(12) STANDARD PATENT (11) Application No. **AU 2011336632 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Compounds

(51) International Patent Classification(s)
C07H 19/06 (2006.01) ***C07H 19/10*** (2006.01)
A61K 31/7068 (2006.01) ***C07H 19/16*** (2006.01)
A61K 31/7072 (2006.01) ***C07H 19/20*** (2006.01)
A61K 31/7076 (2006.01) ***C07H 23/00*** (2006.01)
A61P 31/14 (2006.01)

(21) Application No: **2011336632** (22) Date of Filing: **2011.11.30**

(87) WIPO No: **WO12/075140**

(30) Priority Data

(31) Number	(32) Date	(33) Country
61/417,946	**2010.11.30**	**US**

(43) Publication Date: **2012.06.07**
(44) Accepted Journal Date: **2015.09.03**

(71) Applicant(s)
Gilead Pharmasset LLC

(72) Inventor(s)
Du, Jinfa;Sofia, Michael Joseph

(74) Agent / Attorney
Freehills Patent Attorneys, Level 43 101 Collins Street, Melbourne, VIC, 3000

(56) Related Art
WO 2010/130726

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 June 2012 (07.06.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/075140 A1

(51) International Patent Classification:
C07H 19/06 (2006.01) *A61K 31/7068* (2006.01)
C07H 19/10 (2006.01) *A61K 31/7072* (2006.01)
C07H 19/16 (2006.01) *A61K 31/7076* (2006.01)
C07H 19/20 (2006.01) *A61P 31/14* (2006.01)
C07H 23/00 (2006.01)

(21) International Application Number:
PCT/US2011/062643

(22) International Filing Date:
30 November 2011 (30.11.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/417,946 30 November 2010 (30.11.2010) US

(71) Applicant *(for all designated States except US)*: **PHARMASSET, INC.** [US/US]; 303A College Road East, Princeton, NJ 08540 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DU, Jinfa** [US/US]; 1206 Reins Circle, New Hope, PA 18938 (US). **SOFIA, Michael Joseph** [US/US]; 3066 Antler Drive, Doylestown, PA 18901 (US).

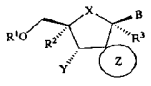
(74) Agents: **KOWALCHYK, Katherine M.** et al.; Merchant & Gould P.C., P.O. Box 2903, Minneapolis, MN 55402-0903 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

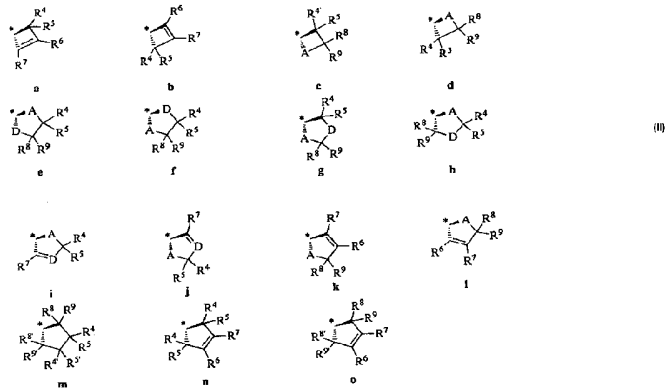
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU,

[Continued on next page]

(54) Title: COMPOUNDS



(I)



(II)

(57) Abstract: Disclosed herein are 2'-spiro-nucleosides of formula I and derivatives thereof useful for treating a subject infected by hepatitis C virus or dengue virus. Formula (I), where z is a four-or five-membered ring selected from among radicals a-o represented by de following structures (II) where * represents the point of attachment to the 2'-carbon.

WO 2012/075140 A1

LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

COMPOUNDS

This application is being filed on 29 November 2011, as a PCT International Patent application in the name of Pharmasset, Inc., a U.S. national corporation, applicant for the designation of all countries except the US, and Jinfa Du and Michael Joseph Sofia, both citizens of the U.S., applicants for the designation of the US only.

Priority

Priority is claimed to U.S. provisional patent application 61/417,946, filed on November 30, 2010.

Field of the Invention

Disclosed herein are 2'-spiro-nucleosides and derivatives thereof useful for treating hepatitis C virus and dengue virus infections.

Background

Hepatitis C virus (HCV) infection is a major health problem that leads to chronic liver disease, such as cirrhosis and hepatocellular carcinoma, in a substantial number of infected individuals, estimated to be 2-15% of the world's population. According to the U.S. Center for Disease Control, there are an estimated 4.5 million infected people in the United States alone. According to the World Health Organization, there are more than 200 million infected individuals worldwide, with at least 3 to 4 million people being infected each year. Once infected, about 20% of people clear the virus, but the rest can harbor HCV the rest of their lives. Ten to twenty percent of chronically infected individuals eventually develop liver-destroying cirrhosis or cancer. The viral disease is transmitted parenterally by contaminated blood and blood products, contaminated needles, or sexually and vertically from infected mothers or carrier mothers to their offspring. Current treatments for HCV infection, which are restricted to immunotherapy with recombinant interferon-α alone or in combination with the nucleoside analog ribavirin, are of limited clinical benefit. Moreover, there is no established vaccine

for HCV. Consequently, there is an urgent need for improved therapeutic agents that effectively combat chronic HCV infection.

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

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

Dengue viral infections are problematic in the tropical and subtropical regions of the word. Shi et al. Top. Med. Chem. (2001) 7: 243-276. The dengue virus (DENV) is transmitted to humans by certain mosquitos, and it is has been estimated that up to about 50 million infections occur each year. Parkinson et al. Future Med. Chem. (2010) 2(7): 1181-1203. At the present, there are no specific treatments for dengue viral infections. Fagundes et al. Drug Development Research (2011) 72: 480-500. DENV is comprised of ten proteins that includes three structural proteins (C, prM, and E) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5). Of these ten proteins, only NS3 and NS5 are known to possess enzymatic activity. A desirable drug substance is one that interferes with the action or function of any one of these ten viral proteins.

Flaviviridae Viruses

The Flaviviridae family of viruses comprises at least three distinct genera: *pestiviruses*, which cause disease in cattle and pigs; *flavivruses*, which are the primary cause of diseases such as dengue fever and yellow fever; and *hepaciviruses*, whose sole member is HCV. The flavivirus genus includes more than 68 members separated into groups on the basis of serological relatedness (Calisher et al., *J. Gen. Virol*, 1993,70,37-43). Clinical symptoms vary and include fever, encephalitis and hemorrhagic fever (*Fields Virology*, Editors: Fields, B. N., Knipe, D. M., and Howley, P. M., Lippincott-Raven Publishers, Philadelphia, PA, 1996, Chapter 31, 931-959). Flaviviruses of global concern that are associated with human disease include the Dengue Hemorrhagic Fever viruses (DHF), yellow fever virus, shock syndrome and Japanese encephalitis virus (Halstead, S. B., *Rev. Infect. Dis.*, 1984, 6, 251-264; Halstead, S. B., *Science*, 239:476-481, 1988; Monath, T. P., *New Eng. J. Med*, 1988, 319, 64 1-643).

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

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

hepaciviruses to grow efficiently in cell culture, bovine viral diarrhea virus (BVDV) is often used as a surrogate to study the HCV virus.

The genetic organization of pestiviruses and hepaciviruses is very similar. These positive stranded RNA viruses possess a single large open reading frame (ORF) encoding all the viral proteins necessary for virus replication. These proteins are expressed as a polyprotein that is co- and post-translationally processed by both cellular and virus-encoded proteinases to yield the mature viral proteins. The viral proteins responsible for the replication of the viral genome RNA are located within approximately the carboxy-terminal. Two-thirds of the ORF are termed nonstructural (NS) proteins. The genetic organization and polyprotein processing of the nonstructural protein portion of the ORF for pestiviruses and hepaciviruses is very similar. For both the pestiviruses and hepaciviruses, the mature nonstructural (NS) proteins, in sequential order from the amino-terminus of the nonstructural protein coding region to the carboxy-terminus of the ORF, consist of p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B.

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

The actual roles and functions of the NS proteins of pestiviruses and hepaciviruses in the lifecycle of the viruses are directly analogous. In both cases, the NS3 serine proteinase is responsible for all proteolytic processing of polyprotein precursors downstream of its position in the ORF (Wiskerchen and Collett, *Virology*, 1991, 184, 341-350; Bartenschlager et al., *J. Virol.* 1993, 67, 3835-3844; Eckart et al. *Biochem. Biophys. Res. Comm.* 1993,192, 399-406; Grakoui et al., *J. Virol.* 1993, 67, 2832-2843; Grakoui et al., *Proc. Natl. Acad Sci. USA* 1993, 90, 10583-10587; Hijikata et al., *J. Virol.* 1993, 67, 4665-4675; Tomė et al., *J. Virol.*, 1993, 67, 4017-4026). The NS4A protein, in both cases, acts as a cofactor with the

NS3 serine protease (Bartenschlager et al., *J. Virol.* 1994, 68, 5045-5055; Failla et al., *J. Virol.* 1994, 68, 3753-3760; Xu et al., *J. Virol.*, 1997, 71:53 12-5322). The NS3 protein of both viruses also functions as a helicase (Kim et al., *Biochem. Biophys. Res. Comm.*, 1995, 215, 160-166; Jin and Peterson, *Arch. Biochem. Biophys.*, 1995, 323, 47-53; Warrener and Collett, *J. Virol.* 1995, 69,1720-1726). Finally, the NS5B proteins of pestiviruses and hepaciviruses have the predicted RNA-directed RNA polymerases activity (Behrens et al., EMBO, 1996, 15, 12-22; Lechmann et al., *J. Virol.*, 1997, 71, 8416-8428; Yuan et al., *Biochem. Biophys. Res. Comm.* 1997, 232, 231-235; Hagedorn, PCT WO 97/12033; Zhong et al, *J. Virol.*, 1998, 72, 9365-9369).

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

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

Nucleoside inhibitors of NS5B polymerase can act either as a non-natural substrate that results in chain termination or as a competitive inhibitor which competes with nucleotide binding to the polymerase. To function as a chain terminator the nucleoside analog must be taken up by the cell and converted *in vivo* to a triphosphate to compete for the polymerase nucleotide binding site. This

conversion to the triphosphate is commonly mediated by cellular kinases which imparts additional structural requirements on a potential nucleoside polymerase inhibitor. Unfortunately, this limits the direct evaluation of nucleosides as inhibitors of HCV replication to cell-based assays capable of *in situ* phosphorylation.

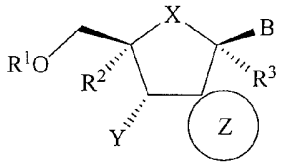
In some cases, the biological activity of a nucleoside is hampered by its poor substrate characteristics for one or more of the kinases needed to convert it to the active triphosphate form. Formation of the monophosphate by a nucleoside kinase is generally viewed as the rate limiting step of the three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

Also limiting the utility of nucleosides as viable therapeutic agents is their sometimes poor physicochemical and pharmacokinetic properties. These poor properties can limit the intestinal absorption of an agent and limit uptake into the target tissue or cell. To improve on their properties prodrugs of nucleosides have been employed. Additional phosphate-containing prodrugs are also known: C. Schultz, Biorg. & Med. Chem. (2003) 11:885-898; C. McGuigan et al., Bioorg. & Med. Chem. Lett. (1994) 4(3): 427-430; C. Meier, Synlett (1998) 233-242; R. J. Jones et al., Antiviral Research (1995) 27: 1-17; G. J. Friis et al., Eur. J. Pharm. Sci. (1996) 4: 49-59; C. Meier Mini Reviews in Medicinal Chemistry (2002) 2(3): 219-234; C. Perigaud et al., Advances in Antiviral Drug Design; DeClerq E., Ed.; Vol. 2; JAI Press, London, 1996. However, there is no general agreement as to which phosphate-containing prodrug provides for the best activity.

In an effort to improve treatment of HCV or DENV, it remains of vital interest to identify compounds capable of inhibiting the action of NS5B polymerase of HCV or of inhibiting the action or function of a particular DENV protein.

Summary

Disclosed herein is a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I**:



I

wherein

1) R^1 is selected from among
   a) hydrogen,
   b) $-P(O)(OH)_2$,
   c) $-P(O)(O(CH_2)_{1\text{-}3}OC(O)O(alkyl))_2$,
   d) $-P(O)(O(CH_2)_{1\text{-}3}OC(O)(alkyl))_2$,
   e) $-P(O)(O(CH_2)_{1\text{-}3}SC(O)(alkyl))_2$,
   f) $-P(O)(O(CH_2)_{1\text{-}3}OCH_2(aryl))_2$,
   g) $-P(O)(O(CH_2)_{1\text{-}3}SCH_2(aryl))_2$,
   h) $-P^*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})$,
   where
   R^{1a} is
      i) hydrogen,
      ii) alkyl,
      iii) cycloalkyl, or
      iv) aryl,
   R^{1b} is
      i) hydrogen,
      ii) $C_{1\text{-}6}$alkyl,
      iii) cycloalkyl,
      iv) alkaryl, or
      v) alk(heteroaryl), and
   R^{1c} is
      i) hydrogen
      ii) alkyl,
      iii) cycloalkyl, or
      iv) alkaryl,
   i) $-P^*(O)(NH(alkaryl)(O(CH_2)_{1\text{-}3}SC(O)(alkyl))$,
   j) a 1,3,2-dioxaphosphinane-2-oxide,
   k) a 4*H*-benzo[d][1,3,2]dioxaphosphinine-2-oxide,
   l) $-P^*(O)(OR^{1c})\sim$, when Y is $-O\sim$, where R^{1c} is defined above,
   m) $-P(O)(OH)-O-P(O)(OH)_2$,
   n) $-P(O)(OH)-O-P(O)(OH)-O-P(O)(OH)_2$,

o) an acyl,
p) a C_{1-6}-alkylene-oxy-acyl, and
q) a –C(O)–O-alkyl;

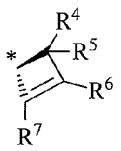
2) R^2 is selected from among
a) hydrogen,
b) fluoro,
c) azido,
d) cyano,
e) a C_{1-6}alkyl,
f) a vinyl, and
g) an ethynyl;

3) R^3 is selected from among
a) hydrogen,
b) methyl, and
c) cyano,

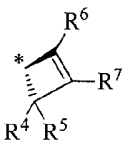
4) Y is selected from among
a) hydrogen,
b) fluoro,
c) –OH,
d) –O~, when R^1 is –P(O)(OR^{1c})~, where R^{1c} is defined above,
e) –O(acyl),
f) –O(C_{1-6}-alkylene-oxy-acyl),
g) –O–C(O)–O-alkyl,
h) $–NH_2$,
i) –NH(acyl),
j) –NH–C(O)–O-alkyl, and
k) azido;

5) X is selected from among
a) –O–,
b) –S–,
c) –NH–,
d) $–CH_2–$,
e) $>C=CH_2$, and
f) –NH–C(O)–O-alkyl;

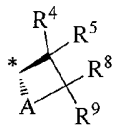
6) (Z) is a four- or five-membered ring selected from among radicals **a-o** represented by the following structures



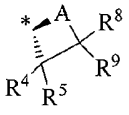
a



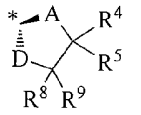
b

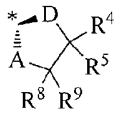


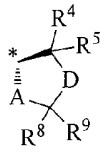
c

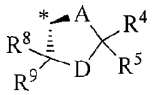


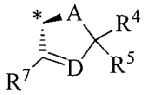
d

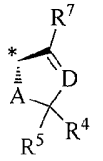

e

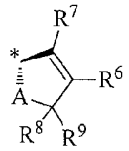

f

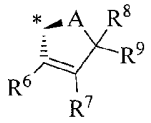

g

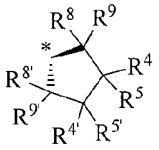

h

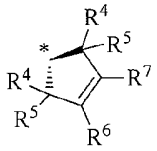

i

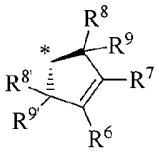

j


k


l


m


n


o

where * represents the point of attachment to the 2'-carbon and where

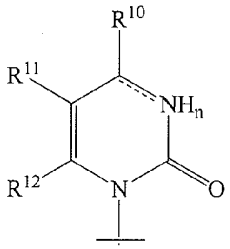
a) A is selected from among
   i) –O–,
   ii) –S–,
   iii) –S(O)–,
   iv) –$S(O)_2$–, and
   v) –NH–,

b) D is selected from among
   i) –O–,
   ii) –S– except for rings i and j,
   iii) –S(O)– except for rings i and j,
   iv) –$S(O)_2$– except for rings i and j, and
   v) –NH– except for rings i and j,
   vi) –N–,
   vii) a methylene except for rings i and j,
   viii) a methine, and
   ix) a vinylidene except for rings i and j,

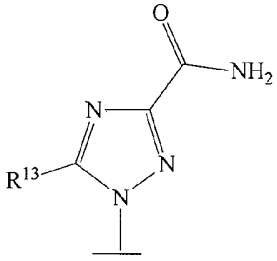
c) R^4, $R^{4'}$, R^5, $R^{5'}$, R^6, R^7, R^8, $R^{8'}$, R^9, and $R^{9'}$ are independently selected from among
   i) hydrogen,
   ii) halo,
   iii) $C_{1\text{-}6}$alkyl,
   iv) hydroxy,
   v) alkoxy,
   vi) cycloalkoxy,
   vii) –O(acyl),
   viii) –O($C_{1\text{-}6}$-alkyleneoxyacyl),
   ix) –O–C(O)–O-alkyl,
   x) $C_{1\text{-}6}$alkylene-oxy(alkyl),
   xi) alkenyl,
   xii) ethynyl,
   xiii) –NH_2,
   xiv) –NH(alkyl),

xv) –NH(cycloalkyl),
xvi) heterocyclyl,
xvii) aryl, and
xviii) heteroaryl; and

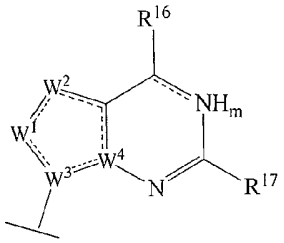
7) B is selected from among B1, B2, and B3 represented by the following structures:



B1



B2



B3

where for B1 n is 0 or 1,

a) when n is 0, ----- is a double-bond and R^{10} is selected from among
i) $–NH_2$,
ii) –NH(alkyl),
iii) –NH(acyl),
iv) –NH–C(O)–O-alkyl,
v) – cycloheteroalkyl,
vi) –heteroaryl,
vii) –O(alkyl),
viii) –O(acyl),
ix) $–O(C_{1\text{-}6}$alkylene-oxyacyl), and
x) –O–C(O)–O-alkyl, or

b) when n is 1, ----- is a single-bond and R^{10} is selected from among
i) =O,
ii) =NH, and
iii) =N(alkyl), and

c) independent of the value of n, R^{11} and R^{12} are independently selected from among
i) hydrogen,
ii) halo,
iii) cyano,
iv) $C_{1\text{-}6}$alkyl,
v) $C_{2\text{-}5}$alkenyl, and
vi) $C_{2\text{-}5}$alkynyl,

where for B2,

a) R^{13} is selected from among
i) hydrogen,
ii) halo,
iii) cyano,
iv) $–C(O)NH_2$,
v) $C_{1\text{-}6}$alkyl,
vi) vinyl, and

vii) ethynyl,

where for B3 m is 0 or 1, and ---- is a single or double bond

a) when m is 0, ----- is a double-bond and R^{16} and R^{17} are independently selected from among

i) hydrogen,
ii) $-NH_2$,
iii) –NH(alkyl),
iv) –NH(acyl),
iv) –NH–C(O)–O-alkyl,
v) – cycloheteroalkyl,
vi) –O(alkyl),
vii) –O(acyl),
viii) $-O(C_{1\text{-}6}$alkyleneoxyacyl), and
ix) –O–C(O)–O-alkyl,
x) –S(alkyl), or

b) when m is 1, ----- is a single-bond

b1) R^{16} is selected from among

i) =O,
ii) =NH, and
iii) =N(alkyl), and

b2) R^{17} is selected from among

i) $-NH_2$,
ii) –NH(alkyl),
iii) –NH(acyl),
iv) –NH–C(O)–O-alkyl, and
v) – cycloheteroalkyl,

c) independent of the value of m, each bonding pair, W^1----W^2, W^2----C, C----W^4, W^4----W^3, and W^3----W^1, contained in the five-membered ring comprises a single or a double bond and

i) W^1 is O, S, N, or CR^{14},
ii) W^2 is N or CR^{15},
iii) W^3 is C or N, and
iv) W^4 is C or N

and where R^{14} and R^{15}, if present, are independently selected from among

i) hydrogen,
ii) halo,
iii) cyano,
iv) $-C(O)NH_2$,
iv) $C_{1\text{-}6}$alkyl,
vii) vinyl, and
viii) ethynyl.

Detailed Description of the Invention

Definitions

The phrase "a" or "an" entity as used herein refers to one or more of that entity; for example, a compound refers to one or more compounds or at least one

compound. As such, the terms "a" (or "an"), "one or more", and "at least one" can be used interchangeably herein.

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

The term "stereoisomer" has its plain and ordinary meaning.

The term "*" denotes the presence of a chiral center. Instances where "*" are not explicitly included in a radical does not necessarily mean that the radical does not contain a chiral center.

The term "P*" means that the phosphorus atom is chiral and that it has a corresponding Cahn-Ingold-Prelog designation of "R" or "S" which have their accepted plain meanings. In some instances, a phosphorus-containing radical does not expressly include an "*" next to the phosphorus atom, e.g., $-P(O)(O(CH_2)_{1-3}OC(O)(alkyl))_2$, $-P(O)(O(CH_2)_{1-3}SC(O)(alkyl))_2$, $-P(O)(O(CH_2)_{1-3}OCH_2(aryl))_2$, $-P(O)(O(CH_2)_{1-3}SCH_2(aryl))_2$. In these (and other) instances, it will be understood that chirality at phosphorus will be dictated by the substituent pattern. That is, when the substituents bound to phosphorus are the same, then achirality at phosphorus will exist, but when the substituents bound to the phosphorus are not the same, then chirality at phosphorus will exist.

The term "salts" or "salt thereof" as described herein, refers to a compound comprising a cation and an anion, which can prepared by any process known to one of ordinary skill, e.g., by the protonation of a proton-accepting moiety and/or deprotonation of a proton-donating moiety. Alternatively, the salt can be prepared by a cation/anion metathesis reaction. It should be noted that protonation of the proton-accepting moiety results in the formation of a cationic species in which the charge is balanced by the presence of a anion, whereas deprotonation of the proton-donating moiety results in the formation of an anionic species in which the charge is balanced by the presence of a cation. It is understood that salt formation can occur under synthetic conditions, such as formation of pharmaceutically acceptable salts, or under conditions formed in the body, in which case the corresponding cation or anion is one that is present in the body. Examples of common cations found in the

body include, but are not limited to: H^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, etc. Examples of common anions found in the body include, but are not limited to, Cl-, HCO_3^-, CO_3^{2-}, $H_2PO_4^-$, HPO_4^{2-}, etc.

The phrase "pharmaceutically acceptable salt" means a salt that is pharmaceutically acceptable. It is understood that the term "pharmaceutically acceptable salt" is encompassed by the expression "salt." Examples of pharmaceutically acceptable salts include, but are not limited to acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as glycolic acid, pyruvic acid, lactic acid, malonic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, salicylic acid, muconic acid, and the like. Additional examples of anionic radicals of the pharmaceutically acceptable salt include but are not limited to: acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate (camphorsulfonate), carbonate, chloride, citrate, edetate, edisylate (1,2-ethanedisulfonate), estolate (lauryl sulfate), esylate (ethanesulfonate), fumarate, gluceptate (glucoheptonate), gluconate, glutamate, glycollylarsanilate (p-glycollamidophenylarsonate), hexylresorcinate, hydrabamine (N,N'-di(dehydroabietyl)ethylenediamine), hydroxynaphthoate, iodide, isethionate (2-hydroxyethanesulfonate), lactate, lactobionate, malate, maleate, mandelate, mesylate, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate,polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, and teoclate (8-chlorotheophyllinate). Basic addition salts formed with the conjugate bases of any of the inorganic acids listed above, wherein the conjugate bases comprise a cationic component selected from among Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Al^{3+}, $NH_gR'''_{4-g}^+$, in which R''' is a C_{1-3} alkyl and g is a number selected from among 0, 1, 2, 3, or 4. Additional examples of cationic radicals of the pharmaceutically acceptable salt, include but are not limited to: penzathine, phloroprocaine, pholine, piethanolamine, pthylenediamine, meglumine, and procaine.

The term "metabolite," as described herein, refers to a compound produced in vivo after administration of a compound or its stereoisomer or its salt or its deuteride thereof represented by formula I to a subject in need thereof or as formed in vitro in an assay. Said metabolite may exist as a salt.

The term "deuteride," as described herein, refers to a deuterated analog of the compound represented by formula I where a hydrogen atom is enriched with its ^2H-isotope, i.e., deuterium (D). Deuterium substitution can be partial or complete. Partial deuterium substitution means that at least one hydrogen is substituted by at least one deuterium. .

The term "halo" or "halogen" as used herein, includes chloro, bromo, iodo and fluoro.

The term "alkyl" refers to an unbranched or branched chain, saturated, monovalent hydrocarbon residue containing 1 to 30 carbon atoms. The term "C_{1-M} alkyl" refers to an alkyl comprising 1 to M carbon atoms, where M is an integer having the following values: 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30.

The term "C_{1-6}alkyl" refers to an alkyl containing 1 to 6 carbon atoms. Examples of a C_{1-6} alkyl group include, but are not limited to, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, *t*-butyl, *n*-pentyl, isopentyl, neopentyl, *t*-pentyl, and hexyl.

The term "C_{1-6}-alkylene" refers to an alkylene radical containing 1 to 6 carbon atoms. Examples of a C_{1-6}-alkylene include, but are not limited to, a methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), methyl-ethylene ($-CH(CH_3)CH_2-$), propylene ($-CH_2CH_2CH_2-$), methyl-propylene ($-CH(CH_3)CH_2CH_2-$ or $-CH_2CH(CH_3)CH_2-$), etc. It is understood that a branched C_{1-6}-alkylene, such as methyl-ethylene or methyl-propylene, contains a chiral center, in which case the individual stereoisomers are contemplated. It is contemplated that a methylene may be substituted with one or two C_{1-6}alkyls.

The term "cycloalkyl" refers to an unsubstituted or substituted carbocycle, in which the carbocycle contains 3 to 10 carbon atoms; preferably 3 to 8 carbon atoms (i.e., a C_{3-8}-cycloalkyl); more preferably 3 to 6 carbon atoms (i.e., a C_{3-6}-cycloalkyl). In the instance of a substituted carbocycle containing 3 to 10, 3 to 8, or 3 to 6 carbon atoms, the substituents are not to be counted for the carbocycle carbon count. For instance, a cyclohexyl substituted with one or more C_{1-6}-alkyl is still, within the

meaning contemplated herein, a C_{3-6}-cycloalkyl. Examples of a C_{3-6}cycloalkyl include, but are not limited to, cyclopropyl, 2-methyl-cyclopropyl, cyclobutyl, 2-methyl-cyclobutyl, cyclopentyl, 2-methyl-cylcopentyl, cyclohexyl, 2-methyl-cyclohexyl, etc.

The term "cycloalkylamino" refers to a unsubstituted or substituted carbocycle comprising an "amino" (–NH–) functional group. The carbocycle contains 3 to 10 carbon atoms; preferably 3 to 8 carbon atoms (i.e., a C_{3-8}-cycloalkyl); more preferably 3 to 6 carbon atoms (i.e., a C_{3-6}-cycloalkyl). In the instance of a substituted carbocycle containing 3 to 10, 3 to 8, or 3 to 6 carbon atoms, the substituents are not to be counted for the carbocycle carbon count. For instance, a cyclohexyl substituted with one or more C_{1-6}-alkyl is still, within the meaning contemplated herein, a C_{3-6}-cycloalkyl. Examples of a C_{3-6}cycloalkylamino (alternatively referred to as $–NHC_{3-6}$cycloalkyl) include, but are not limited to, cyclopropylamino, 2-methyl-cyclopropylamino, cyclobutylamino, 2-methyl-cyclobutylamino, cyclopentylamino, 2-methyl-cyclopentylamino, cyclohexylamino, 2-methyl-cyclohexylamino, etc. One of ordinary skill will know that said cycloalkylaminos are derived from cycloalkylamines, i.e., cycloalkyls substituted by an amine ($–NH_2$) functional group.

The term "alkoxy" refers to an –O–alkyl group or an –O–cycloalkyl group, wherein alkyl and cycloalkyl are as defined above. Examples of –O–alkyl groups include, but are not limited to, methoxy, ethoxy, *n*-propyloxy, *i*-propyloxy, *n*-butyloxy, *i*-butyloxy, *t*-butyloxy, etc. Examples of –O–cycloalkyl groups include, but are not limited to, –O–*c*-propyl, –O–*c*-butyl, –O–*c*-pentyl,–O–*c*-hexyl, etc.

The term "C_{1-6}-alkoxy" refers to an $–O–C_{1-6}$-alkyl group, wherein C_{1-6} alkyl is defined herein.

The term "C_{3-6}-cycloalkoxy" refers to an $–O-C_{3-6}$-cycloalkyl group

The term "C_{1-6}-alkylene-oxy" refers to an $–O–C_{1-6}$-alkylene group, wherein C_{1-6}-alkylene is defined as above. Examples of a C_{1-6}-alkylene-oxy include, but are not limited to, methylene-oxy ($–CH_2O–$), ethylene-oxy ($–CH_2CH_2O–$), methyl-ethylene-oxy ($–CH(CH_3)CH_2O–$), propylene-oxy ($–CH_2CH_2CH_2O–$), methyl-propylene-oxy ($–CH(CH_3)CH_2CH_2O–$ or $–CH_2CH(CH_3)CH_2O–$), etc.

The terms "alkaryl" or "alkylaryl" refer to an alkylene group having 1 to 10 carbon atoms with an aryl substituent, such as benzyl. The term "C_{1-3}alkaryl" refers

to a C_{1-3}alkylene group with an aryl substituent. Benzyl is embraced by the term C_{1-3}alkaryl.

The term "–OC_{1-3}alkaryl" refers a oxygen (–O~) bound to a C_{1-3}alkaryl group. Benzyloxy (–OCH_2Ph) is embraced by the term –OC_{1-3}alkaryl.

The term "aryl," as used herein, and unless otherwise specified, refers to substituted or unsubstituted phenyl (Ph), biphenyl, or naphthyl. The aryl group can be substituted with one or more moieties selected from among alkyl, hydroxyl, F, Cl, Br, I, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, and phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in T.W. Greene and P.G. M. Wuts, "Protective Groups in Organic Synthesis," 3rd ed., John Wiley & Sons, 1999.

The term "heteroaryl" refers to an unsubstituted or substituted aromatic heterocycle containing carbon, hydrogen, and at least one of N, O, and S. Examples of heteroaryls include, but are not limited to, a pyrrole, an imidazole, a diazole, a triazole, a tetrazole, a furan, an oxazole, an indole, a thiazole, etc. Additional examples of heteroaryls can be found in T.L. Gilchrist, in "Heterocyclic Chemistry," John Wiley & Sons, 1985. The heteroaryl group can be substituted with one or more moieties selected from among alkyl, hydroxyl, F, Cl, Br, I, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, and phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in T.W. Greene and P.G. M. Wuts, "Protective Groups in Organic Synthesis," 3rd ed., John Wiley & Sons, 1999.

The term "heterocycle" or "heterocyclyl" refers to an unsubstituted or substituted radical containing carbon, hydrogen and at least one of N, O, and S. Examples of heterocycles, include, but are not limited to, an aziridine, an azetidine, a pyrrolidine, a piperidine, a piperazine, etc. Additional examples of heterocycles can be found in T.L. Gilchrist, in "Heterocyclic Chemistry," John Wiley & Sons, 1985. The heterocycle can be substituted with one or more moieties selected from among alkyl, hydroxyl, F, Cl, Br, I, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, and phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in T.W. Greene and P.G. M. Wuts, "Protective Groups in Organic Synthesis," 3rd ed., John Wiley & Sons, 1999.

The terms "alk(heteroaryl)" and "alk(heterocyclyl)" refers to a C_{1-6}-alkylene group with a heteroaryl and heterocyclyl substituent, respectively.

The term "cycloheteroalkyl" refers to an unsubstituted or substituted heterocycle, in which the heterocycle contains 2 to 9 carbon atoms; preferably 2 to 7 carbon atoms; more preferably 2 to 5 carbon atoms. Examples of cycloheteroalkyls include, but are not limited to, aziridin-1-yl, aziridin-2-yl, *N*-C_{1-3}-alkyl-aziridin-2-yl, azetidinyl, azetidin-1-yl, *N*-C_{1-3}-alkyl-azetidin-m'-yl, pyrrolidin-m'-yl, pyrrolidin-1-yl, *N*-C_{1-3}-alkyl-pyrrolidin-m'-yl, piperidin-m'-yl, piperidin-1-yl, and *N*-C_{1-3}-alkyl-piperidin-m'-yl, where m' is 2, 3, or 4 depending on the cycloheteroalkyl. Specific examples of N-C_{1-3}-alkyl-cycloheteroalkyls include, but are not limited to, N-methyl-aziridin-2-yl, N-methyl-azetidin-3-yl, N-methyl-pyrrolidin-3-yl, N-methyl-pyrrolidin-4-yl, N-methyl-piperidin-2-yl, N-methyl-piperidin-3-yl, and N-methyl-piperidin-4-yl. In the instance of R^{10}, R^{16}, and R^{17}, the point of attachment between the cycloheteroalkyl ring carbon and the ring occurs at any one of m'.

The term "acyl" refers to a substituent containing a carbonyl moiety and a non-carbonyl moiety and is meant to include an amino-acyl. The carbonyl moiety contains a double-bond between the carbonyl carbon and a heteroatom, where the heteroatom is selected from among O, N and S. When the heteroatom is N, the N is substituted by a

C_{1-6}. The non-carbonyl moiety is selected from straight, branched, and cyclic alkyl, which includes, but is not limited to, a straight, branched, or cyclic C_{1-20} alkyl, C_{1-10} alkyl, or a C_{1-6}-alkyl; alkoxyalkyl, including methoxymethyl; aralkyl, including benzyl; aryloxyalkyl, such as phenoxymethyl; or aryl, including phenyl optionally substituted with halogen (F, Cl, Br, I), hydroxyl, C_1 to C_4 alkyl, or C_1 to C_4 alkoxy, sulfonate esters, such as alkyl or aralkyl sulphonyl, including methanesulfonyl, the mono, di or triphosphate ester, trityl or monomethoxytrityl, substituted benzyl, trialkylsilyl (e.g. dimethyl-t-butylsilyl) or diphenylmethylsilyl. When at least one aryl group is present in the non-carbonyl moiety, it is preferred that the aryl group comprises a phenyl group.

The term "C_{2-7}acyl" refers to an acyl group in which the non-carbonyl moiety comprises a C_{1-6}alkyl. Examples of a C_{2-7}-acyl, include, but are not limited to: $-C(O)CH_3$, $-C(O)CH_2CH_3$, $-C(O)CH(CH_3)_2$, $-C(O)CH(CH_3)CH_2CH_3$, $-C(O)C(CH_3)_3$, etc.

The term "aminoacyl" includes N,N-unsubstituted, N,N-monosubstituted, and N,N-disubstituted derivatives of naturally occurring and synthetic α, β γ or δ amino acyls, where the amino acyls are derived from amino acids. The amino-nitrogen can be substituted or unsubstituted or exist as a salt thereof. When the amino-nitrogen is substituted, the nitrogen is either mono- or di-substituted, where the substituent bound to the amino-nitrogen is a C_{1-6}alkyl or an alkaryl. In the instance of its use for the compound of formula **I**, it is understood that an appropriate atom (O or N) is bound to the carbonyl carbon of the aminoacyl.

The term "amino acid" includes naturally occurring and synthetic α, β γ or δ amino acids, and includes but is not limited to, amino acids found in proteins, i.e. glycine, alanine, valine, leucine, isoleucine, methionine, phenylalanine, tryptophan, proline, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartate, glutamate, lysine, arginine and histidine. In a preferred embodiment, the amino acid is in the L-configuration. Alternatively, the amino acid can be a derivative of alanyl, valinyl, leucinyl, isoleucinyl, prolinyl, phenylalaninyl, tryptophanyl, methioninyl, glycinyl, serinyl, threoninyl, cysteinyl, tyrosinyl, asparaginyl, glutaminyl, aspartoyl, glutaroyl, lysinyl, argininyl, histidinyl, β-alanyl, β-valinyl, β-leucinyl, β-isoleucinyl, β-prolinyl, β-phenylalaninyl, β-tryptophanyl, β-methioninyl, β-glycinyl, β-serinyl, β-threoninyl, β-cysteinyl, β-tyrosinyl, β-asparaginyl, β-glutaminyl, β-aspartoyl, β-glutaroyl, β-lysinyl, β-argininyl or β-histidinyl. When the term amino acid is used, it is considered to be a specific and independent disclosure of each of the esters of α, β γ or δ glycine, alanine, valine, leucine, isoleucine, methionine, phenylalanine, tryptophan, proline, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartate, glutamate, lysine, arginine and histidine in the D and L-configurations.

The term "C_{1-6}-alkylene-oxy-acyl" refers to an –O–C_{1-6}-alkylene-acyl group, wherein C_{1-6}-alkylene and acyl are defined as above. Examples of a C_{1-6}-alkylene-oxy-acyl include, but are not limited to, methylene-oxy-acyl (–CH_2O–C(O)alkyl), ethylene-oxy-acyl (–CH_2CH_2O–C(O)alkyl), methyl-ethylene-oxy-acyl (–$CH(CH_3)CH_2O$–C(O)alkyl), propylene-oxy-acyl (–$CH_2CH_2CH_2O$– C(O)alkyl), methyl-propylene-oxy-acyl (–$CH(CH_3)CH_2CH_2O$– C(O)alkyl or –$CH_2CH(CH_3)CH_2O$– C(O)alkyl), etc. As the expression "acyl" encompasses "aminoacyl," further contemplated radicals include but are not limited to C_{1-6}-alkyl-oxy-aminoacyl, where aminoacyl is defined above.

The term "alkenyl" refers to an unsubstituted or a substituted hydrocarbon chain radical having from 2 to 10 carbon atoms having one or more olefinic double bonds. The term "C_{2-N} alkenyl" refers to an alkenyl comprising 2 to N carbon atoms, where N is an integer having the following values: 3, 4, 5, 6, 7, 8, 9, or 10. For example, the term "C_{2-10} alkenyl" refers to an alkenyl comprising 2 to 10 carbon atoms. The term "C_{2-4}alkenyl" refers to an alkenyl comprising 2 to 4 carbon atoms. Examples include, but are not limited to, vinyl, 1-propenyl, 2-propenyl (allyl) or 2-butenyl (crotyl). It is understood that the alkenyl or C_{2-N}-alkenyl can be substituted with one or more radicals selected from among alkyl, halo, alkoxy, aryloxy, nitro, and cyano.

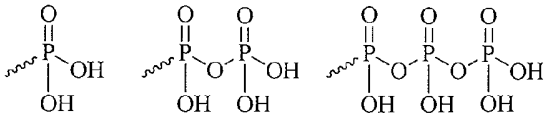
The term "vinyl," which is embraced by the term "C_{2-4}alkenyl," refers to –CR'=CR"R'", where R', R", and R'" are independently selected from among hydrogen, C_{1-6}-alkyl, halo, and C_{1-6}-alkoxy. Examples of a vinyl include, but are not limited to, ethenyl (–CH=CH_2), 2-bromo-ethenyl (–CH=CHBr), etc.

The term "ethynyl," as used herein, refers to –C≡CR', where R' is selected from among hydrogen, C_{1-6}-alkyl, halo, and C_{1-6}-alkoxide.

The term "methine," as used herein, refers to the radical –CR'=, where R' is selected from among hydrogen, C_{1-6}alkyl, halo, and C_{1-6}-alkoxide.

The term "vinylidene," as used herein, refers to >C=CRR', where R and R' are independently selected from among hydrogen, C_{1-6}-alkyl, halo, and C_{1-6}-alkoxide.

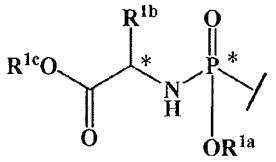
The expressions –P(O)(OH)$_2$, –P(O)(OH)–OP(O)(OH)$_2$, and –P(O)(OH)–O–P(O)(OH)–O–P(O)(OH)$_2$, refer to mono- (P_1), di- (P_2), and tri- (P_3) phosphate radicals, respectively.



P_1 P_2 P_3

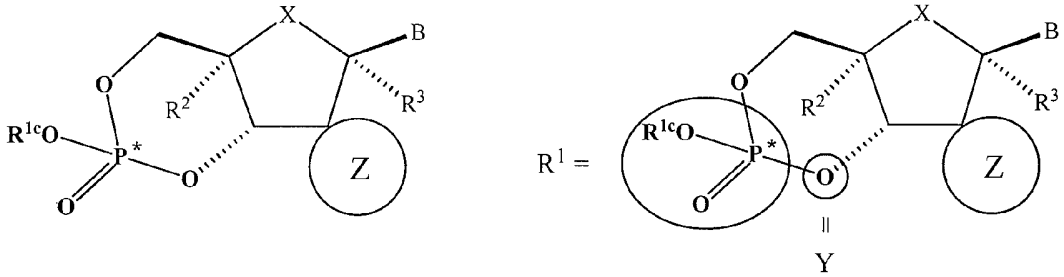
The P_1, P_2, and P_3 phosphate radicals may be introduced at the 5'-OH of a nucleoside compound either by synthetic means in the lab or by enzymatic (or metabolic) means in a cell or biological fluid (either in vivo or in vitro). It is understood that the acidities of the hydroxyl (–OH) substituents vary and that salts of the phosphate radicals are possible.

The term "–P*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})" or "phosphoramidate" as used herein is represented by the following structure:



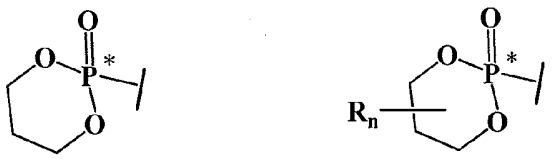
where R^{1a}, R^{1b}, and R^{1c} are as defined above. Examples of phosphoramidate moieties are described in U.S. Patent No. 7,964,580. It will be understood that the ~NHCH*(R^{1b})C(O)OR^{1c} fragment can be derived from an amino acid, which is defined above.

Under the Summary, certain definitions related to R^1, 1)l), and Y, 4)d), include the expressions "–P*(O)(OR^{1c})~" (see R^1, 1)l)) and "–O~" (see Y, 4)d)). It is understood that when R^1 is "–P*(O)(OR^{1c})~" and Y is "–O~" or when Y is "–O~" and R^1 is "–P(O)(OR^{1c})~", then compound **I** has the structure shown on the left, where the R^1 and Y substituents are identified on the right:



It is understood that use of the expression "cyclophosphate" or "cyclic-phosphate" is meant to embrace the left-hand structure. These expressions likewise have the same meanings when recited as definitions for certain embodiments and aspects of those embodiments.

The term " a 1,3,2-dioxaphosphinane-2-oxide," as used herein is represented by an unsubstituted form (j1) or a substituted form (j2), as represented by the following structures:

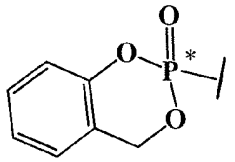


j1) **j2)**

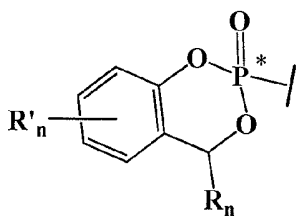
where R_n is selected from among hydroxy, an alkyl, a hydroxyalkyl, an aryloxide, an aryl, such as phenyl, a heteroaryl, such as pyridinyl, where the aryl and the heteroaryl can be substituted by 1-3 substituents independently selected from among an alkyl, an alkoxy, and a halo. A preferred R_n is pyridinyl which can be substituted by 1-3 substituents independently selected from among a C_{1-6}alkyl, a C_{1-6}-alkoxy, and a halo.

The term "aryloxide," or "aryloxy" as used herein, and unless otherwise specified, refers to substituted or unsubstituted phenoxide (PhO–), p-phenyl-phenoxide (p-Ph-PhO–), or naphthoxide, preferably the term aryloxide refers to substituted or unsubstituted phenoxide. The aryloxide group can be substituted with one or more moieties selected from among hydroxyl, F, Cl, Br, I, –C(O)(C_{1-6}alkyl), –C(O)O(C_{1-6}alkyl), amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, and phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in T.W. Greene and P.G. M. Wuts, "Protective Groups in Organic Synthesis," 3rd ed., John Wiley & Sons, 1999.

The term "4H-benzo[d][1,3,2]dioxaphosphine-2-oxide," as used herein is represented by an unsubstituted form (k1) or a substituted form (k2), as represented by the following structures:



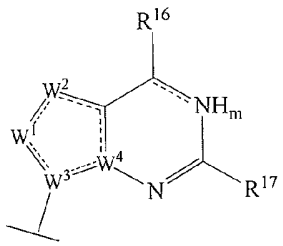
k1)



k2)

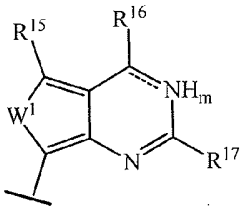
where R_n and R'_n, where R_n is hydrogen and one alkyl radical, or two alkyl radicals independent of one another, and R'_n is one, two, or three radicals selected from among alkyl, alkoxy, aryloxy, and halo. Preferably, R'_n is one, two, or three radicals selected from among a C_{1-6}alkyl, a C_{1-6}, alkoxy, and a halo. More preferably, R'_n is one radical selected from among a C_{1-6}-akyl, a C_{1-6}-alkoxy, and a halo.

In the structure B3, as a possible radical for B, the language "each bonding pair, W^1----W^2, W^2----C, C----W^4, W^4----W^3, and W^3----W^1, contained in the five-membered ring comprises a single or a double bond" is presented above.

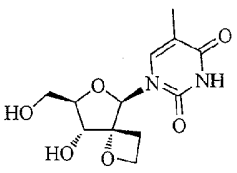


B3

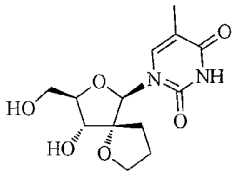
In the event that resolution problems or printing errors might obscure the pictoral representation of **B3**, it is contemplated that there exists a bonding configuration represented by "----" between each one of W^1----W^2, W^2----C, C----W^4, W^4----W^3, and W^3----W^1, within the five-membered ring framework, where "----" is understood to be a single- or double-bond. It is not contemplated that all bonding pairs contained in the five-membered ring therein are all double bonds or all single bonds. Rather, it is contemplated that when a certain definitional requirement is selected, then the bonding arrangement of the five-membered ring satisfies Hückel's rule, i.e., the total number of pi-bond and lone-pair electrons for the selected radicals is 6. For example, when W^1 is O or S, W^2 is CR^{15}, W^3 is C, and W^4 is C (see **I-3-12** or **I-3-13**), then the contemplated structure is:



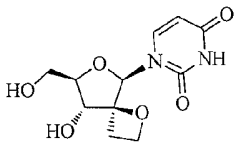
Formula **I** is recited above. Implicit to formula **I** is the exclusion of compounds disclosed in B. R. Babu et al. Org. Biomol. Chem. (2003) 1: 3514-3526, whether said compounds are explicitly or implicitly disclosed therein. For instance, the compounds identified there as **9b**, **14b**, **21**, and **27**, are not contemplated to be within the scope of formula **I** (as well as formula **I-1** presented below)



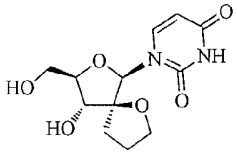
9b



14b



21



27

However, these compounds, as well as derivatives embraced by formula **I**, are contemplated for treating a subject infected by HCV or DENV and are contemplated

for compositions useful for treating a subject infected by HCV or DENV, as explained in further detail below. The compound numbering for compounds **9b**, **14b**, **21**, and **27** is as found in Babu et al. It should be noted that compounds **21** and **27** are exemplified herein with the numbering here of **36** and **32**, respectively.

The term "effective amount" as used herein means an amount required to reduce symptoms of the disease in a subject.

The term "subject," as used herein means a mammal.

The term "medicament," as used herein means a substance used in a method of treatment and/or prophylaxis of a subject in need thereof.

The term "preparation" or "dosage form" is intended to include both solid and liquid formulations of the active compound and one skilled in the art will appreciate that an active ingredient can exist in different preparations depending on the desired dose and pharmacokinetic parameters.

The term "excipient" as used herein refers to a compound that is used to prepare a pharmaceutical composition, and is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipients that are acceptable for veterinary use as well as human pharmaceutical use.

As used herein, "treatment" or "treating" is an approach for obtaining beneficial or desired clinical results. Beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. "Treatment" is an intervention performed with the intention of preventing the development or altering the pathology of a disorder. The term "treatment" of an HCV infection, as used herein, also includes treatment or prophylaxis of a disease or a condition associated with or mediated by HCV infection, or the clinical symptoms thereof.

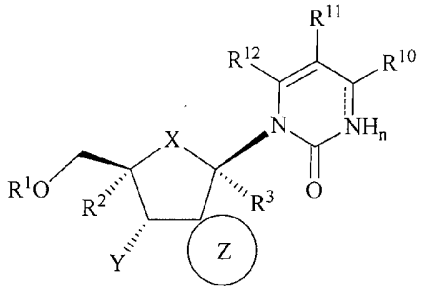
The term "protecting group" which is derived from a "protecting compound," has its plain and ordinary meaning, i.e., at least one protecting or blocking group is bound to at least one functional group (e.g., –OH, $–NH_2$, etc.) that allows chemical modification of at least one other functional group. Examples of protecting groups, include, but are not limited to, benzoyl, acetyl, phenyl-substituted benzoyl,

tetrahydropyranyl, trityl, DMT (4,4'-dimethoxytrityl), MMT (4-monomethoxytrityl), trimethoxytrityl, pixyl (9-phenylxanthen-9-yl) group, thiopixyl (9-phenylthioxanthen-9-yl) or 9-(p-methoxyphenyl)xanthine-9-yl (MOX), etc.; C(O)-alkyl, C(O)Ph, C(O)aryl, C(O)O(C_{1-6}alkyl), C(O)O(C_{1-6}alkylene)aryl (e.g., –C(O)OCH_2Ph), C(O)Oaryl, CH_2O-alkyl, CH_2O-aryl, SO_2-alkyl, SO_2-aryl, a protecting group comprising at least one silicon atom, such as, *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, Si(C_{1-6}alkyl)$_2$OSi(C_{1-6}alkyl)$_2$OH, such as, –Si(^{i}Pr)$_2$OSi(^{i}Pr)$_2$OH or ~OSi(^{i}Pr)$_2$OSi(^{i}Pr)$_2$O~. Additional examples are disclosed in e.g., Protective Groups in Organic Synthesis, 3rd ed. T. W. Greene and P. G. M. Wuts, John Wiley & Sons, New York, N.Y., 1999).

The term "leaving group" ("LG") as used herein, has its plain and ordinary meaning for one of ordinary skill in this art. Examples of leaving groups include, but are not limited to: halogen (Cl, Br, or I); tosylate, mesylate, triflate, acetate, etc.

Embodiments

A first embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-1**



I-1

wherein R^1, R^2, Y, R^3, (Z), X, R^{10}, R^{11}, R^{12}, n, and ---- have the meanings described above.

A first aspect of the first embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-1**

wherein

1) R^1 is selected from among
   a) hydrogen,

b) –P(O)(OH)$_2$,
c) –P(O)(O(CH$_2$)$_{1-3}$OC(O)O(C$_{1-6}$alkyl))$_2$,
d) –P(O)(O(CH$_2$)$_{1-3}$OC(O)(C$_{1-6}$alkyl))$_2$,
e) –P(O)(O(CH$_2$)$_{1-3}$SC(O)(C$_{1-6}$alkyl))$_2$,
f) –P(O)(O(CH$_2$)$_{1-3}$OCH$_2$(aryl))$_2$,
g) –P(O)(O(CH$_2$)$_{1-3}$SCH$_2$(aryl))$_2$,
h) –P*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c}),
wherein
R^{1a} is
i) hydrogen,
ii) C$_{1-6}$alkyl,
iii) C$_{3-6}$cycloalkyl, or
iv) aryl,
R^{1b} is
i) hydrogen,
ii) C$_{1-6}$alkyl,
iii) C$_{3-6}$cycloalkyl,
iv) C$_{1-3}$alkaryl, or
v) alk(heteroaryl), and
R^{1c} is
i) hydrogen
ii) C$_{1-6}$alkyl,
iii) C$_{3-6}$cycloalkyl, or
vi) C$_{1-3}$alkaryl,
i) –P*(O)(NH(alkaryl)(O(CH$_2$)$_{1-3}$SC(O)(alkyl)),
j) a 1,3,2-dioxaphosphinane-2-oxide,
k) a 4*H*-benzo[d][1,3,2]dioxaphosphinine-2-oxide,
l) –P*(O)(OR^{1c})~, when Y is –O~, where R^{1c} is defined above,
m) –P(O)(OH)–O–P(O)(OH)$_2$,
n) –P(O)(OH)–O–P(O)(OH)–O–P(O)(OH)$_2$,
o) a C$_{2-7}$acyl,
p) an aminoacyl
q) a C$_{1-6}$-alkylene-oxy-C$_{2-7}$acyl, and
r) a –C(O)–O-C$_{1-6}$alkyl;

2) R^2 is selected from among
a) hydrogen,
b) fluoro,
c) azido, and
d) cyano;

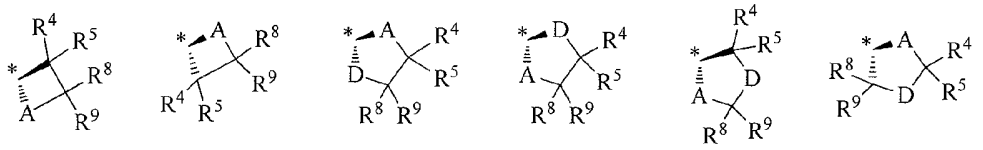
3) R^3 is selected from among
a) hydrogen,
b) methyl, and
c) cyano,

4) Y is selected from among
a) hydrogen,
b) fluoro,
c) –OH,
d) –O~, when R^1 is –P(O)(OR^{1c})~, where R^{1c} is defined above,
e) –O(C$_{2-7}$acyl),
f) –O(aminoacyl),

g) –O(C_{1-6}-alkylene-oxy-acyl),
h) –O–C(O)–O-C_{1-6}alkyl,
i) –NH_2,
j) –NH(C_{2-7}acyl),
k) –NH(aminoacyl),
l) –NH–C(O)–O-C_{1-6}alkyl and
m) azido;

5) X is selected from among
a) –O– and
b) –S–;

6) (Z) is a four- or five-membered ring selected from among radicals **c**, **d**, **e**, **f**, **g**, and **h**, represented by the following structures



c **d** **e** **f** **g** **h**

where * represents the point of attachment to the 2'-carbon and where
a) A is selected from among
i) –O–,
ii) –S–,
iii) –S(O)–,
iv) –$S(O)_2$–, and
v) –NH–,
b) D is selected from among
i) –O–,
ii) –S–,
iii) –S(O)–,
iv) –$S(O)_2$–, and
v) –NH–,
vi) a methylene, and
vii) a vinylidene,
c) R^4, R^5, R^8, and R^9 are independently selected from among
i) hydrogen,
ii) halo,
iii) C_{1-6}alkyl
iv) hydroxy,
v) alkoxy,
vi) cycloalkoxy,
vii) –O(acyl),
viii) –O(C_{1-6}-alkyleneoxyacyl),
ix) –O–C(O)–O-alkyl,
x) C_{1-6}alkylene-oxy(alkyl),
xi) alkenyl,

xii) ethynyl,
xiii) $-NH_2$,
xiv) –NH(alkyl),
xv) –NH(cycloalkyl),
xvi) heterocyclyl,
xvii) aryl, and
xviii) heteroaryl; and

7a) n is 0, ----- is a double-bond and R^{10} is selected from among
i) $-NH_2$,
ii) $-NH(C_{1-6}alkyl)$,
iii) –NH(acyl),
iv) –NH–C(O)–O-alkyl,
v) – cycloheteroalkyl,
vi) –heteroaryl,
vii) –O(alkyl),
viii) –O(acyl),
ix) $-O(C_{1-6}alkylene\text{-}oxyacyl)$, and
x) –O–C(O)–O-alkyl, or

7b) n is 1, ----- is a single-bond and R^{10} is selected from among
i) =O,
ii) =NH, and
iii) =N(alkyl); and

7c) independent of the value of n, R^{11} and R^{12} are independently selected from among
i) hydrogen,
ii) halo,
iii) cyano,
iv) C_{1-6}alkyl,
v) C_{2-5}alkenyl, and
vi) C_{2-5}alkynyl.

A second aspect of the first embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-1**

wherein

1) R^1 is selected from among
a) hydrogen,
b) $-P(O)(OH)_2$,
c) $-P(O)(O(CH_2)_{1-3}OC(O)O(C_{1-6}alkyl))_2$,
d) $-P(O)(O(CH_2)_{1-3}OC(O)(C_{1-6}alkyl))_2$,
e) $-P(O)(O(CH_2)_{1-3}SC(O)(C_{1-6}alkyl))_2$,
f) $-P(O)(O(CH_2)_{1-3}OCH_2(aryl))_2$,
g) $-P(O)(O(CH_2)_{1-3}SCH_2(aryl))_2$,
h) $-P^*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})$,
wherein
R^{1a} is
i) hydrogen,
ii) C_{1-6}alkyl,

iii) C_{3-6}cycloalkyl, or
iv) aryl,

R^{1b} is

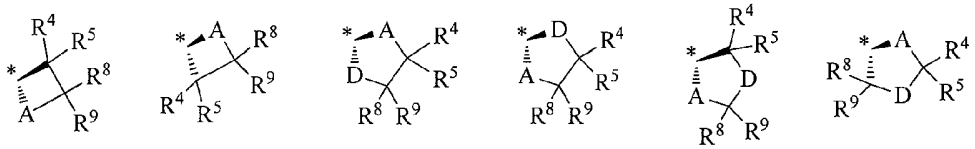
i) hydrogen,
ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl,
iv) C_{1-3}alkaryl, or
v) alk(heteroaryl), and

R^{1c} is

i) hydrogen
ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl, or
iv) C_{1-3}alkaryl,

i) –P*(O)(NH(alkaryl)(O$(CH_2)_{1-3}$SC(O)(alkyl)),
j) a 1,3,2-dioxaphosphinane-2-oxide,
k) a 4*H*-benzo[d][1,3,2]dioxaphosphinine-2-oxide,
l) –P*(O)(OR^{1c})~, when Y is –O~, where R^{1c} is defined above,
m) –P(O)(OH)–O–P(O)(OH)$_2$,
n) –P(O)(OH)–O–P(O)(OH)–O–P(O)(OH)$_2$,
o) a C_{2-7}acyl,
p) an aminoacyl,
q) a C_{1-6}-alkylene-oxy-C_{2-7}acyl, and
r) a –C(O)–O-C_{1-6}alkyl;

2) R^2 is hydrogen;
3) R^3 is hydrogen;
4) Y is selected from among
a) –OH,
b) –O~, when R^1 is –P(O)(OR^{1c})~, where R^{1c} is defined above,
c) –O(C_{2-7}acyl),
d) –O(aminoacyl),
e) –O(C_{1-6}-alkylene-oxy-acyl), and
f) –O–C(O)–O-C_{1-6}alkyl;
5) X is –O–;
6) (Z) is a four- or five-membered ring selected from among radicals **c**, **d**, **e**, **f**, **g**, and **h**, represented by the following structures



c **d** **e** **f** **g** **h**

where * represents the point of attachment to the 2'-carbon and where
a) A is selected from among
i) –O–,
ii) –S–,

iii) –S(O)–,
iv) –$S(O)_2$–, and
v) –NH–,

b) D is selected from among
i) –O–,
ii) –S–,
iii) –S(O)–,
iv) –$S(O)_2$–,
v) –NH–,
vi) a methylene, and
vii) a vinylidene,

c) R^4, R^5, R^8, and R^9 are independently selected from among
i) hydrogen,
ii) halo, and
iii) C_{1-6}alkyl; and

7a) n is 0, ----- is a double-bond and R^{10} is selected from among
i) –NH_2,
ii) –NH(C_{1-6}alkyl),
iii) –NH(C_{2-7}acyl), and
iv) –NH–C(O)–O-C_{1-6}alkyl, or

7b) n is 1, ----- is a single-bond and R^{10} is selected from among
i) =O and
ii) =N(alkyl), and

7c) independent of the value of n, R^{11} and R^{12} are independently selected from among
i) hydrogen,
ii) halo,
iv) C_{1-6}alkyl, and
v) C_{2-4}alkenyl.

A third aspect of the first embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-1**

wherein

1) R^1 is selected from among
a) hydrogen,
b) –$P(O)(OH)_2$,
c) –$P(O)(O(CH_2)_{1-3}OC(O)O(C_{1-6}alkyl))_2$,
d) –$P(O)(O(CH_2)_{1-3}OC(O)(C_{1-6}alkyl))_2$,
e) –$P(O)(O(CH_2)_{1-3}SC(O)(C_{1-6}alkyl))_2$,
f) –$P(O)(O(CH_2)_{1-3}OCH_2(aryl))_2$,
g) –$P(O)(O(CH_2)_{1-3}SCH_2(aryl))_2$,
h) –$P^*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})$,
wherein
R^{1a} is
i) hydrogen,
ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl, or

iv) aryl,

R^{1b} is

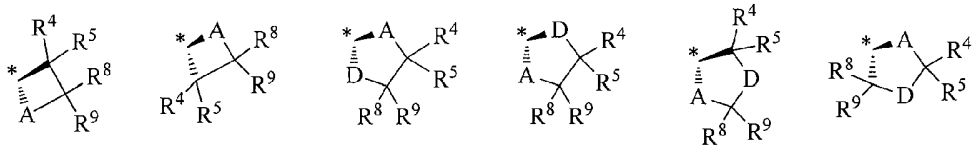
i) hydrogen,
ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl,
iv) C_{1-3}alkaryl, or
v) alk(heteroaryl), and

R^{1c} is

i) hydrogen
ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl, or
vi) C_{1-3}alkaryl,

i) –P*(O)(NH(alkaryl)(O$(CH_2)_{1-3}$SC(O)(alkyl)),
j) a 1,3,2-dioxaphosphinane-2-oxide,
k) a 4*H*-benzo[d][1,3,2]dioxaphosphinine-2-oxide,
l) –P*(O)(OR^{1c})~, when Y is –O~, where R^{1c} is defined above,
m) –P(O)(OH)–O–P(O)$(OH)_2$,
n) –P(O)(OH)–O–P(O)(OH)–O–P(O)$(OH)_2$,
o) a C_{2-7}acyl,
p) an aminoacyl,
q) a C_{1-6}-alkylene-oxy-C_{2-7}acyl, and
r) a –C(O)–O-C_{1-6}alkyl;

2) R^2 is hydrogen;
3) R^3 is hydrogen;
4) Y is selected from among
a) –OH,
b) –O~, when R^1 is –P(O)(OR^{1c})~, where R^{1c} is defined above,
c) –O(C_{2-7}acyl),
d) –O(aminoacyl),
e) –O(C_{1-6}-alkylene-oxy-acyl), and
f) –O–C(O)–O-C_{1-6}alkyl;
5) X is –O–;
6) (Z) is a four- or five-membered ring selected from among radicals **c**, **d**, **e**, **f**, **g**, and **h**, represented by the following structures



c **d** **e** **f** **g** **h**

where * represents the point of attachment to the 2'-carbon and where
a) A is –O–,
b) D is –O– or –CH_2–,
c) R^4, R^5, R^8, and R^9 are each hydrogen; and
7a) n is 0, ----- is a double-bond and R^{10} is selected from among

i) $-NH_2$,
ii) $-NH(C_{1-6}alkyl)$,
iii) $-NH(C_{2-7}acyl)$, and
iv) $-NH-C(O)-O-C_{1-6}alkyl$, or

7b) n is 1, ----- is a single-bond and R^{10} is selected from among
i) =O and
ii) =N(alkyl), and

7c) independent of the value of n, R^{11} and R^{12} are independently selected from among
i) hydrogen,
ii) halo,
iv) C_{1-6}alkyl, and
v) C_{2-4}alkenyl.

A fourth aspect of the first embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-1**

wherein

1) R^1 is selected from among
a) hydrogen,
b) $-P(O)(OH)_2$,
c) $-P(O)(O(CH_2)_{1-3}OC(O)O(C_{1-6}alkyl))_2$,
d) $-P(O)(O(CH_2)_{1-3}OC(O)(C_{1-6}alkyl))_2$,
e) $-P(O)(O(CH_2)_{1-3}SC(O)(C_{1-6}alkyl))_2$,
f) $-P(O)(O(CH_2)_{1-3}OCH_2(aryl))_2$,
g) $-P(O)(O(CH_2)_{1-3}SCH_2(aryl))_2$,
h) $-P^*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})$,
wherein
R^{1a} is
i) hydrogen or
iv) aryl,
R^{1b} is
i) hydrogen or
ii) C_{1-6}alkyl, and
R^{1c} is
i) hydrogen
ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl, or
iv) C_{1-3}alkaryl,
i) $-P^*(O)(NH(alkaryl)(O(CH_2)_{1-3}SC(O)(alkyl))$,
j) a 1,3,2-dioxaphosphinane-2-oxide,
k) a 4*H*-benzo[d][1,3,2]dioxaphosphinine-2-oxide,
l) $-P^*(O)(OR^{1c})$~, when Y is –O~, where R^{1c} is defined above,
m) $-P(O)(OH)-O-P(O)(OH)_2$,
n) $-P(O)(OH)-O-P(O)(OH)-O-P(O)(OH)_2$,
o) a C_{2-7}acyl,
p) an aminoacyl,
q) a C_{1-6}-alkylene-oxy-C_{2-7}acyl, and

r) a –C(O)–O-C_{1-6}alkyl;

2) R^2 is hydrogen;

3) R^3 is hydrogen;

4) Y is selected from among

a) –OH,

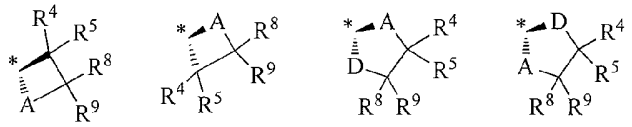
b) –O~, when R^1 is –P(O)(OR^{1c})~, where R^{1c} is defined above,

c) –O(C_{2-7}acyl), and

d) –O(aminoacyl);

5) X is –O–;

6) (Z) is a four- or five-membered ring selected from among radicals **c**, **d**, **e**, and **f** represented by the following structures



c **d** **e** **f**

where * represents the point of attachment to the 2'-carbon and where

a) A is –O–,

b) D is –O– or –CH_2–,

c) R^4, R^5, R^8, and R^9 are each hydrogen; and

7a) n is 0, ----- is a double-bond and R^{10} is selected from among

i) –NH_2,

ii) –NH(C_{1-6}alkyl),

iii) –NH(C_{2-7}acyl), and

iv) –NH–C(O)–O-C_{1-6}alkyl, or

7b) n is 1, ----- is a single-bond and R^{10} is selected from among

i) =O and

ii) =N(alkyl), and

7c) independent of the value of n, R^{11} and R^{12} are independently selected from among

i) hydrogen,

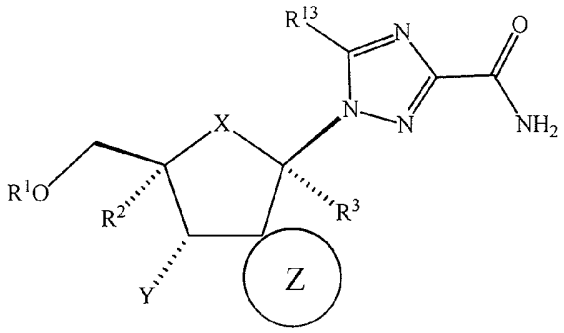
ii) halo,

iv) C_{1-6}alkyl, and

v) C_{2-4}alkenyl.

A second embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-2**

wherein



I-2

wherein R^1, R^2, Y, R^3, (z), X, and R^{13} have the meanings described above.

A first aspect of the second embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-2** wherein

1) R^1 is selected from among
   a) hydrogen,
   b) $-P(O)(OH)_2$,
   c) $-P(O)(O(CH_2)_{1\text{-}3}OC(O)O(C_{1\text{-}6}alkyl))_2$,
   d) $-P(O)(O(CH_2)_{1\text{-}3}OC(O)(C_{1\text{-}6}alkyl))_2$,
   e) $-P(O)(O(CH_2)_{1\text{-}3}SC(O)(C_{1\text{-}6}alkyl))_2$,
   f) $-P(O)(O(CH_2)_{1\text{-}3}OCH_2(aryl))_2$,
   g) $-P(O)(O(CH_2)_{1\text{-}3}SCH_2(aryl))_2$,
   h) $-P^*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})$,
   wherein
   R^{1a} is
      i) hydrogen,
      ii) $C_{1\text{-}6}$alkyl,
      iii) $C_{3\text{-}6}$cycloalkyl, or
      iv) aryl,
   R^{1b} is
      i) hydrogen,
      ii) $C_{1\text{-}6}$alkyl,
      iii) $C_{3\text{-}6}$cycloalkyl,
      iv) $C_{1\text{-}3}$alkaryl, or
      v) alk(heteroaryl), and
   R^{1c} is
      i) hydrogen
      ii) $C_{1\text{-}6}$alkyl,
      iii) $C_{3\text{-}6}$cycloalkyl, or
      iv) $C_{1\text{-}3}$alkaryl,
   i) $-P^*(O)(NH(alkaryl)(O(CH_2)_{1\text{-}3}SC(O)(alkyl))$,
   j) a 1,3,2-dioxaphosphinane-2-oxide,
   k) a 4*H*-benzo[d][1,3,2]dioxaphosphinine-2-oxide,

l) –P*(O)(OR^{1c})~, when Y is –O~, where R^{1c} is defined above,
m) –P(O)(OH)–O–P(O)(OH)$_2$,
n) –P(O)(OH)–O–P(O)(OH)–O–P(O)(OH)$_2$,
o) a C$_{2-7}$acyl,
p) an aminoacyl,
q) a C$_{1-6}$-alkylene-oxy-C$_{2-7}$acyl, and
r) a –C(O)–O-C$_{1-6}$alkyl;

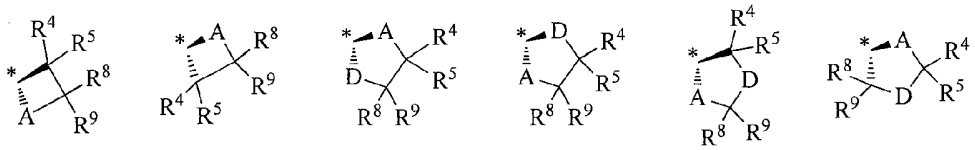
2) R^2 is selected from among
a) hydrogen,
b) fluoro,
c) azido, and
d) cyano;

3) R^3 is selected from among
a) hydrogen,
b) methyl, and
c) cyano,

4) Y is selected from among
a) hydrogen,
b) fluoro,
c) –OH,
d) –O~, when R^1 is –P(O)(OR^{1c})~, where R^{1c} is defined above,
e) –O(C$_{2-7}$acyl),
f) –O(aminoacyl),
g) –O(C$_{1-6}$-alkylene-oxy-acyl),
h) –O–C(O)–O-C$_{1-6}$alkyl,
i) –NH$_2$,
j) –NH(C$_{2-7}$acyl),
k) –NH(aminoacyl),
l) –NH–C(O)–O-C$_{1-6}$alkyl, and
m) azido;

5) X is selected from among
a) –O– and
b) –S–;

6) (Z) is a four- or five-membered ring selected from among radicals **c**, **d**, **e**, **f**, **g**, and **h**, represented by the following structures



c **d** **e** **f** **g** **h**

where * represents the point of attachment to the 2'-carbon and where
a) A is selected from among
i) –O–,
ii) –S–,

iii) –S(O)–,
iv) –S(O)$_2$–, and
v) –NH–,

b) D is selected from among
i) –O–,
ii) –S–,
iii) –S(O)–,
iv) –S(O)$_2$–, and
v) –NH–,
vi) a methylene, and
vii) a vinylidene,

c) R^4, R^5, R^8, and R^9 are independently selected from among
i) hydrogen,
ii) halo,
iii) C_{1-6}alkyl
iv) hydroxy,
v) alkoxy,
vi) cycloalkoxy,
vii) –O(acyl),
viii) –O(C_{1-6}-alkyleneoxyacyl),
ix) –O–C(O)–O-alkyl,
x) C_{1-6}alkylene-oxy(alkyl),
xi) alkenyl,
xii) ethynyl,
xiii) –NH_2,
xiv) –NH(alkyl),
xv) –NH(cycloalkyl),
xvi) heterocyclyl,
xvii) aryl, and
xviii) heteroaryl; and

7) R^{13} is hydrogen.

A second aspect of the second embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-2**

wherein

1) R^1 is selected from among
a) hydrogen,
b) –P(O)(OH)$_2$,
c) –P(O)(O(CH_2)$_{1-3}$OC(O)O(C_{1-6}alkyl))$_2$,
d) –P(O)(O(CH_2)$_{1-3}$OC(O)(C_{1-6}alkyl))$_2$,
e) –P(O)(O(CH_2)$_{1-3}$SC(O)(C_{1-6}alkyl))$_2$,
f) –P(O)(O(CH_2)$_{1-3}$OCH_2(aryl))$_2$,
g) –P(O)(O(CH_2)$_{1-3}$SCH_2(aryl))$_2$,
h) –P*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c}),
wherein
R^{1a} is
i) hydrogen,

ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl, or
iv) aryl,

R^{1b} is

i) hydrogen,
ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl,
iv) C_{1-3}alkaryl, or
v) alk(heteroaryl), and

R^{1c} is

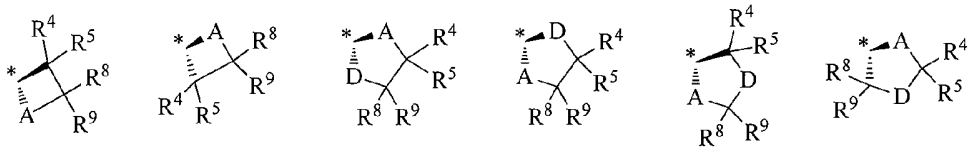
i) hydrogen
ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl, or
iv) C_{1-3}alkaryl,

i) –P*(O)(NH(alkaryl)(O$(CH_2)_{1-3}$SC(O)(alkyl)),
j) a 1,3,2-dioxaphosphinane-2-oxide,
k) a 4*H*-benzo[d][1,3,2]dioxaphosphinine-2-oxide,
l) –P*(O)(OR^{1c})~, when Y is –O~, where R^{1c} is defined above,
m) –P(O)(OH)–O–P(O)(OH)$_2$,
n) –P(O)(OH)–O–P(O)(OH)–O–P(O)(OH)$_2$,
o) a C_{2-7}acyl,
p) an aminoacyl,
q) a C_{1-6}-alkylene-oxy-C_{2-7}acyl, and
r) a –C(O)–O-C_{1-6}alkyl;

2) R^2 is hydrogen;
3) R^3 is hydrogen;
4) Y is selected from among

a) –OH,
b) –O~, when R^1 is –P(O)(OR^{1c})~, where R^{1c} is defined above,
c) –O(C_{2-7}acyl),
d) –O(aminoacyl),
e) –O(C_{1-6}-alkylene-oxy-acyl), and
f) –O–C(O)–O-C_{1-6}alkyl;

5) X is –O–;
6) (Z) is a four- or five-membered ring selected from among radicals **c**, **d**, **e**, **f**, **g**, and **h**, represented by the following structures



c **d** **e** **f** **g** **h**

where * represents the point of attachment to the 2'-carbon and where

a) A is selected from among

i) –O–,

ii) –S–,
iii) –S(O)–,
iv) –$S(O)_2$–, and
v) –NH–,

b) D is selected from among
i) –O–,
ii) –S–,
iii) –S(O)–,
iv) –$S(O)_2$–, and
v) –NH–,
vi) a methylene, and
vii) a vinylidene,

c) R^4, R^5, R^8, and R^9 are independently selected from among
i) hydrogen,
ii) halo,
iii) $C_{1\text{-}6}$alkyl; and

7) R^{13} is hydrogen.

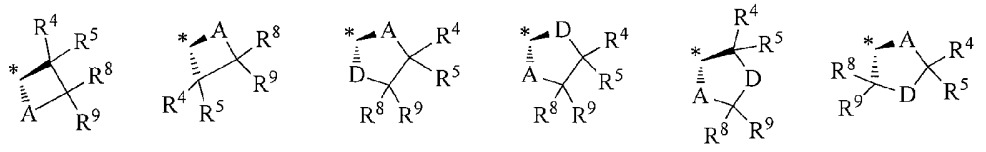
A third aspect of the second embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-2**

wherein

1) R^1 is selected from among
a) hydrogen,
b) –$P(O)(OH)_2$,
c) –$P(O)(O(CH_2)_{1\text{-}3}OC(O)O(C_{1\text{-}6}alkyl))_2$,
d) –$P(O)(O(CH_2)_{1\text{-}3}OC(O)(C_{1\text{-}6}alkyl))_2$,
e) –$P(O)(O(CH_2)_{1\text{-}3}SC(O)(C_{1\text{-}6}alkyl))_2$,
f) –$P(O)(O(CH_2)_{1\text{-}3}OCH_2(aryl))_2$,
g) –$P(O)(O(CH_2)_{1\text{-}3}SCH_2(aryl))_2$,
h) –$P^*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})$,
wherein
R^{1a} is
i) hydrogen,
ii) $C_{1\text{-}6}$alkyl,
iii) $C_{3\text{-}6}$cycloalkyl, or
iv) aryl,
R^{1b} is
i) hydrogen,
ii) $C_{1\text{-}6}$alkyl,
iii) $C_{3\text{-}6}$cycloalkyl,
iv) $C_{1\text{-}3}$alkaryl, or
v) alk(heteroaryl), and
R^{1c} is
i) hydrogen
ii) $C_{1\text{-}6}$alkyl,
iii) $C_{3\text{-}6}$cycloalkyl, or
iv) $C_{1\text{-}3}$alkaryl,

i) –P*(O)(NH(alkaryl)(O(CH_2)$_{1-3}$SC(O)(alkyl)),
j) a 1,3,2-dioxaphosphinane-2-oxide,
k) a 4*H*-benzo[d][1,3,2]dioxaphosphinine-2-oxide,
l) –P*(O)(OR^{1c})~, when Y is –O~, where R^{1c} is defined above,
m) –P(O)(OH)–O–P(O)(OH)$_2$,
n) –P(O)(OH)–O–P(O)(OH)–O–P(O)(OH)$_2$,
o) a C_{2-7}acyl,
p) an aminoacyl,
q) a C_{1-6}-alkylene-oxy-C_{2-7}acyl, and
r) a –C(O)–O-C_{1-6}alkyl;

2) R^2 is hydrogen;
3) R^3 is hydrogen;
4) Y is selected from among
a) –OH,
b) –O~, when R^1 is –P(O)(OR^{1c})~, where R^{1c} is defined above,
c) –O(C_{2-7}acyl),
d) –O(aminoacyl),
e) –O(C_{1-6}-alkylene-oxy-acyl), and
f) –O–C(O)–O-C_{1-6}alkyl;
5) X is –O–;
6) (Z) is a four- or five-membered ring selected from among radicals **c**, **d**, **e**, **f**, **g**, and **h**, represented by the following structures



c **d** **e** **f** **g** **h**

where * represents the point of attachment to the 2'-carbon and where
a) A is –O–,
b) D is –O– or –CH_2–, and
c) R^4, R^5, R^8, and R^9 are each hydrogen; and
7) R^{13} is hydrogen.

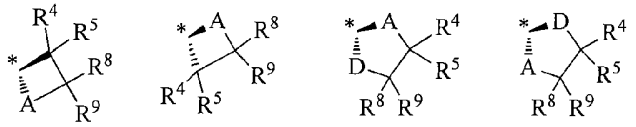
A fourth aspect of the second embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-2**

wherein

1) R^1 is selected from among
a) hydrogen,
b) –P(O)(OH)$_2$,
c) –P(O)(O(CH_2)$_{1-3}$OC(O)O(C_{1-6}alkyl))$_2$,
d) –P(O)(O(CH_2)$_{1-3}$OC(O)(C_{1-6}alkyl))$_2$,

e) –P(O)(O(CH_2)$_{1-3}$SC(O)(C_{1-6}alkyl))$_2$,
f) –P(O)(O(CH_2)$_{1-3}$OCH_2(aryl))$_2$,
g) –P(O)(O(CH_2)$_{1-3}$SCH_2(aryl))$_2$,
h) –P*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c}),
wherein
R^{1a} is
i) hydrogen or
iv) aryl,
R^{1b} is
i) hydrogen or
ii) C_{1-6}alkyl, and
R^{1c} is
i) hydrogen
ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl, or
iv) C_{1-3}alkaryl,
i) –P*(O)(NH(alkaryl)(O(CH_2)$_{1-3}$SC(O)(alkyl)),
j) a 1,3,2-dioxaphosphinane-2-oxide,
k) a 4*H*-benzo[d][1,3,2]dioxaphosphinine-2-oxide,
l) –P*(O)(OR^{1c})~, when Y is –O~, where R^{1c} is defined above,
m) –P(O)(OH)–O–P(O)(OH)$_2$,
n) –P(O)(OH)–O–P(O)(OH)–O–P(O)(OH)$_2$,
o) an C_{2-7}acyl,
p) an aminoacyl,
q) a C_{1-6}-alkylene-oxy-C_{2-7}acyl, and
r) a –C(O)–O-C_{1-6}alkyl;

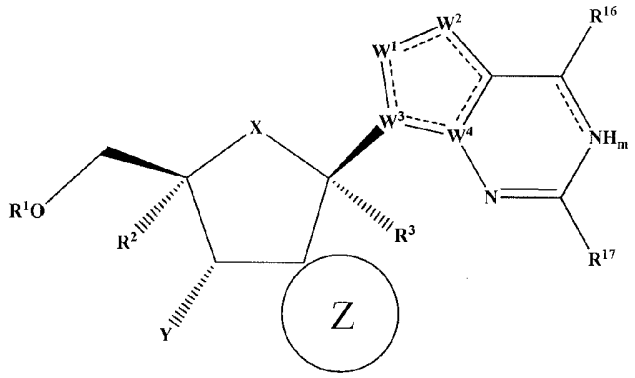
2) R^2 is hydrogen;
3) R^3 is hydrogen;
4) Y is selected from among
a) –OH,
b) –O~, when R^1 is –P(O)(OR^{1c})~, where R^{1c} is defined above,
c) –O(C_{2-7}acyl), and
d) –O(aminoacyl);
5) X is –O–;
6) (Z) is a four- or five-membered ring selected from among radicals **c**, **d**, **e**, and **f** represented by the following structures



c **d** **e** **f**

where * represents the point of attachment to the 2'-carbon and where
a) A is –O–,
b) D is –O– or –CH_2–, and
c) R^4, R^5, R^8, and R^9 are each hydrogen; and
7) R^{13} is hydrogen.

A third embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-3**



I-3

wherein R^1, R^2, Y, R^3, Z, X, W^1, W^2, W^3, W^4, R^{16}, R^{17}, m, and ---- have the meanings described above.

A first aspect of the third embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-3**

wherein

1) R^1 is selected from among
   a) hydrogen,
   b) $-P(O)(OH)_2$,
   c) $-P(O)(O(CH_2)_{1-3}OC(O)O(C_{1-6}alkyl))_2$,
   d) $-P(O)(O(CH_2)_{1-3}OC(O)(C_{1-6}alkyl))_2$,
   e) $-P(O)(O(CH_2)_{1-3}SC(O)(C_{1-6}alkyl))_2$,
   f) $-P(O)(O(CH_2)_{1-3}OCH_2(aryl))_2$,
   g) $-P(O)(O(CH_2)_{1-3}SCH_2(aryl))_2$,
   h) $-P^*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})$,
   wherein
   R^{1a} is
      i) hydrogen,
      ii) C_{1-6}alkyl,
      iii) C_{3-6}cycloalkyl, or
      iv) aryl,
   R^{1b} is
      i) hydrogen,
      ii) C_{1-6}alkyl,
      iii) C_{3-6}cycloalkyl,
      iv) C_{1-3}alkaryl, or
      v) alk(heteroaryl), and
   R^{1c} is
      i) hydrogen

ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl, or
iv) C_{1-3}alkaryl,
i) –P*(O)(NH(alkaryl)(O$(CH_2)_{1-3}$SC(O)(alkyl)),
j) a 1,3,2-dioxaphosphinane-2-oxide,
k) a 4*H*-benzo[d][1,3,2]dioxaphosphinine-2-oxide,
l) –P*(O)(OR^{1c})~, when Y is –O~, where R^{1c} is defined above,
m) –P(O)(OH)–O–P(O)(OH)$_2$,
n) –P(O)(OH)–O–P(O)(OH)–O–P(O)(OH)$_2$,
o) a C_{2-7}acyl,
p) an aminoacyl,
q) a C_{1-6}-alkylene-oxy-C_{2-7}acyl, and
r) a –C(O)–O-C_{1-6}alkyl;

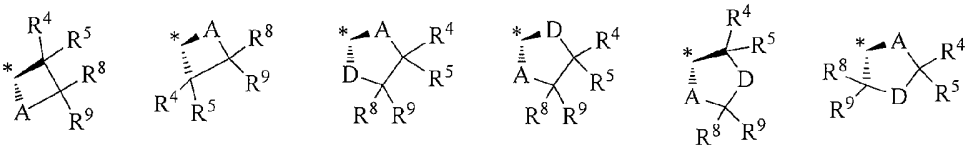
2) R^2 is selected from among
a) hydrogen,
b) fluoro,
c) azido, and
d) cyano;

3) R^3 is selected from among
a) hydrogen,
b) methyl, and
c) cyano;

4) Y is selected from among
a) hydrogen,
b) fluoro,
c) –OH,
d) –O~, when R^1 is –P(O)(OR^{1c})~, where R^{1c} is defined above,
e) –O(C_{2-7}acyl),
f) –O(aminoacyl),
g) –O(C_{1-6}-alkylene-oxy-acyl),
h) –O–C(O)–O-C_{1-6}alkyl,
i) –NH_2,
j) –NH(C_{2-7}acyl),
k) –NH(aminoacyl),
l) –NH–C(O)–O-C_{1-6}alkyl, and
m) azido;

5) X is selected from among
a) –O– and
b) –S–;

6)  is a four- or five-membered ring selected from among radicals **c**, **d**, **e**, **f**, **g**, and **h**, represented by the following structures



c d e f g h

where * represents the point of attachment to the 2'-carbon and where

a) A is selected from among
- i) –O–,
- ii) –S–,
- iii) –S(O)–,
- iv) –$S(O)_2$–, and
- v) –NH–,

b) D is selected from among
- i) –O–,
- ii) –S–,
- iii) –S(O)–,
- iv) –$S(O)_2$–, and
- v) –NH–,
- vi) a methylene, and
- vii) a vinylidene, and

c) R^4, R^5, R^8, and R^9 are independently selected from among
- i) hydrogen,
- ii) halo,
- iii) $C_{1\text{-}6}$alkyl
- iv) hydroxy,
- v) alkoxy,
- vi) cycloalkoxy,
- vii) –O(acyl),
- viii) –O($C_{1\text{-}6}$-alkyleneoxyacyl),
- ix) –O–C(O)–O-alkyl,
- x) $C_{1\text{-}6}$alkylene-oxy(alkyl),
- xi) alkenyl,
- xii) ethynyl,
- xiii) –NH_2,
- xiv) –NH(alkyl),
- xv) –NH(cycloalkyl),
- xvi) heterocyclyl,
- xvii) aryl, and
- xviii) heteroaryl; and

7a) m is 0, ----- is a double-bond and R^{16} and R^{17} are independently selected from among
- i) hydrogen,
- ii) –NH_2,
- iii) –NH($C_{1\text{-}6}$alkyl),
- iv) –NH($C_{2\text{-}7}$acyl),
- iv) –NH–C(O)–O-$C_{1\text{-}6}$alkyl,
- v) – cycloheteroalkyl,

vi) –O(C_{1-6}alkyl),
vii) –O(C_{2-7}acyl),
viii) –O(C_{1-6}alkyleneoxyacyl),
ix) –O–C(O)–O-C_{1-6}alkyl,
x) –S(C_{1-6}alkyl), and
xi) –OC_{1-3}alkaryl,

7b) m is 1, ----- is a single-bond and
b1) R^{16} is selected from among
i) =O,
ii) =NH, and
iii) =N(C_{1-6}alkyl), and
b2) R^{17} is selected from among
i) –NH_2,
ii) –NH(C_{1-6}alkyl),
iii) –NH(C_{2-7}acyl),
iv) –NH–C(O)–O-C_{1-6}alkyl, and
v) – cycloheteroalkyl, and

7c) independent of the value of m, each bonding pair, W^1----W^2, W^2----C, C----W^4, W^4----W^3, and W^3----W^1, contained in the five-membered ring comprises a single or a double bond and
i) W^1 is O, S, N, or CR^{14},
ii) W^2 is N or CR^{15},
iii) W^3 is C or N, and
iv) W^4 is C or N, and

where R^{14} and R^{15}, if present, are independently selected from among
i) hydrogen,
ii) halo,
iii) cyano,
iv) –C(O)NH_2,
iv) C_{1-6}alkyl,
vii) vinyl, and
viii) ethynyl.

A second aspect of the third embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-3**

wherein

1) R^1 is selected from among
a) hydrogen,
b) –P(O)$(OH)_2$,
c) –P(O)$(O(CH_2)_{1-3}OC(O)O(C_{1-6}alkyl))_2$,
d) –P(O)$(O(CH_2)_{1-3}OC(O)(C_{1-6}alkyl))_2$,
e) –P(O)$(O(CH_2)_{1-3}SC(O)(C_{1-6}alkyl))_2$,
f) –P(O)$(O(CH_2)_{1-3}OCH_2(aryl))_2$,
g) –P(O)$(O(CH_2)_{1-3}SCH_2(aryl))_2$,
h) –P*(O)$(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})$,
wherein
R^{1a} is

i) hydrogen,
ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl, or
iv) aryl,

R^{1b} is

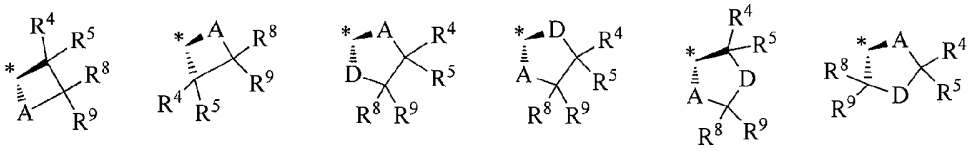
i) hydrogen,
ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl,
iv) C_{1-3}alkaryl, or
v) alk(heteroaryl), and

R^{1c} is

i) hydrogen
ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl, or
iv) C_{1-3}alkaryl,

i) –P*(O)(NH(alkaryl)(O$(CH_2)_{1-3}$SC(O)(alkyl)),
j) a 1,3,2-dioxaphosphinane-2-oxide,
k) a 4*H*-benzo[d][1,3,2]dioxaphosphinine-2-oxide,
l) –P*(O)(OR^{1c})~, when Y is –O~, where R^{1c} is defined above,
m) –P(O)(OH)–O–P(O)(OH)$_2$,
n) –P(O)(OH)–O–P(O)(OH)–O–P(O)(OH)$_2$,
o) a C_{2-7}acyl,
p) an aminoacyl,
q) a C_{1-6}-alkylene-oxy-C_{2-7}acyl, and
r) a –C(O)–O-C_{1-6}alkyl;

2) R^2 is hydrogen;
3) R^3 is hydrogen;
4) Y is selected from among
a) –OH,
b) –O~, when R^1 is –P(O)(OR^{1c})~, where R^{1c} is defined above,
c) –O(C_{2-7}acyl),
d) –O(aminoacyl),
e) –O(C_{1-6}-alkylene-oxy-acyl), and
f) –O–C(O)–O-C_{1-6}alkyl;
5) X is –O–;
6) (Z) is a four- or five-membered ring selected from among radicals **c**, **d**, **e**, **f**, **g**, and **h**, represented by the following structures



c **d** **e** **f** **g** **h**

where * represents the point of attachment to the 2'-carbon and where
a) A is selected from among

i) –O–,
ii) –S–,
iii) –S(O)–,
iv) –$S(O)_2$–, and
v) –NH–,

b) D is selected from among
i) –O–,
ii) –S–,
iii) –S(O)–,
iv) –$S(O)_2$–, and
v) –NH–,
vi) a methylene, and
vii) a vinylidene,

c) R^4, R^5, R^8, and R^9 are independently selected from among
i) hydrogen,
ii) halo, and
iii) C_{1-6}alkyl; and

7a) m is 0, ----- is a double-bond and R^{16} and R^{17} are independently selected from among
i) hydrogen,
ii) –NH_2,
iii) –NH(C_{1-6}alkyl),
iv) –NH(C_{2-7}acyl),
iv) –NH–C(O)–O-C_{1-6}alkyl,
v) – cycloheteroalkyl,
vi) –O(C_{1-6}alkyl),
vii) –O(C_{2-7}acyl),
viii) –O(C_{1-6}alkyleneoxyacyl),
ix) –O–C(O)–O-C_{1-6}alkyl,
x) –S(C_{1-6}alkyl), and
xi) –OC_{1-3}alkaryl,

7b) m is 1, ----- is a single-bond and
b1) R^{16} is selected from among
i) =O,
ii) =NH, and
iii) =N(C_{1-6}alkyl), and
b2) R^{17} is selected from among
i) –NH_2,
ii) –NH(C_{1-6}alkyl),
iii) –NH(C_{2-7}acyl),
iv) –NH–C(O)–O-C_{1-6}alkyl, and
v) – cycloheteroalkyl, and

7c) independent of the value of m, each bonding pair, W^1----W^2, W^2----C, C----W^4, W^4----W^3, and W^3----W^1, contained in the five-membered ring comprises a single or a double bond and
i) W^1 is O, S, N, or CR^{14},
ii) W^2 is N or CR^{15},
iii) W^3 is C or N, and
iv) W^4 is C or N, and

where R^{14} and R^{15}, if present, are independently selected from among

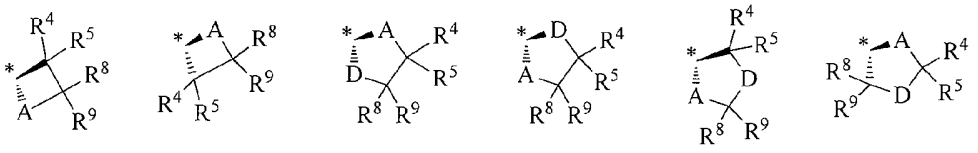
i) hydrogen,
ii) halo,
iii) cyano,
iv) $-C(O)NH_2$,
iv) C_{1-6}alkyl,
vii) vinyl, and
viii) ethynyl.

A third aspect of the third embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-3**

wherein

1) R^1 is selected from among
a) hydrogen,
b) $-P(O)(OH)_2$,
c) $-P(O)(O(CH_2)_{1-3}OC(O)O(C_{1-6}alkyl))_2$,
d) $-P(O)(O(CH_2)_{1-3}OC(O)(C_{1-6}alkyl))_2$,
e) $-P(O)(O(CH_2)_{1-3}SC(O)(C_{1-6}alkyl))_2$,
f) $-P(O)(O(CH_2)_{1-3}OCH_2(aryl))_2$,
g) $-P(O)(O(CH_2)_{1-3}SCH_2(aryl))_2$,
h) $-P^*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})$,
wherein
R^{1a} is
i) hydrogen,
ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl, or
iv) aryl,
R^{1b} is
i) hydrogen,
ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl,
iv) C_{1-3}alkaryl, or
v) alk(heteroaryl), and
R^{1c} is
i) hydrogen
ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl, or
iv) C_{1-3}alkaryl,
i) $-P^*(O)(NH(alkaryl)(O(CH_2)_{1-3}SC(O)(alkyl))$,
j) a 1,3,2-dioxaphosphinane-2-oxide,
k) a 4*H*-benzo[d][1,3,2]dioxaphosphinine-2-oxide,
l) $-P^*(O)(OR^{1c})\sim$, when Y is $-O\sim$, where R^{1c} is defined above,
m) $-P(O)(OH)-O-P(O)(OH)_2$,
n) $-P(O)(OH)-O-P(O)(OH)-O-P(O)(OH)_2$,
o) a C_{2-7}acyl,
p) an aminoacyl,
p) a C_{1-6}-alkylene-oxy-C_{2-7}acyl, and
q) a $-C(O)-O-C_{1-6}$alkyl;

2) R^2 is hydrogen;
3) R^3 is hydrogen;
4) Y is selected from among
  a) –OH,
  b) –O~, when R^1 is –P(O)(OR^{1c})~, where R^{1c} is defined above,
  c) –O(C_{2-7}acyl),
  d) –O(aminoacyl),
  e) –O(C_{1-6}-alkylene-oxy-acyl), and
  f) –O–C(O)–O-C_{1-6}alkyl;
5) X is –O–;
6) (Z) is a four- or five-membered ring selected from among radicals **c**, **d**, **e**, **f**, **g**, and **h**, represented by the following structures



c **d** **e** **f** **g** **h**

where * represents the point of attachment to the 2'-carbon and where
a) A is –O–,
b) D is –O– or –CH_2–,
c) R^4, R^5, R^8, and R^9 are each hydrogen; and
7a) m is 0, ----- is a double-bond and R^{16} and R^{17} are independently selected from among
  i) hydrogen,
  ii) –NH_2,
  iii) –NH(C_{1-6}alkyl),
  iv) –NH(C_{2-7}acyl),
  iv) –NH–C(O)–O-C_{1-6}alkyl,
  v) – cycloheteroalkyl,
  vi) –O(C_{1-6}alkyl),
  vii) –O(C_{2-7}acyl),
  viii) –O(C_{1-6}alkyleneoxyacyl),
  ix) –O–C(O)–O-C_{1-6}alkyl,
  x) –S(C_{1-6}alkyl), and
  xi) –OC_{1-3}alkaryl,
7b) m is 1, ----- is a single-bond and
  b1) R^{16} is selected from among
    i) =O,
    ii) =NH, and
    iii) =N(C_{1-6}alkyl), and
  b2) R^{17} is selected from among
    i) –NH_2,
    ii) –NH(C_{1-6}alkyl),
    iii) –NH(C_{2-7}acyl),

iv) –NH–C(O)–O-C_{1-6}alkyl, and
v) – cycloheteroalkyl,

7c) independent of the value of m, each bonding pair, W^1----W^2, W^2----C, C----W^4, W^4----W^3, and W^3----W^1, contained in the five-membered ring comprises a single or a double bond and

i) W^1 is O, S, N, or CR^{14},
ii) W^2 is N or CR^{15},
iii) W^3 is C or N, and
iv) W^4 is C or N, and

where R^{14} and R^{15}, if present, are independently selected from among

i) hydrogen,
ii) halo,
iii) cyano,
iv) –$C(O)NH_2$,
iv) C_{1-6}alkyl,
vii) vinyl, and
viii) ethynyl.

A fourth aspect of the third embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-3**

wherein

1) R^1 is selected from among

a) hydrogen,
b) –$P(O)(OH)_2$,
c) –$P(O)(O(CH_2)_{1-3}OC(O)O(C_{1-6}alkyl))_2$,
d) –$P(O)(O(CH_2)_{1-3}OC(O)(C_{1-6}alkyl))_2$,
e) –$P(O)(O(CH_2)_{1-3}SC(O)(C_{1-6}alkyl))_2$,
f) –$P(O)(O(CH_2)_{1-3}OCH_2(aryl))_2$,
g) –$P(O)(O(CH_2)_{1-3}SCH_2(aryl))_2$,
h) –$P^*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})$,

wherein

R^{1a} is

i) hydrogen or
iv) aryl,

R^{1b} is

i) hydrogen or
ii) C_{1-6}alkyl, and

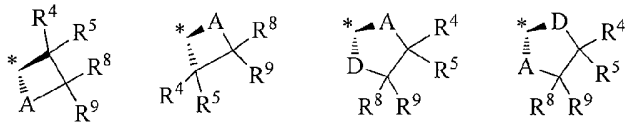
R^{1c} is

i) hydrogen
ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl, or
iv) C_{1-3}alkaryl,

i) –$P^*(O)(NH(alkaryl)(O(CH_2)_{1-3}SC(O)(alkyl))$,
j) a 1,3,2-dioxaphosphinane-2-oxide,
k) a 4*H*-benzo[d][1,3,2]dioxaphosphinine-2-oxide,
l) –$P^*(O)(OR^{1c})$~, when Y is –O~, where R^{1c} is defined above,
m) –P(O)(OH)–O–$P(O)(OH)_2$,

n) –P(O)(OH)–O–P(O)(OH)–O–P(O)(OH)$_2$,
o) an C_{2-7}acyl,
p) an aminoacyl,
q) a C_{1-6}-alkylene-oxy-C_{2-7}acyl, and
r) a –C(O)–O-C_{1-6}alkyl;

2) R^2 is hydrogen;
3) R^3 is hydrogen;
4) Y is selected from among
a) –OH,
b) –O~, when R^1 is –P(O)(OR^{1c})~, where R^{1c} is defined above,
c) –O(C_{2-7}acyl), and
d) –O(aminoacyl);
5) X is –O–;
6) (Z) is a four- or five-membered ring selected from among radicals **c**, **d**, **e**, and **f** represented by the following structures



c **d** **e** **f**

where * represents the point of attachment to the 2'-carbon and where
a) A is –O–,
b) D is –O– or –CH_2–,
c) R^4, R^5, R^8, and R^9 are each hydrogen; and
7a) m is 0, ----- is a double-bond and R^{16} and R^{17} are independently selected from among
i) hydrogen,
ii) –NH_2,
iii) –NH(C_{1-6}alkyl),
iv) –NH(C_{2-7}acyl),
iv) –NH–C(O)–O-C_{1-6}alkyl,
v) – cycloheteroalkyl,
vi) –O(C_{1-6}alkyl),
vii) –O(C_{2-7}acyl),
viii) –O(C_{1-6}alkyleneoxyacyl),
ix) –O–C(O)–O-C_{1-6}alkyl,
x) –S(C_{1-6}alkyl), and
xi) –OC_{1-3}alkaryl,
7b) m is 1, ----- is a single-bond and
b1) R^{16} is selected from among
i) =O,
ii) =NH, and
iii) =N(C_{1-6}alkyl), and
b2) R^{17} is selected from among
i) –NH_2,
ii) –NH(C_{1-6}alkyl),
iii) –NH(C_{2-7}acyl),

iv) –NH–C(O)–O-C_{1-6}alkyl, and
v) – cycloheteroalkyl,

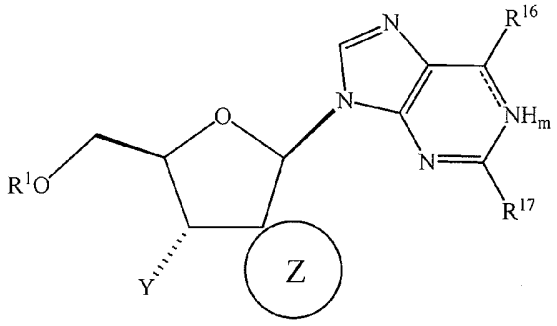
7c) independent of the value of m, each bonding pair, W^1----W^2, W^2----C, C----W^4, W^4----W^3, and W^3----W^1, contained in the five-membered ring comprises a single or a double bond and

i) W^1 is O, S, N, or CR^{14},
ii) W^2 is N or CR^{15},
iii) W^3 is C or N, and
iv) W^4 is C or N, and

where R^{14} and R^{15}, if present, are independently selected from among

i) hydrogen,
ii) halo,
iii) cyano,
iv) –C(O)NH_2,
iv) C_{1-6}alkyl,
vii) vinyl, and
viii) ethynyl.

A fifth aspect of the third embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-3-1**



I-3-1

wherein

1) R^1 is selected from among:

a) hydrogen,
b) –P(O)$(OH)_2$,
c) –P*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c}),

wherein

R^{1a} is

i) hydrogen or
ii) aryl,

R^{1b} is

i) hydrogen or
ii) C_{1-6}alkyl, and

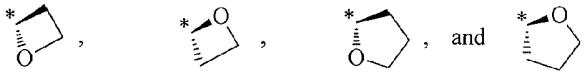
R^{1c} is

i) hydrogen

ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl, or
iv) C_{1-3}alkaryl,
d) a 1,3,2-dioxaphosphinane-2-oxide,
e) a 4*H*-benzo[d][1,3,2]dioxaphosphinine-2-oxide,
f) –P*(O)(OR^{1c})–, when Y is –O–, where R^{1c} is defined above,
g) –P(O)(OH)–O–P(O)$(OH)_2$,
h) –P(O)(OH)–O–P(O)(OH)–O–P(O)$(OH)_2$,
i) a C_{2-7}acyl, and
j) an aminoacyl; and

2) Y is selected from among
a) –OH,
b) –O–, when R^1 is –P(O)(OR^{1c})–, where R^{1c} is defined above,
c) –O(C_{2-7}acyl), and
d) –O(aminoacyl); and

3) (Z) is selected from among



where * represents the point of attachment to the 2'-carbon; and

4a) m is 0, ----- is a double-bond
4a1) R^{16} is selected from among
i) –NH_2,
ii) –NH(C_{1-6}alkyl),
iii) –NH(C_{2-7}acyl),
iv) –cycloalkylamino,
v) –O(C_{1-6}alkyl),
vi) –O(C_{2-7}acyl),
vii) –O(C_{1-6}alkyleneoxyacyl), and
viii) –O–C(O)–O-C_{1-6}alkyl,
ix) –S(C_{1-6}alkyl), and
x) –OC_{1-3}alkaryl, and
4a2) R^{17} is selected from among
i) hydrogen,
ii) –NH_2, and
iii) –NH(C_{1-6}alkyl), or

4b) m is 1, ----- is a single-bond
4b1) R^{16} is =O; and
4b2) R^{17} is selected from among
i) –NH_2 and
ii) –NH(C_{1-6}alkyl).

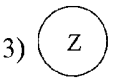
A sixth aspect of the third embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-3-1**

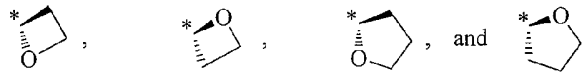
wherein

1) R^1 is selected from among:

a) hydrogen,
b) $-P(O)(OH)_2$,
c) $-P^*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})$,
wherein
R^{1a} is
i) hydrogen,
ii) phenyl,
iii) p-fluorophenyl,
iv) p-chlorophenyl,
v) p-bromophenyl, or
vi) naphthyl,
R^{1b} is
i) hydrogen or
ii) C_{1-6}alkyl, and
R^{1c} is
i) hydrogen
ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl, or
iv) C_{1-3}alkaryl,
d) $-P^*(O)(OR^{1c})\sim$, when Y is $-O\sim$, where R^{1c} is defined above,
e) $-P(O)(OH)-O-P(O)(OH)_2$,
f) $-P(O)(OH)-O-P(O)(OH)-O-P(O)(OH)_2$,
g) a C_{2-7}acyl, and
h) an aminoacyl; and

2) Y is selected from among
a) –OH,
b) $-O\sim$, when R^1 is $-P(O)(OR^{1c})\sim$, where R^{1c} is defined above,
c) $-O(C_{2-7}$acyl), and
d) –O(aminoacyl); and

3)  is selected from among



where * represents the point of attachment to the 2'-carbon; and
4a) m is 0, ----- is a double-bond
4a1) R^{16} is selected from among
i) $-NH_2$,
ii) $-NH(C_{1-6}$alkyl),
iii) $-NH(C_{2-7}$acyl),
iv) –cycloalkylamino,
v) $-O(C_{1-6}$alkyl),
vi) $-O(C_{2-7}$acyl),
vii) $-O(C_{1-6}$alkyleneoxyacyl), and
viii) $-O-C(O)-O-C_{1-6}$alkyl,
ix) $-S(C_{1-6}$alkyl), and
x) $-OC_{1-3}$alkaryl, and
4a2) R^{17} is selected from among
i) hydrogen,
ii) $-NH_2$ and

iiii) –NH(C_{1-6}alkyl), or

4b) m is 1, ----- is a single-bond

4b1) R^{16} is =O and

4b2) R^{17} is selected from among

i) $–NH_2$ and

ii) –NH(C_{1-6}alkyl).

A seventh aspect of the third embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-3-1**

wherein

1) R^1 is selected from among:

a) hydrogen,

b) $–P(O)(OH)_2$,

c) $–P^*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})$,

wherein

R^{1a} is

i) hydrogen,

ii) phenyl,

iii) p-fluorophenyl,

iv) p-chlorophenyl,

v) p-bromophenyl, or

vi) naphthyl,

R^{1b} is

i) hydrogen or

ii) C_{1-6}alkyl, and

R^{1c} is

i) hydrogen

ii) C_{1-6}alkyl,

iii) C_{3-6}cycloalkyl, or

iv) C_{1-3}alkaryl,

d) $–P^*(O)(OR^{1c})–$, when Y is –O–, where R^{1c} is defined above,

e) –P(O)(OH)–O–P(O)(OH)$_2$,

f) –P(O)(OH)–O–P(O)(OH)–O–P(O)(OH)$_2$,

g) a C_{2-7}acyl, and

h) an aminoacyl; and

2) Y is selected from among

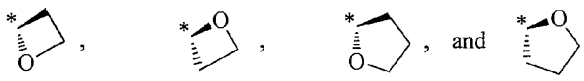
a) –OH,

b) –O–, when R^1 is $–P(O)(OR^{1c})–$, where R^{1c} is defined above,

c) –O(C_{2-7}acyl), and

d) –O(aminoacyl); and

3) (Z) is selected from among



where * represents the point of attachment to the 2'-carbon; and

4a) m is 0, ----- is a double-bond

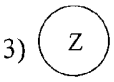
4a1) R^{16} is selected from among
i) $-NH_2$,
ii) $-NH(C_{1-6}alkyl)$,
iii) $-NH(C_{2-7}acyl)$,
iv) –cycloalkylamino,
v) $-O(C_{1-6}alkyl)$,
vi) $-O(C_{2-7}acyl)$,
vii) $-S(C_{1-6}alkyl)$, and
viii) $-OC_{1-3}alkaryl$, and
4a2) R^{17} is selected from among
i) hydrogen,
ii) $-NH_2$, and
iii) $-NH(C_{1-6}alkyl)$, or
4b) m is 1, ----- is a single-bond
4b1) R^{16} is =O and
4b2) R^{17} is selected from among
i) $-NH_2$ and
ii) $-NH(C_{1-6}alkyl)$.

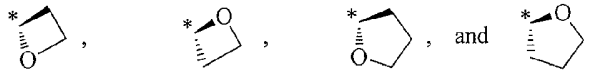
An eighth aspect of the third embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-3-1**

wherein

1) R^1 is selected from among:
a) hydrogen,
b) $-P(O)(OH)_2$,
c) $-P^*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})$,
wherein
R^{1a} is
i) hydrogen,
ii) phenyl,
iii) p-fluorophenyl,
iv) p-chlorophenyl,
v) p-bromophenyl, or
vi) naphtyl,
R^{1b} is
i) hydrogen or
ii) $C_{1-6}alkyl$, and
R^{1c} is
i) hydrogen
ii) $C_{1-6}alkyl$,
iii) $C_{3-6}cycloalkyl$, or
vi) $C_{1-3}alkaryl$,
d) $-P^*(O)(OR^{1c})$~, when Y is –O~, where R^{1c} is defined above,
e) $-P(O)(OH)-O-P(O)(OH)_2$,
f) $-P(O)(OH)-O-P(O)(OH)-O-P(O)(OH)_2$,
g) a $C_{2-7}acyl$, and
h) an aminoacyl; and

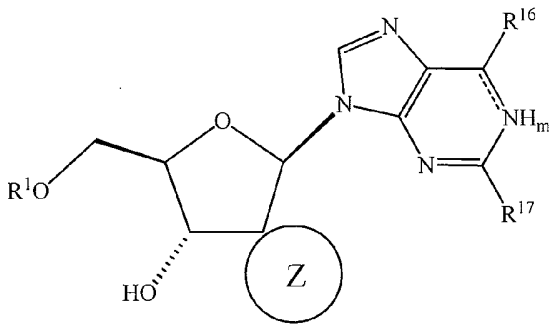
2) Y is selected from among
a) –OH,
b) –O~, when R^1 is –P(O)(OR^{1c})~, where R^{1c} is defined above,
c) –O(C_{2-7}acyl), and
d) –O(aminoacyl); and

3)  is selected from among



where * represents the point of attachment to the 2'-carbon; and
4a) m is 0, ----- is a double-bond
4a1) R^{16} is –O(C_{1-6}alkyl), –OC_{1-3}alkaryl, –S(C_{1-6}alkyl), –NH(C_{1-6}alkyl), or –cycloalkylamino, and
4a2) R^{17} is $–NH_2$ or –NH(C_{1-6}alkyl), or
4a3) R^{16} is $–NH_2$, –O(C_{1-6}alkyl), –OC_{1-3}alkaryl, –S(C_{1-6}alkyl), –NH(C_{1-6}alkyl), or –cycloalkylamino, and
4a4) R^{17} is hydrogen, or
4b) m is 1, ----- is a single-bond
4b1) R^{16} is =O and
4b2) R^{17} is–NH_2 or –NH(C_{1-6}alkyl).

A ninth aspect of the third embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-3-2**



I-3-2

wherein

1) R^1 is selected from among:
a) hydrogen,
b) $–P(O)(OH)_2$,
c) $–P^*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})$,
wherein
R^{1a} is
i) hydrogen,
ii) phenyl,
iii) p-fluorophenyl,

iv) p-chlorophenyl,
v) p-bromophenyl, or
vi) naphthyl,

R^{1b} is

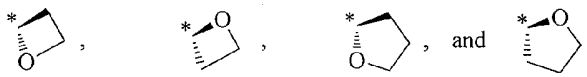
i) hydrogen or
ii) $C_{1\text{-}6}$alkyl, and

R^{1c} is

i) hydrogen
ii) $C_{1\text{-}6}$alkyl,
iii) $C_{3\text{-}6}$cycloalkyl, or
iv) $C_{1\text{-}3}$alkaryl,

d) $-P(O)(OH)-O-P(O)(OH)_2$,
e) $-P(O)(OH)-O-P(O)(OH)-O-P(O)(OH)_2$,
f) a $C_{2\text{-}7}$acyl, and
g) an aminoacyl; and

2)  is selected from among



where * represents the point of attachment to the 2'-carbon; and

3a) m is 0, ----- is a double-bond

3a1) R^{16} is $-O(C_{1\text{-}6}alkyl)$, $-OC_{1\text{-}3}alkaryl$, $-S(C_{1\text{-}6}alkyl)$, $-NH(C_{1\text{-}6}alkyl)$, or
–cycloalkylaminoand

3a2) R^{17} is $-NH_2$ or $-NH(C_{1\text{-}6}alkyl)$, or

3a3) R^{16} is $-NH_2$, $-O(C_{1\text{-}6}alkyl)$, $-OC_{1\text{-}3}alkaryl$, $-S(C_{1\text{-}6}alkyl)$, $-NH(C_{1\text{-}6}alkyl)$, or –cycloalkylamino and

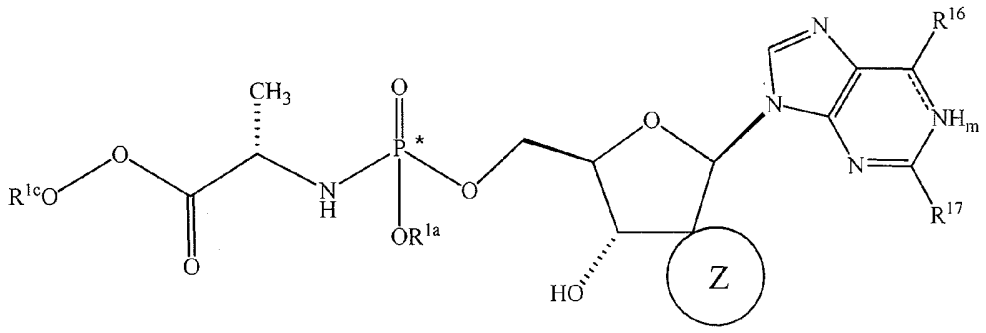
3a4) R^{17} is hydrogen, or

3b) m is 1, ----- is a single-bond

3b1) R^{16} is =O and

3b2) R^{17} is $-NH_2$.

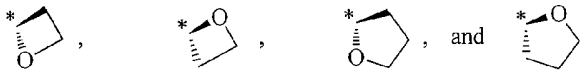
A tenth aspect of the third embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-3-3**



I-3-3

wherein

1) R^{1a} is
   a) hydrogen,
   b) phenyl,
   c) p-fluorophenyl,
   d) p-chlorophenyl,
   e) p-bromophenyl, or
   f) naphthyl, and
2) R^{1c} is
   a) hydrogen
   b) C_{1-6}alkyl,
   c) C_{3-6}cycloalkyl, or
   d) C_{1-3}alkaryl;
3) (Z) is selected from among

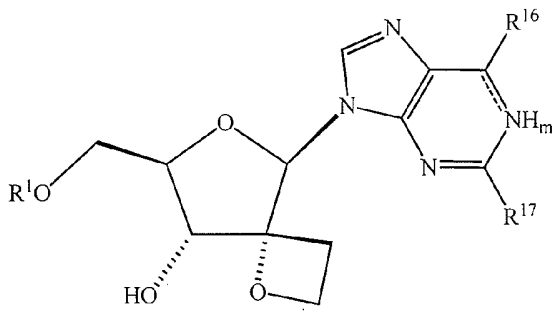


where * represents the point of attachment to the 2'-carbon; and

4a) m is 0, ----- is a double-bond
   4a1) R^{16} is $-O(C_{1-6}alkyl)$, $-OC_{1-3}alkaryl$, $-S(C_{1-6}alkyl)$, $-NH(C_{1-6}alkyl)$, or
   –cycloalkylamino, and
   4a2) R^{17} is $-NH_2$ or $-NH(C_{1-6}alkyl)$, or
   4a3) R^{16} is $-NH_2$, $-O(C_{1-6}alkyl)$, $-OC_{1-3}alkaryl$, $-S(C_{1-6}alkyl)$, $-NH(C_{1-6}alkyl)$, or –cycloalkylamino, and
   4a4) R^{17} is hydrogen, or

4b) m is 1, ----- is a single-bond
   4b1) R^{16} is =O and
   4b2) R^{17} is $-NH_2$ or $-NH(C_{1-6}alkyl)$.

An eleventh aspect of the third embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-3-4**



I-3-4

wherein

1) R^1 is selected from among:
- a) hydrogen,
- b) $-P(O)(OH)_2$,
- c) $-P^*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})$,

wherein

R^{1a} is
- i) hydrogen,
- ii) phenyl,
- iii) p-fluorophenyl,
- iv) p-chlorophenyl,
- v) p-bromophenyl, or
- vi) naphthyl,

R^{1b} is
- i) hydrogen or
- ii) C_{1-6}alkyl, and

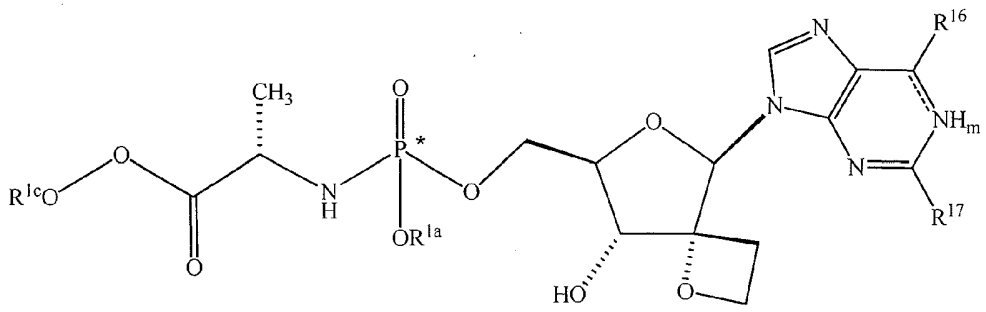
R^{1c} is
- i) hydrogen
- ii) C_{1-6}alkyl,
- iii) C_{3-6}cycloalkyl, or
- iv) C_{1-3}alkaryl,

- d) $-P(O)(OH)-O-P(O)(OH)_2$,
- e) $-P(O)(OH)-O-P(O)(OH)-O-P(O)(OH)_2$,
- f) a C_{2-7}acyl, and
- g) an aminoacyl; and

2a) m is 0, ----- is a double-bond
- 3a1) R^{16} is $-O(C_{1-6}alkyl)$, $-OC_{1-3}$alkaryl, $-S(C_{1-6}alkyl)$, $-NH(C_{1-6}alkyl)$, or –cycloalkylamino, and
- 3a2) R^{17} is $-NH_2$ or $-NH(C_{1-6}alkyl)$, or
- 3a3) R^{16} is $-NH_2$, $-O(C_{1-6}alkyl)$, $-OC_{1-3}$alkaryl, $-S(C_{1-6}alkyl)$, $-NH(C_{1-6}alkyl)$, or –cycloalkylamino and
- 3a4) R^{17} is hydrogen, or

2b) m is 1, ----- is a single-bond
- 3b1) R^{16} is =O and
- 3b2) R^{17} is $-NH_2$ or $-NH(C_{1-6}alkyl)$.

A twelfth aspect of the third embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-3-5**



I-3-5

wherein

1) R^{1a} is
   a) hydrogen,
   b) phenyl, or
   c) naphthyl, and
2) R^{1c} is
   a) hydrogen
   b) C_{1-6}alkyl,
   c) C_{3-6}cycloalkyl, or
   d) C_{1-3}alkaryl; and

3a) m is 0, ----- is a double-bond
   3a1) R^{16} is $-O(C_{1-6}alkyl)$, $-OC_{1-3}$alkaryl, $-S(C_{1-6}alkyl)$, $-NH(C_{1-6}alkyl)$, or
   –cycloalkylamino, and
   3a2) R^{17} is $-NH_2$ or $-NH(C_{1-6}alkyl)$, or
   3a3) R^{16} is $-NH_2$, $-O(C_{1-6}alkyl)$, $-OC_{1-3}$alkaryl,, $-S(C_{1-6}alkyl)$, $-NH(C_{1-6}alkyl)$, or –cycloalkylamino, and
   3a4) R^{17} is hydrogen, or

3b) m is 1, ----- is a single-bond
   3b1) R^{16} is =O and
   3b2) R^{17} is$-NH_2$ or $-NH(C_{1-6}alkyl)$.

A thirteenth aspect of the third embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-3-5**

wherein

1) R^{1a} is
   a) hydrogen,
   b) phenyl, or

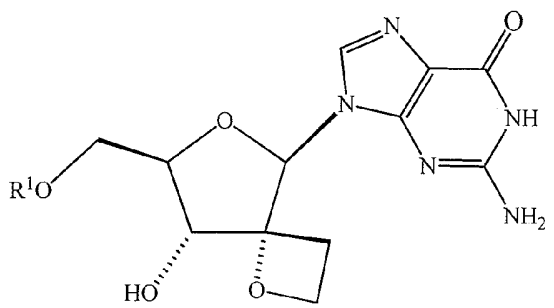
c) naphthyl, and
2) R^{1c} is
a) hydrogen
b) C_{1-6}alkyl,
c) C_{3-6}cycloalkyl, or
d) C_{1-3}alkaryl; and
3a) m is 0, ----- is a double-bond
3a1) R^{16} is $-O(C_{1-6}alkyl)$, $-OC_{1-3}alkaryl$, $-S(C_{1-6}alkyl)$, $-NH(C_{1-6}alkyl)$, or
–cycloalkylamino, and
3a2) R^{17} is $-NH_2$, or
3a3) R^{16} is $-NH_2$, $-O(C_{1-6}alkyl)$, $-OC_{1-3}alkaryl$, $-NH(C_{1-6}alkyl)$, $-S(C_{1-6}alkyl)$, or –cycloalkylamino, and
3a4) R^{17} is hydrogen, or
3b) m is 1, ----- is a single-bond
3b1) R^{16} is =O and
3b2) R^{17} is$-NH_2$.

A fourteenth aspect of the third embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-3-5**

wherein

1) R^{1a} is
a) hydrogen,
b) phenyl, or
c) naphthyl, and
2) R^{1c} is
a) hydrogen
b) C_{1-6}alkyl,
c) C_{3-6}cycloalkyl, or
d) C_{1-3}alkaryl; and
3a) m is 0, ----- is a double-bond
3a1) R^{16} is $-O(C_{1-6}alkyl)$ or $-OC_{1-3}alkaryl$, and
3a2) R^{17} is $-NH_2$, or
3a3) R^{16} is $-NH_2$, and
3a4) R^{17} is hydrogen, or
3b) m is 1, ----- is a single-bond
3b1) R^{16} is =O and
3b2) R^{17} is$-NH_2$.

A fifteenth aspect of the third embodiment is directed to a compound or its salt thereof represented by formula **I-3-6**

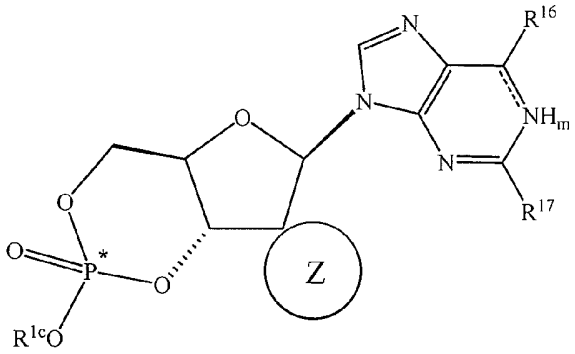


I-3-6

wherein

1) R^1 is hydrogen, $-P(O)(OH)_2$, $-P(O)(OH)-O-P(O)(OH)_2$, or $-P(O)(OH)-O-P(O)(OH)-O-P(O)(OH)_2$.

A sixteenth aspect of the third embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-3-7**

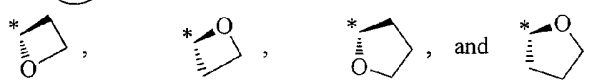


I-3-7

1) R^{1c} is

a) hydrogen
b) C_{1-6}alkyl,
c) C_{3-6}cycloalkyl, or
d) C_{1-3}alkaryl;

2) (Z) is selected from among



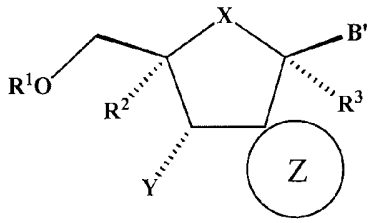
where * represents the point of attachment to the 2'-carbon; and

3a) m is 0, ----- is a double-bond

3a1) R^{16} is $-O(C_{1-6}alkyl)$, $-OC_{1-3}alkaryl$, $-S(C_{1-6}alkyl)$, $-NH(C_{1-6}alkyl)$, or
–cycloalkylamino,and

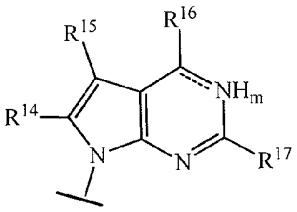
3a2) R^{17} is $-NH_2$, or
3b1) R^{16} is $-NH_2$, $-O(C_{1-6}alkyl)$, $-OC_{1-3}alkaryl$, $-NH(C_{1-6}alkyl)$, $-S(C_{1-6}alkyl)$, or –cycloalkylamino and
3b2) R^{17} is hydrogen, or
3b) m is 1, ----- is a single-bond
3b1) R^{16} is =O and
3b2) R^{17} is $-NH_2$ or $-NH(C_{1-6}alkyl)$.

A seventeenth aspect of the third embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-3-8**

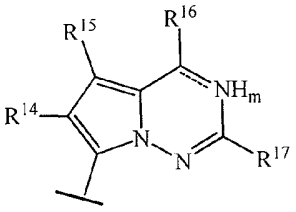


I-3-8

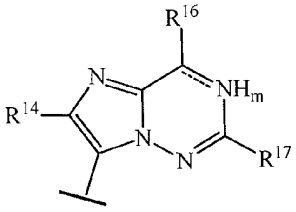
wherein B' is selected from among **B5**, **B6**, **B7**, **B8**, **B9**, and **B10** represented by the following structures



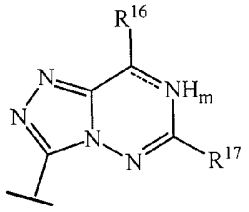
B5



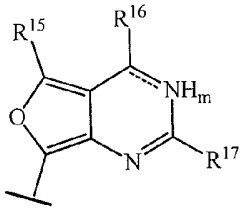
B6



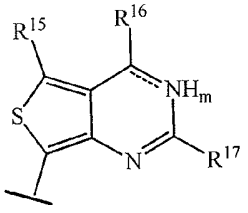
B7



B8



B9



B10

and R^1, R^2, Y, R^3, (z), X, R^{14}, R^{15}, R^{16}, R^{17}, m, and ---- have the meanings described above.

An eighteenth aspect of the third embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-3-8**,

wherein

1) R^1 is selected from among:
   a) hydrogen,
   b) $-P(O)(OH)_2$,
   c) $-P(O)(O(CH_2)_{1-3}OC(O)O(C_{1-6}alkyl))_2$,
   d) $-P(O)(O(CH_2)_{1-3}OC(O)(C_{1-6}alkyl))_2$,
   e) $-P(O)(O(CH_2)_{1-3}SC(O)(C_{1-6}alkyl))_2$,
   f) $-P(O)(O(CH_2)_{1-3}OCH_2(aryl))_2$,
   g) $-P(O)(O(CH_2)_{1-3}SCH_2(aryl))_2$,
   h) $-P^*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})$,
   wherein
   R^{1a} is
      i) hydrogen or
      ii) aryl,
   R^{1b} is
      i) hydrogen or
      ii) C_{1-6}alkyl, and
   R^{1c} is
      i) hydrogen
      ii) alkyl,
      iii) cycloalkyl, or
      vi) $-C_{1-3}$alkaryl,
   i) $-P^*(O)(NH(alkaryl)(O(CH_2)_{1-3}SC(O)(C_{1-6}alkyl))$,
   j) a 1,3,2-dioxaphosphinane-2-oxide,
   k) a 4*H*-benzo[d][1,3,2]dioxaphosphinine-2-oxide,
   l) $-P^*(O)(OR^{1c})\sim$, when Y is $-O\sim$, where R^{1c} is defined above,
   m) $-P(O)(OH)-O-P(O)(OH)_2$,
   n) $-P(O)(OH)-O-P(O)(OH)-O-P(O)(OH)_2$,
   o) an C_{2-7}acyl,
   p) an aminoacyl,
   q) a C_{1-6}-alkylene-oxy-acyl, and
   r) a $-C(O)-O-C_{1-6}$alkyl,
2) R^2 is hydrogen;
3) R^3 is hydrogen or cyano;
4) Y is selected from among
   a) –OH,
   b) $-O\sim$, when R^1 is $-P(O)(OR^{1c})\sim$, where R^{1c} is defined above,
   c) –O(acyl), and
   d) $-O(C_{1-6}$-alkylene-oxyC_{2-7}acyl);
5) X is –O–;
6)  is selected from among

 ,  ,  , and 

where * represents the point of attachment to the 2'-carbon; and

7a) m is 0, ----- is a double-bond and R^{16} and R^{17} are independently selected from among

i) hydrogen,
ii) $-NH_2$,
iii) –NH(alkyl),
iv) –NH(acyl),
iv) –NH–C(O)–O-alkyl,
v) – cycloheteroalkyl,
vi) –O(alkyl),
vii) –O(acyl),
viii) $-O(C_{1-6}$alkyleneoxyacyl),
ix) –O–C(O)–O-alkyl,
x) $-S(C_{1-6}$alkyl), or
xi) $-OC_{1-3}$alkaryl,

7b) m is 1, ----- is a single-bond and

b1) R^{16} is selected from among
i) =O,
ii) =NH,
iii) =N(alkyl), and

b2) R^{17} is selected from among
i) $-NH_2$,
ii) –NH(alkyl),
iii) –NH(acyl),
iv) –NH–C(O)–O-alkyl, and
v) – cycloheteroalkyl,

7c) independent of the value of m, R^{14} and R^{15}, if present,are independently selected from among

i) hydrogen,
ii) halo,
iii) cyano,
iv) $-C(O)NH_2$,
iv) C_{1-6}alkyl,
vii) vinyl, and
viii) ethynyl.

A nineteenth aspect of the third embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-3-8** wherein

1) R^1 is selected from among:

a) hydrogen,
b) $-P(O)(OH)_2$,
c) $-P(O)(O(CH_2)_{1-3}OC(O)O(C_{1-6}alkyl))_2$,
d) $-P(O)(O(CH_2)_{1-3}OC(O)(C_{1-6}alkyl))_2$,
e) $-P(O)(O(CH_2)_{1-3}SC(O)(C_{1-6}alkyl))_2$,
f) $-P(O)(O(CH_2)_{1-3}OCH_2(aryl))_2$,
g) $-P(O)(O(CH_2)_{1-3}SCH_2(aryl))_2$,
h) $-P^*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})$,

wherein
R^{1a} is
i) hydrogen or
ii) aryl,
R^{1b} is
i) hydrogen or
ii) C_{1-6}alkyl, and
R^{1c} is
i) hydrogen,
ii) alkyl,
iii) cycloalkyl, or
vi) $-C_{1-3}$alkaryl,
i) –P*(O)(NH(alkaryl)(O$(CH_2)_{1-3}$SC(O)(C_{1-6}alkyl)),
j) a 1,3,2-dioxaphosphinane-2-oxide,
k) a 4*H*-benzo[d][1,3,2]dioxaphosphinine-2-oxide,
l) –P*(O)(OR^{1c})~, when Y is –O~, where R^{1c} is defined above,
m) –P(O)(OH)–O–P(O)$(OH)_2$,
n) –P(O)(OH)–O–P(O)(OH)–O–P(O)$(OH)_2$,
o) an C_{2-7}acyl,
p) an aminoacyl,
q) a C_{1-6}-alkylene-oxy-acyl, and
r) a –C(O)–O-C_{1-6}alkyl,
2) R^2 is hydrogen;
3) R^3 is hydrogen or cyano;
4) Y is selected from among
a) –OH,
b) –O~, when R^1 is –P(O)(OR^{1c})~, where R^{1c} is defined above,
c) –O(acyl), and
d) –O(C_{1-6}-alkylene-oxyC_{2-7}acyl);
5) X is –O–;
6) (Z) is selected from among

where * represents the point of attachment to the 2'-carbon; and
7a) m is 0, ----- is a double-bond,
7a1) R^{16} is selected from among
i) $-NH_2$,
ii) –NH(C_{1-6}alkyl),
iii) –NH(C_{2-7}acyl),
iv) –NH–C(O)–O-C_{1-6}alkyl,
v) – cycloheteroalkyl,
vi) –O(C_{1-6}alkyl),
vii) –O(C_{2-7}acyl),
viii) –O(C_{1-6}alkyleneoxyacyl),
ix) –O–C(O)–O-C_{1-6}alkyl,
x) –S(C_{1-6}alkyl), and
xi) $-OC_{1-3}$alkaryl, and
7a2) R^{17} is selected from among

i) hydrogen,
ii) $-NH_2$,
iii) $-NH(C_{1-6}alkyl)$,
iv) $-NH(C_{2-7}acyl)$, and
v) $-NH-C(O)-O-C_{1-6}alkyl$, or

7b) m is 1, ----- is a single-bond,
7b1) R^{16} is =O;
7b2) R^{17} is selected from among
i) $-NH_2$,
ii) $-NH(C_{1-6}alkyl)$, and
iii) $-NH(C_{2-7}acyl)$, and

7c) independent of the value of m, R^{14} and R^{15}, if present, are independently selected from among
i) hydrogen,
ii) halo,
iii) cyano,
iv) $-C(O)NH_2$,
iv) $C_{1-6}alkyl$,
vii) vinyl, and
viii) ethynyl.

A twentieth aspect of the third embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-3-8** wherein

1) R^1 is selected from among:
a) hydrogen,
b) $-P(O)(OH)_2$,
c) $-P(O)(O(CH_2)_{1-3}OC(O)O(C_{1-6}alkyl))_2$,
d) $-P(O)(O(CH_2)_{1-3}OC(O)(C_{1-6}alkyl))_2$,
e) $-P(O)(O(CH_2)_{1-3}SC(O)(C_{1-6}alkyl))_2$,
f) $-P(O)(O(CH_2)_{1-3}OCH_2(aryl))_2$,
g) $-P(O)(O(CH_2)_{1-3}SCH_2(aryl))_2$,
h) $-P^*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})$,
wherein
R^{1a} is
i) hydrogen or
ii) aryl,
R^{1b} is
i) hydrogen or
ii) $C_{1-6}alkyl$, and
R^{1c} is
i) hydrogen
ii) alkyl,
iii) cycloalkyl, or
vi) $-C_{1-3}alkaryl$,
i) $-P^*(O)(NH(alkaryl)(O(CH_2)_{1-3}SC(O)(C_{1-6}alkyl))$,
j) a 1,3,2-dioxaphosphinane-2-oxide,
k) a 4*H*-benzo[d][1,3,2]dioxaphosphinine-2-oxide,
l) $-P^*(O)(OR^{1c})\sim$, when Y is $-O\sim$, where R^{1c} is defined above,

m) –P(O)(OH)–O–P(O)(OH)$_2$,
n) –P(O)(OH)–O–P(O)(OH)–O–P(O)(OH)$_2$,
o) a C_{2-7}acyl,
p) an aminoacyl,
q) a C_{1-6}-alkylene-oxy-acyl, and
r) a –C(O)–O-C_{1-6}alkyl,

2) R^2 is hydrogen;
3) R^3 is hydrogen or cyano;
4) Y is selected from among
a) –OH,
b) –O~, when R^1 is –P(O)(OR^{1c})~, where R^{1c} is defined above,
c) –O(C_{2-7}acyl),
d) –O(aminoacyl), and
d) –O(C_{1-6}-alkylene-oxyC_{2-7}acyl);
5) X is –O–;
6) (Z) is selected from among

where * represents the point of attachment to the 2'-carbon; and
7a) m is 0, ----- is a double-bond,
7a1) R^{16} is selected from among
i) –NH_2,
ii) –NH(C_{1-6}alkyl),
iii) –NH(C_{2-7}acyl),
iv) –O(C_{1-6}alkyl),
v) –O(C_{2-7}acyl),
vi) –O(C_{1-6}alkyleneoxyacyl), and
vii) –O–C(O)–O-C_{1-6}alkyl,
viii) –S(C_{1-6}alkyl), and
ix) –OC_{1-3}alkaryl,
7a2) R^{17} is selected from among
i) hydrogen,
ii) –NH_2,
iii) –NH(C_{1-6}alkyl),
iv) –NH(C_{2-7}acyl), and
v) –NH–C(O)–O-C_{1-6}alkyl, or
7b) m is 1, ----- is a single-bond,
7b1) R^{16} is =O;
7b2) R^{17} is selected from among
i) –NH_2,
ii) –NH(C_{1-6}alkyl), and
iii) –NH(C_{2-7}acyl), and
7c) independent of the value of m, R^{14} and R^{15}, if present, are independently selected from among
i) hydrogen,
ii) halo,
iii) cyano,
iv) –$C(O)NH_2$,

iv) C_{1-6}alkyl,
vii) vinyl, and
viii) ethynyl.

A twenty-first aspect of the third embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-3-8** wherein

1) R^1 is selected from among:
a) hydrogen,
b) –P(O)(OH)$_2$,
c) –P*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c}),
wherein
R^{1a} is
i) hydrogen or
ii) aryl,
R^{1b} is
i) hydrogen or
ii) C_{1-6}alkyl, and
R^{1c} is
i) hydrogen
ii) alkyl,
iii) cycloalkyl, or
iv) –C_{1-3}alkaryl,
d) a 1,3,2-dioxaphosphinane-2-oxide,
e) a 4*H*-benzo[d][1,3,2]dioxaphosphinine-2-oxide,
f) –P*(O)(OR^{1c})~, when Y is –O~, where R^{1c} is defined above,
g) –P(O)(OH)–O–P(O)(OH)$_2$,
h) –P(O)(OH)–O–P(O)(OH)–O–P(O)(OH)$_2$,
i) a C_{2-7}acyl,
j) an aminoacyl,
k) a C_{1-6}-alkylene-oxy-acyl, and
l) a –C(O)–O-C_{1-6}alkyl,
2) R^2 is hydrogen;
3) R^3 is hydrogen or cyano;
4) Y is selected from among
a) –OH,
b) –O~, when R^1 is –P(O)(OR^{1c})~, where R^{1c} is defined above,
c) –O(C_{2-7}acyl),
d) –O(aminoacyl), and
e) –O(C_{1-6}-alkylene-oxyC_{2-7}acyl);
5) X is –O–;
6) (Z) is selected from among

where * represents the point of attachment to the 2'-carbon; and
7a) m is 0, ----- is a double-bond,
7a1) R^{16} is selected from among

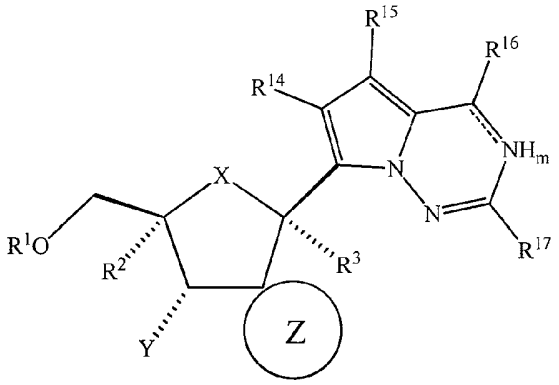
i) $-NH_2$,
ii) $-NH(C_{1-6}alkyl)$,
iii) $-NH(C_{2-7}acyl)$,
iv) $-O(C_{1-6}alkyl)$,
v) $-O(C_{2-7}acyl)$,
vi) $-O(C_{1-6}alkyleneoxyacyl)$, and
vii) $-O-C(O)-O-C_{1-6}alkyl$,
viii) $-S(C_{1-6}alkyl)$, and
ix) $-OC_{1-3}alkaryl$,

7a2) R^{17} is selected from among
i) hydrogen,
ii) $-NH_2$ and
iii) $-NH(C_{1-6}alkyl)$, or

7b) m is 1, ----- is a single-bond,
7b1) R^{16} is =O;
7b2) R^{17} is selected from among
i) $-NH_2$ and
ii) $-NH(C_{1-6}alkyl)$ and

7c) independent of the value of m, R^{14} and R^{15}, if present, are independently selected from among
i) hydrogen,
ii) halo,
iii) cyano,
iv) $-C(O)NH_2$,
iv) $C_{1-6}alkyl$,
vii) vinyl, and
viii) ethynyl.

A twenty-second aspect of the third embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-3-9**



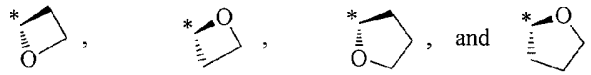
I-3-9

wherein

1) R^1 is selected from among:

a) hydrogen,
b) –P(O)(OH)$_2$,
c) –P*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c}),
wherein
R^{1a} is
i) hydrogen or
ii) aryl,
R^{1b} is
i) hydrogen or
ii) C$_{1-6}$alkyl, and
R^{1c} is
i) hydrogen
ii) alkyl,
iii) cycloalkyl, or
iv) –C$_{1-3}$alkaryl,
d) a 1,3,2-dioxaphosphinane-2-oxide,
e) a 4*H*-benzo[d][1,3,2]dioxaphosphinine-2-oxide,
f) –P*(O)(OR^{1c})~, when Y is –O~, where R^{1c} is defined above,
g) –P(O)(OH)–O–P(O)(OH)$_2$,
h) –P(O)(OH)–O–P(O)(OH)–O–P(O)(OH)$_2$,
i) a C$_{2-7}$acyl,
j) an aminoacyl,
k) a C$_{1-6}$-alkylene-oxy-acyl, and
l) a –C(O)–O-C$_{1-6}$alkyl,

2) R^2 is hydrogen;
3) R^3 is hydrogen or cyano;
4) Y is selected from among
a) –OH,
b) –O~, when R^1 is –P(O)(OR^{1c})~, where R^{1c} is defined above,
c) –O(C$_{2-7}$acyl),
d) –O(aminoacyl), and
d) –O(C$_{1-6}$-alkylene-oxyC$_{2-7}$acyl);
5) X is –O–;
6) (Z) is selected from among



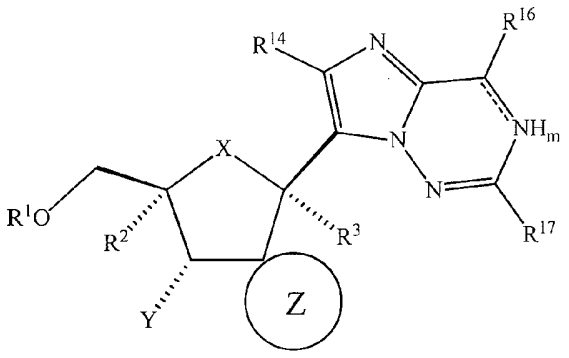
where * represents the point of attachment to the 2'-carbon; and
7a) m is 0, ----- is a double-bond,
7a1) R^{16} is selected from among
i) –NH$_2$,
ii) –NH(C$_{1-6}$alkyl),
iii) –NH(C$_{2-7}$acyl),
iv) –O(C$_{1-6}$alkyl),
v) –O(C$_{2-7}$acyl),
vi) –O(C$_{1-6}$alkyleneoxyacyl), and
vii) –O–C(O)–O-C$_{1-6}$alkyl,
viii) –S(C$_{1-6}$alkyl),
ix) –OC$_{1-3}$alkaryl, and

7a2) R^{17} is selected from among
i) hydrogen,
ii) $-NH_2$ and
iii) $-NH(C_{1-6}alkyl)$, or

7b) m is 1, ----- is a single-bond,
7b1) R^{16} is =O; and
7b2) R^{17} is selected from among
i) $-NH_2$ and
ii) $-NH(C_{1-6}alkyl)$ and

7c) independent of the value of m, R^{14} and R^{15} are independently selected from among
i) hydrogen,
ii) halo,
iii) cyano,
iv) $-C(O)NH_2$,
iv) $C_{1-6}alkyl$,
vii) vinyl, and
viii) ethynyl.

A twenty-third aspect of the third embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-3-10**



I-3-10

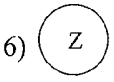
wherein

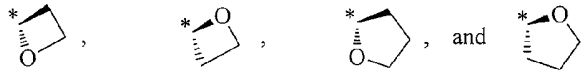
1) R^1 is selected from among:
a) hydrogen,
b) $-P(O)(OH)_2$,
c) $-P^*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})$,
wherein
R^{1a} is
i) hydrogen or
ii) aryl,
R^{1b} is
i) hydrogen or
ii) $C_{1-6}alkyl$, and

R^{1c} is

i) hydrogen
ii) alkyl,
iii) cycloalkyl, or
iv) $-C_{1-3}$alkaryl,

d) a 1,3,2-dioxaphosphinane-2-oxide,
e) a 4*H*-benzo[d][1,3,2]dioxaphosphinine-2-oxide,
f) $-P^*(O)(OR^{1c})\sim$, when Y is $-O\sim$, where R^{1c} is defined above,
g) $-P(O)(OH)-O-P(O)(OH)_2$,
h) $-P(O)(OH)-O-P(O)(OH)-O-P(O)(OH)_2$,
i) a C_{2-7}acyl,
j) an aminoacyl,
k) a C_{1-6}-alkylene-oxy-acyl, and
l) a $-C(O)-O-C_{1-6}$alkyl,

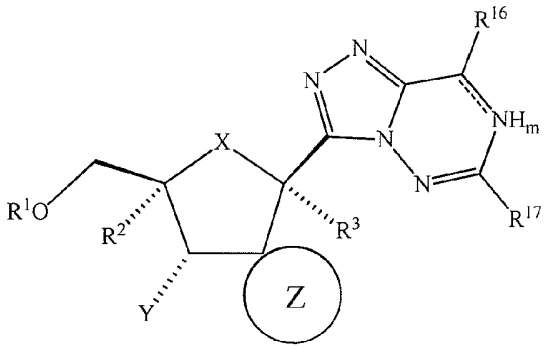
2) R^2 is hydrogen;
3) R^3 is hydrogen or cyano;
4) Y is selected from among
a) –OH,
b) $-O\sim$, when R^1 is $-P(O)(OR^{1c})\sim$, where R^{1c} is defined above,
c) $-O(C_{2-7}$acyl),
d) –O(aminoacyl), and
e) $-O(C_{1-6}$-alkylene-oxyC_{2-7}acyl);
5) X is –O–;
6)  is selected from among



where * represents the point of attachment to the 2'-carbon; and
7a) m is 0, ----- is a double-bond,
7a1) R^{16} is selected from among
i) $-NH_2$,
ii) $-NH(C_{1-6}$alkyl),
iii) $-NH(C_{2-7}$acyl),
iv) $-O(C_{1-6}$alkyl),
v) $-O(C_{2-7}$acyl),
vi) $-O(C_{1-6}$alkyleneoxyacyl), and
vii) $-O-C(O)-O-C_{1-6}$alkyl,
viii) $-S(C_{1-6}$alkyl), and
ix) $-OC_{1-3}$alkaryl,
7a2) R^{17} is selected from among
i) hydrogen,
ii) $-NH_2$ and
iii) $-NH(C_{1-6}$alkyl), or
7b) m is 1, ----- is a single-bond,
7b1) R^{16} is =O;
7b2) R^{17} is selected from among
i) $-NH_2$ and
ii) $-NH(C_{1-6}$alkyl) and
7c) independent of the value of m, R^{14} is selected from among

i) hydrogen,
ii) halo,
iii) cyano,
iv) $-C(O)NH_2$,
iv) C_{1-6}alkyl,
vii) vinyl, and
viii) ethynyl.

A twenty-fourth aspect of the third embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-3-11**

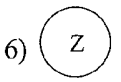


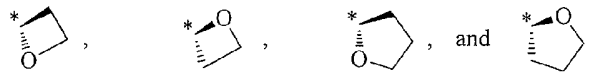
I-3-11

wherein

1) R^1 is selected from among:
a) hydrogen,
b) $-P(O)(OH)_2$,
c) $-P^*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})$,
wherein
R^{1a} is
i) hydrogen or
ii) aryl,
R^{1b} is
i) hydrogen or
ii) C_{1-6}alkyl, and
R^{1c} is
i) hydrogen
ii) alkyl,
iii) cycloalkyl, or
iv) $-C_{1-3}$alkaryl,
d) a 1,3,2-dioxaphosphinane-2-oxide,
e) a 4*H*-benzo[d][1,3,2]dioxaphosphinine-2-oxide,
f) $-P^*(O)(OR^{1c})$~, when Y is –O~, where R^{1c} is defined above,
g) $-P(O)(OH)-O-P(O)(OH)_2$,
h) $-P(O)(OH)-O-P(O)(OH)-O-P(O)(OH)_2$,
i) a C_{2-7}acyl,

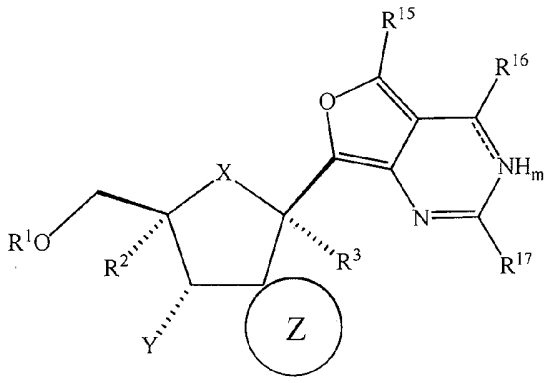
j) an aminoacyl,
k) a C_{1-6}-alkylene-oxy-acyl, and
l) a –C(O)–O-C_{1-6}alkyl,

2) R^2 is hydrogen;
3) R^3 is hydrogen or cyano;
4) Y is selected from among
a) –OH,
b) –O~, when R^1 is –P(O)(OR^{1c})~, where R^{1c} is defined above,
c) –O(C_{2-7}acyl),
d) –O(aminoacyl), and
e) –O(C_{1-6}-alkylene-oxyC_{2-7}acyl);
5) X is –O–;
6)  is selected from among



where * represents the point of attachment to the 2'-carbon; and
7a) m is 0, ----- is a double-bond,
7a1) R^{16} is selected from among
i) –NH_2,
ii) –NH(C_{1-6}alkyl),
iii) –NH(C_{2-7}acyl),
iv) –O(C_{1-6}alkyl),
v) –O(C_{2-7}acyl),
vi) –O(C_{1-6}alkyleneoxyacyl),
vii) –O–C(O)–O-C_{1-6}alkyl,
viii) –S(C_{1-6}alkyl), and
ix) –OC_{1-3}alkaryl, and
7a2) R^{17} is selected from among
i) hydrogen,
ii) –NH_2 and
iii) –NH(C_{1-6}alkyl), or
7b) m is 1, ----- is a single-bond,
7b1) R^{16} is =O;
7b2) R^{17} is selected from among
i) –NH_2 and
ii) –NH(C_{1-6}alkyl).

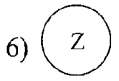
A twenty-fifth aspect of the third embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-3-12**

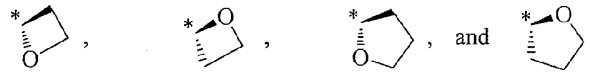


I-3-12

wherein

1) R^1 is selected from among:
   a) hydrogen,
   b) $-P(O)(OH)_2$,
   c) $-P^*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})$,
   wherein
   R^{1a} is
      i) hydrogen or
      ii) aryl,
   R^{1b} is
      i) hydrogen or
      ii) C_{1-6}alkyl, and
   R^{1c} is
      i) hydrogen
      ii) alkyl,
      iii) cycloalkyl, or
      iv) $-C_{1-3}$alkaryl,
   d) a 1,3,2-dioxaphosphinane-2-oxide,
   e) a 4*H*-benzo[d][1,3,2]dioxaphosphinine-2-oxide,
   f) $-P^*(O)(OR^{1c})\sim$, when Y is $-O\sim$, where R^{1c} is defined above,
   g) $-P(O)(OH)-O-P(O)(OH)_2$,
   h) $-P(O)(OH)-O-P(O)(OH)-O-P(O)(OH)_2$,
   i) a C_{2-7}acyl,
   j) an aminoacyl,
   k) a C_{1-6}-alkylene-oxy-acyl, and
   l) a $-C(O)-O-C_{1-6}$alkyl,
2) R^2 is hydrogen;
3) R^3 is hydrogen or cyano;
4) Y is selected from among
   a) –OH,
   b) $-O\sim$, when R^1 is $-P(O)(OR^{1c})\sim$, where R^{1c} is defined above,
   c) $-O(C_{2-7}$acyl),
   d) –O(aminoacyl), and
   e) $-O(C_{1-6}$-alkylene-oxyC_{2-7}acyl);
5) X is –O–;

6)  is selected from among



where * represents the point of attachment to the 2'-carbon; and

7a) m is 0, ----- is a double-bond,

7a1) R^{16} is selected from among

i) $-NH_2$,

ii) $-NH(C_{1-6}alkyl)$,

iii) $-NH(C_{2-7}acyl)$,

iv) $-O(C_{1-6}alkyl)$,

v) $-O(C_{2-7}acyl)$,

vi) $-O(C_{1-6}alkyleneoxyacyl)$,

vii) $-O-C(O)-O-C_{1-6}alkyl$,

viii) $-S(C_{1-6}alkyl)$, and

ix) $-OC_{1-3}alkaryl$,

7a2) R^{17} is selected from among

i) hydrogen,

ii) $-NH_2$ and

iii) $-NH(C_{1-6}alkyl)$, or

7b) m is 1, ----- is a single-bond,

7b1) R^{16} is =O;

7b2) R^{17} is selected from among

i) $-NH_2$ and

ii) $-NH(C_{1-6}alkyl)$ and

7c) independent of the value of m, R^{15} is selected from among

i) hydrogen,

ii) halo,

iii) cyano,

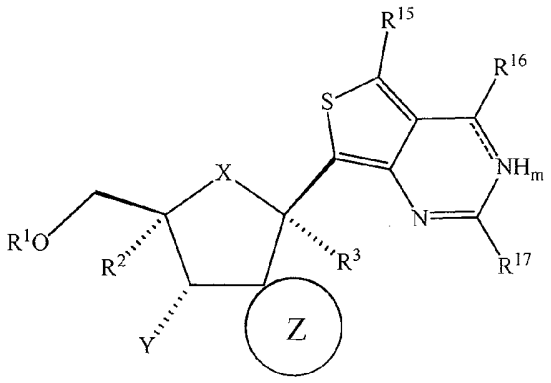
iv) $-C(O)NH_2$,

iv) $C_{1-6}alkyl$,

vii) vinyl, and

viii) ethynyl.

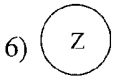
A twenty-sixth aspect of the third embodiment is directed to a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I-3-13**

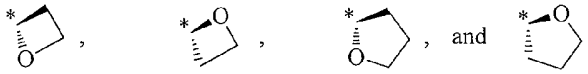


I-3-13

wherein

1) R^1 is selected from among:
   a) hydrogen,
   b) $-P(O)(OH)_2$,
   c) $-P^*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})$,
   wherein
   R^{1a} is
      i) hydrogen or
      ii) aryl,
   R^{1b} is
      i) hydrogen or
      ii) C_{1-6}alkyl, and
   R^{1c} is
      i) hydrogen
      ii) alkyl,
      iii) cycloalkyl, or
      iv) $-C_{1-3}$alkaryl,
   d) a 1,3,2-dioxaphosphinane-2-oxide,
   e) a 4*H*-benzo[d][1,3,2]dioxaphosphinine-2-oxide,
   f) $-P^*(O)(OR^{1c})\sim$, when Y is $-O\sim$, where R^{1c} is defined above,
   g) $-P(O)(OH)-O-P(O)(OH)_2$,
   h) $-P(O)(OH)-O-P(O)(OH)-O-P(O)(OH)_2$,
   i) a C_{2-7}acyl,
   j) an aminoacyl,
   k) a C_{1-6}-alkylene-oxy-acyl, and
   l) a $-C(O)-O-C_{1-6}$alkyl,
2) R^2 is hydrogen;
3) R^3 is hydrogen or cyano;
4) Y is selected from among
   a) –OH,
   b) $-O\sim$, when R^1 is $-P(O)(OR^{1c})\sim$, where R^{1c} is defined above,
   c) $-O(C_{2-7}$acyl),
   d) –O(aminoacyl), and
   e) $-O(C_{1-6}$-alkylene-oxyC_{2-7}acyl);
5) X is –O–;

6)  is selected from among



where * represents the point of attachment to the 2'-carbon; and

7a) m is 0, ----- is a double-bond,

7a1) R^{16} is selected from among

i) $-NH_2$,

ii) $-NH(C_{1-6}alkyl)$,

iii) $-NH(C_{2-7}acyl)$,

iv) $-O(C_{1-6}alkyl)$,

v) $-O(C_{2-7}acyl)$,

vi) $-O(C_{1-6}alkyleneoxyacyl)$,

vii) $-O-C(O)-O-C_{1-6}alkyl$,

viii) $-S(C_{1-6}alkyl)$, and

ix) $-OC_{1-3}alkaryl$,

7a2) R^{17} is selected from among

i) hydrogen,

ii) $-NH_2$ and

iii) $-NH(C_{1-6}alkyl)$, or

7b) m is 1, ----- is a single-bond,

7b1) R^{16} is =O;

7b2) R^{17} is selected from among

i) $-NH_2$ and

ii) $-NH(C_{1-6}alkyl)$ and

7c) independent of the value of m, R^{15} is selected from among

i) hydrogen,

ii) halo,

iii) cyano,

iv) $-C(O)NH_2$,

iv) $C_{1-6}alkyl$,

vii) vinyl, and

viii) ethynyl.

Dosage, Administration, and Use

In the embodiments of this section, the expression "**Compound I**" is meant to encompass a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof represented by formula **I** notwithstanding the excluded subject matter found in the Definitions.

A fourth embodiment is directed to a composition comprising compound **I**.

A first aspect of the fourth embodiment is directed to a composition for treating a subject infected with any one of hepatitis C virus, hepatitis B virus, Hepatitis A virus, West Nile virus, yellow fever virus, dengue virus, rhinovirus, polio virus, bovine viral diarrhea virus, Japanese encephalitis virus, or those viruses

belonging to the groups of Pestiviruses, hepaciviruses, or flavaviruses, said composition comprising an effective amount of compound **I**.

A second aspect of the fourth embodiment is directed to a composition for treating a subject infected with a hepatitis C virus, which comprises an effective amount of compound **I** and optionally a pharmaceutically acceptable medium.

A third aspect of the fourth embodiment is directed to a composition for treating a subject infected with a dengue virus, which comprises an effective amount of compound **I** and optionally a pharmaceutically acceptable medium.

A fourth aspect of the fourth embodiment is directed to a composition for treating a subject infected with any one of a hepatitis B virus, a Hepatitis A virus, a West Nile virus, a yellow fever virus, a rhinovirus, polio virus, a bovine viral diarrhea virus, and a Japanese encephalitis virus, which comprises an effective amount of compound **I** and a pharmaceutically acceptable medium.

A fifth aspect of the fourth embodiment is directed to a composition for treating a subject infected with a hepatitis C virus, which comprises an effective amount of compound **I** and a pharmaceutically acceptable medium.

A sixth aspect of the fourth embodiment is directed to a composition for treating a subject infected with a dengue virus, which comprises an effective amount of compound **I** and a pharmaceutically acceptable medium.

A seventh aspect of the fourth embodiment is directed to a composition for treating a subject infected with a virus from any one of viruses belonging to the groups of Pestiviruses, hepaciviruses, or flavaviruses, which comprises an effective amount of compound **I** and a pharmaceutically acceptable medium.

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

Compound **I** together with one or more conventional excipients, carriers, or diluents, may be placed into the form of pharmaceutical compositions and unit dosages. The pharmaceutical compositions and unit dosage forms may be

comprised of conventional ingredients in conventional proportions, with or without additional active compounds and the unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. The pharmaceutical compositions may be employed as solids, such as tablets or filled capsules, semisolids, powders, sustained release formulations, or liquids such as suspensions, emulsions, or filled capsules for oral use; or in the form of suppositories for rectal or vaginal administration. A typical preparation will contain from about 5% to about 95% active compound or compounds (w/w).

As noted above, the term "effective amount" as used herein means an amount required to reduce symptoms of the disease in a subject. The dose will be adjusted to the individual requirements in each particular case. That dosage can vary within wide limits depending upon numerous factors such as the severity of the disease to be treated, the age and general health condition of the patient, other medicaments with which the patient is being treated, the route and form of administration and the preferences and experience of the medical practitioner involved. For oral administration, a daily dosage of between about 0.001 and about 10 g, including all values in between, such as 0.001, 0.0025, 0.005, 0.0075, 0.01, 0.025, 0.050, 0.075, 0.1, 0.125, 0.150, 0.175, 0.2, 0.25, 0.3, 0.4, 0.5, 0.6, 0.7 0.75, 0.8, 0.9, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, and 9.5, per day should be appropriate in monotherapy and/or in combination therapy. A particular daily dosage is between about 0.01 and about 1 g per day, including all incremental values of 0.01 g (i.e., 10 mg) in between, a preferred daily dosage about 0.01 and about 0.8 g per day, more preferably about 0.01 and about 0.6 g per day, and most preferably about 0.01 and about 0.25 g per day, each of which including all incremental values of 0.01 g in between. Generally, treatment is initiated with a large initial "loading dose" to rapidly reduce or eliminate the virus following by a decreasing the dose to a level sufficient to prevent resurgence of the infection. One of ordinary skill in treating diseases described herein will be able, without undue experimentation and in reliance on knowledge, experience and the disclosures of this application, to ascertain a effective amount of the compound disclosed herein for a given disease and patient.

Compound **I** can be administered alone but will generally be administered in admixture with one or more suitable pharmaceutical excipients, diluents or carriers

selected with regard to the intended route of administration and standard pharmaceutical practice.

Solid form preparations include, for example, powders, tablets, pills, capsules, suppositories, and dispersible granules. A solid carrier may be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. In powders, the carrier generally is a finely divided solid which is a mixture with the finely divided active component. In tablets, the active component generally is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired. Suitable carriers include but are not limited to magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. Solid form preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like. Examples of solid formulations are exemplified in EP 0524579; US 2002/0142050; US 2004/0224917; US 2005/0048116; US 2005/0058710; US 2006/0034937; US 2006/0057196; US 2006/0188570; US 2007/0026073; US 2007/0059360; US 2007/0077295; US 2007/0099902; US 2008/0014228; US 6,267,985; US 6,294,192; US 6,383,471; US 6,395,300; US 6,569,463; US 6,635,278; US 6,645,528; US 6,923,988; US 6,932,983; US 7,060,294; and US 7,462,608.

Liquid formulations also are suitable for oral administration include liquid formulation including emulsions, syrups, elixirs and aqueous suspensions. These include solid form preparations which are intended to be converted to liquid form preparations shortly before use. Examples of liquid formulation are exemplified in U.S. Patent Nos. 3,994,974; 5,695,784; and 6,977,257. Emulsions may be prepared in solutions, for example, in aqueous propylene glycol solutions or may contain emulsifying agents such as lecithin, sorbitan monooleate, or acacia. Aqueous suspensions can be prepared by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well known suspending agents.

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

Compound I may be independently formulated for vaginal administration. Pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate. Certain of these formulations may also be used in conjunction with a condom with or without a spermicidal agent.

Suitable formulations along with pharmaceutical carriers, diluents and excipients are described in *Remington: The Science and Practice of Pharmacy* **1995,** edited by E. W. Martin, Mack Publishing Company, 19th edition, Easton, Pennsylvania. A skilled formulation scientist may modify the formulations within the teachings of the specification to provide numerous formulations for a particular route of administration without rendering compositions containing the compounds contemplated herein unstable or compromising their therapeutic activity.

Additionally, compound I may be independently formulated in conjunction with liposomes, micelles, or complexed to or entrapped in a protein matrix, such as albumin. As to liposomes, it is contemplated that the compound I can be formulated in a manner as disclosed in U.S. Patent Nos. 4,797,285; 5,013,556; 5,077,056; 5,077,057; 5,154,930; 5,192,549; 5,213,804; 5,225,212; 5,277,914; 5,316,771; 5,376,380; 5,549,910; 5,567,434; 5,736,155; 5,827,533; 5,882,679; 5,891,468; 6,060,080; 6,132,763; 6,143,321; 6,180,134; 6,200,598; 6,214,375; 6,224,903; 6,296,870; 6,653,455; 6,680,068; 6,726,925; 7,060,689; and 7,070,801. As to micelles, it is contemplated that compound I can be formulated in a manner as disclosed in U.S. Patent Nos. 5,145,684 and 5,091,188. As to a protein matrix, it is contemplated that compound I can be complexed to or entrapped in a protein matrix as disclosed in any one of U.S. Patent Nos. 5,439,686; 5,498,421; 6,096,331; 6,506,405; 6,537,579; 6,749,868; 6,753,006; and 7,820,788.

A fifth embodiment is directed to a use of compound I for the manufacture of a medicament for the treatment of any condition the result of an infection by any one of the following viral agents: hepatitis C virus, West Nile virus, yellow fever

virus, dengue virus, rhinovirus, polio virus, hepatitis A virus, bovine viral diarrhea virus and Japanese encephalitis virus.

A first aspect of the fifth embodiment is directed to a use of compound **I** for the manufacture of a medicament for the treatment of a hepatitis C virus.

A second aspect of the fifth embodiment is directed to a use of compound **I** for the manufacture of a medicament for the treatment of a dengue virus.

A third aspect of the fifth embodiment is directed to a use of compound **I** for the manufacture of a medicament for the treatment of any condition the result of an infection by any one of the following viral agents: a West Nile virus, a yellow fever virus, a rhinovirus, a polio virus, a hepatitis A virus, a bovine viral diarrhea virus, and a Japanese encephalitis virus.

A fourth aspect of the fifth embodiment is directed to a use of compound **I** for the manufacture of a medicament for the treatment of any condition the result of an infection by a viral agent from any one of viruses belonging to the groups of Pestiviruses, hepaciviruses, or flavaviruses.

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

A sixth embodiment is directed to a method of treating a subject infected with any one of a hepatitis C virus, a West Nile virus, a yellow fever virus, a degue virus, a rhinovirus, a polio virus, a hepatitis A virus, a bovine viral diarrhea virus, a Japanese encephalitis virus or those viruses belonging to the groups of Pestiviruses, hepaciviruses, or flavaviruses, said method comprising administering an effective amount of compound **I** to the subject.

A first aspect of the sixth embodiment is directed to a method of treating a subject infected with a hepatitis C virus, said method comprising administering an effective amount of compound **I** to the subject.

A second aspect of the sixth embodiment is directed to a method of treating a subject infected with a dengue virus, said method comprising administering an

effective amount of compound **I** to the subject. A third aspect of the sixth embodiment is directed to a method of treating a subject injected with any one of a West Nile virus, a yellow fever virus, a rhinovirus, a polio virus, a hepatitis A virus, a bovine viral diarrhea virus, a Japanese encephalitis virus or those viruses belonging to the groups of Pestiviruses, hepaciviruses, or flavaviruses, said method comprising administering an effective amount of compound **I** to the subject.

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

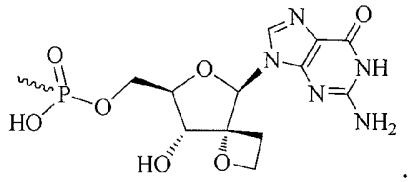
As noted above, the term "subject" means a mammal, which includes, but is not limited to, cattle, pigs, sheep, buffalo, llama, dogs, cats, mice, rats, monkeys, and humans, preferably the subject is a human. It is contemplated that in the method of treating a subject thereof of the ninth embodiment can be any of the compounds contemplated herein, either alone or in combination with another compound disclosed herein.

Therapeutic efficacy can be ascertained from tests of liver function including, but not limited to protein levels such as serum proteins (e.g., albumin, clotting factors, alkaline phosphatase, aminotransferases (e.g., alanine transaminase, aspartate transaminase), 5'-nucleosidase, γ-glutaminyltranspeptidase, etc.), synthesis of bilirubin, synthesis of cholesterol, and synthesis of bile acids; a liver metabolic function, including, but not limited to, carbohydrate metabolism, amino acid and ammonia metabolism. Alternatively the therapeutic effectiveness may be monitored by measuring HCV-RNA. The results of these tests will allow the dose to be optimized.

A fourth aspect of the sixth embodiment is directed to a method of treating a subject infected with hepatitis C virus or a subject infected with a dengue virus, said method comprising administering to the subject an effective amount of compound **I** and an effective amount of another antiviral agent; wherein the administration is concurrent or alternative. It is understood that the time between alternative administration can range between 1-24 hours, which includes any sub-range in

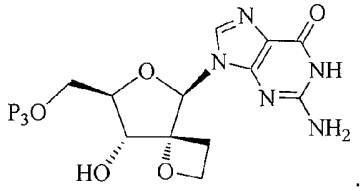
between including, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, and 23 hours. It will be understood that the effective amount of compound **I** and the effective amount of another antiviral agent can be formulated in the same dosage form or formulated in separate dosage forms.

A fifth aspect of the sixth embodiment comprises adding to the 3'-terminus of an HCV RNA strand or a DENV RNA strand a radical or its salt thereof represented by



where ~~~ is the point of attachment to the 3'-terminus. It is understood that addition of said compound to the nascent RNA strand will prevent or substantially increase the likelihood that propagation of the RNA strand having said compound added thereto will come to an end.

A seventh aspect of the sixth embodiment comprises increasing an intracellular concentration of a triphosphate (P_3) compound or its salt thereof represented by



in a cell infected with HCV or DENV.

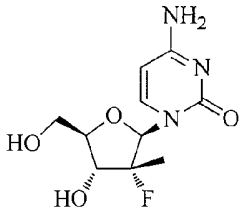
When compound **I** is administered in combination with another antiviral agent the activity may be increased over the activity exhibited for compound **I** alone. When the treatment is combination therapy, such administration may be concurrent or sequential with respect to that of the nucleoside derivatives. "Concurrent administration" as used herein thus includes administration of the agents at the same time or at different times. Administration of two or more agents at the same time can be achieved by a single formulation containing two or more active ingredients or

by substantially simultaneous administration of two or more dosage forms with a single active agent.

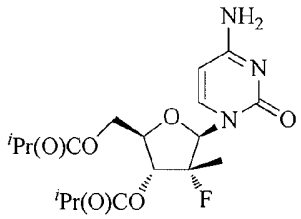
It will be understood that references herein to treatment extend to prophylaxis as well as to the treatment of existing conditions.

Examples of "another antiviral agent" include, but are not limited to: HCV NS3 protease inhibitors (see EP 1881001, US 2003/0187018, US 2005/0267018, US 2003/0119752, US 2003/0187018, US 2005/0090432, US 2009/0291902, US 2005/0267018, US 2005/0267018, US 2011/0237621, US 2009/0281141, US 2009/0105302, US 2009/0062311, US 2009/0281140, US 2007/0054842, US 2008/0108617, and US 2008/0108617); HCV NS5B Inhibitors (see US 2004/0229840, US 2005/0154056, US 2005/0098125, US 2006/0194749, US 2006/0241064, US 2006/0293306, US 2006/0040890, US 2006/0040927, US 2006/0166964, US 2007/0275947, US 6,784,166, US 2007/0275930, US 2002/0147160, US 2002/0147160, US 2003/0176433, US 2004/0024190, US 2005/0043390, US 2005/0026160, US 2004/0171570, US 2005/0130923, US 2008/0146788, US 2007/0123484, US 2007/0024277, US 2007/0004669, US 2004/0142989, US 2004/0142993, US 2006/0004063, US 2006/0234962, US 2007/0231318, US 2007/0142380, WO 2004/096210, US 2007/0135363, WO 2005/103045, US 2008/0021047, US 2007/0265222, US 2006/0046983, US 2008/0280842, WO 2006065590, US 2006/0287300, WO 2007039142, WO 2007039145, US 2007/0232645, US 2007/0232627, WO 2007088148, WO 2007092000, and US 2010/0234316); HCV NS4 Inhibitors (see US 2005/0228013 and US 2007/0265262); HCV NS5A Inhibitors (see US 2006/0276511, US 2007/0155716, US 2008/0182863, US 2009/0156595, and US 2008/0182863); Toll-like receptor agonists (see US 2007/0197478); and other inhibitors (see US 2003/0207922, US 2006/0094706, US 2006/0122154, US 2005/0069522, US 2005/0096364, US 2005/0069522, US 2005/0096364, and US 2005/0215614); PSI-6130 (US 7,429,572); RG7128 (US 7,754,699); Compound A (disclosed in US 2010/0081628, see also compound 19a (PSI-938) and 19b disclosed in the same application, which are individual diastereomers of compound A); PSI-7977 (US 7,964,580, claim 8) and PSI-7976 (disclosed in US 2010/0016251 and US 2010/0298257 (12/783,680) (PSI-7977 (Sp-4) and PSI-7976 (Rp-4)); PSI-353661 (disclosed in US 2010/0279973, see compound 11); telaprevir (also known as VX-950, which is disclosed in US 2010/0015090); boceprevir (disclosed in US

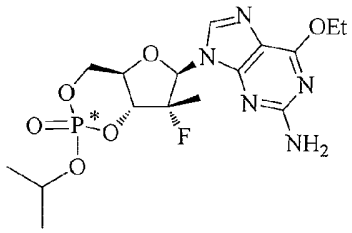
2006/0276405); BMS-790052 (disclosed in US 2008/0050336, see also US 2009/0041716); ITMN-191 (disclosed in US 2009/0269305 at Example 62-1); ANA-598 (shown below and identified as compound 3i in F. Ruebasam et al. Biorg. Med. Chem. Lett. (2008) 18: 3616-3621; and TMC435 (formerly known as TMC435350).



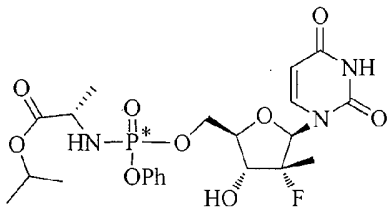
PSI-6130



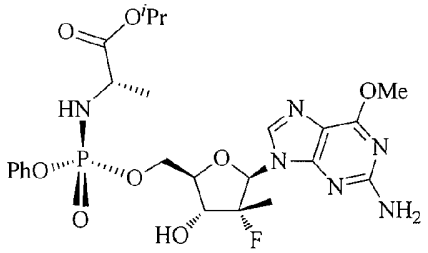
RG7128



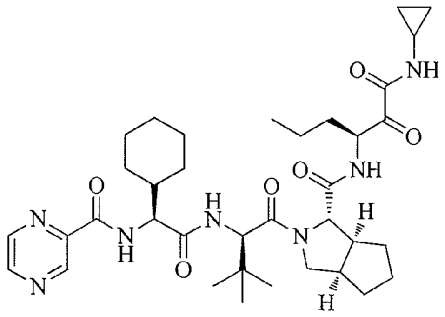
Compound A



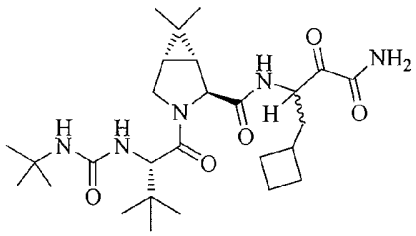
PSI-7977 (Sp-diastereomer)
PSI-7976 (Rp-diastereomer)



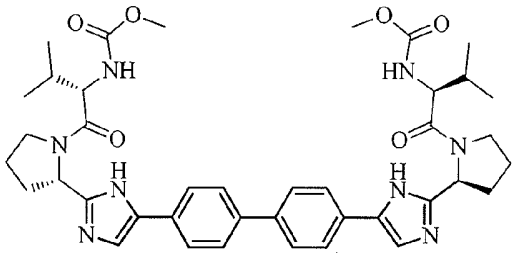
PSI-353661



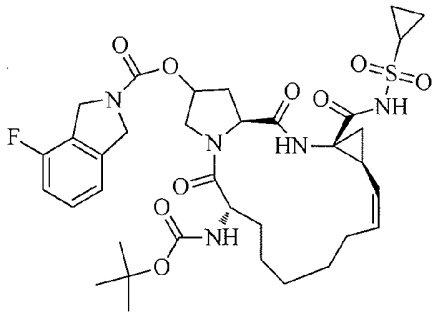
Telaprevir (VX-950)



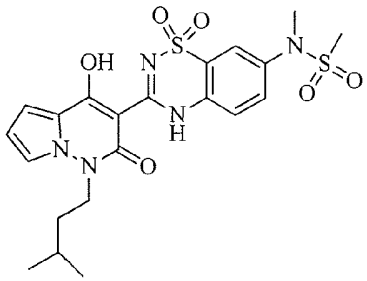
Boceprevir



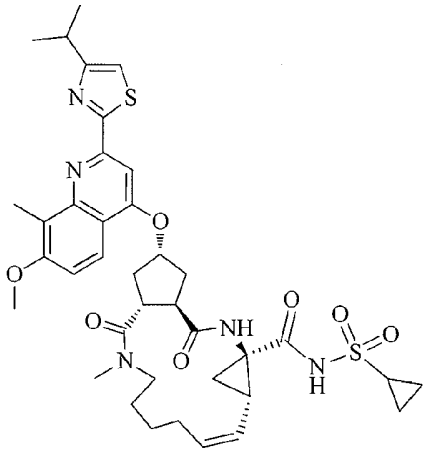
BMS-790052



ITMN-191



ANA-598



TMC435

The antiviral agents can be formulated in a manner known to one of ordinary skill. The respective patent documents provide guidance for the respective formulations. The preferred dosage forms of the antiviral agents are those that are approved by the FDA. However, not to be limited, contemplated dosage forms of the antiviral agents are contemplated as follows: RG7128 (500 mg, 1000 mg, or 1500 mg); Compound A (5 mg to 1000 mg and values inbetween); PSI-7977 (100 mg, 200 mg, or 400 mg); A dosage form for VX-950 is disclosed in McHutchison et al. N. Engl. J. Med. (2009) 360(18): 1827-1838; see also WO 2009/038663; Boceprevir (WO 2009/038663).

Additional examples of "another antiviral agent" and contemplated dosages are identified in the following table.

Drug Name	Drug Category	Company	Clinical Phase	Dosage
RG7128	Polymerase Inhibitor	Roche in collaboration with	Phase I	500 mg BID,100

Drug Name	Drug Category	Company	Clinical Phase	Dosage
		Pharmasset		mg BID
RG7227	Protease Inhibitor	Roche in collaboration with Pharmasset	Phase I	100 mg TID, 200 mg TID
Telaprevir (VX-950)	Protease Inhibitor	Vertex	Phase II	N/A
VX-222	Polymerase Inhibitor	Vertex	Phase II	N/A
BMS 790052	NS5a Inhibitor	Bristol-Myers Squibb	Phase II	60 mg once a day or 600 mg twice a day
BMS 65032	Protease Inhibitor	Bristol-Myers Squibb	Phase II	60 mg once a day or 600 mg twice a day
BMS-824393	NS5A Inhibitor	Bristol-Myers Squibb	Phase I	N/A
INX-189	HCV Polymerase Inhibitor	Inhibitex	Phase I	from 3 mg to 100 mg, once a day
PSI-938	Polymerase Inhibitor	Pharmasset	Phase I	300 mg once a day
PPI-461	NS5A Inhibitor	Presidio Pharmaceuticals	Phase I	four single doses followed by a 5-day, once-a-day dose
IDX375	Polymerase Inhibitor	Idenix	Phase I	25 mg once daily (QD), 50 mg QD, 100 mg QD, 200 mg QD, or 200 mg twice a day
ABT-072	Polymerase Inhibitor	Abbott	Phase I	N/A

Drug Name	Drug Category	Company	Clinical Phase	Dosage
Clemizole	NS4B Inhibitor	Eiger BioPharmaceuticals	Phase I	N/A
MK-3281	Polymerase Inhibitor	Merck	Phase I	N/A
PSI-7851	Polymerase Inhibitor	Pharmasset	Phase I	50mg, 100mg, 200mg, or 400mg
ABT-450 HCV	Protease Inhibitor	Abbott/Enanta	Phase I	N/A
VX-813	Protease Inhibitor	Vertex	Phase I	N/A
PHX1766	Protease Inhibitor	Phenomix	Phase I	400mg BID or 800mg BID
ABT-333	Polymerase Inhibitor	Abbott	Phase I	N/A
VX-916	HCV Polymerase Inhibitor	Vertex	Phase I	N/A
RG7128	Polymerase Inhibitor	Pharmasset/Genentech	Phase I	500 or 100mg BID
VX-500	HCV Protease Inhibitor	Vertex	Phase I	N/A
Filibuvir (PF-00868554)	HCV Polymerase Inhibitor	Pfizer	Phase II	200, 300, or 0500 mg BID (twice a day)
ACH-1625	Protease Inhibitor	Achillion	Phase II	200 or 600 mg
GS-9256	Protease Inhibitor	Gilead	Phase II	N/A
BI 201335	Protease Inhibitor	Boehringer Ingelheim Pharma	Phase II	240mg (once-a-day) or 240 mg (twice-a-day)
VX-222	Polymerase Inhibitor	Vertex	Phase II	250, 500, or 750 mg twice-a-day; 1500 mg once-a-day
RG7227 (Danoprevir)	Protease Inhibitor	InterMune/Genentech	Phase II	N/A
ANA598	Polymerase	Anadys	Phase II	First day

Drug Name	Drug Category	Company	Clinical Phase	Dosage
	Inhibitor	Pharmaceuticals		800 mg BID, followed by 200 or 400 mg twice daily
Vaniprevir (MK-7009)	HCV Protease Inhibitor	Merck	Phase II	300 or 600 mg twice a day; 300 or 600 mg once-a-day
A-832	NS5A Inhibitor	ArrowTherapeutics	Phase II	N/A
GS 9190	Polymerase Inhibitor	Gilead	Phase II	N/A
VX-759	Polymerase Inhibitor	Vertex	Phase II	400 mg TID, 800 mg BID, or 800 mg TID
SCH900518 (Narlaprevir)	Protease Inhibitor	Schering/Merck	Phase II	N/A
BI 207127	Polymerase Inhibitor	Boehringer Ingelheim Pharma	Phase II	N/A
PSI-7977	Polymerase Inhibitor	Pharmasset	Phase IIa	100, 200, or 400 mg once-a-day
TMC435	Protease Inhibitor	Medivir/Tibotec	Phase IIa	N/A
BMS 791325	Polymerase Inhibitor	Bristol-Myers Squibb	Phase IIa	N/A
BMS 650032	Protease Inhibitor	Bristol-Myers Squibb	Phase IIa/b	N/A
BMS 790052	NS5a Inhibitor	Bristol-Myers Squibb	Phase IIb	N/A
Boceprevir (SCH 503034)	Protease Inhibitor	Schering	Phase III	800 mg three times a day
Telaprevir (VX 950)	Protease Inhibitor	Vertex	Phase III	750 mg every 8 hours; 1125 mg dose every 12 hours;

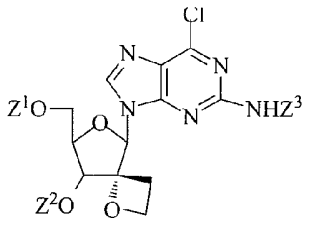
Drug Name	Drug Category	Company	Clinical Phase	Dosage
BMS-824393	Type Unknown	Bristol-Myers Squibb	Phase I	N/A
SCY-635	Cyclophilin Inhibitor	SCYNEXIS	Phase I	up to 900 mg/day
ANA773	TLR Agonist	Anadys Pharmaceuticals	Phase I	800, 1200, 1600, or 200 mg every other day
CYT107	Immunomodulator	Cytheris	Phase I	N/A
CF102	A3AR Agonist	CAN-FITE	Phase I	N/A
IMO-2125	TLR9 Agonist	Idera Pharmaceuticals	Phase I	N/A
Bavituximab (formerly Tarvacin)	Anti-Phospholipid Therapy	Peregrine	Phase I	N/A
NOV-205	Immunomodulator	Novelos Therapeutics	Phase I	N/A
SD-101	TLR9 Agonist	Dynavax	Phase Ib	N/A
Miravirsen Formerly (SPC3649-LNA-antimiR™-122)	microRNA	Santaris Pharma	Phase II	up to 12 mg/kg
CTS-1027	Anti-inflammatory	Conatus	Phase II	N/A
Oglufanide disodium	Immunomodulator	Implicit Bioscience	Phase II	N/A
Alinia (nitazoxanide)	Thiazolides	Romark	Phase II	500 mg twice daily
SCV-07	Broad Spectrum Immune Stimulator	SciClone	Phase II	N/A
MitoQ (mitoquinone)	Inflammation/ Fibrosis Inhibitor	Antipodean Pharmaceuticals	Phase II	N/A
Debio 025	Cyclophilin Inhibitor	Debio	Phase II	600 to 1000 mg/day
PF-03491390 (Formerly IDN-6556)	Pancaspase Inhibitor	Pfizer Pharmaceuticals	Phase II	5 mg to 400 mg daily (given 1 to 3 times a day)

According to the FDA-approved label dated October 8, 2010, the recommended dose of COPEGUS (ribavirin) tablets depends on body weight and the HCV genotype to be treated, as shown in the following table.

HCV Genotype	PEGASYS Dose*	COPEGUS Dose	Duration
Genotypes 1, 4	180 μg	<75 kg = 1000 mg ≥75 kg = 1200 mg	48 weeks 48 weeks
Genotypes 2, 3	180 μ g	800 mg	24 weeks
Genotypes 2 and 3 showed no increased response to treatment beyond 24 weeks. *See PEGASYS Package Insert for further details on PEGASYS dosing and administration			

The COPEGUS label further discloses that the recommended duration of treatment for patients previously untreated with ribavirin and interferon is 24 to 48 weeks. The daily dose of COPEGUS is 800 mg to 1200 mg administered orally in two divided doses. The dose should be individualized to the patient depending on baseline disease characteristics (e.g., genotype), response to therapy, and tolerability of the regimen.

An eighth embodiment is directed to a compound or a salt thereof represented by formula **A**,



A

wherein each one of Z^1, Z^2, and Z^3 is hydrogen or a protecting group (PG).

In a first aspect of the eighth embodiment, PG is selected from among –C(O)alkyl, –C(O)aryl, –C(O)O(C_{1-6}alkyl), –C(O)O(C_{1-6}alkylene)aryl, –C(O)Oaryl, –CH_2O-alkyl, –CH_2O-aryl, –SO_2-alkyl,–SO_2-aryl, and a silicon-containing protecting group. One of ordinary skill will appreciate that Z^1 and Z^2 can be the same, while Z^3 is different or that Z^1 and Z^2 are a part of the same radical, such as in the instance of ~Si(C_{1-6}alkyl)$_2$OSi(C_{1-6}alkyl)$_2$~, which would be derived from, for example, a 1,3-dihalo-1,1,3,3-tetra(C_{1-6}alkyl)disiloxane.

In a second aspect of the eighth embodiment, PG is selected from among, benzoyl, acetyl, –C(O)OCH_2Ph, phenyl-substituted benzoyl, tetrahydropyranyl, trityl, DMT (4,4'-dimethoxytrityl), MMT (4-monomethoxytrityl), trimethoxytrityl,

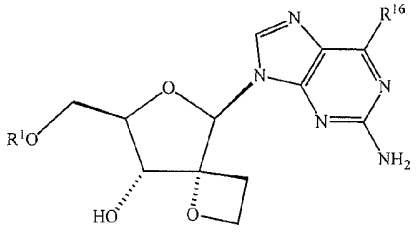
pixyl (9-phenylxanthen-9-yl) group, thiopixyl (9-phenylthioxanthen-9-yl), 9-(p-methoxyphenyl)xanthine-9-yl (MOX), *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, and ~$Si(C_{1-6}alkyl)_2OSi(C_{1-6}alkyl)_2OH$, such as, – $Si(^iPr)_2OSi(^iPr)_2OH$ or ~$Si(^iPr)_2OSi(^iPr)_2$~.

In a third aspect of the eighth embodiment, each of Z^1, Z^2, and Z^3 is hydrogen.

In a fourth aspect of the eighth embodiment, each of Z^1 and Z^2 is hydrogen and Z^3 is benzoyl.

In a fifth aspect of the eighth embodiment, Z^1 and Z^2 are comprised of ~$Si(^iPr)_2OSi(^iPr)_2$~ and Z^3 is hydrogen or benzoyl.

A ninth embodiment is directed to a process for preparing a compound represented by formula **I-3-4'**

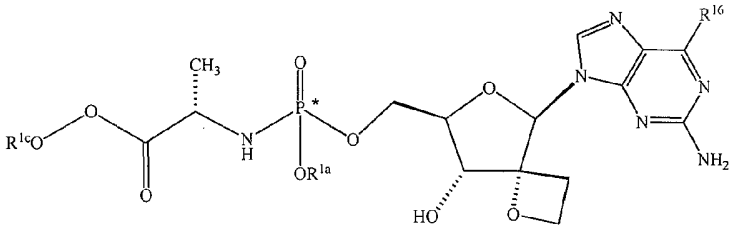


I-3-4'

wherein R^1 is as defined for compound **I-3-4**

or

a compound represented by formula **I-3-5'**,

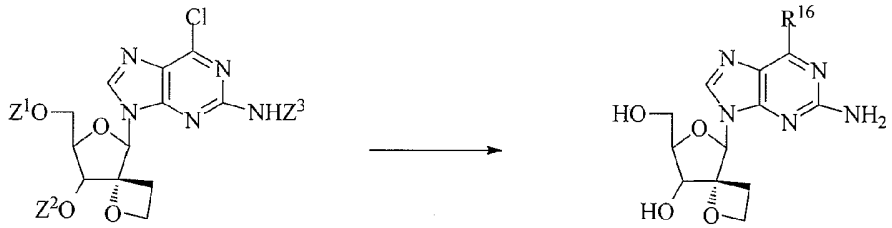


I-3-5'

wherein R^{1a}, R^{1c}, are as defined for compound **I-3-5**

said process comprising

reacting compound **A'** with a nucleophile and optionally deprotecting to obtain compound **B'**



A' B'

wherein the nucleophile is comprised of a radical selected from among –O(C_{1-6}alkyl), –OC_{1-3}alkaryl, –S(C_{1-6}alkyl), –NH(C_{1-6}alkyl), and –cycloalkylamino, and wherein each one of Z^1, Z^2, and Z^3 is hydrogen or a protecting group (PG) and reacting **B'** with an appropriate reagent to obtain either **I-3-4'** or **I-3-5'**.

Conditions for converting **B'** to **I-3-4'** are as described herein. Conditions for converting **B'** to **I-3-5'** are as described herein, e.g., as described in the tenth embodiment.

In a first aspect of the ninth embodiment, the nucleophile is comprised of a C_{1-6}alkoxide. The C_{1-6}alkoxide is obtained from methanol, ethanol, propanol, *i*-propanol, *n*-butanol, *i*-butanol, *s*-butanol, *t*-butanol, *n*-pentanol, isopentanol, neopentanol,
t-pentanol, and hexanol.

In a second aspect of the ninth embodiment, the nucleophile is comprised of a
–OC_{1-3}alkaryl. The –OC_{1-3}alkaryl is obtained from the respective C_{1-3}alkaryl alcohol. For example, –OCH_2Ph is obtained from benzylalcohol.

In a third aspect of the ninth embodiment, the nucleophile is comprised of a C_{1-6}alkylthiolate. The C_{1-6}alkyl thiolate is obtained from methylthiol, ethylthiol, propylthiol, *i*-propylthiol, *n*-butylthiol, *i*-butylthiol, *s*-butylthiol, *t*-butylthiol, *n*-pentylthiol, isopentylthiol, neopentylthiol, *t*-pentylthiol, and hexylthiol.

In a fourth aspect of the ninth embodiment, the nucleophile is comprised of a –NH(C_{1-6}alkyl). The –NH(C_{1-6}alkyl) is obtained from methylamine, ethylamine, propylamine, *i*-propylamine, *n*-butylamine, *i*-butylamine, *s*-butylamine, *t*-butylamine, *n*-pentylamine, isopentylamine, neopentylamine, *t*-pentylamine, and hexylamine.

In a fifth aspect of the ninth embodiment, the nucleophile is comprised of a –cycloalkylamino. The cycloalkylamino is derived from its respective cycloalkylamine.

In a sixth aspect of the ninth embodiment, the nucleophile is comprised of a –C_{3-6}cycloalkylamino. The –C_{3-6}cycloalkylamino is obtained from cyclopropylamine, 2-methyl-cyclopropylamine, cyclobutylamine, 2-methyl-cyclobutylamine, cyclopentylamine, 2-methyl-cyclopentylamine, cyclohexylamine, 2-methyl-cyclohexylamine, etc..

In solution or in the solid-state the nucleophile, i.e., the C_{1-6}alkoxide (C_{1-6}alkylO$^-$), the C_{1-3}alkaryloxide ($^-$O(C_{1-3}alkaryl), the C_{1-6}alkylthiolate (C_{1-6}alkylS$^-$), the C_{1-6}alkylamide (C_{1-6}alkylNH$^-$), and the cycloalkylamide (cycloalkylNH$^-$) (or the C_{3-6}cycloalkylamide ($^-$NHC_{3-6}cycloalkyl)), is associated with a cationic species, M. M is generally an alkali metal cation, such as Li^+, Na^+, K^+, etc. or a tetraalkyammonium, such as tetra-n-butyl-ammonium ($^nBu_4N^+$). However, M can be other cationic species so long as the association with the nucleophile permits reaction with A.

In each of the first six aspects of the ninth embodiment, the nucleophile can be pre-formed or prepared in situ. A pre-formed nucleophile can be obtained commercially or prepared by procedures known to one of ordinary skill. The so-prepared pre-formed nucleophile can optionally be isolated as a solid or used directly in the reaction of the ninth embodiment. A nucleophile prepared in situ may occur in the presence or absence of compound **A**. In the instance of a pre-formed nucleophile or a nucleophile prepared in situ, the solvent used depends on the conditions of the reaction. In certain aspects a suitable solvent is a polar aprotic solvent. Examples of polar aprotic solvents include, but are not limited to, DMSO, HMPA, DMF, THF, 2-methyl-THF, dioxane, cyclopentylmethylether, t-butyl-methylether, etc. In other aspects the nucleophile is obtained directly from the solvent. For example, the solvent for the solvent for the first aspect of the ninth embodiment could be an C_{1-6}alcohol (e.g., methanol, ethanol, etc.), in which the C_{1-6}alkoxide can be obtained according to conventional procedures. Solvents for the second and third aspects of the ninth embodiment include polar aprotic solvent, as well as an alcoholic solvent. The solvent for the fourth aspect of the ninth embodiment could be a C_{1-6}alkylamine (e.g., methylamine, ethylamine, etc.), in

which the
C_{1-6}alkylamide is obtained by adding a base having sufficient basicity to obtain the desired nucleophile. Likewise, the solvent for the fifth and sixth aspects of the ninth embodiment could be a cycloalkylamine or a C_{3-6}cycloalkylamine (e.g., cyclopropylamine, cyclobutylamine, etc.), in which the cycloalkylamide or the C_{3-6}cycloalkylamide is obtained by adding a base having sufficient basicity to obtain the desired nucleophile. The optional deprotection step is done by conventional means.

A seventh aspect of the ninth embodiment is directed to a process for preparing a compound represented by formula **I-3-5'**, which comprises reacting compound **A'** with a nucleophile to obtain compound **B'**, wherein the nucleophile is comprised of a radical selected from among a $-O(C_{1-6}alkyl)$, a $-OC_{1-3}alkaryl$, a $-NH(C_{1-6}alkyl)$, and a C_{3-6}cycloalkylamino, and wherein for compound **I-3-5'**, R^{1a} and R^{1c} are as defined, and R^{16} is a $-O(C_{1-6}alkyl)$. a $-OC_{1-3}alkaryl$, a $-NH(C_{1-6}alkyl)$, and a C_{3-6}cycloalkylamino .

An eighth aspect of the ninth embodiment is directed to a process for preparing a compound represented by formula **I-3-5'**, which comprises reacting compound **A'** with a nucleophile to obtain compound **B'**, wherein the nucleophile is comprised of a radical selected from among a $-O(C_{1-6}alkyl)$ and a $-OC_{1-3}alkaryl$, and wherein for compound **I-3-5'**, R^{1a} are R^{1c} are as defined, and R^{16} is a $-O(C_{1-6}alkyl)$ or a $-OC_{1-3}alkaryl$.

A ninth aspect of the ninth embodiment is directed to a process for preparing a compound represented by formula **I-3-5'**, which comprises reacting compound **A'** with a nucleophile to obtain compound **B'**, wherein the nucleophile is comprised of a $-O(C_{1-6}alkyl)$, and wherein for compound **I-3-5'**, R^{1a} and R^{1c} are as defined, and R^{16} is a $-O(C_{1-6}alkyl)$.

A tenth aspect of the ninth embodiment is directed to a process for preparing a compound represented by formula **I-3-5'**, which comprises reacting compound **A'** with a nucleophile to obtain compound **B'**, wherein the nucleophile is comprised of a
$-OC_{1-3}alkaryl$, and wherein for compound **I-3-5'**, R^{1a} and R^{1c} are as defined, and R^{16} is a
$-OC_{1-3}alkaryl$.

In an eleventh aspect of the ninth embodiment, PG is selected from among –C(O)alkyl, –C(O)aryl, –C(O)O(C_{1-6}alkyl), –C(O)O(C_{1-6}alkylene)aryl, –C(O)Oaryl, –CH_2O-alkyl, –CH_2O-aryl, –SO_2-alkyl,–SO_2-aryl, and a silicon-containing protecting group. One of ordinary skill will appreciate that Z^1 and Z^2 can be the same, while Z^3 is different or that Z^1 and Z^2 are a part of the same radical, such as in the instance of ~Si(C_{1-6}alkyl)$_2$OSi(C_{1-6}alkyl)$_2$~, which would be derived from, for example, a 1,3-dihalo-1,1,3,3-tetra(C_{1-6}alkyl)disiloxane.

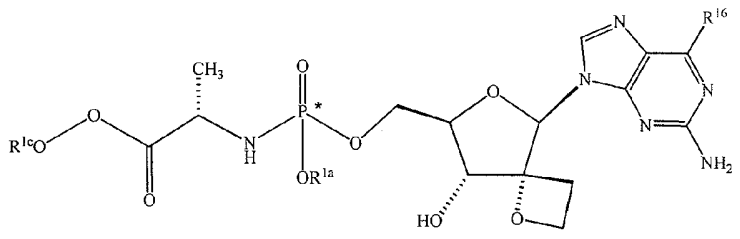
In a twelfth aspect of the ninth embodiment, PG is selected from among, benzoyl, acetyl, –C(O)OCH_2Ph, phenyl-substituted benzoyl, tetrahydropyranyl, trityl, DMT (4,4'-dimethoxytrityl), MMT (4-monomethoxytrityl), trimethoxytrityl, pixyl (9-phenylxanthen-9-yl) group, thiopixyl (9-phenylthioxanthen-9-yl), 9-(p-methoxyphenyl)xanthine-9-yl (MOX), *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, and ~Si(C_{1-6}alkyl)$_2$OSi(C_{1-6}alkyl)$_2$OH, such as, –Si(^{i}Pr)$_2$OSi(^{i}Pr)$_2$OH or ~Si(^{i}Pr)$_2$OSi(^{i}Pr)$_2$~.

In a thirteenth aspect of the ninth embodiment, each of Z^1, Z^2, and Z^3 is hydrogen.

In a fourteenth aspect of the ninth embodiment, each of Z^1 and Z^2 is hydrogen and Z^3 is benzoyl.

In a fifteenth aspect of the ninth embodiment, Z^1 and Z^2 are comprised of ~Si(^{i}Pr)$_2$OSi(^{i}Pr)$_2$~ and Z^3 is hydrogen or benzoyl.

A tenth embodiment is directed to a process for preparing a compound represented by formula **I-3-5"**,



I-3-5"

wherein

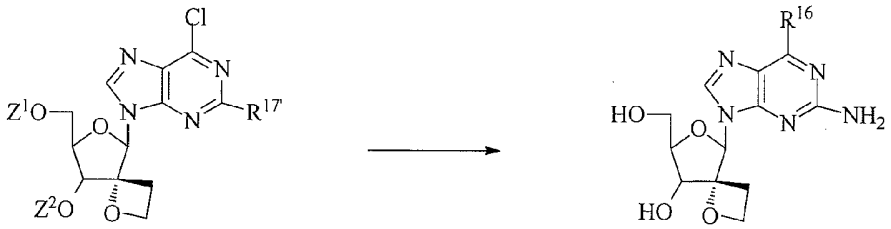
R^{1a} is phenyl or naphthyl;

R^{1c} is hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, or C_{1-3}alkaryl; and

R^{16} is $-O(C_{1-6}alkyl)$, $-OC_{1-3}alkaryl$, $-S(C_{1-6}alkyl)$, $-NH(C_{1-6}alkyl)$, or –cycloalkylamino;

said process comprising:

reacting compound **A"** with a nucleophile and optionally deprotecting to obtain compound **B",**



A" **B"**

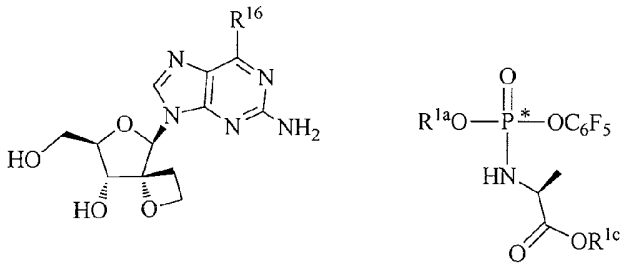
wherein

$R^{17'}$ is $-NHZ^3$, wherein each one of Z^1, Z^2, and Z^3 is hydrogen or a protecting group (PG);

the nucleophile is comprised of a radical selected from among, $-O(C_{1-6}alkyl)$, $-OC_{1-3}alkaryl$, $-S(C_{1-6}alkyl)$, $-NH(C_{1-6}alkyl)$, and –cycloalkylamino;

and

reacting **B"** with a phosphoramidate represented by formula **C** to obtain **I-3-5"**



B" **C**

wherein the phosphoramidate is comprised of a mixture of the S_P- and R_P-diastereomers.

The optional deprotection step is done by conventional means.

In a first aspect of the tenth embodiment, R^{16} is $-O(C_{1-6}alkyl)$, $-OC_{1-3}alkaryl$, $-S(C_{1-6}alkyl)$, $-NH(C_{1-6}alkyl)$, or $-NHC_{3-6}cycloalkyl$.

In a second aspect of the tenth embodiment, R^{16} is $-O(C_{1-6}alkyl)$.

In a third aspect of the tenth embodiment, R^{16} is $-OC_{1-3}$alkaryl.

In a fourth aspect of the tenth embodiment, R^{16} is $-S(C_{1-6}$alkyl).

In a fifth aspect of the tenth embodiment, R^{16} is $-NH(C_{1-6}$alkyl).

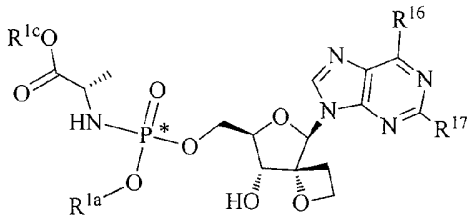
In a sixth aspect of the tenth embodiment, R^{16} is $-NHC_{3-6}$cycloalkyl.

In a seventh aspect of the tenth embodiment, the mole ratio of the S_P-diastereomer to the R_P-diastereomer ranges from about 2 to about 99.99 and all values in between, including 2, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 97, 98, 99, 99.9, and 99.99.

In an eighth aspect of the tenth embodiment, the mole ratio of the R_P-diastereomer to the S_P-diastereomer ranges from about 2 to about 99.99 and all values in between, including 2, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 97, 98, 99, 99.9, and 99.99.

In a ninth aspect of the tenth embodiment, the meanings of the protecting group for **A''** is as described for **A** in the eighth embodiment.

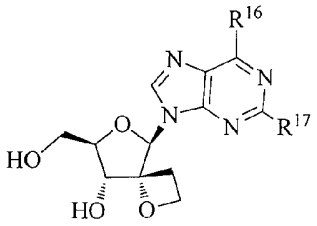
An eleventh embodiment is directed to a process for preparing a compound represented by formula **I-3-5'''**



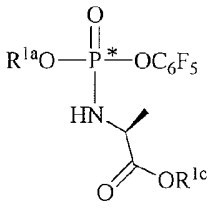
I-3-5'''

wherein R^{1a} is phenyl or naphthyl; R^{1c} is hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, or C_{1-3}alkaryl; R^{16} is $-O(C_{1-6}$alkyl), $-OC_{1-3}$alkaryl, $-S(C_{1-6}$alkyl), $-NH(C_{1-6}$alkyl), or –cycloalkylamino; and R^{17} is –H or $-NH_2$

said process comprising reacting a compound represented by formula **B'''** with a phosphoramidate represented by formula **C** to obtain **I-3-5'''**



B'''



C

wherein the phosphoramidate is comprised of a mixture of the S_P- and R_P-diastereomers.

In a first aspect of the eleventh embodiment, R^{16} is $-O(C_{1-6}alkyl)$, $-OC_{1-3}alkaryl$, $-S(C_{1-6}alkyl)$, $-NH(C_{1-6}alkyl)$, or $-NHC_{3-6}cycloalkyl$ and R^{17} is H or NH_2.

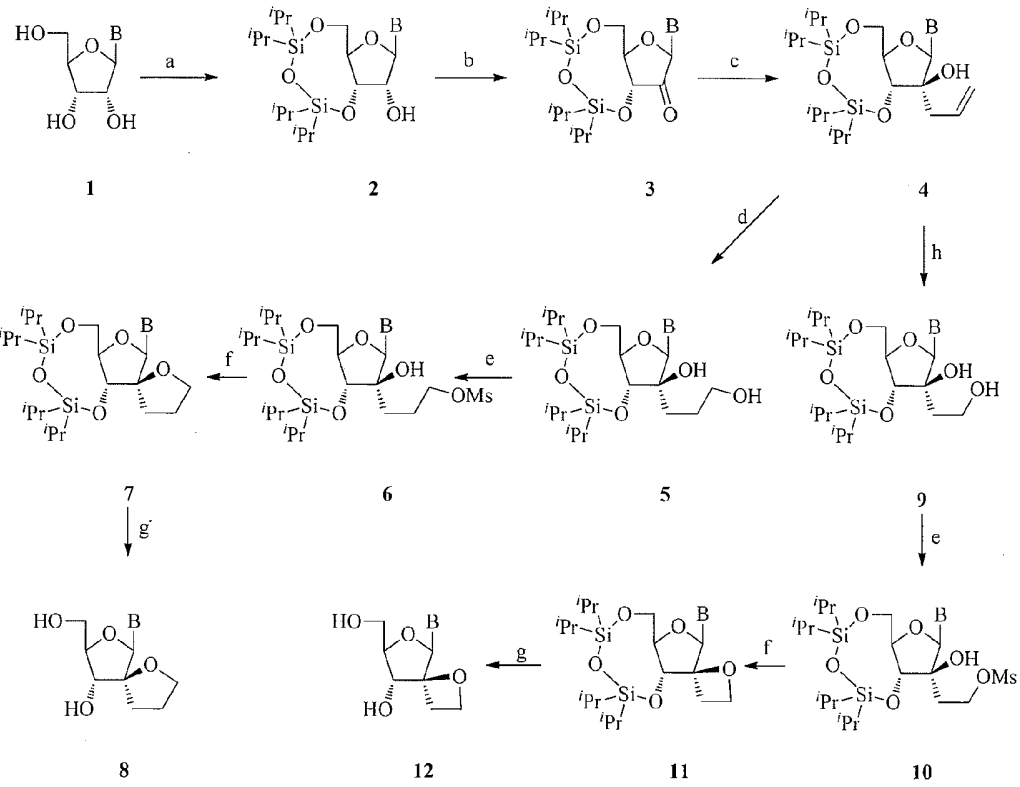
In a second aspect of the eleventh embodiment, the mole ratio of the S_P-diastereomer to the R_P-diastereomer ranges from about 2 to about 99.99 and all values in between, including 2, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 97, 98, 99, 99.9, and 99.99.

In a third aspect of the eleventh embodiment, the mole ratio of the R_P-diastereomer to the S_P-diastereomer ranges from about 2 to about 99.99 and all values in between, including 2, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 97, 98, 99, 99.9, and 99.99.

Preparation

Schemes 1-2 provide general procedures for preparing 2'-spiro-ara and 2'-spiro-ribo-nucleosides.

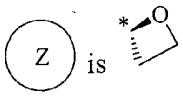
Scheme 1. General Synthesis of 2'-Spiro-ara-nucleosides



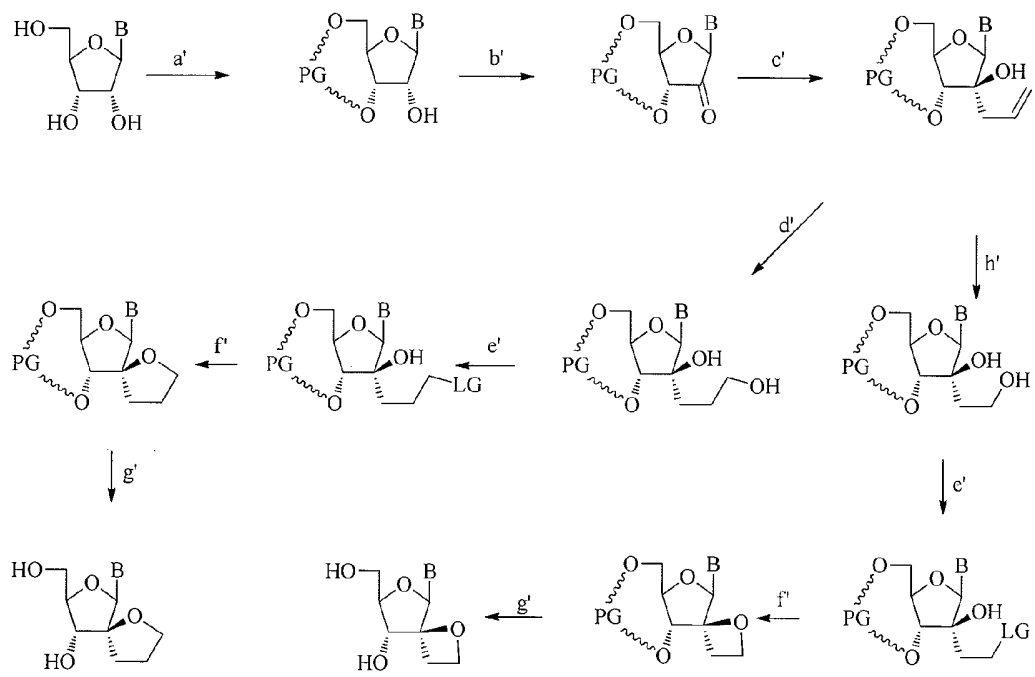
Reagents and conditions: a) TIPSCl/Pyr.; b) CrO_3/AcO_2; c) AllylMgX (X = Cl or Br); d) BH_3/H_2O_2; e) MsCl/Pyr; f) NaH; g) NH_4F; h) 1. O_3, 2. $NaBH_4$.

The disclosed reagents are meant to be exemplary only and should not be meant to narrow the scope of the embodiments disclosed below.

A seventh embodiment is directed to a process for preparing a compound or its stereoisomer or its salt or its metabolite or its deuteride represented by formula I, by any of the processes disclosed herein.

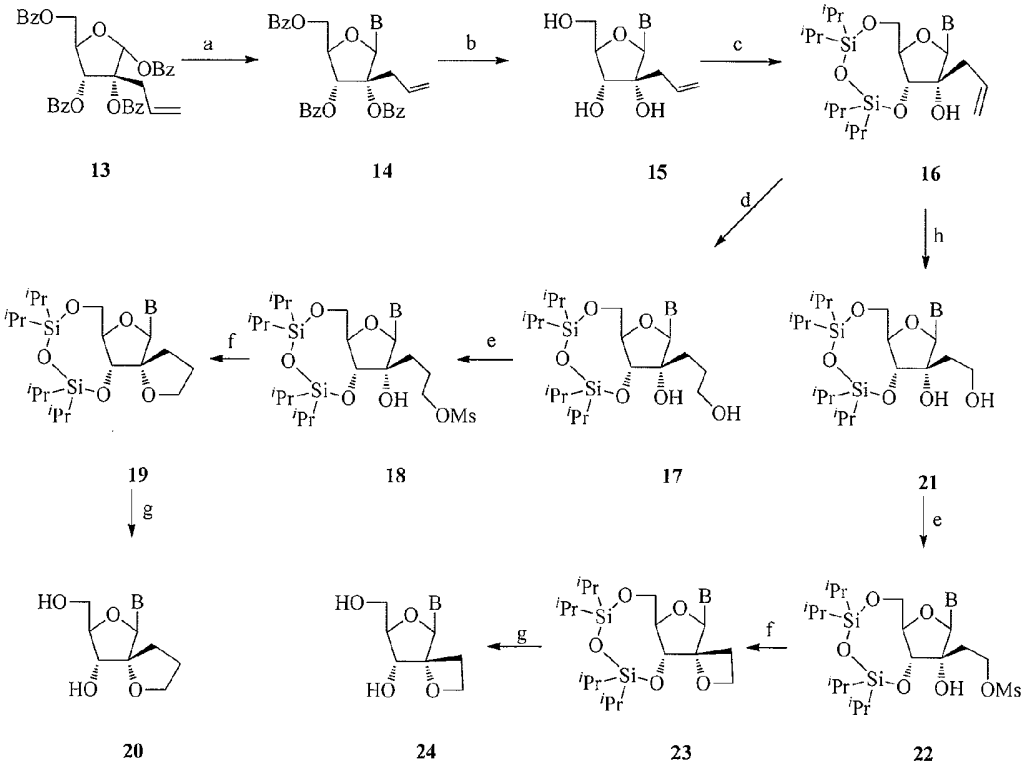
A first aspect of the seventh embodiment is directed to a process for preparing a compound or its stereoisomer or its salt or its metabolite or its deuteride thereof wherein  is or  , said process comprising any one of the following reaction steps a'-h'

PG



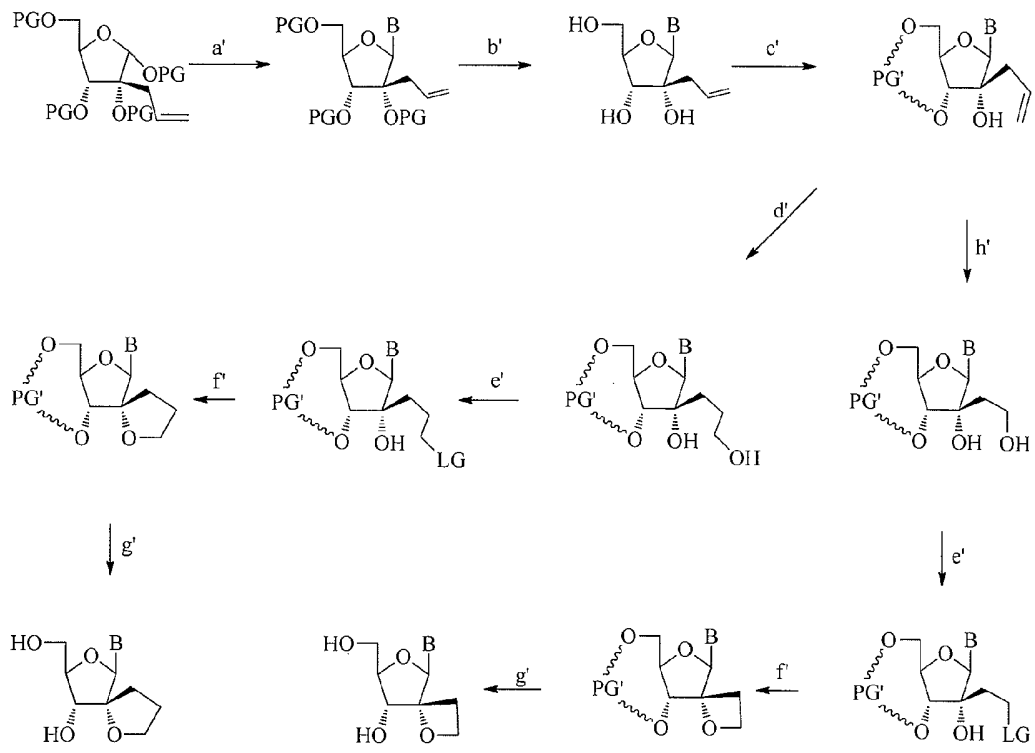
wherein B is defined above, PG is a protecting group, and LG is a leaving group.

Scheme 2. General Synthesis of 2'-Spiro-ribo-nucleosides



Reagents and conditions: a) Silylated base/TMSOT or $SnCl_4$ or base/TMSOTf/DBU; b) NH_3/MeOH; c) TIPSCl/Pyr.; d) BH_3/H_2O_2; e) MsCl/Pyr; f) NaH; g) NH_4F; h) 1. OsO_4/NMO, 2. $NaIO_4$, 3. $NaBH_4$.

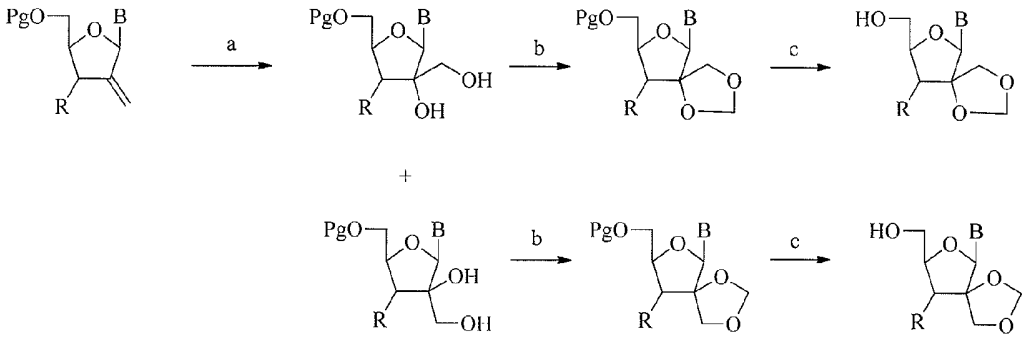
A second aspect of the seventh embodiment is directed to a process for preparing a compound or its stereoisomer or its salt or its metabolite thereof represented by formula I, wherein (Z) is  or  , said process comprising any one of the following reaction steps a'-h'



wherein B is as defined above, PG and PG' are independent of one another leaving groups, and LG is a leaving group.

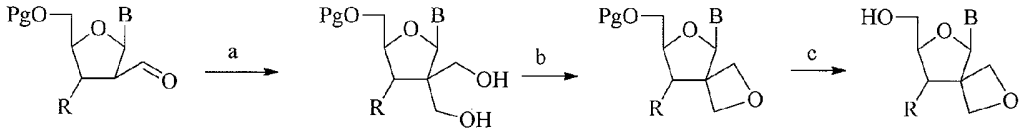
Scheme 3-6 provide general procedures for preparing additional compounds of formula I. In these schemes, Pg, represents a protecting group, which is defined herein. R is a substituent that provides for or is defined by the substituent "Y" as defined herein. As described above, examples of protecting groups are defined herein and disclosed in Protective Groups in Organic Synthesis, 3rd ed. T. W. Greene and P. G. M. Wuts, John Wiley & Sons, New York, N.Y., 1999. One of ordinary skill will appreciate the conditions available to protect and deprotect a given synthetic intermediate. Additionally, it is contemplated that one of ordinary skill would employ known procedures for the deoxygenation steps disclosed below.

Scheme 3. General Procedure for preparing 2'-spiro-(1,3-dioxolan-5-yl) Nucleosides



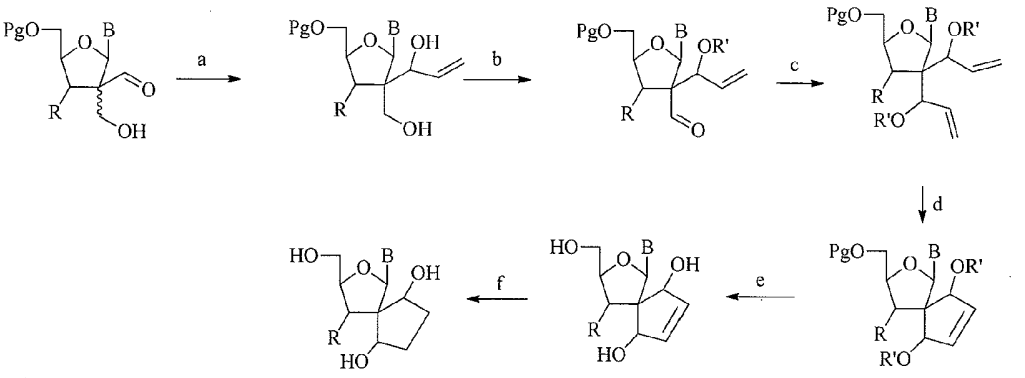
Scheme 3: Reagents: a) OsO_4/NMO; b) HCHO/acid; c) deprotection

Scheme 4. General Procedure for Preparing 2'-spiro-(oxetan-3-yl) Nucleosides



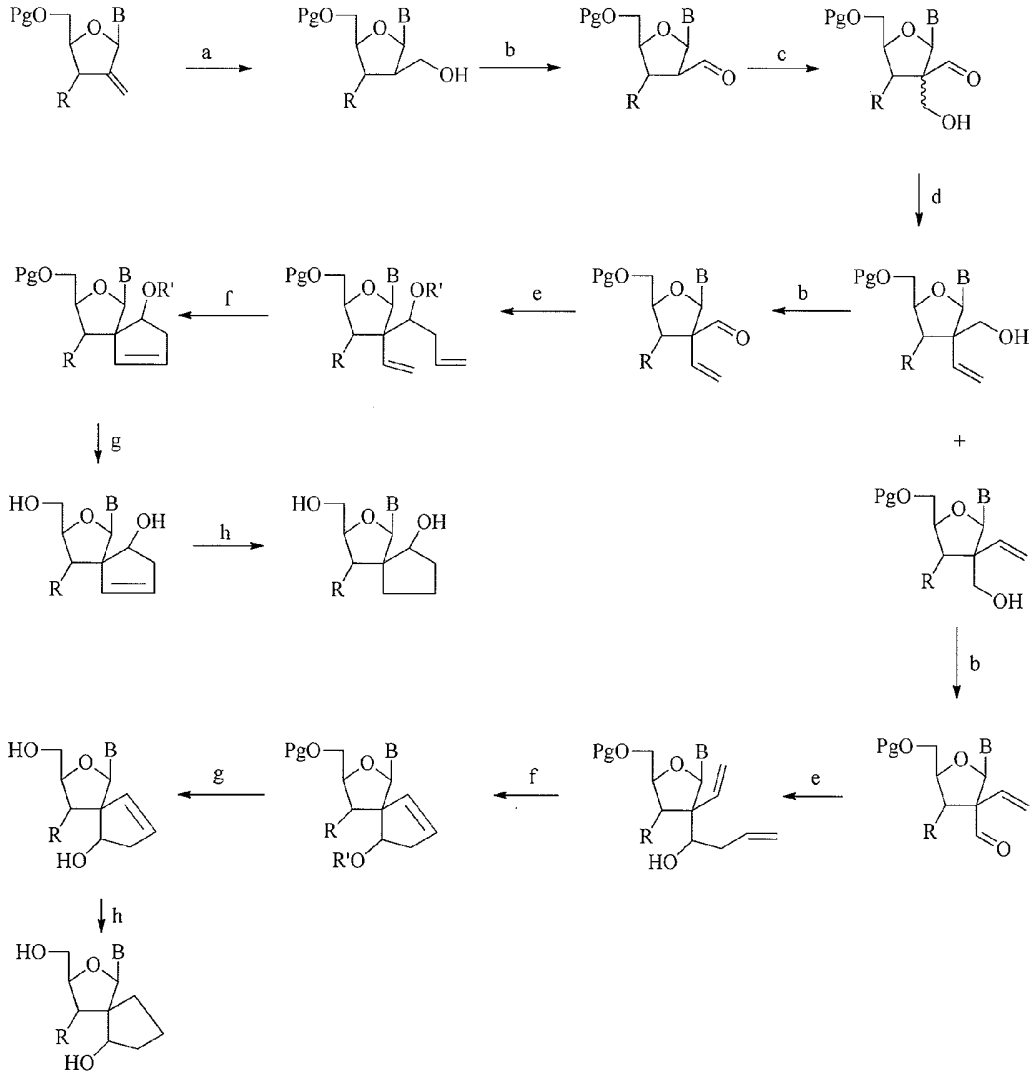
Scheme 4: Reagents: a) 1. HCHO/NaOH, 2. $NaBH_4$; b) Mitsunobu reagents; c) deprotection.

Scheme 5. General Procedure for preparing 2'-spiro-(disubstituted-cyclopentano) and 2'-spiro-(disubstituted-cyclopenteno) Nucleosides



Scheme 5. Reagents: a) vinylMgBr, b) 1. Selective O-protection, 2. CrO_3; c) 1. vinylMgBr, 2. selective O-protection; d) Grubbs' ring closure; e) deprotection; Pd/H_2. Hydroxyl group on spiro-ring can be removed by general deoxygenation method.

Scheme 6. General Procedure for Preparing 2'-spiro-(mono-substituted-cyclopentano) and 2'-spiro-(mono-substituted-cyclopenteno) Nucleosides



Scheme 6. Reagents: a) 1. BH_3, 2. H_2O_2/NaOH; b) CrO_3; c) HCHO/NaOH; d) CH_2=PPh_3; e) allylMgBr; f) Grubb's ring closure; g) deprotection; g) Pd/H_2. Hydroxyl group on spiro-ring can be removed by general deoxygenation methods.

See, e.g., Kim C. M. F. Tjen, et al Chem. Commun., 2000, 699–700.

One of ordinary skill will appreciate that other methods of preparing a compound of formula I are possible.

Procedures for introducing substituents at the 1' or 4' positions are disclosed in WO 2009/132135, as well as US 2009/0318380.

Procedures for preparing nucleosides and nucleotides of the "B" of Compound **I-2** are disclosed in U.S. Patent Nos. 3,798,209, 4,138,547, 4,458,016, 7,285,659, and 7,285,660.

Procedures for preparing nucleosides and nucleotides containing the "B" of Compound **I-3-1** are disclosed in any one of WO 2010/075517, WO 2010/075549, and WO 2010/075554.

Procedures for preparing nucleosides and nucleotides containing the "B6" of Compound **I-3-7** (or **I-3-9**) are disclosed in any one of WO 2010/002877 and WO 2009/132135.

Procedures for preparing nucleosides and nucleotides containing the "B7" of Compound **I-3-7** (or **I-3-10**) are disclosed in any one of WO 2010/036407, WO 2009/132135, and WO 2009/132123.

Procedures for preparing nucleosides and nucleotides containing the "B8" of Compound **I-3-7** (or **I-3-11**) are disclosed in WO 2009/132123.

Procedures for preparing nucleosides and nucleotides containing the "B9" of Compound **I-3-7** (or **I-3-12**) are disclosed in WO 2010/036407.

Procedures for preparing nucleosides and nucleotides containing the "B10" of Compound **I-3-7** (or **I-3-13**) are disclosed in WO 2010/093608.

Procedures for preparing deuterides are known to one of ordinary skill and reference can be made to US 2010/0279973 and procedures disclosed therein.

Procedures for preparing compound **1-3-5'''** are disclosed herein. Additional procedures for preparing and isolating compound **C** are disclosed in US 13/076,552 (US 2011/0251152), filed on March 31, 2011 and US 13/076,842 (US 2011/0245484), filed on March 31, 2011. To the extent necessary, the subject matter of US 13/076,552 and US 13/076,842 is hereby incorporated by reference.

Examples

Not to be limited by way of example, the following examples serve to facilitate a better understanding of the disclosure.

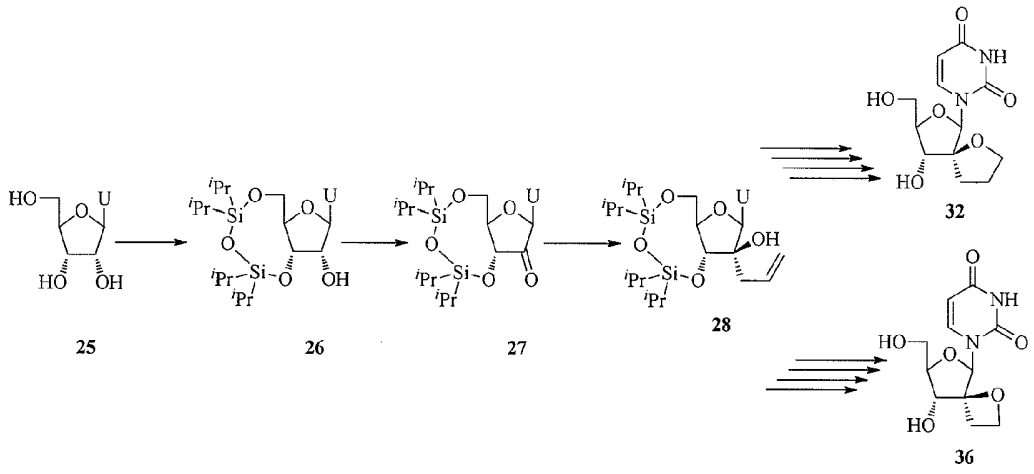
In the examples that follow, certain abbreviations have been used. The following table provides a selected number of abbreviations. It is believed that one of ordinary skill would know or be able to readily deduce the meaning of any abbreviations not specifically identified here.

Abbreviation	Meaning
TMSCl	Trimethylsilylchloride
TIPSCl	1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane
EtOAc	Ethtyl Acetate
Pyr	pyridine
Ac2O	Acetic Anhydride
THF	Tetrahydrofuran
DCM	(≡CH_2Cl_2) Dichloromethane
MsCl	Mesylchloride
HMDS	Hexamethyldisiloxane
MeCN	Acetonitrile
NMO	N-Methylmorpholine-N-oxide
p-TsOH	para-toluene-sulfonic acid
MOPS	3-(N-morpholino)propanesulfonic acid
HCHO	formaldehyde
NaHMDS	Sodium bis(trimethylsilyl)amide
NMI	N-methylimidazole
DTP	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone

I. Preparation of 2'-Spiro-ara-uracil and 2'-Spiro-ribo-uracil Analogs

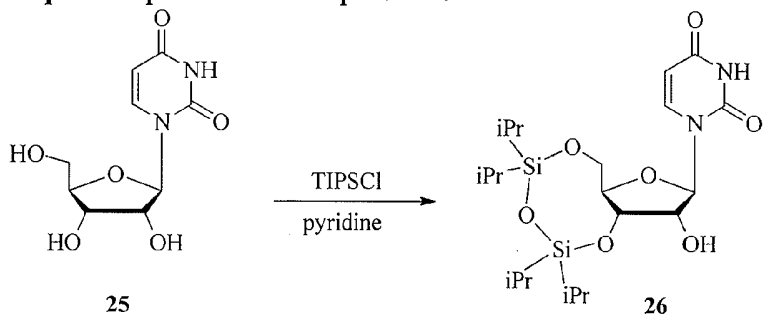
A. Preparation 2'-spiro-ara-uridines

The following scheme describes a possible synthetic route for the preparation of 2'-spiro-ara-uracil analogs, **32** and **36**. A synthetic intermediate common to compounds **32** and **36** is compound **28**, which is obtained by protecting uridine **25** with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (TIPSCl) followed by oxidation of the 2'-carbon to form compound **27**. Compound **28** is prepared by reacting compound **27** with an appropriate allyl-containing reagent.



Example 1. Preparation of 1-((6aR,8R,9S,9aR)-9-allyl-9-hydroxy-2,2,4,4-tetraisopropyltetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-8-yl)pyrimidine-2,4(1H,3H)-dione, **28**.

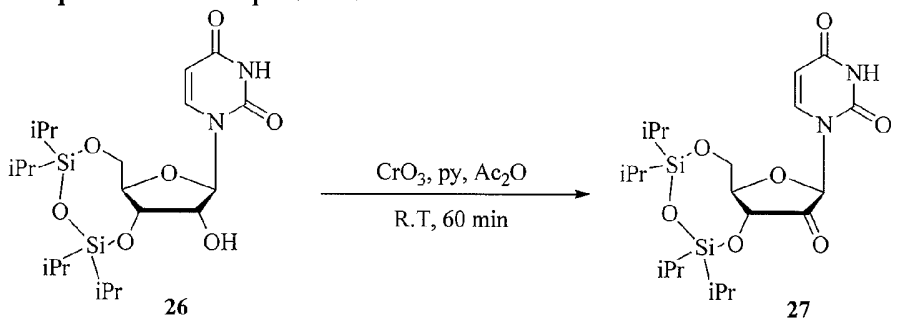
Step 1. Preparation of compound 26.



25 26

To a solution of compound **25** (20.0 g, 82.58 mmmol) in anhydrous pyridine (150 mL) was added 1,3-dichloro-1,1,,3,3-tetraisopropyldisiloxane (TIPSCl, 27.35 g, 86.71 mmol) at room temperature. The mixture was stirred at room temperature for 20 h. The solvent was evaporated under reduced pressure and the residue was dissolved in EtOAc (200 mL). The organic solution was washed with H_2O and the solvent was evaporated to give a crude product **26** which was used for next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.11 (s, 1H), 7.78 (d, J = 8.4 Hz, 1H), 5.73 (s, 1H), 5.68 (d, J = 8.0 Hz, 1H), 4.07-4.38 (m, 4H), 3.96-4.00 (m, 2H), 0.91-1.21 (m, 28H).

Step 2. Preparation of compound 27

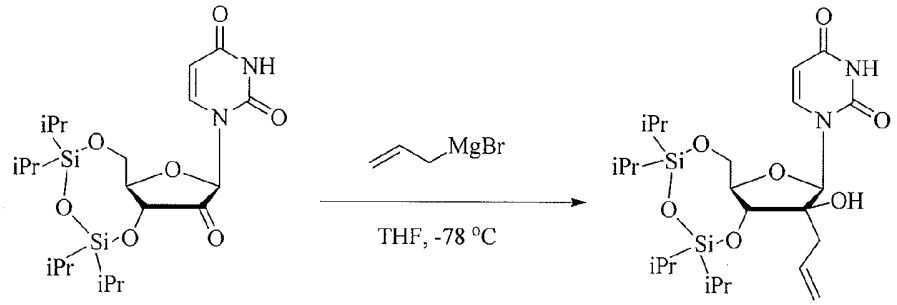


26 27

To a stirred solution of CrO_3 (13.0 g, 130.0 mmol), anhydrous pyridine (22 mL) and Ac_2O (13 mL) was added a solution of compound **26** (20.0 g, 41.28 mmol) in CH_2Cl_2 (50 mL). The mixture was stirred 60 min. The solution was filtered through to a short silica gel column. The solvent was evaporated and the residue was purified by silica gel column chromatography (hexane:EtOAc = 2:1) to give the compound **27** (9.0 g, 45 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.63 (s, 1H), 7.15 (d,

J = 8.0 Hz, 1H), 5.72-5.74 (m, 1H), 5.05 (d, J = 8.8 Hz, 1H), 4.99 (s, 1H), 4.09-4.17 (m, 2H), 3.86-3.91 (m, 1H), 1.00-1.21 (m, 28H).

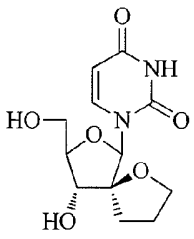
Step 3. Preparation of compound 28.



27 28

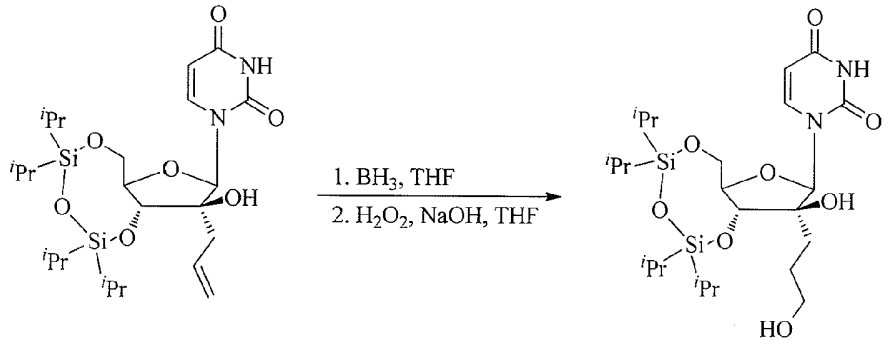
To a solution of compound **27** (5.0 g, 10.32 mmol) in THF (200 mL) was added a solution of allylmagnesium bromide (20.63 mL, 20.63 mmol) at -78°C and the mixture was stirred at the same temperature for 2 h. Then the temperature was raised to -10°C and the reaction was quenched with H_2O. The mixture was extracted with CH_2Cl_2 and the organic solution was dried with Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (Hexanes:EtOAc = 3:1) to give the compound **28** (4.0 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.82 (s, 1H), 7.82 (d, J = 8.0 Hz, 1H), 6.04-56.14 (m. 1H), 5.89 (s, 1H), 5.68 (d, J = 8.0 Hz, 1H), 5.28-5.37 (m, 2H), 4.24 (d, J = 9.2 Hz, 1H), 4.15 (d, J = 9.2 Hz, 1H), 3.97-4.01 (m, 1H), 3.78-3.80 (m, 1H), 2.69-2.75 (m, 1H), 2.48-2.53 (m, 1H), 2.44 (s, 1H), 1.04-1.09 (m, 28H).

Example 2. Preparation of 1-((5S,6R,8R,9R)-9-hydroxy-8-(hydroxymethyl)-1,7-dioxaspiro[4.4]nonan-6-yl)pyrimidine-2,4(1H,3H)-dione, **32** (2'-spiro-THF-ara-uracil)



32

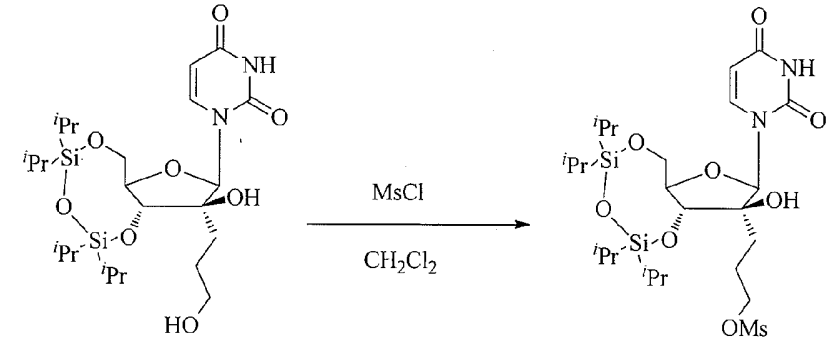
Step 1. Preparation of compound 29.



28 **29**

To a solution of compound **28** (2.0 g, 3.80 mmol) in THF (200 mL) was added BH_3 (0.57 mL, 5.7 mmol) at room temperature and the mixture was stirred at room temperature for 3 hr. The reaction mixture was cooled to 0°C and 2 M aqueous NaOH (3.8 mL, 7.6 mmol) and 30% aqueous H_2O_2 (1.72 mL, 15.21 mmol) was added slowly. The mixture was allowed to warm to room temperature, stirred for 2 h and then poured into a mixture of diethyl ether (150 mL) and H_2O (150 mL). The aqueous phase was extracted with diethyl ether (50 mL) and the combined organic solution was washed with saturated aqueous $NaHCO_3$ (2 × 40 mL), and H_2O (2 × 40 mL), successively. The solution was dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (hexanes:EtOAc = 1:1) to give the compound **29**. (1.1 g, 53 %). ^1H NMR (400 MHz, $CDCl_3$): δ = 10.39 (s, 1H), 8.00 (d, J = 8.0 Hz, 1H), 5.86 (s, 1H), 5.70 (d, J = 8.0 Hz, 1H), 4.14-4.17 (m, 2H), 3.96-3.99 (m, 2H), 3.70-3.73 (m, 1H), 3.47-3.52 (m, 1H), 2.02-2.17 (m, 2H), 1.97-2.00 (m, 1H), 1.89-1.90 (m, 1H), 0.99-1.11 (m, 28H).

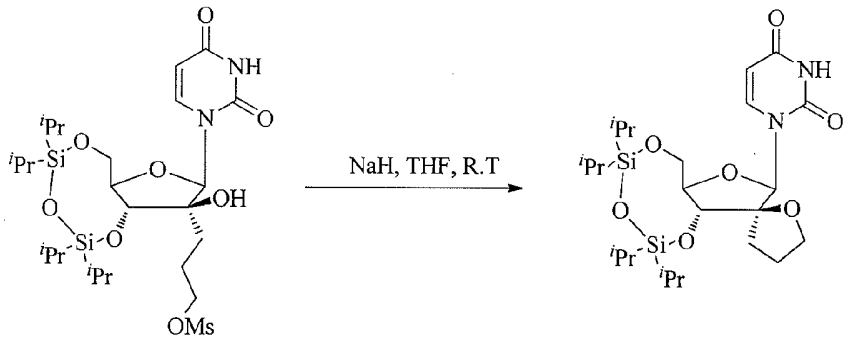
Step 2. Preparation of compound 30.



29 **30**

A solution of MsCl (0.28 g, 2.42 mmol) in anhydrous CH_2Cl_2 (1.0 mL) was added to a solution of nucleoside **29** (1.1 g, 2.02 mmol) in anhydrous pyridine (2.0 mL) drop-wise at room temperature. After stirring for 12 h at room temperature, methanol (0.1 mL) was added and the resulting mixture was evaporated to dryness under reduced pressure. The residue was co-evaporated with anhydrous toluene (2 × 5 mL) and then dissolved in CH_2Cl_2 (50 mL). The solution was washed with saturated aqueous $NaHCO_3$ (2 ×25 mL). The combined aqueous phase was extracted with CH_2Cl_2 (50 mL). The combined organic solution was dried (Na_2SO_4), filtered and evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (hexanes:EtOAc = 2:1) to give compound **30** (0.94 g, 74.6%).

Step 3. Preparation of compound 31.

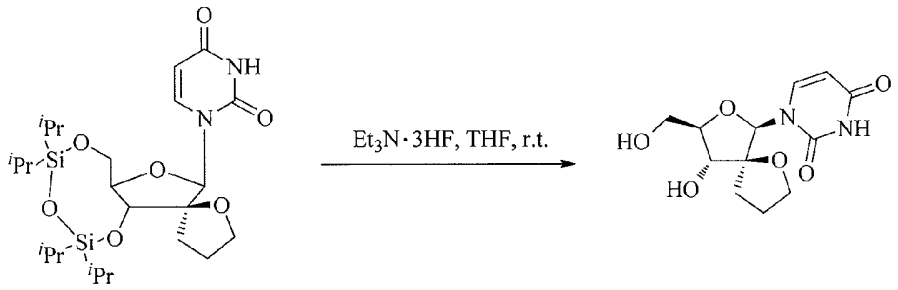


30 **31**

To a stirred suspension of NaH (108.8 mg, 4.53 mmol) in anhydrous THF (20 mL) was added a solution of compound **30** (0.94 g, 1.51 mmol) in THF drop-wise at 0°C and the mixture was stirred for 2 h at room temperature. Ice-cold H_2O (10 mL)

was slowly added followed by addition of CH_2Cl_2 (20 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (2 × 20 mL) and dried (Na_2SO_4). Solvent was evaporated to dryness under reduced pressure and the residue was purified by silica gel column chromatography (Hexanes:EtOAc=2:1) to provide compound **31** (0.43 g, 54.02 %).

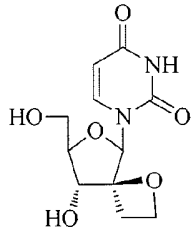
Step 4. Preparation of compound 32.



31 **32**

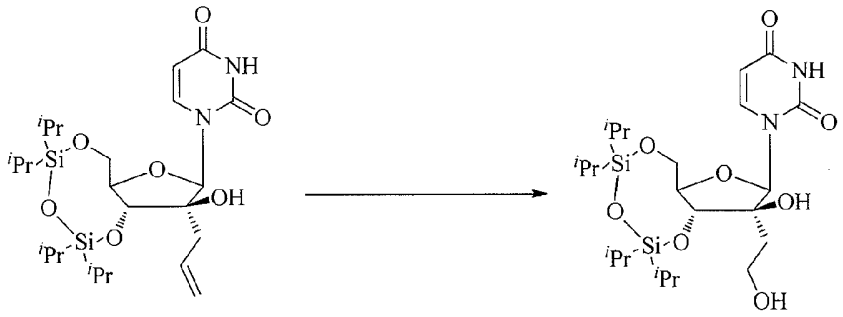
To a solution of compound **31** (150 mg, 0.285 mmol) in anhydrous THF (10 mL) was added Et_3N•3HF (0.3 mL) and the mixture was stirred at room temperature for 2 h. The mixture was then evaporated to dryness under reduced pressure and the residue was purified by silica gel column chromatography (0-15% MeOH in CH_2Cl_2) to give compound **32** (51.37 mg, 63.5 %). ^{1}H NMR (400 MHz, DMSO-*d6*): δ = 11.32 (s, 1H), 7.80 (d, *J* = 8.0Hz, 1H), 5.83 (s, 1H), 5.63 (d, *J* = 4.2Hz, 1H), 5.59 (d, *J* = 8.0Hz, 1H), 5.03-5.05 (m, 1H), 3.83-3.86 (m, 1H), 3.64-3.70 (m, 3H), 3.47-3.60 (m, 2H), 2.27-2.29 (m, 1H), 1.74-1.81 (m, 3H). HRMS(TOF-ESI): Calc. For $C_{12}H_{17}N_2O_6$, 285.1087. found 285.1070.

Example 3. Preparation of 1-((4S,5R,7R,8R)-8-hydroxy-7-(hydroxymethyl)-1,6-dioxaspiro[3.4]octan-5-yl)pyrimidine-2,4(1H,3H)-dione, **36** (2'-spiro-oxetane-ara-uracil)



36

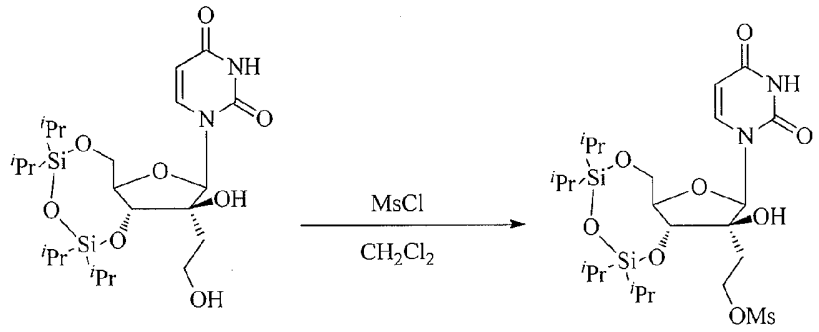
Step 1. Preparation of compound 33.



28 **33**

To a solution of compound **28** (4.8 g, 9.12 mmol) in DCM (200 mL) was bubbled with O_3 and the solution was stirred at -78°C for 3h. To the solution were added Me_2S (1 mL) and $NaBH_4$ (1.73 g, 45.60 mmol) at room temperature and the mixture was stirred overnight. The resulting solution was washed with H_2O and the solvent was evaporated. The residue was purified by silica gel column chromatography (hexanes:EtOAc = 1:1) to give compound **33** (1.2 g, 25.7 %). ^1H NMR (400 MHz, $CDCl_3$): δ 11.16 (s, 1H), 7.92 (d, J = 8.0 Hz, 1H), 6.01 (s, 1H), 5.69-5.72 (m, 1H), 5.64 (s, 1H), 4.58-4.63 (m, 2H), 3.94-4.17 (m, 4H), 3.65-3.68 (m, 1H), 2.49-2.53 (m, 1H), 1.58-1.61 (m, 1H), 1.01-1.11 (m, 28H).

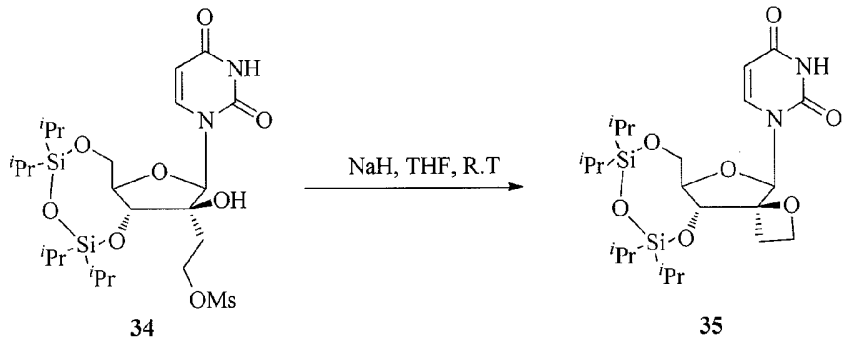
Step 2. Preparation of compound 34.



33 34

A solution of MsCl (0.31g, 2.72 mmol) in anhydrous CH_2Cl_2 (10 mL) was added to a solution of nucleoside **33** (1.2 g, 2.26 mmol) in anhydrous pyridine (2.0 mL) drop-wise at room temperature and the solution was stirred at room temperature for 12 h. Methanol (5.0 mL) was added and the resulting mixture was evaporated to dryness under reduced pressure. The residue was co-evaporated with anhydrous toluene (2 × 5 mL) and purified by silica gel column chromatography (hexanes:EtOAc = 2:1) to provide compound **34** (1.0 g, 73.0%).

Step 3. Preparation of compound 35.

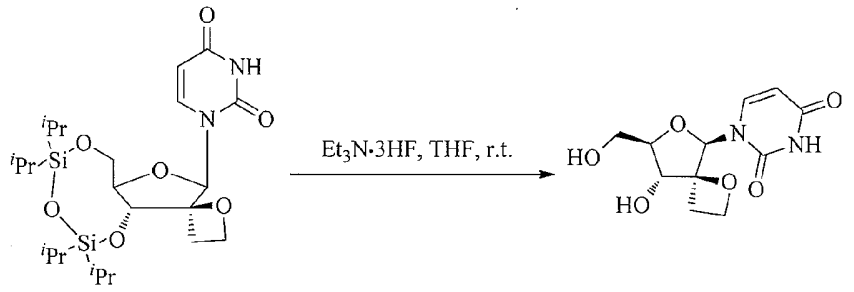


34 35

To a stirred suspension of NaH (59.2 mg, 2.467 mmol) in anhydrous THF was added a solution of compound **10** (1.0 g, 1.65 mmol) in THF (3 mL) drop-wise at 0°C and the mixture was stirred at room temperature for 2 h at room temperature. Ice-cooled H_2O (10 mL) was slowly added to the solution followed by addition of CH_2Cl_2 (20 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (2 × 20 mL) and dried (Na_2SO_4). Solvent was evaporated to dryness under reduced

pressure and the residue was purified by silica gel column chromatography (hexanse:EtOAc=2:1) to give compound **35**. (0.5 g, 59.25 %).

Step 4. Preparation of compound 36.

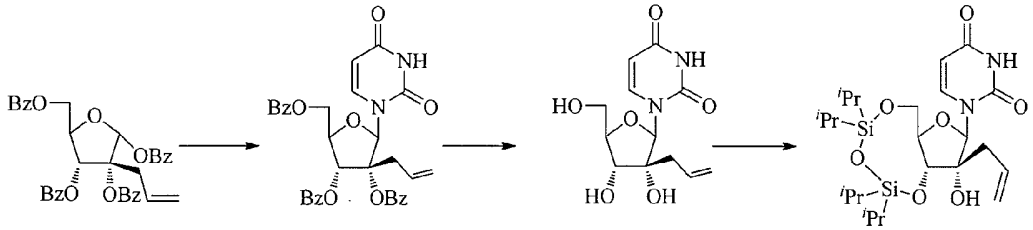


35 **36**

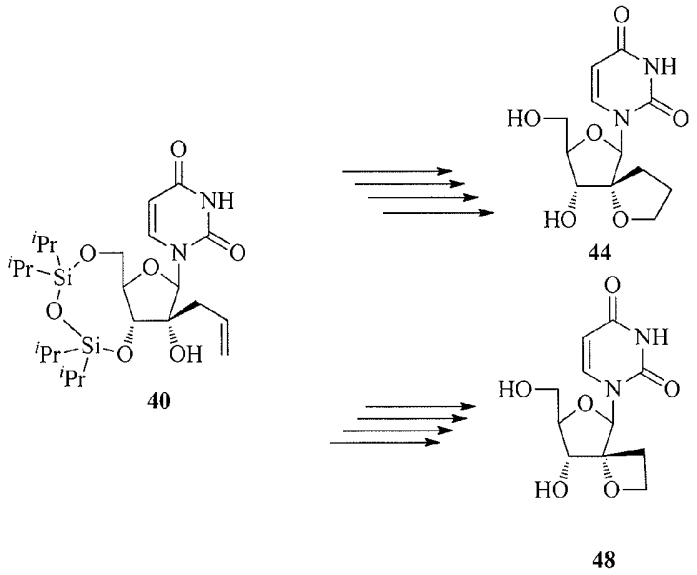
To a solution of compound **35** (300 mg, 0.585 mmol) in anhydrous THF (10 ml) was added $Et_3N•3HF$ (0.15 mL) and the mixture was stirred at room temperature for 2 h. The mixture was then evaporated to dryness under reduced pressure and the residue was purified by silica gel column chromatography (0-15% MeOH in CH_2Cl_2) to give compound **36** (61.26 mg, 38.78 %). ^1H NMR (400 MHz, DMSO-d_6): δ 11.42 (s, 1H), 7.68 (d, J = 8.0Hz, 1H), 6.08 (s, 1H), 5.87 (d, J = 5.2Hz, 1H), 5.60 (d, J = 8.0Hz, 1H), 5.04-5.06 (m, 1H), 4.30-4.35 (m, 1H), 4.19-4.24 (m, 1H), 3.95-3.98 (m, 1H), 3.50-3.61 (m, 3H), 3.01-3.08 (m, 1H), 2.39-2.45 (m, 1H). HRMS (TOF-ESI): Calc. for $C_{11}H_{15}N_2O_6$, 271.0925. found 271.0917.

B. Preparation of 2'-Spiro-Ribo-Uracil Analogs

The following scheme shows that 2'-spiro-ribo-uracil analogs can be prepared from a common synthetic intermediate, compound **40**.



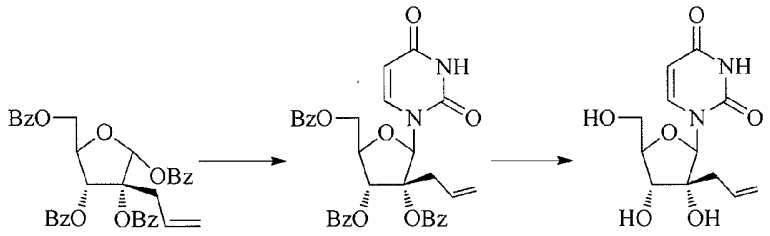
37 **38** **39** **40**



40 44 48

Example 4. Preparation of 1-((6aR,8R,9R,9aR)-9-allyl-9-hydroxy-2,2,4,4-tetraisopropyltetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-8-yl)pyrimidine-2,4(1H,3H)-dione, 40.

Steps 1-2. Compound 39

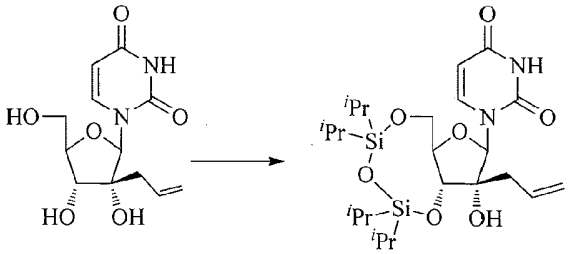


37 38 39

Preparation of compound **39** was accomplished according to literature method (Babu, B et al. Org Biomol. Chem. (2003) 1: 3514-3526). A mixture of uracil (0.74 g, 6.59 mmol) and $(NH_4)_2SO_4$ (20 mg) in HMDS was refluxed for 4h and the clear solution was concentrated to dryness under reduced pressure. The residue was dissolved in MeCN (60 mL). To the solution was added a solution of compound **37** (2.0 g, 3.3 mmol) followed by $SnCl_4$ (1 M in CH_2Cl_2 (8.24 mmol, 8.24 mL) at room temperature and the solution was heated at 65°C for 3h. The solution was poured into ice-water containing excess $NaHCO_3$ and EtOAc (200 mL). Organic solution was washed with brine and dried over Na_2SO_4. Solvent was evaporated and the residue was purified by silica gel column chromatography (19-60% EtOAc in hexanes) to give compound **38** (1.50 g, 76%) as white foam.

A suspension of compound **38** (2.5 g, 4.19 mmol) in 7N methanolic ammonia (40 mL) was stirred at room temperature for 16h and the solution was evaporated to dryness. The residue was purified by silica gel column chromatography (0-20% MeOH in CH_2Cl_2) to give compound **39** (1.0 g, 83%). ^1H NMR (400 MHz, CD_3OD) δ: 7.96 (d, J=8.0Hz, 1H), 6.01 (s, 1H), 5.89 (m, 1H), 5.68 (d, J=8.0Hz, 1H), 4.99 (m, 2H), 3.89 (m, 4H), 2.43 (m, 1H), 2.23 (m, 1H).

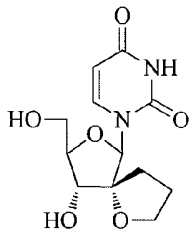
Step 3. Preparation of compound 40.



39 **40**

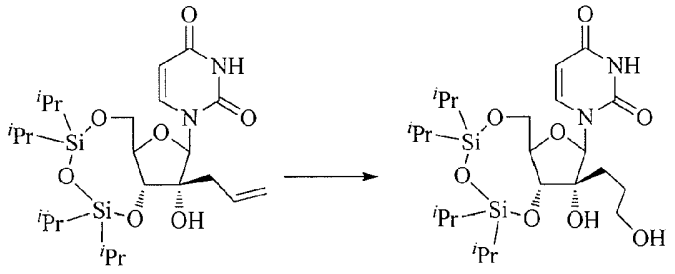
To a solution of **39** (0.60 g, 2.11 mmol) in pyridine (10 mL) and CH_2Cl_2 (20 mL) was added TIPSCl at 0°C within 10 min. The solution was stirred at room temperature for 24h. Solvent was evaporated and the residue was dissolved in EtOAc (100 mL). The solution was washed with brine and dried over Na_2SO_4. Solvent was evaporated and the residue was purified by silica gel column chromatography (0-5% MeOH in CH_2Cl_2) to give product **40** (1.00 g, 90%) as a syrup.

Example 5. Preparation of 1-((5R,6R,8R,9R)-9-hydroxy-8-(hydroxymethyl)-1,7-dioxaspiro[4.4]nonan-6-yl)pyrimidine-2,4(1H,3H)-dione, **44** (2'-spiro-THF-ribo-uracil).



44

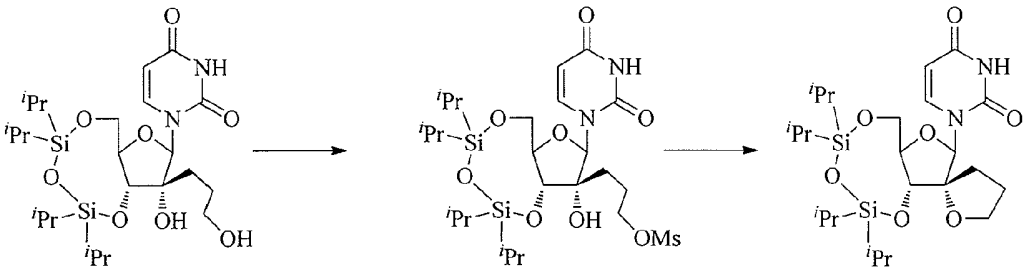
Step 1. Preparation of compound 41.



40 41

To a solution of **40** (1.0 g, 1.9 mmol) in THF (50 mL) was added borane-dimethylsulfide (2.85 mmol, 0.22 g) and the solution was stirred at 0°C for 3h. To the cooled solution was added 2N NaOH (1.9 mL, 3.8 mmol) and the mixture was stirred at room temperature for 2h. EtOAc (100 mL) was added and the solution was washed with brine and dried over Na_2SO_4. Solvent was evaporated and the residue was purified by silica gel column chromatography (0-8% MeOH in CH_2Cl_2) to give product **41** (0.45 g, 44%). ^{1}H NMR (400 MHz, CD_3OD) δ: 8.11 (s, 1H), 7.61 (D, J=8.0Hz, 1H), 6.05 (s, 1H), 5.71 (d, J=8.0Hz, 1H), 4.07 (m, 4H), 3.60 (m, 3H), 3.21 (s, 1H), 1.70 (m, 4H), 1.10 (m, 28H). LC-MS (ESI): 545 $[M+H]^+$.

Steps 2-3. Preparation of compound 43.

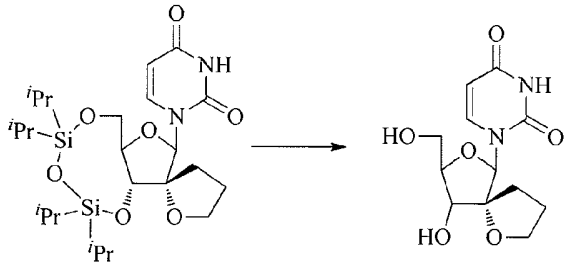


41 42 43

To a solution of **41** (0.30 g, 0.55 mmol) in CH_2Cl_2 (10 mL) and pyridine (2 mL) was added a solution of MsCl (0.09 g, 0.83 mmol) in CH_2Cl_2 (1 mL) and the solution was stirred at room temperature for 3h. Water (5 mL) was added and the mixture was washed with brine and dried over Na_2SO_4. Solvent was evaporated to dryness and the residue was purified by silica gel column chromatography (0-5%

MeOH in CH_2Cl_2) to give intermediate 42 (0.30 g, 87%). To THF (20 mL) was added NaH (60% in mineral oil, 0.05 g, 2.01 mmol) and the mixture was stirred at room temperature for 10 min. To the mixture was added a solution of **42** (0.25 g, 0.40 mmol) in THF (10 mL) and the mixture was stirred at room temperature for 1h. Water (1 mL) was added followed by addition of EtOAc (100 mL). The mixture was washed with brine and dried over Na_2SO_4. Solvent was removed and the residue was purified by silica gel column chromatography (0-50% EtOAc in hexanes) to give compound **43** (0.17 g, 80%). ^{1}H NMR (400 MHz, CD_3OD) δ: 8.17 (s, 1H), 7.90 (d, J=8.4Hz, 1H), 5.88 (s, 1H), 5.68 (dd, J=2.4, 8.4Hz, 1H), 4.26 (d, J=13.2Hz, 1H), 4.01 (m, 5H), 1.90 (m, 4H), 1.05 (m, 12H). LC-MS (ESI): 527 $[M+H]^+$.

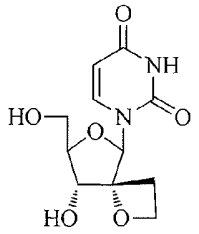
Step 4. Preparation of compound 44.



43 **44**

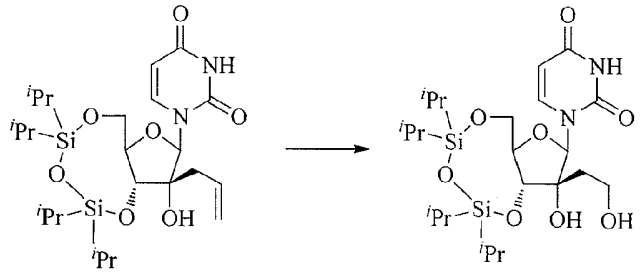
A mixture of **43** (0.05g, 0.09 mmol) and NH_4F (100 mg) and catalytic TBAF in MeOH (10 mL) was refluxed for 5h and the solvent was evaporated to dryness. The residue was purified by silica gel column chromatography (0-10% MeOH in CH_2Cl_2) to give compound **44** (0.02 g, 93%) as white solid. ^{1}H NMR (400 MHz, CD_3OD) δ: 8.09 (d, J=8.4Hz, 1H), 5.91 (s, 1H), 5.68 (d, J=8.4Hz, 1H), 3.90 (m, 6H), 1.95 (m, 4H). LC-MS (ESI): 284 $[M+H]^+$.

Example 6. Preparation of 1-((4R,5R,7R,8R)-8-hydroxy-7-(hydroxymethyl)-1,6-dioxaspiro[3.4]octan-5-yl)pyrimidine-2,4(1H,3H)-dione, **48** (2'-spiro-oxetane-ribo-uracil)



48

Step 1. Preparation of compound 45.

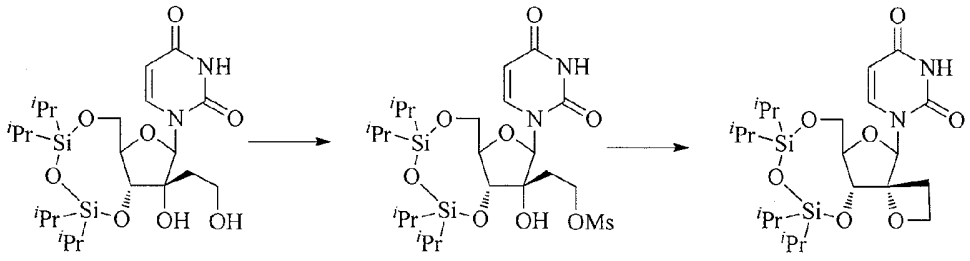


40 **45**

To a solution of **40** (0.25 g, 0.47 mmol) in THF (5 mL), t-BuOH (50 mL) and water (0.8 mL) was added OsO_4 (0.5 mL, 2.5% in t-BuOH) followed by addition of NMO (0.5 mL, 50% in water) and the mixture was stirred at room temperature for 3h. Solvent was evaporated and the residue was co-evaporated with EtOH (20 mL) twice. The residue was dissolved in THF (8 mL) and water (2 mL). To the mixture was added $NaIO_4$ (0.29 g, 1.34 mmol) and the mixture was stirred at room temperature for 2h. To the mixture was added MeOH (10 mL). To the mixture was added $NaBH_4$ (3 mol eq) and the mixture was stirred at room temperature for 1h. EtOAc (10 mL) was added and the mixture was stirred at room temperature for 20 min. Solid was filtered off. Solvent was evaporated and the residue was purified by silica gel column chromatography (0-5% MeOH in CH_2Cl_2) to give compound **45** (0.16 g, 69%). ^1H NMR (400 MHz, $CDCl_3$) δ: 9.35 (s, 1H), 7.68 (d, J=8.0Hz, 1H),

6.05 (s, 1H), 5.71 (d, J=8.0Hz, 1H), 4.00 (m, 8H), 1.80 (m, 2H), 1.00 (m, 12H). LC-MS (ESI): 531 $[M+H]^+$.

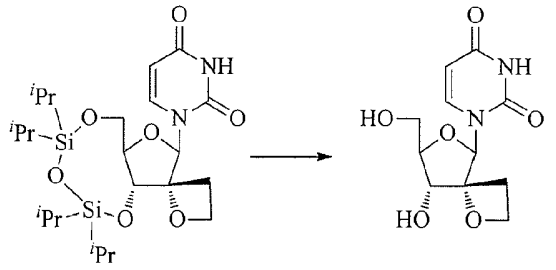
Steps 2-3. Preparation of compound 47.



45 **46** **47**

To a solution of **45** (0.25 g, 0.47 mmol) in CH_2Cl_2 (20 mL) and pyridine (2 mL) was added MsCl (0.10 g, 0.94 mmol) and the solution was stirred at room temperature for 3h. Water (2 mL) was added and the solution was evaporated to dryness. EtOAc (100 mL) was added and the organic solution was washed with water, brine and dried over Na_2SO_4. Solvent was evaporated and the residue was purified by silica gel column chromatography (0.80% EtOAc in hexanes) to give intermediate **46** which was dissolved in THF (10 mL). The solution was added into a mixture of NaH (130 mg, 60% mineral oil) in THF (10 mL). The resulting mixture was stirred at room temperature for 2h and poured into EtOAc (100 mL). The organic solution was washed with water, brine and dried over Na_2SO_4. Solvent was evaporated and the residue was purified by silica gel column chromatography (0-80% EtOAc in hexanes) to give compound **47** (0.054 g, 64%). δ_H ($CDCl_3$): 8.87 (s, 1H), 7.79 (d, J=8.4Hz, 1H), 6.22 (s, 1H), 5.68 (d, J=8.4Hz, 1H), 4.60 (m, 2H), 4.21 (d, J=13.6Hz. 1H), 4.00 (m, 2H), 3.90 (m, 1H), 2.62 (m, 2H), 1.10 (m, 12H). LC-MS (ESI): 513 $[M+H]^+$.

Step 4. Preparation of compound 48.

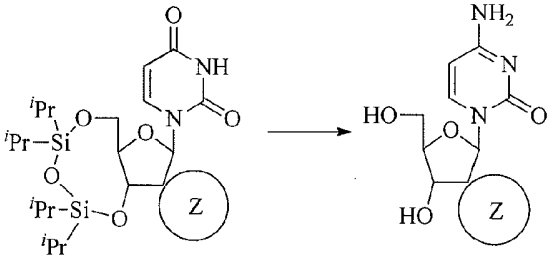


47 48

To a solution of **47** (0.07 g, 0.14 mmol) in MeOH (10 mL) was added NH_4F (100 mg) and the mixture was refluxed for 3h. Solvent was evaporated and the residue was purified by silica gel column chromatography (0-12% MeOH in CH_2Cl_2) to give compound **48**. ^1H NMR (400 MHz, CD_3OD) δ: 7.93 (d, J=8.0Hz, 1H), 6.17 (s, 1H), 5.67 (d, J=8.0Hz, 1H), 4.53 (m, 2H), 3.95 (m, 2H), 3.72 (m, 2H), 2.60 (m, 2H). LC-MS (ESI): 270 $[M+H]^+$.

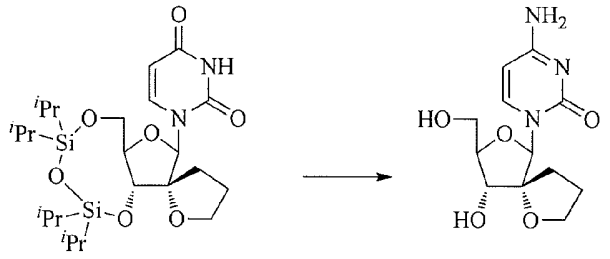
II. Preparation of 2'-Spiro-Cytosine Analogs

Examples 7-10 describe procedures for converting a protected 3'-5'-2'-spiro-uracil derivative to its corresponding cytidine derivative, as shown by the following equation.



Ex	Starting Material	Z	Product
12	43		49
13	31		50
14	35		51
15	47		52

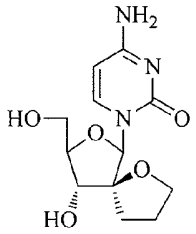
Example 7. Preparation of 4-amino-1-((5R,6R,8R,9R)-9-hydroxy-8-(hydroxymethyl)-1,7-dioxaspiro[4.4]nonan-6-yl)pyrimidin-2(1H)-one, 49. (2'-spiro-THF-ribo-cytidine)



43 49

To a solution of compound **43** (0.08 g, 0.14 mmol) in MeCN (10 mL) was added DMAP (0.02 g, 0.14 mmol) and Et_3N (0.07 g, 0.71 mmol) followed by addition of TsCl (0.08 g, 0.43 mmol) and the solution was stirred at room temperature for 1h. To the solution was added NH_4OH (30%, 2 mL) and the mixture was stirred at room temperature for 1h. Solvent was evaporated to dryness and the residue was co-evaporated with toluene twice to give crude cytosine analog which was dissolved in CH_2Cl_2 (10 mL) and pyridine (1 mL). To the solution was added BzCl (0.1 mL, 0.86 mmol) and the solution was stirred at room temperature for 2h. Water (5 mL) was added and the mixture was evaporated to dryness under reduced pressure. The residue was dissolved in EtOAc (100 mL) and the solution was washed with water, brine and dried over Na_2SO_4. Solvent was evaporated and the residue was purified by silica gel column chromatography (0-60% EtOAc in hexanes) to give N-benzoylcytosine analog which was dissolved in THF (10 mL). To the solution was added TBAF (0.12 g, 0.48 mmol) and the solution was stirred at room temperature for 1h. Solvent was evaporated and the residue was purified by silica gel column (0-8% MeOH in CH_2Cl_2) to give N-benzoyl nucleoside which was dissolved in 7N NH_3 in MeOH (8 mL) and the solution was stirred at room temperature for 20h. Solvent was evaporated and the residue was purified by silica gel column (0-30% MeOH in CH_2Cl_2) to give product **49** (0.09 g, 56% from **43**). ^1H NMR (400 MHz, CD_3OD) δ: 8.09 (d, J=7.6Hz, 1H), 5.99 (s, 1H), 5.87 (d, J=7.6Hz, 1H), 3.95 (m, 6H), 2.80 (m, 4H). LC-MS (ESI): 284 $[M+H]^+$.

Example 8. Preparation of 4-amino-1-((5S,6R,8R,9R)-9-hydroxy-8-(hydroxymethyl)-1,7-dioxaspiro[4.4]nonan-6-yl)pyrimidin-2(1H)-one, 50(2'-spiro-THF-cytidine)

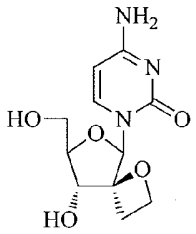


50

Compound **50** is prepared from compound **31** using a procedure that is analogous to that described in Example 7.

Data for **50**: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.65 (d, J = 7.2 Hz, 1H), 7.05-7.19 (m, 2H), 5.98 (s, 1H), 5.68 (d, J = 7.2 Hz, 1H), 5.57 (d, J = 5.6 Hz, 1H), 4.86-4.92 (m, 1H), 3.74-3.77 (m, 1H), 3.54-3.70 (m, 4H), 3.35-3.38 (m, 1H), 2.17-2.24 (m, 1H), 1.66-1.85 (m, 3H). LC-MS(ESI): m/z 283.9 $[M+1]^+$. HRMS(TOF-ESI): Calc. For $C_{12}H_{18}N_3O_5$, 284.1241; found 285.1235.

Example 9. Preparation of 4-amino-1-((4S,5R,7R,8R)-8-hydroxy-7-(hydroxymethyl)-1,6-dioxaspiro[3.4]octan-5-yl)pyrimidin-2(1H)-one, 51 (2'-spiro-oxetane-ara-cytidine)



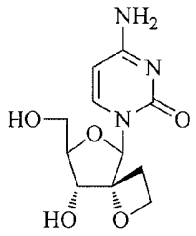
51

Compound **51** is prepared from compound **35** using a procedure that is analogous to that described in Example 7.

Data for **51**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.55 (d, J = 7.2 Hz, 1H), 7.12-7.20 (m, 2H), 6.16 (s, 1H), 5.76 (d, J = 5.2 Hz, 1H), 5.68 (d, J = 8.0 Hz, 1H), 4.91-4.94 (m, 1H), 4.24-4.29 (m, 1H), 4.06-4.11 (m, 1H), 3.93-3.96 (m, 1H), 3.46-

3.63 (m, 3H), 2.87-2.94 (m, 1H), 2.42-2.47 (m, 1H). LC-MS(ESI): *m/z* 269.9 $[M+1]^+$. HRMS (TOF-ESI): Calc. For $C_{11}H_{16}N_3O_5$, 270.1084; found 270.1081.

Example 10. Preparation of 4-amino-1-((4R,5R,7R,8R)-8-hydroxy-7-(hydroxymethyl)-1,6-dioxaspiro[3.4]octan-5-yl)pyrimidin-2(1H)-one, **52** (2'-spiro-oxetane-THF-cytidine)



52

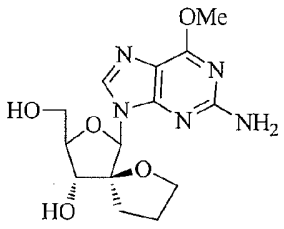
Compound **52** is prepared from compound **47** using a procedure that is analogous to that described in Example 7.

Data for **52**: ^{1}H NMR (400 MHz, CD_3OD) δ: 8.097.98 (d, J=7.6Hz, 1H), 6.26 (s, 1H), 5.87 (d, J=7.6Hz, 1H), 4.55 (m, 2H), 3.96 (m, 2H), 3.74 (m, 2H), 2.54 (m, 2H). LC-MS (ESI): 270 $[M+H]^+$.

III. Preparation of 2'-Spiro-Ara- and 2'-Spiro-Ribo Guanosine Analogs

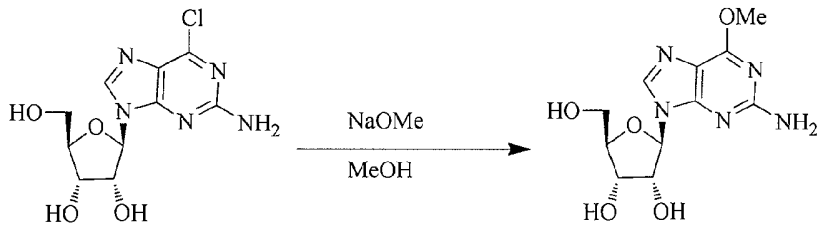
A. Preparation of 2'-Spiro-Ara-Guanosine Analogs

Example 11. Preparation of (5S,6R,8R,9R)-6-(2-amino-6-methoxy-9H-purin-9-yl)-8-(hydroxymethyl)-1,7-dioxaspiro[4.4]nonan-9-ol, 62(2'- spiro-THF-ara-(2-amino-6-methoxy-purine) analogs)



62

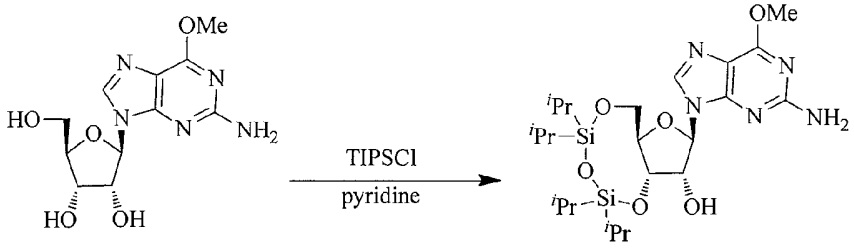
Step 1. Preparation of compound 54.



53 54

To a solution of compound **53**(20.0 g, 66.29 mmol) in anhydrous methanol (400 mL) was added NaOMe (3.58 g, 66.29 mmol) at room temperature. The mixture was heated to reflux for 12h. The solution was filtered and the filtrate was evaporated to give a crude compound **54**. (18.0 g, 91.14%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.09 (s, 1H), 5.75 (d, J = 5.6 Hz, 1H), 4.41-4.44 (m, 1H), 4.02-4.09 (m, 1H), 3.96 (s, 3H), 3.86-3.89 (m, 1H), 3.62 (dd, J = 12.0Hz, 4.0 Hz, 1H), 3.52 (dd, J = 12.0Hz, 4.0 Hz, 1H).

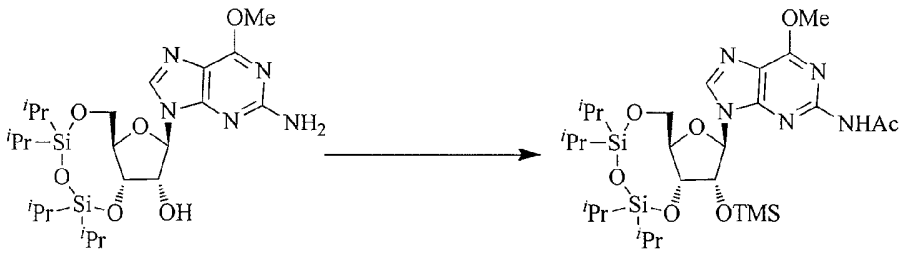
Step 2. Preparation of compound 55.



54 55

To a solution of compound **54** (18.0 g, 60.55 mmol) in anhydrous pyridine (200 mL) was added TIPSCl (22.9 g, 72.66 mmol) at room temperature. The mixture was stirred at room temperature for 20h. Solvent was evaporated under reduced pressure and the residue was dissolved in EtOAc (200 mL). The solution was washed with H_2O, dried over Na_2SO_4 and evaporated to give a crude **55** which was used for next step without further purification. (16.6 g, 50.8 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.94 (s, 1H), 6.47 (s, 1H), 5.76 (s, 1H), 5.63 (d, J = 5.2Hz, 1H), 4.38-4.41 (m, 1H), 4.32-4.35 (m, 1H), 4.00-4.09 (m, 2H), 3.98 (s, 3H), 3.91-3.97 (m, 1H), 0.94-1.04 (m, 28H).

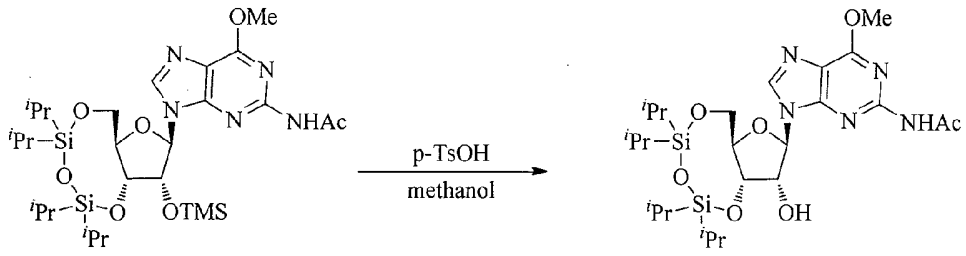
Step 3. Preparation of compound 56.



55 56

To a solution of compound **55** (16.6 g, 30.8 mmol) in anhydrous CH_2Cl_2 (200 mL) was added Et_3N (6.45 mL, 46.2 mmol) and TMSCl (4.99 g, 46.2 mmol) at 0°C. The mixture was stirred room temperature for 10h and the solution was washed with H_2O, dried over Na_2SO_4 and the solvent was evaporated. The residue was purified by silica gel column chromatography (hexanes:EtOAc = 5:1) to give intermediate (16.5 g, 87.53 %) which was dissolved in pyridine (150 mL). To the solution was added solution of CH_3COCl (1.92 ml, 26.96 mmol) in CH_2Cl_2 (5 mL) at 0°C and the solution was stirred overnight at room temperature. The solvent was evaporated and the residue was dissolved in CH_2Cl_2 (200 mL). The organic solution was washed with H_2O, dried with Na_2SO_4 and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes:EtOAc = 5:1) to give the compound **56** (11.0 g, 62.5 %).

Step 4. Preparation of compound 57.

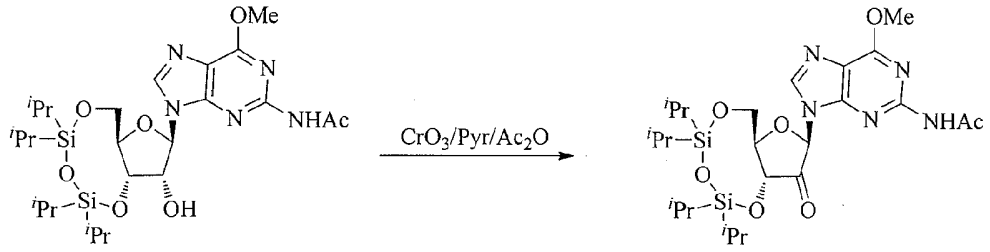


56 57

To a solution of compound **56** (11.0g, 17.65 mmol) in methanol (100 mL) was added p-TsOH (1.1g, 6.39 mmol) and the resulting solution was stirred overnight at room temperature. Solvent was evaporated and the residue was dissolved in EtOAc

(200 mL). The solution was washed with H_2O and dried with Na_2SO_4. Solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexanse:EtOAc= 5:1) to give compound **57** (8.0 g, 77.9 %). ^1H NMR (400 MHz, DMSO-d_6): δ = 10.39 (s, 1H), 8.28 (s, 1H), 5.87 (s, 1H), 5.61 (d, J = 4.4Hz, 1H), 4.49-4.51 (m, 2H), 4.07-4.11 (m, 1H), 4.03 (s, 3H), 4.00-4.02 (m, 1H), 3.91-3.94 (m, 1H), 2.22 (s, 3H), 0.94-1.04 (m, 28H).

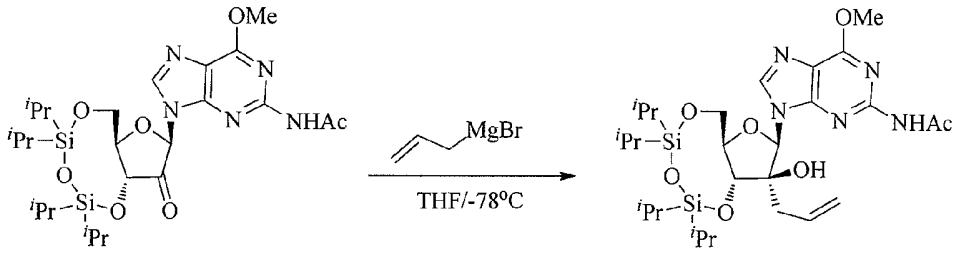
Step 5. Preparation of compound 58.



57 **58**

To a stirred solution of CrO_3 (2.58 g, 25.8 mmol), anhydrous pyridine (4.18 mL, 51.6 mmol) and Ac_2O (2.47 mL, 25.8 mmol) was added a solution of compound **57** (5.0 g, 8.61 mmol) in CH_2Cl_2 (100 mL). The mixture was stirred 60 min and filtered through a short silica gel column. The filtrate was evaporated and the residue was purified by silica gel column chromatography (hexanes:EtOAc = 3:1) to give compound **58** (3.0 g, 60.0 %)

Step 6. Preparation of compound 59.

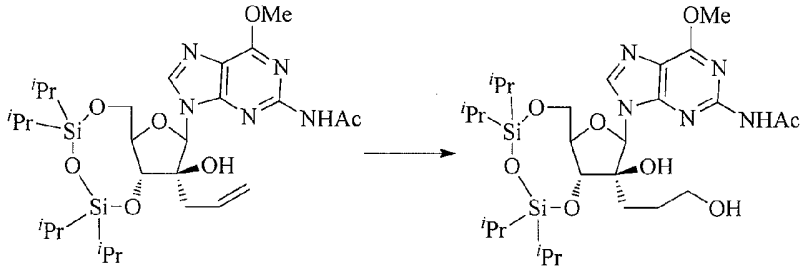


58 **59**

To a solution of compound **58** (3.0 g, 5.18 mmol) in THF (100 mL) was added solution of allylmagnesium bromide (10.36 mL, 10.36 mmol) at -78°C and the

mixture was stirred for 2 h at the same temperature. Then the temperature was raised to -10°C and the reaction was quenched with H_2O. The mixture was extracted with DCM. The organic solution was dried with Na_2SO_4 and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes:EtOAc = 3:1) to give compound **59** (2.0 g, 62.5 %). ^{1}H NMR(400 MHz, DMSO-d_6): δ = 10.36 (s, 1H), 8.17 (s, 1H), 5.99 (s, 1H), 5.82-5.90 (m, 1H), 5.49 (s, 1H), 5.01-5.20 (m, 2H), 4.46 (d, J = 7.2Hz, 1H), 4.07 (s, 3H), 3.97-4.06 (m, 3H), 2.48-2.58 (m, 2H), 2.26 (s, 3H), 0.94-1.04 (m, 28H).

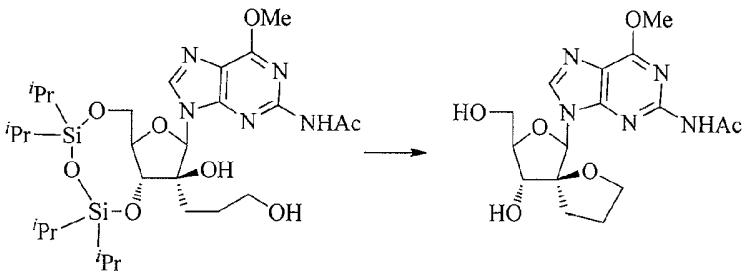
Step 7. Preparation of compound 60.



59 **60**

To a solution of of **59** (1.20 g, 2.07 mmol) in THF (60 mL) was added $BH_3.SMe_2$ (0.5 mL, excess) and the solution was stirred at 0°C for 1h. To the solution was added an additional BH_3•SMe_2 (0.5 mL, excess) and the solution was stirred at 0°C for 2h. To the resulting solution was added 2N NaOH (2 mL) followed by the addition of H_2O_2 (30%, 2 mL) and the mixture was stirred at room temperature for 1h. To the mixture was added additional 2N NaOH (2 mL) followed by the addition of H_2O_2 (30%, 2 mL) and the mixture was stirred at room temperature for 2h. EtOAc (200 mL) was added and the mixture was washed with brine and dried over Na_2SO_4. Solvent was evaporated and the residue was purified by silica gel column (0-80% EtOAc in hexanes) to give product **60** (0.28 g, 22.7%) as foam. ^{1}H NMR (400 MHz $CDCl_3$): 8.48 (s, 1H), 8.07 (s, 1H), 6.41 (br s, 1H), 6.15 (s. 1H), 5.00 (br s, 1H), 4.48 (d, J=9.2Hz, 1H), 4.21 (d, J=13.6Hz, 1H), 4.13-4.03 (m, 2H), 4.00 (s, 3H), 3.81 (J=8.4Hz, 1H), 3.47 (m, 1H), 2.28-1.98 (m, 7H), 1.08 (m, 28H). LC-MS (ESI): 640 $[M+H]^+$.

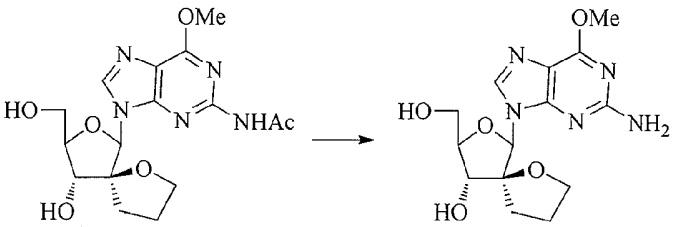
Step 8. Preparation of compound 61.



To a solution of compound **60** (0.28 g, 0.44 mmol) in CH_2Cl_2 (20 mL) and pyridine (1 mL) was added MsCl (0.3 mL, 3.88 mmol), and the solution was stirred at room temperature for 3h. Water (10 mL) was added and the mixture was extracted with EtOAc (100 mL). The organic solution was washed with brine and dried over Na_2SO_4. Solvent was removed and the residue was used for the next reaction without purification.

To a solution of the mesylate obtained above in THF (30 mL) was added NaH (60% in mineral oil, 0.3 g, 7.5 mmol) and the mixture was stirred at room temperature for 2h. Water (10 mL) was added slowly. The mixture was extracted with EtOAc (100 mL). The organic solution was washed with brine and dried over Na_2SO_4. Solvent was evaporated and the residue was dissolved in MeOH (10 mL). To the solution was added NH_4F (0.20 g, 5.40 mmol) and the mixture was heated at reflux for 5h. Solvent was evaporated and the residue was purified by silica gel column (0-10% MeOH in CH_2Cl_2) to give product **61**. (0.20 g, 47.8%). ^{1}NMR (400 MHz CD_3OD): 8.8.46 (s, 1H), 6.26 (s, 1H), 4.20 (m, 4H), 3.90 (m, 1H), 3.85 (m, 2H), 3.71 (m, 1H), 3.34 (m, 1H), 2.41 (m, 1H), 2.34 (s, 3H), 1.86 (m, 3H). LC-MS (ESI): 380 $[M+H]^+$.

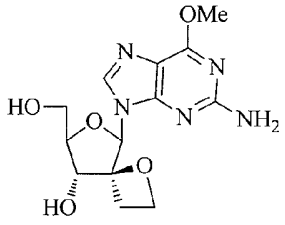
Step 9. Preparation of compound 62.



61 **62**

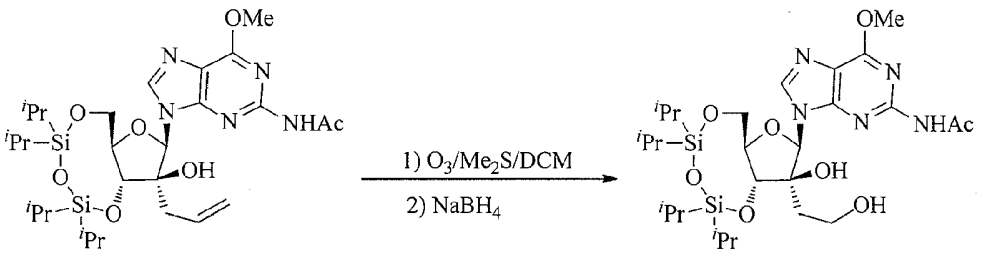
To a solution of compound **61** (0.08 g, 0.21 mmol) in MeOH (5 mL) was added NaOMe (4.8 M, 0.4 mL) and the solution was stirred at room temperature for 24 h. Solvent was evaporated and the residue was purified by silica gel column chromatography (0-15% MeOH in CH_2Cl_2) to give a solid which was recrystallized from MeOH in EtOAc to product **62** as white solid (0.04 g, 56%). ^{1}NMR (400 MHz CD_3OD): 8.05 (s, 1H), 6.07 (s, 1H), 4.08 (m, 1H), 4.91 (m, 1H), 3.83 (m, 2H), 3.75 (m, 1H), 3.35 (m, 1H), 3.30 (s, 3H), 2.40 (m, 1H), 1.86 (m, 2H), 1.61 (m, 1H). LC-MS (ESI): 338 $[M+H]^+$.

Example 12. Preparation of (4S,5R,7R,8R)-5-(2-amino-6-methoxy-9H-purin-9-yl)-7-(hydroxymethyl)-1,6-dioxaspiro[3.4]octan-8-ol, 66 (2'-spiro-oxtane-ara-(2-amino-6-methoxy-purine) analog)



66

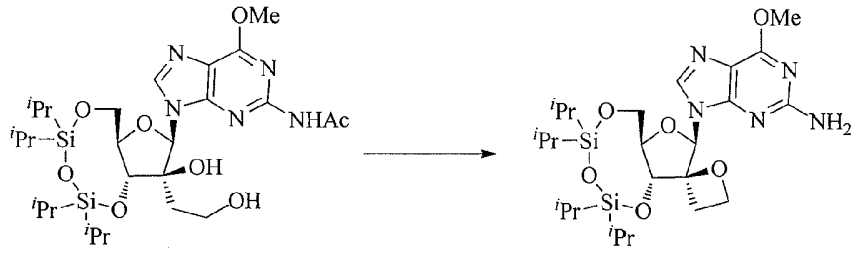
Step 1. Preparation of compound 64.



63 64

To a solution of compound **63** (1.7 g, 2.74 mmol) in DCM (250 mL) was bubbled with O_3 and the solution was stirred at -78°C for 3h. To the solution were added Me_2S (1 mL) and $NaBH_4$ (0.104 g, 2.74 mmol) at room temperature. The mixture was stirred overnight and extracted with CH_2Cl_2. The organic solution was dried with Na_2SO_4. Solvent was evaporated and the residue was purified by silica gel column chromatography (hexanes:EtOAc = 1:1) to give compound **64** (0.8 g, 47.06 %).

Step 2. Preparation of compound 65.



64 65

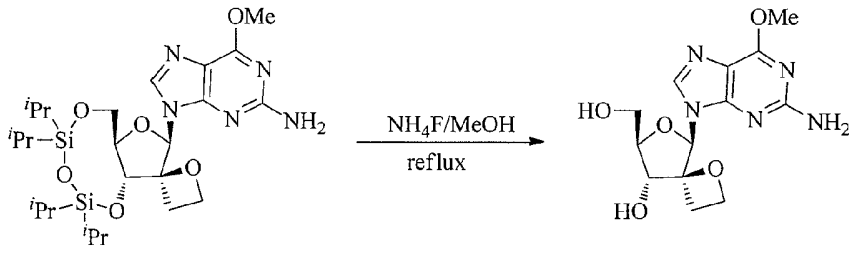
A solution of MsCl (0.22 g, 1.92 mmol) in anhydrous CH_2Cl_2 (3 mL) was added to a solution of **64** (0.80 g, 1.28 mmol) in anhydrous pyridine (5.0 ml) drop-wise at room temperature and the solution was stirred at room temperature for 12 h. Methanol (5.0 mL) was added and the resulting mixture was evaporated to dryness under reduced pressure. The residue was co-evaporated with anhydrous toluene (2 × 5 mL) and purified by silica gel column chromatography (hexanes:EtOAc = 3:1) to give the mesylate (0.50 g, 55.6 %). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.15 (s, 1H),

8.09 (s, 1H), 5.95 (s, 1H), 4.66-4.69 (m, 2H), 4.51 (d, J = 7.6Hz, 1H), 4.10 (s, 3H), 4.05-4.11 (m, 2H), 3.81-3.87 (m, 1H), 2.97 (s, 3H), 2.50-2.58 (m, 1H), 2.38 (s, 3H), 2.19-2.24 (m, 1H), 0.94-1.04 (m, 28H).

To a stirred suspension of NaH (113.8 mg, 2.84 mmol) in anhydrous THF (10 mL) was added a solution of the mesylate (0.50 g, 0.71 mmol) in THF (5 mL) drop-wise at 0°C and the mixture was stirred at room temperature for 2 h. The reaction was quenched by addition of ice-cold H_2O (10 mL) slowly and the mixture was extracted with CH_2Cl_2. The organic phase was washed with saturated aqueous $NaHCO_3$ (2 × 20 mL), dried (Na_2SO_4), filtered and evaporated to dryness under reduced pressure to give 2'-oxetane-intermediate (0.4 g, 92.6 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (s, 1H), 8.19 (s, 1H), 6.29 (s, 1H), 4.86 (d, J = 6.8Hz, 1H), 4.21-4.29 (m, 2H), 4.14 (s, 3H), 3.98-4.03 (m, 1H), 3.81-3.89 (m, 2H), 3.25-3.34 (m, 1H), 2.53 (s, 3H), 2.45-2.52 (m, 1H), 0.94-1.04 (m, 28H).

To a stirred solution of 2'-oxetane-intermediate (400 mg, 0.658 mmol) in anhydrous methanol (50 mL) was added NaOMe (71.28 mg, 1.32 mmol) and the solution was stirred at room temperature for 20 h. The solution was evaporated to give compound **65** (0.3 g, 92.6 %).

Step 3. Preparation of compound 66



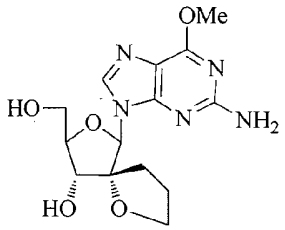
65 **66**

To a stirred solution of **65** (300 mg, 0.53 mmol) in anhydrous methanol (30 mL) was added NH_4F (39.28 mg, 1.06 mmol) at room temperature and the solution was heated to refluxed for 10 h. The solution was evaporated and the residue was purified by silica gel column chromatography (CH_2Cl_2:MeOH = 20:1) to provide compound **66** (36.0 mg, 21.05 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.94 (s, 1H), 6.52 (s, 2H), 6.09 (s, 1H), 5.92 (d, J = 5.2 Hz, 1H), 5.02 (t, J = 5.2 Hz, 1H), 4.28-4.30 (m, 1H), 4.17-4.19 (m, 1H), 3.97 (s, 3H), 3.94-3.97 (m, 1H), 3.69-3.73 (m, 1H),

3.53-3.59 (m, 2H), 2.95-2.98 (m, 1H), 2.35-2.37 (m, 1H). HRMS (TOF-ESI): Calc. For $C_{13}H_{17}N_5O_5$, 324.1308; found 324.1306.

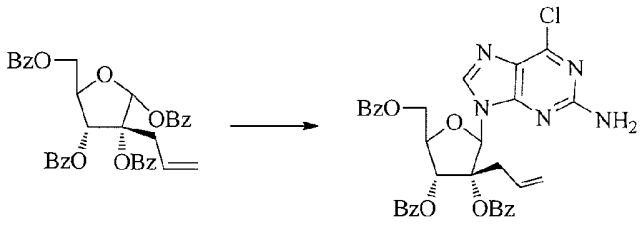
B. Preparation of 2'-Spiro-Ribo-Guanosine Analogs

Example 13. Preparation of (5R,6R,8R,9R)-6-(2-amino-6-methoxy-9H-purin-9-yl)-8-(hydroxymethyl)-1,7-dioxaspiro[4.4]nonan-9-ol, 72 (2'-spiro-THF-ribo-(2-amino-6-methoxy-purine) analog)



72

Step 1. Preparation of compound 67.

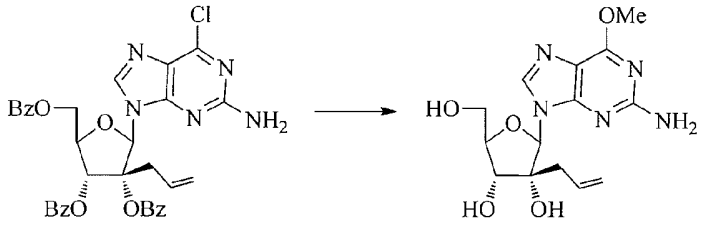


37 67

To a precooled (0 °C) solution of compound **37** (4.00 g, 6.59 mmol) and 6-chloroguanine (1.68 g, 9.89 mmol) in MeCN (80 mL) were added DBN (2.46 g, 19.78 mmol) then TMSOTf (5.86 g, 26.38 mmol), and the solution was heated at 65°C for 5h then room temperature for 16h. The solution was cooled to room temperature and poured into a mixture of EtOAc (300 mL) and excess $NaHCO_3$ with ice. Organic solution was washed with $NaHCO_3$, brine and dried over Na_2SO_4. Solvent was evaporated and the residue was purified by silica gel column chromatography (5-60% EtOAc in hexanes) to give compund **67** (3.2 g, 74%). ^{1}NMR (400 MHz CD_3OD): δ: 8.18-7.25 (m, 16Hz), 6.73 (s, 1H), 5.40 (m, 3H), 5.12

(m, 2H), 4.82 (m, 1H), 4.74 (m, 3H), 3.04 (m, 1H), 2.52 (m, 1H). LC-MS (ESI): 654 $[M+H]^+$.

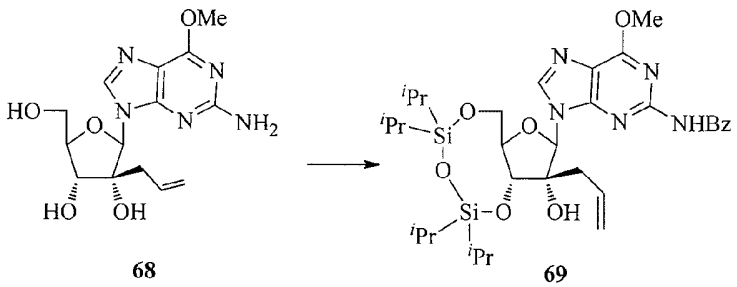
Step 2. Preparation of compound 68.



67 68

To a mixture of compound **67** (3.20 g, 4.89 mmol) in MeOH (80 mL) was added 25% NaOMe in MeOH 1.86 g, 48.92 mmol) and the solution was stirred at room temperature for 24h. Solvent was evaporated and the residue was purified by silica gel column chromatography (0-15% MeOH in CH_2Cl_2) to give product **68** as white solid. ^{1}NMR (400 MHz CD_3OD): δ: 8.13 (s, 1H), 5.97 (s, 1H), 5.67 (m, 1H), 4.77 (m, 1H), 4.56 (m, 1H), 4.45 (d, J=8.8Hz, 1H), 4.13-3.83 (m, 6H), 2.25 (m, 1H), 2.05 (m, 1H). LC-MS (ESI): 338 $[M+H]^+$.

Step 3. Preparation of compound 69.

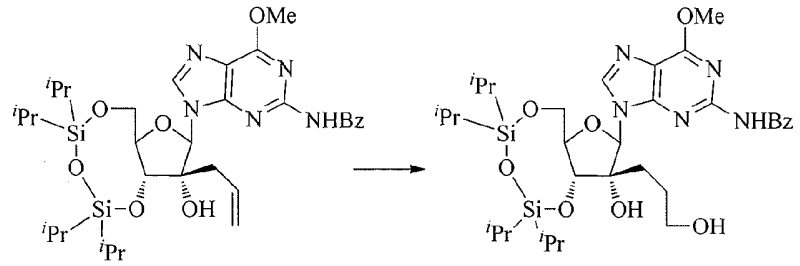


68 69

To a solution of compound **68** (1.33 g, 3.94 mmol) in pyridine (20 mL) was added TIPSCl (1.37 g, 4.34 mmol) and the solution was stirred at room temperature for 16 h. Solvent was evaporated and the residue re-dissolved in EtOAc (400 mL) and the solution was washed with brine and dried over Na_2SO_4. Solvent was evaporated and the residue purified by silica gel column chromatography (0-5% MeOH in CH_2Cl_2) to give intermediate (1.30 g, 57%). ^{1}NMR (400 MHz CD_3OD):

δ: 7.757 (s, 1H), 5.93 (s, 1H), 5.66 (m, 1H), 4.88 (m, 1H), 4.82 (s, 2H), 4.73 (d, J=7.6Hz, 1H), 4.64 (m, 1H), 4.20 (m, 1H), 4.08 (m, 7H), 2.20 (m, 2H), 1.07 (m, 28H). LC-MS (ESI): 450 $[M+H]^+$. To a solution of the intermediate in pyridine (10 mL) and CH_2Cl_2 (20 mL) was added benzoyl chloride (0.63 g, 4.48 mmol) and the solution was stirred at room temperature for 5h. Water (10 mL) was added and the solution was evaporated to give a residue which was dissolved in EtOAc (200 mL). Organic solution was washed with brine and dried over Na_2SO_4. Solvent was evaporated and the residue was purified by silica gel column chromatography (0-5% MeOH in CH_2Cl_2) to give compound **69** (1.50 g, 98%) as foam. δ_H (CD_3OD): 8.46 (s, 1H), 7.78 (m, 6H), 5.98 (s, 1H), 5.72 (m, 1H), 5.00 (d, J=8.0Hz, 1H), 4.83 (d, J=10.4Hz, 1H), 4.50 (m, 1H), 4.35 (m, 1H), 4,10 (m, 5H), 2.32 (m,1H), 2.20 (m, 1H), 1.05 (m, 28H). LC-MS (ESI): 684 $[M+H]^+$.

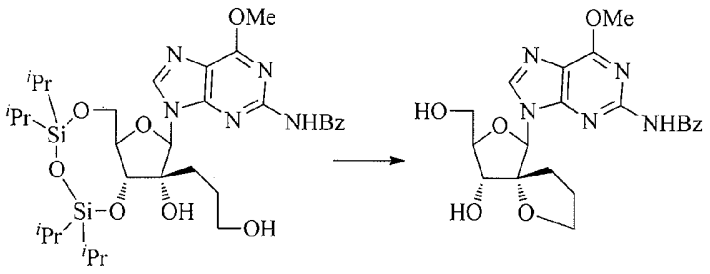
Step 4. Preparation of compound 70.



69 **70**

To a solution of compound **69** (0.20 g, 0.29 mmol) in THF (20 mL) was added BH_3•SMe_2 (0.15 g, 1.46 mmol) and the solution was stirred at 0°C for 3h. To the solution was added 2N NaOH (2N, 1 mL) then H_2O_2 (0.5 mL) at 0°C. The mixture was stirred at room temperature for 2h. EtOAc (100 mL) was added and the solution was washed with brine and dried over Na_2SO_4. Solvent was evaporated and the residue was purified by silica gel column chromatography (0-100% EtOAc in hexanes) to give compound **70** (0.07 g, 33%). ^{1}NMR (400 MHz CD_3OD): δ: 8.60 (s, 1H), 8.31 (s, 1H), 7.65 (m, 5H), 6.26 (s, 1H), 4.47 (d, J=8.8Hz, 1H), 4.26 (m, 2H), 4.10 (m, 4H), 3.50 (m, 2H), 1.83 (m, 1H), 1.61 (m, 2H), 1.27 (m, 1H), 1.10 (m, 28H). LC-MS (ESI): 702 $[M+H]^+$.

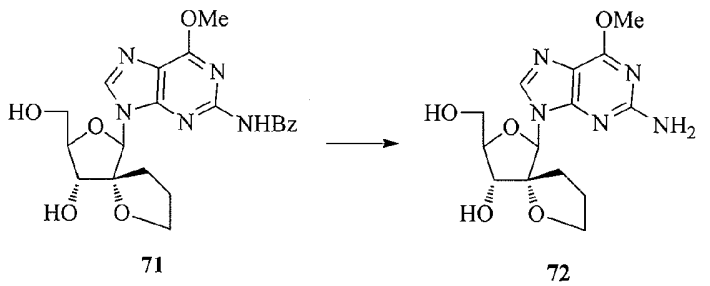
Step 5. Preparation of compound 71.



70 71

To a solution of compound **70** (0.05 g, 0.07 mmol) in CH_2Cl_2 (10 mL) and pyridine (0.5 mL) was added MsCl (0.1 mL g, excess) and the solution was stirred at room temperature for 2 h. EtOAc (100 mL) was added to the reaction. The mixture was washed with brine and dried over Na_2SO_4. Solvent was evaporated and the residue was co-evaporated with toluene twice to give mesylate. To a solution of the mesylate in THF (10 mL) was added NaH (60% in mineral oil, 0.06 g, 1.50 mmol) and the mixture was stirred at room temperature for 2 h. EtOAc (100 mL) was added and the organic solution was washed with brine and dried over Na_2SO_4. Solvent was evaporated and the residue was dissolved in MeOH (10 mL). To the solution was added NH_4F (0.10 g, 2,75 mmol) and the mixture was refluxed at 60 °C for 4 h. Solvent was evaporated and the residue was purified by silica gel column chromatorgraphy (0-10% MeOH in CH_2Cl_2) to give product **71** (0.023 g, 74% from **70**) as white solid. ^{1}NMR (400 MHz CD_3OD): δ: 8.63 (s, 1H), 7.80 (m, 5H), 6.20 (s, 1H), 4.59 (m, 1H), 4.00 (m, 9H), 1.94 (m, 3H), 1.36 (m, 1H). LC-MS (ESI): 440 $[M+H]^+$.

Step 6. Preparation of compound 72.

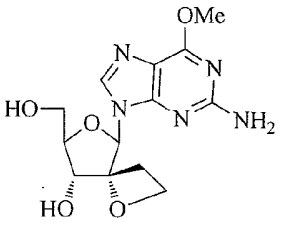


71 72

To a solution of **71** (0.03 g, 0.07 mmol) in MeOH (5 mL) was added NaOMe (0.11 g, 2.00 mmol) and the solution was stirred at room temperature for 2 days. Solvent was evaporated and the residue was purified by silica gel column chromatography (0-15% MeOH in CH_2Cl_2) to give nucleoside **72** (0.02 g, 87%) as white solid. ^{1}NMR (400 MHz CD_3OD): δ: 8.24 (s, 1H), 5.97 (s, 1H), 4.36 (d, J=9.6Hz, 1H), 4.00 (m, 8H), 1.94 (m, 2H), 1.80 (m,1H), 1.34 (m, 1H). LC-MS (ESI): 338 $[M+H]^+$.

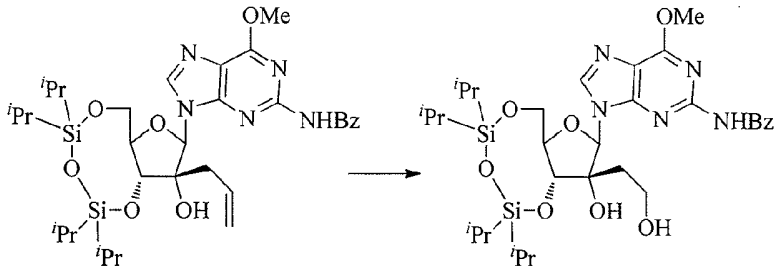
The corresponding guanosine derivative of **72** is prepared in a manner analogous to Example 15.

Example 14. Preparation of (4R,5R,7R,8R)-5-(2-amino-6-methoxy-9H-purin-9-yl)-7-(hydroxymethyl)-1,6-dioxaspiro[3.4]octan-8-ol, 76 (2'-spiro-oxetane-ribo-(2-amino-6-methoxy-purine) analog)



76

Step 1. Preparation of compound 74.

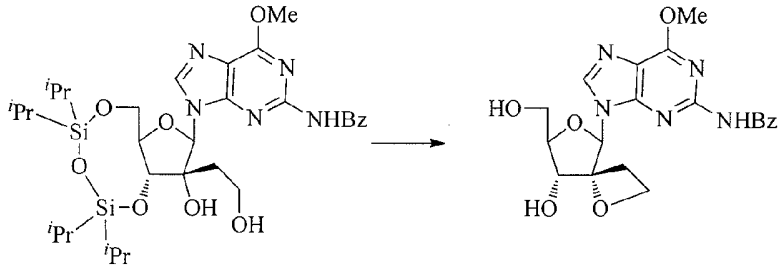


73 **74**

To a mixture of compound **73** (0.30 g. 0.44 mmol) in THF (6 mL), t-Butanol (6 mL) and water (1 mL) was added 0.25% OsO_4 in t-Butanol (0.5 mL) followed by addition of 50% NMO (0.2 mL, 0.85 mmol) and the mixture was stirred at room

temperature for 16 h. Solvent was evaporated and the residue was co-evaporated with toluene twice to give diol as a mixture of diastereomers which was dissolved in THF (10 mL). To the solution was added water (1 mL) followed by addition of $NaIO_4$ (excess) portion-wise until starting material disappeared at room temperature for 3h. EtOAc (100 mL) was added and the solution was washed with brine and dried over Na_2SO_4. Solvent was evaporated and the residue was dissolved in EtOAc (10 mL) and EtOH (10 mL). To the pre-cooled solution at 0°C was added $NaBH_4$ (50.16 mg, 1.32 mmol) and the mixture was stirred at 0°C for 1h. EtOAc (100 mL) was added and the residue was purified by silica gel column chromatography (0-10% MeOH in CH_2Cl_2) to give compound **74** (0.14 g, 43% from **73**). ^{1}NMR (400 MHz $CDCl_3$): δ: 8.57 (s, 1H), 8.48 (s, 1H), 7.70 (m, 5H), 6.26 (s, 1H), 4.15 (m, 9H), 1.28 (m, 2H), 1.15 (m, 28H). LC-MS (ESI): 688 $[M+H]^+$.

Step 2. Preparation of compound 75.



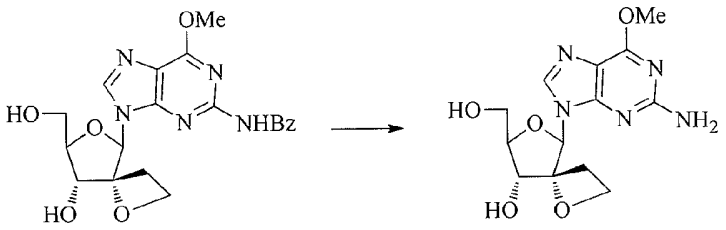
74 75

To a solution of compound **74** (0.33 g, 0.47 mmol) in CH_2Cl_2 (30 mL) and pyridine (3 mL) was added MsCl (0.11 g, 0.94 mmol) and the solution was stirred at room temperature for 3 h. Water (10 mL) was added and the mixture was extracted with EtOAc (100 mL). The solution was washed with brine and dried over Na_2SO_4. Solvent was evaporated and the residue was purified by silica gel column chromatography (0-100% EtOAc in hexanes) to give mesylate (0.30 g, 82%). δ_H ($CDCl_3$): 8.53 (s, 1H), 8.21 (s, 1H), 7.65 (m, 5), 6.14 (s, 1H), 4.80 (s, 1H), 4.54 (m, 2H), 4.33 (m, 1H), 4.16 (s, 3H), 4.10 (m, 3H), 2.95 (s, 3H), 2.05 (m, 2H), 1.05 (m, 28H). LC-MS (ESI): 766 $[M+H]^+$. To a solution of mesylate (0.20 g, 0.26 mmol) in THF (10 mL) was added NaH (60% mineral oil, 110 mg, 2.75 mmol) and the mixture was stirred at room temperature for 1h. The mixture was poured into EtOAc (100 mL) and the solution was washed with brine and dried over Na_2SO_4. Solvent

was evaporated and the residue was purified by silica gel column chromatography (0-80% EtOAc in hexanes) to give oxetane-intermediate (0.15 g, 57%). ^{1}NMR (400 MHz $CDCl_3$): δ: 8.47 (s, 1H), 8.23 (s, 1H), 7.65 (m, 5H), 6.38 (s, 1H), 7.74 (m, 1H), 4.59 (m, 1H), 4.46 (, d, J=9.2Hz, 1H), 4.26 (d, J=13.2Hz, 1H), 4.15 (s, 3H), 4.00 (m, 2H), 2.56 (m, 2H), 1.09 (m, 28H). LC-MS (ESI): 686 $[M+H]^+$.

To the solution of the oxetane-intermediate in MeOH (10 mL) was added NH_4F (1.3 mmol, 46.8 mg) and the mixture was heated at 60 °C for 5h. Solvent was evaporated and the residue was purified by silica gel column chromatography (0-10% MeOH in CH_2Cl_2) to give compound **75** (0.05 g, 43% from **74**) as white solid. LC-MS (ESI): 428 $[M+H]^+$.

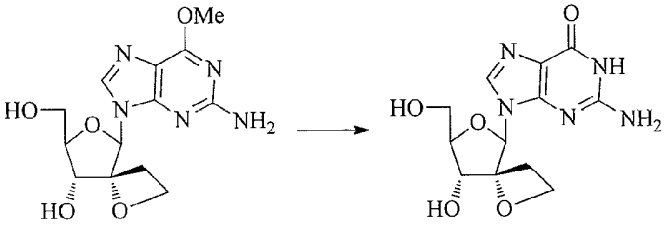
Step 3. Preparation of compound 76.



75 **76**

A solution of compound **75** (0.20 g, 0.45 mmol) in MeOH (10 mL) was added NaOMe (4.8 M, 0.8 mL) and the solution was stirred at room temperature for 20h. Solvent was evaporated and the residue was purified by silica gel column chromatography (0-15% MeOH in CH_2Cl_2) to give compound **76** (0.10 g, 69%). ^{1}NMR (400 MHz CD_3OD): δ: 8.15 (s, 1H), 6.26 (s, 1H), 4.50 (m, 3H), 4.05 (s, 3H), 3.96 (m; 1H), 3.80 (m, 2H), 2.57 (m, 1H), 2.27 (m, 1H). LC-MS (ESI): 324 $[M+H]^+$.

Example 15. Preparation of 2-amino-9-((4R,5R,7R,8R)-8-hydroxy-7-(hydroxymethyl)-1,6-dioxaspiro[3.4]octan-5-yl)-1H-purin-6(9H)-one, 77 (2'-spiro-oxetane-ribo-guanosine)



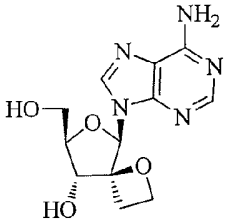
76 77

To a solution of compound **76** (0.04 g, 0.12 mmol) in MOPS buffer (0.1 M, 10 mL) was added adenosine deaminase (2.0 mg) and the solution was kept at 37°C for 2 days. Solvent was evaporated and the residue was purified by silica gel column chromatography (0-30% MeOH in CH_2Cl_2) to give a crude compound **77** which was recrystallized from MeOH to remove crystalline of phosphate salt from buffer. The residue was re-dissolved in MeOH (50 mL) and formic acid (1 mL) was added. The solution was evaporated and the residue was co-evaporated with toluene twice. The resulting solid was purified by silica gel column chromatography (0-30% MeOH in CH_2Cl_2) to give product **77** as white solid (0.02 g, 65%). ^{1}NMR (400 MHz CD_3OD): δ: 8.04 (s, 1H), 6.21 (s, 1H), 4.54 (m, 2H), 4.36 (d, J=8.8Hz, 1H), 4.94 (m, 1H), 3,78 (m, 2H), 2.60 (m, 1H), 2,33 (m, 1H). LC-MS (ESI): 310 $[M+H]^+$.

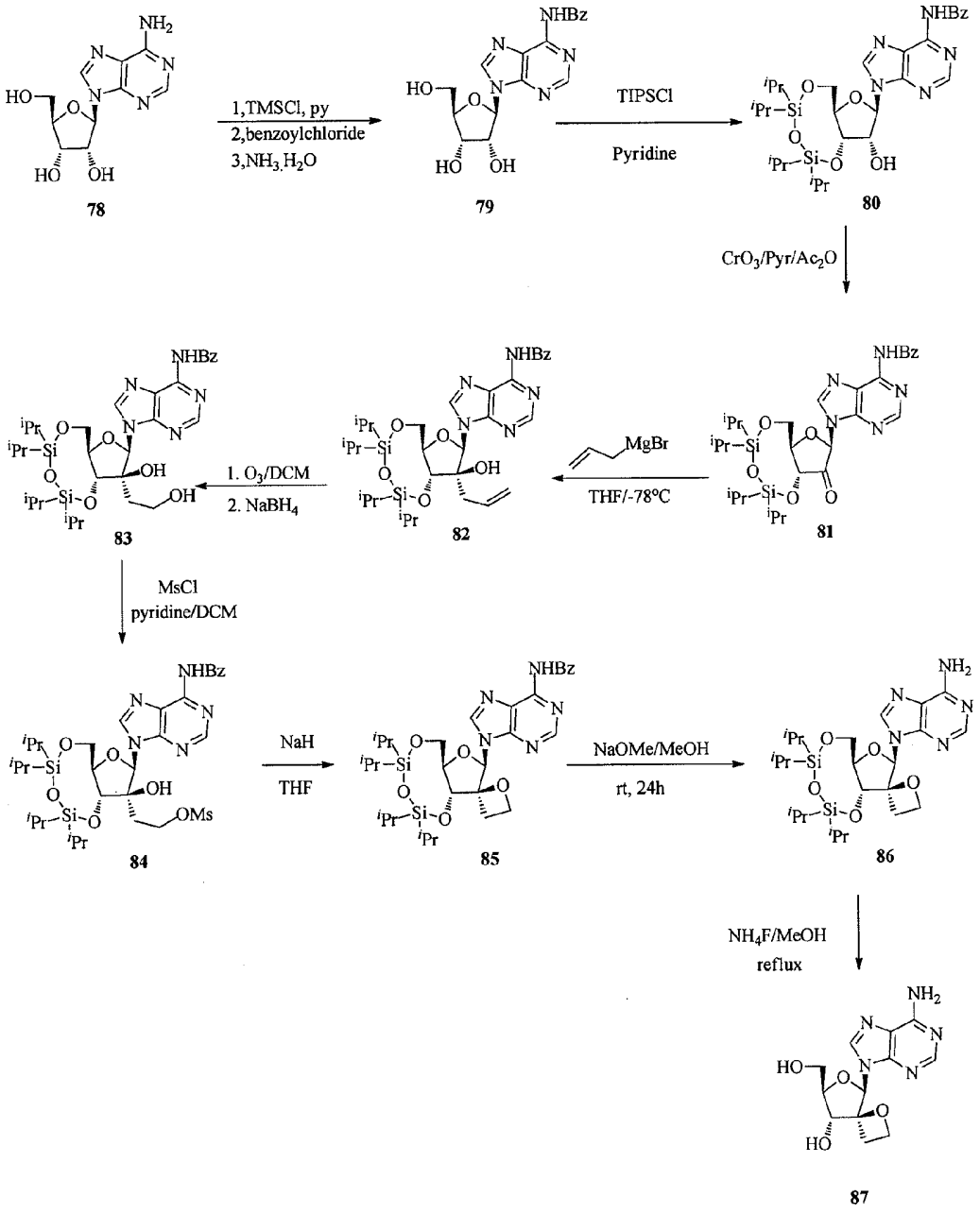
IV. Preparation of 2'-Spiro-Ara- and 2'-Spiro-Ribo-Adenine Analogs

A. Preparation of 2'-Spiro-Ara-Adenine Analogs.

Example 16. Preparation of (4S,5R,7R,8R)-5-(6-amino-9H-purin-9-yl)-7-(hydroxymethyl)-1,6-dioxaspiro[3.4]octan-8-ol, **87**

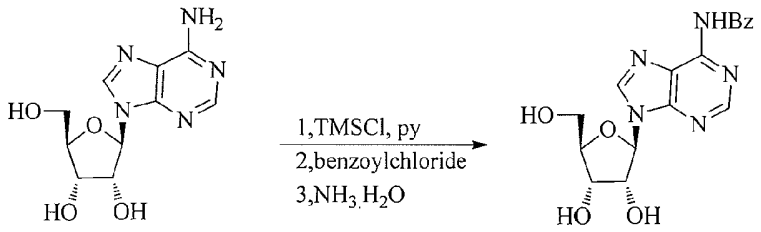


87



Compound **87** is prepared using an eight-step reaction sequence that begins with adenine (**78**).

Step 1: Preparation of compound 79

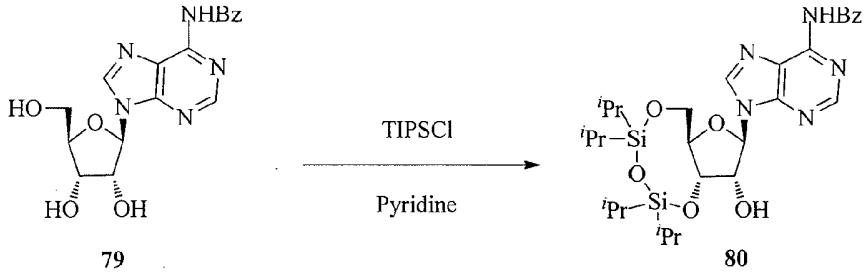


78 79

Compound **78** (30.0 g, 112.26 mmol) was dried by co-evaporation with anhydrous pyridine three times and dissolved in dry pyridine (400 mL). To the solution was added TMSCl (60.98 g, 561.3 mmol) and the solution was stirred for 1h at 0°C. To the resulting solution was added benzoyl chloride (78.9 g, 561.3 mmol) dropwise and the mixture was stirred 3h at room temperature. The mixture was cooled to 0°C and H_2O (120 mL) was added, and the resulting mixture was stirred for 0.5 h. $NH_3.H_2O$ (30%, 230 mL) was added and the mixture was stirred for 2h. Solid was collected by filtration and washed with H_2O and EtOAc to give crude product **79**. (38.0 g, 91.6 %)

^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.77 (s, 1H), 8.74 (s, 1H), 8.05 (d, J = 7.2 Hz, 2H), 7.62-7.66 (m, 1H), 7.53-757 (m, 2H), 6.05 (d, J = 6.0 Hz, 1H), 4.66 (t, J = 5.8 Hz, 1H), 4.20 (t, J = 4.8Hz, 1H), 3.99 (dd, J = 7.6 Hz, 3.6 Hz, 1H), 3.69 (dd, J = 8.0 Hz, 4.0 Hz, 1H), 3.58 (dd, J = 8.0 Hz, 4.0 Hz, 1H),

Step 2: Preparation of compound 80

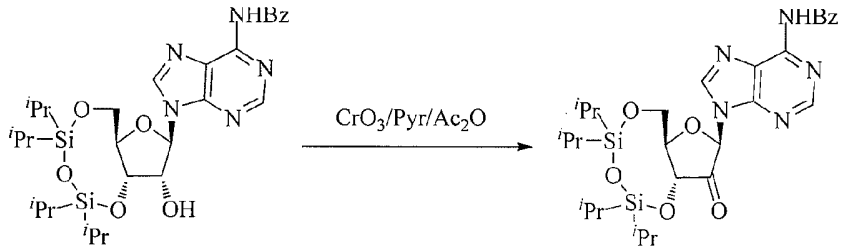


79 80

To a solution of compound **79** (38.0 g, 102.33 mmol) in anhydrous pyridine (200 mL) was added TIPSCl (38.7 g, 122.8 mmol) and the mixture was stirred for 20h at room temperature. Solvent was removed under reduce pressure and the residue was dissolved in EtOAc (200 mL). The solution was washed with H_2O and

the solvent was removed to give **80** which was used for next step without further purification. (45.0 g, 71.62 %)

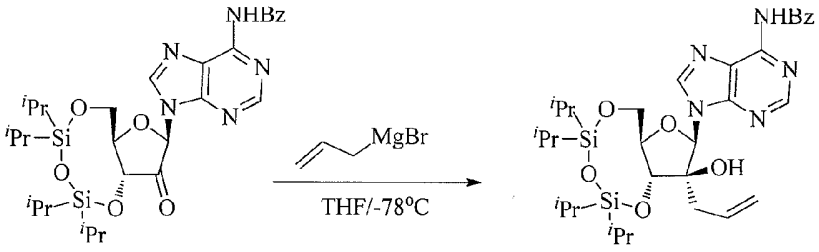
Step 3: Preparation of compound 81



80 **81**

To a stirred solution of CrO_3 (20.0 g, 32.58 mmol), anhydrous pyridine (15.8 mL, 195.48 mmol) and Ac_2O (9.5 mL, 97.74 mmol) was added a solution of compound **80** (20.0 g, 32.58 mmol) in CH_2Cl_2 (100 mL). The mixture was stirred at room temperature for 60 min. The solution was passed through a short silica gel column. Solvent was removed and the residue was purified by silica gel column chromatography (hexane:EtOAc = 3:1) to give compound **81** (4.0 g, 21.2 %)

Step 4: Preparation of compound 82

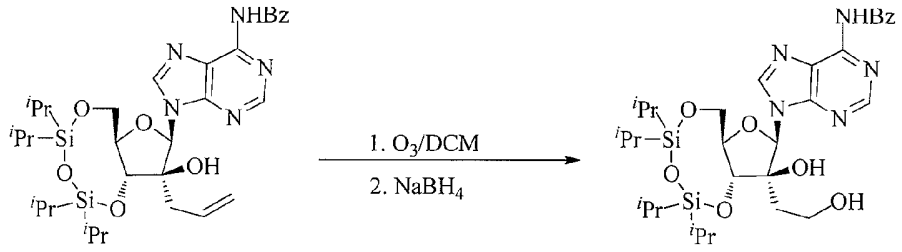


81 **82**

To a solution of compound **81** (4.0 g, 6.9 mmol) in THF (100 mL) was added a solution of allylmagnesium bromide (13.82 mL, 3.82 mmol) at -78°C and the resulting mixture was stirred for 2 hours at the same temperature. Then the temperature was increased to -10°C and the reaction mixture was quenched with H_2O and extracted with DCM. The organic layer was dried with Na_2SO_4 and solvent was removed under reduced pressure. The residue was purificated by silica gel column chromatography. (hexane:EtOAc= 2:1) to give compound **82** (1.6 g, 35.5

%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.20 (s, 1H), 8.73 (s, 1H), 8.39 (s, 1H), 8.04 (d, J = 8.8 Hz, 2H), 7.53-7.65 (m, 3H), 6.17 (s, 1H), 5.82-5.95 (m, 1H), 5.55 (s, 1H), 515-5.23 (m, 1H), 5.02-5.10 (m, 1H), 4.60 (d, J = 7.2 Hz, 1H), 3.85-4.10 (m, 3H), 2.55-2.60 (m, 2H), 0.94-1.04 (m, 28H),

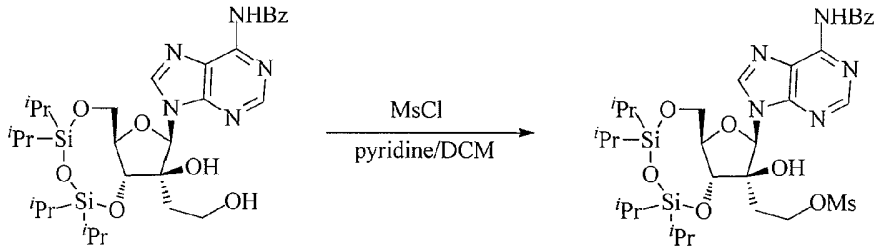
Step 5: Preparation of compound 83



82 83

To a solution of compound **82** (1.6 g, 2.45 mmol) in DCM (100 mL) was bubbled with O_3 at -78°C and the slution was stirred at the same temperature for 3h. To the solution was added 1 ml of Me_2S followed by addition of $NaBH_4$ (92.5 mg, 2.45 mmol) at room temperature. The mixture was stirred overnight. The solution was washed with H_2O and the solvent was removed to give a crude product which was purified by silica gel column chromatography (hexane:EtOAc = 1:1) to give compound **83** (1.0 g, 62.1 %).

Step 6: Preparation of compound 84

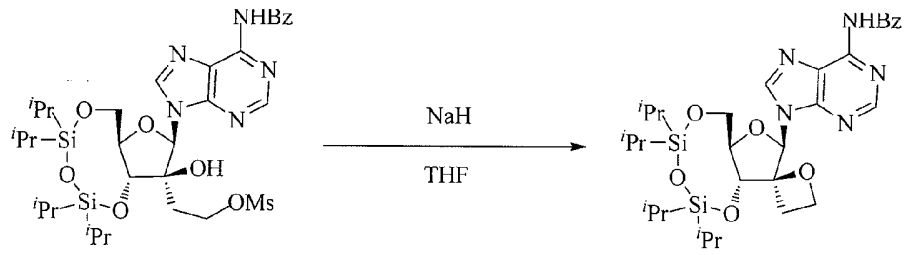


83 84

A solution of MsCl (0.349 g, 3.04 mmol) in anhydrous CH_2Cl_2 (3 mL) was added dropwise to a solution of nucleoside **83** (1.0 g, 1522 mmol) in anhydrous pyridine (5.0 mL) at room temperature. After stirring for 12 h, methanol (5.0 mL) was added and the resulting mixture was evaporated to dryness under reduced

pressure. The residue was co-evaporated with anhydrous toluene (2 × 5 mL) then dissolved in CH_2Cl_2 (50 mL). The solution was washed with saturated aqueous $NaHCO_3$ (2 × 25 mL). The combined aqueous phase was extracted with CH_2Cl_2 (50 mL). The combined organic phase was dried (Na_2SO_4) and solvent was evaporated to dryness under reduced pressure to give compound **84** which was used for the next reaction without further purification.

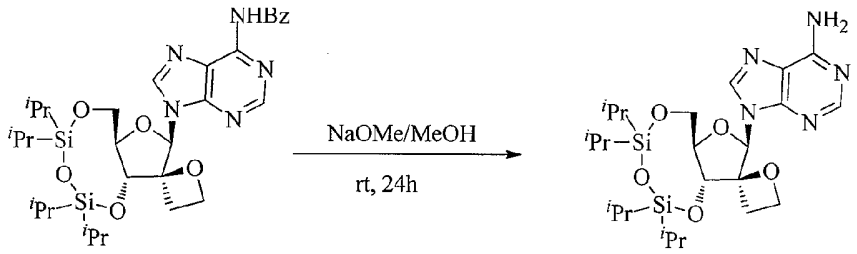
Step 7: Preparation of compound 85



84 **85**

To a stirred suspension of NaH (180 mg, 4.50 mmol) in anhydrous THF (10 mL) was added a solution of compound **84** (1.0 g, 1.50 mmol) in THF (5 mL) at 0°C. After stirring at room temperature for 2 h, ice-water (10 mL) was slowly added. CH_2Cl_2 (50 mL) was added and the separated organic phase was washed with saturated aqueous $NaHCO_3$ (2 × 20 mL). The combined aqueous phase was extracted with CH_2Cl_2 (25 mL). The combined organic phase was dried (Na_2SO_4) and the solvent was evaporated to dryness under reduced pressure to provide **85** which was used for the next reaction without further purification.

Step 8: Preparation of compound 86

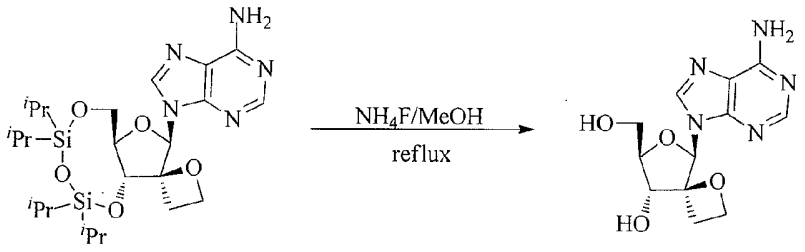


85 **86**

To a stirred solution of compound **85** (1.0 g, 1.55 mmol) in anhydrous methanol (50 mL) was added NaOMe (0.5 g, 9.26 mmol) and the solution was

stirred at room temperature for 20 h. The solution was filtered and the filtrate was evaporated to give crude product **86**.

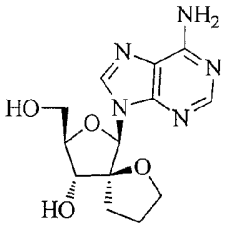
Step 9: Preparation of compound 87.



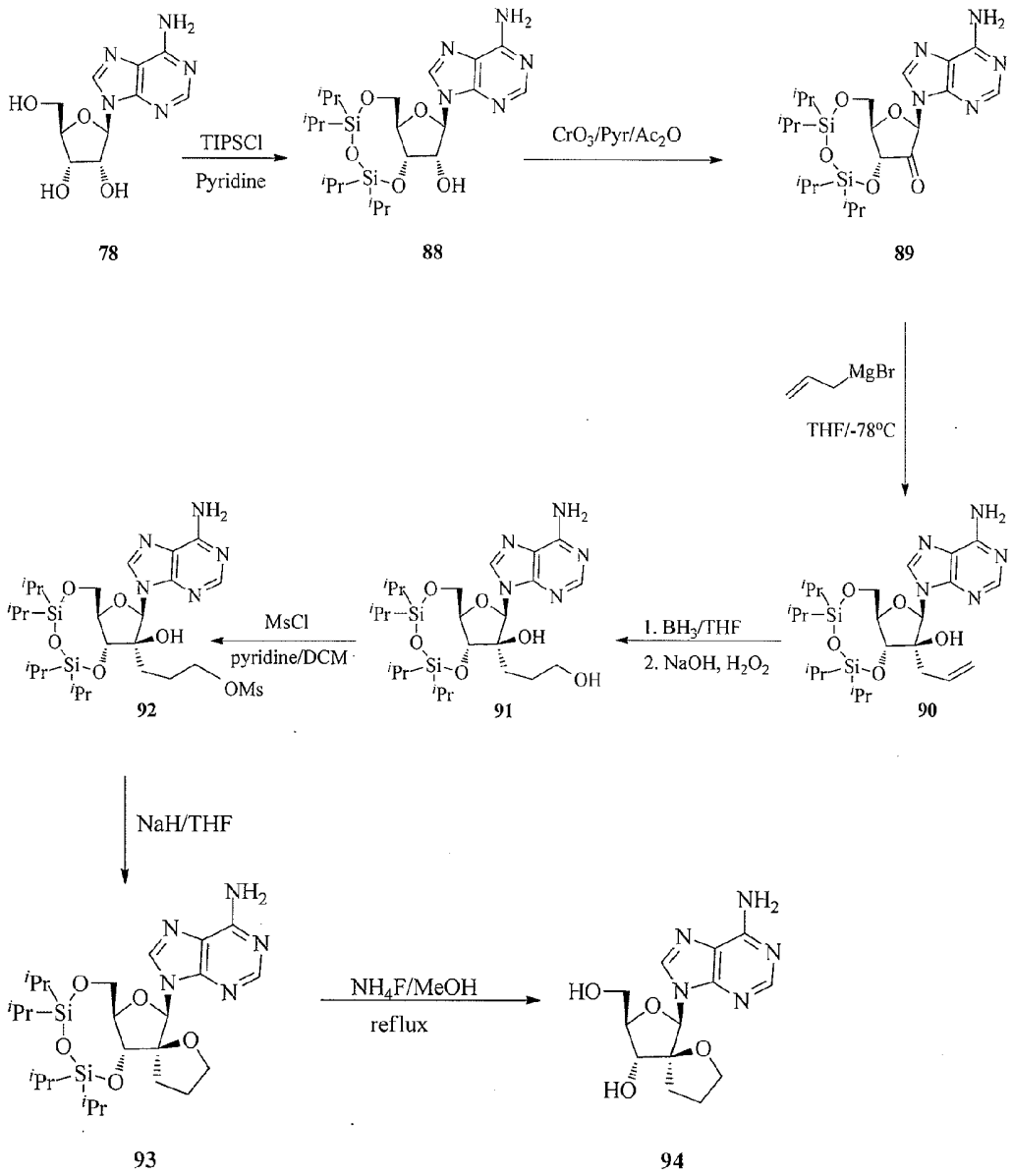
86 **87**

To a stirred solution of compound **86** (0.8 g, 1.49 mmol) in anhydrous methanol (30 mL) was added NH_4F (550 mg, 14.9 mmol) and the mixture was heated at reflux for 10 h. The mixture was filtered and the filtrate was evaporated to give a crude product which was purified by silica gel column chromatography (CH_2Cl_2:MeOH= 20:1) to provide compound **87** (36.0 mg, 21.05 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.21 (s, 1H), 8.17 (s, 1H), 7.29 (s, 2H), 6.26 (s, 1H), 5.90 (d, J = 5.2 Hz, 1H), 5.04 (t, J = 5.2 Hz, 1H), 4.08-4.30 (m, 2H), 3.92-3.97 (m, 1H), 3.70-374 (m, 1H), 3.55-3.66 (m, 2H), 2.98-3.05 (m, 1H), 2.41-2.49 (m, 1H). HRMS(TOF-ESI): Calc. For $C_{12}H_{16}N_5O_4$, 294.1197; found 294.1194.

Example 17. Preparation of (5S,6R,8R,9R)-6-(6-amino-9H-purin-9-yl)-8-(hydroxymethyl)-1,7-dioxaspiro[4.4]nonan-9-ol (94)



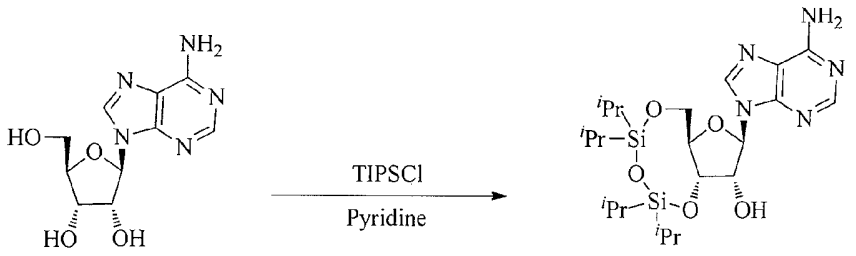
94



78 88 89 90 91 92 93 94

In the preparation of **94**, it is possible to forego protection of the 6-amino-purine, which means that **94** can be prepared from adenine (**78**) using a seven-step sequence.

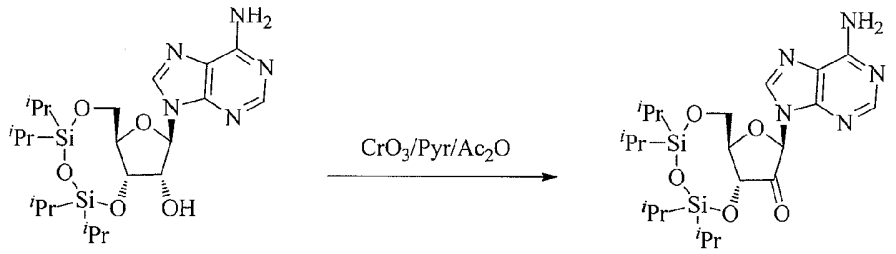
Step 1: Preparation of compound 88



78 88

To a solution of compound **78** (30.0 g, 112.0 mmol) in anhydrous pyridine (200 mL) was added TIPSCl (342.5 g, 113.5 mmol) at 0°C. The mixture was stirred overnight and the solvent was removed under reduce pressure. The residue was dissolved in EtOAc (200 mL). The solution was washed with H_2O and the solvent was removed to give **88** which was used for next reaction without further purification.

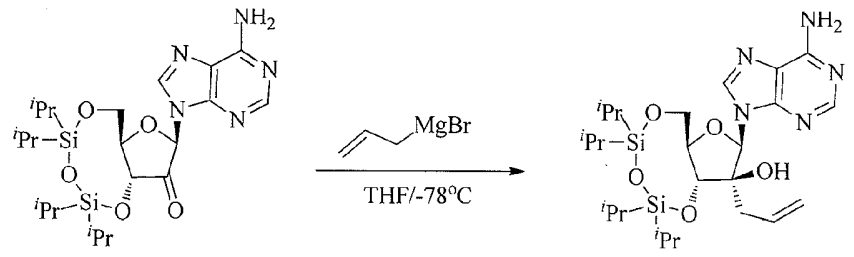
Step 2: Preparation of compound 89



88 89

To a solution of CrO_3 (21.2 g, 212 mmol), anhydrous pyridine (32.42 mL, 414 mmol) and Ac_2O (20.3 ml, 212 mmol) was added compound **88** (54.0 g, 106 mmol) at 0°C. The mixture was stirred for 1 h and passed through a short silica gel column. The solvent was removed and the residue was co-evaporation with anhydrous toluene twice to give a crude compound **89** which was used for the next reaction without further purification.

Step 3: Preparation of compound 90

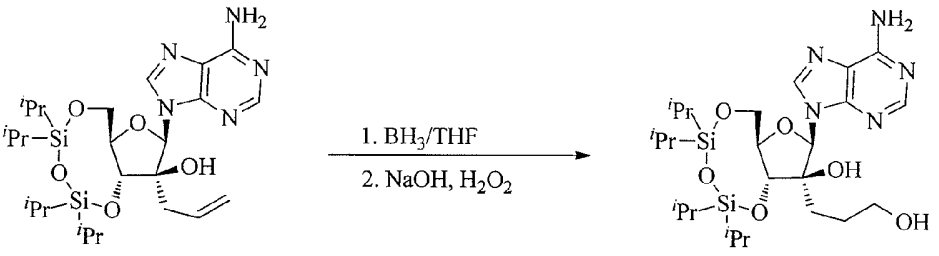


89 90

To a solution of compound **89** (31.0 g, 61.1 mmol) in THF (300 mL) was added a solution of allylmagnesium bromide (122 mL, 122 mmol) in THF (50 mL) at -78°C and the solution was stirred for 2h at the same temperature. The temperature was then raised to -10°C and the reaction mixture was quenched by addition of NH_4Cl solution and the mixture was extracted with DCM. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purificated by silica gel column chromatography (hexane:EtOAc = 3:1) to give product **90** (8.0 g, 23.8%).

^1H NMR (400 MHz, DMSO-d_6) δ: 8.12 (s, 1H), 8.10 (s, 1H), 7.28 (s, 2H), 5.99 (s, 1H), 5.82-5.92 (m, 1H), 5.44 (s, 1H), 5.12-5.19 (m, 1H), 5.01-5.08 (m, 1H), 4.56 (d, J = 6.4 Hz, 1H), 3.96-4.04 (m, 1H), 3.90-3.96 (m, 1H), 3.82-3.89 (m, 1H), 2.46-2.55 (m, 2H), 0.94-1.04 (m, 28H),

Step 4: Preparation of compound 91



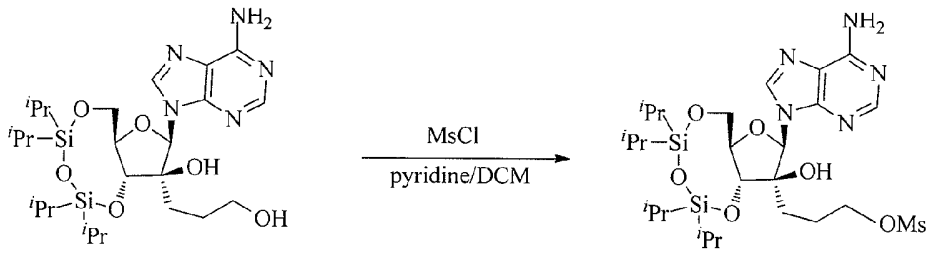
90 91

To a solution of compound **90** (2.0 g, 3.64 mmol) in THF (50 mL) was added a solution of BH_3 (1.82 mL, 18.2 mmol) at 0 °C and stirred for 2h at the same temperature. To the solution was added a mixture of H_2O_2 (4.13 mL, 36.4 mmol) and NaOH (9.1 mL, 18.2 mmol). The resulting mixture was stirred at room temperature overnight and extracted with DCM. The solvent was removed and the

residue was purified by silica gel column chromatography (hexane:EtOAc = 1:1) to give product **91** (0.6 g, 29%).

^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.13 (s, 1H), 8.12 (s, 1H), 7.30 (s, 2H), 5.94 (s, 1H), 5.38 (s, 1H), 4.52-4.59 (m, 1H), 4.41-4.49 (m, 1H), 3.96-4.04 (m, 1H), 3.95-4.05 (m, 2H), 3.75-3.84 (m, 1H), 1.75-1.80 (m, 1H), 1.48-1.60 (m, 2H), 0.94-1.04 (m, 28H),

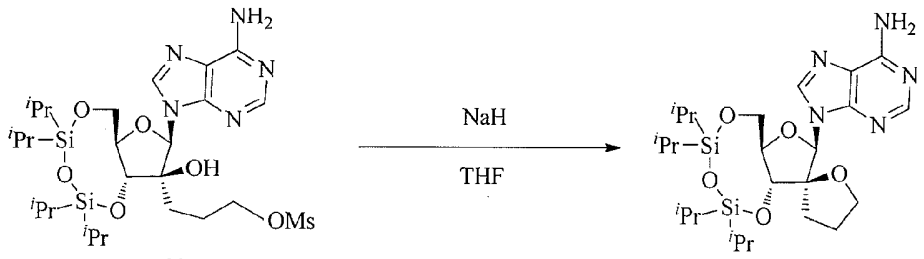
Step 5: **Preparation of compound 92**



91 **92**

A solution of MsCl (0.058 g, 0.51 mmol) in anhydrous CH_2Cl_2 (5.0 mL) was added dropwise to a solution of nucleoside **91** (0.24 g, 0.42 mmol) in anhydrous pyridine (5.0 mL) at room temperature. After stirring for 12 h, methanol (5.0 mL) was added and the resulting mixture was evaporated to dryness under reduced pressure. The residue was co-evaporated with anhydrous toluene (2 × 5 mL). The residue was dissolved in CH_2Cl_2 (50 mL) and the solution was washed with saturated aqueous $NaHCO_3$ (2 × 25 mL). The combined aqueous phase was extracted with CH_2Cl_2 (50 mL). The combined organic phase was dried (Na_2SO_4) and the solvent was evaporated to dryness under reduced pressure to give crude product **92** which was used for the next reaction without further purification.

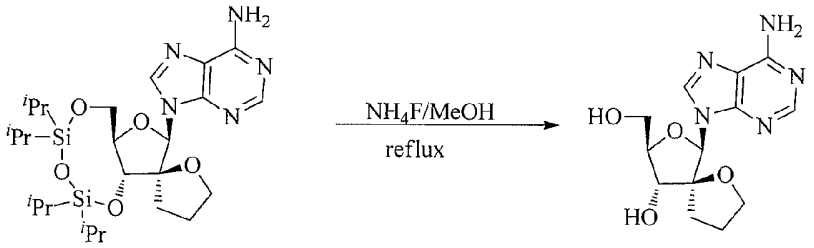
Step 6: **Preparation of compound 93**



92 93

To a stirred suspension of NaH (112 mg, 2.79 mmol) in anhydrous THF was added a solution of compound **92** (0.45 g, 0.697 mmol) in THF dropwise at 0°C. After stirring at room temperature for 2 h, ice-water (10 mL) was slowly added and the mixture was diluted with CH_2Cl_2. The separated organic phase was washed with saturated aqueous $NaHCO_3$ (2 × 20 mL). The combined aqueous phase was extracted with CH_2Cl_2 (25 mL) and the combined organic phase was dried (Na_2SO_4) and the solvent was evaporated to dryness under reduced pressure to provide **93** (330 mg, 86.1%) for the next reaction without further purification.

Step 7: Preparation of compound 94



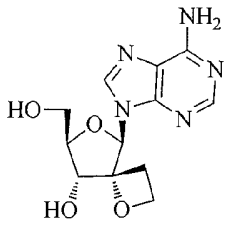
93 94

To a stirred solution of compound **93** (0.25 g, 0.45 mmol) in anhydrous methanol (20 mL) was added NH_4F (200 mg, 5.4 mmol) and the mixture was heated at reflux for 10 h. The solvent was evaporated and the residue was purified by silica gel column chromatography (CH_2Cl_2:MeOH= 20:1) to give **94** (53.4 mg, 38.7 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.26 (s, 1H), 8.14 (s, 1H), 7.28 (s, 2H), 6.02 (s, 1H), 5.69 (d, J = 5.2 Hz, 1H), 5.07 (t, J = 5.2 Hz, 1H), 4.09 (t, J = 5.2 Hz, 1H), 3.72-3.79 (m, 1H), 3.60-3.69 (m, 3H), 3.18-3.24 (m, 1H), 2.29-2.34 (m, 1H), 1.74-1.82

(m, 2H), 1.62-1.64 (m, 1H). HRMS (TOF-ESI): Calc. For $C_{13}H_{18}N_5O_4^+$, 308.1359; found 308.1347.

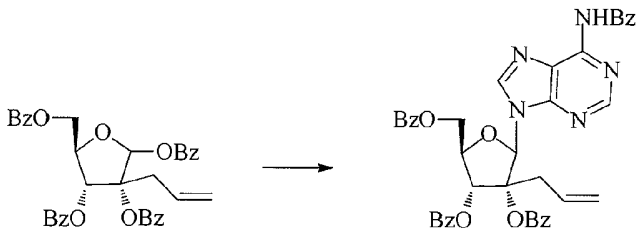
B. Preparation of 2'-Spiro-Ribo-Adenine Analogs.

Example 18. Preparation of (4R,5R,7R,8R)-5-(6-amino-9H-purin-9-yl)-7-(hydroxymethyl)-1,6-dioxaspiro[3.4]octan-8-ol (100)



100

Step 1. Preparation of compound 95.

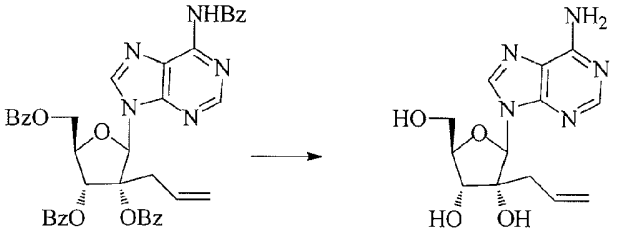


37 **95**

A mixture of N^6-benzoyladenine (3.14 g, 13.19 mmol) in HMDS (30 mL) with $(NH_4)SO_4$ (50 mg) was heated at 140°C for 4h. Solvent was removed and the residue was dissolved in MeCN (50 mL). To the solution was added a solution of sugar **37** in MeCN (30 mL). To the resulting solution was added $SnCl_4$ (39.57 mml, 1M, 39.57 mL) in CH_2Cl_2 at 0°C and the solution was stirred at 60°C for 4h. The reaction solution was cooled to room temperature and poured into ice-water, execess $NaHCO_3$ and EtOAc (200 mL) with stirring. Organic solution was washed with brine and dried over Na_2SO_4. Solvent was removed and the residue was purified by silica gel column chromatography (10-70% EtOAc in hexane) to give compound **95** as foam (1.95 g, 41%). ^1H NMR (400 MHz, $CDCl_3$) δ: 9.04 (s, 1H), 8.89 (s, 1H),

8.26 (s, 1H), 7.35-8.20 (m, 20H), 6.53 (d, J=7.6Hz, 1H), 5.29 (m, 1H), 4.68-5.00 (m, 4H), 2.99 (m, 1H), 2.65 (m, 1H). m/z: 724 (M+1).

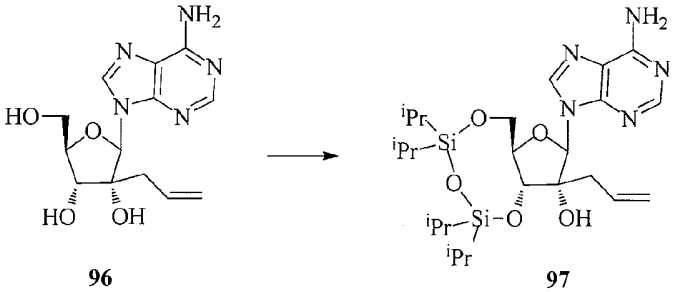
Step 2. Preparation of compound 96.



95 **96**

A solution of compound **95** (1.9 g, 2.63 mmol) in methanolic ammonia (7N, 50 mL) was stirred at room temperature for 24h. Solvent was removed and the residue was purified by silica gel column chromatography (0-15% MeOH in CH_2Cl_2) to give compound **96** (0.47 g, 53%) as white solid. LC-MS (ESI): 308 $[M+H]^+$.

Step 3. Preparation of compound 97.

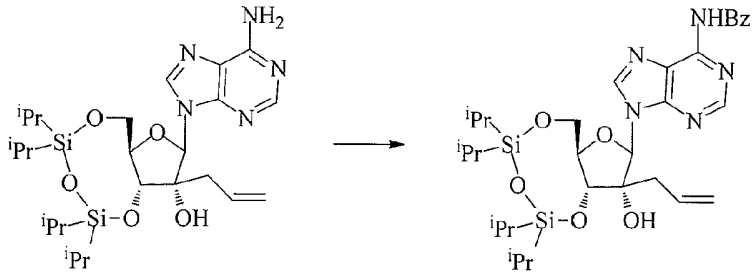


96 **97**

To a solution of compound **96** (0.58 g, 1.84 mmol) in pyridine (50 mL) were added TIPSCl dropwise and the mixture was stirred at 0°C for 2h and room temperature for 16h. Water (10 mL) was added and the mixture was concentrated to dryness under reduced pressure and the residue was dissolved in EtOAc (100 mL). The solution was washed with brine and dried over Na_2SO_4. Solvent was removed and the residue was purified by silica gel column chromatography (0-10% MeOH in CH_2Cl_2) to give compound **97** (0.65 g, 77%) as white foam. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.31 (s, 1H), 7.87 (s, 1H), 5.97 (s, 1H), 5.70 (m, 1H), 5.56 (s, 2H), 5.04

(d, J=8.0Hz, 1H), 4.85 (d, J=10.4Hz, 1H), 4.48 (d, J=17.2Hz, 1H), 4.30 (m, 1H), 4.12 (m, 1H), 4.03 (dd, J=3.2, 12.4Hz, 1H), 3.20 (s, 1H), 2.27 (m, 1H), 2.05 (m, 1H), 1.20 (m, 4H), 1.07 (m, 28H). LC-MS (ESI): 550 $[M+H]^+$.

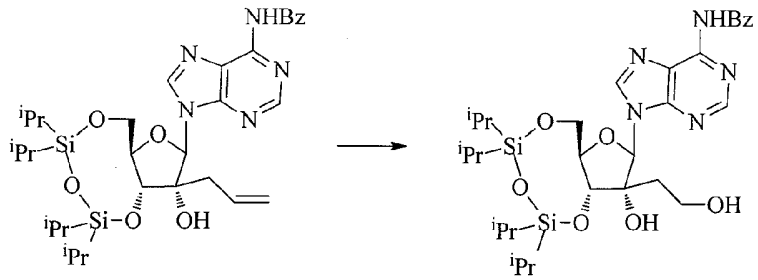
Step 4. Preparation of compound 98.



97 98

To a solution of compound **97** (0.25 g, 0.45 mmol) in CH_2Cl_2 (10 mL) and pyridine (1 mL) was added BzCl (3 eq) and the solution was stirred at 0°C for 3h and room temperature for 2h. To the solution was added 30% NH_4OH (1 mL) slowly. The mixture was stirred at room temperature for 20 min. EtOAc (100 mL) was added and the solution was washed with brine and dried over Na_2SO_4. Solvent was evaporated and the residue was co-evaporated with toluene twice. The residue was purified by silica gel column chromatography (0-8% MeOH in CH_2Cl_2) to give compound **98** (0.10 g, 34%) as white solid. LC-MS (ESI): 654 $[M+H]^+$.

Step 5. Preparation of compound 6.

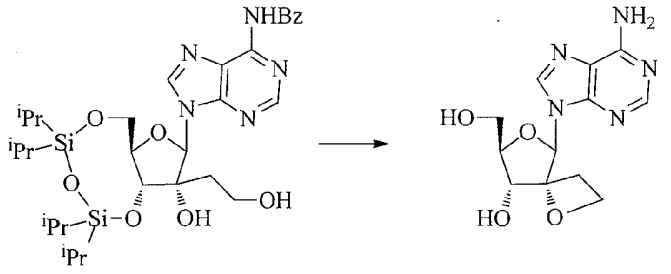


98 99

To a solution of compound **98** (0.12 g, 0.19 mmol) in THF (5 mL) and t-BuOH (5 mL) and water (1 mL) was added 0.025% OsO_4 in t-BuOH (0.5 mL) and NMO (50%, 0.3 mL). The solution was stirred at room temperature for 20h. Solvent

was evaporated and the residue was co-evaporated with EtOH twice. The residue was dissolved in THF (10 mL) and water (1 mL). To the solution was added $NaIO_4$ (10 eq) and the mixture was stirred at room temperature for 5h. Solid was filtered and the filtrate was diluted with EtOAc (100 mL). The organic solution was washed with brine and dried over Na_2SO_4. The solvent was evaporated and the residue was dissolved in EtOAc (5 mL) and EtOH (5 mL). To the solution was added $NaBH_4$ (5 eq) and the mixture was stirred at 0°C for 3h. The mixture was poured into EtOAc (100 mL) and the solution was washed with brine and dried over Na_2SO_4. Solvent was evaporaed and the residue was purified by silica gel column chromatograph (0.8% MeOH in CH_2Cl_2) to give compound **99** (0.10 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.12 (s, 1H), 8.79 (s, 1H), 8.35 (s, 1H), 7.48-8.04 (m, 5H), 6.18 (s, 1H), 4.85 (d, J=8.4Hz, 1H), 4.32 (dd, J=4.4, 12.8Hz, 1H), 4.24 (m, 1H), 4.07 (dd, J=2.8, 12.4Hz, 1H), 3.74 (m, 2H), 3.65 (s, 1H), 3.28 (brs, 1H), 1.86 (m, 1H), 1.42 (m, 1H), 1.06-1.20 (m, 28H). LC-MS (ESI): 658 $[M+H]^+$.

Step 6. Preparation of compound 100.

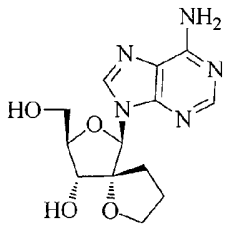


99 **100**

To a solution of compound **99** (0.20 g, 0.30 mmol) in CH_2Cl_2 (10 mL) and pyridine (1 mL) was added MsCl (0.1 mL) and the solution was stirred at 0°C for 2h. Water (5 mL) was added followed by addition of EtOAc (100 mL). The mixture was washed with brine and dried over Na_2SO_4. Solvent was removed and the residue was co-evaporated with toluene twice. The resulting mesylate was dissolved in dry THF (10 mL). To the solution was added NaH (100 mg, 2.5 mmol) and the mixture was stirred at room temperature for 3h. EtOAc (100 mL) was added and the mixture was washed with brine and dried over Na_2SO_4. Solvent was removed and the residue was dissolved in MeOH (10 mL). To the solution was added butylamine (1 mL) and

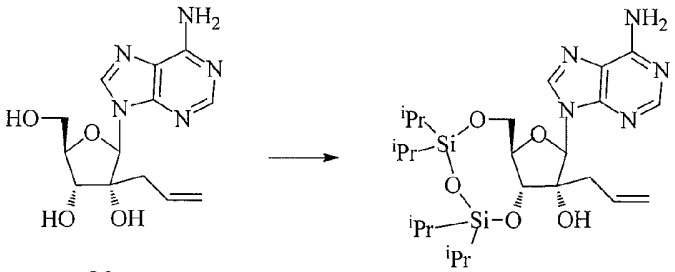
NH_4F (100 mg) and the mixture was refluxed for 5h. Solvent was removed and the residue was purified by silica gel column chromatography (0-15% MeOH in CH_2Cl_2) to give compound **100** as white solid (0.04 g, 45.5%). ^1H NMR (400MHz, DMSO-d_6) δ: 8.37 (s, 1H), 8.18 (s, 1H), 7.35 (brs, 2H), 6.25 (s, 1H), 5.51 (d, J=8.0Hz, 1H, OH), 5.14 (t, J=5.6Hz, 1H, OH), 4.37 (m, 2H), 3.77 (m, 1H), 3.70 (m, 1H), 3.61 (m, 1H), 2.44 (m, 1H), 2.12 (m, 1H). LC-MS (ESI): 294 $[M+H]^+$

Example 19. Preparation of (5R,6R,8R,9R)-6-(6-amino-9H-purin-9-yl)-8-(hydroxymethyl)-1,7-dioxaspiro[4.4]nonan-9-ol (5)



103

Step 1. Preparation of compound 97.

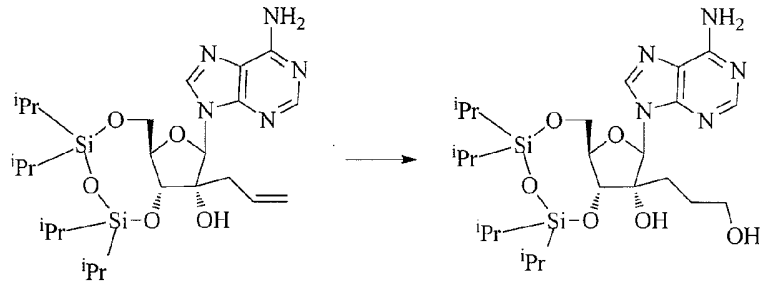


96 **97**

To a solution of compound **96** (0.58 g, 1.84 mmol) in pyridine (50 mL) were added TIPSCl dropwise and the mixture was stirred at 0°C for 2h and room temperature for 16h. Water (10 mL) was added and the mixture was evaporated. The residue was dissolved in EtOAc (100 mL) and the solution was washed with brine and dried over Na_2SO_4. Solvent was removed and the residue was purified by silica gel column chromatography (0-10% MeOH in CH_2Cl_2) to give compound **97** as white foam. ^1H NMR (400 MHz, $CDCl_3$) δ: 98.31 (s, 1H), 7.87 (s, 1H), 5.97 (s, 1H), 5.71 (m,1H), 5.56 (brs, 2H), 5.045 (d, J=8.0Hz, 1H), 4.85 (d, J=10.04Hz, 1H), 4.47 (d, J=17.2Hz, 1H), 4.30 (m, 1H), 4.12 (m, 1H), 4.03 (dd, J=3.2, 12.4Hz, 1H), 3.22

(s, 1H), 2.30 (m, 1H), 2.07 (m, 1H), 1.00-1.25 (m, 28H). LC-MS (ESI): 550 $[M+H]^+$.

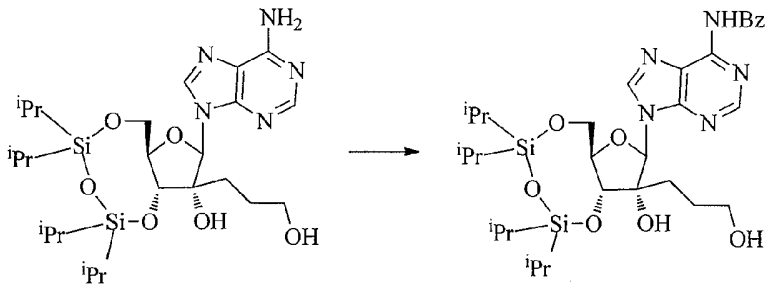
Step 2. Preparation of compound 101.



97 101

To a solution of compound **97** (0.10 g, 0.18 mmol) in THF (10 mL) was added BH_3-SMe_2 (0.3 mL) and the solution was stirred at 0°C for 3h. To the solution was adde H_2O_2 (1 mL) then 2 N NaOH (1 mL) and the mixture was stirred at room temperature for 3h. EtOAc (100 mL) was added and the organic solution was washed with brine and dried over Na_2SO_4. Solvent was removed and the residue was purified by silica gel column chromatography (0-10% MeOH in CH_2Cl_2) to give compound **101** (0.02 g, 24%). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.28 (s, 1H), 8.04 (s, 1H), 6.08 (s, 1H), 5.99 (brs, 2H), 4.81 (d, J=8.0Hz, 1H), 4.26 (m, 1H), 4.15 (m, 1H), 4.05 (m, 1H), 3.72 (brs, 1H), 3.38 (m,2H), 1.63 (m, 1H), 1.37 (m, 1H), 0.93-1.21 (m, 28H). LC-MS (ESI): 568 $[M+H]^+$.

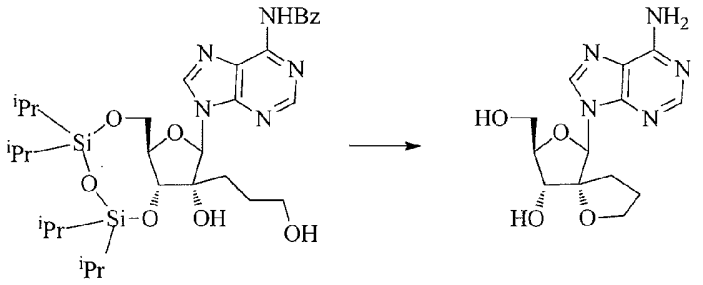
Step 3. Preparation of compound 102.



101 102

To a solution of compound **101** (0.09 g, 0.16 mmol) in CH_2Cl_2 (10 mL) and pyridine (1 mL) was added TMSCl (0.1 mL) and the solution was stirred at 0°C for 1h. To the solution was added BzCl (0.1 mL) and the resulting solution was stirred at 0°C for 1h and room temperature for 4h. 30% NH_4OH (3 mL) was added and the solution was stirred at room temperature for 1h. EtOAc (100 mL) was added and the solution was washed with brine and dried over Na_2SO_4. Solvent was removed and the residue was dissolved in MeOH (10 mL). To the solution was added 30% NH_4OH (1 mL) and the solution was stirred at room temperature for 1h. Solvent was removed and the residue was purified by silica gel chromatography (0-10% MeOH in CH_2Cl_2) to give compound **102** (0.07 g, 62%) as foam. ^1H NMR (400 MHz, $CDCl_3$) δ: 9.24 (s, 1H), 8.76 (s, 1H), 8.21 (s, 1H), 7.50-8.03 (m, 5H), 6.15 (s, 1H), 5.29 (s, 1H), 4.84 (d, J=7.6Hz, 1H), 4.26 (dd, J=4.8, 12.4H, 1H), 4.16 (m, 1H), 4.04 (dd, 3.2, 12.4Hz, 1H), 3.53 (brs, 1H), 5.37 (m, 2H), 1.63 (m, 1H), 1.31 (m, 1H), 0.98-1.21 (m, 28H). LC-MS (ESI): 672 $[M+H]^+$.

Step 4. Preparation of compound 103.



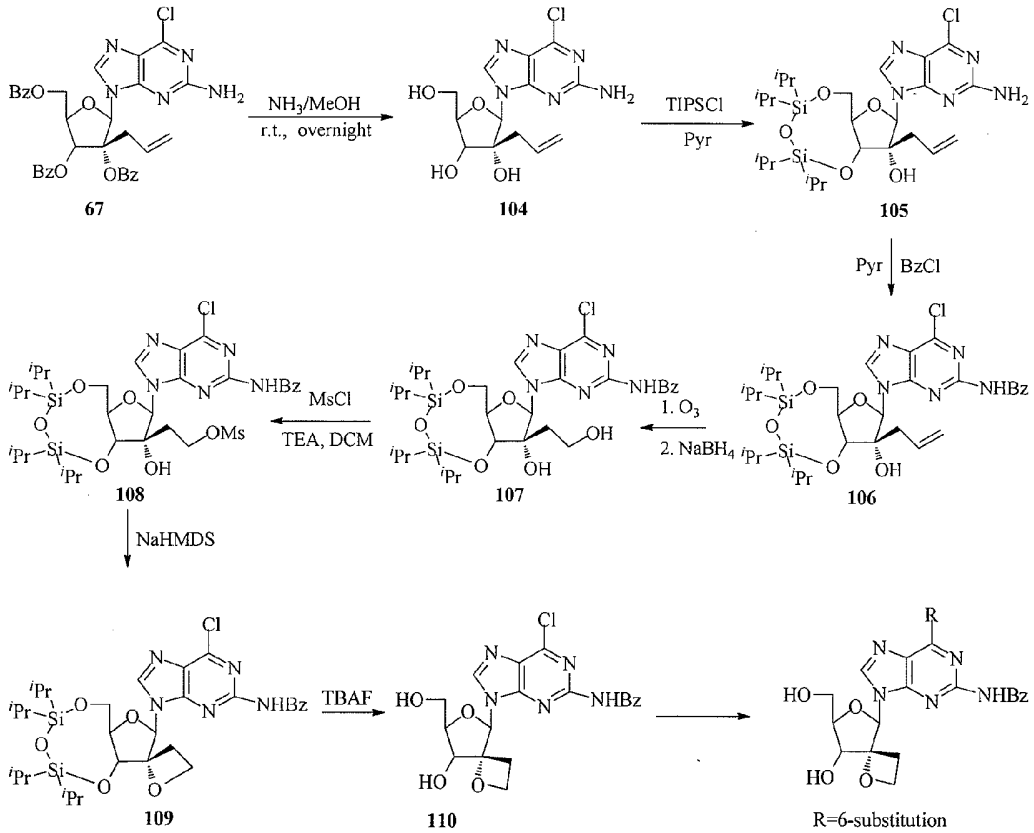
102 **103**

To a solution of compound **102** (0.07 g, 0.10 mmol) in CH_2Cl_2 (10 mL) and pyridine (1 mL) was added MsCl at 0°C and the solution was stirred at room temperature for 3h. To the solution was added water (10 mL) and the mixture was extracted with EtOAc (100 mL). Organic solution was dried over Na_2SO_4. Solvent was removed to give a crude mesylate which was dissolved in THF (10 mL). To the solution was added NaH (60 % in mineral oil, 100 mg) and the mixture was stirred at room temperature for 2h. Water (2 mL) was added slowly then the mixture was extracted with EtOAc (100 mL). The organic solution was washed with brine and dried over Na_2SO_4. Solvent was removed to give protected 2'-spironucleoside which

was dissolved in MeOH (10 mL). To the solution was added NH_4F (200 mg) and $BuNH_2$ (1 mL) and the mixture was refluxed for 5h. Solvent was removed and the residue was purified by silica gel column chromatography (0-15% MeOH in CH_2Cl_2) to give compound **103** (20 mg, as white solid. ^1H NMR (400 MHz, CD_3OD) δ: 8.55 (s, 1H), 8.19 (s, 1H), 6.08 (s, 1H), 4.38 (d, J=9.6Hz, 1H), 3.84-4.12 (m, 5H), 1.90 (m, 2H), 1.78 (m, 1H), 1.30 (m, 1H). LC-MS (ESI): 308 $[M+H]^+$.

V. Preparation of 2'-Spiro-Ribo-(6-Substituted-Purine) Analogs

6-Substituted purine nucleosides can be prepared from common intermediate, 6-chloropurine analogs as shown in the following scheme.

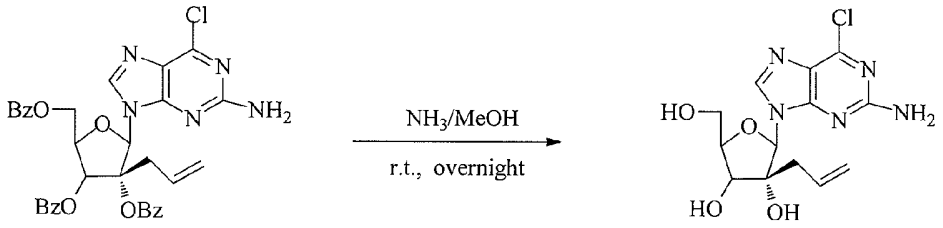


Treatment of compound **67** with methanolic ammonia gave free nucleoside **104**. Selective protection of 3',5'-diol of nucleoside with TIPSCl followed by N-benzoylation provided intermediate **106**. Ozonolysis of compound **106** followed by reduction of the resulting aldehyde gave compound **107**. Selective mesylation of

compound **108** followed by cyclization in the presence of base, such as NaH, or NaHMDS, afforded 2'-oxetanyl compound **109**. Treatment of compound **109** with TBAF provided the key intermediate for the 6-substitution. Treatment of 6-chloropurine intermediate with alcohol or amine or other nucleophile provided 6-substituted 2'-spironucleoside.

Example 20. Preparation of N-(6-chloro-9-((4R,5R,7R,8R)-8-hydroxy-7-(hydroxymethyl)-1,6-dioxaspiro[3.4]octan-5-yl)-9H-purin-2-yl)benzamide (110)

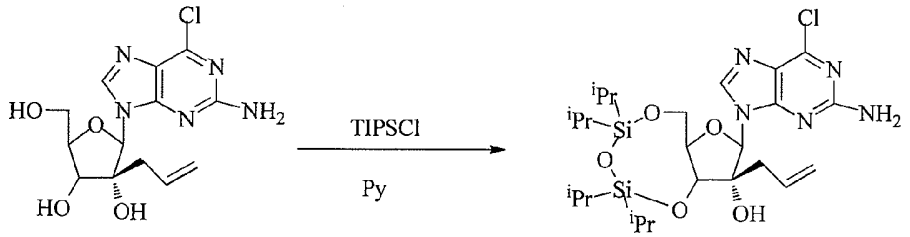
Step 1: Preparation of compound 104



67 **104**

To a solution of compound **67** (6.5 g, 0.01 mol) in dry MeOH (50 mL) was added saturated NH_3/MeOH solution (50 mL). The mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was recrystallized in MeOH/EtOAc to give the pure desired compound **104** (2.3 g, 67%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (s, 1H), 6.98 (s, 2H), 5.86 (s, 1H), 5.54-5.60 (m, 1H), 5.37 (d, J = 6.4Hz, 1H), 5.07 (t, J = 5.2Hz, 1H), 5.07 (s, 1H), 4.66 (dd, J = 10.4Hz, 2.0Hz, 1H), 4.48 (d, J = 17.2Hz, 2.0Hz, 1H), 4.20-4.24 (m, 1H), 3.85-3.88 (m, 1H), 3.76-3.79 (m, 1H), 3.64-3.69 (m, 1H), 2.21 (dd, J = 14.8, 6.8Hz, 1H),1.95 (dd, J = 4.8Hz, 7.2Hz, 1H). LC-MS (ESI): 341 $[M+H]^+$

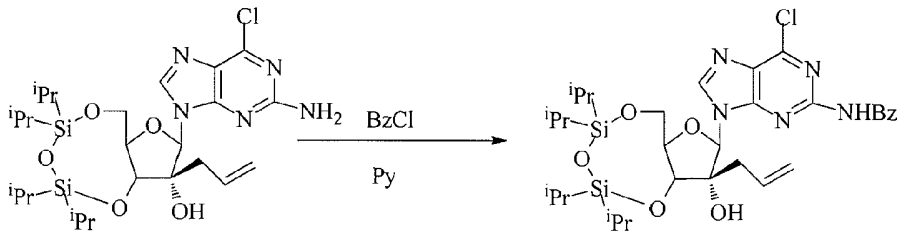
Step 2: Preparation of compound 105.



104 **105**

Compound **104** (0.5 g, 1.4 mmol) in anhydrous pyridine (10 mL) at 0°C was stirred for 30 min untill the solid was dissolved completely. To the solution was added TIPSCl (0.7 g, 2.2 mmol) dropwise and the stirring was continued at 0°C for 3h. Water (2 mL) was added and the solvent was removed under reduced pressure. The mixture was dissolved in EtOAc and the solution was washed with water, brine, and dried over $MgSO_4$. Solvent was evaporated to give crude compound **105** (0.75 g, yield: 88 %). LC-MS (ESI): 584 $[M+H]^+$.

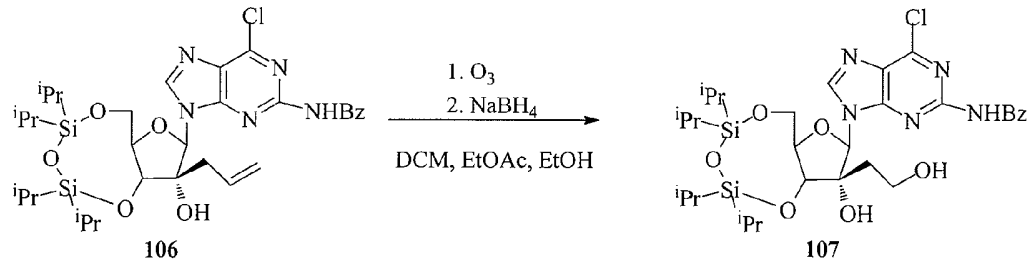
Step 3: Preparation of compound 106



105 **106**

To a solution of compound **105** (0.75 g, 1.2 mmol) in a mixture of dry pyridine (15 mL) and CH_2Cl_2 (30 mL) was added BzCl (0.4 mL) and the solution was stirred at room temperature for 2h. Water (10 mL) was added and the solution was evaporated. The residue was dissolved in EtOAc (200 mL) and the organic phase was washed with brine and dried over $MgSO_4$. Solvent was removed and the residue was purified by silica gel column chromatography (0-2% MeOH in CH_2Cl_2) to give compound **106** as foam (0.8 g, yield: 97%). ^1H NMR (400 MHz, $CDCl_3$): δ 8.79 (s, 1H), 8.05 (d, J = 7.6 Hz, 2H), 7.51 (t, J = 7.6Hz, 1H), 7.45 (d, J = 7.6 Hz, 2H), 7.10 (s, 1H), 5.95 (s, 1H), 5.62-5.73 (m, 1H), 5.00 (d, J = 8.0 Hz, 1H), 4.77 (d, J = 9.2 Hz, 1H), 4.30-4.35 (m, 2H), 4.05 (s, 1H), 3.93 (dd, J_1=12.4 Hz, J2=2.4 Hz, 1H), 3.30 (bs, 1H), 2.32-2.38 (m, 1H), 2.01-2.12 (m, 1H), 1.12-1.32 (m, 2H), 0.85-0.98 (m, 28H); LC-MS (ESI): 688 $[M+H]^+$.

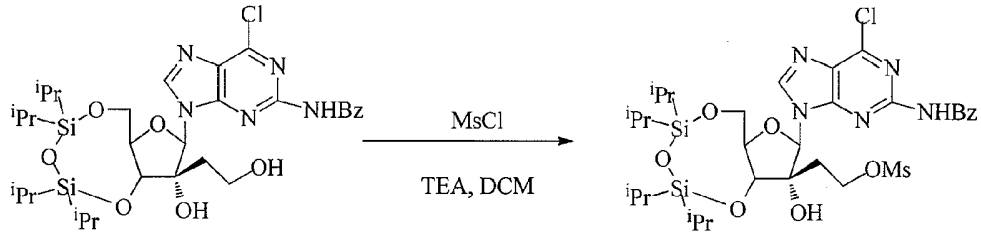
Step 4: Preparation of Compound 107.



106 107

To a solution of compound **106** (0.8 g, 1.1 mmol) in DCM (100 mL) in a 250 mL three-neck flask was bubbled with O_3 at -78°C. After color of reaction solution became blue, the reaction mixture was stirred for additional 5 min. Excess O_3 was removed by bubbling N_2 into the reaction mixture. EtOAc (30 mL) and ethanol (30 mL) was added. To the resulting solution was added $NaBH_4$ (300 mg) and the mixture was stirred at room temperature for additional 2h. Additional EtOAc (300 mL) was added and the solution was washed with brine, water, and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel column chromatography (0~2% MeOH in DCM) to give compound **107** (0.40 g, 50%) as foam. ^1H NMR(400 MHz, $CDCl_3$): δ 8.76 (s, 1H), 8.60 (s, 1H), 7.93 (d, J = 7.6 Hz, 2H), 7.61 (t, J = 7.6Hz, 1H), 7.50 (d, J = 7.6 Hz, 2H), 6.25 (s, 1H), 4.56 (d, J = 7.6 Hz, 2H), 4.40 (s, 1H), 4.10-4.31 (m 3H), 4.02-4.12 (m, 2H), 3.75-3.85 (m, 2H), 2.01-2.12 (m, 1H), 1.35-1.42 (m, 1H), 1.02-1.21 (m, 28H). LC-MS (ESI): 692 $[M+H]^+$.

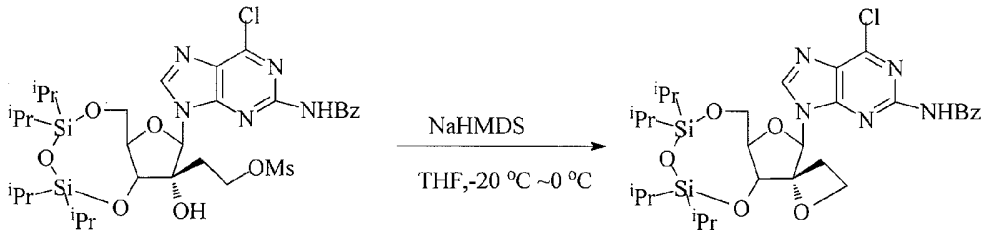
Step 5: Preparation of Compound 108.



107 108

To a solution of compound **107** (3.2 g, 4.5 mmol) in DCM (50 mL) was added triethylamine (3 mL), then MsCl (1 g, 8.8 mmol) was added and the mixture was stirred at 0°C for 2h. DCM (150 mL) was added to the solution and the organic phase was washed with brine, water, and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by silica gel column chromatography (0~2% MeOH in DCM) to give compound **108** as foam (3.3 g, yield: 94 %). ^1H NMR (400 MHz, $CDCl_3$): δ 8.76 (s, 1H), 8.36 (s, 1H), 7.90 (d, J = 7.6 Hz, 2H), 7.61 (t, J = 7.6Hz, 1H), 7.50 (d, J = 7.6 Hz, 2H), 6.15 (s, 1H), 4.90 (bs, 1H), 4.59 (d, J = 7.6 Hz, 1H), 4.40 (bs, 1H), 4.34 (dd, J_1 = 12.8 Hz, J_2 = 4 Hz, 1H), 4.12-4.15 (m, 1H), 4.02 (dd, J_1 = 12.8 Hz, J_2 = 2.8Hz, 1H), 3.28 (s, 1H), 2.98 (s, 3H), 2.03-2.09 (m, 1H), 1.56-1.66 (m, 1H), 1.02-1.21 (m, 28H). LC-MS (ESI): 770 $[M+H]^+$.

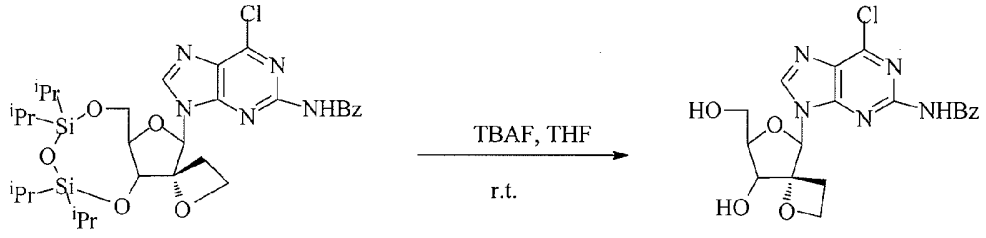
Step 6: Preparation of Compound 13



108 **109**

To a solution of compound **108** (2.8 g, 3.6 mmol) in THF (20 mL) was added 2M NaHMDS (5 mL, 10 mmol) in one portion at -20°C. The reaction mixture was stirred for 2h, during which the temperature rose to 0°C gradually. The reaction mixture was diluted with EtOAc (200 mL) and washed with a solution of ammonium chloride three times. The solution was concentrated in vacuo to give crude compound **109** which was used for the next reaction without further purification. LC-MS (ESI): 692 $[M+H]^+$.

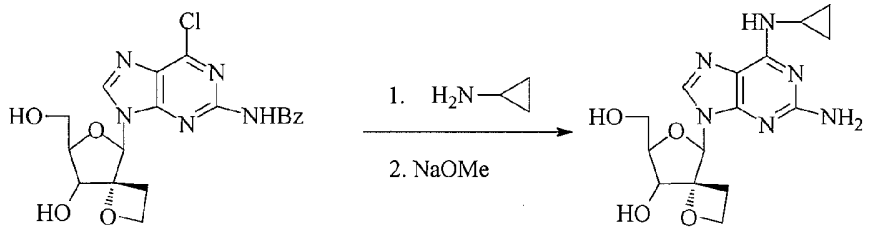
Step 7: Preparation of 110



109 110

To a solution of compound **109** (2.4 g, 3.6 mmol) in THF (40 mL) was added TBAF (1.2 g, 4.5 mmol) and the reaction mixture was stirred at room temperature for 2h. The solvent was evaporated and the residue was purified by silica gel column chromatography (DCM/ MeOH = 60/1) to give compound **110** (1.3 g, 87%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.35(s, 1H), 8.78 (s, 1H), 7.98 (d, J = 7.6 Hz, 2H), 7.58 (t, J = 7.6Hz, 1H), 7.50 (d, J = 7.6 Hz, 2H), 6.28 (s, 1H), 5.45 (bs, 1H), 5.01 (bs, 1H), 4.41-4.45 (m, 3H), 3.55-3.75 (m, 3H), 3.12-3.15 (m, 1H), 2.29-2.31 (m, 1H), 2.25-2.28 (m, 1H)). LC-MS (ESI): 432 $[M+H]^+$.

Example 21. Preparation of (4R,5R,7R,8R)-5-(2-amino-6-(cyclopropylamino)-9H-purin-9-yl)-7-(hydroxymethyl)-1,6-dioxaspiro[3.4]octan-8-ol (111)

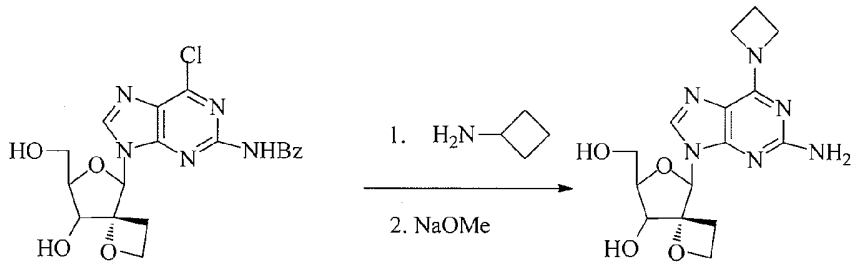


110 111

110 (800 mg, 1.85 mmol) in cyclopropylamine (10 mL) was stirred at room temperature for 24h. To the solution were added MeOH (10 mL) and 5.4 M NaOMe (1.71 mL, 9.26 mmol) and the resulting mixture was stirred at room temperature for 15h. The mixture was concentrated in vacuo, and the residue was purified by silica gel column chromatography (0 to 20% MeOH in CH_2Cl_2) to give 6-cyclopropylamino-nucleoside **111** (500 mg, 76%) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ: 8.02 (s, 1H), 6.21 (s, 1H), 4.53 (m, 2H), 4.43 (d, 1H, J = 8.8 Hz),

3.96 (m, 1H), 3.82-3.77 (m, 2H), 2.91 (m, 1H), 2.56 (m, 1H), 2.27 (m, 1H), 0.83 (m, 2H), 0.60 (m, 2H). LCMS (ESI): 349 $(M+H)^+$.

Example 22. (4R,5R,7R,8R)-5-(2-amino-6-(azetidin-1-yl)-9H-purin-9-yl)-7-(hydroxymethyl)-1,6-dioxaspiro[3.4]octan-8-ol (112) was prepared.

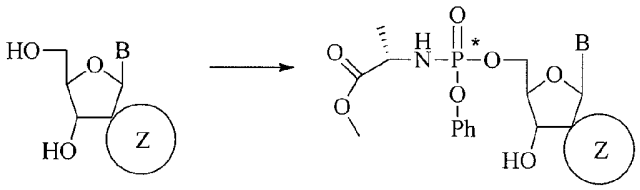


110 **112**

^{1}H NMR (400 MHz, CD_3OD) δ: 8.06 (s, 1H), 6.22 (s, 2H), 4.54 (m, 4H), 4.41 (m, 2H), 3.97 (m, 1H), 3.82 (m, 2H), 2.54 (m, 1H), 2.50 (m, 2H), 2.28 (m, 1H). LCMS (ESI): 349 $(M+H)^+$.

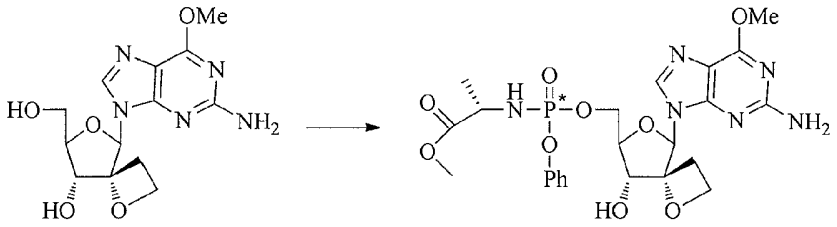
VI. Preparation of 2'-Spiro-Phosphoramidate Analogs

Examples 23-27 describe procedures for converting a corresponding -2'-spiro-nucleoside to its corresponding phosphoramidate, as shown by the following equation.



Ex	Starting Material	Z	B	Product
23	70		2-NH_2-6-OMe-purine	113
24	32		Uracil	114
25	36		Uracil	115
26	44		Uracil	116
27	48		Uracil	117

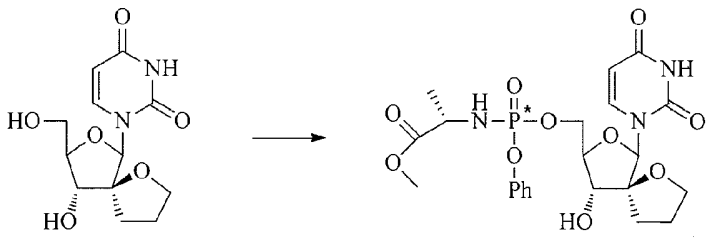
Example 23. Preparation of (2S)-methyl 2-(((((4R,5R,7R,8R)-5-(2-amino-6-methoxy-9H-purin-9-yl)-8-hydroxy-1,6-dioxaspiro[3.4]octan-7-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate, 113



70 113

To a pre-cooled solution of phenyl dichlorophosphate (2.1 g, 9.96 mmol) in CH_2Cl_2 (40 mL) was added L-alanine methyl ester hydrochloride (1.39 g, 9.96 mmol) followed by addition of Et_3N (2.02 g, 19.92 mmol) in CH_2Cl_2 (5 mL) slowly and the mixture was stirred at -78 °C for 1h then at room temperature for 16h. Solvent was evaporated and the residue was filtered with Et_2O (20 mL). Solvent was evaporated to give chlorophosphate reagent which was dissolved in CH_2Cl_2 (10 mL) for the next reaction. To a mixture of compound **70** (0.02 g, 0.06 mmol) in CH_2Cl_2 (15 mL) were added N-methylimidazole (0.2 mL) and a solution of above reagent (0.5 mL, 0.5 mmol), and the resulting mixture was stirred at room temperature for 3h. EtOAc (100 mL) was added and the mixture was washed with water, 1N HCl, aqueous $NaHCO_3$ and brine, sequentially. Organic solution was dried over Na_2SO_4 and evaporated, and the residue was purified by silica gel column chromatography (0-8% MeOH in CH_2Cl_2) to give compound **113** (0.01 g, 41%). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.69, 7.61 (ss, 1H), 7.25 (m, 5H), 6.18 (ss, 1H), 5.08 (ss, 2H), 4.60 (m, 3H), 4.35 (m,1H), 4.06 (ss, 3H), 3.90 (m, 3H), 3.60 (ss, 3H), 3.35 (m, 1H), 2.66 (m, 1H), 2.18 (m, 1H), 1.32 (m, 3H). LC-MS (ESI): 565 $[M+H]^+$.

Example 24. Preparation of (2S)-methyl 2-(((((5S,6R,8R,9R)-6-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-9-hydroxy-1,7-dioxaspiro[4.4]nonan-8-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate, 114.

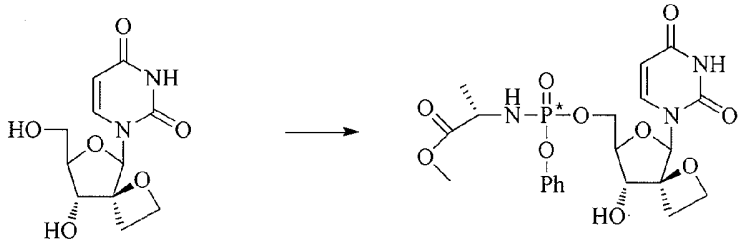


32 114

Compound **114** is prepared from **32** using a procedure analogous to Example 23.

Data for **114**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.75 (s, 1H), 7.60, 7.52 (dd, J=8.0Hz, 1H), 7.24 (m, 5H), 6.05, 6.04 (ss, 1H), 5.65, 5.58 (d, J=8.0, 1H), 4.35 (m, 2H), 4.00 (m, 4H), 3.80 (m, 4H), 3.72, 3.70 (ss, 3H), 2.39 (m, 1H), 1.90 (m, 2H), 1.72 (m, 1H), 1.36 (m, 3H). LC-MS (ESI): 525 $[M+H]^+$.

Example 25. Preparation of (2S)-methyl 2-(((((4S,5R,7R,8R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-8-hydroxy-1,6-dioxaspiro[3.4]octan-7-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate, 115.

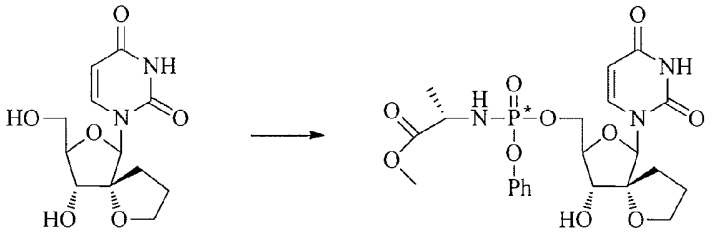


36 115

Compound **115** is prepared from **36** using a procedure analogous to Example 23.

Data for **115**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (s, 1H), 7.30 (m, 6H), 6.12 (ss, 1H), 5.62 (m, 1H), 4.07, 4.113.80 (m, 8H), 3.74, 3.72 (ss, 3H), 3.17 (m, 1H), 2.60 (m, 1H), 1.37 (d, J=7.2Hz, 3H). LC-MS (ESI): 512 $[M+H]^+$.

Example 26. Preparation of (2S)-methyl 2-(((((5R,6R,8R,9R)-6-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-9-hydroxy-1,7-dioxaspiro[4.4]nonan-8-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate, 116.

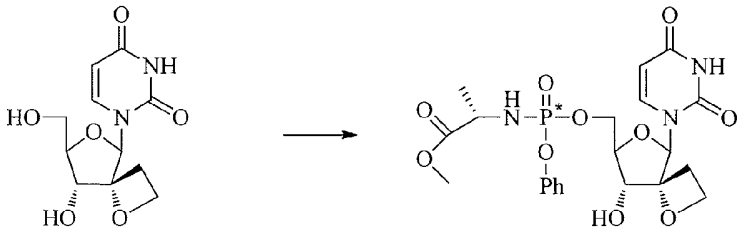


44 116

Compound **116** is prepared from **44** using a procedure analogous to Example 23.

Data for **116**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.51, 8.40 (ss, 1H), 7.48, 7.42 (d, 8.0Hz, 1H), 7.29 (m, 5H), 5.98 (s, 1H), 5.62 (m, 1H), 4.48 (m, 2H), 3.95 (m, 6H), 3.73, 3.72 (ss, 3H), 2.83 (m, 1H), 1.95 (m, 2H), 1.69 (m, 1H), 1.37 (m, 3H). LC-MS (ESI): 526 $[M+H]^+$.

Example 27. Preparation of (2S)-methyl 2-(((((4R,5R,7R,8R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-8-hydroxy-1,6-dioxaspiro[3.4]octan-7-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate, 117.

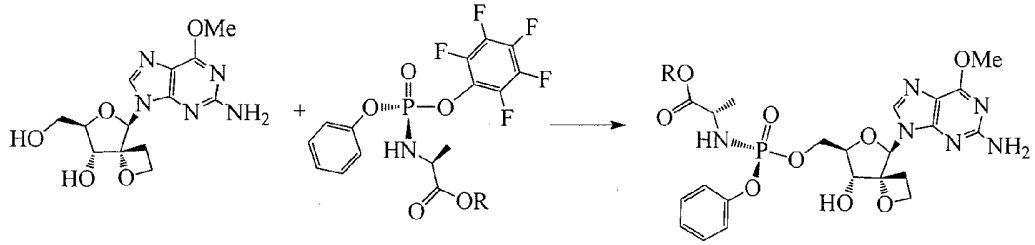


48 117

Compound **117** is prepared from **48** using a procedure analogous to Example 23.

Data for **117**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.15, 9.07 (ss, 1H), 7.26 (m, 7H), 6.19, 6.15 (ss, 1H), 5.65 (m, 1H), 4.50 (m, 4H), 3.95 (m, 4H), 3.72, 3.70 (ss, 3H), 3.42 (s, 1H), 2.75 (m, 1H), 2.46 (m, 1H), 1.35 (m, 3H). LC-MS (ESI): 512 $[M+H]^+$.

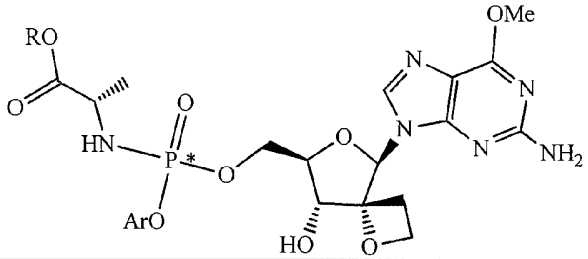
VII. General synthesis of chiral phosphoramidates



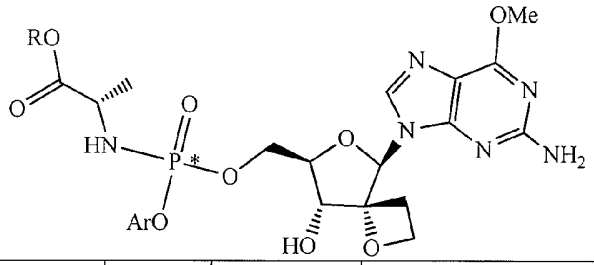
70

Example 29. General Procedure for prepation of chiral 2'-oxetanyl nucleoside phosphoramidates

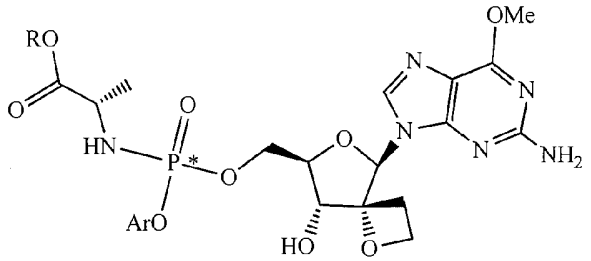
To a solution of the oxetanyl nucleoside **70** (360 mg, 1.11 mmol) in anhydrous THF (15 mL) was added 1.7 M t-butylmagnesium chloride in THF (1.31 mmol) dropwise under ice-water bath. The resulting suspension was stirred at room temperature for 30 min and the chiral pentafluorophenyl phosphoramidate reagent (R = neopentyl (^{neo}Pen), 1.67 mmol) in THF (10 mL) was added over 10 min by which time, the mixture became a clear solution. The mixture was stirred at room temperature for 4h and diluted with EtOAc, (200 mL). The solution was washed with NH_4Cl solution (30 mL x 3), and dried with sodium sulfate. Solvent was evaporated and the residue was purified by silica gel column chromatography (0 to 3% MeOH in CH_2Cl_2) to give the oxetanyl nucleoside phosphoramidate (79%, R = neopentyl) as a white solid.



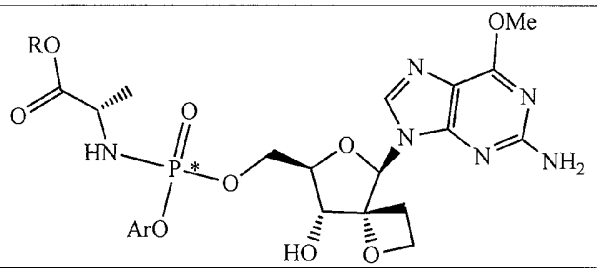
Compound No.	P-Chirality (R_P/S_P)	Ar	R	Analytical data
118	S_P	Ph	$^{i}Pr^{a}$	^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.69 (s, 1H), 7.32-7.12 (m, 5H), 6.16 (s, 1H), 5.09 (s, 2H), 4.96 (m, 1H), 4.73 (dd, 1H, J = 8.8, 10.4 Hz), 4.61-4.53 (m, 3H), 4.33 (m, 1H), 4.06 (s, 3H), 3.98-3.90 (m, 2H), 3.70 (dd, 1H,



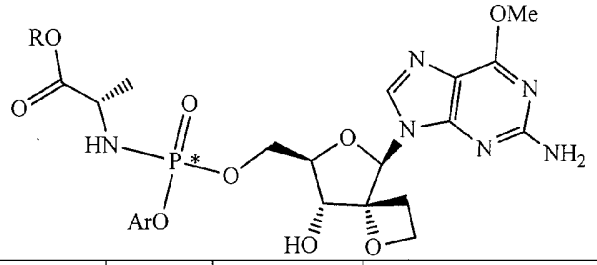
Compound No.	P-Chirality (R_P/S_P)	Ar	R	Analytical data
				J = 9.2, 11.2 Hz), 3.24 (d, 1H, J = 10.0 Hz), 2.68 (m, 1H), 2.17 (m, 1H), 1.30 (d, 3H, J = 7.2 Hz), 1.18 (2d, 6H, J = 6.4 Hz). ^{31}P NMR (162 MHz) δ (ppm) 4.16. LC-MS (ESI): 593 $[M+H]^+$.
119	R_P	Ph	$^{i}Pr^{a}$	^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.62 (s, 1H), 7.32-7.12 (m, 5H), 6.20 (s, 1H), 5.11 (s, 2H), 4.97 (m, 1H), 4.6-4.53 (m, 4H), 4.38 (m, 1H), 4.07 (s, 3H), 3.99-3.92 (m, 2H), 3.85 (t, 1H, J = 11.2 Hz), 3.61 (bs, 1H), 2.62 (m, 1H), 2.15 (m, 1H), 1.98 (bs, 1H), 1.29 (d, 3H, J = 6.8 Hz), 1.20 (t, 3H, J = 6.4 Hz). ^{31}P NMR (162 MHz) δ (ppm) 4.74. LC-MS (ESI): 593 $(M+H)^+$
120	S_P	Ph	$^{neo}Pen^{b}$	^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.69 (s, 1H), 7.32-7.12 (m, 5H), 6.16 (s, 1H), 5.07 (s, 2H), 4.72 (t, 1H, J = 10.0 Hz), 4.60-4.52 (m, 3H), 4.34 (m, 1H), 4.07–4.01 (m, 4H), 3.92 (m, 1H), 3.82 (d, 1H, J = 10.4 Hz), 3.70 (m, 1H), 3.15 (d, 1H, J = 10.0 Hz), 2.68 (m, 1H), 2.17 (m, 1H), 1.35 (d, 3H, J = 6.8 Hz), 0.89 (s, 9H). ^{31}P NMR (162 MHz) δ (ppm) 4.11. LC-MS (ESI): 621 $[M+H]^+$.
121	R_P	Ph	$^{neo}Pen^{b}$	^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.62 (s, 1H), 7.34-7.13 (m, 5H), 6.19 (s, 1H), 5.07 (s, 2H), 4.66-4.52 (m, 4H), 4.38 (m, 1H), 4.11-4.03 (m, 4H), 3.93 (m, 1H), 3.85-3.72 (m, 3H), 3.42 (bs, 1H), 2.63 (m, 1H), 2.15 (m, 1H), 1.34 (d, 3H, J = 7.2 Hz), 0.91 (s, 9H). ^{31}P NMR (162 MHz) δ (ppm) 4.76. LC-MS (ESI): 621 $[M+H]^+$.
122	S_P	Ph	ethyl	^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.70 (s, 1H), 7.32-7.14 (m, 5H), 6.17 (s, 1H), 5.10 (s, 2m), 4.72 (t, 1H, J =



Compound No.	P-Chirality (R_P/S_P)	Ar	R	Analytical data
				9.2 Hz), 4.59-4.54 (m, 3H), 4.35 (m, 1H), 4.15-4.09 (m, 5H), 4.00-3.91 (m, 2H), 3.77 (dd, 1H, J = 9.6, 11.2 Hz), 3.36 (d, 1H, J = 10.4 Hz), 2.67 (m, 1H), 2.18 (m, 1h), 1.31 (d, 3H , J = 7.2 Hz), 1.20 (t, 3H, J = 7.2 Hz). ^{31}P NMR (162 MHz) δ (ppm) 4.08. LC-MS (ESI): 579 $[M+H]^+$.
123	S_P/R_P	Np	^{neo}Pen[b]	^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.10 (m, 1H), 7.82 (m, 1H), 7.69-7.63 (m, 2H), 7.49 (m, 3H), 7.36 (m, 1H), 6.15 (ds, 1H), 5.08 and 5.04 (s, 2H), 4.84-4.60 (m, 2H), 4.54 (t, 2H, J = 7.6 Hz), 4.40 (m, 1H), 4.11 (m, 1H), 4.04 (s, 3H), 3.93 (m, 2H), 3.79 (dd, 1H, J = 1.6, 10.8 Hz), 3.64 (dd, 1H, J = 6.4, 10.0 Hz), 3.37 (broad ds, 1H), 2.66 (m, 1H), 2.16 (m, 1H), 1.31 and 1.28 (s, 3H), 0.86 (s, 9H). ^{31}P NMR (162 MHz) δ (ppm) 5.041, 4.47. LC-MS (ESI): 671 $[M+H]^+$.
124	S_P	Ph	^{i}Bu[c]	^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.71 (s, 1H), 7.31-7.12 (m, 5H), 6.18 (s, 1H), 5.14 (s, 2H), 4.7 (t, 1H, J = 8.8 Hz), 4.60-4.53 (m, 3H), 4.35 (m, 1H), 4.05 (s, 3H), 4.05-3.85 (m, 4H), 3.78 (dd, 1H, J = 6.8, 10.4 Hz), 3.53 (d, 1H, J = 9.6 Hz), 2.66 (m, 1H), 2.17 (m, 1H), 1.87 (m, 1H), 1.33 (d, 3H, J = 6.8 Hz), 0.88 and 0.86 (d, 6H, J = 1.6 Hz). ^{31}P NMR (162 MHz) δ (ppm) 4.15. LC-MS (ESI): 607 $[M+H]^+$.
125	R_P	Ph	^{i}Bu[c]	^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.61 (s, 1H), 7.34-7.13 (m, 5H), 6.19 (s, 1H), 5.05 (s, 2H), 4.68-4.52 (m, 4H), 4.37 (m, 1H), 4.09-3.98 (m, 4H), 3.93-3.82 (m, 3H), 3.74 (t, 1H, J = 9.2 Hz), 3.34 (d, 1H, J = 9.6 Hz), 2.62 (m, 1H), 2.15 (m, 1H), 1.90 (m,



Compound No.	P-Chirality (R_P/S_P)	Ar	R	Analytical data
				1H), 1.32 (d, 3H, J = 7.2 Hz), 0.89 (d, 6H, J = 6.4 Hz). ^{31}P NMR (162 MHz) δ (ppm) 4.74. LC-MS (ESI): 607 $[M+H]^+$.
126	S_P	Ph	^{n}Bu[d]	^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.70 (s, 1H), 7.32-7.12 (m, 5H), 6.17 (s, 1H), 5.11 (s, 2H), 4.71 (t, 1H, J = 6.8 Hz), 4.59-4.52 (m, 3H), 4.35 (m, 1H), 4.11-3.91 (m, 7H), 3.81 (dd, 1H, J = 9.6, 11.6 Hz), 3.41 (d, 1H, J = 10.0 Hz), 2.67 (m, 1H), 2.17 (m, 1H), 1.54 (m, 2H), 1.36-1.27 (m, 5H), 0.87 (t, 3H, J = 7.6 Hz). ^{31}P NMR (162 MHz) δ (ppm) 4.12. LC-MS (ESI): 607 $[M+H]^+$.
127	R_P	Ph	^{n}Bu[d]	^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.62 (s, 1H), 7.33-7.13 (m, 5H), 6.20 (s, 1H), 5.07 (s, 2H), 4.65-4.52 (m, 4H), 4.37 (m, 1H), 4.12-3.88 (m, 6H), 3.93 (m, 1H), 3.79 (t, 1H, J = 11.2 Hz), 3.43 (bs, 1H), 2.63 (m, 1H), 2.15 (m, 1H), 1.57 (m, 2H), 1.38-1.29 (m, 5H), 0.96 (t, 3H, J = 7.2 Hz). ^{31}P NMR (162 MHz) δ (ppm) 4.70. LC-MS (ESI): 607 $[M+H]^+$.
128	S_P	Ph	^{c}Pen[e]	^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.69 (s, 1H), 7.32-7.13 (m, 5H), 6.16 (s, 1H), 5.12 (m, 1H), 5.07 (s, 2H), 4.73 (m, 1H), 4.60-4.53 (m, 3H), 4.34 (m, 1H), 4.06 (s, 3H), 3.98-3.90 (m, 2H), 3.66 (dd, 1H, J = 9.6, 11.2 Hz), 3.17 (d, 1H), 2.68 (m, 1H), 2.17 (m, 1H), 1.80 (m, 2H), 1.68-1.52 (m, 6H), 1.29 (d, 3H, J = 6.8 Hz). ^{31}P NMR (162 MHz) δ (ppm) 4.18. LC-MS (ESI): 619 $[M+H]^+$.
129	R_P	Ph	^{c}Pen[e]	^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.62 (s, 1H), 7.33-7.13 (m, 5H), 6.20 (s, 1H), 5.16-5.13 (m, 3H), 4.64-4.54 (m, 4H), 4.38 (m, 1H), 4.07 (s, 3H),

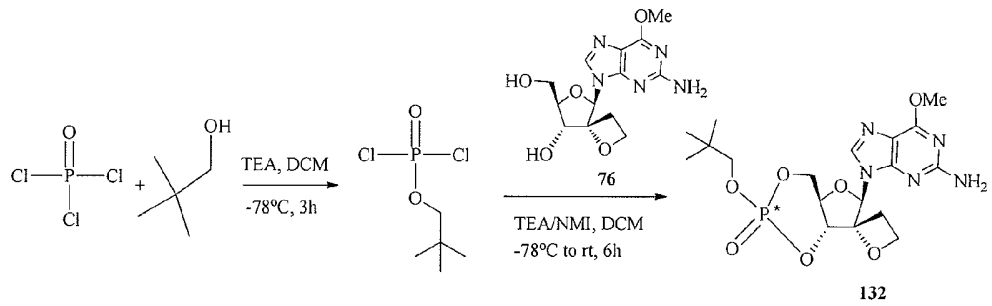


Compound No.	P-Chirality (R_P/S_P)	Ar	R	Analytical data
				3.99-3.91 (m, 2H), 3.83 (dd, 1H, J = 9.6, 11.6 Hz), 2.63 (m, 1H), 2.15 (m, 1H), 1.80 (m, 2H), 1.71-1.55 (m, 6H), 1.28 (d, 3H, J = 6.8 Hz). ^{31}P NMR (162 MHz) δ (ppm) 4.76. LC-MS (ESI): 619 $[M+H]^+$.
130	S_P	Ph	Bn[f]	^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.73 (s, 1H), 7.37-7.11 (m, 10H), 6.17 (s, 1H), 5.09 (s, 2H), 5.07 (s, 2H), 4.75 (m, 1H), 4.58 (m, 3H), 4.40 (m, 1H), 4.09-4.01 (m, 4H), 3.92 (m, 1H), 3.74 (t, 1H, J = 2.6 Hz), 3.36 (bs, 1H), 2.68 (m, 1H), 2.19 (m, 1H), 1.28 (d, 3H, J = 7.2 Hz). ^{31}P NMR (162 MHz) δ (ppm) 4.27. LC-MS (ESI): 641 $[M+H]^+$.
131	R_P	Ph	Bn[f]	^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.60 (s, 1H), 7.36-7.12 (m, 10H), 6.17 (s, 1H), 5.10 (d, 2H, J = 1.2 Hz), 5.05 (s, 2H), 4.66 (m, 1H), 4.62-4.51 (m, 3H), 4.34 (m, 1H), 4.13-4.03 (m, 4H), 3.89 (m, 1H), 3.74 (t, 1H J = 11.2 Hz), 3.31 (d, 1H, J = 7.6 Hz), 2.63 (m, 1H), 2.14 (m, 1H), 1.31 (d, 3H, J = 7.2 Hz). ^{31}P NMR (162 MHz) δ (ppm) 4.64. LC-MS (ESI): 641 $[M+H]^+$.

Notes: [a]iso-propyl. [b]neo-pentyl. [c]iso-butyl. [d]n-butyl. [e]cyclopentyl. [f]benzyl.

VIII. Synthesis of Cyclophosphate Prodrugs

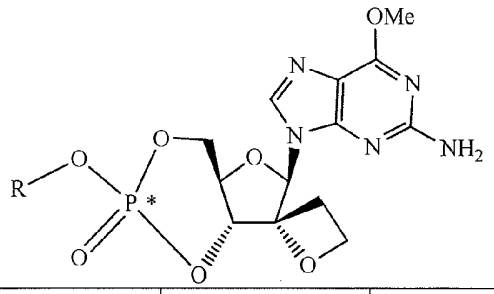
Example 30. Preparation of compound **132**



To a pre-cooled CH_2Cl_2 (2 mL) at -78 °C was added $POCl_3$ (0.07 mL, 0.74 mmol) and neopentyl alcohol (0.74 mmol)) to give a solution to which, Et_3N (0.12 mL, 0.87 mmol) was added dropwise. The resulting mixture was stirred at -78°C for 3h and the oxetanyl nucleoside **76** (70 mg, 0.22 mmol) in THF (2 mL) and then Et_3N (0.24 mL, 1.74 mmol) were added in one portion each. Then NMI (0.17 mL, 2.17 mmol) was added over 3 min. The resulting mixture was stirred for 6h during which the temperature rose to room temperature. The mixture was cooled to -78°C, treated with concentrated HCl to pH 4, diluted with CH_2Cl_2 (10 mL). The organic solution was washed with dilute HCl solution, dried with sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography (0 to 3% MeOH in CH_2Cl_2) to give the oxetanyl nucleoside cyclophosphate **132** as a diastereomeric mixture (6.5 mg, 5.5%) as a syrup.

By the same fashion, the isopropyl cyclophosphate (**133**) was obtained as a diastereomeric mixture as a syrup (6.7 mg, from 100 mg of the oxetanyl nucleoside **76**, 5%).

Cyclopentyl cyclophosphate **134** was also obtained as a diastereomeric mixture as a syrup (30 mg from 150 mg of the oxetanyl nucleoside, 14%).



Compound No.	P-chirality (R_P/S_P)	R	Analytical data
132	1:1 mixture	neopentyl	^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7..71 (s, 1H), 6.21 and 6.20 (m, 1H), 5.11 and 5.09 (s, 2H), 4.73 (m, 1H), 4.63-4.48 (m, 3H), 4.29 (m, 1H), 4.07 and 4.06 (s, 3H), 3.91 (m, 1H), 3.70 (m, 2H), 2,69 (m, 1H), 2.19 (m, 1H), 0.93 and 0.91 (s, 9H). ^{31}P NMR (162 MHz) δ (ppm) 1.71, 1.62. LC-MS (ESI): 488 $[M+H]^+$.
133	3.7:1 mixture	isopropyl	^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.63 and 7.62 (s, 1H), 6.06 and 6.02 (d, 1H, J = 0.8 Hz), 5.65 and 5.34 (2s, 1H, J = 10.4, 9.6 Hz), 5.00-4.79 (m, 3H), 4.67-4.32 (m, 4H), 4.13-4.04 (m, 4H), 2.81-2.65 (m, 1H), 2.41-2.31 (m, 1H), 1.51-1.42 (m, 6H). ^{31}P NMR (162 MHz) δ (ppm) -2.58, -5.77. LC-MS (ESI): 428 $[M+H]^+$.
134	4.7:1 mixture	cyclopentyl	^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.64 (s, 1H), 6.07 and 6.03 (s, 1H), 5.66 and 5.24 (d, 1H, J = 9.6 Hz), 5.51-5.07 (m, 1H), 5.06 and 4.87 (s, 2H), 4.68-4.42 (m, 4H), 4.15-4.07 (m, 4H), 2.82-2.66 (m, 1H), 2.42-2.32 (m, 1H), 2.06-1.78 (m, 8H). ^{31}P NMR (162 MHz) δ (ppm) -2.59, -5.74. LC-MS (ESI): 454 $[M+H]^+$.

IX. Preparation of 2'-Spiro-Analogs

Additional procedures (both non-stereo- and stereoselective) for preparing phosphoramidates are disclosed in U.S. Patent Application Nos. 12/783,680 (US 2010/0298257), filed May 20, 2010 and 13/076,552 (US 2011/0251152), filed on March 31, 2011.

In addition of phosphoramidate analogs, cyclic phosphates are also contemplated. To that end, procedures for preparing cyclic phosphates are disclosed in U.S. Patent Application No. 12/479,075 (US 2010/0081628), filed on June 5, 2009.

Procedures for preparing certain phosphorus-containing compounds are disclosed in U.S. Patent No. 4,816,570.

Procedures for preparing a 1,3,2-dioxaphosphinane-2-oxide are disclosed in U.S. Patent No. 6,752,981 and US 2009/0209481.

Procedures for preparing a 4H-benzo[d][1,3,2]dioxaphosphin-2-oxide are disclosed in U.S. Patent No. 6,312,662.

Procedures for preparing certain 3',5'-diacyl derivatives are disclosed in U.S. Patent No. 7,754,699, see also U.S. Patent No. 5,246,937 for examples of diacyl derivatives.

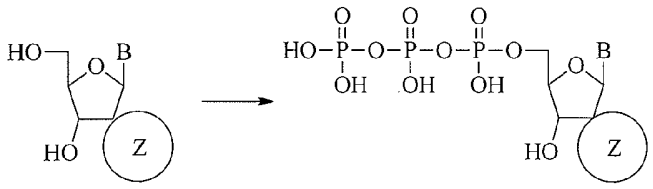
Procedures for preparing aminoacyl derivatives are disclosed in U.S. Patent Nos. 4,957,924 and 6,083,953.

Procedures for preparing a derivative comprised of $-P(O)(O(CH_2)_{1-3}OC(O)(alkyl))_2$ are disclosed in U.S. Patent No. 5,663,159.

Procedures for preparing a derivative comprised of $-P(O)(O(CH_2)_{1-3}OC(O)O(alkyl))_2$ are disclosed in U.S. Patent Nos.5,922,695; 5,977,089; and 6,043,230.

Procedures for preparing a derivative comprised of $-P(O)(O(CH_2)_{1-3}SC(O)alkyl)_2$ are disclosed in U.S. Patent Nos. 5,770,725; 5,849,905; 6,020,482; and 7,105,499.

X. Preparation of 2'-Spiro-Nucleotides



Starting Material	Z	B	Product
32		Uracil	135
48		Uracil	136
49		Cytosine	137
50		Cytosine	138
51		Cytosine	139
52		Cytosine	140

The unprotected nucleoside (0.10 mmol) was dissolved in DTP and cooled to 0-5 °C while maintaining an inert atmosphere. To the stirred solution was added freshly distilled phosphorus oxychloride (0.30 mmol). After 1h at 0-5 °C, tributylamine (0.30 mmol) and freshly dried tributylammonium pyrophosphate (0.25 mmol) were added. The reaction was allowed to warm to ambient temperature for 1 h and then quenched by the addition 1.0 M aqueous triethylamine bicarbonate buffer (1 mL). The reaction solution was directly applied in portions to an ion-exchange HPLC semi-preparative column (Dionex DNA-PAC) and eluted with a gradient of 0.5 M aqueous triethylammonium bicarbonate in water. The product containing fractions were combined and concentrated to dryness. The residue was then dissolved in about 5 mL water and then subjected to lyophilization to yield ca 0.01-0.02 mmol of nucleoside triphosphate as its monotriethylamine salt.

XI. Biological Evaluation of Selected Analogs

HCV replicon assay. HCV replicon assays using Clone A cells and ET-lunet cells were performed as described previously. L. J. Stuyver et al. *Antimicrob. Agents Chemother.* **2004**, *48*, 651-654. Briefly, Clone A cells and ET-lunet cells were seeded at a density of 1500 and 3000 cells per well in a 96-well plate, respectively. Test compounds serially diluted in culture medium without G418 were added to cells. Plates were incubated at 37°C in a 5% CO_2 atmosphere for 4 days. Inhibition of HCV RNA replication was determined by quantitative real time PCR. See, e.g., L. J. Stuyver et al. *Antiviral Chem. Chemother.* **2006**, *17*, 79-87.

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

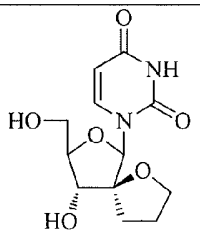
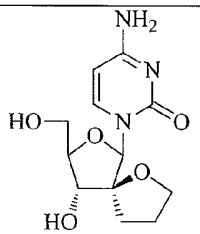
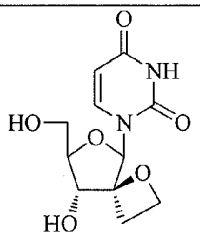
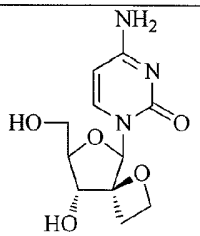
Cell cytotoxicity assays. Each compound (serially diluted from 100 μM) was added to Huh7 (2 x 10^3 cells/well), HepG2 (2 x 10^3 cells/well), BxPC3 (2 x 10^3 cells/well), or CEM (5 x 10^3 cells/well) cells and allowed to incubate for 8 days at 37°C. A medium only control was used to determine the minimum absorbance value and an untreated cell. At the end of the growth period, MTS dye from the CellTiter 96 Aqueous One Solution Cell Proliferation Assay kit (Promega) was added to each well and the plate was incubated for an additional 2 hours. The absorbance at 490 nm was read with a Victor3 plate reader (Perkin Elmer) using the medium only control wells as blanks. The 50% inhibition value (CC_{50}) was determined by comparing the absorbance in wells containing cells and test compound to untreated cell control wells.

The HCV NS5B reaction was performed in a 20 μL mixture containing varying concentrations of the test compound, 1 μM of all four natural ribonucleotides, [α-^{32}P]UTP, 20 ng/μL of genotype 1b (-) IRES RNA template, 1 unit/μL of SUPERase•In (Ambion, Austin, TX), 40 ng/μL of wild type or S282T

NS5B Genotype 1b, 1 mM $MgCl_2$, 0.75 mM $MnCl_2$, and 2 mM DTT in 50 mM Hepes buffer (pH 7.5). The reaction was quenched by adding 80 μL of stop solution (12.5 mM EDTA, 2.25 M NaCl, and 225 mM sodium citrate) after incubating at 27 °C for 30 minutes. The radioactive RNA products were separated from unreacted substrates by passing the quenched reaction mixture through a Hybond N+ membrane (GE Healthcare, Piscataway, NJ) using a dot-blot apparatus. The RNA products were retained on the membrane and the free nucleotides were washed out. The membrane was washed 4 times with a solution containing 0.6 M NaCl and 60 mM sodium citrate. After rinsing the membrane with water followed by ethanol, the membrane was exposed to a phosphorscreen and the products were visualized and quantified using a phosphorimager. The IC_{50} values were calculated using GraFit program version 5 (Erithacus Software, Horley, Surrey, UK). All the reactions were done in duplicate and the results were reported as IC_{50} ± standard error.

The biological activies of selected compounds are presented in Tables 1-5.

Table 1. Anti-HCV activity of selected nucleosides

Ex.	Compound	EC_{50} (μM)	Ex.	Compound	EC_{50} (μM)
32		>100	**50**		>100
36		>100	**51**		>100

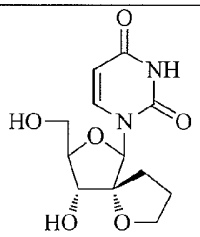
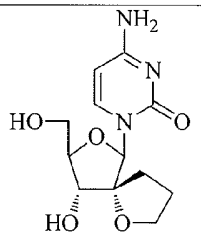
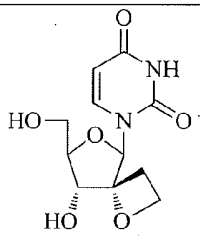
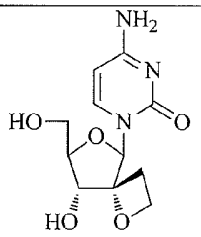
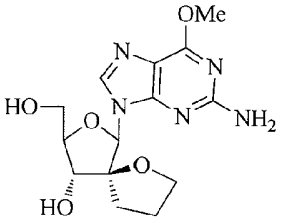
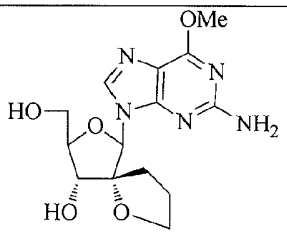
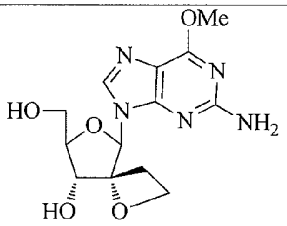
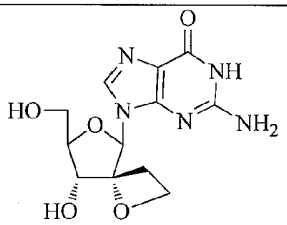
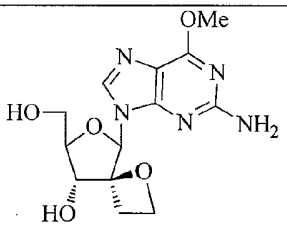
Ex.	Compound	EC_{50} (μM)	Ex.	Compound	EC_{50} (μM)
44		>100	49		>100
48		>100	52		>54.49
62		>20	72		>20
76		>100	77		>20
66		>20			

Table 2. Anti-HCV 1b activity of selected nucleoside phosphoramidates.

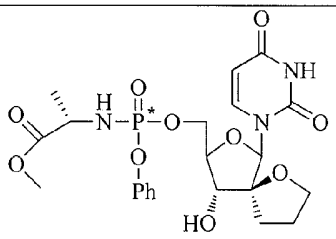
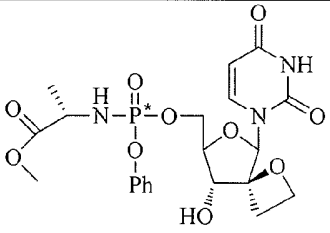
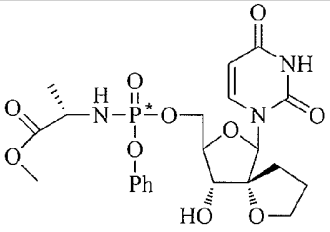
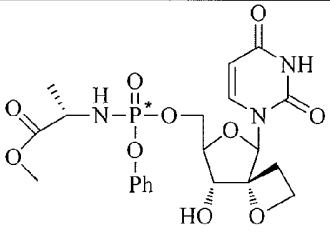
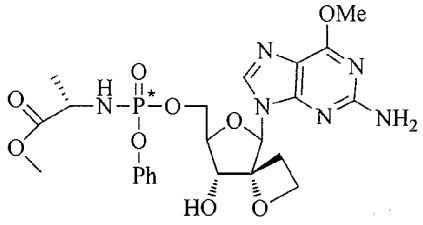
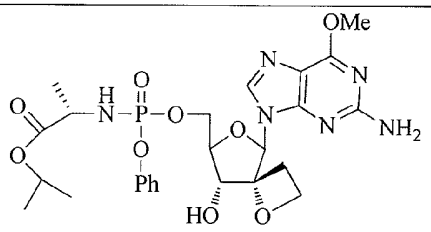
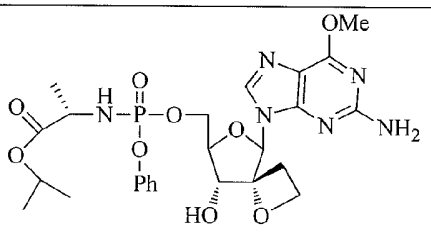
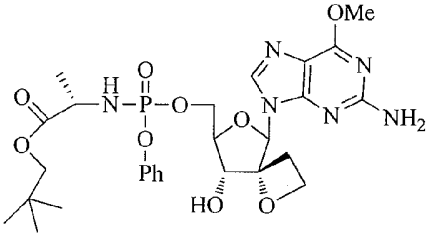
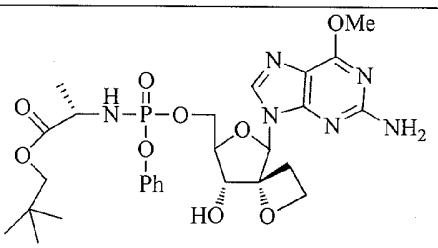
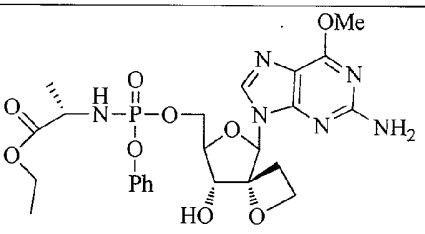
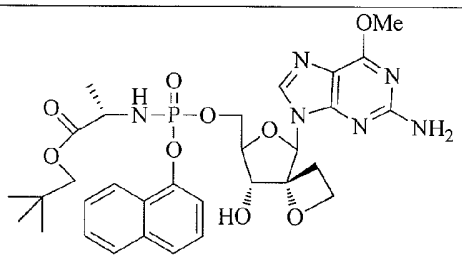
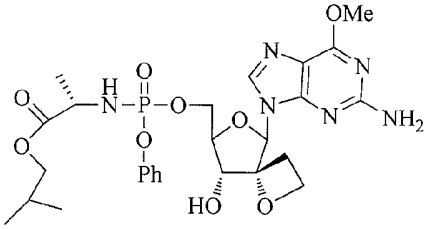
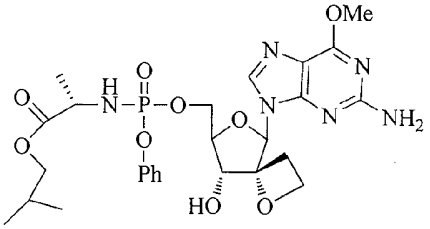
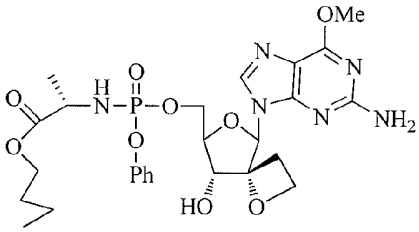
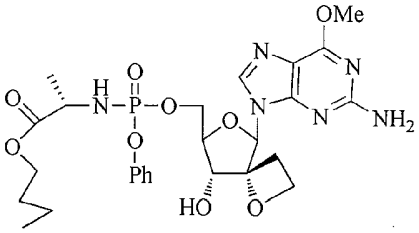
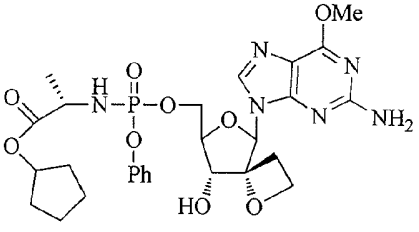
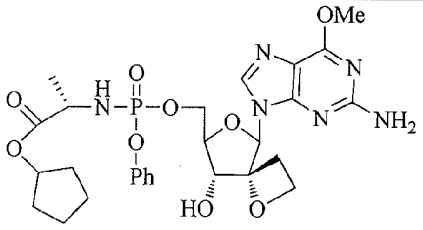
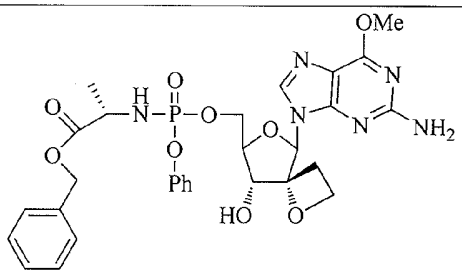
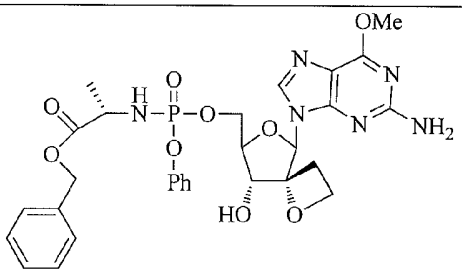
Ex.	Compound	EC_{50}	EC_{90}	CC_{50}
114		20.61	41.69	>100
115		28.5	71.09	>100
116		28.33	81.75	>100
117		16.71	49.20	>100
113		1.55	7.66	>100

Table 3. Anti-HCV 1b activity of selected nucleoside phosphoramidates.

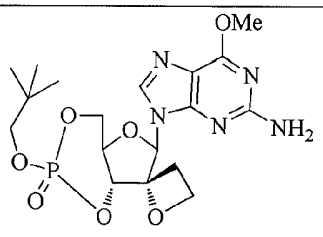
Ex.	Compound	P*[a]	EC_{50} (μM)	EC_{90} (μM)	CC_{50} (μM)
118		S_P	1.49	3.44	>20
119		R_P	4.52	>20	>20
120		S_P	0.39	0.676	>20
121		R_P	9.31	18.5	>20
122		S_P	0.857	3.0	>20

Ex.	Compound	P*[a]	EC_{50} (μM)	EC_{90} (μM)	CC_{50} (μM)
123		S_P/R_P[b]	0.31	0.853	>20
124		S_P	0.566	1.81	>20
125		R_P	4.42	8.45	>20
126		S_P	0.274	0.7	>20
127		R_P	3.1	6.45	>20
128		S_P	0.45	1.09	>20

Ex.	Compound	P*[a]	EC_{50} (μM)	EC_{90} (μM)	CC_{50} (μM)
129		R_P	0.67	1.97	>20
130		S_P	8.65	15.1	>20
131		R_P	11.7	>20	>20

[a]Chirality at Phosphorus (P*). [b]S_P/R_P = mixture of diastereomers.

Table 4. Anti-HCV 1b activity of selected nucleoside cyclic phosphates

Example	Structure	P-chirality (R_P/S_P)	EC_{50} (μM)	EC_{90} (μM)	CC_{50} (μM)
132 (1:1)		(1:1)	>20	>20	>20

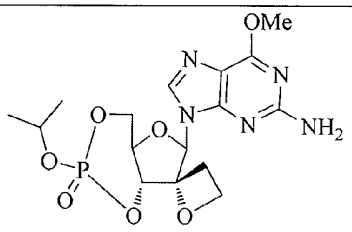
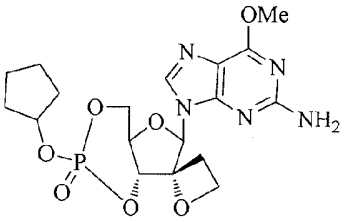
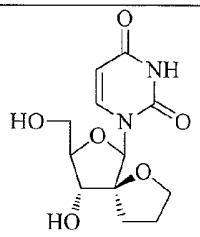
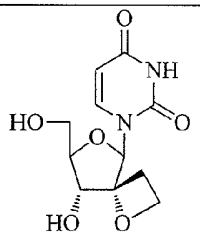
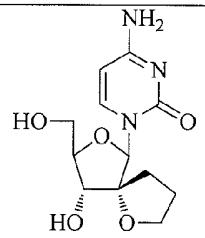
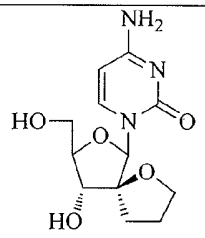
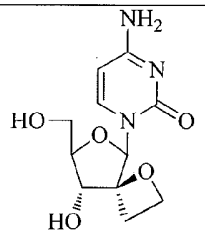
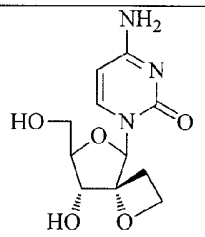
Example	Structure	P-chirality (R_P/S_P)	EC_{50} (μM)	EC_{90} (μM)	CC_{50} (μM)
133 (3.7:1)		(3.7:1)	>20	>20	>20
134 (4.7:1)		(4.7:1)	14.0	>20	>20

Table 5. Anti-HCV activity of selected nucleoside triphosphates against HCV polymerase wild-type and S282T mutant

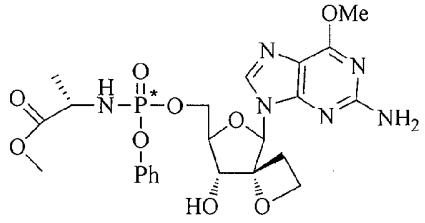
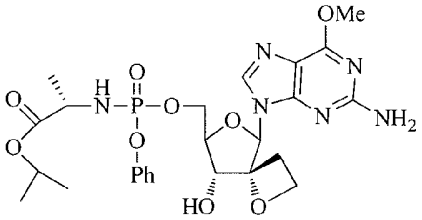
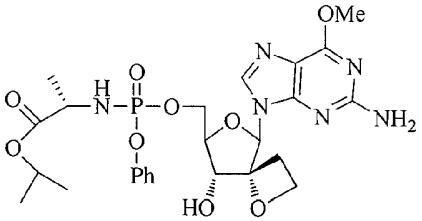
Ex	Compound	Wild-type IC_{50} (μM)	S282T mutant IC_{50} (μM)
135		>100	
136		39.4	>100

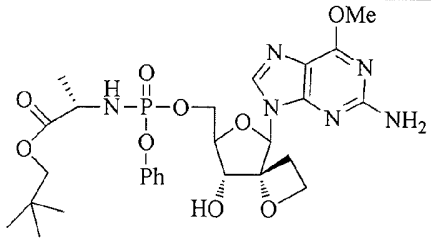
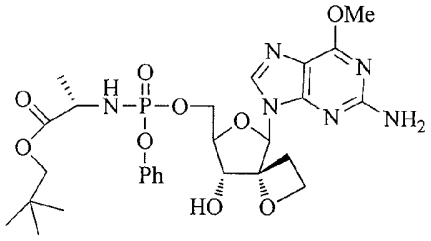
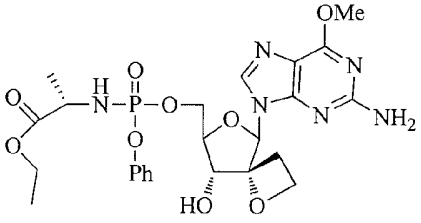
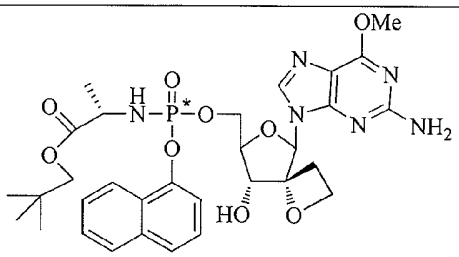
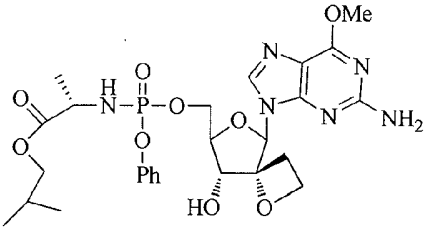
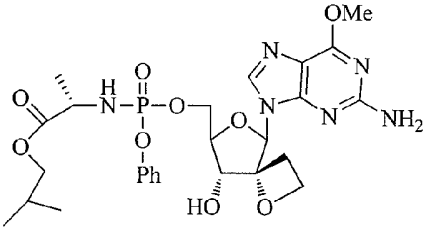
Ex	Compound	Wild-type IC_{50} (μM)	S282T mutant IC_{50} (μM)
137		>45.3	>100
138		>100	
139		>100	
140		>8.48	56.7

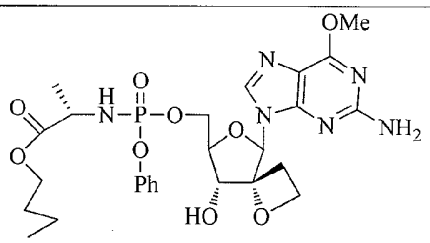
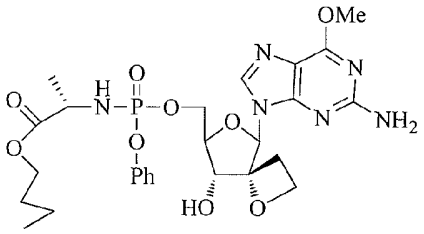
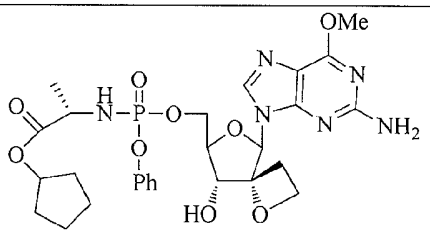
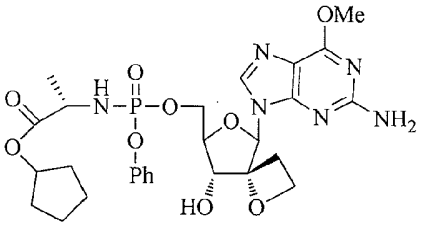
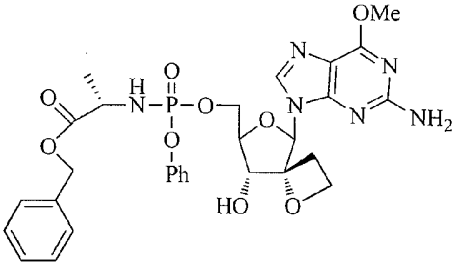
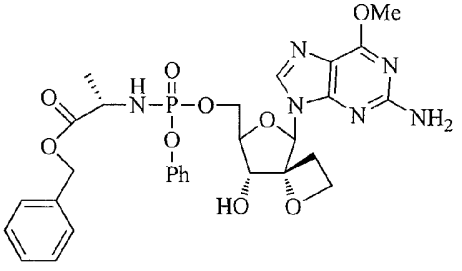
Dengue CPE Assay. To measure cytopathic effect of Dengue virus 2, BHK-21 (Syrian Hamster Kidney, CCL-10 ATCC Manassas, VA) cells were seeded at a density of 20,000 cells/well in a 96-well black/clear bottom plates (Becton Dickinson, Franklin Lakes, NJ) one day prior to start of the assay and allowed to attach overnight in EMEM (ATCC Manassas, VA) +10% FBS (Invitrogen, Carlsbad, CA) at 37°C in a humidified 5% CO_2 atmosphere. The next day, the medium was removed and the cells were infected with Dengue 2 strain New Guinea C (VR-1584, ATCC Manassas, VA) at an MOI of 0.08 pfu/cell for two hours in 50 μL EMEM+2%FBS. For both the single point and dose response assays,

compounds (2 x concentration) were diluted in EMEM+2%FBS and 50 µL was added to infected cells without removing virus. Cells were incubated for 3 days at 37°C in a humidified 5% CO_2 atmosphere. The medium was aspirated and 50 µL of CellTiter-Glo (Promega , Madison, WI) was added to each well and read for 0.1 seconds on a Perkin Elmer Victor3 (Waltham, MA) plate reader. Percent survival was determined by subtracting the average value of infected control wells and normalizing to the non-infected wells. The effective concentration was calculated from the dose response data by forecasting 50% cells surviving with drug treatment.

Table 6. Activity of selected nucleoside phosphoramidates against dengue virus.

Ex.	Compound	P*[a]	EC_{50} (µM)	CC_{50} (µM)
113		R_P/S_P[b]	6.23	**>20**
118		S_P	**5.06**	**>20**
119		R_P	**8.64**	**>20**

Ex.	Compound	P*[a]	EC_{50} (μM)	CC_{50} (μM)
120		S_P	1.88	>20
121		R_P	2.26	>20
122		S_P	5.84	>20
123		S_P/R_P[b]	1.74	>20
124		S_P	2.21	>20
125		R_P	1.98	>20

Ex.	Compound	P*[a]	EC_{50} (μM)	CC_{50} (μM)
126		S_P	2.36	>20
127		R_P	1.61	>20
128		S_P	2.79	>20
129		R_P	2.36	>20
130		S_P	3.84	>20
131		R_P	1.49	>20

Ex.	Compound	P*[a]	EC_{50} (μM)	CC_{50} (μM)
[a]Chirality at Phosphorus (P*). [b]S_P/R_P = mixture of diastereomers.				

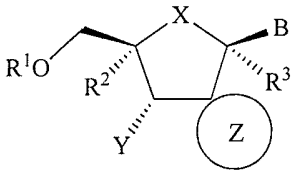
Priority is claimed to U.S. provisional patent application 61/417,946, filed on November 30, 2010.

Although a full and complete description is believed to be contained herein, certain patent and non-patent references may include certain essential subject matter. To the extent that these patent and non-patent references describe essential subject matter, these references are hereby incorporated by reference in their entirety. It is understood that the meanings of the incorporated subject matter are subservient to the meanings of the subject matter disclosed herein. The subject matter of US 61/417,946, filed on November 30, 2010 is hereby incorporated by reference in its entirety. The subject matter of US 13/076,552 and US 13/076,842, both filed on March 31, 2011, is hereby incorporated by reference in its entirety.

The foregoing description of the present invention provides illustration and description, but is not intended to be exhaustive or to limit the invention to the precise one disclosed. Modifications and variations are possible in light of the above teachings or may be acquired from practice of the invention. Thus, it is noted that the scope of the invention is defined by the claims and their equivalents.

What is claimed is:

1. A compound represented by formula **I**:



I

wherein

1) R^1 is selected from among

a) hydrogen,
b) $-P(O)(OH)_2$,
c) $-P(O)(O(CH_2)_{1-3}OC(O)O(alkyl))_2$,
d) $-P(O)(O(CH_2)_{1-3}OC(O)(alkyl))_2$,
e) $-P(O)(O(CH_2)_{1-3}SC(O)(alkyl))_2$,
f) $-P(O)(O(CH_2)_{1-3}OCH_2(aryl))_2$,
g) $-P(O)(O(CH_2)_{1-3}SCH_2(aryl))_2$,
h) $-P^*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})$,
where
R^{1a} is
i) hydrogen,
ii) alkyl,
iii) cycloalkyl, or
iv) aryl,
R^{1b} is
i) hydrogen,
ii) C_{1-6}alkyl,
iii) cycloalkyl,
iv) alkaryl, or
v) alk(heteroaryl), and
R^{1c} is
i) hydrogen
ii) alkyl,
iii) cycloalkyl, or
iv) alkaryl,
i) $-P^*(O)(NH(alkaryl)(O(CH_2)_{1-3}SC(O)(alkyl))$,
j) a 1,3,2-dioxaphosphinane-2-oxide,
k) a 4*H*-benzo[d][1,3,2]dioxaphosphinine-2-oxide,
l) $-P^*(O)(OR^{1c})$ ~, when Y is –O~, where R^{1c} is defined above,
m) $-P(O)(OH)-O-P(O)(OH)_2$,
n) $-P(O)(OH)-O-P(O)(OH)-O-P(O)(OH)_2$,
o) an acyl,
p) a C_{1-6}-alkylene-oxy-acyl, and
q) a –C(O)–O-alkyl;

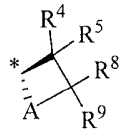
2) R^2 is selected from among
   a) hydrogen,
   b) fluoro,
   c) azido,
   d) cyano,
   e) a $C_{1\text{-}6}$alkyl,
   f) a vinyl, and
   g) an ethynyl;

3) R^3 is selected from among
   a) hydrogen,
   b) methyl, and
   c) cyano;

4) Y is selected from among
   a) hydrogen,
   b) fluoro,
   c) –OH,
   d) –O~, when R^1 is –P(O)(OR^{1c}) ~, where R^{1c} is defined above,
   e) –O(acyl),
   f) –O($C_{1\text{-}6}$-alkylene-oxy-acyl),
   g) –O–C(O)–O-alkyl,
   h) $–NH_2$,
   i) –NH(acyl),
   j) –NH–C(O)–O-alkyl, and
   k) azido;

5) X is selected from among
   a) –O–,
   b) –S–,
   c) –NH–,
   d) $–CH_2–$,
   e) $>C=CH_2$, and
   f) –NH–C(O)–O-alkyl;

6) (Z) is



c

where * represents the point of attachment to the 2'-carbon and where

a) A is selected from among

i) –O–,

ii) –S–,

iii) –S(O)–,

iv) $–S(O)_2–$, and

v) –NH–;

b) R^4, R^5, R^8, and R^9 are independently selected from among

i) hydrogen,

ii) halo,

iii) C_{1-6}alkyl,

iv) hydroxy,

v) alkoxy,

vi) cycloalkoxy,

vii) –O(acyl),

viii) $–O(C_{1-6}$-alkyleneoxyacyl),

ix) –O–C(O)–O-alkyl,

x) C_{1-6}alkylene-oxy(alkyl),

xi) alkenyl,

xii) ethynyl,

xiii) $–NH_2$,

xiv) –NH(alkyl),

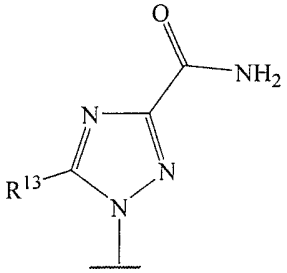
xv) –NH(cycloalkyl),

xvi) heterocyclyl,

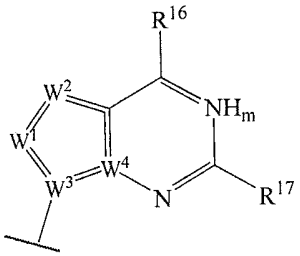
xvii) aryl, and

xviii) heteroaryl; and

7) B is selected from among B2 and B3 represented by the following structures:



B2



B3

where for B2,

a) R^{13} is selected from among

i) hydrogen,

ii) halo,

iii) cyano,

iv) $–C(O)NH_2$,

v) C_{1-6}alkyl,
vi) vinyl, and
vii) ethynyl,

where for B3 m is 0 or 1, and ---- is a single or double bond

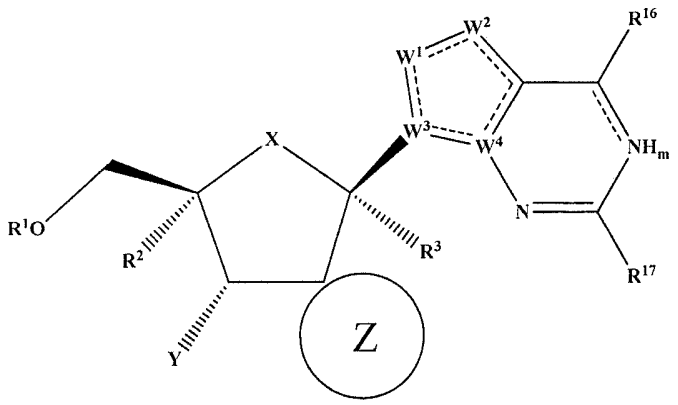
a) when m is 0, ----- is a double-bond and R^{16} and R^{17} are independently selected from among
i) hydrogen,
ii) $-NH_2$,
iii) –NH(alkyl),
iv) –NH(acyl),
iv) –NH–C(O)–O-alkyl,
v) – cycloheteroalkyl,
vi) –O(alkyl),
vii) –O(acyl),
viii) –O(C_{1-6}alkyleneoxyacyl),
ix) –O–C(O)–O-alkyl, and
x) –S(alkyl), or

b) when m is 1, ----- is a single-bond
b1) R^{16} is selected from among
i) =O,
ii) =NH, and
iii) =N(alkyl), and
b2) R^{17} is selected from among
i) $-NH_2$,
ii) –NH(alkyl),
iii) –NH(acyl),
iv) –NH–C(O)–O-alkyl, and
v) – cycloheteroalkyl,

c) independent of the value of m, each bonding pair, W^1----W^2, W^2----C, C----W^4, W^4----W^3, and W^3----W^1, contained in the five-membered ring comprises a single or a double bond and
i) W^1 is O, S, N, or CR^{14},
ii) W^2 is N or CR^{15},
iii) W^3 is C or N, and
iv) W^4 is C or N

and where R^{14} and R^{15}, if present, are independently selected from among
i) hydrogen,
ii) halo,
iii) cyano,
iv) $-C(O)NH_2$,
iv) C_{1-6}alkyl,
vii) vinyl, and
viii) ethynyl.

2. The compound according to claim 1, wherein B is B3, represented by formula I-3



I-3

.

3. The compound according to claim 2, wherein

1) R^1 is selected from among

a) hydrogen,
b) $-P(O)(OH)_2$,
c) $-P(O)(O(CH_2)_{1-3}OC(O)O(C_{1-6}alkyl))_2$,
d) $-P(O)(O(CH_2)_{1-3}OC(O)(C_{1-6}alkyl))_2$,
e) $-P(O)(O(CH_2)_{1-3}SC(O)(C_{1-6}alkyl))_2$,
f) $-P(O)(O(CH_2)_{1-3}OCH_2(aryl))_2$,
g) $-P(O)(O(CH_2)_{1-3}SCH_2(aryl))_2$,
h) $-P^*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})$,

wherein

R^{1a} is

i) hydrogen,
ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl, or
iv) aryl,

R^{1b} is

i) hydrogen,
ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl,
iv) C_{1-3}alkaryl, or
v) alk(heteroaryl), and

R^{1c} is

i) hydrogen
ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl, or
iv) C_{1-3}alkaryl,

i) –P*(O)(NH(alkaryl)(O$(CH_2)_{1-3}$SC(O)(alkyl)),
j) a 1,3,2-dioxaphosphinane-2-oxide,
k) a 4*H*-benzo[d][1,3,2]dioxaphosphinine-2-oxide,
l) –P*(O)(OR^{1c})~, when Y is –O~, where R^{1c} is defined above,
m) –P(O)(OH)–O–P(O)(OH)$_2$,
n) –P(O)(OH)–O–P(O)(OH)–O–P(O)(OH)$_2$,
o) a C_{2-7}acyl,
p) an aminoacyl,
q) a C_{1-6}-alkylene-oxy-C_{2-7}acyl, and
r) a –C(O)–O-C_{1-6}alkyl;

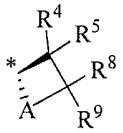
2) R^2 is selected from among
a) hydrogen,
b) fluoro,
c) azido, and
d) cyano;

3) R^3 is selected from among
a) hydrogen,
b) methyl, and
c) cyano;

4) Y is selected from among
a) hydrogen,
b) fluoro,
c) –OH,
d) –O~, when R^1 is –P(O)(OR^{1c})~, where R^{1c} is defined above,
e) –O(C_{2-7}acyl),
f) –O(aminoacyl),
g) –O(C_{1-6}-alkylene-oxy-acyl),
h) –O–C(O)–O-C_{1-6}alkyl,
i) –NH$_2$,
j) –NH(C_{2-7}acyl),
k) –NH(aminoacyl),
l) –NH–C(O)–O-C_{1-6}alkyl, and
m) azido;

5) X is selected from among
a) –O– and
b) –S–;

6) (Z) is



c

where * represents the point of attachment to the 2'-carbon and where

a) A is selected from among

i) –O–,

ii) –S–,

iii) –S(O)–,

iv) $–S(O)_2–$, and

v) –NH–;

c) R^4, R^5, R^8, and R^9 are independently selected from among

i) hydrogen,

ii) halo,

iii) C_{1-6}alkyl

iv) hydroxy,

v) alkoxy,

vi) cycloalkoxy,

vii) –O(acyl),

viii) $–O(C_{1-6}$-alkyleneoxyacyl),

ix) –O–C(O)–O-alkyl,

x) C_{1-6}alkylene-oxy(alkyl),

xi) alkenyl,

xii) ethynyl,

xiii) $–NH_2$,

xiv) –NH(alkyl),

xv) –NH(cycloalkyl),

xvi) heterocyclyl,

xvii) aryl, and

xviii) heteroaryl; and

7a) m is 0, ----- is a double-bond and R^{16} and R^{17} are independently selected from among

i) hydrogen,

ii) $–NH_2$,

iii) $–NH(C_{1-6}$alkyl),

iv) $–NH(C_{2-7}$acyl),

iv) –NH–C(O)–O-C_{1-6}alkyl,

v) – cycloheteroalkyl,

vi) $–O(C_{1-6}$alkyl),

vii) $–O(C_{2-7}$acyl),

viii) $–O(C_{1-6}$alkyleneoxyacyl),

ix) –O–C(O)–O-C_{1-6}alkyl,

x) –S(C_{1-6}alkyl), and
xi) –OC_{1-3}alkaryl, or
7b) m is 1, ----- is a single-bond and
b1) R^{16} is selected from among
i) =O,
ii) =NH, and
iii) =N(C_{1-6}alkyl), and
b2) R^{17} is selected from among
i) –NH_2,
ii) –NH(C_{1-6}alkyl),
iii) –NH(C_{2-7}acyl),
iv) –NH–C(O)–O-C_{1-6}alkyl, and
v) – cycloheteroalkyl,
7c) independent of the value of m, each bonding pair, W^1----W^2, W^2----C, C----W^4, W^4----W^3, and W^3----W^1, contained in the five-membered ring comprises a single or a double bond and
i) W^1 is O, S, N, or CR^{14},
ii) W^2 is N or CR^{15},
iii) W^3 is C or N, and
iv) W^4 is C or N, and
where R^{14} and R^{15}, if present, are independently selected from among
i) hydrogen,
ii) halo,
iii) cyano,
iv) –$C(O)NH_2$,
iv) C_{1-6}alkyl,
vii) vinyl, and
viii) ethynyl.

4. The compound according to claim 2, wherein

1) R^1 is selected from among
a) hydrogen,
b) –$P(O)(OH)_2$,
c) –$P(O)(O(CH_2)_{1-3}OC(O)O(C_{1-6}alkyl))_2$,
d) –$P(O)(O(CH_2)_{1-3}OC(O)(C_{1-6}alkyl))_2$,
e) –$P(O)(O(CH_2)_{1-3}SC(O)(C_{1-6}alkyl))_2$,
f) –$P(O)(O(CH_2)_{1-3}OCH_2(aryl))_2$,
g) –$P(O)(O(CH_2)_{1-3}SCH_2(aryl))_2$,
h) –$P^*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})$,
wherein
R^{1a} is
i) hydrogen,
ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl, or
iv) aryl,

R^{1b} is

i) hydrogen,
ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl,
iv) C_{1-3}alkaryl, or
v) alk(heteroaryl), and

R^{1c} is

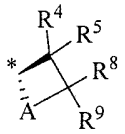
i) hydrogen
ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl, or
iv) C_{1-3}alkaryl,

i) –P*(O)(NH(alkaryl)(O$(CH_2)_{1-3}$SC(O)(alkyl)),
j) a 1,3,2-dioxaphosphinane-2-oxide,
k) a 4*H*-benzo[d][1,3,2]dioxaphosphinine-2-oxide,
l) –P*(O)(OR^{1c})~, when Y is –O~, where R^{1c} is defined above,
m) –P(O)(OH)–O–P(O)(OH)$_2$,
n) –P(O)(OH)–O–P(O)(OH)–O–P(O)(OH)$_2$,
o) a C_{2-7}acyl,
p) an aminoacyl,
q) a C_{1-6}-alkylene-oxy-C_{2-7}acyl, and
r) a –C(O)–O-C_{1-6}alkyl;

2) R^2 is hydrogen;
3) R^3 is hydrogen;
4) Y is selected from among

a) –OH,
b) –O~, when R^1 is –P(O)(OR^{1c})~, where R^{1c} is defined above,
c) –O(C_{2-7}acyl),
d) –O(aminoacyl),
e) –O(C_{1-6}-alkylene-oxy-acyl), and
f) –O–C(O)–O-C_{1-6}alkyl;

5) X is –O–;
6) (Z) is



c

where * represents the point of attachment to the 2'-carbon and where

a) A is selected from among

i) –O–,

ii) –S–,
iii) –S(O)–,
iv) –$S(O)_2$–, and
v) –NH–;

c) R^4, R^5, R^8, and R^9 are independently selected from among
i) hydrogen,
ii) halo, and
iii) C_{1-6}alkyl; and

7a) m is 0, ----- is a double-bond and R^{16} and R^{17} are independently selected from among
i) hydrogen,
ii) $–NH_2$,
iii) –NH(C_{1-6}alkyl),
iv) –NH(C_{2-7}acyl),
iv) –NH–C(O)–O-C_{1-6}alkyl,
v) – cycloheteroalkyl,
vi) –O(C_{1-6}alkyl),
vii) –O(C_{2-7}acyl),
viii) –O(C_{1-6}alkyleneoxyacyl),
ix) –O–C(O)–O-C_{1-6}alkyl,
x) –S(C_{1-6}alkyl), and
xi) –OC_{1-3}alkaryl, or

7b) m is 1, ----- is a single-bond and
b1) R^{16} is selected from among
i) =O,
ii) =NH, and
iii) =N(C_{1-6}alkyl), and
b2) R^{17} is selected from among
i) $–NH_2$,
ii) –NH(C_{1-6}alkyl),
iii) –NH(C_{2-7}acyl),
iv) –NH–C(O)–O-C_{1-6}alkyl, and
v) – cycloheteroalkyl, and

7c) independent of the value of m, each bonding pair, W^1----W^2, W^2----C, C----W^4, W^4----W^3, and W^3----W^1, contained in the five-membered ring comprises a single or a double bond and
i) W^1 is O, S, N, or CR^{14},
ii) W^2 is N or CR^{15},
iii) W^3 is C or N, and
iv) W^4 is C or N, and

where R^{14} and R^{15}, if present, are independently selected from among
i) hydrogen,
ii) halo,
iii) cyano,
iv) $–C(O)NH_2$,
iv) C_{1-6}alkyl,

vii) vinyl, and
viii) ethynyl.

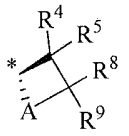
5. The compound according to claim 2, wherein

1) R^1 is selected from among
a) hydrogen,
b) $-P(O)(OH)_2$,
c) $-P(O)(O(CH_2)_{1-3}OC(O)O(C_{1-6}alkyl))_2$,
d) $-P(O)(O(CH_2)_{1-3}OC(O)(C_{1-6}alkyl))_2$,
e) $-P(O)(O(CH_2)_{1-3}SC(O)(C_{1-6}alkyl))_2$,
f) $-P(O)(O(CH_2)_{1-3}OCH_2(aryl))_2$,
g) $-P(O)(O(CH_2)_{1-3}SCH_2(aryl))_2$,
h) $-P^*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})$,
wherein
R^{1a} is
i) hydrogen,
ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl, or
iv) aryl,
R^{1b} is
i) hydrogen,
ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl,
iv) C_{1-3}alkaryl, or
v) alk(heteroaryl), and
R^{1c} is
i) hydrogen
ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl, or
iv) C_{1-3}alkaryl,
i) $-P^*(O)(NH(alkaryl)(O(CH_2)_{1-3}SC(O)(alkyl))$,
j) a 1,3,2-dioxaphosphinane-2-oxide,
k) a 4*H*-benzo[d][1,3,2]dioxaphosphinine-2-oxide,
l) $-P^*(O)(OR^{1c})\sim$, when Y is $-O\sim$, where R^{1c} is defined above,
m) $-P(O)(OH)-O-P(O)(OH)_2$,
n) $-P(O)(OH)-O-P(O)(OH)-O-P(O)(OH)_2$,
o) a C_{2-7}acyl,
p) an aminoacyl,
q) a C_{1-6}-alkylene-oxy-C_{2-7}acyl, and
r) a $-C(O)-O-C_{1-6}$alkyl;
2) R^2 is hydrogen;
3) R^3 is hydrogen;
4) Y is selected from among
a) –OH,
b) $-O\sim$, when R^1 is $-P(O)(OR^{1c})\sim$, where R^{1c} is defined above,

c) –O(C_{2-7}acyl),
d) –O(aminoacyl),
e) –O(C_{1-6}-alkylene-oxy-acyl), and
f) –O–C(O)–O-C_{1-6}alkyl;

5) X is –O–;

6) (Z) is



c

where * represents the point of attachment to the 2'-carbon and where

a) A is –O–,
c) R^4, R^5, R^8, and R^9 are each hydrogen; and
7a) m is 0, ----- is a double-bond and R^{16} and R^{17} are independently selected from among
i) hydrogen,
ii) –NH_2,
iii) –NH(C_{1-6}alkyl),
iv) –NH(C_{2-7}acyl),
iv) –NH–C(O)–O-C_{1-6}alkyl,
v) – cycloheteroalkyl,
vi) –O(C_{1-6}alkyl),
vii) –O(C_{2-7}acyl),
viii) –O(C_{1-6}alkyleneoxyacyl),
ix) –O–C(O)–O-C_{1-6}alkyl,
x) –S(C_{1-6}alkyl), and
xi) –OC_{1-3}alkaryl, or
7b) m is 1, ----- is a single-bond and
b1) R^{16} is selected from among
i) =O,
ii) =NH, and
iii) =N(C_{1-6}alkyl), and
b2) R^{17} is selected from among
i) –NH_2,
ii) –NH(C_{1-6}alkyl),
iii) –NH(C_{2-7}acyl),
iv) –NH–C(O)–O-C_{1-6}alkyl, and
v) – cycloheteroalkyl, and

7c) independent of the value of m, each bonding pair, W^1----W^2, W^2----C, C----W^4, W^4----W^3, and W^3----W^1, contained in the five-membered ring comprises a single or a double bond and

i) W^1 is O, S, N, or CR^{14},
ii) W^2 is N or CR^{15},
iii) W^3 is C or N, and
iv) W^4 is C or N, and

where R^{14} and R^{15}, if present, are independently selected from among

i) hydrogen,
ii) halo,
iii) cyano,
iv) $-C(O)NH_2$,
iv) C_{1-6}alkyl,
vii) vinyl, and
viii) ethynyl.

6. The compound according to claim 2, wherein

1) R^1 is selected from among

a) hydrogen,
b) $-P(O)(OH)_2$,
c) $-P(O)(O(CH_2)_{1-3}OC(O)O(C_{1-6}alkyl))_2$,
d) $-P(O)(O(CH_2)_{1-3}OC(O)(C_{1-6}alkyl))_2$,
e) $-P(O)(O(CH_2)_{1-3}SC(O)(C_{1-6}alkyl))_2$,
f) $-P(O)(O(CH_2)_{1-3}OCH_2(aryl))_2$,
g) $-P(O)(O(CH_2)_{1-3}SCH_2(aryl))_2$,
h) $-P^*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})$,

wherein

R^{1a} is

i) hydrogen or
iv) aryl,

R^{1b} is

i) hydrogen or
ii) C_{1-6}alkyl, and

R^{1c} is

i) hydrogen
ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl, or
iv) C_{1-3}alkaryl,

i) $-P^*(O)(NH(alkaryl)(O(CH_2)_{1-3}SC(O)(alkyl))$,
j) a 1,3,2-dioxaphosphinane-2-oxide,
k) a 4*H*-benzo[d][1,3,2]dioxaphosphinine-2-oxide,
l) $-P^*(O)(OR^{1c})$~, when Y is –O~, where R^{1c} is defined above,
m) $-P(O)(OH)-O-P(O)(OH)_2$,
n) $-P(O)(OH)-O-P(O)(OH)-O-P(O)(OH)_2$,
o) an C_{2-7}acyl,

p) an aminoacyl,
q) a C_{1-6}-alkylene-oxy-C_{2-7}acyl, and
r) a –C(O)–O-C_{1-6}alkyl;

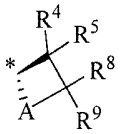
2) R^2 is hydrogen;

3) R^3 is hydrogen;

4) Y is selected from among
a) –OH,
b) –O~, when R^1 is –P(O)(OR^{1c})~, where R^{1c} is defined above,
c) –O(C_{2-7}acyl), and
d) –O(aminoacyl);

5) X is –O–;

6) (Z) is



c

where * represents the point of attachment to the 2'-carbon and where
a) A is –O–,
c) R^4, R^5, R^8, and R^9 are each hydrogen; and
7a) m is 0, ----- is a double-bond and R^{16} and R^{17} are independently selected from among
i) hydrogen,
ii) $–NH_2$,
iii) –NH(C_{1-6}alkyl),
iv) –NH(C_{2-7}acyl),
iv) –NH–C(O)–O-C_{1-6}alkyl,
v) – cycloheteroalkyl,
vi) –O(C_{1-6}alkyl),
vii) –O(C_{2-7}acyl),
viii) –O(C_{1-6}alkyleneoxyacyl),
ix) –O–C(O)–O-C_{1-6}alkyl,
x) –S(C_{1-6}alkyl), and
xi) –OC_{1-3}alkaryl, or

7b) m is 1, ----- is a single-bond and
b1) R^{16} is selected from among
i) =O,
ii) =NH, and
iii) =N(C_{1-6}alkyl), and
b2) R^{17} is selected from among
i) $–NH_2$,
ii) –NH(C_{1-6}alkyl),

ii) –NH(C_{1-6}alkyl),
iii) –NH(C_{2-7}acyl),
iv) –NH–C(O)–O-C_{1-6}alkyl, and
v) – cycloheteroalkyl, and

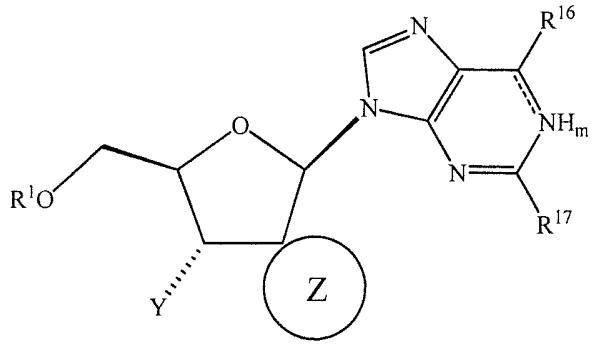
7c) independent of the value of m, each bonding pair, W^1----W^2, W^2----C, C----W^4, W^4----W^3, and W^3----W^1, contained in the five-membered ring comprises a single or a double bond and

i) W^1 is O, S, N, or CR^{14},
ii) W^2 is N or CR^{15},
iii) W^3 is C or N, and
iv) W^4 is C or N, and

where R^{14} and R^{15}, if present, are independently selected from among

i) hydrogen,
ii) halo,
iii) cyano,
iv) –$C(O)NH_2$,
iv) C_{1-6}alkyl,
vii) vinyl, and
viii) ethynyl.

7. The compound according to claim 2, wherein W^1, W^2, W^3, and W^4 are as represented by formula **I-3-1**



I-3-1

and wherein

1) R^1 is selected from among:
a) hydrogen,
b) –$P(O)(OH)_2$,
c) –P*$(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})$,
wherein
R^{1a} is
i) hydrogen or
ii) aryl,
R^{1b} is

i) hydrogen or
ii) C_{1-6}alkyl, and

R^{1c} is

i) hydrogen
ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl, or
iv) C_{1-3}alkaryl,

d) a 1,3,2-dioxaphosphinane-2-oxide,
e) a 4*H*-benzo[d][1,3,2]dioxaphosphinine-2-oxide,
f) –P*(O)(OR^{1c})~, when Y is –O~, where R^{1c} is defined above,
g) –P(O)(OH)–O–P(O)$(OH)_2$,
h) –P(O)(OH)–O–P(O)(OH)–O–P(O)$(OH)_2$,
i) a C_{2-7}acyl, and
j) an aminoacyl; and

2) Y is selected from among
a) –OH,
b) –O~, when R^1 is –P(O)(OR^{1c})~, where R^{1c} is defined above,
c) –O(C_{2-7}acyl), and
d) –O(aminoacyl); and

3) (Z) is

where * represents the point of attachment to the 2'-carbon; and

4a) m is 0, ----- is a double-bond

4a1) R^{16} is selected from among
i) –NH_2,
ii) –NH(C_{1-6}alkyl),
iii) –NH(C_{2-7}acyl),
iv) –cycloalkylamino,
v) –O(C_{1-6}alkyl),
vi) –O(C_{2-7}acyl),
vii) –O(C_{1-6}alkyleneoxyacyl), and
viii) –O–C(O)–O-C_{1-6}alkyl,
ix) –S(C_{1-6}alkyl), and
x) –OC_{1-3}alkaryl, and

4a2) R^{17} is selected from among
i) hydrogen,
ii) –NH_2, and
iii) –NH(C_{1-6}alkyl), or

4b) m is 1, ----- is a single-bond

4b1) R^{16} is =O; and

4b2) R^{17} is selected from among
i) –NH_2 and

ii) –NH(C_{1-6}alkyl).

8. The compound according to claim 7, wherein

1) R^1 is selected from among:
- a) hydrogen,
- b) –P(O)(OH)$_2$,
- c) –P*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c}),

wherein

R^{1a} is
- i) hydrogen,
- ii) phenyl,
- iii) p-fluorophenyl,
- iv) p-chlorophenyl,
- v) p-bromophenyl, or
- vi) naphthyl,

R^{1b} is
- i) hydrogen or
- ii) C_{1-6}alkyl, and

R^{1c} is
- i) hydrogen
- ii) C_{1-6}alkyl,
- iii) C_{3-6}cycloalkyl, or
- iv) C_{1-3}alkaryl,

- d) –P*(O)(OR^{1c})~, when Y is –O~, where R^{1c} is defined above,
- e) –P(O)(OH)–O–P(O)(OH)$_2$,
- f) –P(O)(OH)–O–P(O)(OH)–O–P(O)(OH)$_2$,
- g) a C_{2-7}acyl, and
- h) an aminoacyl;

2) Y is selected from among
- a) –OH,
- b) –O~, when R^1 is –P(O)(OR^{1c})~, where R^{1c} is defined above,
- c) –O(C_{2-7}acyl), and
- d) –O(aminoacyl);

3)  is

where * represents the point of attachment to the 2'-carbon; and

4a) m is 0, ----- is a double-bond

4a1) R^{16} is selected from among
- i) –NH_2,
- ii) –NH(C_{1-6}alkyl),
- iii) –NH(C_{2-7}acyl),
- iv) –cycloalkylamino,

v) –O(C_{1-6}alkyl),
vi) –O(C_{2-7}acyl),
vii) –O(C_{1-6}alkyleneoxyacyl),
viii) –O–C(O)–O-C_{1-6}alkyl,
ix) –S(C_{1-6}alkyl), and
x) –OC_{1-3}alkaryl, and

4a2) R^{17} is selected from among
i) hydrogen,
ii) –NH_2 and
iiii) –NH(C_{1-6}alkyl), or

4b) m is 1, ----- is a single-bond
4b1) R^{16} is =O and
4b2) R^{17} is selected from among
i) –NH_2 and
ii) –NH(C_{1-6}alkyl).

9. The compound according to claim 7, wherein

1) R^1 is selected from among:
a) hydrogen,
b) –P(O)$(OH)_2$,
c) –P*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c}),
wherein
R^{1a} is
i) hydrogen,
ii) phenyl,
iii) p-fluorophenyl,
iv) p-chlorophenyl,
v) p-bromophenyl, or
vi) naphthyl,
R^{1b} is
i) hydrogen or
ii) C_{1-6}alkyl, and
R^{1c} is
i) hydrogen
ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl, or
iv) C_{1-3}alkaryl,
d) –P*(O)(OR^{1c})~, when Y is –O~, where R^{1c} is defined above,
e) –P(O)(OH)–O–P(O)$(OH)_2$,
f) –P(O)(OH)–O–P(O)(OH)–O–P(O)$(OH)_2$,
g) a C_{2-7}acyl, and
h) an aminoacyl;
2) Y is selected from among
a) –OH,
b) –O~, when R^1 is –P(O)(OR^{1c})~, where R^{1c} is defined above,

c) –O(C_{2-7}acyl), and
d) –O(aminoacyl);

3) (Z) is

where * represents the point of attachment to the 2'-carbon; and
4a) m is 0, ----- is a double-bond
4a1) R^{16} is selected from among
i) –NH_2,
ii) –NH(C_{1-6}alkyl),
iii) –NH(C_{2-7}acyl),
iv) –cycloalkylamino,
v) –O(C_{1-6}alkyl),
vi) –O(C_{2-7}acyl),
vii) –S(C_{1-6}alkyl), and
viii) –OC_{1-3}alkaryl, and
4a2) R^{17} is selected from among
i) hydrogen,
ii) –NH_2, and
iii) –NH(C_{1-6}alkyl), or
4b) m is 1, ----- is a single-bond
4b1) R^{16} is =O and
4b2) R^{17} is selected from among
i) –NH_2 and
ii) –NH(C_{1-6}alkyl).

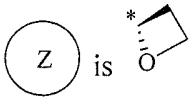
10. The compound according to claim 7, wherein

1) R^1 is selected from among:
a) hydrogen,
b) –P(O)($OH)_2$,
c) –P*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c}),
wherein
R^{1a} is
i) hydrogen,
ii) phenyl,
iii) p-fluorophenyl,
iv) p-chlorophenyl,
v) p-bromophenyl, or
vi) naphtyl,
R^{1b} is
i) hydrogen or
ii) C_{1-6}alkyl, and
R^{1c} is

i) hydrogen
ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl, or
vi) C_{1-3}alkaryl,

d) $-P^*(O)(OR^{1c})\sim$, when Y is $-O\sim$, where R^{1c} is defined above,
e) $-P(O)(OH)-O-P(O)(OH)_2$,
f) $-P(O)(OH)-O-P(O)(OH)-O-P(O)(OH)_2$,
g) a C_{2-7}acyl, and
h) an aminoacyl;

2) Y is selected from among
a) –OH,
b) $-O\sim$, when R^1 is $-P(O)(OR^{1c})\sim$, where R^{1c} is defined above,
c) $-O(C_{2-7}acyl)$, and
d) –O(aminoacyl);

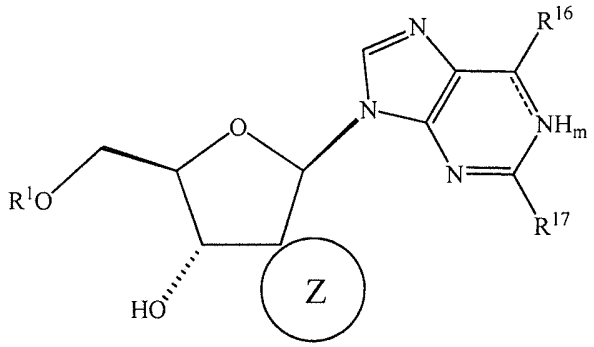
3)  is

where * represents the point of attachment to the 2'-carbon; and

4a) m is 0, ----- is a double-bond
4a1) R^{16} is $-O(C_{1-6}alkyl)$, $-OC_{1-3}alkaryl$, $-S(C_{1-6}alkyl)$, $-NH(C_{1-6}alkyl)$, or –cycloalkylamino, and
4a2) R^{17} is $-NH_2$ or $-NH(C_{1-6}alkyl)$, or
4a3) R^{16} is $-NH_2$, $-O(C_{1-6}alkyl)$, $-OC_{1-3}alkaryl$, $-S(C_{1-6}alkyl)$, $-NH(C_{1-6}alkyl)$, or –cycloalkylamino, and
4a4) R^{17} is hydrogen, or

4b) m is 1, ----- is a single-bond
4b1) R^{16} is =O and
4b2) R^{17} is $-NH_2$ or $-NH(C_{1-6}alkyl)$.

11. The compound according to claim 2, wherein Y, W^1, W^2, W^3, and W^4 are as represented by formula **I-3-2**



I-3-2

and wherein

1) R^1 is selected from among:
- a) hydrogen,
- b) $-P(O)(OH)_2$,
- c) $-P^*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})$,

wherein

R^{1a} is
- i) hydrogen,
- ii) phenyl,
- iii) p-fluorophenyl,
- iv) p-chlorophenyl,
- v) p-bromophenyl, or
- vi) naphthyl,

R^{1b} is
- i) hydrogen or
- ii) C_{1-6}alkyl, and

R^{1c} is
- i) hydrogen
- ii) C_{1-6}alkyl,
- iii) C_{3-6}cycloalkyl, or
- iv) C_{1-3}alkaryl,

- d) $-P(O)(OH)-O-P(O)(OH)_2$,
- e) $-P(O)(OH)-O-P(O)(OH)-O-P(O)(OH)_2$,
- f) a C_{2-7}acyl, and
- g) an aminoacyl;

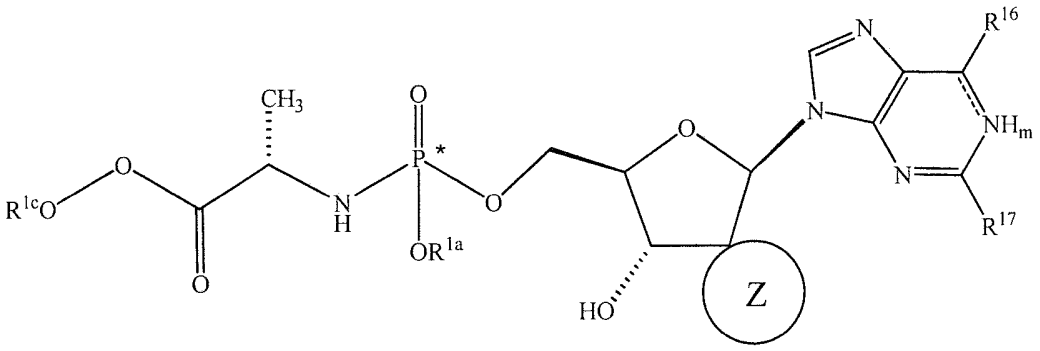
2) (Z) is

where * represents the point of attachment to the 2'-carbon; and

3a) m is 0, ----- is a double-bond
- 3a1) R^{16} is $-O(C_{1-6}alkyl)$, $-OC_{1-3}alkaryl$,$-S(C_{1-6}alkyl)$, $-NH(C_{1-6}alkyl)$, or –cycloalkylaminoand
- 3a2) R^{17} is $-NH_2$ or $-NH(C_{1-6}alkyl)$, or
- 3a3) R^{16} is $-NH_2$, $-O(C_{1-6}alkyl)$, $-OC_{1-3}alkaryl$,$-S(C_{1-6}alkyl)$, $-NH(C_{1-6}alkyl)$, or –cycloalkylamino and
- 3a4) R^{17} is hydrogen, or

3b) m is 1, ----- is a single-bond
- 3b1) R^{16} is =O and
- 3b2) R^{17} is$-NH_2$.

12. The compound according to claim 2, wherein R^1, Y, W^1, W^2, W^3, and W^4 are as represented by formula **I-3-3**



I-3-3

and wherein

1) R^{1a} is selected from among
   a) hydrogen,
   b) phenyl,
   c) p-fluorophenyl,
   d) p-chlorophenyl,
   e) p-bromophenyl, and
   f) naphthyl, and

2) R^{1c} is selected from among
   a) hydrogen
   b) $C_{1\text{-}6}$alkyl,
   c) $C_{3\text{-}6}$cycloalkyl, and
   d) $C_{1\text{-}3}$alkaryl;

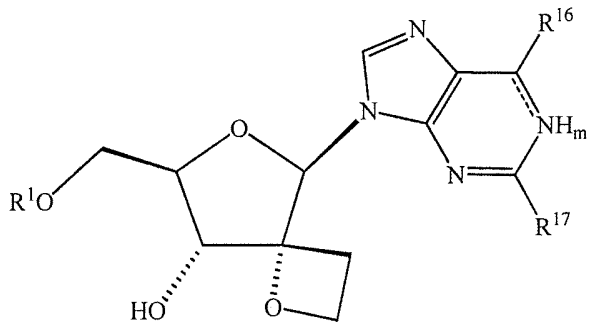
3)  is

where * represents the point of attachment to the 2'-carbon; and

4a) m is 0, ----- is a double-bond
   4a1) R^{16} is $-O(C_{1\text{-}6}alkyl)$, $-OC_{1\text{-}3}alkaryl$, $-S(C_{1\text{-}6}alkyl)$, $-NH(C_{1\text{-}6}alkyl)$, or –cycloalkylamino, and
   4a2) R^{17} is $-NH_2$ or $-NH(C_{1\text{-}6}alkyl)$, or
   4a3) R^{16} is $-NH_2$, $-O(C_{1\text{-}6}alkyl)$, $-OC_{1\text{-}3}alkaryl$, $-S(C_{1\text{-}6}alkyl)$, $-NH(C_{1\text{-}6}alkyl)$, or –cycloalkylamino, and
   4a4) R^{17} is hydrogen, or

4b) m is 1, ----- is a single-bond
   4b1) R^{16} is =O and
   4b2) R^{17} is $-NH_2$ or $-NH(C_{1\text{-}6}alkyl)$.

13. The compound according to claim 2, wherein Y, Z, W^1, W^2, W^3, and W^4 are as represented by formula **I-3-4**



I-3-4

and wherein

1) R^1 is selected from among:
- a) hydrogen,
- b) $-P(O)(OH)_2$,
- c) $-P^*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})$,

wherein

R^{1a} is
- i) hydrogen,
- ii) phenyl,
- iii) p-fluorophenyl,
- iv) p-chlorophenyl,
- v) p-bromophenyl, or
- vi) naphthyl,

R^{1b} is
- i) hydrogen or
- ii) C_{1-6}alkyl, and

R^{1c} is
- i) hydrogen
- ii) C_{1-6}alkyl,
- iii) C_{3-6}cycloalkyl, or
- iv) C_{1-3}alkaryl,

- d) $-P(O)(OH)-O-P(O)(OH)_2$,
- e) $-P(O)(OH)-O-P(O)(OH)-O-P(O)(OH)_2$,
- f) a C_{2-7}acyl, and
- g) an aminoacyl; and

2a) m is 0, ----- is a double-bond

3a1) R^{16} is $-O(C_{1-6}$alkyl), $-OC_{1-3}$alkaryl, $-S(C_{1-6}$alkyl), $-NH(C_{1-6}$alkyl), or –cycloalkylamino, and

3a2) R^{17} is $-NH_2$ or $-NH(C_{1-6}$alkyl), or

3a3) R^{16} is $-NH_2$, $-O(C_{1-6}$alkyl), $-OC_{1-3}$alkaryl, $-S(C_{1-6}$alkyl), $-NH(C_{1-6}$alkyl), or –cycloalkylamino and

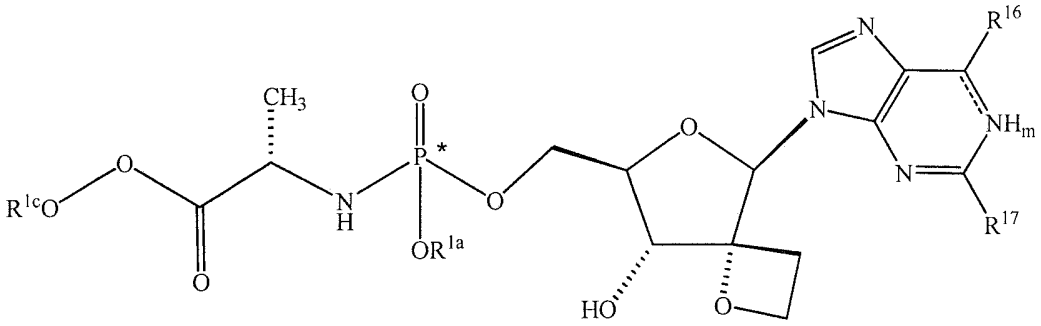
3a4) R^{17} is hydrogen, or

2b) m is 1, ----- is a single-bond

3b1) R^{16} is =O and

3b2) R^{17} is–NH_2 or –NH(C_{1-6}alkyl).

14. The compound according to claim 2, wherein R^1, Y, Z, W^1, W^2, W^3, and W^4 are as represented by formula **I-3-5**



I-3-5

wherein

1) R^{1a} is
   a) hydrogen,
   b) phenyl, or
   c) naphthyl;
2) R^{1c} is
   a) hydrogen
   b) C_{1-6}alkyl,
   c) C_{3-6}cycloalkyl, or
   d) C_{1-3}alkaryl; and

3a) m is 0, ----- is a double-bond
   3a1) R^{16} is –O(C_{1-6}alkyl), –OC_{1-3}alkaryl, –S(C_{1-6}alkyl), –NH(C_{1-6}alkyl), or –cycloalkylamino, and
   3a2) R^{17} is –NH_2 or –NH(C_{1-6}alkyl), or
   3a3) R^{16} is –NH_2, –O(C_{1-6}alkyl), –OC_{1-3}alkaryl, –S(C_{1-6}alkyl), –NH(C_{1-6}alkyl), or –cycloalkylamino, and
   3a4) R^{17} is hydrogen, or

3b) m is 1, ----- is a single-bond
   3b1) R^{16} is =O and
   3b2) R^{17} is–NH_2 or –NH(C_{1-6}alkyl).

15. The compound according to claim 14, wherein

1) R^{1a} is
   a) hydrogen,
   b) phenyl, or
   c) naphthyl,
2) R^{1c} is

a) hydrogen
b) C_{1-6}alkyl,
c) C_{3-6}cycloalkyl, or
d) C_{1-3}alkaryl; and

3a) m is 0, ----- is a double-bond
3a1) R^{16} is –O(C_{1-6}alkyl), –OC_{1-3}alkaryl, –S(C_{1-6}alkyl), –NH(C_{1-6}alkyl), or –cycloalkylamino, and
3a2) R^{17} is $–NH_2$, or
3a3) R^{16} is $–NH_2$, –O(C_{1-6}alkyl), –OC_{1-3}alkaryl, –NH(C_{1-6}alkyl), –S(C_{1-6}alkyl), or –cycloalkylamino, and
3a4) R^{17} is hydrogen, or

3b) m is 1, ----- is a single-bond
3b1) R^{16} is =O and
3b2) R^{17} is–NH_2.

16. The compound according to claim 14, wherein

1) R^{1a} is
a) hydrogen,
b) phenyl, or
c) naphthyl;

2) R^{1c} is
a) hydrogen
b) C_{1-6}alkyl,
c) C_{3-6}cycloalkyl, or
d) C_{1-3}alkaryl; and

3a) m is 0, ----- is a double-bond
3a1) R^{16} is –O(C_{1-6}alkyl) –OC_{1-3}alkaryl, and
3a2) R^{17} is $–NH_2$, or
3a3) R^{16} is $–NH_2$, and
3a4) R^{17} is hydrogen, or

3b) m is 1, ----- is a single-bond
3b1) R^{16} is =O and
3b2) R^{17} is–NH_2.

17. A composition comprising the compound as claimed in any one of claims 1-16 and a pharmaceutically acceptable medium.

18. A composition for treating a hepatitis C virus, which comprises an effective amount of the compound as claimed in any one of claims 1-16 and a pharmaceutically acceptable medium.

19. A composition for treating a dengue virus, which comprises an effective amount of the compound as claimed in any one of claims 1-16 and a pharmaceutically acceptable medium.

20. A method of treating a subject infected by a virus, which comprises:

administering to the subject an effective amount of the compound as claimed in any one of claims 1-16;

wherein the virus is selected from among hepatitis C virus, West Nile virus, a yellow fever virus, a dengue virus, a rhinovirus, a polio virus, a hepatitis A virus, a bovine viral diarrhea virus, and a Japanese encephalitis virus.

21. A method of treating a hepatitis C virus infection in a subject in need thereof, which comprises:

administering to the subject an effective amount of the compound as claimed in any one of claims 1-16.

22. A method of treating a dengue virus infection in a subject in need thereof, which comprises:

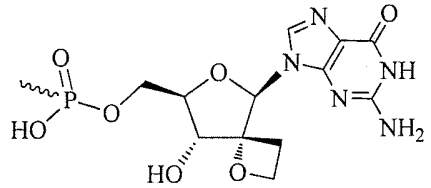
administering to the subject an effective amount of the compound as claimed in any one of claims 1-16.

23. A use of the compound as claimed in any one of claims 1-16 in the manufacture of a medicament for the treatment of a condition that results from an infection by hepatitis C virus, West Nile virus, yellow fever virus, dengue virus, rhinovirus, polio virus, hepatitis A virus, bovine viral diarrhea virus or Japanese encephalitis virus.

24. A use of the compound as claimed in any one of claims 1-16 in the manufacture of a medicament for the treatment of a condition that results from an infection by hepatitis C virus.

25. A use of the compound claimed in any one of claims 1-16 in the manufacture of a medicament for the treatment of a condition that results from an infection by dengue virus.

26. A method of treating a hepatitis C virus (HCV) or dengue (DENV) infection, which comprises adding to the 3'-terminus of an HCV or DENV RNA strand a radical or its salt thereof represented by

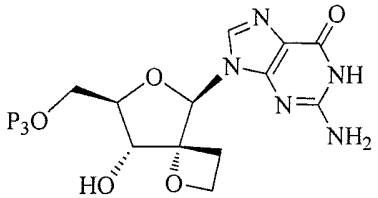


where ~~~ is the point of attachment to the 3'-terminus.

27. The method of claim 26, which comprises adding the radical or its salt thereof to the 3'-terminus of an HCV RNA.

28. The method of claim 26, which comprises adding the radical or its salt thereof to the 3'-terminus of a DENV RNA.

29. A method of treating a hepatitis C virus (HCV) or dengue (DENV) infection, which comprises increasing an intracellular concentration of a triphosphate (P_3) compound or its salt thereof represented by

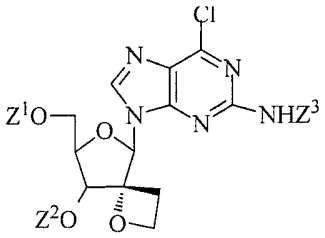


in a cell infected with HCV or DENV.

30. The method of claim 29, which comprises increasing the intracellular concentration of the triphosphate (P_3) compound in an HCV infected cell.

31. The method of claim 29, which comprises increasing the intracellular concentration of the triphosphate (P_3) compound in a DENV infected cell.

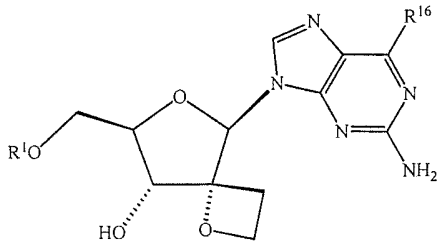
32. A compound or a salt thereof represented by formula **A**,



A

wherein each one of Z^1, Z^2, and Z^3 is hydrogen or a protecting group (PG).

33. A process for preparing a compound represented by formula **I-3-4'**



I-3-4'

wherein

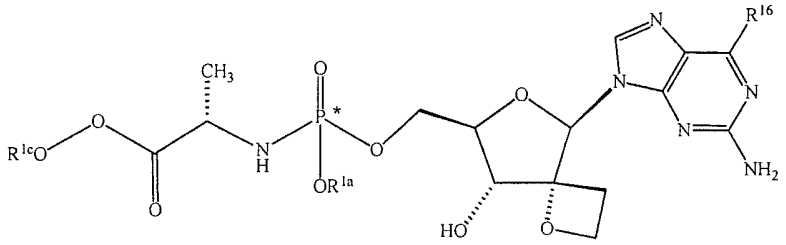
1) R^1 is selected from among:
   a) hydrogen,
   b) $-P(O)(OH)_2$,
   c) $-P^*(O)(OR^{1a})(NHCHR^{1b}C(O)OR^{1c})$,
   wherein
   R^{1a} is
      i) hydrogen,
      ii) phenyl,
      iii) p-fluorophenyl,
      iv) p-chlorophenyl,
      v) p-bromophenyl, or
      vi) naphthyl,
   R^{1b} is
      i) hydrogen or
      ii) $C_{1\text{-}6}$alkyl, and
   R^{1c} is
      i) hydrogen

i) hydrogen
ii) C_{1-6}alkyl,
iii) C_{3-6}cycloalkyl, or
iv) C_{1-3}alkaryl,

d) $-P(O)(OH)-O-P(O)(OH)_2$,
e) $-P(O)(OH)-O-P(O)(OH)-O-P(O)(OH)_2$,
f) a C_{2-7}acyl, and
g) an aminoacyl; and

or

a compound represented by formula **I-3-5'**,



I-3-5'

wherein

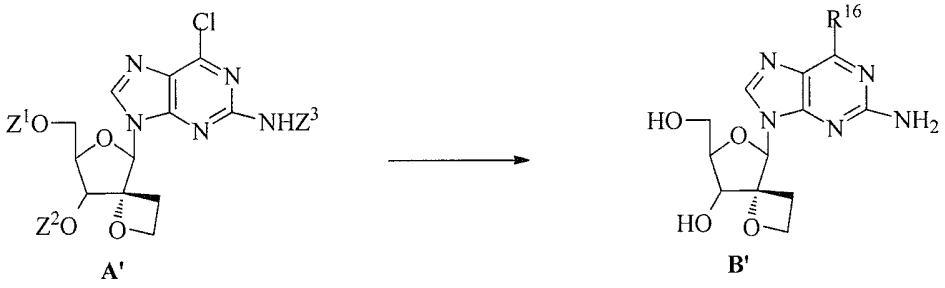
1) R^{1a} is
a) hydrogen,
b) phenyl, or
c) naphthyl, and

2) R^{1c} is
a) hydrogen
b) C_{1-6}alkyl,
c) C_{3-6}cycloalkyl, or
d) C_{1-3}alkaryl; and

3) R^{16} is
a) $-O(C_{1-6}$alkyl),
b)$-OC_{1-3}$alkaryl,
c) $-S(C_{1-6}$alkyl),
d) $-NH(C_{1-6}$alkyl), or
e) –cycloalkylamino,

said process comprising

reacting compound **A'** with a nucleophile and optionally deprotecting to obtain compound **B'**



wherein the nucleophile is comprised of a radical selected from among –O(C_{1-6}alkyl), –OC_{1-3}alkaryl, –S(C_{1-6}alkyl), –NH(C_{1-6}alkyl), and –cycloalkylamino, and wherein PG is a protecting group, and wherein each one of Z^1, Z^2, and Z^3 is hydrogen or a protecting group (PG) and

reacting **B'** with an appropriate reagent to obtain either **I-3-4'** or **I-3-5'**.

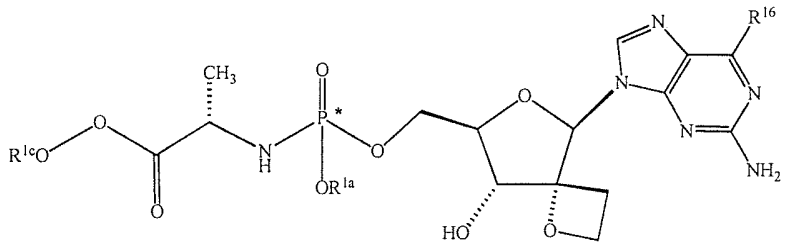
34. The process according to claim 33 for preparing the compound represented by formula **I-3-5'**, wherein R^{16} is a –O(C_{1-6}alkyl). a –OC_{1-3}alkaryl, a –NH(C_{1-6}alkyl), and a C_{3-6}cycloalkylamino and wherein the nucleophile is comprised of a radical selected from among a –O(C_{1-6}alkyl), a –OC_{1-3}alkaryl, a –NH(C_{1-6}alkyl), and a C_{3-6}cycloalkylamino.

35. The process according to claim 33 for preparing the compound represented by formula **I-3-5'**, wherein R^{16} is a –O(C_{1-6}alkyl) or a –OC_{1-3}alkaryl, and wherein the nucleophile is comprised of a radical selected from among a –O(C_{1-6}alkyl) and a –OC_{1-3}alkaryl.

36. The process according to claim 33 for preparing the compound represented by formula **I-3-5'**, wherein R^{16} is a –O(C_{1-6}alkyl), and wherein the nucleophile is comprised of a–O(C_{1-6}alkyl).

37. The process according to claim 34 for preparing the compound represented by formula **I-3-5'**, wherein R^{16} is a –OC_{1-3}alkaryl, and wherein the nucleophile is comprised of a–OC_{1-3}alkaryl.

38. A process for preparing a compound represented by formula **I-3-5''**,



I-3-5''

wherein

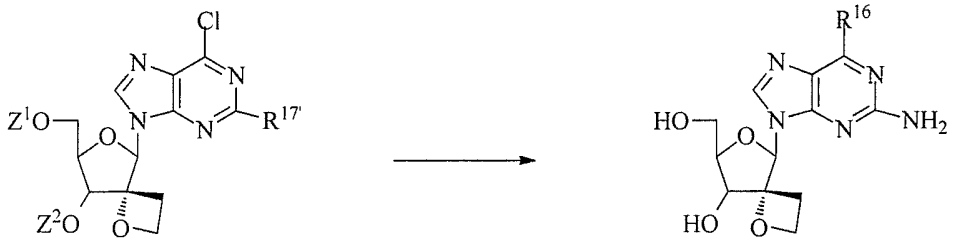
R^{1a} is phenyl or naphthyl;

R^{1c} is hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, or C_{1-3}alkaryl; and

R^{16} is $-O(C_{1-6}alkyl)$, $-OC_{1-3}alkaryl$, $-S(C_{1-6}alkyl)$, $-NH(C_{1-6}alkyl)$, or –cycloalkylamino;

said process comprising:

reacting compound **A''** with a nucleophile and optionally deprotecting to obtain compound **B''**,



A'' **B''**

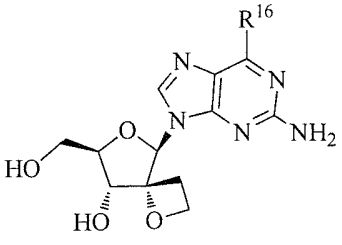
wherein

$R^{17'}$ is $-NHZ^3$, wherein each one of Z^1, Z^2, and Z^3 is hydrogen or a protecting group (PG);

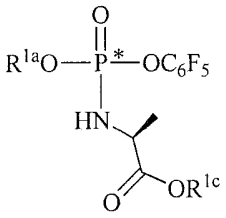
the nucleophile is comprised of a radical selected from among, $-O(C_{1-6}alkyl)$, $-OC_{1-3}alkaryl$, $-S(C_{1-6}alkyl)$, $-NH(C_{1-6}alkyl)$, and –cycloalkylamino;

and

reacting **B''** with a phosphoramidate represented by formula **C** to obtain **I-3-5''**



B''



C

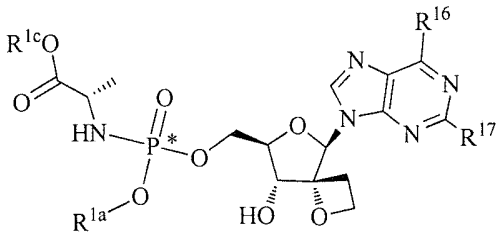
wherein the phosphoramidate is comprised of a mixture of the S_P- and R_P-diastereomers.

39. The process according to claim 38, wherein R^{16} is $-O(C_{1-6}alkyl)$, $-OC_{1-3}alkaryl$, $-S(C_{1-6}alkyl)$, $-NH(C_{1-6}alkyl)$, or $-NHC_{3-6}cycloalkyl$.

40. The process according to claim 38, wherein the mole ratio of the S_P-diastereomer to the R_P-diastereomer ranges from about 2 to about 99.99 and all values in between, including 2, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 97, 98, 99, 99.9, and 99.99.

41. The process according to claim 38, wherein the mole ratio of the R_P-diastereomer to the S_P-diastereomer ranges from about 2 to about 99.99 and all values in between, including 2, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 97, 98, 99, 99.9, and 99.99.

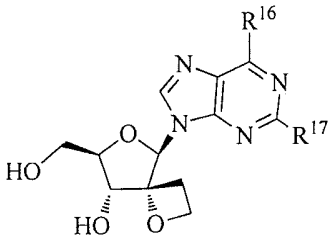
42. A process for preparing a compound represented by formula **I-3-5'''**



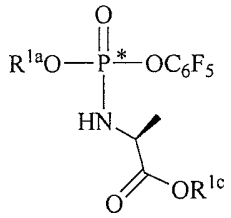
I-3-5'''

wherein R^{1a} is phenyl or naphthyl; R^{1c} is hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, or C_{1-3}alkaryl; R^{16} is –O(C_{1-6}alkyl), –OC_{1-3}alkaryl, –S(C_{1-6}alkyl), –NH(C_{1-6}alkyl), or –cycloalkylamino; and R^{17} is –H or –NH_2

said process comprising reacting a compound represented by formula **B'''** with a phosphoramidate represented by formula **C** to obtain **I-3-5'''**



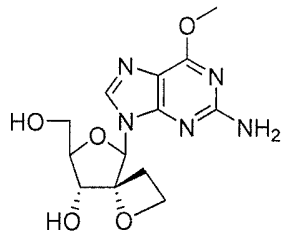
B'''



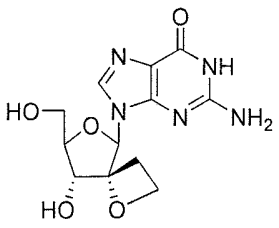
C

wherein the phosphoramidate is comprised of a mixture of the S_P- and R_P-diastereomers.

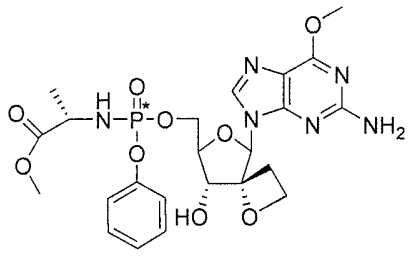
43. A compound selected from the group consisting of:



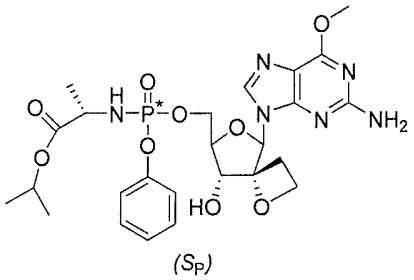
,



,

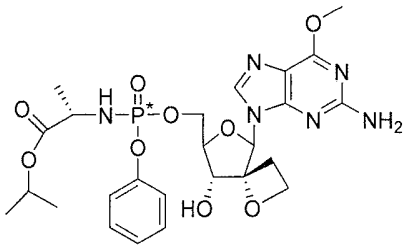


,



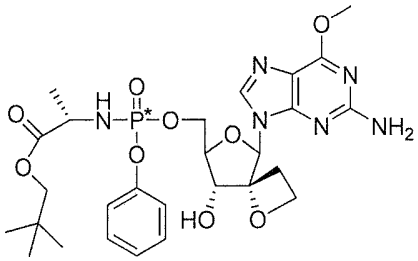
(S_P)

,



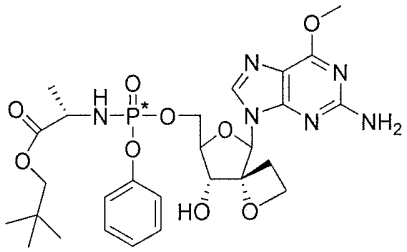
(R_P)

,



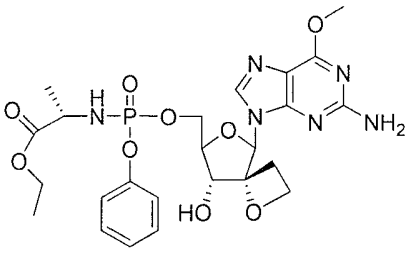
(S_P)

,

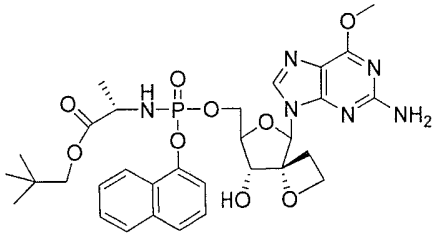


(R_P)

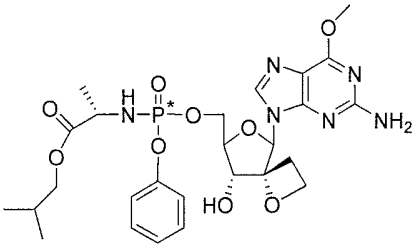
,



,

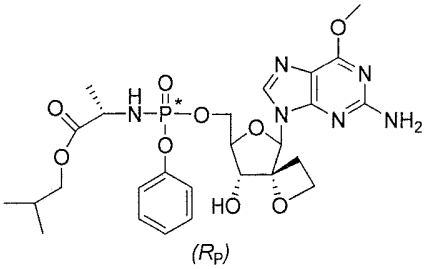


,



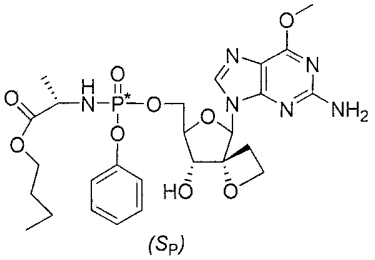
(S_P)

,



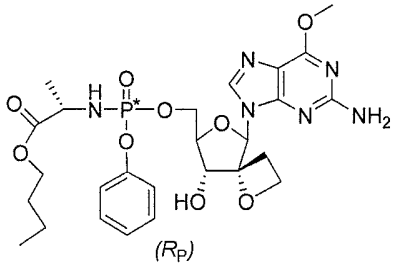
(R_P)

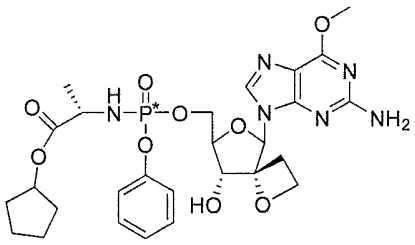
,



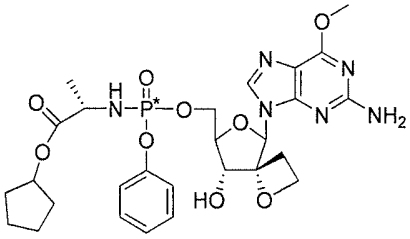
(S_P)

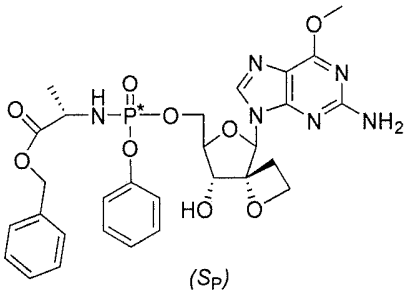
,


(R_P)

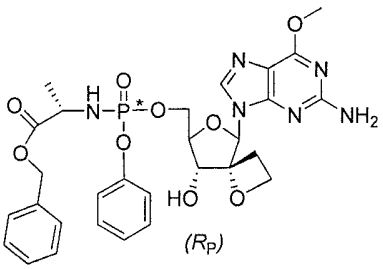

(S_P)

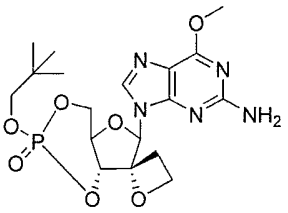
,


(R_P)

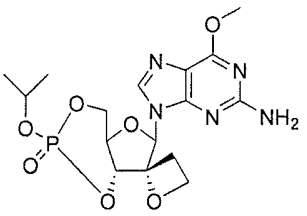

(S_P)

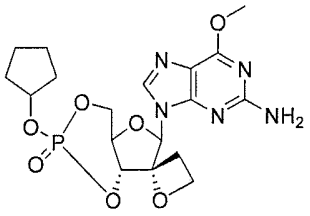
,


(R_P)



,





, and .