

CARBA-NUCLEOSIDE ANALOGS FOR ANTIVIRAL TREATMENT

10

FIELD OF THE INVENTION

The invention relates generally to compounds with antiviral activity, more particularly nucleosides active against *Flaviviridae* infections and most particularly to inhibitors of hepatitis C virus RNA-dependent RNA polymerase.

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BACKGROUND OF THE INVENTION

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

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

- 5 R., Scientific American, Oct.: 80-85, (1999); Gordon, C. P., et al., *J. Med. Chem.* **2005**, 48, 1-20; Maradpour, D.; et al., *Nat. Rev. Micro.* **2007**, 5(6), 453-463). A number of HCV treatments are reviewed by Bymock et al. in *Antiviral Chemistry & Chemotherapy*, 11:2; 79-95 (2000).

RNA-dependent RNA polymerase (RdRp) is one of the best studied targets for
10 the development of novel HCV therapeutic agents. The NS5B polymerase is a target for inhibitors in early human clinical trials (Sommadossi, J., WO 01/90121 A2, US 2004/0006002 A1). These enzymes have been extensively characterized at the biochemical and structural level, with screening assays for identifying selective inhibitors (De Clercq, E. (2001) *J. Pharmacol. Exp. Ther.* 297:1-10; De Clercq, E.
15 (2001) *J. Clin. Virol.* 22:73-89). Biochemical targets such as NS5B are important in developing HCV therapies since HCV does not replicate in the laboratory and there are difficulties in developing cell-based assays and preclinical animal systems.

Currently, there are primarily two antiviral compounds, ribavirin, a nucleoside analog, and interferon-alpha (α) (IFN), which are used for the treatment of chronic
20 HCV infections in humans. Ribavirin alone is not effective in reducing viral RNA levels, has significant toxicity, and is known to induce anemia. The combination of IFN and ribavirin has been reported to be effective in the management of chronic hepatitis C (Scott, L. J., et al. *Drugs* **2002**, 62, 507-556) but less than half the patients given this treatment show a persistent benefit. Other patent applications disclosing
25 the use of nucleoside analogs to treat hepatitis C virus include WO 01/32153, WO 01/60315, WO 02/057425, WO 02/057287, WO 02/032920 and WO 02/18404 but additional treatments for HCV infections have not yet become available for patients. Therefore, drugs having improved antiviral and pharmacokinetic properties with enhanced activity against development of HCV resistance, improved oral
30 bioavailability, greater efficacy, fewer undesirable side effects and extended effective half-life *in vivo* (De Francesco, R. et al. (2003) *Antiviral Research* 58:1-16) are urgently needed.

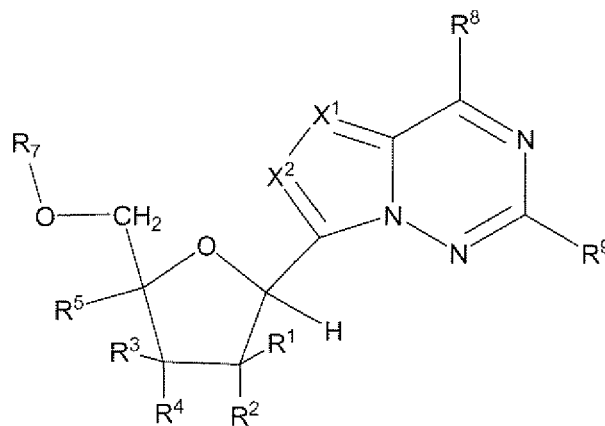
Certain ribosides of the nucleobases pyrrolo[1,2-f][1,2,4]triazine, imidazo[1,5-f][1,2,4]triazine, imidazo[1,2-f][1,2,4]triazine, and [1,2,4]triazolo[4,3-f][1,2,4]triazine
35 have been disclosed in *Carbohydrate Research* 2001, 331(1), 77-82; *Nucleosides & Nucleotides* (1996), 15(1-3), 793-807; *Tetrahedron Letters* (1994), 35(30), 5339-42; *Heterocycles* (1992), 34(3), 569-74; *J. Chem. Soc. Perkin Trans. 1* 1985, 3, 621-30;

5 *J. Chem. Soc. Perkin Trans. I* 1984, 2, 229-38; WO 2000056734; *Organic Letters* (2001), 3(6), 839-842; *J. Chem. Soc. Perkin Trans. I* 1999, 20, 2929-2936; and *J. Med. Chem.* 1986, 29(11), 2231-5. However, these compounds have not been disclosed as useful for the treatment of HCV. Babu, Y. S., WO2008/089105 and WO2008/41079, discloses ribosides of pyrrolo[1,2-f][1,2,4]triazine nucleobases with
 10 antiviral, anti-HCV, and anti-RdRp activity.

SUMMARY OF THE INVENTION

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

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



Formula I

or a pharmaceutically acceptable salt, thereof;

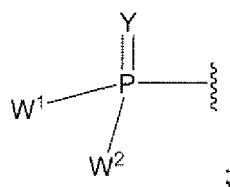
wherein:

25 at least one of R^1 , R^2 , R^3 , R^4 , or R^5 is $N(R^a)_2$, N_3 , CN , NO_2 , $S(O)_nR^a$, halogen, $(C_1-C_8)alkyl$, $(C_4-C_8)carbocyclalkyl$, $(C_1-C_8)substituted alkyl$, $(C_2-C_8)alkenyl$, $(C_2-C_8)substituted alkenyl$, $(C_2-C_8)alkynyl$, $(C_2-C_8)substituted alkynyl$ or $aryl(C_1-C_8)alkyl$ and each remaining R^1 , R^2 , R^3 , R^4 , or R^5 is, independently, H , OR^a , $N(R^a)_2$, N_3 , CN , NO_2 , $S(O)_nR^a$, halogen, $(C_1-C_8)alkyl$, $(C_4-C_8)carbocyclalkyl$,
 30 $(C_1-C_8)substituted alkyl$, $(C_2-C_8)alkenyl$, $(C_2-C_8)substituted alkenyl$, $(C_2-C_8)alkynyl$,

- 5 (C₂-C₈)substituted alkynyl or aryl(C₁-C₈)alkyl or any two R¹, R², R³, R⁴, or R⁵ on adjacent carbon atoms when taken together are -O(CO)O- or when taken together with the ring carbon atoms to which they are attached form a double bond;

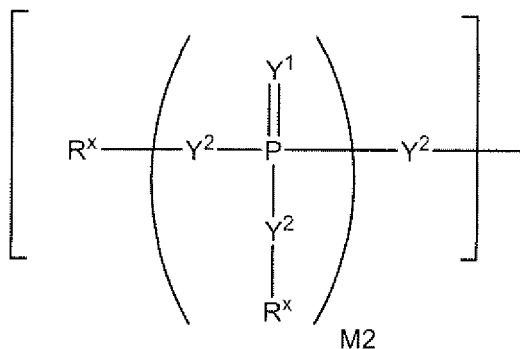
each n is independently 0, 1, or 2;

- each R^a is independently H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl,
 10 aryl(C₁-C₈)alkyl, (C₄-C₈)carbocyclalkyl, -C(=O)R¹¹, -C(=O)OR¹¹, -C(=O)NR¹¹R¹²,
 -C(=O)SR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -S(O)(OR¹¹), -S(O)₂(OR¹¹), -SO₂NR¹¹R¹²;
 R⁷ is H, -C(=O)R¹¹, -C(=O)OR¹¹, -C(=O)NR¹¹R¹², -C(=O)SR¹¹, -S(O)R¹¹, -
 S(O)₂R¹¹, -S(O)(OR¹¹), -S(O)₂(OR¹¹), -SO₂NR¹¹R¹², or



- 15 each Y or Y¹ is, independently, O, S, NR, ⁺N(O)(R), N(OR), ⁺N(O)(OR), or N-NR₂;

W¹ and W², when taken together, are -Y³(C(R^y)₂)₃Y³-; or one of W¹ or W² together with either R³ or R⁴ is -Y³- and the other of W¹ or W² is Formula Ia; or W¹ and W² are each, independently, a group of the Formula Ia:



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Formula Ia

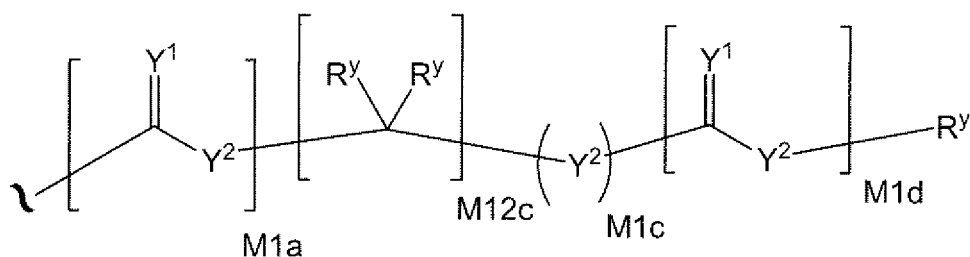
wherein:

each Y² is independently a bond, O, CR₂, NR, ⁺N(O)(R), N(OR), ⁺N(O)(OR), N-NR₂, S, S-S, S(O), or S(O)₂;

- 25 each Y³ is independently O, S, or NR;

M2 is 0, 1 or 2;

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



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wherein:

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

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

each R^y is independently H, F, Cl, Br, I, OH, R, $-\text{C}(=\text{Y}^1)\text{R}$, $-\text{C}(=\text{Y}^1)\text{OR}$, $-\text{C}(=\text{Y}^1)\text{N}(\text{R})_2$, $-\text{N}(\text{R})_2$, $-\text{N}^+(\text{R})_3$, $-\text{SR}$, $-\text{S}(\text{O})\text{R}$, $-\text{S}(\text{O})_2\text{R}$, $-\text{S}(\text{O})(\text{OR})$, $-\text{S}(\text{O})_2(\text{OR})$, $-\text{OC}(=\text{Y}^1)\text{R}$, $-\text{OC}(=\text{Y}^1)\text{OR}$, $-\text{OC}(=\text{Y}^1)\text{N}(\text{R})_2$, $-\text{SC}(=\text{Y}^1)\text{R}$, $-\text{SC}(=\text{Y}^1)\text{OR}$, $-\text{SC}(=\text{Y}^1)\text{N}(\text{R})_2$, $-\text{N}(\text{R})\text{C}(=\text{Y}^1)\text{R}$, $-\text{N}(\text{R})\text{C}(=\text{Y}^1)\text{OR}$, $-\text{N}(\text{R})\text{C}(=\text{Y}^1)\text{N}(\text{R})_2$, $-\text{SO}_2\text{NR}_2$, $-\text{CN}$, $-\text{N}_3$, $-\text{NO}_2$, $-\text{OR}$, or W^3 ; or when taken together, two R^y on the same carbon atom form a carbocyclic ring of 3 to 7 carbon atoms;

each R is independently H, $(\text{C}_1\text{--}\text{C}_8)$ alkyl, $(\text{C}_1\text{--}\text{C}_8)$ substituted alkyl, $(\text{C}_2\text{--}\text{C}_8)$ alkenyl, $(\text{C}_2\text{--}\text{C}_8)$ substituted alkenyl, $(\text{C}_2\text{--}\text{C}_8)$ alkynyl, $(\text{C}_2\text{--}\text{C}_8)$ substituted alkynyl, $\text{C}_6\text{--}\text{C}_{20}$ aryl, $\text{C}_6\text{--}\text{C}_{20}$ substituted aryl, $\text{C}_2\text{--}\text{C}_{20}$ heterocyclyl, $\text{C}_2\text{--}\text{C}_{20}$ substituted heterocyclyl, arylalkyl or substituted arylalkyl;

W^3 is W^4 or W^5 ; W^4 is R, $-\text{C}(\text{Y}^1)\text{R}^y$, $-\text{C}(\text{Y}^1)\text{W}^5$, $-\text{SO}_2\text{R}^y$, or $-\text{SO}_2\text{W}^5$; and W^5 is a carbocycle or a heterocycle wherein W^5 is independently substituted with 0 to 3 R^y groups;

each X^1 or X^2 is independently C--R^{10} or N wherein at least one of X^1 or X^2 is N;

each R^8 is, independently, halogen, $\text{NR}^{11}\text{R}^{12}$, $\text{N}(\text{R}^{11})\text{OR}^{11}$, $\text{NR}^{11}\text{NR}^{11}\text{R}^{12}$, N_3 , NO, NO_2 , CHO, CN, $-\text{CH}(=\text{NR}^{11})$, $-\text{CH}=\text{NHN}(\text{R}^{11})$, $-\text{CH}=\text{N}(\text{OR}^{11})$, $-\text{CH}(\text{OR}^{11})_2$, $-\text{C}(=\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{C}(=\text{S})\text{NR}^{11}\text{R}^{12}$, $-\text{C}(=\text{O})\text{OR}^{11}$, $(\text{C}_1\text{--}\text{C}_8)$ alkyl, $(\text{C}_2\text{--}\text{C}_8)$ alkenyl, $(\text{C}_2\text{--}\text{C}_8)$ alkynyl, $(\text{C}_4\text{--}\text{C}_8)$ carbocyclalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-\text{C}(=\text{O})(\text{C}_1\text{--}\text{C}_8)$ alkyl, $-\text{S}(\text{O})_n(\text{C}_1\text{--}\text{C}_8)$ alkyl or aryl $(\text{C}_1\text{--}\text{C}_8)$ alkyl, OR^{11} or SR^{11} ;

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

5 each R¹¹ or R¹² is independently H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₄-C₈)carbocyclalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(=O)(C₁-C₈)alkyl, -S(O)_n(C₁-C₈)alkyl or aryl(C₁-C₈)alkyl; or R¹¹ and R¹² 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
10 can optionally be replaced with -O-, -S- or -NR^a;

 wherein each (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl or aryl(C₁-C₈)alkyl of each R¹, R², R³, R⁴, R⁵, R¹¹ or R¹² 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 (C₁-C₈)alkyl may be optionally replaced with -O-,
15 -S- or -NR^a.

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

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

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

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

- a) a first pharmaceutical composition comprising a compound of Formula I; or a pharmaceutically acceptable salt, solvate, or ester thereof; and
- b) a second pharmaceutical composition comprising at least one additional therapeutic agent selected from the group consisting of interferons,
35 ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1

5 inhibitors, cyclophilin inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

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

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

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

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

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

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

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

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

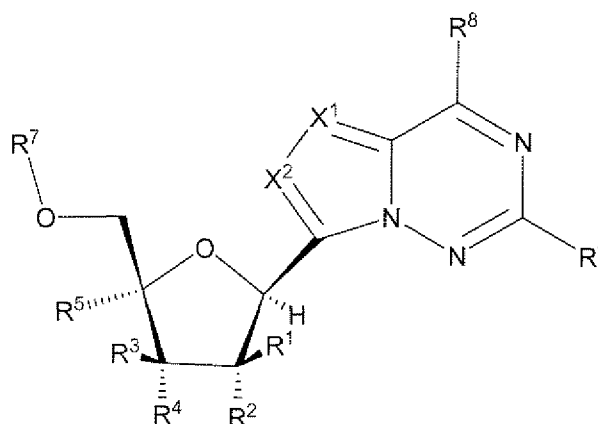
In other aspects, novel methods for synthesis, analysis, separation, isolation, purification, characterization, and testing of the compounds of this invention are provided.

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DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying description, structures and
 20 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.

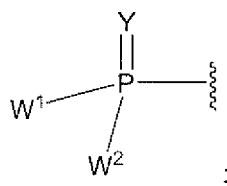
25 In another aspect, compounds of Formula I are represented by Formula II:



Formula II

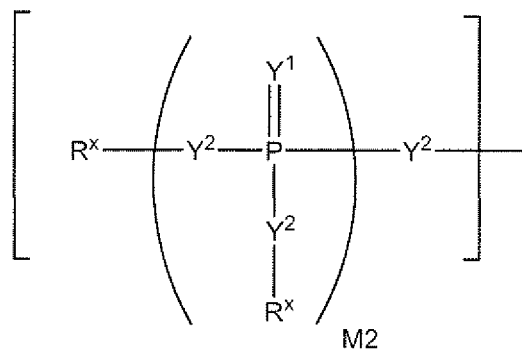
or a pharmaceutically acceptable salt, thereof;
 wherein:

- 5 at least one of R^1 , R^2 , R^3 , R^4 , or R^5 is $N(R^a)_2$, N_3 , CN , NO_2 , $S(O)_nR^a$, halogen, (C_1-C_8) alkyl, (C_4-C_8) carbocyclylalkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl or aryl(C_1-C_8)alkyl and each remaining R^1 , R^2 , R^3 , R^4 , or R^5 is, independently, H , OR^a , $N(R^a)_2$, N_3 , CN , NO_2 , $S(O)_nR^a$, halogen, (C_1-C_8) alkyl, (C_4-C_8) carbocyclylalkyl,
- 10 (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl or aryl(C_1-C_8)alkyl or any two R^1 , R^2 , R^3 , R^4 , or R^5 on adjacent carbon atoms when taken together are $-O(CO)O-$ or when taken together with the ring carbon atoms to which they are attached form a double bond;
- each n is 0, 1, or 2;
- 15 each R^a is independently H , (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, aryl(C_1-C_8)alkyl, (C_4-C_8) carbocyclylalkyl, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$;
- R^7 is H , $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, or



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

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



Formula Ia

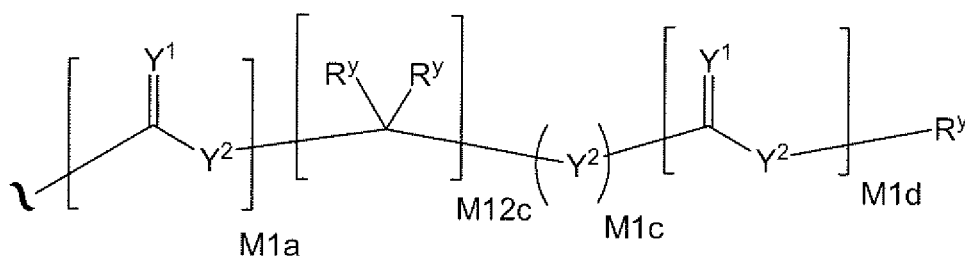
wherein:

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

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

M2 is 0, 1 or 2;

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



wherein:

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

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

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

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

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

each X^1 or X^2 is independently $C-R^{10}$ or N wherein at least one of X^1 or X^2 is N;

30 each R^8 is, independently, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3 , NO, NO_2 , CHO, CN, $-CH(=NR^{11})$, $-CH=NHNR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_4-C_8) carbocyclalkyl, optionally substituted aryl, optionally

5 substituted heteroaryl, $-C(=O)(C_1-C_8)alkyl$, $-S(O)_n(C_1-C_8)alkyl$ or $aryl(C_1-C_8)alkyl$, OR^{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, NO_2 , CHO, CN, $-CH(=NR^{11})$, $-CH=NHNR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, R^{11} , OR^{11} or SR^{11} ;

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

wherein each $(C_1-C_8)alkyl$, $(C_2-C_8)alkenyl$, $(C_2-C_8)alkynyl$ or $aryl(C_1-C_8)alkyl$ of each R^1 , R^2 , R^3 , R^4 , R^5 , R^{11} or R^{12} is, independently, optionally substituted with one or more halo, hydroxy, CN, N_3 , $N(R^a)_2$ or OR^a ; and wherein one or more of the non-terminal carbon atoms of each said $(C_1-C_8)alkyl$ may be optionally replaced with $-O-$,
20 $-S-$ or $-NR^a$.

In one embodiment of Formula II, R^1 is $(C_1-C_8)alkyl$, $(C_2-C_8)alkenyl$ or $(C_2-C_8)alkynyl$. In another embodiment R^1 is $(C_1-C_8)alkyl$. In another embodiment, R^1 is methyl, CH_2OH , CH_2F , ethenyl, or ethynyl. In a preferred embodiment, R^1 is methyl. In another preferred embodiment R^1 is H.

25 In one embodiment of Formula II, R^2 is H, OR^a , $N(R^a)_2$, N_3 , CN, NO_2 , $S(O)_nR^a$, halogen, $(C_1-C_8)alkyl$, $(C_1-C_8)substituted alkyl$, $(C_2-C_8)alkenyl$, $(C_2-C_8)substituted alkenyl$, $(C_2-C_8)alkynyl$, or $(C_2-C_8)substituted alkynyl$. In another aspect of this embodiment, R^2 is H, OR^a , $N(R^a)_2$, N_3 , CN, SR^a or halogen. In another aspect of this embodiment, R^2 is H, OH, NH_2 , N_3 , CN, or halogen. In another aspect
30 of this embodiment, R^2 is OR^a or halogen and R^1 is $(C_1-C_8)alkyl$, $(C_2-C_8)alkenyl$ or $(C_2-C_8)alkynyl$. In another aspect of this embodiment, R^2 is OR^a or F and R^1 is methyl, CH_2OH , CH_2F , ethenyl, or ethynyl. In a preferred aspect of this embodiment, R^2 is OH and R^1 is methyl, CH_2OH , CH_2F , ethenyl, or ethynyl. In another preferred aspect of this embodiment, R^2 is OH, R^1 is H and at least one of R^3 or R^5 is not H. In
35 another preferred aspect of this embodiment, R^2 is F and R^1 is methyl, CH_2OH , CH_2F , ethenyl, or ethynyl. In another preferred aspect of this embodiment, R^2 is OR^a and R^1

5 is methyl. In a particularly preferred aspect of this embodiment, R^2 is OH and R^1 is methyl.

In one embodiment of Formula II, R^3 is H, OR^a , $N(R^a)_2$, N_3 , CN, SR^a , halogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl or (C_2-C_8) alkynyl. In one aspect of this embodiment, R^3 is H or F. In a preferred aspect of this embodiment, R^3 is H. In another preferred aspect of this embodiment, R^3 is H, R^2 is OR^a or halogen and R^1 is (C_1-C_8) alkyl, (C_2-C_8) alkenyl or (C_2-C_8) alkynyl. In another aspect of this embodiment, R^3 is H, R^2 is OR^a or F and R^1 is methyl, CH_2OH , CH_2F , ethenyl, or ethynyl. In another aspect of this embodiment, R^3 is H, R^2 is OR^a and R^1 is methyl. In another aspect of this embodiment, R^3 is H, R^2 is OH and R^1 is methyl. In another aspect of this

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15 embodiment, R^3 and R^1 are H, R^2 is OH and R^5 is not H.

In one embodiment of Formula II, R^4 is H, OR^a , $N(R^a)_2$, N_3 , CN, SR^a , halogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl or (C_2-C_8) alkynyl. In a preferred aspect of this embodiment, R^4 is OR^a . In another preferred aspect of this embodiment, R^4 is OR^a , R^2 is OR^a or halogen and R^1 is (C_1-C_8) alkyl, (C_2-C_8) alkenyl or (C_2-C_8) alkynyl. In another preferred aspect of this embodiment, R^4 is OR^a , R^2 is OR^a or halogen, R^1 is H and R^5 is not H. In another preferred aspect of this embodiment, R^4 is OR^a , R^2 is OR^a or halogen, R^3 is H and R^1 is (C_1-C_8) alkyl, (C_2-C_8) alkenyl or (C_2-C_8) alkynyl. In another preferred aspect of this embodiment, R^4 is OR^a , R^2 is OR^a or F and R^1 is methyl, CH_2OH , CH_2F , ethenyl, or ethynyl. In another preferred aspect of this embodiment R^4 is OR^a , R^2 is OR^a or F, R^3 is H and R^1 is methyl, CH_2OH , CH_2F , ethenyl, or ethynyl. In another preferred aspect of this embodiment, R^4 and R^2 are, independently, OR^a and R^1 is methyl. In another preferred aspect of this embodiment, R^4 and R^2 are, independently OR^a , R^3 is H and R^1 is methyl. In another preferred aspect of this embodiment, one of R^4 or R^2 is OR^a and the other of R^4 or R^2 is OH. .

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30 In another preferred aspect of this embodiment, one of R^4 or R^2 is OR^a wherein R^a is not H and the other of R^4 or R^2 is OH, R^3 is H, and R^1 is methyl, CH_2OH , CH_2F , ethenyl, or ethynyl. In another preferred aspect of this embodiment, R^4 and R^2 are OH, R^3 is H, and R^1 is methyl, CH_2OH , CH_2F , ethenyl, or ethynyl. In another preferred aspect of this embodiment, R^4 and R^2 , taken together, are $-O(CO)O-$, R^3 is H and R^1 is methyl, CH_2OH , CH_2F , ethenyl, or ethynyl.

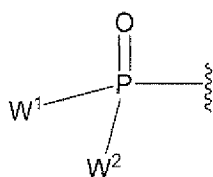
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5 In one embodiment of Formula II, R^5 is H, OR^a , $N(R^a)_2$, N_3 , CN, SR^a , halogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl or (C_2-C_8) alkynyl. In another aspect of this embodiment, R^5 is H, N_3 , CN, (C_1-C_8) alkyl, (C_2-C_8) alkenyl or (C_2-C_8) alkynyl. In another aspect of this embodiment, R^5 is H, N_3 , CN, methyl, CH_2OH , ethenyl or ethynyl, R^4 is OR^a , and R^3 is H. In another aspect of this embodiment, R^5 is H or N_3 , R^4 is OR^a , R^3 is H, and R^2 is F or OR^a . In another aspect of this embodiment, R^5 is H or N_3 , R^4 is OR^a , R^3 is H, R^2 is OR^a and R^1 is methyl, CH_2OH , CH_2F , ethenyl, or ethynyl. In another aspect of this embodiment, R^3 and R^5 are H, R^2 and R^4 are, independently, OR^a , and R^1 is methyl, CH_2OH , CH_2F , ethenyl, or ethynyl. In another aspect of this embodiment, R^3 and R^5 are H, R^2 and R^4 are OH, and R^1 is methyl, CH_2OH , CH_2F , ethenyl, or ethynyl. In another aspect of this embodiment R^1 and R^3 are H, R^2 and R^4 are independently OR^a and R^5 is N_3 . In another preferred aspect of this embodiment, R^4 and R^2 , taken together, are $-O(CO)O-$, R^3 is H and R^1 is methyl, CH_2OH , CH_2F , ethenyl, or ethynyl.

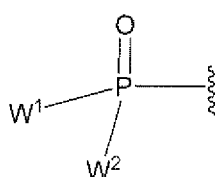
20 In one embodiment of Formula II, R^2 and R^4 are both OR^a and at least one of R^1 , R^3 or R^5 is not H. In another aspect of this embodiment, R^2 and R^4 are both OR^a and R^1 is (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8)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

30 In another embodiment of Formula II, both R^1 and R^2 are H; one of R^3 or R^4 is OR^a and the other of R^3 or R^4 is (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl or aryl(C_1-C_8)alkyl. In another aspect of this embodiment, one of R^3 or R^4 is OH. In another aspect of this embodiment, R^5 is OR^a , $N(R^a)_2$, N_3 , CN, NO_2 , $S(O)_nR^a$, halogen, (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl or aryl(C_1-C_8)alkyl.

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



- . In a preferred aspect of this embodiment, R^7 is H. In another preferred aspect of this embodiment, R^7 is $-C(=O)R^{11}$. In another preferred aspect of this embodiment, R^7 is $-C(=O)R^{11}$ wherein R^{11} is (C_1-C_8) alkyl. In another preferred aspect of this embodiment, R^7 is
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- In one embodiment of Formula II, X^1 is N or CR^{10} . In another aspect of this embodiment, X^1 is N. In another aspect of this embodiment, X^1 is CR^{10} . In another aspect of this embodiment, X^1 is CR^{10} and R^{10} is H, halogen, or CN. In another aspect of this embodiment, X^1 is CR^{10} and R^{10} is H or F. In another aspect of this embodiment, X^1 is CH. In another aspect of this embodiment, each X^1 and X^2 is N. In another aspect of this embodiment, X^1 is N and X^2 is CR^{10} . In another aspect of this embodiment, X^1 is N and X^2 is CR^{10} wherein R^{10} is H, halogen, or CN. In another aspect of this embodiment, X^1 is N and X^2 is CR^{10} wherein R^{10} is H or F. In another aspect of this embodiment, X^1 is N and X^2 is CH. In another aspect of this embodiment, X^1 is N; X^2 is CH; R^1 is methyl, CH_2OH , CH_2F , ethenyl, or ethynyl; R^3 is H; and each R^2 and R^4 is OR^a . In another aspect of this embodiment, X^1 is N; X^2 is CH; R^1 is methyl, CH_2OH , CH_2F , ethenyl, or ethynyl; each R^3 and R^5 is H; and each R^2 and R^4 is OR^a .
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- 25 In another embodiment of Formula II, X^2 is N or CR^{10} . In another aspect of this embodiment, X^2 is N and X^1 is CR^{10} . In another aspect of this embodiment, X^2 is N and X^1 is CR^{10} wherein R^{10} is H, halogen, or CN. In another aspect of this embodiment, X^2 is N and X^1 is CR^{10} wherein R^{10} is H or F. In another aspect of this embodiment, X^2 is N and X^1 is CH.

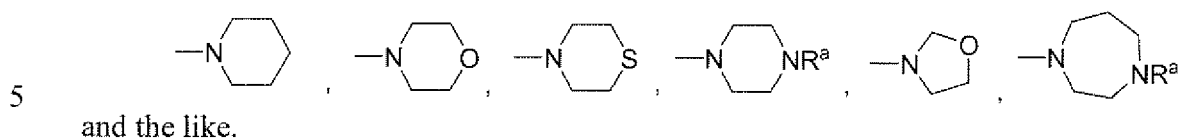
- 30 In another embodiment of Formula II, each R^8 is independently halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3 , NO, NO_2 , CHO, CN, $-CH(=NR^{11})$, $-CH=NHNR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$,

- 5 -C(=O)OR¹¹, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₄-C₈)carbocyclalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(=O)(C₁-C₈)alkyl, -S(O)_n(C₁-C₈)alkyl, aryl(C₁-C₈)alkyl, OR¹¹ or SR¹¹. In another aspect of this embodiment, each R⁸ is, independently, halogen, NR¹¹R¹², N(R¹¹)OR¹¹, NR¹¹NR¹¹R¹², OR¹¹ or SR¹¹. In another aspect of this embodiment, each R⁸ is, independently,
- 10 halogen, NR¹¹R¹², N(R¹¹)OR¹¹, NR¹¹NR¹¹R¹², OR¹¹ or SR¹¹ and R¹ is methyl, CH₂OH, CH₂F, ethenyl, or ethynyl. In another aspect of this embodiment, each R⁸ is, independently, halogen, NR¹¹R¹², N(R¹¹)OR¹¹, NR¹¹NR¹¹R¹², OR¹¹ or SR¹¹ and R⁹ is H, halogen, or NR¹¹R¹². In another aspect of this embodiment, each R⁸ is, independently, halogen, NR¹¹R¹², N(R¹¹)OR¹¹, NR¹¹NR¹¹R¹², OR¹¹ or SR¹¹ and R⁹ is
- 15 H, halogen, or NR¹¹R¹² and R¹ is methyl, CH₂OH, CH₂F, ethenyl, or ethynyl. In another preferred aspect of this embodiment, R⁸ is NH₂ and R⁹ is H or halogen. In another preferred aspect of this embodiment, R⁸ is NH₂ and R⁹ is H or halogen and R¹ is methyl, CH₂OH, CH₂F, ethenyl, or ethynyl. In another preferred aspect of this embodiment, R⁸ and R⁹ are each NH₂. In another preferred aspect of this
- 20 embodiment, R⁸ and R⁹ are each NH₂ and R¹ is methyl, CH₂OH, CH₂F, ethenyl, or ethynyl. In another preferred aspect of this embodiment, R⁸ is OH and R⁹ is NH₂. In another preferred aspect of this embodiment, R⁸ is OH and R⁹ is NH₂ and R¹ is methyl, CH₂OH, CH₂F, ethenyl, or ethynyl.

In another embodiment of Formula II, each R¹⁰ is, independently, H, halogen, NR¹¹R¹², N(R¹¹)OR¹¹, NR¹¹NR¹¹R¹², N₃, NO, NO₂, CHO, CN, -CH(=NR¹¹), -CH=NHNR¹¹, -CH=N(OR¹¹), -CH(OR¹¹)₂, -C(=O)NR¹¹R¹², -C(=S)NR¹¹R¹², -C(=O)OR¹¹, R¹¹, OR¹¹ or SR¹¹. In another aspect of this embodiment, each R¹⁰ is H, halogen, CN or optionally substituted heteroaryl.

In one embodiment of Formula II, R¹¹ or R¹² is independently H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₄-C₈)carbocyclalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(=O)(C₁-C₈)alkyl, -S(O)_n(C₁-C₈)alkyl or aryl(C₁-C₈)alkyl. In another embodiment, R¹¹ and R¹² taken together with a nitrogen to which they are both attached, form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with -O-, -S- or -NR^a-. Therefore, by way of example and not limitation, the moiety -NR¹¹R¹² can be represented by the heterocycles:

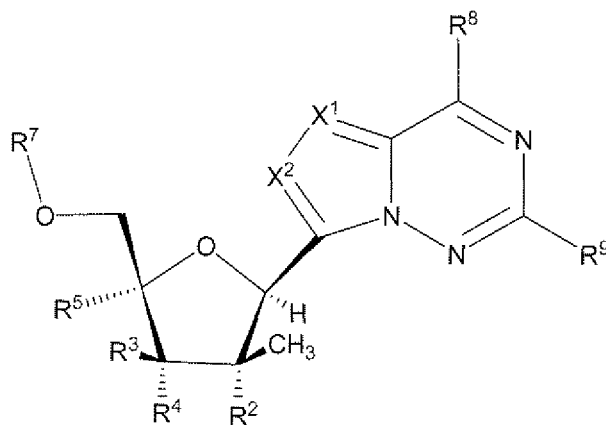
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In another embodiment of Formula II, R^1 , R^2 , R^3 , R^4 , R^5 , R^{11} or R^{12} is, independently, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl or aryl (C_1-C_8) alkyl, wherein said (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl or aryl (C_1-C_8) alkyl are, independently, optionally substituted with one or more halo, hydroxy, CN, N_3 , $N(R^a)_2$ or OR^a . Therefore, by way of example and not limitation, R^1 , R^2 , R^3 , R^4 , R^5 , R^{11} or R^{12} could represent moieties such as $-CH(NH_2)CH_3$, $-CH(OH)CH_2CH_3$, $-CH(NH_2)CH(CH_3)_2$, $-CH_2CF_3$, $-(CH_2)_2CH(N_3)CH_3$, $-(CH_2)_6NH_2$ and the like.

In another embodiment of Formula II, R^1 , R^2 , R^3 , R^4 , R^5 , R^{11} or R^{12} is (C_1-C_8) alkyl wherein one or more of the non-terminal carbon atoms of each said (C_1-C_8) alkyl may be optionally replaced with $-O-$, $-S-$ or $-NR^a-$. Therefore, by way of example and not limitation, R^1 , R^2 , R^3 , R^4 , R^5 , R^{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.

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



Formula III

or a pharmaceutically acceptable salt, thereof wherein all variables are defined as for Formula I.

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

5 of this embodiment, R^2 is OR^a or halogen. In a preferred aspect of this embodiment, R^2 is OH. In another preferred aspect of this embodiment, R^2 is OH and at least one of R^3 or R^5 is not H. In another preferred aspect of this embodiment, R^2 is F. In another preferred aspect of this embodiment, R^2 is OR^a . In another preferred aspect of this embodiment, R^2 is OH.

10 In one embodiment of Formula III, R^3 is H, OR^a , $N(R^a)_2$, N_3 , CN, SR^a , halogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl or (C_2-C_8) alkynyl. In one aspect of this embodiment, R^3 is H or F. In a preferred aspect of this embodiment, R^3 is H. In another preferred aspect of this embodiment, R^3 is H and R^2 is OR^a or halogen. In another aspect of this embodiment, R^3 is H and R^2 is OR^a or F. In another aspect of
15 this embodiment, R^3 is H and R^2 is OR^a . In another aspect of this embodiment, R^3 is H and R^2 is OH. In another aspect of this embodiment, R^3 is H, R^2 is OH and R^5 is not H.

In one embodiment of Formula III, R^4 is H, OR^a , $N(R^a)_2$, N_3 , CN, SR^a , halogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl or (C_2-C_8) alkynyl. In a preferred aspect of
20 this embodiment, R^4 is OR^a . In another preferred aspect of this embodiment, R^4 is OR^a and R^2 is OR^a or halogen. In another preferred aspect of this embodiment, R^4 is OR^a , R^2 is OR^a or halogen, and R^5 is not H. In another preferred aspect of this embodiment, R^4 is OR^a , R^2 is OR^a or halogen and R^3 is H. In another preferred aspect of this embodiment, R^4 is OR^a and R^2 is OR^a or F. In another preferred aspect of this
25 embodiment R^4 is OR^a , R^2 is OR^a or F, and R^3 is H. In another preferred aspect of this embodiment, R^4 and R^2 are, independently, OR^a . In another preferred aspect of this embodiment, R^4 and R^2 are, independently, OR^a and R^3 is H. In another preferred aspect of this embodiment, one of R^4 or R^2 is OR^a and the other of R^4 or R^2 is OH. In another preferred aspect of this embodiment, one of R^4 or R^2 is OR^a wherein R^a is not
30 H and the other of R^4 or R^2 is OH and R^3 is H. In another preferred aspect of this embodiment, R^4 and R^2 are OH and R^3 is H. In another preferred aspect of this embodiment, R^4 and R^2 , taken together, are $-O(CO)O-$ and R^3 is H.

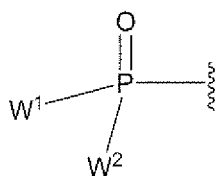
In one embodiment of Formula III, R^5 is H, OR^a , $N(R^a)_2$, N_3 , CN, SR^a , halogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl or (C_2-C_8) alkynyl. In another aspect of this
35 embodiment, R^5 is H, N_3 , CN, (C_1-C_8) alkyl, (C_2-C_8) alkenyl or (C_2-C_8) alkynyl. In another aspect of this embodiment, R^5 is H, N_3 , CN, methyl, CH_2OH , ethenyl or ethynyl, R^4 is OR^a , and R^3 is H. In another aspect of this embodiment, R^5 is H or N_3 ,

- 5 R^4 is OR^a , R^3 is H, and R^2 is F or OR^a . In another aspect of this embodiment, R^5 is H or N_3 , R^4 is OR^a , R^3 is H and R^2 is OR^a . In another aspect of this embodiment, R^3 and R^5 are H and R^2 and R^4 are, independently, OR^a . In another aspect of this embodiment, R^3 and R^5 are H and R^2 and R^4 are OH. In another aspect of this embodiment R^3 is H, R^2 and R^4 are independently OR^a and R^5 is N_3 . In another
10 preferred aspect of this embodiment, R^4 and R^2 , taken together, are $-O(CO)O-$ and R^3 is H.

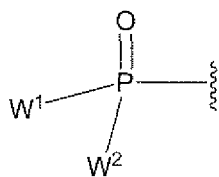
- In one embodiment of Formula III, R^2 and R^4 are both OR^a and at least one of R^3 or R^5 is not H. In another aspect of this embodiment, R^2 and R^4 are both OR^a . In another aspect of this embodiment, R^2 and R^4 are both OR^a and R^3 is (C_1-C_8) alkyl,
15 (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl or aryl (C_1-C_8) alkyl. In another aspect of this embodiment, R^2 and R^4 are both OR^a and R^5 is OR^a , $N(R^a)_2$, N_3 , CN, NO_2 , $S(O)_nR^a$, halogen, (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl or aryl $(C_1-$
20 $C_8)$ alkyl.

- In another embodiment of Formula III, R^2 is H; one of R^3 or R^4 is OR^a and the other of R^3 or R^4 is (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl or aryl (C_1-C_8) alkyl. In another aspect of this embodiment, one of R^3 or R^4 is OH. In another
25 aspect of this embodiment, R^5 is OR^a , $N(R^a)_2$, N_3 , CN, NO_2 , $S(O)_nR^a$, halogen, (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl or aryl (C_1-C_8) alkyl.

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



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



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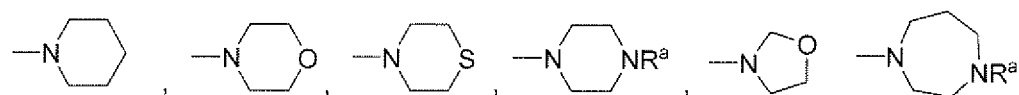
In one embodiment of Formula III, X^1 is N or CR^{10} . In another aspect of this embodiment, X^1 is N. In another aspect of this embodiment, X^1 is CR^{10} . In another aspect of this embodiment, X^1 is CR^{10} and R^{10} is H, halogen, or CN. In another aspect of this embodiment, X^1 is CR^{10} and R^{10} is H or F. In another aspect of this embodiment, X^1 is CH. In another aspect of this embodiment, each X^1 and X^2 is N. In another aspect of this embodiment, X^1 is N and X^2 is CR^{10} . In another aspect of this embodiment, X^1 is N and X^2 is CR^{10} wherein R^{10} is H, halogen, or CN. In another aspect of this embodiment, X^1 is N and X^2 is CR^{10} wherein R^{10} is H or F. In another aspect of this embodiment, X^1 is N and X^2 is CH. In another aspect of this embodiment, X^1 is N; X^2 is CH; R^3 is H; and each R^2 and R^4 is OR^a . In another aspect of this embodiment, X^1 is N; X^2 is CH; each R^3 and R^5 is H; and each R^2 and R^4 is OR^a .

In another embodiment of Formula III, X^2 is N or CR^{10} . In another aspect of this embodiment, X^2 is N and X^1 is CR^{10} . In another aspect of this embodiment, X^2 is N and X^1 is CR^{10} wherein R^{10} is H, halogen, or CN. In another aspect of this embodiment, X^2 is N and X^1 is CR^{10} wherein R^{10} is H or F. In another aspect of this embodiment, X^2 is N and X^1 is CH.

In another embodiment of Formula III, each R^8 is independently halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3 , NO, NO_2 , CHO, CN, $-CH(=NR^{11})$, $-CH=NHNR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_4-C_8) carbocyclylalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)(C_1-C_8)$ alkyl, $-S(O)_n(C_1-C_8)$ alkyl, aryl (C_1-C_8) alkyl, OR^{11} or SR^{11} . In another aspect of this embodiment, each R^8 is, independently, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, OR^{11} or SR^{11} . In another aspect of this embodiment, each R^8 is, independently, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, OR^{11} or SR^{11} and R^9 is H, halogen, or $NR^{11}R^{12}$. In another preferred aspect of this embodiment, R^8 is NH_2 and R^9 is H or halogen. In another preferred aspect of this embodiment, R^8 and R^9 are each NH_2 . In another preferred aspect of this embodiment, R^8 is OH and R^9 is NH_2 .

5 In another embodiment of Formula III, each R^{10} is, independently, H, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3 , NO, NO_2 , CHO, CN, $-CH(=NR^{11})$, $-CH=NHNR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, R^{11} , OR^{11} or SR^{11} . In another aspect of this embodiment, each R^{10} is H, halogen, CN or optionally substituted heteroaryl.

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

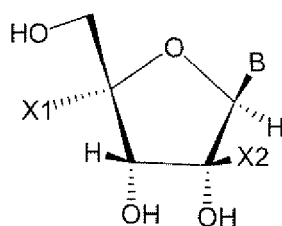


and the like.

20 In another embodiment of Formula III, R^1 , R^2 , R^3 , R^4 , R^5 , R^{11} or R^{12} is, independently, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl or aryl (C_1-C_8) alkyl, wherein said (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl or aryl (C_1-C_8) alkyl are, independently, optionally substituted with one or more halo, hydroxy, CN, N_3 , $N(R^a)_2$ or OR^a . Therefore, by way of example and not limitation, R^1 , R^2 , R^3 , R^4 , R^5 , R^{11} or
25 R^{12} could represent moieties such as $-CH(NH_2)CH_3$, $-CH(OH)CH_2CH_3$, $-CH(NH_2)CH(CH_3)_2$, $-CH_2CF_3$, $-(CH_2)_2CH(N_3)CH_3$, $-(CH_2)_6NH_2$ and the like.

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

In still another embodiment, the compounds of Formula I, Formula II, or Formula III are named below in tabular format (Table 6) as compounds of general
35 Formula IV:



Formula IV

wherein X1 and X2, represent substituents attached to the tetrahydrofuranyl ring as defined in Tables 1-2, below; B is a purine defined in Table 4, below; and X3 represents a ring element of the purine base B as described in Table 3, below.

The point of attachment of the core structure ribose is indicated in each of the structures of X1, X2, and B. The point of attachment of the core structure purine is indicated in each of the structures X3. Each structure in Tables 1-4 is represented by an alphanumeric "code". Each structure of a compound of Formula IV can thus be designated in tabular form by combining the "code" representing each structural moiety using the following syntax: X1.X2.X3.B. Thus, for example, X1a.X2c.X3a.B1 represents the following structure:

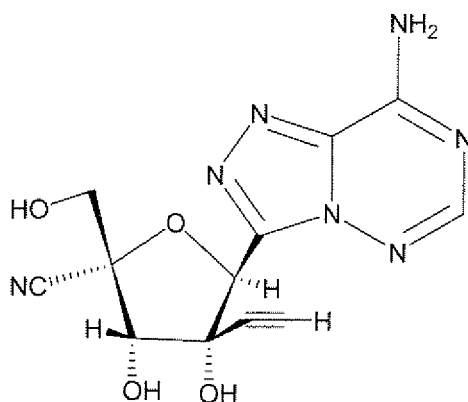


Table 1: X1 Structures

Code	Structure
X1a	CN
X1b	H
X1c	N ₃
X1d	CH ₂ OH

20

Table 2: X2 Structures

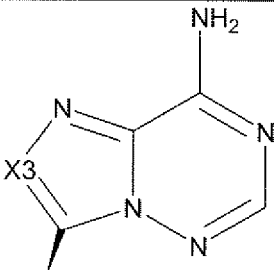
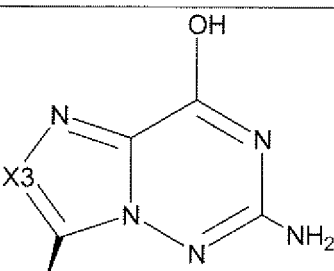
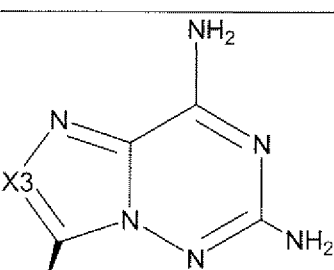
Code	Structure
X2a	H
X2b	CH ₃
X2c	

5

Table 3: X3 Structures

Code	Structure
X3a	-N=
X3b	-CH=
X3c	-CF=

10 Table 4: B Structures

Code	Structure
B1	
B2	
B3	

Code	Structure
B4	

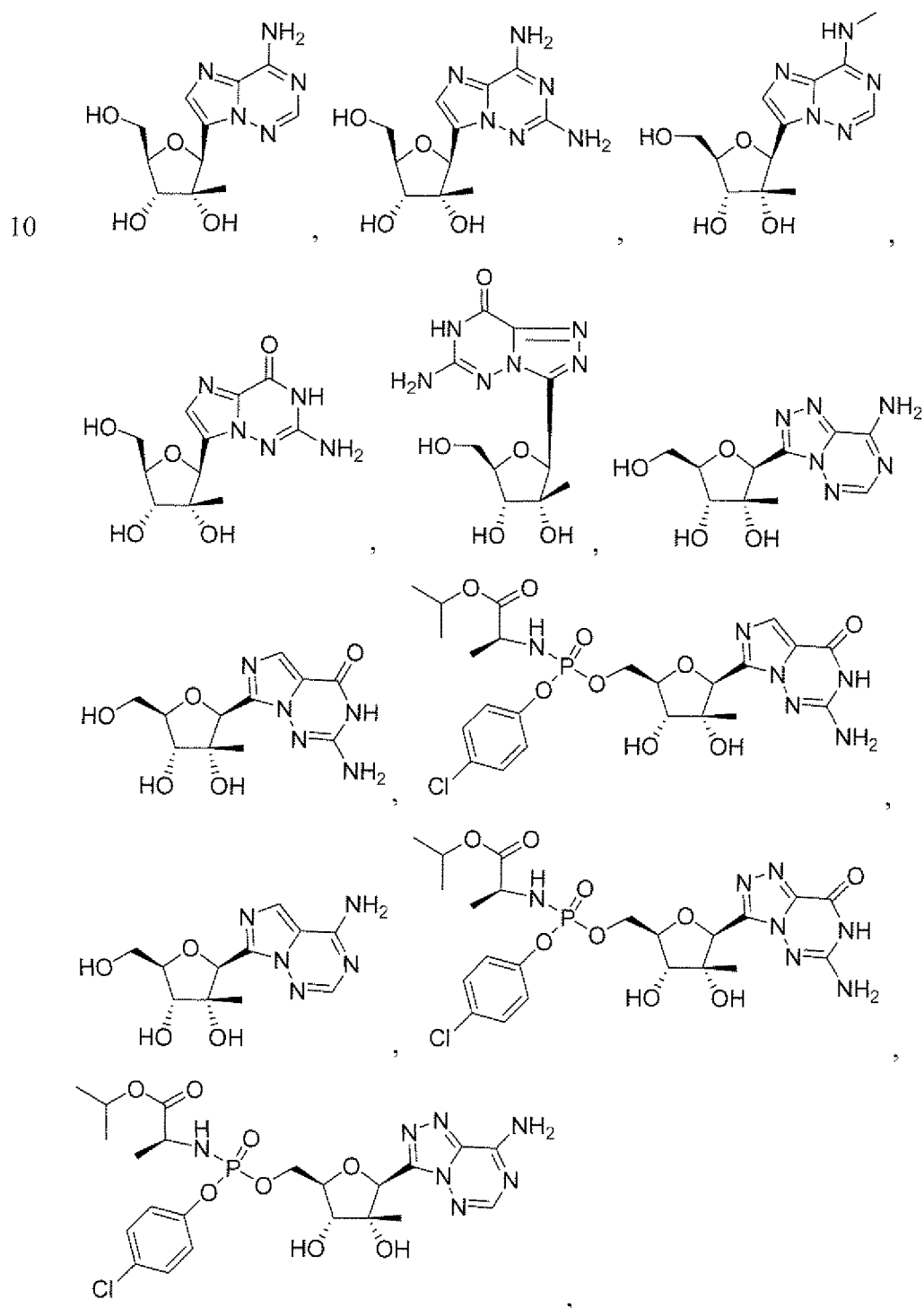
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Table 6: List of Compounds of Formula IV

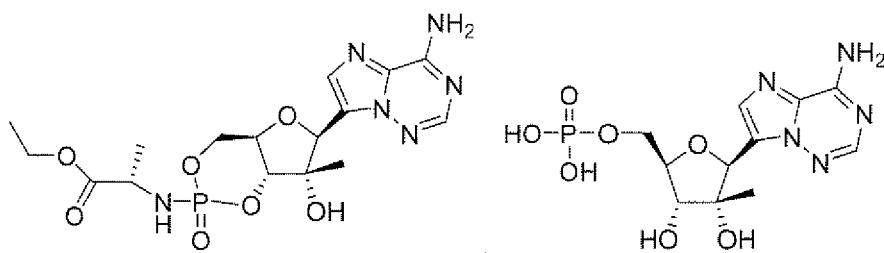
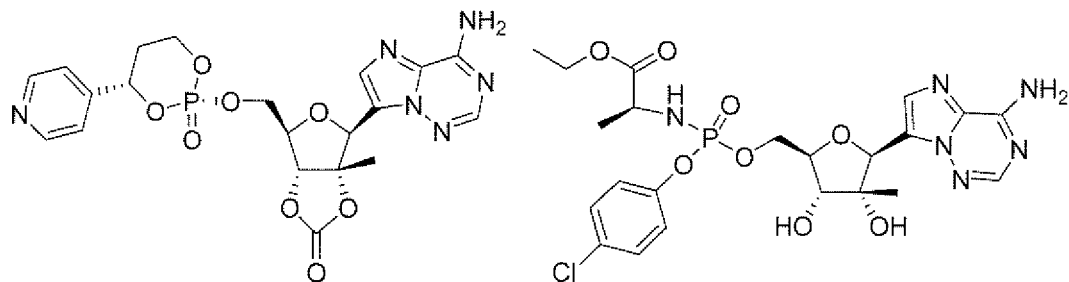
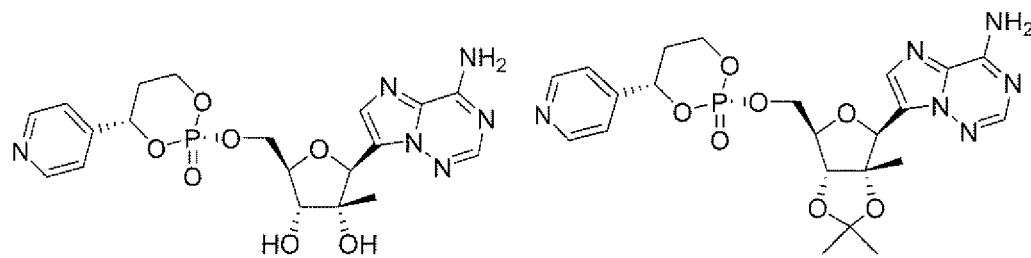
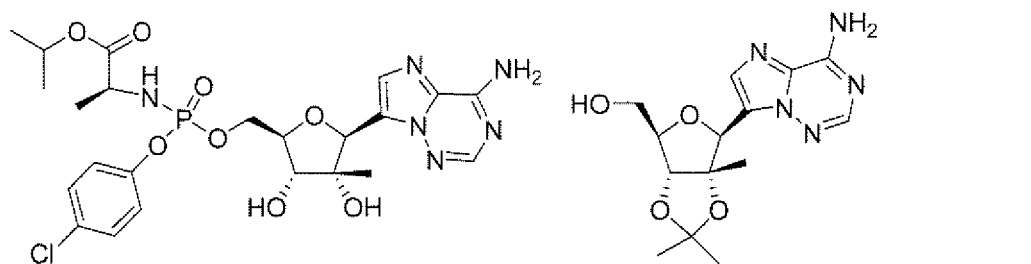
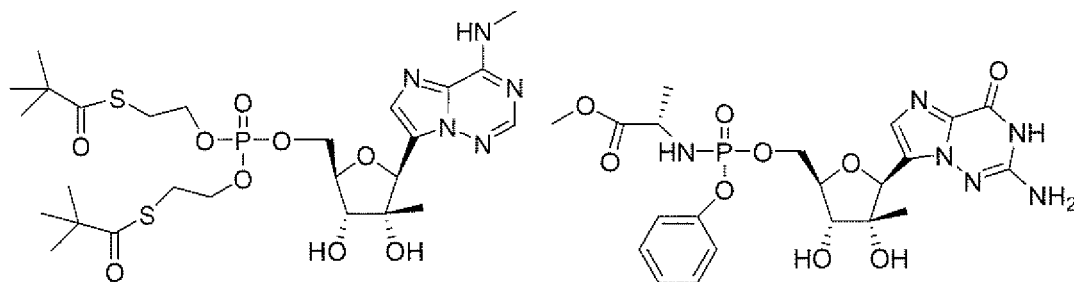
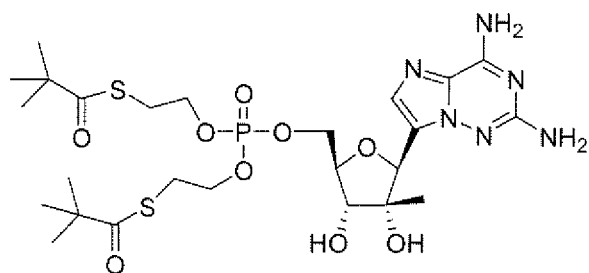
- X1a.X2b.X3a.B1, X1a.X2b.X3a.B2, X1a.X2b.X3a.B3, X1a.X2b.X3a.B4,
 X1a.X2b.X3b.B1, X1a.X2b.X3b.B2, X1a.X2b.X3b.B3, X1a.X2b.X3b.B4,
 10 X1a.X2b.X3c.B1, X1a.X2b.X3c.B2, X1a.X2b.X3c.B3, X1a.X2b.X3c.B4,
 X1a.X2c.X3a.B1, X1a.X2c.X3a.B2, X1a.X2c.X3a.B3, X1a.X2c.X3a.B4,
 X1a.X2c.X3b.B1, X1a.X2c.X3b.B2, X1a.X2c.X3b.B3, X1a.X2c.X3b.B4,
 X1a.X2c.X3c.B1, X1a.X2c.X3c.B2, X1a.X2c.X3c.B3, X1a.X2c.X3c.B4,
 X1b.X2b.X3a.B1, X1b.X2b.X3a.B2, X1b.X2b.X3a.B3, X1b.X2b.X3a.B4,
 15 X1b.X2b.X3b.B1, X1b.X2b.X3b.B2, X1b.X2b.X3b.B3, X1b.X2b.X3b.B4,
 X1b.X2b.X3c.B1, X1b.X2b.X3c.B2, X1b.X2b.X3c.B3, X1b.X2b.X3c.B4,
 X1b.X2c.X3a.B1, X1b.X2c.X3a.B2, X1b.X2c.X3a.B3, X1b.X2c.X3a.B4,
 X1b.X2c.X3b.B1, X1b.X2c.X3b.B2, X1b.X2c.X3b.B3, X1b.X2c.X3b.B4,
 X1b.X2c.X3c.B1, X1b.X2c.X3c.B2, X1b.X2c.X3c.B3, X1b.X2c.X3c.B4,
 20 X1c.X2a.X3a.B1, X1c.X2a.X3a.B2, X1c.X2a.X3a.B3, X1c.X2a.X3a.B4,
 X1c.X2a.X3b.B1, X1c.X2a.X3b.B2, X1c.X2a.X3b.B3, X1c.X2a.X3b.B4,
 X1c.X2a.X3c.B1, X1c.X2a.X3c.B2, X1c.X2a.X3c.B3, X1c.X2a.X3c.B4,
 X1c.X2b.X3a.B1, X1c.X2b.X3a.B2, X1c.X2b.X3a.B3, X1c.X2b.X3a.B4,
 X1c.X2b.X3b.B1, X1c.X2b.X3b.B2, X1c.X2b.X3b.B3, X1c.X2b.X3b.B4,
 25 X1c.X2b.X3c.B1, X1c.X2b.X3c.B2, X1c.X2b.X3c.B3, X1c.X2b.X3c.B4,
 X1c.X2c.X3a.B1, X1c.X2c.X3a.B2, X1c.X2c.X3a.B3, X1c.X2c.X3a.B4,
 X1c.X2c.X3b.B1, X1c.X2c.X3b.B2, X1c.X2c.X3b.B3, X1c.X2c.X3b.B4,
 X1c.X2c.X3c.B1, X1c.X2c.X3c.B2, X1c.X2c.X3c.B3, X1c.X2c.X3c.B4,
 X1d.X2a.X3a.B1, X1d.X2a.X3a.B2, X1d.X2a.X3a.B3, X1d.X2a.X3a.B4,

- 5 X1d.X2a.X3b.B1, X1d.X2a.X3b.B2, X1d.X2a.X3b.B3, X1d.X2a.X3b.B4,
X1d.X2a.X3c.B1, X1d.X2a.X3c.B2, X1d.X2a.X3c.B3, X1d.X2a.X3c.B4.

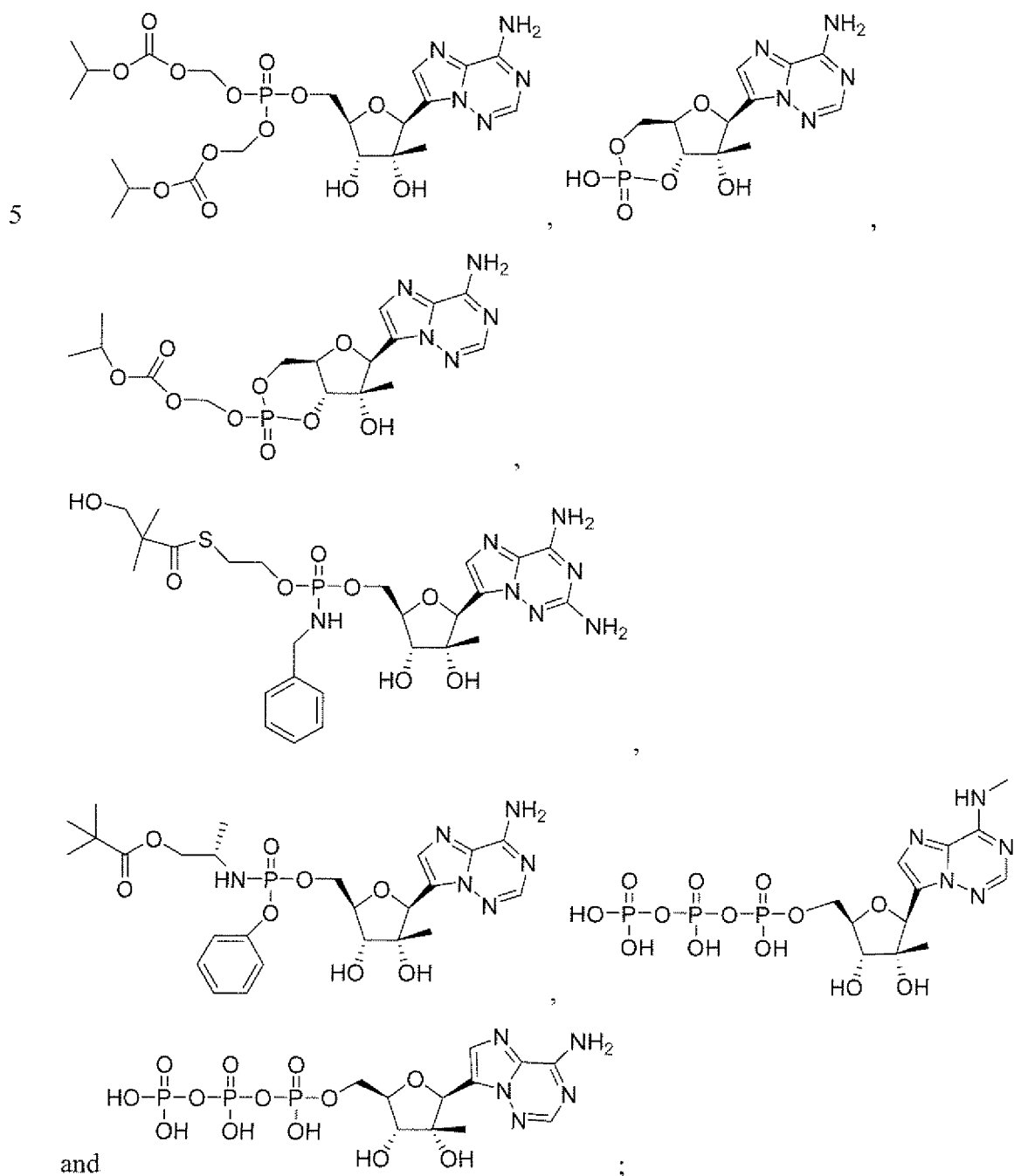
In another embodiment, Formula I-III is a compound selected from the group consisting of



5



10



10 or a pharmaceutically acceptable salt thereof.

DEFINITIONS

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

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

As used herein, "a compound of the invention" or "a compound of Formula I" means a compound of Formula I or a pharmaceutically acceptable salt, thereof.

10 Similarly, with respect to isolatable intermediates, the phrase "a compound of Formula (number)" means a compound of that formula and pharmaceutically acceptable salts, thereof.

"Alkyl" is hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms. For example, an alkyl group can have 1 to 20 carbon atoms (*i.e.*, C₁-C₂₀ alkyl),
 15 1 to 8 carbon atoms (*i.e.*, C₁-C₈ alkyl), or 1 to 6 carbon atoms (*i.e.*, C₁-C₆ alkyl). Examples of suitable alkyl groups include, but are not limited to, methyl (Me, -CH₃), ethyl (Et, -CH₂CH₃), 1-propyl (n-Pr, n-propyl, -CH₂CH₂CH₃), 2-propyl (*i*-Pr, *i*-propyl, -CH(CH₃)₂), 1-butyl (n-Bu, n-butyl, -CH₂CH₂CH₂CH₃), 2-methyl-1-propyl (*i*-Bu, *i*-butyl, -CH₂CH(CH₃)₂), 2-butyl (s-Bu, s-butyl, -CH(CH₃)CH₂CH₃), 2-methyl-2-propyl
 20 (*t*-Bu, *t*-butyl, -C(CH₃)₃), 1-pentyl (n-pentyl, -CH₂CH₂CH₂CH₂CH₃), 2-pentyl (-CH(CH₃)CH₂CH₂CH₃), 3-pentyl (-CH(CH₂CH₃)₂), 2-methyl-2-butyl (-C(CH₃)₂CH₂CH₃), 3-methyl-2-butyl (-CH(CH₃)CH(CH₃)₂), 3-methyl-1-butyl (-CH₂CH₂CH(CH₃)₂), 2-methyl-1-butyl (-CH₂CH(CH₃)CH₂CH₃), 1-hexyl (-CH₂CH₂CH₂CH₂CH₂CH₃), 2-hexyl (-CH(CH₃)CH₂CH₂CH₂CH₃), 3-hexyl (-
 25 CH(CH₂CH₃)(CH₂CH₂CH₃), 2-methyl-2-pentyl (-C(CH₃)₂CH₂CH₂CH₃), 3-methyl-2-pentyl (-CH(CH₃)CH(CH₃)CH₂CH₃), 4-methyl-2-pentyl (-CH(CH₃)CH₂CH(CH₃)₂), 3-methyl-3-pentyl (-C(CH₃)(CH₂CH₃)₂), 2-methyl-3-pentyl (-
 CH(CH₂CH₃)CH(CH₃)₂), 2,3-dimethyl-2-butyl (-C(CH₃)₂CH(CH₃)₂), 3,3-dimethyl-2-butyl (-CH(CH₃)C(CH₃)₃), and octyl (-CH₂)₇CH₃).

30 "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.*, C₁-C₂₀ alkoxy), 1 to 12 carbon atoms (*i.e.*, C₁-C₁₂ alkoxy), or 1 to 6 carbon atoms (*i.e.*, C₁-C₆ alkoxy). Examples of suitable alkoxy groups include, but are not limited to, methoxy (-O-CH₃
 35 or -OMe), ethoxy (-OCH₂CH₃ or -OEt), t-butoxy (-O-C(CH₃)₃ or -OtBu) and the like.

"Haloalkyl" is an alkyl group, as defined above, in which one or more

5 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.*, C₁-C₂₀ haloalkyl), 1 to 12 carbon atoms (*i.e.*, C₁-C₁₂ haloalkyl), or 1 to 6 carbon atoms (*i.e.*, C₁-C₆ alkyl). Examples of suitable haloalkyl groups include, but are not limited to, -CF₃, -CHF₂, -CFH₂, -CH₂CF₃, and the like.

10 "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.*, C₂-C₂₀ alkenyl), 2 to 8 carbon atoms (*i.e.*, C₂-C₈ alkenyl), or 2 to 6 carbon atoms (*i.e.*, C₂-C₆ alkenyl). Examples of suitable alkenyl groups include, but are not limited to, ethylene
15 or vinyl (-CH=CH₂), allyl (-CH₂CH=CH₂), cyclopentenyl (-C₅H₇), and 5-hexenyl (-CH₂CH₂CH₂CH₂CH=CH₂).

"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-C₂₀
20 alkynyl), 2 to 8 carbon atoms (*i.e.*, C₂-C₈ alkyne), or 2 to 6 carbon atoms (*i.e.*, C₂-C₆ alkynyl). Examples of suitable alkynyl groups include, but are not limited to, acetylenic (-C≡CH), propargyl (-CH₂C≡CH), and the like.

"Alkylene" refers to a saturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen
25 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 (-CH₂-), 1,1-ethyl (-CH(CH₃)-), 1,2-ethyl (-CH₂CH₂-), 1,1-propyl (-CH(CH₂CH₃)-), 1,2-propyl (-CH₂CH(CH₃)-), 1,3-propyl (-CH₂CH₂CH₂-), 1,4-butyl (-CH₂CH₂CH₂CH₂-), and the
30 like.

"Alkenylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkene. For example, and alkenylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms,
35 or 1 to 6 carbon atoms. Typical alkenylene radicals include, but are not limited to, 1,2-ethylene (-CH=CH-).

5 “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,
 10 acetylene ($-C\equiv C-$), propargyl ($-CH_2C\equiv C-$), and 4-pentynyl ($-CH_2CH_2CH_2C\equiv C-$).

“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 .
 15 Nonlimiting types of amino include $-NH_2$, $-N(alkyl)_2$, $-NH(alkyl)$, $-N(carbocyclyl)_2$, $-NH(carbocyclyl)$, $-N(heterocyclyl)_2$, $-NH(heterocyclyl)$, $-N(aryl)_2$, $-NH(aryl)$, $-N(alkyl)(aryl)$, $-N(alkyl)(heterocyclyl)$, $-N(carbocyclyl)(heterocyclyl)$, $-N(aryl)(heteroaryl)$, $-N(alkyl)(heteroaryl)$, etc. The term “alkylamino” refers to an amino group substituted with at least one alkyl group. Nonlimiting examples of amino
 20 groups include $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$, $-NH(CH_2CH_3)$, $-N(CH_2CH_3)_2$, $-NH(phenyl)$, $-N(phenyl)_2$, $-NH(benzyl)$, $-N(benzyl)_2$, etc. Substituted alkylamino refers generally to alkylamino groups, as defined above, in which at least one substituted alkyl, as defined herein, is attached to the amino nitrogen atom. Non-limiting examples of substituted alkylamino includes $-NH(alkylene-C(O)-OH)$, $-NH(alkylene-C(O)-O-alkyl)$,
 25 $-N(alkylene-C(O)-OH)_2$, $-N(alkylene-C(O)-O-alkyl)_2$, etc.

“Aryl” means an aromatic hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. For example, an aryl group can have 6 to 20 carbon atoms, 6 to 14 carbon atoms, or 6 to 12 carbon atoms. Typical aryl groups include, but are not limited to, radicals derived from
 30 benzene (e.g., phenyl), substituted benzene, naphthalene, anthracene, biphenyl, and the like.

“Arylalkyl” refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with an aryl radical. Typical arylalkyl groups include, but are not limited to, benzyl,
 35 2-phenylethan-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. The arylalkyl group can comprise 6 to 20

5 carbon atoms, *e.g.*, the alkyl moiety is 1 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms.

“Arylalkenyl” refers to an acyclic alkenyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also an sp^2 carbon atom, is replaced with an aryl radical. The aryl portion of the
 10 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 6 to 20 carbon atoms, *e.g.*, the alkenyl moiety is 1 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms.

“Arylalkynyl” refers to an acyclic alkynyl radical in which one of the
 15 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 6 to 20 carbon atoms, *e.g.*, the
 20 alkynyl moiety is 1 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms.

The term “substituted” in reference to alkyl, alkylene, aryl, arylalkyl, alkoxy, heterocyclyl, heteroaryl, carbocyclyl, etc., for example, “substituted alkyl”, “substituted alkylene”, “substituted aryl”, “substituted arylalkyl”, “substituted heterocyclyl”, and “substituted carbocyclyl” means alkyl, alkylene, aryl, arylalkyl, heterocyclyl, carbocyclyl respectively, in which one or more hydrogen atoms are each
 25 independently replaced with a non-hydrogen substituent. Typical substituents include, but are not limited to, $-X$, $-R^b$, $-O^-$, $=O$, $-OR^b$, $-SR^b$, $-S^-$, $-NR^b_2$, $-N^+R^b_3$, $=NR^b$, $-CX_3$, $-CN$, $-OCN$, $-SCN$, $-N=C=O$, $-NCS$, $-NO$, $-NO_2$, $=N_2$, $-N_3$, $-NHC(=O)R^b$, $-OC(=O)R^b$, $-NHC(=O)NR^b_2$, $-S(=O)_2-$, $-S(=O)_2OH$, $-S(=O)_2R^b$, $-OS(=O)_2OR^b$,
 30 $-S(=O)_2NR^b_2$, $-S(=O)R^b$, $-OP(=O)(OR^b)_2$, $-P(=O)(OR^b)_2$, $-P(=O)(O^-)_2$, $-P(=O)(OH)_2$, $-P(O)(OR^b)(O^-)$, $-C(=O)R^b$, $-C(=O)X$, $-C(S)R^b$, $-C(O)OR^b$, $-C(O)O^-$, $-C(S)OR^b$, $-C(O)SR^b$, $-C(S)SR^b$, $-C(O)NR^b_2$, $-C(S)NR^b_2$, $-C(=NR^b)NR^b_2$, where each X is independently a halogen: F, Cl, Br, or I; and each R^b is independently H, alkyl, aryl, arylalkyl, a heterocycle, or a protecting group or prodrug moiety. Alkylene,
 35 alkenylene, and alkynylene groups may also be similarly substituted. Unless otherwise indicated, when the term “substituted” is used in conjunction with groups such as

- 5 arylalkyl, which have two or more moieties capable of substitution, the substituents can be attached to the aryl moiety, the alkyl moiety, or both.

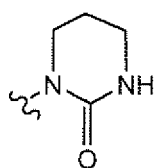
The term "prodrug" as used herein refers to any compound that when administered to a biological system generates the drug substance, i.e., active ingredient, as a result of spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s),
10 photolysis, and/or metabolic chemical reaction(s). A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

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

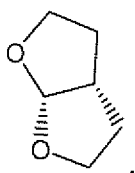
"Heteroalkyl" refers to an alkyl group where one or more carbon atoms have been replaced with a heteroatom, such as, O, N, or S. For example, if the carbon atom of
20 the alkyl group which is attached to the parent molecule is replaced with a heteroatom (e.g., O, N, or S) the resulting heteroalkyl groups are, respectively, an alkoxy group (e.g., -OCH₃, etc.), an amine (e.g., -NHCH₃, -N(CH₃)₂, etc.), or a thioalkyl group (e.g., -SCH₃). 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
25 groups are, respectively, an alkyl ether (e.g., -CH₂CH₂-O-CH₃, etc.), an alkyl amine (e.g., -CH₂NHCH₃, -CH₂N(CH₃)₂, etc.), or a thioalkyl ether (e.g., -CH₂-S-CH₃). 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., -CH₂CH₂-OH), an aminoalkyl group (e.g., -CH₂NH₂), or an alkyl thiol group (e.g.,
30 -CH₂CH₂-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 C₁-C₆ heteroalkyl group means a heteroalkyl group having 1 to 6 carbon atoms.

"Heterocycle" or "heterocyclyl" as used herein includes by way of example and not limitation those heterocycles described in Paquette, Leo A.; Principles of
35 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

- 5 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
 10 (*i.e.*, heteroaromatic rings). Substituted heterocyclyls include, for example, heterocyclic rings substituted with any of the substituents disclosed herein including carbonyl groups. A non-limiting example of a carbonyl substituted heterocyclyl is:



- Examples of heterocycles include by way of example and not limitation
 15 pyridyl, dihydropyridyl, 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,
 20 tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1H-indazolyl, purinyl, 4H-quinolizinyl,
 25 phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, β -carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazolynyl, pyrazolidinyl, pyrazolynyl, piperazinyl, indolynyl, isoindolynyl, quinuclidinyl, morpholynyl, oxazolidinyl, benzotriazolyl,
 30 benzisoxazolyl, oxindolyl, benzoxazolynyl, isatinoyl, and bis-tetrahydrofuranyl:



By way of example and not limitation, carbon bonded heterocycles are bonded

5 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
10 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-
15 thiazolyl, or 5-thiazolyl.

By way of example and not limitation, nitrogen bonded heterocycles are
bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-
pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole,
pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-
20 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-azetetyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and
1-piperidinyl.

“Heterocyclalkyl” refers to an acyclic alkyl radical in which one of the
25 hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is
replaced with a heterocycl radical (*i.e.*, a heterocycl-alkylene- moiety). Typical
heterocycl alkyl groups include, but are not limited to heterocycl- CH_2 -, 2-
(heterocycl)ethan-1-yl, and the like, wherein the “heterocycl” portion includes any
of the heterocycl groups described above, including those described in Principles of
30 Modern Heterocyclic Chemistry. One skilled in the art will also understand that the
heterocycl group can be attached to the alkyl portion of the heterocycl alkyl by
means of a carbon-carbon bond or a carbon-heteroatom bond, with the proviso that
the resulting group is chemically stable. The heterocycl alkyl group comprises 6 to
20 carbon atoms, *e.g.*, the alkyl portion of the arylalkyl group is 1 to 6 carbon atoms
35 and the heterocycl moiety is 5 to 14 carbon atoms. Examples of heterocyclalkyls
include by way of example and not limitation 5-membered sulfur, oxygen, and/or
nitrogen containing heterocycles such as thiazolylmethyl, 2-thiazolylethan-1-yl,

5 imidazolylmethyl, oxazolylmethyl, thiadiazolylmethyl, etc., 6-membered sulfur, oxygen, and/or nitrogen containing heterocycles such as piperidinylmethyl, piperazinylmethyl, morpholinylmethyl, pyridinylmethyl, pyridizylmethyl, pyrimidinylmethyl, pyrazinylmethyl, etc.

“Heterocyclylalkenyl” refers to an acyclic alkenyl radical in which one of the
10 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
15 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 6 to 20 carbon atoms, *e.g.*, the
20 alkenyl portion of the heterocyclyl alkenyl group is 1 to 6 carbon atoms and the heterocyclyl moiety is 5 to 14 carbon atoms.

“Heterocyclylalkynyl” refers to an acyclic alkynyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also an sp carbon atom, is replaced with a heterocyclyl radical (*i.e.*, a heterocyclyl-alkynylene- moiety). The heterocyclyl portion of the heterocyclyl alkynyl group
25 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
30 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 6 to 20 carbon atoms, *e.g.*, the alkynyl portion of the heterocyclyl alkynyl group is 1 to 6 carbon atoms and the heterocyclyl moiety is 5 to 14 carbon atoms.

35 “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

5 heteroaryl rings include all of those listed in the definition of “heterocyclyl”, including pyridinyl, pyrrolyl, oxazolyl, indolyl, isoindolyl, purinyl, furanyl, thienyl, benzofuranyl, benzothiophenyl, carbazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, quinolyl, isoquinolyl, pyridazyl, pyrimidyl, pyrazyl, etc.

“Carbocycle” or “carbocyclyl” refers to a saturated (i.e., cycloalkyl), partially
10 unsaturated (e.g., cycloalkenyl, 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 6 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
15 as a bicyclo [5,6] or [6,6] system, or spiro-fused rings. Non-limiting examples of monocyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, and phenyl. Non-limiting examples of bicyclo carbocycles includes naphthyl.

20 “Carbocyclalkyl” refers to an acyclic alkyl 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 carbocyclalkyl groups include cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl.

25 “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.
30 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.

35 “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 -CH₂-pyridinyl, -CH₂-pyrrolyl,

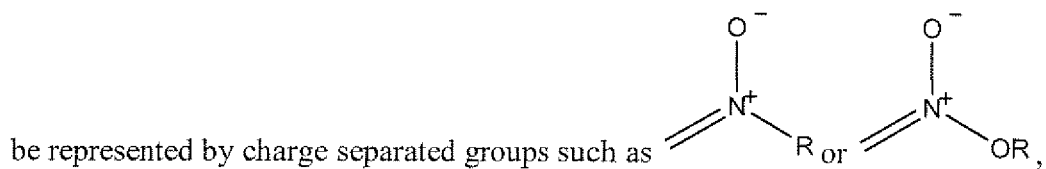
- 5 -CH₂-oxazolyl, -CH₂-indolyl, -CH₂-isoindolyl, -CH₂-purinyl, -CH₂-furanyl,
 -CH₂-thienyl, -CH₂-benzofuranyl, -CH₂-benzothiophenyl, -CH₂-carbazolyl,
 -CH₂-imidazolyl, -CH₂-thiazolyl, -CH₂-isoxazolyl, -CH₂-pyrazolyl, -CH₂-isothiazolyl,
 -CH₂-quinolyl, -CH₂-isoquinolyl, -CH₂-pyridazyl, -CH₂-pyrimidyl, -CH₂-pyrazyl,
 -CH(CH₃)-pyridinyl, -CH(CH₃)-pyrrolyl, -CH(CH₃)-oxazolyl, -CH(CH₃)-indolyl,
 10 -CH(CH₃)-isoindolyl, -CH(CH₃)-purinyl, -CH(CH₃)-furanyl, -CH(CH₃)-thienyl,
 -CH(CH₃)-benzofuranyl, -CH(CH₃)-benzothiophenyl, -CH(CH₃)-carbazolyl,
 -CH(CH₃)-imidazolyl, -CH(CH₃)-thiazolyl, -CH(CH₃)-isoxazolyl,
 -CH(CH₃)-pyrazolyl, -CH(CH₃)-isothiazolyl, -CH(CH₃)-quinolyl,
 -CH(CH₃)-isoquinolyl, -CH(CH₃)-pyridazyl, -CH(CH₃)-pyrimidyl,
 15 -CH(CH₃)-pyrazyl, etc.

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

The term “optionally replaced” in reference to a particular moiety of the compound of Formula I-III (e.g., the carbon atoms of said (C₁-C₈)alkyl may be optionally replaced by -O-, -S-, or -NR^a-) means that one or more of the methylene groups of the (C₁-C₈)alkyl may be replaced by 0, 1, 2, or more of the groups specified
 25 (e.g., -O-, -S-, or -NR^a-).

The term “non-terminal carbon atom(s)” in reference to an alkyl, alkenyl, alkynyl, alkylene, alkenylene, or alkynylene moiety refers to the carbon atoms in the moiety that intervene between the first carbon atom of the moiety and the last carbon atom in the moiety. Therefore, by way of example and not limitation, in the alkyl
 30 moiety -CH₂(C^{*})H₂(C^{*})H₂CH₃ or alkylene moiety -CH₂(C^{*})H₂(C^{*})H₂CH₂- the C^{*} atoms would be considered to be the non-terminal carbon atoms.

Certain Y and Y¹ alternatives are nitrogen oxides such as ⁺N(O)(R) or ⁺N(O)(OR). These nitrogen oxides, as shown here attached to a carbon atom, can also

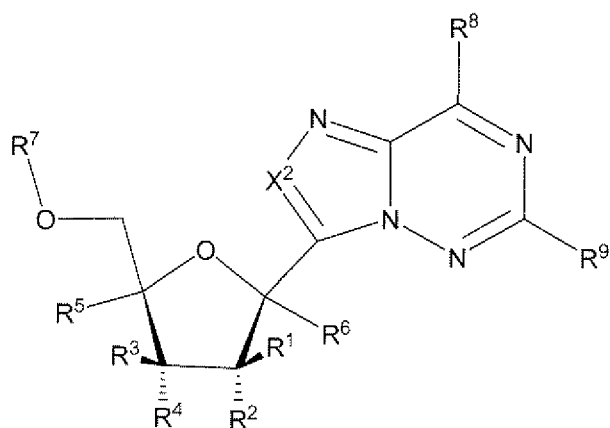


5 respectively, and are intended to be equivalent to the afore mentioned representations for the purposes of describing this invention.

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

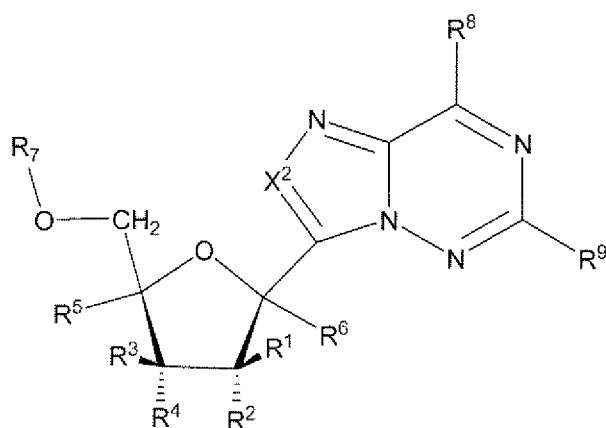
 The terms such as "oxygen-linked", "nitrogen-linked", "carbon-linked", "sulfur-linked", or "phosphorous-linked" mean that if a bond between two moieties can be formed by using more than one type of atom in a moiety, then the bond formed
15 between the moieties is through the atom specified. For example,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

 Unless otherwise specified, the carbon atoms of this invention are intended to have a valence of four. In some chemical structure representations where carbon
20 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,



5

has the same meaning as



“Protecting group” refers to a moiety of a compound that masks or alters the properties of a functional group or the properties of the compound as a whole. The chemical substructure of a protecting group varies widely. One function of a protecting group is to serve as an intermediate in the synthesis of the parental drug substance. Chemical protecting groups and strategies for protection/deprotection are well known in the art. See: "Protective Groups in Organic Chemistry", Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991). Protecting groups are often utilized to mask the reactivity of certain functional groups, to assist in the efficiency of desired chemical reactions, e.g. making and breaking chemical bonds in an ordered and planned fashion. Protection of functional groups of a compound alters other physical properties besides the reactivity of the protected functional group, such as the polarity, lipophilicity (hydrophobicity), and other properties which can be measured by common analytical tools. Chemically protected intermediates may themselves be biologically active or inactive.

20

Protected compounds may also exhibit altered, and in some cases, optimized properties *in vitro* and *in vivo*, such as passage through cellular membranes and

5 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
10 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
15 innocuous.

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

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

Exemplary prodrug moieties include the hydrolytically sensitive or labile acyloxymethyl esters $-\text{CH}_2\text{OC}(=\text{O})\text{R}^{30}$ and acyloxymethyl carbonates $-\text{CH}_2\text{OC}(=\text{O})\text{OR}^{30}$ where R^{30} is C_1 – C_6 alkyl, C_1 – C_6 substituted alkyl, C_6 – C_{20} aryl or
30 C_6 – C_{20} substituted aryl. The acyloxyalkyl ester was used as a prodrug strategy for carboxylic acids and then applied to phosphates and phosphonates by Farquhar et al (1983) *J. Pharm. Sci.* 72: 324; also US Patent Nos. 4816570, 4968788, 5663159 and 5792756. In certain compounds of the invention, a prodrug moiety is part of a phosphate group. The acyloxyalkyl ester may be used to deliver phosphoric acids
35 across cell membranes and to enhance oral bioavailability. A close variant of the acyloxyalkyl ester, the alkoxycarbonyloxyalkyl ester (carbonate), may also enhance oral bioavailability as a prodrug moiety in the compounds of the combinations of the

5 invention. An exemplary acyloxymethyl ester is pivaloyloxymethoxy, (POM) $-\text{CH}_2\text{OC}(=\text{O})\text{C}(\text{CH}_3)_3$. An exemplary acyloxymethyl carbonate prodrug moiety is pivaloyloxymethylcarbonate (POC) $-\text{CH}_2\text{OC}(=\text{O})\text{OC}(\text{CH}_3)_3$.

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

Aryl esters of phosphorus groups, especially phenyl esters, are reported to enhance oral bioavailability (DeLambert et al (1994) *J. Med. Chem.* 37: 498). Phenyl
15 esters containing a carboxylic ester ortho to the phosphate have also been described (Khamnei and Torrence, (1996) *J. Med. Chem.* 39:4109-4115). Benzyl esters are reported to generate the parent phosphonic acid. In some cases, substituents at the *ortho*-or *para*-position may accelerate the hydrolysis. Benzyl analogs with an acylated phenol or an alkylated phenol may generate the phenolic compound through
20 the action of enzymes, e.g. esterases, oxidases, etc., which in turn undergoes cleavage at the benzylic C–O bond to generate the phosphoric acid and the quinone methide intermediate. Examples of this class of prodrugs are described by Mitchell et al (1992) *J. Chem. Soc. Perkin Trans. I* 2345; Brook et al WO 91/19721. Still other benzylic prodrugs have been described containing a carboxylic ester-containing group
25 attached to the benzylic methylene (Glazier et al WO 91/19721). Thio-containing prodrugs are reported to be useful for the intracellular delivery of phosphonate drugs. These proesters contain an ethylthio group in which the thiol group is either esterified with an acyl group or combined with another thiol group to form a disulfide. Deesterification or reduction of the disulfide generates the free thio intermediate
30 which subsequently breaks down to the phosphoric acid and episulfide (Puech et al (1993) *Antiviral Res.*, 22: 155-174; Benzaria et al (1996) *J. Med. Chem.* 39: 4958). Cyclic phosphonate esters have also been described as prodrugs of phosphorus-containing compounds (Erion et al, US Patent No. 6312662).

35 It is to be noted that all enantiomers, diastereomers, and racemic mixtures, tautomers, polymorphs, pseudopolymorphs of compounds within the scope of Formula I, Formula II, or Formula III and pharmaceutically acceptable salts thereof

5 are embraced by the present invention. All mixtures of such enantiomers and diastereomers are within the scope of the present invention.

A compound of Formula I-III and its pharmaceutically acceptable salts may exist as different polymorphs or pseudopolymorphs. As used herein, crystalline polymorphism means the ability of a crystalline compound to exist in different crystal
10 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
15 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.

20 A compound of Formula I-III and its pharmaceutically acceptable salts may also exist as an amorphous solid. As used herein, an amorphous solid is a solid in which there is no long-range order of the positions of the atoms in the solid. This definition applies as well when the crystal size is two nanometers or less. Additives, including solvents, may be used to create the amorphous forms of the instant
25 invention. The instant invention comprises all amorphous forms of the compounds of Formula I-III and their pharmaceutically acceptable salts.

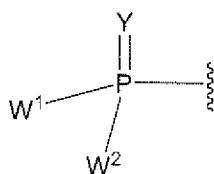
Selected substituents comprising the compounds of Formula I-III are present to a recursive degree. In this context, "recursive substituent" means that a substituent may recite another instance of itself. Because of the recursive nature of such
30 substituents, theoretically, a large number of compounds may be present in any given embodiment. For example, R^x comprises a R^y substituent. R^y can be R . R can be W^3 . W^3 can be W^4 and W^4 can be R or comprise substituents comprising R^y . One of ordinary skill in the art of medicinal chemistry understands that the total number of such substituents is reasonably limited by the desired properties of the compound
35 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.

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

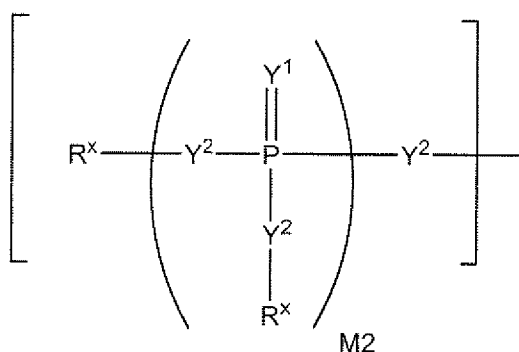
Recursive substituents are an intended aspect of the invention. One of
 15 ordinary skill in the art of medicinal chemistry understands the versatility of such substituents. To the degree that recursive substituents are present in an embodiment of the invention, the total number will be determined as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

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

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



which may be a prodrug moiety wherein each Y or Y^1 is,
 independently, O, S, NR, $^+N(O)(R)$, N(OR), $^+N(O)(OR)$, or N-NR₂; W^1 and W^2 ,
 when taken together, are $-Y^3(C(R^y)_2)Y^3-$; or one of W^1 or W^2 together with either
 25 R^3 or R^4 is $-Y^3-$ and the other of W^1 or W^2 is Formula Ia; or W^1 and W^2 are each,
 independently, a group of Formula Ia:



wherein:

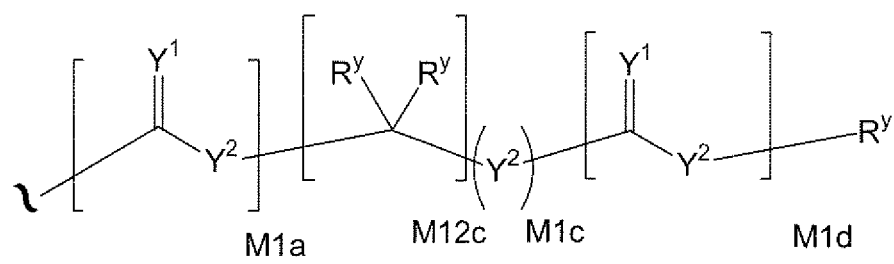
5 each Y^2 is independently a bond, O, CR_2 , NR, $^+N(O)(R)$, $N(OR)$, $^+N(O)(OR)$, $N-NR_2$, S, S-S, S(O), or S(O)₂;

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

M2 is 0, 1 or 2;

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

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



wherein:

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

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

20 each R is H, halogen, (C₁-C₈) alkyl, (C₁-C₈) substituted alkyl, (C₂-C₈) alkenyl, (C₂-C₈) substituted alkenyl, (C₂-C₈) alkynyl, (C₂-C₈) substituted alkynyl, C₆-C₂₀ aryl, C₆-C₂₀ substituted aryl, C₂-C₂₀ heterocycle, C₂-C₂₀ substituted heterocyclyl, arylalkyl, substituted arylalkyl or a protecting group;

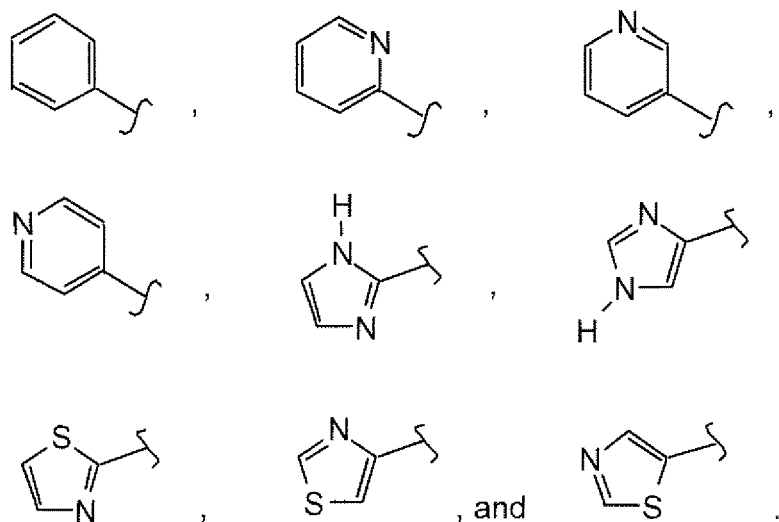
W^3 is W^4 or W^5 ; W^4 is R, $-C(Y^1)R^y$, $-C(Y^1)W^5$, $-SO_2R^y$, or $-SO_2W^5$; and W^5 is a carbocycle or a heterocycle wherein W^5 is independently substituted with 0 to 3 R^y groups.

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

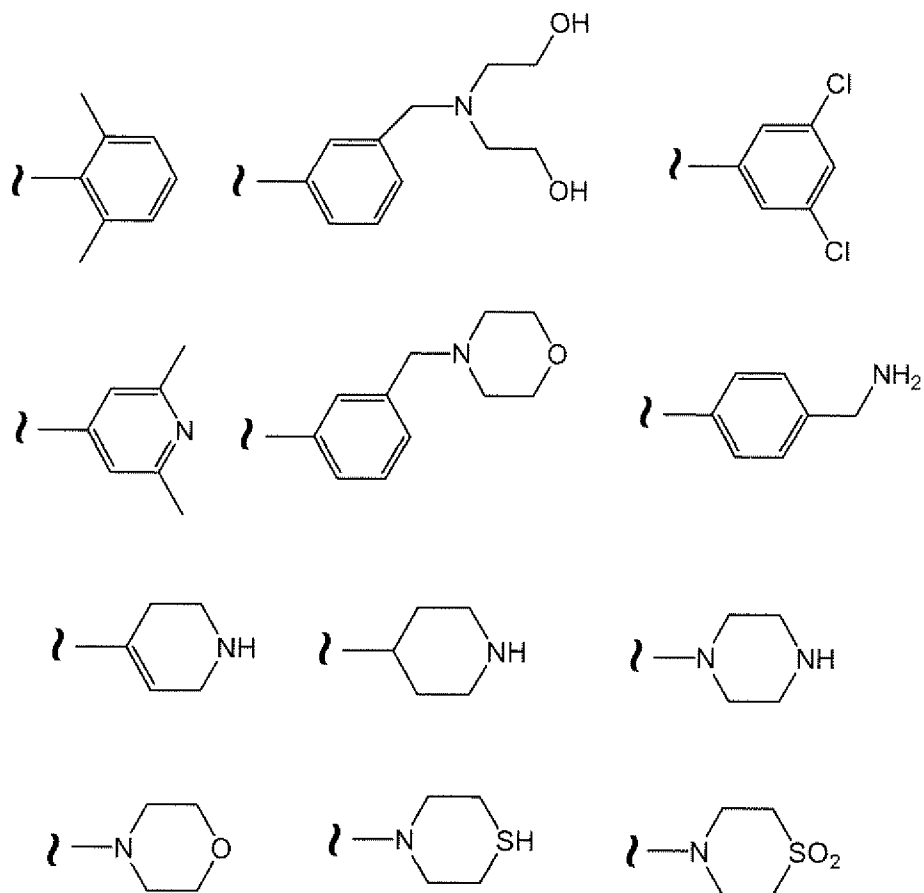
5 aromatic when containing 6 ring atoms.

A W^5 heterocycle may be a monocycle having 3 to 7 ring members (2 to 6 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S) or a bicycle having 7 to 10 ring members (4 to 9 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S). W^5 heterocyclic monocycles may have 3 to 6 ring atoms (2 to 5 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S); or 5 or 6 ring atoms (3 to 5 carbon atoms and 1 to 2 heteroatoms selected from N and S). W^5 heterocyclic bicycles have 7 to 10 ring atoms (6 to 9 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S) arranged as a bicyclo [4,5], [5,5], [5,6], or [6,6] system; or 9 to 10 ring atoms (8 to 9 carbon atoms and 1 to 2 heteroatoms selected from N and S) arranged as a bicyclo [5,6] or [6,6] system. The W^5 heterocycle may be bonded to Y^2 through a carbon, nitrogen, sulfur or other atom by a stable covalent bond.

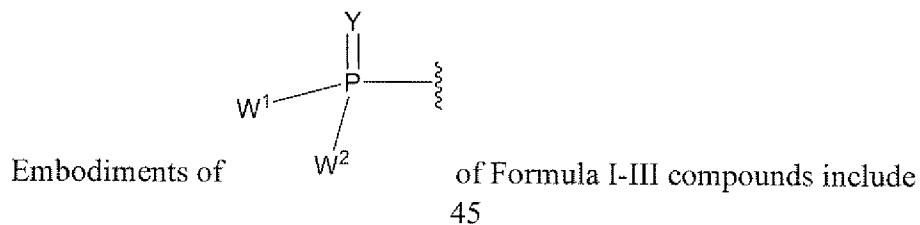
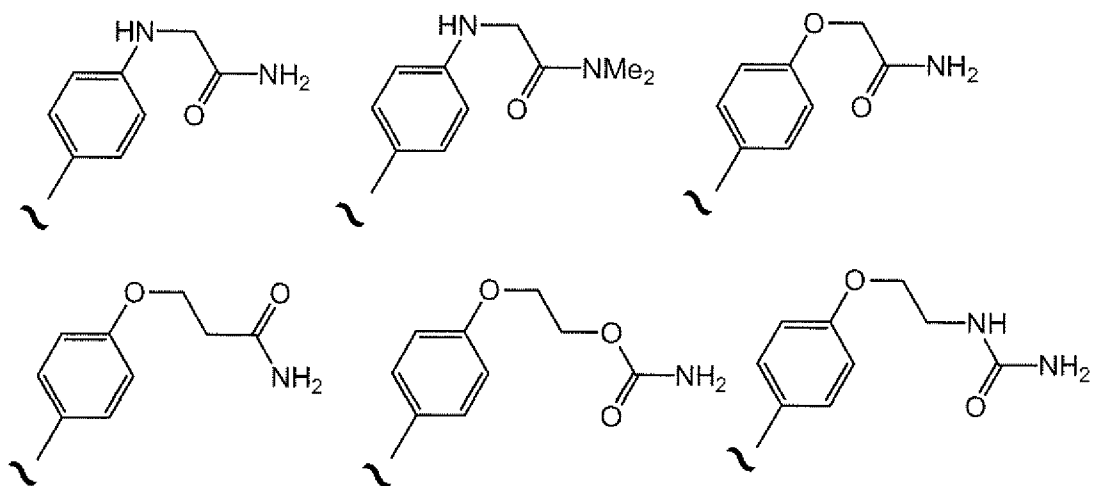
W^5 heterocycles include for example, pyridyl, dihydropyridyl isomers, piperidine, pyridazinyl, pyrimidinyl, pyrazinyl, s-triazinyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, furanyl, thiofuranyl, thienyl, and pyrrolyl. W^5 also includes, but is not limited to, examples such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



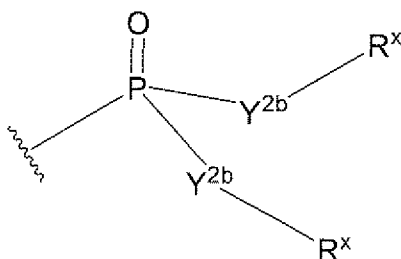
W^5 carbocycles and heterocycles may be independently substituted with 0 to 3 R groups, as defined above. For example, substituted W^5 carbocycles include:



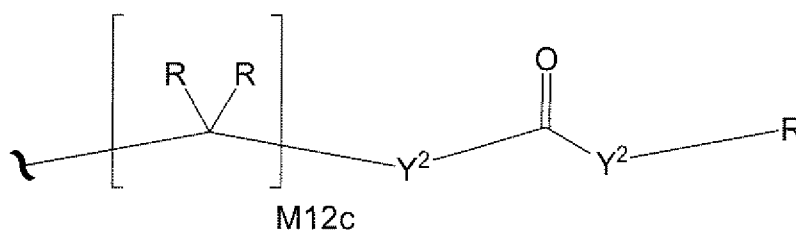
Examples of substituted phenyl carbocycles include:



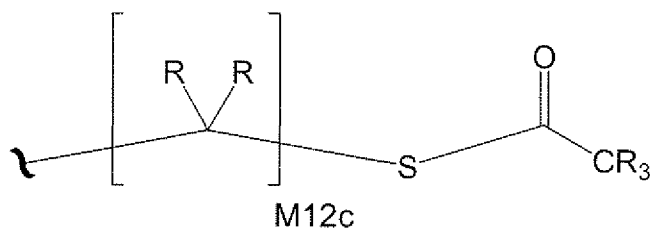
5 substructures such as:



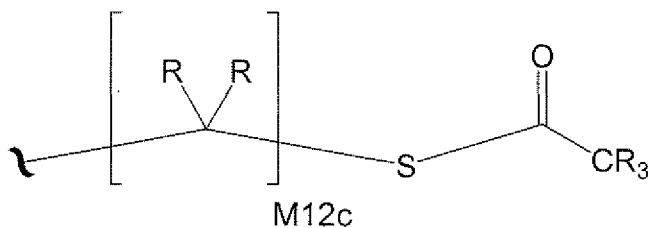
wherein each Y^{2b} is, independently, O or N(R). In a preferred aspect of this embodiment, each Y^{2b} is O and each R^x is independently:



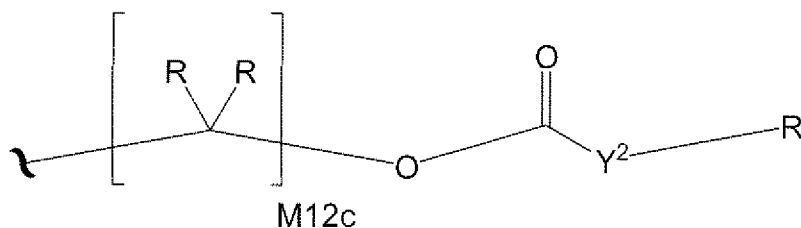
10 wherein M12c is 1, 2 or 3 and each Y^2 is independently a bond, O, CR_2 , or S. In another preferred aspect of this embodiment, one $Y^{2b}-R^x$ is NH(R) and the other $Y^{2b}-R^x$ is O- R^x wherein R^x is:



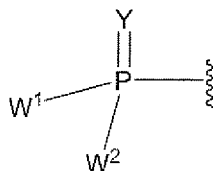
wherein M12c is 2. In another preferred aspect of this embodiment, each Y^{2b} is O and each R^x is independently:



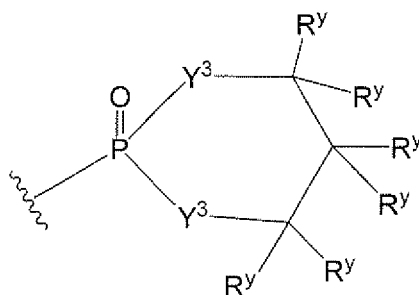
wherein M12c is 2. In another preferred aspect of this embodiment, each Y^{2b} is O and each R^x is independently:



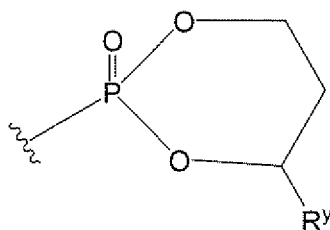
- 5 wherein M12c is 1 and Y^2 is a bond, O, or CR_2 .



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

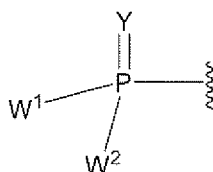


- 10 wherein each Y^3 is, independently, O or N(R). In a preferred aspect of this embodiment, each Y^3 is O. In another preferred aspect of this embodiment, the substructure is:



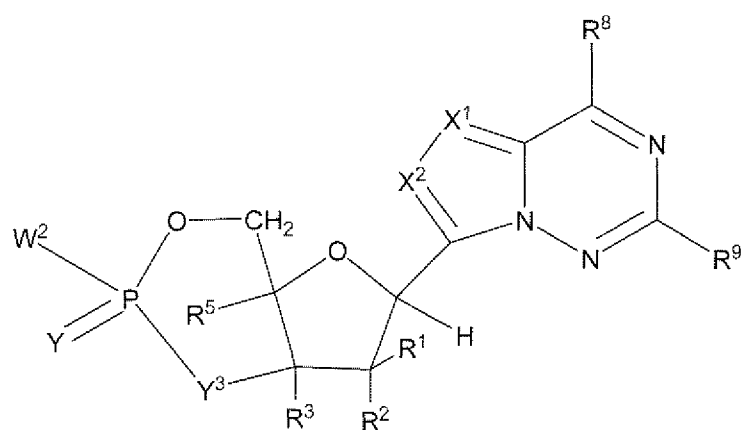
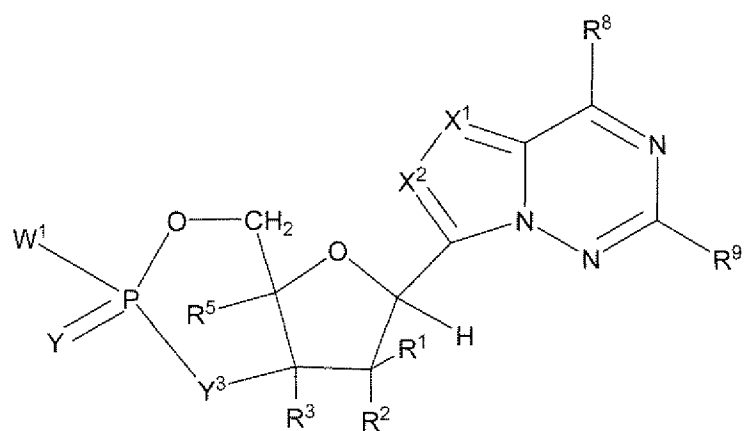
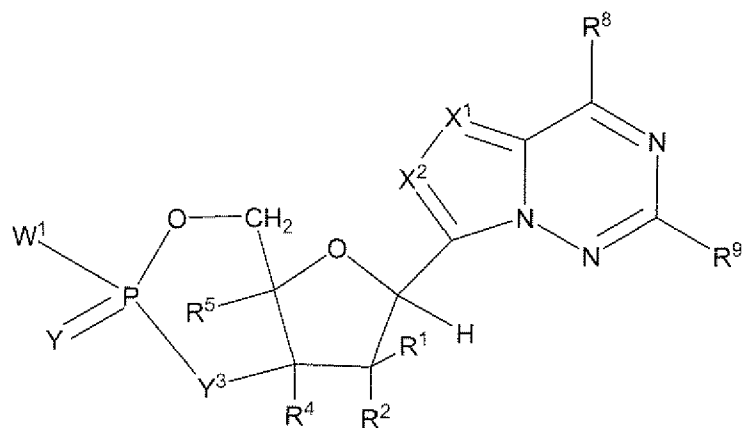
wherein R^y is W^5 as defined herein.

15

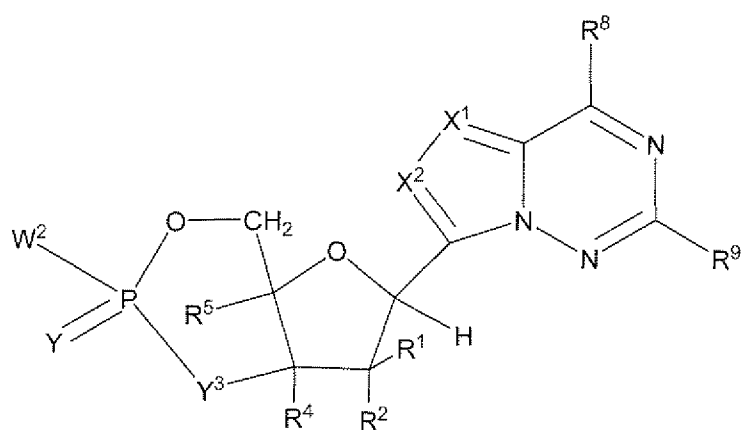


Another embodiment of of Formula I-III compounds includes the substructures wherein one of W^1 or W^2 together with either R^3 or R^4 is – Y^3 - and the other of W^1 or W^2 is Formula Ia. Such an embodiment is represented by a compound of Formula Ib selected from:

5



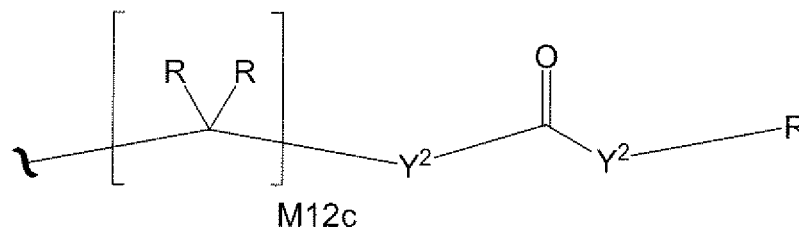
or



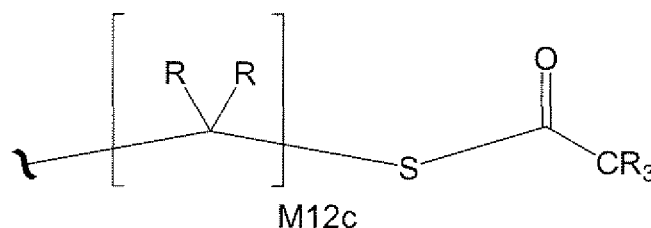
5

Formula Ib

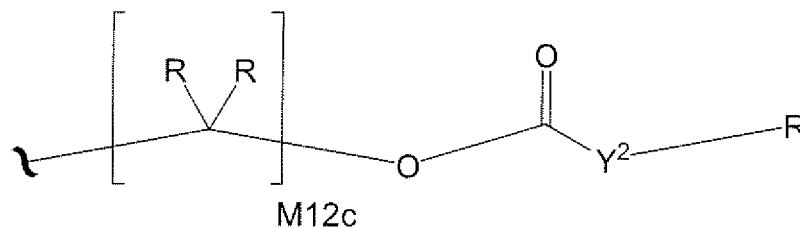
In a preferred aspect of the embodiment of Formula Ib, each Y and Y³ is O. In another preferred aspect of the embodiment of Formula Ib, W¹ or W² is Y^{2b}-R^x; each Y, Y³ and Y^{2b} is O and R^x is:



- 10 wherein M12c is 1, 2 or 3 and each Y² is independently a bond, O, CR₂, or S. In another preferred aspect of the embodiment of Formula Ib, W¹ or W² is Y^{2b}-R^x; each Y, Y³ and Y^{2b} is O and R^x is:

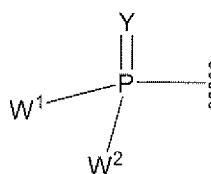


- 15 wherein M12c is 2. In another preferred aspect of the embodiment of Formula Ib, W¹ or W² is Y^{2b}-R^x; each Y, Y³ and Y^{2b} is O and R^x is:

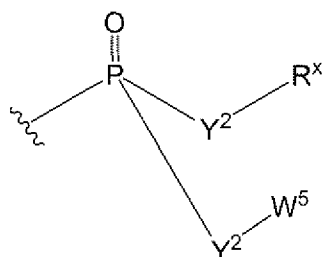


wherein M12c is 1 and Y² is a bond, O, or CR₂.

20

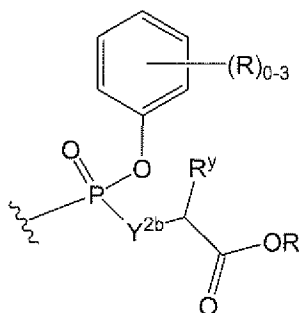


Another embodiment of of Formula I-III compounds includes a substructure:

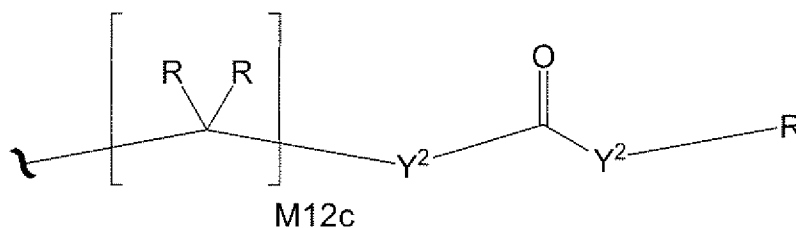


5

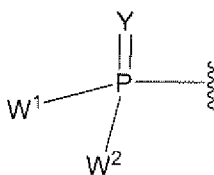
wherein W^5 is a carbocycle such as phenyl or substituted phenyl. In another aspect of this embodiment, the substructure is:



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



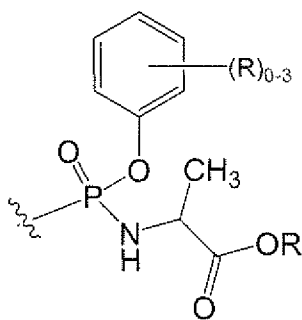
wherein M12c is 1, 2 or 3 and each Y^2 is independently a bond, O, CR_2 , or S.



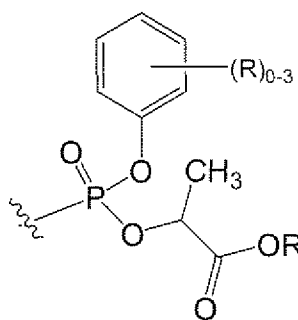
Another embodiment of

of Formula I-III includes

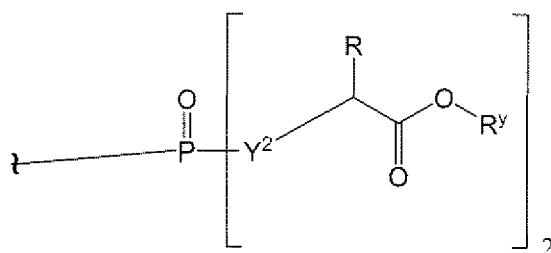
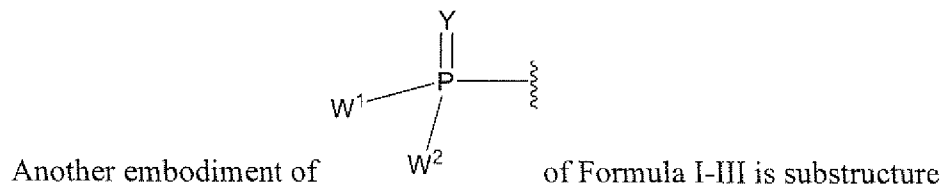
15 substructures:



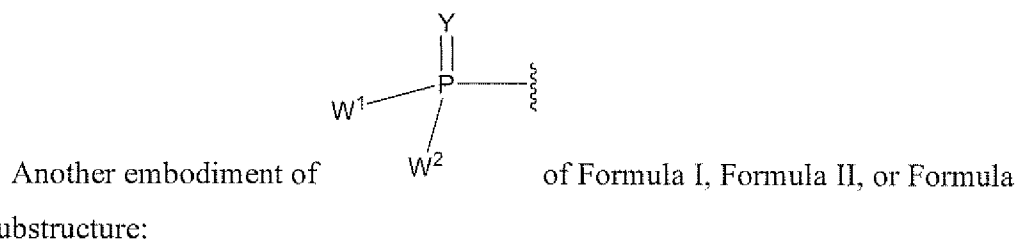
and

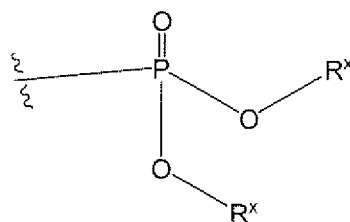


- 5 The chiral carbon of the amino acid and lactate moieties may be either the *R* or *S* configuration or the racemic mixture.



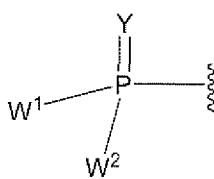
- wherein each Y^2 is, independently, $-O-$ or $-NH-$. In another preferred aspect of this
- 10 embodiment, R^y is (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl or (C_2-C_8) substituted alkynyl. In another preferred aspect of this embodiment, R^y is (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl or (C_2-C_8) substituted alkynyl; and R is CH_3 . In another preferred aspect of this embodiment, R^y is (C_1-C_8)
- 15 alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl or (C_2-C_8) substituted alkynyl; R is CH_3 ; and each Y^2 is $-NH-$. In a preferred aspect of this embodiment, W^1 and W^2 are, independently, nitrogen-linked, naturally occurring amino acids or naturally occurring amino acid esters. In another preferred aspect of this embodiment, W^1 and W^2 are, independently, naturally-occurring 2-
- 20 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.



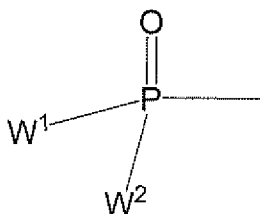


5

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



Another embodiment of of Formulas I-III is



10

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

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

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

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

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

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

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

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

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

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

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

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

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

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

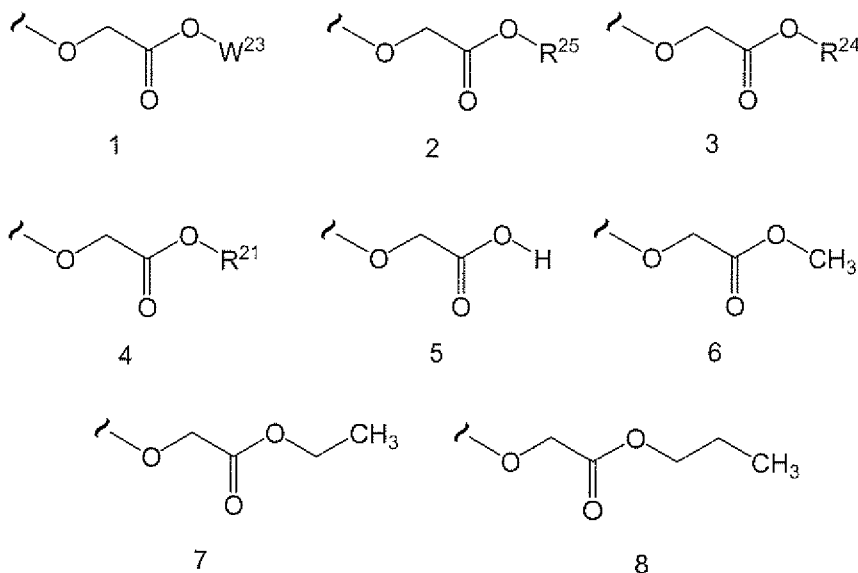
20 each W^{24} is independently R^{25} , $-C(=Y^{21})R^{25}$, $-C(=Y^{21})W^{25}$, $-SO_2R^{25}$, or $-SO_2W^{25}$;

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

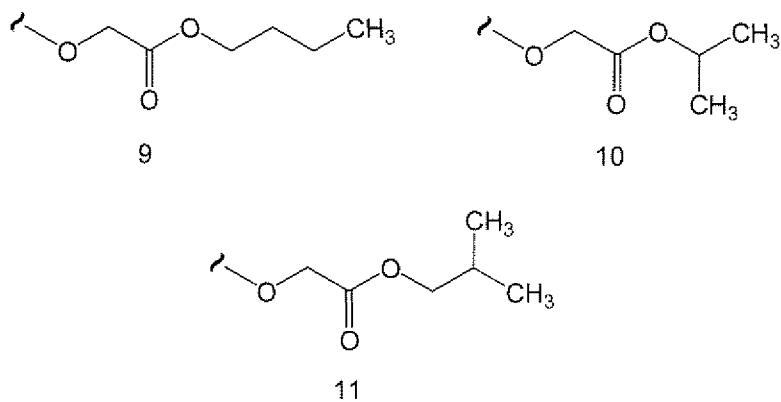
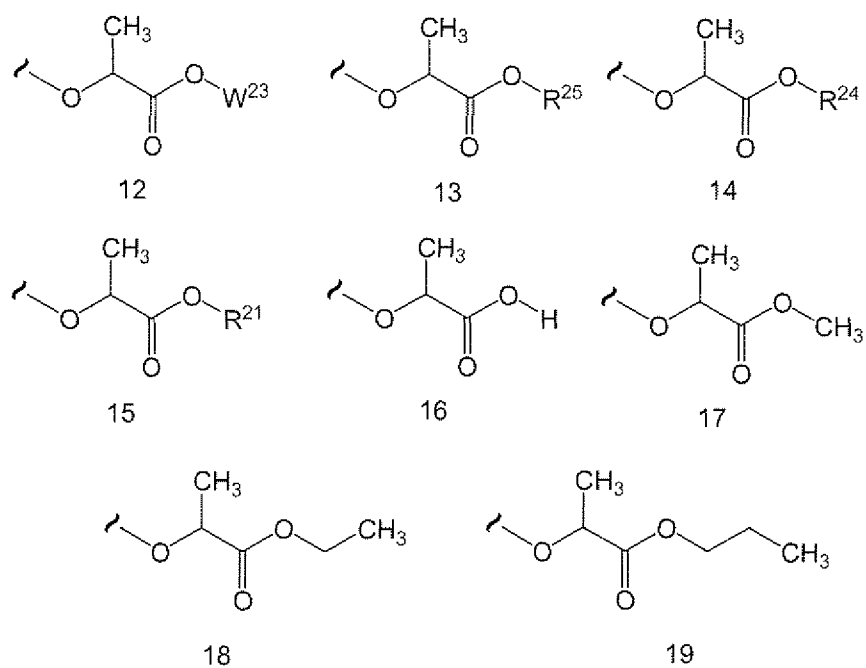
each Y^{21} is independently O or S.

25

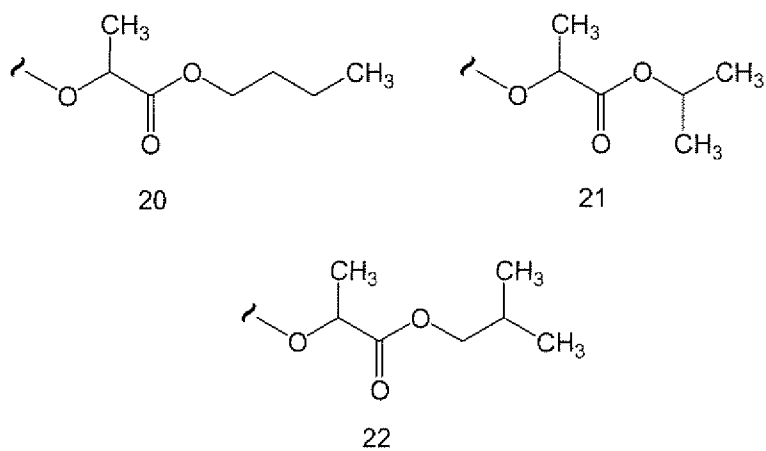
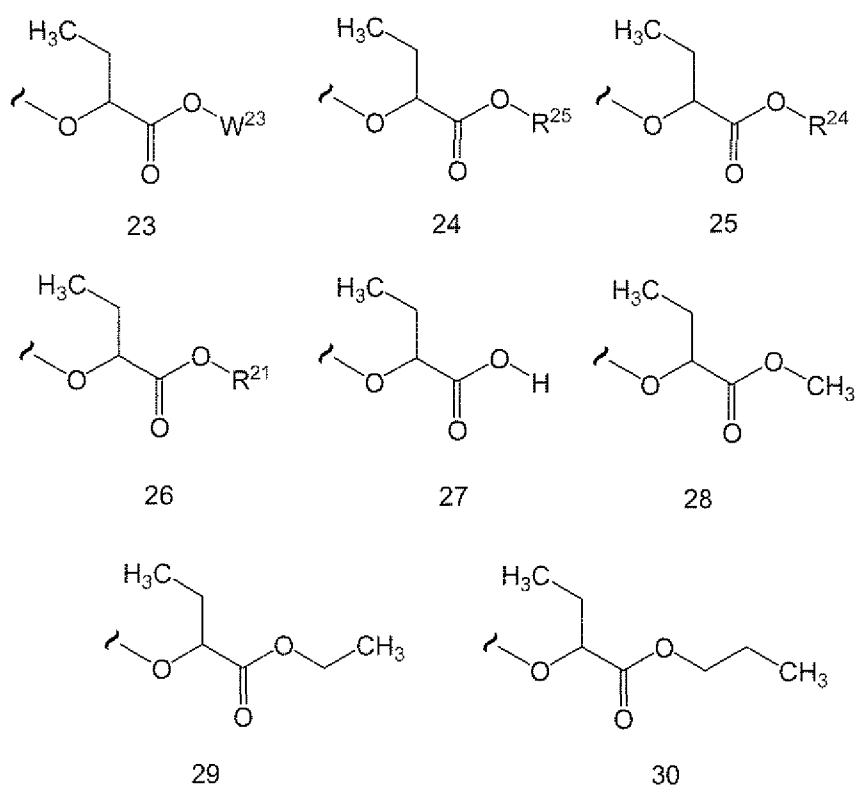
Table 20.1

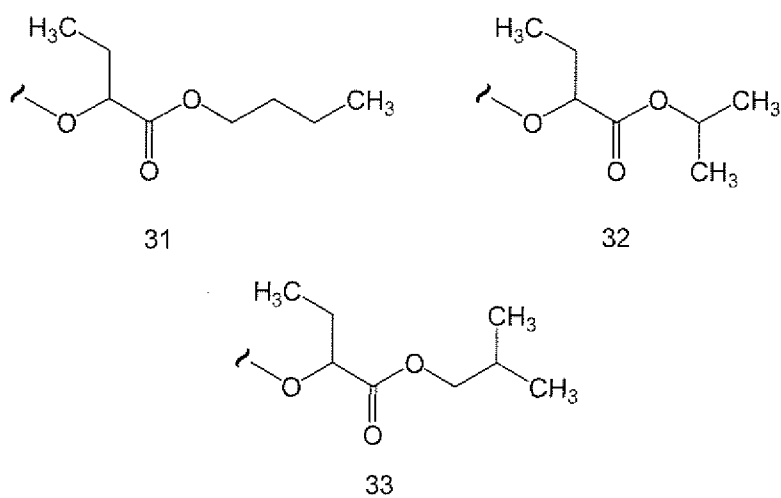
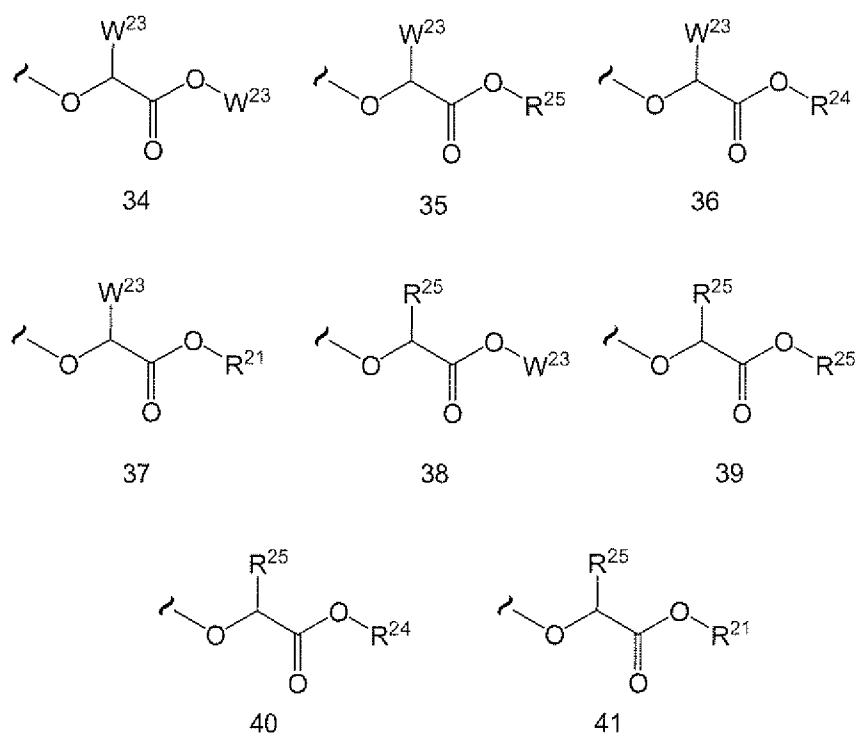


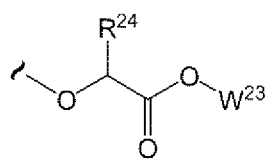
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Table 20.2Table 20.3

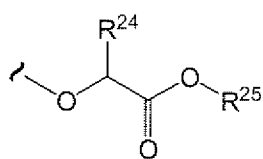
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5 Table 20.4Table 20.5

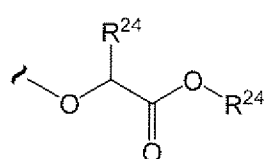
5 Table 20.6Table 20.7

5 Table 20.8

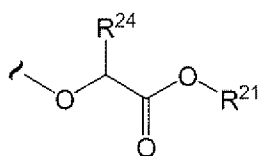
42



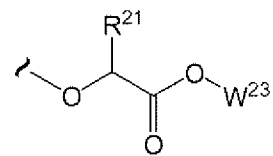
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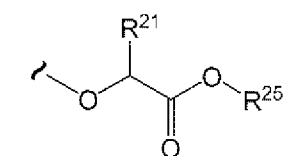
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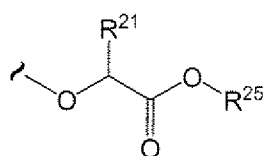
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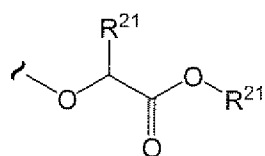
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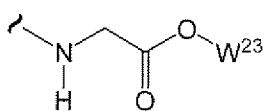
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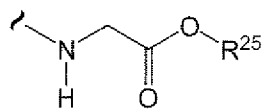
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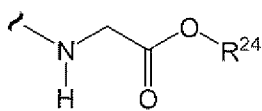
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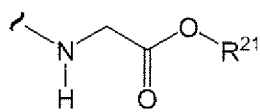
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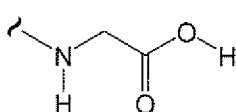
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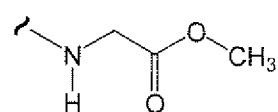
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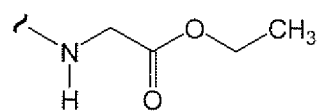
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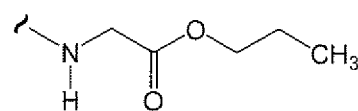
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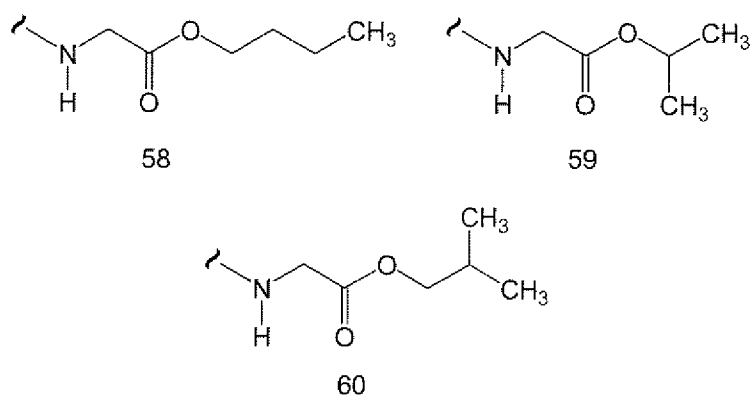
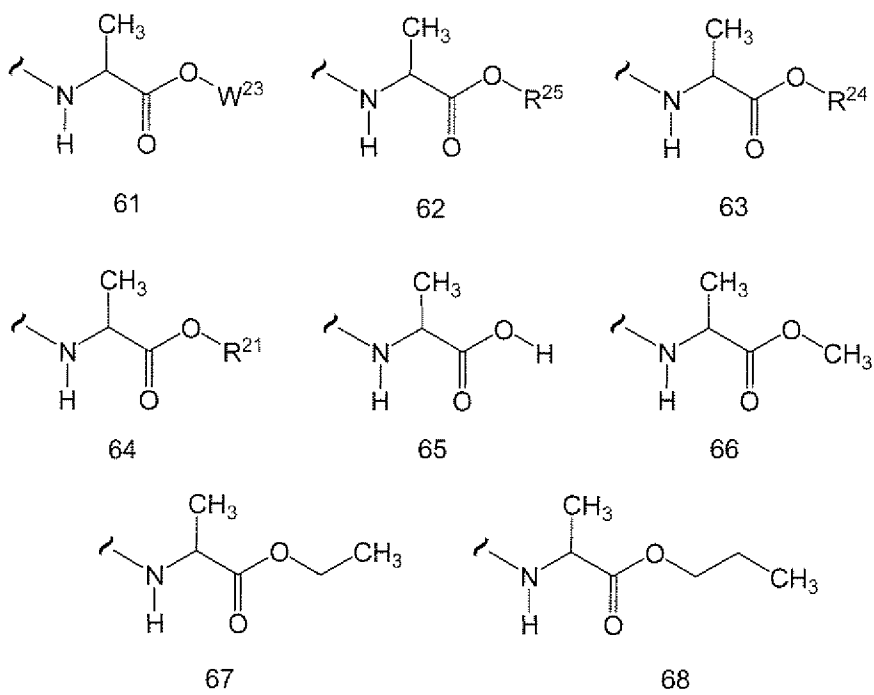
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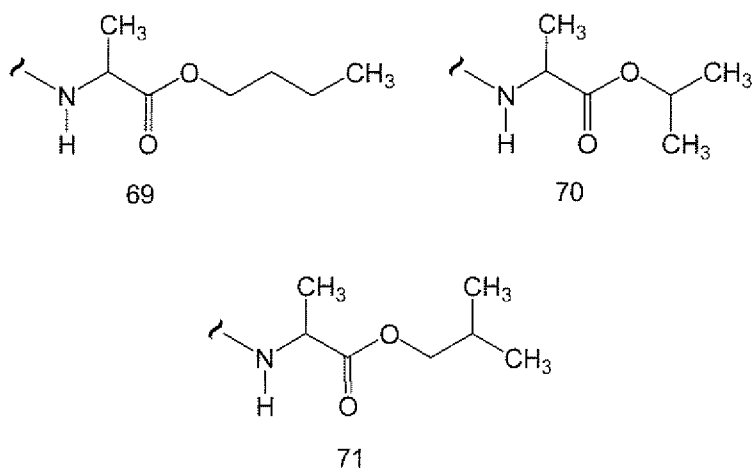
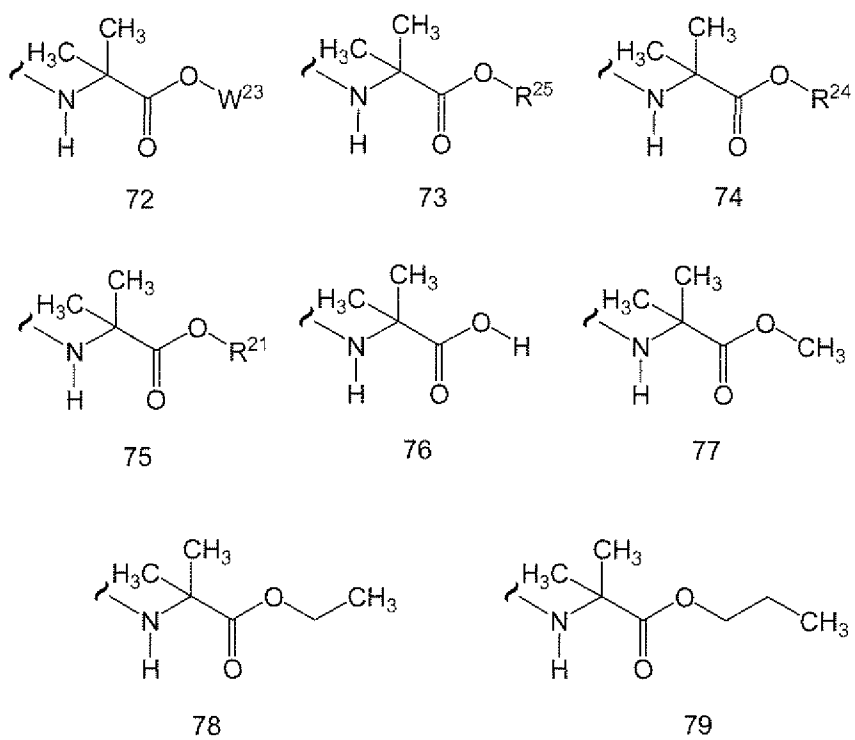


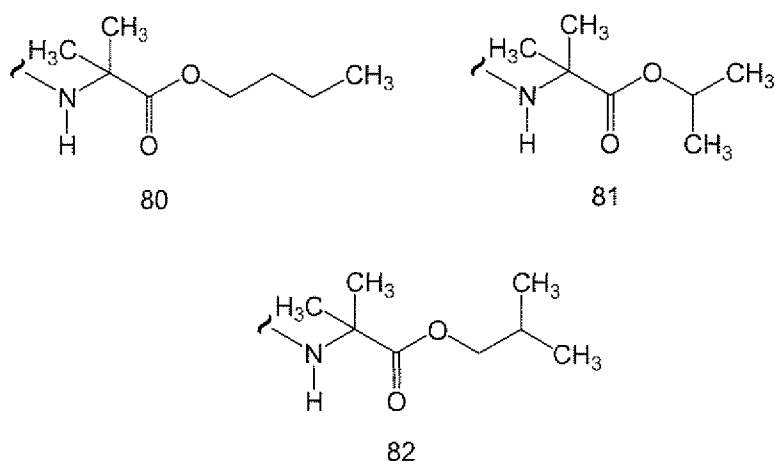
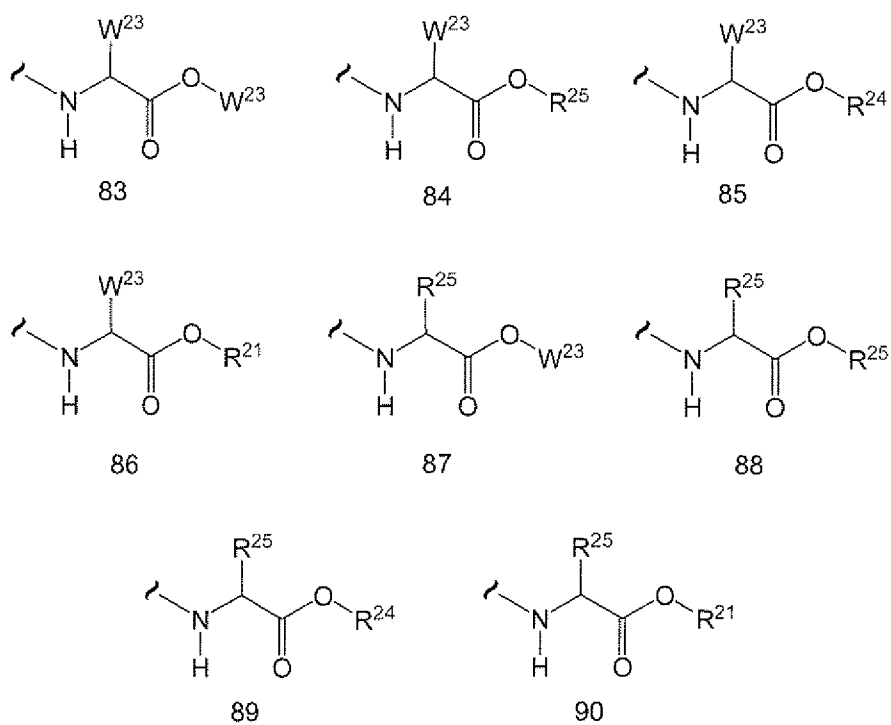
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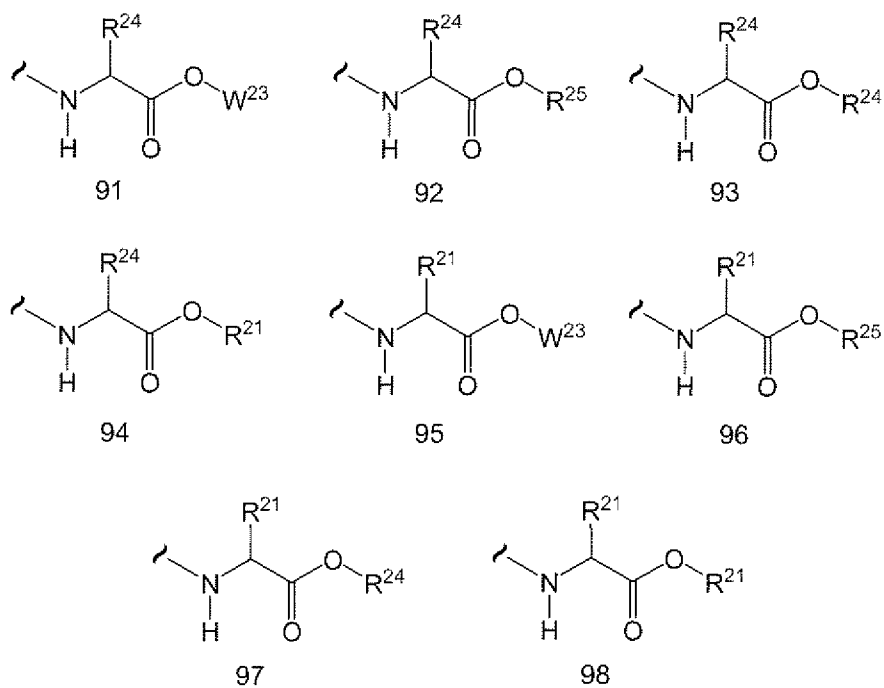
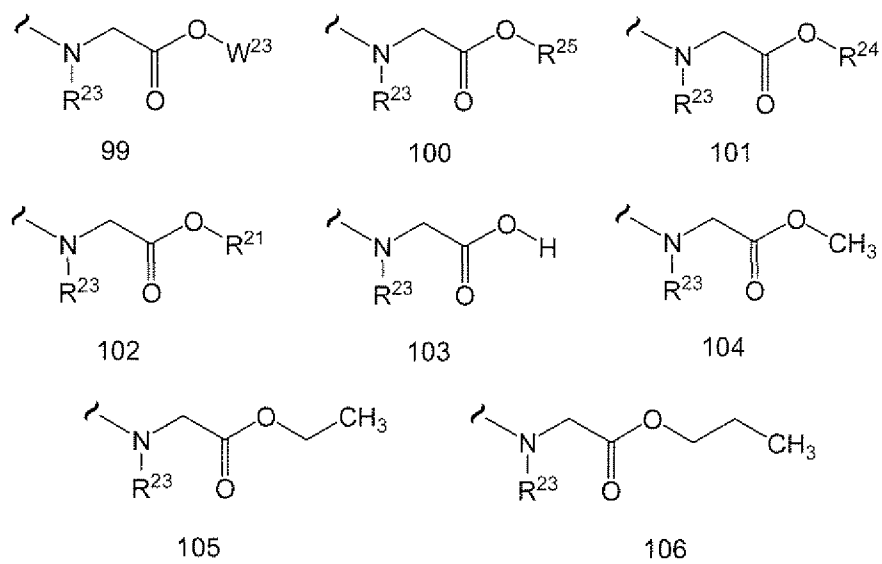


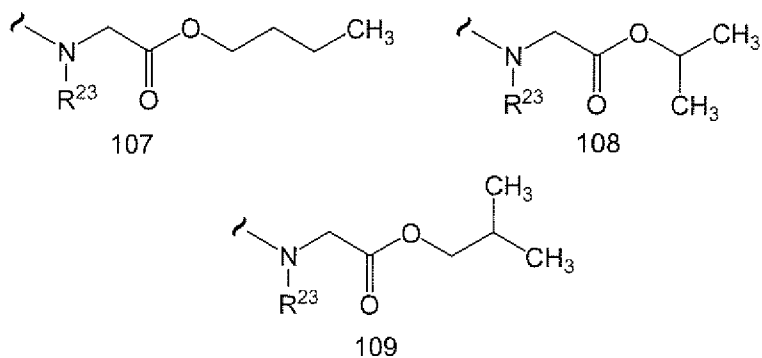
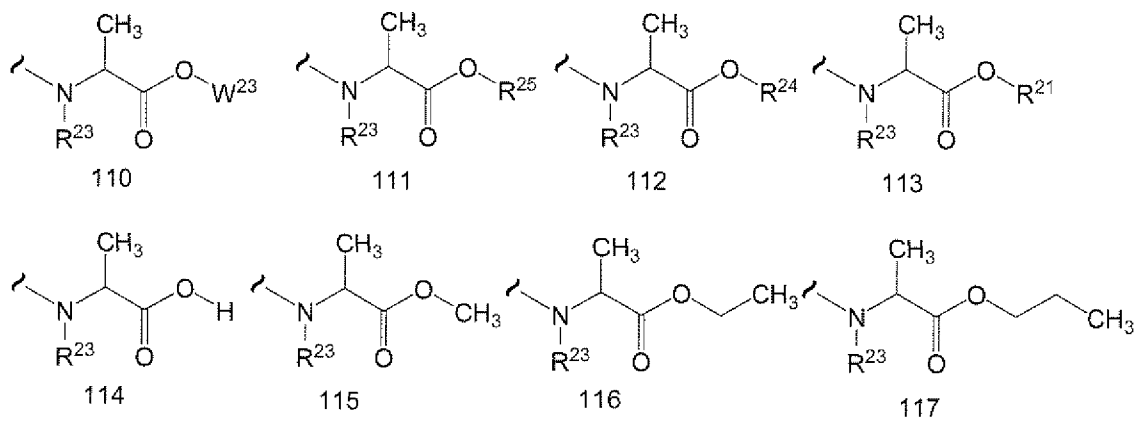
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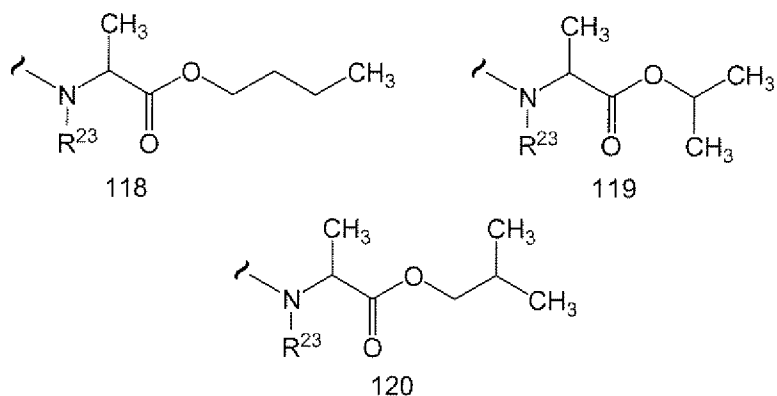
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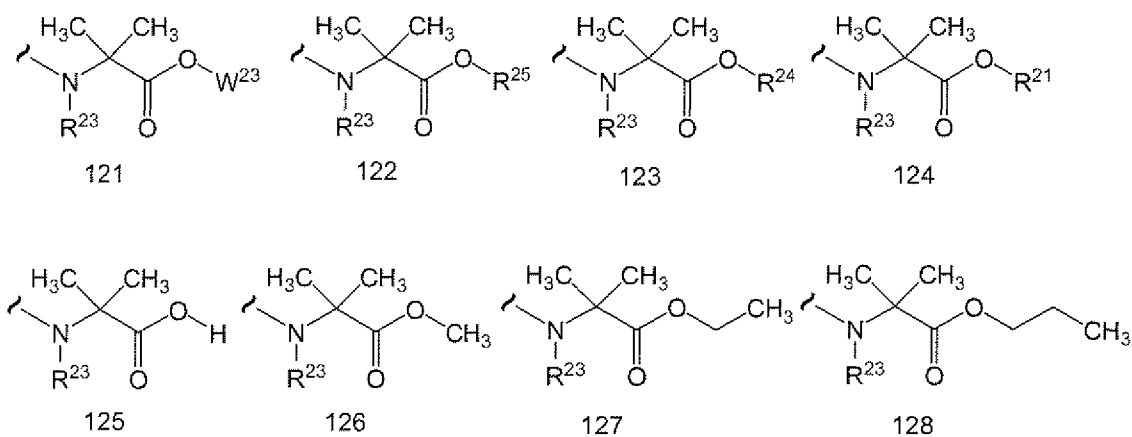
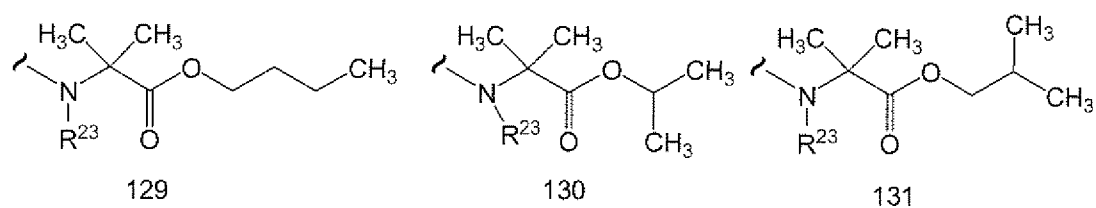
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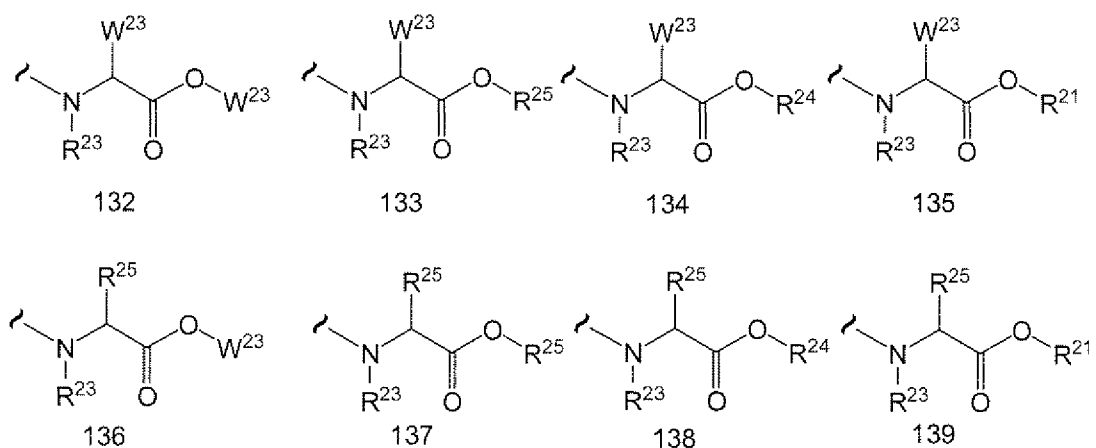
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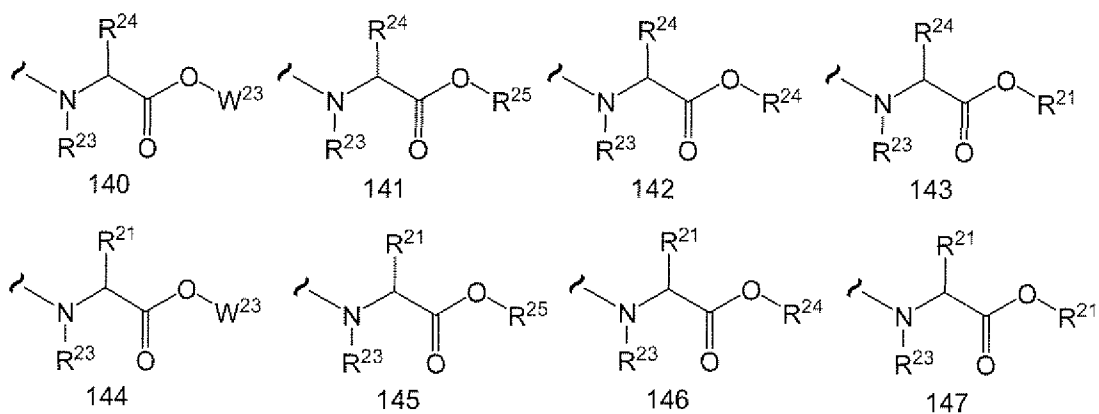
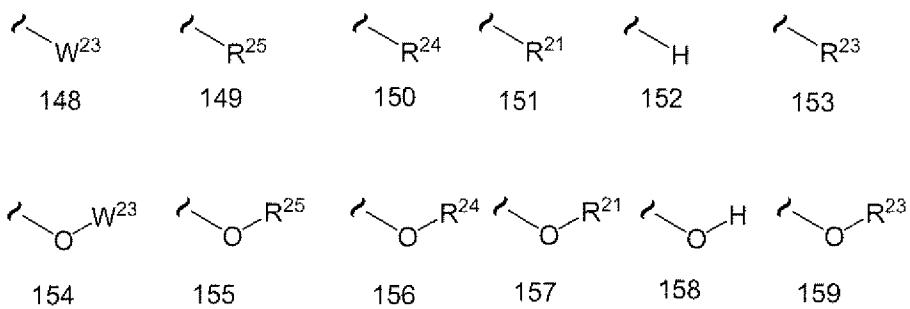
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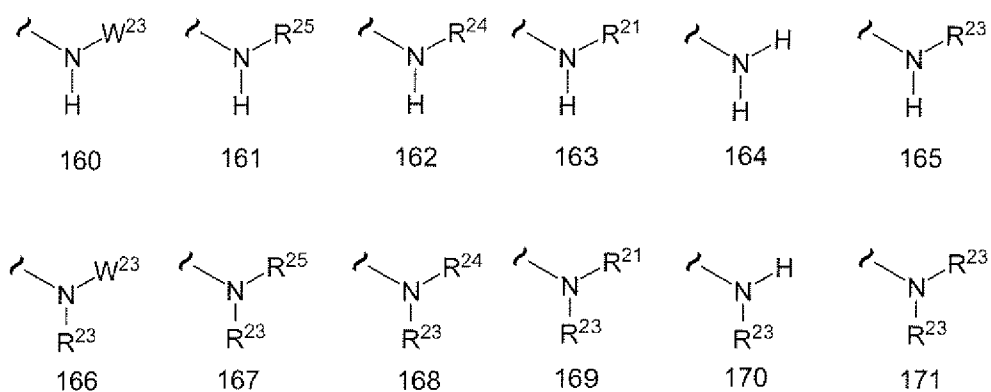
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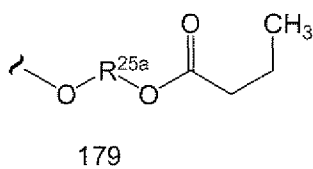
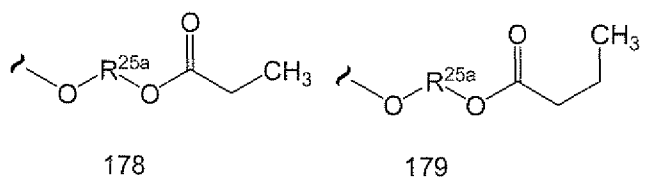
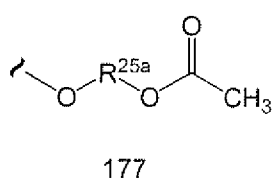
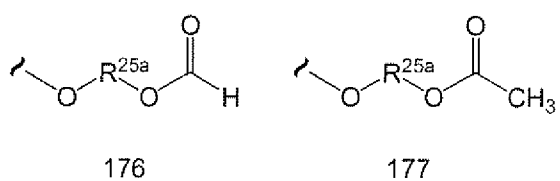
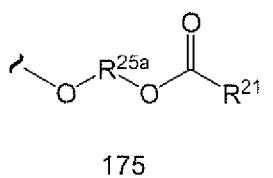
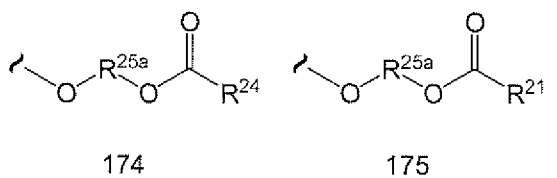
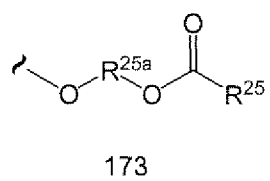
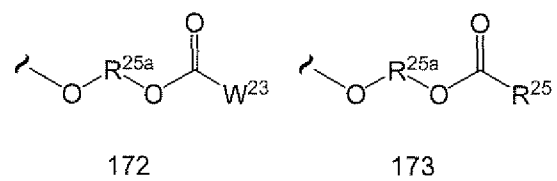
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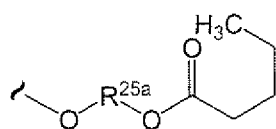
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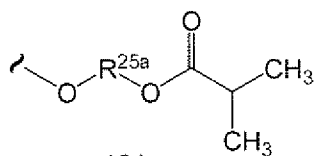
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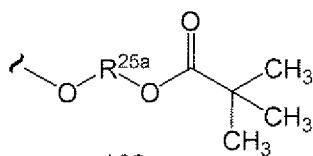
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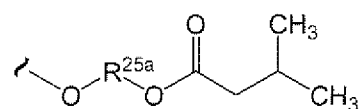
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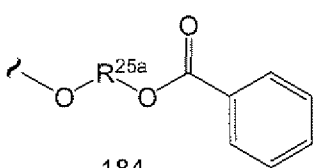
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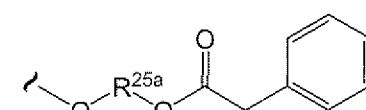
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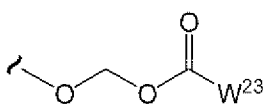
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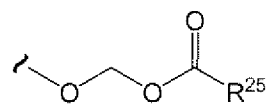
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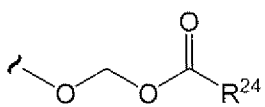
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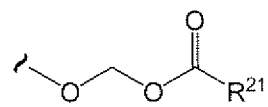
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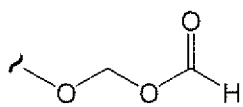
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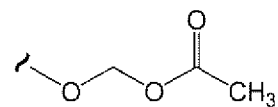
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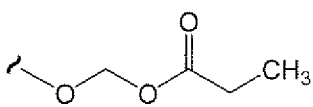
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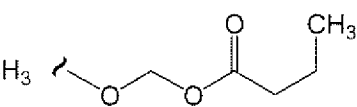
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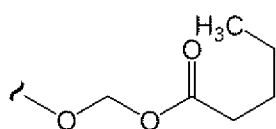
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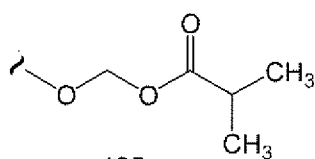
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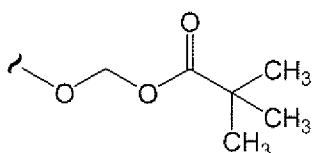
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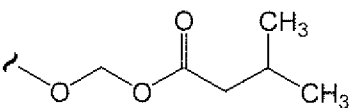
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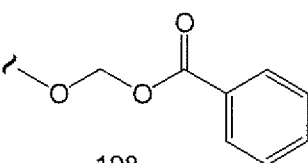
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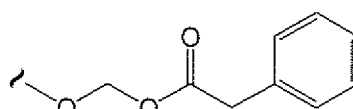
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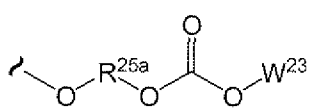
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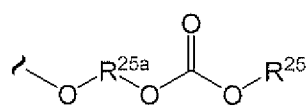
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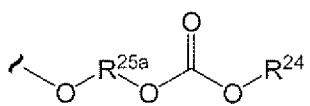
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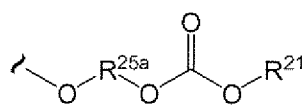
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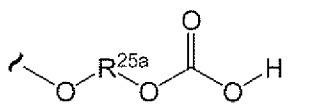
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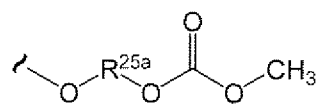
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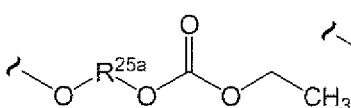
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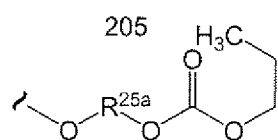
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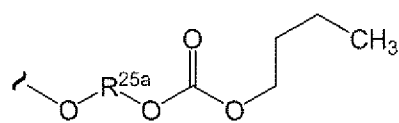


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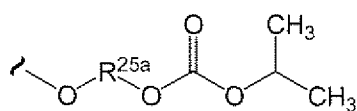


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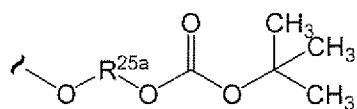
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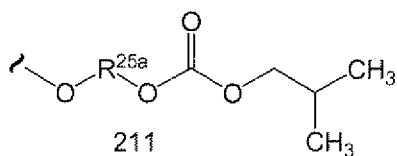
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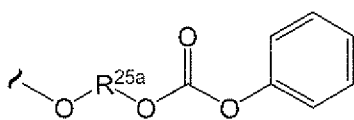
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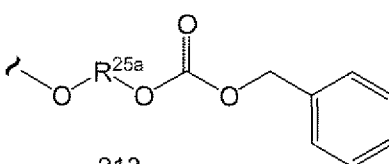
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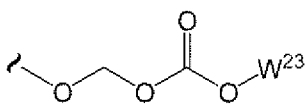
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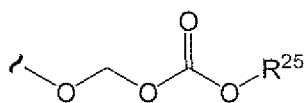
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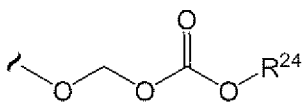
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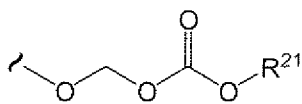
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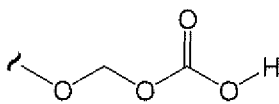
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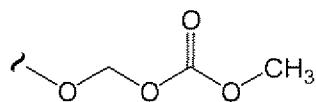
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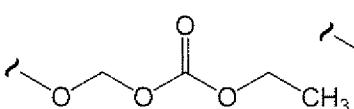
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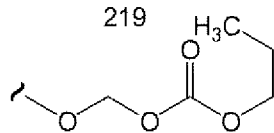
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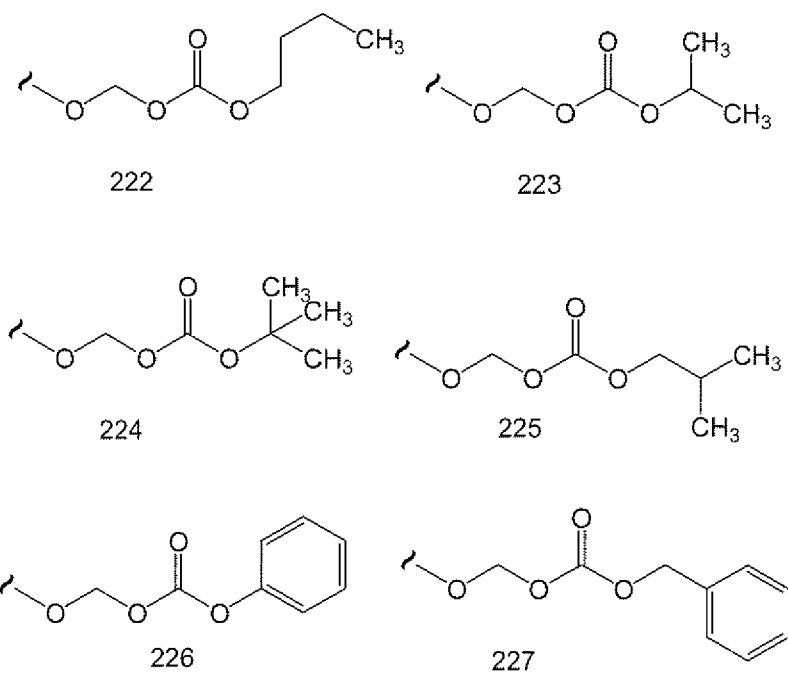
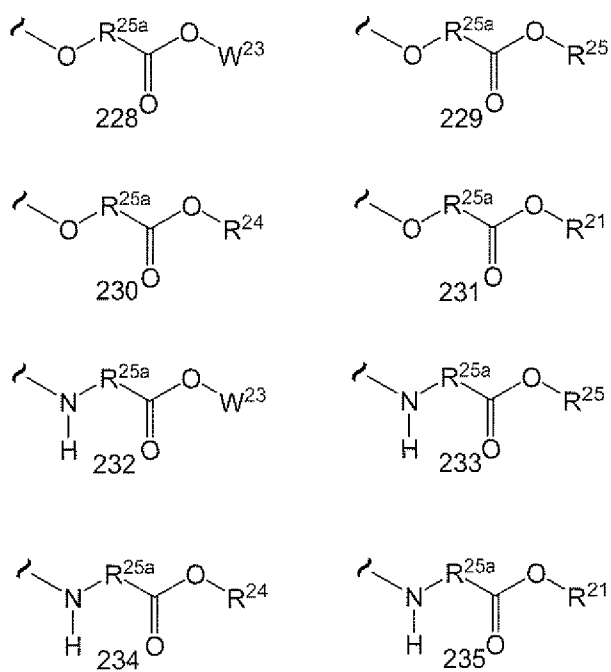
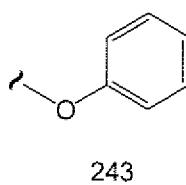
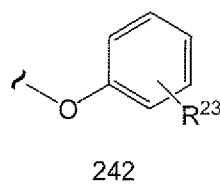
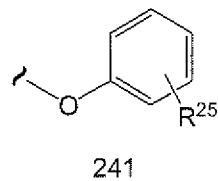
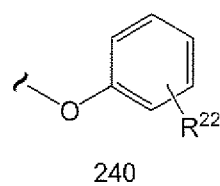
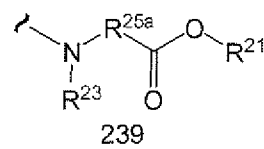
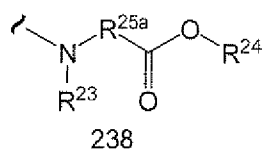
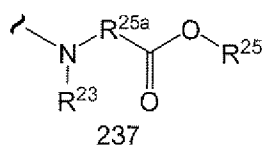
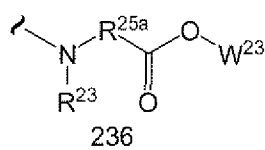
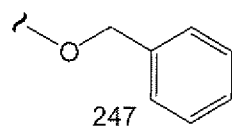
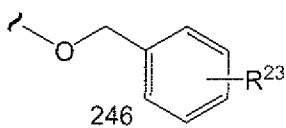
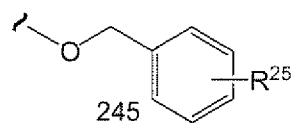
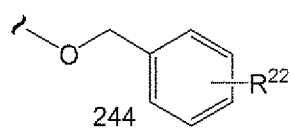
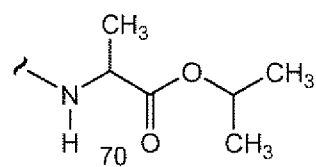
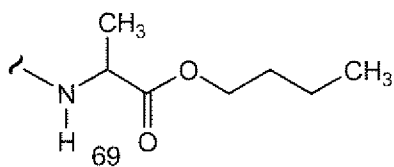
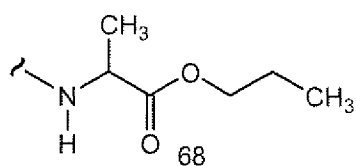
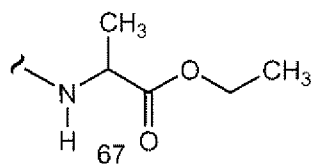
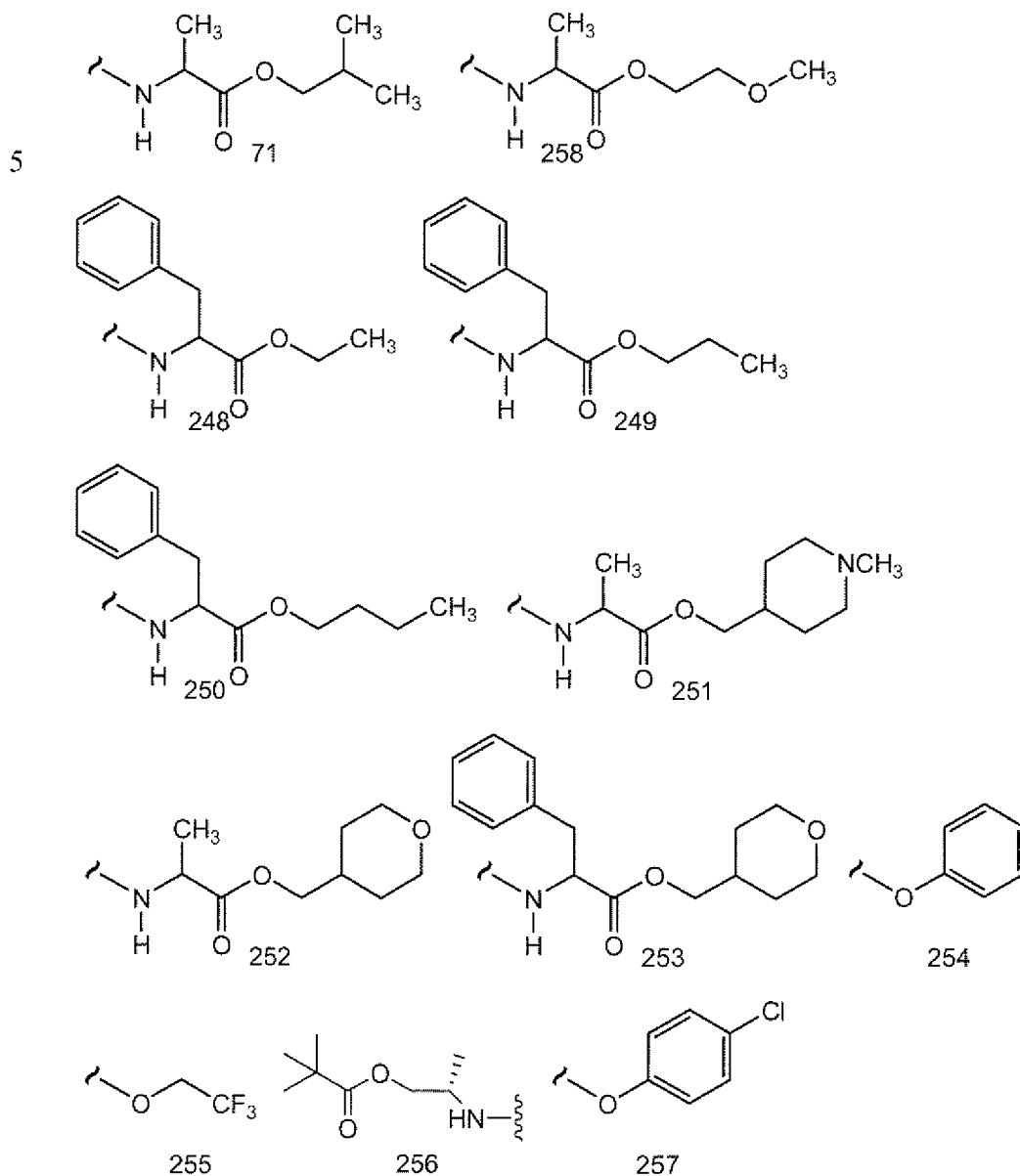


Table 20.35



10

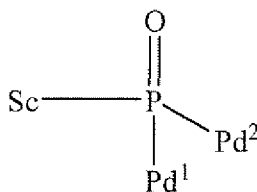
5 Table 20.36Table 20.3710 Table 30.1



10

Phosphate Embodiments of Compounds of Formula I-III

By way of example and not limitation, the phosphate embodiments of Formula I-III may be represented by the general formula "MBF":



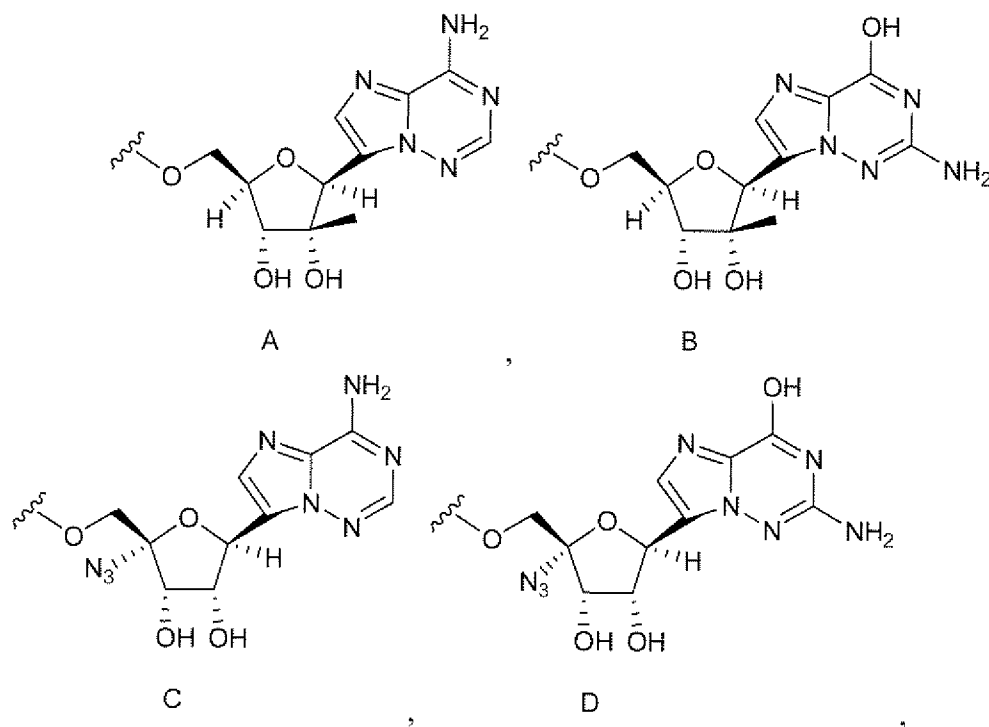
MBF

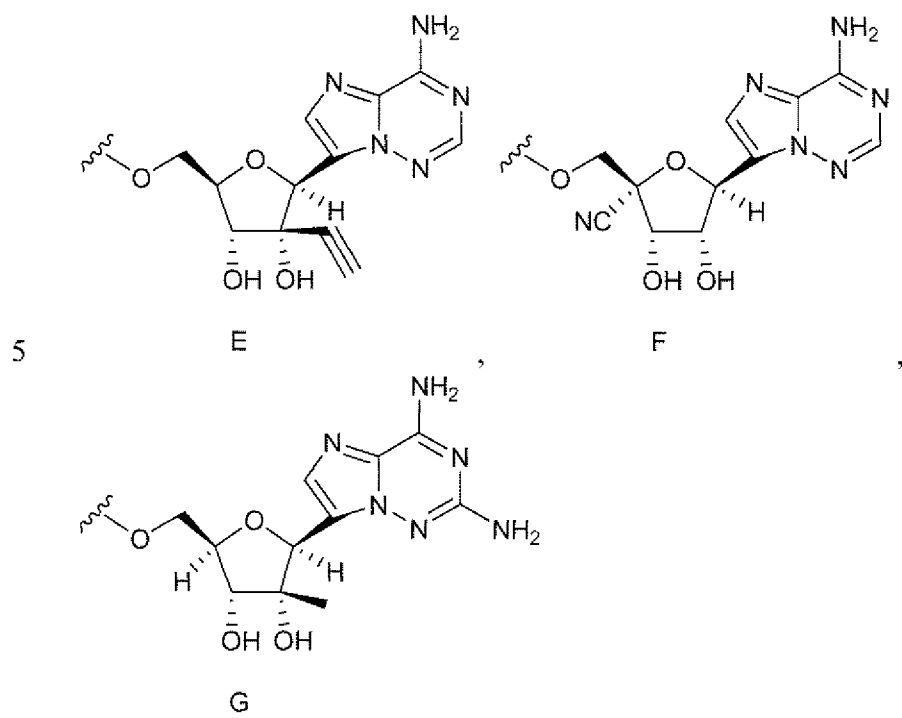
15

5

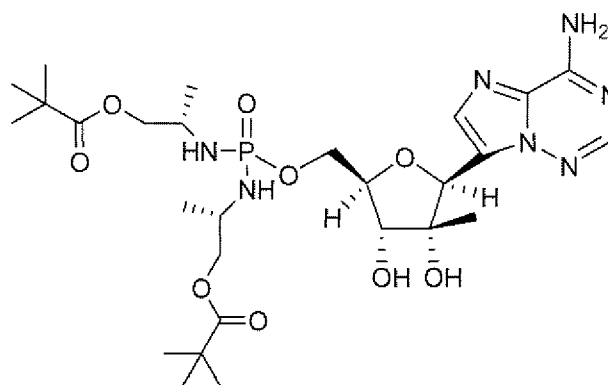
Each embodiment of MBF is depicted as a substituted nucleus (Sc). Sc is described in formulae A-G of Table 1.1 below, wherein Sc is a generic formula for a compound of Formula I, Formula II, or Formula III and the point of attachment to $-P(O)Pd^1Pd^2$ is indicated with a wavy line.

10

Table 1.1



- 5 Combinations of "Sc" and Pd¹ and Pd², independently selected from Table 30.1, can be expressed in the form of Sc.Pd¹.Pd², where Sc is represented by the respective letter A-G from Table 1.1 and Pd¹ and Pd² are represented by the respective number from Table 30.1. Thus, A.256.256 represents the following compound:



10

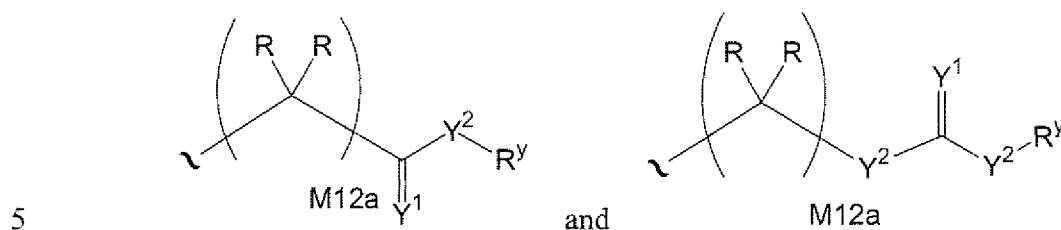
Thereby, Table 7 lists many specific examples of phosphate prodrugs of Formula I-III.

- 15 Table 7: List of Compounds of MBF

- A.254.67, A.254.68, A.254.69, A.254.70, A.254.71, A.254.258, A.254.248,
 A.254.249, A.254.250, A.254.251, A.254.252, A.254.253, B.254.67, B.254.68,
 B.254.69, B.254.70, B.254.71, B.254.258, B.254.248, B.254.249, B.254.250,
 20 B.254.251, B.254.252, B.254.253, C.254.67, C.254.68, C.254.69, C.254.70, C.254.71,
 C.254.258, C.254.248, C.254.249, C.254.250, C.254.251, C.254.252, C.254.253,
 D.254.67, D.254.68, D.254.69, D.254.70, D.254.71, D.254.258, D.254.248,
 D.254.249, D.254.250, D.254.251, D.254.252, D.254.253, E.254.67, E.254.68,
 E.254.69, E.254.70, E.254.71, E.254.258, E.254.248, E.254.249, E.254.250,
 25 E.254.251, E.254.252, E.254.253, F.254.67, F.254.68, F.254.69, F.254.70, F.254.71,
 F.254.258, F.254.248, F.254.249, F.254.250, F.254.251, F.254.252, F.254.253,
 G.254.67, G.254.68, G.254.69, G.254.70, G.254.71, G.254.258, G.254.248,
 G.254.249, G.254.250, G.254.251, G.254.252, G.254.253, A.255.67, A.255.68,
 A.255.69, A.255.70, A.255.71, A.255.258, A.255.248, A.255.249, A.255.250,
 30 A.255.251, A.255.252, A.255.253, B.255.67, B.255.68, B.255.69, B.255.70,

- 5 B.255.71, B.255.258, B.255.248, B.255.249, B.255.250, B.255.251, B.255.252,
B.255.253, C.255.67, C.255.68, C.255.69, C.255.70, C.255.71, C.255.258, C.255.248,
C.255.249, C.255.250, C.255.251, C.255.252, C.255.253, D.255.67, D.255.68,
D.255.69, D.255.70, D.255.71, D.255.258, D.255.248, D.255.249, D.255.250,
D.255.251, D.255.252, D.255.253, E.255.67, E.255.68, E.255.69, E.255.70, E.255.71,
10 E.255.258, E.255.248, E.255.249, E.255.250, E.255.251, E.255.252, E.255.253,
F.255.67, F.255.68, F.255.69, F.255.70, F.255.71, F.255.258, F.255.248, F.255.249,
F.255.250, F.255.251, F.255.252, F.255.253, G.255.67, G.255.68, G.255.69,
G.255.70, G.255.71, G.255.258, G.255.248, G.255.249, G.255.250, G.255.251,
G.255.252, G.255.253, A.67.67, A.68.68, A.69.69, A.70.70, A.71.71, A.258.258,
15 A.248.248, A.249.249, A.250.250, A.251.251, A.252.252, A.253.253, B.67.67,
B.68.68, B.69.69, B.70.70, B.71.71, B.258.258, B.248.248, B.249.249, B.250.250,
B.251.251, B.252.252, B.253.253, C.67.67, C.68.68, C.69.69, C.70.70, C.71.71,
C.258.258, C.248.248, C.249.249, C.250.250, C.251.251, C.252.252, C.253.253,
D.67.67, D.68.68, D.69.69, D.70.70, D.71.71, D.258.258, D.248.248, D.249.249,
20 D.250.250, D.251.251, D.252.252, D.253.253, E.67.67, E.68.68, E.69.69, E.70.70,
E.71.71, E.258.258, E.248.248, E.249.249, E.250.250, E.251.251, E.252.252,
E.253.253, F.67.67, F.68.68, F.69.69, F.70.70, F.71.71, F.258.258, F.248.248,
F.249.249, F.250.250, F.251.251, F.252.252, F.253.253, G.67.67, G.68.68, G.69.69,
G.70.70, G.71.71, G.258.258, G.248.248, G.249.249, G.250.250, G.251.251,
25 G.252.252, G.253.253, A.256.257, B.256.257, C.256.257, D.256.257, E.256.257,
F.256.257, G.256.257, A.256.254, B.256.254, C.256.254, D.256.254, E.256.254,
F.256.254, G.256.254, A.256.250, B.256.250, C.256.250, D.256.250, E.256.250,
F.256.250, G.256.250, A.256.69, B.256.69, C.256.69, D.256.69, E.256.69, F.256.69,
G.256.69, A.256.71, B.256.71, C.256.71, D.256.71, E.256.71, F.256.71, G.256.71,
30 A.256.255, B.256.255, C.256.255, D.256.255, E.256.255, F.256.255, G.256.255.

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



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^{+2}), ammonium and NX_4^+ (wherein X is $\text{C}_1\text{--C}_4$ alkyl). 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 NX_4^+ (wherein X is independently selected from H or a $\text{C}_1\text{--C}_4$ alkyl group).

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

5 derived form a physiologically acceptable acid or base, are within the scope of the present invention.

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

10 The compounds of the invention, exemplified by Formula I-III may have chiral centers, e.g. chiral carbon or phosphorus atoms. The compounds of the invention thus include racemic mixtures of all stereoisomers, including enantiomers, diastereomers, and atropisomers. In addition, the compounds of the invention include enriched or resolved optical isomers at any or all asymmetric, chiral atoms. In other
15 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
20 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.

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

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

30 "Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

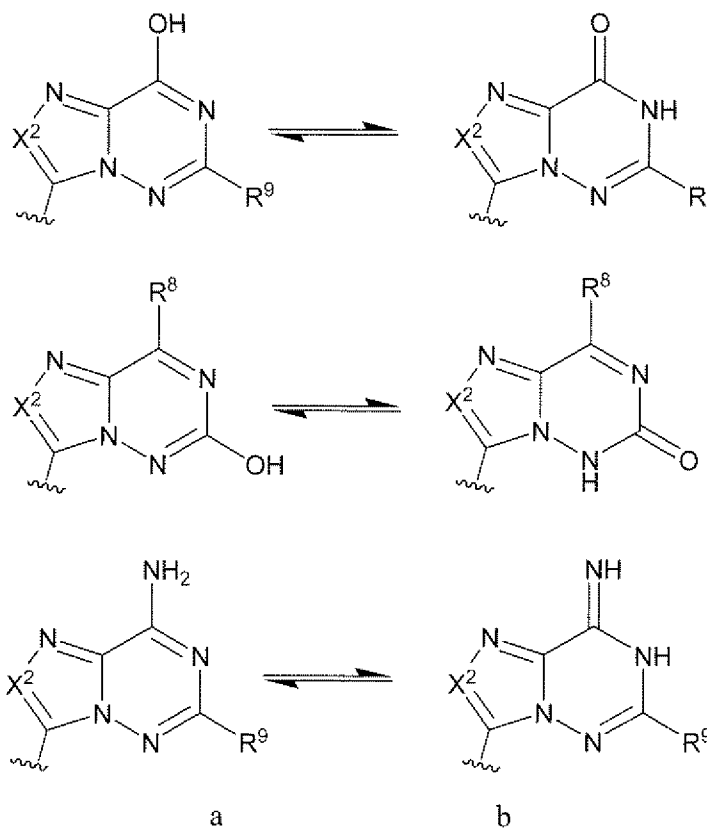
35 "Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

5 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-
10 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
15 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
20 stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

Whenever a compound described herein is substituted with more than one of the same designated group, e.g., "R" or "R¹", then it will be understood that the
25 groups may be the same or different, i.e., each group is independently selected. Wavy lines, ~~~~~, indicate the site of covalent bond attachments to the adjoining substructures, groups, moieties, or atoms.

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

One skilled in the art will recognize that the imidazo[1,5-f][1,2,4]triazine,
35 [1,2,4]triazolo[4,3-f][1,2,4]triazine and imidazo[1,2-f][1,2,4]triazine heterocycles can exist in tautomeric forms. For example, but not by way of limitation, structures (a) and (b) can have equivalent tautomeric forms as shown below:



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

10 Methods of Inhibition of HCV polymerase

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

Compositions of the invention may act as inhibitors of HCV polymerase, as
intermediates for such inhibitors or have other utilities as described below. The
inhibitors will bind to locations on the surface or in a cavity of HCV polymerase
having a geometry unique to HCV polymerase. Compositions binding HCV
polymerase may bind with varying degrees of reversibility. Those compounds
binding substantially irreversibly are ideal candidates for use in this method of the
invention. Once labeled, the substantially irreversibly binding compositions are
useful as probes for the detection of HCV polymerase. Accordingly, the invention
relates to methods of detecting HCV polymerase in a sample suspected of containing
HCV polymerase comprising the steps of: treating a sample suspected of containing

5 HCV polymerase with a composition comprising a compound of the invention bound to a label; and observing the effect of the sample on the activity of the label. Suitable labels are well known in the diagnostics field and include stable free radicals, fluorophores, radioisotopes, enzymes, chemiluminescent groups and chromogens. The compounds herein are labeled in conventional fashion using functional groups
10 such as hydroxyl, carboxyl, sulfhydryl or amino.

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

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

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

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

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

5 primary screening tool.

Screens for HCV polymerase Inhibitors.

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

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

Pharmaceutical Formulations

The compounds of this invention are formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are
20 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,
25 hydroxyalkylmethylcellulose, stearic acid and the like. The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10.

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

The formulations include those suitable for the foregoing administration
35 routes. The formulations may conveniently be presented in unit dosage form and may

5 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
10 intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

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

A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a
20 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
25 so as to provide slow or controlled release of the active ingredient therefrom.

For infections of the eye or other external tissues e.g. mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as
30 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

If desired, the aqueous phase of the cream base may include, for example, at
35 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

5 formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogs.

The oily phase of the emulsions of this invention may be constituted from
10 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
15 emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

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

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as
25 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
30 white soft paraffin and/or liquid paraffin or other mineral oils are used.

Pharmaceutical formulations according to the present invention comprise a combination according to the invention together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form
35 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.

- 5 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.
- 10 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.
- 15 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.
- 20 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 methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally-occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives
- 25 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.
- 30

5 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.

10 These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more

15 preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or

20 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,

25 such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

The pharmaceutical compositions of the invention may be in the form of a

30 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

35 a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may

5 conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

The amount of active ingredient that may be combined with the carrier
10 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
15 (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.

20 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.

25 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.

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

Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns, such as 0.5, 1, 30, 35 etc., which is administered by rapid inhalation through the nasal passage or by inhalation
35 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

- 5 may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis of HCV infections as described below.

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

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may
15 include suspending agents and thickening agents.

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

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

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

30 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.

35 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

- 5 ingredient are controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of a given active ingredient.

Effective dose of active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses) or against an active viral infection, the method of
10 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
15 day. For example, the daily candidate dose for an adult human of approximately 70 kg body weight will range from 1 mg to 1000 mg, preferably between 5 mg and 500 mg, and may take the form of single or multiple doses.

Routes of Administration

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

Combination Therapy

Compositions of the invention are also used in combination with other active ingredients. Preferably, the other active therapeutic ingredients or agents are
30 interferons, ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

Combinations of the compounds of Formula I-III are typically selected based on the condition to be treated, cross-reactivities of ingredients and pharmaco-
35 properties of the combination. For example, when treating an infection (e.g., HCV),

5 the compositions of the invention are combined with other active therapeutic agents (such as those described herein).

Suitable active therapeutic agents or ingredients which can be combined with the compounds of Formula I-III can include interferons, e.g., pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, IFN alpha-2b XL, rIFN-alpha 2a, 10 consensus IFN alpha, infergen, rebif, locteron, AVI-005, PEG-infergen, pegylated IFN-beta, oral interferon alpha, feron, reaferon, intermax alpha, r-IFN-beta, infergen + actimmune, IFN-omega with DUROS, and albuferon; ribavirin analogs, e.g., rebetol, copegus, VX-497, and viramidine (taribavirin); NS5a inhibitors, e.g., A-831, A-689 and BMS-790052; NS5b polymerase inhibitors, e.g., NM-283, valopicitabine, R1626, 15 PSI-6130 (R1656), HCV-796, BILB 1941, MK-0608, NM-107, R7128, VCH-759, PF-868554, GSK625433, and XTL-2125; NS3 protease inhibitors, e.g., SCH-503034 (SCH-7), VX-950 (Telaprevir), ITMN-191, and BILN-2065; alpha-glucosidase 1 inhibitors, e.g., MX-3253 (celgosivir) and UT-231B; hepatoprotectants, e.g., IDN-6556, ME 3738, MitoQ, and LB-84451; non-nucleoside inhibitors of HCV, e.g., 20 benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, and phenylalanine derivatives; and other drugs for treating HCV, e.g., zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), DEBIO-025, VGX-410C, EMZ-702, AVI 4065, bavituximab, oglufanide, PYN-17, KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975, XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, and NIM811.

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

According to the present invention, the therapeutic agent used in combination 30 with the compound of the present invention can be any agent having a therapeutic effect when used in combination with the compound of the present invention. For example, the therapeutic agent used in combination with the compound of the present invention can be interferons, ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, cyclophilin inhibitors, hepatoprotectants, 35 non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

In another embodiment, the present application provides pharmaceutical compositions comprising a compound of the present invention, or a pharmaceutically

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

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

- a) a first pharmaceutical composition comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate, or ester thereof; and
- 25 b) a second pharmaceutical composition comprising at least one additional therapeutic agent selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120
 30 inhibitors, CCR5 inhibitors, interferons, ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, cyclophilin inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV, and combinations thereof.

Combinations of the compounds of Formula I-III and additional active
 35 therapeutic agents may be selected to treat patients infected with HCV and other conditions such as HIV infections. Accordingly, the compounds of Formula I-III may be combined with one or more compounds useful in treating HIV, for example HIV

5 protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, interferons, ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, cyclophilin
 10 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

More specifically, one or more compounds of the present invention may be combined with one or more compounds selected from the group consisting of 1) HIV protease inhibitors, *e.g.*, amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir,
 15 ritonavir, lopinavir + ritonavir, nelfinavir, saquinavir, tipranavir, brexanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), AG1859, DG35, L-756423, RO0334649, KNI-272, DPC-681, DPC-684, and GW640385X, DG17, PPL-100, 2) a HIV non-nucleoside inhibitor of reverse transcriptase, *e.g.*, capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+)
 20 calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MIV-150, and TMC-120, TMC-278 (rilpivirine), efavirenz, BILR 355 BS, VRX 840773, UK-453,061, RDEA806, 3) a HIV nucleoside inhibitor of reverse transcriptase, *e.g.*, zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, racivir ($\pm$ -FTC), D-d4FC,
 25 emtricitabine, phosphazide, fozivudine tidoxil, fosaltivudine tidoxil, apricitibine (AVX754), amdoxovir, KP-1461, abacavir + lamivudine, abacavir + lamivudine + zidovudine, zidovudine + lamivudine, 4) a HIV nucleotide inhibitor of reverse transcriptase, *e.g.*, tenofovir, tenofovir disoproxil fumarate + emtricitabine, tenofovir disoproxil fumarate + emtricitabine + efavirenz, and adefovir, 5) a HIV integrase
 30 inhibitor, *e.g.*, curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, S-1360, zintevir (AR-177), L-870812, and L-
 35 870810, MK-0518 (raltegravir), BMS-707035, MK-2048, BA-011, BMS-538158, GSK364735C, 6) a gp41 inhibitor, *e.g.*, enfuvirtide, sifuvirtide, FB006M, TRI-1144, SPC3, DES6, Locus gp41, CovX, and REP 9, 7) a CXCR4 inhibitor, *e.g.*, AMD-070,

5 8) an entry inhibitor, *e.g.*, SP01A, TNX-355, 9) a gp120 inhibitor, *e.g.*, BMS-488043 and BlockAide/CR, 10) a G6PD and NADH-oxidase inhibitor, *e.g.*, immunitin, 10) a CCR5 inhibitor, *e.g.*, aplaviroc, vicriviroc, INCB9471, PRO-140, INCB15050, PF-232798, CCR5mAb004, and maraviroc, 11) an interferon, *e.g.*, pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, IFN alpha-2b XL, rIFN-alpha 2a,

10 consensus IFN alpha, infergen, rebif, locteron, AVI-005, PEG-infergen, pegylated IFN-beta, oral interferon alpha, feron, reaferon, intermax alpha, r-IFN-beta, infergen + actimmune, IFN-omega with DUROS, and albuferon, 12) ribavirin analogs, *e.g.*, rebetol, copegus, VX-497, and viramidine (taribavirin) 13) NS5a inhibitors, *e.g.*, A-831, A-689 and BMS-790052, 14) NS5b polymerase inhibitors, *e.g.*, NM-283,

15 valopicitabine, R1626, PSI-6130 (R1656), HCV-796, BILB 1941, MK-0608, NM-107, R7128, VCH-759, PF-868554, GSK625433, and XTL-2125, 15) NS3 protease inhibitors, *e.g.*, SCH-503034 (SCH-7), VX-950 (Telaprevir), ITMN-191, and BILN-2065, 16) alpha-glucosidase 1 inhibitors, *e.g.*, MX-3253 (celgosivir) and UT-231B, 17) hepatoprotectants, *e.g.*, IDN-6556, ME 3738, MitoQ, and LB-84451, 18) non-

20 nucleoside inhibitors of HCV, *e.g.*, benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, and phenylalanine derivatives, 19) other drugs for treating HCV, *e.g.*, zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), DEBIO-025, VGX-410C, EMZ-702, AVI 4065, bavituximab, oglufanide, PYN-17, KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975, XTL-6865, ANA 971,

25 NOV-205, tarvacin, EHC-18, and NIM811, 19) pharmacokinetic enhancers, *e.g.*, BAS-100 and SPI452, 20) RNAse H inhibitors, *e.g.*, ODN-93 and ODN-112, 21) other anti-HIV agents, *e.g.*, VGV-1, PA-457 (bevirimat), ampligen, HRG214, cytolin, polymun, VGX-410, KD247, AMZ 0026, CYT 99007, A-221 HIV, BAY 50-4798, MDX010 (iplimumab), PBS119, ALG889, and PA-1050040.

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

35 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

5 that therapeutically effective amounts of the compound of the invention and one or more other active therapeutic agents are both present in the body of the patient.

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

The combination therapy may provide "synergy" and "synergistic", i.e. the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or delivered sequentially, e.g. in separate tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, i.e. serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together. A synergistic anti-viral effect denotes an antiviral effect which is greater than the predicted purely additive effects of the individual compounds of the combination.

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

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

15 In still yet another embodiment, the present application provides for methods of inhibiting HCV polymerase in a cell, comprising: contacting a cell infected with HCV with an effective amount of a compound of Formula I-III, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent selected from the group consisting of interferons, ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

20 In still yet another embodiment, the present application provides for methods of treating HCV in a patient, comprising: administering to the patient a therapeutically effective amount of a compound of Formula I-III, or a pharmaceutically acceptable salt, solvate, and/or ester thereof.

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

30 In still yet another embodiment, the present application provides for methods of treating HCV in a patient, comprising: administering to the patient a therapeutically effective amount of a compound of Formula I-III, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent selected from the group consisting of interferons, ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, cyclophilin inhibitors,

- 5 hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

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

Metabolites of the Compounds of the Invention

 Also falling within the scope of this invention are the *in vivo* metabolic products of the compounds described herein, to the extent such products are novel and unobvious over the prior art. Such products may result for example from the
15 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
20 identified by preparing a radiolabelled (e.g. ^{14}C or ^3H) 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
25 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,
30 so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention even if they possess no HCV polymerase inhibitory activity of their own.

 Recipes and methods for determining stability of compounds in surrogate gastrointestinal secretions are known. Compounds are defined herein as stable in the
35 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

- 5 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.

10

Examples

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

Table 1. List of abbreviations and acronyms.

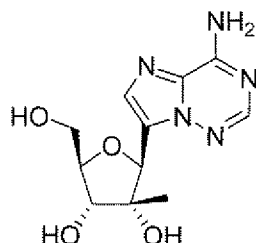
Abbreviation	Meaning
Ac ₂ O	acetic anhydride
AIBN	2,2'-azobis(2-methylpropionitrile)
Bn	benzyl
BnBr	benzylbromide
BSA	bis(trimethylsilyl)acetamide
BzCl	benzoyl chloride
CDI	carbonyl diimidazole
DABCO	1,4-diazabicyclo[2.2.2]octane
DBN	1,5-diazabicyclo[4.3.0]nonene-5
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DBU	1,5-diazabicyclo[5.4.0]undecene-5
DCA	dichloroacetamide
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMTCI	dimethoxytrityl chloride
DMSO	dimethylsulfoxide
DMTr	4, 4'-dimethoxytrityl

DMF	dimethylformamide
EtOAc	ethyl acetate
ESI	electrospray ionization
HMDS	hexamethyldisilazane
HPLC	High pressure liquid chromatography
LDA	lithium diisopropylamide
LRMS	low resolution mass spectrum
MCPBA	meta-chloroperbenzoic acid
MeCN	acetonitrile
MeOH	methanol
MMTC	mono methoxytrityl chloride
m/z or m/e	mass to charge ratio
MH ⁺	mass plus 1
MH ⁻	mass minus 1
MsOH	methanesulfonic acid
MS or ms	mass spectrum
NBS	N-bromosuccinimide
rt or r.t.	room temperature
TBAF	tetrabutylammonium fluoride
TMSCl	chlorotrimethylsilane
TMSBr	bromotrimethylsilane
TMSI	iodotrimethylsilane
TEA	triethylamine
TBA	tributylamine
TBAP	tributylammonium pyrophosphate
TBSCl	t-butyldimethylsilyl chloride
TEAB	triethylammonium bicarbonate
TFA	trifluoroacetic acid
TLC or tlc	thin layer chromatography
Tr	triphenylmethyl
Tol	4-methylbenzoyl
δ	parts per million down field from tetramethylsilane

5

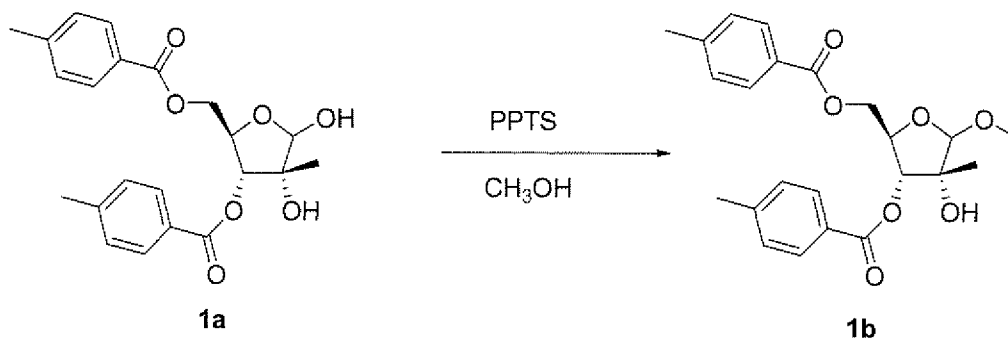
Preparation of Compounds

Compound 1



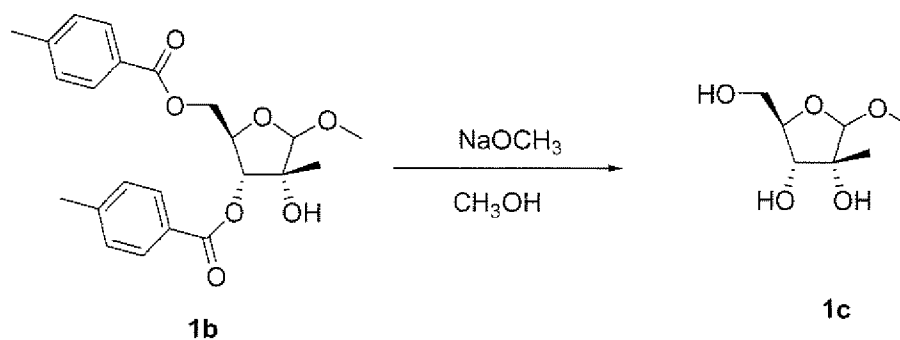
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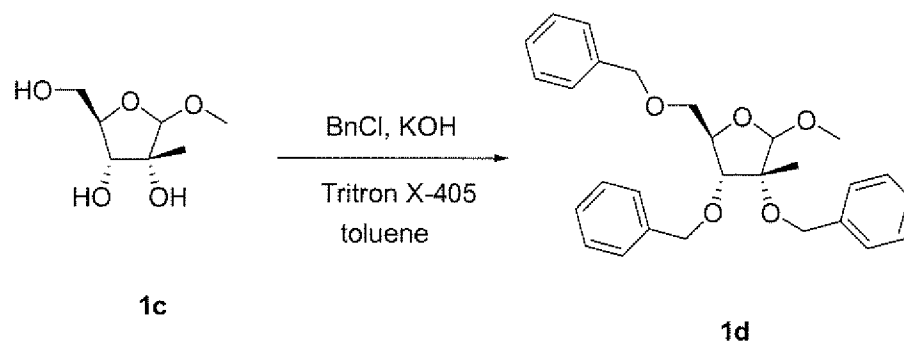


To a solution of **1a** (22.0 g, 54.9 mmol, prepared according to the procedures described in *J.O.C.*, **2004**, 6257) in methanol (300 mL) was dropwise added acetyl chloride (22 mL) at 0 °C using a dropping funnel over a period of 30 min. and then stirred at room temperature for 16 h. The mixture was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

20

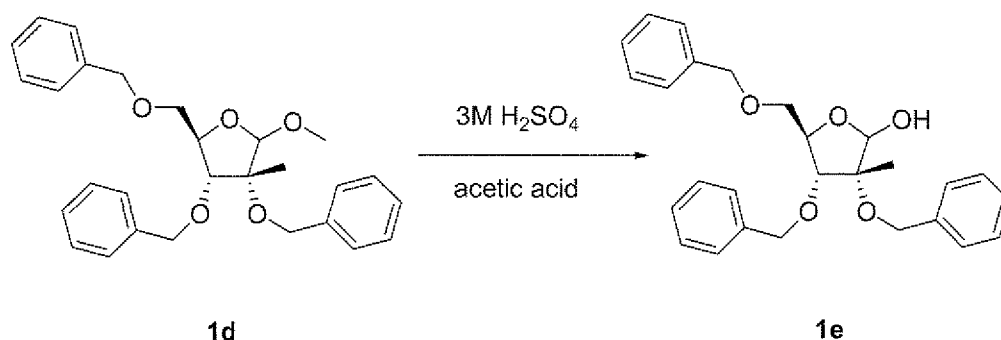


To a solution of **1b** (obtained from the previous step) in methanol (300 mL) was added 0.5 M sodium methoxide solution in methanol (20 mL, 10 mmol), and stirred for 16 h at room temperature. The reaction was quenched with 4.0 N HCl solution in dioxane (2.5 mL, 10 mmol). The mixture was then concentrated,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



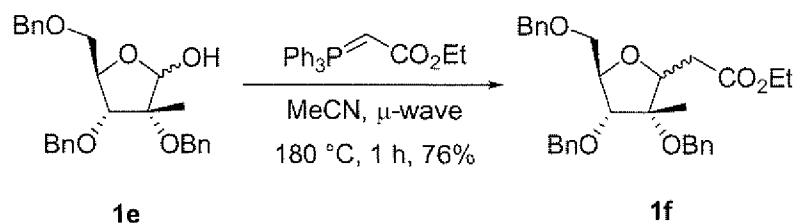
A mixture of **1c** (obtained from the previous step), Triton X-405 (70% in water, 6.0 g), 50% KOH (in water, 85 g) in toluene (500 mL) was heated to reflux with a Dean-Stark trap attached. After 1h collecting ~25 mL of water, benzyl chloride (33 g, 260 mmol) was added and continued to reflux with stirring for 16 h. The mixture was then cooled and partitioned between ethyl acetate (400 mL) and water (300mL). The organic layer was washed with water (300 mL), and concentrated. The residue was purified by silica gel column chromatography (~20% EtOAc / hexanes), affording the methyl ether **1d** as an oil (22.0 g, 89% in three steps).

¹H NMR (300 MHz, CDCl₃): δ 7.3 (m, 15H), 4.5 - 4.9 (m, 7H), 4.37 (m, 1H), 3.87 (d, 1H), 3.56 (m, 2H), 3.52 (s, 3H), 1.40 (s, 3H).

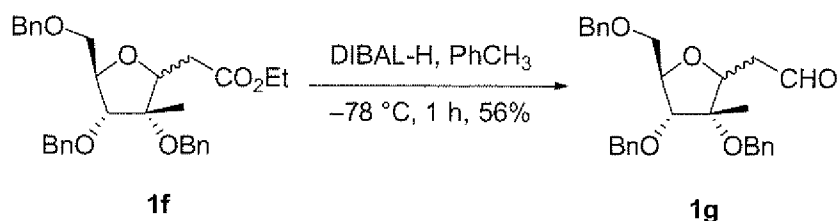


To a solution of **1d** (22.0 g, 49.0 mmol) in acetic acid (110 mL) was added ~ 3 M sulfuric acid (prepared by mixing 4.8 g of concentrated sulfuric acid with 24 mL of

5 water) and stirred at 70 °C for 8 h. The mixture was concentrated to a volume of ~20 mL, and partitioned between ethyl acetate and ice-cold 2N NaOH. The ethyl acetate layer was concentrated, and purified by silica gel column chromatography (~35% EtOAc / hexanes), affording **1e** as an oil (17.0 g, 80%). MS = 457.2 (M+Na⁺).

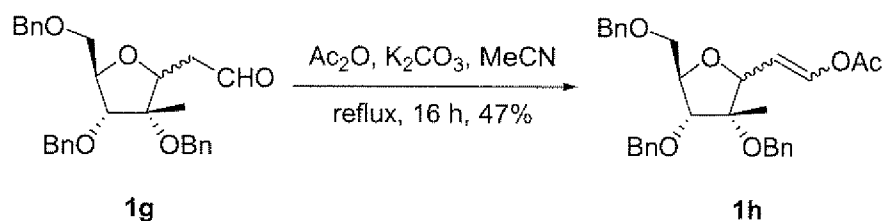


1e (4.58 g, 10.6 mmol) was dissolved in MeCN (7 mL), and the solution was transferred to a micro-wave tube. The tube was charged with (carbethoxymethylene)triphenylphosphorane (7.33 g, 21.2 mmol) and sealed under Ar. The mixture was subjected to micro-wave heating at 180 °C for 1 h. The solvent was removed in vacuo and the mixture was stirred with Et₂O (50 mL) for 15 min. The resulting solid was filtered, washed with Et₂O (3 × 10 mL), and the solvent was removed in vacuo. The mixture was treated to 120 g SiO₂ Combiflash column chromatography (0–30% EtOAc–hexanes gradient) to afford **1f** (4.04 g, 76%) as a mixture of isomers: clear oil; MS (ESI) *m/z* 527 [M + Na⁺].

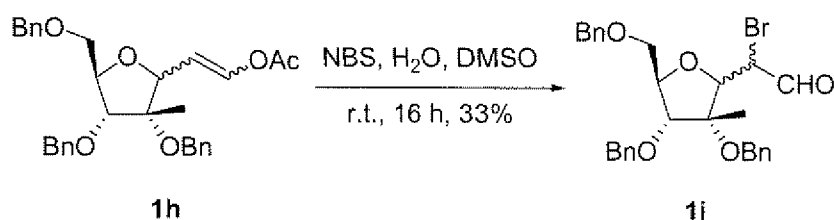


1f (69.18 g, 137 mmol) in PhCH₃ (540 mL) was cooled to –78 °C and treated with DIBAL-H (1.0 M in hexanes, 151 mL, 151 mmol). The solution was stirred for 1 h, MeOH (500 mL) was added, and the solution was warmed to room temperature. The mixture was filtered through Celite and the solids were washed with Et₂O (3 × 100 mL). The solvent was removed in vacuo and the mixture was filtered through a coarse fritted glass filter. The mixture was treated to 330 g SiO₂ Combiflash column chromatography (0–30% EtOAc–hexanes gradient) to afford **1g** (35.46 g, 56%) as a

- 5 mixture of isomers (data for both isomers): clear oil; ^1H NMR (CDCl_3 , 300 MHz) 9.76 (s, 1/2H), 9.73 (s, 1/2H), 7.26 (br m, 15H), 4.86 (d, $J = 11.1$ Hz, 2H), 4.50 (m, 13H), 4.21 (m, 3H), 3.88 (d, $J = 6.9$ Hz, 1H), 3.60 (m, 5H), 2.75 (m, 2H), 2.50 (m, 2H), 1.36 (s, 3/2H), 1.19 (s, 3/2H).

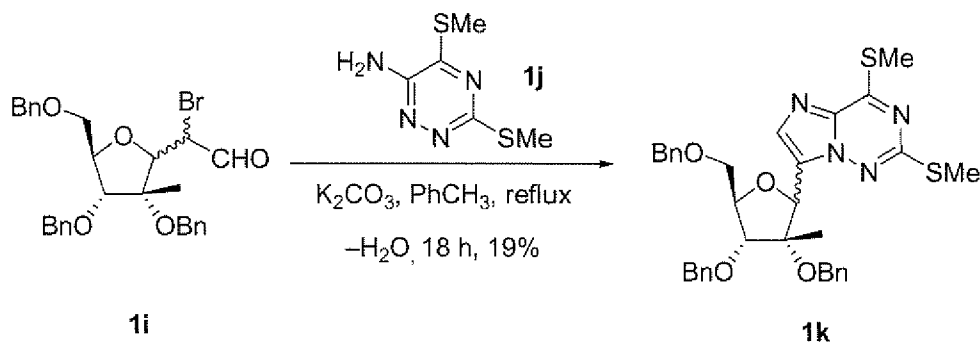


- 10 **1g** (20.0 g, 43.4 mmol) in MeCN (200 mL) was treated with K_2CO_3 (24.0 g, 173 mmol) and Ac_2O (16.4 mL, 173 mmol) and the mixture was stirred at reflux for 16 h. The mixture was cooled and filtered through a coarse fritted glass filter and the solids washed with MeCN (3×25 mL). The solvent was removed in vacuo and the mixture was suspended in DCM (100 mL) and filtered through a medium fritted glass filter. The mixture was treated to 330 g SiO_2 Combiflash column chromatography (0–30% EtOAc–hexanes gradient) to afford **1h** (10.3 g, 47%) as a mixture of isomers (data for all isomers): clear oil; ^1H NMR (CDCl_3 , 300 MHz) 7.30 (br m, 15H), 5.44 (m, 1H), 4.99 (br m, 1H), 4.60 (m, 7H), 4.21 (m, 1H), 3.72 (m, 1H), 3.62 (m, 1H), 2.11 (s, 3H), 2.03 (2, 3H), 1.31 (s, 3H), 1.26 (s, 3H); MS (ESI) m/z 501 $[\text{M} - \text{H}]^-$.

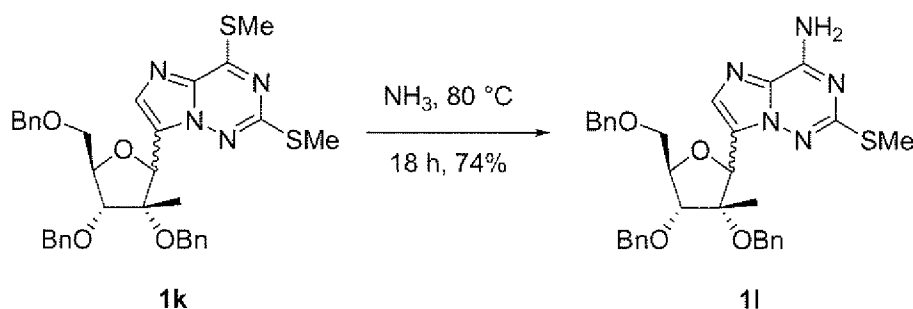


- 25 **1h** (12.6 g, 25.1 mmol) in DMSO (100 mL) was treated with H_2O (904 μL , 50.2 mmol) and recrystallized NBS (8.93 g, 50.2 mmol), and the mixture was stirred for 16 h. The mixture was treated with saturated NaHCO_3 (50 mL), and the solution was extracted with EtOAc (250 mL). The organic layer was washed with H_2O (3×50 mL) and dried over MgSO_4 . The solvent was removed in vacuo and the mixture was
30 was treated to 330 g SiO_2 Combiflash column chromatography (0–25% EtOAc–

- 5 hexanes gradient) to afford **1i** (4.53 g, 33%) as a mixture of isomers (data for all isomers): yellow oil; ^1H NMR (CDCl_3 , 300 MHz) 9.35 (d, $J = 5.1$ Hz, 1/2H), 9.33 (d, $J = 6.0$ Hz, 1/2H), 9.27 (s, 1H), 9.25 (s, 1H), 7.26 (br m, 15H), 3.50–4.61 (complex m, 12H), 1.32 (s, 3/2H), 1.25 (s, 3/2H).

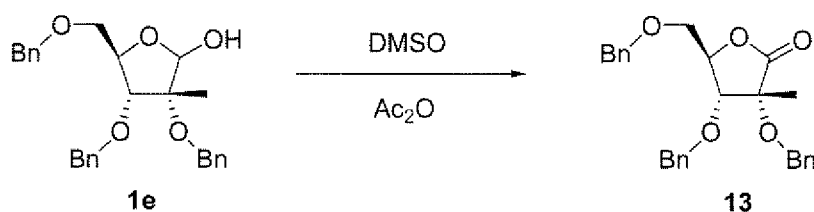


- 1i** (4.5 g, 8.3 mmol) in PhCH_3 (250 mL) was treated with **1j** (1.6 g, 8.3 mmol; prepared according to the procedure found in *J. Chem. Soc., Perkin Trans. 1* **1999**, 2929–2936) and K_2CO_3 (1.4 g, 10 mmol) and the mixture stirred at reflux with
- 15 removal of water for 16 h. The mixture was cooled and filtered through a medium fritted glass filter and the solids washed with EtOAc (3×10 mL). The solvent was removed in vacuo and the mixture was treated to 120 g SiO_2 Combiflash column chromatography (0–40% EtOAc–hexanes gradient) to afford **1k** (1.0 g, 19%) as a mixture of isomers (data for major β -isomer): pale yellow solid; ^1H NMR (CDCl_3 ,
- 20 300 MHz) 7.78 (s, 1H), 7.26 (br m, 15H), 5.71 (s, 1H), 4.74 (s, 2H), 4.59 (m, 4H), 4.35 (br m, 1H), 4.00 (d, $J = 8.1$ Hz, 1H), 3.83 (d, $J = 8.7$ Hz, 1H), 3.66 (d, $J = 10.8$ Hz, 1H), 2.63 (s, 3H), 2.45 (s, 3H), 1.05 (s, 3H); MS (ESI) m/z 629 $[\text{M} + \text{H}]^+$.

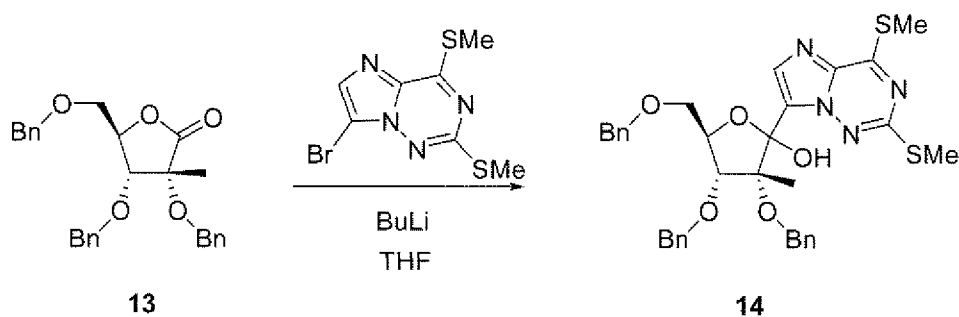


1k (1.0 g, 1.59 mmol) was treated with liquid NH₃ (20 mL) and the mixture was stirred at 80 °C for 16 h in a steel bomb. The mixture was cooled, NH₃ was removed, and the mixture was treated to 120 g SiO₂ Combiflash column chromatography (0–70% EtOAc–hexanes gradient) to afford **1l** (707 mg, 74%) as a mixture of isomers (data for major β-isomer): pale yellow solid; ¹H NMR (CDCl₃, 300 MHz) 7.81 (s, 1H), 7.26 (br m, 15H), 5.71 (s, 1H), 4.74 (s, 2H), 4.58 (m, 4H), 4.40 (m, 1H), 4.06 (d, *J* = 7.2 Hz, 1H), 3.83 (d, *J* = 11.4 Hz, 1H), 3.68 (d, *J* = 10.2 Hz, 1H), 2.47 (s, 3H), 1.18 (s, 3H); MS (ESI) *m/z* 598 [M + H]⁺.

Alternative Synthesis of 11



To a dry, argon purged round bottom flask (100 mL) were added anhydrous DMSO (6 mL) and anhydrous acetic anhydride (4 mL, 42.4 mmol). Compound **1e** (1.0 g, 2.3 mmol) was then added and the reaction mixture was allowed to stir at room temperature until complete disappearance of the starting material. After 17 h, the flask was placed into an ice bath and sat. NaHCO₃ (6 mL) was added to neutralize the reaction. The organic material was then extracted using EtOAc (3 x 10 mL) and the combined organic layers were dried using MgSO₄. The solvent was removed under reduced pressure and the crude material was purified using flash chromatography (hexanes / EtOAc). 955 mg (96 %) of the desired material **13** was isolated. LC/MS = 433.2 (M + H⁺). ¹H NMR (300 MHz, CDCl₃): δ 7.33 (m, 15H), 4.80 (d, 1H), 4.64 (m, 6H), 4.06 (d, 1H), 3.79 (dd, 1H), 3.64 (dd, 1H), 1.54 (s, 3H).

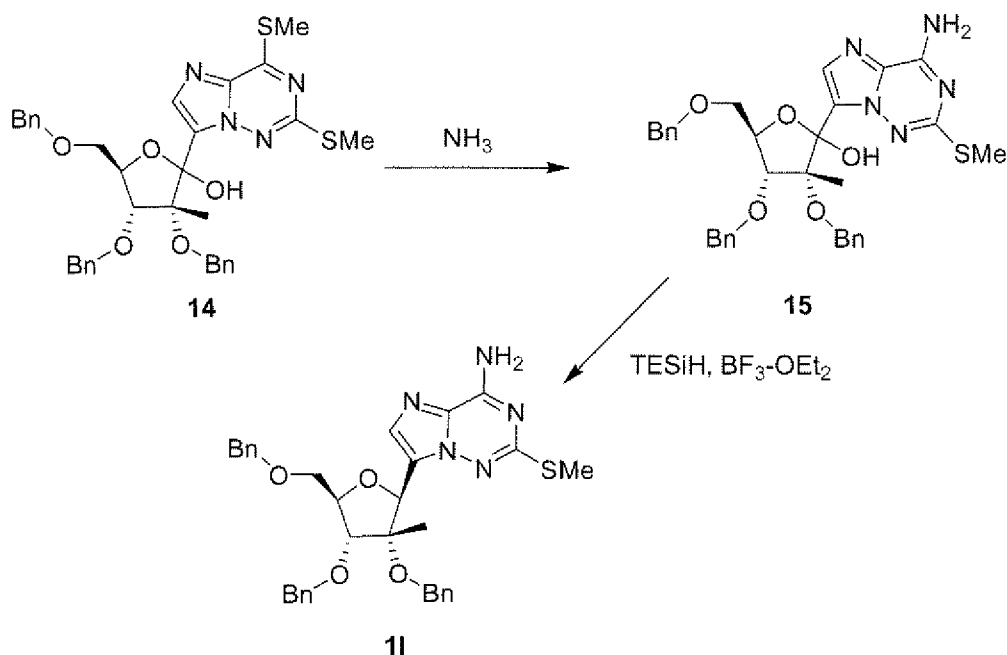


5

To a suspension of 7-bromo-2,4-bis-methylsulfanyl-imidazo[2,1-f][1,2,4]triazine (prepared according to WO2008116064, 600 mg, 2.06 mmol) in anhydrous THF (6 mL) was dropwise added BuLi (1.6 M in hexanes, 1.75 mL, 2.81 mmol) at -78 °C. The suspension became red brown solution after 5 min, and then **13** (810 mg, 1.87 mmol) in THF (0.6 mL) was added dropwise to the mixture. The mixture was then allowed to warm up to room temperature. After 30 min, saturated NH₄Cl was added to quench the reaction. The mixture was diluted with ethyl acetate. The organic layer was washed with brine and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (~40% EtOAc / hexanes), affording **14** as an isomeric mixture (0.77 g, 64%). MS = 645.2 (M + H⁺).

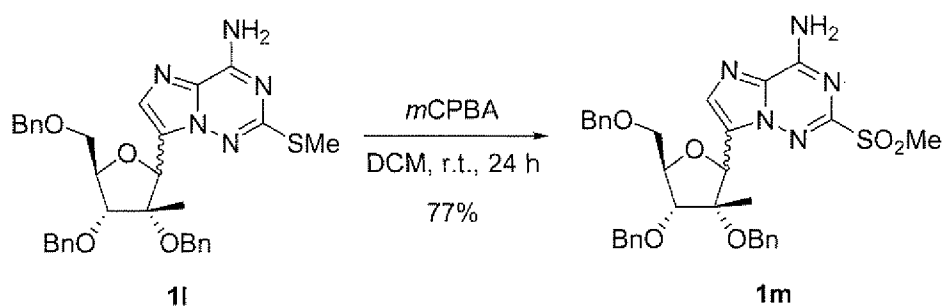
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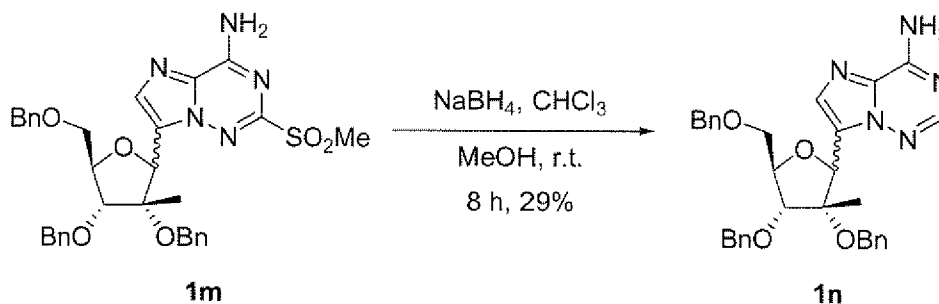
20

5 Compound **14** (2.0 g, 3.10 mmol) was transferred to a steel bomb reactor and cooled down to -78°C . Liquid ammonia (~ 20 mL) was collected at -78°C and added to the bomb reactor. The bomb reactor was tightly sealed and warmed up to room temperature and then heated at 50°C for 20 h. The reaction was complete. After the gas was vented, the residue was purified by silica gel column chromatography (EtOAc / hexanes), affording **15** as a pale yellow solid (1.78 g, 94%). To the product in CH_2Cl_2 (15 mL) at -78°C was added boron trifluoride diethyl etherate (2.2 mL, 17.4 mmol) and triethylsilane (2.8 mL, 17.4 mmol). The mixture was then allowed to stir at 0 to 10°C for 3 h. Saturated aqueous NaHCO_3 was added slowly to quench the reaction, and then CH_2Cl_2 was added to dilute the mixture. The organic layer was washed with brine and concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($\sim 50\%$ EtOAc / hexanes), affording **11** as a white solid (0.81 g, 47%). ^1H NMR (300 MHz, CDCl_3): δ 7.67 (s, 1H), 7.20-7.45 (m, 15H), 5.77 (s, 1H), 4.80-4.92 (m, 2H), 4.57-4.72 (m, 4H), 4.43 (d, $J = 7.8$ Hz, 1H), 4.08 (d, $J = 8.7$ Hz, 1H), 3.95 (d, $J = 10.8$ Hz, 1H), 3.74 (d, $J = 10.8$ Hz, 1H), 2.48 (s, 3H), 1.16 (s, 3H). MS = 598.3 ($\text{M} + \text{H}^+$).



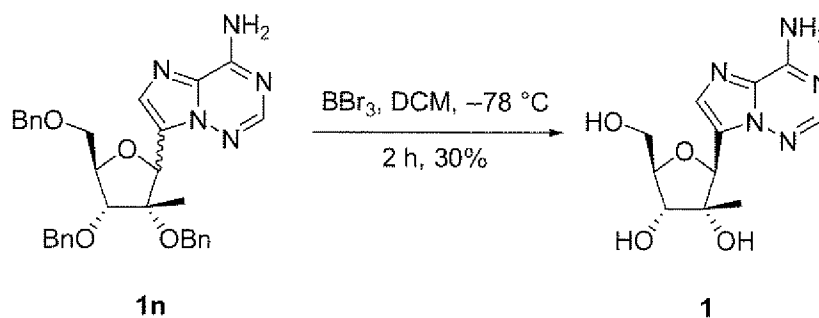
25 **11** (707 mg, 1.18 mmol) in DCM (20 mL) was treated with *m*CPBA (460 mg, 2.66 mmol) and the mixture stirred for 16 h. Additional *m*CPBA (203 mg, 1.18 mmol) was added and the mixture was stirred for 8 h. The mixture was treated with saturated NaHCO_3 (10 mL), and the solution was extracted with EtOAc (250 mL). The organic layer was washed with saturated NaHCO_3 (10 mL) and brine (10 mL) and dried over MgSO_4 . The solvent was removed in *vacuo* and the mixture was treated to 40 g SiO_2 Combiflash column chromatography (0–100% EtOAc–hexanes gradient) to afford **1m** (571 mg, 77%) as a mixture of isomers (data for major β -isomer): white solid; ^1H

- 5 NMR (CDCl₃, 300 MHz) 7.77 (s, 1H), 7.26 (br m, 15H), 5.61 (s, 1H), 4.59 (m, 6H), 4.35 (br m, 1H), 4.00 (d, $J = 7.2$ Hz, 1H), 3.83 (d, $J = 8.7$ Hz, 1H), 3.70 (d, $J = 10.8$ Hz, 1H), 3.06 (s, 3H), 1.05 (s, 3H); MS (ESI) m/z 630 $[M + H]^+$.



10

- 1m** (565 mg, 0.90 mmol) in 1:1 MeOH–CHCl₃ (18 mL) was treated with NaBH₄ (68 mg, 1.8 mmol) and the mixture stirred for 1 h. Additional NaBH₄ (170 mg, 4.5 mmol) was added and the mixture was stirred for 2 h. Additional NaBH₄ (340 mg, 9.0 mmol) was added and the mixture was stirred for 2 h. The mixture was
- 15 treated with H₂O (10 mL), and the solution was extracted with EtOAc (100 mL). The organic layer was washed with saturated NaHCO₃ (10 mL) and brine (2 × 10 mL) and dried over MgSO₄. The solvent was removed in vacuo and the mixture was treated to 40 g SiO₂ Combiflash column chromatography (0–100% EtOAc–hexanes gradient) to afford **1n** (144 mg, 29%) as a mixture of isomers (data for major β -isomer): white
- 20 solid; ¹H NMR (CDCl₃, 300 MHz) 8.08 (s, 1H), 7.87 (s, 1H), 7.26 (br m, 15H), 5.63 (s, 1H), 4.76 (m, 2H), 4.62 (m, 6H), 4.36 (br m, 1H), 4.00 (d, $J = 7.2$ Hz, 1H), 3.81 (m, 1H), 3.63 (m, 1H), 1.07 (s, 3H); MS (ESI) m/z 552 $[M + H]^+$.

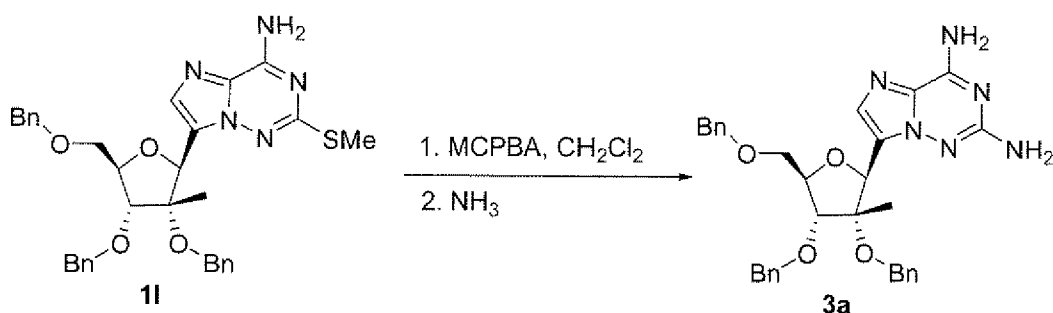
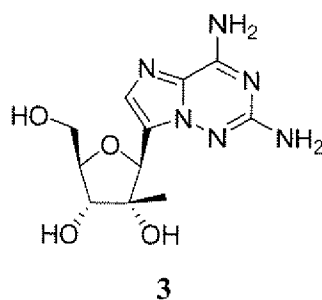


25

- 1n** (144 mg, 0.26 mmol) in DCM (5.2 mL) was cooled to –78 °C and treated with BBr₃ (1.0 M in DCM, 1.3 mL, 1.3 mmol) and the mixture stirred for 2 h. The

5 mixture was treated with 4:1 MeOH–pyridine (500 μ L) and the solution was warmed to room temperature. The solvent was removed in vacuo and the mixture was treated with concentrated NH_4OH (2 mL) followed by removal of solvent ($\times 3$). The mixture was treated to reverse phase HPLC (0–95% MeCN– H_2O gradient) to afford **1** (21 mg, 30%): white solid; ^1H NMR (D_2O , 300 MHz) 7.85 (s, 1H), 7.45 (s, 1H), 5.26 (s, 1H),
 10 3.82 (m, 2H), 3.78 (m, 1H), 3.68 (dd, $J = 12.6, 4.5$ Hz, 1H), 0.81 (s, 3H); MS (ESI) m/z 282 $[\text{M} + \text{H}]^+$.

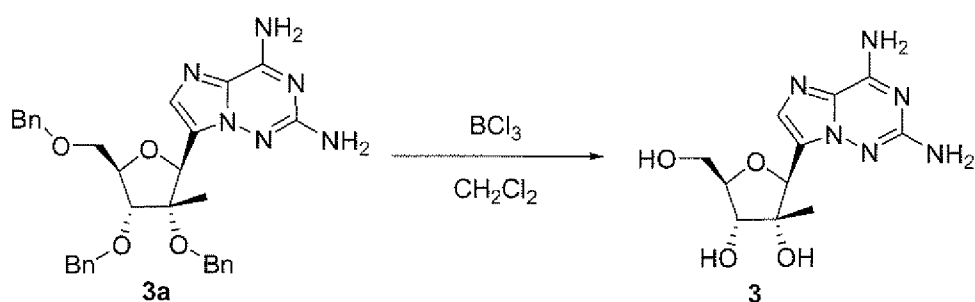
Compound 3



20 To a solution of **11** (0.81 g, 1.36 mmol) in CH_2Cl_2 (7 mL) at 0 $^\circ\text{C}$ was added MCPBA (610 mg, 2.72 mmol). The mixture was stirred at 0 $^\circ\text{C}$ for 3 h. 1 M $\text{Na}_2\text{S}_2\text{O}_3$ in H_2O (2 mL) was added to quench the reaction. After stirring at room temperature for 10 min, the organic layer was washed with saturated aqueous Na_2CO_3 (10 mL $\times$ 2),
 25 brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was then transferred to a steel bomb reactor and cooled at -78 $^\circ\text{C}$. Liquid ammonia (~ 10 mL) was collected at -78 $^\circ\text{C}$ and added to the bomb reactor. The bomb reactor was tightly sealed and warmed up to room temperature. The mixture was then heated at 110 $^\circ\text{C}$ for 48 h. The reaction was complete. The residue was purified by silica gel column

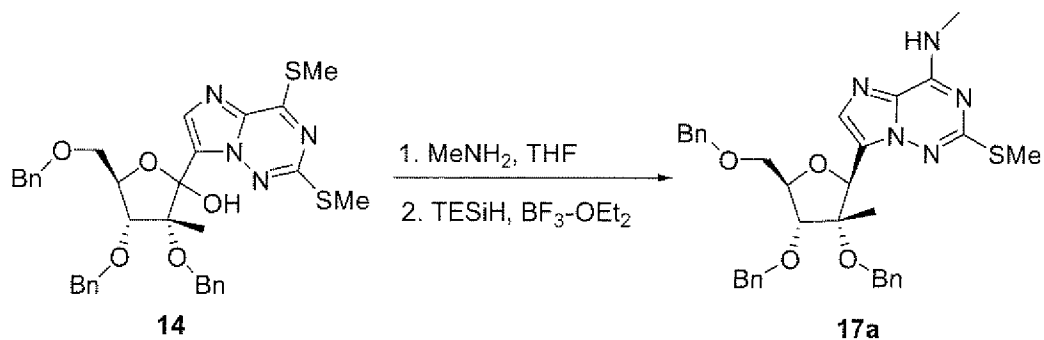
5 chromatography (100% EtOAc / hexanes), affording **3a** as a white solid (0.63 g, 74%). ¹H NMR (300 MHz, CDCl₃): δ 7.55 (s, 1H), 7.20-7.45 (m, 15H), 5.65 (s, 1H), 4.50-4.82 (m, 6H), 4.38-4.42 (m, 1H), 4.05 (d, *J* = 7.8 Hz, 1H), 3.87 (d, *J* = 9.9 Hz, 1H), 3.71 (d, *J* = 8.4 Hz, 1H), 1.17 (s, 3H). MS = 567.3 (M + H⁺).

10



To a solution of **3a** (61 mg, 0.11 mmol) in CH₂Cl₂ (1 mL) at -78 °C was added boron trichloride (1 M in CH₂Cl₂, 1.5 mL, 1.5 mmol). The reaction mixture was stirred at -78 °C for 3 h, and then quenched by addition of pyridine / MeOH (1: 2, 14 mL). The mixture was then allowed to warm up to room temperature. The mixture was concentrated to remove all the solvents. The residue was then co-evaporated with MeOH (5 mL x 3), and then with 27% aqueous NH₄Cl (5 mL x 3). The crude was purified by RP-HPLC (MeCN–H₂O gradient) to give **Compound 3** as a white solid (16.8 mg). ¹H NMR (300 MHz, D₂O): δ 7.31 (s, 1H), 5.20 (s, 1H), 3.82-3.88 (m, 3H), 3.68-3.71 (m, 1H), 0.89 (s, 3H). MS = 297.2 (M + H⁺).

Compound 17

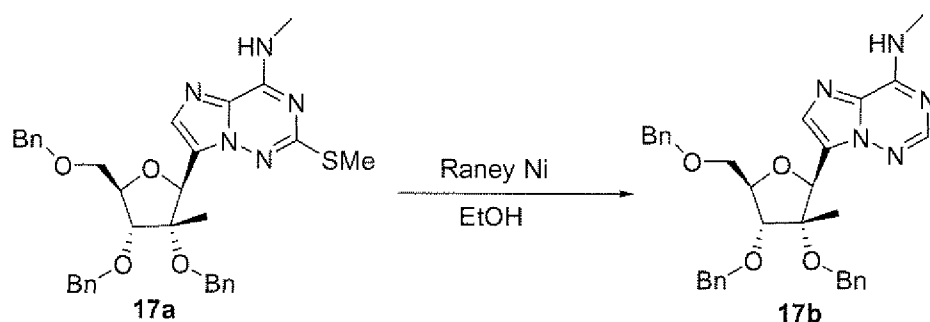


5 To a solution of **14** (120 mg, 0.186 mmol) in THF (0.5 mL) was added methylamine (2 M in THF, 0.46 mL, 0.92 mmol). The sealed reaction mixture was heated at 45 °C for 15 min. The mixture was concentrated *in vacuo* and further dried under high vacuum. To the crude in CH₂Cl₂ (1 mL) at -78 °C was added boron trifluoride diethyl etherate (136 uL, 1.086 mmol) and triethylsilane (174 uL, 1.086

10 mmol). The mixture was then allowed to stir at 0 to 10 °C for 3 h. Saturated aqueous NaHCO₃ was added slowly to quench the reaction, and then CH₂Cl₂ was added to dilute the mixture. The organic layer was washed with brine and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (~50% EtOAc / hexanes), affording **17a** as a white solid (74 mg, 67% over 2 steps). ¹H NMR (300

15 MHz, CDCl₃): δ 7.83 (b, 1H), 7.63 (s, 1H), 7.20-7.45 (m, 15H), 5.76 (s, 1H), 4.80-4.92 (m, 2H), 4.57-4.72 (m, 4H), 4.42 (d, *J* = 8.4 Hz, 1H), 4.08 (d, *J* = 8.4 Hz, 1H), 3.93 (d, *J* = 10.5 Hz, 1H), 3.72 (d, *J* = 11.1 Hz, 1H), 2.50 (s, 3H), 1.15 (s, 3H). MS = 612.3 (M + H⁺).

20

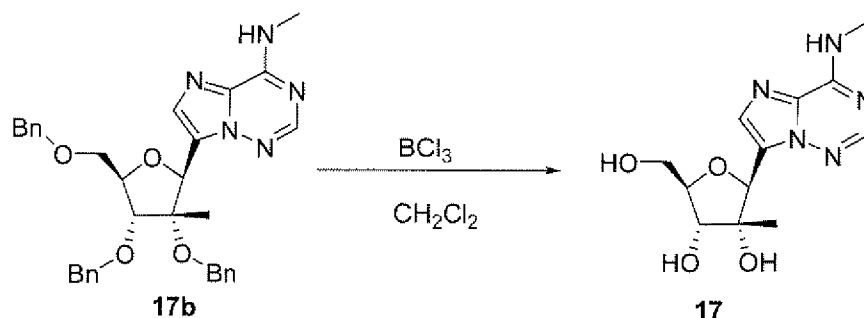


To compound **17a** (180 mg, 0.29 mmol) in ethanol (10 mL) was added Raney Ni (~500 mg) which was neutralized by washing with water. The mixture was then

25 heated at 80 °C for 4 h. The catalyst was removed by filtration and rinsed with MeOH (5 mL x 6). The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (~50% EtOAc / hexanes), affording **17b** as a white solid (118 mg, 71%). ¹H NMR (300 MHz, CD₃OD): δ 8.10 (s, 1H), 7.63 (s, 1H), 7.20-7.45 (m, 15H), 5.69 (s, 1H), 4.54-4.80 (m, 6H), 4.27-4.32 (m, 1H), 4.15 (d, *J* = 8.1 Hz, 1H), 3.84-3.89 (m, 1H), 3.70-3.76 (m, 1H), 3.11 (s, 3H), 1.09 (s, 3H). MS = 566.3 (M + H⁺).

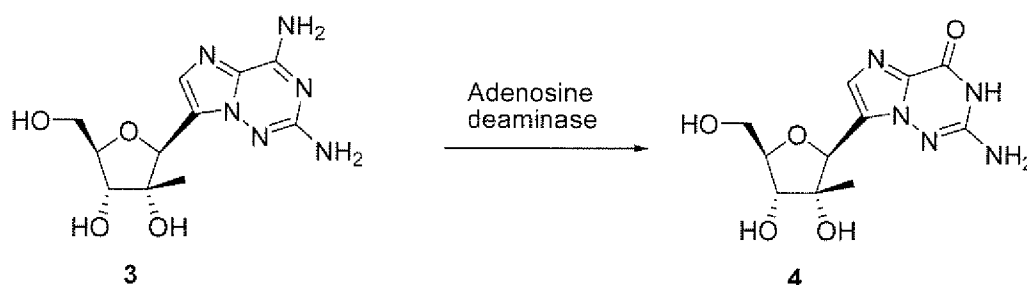
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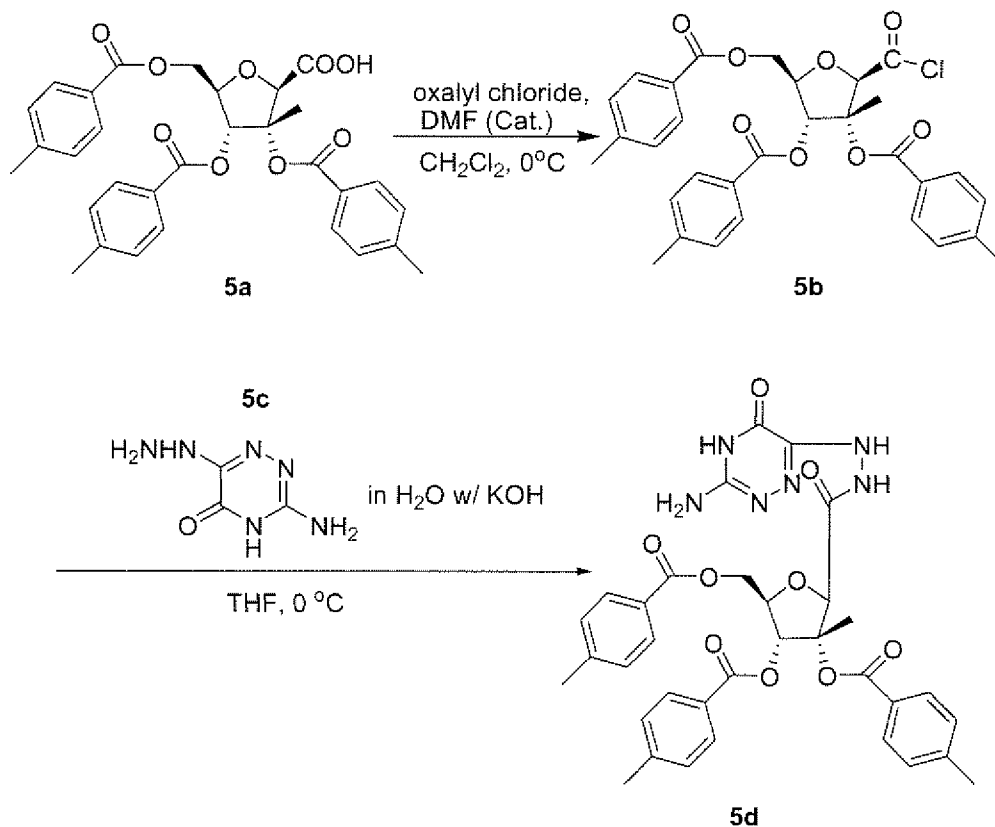
To a solution of **17b** (117 mg, 0.207 mmol) in CH_2Cl_2 (4 mL) at -78°C was added boron trichloride (1 M in CH_2Cl_2 , 3.2 mL, 3.2 mmol). The reaction mixture was stirred at -78°C for 3 h, and then quenched by addition of pyridine / MeOH (1: 2, 20 mL). The mixture was then allowed to warm up to room temperature. The mixture was concentrated to remove all the solvents. The residue was then co-evaporated with MeOH (10 mL x 3), and then with 27% aqueous NH_4Cl (10 mL x 3). The crude was purified by RP-HPLC (MeCN- H_2O gradient) to give **Compound 17** as a white solid (45 mg, 74%). ^1H NMR (300 MHz, CD_3OD): δ 8.11 (s, 1H), 7.62 (s, 1H), 5.44 (s, 1H), 3.90-4.00 (m, 3H), 3.73-3.84 (m, 1H), 3.13 (s, 3H), 1.00 (s, 3H). MS = 296.1 ($\text{M} + \text{H}^+$).

Compound 4

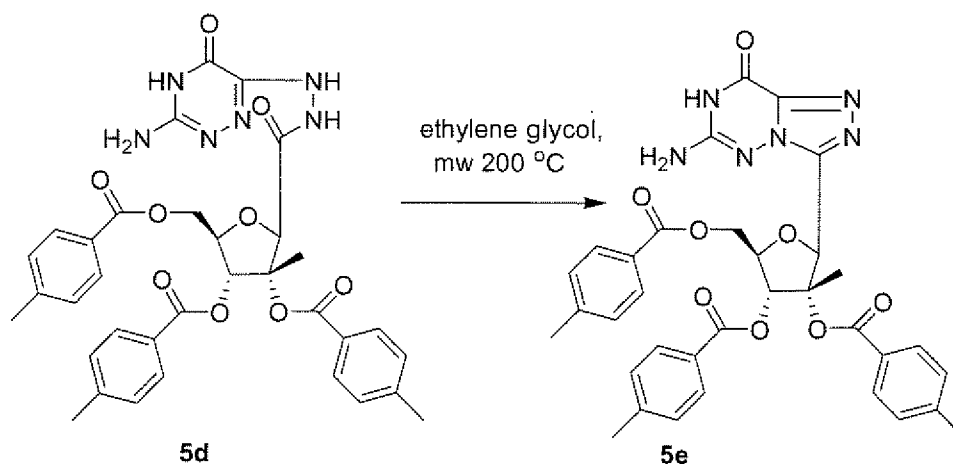


A solution of **3** (220 mg) in about 1000 mL of water was treated with bovin spleen type IX adenosine deaminase (0.125 units/mL, Sigma) at 37°C for 4 hours. The mixture was concentrated and the residue purified by RP-HPLC to give **Compound 4** (152 mg). ^1H NMR (300 MHz, D_2O): δ 7.34 (s, 1H), 5.21 (s, 1H), 3.82-3.87 (m, 3H), 3.70 (d, 1H), 0.93 (s, 3H), 1.00 (s, 3H). MS = 298.1 ($\text{M} + \text{H}^+$).

5 Compound 5



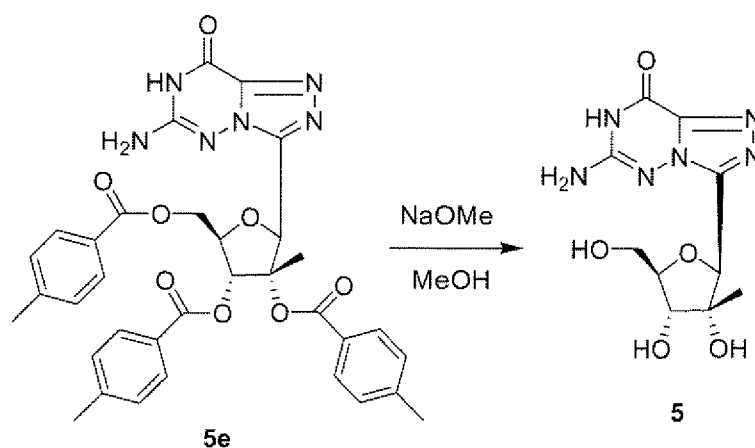
To a solution of **5a** (1.27 g, 2.32 mmol, prepared according to the procedures
 10 similar to those described in *Synthetic Communications*, **1992**, 2815) in
 dichloromethane (30 ml) at 0°C was dropwise added oxalyl chloride (275 μl),
 followed by addition of 3 drops of DMF. The mixture was left stirring at room
 temperature for 1.5 h. The solvents were then removed *in vacuo*. The residue was
 co-evaporated with toluene. The crude **5b** was dissolved in anhydrous THF (43 mL)
 15 and added dropwise to a cooled ($0-5^\circ\text{C}$) solution of **5c** in water (4.3 mL) containing
 potassium hydroxide (278 mg, 4.2 mmol) over a period of 30 min with stirring.
 Chloroform was added to extract the mixture. The organic layer was concentrated *in*
vacuo. The residue was purified by RP HPLC (acetonitrile/water), affording **5d** (0.41
 g, 34%) as a white solid. MS = 671.5 ($\text{M} + \text{H}^+$).



5

A solution of **5d** (200 mg, 0.30 mmol) in ethylene glycol (5.5 ml) in a sealed microwave tube was subjected to microwave at 200 °C for 2.5 h. The mixture was diluted with MeOH and purified by RP HPLC (acetonitrile/water), affording **5e** (80 mg, 41%) as a white solid. NMR (300 MHz, CD₃OD): δ 7.95 (d, J = 7.8 Hz, 2H), 7.92 (d, J = 7.8 Hz, 2H), 7.79 (d, J = 8.1 Hz, 2H), 7.26 (d, J = 7.8 Hz, 2H), 7.21 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 7.5 Hz, 2H), 6.01 (s, 1H), 5.97 (d, J = 4.8 Hz, 1H), 4.72-4.84 (m, 2H), 4.60-4.68 (m, 1H), 2.40 (s, 3H), 2.37 (s, 3H), 2.36 (s, 3H), 1.74 (s, 3H). MS = 653.5 ($M + H^+$).

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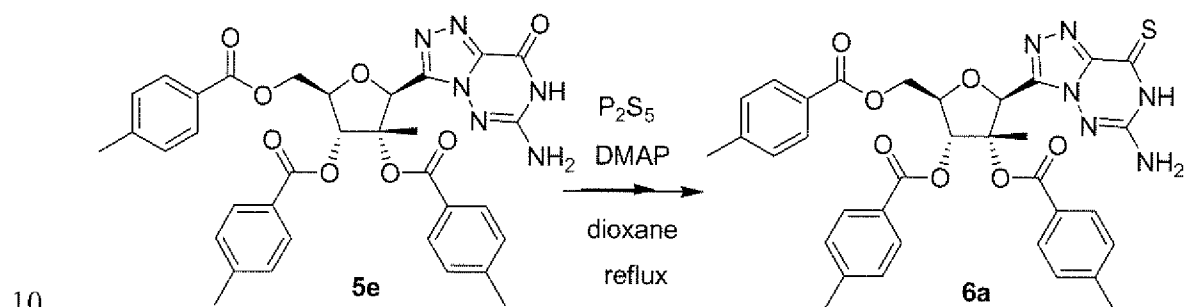
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To a solution of **5e** (80 mg, 0.12 mmol) in anhydrous methanol (4 mL) was added 1 M sodium methoxide solution in methanol (150 μ l), and stirred for 18 h at room temperature. 1.0 N HCl aqueous solution was added to adjust pH to 7. The mixture was purified by RP HPLC (acetonitrile/water), affording **5** (30 mg, 84%) as a

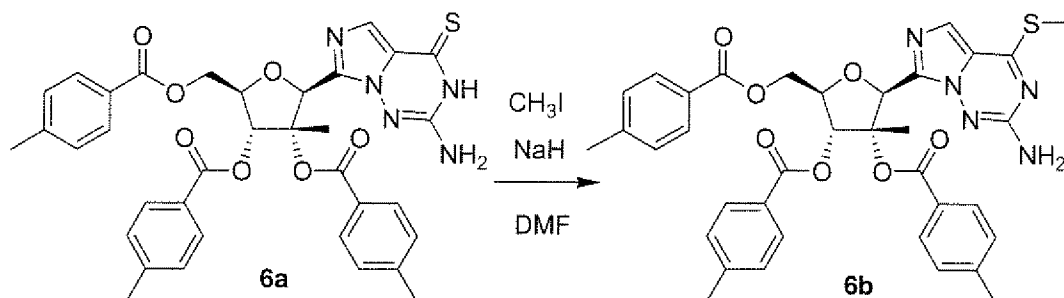
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- 5 white solid. ^1H NMR (300 MHz, CD_3OD): δ 5.28 (s, 1H), 3.9-4.0 (m, 2H), 3.86 (d, J = 8.7Hz, 1H), 3.72-3.78 (m, 1H), 0.93 (s, 3H). MS = 299.0 ($\text{M} + \text{H}^+$).

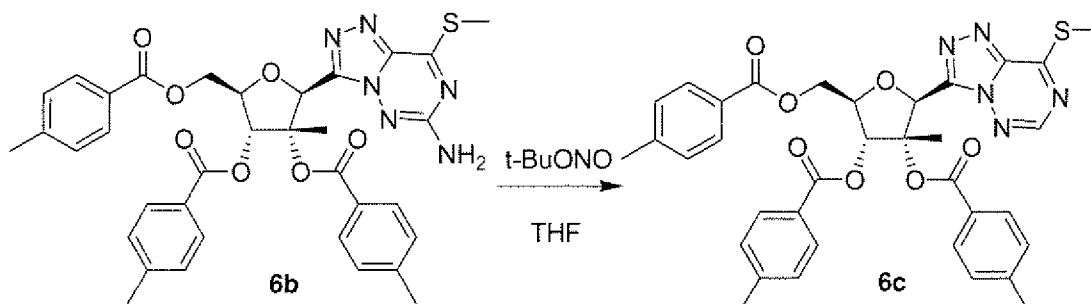
Compound 6



- To a dry, argon purged round bottom flask (100 mL) were added **5e** (220 mg, 0.34 mmol) and anhydrous dioxane (20 mL). P_2S_5 (200 mg, 0.44 mmol) and DMAP (28 mg, 0.23 mmol) were then added and the reaction mixture was heated to a gentle reflux for 25 min. Another portion of P_2S_5 (200 mg, 0.44 mmol) was added and the reaction refluxed for an additional 45 min. The reaction was then cooled to room temp and poured into an Erlenmeyer flask containing ice water (10 mL). The organic material was extracted with chloroform after saturating the aqueous solution with
- 20 NaCl. The combined organic layers were dried using MgSO_4 and the solvent removed under reduced pressure. The crude material was purified using flash chromatography (Hexanes / EtOAc). 200 mg (88 %) of the desired material **6a** was isolated. LC/MS = 669.2 ($\text{M} + \text{H}^+$). ^1H NMR (300 MHz, CDCl_3): δ 7.99 (m, 2H), 7.89 (m, 4H), 7.19 (m, 2H), 7.16 (t, 4H), 6.31 (s, 1H), 5.11 (m, 1H), 4.92 (m, 1H),
- 25 4.76 (m, 2H), 2.45 (s, 3H), 2.40 (s, 3H), 2.37 (s, 3H), 2.01 (s, 2H), 1.74 (s, 3H).



5 To a dry, argon purged round bottom flask (50 mL) were added **6a** (200 mg, 0.30 mmol), anhydrous DMF (4 mL), and anhydrous CH₂Cl₂ (4 mL). NaH (20 mg, 0.50 mmol, 60% in mineral oil) was then added and the heterogeneous mixture stirred at room temp for 30 min. MeI (60 mg, 0.42 mmol) was added to the flask and the reaction mixture continued to stir at room temp for 2hr. The flask was then placed in an ice bath and the pH was adjusted to 5 using 1M HCl. The organics were extracted with EtOAc and the combined layers were dried using MgSO₄. The solvent was removed under reduced pressure and the crude material was purified using a Gilson Preparatory HPLC system (acetonitrile/water). 150 mg (74 %) of the desired material **6b** was isolated. LC/MS = 683.2 (M + H⁺). ¹H NMR (300 MHz, CDCl₃): δ 7.99 (m, 2H), 7.89 (m, 4H), 7.19 (m, 2H), 7.16 (t, 4H), 6.31 (s, 1H), 5.13 (m, 1H), 4.92 (m, 1H), 4.76 (m, 2H), 2.69 (s, 3H), 2.44 (s, 3H), 2.40 (s, 3H), 2.37 (s, 3H), 2.01 (s, 2H), 1.74 (s, 3H).

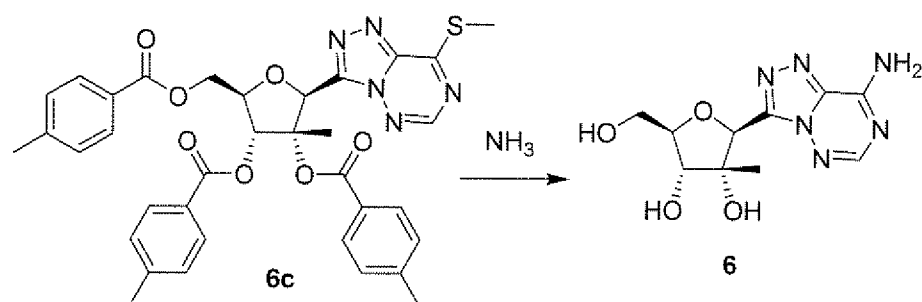


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To a dry, argon purged round bottom flask (100 mL) were added **6b** (225 mg, 0.33 mmol) and anhydrous THF (21 mL). *tert*-Butyl nitrite (0.30 mL, 2.32 mmol) was then added and the flask was placed into a pre-heated oil bath set at 50 °C. After 2.5 h of stirring, the reaction mixture was cooled to room temp and the solvent was removed under reduced pressure. The flask was then placed under high vacuum overnight and the crude material was purified using a Gilson Preparatory HPLC system (acetonitrile/water). 190 mg (86 %) of the desired material **6c** was isolated. LC/MS = 668.2 (M + H⁺). ¹H NMR (300 MHz, CDCl₃): δ 7.99 (m, 3H), 7.89 (m, 4H), 7.19 (m, 2H), 7.16 (t, 4H), 6.31 (s, 1H), 5.13 (m, 1H), 4.92 (m, 1H), 4.76 (m, 2H), 2.69 (s, 3H), 2.44 (s, 3H), 2.40 (s, 3H), 2.37 (s, 3H), 1.76 (s, 3H).

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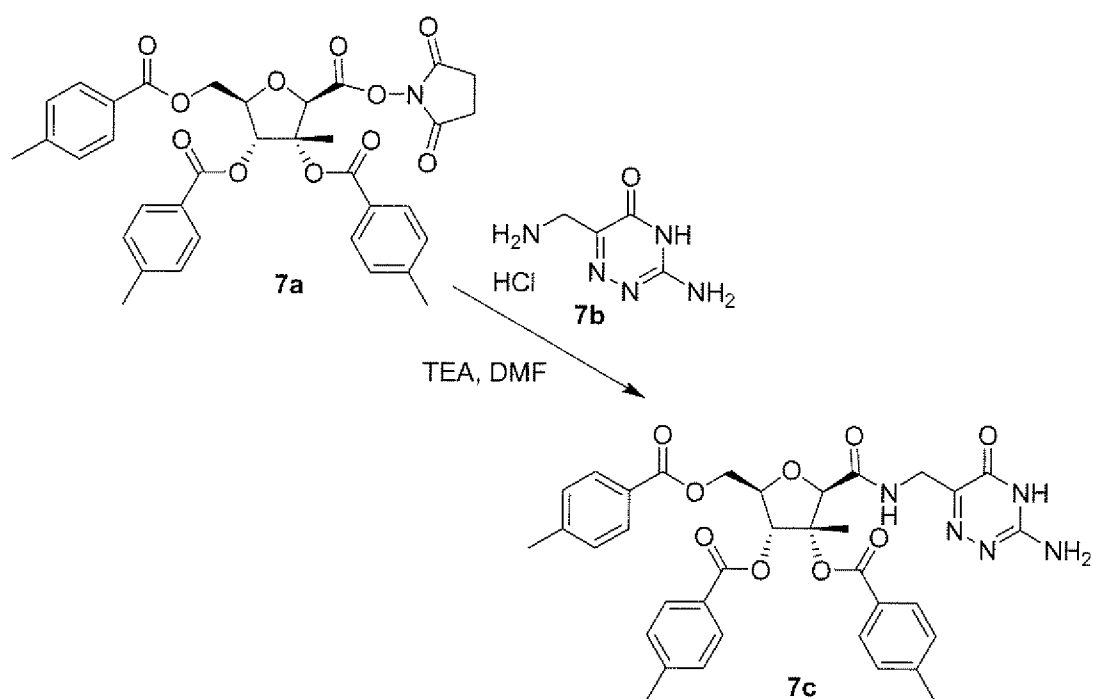
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- 10 To a dry, argon purged Parr bomb vessel was added **6c** (190 mg, 0.28 mmol). NH_3/MeOH (60mL, 7M solution) was then added and the bomb was placed in a pre-heated oil bath set at 80 °C. After 18h, the bomb was cooled to room temp and the solvent was removed under reduced pressure. The crude material was purified using a Gilson Preparatory HPLC system (acetonitrile/water), isolating 56 mg (70 %) of the
- 15 desired product **6**. LC/MS = 283.1 ($\text{M} + \text{H}^+$). ^1H NMR (300 MHz, D_2O): δ 8.09 (s, 1H), 5.54 (s, 1H), 4.19 (m, 1H), 4.11 (m, 1H), 3.99 (m, 1H), 3.85 (m, 1H), 1.01 (s, 3H).

Compound 7

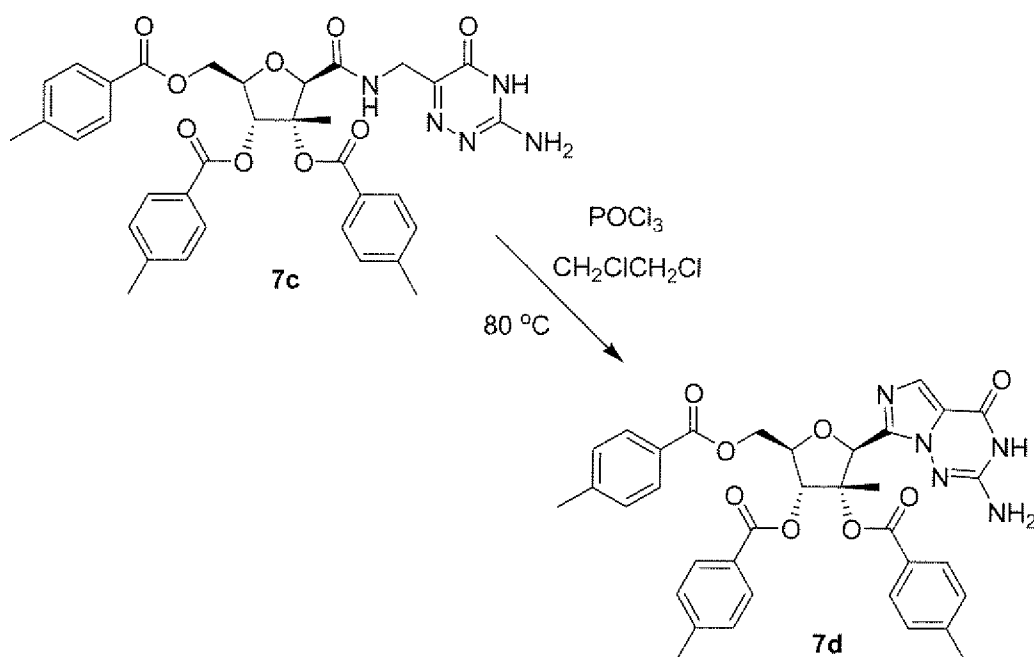
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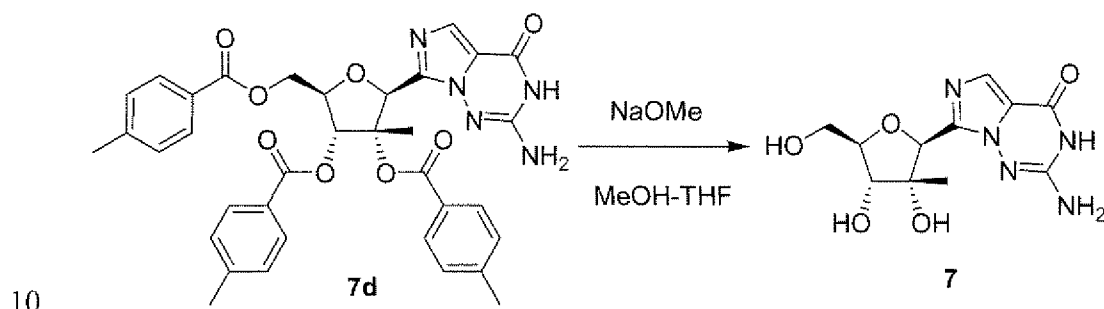
To a suspension mixture of **7a** (1.7 g, 2.64 mmol) and **7b** (0.516 g, 2.91 mmol, prepared according to the procedures described in *J.Heterocycl.Chem*, **1984**, 21, 697) in DMF (10 mL) was added TEA (0.365 g, 3.61 mmol). The resulting mixture was stirred at room temperature for 1 h, then at 45 °C for additional 1 h. The reaction mixture was diluted with ethyl acetate and washed with water. The organic phase was dried over MgSO₄, filtered, and concentrated. The residue was purified by chromatography on silica gel, eluted with 15% methanol-ethyl acetate to afford compound **7c** (0.45 g, 26%) as a colorless solid. MS = 670.0 (M + H⁺).

15



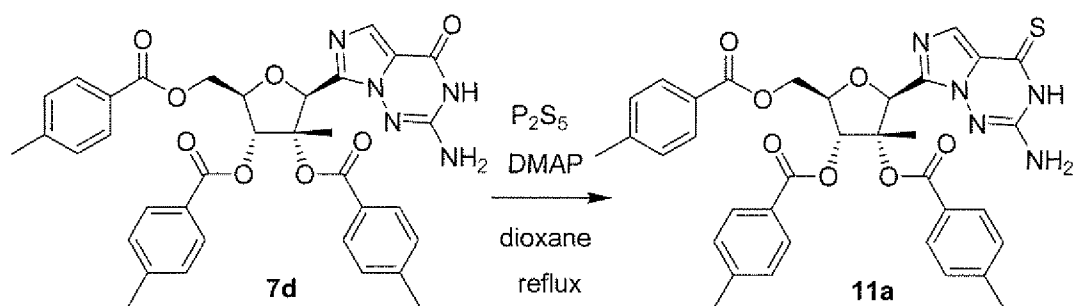
To a suspension of **7c** (0.45 g, 0.67 mmol) in 1,2-dichloroethane (50 mL) was added POCl₃ (0.56 g, 3.6 mmol). The reaction mixture was stirred at 82 °C for 8 h. After cooling down to room temperature, the reaction mixture was treated with NaHCO₃ (5 g) and water (0.5 mL) for 3 h, and concentrated. The residue was partitioned between ethyl acetate and water. The organic phase was separated, dried over MgSO₄, filtered and concentrated. The residue was purified by chromatography on silica gel, eluted with ethyl acetate to afford compound **8d** (0.26 g, 59%). ¹H NMR (300 MHz, DMSO-d₆): δ 11.0 (s, 1H), 7.95 (d, J = 7.8 Hz, 2H), 7.85 (m, 4H), 7.77 (s, 1H), 7.36 (d, J = 7.8 Hz, 2H), 7.27 (m, 4H), 6.33 (s, 2H), 6.20 (d, J = 6.9 Hz,

5 1H), 6.11 (s, 1H), 4.6 (m, 3H), 2.40 (s, 3H), 2.37 (s, 3H), 2.35 (s, 3H), 1.62 (s, 3H).
MS = 652.1 (M + H⁺).



To a solution of **7d** (0.26 g, 0.399 mmol) in MeOH (10 mL) and THF (10 mL) at 0 °C was added NaOMe (0.1 mL, 4.3 M). The resulting mixture was stirred at 0 °C for 0.5 h, and then at room temperature for 2 h. The reaction mixture was cooled to 0 °C, neutralized with HCl (1 mL, 0.5 N), treated with NaHCO₃ (0.1 g), and then
15 concentrated. The residue was purified by C-18 HPLC to afford compound **7** (0.1 g, 84%). ¹H NMR (300 MHz, D₂O): δ 7.63 (s, 1H), 5.31 (s, 1H), 3.70-3.95 (m, 4H), 0.88 (s, 3H). MS = 298.0 (M + H⁺).

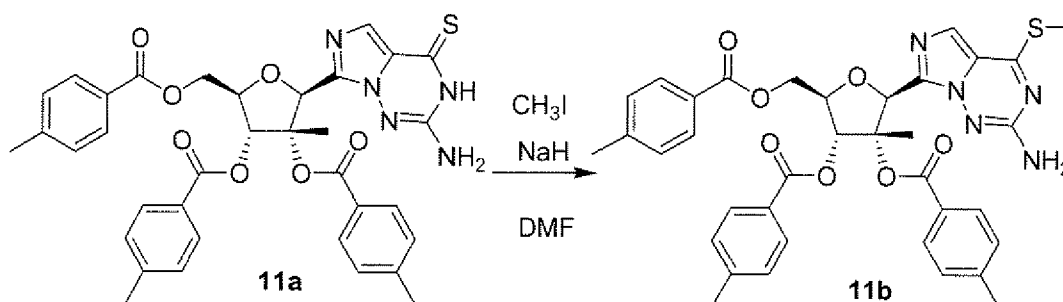
20 Compound 11



25 To a dry, argon purged, round bottom flask (50 mL) were added **7d** (40 mg, 0.067 mmol) and anhydrous dioxane (4 mL). P₂S₅ (68.2 mg, 0.15 mmol) and DMAP (6.1 mg, 0.05 mmol) were then added and the reaction mixture was heated to a gentle reflux for 25 min. Another portion of P₂S₅ (50 mg) was added and the reaction
30 refluxed for an additional 45 min. The reaction was then cooled to room temp and poured into an Erlenmeyer flask containing ice water (3.0 mL). The organic material

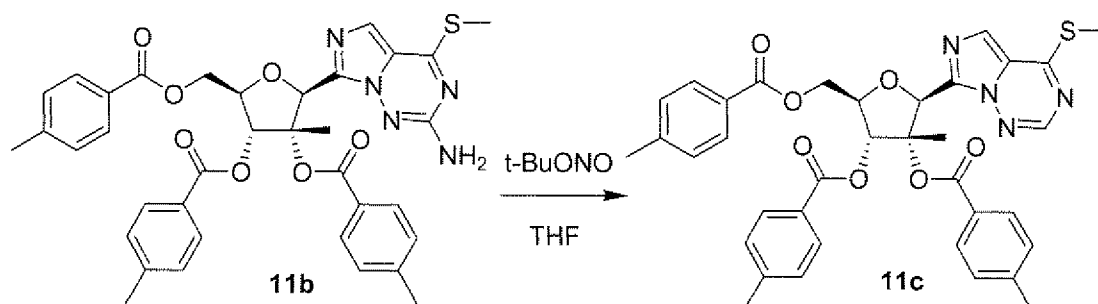
5 was extracted with chloroform after saturating the aqueous solution with NaCl. The combined organic layers were dried using MgSO_4 and the solvent removed under reduced pressure. The crude material (20 mg) was used as is for the next transformation. LC/MS = 668.2 ($\text{M} + \text{H}^+$).

10



To a dry, argon purged, round bottom flask (5 mL) were added the thione adduct **11a** (20 mg, 0.03 mmol), anhydrous DMF (0.25 mL), and anhydrous CH₂Cl₂ (0.25 mL). NaH (1.4mg, 0.035 mmol, 60% in mineral oil) was then added and the heterogeneous mixture stirred at room temp for 40 min. MeI (4.69 mg, 0.033 mmol) was added to the flask and the reaction mixture continued to stir at room temp for 2hr. The flask was then placed in an ice bath and the pH was adjusted to 5 using 1M HCl.

20 The solvent was removed under reduced pressure and the crude product **11b** (10 mg) was used as is for the next transformation. LC/MS = 682.2 ($\text{M} + \text{H}^+$).

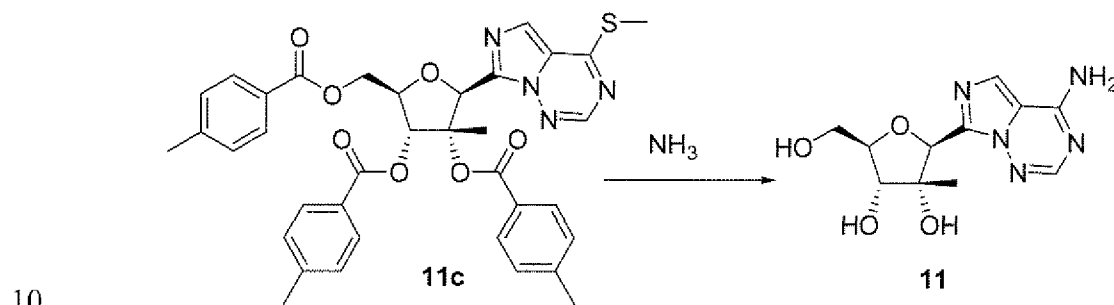


25

To a dry, argon purged, round bottom flask (5 mL) were added the methyl sulfide adduct **11b** (10 mg, 0.0147 mmol) and anhydrous THF (1 mL). *tert*-Butyl nitrite (0.012 mL, 0.10 mmol) was then added and the flask was placed into a pre-heated oil bath set at 50 °C. After 3 h of stirring, the reaction mixture was cooled to

30

- 5 room temp and the solvent was removed under reduced pressure. The flask was then placed under high vacuum overnight and the crude material **11c** (10 mg) was used as is for the next reaction. LC/MS = 667.2 ($M + H^+$).

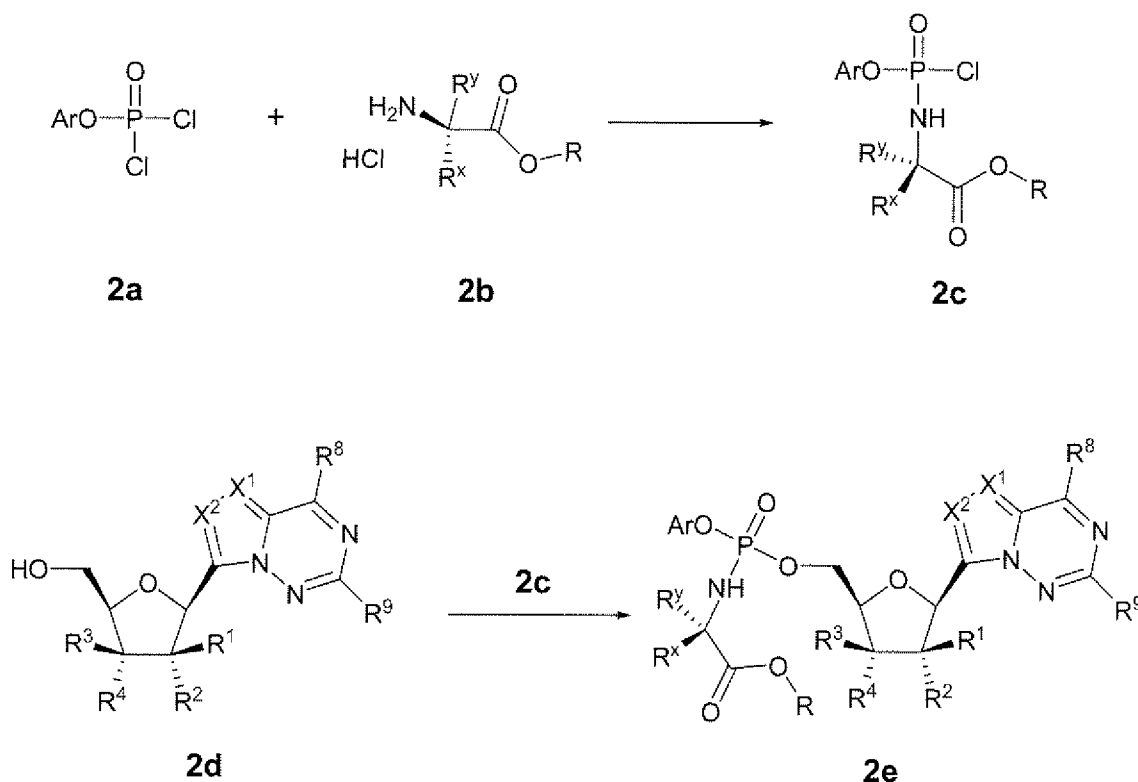


- To a dry, argon purged, Parr bomb vessel was added crude reduced methyl sulfide adduct **11c** (30 mg, 0.107 mmol). NH_3 / MeOH (5mL, 7M solution) was then added and the bomb was placed in a pre-heated oil bath set at 80 °C. After 18h, the bomb was cooled to room temp and the solvent was removed under reduced pressure. The crude material was purified using a Gilson Preparatory HPLC (acetonitrile/water), isolating 2 mg (50 %) of the desired product **11**. LC/MS = 282.1 ($M + H^+$). 1H NMR (300 MHz, D_2O): δ 7.99 (s, 1H), 7.34 (s, 1H), 5.45 (s, 1H), 4.01 (s, 1H), 3.90 (m, 1H), 3.79 (m, 1H), 3.69 (m, 1H), 0.91 (s, 3H) .
- 20

Phosphate Prodrugs

- Non-limiting examples of phosphate prodrugs comprising the instant invention may be prepared according to general Scheme 1.
- 25

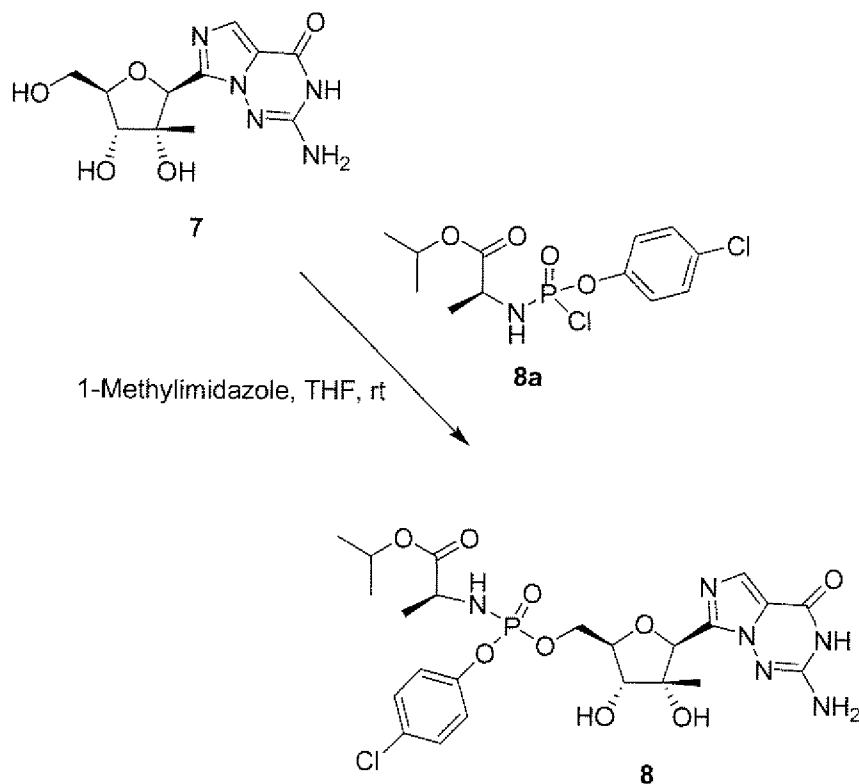
Scheme 1



The general procedure comprises the reaction of an amino acid ester salt **2b**, e.g., HCl salt, with an aryl dichlorophosphate **2a** in the presence of about two to ten equivalents of a suitable base to give the phosphoramidate **2c**. Suitable bases include, but are not limited to, imidazoles, pyridines such as lutidine and DMAP, tertiary amines such as triethylamine and DABCO, and substituted amidines such as DBN and DBU. Tertiary amines are particularly preferred. Preferably, the product of each step is used directly in the subsequent steps without recrystallization or chromatography. Specific, but non-limiting, examples of **2a**, **2b**, and **2c** can be found in WO 2006/121820 that is hereby incorporated by reference in its entirety. A nucleoside base **2d** reacts with the phosphoramidate **2c** in the presence of a suitable base. Suitable bases include, but are not limited to, imidazoles, pyridines such as lutidine and DMAP, tertiary amines such as triethylamine and DABCO, and substituted amidines such as DBN and DBU. The product **2e** may be isolated by recrystallization and/or chromatography.

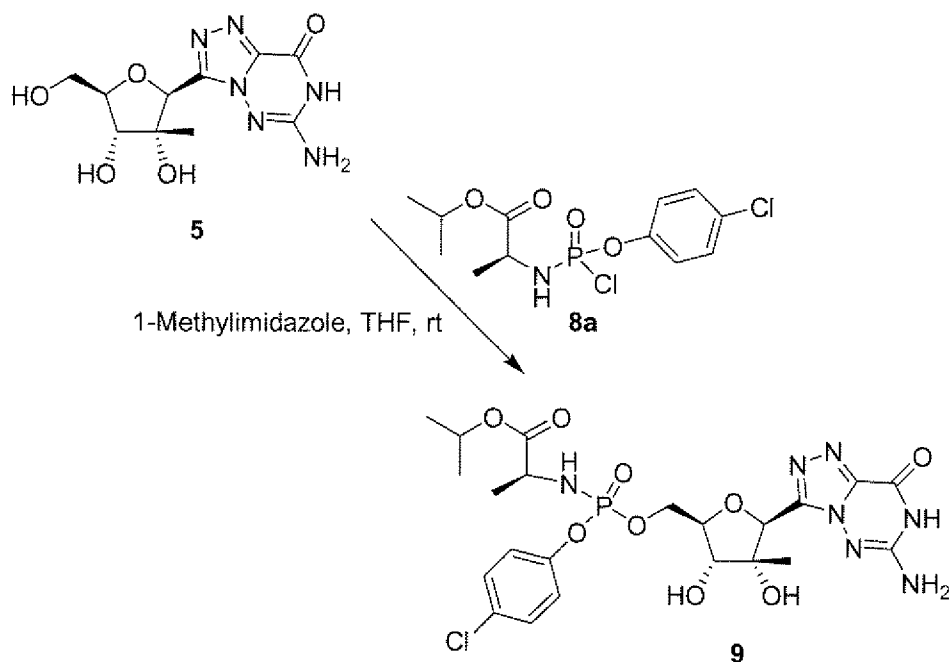
Additional examples of types of phosphate prodrugs are disclosed in *J. Med. Chem.* 2007, 50(16) 3891-96 which is incorporated by reference in its entirety.

5 Compound 8



- 10 Compound **7** was treated with the phosphorochloridate **8a** (prepared according to McGuigan et al, *J. Med. Chem.* **1993**, 36, 1048–1052) according to the general protocol using 1-methylimidazole as base to give compound **8** (20 mg, 50% yield).
¹H NMR (300 MHz, CD₃OD): δ 7.61 (s, 1H), 7.20–7.32 (m, 4H), 5.47 (s, 1H), 4.9 (m, 1H), 4.5 (m, 2H), 4.18 (brs, 2H), 3.9 (m, 1H), 1.3 (m, 3H), 1.15 (m, 6H), 0.99 (brs,
 15 3H). ³¹P NMR (300 MHz, CD₃OD): 4.04, 4.09. MS = 601.0 (M + H⁺).

Compound 9



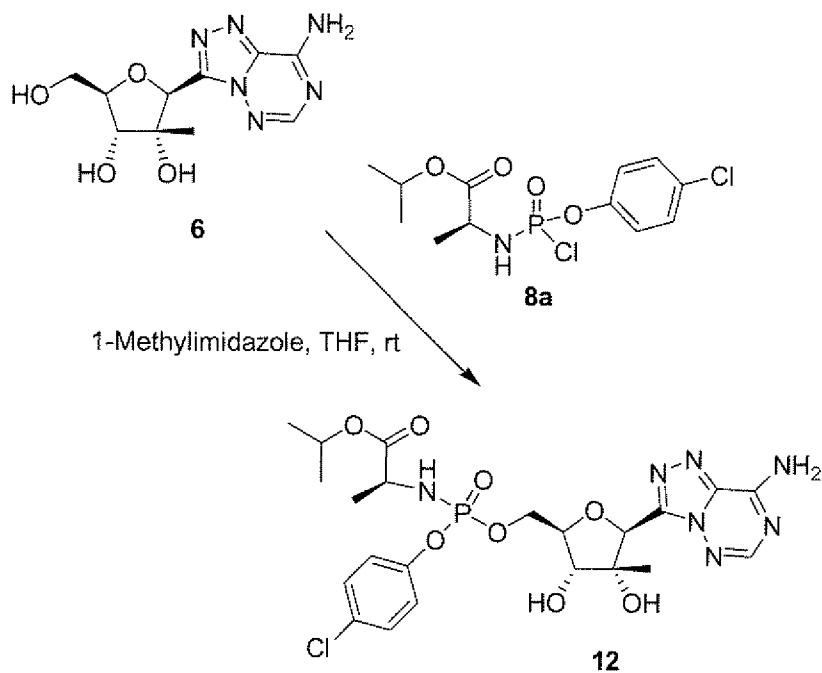
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Compound **5** was treated with the phosphorochloridate **8a** (prepared according to McGuigan et al, *J. Med. Chem.* **1993**, 36, 1048–1052) according to the general protocol using 1-methylimidazole as a base to give compound **9**. ¹H NMR (300 MHz, CD₃OD): δ 7.14–7.27 (m, 4H), 5.37 (s, 1H), 4.9 (m, 1H), 4.5 (m, 2H), 4.20 (brs, 2H), 3.9 (m, 1H), 1.3 (m, 3H), 1.14 (m, 6H), 1.02 (brs, 3H). ³¹P NMR (300 MHz, CD₃OD): 4.00, 4.06; ¹⁹F NMR (CD₃OD, 282 MHz) –78 (s, 3F); MS = 601.9 (M + H⁺).

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Compound 12

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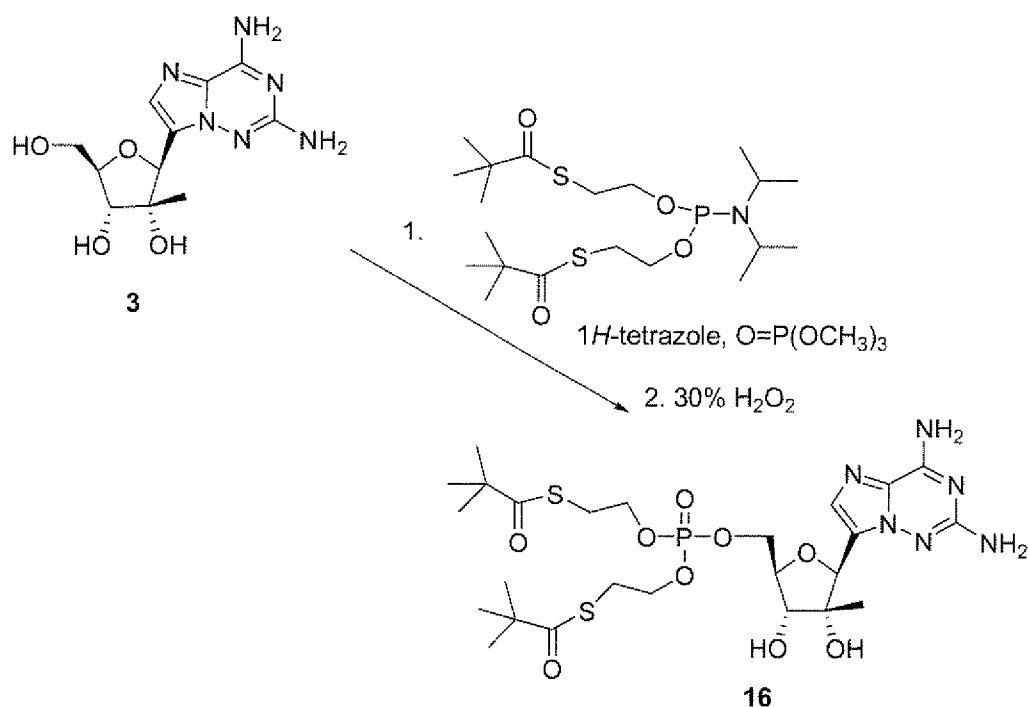


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Compound **12** was prepared according to the same procedure described for the preparation of compounds **8** and **9**. ^1H NMR (300 MHz, CD_3OD): δ 8.08 (2s, 1H), 7.1-7.4 (m, 4H), 5.58 (s, 1H), 4.75 (m, 1H, overlapped with solvent peak), 4.5 (m, 1H), 4.45 (m, 1H), 4.25 (m, 2H), 3.85 (m, 1H), 1.3 (m, 3H), 1.2 (m, 6H), 1.02 (brs, 3H). ^{31}P NMR (300 MHz, CD_3OD): 3.91, 4.02; MS = 586.3 ($\text{M} + \text{H}^+$).

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Compound 16

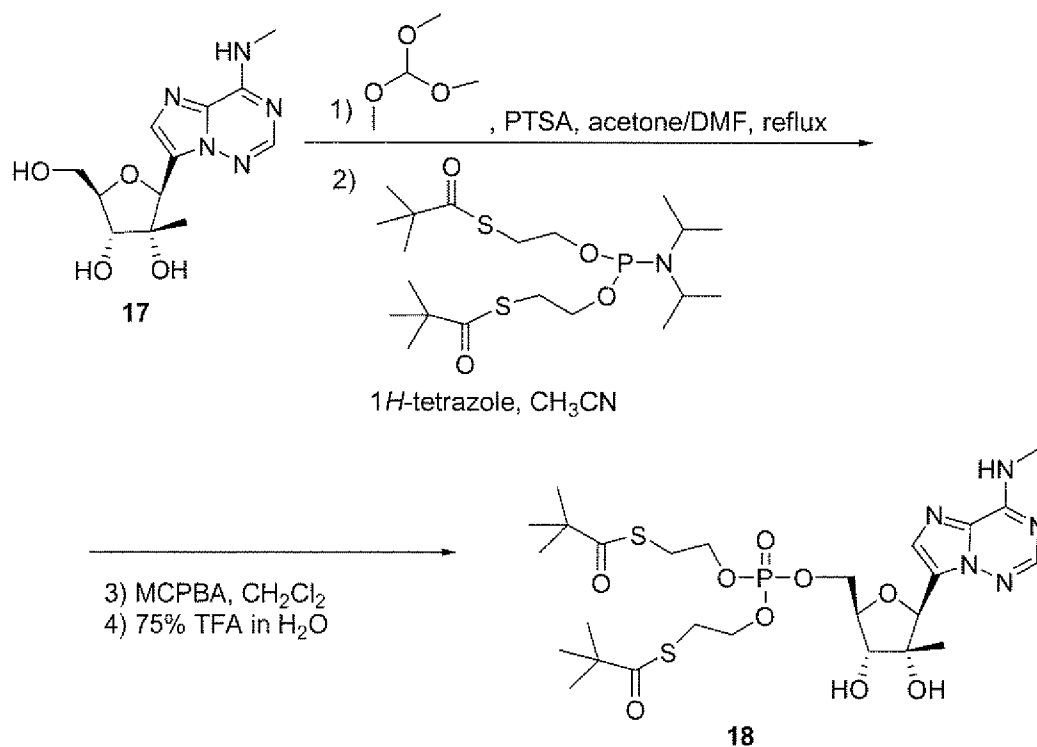


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To a solution of **Compound 3** (13 mg, 0.044 mmol) in trimethylphosphate (0.4 mL) were added *1H*-tetrazole (9.5 mg, 0.132 mmol) followed by addition of 2,2-dimethyl-thiopropionic acid S-(2-{diisopropylamino-[2-(2,2-dimethyl-propionylsulfanyl)-ethoxy]-phosphanyloxy}-ethyl) ester (40 mg, 0.088 mmol) at 0 °C.

- 10 After stirring for 2h, 30% hydrogen peroxide in H_2O (60 μ L) was added to the mixture. The mixture was then allowed to warm up to room temperature. After 30 min stirring, 1 M $Na_2S_2O_3$ in H_2O (2 mL) was added to quench the reaction. The organic layer was washed with saturated aqueous Na_2CO_3 (10mL x 2) and brine and concentrated *in vacuo*. The residue was purified by RP-HPLC (MeCN- H_2O gradient)
- 15 to give **Compound 16** as a white solid (6 mg). 1H NMR (300 MHz, $CDCl_3$): δ 7.45 (s, 1H), 5.29 (s, 1H), 4.40-4.50 (m, 1H), 4.28-4.40 (m, 1H), 4.10-4.25 (m, 6H), 3.14-3.21 (m, 4H), 1.237 (s, 9H), 1.227 (s, 9H), 1.06 (s, 3H); ^{31}P NMR (121.4 MHz, $CDCl_3$): δ -1.322. MS = 665.0 ($M + H^+$).

20 **Compound 18**



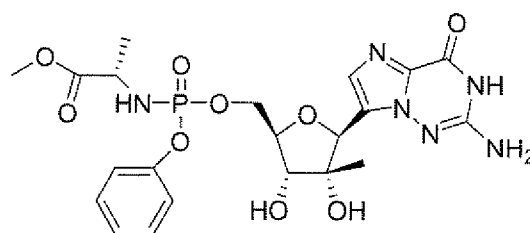
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To a solution of **17** (12 mg, 0.04 mmol) in acetone (0.5 mL) and DMF (0.1 mL) were added trimethylorthoformate (36 μL , 0.32 mmol) and *p*-toluenesulfonic acid monohydrate (8 mg, 0.04 mmol). The mixture was heated to reflux for 1 h. 28% NH_4OH was added to neutralize the mixture and the mixture was concentrated to dryness. The product was isolated by a short bed of silica gel plug (10% MeOH in CH_2Cl_2). The white solid was dissolved in CH_3CN (0.4 mL), added 1*H*-tetrazole followed by addition of 2,2-dimethyl-thiopropionic acid S-(2-{diisopropylamino-[2-(2,2-dimethyl-propionylsulfanyl)-ethoxy]-phosphanyloxy}-ethyl) ester (41 mg, 0.09 mmol) in CH_3CN (0.2 mL) at 0 $^\circ\text{C}$. After stirring for 40 min., the mixture was cooled to -40 $^\circ\text{C}$. MCPBA (40 mg, 0.09 mmol) in CH_2Cl_2 was added to the mixture. The mixture was then allowed to warm up to room temperature. After 10 min stirring, 1 M $\text{Na}_2\text{S}_2\text{O}_3$ in H_2O (2 mL) was added to quench the reaction. The organic layer was washed with saturated aqueous Na_2CO_3 (10mL x 2) and brine and concentrated *in vacuo*. The residue was purified by RP-HPLC (MeCN- H_2O gradient) to give the coupled product as a white solid. The solid was dissolved in cooled 75% TFA in H_2O . The mixture was allowed to stir at 0 to 10 $^\circ\text{C}$ for 3h. The resulting mixture was diluted with EtOAc, washed with saturated NaHCO_3 and concentrated *in vacuo*. The residue was purified by RP-HPLC (MeCN- H_2O gradient) to give the product

5 **Compound 18** as a white solid (12 mg, 44% over 4 steps). ^1H NMR (300 MHz, CDCl_3): δ 8.17 (s, 1H), 7.52 (s, 1H), 7.24 (b, 1H), 5.38 (s, 1H), 4.57 (b, 1H), 4.34-4.45 (m, 2H), 4.11-4.25 (m, 5H), 3.97 (d, $J = 5.4$ Hz, 1H), 3.88 (b, 1H), 3.21 (d, $J = 4.8$ Hz, 3H), 3.16 (t, $J = 6.6$ Hz, 4H), 1.234 (s, 6H), 1.230 (s, 6H), 1.227 (s, 6H), 1.03 (s, 3H); ^{31}P NMR (121.4 MHz, CDCl_3): δ -1.347. MS = 664.0 ($\text{M} + \text{H}^+$).

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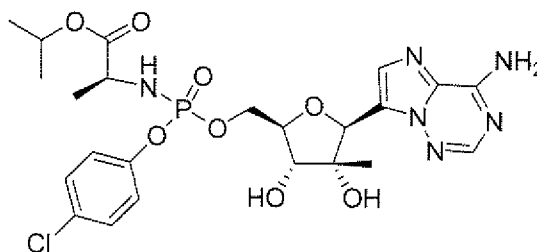
Compound 20



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15 About 3.1 mmol of phenyl methoxyalaninyl phosphorochloridate (prepared according to McGuigan et al, *J. Med. Chem.* **1993**, 36, 1048–1052) in about 3 mL of THF is added to a mixture of about 0.5 mmol of **Compound 4** and about 3.8 mmol of N-methylimidazole in about 3 mL THF. The reaction is stirred for about 24 hours and the solvent is removed under reduced pressure. The residue is purified by
20 reverse-phase HPLC to give **Compound 20**.

Compound 21



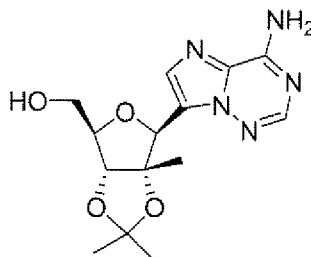
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About 3.1 mmol of 4-chlorophenyl 2-propyloxyalaninyl phosphorochloridate (prepared according to McGuigan et al, *J. Med. Chem.* **1993**, 36, 1048–1052) in about 3 mL of THF is added to a mixture of about 0.5 mmol of **Compound 1** and about 3.8 mmol of N-methylimidazole in about 3 mL THF. The reaction is stirred for about

- 5 24 hours and the solvent is removed under reduced pressure. The residue is purified by reverse-phase HPLC to give **Compound 21**.

Compound 22

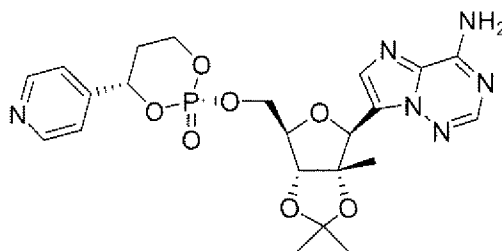


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- A mixture of about 0.52 mmol of **Compound 1** and about 12 mL dry acetone, about 0.7 mL of 2,2,-dimethoxypropane and about 1.28 mmol of di-*p*-nitrophenylphosphoric acid is stirred for about 24 hours to about seven days. The reaction mixture is neutralized with about 20 mL of 0.1 N NaHCO₃ and the acetone is
- 15 evaporated. The desired material is partitioned into chloroform, the chloroform solution is dried, and the solvent is evaporated. **Compound 22** is purified from the residue by conventional means.

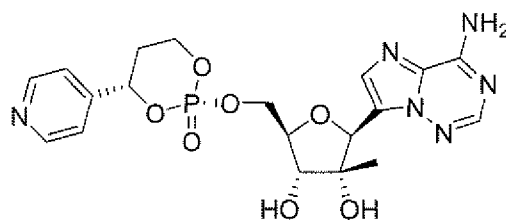
Compound 23



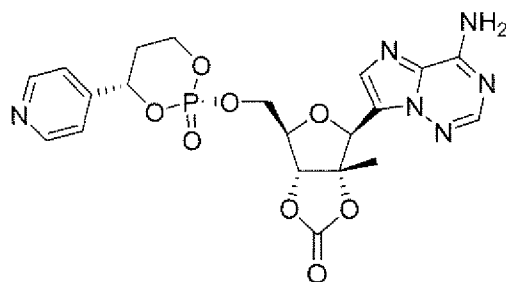
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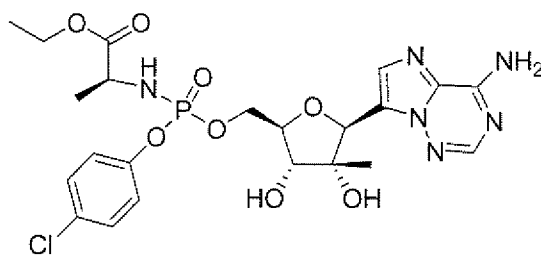
- A solution of about 0.53 mmol of **Compound 22** in about 5 mL of DMF is treated with about 1 mL of a 1 M solution of *t*-butylmagnesium chloride in THF. After about 30 min to about 5 hours, a solution of about 0.65 mmol of *trans*-4-[(*S*)-pyridin-4-yl]-2-(4-nitrophenoxy)-2-oxo-1,3,2-dioxaphosphorinane (Reddy,
- 25 *Tetrahedron Letters* **2005**, 4321-4324) is added and the reaction is stirred for about one to about 24 hours. The solution is concentrated in a vacuum and the residue is purified by chromatography to give **Compound 23**.

5 **Compound 24****24**

A solution of about 70% aqueous trifluoroacetic acid is cooled to 0 °C and is treated with about 0.32 mmol of **Compound 23** for about one to 24 hours. The solution is concentrated and the residue is purified by chromatography to give **Compound 24**.

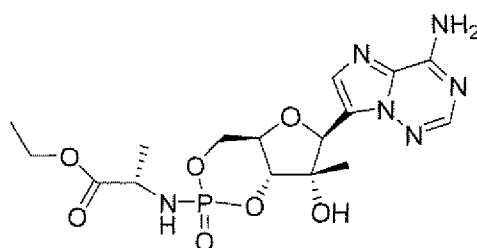
Compound 25**25**

A solution of about 1.56 mmol of **Compound 24** in about 15 mL of THF is treated with about 4.32 mmol of CDI. After about one to about 24 hours, the solvent is evaporated and the residue is purified by chromatography to give **Compound 25**.

Compound 26**26**

5 About 3.1 mmol of 4-chlorophenyl 2-ethoxyalaninyl phosphorochloridate (prepared according to McGuigan et al, *J. Med. Chem.* **1993**, 36, 1048–1052) in about 3 mL of THF is added to a mixture of about 0.5 mmol of **Compound 1** and about 3.8 mmol of N-methylimidazole in about 3 mL THF. The reaction is stirred for about 24 hours and the solvent is removed under reduced pressure. The residue is purified by
10 reverse-phase HPLC to give **Compound 26**.

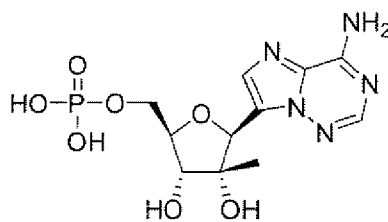
Compound 27



27

15 A solution of **Compound 26** in DMSO is treated with about 3 mole equivalents of potassium *t*-butoxide for about 15 min to 24 hours. The reaction is quenched with 1N HCl and **Compound 27** is isolated by reverse-phase HPLC.

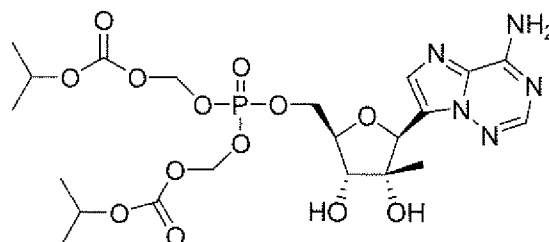
Compound 28



28

A mixture of about 0.05 mmol of **Compound 1** and about 0.5 mL of trimethylphosphate is sealed in a container for about one to about 48 hours. The mixture is cooled to about -10 to about 10 °C and about 0.075 mmol of phosphorous
25 oxychloride is added. After about one to about 24 hours, the reaction is quenched with about 0.5 mL of 1M tetraethylammonium bicarbonate and the desired fraction are isolated by anion exchange chromatography. The appropriate fractions are then desalted by reverse-phase chromatography to give **Compound 28**.

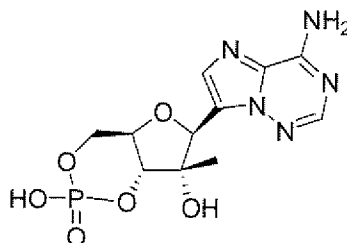
30 Compound 29



29

Compound 28 (about 1.19 mmol) is dried over phosphorous pentoxide in a vacuum for about overnight. The dried material is suspended in about 4 mL of anhydrous DMF and about 4.92 mmol DIPEA. About 7.34 mmol of *iso*-propyl chloromethyl carbonate (*Antiviral Chemistry & Chemotherapy* 8:557 (1997)) is added and the mixture is heated to about 25 to about 60 °C for about 30 min to about 24 hours. Heating is removed for about one to about 48 hours and the reaction filtered. The filtrate is diluted with water, **Compound 29** is partitioned into CH₂Cl₂, the organic solution is dried and evaporated, and the residue is purified by reverse-phase HPLC to isolate **Compound 29**.

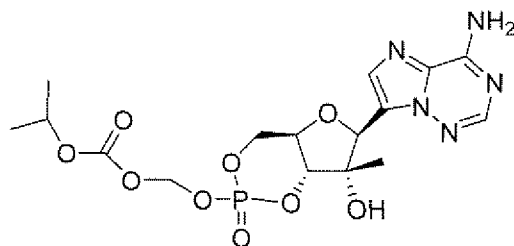
Compound 30



30

Compound 30 is prepared by treating **Compound 28** with about one to about five equivalents of DCC in pyridine and heating the reaction to reflux for about one to about 24 hours. **Compound 30** is isolated by conventional ion exchange and reverse-phase HPLC.

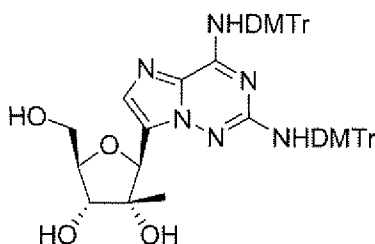
Compound 31



31

A solution of about 0.4 mmol of **Compound 30** in about 10 mL of DMF is treated with about 0.8 mmol of DIPEA and about 0.8 mmol of chloromethyl isopropyl carbonate (WO2007/027248). The reaction is heated to about 25 to about 80 °C for about 15 min to about 24 hours. The solvent is removed under vacuum and the residue is purified by HPLC to give **Compound 31**.

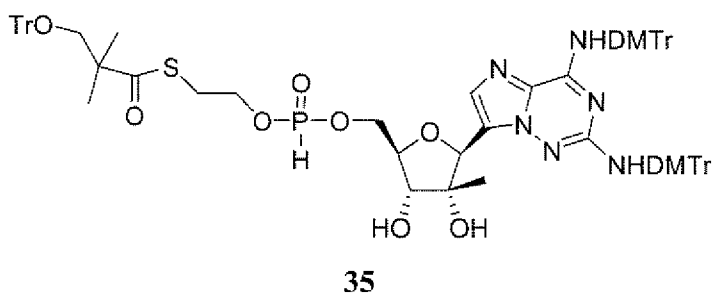
Compound 34



34

Compound **3** (about 0.22 mmol) is dissolved in anhydrous pyridine (about 2 mL) and chlorotrimethylsilane (about 0.17 mL) is added. The mixture is stirred at about 0 to about 25 °C for about one to about 24 hours. Additional chlorotrimethylsilane (about 0.1 mL) is added and the reaction is stirred for about one to about 24 hours. 4,4'-Dimethoxytrityl chloride (about 0.66 mmol) and DMAP (about 0.11 to about 0.22 mmol) is sequentially added. The mixture is stirred for about one to about 24 hours. A solution of TBAF (1.0 M, about 0.22 mL) in THF is added and the reaction is stirred for about one to about 24 hours. The mixture is partitioned between ethyl acetate and water. The ethyl acetate layer is dried and concentrated. The residue is purified chromatography to afford **Compound 34** which may be a mixture of mono and di tritylated compounds.

Compound 35

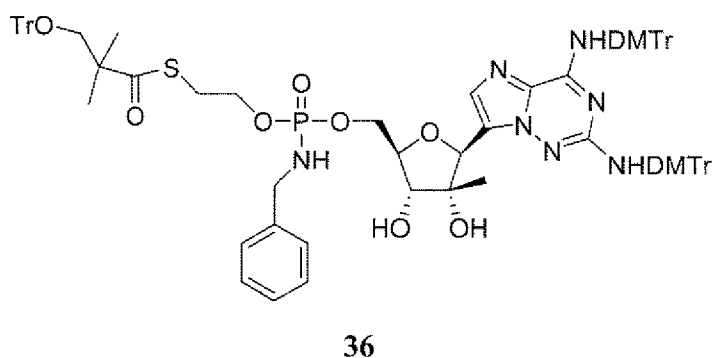


A mixture of about 1.25 mmol of **Compound 34** and about 1.9 mmol of triethylammonium 2-(2,2-dimethyl-3-(trityloxy)propanoylthio)ethyl phosphonate (WO2008082601) is dissolved in anhydrous pyridine (about 19 mL). Pivaloyl chloride (about 2.5 mmol) is added dropwise at about -30 to about 0 °C and the solution is stirred at for about 30 min to about 24 hours. The reaction is diluted with methylene chloride and is neutralized with aqueous ammonium chloride (about 0.5M). The methylene chloride phase is evaporated and the residue is dried and is purified by chromatography to give **Compound 35** which may be a mixture of mono- and di- tritylated compounds.

10

15

Compound 36

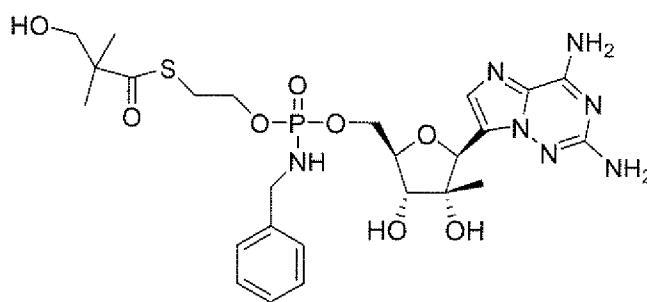


To a solution of about 0.49 mmol of **Compound 35** in anhydrous carbon tetrachloride (about 5 mL) is added dropwise benzylamine (about 2.45 mmol). The reaction mixture is stirred for about one to about 24 hours. The solvent is evaporated and the residue is purified by chromatography to give **Compound 36** which may be a mixture of mono and di tritylated compounds.

20

25

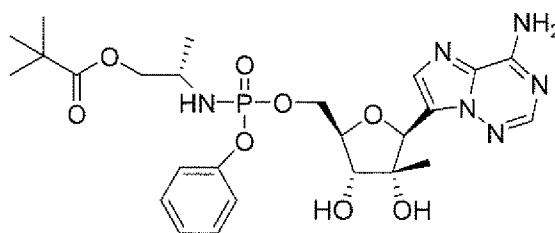
Compound 37



37

A solution of about 2 mmol of **Compound 36** in methylene chloride (about 10 mL) is treated with an aqueous solution of trifluoroacetic acid (90%, about 10 mL).
 10 The reaction mixture is stirred at about 25 to about 60 °C for about one to about 24 hours. The reaction mixture is diluted with ethanol, the volatiles are evaporated and the residue is purified by chromatography to give **Compound 37**.

Compound 38



38

About 90 mM **Compound 1** in THF is cooled to about -78 °C and about 2.2 to about 4.4 equivalents of *t*-butylmagnesium chloride (about 1 M in THF) is added.
 20 The mixture is warmed to about 0 °C for about 30 min and is again cooled to about -78 °C. A solution of (2*S*)-2-[[chloro(1-phenoxy)phosphoryl]amino]propyl pivaloate (WO2008085508) (1 M in THF, about 2 equivalents) is added dropwise. The cooling is removed and the reaction is stirred for about one to about 24 hours. The reaction is quenched with water and the mixture is extracted with ethyl acetate. The extracts are
 25 dried and evaporated and the residue purified by chromatography to give **Compound 38**.

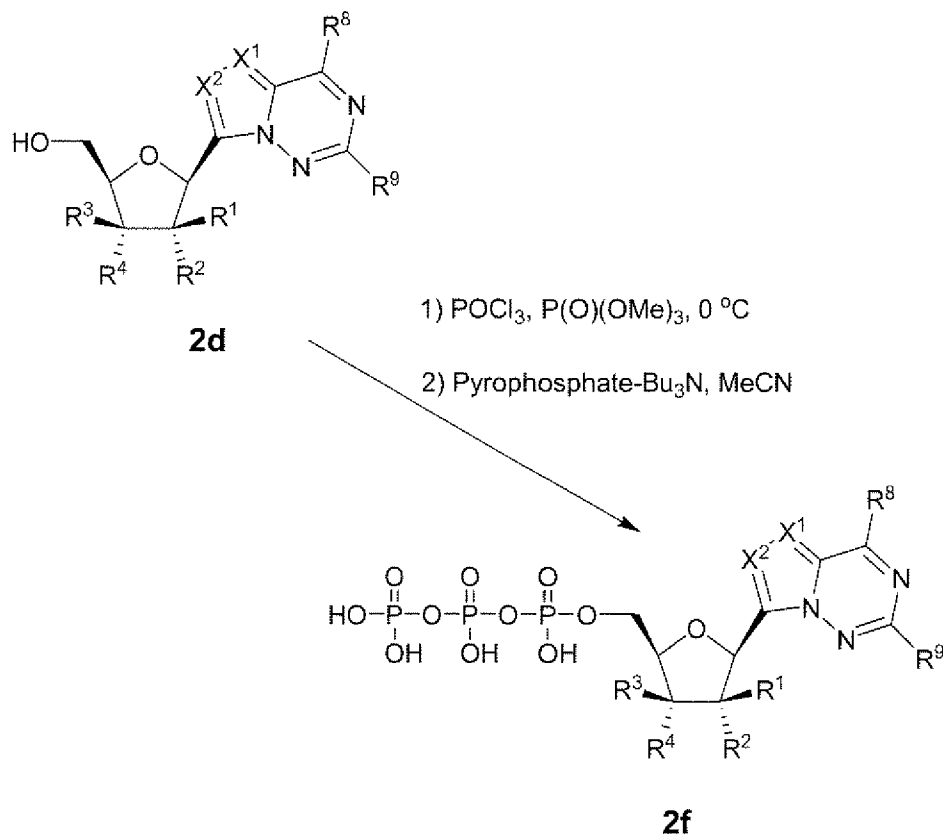
Triphosphates of nucleosides

5

Non-limiting examples of the triphosphates of nucleosides comprising the instant invention may be prepared according to general Scheme 2.

Scheme 2.

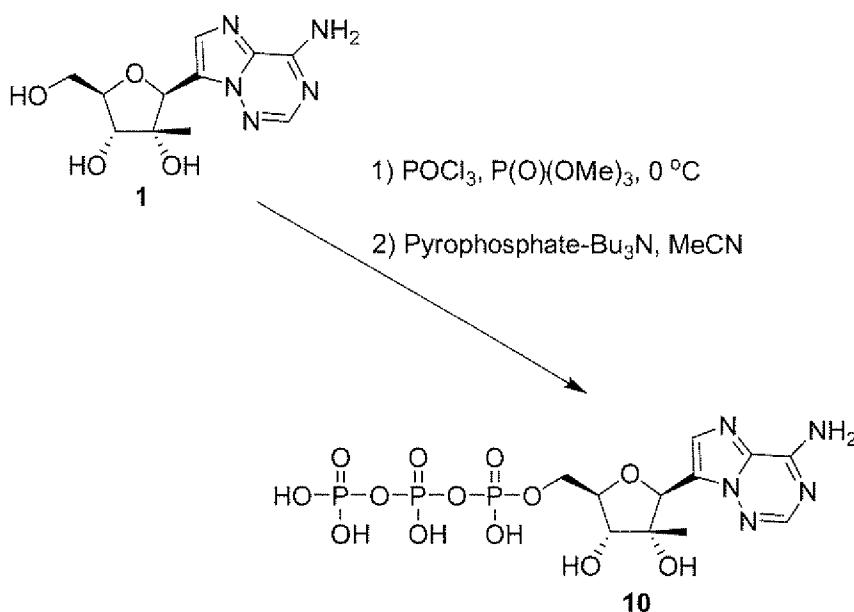
10



To a flask (5-15 mL) is charged with a nucleoside **2d** (~20 mg). Trimethyl phosphate (0.5-1.0 mL) is added. The solution is cooled with ice-water bath. POCl_3 (40-45 mg) is added and stirred at 0°C until the reaction is complete (1 to 4 h; the reaction progress is monitored by ion-exchange HPLC; analytical samples are prepared by taking 3 μL of the reaction mixture and diluting it with 1.0M $\text{Et}_3\text{NH}_2\text{CO}_3$ (30-50 μL)). A solution of pyrophosphate- Bu_3N (250 mg) and Bu_3N (90-105 mg) in MeCN or DMF (1-1.5 mL) is then added. The mixture is stirred at 0°C for 0.3 to 2.5 h, and then the reaction is quenched with 1.0 M $\text{Et}_3\text{NH}_2\text{CO}_3$ (~5 mL). The resulting mixture is stirred for an additional 0.5-1 h while warming up to room temperature. The mixture is concentrated to dryness, re-dissolved in water (4 mL), and purified by ion exchange HPLC. The fractions containing the desired product are concentrated to

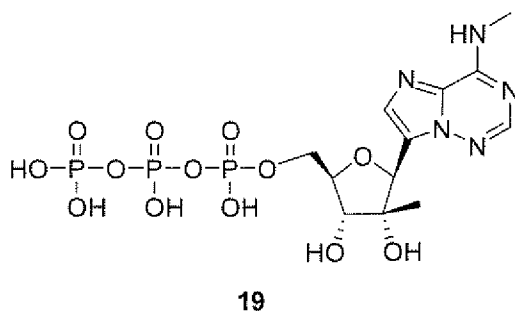
- 5 dryness and co-evaporated with water. The residue is dissolved in water (~5 mL). NaHCO_3 (~30 mg) is added and the mixture is evaporated to dryness. The residue is dissolved in water and evaporated again. The residue is subjected to C-18 HPLC purification, affording the desired product as the sodium salts.

10

Compound 10

- 15 The triphosphate **10** (4 mg, tetra-sodium salts, 35%) was prepared according to the procedure described starting from compound **1**. ^1H NMR (300 MHz, D_2O): δ 7.96 (s, 1H), 7.68 (s, 1H), 5.40 (s, 1H), 4.07-4.30 (m, 4H), 0.91 (s, 3H). ^{31}P NMR (300 MHz, D_2O): -5.6 (d, $J = 48\text{ Hz}$), -10.6 (d, $J = 48\text{ Hz}$), -21.5 (t, $J = 48\text{ Hz}$). MS = 521.8 ($\text{M} + \text{H}^+$).

20

Compound 19

5 **Compound 19** was prepared starting from **17** according to the standard procedure for triphosphate synthesis. ¹H NMR (300 MHz, D₂O): δ 7.97 (s, 1H), 7.60 (s, 1H), 5.37 (s, 1H), 4.00-4.30 (m, 4H), 2.97 (s, 3H), 0.91 (s, 3H); ³¹P NMR (121.4 MHz, D₂O): δ -21.6 (t, *J* = 19.4 Hz), -10.6 (d, *J* = 18.7 Hz), -5.7 (d, *J* = 20.1 Hz).

10 **Antiviral Activity**

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

Within the context of the invention samples suspected of containing a virus
15 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.
20 Typically the sample will be suspected of containing an organism which induces a viral infection, frequently a pathogenic organism such as a tumor virus. Samples can be contained in any medium including water and organic solvent/water mixtures. Samples include living organisms such as humans, and man made materials such as cell cultures.

25 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
30 other method such as observation of the physiological properties of a living organism are also applicable.

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

35 **Cell-based Flavivirus Immunodetection assay**

5 BHK21 or A549 cells are trypsinized, counted and diluted to 2×10^5 cells/mL in Hams F-12 media (A549 cells) or RPMI-1640 media (BHK21 cells) supplemented with 2% fetal bovine serum (FBS) and 1% penicillin/streptomycin. 2×10^4 cells are dispensed in a clear 96-well tissue culture plates per well and placed at 37°C , 5% CO_2 overnight. On the next day, the cells are infected with viruses at multiplicity of infection (MOI) of 0.3 in the presence of varied concentrations of test compounds for 1 hour at 37°C and 5% CO_2 for another 48 hours. The cells are washed once with PBS and fixed with cold methanol for 10 min. After washing twice with PBS, the fixed cells are blocked with PBS containing 1% FBS and 0.05% Tween-20 for 1 hour at room temperature. The primary antibody solution (4G2) is then added at a
10 concentration of 1:20 to 1:100 in PBS containing 1% FBS and 0.05% Tween-20 for 3 hours. The cells are then washed three times with PBS followed by one hour incubation with horseradish peroxidase(HRP)-conjugated anti-mouse IgG (Sigma, 1:2000 dilution). After washing three times with PBS, 50 microliters of 3,3',5,5'-tetramethylbenzidine (TMB) substrate solution (Sigma) is added to each well for two
15 minutes. The reaction is stopped by addition of 0.5 M sulfuric acid. The plates are read at 450 nm absorbance for viral load quantification. After measurement, the cells are washed three times with PBS followed by incubation with propidium iodide for 5 min. The plate is read in a Tecan Safire™ reader (excitation 537 nm, emission 617 nm) for cell number quantification. Dose response curves are plotted from the mean absorbance versus the log of the of the concentration of test compounds. The
20 EC_{50} is calculated by non-linear regression analysis. A positive control such as N-nonyl-deoxynojirimycin may be used.

Cell-based Flavivirus cytopathic effect assay

For testing against West Nile virus or Japanese encephalitis virus, BHK21
30 cells are trypsinized and diluted to a concentration of 4×10^5 cells/mL in RPMI-1640 media supplemented with 2% FBS and 1% penicillin/streptomycin. For testing against dengue virus, Huh-7 cells are trypsinized and diluted to a concentration of 4×10^5 cells/mL in DMEM media supplemented with 5% FBS and 1% penicillin/streptomycin. A 50 microliter of cell suspension (2×10^4 cells) is dispensed
35 per well in a 96-well optical bottom PIT polymer-based plates (Nunc). Cells are grown overnight in culture medium at 37°C , 5% CO_2 , and then infected with West

- 5 Nile virus (e.g. B956 strain) or Japanese encephalitis virus (e.g. Nakayama strain) at MOI = 0.3, or with dengue virus (e.g. DEN-2 NGC strain) at MOI = 1, in the presence of different concentrations of test compounds. The plates containing the virus and the compounds are further incubated at 37°C, 5% CO₂ for 72 hours. At the end of incubation, 100 microliters of CellTiter-Glo™ reagent is added into each well.
- 10 Contents are mixed for 2 minutes on an orbital shaker to induce cell lysis. The plates are incubated at room temperature for 10 minutes to stabilize luminescent signal. Luminescence reading is recorded using a plate reader. A positive control such as N-nonyl-deoxynojirimycin may be used.

Antiviral Activity in a Mouse Model of Dengue Infection.

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

- For testing of antiviral activity, a compound of the invention is dissolved in vehicle fluid, e.g. 10% ethanol, 30% PEG 300 and 60% D5W (5% dextrose in water); or 6N HCl (1.5 eq):1N NaOH (pH adjusted to 3.5): 100 mM citrate buffer pH 3.5 (0.9% v/v:2.5% v/v: 96.6% v/v). Thirty six 6-10 week old AG129 mice are divided
- 30 into six groups of six mice each. All mice are infected with dengue virus as described above (day 0). Group 1 is dosed by oral gavage of 200 µL/mouse with 0.2 mg/kg of a compound of the invention twice a day (once early in the morning and once late in the afternoon) for three consecutive days starting on day 0 (first dose just before dengue infection). Groups 2, 3 and 4 are dosed the same way with 1 mg/kg, 5 mg/kg
- 35 and 25 mg/kg of the compound, respectively. A positive control may be used, such as

- 5 (2R,3R,4R,5R)-2-(2-amino-6-hydroxy-purin-9-yl)-5-hydroxymethyl-3-methyl-tetrahydro-furan-3,4-diol, dosed by oral gavage of 200 microliters/mouse the same way as the previous groups. A further group is treated with only vehicle fluid.

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

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

20 HCV IC₅₀ Determination

Assay Protocol: NS5b polymerase assay (40 µL) was assembled by adding 28 µL polymerase mixture (final concentration: 50 mM Tris-HCl at pH 7.5, 10 mM KCL, 5 mM MgCl₂, 1 mM DTT, 10 mM EDTA, 4 ng/µL of RNA template, and 75 nM HCV Δ21 NS5b polymerase) to assay plates followed by 4 µL of compound
25 dilution. The polymerase and compound were pre-incubated at 35 °C for 10 minute before the addition of 8 µL of nucleotide substrate mixture (33P-α-labeled competing nucleotide at K_M and 0.5 mM of the remaining three nucleotides). The assay plates were covered and incubated at 35 °C for 90 min. Reactions were then filtered through 96-well DEAE-81 filter plates via vacuum. The filter plates were then washed under
30 vacuum with multiple volumes of 0.125 M NaHPO₄, water, and ethanol to remove unincorporated label. Plates were then counted on TopCount to assess the level of product synthesis over background controls. The IC₅₀ value was determined using Prism fitting program.

Preferably, compounds described herein inhibited NS5b polymerase with an
35 IC₅₀'s below 1000 µM, more preferably below 100 µM, and most preferably below 10

- 5 μM . Representative examples of the activity of the compounds of the invention are shown in Table 30 below wherein A represents an IC_{50} below $10 \mu\text{M}$, B represent an IC_{50} from 10 to $200 \mu\text{M}$, and C represents an IC_{50} above $200 \mu\text{M}$.

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

10

Example No.	IC_{50} , μM
1	A
5	B
6	C
7	B
11	C
17	B

HCV EC_{50} Determination

- Replicon cells were seeded in 96-well plates at a density of 8×10^3 cells per well in $100 \mu\text{L}$ of culture medium, excluding Geneticin. Compound was serially
15 diluted in 100% DMSO and then added to the cells at a 1:200 dilution, achieving a final concentration of 0.5% DMSO and a total volume of $200 \mu\text{L}$. Plates were incubated at 37°C for 3 days, after which culture medium was removed and cells were lysed in lysis buffer provided by Promega's luciferase assay system. Following the
20 manufacturer's instruction, $100 \mu\text{L}$ of luciferase substrate was added to the lysed cells and luciferase activity was measured in a TopCount luminometer. Preferably, compounds described herein had EC_{50} 's below $1000 \mu\text{M}$, more preferably below $100 \mu\text{M}$, and most preferably below $10 \mu\text{M}$. For example, compounds 1, 17 and 18 had EC_{50} 's of less than $10 \mu\text{M}$ while compounds 9 and 3 had EC_{50} 's of less than $250 \mu\text{M}$.

25

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

5 Cytotoxicity Cell Culture Assay (Determination of CC50):

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

Assay protocol for determination of CC50:

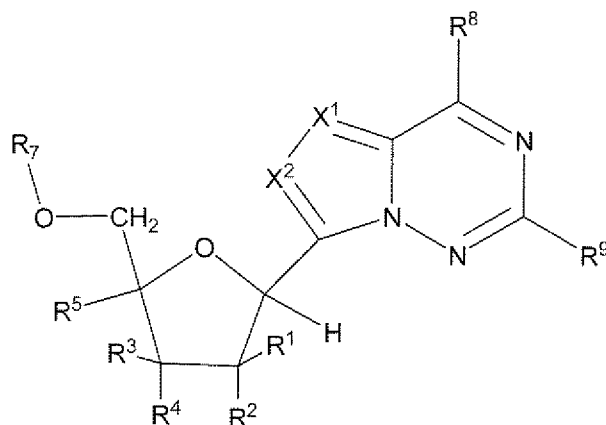
1. Maintain MT-2 cells in RPMI-1640 medium supplemented with 5% fetal bovine
10 serum and antibiotics.
2. Distribute the cells into a 96-well plate (20,000 cell in 100 μ l media per well) and
add various concentrations of the tested compound in triplicate (100 μ l/well).
Include untreated control.
3. Incubate the cells for 5 days at 37 °C.
- 15 4. Prepare XTT solution (6 ml per assay plate) in dark at a concentration of 2mg/ml
in a phosphate-buffered saline pH 7.4. Heat the solution in a water-bath at 55°C
for 5 min. Add 50 μ l of N-methylphenazonium methasulfate (5 μ g/ml) per 6 ml of
XTT solution.
5. Remove 100 μ l media from each well on the assay plate and add 100 μ l of the
20 XTT substrate solution per well. Incubate at 37 °C for 45 to 60 min in a CO₂
incubator.
6. Add 20 μ l of 2% Triton X-100 per well to stop the metabolic conversion of XTT.
7. Read the absorbance at 450 nm with subtracting off the background at 650 nm.
8. Plot the percentage absorbance relative to untreated control and estimate the CC50
25 value as drug concentration resulting in a 50% inhibition of the cell growth.
Consider the absorbance being directly proportional to the cell growth.

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

- 30 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.

5 What is claimed is

1. A compound of Formula I:



Formula I

10 or a pharmaceutically acceptable salt, thereof;

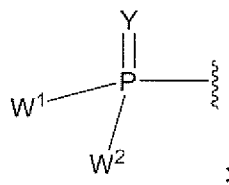
wherein:

at least one of R^1 , R^2 , R^3 , R^4 , or R^5 is $N(R^a)_2$, N_3 , CN , NO_2 , $S(O)_nR^a$, halogen, (C_1-C_8) alkyl, (C_4-C_8) carbocyclylalkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl or aryl(C_1-C_8)alkyl and each remaining R^1 , R^2 , R^3 , R^4 , or R^5 is, independently, H, OR^a , $N(R^a)_2$, N_3 , CN , NO_2 , $S(O)_nR^a$, halogen, (C_1-C_8) alkyl, (C_4-C_8) carbocyclylalkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl or aryl(C_1-C_8)alkyl or any two R^1 , R^2 , R^3 , R^4 , or R^5 on adjacent carbon atoms when taken together are $-O(CO)O-$ or when taken together with the ring carbon atoms to which they are attached form a double bond;

each n is independently 0, 1, or 2;

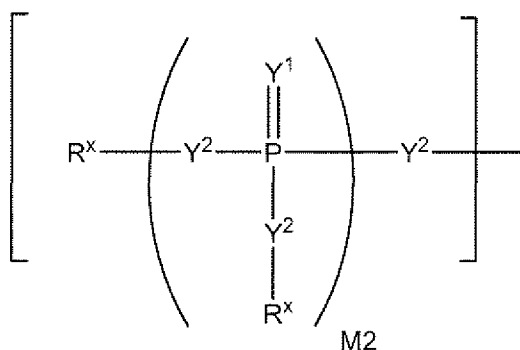
each R^a is independently H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, aryl(C_1-C_8)alkyl, (C_4-C_8) carbocyclylalkyl, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$;

25 R^7 is H, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, or



5 each Y or Y¹ is, independently, O, S, NR, ⁺N(O)(R), N(OR), ⁺N(O)(OR), or N-NR₂;

W¹ and W², when taken together, are -Y³(C(R^y)₂)₃Y³-; or one of W¹ or W² together with either R³ or R⁴ is -Y³- and the other of W¹ or W² is Formula Ia; or W¹ and W² are each, independently, a group of the Formula Ia:



Formula Ia

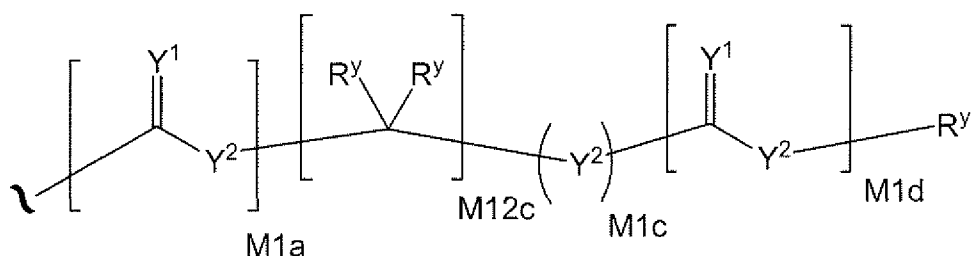
wherein:

each Y² is independently a bond, O, CR₂, NR, ⁺N(O)(R), N(OR), ⁺N(O)(OR), N-NR₂, S, S-S, S(O), or S(O)₂;

15 each Y³ is independently O, S, or NR;

M2 is 0, 1 or 2;

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



wherein:

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

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

each R^y is independently H, F, Cl, Br, I, OH, R, -C(=Y¹)R, -C(=Y¹)OR, -C(=Y¹)N(R)₂, -N(R)₂, -⁺N(R)₃, -SR, -S(O)R, -S(O)₂R, -S(O)(OR), -S(O)₂(OR), -OC(=Y¹)R, -OC(=Y¹)OR, -OC(=Y¹)(N(R)₂), -SC(=Y¹)R, -SC(=Y¹)OR, -

25 SC(=Y¹)(N(R)₂), -N(R)C(=Y¹)R, -N(R)C(=Y¹)OR, -N(R)C(=Y¹)N(R)₂, -SO₂NR₂, -CN, -N₃, -NO₂, -OR, or W³; or when taken together, two R^y on the same carbon atom form a carbocyclic ring of 3 to 7 carbon atoms;

5 each R is independently H, (C₁-C₈) alkyl, (C₁-C₈) substituted alkyl, (C₂-C₈) alkenyl, (C₂-C₈) substituted alkenyl, (C₂-C₈) alkynyl, (C₂-C₈) substituted alkynyl, C₆-C₂₀ aryl, C₆-C₂₀ substituted aryl, C₂-C₂₀ heterocyclyl, C₂-C₂₀ substituted heterocyclyl, arylalkyl or substituted arylalkyl;

W³ is W⁴ or W⁵; W⁴ is R, -C(Y¹)R^y, -C(Y¹)W⁵, -SO₂R^y, or -SO₂W⁵; and W⁵ is
 10 a carbocycle or a heterocycle wherein W⁵ is independently substituted with 0 to 3 R^y groups;

each X¹ or X² is independently C-R¹⁰ or N wherein at least one of X¹ or X² is N;

each R⁸ is, independently, halogen, NR¹¹R¹², N(R¹¹)OR¹¹, NR¹¹NR¹¹R¹², N₃,
 15 NO, NO₂, CHO, CN, -CH(=NR¹¹), -CH=NHNR¹¹, -CH=N(OR¹¹), -CH(OR¹¹)₂, -C(=O)NR¹¹R¹², -C(=S)NR¹¹R¹², -C(=O)OR¹¹, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₄-C₈)carbocyclalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(=O)(C₁-C₈)alkyl, -S(O)_n(C₁-C₈)alkyl or aryl(C₁-C₈)alkyl, OR¹¹ or SR¹¹;

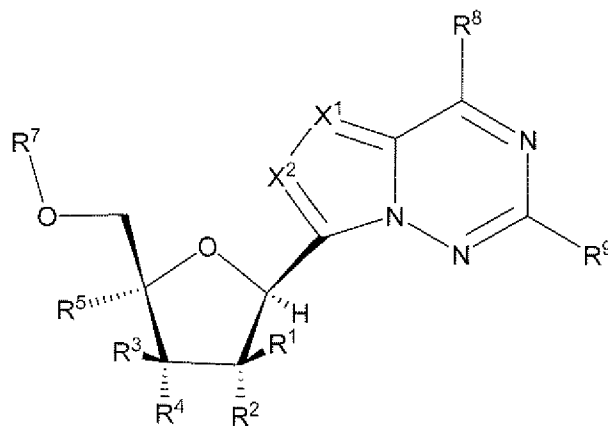
20 each R⁹ or R¹⁰ is independently H, halogen, NR¹¹R¹², N(R¹¹)OR¹¹, NR¹¹NR¹¹R¹², N₃, NO, NO₂, CHO, CN, -CH(=NR¹¹), -CH=NHNR¹¹, -CH=N(OR¹¹), -CH(OR¹¹)₂, -C(=O)NR¹¹R¹², -C(=S)NR¹¹R¹², -C(=O)OR¹¹, R¹¹, OR¹¹ or SR¹¹;

each R¹¹ or R¹² is independently H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₄-C₈)carbocyclalkyl, optionally substituted aryl, optionally
 25 substituted heteroaryl, -C(=O)(C₁-C₈)alkyl, -S(O)_n(C₁-C₈)alkyl or aryl(C₁-C₈)alkyl; or R¹¹ and R¹² taken together with a nitrogen to which they are both attached form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with -O-, -S- or -NR^a-;

wherein each (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl or aryl(C₁-C₈)alkyl
 30 of each R¹, R², R³, R⁴, R⁵, R¹¹ or R¹² 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 (C₁-C₈)alkyl may be optionally replaced with -O-, -S- or -NR^a-.

35 2. A compound according to claim 1 wherein R⁸ is halogen, NR¹¹R¹², N(R¹¹)OR¹¹, NR¹¹NR¹¹R¹², OR¹¹ or SR¹¹.

- 5 3. A compound according to claims 1 or 2 wherein R^9 is H or $NR^{11}R^{12}$.
4. A compound according to any one of claims 1-3 represented by Formula II

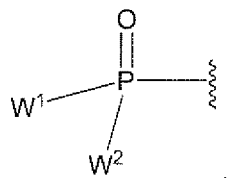


Formula II

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wherein each Y and Y^1 is O.

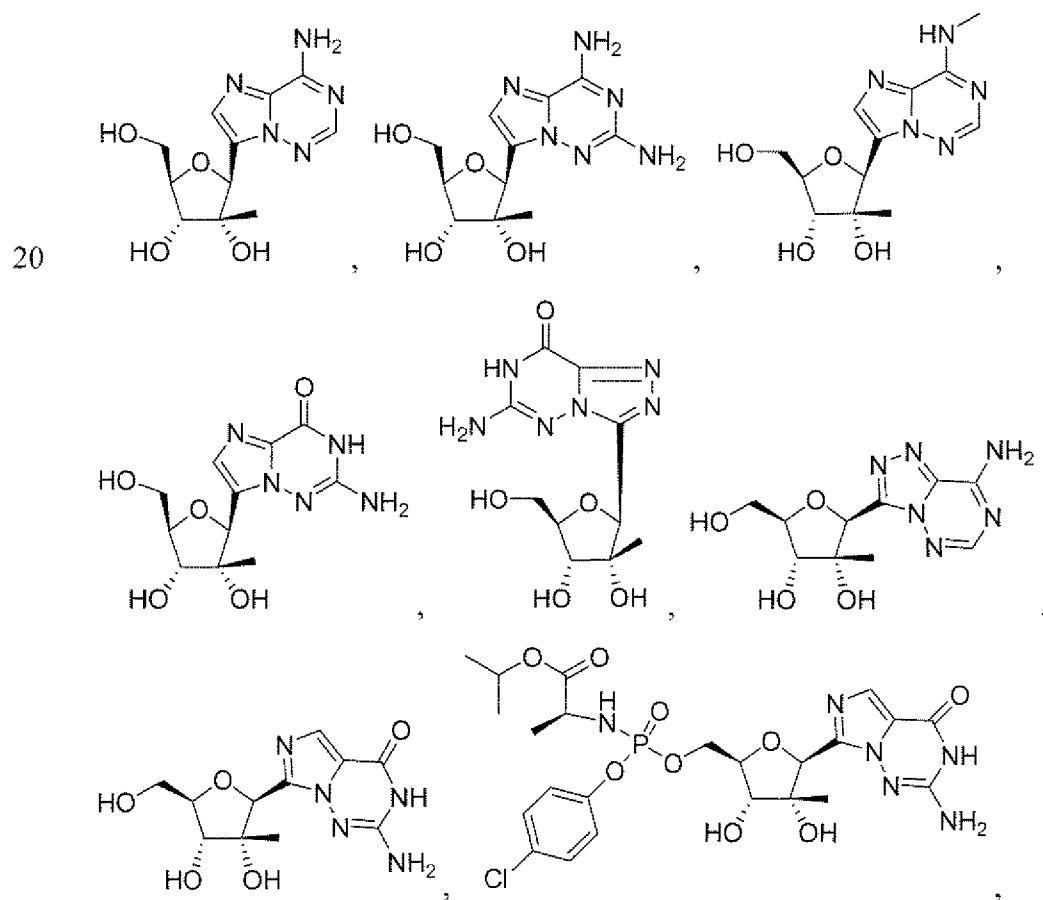
5. A compound according to any one of claims 1-4 wherein R^7 is H or

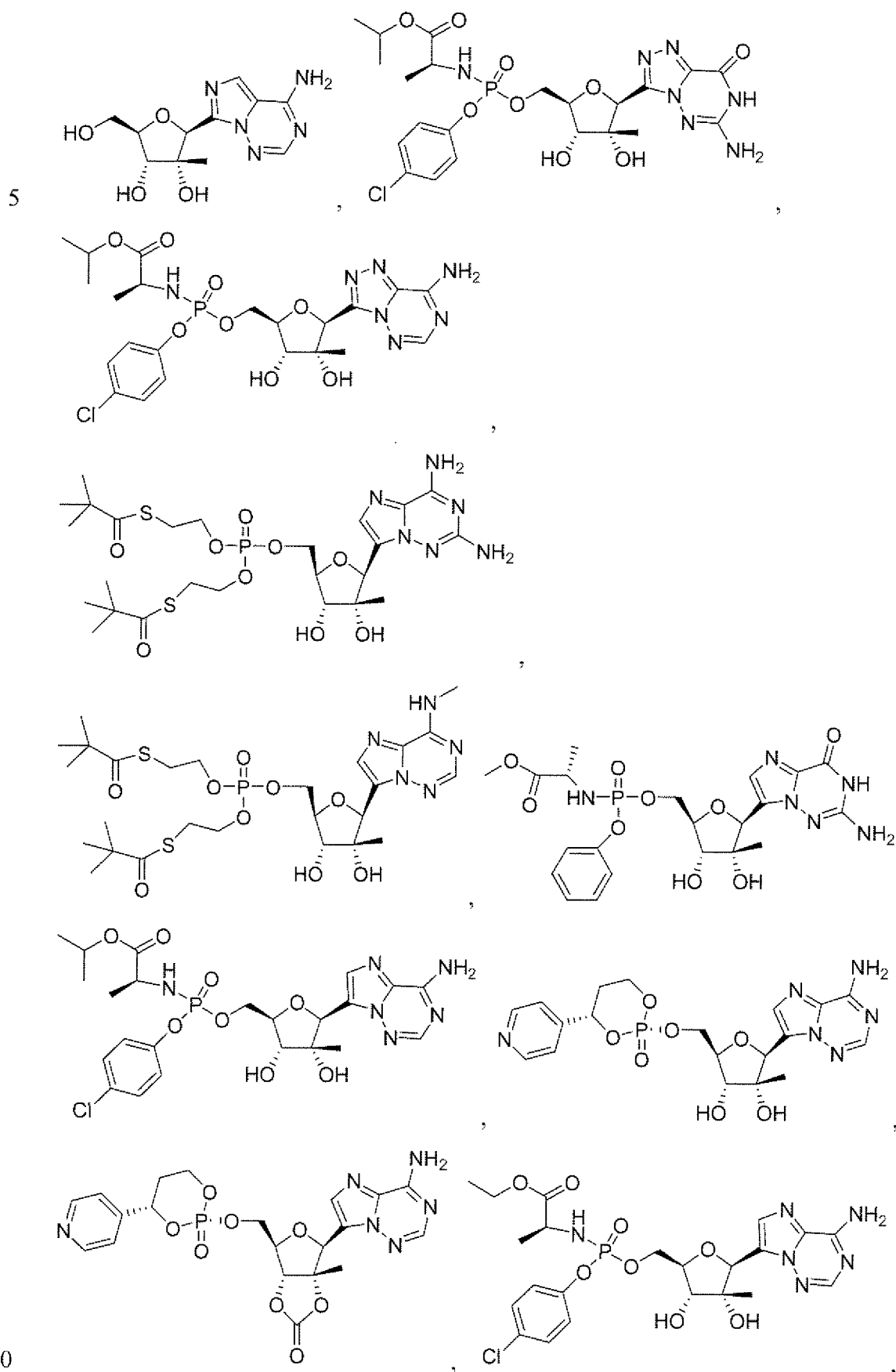


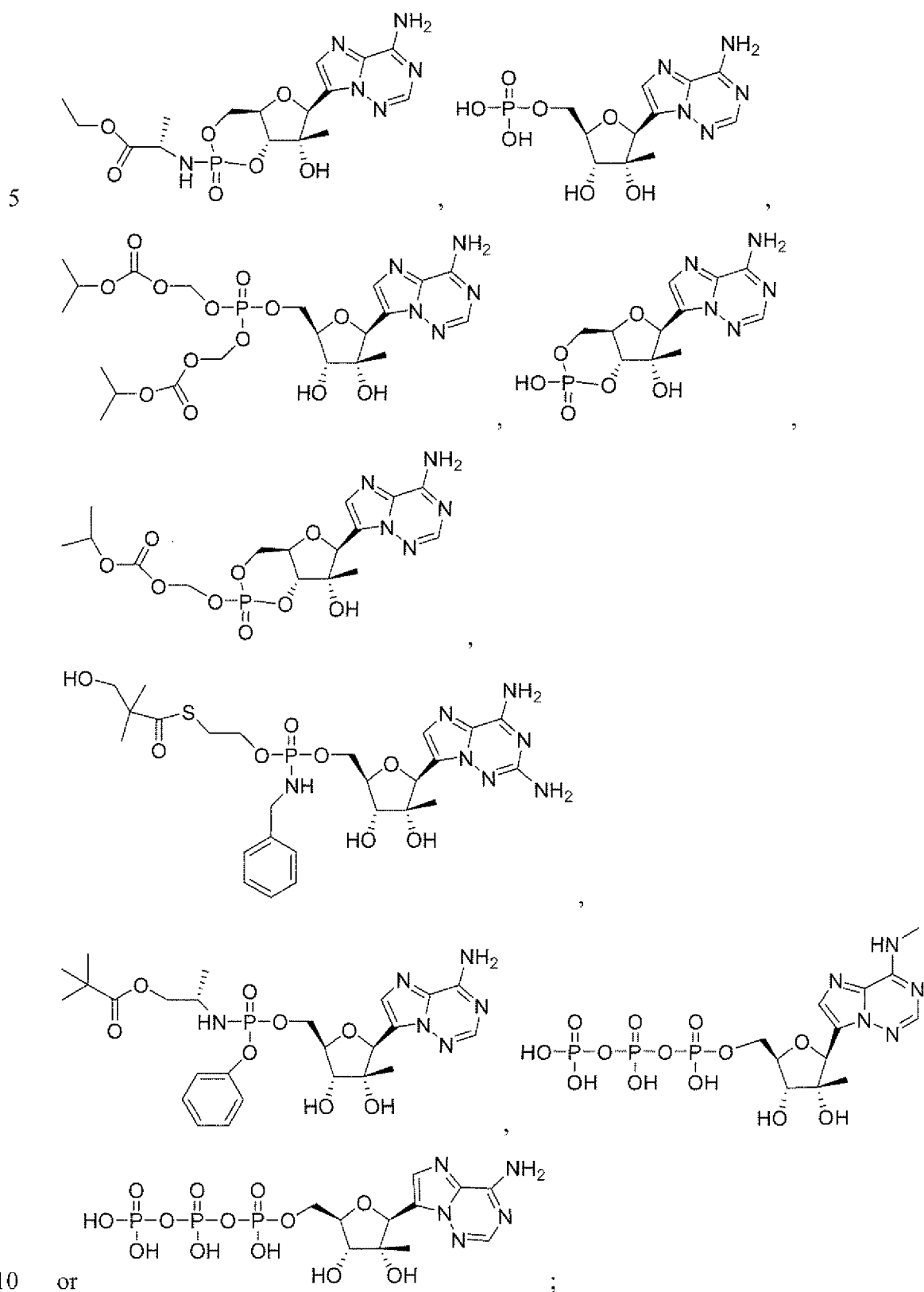
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6. A compound according to any one of claims 1-5 wherein X^1 is N and R^3 is H.
7. A compound according to any one of claims 1-6 wherein at least one of R^2 or R^4 is OR^a .
- 20 8. A compound according to any one of claims 1-7 wherein each R^2 and R^4 is OR^a .
- 25 9. A compound according to any one of claims 1-8 wherein X^2 is CH and R^1 is selected from methyl, CH_2OH , CH_2F , ethenyl, or ethynyl.

- 5 10. A compound according to any one of claims 1-8 wherein X^2 is CH , R^1 is H and R^5 is N_3 , CN , methyl, CH_2OH , ethenyl, or ethynyl.
11. A compound according to any one of claims 1-9 wherein R^1 is methyl.
- 10 12. A compound according to any one of claims 1-9 or 11 wherein R^5 is H .
13. A compound according to any one of claims 1-12 wherein R^2 and R^4 are OH .
14. A compound according to any one of claims 1-13 wherein W^1 and W^2 are
15 each, independently, a group of the Formula Ia.
15. A compound according to any one of claims 1-13 wherein R^7 is H .
16. A compound according to claim 1 that is







5 17. A compound according to any one of claims 1-16 that is in a form of a racemate, enantiomer, diastereomer, tautomer, polymorph, pseudopolymorph or amorphous form.

18. A pharmaceutical composition comprising a therapeutically effective amount
10 of a compound as in any one of claims 1 to 17 and a pharmaceutically acceptable carrier.

19. The pharmaceutical composition of claim 18 further comprising at least one
15 additional therapeutic agent.

20. The pharmaceutical composition of claim 19, wherein said additional
therapeutic agent is selected from the group consisting of interferons, ribavirin
analogs, NS3 protease inhibitors, NS5a inhibitors, NS5b polymerase inhibitors,
alpha-glucosidase 1 inhibitors, cyclophilin inhibitors, hepatoprotectants, non-
20 nucleoside inhibitors of HCV, and other drugs for treating HCV.

21. A method of inhibiting HCV polymerase comprising the administration to a
mammal in need of such treatment a therapeutically effective amount of a compound
of any one of claims 1 to 16.

25 22. A method of treating a viral infection caused by a virus of the *Flaviviridae*
family comprising the administration to a mammal in need of such treatment a
therapeutically effective amount of a compound or pharmaceutical composition of any
one of claims 1 to 16.

30 23. The method of claim 22 wherein the viral infection is caused by a virus
selected from the group consisting of dengue virus, yellow fever virus, West Nile
virus, Japanese encephalitis virus, tick-borne encephalitis virus, Kunjin virus, Murray
Valley encephalitis virus, St. Louis encephalitis virus, Omsk hemorrhagic fever virus,
35 bovine viral diarrhea virus, Zika virus and Hepatitis C virus.

5 24. The method of claim 23 wherein the viral infection is caused by Hepatitis C virus.

25. The method of any one of claims 22-24 further comprising administering at least one additional therapeutic agent.

10

26. The method of claim 25 wherein said at least one additional therapeutic agent is selected from the group consisting of interferons, ribavirin analogs, NS3 protease inhibitors, NS5b polymerase inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, cyclophilin inhibitors, hepatoprotectants, non-nucleoside inhibitors of
15 HCV, and other drugs for treating HCV.

27. A compound as in any one of claims 1 to 16 used in the manufacture of a medicament for treating a viral infection caused by a virus selected from the group consisting of dengue virus, yellow fever virus, West Nile virus, Japanese encephalitis
20 virus, tick-borne encephalitis virus, Kunjin virus, Murray Valley encephalitis virus, St. Louis encephalitis virus, Omsk hemorrhagic fever virus, bovine viral diarrhea virus, Zika virus and Hepatitis C virus.

28. A compound or method as described herein.

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