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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 May 2016 (06.05.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/069827 Al

(51) International Patent Classification:

A61K 31/53 (2006.01)	*C07H 11/00* (2006.01)
A61K 31/675 (2006.01)	*C07H 15/18* (2006.01)
A61K 31/685 (2006.01)	*C07D 487/04* (2006.01)
A61K 31/00 (2006.01)	*C07D 519/00* (2006.01)
C07H 1/00 (2006.01)	*A61P 31/14 (2006.01)*
C07H 1/02 (2006.01)	

(21) International Application Number:
PCT/US20 15/057934

(22) International Filing Date:
29 October 2015 (29.10.201 5)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

62/072,33 1	29 October 2014 (29. 10.2014)	US
62/105,619	20 January 20 15 (20.01.2015)	US

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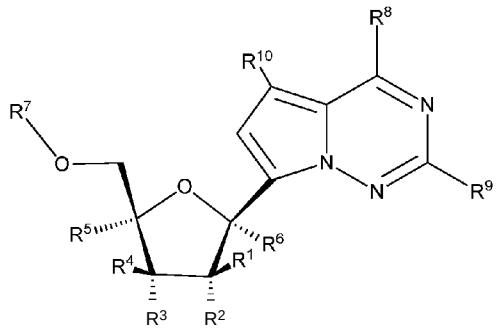
(54) Title: METHODS FOR TREATING FILOVIRIDAE VIRUS INFECTIONS



(I)

(57) Abstract: Provided are compounds, methods, and pharmaceutical compositions for treating *Filoviridae* virus infections by administering ribosides, riboside phosphates and prodrugs thereof, of Formula (I), wherein the position of the nucleoside sugar is substituted. The compounds, compositions, and methods provided are particularly useful for the treatment of Marburg virus, Ebola virus and Cueva virus infections.

WO 2016/069827 A1

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(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, BN, 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, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(H))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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))*

METHODS FOR TREATING *FILOVIRIDAE* VIRUS INFECTIONS

FIELD OF THE INVENTION

[0001] The invention relates generally to methods and compounds for treating *Filoviridae* virus infections, particularly methods and nucleosides for treating Ebola virus, Marburg virus and Cueva virus.

BACKGROUND OF THE INVENTION

[0002] Filoviruses *(e.g.,* Ebola virus (EBOV) and Marburg virus (MARV)) are among the most lethal and destructive viruses. They cause severe, often fatal viral hemorrhagic fevers in humans and nonhuman primates *(e.g.,* monkeys, gorillas, and chimpanzees). Filoviruses are of particular concern as possible biological weapons since they have the potential for aerosol dissemination and weaponization.

[0003] The incubation period for Filovirus infection ranges from 2 to 21 days. The onset of illness is abrupt and is characterized by high fever, headaches, joint and muscle aches, sore throat, fatigue, diarrhea, vomiting, and stomach pain. A rash, red eyes, hiccups and internal and external bleeding may be seen in some patients. Within one week of becoming infected with the virus, most patients experience chest pains and multiple organ failure, go into shock, and die. Some patients also experience blindness and extensive bleeding before dying.

[0004] Filoviridae are a family of RNA viruses. Two members of the Filoviridae family have been identified: EBOV and MARV. Two key pathogenic types of the Filoviridae family have been identified: Ebolavirus and MARV. There is one identified variant of MARV and five identified species of ebolavirus: Zaire (i.e. Ebola virus, EBOV), Sudan, Tai Forest, Bundibugyo, and Reston. The exact origin, locations, and natural habitat of Filoviridae are unknown. However, on the basis of available evidence and the nature of similar viruses, it is postulated that Filoviridae are zoonotic *(i.e.,* animal-borne) and are normally maintained in an animal host that is native to the African continent.

[0005] For more than 30 years, ebolaviruses have been associated with periodic episodes of hemorrhagic fever in Central Africa that produce severe disease in infected patients. Mortality rates in outbreaks have ranged from 50% for the Sudan species of ebolavirus (SEBOV) to up to 90% for the Zaire species of ebolavirus (EBOV, ZEBOV) (Sanchez *et al,* Filoviridae: Marburg and Ebola Viruses, in *Fields Virology* (eds. Knipe, D.M. & Howley, P.M.) 1409-1448 (Lippincott Williams & Wilkins, Philadelphia)). An outbreak late in 2007 caused by an apparently new species of ebolavirus in Uganda resulted in a fatality rate of about 25% (Towner *et al, PLoS Pathog.,* 4:el000212 (2008)). ZEBOV has also decimated populations of wild apes in this same region of Africa (Walsh *et al , Nature,* 422:61 1-614 (2003)).

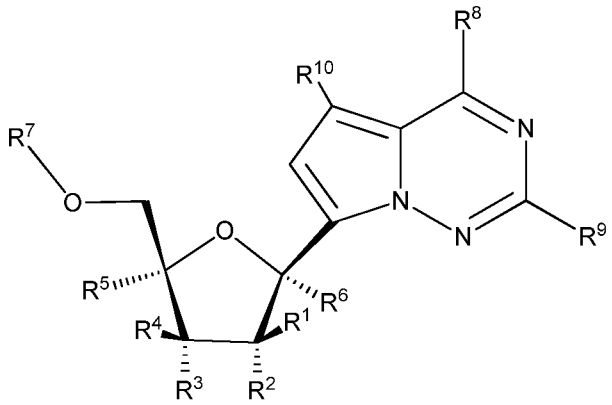
[0006] Prevention and treatment of filovirus infections, including ebolaviruses (i.e. EBOV) presents many challenges. In fact, there are no vaccines or post exposure treatment modalities available for preventing or managing EBOV infections. Patients instead receive supportive therapy, *i.e.,* electrolyte and fluid balancing, oxygen, blood pressure maintenance, and treatment for any secondary infections.

[0007] Thus, there is a need for compositions and methods for treating EBOV infections. The present invention addresses these and other needs.

SUMMARY OF THE INVENTION

[0008] Provided are methods and compounds for the treatment of infections caused by the *Filoviridae* virus family.

[0009] Provided, is a method for treating a *Filoviridae* infection in a human in need thereof comprising administering a therapeutically effective amount of a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt or ester, thereof;

wherein:

each R^1 is H or halogen;

each R^2, R^3, R^4 or R^5 is independently H, OR^a, $N(R^a)_2$, N_3, CN, $N0_2$, $S(0)_nR^a$, halogen, $(Ci\text{-}C_8)$alkyl, $(C_4\text{-}C_8)$carbocyclylalkyl, $(Ci\text{-}C_8)$substituted alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$substituted alkenyl, $(C_2\text{-}C_8)$alkynyl or $(C_2\text{-}C_8)$substituted alkynyl;

wherein

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$(Ci\text{-}C_8)$alkyl, $(C_4\text{-}C_8)$carbocyclylalkyl, -C(=0)R, -C(=0)OR, -C(=0)NR_2, -C(=0)SR, -S(0)R, -S(0)$_2$R, -S(0)(OR), -S(0)$_2$(OR), or -S0$_2$$NR_2$;

each R 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, $C_6\text{-}C_{20}$ aryl, $C_6\text{-}C_{20}$ substituted aryl, $C_2\text{-}C_{20}$ heterocyclyl, $C_2\text{-}C_{20}$ substituted heterocyclyl, arylalkyl or substituted arylalkyl;

or any two R^2, R^3, R^4 or R^5 on adjacent carbon atoms when taken together are -0(CO)0- or when taken together with the ring carbon atoms to which they are attached form a double bond;

R^6 is OR^a, $N(R^a)_2$, N_3, CN, $N0_2$, $S(0)_nR^a$, $-C(=0)R^{11}$, $-C(=0)OR^{11}$, $-C(=0)NR^{11}R^{12}$, $-C(=0)SR^{11}$, $-S(0)R^{11}$, $-S(0)_2R^{11}$, $-S(0)(OR^{11})$, $-S(0)_2(OR^{11})$, $-S0_2NR^{11}R^{12}$, halogen, $(Ci\text{-}C_8)$alkyl, $(C_4\text{-}C_8)$carbocyclylalkyl, $(Ci\text{-}C_8)$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$(Ci\text{-}C_8)$alkyl;

wherein

each 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, $(C_4\text{-}Cs)$carbocyclylalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=0)(C_1\text{-}C_8)$alkyl, $-S(0)_n(Ci\text{-}C_8)$alkyl or aryl$(C_1\text{-}C_8)$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 -0-, -S- or $-NR^a$-;

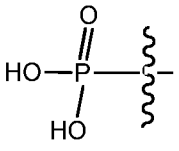
each n is independently 0, 1, or 2;

R^7 is selected from a group consisting of

a) H, $-C(=0)R^{11}$, $-C(=0)OR^{11}$, $-C(=0)NR^{11}R^{12}$, $-C(=0)SR^{11}$, $-S(0)R^{11}$, $-S(0)_2R^{11}$, $-S(0)(OR^{11})$, $-S(0)_2(OR^{11})$, or $-S0_2NR^{11}R^{12}$,

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^{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 $(Ci\text{-}C_8)$alkyl may be optionally replaced with -0-, -S- or $-NR^a$-, and

b)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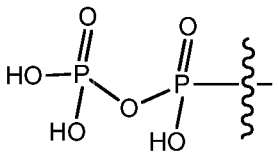
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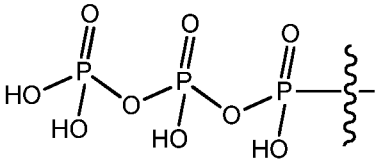
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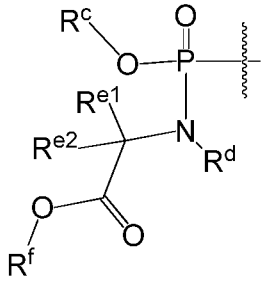
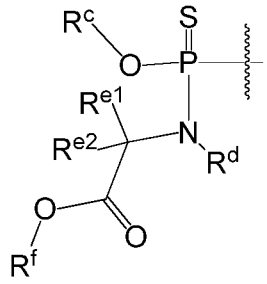
c) a group selected from: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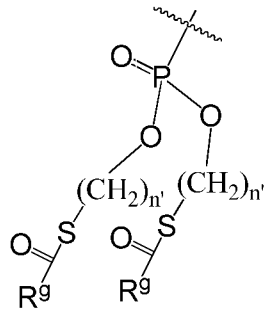
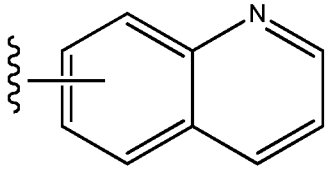


wherein:

R^c is selected from phenyl, 1-naphthyl, 2-naphthyl,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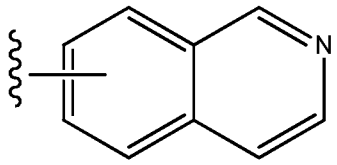

;

R^d is H or CH_3;

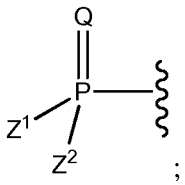
R^{e1} and R^{e2} are each independently H, Ci-C $_6$ alkyl or benzyl;

R^f is selected from H, C_1-C_8 alkyl, benzyl, $_{C3-C6}$ cycloalkyl, and -CH2-C3-C6 cycloalkyl;

R^g is selected from C_1-C_8 alkyl, -0-C $_1$-C_8 alkyl, benzyl, -O-benzyl, -CH_2-C_3-C_6 cycloalkyl, -O-CH2-C3-C6 cycloalkyl, and CF_3; and

n' is selected from 1, 2, 3, and 4; and

d) a group of the formula:


;

wherein

Q is O, S, NR, $^+$N(0)(R), N(OR), $^+$N(0)(OR), or N-NR $_2$;

Z^1 and Z^2, when taken together, are $-Q^1(C(R^y)_2)3Q^1-$;

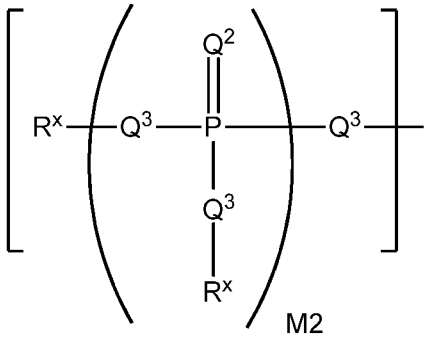
wherein

each Q^1 is independently O, S, or NR; and

each R^y is independently H, F, CI, Br, I, OH, R, $-C(=Q^2)R$, $-C(=Q^2)OR$, $-C(=Q^2)N(R)_2$, $-N(R)_2$, $-^+N(R)_3$, -SR, -S(0)R, $-S(0)_2R$, -S(0)(OR), $-S(0)_2(OR)$, $-OC(=Q^1)R$, $-OC(=Q^2)OR$, $-OC(=Q^2)(N(R)_2)$, $-SC(=Q^2)R$, $-SC(=Q^2)OR$, $-SC(=Q^2)(N(R)_2)$, $-N(R)C(=Q^2)R$, $-N(R)C(=Q^2)OR$, $-N(R)C(=Q^2)N(R)_2$, $-S0_2NR_2$, -CN, $-N_3$, $-N0_2$, -OR, or Z^3; or when taken together, two R^y on the same carbon atom form a carbocyclic ring of 3 to 7 carbon atoms;

each Q^2 is independently, O, S, NR, $^+N(0)(R)$, N(OR), $^+N(0)(OR)$, or $N\text{-}NR_2$; or

Z^1 and Z^2 are each, independently, a group of the Formula la:



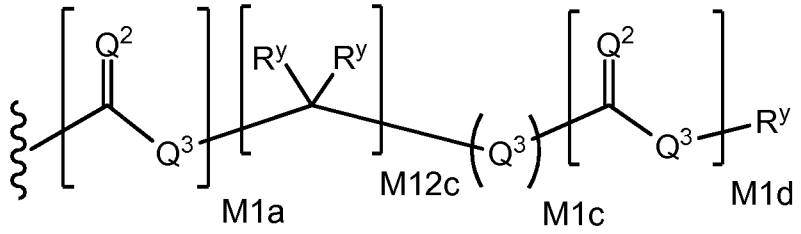
Formula la

wherein:

each Q^3 is independently a bond, O, CR_2, NR, $^+N(0)(R)$, N(OR), $^+N(0)(OR)$, $N\text{-}NR_2$, S, S-S, S(O), or $S(0)_2$;

M2 is 0, 1 or 2;

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



wherein:

each Mia, Mlc, and Mid is independently 0 or 1;

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

Z^3 is Z^4 or Z^5;

Z^4 is R, $-C(Q^2)R^y$, $-C(Q^2)Z^5$, $-S0_2R^y$, or $-S0_2Z^5$; and

Z^5 is a carbocycle or a heterocycle wherein Z^5 is independently substituted with 0 to 3 R^y groups;

each R^8 is halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3, NO, $N0_2$, CHO, CN, $-CH(=NR^{11})$, $-CH=NNHR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=0)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=0)OR^{11}$, $(Ci\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_4\text{-}Cs)$carbocyclylalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=0)(C_1\text{-}C_8)$alkyl, $-S(0)_n(C_1\text{-}C_8)$alkyl, aryl$(C_1\text{-}C_8)$alkyl, OR^{11} or SR^{11};

each 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, $N0_2$, CHO, CN, $-CH(=NR^{11})$, $-CH=NHNR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=0)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=0)OR^{11}$, R^{11}, OR^{11} or SR^{11};

each 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, $-C(=0)(C_1\text{-}C_8)$alkyl, $-S(0)_n(C_1\text{-}C_8)$alkyl or aryl$(C_1\text{-}C_8)$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 -0-, -S- or $-NR^a$-; and

wherein each (Ci-Cs)alkyl, (C_2-C8)alkenyl, (C2 -Cs)alkynyl or aryl(Ci-Cs)alkyl of each R^2, R^3, R^5, or R^6 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 (Ci-Cs)alkyl may be optionally replaced with -0-, -S- or -NR ^{a}-.

[0010] In another embodiment, the method comprises administering a therapeutically effective amount of a racemate, enantiomer, diastereomer, tautomer, polymorph, pseudopolymorph, amorphous form, hydrate or solvate of a compound of Formula I or a pharmaceutically acceptable salt or ester thereof to a mammal in need thereof.

[0011] In another embodiment, the method comprises treating a *Filoviridae* infection in a human in need thereof by administering a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or ester thereof.

[0012] In another embodiment, the method comprises treating an Ebola virus infection in a human in need thereof by administering a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or ester thereof.

[0013] In another embodiment, the method comprises administering a therapeutically effective amount of a pharmaceutical composition comprising an effective amount of a Formula I compound, or a pharmaceutically acceptable salt or ester thereof, in combination with a pharmaceutically acceptable diluent or carrier. Additional separate embodiments are provided of pharmaceutical compositions which each comprise therapeutically effective amount of a compound, respectively, selected from each of the Formulas herein, as well as each subgroup and embodiment thereof, including the group of the compounds of Formula I, Formula II, Formula II, Formula IV, and individual Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, and 32 (Compounds 1-32), or a pharmaceutically acceptable salt, ester, stereoisomer, hydrate, solvate, mixture of stereoisomers, or tautomer thereof.

[0014] In another embodiment, the method comprises administering a therapeutically effective amount of a pharmaceutical composition comprising an effective amount of a Formula I compound, or a pharmaceutically acceptable salt or ester thereof, in combination with at least one additional therapeutic agent.

[0015] In another embodiment, the method comprises administering a therapeutically effective amount of a 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 active against infectious *Filoviridae* viruses.

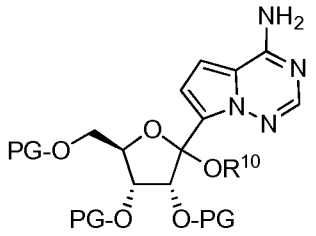
[0016] In another embodiment, the present application provides for a method of inhibiting a *Filoviridae* RNA-dependent RNA polymerase, comprising contacting a cell infected with a *Filoviridae* virus with an effective amount of a compound of Formula I; or a pharmaceutically acceptable salts, solvate, and/or ester thereof.

[0017] In another embodiment, provided is the use of a compound of Formula I or a pharmaceutically acceptable salt, solvate, and/or ester thereof to treat a viral infection caused by a *Filoviridae* virus.

[0018] In another aspect, the invention also provides processes and novel intermediates disclosed herein which are useful for preparing Formula I compounds of the invention.

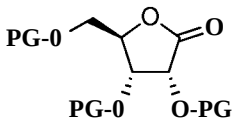
[0019] In other aspects, novel methods for synthesis, analysis, separation, isolation, purification, characterization, and testing of the compounds of this invention are provided.

[0020] In some embodiments, the present invention provides a method of preparing a compound of Formula V:



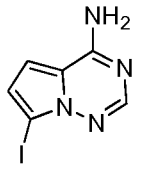
Formula **(V).**

The method of making the compound of Formula V includes forming a reaction mixture having a coupling agent, a halo-silane, a compound of Formula VI:



Formula (VI),

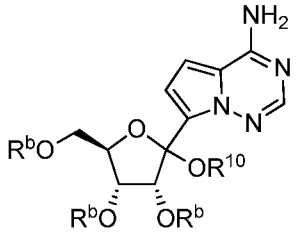
and a compound of Formula VII:



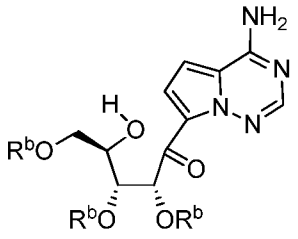
Formula (VII)

under conditions suitable to prepare the compound of Formula V, wherein each PG is independently a hydroxy protecting group, alternatively, two PG groups on adjacent carbons can be combined to form a $-C(R^{19})_2-$ group, R^{10} is H or a silyl group, and R^{19} is H, C_1-C_8 alkyl, phenyl or substituted phenyl.

[0021] In some embodiments, the present invention provides a method of preparing a compound of Formula V-a or V-b:

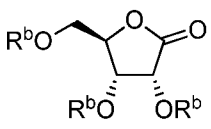


Formula (V-a),



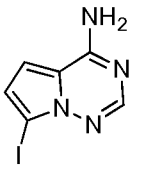
Formula (V-b).

The method of making the compound of Formula V-a or Formula V-b includes forming a reaction mixture having a deprotonating agent, a silylating agent, a coupling agent, an additive, a compound of Formula Vl-a:



Formula (Vl-a),

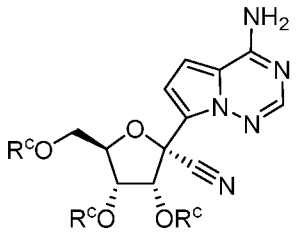
and a compound of Formula VII:



Formula (VII)

under conditions suitable to prepare the compound of Formula V-a or Formula V-b, wherein each R^b is independently a hydroxy protecting group, alternatively, two R^b groups on adjacent carbons can be combined to form a $-C(R^{19})_2-$ group, R^{10} is H or a silyl group, and R^{19} is H, C_1-C_8 alkyl, phenyl or substituted phenyl.

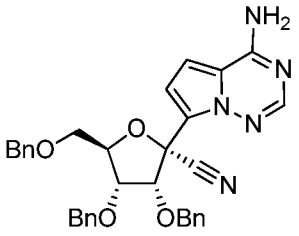
[0022] In some embodiments, the present invention provides a method of preparing a compound of Formula XI:



Formula (XI),

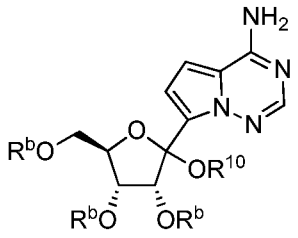
wherein R^c is H or a hydroxyl protecting group, or two R^c on adjacent carbons can be combined to form a $-C(R^{19})_2-$ group, and R^{19} is H or C_1-C_8 alkyl.

[0023] In some embodiments, the present invention provides a method of preparing a compound of Formula Xl-a:

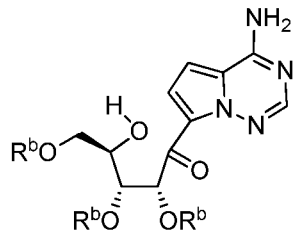


Formula (Xl-a).

wherein the method includes forming a reaction mixture having a cyanating agent, a Lewis Acid, a Broenstedt acid, a solvent, and the compound of Formula V or V-b:



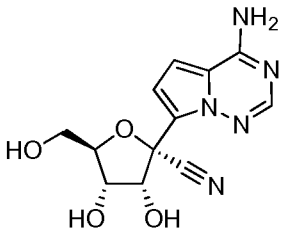
Formula (V-a),



Formula (V-b)

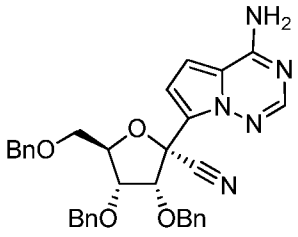
under conditions suitable to prepare the compound of Formula XI, wherein R^b is independently a hydroxy protecting group, alternatively, two R^b groups on adjacent carbons can be combined to form a $-C(R^{19})_2$ group, R^{10} is H or a silyl group, and R^{19} is H, C_1-C_8 alkyl, phenyl or substituted phenyl.

[0024] In some embodiments, the present invention provides a method of preparing a compound of Formula Xl-b:



Formula (Xl-b).

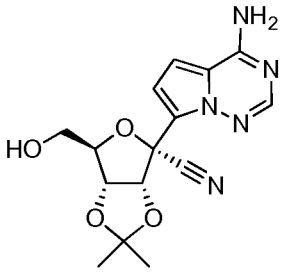
wherein the method includes forming a reaction mixture having a Lewis Acid, a base, a solvent, a filtering agent, and the compound of Formula Xl-a



Formula (Xl-a)

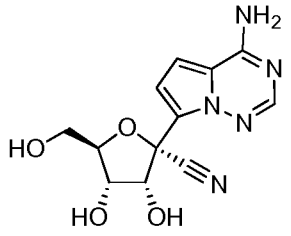
under conditions suitable to prepare the compound of Formula Xl-b.

[0025] In some embodiments, the present invention provides a method of preparing a compound of Formula XI-c:



Formula (XI-c).

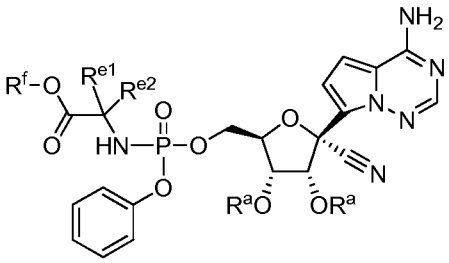
wherein the method includes forming a reaction mixture having a solvent, a reagent, and the compound of Formula Xl-b



Formula (Xl-b)

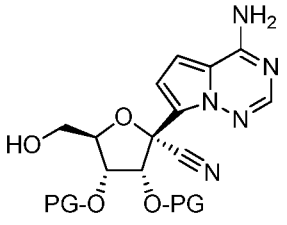
under conditions suitable to prepare the compound of Formula XI-c.

[0026] In some embodiments, the present invention provides a method of preparing a compound of Formula VIII:



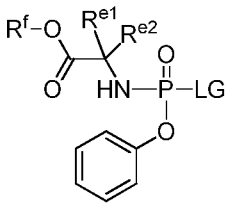
Formula (VIII)

wherein the method includes forming a reaction mixture including a coupling agent, a non-nucleophilic base, a compound of Formula IX:



Formula (IX),

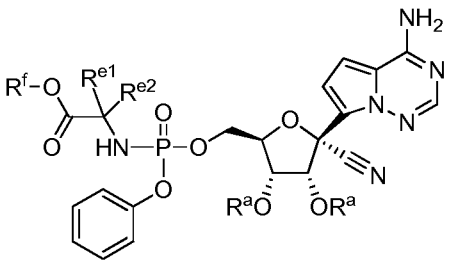
and a compound of Formula X:



Formula (X),

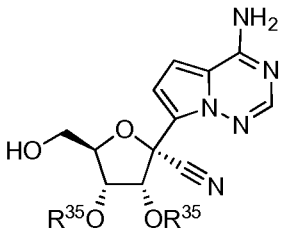
under conditions suitable to form the compound of Formula VIII, wherein each R^a is H or PG, each PG group is a hydroxy protecting group, or both PG groups are combined to form $-C(R^{19})_2-$, R^{e1} and R^{e2} are each independently H, Ci-C_6 alkyl or benzyl, R^f is H, Ci-Cs alkyl, benzyl, C3-C_6 cycloalkyl, or -CH2-C3-C6 cycloalkyl, R^{19} is H, Ci-Cs alkyl, phenyl or substituted phenyl, and LG is a leaving group.

[0027] In some embodiments, the present invention provides a method of preparing a compound of Formula VIII:



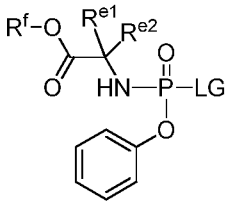
Formula (VIII)

wherein the method includes forming a reaction mixture including a coupling agent, a non-nucleophilic base, a compound of Formula IX-a:



Formula (IX-a),

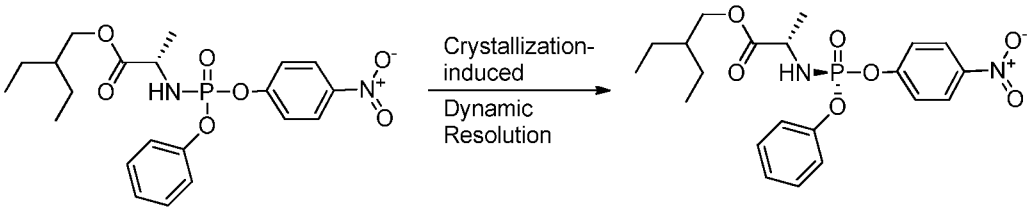
and a compound of Formula X:



Formula (X),

under conditions suitable to form the compound of Formula VIII, wherein R^a is independently H or a hydroxy protecting group, or two R^a on adjacent carbons can be combined to form a -$C(R^{19})_2$- group, R^{35} is independently H or a hydroxy protecting group, or two R^{35} on adjacent carbons can be combined to form a -$C(R^{19})_2$- group, R^{19} is H or C_1-C_8 alkyl, R^{e1} and R^{e2} are each independently H, Ci-C_6 alkyl or benzyl, R^f is H, C_1-C_8 alkyl, benzyl, C3-C6 cycloalkyl, or -CH_2-C3 -C_6 cycloalkyl, R^{19} is H, Ci-Cs alkyl, phenyl or substituted phenyl, and LG is a leaving group.

[0028] In one embodiment, there is provided a method for the crystallization-induced dynamic resolution of (2S)-2-ethylbutyl 2-(((4-nitrophenoxy)(phenoxy)phosphoryl)amino)propanoate (Formula X-a):



Formula X-a
(mixture of diastereomers)

Formula X-b
(diastereomerically pure)

to provide (Formula X-b).

DETAILED DESCRIPTION OF THE INVENTION

I. DEFINITIONS

[0029] Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings:

[0030] When trade names are used herein, applicants intend to independently include the trade name product and the active pharmaceutical ingredient(s) of the trade name product.

[0031] 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 or cocrystal, thereof. Similarly, with respect to isolatable intermediates, the phrase "a compound of Formula (number)" means a compound of that formula and pharmaceutically acceptable salts or cocrystals, thereof.

[0032] "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,* Ci-C_2o alkyl), 1 to 8 carbon

atoms *(i.e.,* C_1-C_8 alkyl), or 1 to 6 carbon atoms *(i.e.,* Ci-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-l -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 (-$(CH_2)_7CH_3$).

[0033] "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(/.e., C_1-C_{12} alkoxy), or 1 to 6 carbon atoms(/.e., Ci-C_6 alkoxy). Examples of suitable alkoxy groups include, but are not limited to, methoxy (-0-CH_3 or -OMe), ethoxy (-OCH_2CH_3 or -OEt), t-butoxy (-0-$C(CH_3)_3$ or -OtBu) and the like.

[0034] "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.,* Ci-C_{20} haloalkyl), 1 to 12 carbon atoms(/.e., Ci-Ci_2 haloalkyl), or 1 to 6 carbon atoms(/.e., Ci-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.

[0035] "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-C8} 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 (-$CH_2CH_2CH_2CH_2CH=CH_2$).

[0036] "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.,* C2-C2$_0$ alkynyl), 2 to 8 carbon atoms *(i.e.,* C_2-C_8 alkyne,), or 2 to 6 carbon atoms *(i.e.,* C_2-C6 alkynyl). Examples of suitable alkynyl groups include, but are not limited to, acetylenic (-C≡CH), propargyl (-CH_2C≡CH), and the like.

[0037] "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(CH¾)-), 1,2-ethyl (-CH2CH2-), 1,1-propyl (-CH(CH_2CH_3)-), 1,2-propyl (-CH_2CH(CH_3)-), 1,3-propyl (-CH2CH2CH2-), 1,4-butyl (-CH2CH2CH2CH2-), and the like.

[0038] "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-).

[0039] "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 (-CH2OC-), and 4-pentynyl (-$CH_2CH_2CH_2$C≡C-).

[0040] "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 -NH2, -N(alky1)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(0)-OH), -NH(alkylene-C(O)-O-alkyl), -N(alkylene-C(0)-OH)$_2$, -N(alkylene-C(0)-0-alkyl)$_2$, etc.

[0041] "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.

[0042] "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-l-yl, naphthylmethyl, 2-naphthylethan-l-yl, naphthobenzyl, 2-naphthophenylethan-l-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.

[0043] "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.

[0044] "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.

[0045] 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, $-R^b$, $-O^-$, =0, $-OR^b$, $-SR^b$, $-S^-$, $-NR^b_2$, $-N^+R^b_3$, $=NR^b$, $-CX_3$, -CN, -OCN, -SCN, -N=C=0, -NCS, -NO, $-N0_2$, $=N_2$, $-N_3$, $-NHC(=0)R^b$, $-OC(=0)R^b$, $-NHC(=0)NR^b_2$, $-S(=0)_2-$, $-S(=0)_2OH$, $-S(=0)_2R^b$, $-OS(=0)_2OR^b$, $-S(=0)_2NR^b_2$, $-S(=0)R^b$, $-OP(=0)(OR^b)_2$, $-P(=0)(OR^b)_2$, $-P(=0)(0^-)_2$, $-P(=0)(OH)_2$, $-P(0)(OR^b)(0^-)$, $-C(=0)R^b$, -C(=0)X, $-C(S)R^b$, $-C(0)OR^b$, $-C(0)0^-$, $-C(S)OR^b$, $-C(0)SR^b$, $-C(S)SR^b$, $-C(0)NR^b_2$, $-C(S)NR^b_2$, $-C(=NR^b)NR^b_2$, where each X is independently a halogen: F, CI, 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.

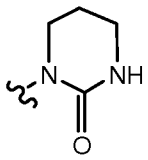
[0046] The term "prodrug" as used herein refers to any compound that when administered to a biological system generates the drug substance, i.e., active ingredient, as a result of spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s), photolysis, and/or metabolic chemical reaction(s). A prodrug is thus a covalently modified analog or latent form of a therapeutically active compound.

[0047] One skilled in the art will recognize that substituents and other moieties of the compounds of Formula I-IV 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-IV which have such stability are contemplated as falling within the scope of the present invention.

[0048] "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

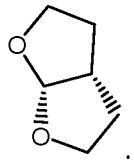
heteroatom (e.g., O, N, or S) the resulting heteroalkyl groups are, respectively, an alkyl ether (e.g., $-CH_2CH_2-O-CH_3$, etc.), an alkyl amine (e.g., $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, etc.), or a thioalkyl ether (e.g.,$-CH_2-S-CH_3$). If a terminal carbon atom of the alkyl group is replaced with a 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 Ci-C_6 heteroalkyl group means a heteroalkyl group having 1 to 6 carbon atoms.

[0049] "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:



[0050] 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-l,2,5-thiadiazinyl, 2H,6H-l,5,2-dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, lH-indazoly, purinyl, 4H-

quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, β-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:



[0051] 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.

[0052] 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, lH-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β-carboline. Still more typically, nitrogen bonded heterocycles include 1-aziridyl, 1-azetedyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

[0053] "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-C¾ -, 2-(heterocyclyl)ethan-l-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-l-yl, imidazolylmethyl, oxazolylmethyl, thiadiazolylmethyl, etc., 6-membered sulfur, oxygen, and/or nitrogen containing heterocycles such as piperidinylmethyl, piperazinylmethyl, morpholinylmethyl, pyridinylmethyl, pyridizylmethyl, pyrimidylmethyl, pyrazinylmethyl, etc.

[0054] "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.

[0055] "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.

[0056] "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.

[0057] "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-l-enyl, l-cyclopent-2-enyl, l-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-l-enyl, l-cyclohex-2-enyl, l-cyclohex-3-enyl, and phenyl. Non-limiting examples of bicyclo carbocycles includes naphthyl, tetrahydronapthalene, and decaline.

[0058] "Carbocyclylalkyl" refers 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.

[0059] "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.

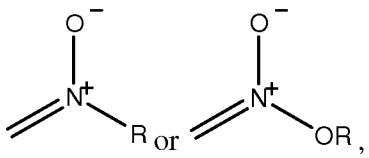
[0060] "Heteroarylalkyl" refers to an alkyl group, as defined herein, in which a hydrogen atom has been replaced with a heteroaryl group as defined herein. Non-limiting examples of heteroaryl alkyl include -C]¾-pyridinyl, -CH_2-pyrrolyl, -CH_2-oxazolyl, -C]¾-indolyl, -C]¾-isoindolyl, -C]¾-purinyl, -CH_2-furanyl, -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.

[0061] The term "optionally substituted" in reference to a particular moiety of the compound of Formula I-IV (e.g., an optionally substituted aryl group) refers to a moiety wherein all substituents 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".

[0062] The term "optionally replaced" in reference to a particular moiety of the compound of Formula I-IV (e.g., the carbon atoms of said (Ci-Cs)alkyl may be optionally replaced by -0-, -S-, or -NR ^{a}-) means that one or more of the methylene groups of the (Ci-Cs)alkyl may be replaced by 0, 1, 2, or more of the groups specified (e.g., -0-, -S-, or -NR ^{a}-).

[0063] 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.

[0064] Certain Q and Q^1 alternatives are nitrogen oxides such as $^+N(0)(R)$ or $^+N(0)(OR)$. 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.

[0065] "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.

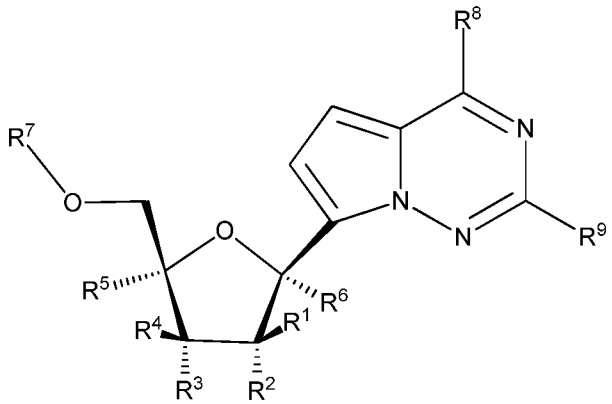
[0066] The terms such as "oxygen-linked", "nitrogen-linked", "carbon-linked", "sulfur-linked", or "phosphorous-linked" mean that if a bond between two moieties can be formed by using more than one type of atom in a moiety, then the bond formed between the moieties is through the atom specified. For example, 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.

[0067] In some embodiments of the compounds of Formula I-IV, one or more of Z^1 or Z^2 are independently a radical of a nitrogen-linked naturally occurring oc-amino acid ester. Examples of naturally occurring amino acids include isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine, alanine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, proline, selenocysteine, serine, tyrosine, arginine, histidine, ornithine and taurine. The esters of these amino acids comprise any of those described for the substituent R, particularly those in which Ris optionally substituted $(C_1\text{-}C_8)$alkyl.

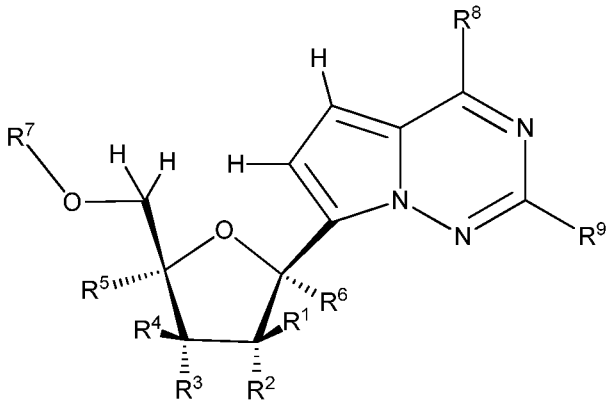
[0068] The term "purine" or "pyrimidine" base comprises, but is not limited to, adenine, N^6-alkylpurines, N^6-acylpurines (wherein acyl is C(0)(alkyl, aryl, alkylaryl, or arylalkyl), N^6-benzylpurine, N^6-halopurine, N^6-vinylpurine, N^6-acetylenic purine, N^6-acyl purine, N^6-hydroxyalkyl purine, N^6-allylaminopurine, N^6-thioallyl purine, N^2-alkylpurines, N^2-alkyl-6-thiopurines, thymine, cytosine, 5-fluorocytosine, 5-methylcytosine, 6-azapyrimidine, including

6-azacytosine, 2- and/or 4-mercaptopyrmidine, uracil, 5-halouracil, including 5-fluorouracil, C^5-alkylpyrimidines, C^5-benzylpyrimidines, C^5-halopyrimidines, C^5-vinylpyrimidine, C^5-acetylenic pyrimidine, C^5-acyl pyrimidine, C^5-hydroxyalkyl purine, C^5-amidopyrimidine, C^5-cyanopyrimidine, C^5-5-iodopyrimidine, C^6-iodo-pyrimidine, C^5-Br-vinyl pyrimidine, C^6-Br-vinyl pyriniidine, C^5-nitropyrimidine, C^5-amino-pyrimidine, N^2-alkylpurines, N^2-alkyl-6-thiopurines, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, and pyrazolopyrimidinyl. Purine bases include, but are not limited to, guanine, adenine, hypoxanthine, 2,6-diaminopurine, and 6-chloropurine. The purine and pyrimidine bases of Formula I-III are linked to the ribose sugar, or analog thereof, through a nitrogen atom of the base. Functional oxygen and nitrogen groups on the base can be protected as necessary or desired. Suitable protecting groups are well known to those skilled in the art, and include trimethylsilyl, dimethylhexylsilyl, t-butyldimethylsilyl, and t-butyldiphenylsilyl, trityl, alkyl groups, and acyl groups such as acetyl and propionyl, methanesulfonyl, and p-toluenesulfonyl.

[0069] Unless otherwise specified, the carbon atoms of the compounds of Formula I-IV 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 substituents needed to provide a valence of four should be assumed to be hydrogen. For example,



has the same meaning as



[0070] "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. See also *Protective Groups in Organic Chemistry,* Peter G. M. Wuts and Theodora W. Greene, 4th Ed., 2006. 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. "Hydroxy protecting groups" refers to those protecting groups useful for protecting hydroxy groups (-OH).

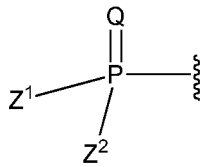
[0071] Protected compounds may also exhibit altered, and in some cases, optimized properties *in vitro* and *in vivo,* such as passage through cellular membranes and resistance to enzymatic degradation or sequestration. In this role, protected compounds with intended therapeutic effects may be referred 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.

[0072] 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.

[0073] 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.

[0074] "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, reactivities and biological properties. For example, the compounds of Formula I-IV may have a chiral phosphorus atom when R^7 is



and Z^1 and Z^2 are different. When at least one of either Z^1 or Z^2 also has a chiral center, for example with Z^1 or Z^2 is a nitrogen-linked, chiral, naturally occurring oc-amino acid ester, then the compound of Formula I-IV will exists as diastereomers because there are two centers of chirality in the molecule. All such diastereomers and their uses described herein are encompassed by the instant invention. Mixtures of diastereomers may be separate under high resolution analytical procedures such as electrophoresis, crystallization and/or chromatography. Diastereomers may have different physical attributes such as, but not limited to, solubility, chemical stabilities and crystallinity and may also have different biological properties such as, but not limited to, enzymatic stability, absorption and metabolic stability.

[0075] "Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

[0076] 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).

[0077] The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

[0078] The term "therapeutically effective amount", as used herein, is the amount of compound of Formula I-IV present in a composition described herein that is needed to provide a desired level of drug in the secretions and tissues of the airways and lungs, or alternatively, in the bloodstream of a subject to be treated to give an anticipated physiological response or desired biological effect when such a composition is administered by the chosen route of administration. The precise amount will depend upon numerous factors, for example the particular compound of Formula I-IV, the specific activity of the composition, the delivery device employed, the physical characteristics of the composition, its intended use, as well as patient considerations such as severity of the disease state, patient cooperation, etc., and can readily be determined by one skilled in the art based upon the information provided herein.

[0079] The term "normal saline" means a water solution containing 0.9% (w/v) NaCl.

[0080] The term "hypertonic saline" means a water solution containing greater than 0.9% (w/v) NaCl. For example, 3% hypertonic saline would contain 3% (w/v) NaCl.

[0081] "Forming a reaction mixture" refers to the process of bringing into contact at least two distinct species such that they mix together and can react. It should be appreciated, however, the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents which can be produced in the reaction mixture.

[0082] "Coupling agent" refers to an agent capable of coupling two disparate compounds. Coupling agents can be catalytic or stoichiometric. For example, the coupling agents can be a lithium based coupling agent or a magnesium based coupling agent such as a Grignard reagent. Exemplary coupling agents include, but are not limited to, n-BuLi, $MgCl_2$, iPrMgCl, tBuMgCl, PhMgCl or combinations thereof.

[0083] "Silane" refers to a silicon containing group having the formula SiR_4, where each R group can be alkyl, alkenyl, cycloalkyl, phenyl, or other silicon containing groups. When the

silane is linked to another compound, the silane is referred to as a "silyl" and has the formula $-SiR_3$.

[0084] "Halo-silane" refers to a silane having at least one halogen group linked to the silicon atom. Representative halo-silanes have the formula Halo-SiR_3, where each R group can be alkyl, alkenyl, cycloalkyl, phenyl, or other silicon containing groups. Specific halo-silanes include Cl-$Si(CH_3)_3$, and Cl-$Si(CH_3)_2CH_2CH_2Si(CH_3)_2$-Cl.

[0085] "Non-nucleophilic base" refers to an electron donor, a Lewis base, such as nitrogen bases including triethylamine, diisopropylethyl amine, N,N-diethylaniline, pyridine, 2,6-lutidine, 2,4,6-collidine, 4-dimethylaminopyridine, and quinuclidine.

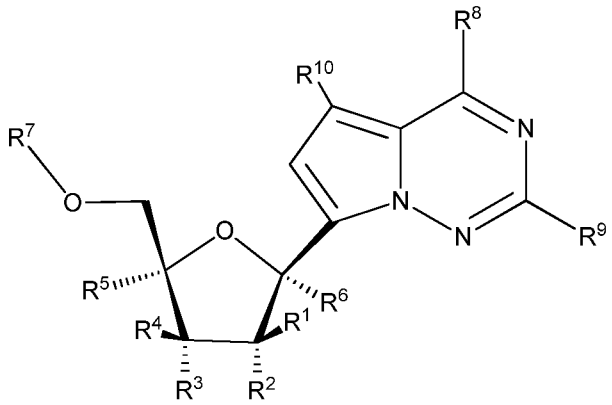
[0086] "Leaving group" refers to groups that maintain the bonding electron pair during heterolytic bond cleavage. For example, a leaving group is readily displaced during a nucleophilic displacement reaction. Suitable leaving groups include, but are not limited to, chloride, bromide, mesylate, tosylate, triflate, 4-nitrobenzenesulfonate, 4-chlorobenzenesulfonate, 4-nitrophenoxy, pentafluorophenoxy, etc. One of skill in the art will recognize other leaving groups useful in the present invention.

[0087] "Deprotection agent" refers to any agent capable of removing a protecting group. The deprotection agent will depend on the type of protecting group used. Representative deprotection agents are known in the art and can be found in *Protective Groups in Organic Chemistry,* Peter G. M. Wuts and Theodora W. Greene, 4th Ed., 2006.

II. COMPOUNDS OF THE PRESENT INVENTION

[0088] 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.

[0089] Provided, is a method for treating a *Filoviridae* infection in a human in need thereof comprising administering a therapeutically effective amount of a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt ester, or cocrystal, thereof;

wherein:

each R^1 is H or halogen;

each R^2, R^3, R^4 or R^5 is independently H, OR^a, $N(R^a)_2$, N_3, CN, $N0_2$, $S(0)_nR^a$, halogen, $(Ci\text{-}C_8)$alkyl, $(C_4\text{-}C_8)$carbocyclylalkyl, $(Ci\text{-}C_8)$substituted alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$substituted alkenyl, $(C_2\text{-}C_8)$alkynyl or $(C_2\text{-}C_8)$substituted alkynyl;

wherein

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$(Ci\text{-}C_8)$alkyl, $(C_4\text{-}C_8)$carbocyclylalkyl, -C(=0)R, -C(=0)OR, -C(=0)NR_2, -C(=0)SR, -S(0)R, -S(0)$_2$R, -S(0)(OR), -S(0)$_2$(OR), or -S0$_2$$NR_2$;

each R 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, $C_6\text{-}C_{20}$ aryl, $C_6\text{-}C_{20}$ substituted aryl, $C_2\text{-}C_{20}$ heterocyclyl, $C_2\text{-}C_{20}$ substituted heterocyclyl, arylalkyl or substituted arylalkyl;

or any two R^2, R^3, R^4 or R^5 on adjacent carbon atoms when taken together are -0(CO)0- or when taken together with the ring carbon atoms to which they are attached form a double bond;

R^6 is OR^a, $N(R^a)_2$, N_3, CN, $N0_2$, $S(0)_nR^a$, $-C(=0)R^{11}$, $-C(=0)OR^{11}$, $-C(=0)NR^{11}R^{12}$, $-C(=0)SR^{11}$, $-S(0)R^{11}$, $-S(0)_2R^{11}$, $-S(0)(OR^{11})$, $-S(0)_2(OR^{11})$, $-S0_2NR^{11}R^{12}$, halogen, $(Ci\text{-}C_8)$alkyl, $_{(C4}$ - $C_8)$carbocyclylalkyl, $(Ci\text{-}C_8)$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$(Ci\text{-}C_8)$alkyl;

wherein

each 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, $_{(C4}$ -Cs)carbocyclylalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=0)(C_1\text{-}C_8)$alkyl, $-S(0)_n(Ci\text{-}C_8)$alkyl or aryl$(C_1\text{-}C_8)$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 -0-, -S- or $-NR^a$-;

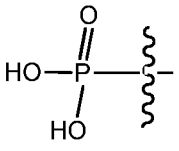
each n is independently 0, 1, or 2;

R^7 is selected from a group consisting of

a) H, $-C(=0)R^{11}$, $-C(=0)OR^{11}$, $-C(=0)NR^{11}R^{12}$, $-C(=0)SR^{11}$, $-S(0)R^{11}$, $-S(0)_2R^{11}$, $-S(0)(OR^{11})$, $-S(0)_2(OR^{11})$, $-S0_2NR^{11}R^{12}$, or $Si(R^{11})_3$;

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^{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 $(Ci\text{-}C_8)$alkyl may be optionally replaced with -0-, -S- or $-NR^a$-, and

b)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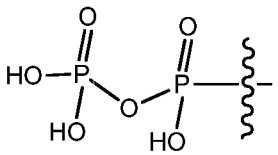
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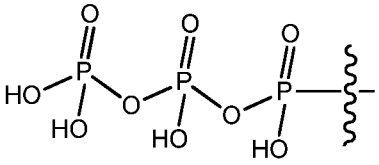
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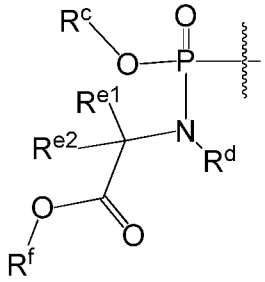
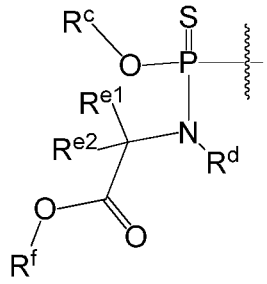
c) a group selected from: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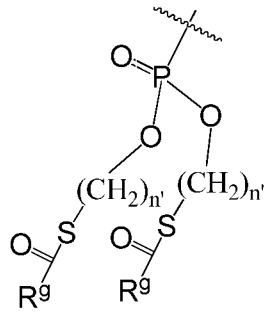
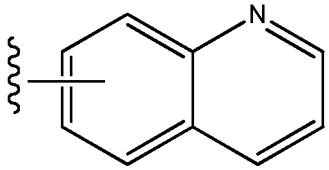


wherein:

R^c is selected from phenyl, 1-naphthyl, 2-naphthyl,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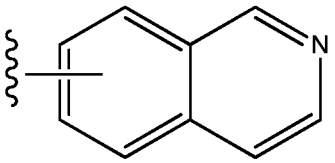

;

R^d is H or CH_3;

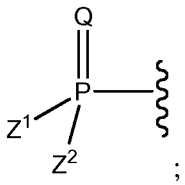
R^{e1} and R^{e2} are each independently H, Ci-C $_6$ alkyl or benzyl;

R^f is selected from H, C_1-C_8 alkyl, benzyl, $_{C3-C6}$ cycloalkyl, and -CH2-C3-C6 cycloalkyl;

R^g is selected from C_1-C_8 alkyl, -0-C $_1$-C_8 alkyl, benzyl, -O-benzyl, -CH_2-C_3-C_6 cycloalkyl, -O-CH2-C3-C6 cycloalkyl, and CF_3; and

n' is selected from 1, 2, 3, and 4; and

d) a group of the formula:


;

wherein

Q is O, S, NR, $^+$N(0)(R), N(OR), $^+$N(0)(OR), or N-NR $_2$;

Z^1 and Z^2, when taken together, are $-Q^1(C(R^y)_2)3Q^1-$;

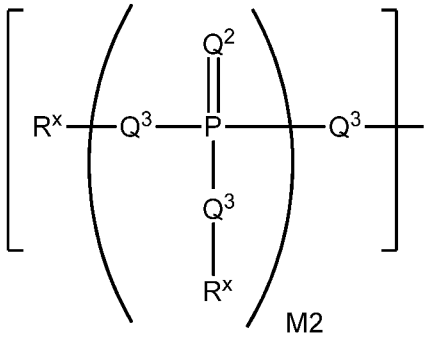
wherein

each Q^1 is independently O, S, or NR; and

each R^y is independently H, F, CI, Br, I, OH, R, $-C(=Q^2)R$, $-C(=Q^2)OR$, $-C(=Q^2)N(R)_2$, $-N(R)_2$, $-^+N(R)_3$, -SR, -S(0)R, $-S(0)_2R$, -S(0)(OR), $-S(0)_2(OR)$, $-OC(=Q^1)R$, $-OC(=Q^2)OR$, $-OC(=Q^2)(N(R)_2)$, $-SC(=Q^2)R$, $-SC(=Q^2)OR$, $-SC(=Q^2)(N(R)_2)$, $-N(R)C(=Q^2)R$, $-N(R)C(=Q^2)OR$, $-N(R)C(=Q^2)N(R)_2$, $-S0_2NR_2$, -CN, $-N_3$, $-N0_2$, -OR, or Z^3; or when taken together, two R^y on the same carbon atom form a carbocyclic ring of 3 to 7 carbon atoms;

each Q^2 is independently, O, S, NR, $^+N(0)(R)$, N(OR), $^+N(0)(OR)$, or $N\text{-}NR_2$; or

Z^1 and Z^2 are each, independently, a group of the Formula la:



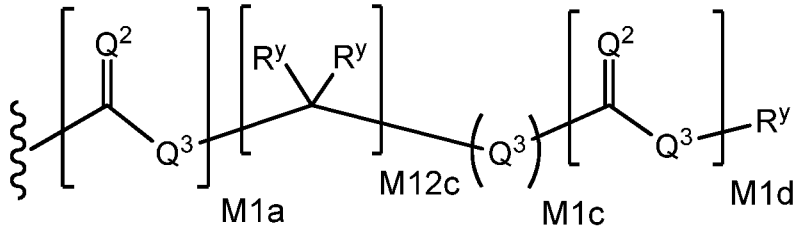
Formula la

wherein:

each Q^3 is independently a bond, O, CR_2, NR, $^+N(0)(R)$, N(OR), $^+N(0)(OR)$, $N\text{-}NR_2$, S, S-S, S(O), or $S(0)_2$;

M2 is 0, 1 or 2;

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



wherein:

each Mia, Mlc, and Mid is independently 0 or 1;

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

Z^3 is Z^4 or Z^5;

Z^4 is R, $-C(Q^2)R^y$, $-C(Q^2)Z^5$, $-S0_2R^y$, or $-S0_2Z^5$; and

Z^5 is a carbocycle or a heterocycle wherein Z^5 is independently substituted with 0 to 3 R^y groups.

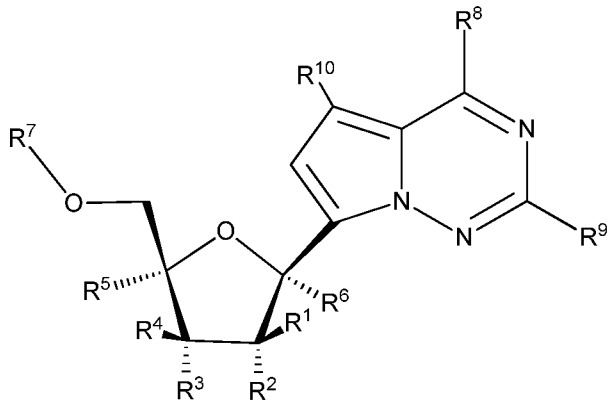
each R^8 is halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3, NO, $N0_2$, CHO, CN, $-CH(=NR^{11})$, $-CH=NNHR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=0)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=0)OR^{11}$, $(Ci\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $(C_4\text{-}Cs)$carbocyclylalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=0)(C_1\text{-}C_8)$alkyl, $-S(0)_n(C_1\text{-}C_8)$alkyl, aryl$(C_1\text{-}C_8)$alkyl, OR^{11} or SR^{11};

each 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, $N0_2$, CHO, CN, $-CH(=NR^{11})$, $-CH=NHNR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=0)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=0)OR^{11}$, R^{11}, OR^{11} or SR^{11};

each 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, $-C(=0)(C_1\text{-}C_8)$alkyl, $-S(0)_n(C_1\text{-}C_8)$alkyl or aryl$(C_1\text{-}C_8)$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 -0-, -S- or $-NR^a$-; and

wherein each (Ci-Cs)alkyl, (C_2-Cs)alkenyl, (C_2-Cs)alkynyl or aryl(Ci-Cs)alkyl of each R^2, R^3, R^5, or R^6 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 (Ci-Cs)alkyl may be optionally replaced with -0-, -S- or -NR^a-.

[0090] In another embodiment, provided is a method of treating a *Filoviridae* infection in a human in need thereof comprising administering a therapeutically effective amount of a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt or ester, thereof;

wherein:

each R^1 is H or halogen;

each R^2, R^3, R^4 or R^5 is independently H, OR^a, $N(R^a)_2$, N_3, CN, $N0_2$, $S(0)_nR^a$, halogen, (Ci-C_8)alkyl, (C_4- C_8)carbocyclylalkyl, (Ci-C_8)substituted alkyl, (C_2- C_8)alkenyl, (C_2-Cs)substituted alkenyl, (C_2-Cs)alkynyl or (C_2-Cs)substituted alkynyl;

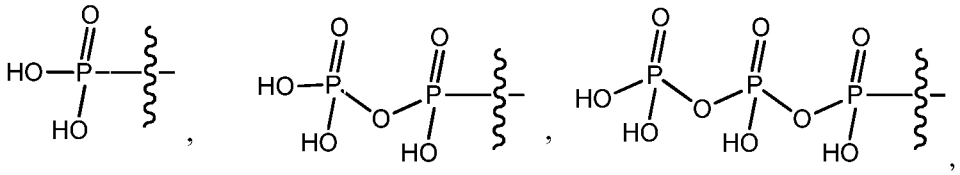
or any two R^2, R^3, R^4 or R^5 on adjacent carbon atoms when taken together are -0(CO)0- or when taken together with the ring carbon atoms to which they are attached form a double bond;

R^6 is OR^a, $N(R^a)_2$, N_3, CN, $N0_2$, $S(0)_nR^a$, -C(=0)R^{11}, -C(=0)OR^{11}, -C(=0)$NR^{11}R^{12}$, -C(=0)SR^{11}, -S(0)R^{11}, -$S(0)_2R^{11}$, -S(0)(OR^{11}), -$S(0)_2(OR^{11})$, -$S0_2NR^{11}R^{12}$, halogen, (Ci-Cs)alkyl, (C_4-Cs)carbocyclylalkyl, (Ci-Cs)substituted alkyl, (C_2-Cs)alkenyl, (C_2-Cs)substituted alkenyl, (C_2-Cs)alkynyl, (C_2-Cs)substituted alkynyl, or (C_6- C_{20})aryl(C_1- C_8)alkyl;

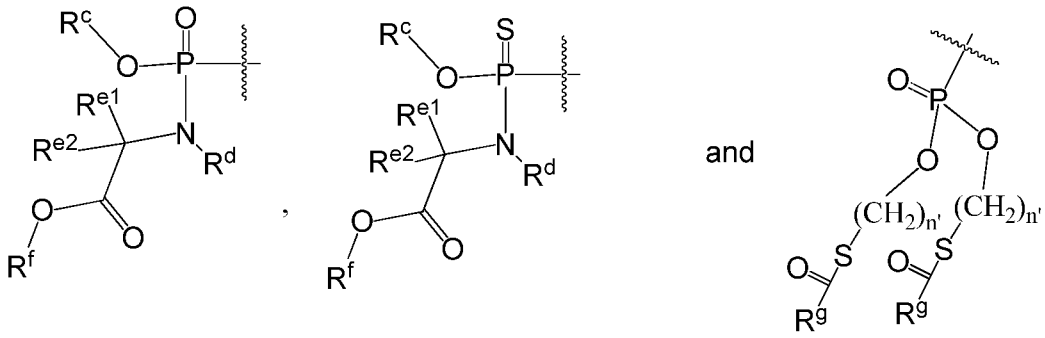
R^7 is selected from a group consisting of

a) H, -C(=0)R ^{11}, -C(=0)OR ^{11}, -C(=0)NR ^{11}R^{12}, -C(=0)SR ^{11}, -S(0)R ^{11}, -S(0) $_2$R^{11}, -S(0)(OR ^{11}), -S(0) $_2$(OR^{11}), or -S0 $_2$NR^{11}R^{12},

wherein each (Ci-Cs)alkyl, (C_2-Cs)alkenyl, (C_2-Cs)alkynyl or (C6 - C_2o)aryl(Ci-Cs)alkyl of each 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 (Ci-Cs)alkyl may be optionally replaced with -0-, -S- or -NR^a-, and

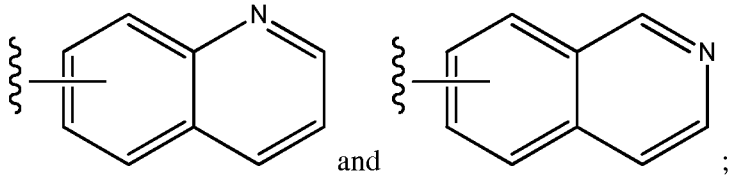
b) 

c) a group selected from:



wherein:

R^c is selected from phenyl, 1-naphthyl, 2-naphthyl,



;

R^d is H or CH_3;

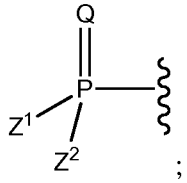
R^{e1} and R^{e2} are each independently H, (C_1- C6)alkyl or benzyl;

R^f is selected from H, (Ci-Cs)alkyl, benzyl, (C_3-C6)cycloalkyl, and -CH_2-(C_3-C_6)cycloalkyl;

R^g is selected from (Ci-C_8)alkyl, -0-(Ci-C_8)alkyl, benzyl, -O-benzyl, -CH_2-(C_3-C_6)cycloalkyl, -0-CH_2-(C_3-C_6)cycloalkyl, and CF_3; and

n' is selected from 1, 2, 3, and 4; and

d) a group of the formula:



;

wherein:

Q is O, S, NR, $^+$N(0)(R), N(OR), $^+$N(0)(OR), or N-NR_2;

Z^1 and Z^2, when taken together, are -$Q^1(C(R^y)_2)_3Q^1$-;

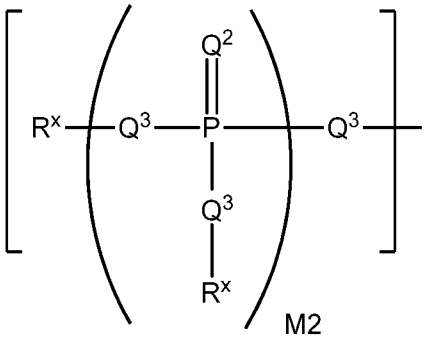
wherein

each Q^1 is independently O, S, or NR; and

each R^y is independently H, F, CI, Br, I, OH, R, -$C(=Q^2)R$, -$C(=Q^2)OR$, -$C(=Q^2)N(R)_2$, -$N(R)_2$, -$^+N(R)_3$, -SR, -S(0)R, -$S(0)_2R$, -S(0)(OR), -$S(0)_2$(OR), -$OC(=Q^1)R$, -$OC(=Q^2)OR$, -$OC(=Q^2)(N(R)_2)$, -$SC(=Q^2)R$, -$SC(=Q^2)OR$, -$SC(=Q^2)(N(R)_2)$, -$N(R)C(=Q^2)R$, -$N(R)C(=Q^2)OR$, -$N(R)C(=Q^2)N(R)_2$, -$S0_2NR_2$, -CN, -N_3, -$N0_2$, -OR, or Z^3; or when taken together, two R^y on the same carbon atom form a carbocyclic ring of 3 to 7 carbon atoms;

each Q^2 is independently, O, S, NR, $^+$N(0)(R), N(OR), $^+$N(0)(OR), or N-NR_2;or

Z^1 and Z^2 are each, independently, a group of the Formula la:



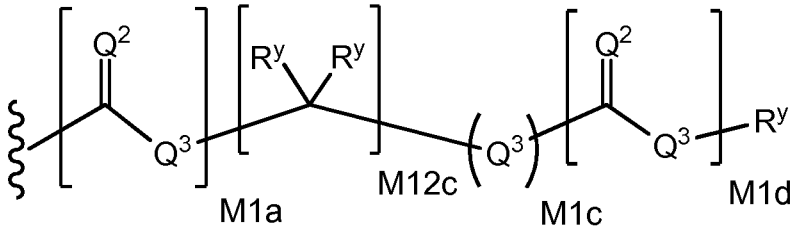
Formula 1a

wherein:

each Q^3 is independently a bond, O, CR_2, NR, $^+N(0)(R)$, N(OR), $^+N(0)(OR)$, N-NR_2, S, S-S, S(O), or $S(0)_2$;

M2 is 0, 1 or 2;

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



wherein:

each Mia, Mlc, and Mid is independently 0 or 1;

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

Z^3 is Z^4 or Z^5;

Z^4 is R, $-C(Q^2)R^y$, $-C(Q^2)Z^5$, $-S0_2R^y$, or $-S0_2Z^5$; and

Z^5 is a carbocycle or a heterocycle wherein Z^5 is independently substituted with 0 to 3 R^y groups;

R^8 is halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3, NO, $N0_2$, CHO, CN, $-CH(=NR^{11})$, $-CH=NNHR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=0)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=0)OR^{11}$, $(Ci\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl,

(C4 -Cs)carbocyclylalkyl, (C6-C2o)optionally substituted aryl, optionally substituted heteroaryl, -C(=O)(C_1–C_8)alkyl, -S(0) $_n$(Ci-C $_8$)alkyl, (C6 - C_2o)aryl(Ci-C $_8$)alkyl, OR^{11} or SR^{11};

each 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, N0 $_2$, CHO, CN, -CH(=NR^{11}), -CH=NHNR^{11}, -CH=N(OR^{11}), -CH(OR^{11})$_2$, -C(=0)$NR^{11}R^{12}$, -C(=S)$NR^{11}R^{12}$, -C(=0)OR^{11}, R^{11}, OR^{11} or SR^{11};

each R^{11} or R^{12} is independently H, (Ci-C $_8$)alkyl, (C_2- C_8)alkenyl, (C_2- C_8)alkynyl, (C4 - C_8)carbocyclylalkyl, (C6 - C_2o)optionally substituted aryl, optionally substituted heteroaryl, -C(=0)(d-C $_8$)alkyl, -S(0) $_n$(Ci-C $_8$)alkyl or (C6 - C_2o)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 -0-, -S- or -NR^a-;

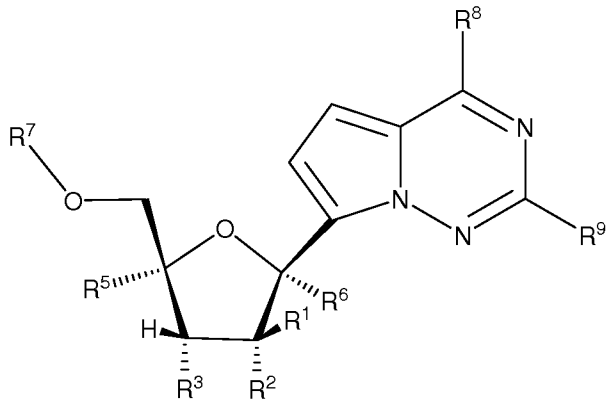
each R^a is independently H, (C_1- C_8)alkyl, (C_2- C_8)alkenyl, (C_2- C_8)alkynyl, (C_6- C_{20})aryl(C_1- C_8)alkyl, (C_4- C_8)carbocyclylalkyl, -C(=0)R, -C(=0)OR, -C(=0)NR_2, -C(=0)SR, -S(0)R, -S(0) $_2$R, -S(0)(OR), -S(0) $_2$(OR), or -S0 $_2NR_2$; wherein

each R is independently H, (Ci-C $_8$) alkyl, (Ci-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_2o)aryl, (C6 - C_2o)substituted aryl, (C_2- C_2o)heterocyclyl, (C_2- C_{2o}) substituted heterocyclyl, (C6 - C_2o)aryl(C_1- C_8)alkyl or substituted (C6 - C_2o)aryl(C_1- C_8)alkyl;

each n is independently 0, 1, or 2; and

wherein each (Ci-C $_8$)alkyl, (C_2- C_8)alkenyl, (C_2- C_8)alkynyl or (C_6- C_{20})aryl(Ci-C $_8$)alkyl of each R^2, R^3, R^5, R^6, R^{11} or R^{12} is, independently, optionally substituted with one or more halo, hydroxy, CN, N3, $N(R^a)_2$ or OR^a; and wherein one or more of the non-terminal carbon atoms of each said (Ci-C_8)alkyl may be optionally replaced with -0-, -S- or -NR^a-.

[0091] In another embodiment, provided is a method of treating a *Filoviridae* infection in a human in need thereof comprising administering a therapeutically effective amount of a compound of Formula I represented by Formula II:



Formula II

or a pharmaceutically acceptable salt or ester, thereof;

wherein

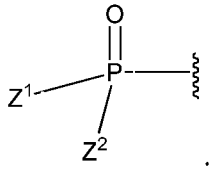
R^1, R^3, R^5, R^7, R^8 and R^9 are as defined above for Formula I;

each R^2 is OR^a or halogen; and

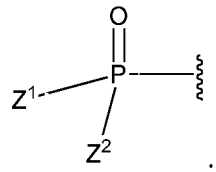
R^6 is OR^a, $N(R^a)_2$, N_3, CN, $S(0)_nR^a$, $-C(=0)R^{11}$, $-C(=0)OR^{11}$, $-C(=0)NR^{11}R^{12}$, $-C(=0)SR^{11}$, $-S(0)R^{11}$, $-S(0)_2R^{11}$, $-S(0)(OR^{11})$, $-S(0)_2(OR^{11})$, $-S0_2NR^{11}R^{12}$, halogen, (Ci-Cs)alkyl, $_{(C4}$-Cs)carbocyclylalkyl, (Ci-Cs)substituted alkyl, (C_2-Cs)alkenyl, (C_2-Cs)substituted alkenyl, (C_2-Cs)alkynyl, or (C_2-Cs)substituted alkynyl.

[0092] In one embodiment of the method of treating a *Filoviridae* infection by administering a compound of Formula II, R^1 of Formula II is H. In another aspect of this embodiment R^6 of Formula II is N_3, CN, halogen, (Ci-C_8)alkyl, (Ci-C_8)substituted alkyl, (C_2- C_8)alkenyl, (C_2-Cs)substituted alkenyl, (C_2-Cs)alkynyl, or (C_2-Cs)substituted alkynyl. In another aspect of this embodiment, R^6 of Formula II is CN, methyl, ethenyl, or ethynyl. In another aspect of this embodiment, R^6 of Formula II is CN. In another aspect of this embodiment, R^6 of Formula II is methyl. In another aspect of this embodiment, R^5 of Formula II is H. In another aspect of this embodiment, R^2 of Formula II is OR^a. In another aspect of this embodiment, R^2 of Formula II is OH. In another aspect of this embodiment, R^2 of Formula II is F. In another aspect of this embodiment, R^3 of Formula II is OR^a. In another aspect of this embodiment, R^3 of Formula II is OH, $-OC(=0)R^{11}$, or $-OC(=0)OR^{11}$. In another aspect of this embodiment, R^3 of Formula II is OH. In another aspect of this embodiment, R^8 of Formula II is $NR^{11}R^{12}$. In another aspect of

this embodiment, R^8 of Formula II is NH_2. In another aspect of this embodiment, R^8 of Formula II is OR^{11}. In another aspect of this embodiment, R^8 of Formula II is OH. In another aspect of this embodiment, R^9 of Formula II is H. In another aspect of this embodiment, R^9 of Formula II is $NR^{11}R^{12}$. In another aspect of this embodiment, R^9 of Formula II is NH_2. In another aspect of this embodiment, R^7 of Formula II is H, -C(=0)R^{11}, -C(=0)OR^{11} or



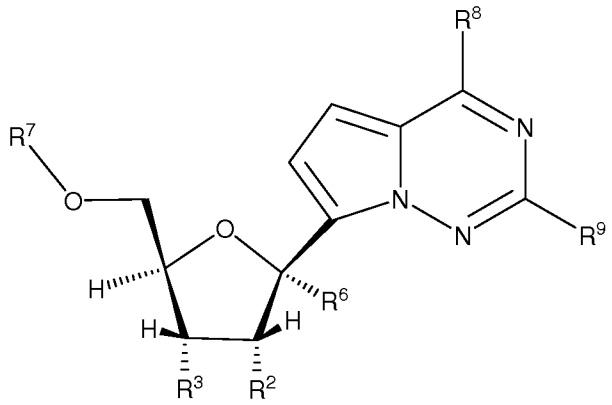
In another aspect of this embodiment, R^7 of Formula II is H. In another aspect of this embodiment, R^7 of Formula II is



[0093] In another embodiment of the method of treating a *Filoviridae* infection comprising administering a compound of Formula II, the *Filoviridae* infection is caused by a *Filoviridae* virus. In another aspect of this embodiment, the *Filoviridae* virus is a Marburg virus, Ebola virus, or Cueva virus. In another aspect of this embodiment, the *Filoviridae* virus is an Ebola virus. In another aspect of this embodiment, the *Filoviridae* virus is a *Bundibugyo ebolavirus, Reston ebolavirus, Sudan ebolavirus, Tai Forest ebolavirus,* or *Zaire ebolavirus.*

[0094] In another embodiment of the method of treating a *Filoviridae* infection comprising administering a compound of Formula II, the *Filoviridae* infection is caused by a *Marburg* virus. In another aspect of this embodiment, the *Filoviridae* virus is a Lloviu virus.

[0095] In another embodiment, provided is a method of treating a *Filoviridae* infection in a human in need thereof comprising administering a therapeutically effective amount of a compound of Formula I represented by Formula III:



Formula III

or a pharmaceutically acceptable salt or ester, thereof;

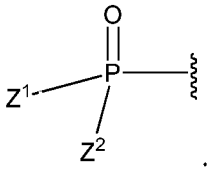
wherein

R^6, R^7, R^8 and R^9 are as defined above for Formula II;

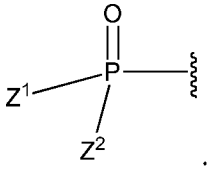
each R^2 is OR^a or F; and

each R^3 is OR^a.

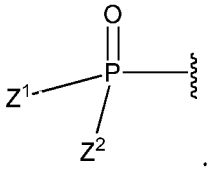
[0096] In one embodiment of the method of treating a *Filoviridae* infection comprising administering a compound of Formula III, R^6 of Formula III is N_3, CN, halogen, (Ci-Cs)alkyl, (Ci-Cs)substituted alkyl, (C_2-Cs)alkenyl, (C_2-Cs)substituted alkenyl, (C_2-Cs)alkynyl, or (C_2-Cs)substituted alkynyl. In another aspect of this embodiment, R^6 of Formula III is CN, methyl, ethenyl, or ethynyl. In another aspect of this embodiment, R^6 of Formula III is CN. In another aspect of this embodiment, R^6 of Formula III is methyl. In another aspect of this embodiment, R^2 of Formula III is OR^a. In another aspect of this embodiment, R^2 of Formula III is OH. In another aspect of this embodiment, R^2 of Formula III is F. In another aspect of this embodiment, R^3 of Formula III is OH, -OC(=0)R^{11}, or -OC(=0)OR^{11}. In another aspect of this embodiment, R^3 of Formula III is OH. In another aspect of this embodiment, R^8 of Formula III is $NR^{11}R^{12}$. In another aspect of this embodiment, R^8 of Formula III is N¾. In another aspect of this embodiment, R^8 of Formula III is OR^{11}. In another aspect of this embodiment, R^8 of Formula III is OH. In another aspect of this embodiment, R^9 of Formula III is H. In another aspect of this embodiment, R^9 of Formula III is $NR^{11}R^{12}$. In another aspect of this embodiment, R^9 of Formula III is N¾. In another aspect of this embodiment, R^7 of Formula III is H, -C(=0)R^{11}, -C(=0)OR^{11} or



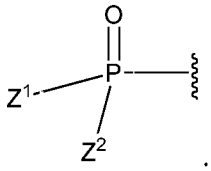
In another aspect of this embodiment, R^7 of Formula III is H. In another aspect of this embodiment, R^7 of Formula III is



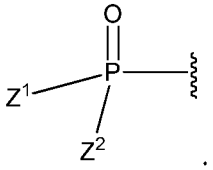
[0097] In another embodiment of the method of treating a *Filoviridae* infection comprising administering a compound of Formula III, R^6 of Formula III is N_3, CN, halogen, (Ci-Cs)alkyl, (Ci-Cs)substituted alkyl, (C_2-Cs)alkenyl, (C_2-Cs)substituted alkenyl, (C_2-Cs)alkynyl, or (C_2-Cs)substituted alkynyl and R^8 is NH_2. In another aspect of this embodiment, R^6 of Formula III is CN, methyl, ethenyl, or ethynyl. In another aspect of this embodiment, R^6 of Formula III is CN. In another aspect of this embodiment, R^6 of Formula III is methyl. In another aspect of this embodiment, R^2 of Formula III is OR^a. In another aspect of this embodiment, R^2 of Formula III is OH, -OC**(=0**)R^{11}, or -OC**(=0**)OR^{11}. In another aspect of this embodiment, R^2 of Formula III is OH. In another aspect of this embodiment, R^2 of Formula III is F. In another aspect of this embodiment, R^3 of Formula III is OH, -OC**(=0**)R^{11}, or -OC**(=0**)OR^{11}. In another aspect of this embodiment, R^3 of Formula III is OH. In another aspect of this embodiment, R^9 of Formula III is H. In another aspect of this embodiment, R^9 of Formula III is $NR^{11}R^{12}$. In another aspect of this embodiment, R^9 of Formula III is NH_2. In another aspect of this embodiment, R^7 of Formula III is H, -C**(=0**)R^{11}, -C**(=0**)OR^{11} or



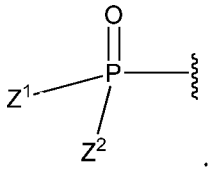
In another aspect of this embodiment, R^7 of Formula III is H. In another aspect of this embodiment, R^7 of Formula III is



[0098] In another embodiment of the method of treating a *Filoviridae* infection comprising administering a compound of Formula III, R^6 of Formula III is CN, methyl, ethenyl, or ethynyl, R^8 is NH_2, and R^9 is H. In another aspect of this embodiment, R^6 of Formula III is CN. In another aspect of this embodiment, R^6 of Formula III is methyl. In another aspect of this embodiment, R^2 of Formula III is OR^a. In another aspect of this embodiment, R^2 of Formula III is OH, -OC(=0)R^{11}, or -OC(=0)OR^{11}. In another aspect of this embodiment, R^2 of Formula III is OH. In another aspect of this embodiment, R^2 of Formula III is F. In another aspect of this embodiment, R^3 of Formula III is OH, -OC(=0)R^{11}, or -OC(=0)OR^{11}. In another aspect of this embodiment, R^3 of Formula III is OH. In another aspect of this embodiment, R^7 of Formula III is H, -C(=0)R^{11}, -C(=0)OR^{11} or



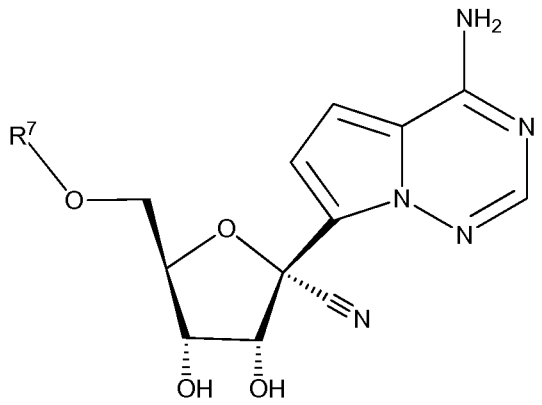
In another aspect of this embodiment, R^7 of Formula III is H. In another aspect of this embodiment, R^7 of Formula III is



[0099] In another embodiment of the method of treating a *Filoviridae* infection comprising administering a compound of Formula III, the *Filoviridae* infection is caused by a *Filoviridae* virus. In another aspect of this embodiment, the *Filoviridae* virus is a Marburg virus, Ebola virus or Cueva virus. In another aspect of this embodiment, the *Filoviridae* virus is an Ebola virus. In another aspect of this embodiment, the *Filoviridae* virus is a *Bundibugyo ebolavirus, Reston ebolavirus, Sudan ebolavirus, Tai Forest ebolavirus,* or *Zaire ebolavirus.*

[0100] In another embodiment of the method of treating a *Filoviridae* infection comprising administering a compound of Formula III, the *Filoviridae* infection is caused by a *Marburg* virus. In another aspect of this embodiment, the *Filoviridae* virus is Lloviu virus.

[0101] In another embodiment, provided is a compound of Formula IV:



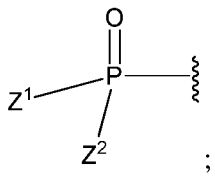
Formula IV

or a pharmaceutically acceptable salt or ester, thereof;

wherein R^7 is as defined above for Formula I.

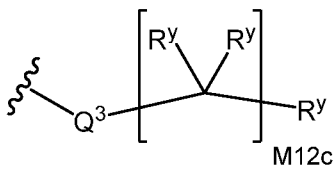
[0102] In another embodiment of a compound of Formula IV, R^7 can be H. In another embodiment of a compound of Formula IV, R^7 is selected from the group of a), b), or c) as defined for Formula I.

[0103] In another embodiment of a compound of Formula IV, R^7 is



;

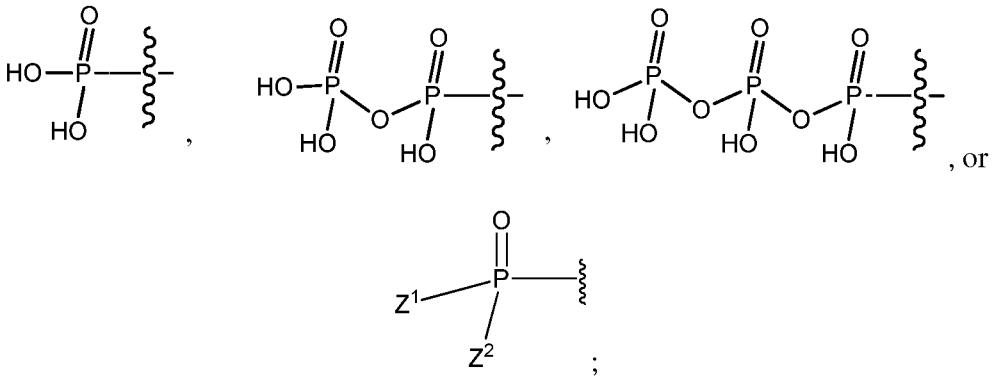
wherein Z^1 and Z^2 are each, independently, a group having the structure:



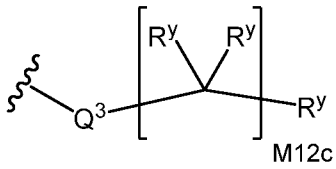
M12c

and Z^3 is Z^5.

[0104] In another embodiment of a compound of Formula IV, R^7 is

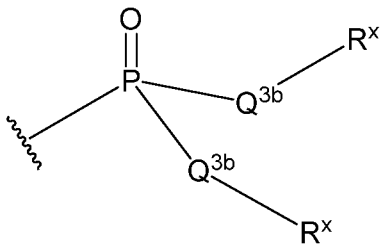


wherein Z^1 and Z^2 are each, independently, a group having the structure:

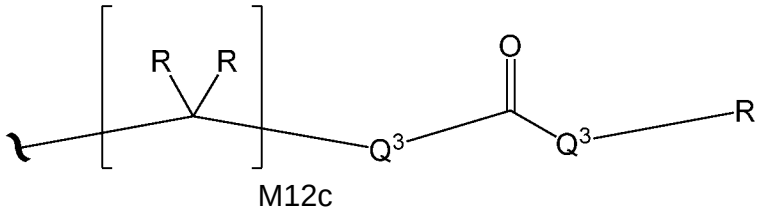


and Z^3 is Z^5.

[0105] In another embodiment of a compound of Formula IV, R^7 is



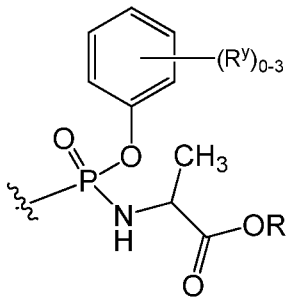
wherein each Q^{3b} is, independently, O or N(R). In another embodiment, each Q^{3b} is O and each R^x is independently:



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

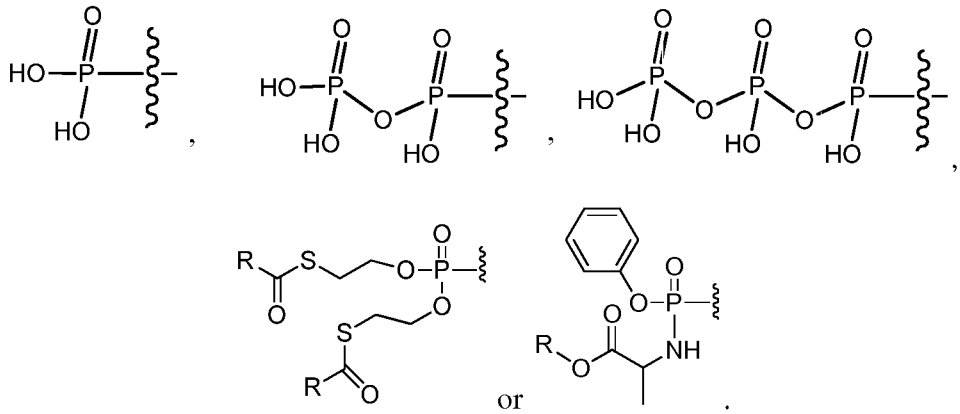
[0106] In some embodiments, R^{e1} and R^{e2} can each independently be H, Ci-C_6 alkyl or benzyl. In some embodments, R^{e1} can be H, Ci-C_6 alkyl or benzyl, and R^{e2} can be H or Ci-C_6 alkyl. In some embodiments, R^{e1} and R^{e2} can each independently be H or Ci-C_6 alkyl. In some embodiments, R^{e1} and R^{e2} can each independently be H or benzyl. In some embodiments, R^{e1} can be H, methyl or benzyl, and R^{e2} can be H or methyl. In some embodiments, R^{e1} can be H or methyl, and R^{e2} can be H or methyl. In some embodiments, R^{e1} can be methyl, and R^{e2} can be H or methyl. In some embodiments, R^{e1} can be H or benzyl, and R^{e2} can be H or methyl.

[0107] In another embodiment of a compound of Formula IV, R^7 is



.

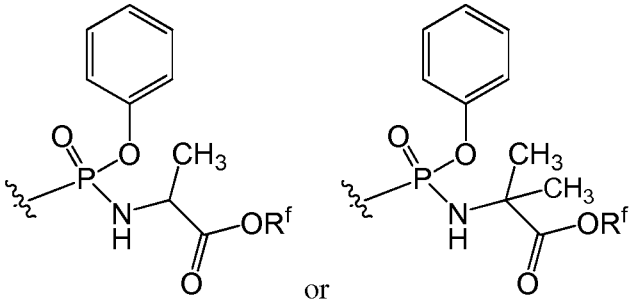
[0108] In another embodiment of a compound of Formula IV, R^7 is



or

.

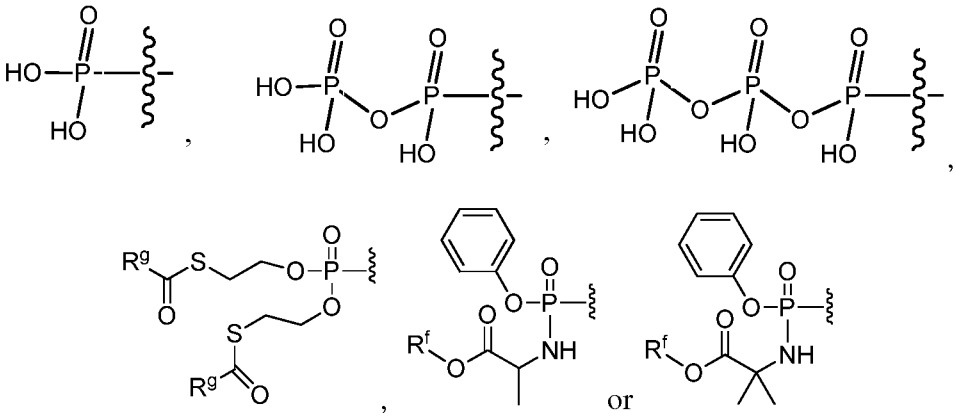
[0109] In another embodiment of a compound of Formula IV, R^7 is



or

wherein R^f is selected from the group of from H, CrC $_8$ alkyl, benzyl, $_{C3-C6}$ cycloalkyl, and -CH2-C3-C6 cycloalkyl. In another embodiment of a compound of Formula IV, R^f is C_1-C_8 alkyl.

[0110] In another embodiment of a compound of Formula IV, R^7 is

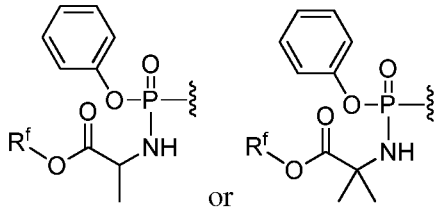


wherein

R^f is selected from H, Ci-Cs alkyl, benzyl, $_{C3-C6}$ cycloalkyl, and -CH2-C3-C6 cycloalkyl; and

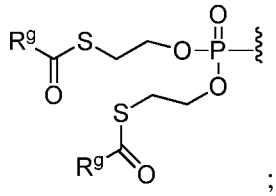
R^g is selected from C_1-C_8 alkyl, **-0** -C_1-C_8 alkyl, benzyl, -O-benzyl, -CH_2-C_3-C_6 cycloalkyl, -O-CH2-C3-C6 cycloalkyl, and **CF3.**

[0111] In another embodiment of a compound of Formula IV, R^7 is



wherein R^f is selected from H, C_1-C_8 alkyl, benzyl, $_{C3-C6}$ cycloalkyl, and -CH2-C3-C6 cycloalkyl. In another embodiment of a compound of Formula IV, R^f is CrC $_8$ alkyl. In another embodiment of a compound of Formula IV, R^f is Ci-C_6 alkyl.

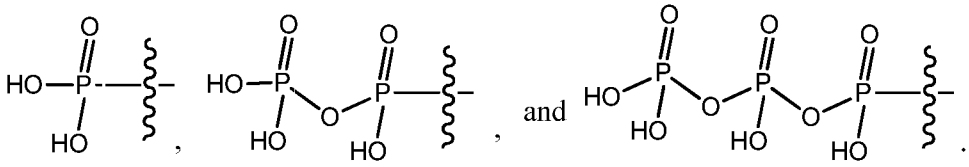
[0112] In another embodiment of a compound of Formula IV, R^7 is:



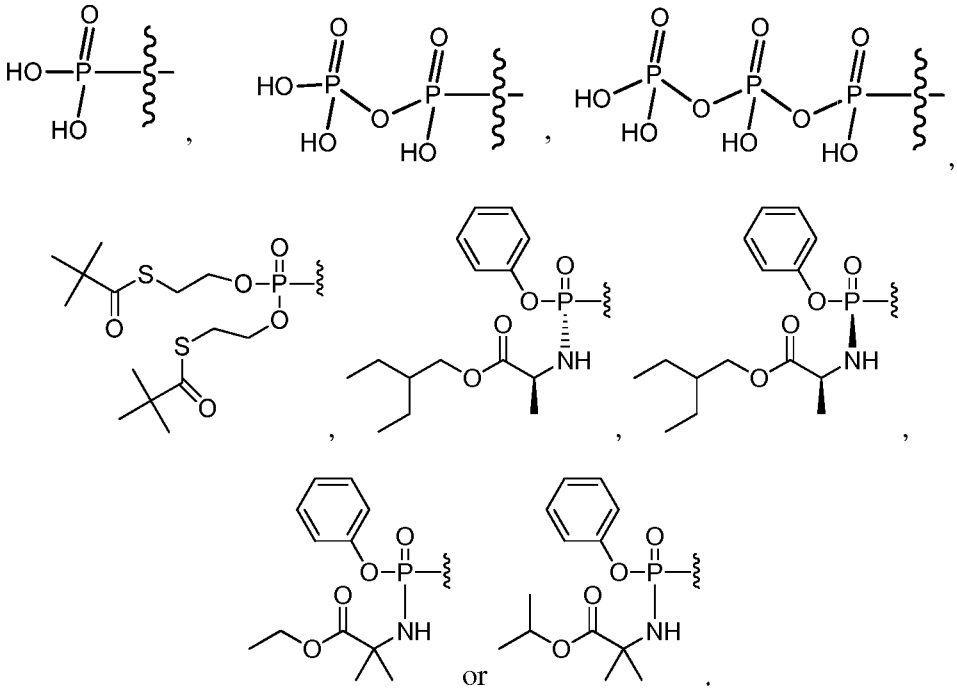
;

wherein R^g is selected from Ci-Cs alkyl, -O-Ci-Cs alkyl, benzyl, -O-benzyl, -CH2-C3-C6 cycloalkyl, -O-CH2-C3-C6 cycloalkyl, and CF_3. In another embodiment of a compound of Formula IV, R^f is Ci-Cs alkyl. In another embodiment of a compound of Formula IV, R^f is Cr C_6 alkyl.

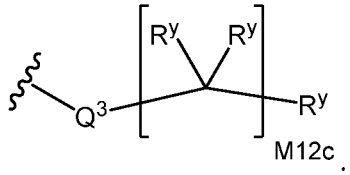
[0113] In another embodiment of a compound of Formula IV, R^7 is selected from the group of:



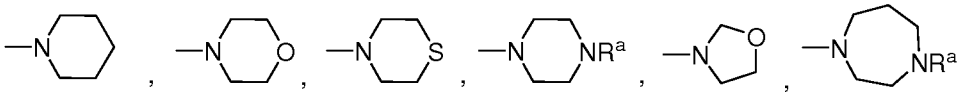
[0114] In another embodiment of a compound of Formula IV, R^7 is



[0115] In another embodiment of a compound of Formula IV, Z^1 and Z^2 can each be:



[0116] In another embodiment, provided is a method of treating a *Filoviridae* infection in a human in need thereof comprising administering a therapeutically effective amount of a compound of Formulas I-IV, wherein R^{11} or R^{12} is independently H, (Ci-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(=0)(C $_1$-C_8)alkyl, -S(0) $_n$(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 -0-, -S- or -NR ^{a}-. Therefore, by way of example and not limitation, the moiety -NR ^{11}R^{12} can be represented by the heterocycles:



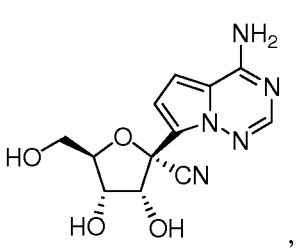
and the like.

[0117] In another embodiment, provided is a method of treating a *Filoviridae* infection in a human in need thereof comprising administering a therapeutically effective amount of a compound of Formula I-IV, wherein each R^3, R^4, R^5, R^6, R^{11} or R^{12} is, independently, (Cr 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(Ci-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^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)$_2$CH(N_3)CH_3, -(CH_2)$_6$$NH_2$ and the like.

[0118] In another embodiment, provided is a method of treating a *Filoviridae* infection in a human in need thereof comprising administering a therapeutically effective amount of a compound of Formula I-IV, wherein R^3, R^4, R^5, R^6, R^{11} or R^{12} is (C_1-C_8)alkyl wherein one or more of the non-terminal carbon atoms of each said (Ci-C_8)alkyl may be optionally replaced with -0-, -S- or -NR ^{a}-. Therefore, by way of example and not limitation, 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.

[0119] In another embodiment, provided is a compound of Formula I that is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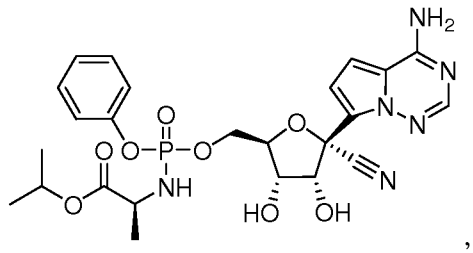
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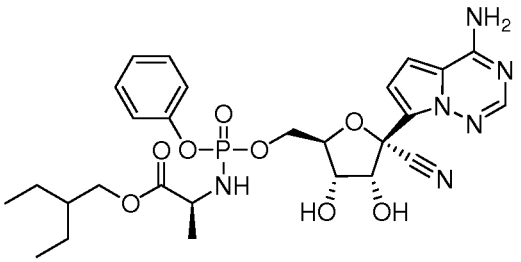
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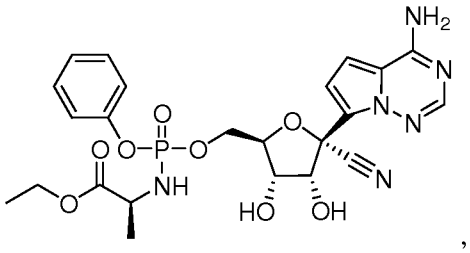
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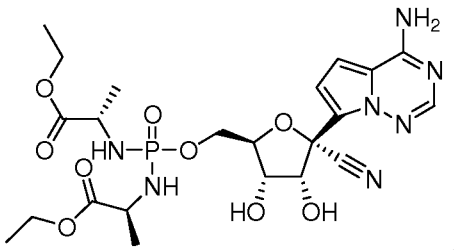
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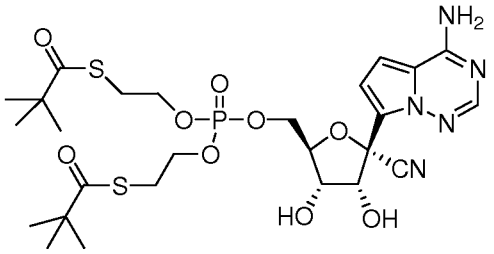
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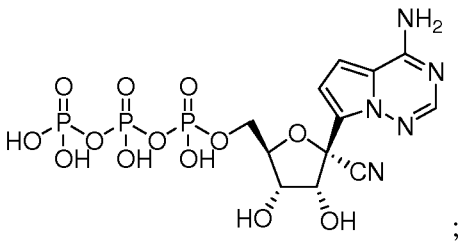
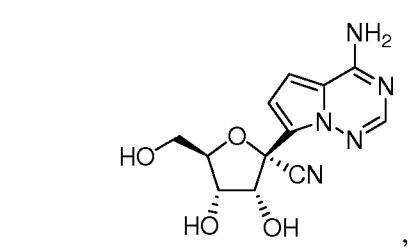

;

or a pharmaceutically acceptable salt or ester thereof.

[0120] In another embodiment, provided is a compound of Formula I that is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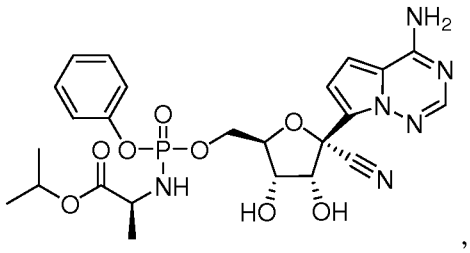
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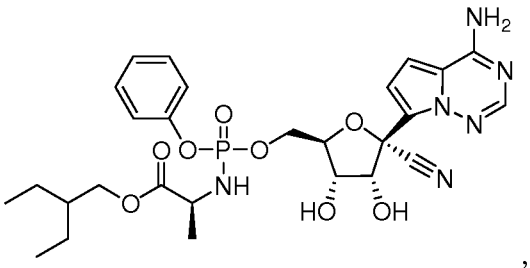
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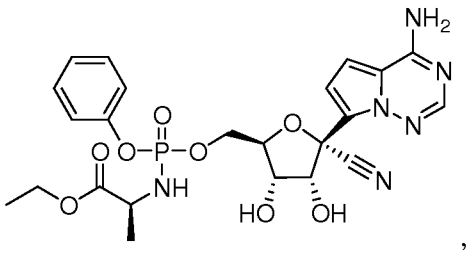
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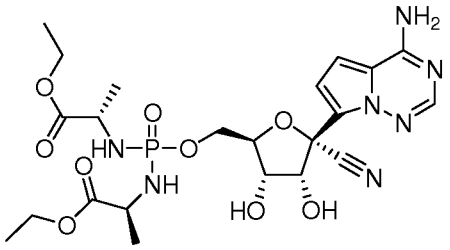
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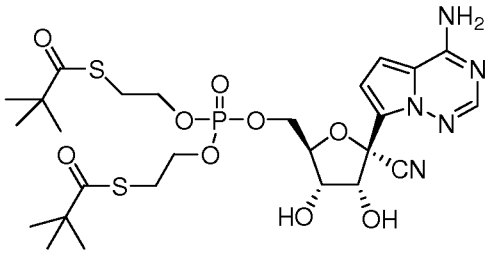
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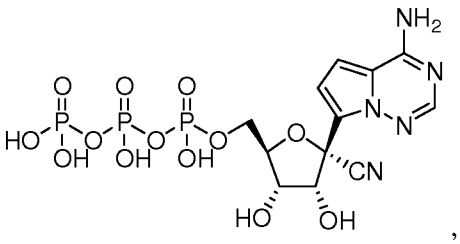
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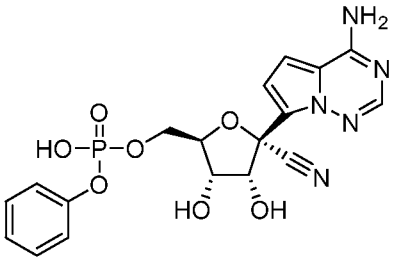
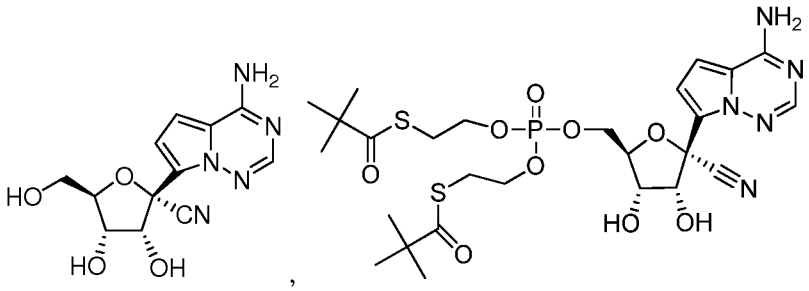

;

or a pharmaceutically acceptable salt or ester thereof.

[0121] In another embodiment, provided is a compound of Formula I that is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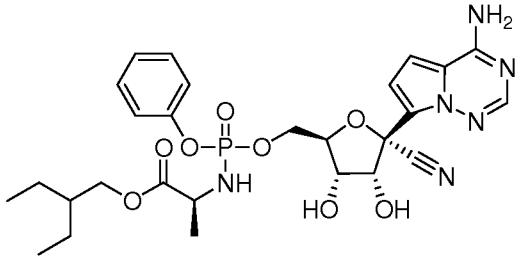
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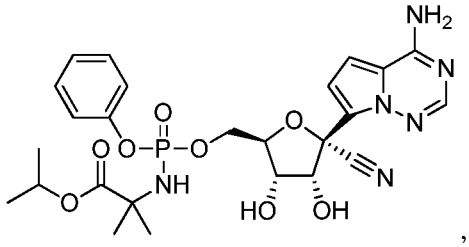
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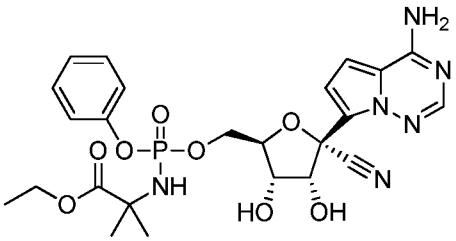
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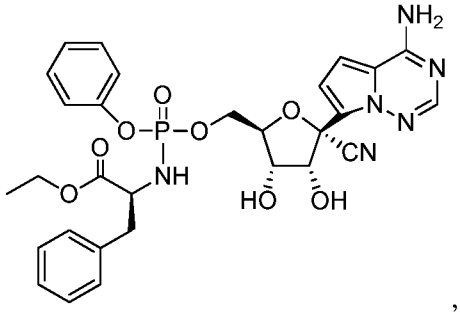
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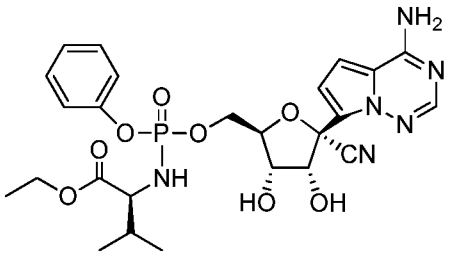
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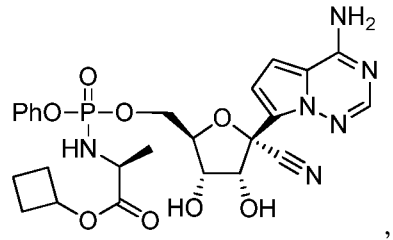
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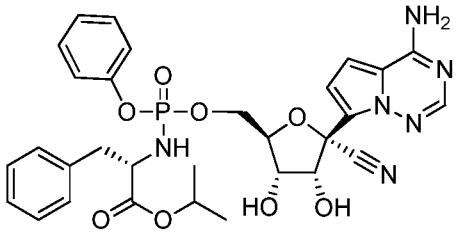
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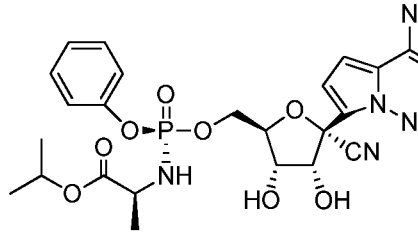
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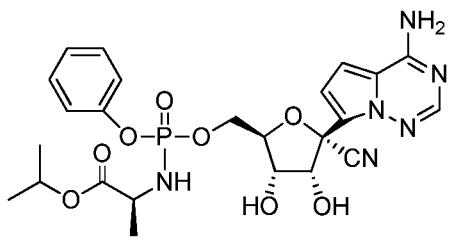
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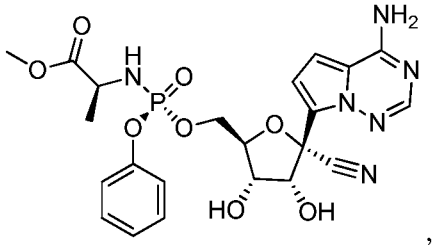
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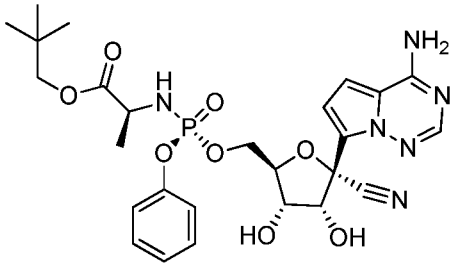
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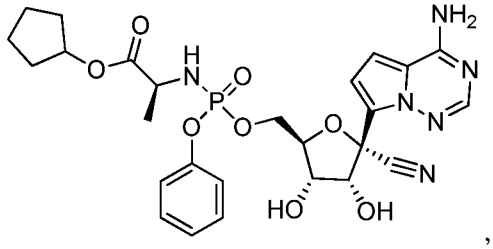
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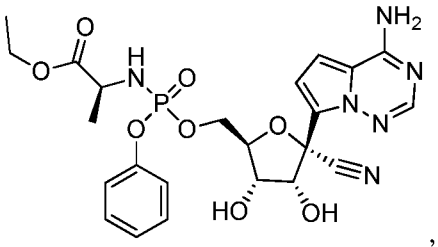
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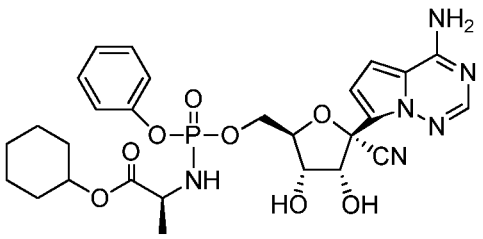
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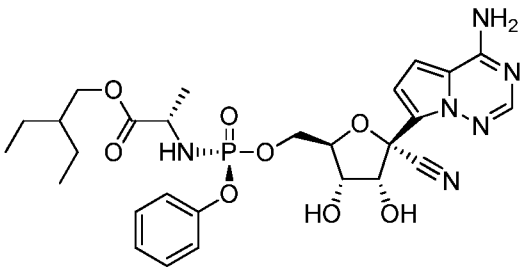
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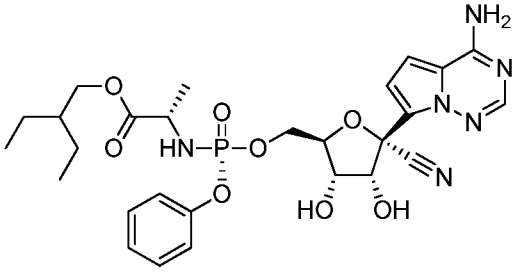
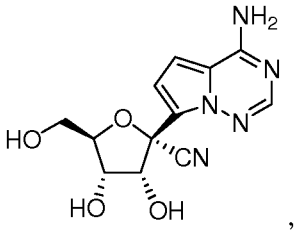

;

or a pharmaceutically acceptable salt or ester thereof.

[0122] In another embodiment, provided is a compound of Formula IV that is: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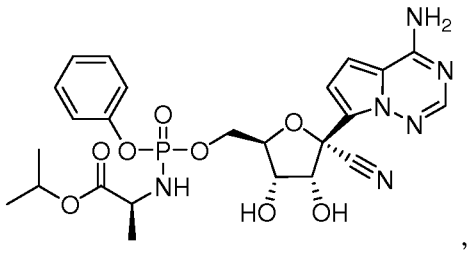
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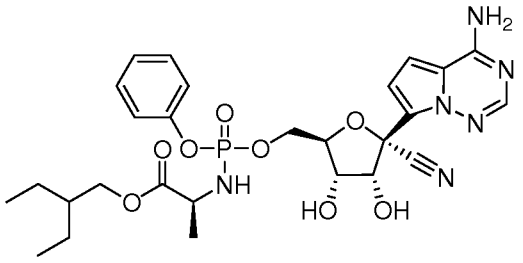
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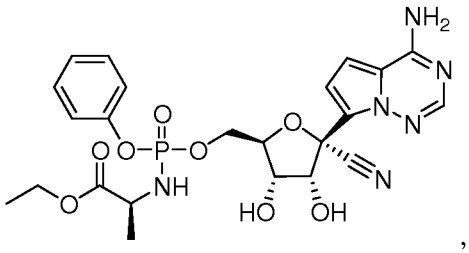
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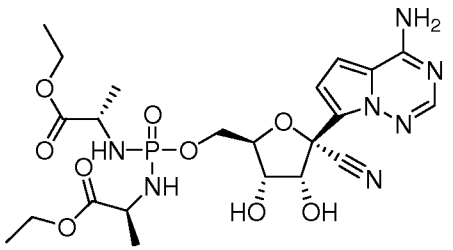
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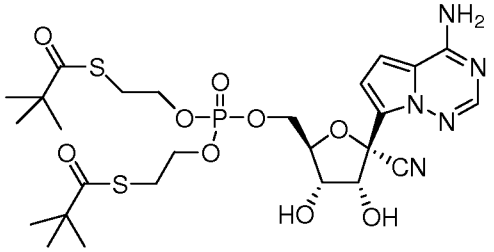
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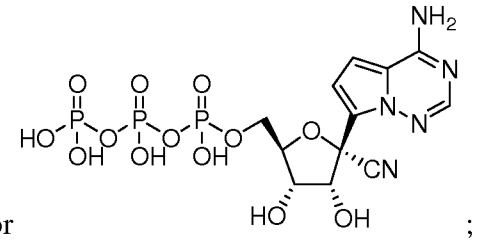
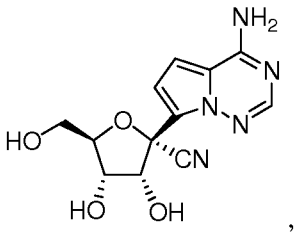

;

or a pharmaceutically acceptable salt or ester thereof.

[0123] In another embodiment, provided is a compound of Formula IV that is: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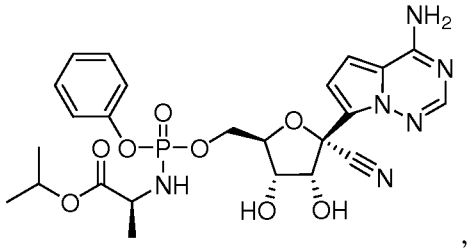
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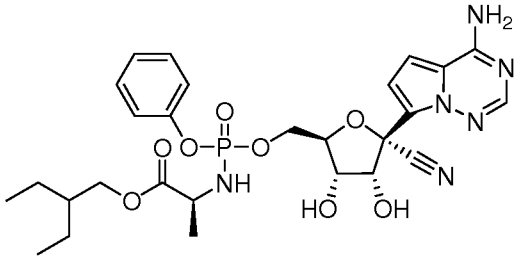
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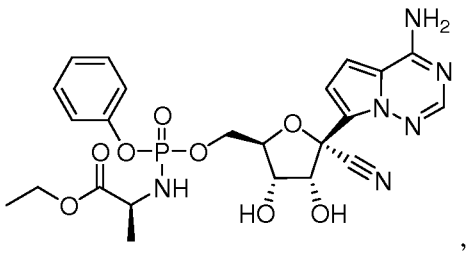
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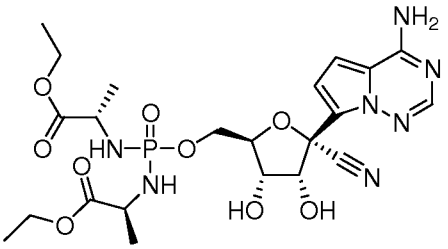

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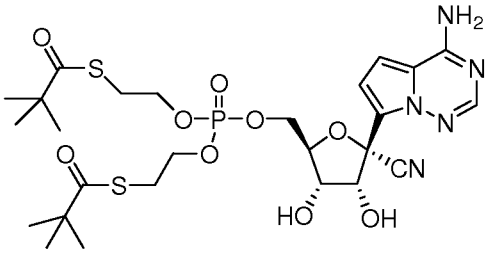

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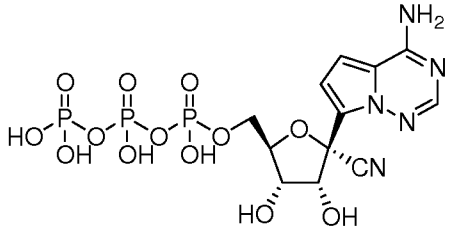

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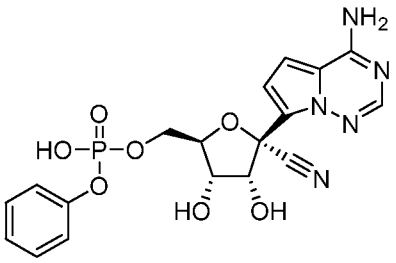
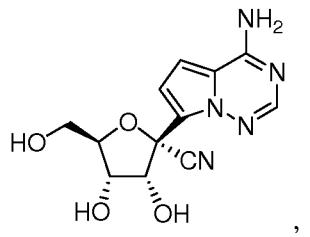


;

or a pharmaceutically acceptable salt or ester thereof.

[0124] In another embodiments, provided is a compound of Formula IV that is:



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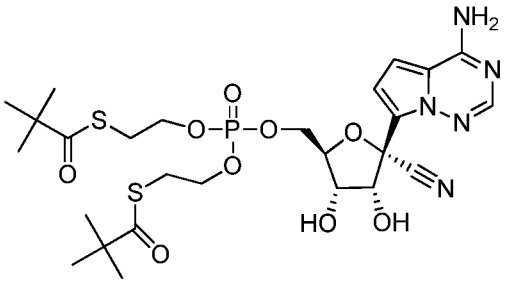

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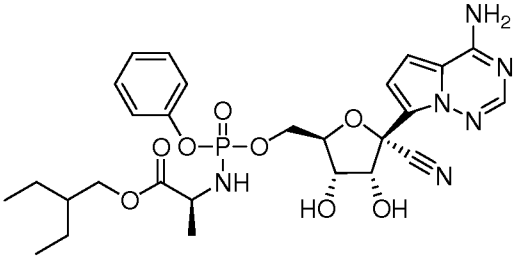

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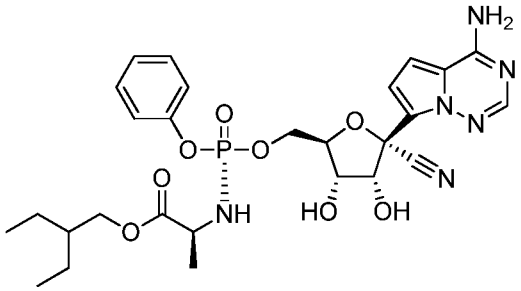

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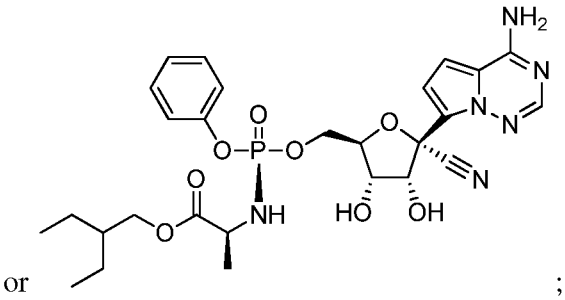
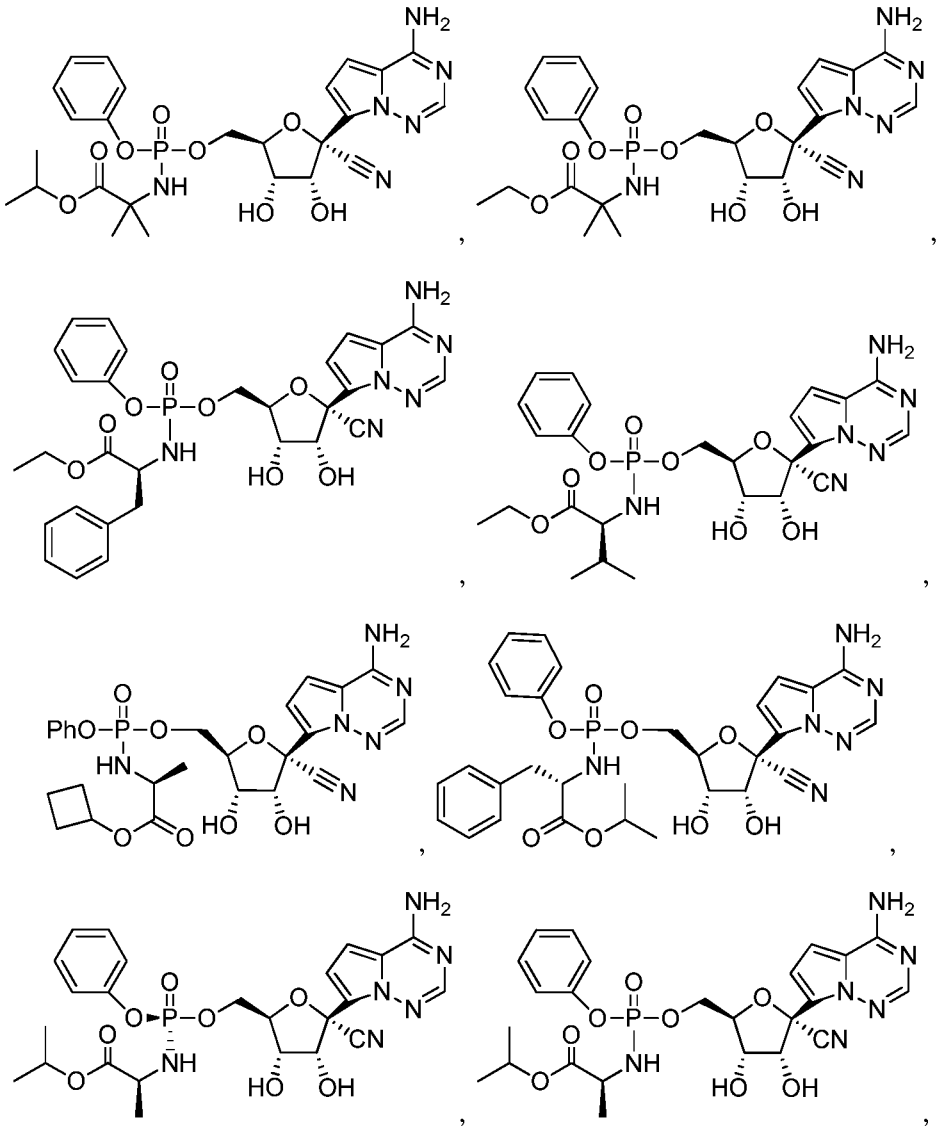
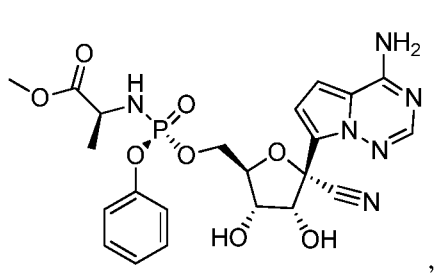


or ;

or a pharmaceutically acceptable salt or ester thereof.

[0125] In another embodiment, the present invention provides a compound that is

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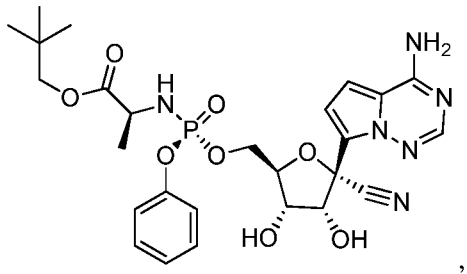
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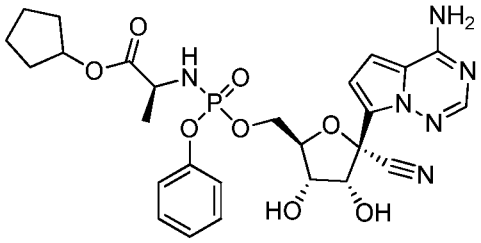
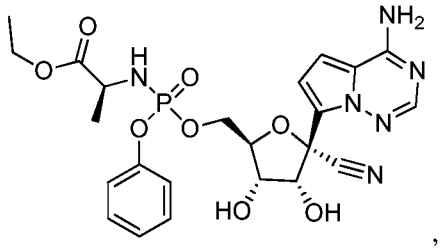
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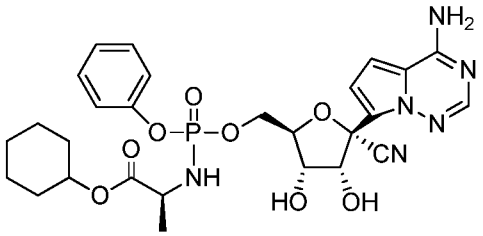
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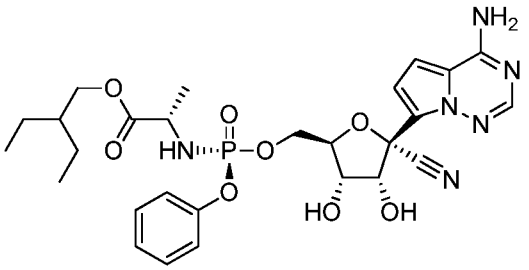
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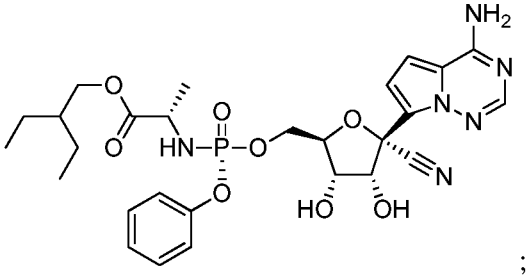
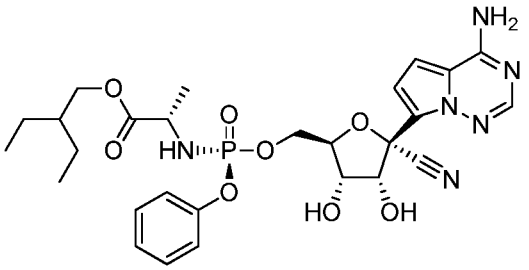

;

or a pharmaceutically acceptable salt or ester thereof.

[0126] In another embodiment, the present invention provides a compound that is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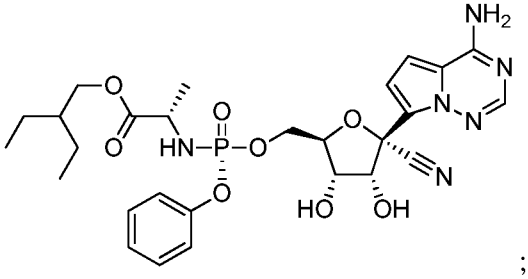
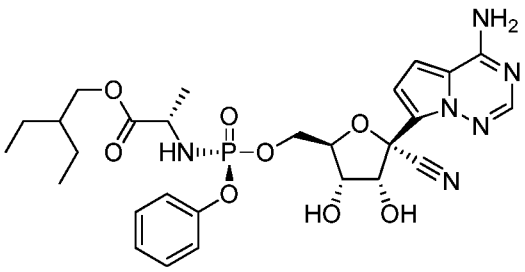

;

or a pharmaceutically acceptable salt or ester thereof.

[0127] In another embodiment, the present invention provides a compound that is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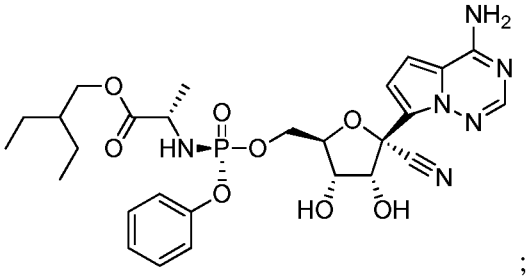
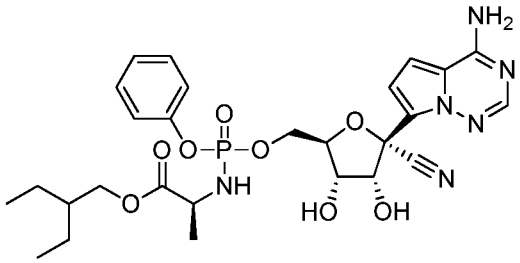
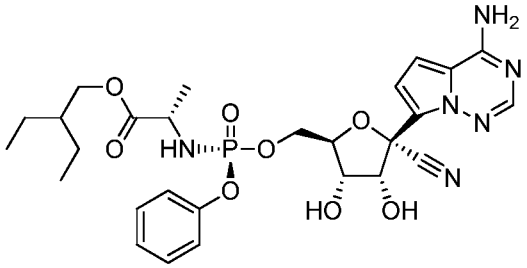

;

or a pharmaceutically acceptable salt or ester thereof.

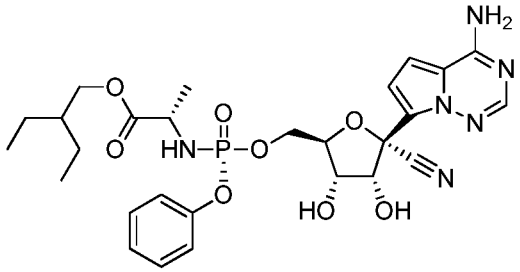
[0128] Names of compounds of the present disclosure are provided using ACD/Name software for naming chemical compounds (Advanced Chemistry Development, Inc., Toronto, Canada). Other compounds or radicals may be named with common names or systematic or non-systematic names. The naming and numbering of the compounds of the disclosure is illustrated with a representative compound of Formula I:



which is named (2S)-2-ethylbutyl 2-((((2R,3S,4R,5R)-5-(4-aminopyrrolo[l,2-f][l,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate. Other compounds of the present invention include:

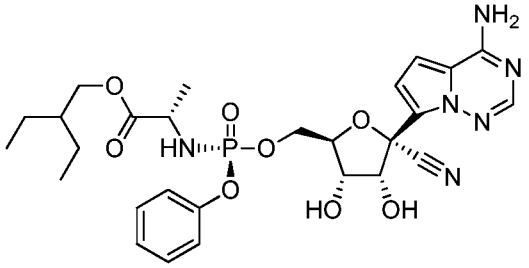


which is named (S)-2-ethylbutyl 2-(((S)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,l-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate, and

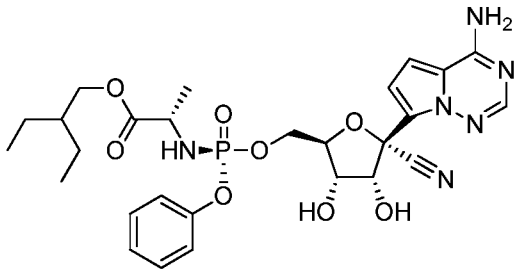


which is named (S)-2-ethylbutyl 2-(((R)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,l-f][l,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate.

Other compounds of the present invention include:



which is named (S)-2-ethylbutyl 2-(((S)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,l-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate, and



which is named (S)-2-ethylbutyl 2-(((R)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,l-f][l,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate.

[0129] Any reference to the compounds of the invention described herein 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 $Mg^{+¾}$, 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^+.

[0130] A compound of Formula **I-IV** 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.

[0131] A compound of Formula **I-IV** 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-IV and their pharmaceutically acceptable salts.

[0132] 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.

[0133] 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.

[0134] It is to be noted that all enantiomers, diastereomers, and racemic mixtures, tautomers, polymorphs, pseudopolymorphs of compounds within the scope of Formula I-IV 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.

[0135] The compounds of the invention, exemplified by Formula I-IV 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.

[0136] 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.

[0137] 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.

[0138] Any formula or structure given herein, including Formula I compounds, is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as, but not limited to ^{2}H (deuterium, D), ^{3}H (tritium), ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F, ^{31}P, ^{32}P, ^{35}S, ^{36}C l and ^{125}I. Various isotopically labeled compounds of the present disclosure, for example those into which radioactive isotopes such as ^{3}H, ^{13}C and ^{14}C are incorporated. Such isotopically labelled compounds may be useful in metabolic studies, reaction kinetic studies, detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays or in radioactive treatment of patients.

[0139] The disclosure also included compounds of Formula I in which from 1 to n hydrogens attached to a carbon atom is/are replaced by deuterium, in which n is the number of hydrogens in the molecule. Such compounds exhibit increased resistance to metabolism and are thus useful for increasing the half-life of any compound of Formula I when administered to a mammal, particularly a human. See, for example, Foster, "Deuterium Isotope Effects in Studies of Drug Metabolism", Trends Pharmacol. Sci. 5(12):524-527 (1984). Such compounds are synthesized by means well known in the art, for example by employing starting materials in which one or more hydrogens have been replaced by deuterium.

[0140] Deuterium labeled or substituted therapeutic compounds of the disclosure may have improved DMPK (drug metabolism and pharmacokinetics) properties, relating to distribution, metabolism and excretion (ADME). Substitution with heavier isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life, reduced dosage requirements and/or an improvement in therapeutic index. An ^{18}F labeled compound may be useful for PET or SPECT studies. Isotopically labeled compounds of this disclosure and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent. It is understood that deuterium in this context is regarded as a substituent in the compound of Formula I.

[0141] The concentration of such a heavier isotope, specifically deuterium, may be defined by an isotopic enrichment factor. In the compounds of this disclosure any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. Accordingly, in the compounds of this disclosure any atom specifically designated as a deuterium (D) is meant to represent deuterium.

[0142] 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.

[0143] Selected substituents comprising the compounds of Formula I-IV 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 Z^3. Z^3 can be Z^4 and Z^4 can be R or comprise substituents comprising R^y. Alternatively, Z^3 can be Z^5 which can 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.

[0144] By way of example and not limitation, Z^3 and R^y are recursive substituents in certain embodiments. Typically, each recursive substituent can independently occur 20, 19, 18, 17, 16, 15, 14, 13, 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 12 or fewer times in a given embodiment. Even more typically, each recursive substituent can independently occur 3 or fewer times in a given embodiment. For example, Z^3 will occur 0 to 8 times, R^y will occur 0 to 6 times in a given embodiment. Even more typically, Z^3 will occur 0 to 6 times and R^y will occur 0 to 4 times in a given embodiment.

[0145] 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.

[0146] The compounds of the present invention can be prepared by methods known to one of skill in the art. For example, the compounds of the present invention can be prepared according to the methods described in U.S. Patent No. 8,008,264 and U.S. Application Publication No. US 2012/0027752.

A. Substituted Forms of the Compounds

[0147] The compounds of the Formula I-IV may comprise a phosphate group as R^7, R^7 is selected from the group of

a) H, -C(=0)R^{11}, -C(=0)OR^{11}, -C(=0)N$R^{11}R^{12}$, -C(=0)SR^{11}, -S(0)R^{11}, -S(0)$_2R^{11}$, -S(0)(OR^{11}), -S(0)$_2$(OR^{11}), -S0$_2$N$R^{11}R^{12}$

wherein

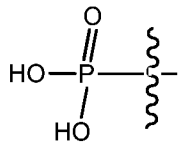
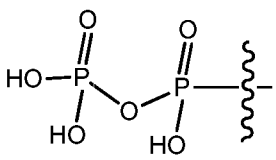
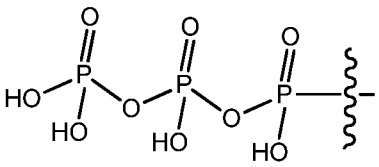
each R^{11} or R^{12} is independently H, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_4-Cs)carbocyclylalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(=0)(C_1-C_8)alkyl, -S(0)$_n$(C_1-C_8)alkyl or aryl(C_1-C_8)alkyl; or R^{11} and R^{12} taken together with a nitrogen 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 -0-, -S- or -NR^a-;

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(=0)R, -C(=0)OR, -C(=0)NR_2, -C(=0)SR, -S(0)R, -S(0)$_2$R, -S(0)(OR), -S(0)$_2$(OR), or -S0$_2$NR_2;

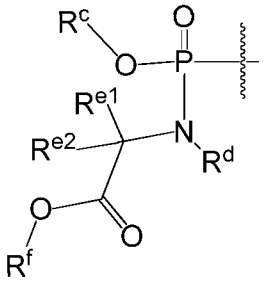
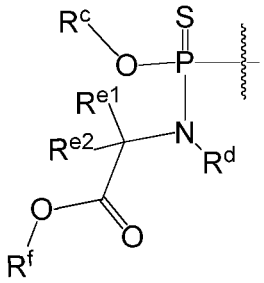
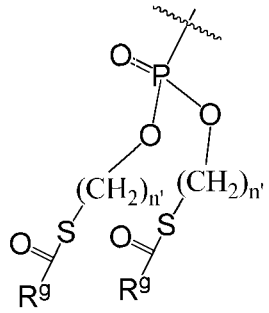
wherein each R is independently H, (Ci-C_8) alkyl, (Ci-C_8) substituted alkyl, (C_2-C_8)alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, C_6-C_2o aryl, C_6-C_2o substituted aryl, C_2-C_2o heterocyclyl, C_2-C_2o substituted heterocyclyl, arylalkyl or substituted arylalkyl; and

wherein each (Ci-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl or aryl(Ci-C_8)alkyl of each 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 (Ci-C_8)alkyl may be optionally replaced with -0-, -S- or -NR^a-, and

b)

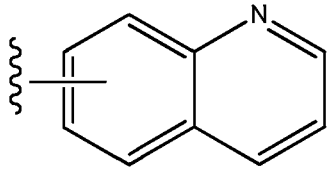
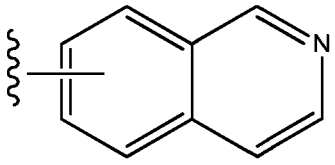

,

,

,

c) a group selected from:


,

and


wherein:

R^c is selected from phenyl, 1-naphthyl, 2-naphthyl,


and

;

R^d is H or CH_3;

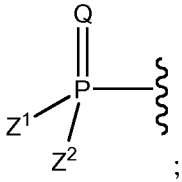
R^{e1} and R^{e2} are each independently H, Ci-C_6 alkyl or benzyl;

R^f is selected from H, Ci-C_8 alkyl, benzyl, C_3-C_6 cycloalkyl, and -CH_2-C_{3-C6} cycloalkyl;

R^g is selected from Ci-C_8 alkyl, -0-Ci-C_8 alkyl, benzyl, -O-benzyl, -CH_2-C_3-C_6 cycloalkyl, -0-CH_2-C_{3-C6} cycloalkyl, and CF_3; and

n' is selected from 1, 2, 3, and 4; and

d) a group of the formula:


;

wherein

Q is O, S, NR, $^{+}$N(0)(R), N(OR), $^{+}$N(0)(OR), or N-NR $_2$;

Z^1 and Z^2, when taken together, are - $Q^1(C(R^y)_2)3Q^1$-;

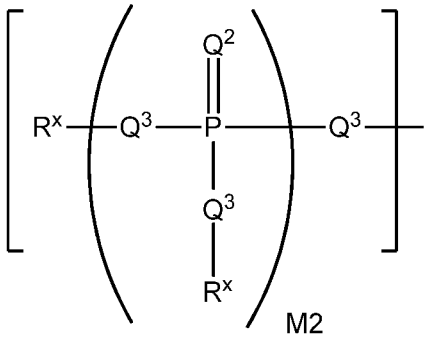
wherein

each Q^1 is independently O, S, or NR; and

each R^y is independently H, F, CI, Br, I, OH, R, -C(=Q^2)R, -C(=Q^2)OR, -C(=Q^2)N(R)$_2$, -N(R)$_2$, -$^{+}$N(R)$_3$, -SR, -S(0)R, -S(0)$_2$R, -S(0)(OR), -S(0)$_2$(OR), -OC(=Q^2)R, -OC(=Q^2)OR, -OC(=Q^2)(N(R)$_2$), -SC(=Q^2)R, -SC(=Q^2)OR, -SC(=Q^2)(N(R)$_2$), -N(R)C(=Q^2)R, -N(R)C(=Q^2)OR, -N(R)C(=Q^2)N(R)$_2$, -S0 $_2$NR$_2$, -CN, - N$_3$, -N0 $_2$, -OR, or Z^3; or when taken together, two R^y on the same carbon atom form a carbocyclic ring of 3 to 7 carbon atoms;

each Q^2 is independently, O, S, NR, $^{+}$N(0)(R), N(OR), $^{+}$N(0)(OR), or N-NR $_2$;or

Z^1 and Z^2 are each, independently, a group of the Formula la:



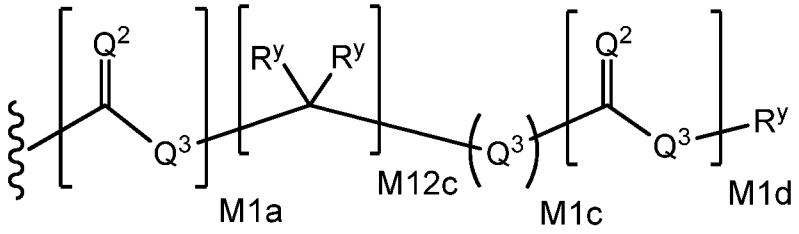
Formula la

wherein:

each Q^3 is independently a bond, O, CR_2, NR, $^{+}$N(0)(R), N(OR), $^{+}$N(0)(OR), N-NR $_2$, S, S-S, S(O), or S(0)$_2$;

M2 is 0, 1 or 2;

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



wherein:

each Mia, Mlc, and Mid is independently 0 or 1;

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

Z^3 is Z^4 or Z^5;

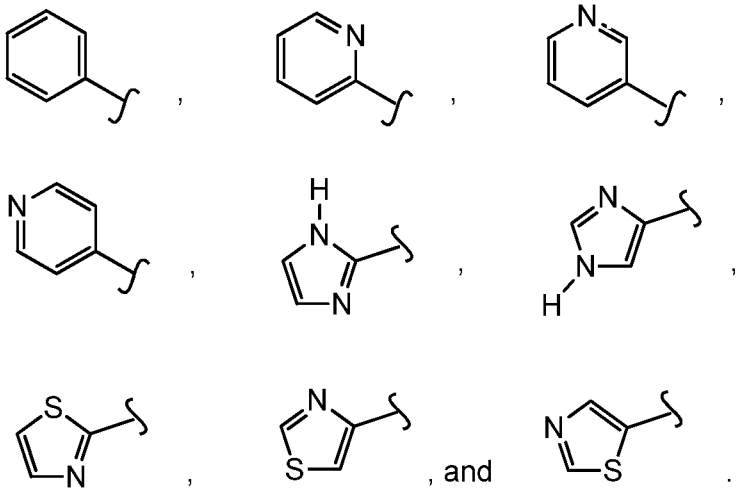
Z^4 is R, $-C(Q^2)R^y$, $-C(Q^2)Z^5$, $-S0_2R^y$, or $-S0_2Z^5$; and

Z^5 is a carbocycle or a heterocycle wherein Z^5 is independently substituted with 0 to 3 R^y groups.

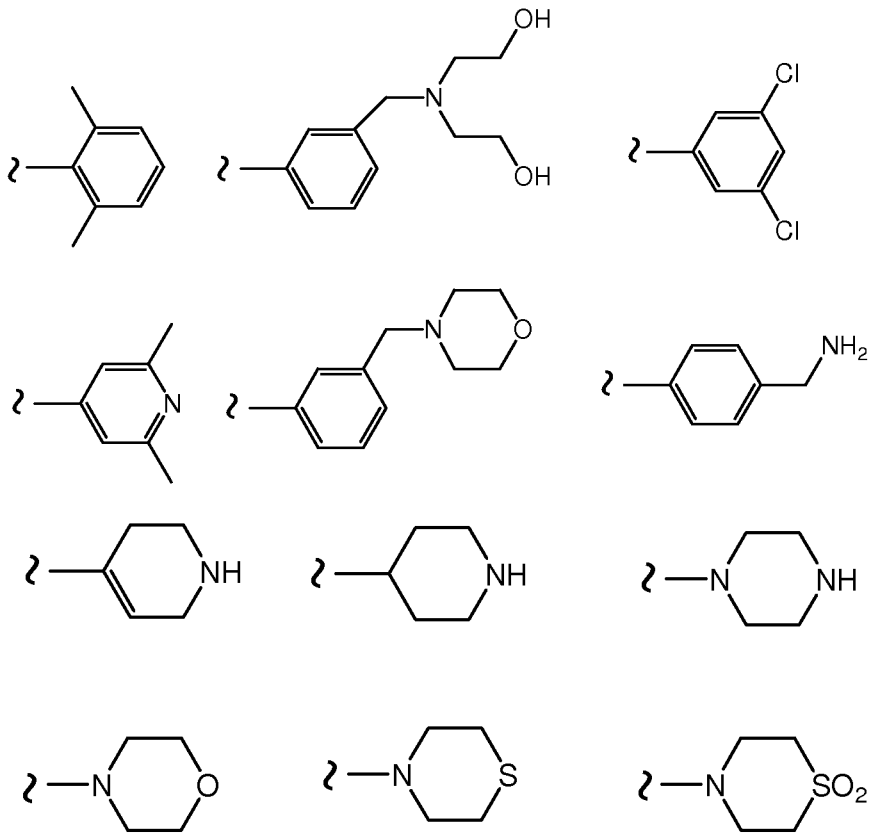
[0148] Z^5 carbocycles and Z^5 heterocycles may be independently substituted with 0 to 3 R^y groups. Z^5 may be a saturated, unsaturated or aromatic ring comprising a mono- or bicyclic carbocycle or heterocycle. Z^5 may have 3 to 10 ring atoms, e.g., 3 to 7 ring atoms. The Z^5 rings are saturated when 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.

[0149] A Z^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). Z^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). Z^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 Z^5 heterocycle may be bonded to Q^2 through a carbon, nitrogen, sulfur or other atom by a stable covalent bond.

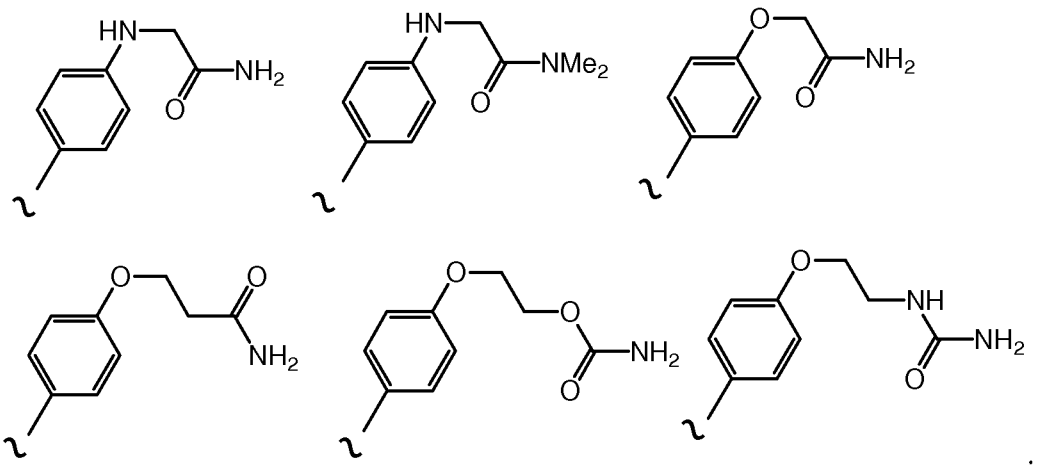
[0150] Z^5 heterocycles include for example, pyridyl, dihydropyridyl isomers, piperidine, pyridazinyl, pyrimidinyl, pyrazinyl, s-triazinyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, furanyl, thiofuranyl, thienyl, and pyrrolyl. Z^5 also includes, but is not limited to, examples such as:



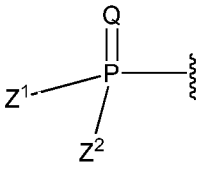
[0151] Z^5 carbocycles and heterocycles may be independently substituted with 0 to 3 **R** groups, as defined above. For example, substituted Z^5 carbocycles include:

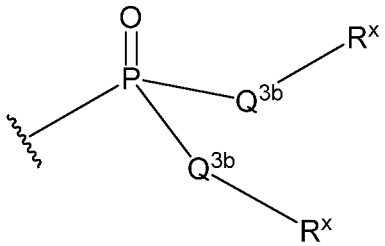


[0152] Examples of substituted phenyl carbocycles include:

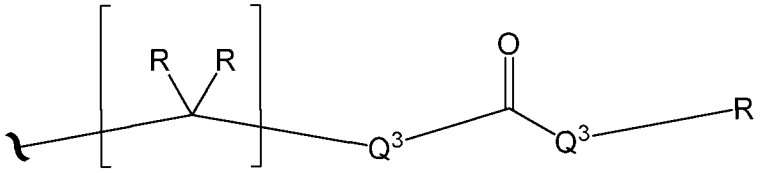


[0153] In another embodiment, Z^5 of the compounds of Formula I-IV is a carbocycle or a heterocycle wherein Z^5 is independently substituted with 0 to 3 R^z groups, wherein each R^z is independently H, F, CI, Br, I, OH, R, $-C(=Q^2)R$, $-C(=Q^2)OR$, $-C(=Q^2)N(R)_2$, $-N(R)_2$, $-^+N(R)_3$, -SR, $-S(0)R$, $-S(0)_2R$, $-S(0)(OR)$, $-S(0)_2(OR)$, $-OC(=Q^1)R$, $-OC(=Q^2)OR$, $-OC(=Q^2)(N(R)_2)$, $-SC(=Q^2)R$, $-SC(=Q^2)OR$, $-SC(=Q^2)(N(R)_2)$, $-N(R)C(=Q^2)R$, $-N(R)C(=Q^2)OR$, $-N(R)C(=Q^2)N(R)_2$, $-S0_2NR_2$, -CN, $-N_3$, $-N0_2$, or -OR.

[0154] Embodiments of  of Formula I-IV compounds include substructures such as:

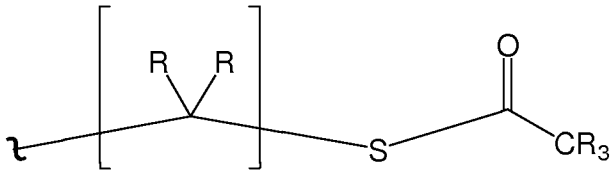


wherein each Q^{3b} is, independently, O or N(R). In another aspect of this embodiment, each Q^{3b} is O and each R^x is independently:



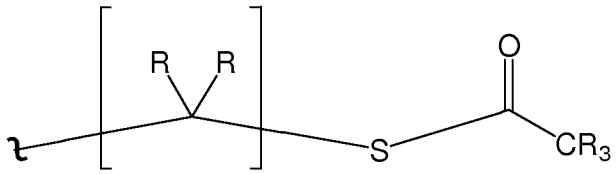
M12c

wherein M12c is 1, 2 or 3 and each Q^3 is independently a bond, O, CR_2, or S. In another aspect of this embodiment, one Q^{3b}-R^x is NH(R) and the other Q^{3b}-R^x is 0-R^x wherein R^x is:



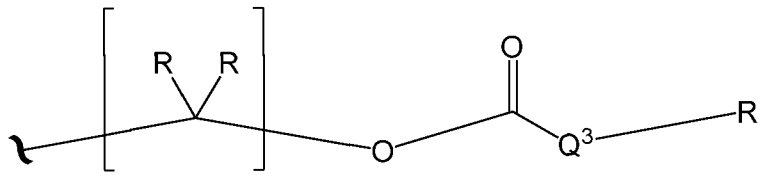
M12c

wherein M12c is 2. In another aspect of this embodiment, each Q^{3b} is O and each R^x is independently:



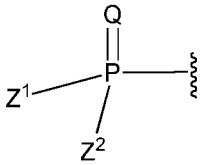
M12C

wherein M12c is 2. In another aspect of this embodiment, each Q^{3b} is O and each R^x is independently:

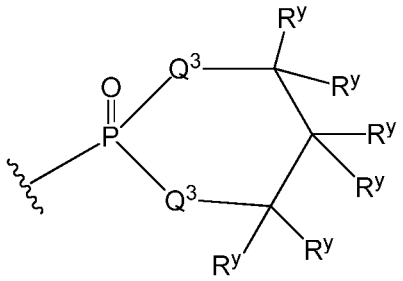


M12c

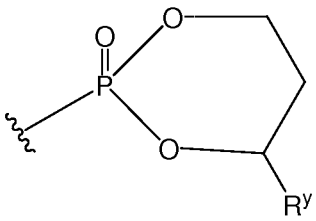
wherein M12c is 1 and Q^3 is a bond, O, or CR_2.



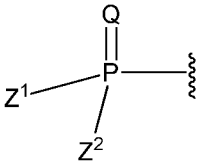
[0155] Other embodiments of of Formulas I-IV compounds include substructures such as:



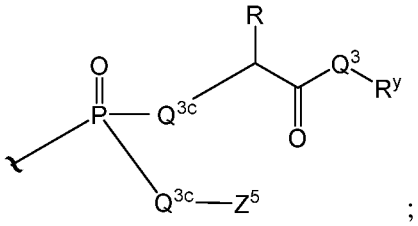
wherein each Q^3 is, independently, O or N(R). In another aspect of this embodiment, each Q^3 is O. In another aspect of this embodiment, the substructure is:



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

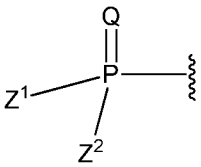


[0156] Another embodiment of of Formula I-IV includes the substructures:

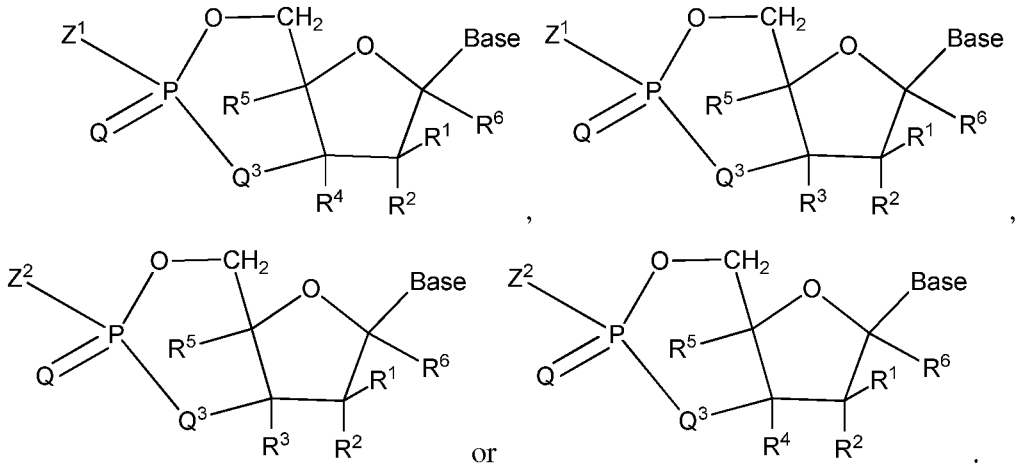


;

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

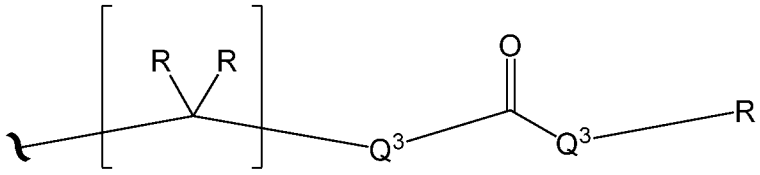


[0157] Another embodiment of of Formula I-IV compounds includes the substructures wherein one of Z^1 or Z^2 together with either R^3 or R^4 is - Q^3- and the other of Z^1 or Z^2 is Formula Ia. Such an embodiment is represented by a compound of Formula Ib selected from:



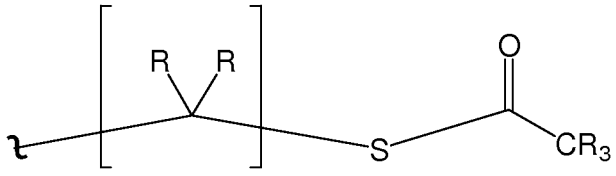
Formula lb

[0158] In another aspect of the embodiment of Formula lb, each Q and Q^3 is O. In another aspect of the embodiment of Formula lb, Z^1 or Z^2 is Q^{3b}-R^x; each Q, Q^3 and Q^{3b} is O and R^x is:



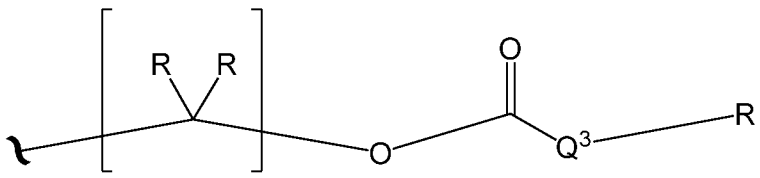
M12c

wherein M12c is 1, 2 or 3 and each Q^3 is independently a bond, O, CR_2, or S. In another aspect of the embodiment of Formula lb, Z^1 or Z^2 is Q^{3b}-R^x; each Q, Q^3 and Q^{3b} is O and R^x is:



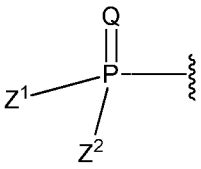
M12C

wherein M12c is 2. In another aspect of the embodiment of Formula lb, Z^1 or Z^2 is Q^{3b}-R^x; each Q, Q^3 and Q^{3b} is O and R^x is:

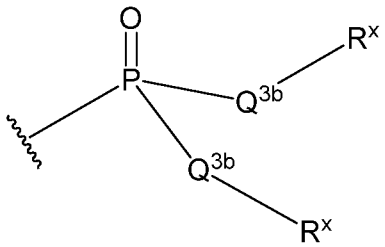


M12c

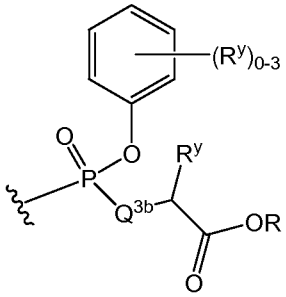
wherein M12c is 1 and Q^3 is a bond, O, or CR_2.



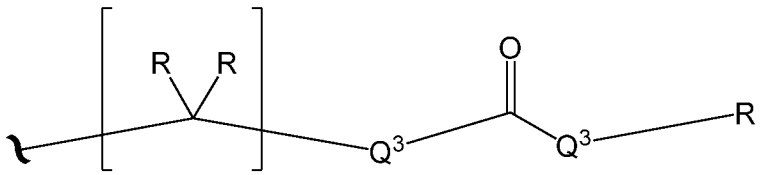
[0159] Another embodiment of of Formula I-IV compounds includes a substructure:



wherein Z^5 is a carbocycle such as phenyl or substituted phenyl. In another aspect of this embodiment, the substructure is:

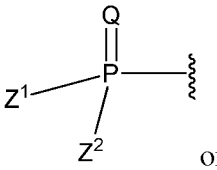


wherein Q^{3b} is O or N(R) and the phenyl carbocycle is substituted with 0 to 3 R groups. In another aspect of this embodiment of the substructure, R^x is:

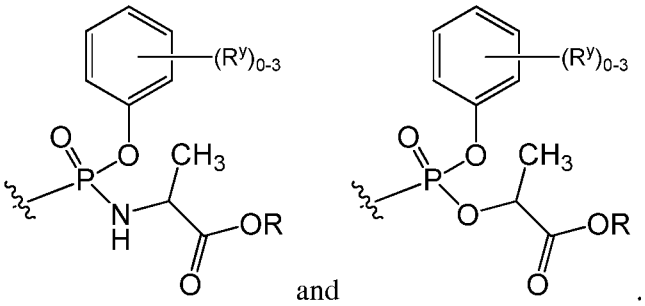


M12c

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

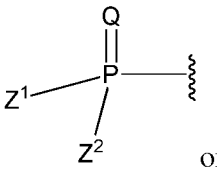


[0160] Another embodiment of of Formula I-IV includes substructures:

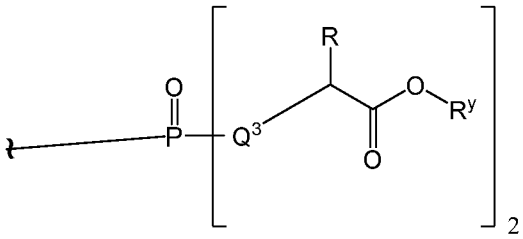


and .

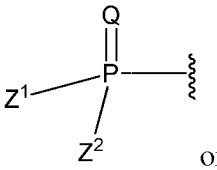
[0161] The chiral carbon of the amino acid and lactate moieties may be either the *R* or *S* configuration or the racemic mixture.



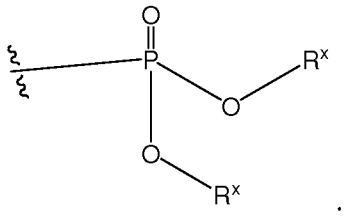
[0162] Another embodiment of of Formula I-IV is substructure



wherein each Q^3 is, independently, -O- or -NH-. In another aspect of this embodiment, R^y is (Ci-Cs) 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^y is (Ci-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 aspect of this embodiment, R^y is (Ci-C_8) alkyl, (Ci-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 Q^3 is -NH-. In another aspect of this embodiment, Z^1 and Z^2 are, independently, nitrogen-linked, naturally occurring amino acids or naturally occurring amino acid esters. In another aspect of this embodiment, Z^1 and Z^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.



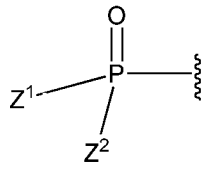
[0163] Another embodiment of of Formula I-IV is substructure:



.

[0164] In one aspect of this embodiment, each R^x is, independently, (Ci-Cs) alkyl. In another aspect of this embodiment, each R^x is, independently, C6-C2$_0$ aryl or C6-C2$_0$ substituted aryl.

[0165] In a preferred embodiment,



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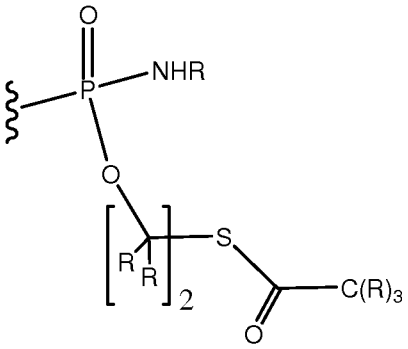

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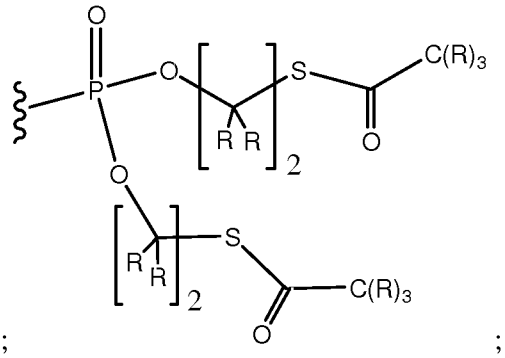

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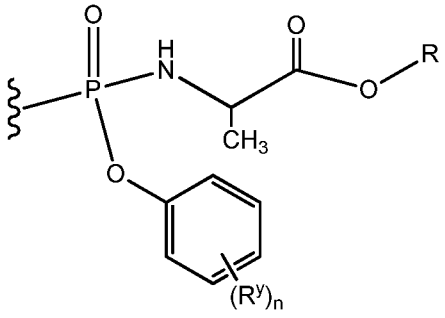
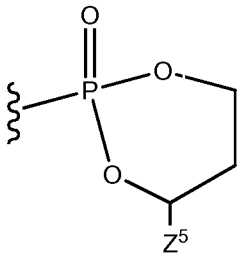
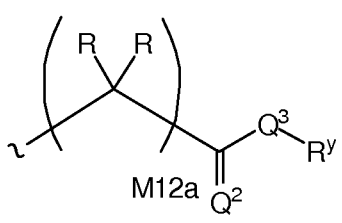


or

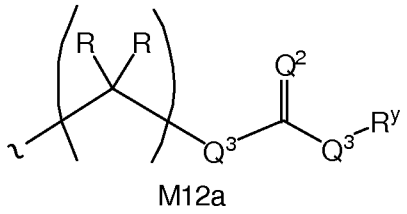


.

[0166] Embodiments of R^x include esters, carbamates, carbonates, thioesters, amides, thioamides, and urea groups:



and



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B. Metabolites of the Compounds of the Invention

[0167] 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 ¾) 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 anti filoviridae activity of their own.

[0168] 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.

III. PHARMACEUTICAL FORMULATIONS

[0169] 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. In some embodiments, the pH of the formulations ranges from about 2 to about 5, but is ordinarily about 3 to about 4. In some embodiments, the pH of the formulations ranges from about 2 to about 10, but is ordinarily about 3.5 to about 8.5.

[0170] 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, particularly those additional therapeutic ingredients as discussed herein. 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.

[0171] 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.

[0172] 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.

[0173] 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.

[0174] 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.

[0175] 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.

[0176] 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.

[0177] 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. Further emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween® 80.

[0178] 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.

[0179] 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.

[0180] 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.

[0181] 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). Further non-limiting examples of suspending agents include Captisol® (sulfobutyl ether beta-cyclodextrin, SBE-**P**-CD). 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.

[0182] 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.

[0183] 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.

[0184] 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.

[0185] 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. The sterile injectable preparation may also be a sterile injectable solution or suspension in a parenterally acceptable diluent or solvent. 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. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution isotonic sodium chloride solution, hypertonic sodium chloride solution, and hypotonic sodium chloride solution.

[0186] 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.

[0187] 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.

[0188] 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.

[0189] Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

[0190] 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 *Filoviridae* infections as described below.

[0191] 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.

[0192] 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.

[0193] 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.

[0194] 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.

[0195] The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefor.

[0196] 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.

[0197] 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.

IV. ROUTES OF ADMINISTRATION

[0198] 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, pulmonary, 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.

[0199] In the methods of the present invention for the treatment of *Filoviridae* infection, the compounds of the present invention can be administered at any time to a human who may come into contact with humans suffering from *Filoviridae* infection or is already suffering from *Filoviridae* infection. In some embodiments, the compounds of the present invention can be administered prophylactically to humans coming into contact with humans suffering from *Filoviridae* infection. In some embodiments, administration of the compounds of the present invention can be to humans testing positive for *Filoviridae* infection but not yet showing symptoms of *Filoviridae* infection. In some embodiments, administration of the compounds of the present invention can be to humans upon commencement of symptoms of *Filoviridae* infection.

[0200] 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.

[0201] The effective dose of a compound of the present invention for treating the *Filoviridae* infection can depend on whether the dose is to be used prophylactically or to treat a human already suffering from *Filoviridae* infection. Moreover, the dose can depend on whether the human suffering from *Filoviridae* infection does not yet show symptoms or is already showing symptoms of *Filoviridae* infection. Larger doses may be necessary for treating humans testing positive for *Filoviridae* infection and for humans showing symptoms of *Filoviridae* infection as compared to humans receiving prophylactic treatment.

[0202] Any suitable period of time for administration of the compounds of the present invention is contemplated. For example, administration can be for from 1 day to 100 days, including 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, or 90 days. The administration can also be for from 1 week to 15 weeks, including 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 weeks. Longer periods of administration are also contemplated. The time for administration can depend on whether the compound is being administered prophylactically or to treat a human suffering from a *Filoviridae* infection. For example, a prophylactic administration can be for a period of time while the human is in regular contact with other humans suffering from a *Filoviridae* infection, and for a suitable period of time following the last contact with a human suffering from a *Filoviridae* infection. For humans already suffering from a *Filoviridae* infection, the period of administration can be for any length of time necessary to treat the patient and a suitable period of time following a negative test for *Filoviridae* infection to ensure the *Filoviridae* infection does not return.

V. COMBINATION THERAPY

[0203] Compositions of the invention are also used in combination with other active ingredients. For the treatment of *Filoviridae* virus infections, preferably, the other active therapeutic agent is active against *Filoviridae* virus infections, particularly Marburg virus, Ebola virus and Cueva virus infections. Non-limiting examples of these other active therapeutic agents are ribavirin, palivizumab, motavizumab, RSV-IGIV (RespiGam®), MEDI-557, A-60444, MDT-637, BMS-433771, amiodarone, dronedarone, verapamil, Ebola Convalescent Plasma (ECP), TKM-100201, BCX4430 ((2S,3S,4R,5R)-2-(4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-5-(hydroxymethyl)pyrrolidine-3,4-diol), favipiravir (also known as T-705 or Avigan),T-705 monophosphate, T-705 diphosphate, T-705 triphosphate, FGI-106 (l-N,7-N-bis[3-(dimethylamino)propyl]-3,9-dimethylquinolino[8,7-h]quinolone-l,7-diamine), JK-05, TKM-Ebola, ZMapp, rNAPc2, VRC-EBOADC076-00-VP, OS-2966, MVA-BN filo, brincidofovir, Vaxart adenovirus vector 5-based ebola vaccine, Ad26-ZEBOV, FiloVax vaccine, GOVX-E301, GOVX-E302, ebola virus entry inhibitors (NPC1 inhibitors), and rVSV-EBOV, and mixtures thereof. The compounds and compositions of the present invention may also be used in combination with phosphoramidate morpholino oligomers (PMOs), which are synthetic antisense oligonucleotide analogs designed to interfere with translational processes by forming base-pair duplexes with specific RNA sequences. Examples of PMOs include AVI-7287, AVI-7288, AVI-7537, AVI-7539, AVI-6002, and AVI-6003. The compounds and compositions of

the present invention are also intended for use with general care provided patients with Filoviridae viral infections, including parenteral fluids (including dextrose saline and Ringer's lactate) and nutrition, antibiotic (including metronidazole and cephalosporin antibiotics, such as ceftriaxone and cefuroxime) and/or antifungal prophylaxis, fever and pain medication, antiemetic (such as metoclopramide) and/or antidiarrheal agents, vitamin and mineral supplements (including Vitamin K and zinc sulfate), anti-inflammatory agents (such as ibuprofen), pain medications, and medications for other common diseases in the patient population, such anti-malarial agents (including artemether and artesunate-lumefantrine combination therapy), typhoid (including quinolone antibiotics, such as ciprofloxacin, macrolide antibiotics, such as azithromycin, cephalosporin antibiotics, such as ceftriaxone, or aminopenicillins, such as ampicillin), or shigellosis.

[0204] It is also possible to combine any compound of the invention with one or more additional 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.

[0205] 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.

[0206] 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.

[0207] 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.

[0208] In still yet another embodiment, the present application provides for methods of inhibiting *Filoviridae* polymerase in a cell, comprising: contacting a cell infected with a Filovirus with an effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, whereby *Filoviridae* polymerase is inhibited.

[0209] In still yet another embodiment, the present application provides for methods of inhibiting *Filoviridae* polymerase in a cell, comprising: contacting a cell infected with Filovirus with an effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent, whereby *Filoviridae* polymerase is inhibited.

[0210] In still yet another embodiment, the present application provides for methods of inhibiting *Filoviridae* polymerase in a cell, comprising: contacting a cell infected with *Filoviridae* virus with an effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent selected

[0211] In still yet another embodiment, the present application provides for methods of treating *Filoviridae* virus infection in a human, comprising: administering to the patient a

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

[0212] In still yet another embodiment, the present application provides for methods of treating *Filoviridae* virus infection in a human, comprising: administering to the patient a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent, whereby *Filoviridae* polymerase is inhibited.

[0213] In still yet another embodiment, the present application provides for methods of treating *Filoviridae* virus infection in a human, comprising: administering to the patient a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent.

[0214] Also provided is a kit that includes a compound of Formula I, or a pharmaceutically acceptable salt, pharmaceutically acceptable ester, stereoisomer, mixture of stereoisomers or tautomer thereof. In separate embodiments individual kits are provided includes a compound selected from the group of each of the Formulas herein, as well as each subgroup and embodiment thereof, including Formula II, Formula II, Formula IV, and individual Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, and 32 (Compounds 1-32), or a pharmaceutically acceptable salt, pharmaceutically acceptable ester, stereoisomer, mixture of stereoisomers or tautomer thereof. In one aspect, the kit comprises a compound of Formula I, or a pharmaceutically acceptable salt thereof. Each of the individual kits described herein may comprise a label and/or instructions for use of the compound in the treatment of a disease or condition in a subject (e.g., human) in need thereof. In some embodiments, the disease or condition is a human Filoviridae viral infection, including an Ebola viral infection or a Marburg viral infection. In other embodiments, each separate kit may also contain instructions for use of additional medical agents in combination with the compound of Formula I in the treatment of a disease or condition in a subject (e.g., human) in need thereof. In certain of these embodiments, the disease or condition is a human Filoviridae viral infection, including an Ebola viral infection or a Marburg viral infection. In each of the kits herein there is a further embodiment in which the kit comprises individual dose units of a compound as described herein, or a pharmaceutically acceptable salt, racemate, enantiomer, diastereomer, tautomer, polymorph, pseudopolymorph, amorphous form, hydrate or solvate thereof. Examples of individual dosage units may include pills, tablets, capsules, prefilled

syringes or syringe cartridges, IV bags, etc., each comprising a therapeutically effective amount of the compound in question, or a pharmaceutically acceptable salt, racemate, enantiomer, diastereomer, tautomer, polymorph, pseudopolymorph, amorphous form, hydrate or solvate thereof. In some embodiments, the kit may contain a single dosage unit and in others multiple dosage units are present, such as the number of dosage units required for a specified regimen or period.

[0215] Also provided are articles of manufacture that include a compound of Formula I, or a pharmaceutically acceptable salt, pharmaceutically acceptable ester, stereoisomer, mixture of stereoisomers or tautomer thereof; and a container. In one aspect, the article of manufacture comprises a compound of Formula I, Formula II, Formula II, Formula IV, and individual Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, and 32 (Compounds 1-32), or a pharmaceutically acceptable salt thereof, and a container. In separate embodiments, the container of the article of manufacture may be a vial, jar, ampoule, preloaded syringe, blister package, tin, can, bottle, box, or an intravenous bag.

VI. METHODS OF INHIBITION OF A *FILOVIRIDAE* POLYMERASE

[0216] Another aspect of the invention relates to methods of inhibiting the activity of *Filoviridae* polymerase comprising the step of treating a sample suspected of containing *Filoviridae* with a compound or composition of the invention.

[0217] *Filoviridae* that can be treated using the methods of the present invention are single-stranded negative sense RNA viruses that typically infect primates. Filoviruses are able to multiply in virtually all cell types. The Filovirus antigens and virions are found primarily in fibroblasts and interstitium of an infected individual. There are three identified genera of Filoviruses: the Ebola virus (EBOV; five species); the Marburg virus (MARV); and the Cuevavirus, also known as the Lloviu virus (LLOV). The virions (viral particles) are characteristically shaped as long, cylindrical, filamentous particles which may be straight, curved, coiled, or found in a "6" or "U" shaped configuration. They are occasionally branched and the particles vary greatly in length, but the diameter (about 80 nm) is consistent. The filovirus genome comprises seven genes that encode 4 virion structural proteins (VP30, VP35, nucleoprotein (NP), and a polymerase protein (L-pol)) and 3 membrane-associated proteins (VP40, glycoprotein (GP), and VP24).

[0218] The Ebola virus genus includes five known species: (1) *Bundibugyo ebolavirus,* also known as Bundibugyo virus (BDBV, previously BEBOV); (2) *Reston ebolavirus,* also known as Reston virus or Ebola-Reston (RESTV, previously REBOV); (3) *Sudan ebolavirus,* also known as Sudan virus or Ebola-Sudan (SUDV, previously SEBOV); (4) *Tai Forest ebolavirus,* also known as Tai Forest virus or Ebola-Tai (TAFV, previously CIEBOV); and (5) *Zaire ebolavirus,* also known as Ebola virus or Ebola-Zaire (EBOV, previously ZEBOV).

[0219] The Marburg virus genus includes the species *Marburg marburgvirus,* also known as Marburg virus (MARV) or Ravn virus (RAW). The Cuevavirus genus includes the species *Lloviu cuevavirus,* also known as the Lloviu virus (LLOV).

[0220] Compositions of the invention may act as inhibitors of *Filoviridae* 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 *Filoviridae* polymerase having a geometry unique to *Filoviridae* polymerase . Compositions binding *Filoviridae* 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 *Filoviridae* polymerase. Accordingly, the invention relates to methods of detecting *Filoviridae* polymerase in a sample suspected of containing *Filoviridae* polymerase comprising the steps of: treating a sample suspected of containing *Filoviridae* 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.

[0221] Within the context of the invention, samples suspected of containing *Filoviridae* 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 *Filoviridae* polymerase, frequently a pathogenic organism such as a *Filoviridae* virus. Samples can be contained in any medium including water

and organic solventWater mixtures. Samples include living organisms such as humans, and manmade materials such as cell cultures.

[0222] 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.

[0223] If desired, the activity of *Filoviridae* polymerase after application of the composition can be observed by any method including direct and indirect methods of detecting *Filoviridae* polymerase activity. Quantitative, qualitative, and semiquantitative methods of determining *Filoviridae* 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.

[0224] Organisms that contain *Filoviridae* polymerase include the *Filoviridae* virus. The compounds of this invention are useful in the treatment or prophylaxis of *Filoviridae* infections in animals or in man.

[0225] However, in screening compounds capable of inhibiting human *Filoviridae* 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.

[0226] In another embodiment, the present application provides for methods of treating *Filoviridae* virus infection in a human, comprising: administering to the patient a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, solvate, and/or ester thereof. In some embodiments, the *Filoviridae* infection is caused by a *Filoviridae* virus. In some embodiments, the *Filoviridae* infection is caused by an Ebola virus. In some embodiments, the *Filoviridae* infection is caused by *Bundibugyo ebolavirus, Reston ebolavirus, Sudan ebolavirus, Tai Forest ebolavirus,* or *Zaire ebolavirus.* In some embodiments, the *Filoviridae* infection is caused by a *Marburg* virus. In some embodiments, the *Filoviridae* infection is caused by a Lloviu virus. In some embodiments, a Filoviridae polymerase is inhibited.

[0227] The compounds of the present invention can be used in the treatment of a human already suffering from a *Filoviridae* infection, or can be administered prophylactically to reduce or prevent the chance of a *Filoviridae* infection. *Filoviridae* infections can be characterized by

hemorrhagic fever, hematemesis, diarrhea, retrosternal abdominal pain and prostration. The incubation period is around 21 days following contact with a human suffering from *Filoviridae* infection. The outcome of *Filoviridae* infection is typically death.

[0228] Also provided as separate embodiments are a compound selected from each of the Formulas herein, as well as each subgroup and embodiment thereof, including a compound selected from the group of Formula (I), Formula (II), Formula (III), Formula (IV), or one of the specific compounds of the examples herein, including Compounds 1-32, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, for use in a method of treating a *Filoviridae* infection in a human. Also provided as separate embodiments are a compound selected from each of the Formulas herein, as well as each subgroup and embodiment thereof, including a compound selected from the group of Formula (I), Formula (II), Formula (III), Formula (IV), or one of the specific compounds of the examples herein, including Compounds 1-32, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, for use in a method of treating an Ebola virus infection in a human. Also provided as separate embodiments are a compound selected from each of the Formulas herein, as well as each subgroup and embodiment thereof, including a compound selected from the group of Formula (I), Formula (II), Formula (III), Formula (IV), or one of the specific compounds of the examples herein, including Compounds 1-32, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, for use in a method of treating a Marburg virus infection in a human. Within each of the embodiments herein in which the *Filoviridae* infection is an Ebola virus, there are further separate embodiments with them wherein the *Filoviridae* infection is caused, respectively, by *Bundibugyo ebolavirus*, *Reston ebolavirus*, *Sudan ebolavirus*, *Tai Forest ebolavirus*, or *Zaire ebolavirus*. In some embodiments, the *Filoviridae* infection is caused by a *Marburg* virus. In some embodiments, the *Filoviridae* infection is caused by a Lloviu virus.

[0229] Also provided as separate embodiments are the uses of a compound selected from each of the Formulas herein, as well as each subgroup and embodiment thereof, including a compound selected from the group of Formula (I), Formula (II), Formula (III), Formula (IV), or one of the specific compounds of the examples herein, including Compounds 1-32, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in the preparation of a medicament for use in treating a Filoviridae infection in a human. Also provided as separate embodiments are the uses of a compound selected from each of the Formulas herein, as well as each subgroup and embodiment thereof, including a compound selected from the group of

Formula (I), Formula (II), Formula (III), Formula (IV), or one of the specific compounds of the examples herein, including Compounds 1-32, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in the preparation of a medicament for use in treating an Ebola virus infection in a human. Also provided as separate embodiments are the uses of a compound selected from each of the Formulas herein, as well as each subgroup and embodiment thereof, including a compound selected from the group of Formula (I), Formula (II), Formula (III), Formula (IV), or one of the specific compounds of the examples herein, including Compounds 1-32, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in the preparation of a medicament for use in treating a Marburg virus infection in a human.

VII. SCREENS FOR *FILOVIRIDAE* POLYMERASE INHIBITORS.

[0230] Compositions of the invention are screened for inhibitory activity against *Filoviridae* 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 *Filoviridae* polymerase *in vitro* and compositions showing inhibitory activity are then screened for activity *in vivo*. Compositions having *in vitro* Ki (inhibitory constants) of less than about 5×10^{-6} M and preferably less than about 1×10^{-7} M are preferred for *in vivo* use.

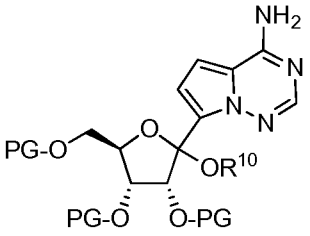
[0231] Useful *in vitro* screens have been described in detail and will not be elaborated here. However, the examples describe suitable *in vitro* assays.

VIII. PREPARATION OF COMPOUNDS

[0232] The compounds of the present invention can be prepared by a variety of means. For example, protected nucleosides of Formula V can be prepared by reaction of a protected lactone with an iodo-substituted base under suitable coupling conditions. The nucleosides can then be modified with a prodrug moiety by reaction of a partially protected nucleoside with a suitable prodrug moiety, following be removal of the protecting groups, to afford the compounds of the present invention.

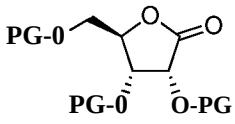
A. Preparation of Nucleosides via Iodo-Base

[0233] In some embodiments, the present invention provides a method of preparing a compound of Formula V:



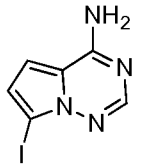
Formula (V).

The method of making the compound of Formula V includes forming a reaction mixture having a coupling agent, a halo-silane, a compound of Formula VI:



Formula (VI),

and a compound of Formula VII:



Formula (VII)

under conditions suitable to prepare the compound of Formula V, wherein each PG is independently a hydroxy protecting group, alternatively, two PG groups on adjacent carbons can be combined to form a $-C(R^{19})_2-$ group, R^{10} is H or a silyl group, and R^{19} is H, C_1-C_8 alkyl, phenyl or substituted phenyl.

[0234] Any suitable coupling agent can be used in the method of making the compound of Formula V. The coupling agent can be a lithium coupling agent, a sodium coupling agent, a magnesium coupling agent, or others. For example, the coupling agent can be a deprotonating agent such as n-butyl lithium (n-BuLi), sodium hydride (NaH), lithium aluminum hydride (LAH or $L1AIH_4$), and others. The coupling agent can also be a magnesium based coupling agent such as, but not limited to, $MgCl_2$, iPrMgCl, tBuMgCl, PhMgCl, or combinations thereof. In some embodiments, the coupling agent can be a lithium coupling agent or a magnesium coupling agent. In some embodiments, the coupling agent can be n-BuLi, $MgCl_2$, iPrMgCl, tBuMgCl, PhMgCl, or combinations thereof. In some embodiments, the coupling agent can be n-BuLi. In some embodiments, the coupling agent can be PhMgCl and iPrMgCl.

[0235] The coupling agent can be present in any suitable amount. For example, the coupling agent can be present in an amount of at least 1.0 eq. (mol/mol) to the compound of Formula V, such as about 1.0, 2, 3, 4, 5, 6, 7, 8, 9, or about 10.0 eq. (mol/mol). The coupling agent can also be present in an amount of from about 1.0 to about 10.0 eq. (mol/mol) to the compound of

Formula V, such as of from about 1.0 to about 5.0 eq. (mol/mol), or of from about 1.0 to about 2.0 eq. (mol/mol). In some embodiments, the coupling agent can be present in an amount of from about 1.0 to about 5.0 eq. (mol/mol) to the compound of Formula V. In some embodiments, the coupling agent can be present in an amount of from about 1.0 to about 2.0 eq. (mol/mol) to the compound of Formula V.

[0236] Any suitable halo-silane can be used in the method of making the compound of Formula V. For example, the halo-silane can be a fluoro-silane, a chloro-silane, a bromo-silane or an iodo-silane. The silane portion can have any suitable substituents, such as alkyl, alkenyl, alkynyl, cycloalkyl, or phenyl. Exemplary halo-silanes include, but are not limited to, Cl-$Si(CH_3)_3$, or Cl-$Si(CH_3)$2CH2CH2$Si(CH_3)_2$-Cl. In some embodiments, the halo-silane can be a chloro-silane. In some embodiments, the halo-silane can be Cl-$Si(CH_3)_3$, or Cl-$Si(CH_3)$2CH2$CH_2Si(CH_3)$2-Cl. In some embodiments, the halo-silane can be TMSC1.

[0237] The silyl group of R^{10} can be any suitable group, but can depend on the choice of the halo-silane. For example, when the halo-silane is TMSC1, the silyl group can be trimethylsilyl.

[0238] The halo-silane can be present in any suitable amount. For example, the halo-silane can be present in an amount of at least 1.0 eq. (mol/mol) to the compound of Formula V, such as about 1.0, 2, 3, 4, 5, 6, 7, 8, 9, or about 10.0 eq. (mol/mol). The halo-silane can also be present in an amount of from about 1.0 to about 10.0 eq. (mol/mol) to the compound of Formula V, such as of from about 1.0 to about 5.0 eq. (mol/mol), or of from about 1.0 to about 2.0 eq. (mol/mol). In some embodiments, the halo-silane can be present in an amount of from about 1.0 to about 5.0 eq. (mol/mol) to the compound of Formula V. In some embodiments, the halo-silane can be present in an amount of from about 1.0 to about 2.0 eq. (mol/mol) to the compound of Formula V.

[0239] The hydroxy protecting group can be any protecting group suitable for a hydroxy functional group. Representative hydroxy protecting groups include, but are not limited to, silanes such as trimethyl silane (TMS), t-butyl dimethyl silane (TBDMS), or t-butyl diphenyl silane (TBDPS), ethers such as methyl-methoxy (MOM), tetrahydropyran (THP), t-butyl, allyl, or benzyl, and esters such as acetyl, pivaloyl, or benzoyl. In some embodiments, the hydroxy protecting group can be trimethyl silane (TMS), t-butyl dimethyl silane (TBDMS), t-butyl diphenyl silane (TBDPS), methyl-methoxy (MOM), tetrahydropyran (THP), t-butyl, allyl, benzyl, acetyl, pivaloyl, or benzoyl. In some embodiments, the hydroxy protecting group can be benzyl.

[0240] Hydroxy groups on adjacent carbons, referred to as 1,2-hydroxy groups, can form a cyclic protecting group called an acetonide by reaction with a ketone of di-ether. Exemplary acetonides include, but are not limited to acetonide and benzylidene acetal. In some embodiments, the hydroxy protecting groups of hydroxy groups on adjacent carbons can be combined to form acetonide.

[0241] When the R^{19} group is Ci-Cs alkyl, R^{19} can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-buty, t-butyl, pentyl, iso-pentyl, neo-pentyl, hexyl, isohexyl, neohexyl, septyl or octyl. In some embodiments, the R^{19} group can be methyl.

[0242] Any suitable solvent can be used in the method of the present invention. Representative solvents include, but are not limited to, pentane, pentanes, hexane, hexanes, heptane, heptanes, petroleum ether, cyclopentanes, cyclohexanes, benzene, toluene, xylene, trifluoromethylbenzene, halobenzenes such as chlorobenzene, fluorobenzene, dichlorobenzene and difluorobenzene, methylene chloride, chloroform, acetone, ethyl acetate, diethyl ether, tetrahydrofuran, or combinations thereof. In some embodiments, the solvent can be tetrahydrofuran.

[0243] The reaction mixture of the method can be at any suitable temperature. For example, the temperature of the reaction mixture can be of from about -78 °C to about 100 °C, or of from about -50 °C to about 100 °C, or of from about -25 °C to about 50 °C, or of from about -10 °C to about 25 °C, or of from about 0 °C to about 20 °C. In some embodiments, the temperature of the reaction mixture can be of from about 0 °C to about 20 °C.

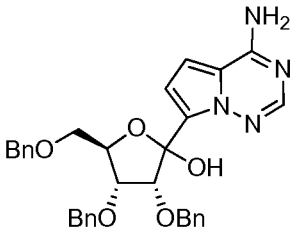
[0244] The reaction mixture of the method can be at any suitable pressure. For example, the reaction mixture can be at atmospheric pressure. The reaction mixture can be also be exposed to any suitable environment, such as atmospheric gasses, or inert gasses such as nitrogen or argon.

[0245] The method of the present invention can provide the compound of Formula V in any suitable yield. For example, the compound of Formula V can be prepared in a yield of at least about 50%, 55, 60, 65, 70, 75, 80, 85, 90 or at least about 95%.

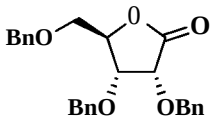
[0246] The method of the present invention can provide the compound of Formula V in any suitable purity. For example, the compound of Formula V can be prepared in a purity of at least about 90, 95, 96, 97, 98 or at least about 99%. In some embodiments, the compound of Formula V can be prepared in at least 95% purity. In some embodiments, the compound of Formula V

can be prepared in at least 98% purity. In some embodiments, the compound of Formula V can be prepared in at least 99% purity.

[0247] In some embodiments, the method including preparing the compound of Formula V:

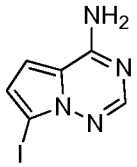


wherein the method includes forming the reaction mixture having TMSCl, PhMgCl, iPrMgCl, the compound of Formula VI:



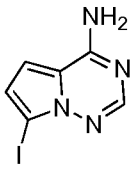
,

and the compound of Formula VII:



under conditions suitable to prepare the compound of Formula V.

[0248] In some embodiments, the present invention provides the compound:



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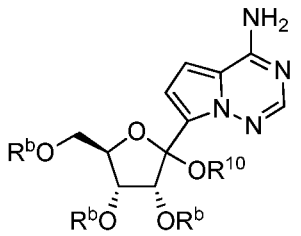
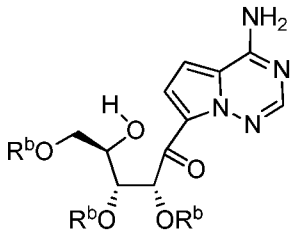
[0249] In some embodiments, the present invention provides a method of preparing a compound of Formula V-a or V-b:

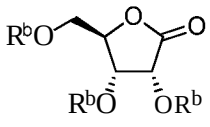


Formula (V-a),



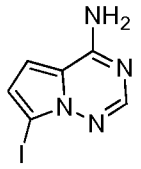
Formula (V-b).

The method of making the compound of Formula V-a or Formula V-b includes forming a reaction mixture having a deprotonating agent, a silylating agent, a coupling agent, an additive, a compound of Formula Vl-a:



Formula (Vl-a),

and a compound of Formula VII:



Formula (VII)

under conditions suitable to prepare the compound of Formula V-a or Formula V-b, wherein each R^b is independently a hydroxy protecting group, alternatively, two R^b groups on adjacent carbons can be combined to form a -C(R^{19})$_2$- group, R^{10} is H or a silyl group, and R^{19} is H, Cr C_8 alkyl, phenyl or substituted phenyl.

[0250] Any suitable deprotonating agent can be used in the method of making the compound of Formula V-a or Formula V-b. The deprotonating agent can be a sodium deprotonating agent, a magnesium based deprotonating agent, lithium based deprotonating agent, potassium based deprotonating agent, or others. For example, the deprotonating agent can be sodium hydride (NaH), isopropylmagnesium chloride (iPrMgCl), tert-butylmagnesium chloride (tBuMgCl), phenylmagnesium chloride (PhMgCl), phenylmagnesium bromide (PhMgBr), butyllithium (BuLi), methyllithium (MeLi), methylmagnesium chloride (MeMgCl), methylmagnesium bromide (MeMgBr), tert-butyllithium (tBuLi), isopropyllithium (iPrLi), phenyllithium (PhLi), lithium hydride (LiH), potassium hydride (KH), ethyllithium (EtLi), ethylmagnesium bromide (EtMgBr), ethylmagnesium chloride (EtMgCl), propyllithium (PrLi), propylmagnesium bromide (PrMgBr), propylmagnesium chloride (PrMgCl), cyclohexanelithium (cyHexLi), cyclohexanemagnesium bromide (cyHexMgBr), cyclohexanemagnesium chloride

(cyHexMgCl), or combinations thereof. In some embodiments, the deprotonating agent can be PhMgCl.

[0251] The deprotonating agent can be present in any suitable amount. For example, the deprotonating agent can be present in an amount of at least 0.1 eq. (mol/mol) to the compound of Formula VII, such as about 0.1, 0.5, 1.0, 2, 3, 4, 5, 6, 7, 8, 9, or about 10.0 eq. (mol/mol). The deprotonating agent can also be present in an amount of from about 0.1 to about 10.0 eq. (mol/mol) to the compound of Formula VII, such as of from about 0.1 to about 3.0 eq. (mol/mol), or of from about 1.0 to about 2.0 eq. (mol/mol). In some embodiments, the deprotonating agent can be present in an amount from about 0.1 to 1.0 eq. (mol/mol) to the compound of Formula VII. In some embodiments, the deprotonating agent can be present in an amount of from about 1.0 to about 2.0 eq. (mol/mol) to the compound of Formula VII.

[0252] Any suitable silylating agent can be used in the method of making the compound of Formula V-a or Formula V-b. For example, the silylating agent can be a fluoro-silane, a chloro-silane, a bromo-silane or an iodo-silane. For example, the silylating agent can be a tri-substituted silyl chloride, a tri-substituted silyl bromide, a tri-substituted silyl iodide, or a tri-substituted silyl fluoride. The silyl portion can have any suitable substituents, such as alkyl, alkenyl, alkynyl, cycloalkyl, or phenyl. Exemplary silylating agents include, but are not limited to, Cl-Si(CH_3)$_3$, Cl-Si(CH_3)$_2$$CH_2$$CH_2$Si($CH_3$)$_2$-Cl, or tert-butyldiphenylsilyl (TBDPS). In some embodiments, the silylating agent can be a chloro-silane. In some embodiments, the silylating agent can be Cl-Si(CH_3)$_3$, or Cl-Si(CH_3)$_2$$CH_2$$CH_2$Si($CH_3$)$_2$-Cl. In some embodiments, the silylating agent can be TMSC1.

[0253] The silyl group of R^{10} can be any suitable group, but can depend on the choice of the silylating agent. For example, when the silylating agent is TMSC1, the silyl group can be trimethylsilyl.

[0254] The silylating agent can be present in any suitable amount. For example, the silylating agent can be present in an amount of at least 0.0 eq. (mol/mol) to the compound of Formula VII, such as about 0.0, 0.1, 0.5, 1.0, 2, 3, 4, 5, 6, 7, 8, 9, or about 10.0 eq. (mol/mol). The silylating agent can also be present in an amount of from about 0.0 to about 10.0 eq. (mol/mol) to the compound of Formula VII, such as of from about 0.0 to about 3.0 eq. (mol/mol), or of from about 1.0 to about 2.0 eq. (mol/mol). In some embodiments, the silylating agent can be present in an amount from about 0.0 to 1.0 eq. (mol/mol) to the compound of Formula VII. In some

embodiments, the silylating agent can be present in an amount of from about 1.0 to about 2.0 eq. (mol/mol) to the compound of Formula VII.

[0255] Any suitable coupling agent can be used in the method of making the compound of Formula V-a or Formula V-b. The coupling agent can be a lithium coupling agent, a magnesium based deprotonating agent, or others. For example, the coupling agent can be n-butyllithium (nBuLi), magnesium chloride ($MgCl_2$), isopropylmagnesium chloride (iPrMgCl), isopropylmagnesium chloride - lithium chloride (iPrMgCl-LiCl), tert-butylmagnesium chloride (tBuMgCl), phenylmagnesium chloride (PhMgCl), methyllithium (MeLi), methylmagnesium chloride (MeMgCl), methylmagnesium bromide (MeMgBr), tert-butyllithium (tBuLi), isopropyllithium (iPrLi), phenyllithium (PhLi), lithium hydride (LiH), potassium hydride (KH), sodium hydride (NaH), ethyllithium (EtLi), ethylmagnesium bromide (EtMgBr), ethylmagnesium chloride (EtMgCl), propyllithium (PrLi), propylmagnesium bromide (PrMgBr), propylmagnesium chloride (PrMgCl), cyclohexanelithium (cyHexLi), cyclohexanemagnesium bromide (cyHexMgBr), cyclohexanemagnesium chloride (cyHexMgCl), or combinations thereof. In some embodiments, the coupling agent can be iPrMgCl.

[0256] The coupling agent can be present in any suitable amount. For example, the coupling agent can be present in an amount of at least 0.1 eq. (mol/mol) to the compound of Formula VII, such as about 0.1, 0.5, 1.0, 2, 3, 4, 5, 6, 7, 8, 9, or about 10.0 eq. (mol/mol). The coupling agent can also be present in an amount of from about 0.1 to about 10.0 eq. (mol/mol) to the compound of Formula VII, such as of from about 0.1 to about 3.0 eq. (mol/mol), or of from about 1.0 to about 2.0 eq. (mol/mol). In some embodiments, the coupling agent can be present in an amount from about 0.1 to 1.0 eq. (mol/mol) to the compound of Formula VII. In some embodiments, the coupling agent can be present in an amount of from about 1.0 to about 2.0 eq. (mol/mol) to the compound of Formula VII.

[0257] Any suitable additive can be used in the method of making the compound of Formula V-a of Formula V-b. The additive can be BF_3-OEt_2, $SmOTf)_3$, $Sc(OTf)_3$, $FeCl_3$, LiCl, LiBr, $TiCl(OiPr)_3$, $ScCl_3$, Bu_4NBr+$LaCl_3$-2LiCl , $nLaCl_3$+mLiCl, wherein m is 0.5 to 50, n is 1 to 100, $LaCl_3$+2LiCl, $Sm(OTf)_3$+ LiCl, $SmCl_3$,Bis[2-(N,N-dimethylamino)ethyl] ether, TMEDA, $NdCl_3$, $NdCl_3$+CsCl, $nNdCl_3$+mLiCl, wherein m is 0.5 to 50, n is 1 to 100, $NdCl_3$+2LiCl, $NdCl_3$+LiBr, $NdCl_3$+LiI, $NdBr_3$, $NdBr_3$+CsCl, $nNdBr_3$+mLiCl, wherein m is 0.5 to 50, n is 1 to 100, $NdBr_3$+2LiCl, $NdBr_3$+LiBr, $NdBr_3$+LiI, $Nd(OTf)_3$, $CeCl_3$, $CeCl_3$+CsCl, $nCeCl_3$+mLiCl, wherein m is 0.5 to 50, n is 1 to 100, $CeCl_3$+2LiCl, $CeCl_3$+LiBr, $CeCl_3$+LiI ,$CeBr_3$, $Ce(OTf)_3$,

$YC1_3$, YCl_3+CsCl, nYCls+mLiCl, wherein m is 0.5 to 50, n is 1 to 100, YCl_3+2LiCl, YCl_3+LiBr, YCl_3+LiI, YBr_3, YBr_3+CsCl, nYBr_3+mLiCl, wherein m is 0.5 to 50, n is 1 to 100, YBr_3+2LiCl, YBr_3+LiBr, YBr_3+LiI, $Y(OTf)_3$, $LaCl_3$, $La(OTf)_3$, $MgCl_2$, $T1CI_4$, $SnCl_4$, $A1C1_3$, Bu_4NCl, Diethyleneglycol diethylether (DGDE), DGDE+Bu_4NCl, DGDE+Bu_4NBr, DGDE+Bu_4NI, $CaCl_2$, $CaBr_2$, Cal_2, $Ca(OTf)_2$, $YC1_3$, YCl_3-2LiCl, YCl_3-LiCl or a combination thereof. In some embodiments, the additive can be LiCl, $Ca(OTf)_2$, $CaCl_2$ and $MgCl_2$, $CeCl_3$, $LaCl_3$, or a combination thereof. In some embodiments, the additive can be $YC1_3$, $CeCl_3$, $NdCl_3$, $LaCl_3$, or a combination thereof.

[0258] The additive can be present in any suitable amount. For example, the additive can be present in an amount of at least 0.1 eq. (mol/mol) to the compound of Formula VII, such as about 0.1, 0.5, 1.0, 2, 3, 4, 5, 6, 7, 8, 9, or about 10.0 eq. (mol/mol). The additive can also be present in an amount of from about 0.1 to about 10.0 eq. (mol/mol) to the compound of Formula VII, such as of from about 0.1 to about 3.0 eq. (mol/mol), or of from about 1.0 to about 2.0 eq. (mol/mol). In some embodiments, the additive can be present in an amount from about 0.1 to 1.0 eq. (mol/mol) to the compound of Formula VII. In some embodiments, the additive can be present in an amount of from about 1.0 to about 2.0 eq. (mol/mol) to the compound of Formula VII.

[0259] In some embodiments, the additive is $LaCl_3$-2LiCl and is present in an amount of at least 0.1 eq. (mol/mol) to the compound of Formula VII, such as about 0, 0.1, 0.3, 0.5, 1.0, 2, or about 2.0 eq. (mol/mol). In some embodiments, the additive is $LaCl_3$-2LiCl and is present in an amount of from about 0 to about 2.0 eq. (mol/mol) to the compound of Formula VII, such as of from about 0 to about 0.3 eq. (mol/mol), or of from about 0 to about 0.5 eq. (mol/mol). In some embodiments, the additive is $LaCl_3$-2LiCl and is present in an amount from about 0 to 0.5 eq. (mol/mol) to the compound of Formula VII. In some embodiments, the the additive is $LaCl_3$-2LiCl and is present in an amount of about 0.5 eq. (mol/mol) to the compound of Formula VII.

[0260] In some embodiments, the additive is $CeCl_3$ and is present in an amount of at least 0.1 eq. (mol/mol) to the compound of Formula VII, such as about 0, 0.1, 0.3, 0.5, 1.0, 2, or about 2.0 eq. (mol/mol). In some embodiments, the additive is $CeCl_3$ and is present in an amount of from about 0 to about 2.0 eq. (mol/mol) to the compound of Formula VII, such as of from about 0 to about 0.3 eq. (mol/mol), or of from about 0 to about 0.5 eq. (mol/mol). In some embodiments, the additive is $CeCl_3$ and is present in an amount from about 0 to 0.5 eq. (mol/mol) to the

compound of Formula VII. In some embodiments, the the additive is CeCl3 and is present in an amount of about 0.5 eq. (mol/mol) to the compound of Formula VII.

[0261] In some embodiments, the additive is NdCl3 and is present in an amount of at least 0.1 eq. (mol/mol) to the compound of Formula VII, such as about 0, 0.1, 0.3, 0.5, 1.0, 2, or about 2.0 eq. (mol/mol). In some embodiments, the additive is NdCl3 and is present in an amount of from about 0 to about 2.0 eq. (mol/mol) to the compound of Formula VII, such as of from about 0 to about 0.3 eq. (mol/mol), or of from about 0 to about 0.5 eq. (mol/mol). In some embodiments, the additive is NdCl3 and is present in an amount from about 0 to 0.5 eq. (mol/mol) to the compound of Formula VII. In some embodiments, the the additive is NdCl3 and is present in an amount of about 0.5 eq. (mol/mol) to the compound of Formula VII.

[0262] In some embodiments, the additive is YCl_3 and is present in an amount of at least 0.1 eq. (mol/mol) to the compound of Formula VII, such as about 0, 0.1, 0.3, 0.5, 1.0, 2, or about 2.0 eq. (mol/mol). In some embodiments, the additive is YCl_3 and is present in an amount of from about 0 to about 2.0 eq. (mol/mol) to the compound of Formula VII, such as of from about 0 to about 0.3 eq. (mol/mol), or of from about 0 to about 0.5 eq. (mol/mol). In some embodiments, the additive is YCl_3 and is present in an amount from about 0 to 0.5 eq. (mol/mol) to the compound of Formula VII. In some embodiments, the the additive is YCl_3 and is present in an amount of about 0.5 eq. (mol/mol) to the compound of Formula VII.

[0263] When the R^{19} group is Ci-Cs alkyl, R^{19} can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-buty, t-butyl, pentyl, iso-pentyl, neo-pentyl, hexyl, isohexyl, neohexyl, septyl or octyl. In some embodiments, the R^{19} group can be methyl.

[0264] When the R^b group is a hydroxyl protecting group, R^b can be any example protecting group described in *Protective Groups in Organic Chemistry*, Peter G. M. Wuts and Theodora W. Greene, 4th Ed., 2006. In some embodiments, the R^b group can be benzyl. In some embodiments, the R^b group can be TBS.

[0265] The hydroxy protecting group can be any protecting group suitable for a hydroxy functional group. Representative hydroxy protecting groups include, but are not limited to, silanes, ethers, esters, or others. Representative hydroxy protecting groups include, but are not limited to trimethyl silane (TMS), t-butyl dimethyl silane (TBDMS), t-butyl diphenyl silane (TBDPS), methyl-methoxy (MOM), tetrahydropyran (THP), t-butyl, allyl, benzyl, acetyl, pivaloyl, or benzoyl. In some embodiments, the hydroxy protecting group can be trimethyl silane (TMS), t-butyl dimethyl silane (TBDMS), t-butyl diphenyl silane (TBDPS), methyl-

methoxy (MOM), tetrahydropyran (THP), t-butyl, allyl, benzyl, acetyl, pivaloyl, or benzoyl. In some embodiments, the hydroxy protecting group can be benzyl. In some embodiments, the hydroxy protecting group can be TBS.

[0266] Hydroxy groups on adjacent carbons, referred to as 1,2-hydroxy groups, can form a cyclic protecting group called an acetal or a ketal by reaction with an aldehyde, an acetale, aketoneor a ketal. Exemplary acetals and ketals include, but are not limited to a, benzylidene acetal and an acetonide. In some embodiments, the hydroxy protecting groups of hydroxy groups on adjacent carbons can be combined to form acetonide.

[0267] Any suitable solvent can be used in the method of the present invention. Representative solvents include, but are not limited to, pentane, pentanes, hexane, hexanes, heptane, heptanes, petroleum ether, cyclopentanes, cyclohexanes, benzene, toluene, xylene, dichloromethane, trifluoromethylbenzene, halobenzenes such as chlorobenzene, fluorobenzene, dichlorobenzene and difluorobenzene, methylene chloride, chloroform, acetone, ethyl acetate, diethyl ether, tetrahydrofuran (THF), 2-methyltetrahydrofuran, dibutyl ether, diisopropyl ether, methyl tert-butyl ether, dimethoxyethane, dioxanes (1.4 dioxane), N-methyl pyrrolidinone (NMP), diisopropyl ether, or combinations thereof. In certain embodiments, the solvent can be THF, MeTHF, toluene, THF+dioxane, THF+pyridine, or THF+DCM, or combinations thereof. In some embodiments, the solvent can be THF.

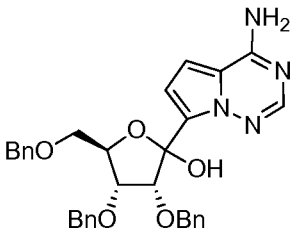
[0268] The reaction mixture of the method can be at any suitable temperature. For example, the temperature of the reaction mixture can be from about -78 °C to about 100 °C, or from about -50 °C to about 100 °C, or from about -25 °C to about 50 °C, or from about -10 °C to about 25 °C, or from about 0 °C to about 20 °C. In some embodiments, the temperature of the reaction mixture can be from about 0 °C to about 20 °C. In some embodiments, the temperature of the reaction mixture can be from about -30 °C to about -10 °C.

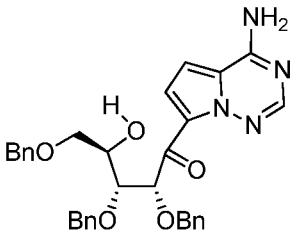
[0269] The reaction mixture of the method can be at any suitable pressure. For example, the reaction mixture can be at atmospheric pressure. The reaction mixture can be also be exposed to any suitable environment, such as atmospheric gasses, or inert gasses such as nitrogen or argon.

[0270] The method of the present invention can provide the compound of Formula V-a or Formula V-b in any suitable yield. For example, the compound of Formula V-a or Formula V-b can be prepared in a yield of at least about 50%, 55, 60, 65, 70, 75, 80, 85, 90 or at least about 95%.

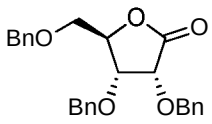
[0271] The method of the present invention can provide the compound of Formula V-a or Formula V-b in any suitable purity. For example, the compound of Formula V-a or Formula V-b can be prepared in a purity of at least about 90, 95, 96, 97, 98 or at least about 99%. In some embodiments, the compound of Formula V-a or Formula V-b can be prepared in at least 95% purity. In some embodiments, the compound of Formula V-a or Formula V-b can be prepared in at least 98% purity. In some embodiments, the compound of Formula V-a or Formula V-b can be prepared in at least 99% purity.

[0272] In some embodiments, the method includes preparing the compound of Formula V-a or Formula V-b:



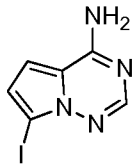


wherein the method includes forming the reaction mixture having TMSC1, PhMgCl, iPrMgCl, La(¾-2LiCl the compound of Formula VI:



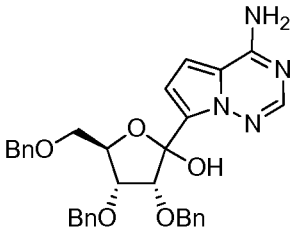
,

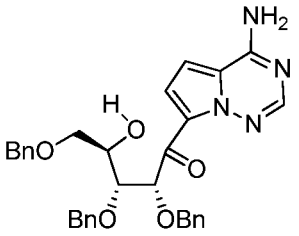
and the compound of Formula VII:



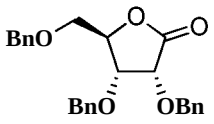
under conditions suitable to prepare the compound of Formula V-a or Formula V-b.

[0273] In some embodiments, the method includes preparing the compound of Formula V-a or Formula V-b:



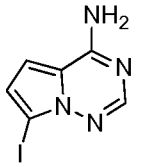


wherein the method includes forming the reaction mixture having TMSCl, PhMgCl, iPrMgCl, $CeCl_3$ the compound of Formula VI:



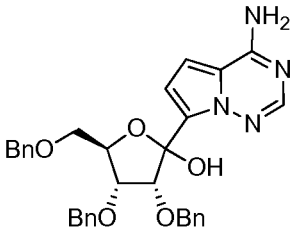
,

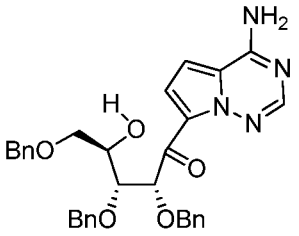
and the compound of Formula VII:



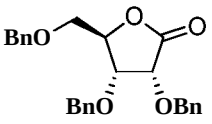
under conditions suitable to prepare the compound of Formula V-a or Formula V-b.

[0274] In some embodiments, the method includes preparing the compound of Formula V-a or Formula V-b:



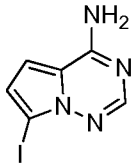


wherein the method includes forming the reaction mixture having TMSCl, PhMgCl, iPrMgCl, $NdCl_3$ the compound of Formula VI:



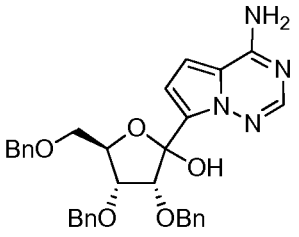
,

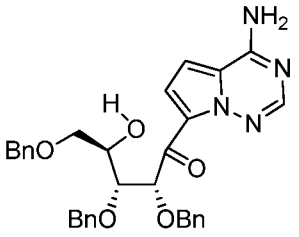
and the compound of Formula VII:



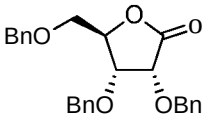
under conditions suitable to prepare the compound of Formula V-a or Formula V-b.

[0275] In some embodiments, the method includes preparing the compound of Formula V-a or Formula V-b:



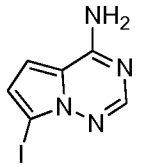


wherein the method includes forming the reaction mixture having TMSCl, PhMgCl, iPrMgCl, YCI_3 the compound of Formula VI:



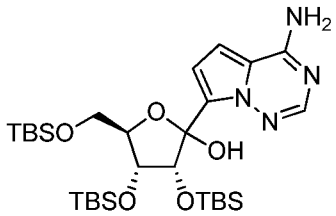
,

and the compound of Formula VII:

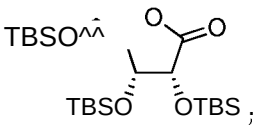


under conditions suitable to prepare the compound of Formula V-a or Formula V-b.

[0276] In some embodiments, the method includes preparing the compound of Formula V-a:

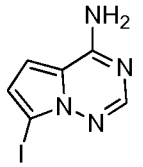


wherein the method includes forming the reaction mixture having TMSCl, PhMgCl, iPrMgCl-LiCl, LaCl3-2LiCl the compound of Formula VI:



;

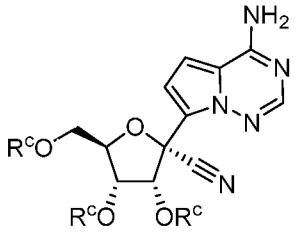
and the compound of Formula VII:



under conditions suitable to prepare the compound of Formula V-a.

B. Preparation of Cyano Nucleosides

[0277] In some embodiments, the present invention provides a method of preparing a compound of Formula XI:



Formula (XI),

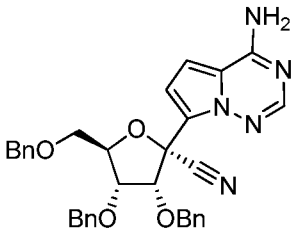
wherein R^c is H or a hydroxyl protecting group, or two R^c on adjacent carbons can be combined to form a $-C(R^{19})_2-$ group, and R^{19} is H or C_1-C_8 alkyl.

[0278] When the R^{19} group is Ci-Cs alkyl, R^{19} can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-buty, t-butyl, pentyl, iso-pentyl, neo-pentyl, hexyl, isohexyl, neohexyl, septyl or octyl. In some embodiments, the R^{19} group can be methyl.

[0279] When the R^c group is a hydroxyl protecting group, the hydroxy protecting group can be any protecting group suitable for a hydroxy functional group. Representative hydroxy protecting groups include, but are not limited to, silanes, ethers, esters, or others. Representative hydroxy protecting groups include, but are not limited to trimethyl silane (TMS), t-butyl dimethyl silane (TBDMS), t-butyl diphenyl silane (TBDPS), methyl-methoxy (MOM), tetrahydropyran (THP), t-butyl, allyl, benzyl, acetyl, pivaloyl, or benzoyl. In some embodiments, the hydroxy protecting group can be trimethyl silane (TMS), t-butyl dimethyl silane (TBDMS), t-butyl diphenyl silane (TBDPS), methyl-methoxy (MOM), tetrahydropyran (THP), t-butyl, allyl, benzyl, acetyl, pivaloyl, or benzoyl. In some embodiments, the hydroxy protecting group can be benzyl. In some embodiments, the hydroxy protecting group can be TBS

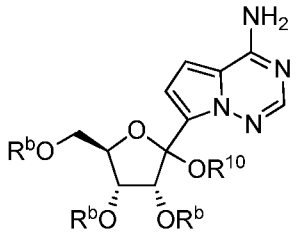
[0280] Hydroxy groups on adjacent carbons, referred to as 1,2-hydroxy groups, can form a cyclic protecting group called an acetal or a ketal by reaction with an aldehyde, an acetale, aketoneor a ketal. Exemplary acetals and ketals include, but are not limited to a, benzylidene acetal and an acetonide. In some embodiments, the hydroxy protecting groups of hydroxy groups on adjacent carbons can be combined to form acetonide.

[0281] In some embodiments, the present invention provides a method of preparing a compound of Formula Xl-a:

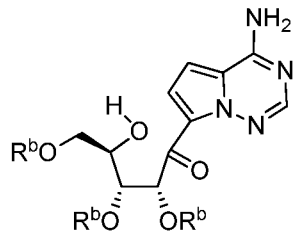


Formula (XI-a).

wherein the method includes forming a reaction mixture having a cyanating agent, a Lewis Acid, a Broenstedt acid, a solvent, and the compound of Formula V-a or V-b:



Formula (V-a),



Formula (V-b)

under conditions suitable to prepare the compound of Formula XI-a, wherein R^b is independently a hydroxy protecting group, alternatively, two R^b groups on adjacent carbons can be combined to form a $-C(R^{19})_2$ group, R^{10} is H or a silyl group, and R^{19} is H, C_1-C_8 alkyl, phenyl or substituted phenyl.

[0282] Any suitable cyanating agent can be used in the method of making the compound of Formula XI-a. For example, the cyanating agent can be TMSCN, TBSCN, TESCN, HCN, KCN, NaCN, 4-toluenesulfonyl cyanide, CuCN, CuCn*LiCl, LiCN, $Zn(CN)_2$, $K4[Fe(CN)_6]$, tetrabutylammonium cyanide, tetrmethylammonium cyanide, tetraethylammonium cyanide, tetrabutylammonium cyanide, (including tetraalkylammonium cyanide with alkyl independently being Me, Et, Pr, iPr, Bu, iBu, tertBu, Pent, Hex), tributyltn cyanide, trimethyltin cyanide, triethyltin cyanide, tripropyltin cyanide, (including trialkyltin cyanide cyanide with alkyl independently being Me, Et, Pr, iPr, Bu, iBu, tertBu, Pent, Hex), 2-hydroxy-2-methylpropanenitrile; or combinations thereof. In some embodiments, the cyanating agent can be TMSCN.

[0283] The cyanating agent can be present in any suitable amount. For example, the cyanating agent can be present in an amount of at least 0.1 eq. (mol/mol) to the compound of Formula V-a or Formula V-b, such as about 0.1, 0.5, 1.0, 2, 3, 4, 5, 6, 7, 8, 9, or about 10.0 eq. (mol/mol). The cyanating agent can also be present in an amount of from about 0.1 to about 10.0 eq. (mol/mol) to the compound of Formula V-a or Formula V-b, such as of from about 0.1 to about 3.0 eq. (mol/mol), or of from about 1.0 to about 2.0 eq. (mol/mol). In some embodiments, the cyanating agent can be present in an amount from about 0.1 to 1.0 eq. (mol/mol) to the compound of Formula V-a or Formula V-b. In some embodiments, the cyanating agent can be present in an amount of from about 1.0 to about 2.0 eq. (mol/mol) to the compound of Formula V-a or Formula V-b.

[0284] Any suitable Lewis Acid can be used in the method of making the compound of Formula XI-a. For example, the Lewis Acid can be TMSOTf, TMSOTf, TBSOTf, TESOTf,BF_3, BF_3-OEt_2, $BC1_3$, BF_3-THF, $MgCl_2$, MgI_2, $MgBr_2$, $MgBr_2$-OEt_2, $ZnCl_2$, $ZnBr_2$, ZnI_2, LiCl, LiBr, LiI, $A1C1_3$, $AlBr_3$, $A1I_3$, $Me_2Si(OTf)_2$, $Et_2Si(OTf)_2$, $Pr_2Si(OTf)_2$, $iPr_2Si(OTf)_2$,$(tBu)_2Si(OTf)_2$, $(C_6F_5)_3B$, $MeSiCl_3$, Me_2SiCl_2, $SiCl_4$, TMSC1, TMSI, TMSVr, TBSC1, TBSBr, TBSI, TESC1, TESBr, TESI, $SmCl_3$, $SmBr_3$, SmI_2, SmI_3, ScI_3, $ScBr_3$, ScI_3, $Sm(OTf)_3$, $Sc(OTf)_3$, $TiCl_4$, $Ti(OiPr)_4$, $Ti(OiPr)_3Cl$, $Ti(OiPr)_2Cl_2$, $Ti(OiPr)Cl_3$,$Zn(BF_4)_2$, $LiBF_4$, $Mg(BF4)_2$, $ZrCl_4$, $FeCl_2$, $FeCl_3$, $FeBr_2$, $FeBr_3$, FeI_2, FeI_3, Cu(OTf), $Cu(OTf)_2$, 4-toluenesulfonylchoride, benzenesulfonylchlopride, 4-toluenesulfonyl triflate, benzenesulfonyl triflate, methylsulfonyl chloride, methylsulfonic anhydrate, $InCl_3$, $InBr_3$, InI_3, $In(OTf)_3$, $Mg(SO_4)_2$, $NaSO_4$; or combinations thereof. In some embodiments, the Lewis Acid can be TMSOTf. In some embodiments, the following may be used in the method of making the compound of Formula XI-a instead of a Lewis Acid: dicyclohexylcarbodiimide, l-Ethyl-3-(3-dimethylaminopropyl)carbodiimide, benzenesulfonic acid, HC1, 4-toluenesulfonic acid, triflic acid, trifluoroacetic acid, 4-nitrobenzolic acid, methylsoulfonic acid, sulfuric acid, phosphoric acid, HBr, acetic acid, formic acid, HI; or combinations thereof.

[0285] The Lewis Acid can be present in any suitable amount. For example, the Lewis Acid can be present in an amount of at least 0.0 eq. (mol/mol) to the compound of Formula V-a or Formula V-b, such as about 0.0, 0.5, 1.0, 2, 3, 4, 5, 6, 7, 8, 9, or about 10.0 eq. (mol/mol). The Lewis Acid can also be present in an amount of from about 0.0 to about 10.0 eq. (mol/mol) to the compound of Formula V-a or Formula V-b, such as of from about 0.0 to about 3.0 eq. (mol/mol), or of from about 1.0 to about 2.0 eq. (mol/mol). In some embodiments, the Lewis Acid can be present in an amount from about 0.0 to 1.0 eq. (mol/mol) to the compound of

Formula V-a or Formula V-b. In some embodiments, the Lewis Acid can be present in an amount of from about 1.0 to about 2.0 eq. (mol/mol) to the compound of Formula V-a or Formula V-b.

[0286] Any suitable Broenstedt acid can be used in the method of making the compound of Formula XI-a. For example, the Broenstedt acid can be TFA, benzenesulfonic acid, HC1, 4-toluenesulfonic acid, triflic acid, trifluoroacetic acid, 4-nitrobenzoic acid, methylsoulfonic acid, sulfuric acid, phosphoric acid, HBr, acetic acid, formic acid, HI, trifluoromethylsulfonic acid, 4-fluorobenzoic acid, pivalic acid, HBF_4, nitric acid, 4-chloro-benzoic acid, pentafluorophenol, HPF_6, Camphorsulfonic acid; or combinations thereof. In some embodiments, the Broenstedt acid can be TFA.

[0287] The Broenstedt acid can be present in any suitable amount. For example, the Broenstedt acid can be present in an amount of at least about 0.0 eq. (mol/mol) to the compound of Formula V-a or Formula V-b, such as about 0.0, 0.5, 1.0, 2, 3, 4, 5, 6, 7, 8, 9, or about 10.0 eq. (mol/mol). The Broenstedt acid can also be present in an amount of from about 0.0 to about 10.0 eq. (mol/mol) to the compound of Formula V-a or Formula V-b, such as of from about 0.0 to about 3.0 eq. (mol/mol), or of from about 1.0 to about 2.0 eq. (mol/mol). In some embodiments, the Broenstedt acid can be present in an amount from about 0.0 to about 1.0 eq. (mol/mol) to the compound of Formula V-a or Formula V-b. In some embodiments, the Broenstedt acid can be present in an amount of from about 1.0 to about 2.0 eq. (mol/mol) to the compound of Formula V-a or Formula V-b.

[0288] Any suitable solvent can be used in the method of making the compound of Formula XI-a. For example, the solvent can be DCM, THF, MeTHF, Et_20, MeCN, EtCN, toluene, benzene, chlorobenzene, nitrobenzene, flurorbenzene, methanol, ethanol, 2-propanol, propanol, butanol, MTBE, EtOAc, iPrOAc, Me20, (TMS)20, acetone, 2-butanone, chloroform, 1,2-dichloroethane, diglyme, dioxane, acetic acid, formic acid,trifluoroacetic acid, methylisobutylketone, DMAc, DMF, NMP, DMSO; or combinations thereof. In some embodiments, the solvent can be DCM.

[0289] The solvent can be present in any suitable amount. For example, the solvent can be present in an amount of at least 0.0 eq. (mol/mol) to the compound of Formula V-a or Formula V-b, such as about 0.0, 0.1, 0.5, 1.0, 2, 3, 4, 5, 6, 7, 8, 9, or about 10.0 eq. (mol/mol). The solvent can also be present in an amount of from about 0.0 to about 10.0 eq. (mol/mol) to the compound of Formula V-a or Formula V-b, such as of from about 0.0 to about 3.0 eq.

(mol/mol), or of from about 1.0 to about 2.0 eq. (mol/mol). In some embodiments, the solvent can be present in an amount from about 0.1 to about 1.0 eq. (mol/mol) to the compound of Formula V-a or Formula V-b. In some embodiments, the solvent can be present in an amount of from about 1.0 to about 2.0 eq. (mol/mol) to the compound of Formula V-a or Formula V-b.

[0290] The reaction mixture of the method can be at any suitable temperature. For example, the temperature of the reaction mixture can be of from about -150 °C to about 0 °C, or of from about -120 °C to about 0 °C, or of from about -100 °C to about 0 °C, or of from about -100 °C to about -50 °C, or of from about -100 °C to about -70 °C. In some embodiments, the temperature of the reaction mixture can be of from about -120 °C to about -70 °C. In some embodiments, the temperature of the reaction mixture can be of from about -120 °C to about -100 °C. In some embodiments, the temperature of the reaction mixture can be of from about -80 °C to about -30 °C.

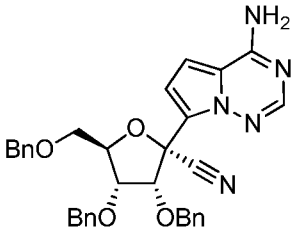
[0291] The reaction mixture of the method can be at any suitable pressure. For example, the reaction mixture can be at atmospheric pressure. The reaction mixture can be also be exposed to any suitable environment, such as atmospheric gasses, or inert gasses such as nitrogen or argon.

[0292] The method of the present invention can provide the compound of Formula XI-a in any suitable yield. For example, the compound of Formula XI-a can be prepared in a yield of at least about 50%, 55, 60, 65, 70, 75, 80, 85, 90 or at least about 95%.

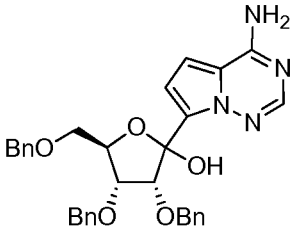
[0293] The method of the present invention can provide the compound of Formula XI-a in any suitable purity. For example, the compound of Formula XI-a can be prepared in a purity of at least about 90, 95, 96, 97, 98 or at least about 99%. In some embodiments, the compound of Formula XI-a can be prepared in at least about 95% purity. In some embodiments, the compound of Formula XI-a can be prepared in at least about 98% purity. In some embodiments, the compound of Formula XI-a can be prepared in at least about 99% purity.

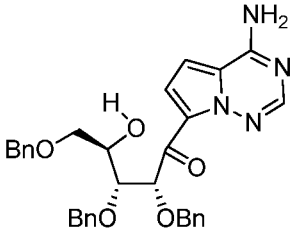
[0294] In some embodiments, the method of the present invention can be performed as a batch mode process. In some embodiments, the method of the present invention can be performed as a flow process.

[0295] In some embodiments, the method includes preparing the compound of Formula Xl-a:



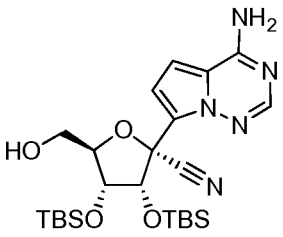
wherein the method includes forming the reaction mixture having TFA, TMSCN, TMSOTf and the compound of Formula Va or Formula V-b:





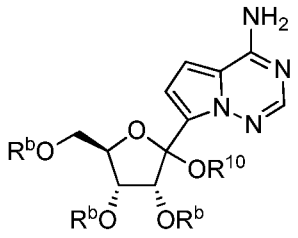
under conditions suitable to prepare the compound of Formula Xl-a. In certain embodiments, the method of preparing Fomula Xl-a is performed between about -120 °C and about 20 °C. In another embodiment, the method of preparing Formula XI-a is performed between about -120 °C and about 0 °C. In another embodiment, the method of preparing Formula Xl-a is performed between about -40 °C and about -20 °C.

[0296] In some embodiments, the present invention provides a method of preparing a compound of Formula Xl-a^2:



Formula (XI-a^2).

wherein the method includes forming a reaction mixture having a cyanating agent, a Lewis Acid, a Broenstedt acid, solvent, and the compound of Formula V-a:



Formula (V-a),

under conditions suitable to prepare the compound of Formula XI-a^2, wherein R^b is independently a hydroxy protecting group, alternatively, two R^b groups on adjacent carbons can be combined to form a -C(R^{19})$_2$ group, R^{10} is H or a silyl group, and R^{19} is H, C_1-C_8 alkyl, phenyl or substituted phenyl.

[0297] Any suitable cyanating agent can be used in the method of making the compound of Formula XI-a^2. For example, the cyanating agent can be TMSCN, TBSCN, TESCN, HCN, KCN, NaCN, 4-toluenesulfonyl cyanide, CuCN, CuCn*LiCl, LiCN, Zn(CN)$_2$, K4[Fe(CN)$_6$], tetrabutylammonium cyanide, tetrmethylammonium cyanide, tetraethylammonium cyanide, tetrabutylammonium cyanide, (including tetraalkylammonium cyanide with alkyl independently being Me, Et, Pr, iPr, Bu, iBu, tertBu, Pent, Hex), tributyltn cyanide, trimethyltin cyanide, triethyltin cyanide, tripropyltin cyanide, (including trialkyltin cyanide cyanide with alkyl independently being Me, Et, Pr, iPr, Bu, iBu, tertBu, Pent, Hex), 2-hydroxy-2-methylpropanenitrile; or combinations thereof. In some embodiments, the cyanating agent can be TMSCN.

[0298] The cyanating agent can be present in any suitable amount. For example, the cyanating agent can be present in an amount of at least 0.1 eq. (mol/mol) to the compound of Formula V-a, such as about 0.1, 0.5, 1.0, 2, 3, 4, 5, 6, 7, 8, 9, or about 10.0 eq. (mol/mol). The cyanating agent can also be present in an amount of from about 0.1 to about 10.0 eq. (mol/mol) to the compound of Formula V-a, such as of from about 0.1 to about 3.0 eq. (mol/mol), or of from about 1.0 to about 2.0 eq. (mol/mol). In some embodiments, the cyanating agent can be present in an amount from about 0.1 to 1.0 eq. (mol/mol) to the compound of Formula V-a. In some embodiments, the cyanating agent can be present in an amount of from about 1.0 to about 2.0 eq. (mol/mol) to the compound of Formula V-a.

[0299] Any suitable Lewis Acid can be used in the method of making the compound of Formula XI-a^2. For example, the Lewis Acid can be TMSOTf, TMSOTf, TBSOTf, TESOTf,BF_3, BF_3-OEt_2, $BC1_3$, BF_3-THF, $MgCl_2$, MgI_2, $MgBr_2$, $MgBr_2$-OEt_2, $ZnCl_2$, $ZnBr_2$, ZnI_2, LiCl, LiBr, LiI, $A1C1_3$, $AlBr_3$, $A1I_3$, $Me_2Si(OTf)_2$, $Et_2Si(OTf)_2$, $Pr_2Si(OTf)_2$,

$iPr_2Si(OTf)2$,$(tBu)_2Si(OTf)2$, $(C_6F_5)_3B$, $MeSiCl_3$, Me_2SiCl_2, $SiCl_4$, TMSC1, TMSI, TMSVr, TBSC1, TBSBr, TBSI, TESC1, TESBr, TESI, $SmCl_3$, $SmBr_3$, Sml_2, Sml_3, Scl_3, $ScBr_3$, Scl_3, $Sm(OTf)_3$, $Sc(OTf)_3$, $TiCl_4$, $Ti(OiPr)_4$, $Ti(OiPr)_3Cl$, $Ti(OiPr)_2Cl_2$, $Ti(OiPr)Cl_3$,$Zn(BF_4)_2$, $LiBF_4$, $Mg(BF4)_2$, $ZrCl_4$, $FeCl_2$, $FeCl_3$, $FeBr_2$, $FeBr_3$, Fel_2, Fel_3, Cu(OTf), $Cu(OTf)_2$, 4-toluenesulfonylchoride, benzenesulfonylchlopride, 4-toluenesulfonyl triflate, benzenesulfonyl triflate, methylsulfonyl chloride, methylsulfonic anhydrate, $InCl_3$, $InBr_3$, Inl_3, $In(OTf)_3$, $Mg(S0_4)_2$, $NaS0_4$; or combinations thereof. In some embodiments, the Lewis Acid can be TMSOTf. In some embodiments, the following may be used in the method of making the compound of Formula XI-a^2 instead of a Lewis Acid: dicyclohexylcarbodiimide, l-Ethyl-3-(3-dimethylaminopropyl)carbodiimide, benzenesulfonic acid, HC1, 4-toluenesulfonic acid, triflic acid, trifluoroacetic acid, 4-nitrobenzolic acid, methylsoulfonic acid, sulfuric acid, phosphoric acid, HBr, acetic acid, formic acid, HI; or combinations thereof.

[0300] The Lewis Acid can be present in any suitable amount. For example, the Lewis Acid can be present in an amount of at least 0.1 eq. (mol/mol) to the compound of Formula V-a, such as about 0.1, 0.5, 1.0, 2, 3, 4, 5, 6, 7, 8, 9, or about 10.0 eq. (mol/mol). The Lewis Acid can also be present in an amount of from about 0.1 to about 10.0 eq. (mol/mol) to the compound of Formula V-a, such as of from about 0.1 to about 3.0 eq. (mol/mol), or of from about 1.0 to about 2.0 eq. (mol/mol). In some embodiments, the Lewis Acid can be present in an amount from about 0.1 to 1.0 eq. (mol/mol) to the compound of Formula V-a. In some embodiments, the Lewis Acid can be present in an amount of from about 1.0 to about 2.0 eq. (mol/mol) to the compound of Formula V-a.

[0301] Any suitable Broenstedt acid can be used in the method of making the compound of Formula XI-a^2. For example, the Broenstedt acid can be TFA, benzenesulfonic acid, HC1, 4-toluenesulfonic acid, triflic acid, trifluoroacetic acid, 4-nitrobenzoic acid, methylsoulfonic acid, sulfuric acid, phosphoric acid, HBr, acetic acid, formic acid, HI, trifluoromethylsulfonic acid, 4-fluorobenzoic acid, pivalic acid, HBF_4, nitric acid, 4-chloro-benzoic acid, pentafluorophenol, HPF_6, Camphorsulfonic acid; or combinations thereof. In some embodiments, the Broenstedt acid can be TFA.

[0302] The Broenstedt acid can be present in any suitable amount. For example, the Broenstedt acid can be present in an amount of at least about 0.1 eq. (mol/mol) to the compound of Formula V-a, such as about 0.1, 0.5, 1.0, 2, 3, 4, 5, 6, 7, 8, 9, or about 10.0 eq. (mol/mol). The Broenstedt acid can also be present in an amount of from about 0.1 to about 10.0 eq. (mol/mol)

to the compound of Formula V-a, such as of from about 0.1 to about 3.0 eq. (mol/mol), or of from about 1.0 to about 2.0 eq. (mol/mol). In some embodiments, the Broenstedt acid can be present in an amount from about 0.1 to about 1.0 eq. (mol/mol) to the compound of Formula V-a. In some embodiments, the Broenstedt acid can be present in an amount of from about 1.0 to about 2.0 eq. (mol/mol) to the compound of Formula V-a.

[0303] Any suitable solvent can be used in the method of making the compound of Formula XI or XI-a2. For example, the solvent can be DCM, THF, MeTHF, Et_20 , MeCN, EtCN, toluene, benzene, chlorobenzene, nitrobenzene, flurorbenzene, methanol, ethanol, 2-propanol, propanol, butanol, MTBE, EtOAc, iPrOAc, Me20, (TMS)20, acetone, 2-butanone, chloroform, 1,2-dichloroethane, diglyme, dioxane, acetic acid, formic acid,trifluoroacetic acid, methylisobutylketone, DMAc, DMF, NMP, DMSO; or combinations thereof. In some embodiments, the solvent can be DCM.

[0304] The solvent can be present in any suitable amount. For example, the solvent can be present in an amount of at least 0.0 eq. (mol/mol) to the compound of Formula V-a, such as about 0.0, 0.1, 0.5, 1.0, 2, 3, 4, 5, 6, 7, 8, 9, or about 10.0 eq. (mol/mol). The solvent can also be present in an amount of from about 0.0 to about 10.0 eq. (mol/mol) to the compound of Formula V-a, such as of from about 0.0 to about 3.0 eq. (mol/mol), or of from about 1.0 to about 2.0 eq. (mol/mol). In some embodiments, the solvent can be present in an amount from about 0.1 to about 1.0 eq. (mol/mol) to the compound of Formula V-a. In some embodiments, the solvent can be present in an amount of from about 1.0 to about 2.0 eq. (mol/mol) to the compound of Formula V-a.

[0305] The reaction mixture of the method can be at any suitable temperature. For example, the temperature of the reaction mixture can be of from about -150 °C to about 0 °C, or of from about -120 °C to about 0 °C, or of from about -100 °C to about 0 °C, or of from about -100 °C to about -50 °C, or of from about -100 °C to about -70 °C. In some embodiments, the temperature of the reaction mixture can be of from about -120 °C to about -70 °C. In some embodiments, the temperature of the reaction mixture can be of from about -120 °C to about -100 °C. In some embodiments, the temperature of the reaction mixture can be of from about -80 °C to about -30 °C.

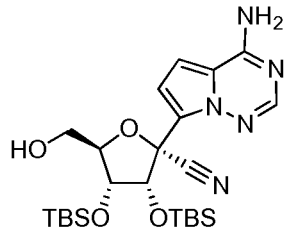
[0306] The reaction mixture of the method can be at any suitable pressure. For example, the reaction mixture can be at atmospheric pressure. The reaction mixture can be also be exposed to any suitable environment, such as atmospheric gasses, or inert gasses such as nitrogen or argon.

[0307] The method of the present invention can provide the compound of Formula Xl-a^2 in any suitable yield. For example, the compound of Formula Xl-a^2 can be prepared in a yield of at least about 50%, 55, 60, 65, 70, 75, 80, 85, 90 or at least about 95%.

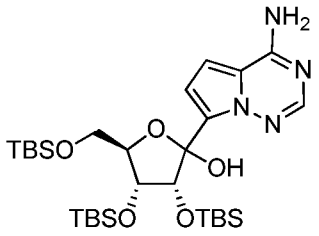
[0308] The method of the present invention can provide the compound of Formula Xl-a^2 in any suitable purity. For example, the compound of Formula Xl-a^2 can be prepared in a purity of at least about 90, 95, 96, 97, 98 or at least about 99%. In some embodiments, the compound of Formula Xl-a^2 can be prepared in at least about 95% purity. In some embodiments, the compound of Formula Xl-a^2 can be prepared in at least about 98% purity. In some embodiments, the compound of Formula Xl-a^2 can be prepared in at least about 99% purity.

[0309] In some embodiments, the method of the present invention can be performed as a batch mode process. In some embodiments, the method of the present invention can be performed as a flow process.

[0310] In some embodiments, the method includes preparing the compound of Formula Xl-a^2:

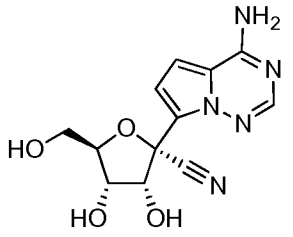


wherein the method includes forming the reaction mixture having TFA, TMSCN, TMSOTf and the compound of Formula Va:



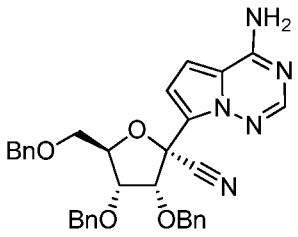
under conditions suitable to prepare the compound of Formula Xl-a^2. In certain embodiments, the method of preparing Fomula Xl-a^2 is performed between about -120 °C and about 20 °C. In another embodiment, the method of preparing Formula XI-a^2 is performed between about -120 °C and about 0 °C. In another embodiment, the method of preparing Formula Xl-a^2 is performed between about -40 °C and about -20 °C.

[0311] In some embodiments, the present invention provides a method of preparing a compound of Formula Xl-b:



Formula (Xl-b).

wherein the method includes forming a reaction mixture having a Lewis Acid, a base, a solvent, a filtering agent, and the compound of Formula Xl-a



Formula (Xl-a)

under conditions suitable to prepare the compound of Formula Xl-b.

[0312] Any suitable Lewis Acid can be used in the method of making the compound of Formula Xl-b. For example, the Lewis Acid can be TMSOTf, TMSOTf, TBSOTf, TESOTf,BF_3, BF_3-OEt_2, BC1$_3$, BF_3-THF, $MgCl_2$, MgI_2, $MgBr_2$, $MgBr_2$-OEt_2, $ZnCl_2$, $ZnBr_2$, ZnI_2, LiCl, LiBr, Lil, AICI$_3$, $AlBr_3$, A П$_3$, $Me_2Si(OTf)_2$, $Et_2Si(OTf)_2$, $Pr_2Si(OTf)_2$, $iPr_2Si(OTf)_2$,$(tBu)_2Si(OTf)_2$, $(C_6F_5)_3B$, $MeSiCl_3$, Me_2SiCl_2, $SiCl_4$, TMSC1, TMSI, TMSVr, TBSC1, TBSBr, TBSI, TESC1, TESBr, TESI, $SmCl_3$, $SmBr_3$, SmI_2, SmI_3, ScI_3, $ScBr_3$, ScI_3, $Sm(OTf)_3$, $Sc(OTf)_3$, $TiCl_4$, $Ti(OiPr)_4$, $Ti(OiPr)_3Cl$, $Ti(OiPr)_2Cl_2$, $Ti(OiPr)Cl_3$,$Zn(BF_4)_2$, L1BF4, $Mg(BF4)_2$, $ZrCl_4$, $FeCl_2$, $FeCl_3$, $FeBr_2$, $FeBr_3$, FeI_2, FeI_3, Cu(OTf), $Cu(OTf)_2$, 4-toluenesulfonylchoride, benzenesulfonylchlopride, 4-toluenesulfonyl triflate, benzenesulfonyl triflate, methylsulfonyl chloride, methylsulfonic anhydrate, Iη(¾ , $InBr_3$, InL, In(OTf)3, $Mg(SO_4)_2$, $NaSO_4$; or combinations thereof. In some embodiments, the Lewis Acid can be BCL_3. In some embodiments, the following may be used in the method of making the compound of Formula Xl-b instead of a Lewis Acid: dicyclohexylcarbodiimide, l-Ethyl-3-(3-dimethylaminopropyl)carbodiimide, benzenesulfonic acid, HC1, 4-toluenesulfonic acid, triflic acid, trifluoroacetic acid, 4-nitrobenzolic acid, methylsoulfonic acid, sulfuric acid, phosphoric acid, HBr, acetic acid, formic acid, HI; or combinations thereof.

[0313] The Lewis Acid can be present in any suitable amount. For example, the Lewis Acid can be present in an amount of at least 0.1 eq. (mol/mol) to the compound of Formula Xl-a, such as about 0.1, 0.5, 1.0, 2, 3, 4, 5, 6, 7, 8, 9, or about 10.0 eq. (mol/mol). The Lewis Acid can also be present in an amount of from about 0.1 to about 10.0 eq. (mol/mol) to the compound of Formula Xl-a, such as of from about 0.1 to about 3.0 eq. (mol/mol), or of from about 1.0 to about 2.0 eq. (mol/mol). In some embodiments, the Lewis Acid can be present in an amount from about 0.1 to 1.0 eq. (mol/mol) to the compound of Formula Xl-a. In some embodiments, the Lewis Acid can be present in an amount of from about 1.0 to about 2.0 eq. (mol/mol) to the compound of Formula Xl-a.

[0314] Any suitable base can be used in the method of making the compound of Formula XI-b. For example, the base can be $(Ci_{-8}Alkyl)_3N$. In some embodiments, the base can be Et_3N.

[0315] The base can be present in any suitable amount. For example, the base can be present in an amount of at least 0.1 eq. (mol/mol) to the compound of Formula Xl-a, such as about 0.1, 0.5, 1.0, 2, 3, 4, 5, 6, 7, 8, 9, or about 10.0 eq. (mol/mol). The base can also be present in an amount of from about 0.1 to about 10.0 eq. (mol/mol) to the compound of Formula Xl-a, such as of from about 0.1 to about 3.0 eq. (mol/mol), or of from about 1.0 to about 2.0 eq. (mol/mol). In some embodiments, the base can be present in an amount from about 0.1 to 1.0 eq. (mol/mol) to the compound of Formula Xl-a. In some embodiments, the base can be present in an amount of from about 1.0 to about 2.0 eq. (mol/mol) to the compound of Formula Xl-a.

[0316] Any suitable solvent can be used in the method of making the compound of Formula XI-b. For example, the solvent can be MeOH, DCM, THF, MeTHF, Et_20, MeCN, EtCN, toluene, benzene, chlorobenzene, nitrobenzene, flurorbenzene, methanol, ethanol, 2-propanol, propanol, butanol, MTBE, EtOAc, iPrOAc, Me20, (TMS)20, acetone, 2-butanone, chloroform, 1,2-dichloroethane, diglyme, dioxane, acetic acid, formic acid,trifluoroacetic acid, methylisobutylketone, DMAc, DMF, NMP, DMSO; or combinations thereof. In some embodiments, the solvent can be MeOH.

[0317] The solvent can be present in any suitable amount. For example, the solvent can be present in an amount of at least 0.1 eq. (mol/mol) to the compound of Formula Xl-a, such as about 0.1, 0.5, 1.0, 2, 3, 4, 5, 6, 7, 8, 9, or about 10.0 eq. (mol/mol). The solvent can also be present in an amount of from about 0.1 to about 10.0 eq. (mol/mol) to the compound of Formula Xl-a, such as of from about 0.1 to about 3.0 eq. (mol/mol), or of from about 1.0 to about 2.0 eq. (mol/mol). In some embodiments, the solvent can be present in an amount from about 0.1 to

about 1.0 eq. (mol/mol) to the compound of Formula XI-a. In some embodiments, the solvent can be present in an amount of from about 1.0 to about 2.0 eq. (mol/mol) to the compound of Formula Xl-a.

[0318] Any suitable filtering agent can be used in the method of making the compound of Formula XI-b. For example, the filtering agent can be silica gel, Celite® or combinations thereof. In some embodiments, the filtering agent can be Celite®.

[0319] The filtering agent can be present in any suitable amount. For example, the filtering agent can be present in an amount of at least 0.1 eq. (mol/mol) to the compound of Formula XI-a, such as about 0.1, 0.5, 1.0, 2, 3, 4, 5, 6, 7, 8, 9, or about 10.0 eq. (mol/mol). The filtering agent can also be present in an amount of from about 0.1 to about 10.0 eq. (mol/mol) to the compound of Formula Xl-a, such as of from about 0.1 to about 3.0 eq. (mol/mol), or of from about 1.0 to about 2.0 eq. (mol/mol). In some embodiments, the filtering agent can be present in an amount from about 0.1 to about 1.0 eq. (mol/mol) to the compound of Formula Xl-a. In some embodiments, the filtering agent can be present in an amount of from about 1.0 to about 2.0 eq. (mol/mol) to the compound of Formula Xl-a.

[0320] The reaction mixture of the method can be at any suitable temperature. For example, the temperature of the reaction mixture can be of from about -50 °C to about 0 °C, or of from about -40 °C to about 0 °C, or of from about -30 °C to about 0 °C, or of from about -20 °C to about 0 °C, or of from about -20 °C to about -10 °C. In some embodiments, the temperature of the reaction mixture can be of from about -30 °C to about 0 °C. In some embodiments, the temperature of the reaction mixture can be of from about -20 °C to about -10 °C. In some embodiments, the temperature of the reaction mixture can be of from about -25 °C to about -15 °C.

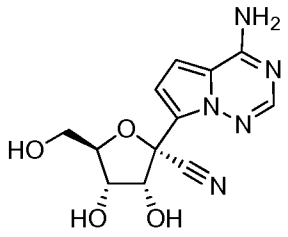
[0321] The reaction mixture of the method can be at any suitable pressure. For example, the reaction mixture can be at atmospheric pressure. The reaction mixture can be also be exposed to any suitable environment, such as atmospheric gasses, or inert gasses such as nitrogen or argon.

[0322] The method of the present invention can provide the compound of Formula XI-b in any suitable yield. For example, the compound of Formula XI-b can be prepared in a yield of at least about 50%, 55, 60, 65, 70, 75, 80, 85, 90 or at least about 95%.

[0323] The method of the present invention can provide the compound of Formula XI-b in any suitable purity. For example, the compound of Formula XI-b can be prepared in a purity of at

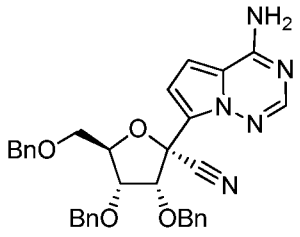
least about 90, 95, 96, 97, 98 or at least about 99%. In some embodiments, the compound of Formula Xl-b can be prepared in at least about 95% purity. In some embodiments, the compound of Formula Xl-b can be prepared in at least about 98% purity. In some embodiments, the compound of Formula Xl-b can be prepared in at least about 99% purity.

[0324] In some embodiments, the present invention provides a method of preparing a compound of Formula Xl-b:



Formula (Xl-b).

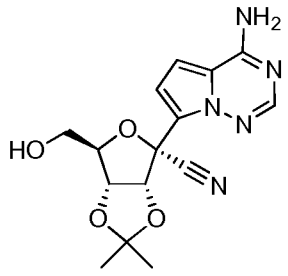
wherein the method includes forming a reaction mixture having BCL_3, Et_2N, MeOH, Celite®, and the compound of Formula Xl-a



Formula (Xl-a)

under conditions suitable to prepare the compound of Formula XI-b.In certain embodiments, the method of preparing Fomula Xl-b is performed between about -30 °C and about 0 °C. In another embodment, the method of preparing Formula XI is performed between about -20 °C and about 0 °C.

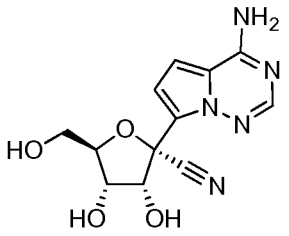
[0325] In some embodiments, the present invention provides a method of preparing a compound of Formula XI-c:



Formula (XI-c).

wherein the method includes forming a reaction mixture having a solvent, a reagent, an acid,

and the compound of Formula Xl-b



Formula (Xl-b)

under conditions suitable to prepare the compound of Formula XI-c.

[0326] Any suitable solvent can be used in the method of making the compound of Formula XI-c. For example, the solvent can be acetone, MeOH, DCM, THF, MeTHF, Et_20 , MeCN, EtCN, toluene, benzene, chlorobenzene, nitrobenzene, flurorbenzene, methanol, ethanol, 2-propanol, propanol, butanol, MTBE, EtOAc, iPrOAc, Me20, (TMS)20, acetone, 2-butanone, chloroform, 1,2-dichloroethane, diglyme, dioxane, acetic acid, formic acid,trifluoroacetic acid, methylisobutylketone, DMAc, DMF, NMP, DMSO; or combinations thereof. In some embodiments, the solvent can be acetone.

[0327] The solvent can be present in any suitable amount. For example, the solvent can be present in an amount of at least 0.1 eq. (mol/mol) to the compound of Formula Xl-b, such as about 0.1, 0.5, 1.0, 2, 3, 4, 5, 6, 7, 8, 9, or about 10.0 eq. (mol/mol). The solvent can also be present in an amount of from about 0.1 to about 10.0 eq. (mol/mol) to the compound of Formula Xl-b, such as of from about 0.1 to about 3.0 eq. (mol/mol), or of from about 1.0 to about 2.0 eq. (mol/mol). In some embodiments, the solvent can be present in an amount from about 0.1 to 1.0 eq. (mol/mol) to the compound of Formula Xl-b. In some embodiments, the solvent can be present in an amount of from about 1.0 to about 2.0 eq. (mol/mol) to the compound of Formula Xl-b.

[0328] Any suitable reagent can be used in the method of making the compound of Formula XI-c. For example, the reagent can be 2,2-dimethoxypropane, acetone, 2-methoxypropene, 2,2-diethylpropane, 2-ethoxypropene, 2,2-dimethyl-l,3-dioxolane, 2,2-dimethyl-l,3-dioxane; or combinations thereof. In some embodiments, the reagent can be 2,2-dimethoxypropane.

[0329] The reagent can be present in any suitable amount. For example, the reagent can be present in an amount of at least 0.1 eq. (mol/mol) to the compound of Formula Xl-b, such as about 0.1, 0.5, 1.0, 2, 3, 4, 5, 6, 7, 8, 9, or about 10.0 eq. (mol/mol). The reagent can also be present in an amount of from about 0.1 to about 10.0 eq. (mol/mol) to the compound of Formula

XI-b, such as of from about 0.1 to about 3.0 eq. (mol/mol), or of from about 1.0 to about 2.0 eq. (mol/mol). In some embodiments, the reagent can be present in an amount from about 0.1 to 1.0 eq. (mol/mol) to the compound of Formula XI-b. In some embodiments, the reagent can be present in an amount of from about 1.0 to about 2.0 eq. (mol/mol) to the compound of Formula XI-b.

[0330] Any suitable acid can be used in the method of making the compound of Formula XI-c. For example, the acid can be TMSOTf, TMSOTf, TBSOTf, TESOTf,BF_3, BF_3-OEt_2, $BC1_3$, BF_3-THF, $MgCl_2$, MgI_2, $MgBr_2$, $MgBr_2$-OEt_2, $ZnCl_2$, $ZnBr_2$, ZnI_2, LiCl, LiBr, LiI, $A1C1_3$, $AlBr_3$, $A1I_3$, $Me_2Si(OTf)_2$, $Et_2Si(OTf)_2$, $Pr_2Si(OTf)_2$, $iPr_2Si(OTf)_2$,$(tBu)_2Si(OTf)_2$, $(C_6F_5)_3B$, $MeSiCl_3$, Me_2SiCl_2, $SiCl_4$, TMSC1, TMSI, TMSVr, TBSC1, TBSBr, TBSI, TESC1, TESBr, TESI, $SmCl_3$, $SmBr_3$, SmI_2, SmI_3, ScI_3, $ScBr_3$, ScI_3, $Sm(OTf)_3$, $Sc(OTf)_3$, $TiCl_4$, $Ti(OiPr)_4$, $Ti(OiPr)_3Cl$, $Ti(OiPr)_2Cl_2$, $Ti(OiPr)Cl_3$,$Zn(BF_4)_2$, $L1BF_4$, $Mg(BF4)_2$, $ZrCl_4$, $FeCl_2$, $FeCl_3$, $FeBr_2$, $FeBr_3$, FeI_2, FeI_3, Cu(OTf), $Cu(OTf)_2$, 4-toluenesulfonylchoride, benzenesulfonylchlopride, 4-toluenesulfonyl triflate, benzenesulfonyl triflate, methylsulfonyl chloride, methylsulfonic anhydrate, $InCl_3$, $InBr_3$, InI_3, $In(OTf)_3$, $Mg(S0_4)_2$, $NaS0_4$, dicyclohexylcarbodiimide, l-Ethyl-3-(3-dimethylaminopropyl)carbodiimide, benzenesulfonic acid, HC1, 4-toluenesulfonic acid, triflic acid, trifluoroacetic acid, 4-nitrobenzolic acid, methylsoulfonic acid, sulfuric acid, phosphoric acid, HBr, acetic acid, formic acid, HI, TFA, benzenesulfonic acid, HC1, 4-toluenesulfonic acid, triflic acid, trifluoroacetic acid, 4-nitrobenzoic acid, methylsoulfonic acid, sulfuric acid, phosphoric acid, HBr, acetic acid, formic acid, HI, trifluoromethylsulfonic acid, 4-fluorobenzoic acid, pivalic acid, HBF_4, nitric acid, 4-chloro-benzoic acid, pentafluorophenol, HPF_6, Camphorsulfonic acid; or combinations thereof. In some embodiments, the acid can be sulfuric acid.

[0331] The acid can be present in any suitable amount. For example, the acid can be present in an amount of at least 0.0 eq. (mol/mol) to the compound of Formula XI-b, such as about 0.0, 0.5, 1.0, 2, 3, 4, 5, 6, 7, 8, 9, or about 10.0 eq. (mol/mol). The acid can also be present in an amount of from about 0.0 to about 10.0 eq. (mol/mol) to the compound of Formula XI-b, such as of from about 0.0 to about 3.0 eq. (mol/mol), or of from about 1.0 to about 2.0 eq. (mol/mol). In some embodiments, the acid can be present in an amount from about 0.0 to 1.0 eq. (mol/mol) to the compound of Formula XI-b. In some embodiments, the acid can be present in an amount of from about 1.0 to about 2.0 eq. (mol/mol) to the compound of Formula XI-b.

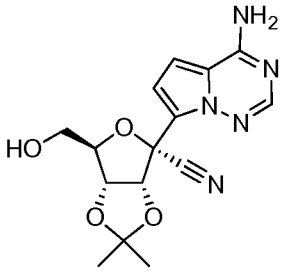
[0332] The reaction mixture of the method can be at any suitable temperature. For example, the temperature of the reaction mixture can be of from about -50 °C to about 50 °C, or of from about 0 °C to about 50 °C, or of from about 0 °C to about 40 °C, or of from about 0 °C to about 30 °C, or of from about 0 °C to about 25 °C. In some embodiments, the temperature of the reaction mixture can be of from about 0 °C to about 23 °C. In some embodiments, the temperature of the reaction mixture can be of from about 0 °C to about 25 °C. In some embodiments, the temperature of the reaction mixture can be of from about 0 °C to about 30 °C.

[0333] The reaction mixture of the method can be at any suitable pressure. For example, the reaction mixture can be at atmospheric pressure. The reaction mixture can be also be exposed to any suitable environment, such as atmospheric gasses, or inert gasses such as nitrogen or argon.

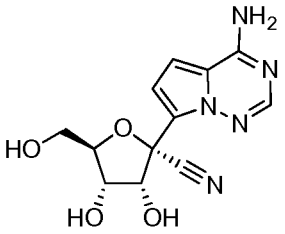
[0334] The method of the present invention can provide the compound of Formula XI-c in any suitable yield. For example, the compound of Formula XI-c can be prepared in a yield of at least about 50%, 55, 60, 65, 70, 75, 80, 85, 90 or at least about 95%.

[0335] The method of the present invention can provide the compound of Formula XI-c in any suitable purity. For example, the compound of Formula XI-c can be prepared in a purity of at least about 90, 95, 96, 97, 98 or at least about 99%. In some embodiments, the compound of Formula XI-b can be prepared in at least about 95% purity. In some embodiments, the compound of Formula XI-b can be prepared in at least about 98% purity. In some embodiments, the compound of Formula XI-b can be prepared in at least about 99% purity.

[0336] In some embodiments, the method includes preparing the compound of Formula XI-c:



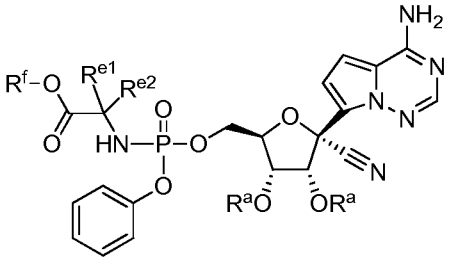
wherein the method includes forming a reaction mixture having acetone, 2,2-dimethoxypropane, sulfuric acid, and the compound of Formula Xl-b



under conditions suitable to prepare the compound of Formula XI-c. In certain embodiments, the method of preparing Fomula XI-c is performed between about 0 °C and about 30 °C. In another embodment, the method of preparing Formula XI is performed between about 10 °C and about 30 C.

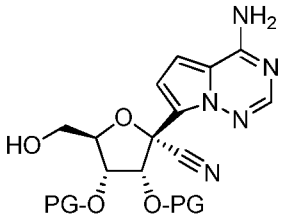
C. Addition of Prodrug Moiety

[0337] The present invention also provides a method of coupling a prodrug moiety to a nucleoside to provide a compound of the present invention. In some embodiments, the present invention provides a method of preparing a compound of Formula VIII:



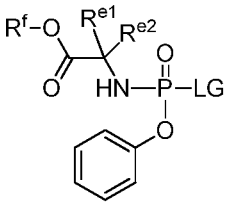
Formula (VIII)

wherein the method includes forming a reaction mixture including a coupling agent, a non-nucleophilic base, a compound of Formula IX:



Formula (IX),

and a compound of Formula X:



Formula (X),

under conditions suitable to form the compound of Formula VIII, wherein each R^a is H or PG, each PG group is a hydroxy protecting group, or both PG groups are combined to form $-C(R^{19})_2-$, R^{e1} and R^{e2} are each independently H, Ci-C_6 alkyl or benzyl, R^f is H, Ci-Cs alkyl, benzyl, C3-C_6 cycloalkyl, or -CH2-C3-C6 cycloalkyl, R^{19} is H, Ci-Cs alkyl, phenyl or substituted phenyl, and LG is a leaving group.

[0338] Any suitable coupling agent can be used in the method of making the compound of Formula VIII, as described above for the method of making the compound of Formula V. In some embodiments, the coupling agent can be a magnesium coupling agent. In some embodiments, the coupling agent can be $MgCl_2$, iPrMgCl, tBuMgCl, PhMgCl, or combinations thereof. In some embodiments, the coupling agent can be $MgCl_2$.

[0339] Any suitable non-nucleophilic base can be used in the method of making the compound of Formula VIII. Representative non-nucleophilic bases include, but are not limited to, triethylamine, diisopropylethyl amine, N,N-diethylaniline, pyridine, 2,6-lutidine, 2,4,6-collidine, 4-dimethylaminopyridine, and quinuclidine. In some embodiments, the non-nucleophilic base can be di-isopropyl ethyl amine (DIPEA).

[0340] The protecting groups PG can be any suitable hydroxy protecting groups, as described above for the method of making the compound of Formula V. Exemplary protecting groups PG can be benzyl, or the PG groups can be combined to form an acetonide. Exemplary acetonides include, but are not limited to acetonide and benzylidene acetal. In some embodiments, the hydroxy protecting groups of hydroxy groups on adjacent carbons can be combined to form acetonide. In some embodiments, the PG groups are combined to form $-C(R^{19})_2-$. In some embodiments, each R^a is the protecting group PG where the PG groups are combined to form $-C(Me)_2-$.

[0341] When the R^e group is Ci-Cs alkyl, each R^e can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-buty, t-butyl, pentyl, iso-pentyl, neo-pentyl, hexyl, isohexyl, neohexyl, septyl or octyl. In some embodiments, each R^e group can be methyl.

[0342] When the R^f group is C_1-C_8 alkyl, R^f can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-buty, t-butyl, pentyl, iso-pentyl, neo-pentyl, hexyl, isohexyl, neohexyl, septyl or octyl. In some embodiments, the R^f group can be methyl, ethyl, isopropyl, t-butyl, or iso-hexyl. When the R^f group is C3-C6 cycloalkyl, R^f can be cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. In some embodiments, R^f can be cyclobutyl, cyclopentyl or cyclohexyl.

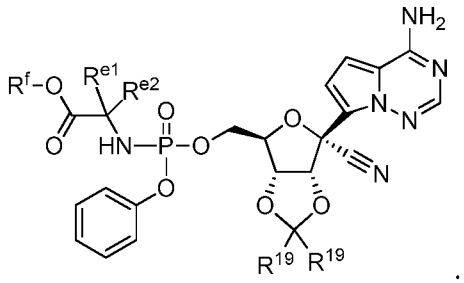
[0343] When the R^{19} group is C_1-C_8 alkyl, R^{19} can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-buty, t-butyl, pentyl, iso-pentyl, neo-pentyl, hexyl, isohexyl, neohexyl, septyl or octyl. In some embodiments, the R^{19} group can be methyl.

[0344] The leaving group can be any suitable leaving group. Suitable leaving groups LG include, but are not limited to, chloride, bromide, mesylate, tosylate, triflate, 4-nitrobenzenesulfonate, 4-chlorobenzenesulfonate, 4-nitrophenoxy, pentafluorophenoxy, etc. In some embodiments, the leaving group LG can be 4-nitrophenoxy or pentafluorophenoxy. In some embodiments, the leaving group LG can be 4-nitrophenoxy.

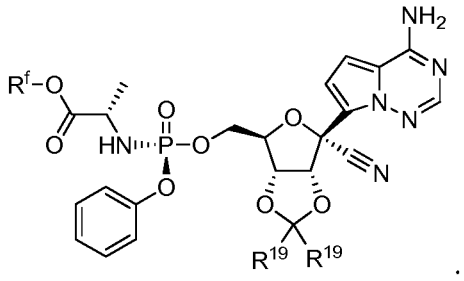
[0345] In some embodiments, each R^a is PG where the PG groups are combined to form $-C(R^{19})_2-$, R^f is C_1-Cs alkyl, R^{19} is Ci-Cs alkyl, and the leaving group LG is 4-nitrophenoxy or pentafluorophenoxy.

[0346] In some embodiments, the coupling agent is $MgCl_2$, and the non-nucleophilic base is di-isopropyl ethyl amine.

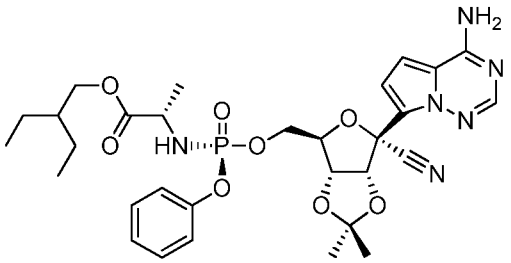
[0347] In some embodiments, the compound of Formula VIII can be



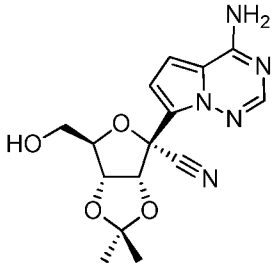
In some embodiments, the compound of Formula VIII can be



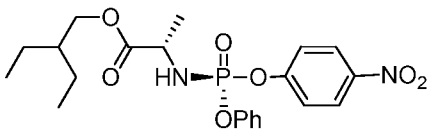
In some embodiments, the compound of Formula VIII can be



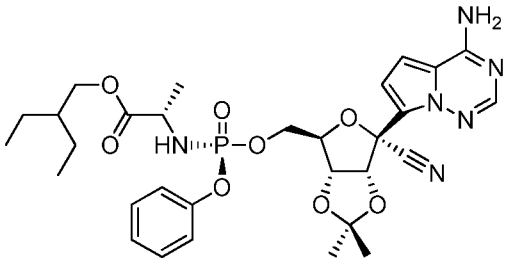
[0348] In some embodiments, the method of making the compound Formula VIII includes forming the reaction mixture including $MgCl_2$, DIPEA, the compound of Formula IX:



and the compound of Formula X:



under conditions suitable to form the compound of Formula VIII:



[0349] When the R^a groups of the compound of Formula VIII are the hydroxy protecting groups PG, the method can include the additional step of removing the protecting groups to form the compound of Formula VIII where each R^a is H. In some embodiments, the method of preparing the compound of Formula VIII includes forming a second reaction mixture including a deprotection agent and the compound Formula VIII wherein each R^a group is the protecting group PG, under suitable conditions to form the compound of Formula VIII where each R^a is H. The deprotection agent can be any suitable agent to remove the protecting groups PG such as hydrogen and a hydrogenation catalyst, or acid. For example, if the protecting group PG is benzyl, the deprotection agent can be hydrogen and platinum on carbon. Alternatively, when the

protecting group PG is an acetonide, the deprotection agent can be an acid. Representative acids include, but are not limited to, acetic acid, glacial acetic acid, trifluoroacetic acid (TFA), hydrochloric acid, concentrated hydrochloric acid, and others. In some embodiments, the method of preparing the compound of Formula VIII includes forming a second reaction mixture including an acid and the compound Formula VIII wherein the R^a groups are combined to form $-C(R^{19})_2-$, under suitable conditions to form the compound of Formula VIII where each R^a is H. In some embodiments, the acid can be hydrochloric acid.

[0350] Any suitable solvent can be used in the method of the present invention. Representative solvents include, but are not limited to, pentane, pentanes, hexane, hexanes, heptane, heptanes, petroleum ether, cyclopentanes, cyclohexanes, benzene, toluene, xylene, trifluoromethylbenzene, halobenzenes such as chlorobenzene, fluorobenzene, dichlorobenzene and difluorobenzene, methylene chloride, chloroform, acetone, ethyl acetate, diethyl ether, tetrahydrofuran, acetonitrile, or combinations thereof. In some embodiments, the solvent can be acetonitrile.

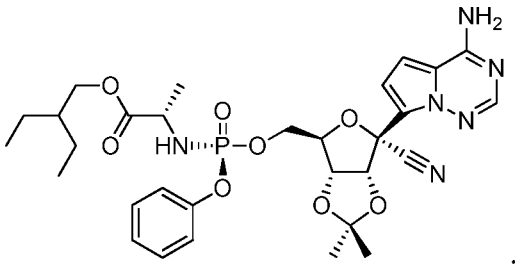
[0351] The reaction mixture of the method can be at any suitable temperature. For example, the temperature of the reaction mixture can be of from about -78 °C to about 100 °C, or of from about -50 °C to about 100 °C, or of from about -25 °C to about 50 °C, or of from about -10 °C to about 25 °C, or of from about 0 °C to about 20 °C. In some embodiments, the temperature of the reaction mixture can be of from about 0 °C to about 20 °C.

[0352] The reaction mixture of the method can be at any suitable pressure. For example, the reaction mixture can be at atmospheric pressure. The reaction mixture can be also be exposed to any suitable environment, such as atmospheric gasses, or inert gasses such as nitrogen or argon.

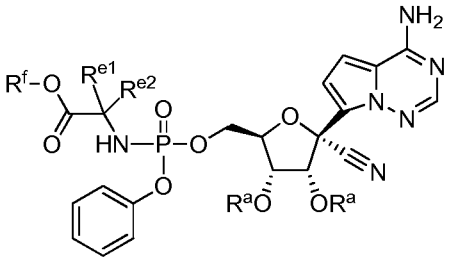
[0353] The method of the present invention can provide the compound of Formula VIII in any suitable yield. For example, the compound of Formula VIII can be prepared in a yield of at least about 50%, 55, 60, 65, 70, 75, 80, 85, 90 or at least about 95%.

[0354] The method of the present invention can provide the compound of Formula VIII in any suitable purity. For example, the compound of Formula VIII can be prepared in a purity of at least about 90, 95, 96, 97, 98 or at least about 99%. In some embodiments, the compound of Formula VIII can be prepared in at least 95% purity. In some embodiments, the compound of Formula VIII can be prepared in at least 98% purity. In some embodiments, the compound of Formula VIII can be prepared in at least 99% purity.

[0355] In some embodiments, the present invention provides the compound

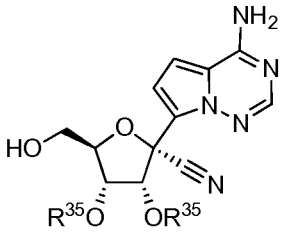


[0356] In some embodiments, the present invention provides a method of preparing a compound of Formula VIII:



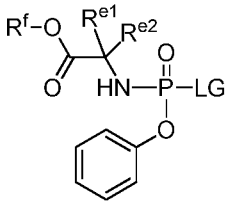
Formula (VIII)

wherein the method includes forming a reaction mixture including a coupling agent, a non-nucleophilic base, a compound of Formula IX-a:



Formula (IX-a),

and a compound of Formula X:



Formula (X),

under conditions suitable to form the compound of Formula VIII, wherein R^a is independently H or a hydroxy protecting group, or two R^a on adjacent carbons can be combined to form a -$C(R^{19})_2$- group, R^{35} is independently H or a hydroxy protecting group, or two R^{35} on adjacent carbons can be combined to form a -$C(R^{19})_2$- group, R^{19} is H or C_1-C_8 alkyl, R^{e1} and R^{e2} are each independently H, Ci-C_6 alkyl or benzyl, R^f is H, C_1-C_8 alkyl, benzyl, $_{C3-C6}$ cycloalkyl, or -

CH2-C3-C6 cycloalkyl, R^{19} is H, Ci-Cs alkyl, phenyl or substituted phenyl, and LG is a leaving group.

[0357] Any suitable coupling agent can be used in the method of making the compound of Formula VIII, as described above for the method of making the compound of Formula V. In some embodiments, the coupling agent can be a magnesium coupling agent. In some embodiments, the coupling agent can be MgCl2, iPrMgCl, tBuMgCl, PhMgCl, or combinations thereof. In some embodiments, the coupling agent can be $MgCl_2$.

[0358] Any suitable non-nucleophilic base can be used in the method of making the compound of Formula VIII. Representative non-nucleophilic bases include, but are not limited to, triethylamine, diisopropylethyl amine, N,N-diethylaniline, pyridine, 2,6-lutidine, 2,4,6-collidine, 4-dimethylaminopyridine, and quinuclidine. In some embodiments, the non-nucleophilic base can be di-isopropyl ethyl amine (DIPEA).

[0359] The hydroxy protecting groups, as described above for the method of making the compound of Formula V. Exemplary hydroxy protecting group can be benzyl, $S1R_3$, wherein each R group can be hydrogen, alkyl, alkenyl, cycloalkyl, phenyl, or other silicon containing groups, or the PG groups can be combined to form an acetonide. Exemplary silanes include, but are not limited to tert-butyldimethylsilyl (TBS). Exemplary acetonides include, but are not limited to acetonide and benzylidene acetal. In some embodiments, the hydroxy protecting groups of hydroxy groups on adjacent carbons can be combined to form acetonide. In some embodiments, the PG groups are combined to form $-C(R^{19})_2-$. In some embodiments, each R^a is the protecting group PG where the PG groups are combined to form $-C(Me)_2-$. In other embodiments, PG is a $S1R_3$. In other embodiments, PG is tert-butyldimethylsilyl (TBS).

[0360] When the R^e group is Ci-Cs alkyl, each R^e can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-buty, t-butyl, pentyl, iso-pentyl, neo-pentyl, hexyl, isohexyl, neohexyl, septyl or octyl. In some embodiments, each R^e group can be methyl.

[0361] When the R^f group is C_1-C_8 alkyl, R^f can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-buty, t-butyl, pentyl, iso-pentyl, neo-pentyl, hexyl, isohexyl, neohexyl, septyl or octyl. In some embodiments, the R^f group can be methyl, ethyl, isopropyl, t-butyl, or iso-hexyl. When the R^f group is **C3-C6** cycloalkyl, R^f can be cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. In some embodiments, R^f can be cyclobutyl, cyclopentyl or cyclohexyl.

[0362] When the R^{19} group is C_1-C_8 alkyl, R^{19} can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-buty, t-butyl, pentyl, iso-pentyl, neo-pentyl, hexyl, isohexyl, neohexyl, septyl or octyl. In some embodiments, the R^{19} group can be methyl.

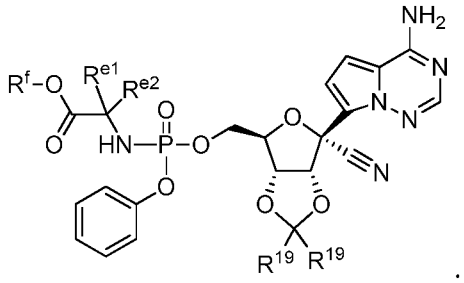
[0363] When the R^{35} group is a hydroxyl protecting group, R^{35} can be any example protecting group described in *Protective Groups in Organic Chemistry*, Peter G. M. Wuts and Theodora W. Greene, 4th Ed., 2006. In some embodiments, the R^{35} group can be benzyl. In some embodiments, the R^{35} group can be TBS.

[0364] The leaving group can be any suitable leaving group. Suitable leaving groups LG include, but are not limited to, chloride, bromide, mesylate, tosylate, triflate, 4-nitrobenzenesulfonate, 4-chlorobenzenesulfonate, 4-nitrophenoxy, pentafluorophenoxy, etc. In some embodiments, the leaving group LG can be 4-nitrophenoxy or pentafluorophenoxy. In some embodiments, the leaving group LG can be 4-nitrophenoxy.

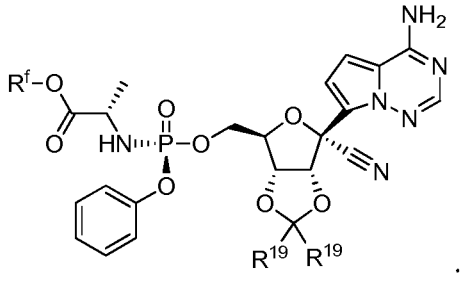
[0365] In some embodiments, each R^a is PG where the PG groups are combined to form $-C(R^{19})_2-$, R^f is C_1-C_8 alkyl, R^{19} is Ci-Cs alkyl, and the leaving group LG is 4-nitrophenoxy or pentafluorophenoxy.

[0366] In some embodiments, the coupling agent is $MgCl_2$, and the non-nucleophilic base is di-isopropyl ethyl amine.

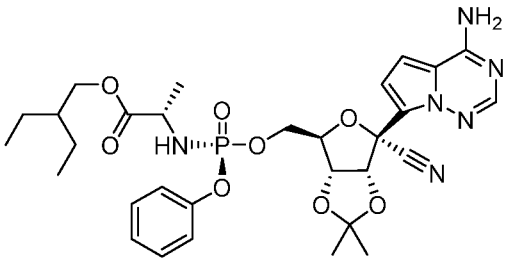
[0367] In some embodiments, the compound of Formula VIII can be



In some embodiments, the compound of Formula VIII can be



In some embodiments, the compound of Formula VIII can be



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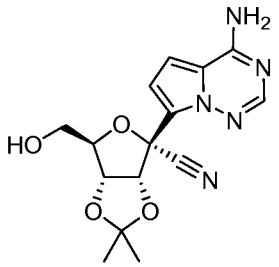
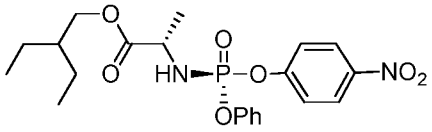
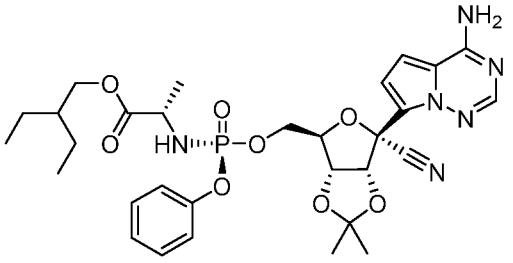
[0368] In some embodiments, the method of making the compound Formula VIII includes forming the reaction mixture including $MgCl_2$, DIPEA, the compound of Formula IX:



and the compound of Formula X:



under conditions suitable to form the compound of Formula VIII:



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[0369] When the R^a groups of the compound of Formula VIII are the hydroxy protecting groups PG, the method can include the additional step of removing the protecting groups to form the compound of Formula VIII where each R^a is H. In some embodiments, the method of preparing the compound of Formula VIII includes forming a second reaction mixture including a deprotection agent and the compound Formula VIII wherein each R^a group is the protecting group PG, under suitable conditions to form the compound of Formula VIII where each R^a is H. The deprotection agent can be any suitable agent to remove the protecting groups PG such as

hydrogen and a hydrogenation catalyst, or acid. For example, if the protecting group PG is benzyl, the deprotection agent can be hydrogen and platinum on carbon. Alternatively, when the protecting group PG is an acetonide, the deprotection agent can be an acid. Representative acids include, but are not limited to, acetic acid, glacial acetic acid, trifluoroacetic acid (TFA), hydrochloric acid, concentrated hydrochloric acid, formic acids, toluenesulfonic acid, sulfuric acid, and others. Additional representative acids include, but are not limited to those found in Greene, T. W.; Wuts, P. G. M. *Protective Groups In Organic Synthesis, 4th Ed.,* John Wiley & Sons: New York, **2006.** In some embodiments, the method of preparing the compound of Formula VIII includes forming a second reaction mixture including an acid and the compound Formula VIII wherein the R^a groups are combined to form $-C(R^{19})_2-$, under suitable conditions to form the compound of Formula VIII where each R^a is H. In some embodiments, the acid can be hydrochloric acid. Alternatively, when the protecting group PG is $S1R_3$, the deprotection agent can be TBAF, pyridine HF, HC1, TsOH, camphor sulfonic acid, AcCl in MeOH, BF^3 OEt^2, TFA, AcOG, Formic Acid, HBr, F, HF, Et_3N-HF, KF-H_20 , KHF_2, NaF, LiF, LiCl, LiBr, Lil, and others.

[0370] Any suitable solvent can be used in the method of the present invention. Representative solvents include, but are not limited to, pentane, pentanes, hexane, hexanes, heptane, heptanes, petroleum ether, cyclopentanes, cyclohexanes, benzene, toluene, xylene, trifluoromethylbenzene, halobenzenes such as chlorobenzene, fluorobenzene, dichlorobenzene and difluorobenzene, methylene chloride, chloroform, acetone, ethyl acetate, diethyl ether, tetrahydrofuran, acetonitrile, or combinations thereof. In some embodiments, the solvent can be acetonitrile. In some embodiments, the solvent can be MeCN. In some embodiments, the solvent can be tetrahydrofuran.

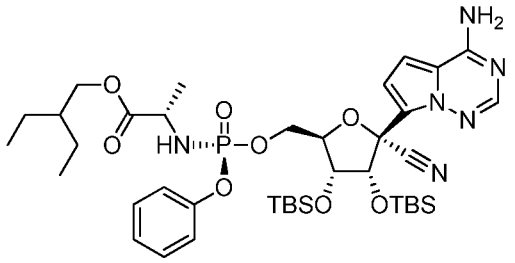
[0371] The reaction mixture of the method can be at any suitable temperature. For example, the temperature of the reaction mixture can be of from about -78 °C to about 100 °C, or of from about -50 °C to about 100 °C, or of from about -25 °C to about 50 °C, or of from about -10 °C to about 25 °C, or of from about 0 °C to about 20 °C. In some embodiments, the temperature of the reaction mixture can be of from about 0 °C to about 20 °C.

[0372] The reaction mixture of the method can be at any suitable pressure. For example, the reaction mixture can be at atmospheric pressure. The reaction mixture can be also be exposed to any suitable environment, such as atmospheric gasses, or inert gasses such as nitrogen or argon.

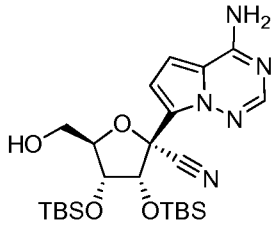
[0373] The method of the present invention can provide the compound of Formula VIII in any suitable yield. For example, the compound of Formula VIII can be prepared in a yield of at least about 50%, 55, 60, 65, 70, 75, 80, 85, 90 or at least about 95%.

[0374] The method of the present invention can provide the compound of Formula VIII in any suitable purity. For example, the compound of Formula VIII can be prepared in a purity of at least about 90, 95, 96, 97, 98 or at least about 99%. In some embodiments, the compound of Formula VIII can be prepared in at least about 95% purity. In some embodiments, the compound of Formula VIII can be prepared in at least about 98% purity. In some embodiments, the compound of Formula VIII can be prepared in at least about 99% purity.

In some embodiments, the compound of Formula VIII can be

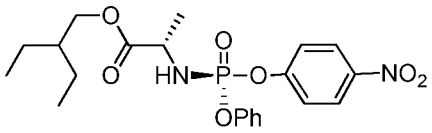


[0375] In some embodiments, the method of making the compound Formula VIII includes forming the reaction mixture including $MgCl_2$, DIPEA, the compound of Formula IX-a^2:

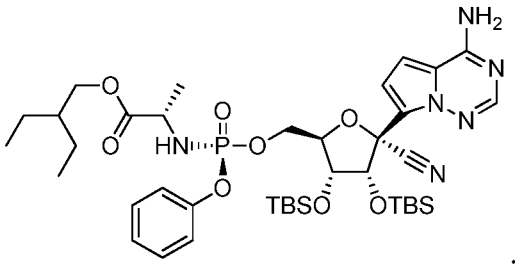


(Formula IX-a^2)

and the compound of Formula X:



under conditions suitable to form the compound of Formula VIII:



[0376] The method can include the additional step of removing the protecting groups to form the compound of Formula VIII where each TBS is H.

[0377] The reaction mixture of the method can be at any suitable temperature. For example, the temperature of the reaction mixture can be of from about -78 °C to about 100 °C, or of from about -50 °C to about 100 °C, or of from about -25 °C to about 50 °C, or of from about -10 °C to about 25 °C, or of from about 0 °C to about 20 °C. In some embodiments, the temperature of the reaction mixture can be of from about 0 °C to about 20 °C.

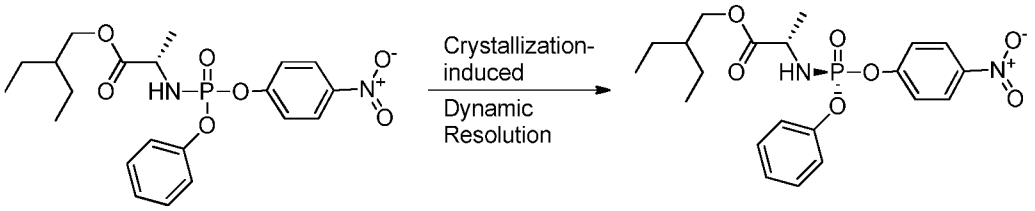
[0378] The reaction mixture of the method can be at any suitable pressure. For example, the reaction mixture can be at atmospheric pressure. The reaction mixture can be also be exposed to any suitable environment, such as atmospheric gasses, or inert gasses such as nitrogen or argon.

[0379] The method of the present invention can provide the compound of Formula VIII in any suitable yield. For example, the compound of Formula VIII can be prepared in a yield of at least about 50%, 55, 60, 65, 70, 75, 80, 85, 90 or at least about 95%.

[0380] The method of the present invention can provide the compound of Formula VIII in any suitable purity. For example, the compound of Formula VIII can be prepared in a purity of at least about 90, 95, 96, 97, 98 or at least about 99%. In some embodiments, the compound of Formula VIII can be prepared in at least about 95% purity. In some embodiments, the compound of Formula VIII can be prepared in at least about 98% purity. In some embodiments, the compound of Formula VIII can be prepared in at least about 99% purity.

D. Preparation of Formula X-b by Crystallization-induced Dynamic Resolution

[0381] In one embodiment, there is provided a method for the crystallization-induced dynamic resolution of (2S)-2-ethylbutyl 2-(((4-nitrophenoxy)(phenoxy)phosphoryl)amino)propanoate (Formula X-a):



Formula X-a
(mixture of diastereomers)

Formula X-b
(diastereomerically pure)

to provide (S)-2-ethylbutyl 2-(((S)-(4-nitrophenoxy)(phenoxy)phosphoryl)amino)propanoate (Formula X-b). The method comprises subjecting a solution comprising: a) a suitable solvent; b) a suitable base; c) (2S)-2-ethylbutyl 2-(((4-nitrophenoxy)(phenoxy)phosphoryl)amino) propanoate; and, optionally, d) one or more seed crystals of (S)-2-ethylbutyl 2-(((S)-(4-nitrophenoxy)(phenoxy)phosphoryl)amino)propanoate, to conditions that provide for the epimerization of the phosphorus center, under conditions that also provide selective crystallization of (S)-2-ethylbutyl 2-(((S)-(4-nitrophenoxy)(phenoxy)phosphoryl)amino) propanoate.

[0382] The crystallization can be carried out in any suitable solvent. For example, it can be carried out in an aprotic organic solvent, or in a mixture thereof. For example, the aprotic organic solvent may comprise ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, diethyl ether, diisopropyl ether, tetrahydrofuran, dichloromethane, acetone, methyl ethyl ketone, methyl ferf-butylether, toluene, or acetonitrile, or a mixture thereof. In one embodiment, the solvent comprises acetonitrile.

[0383] The resolution can be carried out in the presence of any suitable base. For example, the resolution can be carried out in the presence of a base selected from 1,5-diazobicyclo [4.3.0]non-5-ene (DBN), l,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 7-methyl-l,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), triethylamine (Et_3N), Hunig's Base (iP^NEt), tetramethylguanidine, a Verkade base (e.g., 2,8,9-triisopropyl-2,5,8,9-tetraaza-l-phosphabicyclo[3.3.3]undecane, and 2,8,9-triisobutyl-2,5,8,9-tetraaza-l-phosphabicyclo [3.3.3]undecane), a metal carbonate (e.g., M_xC0_3), a metal phenoxide (M^+ OPh), and PhOTMS in combination with a fluoride ion source (e.g., R_4N^+ ^-F, TASF (tris(dimethylamino) sulfonium difluorotrimethylsilicate), or TBAT (tetrabutylammonium triphenyldifluorosilicate), and mixtures thereof, wherein each M is a suitable metal such as an alkali metal or an alkaline

earth metal, and each R is, for example, a $(C_1\text{-}Ce)$ alkyl. In one specific embodiment, the base is DBU.

[0384] The resolution can also be carried out at any suitable temperature, for example, a temperature in the range of from about 0 °C to about 50 °C. In one specific embodiment, the resolution is carried out at a temperature of about 0 °C.

[0385] In one specific embodiment, the resolution is carried out in the presence of phenol.

[0386] The percentage of (S)-2-ethylbutyl 2-(((S)-(4-nitrophenoxy)(phenoxy)phosphoryl) amino)propanoate the starting diastereomeric mixture can be anywhere in the range from about 0% to about 99%. In one embodiment of the invention, the percentage of (S)-2-ethylbutyl 2-(((S)-(4-nitrophenoxy)(phenoxy)phosphoryl)amino)propanoate in the starting diastereomeric mixture is in the range from about 0% to about 20%. In one embodiment, the percentage of Compound (S)-2-ethylbutyl 2-(((S)-(4-nitrophenoxy)(phenoxy)phosphoryl)amino)propanoate in the starting diastereomeric mixture is in the range from about 20% to about 99%. In one embodiment, the percentage of Compound (S)-2-ethylbutyl 2-(((S)-(4-nitrophenoxy)(phenoxy) phosphoryl)amino)propanoate in the starting diastereomeric mixture is in the range from about 50% to about 99%. In one embodiment, the final Compound (S)-2-ethylbutyl 2-(((S)-(4-nitrophenoxy)(phenoxy)phosphoryl)amino)propanoate is at least about 90%, about 95%, about 97%, or about 99% diastereomerically pure. In one embodiment, the final Compound (S)-2-ethylbutyl 2-(((S)-(4-nitrophenoxy)(phenoxy)phosphoryl)amino)propanoate contains less than 1% of any diastereomeric impurities. In one embodiment, the final Compound (S)-2-ethylbutyl 2-(((S)-(4-nitrophenoxy)(phenoxy)phosphoryl)amino)propanoate is free of any detectable diastereomeric impurities.

EXAMPLES

[0387] 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.

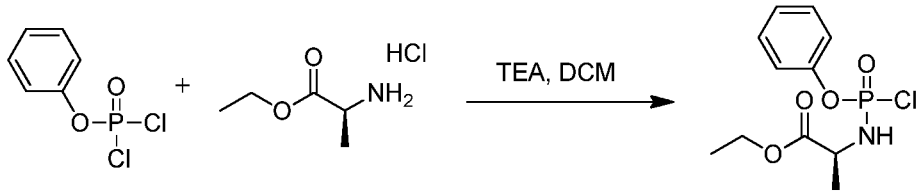
Abbreviation	Meaning
Ac_2O	acetic anhydride
AIBN	2,2'-azobis(2-methylpropionitrile)

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]non-5-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DBU	1,5-diazabicyclo[5.4.0]undec-5-ene
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
EtOAc	ethyl acetate
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
MTBE	tert-butylmethyl ether
NBS	N-bromosuccinimide
Ph	phenyl
rt or r.t.	room temperature
TBAF	tetrabutylammonium fluoride
THF	tetrahydrofuran

TMSC1	chlorotrimethylsilane
TMSBr	bromotrimethylsilane
TMSI	iodotrimethylsilane
TMSOTf	(trimethylsilyl)trifluoromethylsulfonate
TEA	triethylamine
TBA	tributylamine
TBAP	tributylammonium pyrophosphate
TBSC1	t-butyldimethylsilyl chloride
TEAB	triethylammonium bicarbonate
TFA	trifluoroacetic acid
TLC or tic	thin layer chromatography
Tr	triphenylmethyl
Tol	4-methylbenzoyl
Turbo Grignard	1:1 mixture of isopropylmagnesium chloride and lithium chloride
δ	parts per million down field from tetramethylsilane

E. Preparation of Compounds

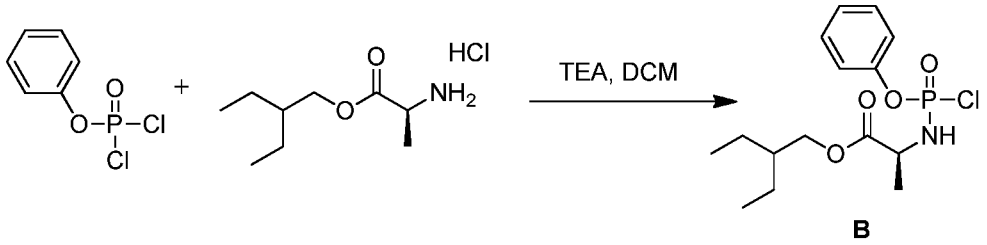
Example 1. (2S)-ethyl 2-(chloro(phenoxy)phosphorylamino)propanoate (Chloridate A)



A

[0388] Ethyl alanine ester hydrochloride salt (1.69 g, 11 mmol) was dissolved in anhydrous CH2CI2 (10 mL) and the mixture stirred with cooling to 0 °C under N_2(g). Phenyl dichlorophosphate (1.49 mL, 10 mmol) was added followed by dropwise addition of Et_3N over about 10 min. The reaction mixture was then slowly warmed to RT and stirred for about 12 h. Anhydrous Et_20 (50 mL) was added and the mixture stirred for about 30 min. The solid that formed was removed by filtration, and the filtrate concentrated under reduced pressure. The residue was subjected to silica gel chromatography eluting with 0-50% EtOAc in hexanes to provide intermediate A. ^{1}H NMR (300 MHz, $CDC1_3$) δ 7.39-7.27 (m, 5H), 4.27 (m, 3H), 1.52 (m, 3H), 1.32 (m, 3H). ^{31}P NMR (121.4 MHz, $CDC1_3$) δ 8.2, 7.8.

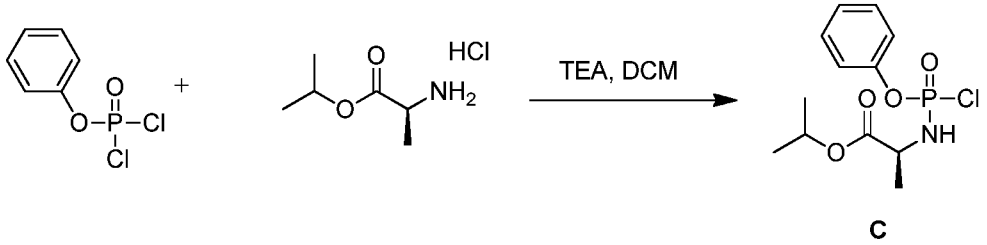
Example 2. (2S)-2-ethylbutyl 2-(chloro(phenoxy)phosphorylamino)propanoate (Chloridate B)



B

[0389] The 2-ethylbutyl alanine chlorophosphoramidate ester **B** was prepared using the same procedure as chloridate **A** except substituting 2-ethylbutyl alanine ester for ethyl alanine ester. The material is used crude in the next reaction. Treatment with methanol or ethanol forms the displaced product with the requisite LCMS signal.

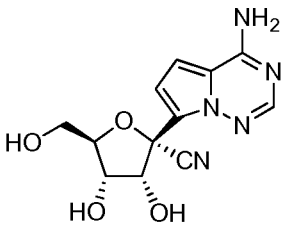
Example 3. (2S)-isopropyl 2-(chloro(phenoxy)phosphorylamino)propanoate (Chloridate C)



C

[0390] The isopropyl alanine chlorophosphoramidate ester **C** was prepared using the same procedure as chloridate **A** except substituting isopropyl alanine ester for the ethyl alanine ester. The material is used crude in the next reaction. Treatment with methanol or ethanol forms the displaced product with the requisite LCMS signal.

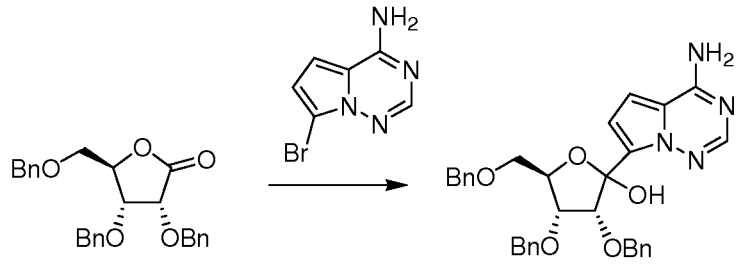
Example 4. (2R. 3R. 4S. 5R)-2-(4-aminopyrrolori.2-firi.2.41triazin-7-vn-3.4-dihvdroxy-5-(hvdroxymethyl)tetrahvdrofuran-2-carbonitrile (Compound 1)



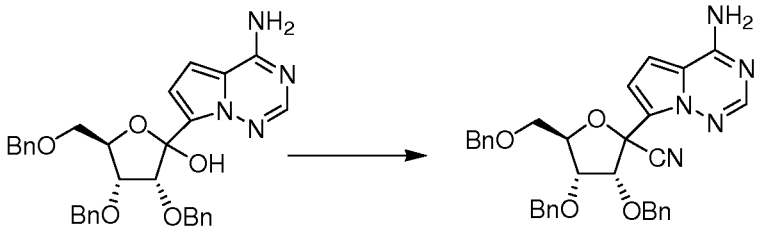
1

[0391] The preparation of (2R, 3R, 4S, 5R)-2-(4-aminopyrrolo[l,2-f][l,2,4]triazin-7-yl)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile is described below.

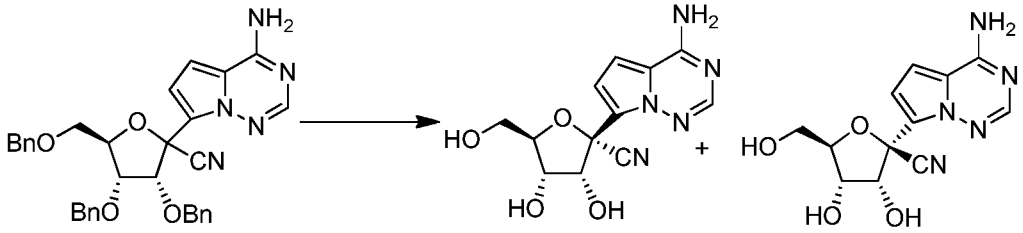
[0392] The commercially available lactol (10 g, 23.8 mmol) was dissolved in anhydrous DMSO (30 mL) under N_2(g). Ac_20 (20 mL) was added and the resultant reaction mixture stirred at RT for about 48 h. The reaction mixture was poured onto ice H_20 (500 mL) and the mixture stirred for 20 min. The mixture was extracted with EtOAc (3 x 200 mL) and the combined organic extracts were then washed with H_20 (3 x 200 mL). The organic extract was dried over anhydrous $MgS0_4$, filtered and concentrated under reduced pressure. The residue was dissolved in CH_2C1_2 and subjected to silica gel chromatography eluting with 25% EtOAc in hexanes to provide the lactone. ^{1}H NMR (400 MHz, DMSO) δ 7.30-7.34 (m, 13H), 7.19-7.21 (m, 2H), 4.55-4.72 (m, 6H), 4.47 (s, 2H), 4.28 (d, *J* = 3.9 Hζ,IH), 3.66 (m, 2H). LCMS m/z 436.1 [M+H_20], 435.2 [M+OH]- Tr = 2.82 min. HPLC Tr = 4.59 [2-98% ACN in H2) over 5 min at 2 mL/min flow.



[0393] The bromopyrazole (prepared according to WO2009/132135) (0.5 g, 2.4 mmol) was suspended in anhydrous THF (10 mL) under N_2(g). The suspension was stirred and TMSC1 (0.67 mL, 5.28 mmol) was added. The mixture was stirred for 20 min. at RT and then cooled to about -78 °C after which time a solution of n-BuLi (6 mL, 1.6 N in hexanes, 9.6 mmol) was added slowly. The reaction mixture was stirred for 10 min. at about -78 °C and then the lactone (1 g, 2.4 mmol) was added *via* syringe. When the reaction was complete as measured by LCMS, AcOH was added to quench the reaction. The mixture was concentrated under reduced pressure and the residue dissolved in a mixture of CH_2C1_2 and H_20 (100 mL, 1:1). The organic layer was separated and washed with H_20 (50 mL). The organic layer was then dried over anhydrous $MgS0_4$, filtered and concentrated under reduced pressure. The residue was subjected to silica gel chromatography eluting with 0-50% EtOAc in hexanes to provide the product as a 1:1 mixture of anomers. LCMS *m/z* 553 [M+H].



[0394] The hydroxy nucleoside (1.1 g, 2.0 mmol) was dissolved in anhydrous CH2CI2 (40 mL) and the solution cooled with stirring to about -78 °C under N_2(g). TMSCN (0.93 1 mL, 7 mmol) was added and the mixture stirred for a further 10 min. TMSOTf (1.63 mL, 9.0 mmol) was slowly added to the reaction and the mixture stirred for 1 h. The reaction mixture was then diluted with CH2CI2 (120 mL) and aqueous $NaHCO_3$ (120 mL) was added to quench the reaction. The reaction mixture was stirred for a further 10 min and the organic layer separated. The aqueous layer was extracted with ¾ ¾ (150 mL) and the combined organic extracts dried over anhydrous $MgS0_4$, filtered and concentrated under reduced pressure. The residue was dissolved in a minimal amount of CH2CI2 and subjected to silica gel chromatography eluting with a gradient of 0-75% EtOAc and hexanes to provide the tribenzyl cyano nucleoside as a mixture of anomers. ^{1}H NMR (300 MHz, CD_3CN) δ 7.94 (s, 0.5H), 7.88 (s, 0.5H), 7.29-7.43 (m, 13H), 7.11-7.19 (m, 1H), 6.82-6.88 (m, lH), 6.70-6.76 (m, 1H), 6.41 (bs, 2H), 5.10 (d, **J** = 3.9 Hz, 0.5H), 4.96 (d, **J** = 5.1 Hz, 0.5H), 4.31-4.85 (m, 7H), 4.09-4.18 (m, 2H), 3.61-3.90 (m, 2H). LCMS ***m/z*** 562 [M+H].

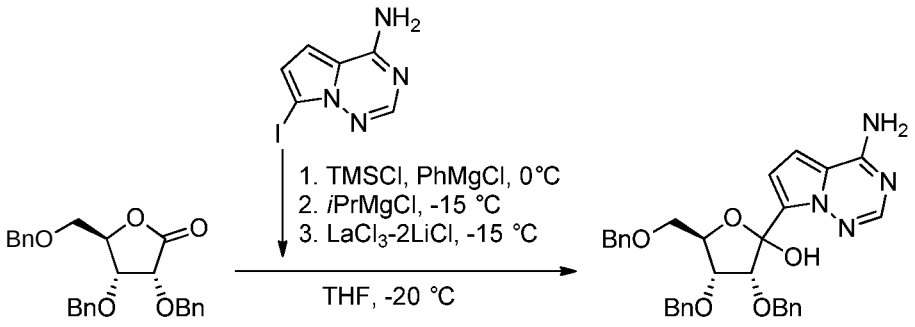


beta 1

[0395] The tribenzyl cyano nucleoside (70 mg, 0.124 mmol) was dissolved in anhydrous CH2CI2 (2 mL) and cooled to about -20 °C under N_2(g). A solution of $BC1_3$ (IN in CH_2C1_2, 0.506 mL, 0.506 mmol) was added and the reaction mixture stirred for 1 h. at -78 °C. When the reaction was complete by LC/MS, MeOH was added to quench the reaction. The reaction mixture was allowed to warm to RT and the solvent removed under reduced pressure. The residue was subjected to C18 reverse phase HPLC, eluting for 5 min with ¾ 0 (0.1 % TFA), followed by a gradient of 0-70% MeCN in H_20 (0.1 % TFA) over 35 min, to elute the a-anomer, and β-anomer **1. (a-anomer)** ^{1}H NMR (300 MHz, D_20) δ 7.96 (s, 1H), 7.20 (d, ***J*** = 4.8

Hz, 1H), 6.91 (d, *J* = 4.8 Hz, 1H), 4.97 (d, *J = 4.4* Hz, 1H), 4.56-4.62 (m, 1H), 4.08-4.14 (m, 1H), 3.90 (dd, J = 12.9, 2.4 Hz, 1H), 3.70 (dd, J = 13.2, 4.5 Hz, 1H). **(β-anomer)** ^{1}H NMR (400 MHz, DMSO) δ 7.91 (s, 1H), 7.80-8.00 (br s, 2H), 6.85-6.89 (m, 2H), 6.07 (d, *J* = 6.0 Hz, 1H), 5.17 (br s, 1H), 4.90 (br s, 1H), 4.63 (t, *J* = 3.9 Hz, 1H), 4.02-4.06 (m, 1H), 3.94 (br s, 1H), 3.48-3.64 (m, 2H). LCMS m/z 292.2 [M+H], 290.0 [M-H]. Tr= 0.35 min. 13C NMR (400 MHZ, DMSO), 156.0, 148.3, 124.3, 117.8, 117.0, 111.2, 101.3, 85.8, 79.0, 74.7, 70.5, 61.4. HPLC Tr = 1.32 min

Preparation of (3R,4R,5R)-2-(4-aminopyrrolor2,l-Fin,2,41triazin-7-yl)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-ol using LaC¾-2LiCl



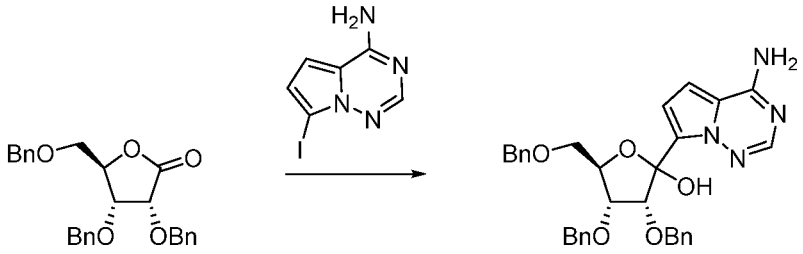
[0396] A solution of 7-iodopyrrolo[2,l-f][l,2,4]triazin-4-amine (7.5 g, 28.8 mmol, 1.0 equiv) was prepared in THF (67 mL). The solution was cooled to about 0 °C, and TMSCl (3.3 mL, 30.3 mmol, 1.05 equiv) was added. The reaction mixture was stirred for about 30 min, and then PhMgCl (2 M in THF; 28 mL, 56.8 mmol, 1.97 equiv) was added while maintaining an internal temperature below 5 °C. The reaction mixture was agitated at about 0 °C for about 35 min, and then cooled to about -15 °C. *i*PrMgCl (2 M in THF, 14 mL, 30.2 mmol, 1.05 equiv) was then added while maintaining an internal temperature below about -10 °C. After approximately 15 minutes at about -15 °C, $LaCl_3$-2LiCl (0.6 M in THF, 50 mL, 14.4 mmol, 0.5 equiv) was added while maintaining an internal temperature below about -15 °C. The reaction mixture was agitated for about 25 min at about -20 °C.

[0397] In a separate flask, a solution of (3R,4R,5R)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl) dihydrofuran-2(3H)-one (10.0 g, 23.9 mmol, 0.83 equiv) was prepared in THF (45 mL). The solution was cooled to about -20 °C, and then transferred to the Grignard solution while maintaining an internal temperature below about -15 °C. The resulting reaction mixture was agitated at about -20 °C for about 30 min.

The reaction was quenched with 2 M HC1 (53 mL), and the mixture warmed to about 15 °C. *i*PrOAc (38 mL) was added, and the organic and aqueous phases were separated. The bottom aqueous layer was discharged, and the upper organic layer was washed sequentially with 2.5 wt% NaHC0 $_3$ (53 mL), 2.5 wt% NaHC0 $_3$ (53 mL), and 10 wt% NaCl (53 mL).

[0398] The organic phase was concentrated to about 45 mL, and then diluted with *i*PrOAc (75 mL). The solution was concentrated again to about 45 mL, and then diluted with *i*PrOAc (23 mL). The solution was concentrated to about 45 mL, and then filtered over a pad of Celite. The filtered solution was concentrated to about 26 mL, and then diluted with MTBE (75 mL). After 2h, heptane (23 mL) was slowly added and the slurry was stirred at about 25 °C for about 2 h, and was then cooled to about -5 °C over about 8 h. The solids were isolated by filtration, and the filter cake was washed with MTBE/heptane (4: 1, 23 mL). The solids were dried in a vacuum oven at no more than about 35 °C to afford (3R,4R,5R)-2-(4-aminopyrrolo[2,l-f][l,2,4]triazin-7-yl)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-ol.

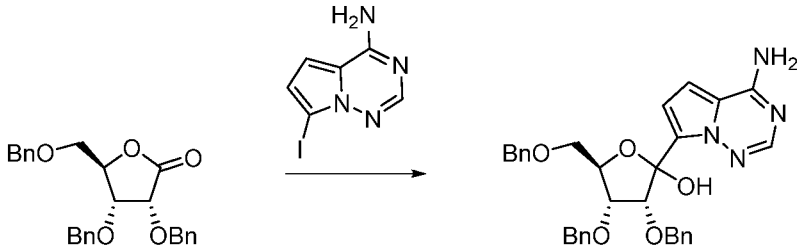
Preparation of (3R,4R,5R)-2-(4-aminopyrrolor2,l -f**i**[**i** ,2,41triazin-7-yl)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-ol using *CeCl*$_3$



[0399] The iodopyrazole (5.02 g, 19.3 mmol) was dissolved in THF (45 g) and the solution was cooled to about 0 °C with stirring. TMSC1 (2.04 g, 18.7 mmol) was added, and after about 1 h phenyl magnesium chloride (2.0 M in THF, 19.9 g, 38.2 mmol) was added. The reaction mixture was cooled to about -20 °C and *iso*-propyl magnesium chloride (2.0 M in THF, 9.99 g, 20.5 mmol) was added slowly. After about 30 min, the reaction mixture was transferred to a mixture of anhydrous cerium chloride (4.75 g, 19.3 mmol) in THF (22 g) at about -20 °C. After about 1.5 h a solution of lactone (6.73 g, 16.1 mmol) in THF (22 g) was added slowly, and the resulting reaction mixture was stirred for about 1 h. 2 M HC1 (41 g) was added, the mixture was warmed to about 15 °C, and *iso*-propyl acetate (35 g) was added. The layers were separated and the organic layer was washed with 2.5% NaHCC>3 (2 x 40 g), 10% NaCl (1 x 35 g) and concentrated to about 30 mL volume. *iso*-Propyl acetate (44 g) was charged and the solution was concentrated

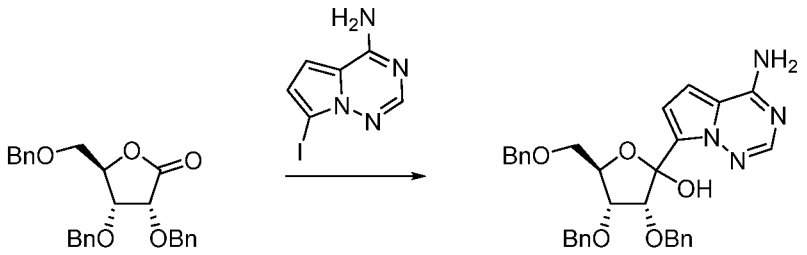
to about 30 mL volume. *iso*-Propyl acetate (43 g) was charged and the solution was concentrated to about 30 mL volume. The solution was filtered and the filtrate was concentrated to about 18 mL volume. ferf-Butylmethyl ether (37 g) was added followed by product seed crystals (10.7 mg). After about 14 h n-heptane (10.5 g) was added and the mixture was cooled to about -5 °C and filtered. The solids were washed with ferf-butylmethyl ether (9 g) at about -5 °C and dried under vacuum at about 34 °C for about 15 h to provide the product.

Preparation of (3R,4R,5R)-2-(4-aminopyrrolor2,l -f**i**[**i** ,2,41triazin-7-yl)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-ol using $CeCl_3$ and iPrMgCl-LiCl



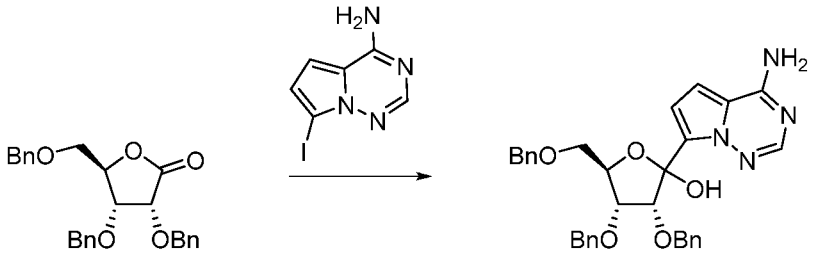
[0400] The iodopyrazole (5.03 g, 19.3 mmol) was dissolved in THF (45 g) and the solution was cooled to about 0 °C with stirring under N_2(g). TMSCl (2.06 g, 19.0 mmol) was added, and after about 1 h phenyl magnesium chloride (2.0 M in THF, 20.23 g, 38.8 mmol) was added. The reaction mixture was cooled to about -20 °C and *iso*-propyl magnesium chloride-lithium chloride complex (2.0 M in THF, 15.37 g, 21.0 mmol) was added slowly. After about 1 h, the reaction mixture was transferred to a mixture of cerium chloride (4.77 g, 19.4 mmol) in THF (22 g) at about -20 °C. After about 1 h a solution of lactone (6.75 g, 16.1 mmol) in THF (23 g) was added slowly, and the resulting reaction mixture was stirred for about 1.5 h. 2 M HC1 (40 g) was added, the mixture was warmed to about 15 °C and *iso*-propyl acetate (35 g) was added. The layers were separated and the organic layer was washed with 2.5% NaHCC>3 (2 x 40 g), 10% NaCl (1 x 36 g) and concentrated to about 30 mL volume. *iso*-Propyl acetate (44 g) was added and the solution was concentrated to about 30 mL volume. The solution was filtered and the filtrate was concentrated to about 18 mL volume. ferf-Butylmethyl ether (37 g) was added followed by product seed crystals (10.5 mg). After about 14 h w-heptane (11 g) was added and the mixture was cooled to about -5 °C and filtered. The solids were washed with ferf-butylmethyl ether (9 g) at about -5 °C and dried under vacuum at about 34 °C for about 15 h to provide the product.

Preparation of (3R^R,5R)-2-(4-aminopyrrolor2,l-firi,2,41triazin-7-yl)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-ol using YCl_3



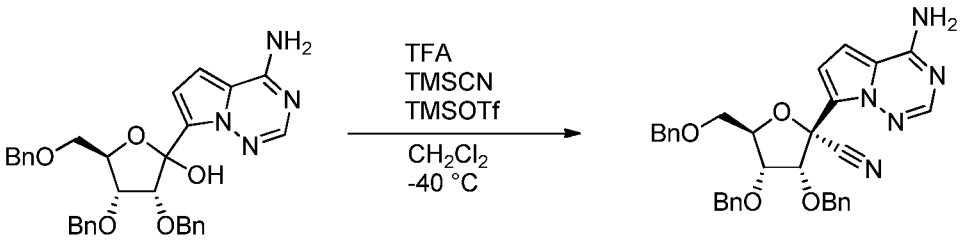
[0401] The iodopyrazole (4.99 g, 19.2 mmol) was dissolved in THF (44 g) and the solution was cooled to about 0 °C with stirring. TMSC1 (2.45 mL, 19.4 mmol) was added, and after about 30 min phenyl magnesium chloride (2.0 M in THF, 20.29 g, 39.0 mmol) was added. The reaction mixture was cooled to about -20 °C and *iso*-propyl magnesium chloride (2.0 M in THF, 9.85 g, 20.1 mmol) was added slowly. After about 30 min, the reaction mixture was transferred into a mixture of anhydrous yttrium chloride (3.76 g, 19.3 mmol) and lactone (6.68 g, 16.0 mml) in THF (24 g) at about -20 °C. After about 2.5 h 2 M HC1 (30 g) was added, the mixture was warmed to about 15 °C, and *iso*-propyl acetate (22 g) was added. The layers were separated and the organic layer was washed with 2.5% $NaHC0_3$ (2 x 40 g), 10% NaCl (1 x 35 g) and concentrated to about 30 mL volume. *iso*-Propyl acetate (44 g) was charged and the solution was concentrated to about 30 mL volume. *iso*-Propyl acetate (45 g) was charged and the solution was concentrated to about 30 mL volume. The solution was filtered and the filtrate was concentrated to about 18 mL volume. ferf-Butylmethyl ether (37 g) was added followed by product seed crystals (11.5 mg). After about 1 h *n*-heptane (15 mL) was added and the mixture was cooled to about -5 °C and agitated for about 17 h. The slurry was filtered and the solids were washed with a ferf-butylmethyl ether (8 g)/w-heptane (2 g) mixture precooled to about -5 °C. The resulting solids were dried under vacuum at about 34 °C for about 22 h to afford the product.

Preparation of (3R,4R,5R)-2-(4-aminopyrrolor2,l -**Firi**,2,41triazin-7-yl)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-ol using NdC¾



[0402] The iodopyrazole (5.02 g, 19.3 mmol) was dissolved in THF (38 g) and the solution was cooled to about 0 °C with stirring under N_2(g). TMSC1 (2.45 mL, 19.4 mmol) was added, and after about 1 h phenylmagnesium chloride (2.0 M in THF, 19.75 g, 38.0 mmol) was added. The reaction mixture was cooled to about -20 °C and *iso*-propylmagnesium chloride (2.0 M in THF, 9.40 g, 19.2 mmol) was added slowly. After about 1.5 h, the reaction mixture was transferred into a mixture of anhydrous neodymium (III) chloride (4.03 g, 16.1 mmol) and lactone (6.70 g, 16.0 mml) in THF (22 g) at about -20 °C. After about 1.5 h the reaction mixture was warmed to -10 °C and, after an additional 2 h, 2 M HC1 (36 g) was added. The mixture was warmed to about 15 °C and *iso*-propyl acetate (23 g) was added. The layers were separated and the organic layer was washed with 2.5% NaHC0 $_3$ (2 x 44 g), 10% NaCl (1 x 41 g) and concentrated to about 30 mL volume. *iso*-Propyl acetate (44 g) was charged and the solution was concentrated to about 30 mL volume. *iso*-Propyl acetate (45 g) was charged and the solution was concentrated to about 30 mL volume. The solution was filtered and the filtrate was concentrated to about 18 mL volume. ferf-Butylmethyl ether (37 g) was added followed by product seed crystals (11.9 mg). After about 1 h *n*-heptane (15 mL) was added and the mixture was cooled to about -5 °C and agitated for about 15 h. The slurry was filtered and the solids were washed with a *tert*-butylmethyl ether (8 *g)/n*-heptane (11 g) mixture precooled to about -5 °C. The resulting solids were dried under vacuum at about 34 °C for about 25 h to afford the product.

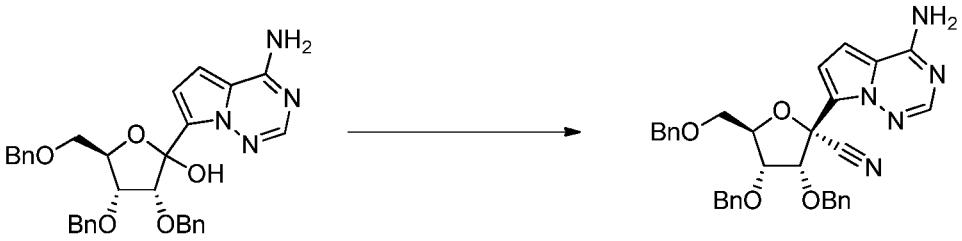
Preparation of (2R,3R,4R,5R)-2-(4-aminopyrrolor2,l-firi,2,41triazin-7-yl)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-carbonitrile



[0403] To a pre-cooled (-40 °C) solution of (3R,4R,5R)-2-(4-aminopyrrolo[2,l-f][l,2,4]triazin-7-yl)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-ol (10.0 grams, 18.1 mmols, 1.0 equiv.) in DCM (100 mL) was charged trifluoroacetic acid (6.19 grams, 54.3 mmols, 3.0 equiv.), followed by a pre-cooled (-30 °C) solution of TMSOTf (24.1 grams, 108.6 mmols, 6.0 equiv.) and TMSCN (10.8 grams, 108.6 mmols, 6.0 equiv.) in DCM (50 mL) while maintaining the internal temperature below about -25 °C. The reaction mixture was agitated at below about

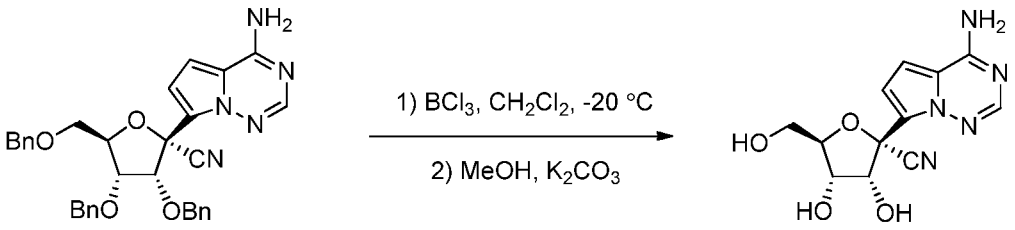
-30 °C for no less than 10 minutes and quenched into a pre-cooled (about -10 °C) solution of 20 wt. % KOH aq. (120 mL). The bi-phasic mixture was warmed to ambient temperature. The organic layer was separated and washed with 10 wt. % NaCl aq. (3 X 50 mL). The organic phase was filtered, concentrated under vacuum to about 50 mL, re-diluted with toluene (200 mL) and concentrated under vacuum to 140 mL at about 50 °C. The solution was seeded with (2R,3R,4R,5R)-2-(4-aminopyrrolo[2,l-f][l,2,4]triazin-7-yl)-3,4-bis(benzyloxy)-5-((benzyloxy) methyl)tetrahydrofuran-2-carbonitrile at about 55 °C. Agitated at about 55 °C for about an hour and cooled to about 0 °C over about 6 hours. The solids were isolated by filtration and the filter cake was washed with toluene (30 mL). The solids were dried under vacuum at about 50 °C.

Preparation of (2R,3R,4R,5R)-2-(4-aminopyrrolor2,l **-firi**,2,41triazin-7-yl)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-carbonitrile via Flow Chemistry



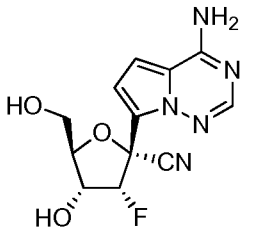
[0404] Solutions of (3R,4R,5R)-2-(4-aminopyrrolo[2,l-f][l,2,4]triazin-7-yl)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-ol (23.0 g in 460.07 g of DCM), TMSOTf (55.81 g in 138.07 g of DCM) and TMSCN (25.03 g in 138. 10 g of DCM) were sequentially pumped, into a tube reactor at about -40 °C. The reaction mixture was collected in a flask, kept in ice bath, containing 20% KOH aqueous solution (46.91 g KOH and 210 g of water). The layers were separated and the organic phase was sequentially washed with 10% KOH aqueous solution (10 g KOH and 90 mL of water) and withl0% brine (2 xlOO g). The organic phase was concentrated under vacuum to about 4 volumes, isopropyl alcohol was charged (162.89 g) and the mixture was concentrated under vacuum to about 10 volumes. The contents were warmed to about 60 °C, then adjusted to about 0 °C over about 6.5 h and agitated at about 0 °C for about 15.5 h. The resulting slurry was filtered, the solids were rinsed with isopropyl alcohol (61.79 g) and then dried at about 50 °C under reduced pressure overnight to afford the product.

Preparation of (2R, 3R, 4S. 5R)-2-r4-aminopyrrolori,2-firi,2,41triazin-7-yl)-3,4-dihvdroxy-5-(hvdroxymethyl)tetrahydrofuran-2-carbonitrile



[0405] The tribenzyl cyano nucleoside (48.8 g, 86.9 mmol, 1.0 equiv.) was dissolved in anhydrous CH_2Cl_2 (244 mL) and cooled to about -20 °C . A solution of BCl_3 (1M in CH_2Cl_2, 295 mL, 295 mmol, 3.4 equiv.) was added dropwise, maintaining the internal temperature below about -15 °C. Following addition, the reaction mixture was stirred for 1 h at about -20 °C. MeOH (340 ml) was added dropwise, maintaining the internal temperature below -15 °C. The resulting solution was distilled to about 250 ml, then refilled with about 250 ml MeOH. The resulting solution was again distilled to about 250 ml, then refilled with about 250 ml MeOH, and finally distilled to about 125 ml. Water (125 ml) was added, followed by K_2CO_3 solution (20 wt% in water, 125 ml). The pH was checked, and found to be ~3. K_2CO_3 solution was added (20 wt% in water, 50 ml), and the pH was found to be ~8. The resulting slurry was stirred overnight, then filtered and washed with water (50 ml) and MeOH (50 ml). The wet product cake was dried overnight at about 40 °C overnight. ^1H NMR (300 MHz, D_2O) δ 7.96 (s, 1H), 7.20 (d, *J* = 4.8 Hz, 1H), 6.91 (d, *J* = 4.8 Hz, 1H), 4.97 (d, *J* = 4.4 Hz, 1H), 4.56-4.62 (m, 1H), 4.08-4.14 (m, 1H), 3.90 (dd, J = 12.9, 2.4 Hz, 1H), 3.70 (dd, J = 13.2, 4.5 Hz, 1H).

Example 5. (2R.3R.4R.5R)-2-(4-aminopyrrolori.2-firi.2.41triazin-7-yl)-3-fluoro-4-hvdroxy-5-(hvdroxymethyl)tetrahvdrofuran-2-carbonitrile (Compound 2)



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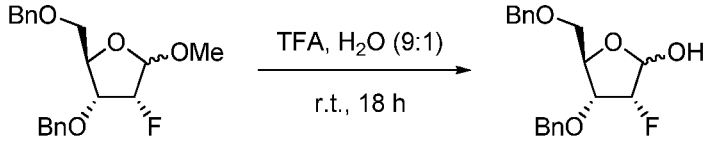
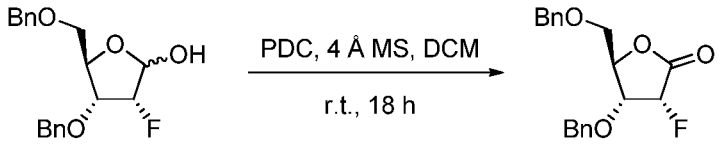
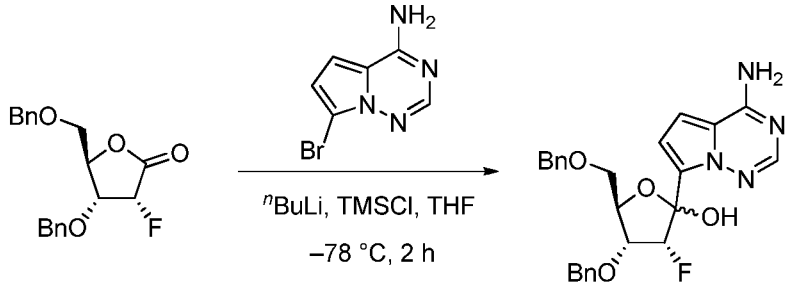
[0406] The preparation of (2R,3R,4R,5R)-2-(4-aminopyrrolo[l,2-f][l,2,4]triazin-7-yl)-3-fluoro-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile is described below.



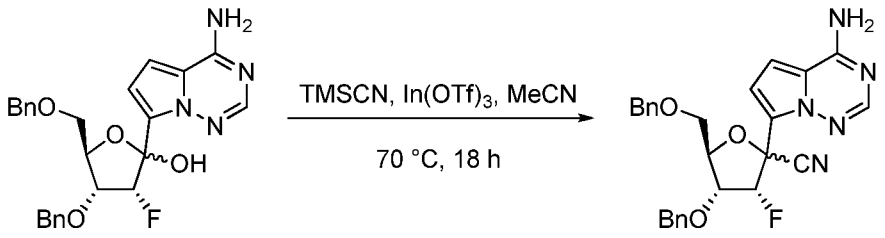
[0407] 2-Deoxy-2-fluoro-4,5-0,0-dibenzyl-D-arabinose. 1'-Methoxy-2-deoxy-2-fluoro-4,5-0,0-dibenzyl-D-arabinose (1.0 g, 2.88 mmol) in TFA (13.5 mL) was treated with H_20 (1.5 mL) and the resultant mixture stirred for 5 h. The mixture was then diluted with EtOAc (100 mL) and treated with saturated NaHCC>3 (50 mL). The organic layer was separated and washed with NaCl (50 mL), dried over anhydrous $MgS0_4$, filtered and concentrated under reduced pressure. The residue was subjected to silica gel chromatography (80 g $Si0_2$ Combiflash HP Gold Column) eluting with 0-100% EtOAc in hexanes to afford 2-deoxy-2-fluoro-4,5-0,0-dibenzyl-D-arabinose as a white solid: R_f = 0.52 (25% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDC1_3$) δ 7.30 (m, 10H), 5.35 (m, 1H), 4.68-4.29 (m, 7H), 3.70 (d, *J* = 10.5 Hz, 1H), 3.50 (d, *J* = 10.5 Hz, 2H). ^{19}F NMR (282.2 MHz, $CDC1_3$) δ -207 (m), -211 (m). LCMS *m/z* 350 [M+H_20].



[0408] ***(3R, 4R,*** **5^)-4-(benzyloxy)-5-(benzyloxymethyl)-3-fluorodihydrofuran-2(3H)-one.** 2-Deoxy-2-fluoro-4, 5-0,0-dibenzyl-D-arabinose (4.3 g, 12.8 mmol) was dissolved in CH_2C1_2 (85 mL) was treated with 4 Å MS (10 g) and pyridinium dichromate (14.4 g, 38.3 mmol). The resultant mixture was stirred for 24 h and then filtered through a pad of Celite®. The eluant was concentrated under reduced pressure and the residue subjected to silica gel chromatography (120 g $Si0_2$ HP Gold Combiflash Column) eluting with 0-100% EtOAc in hexanes to afford *(3R, 4R,* 5/?)-4-(benzyloxy)-5-(benzyloxymethyl)-3-fluorodihydrofuran-2(3H)-one as a clear oil (3.5 g, 83%): R_f = 0.25 (25% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDC1_3$) δ 7.37 (m, 10H), 5.45 (dd, *J = 49,* 5.7, Hz, 1H), 4.85 (d, *J* = 11.7 Hz, 1H), 4.52 (m, 4 H), 4.29 (d, *J* = 5.4 Hz, 1H), 2.08 (dd, *J* = 15.3, 10.2 Hz, 2H). ^{19}F NMR (282.2 MHz, $CDC1_3$) δ -216. LCMS *m/z* 348 [M+H_20]. HPLC (6-98% MeCN-H_20 gradient, 0.05% TFA modifier) t_R = 5.29 min. Phenomenex Synergi 4 m Hydro-RP 80 A, 50 **x** 4.60 mm, 4 micron; 2 mL/min flow rate

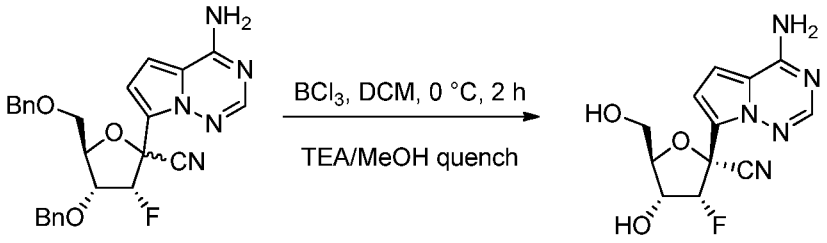


[0409] ***(3R, 4R,*** **5^)-2-(4-aminopyrrolo[l,2-f][l,2,4]triazin-7-yl)-4-(benzyloxy)-5-(benzyloxymethyl)-3-fluorotetrahydrofuran-2-ol.** 7-Bromopyrrolo[l,2-f][l,2,4]-triazin-4-amine (68 mg, 0.319 mmol) in THF (1.4 mL) was treated with TMSCl (89 μL, 0.703 mmol) and the mixture stirred for 2 h. The mixture was then cooled to about -78 °C and treated with wBuLi (1.0 M in hexanes, 1.09 mL, 1.09 mmol). The solution was stirred for about 30 min and then treated with *(3R, 4R,* 5/?)-4-(benzyloxy)-5-(benzyloxymethyl)-3-fluorodihydrofuran-2(3H)-one (106 mg, 0.319 mmol) dropwise in THF (1.4 mL). The resultant mixture was stirred for 30 min and then AcOH (83 μL, 1.44 mmol) in THF (1.0 mL) was added to quench the reaction. The mixture was warmed to RT and then concentrated under reduced pressure. The residue was diluted with EtOAc (100 mL) and washed with saturated NaCl solution (50 mL). The organic layer was dried over anhydrous MgS0 $_4$, filtered and concentrated under reduced pressure. The residue was subjected to silica gel chromatography (40 g Si0 $_2$ HP Gold Combiflash Column) eluting with 0-100% EtOAc in hexanes followed by a 0-100% gradient of (20% MeOH in EtOAc) in EtOAc to afford *(3R, 4R,* 5¾-2-(4-aminopyrrolo[l,2-f][l,2,4]triazin-7-yl)-4-(benzyloxy)-5-(benzyloxymethyl)-3-fluorotetrahydrofuran-2-ol as a white solid (68 mg, 44%, 60/40 mixture of α/β isomers). R_f = 0.32 (EtOAc). ^{1}H NMR (300 MHz, CDC1$_3$) δ 8.05 (s, IH), 7.86 (s, IH), 7.81 (s, IH), 7.64 (s, IH), 7.26 (m, 10H), 6.95 (m, IH), 6.71 (m, IH), 6.08 (m, IH), 5.34 (m, IH), 4.65 (m, 6H), 4.71 (m, 2H). ^{19}F NMR (282.2 MHz, CDC1$_3$) δ -211 (m). LCMS *m/z* 465 [M+H]. HPLC (6-98% MeCN-H $_2$0 gradient, 0.05% TFA modifier) t_R = 4.37 min. (a-isomer), 4.54 min. (β-isomer).



[0410] ***(3R, 4R,*** **5^)-2-(4-aminopyrrolo[l,2-f][l,2,4]triazin-7-yl)-4-(benzyloxy)-5-(benzyloxymethyl)-3-fluorotetrahydrofuran-2-carbonitrile:** *(3R, 4R, 5R)-2-(4-*

aminopyrrolo[l,2-f][l,2,4]triazin-7-yl)-4-(benzyloxy)-5-(benzyloxymethyl)-3-fluorotetrahydrofuran-2-ol (195 mg, 0.42 mmol) was dissolved in MeCN (1.4 mL) was treated with TMSCN (336 uL, 2.52 mmol) and $In(OTf)_3$ (708 mg, 1.26 mmol). The solution was stirred at about 70 °C for 18 h and then cooled to about 0 °C. The mixture was treated with saturated $NaHC0_3$ solution (20 drops) then warmed to RT and diluted with EtOAc (100 mL) and H_20 (50 mL). The organic layer was separated and washed with saturated NaCl solution (50 mL), dried over $MgS0_4$, filtered and concentrated under reduced pressure. The residue was subjected to silica gel chromatography (40 g $Si0_2$ HP Gold Combiflash Column) eluting with 0-100% EtOAc in hexanes to afford *(3R, 4R,* 5^)-2-(4-aminopyrrolo[l,2-f][l,2,4]triazin-7-yl)-4-(benzyloxy)-5-(benzyloxymethyl)-3-fluorotetrahydrofuran-2-carbonitrile as a white solid (60/40 mixture of α/β isomers). Data for both isomers: R_f = 0.53 (EtOAc). ^{1}H NMR (300 MHz, $CDC1_3$) δ 8.01 (s, 1H), 7.94 (s, 1H), 7.30 (m, 10H), 7.00 (d, *J* = 4.5 Hz, 1H), 6.93 (d, *J* = 4.8 Hz, 1H), 6.87 (d, *J* = 5.4 Hz, 1H), 6.70 (d, *J* = 4.8 Hz, 1H), 5.85 (dd, *J* = 52, 3.3 Hz, 1H), 5.55 (dd, *J* = 53, 4.5 Hz, 1H), 4.71 (m, 7H), 3.87 (m, 2H), 3.72 (m, 2H). ^{19}F NMR (282.2 MHz, $CDC1_3$) δ -196 (m), -203 (m). LCMS *m/z* 474 [M+H]. HPLC (6-98% MeCN-H_20 gradient, 0.05% TFA modifier) ¾ = 4.98 min.



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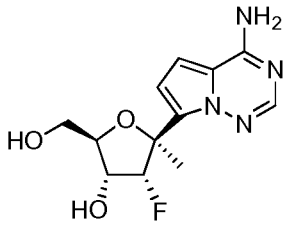
[0411] ***(2R, 3R, 4R,* 5^)-2-(4-aminopyrrolo[l,2-f][l,2,4]triazin-7-yl)-3-fluoro-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile (2)** *(3R, 4R,* 5/?)-2-(4-aminopyrrolo[l,2-f][l,2,4]triazin-7-yl)-4-(benzyloxy)-5-(benzyloxymethyl)-3-fluorotetrahydrofuran-2-carbonitrile (110 mg, 0.23 mmol) was dissolved in CH_2C1_2 (1.5 mL) and cooled to about 0 °C. The reaction mixture was treated with $BC1_3$ (1.0 M in CH_2C1_2, 766 μL, 0.77 mmol) and stirred for 2 h. The mixture was then cooled to about -78 °C and treated with Et_3N (340 μL, 2.44 mmol) followed by MeOH (2 mL) before allowing to warm to RT. The reaction was concentrated under reduced pressure and then co-evaporated with MeOH (3 x 5 mL). The residue was then suspended in H_20 (5 mL) and treated with $NaHC0_3$ (1 g). The solution was stirred for 10 min and then concentrated under reduced pressure. The residue was filtered and washed with MeOH (3 x 10

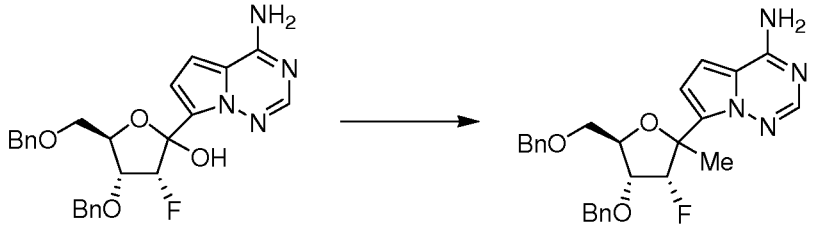
mL) on a fritted glass funnel (coarse) and the eluant concentrated under reduced pressure. The residue was subjected to reverse phase HPLC (6-98% MeCN in H_20 gradient with 0.05% TFA modifier) to afford *(2R, 3R, 4R,* 5^)-2-(4-aminopyrrolo[l,2-f][l,2,4]triazin-7-yl)-3-fluoro-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile 2 as a white solid and the oc-isomer. Data for the β-isomer: R_f = 0.13 (10% MeOH in EtOAc). ^{1}H NMR (300 MHz, CD_3OD) δ 8.09 (s, 1H), 7.28 (d, *J* = 5.1 Hz, 1H), 7.17 (d, *J* = 5.1 Hz, 1H), 5.42 (dd, *J* = 53, 3.3 Hz, 1H), 4.20 (m, 2H), 3.99 (d, *J* = 3.6 Hz, 1H), 3.77 (d, *J* = 3.6 Hz, 1H). ^{19}F NMR (282.2 MHz, $CDC1_3$) δ -197 (m). LCMS *m/z* 294 [M+H]. HPLC (2-98% MeCN-H_20 gradient, 0.05% TFA modifier) t_R = 1.49 min.

Example 6. (2R, 3R, 4R, 5S)-5-(4-aminopyrrolori,2-firi,2,41triazin-7-yl)-4-fluoro-2-(hvdroxymethyl)-5-methyltetrahvdrofuran-3-ol (Compound 3)



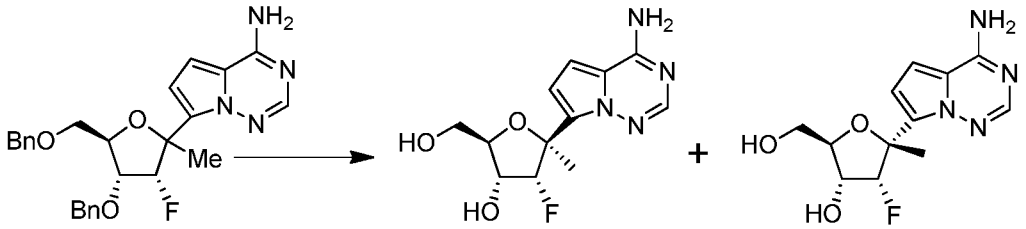
3

[0412] The preparation of (2R, 3R, 4R, 5S)-5-(4-aminopyrrolo[l,2-f][l,2,4]triazin- 7-yl)-4-fluoro-2-(hydroxymethyl)-5-methyltetrahydrofuran-3-ol is described below.



[0413] The starting nucleoside (prepared as described in the sysnthesis of compound **2)** (0.355 g, 0.765 mmol) was dissolved in anhydrous THF (35 mL) and cooled to about 0 °C with stirring under N_2(g). A solution of methyl magnesium chloride (2 mL, 6 mmol) (3N in THF) was added and the resultant mixture stirred overnight. Acetic acid (7 mmol) was added to quench the reaction and then the solvents were removed by rotory under reduced pressure. The residue was re-dissolved in CH_2C1_2 and the solution subjected to a plug of silica gel to isolate the product (0.355 g) as a crude mixture. LC/MS (m/z : 480, M^{+1}). The crude material was dissolved in anhydrous CH_2C1_2 (20 mL) and placed under N_2(g). The solution was stirred and treated with

methanesulfonic acid (0.2 mL, 2.74 mmol). The reaction mixture was stirred for about 12 h at RT and then quenched by the addition of Et_3N (3.5 mmol). The mixture was concentrated under reduced pressure and the residue subjected to silica gel chromatography to provide the methyl substituted nucleoside as a 4:1 mixture of beta- and alpha-anomers respectively. ^1H NMR (300 MHz, CD_3CN) major anomer δ 7.87 (s, 1H), 7.27-7.40 (m, 10 H), 6.77 (d, J = 4.5 HZ, 1H), 6.70 (d, J = 4.5 Hz, 1H), 6.23 (br s, 2H), 5.53 (dd, J = 55, 3.3 Hz, 1H), 4.42-4.75 (m, 4H), 4.19-4.26 (m, 1H), 3.65-4.00 (m, 3H), 1.74 (d, J = 3.9 Hz, 3H). ^{19}F NMR (282.2 MHz, CD_3CN) major anomer δ -207 (m, IF). LCMS ***m/z*** 463 [M+H].

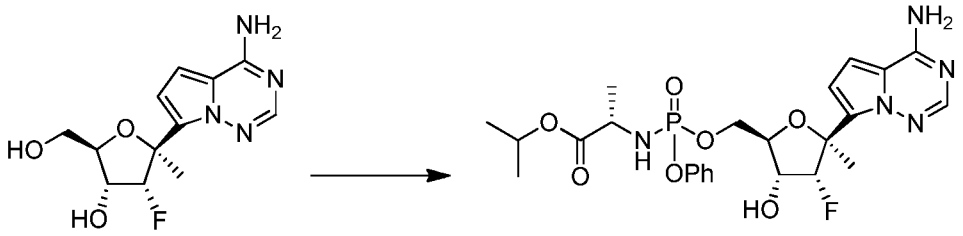


beta, 3 **alpha**

[0414] The benzylated nucleoside material (0.134 g, 0.290 mmol), Degussa catalyst (0.268 g) and AcOH (30 mL) were mixed together. The reaction atmosphere was charged with H_2 (g) and the reaction stirred for about 2 h. The catalyst was removed by filtration and the mixture concentrated under reduced pressure. The residue was dissolved in a minimal amount of H_20 and subjected to reverse phase HPLC (C^{18} hydro RP column) to isolate the β-anomer **3.** ^1H NMR (300 MHz, D_20) δ 7.87 (s, 1H), 7.22 (d, J = 4.8 Hz, 1H), 6.87 (d, J = 4.8 Hz, 1H), 5.35 (dd, J = 54, 3.6 Hz, 1H), 3.97-4.10 (m, 2H), 3.81 (dd, J = 12.6, 2.1 Hz, 1H), 3.64 (dd, J = 12.6, 4.8 Hz, 1H), 1.65 (d, J = 4.2 Hz, 3H). ^{19}F NMR (282.2 MHz, CD_3CN) δ -207 (m, IF).

[0415] A small amount of alpha anomer was characterized as follows. ^1H NMR (300 MHz, D_20) δ 7.86 (s, 1H), 7.26 (d, J = 4.8 Hz, 1H), 6.85 (d, J = 4.8 Hz, 1H), 5.31 (dd, J = 54, 3.9 Hz, 1H), 4.39 (ddd, J = 26.1, 9.9, 3.6 Hz, 2H), 4.00 - 4.05 (m, 1H), 3.90 (dd, J = 12.3, 2.1 Hz, 1H), 3.66 (dd, J = 12.6, 4.8, 1H), 1.56 (s, 3H). ^{19}F NMR (282.2 MHz, CD_3CN) δ -198 (dd, J = 54, 26 Hz, IF).

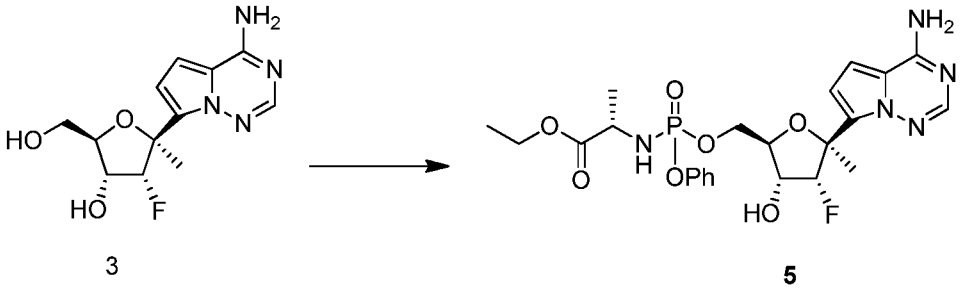
Example 7. (2S)-isopropyl 2-(((((2R,3R,4R,5S)-5-(4-aminopyrrolor2 ,l-firi,2,41triazin-7-yl)-4-fluoro-3-hvdroxy-5-methyltetrahvdrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino) propanoate (Compound 4)



3 4

[0416] The nucleoside **3** (0.01 1 g, 0.04 mmol) was dissolved in trimethylphosphate (2 mL) and cooled to 0 °C. The mixture was stirred under an atmosphere of N_2(g) and 1-Methylimidazole (0.320 mL, 5 mmol) followed by the alaninylmonoisopropyl, monophenol phosphorchloridate **C** (0.240 mL, 4.4 mmol) was added. The reaction mixture was stirred for 2 h. at 0 °C and then allowed to warm slowly to RT. while monitoring by LC/MS. When complete by LCMS, the reaction mixture was treated with H_20 (5 mL) and then concentrated under reduced pressure. The residue was dissolved in CH_2C1_2 and subjected to silica gel chromatography eluting with 0-100% EtOAc in hexanes. The product fractions were collected and concentrated. The residue was subjected to prep HPLC to yield the alanine isopropyl monoamidate prodrug **4** as a mixture of isomers. ^{1}H NMR (300 MHz, CD3CN) δ 7.87 (s, 1H), 7.17-7.44 (m, 5 H), 6.71-6.83 (m, 2H), 6.14 (br, s, 2H), 5.38 (dd, **J** = 56, 3.3 Hz, 1H), 4.92-5.01 (m, 1H), 3.86-4.46 (m, 6H), 3.58 (m, 1H), 1.73 (m, 3H), 1.18-1.34 (m, 9H). LCMS ***m/z*** 552 [M+H].

Example 8. (2S)-ethyl 2-(((((2R,3R,4R,5S)-5-(4-aminopyrrolor2,l-firi,2,41triazin-7-yl)-4-fluoro-3-hvdroxy-5-methyltetrahvdrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino) propanoate (Compound 5)

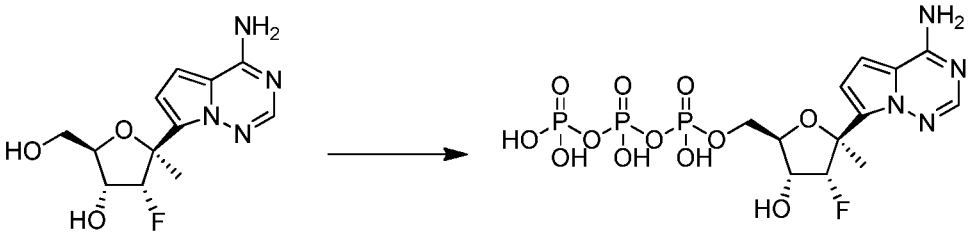


3 5

[0417] The nucleoside **3** (0.026 g, 0.092 mmol) was dissolved in trimethylphosphate (2 mL) and cooled to 0 °C. The mixture was stirred under N_2(g) and 1-methylimidazole (0.062 mL, 0.763 mmol) followed by the chloridate **A** (0.160 g, 0.552 mmol) were added. The reaction mixture was stirred for 2 h. at 0 °C and then allowed to warm slowly to RT. H_20 (5 mL) was

added to quench the reaction and then the mixture concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and subjected to silica gel chromatography eluting with 0-100% EtOAc in hexanes. The product fractions were collected and concentrated. . Crude product was eluted using 0 to 100 percent EtOAc in hexanes. The crude product was collected and concentrated under reduced pressure. The residue was subjected to prep HPLC to yield compound **5**. LCMS *m/z* 538 [M+H].

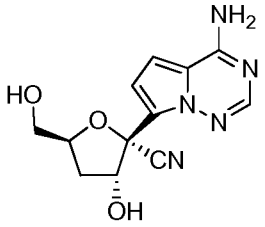
Example 9. ((2R, 3R, 4R, 5S)-5-(4-aminopyrrolori,2-firi,2,41triazin-7-yl)-4-fluoro-3-hvdroxy-5-methyltetrahvdrofuran-2-yl)methyl tetrahydrogen triphosphate (Compound 6)



3 **6**

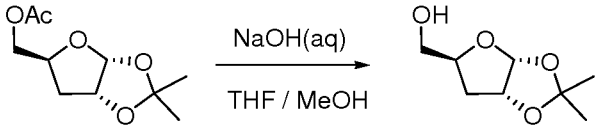
[0418] The nucleoside **3** (0.022 g, 0.056 mmol) was dissolved in trimethylphosphate (1 mL) and stirred under N_2(g). Phosphorous oxychloride (0.067 mL, 0.73 mmol) was added and the mixture stirred for about 2 h. Monitoring by analytical ion-exchange column determined the time at which > 80 percent of monophosphate was formed. A solution of tributylamine (0.44 mL, 1.85 mmol) and triethylammonium pyrophosphate (0.327 g, 0.72 mmol) dissolved in anhydrous DMF (1 mL) was added. The reaction mixture was stirred for 20 min and then quenched by the addition of IN triethylammonium bicarbonate solution in H_20 (5 mL). The mixture was concentrated under reduced pressure and the residue re-dissolved in H_20. The solution was subjected to ion exchange chromatography to yield the title product compound **6**. LCMS *m/z* 521 [M-H]. Tr = 0.41. HPLC ion exchange TR = 9.40 min

Example 10. (2R,3R,5S)-2-(4-aminopyrrolori,2-firi,2,41triazin-7-yl)-3-hvdroxy-5-(hvdroxymethyl)-tetrahvdrofuran-2-carbonitrile (Compound 7)

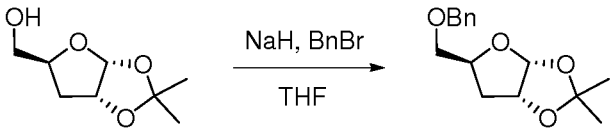


7

[0419] The preparation of (2R,3R,5S)-2-(4-aminopyrrolo[l,2-f][l,2,4]triazin-7-yl)-3-hydroxy-5-(hydroxymethyl)-tetrahydrofuran-2-carbonitrile is described below.

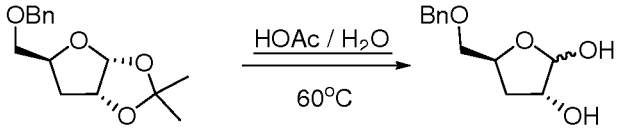


[0420] **((3aR,5S,6ocR)-2,2-dimethyl-tetrahydrofuro[2,3-d][l,3]dioxol-5-yl)methanol.** The acetate material (1.2 g, 5.5 mmol) **(J.** Org. Chem. 1985, 50, 3457, De Bernardo et al) was dissolved in a 1:1 mixture MeOH and THF (10 mL). A IN solution of NaOH(aq) (lOmL) was added until the pH was 13. The reaction mixture was stirred for about 2h and then neutralized to pH 8-9 by the addition of AcOH. The mixture was extracted with EtOAc (10 x 30 mL) and the combined organic extracts dried over anhydrous Na_2S0_4, filtered and concentrated under reduced pressure. The residue was subjected to silica gel chromatography eluting with 0-70% EtOAc in hexanes to give the desired product (866 mg, 90%). ^{1}H NMR (300 MHz, $CDC1_3$) δ 5.84 (d, *J* = 3.6 Hz, 1H), 4.78 (t, *J* = 4.5 Hz, 1H), 4.38 (m, 1H), 3.93-3.54 (m, 2H), 2.04-1.84 (m, 2H), 1.52 (s, 3H), 1.33 (s, 3H).

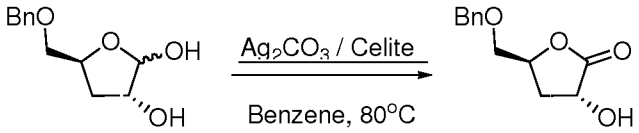


[0421] **(3ocR,5S,6aR)-5-(benzyloxymethyl)-2,2-dimethyl-tetrahydrofuro[2,3-d][l,3]dioxole.** Sodium hydride (188 mg, 7.46 mmol) was dissolved in anhydrous THF (5 mL) and stirred under N_2(g) at RT. The alcohol (866 mg, 4.97 mmol) was dissolved in anhydrous THF (3 mL) and then added in portions over 5 min. to the sodium hydride mixture. The resultant mixture was stirred for about 20 min. and then benzyl bromide (892 μL, 7.46 mmol) was added. The reaction was stirred for about 2 h and then poured onto a mixture of ice cold aqueous NaHCC>3 and EtOAc (30 mL). The organic layer was separated and then the aqueous layer re-extracted with EtOAc (30 mL). The combined organic extracts were dried over anhydrous

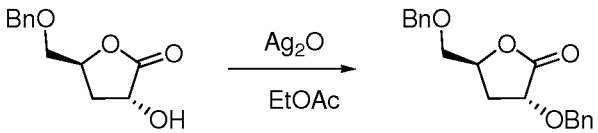
Na_2S0_4, filtered and concentrated under reduced pressure. The residue was subjected to silica gel chromatography eluting with 0-40% EtOAc in hexanes to give the benzyl ether product. ^1H NMR (300 MHz, $CDC1_3$) δ 7.35-7.27 (m, 5H), 5.86 (d, *J* = 3.6 Hz, 1H), 4.74 (t, *J* = 4.2 Hz, 1H), 4.60 (s, 2H), 4.42 (m, 1H), 3.69-3.53 (m, 2H), 2.10-2.04 (m, 1H), 1.83-1.77 (m, 1H), 1.52 (s, 3H), 1.33 (s, 3H).



[0422] (3R,5S)-5-(benzyloxymethyl)-tetrahydrofuran-2,3-diol. The benzyl ether (910 mg, 3.44 mmol) was dissolved in a 1:1 AcOH and H_20 (20 mL) mixture and stirred at about 60 °C for about 7h. The mixture was concentrated under reduced pressure and the residue subjected to silica gel chromatography eluting with 0-70% EtOAc in hexanes to give the diol product (705 mg, 91%). ^1H NMR (300 MHz, $CDC1_3$) δ 7.36-7.27 (m, 5H), 5.40 (d, *J* = 3.9 Hz, 0.5H), 5.17 (s, 0.5H), 4.67-4.56 (m, 3H), 4.33 (m, 0.5H), 4.24 (d, *J* = 4.8 Hz, 0.5H), 3.71-3.67 (m, 1H), 3.56-3.42 (m, 2H), 2.31-2.22 (m, 1H), 2.08-1.89 (m, 2H).

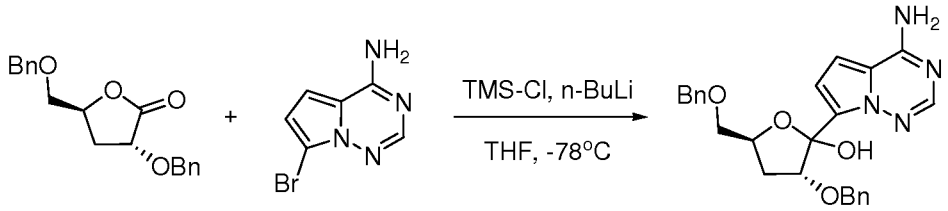


[0423] (3R,5S)-5-(benzyloxymethyl)-3-hydroxy-dihydrofuran-2(3H)-one. The diol (705 mg, 3.14 mmol) was dissolved in benzene (30 mL) and treated with a silver carbonate celite mixture (3.46 g, 6.28 mmol). The resultant mixture was stirred at about 80 °C under N_2(g) for about 2h. The mixture was then cooled to RT, filtered and concentrated under reduced pressure. The residue was subjected to silica gel chromatography eluting with 0-70% EtOAc in hexanes to give the lactone product. ^1H NMR (300 MHz, $CDC1_3$) δ 7.39-7.27 (m, 5H), 4.75-4.68 (m, 1H), 4.60-4.49 (m, 2H), 3.74-3.54 (m, 2H), 2.61-2.35 (m, 2H), 2.38-2.28 (m, 1H).

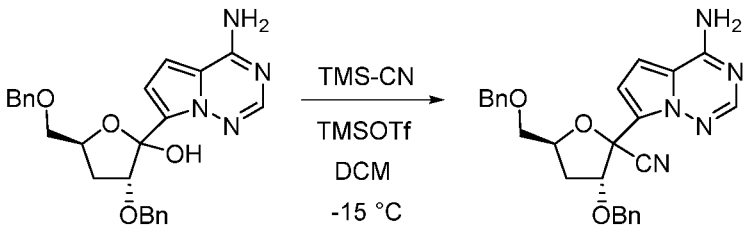


[0424] (3R, 5S)-3-(benzyloxy)-5-(benzyloxymethyl)-dihydrofuran-2(3H)-one. The lactone (600 mg, 2.7 mmol) was dissolved in EtOAc (30mL) and treated with silver oxide (626 mg, 2.7 mmol) followed by benzyl bromide (387 μE, 3.24 mmol). The reaction mixture was then stirred

at about 50 °C under N_2(g) for about 8h. Additional silver oxide (300 mg) was then added and the resultant mixture stirred at about 50 °C for about 16h. Additional benzyl bromide (50 uL) and silver oxide (150 mg) were added and the mixture stirred for an additional about 8h. The reaction mixture was allowed to cool, filtered and then concentrated under reduced pressure. The residue was subjected to silica gel chromatography eluting with 0-20% EtOAc in hexanes to give the title product. ^{1}H NMR (300 MHz, $CDC1_3$) δ 7.39-7.27 (m, 10H), 4.99 (d, *J* = 11.4 Hz, 1H), 4.72 (m, 2H), 4.56 (m, 2H), 4.39 (t, *J* = 8.1 Hz, 1H), 3.72-3.51 (m, 2H), 2.42-2.25 (m, 2H).

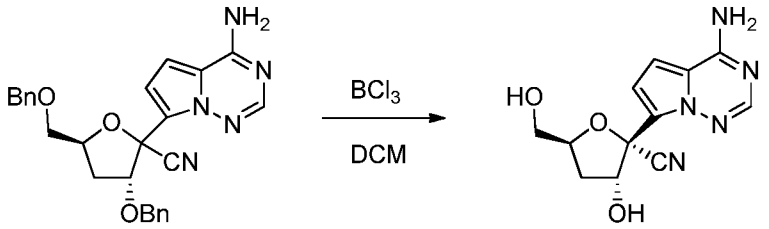


[0425] (3R,5S)-2-(4-aminopyrrolo[l,2-f][l,2,4]triazin-7-yl)-3-(benzyloxy)-5-(benzyloxymethyl)-tetrahydrofuran-2-ol. The 7-bromopyrrolo[1,2-f] [1,2,4]triazin-4-amine (607 mg, 2.85 mmol) was dissolved in anhydrous THF (10 mL) and stirred under Ar(g) at RT. TMSC1 (1.1 mL, 8.55 mmol) was added drop wise and the mixture stirred for about 2h. The reaction was concentrated under reduced pressure and then dried under high vacuum. The residue was suspended in THF (20 mL) and stirred under Ar(g) at about -78 °C. A 2.5M n-BuLi solution in hexane (2.28 mL, 5.7 mmol) was added dropwise over about 10 min. and the resultant mixture stirred for about 60 min. The lactone (742 mg, 2.37 mmol) dissolved in anhydrous THF (7 mL) was added to the above mixture over about 20 min. The reaction mixture was stirred for about 2 h. and then quenched with AcOH until pH was 5-6. The mixture was allowed to warm to RT and then diluted with EtOAc. The solution was washed with saturated NaHCC>3 solution, saturated NaCl, dried over anhydrous $Na_2SC>4$ and concentrated under reduced pressure. The residue was subjected to silica gel chromatography eluting with 0-80% EtOAc in hexanes to give the title product. LCMS *m/z* 447. 2 [M+H], 445.1 [M-H].



[0426] (3R,5S)-2-(4-aminopyrrolo[l,2-f][l,2,4]triazin-7-yl)-3-(benzyloxy)-5-(benzyloxymethyl)-tetrahydrofuran-2-carbonitrile. The alcohol (250 mg, 0.56 mmol) was

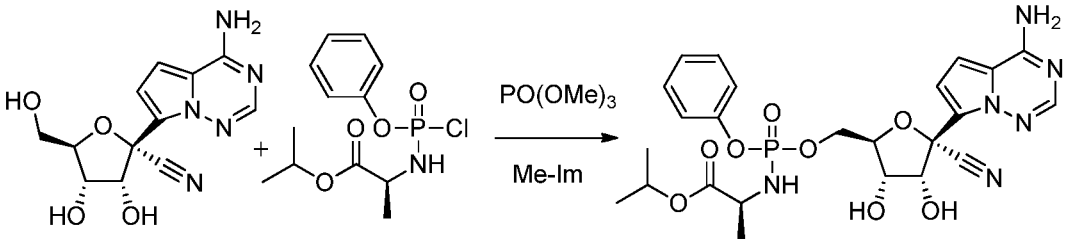
dissolved in anhydrous CH_2Cl_2 (10 mL) and stirred under Ar(g) at about -15 °C. TMSCN (448 μL, 3.36 mmol) was added dropwise and the mixture stirred for about 10 min. TMSOTf (466 μL, 2.58 mmol) was added dropwise over 10 min and the resultant mixture stirred for about 90 min. at about -15 °C. Additional TMSCN (224 μL, 3 eq.) and TMSOTf (202 μL, *2* eq.) was added and stirring continued for about 5 h. Saturated aqueous NaHCC>3 solution was added to quench the reaction and the mixture stirred for about 10 min. The organic layer was separated and washed with saturated aqueous NaHCC>3 solution, saturated NaCl solution, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was subjected to silica gel chromatography eluting with 0-70% EtOAc in hexanes to give the title product. LCMS *m/z* 456.3 [M+H], 454.1 [M-H].



7

[0427] (2R,3R,5S)2-(4-aminopyrrolo[l,2-f][l,2,4]triazin-7-yl)-3-hydroxy-5-(hydroxymethyl)-tetrahydrofuran-2-carbonitrile (7). The benzyl ether (150 mg, 0.329 mmol) was dissolved in anhydrous CH_2Cl_2 (2 mL) and the mixture stirred under Ar(g) at about -20°C. A 1M BCI_3 solution in CH_2Cl_2 (724 μL, 0.724 mmol) was added dropwise and the resultant mixture stirred for about 2h. Additional 1M $BC1_3$ in CH_2Cl_2 (724 μL, 0.724 mmol) was added and stirring continued for 2h. The mixture was then cooled to about -78°C and slowly treated with a 2:1 mixture of Et_3N and MeOH (3 mL). The mixture was stirred for about 10 min and then treated with MeOH (10 mL). The reaction was allowed to warm to RT and then concentrated under reduced pressure. The residue was dissolved in MeOH and concentrated under reduced pressure. The residue was dissolved in MeOH again and treated with solid $NaHC0_3$. The mixture was stirred for about 5 min and then the solid removed by filtration. The solution was concentrated under reduced pressure and subjected to preparative HPLC to provide the desired product 7. ^{1}H NMR (300 MHz, D_20) δ 7.71 (s, 1H), 6.75 (d, *J* = 4.5 Hz, 1H), 6.65 (d, *J* = 4.8 Hz, 1H), 4.91 (t, *J* = 6.3 Hz, 1H), 4.57 (m, 1H), 3.67-3.47 (m, 2H), 2.18 (m, 2H). LCMS *m/z* 276.1 [M+H], 274.0 [M-H].

Example 11. (2S)-isopropyl 2-((((2R,3S,4R,5R)-5-(4-aminopyrrolori,2-firi,2,41triazin-7-yl)-5-cvano-3,4-dihvdroxytetrahvdrofuran-2-yl)methoxy)(phenoxy)-phosphorylamino) propanoate (Compound 8)

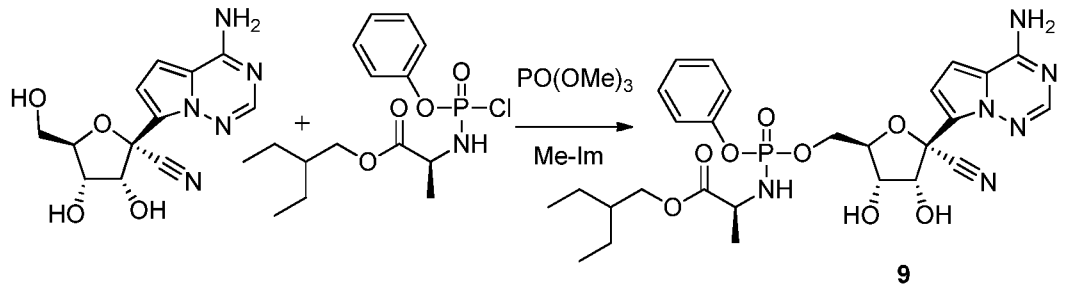


[0428] The nucleoside **1** (45mg, 0.15mmol) was dissolved in anhydrous trimethyl phosphate (0.5 mL) and the solution stirred under N_2(g) at about 0 °C. Methyl imidazole (36 μL, 0.45 mmol) was added to the solution. Chlorophosphoramidate **C** (69 mg, 0.225 mmol) was dissolved in anhydrous THF (0.25 mL) and added dropwise to the nucleoside mixture. When the reaction was complete by LCMS, the reaction mixture was diluted with EtOAc and washed with saturated aqueous $NaHCC_3$ solution, saturated NaCl, dried over anhydrous Na_2S0_4, filtered and concentrated under reduced pressure. The residue was subjected to silica gel chromatography eluting with 0-5% MeOH in CH_2CI_2 followed by preparative HPLC to give the product. ^{1}H NMR (300 MHz, CD_3OD) δ 7.95 (m, 1H), 7.31-6.97 (m, 7H), 4.94 (m, 1H), 4.78 (m, 1H), 4.43 (m, 3H), 4.20 (m, 1H), 3.80 (d, 1H), 1.30-1.18 (m, 9H). ^{31}P NMR (121.4 MHz, CD_3OD) δ 3.8. LCMS *m/z* 561.0 [M+H], 559.0 [M-H].

Example 12. (2S)-2-ethylbutyl 2-((((2R.3S.4R.5R)-5-(4-aminopyrrolori.2-firi.2.41triazin-7-yl)-5-cvano-3,4-dihvdroxytetrahvdrofuran-2-yl)methoxy)(phenoxy)phosphorylamino) propanoate (Compound 9)

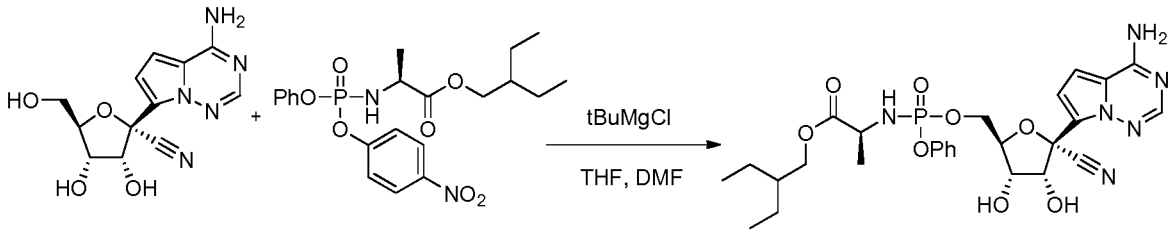
[0429] Compound 9 can be prepared by several methods described below.

Procedure 1



[0430] Prepared from Compound **1** and chloridate **B** according to the same method as for the preparation of compound **8**. ^{1}H NMR (300 MHz, CD_3OD) δ 7.87 (m, 1H), 7.31-7.16 (m, 5H), 6.92-6.89 (m, 2H), 4.78 (m, 1H), 4.50-3.80 (m, 7H), 1.45-1.24 (m, 8H), 0.95-0.84 (m, 6H). ^{31}P NMR (121.4 MHz, CD_3OD) δ 3.7. LCMS *m/z* 603.1 [M+H], 601.0 [M-H].

Procedure 2



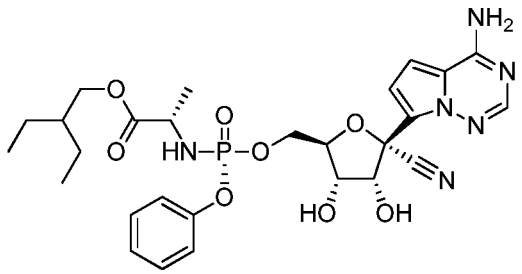
[0431] (2S)-2-ethylbutyl 2-(((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,l-f][l,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino) propanoate. (2S)-2-ethylbutyl 2-(((4-nitrophenoxy)(phenoxy)phosphoryl)amino)propanoate (1.08 g, 2.4 mmol) was dissolved in anhydrous DMF (9 mL) and stirred under a nitrogen atmosphere at RT. (2R,3R,4S,5R)-2-(4-aminopyrrolo[2,l-f][l,2,4]triazin-7-yl)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile (350 mg, 1.2 mmol) was added to the reaction mixture in one portion. A solution of i-butylmagnesium chloride in THF (1M, 1.8 mL, 1.8 mmol) was then added to the reaction dropwise over about 10 minutes. The reaction was stirred for about 2 h, at which point the reaction mixture was diluted with ethyl acetate (50 mL) and washed with saturated aqueous sodium bicarbonate solution (3 x 15 mL) followed by saturated aqueous sodium chloride solution (15 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting oil was purified with silica gel column chromatography (0-10% MeOH in DCM) to afford (2S)-2-ethylbutyl 2-(((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,l-f][l,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino) propanoate (311 mg, 43%, 1:0.4 diastereomeric mixture at phosphorus) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.85 (m, 1H), 7.34 - 7.23 (m, 2H), 7.21 - 7.09 (m, 3H), 6.94 - 6.84 (m, 2H), 4.78 (d, *J* = 5.4 Hz, 1H), 4.46 - 4.33 (m, 2H), 4.33 - 4.24 (m, 1H), 4.18 (m, 1H), 4.05 - 3.80 (m, 3H), 1.52 - 1.39 (m, 1H), 1.38 - 1.20 (m, 7H), 0.85 (m, 6H). ^{31}P NMR (162 MHz, CD_3OD) δ 3.71, 3.65. LCMS *m/z* 603.1 [M+H], 600.9 [M-H]. HPLC (2-98% MeCN-$H_2$0 gradient with 0.1%

TFA modifier over 8.5 min, 1.5mL/min, Column: Phenomenex Kinetex C18, 2.6 um 100 Å, 4.6 x 100 mm) t_R = 5.544 min, 5.601 min

Separation of the (S) and (R) Diastereomers

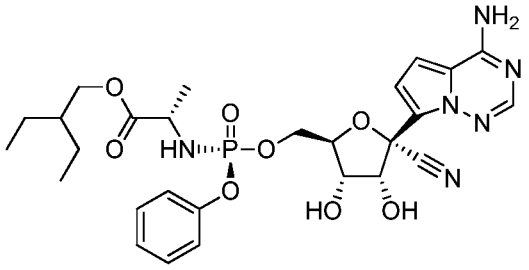
[0432] (2S)-2-ethylbutyl 2-(((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,l-f][l,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino) propanoate was dissolved in acetonitrile. The resulting solution was loaded onto Lux Cellulose-2 chiral column, equilibrated in acetonitrile, and eluted with isocratic acetonitrile/methanol (95:5 vol/vol). The first eluting diastereomer had a retention time of 17.4 min, and the second eluting diastereomer had a retention time of 25.0 min.

[0433] First Eluting Diastereomer is (S)-2-ethylbutyl 2-(((R)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2, 1-f][1,2,4]triazin-7-yl)-5-cyano-3 ,4-dihydroxytetrahydrofuran-2-yl)methoxy) (phenoxy)phosphoryl)amino)propanoate:



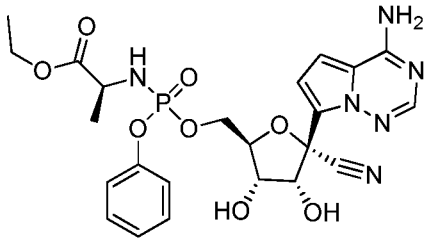
^{1}HNMR (400 MHz, CD_3OD) δ 8.05 (s, 1H), 7.36 (d, *J* = 4.8 Hz, 1H), 7.29 (br *t*, *J* = 7.8 Hz, 2H), 7.19 - 7.13 (m, 3H), 7.11 (d, *J* = 4.8 Hz, 1H), 4.73 (d, *J* = 5.2 Hz, 1H), 4.48 - 4.38 (m, 2H), 4.37 - 4.28 (m, 1H), 4.17 (t, *J* = 5.6 Hz, 1H), 4.08 - 3.94 (m, 2H), 3.94 - 3.80 (m, 1H), 1.48 (sep, *J* = 12.0, 6.1 Hz, 1H), 1.34 (p, *J* = 7.3 Hz, 4H), 1.29 (d, *J* = 7.2 Hz, 3H), 0.87 (t, *J* = 7.4 Hz, 6H). ^{31}PNMR (162 MHz, CD_3OD) δ 3.71 (s). HPLC (2-98% MeCN-H_20 gradient with 0.1% TFA modifier over 8.5 min, 1.5mL/min, Column: Phenomenex Kinetex C18, 2.6 um 100 Å, 4.6 x 100 mm) t_R = 5.585 min.

[0434] Second Eluting Diastereomer is (S)-2-ethylbutyl 2-(((S)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2, 1-f][1,2,4]triazin-7-yl)-5-cyano-3 ,4-dihydroxytetrahydrofuran-2-yl)methoxy) (phenoxy)phosphoryl)amino)propanoate:



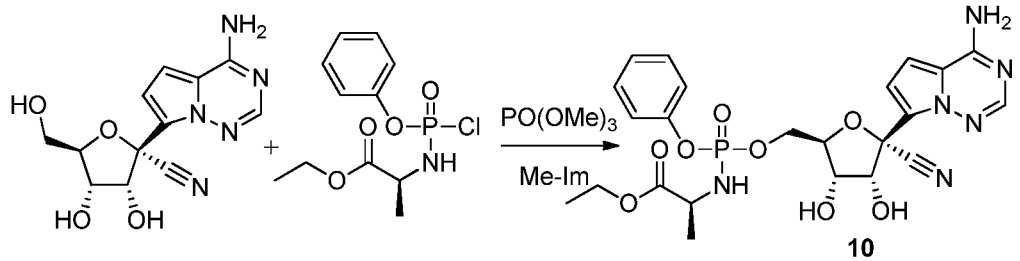
^{1}HNMR (400 MHz, CD_3OD) δ 8.08 (s, IH), 7.36 - 7.28 (m, 3H), 7.23 - 7.14 (m, 3H), 7.08 (d, *J* = 4.8 Hz, IH), 4.71 (d, *J* = 5.3 Hz, IH), 4.45 - 4.34 (m, 2H), 4.32 - 4.24 (m, IH), 4.14 (t, *J* = 5.8 Hz, IH), 4.08 - 3.94 (m, 2H), 3.93 - 3.85 (m, IH), 1.47 (sep, *J* = 6.2 Hz, IH), 1.38 - 1.26 (m, 7H), 0.87 (t, *J* = 7.5 Hz, 6H). ^{31}PNMR (162 MHz, CD_3OD) δ 3.73 (s). HPLC (2-98% MeCN-H_20 gradient with 0.1% TFA modifier over 8.5 min, 1.5mL/min, Column: Phenomenex Kinetex C18, 2.6 urn 100 Å, 4.6 x 100 *mm*) t_R = 5.629 min.

Example 13. (2S)-ethyl 2-((((2R.3S.4R.5R)-5-(4-aminopyrrolori.2-firi.2.41triazin-7-yl)-5-cvano-3,4-dihvdroxytetrahvdrofuran-2-yl)methoxy)(phenoxy)phosphorylamino) propanoate (Compound 10)



[0435] The preparation of (2S)-ethyl 2-(((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,l-f][l,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate is described below.

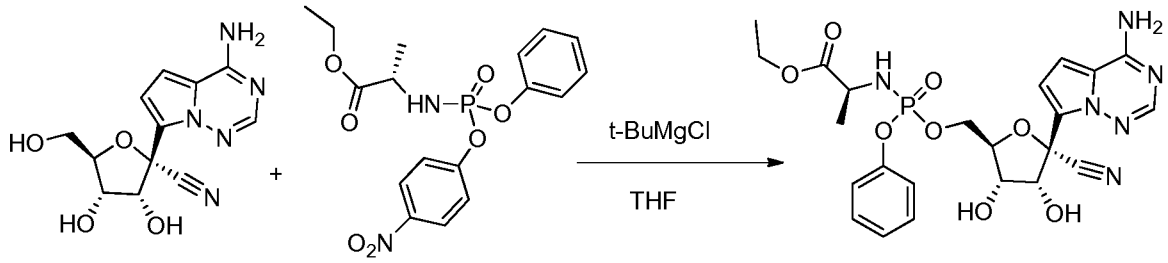
Procedure 1. Preparation via Chloridate A



[0436] Prepared from Compound **1** and chloridate **A** using same method as for the preparation of compound **8.** ^{1}H NMR (300 MHz, CD_3OD) δ 7.95 (m, IH), 7.32-6.97 (m, 7H), 4.78 (m, IH),

4.43-4.08 (m, 6H), 3.83 (m, 1H), 1.31-1.18 (m, 6H). ^{31}P NMR (121.4 MHz, CD_3OD) δ 3.7. LCMS *m/z* 547.0 [M+H], 545.0 [M-H].

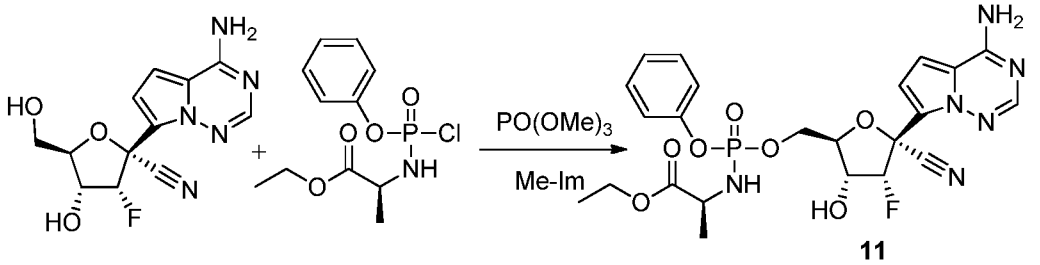
Procedure 2. Preparation via Nitro-Benzene Compound L



1 L 10

[0437] Compound **1** (50 mg, 0.17 mmol) was dissolved in NMP-THF (1:1 mL)) and cooled with ice bath. tBuMgCl (0.257 mL, 0.257 mmol) was then added over about 5 min. The resulting mixture was allowed to warm to RT and was stirred for about 30 min. Then a solution of compound **L** (Prepared according to US20 120009 147, 74.6 mg, 0.189 mmol) in THF (2 mL) was added. After about 30 min, the reaction mixture was purified by HPLC (acetonitrile 10 to 80% in water) to give compound **29** as a yellow solid. The solid was further purified with silica gel chromatography (MeOH 0 to 20% DCM) to afford compound **29.** ^{1}H NMR (400 MHz, CD_3OD) δ 7.76 (d, *J* = 6.0 Hz, 1H), 7.25 - 7.14 (m, 2H), 7.11 - 6.99 (m, 3H), 6.87 - 6.72 (m, 2H), 4.70 (d, *J* = 5.4 Hz, 1H), 4.39 - 4.24 (m, 2H), 4.20 (dddd, *J* = 9.7, 7.9, 5.1, 2.8 Hz, 1H), 4.10 (dt, *J* = 12.8, 5.5 Hz, 1H), 4.06 - 3.91 (m, 2H), 3.72 (ddq, *J* = 14.3, 9.3, 7.1 Hz, 1H), 1.17 (dd, *J* = 7.1, 1.0 Hz, 1H), 1.14 - 1.06 (m, 5H). ^{31}P NMR (162 MHz, CD_3OD) δ 3.73, 3.68. MS m/z = 547 (M+l)+.

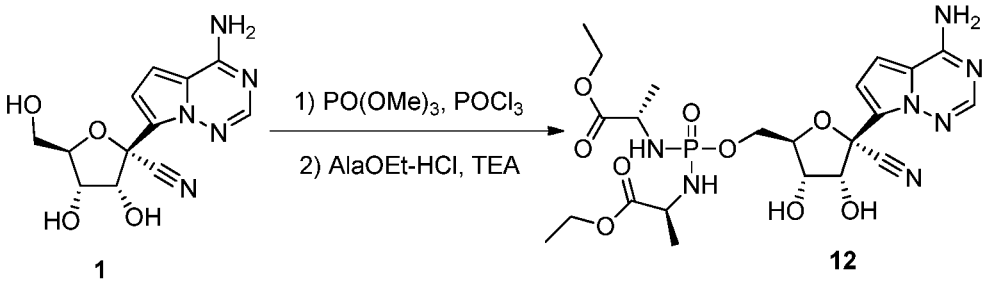
Example 14. (2S)-ethyl 2-((((2R,3R,4R,5R)-5-(4-aminopyrrolori,2-firi,2,41triazin-7-yl)-5-cvano-4-fluoro-3-hvdroxytetrahvdrofuran-2-yl)methoxy)(phenoxy)phosphorylamino) propanoate (Compound 11)



11

[0438] Compound **11** was prepared from Compound **2** and chloridate **A** using same method as for the preparation of compound **8.** ^{1}H NMR (300 MHz, CD_3OD) δ 7.91 (m, 1H), 7.33-7.16 (m, 5H), 6.98-6.90 (m, 2H), 5.59 (m, 1H), 4.50-4.15 (m, 4H), 4.12-3.90 (m, 3H), 1.33-1.18 (m, 6H). ^{31}P NMR (121.4 MHz, CD_3OD) δ 3.8. LCMS *m/z* 549.0 [M+H], 547.1 [M-H].

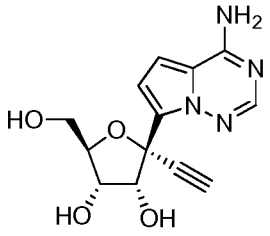
Example 15. (2S,2'S)-diethyl 2,2'-((((2R,3S,4R,5R)-5-(4-aminopyrrolori,2-firi,2,41triazin-7-yl)-5-cvano-3,4-dihvdroxytetrahvdrofuran-2-yl)methoxy)phosphoryl)bis(azanediyl) dipropanoate (Compound 12)



1 12

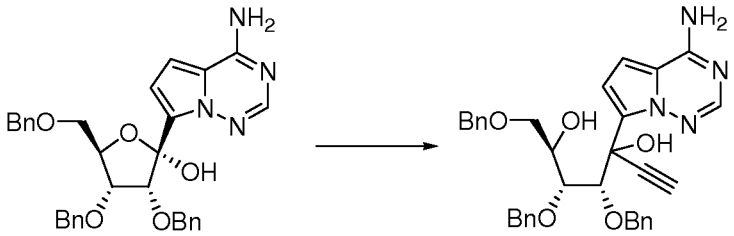
[0439] The nucleoside **1** (14.6 mg, 0.05 mmol) was dissolved in anhydrous trimethyl phosphate (0.5 mL) and stirred under N_2(g) at RT. $POCI_3$ (9.2 μL, 0.1 mmol) was added and the mixture stirred for about 60 min. Alanine ethyl ester hydrochloride (61 mg, 0.4 mmol) and then Et_3N (70 μL, 0.5 mmol) was added. The resultant mixture was stirred for about 15 min. and then additional Et_3N (70 μï, 0.5 mmol) was added to give a solution pH of 9-10. The mixture was stirred for about 2 h. and then diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ solution followed by saturated aqueous NaCl solution. The organic layer was dried over anhydrous Na_2S0_4 and concentrated under reduced pressure. The residue was subjected to preparative HPLC (Ci_8 column) to yield the product **12.** ^{1}H NMR (400 MHz, CD_3OD) δ 8.13 (s, 1H), 7.41 (d, *J* = 4.8 Hz, 1H), 7.18 (d, *J* = 4.8 Hz, 1H), 4.78 (d, *J* = 5.6 Hz, 1H), 4.36 (m, 1H), 4.25-4.08 (m, 7H), 3.83 (m, 2H), 1.33-1.23 (m, 12H). ^{31}P NMR (121.4 MHz, CD_3OD) δ 13.8. LCMS *m/z* 570.0 [M+H], 568.0 [M-H].

Example 16. (2S.3R.4S.5R)-2-(4-aminopyrrolori.2-firi.2.41triazin-7-yl)-2-ethvnyl-5-(hvdroxymethyl)tetrahvdrofuran-3,4-diol (Compound 13)

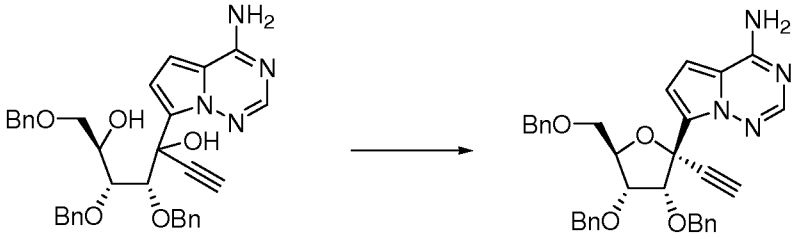


13

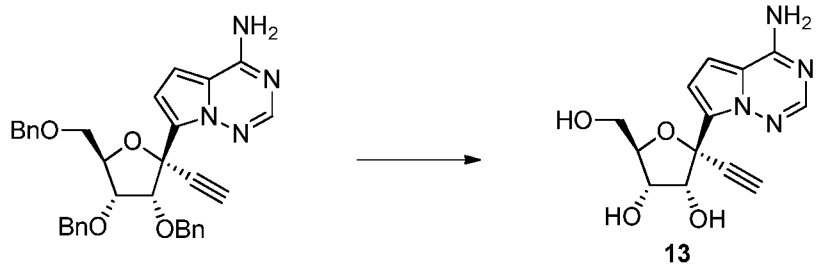
[0440] The preparation of (2S,3R,4S,5R)-2-(4-aminopyrrolo[l,2-f][l,2,4]triazin-7-yl)-2-ethynyl-5-(hydroxymethyl)tetrahydrofuran-3,4-diol is described below.



[0441] The nucleoside alcohol (0.6 g, 1.08 mmol) (prepared as described in Compound **1** synthesis) was dissolved in anhydrous THF (8mL) and placed under N_2(g). The reaction mixture was stirred and cooled to about 0°C and then treated with a 0.5N solution of ethynyl magnesium bromide in THF (17.2 mL, 17.2 mmol). The reaction mixture was stirred overnight at RT. AcOH (1.5 mL) was added to quench the reaction. The mixture was concentrated under reduced pressure and the residue redissolved in CH2CI2. The solution subjected to a plug of silca gel eluting with 0 to 80% EtOAc in Hexanes to provide the title product as a crude mixture. LCMS ***m/z*** 579 [M+H].



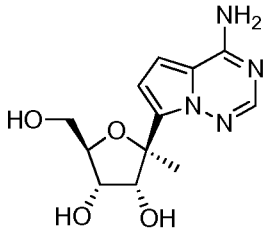
[0442] The crude ethynyl alcohol (0.624 g, 1.08 mmol) was dissolved in anhydrous CH2CI2 (10 mL) and placed under N_2(g). The mixture was stirred and sulfonic acid (0.2 mL, 2.74 mmol) was added. The reaction mixture was stirred for about 12 h. at RT. When complete by LCMS, Et_3N (0.56 mL) was added to quench the reaction. The reaction was concentrated under reduced pressure and the residue subjected to silica gel chromatography eluting with 0 to 75% EtOAc in Hexanes to yield the ethynyl nucleoside as a mixture of anomers. LCMS ***m/z*** 561 [M+H].



13

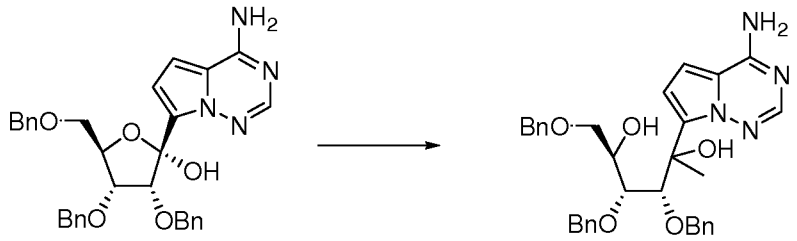
[0443] The tribenzyl nucleoside (0.650 g, 1.16 mmol) was dissolved in anhydrous CH2CI2 (30 mL) and cooled to -78°C under N_2(g). A solution of boron tribromide (1 N in CH2CI2, 5.5 mL) was added and the reaction mixture stirred for 1 h. at -78°C. A solution of MeOH (10 mL) and pyridine (2 mL) was added to quench the reaction and the mixture was allowed to rise to RT. The mixture was concentrated under reduced pressure and subjected to preparative HPLC to provide the a-anomer (20 mg) and β-anomer **13** (110 mg). **(β -anomer)** ^{1}H NMR (300 MHz, DMSO) δ 7.81 (s, 1H), 7.76 (br s, 2H), 6.80-6.85 (m, 2H), 5.11 (d, J = 7.2 Hz, 1H), 4.90 (d, J = 6.0 Hz, 1H), 4.82 (dd, J = 7.2, 4.8 Hz, 1H), 4.62 (t, J = 6.3 Hz, 1H), 3.95-3.99 (m, 1H), 3.85-3.91 (dd, J = 11.4, 5.7 Hz, 1H), 3.61-3.67 (m, 1H), 3.47-3.55 (m, 1H), 3.52 (d, J = 0.9 Hz, 1H). **(a -anomer)** ^{1}H NMR (300 MHz, DMSO) δ 7.80 (s, 1H), 7.59 (bs, 2H), 6.80 (d, J = 4.5 Hz, 1H), 6.54 (d, J = 4.2 Hz, 1H), 5.00 (d, J = 7.2 Hz, 1H), 4.89 (d, J = 4.8 Hz, 1H), 4.74 (t, J = 5.7 Hz, 1H), 4.58 (t, J = 4.5 Hz, 1H), 4.27 (m, 1H), 3.88 (m, 1H), 3.64-3.72 (m, 1H), 3.51-3.59 (m, 1H), 3.48 (d, J = 0.6 Hz, 1H). LCMS ***m/z*** 291 [M+H].

Example 17. (2R,3R,4R)-5-(4-aminopyrrolori,2-firi,2,41triazin-7-yl)-l,3,4-tris(benzyloxy) hexane-2,5-diol (Compound 14)

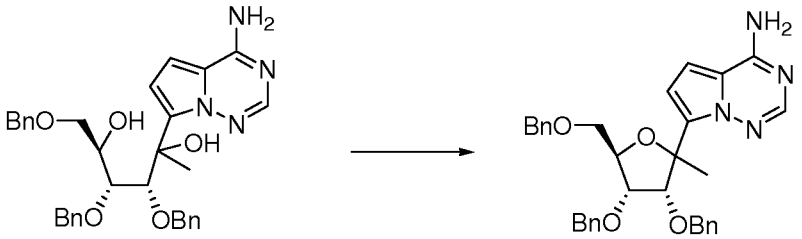


14

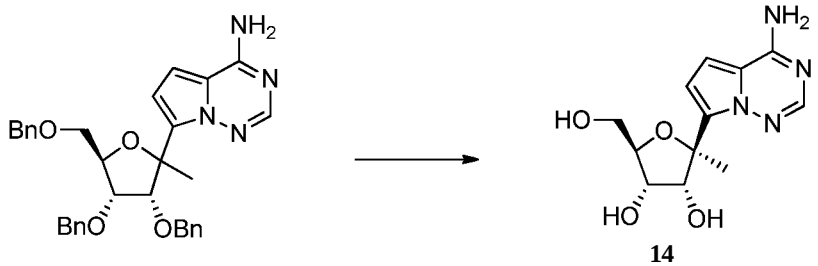
[0444] The preparation of (2R,3R,4R)-5-(4-aminopyrrolo[l,2-f][l,2,4]triazin-7-yl)-l,3,4-tris(benzyloxy)hexane-2,5-diol is described below.



[0445] The tribenzyl alcohol from Compound **1** synthesis (0.250 g, 0.453 mmol) was dissolved in anhydrous THF (25 mL) and stirred under N_2(g). The reaction mixture was cooled to 0°C and then a 3.0 N solution of methyl magnesium chloride in THF(1.2 mL, 3.62 mmol) was added. The reaction mixture was stirred overnight at RT. Acetic acid (1.5 mL) was added to quench the reaction and then the mixture was concentrated under reduced pressure. The residue was redissoved in CH_2CI_2 and subjected to a plug of silca gel eluting with 0 to 80% EtOAc in hexanes. The crude product (0.452 g) was then used in the next reaction without further purification. LCMS ***m/z*** 569 [M+H].



[0446] The crude methyl nucleoside (0.452 g, 0.796 mmol) was dissolved in anhydrous CH_2CI_2 (20 mL) and stirred under N_2(g). Methanesulfonic acid (0.2 mL, 2.78 mmol) was added and the reaction stirred for about 12 hr at RT. Et_3N (0.56 mL) was added to quench the reaction and then the mixture concentrated under reduced pressure. The residue was subjected to silica gel chromatography eluting with 0 to 75% EtOAc in Hexanes to yield the product as a mixture of anomers. LCMS ***m/z*** 551 [M+H].

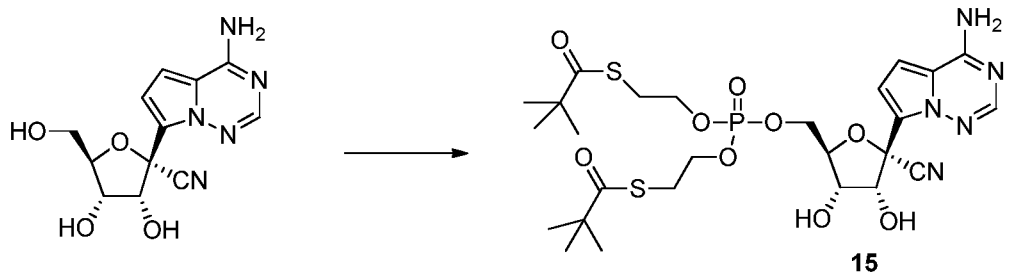


14

[0447] The tribenzyl nucleoside (0.20 g, 0.364 mmol) was dissolved in AcOH (30 mL). and charged with Pd/C (Degussa) (400 mg). The stirred mixture was flushed with N_2(g) three times and then ¾ (g) was introduced, The reaction was stirred under ¾ (g) for 2 h. and then the

catalyst removed by filtration. The solution was concentrated under reduced pressure and under the residue was re-dissolved in H_20. The solution was subjected to preparative HPLC under neutral conditions to provide the a-anomer and β-anomer **14.** **(a-anomer)** ^{1}H NMR (300 MHz, D_20) δ 7.81 (s, IH), 7.22 (d, IH), 6.75 (d, IH), 4.47 (d, IH), 4.25-4.31 (m, IH), 3.88-4.95 (m, IH), 3.58-3.86 (dd, 2H), 1.50 (s, 3H). **(β-anomer)** ^{1}H NMR (300 MHz, D_20) δ 7.91 (s, IH), 7.26 (d, IH), 6.90 (d, IH), 4.61 (d, IH), 4.00-4.09 (m, 2H), 3.63-3.82 (dd, 2H), 1.67 (s, 3H). LCMS *m/z* 281 [M+H].

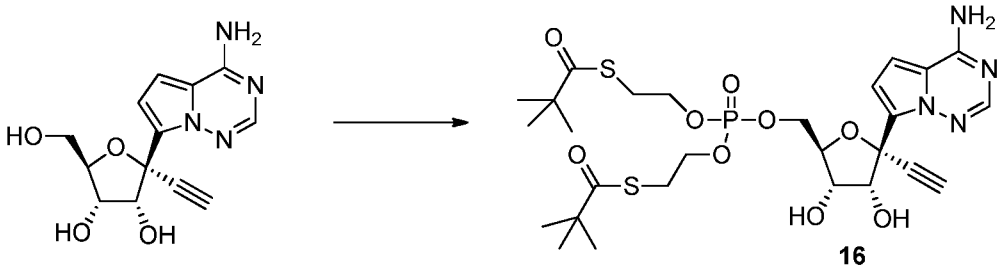
Example 18. 8,8'-2,2'-((((2R,38,4R,5R)-5-(4-aïηίηορνΓΓθ1οη,2-ηη,2,4]triaζίη-7-ν1)-5-cvano-3,4-dihvdroxytetrahvdrofuran-2-yl)methoxy)phosphoryl)bis(oxy)bis(ethane-2,l-diyl) bis(2,2-dimethylpropanethioate) (Compound 15)



15

[0448] The nucleoside **1** (0.028 g, 0.096 mmol) was dissolved in trimethylphosphate (1 mL). The reaction was stirred under N_2(g) and then treated with lH-tetrazole (0.021 g, 0.29 mmol). The reaction mixture was cooled to 0 °C and the phosphane (Nucleoside Nucleotides, Nucleic acids; 14; 3-5; 1995; 763 - 766. Lefebvre, Isabelle; Pompon, Alain; Perigaud, Christian; Girardet, Jean-Luc; Gosselin, Gilles; et al.) (87 mg, 0.192 mmol) was added. The reaction was stirred for 2 h. and then quenched with 30% hydrogen peroxide (0.120 mL). The mixture was stirred for 30 min at RT and then treated with saturated aqueous sodium thiosulfate (1 mL). The mixture was stirred for 10 min. and then concentrated under reduced pressure. The residue was subjected to preparative HPLC to isolate the title product **15.** ^{1}H NMR (300 MHz, CD_3CN) δ 7.98 (s, IH), 6.92 (d, IH), 6.81 (d, IH), 6.44 (bs, 2H), 4.82 (m, 2H), 4.47 (m, IH), 4.24 (m, 2H), 4.00 (m, 4H), 3.80 (bs, IH), 3.11 (m, 4H), 1.24 (s, 9H). ^{31}P NMR (121.4 MHz, CD_3CN) δ -1.85 (s). LCMS *m/z* 661 [M+H].

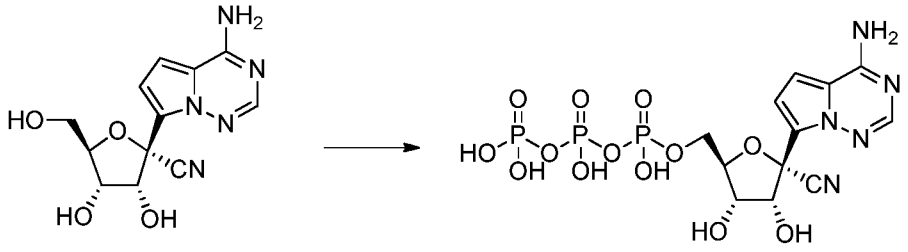
Example 19. S,S'-2,2'-((((2R, 3S, 4R, 5S)-5-(4-aminopyrrolori,2-firi,2,41triazin-7-yl)-5-ethvnyl-3,4-dihvdroxytetrahvdrofuran-2-yl)methoxy)phosphoryl)bis(oxy)bis(ethane-2,l-diyl) bis(2,2-dimethylpropanethioate) (Compound 16)



16

[0449] Compound **16** was prepared using the same method as compound **15** except substituting compound **13** as the starting nucleoside. ^{1}H NMR (300 MHz, CD_3CN) δ 7.91 (s, 1H), 6.86 (d, J = 4,8 Hz, 1H), 6.76 (d, J = 4.5 Hz, 1H), 6.29 (bs, 2H), 4.69 (t, J = 2.7 Hz, 1H), 4.58 (d, J = 5.7 Hz, 1H), 4.14-4.33 (m, 5H), 3.99-4.07 (m, 4H), 3.53 (d, J = 5.4 Hz, 1H), 3.11 (q, J = 5.7 Hz, 4H), 1.22 (s, 18H). LCMS ***m/z*** 658.9 [M+]. Tr=2.31

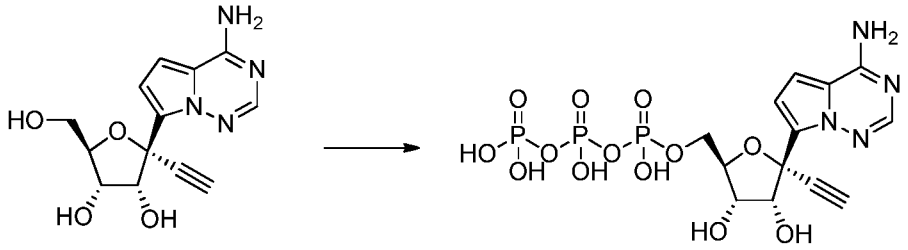
Example 20. ((2R. 3S. 4R. 5R)-5-(4-aminopyrrolori.2-flri.2.41triazin-7-yl)-5-cvano-3.4-dihydroxytetrahvdrofuran-2-yl)methyl tetrahydrogen triphosphate (Compound 17)



17

[0450] Compound **17** was prepared from compound **1** using a similar procedure to the preparation of compound **6**. The product was isolated as the sodium salt. ^{1}H NMR (400 MHz, D_20) δ 7.76 (s, 1H), 6.88 (d, J = 4.8 Hz, 1H), 6.73 (d, J = 4.4 Hz, 1H), 4.86 (d, J = 5.2 Hz, 1H), 4.43 (m, 1H), 4.39 (m, 1H), 4.05 (m, 1H), 3.94 (m, 1H). ^{31}P NMR (121.4 MHz, D_20) δ -5.4 (d, IP), -10.8 (d, IP), -21.1 (t, IP). LCMS ***m/z*** 530 [M-H], 531.9 [M+H] Tr = 0.22 min. HPLC ion exchange Tr=9.95 min.

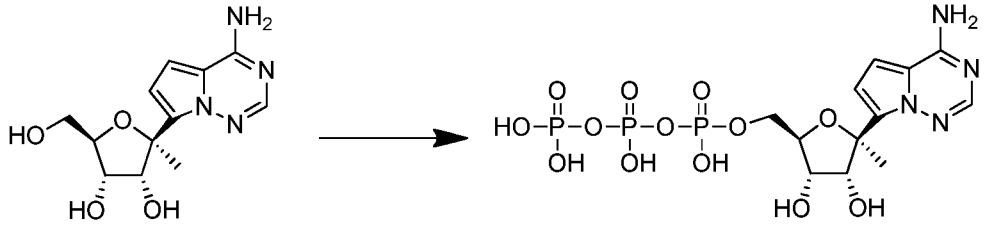
Example 21. ((2R, 3S, 4R, 5S)-5-(4-aminopyrrolori.2-firi.2.41triazin-7-yl)-5-ethvnyl-3.4-dihydroxytetrahvdrofuran-2-yl)methyl_tetrahydrogen_triphosphate_(Compound_18)



18

[0451] Compound **18** was prepared from compound **13** using a similar procedure to the preparation of compound **6**. The product was isolated as the TEA salt. ^{1}H NMR (300 MHz, D_2O) δ 7.85 (s, 1H), 7.09 (d, J = 4.6 Hz, 1H), 6.95 (d, J = 4.7 Hz, 1H), 4.23 (m, 2H), 4.08 (m, 2H), 3.06 (q, J = 7.4 Hz, 20H), 1.14 (t, J = 7.3 Hz, 30H). ^{31}P NMR (121.4 MHz, D_2O) δ -10.8 (d, IP), -11.2 (d, IP), -23.2 (t, IP). LCMS *m/z* 530.8 [M+H], Tr = 0.46. HPLC ion exchange Tr = 9.40 min.

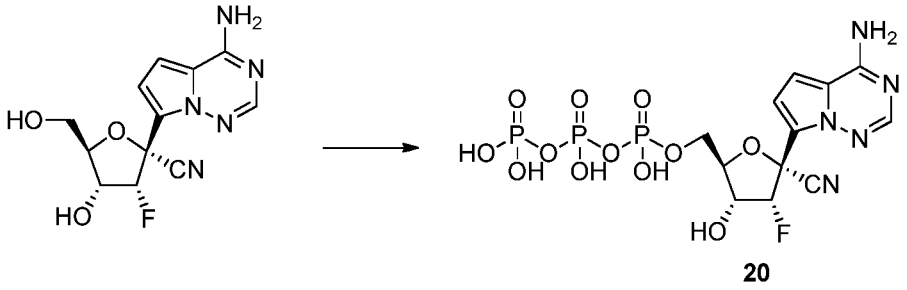
Example 22. ((2R, 3S, 4R, 5S)-5-(4-aminopyrrolori,2 -flri,2,41triazin-7-yl)-3,4-dihvdroxy-5-methyltetrahvdrofuran-2-yl)methyl tetrahydrogen triphosphate (Compound 19)



19

[0452] Compound **19** was prepared from compound **14** using a similar procedure to the preparation of compound **6**. ^{1}H NMR (400 MHz, D_2O) δ 7.78 (s, 1H), 6.98 (m, 1H), 6.84 (m, 1H), 4.45 (m, 1H), 4.04 (m, 4H), 1.54 (s, 3H). ^{31}P NMR (161 MHz, D_2O) δ -10.6 (m), -23.0 (m). LCMS *m/z* 521.0 [M+H].

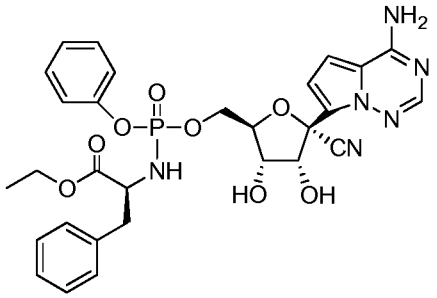
Example 23. ((2R.3R.4R.5R)-5-(4-aminopyrrolori.2-firi.2.41triazin-7-yl)-5-cvano-4-fluoro-3-hydroxytetrahvdrofuran-2-yl)methyl tetrahydrogen triphosphate (Compound 20)



20

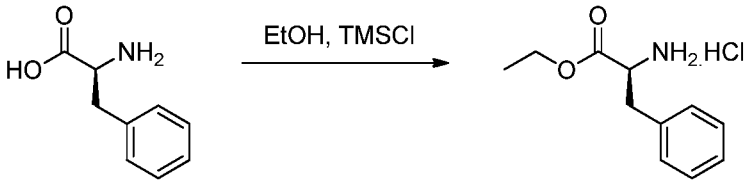
[0453] Compound **20** was prepared from compound **2** using a similar procedure to the preparation of compound **6**. ^{1}H NMR (400 MHz, D_2O) δ 7.78 (s, 1H), 6.93 (d, J = 4.4 Hz, 1H), 6.78 (d, J = 4.8 Hz, 1H), 5.45 (dd, J = 53, 4.4 Hz, 1H), 4.38-4.50 (m, 2H), 4.13-4.20 (m, 2H). ^{31}P NMR (161 MHz, D_2O) δ -5.7 (d, IP), -11.0 (d, IP), -21.5 (t, IP). LCMS ***m/z*** 533.9.0 [M+H], 532.0 [M-H] Tr = 1.25 min. HPLC ion exchange Tr=11.0 min.

Example 24. (2S)-ethyl 2-(((((2R,3S,4R,5R)-5-(4-aminopyrrolor2 ,l-firi,2,41triazin-7-yl)-5-cvano-3,4-dihvdroxytetrahvdrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)-3-phenylpropanoate (21)



[0454] The preparation of (2S)-ethyl 2-(((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,l-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)-3-phenylpropanoate is described below.

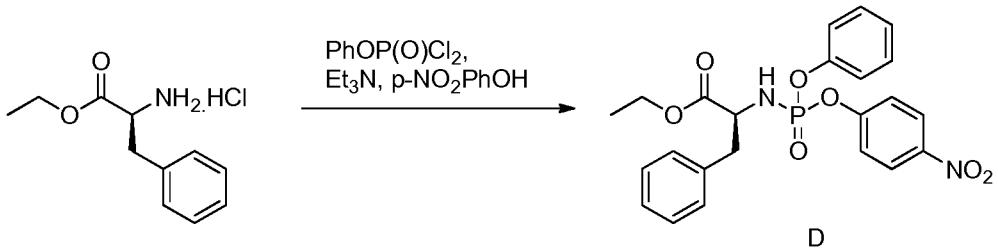
Preparation of (S)-ethyl 2-amino-3-phenylpropanoate hydrochloride.



[0455] L-Phenylalanine (5 g, 30 mmol) was taken up in EtOH (30 mL). TMSC1 (6.915 mL, 54 mmol) was added to the reaction at RT. The reaction vessel was fitted with a reflux condenser

and the reaction was placed in an 80 °C bath. The reaction was stirred overnight. The next day the reaction was cooled to RT, concentrated under reduced pressure and the resulting residue was taken up in Et_20. The resulting slurry was filtered and the isolate solids were further washed with Et_20. The washed solids were placed under high vacuum to yield example (S)-ethyl 2-amino-3-phenylpropanoate hydrochloride. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 (s, 3H), 7.30 (m, 5H), 4.24 ***(ABX,*** J_{AX} = 7.8 Hz, J_{BX} = 6.2 Hz, 1H), 4.11 (m, 2H), 3.17, 3.05 ***(ABX,*** J_{AB} = -14 Hz, J_{BX} = 5.8 Hz, J_{AX} = 7.6 Hz, 2H), 1.09 (t, *J* =6.8 Hz, 3H).

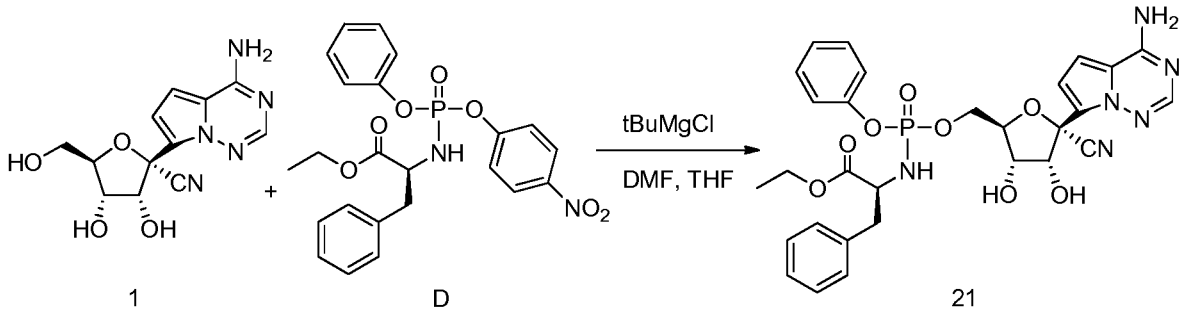
Preparation of (2S)-ethyl 2-(((4-nitrophenoxy)(phenoxy)phosphoryl)amino)-3-phenylpropanoate (Compound D)



D

[0456] (S)-ethyl 2-amino-3-phenylpropanoate hydrochloride (1.01 g, 4.41 mmol) was dissolved in DCM (50 mL). This solution was cooled to about 0 °C and $PhOP(0)Cl_2$ (0.656 mL, 4.41 mmol) was added, followed by the slow addition of Et_3N (1.62 mL, 11.5 mmol) over 5 min. The cold bath was removed and the reaction was allowed to warm to RT and stir over a period of 80 min. p-$N0_2PhOH$ (0.583 g, 4.19 mmol) was added, followed by more Et_3N (0.3 mL, 2.1 mmol). The reaction progress was monitored by LC/MS. Upon completion of the reaction, it was diluted with Et_20, and the resulting solids were removed by filtration. The filtrate was concentrated and compound **D** was isolated by silica gel column chromatography (25 g dry load cartridge, 120 g column; eluent: 100% hexanes ramping to 55% EtOAc in hexanes). ^{1}H NMR (400 MHz, CD_3OD) δ 8.17 (m, 2H), 7.33 (m, 2H), 7.09-7.25 (m, 10H), 4.17 (m, 1H), 4.07 (m, 2H), 3.08 (m, 1H), 2.84 (m, 1H), 1.14 (m, 3H). ^{31}P NMR (162 MHz, DMSO-d_6) δ -1.479 (s), -1.719 (s). MS ***m/z*** = 471.01 [M+l].

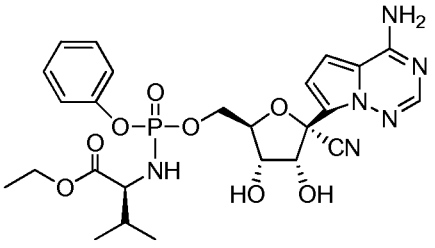
Preparation of (2S)-ethyl 2-rrrrr2R.3S.4R.5R)-5-r4-aminopyrrolor2.1-firi.2.41triazin-7-yl)-5-cvano-3^-dihvdroxytetrahvdrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)-3-phenylpropanoate (Compound 21)



1 D 21

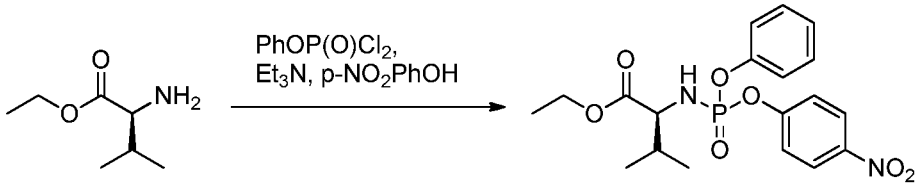
[0457] Compound **1** (0.030 g, 0.103 mmol) was dissolved in DMF (1 mL) and then THF (0.5 mL) was added. i-BuMgCl (1M/THF, 154.5 μL, 0.154 μιηοϊ) was added to the reaction in a drop-wise manner with vigorous stirring. The resulting white slurry was stirred at RT for about 30 min. A solution of compound **D** (0.058 g, 0.124 mmol) in THF (1 mL) was added in a drop-wise manner to the reaction at RT. The reaction progress was monitored by LC/MS. When the reaction progressed to 50% conversion, the reaction was cooled in an ice bath and quenched with glacial acetic acid (70 μL). The reaction was concentrated and compound **21** was isolated from the residue by reverse phase HPLC. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.91 (d, *J* = 4 Hz, 1H), 7.90 (brs, 2H), 7.09-7.30 (m, 8H), 7.01, (t, *J* = 8.2 Hz, 2H), 6.89 (d, *J* = 4.4 Hz, 1H), 6.82 (t, *J* = 4.4 Hz, 1H), 6.27 (m, 1H), 6.14 (m, 1H), 5.34 (m, 1H), 4.62 (t, *J* = 5.6 Hz, 1H), 4.15 (m, 1H), 3.78-4.01 (m, 6H), 2.92 (m, 1H), 2.78 (m, 1H), 1.04 (m, 3H). ^{31}P NMR (162 MHz, DMSO-d$_6$) δ 3.69 (s), 3.34 (s). MS *m/z* = 623.0 [M+H].

Example 25. (2S)-ethyl 2-(((((2R.3S.4R.5R)-5-(4-aminopyrrolor2.1-firi.2.41triazin-7-yl)-5-cvano-3,4-dihvdroxytetrahvdrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)-3-methylbutanoate (22)



[0458] The preparation of (2S)-ethyl 2-(((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2, 1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)-3-methylbutanoate is described below.

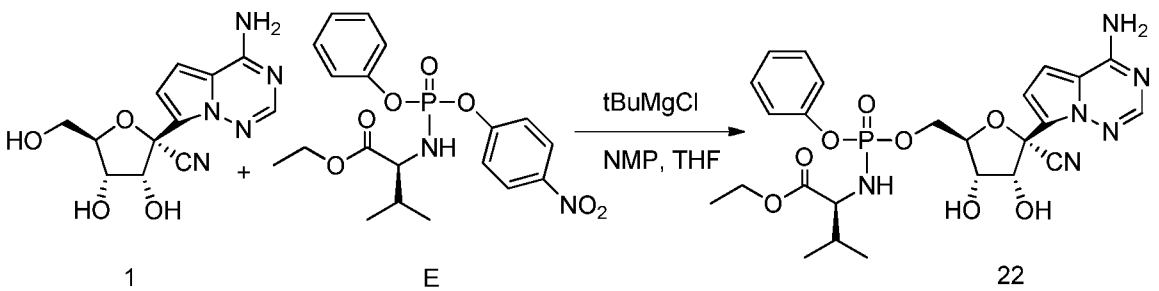
Preparation of (2S)-ethyl 3-methyl-2-(((4-nitrophenoxy)(phenoxy)phosphoryl)amino) butanoate (Compound E)



E

[0459] The (S)-ethyl 2-amino-3-methylbutanoate (0.351 g, 1.932 mmol) was dissolved in DCM (17 mL). This solution was cooled in an ice bath and $PhOP(O)Cl_2$ (0.287 mL, 1.932 mmol) was added, followed by the slow addition of Et_3N (1.62 mL, 11.4 mmol) over about 5 min. The cold bath was removed and the reaction was allowed to warm to RT and stir over a period of 1 h. *p*-NO_2PhOH (0.255 g, 1.836 mmol) was added, and the reaction progress was monitored by LC/MS. Upon completion of the reaction, the mixture was diluted with Et_2O, and the resulting solids were removed by filtration. The filtrate was concentrated and compound **E** was isolated by silica gel column chromatography (12 g dry load cartridge, 80 g column; eluent: 100% hexanes ramping to 55% EtOAc in hexanes). ^1H NMR (400 MHz, DMSO-d_6) δ 8.30 (d, ***J*** = 9.2 Hz, 2H), 7.48 (t, *J* = 9.6 Hz, 2H), 7.40 (t, *J* = 7.8 Hz, 2H), 7.20-7.27 (m, 3H), 6.60 (quart, ***J*** = 11.6 Hz, 1H), 4.01 (m, 2H), 3.61 (m, 1H), 1.93 (m , 1H), 1.11 (m, 3H), 0.79 (m, 6H). ^{31}P NMR (162 MHz, DMSO-d_6) δ -0.342 (s), -0.578 (s). MS ***m/z*** = 422.9 [M+H].

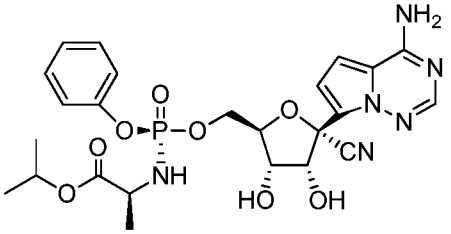
Preparation of (2S)-ethyl 2-(((((2R,3S,4R,5R)-5-(4-aminopyrrolor2, 1-firi,2,41triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)-3-methylbutanoate (Compound 22)



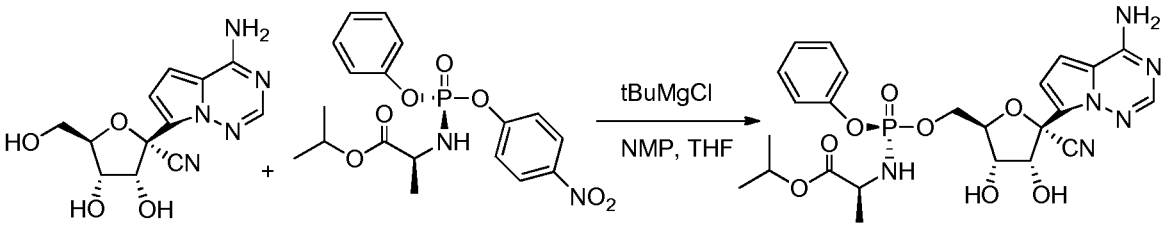
1 E 22

[0460] Compound **1** (0.040 g, 0.137 mmol) was dissolved in NMP (1.5 mL) and then THF (0.25 mL) was added. This solution was cooled in an ice bath and i-BuMgCl (1M/THF, 425.7 μL, 0.426 μιηοϊ) was added in a drop-wise manner with vigorous stirring. The ice bath was removed and the resulting white slurry was stirred at RT for about 15 min. A solution of compound **E** (0.081 g, 0.192 mmol) in THF (0.5 mL) was added in a drop-wise manner to the reaction at RT. The reaction progress was monitored by LC/MS. When the reaction progressed to 50% conversion, the reaction was cooled in an ice bath and quenched with glacial acetic acid (70 μL). The reaction was concentrated and compound **22** was semi-purified from the residue by reverse phase HPLC. The semi-pure material was further purified by silica gel column chromatography (12 g dry load cartridge, 40 g column; eluent: 100% EtOAc ramping to 10% MeOH in EtOAc) to yield compound **22.** ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.91 (d, *J* = 1.6 Hz, 1H), 7.88 (brs, 2H), 7.32 (m, 2H), 7.15 (m, 3H), 6.90 (t, *J* = 4.2 Hz, 1H), 6.84 (d, *J* = 4.8 Hz, 1H), 6.26 (dd, *J* = 13.4, 6.2 Hz, 1H), 5.87 (quart. *J* = 11.2 Hz, 1H), 5.35 (m, 1H), 4.64 (m, 1H), 4.25 (m, 2H), 3.93-4.15 (m, 4H), 3.45 (m, 1H), 1.87 (m, 1H), 1.09-1.16 (m, 3H), 0.70-0.83 (m ,6H). ^{31}P NMR (162 MHz, DMSO-d$_6$) δ 4.59 (s), 4.47 (s). MS ***m/z*** = 575.02 [M+H].

Example 26. (S)-isopropyl 2-(((R)-(((2R,3S,4R,5R)-5-(4-aminopyrrolor2 ,l-firi,2,41triazin-7-yl)-5-cvano-3,4-dihvdroxytetrahvdrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino) propanoate (23)



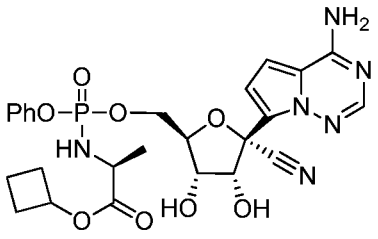
[0461] The preparation of (S)-isopropyl 2-(((R)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2, 1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate is described below.



1 **F** **23**

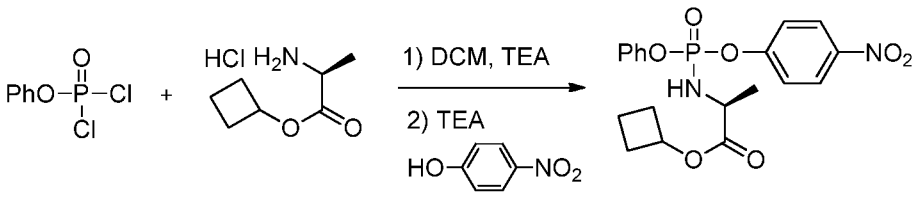
[0462] Compound **1** (60.0 mg, 206 μηοϊ) was dissolved in NMP (0.28 mL). THF (0.2 mL) was added followed by tert-butyl magnesium chloride (1.0M solution in tetrahydrofuran, 0.309 mL) at RT under an argon atmosphere. After 20 min, a solution of compound **F** (Prepared according to Cho, A. et al *J. Med. Chem.* **2014,** 57, 1812-1825., 81 mg, 206 μηοϊ) in THF (0.2 mL) was added, and the resulting mixture was warmed to about 50 °C. After 3 h, the reaction mixture was allowed to cool to RT and was purified directly by preparatory HPLC (Phenominex Synergi 4u Hydro-RR 80Å 150 x 30 mm column, 5-100% acetonitrile/water gradient) to afford compound **23.** ^{1}H NMR (400 MHz, CD_3OD) δ 7.86 (s, 1H), 7.34 - 7.26 (m, 2H), 7.21 - 7.12 (m, 3H), 6.91 (d, *J* = 4.6 Hz, 1H), 6.87 (d, *J* = 4.6 Hz, 1H), 4.92 (sept, *J* = 6.3 Hz, 1H), 4.80 (d, *J* = 5.4 Hz, 1H), 4.43 - 4.34 (m, 1H), 4.33 - 4.24 (m, 1H), 4.18 (t, *J* = 5.6 Hz, 1H), 3.82 (dq, *J* = 9.7, 7.1 Hz, 2H), 1.27 (dd, *J* = 7.1, 1.0 Hz, 3H), 1.18 (dd, *J* = 6.3, 4.8 Hz, 6H). ^{31}P NMR (162 MHz, CD_3OD) δ 3.72 (s). LC/MS: t_R = 1.39 min, MS *m/z* = 561.11 [M+H]; LC system: Thermo Accela 1250 UHPLC; MS system: Thermo LCQ Fleet; Column: Kinetex 2.6μ XB-C18 100A, 50 x 4.6 mm; Solvents: ACN with 0.1% acetic acid, water with 0.1% acetic acid; Gradient: 0 min-2.0 min 2-100% ACN, 2.0 min-3.05 min 100% ACN, 3.05 min-3.2 min 100%-2% ACN, 3.2 min-3.5 min 2% ACN at 2μι/ηιη. HPLC: t_R = 2.523 min; HPLC system: Agilent 1100 series.; Column: Gemini 5μ C18 110A, 50 x 4.6 mm; Solvents: ACN with 0.1% TFA, Water with 0.1% TFA; Gradient: 0 min-5.0 min 2-98% ACN, 5.0 min-6.0 min 98% ACN at 2 mL/min.

Example 27. (2S)-cvclobutyl 2-(((((2R,3S,4R,5R)-5-(4-aminopyrrolor2,l-firi,2,41triazin-7-yl)-5-cvano-3,4-dihvdroxytetrahvdrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino) propanoate (24)



[0463] The preparation of (2S)-cyclobutyl 2-(((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,l-f][l,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy) phosphoryl)amino)propanoate is described below.

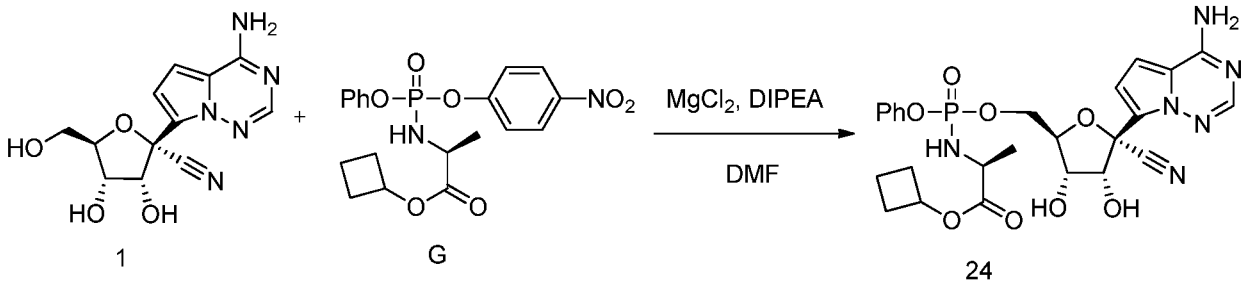
Preparation of (2S)-cyclobutyl 2-(((4-nitrophenoxy)(phenoxy)phosphoryl)amino)propanoate (Compound G)



G

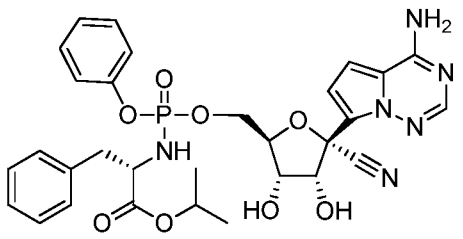
[0464] Phenyl dichlorophosphate (1.49 mL, 10 mmol) was dissolved in 10 mL of anhydrous DCM and stirred under atmosphere nitrogen in an ice bath. L-Alanine isobutyl ester hydrochloride (0.9 g, 5 mmol) was added in one portion. Triethylamine (765 µL, 5.5 mmol) was then added dropwise. Reaction stirred for about 1 h. More Triethylamine (765 µL, 5.5 mmol) was added dropwise and the reaction was stirred for about 45 min. p-Nitrophenol (1.25g, 9mmol) was added in one portion and stirred for about 30 min. Triethylamine (765 µL, 5.5 mmol) was added and the reaction mixture was stirred for about 2 h. Additional p-nitrophenol (1.25g, 9 mmol) and triethylamine (765 µL, 5.5mmol) were then added, and the reaction was stirred for another about 2 h. The reaction mixture was concentrated under reduced pressure. The resulting crude was diluted with EtOAc and washed twice with 5% aqueous citric acid solution, followed with saturated aqueous sodium chloride solution. The organic layer was then dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude residue was purified with silica gel column (0-20-50% EtOAc in hexanes) to give compound **G**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.33 - 8.23 (m, 2H), 7.52 - 7.33 (m, 4H), 7.33 - 7.17 (m, 3H), 4.96 - 4.85 (m, 1H), 4.07 - 3.96 (m, 1H), 2.27 (m, 2H), 2.07 - 1.91 (m, 2H), 1.83 - 1.70 (m, 1H), 1.70 - 1.55 (m, 1H), 1.32 (m, 3H). ^{31}P NMR (162 MHz, CD_3OD) δ -1.36, -1.59. MS *m/z* = 420.9 [M+H].

Preparation (2S)-cvclobutyl 2-rrrrr2R,3S,4R,5R)-5-r4-aminopyrrolor2,l-firi,2,41triazin-7-yl)-5-cvano-3,4-dihvdroxytetrahvdrofuran-2-yl)methoxy)(phenoxy)phosphoryl)arnino)propanoate (Compound 24)



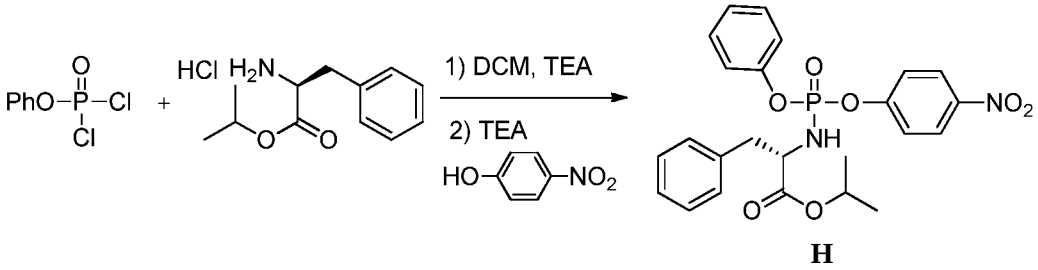
[0465] Compound **1** (58 mg, 0.2 mmol) was mixed with compound **G** (101 mg, 0.24 mmol) in 2 mL of anhydrous DMF. Magnesium chloride (42 mg, 0.44 mmol) was added in one portion. The reaction mixture was heated to about 50 °C. DIPEA (87 μE, 0.5 mmol) was added, and the reaction was stirred for about 2 h at about 50 °C. The reaction mixture was cooled to room temperature, was diluted with EtOAc and was washed with 5% aqueous citric acid solution followed by saturated aqueous sodium chloride solution. The organic layer was then dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude residue was purified with silica gel column (0-2-5% MeOH in DCM) to afford compound **24.** ^{1}H NMR (400 MHz, Methanol-^) δ 7.85 (m, 1H), 7.34 - 7.22 (m, 2H), 7.22 - 7.08 (m, 3H), 6.94 - 6.84 (m, 2H), 4.95 - 4.85 (m, 1H), 4.79 (m, 1H), 4.46 - 4.34 (m, 2H), 4.34 - 4.24 (m, 1H), 4.19 (m, 1H), 3.81 (m, 1H), 2.27 (m, 2H), 2.01 (m, 2H), 1.84 - 1.68 (m, 1H), 1.62 (m, 1H), 1.30 - 1.16 (m, 3H). ^{31}P NMR (162 MHz, cd_3od) δ 3.70, 3.65. MS *mJz* = 573.0 [M+H].

Example 28. (2S)-isopropyl 2-(((((2R,3S,4R,5R)-5-(4-aminopyrrolor2,l-firi,2,41triazin-7-yl)-5-cvano-3,4-dihvdroxytetrahvdrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)-3-phenylpropanoate (25)



[0466] The preparation of (2S)-isopropyl 2-(((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,l-f][l,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)-3-phenylpropanoate is described below.

Preparation of (2S)-isopropyl 2-(((4-nitrophenoxy)(phenoxy)phosphoryl)amino)-3-phenylpropanoate (Compound H)

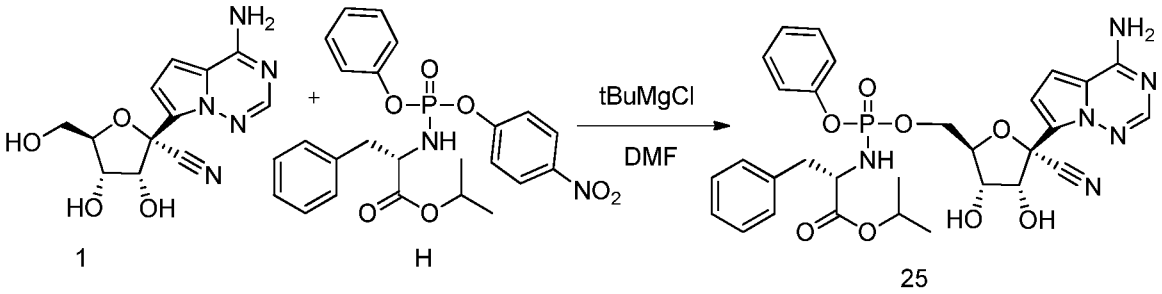


H

[0467] Phenyl dichlorophosphate (718 μL, 4.8 mmol) was dissolved in 10 mL of anhydrous DCM and stirred under a nitrogen atmosphere in an ice bath. L-Phenylalanine isopropyl ester hydrochloride (1 g, 4.1 mmol) was added in one portion. Another 10 mL of anhydrous DCM was added. Triethylamine (736 μL, 5.3 mmol) was added dropwise and the reaction mixture was stirred for about 30 min. More triethylamine (736 μL, 5.3 mmol) was then added dropwise and the reaction mixture was stirred for 30 min. Additional triethylamine (736 μL, 5.3 mmol) was then added dropwise and the reaction mixture was stirred for about 15 min. p-Nitrophenol (600 mg, 4.32 mmol) was then added. The ice bath was then removed and the reaction mixture was allowed to warm to room temperature and stirred for about 2 h. More p-nitrophenol (50 mg) and triethylamine (736 μL, 5.3 mmol) were the added and the reaction mixture was stirred for about l h.

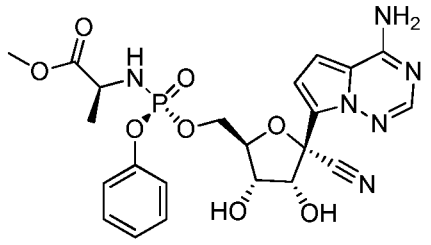
[0468] The reaction mixture was then concentrated under reduced pressure, and was diluted with EtOAc and washed twice with 5% aqueous citric acid solution, followed with saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate and was concentrated under reduced pressure. The crude was purified with silica gel column (0-15% EtOAc in hexanes) to give compound **H.** ^{1}H NMR (400 MHz, $CDC1_3$) δ 8.17 (m, 2H), 7.38 - 7.13 (m, 10H), 7.13 - 7.02 (m, 2H), 4.95 (m, 1H), 4.31 (m, 1H), 3.69 (m, 1H), 3.02 (dd, *J* = 6.1, 1.8 Hz, 2H), 1.21 - 1.08 (m, 6H). ^{31}P NMR (162 MHz, cdcl3) δ -2.96, -2.98. MS *m/z* = 485.0 [M+H].

Preparation of (2S)-isopropyl 2-rrrrr2R,3S,4R,5R)-5-r4-aminopyrrolor2,l-firi,2,41triazin-7-yl)-5-cvano-3^-dihvdroxytetrahvdrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)-3-phenylpropanoate (Compound 25)

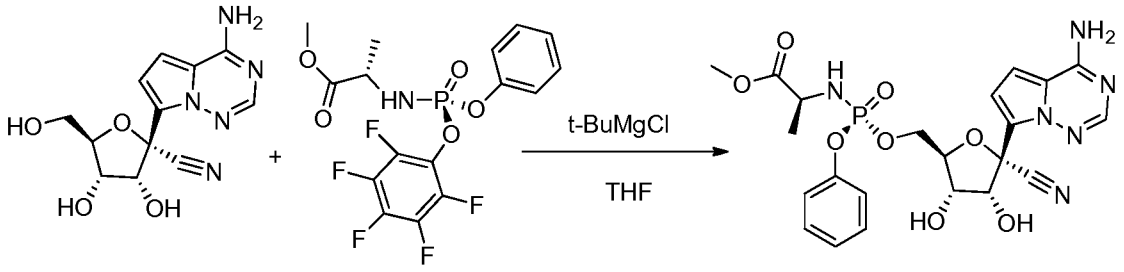


[0469] Compound **1** (58 mg, 0.2 mmol) and compound **H** (116 mg, 0.24 mmol) were mixed and 2 mL of anhydrous DMF was added. The reaction mixture was stirred under a nitrogen atmosphere at room temperature. 1M tBuMgCl in THF (300 μL, 0.3 mmol) was added dropwise over 3 minutes and the reaction mixture was then stirred for about 16 h. The reaction mixture was diluted with EtOAc and washed with 5% aqueous citric acid solution, saturated aqueous sodium bicarbonate solution and then saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude residue was purified with silica gel column (0-5% MeOH in DCM) to give compound **25.** ^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (m, 1H), 7.27 - 7.08 (m, 8H), 7.08 - 6.97 (m, 2H), 6.88 (m, 2H), 4.91 - 4.84 (m, 1H), 4.74 (m, 1H), 4.26 (m, 1H), 4.19 - 4.04 (m, 2H), 4.04 - 3.91 (m, 2H), 2.97 (m, 1H), 2.82 (m, 1H), 1.14 (m, 3H), 1.06 (m, 3H). ^{31}P NMR (162 MHz, CD_3OD) δ 3.63, 3.25. MS *m/z* = 637.0 [M+H].

Example 29. (S)-methyl 2-(((S)-(((2R,3S,4R,5R)-5-(4-aminopyrrolor2 ,l-firi,2,41triazin-7-yl)-5-cvano-3,4-dihvdroxytetrahvdrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino) propanoate (26)



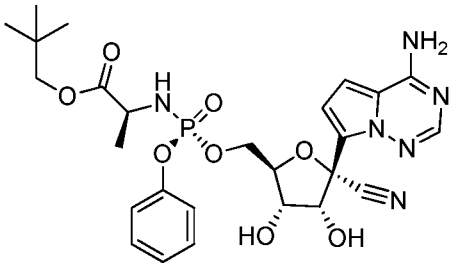
[0470] The preparation of (S)-methyl 2-(((S)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,l-f][l,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate is described below.



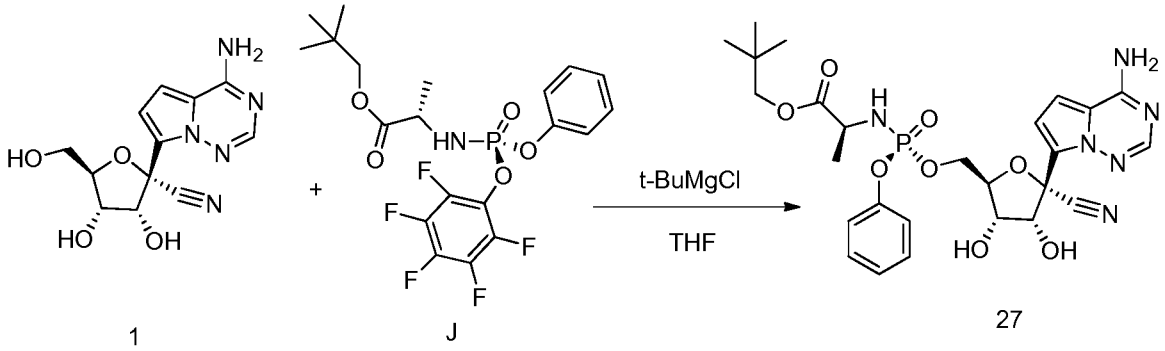
1 I **26**

[0471] Compound **1** (100 mg, 0.34 mmol) was dissolved in THF (2 mL) and cooled with an ice water bath. Then 1M t-BuMgCl (0.52 mL, 0.77 mmol) was added dropwise slowly. The resulting mixture was stirred for about 30 min at room temperature. Then compound I (Prepared according to WO 2012142085, 219 mg, 0.52 mmol) in THF (2 mL) was added over 5 min and the resulting mixture was stirred for about 24 h at room temperature. The reaction mixture was then diluted with EtOAc, cooled under ice-water bath, washed with aq $NaHC0_3$ (2 mL), washed with brine, dried with sodium sulfate, and concentrated *in vacuo.* The resulting mixture was purified by silica gel column chromatography (MeOH 0 to 20% in DCM) and prep-HPLC (acetonitrile 10 to 80% in water) to give compound **26.** ^1H NMR (400 MHz, CD_3OD) δ 7.86 (s, 1H), 7.29 (dd, *J* = 8.6, 7.2 Hz, 2H), 7.21 - 7.09 (m, 3H), 6.94 - 6.81 (m, 2H), 4.79 (d, *J* = 5.4 Hz, 1H), 4.38 (ddq, *J* = 10.8, 5.3, 2.7 Hz, 2H), 4.33 - 4.23 (m, 1H), 4.18 (t, *J* = 5.5 Hz, 1H), 3.86 (dq, *J* = 9.9, 7.1 Hz, 1H), 3.62 (s, 3H), 1.27 (dd, *J* = 7.2, 1.1 Hz, 3H). MS m/z = 533 $(M+l)^+$.

Example 30. (S)-neopentyl 2-(((S)-(((2R,3S,4R,5R)-5-(4-aminopyrrolor2 ,l-firi,2,41triazin-7-yl)-5-cvano-3,4-dihvdroxytetrahvdrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino) propanoate (27)

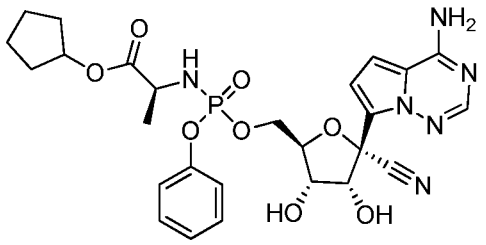


[0472] The preparation of (S)-neopentyl 2-(((S)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate is described below.

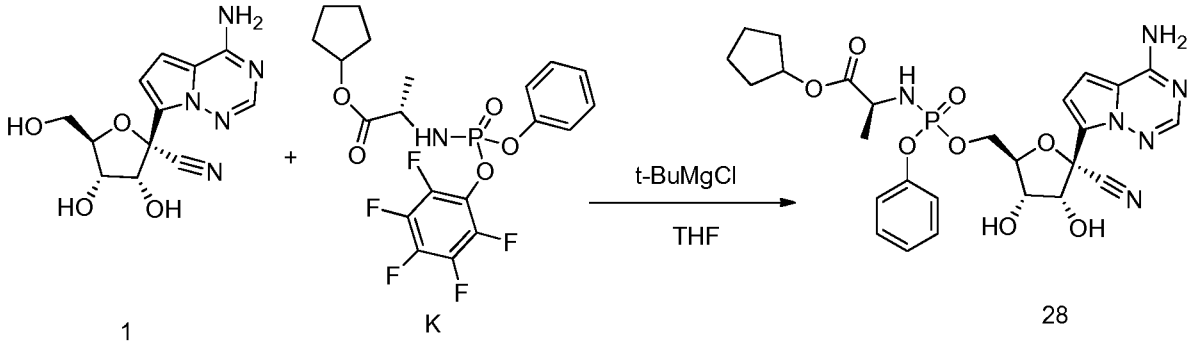


[0473] Compound **1** (100 mg, 0.34 mmol) was dissolved in THF (2 mL) and cooled under ice water bath. Then 1M t-BuMgCl (0.52 mL, 0.77 mmol) was added dropwise slowly. The resulting mixture was stirred for about 30 min at room temperature. Then compound **J** (Prepared according to WO2012075140, 248 mg, 0.52 mmol) was added over about 5 min and the resulting mixture was stirred for about 24 h at room temperature, diluted with EtOAc, cooled under ice-water bath, treated with aq $NaHCO_3$ (2 mL), washed with brine, dried with sodium sulfate, and concentrated *in vacuo*. The resulting mixture was purified by silica gel column chromatography (MeOH 0 to 20% in DCM) and prep-HPLC (acetonitrile 10 to 80% in water) to give Compound **27.** ^{1}H NMR (400 MHz, CD_3OD) δ 7.86 (s, 1H), 7.36 - 7.24 (m, 2H), 7.23 - 7.10 (m, 3H), 6.96 - 6.85 (m, 2H), 4.78 (d, *J* = 5.4 Hz, 1H), 4.38 (tdd, *J* = 10.0, 4.9, 2.5 Hz, 2H), 4.32 - 4.24 (m, 1H), 4.17 (t, *J* = 5.6 Hz, 1H), 3.91 (dq, *J* = 9.8, 7.1 Hz, 1H), 3.81 (d, *J* = 10.5 Hz, 1H), 3.69 (d, *J* = 10.5 Hz, 1H), 1.31 (dd, *J* = 7.2, 1.1 Hz, 3H), 0.89 (s, 9H). MS m/z = 589 **$(M+l)^+$.**

Example 31. (2S)-cvclopentyl 2-(((((2R,3S,4R,5R)-5-(4-aminopyrrolor2,l-firi,2,41triazin-7-yl)-5-cvano-3,4-dihvdroxytetrahvdrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino) propanoate (28)

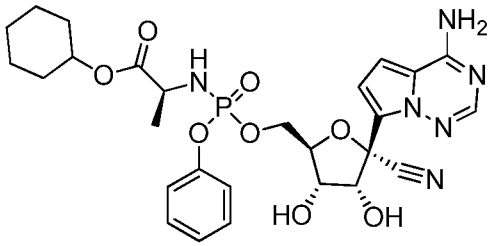


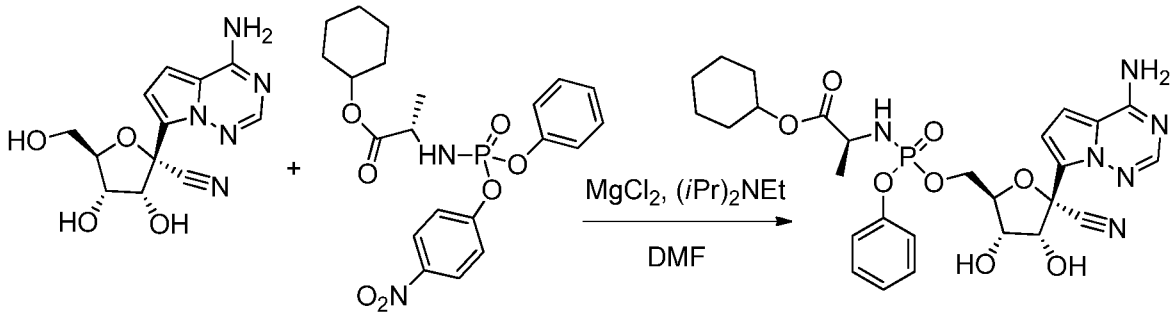
[0474] The preparation of (2S)-cyclopentyl 2-(((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,l-f][l,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate is described below.



[0475] Compoundl (100 mg, 0.34 mmol) was dissolved in THF (2 mL) and cooled under ice water bath. Then 1M t-BuMgCl (0.52 mL, 0.77 mmol) was added dropwise slowly. The resulting mixture was stirred for about 30 min at room temperature. Then compound **K** (Prepared according to WO2012075140, 247 mg, 0.52 mmol) in THF (2 mL) was added over about 5 min and the resulting mixture was stirred for about 24 h at room temperature, diluted with EtOAc, cooled under ice-water bath, treated with aq $NaHCO_3$ (2mL), washed with brine, dried with sodium sulfate, and concentrated *in vacuo.* The resulting mixture was purified by silica gel column chromatography (MeOH 0 to 20% in DCM) and prep-HPLC (acetonitrile 10 to 80% in water) to give example **28.** ^{1}H NMR (400 MHz, CD_3OD) δ 7.85 (s, 1H), 7.33 - 7.22 (m, 2H), 7.14 (tdd, *J* = 7.6, 2.1, 1.1 Hz, 3H), 6.95 - 6.87 (m, 2H), 5.13 - 5.00 (m, 1H), 4.78 (d, *J* = 5.4 Hz, 1H), 4.48 - 4.35 (m, 2H), 4.30 (ddd, *J* = 10.6, 5.7, 3.6 Hz, 1H), 4.19 (t, *J* = 5.4 Hz, 1H), 3.78 (dq, *J* = 9.2, 7.1 Hz, 1H), 1.81 (dtd, *J* = 12.5, 5.9, 2.4 Hz, 2H), 1.74 - 1.49 (m, 6H), 1.21 (dd, *J = 1.1,* 1.2 Hz, 3H). MS m/z = 587 $(M+l)^+$.

Example 32. (2S)-cvclohexyl 2-(((((2R.3S.4R.5R)-5-(4-aminopyrrolor2.1-firi.2.41triazin-7-yl)-5-cvano-3,4-dihvdroxytetrahvdrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino) propanoate *(29)*

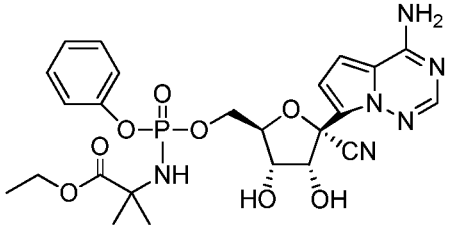




1 M 29

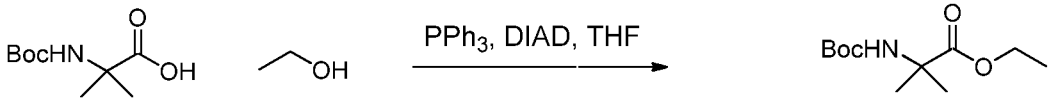
[0476] To a mixture of compound **1** (50 mg, 0.343 mmol), compound M (Prepared according to US20130143835, 93 mg, 0.209 mmol), and MgCl2 (24.5 mg, 0.257 mmol) in DMF (1 mL) was added diisopropylethylamine (0.075 mL, 0.43 mmol) dropwise over about 5 min at about 0 °C. The resulting mixture was stirred at about 50 °C for about 1 h. The reaction mixture was then cooled with an ice-water bath, treated with 1M citric acid (0.5 mL), and was purified directly by prep-HPLC (ACN 0 to 70% in water) to afford compound **29.** ^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (s, 1H), 7.32 - 7.23 (m, 2H), 7.18 - 7.10 (m, 3H), 6.93 - 6.87 (m, 2H), 4.78 (d, *J* = 5.4 Hz, 1H), 4.67 (td, *J* = 8.7, 4.2 Hz, 1H), 4.48 - 4.35 (m, 2H), 4.30 (ddd, *J* = 10.8, 5.7, 3.7 Hz, 1H), 4.20 (t, *J* = 5.4 Hz, 1H), 3.88 - 3.71 (m, 1H), 1.83 - 1.63 (m, 4H), 1.58 - 1.46 (m, 1H), 1.46 - 1.24 (m, 5H), 1.24 (s, 3H). ^{31}P NMR (162 MHz, CD_3OD) δ 3.75. MS m/z = 601 (M+l)+.

Example 33. Ethyl 2-(((((2R,3S,4R,5R)-5-(4-aminopyrrolor2,l-firi,2,41triazin-7-yl)-5-cvano-3,4-dihvdroxytetrahvdrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)-2-methylpropanoate (30)



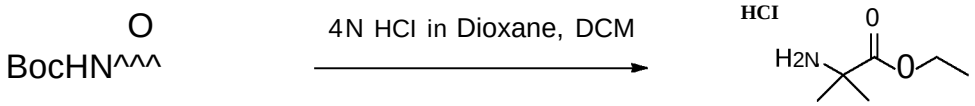
[0477] The preparation of ethyl 2-(((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,l-f][l,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)-2-methylpropanoate is described below.

Preparation of Ethyl 2-((tert-butoxycarbonyl)amino)-2-methylpropanoate



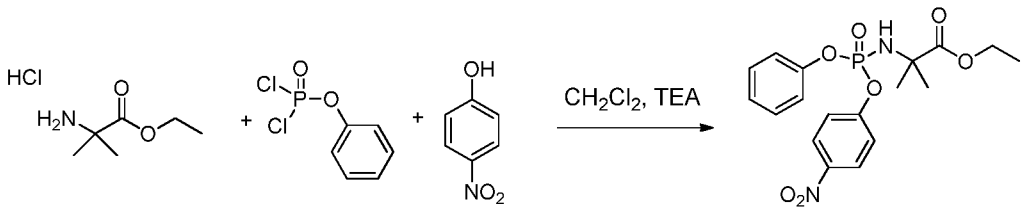
[0478] Take up triphenylphosphine (6.18 g, 25.00 mmol) in THF (30mL). Next charge DIAD (4.92 mL, 25.00 mmol) and stir at room temperature for 10 min. Dissolve 2-((tert-butoxycarbonyl)amino)-2-methylpropanoic acid (5.08 g, 25.00 mmol) in THF (20 mL) and add to the reaction mixture followed by the addition of ethanol (2.19 mL, 37.49 mmol). Allow the reaction to stir at room temperature for about 1 h. The solvents were removed under reduced pressure and the crude was taken up in 1:1 Et_20:Hexanes (120 mL). The solid triphenylphosphine oxide was filtered off and the solvent was removed under reduced pressure. The crude was taken up in minimal CH_2CI_2 and purified by silica gel chromatography 0-50% EtOAc/Hex to afford ethyl 2-((tert-butoxycarbonyl)amino)-2-methylpropanoate. ^{1}H NMR (400 MHz, Chloroform-if) δ 4.18 (q, *J* = 7.1 Hz, 2H), 1.49 (s, 6H), 1.43 (s, 9H), 1.27 (t, *J* = 7.1 Hz, 3H).

Preparation of Ethyl 2-amino-2-methylpropanoate hydrochloride



[0479] Take up ethyl 2-((tert-butoxycarbonyl)amino)-2-methylpropanoate (2.71 g, 11.72 mmol) in CH_2CI_2 (25 mL) and slowly add 4N HCI in dioxane (25 mmol) and stir at room temperature. At lh, the reaction was determined to be complete by TLC. The solvents were removed under reduced pressure and the crude was coevaporated with Et_20 two times then placed under high vacuum to afford ethyl 2-amino-2-methylpropanoate hydrochloride. ^{1}H NMR (400 MHz, DMSO-4) δ 8.70 (s, 3H), 4.18 (q, *J* = 7.1 Hz, 2H), 1.46 (s, 6H), 1.21 (t, *J* = 7.1 Hz, 3H).

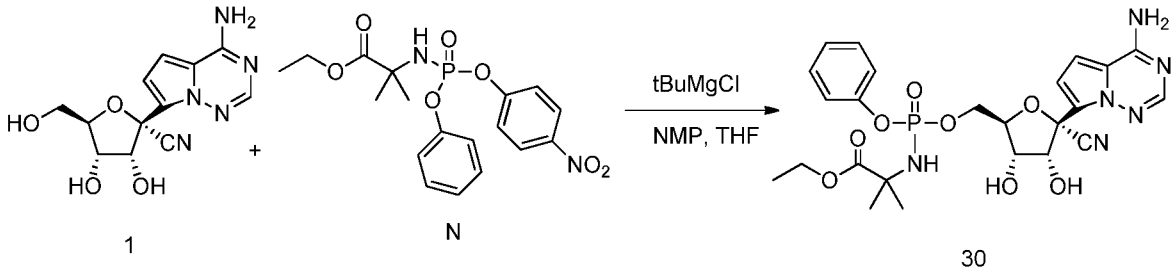
Preparation of Ethyl 2-methyl-2-(((4-nitrophenoxy)(phenoxy)phosphoryl)amino)propanoate (Compound N)



N

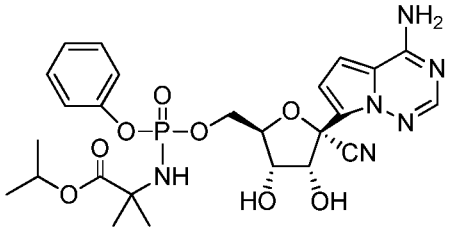
[0480] Take up phenyl dichlorophosphate (0.97mL, 6.50mmol) and ethyl 2-amino-2-methylpropanoate hydrochloride (1.09 g, 6.50 mmol) in CH_2CI_2 (50 mL). Cool the reaction mixture to about 0 °C and slowly add TEA (1.75 mL, 12.45 mmol). Remove the cold bath and allow the reaction mixture to stir at room temperature. After about 2 h, the addition of the amino acid was determined to be complete by ^{31}P NMR. Charge p-nitrophenol (0.860 g, 6.17 mmol) followed by the addition of TEA (0.87 g, 7.69 mmol). Allow the reaction to stir at room temperature. After about 2 h, the reaction was determined to be complete by LCMS. The reaction was diluted with Et_20 and the TEA»HC1 salts were filtered off. The crude was concentrated and purified by silica gel chromatography (0-50% EtOAc/Hex) to afford compound N. ^{1}H NMR (400 MHz, DMSO-i¾ δ 8.37 - 8.21 (m, 2H), 7.55 - 7.44 (m, 2H), 7.43 - 7.33 (m, 2H), 7.30 - 7.09 (m, 3H), 6.57 (d, *J* = 10.1 Hz, 1H), 3.99 (q, *J* = 7.1 Hz, 2H), 1.39 (s, 6H), 1.08 (t, *J* = 7.1 Hz, 3H). ^{31}P NMR (162 MHz, DMSO-i¾ δ -2.87. LC/MS: t_R = 1.65 min, MS ***m/z*** = 408.97 [M+l].; LC system: Thermo Accela 1250 UHPLC; MS system: Thermo LCQ Fleet; Column: Kinetex 2.6µ XB-C18 100A, 50 x 3.00 mm; Solvents: Acetonitrile with 0.1% formic acid, Water with 0.1% formic acid; Gradient: 0 min-2.4 min 2-100% ACN, 2.4 min-2.80 min 100% ACN, 2.8 min-2.85 min 100%-2% ACN, 2.85 min-3.0 min 2% ACN at 1.8mL/min.

Preparation of ethyl 2-(((((2R,3S,4R,5R)-5-(4-aminopyrrolor2,l-firi^ triazin-7-yl)-5-cyano-3,4-dihvdroxytetrahvdrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)-2-methylpropanoate (Compound 30)



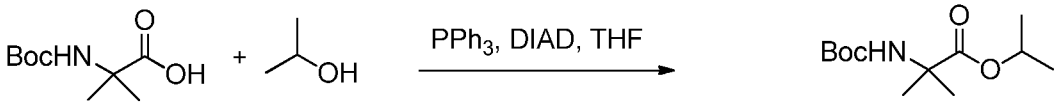
[0481] Take up compound **1** (66 mg, 0.23 mmol) in NMP (2.0 mL). Cool the mixture to about 0 °C and slowly add tBuMgCl (1.0M in THF, 0.34 mL, 0.34 mmol). Allow the reaction to stir at about 0 °C for about 30 min, then add a solution of compound N (139mg, 0.34mmol) dissolved in THF (1.0 mL). Remove the cold bath and place the reaction in about 50 °C preheated oil bath. After about 2 h, the reaction was cooled to room temperature and quenched with acetic acid and methanol. The crude was concentrated and purified by reverse phase HPLC without modifier to afford compound **30.** ^{1}H NMR (400 MHz, DMSO-i¾ δ 7.89 (m, 3H), 7.31 (q, *J* = 8.1 Hz, 2H), 7.22 - 7.05 (m, 3H), 6.87 (d, *J* = 4.5, 1H), 6.80 (d, *J* = 4.5 Hz, 1H), 6.27 (d, *J* = 11.7, 1H), 5.81 (d, *J* = 9.7, 1H), 5.35 (d, ***J*** = 5.6 Hz, 1H), 4.64 (dt, ***J*** = 9.0, 5.6 Hz, 1H), 4.24 (m, 2H), 4.11 (m, 1H), 4.04 - 3.90 (m, 3H), 1.39 - 1.23 (m, 6H), 1.10 (t, *J* = 7.1, 3H). ^{31}P NMR (162 MHz, DMSO-4) δ 2.45, 2.41. LC/MS: t_R = 1.03 min, MS ***m/z*** = 561.03 [M+l]; LC system: Thermo Accela 1250 UHPLC; MS system: Thermo LCQ Fleet; Column: Kinetex 2.6µ XB-C18 100A, 50 x 3.00 mm; Solvents: Acetonitrile with 0.1% formic acid, Water with 0.1% formic acid; Gradient: 0 min-2.4 min 2-100% ACN, 2.4 min-2.80 min 100% ACN, 2.8 min-2.85 min 100%-2% ACN, 2.85 min-3.0 min 2% ACN at 1.8mL/min.

Example 34. Isopropyl 2-(((((2R,3S,4R,5R)-5-(4-aminopyrrolor2,l-firi,2,41triazin-7-yl)-5-cvano-3,4-dihvdroxytetrahvdrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)-2-methylpropanoate (31)



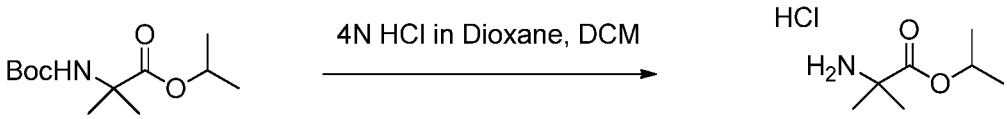
[0482] The preparation of Isopropyl 2-(((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,l-f][l,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)mettoxy)(phenoxy)phosphoryl)amino)-2-methylpropanoate is described below.

Preparation of Isopropyl 2-((tert-butoxycarbonyl)amino)-2-methylpropanoate



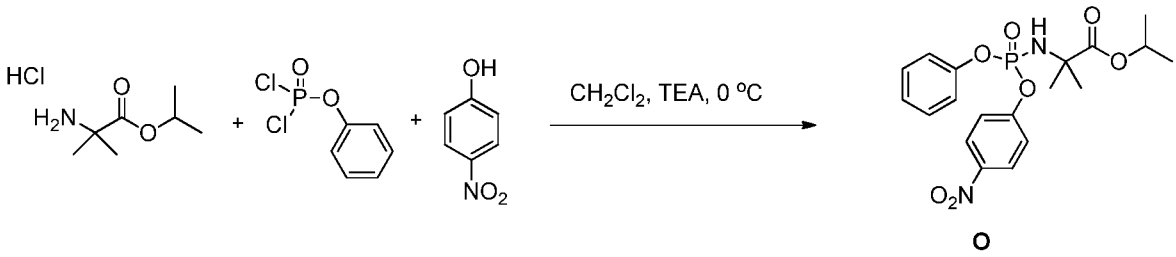
[0483] Take up triphenylphosphine (6.17 g, 25.00 mmol) in THF (30 mL). Next charge DIAD (4.92 mL, 25.00 mmol) and stir at room temperature for about 10 min. Dissolve 2-((tert-butoxycarbonyl)amino)-2-methylpropanoic acid (5.07 g, 25.00 mmol) dissolved in THF (20mL) and add to the reaction mixture followed by the addition of isopropanol (1.91 mL, 25.00 mmol). Allow the reaction to stir at room temperature for about lh. The solvents were removed under reduced pressure and the crude was taken up in 1:1 Et_20:Hexanes (120 mL). The solid triphenylphosphine oxide was filtered off and the solvent was removed under reduced pressure. The crude was taken up in minimal CH_2CI_2 and purified by silica gel chromatography (0-50% EtOAc/Hex) to afford isopropyl 2-((tert-butoxycarbonyl)amino)-2-methylpropanoate. ^{1}H NMR (400 MHz, Chloroform-if) δ 5.03 (p, *J* = 6.2 Hz, 1H), 1.48 (s, 6H), 1.40 (d, *J* = 6.2 Hz, 9H), 1.24 (d, *J* = 6.3 Hz, 6H).

Preparation of Isopropyl 2-amino-2-methylpropanoate hydrochloride



[0484] Take up isopropyl 2-((tert43utoxycarbonyl)amino)-2-methylpropanoate (4.09 g, 16.67 mmol) in CH_2CI_2 (50 mL) and slowly add 4N HCI in dioxane (50 mmol) and stir at room temperature. At about 1 h, the reaction was determined to be complete by TLC. The solvents were removed under reduced pressure and the crude was coevaporated with Et_20 two times then placed under high vacuum to afford isopropyl 2-amino-2-methylpropanoate hydrochloride. ^{1}H NMR (400 MHz, DMSO-4) δ 8.61 (s, 3H), 4.96 (p, *J* = 6.2 Hz, 1H), 1.44 (s, 6H), 1.22 (d, *J* = 6.2 Hz, 6H).

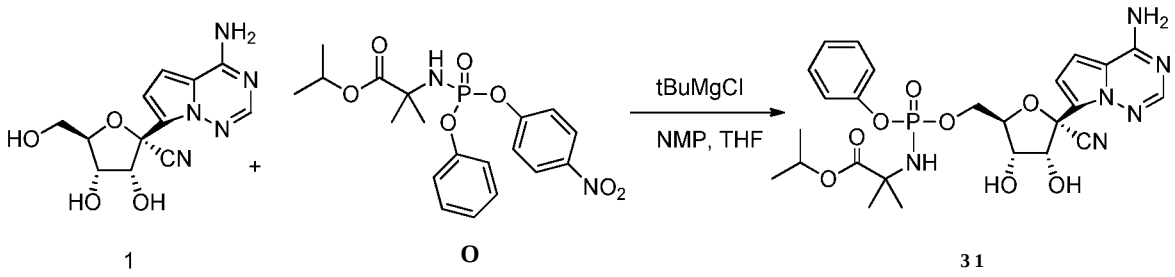
Preparation of Isopropyl2-methyl-2-(((4-nitrophenoxy)(phenoxy)phosphoryl)amino) propanoate (Compound O)



O

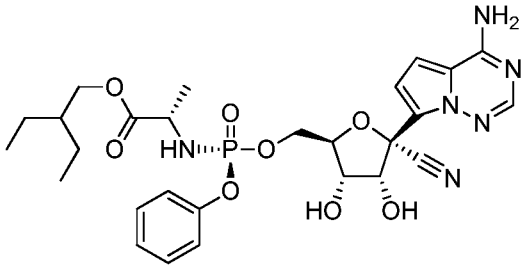
[0485] Take up phenyl dichlorophosphate (0.83 mL, 5.58 mmol) and isopropyl 2-amino-2-methylpropanoate hydrochloride (1.01 g, 5.58 mmol) in CH2CI2 (50 mL). Cool the reaction mixture to 0 °C and slowly add TEA (1.61 mL, 11.45 mmol). Remove the cold bath and allow the reaction mixture to stir at room temperature. After about 2 h, the addition of the amino acid was determined to be complete by ^{31}P NMR. Charge p-nitrophenol (0.74 g, 5.30 mmol) followed by the addition of TEA (0.81, 5.84 mmol). Allow the reaction to stir at room temperature. After about 2 h, the reaction was determined to be complete by LCMS. The reaction was diluted with Et_20 and the TEA»HC1 salts were filtered off. The crude was concentrated and purified by silica gel chromatography (0-50% EtOAc/Hex) to afford compound **O**. ^{1}H NMR (400 MHz, DMSO-i¾ δ 8.42 - 8.19 (m, 2H), 7.55 - 7.43 (m, 2H), 7.39 (dd, *J* = 8.6, 7.2 Hz, 2H), 7.30 - 7.12 (m, 3H), 6.53 (d, *J* = 10. 1 Hz, 1H), 4.82 (hept, ***J* = *6.3*** Hz, 1H), 1.38 (s, 6H), 1.09 (d, *J* = 6.3, 6H). ^{31}P NMR (162 MHz, DMSO-i¾ δ -2.84. LC/MS: t_R = 1.73 min, MS ***m/z*** = 422.92 [M+l]; LC system: Thermo Accela 1250 UHPLC; MS system: Thermo LCQ Fleet; Column: Kinetex 2.6µ XB-C18 100A, 50 x 3.00 mm; Solvents: Acetonitrile with 0.1% formic acid, Water with 0.1% formic acid; Gradient: 0 min-2.4 min 2-100% ACN, 2.4 min-2.80 min 100% ACN, 2.8 min-2.85 min 100%-2% ACN, 2.85 min-3.0 min 2% ACN at 1.8mL/min.

Preparation of Isopropyl 2-rrrrr2R,3S,4R,5R)-5-r4-aminopyrrolor2,l-firi,2,41triazin-7-yl)-5-cvano-3^-dihvdroxytetrahvdrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)-2-methylpropanoate (Compound 31)



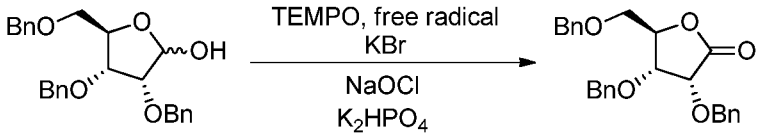
[0486] Take up compound **1** (66 mg, 0.23 mmol) in NMP (2.0 mL). Cool the mixture to about 0 °C and slowly add tBuMgCl (1.0M in THF, 0.57mL, 0.57mmol). Allow the reaction to stir at about 0 °C for about 30 min, then add a solution of compound **O** (143 mg, 0.34 mmol) dissolved in THF (1.0 mL). Remove the cold bath and place the reaction in an about 50 °C preheated oil bath. After about 2 h, the reaction was cooled to room temperature and was quenched with acetic acid and methanol. The crude was concentrated and purified by reverse phase HPLC without modifier to afford compound **31.** ^{1}H NMR (400 MHz, DMSO-i¾ δ 7.88 (m, 3H), 7.30 (td, *J* = 8.5, 7.0 Hz, 2H), 7.20 - 7.04 (m, 3H), 6.87 (d, *J* = 4.5, 1H), 6.80 (d, *J* = 4.5 Hz, 1H), 6.27 (d, 6.1 Hz, 1H), 5.75 (t, *J* = 9.1 Hz, 1H), 5.34 (d, *J* = 5.7 Hz, 1H), 4.81 (p, *J* = 6.3 Hz, 1H), 4.71 - 4.50 (m, 1H), 4.23 (m, 2H), 4.11 (m, 1H), 4.03 - 3.83 (m, 1H), 1.37 - 1.23 (m, 6H), 1.18 - 1.04 (m, 6H). ^{31}P NMR (162 MHz, DMSO) δ 2.47, 2.43. LC/MS: t_R = 1.08 min, MS *m/z* = 575.06 [M+l]; LC system: Thermo Accela 1250 UHPLC; MS system: Thermo LCQ Fleet; Column: Kinetex 2.6µ XB-C18 100A, 50 x 3.00 mm; Solvents: Acetonitrile with 0.1% formic acid, Water with 0.1% formic acid; Gradient: 0 min-2.4 min 2-100% ACN, 2.4 min-2.80 min 100% ACN, 2.8 min-2.85 min 100%-2% ACN, 2.85 min-3.0 min 2% ACN at 1.8mL/min.

Example 35. (S)-2-ethylbutyl 2-(((S)-(((2R,3S,4R,5R)-5-(4-aminopyrrolor2,l-f1[l,2,41triazin-7-yl)-5-cvano-3,4-dihvdroxytetrahydrofuran-2-yl)methoxy)(phenoxy) phosphoryl)amino)propanoate (32)



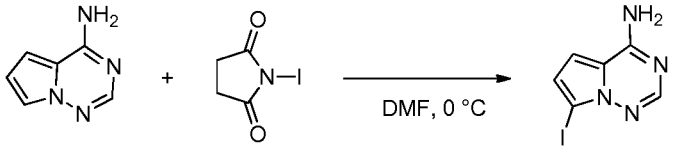
[0487] The preparation of (S)-2-ethylbutyl 2-(((S)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate is described below.

Preparation of (3R,4R,5R)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)dihydrofuran-2(3H)-one.



[0488] (3R,4R,5R)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-ol (15.0 g) was combined with MTBE (60.0 mL), KBr (424.5 mg), aqueous K_2HP0_4 solution (2.5M, 14.3 mL), and TEMPO (56 mg). This mixture was cooled to about 1 °C. Aqueous bleach solution (7.9%wt.) was slowly charged in portions until complete consumption of starting material as indicated through a starch/iodide test. The layers were separated, and the aqueous layer was extracted with MTBE. The combined organic phase was dried over $MgS0_4$ and concentrated under reduced pressure to yield the product as a solid.

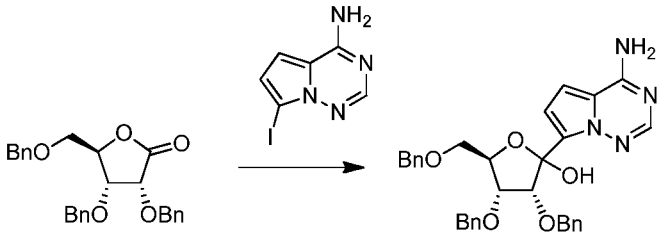
Preparation (4-amino-7-iodopyrrolor2,l-F| ri,2,41triazine)



[0489] To a cold solution of 4-aminopyrrolo[2,1-f][1,2,4]-triazine (10.03 g; 74.8 mmol) in N,N-dimethylformamide (70.27 g), N-iodosuccinimide (17.01g; 75.6 mmol) was charged in portions, while keeping the contents at about 0 °C. Upon reaction completion (about 3 h at about 0 °C), the reaction mixture was transferred into a 1 M sodium hydroxide aqueous solution (11 g NaOH and 276 mL water) while keeping the contents at about 20-30 °C. The resulting slurry was agitated at about 22 °C for 1.5 h and then filtered. The solids are rinsed with water (50 mL) and dried at about 50 °C under vacuum to yield 4-amino-7-iodopyrrolo[2,1-f] [1,2,4]triazine as a

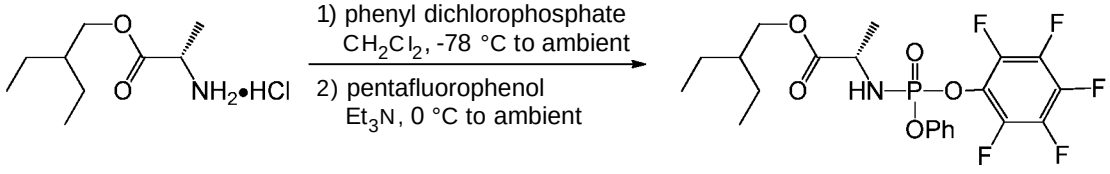
solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.90 (s, 1H), 7.78 (br s, 2H), 6.98 (d, J = 4.4 Hz, 1H), 6.82 (d, J = 4.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d6) δ 155.7, 149.1, 118.8, 118.1, 104.4, 71.9. MS m/z = 260.97 [M+H].

Preparation (3R,4R,5R)-2-(4-aminopyrrolor2,l -firi,2,41triazin-7-yl)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-ol via (4-amino-7-iodopyrrolor2,l-F| |T,2,41triazine)



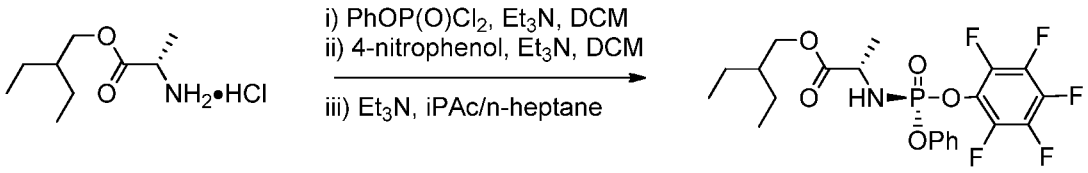
[0490] To a reactor under a nitrogen atmosphere was charged iodobase 2 (81 g) and THF (1.6 L). The resulting solution was cooled to about 5 °C, and TMSC1 (68 g) was charged. PhMgCl (345mL, 1.8 M in THF) was then charged slowly while maintaining an internal temperature at about ≤ 5 °C. The reaction mixture was stirred at about 0 °C for 30 min, and then cooled to about -15 °C. *i*PrMgCl- LiCI (311 mL, 1.1 M in THF) was charged slowly while maintaining an internal temperature below about -12 °C. After about 10 minutes of stirring at about -15 °C, the reaction mixture was cooled to about -20 °C, and a solution of lactone **1** (130 g) in THF (400 mL) was charged. The reaction mixture was then agitated at about -20 °C for about 1 h and quenched with AcOH (57 mL). The reaction mixture was warmed to about 0 °C and adjusted to pH 7-8 with aqueous NaHCC>3 (5 wt%, 1300 mL). The reaction mixture was then diluted with EtOAc (1300 mL), and the organic and aqueous layers were separated. The organic layer was washed with IN HC1 (1300 mL), aqueous $NaHC0_3$ (5 wt%, 1300 mL), and brine (1300 mL), and then dried over anhydrous Na_2S0_4 and concentrated to dryness. Purification by silica gel column chromatography using a gradient consisting of a mixture of MeOH and EtOAc afforded the product.

Preparation ((2S)-2-ethylbutyl 2-(((perfluorophenoxy)(phenoxy)phosphoryl)amino)propanoate) (mixture of *Sp* and *Rp*):



[0491] L-Alanine 2-ethylbutyl ester hydrochloride (5.0 g, 23.84 mmol) was combined with methylene chloride (40 mL), cooled to about -78 °C, and phenyl dichlorophosphate (3.65 mL, 23.84 mmol) was added. Triethylamine (6.6 mL, 47.68 mmol) was added over about 60 min at about -78 °C and the resulting mixture was stirred at ambient temperature for 3h. The reaction mixture was cooled to about 0 °C and pentafluorophenol (4.4 g, 23.84 mmol) was added. Triethylamine (3.3 mL, 23.84 mmol) was added over about 60 min. The mixture was stirred for about 3h at ambient temperature and concentrated under reduced pressure. The residue was dissolved in EtOAc, washed with an aqueous sodium carbonate solution several times, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using a gradient of EtOAc and hexanes (0 to 30%). Product containing fractions were concentrated under reduced pressure to give (2S)-2-ethylbutyl 2-(((perfluorophenoxy)(phenoxy)phosphoryl)amino)propanoate as a solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.41 - 7.32 (m, 4H), 7.30 - 7.17 (m, 6H), 4.24 - 4.16 (m, 1H), 4.13 - 4.03 (m, 4H), 4.01 - 3.89 (m, 1H), 1.59 - 1.42 (m, 8H), 1.40 - 1.31 (m, 8H), 0.88 (t, J = 7.5 Hz, 12H). ^{31}P NMR (162 MHz, Chloroform-d) δ -1.52. ^{19}F NMR (377 MHz, Chloroform-d) δ -153.63, -153.93 (m), -160.05 (td, J = 21.9, 3.6 Hz), -162.65 (qd, J = 22.4, 20.5, 4.5 Hz). MS m/z = 496 [M+H].

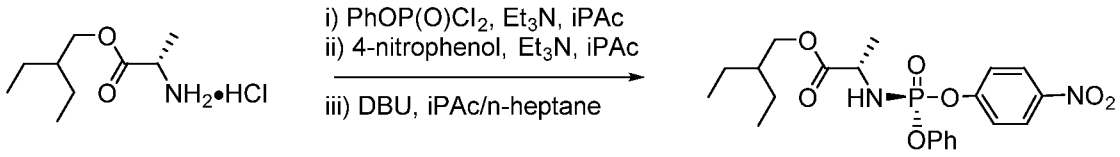
Preparation ((2S)-2-ethylbutyl 2-(((perfluorophenoxy)(phenoxy)phosphoryl)amino)propanoate) :



L-alanine-2-ethylbutylester hydrochloride (40.10 g, 0.191 mmol) was dissolved in dichloromethane (533 g) and the solution was cooled with stirring to about -15 °C under N_2(g). Phenyl dichlorophosphate (40.32 g, 0.191 mol) was added followed by slow addition of triethylamine (41.58 g, 0.411 mmol) and the reaction mixture was stirred at about -15 °C for about 1.5 h. Pentafluorophenol (35.14 g, 0.191 mol) was added, followed by triethylamine (19.23 g, 0.190 mol) and the reaction mixture was stirred for about 2 h. The reaction mixture was warmed to about 0 °C and 0.5 M HC1 (279. 19 g) was added. The mixture was warmed to about 22 °C and the organic layer was separated and washed with 5% $KHCO_3$ aqueous solution (281 g), then water (281 g). An aliquot of the organic layer (453.10 g of the 604.30 g solution) was concentrated to about 120 mL volume, isopropyl acetate (157 g) was added and the solution

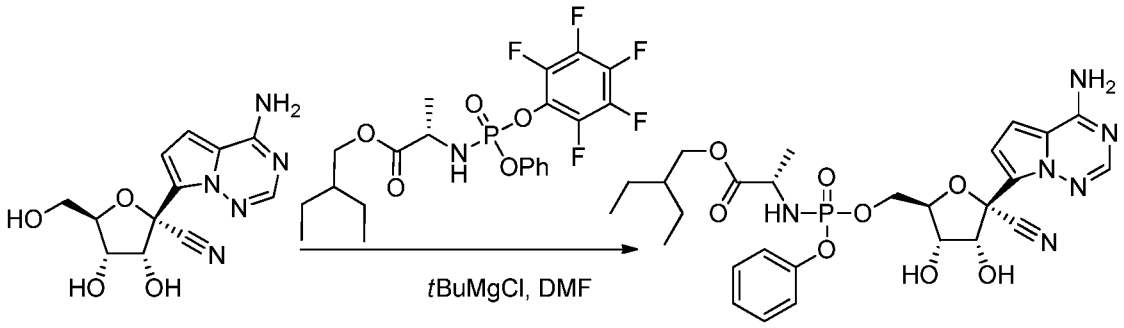
was concentrated to dryness. The residue was dissolved in isopropyl acetate (158 g). The resulting solution was concentrated to about 120 mL volume and the temperature was adjusted to about 45 °C. n-Heptane (165 g) was added and the mixture was cooled to 22 °C over about 1 h. n-Heptane (167 g) was added and the mixture was cooled to about 0 °C. Triethylamine (2.90 g, 0.0287 mol) was added and the mixture was stirred at 0 °C for about 17 h. The mixture was filtered, the solids were rinsed with n-heptane (145 g) and the solids were dried under vacuum at about 40 °C for about 15 h to provide 2-ethylbutyl ((S)-(penthafluorophenoxy)(phenoxy)phosphoryl)-L-alaninate.

Preparation 2-ethylbutyl ((S)-(4-nitrophenoxy)(phenoxy)phosphoryl)-L-alaninate:



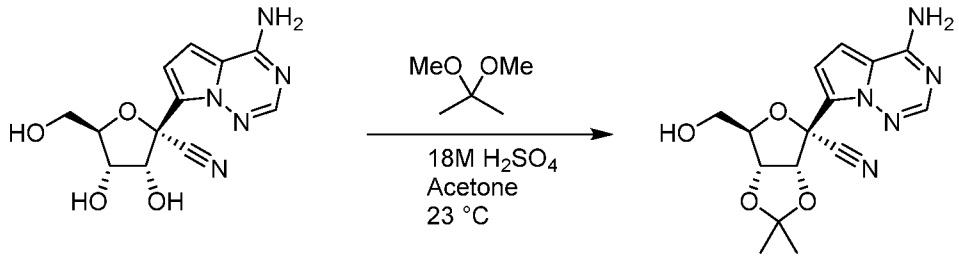
A slurry of L-alanine-2-ethylbutylester hydrochloride (20.08 g, 95.8 mmol) and isopropyl acetate (174 g) was cooled with stirring to about -20 °C). Phenyl dichlorophosphate (20.37 g, 96.5 mmol) was added, followed by slow addition of triethyl amine (20.97 g, 207.2 mmol) and the mixture was stirred at about -20 °C for about 1 h. 4-Nitrophenol (13.23 g, 95.1 mmol) was added, followed by slow addition of triethylamine (10.01 g, 98.8 mmol) and the reaction mixture was stirred for about 1.5 h. The reaction mixture was warmed to about 0 °C and 0.5 M HCl (140 g) was added. The organic layer was separated and washed with 5% $Na_{2}CC>3$ (2 x 100 g) and 10% NaCl (2 x 100 g). The organic layer was then concentrated to about 80 mL volume and isopropylacetate (4 g) was added, followed by n-heptane (110 g). Product seed crystals (0.100 g) were added followed by a second portion of n-heptane (110 g) and the mixture was cooled to about 0 °C. l,8-Diazabicycloundec-7-ene (1.49 g, 9.79 mmol) was added and the mixture was stirred at about 0 °C for about 21 h. The resultant solids were filtered and washed first with n-heptane (61 g) and then with $H_{2}0$ (2 x 100 g). The solids were stirred with $H_{2}0$ (200 g) for about 1.5 h, filtered, and rinsed with $H_{2}0$ (3 x 100 g), then n-heptane (61 g). The obtained solids were dried under vacuum at about 40 °C for about 19 h to provide 2-ethylbutyl ((S)-(4-nitrophenoxy)(phenoxy)phosphoryl)-L-alaninate.

Preparation of Title Compound (mixture of *Sp* and *Rp*):



[0492] The nucleoside (29 mg, 0.1 mmol) and the phosphonamide (60 mg, 0.12 mmol) and N,N-dimethylformamide (2 mL) were combined at ambient temperature. 7¾r£-Butyl magnesium chloride (1M in THF, 0.15 mL) was slowly added. After about lh, the reaction was diluted with ethyl acetate, washed with aqueous citric acid solution (5%wt.), aqueous saturated NaHCC>3 solution and saturated brine solution. The organic phase was dried over Na_2S04 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using a gradient of methanol and CH2CI2 (0 to 5%). Product containing fractions were concentrated under reduced pressure to provide the product.

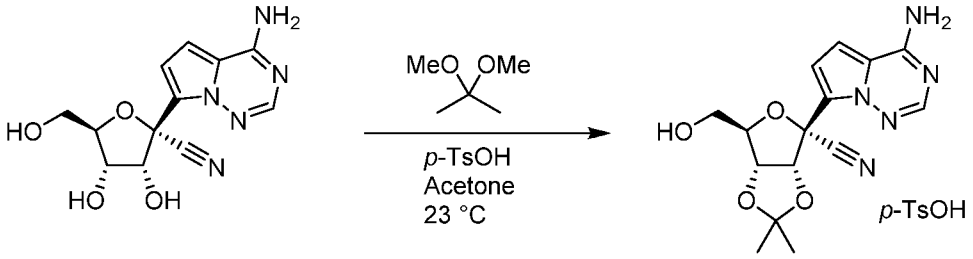
Preparation of (3aR,4R,6R,6aR)-4-(4-aminopyrrolor2,l -f**iri**,2,41triazin-7-yl)-6-(hydroxymethyl)-2,2-dimethyltetrahydrofuror3,4-diri,31dioxole-4-carbonitrile:



[0493] To a mixture of (2R,3R,4S,5R)-2-(4-aminopyrrolo[2,l-f][l,2,4]triazin-7-yl)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile (5.8g, 0.02 mol), 2,2-dimethoxypropane (11.59 mL, 0.09 mol) and acetone (145 mL) at ambient temperature was added sulfuric acid (18M, 1.44 mL). The mixture was warmed to about 45 °C. After about 30 min, the mixture was cooled to ambient temperature and sodium bicarbonate (5.8 g) and water 5.8 mL) were added. After 15 min, the mixture was concentrated under reduced pressure. The residue was taken up in ethyl acetate (150 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic phase was dried over sodium

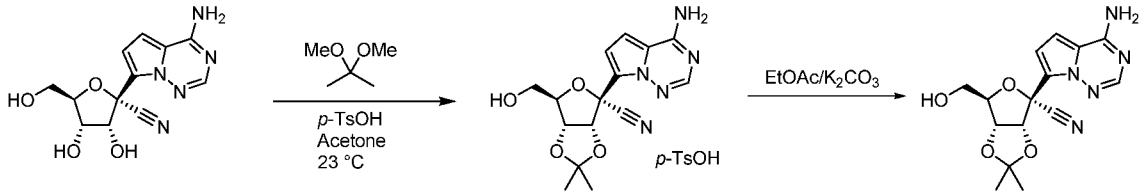
sulfate and concentrated under reduced pressure to give crude (2R,3R,4S,5R)-2-(4-aminopyrrolo[2 ,1-f][1,2,4]triazin-7-yl)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile. ^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (s, 1H), 6.93 (d, *J* = *4.6* Hz, 1H), 6.89 (d, *J* = 4.6 Hz, 1H), 5.40 (d, *J* = 6.7 Hz, 1H), 5.00 (dd, *J* = 6.7, 3.3 Hz, 1H), 4.48 - 4.40 (m, 1H), 3.81 – 3.72 (m, 2H), 1.71 (s, 3H), 1.40 (s, 3H). MS m/z = 332.23 [M+l].

Preparation of (3aR,4R,6R,6aR)-4-(4-aminopyrrolor2,l -f**iri** ,2,41triazin-7-yl)-6-(hvdroxymethyl)-2,2-dimethyltetrahvdrofuror3,4-diri,31dioxole-4-carbonitrile TsOH salt:



[0494] To a mixture of (2R,3R,4S,5R)-2-(4-aminopyrrolo[2,l-f][l,2,4]triazin-7-yl)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile (5.0 g, 17.2 mmol, 1.0 equiv.), 2,2-dimethoxypropane (10.5 mL, 86 mmol, 5.0 equiv.) and acetone (25 mL) at ambient temperature was added p-tolylsulfonic acid (3.59 g, 1.1 equiv.). The mixture was stirred at ambient temperature. After about 30 min, isopropyl acetate (25 mL) was added over about one hour. The resulting slurry was filtered and rinsed with 2:1 heptane:isopropyl acetate (25 ml). The product was dried under vacuum at about 40 °C.

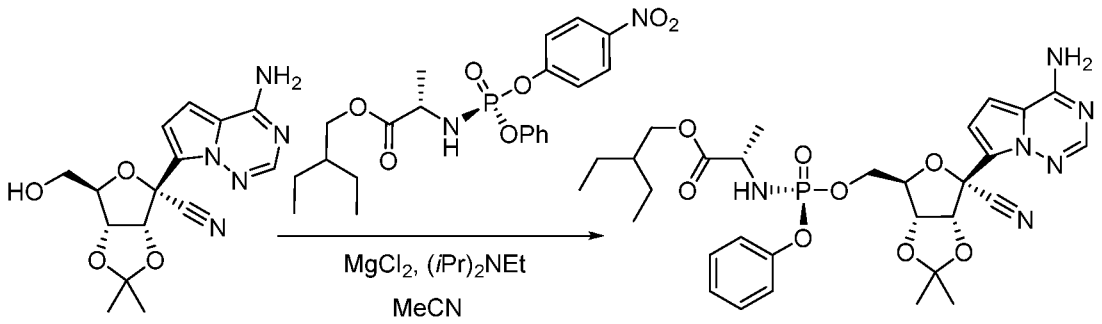
Preparation of (3aR,4R,6R,6aR)-4-(4-aminopyrrolor2,l -f**iri** ,2,41triazin-7-yl)-6-(hvdroxymethyl)-2,2-dimethyltetrahvdrofuror3,4-diri,31dioxole-4-carbonitrile:



[0495] To a mixture of (2R,3R,4S,5R)-2-(4-aminopyrrolo[2,l-f][l,2,4]triazin-7-yl)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile (5 g, 17.2 mmol, 1.0 equiv.), 2,2-dimethoxypropane (10.5 mL, 86 mmol, 5.0 equiv.) and acetone (25 mL) at ambient temperature was added p-tolylsulfonic acide (3.59 g, 1.1 equiv.). The mixture was stirred at ambient temperature. After 30 min, isopropyl acetate (25 mL) was added over one hour. The resulting

slurry was filtered and rinsed with 2:1 heptane :isopropyl acetate (25 ml). The product was dried under vacuum at 40 °C. The isolated solid was added to a reactor and 5% $K2CO_3$ solution (50 ml) and ethyl acetate (50 mL) were added. The layers were separated, and the aqueous layer washed with ethyl acetate (25 ml). The combined organic layers were washed with water (25 ml), then concentrated to ca.25 ml. The reactor was refilled with isopropyl acetate (25 ml) and concentrated to ca. 25 ml. The reactor was again refilled with isopropyl acetate (25 ml) and concentrated to 25 ml. The resulting solution was seeded, producing a thick slurry. To this was added heptane (25 ml) over one hour. The resulting slurry was filtered and rinsed with 2:1 heptane:isopropyl acetate (25 ml). The product was dried under vacuum at 40 °C. () (2R,3R,4S,5R)-2-(4-aminopyrrolo[2,l-f][l,2,4]triazin-7-yl)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile. ^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (s, 1H), 6.93 (d, *J* = 4.6 Hz, 1H), 6.89 (d, *J* = 4.6 Hz, 1H), 5.40 (d, *J* = 6.7 Hz, 1H), 5.00 (dd, *J* = 6.7, 3.3 Hz, 1H), 4.48 - 4.40 (m, 1H), 3.81 - 3.72 (m, 2H), 1.71 (s, 3H), 1.40 (s, 3H). MS m/z = 332.23 [M+l].

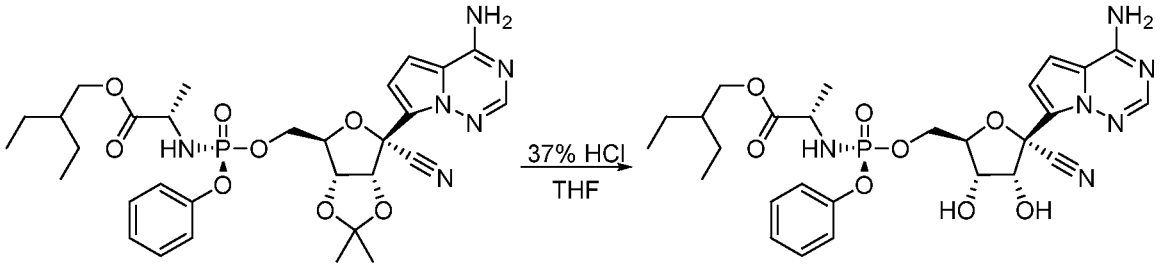
Preparation of (2S)-2-ethylbutyl 2-(((((2R.3S.4R.5R)-5-(4-aminopyrrolor2.1-firi.2.41triazin-7-yl)-5-cvano-3,4-dihvdroxytetrahvdrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino) propanoate:



[0496] Acetonitrile (100 mL) was combined with (2S)-2-ethylbutyl 2-(((4-nitrophenoxy)(phenoxy)phosphoryl)-amino)propanoate (9.6 g, 21.31 mmol), the substrate alcohol (6.6 g, 0.02 mol),), magnesium chloride ((1.9 g, 19.91 mmol) at ambient temperature. The mixture was agitated for about 15 min and *N,N* -diisopropylethylamine (8.67 mL, 49.78 mmol) was added. After about 4h, the reaction was diluted with ethyl acetate (100 mL), cooled to about 0 °C and combined with aqueous citric acid solution (5%wt., 100 mL). The organic phase was washed with aqueous citric acid solution (5%wt., 100 mL) and aqueous saturated ammonium chloride solution (40 mL), aqueous potassium carbonate solution (10%wt., 2 x 100 mL), and aqueous saturated brine solution (100 mL). The organic phase was dried with sodium

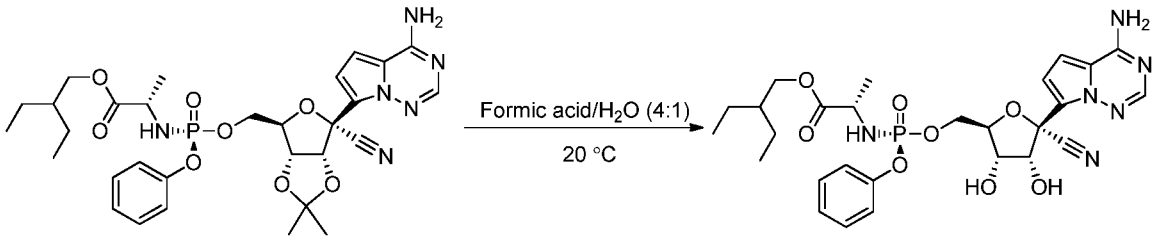
sulfate and concentrated under reduced pressure to provide crude product. ^{1}H NMR (400 MHz, CD_3OD) δ 7.86 (s, 1H), 7.31 - 7.22 (m, 2H), 7.17 - 7.09 (m, 3H), 6.93 - 6.84 (m, 2H), 5.34 (d, *J* = 6.7 Hz, 1H), 4.98 (dd, *J* = 6.6, 3.5 Hz, 1H), 4.59 - 4.50 (m, 1H), 4.36 - 4.22 (m, 2H), 4.02 (dd, *J* = 10.9, 5.7 Hz, 1H), 3.91 (dd, *J* = 10.9, 5.7 Hz, 1H), 3.83 (dq, *J* = 9.7, 7.1 Hz, 1H), 1.70 (s, 3H), 1.50 - 1.41 (m, 1H), 1.39 (s, 3H), 1.36 - 1.21 (m, 7H), 0.86 (t, *J* = 7.4 Hz, 6H). MS m/z = 643.21 [M+l].

Preparation of (S)-2-ethylbutyl 2-(((S)-(((2R,3S,4R,5R)-5-(4-aminopyrrolor2,l-firi,2,41triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino) propanoate (Compound 32)



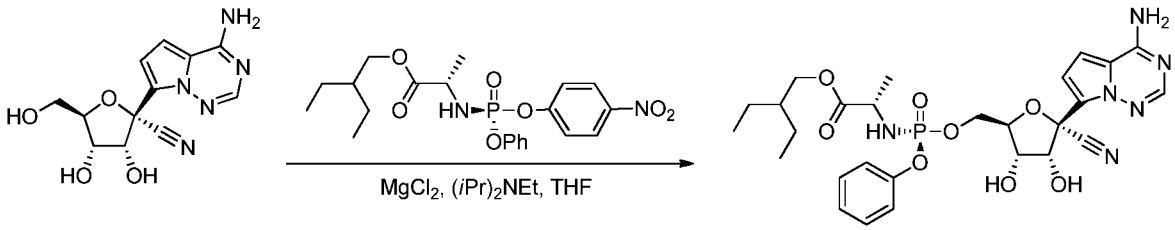
[0497] The crude acetonide (12.85 g) was combined with tetrahydrofuran (50 mL) and concentrated under reduced pressure. The residue was taken up in tetrahydrofuran (100 mL), cooled to about 0 °C and concentrated HC1 (20 mL) was slowly added. The mixture was allowed to warm to ambient temperature. After consumption of the starting acetonide as indicated by HPLC analysis, water (100 mL) was added followed by aqueous saturated sodium bicarbonate solution (200 mL). The mixture was extracted with ethyl acetate (100 mL), the organic phase washed with aqueous saturated brine solution (50 mL), dried over sodium sulfated and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using a gradient of methanol and ethyl acetate (0 to 20%). Product containing fractions were concentrated under reduced pressure to provide the product.

Preparation of (S)-2-ethylbutyl 2-**rrrS)-rrr2R**.3S.4R.5R)-5-r4-aminopyrrolor2.1 **-fi ri** .2.41triazin-7-yl)-5-cvano-3,4-dihvdroxytetrahvdrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino) propanoate (Compound 32)



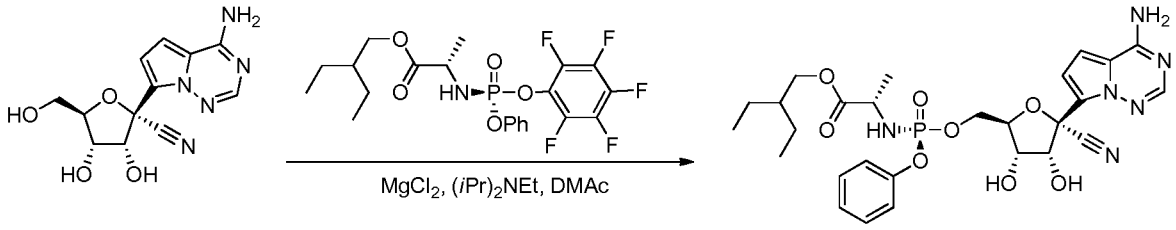
To a vial containing (S)-2-ethylbutyl 2-(((S)-(((3aR,4R,6R,6aR)-6-(4-aminopyrrolo[2,l-f][l,2,4]triazin-7-yl)-6-cyano-2,2-dimethyltetrahydrofuro[3,4-d][l,3]dioxol-4-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate (30 mg, 0.05 mmol) was added an 80% aqueous formic acid solution (1.5 mL). After 18 h at about 20 °C complete conversion was confirmed by HPLC and LC-MS. MS (m/z) = 603$(M+1)^+$.

Preparation of (S)-2-ethylbutyl 2-(((S)-(((2R,3S,4R,5R)-5-(4-aminopyrrolor2,l-firi,2,41triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)mem^ xy)(phenoxy)phosphoryl)amino) propanoate (Compound 32) via Direct Coupling



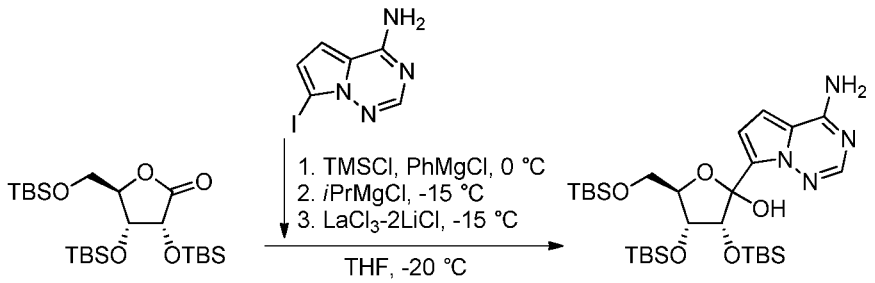
[0498] To a mixture of (2R,3R,4S,5R)-2-(4-aminopyrrolo[2,l-f][l,2,4]triazin-7-yl)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile (0.5 g, 2mmol), (S)-2-ethylbutyl 2-(((S)-(4-nitrophenoxy)(phenoxy)phosphoryl)amino)propanoate (0.9 g, 2 mmol), and $MgCl_2$ (0.2 g, 2 mmol), was charged N,N-dimethylacetamide (10 mL). The resulting mixture was warmed to about 30 °C with constant stirring. N,N-Diisopropylethylamine (0.7 mL, 4 mmol) was then added slowly, and the reaction mixture was stirred for about 6 h. Water (10 mL) was charged H_20 , followed by 2-MeTHF (10 mL), and the organic and aqueous phases were separated. The aqueous layer was then back-extracted with 2-MeTHF (10 mL). The organic layers were combined, and washed with 10 wt% citric acid solution (10 mL), followed by 10 wt% K2CO 3

solution (10 mL), and H_20 (10 mL). A small amount of brine was added to resolve emulsions in the water wash before the layers were separated. The organic layer was evaporated to dryness to afford 0.65 g of a foam. *i*PrOAc (2.6 mL) was added then added, and the mixture was warmed to about 40 °C to achieve dissolution. The solution was cooled to about 20 °C, and the mixture was stirred for about 3 days. The solids were isolated by filtration, and the filter cake was washed with a small amount of *i*PrOAc. The solids were dried to afford (S)-2-ethylbutyl 2-(((S)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,l-f][l,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate.



[0499] To a mixture of (2R,3R,4S,5R)-2-(4-aminopyrrolo[2,l-f][l,2,4]triazin-7-yl)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile (0.2 g, 0.7 mmol), (S)-2-ethylbutyl 2-(((S)-(perfluorophenoxy)(phenoxy)phosphoryl)amino)propanoate (0.3 g, 0.7 mmol), and $MgCl_2$ (0.1 g, 1 mmol), was charged N,N-dimethylacetamide (4 mL). The resulting mixture was warmed to about 30 °C with constant stirring. N,N-Diisopropylethylamine (0.3 mL, 2 mmol) was then added slowly, and the reaction mixture was stirred for 5 h. Conversion to the product was confirmed through UPLC analysis.

Preparation of (3R,4R,5R)-2-(4-aminopyrrolor2,l-firi,2,41triazin-7-yl)-3,4-bis((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-ol



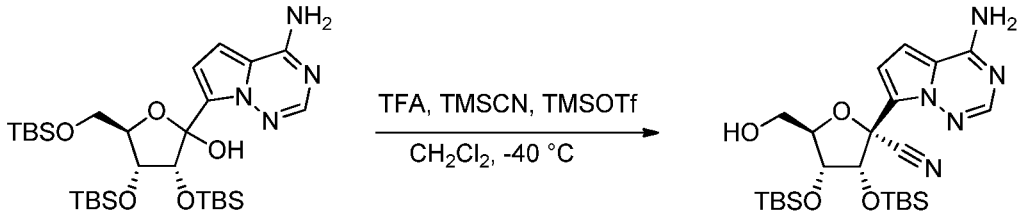
[0500] A solution of 7-iodopyrrolo[2,l-f][l,2,4]triazin-4-amine (13.9 g, 53.5 mmol) was prepared in THF (280 mL). The solution was cooled to about 0 °C, and TMSCI (13.6 mL, 107 mmol) was added. The reaction mixture was stirred for about 20 min, and then PhMgCI (2 M in

THF; 53.5 mL, 56.8 mmol) was added while maintaining an internal temperature below about 5 °C. The reaction mixture was agitated at about 0 °C for about 30 min, and then cooled to about -20°C. *i*PrMgCl-LiCl (1.3 M in THF, 43.1 mL, 56 mmol) was then added while maintaining an internal temperature below about -15 °C. The reaction mixture was agitated for about 30 min at about -20 °C.

[0501] In a separate flask, a solution of (3R,4R,5R)-3,4-bis((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)dihydrofuran-2(3H)-one (25.0 g, 50.9 mmol, 0.83 equiv) was prepared in $LaCl_3$-2LiCl (0.6 M in THF, 85 mL, 50.9 mmol). The solution was then transferred to the Grignard solution while maintaining an internal temperature below -20°C. The resulting reaction mixture was agitated at about -20 °C for about 4 h.

[0502] The reaction was quenched with 1 M HCl (140 mL), and the mixture warmed to ambient temperature. EtOAc (140 mL) was added, and the organic and aqueous phases were separated. The water layer was extracted with EtOAc (200 mL). The combined EtOAc layers were extracted sequentially with saturated aqueous $NaHCO_3$ (2 x 200 mL) , water (200 mL), and brine (200 mL). The organic layer was concentrated, and then purified by silica gel chromatography (30% EtOAc/hexane) to afford (3R,4R,5R)-2-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-bis((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-ol. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 - 7.88 (m, 1H), 7.51 (d, *J* = 4.8 Hz, 0.5H), 7.02 - 6.92 (m, 0.5H), 6.65 - 6.57 (m, 1H), 5.66 - 5.24 (m, 3H), 4.49 - 3.50 (m, 4H), 0.97 - 0.78 (26H), 0.65 (s, 1.5H), 0.19 - 0.00 (m, 15.5H), -0.22 (s, 1H), -0.55 (s, 1H). . MS m/z = 626 (M+H).

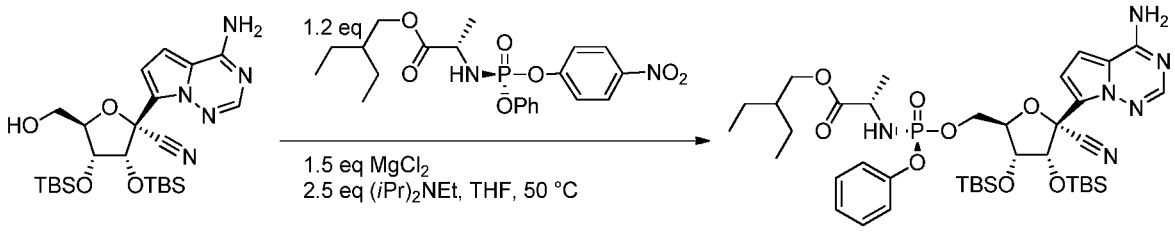
Preparation of (2R,3R,4R,5R)-2-(4-aminopyrrolor2,1 -**Firi**,2,41triazin-7-yl)-3,4-bis((tert-butyldimethylsilyl)oxy)-5-(hvdroxymethyl)tetrahydrofuran-2-carbonitrile



[0503] A solution of (3R,4R,5R)-2-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-bis((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-ol (1.50 g, 2.40 mmol) in CH_2Cl_2 (15 mL) was cooled to about -40 °C. Trifluoroacetic acid (0.555 mL, 7.20

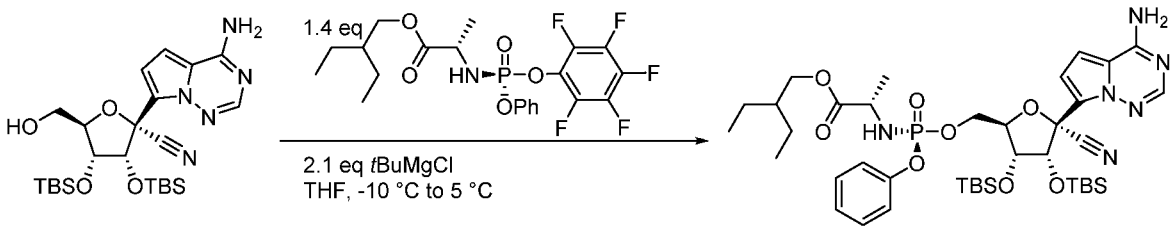
mmol) was added keeping the temperature below -20°C. In a separate flask, trimethylsilyl trifluoromethanesulfonate (2.60 mL, 14.4 mmol) was added to 5 ml of CH_2C1_2 (5 mL) at about 15 °C, followed by trimethylsilyl cyanide (1.92 mL, 14.4 mmol), and the solution was cooled to about -30 °C. The cooled solution was added to the solution of (3R,4R,5R)-2-(4-aminopyrrolo[2,l-f][l,2,4]triazin-7-yl)-3,4-bis((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-ol while keeping the temperature below -25 °C. The reaction mixture was stirred for 15 min at about -30 °C. The reaction was quenched with triethylamine (3.34 mL, 24.0 mmol) and the mixture was warmed to about 0 °C. Water (50 mL) was added while keeping the temperature below about 20 °C. When the addition was complete the mixture was stirred for 15 min at room temperature. The layers were separated and the organic layer was washed sequentially with KOH (20 mL), water (20 mL), and brine (20 mL). The organic layer was dried over $Na_2SC>_4$, concentrated, and then purified by silica gel chromatography (30% EtOAc / hexane) to afford the product as a 3.8:1 mixture of diastereomers). The mixture was purified further by prep-HPLC (ACN 0 to 95% in water) to afford the product as a single diastereomer. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.14-7.92 (m, 2H), 7.89 (s, 1H), 6.95 (d, *J* = 4.8 Hz, 1H), 6.88 (d, *J* = 4.4 Hz, 1H),5.27 (d, J = 4.6 Hz, 1H), 5.10 (dd, J = 7.7, 4.6 Hz, 1H), 4.31 (dd, J = 4.7, 1.4 Hz, 1H), 4.12 (ddd, J = 5.9, 4.1, 1.4 Hz, 1H), 3.80 - 3.69 (m, 1H), 3.56 (td, J = 7.8, 3.9 Hz, 1H), 0.93 (s, 9H), 0.75 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), -0.15 (s, 3H), -0.62 (s, 3H). MS m/z = 520 (M+H).

Preparation of (S)-2-ethylbutyl 2-(((S)-(((2R.3R.4R.5R)-5-(4-aminopyrrolor2.1-fin.2.41triazin-7-yl)-3,4-bis((tert-butyldimethylsilyl)oxy)-5-cvanotetrahydrofuran-2-yl)methoxy)(phenoxy) phosphoryl)amino)propanoate



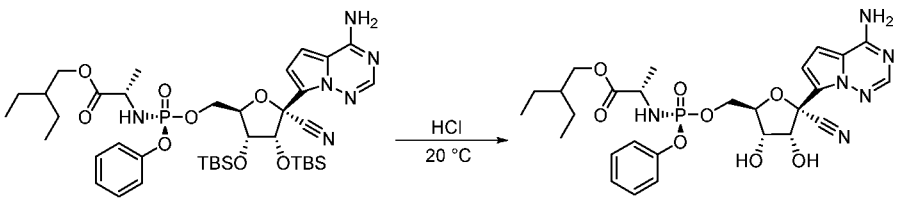
To a mixture of (2R,3R,4R,5R)-2-(4-aminopyrrolo[2,l-f][l,2,4]triazin-7-yl)-3,4-bis((tert-butyldimethylsilyl)oxy)-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile (16 mg, 0.03 mmol), (S)-2-ethylbutyl 2-(((S)-(4-nitrophenoxy)(phenoxy)phosphoryl)amino)propanoate (17 mg, 0.04 mmol), and $MgCl_2$ (4 mg, 0.05 mmol), was charged THF (0.3 mL). The resulting mixture was warmed to about 50 °C with constant stirring. N,N-Diisopropylethylamine (0.013 mL, 0.08

mmol) was then added, and the reaction mixture was stirred for 21 h. Conversion to the product was confirmed through UPLC and LC-MS analysis. MS m/z = 831 (M+H).



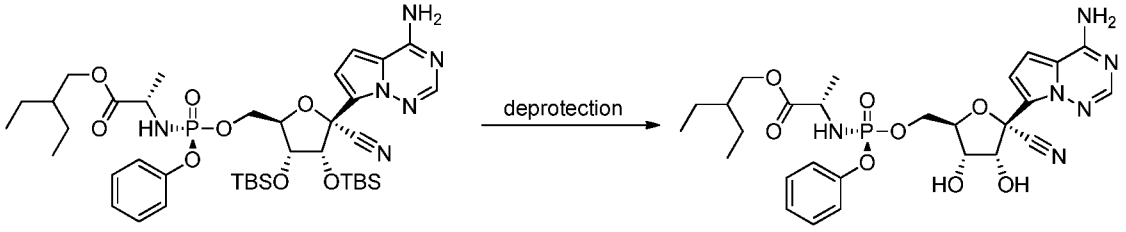
A solution of (2R,3R,4R,5R)-2-(4-aminopyrrolo[2,l-f][l,2,4]triazin-7-yl)-3,4-bis((tert-butyldimethylsilyl)oxy)-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile (16 mg, 0.03 mmol) in THF (0.3 mL) was cooled to -10 °C. iBuMgCl was added dropwise (0.07 mL, 0.07 mmol), followed by a solution of (S)-2-ethylbutyl 2-(((S)-(perfluorophenoxy)(phenoxy)phosphoryl)amino)propanoate (22 mg, 0.04 mmol) in THF (0.15 mL). The reaction mixture was warmed to 5 °C, and stirred for 16 h. The reaction was quenched with MeOH, concentrated, and then purified by silica gel chromatography (EtOAc /hexanes) to afford the product . 1H NMR (400 MHz, $CDC1_3$) δ 7.97 (s, 1H), 7.38 - 7.29 (m, 2H), 7.25 - 7.21 (m, 2H), 7.21 - 7.13 (m, 1H), 7.11 (d, J = 4.6 Hz, 1H), 6.65 (d, J = 4.6 Hz, 1H), 5.88 (br s, 2H), 5.35 (d, J = 4.4 Hz, 1H), 4.49 - 4.41 (m, 1H), 4.41 - 4.35 (m, 1H), 4.32 - 4.26 (m, 1H), 4.24 (dd, J = 4.5, 1.7 Hz, 1H), 4.10 - 3.99 (m, 2H), 3.96 (dd, J = 10.9, 5.7 Hz, 1H), 3.80 - 3.72 (m, 1H), 1.48 (h, J = 6.2 Hz, 1H), 1.39 - 1.28 (m, 7H), 0.96 (s, 9H), 0.85 (t, J = 7.5 Hz, 6H), 0.80 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), -0.13 (s, 3H), -0.56 (s, 3H). 31P NMR (162 MHz, CDC13) δ 2.74 (s). MS m/z = 831 (M+H).

Preparation of (S)-2-ethylbutyl 2-(((S)-(((2R.3S.4R.5R)-5-(4-aminopyrrolor2.1-firi.2.41triazin-7-yl)-5-cvano-3,4-dihvdroxytetrahvdrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino) propanoate



A crude solution of (S)-2-ethylbutyl 2-(((S)-(((2R,3R,4R,5R)-5-(4-aminopyrrolo[2,l-f][l,2,4]triazin-7-yl)-3,4-bis((tert-butyldimethylsilyl)oxy)-5-cyanotetrahydrofuran-2-

yl)methoxy)(phenoxy)phosphoryl)amino)propanoate was cooled to about 0 °C and cone HC1 (0.05 mL, 0.62 mmol) was slowly added. The reaction mixture was stirred for about 72 hours at about 20 °C. Conversion to the product was confirmed through UPLC and LC-MS analysis. MS m/z = 603 (M+H).



A solution of (S)-2-ethylbutyl 2-(((S)-(((2R,3R,4R,5R)-5-(4-aminopyrrolo[2,l-f][l,2,4]triazin-7-yl)-3,4-bis((tert-butyldimethylsilyl)oxy)-5-cyanotetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate in a fluoride or acid can deprotect to a solution of (S)-2-ethylbutyl 2-(((S)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,l-f][l,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate. Representative fluorides include, but are not limited to TBAF, KF, pyridinium hydrofluoride, triethylammonium hydrofluoride, hydrogen fluoride, hydrochloric acid, toluenesulfonic acid, or any other suitable fluoride source. Representative acids include, but are not limited to those found in Greene, T. W.; Wuts, P. G. M. *Protective Groups In Organic Synthesis, 4th Ed.,* John Wiley & Sons: New York, **2006.**

F. Antiviral Activity

[0504] 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.

[0505] 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 solventWater

mixtures. Samples include living organisms such as humans, and man made materials such as cell cultures.

[0506] 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.

[0507] 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.

Virus	Cell line	Plate format	Cell number	MOI (pfu/cell)	Incubation (Days)	Read out	Values
EBOV (Zaire)	Hela	384	4000	0.5	2	HCS	EC50
EBOV (Zaire)	HFF-1			2		HCS	
EBOV-GFP	Huh-7	96	10000	0.1	4	GFP	
EBOV-GFP	HMVEC-TERT					GFP	
EBOV-LUC	Huh-7					LUC	
MARV-GFP	Huh-7					GFP	
NiV	Hela					CPE	
NiV-GFP	HMVEC-TERT					GFP	
NiV-LUC	HMVEC-TERT					LUC	

EBOV: Ebola virus strain Zaire
EBOV-GFP: Ebola reporter virus expressing green fluorescent protein
EBOV-LUC: Ebola reporter virus expressing luciferase
MARV-GFP: Marburg virus expressing green fluorescent protein
NiV: Nipah virus
NiV-GFP: Nipah reporter virus expressing green fluorescent protein
NiV-LUC: Nipah reporter virus expressing luciferase

HCS: High content imaging (immuno-staining of ebolavirus GP-protein)
GFP: Green fluorescent protein
LUC: Luciferase
CPE Cytopathic effects measured by cell titer glo (CTG) reagent

Hela: Hela epithelial cell (cervical carcinoma)
HFF-1: Human foreskin fibroblast
Huh-7: Hepatocyte

HVMEC-TERT: Human microvascular endothelial cells i mmortalized with the telomerase catalytic protein

Example 36. Ebola virus antiviral activity and cytotoxicity assays

[0508] Antiviral activity of Compound 1 and Compound 9 was measured against Ebola virus (EBOV), Marburg virus (MARV) (Table 2), and Nipah virus (NiV) (Table 3) using fully replicating reporter viruses expressing luciferase or green fluorescent protein (GFP) (Uebelhoer, L.S., 2014. AVR; Hoenen, T., 2013. AVR). Further antiviral activity of Compound 1 and Compound 9 was measured against Ebola virus (EBOV), Marburg virus (MARV) (Table 2-a), using fully replicating reporter viruses expressing luciferase or green fluorescent protein (GFP) (Uebelhoer, L.S., 2014. AVR; Hoenen, T., 2013. AVR).A11 studies were conducted in biosafety level-4 containment (BSL-4) at the Centers for Disease Control and Prevention (CDC). Ebola virus antiviral assays were conducted in primary human microvascular endothelial cells immortalized with the telomerase catalytic protein (HMVEC-TERT) and in Huh-7 cells (Shao, R., 2004, BBRC). Nipah virus antiviral activity was measured in HMVEC-TERT and Hela cells.

[0509] Antiviral assays were conducted in 96well plates. Eight to ten concentrations of compound were diluted in 3-fold serial dilution increments in media and 100 uL/well of each dilution was transferred in triplicate onto plates containing preseeded cell monolayers. The plates were transferred to BSL-4 containment and the appropriate dilution of virus stock, previously determined by titration and prepared in cell culture media, was added to test plates containing cells and serially diluted compounds. Each plate included three wells of infected untreated cells and three wells of uninfected cells that served as 0% and 100% virus inhibition control, respectively. Following the infection, test plates were incubated for 3 to 4 days in a tissue culture incubator. After the incubation, virus replication was measured in an Envision plate reader by direct fluorescence for GFP reporter viruses or after subsequent addition of luciferase substrate for luciferase reporter viruses. For virus yield assays, media from infected cells was removed and a portion was used to quantify viral RNA by reverse transcription quantitative polymerase chain reaction (RT-qPCR). The remaining media was serially diluted and the amount of infectious virus was measured by using the diluted media to infect fresh cell monolayers to determine the tissue culture infectious dose that caused 50% cytopathic effects (TCID50) using Cell TiterGlo reagent (Promega, Madison, WI). For virus cytopathic effect (CPE) assays, viability of infected cells was measure using Cell TiterGlo reagent.

[0510] The percentage inhibition was calculated for each tested concentration relative to the 0% and 100% inhibition controls and the $EC5_0$ value for each compound was determined by non-linear regression as the effective concentration of compound that inhibited virus replication by 50%.

Example 37. EBOV-GFP HMVEC-TERT cells

[0511] HMVEC-TERT cells were seeded in 96 well plates. Eight to ten concentrations of compound were diluted in 3-fold serial dilution increments in media and 100 uL/well of each dilution was transferred in triplicate onto 96 well plates containing preseeded HMVEC-TERT monolayers. The plates were transferred to BSL-4 containment and the appropriate dilution of EBOV-GFP virus stock, previously determined by titration and prepared in cell culture media, was added to test plates containing cells and serially diluted compounds. Each plate included three wells of infected untreated cells and three wells of uninfected cells that served as 0% and 100% virus inhibition control, respectively. Following the infection, test plates were incubated for 3 to 4 days in a tissue culture incubator. After the incubation, virus replication was measured in an Envision plate reader by direct fluorescence to measure GFP expression from the reporter virus. The percentage inhibition was calculated for each tested concentration relative to the 0% and 100% inhibition controls and the $EC5_0$ value for each compound was determined by non-linear regression as the effective concentration of compound that inhibited virus replication by 50%.

Example 38. EBOV-GFP Huh-7 cells

[0512] Huh-7 cells were seeded in 96 well plates. Eight to ten concentrations of compound were diluted in 3-fold serial dilution increments in media and 100 uL/well of each dilution was transferred in triplicate onto 96 well plates containing preseeded Huh-7 monolayers. The plates were transferred to BSL-4 containment and the appropriate dilution of EBOV-GFP virus stock, previously determined by titration and prepared in cell culture media, was added to test plates containing cells and serially diluted compounds. Each plate included three wells of infected untreated cells and three wells of uninfected cells that served as 0% and 100% virus inhibition control, respectively. Following the infection, test plates were incubated for 3 to 4 days in a tissue culture incubator. After the incubation, virus replication was measured in an Envision plate reader by direct fluorescence to measure GFP expression from the reporter virus. The percentage inhibition was calculated for each tested concentration relative to the 0% and 100%

inhibition controls and the $EC5_0$ value for each compound was determined by non-linear regression as the effective concentration of compound that inhibited virus replication by 50%.

Example 39. EBOV-Luc Huh-7 cells

[0513] Huh-7 cells were seeded in 96well plates. Eight to ten concentrations of compound were diluted in 3-fold serial dilution increments in media and 100 uL/well of each dilution was transferred in triplicate onto plates containing preseeded cell monolayers. The plates were transferred to BSL-4 containment and the appropriate dilution of the EBOV-Luc virus stock, previously determined by titration and prepared in cell culture media, was added to test plates containing cells and serially diluted compounds. Each plate included three wells of infected untreated cells and three wells of uninfected cells that served as 0% and 100% virus inhibition control, respectively. Following the infection, test plates were incubated for 3 to 4 days in a tissue culture incubator. After the incubation, virus replication was measured in an Envision plate reader after subsequent addition of luciferase substrate. The percentage inhibition was calculated for each tested concentration relative to the 0% and 100% inhibition controls and the $EC5_0$ value for each compound was determined by non-linear regression as the effective concentration of compound that inhibited virus replication by 50%.

Example 40. MARV-GFP Huh-7 cells

[0514] Huh-7 cells were seeded in 96 well plates. Eight to ten concentrations of compound were diluted in 3-fold serial dilution increments in media and 100 uL/well of each dilution was transferred in triplicate onto 96 well plates containing preseeded Huh-7 monolayers. The plates were transferred to BSL-4 containment and the appropriate dilution of MARV-GFP virus stock, previously determined by titration and prepared in cell culture media, was added to test plates containing cells and serially diluted compounds. Each plate included three wells of infected untreated cells and three wells of uninfected cells that served as 0% and 100% virus inhibition control, respectively. Following the infection, test plates were incubated for 3 to 4 days in a tissue culture incubator. After the incubation, virus replication was measured in an Envision plate reader by direct fluorescence to measure GFP expression from the reporter virus. The percentage inhibition was calculated for each tested concentration relative to the 0% and 100% inhibition controls and the $EC5_0$ value for each compound was determined by non-linear regression as the effective concentration of compound that inhibited virus replication by 50%.

Example 41. Ebola Huh-7 (RNA)

[0515] Huh-7 cells were seeded in 96 well plates. Eight to ten concentrations of compound were diluted in 3-fold serial dilution increments in media and 100 uL/well of each dilution was transferred in triplicate onto plates containing preseeded Huh-7 cell monolayers. The plates were transferred to BSL-4 containment and the appropriate dilution of EBOV virus stock, previously determined by titration and prepared in cell culture media, was added to test plates containing cells and serially diluted compounds. Each plate included three wells of infected untreated cells and three wells of uninfected cells that served as 0% and 100% virus inhibition control, respectively. Following the infection, test plates were incubated for 3 to 4 days in a tissue culture incubator. After the incubation, media from infected cells was removed and a portion was used to quantify viral RNA by reverse transcription quantitative polymerase chain reaction (RT-qPCR). The percentage inhibition was calculated for each tested concentration relative to the 0% and 100% inhibition controls and the $EC5_0$ value for each compound was determined by non-linear regression as the effective concentration of compound that inhibited virus replication by 50%.

Example 42. Ebola Huh-7 (Yield)

[0516] Huh-7 cells were seeded in 96 well plates. Eight to ten concentrations of compound were diluted in 3-fold serial dilution increments in media and 100 uL/well of each dilution was transferred in triplicate onto plates containing preseeded Huh-7 cell monolayers. The plates were transferred to BSL-4 containment and the appropriate dilution of EBOV virus stock, previously determined by titration and prepared in cell culture media, was added to test plates containing cells and serially diluted compounds. Each plate included three wells of infected untreated cells and three wells of uninfected cells that served as 0% and 100% virus inhibition control, respectively. Following the infection, test plates were incubated for 3 to 4 days in a tissue culture incubator. After the incubation, media from infected cells was removed and diluted in 10-fold serial dilutions. The amount of infectious virus was measured by using the diluted media to infect fresh cell monolayers to determine the tissue culture infectious dose that caused 50% cytopathic effects (TCID50) using Cell TiterGlo reagent (Promega, Madison, WI). The percentage inhibition was calculated for each tested concentration relative to the 0% and 100% inhibition controls and the $EC5_0$ value for each compound was determined by non-linear regression as the effective concentration of compound that inhibited virus replication by 50%.

Example 43. Ebola HeLa cells

[0517] The antiviral activity of selected compounds was measured against ebolavirus (EBOV) strain Zaire conducted in biosafety level-4 containment (BSL-4) at the US Army Medical Research Institute for Infections Disease (USAMRIID). Hela cells were seeded in 384 well plates at 5000 cells / well. The antiviral activity of each compound was measured in quadruplicate. Eight to ten concentrations of compound were added directly to the cell cultures using the HP300 digital dispenser in 3-fold serial dilution increments 2h prior to infection. The plates were transferred to BSL-4 containment and the appropriate dilution of virus stock, previously determined by titration and prepared in cell culture media, was added to test plates containing cells and serially diluted compounds. Each plate included three wells of infected untreated cells and three wells of uninfected cells that served as 0% and 100% virus inhibition control, respectively. Following the infection, test plates were incubated for 2 days in a tissue culture incubator. After the incubation, the cells were fixed in formalin solution and virus replication was measured by quantifying Ebola glycoprotein levels after immunostaining and high content imaging using the Perkin Elmer Opera confocal microscopy instrument. The percentage inhibition was calculated for each tested concentration relative to the 0% and 100% inhibition controls and the $EC5_0$ value for each compound was determined by non-linear regression as the effective concentration of compound that inhibited virus replication by 50%.

Example 44. Ebola Macrophage cultures

[0518] The antiviral activity of selected compounds was measured against ebolavirus (EBOV) strain Zaire conducted in biosafety level-4 containment (BSL-4) at the US Army Medical Research Institute for Infections Disease (USAMRIID). Macrophage cultures were isolated from fresh human PBMCs and differentiated in the presence of 5ng/ml GM-CSF and 50uM B-mercaptoethanol. The media was changed every 2 days and cells that adhered to the tissue culture plate after 7 days were removed with 0.5M EDTA in 1x PBS, concentrated by centrifugation at 200 x g for 10 minutes and plated in 384 well assay plates at 40,000 cells / well. The antiviral activity of each compound was measured in quadruplicate. Eight to ten concentrations of compound were added directly to the cell cultures using the HP300 digital dispenser in 3-fold serial dilution increments 2h prior to infection. The plates were transferred to BSL-4 containment and the appropriate dilution of virus stock, previously determined by titration and prepared in cell culture media, was added to test plates containing cells and serially diluted compounds. Each plate included three wells of infected untreated cells and three wells of uninfected cells that served as 0% and 100% virus inhibition control, respectively. Following the

infection, test plates were incubated for 2 days in a tissue culture incubator. After the incubation, the cells were fixed in formalin solution and virus replication was measured by quantifying Ebola glycoprotein levels after immunostaining and high content imaging using the Perkin Elmer Opera confocal microscopy instrument. The percentage inhibition was calculated for each tested concentration relative to the 0% and 100% inhibition controls and the $EC5_0$ value for each compound was determined by non-linear regression as the effective concentration of compound that inhibited virus replication by 50%.

Example 45. Nipah-GFP HMVEC-TERT cells

[0519] HMVEC-TERT cells were seeded in 96 well plates. Eight to ten concentrations of compound were diluted in 3-fold serial dilution increments in media and 100 uL/well of each dilution was transferred in triplicate onto 96 well plates containing preseeded HMVEC-TERT monolayers. The plates were transferred to BSL-4 containment and the appropriate dilution of NiV-GFP virus stock, previously determined by titration and prepared in cell culture media, was added to test plates containing cells and serially diluted compounds. Each plate included three wells of infected untreated cells and three wells of uninfected cells that served as 0% and 100% virus inhibition control, respectively. Following the infection, test plates were incubated for 3 to 4 days in a tissue culture incubator. After the incubation, virus replication was measured in an Envision plate reader by direct fluorescence to measure GFP expression from the reporter virus. The percentage inhibition was calculated for each tested concentration relative to the 0% and 100% inhibition controls and the $EC5_0$ value for each compound was determined by non-linear regression as the effective concentration of compound that inhibited virus replication by 50%.

Example 46. NiV-Luc HMVEC-TERT

[0520] HMVEC-TERT cells were seeded in 96well plates. Eight to ten concentrations of compound were diluted in 3-fold serial dilution increments in media and 100 uL/well of each dilution was transferred in triplicate onto plates containing preseeded cell monolayers. The plates were transferred to BSL-4 containment and the appropriate dilution of the Niv-Luc virus stock, previously determined by titration and prepared in cell culture media, was added to test plates containing cells and serially diluted compounds. Each plate included three wells of infected untreated cells and three wells of uninfected cells that served as 0% and 100% virus inhibition control, respectively. Following the infection, test plates were incubated for 3 to 4 days in a tissue culture incubator. After the incubation, virus replication was measured in an

Envision plate reader after subsequent addition of luciferase substrate. The percentage inhibition was calculated for each tested concentration relative to the 0% and 100% inhibition controls and the $EC5_0$ value for each compound was determined by non-linear regression as the effective concentration of compound that inhibited virus replication by 50%.

Example 47. NiV Hela (Yield)

[0521] Hela cells were seeded in 96 well plates. Eight to ten concentrations of compound were diluted in 3-fold serial dilution increments in media and 100 uL/well of each dilution was transferred in triplicate onto plates containing preseeded Hela cell monolayers. The plates were transferred to BSL-4 containment and the appropriate dilution of Niv virus stock, previously determined by titration and prepared in cell culture media, was added to test plates containing cells and serially diluted compounds. Each plate included three wells of infected untreated cells and three wells of uninfected cells that served as 0% and 100% virus inhibition control, respectively. Following the infection, test plates were incubated for 4 days in a tissue culture incubator. After the incubation, media from infected cells was removed and diluted in 10-fold serial dilutions. The amount of infectious virus was measured by using the diluted media to infect fresh cell monolayers to determine the tissue culture infectious dose that caused 50% cytopathic effects (TCID50) using Cell TiterGlo reagent (Promega, Madison, WI). The percentage inhibition was calculated for each tested concentration relative to the 0% and 100% inhibition controls and the $EC5_0$ value for each compound was determined by non-linear regression as the effective concentration of compound that inhibited virus replication by 50%.

Example 48. Niv Hela (RNA)

[0522] Huh-7 cells were seeded in 96 well plates. Eight to ten concentrations of compound were diluted in 3-fold serial dilution increments in media and 100 uL/well of each dilution was transferred in triplicate onto plates containing preseeded Hela cell monolayers. The plates were transferred to BSL-4 containment and the appropriate dilution of Niv virus stock, previously determined by titration and prepared in cell culture media, was added to test plates containing cells and serially diluted compounds. Each plate included three wells of infected untreated cells and three wells of uninfected cells that served as 0% and 100% virus inhibition control, respectively. Following the infection, test plates were incubated for 3 to 4 days in a tissue culture incubator. After the incubation, media from infected cells was removed and a portion was used to quantify viral RNA by reverse transcription quantitative polymerase chain reaction

(RT-qPCR). The percentage inhibition was calculated for each tested concentration relative to the 0% and 100% inhibition controls and the $EC5_0$ value for each compound was determined by non-linear regression as the effective concentration of compound that inhibited virus replication by 50%.

Table 2: Ebola and Marburg virus antiviral assays

	EC_{50} (nM)							
Assay	**Reporter Virus**				**RNA**	**Yield**	**Antigen expression (high content imaging)**	
Virus	**EBOV-GFP**		**EVOV-Luc**	**MARV-GFP**	**Ebola**			
Cell line	**HMVEC-TERT**	**Huh-7**	**Huh-7**	**Huh-7**	**Huh-7**		**Hela**	**Macrophage**
Compound 1	771	1492	3126	1726	ND	ND	>20,000	>20,000
Compound 9	121	90	ND	ND	1	1029	290	501
(R)-Diastereomer of Compound 9	62	70	ND	ND	ND	ND		
(S)-Diastereomer of Compound 9 (Compound 32)	40	81	ND	ND	ND	ND		
Compound 10								
Compound 15	630	271	ND	ND	ND	ND		
Compound 21	905							270
Compound 22	ND	ND	ND	ND	ND	ND		
Compound 23	458						1650	243,350
Compound 24								
Compound 25								
Compound 26	283						970, 1180	1180
Compound 27	82						182	
Compound 28	102						975	120
Compound 29								
Compound 30								
Compound 31	11061						>20,000	1230

EBOV-GFP: Ebola virus expressing the GFP reporter gene
EBOV-Luc: Ebola virus expressing he luciferase reporter gene
MARV-GFP: Marburg virus expressing the GFP reporter gene
Ebola: Ebolavirus strain 2014

Table 2-a: Ebola and Marburg virus antiviral assays

	EC_{50} (nM)							
Assay	**Reporter Virus**				**RNA**	**Yield**	**Antigen expression (high content imaging)**	
Virus	**EBOV-GFP**		**EVOV-Luc**	**MARV-GFP**	**Ebola**			
Cell line	**HMVEC-TERT**	**Huh-7**	**Huh-7**	**Huh-7**	**Huh-7**		**Hela**	**Macrophage**
Compound 1	771	1492	3126	1726	ND	ND	>20,000	>20,000
Compound 9	121	90	ND	ND	1	1029	290, 270	501, 70
(R)-Diastereomer of Compound 9	62	70	ND	ND	ND	ND	210	112
(S)-Diastereomer of Compound 9 (Compound 32)	40	81	ND	ND	ND	ND	100	87
Compound 10							3200	
Compound 15	630	271	ND	ND	ND	ND	520	501
Compound 21	905, 473							270
Compound 22	ND	ND	ND	ND	ND	ND	11570	
Compound 23	458						1650, 1845	243, 350, 297
Compound 24							785	
Compound 25							6720	
Compound 26	283						970, 1180, 1103	1180, 1290
Compound 27	82						182	
Compound 28	102						975, 682	120
Compound 29							275	
Compound 30	11061						>20000	1230
Compound 31	11061						>20,000, >10000	

EBOV-GFP: Ebola virus expressing the GFP reporter gene
EBOV-Luc: Ebola virus expressing he luciferase reporter gene
MARV-GFP: Marburg virus expressing the GFP reporter gene
Ebola: Ebolavirus strain 2014

Table 3: Nipah and Hendra virus antiviral assays

	EC_{50} (nM)			
Assay	**Reporter Virus**		**CPE**	**Yield**
Virus	**NiV GFP**	**NiV Luc**	**NiV**	
Cell line	**HMVEC-TERT**		**Hela**	
Compound 1	13420	3500	1484	1000
Compound 9	60	30	ND	ND

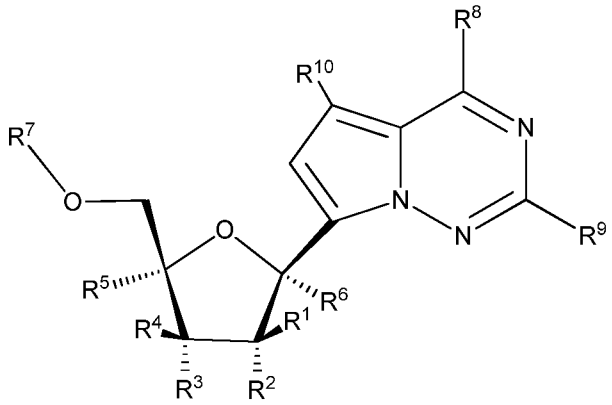
NiV GFP: Nipah virus expressing the GFP reporter gene
NiV-Luc: Nipah virus expressing the luciferase reporter gene
NiV: Nipah virus

[0523] All publications, patents, and patent documents cited herein above are incorporated by reference herein, as though individually incorporated by reference.

[0524] 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.

WHAT IS CLAIMED IS:

1. A method of treating a *Filoviridae* infection in a human in need thereof comprising administering to the human a therapeutically effective amount of a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof;

wherein:

each R^1 is H or halogen;

each R^2, R^3, R^4 or R^5 is independently H, OR^a, $N(R^a)_2$, N_3, CN, $N0_2$, $S(0)_nR^a$, halogen, $(Ci\text{-}C_8)$alkyl, $(C_4\text{-}C_8)$carbocyclylalkyl, $(Ci\text{-}C_8)$substituted alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}Cs)$substituted alkenyl, $(C_2\text{-}Cs)$alkynyl or $(C_2\text{-}Cs)$substituted alkynyl;

or any two R^2, R^3, R^4 or R^5 on adjacent carbon atoms when taken together are -0(CO)0- or when taken together with the ring carbon atoms to which they are attached form a double bond;

R^6 is OR^a, $N(R^a)_2$, N_3, CN, $N0_2$, $S(0)_nR^a$, $-C(=0)R^{11}$, $-C(=0)OR^{11}$, $-C(=0)NR^{11}R^{12}$, $-C(=0)SR^{11}$, $-S(0)R^{11}$, $-S(0)_2R^{11}$, $-S(0)(OR^{11})$, $-S(0)_2(OR^{11})$, $-S0_2NR^{11}R^{12}$, halogen, (Ci-Cs)alkyl, $(C_4$-Cs)carbocyclylalkyl, (Ci-Cs)substituted alkyl, $(C_2$-Cs)alkenyl, $(C_2$-Cs)substituted alkenyl, $(C_2$-Cs)alkynyl, $(C_2$-Cs)substituted alkynyl, or $(C_6\text{-}C_{20})$aryl$(C_1\text{-}C_8)$alkyl;

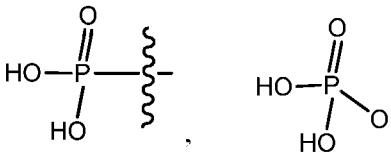
R^7 is selected from a group consisting of

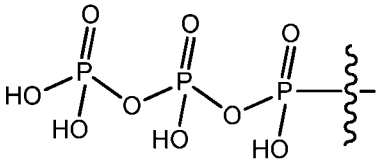
a) H, $-C(=0)R^{11}$, $-C(=0)OR^{11}$, $-C(=0)NR^{11}R^{12}$, $-C(=0)SR^{11}$, $-S(0)R^{11}$, $-S(0)_2R^{11}$, $-S(0)(OR^{11})$, $-S(0)_2(OR^{11})$, or $-S0_2NR^{11}R^{12}$,

wherein each (Ci-Cs)alkyl, $(C_2$-Cs)alkenyl, $(C_2\text{-}C_8)$alkynyl or $(C_6\text{-}C_{20})$aryl(Ci-Cs)alkyl of each R^{11} or R^{12} is, independently,

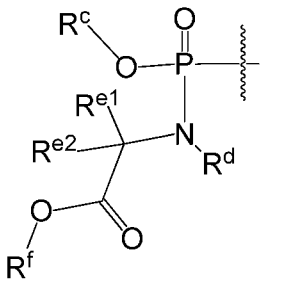
optionally substituted with one or more halo, hydroxy, CN, N_3, $N(R^a)_2$ or OR^a; and wherein one or more of the non-terminal carbon atoms of each said (Ci-Cs)alkyl may be optionally replaced with -0-, -S- or -NR^a-, and

b) a group selected from:


, and


,

c) a group selected from: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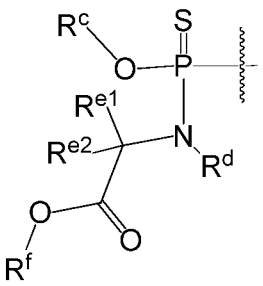
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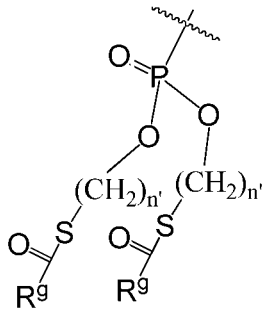
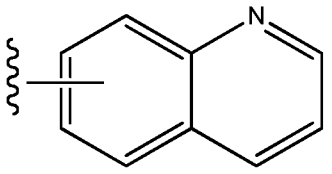


wherein:

R^c is selected from phenyl, 1-naphthyl, 2-naphthyl,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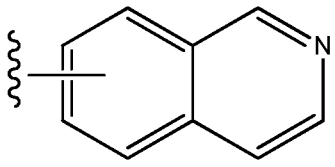

;

R^d is H or CH_3;

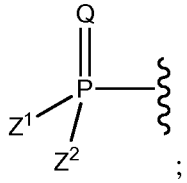
R^{e1} and R^{e2} are each independently H, (d-C6)alkyl or benzyl;

R^f is selected from H, (Ci-Cs)alkyl, benzyl, $_{(C3}$ -C6)cycloalkyl, and -CH_2-(C_3-C_6)cycloalkyl;

R^g is selected from (Ci-C_8)alkyl, -0-(Ci-C_8)alkyl, benzyl, -O-benzyl, -CH_2-(C_3-C_6)cycloalkyl, -0-CH_2-(C_3-C_6)cycloalkyl, and CF_3; and

n' is selected from 1, 2, 3, and 4; and

d) a group of the formula:



;

wherein:

Q is O, S, NR, $^+$N(0)(R), N(OR), $^+$N(0)(OR), or N-NR_2;

Z^1 and Z^2, when taken together, are -$Q^1(C(R^y)_2)_3Q^1$-;

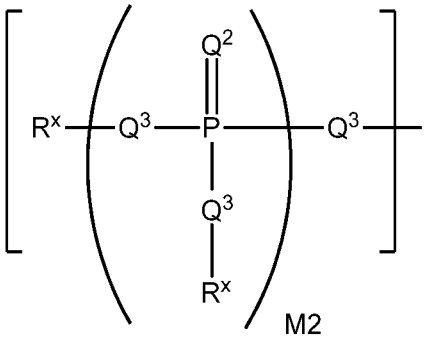
wherein

each Q^1 is independently O, S, or NR; and

each R^y is independently H, F, CI, Br, I, OH, R, -$C(=Q^2)R$, -$C(=Q^2)OR$, -$C(=Q^2)N(R)_2$, -$N(R)_2$, -$^+N(R)_3$, -SR, -S(0)R, -$S(0)_2R$, -S(0)(OR), -$S(0)_2$(OR), -$OC(=Q^1)R$, -$OC(=Q^2)OR$, -$OC(=Q^2)(N(R)_2)$, -$SC(=Q^2)R$, -$SC(=Q^2)OR$, -$SC(=Q^2)(N(R)_2)$, -$N(R)C(=Q^2)R$, -$N(R)C(=Q^2)OR$, -$N(R)C(=Q^2)N(R)_2$, -$S0_2NR_2$, -CN, -N_3, -$N0_2$, -OR, or Z^3; or when taken together, two R^y on the same carbon atom form a carbocyclic ring of 3 to 7 carbon atoms;

each Q^2 is independently, O, S, NR, $^+$N(0)(R), N(OR), $^+$N(0)(OR), or N-NR_2;or

Z^1 and Z^2 are each, independently, a group of the Formula la:



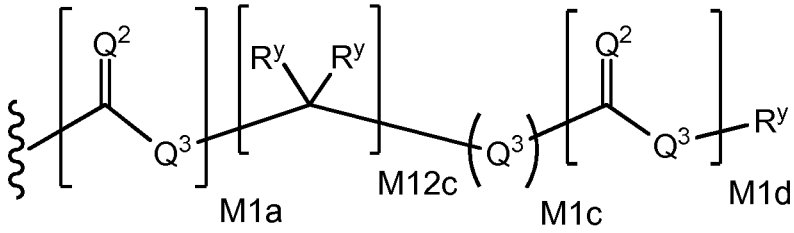
Formula 1a

wherein:

each Q^3 is independently a bond, O, CR_2, NR, $^+N(0)(R)$, N(OR), $^+N(0)(OR)$, N-NR_2, S, S-S, S(O), or $S(0)_2$;

M2 is 0, 1 or 2;

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



wherein:

each Mia, Mlc, and Mid is independently 0 or 1;

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

Z^3 is Z^4 or Z^5;

Z^4 is R, $-C(Q^2)R^y$, $-C(Q^2)Z^5$, $-S0_2R^y$, or $-S0_2Z^5$; and

Z^5 is a carbocycle or a heterocycle wherein Z^5 is independently substituted with 0 to 3 R^y groups;

R^8 is halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3, NO, $N0_2$, CHO, CN, $-CH(=NR^{11})$, $-CH=NNHR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=0)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=0)OR^{11}$, $(Ci\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl,

(C4 -Cs)carbocyclylalkyl, (C6-C2o)optionally substituted aryl, optionally substituted heteroaryl, -C(=O)(C_1–C_8)alkyl, -S(0) $_n$(Ci-C $_8$)alkyl, (C6 - C_2o)aryl(Ci-C $_8$)alkyl, OR^{11} or SR^{11};

each 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, N0 $_2$, CHO, CN, -CH(=NR^{11}), -CH=NHNR^{11}, -CH=N(OR^{11}), -CH(OR^{11})$_2$, -C(=0)$NR^{11}R^{12}$, -C(=S)$NR^{11}R^{12}$, -C(=0)OR^{11}, R^{11}, OR^{11} or SR^{11};

each R^{11} or R^{12} is independently H, (Ci-C $_8$)alkyl, (C_2- C_8)alkenyl, (C_2- C_8)alkynyl, (C4 - C_8)carbocyclylalkyl, (C6 - C_2o)optionally substituted aryl, optionally substituted heteroaryl, -C(=0)(d-C $_8$)alkyl, -S(0) $_n$(Ci-C $_8$)alkyl or (C6 - C_2o)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 -0-, -S- or -NR^a-;

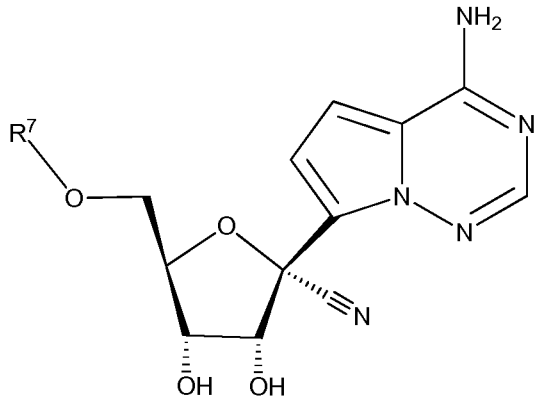
each R^a is independently H, (C_1- C_8)alkyl, (C_2- C_8)alkenyl, (C_2- C_8)alkynyl, (C_6- C_{20})aryl(C_1- C_8)alkyl, (C_4- C_8)carbocyclylalkyl, -C(=0)R, -C(=0)OR, -C(=0)NR_2, -C(=0)SR, -S(0)R, -S(0) $_2$R, -S(0)(OR), -S(0) $_2$(OR), or -S0 $_2NR_2$; wherein

each R is independently H, (Ci-C $_8$) alkyl, (Ci-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_2o)aryl, (C6 - C_2o)substituted aryl, (C_2- C_2o)heterocyclyl, (C_2- C_{2o}) substituted heterocyclyl, (C6 - C_2o)aryl(C_1- C_8)alkyl or substituted (C6 - C_2o)aryl(C_1- C_8)alkyl;

each n is independently 0, 1, or 2; and

wherein each (Ci-C $_8$)alkyl, (C_2- C_8)alkenyl, (C_2- C_8)alkynyl or (C_6- C_{20})aryl(Ci-C $_8$)alkyl of each R^2, R^3, R^5, R^6, R^{11} or R^{12} is, independently, optionally substituted with one or more halo, hydroxy, CN, N3, $N(R^a)_2$ or OR^a; and wherein one or more of the non-terminal carbon atoms of each said (Ci-C_8)alkyl may be optionally replaced with -0-, -S- or -NR^a-.

2. The method of claim 1 wherein the compound of Formula I is represented by Formula IV:



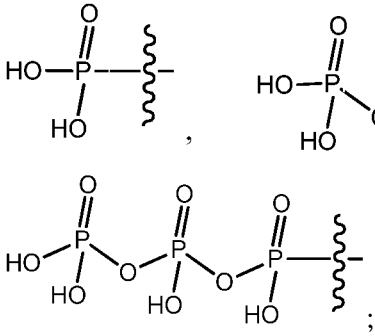
Formula IV

or a pharmaceutically acceptable salt thereof.

3. The method of claim 1 wherein R^7 is H.

4. The method of claim **1** wherein $\mathbf{R^7}$ is

b) a group selected from:

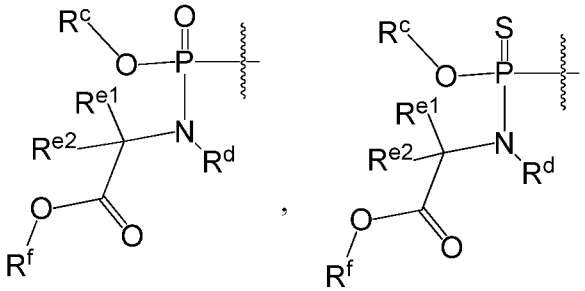


and

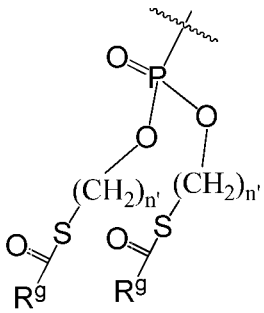
;

or

c) a group selected from:

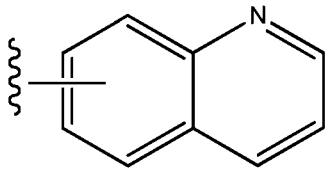


and



wherein:

$\mathbf{R^c}$ is selected from phenyl, **1**-naphthyl, 2-naphthyl,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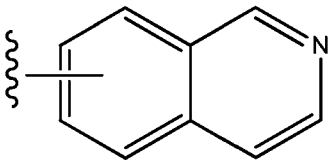

;

R^d is H or CH_3;

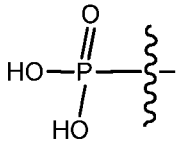
R^{e1} and R^{e2} are each independently H, (C_1- C_6)alkyl or benzyl;

R^f is selected from H, (Ci-C_8)alkyl, benzyl, (C_3-C_6)cycloalkyl, and -CH_2-(C_3-C_6)cycloalkyl;

R^g is selected from (Ci-C_8)alkyl, -0-(Ci-C_8)alkyl, benzyl, -O-benzyl, -CH_2-(C_3-C_6)cycloalkyl, -0-CH_2-(C_3-C_6)cycloalkyl, and CF_3; and

n' is selected from 1, 2, 3, and 4.

5. The method of any of claims 1 or 4 wherein R^7 is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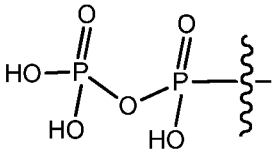
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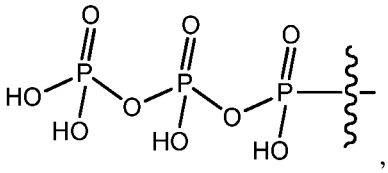
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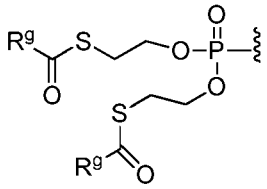
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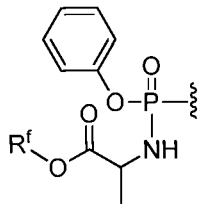
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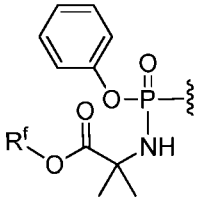
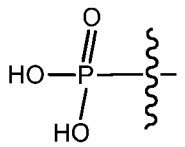


wherein

R^f is selected from H, Ci-Cs alkyl, benzyl, C_3-C_6 cycloalkyl, and -CH_2-C_{3-C6} cycloalkyl; and

R^g is selected from C_1-C_8 alkyl, -0-Ci-C_8 alkyl, benzyl, -O-benzyl, -CH_2-C_3-C_6 cycloalkyl, -0-CH_2-C_3-C_6 cycloalkyl, and CF_3.

6. The method of any of claims 1, 4, or 5 wherein R^7 is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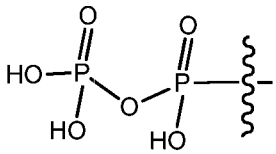
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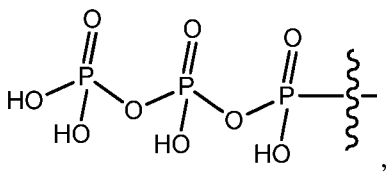
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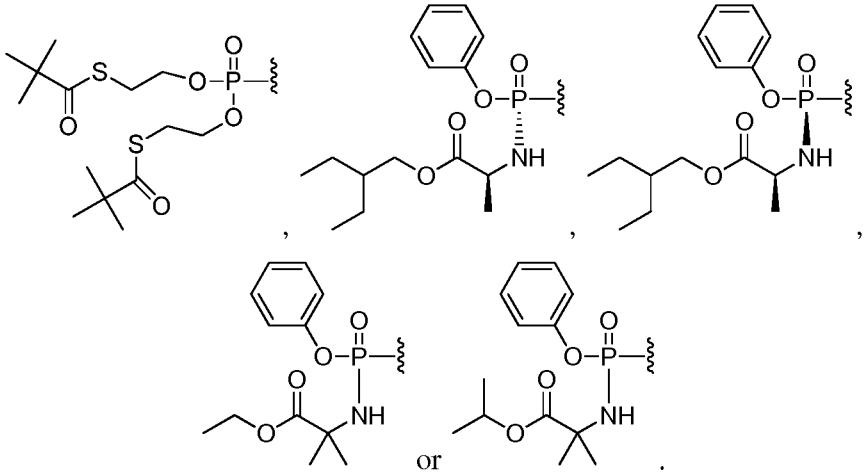
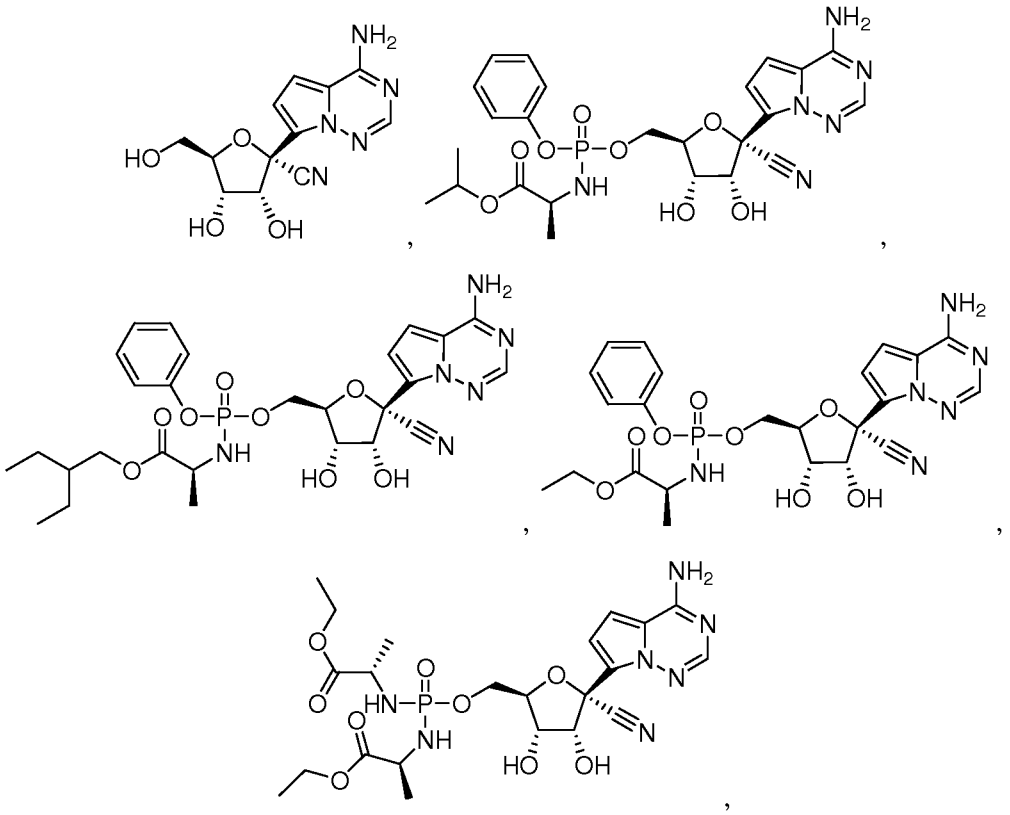
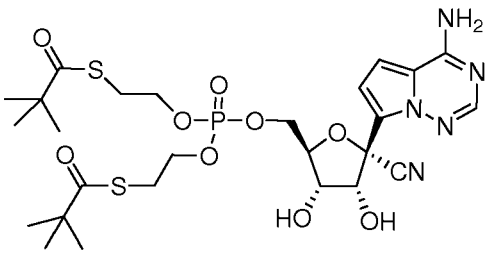


or .

7. The method of claim 1 wherein the compound of Formula I is:

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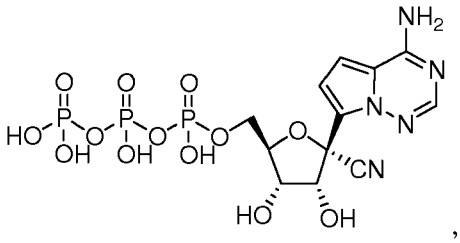
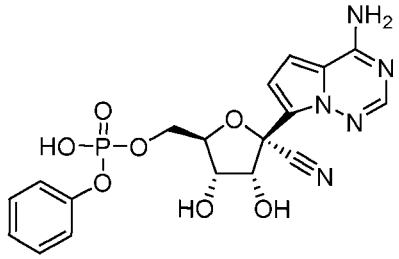
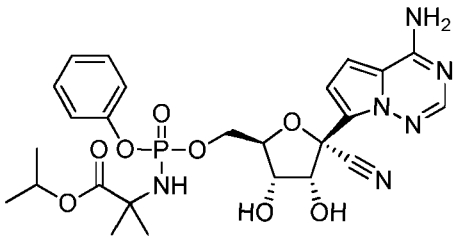

, or

;

or a pharmaceutically acceptable salt thereof.

8. The method of claim 1 wherein the compound of Formula I is: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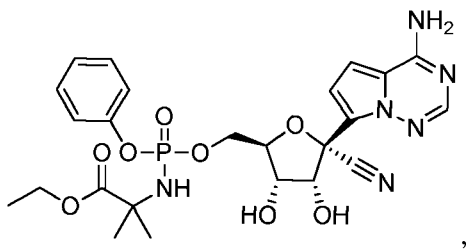
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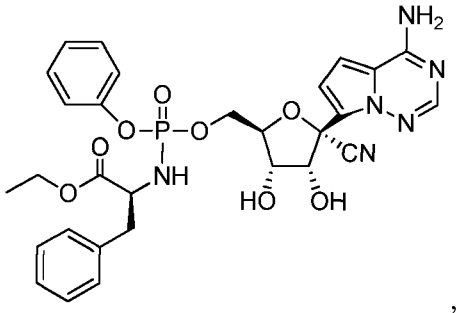
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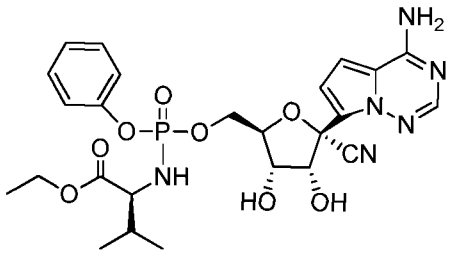
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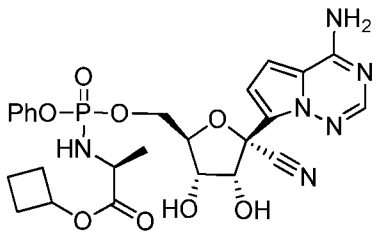
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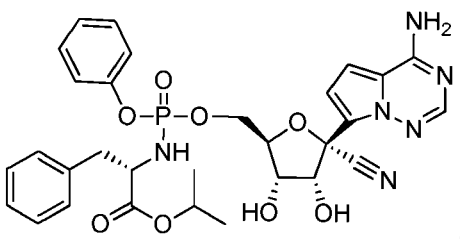
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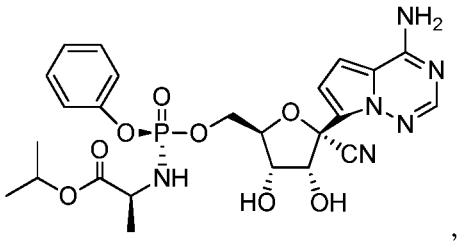
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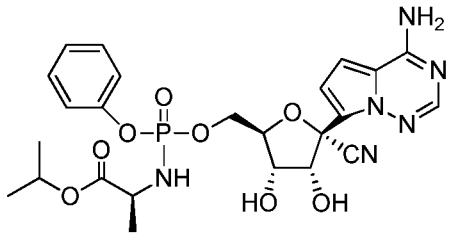
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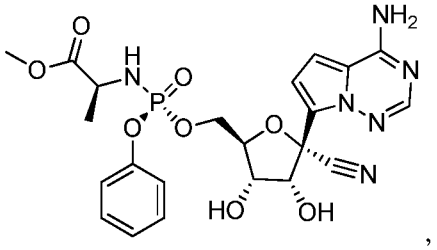
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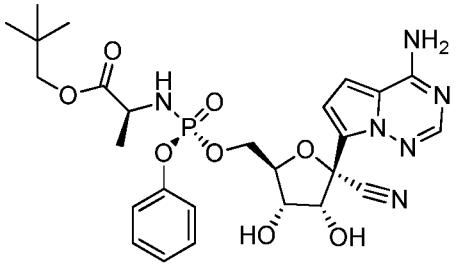
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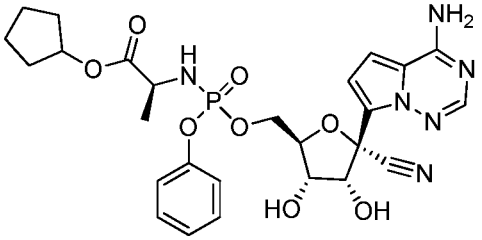
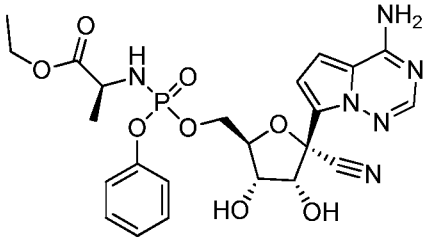
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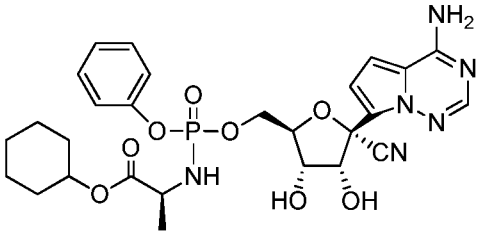
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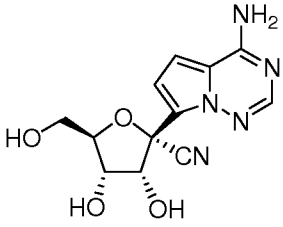
or a pharmaceutically acceptable salt thereof.

9. The method of claim 1 wherein the compound of Formula I is: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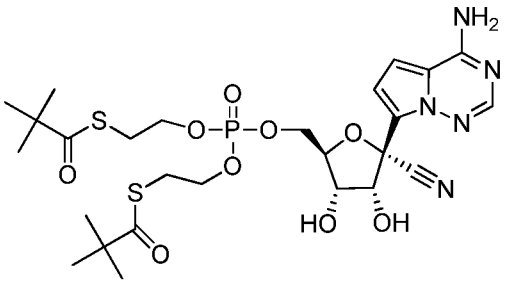
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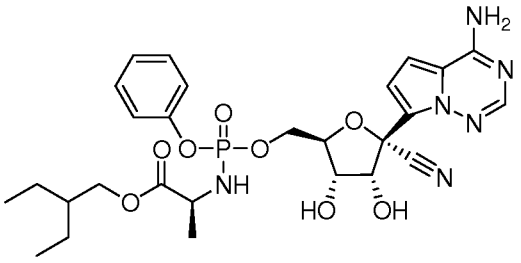
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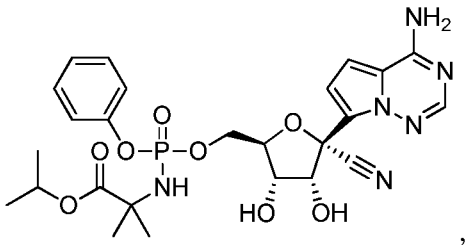
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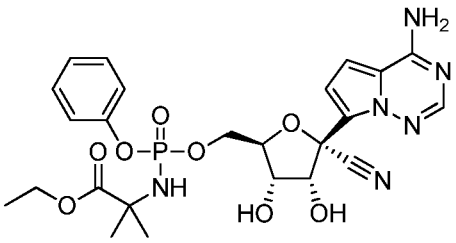
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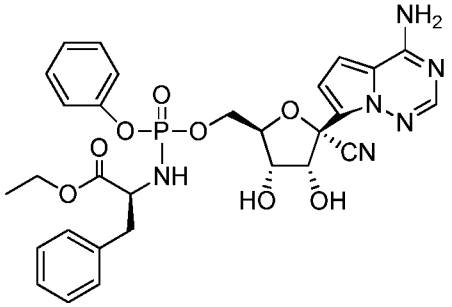
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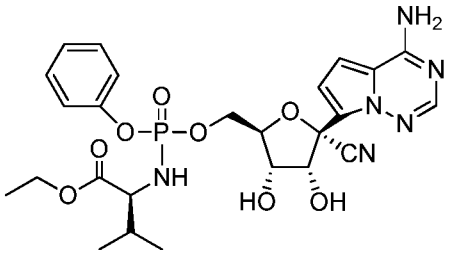
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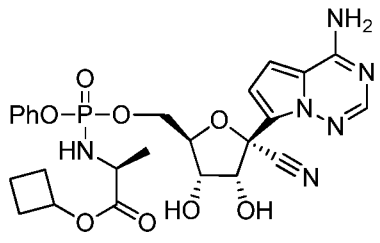
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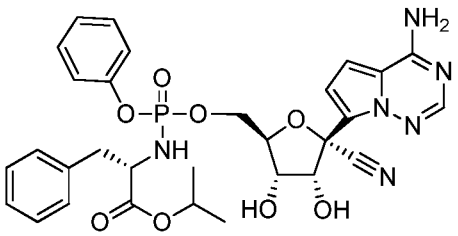
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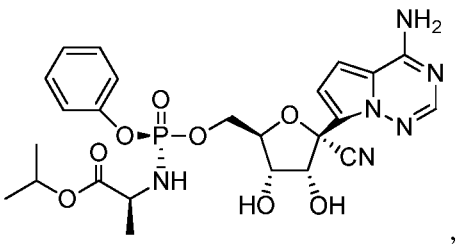
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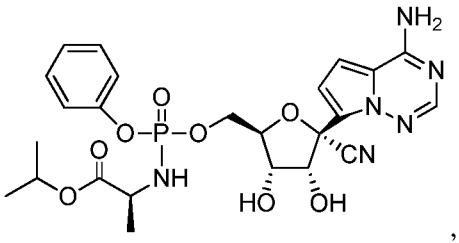
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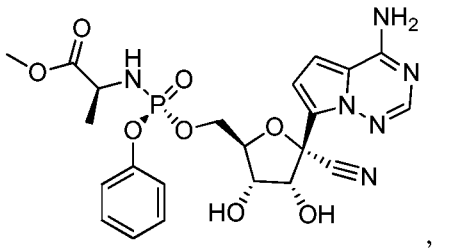
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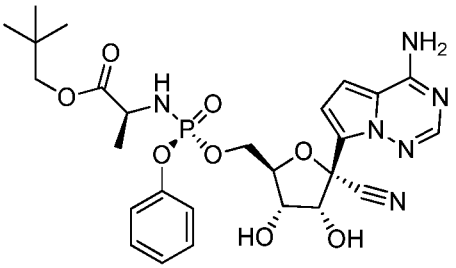
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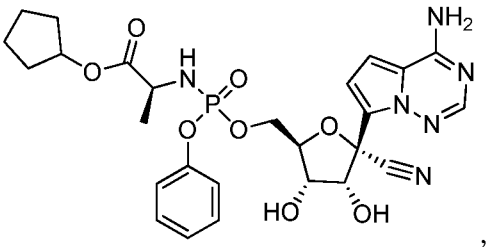
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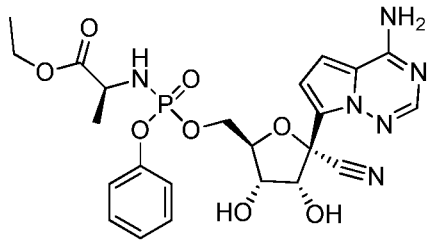
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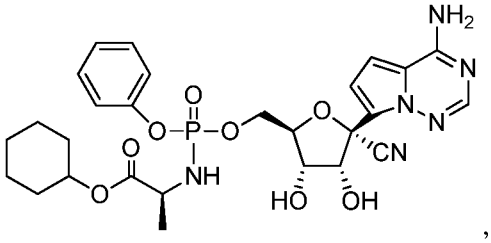
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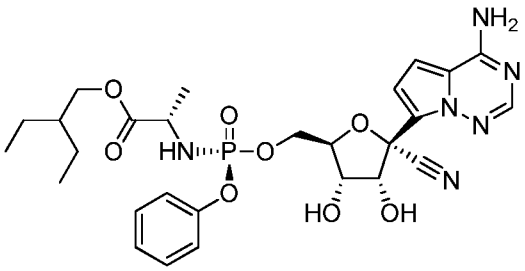
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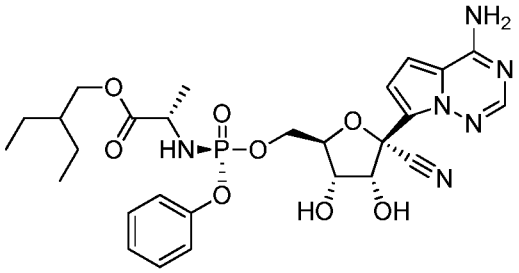
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or a pharmaceutically acceptable salt thereof.

10. The method of any of claims 1-9 further comprising a pharmaceutically acceptable carrier or excipient.

11. The method of any of claims 1-9 further comprising administering a therapeutically effective amount of at least one other thereapeutic agent or composition thereof selected from the group consisting of a corticosteroid, an anti-inflammatory signal transduction modulator, a P2-adrenoreceptor agonist bronchodilator, an anticholinergic, a mucolytic agent, hypertonic saline and other drugs for treating *Filoviridae* virus infections; or mixtures thereof.

12. The method of claim 11 wherein the at least one other thereapeutic agent is ribavirin, palivizumab, motavizumab, RSV-IGIV (RespiGam®), MEDI-557, A-60444, MDT-637, BMS-433771, amiodarone, dronedarone, verapamil, Ebola Convalescent Plasma (ECP), TKM-100201, BCX4430 ((2S,3S,4R,5R)-2-(4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-5-(hydroxymethyl)pyrrolidine-3,4-diol), favipiravir (also known as T-705 or Avigan),T-705 monophosphate, T-705 diphosphate, T-705 triphosphate, FGI-106 (l-N,7-N-bis[3-(dimethylamino)propyl]-3,9-dimethylquinolino[8,7-h]quinolone-l,7-diamine), JK-05, TKM-Ebola, ZMapp, rNAPc2, VRC-EBOADC076-00-VP, OS-2966, MVA-BN filo, brincidofovir, Vaxart adenovirus vector 5-based ebola vaccine, Ad26-ZEBOV, FiloVax vaccine, GOVX-E301, GOVX-E302, ebola virus entry inhibitors (NPC1 inhibitors), or rVSV-EBOV or mixtures thereof.

13. The method of any of claims 1-9 wherein the *Filoviridae* infection is caused by a *Filoviridae* virus.

14. The method of any of claims 1-9 wherein the *Filoviridae* infection is caused by an ebolavirus.

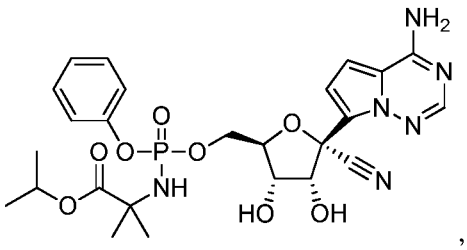
15. The method of any of claims 1-9 wherein the *Filoviridae* infection is caused by *Bundibugyo ebolavirus, Reston ebolavirus, Sudan ebolavirus, Tai Forest ebolavirus,* or *Zaire ebolavirus.*

16. The method of any of claims 1-9 wherein the *Filoviridae* infection is caused by a *Marburg* virus.

17. The method of any of claims 1-9 wherein the *Filoviridae* infection is caused by a Lloviu virus.

18. The method of any of claims 1-9 wherein a *Filoviridae* polymerase is inhibited.

19. A compound having the following structure:



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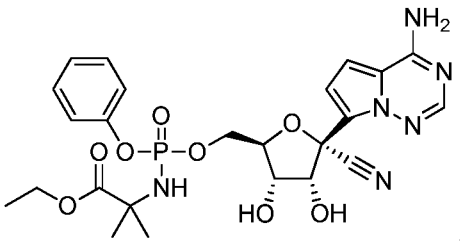

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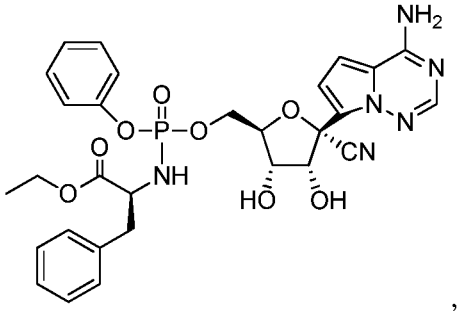

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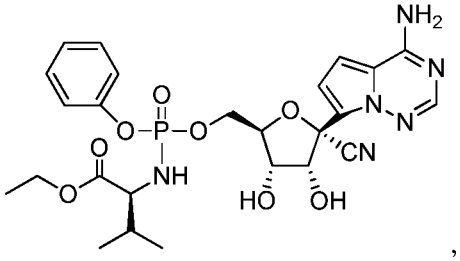

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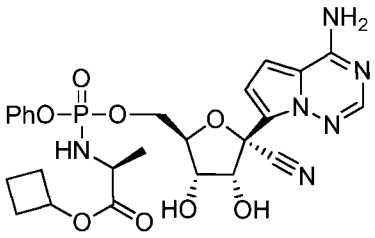
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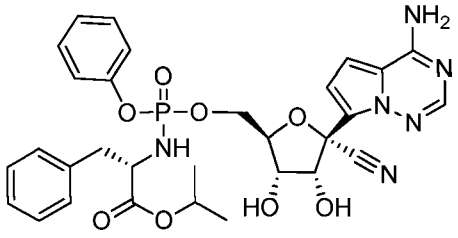
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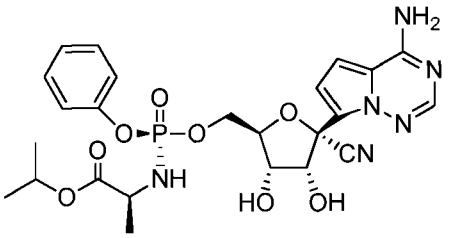
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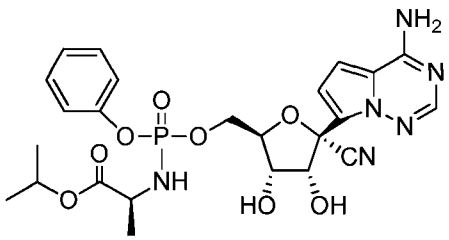
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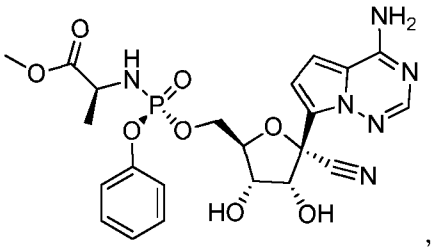
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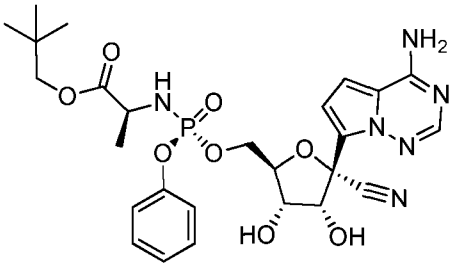
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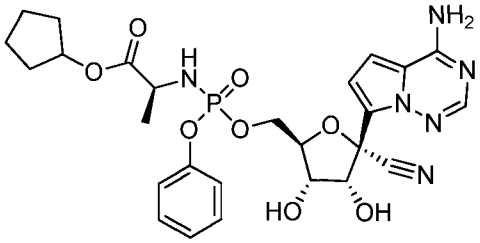
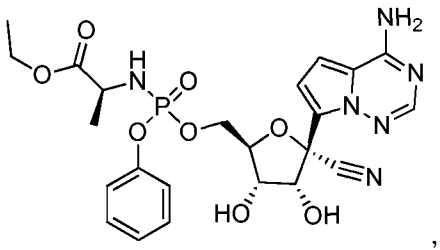
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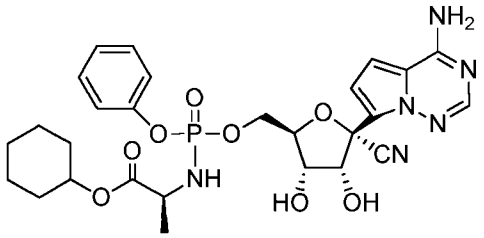
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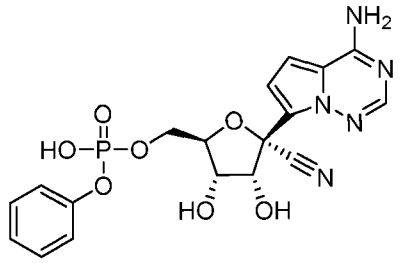
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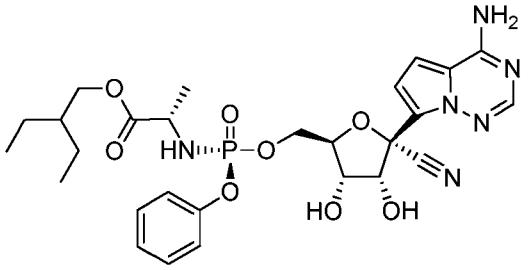
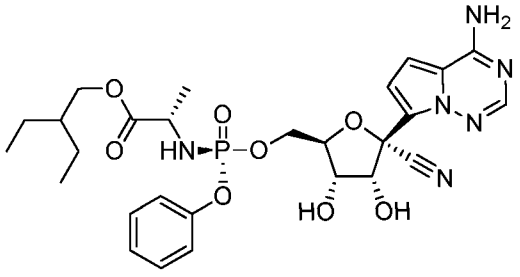
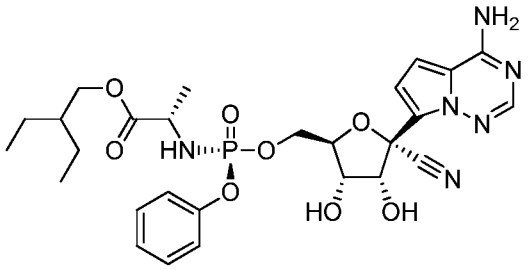


or

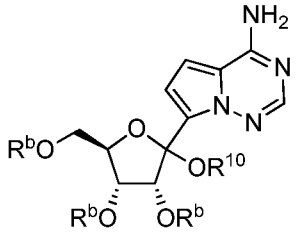
or a pharmaceutically acceptable salt thereof.

20. The compound of claim 19, having the structure:

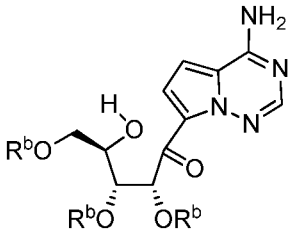


or a pharmaceutically acceptable salt thereof.

21. A method of preparing a compound of Formula V-a or V-b:



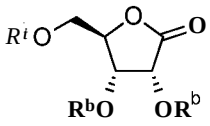
Formula (V-a),



Formula (V-b)

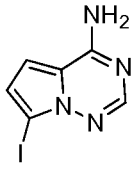
the method comprising:

forming a reaction mixture comprising a deprotonating agent, a silylating agent, a coupling agent, an additive, a compound of Formula Vl-a:



Formula (Vl-a),

and a compound of Formula VII:



Formula (VII)

under conditions suitable to prepare the compound of Formula V-a or V-b, wherein

each $\mathbf{R}^b$ is independently a hydroxy protecting group;

alternatively, two $\mathbf{R}^b$ groups on adjacent carbons can be combined to form a $-\mathbf{C}(\mathbf{R}^{19})_2-$ group;

$\mathbf{R}^{10}$ is **H** or a silyl group; and

$\mathbf{R}^{19}$ is **H**, C_1-C_8 alkyl, phenyl or substituted phenyl.

22. The method of claim 21 wherein the deprotonating agent is a lithium coupling agent or a magnesium coupling agent; the silylating agent is a chloro-silane; the coupling agent is a magnesium based coupling agent; and the additive is YCI_3, $CeCl_3$, NdC¾, or $LaCl_3$.

23. The method of claim 21 wherein

the deprotonating agent is PhMgCl;

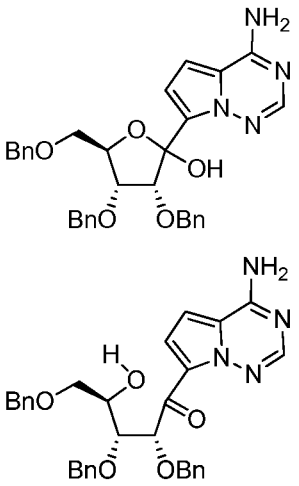
the silylating agent is TMSCl;

the coupling agent is iPrMgCl;

the additive is $YC1_3$, $CeCl_3$, $NdCl_3$, or $LaCl_3$; and

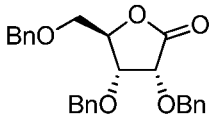
the hydroxyl protecting group is benzyl.

24. The method of claim 21 preparing the compound of Formula V-a or Formula V-b:



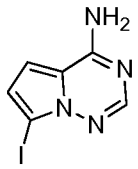
the method comprising:

forming the reaction mixture comprising TMSCl, PhMgCl, iPrMgCl, an additive, the compound of Formula Vl-a:



,

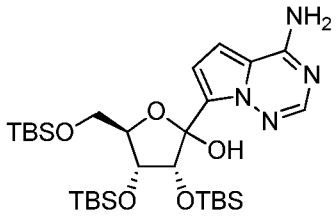
and the compound of Formula VII:



under conditions suitable to prepare the compound of Formula V-a or Formula V-b, wherein

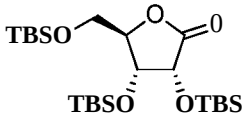
the additive is $LaCl_3$-2LiCl, $LaCl_3$, $CeCl_3$, $NdCl_3$, or $YC1_3$.

25. The method of claim 21, preparing the compound of Formula V-a:



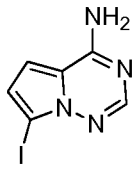
the method comprising:

forming the reaction mixture comprising TMSCl, PhMgCl, iPrMgCl-LiCl, an additive, the compound of Formula Vl-a:



,

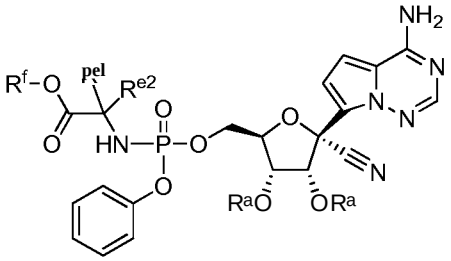
and the compound of Formula VII:



under conditions suitable to prepare the compound of Formula V-a, wherein

the additive is $LaCl_3$-2LiCl, $LaCl_3$, $CeCl_3$, $NdCl_3$, or $YC1_3$.

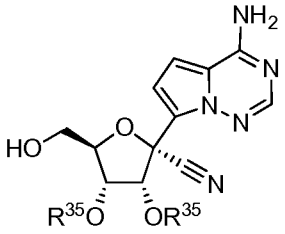
26. A method of preparing a compound of Formula VIII:



Formula (VIII)

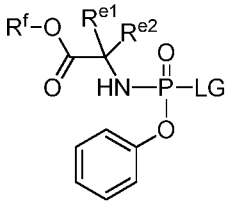
the method comprising:

forming a reaction mixture comprising a coupling agent, a non-nucleophilic base, a compound of Formula IX-a:



Formula (IX-a),

and a compound of Formula X:



Formula (X),

under conditions suitable to form the compound of Formula VIII,

wherein

each R^a is H or a hydroxy protecting group;

each R^{35} is independently H or a hydroxy protecting group, or both R^{35} groups are combined to form $-C(R^{19})_2-$;

R^{e1} and R^{e2} are each independently H, Ci-C_6 alkyl or benzyl;

R^f is H, C_1-C_8 alkyl, benzyl, $_{C3-C6}$ cycloalkyl, or -CH2-C3-C6 cycloalkyl;

R^{19} is H, C_1-C_8 alkyl, phenyl or substituted phenyl; and

LG is a leaving group.

27. The method of claim 26 wherein

each R^{35} are combined to form $-C(R^{19})_2-$;

R^f is Ci-Cs alkyl;

R^{19} is Ci-Cs alkyl; and

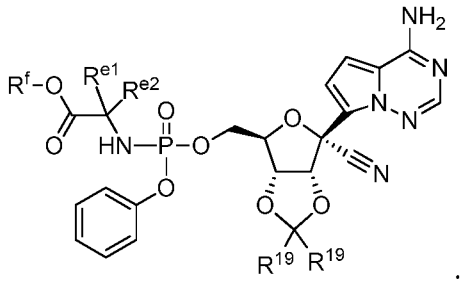
the leaving group LG is $_4$-nitrophenoxy or pentafluorophenoxy.

28. The method of claim 26 wherein

the coupling agent is $MgCl_2$; and

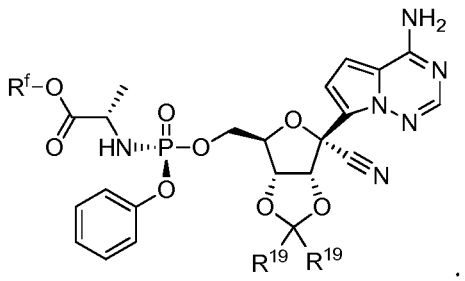
the non-nucleophilic base is di-isopropyl ethyl amine.

29. The method of claim 26 wherein the compound of Formula VIII is



.

30. The method of claim 26 wherein the compound of Formula VIII is



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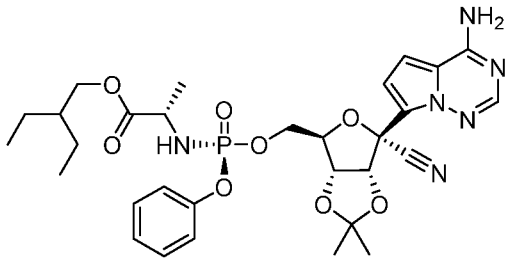
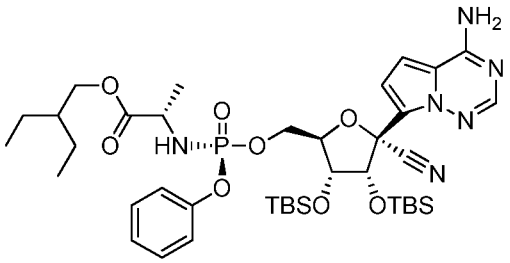
31. The method of claim 26 wherein the compound of Formula VIII is



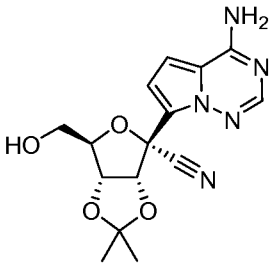
.

32. The method of claim 26 wherein the compound of Formula VIII is

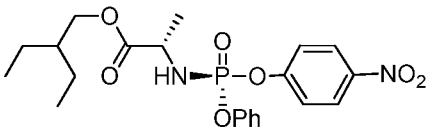


33. The method of claim 26 wherein the method comprises:

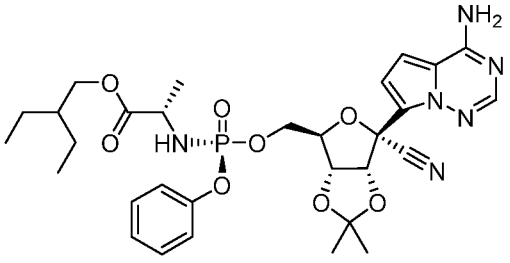
forming the reaction mixture comprising $MgCl_2$, DIPEA, the compound of Formula IX:



and the compound of Formula X:

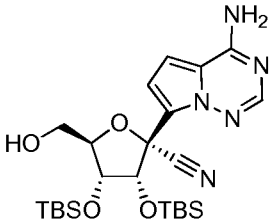


under conditions suitable to form the compound of Formula VIII:

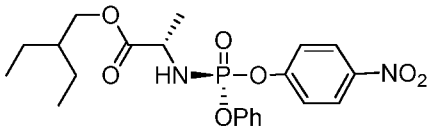


34. The method of claim 26 wherein the method comprises:

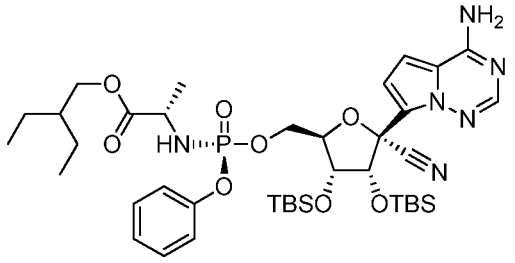
forming the reaction mixture comprising $MgCl_2$, DIPEA, the compound of Formula IX-a[2]:



and the compound of Formula X:



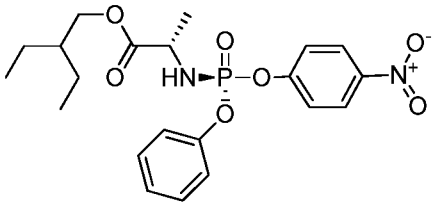
under conditions suitable to form the compound of Formula VIII:



35. The method of claim 26 further comprising:

forming a second reaction mixture comprising a deprotection agent and the compound Formula VIII wherein each R^{35} group is a hydroxyl protecting group, under suitable conditions to form the compound of Formula VIII where each R^a is H.

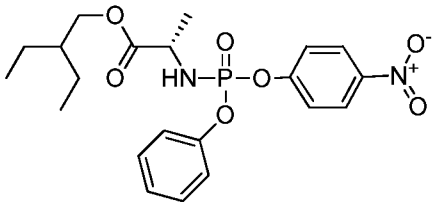
36. A method of preparing a compound of Formula X-b:



Formula X-b
(diastereomerically pure)

the method comprising:

forming a reaction mixture comprising a suitable solvent, a suitable base, and a compound of Formula X-a:



Formula X-a
(mixture of diastereomers)

Formula (X-a), and

optionally one or more seed cystals of Formula X-b

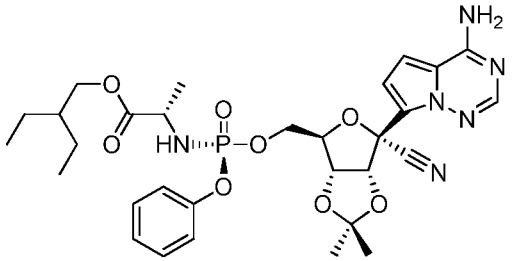
under conditions suitable to form the compound of Formula X-b.

37. The method of claim 36 wherein

the suitable solvent is acetonitrile; and

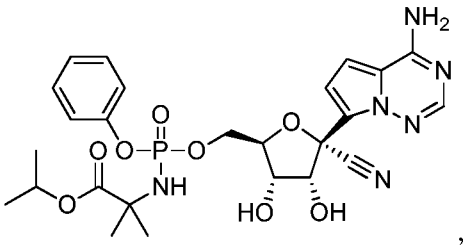
the suitable base is DBU.

38. A compound of the formula



or a pharmaceutically acceptable salt or ester thereof.

39. A pharmaceutical composition comprising a therapeutically effective amount of a compound selected from the group of: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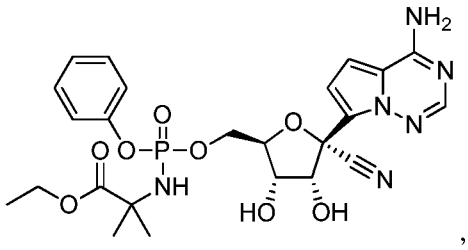
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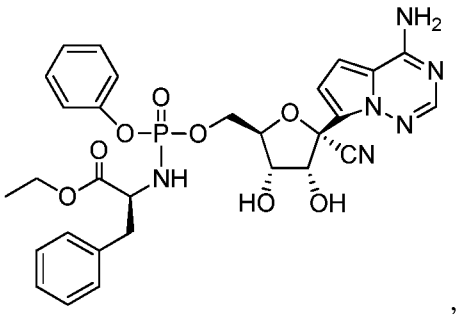
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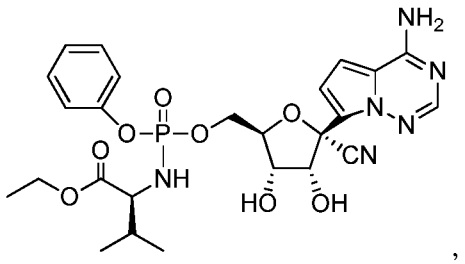
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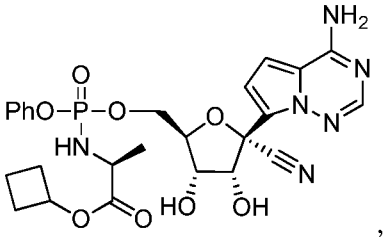
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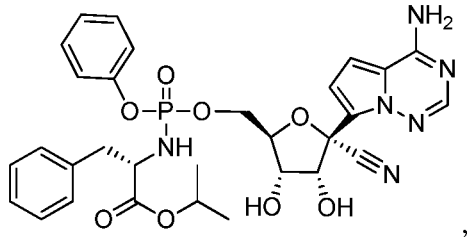
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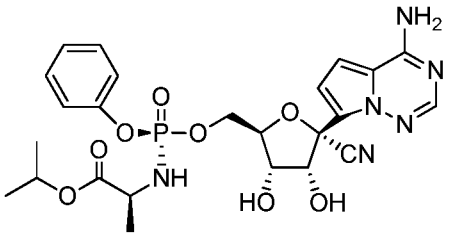
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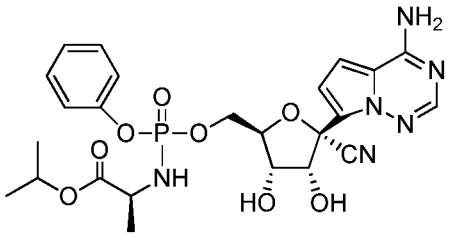
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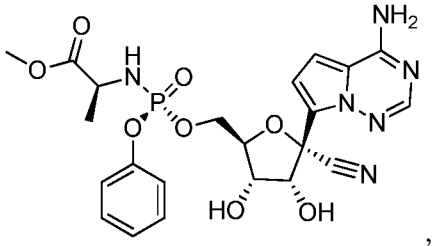
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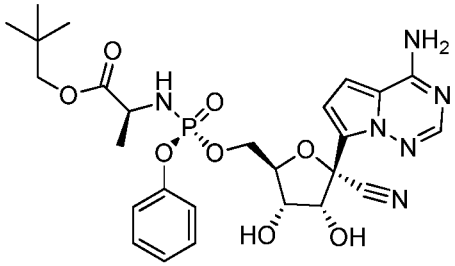
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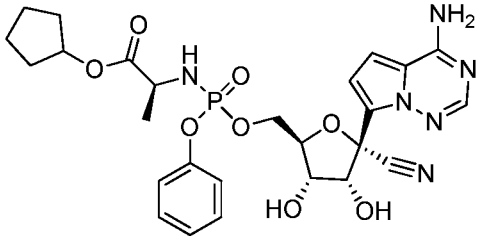
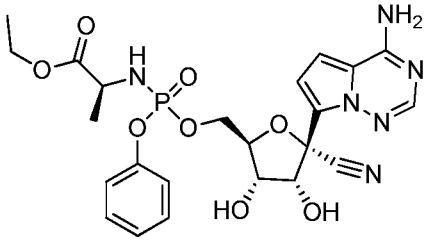
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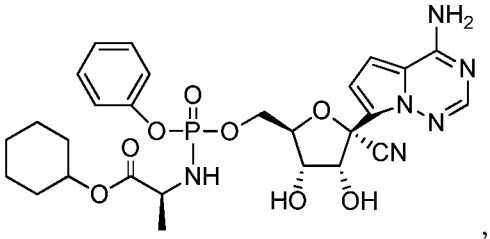
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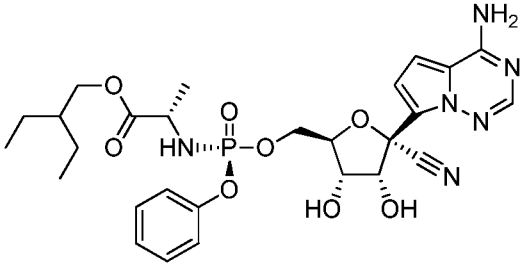
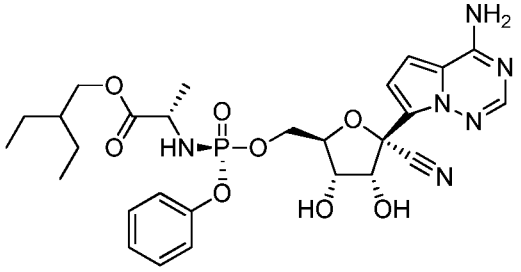
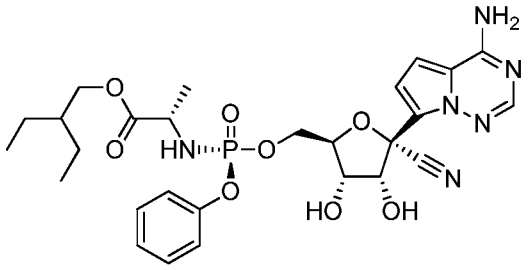


or

or a pharmaceutically acceptable salt or ester thereof.

40. A pharmaceutical composition comprising a therapeutically effective amount of a compound of the formula:



or a pharmaceutically acceptable salt thereof.

41. A compound as described in any one of claims 1-9 and 19-20, or a pharmaceutically acceptable salt thereof, for use in treating a *Filoviridae* virus infection in a human.

42. A compound as described in any one of claims 1-9 and 19-20, or a pharmaceutically acceptable salt thereof, for use in treating an ebolavirus infection in a human.

43. A compound as described in any one of claims 1-9 and 19-20, or a pharmaceutically acceptable salt thereof, for use in treating an ebolavirus infection in a human.

44. A compound as described in any of claims 1-9 and 19-20, or a pharmaceutically acceptable salt or ester thereof, for use in treating a Marburg virus infection in a human.

45. The use of a compound as described in any of claims 1-9 and 19-20, or a pharmaceutically acceptable salt or ester thereof, for use the preparation of a medicament useful in treating a *Filoviridae* virus infection in a human.

46. The use of a compound as described in any of claims 1-9 and 19-20, or a pharmaceutically acceptable salt or ester thereof, for use the preparation of a medicament useful in treating an Ebola virus infection in a human.

47. The use of a compound as described in any of claims 1-9 and 19-20, or a pharmaceutically acceptable salt or ester thereof, for use the preparation of a medicament useful in treating a Marburg virus infection in a human.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/057934

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

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

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

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

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

see additional sheet

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

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

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

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

Remark on Protest

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

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

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/057934

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/53 A61K31/675 A61K31/685 A61K31/00 C07H1/00
C07H1/02 C07H11/00 C07H15/18 C07D487/04 C07D519/00
ADD. A61P31/14
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal , BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/012776 A1 (GILEAD SCIENCES INC [US]; MACKMAN RICHARD L [US]; PARRISH JAY P [US];) 26 January 2012 (2012-01-26)	19, 21-26,39
Y	compounds of claim 13, in particular penultimate compound of p. 152; p. 128, compound 9; first compound of p. 153	21-35
X	US 2010/015094 A1 (BABU YARLAGADDA S [US] ET AL) 21 January 2010 (2010-01-21)	1-7, 9-15, 17, 18, 41-43, 45-47
	claims 1-7, 25 24; 0011; 0178	

-/- .

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" documentwhich may throw doubts on priority claim(s) orwhich is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 March 2016	18/03/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Dahse, Thomas

4

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	scheme 2, compound 5; p. 485, bridging	21-25
A	col. 1/2	1-20, 38-47

X	AESOP CHO ET AL: "Synthesis and antiviral activity of a series of 1'-substituted 4-aza-7,9-dideazaadenosine C-nucleosides", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 22, no. 8, 1 April 2012 (2012-04-01), pages 2705-2707, XP055238769, AMSTERDAM, NL ISSN: 0960-894X, D0I: 10.1016/j.bmcl.2012.02.105	21-25
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A	compounds 8a-d and 9a-d	1-20, 26-47

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A	p. 84, compound 13	1-20, 38-47

X	US 2013/143835 A1 (ENER0TH ANDERS [SE] ET AL) 6 June 2013 (2013-06-06) p. 14, 0169, compound 1-14; 0172-0173;	36

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4

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-20, 38-47

   directed to compounds of formula I and their use in the treatment of Filoviridae infection

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2. claims: 21-25

   directed to the preparation of a compound of formula V-a or V-b

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3. claims: 26-35

   directed to the preparation of a compound of formula VIII.

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4. claims: 36, 37

   directed to the preparation of a compound of formula X-b.
