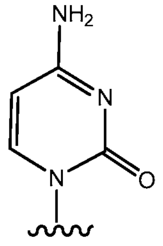
(Ib)

or a pharmaceutically acceptable salt thereof,

wherein:

A is C_2-C_6 alkynyl or $-NH_2$;

B is:



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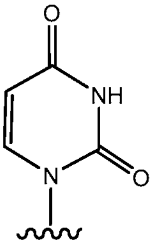
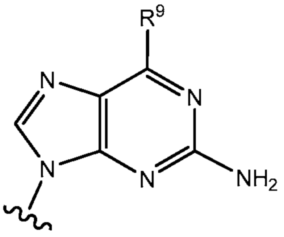
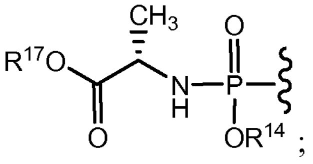


or



;

R^1 is:



;

R^9 is –OH or $-O-(C_1-C_6$ alkyl);

R^{14} is phenyl, which can be optionally substituted with up to 2 halo groups, which can be the same or different; and

R^{17} is C_1-C_6 alkyl.

In one embodiment, for the Compounds of Formula (Ib), A is C_2-C_6 alkynyl.

In another embodiment, for the Compounds of Formula (Ib), A is -C≡CH.

In another embodiment, for the Compounds of Formula (Ib), A is $-NH_2$.

In one embodiment, for the Compounds of Formula (Ib), R^{14} is unsubstituted phenyl.

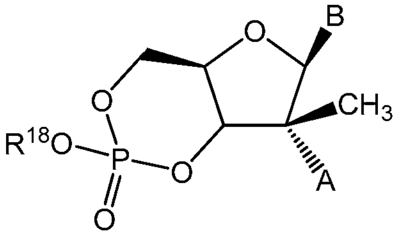
In another embodiment, for the Compounds of Formula (Ib), R^{17} is ethyl or isopropyl.

In one embodiment, for the Compounds of Formula (Ib), R^{14} is unsubstituted phenyl and R^{17} is ethyl or isopropyl.

In another embodiment, for the Compounds of Formula (Ib), R^{14} is unsubstituted phenyl and R^{17} is ethyl.

In still another embodiment, for the Compounds of Formula (Ib), R^{14} is unsubstituted phenyl and R^{17} is isopropyl.

In one embodiment, the Compounds of Formula (I) have the formula (Ib):



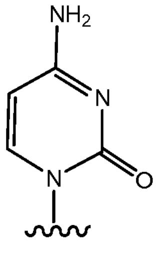
(Ic)

or a pharmaceutically acceptable salt thereof,

wherein:

A is C_2-C_6 alkynyl or $-NH_2$;

B is:



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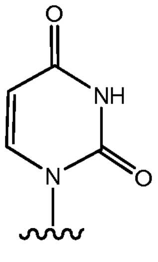
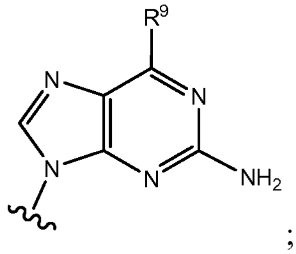


or



; and

R^{18} is aryl or C_1-C_6 alkyl.

In one embodiment, for the Compounds of Formula (Ic), A is C_2-C_6 alkynyl.

In another embodiment, for the Compounds of Formula (Ic), A is -C≡CH.

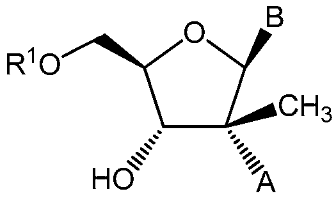
In another embodiment, for the Compounds of Formula (Ic), A is $-NH_2$.

In one embodiment, for the Compounds of Formula (Ib), R^{18} is C_1-C_6 alkyl.

In another embodiment, for the Compounds of Formula (Ic), R^{18} is isopropyl.

In another embodiment, for the Compounds of Formula (Ic), R^{18} is methyl.

In one embodiment, the Compounds of Formula (I) have the formula (Id):



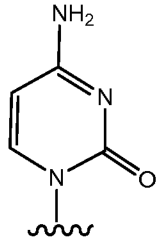
(Id)

or a pharmaceutically acceptable salt thereof,

wherein:

A is C_2-C_6 alkynyl or $-NH_2$;

B is:



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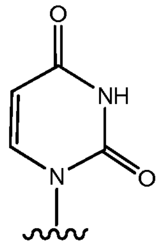

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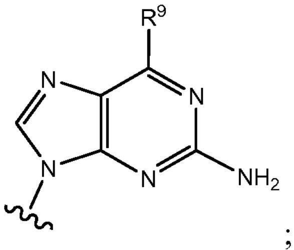

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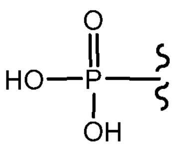
R^1 is:



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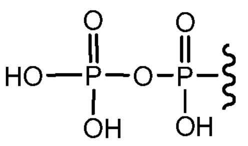

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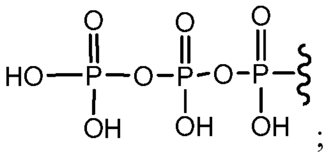
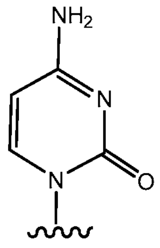


; and

R^9 is –OH or -O-(C_1-C_6 alkyl).

In one embodiment, for the Compounds of Formula (Ib), (Ic) or (Id), B is



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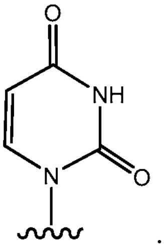
In another embodiment, for the Compounds of Formula (Ib), (Ic) or (Id), B is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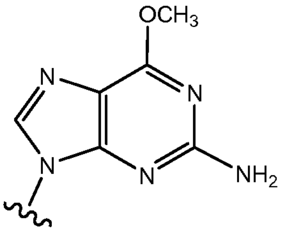
In another embodiment, for the Compounds of Formula (Ib), (Ic) or (Id), B is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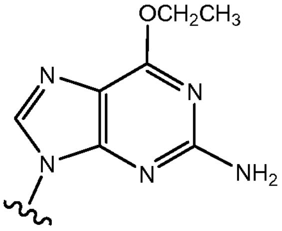
In another embodiment, for the Compounds of Formula (Ib), (Ic) or (Id), B is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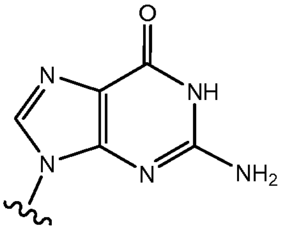
In another embodiment, for the Compounds of Formula (Ib), (Ic) or (Id), B is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In one embodiment, variables A, B, X, R^1, R^2 and R^3 for the Compounds of Formula (I) are selected independently of each other.

In another embodiment, for the Compounds of Formula (I) are in substantially purified form.

Other embodiments of the present invention include the following:

(a) A pharmaceutical composition comprising an effective amount of a Compound of Formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

(b) The pharmaceutical composition of (a), further comprising a second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

(c) The pharmaceutical composition of (b), wherein the HCV antiviral agent is an antiviral selected from the group consisting of HCV protease inhibitors, HCV NS5B polymerase inhibitors and HCV NS5A inhibitors.

(d) A pharmaceutical combination that is (i) a Compound of Formula (I) and (ii) a second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents; wherein the Compound of Formula (I) and the second therapeutic agent are each employed in an amount that renders the combination effective for inhibiting HCV replication, or for treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection.

(e) The combination of (d), wherein the HCV antiviral agent is an antiviral selected from the group consisting of HCV protease inhibitors, HCV NS5B polymerase inhibitors, and HCV NS5A inhibitors.

(f) A method of inhibiting HCV replication in a subject in need thereof which comprises administering to the subject an effective amount of a Compound of Formula (I).

(g) A method of treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection in a subject in need thereof which comprises administering to the subject an effective amount of a Compound of Formula (I).

(h) The method of (g), wherein the Compound of Formula (I) is administered in combination with an effective amount of at least one second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

(i) The method of (h), wherein the HCV antiviral agent is an antiviral selected from the group consisting of HCV protease inhibitors, HCV NS5B polymerase inhibitors and HCV NS5A inhibitors.

(j) A method of inhibiting HCV replication in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b) or (c) or the combination of (d) or (e).

(k) A method of treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b) or (c) or the combination of (d) or (e).

The present invention also includes a compound of the present invention for use (i) in, (ii) as a medicament for, or (iii) in the preparation of a medicament for: (a) medicine, (b) inhibiting HCV replication or (c) treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection. In these uses, the compounds of the present invention can optionally be employed in combination with one or more second therapeutic agents selected from HCV antiviral agents, anti-infective agents, and immunomodulators.

Additional embodiments of the invention include the pharmaceutical compositions, combinations and methods set forth in (a)-(k) above and the uses set forth in the preceding paragraph, wherein the compound of the present invention employed therein is a compound of one of the embodiments, aspects, classes, sub-classes, or features of the compounds described above. In all of these embodiments, the compound may optionally be used in the form of a pharmaceutically acceptable salt or hydrate as appropriate. It is understood that references to compounds would include the compound in its present form as well as in different forms, such as polymorphs, solvates and hydrates, as applicable.

In one embodiment, the present invention includes the use of a compound of the present invention, or a pharmaceutically acceptable salt thereof, in a pharmaceutical composition for inhibiting HCV NS5A activity or for preventing and/or treating infection by HCV in a patient in need thereof.

It is further to be understood that the embodiments of compositions and methods provided as (a) through (k) above are understood to include all embodiments of the compounds, including such embodiments as result from combinations of embodiments.

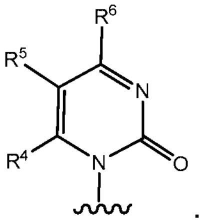
The Compounds of Formula (I) may be referred to herein by chemical structure and/or by chemical name. In the instance that both the structure and the name of a Compound of Formula (I) are provided and a discrepancy is found to exist between the chemical structure and the corresponding chemical name, it is understood that the chemical structure will predominate.

Non-limiting examples of the Compounds of Formula (I) include compounds **1-99** as set forth in the Examples below, and pharmaceutically acceptable salts thereof.

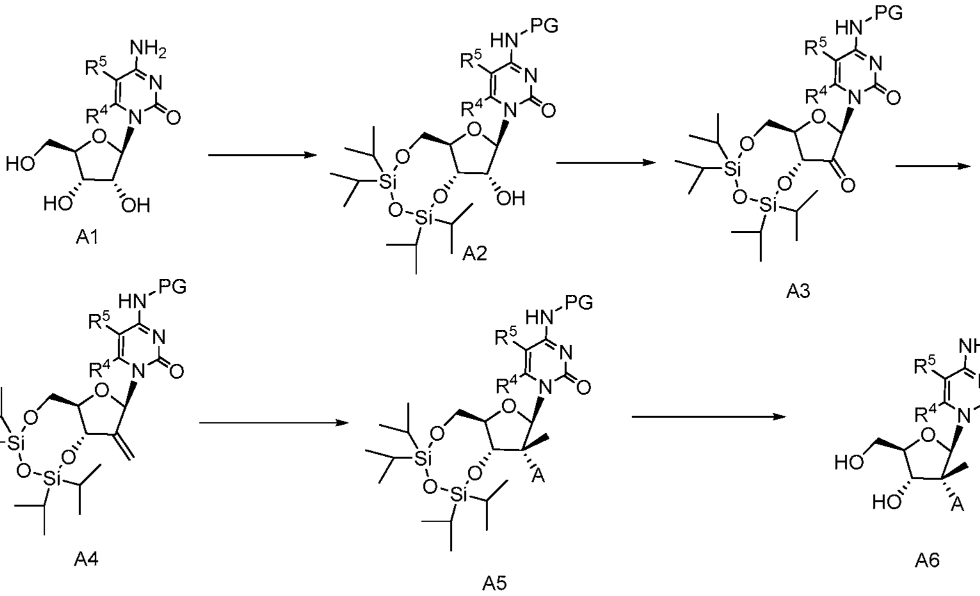
Methods for Making the Compounds of Formula (I)

The Compounds of Formula (I) may be prepared from known or readily prepared starting materials, following methods known to one skilled in the art of organic synthesis. Methods useful for making the Compounds of Formula (I) are set forth in the Examples below and generalized in Schemes A-S below. Alternative synthetic pathways and analogous structures will be apparent to those skilled in the art of organic synthesis.

Scheme A shows a method useful for making nucleoside compounds of formula **A6**, which correspond to the Compounds of Formula (I), wherein X is O; R^1 and R^2 are each H; R^3 is methyl and B is:



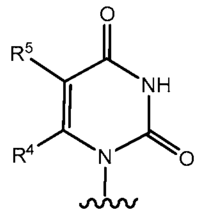
Scheme A



Wherein PG is a protecting group and A, R^4 and R^5 are as defined above for the Compounds of Formula (I).

Nucleoside compounds of formula **A1** can be bis-protected at the ribose 3' and 5' positions using the tetraisopropyldisiloxanyl group to provide compounds of formula **A2**. Compounds of formula **A2** are then oxidized, using for example, the Dess-Martin Periodinane, to provide the 2'-ketone of formula **A3**. Wittig olefination with methyltriphenylphosphonium bromide/potassium hexamethyldisilazide provides compounds of formula **A4**. The olefin moiety of the compounds of formula **A4** can be manipulated using methods well-known to those skilled in the art of organic synthesis to provide the 2'-substituted compounds of formula **A5**. The silyl protecting group is then removed using tetrabutylammonium fluoride and the cytidine protecting group is then removed with methanolic ammonia to provide the compounds of formula **A6**.

Scheme B shows a method useful for making nucleoside compounds of formula **B6**, which correspond to the Compounds of Formula (I), wherein X is O; R^1 and R^2 are each H; R^3 is methyl and B is:



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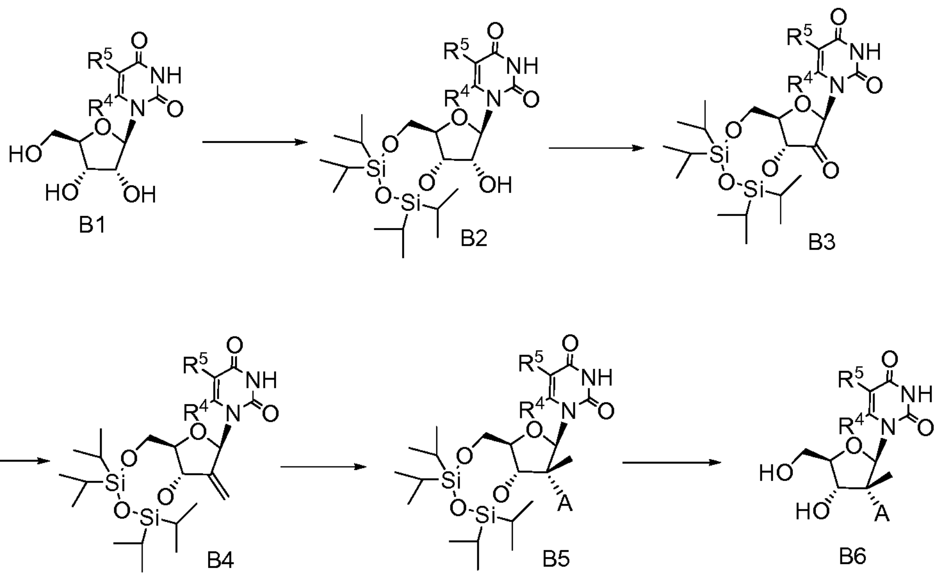
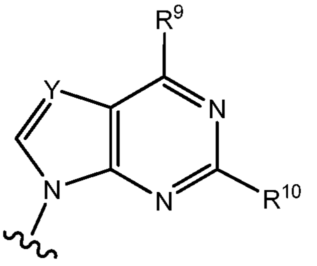
Scheme B



Wherein A, R^4 and R^5 are as defined above for the Compounds of Formula (I).

Compounds of formula **B1** were protected at the ribose 3' and 5' positions using the tetraisopropyldisiloxanyl group to provide compounds of formula **B2**. Compounds of formula **B2** were treated with Dess-Martin Periodinane to provide the desired 2'-ketone of formula **B3**. Wittig olefination with methyltriphenylphosphonium bromide/potassium hexamethyldisilazide provided compounds of formula **B4**. The olefin moiety of the compounds of formula **B4** can be manipulated using methods well-known to those skilled in the art of organic synthesis to provide the 2'-substituted compounds of formula **B5**. The tetraisopropyldisiloxanyl protecting group is then removed using tetrabutylammonium fluoride to provide the compounds of formula **A6**.

Scheme C shows a method useful for making nucleoside compounds of formula **C9**, which correspond to the Compounds of Formula (I), wherein X is O; R^1 and R^2 are each H; R^3 is methyl and B is:



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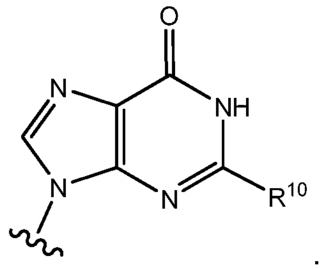

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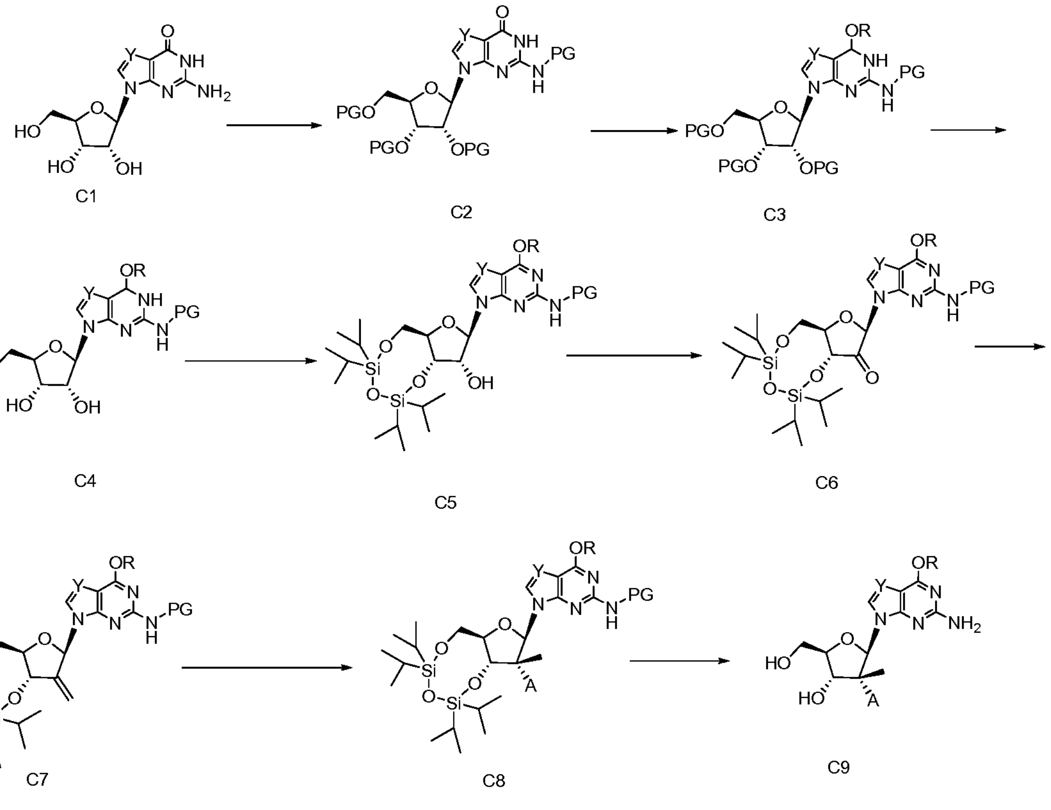
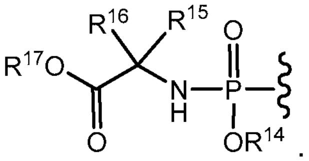
Scheme C



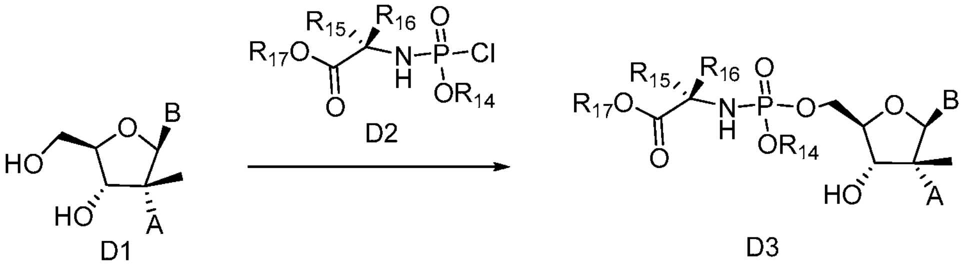
Wherein PG is a protecting group and R^4 and R^5 are as defined above for the Compounds of Formula (I).

A compound of formula **C1** can have all of its hydroxyl groups protected using well known methods to provide the compounds of formula **C2**. A compound of formula **C2** can then be subjected to Mitsunobu conditions to provide purine ethers of formula **C3**. The hydroxyl groups of C3 are then deprotecting to provide the compounds of formula **C4**, which can subsequently have their 3'-OH and 5'-OH protected using the tetraisopropyldisiloxanyl group to provide the compounds of formula **C5**. Compounds of formula **C5** are then oxidized, using for example, the Dess-Martin Periodinane, to provide the 2'-ketone compounds of formula **C6**. Wittig olefination with methyltriphenylphosphonium bromide/potassium hexamethyldisilazide provides the compounds of formula **C7**. The olefin moiety of the compounds of formula **C7** can be manipulated using methods well-known to those skilled in the art of organic synthesis to provide the 2'-substituted compounds of formula **C8**. The tetraisopropyldisiloxanyl protecting group is then removed using tetrabutylammonium fluoride, followed by deprotection of the protected aryl amine group to provide the compounds of formula **C9**.

Scheme D shows a method useful for making nucleoside compounds of formula **D3**, which correspond to the Compounds of Formula (I), wherein X is O; R^2 is H; R^3 is methyl; B is as defined above for the Compounds of Formula (I); and R^1 is:



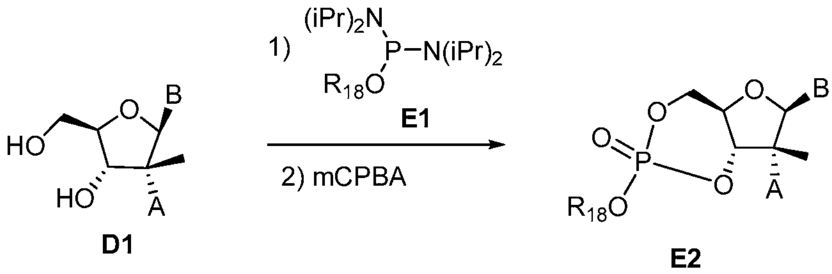
Scheme D



Wherein B, R^{14}, R^{15}, R^{16} and R^{17} are as defined above for the Compounds of Formula (I).

A compound of formula **D1** can be coupled with a compound of formula **D2** (compounds of formula **D2** can be synthesized using methods described in US Patent No. 7,879,815) in the presence of either t-butylmagnesium bromide or N-methylimidazole to provide the compounds of formula **D3**.

Scheme E

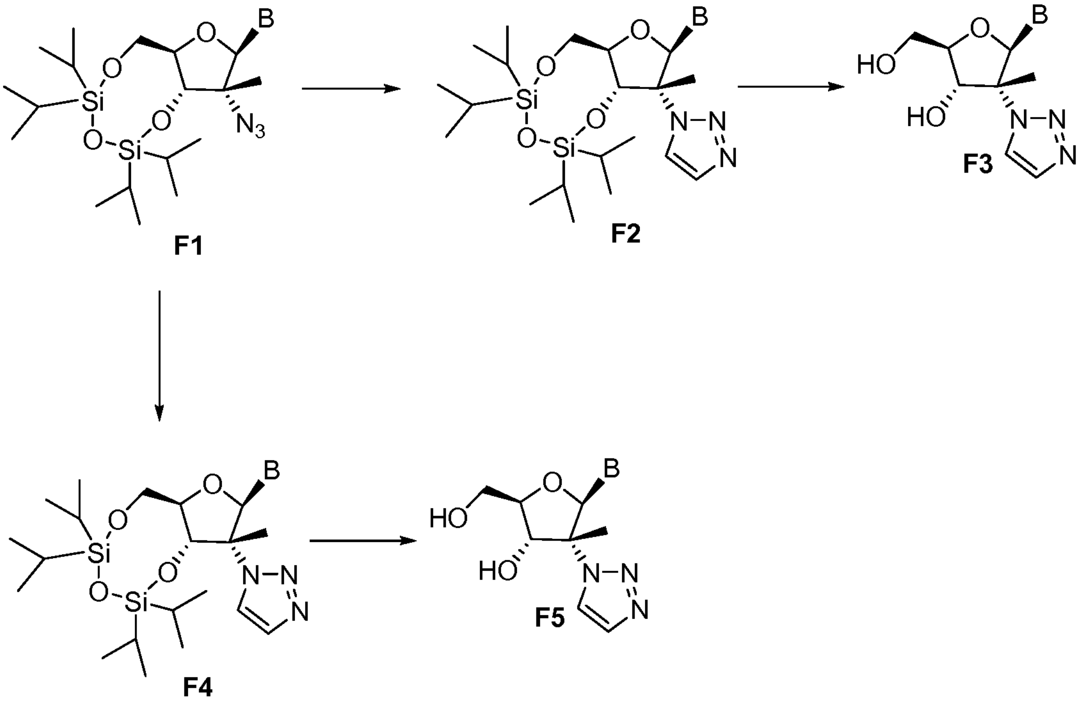


Wherein B and R^{18} are as defined above for the Compounds of Formula (I).

A compound of formula **D1** can be reacted with a phosphoramidate compound of formula **E1**, followed by oxidation with, for example m-chloroperoxybenzoic acid, to provide a cyclic phosphate ester of formula **E2**.

Scheme F shows a method useful for making nucleoside compounds of formula **F3**, which correspond to the Compounds of Formula (I) wherein A is triazolyl or tetrazolyl.

Scheme F

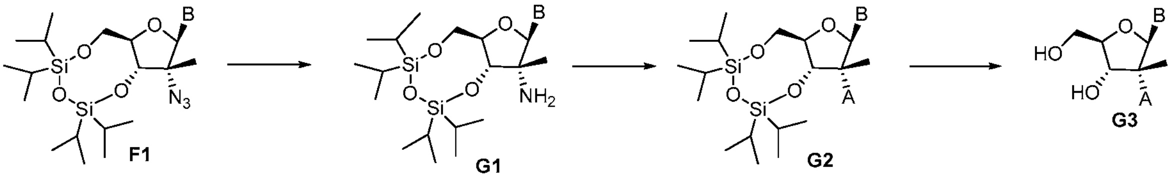


Wherein A is heteroaryl and B is defined above for the Compounds of Formula (I).

Compounds of formula **F1** can be treated with refluxing vinyl acetates to provide the triazole intermediates of formula **F2.** These triazoles can be functionalized depending on the substitution pattern of the vinyl acetate. Removal of the silyl protecting group using tetrabutylammonium fluoride provides the triazole compounds of formula **F3**. Alternatively, a compound of formula **F1** can be treated with a nitrile in order to provide to provide the tetrazole intermediates of formula **F4.** These tetrazoles can be functionalized depending on the substitution pattern of the nitrile. Removal of the silyl protecting group using tetrabutylammonium fluoride provides the tetrazole compounds of formula **F5**.

Scheme G shows a method useful for making nucleoside compounds of formula **G3**, which correspond to the Compounds of Formula (I) wherein A is -N(R^{20})$_2$, -NHSO$_2$-(C_1-C_6 alkyl), -NHC(O)N(R^{20})$_2$, -NHOH, -NHC(O)R^{20} or -NHC(O)OR^{20}.

Scheme G

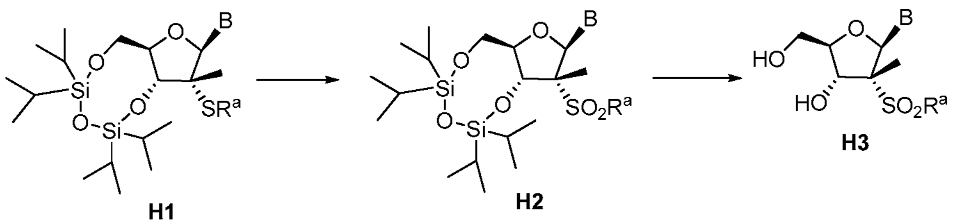


Wherein A is -N(R^{20})$_2$, -NHSO$_2$-(C_1-C_6 alkyl), -NHC(O)N(R^{20})$_2$, -NHOH, -NHC(O)R^{20} or -NHC(O)OR^{20}, and R^{20} and B are as defined above for the Compounds of Formula (I).

An azide compound of formula **F1** can be hydrogenated using for example, palladium catalysis in the presence of hydrogen gas, to provide the corresponding amine derivatives of formula **G1**. The amine group of a compound of formula **G1** can then converted to a variety of functional groups using methods and reagents (such as acyl chlorides, isocyanates and chloroformates) well-known to those skilled in the art of organic synthesis to provide the compound of formula **G2**. These compounds were then silyl deprotected using tetrabutylammonium fluoride to provide the compounds of type **G3**, which correspond to the Compounds of Formula (I) wherein A is -N(R^{20})$_2$, -NHSO$_2$-(C_1-C_6 alkyl), -NHC(O)N(R^{20})$_2$, -NHOH, -NHC(O)R^{20} or -NHC(O)OR^{20}.

Scheme H shows a method useful for making nucleoside compounds of formula **H3**, which correspond to the Compounds of Formula (I) wherein A is –SO$_2$-(C_1-C_6 alkyl).

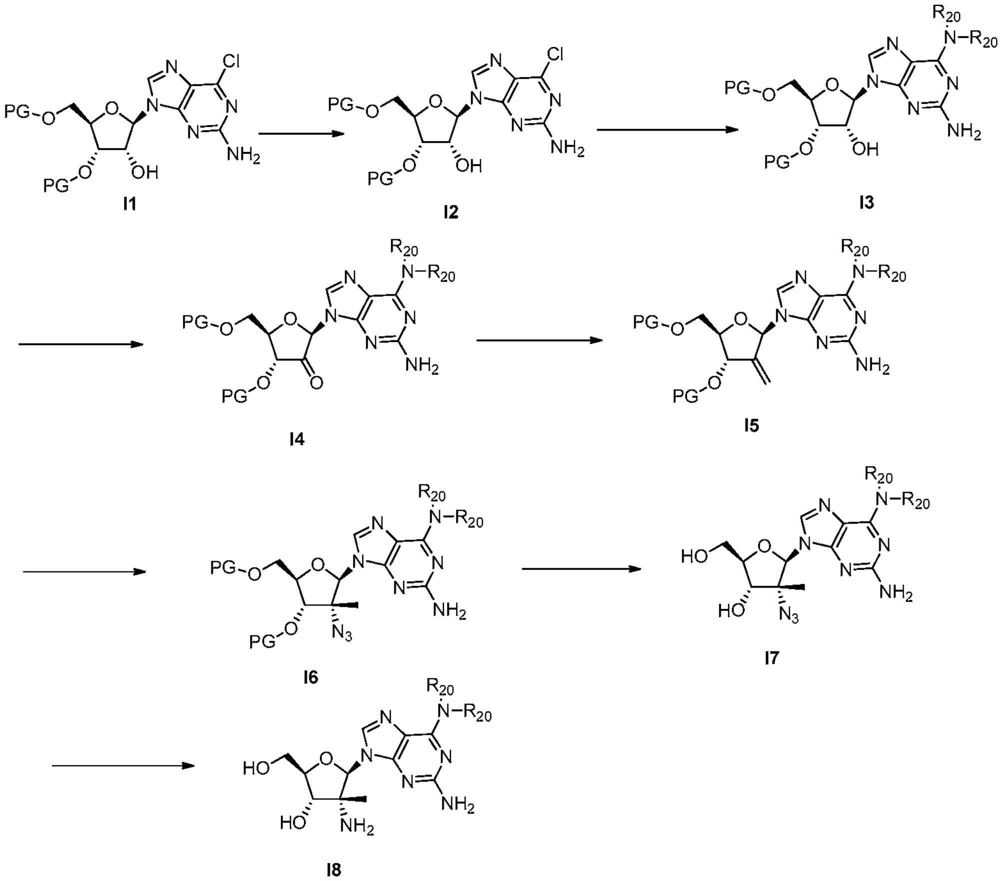
Scheme H



Wherein R^a is C_1-C_6 alkyl and is heteroaryl and B is defined above for the Compounds of Formula (I).

Thiol compounds of formula **H1** can be reacted with meta-chloroperoxybenzoic acid to produce the corresponding sulfones of formula **H2**. These compounds were then silyl deprotected using tetrabutylammonium fluoride to provide the compounds of type **H3**, which correspond to the Compounds of Formula (I) wherein A is A is $-SO_2-(C_1-C_6$ alkyl).

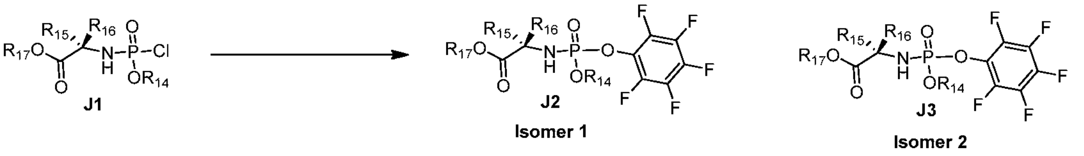
Scheme I

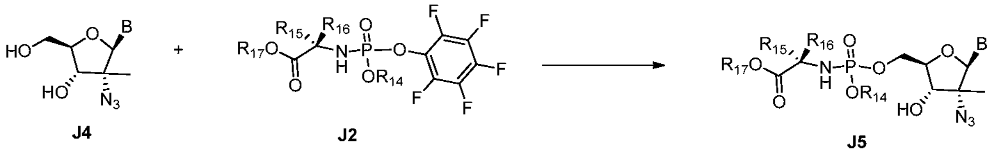


Wherein and R^{20} is as defined above for the Compounds of Formula (I).

A compound **I1** can be preferentially protected to provide compound **I2** which can then be reacted with a variety of amines to give access to compounds of type **I3**. Oxidation of the 2'-OH using a reagent such as Dess Martin Periodinane provides **I4**. Wittig olefination followed by a stereoselective hydroazidation reaction gives access to **I6**. Global deprotection followed by reduction of the azido using hydrogenolysis gives the final compound **I8**.

Scheme J

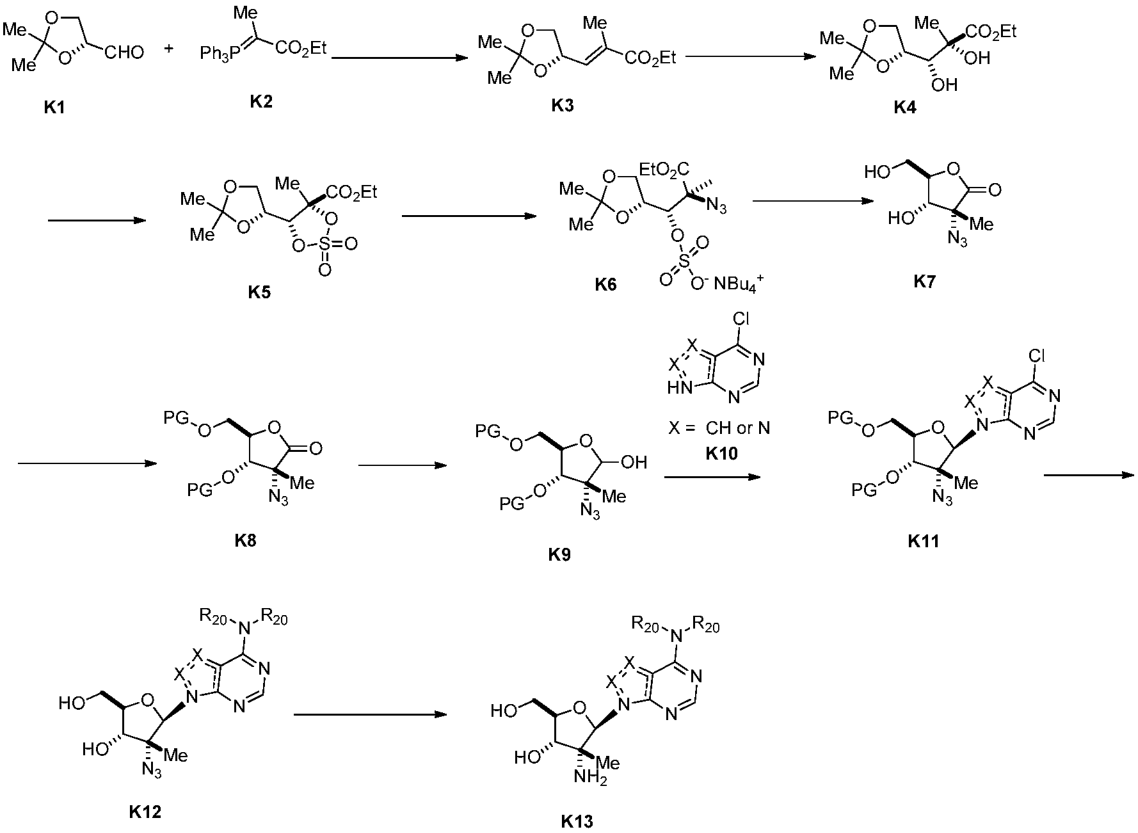




Wherein B, R^{14}, R^{15}, R^{16} and R^{17} are as defined above for the Compounds of Formula (I).

A compound **J1** can be reacted with pentafluoro phenol to produce two isomers **J2** and **J3**. These isomers can be individually reacted with **J4** to produce compounds of structure **J5**.

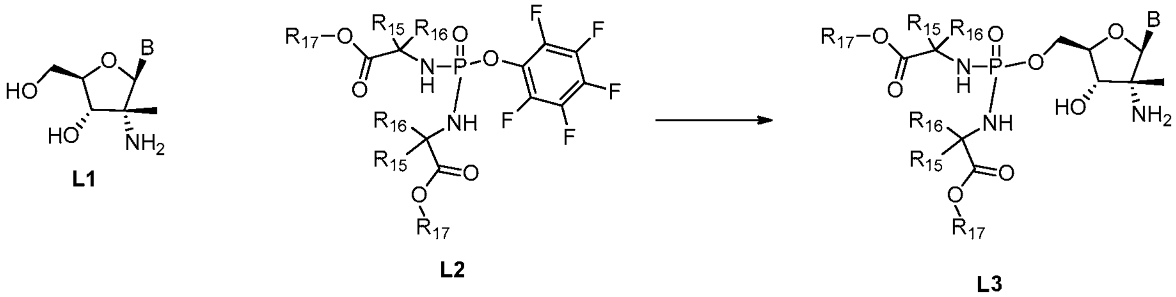
Scheme K



Wherein R^{20} is as defined above for the Compounds of Formula (I).

Compound **K1** can be reacted with **K2** to provide **K3**. This compound can be dihydroxylated with appropriate reagents to provide compound **K4**. Sulfonylation of the alcohols using sulfuryl chloride provides compound **K5**. The cyclic sulfate can be opened using azide sources to provide **K6**. Treatement of compound **K6** with acidic conditions provides compound **K7**. The diol of **K7** can be protected with a variety of protecting groups to access **K8**. Lactone **K8** can be reduced to the corresponding lactol **K9** using a reagent such as lithium aluminum t-butoxy hydride. This lactol can react with **K10** under Mitsunobu conditions to provide **K11** which can be subject to ammonia to provide the nucleoside analog **K12**. Reduction of the azido group can be achieved using hydrogenation to provide compound **K13**.

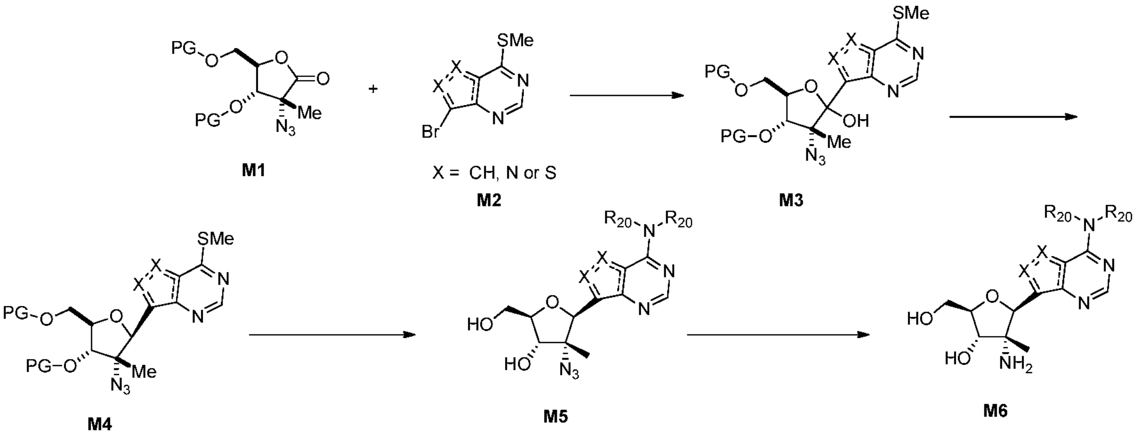
Scheme L



Wherein B, R^{15}, R^{16}, R^{17} and R^{20} are as defined above for the Compounds of Formula (I).

Compounds of type **L1** can react with compounds of type **L2** to provide compounds of type **L3**.

Scheme M

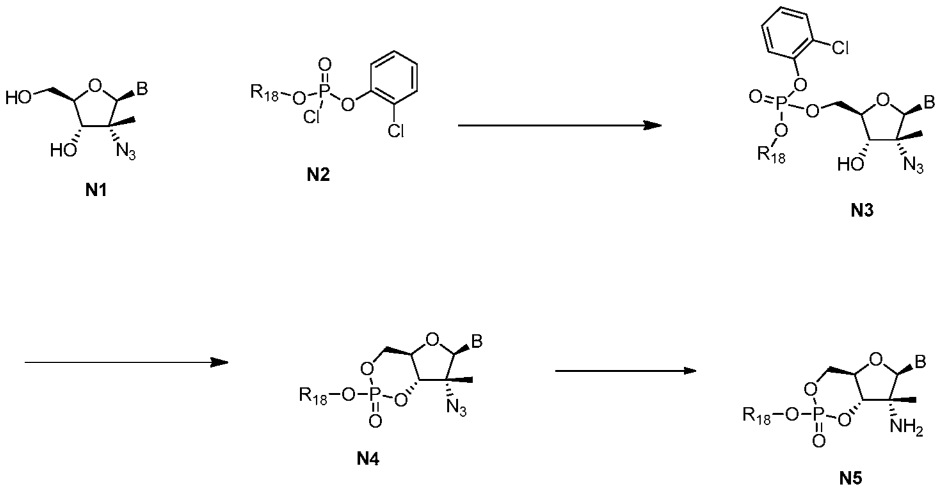


Wherein R^{20} is as defined above for the Compounds of Formula (I).

Compound **M1** (synthesized as described in Scheme K) can be reacted with **M2** to provide **M3**. This compound can be dihydroxylated with appropriate reagents to provide compound **M4**. Sulfonylation of the alcohols using sulfuryl chloride provides compound **M5**.

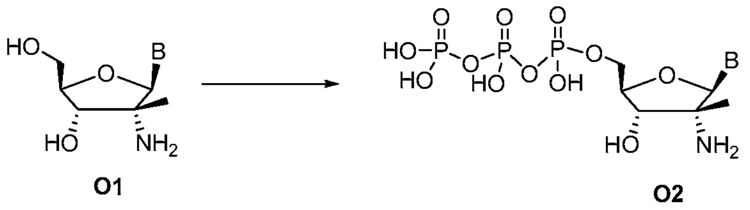
The cyclic sulfate can be opened using azide sources to provide **M6**. Treatement of compound **M6** with acidic conditions provides compound **M7**. The diol of **M7** can be protected with a variety of protecting groups to access **M8**. Treatment of **M2** with n-BuLi followed by the addition of **M1** gives access to **M3**. The 1'-hydroxy group can be removed to provide **M4** which can then be globally deprotected to provide nucleoside **M5**. Reduction of the azido group can be achieved using hydrogenation to provide compound **M6**.

Scheme N



Compounds of type **N1** (synthesis described in Scheme A) can be treated with **N2** (synthesized by the treatment of commercially available 2-chlorophenyl phosphorodichloridate with a variety of alcohols in the presence of 2,6 lutidine) provide compounds of type **N3**. **N3** can be treated with bases such as potassium t-butoxide to induce cyclization to form compounds such as **N4**. Reduction of the azido group can be achieved using hydrogenation to provide compound **N5.**

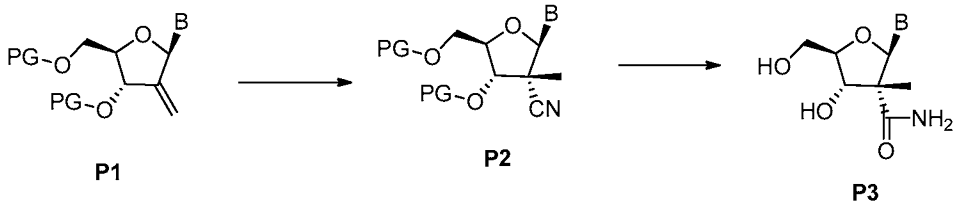
Scheme O



Wherein B is as defined above for the Compounds of Formula (I).

Nucleosides such as **O1** (synthesis described in example G) can be converted to the triphosphate **O2** by treatment with phosphorus oxychloride followed by pyrophosphate.

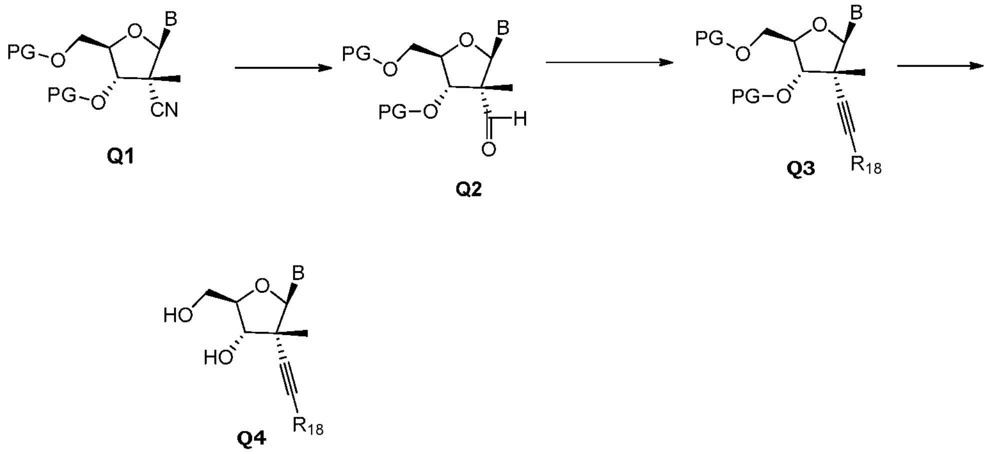
Scheme P



Wherein B is as defined above for the Compounds of Formula (I).

Compounds of type **P1** (synthesized as described in Schemes A-C) can be converted to compounds of type **P2** by a cobalt-catalyzed hydrocyanation reaction. **P2** can then be converted to **P3** using HCl in methanol.

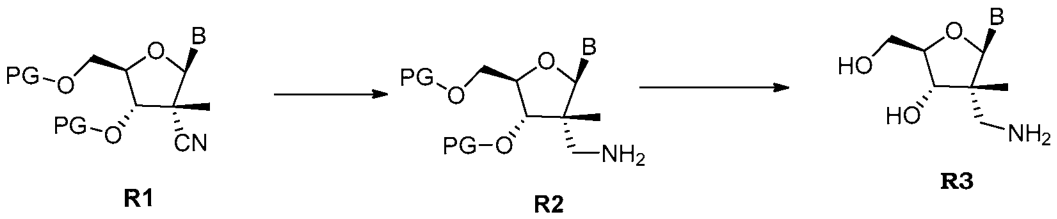
Scheme Q



Wherein B and R^{18} are as defined above for the Compounds of Formula (I).

Compounds of type **Q1** (synthesis described in Scheme P) can be treated with a variety of hydride sources to provide compound **Q2**. **Q2** can be converted to the alkyne **Q3** which can then be globally deprotected to provide **Q4**.

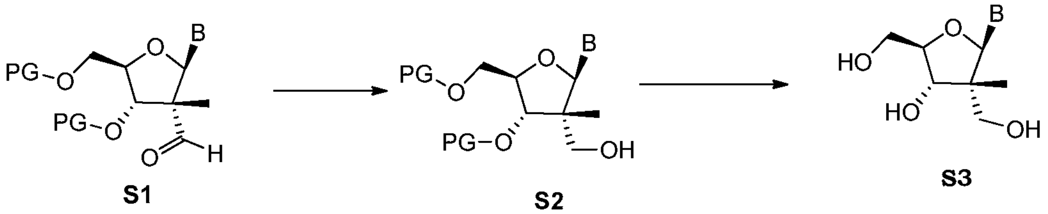
Scheme R



Wherein B is as defined above for the Compounds of Formula (I).

Compounds of type **R1** (synthesis described in Scheme P) can be treated with hydride sources such as DIBAL-H to provide compounds of type **R2**. Global deprotection provides **R3**.

Scheme S



Wherein B is as defined above for the Compounds of Formula (I).

Compounds of type **S1** (synthesis described in Scheme Q) can be reduced using hydride reagents such as sodium borohydride to produce **S2**. Global deprotection provides compound **S3**.

Compounds of formula **A6**, **B6**, **C9**, **D3**, **E2**, **F3**, **G3**, **H3**, **I8**, **J5**, **K13**, **L3**, **M6**, **N5**, **O2**, **P3**, **Q4**, **R3** and **S3** may be further elaborated using methods that are be well-known to those skilled in the art of organic synthesis or, for example, the methods described in the Examples below, to make the full scope of the Compounds of Formula (I).

One skilled in the art of organic synthesis will recognize that the synthesis of compounds with multiple reactive functional groups, such as –OH and NH_2, may require protection of certain functional groups (*i.e.*, derivatization for the purpose of chemical compatibility with a particular reaction condition). Suitable protecting groups for the various functional groups of these compounds and methods for their installation and removal are well known in the art of organic chemistry. A summary of many of these methods can be found in Greene

One skilled in the art of organic synthesis will also recognize that one route for the synthesis of the Compounds of Formula (I) may be more desirable depending on the choice of appendage substituents. Additionally, one skilled in the relevant art will recognize that in some cases the order of reactions may differ from that presented herein to avoid functional group incompatibilities and thus adjust the synthetic route accordingly.

The starting materials used and the intermediates prepared using the methods set forth in Schemes A-S may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography and alike. Such materials can be characterized using conventional means, including physical constants and spectral data.

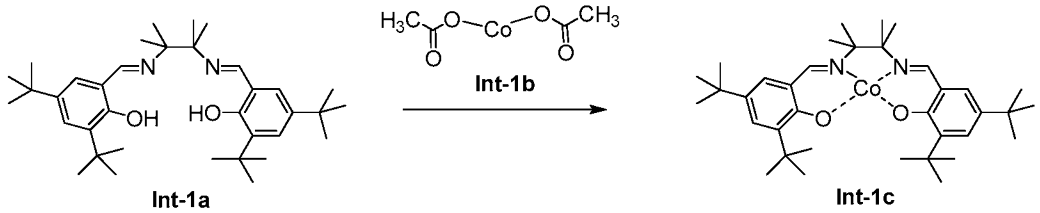
EXAMPLES

General Methods

Solvents, reagents, and intermediates that are commercially available were used as received. Reagents and intermediates that are not commercially available were prepared in the manner as described below. ^{1}H NMR spectra were obtained on a Varian VNMR System 400 (400 MHz) and are reported as ppm downfield from Me4Si with number of protons, multiplicities, and coupling constants in Hertz indicated parenthetically. Where LC/MS data are presented, analyses was performed using an Agilent 6110A MSD or an Applied Biosystems API-100 mass spectrometer and Shimadzu SCL-10A LC column: Altech platinum C18, 3 micron, 33 mm x 7mm ID; gradient flow: 0 minutes – 10% CH_3CN, 5 minutes – 95% CH_3CN, 5-7 minutes – 95% CH_3CN, 7 minutes – stop. The parent ion is given. Flash chromatography on silica gel was performed using pre-packed normal phase silica from Isco, Biotage, Inc. or bulk silica from Fisher Scientific. Unless otherwise indicated, flash chromatography on silica gel was performed using a gradient elution of hexanes/ethyl acetate, from 100% hexanes to 100% ethyl acetate.

EXAMPLE 1

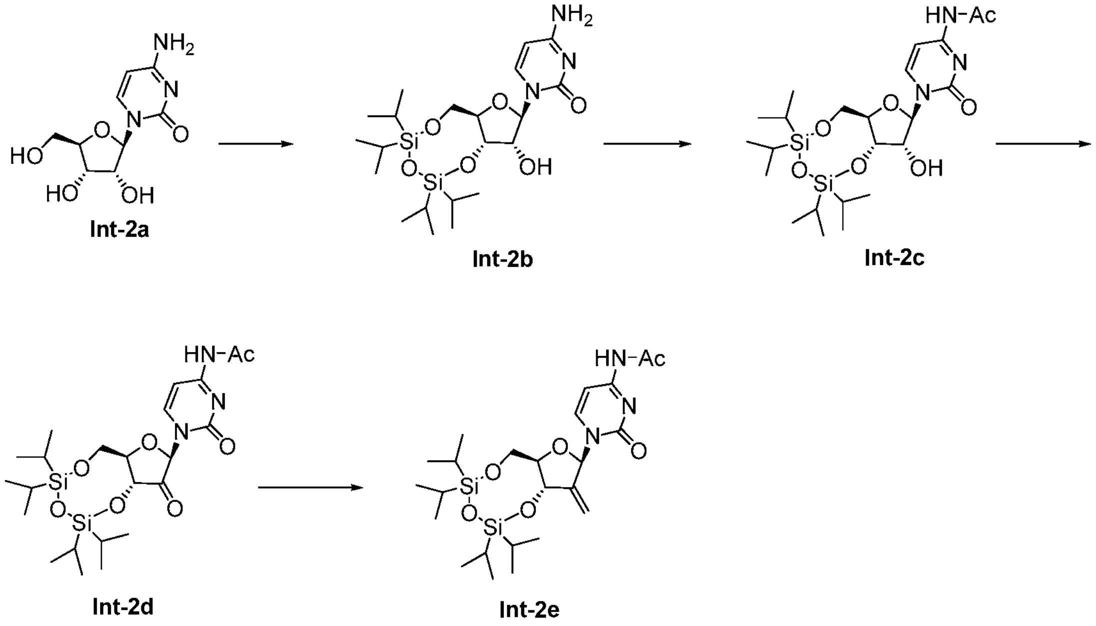
Preparation of Intermediate Compound **Int-1c**



Compound **Int-1a** (733 mg, 1.33 mmol) was suspended in ethanol (10 mL) and the resulting suspension was heated to 80 °C and allowed to stir for 5 minutes. Compound **Int-1b** (236 mg, 1.33 mmol) was then added and the resulting reaction was allowed to stir at 80 °C for an additional 2 hours. The reaction was then cooled to room temperature using in an ice bath and the reaction mixture was filtered. The collected red solid was dried under vacuum to provide compound **Int-1c** (579 mg, 72%).

EXAMPLE 2

Preparation of Intermediate Compound **Int-2e**



Step A – Synthesis of Compound Int-2b

Cytidine (**Int-2a**, 8.0 g, 32.89 mmol) was azeotroped with pyridine (2 x15 mL) and then suspended in pyridine (25 mL). To the suspension was added tetraisopropyldisiloxanedichloride (12.0 mL, 35.4 mmol) dropwise over fifteen minutes and the resulting reaction was allowed to stir for about 15 hours at room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic extracte were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue obtained was triturated with heptane to provide 13.5 g of compound **Int-2b** as a white solid [M+H] = 486.5.

Step B – Synthesis of Compound Int-2c

Compound **Int-2b** (13.5 mmol, 27.8 mmol) was dissolved in ethanol (200 mL) and treated with acetic anhydride (10 mL). The resulting reaction was heated to 65 °C and allowed to stir at this temperature for 3 hours, then the reaction mixture was concentrated *in vacuo*. The residue obtained was cooled to 0 °C in an ice bath and treated with saturated sodium bicarbonate, then extracted with ethyl acetate. The organic extract was dried over sodium sulfate, filtered and concentrated *in vacuo* to provide 14.5 g of compound **Int-2c**, which was used without further purification. [M+H] = 528.6

Step C – Synthesis of Compound Int-2d

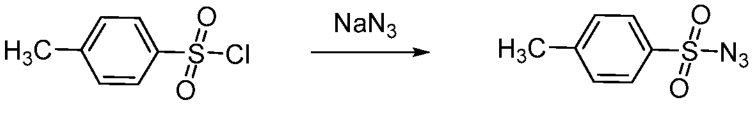
A solution of compound **Int-2c** (8.0 g, 15.15 mmol) in methylene chloride (120 mL) was cooled to 0 °C, then the Dess Martin Periodinane (15 g, 34.3 mmol) was added. The resulting reaction was allowed to stir for about 15 hours at room temperature and was then diluted with diethyl ether (400 mL). The resulting solution was washed with a mixture of saturated sodium bicarbonate and 10% sodium thiosulfate (1:1). The organic phase was collected and was dried over sodium sulfate, filtered and concentrated *in vacuo* to provide 7.8 g of compound **Int-2d**, which was used without purification. [M+H] = 526.

Step D – Synthesis of Compound Int-2e

Methyltriphenylphosphonium bromide (2.72 g, 7.6 mmol) was diluted with tetrahydrofuran (25 mL) and to the resulting suspension was added KHMDS (0.5 M, 14.5 mL, 7.22 mmol). The resulting reaction was allowed to stir at room temperature for 20 minutes, then the reaction was cooled to 0 °C using an ice bath and a solution of compound **Int-2d** (1.0 g, 1.9 mmol) in tetrahydrofuran (5 mL) was added dropwise. The resulting reaction was warmed to room temperature and stirred for 4 hours, then the reaction was quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic extract was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified using flash chromatography on silica gel (2:1 hexanes/ethyl acetate) to provide 750 mg of compound **Int-2e**. [M+H] = 524.5

EXAMPLE 3

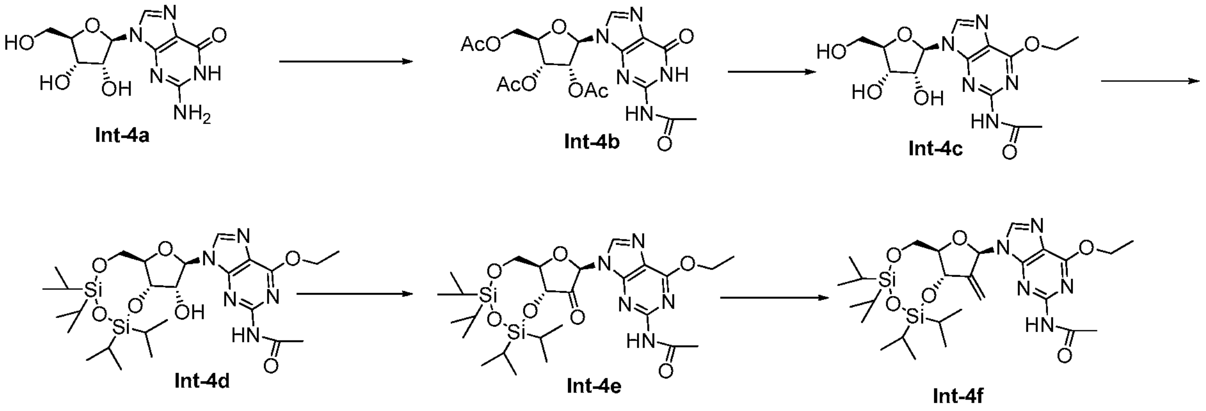
Preparation of Intermediate Compound **Int-3b**



p-Toluenesulfonyl chloride (46 g, 241 mmol) was suspended in acetone (350 mL) and water (350 mL) and cooled in an ice bath. Sodium azide (47.1 g, 724 mmol) was added in portions over 15 minutes and the reaction was allowed to stir for about 15 hours at room temperature. The reaction was diluted with water and ethyl acetate. The organic layer was washed with water, dried over sodium sulfate, filtered and concentrated *in vacuo* to provide the compound **Int-3b** (47%).

EXAMPLE 4

Preparation of Intermediate Compound **Int-4f**



Step A – Synthesis of Compound Int-4b

Guanosine hydrate (**Int-4a**, 15 g, 53 mmol) was dissolved in pyridine (120 mL) and acetic anhydride (60 mL). N,N-dimethylaminopyridine (6.46 g, 53 mmol) was added and the reaction was heated to 70 °C and allowed to stir at this temperature for 3 hours. The reaction was then cooled in an ice bath and treated dropwise with methanol (60 mL). The reaction mixture was then partially concentrated *in vacuo* to half of its volume. The resulting solution was diluted with dichloromethane and washed sequentially with 0.2 M potassium dihydrogen sulfate, water, and sodium bicarbonate. The organic phase was then dried over sodium sulfate, filtered and concentrated *in vacuo* to provide a residue which was purified using flash chromatography on silica gel (5% methanol in dichloromethane) to provide 22 g of compound **Int-4b**. [M+H] = 452.2

Step B – Synthesis of Compound Int-4c

Compound **Int-4b** (3.2 g, 7.09 mmol) was dissolved in dioxane (50 mL) and treated with triphenylphosphine (2.23 g, 8.5 mmol), diisopropylazodicarboxylate (1.65 mL, 8.5 mmol) and ethanol (391 mg, 8.5 mmol). The reaction was allowed to stir for fifteen minutes at room temperature, then the reaction mixture was concentrated *in vacuo*. The residue obtained was dissolved in methanol (15 mL) and ammonium hydroxide (15 mL) and allowed to stir for 3 hours. The reaction mixture was filtered and the collected solid was dried *in vacuo* to provide 1.4 g of compound **Int-4c**. The filtrate was then concentrated *in vacuo* and the resulting residue was triturated with chloroform to provide an additional 0.5 g of compound **Int-4c**. [M+H] = 354.2

Step C – Synthesis of Compound Int-4d

Compound **Int-4c** (1.46 g, 4.13 mmol) was azeotroped with pyridine (2 x 20 mL) and then suspended in pyridine (30 mL). Tetraisopropyldisiloxanedichloride (1.43 g, 4.43 mmol) was added dropwise over fifteen minutes and the reaction was allowed to stir at room temperature for 3 hours. The reaction was diluted with water (1 mL) and the resulting solution was concentrated *in vacuo*. The residue obtained was diluted with water and ethyl acetate and the organic layer was collected and washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was azeotroped with toluene (2 x 50 mL) and purified using flash chromatography on silica gel (5% methanol in dichloromethane) to provided 2.25 g of compound **Int-4d** as a white solid [M+H] = 596.2.

Step D – Synthesis of Compound Int-4e

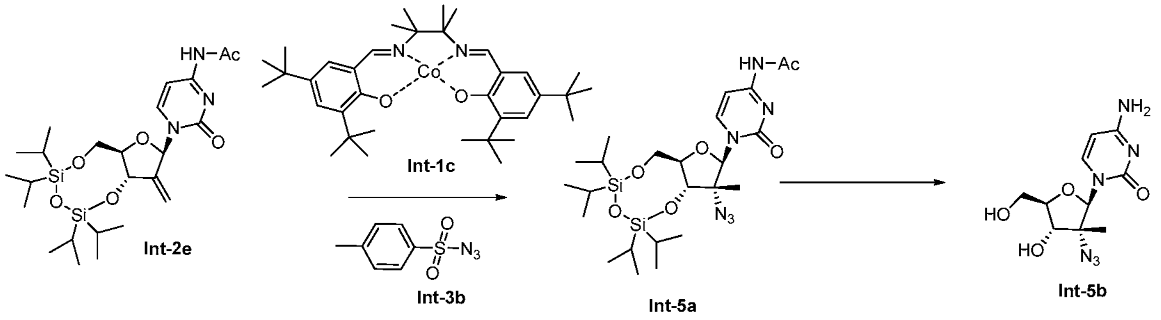
Using the method described in Example 2, Step C, compound **Int-4d** was converted to compound **Int-4e**. The product was purified using flash chromatography on silica gel (hexanes/ethyl acetate 0% →100%) to provide 260 mg compound **Int-4e**. [M+H] = 594.2

Step E – Synthesis of Compound Int-4f

Using the method described in Example 2, Step D, compound **Int-4e** was converted to compound **Int-4f**, which was purified using flash chromatography on silica gel (2:1 hexanes/ethyl acetate) to provide 170 mg of compound **Int-4f**. [M+H] = 592.2

EXAMPLE 5

Preparation of Intermediate Compound **Int-5b**



Step A – Synthesis of Compound Int-4b

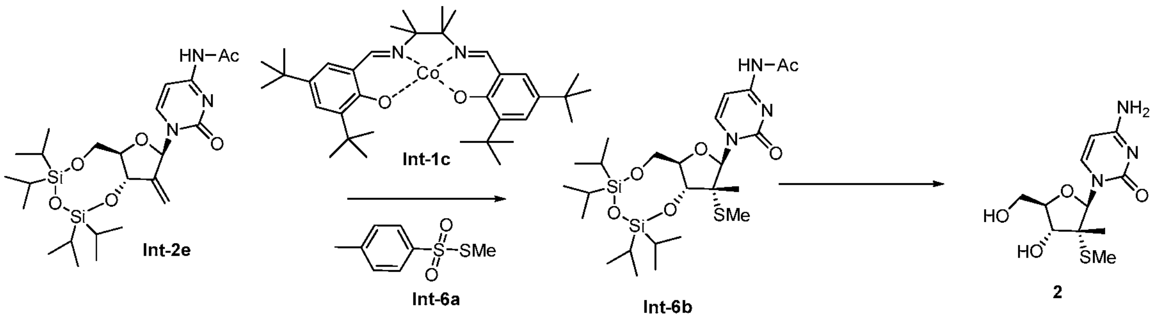
Compound **Int-2e** (500 mg, 0.955 mmol) and Compound **Int-1c** (20 mg, 0.033 mmol) were dissolved in Compound **Int-3b** (3.0g, 15.01 mmol) and the resulting mixture was allowed to stir for 5 minutes at room temperature. A solution of phenylsilane (121 mg, 1.11 mmol) in ethanol (3 mL) was added dropwise over 2 minutes and the reaction was allowed to stir for an additional 30 minutes. The reaction was then quenched with brine and extracted with ethyl acetate. The organic extract was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified using flash column chromatography on silica gel (2:1 hexanes/ethyl acetate) to provide 197 mg of compound **Int-5a**. [M+H] = 567.2

Step B – Synthesis of Compound Int-5b

Compound **Int-5a** (75 mg, 0.132 mmol) was dissolved in tetrahydrofuran (1 mL) and treated with 1.0M tetrabutylammonium fluoride (0.265 mmol). The reaction was allowed to stir for 1 hour and then the reaction mixture was concentrated *in vacuo*. The residue obtained was dissolved in 7M ammonia in methanol (2 mL) and allowed to stir for 3 hours at room temperature. The reaction was concentrated *in vacuo* and the residue obtained was purified using flash column chromatography on silica gel (20% methanol in dichloromethane) to provide 11 mg of compound **Int-5b**. [M+H] = 283.7

EXAMPLE 6

Preparation of Compound 2



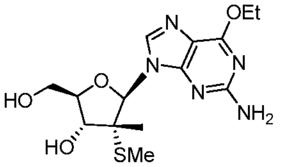
Step A – Synthesis of Compound Int-6a

Compound **Int-2e** (220 mg, 0.42 mmol), Compound **Int-1c** (15 mg), and Compound **Int-6a** (2.53 g, 12.61 mmol) were dissolved in dioxane (2 mL) and the resulting reaction was allowed to stir for 5 minutes at room temperature. A solution of phenylsilane (59 mg, 0.54 mmol) in ethanol (1 mL) was added dropwise over 2 minutes and the reaction was allowed to stir for and additional 30 minutes. The reaction was quenched with brine and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified using flash column chromatography on silica gel (2:1 hexanes/ethyl acetate) to provide 150 mg of compound **Int-6b**. [M+H] = 572.2

Step B – Synthesis of Compound 2

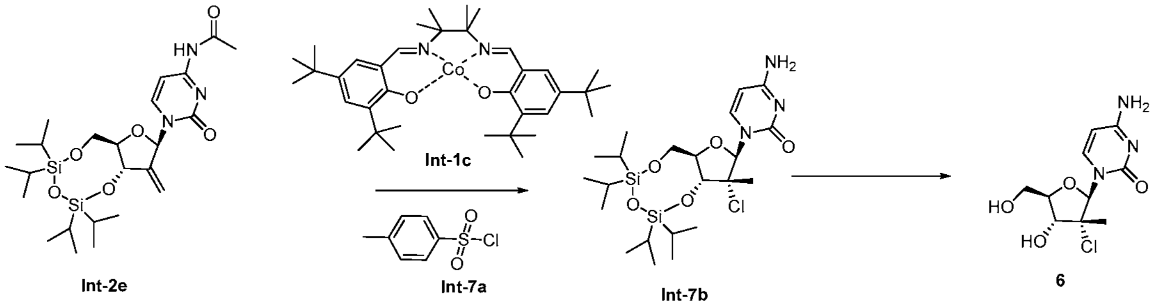
Compound **Int-6b** (150 mg, 0.26 mmol) was dissolved in tetrahydrofuran (1 mL) and treated with 1.0M tetrabutylammonium fluoride (0.52 mmol). The reaction was allowed to stir for 1 hour and then the reaction mixture was concentrated *in vacuo*. The residue obtained was dissolved in 7M ammonia in methanol (5 mL) and allowed to stir for 3 hours at room temperature. The reaction mixture was concentrated *in vacuo* and the residue obtained was purified using flash column chromatography on silica gel (20% methanol in dichloromethane) to provide 70 mg of compound **2**. [M+Na] = 593.2. ^{1}H-NMR (400 MHz, CD_3OD): δ:8.29 (d, 1H, J = 7.49 Hz), 6.34 (s, 1H), 5.86 (d, 1H, J = 7.5 Hz), 4.09 (m, 2H), 3.99 (m, 1H), 3.78 (m, 1H), 2.27 (s, 3H), 1.27 (s, 3H).

The following compound of the present invention was made using the methods described in the Example above and using the appropriate reactants and reagents.

Compound No.	Structure	Starting Material	MS (M + H)
17		Int-4f	378.2 [M+Na]

EXAMPLE 7

Preparation of Compound **6**



Step A – Synthesis of Compound Int-7b

Compound **Int-2e** (310 mg, 0.592 mmol), compound **Int-1c** (10.7 mg, 0.018 mmol), and compound **Int-7a** (2.5 g, 13.11 mmol) were dissolved in dioxane (1 mL) and the resulting reaction was allowed to stir for 5 minutes. A solution of phenylsilane (83 mg, 0.769 mmol) in ethanol (0.5 mL) was added dropwise and the reaction was allowed to stir for 30 minutes. The reaction mixture was diluted with ethyl acetate and brine and the collected organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue obtained was purified using flash column chromatography on silica gel (hexanes/EtOAc 0%-->40%) to provide compound **Int-7b** (35 mg). [M+H] = 518.2

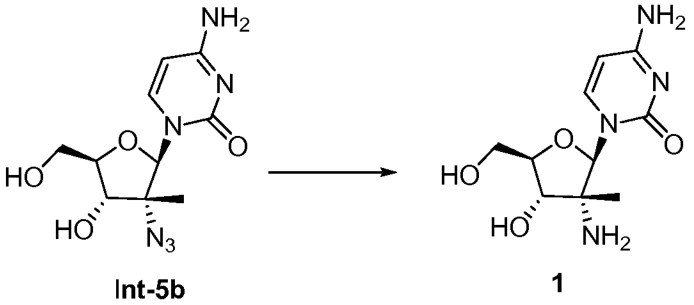
Step B – Synthesis of Compound 6

Compound **Int-7b** (30 mg, 0.058 mmol) was dissolved in tetrahydrofuran (1 mL) and treated with tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 0.116 mL). The reaction was allowed to stir for 2 hours, then the reaction mixture was concentrated *in vacuo*.

The residue obtained was purified using flash column chromatography on silica gel (dichloromethane/methanol 0% --> 25%) to provide 15 mg of compound **6**. [M+H] = 276.06. ^{1}H-NMR (400 MHz, CD_3OD): δ:8.28 (d, 1H, J = 7.6 Hz), 6.44 (s, 1H), 5.87 (d, 1H, J = 7.6 Hz), 4.03-4.0 (m, 3H), 3.81 (m, 1H), 1.47 (s, 3H).

EXAMPLE 8

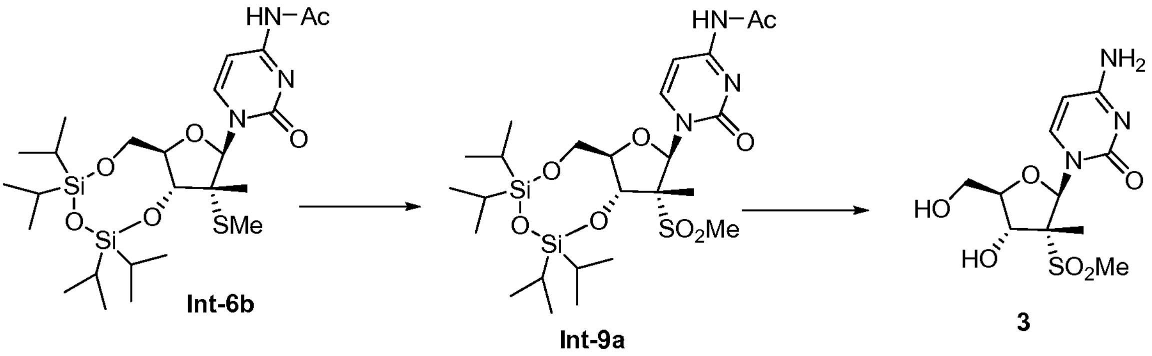
Preparation of Compound **1**



Compound **Int-5b** (10 mg, 0.035 mmol) was dissolved in methanol (10 mL) and to the resulting solution was added 10% palladium on carbon (100 mg). The resulting reaction was evacuated and placed under hydrogen atmosphere (using a hydrogen filled balloon) and allowed to stir for 2 hours. The reaction mixture was then filtered through a short pad of celite and the filtrate was concentrated *in vacuo* to provide 9.5 mg of compound **1**, which was used without further purification. [M+H] = 257.3. ^{1}H-NMR (400 MHz, CD_3OD): δ:8.15 (d, 1H, J = 7.51 Hz), 5.93 (s, 1H), 5.87 (d, 1H, J = 7.51 Hz), 4.0-3.9 (m, 2H), 3.85 (m, 1H), 3.77 (m, 1H), 1.02 (s, 3H).

EXAMPLE 9

Preparation of Compound **3**



Step A – Synthesis of Compound Int-9a

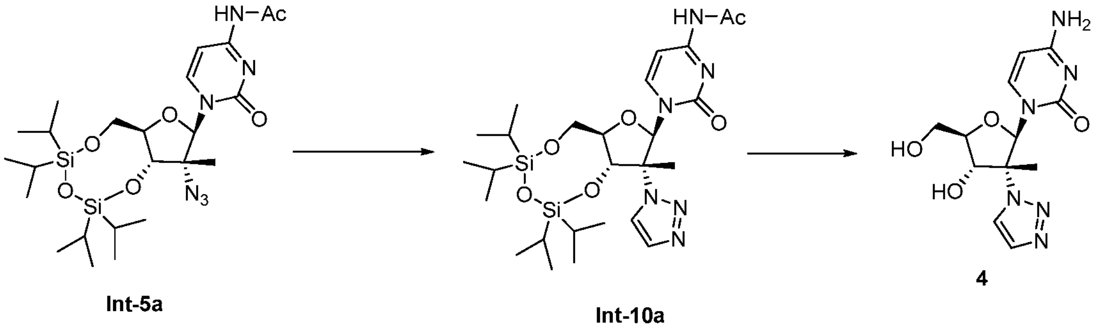
Compound **Int-6b** (60 mg, 0.105 mmol) was dissolved in dichloromethane (10 mL) and to the resulting solution was added *m*-chloroperbenzoic acid (77%, 58 mg, 0.262 mmol). The resulting reaction was allowed to stir for 30 minutes, then the reaction was quenched with saturated sodium bicarbonate and extracted with dichloromethane. The organic extract was dried over sodium sulfate, filtered and concentrated *in vacuo* and the residue obtained was purified using flash column chromatography on silica gel (EtOAc) to provide 30 mg of compound **Int-9a**. [M+H] = 604.5

Step B – Synthesis of Compound 3

Compound **Int-9a** (30 mg, 0.049 mmol) was dissolved in tetrahydrofuran (1 mL) and to the resulting solution was added tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 0.1 mmol). The reaction was allowed to stir for 1 hour and then the reaction mixture was concentrated *in vacuo*. The residue obtained was dissolved in 7M ammonia in methanol (2 mL) and allowed to stir for 3 hours at room temperature. The reaction was then concentrated *in vacuo* and the residue obtained was purified using flash column chromatography on silica gel (15% methanol in dichloromethane) to provide 13 mg of compound **3**. [M+Na] = 342.2. ^{1}H-NMR (400 MHz, CD_3OD): δ:8.41 (d, 1H, J = 7.6 Hz), 8.13 (bs, 1H), 7.78 (bs, 1H), 6.96 (s, 1H), 6.01 (d, 1H, J = 7.6 Hz), 4.23 (m, 2H), 4.02 (m, 1H), 3.74 (m, 1H), 1.63 (s, 3H).

EXAMPLE 10

Preparation of Compound **4**



Step A – Synthesis of Compound Int-10a

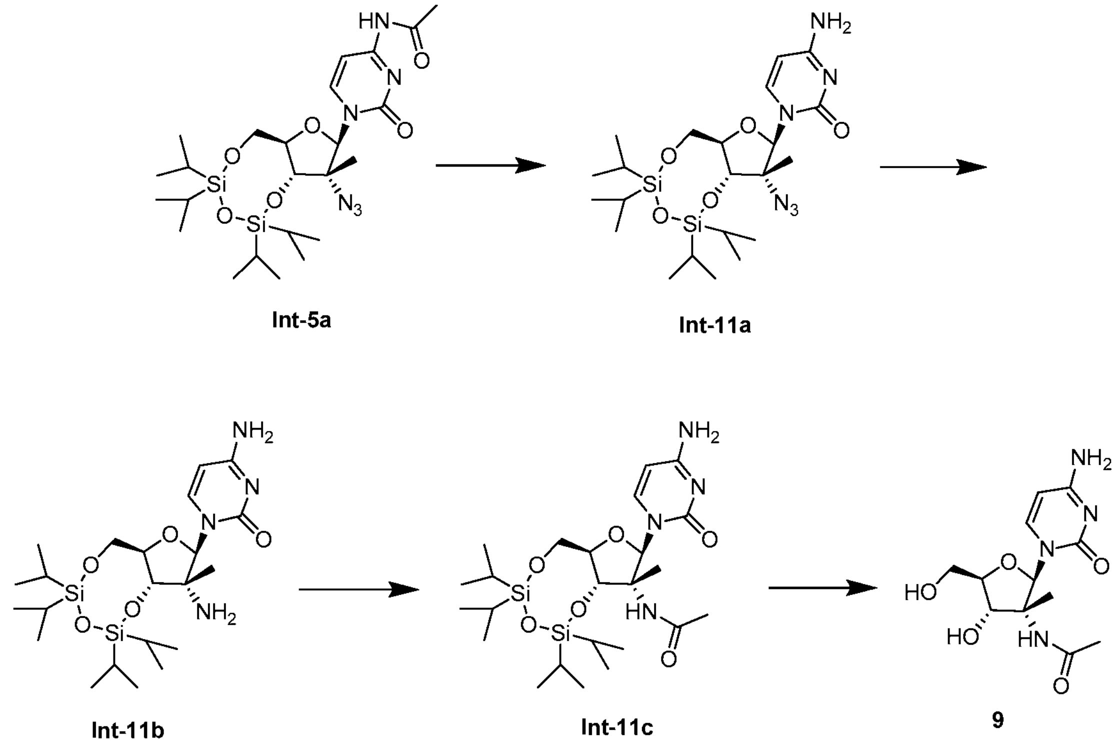
Compound **Int-5a** (60 mg, 0.206 mmol) was dissolved in vinyl acetate (2 mL) in a pressure tube and the resulting reaction was heated to 140 °C and allowed to stir at this temperature for about 15 hours, after which time TLC and LCMS analysis indicated that the reaction was about 10% complete. The reaction vessel was then transferred to a Biotage Initiator microwave reactor and the reaction temperature was held at 140 °C using 100% power for 4 hours, after which time TLC and LCMS analysis showed that the reaction was 50% complete. The solvent was then removed *in vacuo* and the residue obtained was purified using flash column chromatography on silica gel (hexanes/ethyl acetate 0% → 100%) to provide 24 mg of compound **Int-10a**. [M+H] = 593.2.

Step B – Synthesis of Compound 4

Compound **Int-10a** (24 mg, 0.145 mmol) was dissolved in tetrahydrofuran (1 mL) and to the resulting solution was added tetrabutylammonium fluoride tetrabutylammonium fluoride (10.081 mmol). The reaction was allowed to stir for 1 hour and then the reaction mixture was concentrated *in vacuo*. The residue obtained was dissolved in 7M ammonia in methanol (2 mL) and allowed to stir for 3 hours at room temperature. The reaction was concentrated *in vacuo* and the residue obtained was purified using flash column chromatography on silica gel (25% methanol in dichloromethane) to provide 11 mg of compound **4**. [M+H] = 309.2.

EXAMPLE 11

Preparation of Compound 9



Step A – Synthesis of Compound Int-11a

Compound **Int-5a** (50 mg, 0.088 mmol) was dissolved in methanol (1 mL) and to the resulting solution was added 7M ammonia in methanol (2 mL). The reaction was allowed to stir for about 15 hours and the reaction mixture was concentrated *in vacuo* to provide compound **Int-11a** (49 mg), which was used without further purification. [M+H] = 525.2

Step B – Synthesis of Compound Int-11b

Compound **Int-11a** (100 mg, 0.1905 mmol) was dissolved in methanol (7 mL) and to the resulting solution was added 10% palladium on carbon (15 mg). The resulting reaction was evacuated and placed under hydrogen atmosphere (using a hydrogen filled balloon) and allowed to stir for 3 hours. The reaction mixture was then filtered through a short pad of celite and the filtrate was concentrated *in vacuo* and the residue obtained was purified using reverse phase chromatography (0% → 100% water/acetonitrile) to provide compound **Int-11b** (44 mg). [M+H] = 499.2

Step C – Synthesis of Compound Int-11c

Compound **Int-11b** (41 mg, 0.082 mmol) was dissolved in a mixture of dichloromethane (1 mL) and triethylamine (42 mg, 0.411 mmol). The resulting reaction was cooled to 0 °C using an ice bath, and a solution of acetyl chloride (13 mg, 0.164 mmol) in dichloromethane (1 mL) was added dropwise. The reaction was then allowed to stir for about 15 hours at room temperature and was quenched with water and extracted with dichloromethane. The organic extract was dried over sodium sulfate, filtered and concentrated *in vacuo* and the resulting residue was dissolved in 7M methanolic ammonia (3 mL) and stirred for 3 hours. The reaction mixture was then concentrated in vacuo and the residue obtained was purified using flash column chromatography on silica gel (hexanes/ethyl acetate 30:70%) to provide **Int-11c** (33 mg). [M+H] = 541.2

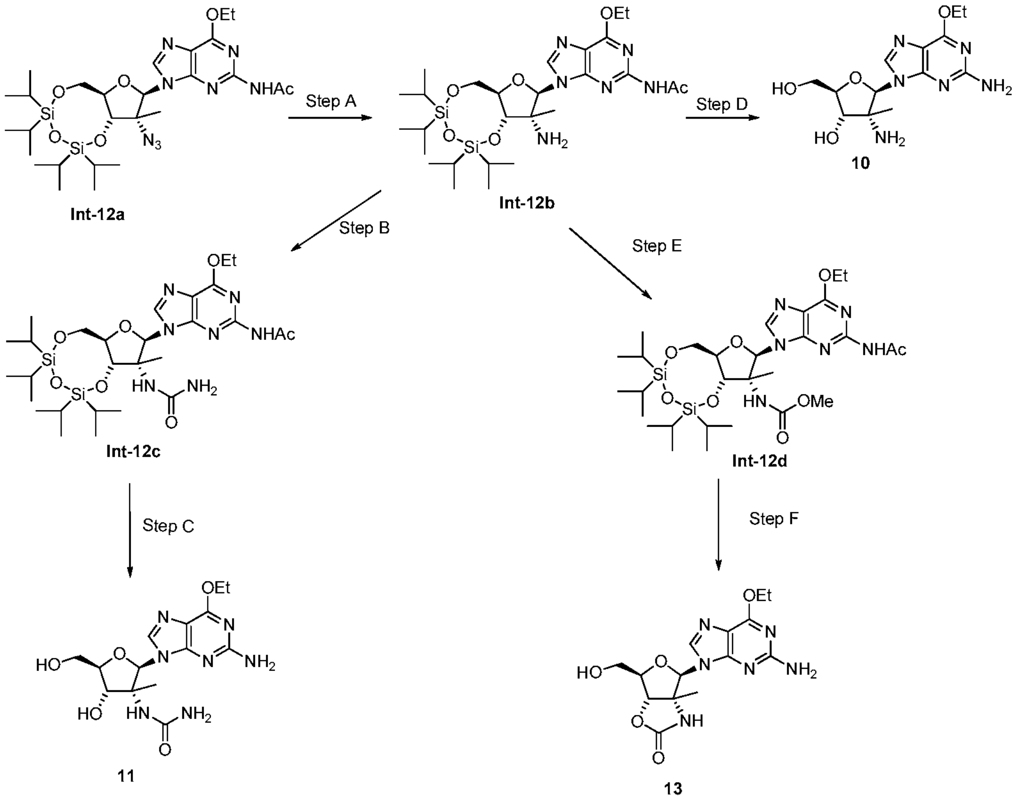
Step D – Synthesis of Compound 9

Compound **Int-11c** (33 mg, 0.06 mmol) was dissolved in tetrahydrofuran (1 mL) and to the resulting solution was added tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 0.12 mL). The resulting reaction was allowed to stir for 2 hours, then the reaction mixture was concentrated *in vacuo* and the residue obtained was purified using reverse phase chromatography

(0% → 100% water/acetonitrile) followed by preparatory plate purification (CH_2Cl_2:7N methanol:NH_3 (0-20%) to provide 12.6 mg of compound **9**. [M+Na] = 321.2.

EXAMPLE 12

Preparation of Compounds **10, 11** and **13**



Step A – Synthesis of Compound Int-12b

Compound **Int-12a** (137 mg, 0.216 mmol, prepared from compound **Int-4f** using the methods described in Example 5) was dissolved in methanol (10 mL) and $Pd(OH)_2$ (100 mg) was added. The resulting reaction was evacuated and placed under hydrogen atmosphere (using a hydrogen filled balloon) and allowed to stir for 50 minutes. The reaction mixture was then filtered through a short pad of celite and the filtrate was concentrated *in vacuo*. The residue obtained was purified using flash column chromatography on silica gel (0 to 10% methanol/CH_2Cl_2) to provide compound **Int-12b** (69 mg, 0.113 mmol, 53%).

Step B – Synthesis of Compound Int-12c

Compound **Int-12b** (100 mg, 0.164 mmol) was dissolved in isopropanol and to the resulting solution was added trimethysilyl isocyanate (26.5 mg, 0.230 mmol, 1.4 eq). The resulting reaction was allowed to stir for about 15 hours. The reaction mixture was then concentrated *in vacuo* and the residue obtained was purified using flash column chromatography on silica gel (0 to 10% methanol/CH_2Cl_2) to provide compound **Int-12c** (40 mg, 0.061 mmol, 37%).

Step C – Synthesis of Compound 11

Compound **Int-12c** (40 mg, 0.061 mmol) was dissolved in tetrahydrofuran (1 mL) and to the resulting solution was added tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 0.12 mL). The resulting reaction was allowed to stir for 45 minutes, then the reaction mixture was concentrated *in vacuo*. To the resulting residue was added NH_3 (7 N in methanol, 3 mL) and NH_4OH (28% aqueous, 0.5 mL) and the resulting reaction was allowed to stir at 100 °C for 3.5 hours. The reaction mixture was cooled to room temperature, then was concentrated *in vacuo* and the residue obtained was purified using flash column chromatography on silica gel (0 to 20% methanol/CH_2Cl_2). Some fractions contained product with acetimide still present. These fractions were resubjected to the reaction conditions and purified in the same manner. The total yield of compound **11** was 9.5 mg (42%). [M+H] = 368.2.

Step D – Synthesis of Compound 10

Compound **Int-12b** (69 mg, 0.113 mmol) was dissolved in tetrahydrofuran (1 mL) and to the resulting solution was added tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 0.227 mL). The resulting reaction was allowed to stir for 45 minutes, then the reaction mixture was concentrated *in vacuo*. To the resulting residue was added NH_3 (7 N in methanol, 3 mL) and NH_4OH (28% aqueous, 0.5 mL) and the resulting reaction was allowed to stir at 100 °C for 3.5 hours. The reaction mixture was cooled to room temperature, then was concentrated *in vacuo* and the residue obtained was purified using flash column chromatography on silica gel (0 to 25% methanol/CH_2Cl_2). The total yield of compound **10** was 31 mg (84%). [M+H] = 325.5. ^{1}H NMR (400 MHz, CD_3OD) δ 8.29 (s, 1H), 5.92 (s, 1H), 4.53 (q, 2H, J = 7.0 Hz), 4.21 (d, 1H, J = 8.2 Hz), 4.05-3.97 (m, 2H), 3.83 (dd, 1H, J = 12.1, 2.5 Hz), 1.43 (t, 3H, J = 7.0 Hz), 0.86 (s, 3H).

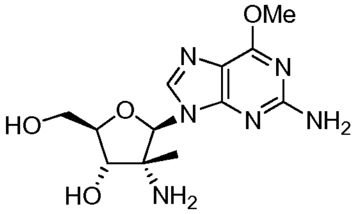
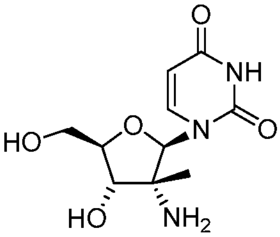
Step E - Synthesis of Compound Int 12d

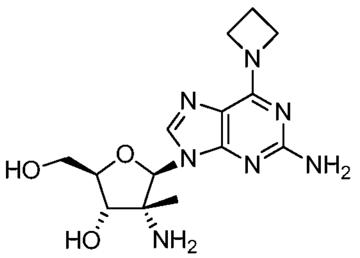
Compound **Int-12b** (100 mg, 0.164 mmol) was dissolved in dichloromethane (10 mL) and treated with triethylamine (0.070 mL, 0.5 mmol) followed by methyl chloroformate (34 mg, 0.36 mmol). The reaction was stirred at room temperature for 3 hours and then was quenched with water and extracted with dichloromethane. The organic extract was dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified using flash column chromatography on silica gel (0 to 10% MeOH/DCM) followed by (0 to 100% EtOAc/hexanes) to provide 10 mg of methyl carbamate product **Int 12d**. .[M+H] = 667.2

Step F - Synthesis of Compound 13

Compound **Int 12d** (18 mg, 0.027 mmol) was dissolved in tetrahydrofuran (1 mL) and to the resulting solution was added tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 0.054 mL). The resulting reaction was allowed to stir for 45 minutes, then the reaction mixture was concentrated *in vacuo*. To the resulting residue was added NH_3 (7 N in methanol, 3 mL) and NH_4OH (28% aqueous, 0.1 mL) and the resulting reaction was allowed to stir at 100 °C for 3.5 hours. The reaction mixture was cooled to room temperature, then was concentrated *in vacuo* and the residue obtained was purified using flash column chromatography on silica gel (0 to 15% methanol/CH_2Cl_2) to provide 8 mg of compound **13**. [M+H] = 351.2.

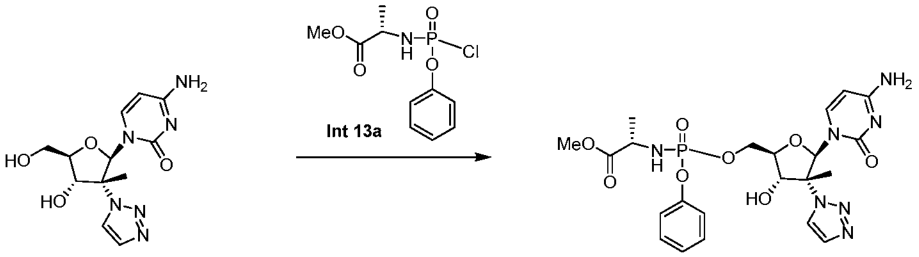
The following compounds of the present invention was made using the methods described in the Example above and substituting the appropriate reactants and/or reagents.

Compound No.	Structure	Starting Material	MS (M + H)
15		**Int-17a (6-OMe analog)**	311.0
16		**Int-16a**	258.0

18		**Compound 88**	336.3

EXAMPLE 13

Preparation of Compound **5**

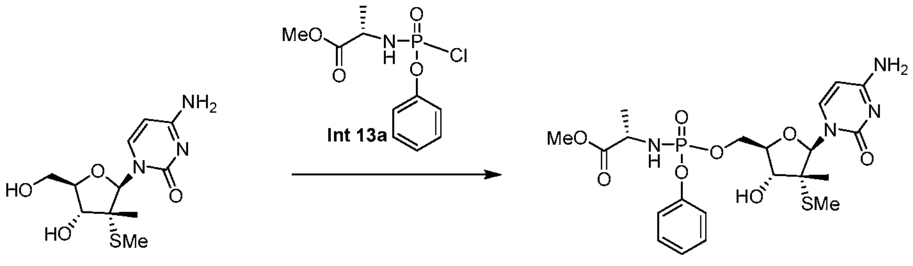


4 5

Compound **4** (9 mg, 0.029 mmol) was suspended in tetrahydrofuran (2 mL) and the resulting solution was cooled to 0 °C using an ice bath. To the cooled solution was added t-butylmagnesium chloride (1.0 M, 0.146 mL). After five minutes of stirring, a solution of compound **Int-13a** (12.1 mg, 0.044 mmol) in tetrahydrofuran (1 mL) was added dropwise (note that the reactants of formula **Int-13a** can be prepared using the methods described in US Patent No. 7,879,815). The resulting reaction was allowed to stir for about 15 hours at room temperature and then quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic extract was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified using flash column chromatography on silica gel (0% to 20 % dichloromethane/methanol) to provide 1.8 mg of compound **5**. [M+H] = 550.1

EXAMPLE 14

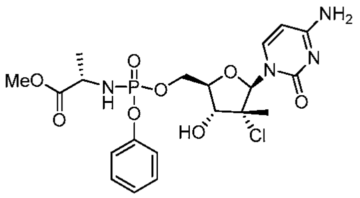
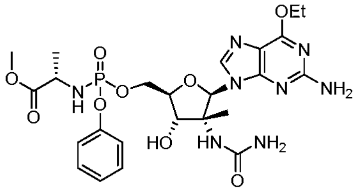
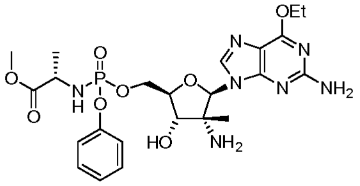
Preparation of Compound **7**



2 7

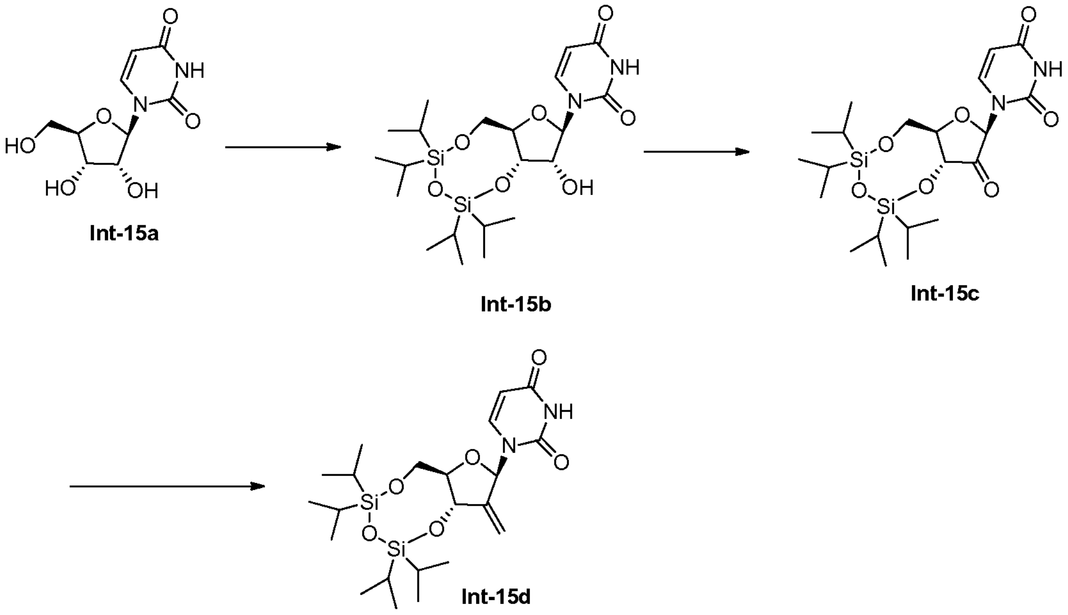
Compound **2** (13 mg, 0.045 mmol) was dissolved in tetrahydrofuran (1 mL) and DMF (1 mL). To the resulting solution was added N-methylimidazole (44.6 mg, 0.54 mmol). The resulting reaction was allowed to stir for 5 minutes, then a solution of compound **Int-13a** (100 mg, 0.36 mmol) in tetrahydrofuran (1 mL) was added dropwise. The reaction was allowed to stir for 48 hours at room temperature, then the reaction mixture was concentrated *in vacuo*. The residue was dissolved in ethyl acetate and washed with water. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue obtained was purified using flash column chromatography on silica gel (0 to 20 % dichloromethane/methanol) to provide 5 mg of compound **7**. [M+H] = 529.1

The following compounds of the present invention were made from the indicated starting material using the method described above.

Compound No.	Structure	Starting Material	MS (M + H)
8		Compound **6**	517.2
12		Compound **11**	609.2
14		Compound **10**	566.2

EXAMPLE 15

Preparation of Intermediate Compound **Int-15d**



Int-15a **Int-15b** **Int-15c** **Int-15d**

Step A – Synthesis of Compound Int-15b

Uridine (**Int-15a**, 5.0 g, 18.0 mmol) was azeotroped with pyridine (2 x 15 mL) and then suspended in pyridine (25 mL). Tetraisopropyldisiloxanedichloride (6.06 mL mL, 18.95 mmol) was added dropwise over fifteen minutes and the reaction was allowed to stir for about 15 hours at room temperature. The reaction was diluted with water and extracted with ethyl acetate. The organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was azeotroped with toluene (2X50 mL) to provide 7.8 g of compound **Int-15b** as a white solid that was used without purification [M+H] = 487.42.

Step B – Synthesis of Compound Int-15c

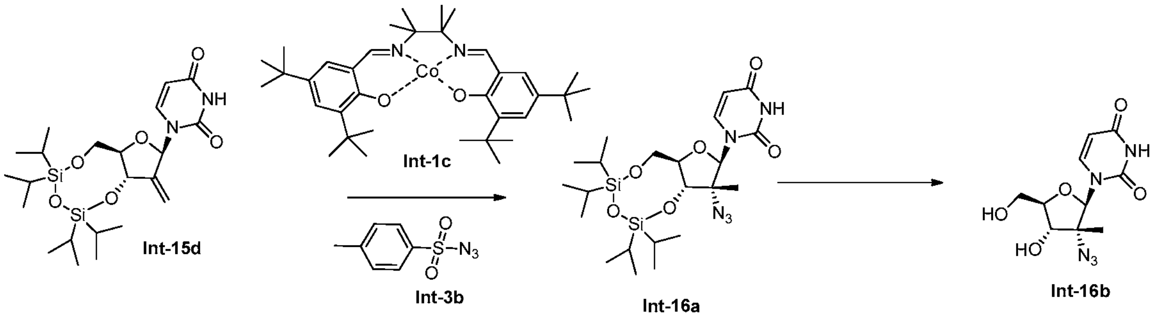
Compound **Int-15b** (4.0 g, 8.2 mmol) was dissolved in dichloromethane (100 mL), cooled in an ice bath and then treated with Dess Martin Periodinane (7 g, 16.46 mmol). The reaction was allowed to stir for about 15 hours and then filtered through a pad of silica and sodium sulfate. The solution was diluted with diethyl ether (400 mL) and washed with a mixture of saturated sodium bicarbonate and 10% sodium thiosulfate (1:1). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to provide 3.8 g of compound **Int-15c** that was used without purification. [M+H] = 485.2 (hydrate was also seen)

Step C – Synthesis of Compound Int-15d

Methyltriphenylphosphonium bromide (5.4 g, 15.2 mmol) was suspended in tetrahydrofuran (50 mL) and treated with 0.5 M KHMDS (29 mL, 14.4 mmol). After the mixture stirred at room temperature for 20 minutes, the reaction was cooled in an ice bath and compound **Int-15c** (2.0 g, 4.13 mmol) was added dropwise in tetrahydrofuran (10 mL). The reaction was warmed to room temperature and stirred for 4 hours. Upon completion of the reaction by TLC and LCMS, the reaction was quenched with saturated ammonium chloride and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue obtained was purified using flash columnchromatography on silica gel (2:1 hexanes/ethyl acetate) to provide 750 mg of compound **Int-15d**. [M+H] = 505.2

EXAMPLE 16

Preparation of Compound **Int-16b**



Step A – Synthesis of Compound Int-16a

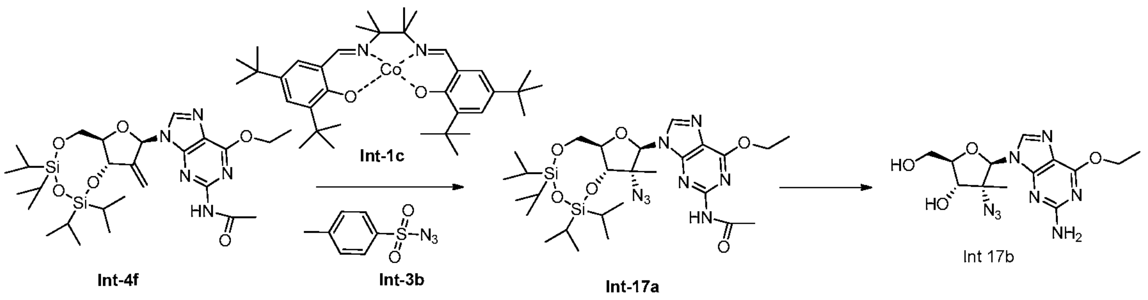
A solution of compound **Int-15d** (5.0 g, 10.36 mmol), compound **Int-1c** (125 mg, 0.207mmol) and compound **Int-3b** (24 g, 122 mmol) was allowed to stir for 5 minutes, then a solution of phenylsilane (1.34 g, 12.43 mmol) in ethanol (25 mL) was added dropwise over 30 minutes. The resulting reaction was allowed to stir for 30 minutes, then the reaction was quenched with brine and extracted with ethyl acetate. The organic extract was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified using flash column chromatography on silica gel (4:1 hexanes/ethyl acetate) to provide 2.5 g of compound **Int-16a**. [M+H] = 526.2

Step B – Synthesis of Compound 16b

To a solution of compound **Int-16a** (1.6 g, 3.04 mmol) in tetrahydrofuran (35 mL) was added tetrabutylammonium fluoride (1.0 M, 6.09 mmol). The resulting reaction was allowed to stir for 1 hour, then the reaction mixture was concentrated *in vacuo*. The residue obtained was purified using flash column chromatography on silica gel (10% methanol in dichloromethane) to provide 650 mg of compound **16b**. [M+Na] = 306.0

EXAMPLE 17

Preparation of Compound **Int-17b**



Step A – Synthesis of Compound Int-17a

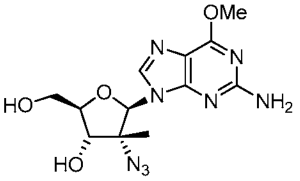
Compound **Int-4f** was converted to compound **Int-17a** using the method described in Example 16, Step A. [M+H] = 635.2.

Step B – Synthesis of Compound 17b

To a solution of compound **Int-17a** (80 mg, 0.126 mmol) in tetrahydrofuran (1 mL) was added tetrabutylammonium fluoride (1.0 M, 0.252 mL). The reaction was allowed to stir for 2 hours, then was concentrated *in vacuo* and the resulting residue was dissolved in 7M ammonia in methanol (3 mL) and allowed to stir at 100 °C in a pressure tube for about 15 hours. The reaction mixture was then cooled to room temperature and concentrated *in vacuo* and the resulting residue was purified using column chromatography (dichloromethane/methanol 0% to 5%) to provide 29 mg of compound **17b**. [M+H] = 373.2

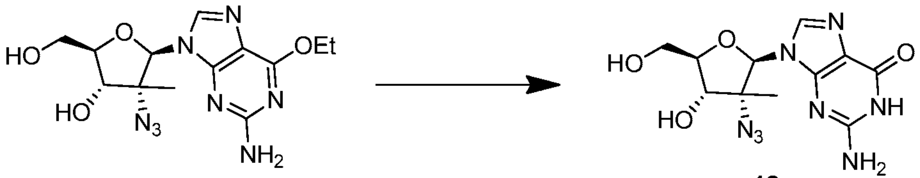
The following compound of the present invention was made using the methods described in the Example above and substituting the appropriate reactants and/or reagents.

Compound No.	Structure	Starting Material	MS (M + H)

19		Compound **Int-4f** methyl ether analog	337.2

EXAMPLE 18

Preparation of Compound **Int-18a**

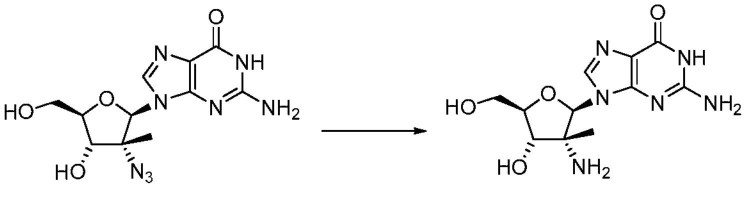


Int-17b **18a**

A solution of compound **Int-17b** (5 mg, 10.4 umol) and 1M HCl (0.5 mL) in tetrahydrofuran (0.5 mL) and was heated to 50 °C and allowed to stir at this temperature for 24 hours. The reaction mixture was then concentrated *in vacuo* and the residue obtained was purified using flash column chromatography on silica gel (0 to 20% dichloromethane/methanol) to provide 3 mg of compound **18a**. [M+H] = 323.2

EXAMPLE 19

Preparation of Compound **Int-19a**

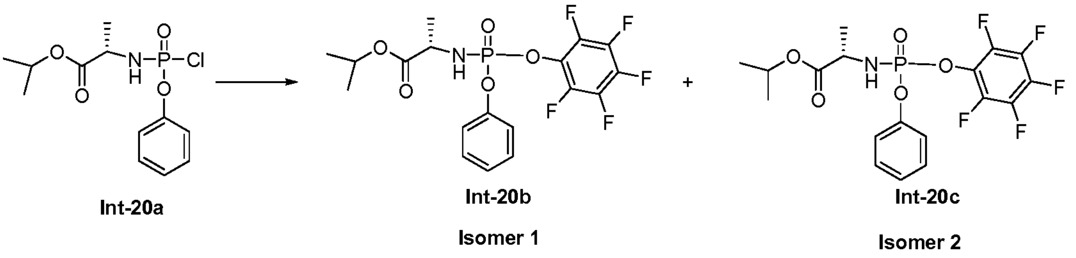


Int-18a **Int-19a**

The azide **Int-18a** (30 mg, 0.09 mmol) was dissolved in MeOH (2 mL) and a small portion of $Pd(OH)_2$ was added. To the flask was affixed a balloon of H_2 and the flask was filled and purged 5x, then allowed to stir under H_2 for 1 hour. The reaction was complete by TLC and LCMS analysis. The solution was filtered over celite and washed with MeOH, then concentrated *in vacuo* to give the pure amine product **Int-19a** as a white solid (25 mg, 91%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.05 (s, 1H), 6.03 (s, 1H), 4.30 (d, 1H, J = 7.2 Hz), 3.99 (ddd, 1H, J = 7.2, 3.3, 2.7 Hz), 3.92 (dd, 1H, J = 12.5, 2.5 Hz), 3.77 (dd, 1H, J = 12.7, 3.5 Hz), 1.09 (s, 3H).

EXAMPLE 20

Preparation of Compounds **Int-20b** and **Int-20c**

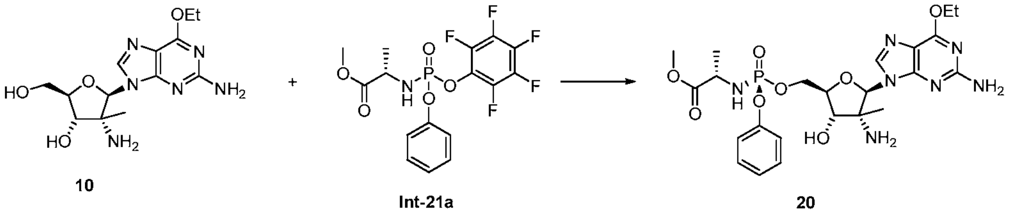


A stirred solution of **Int-20a** (14.2 g, 46.4 mmol) in dichloromethane (112 mL) was treated with pentafluorophenol (8.55 g, 46.4 mmol) in one portion. The solution was cooled to 0 °C and triethylamine (6.47 mL, 46.4 mmol) was added dropwise under nitrogen. The reaction was stirred overnight at room temperature. LCMS shows mainly product. The reaction mixture was washed with water (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue obtained was purified by silica gel column chromatography (0-30% hexanes/ethyl acetate) to provide 12.56 g of a white solid. The solid was recrystallized using 10% MBTE/hexanes to provide compound **Int 20b** (6.15 g) as a white solid. The mother liquor (5.3 g of a 4:1 mixture isomer 2/isomer 1) was purified by silica gel chromatography (1:1 hexanes/ethyl acetate) to provide **Int 20c** (4.04 g) and additional **Int 20b** (805 mg).

Phosphorylamino chloride reactants of type **Int-20a** can be synthesized using the methods described in US Patent No. 7,879,815.

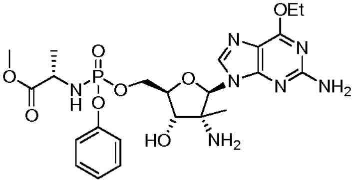
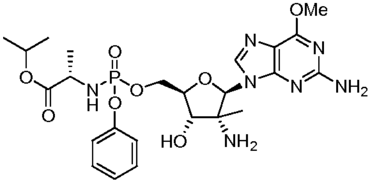
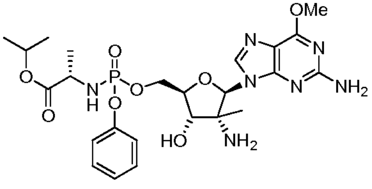
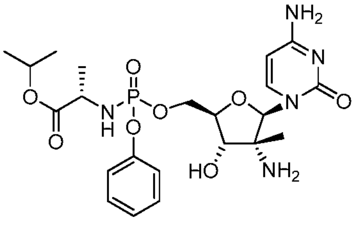
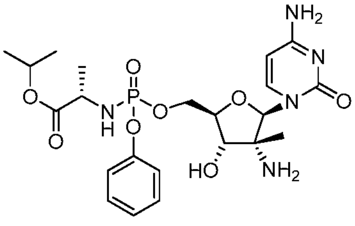
EXAMPLE 21

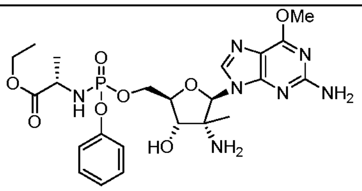
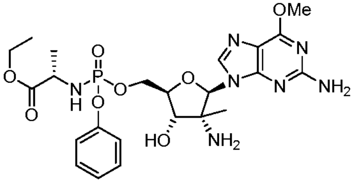
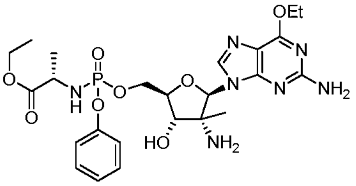
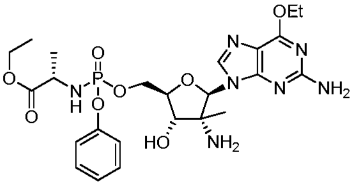
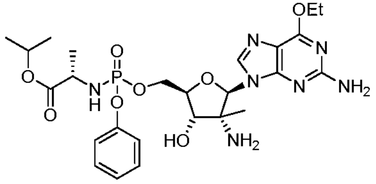
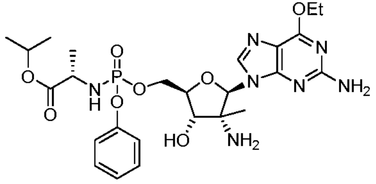
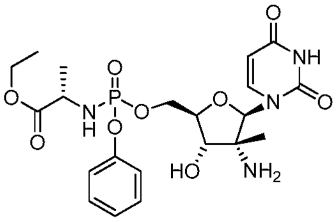
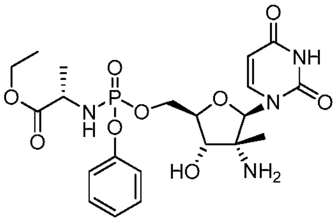
Preparation of Compound **20**

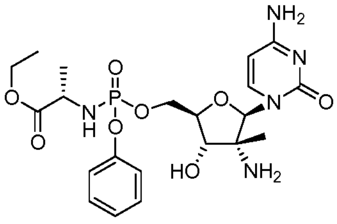
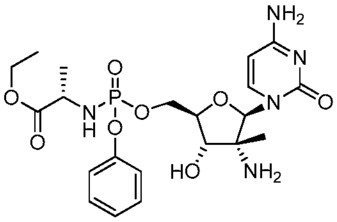
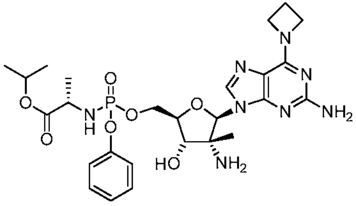
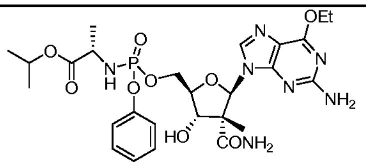
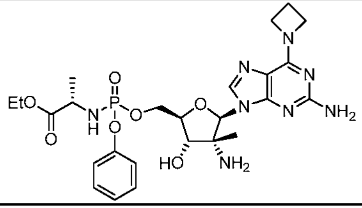
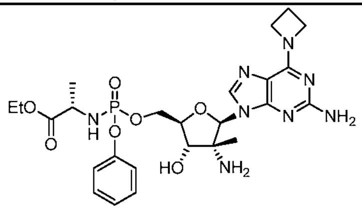
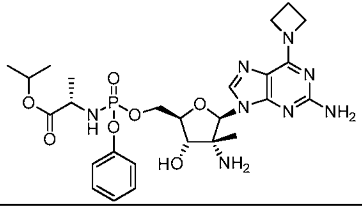


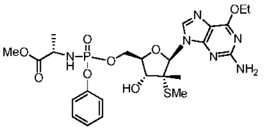
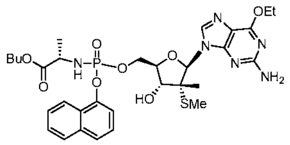
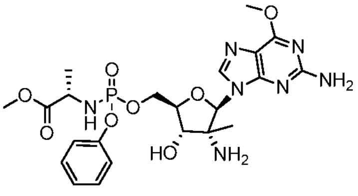
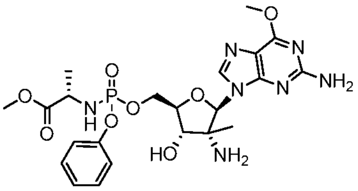
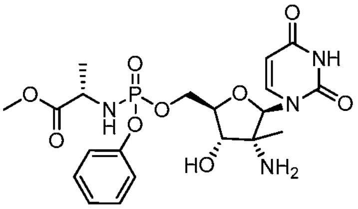
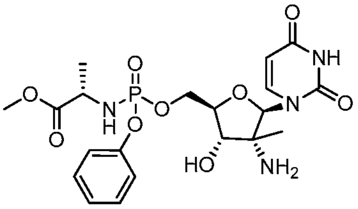
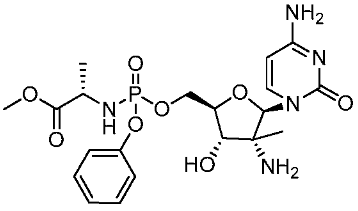
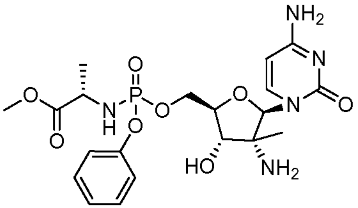
To the starting nucleoside **10** (100 mg, 0.3 mmol) in THF (3 mL) under N_2 was added t-BuMgCl (0.65 mL, 1 M in THF, 0.65 mmol, 2.1 equiv) via syringe. The reaction was allowed to stir for 15 minutes, then the prodrug intermediate **Int-21a** (157 mg, 0.37 mmol, 1.2 equiv., made using the methods described above in Example 20) was added as a solid in one portion. The reaction was allowed to stir at room temperature for 3 days. The reaction was quenched with MeOH (5 mL), concentrated *in vacuo*, and purified via flash column chromatography (0 to 20% MeOH/CH_2Cl_2) to give 140 mg of product **20** as white solid (80%).

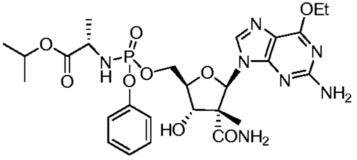
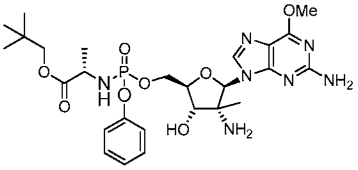
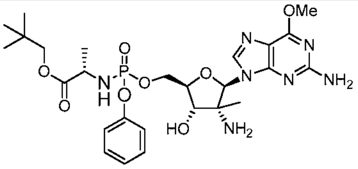
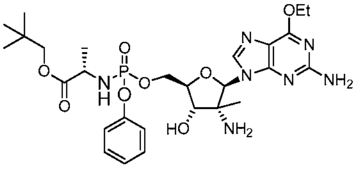
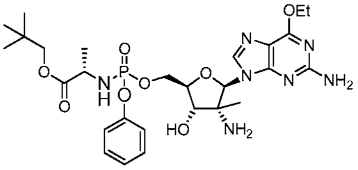
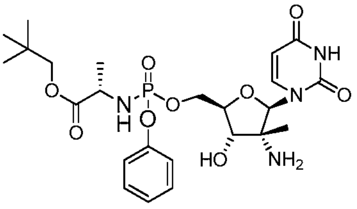
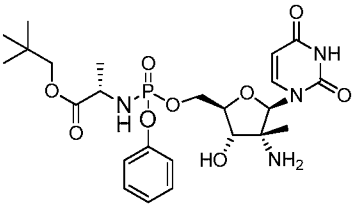
The following compounds of the present invention were made using the methods described in the Example above and substituting the appropriate reactants and/or reagents.

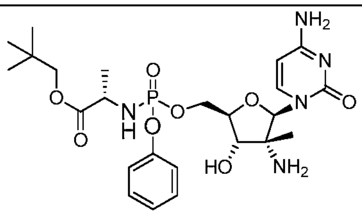
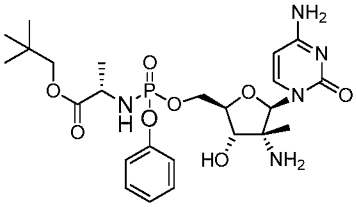
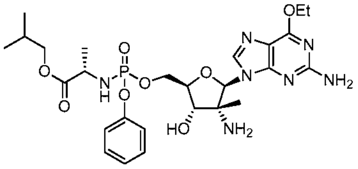
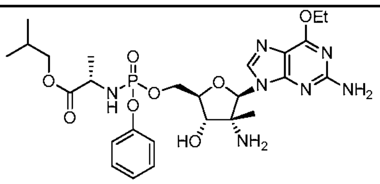
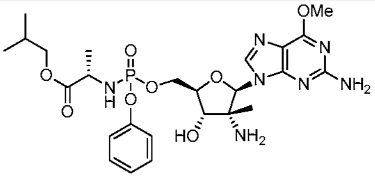
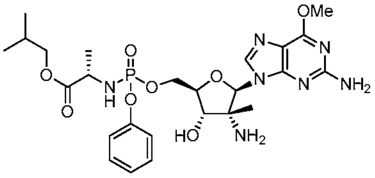
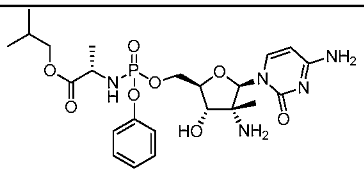
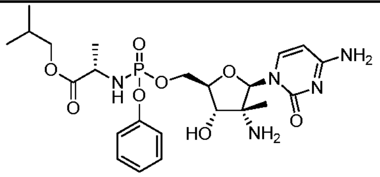
Compound No.	**Structure**	**Starting Material**	**MS (M + H)**
21	 Isomer 2	Compound 10	566.2
22	 Isomer 1	Compound 15	579.8
23	 Isomer 2	Compound 15	579.8
26	 Isomer 1	Compound 1	525.8
27	 Isomer 2	Compound 1	525.8

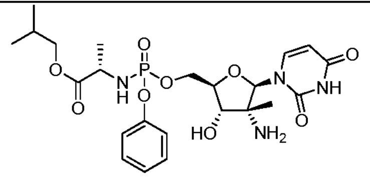
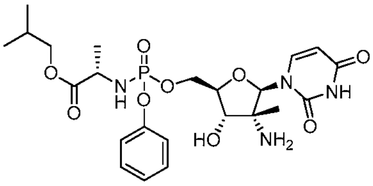
28	 Isomer 1	Compound 15	565.8
29	 Isomer 2	Compound 15	565.8
30	 Isomer 1	Compound 10	580.2
31	 Isomer 2	Compound 10	580.2
32	 Isomer 1	Compound 10	594.2
33	 Isomer 2	Compound 10	594.2
34	 Isomer 1	Compound 16	513.2
35		Compound 16	513.2

	Isomer 2		
36	 Isomer 1	Compound 1	512.2
37	 Isomer 2	Compound 1	512.2
38		Compound 89	605.5
39	 Isomer 1	Compound 87	622.2
40		Compound 88	591.4
41		Compound 88	591.4
42		Compound 88	605.4

43		Compound 15	597.2
44		Compound 15	689.2
45	 Isomer 1	Compound 15	552.20
46	 Isomer 2	Compound 15	552.2
47	 Isomer 1	Compound 16	499.20
48	 Isomer 2	Compound 16	499.20
49	 Isomer 1	Compound 1	498.20
50		Compound 1	498.20

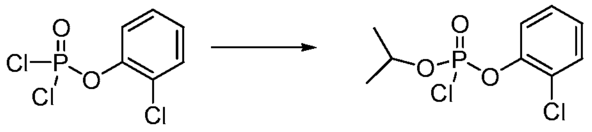
	Isomer 2		
51	 Isomer 1	Compound 87	622.2
52	 Isomer 1	Compound 15	608.2
53	 Isomer 2	Compound 15	608.2
54	 Isomer 1	Compound 10	622.2
55	 Isomer 2	Compound 10	622.2
56	 Isomer 1	Compound 16	555.2
57	 Isomer 2	Compound 16	555.2

58	 Isomer 1	Compound 1	554.2
59	 Isomer 2	Compound 1	554.2
60	 Isomer 1	Compound 10	608.3 (M+1)
61	 Isomer 2	Compound 10	608.2 (M+1)
62	 Isomer 1	Compound 15	594.3 (M+1)
63	 Isomer 2	Compound 15	594.3 (M+1)
64	 Isomer 1	Compound 1	540.2 (M+1)
65	 Isomer 2	Compound 1	540.4 (M+1)

66	 Isomer 1	Compound 16	541.2 (M+1)
67	 Isomer 2	Compound 16	541.1 (M+1)

EXAMPLE 22

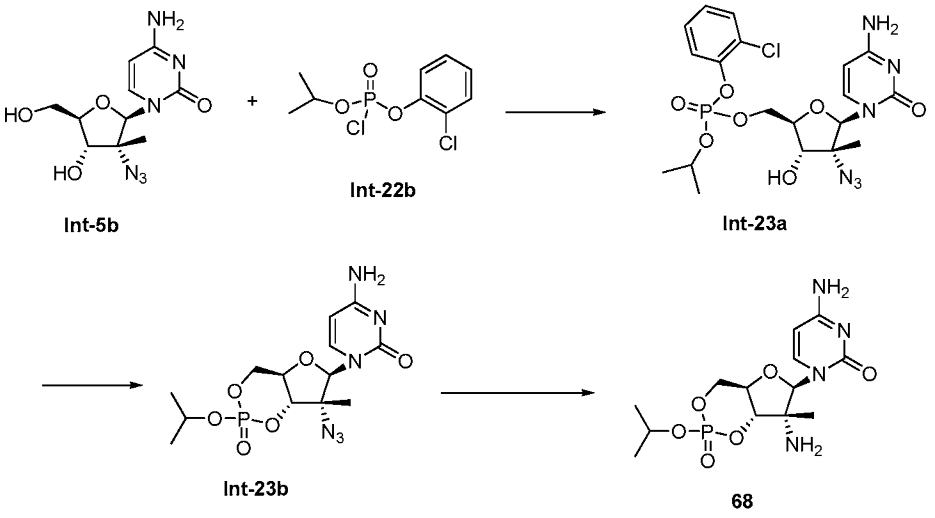
Preparation of Compound **Int-22b**


Int-22a **Int-22b**

A stirred solution of **Int-22a** (2.0 g, 8.15 mmol) in THF (15 mL) was cooled on an ice bath and treated with isopropanol (490 mg, 8.15 mmol) followed by the dropwise addition of 2,6-lutidine (873 mg, 8.15 mmol). The reaction was allowed to warm to room temperature for 2 hours. The solids were filtered and the filtrate was concentrated *in vacuo* to provide an oil with some solid. The residue was suspended in THF (15 mL) and stirred for 30 minutes. The solids were filtered off again and the filtrate was concentrated *in vacuo* to provide the **Int-22b** as a clear oil (1.9 g, 87%). Used without further purification.

EXAMPLE 23

Preparation of Compound **68**



Step A: Synthesis of Intermediate Compound Int-23a

To the starting nucleoside **Int-5b** (100 mg, 0.35 mmol) in THF (3.5 mL) was added NMI (280 uL, 3.5 mmol, 10 equiv). After 5 min, the phosphorous reagent **Int 22b**(190 mg, 0.7 mmol, 2 equiv) was added and the reaction was allowed to stir for 16 hours. The reaction was quenched with water (5 mL) and extracted with EtOAc (2 x 50 mL), the organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified via silica gel flash column chromatography (0 to 20% MeOH/CH_2Cl_2) to give the product **Int 23a** (10 mg, 5%).

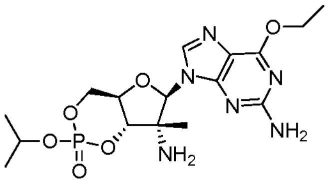
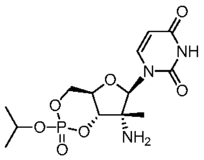
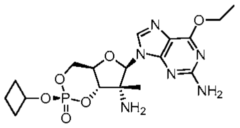
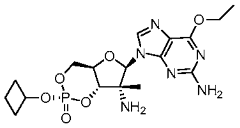
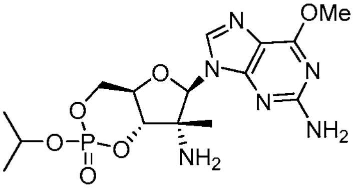
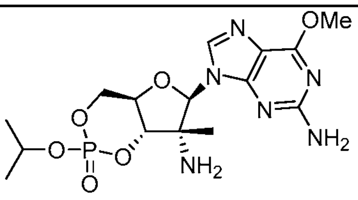
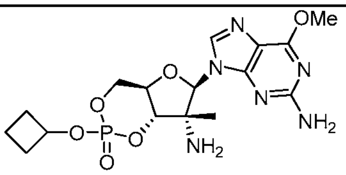
Step B: Synthesis of Intermediate Compound Int-23b

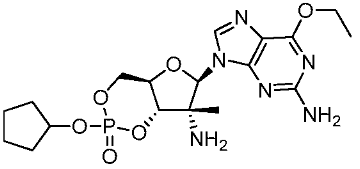
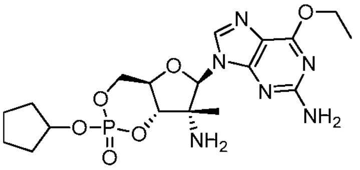
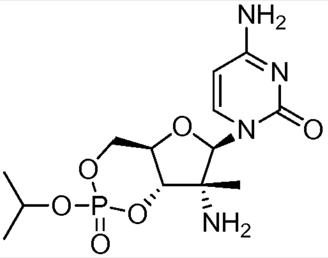
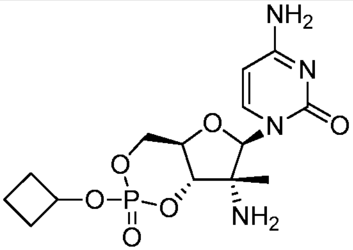
To the starting nucleotide **Int-23a** (10 mg, 0.02 mmol) dissolved in THF (1 mL) was added KOtBu (2 mg, 0.02 mmol, 1 equiv) and the reaction was stirred for 4 hours, concentrated *in vacuo* and purified via silica gel flash column chromatography (0 to 20% MeOH/CH_2Cl_2) followed by another purification via silica gel flash column chromatography (0 to 15% MeOH/CH_2Cl_2) to give the product **Int 23b** (5 mg, 67%).

Step C: Synthesis of compound 68

A solution of the azide **Int 23b** (1 mg, 0.003 mmol) in MeOH (1 mL) was treated with a small portion of $Pd(OH)_2$. To the vial was affixed a balloon of H_2 and the flask was filled and purged 5x, then allowed to stir under H_2 for 1 hour. The reaction was complete by TLC and LCMS analysis. The solution was filtered over celite and washed with MeOH, then concentrated *in vacuo* to give the pure amine product **68** (1 mg, quant.).

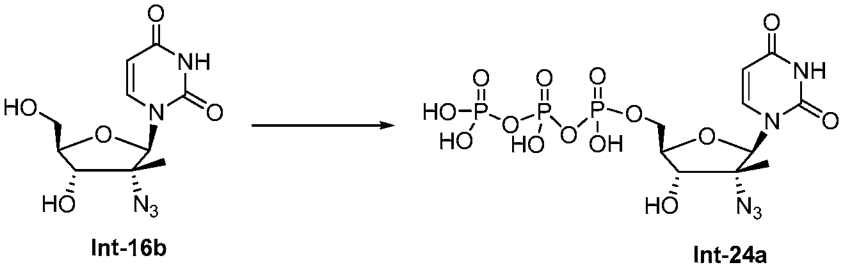
The following compounds of the present invention were made using the methods described in the Example above and substituting the appropriate reactants and/or reagents.

Compound No.	**Structure**	**Starting Material**	**MS (M + H)**
69		Compound 10	429.2
70		Compound 16	362.2
71	 **Isomer 1**	Compound 10	441.2
72	 **Isomer 2**	Compound 10	441.2
73	 Isomer 1	Compound 19	415.2
74	 Isomer 2	Compound 19	415.2
75	 Isomer 1	Compound 19	427.2

76		Compound 10	455.30
77		Compound 10	455.32
78		Compound 1	361.2
79		Compound 1	373.2

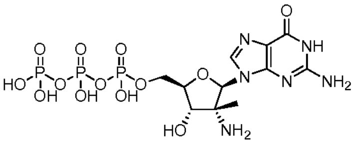
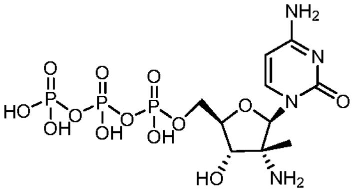
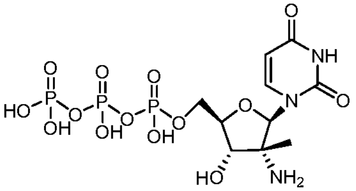
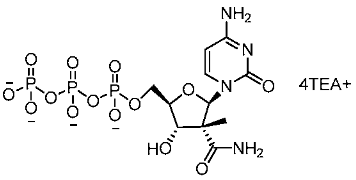
EXAMPLE 24

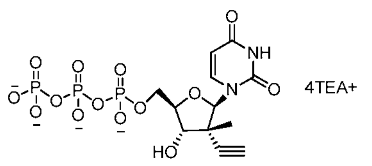
Preparation of **Int-24a**



A solution of compound **Int-16b** (15 mg, 0.05 mmol, 1.00 equiv) in trimethyl phosphate (1.0 mL) was placed under nitrogen atmosphere and to the solution was added proton sponge (17 mg, 0.08 mmol, 1.50 equiv). The reaction was cooled to 0 °C , then phosphoryl trichloride (32 mg, 0.21 mmol, 4.50 equiv) was added at 0°C. The resulting reaction was allowed to stir for 4 hours at 0 °C, then a solution of pyrophosphate (200 mg, 0.37 mmol, 5.00 equiv), N,N-dimethylformamide (1.0 mL) and tributylamine (0.03 mL, 10.00 equiv) was added. The resulting reaction was allowed to stir for 1 hour at 0 °C, then the reaction was then quenched by the addition of 3.0 mL of triethylammonium bicarbonate buffer (1M). The reaction mixture was concentrated *in vacuo* and the residue obtained was purified using Prep-HPLC with the following conditions (1#-Pre-HPLC-001(SHIMADZU)): Column, 1#-PrepC-008(Atlantis HILIC Silica 19*150 186003959 0110182551kk 03), mobile phase: acetonitrile and Water with 50mmol ammonium bicarbonate (88% Water with 50mmol ammonium bicarbonate down to 62% in 17 min); Detector, UV 220 & 254 nm. This provided 12 mg (43%) of compound **Int-24a** as a light yellow solid. (ES, *m/z*): 522 [M-H]$^-$; H-NMR (D_2O, 400MHz, *ppm*): δ 7.86 (s, 1H), 6.05 (s, 1H), 5.85 (s, 1H), 3.99-4.70 (m, 4H), 1.40 (s, 3H); P-NMR (D_2O, 162MHz, *ppm*): δ -6.09 (s, 1P), -11.12 (s, 1P) , -21.33 (s, 1P).

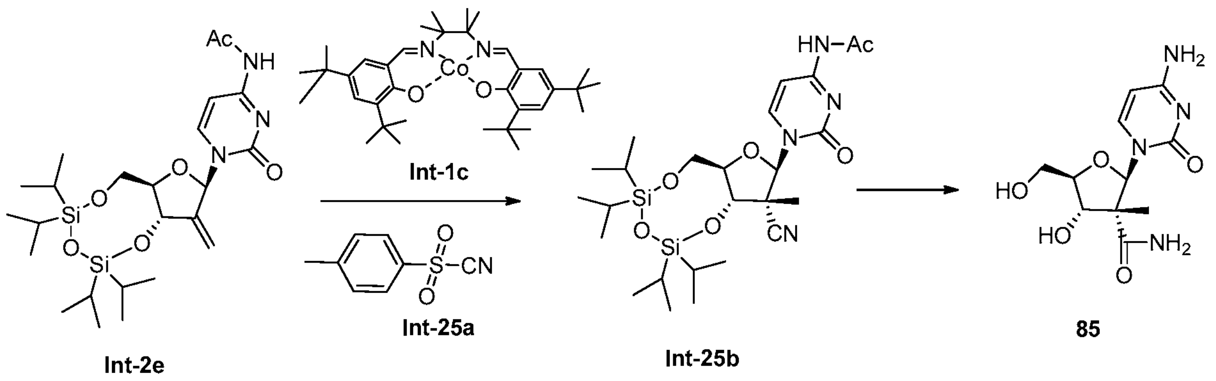
The following compounds of the present invention were made using the methods described in the Example above and substituting the appropriate reactants and/or reagents.

Compound No.	Structure	Starting Material	MS ESI deconvoluted
80		Compound Int-19a	535.8
81		Compound 1	495.8
82		Compound 16	496.8
83		Compound 85	524.8

84		Compound 89	506.0

EXAMPLE 25

Preparation of Compound **85**



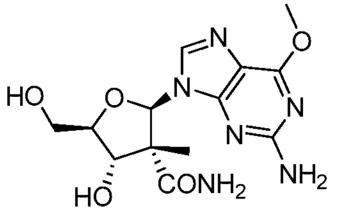
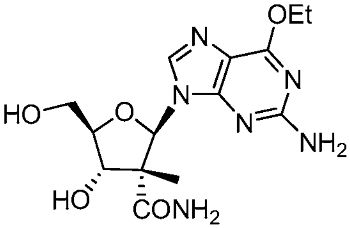
Step A: Synthesis of Intermediate Compound Int-25a

Compound **Int-2e** (300 mg, 0.57 mmol), Compound **Int-1c** (10 mg), and Compound **Int-25a** (3.1 g, 17.1 mmol) were dissolved in dioxane (2 mL) and the resulting reaction was allowed to stir for 5 minutes at room temperature. A solution of phenylsilane (68 mg, 0.63 mmol) in ethanol (1 mL) was then added dropwise over 2 minutes and the reaction was allowed to stir for and additional 30 minutes. The reaction was then quenched with brine and extracted with ethyl acetate. The organic extract was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue obtained was purified using flash chromatography on silica gel (2:1 hexanes/ethyl acetate) to provide compound **Int-25b** (80 mg). [M+H] = 551.5

Step B: Synthesis of compound 85

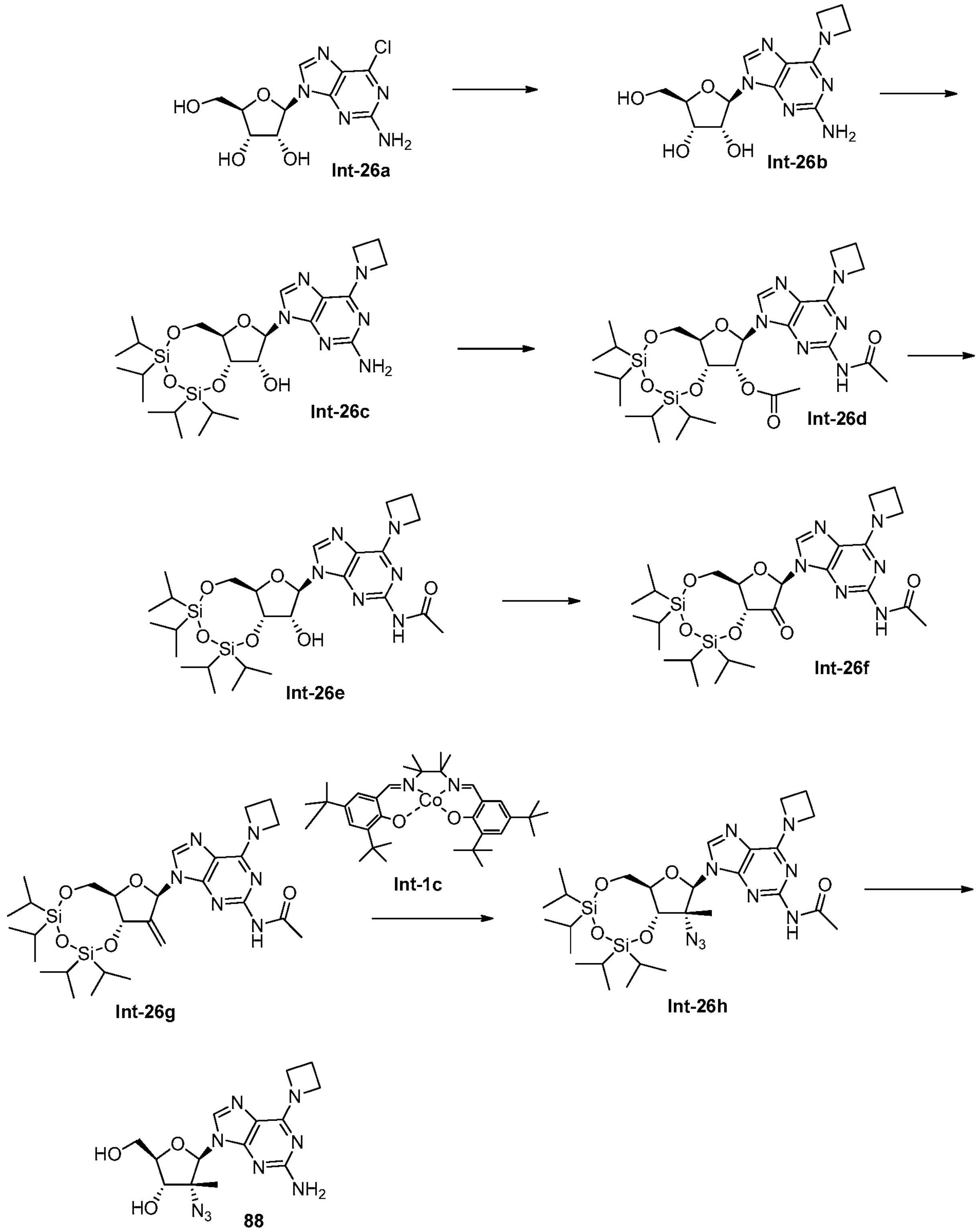
Into a cooled solution of starting nitrile **Int-25b** (90 mg, 0.163 mmol) in 8.1 mL of MeOH to 0 °C was bubbled HCl from a gas tank for 20 minutes. The reaction was stoppered and the reaction was stirred overnight over which period the reaction was allowed to warm up. The cycles of cooling and HCl saturation were continued for 5 days (once per day). On the last day the HCl was removed by streaming nitrogen through the reaction and the solvent was removed *in vacuo*. The residue was co-evaporated with 7N NH_3/ammonia to ensure conversion to free-base and then chromatographed on 12 g SiO_2 column using 0-50% MeOH/DCM gradient over 30 minutes to provide compound **85** (12 mg). ^{1}H NMR (400 MHz, CD_3OD) δ 8.42 (s, 1H), 6.50 (m, 1H), 5.95 (m, 1H), 3.94 (m, 3H), 7.75 (m, 1H), 1.15 (s, 3H). ESI [M+Na]=307, [M+H]=285.

The following compounds of the present invention were made using the methods described in the Example above and substituting the appropriate reactants and/or reagents.

Compound No.	Structure	Starting Material	MS (M + H)
86		Int 4f (6-OMe)	339.7
87		Int-4f	353.2 375 [M+Na]

EXAMPLE 26

Preparation of Compound **88**



Step A: Synthesis of Intermediate Compound Int-26b

To a 150mL thick-walled glass tube was added azetidine (4.00g) and 200 proof EtOH (81mL). To this stirring solution was added 6-chloroguanosine, **Int-26a** (4.23g). The glass tube was sealed and heated in an oil bath at 65 °C. After 50 hours, the reaction mixture was allowed to cool to room temperature. The reaction mixture was transferred to a 1000mL roundbottom flask and concentrated *in vacuo*. The residue was co-evaporated with 80% MeOH:DCM (500mL) and dried under high vacuum at room temperature. The crude material **Int-26b** was used without purification in the next step.

Step B: Synthesis of Intermediate Compound Int-26c

To the 1000mL roundbottom containing compound **Int-26b** (from above) was added pyridine (100 mL). The flask was flushed with nitrogen, capped with a rubber septum, and the system kept under a slight nitrogen stream. To the stirring mixture was added TIPDSiCl$_2$ (4.93mL); dropwise over 20 minutes. After 2.5 hours of stirring at room temperature, water (~5-8 mL) was added dropwise and stirred for additional 5minutes. The reaction mixture was diluted with EtOAc (2000 mL) and H$_2$O (1700 mL) and stirred vigorously for 0.25 hours. The layers were separated, and the aqueous layer was extracted again with EtOAc (2000 mL). The organic layers were combined, dried over Na$_2$SO$_4$, and filtered. The filtrate was concentrated *in vacuo* and the residue was purified using silica gel chromatography 0/100 to 4/96 MeOH/CH$_2$Cl$_2$. to provide **Int-26c (**3.52 g). LC-MS (M+H)$^+$ 565.3

Step C: Synthesis of Intermediate Compound Int-26d

To a dry, nitrogen flushed 1000mL roundbottom flask was added **Int-26c** (6.317g) and pyridine (103 mL). To this stirring solution were added Ac$_2$O (105.5mL) and DMAP (1.367g), respectively. The flask was capped and the solution was stirred at room temperature. After 22 hours, the reaction mixture was concentrated *in vacuo* and co-evaporated *in vacuo* with toluene (5x400 mL). The residue was taken up in EtOAc (2000 mL) and washed with satd NH$_4$Cl (1000 mL). The aqueous layer was extracted with EtOAc (1500mL). The combined organic layers were washed with saturated NH$_4$Cl (1000 mL), brine (1000 mL), dried over Na$_2$SO$_4$, filtered, and concentrated *in vacuo*. The crude product **Int-26d** was carried forward without purification.

Step D: Synthesis of Intermediate Compound Int-26e

To the 3000 mL roundbottom containing **Int-26d** (from above) was added 7N NH$_3$ in MeOH (205.3 mL). The reaction was sealed and stirred at room temperature overnight. The solvent was concentrated *in vacuo*. The residue was purified using silica gel chromatography 0/100 to 10/90 MeOH/CH$_2$Cl$_2$ to provide **Int 26e (**3.52 g). LC-MS (M+H)$^+$ 607.3

Step E: Synthesis of Intermediate Compound Int-26f

To a solution of **Int-26e** (3g) in CH_2Cl_2 (30 ml) and water (6 ml) cooled in an ice bath were added KBr (59 mg) and TEMPO (77 mg). The reaction was treated with a mixture of bleach (6%, 6.1 ml)/aq. NaHCO3 (1.25g in 6 mL water) dropwise over 15 minutes. Mass spec analysis showed SM and some product (as MeOH adduct). Added another portion of bleach (~6 ml) dropwise, and the reaction was stirred vigorously overnight (bath temp ~10°C). The reaction was quenched by the addition of satd $Na_2S_2O_3$ solution (150 ml), and EtOAc (125 ml). The aqueous layer was extracted with EtOAc (125 ml), and the combined organic layers were washed with brine (150 ml), dried (Na_2SO_4), filtered and concentrated *in vacuo* to provide **Int-26f** (3g, white foam) that was used without purification.

Step F: Synthesis of Intermediate Compound Int-26g

To methyl triphenylphosphonium bromide (10.6 g) in THF (50 ml) was added KHMDS in THF (1M, 29.6 ml). The reaction mixture turned to deep yellow color and remained. The reaction was then cooled to 0°C, and treated dropwise with **Int-26f** (2.99 g) in THF (50 ml). The reaction was warmed to room temperature overnight and then quenched with saturated NH_4Cl (150 ml)/brine (100 ml) and extracted with EtOAc (2 x 250 ml). The combined organic layers were washed with brine (200 ml), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude material was purified using silica gel chromatography 0/100 to 100/0 of EtOAc/hexanes that afforded **Int-26g** (1.4g). LC-MS $(M+H)^+$ 603.2

Step G: Synthesis of Intermediate Compound Int-26h

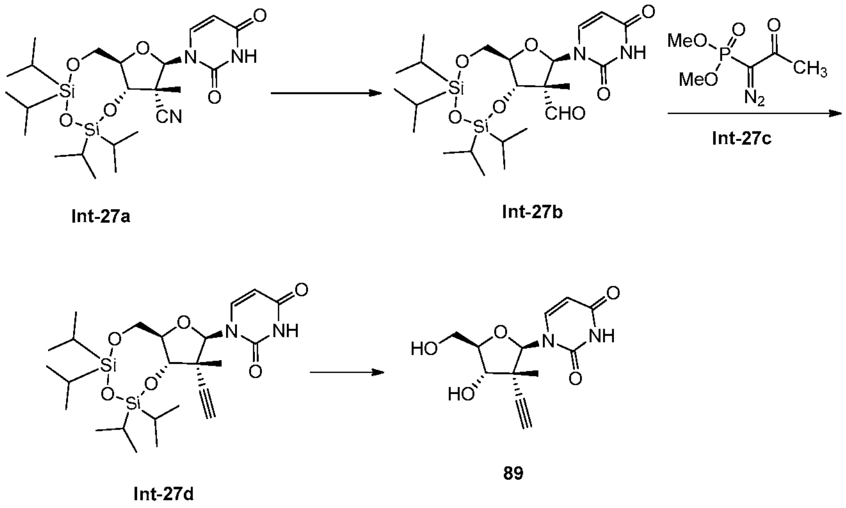
To **Int-26g** (1.4g) and catalyst **Int-1c** (28 mg) was added tosyl azide (13.74 g). The solution was stirred for 5 minutes and then phenyl silane (302 mg) in EtOH (6 ml), was added dropwise, over 45 minutes. The reaction was quenched with EtOAc (150 ml) and brine (150 ml). The aqueous layer was extracted with EtOAc (150 ml). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude material was purified using silica gel chromatography 0/100 to 60/40 of EtOAc/hexanes to provide **Int-26h** (710 mg). LC-MS $(M+H)^+$ 646.2

Step H: Synthesis of Compound 88

To a solution of **Int-26h** (700mg) in THF (20 ml) at was added TBAF in THF (1M, 2.17 ml) dropwise. The reaction mixture was stirred for 2 hours and then was concentrated *in vacuo*. The residue was taken in 7N NH_3 in MeOH (22 ml) and transferred to a thick-walled glass tube. A solution of NH_4OH (8 ml) was added and the reaction was heated to 100°C for 48hours. The reaction was concentrated *in vacuo* and the crude residue was purified using silica gel chromatography 0/100 to 10/90 of MeOH/CH_2Cl_2 to provide compound **88** (365 mg). LC-MS $(M+H)^+$ 362.2

EXAMPLE 27

Preparation of Compound **89**



Step A – Synthesis of Compound Int-27b

Compound **Int-27a** (178 mg, 0.349 mmol, synthesized from **Int-15d** using the procedure described in Example 25) in dichloromethane (7 mL) was treated with bis(cyclopentadienyl)zirconium chloride hydride (900 mg, 3.49 mmol). The reaction was stirred at room temperature for 30 minutes. Saturated sodium potassium tartrate solution (10 mL) and ethyl acetate (10 mL) were added and the mixture was stirred until clear. The layers were separated and the aqueous phase was extracted with ethyl acetate (2x10 mL). The organic extracts were washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to provide compound **Int-27b** (151 mg) as a yellow foam. [M+H] = 513.3.

Step B – Synthesis of Compound Int-27d

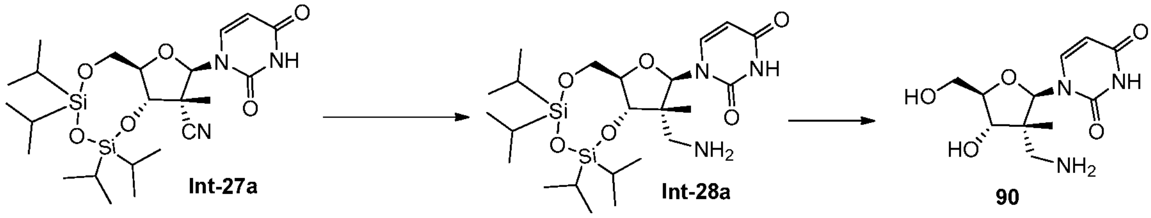
To a solution of **Int-27b** (186 mg, 0.362 mmol) in MeOH (3 mL) at 0 °C was added **Int-27c** (104 mg, 0.543 mmol) and K_2CO_3 (150 mg, 1.086 mmol). The reaction was stirred from 0°C to room temperature for 6 hours. The reaction was diluted with water (10 mL) and extracted with ethyl acetate (2x20 mL). The combined organic phase was washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The reaction was purified by preparative TLC (50% ethyl acetate/hexanes) to give **Int-27d** (42.5 mg). [M+H] = 509.3.

Step C – Synthesis of Compound 89

To a solution of compound **Int-27d** (48.5 mg, 0.095 mmol) in tetrahydrofuran (5 mL) was added tetrabutylammonium fluoride solution (0.19 mL, 0.191 mmol, 1 M in THF). The reaction was allowed to stir for 30 minutes. The reaction mixture was concentrated *in vacuo* and the residue obtained was purified by silica gel preparative TLC (5% methanol in dichloromethane) to provide 14.3 mg of compound **89**. [M+H] = 267.7; ^1H NMR (400 MHz, CD_3OD) δ 8.25 (d, J = 8.0 Hz, 1H), 6.23 (s, 1H), 5.68 (d, J = 8.0 Hz), 4.01-3.97 (m, 2H), 3.91 (d, J = 9.2 Hz, 1H), 3.80 (dd, J = 13.2, 2.8 Hz, 1H), 2.82 (s, 1H), 1.22 (s, 3H).

EXAMPLE 28

Preparation of Compound **90**



Step A – Synthesis of Compound Int-28a

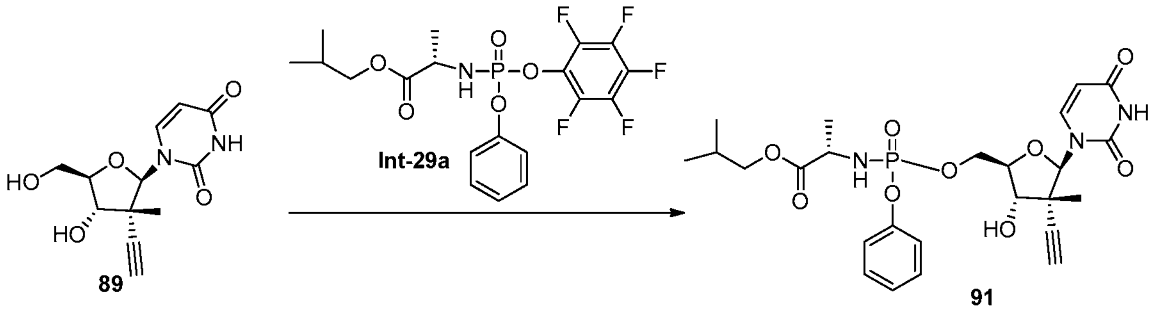
Compound **Int-27a** (58.1 mg, 0.114 mmol, synthesized from **Int-15d** using the procedure described in Example 25) in dichloromethane (4 mL) at – 78 °C was treated with DIBAL-H solution (1.14 mL mg, 1.14 mmol, 1 M in hexanes). The reaction was stirred at – 78 °C for 3.5 hours. The reaction was quenched with MeOH (1 mL). Saturated sodium potassium tartrate solution (10 mL) was added and the mixture was stirred until clear. The layers were separated and the aqueous phase was extracted with dichloromethane (2x20 mL). The organic phase was dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified using flash column chromatography on silica gel (50% ethyl acetate/hexanes) to provide compound **Int-28a** (11.2 mg). [M+H] = 514.4.

Step B – Synthesis of Compound 90

To a solution of compound **Int-28a** (6.3 mg, 0.012 mmol) in tetrahydrofuran (1 mL) was added tetrabutylammonium fluoride solution (25 µL, 0.025 mmol, 1 M in THF). The reaction was allowed to stir for 20 hours. The reaction mixture was concentrated *in vacuo* and the residue obtained was purified by reverse phase HPLC (2% to 95% water in acetonitrile containing 0.1% TFA over 20-25 min) to provide 4.3 mg of compound **90**.

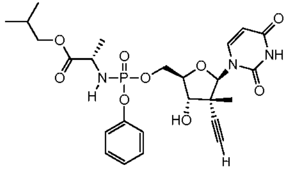
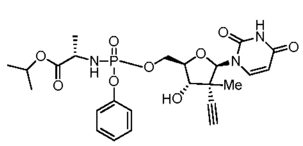
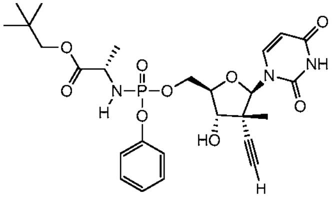
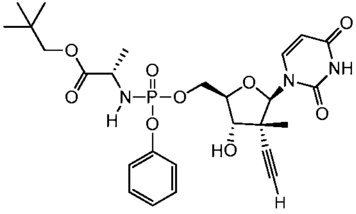
EXAMPLE 29

Preparation of Compound **91**



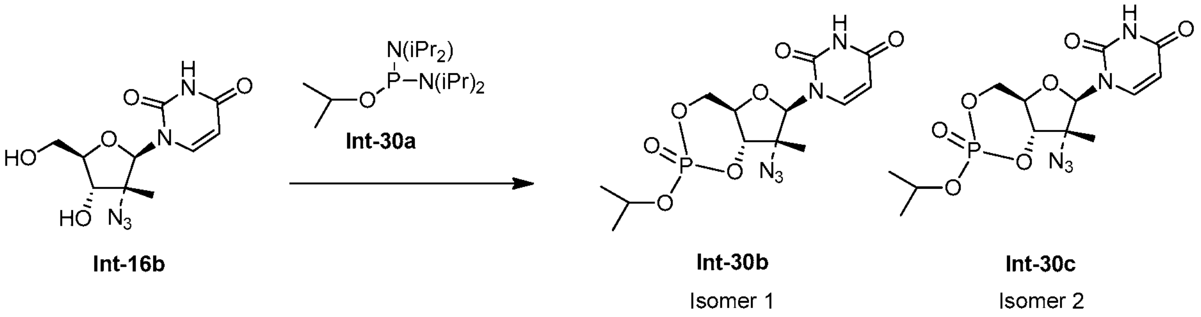
Compound **89** (20 mg, 0.075 mmol) in tetrahydrofuran (3 mL) at 0 °C was treated with *t*-butylMgCl solution (94 µL, 0.188 mmol, 2M in THF). The reaction was allowed to stir for 15 minutes. A solution of compound **Int-29a** (42.1 mg, 0.090 mmol, synthesized using the methods described in Example 20) in tetrahydrofuran (2 mL) was added dropwise. The reaction was allowed to warm to room temperature and stir for 8.5 hours. The reaction was quenched with saturated ammonium chloride (10 mL) and extracted with ethyl acetate (2x10 mL). The organic phase was dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue obtained was purified by silica gel preparative TLC (5% dichloromethane/methanol) to provide compound **91** (14.5 mg). ^{1}H NMR (400 MHz, CD_3OD) δ 7.72 (d, *J* = 8.0 Hz, 1H), 7.40-7.36 (m, 2H), 7.29-7.19 (m, 3H), 6.25 (s, 1H), 5.60 (d, *J* = 8.0 Hz), 4.51 (ddd, *J* = 11.8, 5.6, 2.2 Hz, 1H), 4.39 (ddd, *J* = 11.8, 5.6, 3.6 Hz, 1H), 4.18-4.14 (m, 1H), 4.03-3.95 (m, 1H), 3.92-3.83 (m, 3H), 1.96-1.85 (m, 1H), 1.91 (m, 1H), 1.38 (dd, *J* = 7.2, 0.8 Hz, 3 H), 1.21 (s, 3H), 0.92 (dd, *J* = 6.8, 0.8 Hz, 6 H). Mass calculated for formula $C_{25}H_{32}N_3O_9P$ 549.2; observed MH$^+$ (LCMS) 550.2 (*m/z*).

The following compounds of the present invention were made using the methods described in the Example above and substituting the appropriate reactants and/or reagents.

Compound No.	Structure	Starting Material	MS (M + H)
92	 single isomer	Compound 89	550
93		Compound 89	536.2
94	 Isomer 1	Compound 89	564.2
95	 Isomer 2	Compound 89	564.2

EXAMPLE 30

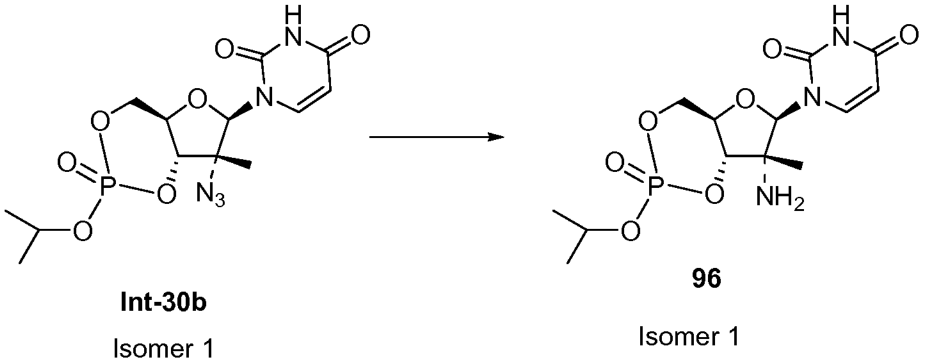
Preparation of Compounds **Int-30b** and **Int-30c**



Int-30a (61.5 mg; 0.212 mmol) was added dropwise to a stirred mixture of tetrazole (29.7mg; 0.424mmol) and compound **Int-16b** (40 mg; 0.141 mmol) in acetonitrile (3 ml). The resulting mixture was stirred at room temperature for 3 hours, and *tert*-butyl hydroperoxide (80% aqueous solution; 0.068 ml; 0.565 mmol) was added and the mixture stirred overnight.. The volatiles were removed *in vacuo* and the residue was subjected to silica gel column chromatography (99:1 to 97:3; CH_2Cl_2; MeOH) to provide compound **Int-30b** (3 mg; 5.5%), and **Int-30c** (2 mg, 3.7%). ^{1}H NMR: **Int-30b** (CD_3OD): δ7.62 (1H, d, J=10.0Hz), 6.06 (1H, s), 5.76 (1H, d, J=10.0Hz), 4.70-4.81 (2H, m), 4.60-4.66 (1H, m), 4.54-4.56 (1H, m), 4.39-4.45 (1H, m), 1.47 (3H, s), 1.40 (6H, d, J=10Hz). LC-MS: **Int-30b**: (ES, *m/z*): 388.2 LC-MS: **Int-30c**: (ES, *m/z*): 388.2

EXAMPLE 31

Preparation of Compounds **96**



Int-30b

Isomer 1

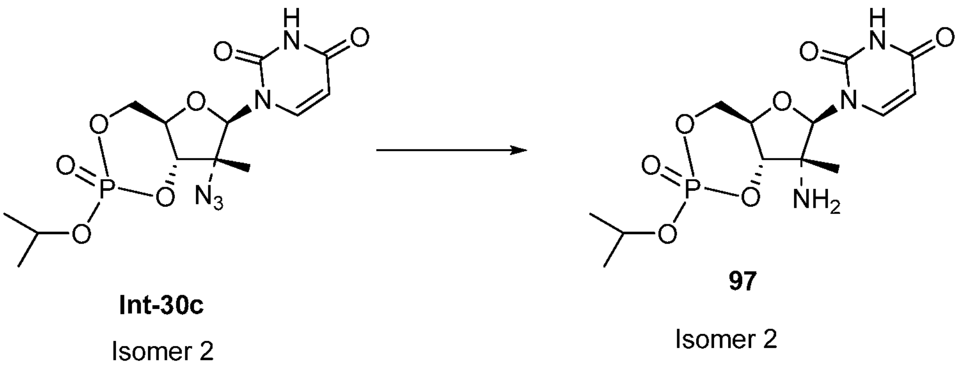
96

Isomer 1

A solution of **Int-30b** (32 mg, 0.083 mmol) in methanol was treated with $Pd(OH)_2$ (20 mg) and stirred under a hydrogen atmosphere for 30 minutes. The reaction mixture was filtered through celite and the solvent was removed *in vacuo* to provide the desired product compound **96** (24 mg). ^{1}H NMR: **96** (CD_3OD): δ7.65 (d, J=10.0Hz,1H), 6.04 (s, 1H), 5.76 (d, J=10.0Hz, 1H), 4.80-4.71 (m, 2H), 4.66-4.60 (m, 1H), 4.54-4.49 (m, 1H), 4.4-4.3 (m, 1H), 1.40 (s, 3H), 1.40 (d, J=10 Hz, 6H). LC-MS: **96**: (ES, *m/z*): 362.2

EXAMPLE 32

Preparation of Compounds **97**



Int-30c

Isomer 2

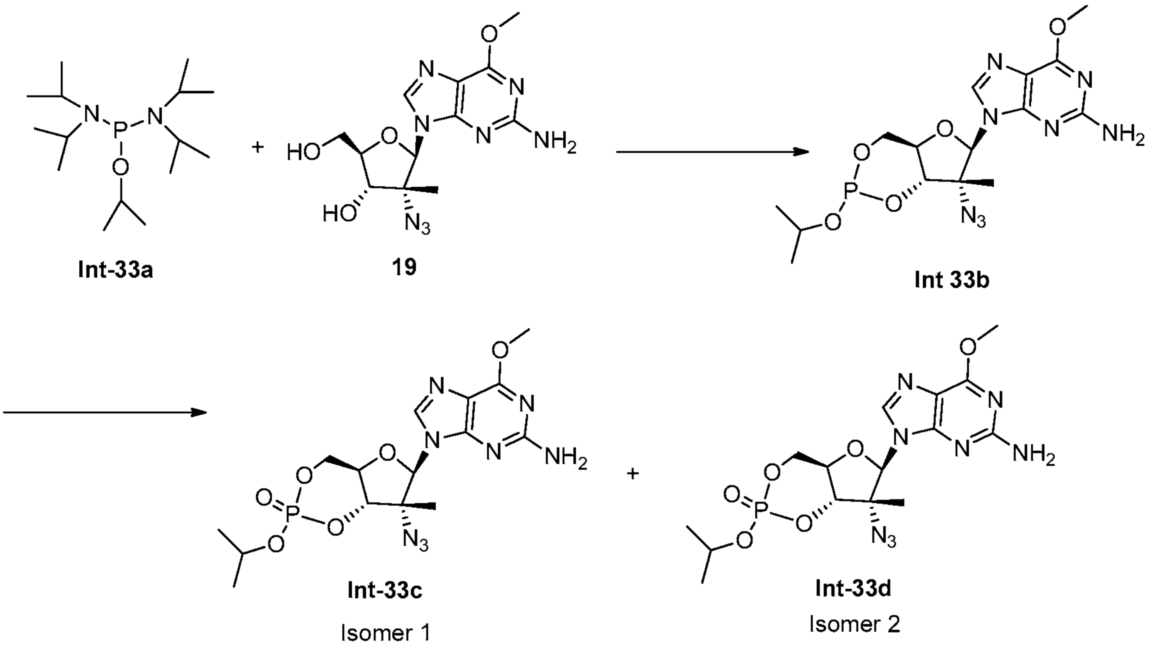
97

Isomer 2

A solution of **Int-30c** (32 mg, 0.083 mmol) in methanol was treated with $Pd(OH)_2$ (20 mg) and stirred under a hydrogen atmosphere for 30 minutes. The reaction mixture was filtered through celite and the solvent was removed *in vacuo* to provide the desired product compound **97** (21 mg). ^1H NMR: **97** (CD_3OD): δ7.69 (d, J=10.0Hz,1H), 6.02 (s, 1H), 5.76 (d, J=10.0Hz, 1H), 4.80-4.65 (m, 2H), 4.62-4.55 (m, 1H), 4.42-4.36 (m, 1H), 4.16-4.12 (m, 1H), 1.43 (d, J=10 Hz, 6H), 1.43 (s, 3H). LC-MS: **97**: (ES, *m/z*): 362.2

EXAMPLE 33

Preparation of Compounds **Int-33c** and **Int-33d**



Step A: Synthesis of Int 33b

To a stirred solution of compound **19** (30 mg, 0.09 mmol, 1.00 equiv) in acetonitrile (3 mL) was added 1H-imidazole-4,5-dicarbonitrile (36.8 mg, 0.31 mmol, 3.50 equiv) and molecular sieves (4 Å). The resulting solution was stirred at 25°C for 30 minutes. The reaction was cooled in an ice bath and a solution of **Int 33a** (33.6 mg, 0.12 mmol, 1.30 equiv) in acetonitrile (1.0 mL) was added dropwise over 15 minutes. The resulting solution was stirred at 25°C for 3 hours and at 50°C for 1 hour. The reaction was concentrated *in vacuo* to give 100 mg (crude) of **Int 33 b** as a white solid which was used for the next step directly without further purification.

Step B: Synthesis of compounds Int-33c and Int-33d

A solution of **Int 33b** (100 mg, 0.24 mmol, 1.00 equiv) in tetrahydrofuran / pyridine / water (78:20:2) (4 mL) was added iodine (101 mg, 0.24 mmol). The resulting solution was stirred at 0°C for 1 hour and then quenched by the addition of aqueous sodium thiosulfate (0.1M, 5 mL) and extracted with ethyl acetate (3x15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product (20 mg) was purified by Prep-HPLC with the following conditions (1#-Pre-HPLC-011(Waters)): Column, SunFire Prep C18, 19*150mm 5um; mobile phase, water and acetonitrile (20.0% acetonitrile up to 57.0% in 7 min, up to 100.0% in 2 min, down to 20.0% in 1 min); Detector, UV 254 & 220nm. This resulted in 7.22 mg (6.96%) of **Int-33c** (isomer 1) as a white solid and 13.5 mg (13.01%) of **Int-33d** (isomer 2) as a white solid. LC-MS-**Int-33c** (isomer 1): (ES, *m/z*): 441 $[M+H]^+$

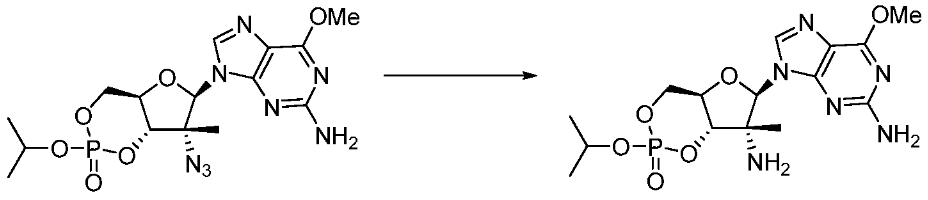
^1H-NMR-**Int-33c** (isomer 1): (400MHz, $CDCl_3$, *ppm*): δ 7.58 (s, 1H), 5.77 (s, 1H), 4.88-4.94 (m, 2H), 4.58-4.67(m, 1H), 4.49-4.54 (m, 1H), 4.39-4.4 5(m, 1H), 4.10 (s, 3H), 1.45-1.50 (m, 6H), 1.32 (s, 3H). ^{31}P-NMR-**Int-33c** (isomer 1): (121MHz, $CDCl_3$, *ppm*): δ -7.43

LC-MS-**Int-33d** (isomer 2): (ES, *m/z*): 441 $[M+H]^+$

^1H-NMR-**Int-33d** (isomer 2): (400MHz, $CDCl_3$, *ppm*): δ 7.55 (s, 1H), 5.73 (s, 1H), 5.05-5.10 (m, 1H), 4.82-4.87 (m, 1H), 4.57-4.67 (m, 2H), 4.42-4.48 (m, 1H), 4.09 (s, 3H), 1.45 (s, 3H), 1.44 (s, 3H), 1.37 (s, 3H) ^{31}P-**Int-33d** (isomer 2): (121MHz, $CDCl_3$, *ppm*): δ -4.24

EXAMPLE 34

Preparation of Compound 98



Int-33c
isomer 1

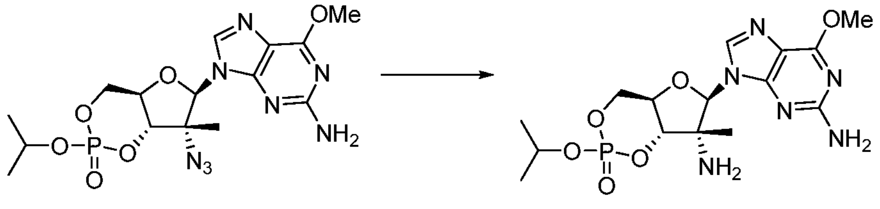
98
isomer 1

To the starting azide **Int-33c** (254 mg, 0.58 mmol) dissolved in MeOH (3 mL) was added a spatula tip of $Pd(OH)_2$ and a balloon of H_2 was affixed. The vessel was purged and refilled with H_2 5 times, then allowed to stir at room temperature 2 hours. The reaction was complete by LC-MS and TLC analysis. The mixture was filtered over celite, concentrated *in vacuo*, and then purified via silica gel flash column chromatography (0 to 15% $MeOH/CH_2Cl_2$) to give the product **98** (180 mg, 75%) as a white powder. ^1H NMR (500 MHz,

CD_3OD) δ 7.96 (s, 1H), 5.95 (s, 1H), 4.82-4.75 (m, 2H), 4.68 (dd, 1H, *J* = 4.7, 9.5 Hz), 4.64 (dd, 1H, *J* = 4.8, 9.5 Hz), 4.47 (ddd, 1H, *J* = 4.8, 10.0, 10.0 Hz), 4.07 (s, 3H), 1.47 (d, 3H, *J* = 6.0 Hz), 1.44 (d, 3H, *J* = 6.0 Hz), 1.00 (s, 3H).

EXAMPLE 35

Preparation of Compound **99**



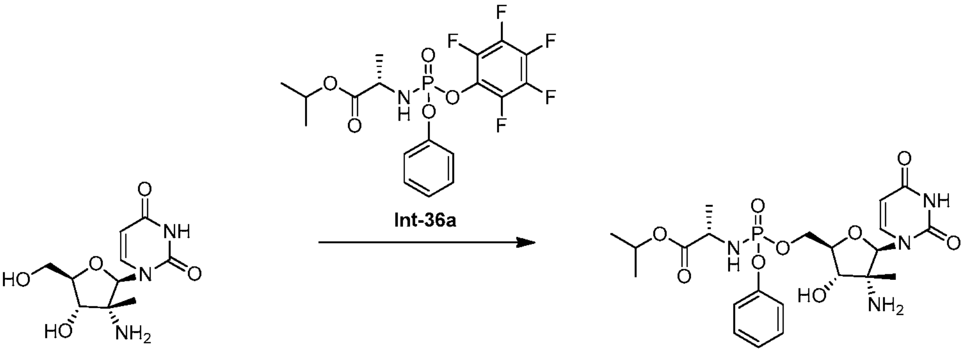
Int-33d
isomer 2

99
isomer 2

To the starting azide **Int-33d** (74 mg, 0.17 mmol) dissolved in MeOH (3 mL) was added a spatula tip of $Pd(OH)_2$ and a balloon of H_2 was affixed. The vessel was purged and refilled with H_2 5 times, then allowed to stir at room temperature for 2 hours. The reaction was complete by LC-MS and TLC analysis. The mixture was filtered over celite, concentrated *in vacuo*, and then purified via silica gel flash column chromatography (0 to 15% $MeOH/CH_2Cl_2$) to give the product **99** (45 mg, 65%) as a white powder. ^{1}H NMR (500 MHz, CD_3OD) δ 7.90 (s, 1H), 5.91 (s, 1H), 4.84-4.77 (m, 1H), 4.76-4.64 (m, 3H), 4.57-4.51 (m, 1H), 4.06 (s, 3H), 1.41 (app t, 6H, *J* = 6.5 Hz), 1.07 (s, 3H).

EXAMPLE 36

Preparation of Compounds **24** and **25**

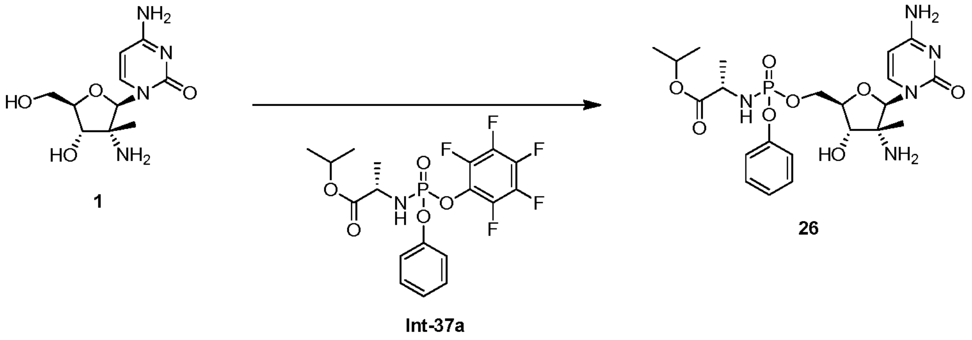


16 **24**

To the starting nucleoside **16** (100 mg, 0.39 mmol) in THF (2 mL) was added *t*BuMgCl (0.78 mL, 1 M in THF, 0.78 mmol) and the reaction was stirred for 15 minutes at room temperature. The phosphorous reagent Int-36a (194 mg, 0.429 mmol) was added all at once and the reaction was allowed to stir for 16 hours. The reaction was quenched with MeOH, concentrated *in vacuo*, and the residue was purified by silica gel flash column chromatography (0 to 10 to 25% MeOH/CH_2Cl_2) to provide Compound **24** (80 mg, 39%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.67 (d, 1H, *J* = 8.2), 7.33-7.28 (m, 2H), 7.19-7.11 (m, 3H), 5.90 (s, 1H), 5.60 (d, 1H, *J* = 8.0 Hz), 4.91 (sept, 1H, 6.3 Hz), 4.49 (ddd, 1H, *J* = 11.9, 5.3, 2.3 Hz), 4.34 (ddd, 1H, *J* = 11.9, 6.1, 3.1 Hz), 4.10-4.06 (m, 1H), 3.88 (d, 1H, *J* = 8.0 Hz), 3.88-3.80 (m, 1H), 1.25 (dd, 3H, *J* = 7.2, 1.2 Hz), 1.16 (d, 1H, 6.3 Hz), 1.15 (d, 1H, 6.3 Hz), 1.06 (s, 3H).

EXAMPLE 37

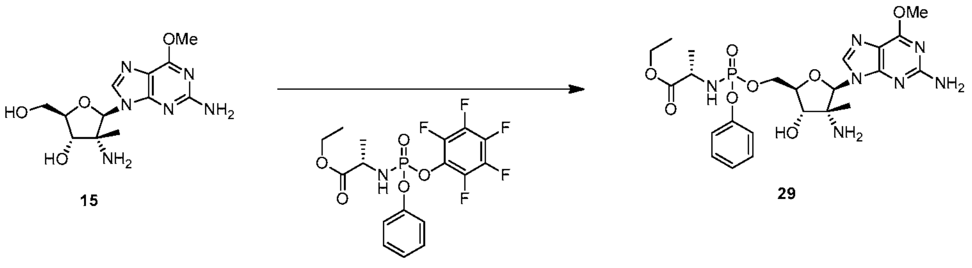
Preparation of Compound **26**



To the starting nucleoside **1** (50 mg, 0.2 mmol) in THF (0.85 mL) and NMP (0.15 mL) was added *t*BuMgCl (0.22 mL, 1 M in THF, 0.22 mmol) and the reaction was stirred for 15 minutes at room temperature. The phosphorous reagent **Int-37a** (99 mg, 0.22 mmol) was added all at once and the reaction was allowed to stir for 16 hours. The reaction was quenched with MeOH, concentrated *in vacuo*, and the residue was purified by silica gel flash column chromatography (0 to 10 to 40% MeOH/CH_2Cl_2) to give the product (31 mg, 30%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.72 (d, 1H, *J* = 7.6 Hz), 7.40-7.35 (m, 2H), 7.28-7.16 (m, 3H), 5.93 (s, 1H), 5.87 (d, 1H, *J* = 7.4 Hz), 4.99-4.92 (m, 1H), 4.50 (ddd, 1H, *J* = 11.9 6.6, 2.1 Hz), 4.34 (ddd, 1H, *J* = 11.9, 6.8, 3.7 Hz), 4.13-4.08 (m, 1H), 3.96-3.84 (m, 1H), 3.87 (1H, d, *J* = 8.0 Hz), 1.35 (dd, 3H, *J* = 7.0, 1.0 Hz), 1.21 (d, 6H, *J* = 6.3 Hz), 1.03 (s, 3H).

EXAMPLE 38

Preparation of Compounds **29**



15

Int-38a

29

To the starting nucleoside **15** (100 mg, 0.32 mmol) in THF (3 mL) was added *t*BuMgCl (0.68 mL, 1 M in THF, 0.68 mmol) and the reaction was stirred for 15 minutes at room temperature. The phosphorous reagent **Int-38a** (155 mg, 0.35 mmol) was added in one portion and the reaction was allowed to stir for 2.5 days. The reaction was quenched with MeOH, concentrated *in vacuo*, and the residue was purified by silica gel flash column chromatography (0 to 7 to 20% MeOH/CH_2Cl_2) to give the product (78 mg, 43%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.96 (s, 1H), 7.35-7.14 (m, 5H), 6.05 (s, 1H), 4.60-4.46 (m, 2H), 4.30-4.22 (m, 2H), 4.13-4.04 (m, 2H), 4.05 (s, 3H), 3.99-3.83 (m, 1H), 1.30 (dd, 3H, J = 7.2, 1.2 Hz), 1.20 (t, 3H, J = 7.0 Hz), 0.94 (s, 3H).

EXAMPLE 39

Cell-Based HCV Replicon Assay

To measure cell-based anti-HCV activity of selected compounds of the present invention, replicon cells were seeded at 5000 cells/well in 96-well collagen I-coated Nunc plates in the presence of the test compound. Various concentrations of test compound, typically in 10 serial 2-fold dilutions, were added to the assay mixture, with the starting concentration ranging from 250 μM to 1 μM. The final concentration of dimethylsulfoxide was 0.5%, fetal bovine serum was 5%, in the assay media. Cells were harvested on day 3 by the addition of 1x cell lysis buffer (Ambion cat #8721). The replicon RNA level was measured using real time PCR (Taqman assay). The amplicon was located in 5B. The PCR primers were: 5B.2F, ATGGACAGGCGCCCTGA (SEQ ID. NO. 1); 5B.2R, TTGATGGGCAGCTTGGTTTC (SEQ ID. NO. 2); the probe sequence was FAM-labeled CACGCCATGCGCTGCGG (SEQ ID. NO. 3). GAPDH RNA was used as endogenous control and was amplified in the same reaction as NS5B (multiplex PCR) using primers and VIC-labeled probe recommended by the manufacturer (PE Applied Biosystem). The real-time RT-PCR reactions were run on ABI PRISM 7900HT Sequence Detection System using the following program: 48°C for 30 minutes, 95°C for 10 minutes, 40 cycles of 95°C for 15 sec, 60°C for 1 minute. The ΔCT values (CT_{5B}-CT_{GAPDH}) were plotted against the concentration of test compound and fitted to the sigmoid dose-response model using XLfit4 (MDL). EC_{50} was defined as the concentration of inhibitor necessary to achieve $\Delta CT=1$ over the projected baseline; EC_{90} the concentration necessary to achieve $\Delta CT=3.2$ over the baseline. Alternatively, to quantitate the absolute amount of replicon RNA, a standard curve was established by including serially diluted T7 transcripts of replicon RNA in the Taqman assay. All Taqman reagents were from PE Applied Biosystems. Such an assay procedure was described in detail in *e.g.* Malcolm *et al., Antimicrobial Agents and Chemotherapy* 50: 1013-1020 (2006).

HCV replicon assay data was calculated for selected compounds of the present invention using this method and the replicon EC_{50} data obtained is provided in the table below.

Compound No.	**1b EC_{50} (μM)**	**Compound No.**	**1b EC_{50} (μM)**	**Compound No.**	**1b EC_{50} (μM)**
1	100	**17**	>100	**56**	0.7
2	>100	**20**	2.5	**57**	9.9
3	>100	**21**	2.6	**58**	4.4
4	>100	**22**	2.6	**59**	11
5	90	**23**	>100	**64**	6.6

6	10	**24**	5.0	**67**	6.8
7	29	**25**	3.1	**78**	30
8	34	**28**	0.1	**79**	2.8
9	100	**29**	0.1	**80**	IC_{50} = 0.6
10	29	**43**	38	**81**	IC_{50} = 2.3
11	>100	**44**	24	**82**	IC_{50} = 13
12	>100	**52**	0.9	**85**	45
13	>100	**53**	2.7	**89**	>100
15	>100	**54**	1.5	**90**	>100

16	>100	**55**	3.1	**98**	43

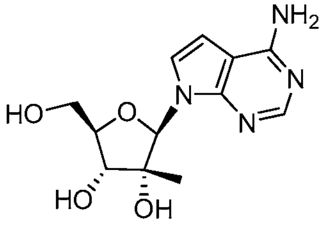
EXAMPLE 40

In Vitro Conversion of Prodrug to Nucleoside Triphosphate

The degree of conversion of a prodrug compound of the present invention to its corresponding nucleoside triphosphate is measured *in vitro* using the procedure described below.

A 2 mM stock solution of the prodrug test compound is prepared in 5% DMSO/95% MeOH to provide a final sample concentration of 10 μM. A 5 μL aliquot is removed from this stock solution and added to 1 mL of either a rat or human cryopreserved hepatocyte sample to provide a control sample at a concentration of 1 million cells/mL. This sample is assayed in triplicate and used as a test sample.

A 2 mM stock solution of Compound A is prepared in 5% DMSO/95% MeOH to give a final sample concentration of 10 μM.



Compound A

A 5μL aliquot is removed from this stock solution and added to 1 mL of either a rat or human cryopreserved hepatocyte sample to provide a control sample at a concentration of 1 million cells/mL. This sample is assayed in triplicate and used as a control standard.

Human and rat hepatocytes are removed from liquid nitrogen storage and thawed by submerging the hepatocyte tube into a pre-heated 37 °C waterbath and gently shaking the tube back & forth until thawed. The thawed hepatocytes are then gently poured into a container of Hepatocyte Basal Medium (50 mL, pre-warmed to 37 °C) and washed. The hepatocyte tube is then rinsed out with pre-warmed Hepatocyte Basal Medium and the washed hepatocytes and rinse are combined and centrifuged at 500 rpm for 4 minutes at room temperature. The supernatant is then discarded and the resulting hepatocyte pellet is resuspended with Hepatocyte Basal Medium (pre-warmed to 37 °C) and the final hepatocyte concentration is adjusted to 1 million cells/mL to provide the final hepatocyte suspension.

A 1 mL aliquot is removed from the 1 million cells/mL final hepatocyte suspension, analyzed in triplicate and placed into 20 mL scintillation vial without a cap. 2 mM of the prodrug test sample is then added into the hepatocyte suspension to provide a 10 μM final concentration in the 1 mL hepatocyte sample. The sample is then incubated at 37°C / 5%CO_2 for 4 hours. A blank hepatocyte sample as well as the control standard are also incubated in this fashion.

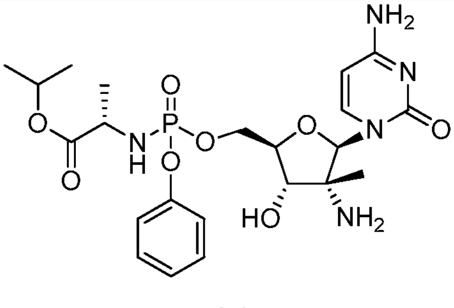
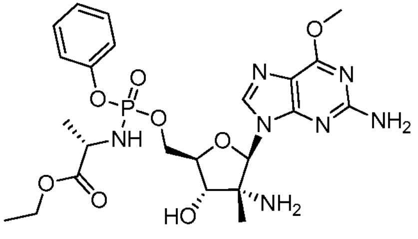
The incubated hepatocyte suspension samples are transferred to a micro-centrifuge tube using a transfer pipette and centrifuged at 500 rpm for 4 minutes at room temperature. The supernatant is discarded and the resulting hepatocyte pellet was resuspended and the cells are extracted with 0.25 mL of a 4 °C solution of 70% methanol / 30%(20 mM EDTA / 20 mM EGTA) that has been adjusted to pH 8 using sodium hydroxide. The resulting extract solution is then stored in a refrigerator at 4°C until ready for use, at which point the sample is first subjected to vortexing/sonication to ensure that all hepatocyte cells have burst. The sample is then centrifuged at 4000 rpm for 10 minutes at 4°C and a 100 μL aliquot of the resulting supernatant is added into a bioanalytical plate (2mL Square 96well plate w/ 100uL Tapered Reservoir), with the remaining supernatant immediately stored at -80 °C for re-assay if necessary. The blank control supernatant is transferred to a new tube for use as a control matrix in standard curves.

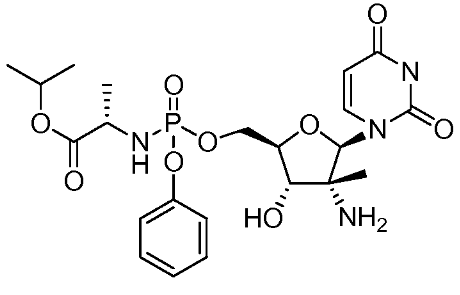
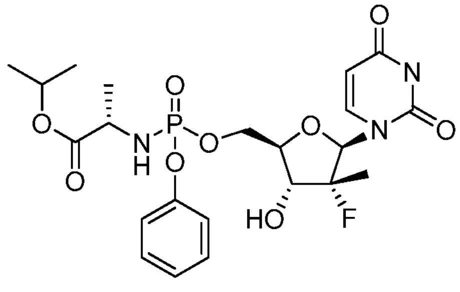
Alternatively, cryopreserved plateable hepatocytes are obtained from Celsis-In Vitro Technologies (Baltimore, MD), and plated according to manufacturer's protocol at 0.7×10^6 cells/mL in InVitro GRO CP Medium (1.75×10^6 cells/well in 6-well plates) three hours prior to inhibitor treatment. An inhibitor in DMSO at the indicated concentration in InVitro GRO CP Medium is added to the hepatocytes at t=0. At indicated times up to 48 hours post dosing, cells are washed in ice-cold PBS, extracted with ice-cold 1 mL 70% methanol: 30% 20 mM EDTA/EGTA and centrifuged. The supernatant is stored at -80°C until analysis. For intracellular NTP analysis, an NTP calibration curve is first generated by spiking a blank extraction buffer with known concentrations of the NTP standard. LC/ESI-MS analysis is performed on a QTRAP 5500 LC/MS/MS system (Applied Biosystems, Foster City, CA) coupled to a Shimazu UFLC system, operated in the positive-ion mode. The HPLC system is consisted of solvent delivery module (LC20-AD XR), auto injector (SIL-20ACXR), and photodiode array detector (SPD-M20A PDA) (Shimadzu Corporation, Tokyo, Japan). All HPLC separations are performed at 40 °C. The test samples are analyzed on a BioBasic AX column (5μm particle size, 100 x 2.1mm I.D., Thermo Scientific) using A (Acetonitrile:10 mM NH_4Ac =

30 : 70, v : v , pH=6) and B (Acetonitrile : 1 mM NH_4Ac = 30 : 70, v : v, pH=10) as mobile phases at a flow rate of 1.0 mL/min. The injection volume is 50 μL. The mobile phase gradient starts at 0% B, and linearly increases to 100% B over 6 min. The MS analysis of all NTPs is performed on the same QTRAP 5500 MS instrument in the multiple ion monitoring mode (MRM), with Turbo-Ion-Spray ionization. The collision energy is 40 eV for all the analytes and standards. The quadrupole mass analyzer is set to unit resolution.

Results are reported in pmol of triphosphate per µL of cells. To estimate µM intracellular concentration of nucleoside triphosphate, the following conversion is applied: 1×10^6 hepatocytes is 3 µL in volume.

Data was obtained using this method for selected compounds of the present invention, tested at 10 µM, and is presented in the table below. This data indicates that the compounds are efficiently converted to its corresponding NTP in vitro resulting in significant coverage over its intrinsic potency (Ki). Data is also presented for a comparative compound, labeled as Compound B.

Compound	Human Hepatocyte NTP (4 hour at 10 µM)/Ki
 **26**	460x
 **29**	32x

 **24**	30x
 **Compound B**	~80x

EXAMPLE 41

Determination of In Vivo Conversion of Prodrug to Nucleoside Triphosphate

The degree of conversion of a prodrug compound of the present invention to its corresponding nucleoside triphosphate is measured *in vivo* using the procedure described below.

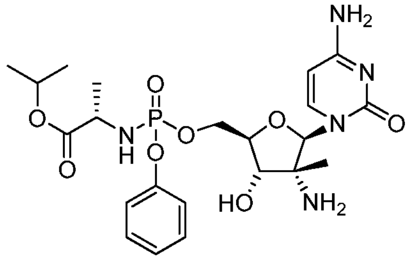
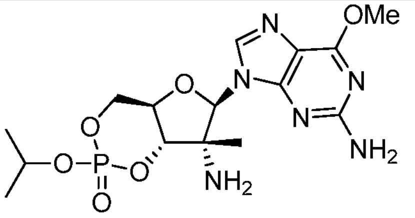
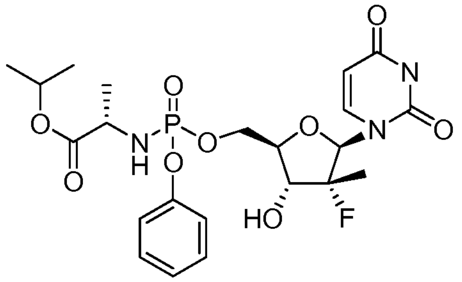
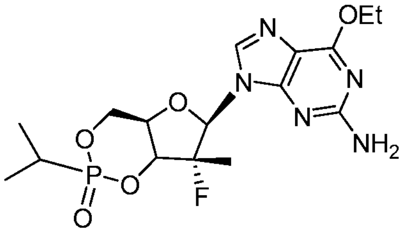
Liver samples are collected from either Wistar Hannover Rats or Beagle Dogs dosed with the prodrug via the freeze clamp procedure (animals anesthetized via isofluorane, the liver is clamped with modified clamps that are frozen in liquid nitrogen, and then the clamped liver piece is placed in liquid nitrogen to ensure frozen completely; repeat liver clamp procedure to get a second piece of liver sample; samples stored at -80 ^{0}C). Liver samples are homogenized using a a Spex Sample Prep Freezer/Mill (Cryomill); settings for the cryomill operation are 1 Cycle, 2 minute pre-chill time, 2 minute run time, 1 minute cool time, and a rate of 15 cycles/second (cps). Control liver samples collected from rats dosed with vehicle are cryomilled in the same manner. During this process it is imperative that anything that will come into contact with the liver samples remain frozen on dry ice at all times, such as all Cryomill sample containers/lids and spatulas.

The cryomilled control liver sample is used to generate the standard curve. Weigh out an appropriate amount of cryomilled control liver sample into a conical tube, depending on how many standard curves are needed, place on wet ice and suspend with cold (approx. 0 °C) 70% Methanol / 30% (20mM EDTA/EGTA) that had been adjusted to pH 8 with sodium hydroxide at a ratio of 1:4 (liver:MeOH/EDTA-EGTA). The suspended liver homogenate is vortexed until a homogenous suspension is obtained. The standard curve ranges from 10 ng/mL to 50,000 ng/mL of NTP standard, as well as a QC sample at 10,000 ng/mL. A 500 μL aliquot of suspended control liver homogenate per each point on the standard curve and each QC is removed and placed into a 1.5 mL centrifuge tube, and 125 μL of each corresponding standard curve or QC standard solution is added to each individual control aliquot and re-vortexed. Liver sample aliquots are centrifuged at 4 ^{0}C, 3645 x g, for 10 minutes, and 450 μL of the supernatant is aliquoted into a 2 mL Square 96 well bioanalytical plate. Single and double blank samples are also generated from the suspended control liver homogenate using the procedure above, substituting the 125 μL of standard solution with 125 μL of water.

Approximately 1-2 grams of the cryomilled liver sample is weighed out into a 50mL conical tube and placed on wet ice and suspended with cold 70% Methanol / 30% (20mM EDTA/EGTA) that had been adjusted to pH 8 with sodium hydroxide at a ratio of 1:4 (liver:MeOH/EDTA-EGTA); the remaining cryomilled liver sample is stored at -80 ^{0}C for possible re-assay if needed. The suspended liver homogenate is vortexed until a homogenous suspension is obtained. A 500 μL aliquot of each unknown liver sample is removed and placed into a 1.5 mL centrifuge tube, and 125 μL of water is added to each aliquot and re-vortexed. Standard curve/QC liver sample aliquots are centrifuged at 4 ^{0}C, 3645 x g, for 10 minutes, and 450 μL of the supernatant is aliquoted into a 2 mL square 96 well bioanalytical plate, and an appropriate internal standard is added to all sample wells, standard curve/QC wells, and the single blank well. The sample plate is stored at -80 ^{0}C until analysis and results are reported in μM of NTP measured.

Data was obtained using this method for selected compounds of the present invention, tested at 10 μM, and is presented in the table below. This data indicates that the compounds are efficiently converted to their corresponding NTPs in vivo, resulting in significant coverage over their intrinsic potency (Ki). Data is also presented for comparative compounds, labeled as Compound B and Compound C.

Compound	In Vivo Rat NTP (50 mpk, 4h)/ Ki

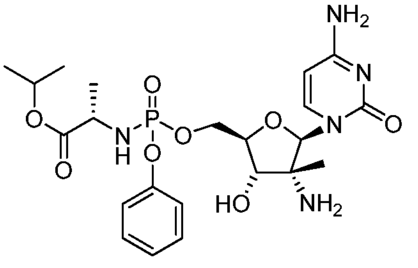
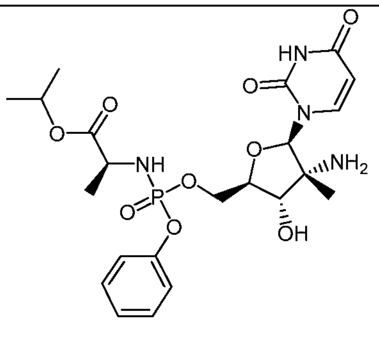
 **26**	11x
 **99**	45X
 **Compound B**	10x
 **Compound C**	1400x

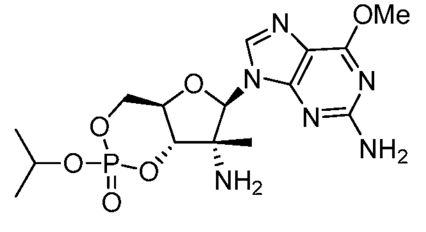
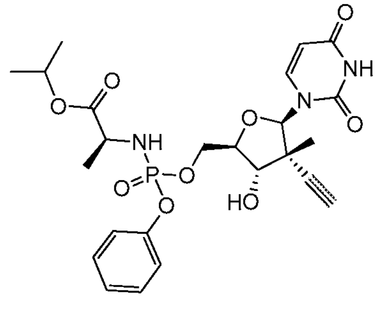
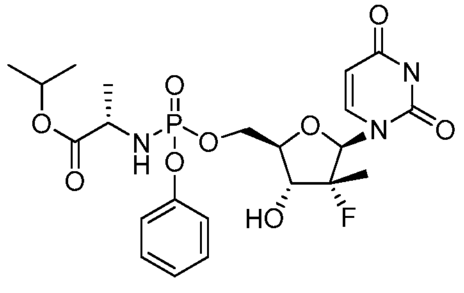
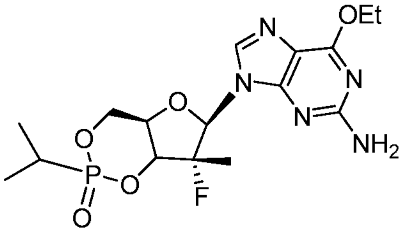
EXAMPLE 42

Inhibition of HCV NS5B Polymerase by Nucleoside Triphosphate Analogs

To measure inhibition of the enzymatic activity of the HCV NS5B RNA-dependent RNA polymerase by the nucleoside triphosphate compounds of the present invention, a radiolabeled nucleotide incorporation assay was used. This assay is a modified version of the assay described in International Publication No. WO2002/057287. Briefly, 50 μL reactions containing 20 mM HEPES (pH 7.3); 7.5 mM DTT; 20 units/ml RNasIN; 1 μM each of ATP, GTP, UTP and CTP; 20 μCi/mL [^{33}P]-CTP; 10 mM MgCl; 60 mM NaCl; 100 μg/ml BSA; 0.021 μM DCoH heteropolymer RNA template; and 5 nM NS5B (1b-BKΔ55) enzyme are incubated at room temperature for 1 hour. The assay is then terminated by the addition of 500 mM EDTA (50 μL). The reaction mixture is transferred to a Millipore DE81 filter plate and the incorporation of labeled CTP is determined using Packard TopCount. Compound IC_{50} values can then be calculated from experiments with 10 serial 3-fold dilutions of the inhibitor in duplicate. The intrinsic potency (Ki) of an NTP inhibitor is derived from its NS5B IC_{50} using the Cheng-Prusoff equation for a competitive inhibitor, as described in Cheng *et al., Biochem Pharmacol* 22:3099-3108 (1973): $Ki = IC_{50} / (1+[S]/K_m)$, where $[S] = 1$ μM, and K_m is the concentration of cognate NTP yielding half-maximal enzyme activity in the assay absent exogenous inhibitors.

Data was obtained using this method for the NTP analogs of selected compounds below of the present invention, and is set forth below. This data indicates that the nucleoside triphosphate (NTP) of the compounds are potent and effective inhibitors of HCV NS5B polymerase. Data is also presented for comparative compounds, labeled as Compound B and Compound C.

Compound	**NTP Ki (μM)**
 **26**	0.07
 **24**	4.7

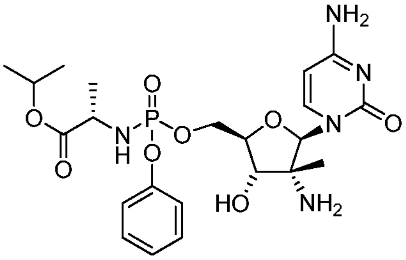
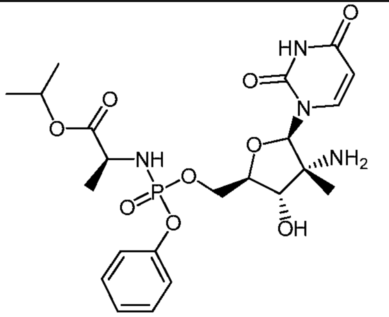
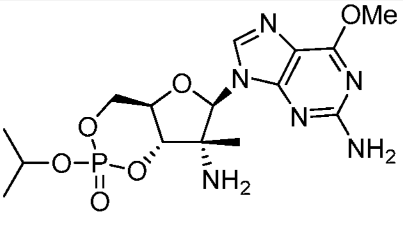
 **99**	0.06
 **93**	6.0
 **Compound B**	1.5
 **Compound C**	0.03

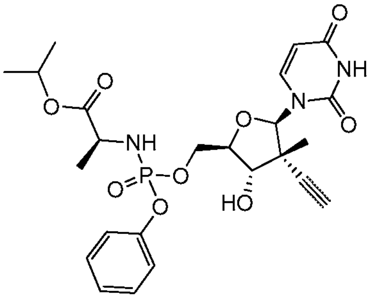
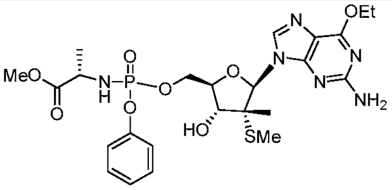
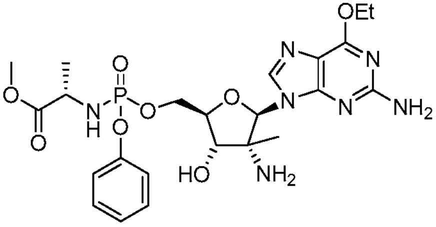
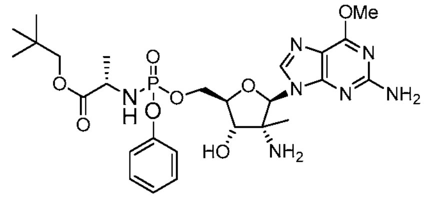
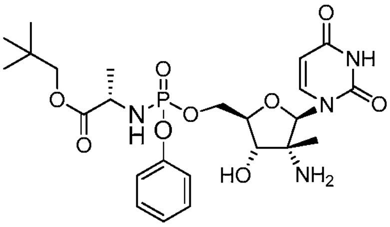
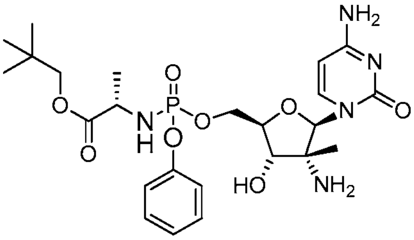
EXAMPLE 43

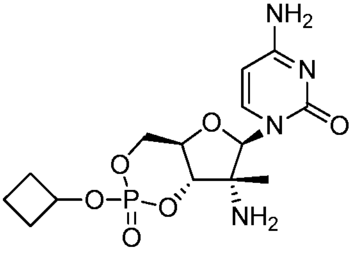
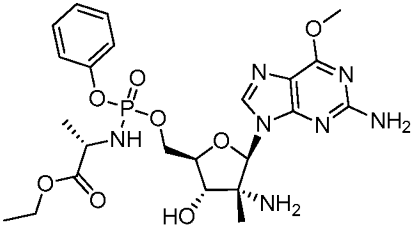
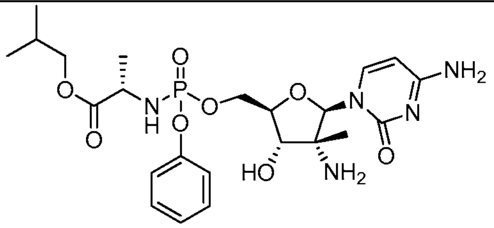
Replicon Activity and Cytotoxicity Assays

To measure cell-based anti-HCV activity of the compounds of the present invention, replicon cells (1b-Con1) are seeded at 5000 cells/well in 96-well plates one day prior to treatment with a compound of the invention. Various concentrations of a test compound of the invention in DMSO are then added to the replicon cells, with the final concentration of DMSO at 0.5% and fetal bovine serum at 10% in the assay media. Cells are harvested three days post-dosing and the replicon RNA level is determined using real-time RT-PCR (Taqman assay) with GAPDH RNA as endogenous control. EC_{50} values are calculated from experiments with 10 serial twofold dilutions of the inhibitor in triplicate. To measure cytotoxicity in replicon cells of an inhibitor, an MTS assay is performed according to the manufacturer's protocol for CellTiter 96 Aqueous One Solution Cell Proliferation Assay (Promega, Cat # G3580) three days post dosing on cells treated identically as in replicon activity assays. CC_{50} is the concentration of inhibitor that yields 50% inhibition compared to vehicle-treated cells. Cytotoxicity in other types of cells can be measured using the same MTS protocol.

Data was obtained using this method for selected compounds of the present invention, and is set forth below. This data indicates that the compound possesses significant cytotoxicity windows over replicon activity.

Compound	**Replicon (1b) EC_{50} (μM)**	**Cytotoxicity (μM)**
 **26**	5.5	>100
 **24**	3.1	>100
 **99**	43.7	>100

 **93**	2.3	>100
 **43**	38	>100
 **20**	2.5	>100
 **52**	0.9	>100
 **56**	0.7	>100
 **58**	4.4	>100

 **79**	2.8	>50
 **29**	0.1	>100
 **64**	6.6	50

EXAMPLE 44

Mitochondrial Toxicity Assay

Mitochondrial toxicity in replicon cells of an inhibitor can be evaluated by its effect on the mitochondrial genome copy number relative to a nuclear gene control. Replicon cells are seeded at 60,000 cells/well in 6-well plates one day prior to inhibitor treatment. Various concentrations of an inhibitor in culture medium are added on the first day of treatment and dosing media are refreshed every three days thereafter. Cells are harvested at the indicated days post dosing; the total DNA is isolated using DNeasy Blood & Tissue Kit (Qiagen, Cat # 69504) and quantitated by standard spectrophotometric methods. Two alternative sets of mitochondrial-specific DNA primer can be used: 1) 5'-CACCCAAGAACAGGGTTTGT-3' (SEQ. ID. NO. 4) (F3212, forward), 5'-TGGCCATGGGTATGTTGTTAA-3' (SEQ. ID. NO. 5) (R3319, reverse), 6-FAM-5'-TTACCGGGCTCTGCCATCT-3'-TAMRA (SEQ. ID. NO. 6) (probe) (see Bai *et al., Ann NY Acad Sci* 1011:304-309 (2004)); or 2) 5'-TGCCCGCCATCATCCTA-3' (SEQ. ID. NO. 7) (COX II, forward), 5'-CGTCTGTTATGTAAAGGATGCGT-3' (SEQ. ID. NO. 8) (COX II, reverse), 6-FAM-5'-TCCTCATCGCCCTCCCATCCC-3'-TAMRA (SEQ. ID. NO. 9) (probe) (see Stuyver *et al., Antimicrob Agents Chemother* 46:3854-3860 (2002)). Primers are used at 500 nM and probes at 200 nM in the Taqman quantitative PCR assay. The nuclear gene control quantitation is run in parallel for 18S DNA using ABI PDAR part # 4310875 (20X). The ΔCT value (CT difference between mt DNA and 18S DNA) from inhibitor-treated cells is compared to that of vehicle-treated cells. Mitochondrial toxicity in other types of cells can be measured using the same protocol.

Uses of the 2'-Substituted Nucleoside Derivatives

The 2'-Substituted Nucleoside Derivatives are useful in human and veterinary medicine for treating or preventing a viral infection in a patient. In one embodiment, the 2'-Substituted Nucleoside Derivatives can be inhibitors of viral replication. In another embodiment, the 2'-Substituted Nucleoside Derivatives can be inhibitors of HCV replication. Accordingly, the 2'-Substituted Nucleoside Derivatives are useful for treating viral infections, such as HCV. In accordance with the invention, the 2'-Substituted Nucleoside Derivatives can be administered to a patient in need of treatment or prevention of a viral infection.

Accordingly, in one embodiment, the invention provides methods for treating a viral infection in a patient comprising administering to the patient an effective amount of at least one 2'-Substituted Nucleoside Derivative or a pharmaceutically acceptable salt thereof.

Treatment or Prevention of a Flaviviridae Virus

The 2'-Substituted Nucleoside Derivatives can be useful for treating or preventing a viral infection caused by the Flaviviridae family of viruses.

Examples of Flaviviridae infections that may be treated or prevented using the present methods include one or more of: dengue fever, Japanese encephalitis, Kyasanur Forest disease, Murray Valley encephalitis, St. Louis encephalitis, Tick-borne encephalitis, West Nile encephalitis, yellow fever and Hepatitis C Virus (HCV) infection.

In one embodiment, the Flaviviridae infection being treated is hepatitis C virus infection.

Treatment or Prevention of HCV Infection

The 2'-Substituted Nucleoside Derivatives are useful in the inhibition of HCV, the treatment of HCV infection and/or reduction of the likelihood or severity of symptoms of HCV infection and the inhibition of HCV viral replication and/or HCV viral production in a cell-based system. For example, the 2'-Substituted Nucleoside Derivatives are useful in treating infection by HCV after suspected past exposure to HCV by such means as blood transfusion, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery or other medical procedures.

In one embodiment, the hepatitis C infection is acute hepatitis C. In another embodiment, the hepatitis C infection is chronic hepatitis C.

Accordingly, in one embodiment, the invention provides methods for treating HCV infection in a patient, the methods comprising administering to the patient an effective amount of at least one 2'-Substituted Nucleoside Derivative or a pharmaceutically acceptable salt thereof. In a specific embodiment, the amount administered is effective to treat or prevent infection by HCV in the patient. In another specific embodiment, the amount administered is effective to inhibit HCV viral replication and/or viral production in the patient.

The 2'-Substituted Nucleoside Derivatives are also useful in the preparation and execution of screening assays for antiviral compounds. For example the 2'-Substituted Nucleoside Derivatives are useful for identifying resistant HCV replicon cell lines harboring mutations within NS5B, which are excellent screening tools for more powerful antiviral compounds. Furthermore, the 2'-Substituted Nucleoside Derivatives are useful in establishing or determining the binding site of other antivirals to the HCV NS5B polymerase.

The compositions and combinations of the present invention can be useful for treating a patient suffering from infection related to any HCV genotype. HCV types and subtypes may differ in their antigenicity, level of viremia, severity of disease produced, and response to interferon therapy as described in Holland *et al.*, *Pathology*, 30(2):192-195 (1998). The nomenclature set forth in Simmonds *et al.*, *J Gen Virol*, 74(Pt11):2391-2399 (1993) is widely used and classifies isolates into six major genotypes, 1 through 6, with two or more related subtypes, *e.g.*, 1a and 1b. Additional genotypes 7-10 and 11 have been proposed, however the phylogenetic basis on which this classification is based has been questioned, and thus types 7, 8, 9 and 11 isolates have been reassigned as type 6, and type 10 isolates as type 3 (see Lamballerie *et al., J Gen Virol*, 78(Pt1):45-51 (1997)). The major genotypes have been defined as having sequence similarities of between 55 and 72% (mean 64.5%), and subtypes within types as having 75%-86% similarity (mean 80%) when sequenced in the NS-5 region (see Simmonds *et al.*, *J Gen Virol*, 75(Pt 5):1053-1061 (1994)).

Combination Therapy

In another embodiment, the present methods for treating or preventing HCV infection can further comprise the administration of one or more additional therapeutic agents which are not 2'-Substituted Nucleoside Derivatives.

In one embodiment, the additional therapeutic agent is an antiviral agent.

In another embodiment, the additional therapeutic agent is an immunomodulatory agent, such as an immunosuppressive agent.

Accordingly, in one embodiment, the present invention provides methods for treating a viral infection in a patient, the method comprising administering to the patient: (i) at least one 2'-Substituted Nucleoside Derivative (which may include two or more different 2'-Substituted Nucleoside Derivatives), or a pharmaceutically acceptable salt thereof, and (ii) at least one additional therapeutic agent that is other than a 2'-Substituted Nucleoside Derivative, wherein the amounts administered are together effective to treat or prevent a viral infection.

When administering a combination therapy of the invention to a patient, therapeutic agents in the combination, or a pharmaceutical composition or compositions comprising therapeutic agents, may be administered in any order such as, for example, sequentially, concurrently, together, simultaneously and the like. The amounts of the various actives in such combination therapy may be different amounts (different dosage amounts) or same amounts (same dosage amounts). Thus, for non-limiting illustration purposes, a 2'-Substituted Nucleoside Derivative and an additional therapeutic agent may be present in fixed amounts (dosage amounts) in a single dosage unit (*e.g.*, a capsule, a tablet and the like).

In one embodiment, the at least one 2'-Substituted Nucleoside Derivative is administered during a time when the additional therapeutic agent(s) exert their prophylactic or therapeutic effect, or *vice versa*.

In another embodiment, the at least one 2'-Substituted Nucleoside Derivative and the additional therapeutic agent(s) are administered in doses commonly employed when such agents are used as monotherapy for treating a viral infection.

In another embodiment, the at least one 2'-Substituted Nucleoside Derivative and the additional therapeutic agent(s) are administered in doses lower than the doses commonly employed when such agents are used as monotherapy for treating a viral infection.

In still another embodiment, the at least one 2'-Substituted Nucleoside Derivative and the additional therapeutic agent(s) act synergistically and are administered in doses lower than the doses commonly employed when such agents are used as monotherapy for treating a viral infection.

In one embodiment, the at least one 2'-Substituted Nucleoside Derivative and the additional therapeutic agent(s) are present in the same composition. In one embodiment, this composition is suitable for oral administration. In another embodiment, this composition is suitable for intravenous administration. In another embodiment, this composition is suitable for subcutaneous administration. In still another embodiment, this composition is suitable for parenteral administration.

Viral infections and virus-related disorders that can be treated or prevented using the combination therapy methods of the present invention include, but are not limited to, those listed above.

In one embodiment, the viral infection is HCV infection.

The at least one 2'-Substituted Nucleoside Derivative and the additional therapeutic agent(s) can act additively or synergistically. A synergistic combination may allow the use of lower dosages of one or more agents and/or less frequent administration of one or more agents of a combination therapy. A lower dosage or less frequent administration of one or more agents may lower toxicity of therapy without reducing the efficacy of therapy.

In one embodiment, the administration of at least one 2'-Substituted Nucleoside Derivative and the additional therapeutic agent(s) may inhibit the resistance of a viral infection to these agents.

Non-limiting examples of additional therapeutic agents useful in the present compositions and methods include an interferon, an immunomodulator, a viral replication inhibitor, an antisense agent, a therapeutic vaccine, a viral polymerase inhibitor, a nucleoside inhibitor, a viral protease inhibitor, a viral helicase inhibitor, a virion production inhibitor, a viral entry inhibitor, a viral assembly inhibitor, an antibody therapy (monoclonal or polyclonal), and any agent useful for treating an RNA-dependent polymerase-related disorder.

In one embodiment, the additional therapeutic agent is a viral protease inhibitor.

In another embodiment, the additional therapeutic agent is a viral replication inhibitor.

In another embodiment, the additional therapeutic agent is an HCV NS3 protease inhibitor.

In still another embodiment, the additional therapeutic agent is an HCV NS5B polymerase inhibitor.

In another embodiment, the additional therapeutic agent is a nucleoside inhibitor.

In another embodiment, the additional therapeutic agent is an interferon.

In yet another embodiment, the additional therapeutic agent is an HCV replicase inhibitor.

In another embodiment, the additional therapeutic agent is an antisense agent.

In another embodiment, the additional therapeutic agent is a therapeutic vaccine.

In a further embodiment, the additional therapeutic agent is a virion production inhibitor.

In another embodiment, the additional therapeutic agent is an antibody therapy.

In another embodiment, the additional therapeutic agent is an HCV NS2 inhibitor.

In still another embodiment, the additional therapeutic agent is an HCV NS4A inhibitor.

In another embodiment, the additional therapeutic agent is an HCV NS4B inhibitor.

In another embodiment, the additional therapeutic agent is an HCV NS5A inhibitor

In yet another embodiment, the additional therapeutic agent is an HCV NS3 helicase inhibitor.

In another embodiment, the additional therapeutic agent is an HCV IRES inhibitor.

In another embodiment, the additional therapeutic agent is an HCV p7 inhibitor.

In a further embodiment, the additional therapeutic agent is an HCV entry inhibitor.

In another embodiment, the additional therapeutic agent is an HCV assembly inhibitor.

In one embodiment, the additional therapeutic agents comprise a viral protease inhibitor and a viral polymerase inhibitor.

In still another embodiment, the additional therapeutic agents comprise a viral protease inhibitor and an immunomodulatory agent.

In yet another embodiment, the additional therapeutic agents comprise a polymerase inhibitor and an immunomodulatory agent.

In another embodiment, the additional therapeutic agents comprise a viral protease inhibitor and a nucleoside.

In another embodiment, the additional therapeutic agents comprise an immunomodulatory agent and a nucleoside.

In one embodiment, the additional therapeutic agents comprise an HCV protease inhibitor and an HCV polymerase inhibitor.

In another embodiment, the additional therapeutic agents comprise a nucleoside and an HCV NS5A inhibitor.

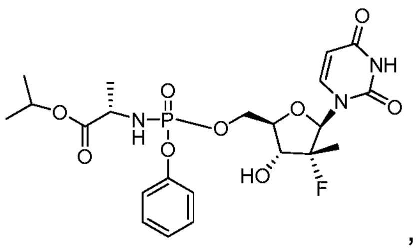
In another embodiment, the additional therapeutic agents comprise a viral protease inhibitor, an immunomodulatory agent and a nucleoside.

In a further embodiment, the additional therapeutic agents comprise a viral protease inhibitor, a viral polymerase inhibitor and an immunomodulatory agent.

In another embodiment, the additional therapeutic agent is ribavirin.

HCV polymerase inhibitors useful in the present compositions and methods include, but are not limited to, VP-19744 (Wyeth/ViroPharma), PSI-7851 (Pharmasset), RG7128 (Roche/Pharmasset), PSI-7977 (Pharmasset), PSI-938 (Pharmasset), PSI-879 (Pharmasset), PSI-661 (Pharmasset), PF-868554/filibuvir (Pfizer), VCH-759/VX-759 (ViroChem Pharma/Vertex), HCV-371 (Wyeth/VirroPharma), HCV-796 (Wyeth/ViroPharma), IDX-184 (Idenix), IDX-375 (Idenix), NM-283 (Idenix/Novartis), GL-60667 (Genelabs), JTK-109 (Japan Tobacco), PSI-6130 (Pharmasset), R1479 (Roche), R-1626 (Roche), R-7128 (Roche), MK-0608 (Isis/Merck), INX-8014 (Inhibitex), INX-8018 (Inhibitex), INX-189 (Inhibitex), GS 9190 (Gilead), A-848837 (Abbott), ABT-333 (Abbott), ABT-072 (Abbott), A-837093 (Abbott), BI-207127 (Boehringer-Ingelheim), BILB-1941 (Boehringer-Ingelheim), MK-3281 (Merck), VCH-222/VX-222 (ViroChem/Vertex), VCH-916 (ViroChem), VCH-716(ViroChem), GSK-71185 (Glaxo SmithKline), ANA598 (Anadys), GSK-625433 (Glaxo SmithKline), XTL-2125 (XTL Biopharmaceuticals), and those disclosed in Ni *et al.*, *Current Opinion in Drug Discovery and Development*, 7(4):446 (2004); Tan *et al.*, *Nature Reviews*, 1:867 (2002); and Beaulieu *et al.*, *Current Opinion in Investigational Drugs*, 5:838 (2004).

Other HCV polymerase inhibitors useful in the present compositions and methods include, but are not limited to, those disclosed in International Publication Nos. WO 08/082484, WO 08/082488, WO 08/083351, WO 08/136815, WO 09/032116, WO 09/032123, WO 09/032124 and WO 09/032125; and the following compounds: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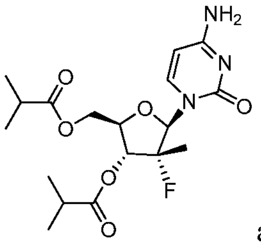
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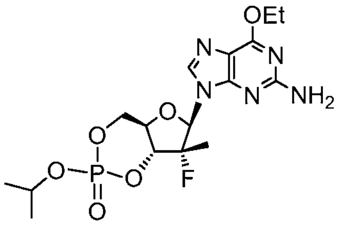


and pharmaceutically acceptable salts thereof.

Interferons useful in the present compositions and methods include, but are not limited to, interferon alfa-2a, interferon alfa-2b, interferon alfacon-1 and PEG-interferon alpha conjugates. "PEG-interferon alpha conjugates" are interferon alpha molecules covalently attached to a PEG molecule. Illustrative PEG-interferon alpha conjugates include interferon alpha-2a (Roferon^{TM}, Hoffman La-Roche, Nutley, New Jersey) in the form of pegylated interferon alpha-2a (*e.g.*, as sold under the trade name Pegasys^{TM}), interferon alpha-2b (Intron^{TM}, from Schering-Plough Corporation) in the form of pegylated interferon alpha-2b (*e.g.*, as sold under the trade name PEG-Intron^{TM} from Schering-Plough Corporation), interferon alpha-2b-XL (*e.g.*, as sold under the trade name PEG-Intron^{TM}), interferon alpha-2c (Berofor Alpha^{TM}, Boehringer Ingelheim, Ingelheim, Germany), PEG-interferon lambda (Bristol-Myers Squibb and ZymoGenetics), interferon alfa-2b alpha fusion polypeptides, interferon fused with the human blood protein albumin (Albuferon^{TM}, Human Genome Sciences), Omega Interferon (Intarcia), Locteron controlled release interferon (Biolex/OctoPlus), Biomed-510 (omega interferon), Peg-IL-29 (ZymoGenetics), Locteron CR (Octoplus), R-7025 (Roche), IFN-α-2b-XL (Flamel Technologies), belerofon (Nautilus) and consensus interferon as defined by determination of a consensus sequence of naturally occurring interferon alphas (Infergen^{TM}, Amgen, Thousand Oaks, California).

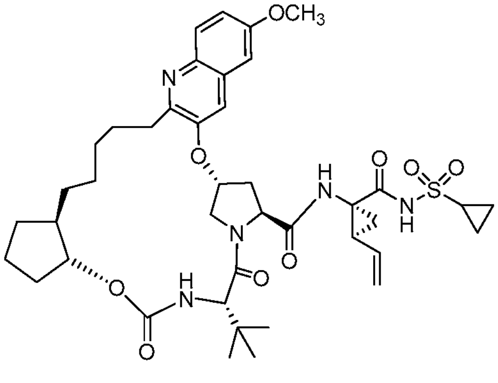
Antibody therapy agents useful in the present compositions and methods include, but are not limited to, antibodies specific to IL-10 (such as those disclosed in US Patent Publication No. US2005/0101770, humanized 12G8, a humanized monoclonal antibody against human IL-10, plasmids containing the nucleic acids encoding the humanized 12G8 light and heavy chains were deposited with the American Type Culture Collection (ATCC) as deposit numbers PTA-5923 and PTA-5922, respectively), and the like).

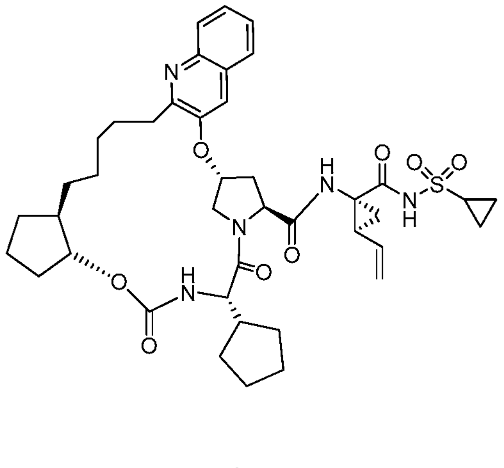
Examples of viral protease inhbitors useful in the present compositions and methods include, but are not limited to, an HCV protease inhibitor.

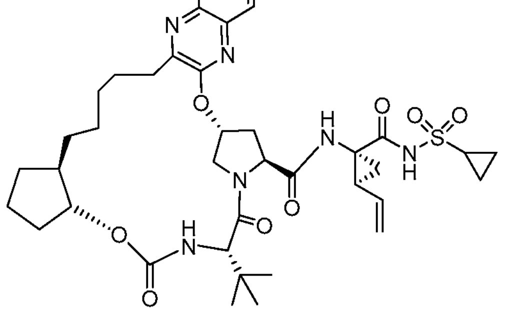
HCV protease inhibitors useful in the present compositions and methods include, but are not limited to, those disclosed in U.S. Patent Nos. 7,494,988, 7,485,625, 7,449,447, 7,442,695, 7,425,576, 7,342,041, 7,253,160, 7,244,721, 7,205,330, 7,192,957, 7,186,747, 7,173,057, 7,169,760, 7,012,066, 6,914,122, 6,911,428, 6,894,072, 6,846,802, 6,838,475, 6,800,434, 6,767,991, 5,017,380, 4,933,443, 4,812,561 and 4,634,697; U.S. Patent Publication Nos. US20020068702, US20020160962, US20050119168, US20050176648, US20050209164, US20050249702 and US20070042968; and International Publication Nos. WO 03/006490, WO 03/087092, WO 04/092161 and WO 08/124148.

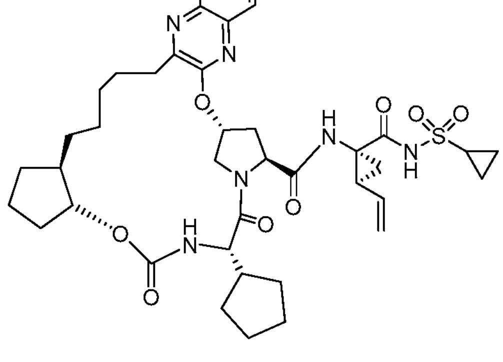
Additional HCV protease inhibitors useful in the present compositions and methods include, but are not limited to, VX-950 (Telaprevir, Vertex), VX-500 (Vertex), VX-813 (Vertex), VBY-376 (Virobay), BI-201335 (Boehringer Ingelheim), TMC-435 (Medivir/Tibotec), ABT-450 (Abbott/Enanta), TMC-435350 (Medivir), RG7227 (Danoprevir, InterMune/Roche), EA-058 (Abbott/Enanta), EA-063 (Abbott/Enanta), GS-9256 (Gilead), IDX-320 (Idenix), ACH-1625 (Achillion), ACH-2684 (Achillion), GS-9132 (Gilead/Achillion), ACH-1095 (Gilead/Achillon), IDX-136 (Idenix), IDX-316 (Idenix), ITMN-8356 (InterMune), ITMN-8347 (InterMune), ITMN-8096 (InterMune), ITMN-7587 (InterMune), BMS-650032 (Bristol-Myers Squibb), VX-985 (Vertex) and PHX1766 (Phenomix).

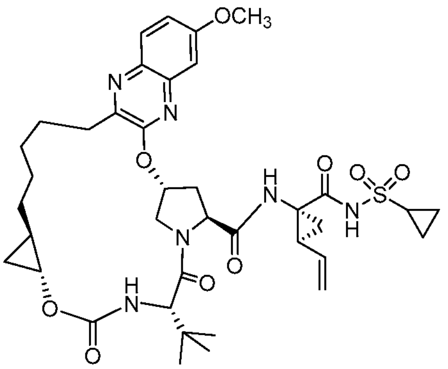
Further examples of HCV protease inhibitors useful in the present compositions and methods include, but are not limited to, the following compounds:

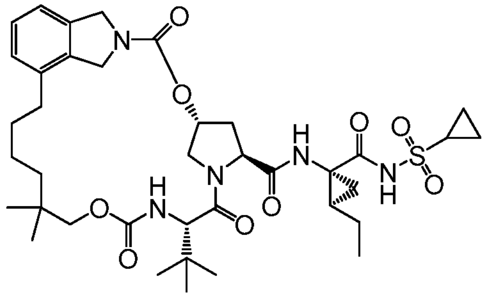


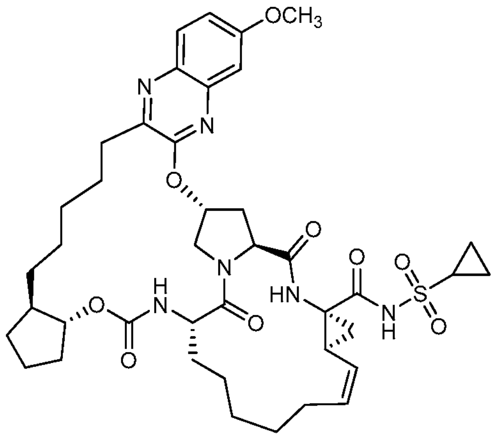


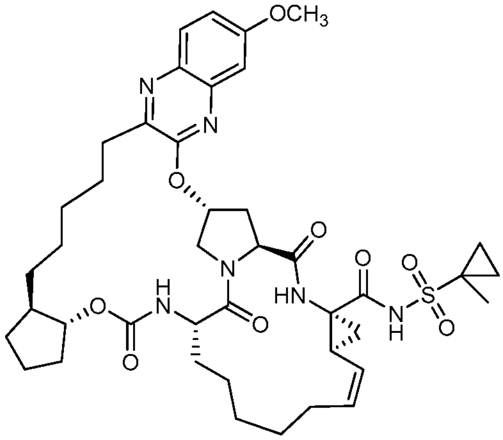


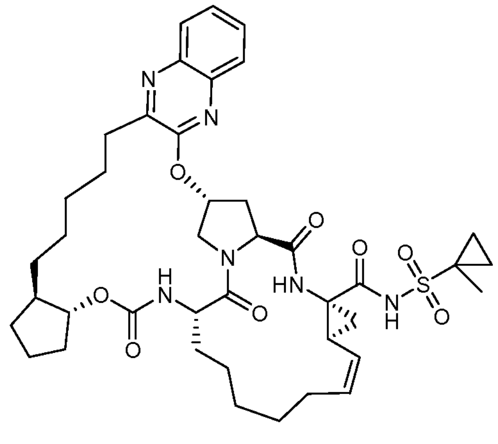


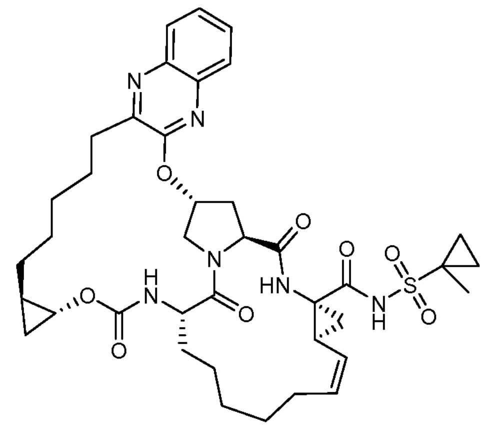


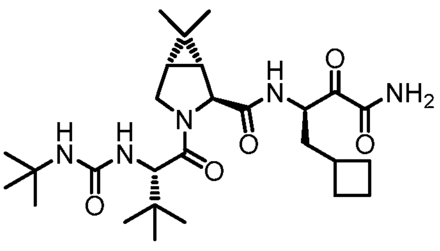


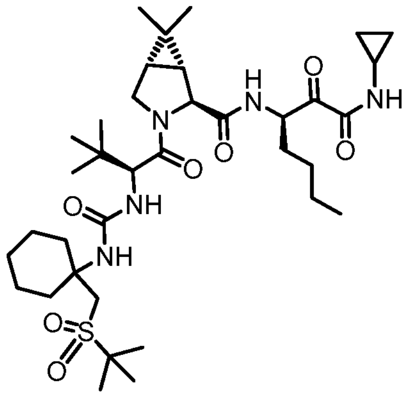


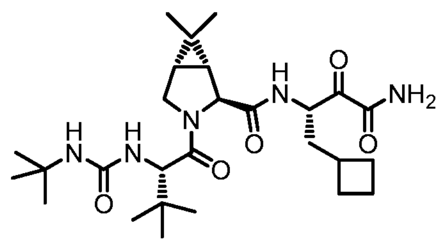


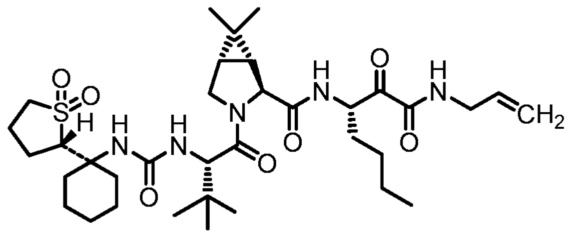


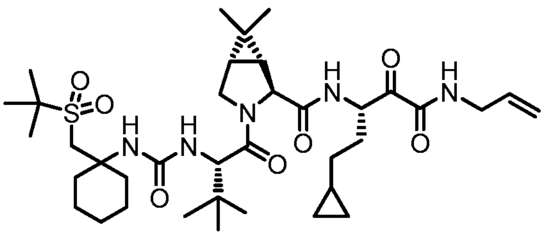


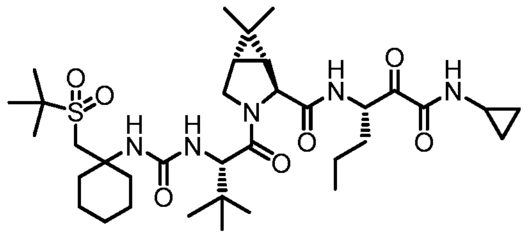


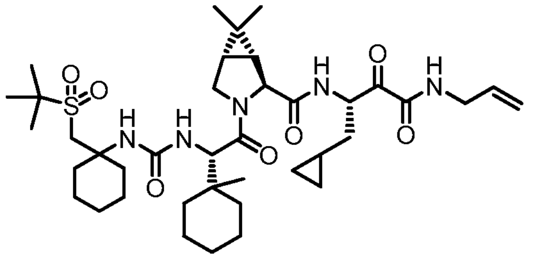


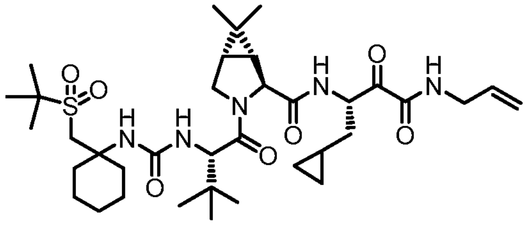


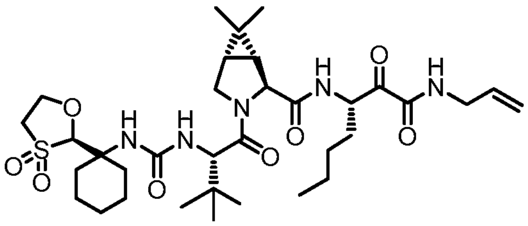


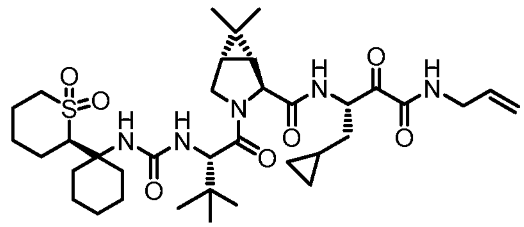


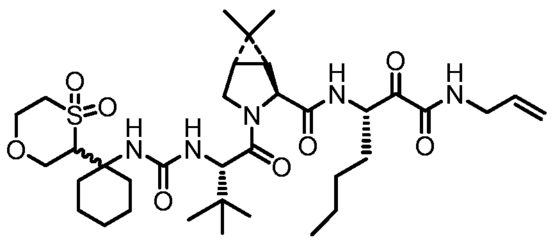


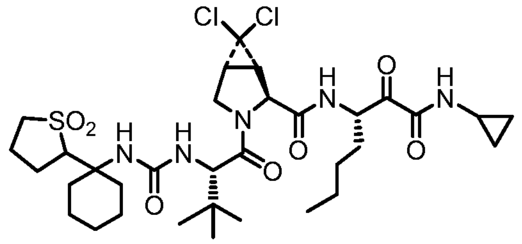


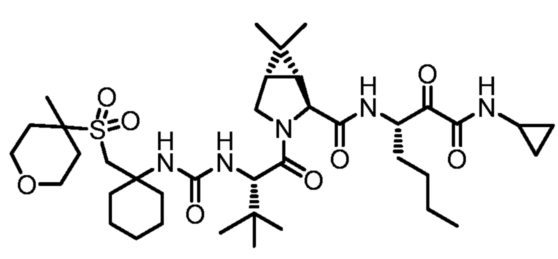


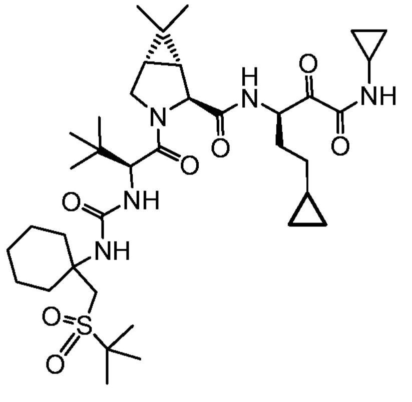


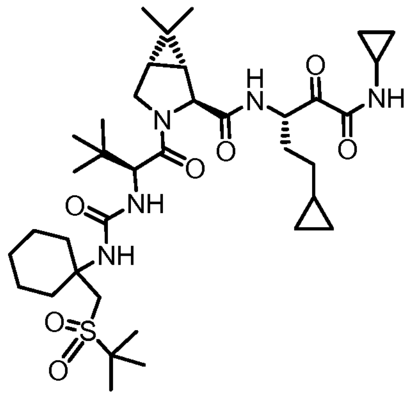


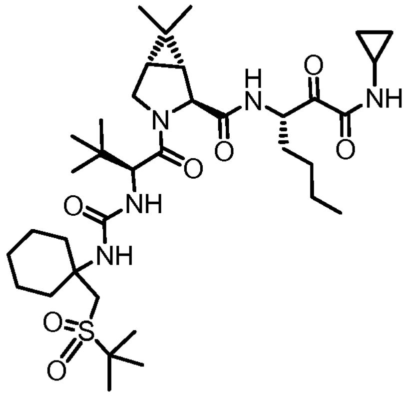


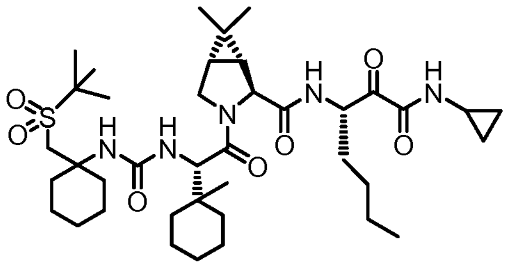


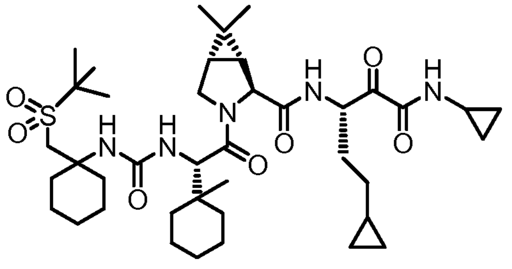












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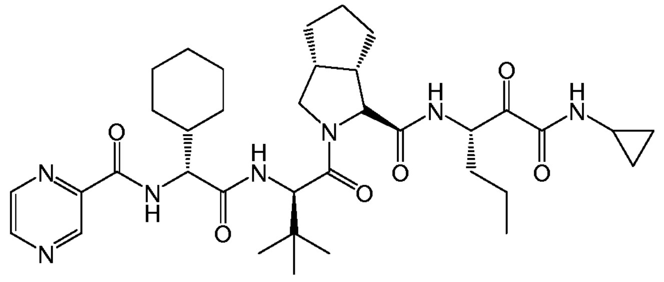


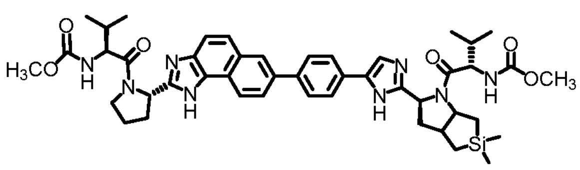
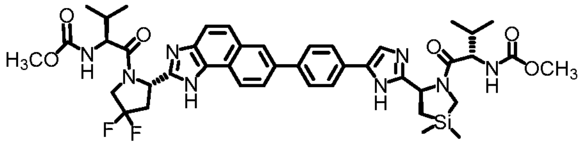
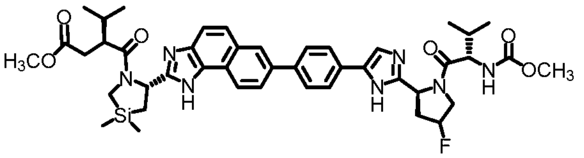
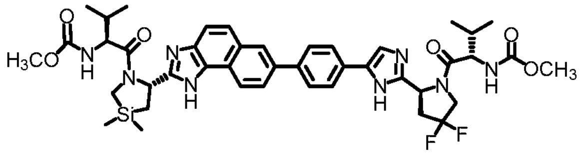
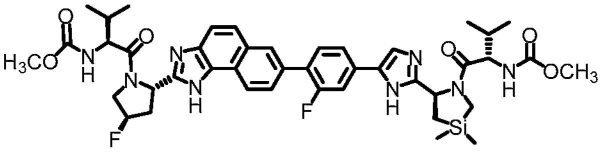
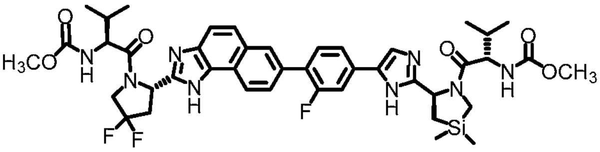
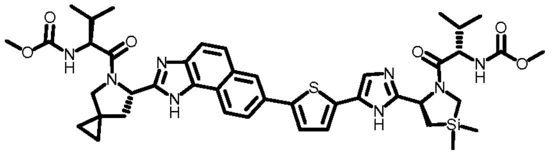
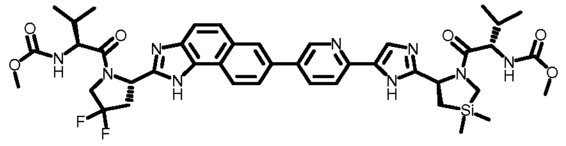
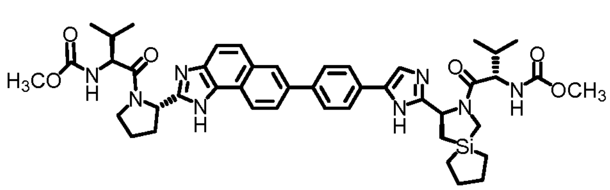
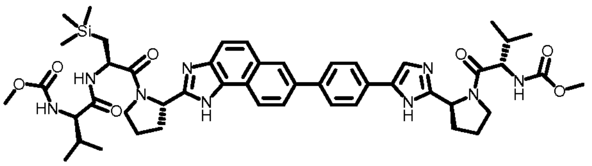
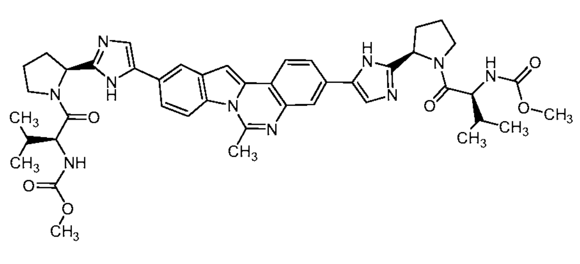
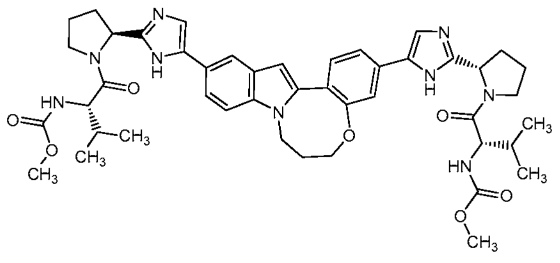
and pharmaceutically acceptable salts thereof.

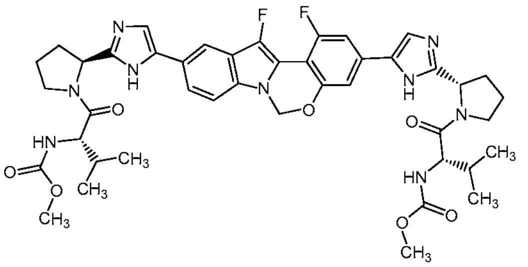
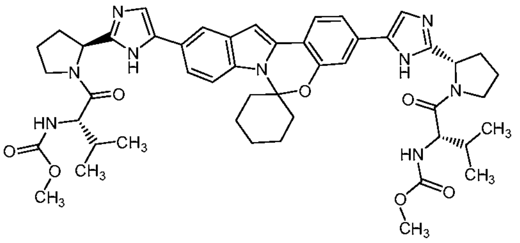
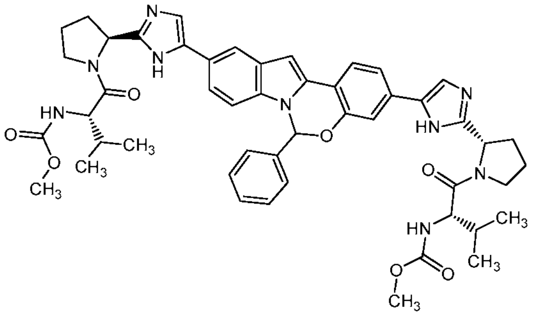
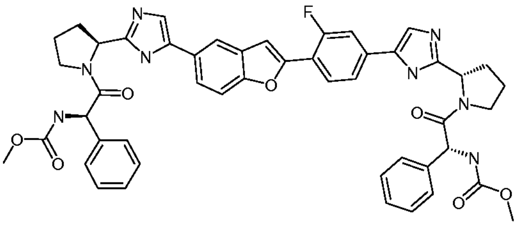
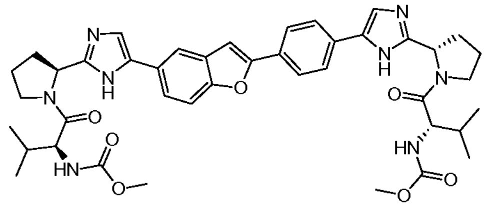
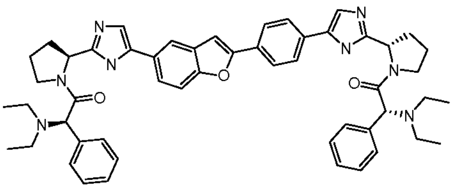
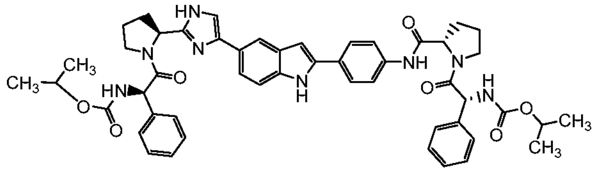
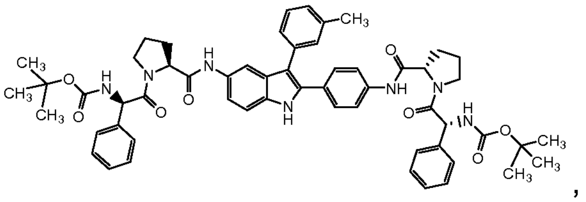
Viral replication inhibitors useful in the present compositions and methods include, but are not limited to, HCV replicase inhibitors, IRES inhibitors, NS4A inhibitors, NS3 helicase inhibitors, NS5A inhibitors, NS5B inhibitors, ribavirin, AZD-2836 (Astra Zeneca), viramidine, A-831 (Arrow Therapeutics), EDP-239 (Enanta), ACH-2928 (Achillion), GS-5885 (Gilead); an antisense agent or a therapeutic vaccine.

Viral entry inhibitors useful as second additional therapeutic agents in the present compositions and methods include, but are not limited to, PRO-206 (Progenics), REP-9C (REPICor), SP-30 (Samaritan Pharmaceuticals) and ITX-5061 (iTherx).

HCV NS4A inhibitors useful in the useful in the present compositions and methods include, but are not limited to, those disclosed in U.S. Patent Nos. 7,476,686 and 7,273,885; U.S. Patent Publication No. US20090022688; and International Publication Nos. WO 2006/019831 and WO 2006/019832. Additional HCV NS4A inhibitors useful as second additional therapeutic agents in the present compositions and methods include, but are not limited to, AZD2836 (Astra Zeneca), ACH-1095 (Achillion) and ACH-806 (Achillion).

HCV NS5A inhibitors useful in the present compositions and methods include, but are not limited to, ACH-2928 (Achilon), A-832 (Arrow Therpeutics), AZD-7295 (Astra Zeneca/Arrow), GS-5885 (Gilead), PPI-461 (Presidio), PPI-1301 (Presidio), BMS-824383 (Bristol-Myers Squibb) and BMS-790052 (Bristol-Myers Squibb). Additional HCV NS4A inhibitors useful as second additional therapeutic agents in the present compositions and methods include, but are not limited to those disclosed in International Publication No. WO 2010/111483 and the following compounds:

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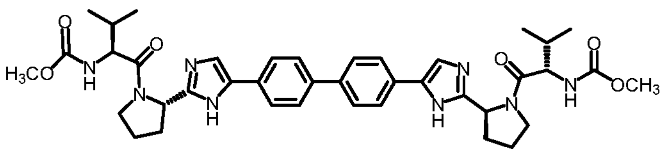


and pharmaceutically acceptable salts thereof.

HCV replicase inhibitors useful in the present compositions and methods include, but are not limited to, those disclosed in U.S. Patent Publication No. US20090081636.

Therapeutic vaccines useful in the present compositions and methods include, but are not limited to, IC41 (Intercell Novartis), CSL123 (Chiron/CSL), GI 5005 (Globeimmune), TG-4040 (Transgene), GNI-103 (GENimmune), Hepavaxx C (ViRex Medical), ChronVac-C (Inovio/Tripep), PeviPROTM (Pevion Biotect), HCV/MF59 (Chiron/Novartis), MBL-HCV1 (MassBiologics), GI-5005 (GlobeImmune), CT-011 (CureTech/Teva) and Civacir (NABI).

Examples of further additional therapeutic agents useful in the present compositions and methods include, but are not limited to, Ritonavir (Abbott), TT033

(Benitec/Tacere Bio/Pfizer), Sirna-034 (Sirna Therapeutics), GNI-104 (GENimmune), GI-5005 (GlobeImmune), IDX-102 (Idenix), Levovirin^{TM} (ICN Pharmaceuticals, Costa Mesa, California); Humax (Genmab), ITX-2155 (Ithrex/Novartis), PRO 206 (Progenics), HepaCide-I (NanoVirocides), MX3235 (Migenix), SCY-635 (Scynexis); KPE02003002 (Kemin Pharma), Lenocta (VioQuest Pharmaceuticals), IET – Interferon Enhancing Therapy (Transition Therapeutics), Zadaxin (SciClone Pharma), VP 50406^{TM} (Viropharma, Incorporated, Exton, Pennsylvania); Taribavirin (Valeant Pharmaceuticals); Nitazoxanide (Romark); Debio 025 (Debiopharm); GS-9450 (Gilead); PF-4878691 (Pfizer); ANA773 (Anadys); SCV-07 (SciClone Pharmaceuticals); NIM-881 (Novartis); ISIS 14803^{TM} (ISIS Pharmaceuticals, Carlsbad, California); Heptazyme^{TM} (Ribozyme Pharmaceuticals, Boulder, Colorado); Thymosin^{TM} (SciClone Pharmaceuticals, San Mateo, California); Maxamine^{TM} (Maxim Pharmaceuticals, San Diego, California); NKB-122 (JenKen Bioscience Inc., North Carolina); Alinia (Romark Laboratories), INFORM-1 (a combination of R7128 and ITMN-191); and mycophenolate mofetil (Hoffman-LaRoche, Nutley, New Jersey).

The doses and dosage regimen of the other agents used in the combination therapies of the present invention for the treatment or prevention of HCV infection can be determined by the attending clinician, taking into consideration the approved doses and dosage regimen in the package insert; the age, sex and general health of the patient; and the type and severity of the viral infection or related disease or disorder. When administered in combination, the 2'-Substituted Nucleoside Derivative(s) and the other agent(s) can be administered simultaneously (*i.e.,* in the same composition or in separate compositions one right after the other) or sequentially. This particularly useful when the components of the combination are given on different dosing schedules, *e.g.*, one component is administered once daily and another component is administered every six hours, or when the preferred pharmaceutical compositions are different, *e.g.,* one is a tablet and one is a capsule. A kit comprising the separate dosage forms is therefore advantageous.

Generally, a total daily dosage of the at least one 2'-Substituted Nucleoside Derivative(s) alone, or when administered as combination therapy, can range from about 1 to about 2500 mg per day, although variations will necessarily occur depending on the target of therapy, the patient and the route of administration. In one embodiment, the dosage is from about 10 to about 1000 mg/day, administered in a single dose or in 2-4 divided doses. In another embodiment, the dosage is from about 1 to about 500 mg/day, administered in a single dose or in 2-4 divided doses. In still another embodiment, the dosage is from about 1 to about 100 mg/day, administered in a single dose or in 2-4 divided doses. In yet another embodiment, the dosage is from about 1 to about 50 mg/day, administered in a single dose or in 2-4 divided doses. In another embodiment, the dosage is from about 500 to about 1500 mg/day, administered in a single dose or in 2-4 divided doses. In still another embodiment, the dosage is from about 500 to about 1000 mg/day, administered in a single dose or in 2-4 divided doses. In yet another embodiment, the dosage is from about 100 to about 500 mg/day, administered in a single dose or in 2-4 divided doses.

In one embodiment, when the additional therapeutic agent is INTRON-A interferon alpha 2b (commercially available from Schering-Plough Corp.), this agent is administered by subcutaneous injection at 3MIU(12 mcg)/0.5mL/TIW for 24 weeks or 48 weeks for first time treatment.

In another embodiment, when the additional therapeutic agent is PEG-INTRON interferon alpha 2b pegylated (commercially available from Schering-Plough Corp.), this agent is administered by subcutaneous injection at 1.5 mcg/kg/week, within a range of 40 to 150 mcg/week, for at least 24 weeks.

In another embodiment, when the additional therapeutic agent is ROFERON A interferon alpha 2a (commercially available from Hoffmann-La Roche), this agent is administered by subcutaneous or intramuscular injection at 3MIU(11.1 mcg/mL)/TIW for at least 48 to 52 weeks, or alternatively 6MIU/TIW for 12 weeks followed by 3MIU/TIW for 36 weeks.

In still another embodiment, when the additional therapeutic agent is PEGASUS interferon alpha 2a pegylated (commercially available from Hoffmann-La Roche), this agent is administered by subcutaneous injection at 180 mcg/1mL or 180 mcg/0.5mL, once a week for at least 24 weeks.

In yet another embodiment, when the additional therapeutic agent is INFERGEN interferon alphacon-1 (commercially available from Amgen), this agent is administered by subcutaneous injection at 9 mcg/TIW is 24 weeks for first time treatment and up to 15 mcg/TIW for 24 weeks for non-responsive or relapse treatment.

In a further embodiment, when the additional therapeutic agent is Ribavirin (commercially available as REBETOL ribavirin from Schering-Plough or COPEGUS ribavirin from Hoffmann-La Roche), this agent is administered at a daily dosage of from about 600 to about 1400 mg/day for at least 24 weeks.

In one embodiment, one or more compounds of the present invention are administered with one or more additional therapeutic agents selected from: an interferon, an immunomodulator, a viral replication inhibitor, an antisense agent, a therapeutic vaccine, a viral polymerase inhibitor, a nucleoside inhibitor, a viral protease inhibitor, a viral helicase inhibitor, a viral polymerase inhibitor a virion production inhibitor, a viral entry inhibitor, a viral assembly inhibitor, an antibody therapy (monoclonal or polyclonal), and any agent useful for treating an RNA-dependent polymerase-related disorder.

In another embodiment, one or more compounds of the present invention are administered with one or more additional therapeutic agents selected from an HCV protease inhibitor, an HCV polymerase inhibitor, an HCV replication inhibitor, a nucleoside, an interferon, a pegylated interferon and ribavirin. The combination therapies can include any combination of these additional therapeutic agents.

In another embodiment, one or more compounds of the present invention are administered with one additional therapeutic agent selected from an HCV protease inhibitor, an interferon, a pegylated interferon and ribavirin.

In still another embodiment, one or more compounds of the present invention are administered with two additional therapeutic agents selected from an HCV protease inhibitor, an HCV replication inhibitor, a nucleoside, an interferon, a pegylated interferon and ribavirin.

In another embodiment, one or more compounds of the present invention are administered with an HCV protease inhibitor and ribavirin. In another specific embodiment, one or more compounds of the present invention are administered with a pegylated interferon and ribavirin.

In another embodiment, one or more compounds of the present invention are administered with three additional therapeutic agents selected from an HCV protease inhibitor, an HCV replication inhibitor, a nucleoside, an interferon, a pegylated interferon and ribavirin.

In one embodiment, one or more compounds of the present invention are administered with one or more additional therapeutic agents selected from an HCV polymerase inhibitor, a viral protease inhibitor, an interferon, and a viral replication inhibitor. In another embodiment, one or more compounds of the present invention are administered with one or more additional therapeutic agents selected from an HCV polymerase inhibitor, a viral protease inhibitor, an interferon, and a viral replication inhibitor. In another embodiment, one or more compounds of the present invention are administered with one or more additional therapeutic agents selected from an HCV polymerase inhibitor, an HCV NS5A inhibitor, a viral protease inhibitor, an interferon, and ribavirin.

In one embodiment, one or more compounds of the present invention are administered with one additional therapeutic agent selected from an HCV polymerase inhibitor, a viral protease inhibitor, an interferon, and a viral replication inhibitor. In another embodiment, one or more compounds of the present invention are administered with ribavirin.

In one embodiment, one or more compounds of the present invention are administered with two additional therapeutic agents selected from an HCV polymerase inhibitor, a viral protease inhibitor, an interferon, and a viral replication inhibitor.

In another embodiment, one or more compounds of the present invention are administered with ribavirin, interferon and another therapeutic agent.

In another embodiment, one or more compounds of the present invention are administered with ribavirin, interferon and another therapeutic agent, wherein the additional therapeutic agent is selected from an HCV polymerase inhibitor, a viral protease inhibitor, and a viral replication inhibitor.

In still another embodiment, one or more compounds of the present invention are administered with ribavirin, interferon and a viral protease inhibitor.

In another embodiment, one or more compounds of the present invention are administered with ribavirin, interferon and an HCV protease inhibitor.

In another embodiment, one or more compounds of the present invention are administered with ribavirin, interferon and boceprevir or telaprevir.

In a further embodiment, one or more compounds of the present invention are administered with ribavirin, interferon and an HCV polymerase inhibitor.

In another embodiment, one or more compounds of the present invention are administered with pegylated-interferon alpha and ribavirin.

Compositions and Administration

Due to their activity, the 2'-Substituted Nucleoside Derivatives are useful in veterinary and human medicine. As described above, the 2'-Substituted Nucleoside Derivatives are useful for treating or preventing HCV infection in a patient in need thereof.

When administered to a patient, the 2'-Substituted Nucleoside Derivatives can be administered as a component of a composition that comprises a pharmaceutically acceptable carrier or vehicle. The present invention provides pharmaceutical compositions comprising an effective amount of at least one 2'-Substituted Nucleoside Derivative and a pharmaceutically acceptable carrier. In the pharmaceutical compositions and methods of the present invention, the active ingredients will typically be administered in admixture with suitable carrier materials suitably selected with respect to the intended form of administration, *i.e.,* oral tablets, capsules (either solid-filled, semi-solid filled or liquid filled), powders for constitution, oral gels, elixirs, dispersible granules, syrups, suspensions, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of tablets or capsules, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable inert carrier, such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, talc, mannitol, ethyl alcohol (liquid forms) and the like. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. Powders and tablets may be comprised of from about 0.5 to about 95 percent inventive composition. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

Moreover, when desired or needed, suitable binders, lubricants, disintegrating agents and coloring agents may also be incorporated in the mixture. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Among the lubricants there may be mentioned for use in these dosage forms, boric acid, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrants include starch, methylcellulose, guar gum, and the like. Sweetening and flavoring agents and preservatives may also be included where appropriate.

Liquid form preparations include solutions, suspensions and emulsions and may include water or water-propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for intranasal administration.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Additionally, the compositions of the present invention may be formulated in sustained release form to provide the rate controlled release of any one or more of the components or active ingredients to optimize therapeutic effects, *i.e.*, antiviral activity and the like. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

In one embodiment, the one or more 2'-Substituted Nucleoside Derivatives are administered orally.

In another embodiment, the one or more 2'-Substituted Nucleoside Derivatives are administered intravenously.

In one embodiment, a pharmaceutical preparation comprising at least one 2'-Substituted Nucleoside Derivative is in unit dosage form. In such form, the preparation is subdivided into unit doses containing effective amounts of the active components.

Compositions can be prepared according to conventional mixing, granulating or coating methods, respectively, and the present compositions can contain, in one embodiment, from about 0.1% to about 99% of the 2'-Substituted Nucleoside Derivative(s) by weight or volume. In various embodiments, the present compositions can contain, in one embodiment, from about 1% to about 70% or from about 5% to about 60% of the 2'-Substituted Nucleoside Derivative(s) by weight or volume.

The quantity of 2'-Substituted Nucleoside Derivative in a unit dose of preparation may be varied or adjusted from about 1 mg to about 2500 mg. In various embodiment, the quantity is from about 10 mg to about 1000 mg, 1 mg to about 500 mg, 1 mg to about 100 mg, and 1 mg to about 100 mg.

For convenience, the total daily dosage may be divided and administered in portions during the day if desired. In one embodiment, the daily dosage is administered in one portion. In another embodiment, the total daily dosage is administered in two divided doses over a 24 hour period. In another embodiment, the total daily dosage is administered in three divided doses over a 24 hour period. In still another embodiment, the total daily dosage is administered in four divided doses over a 24 hour period.

The amount and frequency of administration of the 2'-Substituted Nucleoside Derivatives will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. Generally, a total daily dosage of the 2'-Substituted Nucleoside Derivatives range from about 0.1 to about 2000 mg per day, although variations will necessarily occur depending on the target of therapy, the patient and the route of administration. In one embodiment, the dosage is from about 1 to about 200 mg/day, administered in a single dose or in 2-4 divided doses. In another embodiment, the dosage is from about 10 to about 2000 mg/day, administered in a single dose or in 2-4 divided doses. In another embodiment, the dosage is from about 100 to about 2000 mg/day, administered in a single dose or in 2-4 divided doses. In still another embodiment, the dosage is from about 500 to about 2000 mg/day, administered in a single dose or in 2-4 divided doses.

The compositions of the invention can further comprise one or more additional therapeutic agents, selected from those listed above herein. Accordingly, in one embodiment, the present invention provides compositions comprising: (i) at least one 2'-Substituted Nucleoside Derivative or a pharmaceutically acceptable salt thereof; (ii) one or more additional therapeutic agents that are not a 2'-Substituted Nucleoside Derivative; and (iii) a pharmaceutically acceptable carrier, wherein the amounts in the composition are together effective to treat HCV infection.

In one embodiment, the present invention provides compositions comprising a Compound of Formula (I) and a pharmaceutically acceptable carrier.

In another embodiment, the present invention provides compositions comprising a Compound of Formula (I), a pharmaceutically acceptable carrier, and a second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

In another embodiment, the present invention provides compositions comprising a Compound of Formula (I), a pharmaceutically acceptable carrier, and wto additional therapeutic agents, each of which are independently selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

Kits

In one aspect, the present invention provides a kit comprising a therapeutically effective amount of at least one 2'-Substituted Nucleoside Derivative, or a pharmaceutically acceptable salt, solvate, ester or prodrug of said compound and a pharmaceutically acceptable carrier, vehicle or diluent.

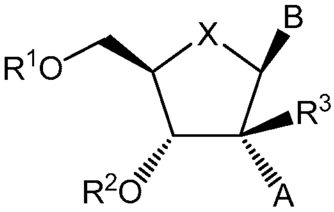
In another aspect the present invention provides a kit comprising an amount of at least one 2'-Substituted Nucleoside Derivative, or a pharmaceutically acceptable salt, solvate, ester or prodrug of said compound and an amount of at least one additional therapeutic agent listed above, wherein the amounts of the two or more active ingredients result in a desired therapeutic effect. In one embodiment, the one or more 2'-Substituted Nucleoside Derivatives and the one or more additional therapeutic agents are provided in the same container. In one embodiment, the one or more 2'-Substituted Nucleoside Derivatives and the one or more additional therapeutic agents are provided in separate containers.

The present invention is not to be limited by the specific embodiments disclosed in the examples that are intended as illustrations of a few aspects of the invention and any embodiments that are functionally equivalent are within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art and are intended to fall within the scope of the appended claims.

A number of references have been cited herein, the entire disclosures of which are incorporated herein by reference.

WHAT IS CLAIMED IS:

1. A compound having the structure:



(I)

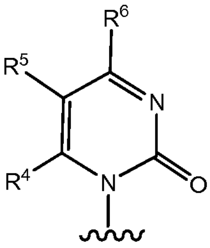
or a pharmaceutically acceptable salt thereof,

wherein:

X is O, S or CH_2;

A is C_2-C_6 alkenyl, C_2-C_6 alkynyl, 5- or 6-membered monocyclic heteroaryl, Cl, -$N(R^{20})_2$, -S-(C_1-C_6 alkyl), -S(O)-(C_1-C_6 alkyl), -$S(O)_2$-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-OH, -(C_1-C_6 alkylene)-$N(R^{20})_2$, -$NHSO_2$-(C_1-C_6 alkyl), -NHC(O)$N(R^{20})_2$, -NHOH, -C(O)OR^{20}, -C(O)$N(R^{20})_2$, -NHC(O)R^{20} or -NHC(O)OR^{20}, or group A and the –OR^2 group of formula (I) can join to form -OC(O)-NH-;

B is a natural or non-natural purine or pyrimidine base, or B is selected from one of the following groups: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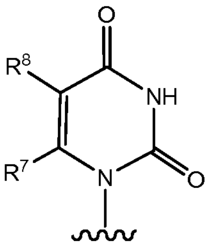
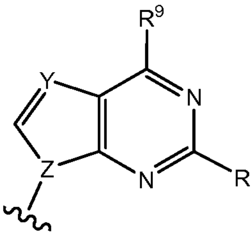
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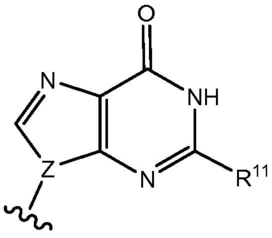
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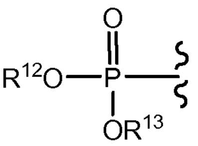
Y is N or –C(R^{19})-;

Z is N or –CH-;

R^1 is H,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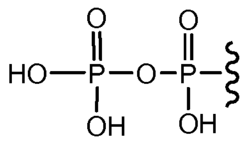
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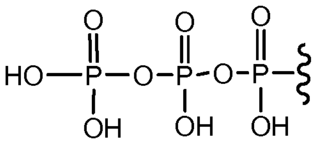
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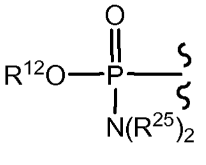
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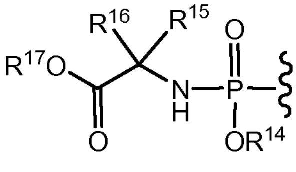
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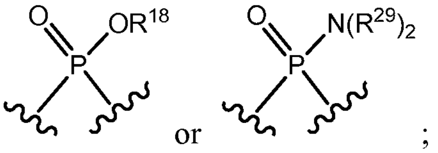
R^2 is H, or R^1 and R^2 join to form a group having the formula:



;

R^3 is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_7 cycloalkyl;

R^4, R^5, R^7 and R^8 are each independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, halo, $-OR^{20}$, $-SR^{20}$ or $-N(R^{20})_2$;

R^6, R^9, R^{10}, R^{11} are each independently selected from H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, 4- to 7-membered heterocycloalkyl, 5- or 6-membered monocyclic heteroaryl, 9- or 10-membered bicyclic heteroaryl, halo, $-OR^{20}$, $-SR^{20}$, $-S(O)R^{20}$, $-S(O)_2R^{20}$, $-S(O)_2N(R^{20})_2$, $-NHC(O)OR^{20}$, $-NHC(O)N(R^{20})_2$, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, -O-(C_1-C_6 haloalkyl), -CN, $-NO_2$, $-N(R^{20})_2$, -NH(C_1-C_6 alkylene)-(5- or 6-membered monocyclic heteroaryl), -NH(C_1-C_6 alkylene)-(9- or 10-membered bicyclic heteroaryl), $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)N(R^{20})_2$ and $-NHC(O)R^{20}$, wherein said C_2-C_6 alkenyl group and said C_2-C_6 alkynyl group can be optionally substituted a halo group;

R^{12} is H or –(C_1-C_6 alkylene)-T-R^{21};

R^{13} is H or –(C_1-C_6 alkylene)-T-R^{21}, or R^{12} and R^{13} can join to form a C_2-C_4 alkylene group between the oxygen atoms that R^{12} and R^{13} are attached to, wherein said C_2-C_4 alkylene group is substituted with at least one C_6-C_{10} aryl group;

R^{14} is H, C_6-C_{10} aryl, 5- or 6-membered monocyclic heteroaryl or 9- or 10-membered bicyclic heteroaryl, wherein said C_6-C_{10} aryl group, said 5- or 6-membered monocyclic heteroaryl group and said 9- or 10-membered bicyclic heteroaryl group can be optionally substituted with R^{22};

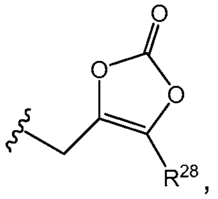
R^{15} is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl or benzyl, wherein said C_1-C_6 alkyl can be optionally substituted with a group selected from halo, $-OR^{20}$, $-SR^{20}$, guanidino, $-N(R^{20})_2$, $-C(O)OR^{20}$, $-C(O)N(R^{20})_2$, $-NHC(O)R^{20}$, 5- or 6-membered monocyclic heteroaryl and 9- or 10-membered bicyclic heteroaryl, and wherein said phenyl group and said benzyl group can be optionally substituted with up to 2 groups, each independently selected from C_1-C_6 alkyl, halo and $-OR^{20}$;

R^{16} is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, phenyl or benzyl, wherein said C_1-C_6 alkyl can be optionally substituted with a group selected from halo, $-OR^{20}$, $-SR^{20}$, guanidino, $-N(R^{20})_2$, $-C(O)OR^{20}$, $-C(O)N(R^{20})_2$, $-NHC(O)R^{20}$, 5- or 6-membered monocyclic heteroaryl and

9- or 10-membered bicyclic heteroaryl, and wherein said phenyl group and said benzyl group can be optionally substituted with up to 2 groups, each independently selected from C_1-C_6 alkyl, halo and –OR^{20};

R^{17} is H, C_1-C_{20} alkyl, C_2-C_{20} alkenyl, -(C_1-C_3 alkylene)$_m$-C_3-C_7 cycloalkyl, -(C_1-C_3 alkylene)$_m$-C_6-C_{10} aryl or adamantyl, wherein said C_1-C_{20} alkyl group, said C_2-C_{20} alkenyl group, said C_6-C_{10} aryl group and said adamantyl group can be optionally substituted with up to three groups, each independently selected from halo, -OR^{20}, -C(O)OR^{20}, CN, NO_2, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_3-C_7 cycloalkyl, C_6-C_{10} aryl, 5- or 6-membered monocyclic heteroaryl, 9- or 10-membered bicyclic heteroaryl, -$N(R^{20})_2$, -C(O)$N(R^{20})_2$ -SR^{20}, -S(O)R^{20}, -$S(O)_2R^{20}$, –$S(O)_2N(R^{20})_2$, -NHC(O)R^{20}, -NHC(O)OR^{20} and -NHC(O)$N(R^{20})_2$ and;

R^{18} is H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, -(C_1-C_3 alkylene)$_m$-C_6-C_{10} aryl, 5- or 6-membered monocyclic heteroaryl, 9- or 10-membered bicyclic heteroaryl or:



wherein said C_6-C_{10} aryl group, said 5- or 6-membered monocyclic heteroaryl group and said 9- or 10-membered bicyclic heteroaryl group can be optionally substituted with up to five groups, each independently selected from C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halo, -OR^{20}, -SR^{20}, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, -O-(C_1-C_6 haloalkyl), -CN, -NO_2, -$N(R^{20})_2$, -C(O)OR^{20}, -C(O)$N(R^{20})_2$ and -NHC(O)R^{20};

R^{19} is H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, halo, -OR^{20}, -SR^{20}, $N(R^{20})_2$, C_3-C_7 cycloalkyl, C_6-C_{10} aryl, 5- or 6-membered monocyclic heteroaryl or 9- or 10-membered bicyclic heteroaryl;

each occurrence of R^{20} is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, -(C_1-C_3 alkylene)$_m$-(C_3-C_7 cycloalkyl), -(C_1-C_3 alkylene)$_m$-(C_6-C_{10} aryl), -(C_1-C_3 alkylene)$_m$-(4 to 7-membered heterocycloalkyl), -(C_1-C_3 alkylene)$_m$-(5- or 6-membered monocyclic heteroaryl) or -(C_1-C_3 alkylene)$_m$-(9- or 10-membered bicyclic heteroaryl), wherein said C_3-C_7 cycloalkyl group, said C_6-C_{10} aryl group, said 4 to 7-membered heterocycloalkyl group, said -(5- or 6-membered monocyclic heteroaryl group or said 9- or 10-membered bicyclic heteroaryl group can be optionally substituted with R^{26};

each occurrence of R^{21} is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkenyl, 5- or 6-

membered monocyclic heteroaryl, 9- or 10-membered bicyclic heteroaryl, $-OR^{20}$, $-O-(C_1-C_6$ haloalkyl) or $-N(R^{20})_2$, wherein said C_2-C_6 alkenyl group, said C_2-C_6 alkynyl group, said C_3-C_7 cycloalkyl group, said C_3-C_7 cycloalkenyl group, said C_6-C_{10} aryl group, said 5- or 6-membered monocyclic heteroaryl group and said 9- or 10-membered bicyclic heteroaryl group can be optionally substituted with up to five groups, each independently selected from C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halo, $-OR^{20}$, $-SR^{20}$, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, $-O-(C_1-C_6$ haloalkyl), -CN, $-NO_2$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)N(R^{20})_2$ and $-NHC(O)R^{20}$;

R^{22} represents from one to five substituent groups, each independently selected from C_1-C_6 alkyl, halo, $-OR^{20}$, $-SR^{20}$, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, $-O-(C_1-C_6$ haloalkyl), -CN, $-NO_2$, $-N(R^{20})_2$, $-C(O)OR^{20}$, $-C(O)N(R^{20})_2$ and $-NHC(O)R^{20}$, or any two R^{22} groups on adjacent ring carbon atoms can combine to form $–O-R^{23}-O-$;

R^{23} is $–[C(R^{24})_2]_n-$;

each occurrence of R^{24} is independently H or C_1-C_6 alkyl;

each occurrence of R^{25} is independently H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, $-(C_1-C_3$ alkylene$)_m-(C_6-C_{10}$ aryl), 4 to 7-membered heterocycloalkyl, 5- or 6-membered monocyclic heteroaryl or 9- or 10-membered bicyclic heteroaryl, wherein said C_1-C_6 alkyl group, said C_2-C_6 alkenyl group, said C_2-C_6 alkynyl group, said C_3-C_7 cycloalkyl group, said C_6-C_{10} aryl group, said 4 to 7-membered heterocycloalkyl group, said -(5- or 6-membered monocyclic heteroaryl group or said 9- or 10-membered bicyclic heteroaryl group can be optionally substituted with R^{26}; or two R^{25} groups, together with the common nitrogen atom to which they are attached, join to form a 4- to 7-membered heterocycloalkyl group;

R^{26} represents from one to five substituent groups, each independently selected from C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halo, $-OR^{27}$, $-SR^{27}$, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, $-O-(C_1-C_6$ haloalkyl), -CN, $-NO_2$, $-N(R^{27})_2$, $-C(O)OR^{27}$, $-C(O)N(R^{27})_2$ and $-NHC(O)R^{27}$;

each occurrence of R^{27} is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, $-(C_1-C_3$ alkylene$)_m-(C_3-C_7$ cycloalkyl), $-(C_1-C_3$ alkylene$)_m-(C_6-C_{10}$ aryl), $-(C_1-C_3$ alkylene$)_m$-(4 to 7-membered heterocycloalkyl), $-(C_1-C_3$ alkylene$)_m$-(5- or 6-membered monocyclic heteroaryl) or $-(C_1-C_3$ alkylene$)_m$-(9- or 10-membered bicyclic heteroaryl);

R^{28} is H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkenyl, 5- or 6-membered monocyclic heteroaryl, 9- or 10-membered bicyclic heteroaryl, $-OR^{20}$, $-O-(C_1-C_6$ haloalkyl) or $-N(R^{20})_2$, wherein said C_2-C_6 alkenyl group, said C_2-C_6 alkynyl group, said C_3-C_7 cycloalkyl group, said C_3-C_7 cycloalkenyl group, said C_6-C_{10} aryl group, said 5- or 6-membered monocyclic heteroaryl group and said 9- or 10-membered bicyclic heteroaryl group can be optionally substituted with up to five groups, each independently selected from C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halo, -OR^{20}, -SR^{20}, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, -O-(C_1-C_6 haloalkyl), -CN, -NO$_2$, -N(R^{20})$_2$, -C(O)R^{20}, -C(O)OR^{20}, -C(O)N(R^{20})$_2$ and -NHC(O)R^{20};

each occurrence of R^{29} is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, -(C_1-C_3 alkylene)$_m$-(C_3-C_7 cycloalkyl), -(C_1-C_3 alkylene)$_m$-(C_6-C_{10} aryl), -(C_1-C_3 alkylene)$_m$-(4 to 7-membered heterocycloalkyl), -(C_1-C_3 alkylene)$_m$-(5- or 6-membered monocyclic heteroaryl) or -(C_1-C_3 alkylene)$_m$-(9- or 10-membered bicyclic heteroaryl), wherein said C_3-C_7 cycloalkyl group, said C_6-C_{10} aryl group, said 4 to 7-membered heterocycloalkyl group, said -(5- or 6-membered monocyclic heteroaryl group or said 9- or 10-membered bicyclic heteroaryl group can be optionally substituted with R^{26};

each occurrence of T is independently –S-, -O-, -SC(O)-, -SC(S)-, -OC(O)- and –OC(S)-;

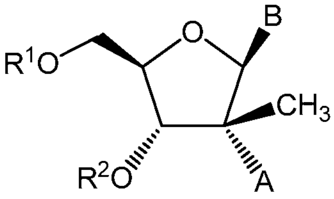
each occurrence of m is independently 0 or 1; and

each occurrence of n is independently 1 or 2.

2. The compound of claim 1, wherein X is O.

3. The compound of claim 1 or 2, wherein R^3 is methyl.

4. The compound of claim 1 having the formula:



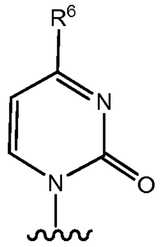
(Ia)

or a pharmaceutically acceptable salt thereof,

wherein:

A is 5- or 6-membered monocyclic heteroaryl, C_2-C_6 alkynyl, -CH$_2$NH$_2$, -N(R^{20})$_2$, -S-(C_1-C_6 alkyl), -S(O)$_2$-(C_1-C_6 alkyl), -NHC(O)N(R^{20})$_2$, -C(O)N(R^{20})$_2$, -NHC(O)R^{20} or group A and the –OR^2 group of formula (I) can join to form -OC(O)-NH-;

B is:



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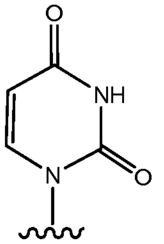
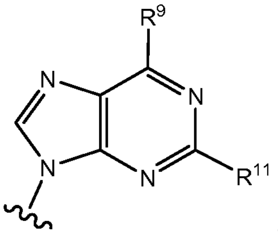
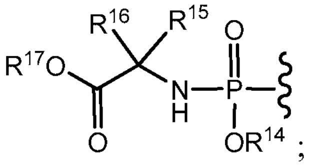


or



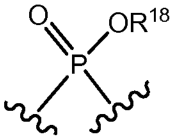
;

R^1 is H or:



;

R^2 is H, or R^1 and R^2 join to form a group having the formula:



;

R^6 and R^{11} are each independently $-N(R^{20})_2$;

R^9 is $-OH$ or $-O-(C_1-C_6$ alkyl);

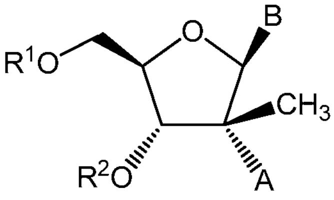
R^{14} is C_6-C_{10} aryl;

R^{15} and R^{16} are each independently H or C_1-C_6 alkyl;

R^{17} and R^{18} are each independently C_1-C_6 alkyl; and

each occurrence of R^{20} is independently H or $-C(O)-(C_1-C_6$ alkyl).

5. The compound of claim 1 having the formula:



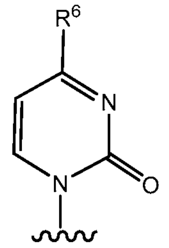
(Ia')

or a pharmaceutically acceptable salt thereof,

wherein:

A is 5- or 6-membered monocyclic heteroaryl, C_2-C_6 alkynyl, $-CH_2NH_2$, $-N(R^{20})_2$, $-S-(C_1-C_6$ alkyl), $-S(O)_2-(C_1-C_6$ alkyl), $-NHC(O)N(R^{20})_2$, $-C(O)N(R^{20})_2$, $-NHC(O)R^{20}$ or group A and the $-OR^2$ group of formula (I) can join to form $-OC(O)-NH-$;

B is:



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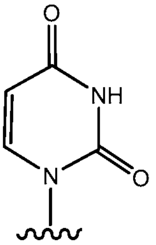

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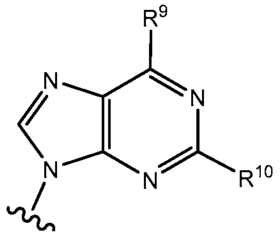
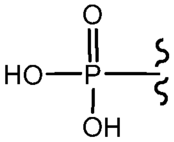


;

R^1 is:



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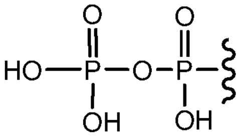

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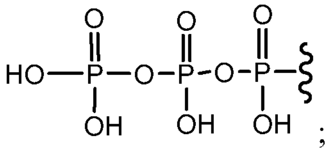


;

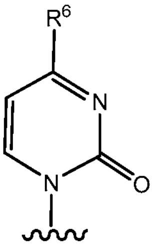
R^6 and R^{10} are each independently $-N(R^{20})_2$;

R^9 is –OH or $-O-(C_1-C_6$ alkyl); and

each occurrence of R^{20} is independently H or $-C(O)-(C_1-C_6$ alkyl).

6. The compound of any of claims 1-4, wherein A is $-NH_2$.

7. The compound of any one of claims 1-6, wherein B is:



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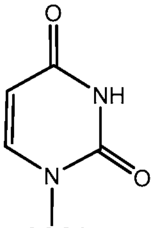

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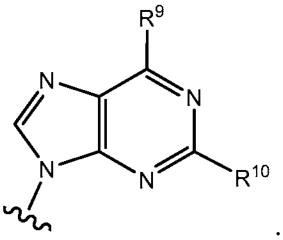
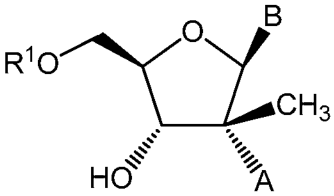


;

R^6 is $-NH_2$ or $-NHC(O)CH_3$; R^9 is –OH or $-O-(C_1-C_6$ alkyl); and R^{10} is $-NH_2$.

8. The compound of claim 1 having the formula:



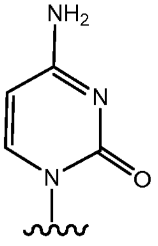
(Ib)

or a pharmaceutically acceptable salt thereof,

wherein:

A is C_2-C_6 alkynyl or $-NH_2$;

B is:



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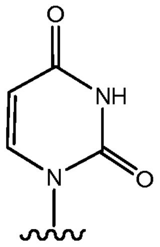

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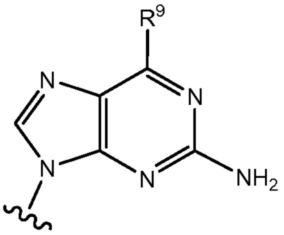
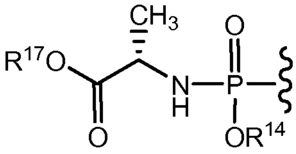


;

R^1 is:



;

R^9 is –OH or -O-(C_1-C_6 alkyl);

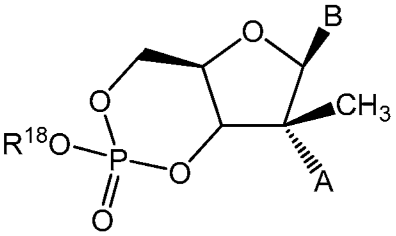
R^{14} is phenyl, which can be optionally substituted with up to 2 halo groups, which can be the same or different; and

R^{17} is C_1-C_6 alkyl.

9. The compound of any one of claims 1-4 or 6-8, wherein R^{14} is phenyl.

10. The compound of any one of claims 1-4 or 6-9, wherein R^{17} is ethyl or isopropyl.

11. The compound of claim 1 having the formula:



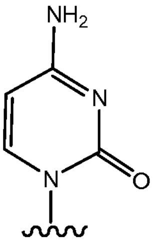
(Ic)

or a pharmaceutically acceptable salt thereof,

wherein:

A is C_2-C_6 alkynyl or $-NH_2$;

B is: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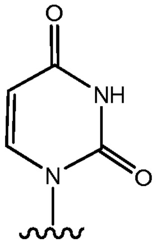
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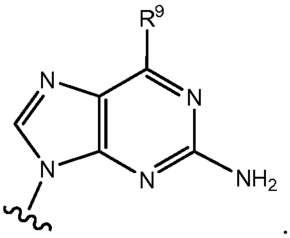
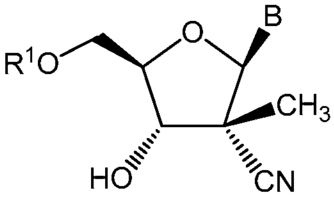

; and

R^{18} is aryl or C_1-C_6 alkyl.

12. The compound of claim 11, wherein R^{18} is isopropyl.

13. The compound of claim 1 having the formula:

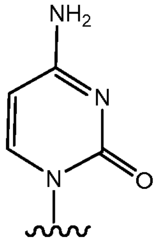


(Id)

or a pharmaceutically acceptable salt thereof,

wherein:

B is: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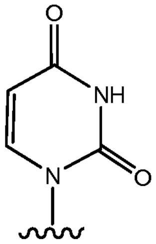
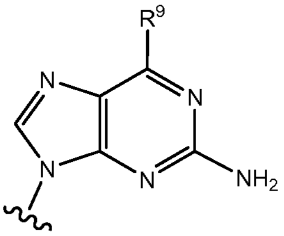
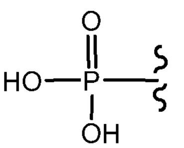

or

;

R^1 is: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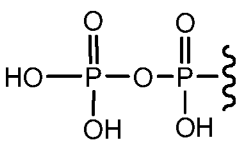
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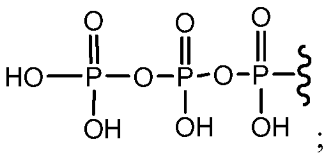
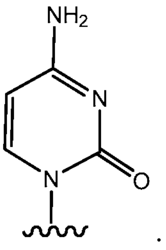
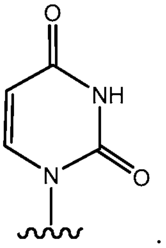

; and

R^9 is –OH or -O-(C_1-C_6 alkyl).

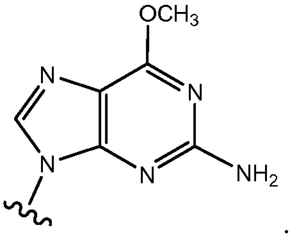
14. The compound of any of claims 1-13, wherein B is



15. The compound of any of claims 1-13, wherein B is

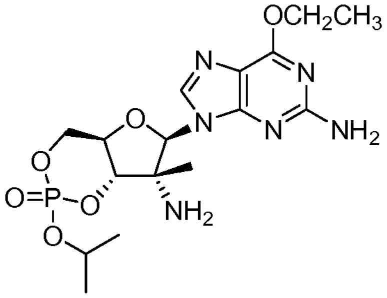
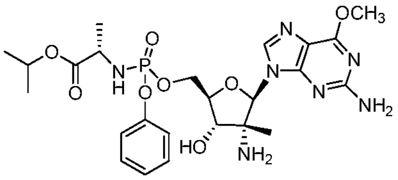


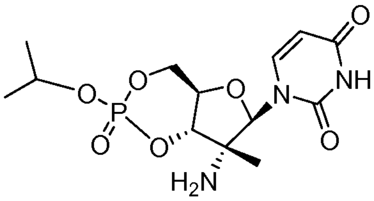
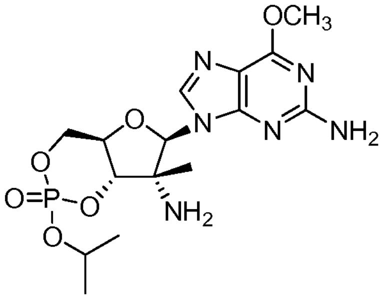
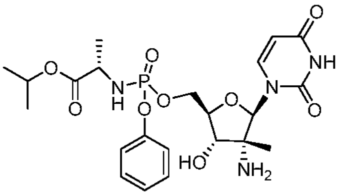
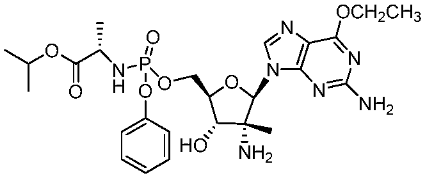
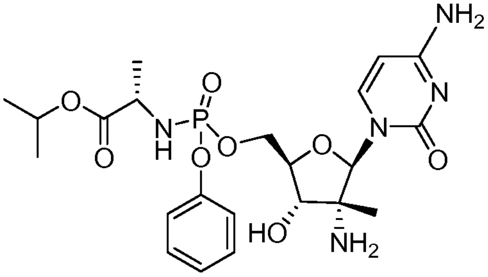
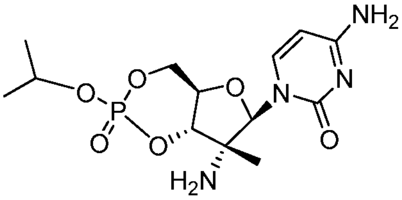
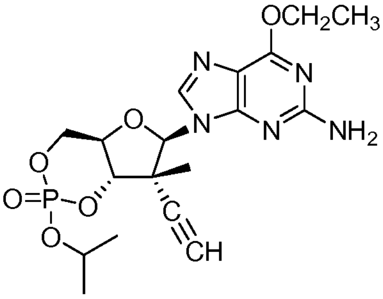
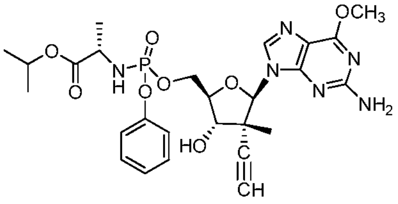
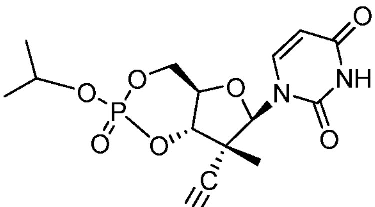
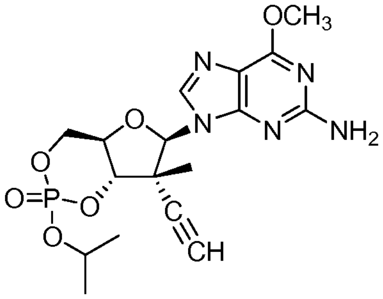
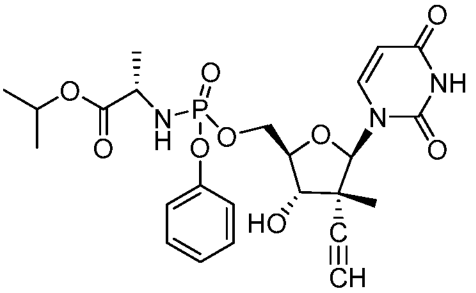
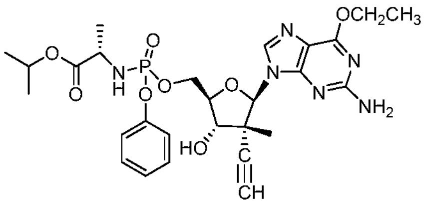
16. The compound of any of claims 1-13, wherein B is

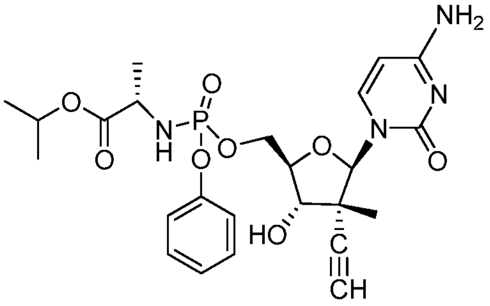
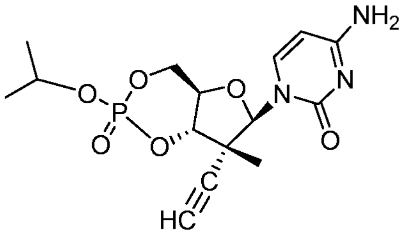


17. The compound of claim 1, being any one of the compounds numbered 1-99 in the above specification, or a pharmaceutically acceptable salt thereof.

18. The compound of claim 1, having the structure:

or a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition comprising an effective amount of the compound of any of claims 1 to 18, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

20. The pharmaceutical composition according to claim 19, further comprising a second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

21. The pharmaceutical composition according to claim 19, further comprising a third therapeutic agent selected from the group consisting of HCV protease inhibitors, HCV NS5A inhibitors and HCV NS5B polymerase inhibitors.

22. The use of the compound according to any of claims 1 to 18, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for inhibiting HCV NS5A activity or for preventing and/or treating infection by HCV in a patient in need thereof.

23. A method of treating a patient infected with HCV comprising the step of administering an amount of (i) the compound according to any of claims 1 to 18, or a pharmaceutically acceptable salt thereof, or (ii) the composition according to any of claims 19-21 effective to prevent and/or treat infection by HCV in said patient.

24. The method according to claim 23, further comprising the step of administering pegylated-interferon alpha and an HCV protease inhibitor to said patient.

25. The method according to claim 23 or 24, further comprising the step of administering ribavirin to said patient.

26. The use of the compound according to any of claims 1 to 18, or a pharmaceutically acceptable salt thereof, in a pharmaceutical composition for inhibiting HCV NS5A activity or for preventing and/or treating infection by HCV in a patient in need thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/33017

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/08; A61K 31/34 (2012.01)
USPC - 514/461
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 514/461

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/430, 438, 449, 455, 763 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST, PGPB, USPT, EPAB, JPAB, Dialog
Nucleoside derivative, antiviral, purine, fused, hepatitis

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2007/0265222 A1 (MACCOSS et al.) 15 November 2007 (15.11.2007) para [0039]-[0052]	1-5, 8, 11-13 and 17-18
Y	US 2010/0104532 A1 (CHEN et al.) 29 April 2010 (29.04.2010) para [0007], [0055]-[0060], [0065]-[0069], [0365], [0409]	1-5, 8, 11-13 and 17-18
Y	US 2010/0021425 A1 (BUTLER et al.) 28 Jan 2010 (28.01.2010) pg 13, col 2, 5th compound down	11-12

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search 29 June 2012 (29.06.2012)	Date of mailing of the international search report 23 JUL 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/33017

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 6-7, 9-10, 14-16 and 19-26
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.