(12) STANDARD PATENT (11) Application No. **AU 2010213873 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Carba-nucleoside analogs for antiviral treatment

(51) International Patent Classification(s)
C07H 19/24 (2006.01) ***A61P 31/14*** (2006.01)
A61K 31/7064 (2006.01)

(21) Application No: **2010213873** (22) Date of Filing: **2010.02.09**

(87) WIPO No: **WO10/093608**

(30) Priority Data

(31) Number	(32) Date	(33) Country
61/151,248	**2009.02.10**	**US**

(43) Publication Date: **2010.08.19**
(44) Accepted Journal Date: **2015.07.09**

(71) Applicant(s)
Gilead Sciences, Inc.

(72) Inventor(s)
Butler, Thomas;Cho, Aesop;Kim, Choung U.;Xu, Jie

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

(56) Related Art
WO 2010/036407 A2 (BIOCRYST PHARMACEUTICALS, INC.) 01 April 2010

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 August 2010 (19.08.2010)

PCT

(10) International Publication Number
WO 2010/093608 A1

(51) International Patent Classification:
C07H 19/24 (2006.01) *A61P 31/14* (2006.01)
A61K 31/7064 (2006.01)

(21) International Application Number:
PCT/US2010/023586

(22) International Filing Date:
9 February 2010 (09.02.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/151,248 10 February 2009 (10.02.2009) US

(71) Applicant *(for all designated States except US)*: **GILEAD SCIENCES, INC.** [US/US]; 333 Lakeside Drive, Foster City, CA 94404 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BUTLER, Thomas** [US/US]; 601 Baltic Circle #605, Redwood City, CA 94065 (US). **CHO, Aesop** [US/US]; 1656 Notre Dame Drive, Mountain View, CA 94040 (US). **KIM, Choung, U.** [US/US]; 1750 Elizabeth Street, San Carlos, CA 94070 (US). **XU, Jie** [US/US]; 812 Rigel Lane, Foster City, CA 94404 (US).

(74) Agents: **WARD, John, S.** et al.; 333 Lakeside Drive, Foster City, CA 94404 (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, RO, RS, RU, 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, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, 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))*

WO 2010/093608 A1

(54) **Title**: CARBA-NUCLEOSIDE ANALOGS FOR ANTIVIRAL TREATMENT

(57) **Abstract**: Provided are thieno[3,4-d]pyrimidin-7-yl and furo[3,4-d]pyrimidin-7-yl ribosides, riboside phosphates and prodrugs thereof as well as intermediates and methods of preparation. The compounds, compositions, and methods provided are useful for the treatment of *Flaviviridae* virus infections.

CARBA-NUCLEOSIDE ANALOGS FOR ANTIVIRAL TREATMENT

FIELD OF THE INVENTION

The invention relates generally to compounds with antiviral activity, more particularly nucleosides active against *Flaviviridae* virus infections.

BACKGROUND OF THE INVENTION

Viruses comprising the *Flaviviridae* family comprise at least three distinquishable genera including *pestiviruses*, *flaviviruses*, and *hepaciviruses* (Calisher, *et al.*, J. Gen. Virol., 1993, 70, 37-43). While *pestiviruses* cause many economically important animal diseases such as bovine viral diarrhea virus (BVDV), classical swine fever virus (CSFV, hog cholera) and border disease of sheep (BDV), their importance in human disease is less well characterized (Moennig, V., *et al.*, Adv. Vir. Res. 1992, 48, 53-98). *Flaviviruses* are responsible for important human diseases such as dengue fever and yellow fever while *hepaciviruses* cause hepatitis C virus infections in humans. Other important viral infections caused by the *Flaviviridae* family include West Nile virus (WNV) Japanese encephalitis virus (JEV), tick-borne encephalitis virus, Junjin virus, Murray Valley encephalitis, St. Louis encephalitis, Omsk hemorrhagic fever virus and Zika virus. Combined, infections from the *Flaviviridae* virus family cause significant mortality, morbidity and economic losses throughout the world. Therefore, there is a need to develop effective treatments for *Flaviviridae* virus infections.

The hepatitis C virus (HCV) is the leading cause of chronic liver disease worldwide (Boyer, N. et al. J Hepatol. 32:98-112, 2000) so a significant focus of current antiviral research is directed toward the development of improved methods of treatment of chronic HCV infections in humans (Di Besceglie, A.M. and Bacon, B. R., Scientific American, Oct.: 80-85, (1999); Gordon, C. P., et al., *J. Med. Chem.*

2005, *48*, 1-20; Maradpour, D.; et al., *Nat. Rev. Micro.* **2007**, *5*(6), 453-463). A number of HCV treatments are reviewed by Bymock et al. in Antiviral Chemistry & Chemotherapy, 11:2; 79-95 (2000).

RNA-dependent RNA polymerase (RdRp) is one of the best studied targets for the development of novel HCV therapeutic agents. The NS5B polymerase is a target for inhibitors in early human clinical trials (Sommadossi, J., WO 01/90121 A2, US 2004/0006002 A1). These enzymes have been extensively characterized at the biochemical and structural level, with screening assays for identifying selective inhibitors (De Clercq, E. (2001) J. Pharmacol. Exp.Ther. 297:1-10; De Clercq, E. (2001) J. Clin. Virol. 22:73-89). Biochemical targets such as NS5B are important in developing HCV therapies since HCV does not replicate in the laboratory and there are difficulties in developing cell-based assays and preclinical animal systems.

Currently, there are primarily two antiviral compounds, ribavirin, a nucleoside analog, and interferon-alpha (α) (IFN), that are used for the treatment of chronic HCV infections in humans. Ribavirin alone is not effective in reducing viral RNA levels, has significant toxicity, and is known to induce anemia. The combination of IFN and ribavirin has been reported to be effective in the management of chronic hepatitis C (Scott, L. J., et al. *Drugs* **2002**, *62*, 507-556) but less than half the patients given this treatment show a persistent benefit. Other patent applications disclosing the use of nucleoside analogs to treat hepatitis C virus include WO 01/32153, WO 01/60315, WO 02/057425, WO 02/057287, WO 02/032920, WO 02/18404, WO 04/046331, WO2008/089105 and WO2008/141079 but additional treatments for HCV infections have not yet become available for patients.

Virologic cures of patients with chronic HCV infection are difficult to achieve because of the prodigous amount of daily virus production in chronically infected patients and the high spontaneous mutability of HCV virus (Neumann, et al., *Science* **1998**, *282*, 103-7; Fukimoto, et al., *Hepatology*, **1996**, *24*, 1351-4; Domingo, et al., *Gene*, **1985**, *40*, 1-8; Martell, et al., *J. Virol.* **1992**, *66*, 3225-9. Experimental anti-viral nucleoside analogs have been shown to induce viable mutations in the HCV virus both *in vivo* and *in vitro* (Migliaccio, et al., *J. Biol. Chem.* **2003**, 926; Carroll, et al., *Antimicrobial Agents Chemotherapy* **2009**, 926; Brown, A. B., *Expert Opin.*

2010213873 03 Jun 2015

Investig. Drugs **2009**, *18*, 709-725). Therefore, drugs having improved antiviral properties, particularly enhanced activity against resistant strains of virus; improved oral bioavailability; fewer undesirable side effects and extended effective half-life *in vivo* (De Francesco, R. et al. (2003) Antiviral Research 58:1-16) are urgently needed.

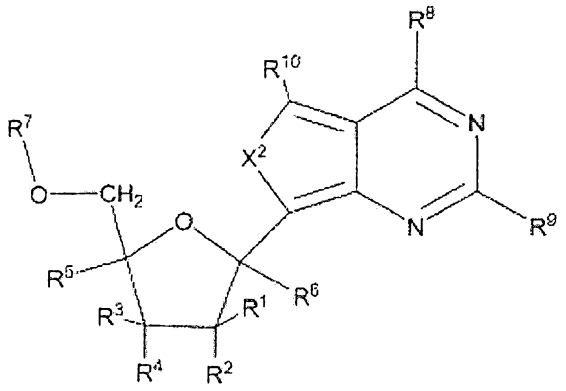
Certain 7-ribosyl-thieno[3,4-d]pyrimidines have been disclosed (Moscow, et al.; *International Journal of Cancer* **1997**, 72, p 184-190; Otter, et al., *Nucleosides & Nucleotides* **1996**, p 793-807; Patil, et al., *J. Heterocyclic Chemistry* **1993**, p 509-515; Patil, et al., *Nucleosides & Nucleotides* **1990**, p 937-956; Rao, et al.; *Tetrahedron Letters* **1988**, p 3537-3540; Hamann, et al., *Collection Symposium Series* **2008**, *10*, p 347-349; Hamann, et al., *Bioorg. Med. Chem.* **2009**, *17*, p 2321-2326), but there is no indication that such compounds are useful for the treatment of *Flaviviridae* virus infections.

Reference to any prior art in the specification is not, and should not be taken as, an acknowledgment, or any form of suggestion, that this prior art forms part of the common general knowledge in Australia or any other jurisdiction or that this prior art could reasonably be expected to be ascertained, understood and regarded as relevant by a person skilled in the art.

SUMMARY OF THE INVENTION

The instant invention provides compounds that inhibit viruses of the *Flaviviridae* family. The invention also comprises compounds that inhibit viral nucleic acid polymerases, particularly HCV RNA-dependent RNA polymerase (RdRp), rather than cellular nucleic acid polymerases. Therefore, the compounds of the instant invention are useful for treating *Flaviviridae* infections in humans and other animals.

In one aspect, this invention provides a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt or ester, thereof;

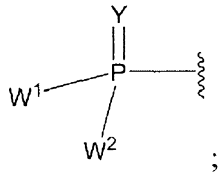
wherein:

each R^1, R^2, R^3, R^4, R^5 or R^6 is independently H, OR^a, $N(R^a)_2$, N_3, CN, NO_2, $S(O)_nR^a$, halogen, $(C_1–C_8)$alkyl, $(C_4–C_8)$carbocyclylalkyl, $(C_1–C_8)$substituted alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$substituted alkenyl, $(C_2–C_8)$alkynyl, $(C_2–C_8)$substituted alkynyl, or aryl$(C_1$-$C_8)$alkyl or any two R^1, R^2, R^3, R^4, R^5 or R^6 on adjacent carbon atoms together are –O(CO)O-;

each n is independently 0, 1, or 2;

each R^a is independently H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, aryl$(C_1$-$C_8)$alkyl, $(C_4–C_8)$carbocyclylalkyl, -C(=O)R^{11}, -C(=O)OR^{11}, -C(=O)$N(R^{11})_2$, -C(=O)SR^{11}, -S(O)R^{11}, -$S(O)_2R^{11}$, -S(O)(OR^{11}), -$S(O)_2(OR^{11})$, or $–SO_2N(R^{11})_2$;

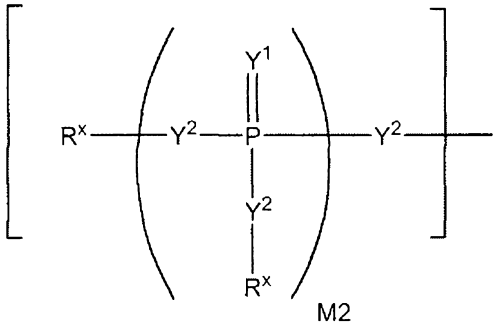
R^7 is H, -C(=O)R^{11}, -C(=O)OR^{11}, -C(=O)$N(R^{11})_2$, -C(=O)SR^{11}, -S(O)R^{11}, -$S(O)_2R^{11}$, -S(O)(OR^{11}), -$S(O)_2(OR^{11})$, $–SO_2N(R^{11})_2$, or



;

each Y or Y^1 is, independently, O, S, NR, $^+N(O)(R)$, N(OR), $^+N(O)(OR)$, or $N–NR_2$;

W^1 and W^2, when taken together, are $–Y^3(C(R^y)_2)_3Y^3$-; or one of W^1 or W^2 together with either R^3 or R^4 is $–Y^3$- and the other of W^1 or W^2 is Formula Ia; or W^1 and W^2 are each, independently, a group of the Formula Ia:



M2

Formula Ia

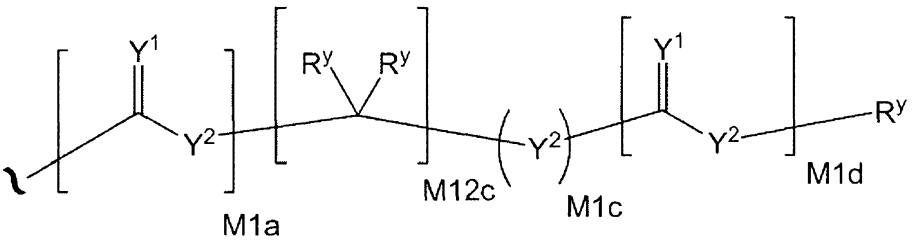
wherein:

each Y^2 is independently a bond, O, CR_2, NR, $^+N(O)(R)$, N(OR), $^+N(O)(OR)$, $N–NR_2$, S, S–S, S(O), or $S(O)_2$;

each Y^3 is independently O, S, or NR;

M2 is 0, 1 or 2;

each R^x is independently R^y or the formula:



;

wherein:

each M1a, M1c, and M1d is independently 0 or 1;

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

each R^y is independently H, F, Cl, Br, I, OH, R, $-C(=Y^1)R$, $-C(=Y^1)OR$, $-C(=Y^1)N(R)_2$, $-N(R)_2$, $-^+N(R)_3$, -SR, -S(O)R, $-S(O)_2R$, -S(O)(OR), $-S(O)_2(OR)$, $-OC(=Y^1)R$, $-OC(=Y^1)OR$, $-OC(=Y^1)(N(R)_2)$, $-SC(=Y^1)R$, $-SC(=Y^1)OR$, $-SC(=Y^1)(N(R)_2)$, $-N(R)C(=Y^1)R$, $-N(R)C(=Y^1)OR$, $-N(R)C(=Y^1)N(R)_2$, $–SO_2NR_2$, –CN, $–N_3$, $–NO_2$, –OR, or W^3; or when taken together, two R^y on the same carbon atom form a carbocyclic ring of 3 to 7 carbon atoms;

each R is independently H, (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8)alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, $C_6–C_{20}$ aryl, $C_6–C_{20}$ substituted aryl, $C_2–C_{20}$ heterocyclyl, or $C_2–C_{20}$ substituted heterocyclyl;

W^3 is W^4 or W^5; W^4 is R, $-C(Y^1)R^y$, $-C(Y^1)W^5$, $-SO_2R^y$, or $-SO_2W^5$; and W^5 is a carbocycle or a heterocycle wherein W^5 is independently substituted with 0 to 3 R^y groups;

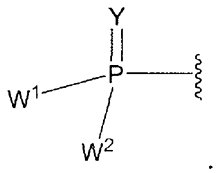
each X^2 is independently O, S, S(O), or $S(O)_2$;

each R^8, R^9 or R^{10} is independently H, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3, NO, NO_2, CHO, CN, $-CH(=NR^{11})$, $-CH=NHNR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, R^{11}, OR^{11} or SR^{11};

each R^{11} or R^{12} is independently H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_4$–$C_8)$carbocyclylalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(=O)$(C_1$-$C_8)$alkyl, -S(O)$_n(C_1$-$C_8)$alkyl or aryl$(C_1$-$C_8)$alkyl; or R^{11} and R^{12} taken together with a nitrogen to which they are both attached form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with -O-, -S- or –NR^a-; and

wherein each $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl or aryl$(C_1$-$C_8)$alkyl of each R^1, R^2, R^3, R^4, R^5, R^6, R^{11} or R^{12} is, independently, optionally substituted with one or more halo, hydroxy, CN, N_3, $N(R^a)_2$ or OR^a; and wherein one or more of the non-terminal carbon atoms of each said $(C_1$-$C_8)$alkyl may be optionally replaced with -O-, -S- or –NR^a-;

provided that when X^2 is S, each of R^9 and R^{10} is H and R^8 is NH_2, OH, SH, or SCH_3, then at least one of R^1, R^2, R^3, R^4, R^5 or R^6 is $N(R^a)_2$, N_3, CN, NO_2, $S(O)_nR^a$, halogen, $(C_1$–$C_8)$alkyl, $(C_4$–$C_8)$carbocyclylalkyl, $(C_1$–$C_8)$substituted alkyl, $(C_2$–$C_8)$alkenyl, $(C_2$–$C_8)$substituted alkenyl, $(C_2$–$C_8)$alkynyl, $(C_2$–$C_8)$substituted alkynyl or aryl$(C_1$-$C_8)$alkyl or R^7 is -C(=O)OR^{11}, -C(=O)$N(R^{11})_2$, -C(=O)SR^{11}, -S(O)R^{11}, -$S(O)_2R^{11}$, -S(O)(OR^{11}), -$S(O)_2(OR^{11})$, –$SO_2N(R^{11})_2$, or



In another aspect, the present invention includes compounds of Formula I and pharmaceutically acceptable salts thereof and all racemates, enantiomers, diastereomers, tautomers, polymorphs, pseudopolymorphs and amorphous forms thereof.

In another aspect, the present invention provides novel compounds of Formula I with activity against infectious *Flaviviridae* viruses. Without wishing to be bound by theory, the compounds of the invention may inhibit viral RNA-dependent RNA polymerase and thus inhibit the replication of the virus. They are useful for treating human patients infected with a human virus such as hepatitis C.

In another aspect, the invention provides a pharmaceutical composition comprising an effective amount of a Formula I compound, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable diluent or carrier.

In another embodiment, the present application provides for combination pharmaceutical agent comprising:

a) a first pharmaceutical composition comprising a compound of Formula I; or a pharmaceutically acceptable salt, solvate, or ester thereof; and

b) a second pharmaceutical composition comprising at least one additional therapeutic agent selected from the group consisting of interferons, ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

In another embodiment, the present application provides for a method of inhibiting HCV polymerase, comprising contacting a cell infected with HCV with an effective amount of a compound of Formula I; or a pharmaceutically acceptable salts, solvate, and/or ester thereof.

In another embodiment, the present application provides for a method of inhibiting HCV polymerase, comprising contacting a cell infected with HCV with an effective amount of a compound of Formula I; or a pharmaceutically acceptable salts, solvate, and/or ester thereof; and at least one additional therapeutic agent.

In another embodiment, the present application provides for a method of treating and/or preventing a disease caused by a viral infection wherein the viral infection is caused by a virus selected from the group consisting of dengue virus, yellow fever virus, West Nile virus, Japanese encephalitis virus, tick-borne encephalitis virus, Junjin virus, Murray Valley encephalitis virus, St Louis encephalitis virus, Omsk hemorrhagic fever virus, bovine viral disarrhea virus, Zika virus and Hepatitis C virus; by administering a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof; to a subject in need thereof.

In another embodiment, the present application provides for a method of treating HCV in a patient, comprising administering to said patient a therapeutically effective amount of a compound of Formula I; or a pharmaceutically acceptable salt, solvate, and/or ester thereof.

In another embodiment, the present application provides for a method of treating HCV in a patient, comprising administering to said patient a therapeutically effective amount of a compound of Formula I; or a pharmaceutically acceptable salt, solvate, and/or ester thereof; and at least one additional therapeutic agent.

Another aspect of the invention provides a method for the treatment or prevention of the symptoms or effects of an HCV infection in an infected animal which comprises administering to, i.e. treating, said animal with a pharmaceutical combination composition or formulation comprising an effective amount of a Formula I compound, and a second compound having anti-HCV properties.

In another aspect, the invention also provides a method of inhibiting HCV, comprising administering to a mammal infected with HCV an amount of a Formula I compound, effective to inhibit the growth of said HCV infected cells.

In another aspect, the invention also provides processes and novel intermediates disclosed herein which are useful for preparing Formula I compounds of the invention.

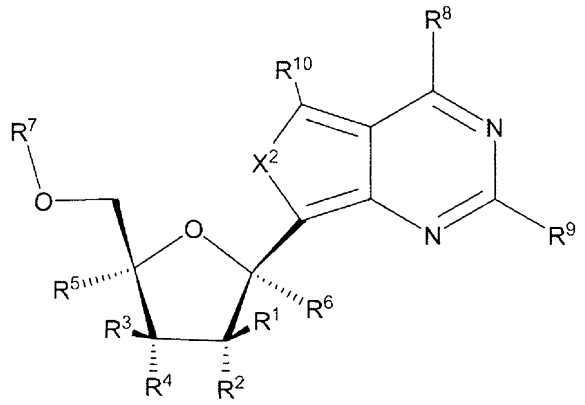
In other aspects, novel methods for synthesis, analysis, separation, isolation, purification, characterization, and testing of the compounds of this invention are provided.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying description, structures and formulas. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all

alternatives, modifications, and equivalents, which may be included within the scope of the present invention.

In another aspect, compounds of Formula I are represented by Formula II:



Formula II

or a pharmaceutically acceptable salt or ester, thereof;

wherein all variables are defined as in Formula I.

In one embodiment of Formula II, R^1 is $(C_1–C_8)$alkyl, $(C_2–C_8)$ alkenyl or $(C_2–C_8)$alkynyl. In another embodiment, R^1 is $(C_1–C_8)$alkyl. In another embodiment, R^1 is methyl, ethenyl, or ethynyl. In a preferred embodiment, R^1 is methyl. In another preferred embodiment, R^1 is H.

In one embodiment of Formula II, R^2 is H, OR^a, $N(R^a)_2$, N_3, CN, NO_2, $S(O)_nR^a$, halogen, $(C_1–C_8)$alkyl, $(C_1–C_8)$substituted alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$substituted alkenyl, $(C_2–C_8)$alkynyl, or $(C_2–C_8)$substituted alkynyl. In another aspect of this embodiment, R^1 is H. In another aspect of this embodiment, R^1 is $(C_1–C_8)$alkyl, $(C_2–C_8)$ alkenyl or $(C_2–C_8)$alkynyl. In another aspect of this embodiment, R^1 is methyl, ethenyl, or ethynyl. In another aspect of this embodiment, R^2 is H, OR^a, $N(R^a)_2$, N_3, CN, SR^a or halogen. In another aspect of this embodiment R^2 is H, OH, NH_2, N_3, CN, or halogen. In another aspect of this embodiment, R^2 is OR^a or halogen and R^1 is $(C_1–C_8)$alkyl, $(C_2–C_8)$ alkenyl or $(C_2–C_8)$alkynyl. In another aspect of this embodiment, R^2 is OR^a or F and R^1 is methyl, ethenyl, or ethynyl. In a preferred aspect of this embodiment, R^2 is OH and R^1 is methyl, ethenyl, or ethynyl. In another preferred aspect of this embodiment, R^2

is OR^a and R^1 is H. In another preferred aspect of this embodiment, R^2 is OR^a, R^1 is H and at least one of R^3, R^5, or R^6 is not H. In another preferred aspect of this embodiment, R^2 is F. In another preferred aspect of this embodiment, R^2 is F and R^1 is methyl, ethenyl, or ethynyl. In another preferred aspect of this embodiment, R^2 is OR^a and R^1 is methyl. In a particularly preferred aspect of this embodiment, R^2 is OH and R^1 is methyl.

In one embodiment of Formula II, R^3 is H, OR^a, $N(R^a)_2$, N_3, CN, SR^a, halogen, $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl or $(C_2–C_8)$alkynyl. In another aspect of this embodiment, R^1 is H. In another aspect of this embodiment, R^1 is $(C_1–C_8)$alkyl, $(C_2–C_8)$ alkenyl or $(C_2–C_8)$alkynyl. In another aspect of this embodiment, R^1 is methyl, ethenyl, or ethynyl. In another aspect of this embodiment, R^3 is H or F. In a preferred aspect of this embodiment, R^3 is H. In another preferred aspect of this embodiment, R^3 is H, R^2 is OR^a or halogen and R^1 is $(C_1–C_8)$alkyl, $(C_2–C_8)$ alkenyl or $(C_2–C_8)$alkynyl. In another aspect of this embodiment, R^3 is H, R^2 is OR^a or F and R^1 is methyl, ethenyl, or ethynyl. In another aspect of this embodiment, R^3 is H, R^2 is OR^a and R^1 is methyl. In another embodiment, R^3 is H, R^2 is OH and R^1 is methyl. In another embodiment, R^3 and R^1 are H and R^2 is OR^a. In another embodiment, R^3 and R^1 are H, R^2 is OR^a and at least one of R^5 or R^6 is not H.

In one embodiment of Formula II, R^4 is H, OR^a, $N(R^a)_2$, N_3, CN, SR^a, halogen, $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl or $(C_2–C_8)$alkynyl. In another aspect of this embodiment, R^1 is H. In another aspect of this embodiment, R^1 is $(C_1–C_8)$alkyl, $(C_2–C_8)$ alkenyl or $(C_2–C_8)$alkynyl. In another aspect of this embodiment, R^1 is methyl, ethenyl, or ethynyl. In a preferred aspect of this embodiment, R^4 is OR^a. In another preferred aspect of this embodiment, R^4 is OR^a, R^2 is OR^a or halogen and R^1 is $(C_1–C_8)$alkyl, $(C_2–C_8)$ alkenyl or $(C_2–C_8)$alkynyl. In another preferred aspect of this embodiment, R^4 is OR^a, R^2 is OR^a or halogen and R^1 is H. In another preferred aspect of this embodiment, R^4 is OR^a, R^2 is OR^a or halogen, R^1 is H and at least one of R^5 or R^6 is not H. In another preferred aspect of this embodiment, R^4 is OR^a, R^2 is OR^a or halogen, R^3 is H and R^1 is $(C_1–C_8)$alkyl, $(C_2–C_8)$ alkenyl or $(C_2–C_8)$alkynyl. In another preferred aspect of this embodiment R^4 is OR^a, R^2 is OR^a or F and R^1 is

methyl, ethenyl, or ethynyl. In another preferred aspect of this embodiment R^4 is OR^a, R^2 is OR^a or F, R^3 is H and R^1 is methyl, ethenyl, or ethynyl. In another preferred aspect of this embodiment, R^4 and R^2 are, independently, OR^a and R^1 is methyl. In another preferred aspect of this embodiment, R^4 and R^2 are, independently OR^a, R^3 is H and R^1 is methyl. In another preferred aspect of this embodiment, one of R^4 or R^2 is OR^a and the other of R^4 or R^2 is OH. . In another preferred aspect of this embodiment, one of R^4 or R^2 is OR^a wherein R^a is not H and the other of R^4 or R^2 is OH, R^3 is H, and R^1 is methyl. In another preferred aspect of this embodiment, R^4 and R^2 are OH, R^3 is H, and R^1 is methyl. In another preferred aspect of this embodiment, R^4 and R^2 are OR^a, R^3 is H, and R^1 is H. In another preferred aspect of this embodiment, R^4 and R^2 are OH, R^3 is H, and R^1 is H.

In another embodiment of Formula II, R^4 and R^2, taken together, are –O(CO)O-. In another aspect of this embodiment, R^1 is H. In another aspect of this embodiment, R^1 is $(C_1–C_8)$alkyl, $(C_2–C_8)$ alkenyl or $(C_2–C_8)$alkynyl. In another aspect of this embodiment, R^1 is methyl, ethenyl, or ethynyl. In another aspect of this embodiment, R^3 is H and R^1 is methyl.

In one embodiment of Formula II, R^5 and R^6 are, independently, H, OR^a, $N(R^a)_2$, N_3, CN, SR^a, halogen, $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl or $(C_2–C_8)$alkynyl. In another aspect of this embodiment, R^1 is H. In another aspect of this embodiment, R^1 is $(C_1–C_8)$alkyl, $(C_2–C_8)$ alkenyl or $(C_2–C_8)$alkynyl. In another aspect of this embodiment, R^1 is methyl, ethenyl, or ethynyl. In another aspect of this embodiment, R^6 is H, $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl or $(C_2–C_8)$alkynyl and R^5 is H, OR^a, $N(R^a)_2$, N_3, CN, SR^a, halogen, $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl or $(C_2–C_8)$alkynyl. In another aspect of this embodiment, R^6 is H and R^5 is H, N_3, CN, $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl or $(C_2–C_8)$alkynyl. In another aspect of this embodiment, R^6 is H, R^5 is H, N_3, CN, methyl, ethenyl or ethynyl, R^4 is OR^a, and R^3 is H. In another aspect of this embodiment, R^6 is H, R^5 is H or N_3, R^4 is OR^a, R^3 is H, and R^2 is F or OR^a. In another aspect of this embodiment, R^6 is H, R^5 is H or N_3, R^4 is OR^a, R^3 is H, R^2 is OR^a and R^1 is methyl, ethenyl, or ethynyl. In another aspect of this embodiment, R^3, R^5, and R^6 are H, R^2 and R^4 are, independently, OR^a, and R^1 is methyl. In another

aspect of this embodiment, R^3, R^5, and R^6 are H, R^2 and R^4 are OH, and R^1 is methyl. In another aspect of this embodiment, R^3, R^5, and R^6 are H, R^2 and R^4, taken together, are –O(CO)O-, and R^1 is methyl. In another aspect of this embodiment R^1, R^3 and R^6 are H, R^2 and R^4 are independently OR^a and R^5 is N_3.

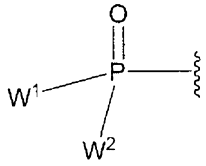
In one embodiment of Formula II, R^6 is halogen, OR^a, N_3, CN, $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl or $(C_2–C_8)$alkynyl. In another aspect of this embodiment, R^1 is H. In another aspect of this embodiment, R^1 is $(C_1–C_8)$alkyl, $(C_2–C_8)$ alkenyl or $(C_2–C_8)$alkynyl. In another aspect of this embodiment, R^1 is methyl, ethenyl, or ethynyl. In another aspect of this embodiment, R^6 is OR^a, CN, methyl, ethenyl, or ethynyl. In another aspect of this embodiment, R^6 is OR^a, CN, methyl, ethenyl, or ethynyl and R^1 is H. In another aspect of this embodiment, R^6 is OR^a, CN, methyl, ethenyl, or ethynyl and R^1 is methyl, ethenyl, or ethynyl. In another aspect of this embodiment, R^6 is OR^a, CN, methyl, ethenyl, or ethynyl and R^1 is methyl. In another aspect of this embodiment, R^6 is OR^a or CN. In another aspect of this embodiment, R^6 is OR^a or CN and R^1 is H. In another aspect of this embodiment, R^6 is OR^a or CN and R^1 is methyl, ethenyl, or ethynyl. In another aspect of this embodiment, R^6 is OR^a or CN and R^1 is methyl.

In one embodiment of Formula II, R^2 and R^4 are both OR^a and at least one of R^1, R^3, R^5, or R^6 is not H. In another aspect of this embodiment, R^2 and R^4 are both OR^a and R^1 is $(C_1–C_8)$alkyl, $(C_1–C_8)$substituted alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$substituted alkenyl, $(C_2–C_8)$alkynyl, $(C_2–C_8)$substituted alkynyl or aryl$(C_1$-$C_8)$alkyl. In another aspect of this embodiment, R^2 and R^4 are both OR^a and R^3 is $(C_1–C_8)$alkyl, $(C_1–C_8)$substituted alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$substituted alkenyl, $(C_2–C_8)$alkynyl, $(C_2–C_8)$substituted alkynyl or aryl$(C_1$-$C_8)$alkyl. In another aspect of this embodiment, R^2 and R^4 are both OR^a and R^5 is OR^a, $N(R^a)_2$, N_3, CN, NO_2, $S(O)_nR^a$, halogen, $(C_1–C_8)$alkyl, $(C_1–C_8)$substituted alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$substituted alkenyl, $(C_2–C_8)$alkynyl, $(C_2–C_8)$substituted alkynyl or aryl$(C_1$-$C_8)$alkyl. In another aspect of this embodiment, R^2 and R^4 are both OR^a and R^6 is OR^a, $N(R^a)_2$, N_3, CN, NO_2, $S(O)_nR^a$, halogen, $(C_1–C_8)$alkyl, $(C_1–C_8)$substituted alkyl,

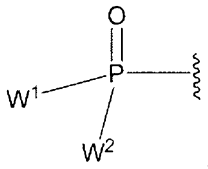
$(C_2–C_8)$alkenyl, $(C_2–C_8)$substituted alkenyl, $(C_2–C_8)$alkynyl, $(C_2–C_8)$substituted alkynyl or aryl$(C_1$-$C_8)$alkyl.

In another embodiment of Formula II, each of R^1 and R^2 is H and one of R^3 or R^4 is OR^a and the other of R^3 or R^4 is $(C_1–C_8)$alkyl, $(C_1–C_8)$substituted alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$substituted alkenyl, $(C_2–C_8)$alkynyl, $(C_2–C_8)$substituted alkynyl or aryl$(C_1$-$C_8)$alkyl or one of R^5 or R^6 is not H. In another embodiment, both R^1 and R^2 are H, one of R^3 or R^4 is OR^a and the other of R^3 or R^4 is $(C_1–C_8)$alkyl, $(C_1–C_8)$substituted alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$substituted alkenyl, $(C_2–C_8)$alkynyl, $(C_2–C_8)$substituted alkynyl or aryl$(C_1$-$C_8)$alkyl. In another embodiment, both R^1 and R^2 are H, one of R^3 or R^4 is OR^a and one of R^5 or R^6 is OR^a, $N(R^a)_2$, N_3, CN, NO_2, $S(O)_nR^a$, halogen, $(C_1–C_8)$alkyl, $(C_1–C_8)$substituted alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$substituted alkenyl, $(C_2–C_8)$alkynyl, $(C_2–C_8)$substituted alkynyl or aryl$(C_1$-$C_8)$alkyl.

In one embodiment of Formula II, R^7 is H, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)SR^{11}$ or



. In a preferred aspect of this embodiment, R^7 is H. In another preferred aspect of this embodiment, R^7 is $-C(=O)R^{11}$. In another preferred aspect of this embodiment, R^7 is $-C(=O)R^{11}$ wherein R^{11} is $(C_1$-$C_8)$alkyl. In another preferred aspect of this embodiment, R^7 is



.

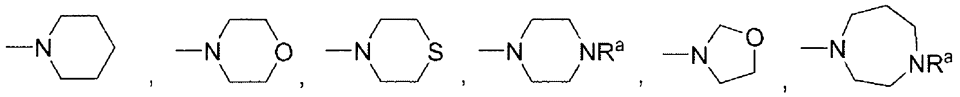
In one embodiment of Formula II, X^2 is O or S. In another aspect of this embodiment, X^2 is S. In another aspect of this embodiment, R^{10} is H, halogen, or CN. In another aspect of this embodiment, R^{10} is H or F. In another aspect of this embodiment, R^{10} is H. In another aspect of this embodiment, X^2 is S and R^{10} is H,

halogen, or CN. In another aspect of this embodiment, X^2 is S and R^{10} is H or F. In another aspect of this embodiment, X^2 is S and R^{10} is H.

In another embodiment of Formula II, each R^8 or R^9 is, independently, H, halo, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3, NO, NO_2, CHO, CN, $-CH(=NR^{11})$, $-CH=NHNR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, R^{11}, OR^{11} or SR^{11}. In another aspect of this embodiment, each R^8 or R^9 is, independently, H, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, R^{11}, OR^{11} or SR^{11}. In a preferred aspect of this embodiment each R^8 or R^9 is, independently, H, $NR^{11}R^{12}$, OR^{11} or SR^{11}, wherein R^{11} and R^{12} are H. In another preferred aspect of this embodiment, R^8 is NH_2 and R^9 is H. In another preferred aspect of this embodiment, R^8 and R^9 are NH_2. In another preferred aspect of this embodiment, R^8 is OH and R^9 is NH_2.

In one embodiment of Formula II, R^{11} or R^{12} is independently H, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_4\text{–}C_8)$carbocyclylalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)(C_1\text{-}C_8)$alkyl, $-S(O)_n(C_1\text{-}C_8)$alkyl or aryl$(C_1\text{-}C_8)$alkyl.

In another embodiment of Formula II, R^{11} and R^{12} taken together with a nitrogen to which they are both attached, form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with -O-, -S- or $-NR^a$-. Therefore, by way of example and not limitation, the moiety $-NR^{11}R^{12}$ can be represented by the heterocycles:

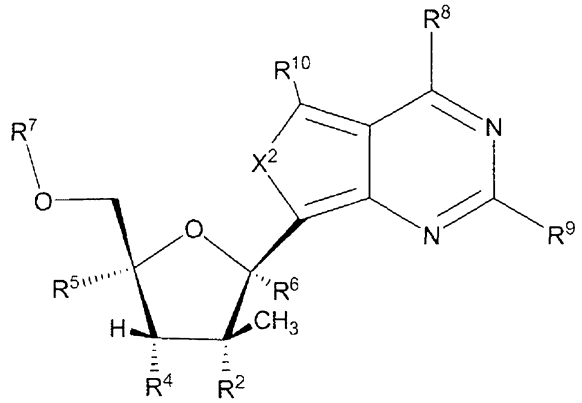


and the like.

In another embodiment of Formula II, R^1, R^2, R^3, R^4, R^5, R^6, R^a, R^{11} or R^{12} is, independently, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl or aryl$(C_1\text{-}C_8)$alkyl, wherein said $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl or aryl$(C_1\text{-}C_8)$alkyl are, independently, optionally substituted with one or more halo, hydroxy, CN, N_3, $N(R^a)_2$ or OR^a. Therefore, by way of example and not limitation, R^1, R^2, R^3, R^4, R^5, R^6, R^{11} or R^{12} could represent moieties such as $-CH(NH_2)CH_3$, -CH(OH)CH2CH3, $-CH(NH_2)CH(CH_3)_2$, $-CH_2CF_3$, $-(CH_2)_2CH(N_3)CH_3$, $-(CH_2)_6NH_2$ and the like.

In another embodiment of Formula II, R^1, R^2, R^3, R^4, R^5, R^6, R^a, R^{11} or R^{12} is $(C_1$-$C_8)$alkyl wherein one or more of the non-terminal carbon atoms of each said $(C_1$-$C_8)$alkyl may be optionally replaced with -O-, -S- or $-NR^a$-. Therefore, by way of example and not limitation, R^1, R^2, R^3, R^4, R^5, R^6, R^{11} or R^{12} could represent moieties such as $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2OCH(CH_3)_2$, $-CH_2SCH_3$, $-(CH_2)_6OCH_3$, $-(CH_2)_6N(CH_3)_2$ and the like.

In another embodiment, compounds of Formula I are represented by Formula III:



Formula III

or a pharmaceutically acceptable salt or ester, thereof;

wherein all remaining variables are defined as for Formula I.

In one embodiment of Formula III, R^2 is H, OR^a, $N(R^a)_2$, N_3, CN, NO_2, $S(O)_nR^a$, halogen, $(C_1$–$C_8)$alkyl, $(C_1$–$C_8)$substituted alkyl, $(C_2$–$C_8)$alkenyl, $(C_2$–$C_8)$substituted alkenyl, $(C_2$–$C_8)$alkynyl, or $(C_2$–$C_8)$substituted alkynyl. In another aspect of this embodiment, R^2 is H, OR^a, $N(R^a)_2$, N_3, CN, SR^a or halogen. In another aspect of this embodiment R^2 is H, OH, NH_2, N_3, CN, or halogen. In another aspect of this embodiment, R^2 is OR^a or F. In another aspect of this embodiment, R^2 is OH or F. In another aspect of this embodiment, R^2 is F.

In one embodiment of Formula III, R^4 is H, OR^a, $N(R^a)_2$, N_3, CN, SR^a, halogen, $(C_1$–$C_8)$alkyl, $(C_2$–$C_8)$alkenyl or $(C_2$–$C_8)$alkynyl. In a preferred aspect of this embodiment, R^4 is OR^a. In another preferred aspect of this embodiment, R^4 is OR^a and R^2 is OR^a or F. In another preferred aspect of this embodiment, R^4 is OR^a and R^2 is F. In another preferred aspect of this embodiment, R^4 and R^2 are,

independently OR^a. In another preferred aspect of this embodiment, one of R^4 or R^2 is OR^a and the other of R^4 or R^2 is OH. In another preferred aspect of this embodiment each of R^4 and R^2 is OH.

In another embodiment of Formula III, R^4 and R^2, taken together, are –O(CO)O-.

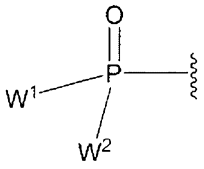
In one embodiment of Formula III, R^5 is H, OR^a, $N(R^a)_2$, N_3, CN, SR^a, halogen, $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl or $(C_2–C_8)$alkynyl. In another aspect of this embodiment, R^5 is H, N_3, CN, $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl or $(C_2–C_8)$alkynyl. In another aspect of this embodiment, R^5 is H, N_3, CN, methyl, ethenyl or ethynyl and R^4 is OR^a. In another aspect of this embodiment, R^5 is H or N_3, R^4 is OR^a and R^2 is F. In another aspect of this embodiment, R^5 is H or N_3, R^4 is OR^a and R^2 is OR^a. In another aspect of this embodiment, R^5 is H, R^4 is OR^a and R^2 is F. In another aspect of this embodiment, R^5 is H and R^2 and R^4 are, independently, OR^a. In another aspect of this embodiment, R^5 is H and R^2 and R^4 are OH. In another aspect of this embodiment, R^5 is H and R^2 and R^4, taken together, are –O(CO)O-.

In one embodiment of Formula III, R^6 is H, OR^a, $N(R^a)_2$, N_3, CN, SR^a, halogen, $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl or $(C_2–C_8)$alkynyl. In another aspect of this embodiment, R^6 is H. In another aspect of this embodiment, R^6 is OR^a. In another aspect of this embodiment, R^6 is CN. In another aspect of this embodiment, R^6 is H and R^4 is OR^a. In another aspect of this embodiment, R^6 is H, R^4 is OR^a and R^2 is F. In another aspect of this embodiment, R^6 is H, R^4 is OR^a and R^2 is OR^a. In another aspect of this embodiment, R^6 is OR^a, R^4 is OR^a and R^2 is F. In another aspect of this embodiment, R^6 is OR^a and R^2 and R^4 are, independently, OR^a. In another aspect of this embodiment, R^6 is OR^a and R^2 and R^4 are OH. In another aspect of this embodiment, R^6 is OR^a and R^2 and R^4, taken together, are –O(CO)O-. In another aspect of this embodiment, R^6 is CN, R^4 is OR^a and R^2 is F. In another aspect of this embodiment, R^6 is CN and R^2 and R^4 are, independently, OR^a. In another aspect of this embodiment, R^6 is CN and R^2 and R^4 are OH. In another aspect of this embodiment, R^6 is CN and R^2 and R^4, taken together, are –O(CO)O-.

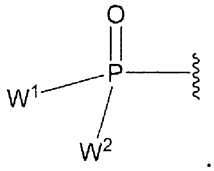
In one embodiment of Formula III, R^5 is H and R^6 is H, OR^a, $N(R^a)_2$, N_3, CN, SR^a, halogen, $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl or $(C_2–C_8)$alkynyl. In another aspect of

this embodiment, R^6 is H. In another aspect of this embodiment, R^6 is OR^a. In another aspect of this embodiment, R^6 is CN. In another aspect of this embodiment, R^6 is H and R^4 is OR^a. In another aspect of this embodiment, R^6 is H, R^4 is OR^a and R^2 is F. In another aspect of this embodiment, R^6 is H, R^4 is OR^a and R^2 is OR^a. In another aspect of this embodiment, R^6 is OR^a, R^4 is OR^a and R^2 is F. In another aspect of this embodiment, R^6 is OR^a and R^2 and R^4 are, independently, OR^a. In another aspect of this embodiment, R^6 is OR^a and R^2 and R^4 are OH. In another aspect of this embodiment, R^6 is OR^a and R^2 and R^4, taken together, are –O(CO)O-. In another aspect of this embodiment, R^6 is CN, R^4 is OR^a and R^2 is F. In another aspect of this embodiment, R^6 is CN and R^2 and R^4 are, independently, OR^a. In another aspect of this embodiment, R^6 is CN and R^2 and R^4 are OH. In another aspect of this embodiment, R^6 is CN and R^2 and R^4, taken together, are –O(CO)O-.

In one embodiment of Formula III, R^7 is H, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)SR^{11}$ or



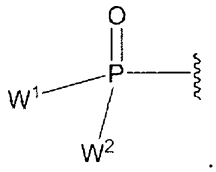
. In a preferred aspect of this embodiment, R^7 is H. In another preferred aspect of this embodiment, R^7 is $-C(=O)R^{11}$. In another preferred aspect of this embodiment, R^7 is $-C(=O)R^{11}$ wherein R^{11} is $(C_1\text{-}C_8)$alkyl. In another preferred aspect of this embodiment, R^7 is



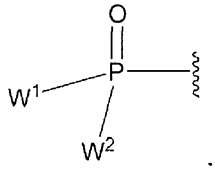
.

In one embodiment of Formula III, X^2 is O or S. In another aspect of this embodiment, X^2 is S. In another aspect of this embodiment, R^{10} is H, halogen, or CN. In another aspect of this embodiment, R^{10} is H or F. In another aspect of this embodiment, R^{10} is H. In another aspect of this embodiment, X^2 is S and R^{10} is H, halogen, or CN. In another aspect of this embodiment, X^2 is S and R^{10} is H or F. In another aspect of this embodiment, X^2 is S and R^{10} is H.

In one embodiment of Formula III, X^2 is S, R^4 is OR^a, R^5 is H and R^6 is H, OR^a, $N(R^a)_2$, N_3, CN, SR^a, halogen, $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl or $(C_2–C_8)$alkynyl. In another aspect of this embodiment, R^6 is H. In another aspect of this embodiment, R^6 is OR^a. In another aspect of this embodiment, R^6 is CN. In another aspect of this embodiment, R^6 is H and R^2 is F. In another aspect of this embodiment, R^6 is H and R^2 is OR^a. In another aspect of this embodiment, R^6 is OR^a and R^2 is F. In another aspect of this embodiment, R^6 is OR^a and R^2 is OR^a. In another aspect of this embodiment, R^6 is OR^a and R^2 is OH. In another aspect of this embodiment, R^6 is CN and R^2 is F. In another aspect of this embodiment, R^6 is CN and R^2 is OR^a. In another aspect of this embodiment, R^6 is CN and each R^2 and R^4 is OH. In a preferred aspect of this embodiment, R^7 is H. In another preferred aspect of this embodiment, R^7 is $-C(=O)R^{11}$. In another preferred aspect of this embodiment, R^7 is $-C(=O)R^{11}$ wherein R^{11} is (C_1-C_8)alkyl. In another preferred aspect of this embodiment, R^7 is

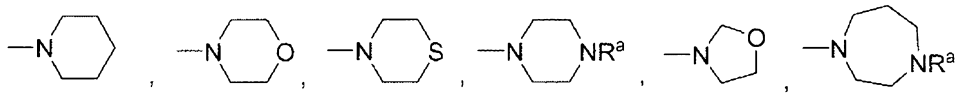


In one embodiment of Formula III, X^2 is S, R^2 and R^4, taken together, are –O(CO)O-, R^5 is H and R^6 is H, OR^a, $N(R^a)_2$, N_3, CN, SR^a, halogen, $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl or $(C_2–C_8)$alkynyl. In another aspect of this embodiment, R^6 is H. In another aspect of this embodiment, R^6 is OR^a. In another aspect of this embodiment, R^6 is CN. In a preferred aspect of this embodiment, R^7 is H. In another preferred aspect of this embodiment, R^7 is $-C(=O)R^{11}$. In another preferred aspect of this embodiment, R^7 is $-C(=O)R^{11}$ wherein R^{11} is (C_1-C_8)alkyl. In another preferred aspect of this embodiment, R^7 is



In another embodiment of Formula III, each R^8 or R^9 is, independently, H, halo, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3, NO, NO_2, CHO, CN, $-CH(=NR^{11})$, $-CH=NHNR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, R^{11}, OR^{11} or SR^{11}. In another embodiment, each R^8 or R^9 is, independently, H, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, R^{11}, OR^{11} or SR^{11}. In a preferred embodiment each R^8 or R^9 is, independently, H, $NR^{11}R^{12}$, OR^{11} or SR^{11}, wherein R^{11} and R^{12} are H. In another preferred embodiment, R^8 is NH_2 and R^9 is H. In another preferred embodiment, R^8 and R^9 are NH_2. In another preferred embodiment, R^8 is OH and R^9 is NH_2.

In one embodiment of Formula III, R^{11} or R^{12} is independently H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_4$–$C_8)$carbocyclylalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)(C_1$-$C_8)$alkyl, $-S(O)_n(C_1$-$C_8)$alkyl or aryl$(C_1$-$C_8)$alkyl. In another embodiment, R^{11} and R^{12} taken together with a nitrogen to which they are both attached, form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with -O-, -S- or $-NR^a$-. Therefore, by way of example and not limitation, the moiety $-NR^{11}R^{12}$ can be represented by the heterocycles:



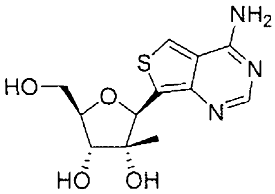
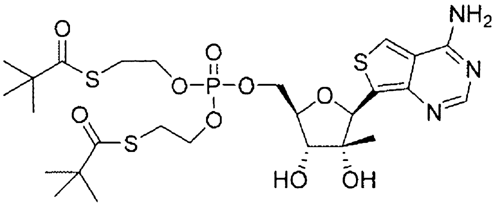
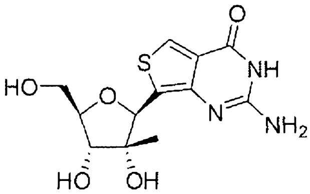
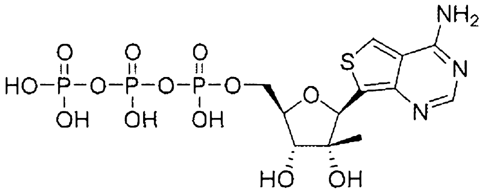
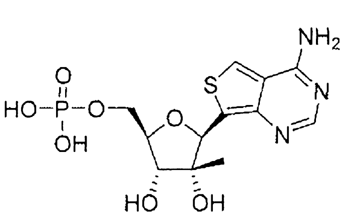
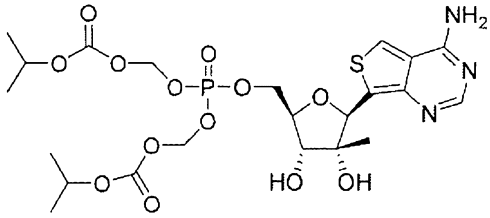
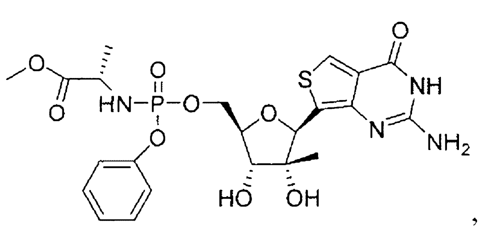
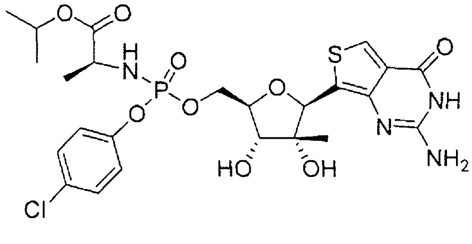
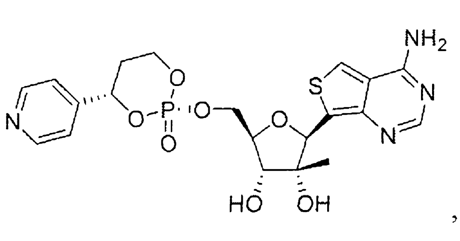
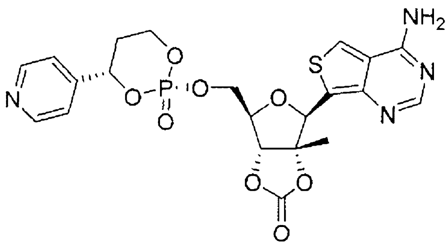
and the like.

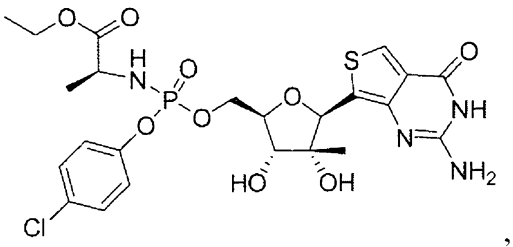
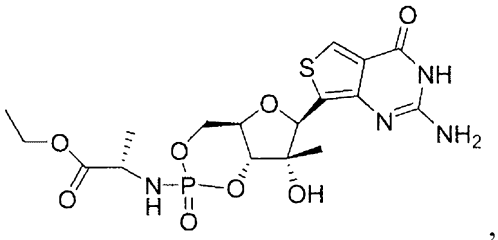
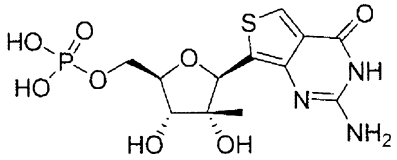
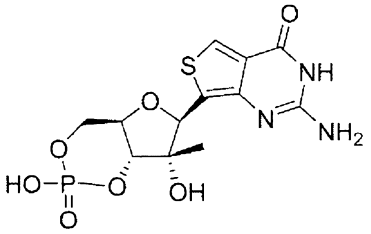
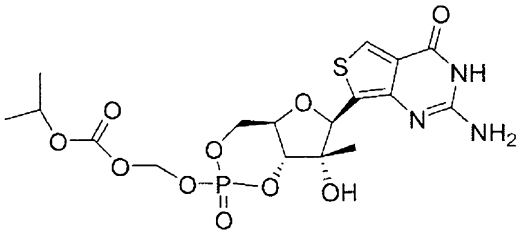
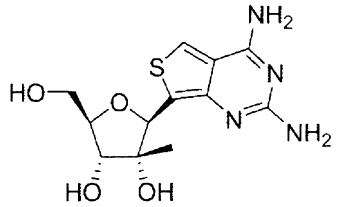
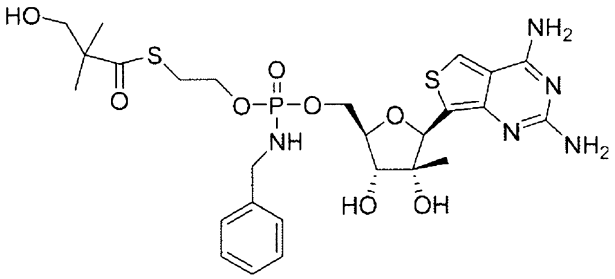
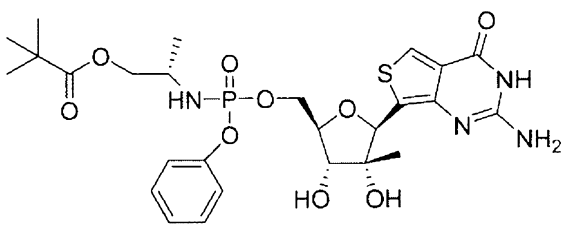
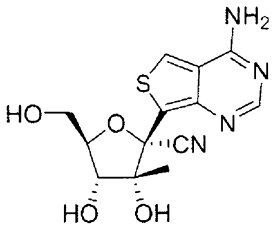
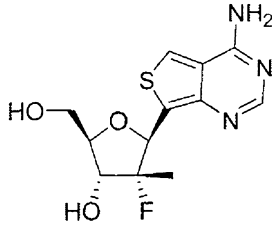
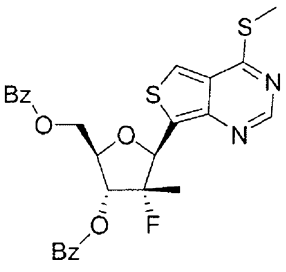
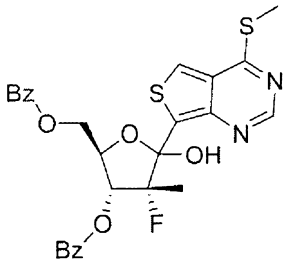
In another embodiment of Formula III, R^2, R^4, R^5, R^a, R^{11} or R^{12} is, independently, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl or aryl$(C_1$-$C_8)$alkyl, wherein said $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl or aryl$(C_1$-$C_8)$alkyl are, independently, optionally substituted with one or more halo, hydroxy, CN, N_3, $N(R^a)_2$ or OR^a. Therefore, by way of example and not limitation, R^2, R^4, R^5, R^a, R^{11} or R^{12} could represent moieties such as $-CH(NH_2)CH_3$, -CH(OH)CH2CH3, $-CH(NH_2)CH(CH_3)_2$, $-CH_2CF_3$, $-(CH_2)_2CH(N_3)CH_3$, $-(CH_2)_6NH_2$ and the like.

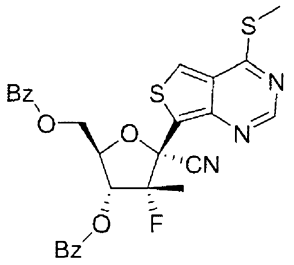
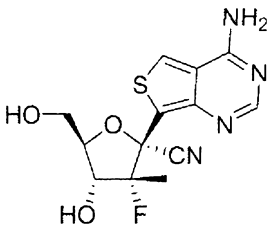
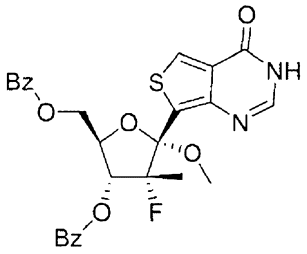
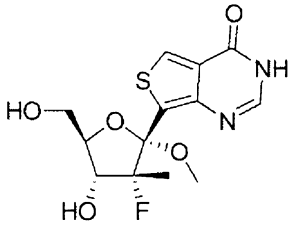
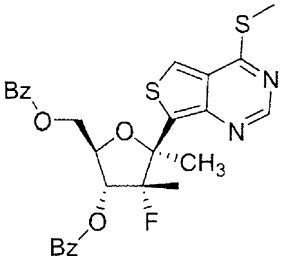
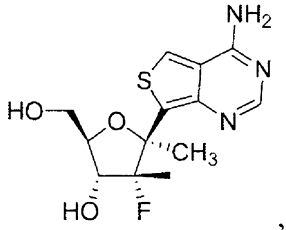
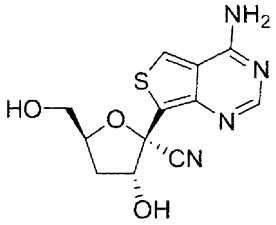
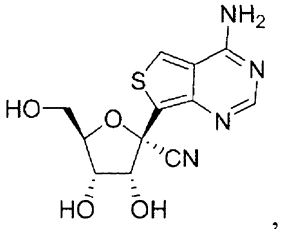
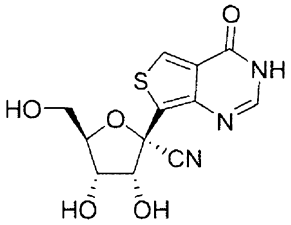
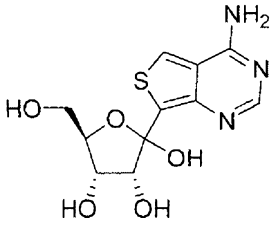
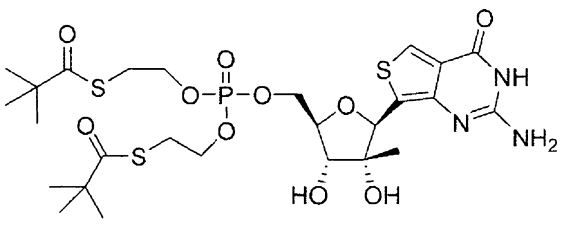
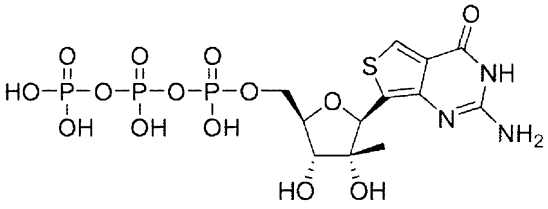
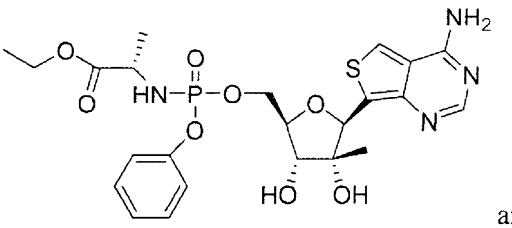
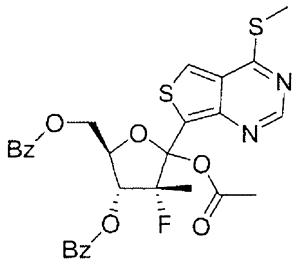
In another embodiment of Formula III, R^2, R^4, R^5, R^a, R^{11} or R^{12} is $(C_1$-$C_8)$alkyl wherein one or more of the non-terminal carbon atoms of each said $(C_1$-$C_8)$alkyl may be optionally replaced with -O-, -S- or $-NR^a$-. Therefore, by way of example and not limitation, R^2, R^4, R^5, R^a, R^{11} or R^{12} could represent moieties such as

$-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2OCH(CH_3)_2$, $-CH_2SCH_3$, $-(CH_2)_6OCH_3$, $-(CH_2)_6N(CH_3)_2$ and the like.

In another embodiment, Formula I-III is a compound selected from the group consisting of


,

,

,

,

,

,

,

,

,

,

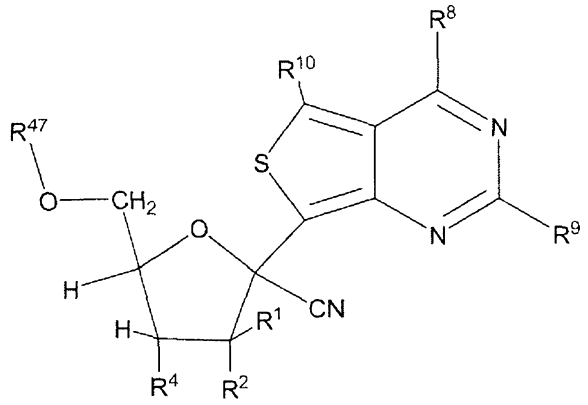













and ; or

a pharmaceutically acceptable salt or ester thereof.

Provided is a method for preparing a compound represented by Formula IV:



Formula IV

or an acceptable salt or ester, thereof;

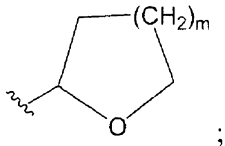
wherein:

R^1 is H, $(C_1–C_8)$alkyl, $(C_4–C_8)$carbocyclylalkyl, $(C_1–C_8)$substituted alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$substituted alkenyl, $(C_2–C_8)$alkynyl, $(C_2–C_8)$substituted alkynyl, or aryl$(C_1$-$C_8)$alkyl;

each R^2 or R^4 is independently H, F or OR^{44};

each R^{43} is independently $(C_1$-$C_8)$ alkyl, $(C_1$-$C_8)$ substituted alkyl, $C_6–C_{20}$ aryl, $C_6–C_{20}$ substituted aryl, $C_2–C_{20}$ heterocyclyl, $C_2–C_{20}$ substituted heterocyclyl, C_7-C_{20} arylalkyl, C_7-C_{20} substituted arylalkyl, $(C_1$-$C_8)$ alkoxy, or $(C_1$-$C_8)$ substituted alkoxy;

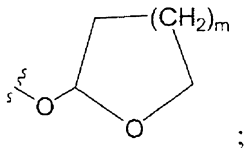
each R^{44} or R^{47} is independently $–C(R^{45})_2R^{46}$, $Si(R^{43})_3$, $C(O)R^{45}$, $C(O)OR^{45}$, $-(C(R^{45})_2)_m$-R^{55} or



;

or any two of R^{44} or R^{47} when taken together are $–C(R^{59})_2$-, -C(O)- or $-Si(R^{43})_2(X^{42})_mSi(R^{43})_2$-;

each R^{55} is independently $–O$-$C(R^{45})_2R^{46}$, $-Si(R^{43})_3$, $-OC(O)OR^{45}$, $-OC(O)R^{45}$ or



;

each R^{45}, R^{58} or R^{59} is independently H, (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8)alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heterocyclyl, C_2–C_{20} substituted heterocyclyl, C_7-C_{20} arylalkyl or C_7-C_{20} substituted arylalkyl;

each R^{46} is independently C_6–C_{20} aryl, C_6–C_{20} substituted aryl, or optionally substituted heteroaryl;

each R^a is independently H, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, aryl(C_1-C_8)alkyl, (C_4–C_8)carbocyclylalkyl, -C(=O)R^{11}, -C(=O)OR^{11}, -C(=O)$NR^{11}R^{12}$, -C(=O)SR^{11}, -S(O)R^{11}, -$S(O)_2R^{11}$, -S(O)(OR^{11}), -$S(O)_2$(OR^{11}), or –$SO_2NR^{11}R^{12}$;

each X^{42} is O or CH_2;

each m is 1 or 2;

each n is independently 0, 1 or 2;

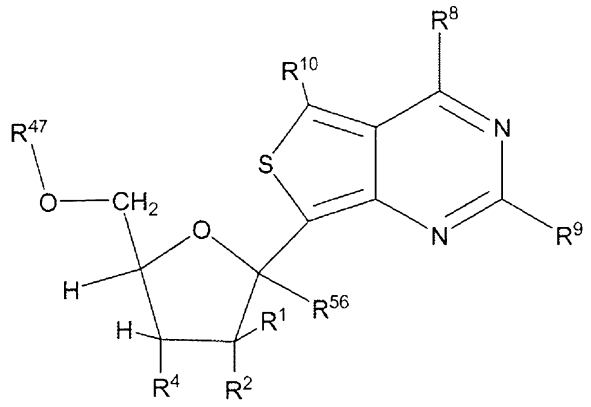
each R^8, R^9 or R^{10} is independently H, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3, NO, NO_2, CHO, CN, -CH(=NR^{11}), -CH=$NHNR^{11}$, -CH=$N(OR^{11})$, -$CH(OR^{11})_2$, -C(=O)$NR^{11}R^{12}$, -C(=S)$NR^{11}R^{12}$, -C(=O)OR^{11}, R^{11}, OR^{11} or SR^{11};

each R^{11} or R^{12} is independently H, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3–C_8)carbocyclyl, (C_4–C_8)carbocyclylalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(=O)(C_1-C_8)alkyl, -$S(O)_n$(C_1-C_8)alkyl, aryl(C_1-C_8)alkyl or $Si(R^3)_3$; or R^{11} and R^{12} taken together with a nitrogen to which they are both attached form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with -O-, -$S(O)_n$- or –NR^a-; or R^{11} and R^{12} taken together are -$Si(R^{43})_2(X^{42})_mSi(R^{43})_2$-;

wherein each (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl or aryl(C_1-C_8)alkyl of each R^1, R^{43}, R^{45}, R^{58}, R^{59}, R^{11} or R^{12} is, independently, optionally substituted with one or more halo, hydroxy, CN, N_3, $N(R^a)_2$ or OR^a; and wherein one or more of the non-terminal carbon atoms of each said (C_1-C_8)alkyl is optionally replaced with -O-, -$S(O)_n$- or –NR^a-;

said method comprising :

(a) providing a compound of Formula V



Formula V

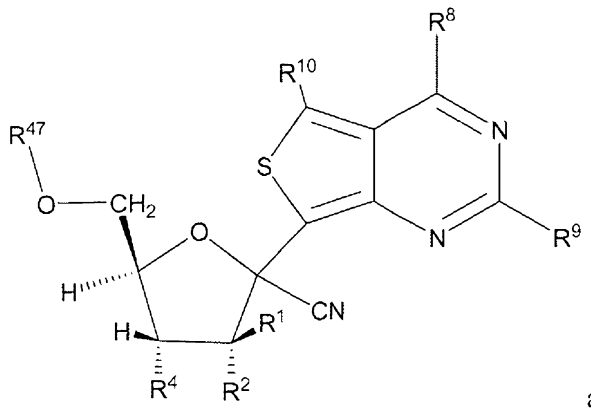
wherein R^{56} is OH, -OC(O)OR^{58} or -OC(O)R^{58};

(b) treating the compound of Formula V with a cyanide reagent and a Lewis acid;

thereby forming the compound of Formula IV.

The compounds of Formula IV are useful for the preparation of the anti-viral compounds of Formula I.

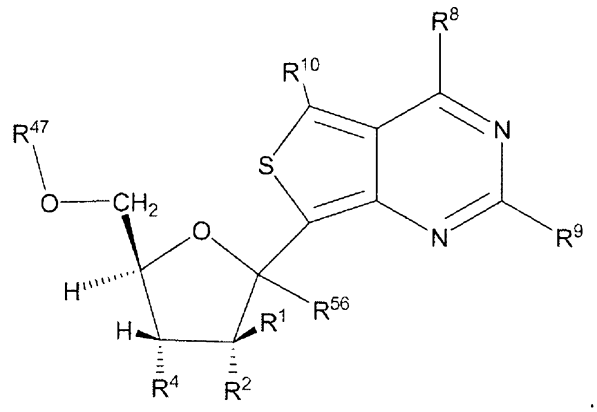
In one embodiment of the method, the compound of Formula IV is Formula IVb



Formula IVb

and

the compound of Formula V is Formula Vb:



Typically, the method of preparing compounds of Formula IVb from Formula Vb are preformed in a suitable aprotic solvent at about -78 to 80 °C for about 10 minutes to 24 hours. Non-limiting examples of suitable aprotic solvents include CH_2Cl_2, acetonitrile, CH_2ClCH_2Cl or other halocarbon solvents. More typically, the method is performed at about -10 to about 65 °C for about 10 minutes to 4 hours. The mole ratio of the compound of Formula Vb to cyanide reagent is about 1:1 to 1:10, more typically about 1:2 to 1:6. The mole ratio of the compound of Formula Vb to Lewis acid is about 1:0.1 to about 1:10, more typically about 1:0.7 to about 1:6.

Typical, but non-limiting, cyanide reagents comprise $(R^{43})_3SiCN$, $R^{45}C(O)CN$, and $R^{43}C(O)CN$ wherein R^{43} and R^{45} are defined as above. A preferred cyanide reagent is $(CH_3)_3SiCN$. Another preferred cyanide reagent is $R^{43}C(O)CN$ wherein R^{43} is $(C_1\text{-}C_8)$ alkoxy or $(C_1\text{-}C_8)$ substituted alkoxy.

The conversion of the compounds of Formula Vb to a compound of Formula IVb is promoted by Lewis acids. Many Lewis acids may promote this conversion including many that are commercially available. Non-limiting examples of Lewis acids comprising boron that are suitable for promoting this conversion are boron trifluoride etherates of methyl, ethyl, propyl, and butyl ethers; boron trifluoride-*tert*-butyl methyl etherate; boron trifluoride and boron trifluoride methyl sulfide complex. Non-limiting examples of Lewis acids comprising trialkylsilyl groups that are suitable for promoting this conversion are trimethylsilyl trifluoromethanesulfonate, other trimethylsilyl polyfluoroalkylsulfonates, *tert*-butyldimethylsilyl trifluoromethanesulfonate and triethylsilyl trifluoromethanesulfonate. Additional non-

limiting examples of Lewis acids suitable for promoting this conversion are $TiCl_4$, $AlCl_3$, $ZnCl_2$, ZnI_2, $SnCl_4$, $InCl_3$, Sc(trifluoromethanesulfonate)$_3$, silver trifluoromethanesulfonate, zinc trifluoromethanesulfonate, magnesium trifluoromethanesulfonate, thallium triflate, lanthanum trifluoromethanesulfonate, indium(III) trifluoromethanesulfonate, cerium(IV) trifluoromethanesulfonate, erbium(III) trifluoromethanesulfonate, gadolinium(III) trifluoromethanesulfonate, lutetium(III) trifluoromethanesulfonate, neodymium(III) trifluoromethanesulfonate, praseodymium(III) trifluoromethanesulfonate, samarium(III) trifluoromethanesulfonate, terbium(III) trifluoromethanesulfonate, dysprosium(III) trifluoromethanesulfonate, europium trifluoromethanesulfonate, holmium(III) trifluoromethanesulfonate, thulium(III) trifluoromethanesulfonate, yttrium(III) trifluoromethanesulfonate, trifluoromethanesulfonic acid nickel salt, hafnium trifluoromehtanesulfonate, bismuth(III) trifluoromethanesulfonate, gallium(III) trifluoromethanesulfonate, cerium(III) trifluoromethanesulfonate, ytterbium(III) trifluoromethanesulfonate, tellurium(IV) trifluoromethanesulfonate, zirconium(IV) trifluoromethanesulfonate, bismuth trifluoromethanesulfonate, iron(II) trifluoromethanesulfonate, Sn(trifluoromethanesulfonate)$_2$, $InBr_3$, $AuCl_3$, montmorilite clays, Cu(trifluoromethanesulfonate)$_2$, vanadyl trifluoromethanesulfonate, and salen complexes of Ti and Vn (Belokon, et al., Tetrahedron 2001, 771). In a preferred embodiment, the Lewis acid is trimethylsilyl trifluoromethanesulfonate. In another preferred embodiment, the Lewis acid is trimethylsilyl trifluoromethanesulfonate and the yield of the compound of Formula IVb is 50% or greater. In another preferred embodiment, the Lewis acid is trimethylsilyl trifluoromethanesulfonate and the yield of the compound of Formula IVb is 70% or greater. In another preferred embodiment, the Lewis acid is trimethylsilyl trifluoromethanesulfonate and the yield of the compound of Formula IVb is 90% or greater.

In another embodiment of the method of preparing a compound of Formula IVb, R^{56} of Formula Vb is OH. Additional independent aspects of this embodiment are:

(a) R^1 is H. R^1 is CH_3.

(b) R^8 is $NR^{11}R^{12}$. R^8 is OR^{11}. R^8 is SR^{11}.

(c) R^9 is H. R^9 is $NR^{11}R^{12}$. R^9 is SR^{11}.

(d) R^2 is OR^{44}. R^2 is F. Each R^4 and R^2 is independently OR^{44}. R^2 is OR^{44} and R^2 is F. R^4 is OR^{44}, R^2 is F and R^{44} is $C(O)R^{45}$. R^4 is OR^{44}, R^{2b} is F and R^{44} is $C(O)R^{45}$ wherein R^{45} is phenyl or substituted phenyl. R^2 is OR^{44} wherein R^{44} is $C(R^{45})_2R^{46}$ and R^{46} is phenyl or substituted phenyl. R^2 is OR^{44} wherein R^{44} is CH_2R^{46} and R^{46} is phenyl. R^2 is OR^{44} wherein R^{44} is CH_2R^{46} and R^{46} is substituted phenyl. Each R^4 and R^2 is OR^{44} wherein each R^{44} is independently $C(R^{45})_2R^{46}$ and R^{46} is phenyl or substituted phenyl. Each R^4 and R^2 is OR^{44} wherein each R^{44} is CH_2R^{46} and R^{46} is phenyl. Each R^4 and R^2 is OR^{44} wherein each R^{44} is CH_2R^{46} and each R^{46} is independently substituted phenyl. Each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(R^{59})_2-$. Each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. Each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$. Each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$ wherein R^{59} is phenyl or substituted phenyl. R^4 is OR^{44} wherein R^{44} is $C(R^{45})_2R^{46}$, R^{46} is phenyl or substituted phenyl and R^2 is F. R^4 is H.

(e) R^{47} is $C(O)R^{45}$. R^{47} is $C(R^{45})_2R^{46}$ and R^{46} is phenyl or substituted phenyl. R^{47} is CH_2R^{46} and R^{46} is phenyl. R^{47} is CH_2R^{46} and R^{46} is substituted phenyl. R^{47} is $C(R^{45})_2R^{46}$ and each R^{45} and R^{46} is independently phenyl or substituted phenyl. R^{47} is $Si(R^{43})_3$. R^{47} is $Si(R^{43})_2(t\text{-butyl})$ wherein each R^{43} is CH_3. R^{47} is $Si(R^{43})_2(t\text{-butyl})$ wherein each R^{43} is independently phenyl or substituted phenyl. R^{47} is tetrahydro-*2H*-pyran-2-yl. R^{47} is $C(R^{45})_2R^{46}$ wherein each R^{45} and R^{46} is independently phenyl or substituted phenyl and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. R^{47} is $Si(R^{43})_3$ and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. R^{47} is $Si(R^{43})_2(t\text{-butyl})$ wherein each R^{43} is CH_3 and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. R^{47} is $Si(R^{43})_2(t\text{-butyl})$ wherein each R^{43} is independently phenyl or substituted phenyl and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. R^{47} is tetrahydro-*2H*-pyran-2-yl and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. R^{47} is $C(O)R^{45}$ and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. R^{47} is $C(R^{45})_2R^{46}$ wherein each R^{45} and R^{46} is independently phenyl or substituted phenyl and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken

together are –CH(R^{59})- wherein R^{59} is phenyl or substituted phenyl. R^{47} is Si(R^{43})$_3$ and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are –CH(R^{59})- wherein R^{59} is phenyl or substituted phenyl. R^{47} is Si(R^{43})$_2$(*t*-butyl) wherein each R^{43} is CH_3 and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are –CH(R^{59})- wherein R^{59} is phenyl or substituted phenyl. R^{47} is Si(R^{43})$_2$(*t*-butyl) wherein each R^{43} is independently phenyl or substituted phenyl and each $R^4$and R^2 is OR^{44} wherein the two R^{44} taken together are –CH(R^{59})- wherein R^{59} is phenyl or substituted phenyl. R^{47} is tetrahydro-*2H*-pyran-2-yl and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are –CH(R^{59})- wherein R^{59} is phenyl or substituted phenyl. R^{47} is C(O)R^{45} and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are –CH(R^{59})- wherein R^{59} is phenyl or substituted phenyl. R^{47} is C(O)R^{45} wherein R^{45} is phenyl or substituted phenyl and R^2 is F.

(f) The cyanide reagent is (R^{43})$_3$SiCN. The cyanide reagent is (CH_3)$_3$SiCN. The cyanide reagent is R^{45}C(O)CN. The cyanide reagent is R^{43}C(O)CN. The cyanide reagent is R^{43}C(O)CN wherein R^{43} is (C_1-C_8) alkoxy or (C_1-C_8) substituted alkoxy.

(g) The Lewis acid comprises boron. The Lewis acid comprises BF_3 or BCl_3. The Lewis acid is BF_3-O(R^{53})$_2$, BF_3-S(R^{53})$_2$, BCl_3- O(R^{53})$_2$ or BCl_3- S(R^{53})$_2$ wherein each R^{53} is independently (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8)alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heterocyclyl, C_2–C_{20} substituted heterocyclyl, C_7-C_{20} arylalkyl, or C_7-C_{20} substituted arylalkyl; wherein each (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl or aryl(C_1-C_8)alkyl of each R^{53} is, independently, optionally substituted with one or more halogens and wherein one or more of the non-terminal carbon atoms of each said (C_1-C_8)alkyl is optionally replaced with -O- or –S(O)$_n$-; or two R^{53} when taken together with the oxygen to which they are both attached form a 3 to 7 membered heterocyclic ring wherein one carbon atom of said heterocyclic ring can optionally be replaced with -O- or –S(O)$_n$-. The Lewis acid is BF_3-O(R^{53})$_2$ and R^{53} is (C_1-C_8) alkyl. The Lewis acid comprises R^{57}S(O)$_2$OSi(R^{43})$_3$ wherein R^{57} is substituted with two or more halogens and is (C_1-C_8)alkyl or substituted (C_1-C_8)alkyl. The Lewis acid is R^{57}S(O)$_2$OSi(CH_3)$_3$ and R^{57} is (C_1-C_8)alkyl substituted with three or more fluorines. The Lewis acid is trimethylsilyltriflate. The Lewis acid comprises a

transition metal or salt thereof. The Lewis acid comprises titanium or a salt thereof. The Lewis acid comprises $TiCl_4$. The Lewis acid comprises a lanthanide or a salt thereof. The Lewis acid comprises scandium or a salt thereof. The Lewis acid comprises vanadium or a salt thereof. The Lewis acid comprises tin or a salt thereof. The Lewis acid comprises $SnCl_4$. The Lewis acid comprises zinc or a salt thereof. The Lewis acid comprises $ZnCl_2$. The Lewis acid comprises samarium or a salt thereof. The Lewis acid comprises nickel or a salt thereof. The Lewis acid comprises copper or a salt thereof. The Lewis acid comprises aluminum or a salt thereof. The Lewis acid comprises gold or a salt thereof. The Lewis acid comprises zinc trifluoromethanesulfonate. The Lewis acid comprises indium(III) trifluoromethanesulfonate, The Lewis acid comprises scandium(III) trifluoromethanesulfonate. The Lewis acid comprises yttrium(III) trifluoromethanesulfonate.

In another embodiment of the method of preparing a compound of Formula IVb, R^{16} of Formula Vb is $-OC(O)R^{58}$ or $-OC(O)OR^{58}$. Additional independent aspects of this embodiment are:

(a) R^1 is H. R^1 is CH_3.

(b) R^8 is $NR^{11}R^{12}$. R^8 is OR^{11}. R^8 is SR^{11}.

(c) R^9 is H. R^9 is $NR^{11}R^{12}$. R^9 is SR^{11}.

(d) R^2 is OR^{44}. R^2 is F. Each R^4 and R^2 is independently OR^{44}. R^2 is OR^{44} and R^2 is F. R^4 is OR^{44}, R^2 is F and R^{44} is $C(O)R^{45}$. R^4 is OR^{44}, R^{2b} is F and R^{44} is $C(O)R^{45}$ wherein R^{45} is phenyl or substituted phenyl. R^2 is OR^{44} wherein R^{44} is $C(R^{45})_2R^{46}$ and R^{46} is phenyl or substituted phenyl. R^2 is OR^{44} wherein R^{44} is CH_2R^{46} and R^{46} is phenyl. R^2 is OR^{44} wherein R^{44} is CH_2R^{46} and R^{46} is substituted phenyl. Each R^4 and R^2 is OR^{44} wherein each R^{44} is independently $C(R^{45})_2R^{46}$ and R^{46} is phenyl or substituted phenyl. Each R^4 and R^2 is OR^{44} wherein each R^{44} is CH_2R^{46} and R^{46} is phenyl. Each R^4 and R^2 is OR^{44} wherein each R^{44} is CH_2R^{46} and each R^{46} is independently substituted phenyl. Each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(R^{59})_2-$. Each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. Each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$. Each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$

wherein R^{59} is phenyl or substituted phenyl. R^4 is OR^{44} wherein R^{44} is $C(R^{45})_2R^{46}$, R^{46} is phenyl or substituted phenyl and R^2 is F. R^4 is H.

(e) R^{47} is $C(O)R^{45}$. R^{47} is $C(R^{45})_2R^{46}$ and R^{46} is phenyl or substituted phenyl. R^{47} is CH_2R^{46} and R^{46} is phenyl. R^{47} is CH_2R^{46} and R^{46} is substituted phenyl. R^{47} is $C(R^{45})_2R^{46}$ and each R^{45} and R^{46} is independently phenyl or substituted phenyl. R^{47} is $Si(R^{43})_3$. R^{47} is $Si(R^{43})_2$(*t*-butyl) wherein each R^{43} is CH_3. R^{47} is $Si(R^{43})_2$(*t*-butyl) wherein each R^{43} is independently phenyl or substituted phenyl. R^{47} is tetrahydro-*2H*-pyran-2-yl. R^{47} is $C(R^{45})_2R^{46}$ wherein each R^{45} and R^{46} is independently phenyl or substituted phenyl and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. R^{47} is $Si(R^{43})_3$ and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. R^{47} is $Si(R^{43})_2$(*t*-butyl) wherein each R^{43} is CH_3 and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. R^{47} is $Si(R^{43})_2$(*t*-butyl) wherein each R^{43} is independently phenyl or substituted phenyl and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. R^{47} is tetrahydro-*2H*-pyran-2-yl and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. R^{47} is $C(O)R^{45}$ and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. R^{47} is $C(R^{45})_2R^{46}$ wherein each R^{45} and R^{46} is independently phenyl or substituted phenyl and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$ wherein R^{59} is phenyl or substituted phenyl. R^{47} is $Si(R^{43})_3$ and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$ wherein R^{59} is phenyl or substituted phenyl. R^{47} is $Si(R^{43})_2$(*t*-butyl) wherein each R^{43} is CH_3 and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$ wherein R^{59} is phenyl or substituted phenyl. R^{47} is $Si(R^{43})_2$(*t*-butyl) wherein each R^{43} is independently phenyl or substituted phenyl and each $R^4$and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$ wherein R^{59} is phenyl or substituted phenyl. R^{47} is tetrahydro-*2H*-pyran-2-yl and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$ wherein R^{59} is phenyl or substituted phenyl. R^{47} is $C(O)R^{45}$ and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$ wherein R^{59} is phenyl or substituted phenyl. R^{47} is $C(O)R^{45}$ wherein R^{45} is phenyl or substituted phenyl and R^2 is F.

(f) The cyanide reagent is $(R^{43})_3SiCN$. The cyanide reagent is $(CH_3)_3SiCN$. The cyanide reagent is $R^{45}C(O)CN$. The cyanide reagent is $R^{43}C(O)CN$. The cyanide reagent is $R^{43}C(O)CN$ wherein R^{43} is $(C_1\text{-}C_8)$ alkoxy or $(C_1\text{-}C_8)$ substituted alkoxy.

(g) The Lewis acid comprises boron. The Lewis acid comprises BF_3 or BCl_3. The Lewis acid is $BF_3\text{-}O(R^{53})_2$, $BF_3\text{-}S(R^{53})_2$, $BCl_3\text{-}O(R^{53})_2$ or $BCl_3\text{-}S(R^{53})_2$ wherein each R^{53} is independently $(C_1\text{-}C_8)$ alkyl, $(C_1\text{-}C_8)$ substituted alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$ substituted alkenyl, $(C_2\text{-}C_8)$ alkynyl, $(C_2\text{-}C_8)$ substituted alkynyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heterocyclyl, C_2–C_{20} substituted heterocyclyl, $C_7\text{-}C_{20}$ arylalkyl, or $C_7\text{-}C_{20}$ substituted arylalkyl; wherein each $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl or aryl$(C_1\text{-}C_8)$alkyl of each R^{53} is, independently, optionally substituted with one or more halogens and wherein one or more of the non-terminal carbon atoms of each said $(C_1\text{-}C_8)$alkyl is optionally replaced with -O- or $-S(O)_n$-; or two R^{53} when taken together with the oxygen to which they are both attached form a 3 to 7 membered heterocyclic ring wherein one carbon atom of said heterocyclic ring can optionally be replaced with -O- or $-S(O)_n$-. The Lewis acid is $BF_3\text{-}O(R^{53})_2$ and R^{53} is $(C_1\text{-}C_8)$ alkyl. The Lewis acid comprises $R^{57}S(O)_2OSi(R^{43})_3$ wherein R^{57} is substituted with two or more halogens and is $(C_1\text{-}C_8)$alkyl or substituted $(C_1\text{-}C_8)$alkyl. The Lewis acid is $R^{57}S(O)_2OSi(CH_3)_3$ and R^{57} is $(C_1\text{-}C_8)$alkyl substituted with three or more fluorines. The Lewis acid is trimethylsilyltriflate. The Lewis acid comprises a transition metal or salt thereof. The Lewis acid comprises titanium or a salt thereof. The Lewis acid comprises $TiCl_4$. The Lewis acid comprises a lanthanide or a salt thereof. The Lewis acid comprises scandium or a salt thereof. The Lewis acid comprises vanadium or a salt thereof. The Lewis acid comprises tin or a salt thereof. The Lewis acid comprises $SnCl_4$. The Lewis acid comprises zinc or a salt thereof. The Lewis acid comprises $ZnCl_2$. The Lewis acid comprises samarium or a salt thereof. The Lewis acid comprises nickel or a salt thereof. The Lewis acid comprises copper or a salt thereof. The Lewis acid comprises aluminum or a salt thereof. The Lewis acid comprises gold or a salt thereof. The Lewis acid comprises zinc trifluoromethanesulfonate. The Lewis acid comprises indium(III) trifluoromethanesulfonate, The Lewis acid comprises scandium(III)

trifluoromethanesulfonate. The Lewis acid comprises yttrium(III) trifluoromethanesulfonate.

(*i*) R^{58} is (C_1-C_8)alkyl or substituted (C_1-C_8)alkyl. R^{58} is (C_1-C_8)alkyl. R^{58} is methyl.

Provided is a method of preparing a compound of Formula Vb wherein R^{56} is -$OC(O)R^{58}$ or $OC(O)OR^{58}$,

the method comprising:

(c) providing a compound of Formula Vb wherein R^{56} is OH; and

(d) treating the compound of Formula Vb wherein R^{56} is OH with $YC(O)R^{58}$ or $YC(O)OR^{58}$ wherein Y is selected from halogen, cyano, imidazol-1-yl; pyrazol-1-yl, –O-$C(O)R^{58}$ or –O-$C(O)OR^{58}$;

thereby forming a compound of Formula Vb wherein R^{56} is -$OC(O)R^{58}$ or $OC(O)OR^{58}$.

In one embodiment of the method of preparing a compound of Formula Vb wherein R^{56} is -$OC(O)R^{58}$ or $OC(O)OR^{58}$, the mole ratio of the compound of Formula Vb wherein R^{56} is OH to $YC(O)R^{58}$ or $YC(O)OR^{58}$ is about 1:1 to about 1:10, preferably about 1:1 to about 1:6.5. Typically, the compound of Formula Vb wherein R^{56} is OH is treated with $YC(O)R^{58}$ or $YC(O)OR^{58}$ in an aprotic solvent such as, but not limited to, pyridine, THF or ether at about -30 to about 125 ^{0}C for about 30 minutes to about 24 hours. In one aspect of this embodiment, Y is halogen. In another aspect of this embodiment, Y is Cl. In another aspect of this embodiment, Y is cyano. In another aspect of this embodiment, Y is imidazol-1-yl. In another aspect of this embodiment, Y is pyrazol-1-yl. In another aspect of this embodiment, Y is –O-$C(O)R^{58}$. In another aspect of this embodiment, Y is –O-$C(O)OR^{58}$. In another aspect of this embodiment, R^{58} is C_1-C_6 alkyl. In another aspect of this embodiment, R^{58} is CH_3. In another aspect of this embodiment, R^{58} is C_1-C_6 alkyl and Y is –O-$C(O)R^{58}$. In another aspect of this embodiment, R^{58} is CH_3 and Y is –O-$C(O)R^{58}$.

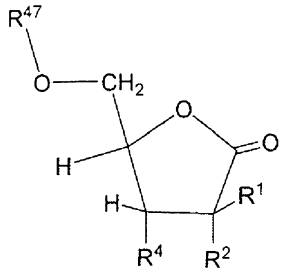
The reaction of the compound of Formula Vb wherein R^{56} is OH with $YC(O)R^{58}$ or $YC(O)OR^{58}$ may be catalyzed or accelerated in the presence of a suitable base. Non-limiting examples of suitable bases include triethylamine, di-

isopropylethylamine, pyridine, 4-dimethylaminopyridine, DBU, NaH and KH. The mole ratio of $YC(O)R^{58}$ or $YC(O)OR^{58}$ to base is typically about 1:1 to 1:4.

Provided is a method of preparing a compound of Formula V wherein R^{56} is OH,

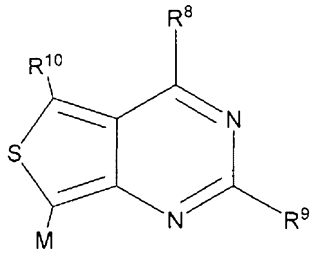
the method comprising:

(e) providing a compound of Formula VI:



Formula VI

(f) treating the compound of Formula VI with an organometallic compound of Formula VII:

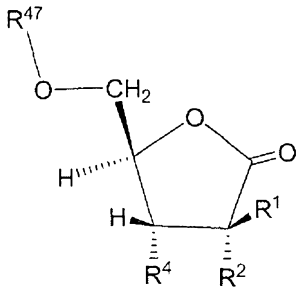


Formula VII

wherein M is MgX^3 or Li and X^3 is halogen;

thereby forming a compound of Formula V wherein R^{56} is OH.

In another embodiment of the method of preparing a compound of Formula V wherein R^{56} is OH, the compound of Formula V is Formula Vb wherein R^{56} is OH and the compound of Formula VI is a compound of Formula VIb:



Formula VIb

Additional independent aspects of this embodiment are:

(a) R^1 is H. R^1 is CH_3.

(b) R^8 is $NR^{11}R^{12}$. R^8 is OR^{11}. R^8 is SR^{11}.

(c) R^9 is H. R^9 is $NR^{11}R^{12}$. R^9 is SR^{11}.

(d) R^2 is OR^{44}. R^2 is F. Each R^4 and R^2 is independently OR^{44}. R^2 is OR^{44} and R^2 is F. R^4 is OR^{44}, R^2 is F and R^{44} is $C(O)R^{45}$. R^4 is OR^{44}, R^{2b} is F and R^{44} is $C(O)R^{45}$ wherein R^{45} is phenyl or substituted phenyl. R^2 is OR^{44} wherein R^{44} is $C(R^{45})_2R^{46}$ and R^{46} is phenyl or substituted phenyl. R^2 is OR^{44} wherein R^{44} is CH_2R^{46} and R^{46} is phenyl. R^2 is OR^{44} wherein R^{44} is CH_2R^{46} and R^{46} is substituted phenyl. Each R^4 and R^2 is OR^{44} wherein each R^{44} is independently $C(R^{45})_2R^{46}$ and R^{46} is phenyl or substituted phenyl. Each R^4 and R^2 is OR^{44} wherein each R^{44} is CH_2R^{46} and R^{46} is phenyl. Each R^4 and R^2 is OR^{44} wherein each R^{44} is CH_2R^{46} and each R^{46} is independently substituted phenyl. Each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(R^{59})_2-$. Each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. Each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$. Each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$ wherein R^{59} is phenyl or substituted phenyl. R^4 is OR^{44} wherein R^{44} is $C(R^{45})_2R^{46}$, R^{46} is phenyl or substituted phenyl and R^2 is F. R^4 is H.

(e) R^{47} is $C(O)R^{45}$. R^{47} is $C(R^{45})_2R^{46}$ and R^{46} is phenyl or substituted phenyl. R^{47} is CH_2R^{46} and R^{46} is phenyl. R^{47} is CH_2R^{46} and R^{46} is substituted phenyl. R^{47} is $C(R^{45})_2R^{46}$ and each R^{45} and R^{46} is independently phenyl or substituted phenyl. R^{47} is $Si(R^{43})_3$. R^{47} is $Si(R^{43})_2(t\text{-butyl})$ wherein each R^{43} is CH_3. R^{47} is $Si(R^{43})_2(t\text{-butyl})$ wherein each R^{43} is independently phenyl or substituted phenyl. R^{47} is tetrahydro-*2H*-pyran-2-yl. R^{47} is $C(R^{45})_2R^{46}$ wherein each R^{45} and R^{46} is independently phenyl or

substituted phenyl and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. R^{47} is $Si(R^{43})_3$ and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. R^{47} is $Si(R^{43})_2$(*t*-butyl) wherein each R^{43} is CH_3 and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. R^{47} is $Si(R^{43})_2$(*t*-butyl) wherein each R^{43} is independently phenyl or substituted phenyl and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. R^{47} is tetrahydro-*2H*-pyran-2-yl and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. R^{47} is $C(O)R^{45}$ and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. R^{47} is $C(R^{45})_2R^{46}$ wherein each R^{45} and R^{46} is independently phenyl or substituted phenyl and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$ wherein R^{59} is phenyl or substituted phenyl. R^{47} is $Si(R^{43})_3$ and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$ wherein R^{59} is phenyl or substituted phenyl. R^{47} is $Si(R^{43})_2$(*t*-butyl) wherein each R^{43} is CH_3 and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$ wherein R^{59} is phenyl or substituted phenyl. R^{47} is $Si(R^{43})_2$(*t*-butyl) wherein each R^{43} is independently phenyl or substituted phenyl and each $R^4$and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$ wherein R^{59} is phenyl or substituted phenyl. R^{47} is tetrahydro-*2H*-pyran-2-yl and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$ wherein R^{59} is phenyl or substituted phenyl. R^{47} is $C(O)R^{45}$ and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$ wherein R^{59} is phenyl or substituted phenyl. R^{47} is $C(O)R^{45}$ wherein R^{45} is phenyl or substituted phenyl and R^2 is F.

In another embodiment of the method of preparing a compound of Formula Vb wherein R^{56} is OH, the compound of Formula VII comprises the following independent aspects:

(a) R^8 is $NR^{11}R^{12}$. R^8 is OR^{11}. R^8 is SR^{11}.

(b) R^9 is H. R^9 is $NR^{11}R^{12}$. R^9 is SR^{11}.

(c) Each R^{11} or R^{12} is independently $(C_1\text{-}C_8)$alkyl, $-C(=O)(C_1\text{-}C_8)$alkyl, $-S(O)_n(C_1\text{-}C_8)$alkyl, aryl$(C_1\text{-}C_8)$alkyl or $Si(R^{43})_3$; or R^{11} and R^{12} taken together with a nitrogen to which they are both attached form a 3 to 7 membered heterocyclic ring; or R^{11} and R^{12} taken together are $-Si(R^{43})_2(X^{42})_mSi(R^{43})_2-$. Each R^{11} or R^{12} is

independently (C_1-C_8)alkyl. Each R^{11} or R^{12} is independently $Si(R^{43})_3$. Each R^{11} or R^{12} is independently $Si(R^{43})_3$ wherein at least two of R^{43} are CH_3 or phenyl. Each R^{11} or R^{12} is independently $Si(CH_3)_3$. Each R^{11} and R^{12} of $NR^{11}R^{12}$ is independently selected from $Si(R^{43})_3$ or R^{11} and R^{12} of $NR^{11}R^{12}$ taken together are -$Si(R^{43})_2(X^{42})_mSi(R^{43})_2$-. Each R^{11} and R^{12} of $NR^{11}R^{12}$ is independently selected from $Si(R^{43})_3$ or R^{11} and R^{12} of $NR^{11}R^{12}$ taken together are -$Si(R^{43})_2(X^{42})_mSi(R^{43})_2$-; and each R^{43} is methyl.

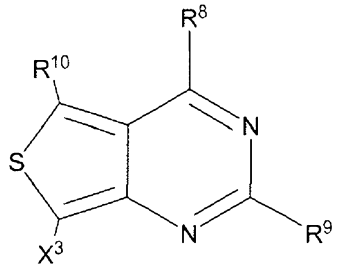
(d) M is MgX^3. M is Li.

Typically, the method of preparing a compound of Formula Vb wherein R^{56} is OH is performed in a suitable aprotic solvent at about -100 to about to abut 50 ^{0}C for about 5 minutes to 24 hours. Non-limiting examples of suitable aprotic solvents include THF, dioxane and ether. More typically, the suitable solvent is THF and the preferred temperature is about -78 to 0 ^{0}C. The mole ratio of the compound of Formula VII to the compound of Formula VIb is about 1:2 to 2:1; preferably about 1:1.

Provided is a method of preparing a compound of Formula VII wherein M is MgX^3 or Li and X^3 is halogen,

the method comprising:

(g) providing a compound of Formula VIII:



Formula VIII

wherein X^3 is Cl, Br or I and

(h) treating the compound of Formula VIII with an organometallic reagent comprising an organomagnesium or organolithium compound;

thereby forming a compound of Formula VII.

In another embodiment, the method of preparing a compound of Formula VII from a compound of Formula VIII comprises the following independent aspects.

(a) R^8 is $NR^{11}R^{12}$. R^8 is OR^{11}. R^8 is SR^{11}.

(b) R^9 is H. R^9 is $NR^{11}R^{12}$. R^9 is SR^{11}.

(c) Each R^{11} or R^{12} is independently $(C_1\text{-}C_8)$alkyl, $-C(=O)(C_1\text{-}C_8)$alkyl, $-S(O)_n(C_1\text{-}C_8)$alkyl, aryl$(C_1\text{-}C_8)$alkyl or $Si(R^{43})_3$; or R^{11} and R^{12} taken together with a nitrogen to which they are both attached form a 3 to 7 membered heterocyclic ring; or R^{11} and R^{12} taken together are $-Si(R^{43})_2(X^{42})_mSi(R^{43})_2-$. Each R^{11} or R^{12} is independently $(C_1\text{-}C_8)$alkyl. Each R^{11} or R^{12} is independently $Si(R^{43})_3$. Each R^{11} or R^{12} is independently $Si(R^{43})_3$ wherein at least two of R^{43} are CH_3 or phenyl. Each R^{11} or R^{12} is independently $Si(CH_3)_3$. Each R^{11} and R^{12} of $NR^{11}R^{12}$ is independently selected from $Si(R^{43})_3$ or R^{11} and R^{12} of $NR^{11}R^{12}$ taken together are $-Si(R^{43})_2(X^{42})_mSi(R^{43})_2-$. Each R^{11} and R^{12} of $NR^{11}R^{12}$ is independently selected from $Si(R^{43})_3$ or R^{11} and R^{12} of $NR^{11}R^{12}$ taken together are $-Si(R^{43})_2(X^{42})_mSi(R^{43})_2-$; and each R^{43} is methyl.

(d) X^3 is Cl. X^3 is Br. X^3 is I.

In another embodiment, the method of preparing a compound of Formula VII by treating a compound of Formula VIII with an organometllic reagent comprises the use of an organomagnesium compound. Typically, the transmetalation reaction is performed in a suitable aprotic solvent at about -78 to about to abut 50 ^{0}C for about 5 minutes to 24 hours. Non-limiting examples of suitable aprotic solvents include THF, dioxane and ether. In one embodiment, the mole ratio of the compound of Formula VIII to organomagnesium compound is about 1:1 to about 1:3, preferably about 1:2. In one embodiment, the organomagnesium compound comprises an alkylmagnesium chloride, bromide, or iodide. In another embodiment, the organomagnesium compound comprises 2-propylmagnesium chloride. In one embodiment, the organomagnesium compound comprises an alkylmagnesium chloride, bromide, or iodide and lithium chloride. In another embodiment, the organomagnesium compound comprises 2-propylmagnesium chloride and lithium chloride. In another embodiment, the organomagnesium compound is 2-propylmagnesium choride and

lithium choride in about a 1:1 mole ratio. In a preferred embodiment, the organomagnesium compound comprises 2-propylmagnesium chloride and lithium chloride in a 1:1 mole ratio and the X^3 of Formula VIII is Br or I.

In another embodiment, the method of preparing a compound of Formula VII by treating a compound of Formula VIII with an organometllic reagent, the compound of Formula VIII may be treated with more than one organomagnesium compound. This procedure would be preferable when the compound of Formula VIII comprises a substituent with an acidic hydrogen. Non-limiting examples of the substituents with acidic hydrogens are NH_2, OH, SH, $NH(C_1\text{-}C_6$ alkyl) and the like. One skilled in the art will recognize that the acidic hydrogen group of the substituent of the compound of Formula VIII will consume one mole equivalent of the organomagnesium compound. The organomagnesium compound consumed may be different from the organomagnesium compound that produces the transmetalation reaction. For example, but not by way of limitation, treating the compound of Formula VIII with about one mole equivalent of methylmagnesium chloride would neutralize an acidic hydrogen of $NH(C_1\text{-}C_6$ alkyl), OH, or SH substituent by forming a magnesium salt and the X^3 group (Cl, Br, or I group) of the compound of Formula VIII may be transmetalated with another organomagnesium compound such as 2-propylmagnesium chloride or 2-propylmagnesium chloride and lithium chloride. Similarly, if additional acidic hydrogens are present, an additional about equivalent amount of organomagnesium compound would be required to neutralize each additional acidic hydrogen, e.g., each additional NH_2 substituent would require about two additional equivalents of organomagnesium compound. Typically, the transmetalation reactions of this aspect are performed in a suitable aprotic solvent at about -78 to about to abut 50 ^{0}C for about 5 minutes to 24 hours. Non-limiting examples of suitable aprotic solvents include THF, dioxane and ether.

In one embodiment, the compound of Formula VII is prepared by treating the compound of Formula VIII with about one mole equivalent of a first organomagnesium compound for each acidic hydrogen in a substitutent followed by treatment with a second organomagnesium compound to transmetallate the X^3 group of Formula VIII. In another aspect of this embodiment, the mole ratio of the first

organomagnesium compound to each acid hydrogen in a substituent of a molecule of Formula VIII is about 1:1 to about 1:1.4 and the mole ratio of the second organomagnesium compound to the compound of Formula VIII is about 1:0.8 to about 1:2. In another aspect of this embodiment, the first organomagnesium compound comprises an alkylmagnesium chloride, bromide, or iodide. In another aspect of this embodiment, the first organomagnesium compound comprises methylmagnesium chloride. In another aspect of this embodiment, the second organomagnesium compound comprises an alkylmagnesium chloride, bromide, or iodide. In another aspect of this embodiment, the second alkylmagnesium compound comprises 2-propylmagnesium chloride. In another aspect of this embodiment, the second organomagnesium compound comprises an alkylmagnesium chloride, bromide, or iodide and lithium chloride. In another aspect of this embodiment the second organomagnesium compound is 2-propylmagnesium chloride and lithium chloride in a 1:1 mole ratio. In a preferred aspect of this embodiment, the first organomagnesium compound is methylmagnesium chloride and the second organomagnesium compound comprises 2-propylmagnesium chloride. In another preferred aspect of this embodiment the first organomagnesium compound is methylmagnesium chloride and the second organomagnesium compound is 2-propylmagnesium chloride and lithium chloride in a 1:1 mole ratio. In another preferred aspect of this embodiment the first organomagnesium compound is methylmagnesium chloride, the second organomagnesium compound is 2-propylmagnesium chloride and lithium chloride in about 1:1 mole ratio, and the X^3 of Formula VIII is Br or I. In another preferred aspect of this embodiment the first organomagnesium compound is methylmagnesium chloride, the second organomagnesium compound is 2-propylmagnesium chloride and lithium chloride in about 1:1 mole ratio, the X^3 of Formula VIII is Br or I and R^8 is NH_2.

The magnesium salts of the substituents of Formula VIII discussed above may be converted to a protected form of the substituent such as, but not limited to, a silyl protected substituent. Subsequently, the X^3 group (Cl, Br, or I group) of the compound of Formula VIII may be transmetalated with the same or a different organomagnesium compound such as 2-propylmagnesium chloride or 2-

propylmagnesium chloride and lithium chloride. Similarly, if additional acidic hydrogens are present, an additional about one equivalent amount of organomagnesium compound would be required to neutralize each additional acidic hydrogen, e.g., each additional NH_2 substituent would require about two additional equivalents of organomagnesium compound and the resulting magnesium salts could be converted to protecting groups, such as but not limited to, silyl protecting groups. Non-limiting examples of the resulting protected substituents would be $OSi(R^{43})_3$, $SSi(R^{43})_3$, $N[Si(R^{43})_3][C_1\text{-}C_6$ alkyl], $N[Si(R^{43})_2(CH_2)_2$ $Si(R^{43})_2]$ and $N[Si(R^{43})_3]_2$. All such intermediates with protected substituents are within the scope of the instant invention. Non-limiting examples of silylating reagents to convert the intermediate magnesium salt of the substituents to protected substituents include $X^3Si(R^{43})_3$, $X^3Si(R^{43})_2(CH_2)_2Si(R^{43})_2X^3$ and $R^{57}S(O)_2OSi(R^{43})_3$; more specifically $ClSi(R^{43})_3$, $ClSi(R^{43})_2(CH_2)_2Si(R^{43})_2Cl$ and $CF_3S(O)_2OSi(R^{43})_3$; and most specifically $ClSi(CH_3)_3$, $ClSi(CH_3)_2(CH_2)_2$ $Si(CH_3)_2Cl$ and $CF_3S(O)_2OSi(CH_3)_3$. These silylating reagents may be present before the addition of the initial organometallic agent if the temperature of the reaction is sufficiently controlled or they may be added after conversion of the substituent to the magnesium salt. Typically, the conversion of substituents of Formula VIII with acidic hydrogens to protected substituents are performed in a suitable aprotic solvent at about -78 to about to abut 50 ^{0}C for about 5 minutes to 24 hours. Non-limiting examples of suitable aprotic solvents include THF, dioxane and ether.

In one embodiment, the compound of Formula VII is prepared by treating the compound of Formula VIII comprising substituents with acidic hydrogens with about one mole equivalent of a first organomagnesium compound for each acidic hydrogen in a substitutent, treatment with about 1-1.4 equivalents of protecting group reagent for each acid hydrogen, and treatment with 1-2 equivalents of the same or a different organomagnesium compound to transmetallate the X^3 group of Formula VIII.

In another embodiment, the compound of Formula VII is prepared by treating a mixture of compound of Formula VIII and about 1-1.4 equivalents of protecting group reagent per acidic hydrogen in Formula VIII with about 1-1.4 equivalents of a first organomagnesium compound for each acid hydrogen in a substitutent, followed

by treatment with 1-2 equivalents of the same or a different organomagnesium compound to transmetallate the X^3 group of Formula VIII.

In another embodiment, the compound of Formula VII is prepared by treating a mixture of compound of Formula VIII and about 1-1.4 equivalents of protecting reagent per acidic hydrogen in Formula VIII with about 1-1.4 equivalents of a organomagnesium compound for each acid hydrogen in a substitutent and an additional 1-2 equivalents of organomagnesium compound to transmetallate the X^3 group of Formula VIII. In another aspect of this embodiment, the X^3 of Formula VIII is Br or I and R^8 of Formula VIII is NH_2.

In another embodiment, the method of preparing a compound of Formula VII wherein M is Li comprises treating a compound of Formula VIII with an organolithium compound. Typically, the transmetalation reaction is performed in a suitable aprotic solvent at about -100 to about to abut 20 ^{0}C for about 5 minutes to 24 hours. Non-limiting examples of suitable aprotic solvents include THF and ether. In one aspect of this embodiment, the mole ratio of the compound of Formula VIII to organolithium compound is about 1:1 to about 1:3, preferably about 1:1.4. In another aspect of this embodiment, the organolithium compound comprises an alkyllithium compound. In another aspect of this embodiment, the organolithium compound comprises *n*-butyllithium. In another aspect of this embodiment, the organolithium compound comprises *iso*-butyllithium. In another aspect of this embodiment, the organolithium compound comprises *tert*-butyllithium. In a preferred aspect of this embodiment, the organolithium compound comprises an alkyllithium compound and the X^3 of Formula VIII is Br or I.

In another embodiment wherein the compound of Formula VII is prepared by treating a compound of Formula VIII with an organolithium compound, the compound of Formula VIII may be treated with more than one mole equivalent of organolithium compound. This procedure would be preferable when the compound of Formula V is comprised of a substituent with an acidic hydrogen. Non-limiting examples of the substituents with acidic hydrogens are NH_2, OH, SH, $NH(C_1$-C_6 alkyl) and the like. One skilled in the art will recognize that the acidic hydrogen group of the substituent of the compound of Formula VIII will consume one mole

equivalent of the organolithium compound. For example, but not by way of limitation, treating the compound of Formula V with about one mole equivalent of organolithium compound would neutralize an acidic hydrogen of NH(C_1-C_6 alkyl), OH, or SH substituent by forming a lithium salt and the X^3 group (Cl, Br, or I group) of the compound of Formula VIII may be transmetalated with another mole equivalent of organolithium compound. Similarly, if additional acidic hydrogens are present, an additional about equivalent amount of organolithium compound would be required to neutralize each additional acidic hydrogen, e.g., each additional NH_2 substituent would require about two additional equivalents of organolithium compound. Typically, the transmetalation reactions of this aspect are performed in a suitable aprotic solvent at about -100 to about to abut 20 ^{0}C for about 5 minutes to 24 hours. Non-limiting examples of suitable aprotic solvents include THF, dioxane and ether. In one aspect of this embodiment, the mole ratio of the organolithium compound to the each acid hydrogen in a substituent of a molecule of Formula VIII is about 1:1 to about 1:1.4 and the mole ratio of the additional amount of organolithium compound to the compound of Formula VIII is about 1:0.8 to about 1:1.4. In another aspect of this embodiment, the organolithium compound comprises an alkyllithium compound. In another aspect of this embodiment, the organolithium compound comprises *n*-butyllithium. In another aspect of this embodiment, the organolithium compound comprises *iso*-butyllithium. In another aspect of this embodiment, the organolithium compound comprises *tert*-butyllithium. In a preferred aspect of this embodiment, the organolithium compound comprises a (C_1-C_6)alkyllithium compound and the X^3 of Formula VIII is Br or I.

The lithium salts of the substituents of Formula VIII discussed above may be converted to a protected form of the substituent such as, but not limited to, a silyl protected substituent. Subsequently, the X^3 group (Cl, Br, or I group) of the compound of Formula VIII may be transmetalated with the same or a different organolithium compound. Similarly, if additional acidic hydrogens are present, an additional about one equivalent amount of organolithium compound would be required to neutralize each additional acidic hydrogen, e.g., each additional NH_2 substituent would require about two additional equivalents of organolithium

compound and the resulting lithium salts could be converted to protecting groups, such as but not limited to, silyl protecting groups. Non-limiting examples of the resulting protected substituents would be $OSi(R^{43})_3$, $SSi(R^{43})_3$, $N[Si(R^{43})_3][C_1\text{-}C_6$ alkyl], $N[Si(R^{43})_2(CH_2)_2\ Si(R^{43})_2]$ and $N[Si(R^{43})_3]_2$. All such intermediates with protected substituents are within the scope of the instant invention. Non-limiting examples of silylating reagents to convert the intermediate lithium salt of the substituents to protected substituents include $X^3Si(R^{43})_3$, $X^3Si(R^{43})_2(CH_2)_2\ Si(R^{43})_2X^3$ and $R^{57}S(O)_2OSi(R^{43})_3$; more specifically $ClSi(R^{43})_3$, $ClSi(R^{43})_2(CH_2)_2\ Si(R^{43})_2Cl$ and $CF_3S(O)_2OSi(R^{43})_3$, and most specifically $ClSi(CH_3)_3$, $ClSi(CH_3)_2(CH_2)_2\ Si(CH_3)_2Cl$ and $CF_3S(O)_2OSi(CH_3)_3$. These silylating reagents may be present before the addition of the initial organometallic agent if the temperature of the reaction is sufficiently controlled or they may be added after conversion of the substituent to the lithium salt.

Typically, the conversion of substituents of Formula VIII with acid hydrogens to protected substituents are performed in a suitable aprotic solvent at about -100 to about to abut 20 ^{0}C for about 5 minutes to 24 hours. Non-limiting examples of suitable aprotic solvents include THF, dioxane and ether.

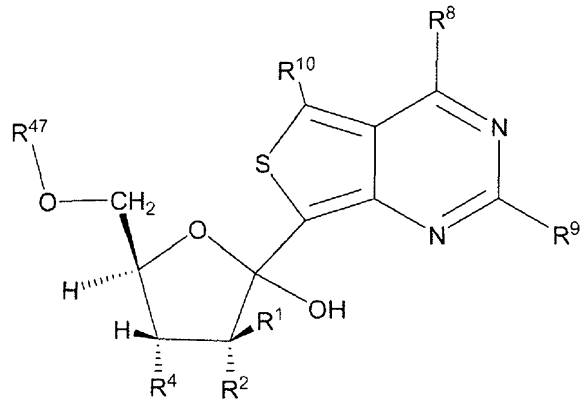
In one embodiment, the compound of Formula VII is prepared by treating the compound of Formula VIII comprising substituents with acid hydrogens with about 1-1.4 mole equivalent of a organolithium compound for each acid hydrogen in a substitutent, treatment with about 1-1.4 equivalents of protecting group reagent for each acid hydrogen, and treatment with 1-1.4 equivalents of the same or a different organolithium compound to transmetallate the X^3 group of Formula VIII.

In another embodiment, the compound of Formula VII is prepared by treating a mixture of compound of Formula VIII and about 1-1.4 equivalents of protecting group reagent per acidic hydrogen in Formula VIII with about 1-1.4 equivalents of a first organolithium compound for each acid hydrogen in a substitutent, followed by treatment with 1-1.4 equivalents of the same or a different organolithium compound to transmetallate the X^3 group of Formula VIII.

In another embodiment, the compound of Formula VII is prepared by treating a mixture of compound of Formula VIII and about 1-1.4 equivalents of protecting reagent per acidic hydrogen in Formula VIII with about 1-1.4 equivalents of a

organolithium compound for each acid hydrogen in a substitutent and an additional 1-1.4 equivalents of organolithium compound to transmetallate the X^3 group of Formula VIII. In another aspect of this embodiment, the X^3 of Formula VIII is Br or I. and R^8 of Formula VIII is NH_2. In another aspect of this embodiment, the organolithium compound comprises an alkyllithium compound. In another embodiment, the organolithium compound comprises *n*-butyllithium. In another embodiment, the organolithium compound comprises *iso*-butyllithium. In another embodiment, the organolithium compound comprises *tert*-butyllithium. In a preferred embodiment, the organolithium compound comprises a $(C_1\text{-}C_6)$alkyllithium compound and the X^3 of Formula VIII is Br or I. In another embodiment, the protecting group reagent is a silylating reagent. In another embodiment, the protecting group reagent is $X^3Si(R^{43})_3$ or $R^{57}S(O)_2OSi(R^{43})_3$. In another embodiment, the protecting group reagent is $ClSi(R^{43})_3$ or $CF_3S(O)_2OSi(R^{43})_3$. In another embodiment, the protecting group reagent is $ClSi(CH_3)_3$ or $CF_3S(O)_2OSi(CH_3)_3$.

Provided is a compound useful for the synthesis of an anti-viral compound of Formula Ib represented by Formula IX:



Formula IX

or an acceptable salt or ester, thereof;

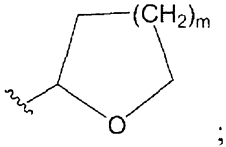
wherein:

R^1 is H, $(C_1\text{–}C_8)$alkyl, $(C_4\text{–}C_8)$carbocyclylalkyl, $(C_1\text{–}C_8)$substituted alkyl, $(C_2\text{–}C_8)$alkenyl, $(C_2\text{–}C_8)$substituted alkenyl, $(C_2\text{–}C_8)$alkynyl, $(C_2\text{–}C_8)$substituted alkynyl, or aryl$(C_1\text{-}C_8)$alkyl;

each R^2 or R^4 is independently H, F or OR^{44};

each R^{43} is independently $(C_1\text{-}C_8)$ alkyl, $(C_1\text{-}C_8)$ substituted alkyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heterocyclyl, C_2–C_{20} substituted heterocyclyl, $C_7\text{-}C_{20}$ arylalkyl, $C_7\text{-}C_{20}$ substituted arylalkyl, $(C_1\text{-}C_8)$ alkoxy, or $(C_1\text{-}C_8)$ substituted alkoxy;

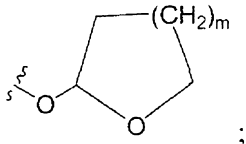
each R^{44} or R^{47} is independently $-C(R^{45})_2R^{46}$, $Si(R^{43})_3$, $C(O)R^{45}$, $C(O)OR^{45}$, $-(C(R^{45})_2)_m\text{-}R^{55}$ or



;

or any two of R^{44} or R^{47} when taken together are $-C(R^{59})_2$-, -C(O)- or -$Si(R^{43})_2(X^{42})_mSi(R^{43})_2$-;

each R^{55} is independently $-O\text{-}C(R^{45})_2R^{46}$, $-Si(R^{43})_3$, $-OC(O)OR^{45}$, $-OC(O)R^{45}$ or



;

each R^{45}, R^{58} or R^{59} is independently H, $(C_1\text{-}C_8)$ alkyl, $(C_1\text{-}C_8)$ substituted alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$ substituted alkenyl, $(C_2\text{-}C_8)$ alkynyl, $(C_2\text{-}C_8)$ substituted alkynyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heterocyclyl, C_2–C_{20} substituted heterocyclyl, $C_7\text{-}C_{20}$ arylalkyl or $C_7\text{-}C_{20}$ substituted arylalkyl;

each R^{46} is independently C_6–C_{20} aryl, C_6–C_{20} substituted aryl, or optionally substituted heteroaryl;

each R^a is independently H, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, aryl$(C_1\text{-}C_8)$alkyl, $(C_4$–$C_8)$carbocyclylalkyl, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, or $-SO_2NR^{11}R^{12}$;

each X^{42} is O or CH_2;

each m is 1 or 2;

each n is independently 0, 1 or 2;

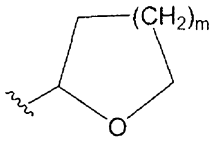
wherein:

R^1 is H, $(C_1–C_8)$alkyl, $(C_4–C_8)$carbocyclylalkyl, $(C_1–C_8)$substituted alkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$substituted alkenyl, $(C_2–C_8)$alkynyl, $(C_2–C_8)$substituted alkynyl, or aryl$(C_1$-$C_8)$alkyl;

each R^2 or R^4 is independently H, F or OR^{44};

each R^{43} is independently $(C_1$-$C_8)$ alkyl, $(C_1$-$C_8)$ substituted alkyl, $C_6–C_{20}$ aryl, $C_6–C_{20}$ substituted aryl, $C_2–C_{20}$ heterocyclyl, $C_2–C_{20}$ substituted heterocyclyl, C_7-C_{20} arylalkyl, C_7-C_{20} substituted arylalkyl, $(C_1$-$C_8)$ alkoxy, or $(C_1$-$C_8)$ substituted alkoxy;

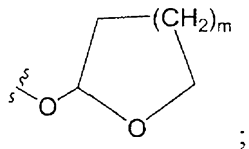
each R^{44} or R^{47} is independently $–C(R^{45})_2R^{46}$, $Si(R^{43})_3$, $C(O)R^{45}$, $C(O)OR^{45}$, $-(C(R^{45})_2)_m$-R^{55} or



;

or any two of R^{44} or R^{47} when taken together are $–C(R^{59})_2$-, -C(O)- or -$Si(R^{43})_2(X^{42})_mSi(R^{43})_2$-;

each R^{55} is independently $–O$-$C(R^{45})_2R^{46}$, -$Si(R^{43})_3$, $C(O)OR^{45}$, -$OC(O)R^{45}$ or



;

each R^{45}, R^{58} or R^{59} is independently H, $(C_1$-$C_8)$ alkyl, $(C_1$-$C_8)$ substituted alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$ substituted alkenyl, $(C_2$-$C_8)$ alkynyl, $(C_2$-$C_8)$ substituted alkynyl, $C_6–C_{20}$ aryl, $C_6–C_{20}$ substituted aryl, $C_2–C_{20}$ heterocyclyl, $C_2–C_{20}$ substituted heterocyclyl, C_7-C_{20} arylalkyl or C_7-C_{20} substituted arylalkyl;

each R^{46} is independently $C_6–C_{20}$ aryl, $C_6–C_{20}$ substituted aryl, or optionally substituted heteroaryl;

each R^a is independently H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, aryl$(C_1$-$C_8)$alkyl, $(C_4–C_8)$carbocyclylalkyl, -$C(=O)R^{11}$, -$C(=O)OR^{11}$, -$C(=O)NR^{11}R^{12}$, -$C(=O)SR^{11}$, -$S(O)R^{11}$, -$S(O)_2R^{11}$, -$S(O)(OR^{11})$, -$S(O)_2(OR^{11})$, or $–SO_2NR^{11}R^{12}$;

each X^{42} is O or CH_2;

each m is 1 or 2;

each n is independently 0, 1 or 2;

each R^8, R^9 or R^{10} is independently H, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3, NO, NO_2, CHO, CN, -CH(=NR^{11}), -CH=$NHNR^{11}$, -CH=$N(OR^{11})$, -$CH(OR^{11})_2$, -C(=O)$NR^{11}R^{12}$, -C(=S)$NR^{11}R^{12}$, -C(=O)OR^{11}, R^{11}, OR^{11} or SR^{11};

each R^{11} or R^{12} is independently H, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3–C_8)carbocyclyl, (C_4–C_8)carbocyclylalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(=O)(C_1-C_8)alkyl, -$S(O)_n$(C_1-C_8)alkyl, aryl(C_1-C_8)alkyl or $Si(R^3)_3$; or R^{11} and R^{12} taken together with a nitrogen to which they are both attached form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with -O-, -$S(O)_n$- or –NR^a-; or R^{11} and R^{12} taken together are -$Si(R^{43})_2(X^{42})_mSi(R^{43})_2$-; and

wherein each (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl or aryl(C_1-C_8)alkyl of each R^1, R^{43}, R^{45}, R^{58}, R^{59}, R^{11} or R^{12} is, independently, optionally substituted with one or more halo, hydroxy, CN, N_3, $N(R^a)_2$ or OR^a; and wherein one or more of the non-terminal carbon atoms of each said (C_1-C_8)alkyl is optionally replaced with -O-, -$S(O)_n$- or –NR^a-.

Additional independent embodiments of Formula IX are:

(a) R^1 is H. R^1 is CH_3.

(b) R^8 is $NR^{11}R^{12}$. R^8 is OR^{11}. R^8 is SR^{11}.

(c) R^9 is H. R^9 is $NR^{11}R^{12}$. R^9 is SR^{11}.

(b) R^8 is $NR^{11}R^{12}$. R^8 is OR^{11}. R^8 is SR^{11}.

(c) R^9 is H. R^9 is $NR^{11}R^{12}$. R^9 is SR^{11}.

(d) R^2 is OR^{44}. R^2 is F. Each R^4 and R^2 is independently OR^{44}. R^2 is OR^{44} and R^2 is F. R^4 is OR^{44}, R^2 is F and R^{44} is C(O)R^{45}. R^4 is OR^{44}, R^{2b} is F and R^{44} is C(O)R^{45} wherein R^{45} is phenyl or substituted phenyl. R^2 is OR^{44} wherein R^{44} is $C(R^{45})_2R^{46}$ and R^{46} is phenyl or substituted phenyl. R^2 is OR^{44} wherein R^{44} is CH_2R^{46} and R^{46} is phenyl. R^2 is OR^{44} wherein R^{44} is CH_2R^{46} and R^{46} is substituted phenyl. Each R^4 and R^2 is OR^{44} wherein each R^{44} is independently $C(R^{45})_2R^{46}$ and R^{46} is phenyl or substituted phenyl. Each R^4 and R^2 is OR^{44} wherein each R^{44} is CH_2R^{46} and R^{46} is phenyl. Each R^4 and R^2 is OR^{44} wherein each R^{44} is CH_2R^{46} and each R^{46} is independently substituted phenyl. Each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are –$C(R^{59})_2$-. Each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together

are $-C(CH_3)_2-$. Each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$. Each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$ wherein R^{59} is phenyl or substituted phenyl. R^4 is OR^{44} wherein R^{44} is $C(R^{45})_2R^{46}$, R^{46} is phenyl or substituted phenyl and R^2 is F. R^4 is H.

(e) R^{47} is $C(O)R^{45}$. R^{47} is $C(R^{45})_2R^{46}$ and R^{46} is phenyl or substituted phenyl. R^{47} is CH_2R^{46} and R^{46} is phenyl. R^{47} is CH_2R^{46} and R^{46} is substituted phenyl. R^{47} is $C(R^{45})_2R^{46}$ and each R^{45} and R^{46} is independently phenyl or substituted phenyl. R^{47} is $Si(R^{43})_3$. R^{47} is $Si(R^{43})_2(t\text{-butyl})$ wherein each R^{43} is CH_3. R^{47} is $Si(R^{43})_2(t\text{-butyl})$ wherein each R^{43} is independently phenyl or substituted phenyl. R^{47} is tetrahydro-*2H*-pyran-2-yl. R^{47} is $C(R^{45})_2R^{46}$ wherein each R^{45} and R^{46} is independently phenyl or substituted phenyl and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. R^{47} is $Si(R^{43})_3$ and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. R^{47} is $Si(R^{43})_2(t\text{-butyl})$ wherein each R^{43} is CH_3 and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. R^{47} is $Si(R^{43})_2(t\text{-butyl})$ wherein each R^{43} is independently phenyl or substituted phenyl and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. R^{47} is tetrahydro-*2H*-pyran-2-yl and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. R^{47} is $C(O)R^{45}$ and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. R^{47} is $C(R^{45})_2R^{46}$ wherein each R^{45} and R^{46} is independently phenyl or substituted phenyl and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$ wherein R^{59} is phenyl or substituted phenyl. R^{47} is $Si(R^{43})_3$ and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$ wherein R^{59} is phenyl or substituted phenyl. R^{47} is $Si(R^{43})_2(t\text{-butyl})$ wherein each R^{43} is CH_3 and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$ wherein R^{59} is phenyl or substituted phenyl. R^{47} is $Si(R^{43})_2(t\text{-butyl})$ wherein each R^{43} is independently phenyl or substituted phenyl and each $R^4$and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$ wherein R^{59} is phenyl or substituted phenyl. R^{47} is tetrahydro-*2H*-pyran-2-yl and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$ wherein R^{59} is phenyl or substituted phenyl. R^{47} is $C(O)R^{45}$ and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$ wherein

R^{59} is phenyl or substituted phenyl. R^{47} is $C(O)R^{45}$ wherein R^{45} is phenyl or substituted phenyl and R^2 is F.

(f) R^1 is H and R^8 is $NR^{11}R^{12}$. R^1 is H and R^8 is NH_2. R^1 is CH_3 and R^8 is $NR^{11}R^{12}$. R^1 is CH_3 and R^8 is NH_2. R^1 is H and R^9 is $NR^{11}R^{12}$. R^1 is H and R^9 is NH_2. R^1 is H and R^9 is SR^{11}. R^1 is H and R^9 is SH. R^1 is H and R^9 is H. R^1 is CH_3 and R^9 is $NR^{11}R^{12}$. R^1 is CH_3 and R^9 is NH_2. R^1 is CH_3 and R^9 is SR^{11}. R^1 is CH_3 and R^9 is SH. R^1 is CH_3 and R^9 is H.

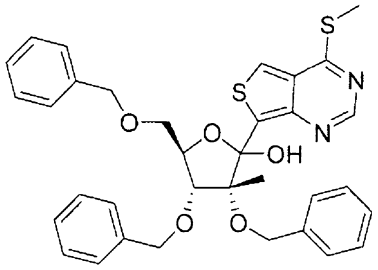
(g) R^1 is H and R^8 is OR^{11}. R^1 is H and R^8 is OH. R^1 is CH_3 and R^8 is OR^{11}. R^1 is CH_3 and R^8 is OH.

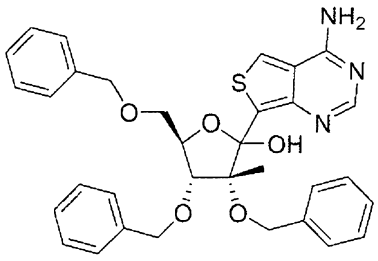
(h) R^1 is H and R^8 is SR^{11}. R^1 is H and R^8 is SH. R^1 is CH_3 and R^8 is SR^{11}. R^1 is CH_3 and R^8 is SH.

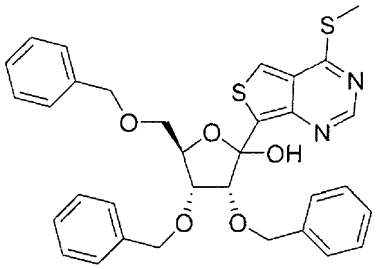
(i) R^1 is H, R^9 is H and R^8 is $NR^{11}R^{12}$. R^1 is H, R^9 is H and R^8 is NH_2. R^1 is CH_3, R^9 is H and R^8 is $NR^{11}R^{12}$. R^1 is CH_3, R^9 is H and R^8 is NH_2. R^1 is H, R^9 is $NR^{11}R^{12}$ and R^8 is $NR^{11}R^{12}$. R^1 is H, R^9 is $NR^{11}R^{12}$ and R^8 is NH_2. R^1 is CH_3, R^9 is $NR^{11}R^{12}$ and R^8 is $NR^{11}R^{12}$. R^1 is CH_3, R^9 is $NR^{11}R^{12}$ and R^8 is NH_2.

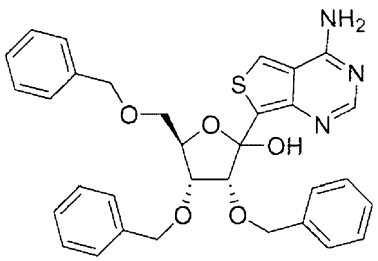
(j) R^1 is H and R^8 and R^9 are independently SR^{11}. R^1 is CH_3 and R^8 and R^9 are independently SR^{11}.

In another embodiment, the compound of Formula IX is selected from the group consisting of

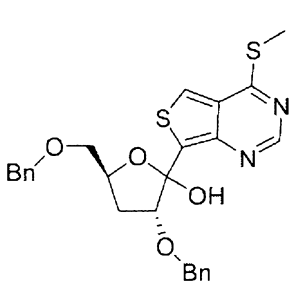
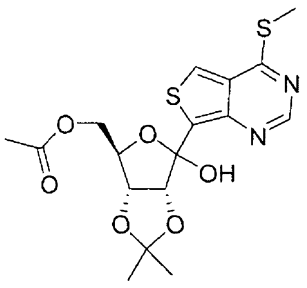
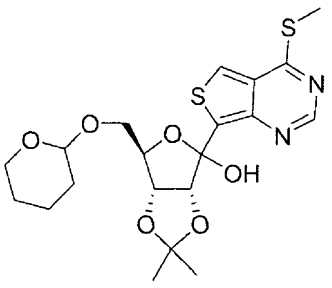
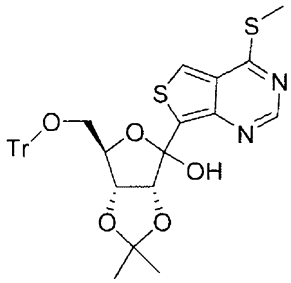
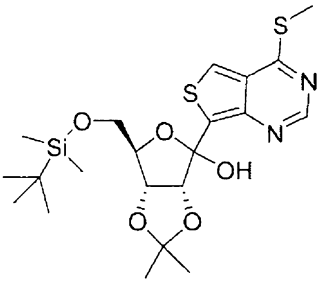
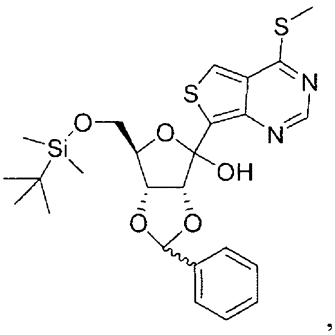
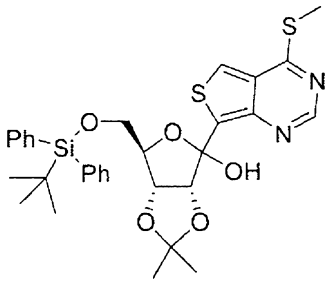
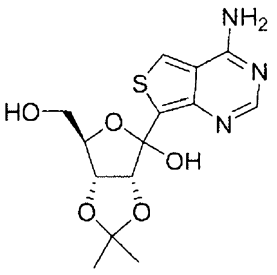


,


,


,


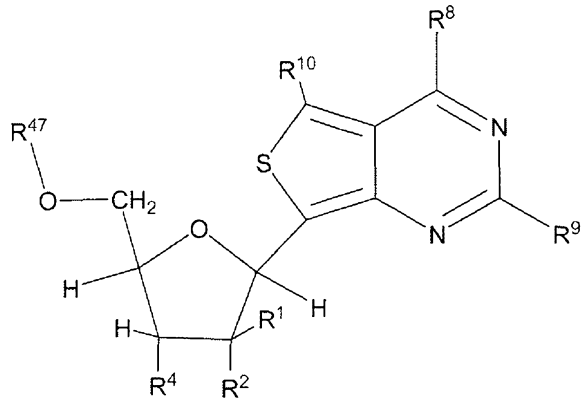
,

and or

a salt or ester thereof.

Provided is a method for preparing a compound of Formula X:



Formula X

or an acceptable salt or ester, thereof;

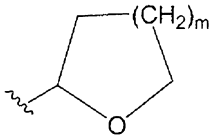
wherein:

R^1 is H, (C_1–C_8)alkyl, (C_4–C_8)carbocyclylalkyl, (C_1–C_8)substituted alkyl, (C_2–C_8)alkenyl, (C_2–C_8)substituted alkenyl, (C_2–C_8)alkynyl, (C_2–C_8)substituted alkynyl, or aryl(C_1-C_8)alkyl;

each R^2 or R^4 is independently H, F or OR^{44};

each R^{43} is independently (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heterocyclyl, C_2–C_{20} substituted heterocyclyl, C_7-C_{20} arylalkyl, C_7-C_{20} substituted arylalkyl, (C_1-C_8) alkoxy, or (C_1-C_8) substituted alkoxy;

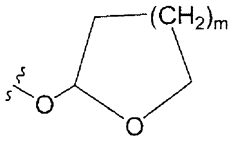
each R^{44} or R^{47} is independently $-C(R^{45})_2R^{46}$, $Si(R^{43})_3$, $C(O)R^{45}$, $C(O)OR^{45}$, $-(C(R^{45})_2)_m$-R^{55} or



;

or any two of R^{44} or R^{47} when taken together are $-C(R^{59})_2$-, -C(O)- or -$Si(R^{43})_2(X^{42})_mSi(R^{43})_2$-;

each R^{55} is independently $-O$-$C(R^{45})_2R^{46}$, -$Si(R^{43})_3$, -$OC(O)OR^{45}$, -$OC(O)R^{45}$ or



;

each R^{45}, R^{58} or R^{59} is independently H, (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8)alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heterocyclyl, C_2–C_{20} substituted heterocyclyl, C_7-C_{20} arylalkyl or C_7-C_{20} substituted arylalkyl;

each R^{46} is independently C_6–C_{20} aryl, C_6–C_{20} substituted aryl, or optionally substituted heteroaryl;

each R^a is independently H, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, aryl(C_1-C_8)alkyl, (C_4–C_8)carbocyclylalkyl, -$C(=O)R^{11}$, -$C(=O)OR^{11}$, -$C(=O)NR^{11}R^{12}$, -$C(=O)SR^{11}$, -$S(O)R^{11}$, -$S(O)_2R^{11}$, -$S(O)(OR^{11})$, -$S(O)_2(OR^{11})$, or $-SO_2NR^{11}R^{12}$;

each X^{42} is O or CH_2;

each m is 1 or 2;

each n is independently 0, 1 or 2;

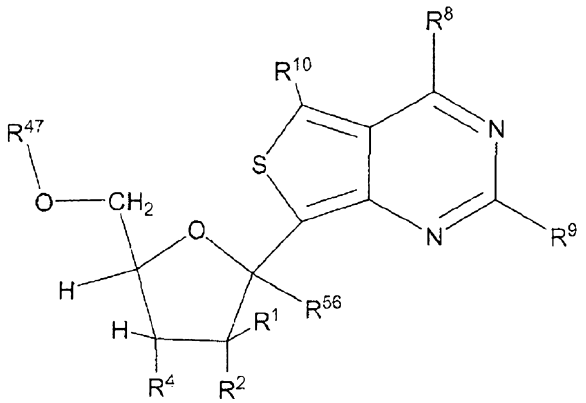
each R^8, R^9 or R^{10} is independently H, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3, NO, NO_2, CHO, CN, $-CH(=NR^{11})$, $-CH=NHNR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, R^{11}, OR^{11} or SR^{11};

each R^{11} or R^{12} is independently H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$–$C_8)$carbocyclyl, $(C_4$–$C_8)$carbocyclylalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)(C_1$-$C_8)$alkyl, $-S(O)_n(C_1$-$C_8)$alkyl, aryl$(C_1$-$C_8)$alkyl or $Si(R^3)_3$; or R^{11} and R^{12} taken together with a nitrogen to which they are both attached form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with -O-, $-S(O)_n$- or $-NR^a$-; or R^{11} and R^{12} taken together are $-Si(R^{43})_2(X^{42})_mSi(R^{43})_2$-;

wherein each $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl or aryl$(C_1$-$C_8)$alkyl of each R^1, R^{43}, R^{45}, R^{58}, R^{59}, R^{11} or R^{12} is, independently, optionally substituted with one or more halo, hydroxy, CN, N_3, $N(R^a)_2$ or OR^a; and wherein one or more of the non-terminal carbon atoms of each said $(C_1$-$C_8)$alkyl is optionally replaced with -O-, $-S(O)_n$- or $-NR^a$-;

said method comprising :

(a) providing a compound of Formula V



Formula V

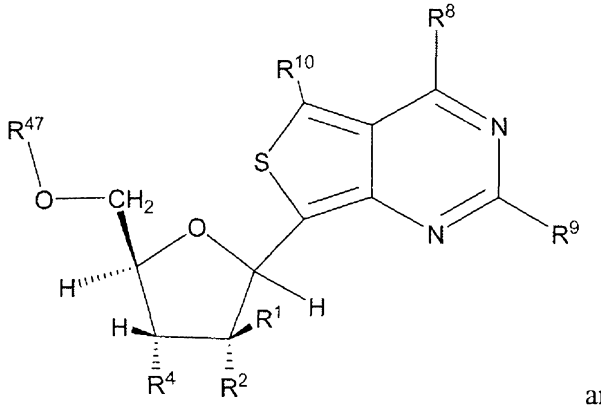
wherein R^{56} is OH, $-OC(O)OR^{58}$ or $-OC(O)R^{58}$;

(b) treating the compound of Formula V with a Lewis acid and a reducing agent that is $HSi(R^{43})_3$;

thereby forming the compound of Formula X.

The compounds of Formula X are useful for the preparation of anti-viral compounds of Formula I.

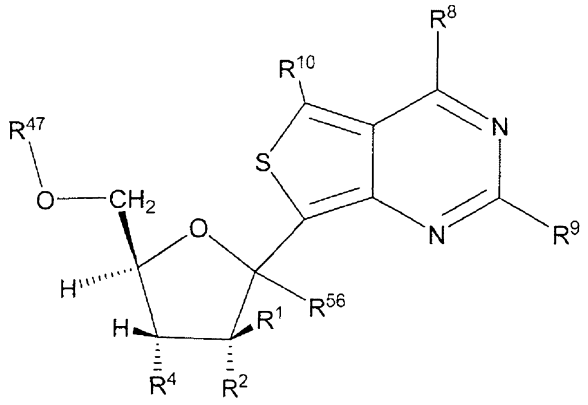
In one embodiment of the method, the compound of Formula X is Formula Xb



Formula Xb

and

the compound of Formula V is Formula Vb:



Typically, the method of preparing compounds of Formula Xb from Formula Vb is preformed in a suitable aprotic solvent at about -78 to 80 °C for about 10 minutes to 7 days. Non-limiting examples of suitable aprotic solvents include CH_2Cl_2, acetonitrile, CH_2ClCH_2Cl or other halocarbon solvents. More typically, the method is performed at about -78 to about 25 °C for about 3 hours to 7 days. The mole ratio of

the compound of Formula Vb to $HSi(R^{43})_3$ is about 1:1 to 1:10, more typically about 1:2 to 1:6. The mole ratio of the compound of Formula Vb to Lewis acid is about 1:0.1 to about 1:10, more typically about 1:1 to about 1:6. Typically the mole ratio of Lewis acid to $HSi(R^{43})_3$ is about 0.1: 1 to about 1:10; preferably about 1:1.

The conversion of the compound of Formula Vb to a compound of Formula Xb is promoted by Lewis acids. Many Lewis acids may promote this conversion including many that are commercially available. Non-limiting examples of Lewis acids comprising boron that are suitable for promoting this conversion are boron trifluoride etherates of methyl, ethyl, propyl, and butyl ethers; boron trifluoride-*tert*-butyl methyl etherate; boron trifluoride and boron trifluoride methyl sulfide complex. Non-limiting examples of Lewis acids comprising trialkylsilyl groups that are suitable for promoting this conversion are trimethylsilyl trifluoromethanesulfonate, other trimethylsilyl polyfluoroalkylsulfonates, *tert*-butyldimethylsilyl trifluoromethanesulfonate and triethylsilyl trifluoromethanesulfonate. Additional non-limiting examples of Lewis acids suitable for promoting this conversion are $TiCl_4$, $AlCl_3$, $ZnCl_2$, ZnI_2, $SnCl_4$, $InCl_3$, Sc(trifluoromethanesulfonate)$_3$, silver trifluoromethanesulfonate, zinc trifluoromethanesulfonate, magnesium trifluoromethanesulfonate, thallium triflate, lanthanum trifluoromethanesulfonate, indium(III) trifluoromethanesulfonate, cerium(IV) trifluoromethanesulfonate, erbium(III) trifluoromethanesulfonate, gadolinium(III) trifluoromethanesulfonate, lutetium(III) trifluoromethanesulfonate, neodymium(III) trifluoromethanesulfonate, praseodymium(III) trifluoromethanesulfonate, samarium(III) trifluoromethanesulfonate, terbium(III) trifluoromethanesulfonate, dysprosium(III) trifluoromethanesulfonate, europium trifluoromethanesulfonate, holmium(III) trifluoromethanesulfonate, thulium(III) trifluoromethanesulfonate, yttrium(III) trifluoromethanesulfonate, trifluoromethanesulfonic acid nickel salt, hafnium trifluoromehtanesulfonate, bismuth(III) trifluoromethanesulfonate, gallium(III) trifluoromethanesulfonate, cerium(III) trifluoromethanesulfonate, ytterbium(III) trifluoromethanesulfonate, tellurium(IV) trifluoromethanesulfonate, zirconium(IV) trifluoromethanesulfonate, bismuth trifluoromethanesulfonate, iron(II) trifluoromethanesulfonate, Sn(trifluoromethanesulfonate)$_2$, $InBr_3$, $AuCl_3$, montmorilite

clays, Cu(trifluoromethanesulfonate)$_2$, vanadyl trifluoromethanesulfonate, and salen complexes of Ti and Vn (Belokon, et al., Tetrahedron 2001, 771). In a preferred embodiment, the Lewis acid is boron trifluoride etherate. In another preferred embodiment, the Lewis acid is boron trifluoride etherate and the yield of the compound of Formula Xb is 50% or greater. In another preferred embodiment, the Lewis acid is boron trifluoride etherate and the yield of the compound of Formula Xb is 70% or greater. In another preferred embodiment, the Lewis acid is boron trifluoride etherate and the yield of the compound of Formula Xb is 90% or greater.

In another embodiment of the method of preparing a compound of Formula Xb, R^{56} of Formula Vb is OH. Additional independent aspects of this embodiment are:

(a) R^1 is H. R^1 is CH_3.

(b) R^8 is $NR^{11}R^{12}$. R^8 is OR^{11}. R^8 is SR^{11}.

(c) R^9 is H. R^9 is $NR^{11}R^{12}$. R^9 is SR^{11}.

(d) R^2 is OR^{44}. R^2 is F. Each R^4 and R^2 is independently OR^{44}. R^2 is OR^{44} and R^2 is F. R^4 is OR^{44}, R^2 is F and R^{44} is $C(O)R^{45}$. R^4 is OR^{44}, R^{2b} is F and R^{44} is $C(O)R^{45}$ wherein R^{45} is phenyl or substituted phenyl. R^2 is OR^{44} wherein R^{44} is $C(R^{45})_2R^{46}$ and R^{46} is phenyl or substituted phenyl. R^2 is OR^{44} wherein R^{44} is CH_2R^{46} and R^{46} is phenyl. R^2 is OR^{44} wherein R^{44} is CH_2R^{46} and R^{46} is substituted phenyl. Each R^4 and R^2 is OR^{44} wherein each R^{44} is independently $C(R^{45})_2R^{46}$ and R^{46} is phenyl or substituted phenyl. Each R^4 and R^2 is OR^{44} wherein each R^{44} is CH_2R^{46} and R^{46} is phenyl. Each R^4 and R^2 is OR^{44} wherein each R^{44} is CH_2R^{46} and each R^{46} is independently substituted phenyl. Each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(R^{59})_2-$. Each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. Each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$. Each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$ wherein R^{59} is phenyl or substituted phenyl. R^4 is OR^{44} wherein R^{44} is $C(R^{45})_2R^{46}$, R^{46} is phenyl or substituted phenyl and R^2 is F. R^4 is H.

(e) R^{47} is $C(O)R^{45}$. R^{47} is $C(R^{45})_2R^{46}$ and R^{46} is phenyl or substituted phenyl. R^{47} is CH_2R^{46} and R^{46} is phenyl. R^{47} is CH_2R^{46} and R^{46} is substituted phenyl. R^{47} is $C(R^{45})_2R^{46}$ and each R^{45} and R^{46} is independently phenyl or substituted phenyl. R^{47} is

$Si(R^{43})_3$. R^{47} is $Si(R^{43})_2$(*t*-butyl) wherein each R^{43} is CH_3. R^{47} is $Si(R^{43})_2$(*t*-butyl) wherein each R^{43} is independently phenyl or substituted phenyl. R^{47} is tetrahydro-*2H*-pyran-2-yl. R^{47} is $C(R^{45})_2R^{46}$ wherein each R^{45} and R^{46} is independently phenyl or substituted phenyl and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. R^{47} is $Si(R^{43})_3$ and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. R^{47} is $Si(R^{43})_2$(*t*-butyl) wherein each R^{43} is CH_3 and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. R^{47} is $Si(R^{43})_2$(*t*-butyl) wherein each R^{43} is independently phenyl or substituted phenyl and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. R^{47} is tetrahydro-*2H*-pyran-2-yl and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. R^{47} is $C(O)R^{45}$ and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-C(CH_3)_2-$. R^{47} is $C(R^{45})_2R^{46}$ wherein each R^{45} and R^{46} is independently phenyl or substituted phenyl and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$ wherein R^{59} is phenyl or substituted phenyl. R^{47} is $Si(R^{43})_3$ and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$ wherein R^{59} is phenyl or substituted phenyl. R^{47} is $Si(R^{43})_2$(*t*-butyl) wherein each R^{43} is CH_3 and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$ wherein R^{59} is phenyl or substituted phenyl. R^{47} is $Si(R^{43})_2$(*t*-butyl) wherein each R^{43} is independently phenyl or substituted phenyl and each $R^4$and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$ wherein R^{59} is phenyl or substituted phenyl. R^{47} is tetrahydro-*2H*-pyran-2-yl and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$ wherein R^{59} is phenyl or substituted phenyl. R^{47} is $C(O)R^{45}$ and each R^4 and R^2 is OR^{44} wherein the two R^{44} taken together are $-CH(R^{59})-$ wherein R^{59} is phenyl or substituted phenyl. R^{47} is $C(O)R^{45}$ wherein R^{45} is phenyl or substituted phenyl and R^2 is F.

(f) The reducing agent is $(R^{43})_3SiH$. The reducing agent is $(R^{43})_3SiH$ wherein R^{43} is (C_1-C_8) alkyl or substituted (C_1-C_8) alkyl. The reducing agent is $(CH_3CH_2)_3SiH$.

(g) The Lewis acid comprises boron. The Lewis acid comprises BF_3 or BCl_3. The Lewis acid is BF_3-$O(R^{53})_2$, BF_3-$S(R^{53})_2$, BCl_3- $O(R^{53})_2$ or BCl_3- $S(R^{53})_2$ wherein each R^{53} is independently (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8)alkenyl,

2010213873 03 Jun 2015

(C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heterocyclyl, C_2–C_{20} substituted heterocyclyl, C_7-C_{20} arylalkyl, or C_7-C_{20} substituted arylalkyl; wherein each (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl or aryl(C_1-C_8)alkyl of each R^{53} is, independently, optionally substituted with one or more halogens and wherein one or more of the non-terminal carbon atoms of each said (C_1-C_8)alkyl is optionally replaced with -O- or $-S(O)_n-$; or two R^{53} when taken together with the oxygen to which they are both attached form a 3 to 7 membered heterocyclic ring wherein one carbon atom of said heterocyclic ring can optionally be replaced with -O- or $-S(O)_n-$. The Lewis acid is BF_3-$O(R^{53})_2$ and R^{53} is (C_1-C_8) alkyl. The Lewis acid comprises $R^{57}S(O)_2OSi(R^{53})_3$ wherein R^{57} is substituted with two or more halogens and is (C_1-C_8)alkyl or substituted (C_1-C_8)alkyl. The Lewis acid is $R^{57}S(O)_2OSi(CH_3)_3$ and R^{57} is (C_1-C_8)alkyl substituted with three or more fluorines. The Lewis acid is trimethylsilyltriflate. The Lewis acid comprises a transition metal or salt thereof. The Lewis acid comprises titanium or a salt thereof. The Lewis acid comprises $TiCl_4$. The Lewis acid comprises a lanthanide or a salt thereof. The Lewis acid comprises scandium or a salt thereof. The Lewis acid comprises vanadium or a salt thereof. The Lewis acid comprises tin or a salt thereof. The Lewis acid comprises $SnCl_4$. The Lewis acid comprises zinc or a salt thereof. The Lewis acid comprises $ZnCl_2$. The Lewis acid comprises samarium or a salt thereof. The Lewis acid comprises nickel or a salt thereof. The Lewis acid comprises copper or a salt thereof. The Lewis acid comprises aluminum or a salt thereof. The Lewis acid comprises gold or a salt thereof. The Lewis acid comprises zinc trifluoromethanesulfonate. The Lewis acid comprises indium(III) trifluoromethanesulfonate, The Lewis acid comprises scandium(III) trifluoromethanesulfonate. The Lewis acid comprises yttrium(III) trifluoromethanesulfonate.

DEFINITIONS

Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings:

As used herein, except where the context requires otherwise, the term "comprise" and variations of the term, such as "comprising", "comprises" and "comprised", are not intended to exclude other additives, components, integers or steps.

When trade names are used herein, applicants intend to independently include the tradename product and the active pharmaceutical ingredient(s) of the tradename product.

As used herein, "a compound of the invention" or "a compound of Formula I" means a compound of Formula I or a pharmaceutically acceptable salt, thereof. Similarly, with respect to isolatable intermediates, the phrase "a compound of Formula (number)" means a compound of that formula and pharmaceutically acceptable salts, thereof.

"Alkyl" is hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms. For example, an alkyl group can have 1 to 20 carbon atoms (*i.e*, C_1-C_{20} alkyl), 1 to 8 carbon atoms (*i.e.*, C_1-C_8 alkyl), or 1 to 6 carbon atoms (*i.e.*, C_1-C_6 alkyl). Examples of suitable alkyl groups include, but are not limited to, methyl (Me, -CH_3), ethyl (Et, -CH_2CH_3), 1-propyl (n-Pr, n-propyl, -$CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, -$CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, -$CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, -$CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, -$CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, -$C(CH_3)_3$), 1-pentyl (n-pentyl, -$CH_2CH_2CH_2CH_2CH_3$), 2-pentyl (-$CH(CH_3)CH_2CH_2CH_3$), 3-pentyl (-$CH(CH_2CH_3)_2$), 2-methyl-2-butyl (-$C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl (-$CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl (-$CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl (-$CH_2CH(CH_3)CH_2CH_3$), 1-hexyl (-$CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl (-$CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl (-$CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl (-$C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl (-$CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl (-$CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl (-$C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl (-$CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl (-$C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl (-$CH(CH_3)C(CH_3)_3$, and octyl (-$(CH_2)_7CH_3$).

"Alkoxy" means a group having the formula –O-alkyl, in which an alkyl group, as defined above, is attached to the parent molecule via an oxygen atom. The alkyl portion of an alkoxy group can have 1 to 20 carbon atoms (*i.e.*, C_1-C_{20} alkoxy), 1 to 12 carbon atoms(*i.e.*, C_1-C_{12} alkoxy), or 1 to 6 carbon atoms(*i.e.*, C_1-C_6 alkoxy). Examples of suitable alkoxy groups include, but are not limited to, methoxy (-O-CH_3 or –OMe), ethoxy (-OCH_2CH_3 or -OEt), t-butoxy (-O-$C(CH_3)_3$ or –OtBu) and the

like.

"Haloalkyl" is an alkyl group, as defined above, in which one or more hydrogen atoms of the alkyl group is replaced with a halogen atom. The alkyl portion of a haloalkyl group can have 1 to 20 carbon atoms (*i.e.*, C_1-C_{20} haloalkyl), 1 to 12 carbon atoms(*i.e.*, C_1-C_{12} haloalkyl), or 1 to 6 carbon atoms(*i.e.*, C_1-C_6 alkyl). Examples of suitable haloalkyl groups include, but are not limited to, $-CF_3$, $-CHF_2$, $-CFH_2$, $-CH_2CF_3$, and the like.

"Alkenyl" is a hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, *i.e.* a carbon-carbon, sp^2 double bond. For example, an alkenyl group can have 2 to 20 carbon atoms (*i.e.*, C_2-C_{20} alkenyl), 2 to 8 carbon atoms (*i.e.*, C_2-C_8 alkenyl), or 2 to 6 carbon atoms (*i.e.*, C_2-C_6 alkenyl). Examples of suitable alkenyl groups include, but are not limited to, ethylene or vinyl ($-CH=CH_2$), allyl ($-CH_2CH=CH_2$), cyclopentenyl ($-C_5H_7$), and 5-hexenyl ($-CH_2CH_2CH_2CH_2CH=CH_2$).

"Alkynyl" is a hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, *i.e.* a carbon-carbon, *sp* triple bond. For example, an alkynyl group can have 2 to 20 carbon atoms (*i.e.*, C_2-C_{20} alkynyl), 2 to 8 carbon atoms (*i.e.*, C_2-C_8 alkyne,), or 2 to 6 carbon atoms (*i.e.*, C_2-C_6 alkynyl). Examples of suitable alkynyl groups include, but are not limited to, acetylenic ($-C\equiv CH$), propargyl ($-CH_2C\equiv CH$), and the like.

"Alkylene" refers to a saturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. For example, an alkylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Typical alkylene radicals include, but are not limited to, methylene ($-CH_2-$), 1,1-ethyl ($-CH(CH_3)-$), 1,2-ethyl ($-CH_2CH_2-$), 1,1-propyl ($-CH(CH_2CH_3)-$), 1,2-propyl ($-CH_2CH(CH_3)-$), 1,3-propyl ($-CH_2CH_2CH_2-$), 1,4-butyl ($-CH_2CH_2CH_2CH_2-$), and the like.

"Alkenylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkene.

For example, and alkenylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Typical alkenylene radicals include, but are not limited to, 1,2-ethylene (-CH=CH-).

"Alkynylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkyne. For example, an alkynylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Typical alkynylene radicals include, but are not limited to, acetylene (-C≡C-), propargyl (-CH_2C≡C-), and 4-pentynyl (-$CH_2CH_2CH_2$C≡CH-).

"Amino" refers generally to a nitrogen radical which can be considered a derivative of ammonia, having the formula –$N(X)_2$, where each "X" is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, etc. The hybridization of the nitrogen is approximately sp^3. Nonlimiting types of amino include –NH_2, -$N(alkyl)_2$, -NH(alkyl), -$N(carbocyclyl)_2$, -NH(carbocyclyl), -$N(heterocyclyl)_2$, -NH(heterocyclyl), -$N(aryl)_2$, -NH(aryl), -N(alkyl)(aryl), -N(alkyl)(heterocyclyl), -N(carbocyclyl)(heterocyclyl), -N(aryl)(heteroaryl), -N(alkyl)(heteroaryl), etc. The term "alkylamino" refers to an amino group substituted with at least one alkyl group. Nonlimiting examples of amino groups include –NH_2, -$NH(CH_3)$, -$N(CH_3)_2$, -$NH(CH_2CH_3)$, -$N(CH_2CH_3)_2$, -NH(phenyl), -$N(phenyl)_2$, -NH(benzyl), -$N(benzyl)_2$, etc. Substituted alkylamino refers generally to alkylamino groups, as defined above, in which at least one substituted alkyl, as defined herein, is attached to the amino nitrogen atom. Non-limiting examples of substituted alkylamino includes -NH(alkylene-C(O)-OH), -NH(alkylene-C(O)-O-alkyl), -N(alkylene-C(O)-$OH)_2$, -N(alkylene-C(O)-O-$alkyl)_2$, etc.

"Aryl" means an aromatic hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. For example, an aryl group can have 6 to 20 carbon atoms, 6 to 14 carbon atoms, or 6 to 10 carbon atoms. Typical aryl groups include, but are not limited to, radicals derived from benzene (e.g., phenyl), substituted benzene, naphthalene, anthracene, biphenyl, and the like.

"Arylalkyl" refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with an aryl radical. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. The arylalkyl group can comprise 7 to 20 carbon atoms, *e.g.*, the alkyl moiety is 1 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms.

"Arylalkenyl" refers to an acyclic alkenyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also an sp^2 carbon atom, is replaced with an aryl radical. The aryl portion of the arylalkenyl can include, for example, any of the aryl groups disclosed herein, and the alkenyl portion of the arylalkenyl can include, for example, any of the alkenyl groups disclosed herein. The arylalkenyl group can comprise 8 to 20 carbon atoms, *e.g.*, the alkenyl moiety is 2 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms.

"Arylalkynyl" refers to an acyclic alkynyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also an sp carbon atom, is replaced with an aryl radical. The aryl portion of the arylalkynyl can include, for example, any of the aryl groups disclosed herein, and the alkynyl portion of the arylalkynyl can include, for example, any of the alkynyl groups disclosed herein. The arylalkynyl group can comprise 8 to 20 carbon atoms, *e.g.*, the alkynyl moiety is 2 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms.

The term "substituted" in reference to alkyl, alkylene, aryl, arylalkyl, alkoxy, heterocyclyl, heteroaryl, carbocyclyl, etc. , for example, "substituted alkyl", "substituted alkylene", "substituted aryl", "substituted arylalkyl", "substituted heterocyclyl", and "substituted carbocyclyl" means alkyl, alkylene, aryl, arylalkyl, heterocyclyl, carbocyclyl respectively, in which one or more hydrogen atoms are each independently replaced with a non-hydrogen substituent. Typical substituents include, but are not limited to, -X, $-R^b$, $-O^-$, =O, $-OR^b$, $-SR^b$, $-S^-$, $-NR^b_2$, $-N^+R^b_3$, $=NR^b$, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, $-NHC(=O)R^b$, $-OC(=O)R^b$, $-NHC(=O)NR^b_2$, $-S(=O)_2-$, $-S(=O)_2OH$, $-S(=O)_2R^b$, $-OS(=O)_2OR^b$, $-S(=O)_2NR^b_2$, $-S(=O)R^b$, $-OP(=O)(OR^b)_2$, $-P(=O)(OR^b)_2$, $-P(=O)(O^-)_2$, $-P(=O)(OH)_2$,

$-P(O)(OR^b)(O^-)$, $-C(=O)R^b$, -C(=O)X, $-C(S)R^b$, $-C(O)OR^b$, $-C(O)O^-$, $-C(S)OR^b$, $-C(O)SR^b$, $-C(S)SR^b$, $-C(O)NR^b_2$, $-C(S)NR^b_2$, $-C(=NR^b)NR^b_2$, where each X is independently a halogen: F, Cl, Br, or I; and each R^b is independently H, alkyl, aryl, arylalkyl, a heterocycle, or a protecting group or prodrug moiety. Alkylene, alkenylene, and alkynylene groups may also be similarly substituted. Unless otherwise indicated, when the term "substituted" is used in conjunction with groups such as arylalkyl, which have two or more moieties capable of substitution, the substituents can be attached to the aryl moiety, the alkyl moiety, or both.

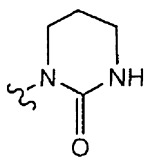
The term "prodrug" as used herein refers to any compound that when administered to a biological system generates the drug substance, i.e., active ingredient, as a result of spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s), photolysis, and/or metabolic chemical reaction(s). A prodrug is thus a covalently modified analog or latent form of a therapeutically active compound.

One skilled in the art will recognize that substituents and other moieties of the compounds of Formula I-III should be selected in order to provide a compound which is sufficiently stable to provide a pharmaceutically useful compound which can be formulated into an acceptably stable pharmaceutical composition. Compounds of Formula I-III which have such stability are contemplated as falling within the scope of the present invention.

"Heteroalkyl" refers to an alkyl group where one or more carbon atoms have been replaced with a heteroatom, such as, O, N, or S. For example, if the carbon atom of the alkyl group which is attached to the parent molecule is replaced with a heteroatom (e.g., O, N, or S) the resulting heteroalkyl groups are, respectively, an alkoxy group (e.g., $-OCH_3$, etc.), an amine (e.g., $-NHCH_3$, $-N(CH_3)_2$, etc.), or a thioalkyl group (e.g., $-SCH_3$). If a non-terminal carbon atom of the alkyl group which is not attached to the parent molecule is replaced with a heteroatom (e.g., O, N, or S) the resulting heteroalkyl groups are, respectively, an alkyl ether (e.g., $-CH_2CH_2-O-CH_3$, etc.), an alkyl amine (e.g., $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, etc.), or a thioalkyl ether (e.g.,$-CH_2-S-CH_3$). If a terminal carbon atom of the alkyl group is replaced with a heteroatom (e.g., O, N, or S), the resulting heteroalkyl groups are, respectively, a hydroxyalkyl group (e.g., $-CH_2CH_2-OH$), an aminoalkyl group (e.g., $-CH_2NH_2$), or an alkyl thiol group (e.g.,

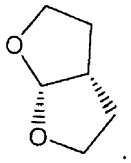
-CH_2CH_2-SH). A heteroalkyl group can have, for example, 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. A C_1-C_6 heteroalkyl group means a heteroalkyl group having 1 to 6 carbon atoms.

"Heterocycle" or "heterocyclyl" as used herein includes by way of example and not limitation those heterocycles described in Paquette, Leo A.; Principles of Modern Heterocyclic Chemistry (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; The Chemistry of Heterocyclic Compounds, A Series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and *J. Am. Chem. Soc.* (1960) 82:5566. In one specific embodiment of the invention "heterocycle" includes a "carbocycle" as defined herein, wherein one or more (*e.g.* 1, 2, 3, or 4) carbon atoms have been replaced with a heteroatom (*e.g.* O, N, or S). The terms "heterocycle" or "heterocyclyl" includes saturated rings, partially unsaturated rings, and aromatic rings (*i.e.*, heteroaromatic rings). Substituted heterocyclyls include, for example, heterocyclic rings substituted with any of the substituents disclosed herein including carbonyl groups. A non-limiting example of a carbonyl substituted heterocyclyl is:



Examples of heterocycles include by way of example and not limitation pyridyl, dihydroypyridyl, tetrahydropyridyl (piperidyl), thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1H-indazoly, purinyl, 4H-quinolizinyl,

phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, ß-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, isatinoyl, and bis-tetrahydrofuranyl:



By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

By way of example and not limitation, nitrogen bonded heterocycles are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or ß-carboline. Still more typically, nitrogen bonded heterocycles include 1-aziridyl, 1-azetedyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

"Heterocyclylalkyl" refers to an acyclic alkyl radical in which one of the

hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with a heterocyclyl radical (*i.e.*, a heterocyclyl-alkylene- moiety). Typical heterocyclyl alkyl groups include, but are not limited to heterocyclyl-CH_2-, 2-(heterocyclyl)ethan-1-yl, and the like, wherein the "heterocyclyl" portion includes any of the heterocyclyl groups described above, including those described in Principles of Modern Heterocyclic Chemistry. One skilled in the art will also understand that the heterocyclyl group can be attached to the alkyl portion of the heterocyclyl alkyl by means of a carbon-carbon bond or a carbon-heteroatom bond, with the proviso that the resulting group is chemically stable. The heterocyclyl alkyl group comprises 3 to 20 carbon atoms, *e.g.*, the alkyl portion of the arylalkyl group is 1 to 6 carbon atoms and the heterocyclyl moiety is 2 to 14 carbon atoms. Examples of heterocyclylalkyls include by way of example and not limitation 5-membered sulfur, oxygen, and/or nitrogen containing heterocycles such as thiazolylmethyl, 2-thiazolylethan-1-yl, imidazolylmethyl, oxazolylmethyl, thiadiazolylmethyl, etc., 6-membered sulfur, oxygen, and/or nitrogen containing heterocycles such as piperidinylmethyl, piperazinylmethyl, morpholinylmethyl, pyridinylmethyl, pyridizylmethyl, pyrimidylmethyl, pyrazinylmethyl, etc.

"Heterocyclylalkenyl" refers to an acyclic alkenyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also a sp^2 carbon atom, is replaced with a heterocyclyl radical (*i.e.*, a heterocyclyl-alkenylene- moiety). The heterocyclyl portion of the heterocyclyl alkenyl group includes any of the heterocyclyl groups described herein, including those described in Principles of Modern Heterocyclic Chemistry, and the alkenyl portion of the heterocyclyl alkenyl group includes any of the alkenyl groups disclosed herein. One skilled in the art will also understand that the heterocyclyl group can be attached to the alkenyl portion of the heterocyclyl alkenyl by means of a carbon-carbon bond or a carbon-heteroatom bond, with the proviso that the resulting group is chemically stable. The heterocyclyl alkenyl group comprises 4 to 20 carbon atoms, *e.g.*, the alkenyl portion of the heterocyclyl alkenyl group is 2 to 6 carbon atoms and the heterocyclyl moiety is 2 to 14 carbon atoms.

"Heterocyclylalkynyl" refers to an acyclic alkynyl radical in which one of the

hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also an sp carbon atom, is replaced with a heterocyclyl radical (*i.e.*, a heterocyclyl-alkynylene- moiety). The heterocyclyl portion of the heterocyclyl alkynyl group includes any of the heterocyclyl groups described herein, including those described in Principles of Modern Heterocyclic Chemistry, and the alkynyl portion of the heterocyclyl alkynyl group includes any of the alkynyl groups disclosed herein. One skilled in the art will also understand that the heterocyclyl group can be attached to the alkynyl portion of the heterocyclyl alkynyl by means of a carbon-carbon bond or a carbon-heteroatom bond, with the proviso that the resulting group is chemically stable. The heterocyclyl alkynyl group comprises 4 to 20 carbon atoms, *e.g.*, the alkynyl portion of the heterocyclyl alkynyl group is 2 to 6 carbon atoms and the heterocyclyl moiety is 2 to 14 carbon atoms.

"Heteroaryl" refers to an aromatic heterocyclyl having at least one heteroatom in the ring. Non-limiting examples of suitable heteroatoms which can be included in the aromatic ring include oxygen, sulfur, and nitrogen. Non-limiting examples of heteroaryl rings include all of those aromatic rings listed in the definition of "heterocyclyl", including pyridinyl, pyrrolyl, oxazolyl, indolyl, isoindolyl, purinyl, furanyl, thienyl, benzofuranyl, benzothiophenyl, carbazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, quinolyl, isoquinolyl, pyridazyl, pyrimidyl, pyrazyl, etc.

"Carbocycle" or "carbocyclyl" refers to a saturated (i.e., cycloalkyl), partially unsaturated (e.g., cycloakenyl, cycloalkadienyl, etc.) or aromatic ring having 3 to 7 carbon atoms as a monocycle, 7 to 12 carbon atoms as a bicycle, and up to about 20 carbon atoms as a polycycle. Monocyclic carbocycles have 3 to 7 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles have 7 to 12 ring atoms, *e.g.*, arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system, or spiro-fused rings. Non-limiting examples of monocyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, and phenyl. Non-limiting examples of bicyclo carbocycles includes naphthyl, tetrahydronapthalene, and decaline.

"Carbocyclylalkyl" refers to to an acyclic akyl radical in which one of the hydrogen atoms bonded to a carbon atom is replaced with a carbocyclyl radical as described herein. Typical, but non-limiting, examples of carbocyclylalkyl groups include cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl.

"Arylheteroalkyl" refers to a heteroalkyl as defined herein, in which a hydrogen atom (which may be attached either to a carbon atom or a heteroatom) has been replaced with an aryl group as defined herein. The aryl groups may be bonded to a carbon atom of the heteroalkyl group, or to a heteroatom of the heteroalkyl group, provided that the resulting arylheteroalkyl group provides a chemically stable moiety. For example, an arylheteroalkyl group can have the general formulae -alkylene-O-aryl, -alkylene-O-alkylene-aryl, -alkylene-NH-aryl, -alkylene-NH-alkylene-aryl, -alkylene-S-aryl, -alkylene-S-alkylene-aryl, etc. In addition, any of the alkylene moieties in the general formulae above can be further substituted with any of the substituents defined or exemplified herein.

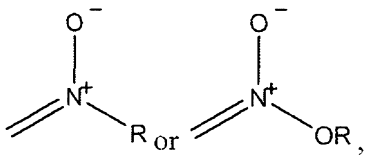
"Heteroarylalkyl" refers to an alkyl group, as defined herein, in which a hydrogen atom has been replaced with a heteroaryl group as defined herein. Non-limiting examples of heteroaryl alkyl include $-CH_2$-pyridinyl, $-CH_2$-pyrrolyl, $-CH_2$-oxazolyl, $-CH_2$-indolyl, $-CH_2$-isoindolyl, $-CH_2$-purinyl, $-CH_2$-furanyl, $-CH_2$-thienyl, $-CH_2$-benzofuranyl, $-CH_2$-benzothiophenyl, $-CH_2$-carbazolyl, $-CH_2$-imidazolyl, $-CH_2$-thiazolyl, $-CH_2$-isoxazolyl, $-CH_2$-pyrazolyl, $-CH_2$-isothiazolyl, $-CH_2$-quinolyl, $-CH_2$-isoquinolyl, $-CH_2$-pyridazyl, $-CH_2$-pyrimidyl, $-CH_2$-pyrazyl, $-CH(CH_3)$-pyridinyl, $-CH(CH_3)$-pyrrolyl, $-CH(CH_3)$-oxazolyl, $-CH(CH_3)$-indolyl, $-CH(CH_3)$-isoindolyl, $-CH(CH_3)$-purinyl, $-CH(CH_3)$-furanyl, $-CH(CH_3)$-thienyl, $-CH(CH_3)$-benzofuranyl, $-CH(CH_3)$-benzothiophenyl, $-CH(CH_3)$-carbazolyl, $-CH(CH_3)$-imidazolyl, $-CH(CH_3)$-thiazolyl, $-CH(CH_3)$-isoxazolyl, $-CH(CH_3)$-pyrazolyl, $-CH(CH_3)$-isothiazolyl, $-CH(CH_3)$-quinolyl, $-CH(CH_3)$-isoquinolyl, $-CH(CH_3)$-pyridazyl, $-CH(CH_3)$-pyrimidyl, $-CH(CH_3)$-pyrazyl, etc.

The term "optionally substituted" in reference to a particular moiety of the compound of Formula I-III (e.g., an optionally substituted aryl group) refers to a

moiety wherein all substiutents are hydrogen or wherein one or more of the hydrogens of the moiety may be replaced by substituents such as those listed under the definition of "substituted".

The term "optionally replaced" in reference to a particular moiety of the compound of Formula I-III (e.g., the carbon atoms of said (C_1-C_8)alkyl may be optionally replaced by –O-, -S-, or –NR^a-) means that one or more of the methylene groups of the (C_1-C_8)alkyl may be replaced by 0, 1, 2, or more of the groups specified (e.g., –O-, -S-, or –NR^a-).

The term "non-terminal carbon atom(s)" in reference to an alkyl, alkenyl, alkynyl, alkylene, alkenylene, or alkynylene moiety refers to the carbon atoms in the moiety that intervene between the first carbon atom of the moiety and the last carbon atom in the moiety. Therefore, by way of example and not limitation, in the alkyl moiety -$CH_2(C^*)H_2(C^*)H_2CH_3$ or alkylene moiety -$CH_2(C^*)H_2(C^*)H_2CH_2$- the C^* atoms would be considered to be the non-terminal carbon atoms.

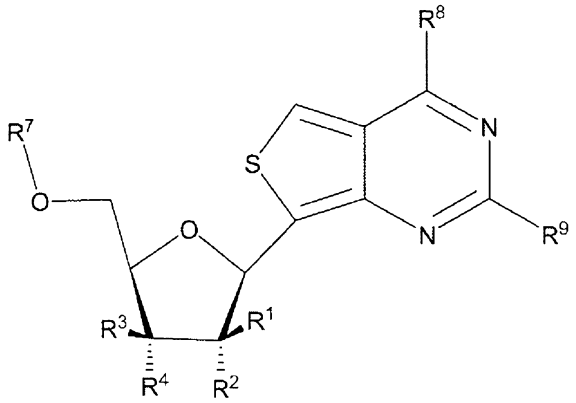
Certain Y and Y^1 alternatives are nitrogen oxides such as $^+N(O)(R)$ or $^+N(O)(OR)$. These nitrogen oxides, as shown here attached to a carbon atom, can also be represented by charge separated groups such as  respectively, and are intended to be equivalent to the aforementioned representations for the purposes of describing this invention.

"Linker" or "link" means a chemical moiety comprising a covalent bond or a chain of atoms. Linkers include repeating units of alkyloxy (e.g. polyethyleneoxy, PEG, polymethyleneoxy) and alkylamino (e.g. polyethyleneamino, Jeffamine™); and diacid ester and amides including succinate, succinamide, diglycolate, malonate, and caproamide.

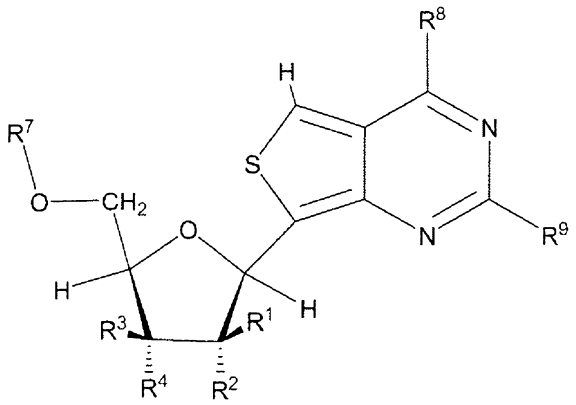
The terms such as "oxygen-linked", "nitrogen-linked", "carbon-linked", "sulfur-linked", or "phosphorous-linked" mean that if a bond between two moieties can be formed by using more than one type of atom in a moiety, then the bond formed between the moieties is through the atom specified. For example, a nitrogen-linked

amino acid would be bonded through a nitrogen atom of the amino acid rather than through an oxygen or carbon atom of the amino acid.

Unless otherwise specified, the carbon atoms of this invention are intended to have a valence of four. In some chemical structure representations where carbon atoms do not have a sufficient number of variables attached to produce a valence of four, the remaining carbon substitutents needed to provide a valence of four should be assumed to be hydrogen. For example,



has the same meaning as



"Protecting group" refers to a moiety of a compound that masks or alters the properties of a functional group or the properties of the compound as a whole. The chemical substructure of a protecting group varies widely. One function of a protecting group is to serve as an intermediate in the synthesis of the parental drug substance. Chemical protecting groups and strategies for protection/deprotection are well known in the art. See: "Protective Groups in Organic Chemistry", Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991. Protecting groups are often

utilized to mask the reactivity of certain functional groups, to assist in the efficiency of desired chemical reactions, e.g. making and breaking chemical bonds in an ordered and planned fashion. Protection of functional groups of a compound alters other physical properties besides the reactivity of the protected functional group, such as the polarity, lipophilicity (hydrophobicity), and other properties which can be measured by common analytical tools. Chemically protected intermediates may themselves be biologically active or inactive.

Protected compounds may also exhibit altered, and in some cases, optimized properties *in vitro* and *in vivo*, such as passage through cellular membranes and resistance to enzymatic degradation or sequestration. In this role, protected compounds with intended therapeutic effects may be referred to as prodrugs. Another function of a protecting group is to convert the parental drug into a prodrug, whereby the parental drug is released upon conversion of the prodrug *in vivo*. Because active prodrugs may be absorbed more effectively than the parental drug, prodrugs may possess greater potency *in vivo* than the parental drug. Protecting groups are removed either *in vitro,* in the instance of chemical intermediates, or *in vivo*, in the case of prodrugs. With chemical intermediates, it is not particularly important that the resulting products after deprotection, e.g. alcohols, be physiologically acceptable, although in general it is more desirable if the products are pharmacologically innocuous.

"Prodrug moiety" means a labile functional group which separates from the active inhibitory compound during metabolism, systemically, inside a cell, by hydrolysis, enzymatic cleavage, or by some other process (Bundgaard, Hans, "Design and Application of Prodrugs" in Textbook of Drug Design and Development (1991), P. Krogsgaard-Larsen and H. Bundgaard, Eds. Harwood Academic Publishers, pp. 113-191). Enzymes which are capable of an enzymatic activation mechanism with the phosphonate prodrug compounds of the invention include, but are not limited to, amidases, esterases, microbial enzymes, phospholipases, cholinesterases, and phosphases. Prodrug moieties can serve to enhance solubility, absorption and lipophilicity to optimize drug delivery, bioavailability and efficacy.

A prodrug moiety may include an active metabolite or drug itself.

Exemplary prodrug moieties include the hydrolytically sensitive or labile acyloxymethyl esters $-CH_2OC(=O)R^{30}$ and acyloxymethyl carbonates $-CH_2OC(=O)OR^{30}$ where R^{30} is C_1-C_6 alkyl, C_1-C_6 substituted alkyl, C_6-C_{20} aryl or C_6-C_{20} substituted aryl. The acyloxyalkyl ester was used as a prodrug strategy for carboxylic acids and then applied to phosphates and phosphonates by Farquhar et al (1983) *J. Pharm. Sci.* 72: 324; also US Patent Nos. 4816570, 4968788, 5663159 and 5792756. In certain compounds of the invention, a prodrug moiety is part of a phosphate group. The acyloxyalkyl ester may be used to deliver phosphoric acids across cell membranes and to enhance oral bioavailability. A close variant of the acyloxyalkyl ester, the alkoxycarbonyloxyalkyl ester (carbonate), may also enhance oral bioavailability as a prodrug moiety in the compounds of the combinations of the invention. An exemplary acyloxymethyl ester is pivaloyloxymethoxy, (POM) $-CH_2OC(=O)C(CH_3)_3$. An exemplary acyloxymethyl carbonate prodrug moiety is pivaloyloxymethylcarbonate (POC) $-CH_2OC(=O)OC(CH_3)_3$.

The phosphate group may be a phosphate prodrug moiety. The prodrug moiety may be sensitive to hydrolysis, such as, but not limited to those comprising a pivaloyloxymethyl carbonate (POC) or POM group. Alternatively, the prodrug moiety may be sensitive to enzymatic potentiated cleavage, such as a lactate ester or a phosphonamidate-ester group.

Aryl esters of phosphorus groups, especially phenyl esters, are reported to enhance oral bioavailability (DeLambert et al (1994) *J. Med. Chem.* 37: 498). Phenyl esters containing a carboxylic ester ortho to the phosphate have also been described (Khamnei and Torrence, (1996) *J. Med. Chem.* 39:4109-4115). Benzyl esters are reported to generate the parent phosphonic acid. In some cases, substituents at the *ortho*-or *para*-position may accelerate the hydrolysis. Benzyl analogs with an acylated phenol or an alkylated phenol may generate the phenolic compound through the action of enzymes, e.g. esterases, oxidases, etc., which in turn undergoes cleavage at the benzylic C–O bond to generate the phosphoric acid and the quinone methide intermediate. Examples of this class of prodrugs are described by Mitchell et al (1992) *J. Chem. Soc. Perkin Trans. I* 2345; Brook et al WO 91/19721. Still other

benzylic prodrugs have been described containing a carboxylic ester-containing group attached to the benzylic methylene (Glazier et al WO 91/19721). Thio-containing prodrugs are reported to be useful for the intracellular delivery of phosphonate drugs. These proesters contain an ethylthio group in which the thiol group is either esterified with an acyl group or combined with another thiol group to form a disulfide. Deesterification or reduction of the disulfide generates the free thio intermediate which subsequently breaks down to the phosphoric acid and episulfide (Puech et al (1993) *Antiviral Res.*, 22: 155-174; Benzaria et al (1996) *J. Med. Chem.* 39: 4958). Cyclic phosphonate esters have also been described as prodrugs of phosphorus-containing compounds (Erion et al, US Patent No. 6312662).

It is to be noted that all enantiomers, diastereomers, and racemic mixtures, tautomers, polymorphs, pseudopolymorphs of compounds within the scope of Formula I, Formula II, or Formula III and pharmaceutically acceptable salts thereof are embraced by the present invention. All mixtures of such enantiomers and diastereomers are within the scope of the present invention.

A compound of Formula I-III and its pharmaceutically acceptable salts may exist as different polymorphs or pseudopolymorphs. As used herein, crystalline polymorphism means the ability of a crystalline compound to exist in different crystal structures. The crystalline polymorphism may result from differences in crystal packing (packing polymorphism) or differences in packing between different conformers of the same molecule (conformational polymorphism). As used herein, crystalline pseudopolymorphism means the ability of a hydrate or solvate of a compound to exist in different crystal structures. The pseudopolymorphs of the instant invention may exist due to differences in crystal packing (packing pseudopolymorphism) or due to differences in packing between different conformers of the same molecule (conformational pseudopolymorphism). The instant invention comprises all polymorphs and pseudopolymorphs of the compounds of Formula I-III and their pharmaceutically acceptable salts.

A compound of Formula I-III and its pharmaceutically acceptable salts may also exist as an amorphous solid. As used herein, an amorphous solid is a solid in which there is no long-range order of the positions of the atoms in the solid. This

definition applies as well when the crystal size is two nanometers or less. Additives, including solvents, may be used to create the amorphous forms of the instant invention. The instant invention comprises all amorphous forms of the compounds of Formula I-III and their pharmaceutically acceptable salts.

Recursive Substituents

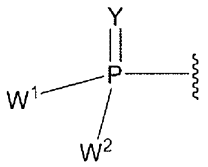
Selected substituents comprising the compounds of the invention are present to a recursive degree. In this context, "recursive substituent" means that a substituent may recite another instance of itself. Because of the recursive nature of such substituents, theoretically, a large number of compounds may be present in any given embodiment. For example, R^x comprises a R^y substituent. R^y can be R. R can be W^3. W^3 can be W^4 and W^4 can be R or comprise substituents comprising R^y. One of ordinary skill in the art of medicinal chemistry understands that the total number of such substituents is reasonably limited by the desired properties of the compound intended. Such properties include, by way of example and not limitation, physical properties such as molecular weight, solubility or log P, application properties such as activity against the intended target, and practical properties such as ease of synthesis.

By way of example and not limitation, W^3 and R^y are recursive substituents in certain embodiments. Typically, each recursive substituent can independently occur 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0, times in a given embodiment. More typically, each recursive substituent can independently occur 10 or fewer times in a given embodiment. More typically yet, W^3 will occur 0 to 8 times, R^y will occur 0 to 6 times in a given embodiment. Even more typically, W^3 will occur 0 to 6 times and R^y will occur 0 to 4 times in a given embodiment.

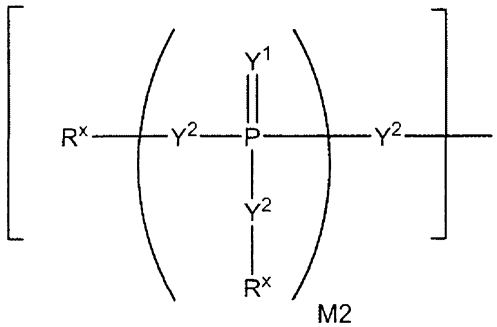
Recursive substituents are an intended aspect of the invention. One of ordinary skill in the art of medicinal chemistry understands the versatility of such substituents. To the degree that recursive substituents are present in an embodiment of the invention, the total number will be determined as set forth above.

The modifier "about" used in connection with a quantity is inclusive of the stated value and has the meaning dictated by the context (e.g., includes the degree of error associated with measurement of the particular quantity).

The compounds of the Formula I-III may comprise a phosphate group as R^7,



which may be a prodrug moiety wherein each Y or Y^1 is, independently, O, S, NR, $^+N(O)(R)$, N(OR), $^+N(O)(OR)$, or $N–NR_2$; W^1 and W^2, when taken together, are $–Y^3(C(R^y)_2)_3Y^3$-; or one of W^1 or W^2 together with either R^3or R^4 is $–Y^3$- and the other of W^1 or W^2 is Formula Ia; or W^1 and W^2 are each, independently, a group of Formula Ia:



M2

wherein:

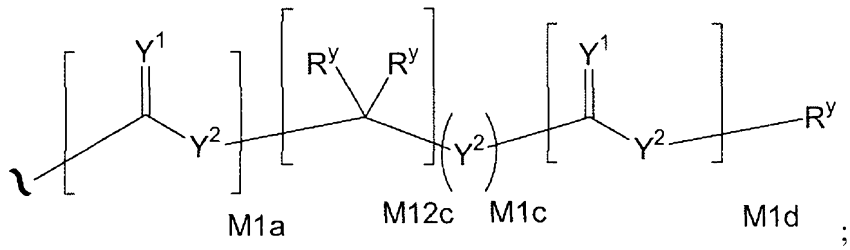
each Y^2 is independently a bond, O, CR_2, NR, $^+N(O)(R)$, N(OR), $^+N(O)(OR)$, $N–NR_2$, S, S–S, S(O), or $S(O)_2$;

each Y^3 is independently O, S, or NR;

M2 is 0, 1 or 2;

each R^y is independently H, F, Cl, Br, I, OH, R, $-C(=Y^1)R$, $-C(=Y^1)OR$, $-C(=Y^1)N(R)_2$, $-N(R)_2$, $-^+N(R)_3$, -SR, -S(O)R, $-S(O)_2R$, -S(O)(OR), $-S(O)_2(OR)$, $-OC(=Y^1)R$, $-OC(=Y^1)OR$, $-OC(=Y^1)(N(R)_2)$, $-SC(=Y^1)R$, $-SC(=Y^1)OR$, $-SC(=Y^1)(N(R)_2)$, $-N(R)C(=Y^1)R$, $-N(R)C(=Y^1)OR$, or $-N(R)C(=Y^1)N(R)_2$, $–SO_2NR_2$, –CN, $–N_3$, $–NO_2$, –OR, a protecting group or W^3; or when taken together, two R^y on the same carbon atom form a carbocyclic ring of 3 to 7 carbon atoms;

each R^x is independently R^y, a protecting group, or the formula:



;

wherein:

M1a, M1c, and M1d are independently 0 or 1;

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

each R is H, halogen, (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heterocycle, C_2–C_{20} substituted heterocyclyl, arylalkyl, substituted arylalkyl or a protecting group;

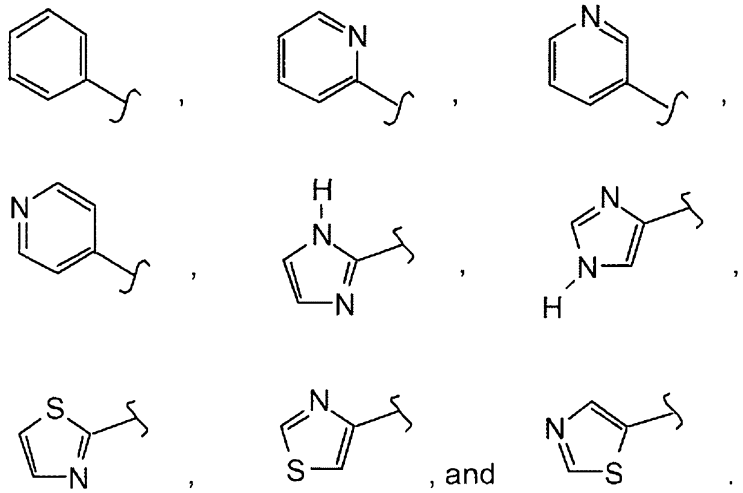
W^3 is W^4 or W^5; W^4 is R, $-C(Y^1)R^y$, $-C(Y^1)W^5$, $-SO_2R^y$, or $-SO_2W^5$; and W^5 is a carbocycle or a heterocycle wherein W^5 is independently substituted with 0 to 3 R^y groups.

W^5 carbocycles and W^5 heterocycles may be independently substituted with 0 to 3 R^y groups. W^5 may be a saturated, unsaturated or aromatic ring comprising a mono- or bicyclic carbocycle or heterocycle. W^5 may have 3 to 10 ring atoms, e.g., 3 to 7 ring atoms. The W^5 rings are saturated when containing 3 ring atoms, saturated or mono-unsaturated when containing 4 ring atoms, saturated, or mono- or di-unsaturated when containing 5 ring atoms, and saturated, mono- or di-unsaturated, or aromatic when containing 6 ring atoms.

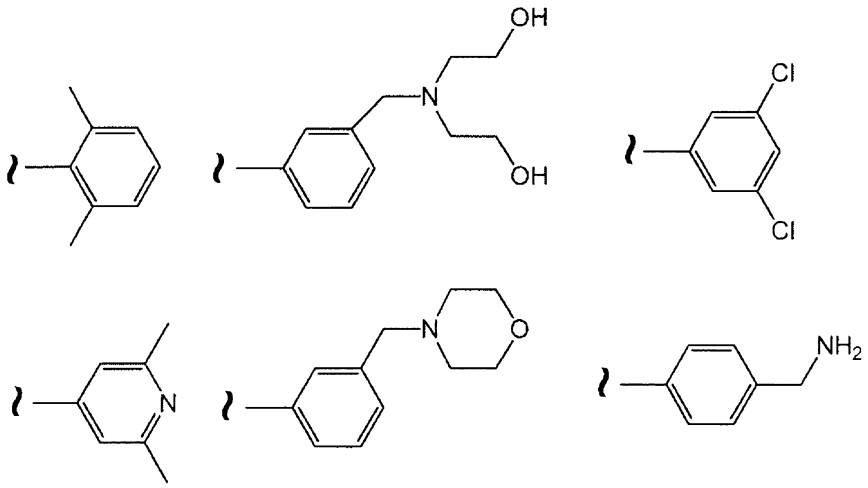
A W^5 heterocycle may be a monocycle having 3 to 7 ring members (2 to 6 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S) or a bicycle having 7 to 10 ring members (4 to 9 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S). W^5 heterocyclic monocycles may have 3 to 6 ring atoms (2 to 5 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S); or 5 or 6 ring atoms (3 to 5 carbon atoms and 1 to 2 heteroatoms selected from N and S). W^5 heterocyclic bicycles have 7 to 10 ring atoms (6 to 9 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S) arranged as a bicyclo [4,5], [5,5], [5,6], or [6,6] system; or 9 to 10

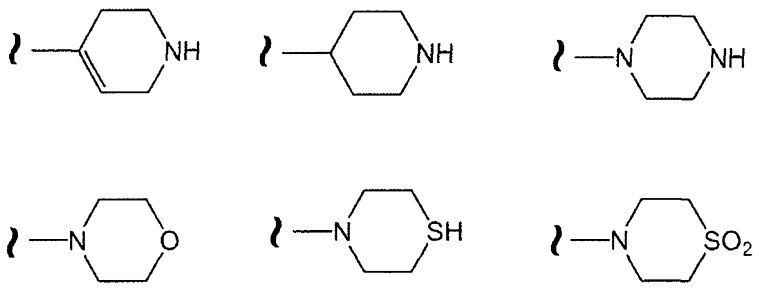
ring atoms (8 to 9 carbon atoms and 1 to 2 hetero atoms selected from N and S) arranged as a bicyclo [5,6] or [6,6] system. The W^5 heterocycle may be bonded to Y^2 through a carbon, nitrogen, sulfur or other atom by a stable covalent bond.

W^5 heterocycles include for example, pyridyl, dihydropyridyl isomers, piperidine, pyridazinyl, pyrimidinyl, pyrazinyl, s-triazinyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, furanyl, thiofuranyl, thienyl, and pyrrolyl. W^5 also includes, but is not limited to, examples such as:

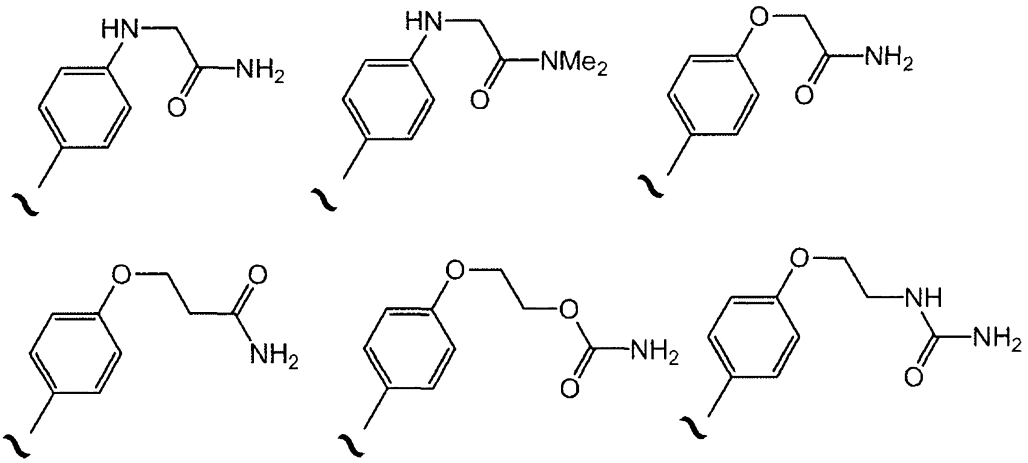


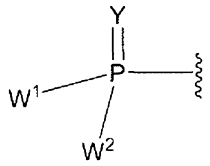
W^5 carbocycles and heterocycles may be independently substituted with 0 to 3 R groups, as defined above. For example, substituted W^5 carbocycles include:



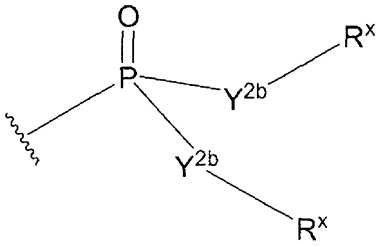


Examples of substituted phenyl carbocycles include:

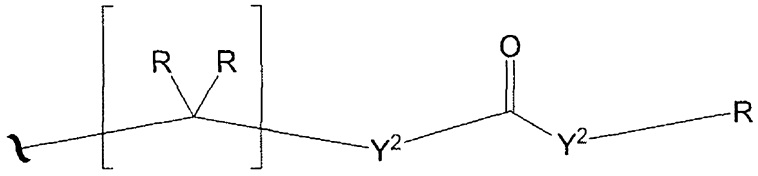




Embodiments of of Formula I-III compounds include substructures such as:

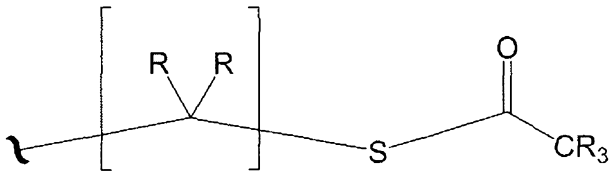


wherein each Y^{2b} is, independently, O or N(R). In a preferred embodiment, each Y^{2b} is O and each R^x is independently:



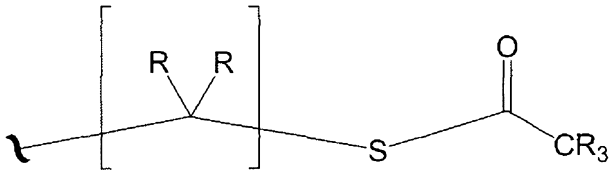
M12c

wherein M12c is 1, 2 or 3 and each Y^2 is independently a bond, O, CR_2, or S. In another preferred embodiment, one Y^{2b}-R^x is NH(R) and the other Y^{2b}-R^x is O-R^x wherein R^x is:



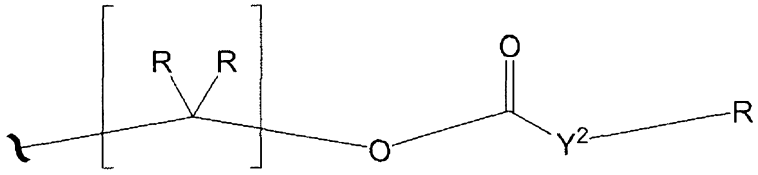
M12c

wherein M12c is 2. In another preferred embodiment, each Y^{2b} is O and each R^x is independently:



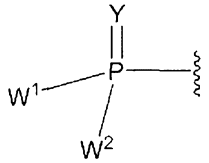
M12c

wherein M12c is 2. In another preferred embodiment, each Y^{2b} is O and each R^x is independently:

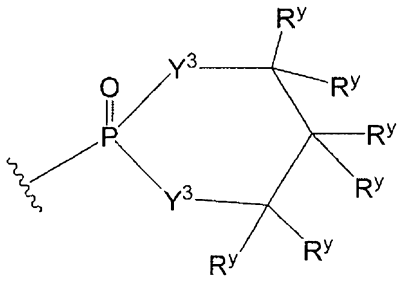


M12c

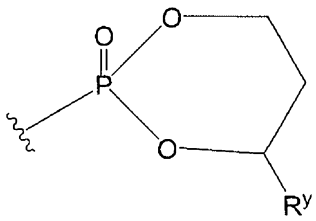
wherein M12c is 1 and Y^2 is a bond, O, or CR_2.



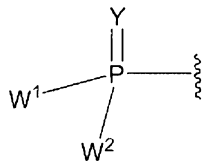
Other embodiments of of Formulas I-III compounds include substructures such as:

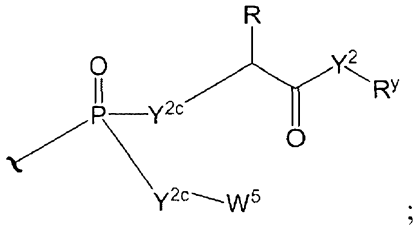


wherein each Y^3 is, independently, O or N(R). In a preferred embodiment, each Y^3 is O. In another preferred embodiment the substructure is:



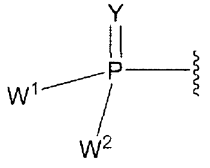
wherein R^y is W^5 as defined herein.

Another embodiment of  of Formula I-III includes the substructures:

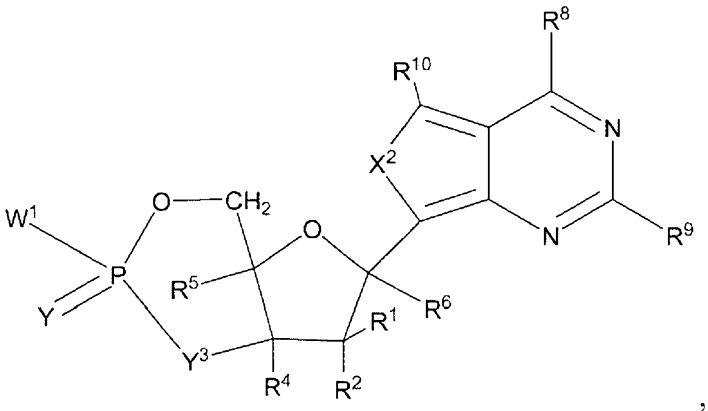


;

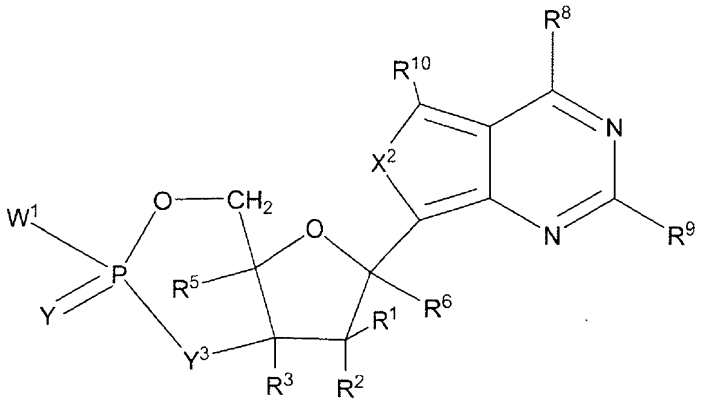
wherein each Y^{2c} is, independently, O, N(R) or S.

Another embodiment of  of Formula I-III compounds includes the substructures wherein one of W^1 or W^2 together with either R^3 or R^4 is –

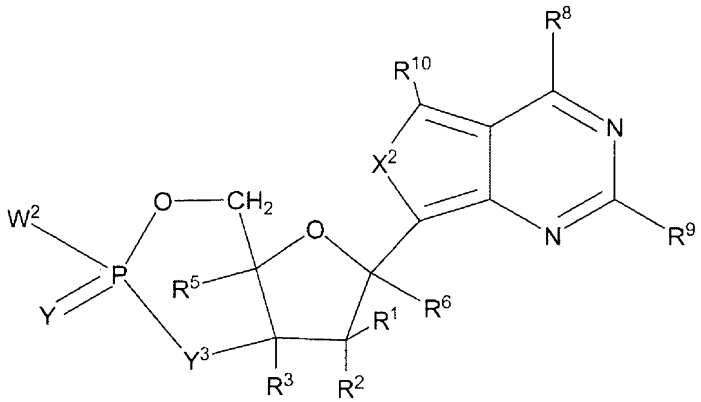
Y^3- and the other of W^1 or W^2 is Formula Ia. Such an embodiment is represented by a compound of Formula Ib selected from:



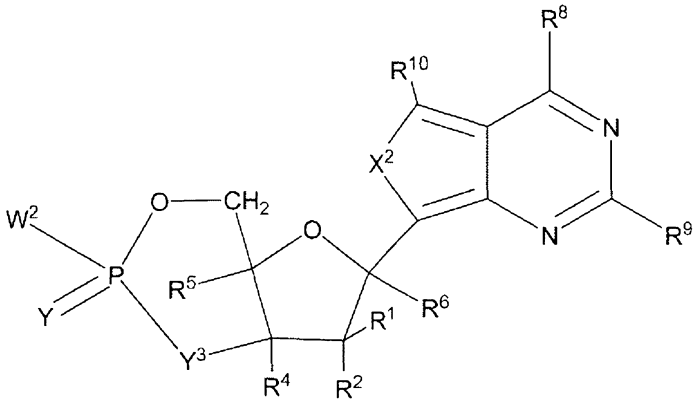
,



,

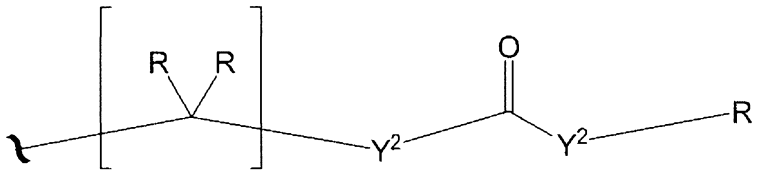


or



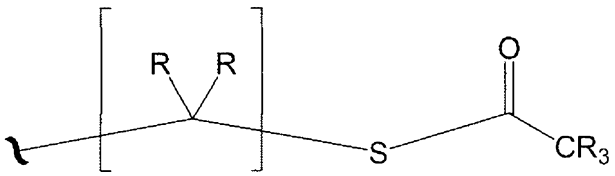
Formula Ib

In a preferred embodiment of Formula Ib, each Y and Y^3 is O. In another preferred embodiment of Formula Ib, W^1 or W^2 is Y^{2b}-R^x; each Y, Y^3 and Y^{2b} is O and R^x is:



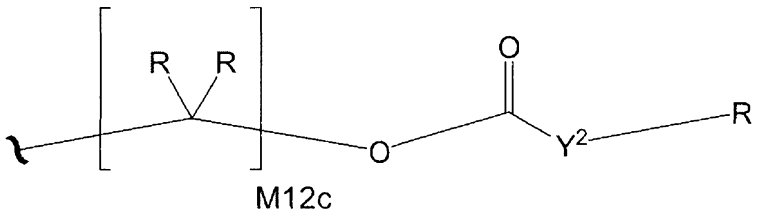
M12c

wherein M12c is 1, 2 or 3 and each Y^2 is independently a bond, O, CR_2, or S. In another preferred embodiment of Formula Ib, W^1 or W^2 is Y^{2b}-R^x; each Y, Y^3 and Y^{2b} is O and R^x is:



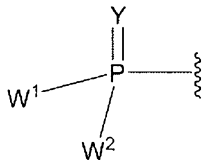
M12c

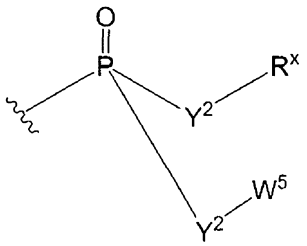
wherein M12c is 2. In another preferred embodiment of Formula Ib, W^1 or W^2 is Y^{2b}-R^x; each Y, Y^3 and Y^{2b} is O and R^x is:



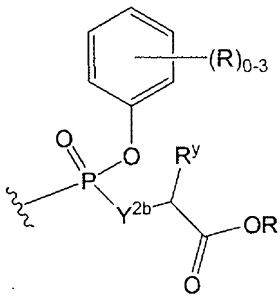
M12c

wherein M12c is 1 and Y^2 is a bond, O, or CR_2.

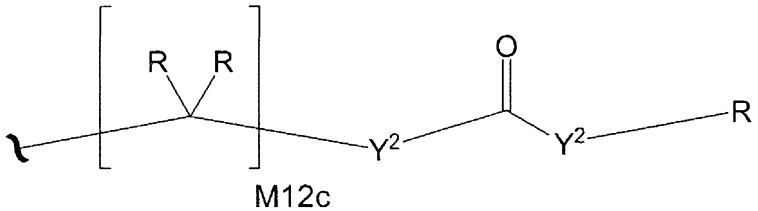
Another embodiment of  of Formula I-III compounds includes a substructure:



wherein W^5 is a carbocycle such as phenyl or substituted phenyl. In another embodiment, the substructure is:

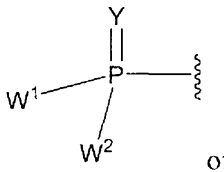


wherein Y^{2b} is O or N(R) and the phenyl carbocycle is substituted with 0 to 3 R groups. In another embodiment of the substructure, R^x is:

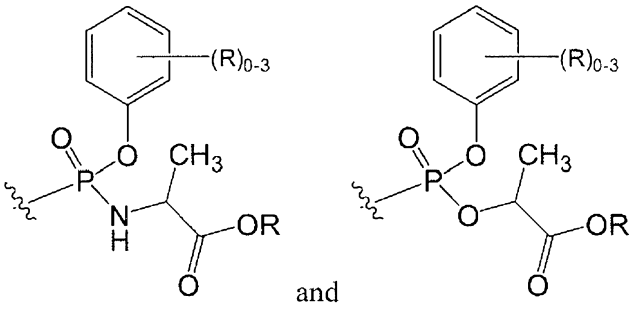


M12c

wherein M12c is 1, 2 or 3 and each Y^2 is independently a bond, O, CR_2, or S.

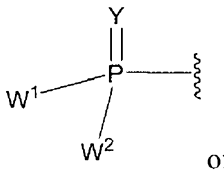


Another embodiment of of Formula I-III includes substructures:

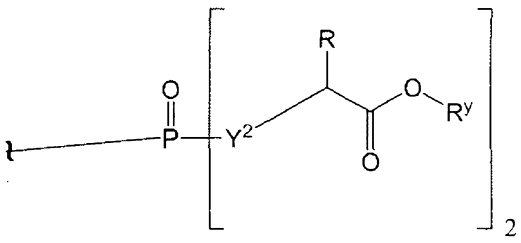


and .

The chiral carbon of the amino acid and lactate moieties may be either the *R* or *S* configuration or the racemic mixture.

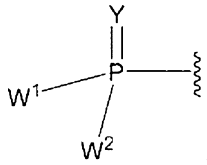


Another embodiment of of Formula I-III is substructure

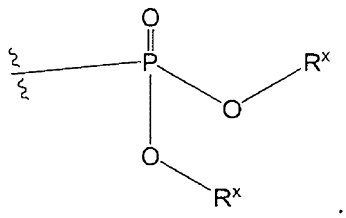


wherein each Y^2 is, independently, –O- or -NH-. In another preferred embodiment, R^y is (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl or (C_2-C_8) substituted alkynyl. In another preferred embodiment, R^y is (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl or (C_2-C_8) substituted alkynyl; and R is CH_3. In another preferred embodiment, R^y is (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl or (C_2-C_8) substituted alkynyl; R is CH_3; and each Y^2 is –NH-. In a preferred embodiment, W^1 and W^2 are,

independently, nitrogen-linked, naturally occurring amino acids or naturally occurring amino acid esters. In another preferred embodiment, W^1 and W^2 are, independently, naturally-occurring 2-hydroxy carboxylic acids or naturally-occurring 2-hydroxy carboxylic acid esters wherein the acid or ester is linked to P through the 2-hydroxy group.

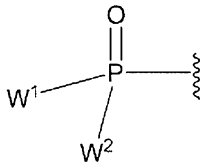


Another embodiment of of Formula I, Formula II, or Formula III is substructure:

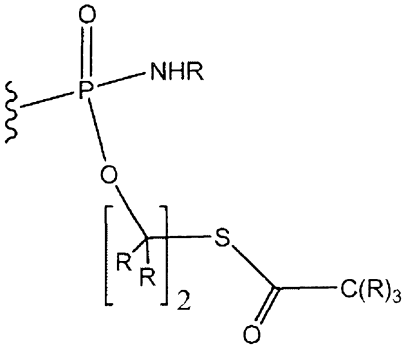


In one preferred embodiment each R^x is, independently, $(C_1\text{-}C_8)$ alkyl. In another preferred embodiment each R^x is, independently, $C_6\text{-}C_{20}$ aryl or $C_6\text{-}C_{20}$ substituted aryl.

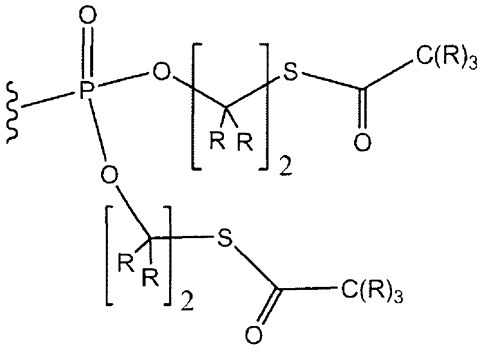
In a preferred embodiment,



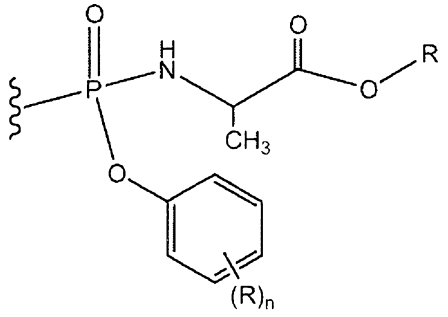
is selected from



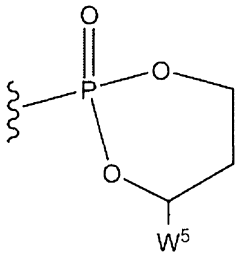
;



;

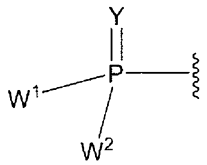


or

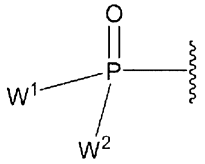


.

Another embodiment of



of Formulas I-III is substructure



wherein W^1 and W^2 are independently selected from one of the formulas in Tables 20.1-20.37 and Table 30.1 below. The variables used in Tables 20.1-20.37 (e.g., W^{23}, R^{21}, etc.) pertain only to Tables 20.1-20.37, unless otherwise indicated.

The variables used in Tables 20.1 to 20.37 have the following definitions:

each R^{21} is independently H or $(C_1\text{-}C_8)$alkyl;

each R^{22} is independently H, R^{21}, R^{23} or R^{24} wherein each R^{24} is independently substituted with 0 to 3 R^{23};

each R^{23} is independently R^{23a}, R^{23b}, R^{23c} or R^{23d}, provided that when R^{23} is bound to a heteroatom, then R^{23} is R^{23c} or R^{23d};

each R^{23a} is independently F, Cl, Br, I, -CN, N_3 or $-NO_2$;

each R^{23b} is independently Y^{21};

each R^{23c} is independently $-R^{2x}$, $-N(R^{2x})(R^{2x})$, $-SR^{2x}$, $-S(O)R^{2x}$, $-S(O)_2R^{2x}$, $-S(O)(OR^{2x})$, $-S(O)_2(OR^{2x})$, $-OC(=Y^{21})R^{2x}$, $-OC(=Y^{21})OR^{2x}$, $-OC(=Y^{21})(N(R^{2x})(R^{2x}))$, $-SC(=Y^{21})R^{2x}$, $-SC(=Y^{21})OR^{2x}$, $-SC(=Y^{21})(N(R^{2x})(R^{2x}))$, $-N(R^{2x})C(=Y^{21})R^{2x}$, $-N(R^{2x})C(=Y^{21})OR^{2x}$, or $-N(R^{2x})C(=Y^{21})(N(R^{2x})(R^{2x}))$;

each R^{23d} is independently $-C(=Y^{21})R^{2x}$, $-C(=Y^{21})OR^{2x}$ or $-C(=Y^{21})(N(R^{2x})(R^{2x}))$;

each R^{2x} is independently H, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, aryl, heteroaryl; or two R^{2x} taken together with a nitrogen to which they are both attached form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with -O-, -S- or $-NR^{21}$-; and wherein one or more of the non-terminal carbon atoms of each said $(C_1\text{-}C_8)$alkyl may be optionally replaced with -O-, -S- or $-NR^{21}$-;

each R^{24} is independently $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, or $(C_2\text{-}C_8)$alkynyl;

each R^{25} is independently R^{24} wherein each R^{24} is substituted with 0 to 3 R^{23} groups;

each R^{25a} is independently $(C_1\text{-}C_8)$alkylene, $(C_2\text{-}C_8)$alkenylene, or $(C_2\text{-}C_8)$alkynylene any one of which said $(C_1\text{-}C_8)$alkylene, $(C_2\text{-}C_8)$alkenylene, or $(C_2\text{-}C_8)$alkynylene is substituted with 0-3 R^{23} groups;

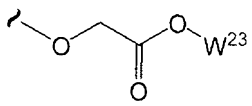
each W^{23} is independently W^{24} or W^{25};

each W^{24} is independently R^{25}, $-C(=Y^{21})R^{25}$, $-C(=Y^{21})W^{25}$, $-SO_2R^{25}$, or $-SO_2W^{25}$;

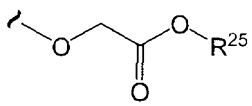
each W^{25} is independently carbocycle or heterocycle wherein W^{25} is independently substituted with 0 to 3 R^{22} groups; and

each Y^{21} is independently O or S.

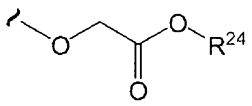
Table 20.1



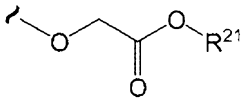
1



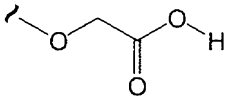
2



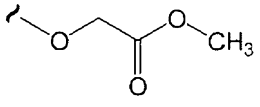
3



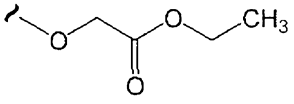
4



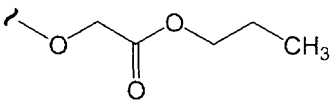
5



6

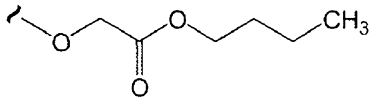


7

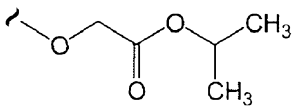


8

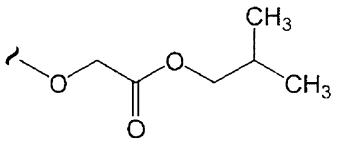
Table 20.2



9



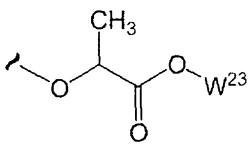
10



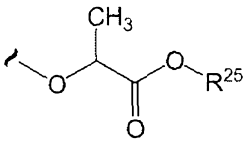
11

10

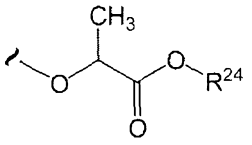
Table 20.3



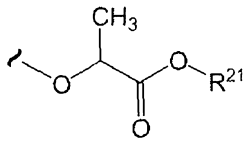
12



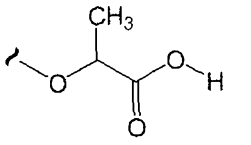
13



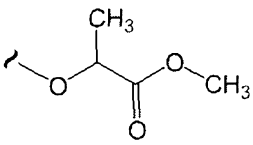
14



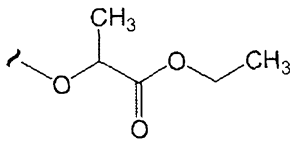
15



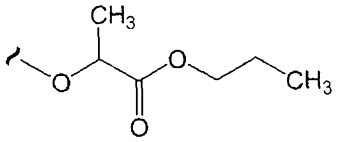
16



17

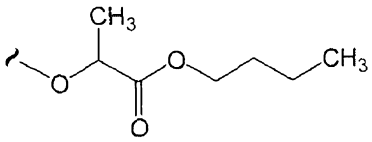


18

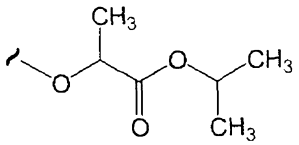


19

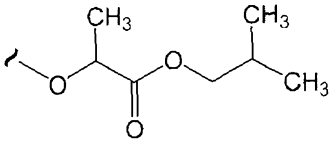
Table 20.4



20



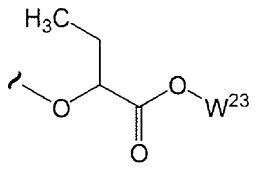
21



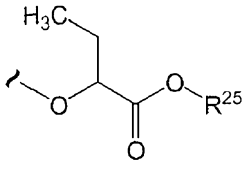
22

10

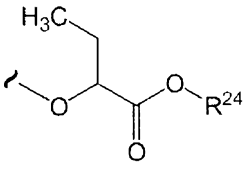
Table 20.5



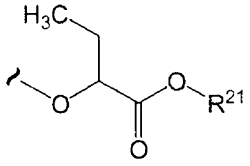
23



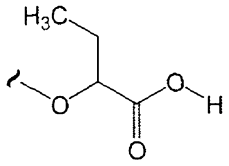
24



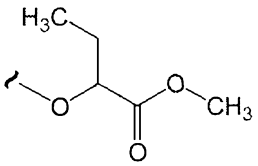
25



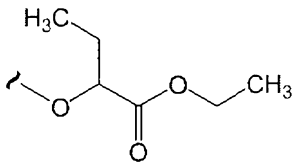
26



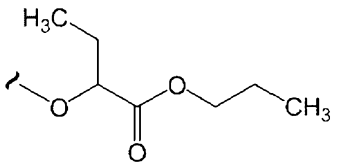
27



28

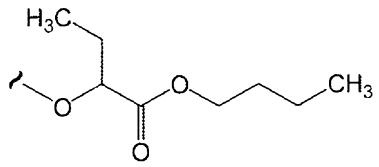


29

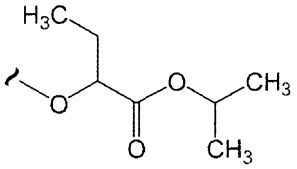


30

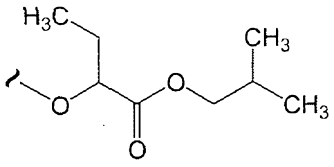
Table 20.6



31

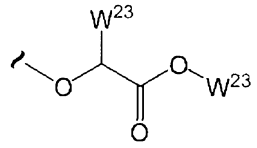


32

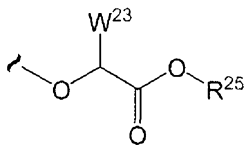


33

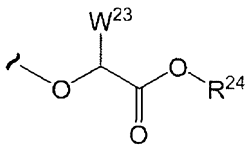
Table 20.7



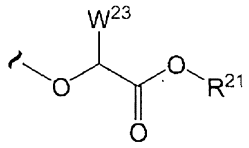
34



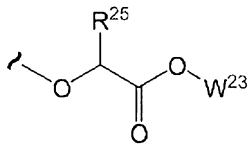
35



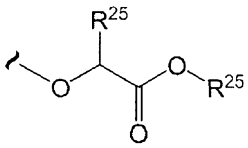
36



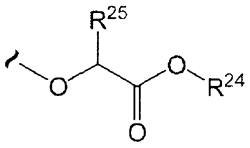
37



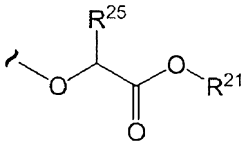
38



39

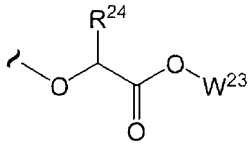


40

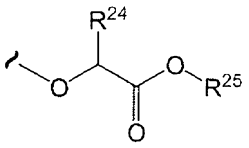


41

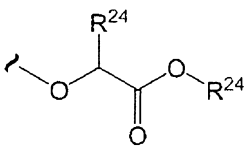
Table 20.8



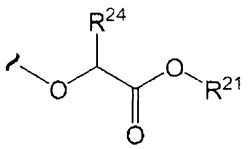
42



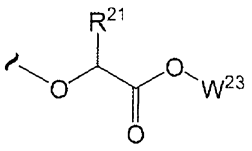
43



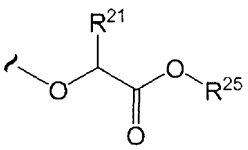
44



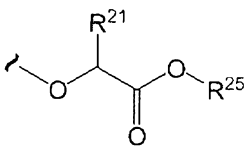
45



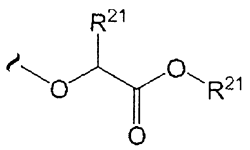
46



47

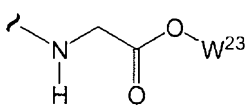


48

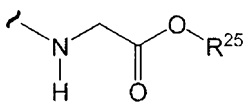


49

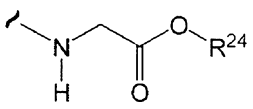
Table 20.9



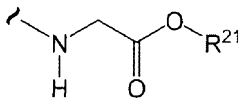
50



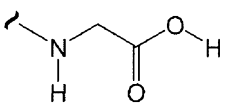
51



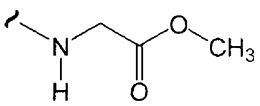
52



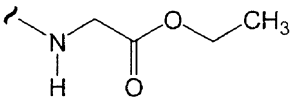
53



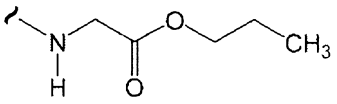
54



55

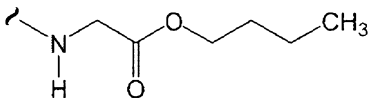


56

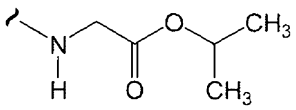


57

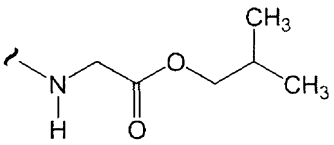
Table 20.10



58

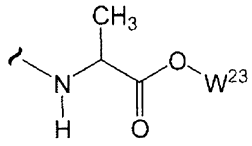


59

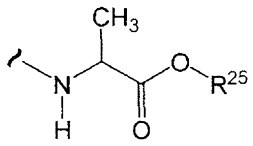


60

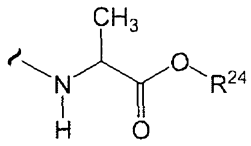
Table 20.11



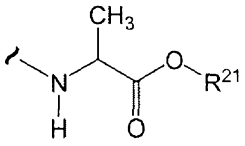
61



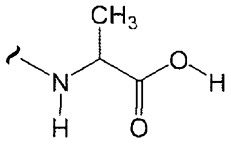
62



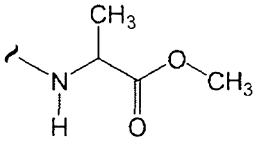
63



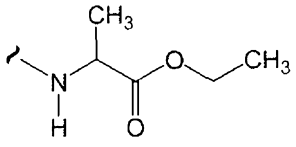
64



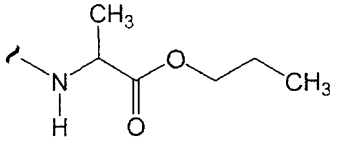
65



66

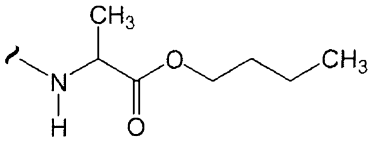


67

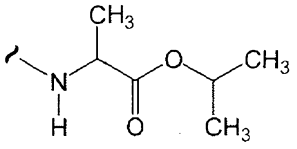


68

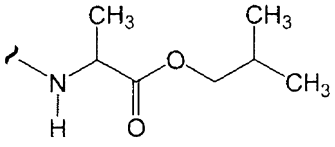
Table 20.12



69

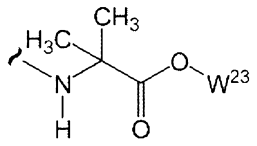


70

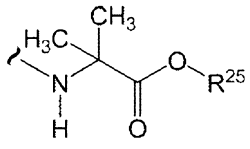


71

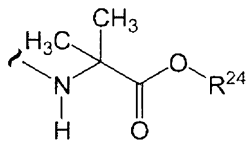
Table 20.13



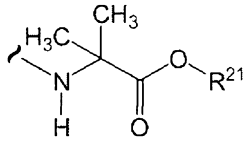
72



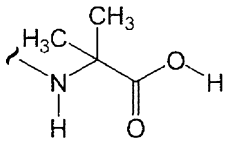
73



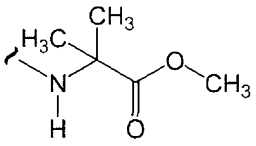
74



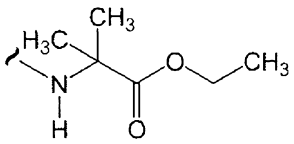
75



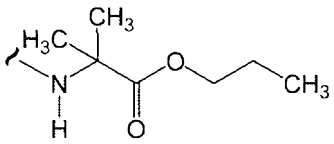
76



77

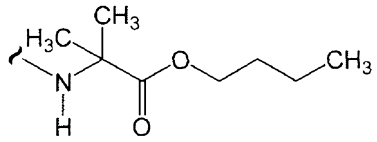


78

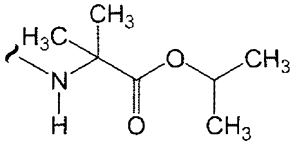


79

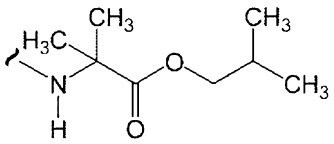
Table 20.14



80

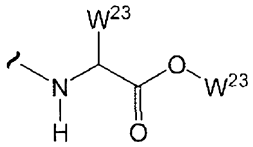


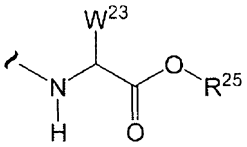
81

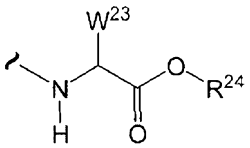


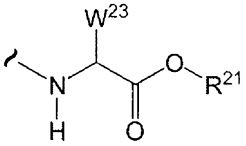
82

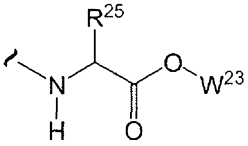
Table 20.15

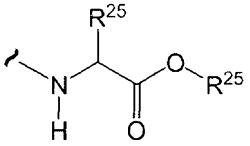

83

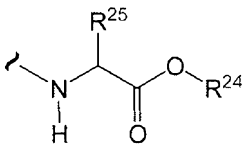

84


85


86


87


88


89

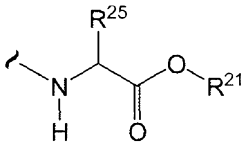
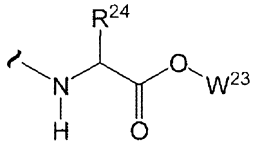
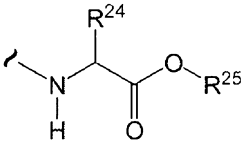
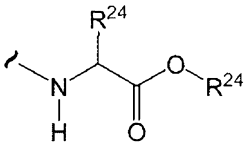
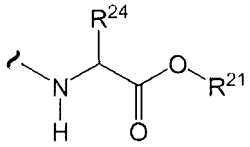

90

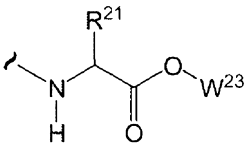
Table 20.16

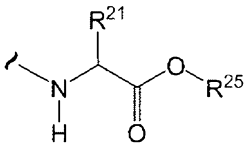

91

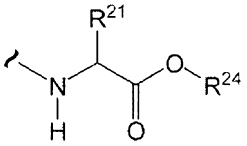

92


93


94


95


96


97

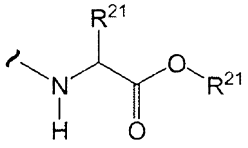
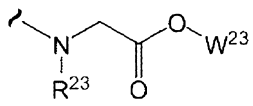
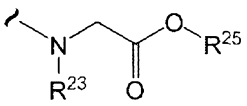

98

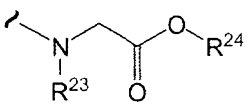
Table 20.17



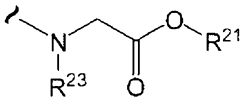
99



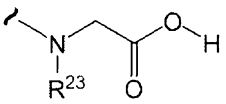
100



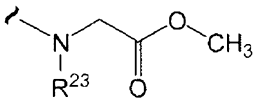
101



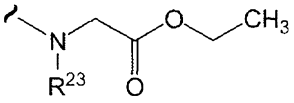
102



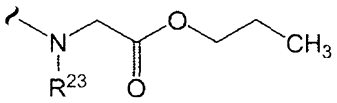
103



104

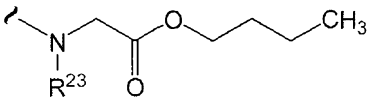


105

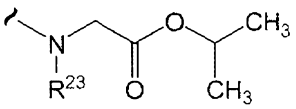


106

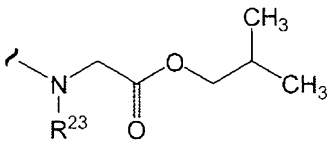
Table 20.18



107

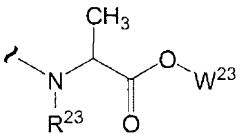


108

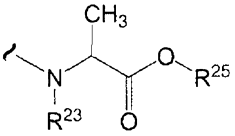


109

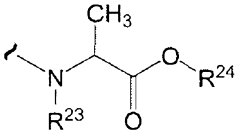
Table 20.19



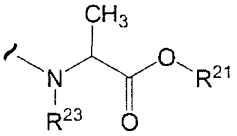
110



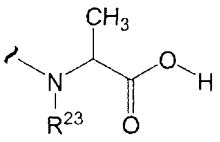
111



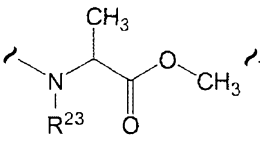
112



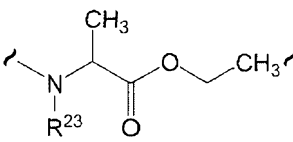
113



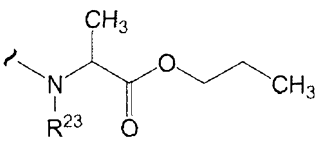
114



115

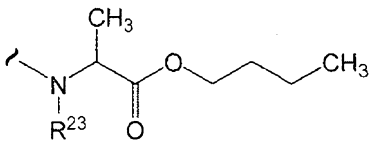


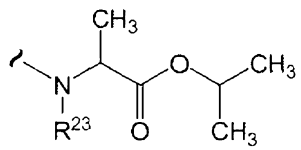
116



117

Table 20.20


118


119

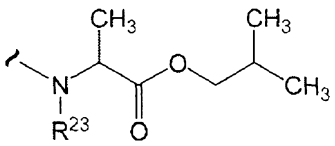
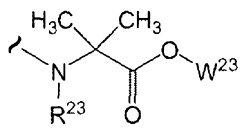
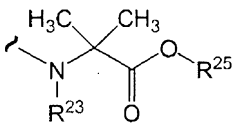
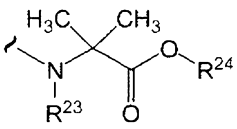
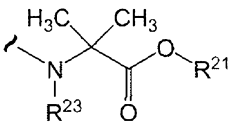

120

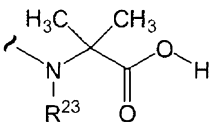
Table 20.21

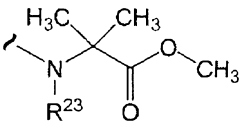

121

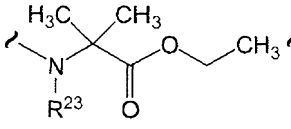

122


123


124


125


126


127

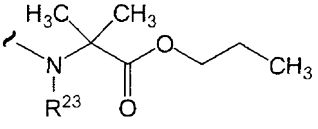
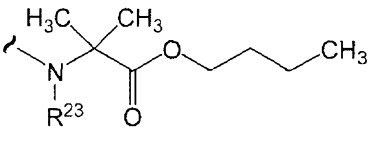
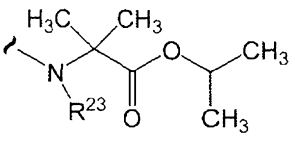

128

Table 20.22


129


130

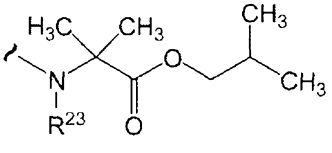
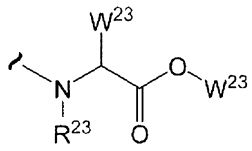
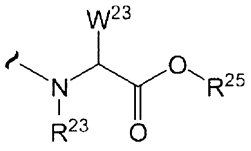
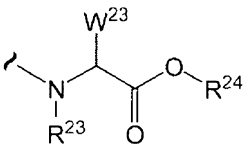
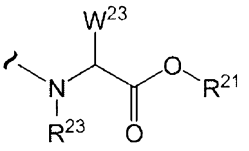

131

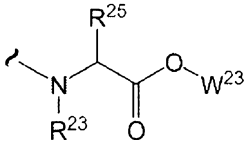
Table 20.23

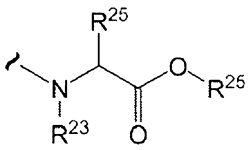

132

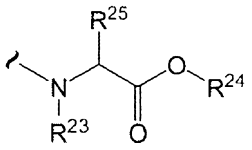

133


134


135


136


137


138

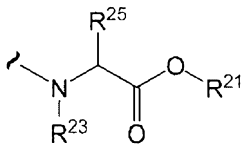
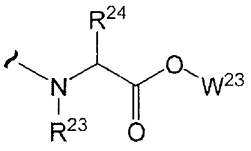
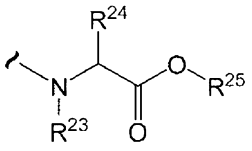
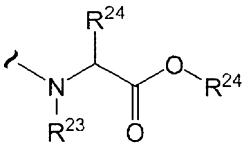
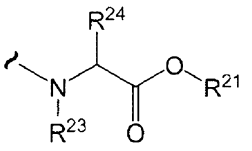

139

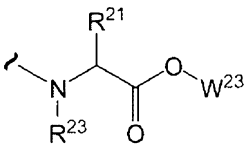
Table 20.24

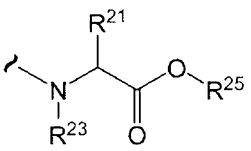

140

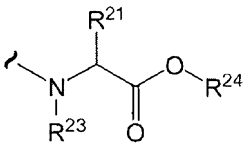

141


142


143


144


145


146

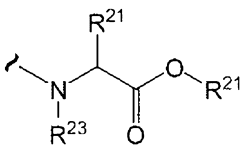

147

Table 20.25


148

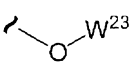

149

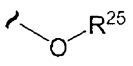

150

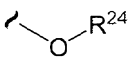

151

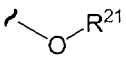

152

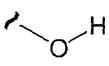

153


154


155


156


157


158

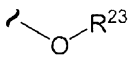
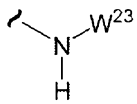
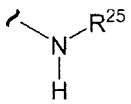
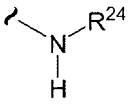
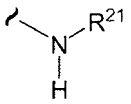

159

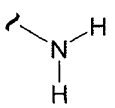
Table 20.26

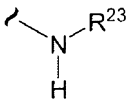

160

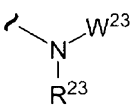

161

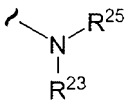

162

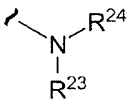

163

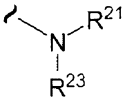

164

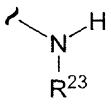

165


166


167


168


169


170

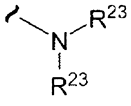
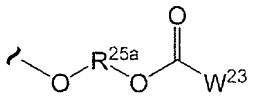
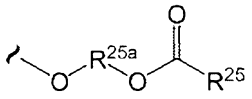
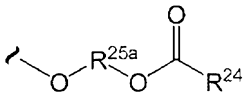
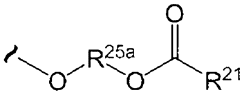

171

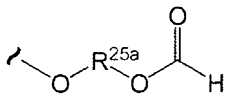
Table 20.27

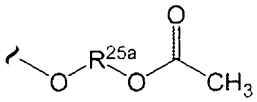

172

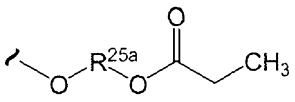

173


174


175


176


177


178

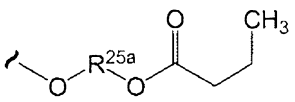
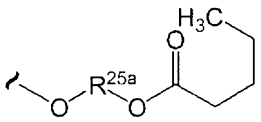
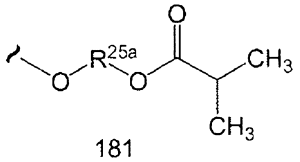

179

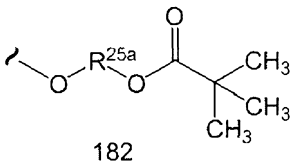
Table 20.28



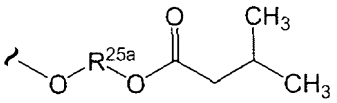
180



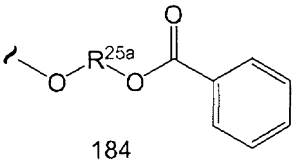
181



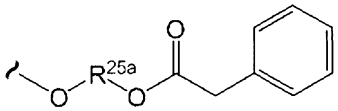
182



183

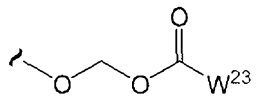


184

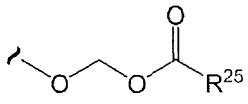


185

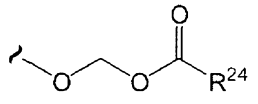
Table 20.29



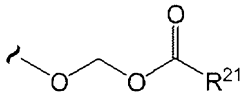
186



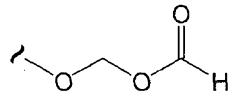
187



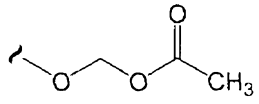
188



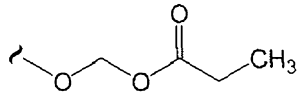
189



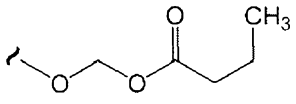
190



191

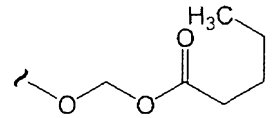


192

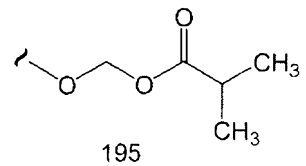


193

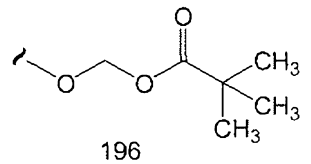
Table 20.30



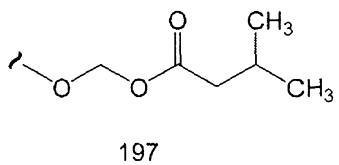
194



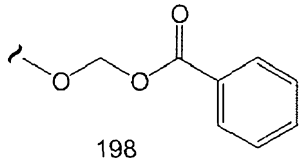
195



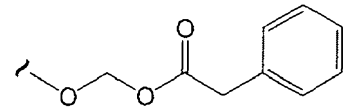
196



197

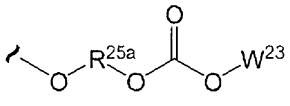


198

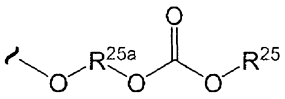


199

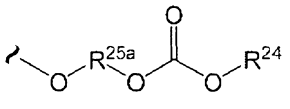
Table 20.31



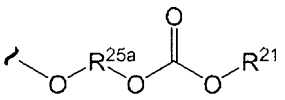
200



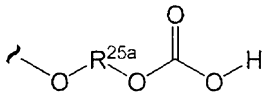
201



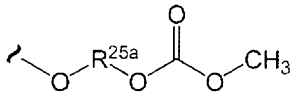
202



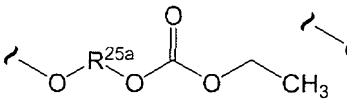
203



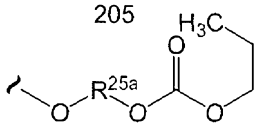
204



205

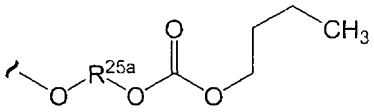


206

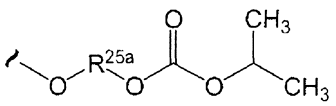


207

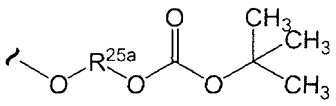
Table 20.32



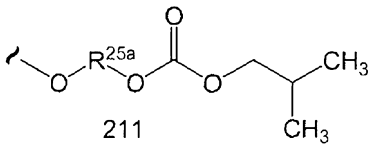
208



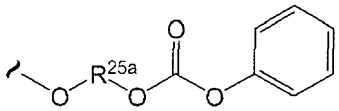
209



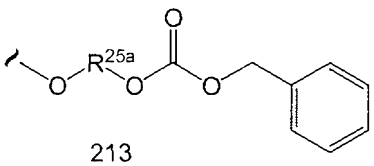
210



211



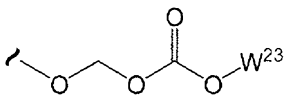
212



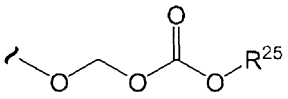
213

5

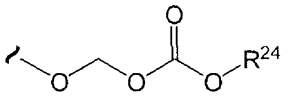
Table 20.33



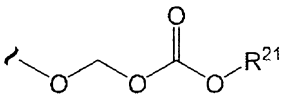
214



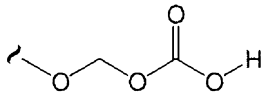
215



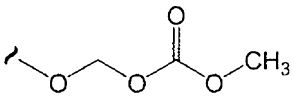
216



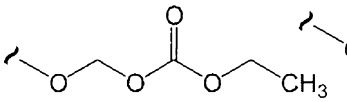
217



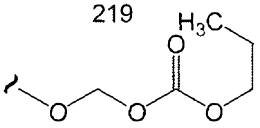
218



219

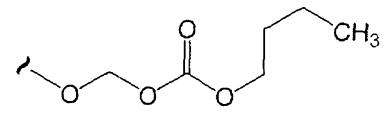


220

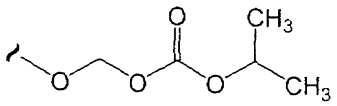


221

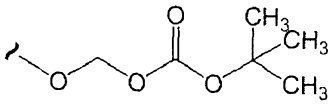
Table 20.34



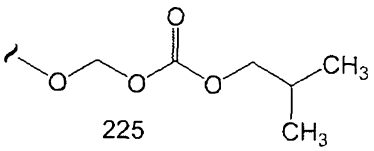
222



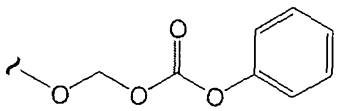
223



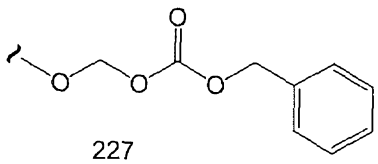
224



225

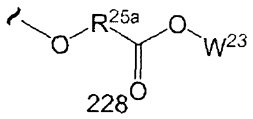


226

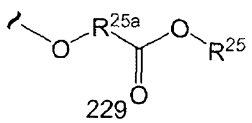


227

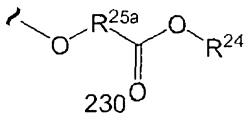
Table 20.35



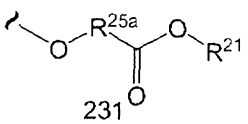
228



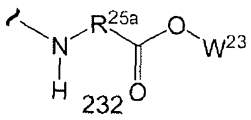
229



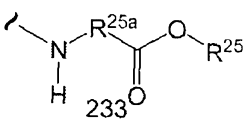
230



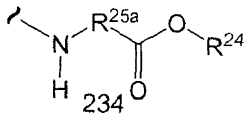
231



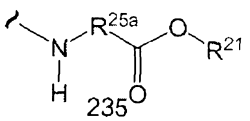
232



233

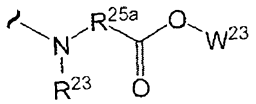


234

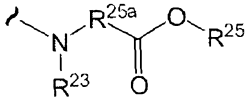


235

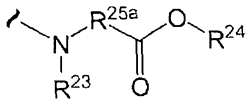
Table 20.36



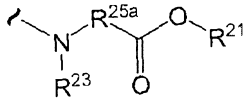
236



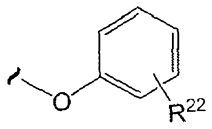
237



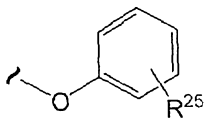
238



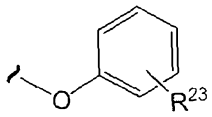
239



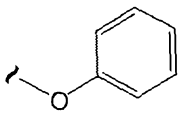
240



241

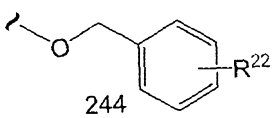


242

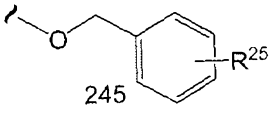


243

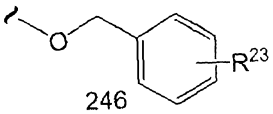
Table 20.37



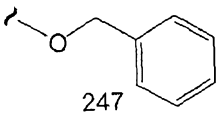
244



245

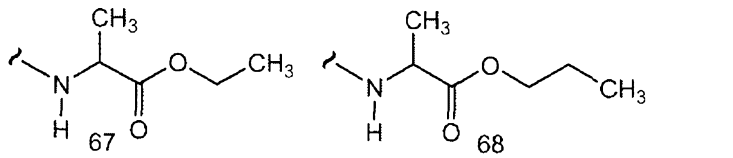


246

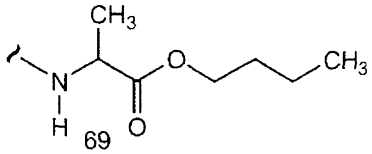


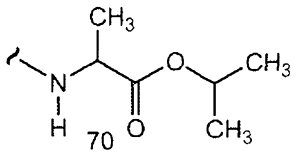
247

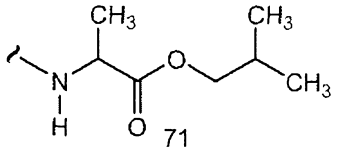
Table 30.1

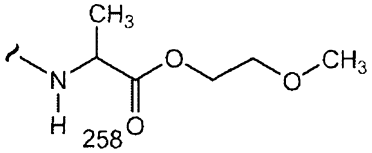

67

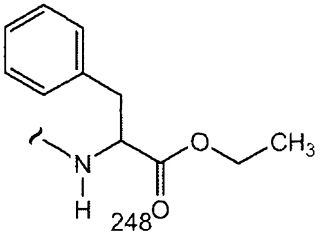
68

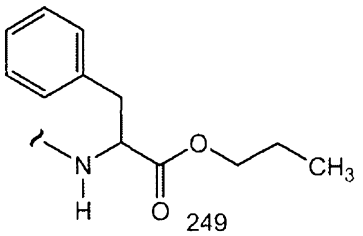

69

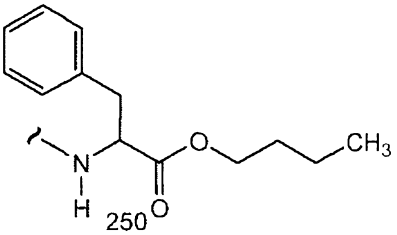

70

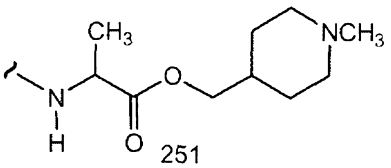

71

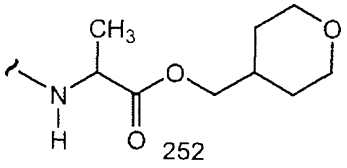

258

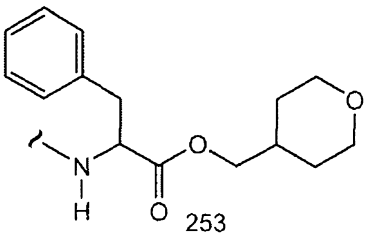

248

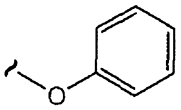

249

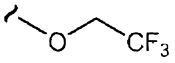

250


251

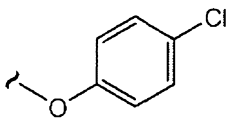

252


253

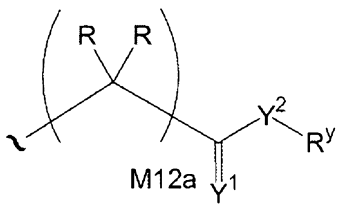

254


255

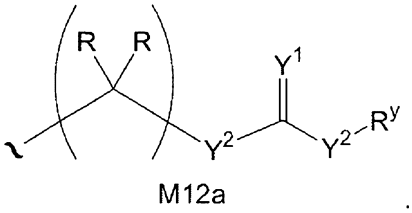

256


257

Embodiments of R^x include esters, carbamates, carbonates, thioesters, amides, thioamides, and urea groups:



and



Any reference to the compounds of the invention described heerein also includes a reference to a physiologically acceptable salt thereof. Examples of physiologically acceptable salts of the compounds of the invention include salts derived from an appropriate base, such as an alkali metal or an alkaline earth (for example, Na^+, Li^+, K^+, Ca^{+2} and Mg^{+2}), ammonium and NR_4^+ (wherein R is defined herein). Physiologically acceptable salts of a nitrogen atom or an amino group include (a) acid addition salts formed with inorganic acids, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acids, phosphoric acid, nitric acid and the like; (b) salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, maleic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, isethionic acid, lactobionic acid, tannic acid, palmitic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, benzenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, malonic acid, sulfosalicylic acid, glycolic acid, 2-hydroxy-3-naphthoate, pamoate, salicylic acid, stearic acid, phthalic acid, mandelic acid, lactic acid, ethanesulfonic acid, lysine, arginine, glutamic acid, glycine, serine, threonine, alanine, isoleucine, leucine and the like; and (c) salts formed from elemental anions for example, chlorine, bromine, and iodine. Physiologically acceptable salts of a compound of a hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+ and NR_4^+.

For therapeutic use, salts of active ingredients of the compounds of the invention will be physiologically acceptable, i.e. they will be salts derived from a

physiologically acceptable acid or base. However, salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a physiologically acceptable compound. All salts, whether or not derived form a physiologically acceptable acid or base, are within the scope of the present invention.

Finally, it is to be understood that the compositions herein comprise compounds of the invention in their un-ionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

The compounds of the invention, exemplified by Formula I-III may have chiral centers, e.g. chiral carbon or phosphorus atoms. The compounds of the invention thus include racemic mixtures of all stereoisomers, including enantiomers, diastereomers, and atropisomers. In addition, the compounds of the invention include enriched or resolved optical isomers at any or all asymmetric, chiral atoms. In other words, the chiral centers apparent from the depictions are provided as the chiral isomers or racemic mixtures. Both racemic and diastereomeric mixtures, as well as the individual optical isomers isolated or synthesized, substantially free of their enantiomeric or diastereomeric partners, are all within the scope of the invention. The racemic mixtures are separated into their individual, substantially optically pure isomers through well-known techniques such as, for example, the separation of diastereomeric salts formed with optically active adjuncts, e.g., acids or bases followed by conversion back to the optically active substances. In most instances, the desired optical isomer is synthesized by means of stereospecific reactions, beginning with the appropriate stereoisomer of the desired starting material.

The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

"Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties,

and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

"Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

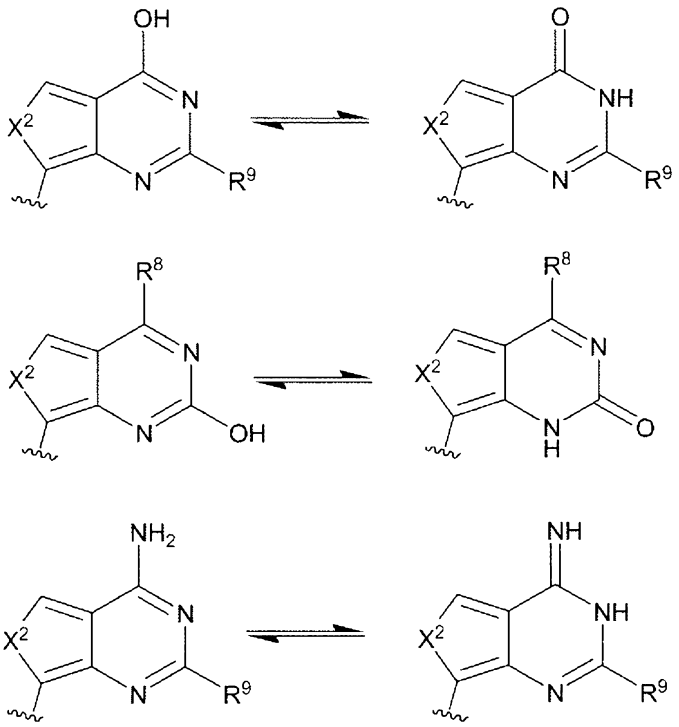
Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., Stereochemistry of Organic Compounds (1994) John Wiley & Sons, Inc., New York. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l, D and L, or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with S, (-), or l meaning that the compound is levorotatory while a compound prefixed with R, (+), or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

Whenever a compound described herein is substituted with more than one of the same designated group, e.g., "R" or "R^1", then it will be understood that the groups may be the same or different, i.e., each group is independently selected. Wavy lines, ~~~~, indicate the site of covalent bond attachments to the adjoining substructures, groups, moieties, or atoms.

The compounds of the invention can also exist as tautomeric isomers in certain cases. Although only one delocalized resonance structure may be depicted, all such forms are contemplated within the scope of the invention. For example, ene-amine tautomers can exist for purine, pyrimidine, imidazole, guanidine, amidine, and

tetrazole systems and all their possible tautomeric forms are within the scope of the invention.

One skilled in the art will recognize that the thieno[3,4-d]pyrimidinyl and furo[3,4-d]pyrimidinyl heterocycles can exist in tautomeric forms. For example, but not by way of limitation, structures (a) and (b) can have equivalent tautomeric forms as shown below:



a b

All possible tautomeric forms of the heterocycles in all of the embodiments disclosed herein are within the scope of the invention.

Methods of Inhibition of HCV polymerase

Another aspect of the invention relates to methods of inhibiting the activity of HCV polymerase comprising the step of treating a sample suspected of containing HCV with a composition of the invention.

Compositions of the invention may act as inhibitors of HCV polymerase , as intermediates for such inhibitors or have other utilities as described below. The

inhibitors will bind to locations on the surface or in a cavity of HCV polymerase having a geometry unique to HCV polymerase . Compositions binding HCV polymerase may bind with varying degrees of reversibility. Those compounds binding substantially irreversibly are ideal candidates for use in this method of the invention. Once labeled, the substantially irreversibly binding compositions are useful as probes for the detection of HCV polymerase . Accordingly, the invention relates to methods of detecting HCV polymerase in a sample suspected of containing HCV polymerase comprising the steps of: treating a sample suspected of containing HCV polymerase with a composition comprising a compound of the invention bound to a label; and observing the effect of the sample on the activity of the label. Suitable labels are well known in the diagnostics field and include stable free radicals, fluorophores, radioisotopes, enzymes, chemiluminescent groups and chromogens. The compounds herein are labeled in conventional fashion using functional groups such as hydroxyl, carboxyl, sulfhydryl or amino.

Within the context of the invention, samples suspected of containing HCV polymerase include natural or man-made materials such as living organisms; tissue or cell cultures; biological samples such as biological material samples (blood, serum, urine, cerebrospinal fluid, tears, sputum, saliva, tissue samples, and the like); laboratory samples; food, water, or air samples; bioproduct samples such as extracts of cells, particularly recombinant cells synthesizing a desired glycoprotein; and the like. Typically the sample will be suspected of containing an organism which produces HCV polymerase , frequently a pathogenic organism such as HCV. Samples can be contained in any medium including water and organic solvent\water mixtures. Samples include living organisms such as humans, and man made materials such as cell cultures.

The treating step of the invention comprises adding the composition of the invention to the sample or it comprises adding a precursor of the composition to the sample. The addition step comprises any method of administration as described above.

If desired, the activity of HCV polymerase after application of the composition can be observed by any method including direct and indirect methods of detecting

HCV polymerase activity. Quantitative, qualitative, and semiquantitative methods of determining HCV polymerase activity are all contemplated. Typically one of the screening methods described above are applied, however, any other method such as observation of the physiological properties of a living organism are also applicable.

Organisms that contain HCV polymerase include the HCV virus. The compounds of this invention are useful in the treatment or prophylaxis of HCV infections in animals or in man.

However, in screening compounds capable of inhibiting human immunodeficiency viruses, it should be kept in mind that the results of enzyme assays may not correlate with cell culture assays. Thus, a cell based assay should be the primary screening tool.

Screens for HCV polymerase Inhibitors.

Compositions of the invention are screened for inhibitory activity against HCV polymerase by any of the conventional techniques for evaluating enzyme activity. Within the context of the invention, typically compositions are first screened for inhibition of HCV polymerase *in vitro* and compositions showing inhibitory activity are then screened for activity *in vivo*. Compositions having *in vitro* Ki (inhibitory constants) of less then about 5 X 10^{-6} M, typically less than about 1 X 10^{-7} M and preferably less than about 5 X 10^{-8} M are preferred for *in vivo* use.

Useful *in vitro* screens have been described in detail and will not be elaborated here. However, the examples describe suitable *in vitro* assays.

Pharmaceutical Formulations

The compounds of this invention are formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will optionally contain excipients such as those set forth in the "Handbook of Pharmaceutical Excipients" (1986). Excipients include ascorbic acid and other antioxidants, chelating agents such

as EDTA, carbohydrates such as dextran, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10.

While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, of the invention comprise at least one active ingredient, as above defined, together with one or more acceptable carriers therefor and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, PA). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid

diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom.

For infections of the eye or other external tissues e.g. mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogs.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

The choice of suitable oils or fats for the formulation is based on achieving the

desired cosmetic properties. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

Pharmaceutical formulations according to the present invention comprise a combination according to the invention together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcelluose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally-occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally-occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

The pharmaceutical compositions of the invention may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily

measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 μg of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10%, and particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns, such as 0.5, 1, 30, 35 etc., which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis of HCV infections as described below.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the

intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

The formulations are presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefor.

Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

Compounds of the invention are used to provide controlled release pharmaceutical formulations containing as active ingredient one or more compounds of the invention ("controlled release formulations") in which the release of the active ingredient are controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of a given active ingredient.

Effective dose of active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses) or against an active viral infection, the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies. It can be expected to be from about

0.0001 to about 100 mg/kg body weight per day; typically, from about 0.01 to about 10 mg/kg body weight per day; more typically, from about .01 to about 5 mg/kg body weight per day; most typically, from about .05 to about 0.5 mg/kg body weight per day. For example, the daily candidate dose for an adult human of approximately 70 kg body weight will range from 1 mg to 1000 mg, preferably between 5 mg and 500 mg, and may take the form of single or multiple doses.

Routes of Administration

One or more compounds of the invention (herein referred to as the active ingredients) are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the condition of the recipient. An advantage of the compounds of this invention is that they are orally bioavailable and can be dosed orally.

Combination Therapy

Compositions of the invention are also used in combination with other active ingredients. Preferably, the other active therapeutic ingredients or agents are interferons, ribavirin or its analogs, HCV NS3 protease inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, nucleoside or nucleotide inhibitors of HCV NS5B polymerase, non-nucleoside inhibitors of HCV NS5B polymerase, HCV NS5A inhibitors, TLR-7 agonists, cyclophilin inhibitors, HCV IRES inhibitors, pharmacokinetic enhancers, and other drugs for treating HCV, or mixtures thereof. Combinations of the compounds of Formula I-III are typically selected based on the condition to be treated, cross-reactivities of ingredients and pharmaco-properties of the combination. For example, when treating an infection (e.g., HCV), the compositions of the invention are combined with other active therapeutic agents (such as those described herein).

Suitable active therapeutic agents or ingredients which can be combined with the compounds of Formula I-III can include interferons, e.g., pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, IFN alpha-2b XL, rIFN-alpha 2a, consensus IFN alpha, infergen, rebif, locteron, AVI-005, PEG-infergen, pegylated IFN-beta, oral interferon alpha, feron, reaferon, intermax alpha, r-IFN-beta, infergen + actimmune, IFN-omega with DUROS, and albuferon; ribavirin analogs, e.g., rebetol, copegus, VX-497, and viramidine (taribavirin); NS5a inhibitors, e.g., A-831, A-689 and BMS-790052; NS5b polymerase inhibitors, e.g., NM-283, valopicitabine, R1626, PSI-6130 (R1656), PSI-7851, PSI-7977, HCV-796, BILB 1941, MK-0608, NM-107, R7128, VCH-759, PF-868554, GSK625433, and XTL-2125; NS3 protease inhibitors, e.g., SCH-503034 (SCH-7), VX-950 (Telaprevir), ITMN-191, and BILN-2065; alpha-glucosidase 1 inhibitors, e.g., MX-3253 (celgosivir) and UT-231B; hepatoprotectants, e.g., IDN-6556, ME 3738, MitoQ, and LB-84451; non-nucleoside inhibitors of HCV, e.g., benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, and phenylalanine derivatives; and other drugs for treating HCV, *e.g.*, zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), DEBIO-025, VGX-410C, EMZ-702, AVI 4065, bavituximab, oglufanide, PYN-17, KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975, XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, and NIM811.

In yet another embodiment, the present application discloses pharmaceutical compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in combination with at least one additional therapeutic agent, and a pharmaceutically acceptable carrier or exipient.

According to the present invention, the therapeutic agent used in combination with the compound of the present invention can be any agent having a therapeutic effect when used in combination with the compound of the present invention. For example, the therapeutic agent used in combination with the compound of the present invention can be interferons, ribavirin or its analogs, HCV NS3 protease inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, nucleoside or nucleotide inhibitors of HCV NS5B polymerase, non-nucleoside inhibitors of HCV NS5B polymerase,

HCV NS5A inhibitors, TLR-7 agonists, cyclophilin inhibitors, HCV IRES inhibitors, pharmacokinetic enhancers, and other drugs for treating HCV, or mixtures thereof.

In another embodiment, the present application provides pharmaceutical compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in combination with at least one additional therapeutic agent selected from the group consisting of pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, IFN alpha-2b XL, rIFN-alpha 2a, consensus IFN alpha, infergen, rebif, locteron, AVI-005, PEG-infergen, pegylated IFN-beta, oral interferon alpha, feron, reaferon, intermax alpha, r-IFN-beta, infergen + actimmune, IFN-omega with DUROS, albuferon, rebetol, copegus, VX-497, viramidine (taribavirin), A-831, A-689, NM-283, valopicitabine, R1626, PSI-6130 (R1656), PSI-7851, PSI-7977, HCV-796, BILB 1941, MK-0608, NM-107, R7128, VCH-759, PF-868554, GSK625433, XTL-2125, SCH-503034 (SCH-7), VX-950 (Telaprevir), ITMN-191, and BILN-2065, MX-3253 (celgosivir), UT-231B, IDN-6556, ME 3738, MitoQ, and LB-84451, benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, and phenylalanine derivatives, zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), DEBIO-025, VGX-410C, EMZ-702, AVI 4065, bavituximab, oglufanide, PYN-17, KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975, XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, and NIM811 and a pharmaceutically acceptable carrier or exipient.

In yet another embodiment, the present application provides a combination pharmaceutical agent comprising:

a) a first pharmaceutical composition comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate, or ester thereof; and

b) a second pharmaceutical composition comprising at least one additional therapeutic agent selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, interferons, ribavirin analogs, NS3 protease inhibitors,

NS5a inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV, and combinations thereof.

Combinations of the compounds of Formula I-III and additional active therapeutic agents may be selected to treat patients infected with HCV and other conditions such as HIV infections. Accordingly, the compounds of Formula I-III may be combined with one or more compounds useful in treating HIV, for example HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, interferons, ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

More specifically, one or more compounds of the present invention may be combined with one or more compounds selected from the group consisting of 1) HIV protease inhibitors, *e.g.*, amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, lopinavir + ritonavir, nelfinavir, saquinavir, tipranavir, brecanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), AG1859, DG35, L-756423, RO0334649, KNI-272, DPC-681, DPC-684, and GW640385X, DG17, PPL-100, 2) a HIV non-nucleoside inhibitor of reverse transcriptase, *e.g.,* capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MIV-150, and TMC-120, TMC-278 (rilpivirine), efavirenz, BILR 355 BS, VRX 840773, UK-453,061, RDEA806, 3) a HIV nucleoside inhibitor of reverse transcriptase, *e.g.,* zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, racivir (±-FTC), D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, fosalvudine tidoxil, apricitibine (AVX754), amdoxovir, KP-1461, abacavir + lamivudine, abacavir + lamivudine + zidovudine, zidovudine + lamivudine, 4) a HIV nucleotide inhibitor of reverse transcriptase, *e.g.,* tenofovir, tenofovir disoproxil fumarate + emtricitabine, tenofovir disoproxil fumarate + emtricitabine + efavirenz, and adefovir, 5) a HIV integrase inhibitor, *e.g.*, curcumin, derivatives of curcumin, chicoric acid, derivatives of

chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, S-1360, zintevir (AR-177), L-870812, and L-870810, MK-0518 (raltegravir), BMS-707035, MK-2048, BA-011, BMS-538158, GSK364735C, 6) a gp41 inhibitor, *e.g.*, enfuvirtide, sifuvirtide, FB006M, TRI-1144, SPC3, DES6, Locus gp41, CovX, and REP 9, 7) a CXCR4 inhibitor, *e.g.*, AMD-070, 8) an entry inhibitor, *e.g.*, SP01A, TNX-355, 9) a gp120 inhibitor, *e.g.*, BMS-488043 and BlockAide/CR, 10) a G6PD and NADH-oxidase inhibitor, *e.g.*, immunitin, 10) a CCR5 inhibitor, *e.g.*, aplaviroc, vicriviroc, INCB9471, PRO-140, INCB15050, PF-232798, CCR5mAb004, and maraviroc, 11) an interferon, *e.g.*, pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, IFN alpha-2b XL, rIFN-alpha 2a, consensus IFN alpha, infergen, rebif, locteron, AVI-005, PEG-infergen, pegylated IFN-beta, oral interferon alpha, feron, reaferon, intermax alpha, r-IFN-beta, infergen + actimmune, IFN-omega with DUROS, and albuferon, 12) ribavirin analogs, e.g., rebetol, copegus, VX-497, and viramidine (taribavirin) 13) NS5a inhibitors, e.g., A-831, A-689 and BMS-790052, 14) NS5b polymerase inhibitors, e.g., NM-283, valopicitabine, R1626, PSI-6130 (R1656), PSI-7851, PSI-7977, HCV-796, BILB 1941, MK-0608, NM-107, R7128, VCH-759, PF-868554, GSK625433, and XTL-2125, 15) NS3 protease inhibitors, e.g., SCH-503034 (SCH-7), VX-950 (Telaprevir), ITMN-191, and BILN-2065, 16) alpha-glucosidase 1 inhibitors, e.g., MX-3253 (celgosivir) and UT-231B, 17) hepatoprotectants, e.g., IDN-6556, ME 3738, MitoQ, and LB-84451, 18) non-nucleoside inhibitors of HCV, e.g., benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, and phenylalanine derivatives, 19) other drugs for treating HCV, *e.g.*, zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), DEBIO-025, VGX-410C, EMZ-702, AVI 4065, bavituximab, oglufanide, PYN-17, KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975, XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, and NIM811, 19) pharmacokinetic enhancers, e.g., BAS-100 and SPI452, 20)RNAse H inhibitors, e.g., ODN-93 and ODN-112, 21) other anti-HIV agents, e.g., VGV-1, PA-457 (bevirimat), ampligen, HRG214, cytolin, polymun, VGX-410, KD247, AMZ 0026, CYT 99007,

A-221 HIV, BAY 50-4798, MDX010 (iplimumab), PBS119, ALG889, and PA-1050040.

It is also possible to combine any compound of the invention with one or more other active therapeutic agents in a unitary dosage form for simultaneous or sequential administration to a patient. The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations.

Co-administration of a compound of the invention with one or more other active therapeutic agents generally refers to simultaneous or sequential administration of a compound of the invention and one or more other active therapeutic agents, such that therapeutically effective amounts of the compound of the invention and one or more other active therapeutic agents are both present in the body of the patient.

Co-administration includes administration of unit dosages of the compounds of the invention before or after administration of unit dosages of one or more other active therapeutic agents, for example, administration of the compounds of the invention within seconds, minutes, or hours of the administration of one or more other active therapeutic agents. For example, a unit dose of a compound of the invention can be administered first, followed within seconds or minutes by administration of a unit dose of one or more other active therapeutic agents. Alternatively, a unit dose of one or more other therapeutic agents can be administered first, followed by administration of a unit dose of a compound of the invention within seconds or minutes. In some cases, it may be desirable to administer a unit dose of a compound of the invention first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of one or more other active therapeutic agents. In other cases, it may be desirable to administer a unit dose of one or more other active therapeutic agents first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a compound of the invention.

The combination therapy may provide "synergy" and "synergistic", i.e. the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or

delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or delivered sequentially, e.g. in separate tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, i.e. serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together. A synergistic anti-viral effect denotes an antiviral effect which is greater than the predicted purely additive effects of the individual compounds of the combination.

In still yet another embodiment, the present application provides for methods of inhibiting HCV polymerase in a cell, comprising: contacting a cell infected with HCV with an effective amount of a compound of Formula I-III, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, whereby HCV polymerase is inhibited.

In still yet another embodiment, the present application provides for methods of inhibiting HCV polymerase in a cell, comprising: contacting a cell infected with HCV with an effective amount of a compound of Formula I-III, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent, whereby HCV polymerase is inhibited.

In still yet another embodiment, the present application provides for methods of inhibiting HCV polymerase in a cell, comprising: contacting a cell infected with HCV with an effective amount of a compound of Formula I-III, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent selected from the group consisting of interferons, ribavirin or its analogs, HCV NS3 protease inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, nucleoside or nucleotide inhibitors of HCV NS5B polymerase, non-nucleoside inhibitors of HCV NS5B polymerase, HCV NS5A inhibitors, TLR-7 agonists, cyclophilin inhibitors, HCV IRES inhibitors, pharmacokinetic enhancers, and other drugs for treating HCV, or mixtures thereof.

In still yet another embodiment, the present application provides for methods of treating HCV in a patient, comprising: administering to the patient a therapeutically

effective amount of a compound of Formula I-III, or a pharmaceutically acceptable salt, solvate, and/or ester thereof.

In still yet another embodiment, the present application provides for methods of treating HCV in a patient, comprising: administering to the patient a therapeutically effective amount of a compound of Formula I-III, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent, whereby HCV polymerase is inhibited.

In still yet another embodiment, the present application provides for methods of treating HCV in a patient, comprising: administering to the patient a therapeutically effective amount of a compound of Formula I-III, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent selected from the group consisting of interferons, ribavirin or its analogs, HCV NS3 protease inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, nucleoside or nucleotide inhibitors of HCV NS5B polymerase, non-nucleoside inhibitors of HCV NS5B polymerase, HCV NS5A inhibitors, TLR-7 agonists, cyclophilin inhibitors, HCV IRES inhibitors, pharmacokinetic enhancers, and other drugs for treating HCV, or mixtures thereof.

In still yet another embodiment, the present application provides for the use of a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, for the preparation of a medicament for treating an HCV infection in a patient.

Metabolites of the Compounds of the Invention

Also falling within the scope of this invention are the *in vivo* metabolic products of the compounds described herein, to the extent such products are novel and unobvious over the prior art. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes novel and unobvious compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are

identified by preparing a radiolabelled (e.g. ^{14}C or ^{3}H) compound of the invention, administering it parenterally in a detectable dose (e.g. greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g. by MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention even if they possess no HCV polymerase inhibitory activity of their own.

Recipes and methods for determining stability of compounds in surrogate gastrointestinal secretions are known. Compounds are defined herein as stable in the gastrointestinal tract where less than about 50 mole percent of the protected groups are deprotected in surrogate intestinal or gastric juice upon incubation for 1 hour at 37°C. Simply because the compounds are stable to the gastrointestinal tract does not mean that they cannot be hydrolyzed *in vivo*. The prodrugs of the invention typically will be stable in the digestive system but may be substantially hydrolyzed to the parental drug in the digestive lumen, liver or other metabolic organ, or within cells in general.

Examples

Certain abbreviations and acronyms are used in describing the experimental details. Although most of these would be understood by one skilled in the art, Table 1 contains a list of many of these abbreviations and acronyms.

Table 1. List of abbreviations and acronyms.

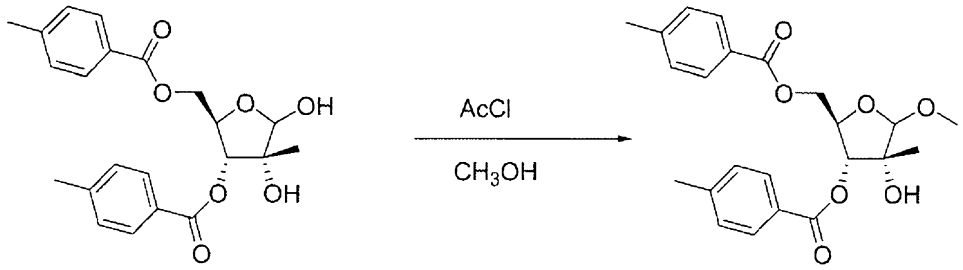
Abbreviation	Meaning

AIBN	2,2'-azobis(2-methylpropionitrile)
Bn	benzyl
BnBr	benzylbromide
BSA	bis(trimethylsilyl)acetamide
BzCl	benzoyl chloride
CDI	carbonyl diimidazole
DABCO	1,4-diazabicyclo[2.2.2]octane
DBN	1,5-diazabicyclo[4.3.0]nonene-5
Ac_2O	acetic anhydride
DBU	1,5-diazabicyclo[5.4.0]undecene-5
DCA	dichloroacetamide
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMTCl	dimethoxytrityl chloride
DMSO	dimethylsulfoxide
DMTr	4, 4'-dimethoxytrityl
DMF	dimethylformamide
EtOAc	ethyl acetate
ESI	electrospray ionization
HMDS	hexamethyldisilazane
HPLC	High pressure liquid chromatography
LDA	lithium diisopropylamide
LRMS	low resolution mass spectrum
mCPBA	meta-chloroperbenzoic acid
MeCN	acetonitrile
MeOH	methanol
MMTC	mono methoxytrityl chloride
m/z or m/e	mass to charge ratio

MH^+	mass plus 1
MH^-	mass minus 1
MsOH	methanesulfonic acid
MS or ms	mass spectrum
NBS	N-bromosuccinimide
rt or r.t.	room temperature
TBAF	tetrabutylammonium fluoride
TMSCl	chlorotrimethylsilane
TMSBr	bromotrimethylsilane
TMSI	iodotrimethylsilane
TEA	triethylamine
TBA	tributylamine
TBAP	tributylammonium pyrophosphate
TBSCl	t-butyldimethylsilyl chloride
TEAB	triethylammonium bicarbonate
TFA	trifluoroacetic acid
TLC or tlc	thin layer chromatography
Tr	triphenylmethyl
Tol	4-methylbenzoyl
δ	parts per million down field from tetramethylsilane

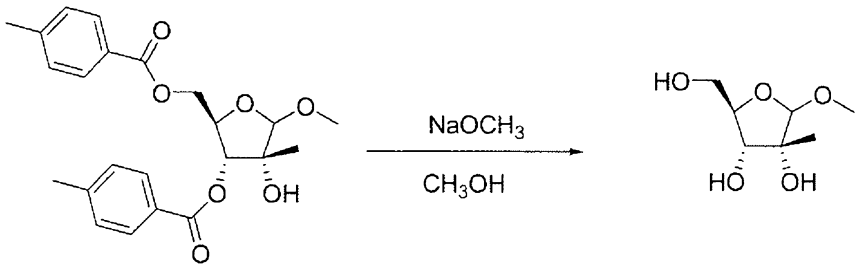
Preparation of Compounds

Compound 1



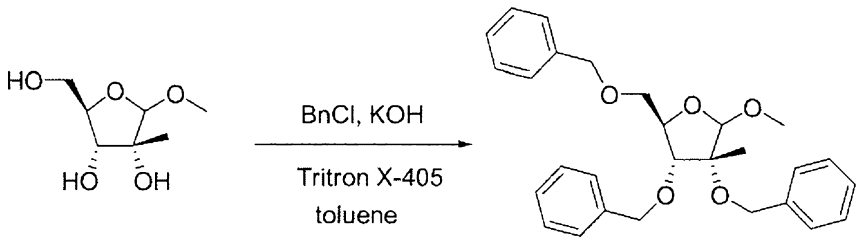
1a 1b

To a solution of **1a** (22.0 g, 54.9 mmol, prepared according to the procedures described in *J.O.C.*, **2004**, 6257) in methanol (300 mL) was dropwise added acetyl chloride (22 mL) at 0 °C using a dropping funnel over a period of 30 min. and then stirred at room temperature for 16 h. The mixture was concentrated, re-dissolved in ethyl acetate (400 mL), washed with ice-cold 2 N NaOH, and concentrated to dryness, affording the crude methyl ether **1b** as an oil. MS = 437.2 ($M+Na^+$).



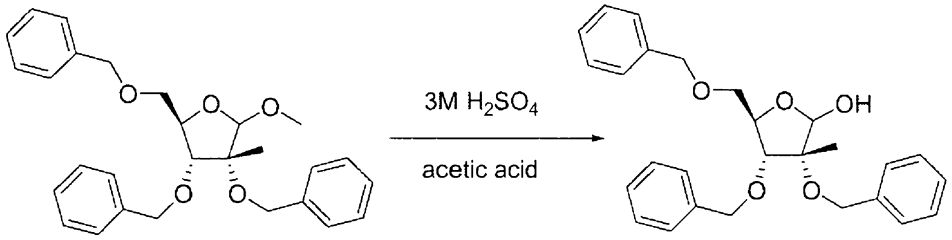
1b 1c

To a solution of **1b** (obtained from the previous step) in methanol (300 mL) was added 0.5 M sodium methoxide solution in methanol (20 mL, 10 mmol), and stirred for 16 h at room temperature. The reaction was quenched with 4.0 N HCl solution in dioxane (2.5 mL, 10 mmol). The mixture was then concentrated, affording the crude **1c**. MS = 201.0 ($M+Na^+$).



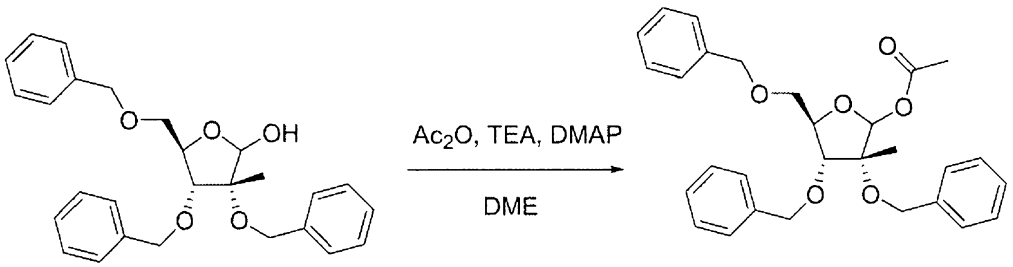
1c **1d**

A mixture of **1c** (obtained from the previous step), Tritron X-405 (70% in water, 6.0 g), 50% KOH (in water, 85 g) in toluene (500 mL) was heated to reflux with a Dean-Stark trap attached. After 1h collecting ~25 mL of water, benzyl chloride (33 g, 260 mmol) was added and continued to reflux with stirring for 16 h. The mixture was then cooled and partitioned between ethyl acetate (400 mL) and water (300mL). The organic layer was washed with water (300 mL), and concentrated. The residue was purified by silica gel column chromatography (~20% EtOAc / hexanes), affording the methyl ether **1d** as an oil (22.0 g, 89% in three steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.3 (m, 15H), 4.5 - 4.9 (m, 7H), 4.37 (m, 1H), 3.87 (d, 1H), 3.56 (m, 2H), 3.52 (s, 3H), 1.40 (s, 3H).



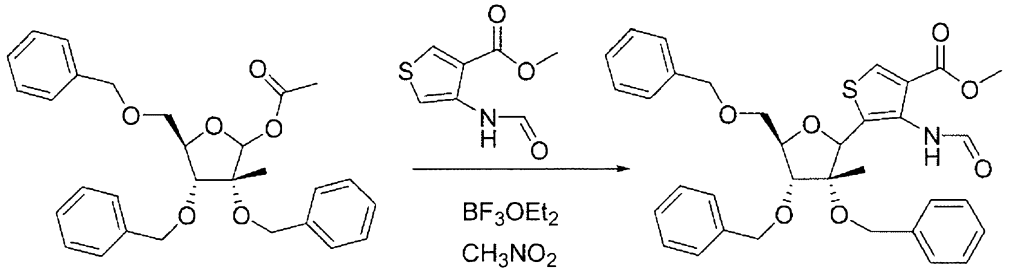
1d **1e**

To a solution of **1d** (22.0 g, 49.0 mmol) in acetic acid (110 mL) was added ~ 3 M sulfuric acid (prepared by mixing 4.8 g of concentrated sulfuric acid with 24 mL of water) and stirred at 70 °C for 8 h. The mixture was concentrated to a volume of ~20 mL, and partitioned between ethyl acetate and ice-cold 2N NaOH. The ethyl acetate layer was concentrated, and purified by silica gel column chromatography (~35% EtOAc / hexanes), affording **1e** as an oil (17.0 g, 80%). MS = 457.2 (M + Na^+).



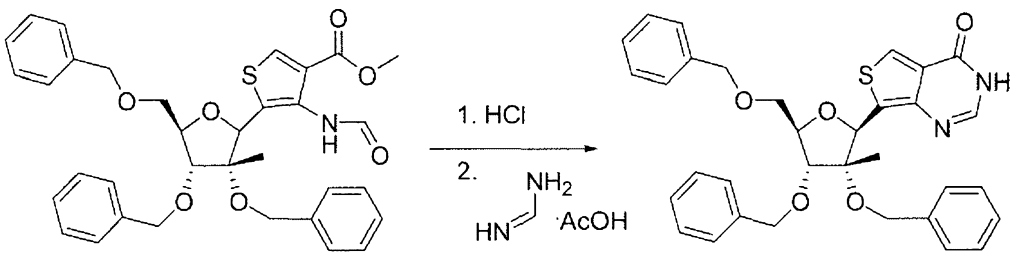
1e **1f**

To a solution of **1e** (21.0 g, 48.4 mmol), DMAP (790 mg, 4.84 mmol) and triethylamine (21.0 mL, 145 mmol) in dimethoxyethane (200 mL) was added acetic anhydride (6.85 mL, 72.5 mmol) at 0 °C. The resulting mixture was then stirred at room temperature for 16 h. The mixture was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (~10% EtOAc / hexanes), affording **1f** as an oil (22.8 g, 99%). MS = 499.0 ($M + Na^+$).



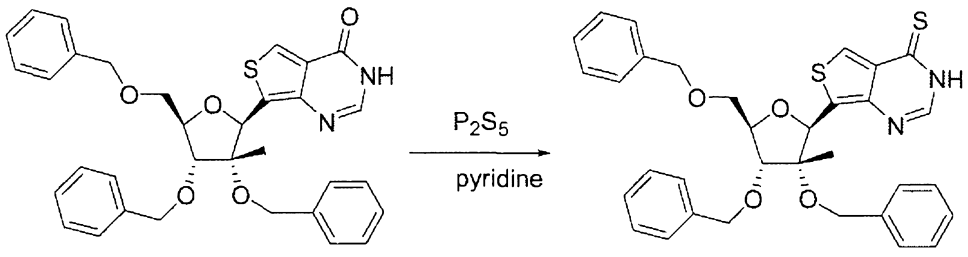
1f **1g**

To a solution of **1f** (1.70 g, 3.57 mmol) and 4-(*N*-formylamino)thiophene-3-carboxylic acid methyl ester (2.64 g, 14.3 mmol) in anhydrous nitromethane (12 mL) was added boron trifluoride diethyl ether complex (1.30 mL, 10.4 mmol) and stirred at room temperature for 16 h. The resulting mixture was poured into ice / saturated sodium bicarbonate. Ethyl acetate was added. The diphasic solution was stirred until the ice was melted completely. The ethyl acetate layer was then taken and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (~40% EtOAc / hexanes), affording **1g** as an oil (0.39 g, 18%). MS = 600.2 ($M - H^+$).



1g 1h

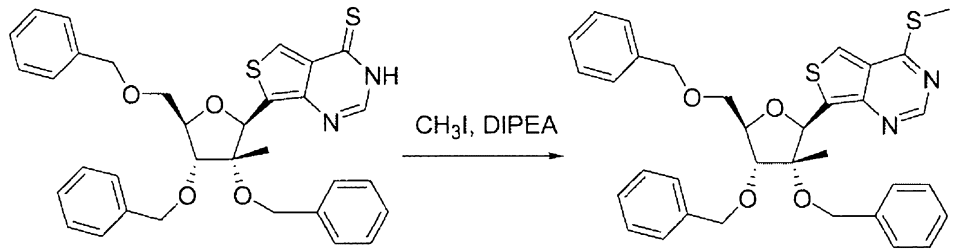
To a suspension of **1g** (390 mg, 0.65 mmol) in methanol (26 mL) was dropwise added concentrated HCl (4.5 mL) while stirring. The mixture was stirred at room temperature for 1 h. The resulting solution was concentrated *in vacuo* and dried. The residue was then dissolved in ethanol (20 mL). Formamidine acetate (680 mg, 6.5 mmol) and triethylamine (0.09 mL, 0.65 mmol) were added, and the mixture was stirred at reflux for 11 h. After cooling, the mixture was concentrated and partitioned between ethyl acetate and water. The ethyl acetate layer was concentrated and the residue was purified by silica gel column chromatography (~70% EtOAc / hexanes), affording **1h** as an oil (0.16 g, 43%). MS = 567.2 (M - H^+). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (s, 1H), 7.71 (s, 1H), 7.2-7.4 (m, 15H), 6.00 (s, 1H), 4.81 (ABq, 2H), 4.65 (m, 4H), 4.39 (m, 1H), 3.93 (d, 1H), 3.77 (ABdq, 2H), 1.10 (s, 3H).



1h 1i

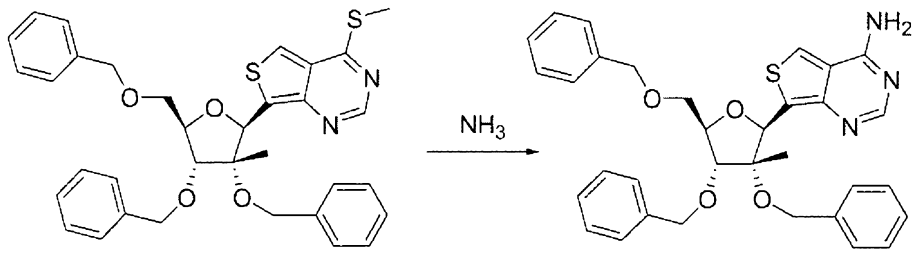
A mixture of **1h** (160 mg, 0.28 mmol) and P_2S_5 (137 mg, 0.31 mmol) in pyridine (2 mL) was heated to reflux for 30 min. The resulting mixture was concentrated and treated with 5% ammonium hydroxide (25 mL). The mixture was stirred for 30 min., and extracted with ethyl acetate. The ethyl acetate extract was concentrated, and the residue was purified by silica gel column chromatography

(~40% EtOAc / hexanes), affording **1i** as an oil (100 mg, 61%). MS = 585.1 ($M + H^+$). ^1H NMR (300 MHz, $CDCl_3$): δ 8.40 (s, 1H), 7.66 (s, 1H), 7.2-7.4 (m, 15H), 5.99 (s, 1H), 4.82 (ABq, 2H), 4.66 (m, 4H), 4.40 (m, 1H), 3.93 (d, 1H), 3.77 (ABdq, 2H), 1.08 (s, 3H).



1i **1j**

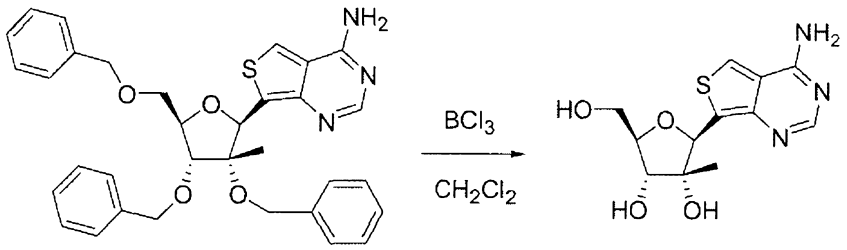
To a solution of **1i** (218 mg, 0.37 mmol) and diisopropylethylamine (0.13 mL, 0.75 mmol) in dichloromethane (3 mL) was added methyl iodide (0.035 mL, 0.56 mmol), and stirred at room temperature for 3 days. The mixture was concentrated, and the residue was purified by silica gel column chromatography (EtOAc / hexanes), affording **1j** as a yellow solid (221 mg, 99%). ^1H NMR (300 MHz, $CDCl_3$): δ 8.62 (s, 1H), 7.91 (s, 1H), 7.2-7.5 (m, 15H), 6.22 (s, 1H), 4.92 (ABq, 2H), 4.70 (m, 4H), 4.45 (m, 1H), 3.98 (d, 1H), 3.83 (ABdq, 2H), 2.71 (s, 3H), 1.06 (s, 3H).



1j **1k**

A mixture of **1j** (89 mg, 0.15 mmol) and ammonia in a bomb reactor was stirred at 40 °C for 16 h. After removal of ammonia, the residue was purified by silica gel column chromatography (EtOAc / hexanes), affording **1k** as a bright yellow solid (54 mg, 66%). MS = 568.3 ($M + H^+$). ^1H NMR (300 MHz, $CDCl_3$): δ 8.30 (s,

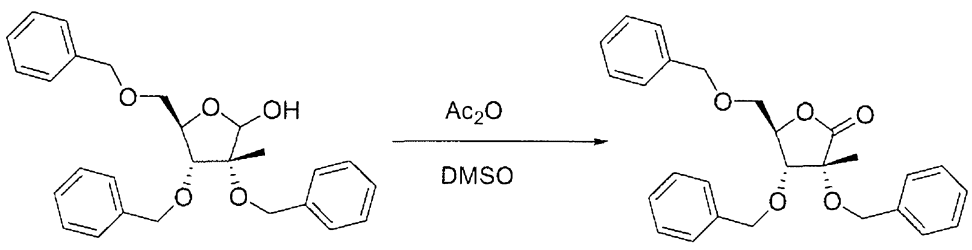
1H), 7.71 (s, 1H), 7.2-7.4 (m, 15H), 6.18 (s, 1H), 5.55 (brs, 2H), 4.86 (ABq, 2H), 4.64 (m, 4H), 4.43 (m, 1H), 3.98 (d, 1H), 3.83 (ABdq, 2H), 1.09 (s, 3H).



1k **Compound 1**

To a cooled (-78 °C) solution of **1k** (179 mg, 0.315 mmol) in dichloromethane (6 mL) was added 1.0 M solution of BCl_3 in dichloromethane (6 mL) and stirred for 1 h at the same temperature. A mixture of pyridine and methanol (1:2, 9 mL) was then added to quench the reaction. The resulting mixture was slowly warmed up to room temperature and concentrated. The residue was suspended in 27% ammonium hydroxide (30 mL) and concentrated. This process was repeated twice. The residue was re-dissolved in methanol (60 mL) and concentrated. This process was repeated once. The residue was purified by RP-HPLC (acetonitrile / water), affording **Compound 1** (75 mg, 80%) as an off-white solid. MS = 298.1 ($M + H^+$). ^1H NMR (300 MHz, CD_3OD): δ 8.55 (s, 1H), 8.20 (s, 1H), 5.48 (s, 1H), 3.8-4.1 (m, 4H), 0.96 (s, 3H).

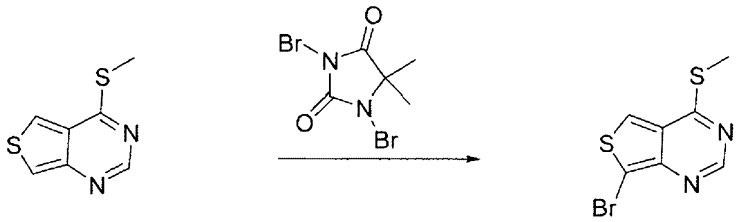
Compound 1m



1e **1m**

To a dry, argon purged round bottom flask (100 mL) were added anhydrous DMSO (6 mL) and anhydrous acetic anhydride (4 mL, 42.4 mmol). Compound **1e** (1.0 g, 2.3 mmol) was then added and the reaction mixture was allowed to stir at room temperature until complete disappearance of the starting material. After 17 h, the flask was placed into an ice bath and sat. $NaHCO_3$ (6 mL) was added to neutralize the reaction mixture. The organic material was then extracted using EtOAc (3 x 10 mL) and the combined organic layers were dried using $MgSO_4$. The solvent was removed under reduced pressure and the crude material was purified using flash silica gel chromatography (hexanes / EtOAc). 955 mg (96 %) of the desired material **1m** was isolated. LC/MS = 433.2 ($M + H^+$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.33 (m, 15H), 4.80 (d, 1H), 4.64 (m, 6H), 4.06 (d, 1H), 3.79 (dd, 1H), 3.64 (dd, 1H), 1.54 (s, 3H).

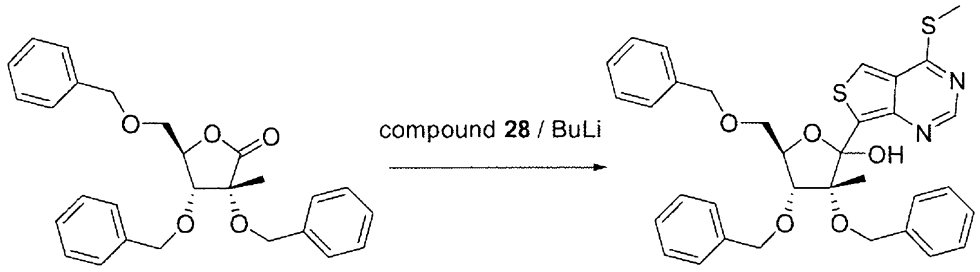
Compound 28: 7-bromo-4-(methylthio)thieno[3,4-d]pyrimidine



27 **28**

To a dry, argon purged round bottom flask (250 mL) were added 4-methylsulfanyl-thieno[3,4-d]pyrimidine (compound **27**, obtained according to *J. Heterocyclic Chem.*, **1993**, 30, 509; 3.9 g, 21.4 mmol) and anhydrous DMF (30 mL) The flask was then placed into an ice/brine bath (~ -20 °C) and allowed to stir for 15 min. 1,3-Dibromo-5,5-dimethylhydantoin (3.06 g, 10.7 mmol) was added in portions and the reaction mixture was allowed to stir until complete disappearance of the starting material. After 1.5 h, the flask was quenched with saturated aqueous $Na_2S_2O_3$, and the organic material was extracted using ethyl acetate (3 x 10 mL). The combined organic layers were dried using $MgSO_4$. The solvent was removed under reduced pressure and the crude material was purified using flash chromatography (ethyl acetate). 2.8 g (50 %) of the desired material **28** was isolated. LC/MS = 260.9 ($M + H^+$). ^1H NMR (400 MHz, CD_3OD): δ 9.02 (s, 1H), 7.09 (s, 1H), 2.47 (s, 3H).

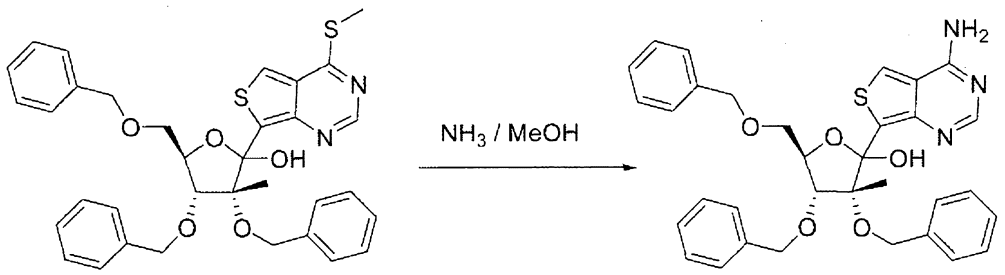
Compound 1n



1m **1n**

To a dry, argon purged round bottom flask were added 7-bromo-4-methylsulfanyl-thieno[3,4-d]pyrimidine (compound **28** shown above, 2.0 g, 7.66 mmol) and anhydrous THF (20 mL). The flask was then placed into a dry ice/acetone bath (-78 °C) and allowed to stir for 15 min. A solution of BuLi (6.56 mL, 10.5 mmol, 1.6 M in hexanes) was added dropwise. After 15 min, a solution of **1m** (3.02 g, 7.0 mmol) in THF (5 mL) was added to the flask at -78 °C via cannula. After 2 h of stirring at -78 °C, the flask was warmed to 0 °C. Saturated NH_4Cl (50 mL) was added to quench the reaction. The mixture was extracted using ethyl acetate (3 x 50 mL), and the combined organic layers were dried using $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified using flash silica gel chromatography (hexanes / ethyl acetate). 2.0 g (47 %) of the desired material **1n** was isolated. LC/MS = 615.2 ($M + H^+$). ^1H NMR (400 MHz, CD_3OD): δ 8.51 (s, 1H), 8.21 (s, 1H), 7.29 (m, 10H), 7.13 (m, 3H), 6.97 (m, 2H), 4.82 (d, 1H), 4.71 (t, 2H), 4.58 (q, 2H), 4.42 (m, 1H), 4.43 (d, 1H), 4.29 (m, 2H), 4.27 (d, 1H), 3.70 (m, 2H), 2.69 (s, 3H), 1.57 (s, 3H).

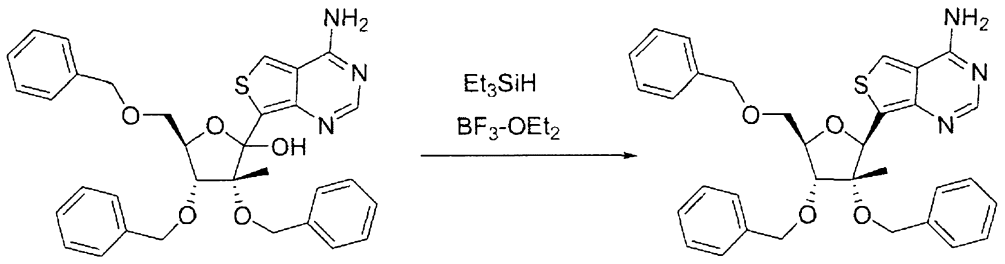
Compound 1o



1n **1o**

To a dry, argon purged round bottom flask were added 3,4-bis-benzyloxy-5-benzyloxymethyl-3-methyl-2-(4-methylsulfanyl-thieno[3,4-d]pyrimidin-7-yl)-tetrahydro-furan-2-ol (**1n**, 1.80 g, 2.93 mmol) and 7 N NH_3 in methanol (100 mL). The flask was then placed into a heating apparatus set at 45 °C and allowed to stir for 16 h. The solvent was then removed under reduced pressure, and the crude material was purified using flash silica gel chromatography (10 % methanol / ethyl acetate). 950 mg (56 %) of the desired material **1o** was isolated. LC/MS = 584.2 ($M + H^+$). ^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (s, 1H), 7.62 (s, 1H), 7.1 – 7.4 (m, 15H), 5.62 (brs, 2H), 5.04 (d, 1H), 4.64 (ABq, 2H), 4.57 (ABq, 2H), 4.43 (m, 2H), 4.28 (d, 1H), 3.67 (d, 2H), 1.44 (s, 3H).

Alternative Synthesis of Compound 1k

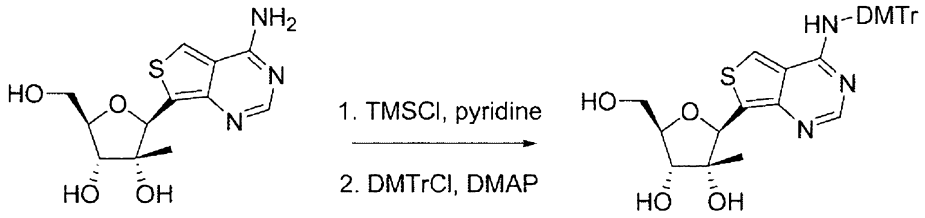


1o **1k**

To a solution of compound **1o** (950 mg, 1.63 mmol) in dichloromethane (13 mL) at -78 °C were added BF_3-OEt_2 (0.61 mL, 4.88 mmol) and Et_3SiH (0.78 mL, 4.88 mmol). The reaction mixture was warmed to 0 °C and allowed to stir for 1.5 h. The reaction was quenched with saturated aqueous sodium bicarbonate at 0 °C, and diluted

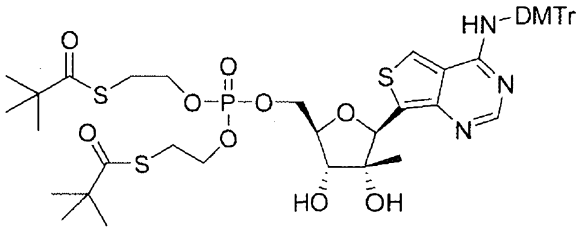
with ethyl acetate. The organic phase was separated, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel, eluted with ethyl acetate (100 %) to give 763 mg of the desired compound **1k** as a single stereoisomer (82 %). MS = 568.2 ($M + H^+$). ^1H NMR (400 MHz, $CDCl_3$): δ 8.28 (s, 1H), 7.69 (s, 1H), 7.30 (m, 15H), 6.17 (s, 1H), 4.91 (q, 1H), 4.72 (m, 5H), 4.41 (m, 1H), 3.97 (d, 1H), 3.75 (dq, 2H), 1.08 (s, 3H).

Compound 2



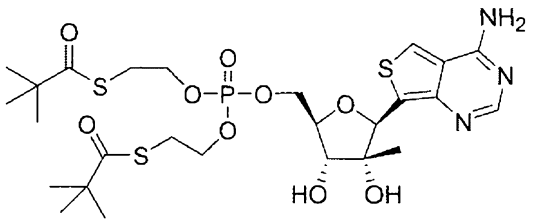
Compound 1 **2a**

Compound **1** (65 mg, 0.22 mmmol) was dissolved in anhydrous pyridine (2 mL) and chlorotrimethylsilane (0.17 mL) was added. The mixture was stirred at room temperature for 2 h. An additional chlorotrimethylsilane (0.1 mL) was added and stirred for 16 h. 4.4'-Dimethoxytrityl chloride (112 mg, 0.33 mmol) and DMAP (14 mg, 0.11 mmol) were sequentially added. The mixture was stirred overnight. A solution of TBAF (1.0 M, 0.22 mL) in THF was added and stirred at room temperature for 1 h. The mixture was partitioned between ethyl acetate and water. The ethyl acetate layer was taken and concentrated. The residue was purified by silica gel column chromatography (MeOH / dichloromethane), affording **2a** as a pale yellow solid (39 mg, 30%). MS = 600.1 ($M + H^+$). ^1H NMR (300 MHz, DMSO-d_6): δ 8.81 (s, 1H), 8.62 (s, 1H, NH), 7.76 (s, 1H), 7.1-7.4 (m, 9H), 6.83 (d, 4H), 5.53 (s, 1H), 5.02 (s, 1H, OH), 4.92 (d, 1H, OH), 4.81 (t, 1H, OH), 3.5-3.8 (m, 10H), 0.80 (s, 3H).



2b

To a solution of **2a** (32 mg, 0.053 mmol) and 1*H*-tetrazole (7.4 mg, 0.11 mmol) in anhydrous acetonitrile (5 mL) was added a solution of bis(*S*-pivaloyl-2-thioethyl) *N,N*-diisopropylphosphoramidite (29 mg, 0.064 mmol, prepared according to the procedure described in *J. Med. Chem.*, **1995**, 3941) in acetonitrile (0.2 mL) at 0 °C and allowed to warm to room temperature for 30 min. After stirring for 1.5 h, additional 1*H*-tetrazole (7 mg) and bis(*S*-pivaloyl-2-thioethyl) *N,N*-diisopropylphosphoramidite (15 mg) were added. The mixture was stirred for 5 min. at the same temperature and then stored in the freezer (-20 °C) overnight. The mixture was cooled to -40 °C. A solution of MCPBA (18 mg, 0.11 mmol) in dichloromethane (0.2 mL) was added and allowed to warm to room temperature for 30 min. Aqueous sodium sulfite (10%, 5 mL) and dichloromethane (~20 mL) were added while stirring. The organic layer was concentrated and the residue was purified by RP-HPLC (acetonitrile / water) to give **2b** as an oil (32 mg, 62%). MS = 968.2 (M + H^+).

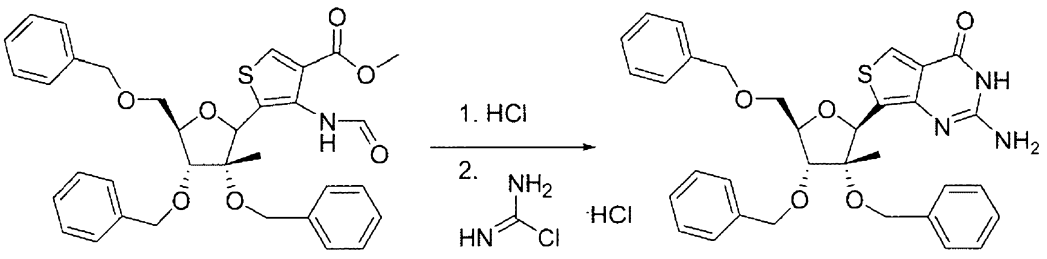


Compound 2

Compound **2b** (32 mg, 0.033 mmol) was dissolved in acetic acid (1.6 mL) and water (0.4 mL), and stirred at room temperature overnight. The mixture was then stirred at 35 °C for 4 additional hours to complete the reaction. The mixture was

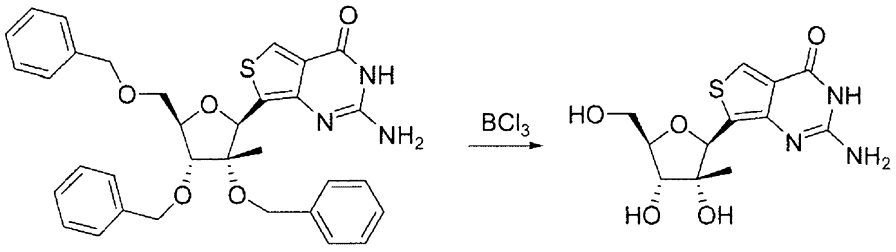
concentrated and purified by RP-HPLC (acetonitrile / water), affording **Compound 2** as a white solid (18 mg, 82%). MS = 666.0 ($M + H^+$). ^1H NMR (300 MHz, DMSO-d_6): δ 8.6 (brs, 2H), 8.58 (s, 1H), 8.17 (s, 1H), 5.58 (s, 1H), 5.34 (brs, 1H), 3.9-4.4 (m, 7H), 3.67 (t, 1H), 3.11 (m, 4H), 1.16 (s, 9H), 1.15 (s, 9H), 0.82 (s, 3H).

Compound 3



1g **3a**

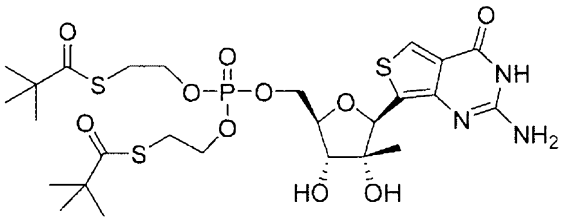
To a suspension of **1g** (400 mg, 0.66 mmol) in methanol (26 mL) was dropwise added concentrated HCl (4.5 mL) while stirring. The mixture was stirred at room temperature for 1 h. The resulting solution was concentrated *in vacuo* and dried. The residue was then mixed with methyl sulfone (6 g) and chloroamidine hydrochloride (113 mg, 0.99 mmol) in a microwave vial, and heated at 150 °C for 1 h. While cooling to room temperature, the mixture was treated with 1N ammonium hydroxide (5 mL) and ethyl acetate (5 mL) with vigorous stirring. The organic layer was concentrated and the residue was purified by silica gel column chromatography (EtOAc / hexanes), affording **3a** as an oil (0.05 g, 13%). MS = 584.0 ($M + H^+$). ^1H NMR (300 MHz, $CDCl_3$): δ 8.09 (s, 1H), 7.2-7.4 (m, 15H), 5.33 (s, 1H), 4.4-4.8 (m, 7H), 3.96 (m, 1H), 3.86 (m, 2H), 1.16 (s, 3H).



3a Compound 3

Compound 3 was obtained in a similar manner described for the preparation of **compound 1,** except starting with **3a**. MS = 313.9 ($M + H^+$). ^1H NMR (300 MHz, D_2O): δ 8.20 (s, 1H), 5.24 (s, 1H), 3.7-3.9 (m, 4H), 0.88 (s, 3H).

Compound 62



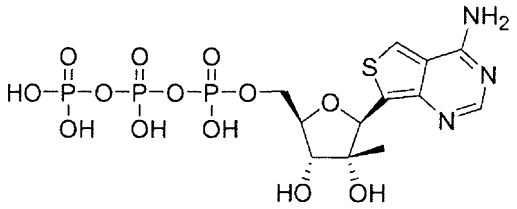
Compound 62 was prepared in the same manner as **Compound 2** starting with **Compound 3**. MS = 682.2 ($M + H^+$). ^1H NMR (300 MHz, DMSO-d_6): δ 8.36 (s, 1H), 7.4 (brs, 2H), 5.26 (s, 1H), 4.27 (m, 1H), 4.13 (m, 1H), 4.04 (m, 4H), 3.96 (m, 1H), 3.61 (d, 1H), 3.11 (t, 4H), 1.16 (s, 9H), 1.15 (s, 9H), 0.88 (s, 3H). ^{31}P NMR (121.4 MHz, DMSO-d_6): δ -1.58 (s).

General procedure for preparation of a nucleoside triphosphate:

To a pear-shaped flask (5-15 mL) was charged with a nucleoside (~20 mg). Trimethyl phosphate (0.5-1.0 mL) was added. The solution was cooled with ice-water bath. $POCl_3$ (40-45 mg) was added and stirred at 0 °C until the reaction was complete (1 to 4 h; the reaction progress was monitored by ion-exchange HPLC; analytical samples were prepared by taking ~3 uL of the reaction mixture and diluting

it with 1.0 M $Et_3NH_2CO_3$ (30-50 uL)). A solution of pyrophosphate-Bu_3N (250 mg) and Bu_3N (90-105 mg) in acetonitrile or DMF (1-1.5 mL) was then added. The mixture was stirred at 0 °C for 0.3 to 2.5 h, and then the reaction was quenched with 1.0 M $Et_3NH_2CO_3$ (~5 mL). The resulting mixture was stirred for additional 0.5-1 h while warming up to room temperature. The mixture was concentrated to dryness, re-dissolved in water (4 mL), and purified by ion exchange HPLC. The fractions containing the desired product was concentrated to dryness, dissolved in water (~5 mL), concentrated to dryness, and again dissolved in water (~5 mL). $NaHCO_3$ (30-50 mg) was added and concentrated to dryness. The residue was dissolved in water and concentrated to dryness again. This process was repeated 2-5 times. The residue was then subjected to C-18 HPLC purification, affording the desired product as sodium salts. Alternatively, the crude reaction mixture was purified by C-18 HPLC first and then by ion exchange HPLC.

Compound 4

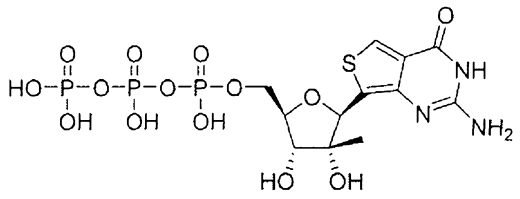


Compound 4

Compound 4 was prepared according to the procedure described above, starting with **Compound 1**.

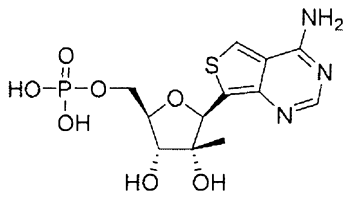
^1H NMR (300 MHz, D_2O): δ 8.20 (s, 1H), 7.92 (s, 1H), 5.69 (s, 1H), 4.00-4.30 (m, 4H), 0.83 (s, 3H). ^{31}P NMR (121.4 MHz, D_2O): -5.7 (d, J = 20.2 Hz), -10.7 (d, *J* = 19.4 Hz), -21.6 (dd, *J* = 20.2, 19.4 Hz).

Compound 63



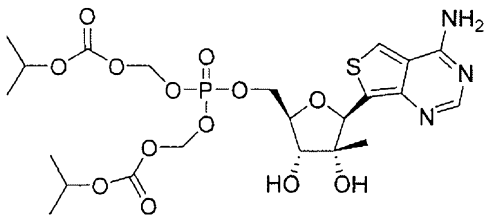
Compound 63 was prepared according to the procedure described above, starting with **Compound 3** and was isolated as a triethylamine salt. MS = 551.9 ($M - H^+$). ^1H NMR (300 MHz, D_2O): δ 8.03 (s, 1H), 4.99 (s, 1H), 4.1-4.3 (m, 2H), 3.9 (brs, 1H), 3.85 (d, 1H), 3.04 (m, $N\underline{CH_2}$), 1.12 (m, $CH_2\underline{CH_3}$), 0.87 (s, 3H). ^{31}P NMR (121.4 MHz, D_2O): -10.4 (d), -10.7 (d), -22.9 (t).

Compound 5



A mixture of about 0.05 mmol of **Compound 1** and about 0.5 mL of trimethylphosphate is sealed in a container. The mixture is cooled to about -10 to about 10 ^0C and about 0.075 mmol of phosphorous oxychloride is added. After about one to about 24 hours, the reaction is quenched with about 0.5 mL of 1M tetraethylammonium bicarbonate and the desired fractions are isolated by anion exchange chromatography. The appropriate fractions are then desalted by reverse-phase chromatography to give **Compound 5**.

Compound 6



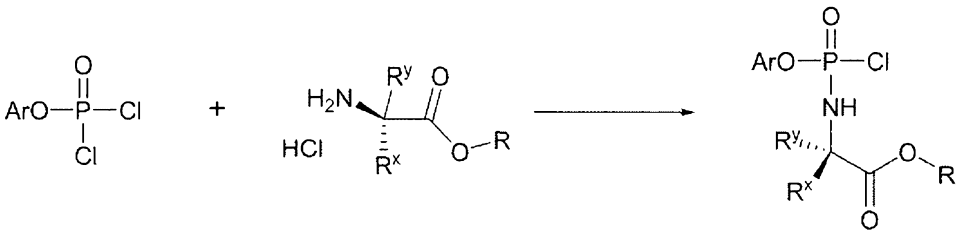
Compound 5 (about 1.19 mmol) is dried over phosphorous pentoxide in a vacuum for about overnight. The dried material is suspended in about 4 mL of anhydrous DMF and about 4.92 mmol DIPEA. About 7.34 mmol of *iso*-propyl chloromethyl carbonate (*Antiviral Chemistry & Chemotherapy* 8:557 (1997)) is added and the mixture is heated to about 25 to about 60 ^{0}C for about 30 min to about 24 hours. Heating is removed for about one to about 48 hours and the reaction filtered. The filtrate is diluted with water, **Compound 6** is partitioned into CH_2Cl_2, the organic solution is dried and evaporated, and the residue is purified by reverse-phase HPLC to isolate **Compound 6.**

Example 7

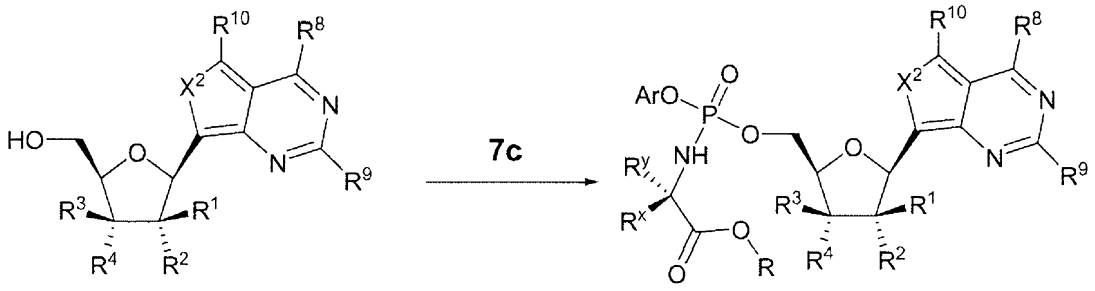
Mono Phosphoramidate Prodrugs

Non-limiting examples of mono-phosphoramidate prodrugs comprising the instant invention may be prepared according to general Scheme 1.

Scheme 1



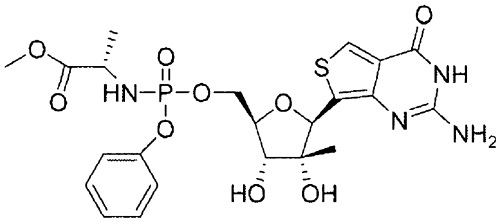
7a 7b 7c



7d 7e

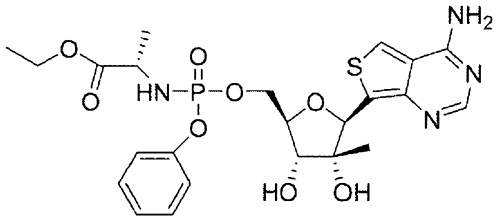
The general procedure comprises the reaction of an amino acid ester salt **7b**, e.g., HCl salt, with an aryl dichlorophosphate **7a** in the presence of about two to ten equivalents of a suitable base to give the phosphoramidate **7c**. Suitable bases include, but are not limited to, imidazoles, pyridines such as lutidine and DMAP, tertiary amines such as triethylamine and DABCO, and substituted amidines such as DBN and DBU. Tertiary amines are particularly preferred. Preferably, the product of each step is used directly in the subsequent steps without recrystallization or chromatography. Specific, but non-limiting, examples of **7a**, **7b**, and **7c** can be found in WO 2006/121820 that is hereby incorporated by reference in its entirety. A nucleoside base **7d** reacts with the phosphoramidate **7c** in the presence of a suitable base. Suitable bases include, but are not limited to, imidazoles, pyridines such as lutidine and DMAP, tertiary amines such as triethylamine and DABCO, and substituted amidines such as DBN and DBU. The product **7e** may be isolated by recrystallization and/or chromatography.

Compound 8



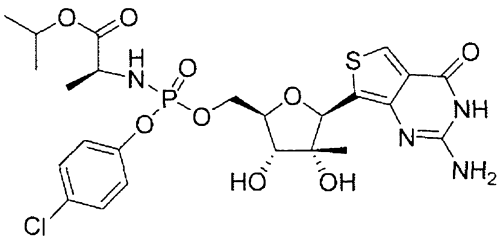
About 3.1 mmol of phenyl methoxyalaninyl phosphorochloridate (prepared according to McGuigan et al, *J. Med. Chem.* **1993**, *36*, 1048–1052) in about 3 mL of THF is added to a mixture of of about 0.5 mmol of **Compound 3** and about 3.8 mmol of N-methylimidazole in about 3 mL THF or anhydrous trimethylphosphate. The reaction is stirred for about 24 hours and the solvent is removed under reduced pressure. The residue is purified by reverse-phase HPLC to give **Compound 8**.

Compound 64



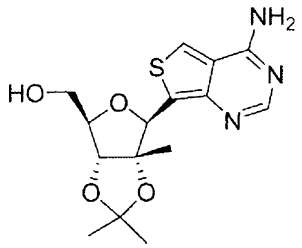
To a dry, argon purged round bottom flask (50 mL) were added **compound 1** (250 mg, 0.84 mmol) and anhydrous trimethylphosphate (15 mL). *N*-methyl imidazole (0.53 mL, 6.7 mmol) was then added and the flask was placed into an ice bath. After stiring for 15 min, phenyl ethoxyalaninyl phosphorochloridate (prepared according to McGuigan et al, *J. Med. Chem.* **1993**, *36*, 1048–1052; 1.6 g, 5.47 mmol) was added dropwise neat. The ice bath was removed and the reaction mixture warmed to room temperature, and was allowed to stir until complete disappearance of the starting material. After 45 min, MeOH (5 mL) was added to the flask and the mixture stirred for an additional 5 min. The solvent was then removed under reduced pressure, and the crude material was purified by HPLC to give 38 mg of **compound 64** (8%) as a mixture of two diasteroisomers. LC/MS = 551.2 ($M + H^+$). ^{31}P NMR (161.9 MHz, $CDCl_3$) 10.0

Compound 9



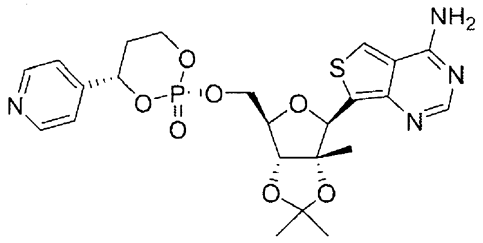
About 3.1 mmol of 4-chlorophenyl 2-propyloxyalaninyl phosphorochloridate (prepared according to McGuigan et al, *J. Med. Chem.* **1993**, *36*, 1048–1052) in about 3 mL of THF is added to a mixture of of about 0.5 mmol of **Compound 3** and about 3.8 mmol of N-methylimidazole in about 3 mL THF or anhydrous trimethylphosphate. The reaction is stirred for about 24 hours and the solvent is removed under reduced pressure. The residue is purified by reverse-phase HPLC to give **Compound 9**.

Compound 10



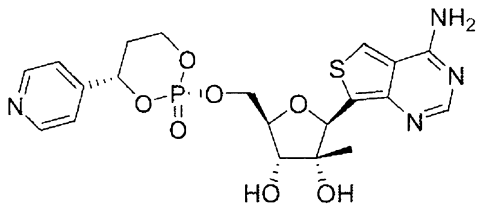
A mixture of about 0.52 mmol of **Compound 1** and about 12 mL dry acetone, about 0.7 mL of 2,2,-dimethoxypropane and about 1.28 mmol of di-*p*-nitrophenylphosphoric acid is stirred for about 24 hours to about seven days. The reaction mixture is neutralized with about 20 mL of 0.1 N $NaHCO_3$ and the acetone is evaporated. The desired material is partitioned into chloroform, the chloroform solution is dried, and the solvent is evaporated. **Compound 10** is purified from the residue by conventional means.

Compound 11



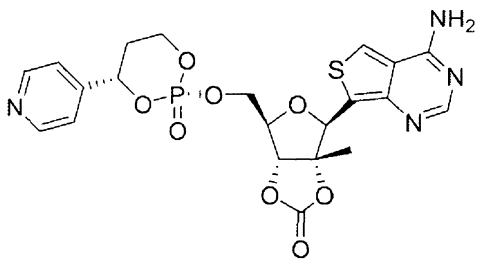
A solution of about 0.53 mmol of **Compound 10** in about 5 mL of DMF is treated with about 1 mL of a 1 M solution of *t*-butylmagnesium chloride in THF. After about 30 min to about 5 hours, a solution of about 0.65 mmol of *trans*-4-[(*S*)-pyridin-4-yl]-2-(4-nitrophenoxy)-2-oxo-1,3,2-dioxaphosphorinane (Reddy, *Tetrahedron Letters* **2005**, 4321-4324) is added and the reaction is stirred for about one to about 24 hours. The solution is concentrated in a vacuum and the residue is purified by chromatography to give **Compound 11.**

Compound 12



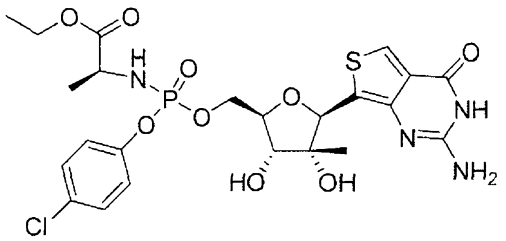
A solution of about 70% aqueous trifluoroacetic acid is cooled to 0 ^{0}C and is treated with about 0.32 mmol of **Compound 11** for about one to 24 hours. The solution is concentrated and the residue is purified by chromatography to give **Compound 12**.

Compound 13



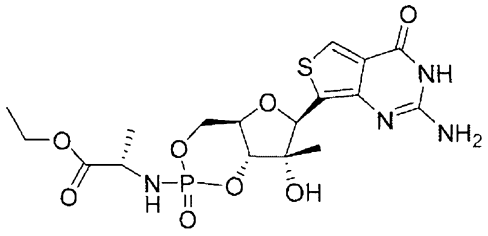
A solution of about 1.56 mmol of **Compound 12** in about 15 mL of THF is treated with about 4.32 mmol of CDI. After about one to about 24 hours, the solvent is evaporated and the residue is purified by chromatography to give **Compound 13**.

Compound 14



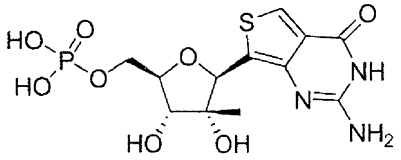
About 3.1 mmol of 4-chlorophenyl 2-ethoxyalaninyl phosphorochloridate (prepared according to McGuigan et al, *J. Med. Chem.* **1993**, *36*, 1048–1052) in about 3 mL of THF is added to a mixture of of about 0.5 mmol of **Compound 3** and about 3.8 mmol of N-methylimidazole in about 3 mL THF or anhydrous trimethylphosphate. The reaction is stirred for about 24 hours and the solvent is removed under reduced pressure. The residue is purified by reverse-phase HPLC to give **Compound 14**.

Compound 15



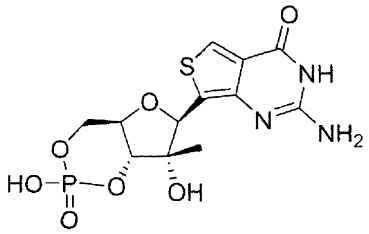
A solution of **Compound 14** in DMSO is treated with about 3 mole equivalents of potassium *t*-butoxide for about 15 min to 24 hours. The reactions is quenched with 1N HCl and **Compound 15** is isolated by reverse-phase HPLC.

Compound 16



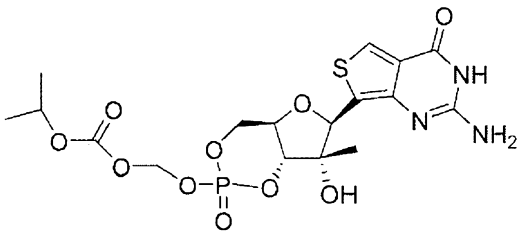
Compound 16 is prepared in the same manner as **Compound 5** but using **Compound 3** as a starting material.

Compound 17



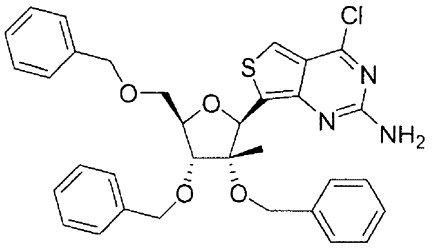
Compound 17 is prepared by treating **Compound 16** with about one to about five equivalents of DCC in pyridine and heating the reaction to reflux for about one to about 24 hours. **Compound 17** is isolated by conventional ion exchange and reverse-phase HPLC.

Compound 18



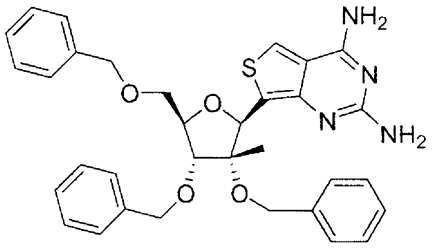
A solution of about 0.4 mmol of **Compound 17** in about 10 mL of DMF is treated with about 0.8 mmol of DIPEA and about 0.8 mmol of chloromethyl isopropyl carbonate (WO2007/027248). The reaction is heated to about 25 to about 80 ^{0}C for about 15 min to about 24 hours. The solvent is removed under vacuum and the residue is purified by HPLC to give **Compound 18**.

Compound 19



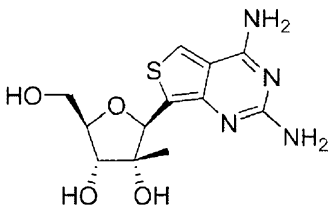
A solution of about 0.85 mmol of **Compound 3a** in about 5 mL acetonitrile is treated with about 1.7 mmol of benzyl triethylammonium chloride and about 1.28 mmol of *N,N* dimethylaniline. The reaction is heated to about 80 ^{0}C and is treated with about 5.1 mmol of phosphorus oxychloride for about 30 min to about 24 hours. The reaction is then concentrated, is treated with cold water, and is partitioned into chloroform. The extracts are dried, the solvent is evaporated, and the residue is purified by chromatograph to give **Compound 19**.

Compound 20



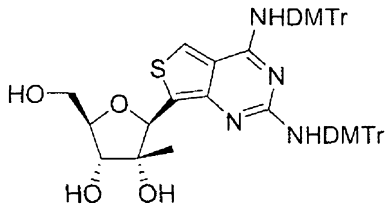
A mixture of **Compound 19** and ammonia in a bomb reactor is stirred at about 40 ^{o}C for about one to 24 hours. After removal of ammonia, the residue is purified by chromatography to give **Compound 20.**

Compound 21



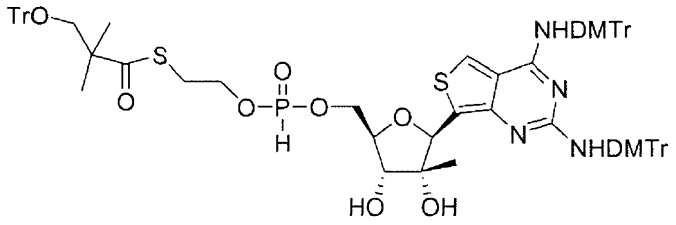
A solution of about 0.315 mmol of **Compound 20** in about 6 mL of dichloromethane is cooled to about -78 °C and about 6 mL of a 1.0 M solution of BCl_3 in dichloromethane is added. After about one to about 24 hours a mixture of pyridine and methanol (1:2, 9 mL) is added to quench the reaction. The resulting mixture is slowly warmed up to room temperature and is concentrated. The residue is suspended in 27% ammonium hydroxide (30 mL) and concentrated. The residue is re-dissolved in methanol (60 mL) and concentrated. The residue is purified by RP-HPLC to provide **Compound 21**.

Compound 22



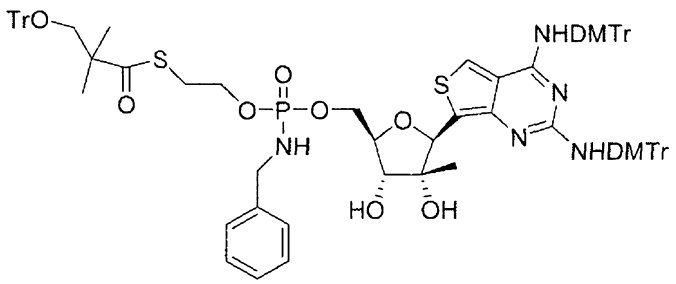
Compound **21** (about 0.22 mmmol) is dissolved in anhydrous pyridine (about 2 mL) and chlorotrimethylsilane (0.17 mL) is added. The mixture is stirred at about 0 to about 25 °C for about one to about 24 hours. Additional chlorotrimethylsilane (about 0.1 mL) is added and the reaction is stirred for about one to about 24 hours. 4.4'-Dimethoxytrityl chloride (about 0.66 mmol) and DMAP (about 0.11 to about 0.22 mmol) is sequentially added. The mixture is stirred for about one to about 24 hours. A solution of TBAF (1.0 M, about 0.22 mL) in THF is added and the reaction is stirred for about one to about 24 hours. The mixture is partitioned between ethyl acetate and water. The ethyl acetate layer is dried and concentrated. The residue is purified chromatography to afford **Compound 22.**

Compound 23



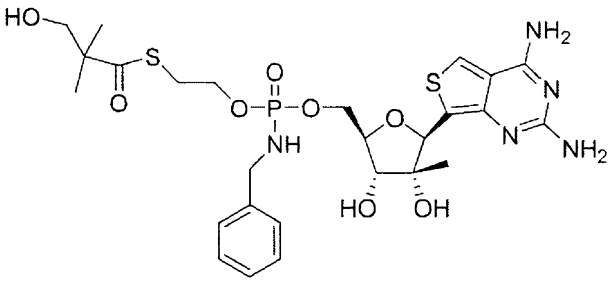
A mixture of about 1.25 mmol of **Compound 22** and about 1.9 mmol of triethylammonium 2-(2,2-dimethyl-3-(trityloxy)propanoylthio)ethyl phosphonate (WO2008082601) is dissolved in anhydrous pyridine (about 19 mL). Pivaloyl chloride (about 2.5 mmol) is added dropwise at about -30 to about 0 ^{0}C and the solution is stirred at for about 30 min to about 24 hours. The reaction is diluted with methylene chloride and is neutralized with agueous ammonium chloride (about 0.5M). The methylene chloride phase is evaporated and the residue is dried and is purified by chromatography to give **Compound 23**.

Compound 24



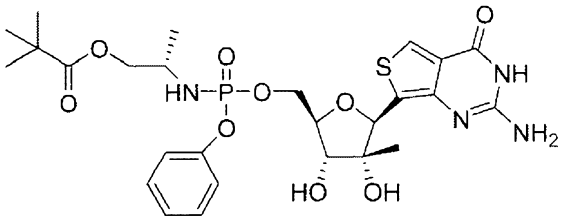
To a solution of about 0.49 mmol of **Compound 23** in anhydrous carbon tetrachloride (about 5 mL) is added dropwise benzylamine (about 2.45 mmol). The reaction mixture is stirred for about one to about 24 hours. The solvent is evaporated and the residue is purified by chromatography to give **Compound 24**.

Compound 25



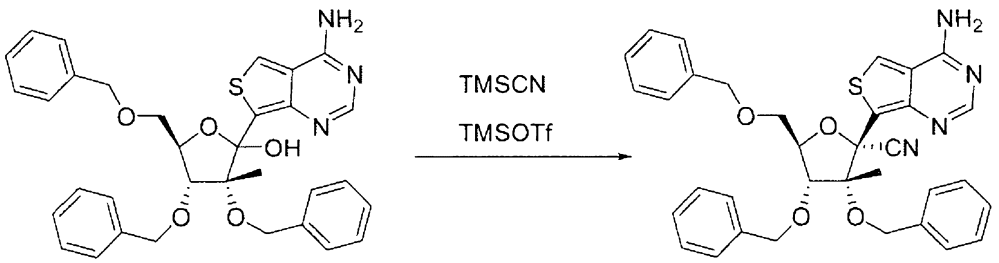
A solution of about 2 mmol of **Compound 24** in methylene chloride (about 10 mL) is treated with an aqueous solution of trifluoroacetic acid (90%, about 10 mL). The reaction mixture is stirred at about 25 to about 60 ^{0}C for about one to about 24 hours. The reaction mixture is diluted with ethanol, the volatiles are evaporated and the residue is purified by chromatography to give **Compound 25**.

Compound 26

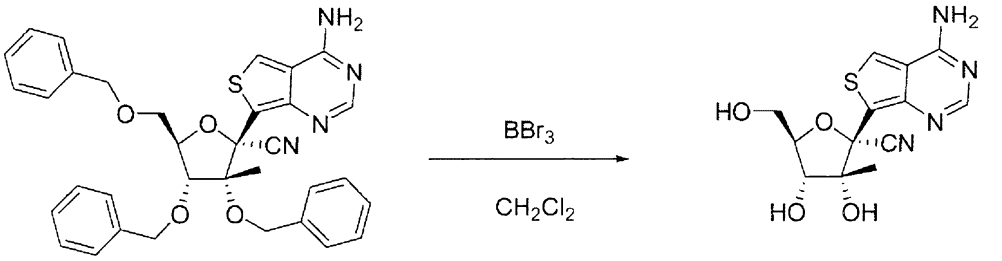


About 90 mM **Compound 3** in THF is cooled to about -78 ^{0}C and about 2.2 to about 4.4 equivalents of *t*-butylmagneisum chloride (about 1 M in THF) is added. The mixture is warmed to about 0 ^{0}C for about 30 min and is again cooled to about -78 ^{0}C. A solution of (*2S*)-2-{[chloro(1-phenoxy)phosphoryl]amino}propyl pivaloate (WO2008085508) (1 M in THF, about 2 equivalents) is added dropwise. The cooling is removed and the reaction is stirred for about one to about 24 hours. The reaction is quenched with water and the mixture is extracted with ethyl acetate. The extracts are dried and evaporated and the residue purified by chromatography to give **Compound 26**.

Compound 29



1o **29a**



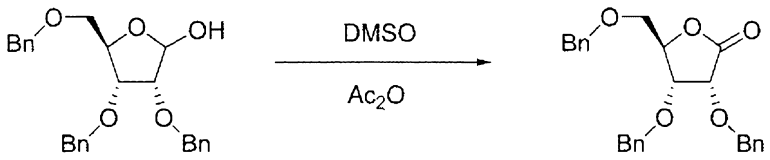
29a **29**

To a solution of compound **1o** (400 mg, 0.69 mmol) in dichloromethane (3.0 mL) at -15 °C was added TMSOTf (0.57 mL, 3.17 mmol) dropwise. Then, TMSCN (0.55 mL, 4.11 mmol) was added dropwise. The reaction mixture was stirred at -15 °C for 1.5 h, and then warmed to 0 °C for an additional 20 h. The reaction was quenched with saturated aqueous sodium bicarbonate (75 mL) at 0 °C, and diluted with dichloromethane (20 mL). The organic phase was separated, washed with brine (150 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel, eluted with hexanes-ethyl acetate (0 to 100 %), to give the desired compound **29a** as a single stereoisomer 120 mg (29 %). MS = 593.2 ($M + H^+$).

To a solution of compound **29a** (120 mg, 0.20 mmol) in dichloromethane (12 mL) at -78 °C was added BBr_3 (5 mL, 1M in dichloromethane). The reaction mixture was stirred at -78 °C for 1 h. The reaction was quenched at -78 °C by reverse dropwise addition into a flask of methanol (100 mL) at 0 °C. The mixture was allowed to warm up to room temperature, evaporated, and co-evaporated with methanol several times. The residue was dissolved in water, filtered, concentrated

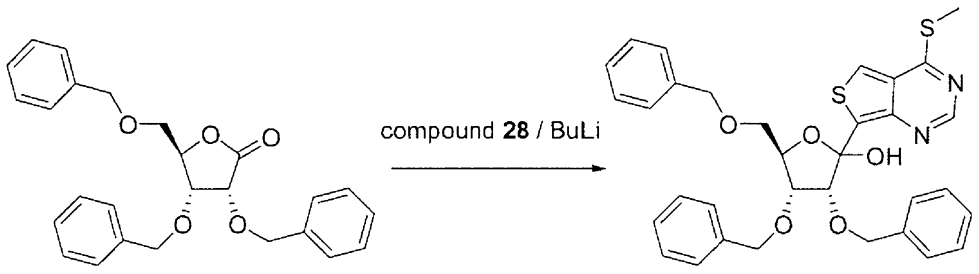
and purified by HPLC to give 5 mg of the desired compound **29** (8 %). LC/MS = 323.1 ($M + H^+$). ^1H NMR (400 MHz, D_2O): δ 8.37 (s 1H), 8.07 (s, 1H), 4.24 (m, 1H), 3.88 (m, 3H), 0.97 (s, 3H).

Compound 30



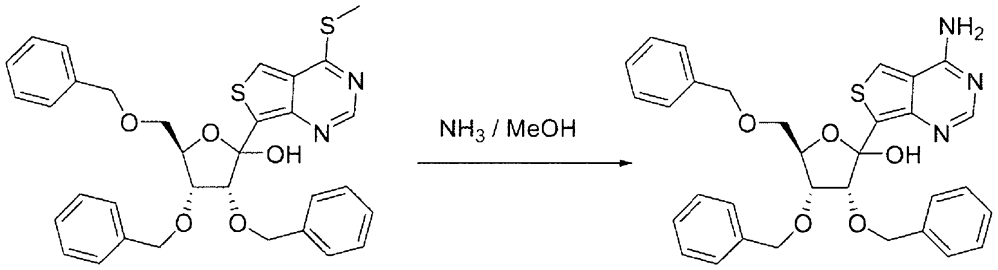
30a **30b**

Compound **30a** (prepared according to *J. Org. Chem.*, **1961**, *26*, 4605; 10.0 g, 23.8 mmol) was dissolved in anhydrous DMSO (30 mL) and placed under nitrogen. Acetic anhydride (20 mL) was added, and the mixture was stirred for 48 h at room temperature. When the reaction was complete by LC/MS, it was poured onto 500 mL ice water and stirred for 20 min. The aqueous layer was extracted with ethyl acetate (3 x 200 mL). The organic extracts were combined and washed with water (3 x 200 mL). The aqueous layers were discarded and the organic was dried over anhydrous $MgSO_4$ and evaporated to dryness. The residue was taken up in DCM and loaded onto a silica gel column. The final product **30b** was purified by elution with 25% EtOAc / hexanes; 96% yield. ^1H-NMR (CD_3CN): δ 3.63-3.75 (m, 2H), 4.27 (d, 1H), 4.50-4.57 (m, 3H), 4.65 (s, 3H), 4.69-4.80 (m, 2H), 7.25 (d, 2H), 7.39 (m, 13H).



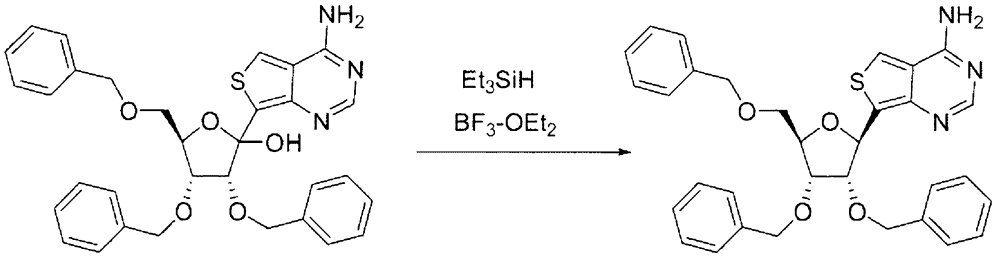
30b **30c**

Compound 30c may be obtained in the same manner as **Compound 1n** by substituting **Compound 30b** for **Compound 1m** in the reaction.



30c **30d**

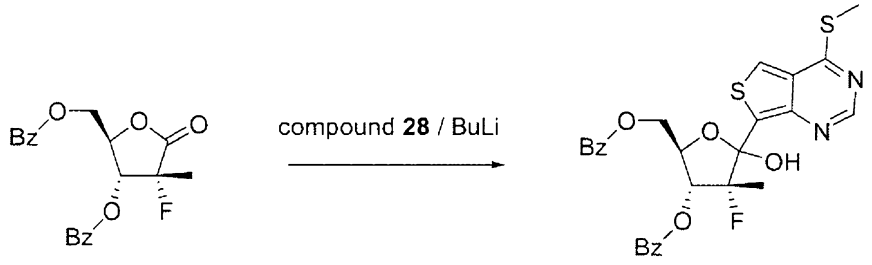
Compound 30d may be obtained in the same manner as **Compound 1o** by substituting **Compound 30c** for **Compound 1n** in the reaction.



30d **30**

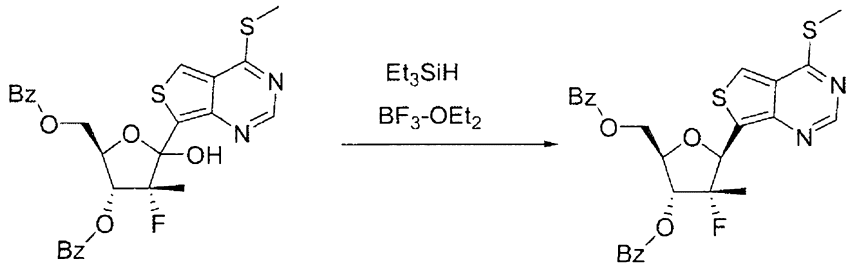
Compound 30 may be obtained in the same manner as **Compound 1k** by substituting **Compound 30d** for **Compound 1o** in the reaction.

Compound 31



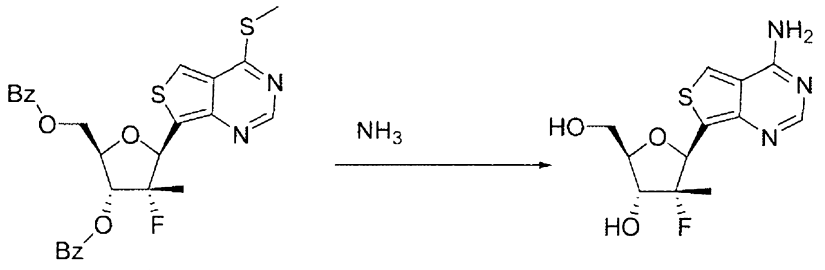
31a **31b**

A suspension of 7-bromo-4-(methylthio)thieno[3,4-d]pyrimidine (**28**) (about 10 mmol) in THF (about 20 mL) is cooled to about -78 °C and a solution of BuLi (about 11 mmol) in hexanes is added dropwise. The mixture is stirred for about 30 min. to about 4 h at the same temperature. A solution of **31a** (prepared according to WO 200631725, about 12 mmol) in THF (about 10 mL) is then added and the reaction is stirred for about 1 h to about 8 h at about -78 °C. Saturated ammonium chloride is added to quench the reaction. The mixture is extracted with ethyl acetate. The organic extract is concentrated *in vacuo* and the residue is purified by chromatography to give **31b**.



31b **31c**

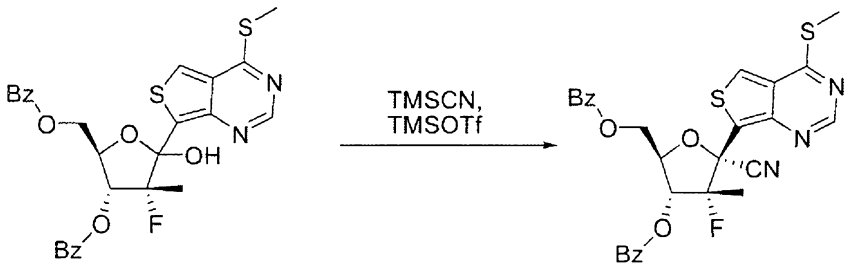
A solution of **31b** (about 1.40 mmol) in dichloromethane (about 20 mL) is treated with boron trifluoride etherate (about 2 mL) and triethylsilane (about 2 mL), and is stirred at about room temperature for about 1h to about 24h. Additional boron trifluoride etherate and triethylsilane may be added to complete the reduction. The mixture is diluted with dichloromethane and saturated sodium bicarbonate. The organic layer is washed sequentially with water, saturated ammonium chloride and brine, is dried over magnesium sulfate, and is concentrated. The residue is purified by chromatography to afford **31c**.



31c 31

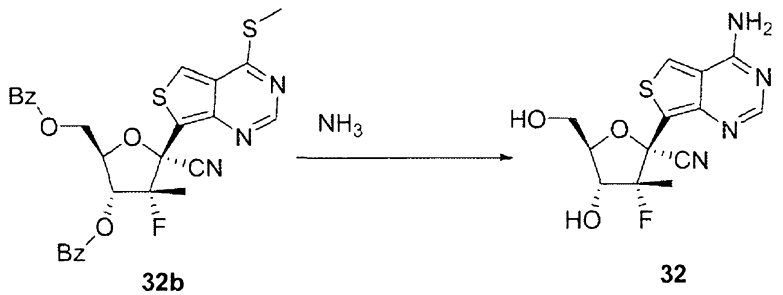
Compound **31c** (about 1.12 mmol) is placed in a steel bomb reactor that is charged with liquid ammonia (~30 mL). The bomb reactor is tightly sealed and the mixture is stirred at about 23 to about 80 °C for about 1 h to about 24 h. The ammonia is evaporated and the solid residue is dissolved in THF (about 10 mL) and MeOH (about 10 mL). Sodium ethoxide (about 25% wt., about 0.63 mL) is added and the mixture is stirred at about 23 to about 65 °C for about 10 min to about 6 h. The mixture is neutralized with AcOH and concentrated. The residue is purified by chromatography to afford **31**.

Compound 32



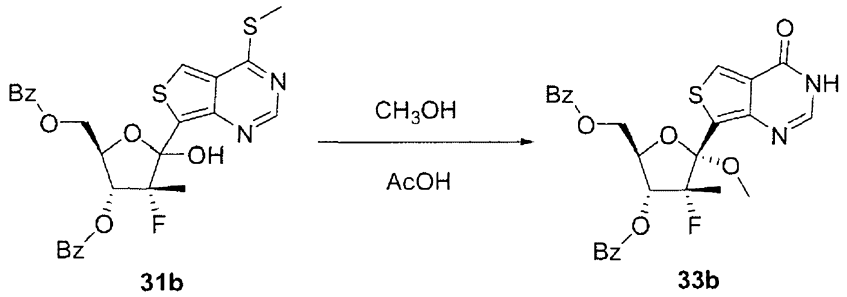
31b 32b

A solution of compound **31b** (about 0.1 mmol) and TMSCN (about 0.5 mmol) in acetonitrile (about 2.0 mL) at about 0 to about 25 °C is treated with TMSOTf (about 0.5 mmol). The reaction mixture is stirred at about room temperature for 1 h, then at about 65 °C for about 3 days. The reaction is quenched with saturated $NaHCO_3$ and diluted with CH_3CO_2Et. The organic phase is separated, is washed with brine, is dried over Na_2SO_4, is filtered and is concentrated. The residue is purified by chromatography to give **32b.**

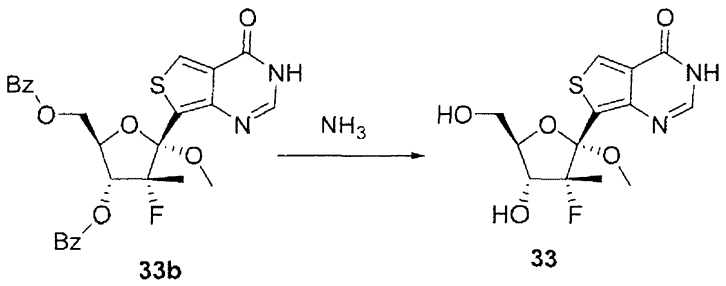


Compound **32** is prepared from **32b** by the same procedure that is used to convert **31c** to **31**.

Compound 33

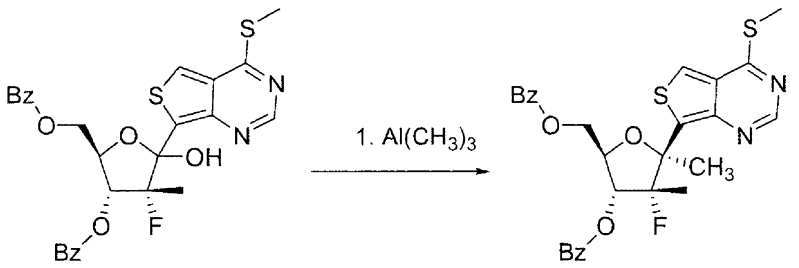


Compound 31b (about 0.04 mmol) and anhydrous MeOH (about 5 mL) is treated with acetic acid (about 5 mL) and the reaction is stirred overnight at about room temperature. Saturated $NaHCO_3$ is added to neutralize the reaction mixture and the crude material is purified by chromatography to give **33b**.



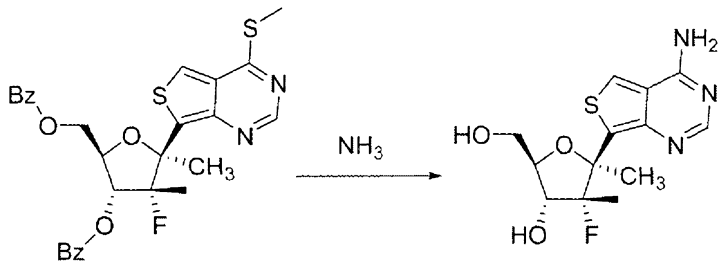
Compound **33** is prepared from **33b** by the same procedure that is used to convert **31c** to **31**.

Compound 34



31b **34b**

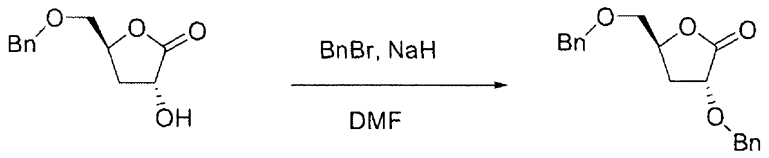
To a dry, argon purged round bottom flask (50 mL) is added compound **31b** (about 0.39 mmol) and anhydrous dichloromethane (about 10 mL). The flask is placed into a dry ice/acetone bath (~ -78 °C) and the solution is stirred for about 10 min. BF_3-Et_2O (about 0.10 mL) is added dropwise and the reaction is stirred for about 10 min. $AlMe_3$ (about 1.16 mmol, 2.0 M in toluene) is then added. After a few minutes, the dry ice/acetone bath is removed and the reaction mixture is stirred at room temperature to about 45 °C over about 4 h to about 4 d. A solution of pyridine (about 2 mL) in MeOH (about 10 mL) is added and the solvent is removed under reduced pressure. The crude material is purified by chromatography to give **34b**.



34b **34**

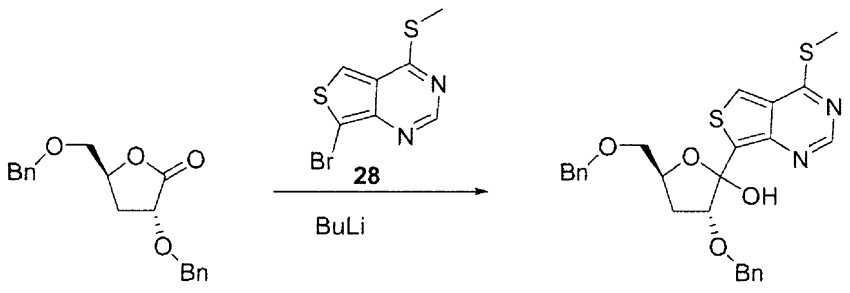
Compound **34** is prepared from **34b** by the same procedure that is used to convert **31c** to **31**.

Compound 35



35a **35b**

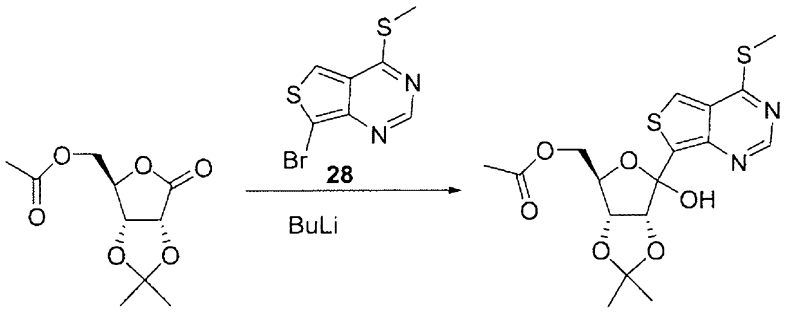
To a suspension of sodium hydride (about 60% suspension in oil, about 10 mmol) in DMF (about 20 mL) is added dropwise a solution of **35a** (prepared according to *J. Chem. Soc., Perkin Trans 1*, **1991**, 490, about 2.2 g, 10 mmol) in DMF (about 10 mL) at about 0 °C. The mixture is then stirred at about room temperature until the gas evolution ceases. Benzyl bromide (about 1 eq.) is added and the mixture is stirred for about 1 to16 h at about 0 to 100 °C. The mixture is poured into ice-water (300 mL) and extracted with ethyl acetate. The organic extract may be purified by silica gel chromatography to give **35b**.



35b **35**

A suspension of 7-bromo-4-(methylthio)thieno[3,4-d]pyrimidine (**28**) (about 10 mmol) in THF (about 20 mL) is cooled to about -78 °C and a solution of BuLi (about 11 mmol) in hexanes is added dropwise. The mixture is stirred for about 30 min. to about 4 h at the same temperature. A solution of **35b** (about 12 mmol) in THF (about 10 mL) is then added and the reaction is stirred for about 1 h to about 8 h at about -78 °C. Saturated ammonium chloride is added to quench the reaction. The mixture is extracted with ethyl acetate. The organic extract is concentrated *in vacuo* and the residue is purified by chromatography to give **35**.

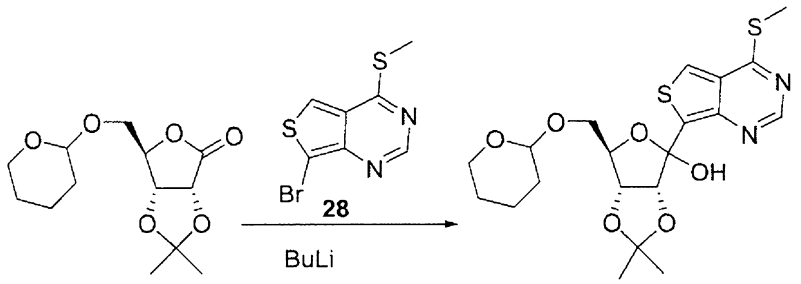
Compound 36



36a **36**

Compound 36 may be synthesized in the same manner as **35** by substituting **Compound 36a** (Ogura, et al. *J. Org. Chem.* **1972**, *37*, 72-75) for **35b** in the reaction.

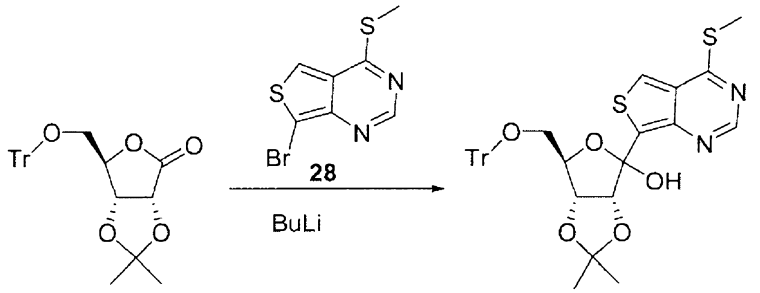
Compound 37



37a **37**

Compound 37 may be synthesized in the same manner as **35** by substituting **Compound 37a** (Ogura, et al. *J. Org. Chem.* **1972**, *37*, 72-75) for **35b** in the reaction.

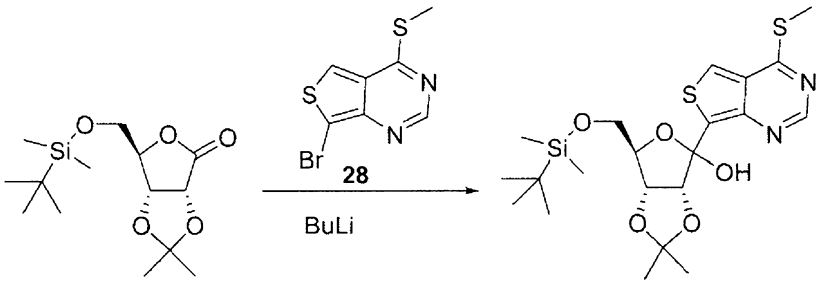
Compound 38



38a **38**

Compound 38 may be synthesized in the same manner as **35** by substituting **Compound 38a** (Camps, et al.; *Tetrahedron* **1982**, *38*, 2395-2402) for **35b** in the reaction.

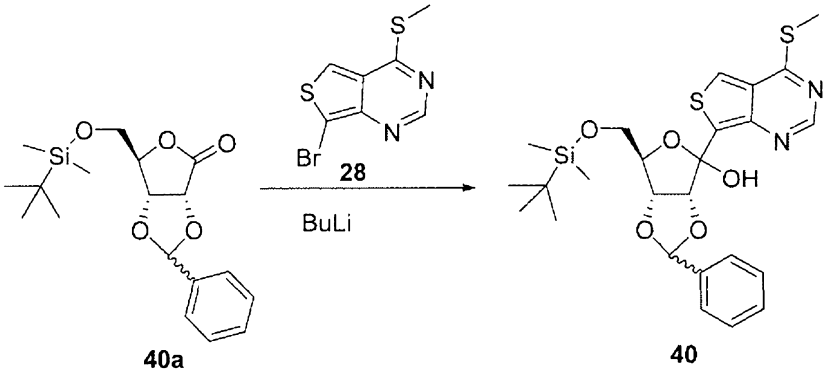
Compound 39



39a **39**

Compound 39 may be synthesized in the same manner as **35** by substituting **Compound 39a** (Alessandrini, et al.; *J. Carbohydrate Chem.* **2008**, *27*, 322-344) for **35b** in the reaction.

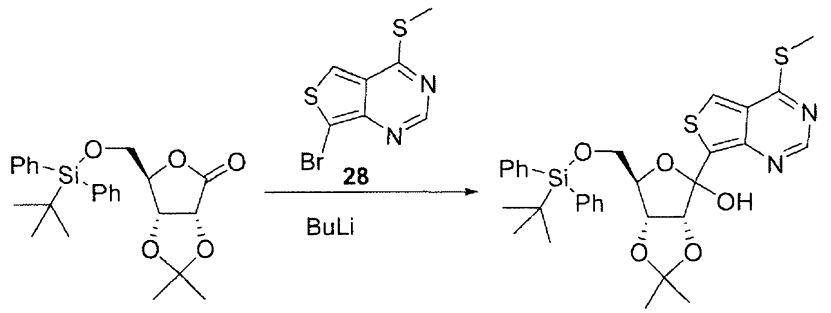
Compound 40



40a **40**

Compound 40 may be synthesized in the same manner as **35** by substituting **Compound 40a** (Alessandrini, et al.; *J. Carbohydrate Chem.* **2008**, *27*, 322-344) for **35b** in the reaction.

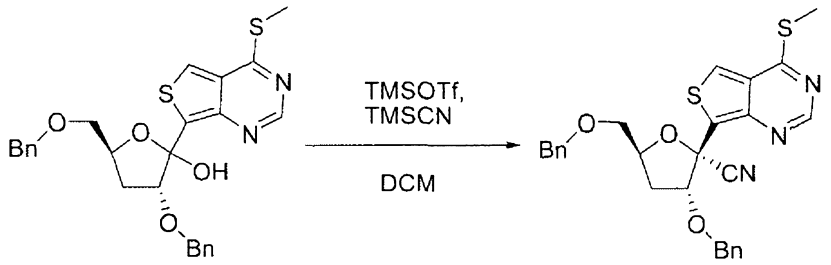
Compound 41



41a 41

Compound 41 may be synthesized in the same manner as **35** by substituting **Compound 41a** (Piccirilli, et al.; *Helvetica Chimica Acta* **1991**, *74*, 397-406) for **35b** in the reaction.

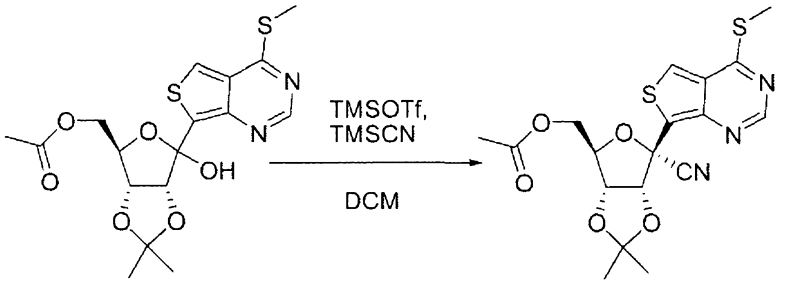
Compound 42



35 42

Compound 42 may be synthesized in the same manner as **32b** by substituting **Compound 35** for **31b** in the reaction. Alternatively, the method for synthesizing **Compound 29a** from **Compound 1o** may be used by substituting **35** for **1o**.

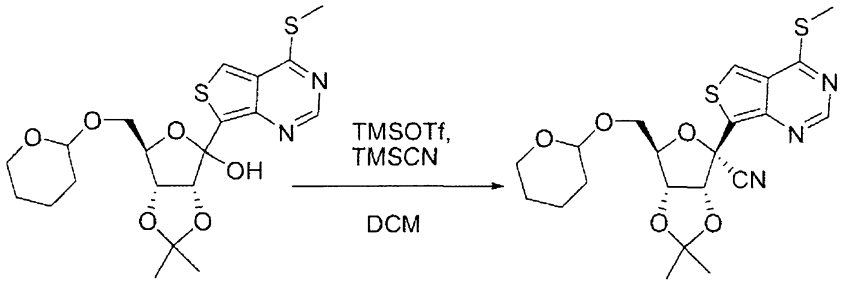
Compound 43



36 43

Compound 43 may be synthesized in the same manner as **32b** by substituting **Compound 36** for **31b** in the reaction. Alternatively, the method for synthesizing **Compound 29a** from **Compound 1o** may be used by substituting **36** for **1o**.

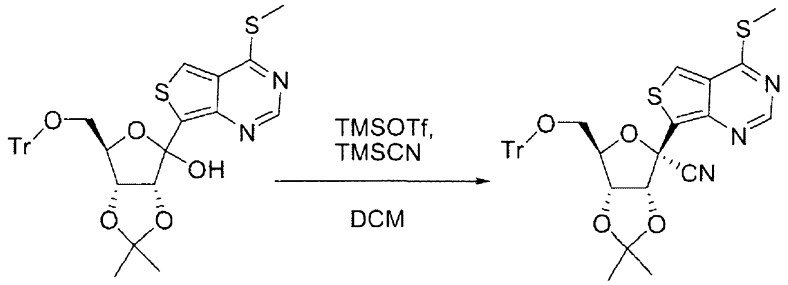
Compound 44



37 44

Compound 44 may be synthesized in the same manner as **32b** by substituting **Compound 37** for **31b** in the reaction. Alternatively, the method for synthesizing **Compound 29a** from **Compound 1o** may be used by substituting **37** for **1o**.

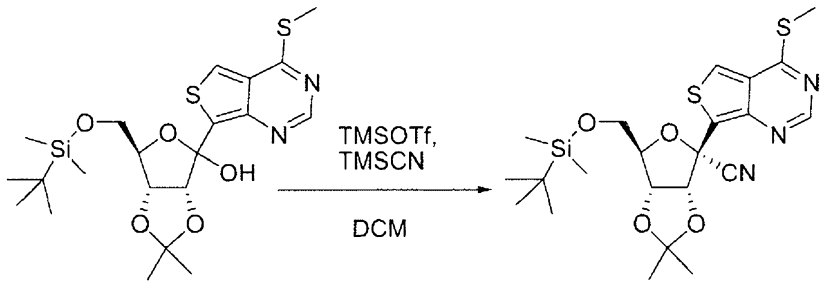
Compound 45



38 45

Compound 45 may be synthesized in the same manner as **32b** by substituting **Compound 38** for **31b** in the reaction. Alternatively, the method for synthesizing **Compound 29a** from **Compound 1o** may be used by substituting **38** for **1o**.

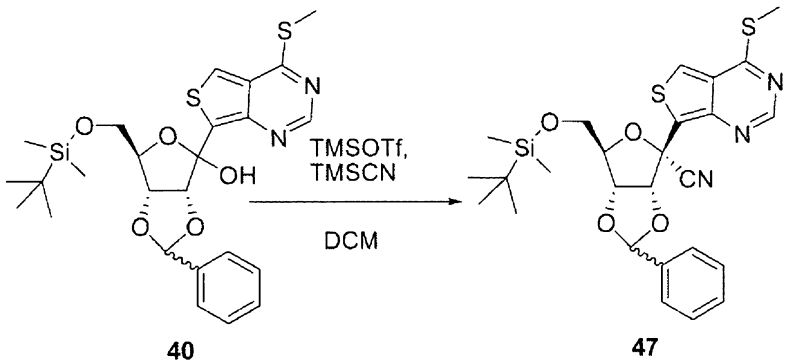
Compound 46



39 **46**

Compound 46 may be synthesized in the same manner as **32b** by substituting **Compound 39** for **31b** in the reaction. Alternatively, the method for synthesizing **Compound 29a** from **Compound 1o** may be used by substituting **39** for **1o**.

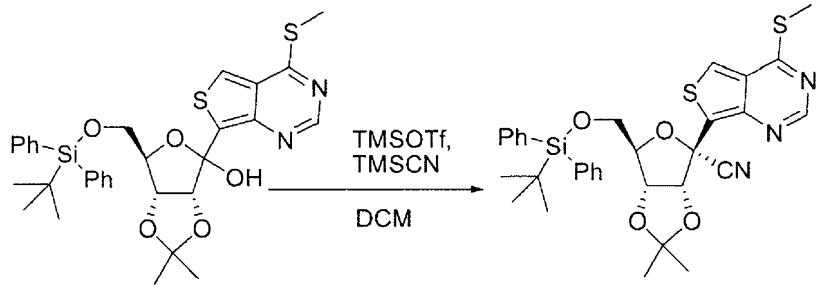
Compound 47



40 **47**

Compound 47 may be synthesized in the same manner as **32b** by substituting **Compound 40** for **31b** in the reaction. Alternatively, the method for synthesizing **Compound 29a** from **Compound 1o** may be used by substituting **40** for **1o**.

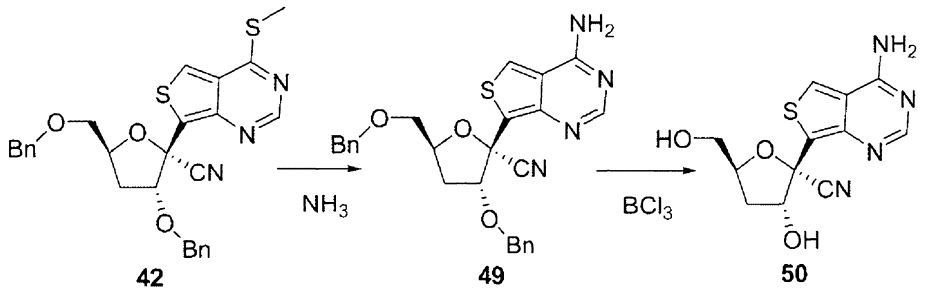
Compound 48



41 48

Compound 48 may be synthesized in the same manner as **32b** by substituting **Compound 41** for **31b** in the reaction. Alternatively, the method for synthesizing **Compound 29a** from **Compound 1o** may be used by substituting **41** for **1o**.

Compound 50

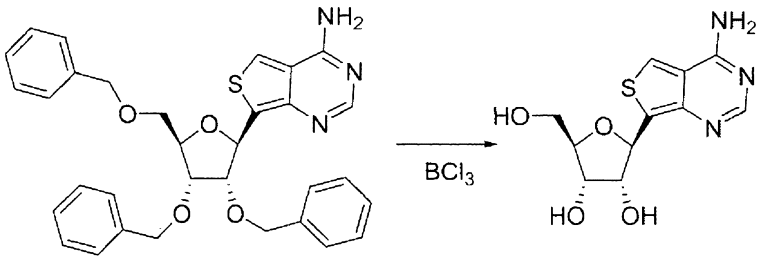


42 49 50

A mixture of **42** (about 0.15 mmol) and ammonia in a bomb reactor is stirred at about 40 °C for about 4 to 16 h. After removal of ammonia, the residue is purified by chromatography to give **49**.

A solution of **49** (about 0.315 mmol) in dichloromethane (about 6 mL) is cooled to about -78 °C and 1.0 M solution of BCl_3 in dichloromethane (about 4 mL) is added. The mixture is stirred for about 1 h to about 24 h at the same temperature. A mixture of pyridine and methanol (about 1:2, about 9 mL) is added to quench the reaction. The resulting mixture is slowly warmed up to room temperature and concentrated. The residue is suspended in 27% ammonium hydroxide (about 30 mL) and concentrated. This latter process may be repeated several times. The residue is purified by RP-HPLC to give **Compound 50**.

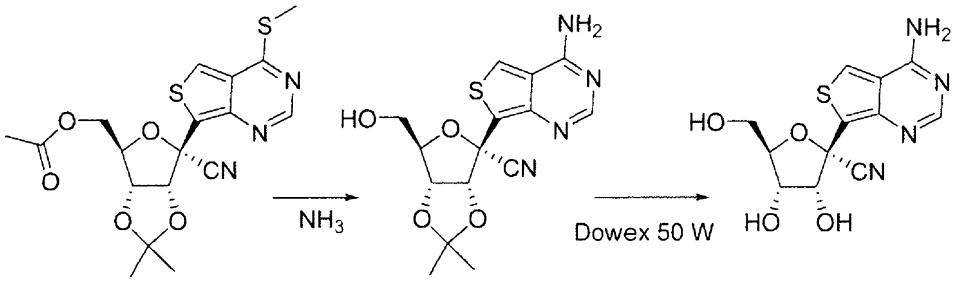
Compound 51



30 51

A solution of **30** (about 0.315 mmol) in dichloromethane (about 6 mL) is cooled to about -78 °C and 1.0 M solution of BCl_3 in dichloromethane (about 4 mL) is added. The mixture is stirred for about 1 h to about 24 h at the same temperature. A mixture of pyridine and methanol (about 1:2, about 9 mL) is added to quench the reaction. The resulting mixture is slowly warmed up to room temperature and concentrated. The residue is suspended in 27% ammonium hydroxide (about 30 mL) and concentrated. This latter process may be repeated several times. The residue is purified by RP-HPLC to give **Compound 51**.

Compound 53

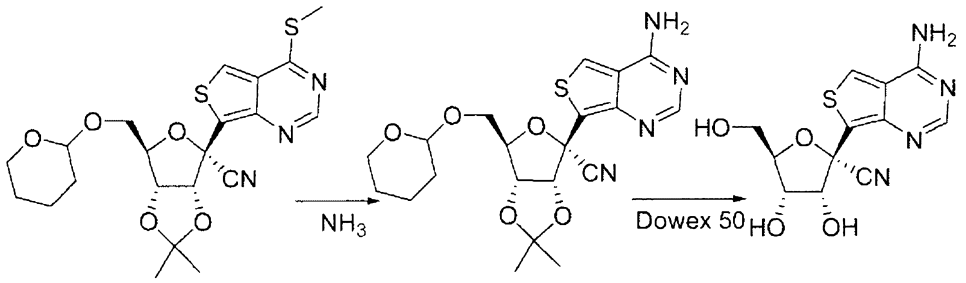


43 52 53

A mixture of **43** (about 0.15 mmol) and ammonia in a bomb reactor is stirred at about 40 °C for about 4 to 16 h. After removal of ammonia, the residue is purified by chromatography to give **52**.

A mixture of **52** (about 0.1 mmol) and H_2O (about 1 mL) is treated with Dowex 50 W (H^+ form, about 0.21 g, about 10 equivalents) and the mixture is stirred at about 25 to about 80 °C for about 30 min. to about 24 hours. The reaction is filtered and concentrated. The residue is purified by chromatography to give

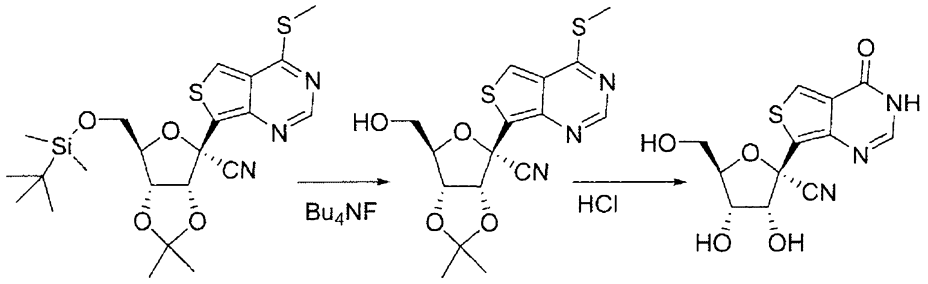
Alternative Synthesis of Compound 53.



44 **54** **53**

Compound 54 is prepared in the same manner as **Compound 52** using **44** as a substrate. A solution of **54** is treated with Dowex 50 W (H^+ form) as for the **52** to **53** conversion to give **Compound 53.**

Compound 56

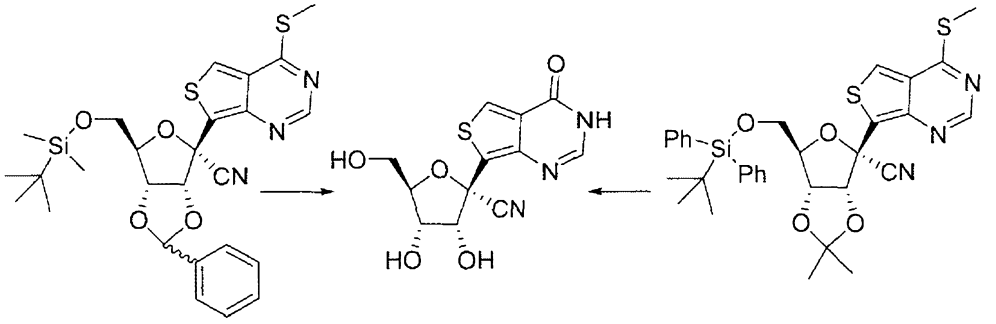


46 **55** **56**

A solution of **46** (about 0.39 mmol) in THF (about 3 mL) is added a solution of tetrabutylammonium fluoride (1 M, about 0.39 mL). The reaction is stirred for about 30 min to about 24 h. The solution is concentrated and **Compound 55** is isolated by chromatography.

A mixture of **55** (about 0.1 mmol) and aqueous methanol (about 1 mL) is treated with about 0.1 to about 1 N aqueous HCl (about 5 mL) and the mixture is stirred at about 25 to about 80 °C for about 30 min. to about 24 hours. The reaction is filtered and concentrated. The residue is purified by chromatography to give **Compound 56**.

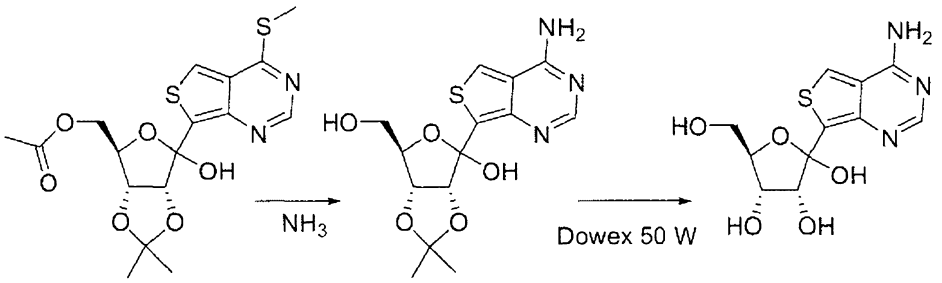
Alternative Syntheses of Compound 56



47 56 48

Compounds 47 and 48 may be converted to **Compound 56** using reaction conditions similar to those just described for the conversion of **46** to **56**.

Compound 58

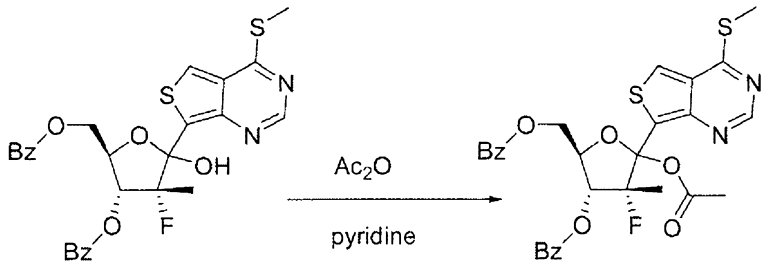


36 57 58

A mixture of **36** (about 0.15 mmol) and ammonia in a bomb reactor is stirred at about 40 °C for about 4 to 16 h. After removal of ammonia, the residue is purified by chromatography to give **57**.

A mixture of **57** (about 0.1 mmol) and H_2O (about 1 mL) is treated with Dowex 50 W (H^+ form, about 0.21 g, about 10 equivalents) and the mixture is stirred at about 25 to about 80 °C for about 30 min. to about 24 hours. The reaction is filtered and concentrated. The residue is purified by chromatography to give **Compound 58**.

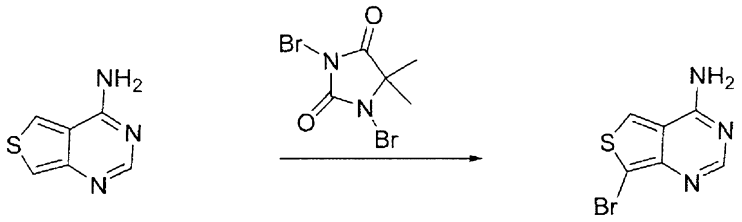
Compound 59



31b **59**

A solution of **31b** (about 0.51 mmol) in pyridine (about 1.5 mL) is treated with acetic anhydride (about 3.08 mmol) and is stirred at about 25 to about 120 °C for about 1 h to about 24 h. After cooling to room temperature, ethyl acetate and water are added. The organic layer is washed with dilute HCl followed by saturated ammonium chloride, is dried over magnesium sulfate, and is concentrated. The residue is purified by chromatography to give two stereoisomers of **Compound 59**.

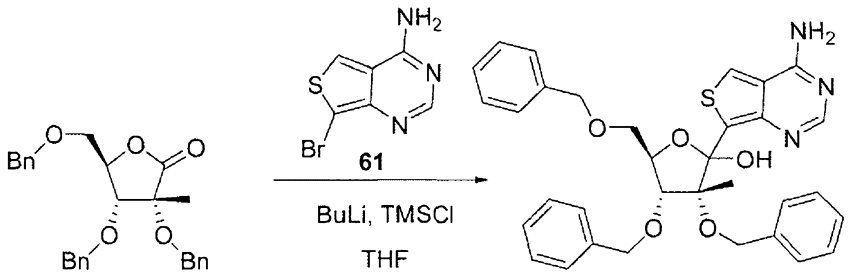
Compound 61



60 **61**

Compound 61 may be obtained in the same manner as **Compound 28** by substituting **Compound 60** (obtained according to *J. Heterocyclic Chem.*, **1993**, 30, 509) for **Compound 27** in the reaction.

Alternative Syntheses of Compound 1o



1m 1o

Alternative 1

To a dry, argon purged round bottom flask (100 mL) is added **Compound 61** (about 1.10 mmol) and anhydrous THF (about 1.5 mL). TMSCl (276 μL, about 2.2 mmol) is then added and the reaction mixture stirred for about 1 to about 24 h. The flask is placed into a dry ice/acetone bath (~ -78 °C) and BuLi (about 4.0 mmol, 1.6 M in hexanes) was added dropwise. After about 30 min to about 2 h, a solution of **1m** (about 1.0 mmol) in THF is cooled to 0 °C and then added to the reaction flask dropwise. After about 30 min to about 2 h of stirring at about -78 °C, the flask is warmed to about 0 °C and sat. NH_4Cl (about 5 mL) is added to quench the reaction. The organics are extracted using EtOAc (3 x 10 mL) and the combined organic layers are dried. The solvent is removed under reduced pressure and the crude material is purified by chromatography to give **1o**.

Alternative 2

To a dry, argon purged round bottom flask is added **Compound 61** (about 45 mmol) and anhydrous THF (about 60 mL). TMSCl (about 99 mmol) is then added and the reaction mixture is stirred for about 1 to 24 h. The flask is placed into a dry ice/acetone bath (~ -78 °C) and BuLi (about 158 mmol, 1.6M in hexanes) is added dropwise. After about 30 min to about 2 h, the reaction mixture is added to a solution of **1m** (about 30 mmol) in THF at about -78 °C via cannula. After about 30 min to about 2 h of stirring at about -78 °C, the flask is warmed to about 0 °C. Saturated NH_4Cl (about 150 mL) is added to quench the reaction. The organics are extracted

using EtOAc (3 x 100 mL) and the combined organic layers are dried. The solvent is removed under reduced pressure and the crude material is purified by chromatography to give **1o**.

Alternative 3

To a suspension of **Compound 61** (about 10 mmol) in about 0.5 M LiCl solution of anhydrous THF (about 20 mL) is added TMSCl (about 20 mmol) and the reaction is stirred at about room temperature for about 1 to about 24 h. After cooling to about -20 °C, about 3.0 M methyl magnesium chloride in diethyl ether (about 6.67 mL) is added dropwise while stirring. The mixture is then allowed to warm to room temperature over a period of about 30 min to about 4 h. After cooling back to about -20 °C, Turbo Grignard (1.3 M in THF) is added in portions until the magnesium-bromine exchange is nearly complete (about 15.5 mL over a period of about 30 min to about 4 h). A solution of **1m** (about 12 mmol) is then added. The resulting mixture is allowed to warm to room temperature. The reaction is quenched with methanol and **1o** is isolated as described above.

Alternative 4

To a suspension of **Compound 61** (about 2.35 mmol) in THF (about 6.5 mL) is added BuLi (1.6 M in hexanes, about 1.6 mL) at about -78 °C. After about 30 min. to about 2 h, a solution of 1,2-bis-[(chlorodimethyl)silanyl]ethane (about 2.4 mmol) in THF (about 1.2 mL) is added. After about 30 min. to about 2 h, BuLi (about 1.6 mL) is added. After an additional about 30 min. to about 2 h, BuLi (about 1.5 mL) is added. After about 30 min. to about 2 h, a solution of **1m** (about 1.64 mmol) in THF (about 2 mL) is then added dropwise. The resulting mixture is stirred at about -78 °C for about 30 min. to about 2 h under argon. Acetic acid (about 0.7 mL) is added dropwise to quench the reaction, followed by addition of saturated ammonium chloride. The mixture is extracted with ethyl acetate and the organic extract is concentrated *in vacuo*. The residue is purified by chromatography to give **1o**.

Antiviral Activity

Another aspect of the invention relates to methods of inhibiting viral infections, comprising the step of treating a sample or subject suspected of needing such inhibition with a composition of the invention.

Within the context of the invention samples suspected of containing a virus include natural or man-made materials such as living organisms; tissue or cell cultures; biological samples such as biological material samples (blood, serum, urine, cerebrospinal fluid, tears, sputum, saliva, tissue samples, and the like); laboratory samples; food, water, or air samples; bioproduct samples such as extracts of cells, particularly recombinant cells synthesizing a desired glycoprotein; and the like. Typically the sample will be suspected of containing an organism which induces a viral infection, frequently a pathogenic organism such as a tumor virus. Samples can be contained in any medium including water and organic solvent\water mixtures. Samples include living organisms such as humans, and man made materials such as cell cultures.

If desired, the anti-virus activity of a compound of the invention after application of the composition can be observed by any method including direct and indirect methods of detecting such activity. Quantitative, qualitative, and semiquantitative methods of determining such activity are all contemplated. Typically one of the screening methods described above are applied, however, any other method such as observation of the physiological properties of a living organism are also applicable.

The antiviral activity of a compound of the invention can be measured using standard screening protocols that are known. For example, the antiviral activity of a compound can be measured using the following general protocols.

Cell-based Flavivirus Immunodetection assay

BHK21 or A549 cells are trypsinized, counted and diluted to $2x10^5$ cells/mL in Hams F-12 media (A549 cells) or RPMI-1640 media (BHK21 cells) supplemented with 2% fetal bovine serum (FBS) and 1% penicillin/streptomycin. $2x10^4$ cells are

dispensed in a clear 96-well tissue culture plates per well and palced at 37° C, 5% CO_2 overnight. On the next day, the cells are infected with viruses at multiplicity of infection (MOI) of 0.3 in the presence of varied concentrations of test compounds for 1 hour at 37° C and 5% CO_2 for another 48 hours. The cells are washed once with PBS and fixed with cold methanol for 10 min. After washing twice with PBS, the fixed cells are blocked with PBS containing 1% FBS and 0.05% Tween-20 for 1 hour at room temperature. The primary antibody solution (4G2) is then added at a concentration of 1:20 to 1:100 in PBS containing 1% FBS and 0.05% Tween-20 for 3 hours. The cells are then washed three times with PBS followed by one hour incubation with horseradish peroxidase(HRP)-conjugated anti-mouse IgG (Sigma, 1:2000 dilution). After washing three times with PBS, 50 microliters of 3,3',5,5'-tetramethylbenzidine (TMB) substrate solution (Sigma) is added to each well for two minutes. The reaction is stopped by addition of 0.5 M sulfuric acid. The plates are read at 450 nm absorbance for viral load quantification. After measurement, the cells are washed three times with PBS followed by incubation with propidium iodide for 5 min. The plate is read in a Tecan Safire™ reader (excitation 537 nm, emission 617 nm) for cell number quantification. Dose response curves are plotted from the mean absorbance versus the log of the concentration of test compounds. The EC_{50} is calculated by non-linear regression analysis. A positive control such as N-nonyl-deoxynojirimycin may be used.

Cell-based Flavivirus cytopathic effect assay

For testing against West Nile virus or Japanese encephalitis virus, BHK21 cells are trypsinized and diluted to a concentration of 4 x 10^5 cells/mL in RPMI-1640 media supplemented with 2% FBS and 1% penicillin/streptomycin. For testing against dengue virus, Huh7 cells are trypsinized and diluted to a concentration of 4 x 10^5 cells/mL in DMEM media supplemented with 5% FBS and 1% penicillin/streptomycin. A 50 microliter of cell suspension (2 x 10^4 cells) is dispensed per well in a 96-well optical bottom PIT polymer-based plates (Nunc). Cells are grown overnight in culture medium at 37° C, 5% CO_2, and then infected with West Nile virus (e.g. B956 strain) or Japanese encephalitis virus (e.g. Nakayama strain) at

MOI = 0.3, or with dengue virus (e.g. DEN-2 NGC strain) at MOI = 1, in the presence of different concentrations of test compounds. The plates containing the virus and the compounds are further incubated at 37°C, 5% CO_2 for 72 hours. At the end of incubation, 100 microliters of CellTiter-Glo™ reagent is added into each well. Contents are mixed for 2 minutes on an orbital shaker to induce cell lysis. The plates are incubated at room temperature for 10 minutes to stabilize luminescent signal. Lumnescence reading is recorded using a plate reader. A positive control such as N-nonyl-deoxynojirimycin may be used.

Antiviral Activity in a Mouse Model of Dengue Infection.

Compounds are tested *in vivo* in a mouse model of dengue virus infection (Schul *et al.* J. Infectious Dis. 2007; 195:665-74). Six to ten week old AG129 mice (B&K Universal Ltd, Hll, UK) are housed in individually ventilated cages. Mice are injected intraperitoneally with 0.4 mL TSV01 dengue virus 2 suspension. Blood samples are taken by retro orbital puncture under isoflurane anaesthesia. Blood samples are collected in tubes containing sodium citrate to a final concentration of 0.4%, and immediately centrifuged for 3 minutes at 6000g to obtain plasma. Plasma (20 microliters) is diluted in 780 microliters RPMI-1640 medium and snap frozen in liquid nitrogen for plaque assay analysis. The remaining plasma is reserved for cytokine and NS1 protein level determination. Mice develop dengue viremia rising over several days, peaking on day 3 post-infection.

For testing of antiviral activity, a compound of the invention is dissolved in vehicle fluid, e.g. 10% ethanol, 30% PEG 300 and 60% D5W (5% dextrose in water; or 6N HCl (1.5 eq):1N NaOH (pH adjusted to 3.5): 100 mM citrate buffer pH 3.5 (0.9% v/v:2.5% v/v: 96.6% v/v). Thirty six 6-10 week old AG129 mice are divided into six groups of six mice each. All mice are infected with dengue virus as described above (day 0). Group 1 is dosed by oral gavage of 200 mL/mouse with 0.2 mg/kg of a compound of the invention twice a day (once early in the morning and once late in the afternoon) for three consecutive days starting on day 0 (first dose just before dengue infection). Groups 2, 3 and 4 are dosed the same way with 1 mg/kg, 5 mg/kg

and 25 mg/kg of the compound, respectively. A positive control may be used, such as (2R,3R,4R,5R)-2-(2-amino-6-hydroxy-purin-9-yl)-5-hydroxymethyl-3-methyl-tetrahydro-furan-3,4-diol, dosed by oral gavage of 200 microliters/mouse the same way as the previous groups. A further group is treated with only vehicle fluid.

On day 3 post-infection approximately 100 microliter blood samples (anti-coagulated with sodium citrate) are taken from the mice by retro-orbital puncture under isoflurane anaesthesia. Plasma is obtained from each blood sample by centrifugation and snap frozen in liquid nitrogen for plague assay analysis. The collected plasma samples are analyzed by plague assay as described in Schul *et al.* Cytokines are also analysed as as described by Schul. NS1 protein levels are analysed using a Platelia™ kit (BioRad Laboratories). An anti-viral effect is indicated by a reduction in cytokine levels and/or NS1 protein levels.

Typically, reductions in viremia of about 5-100 fold, more typically 10-60 fold, most typically 20-30 fold, are obtained with 5-50 mg/kg bid dosages of the compounds of the invention.

HCV IC_{50} Determination

Assay Protocol: Either wild type or S282T (Migliaccio, et al, *J. Biol. Chem.* **2003**, 49164-49170; Klumpp, et al., *J. Biol. Chem.* **2006**, 3793-3799) mutant polymerase enzyme was used in this assay. NS5b polymerase assay (40 μL) was assembled by adding 28 μL polymerase mixture (final concentration: 50 mM Tris-HCl at pH 7.5, 10 mM KCL, 5 mM $MgCl_2$, 1 mM DTT, 10 mM EDTA, 4 ng/μL of RNA template, and 75 nM HCV Δ21 NS5b polymerase) to assay plates followed by 4 μL of compound dilution. The polymerase and compound were pre-incubated at 35 °C for 10 minute before the addition of 8 μL of nucleotide substrate mixture (33P-α-labeled competing nucleotide at K_M and 0.5 mM of the remaining three nucleotides). The assay plates were covered and incubated at 35 °C for 90 min. Reactions were then filtered through 96-well DEAE-81 filter plates via vacuum. The filter plates were then

washed under vacuum with multiple volumes of 0.125 M $NaHPO_4$, water, and ethanol to remove unincorporated label. Plates were then counted on TopCount to assess the level of product synthesis over background controls. The IC50 value is determined using Prism fitting program.

Preferably, compounds described herein inhibited NS5b polymerase with an IC_{50}'s below 1000 μM, more preferably below 100 μM, and most preferably below 10 μM. Representative examples of the activity of the compounds of the invention are shown in Table 30 below.

Table 30. Representative IC_{50}'s for examples of the invention.

Compound No.	IC_{50}, μM
4	0.37
63	0.27

HCV EC_{50} Determination

Replicon cells were seeded in 96-well plates at a density of 8 x 10^3 cells per well in 100 μL of culture medium, excluding Geneticin. Compound was serially diluted in 100% DMSO and then added to the cells at a 1:200 dilution, achieving a final concentration of 0.5% DMSO and a total volume of 200 μL. Plates were incubated at 37°C for 3 days, after which culture medium was removed and cells were lysed in lysis buffer provided by Promega's luciferase assay system. Following the manufacturer's instruction, 100 μL of luciferase substrate was added to the lysed cells and luciferase activity was measured in a TopCount luminometer. Preferably, compounds described herein have EC50's below 1000 μM, more preferably below 100 μM, and most preferably below 10 μM. Representative examples of the activity of the compounds of the invention are shown in Table 31 below.

Table 31. Representative EC_{50}'s for examples of the invention.

Compound No.	EC_{50}, μM
1	90
2	6.1
62	24
64	2.9

The cytotoxicity of a compound of the invention can be determined using the following general protocol.

Cytotoxicity Cell Culture Assay (Determination of CC50):

The assay is based on the evaluation of cytotoxic effect of tested compounds using a metabolic substrate.

Assay protocol for determination of CC50:

1. Maintain MT-2 cells in RPMI-1640 medium supplemented with 5% fetal bovine serum and antibiotics.
2. Distribute the cells into a 96-well plate (20,000 cell in 100 μl media per well) and add various concentrations of the tested compound in triplicate (100 μl/well). Include untreated control.
3. Incubate the cells for 5 days at 37 °C.
4. Prepare XTT solution (6 ml per assay plate) in dark at a concentration of 2mg/ml in a phosphate-buffered saline pH 7.4. Heat the solution in a water-bath at 55°C for 5 min. Add 50 μl of N-methylphenazonium methasulfate (5 μg/ml) per 6 ml of XTT solution.
5. Remove 100 μl media from each well on the assay plate and add 100 μl of the XTT substrate solution per well. Incubate at 37 °C for 45 to 60 min in a CO_2 incubator.
6. Add 20 μl of 2% Triton X-100 per well to stop the metabolic conversion of XTT.
7. Read the absorbance at 450 nm with subtracting off the background at 650 nm.

8. Plot the percentage absorbance relative to untreated control and estimate the CC50 value as drug concentration resulting in a 50% inhibition of the cell growth. Consider the absorbance being directly proportional to the cell growth.

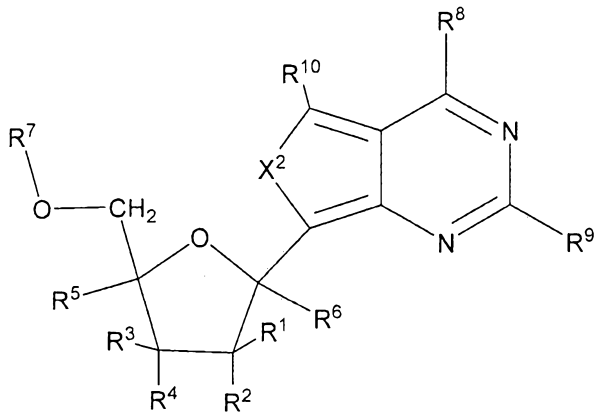
All publications, patents, and patent documents cited herein above are incorporated by reference herein, as though individually incorporated by reference.

The invention has been described with reference to various specific and preferred embodiments and techniques. However, one skilled in the art will understand that many variations and modifications may be made while remaining within the spirit and scope of the invention.

2010213873 03 Jun 2015

What is claimed is:

1. A compound of Formula I:



Formula I

or a pharmaceutically acceptable salt or ester, thereof;

wherein:

R^1 is H or $(C_1$-$C_8)$alkyl;

R^2 is OR^a or F;

R^3 is H;

R^4 is H or OR^a;

R^5 is H;

R^6 is OR^a, CN, or $(C_1$-$C_8)$alkyl;

each R^a is independently H, $(C_1$-$C_8)$alkyl, or $-C(=O)R^{11}$;

R^7 is H;

X^2 is S;

R^8 is OH or NH_2;

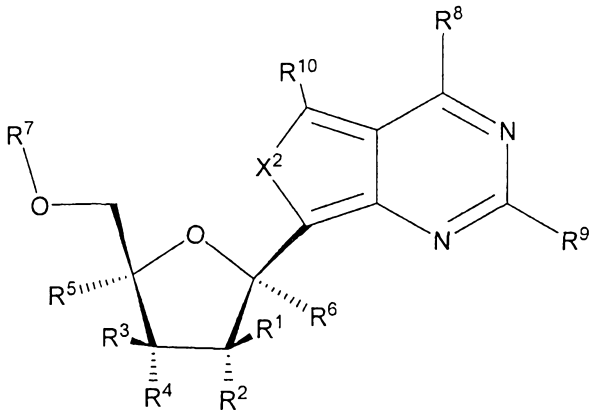
R^9 is NH_2 or, if R^8 is NH_2, R^9 may also be H;

R^{10} is H; and

R^{11} is $(C_1$-$C_8)$alkyl.

2. The compound according to claim 1 represented by Formula II

2010213873 03 Jun 2015



Formula II

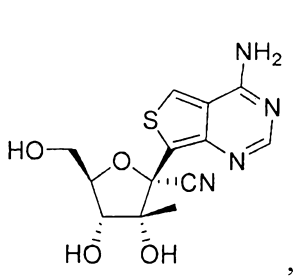
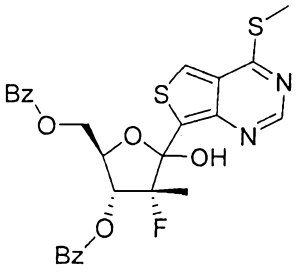
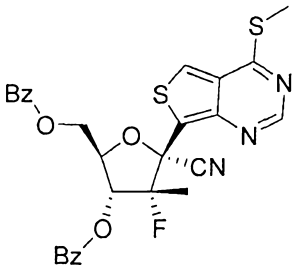
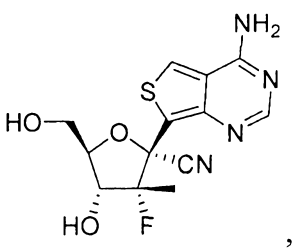
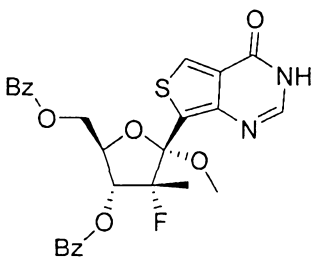
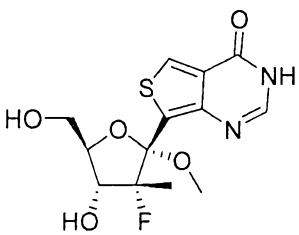
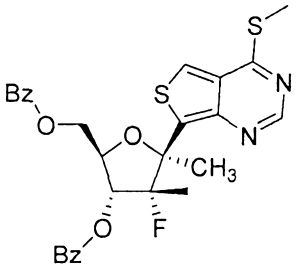
3. The compound according to claim 1 or 2 wherein R^6 is OR^a, CN, or methyl.

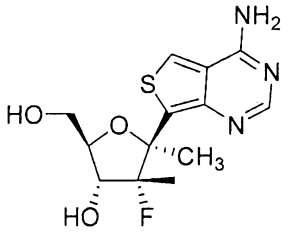
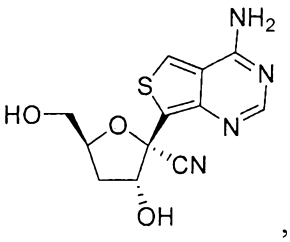
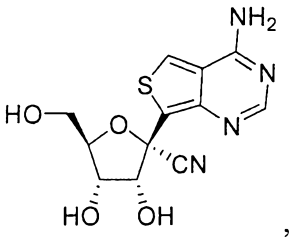
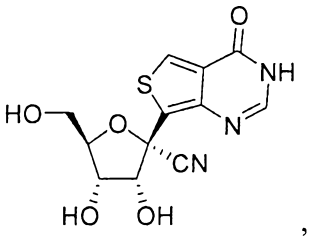
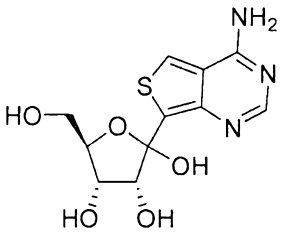
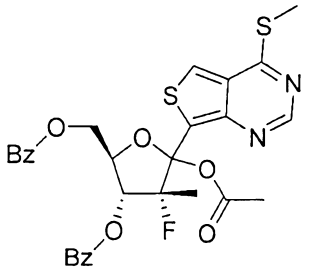
4. The compound according to any one of claims 1-3 wherein R^4 is OR^a.

5. The compound according to any one of claims 1-4 wherein R^1 is CH_3.

6. The compound according to any one of claims 1-5 wherein R^6 is CN or OR^a.

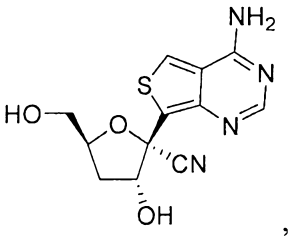
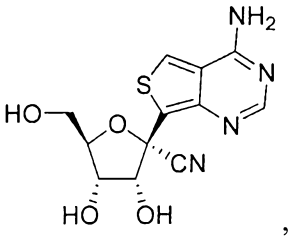
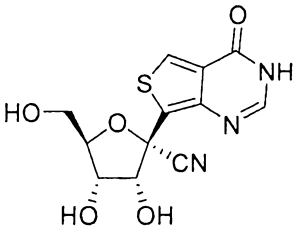
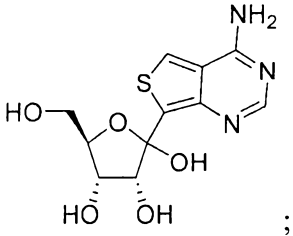
7. A compound that is


,

,

,

,

,

,

,


,

,

,

,

, or

; or

a pharmaceutically acceptable salt or ester thereof.

8. The compound of claim 7, selected from the group consisting of


,

,

, and

; or

a pharmaceutically acceptable salt or ester thereof.

9. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of claims 1-8 and a pharmaceutically acceptable carrier.

10. The pharmaceutical composition of claim 9 further comprising at least one additional therapeutic agent.

11. The pharmaceutical composition of claim 10 further comprising at least one additional therapeutic agent selected from the group consisting of interferons, ribavirin or its analogs, HCV NS3 protease inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, nucleoside

2010213873 03 Jun 2015

or nucleotide inhibitors of HCV NS5B polymerase, non-nucleoside inhibitors of HCV NS5B polymerase, HCV NS5A inhibitors, TLR-7 agonists, cyclophilin inhibitors, HCV IRES inhibitors, pharmacokinetic enhancers, or other drugs for treating HCV or mixtures thereof.

12 A method of treating a viral infection caused by a *Flaviviridae* virus comprising administering to a mammal in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 8 or pharmaceutical composition according to any one of claims 9 to 11.

13. The method of claim 12 wherein the virus is selected from the group consisting of dengue virus, yellow fever virus, West Nile virus, Japanese encephalitis virus, tick-borne encephalitis virus, Kunjin virus, Murray Valley encephalitis virus, St. Louis encephalitis virus, Omsk hemorrhagic fever virus, bovine viral diarrhea virus, Zika virus and Hepatitis C virus.

14. The method of claim 13 wherein the viral infection is caused by Hepatitis C virus.

15. The method of claims 13 or 14 further comprising at least one additional therapeutic agent selected from the group consisting of interferons, ribavirin or its analogs, HCV NS3 protease inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, nucleoside or nucleotide inhibitors of HCV NS5B polymerase, non-nucleoside inhibitors of HCV NS5B polymerase, HCV NS5A inhibitors, TLR-7 agonists, cyclophilin inhibitors, HCV IRES inhibitors, pharmacokinetic enhancers, and other drugs for treating HCV, or mixtures thereof.

16. Use of a compound according to any one of claims 1 – 8 for the manufacture of a medicament for the treatment of a *Flaviviridae* viral infection.

17. Use according to claim 16 wherein the viral infection is caused by Hepatitis C virus.

18. A compound according to any one of claims 1 – 8 for the use in treating a *Flaviviridae* viral infection.

19. A compound according to claim 18 wherein the viral infection is caused by Hepatitis C virus.

20. A compound according to claim 1 or 7 substantially as hereinbefore described.