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(54) **NUCLEOTIDE ANALOGS**

NUKLEOTIDANALOGA

ANALOGUES NUCLÉOTIDIQUES

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(56) References cited:
WO-A2-2007/002912 **WO-A2-2008/104408**
US-A1- 2009 291 922 **US-A1- 2012 116 067**
US-A1- 2013 029 940 **US-A1- 2014 274 959**

- **REDDY, KR ET AL.: 'Pradefovir: A Prodrug That Targets Adefovir to the Liver for the Treatment of Hepatitis B';' JOURNAL OF MEDICINAL CHEMISTRY vol. 51, no. ISSUE, 14 February 2008, pages 666 - 676, XP055368521**

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EP 3 350 191 B9

Description

STATEMENT OF RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/380,205 filed September 15, 2015.

FIELD

[0002] The present application is directed to nucleotide analogs, pharmaceutical compositions that include a disclosed nucleotide analog, and processes for their synthesis. The invention also includes methods of treating diseases and/or conditions with the disclosed nucleotide analog, alone or in combination therapy with one or more other agents, including in particular for the treatment of a viral infection in a host such as that caused by a papillomavirus.

BACKGROUND OF THE INVENTION

[0003] Viruses are infectious particles that can replicate their DNA or RNA only within host cells. Viral infections may lead to mild to severe illnesses in humans and mammals, and in some instances, can result in death. Examples of viral infections include hepatitis B and C, smallpox, herpes simplex, cytomegalovirus, human immunodeficiency virus (HIV), influenza, adenovirus, chickenpox, BK virus, JC virus and papillomavirus. Viral infection can lead to cancer in humans and other species. Viruses known to cause cancer include human papillomavirus (HPV), hepatitis B virus (HBV), hepatitis C virus (HCV), HIV and Epstein Barr virus (EBV).

[0004] Papillomaviruses are a group of non-enveloped DNA viruses, which in humans infect keratinocytes of skin and mucous membranes including in the anogenital area. They are known to cause skin warts, genital warts, and respiratory papillomatosis and cancer. In women, Papillomaviruses can cause precancerous cervical lesions which lead to cervical intraepithelial neoplasia, vaginal and anal intraepithelial neoplasia, and ultimately cervical cancer.

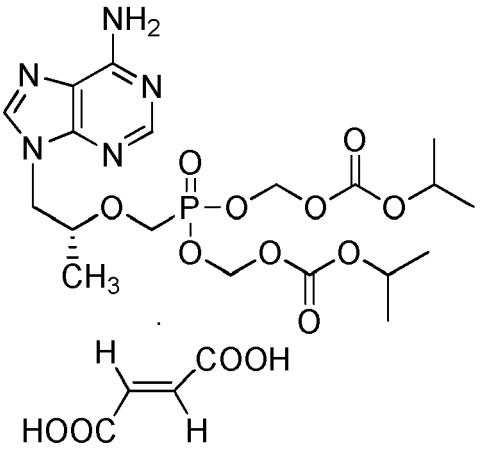
[0005] Several species of the alpha-papillomavirus genus contain high risk types of HPV which are more likely to lead to human cancer. Most of the cancer-causing HPV types are from the alpha-7 and alpha-9 species and include types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82. Cancers caused by HPV include cervical, rectal, penile, vaginal and oropharyngeal cancer. The most common cancer-causing HPV types are 16 and 18. HPV-16 and -18 are reported to be the cause of 70% of cervical cancers; and 90% of venereal warts are caused by the low risk HPV types 6 and 11. The presence of a HPV infection can be detected using a PAP smear and/or DNA probe testing with products such as CEREVISTA® (Hologic), COBAS® (Roche) and other commercially available products. Currently available HPV DNA tests detect DNA from 14 high-risk HPV types, including HPV-16 and HPV 18. Vaccines have been developed for HPV 6, 11, 16 and 18, which may be effective if administered prior to sexual debut. However, the HPV vaccines may provide little benefit in sexually active women who have already been infected with HPV.

[0006] HPV replication and viral DNA synthesis that produce mature virions first takes place in the basilar layer of cervical epithelial cells and amplifies to involve the suprabasilar cells as the infection proceeds. After months or years of infection, elements of the HPV DNA episome can become integrated into the epithelial cell genomic DNA. The integrated elements generally include viral L1, the long control region (LCR), and the E6 and E7 oncogenes. This results in overexpression of E6 and E7 oncoproteins that over time cause the loss of cell cycle controls and progression to cervical cancer. However, in cervical cancer cell lines which have integrated HPV DNA such as HeLa (HPV18), SiHa (HPV16), CaSki (HPV16) and Me180 (HPV39) productive viral replication is not occurring. Thus, studies of compounds which inhibit cell division of human cervical cancer cell lines that contain integrated E6 and E7 do not provide knowledge about the inhibition of productive viral DNA synthesis. Additional information regarding HPV and its replication is provided in Fields Virology 1662-1703 (David M. Knipe, Ph.D. and Peter M. Howley, MD eds., 6th ed., Wolters Kluwer, 2013) (2001). There is presently no approved antiviral treatment for a human papillomavirus infection.

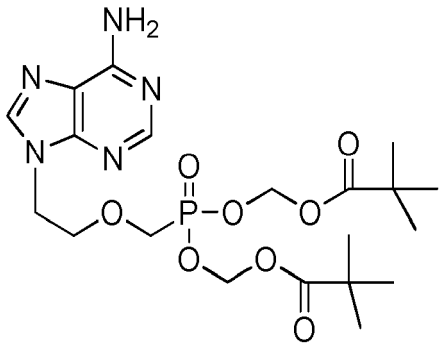
[0007] One class of antiviral drugs are nucleoside or nucleotide analogs, which interfere with DNA or RNA replication necessary for viral growth. Examples of antiviral nucleoside analogs include RETROVIR®, ZOVIRAX®, CYTOVENE®, EPIVIR® and EMTRIVA®.

[0008] Nucleotide analogs include the acyclic nucleoside phosphonates (ANPs). Nucleotide analogs were initially designed to circumvent the first phosphorylation of a parent nucleoside. This first phosphorylation has been identified as the limiting step in the generation of the active nucleoside triphosphate. Examples of ANPs include adefovir, tenofovir and cidofovir (CDV) which are active against human infections such as HBV, HIV and CMV, respectively. ANPs are known in the art to be poorly adsorbed from the gastrointestinal tract of mammals due to 1) their molecular weight and 2) the presence of a double negative charge on the phosphonate moiety. Because of their poor oral pharmacokinetic properties, ANPs have been converted to prodrugs to produce clinically useful therapeutic agents. For example, tenofovir is marketed as VIREAD®; a disoproxil (diester) fumarate salt, for the treatment of HIV. Adefovir is marketed as HEPSE-

RA®; a dipivoxil ester, for the treatment of HBV.

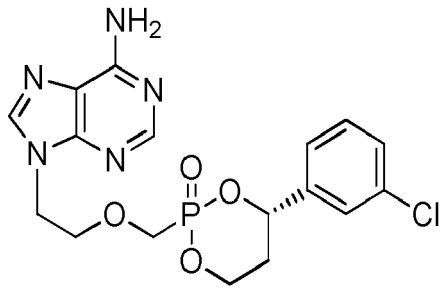


VIREAD®, tenofovir disoproxil fumarate

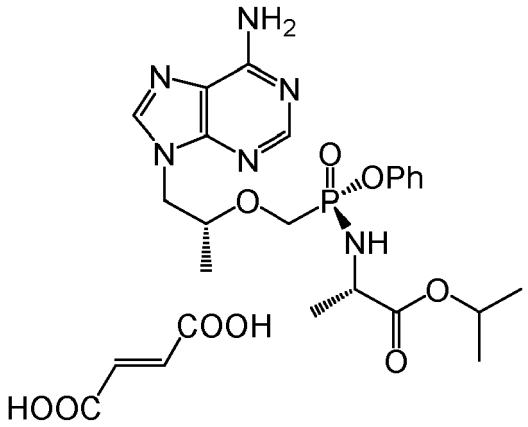


HEPSERA®, adefovir dipivoxil

[0009] Additional examples of ANP prodrugs include pradefovir (Phase III) and GS-7340. GS-7340, tenofovir alafenamide, has been approved for the treatment of HIV and is part of the fixed-dose combinations GENVOYA®, ODEFSEY® and DESCOVY®. See, for example, Pradere, U. et al., "Synthesis of Nucleoside and Phosphonate Prodrugs", Chemical Reviews, 2014, 114, 9154-9218 and the structures below.



Pradefovir



GS-7340

[0010] An alternate approach to increasing the oral bioavailability of ANPs has been to prepare alkoxyalkyl monoesters or alkyl monoesters. See, for example, Beadle et al., "Synthesis and Antiviral Evaluation of Alkoxyalkyl Derivatives of 9-(S)-(3-Hydroxy-2-phosphono-methoxypropyl)adenine against Cytomegalovirus", J. Med. Chem., 2006, 49:2010-215; Painter et al., "Evaluation of Hexadecyloxypropyl-9-R-[2-(Phosphonomethoxy)Propyl]-Adenine, CMX157, as a Potential Treatment for Human Immunodeficiency Virus Type 1 and Hepatitis B Virus Infections," Antimicrobial Agents and Chemotherapy, 2007, 51:3505-3509; Valiaeva et al., "Synthesis and antiviral evaluation of alkoxyalkyl esters of acyclic purine and pyrimidine nucleoside phosphonates against HIV-1 in vitro", Antiviral Research, 2006, 72:10-19; Aldern et al., "Update and Metabolism of Cidofovir and Oleyloxyethyl-cidofovir in Human Papillomavirus Positive ME-180 Human Cervical Cancer Cells" Abstract 173 Antiviral Res., 2007, 74(3):A83; Hostetler et al., "Enhanced Anti-proliferative effects of alkoxyalkyl esters of cidofovir in human cervical cancer cells in vitro" Mol. Cancer Ther., 2006, 51(1):156-158; Trahan et al., "Anti-proliferative Effects of Octadecyloxyethyl-Phosphonomethoxyethylguanine (ODE-PMEG) on the Growth of Human Papilloma Virus Positive Cervical Carcinoma (ME-180) Cells in Vitro and Solid Tumors in Athymic Nude Mice" Abstract 85 Antiviral Res., 2009, 82(2):A42; Valiaeva et al., "Anti-proliferative Effects of Octadecyloxyethyl 9-[2-(Phosphonomethoxy)Ethyl] Guanine against Me-180 Human Cervical Cancer Cells in vitro and in vivo", Chemotherapy, 2010, 56:(1)54-59; Valiaeva et al., "Synthesis and antiviral evaluation of 9-(S)-[3-alkoxy-2-(phosphonomethoxy)-propyl] nucleoside alkoxyalkyl esters: Inhibitors of hepatitis C virus and HIV-1 replication", Bioorganic and Medicinal Chemistry,

2011, 19:4616-4625. In addition, see the patent applications and patents to Hostetler: US Pat. Nos.: 6,716,825; 7,034,014; 7,094,772; 7,098,197; 7,652,001; 7,452,898; 7,790,703; 7,687,480; 7,749,983; 7,994,143; 8,101,745; 8,008,308; 8,193,167; 8,309,565; 8,318,700; 8,846,643; 8,710,030; 8,889,658, 9,156,867; 9,387,217 and US 2015/0080344; The Regents of The University of California: WO 1996/39831; WO 2001/039724; WO 2005/087788; WO 2006/066074; WO 2006/076015; and WO 2011/130557; and the Dana Farber Cancer Institute, Inc.: WO/1998/38202.

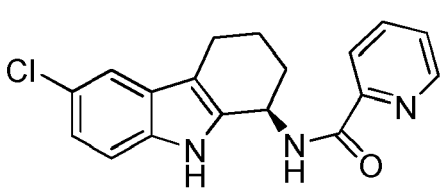
[0011] A hexadecyloxypropyl ester of cidofovir, HDP-CDV (brincidofovir), is currently being developed for the treatment of adenovirus. The drug is currently in Phase III. See, for example, US 9,006,218; US 8,993,542; US 8,962,829; US 8,614,200; US 8,569,321; US 7,994,143; US 7,749,983; US 6,599,887; US 6,448,392; WO 2007/130783; WO 2008/133966; WO 2009/094190; WO 2011/011519; WO 2011/011710; WO 2011/017253 and WO 2011/053812.

[0012] The synthesis of phosphonomethoxyethyl or 1,3-bis(phosphonomethoxy)propan-2-yl lipophilic esters of acyclic nucleoside phosphonates, and alkyl diesters of ANPs have been disclosed See, Holy et al., "Structure-Antiviral Activity Relationship in the Series of Pyrimidine and Purine N-[2-(2-Phosphono-methyloxy)ethyl] Nucleotide Analogues. Derivatives Substituted at the Carbon Atoms of the base", J. Med. Chem., 1999, 42(12):2064-2086; Holy et al., "Synthesis of phosphonomethoxyethyl or 1,3-bis(phosphonomethoxy) propan-2-yl lipophilic esters of acyclic nucleoside phosphonates", Tetrahedron, 2007, 63:11391-11398. The synthesis of anti-cancer phosphonate analogs has also been investigated; see, WO 2004/096235; WO 2005/066189 and WO 2007/002808. The synthesis of prodrugs of ANPs has also been investigated; see, WO 2006/114064 and WO 2006/114065. The synthesis of purine nucleoside monophosphate prodrugs for the treatment of cancer and viral infections has also been investigated; see, WO 2010/091386.

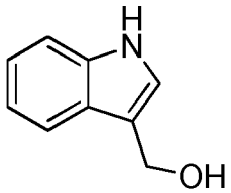
[0013] Certain acyclic nucleoside phosphonate diesters are disclosed in U.S. Pat Nos. 8,835,630; 9,156,867; and 9,387,217.

[0014] While there are currently no approved pharmaceutical drugs that are used to treat an early HPV infection that has not yet progressed to cancer, certain epicatechins, epicatechin oligomers or thiolated epicatechins from *Theobroma cacao* for treatment of genital warts have been disclosed; see, US 2015/0011488.

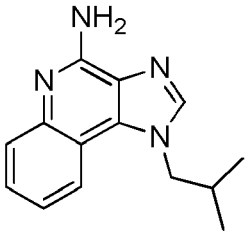
[0015] The pyrimidine, 5-fluorouracil, is active against HPV but is highly toxic. The broad spectrum antiviral agent GSK983 has been shown to have anti HPV activity but has not been studied extensively in humans yet. Other small molecules having anti-HPV activity include the cobalt complex CDC-96, indol-3-carbinol (I3C) and the immunomodulatory Imiquimod, see, US 2015/0011488.



GSK983



I3C



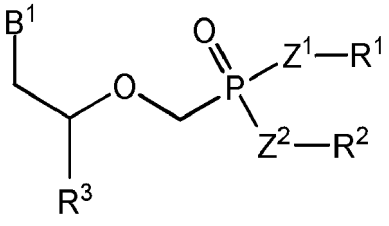
Imiquimod

[0016] To date, there are no approved pharmaceutical drugs that are used to treat an early HPV infection that has not yet progressed to cancer. Provided herein are solutions to these and other problems in the art.

[0017] WO 2007/002912 A2 describes compounds and compositions and methods of use thereof, useful for treating viral infections, in particular human papillomavirus.

BRIEF SUMMARY OF THE INVENTION

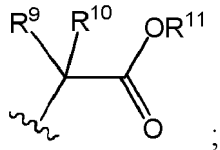
[0018] The present invention provides new compounds, composition and compounds for use in methods for the treatment of viral diseases including in particular including those caused by papillomaviruses. Specifically, the invention provides compounds of the structure of Formula (I), or a pharmaceutically acceptable salt thereof:



(I),

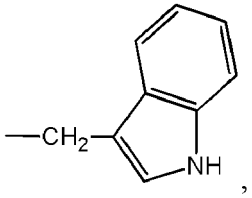
wherein:

B^1 is selected from adenine, hypoxanthine, xanthine, theobromine, caffeine, uric acid, isoguanine, 2,6-diaminopurine, cytosine, thymine or uracil, guanine-7-yl, adenine-9-yl, cytosine-1-yl, thymin-1-yl, uracil-1-yl, 2,6-diaminopurin-9-yl, 5-fluorouracil, 5-fluorocytosine, 7-deazaguanine and 9-deazaguanine;
Z^1 is NH;
Z^2 is O or NR^Z;
R^Z is hydrogen or C_{1-4} alkyl;
R^1 is



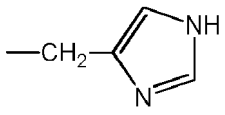
;

R^2 is aryl(C_{1-4} alkyl)-;
R^3 is hydrogen, alkyl or heteroalkyl;
each R^9 and each R^{10} are independently selected from hydrogen, C_{1-6} alkyl, $-CH_2SH$, $-CH_2(C=O)NH_2$, $-CH_2CH_2(C=O)NH_2$, $-CH_2CH_2S\,CH_3$, CH_2- phenyl, $-CH_2OH$, $-CH(OH)CH_3$,



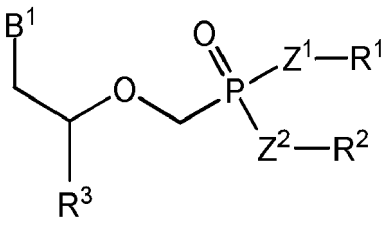
,

$-CH_2(C=O)OH$, $-CH_2CH_2(C=O)OH$, $-(CH_2)_3NH(C=NH)NH_2$,



and $-(CH_2)_4NH_2$; and
each R^{11} is independently selected from hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, alkynyl, cycloalkyl, cycloalkyl(C_1-C_4 alkyl)-, cycloalkenyl, cycloalkenyl(C_1-C_4 alkyl)-, aryl, aryl(C_{1-4} alkyl)-, heteroaryl, heteroaryl(C_1-C_4 alkyl)-, heterocyclyl, and heterocyclyl(C_1-C_4 alkyl)-.

[0019] Also provided is a compound of the structure of Formula (I), or a pharmaceutically acceptable salt thereof:

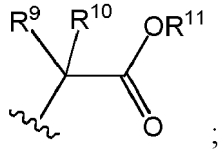


(I),

wherein:

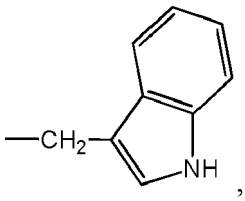
B^1 is guanine;
Z^1 is NH;
Z^2 is O or NR^Z;
R^Z is hydrogen or C_{1-4} alkyl;

R^1 is



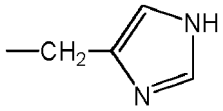
;

R^2 is aryl(C_{1-4} alkyl)-;
R^3 is alkyl or heteroalkyl;
each R^9 and each R^{10} are independently selected from hydrogen, C_{1-6} alkyl, $-CH_2SH$, $-CH_2(C=O)NH_2$, $-CH_2CH_2(C=O)NH_2$, $-CH_2CH_2S\,CH_3$, CH_2-phenyl, $-CH_2OH$, $-CH(OH)CH_3$,



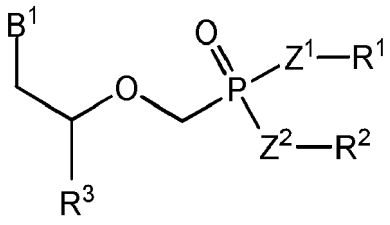
,

$-CH_2(C=O)OH$, $-CH_2CH_2(C=O)OH$, $-(CH_2)_3NH(C=NH)NH_2$,



and $-(CH_2)_4NH_2$; and
each R^{11} is independently selected from hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, alkynyl, cycloalkyl, cycloalkyl(C_1-C_4 alkyl)-, cycloalkenyl, cycloalkenyl(C_1-C_4 alkyl)-, aryl, aryl(C_{1-4} alkyl)-, heteroaryl, heteroaryl(C_1-C_4 alkyl)-, heterocyclyl, and heterocyclyl(C_1-C_4 alkyl)-.

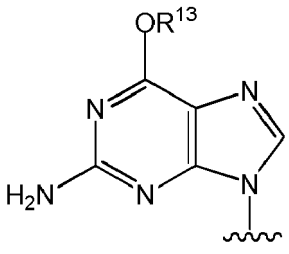
[0020] Also provided is a compound of the structure of Formula (I), or a pharmaceutically acceptable salt thereof:



(I),

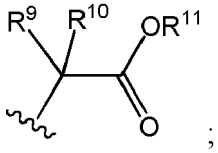
wherein:

B^1 is



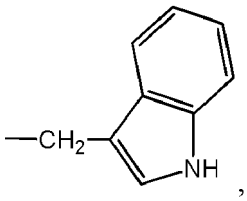
;

Z^1 is NH;
Z^2 is O or NR^Z;
R^Z is hydrogen or C_{1-4} alkyl;
R^1 is



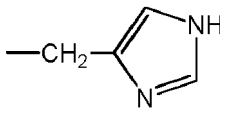
;

R^2 is aryl(C_{1-4} alkyl)-;
R^3 is alkyl or heteroalkyl;
each R^9 and each R^{10} are independently selected from hydrogen, C_{1-6} alkyl, $-CH_2SH$, $-CH_2(C=O)NH_2$, $-CH_2CH_2(C=O)NH_2$, $-CH_2CH_2S\ CH_3$, CH_2-phenyl, $-CH_2OH$, $-CH(OH)CH_3$,



,

$-CH_2(C=O)OH$, $-CH_2CH_2(C=O)OH$, $-(CH_2)_3NH(C=NH)NH_2$,

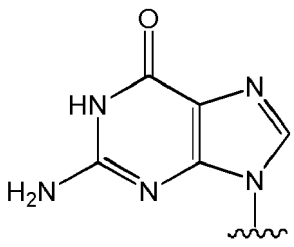


and $-(CH_2)_4NH_2$; and
each R^{11} is independently selected from hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, alkynyl, cycloalkyl, cycloalkyl(C_1-C_4 alkyl)-, cycloalkenyl, cycloalkenyl(C_1-C_4 alkyl)-, aryl, aryl(C_{1-4} alkyl)-, heteroaryl, heteroaryl(C_1-C_4 alkyl)-, heterocyclyl, and heterocyclyl(C_1-C_4 alkyl)-; and
R^{13} is unsubstituted C_{1-6} alkyl or an unsubstituted C_{3-6} cycloalkyl.

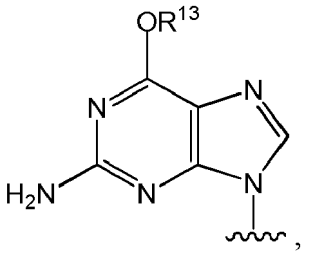
[0021] Also provided is a pharmaceutical composition comprising an effective amount of a compound as defined herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0022] Also provided is a compound as defined herein, or a pharmaceutically acceptable salt thereof, for use in treating a viral disease in a subject in need thereof, wherein the viral disease is human papilloma virus.

[0023] In an alternative embodiment, when B^1 is



or



R^{13} can be an unsubstituted C_{1-6} alkyl or an unsubstituted C_{3-6} cycloalkyl and R^3 can be selected from alkyl, or heteroalkyl such as OCH_3.

[0024] PMEG diphosphate is one of the most potent chain-terminating inhibitors of DNA polymerases alpha, delta and epsilon (Kramata P, Votruba I, Otová B, Holý A. Different inhibitory potencies of acyclic phosphonomethoxyalkyl nucleotide analogs toward DNA polymerases alpha, delta and epsilon. Mol Pharmacol. 1996 Jun;49(6): 1005-11. PubMed PMID: 8649338). However its inhibition of polymerases beta, gamma and epsilon is less pronounced. Pol delta and epsilon are involved in DNA repair and have exonuclease activity. Kramata et al have shown that PMEG-terminated primers cannot be repaired by pol delta (Kramata P, Downey KM, Paborsky LR. Incorporation and excision of 9-(2-phosphonylmethoxyethyl)guanine (PMEG) by DNA polymerase delta and epsilon in vitro. J Biol. Chem. 1998 Aug 21;273(34):21966-71. PubMed PMID: 9705337).

[0025] The mechanism of action of the antiviral compounds of the present invention that are metabolized to PMEG diphosphate is not known with certainty, however, it is possible that rapidly dividing epithelial cells cannot effectively repair PMEG terminated viral primers. Certain of the active compounds described herein release PMEG very slowly which tends to moderate intracellular levels of PMEG diphosphate, the active metabolite favoring antiviral activity and inhibition of HPV DNA synthesis, while higher intracellular levels of PMEG diphosphate (resulting from prodrugs that release PMEG diphosphate more quickly in the cell) lead to inhibition of cell division in a number of human cancers. This invention is based on the discovery that the anti-proliferative activity of the active metabolite PMEG diphosphate can be separated from the antiviral action of the active metabolite PMEG diphosphate by careful selection of the prodrug moiety to moderate the release rate of the active metabolite in the cell.

[0026] In embodiments, the invention describes compounds with antiviral activity against a papillomavirus in the absence of a significant anti-proliferative host cell effect.

[0027] The invention includes antiviral agents that selectively inhibit and/or block viral DNA synthesis and/or the production of virions of high risk HPV types. Inhibition and/or blockage of viral DNA synthesis and/or the production of virions of high risk HPV types can then eradicate the papillomavirus infection before cellular changes take place which can lead to invasive cancers, such as those described herein, and thus represent an advance in the art.

[0028] Also disclosed is the provision of an effective amount of an antiviral compound of Formula (I), or a pharmaceutically acceptable salt thereof, for treating a host infected with a human papillomavirus, by inhibiting the synthesis of viral DNA. Also disclosed is a compound for use in a method for treating a host infected with a human papillomavirus that includes contacting a cell infected with the human papillomavirus and/or administering to a subject infected with the human papillomavirus an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the human papillomavirus can be treated by selectively inhibiting viral replication by inhibiting the synthesis of viral DNA.

[0029] The present invention includes at least the following features:

(a) an antiviral compound of Formula I as described herein, and pharmaceutically acceptable salts thereof (each of which and all subgenera and species thereof considered individually and specifically described);

(b) an antiviral Formula I as described herein, and pharmaceutically acceptable salts thereof, for use in treating or preventing a viral infection such as papillomavirus in a host;

(c) use of Formula I, and pharmaceutically acceptable salts thereof in the manufacture of a medicament for use in treating or preventing a viral disease such as papillomavirus in a host;

(d) a process for manufacturing a medicament intended for the therapeutic use for treating or preventing treating or preventing a viral disease such as papillomavirus in a host further herein characterized in that Formula I as described herein is used in the manufacture;

(e) a pharmaceutical formulation comprising an effective host-treating amount of the Formula I or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent;

(f) Formula I as described herein in substantially pure form, including substantially isolated from other chemical entities (e.g., at least 90 or 95%);

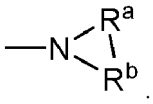
(g) processes for the manufacture of the compounds of Formula I and salts, compositions, dosage forms thereof; and
(h) processes for the preparation of therapeutic products that contain an effective amount of Formula I, as described herein.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0030] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0031] As used herein, any "R" group(s) such as, without limitation, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} represent substituents that can be attached to the indicated atom. An R group may be substituted or unsubstituted. If two "R" groups are described as being "taken together" the R groups and the atoms they are attached to can form a cycloalkyl, cycloalkenyl, aryl, heteroaryl or heterocycle. For example, without limitation, if R^a and R^b of an NR^aR^b group are indicated to be "taken together," it means that they are covalently bonded to one another to form a ring:



[0032] In addition, if two "R" groups are described as being "taken together" with the atom(s) to which they are attached to form a ring as an alternative, the R groups are not limited to the variables or substituents defined previously.

[0033] Whenever a group is described as being "optionally substituted" that group may be unsubstituted or substituted with one or more of the indicated substituents. Likewise, when a group is described as being "unsubstituted or substituted" if substituted, the substituent(s) may be selected from one or more of the indicated substituents. If no substituents are indicated, it is meant that the indicated "optionally substituted" or "substituted" group may be substituted with one or more group(s) individually and independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl), (heterocyclyl)alkyl, hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, azido, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, an amino, a mono-substituted amino group and a di-substituted amino group.

[0034] As used herein, "C_a to C_b," "C_a - C_b," "C_{a-b}" and the like in which "a" and "b" are integers, refer to the number of carbon atoms in an alkyl, alkenyl or alkynyl group, or the number of carbon atoms in the ring of a cycloalkyl, cycloalkenyl, aryl, heteroaryl or heterocyclyl group. That is, the alkyl, alkenyl, alkynyl, ring of the cycloalkyl, ring of the cycloalkenyl, ring of the aryl, ring of the heteroaryl or ring of the heterocyclyl can contain from "a" to "b", inclusive, carbon atoms. Thus, for example, a "C_1 to C_4 alkyl" group refers to all alkyl groups having from 1 to 4 carbons, that is, CH_3-, CH_3CH_2-, $CH_3CH_2CH_2$-, $(CH_3)_2CH$-, $CH_3CH_2CH_2CH_2$-, $CH_3CH_2CH(CH_3)$- and $(CH_3)_3C$-. If no "a" and "b" are designated with regard to an alkyl, alkenyl, alkynyl, cycloalkyl cycloalkenyl, aryl, heteroaryl or heterocyclyl group, the broadest range described in these definitions is to be assumed.

[0035] As used herein, "alkyl" refers to a straight or branched hydrocarbon chain that comprises a fully saturated (no double or triple bonds) hydrocarbon group. The alkyl group may have 1 to 20 carbon atoms (whenever it appears herein, a numerical range such as "1 to 20" refers to each integer in the given range; e.g., "1 to 20 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc., up to and including 20 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated). The alkyl group may also be a medium size alkyl having 1 to 10 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 6 carbon atoms. The alkyl group of the compounds may be designated as "C_1-C_4 alkyl" or similar designations. By way of example only, "C_1-C_4 alkyl" indicates that there are one to four carbon atoms in the alkyl chain, i.e., the alkyl chain is selected from methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl and t-butyl. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl and hexyl. The alkyl group may be substituted or unsubstituted.

[0036] As used herein, "alkenyl" refers to an alkyl group that contains in the straight or branched hydrocarbon chain one or more double bonds. An alkenyl group may be unsubstituted or substituted.

[0037] As used herein, "alkynyl" refers to an alkyl group that contains in the straight or branched hydrocarbon chain one or more triple bonds. An alkynyl group may be unsubstituted or substituted.

[0038] As used herein, "cycloalkyl" refers to a completely saturated (no double or triple bonds) mono- or multi- cyclic

hydrocarbon ring system. When composed of two or more rings, the rings may be joined together in a fused fashion. Cycloalkyl groups can contain 3 to 10 atoms in the ring(s) or 3 to 8 atoms in the ring(s). A cycloalkyl group may be unsubstituted or substituted. Typical cycloalkyl groups include, but are in no way limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

[0039] As used herein, "cycloalkenyl" refers to a mono- or multi- cyclic hydrocarbon ring system that contains one or more double bonds in at least one ring; although, if there is more than one, the double bonds cannot form a fully delocalized pi-electron system throughout all the rings (otherwise the group would be "aryl," as defined herein). When composed of two or more rings, the rings may be connected together in a fused fashion. A cycloalkenyl group may be unsubstituted or substituted.

[0040] As used herein, "aryl" refers to a carbocyclic (all carbon) monocyclic or multicyclic aromatic ring system (including fused ring systems where two carbocyclic rings share a chemical bond) that has a fully delocalized pi-electron system throughout all the rings. The number of carbon atoms in an aryl group can vary. For example, the aryl group can be a C_6-C_{14} aryl group, a C_6-C_{10} aryl group, or a C_6 aryl group. Examples of aryl groups include, but are not limited to, benzene, naphthalene and azulene. An aryl group may be substituted or unsubstituted.

[0041] As used herein, "heteroaryl" refers to a monocyclic or multicyclic aromatic ring system (a ring system with fully delocalized pi-electron system) that contain(s) one or more heteroatoms, that is, an element other than carbon, including but not limited to, nitrogen, oxygen and sulfur. The number of atoms in the ring(s) of a heteroaryl group can vary. For example, the heteroaryl group can contain 4 to 14 atoms in the ring(s), 5 to 10 atoms in the ring(s) or 5 to 6 atoms in the ring(s). Furthermore, the term "heteroaryl" includes fused ring systems where two rings, such as at least one aryl ring and at least one heteroaryl ring, or at least two heteroaryl rings, share at least one chemical bond. Examples of heteroaryl rings include, but are not limited to, furan, furazan, thiophene, benzothiophene, phthalazine, pyrrole, oxazole, benzoxazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, thiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, benzothiazole, imidazole, benzimidazole, indole, indazole, pyrazole, benzopyrazole, isoxazole, benzoisoxazole, isothiazole, triazole, benzotriazole, thiadiazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, purine, pteridine, quinoline, isoquinoline, quinazoline, quinoxaline, cinnoline and triazine. A heteroaryl group may be substituted or unsubstituted.

[0042] As used herein, "heterocyclyl" or "heteroalicyclyl" refer to three-, four-, five-, six-, seven-, eight-, nine-, ten-, up to 18-membered monocyclic, bicyclic and tricyclic ring system wherein carbon atoms together with from 1 to 5 heteroatoms constitute said ring system. A heterocycle may optionally contain one or more unsaturated bonds situated in such a way, however, that a fully delocalized pi-electron system does not occur throughout all the rings. The heteroatom(s) is an element other than carbon including, but not limited to, oxygen, sulfur and nitrogen. A heterocycle may further contain one or more carbonyl or thiocarbonyl functionalities, so as to make the definition include oxo-systems and thio-systems such as lactams, lactones, cyclic imides, cyclic thioimides and cyclic carbamates. When composed of two or more rings, the rings may be joined together in a fused fashion. Additionally, any nitrogens in a heterocyclyl or a heteroalicyclyl may be quaternized. Heterocyclyl or heteroalicyclic groups may be unsubstituted or substituted. Examples of such "heterocyclyl" or "heteroalicyclyl" groups include but are not limited to, 1,3-dioxin, 1,3-dioxane, 1,4-dioxane, 1,2-dioxolane, 1,3-dioxolane, 1,4-dioxolane, 1,3-oxathiane, 1,4-oxathiin, 1,3-oxathiolane, 1,3-dithiole, 1,3-dithiolane, 1,4-oxathiane, tetrahydro-1,4-thiazine, 2H-1,2-oxazine, maleimide, succinimide, barbituric acid, thiobarbituric acid, dioxopiperazine, hydantoin, dihydrouracil, trioxane, hexahydro-1,3,5-triazine, imidazoline, imidazolidine, isoxazoline, isoxazolidine, oxazoline, oxazolidine, oxazolidinone, thiazoline, thiazolidine, morpholine, oxirane, piperidine N-Oxide, piperidine, piperazine, pyrrolidine, pyrrolidone, pyrrolidione, 4-piperidone, pyrazoline, pyrazolidine, 2-oxopyrrolidine, tetrahydropyran, 4H-pyran, tetrahydrothiopyran, thiamorpholine, thiamorpholine sulfoxide, thiamorpholine sulfone and their benzo-fused analogs (e.g., benzimidazolidinone, tetrahydroquinoline and 3,4-methylenedioxyphenyl).

[0043] As used herein, "aralkyl" and "aryl(alkyl)" refer to an aryl group connected, as a substituent, via a lower alkylene group. The lower alkylene and aryl group of an aryl(alkyl) may be substituted or unsubstituted. Examples include but are not limited to benzyl, 2-phenyl(alkyl), 3-phenyl(alkyl), and naphthyl(alkyl).

[0044] As used herein, "heteroaralkyl" and "heteroaryl(alkyl)" refer to a heteroaryl group connected, as a substituent, via a lower alkylene group. The lower alkylene and heteroaryl group of heteroaryl(alkyl) may be substituted or unsubstituted. Examples include but are not limited to 2-thienyl(alkyl), 3-thienyl(alkyl), furyl(alkyl), thienyl(alkyl), pyrrolyl(alkyl), pyridyl(alkyl), isoxazolyl(alkyl), imidazolyl(alkyl), and their benzo-fused analogs.

[0045] A "(heteroalicyclyl)alkyl" and "(heterocyclyl)alkyl" refer to a heterocyclic or a heteroalicyclylic group connected, as a substituent, via a lower alkylene group. The lower alkylene and heterocyclyl of a (heteroalicyclyl)alkyl may be substituted or unsubstituted. Examples include but are not limited tetrahydro-2H-pyran-4-yl(methyl), piperidin-4-yl(ethyl), piperidin-4-yl(propyl), tetrahydro-2H-thiopyran-4-yl(methyl) and 1,3-thiazinan-4-yl(methyl).

[0046] "Lower alkylene groups" are straight-chained -CH_2- tethering groups, forming bonds to connect molecular fragments via their terminal carbon atoms. Examples include but are not limited to methylene (-CH_2-), ethylene (-CH_2CH_2-), propylene (-$CH_2CH_2CH_2$-) and butylene (-$CH_2CH_2CH_2CH_2$-). A lower alkylene group can be substituted by replacing one or more hydrogen of the lower alkylene group with a substituent(s) listed under the definition of "substituted."

[0047] As used herein, "alkoxy" refers to the formula -OR wherein R is an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, aralkyl, (heteroaryl)alkyl or (heterocyclyl)alkyl is defined herein. A non-limiting list of alkoxys are methoxy, ethoxy, n-propoxy, 1-methylethoxy (isopropoxy), n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, phenoxy, benzyloxy, hexadecyloxy and octadecyloxy. An alkoxy may be substituted or unsubstituted.

[0048] As used herein, "acyl" refers to a hydrogen an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heteroalicyclyl, aralkyl, heteroaryl(alkyl) or heterocyclyl(alkyl) connected, as substituents, via a carbonyl group. Examples include formyl, acetyl, propanoyl, benzoyl, and acryl. An acyl may be substituted or unsubstituted.

[0049] As used herein, "hydroxyalkyl" refers to an alkyl group in which one or more of the hydrogen atoms are replaced by a hydroxy group. Exemplary hydroxyalkyl groups include but are not limited to, 2-hydroxyethyl, 3-hydroxypropyl, 2-hydroxypropyl and 2,2-dihydroxyethyl. A hydroxyalkyl may be substituted or unsubstituted.

[0050] As used herein, "haloalkyl" refers to an alkyl group in which one or more of the hydrogen atoms are replaced by a halogen (e.g., mono-haloalkyl, di-haloalkyl and tri-haloalkyl). Such groups include but are not limited to, chloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1-chloro-2-fluoromethyl and 2-fluoroisobutyl. A haloalkyl may be substituted or unsubstituted.

[0051] As used herein, "haloalkoxy" refers to an alkoxy group in which one or more of the hydrogen atoms are replaced by a halogen (e.g., mono-haloalkoxy, di- haloalkoxy and tri-haloalkoxy). Such groups include but are not limited to, chloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 1-chloro-2-fluoromethoxy and 2-fluoroisobutoxy. A haloalkoxy may be substituted or unsubstituted.

[0052] A "sulfenyl" group refers to an "-SR" group in which R can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aralkyl, (heteroaryl)alkyl or (heterocyclyl)alkyl. A sulfenyl may be substituted or unsubstituted.

[0053] A "sulfinyl" group refers to an "-S(=O)-R" group in which R can be the same as defined with respect to sulfenyl. A sulfinyl may be substituted or unsubstituted.

[0054] A "sulfonyl" group refers to an "SO_2R" group in which R can be the same as defined with respect to sulfenyl. A sulfonyl may be substituted or unsubstituted.

[0055] An "O-carboxy" group refers to a "RC(=O)O-" group in which R can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aralkyl, (heteroaryl)alkyl or (heterocyclyl)alkyl, as defined herein. An O-carboxy may be substituted or unsubstituted.

[0056] The terms "ester" and "C-carboxy" refer to a "-C(=O)OR" group in which R can be the same as defined with respect to O-carboxy. An ester and C-carboxy may be substituted or unsubstituted.

[0057] A "thiocarbonyl" group refers to a "-C(=S)R" group in which R can be the same as defined with respect to O-carboxy. A thiocarbonyl may be substituted or unsubstituted.

[0058] A "trihalomethanesulfonyl" group refers to an "X_3CSO_2-" group wherein each X is a halogen.

[0059] A "trihalomethanesulfonamido" group refers to an "$X_3CS(O)_2N(R^A)$-" group wherein each X is a halogen, and R^A is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aralkyl, (heteroaryl)alkyl or (heterocyclyl)alkyl.

[0060] The term "amino" as used herein refers to a "$-NH_2$" group.

[0061] As used herein, the term "hydroxy" refers to a "-OH" group.

[0062] A "cyano" group refers to a "-CN" group.

[0063] The term "azido" as used herein refers to a "$-N_3$" group.

[0064] An "isocyanato" group refers to a "-NCO" group.

[0065] A "thiocyanato" group refers to a "-CNS" group.

[0066] An "isothiocyanato" group refers to an "-NCS" group.

[0067] A "mercapto" group refers to an "-SH" group.

[0068] A "carbonyl" group refers to a "C=O" group.

[0069] An "S-sulfonamido" group refers to a "$-SO_2N(R^AR^B)$" group in which R^A and R^B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aralkyl, (heteroaryl)alkyl or (heterocyclyl)alkyl. An S-sulfonamido may be substituted or unsubstituted.

[0070] An "N-sulfonamido" group refers to a "$RSO_2N(R^A)$-" group in which R and R^A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aralkyl, (heteroaryl)alkyl or (heterocyclyl)alkyl. An N-sulfonamido may be substituted or unsubstituted.

[0071] An "O-carbamyl" group refers to a "$-OC(=O)N(R^AR^B)$" group in which R^A and R^B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aralkyl, (heteroaryl)alkyl or (heterocyclyl)alkyl. An O-carbamyl may be substituted or unsubstituted.

[0072] An "N-carbamyl" group refers to an "$ROC(=O)N(R^A)$-" group in which R and R^A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aralkyl, (heteroaryl)alkyl or (heterocyclyl)alkyl. An N-carbamyl may be substituted or unsubstituted.

[0073] An "O-thiocarbamyl" group refers to a "$-OC(=S)-N(R^AR^B)$" group in which R^A and R^B can be independently

hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aralkyl, (heteroaryl)alkyl or (heterocyclyl)alkyl. An O-thiocarbamyl may be substituted or unsubstituted.

[0074] An "N-thiocarbamyl" group refers to an "ROC(=S)N(R^A)-" group in which R and R^A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aralkyl, (heteroaryl)alkyl or (heterocyclyl)alkyl. An N-thiocarbamyl may be substituted or unsubstituted.

[0075] A "C-amido" group refers to a "-C(=O)N(R^AR^B)" group in which R^A and R^B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aralkyl, (heteroaryl)alkyl or (heterocyclyl)alkyl. A C-amido may be substituted or unsubstituted.

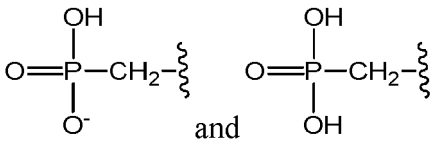
[0076] An "N-amido" group refers to a "RC(=O)N(R^A)-" group in which R and R^A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aralkyl, (heteroaryl)alkyl or (heterocyclyl)alkyl. An N-amido may be substituted or unsubstituted.

[0077] The term "halogen atom" or "halogen" as used herein, means any one of the radio-stable atoms of column 7 of the Periodic Table of the Elements, such as, fluorine, chlorine, bromine and iodine.

[0078] Where the numbers of substituents is not specified (e.g. haloalkyl), there may be one or more substituents present. For example "haloalkyl" may include one or more of the same or different halogens. As another example, "C_1-C_3 alkoxyphenyl" may include one or more of the same or different alkoxy groups containing one, two or three atoms.

[0079] As used herein, the abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with their common usage, recognized abbreviations, or the IUPAC-IUB Commission on Biochemical Nomenclature (See, Biochem. 11:942-944 (1972)).

[0080] As used herein, the term "phosphonate" is used in its ordinary sense as understood by those skilled in the art, and includes its protonated forms (for example,



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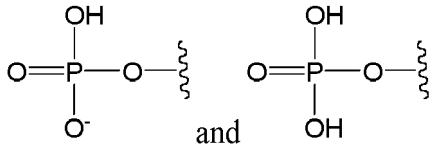
[0081] As used herein, the terms "monophosphonate" and "diphosphonate" are used in their ordinary sense as understood by those skilled in the art, and include protonated forms.

[0082] Additionally, the term "phosphate" is used in its ordinary sense as understood by those skilled in the art, and includes its protonated forms (for example,



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[0083] The terms "monophosphate," "diphosphate," and "triphosphate" are also used in their ordinary sense as understood by those skilled in the art, and include protonated forms.

[0084] The terms "protecting group" and "protecting groups" as used herein refer to any atom or group of atoms that is added to a molecule in order to prevent existing groups in the molecule from undergoing unwanted chemical reactions. Examples of protecting group moieties are described in T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 3. Ed. John Wiley & Sons, 1999, and in J.F.W. McOmie, Protective Groups in Organic Chemistry Plenum Press, 1973. The protecting group moiety may be chosen in such a way, that they are stable to certain reaction conditions and readily removed at a convenient stage using methodology known from the art. A non-limiting list of protecting groups include benzyl; substituted benzyl; alkylcarbonyls and alkoxycarbonyls (e.g., t-butoxycarbonyl (BOC), acetyl, or isobutyryl); arylalkylcarbonyls and arylalkoxycarbonyls (e.g., benzyloxycarbonyl); substituted methyl ether (e.g. methoxymethyl ether); substituted ethyl ether; a substituted benzyl ether; tetrahydropyranyl ether; silyls (e.g., trimethylsilyl, triethylsilyl, triisopropylsilyl, t-butyldimethylsilyl, tri-iso-propylsilyloxymethyl, [2-(trimethylsilyl)ethoxy]methyl or t-butyldiphenylsilyl); esters (e.g. benzoate ester); carbonates (e.g. methoxymethylcarbonate); sulfonates (e.g. tosylate or mesylate); acyclic ketal (e.g. dimethyl acetal); cyclic ketals (e.g., 1,3-dioxane, 1,3-dioxolanes and those described herein); acyclic acetal; cyclic acetal (e.g., those described herein); acyclic hemiacetal; cyclic hemiacetal; cyclic dithioketals (e.g., 1,3-dithiane or 1,3-dithiolane); orthoesters (e.g., those described herein) and triarylmethyl groups (e.g., trityl; monomethoxytrityl (MMTr); 4,4'-dimethoxytrityl (DMTr); 4,4',4"-trimethoxytrityl (TMTr); and those described herein).

[0085] The term "pharmaceutically acceptable salt" refers to a salt of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In some embodiments, the salt is an acid addition salt of the compound. Pharmaceutical salts can be obtained by reacting a compound with inorganic acids such as hydrohalic acid (e.g., hydrochloric acid or hydrobromic acid), sulfuric acid, nitric acid and phosphoric acid. Pharmaceutical salts can also be obtained by reacting a compound with an organic acid such as aliphatic or aromatic carboxylic or sulfonic acids, for example formic, acetic, succinic, lactic, malic, tartaric, citric, ascorbic, nicotinic, methanesulfonic, ethanesulfonic, p-toluenesulfonic, salicylic or naphthalenesulfonic acid. Pharmaceutical salts can also be obtained by reacting a compound with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, C_1-C_7 alkylamine, cyclohexylamine, triethanolamine, ethylenediamine, and salts with amino acids such as arginine and lysine.

[0086] Terms and phrases used in this application, and variations thereof, especially in the appended claims, unless otherwise expressly stated, should be construed as open ended as opposed to limiting. As examples of the foregoing, the term 'including' should be read to mean 'including, without limitation,' 'including but not limited to,' or the like; the term 'comprising' as used herein is synonymous with 'including,' 'containing,' or 'characterized by,' and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps; the term 'having' should be interpreted as 'having at least;' the term 'includes' should be interpreted as 'includes but is not limited to;' the term 'example' is used to provide exemplary instances of the item in discussion, not an exhaustive or limiting list thereof; and use of terms like 'preferably,' 'preferred,' 'desired,' or 'desirable,' and words of similar meaning should not be understood as implying that certain features are critical, essential, or even important to the structure or function, but instead as merely intended to highlight alternative or additional features that may or may not be utilized in a particular embodiment. In addition, the term "comprising" is to be interpreted synonymously with the phrases "having at least" or "including at least". When used in the context of a process, the term "comprising" means that the process includes at least the recited steps, but may include additional steps. When used in the context of a compound, composition or device, the term "comprising" means that the compound, composition or device includes at least the recited features or components, but may also include additional features or components. Likewise, a group of items linked with the conjunction 'and' should not be read as requiring that each and every one of those items be present in the grouping, but rather should be read as 'and/or' unless expressly stated otherwise. Similarly, a group of items linked with the conjunction 'or' should not be read as requiring mutual exclusivity among that group, but rather should be read as 'and/or' unless expressly stated otherwise.

[0087] With respect to the use of substantially any plural and/or singular terms herein, those having skill in the art can translate from the plural to the singular and/or from the singular to the plural as is appropriate to the context and/or application. The various singular/plural permutations may be expressly set forth herein for sake of clarity. The indefinite article "a" or "an" does not exclude a plurality. A single processor or other unit may fulfill the functions of several items recited in the claims. The mere fact that certain measures are recited in mutually different dependent claims does not indicate that a combination of these measures cannot be used to advantage. Any reference signs in the claims should not be construed as limiting the scope.

[0088] It is understood that, in any compound described herein having one or more chiral centers, if an absolute stereochemistry is not expressly indicated, then each center may independently be of R-configuration or S-configuration or a mixture thereof. Thus, the compounds provided herein may be enantiomerically pure, enantiomerically enriched, racemic mixture, diastereomerically pure, diastereomerically enriched, or a stereoisomeric mixture. In addition it is understood that, in any compound described herein having one or more double bond(s) generating geometrical isomers that can be defined as E or Z, each double bond may independently be E or Z a mixture thereof.

[0089] Likewise, it is understood that, in any compound described, all tautomeric forms are also intended to be included. For example all tautomers of phosphonates and heterocyclic bases known in the art are intended to be included, including tautomers of natural and non-natural purine-bases and pyrimidine-bases are intended to be included.

[0090] It is to be understood that where compounds disclosed herein have unfilled valencies, then the valencies are to be filled with hydrogens or isotopes thereof, e.g., hydrogen-1 (protium) and hydrogen-2 (deuterium).

[0091] It is understood that the compounds described herein can be labeled isotopically. Substitution with isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased in vivo half-life or reduced dosage requirements. Each chemical element as represented in a compound structure may include any isotope of said element. For example, in a compound structure a hydrogen atom may be explicitly disclosed or understood to be present in the compound. At any position of the compound that a hydrogen atom may be present, the hydrogen atom can be any isotope of hydrogen, including but not limited to hydrogen-1 (protium) and hydrogen-2 (deuterium). Thus, reference herein to a compound encompasses all potential isotopic forms unless the context clearly dictates otherwise.

[0092] It is understood that the methods and combinations described herein include crystalline forms (also known as polymorphs, which include the different crystal packing arrangements of the same elemental composition of a compound),

amorphous phases, salts, solvates and hydrates. In some embodiments, the compounds described herein exist in solvated forms with pharmaceutically acceptable solvents such as water, ethanol, or the like. In other embodiments, the compounds described herein exist in unsolvated form. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and may be formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, or the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

[0093] Where a range of values is provided, it is understood that the upper and lower limit, and each intervening value between the upper and lower limit of the range is encompassed within the embodiments.

[0094] As used herein, a "subject" refers to an animal that is a host for a viral infection as described herein. "Animal" includes a mammal. "Mammals" includes, without limitation, mice, rats, rabbits, guinea pigs, dogs, cats, sheep, goats, cows, horses, primates, such as monkeys, chimpanzees, and apes, and, in particular, humans. In a typical embodiment, the subject is human.

[0095] As used herein, the terms "treating," "treatment," "therapeutic," or "therapy" do not necessarily mean total cure or abolition of the disease or condition. Any alleviation of any undesired signs or symptoms of a disease or condition, to any extent can be considered treatment and/or therapy. Furthermore, treatment may include acts that may worsen the patient's overall feeling of well-being or appearance.

[0096] The terms "therapeutically effective amount" and "effective amount" are used to indicate an amount of an active compound, or pharmaceutical agent, that elicits the biological or medicinal response indicated. For example, an effective amount of compound can be the amount needed to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated This response may occur in a tissue, system, animal or human and includes alleviation of the signs or symptoms of the disease being treated. Determination of an effective amount is well within the capability of those skilled in the art, in view of the disclosure provided herein. The effective amount of the compounds disclosed herein required as a dose will depend on the route of administration, the type of animal, including human, being treated, and the physical characteristics of the specific animal under consideration. The dose can be tailored to achieve a desired effect, but will depend on such factors as weight, diet, concurrent medication and other factors which those skilled in the medical arts will recognize.

[0097] Some embodiments disclosed herein include the use of an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the preparation of a medicine for treating a host infected with a human papillomavirus, by inhibiting the synthesis of viral DNA. Other embodiments disclosed herein include the use of an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for treating a host infected with a human papillomavirus, wherein the human papillomavirus can be ameliorated by inhibiting the synthesis of viral DNA. Still other embodiments disclosed herein include a compound for use in a method for treating a host infected with a human papillomavirus that can include contacting a cell infected with the human papillomavirus in a subject infected with the human papillomavirus with an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. Yet still other embodiments disclosed herein include a compound for use in a method for treating a host infected with a human papillomavirus that can includes administering to a subject infected with the human papillomavirus an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, by inhibiting the synthesis of viral DNA. Some embodiments disclosed herein include compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use treating a host infected with a human papillomavirus, by inhibiting viral replication by inhibiting the synthesis of viral DNA.

[0098] In some embodiments, the human papillomavirus can be a high-risk human papillomavirus, such as those described herein. For example, the high-risk human papillomavirus can be selected from HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, HPV-59, HPV-68, HPV-73 and HPV-82. In some embodiments, the human papillomavirus can be HPV-16. In some embodiments, the human papillomavirus can be HPV-18. In some embodiments, the human papillomavirus can be one or more of the following high-risk types: HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, HPV-59, HPV-68, HPV-73 and HPV-82. As described herein, the presence of a HPV infection can be detected using a PAP smear and/or DNA probe testing (for example, HPV DNA probe testing for one or more high-risk HPV types). Therefore, in some embodiments, an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be provided to a subject diagnosed with a HPV infection, for example a high-risk HPV infection, by a DNA test, such as one of the HPV DNA tests described herein.

[0099] In some embodiments, the human papillomavirus can be a low-risk human papillomavirus, including those described herein. In some embodiments, the human papillomavirus can be HPV-6. In some embodiments, the human papillomavirus can be HPV-11.

[0100] A compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be used to treat a host infected with one or more types of human papillomaviruses. For example, a compound of Formula (I), or a pharmaceutically

acceptable salt thereof, can be used to treat HPV-16 and HPV-18. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be used to treat both high-risk and low-risk HPV.

[0101] As will be readily apparent to one skilled in the art, the useful in vivo dosage to be administered and the particular mode of administration will vary depending upon the age, weight, the severity of the affliction, and mammalian species treated, the particular compounds employed, and the specific use for which these compounds are employed. The determination of effective dosage levels, that is the dosage levels necessary to achieve the desired result, can be accomplished by one skilled in the art using routine methods, for example, human clinical trials and in vitro studies.

[0102] The dosage may range broadly, depending upon the desired effects and the therapeutic indication. Alternatively dosages may be based and calculated upon the surface area of the patient, as understood by those of skill in the art. Although the exact dosage will be determined on a drug-by-drug basis, in most cases, some generalizations regarding the dosage can be made. The daily dosage regimen for an adult human patient may be, for example, an oral dose of between 0.01 mg and 3000 mg of each active ingredient, preferably between 1 mg and 700 mg, e.g. 5 to 200 mg. For a topical or intravaginal administration, the dose may be between 0.02 mg to 200 mg. The dosage may be a single one or a series of two or more given in the course of one or more days, as is needed by the subject. In some embodiments, the compounds will be administered for a period of continuous therapy, for example for a week or more, or for months or years. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered less frequently compared to the frequency of administration of another agent. In some embodiments, the total time of the treatment regime with a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can less compared to the total time of the treatment regime with another agent.

[0103] In instances where human dosages for compounds have been established for at least some condition, those same dosages may be used, or dosages that are between about 0.1% and 500%, more preferably between about 25% and 250% of the established human dosage. Where no human dosage is established, as will be the case for newly-discovered pharmaceutical compositions, a suitable human dosage can be inferred from ED_{50} or ID_{50} values, or other appropriate values derived from in vitro or in vivo studies, as qualified by toxicity studies and efficacy studies in animals.

[0104] In cases of administration of a pharmaceutically acceptable salt, dosages may be calculated as the free base. As will be understood by those of skill in the art, in certain situations it may be necessary to administer the compounds disclosed herein in amounts that exceed, or even far exceed, the above-stated, preferred dosage range in order to effectively and aggressively treat particularly aggressive diseases or infections.

[0105] Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the modulating effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from in vitro data. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations. Dosage intervals can also be determined using MEC value. Compositions should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%. In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

[0106] It should be noted that the attending physician would know how to and when to terminate, interrupt, or adjust administration due to toxicity or organ dysfunctions. Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical response were not adequate (precluding toxicity). The magnitude of an administrated dose in the management of the disorder of interest will vary with the severity of the condition to be treated and to the route of administration. The severity of the condition may, for example, be evaluated, in part, by standard prognostic evaluation methods. Further, the dose and perhaps dose frequency, will also vary according to the age, body weight, and response of the individual patient. A program comparable to that discussed above may be used in veterinary medicine.

[0107] Compounds disclosed herein can be evaluated for efficacy and toxicity using known methods. For example, the toxicology of a particular compound, or of a subset of the compounds, sharing certain chemical moieties, may be established by determining in vitro toxicity towards a cell line, such as a mammalian, and preferably human, cell line. The results of such studies are often predictive of toxicity in animals, such as mammals, or more specifically, humans. Alternatively, the toxicity of particular compounds in an animal model, such as mice, rats, rabbits, or monkeys, may be determined using known methods. The efficacy of a particular compound may be established using several recognized methods, such as in vitro methods, animal models, or human clinical trials. When selecting a model to determine efficacy, the skilled artisan can be guided by the state of the art to choose an appropriate model, dose, route of administration and/or regime.

[0108] As described herein, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can have a moiety(ies) that neutralize the charge of the phosphonate. By neutralizing the charge on the phosphonate, penetration of the cell membrane may be facilitated as a result of the increased lipophilicity of the compound. Once absorbed and taken inside the cell, the groups attached to the phosphorus can be easily removed by esterases, proteases and/or other enzymes. In some embodiments, the groups attached to the phosphorus can be removed by simple hydrolysis. Inside the cell, the phosphonate thus released may then be metabolized by cellular enzymes to the monophosphate or to the

diphosphate, the active metabolite. Furthermore, in some embodiments, varying the substituents on a compound described herein, such as a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can help maintain the efficacy of the compound by reducing undesirable effects, such as isomerization.

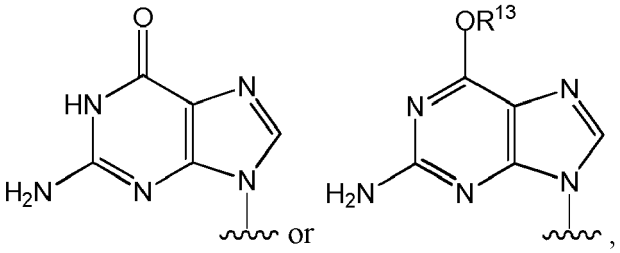
[0109] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can act as a chain terminator of DNA synthesis. Once the compound is incorporated into a DNA chain, no further elongation is observed to occur. In some embodiments, a compound of Formula (I) or a pharmaceutically acceptable salt thereof, is metabolized such that the groups attached to the phosphorus atom are removed to generate a phosphonic acid. The phosphonic acid can then be anabolized to a diphosphate, the active metabolite, that can act as a chain terminator of DNA synthesis. Once the compound is incorporated into a DNA chain, no further elongation is observed to occur.

[0110] Additionally, in some embodiments, the presence of a moiety(ies) that neutralizes the charge of the phosphonate can increase the stability of the compound by inhibiting its degradation. Also, in some embodiments, the presence of a moiety(ies) that neutralizes the charge of the phosphonate can make the compound more resistant to cleavage in vivo and provide sustained, extended efficacy. In some embodiments, a moiety(ies) that neutralizes the charge of the phosphonate can facilitate the penetration of the cell membrane by a compound of Formula (I) by making the compound more lipophilic. In some embodiments, a moiety(ies) that neutralizes the charge of the phosphonate can have improved oral bioavailability, improved aqueous stability and/or reduced risk of byproduct-related toxicity.

Compounds

[0111] Disclosed herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof as defined in the claims;.

[0112] In embodiments, when B^1 is

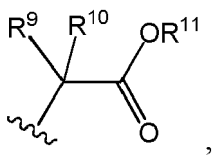


R^3 can be selected from alkyl, or heteroalkyl such as OCH_3.

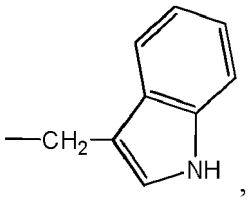
[0113] In embodiments, R^2 can be benzyl. In some embodiments of this paragraph, Z^2 can be O.

[0114] The term "N-linked alpha-amino acid ester" refers to an amino acid that is attached to the indicated moiety via a main-chain amino or mono-substituted amino group and wherein the main-chain carboxylic acid group has been converted to an ester group. Examples of alpha-amino acids include, but are not limited to, alanine, asparagine, aspartate, cysteine, glutamate, glutamine, glycine, proline, serine, tyrosine, arginine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine. When the amino acid is attached in an -N-linked amino acid, one of the hydrogens that is part of the main-chain amino or mono-substituted amino group is not present and the amino acid is attached via the nitrogen. In embodiments, the ester group has a formula selected from alkyl-O-C(=O)-, cycloalkyl-O-C(=O)-, aryl-O-C(=O)- and aryl(alkyl)-O-C(=O)-. N-linked alpha-amino acid esters can be substituted or unsubstituted. When R^1 is an N-linked alpha-amino acid ester, the main-chain nitrogen of the main-chain amino or mono-substituted amino group is the nitrogen of Z^1.

[0115] In embodiments, R^1 is



wherein Z^1 can be NH. In embodiments, R^9 can be hydrogen. In other embodiments, R^9 can be an $C_{1\text{-}6}$ alkyl. In embodiments, R^{10} can be hydrogen. In other embodiments, R^{10} can be an unsubstituted $C_{1\text{-}6}$ alkyl, $-CH_2SH$, $-CH_2(C{=}O)NH_2$, $-CH_2CH_2(C{=}O)NH_2$, $-CH_2CH_2S\,CH_3$, CH_2-an optionally substituted phenyl, $-CH_2OH$, $-CH(OH)CH_3$,



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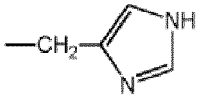
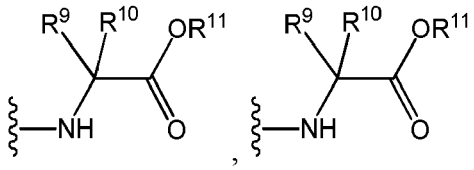
$-CH_2(C=O)OH$, $-CH_2CH_2(C=O)OH$, $-(CH_2)_3NH(C=NH)NH_2$,



or $-(CH_2)_4NH_2$. In embodiments, R^{11} can be hydrogen. In embodiments, R^{11} can be C_{1-8} alkyl. In still other embodiments, R^{11} can cycloalkyl, such as C_{3-6} cycloalkyl. In yet still other embodiments, R^{11} can be aryl. For example, R^{11} can be unsubstituted phenyl. In embodiments, R^{11} can be aryl(C_{1-4} alkyl) (such as benzyl).

[0116] When Z^1 and R^1 form



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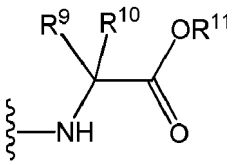
can be N-linked alpha-amino acid ester. N-linked alpha-amino acid esters are described herein. In embodiments,



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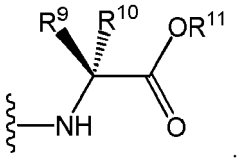

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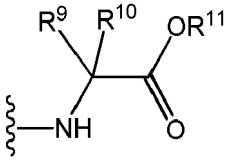
In other embodiments,



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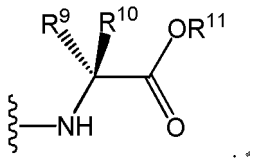
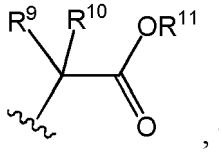


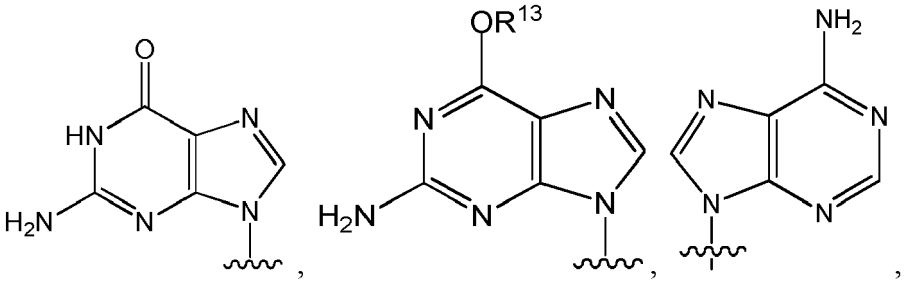
In embodiments, R^1 can be

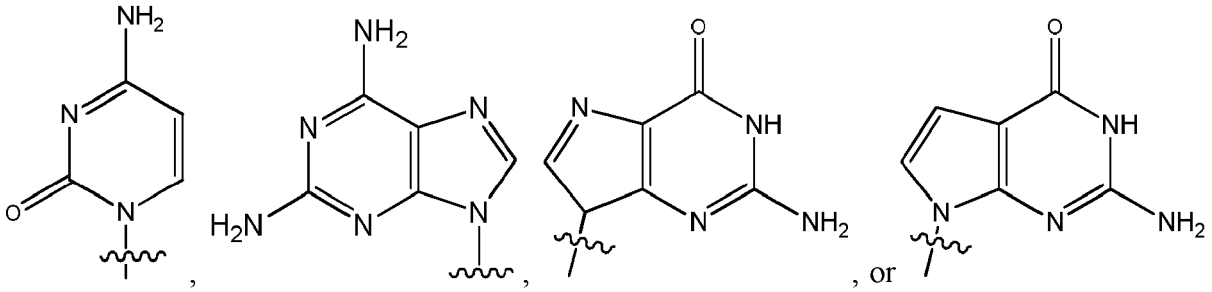


wherein Z^1 can be NH; and R^2 can be an optionally substituted aryl(C_{1-4} alkyl) (for example, an optionally substituted benzyl), and form an optionally substituted benzyl phosphonoamidate prodrug.

[0117] In embodiments, Z^1 or Z^2 can be NH. In embodiments, Z^2 can be N-an unsubstituted C_{1-4} alkyl. For example, Z^2 can be N-methyl, N-ethyl, N-(n-propyl), N-(iso-propyl), N-(n-butyl), N-(iso-butyl) or N-(t-butyl).

[0118] As described herein, B^1 can be a naturally occurring purine, naturally occurring pyrimidine, non-naturally occurring purine or a non-naturally occurring pyrimidine. For example, B^1 can be





wherein R^{13} can be an unsubstituted C_{1-6} alkyl or an unsubstituted C_{3-6} cycloalkyl. In some embodiments, R^{13} can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl (branched or straight chained) or hexyl (branched or straight chained). In other embodiments, R^{13} can be cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

[0119] In some embodiments, the human papillomavirus cannot be HPV-16 and/or HPV-18. In some embodiments, the human papillomavirus cannot be HPV-11.

Pharmaceutical Compositions

[0120] Some embodiments described herein relates to a pharmaceutical composition, that can include an effective amount of one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) and a pharmaceutically acceptable carrier, diluent, excipient or combination thereof. In some embodiments, the pharmaceutical composition can include a single diastereomer of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, (for example, a single diastereomer is present in the pharmaceutical composition at a concen-

tration of greater than 99% compared to the total concentration of the other diastereomers). In other embodiments, the pharmaceutical composition can include a mixture of diastereomers of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. For example, the pharmaceutical composition can include a concentration of one diastereomer of > 50%, ≥ 60%, ≥ 70%, ≥ 80%, ≥ 90%, ≥ 95%, or ≥ 98%, as compared to the total concentration of the other diastereomers. In some embodiments, the pharmaceutical composition includes a 1:1 mixture of two diastereomers of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0121] The term "pharmaceutical composition" refers to a mixture of one or more compounds disclosed herein with other chemical components, such as diluents or carriers. The pharmaceutical composition facilitates administration of the compound to an organism. Pharmaceutical compositions can also be obtained by reacting compounds with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid and salicylic acid. Pharmaceutical compositions will generally be tailored to the specific intended route of administration. A pharmaceutical composition is suitable for human and/or veterinary applications.

[0122] The term "physiologically acceptable" defines a carrier, diluent or excipient that does not abrogate the biological activity and properties of the compound.

[0123] As used herein, a "carrier" refers to a compound that facilitates the incorporation of a compound into cells or tissues. For example, without limitation, dimethyl sulfoxide (DMSO) is a commonly utilized carrier that facilitates the uptake of many organic compounds into cells or tissues of a subject.

[0124] As used herein, a "diluent" refers to an ingredient in a pharmaceutical composition that lacks pharmacological activity but may be pharmaceutically necessary or desirable. For example, a diluent may be used to increase the bulk of a potent drug whose mass is too small for manufacture and/or administration. It may also be a liquid for the dissolution of a drug to be administered by injection, ingestion or inhalation. A common form of diluent in the art is a buffered aqueous solution such as, without limitation, phosphate buffered saline that mimics the composition of human blood.

[0125] As used herein, an "excipient" refers to an inert substance that is added to a pharmaceutical composition to provide, without limitation, bulk, consistency, stability, binding ability, lubrication, disintegrating ability etc., to the composition. A "diluent" is a type of excipient.

[0126] The pharmaceutical compositions described herein can be administered to a human patient per se, or in pharmaceutical compositions where they are mixed with other active ingredients, as in combination therapy, or carriers, diluents, excipients or combinations thereof. Proper formulation is dependent upon the route of administration chosen. Techniques for formulation and administration of the compounds described herein are known to those skilled in the art.

[0127] The pharmaceutical compositions disclosed herein may be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tableting processes. Additionally, the active ingredients are contained in an amount effective to achieve its intended purpose. Many of the compounds used in the pharmaceutical combinations disclosed herein may be provided as salts with pharmaceutically compatible counterions.

[0128] Multiple techniques of administering a compound exist in the art including, but not limited to, oral, rectal, topical, aerosol, injection and parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, intrathecal, direct intraventricular, intraperitoneal, intranasal, intravaginal and intraocular injections.

[0129] One may also administer the compound in a local rather than systemic manner, for example, via application of the compound directly to the infected area. The compound can be administered as a gel, a cream and/or a suppository. In addition, the compound can be administered in a depot or sustained release formulation (for example, as nanoparticles and/or an intravaginal ring). Furthermore, one may administer the compound in a targeted drug delivery system, for example, in a liposome coated with a tissue-specific antibody. The liposomes will be targeted to and taken up selectively by the organ.

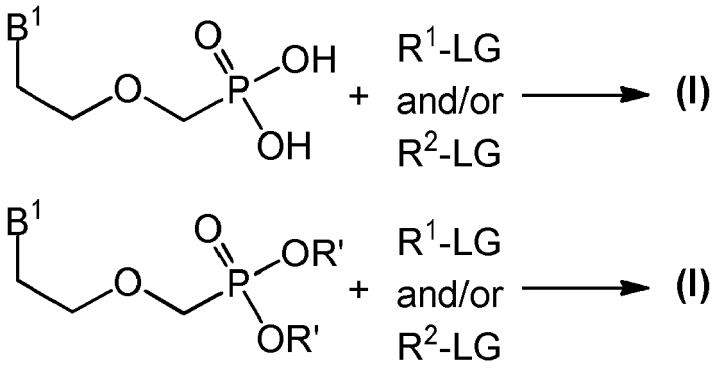
[0130] The compositions may, if desired, be presented in a pack, applicator or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, may be the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. Compositions that can include a compound described herein formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

Synthesis

[0131] Compounds of Formula (I) and those described herein may be prepared in various ways. General synthetic routes to the compound of Formula (I) and some examples of starting materials used to synthesize compounds of

Formula (I) are shown in Scheme 1 and described herein. The routes shown and described herein are illustrative only and are not intended, nor are they to be construed, to limit the scope of the claims in any manner whatsoever. Those skilled in the art will be able to recognize modifications of the disclosed syntheses and to devise alternate routes based on the disclosures herein; all such modifications and alternate routes are within the scope of the claims.

Scheme 1



[0132] A shown in Scheme 1, the acyclic nucleoside phosphonate can be coupled with R^1-LG and then with R^2-LG, wherein LG is a suitable leaving group (for example, Cl). Alternatively, the OH groups attached to the phosphorus can be transformed and then replaced with R^1 and R^2. For example, the hydrogens of the OH groups can be transformed to alkali metal ions, such as Na^+ (shown as R' in Scheme 1). Methods for coupling an acyclic nucleoside phosphonate are known to those skilled in the art. For examples, see methods described and referenced in Pradere, U. et al., Chem. Rev., 2014, 114:9154-9218.

[0133] An acyclic nucleoside phosphonate can be esterified by methods known to one skilled in the art and then reacted with an amine by methods known to one skilled in the art to generate a phosphoramidate ester of Formula I.

[0134] An acyclic nucleoside phosphonate can be reacted with an amine by methods known to one skilled in the art to generate a phosphoramidate and subsequently reacted with an amine by methods known to one skilled in the art to generate a bisphosphoramidate of Formula I.

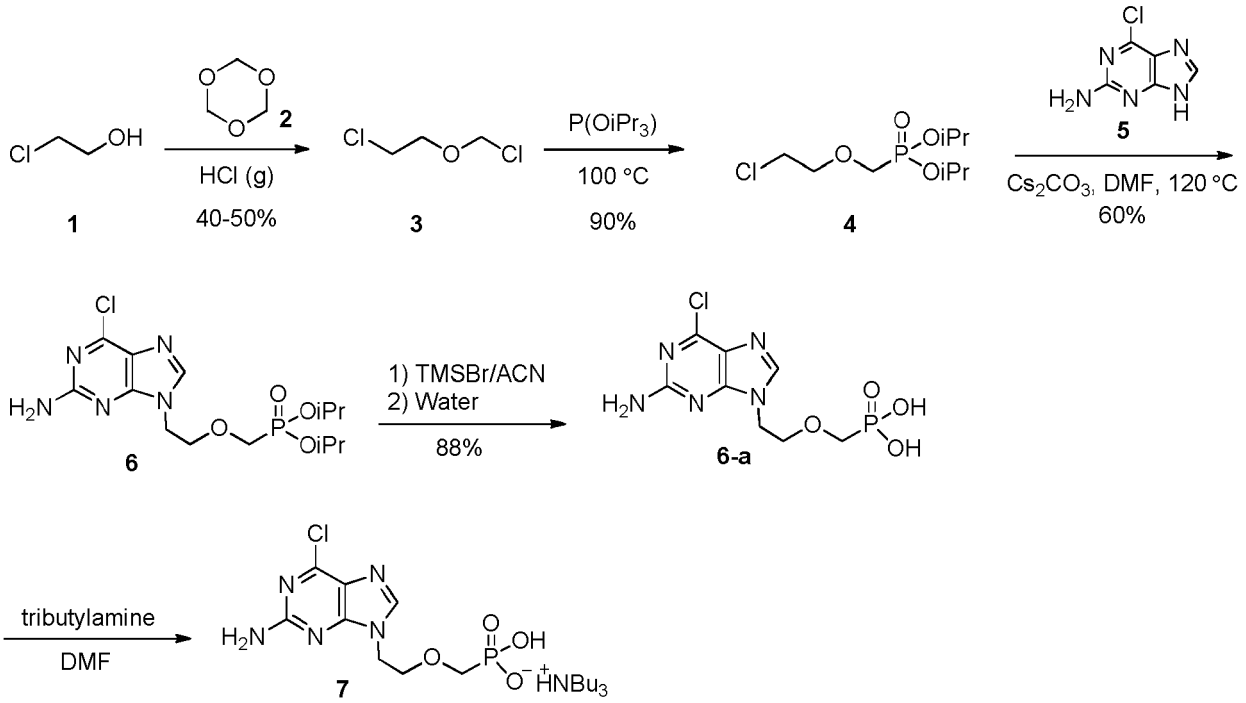
[0135] Compounds of Formula I can be synthesized according to or analogously to the syntheses shown below. In certain embodiments, the person of ordinary skill in the art can replace guanine with another selected base described herein according to the present invention.

Examples

Reference Example 1. 9-[(2-phosphonomethoxy)ethyl]-2-amino-6-chloropurine, tributylamine salt (7)

[0136] Compound 6 was prepared as shown in Scheme A and converted to the phosphonic acid (6-a) by treatment with bromotrimethylsilane, followed by hydrolysis. The detailed methods are described in Holy, A. et al. J. Med. Chem. (1999) 42(12):2064-2086. To prepare 7, a 1 L flask was equipped with a magnetic stirrer, a nitrogen inlet, and an addition funnel. Compound 6-a (18.8 g, 61 mmol) and N,N-DMF (200 mL) were added, and the resulting slurry was stirred. Tributylamine (14.9 mL, 62 mmol) was added dropwise over 15-20 mins. The resulting solution was stirred at ambient temperature for 10 mins. Toluene (470 mL) was added, and stirring was continued for 30-40 mins. Seed crystals (50 mg) of compound 7 were added. The mixture was stirred for 5 h, after which the precipitated solids were filtered. The solids were washed with toluene (150 mL) and dried under vacuum for several hours to give 7 (25.6 g, 85% yield) as an off-white powder. The solid was analyzed by ^{1}H NMR and ^{31}P NMR spectroscopy. ^{1}H NMR (DMSO-d_6) δ 8.20 (s, 1H), 6.91 (s, 2H), 4.20 (t, 2H), 3.81 (t, 2H), 3.45 (d, 2H), 2.73 (m, 2H), 1.51 (m, 2H), 1.26 (septet, 2H), 0.87 (t, 3H). The spectra were found to be consistent with 7.

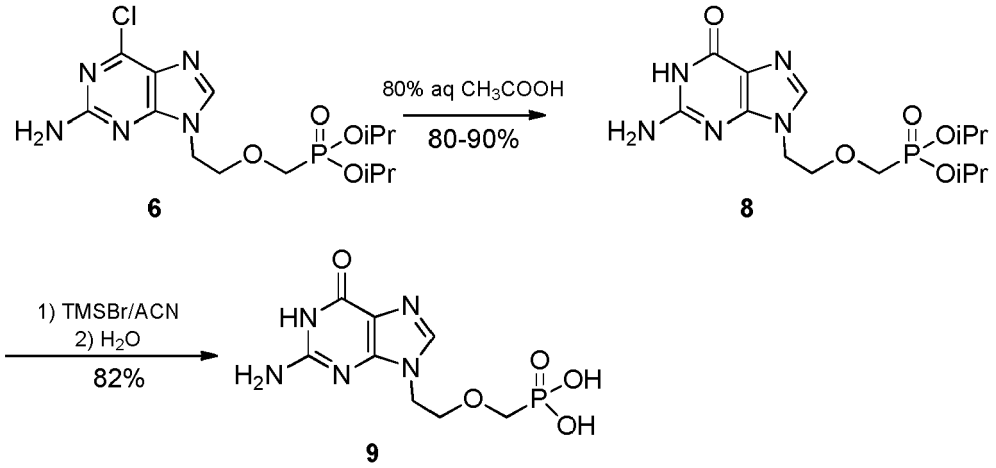
Scheme A



Reference Example 2. 9-[(2-phosphonomethoxy)ethyl]guanine (PMEG, 9)

[0137] Compound 9 was prepared by acidic hydrolysis of 6 as shown in Scheme B. Compound 6 (4.95 g, 12.6 mmol) was dissolved in 80% aq. CH_3COOH. The mixture was stirred and heated at reflux for 3 h. The mixture was then cooled. The solvent was evaporated under vacuum to give crude 8 as an off-white powder, which was dried in a vacuum oven at 45 °C. Compound 8 was dissolved in CH_3CN (30 mL), treated with bromotrimethylsilane (11.6 g, 76 mmol) and stirred overnight. The mixture was evaporated under vacuum. Water/crushed ice (50 mL) was added to the residue. The slurry was stirred for 1 h, and the precipitate was collected by filtration to provide 9 (PMEG, 3.1 g, 85% yield). Additional details for preparing PMEG are described in Holy, A. et al. J. Med. Chem. (1999) 42(12):2064-2086.

Scheme B



Reference Example 3. Octadecyloxyethyl PMEG (ODE-PMEG, 11)

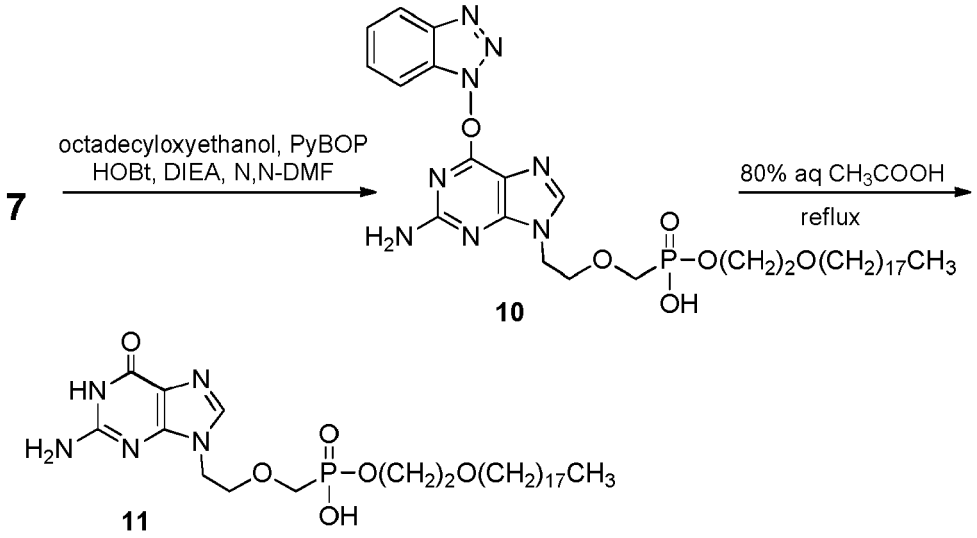
[0138] Method A: Compound 11 was prepared by esterification of 7 according to Scheme C. A 1 L flask was equipped with a magnetic stirrer, then compound 7 (21.7 g, 44 mmol), 2-octadecyloxyethanol (ODE-OH, 14.2 g, 45 mmol) and anhydrous N,N-DMF (300 mL) were added. The mixture was stirred and (benzotriazol-1-yloxy)-tripyrrolidinophosphonium

hexafluorophosphate (PYBOP®, 35 g, 67.5 mmol) was subdivided in five equal portions (7 g each) and each portion was then added at 30 mins intervals. After the addition of PYBOP®, diisopropylethylamine (DIEA, 5.8 g, 45 mmol) and 1-hydroxybenzotriazole (HOBt, 3.0 g, 22.5 mmol) were added. The resulting mixture was stirred at 22-25 °C, and the progress of the reaction was monitored by TLC (70:30:3:3 $CHCl_3$: MeOH: conc. NH_4OH: H_2O) on silica gel plates (Analtech, UNIPLATES™ Silica gel G, 250 microns). After the reaction was judged complete (16-20 h), the reaction mixture was slowly poured into a stirred acidic mixture comprised of conc. HCl (10 mL), water (750 mL) and crushed ice (750 mL). Stirring was continued for 10 mins. The precipitated solid was collected by filtration, washed with cold water (2 x 100 mL) and dried under vacuum to give crude 10 (32.7 g). The crude product was purified by silica gel column chromatography with elution of the product by CH_2Cl_2:MeOH 90:10 to yield 10 (9.5 g, 30.7% yield).

[0139] A 1 L reaction flask was equipped with a magnetic stirrer and a condenser. Compound 10 (9.5 g, 13.5 mmol), acetic acid (240 mL) and water (60 mL) were added. The resulting mixture was stirred and heated to reflux. The progress of the reaction was monitored by TLC (70:30:3:3 $CHCl_3$: MeOH: conc. NH_4OH: H_2O) on silica gel plates (Analtech, UNIPLATES™ Silica gel G, 250 microns) using a UV lamp and charring. After the reaction was complete (3.5 h), the reaction mixture was cooled to 5 °C, stirred for 2 h and filtered. The product was dried under vacuum to give 11 (7.5 g). The crude product was recrystallized in 80:20 isopropanol:water. After treatment with decolorizing carbon, the filtrate was allowed to cool to room temperature (RT) and then in an ice-bath. The precipitated solids were filtered and dried under vacuum to give 11 (6.2 g, 78%) as off-white powder.

[0140] Method B: Octadecyloxyethyl 9-[2-(phosphonomethoxy)ethyl]guanine (ODE-PMEG) was prepared according to the method described in Valiaeva, N. et al.; Antiviral Research (2006) 72: 10-19.

Scheme C



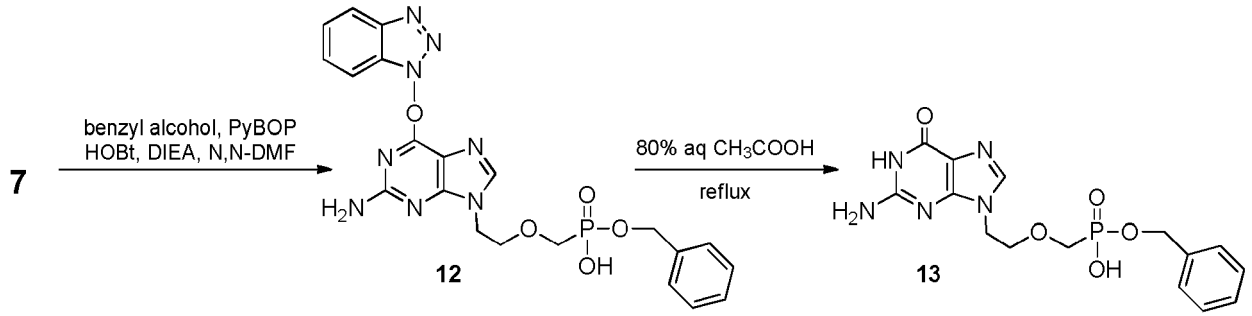
Reference Example 4. Benzyl PMEG (Bn-PMEG, 13)

[0141] Compound 13 was prepared by esterification of 7 with benzyl alcohol according to Scheme D. A 100 mL flask was equipped with a magnetic stirrer, then compound 7 (2.0 g, 4 mmol), benzyl alcohol (860 mg, 8 mmol) and anhydrous N,N-DMF (30 mL) were added. The mixture was stirred. (Benzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate (PYBOP®, 3.2 g, 6 mmol) was subdivided in five equal portions (640 mg each) and each portion was then added at 30 mins intervals. After the addition of PYBOP®, diisopropylethylamine (DIEA, 516 mg, 4 mmol) and 1-hydroxybenzotriazole (HOBt, 270 mg, 2 mmol) were added. The reaction mixture was stirred at 22-25 °C, and the progress of the reaction was monitored by TLC (70:30:3:3 $CHCl_3$: MeOH: conc. NH_4OH: H_2O) on silica gel plates (Analtech, UNIPLATES™ Silica gel G, 250 microns). After the reaction was judged complete (16-20 h), the reaction mixture was concentrated in vacuo. The crude product was purified by silica gel column chromatography with elution of the product by CH_2Cl_2:MeOH 55:45 to yield 12 (840 mg).

[0142] A 100 mL reaction flask was equipped with a magnetic stirrer and a condenser. Compound 12 (840 mg), acetic acid (24 mL) and water (6 mL) were added. The resulting mixture was stirred and heated to reflux. The progress of the reaction was monitored by TLC (70:30:3:3 $CHCl_3$:MeOH:conc. NH_4OH:H_2O) on silica gel plates (Analtech, UNIPLATES™ Silica gel G, 250 microns) using a UV lamp and charring. After the reaction was complete (3 h), the reaction mixture was evaporated under vacuum. The product was dried under vacuum to afford 13 (7.5 g). The crude product was purified by silica gel column chromatography with elution of the product by CH_2Cl_2:MeOH 50:50 to yield purified 13 (620 mg) as

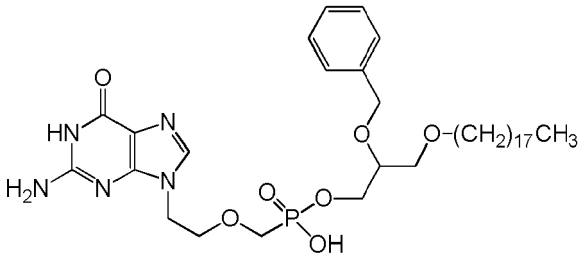
an off-white powder. ^{1}H NMR (400 MHz, $CDCl_3$+methanol) δ 7.87(s, 1 H) 7.20 - 7.36 (m, 5 H) 4.92 (d, J=7.33 Hz, 2 H) 4.17 (br. s., 2 H) 3.78 (br. s., 2 H) 3.66 (d, J=8.07 Hz, 2 H).

Scheme D



Reference Example 5. 1-O-Octadecyl-2-O-benzyl-sn-glyceryl PMEG (ODBG-PMEG, 14)

[0143]



14

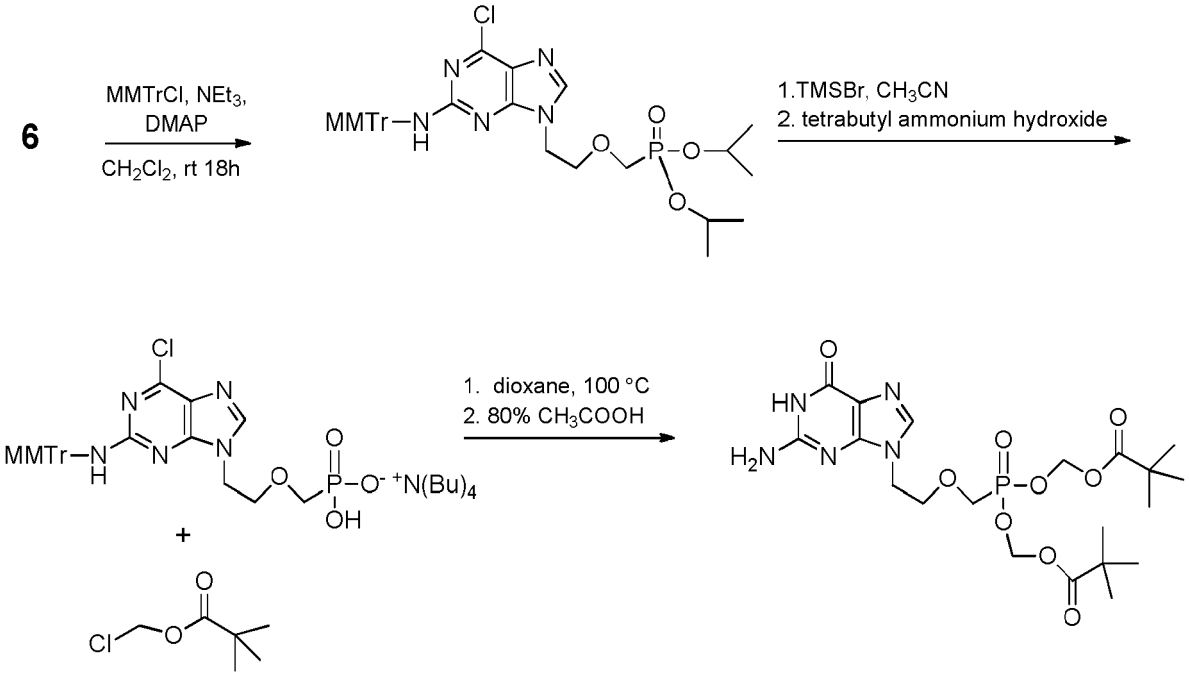
[0144] ODBG-PMEG was prepared by esterification of 7 with 1-O-octadecyl-2-O-benzyl-sn-glycerol (ODBG-OH). A 500 mL flask was equipped with a magnetic stirrer, then compound 7 (9.0 g, 18.25 mmol), ODBG-OH (20.7 mmol) and anhydrous N,N-DMF (200 mL) were added. The mixture was stirred and (benzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate (PYBOP®, 15.6 g, 30 mmol) was subdivided in 3 equal portions (5.2 g each) and each portion was then added at 30 mins intervals. After the addition of PYBOP®, diisopropylethylamine (DIEA, 2.6 g, 20 mmol) and 1-hydroxybenzotriazole (HOBt, 1.2 g, 9 mmol) were added. The reaction mixture was stirred at 22-25 °C, and the progress of the reaction was monitored by TLC (70:30:3:3 $CHCl_3$: MeOH: conc. NH_4OH: H_2O) on silica gel plates (Analtech, UNIPLATES™ Silica gel G, 250 microns). After the reaction was judged complete (16-20 h), the reaction mixture was concentrated in vacuo. The crude product was purified by silica gel column chromatography with elution of the product by CH_2Cl_2:EtOH 80:20 to yield the esterified intermediate (7.5 g, 50% yield).

[0145] A 500 mL reaction flask was equipped with a magnetic stirrer and a condenser. The esterified intermediate from the previous step (7.5 g), acetic acid (80 mL) and water (20 mL) were added. The resulting mixture was stirred and heated to reflux. The progress of the reaction was monitored by TLC (70:30:3:3 $CHCl_3$:MeOH:conc. NH_4OH:H_2O) on silica gel plates (Analtech, UNIPLATES™ Silica gel G, 250 microns) using a UV lamp and charring. After the reaction was complete (3 h), the reaction mixture was evaporated under vacuum. The crude product was purified by silica gel column chromatography with elution of the product by CH_2Cl_2:MeOH 80:20 to yield 14 (5.2 g, 81% yield) as an off-white powder.

Reference Example 6. Acyloxyalkyl ester of 9-[2-(phosphonomethoxy)ethyl]-guanine

[0146] Acyloxyalkyl esters of PMEG are prepared using methods similar to those described by Srivasta, et al. Bioorg. Chem. (1984) 12:118-129 and Starrett et al. J. Med. Chem. (1994) 37 1857-1864. A typical approach to synthesis is shown in Scheme E.

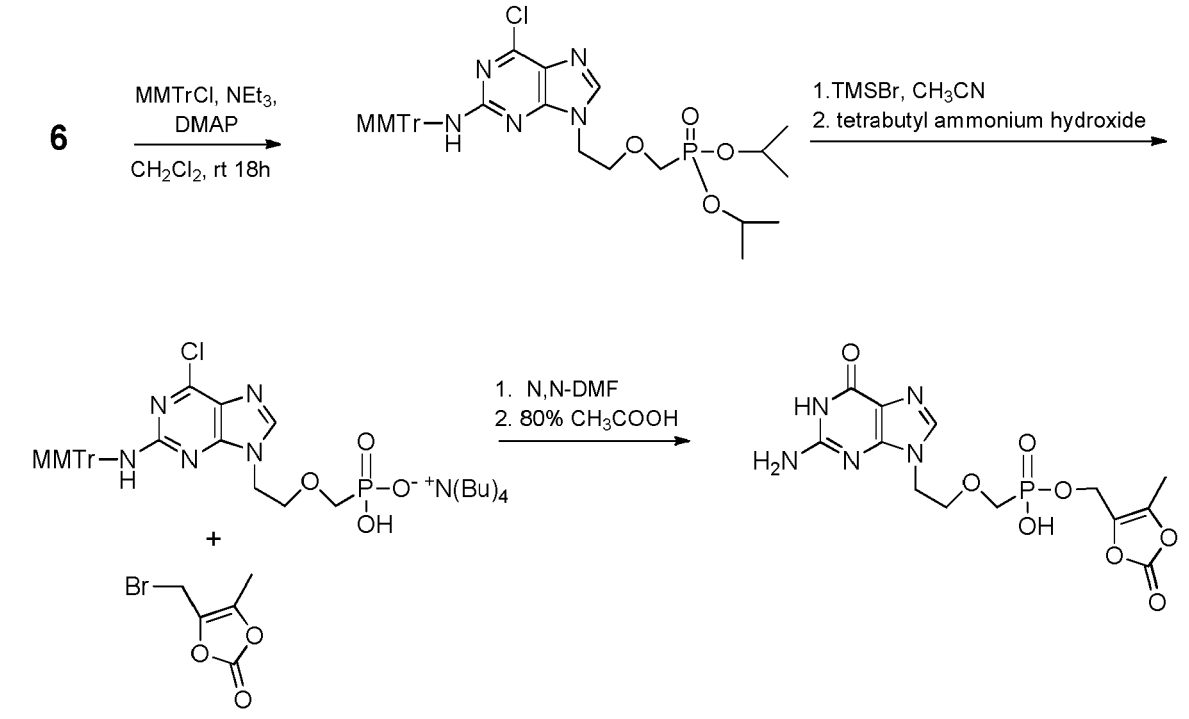
Scheme E



Reference Example 7. (5-Methyl-2-oxo-1,3-dioxolen-4-yl)methyl ester of 9-[2-(phosphonomethoxy)-ethyl]guanine

[0147] 9-[2-(phosphonomethoxy)ethyl]-guanine (PMEG) is neutralized with a 1M solution of methanolic tetrabutylammonium bromide in MeOH. The solution is evaporated and co-distilled with EtOH and toluene. The residue is dissolved in anhydrous DMF and treated with (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl bromide at RT for 4 days according to the procedure for preparing the corresponding adefovir prodrugs (see Tichý et al., Bioorg. & Med. Chem. (2011) 19(11):3527-3539.

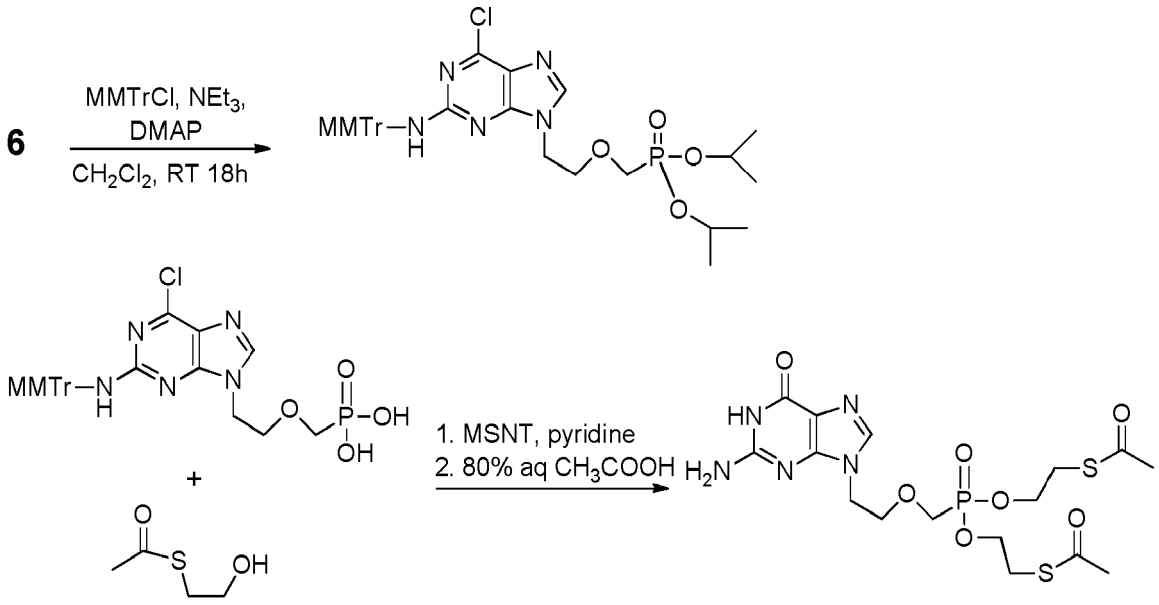
Scheme F



Reference Example 8. S-acylthioethyl (SATE) esters of PMEG

[0148] The general procedure for the synthesis of (S-acylthioethyl) (SATE) esters of PMEG are shown in Scheme G. Procedures are analogous to those described for preparing the adefovir SATE esters in Benzaria, S. et al., J. Med. Chem. (1996) 39(25):4958-4965.

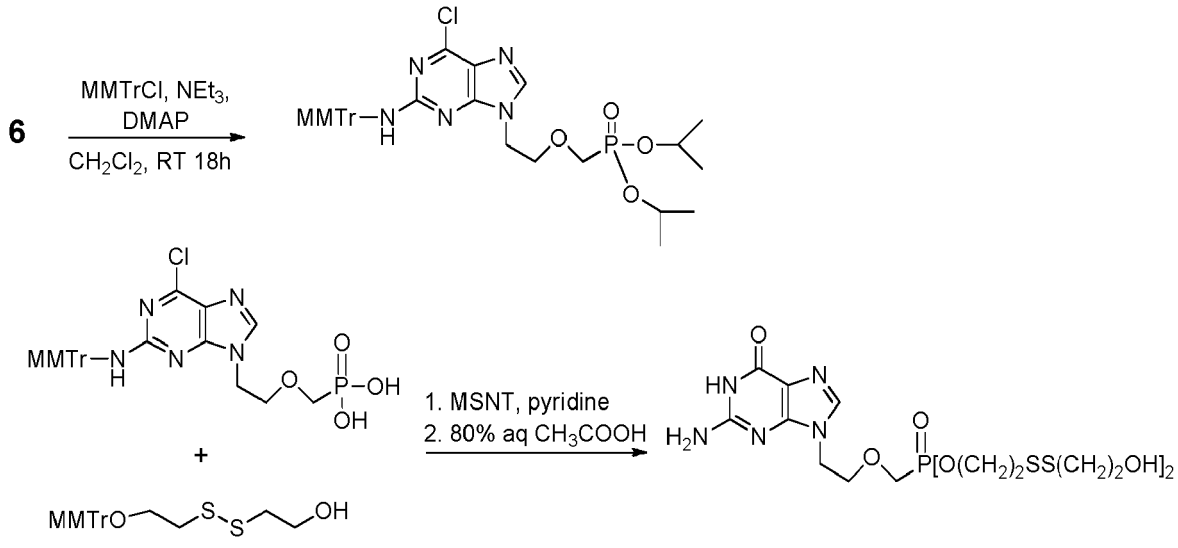
Scheme G



Reference Example 9. bis[S-2-hydroxyethylsufidyl)-2-thioethyl] esters of PMEG

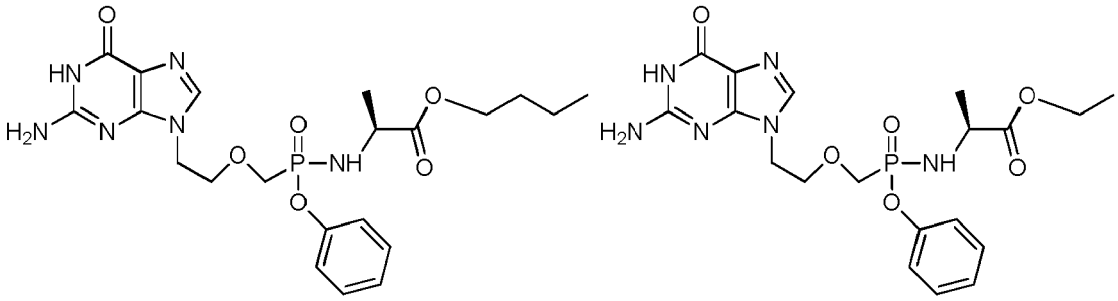
[0149] Bis[S-2-hydroxyethylsulfidyl)-2-thioethyl] PMEG esters (Scheme H) are prepared following similar procedures provided in Puech, F. et al. Antiviral Research (1993) 22:155-174.

Scheme H



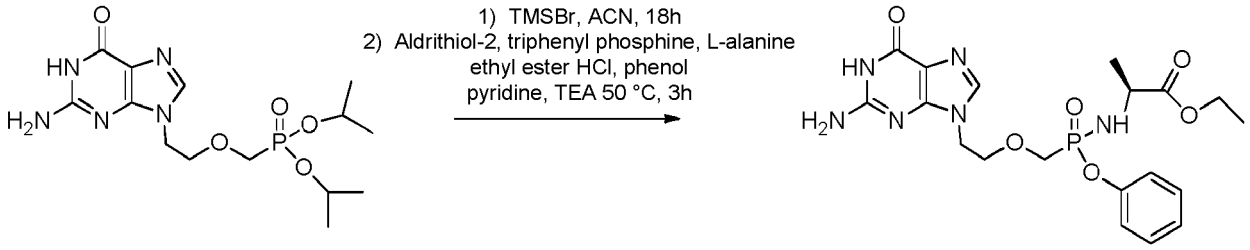
Reference Example 10. Aryl phosphonoamidate PMEG prodrugs

[0150] Aryl phosphonoamidate PMEG prodrugs are prepared following similar procedures provided in U.S. 8,088,754. Examples are shown below.



Synthesis of 9-[2-(phenyloxy-(ethoxy-L-alaninyl))-phosphonomethoxy)ethyl]guanine

[0151]



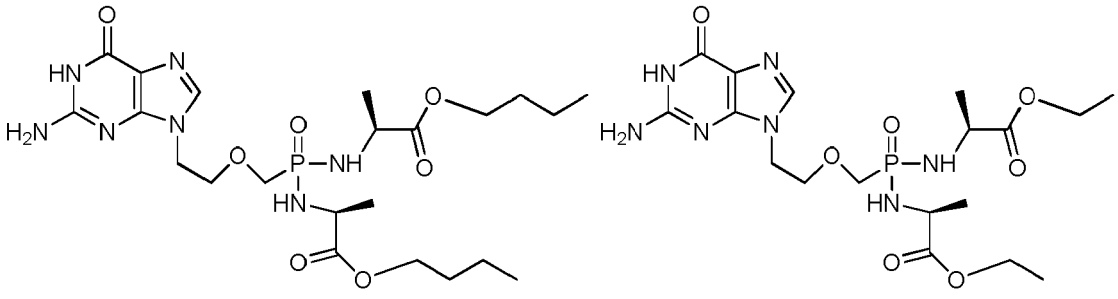
diisopropyl PMEG

9-[2-(phenyloxy-(ethoxy-L-alaninyl))-phosphonomethoxy)ethyl]guanine

[0152] To a solution of diisopropyl PMEG (1.0 g, 3 mmol) in dry acetonitrile (30 mL), bromotrimethylsilane (2.3 g, 15 mmol) was added and the reaction was stirred at room temperature overnight. The solvents were then removed under vacuum. The residue was dissolved in anhydrous Et3N (6 mL) and pyridine (25 mL), L-alanine ethyl ester HCl (0.69 g, 4.5 mmol) and phenol (0.42g, 4.5 mmol) were added. A solution of Aldrithiol-2 (4.0 g, 18 mmol eq) and Ph_3P (4.7 g, 18 mmol) in anhydrous pyridine (30 ml) was added to the reaction. The resulting mixture was heated to 50 °C and stirred for 3 hours. After cooling, the solvents were removed under reduced pressure and the residue was adsorbed on silica gel. The product was isolated as a mixture of diastereomers by flash chromatography on silica gel eluted with 0 to 5% MeOH in dichloromethane (410 mg, 29%). ^{1}H NMR (DMSO-d_6) δ 10.65 (s, 2H), 7.69 (s, 1H), 7.68 (s, 1H), 7.35-7.30 (m, 4H), 7.17 - 7.11 (m, 6H), 6.52 (s, 4H), 5.71 (t, 4H), 5.64 (t, 4H), 4.15 - 4.11 (m, 2H), 4.03 - 3.99 (m, 2H), 3.91-3.81 (m, 4H), 3.36 (s, 2H), 3.07 (q, 2H), 1.20 (d, 3H), 1.15 (d, 3H), 1.13 (t, 6H). MS (ESI) 465.20 [M+H]+, 487.19 [M+Na]+, 509.17 M-H+2Na]+.

Reference Example 11. Bis(phosphonoamidate) PMEG prodrugs

[0153] Bis(phosphonoamidate) PMEG prodrugs are prepared following similar procedures provided in U.S. 8,088,754. Examples are shown below.

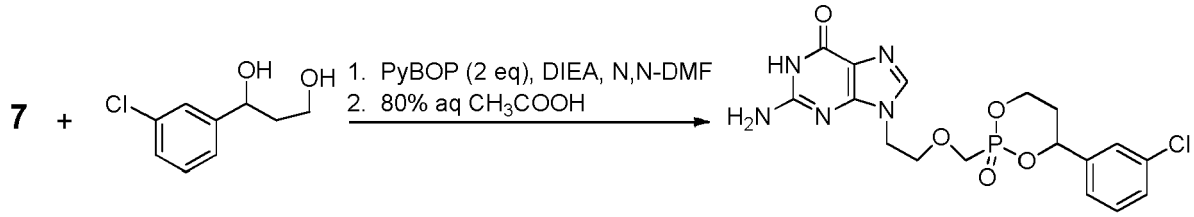


[0154] The compound 9-[2-(bis-(ethyloxy-L-alaninyl)-phosphonomethoxy)ethyl]guanine, illustrated above, was prepared as described in Lansa, P. et al. European Journal of Medicinal Chemistry, 2011, 46:3748-3754.

Reference Example 12. Cyclic 1-aryl-1,3-propanyl PMEG esters

[0155] Cyclic 1-aryl-1,3-propanyl PMEG esters are prepared following similar procedures provided in Reddy, et al., J. Med. Chem. (2008) 51:666-676. A general procedure for preparing cyclic 1-aryl-1,3-propanyl PMEG esters is shown in Scheme I.

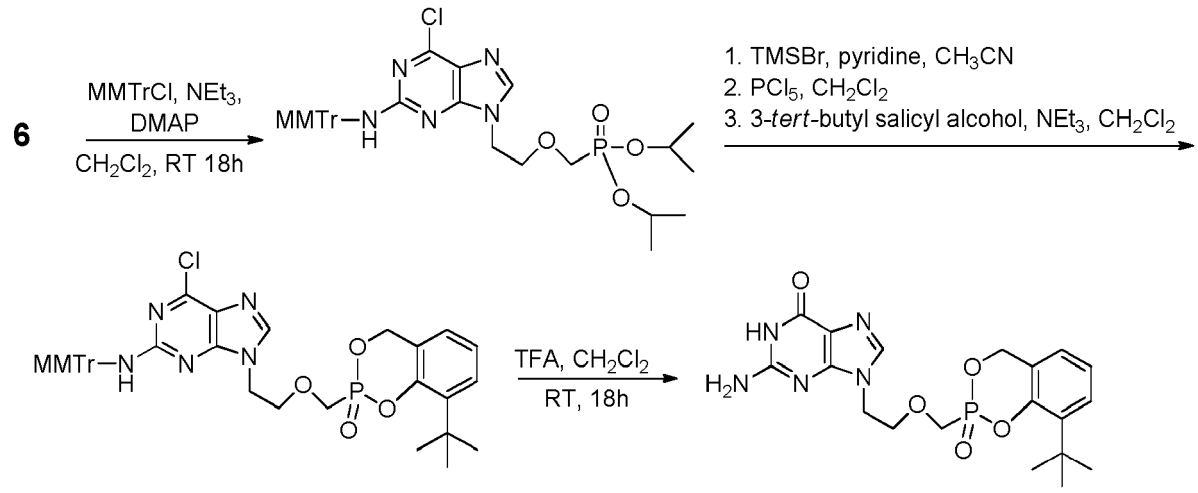
Scheme I



Reference Example 13. Cyclosal PMEG esters

[0156] Cyclosal PMEG esters are prepared following similar procedures provided in Meier, C. et al., J. Med. Chem. (2005) 48:8079-8086. A general procedure for preparing cyclosal PMEG esters is shown in Scheme J.

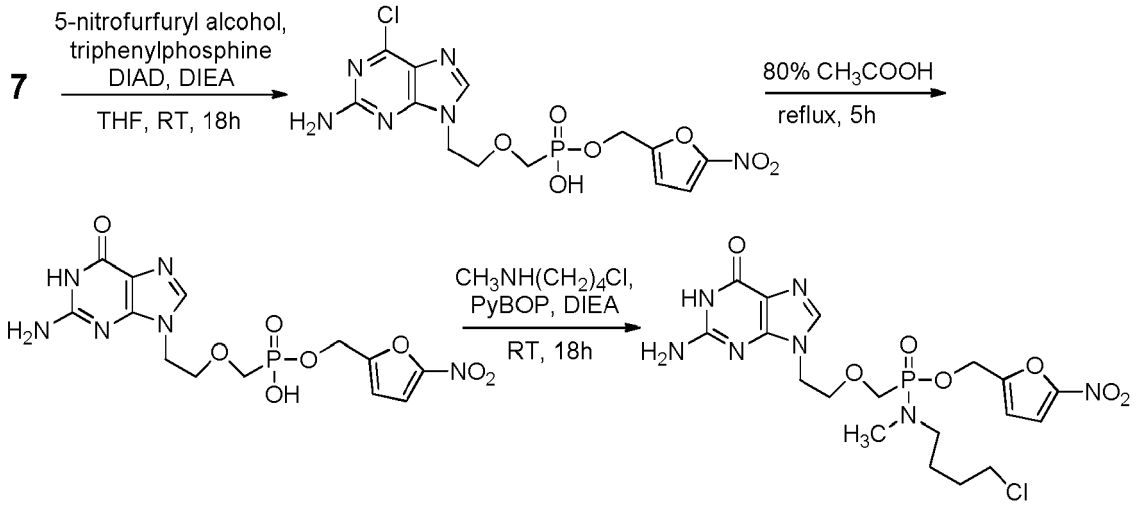
Scheme J



Reference Example 14. Nitrofuranylmethyl PMEG prodrugs

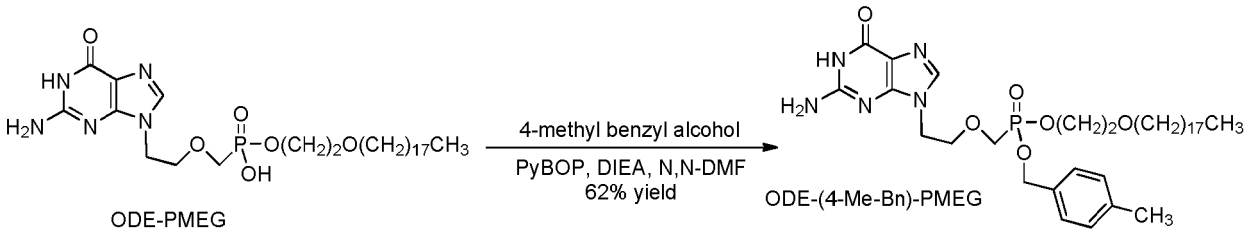
[0157] Nitrofuranylmethyl phosphonoamidate derivatives of PMEG are synthesized by sequential esterification of compound 7 with 5-nitrofurfuryl alcohol and N-methyl-N-4-chlorobutylamine as depicted in Scheme K. The nitrofuranylmethyl group has been shown (Tobias, S. C. et al., Mol. Pharmaceutics (2004) 1:112-116) to be readily taken up by cells, then cleaved intracellularly by a reductase enzyme which, in turn, leads to the formation of an intermediate chlorobutyl phosphonoamidate. Cyclization of the intermediate by nucleophilic attack of the nitrogen atom forms an N-phosphonotrialkyl ammonium species that can afford the unmasked phosphonate PMEG after hydrolysis.

Scheme K



Reference Example 15. Synthesis of ODE-(4-Me-Bn)-PMEG

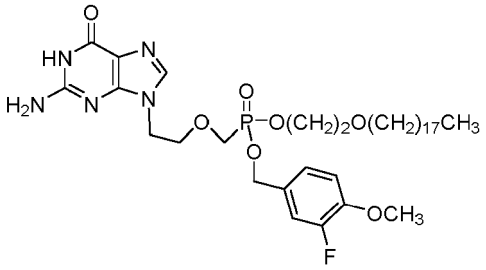
[0158]



[0159] ODE-PMEG (150 mg, 0.26 mmol), 4-methylbenzyl alcohol (70 mg, 0.52 mmol) and (1H-bentriazol-1-yloxy)-tripyrrolidinophosphonium hexafluoride (PyBOP, 200 mg, 0.4 mmol) were weighed into a dried 100 mL round bottom flask. Anhydrous N,N-dimethylformamide (5 mL) and diisopropylethylamine (0.1 mL, 0.52 mmol) were then added and the reaction was stirred at room temperature for 4 hours. The mixture was then concentrated under vacuum to an oil. The residue was adsorbed on silica gel and the product was isolated by column chromatography on silica gel (eluant: 0 to 10% MeOH in dichloromethane) to yield ODE-(4-Me-Bn)-PMEG as an off-white waxy solid. (60 mg, 33% yield). ^{1}H NMR (400 MHz, $CDCl_3$+methanol-d4) δ 7.64 (s, 1 H) 7.22 - 7.28 (m, 2 H) 7.15 - 7.20 (m, 2 H) 5.04 (dd, J=8.80, 2.20 Hz, 2 H) 4.19 (t, J=4.95 Hz, 2 H) 4.12 (m, 2 H) 3.82 - 3.87 (m, 2 H) 3.55 - 3.59 (m, 2 H) 3.43 (t, J=6.60 Hz, 2 H) 3.35 (dt, J=3.30, 1.65 Hz, 2 H) 2.35 (s, 3 H) 1.49 - 1.60 (m, 2 H) 1.16 - 1.37 (m, 30 H) 0.86 (t, J=7Hz, 3H). MS (ESI): 690.67 (M+H)+, 712.53 (M+Na)+, 734.51(M+2Na-H)+.

Reference Example 16. Synthesis of ODE-(3-F-4-OMe-Bn)-PMEG

[0160]

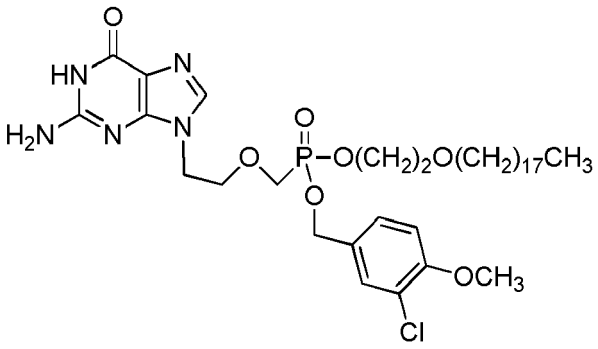


[0161] ODE-(3-F-4-OMe-Bn)-PMEG was prepared by the method of Example 4, using 3-fluoro-4-methoxybenzyl al-

cohol. The product was obtained as a waxy solid (100 mg, 52%). ^{1}H NMR (400 MHz, $CDCl_3$ + methanol-d4) δ 7.65 (s, 1 H) 7.06 - 7.17 (m, 2 H) 6.96 - 7.05 (m, 1 H) 5.00 (dd, J=8.80, 1.83 Hz, 2 H) 4.21 (t, J=5.13 Hz, 2 H) 4.14 (m, 2 H) 3.81 - 3.93 (m, 2 H) 3.59 (dd, J=4.95, 3.85 Hz, 2 H) 3.45 (t, J=6.78 Hz, 2 H) 3.35 (s, 3 H) 1.49 - 1.60 (m, 2 H) 1.07 - 1.45 (m, 30 H) 0.86 (t, J=7Hz, 3H). MS (ESI): 724.56 (M+H)+, 746.49 (M+Na)+.

Reference Example 17. Synthesis of ODE-(3-Cl-4-OMe-Bn)-PMEG

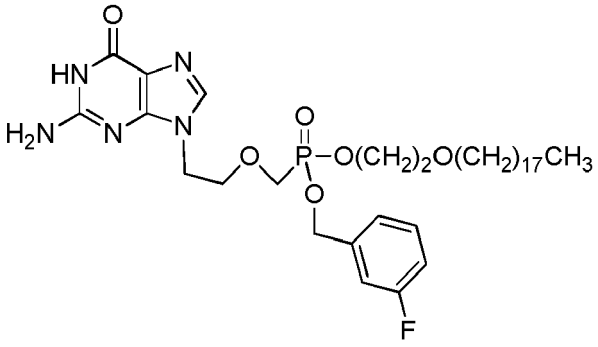
[0162]



[0163] ODE-(3-Cl-4-OMe-Bn)-PMEG was prepared by the method of Example 4, using 3-chloro-4-methoxybenzyl alcohol. The product was obtained as a waxy solid (90 mg, 46%). ^{1}H NMR (400 MHz, $CDCl_3$+methanol-d_4) δ ppm 7.66 (s., 1 H) 7.64 - 7.68 (m, 1 H) 7.38 - 7.42 (m, 1 H) 7.40 (d, J=2.20 Hz, 1 H) 4.95 - 5.05 (m, 2 H) 4.21 (t, J=5.13 Hz, 2 H) 4.11 - 4.17 (m, 2 H) 3.87-3.91 (m, 2 H) 3.84 - 3.89 (m, 2 H) 3.58 (dd, J=4.95, 3.85 Hz, 2 H) 3.44 (t, J=6.60 Hz, 2 H) 3.35 (s, 3 H) 1.51 - 1.59 (m, 2 H) 1.06 - 1.45 (m, 30 H) 0.89 (t, J=7Hz, 3 H).). MS (ESI): 740.52 (M+H)+, 762.47 (M+Na)+.

Reference Example 18. Synthesis of ODE-(3-F-Bn)-PMEG

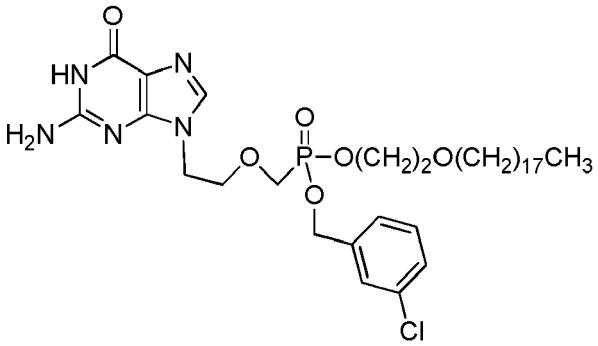
[0164]



[0165] ODE-(3-F-Bn)-PMEG was prepared by the method of Example 4, using 3-fluorobenzyl alcohol. The product was obtained as an off-white solid (80 mg, 44%). ^{1}H NMR (400 MHz, $CDCl_3$ + methanol-d_4) δ 7.64 (s, 1 H) 7.42 - 7.50 (m, 1 H) 7.33 - 7.40 (m, 1 H) 6.97 - 7.19 (m, 2 H) 5.03 - 5.16 (m, 2 H) 4.11 - 4.25 (m, 4 H) 3.84 - 3.95 (m, 2 H) 3.55 - 3.65 (m, 2 H) 3.41 - 3.49 (m, 4 H) 3.35 (s, 3 H) 1.49 - 1.61 (m, 2H) 1.07-1.39 (m, 30 H) 0.88 (t, J=7Hz, 3 H). MS (ESI): 694.45 (M+H)+, 716.44 (M+Na)+, 738.44(M+2Na-H)+.

Reference Example 19. Synthesis of ODE-(3-Cl-Bn)-PMEG

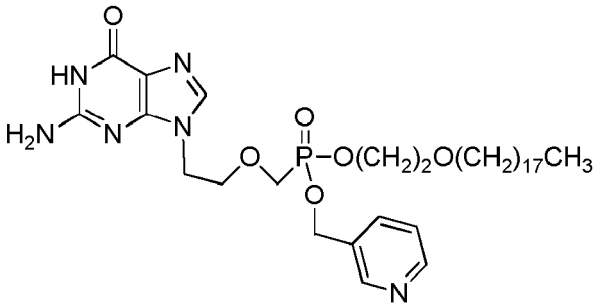
[0166]



[0167] ODE-(3-Cl-Bn)-PMEG was prepared by the method of Example 4, using 3-chlorobenzyl alcohol. The product was obtained as an off-white solid (80 mg, 42%). ^{1}H NMR (400 MHz, $CDCl_3$+methanol-d_4) δ 7.63 (s, 1 H) 7.45 (t, J=6.42 Hz, 1 H) 7.23 - 7.41 (m, 3 H) 5.06 (d, J=8.80 Hz, 2 H) 4.17-4.21 (m, 4 H) 3.80 - 3.94 (m, 4 H) 3.59 (d, J=4.77 Hz, 2 H) 3.44 (t, J=6.78 Hz, 2 H) 3.36 (s, 4 H) 1.50-1.56 (m, 2 H) 1.11-1.24 (m, 30 H) 0.88 (t, J=6.78 Hz, 3 H). MS (ESI) [M+H]+ 710.46, [M+Na]+ 732.43.

Reference Example 20. Synthesis of ODE-(3-picolyl)-PMEG

[0168]



[0169] ODE-(3-picolyl)-PMEG was prepared by the method of Example 4, using 3-pyridinemethanol. The product was obtained as an off-white solid (110 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$+methanol-d_4) δ 7.60 (s, 1 H) 7.40-7.42 (m, 1 H) 7.23 - 7.31 (m, 3 H) 5.16 (d, J=8.80 Hz, 2 H) 4.15-4.20 (m, 4 H) 3.86 - 3.95 (m, 4 H) 3.56 - 3.60 (m, 2 H) 3.41 - 3.49 (m, 2 H) 3.36 (s, 3 H) 1.50-1.56 (m, 2 H) 1.11-1.24 (m, 30 H) 0.88 (t, J=6.78 Hz, 3 H). MS (EI): 677.46 (M+H)+, 699.47 (M+Na)+, 721.41(M+2Na-H)+.

Reference Example 21. Low Risk and High Risk HPV Assays

[0170] An origin-containing low risk or high risk HPV plasmid was co-transfected with homologous E1 and E2 protein expression vectors into HEK 293 cells. At 4 h post-transfection, cells were treated with test compound dilutions and then incubated for 48 h. HPV origin plasmid replication was detected after digestion with DpnI and exonuclease III to remove unreplicated transfected plasmids. Remaining replicated DNA was quantified by quantitative real time PCR (qPCR). In a parallel experiment in uninfected cells cytotoxicity was determined by trypan blue exclusion or CELLTITER-GLO® to find the concentration that reduced viable cell number by 50% (CC50). CC_{50} values were determined by trypan blue exclusion or CELLTITER-GLO® and the selectivity index calculated (Selectivity index = CC_{50}/EC_{50}). The low risk HPV tested was HPV-11, and the high-risk HPV tested was HPV-16 and HPV-18.

[0171] The results are provided in Table A and Table B. As shown in Table A, compounds of Formula (I) are active against both low-risk and high-risk HPV.

Table A

Compound	Low Risk	High Risk
PMEG	C	C

(continued)

Compound	Low Risk	High Risk
ODE-PMEG	A	A
ODBG-PMEG	B	B

'A' indicates an EC_{50} < 0.3 μM, 'B' indicates an EC_{50} of ≥0.3 μM and < 3.0 μM and 'C' indicates an EC_{50} ≥ 3.0 μM and < 30 μM. For all the tested compounds, the selectivity indexes were >10.

[0172] The results are provided in Table B. As shown in Table B, compounds of Formula (I) are active against both low-risk and high-risk HPV.

Table B. Antiviral Activity against HPV-11 in HEK-293 Cells

Compound	EC_{50} (μM)	EC_{90} (μM)	CC_{50} (μM)	SI_{50}
ODE-(4-Me-Bn)-PMEG	0.93± 0.91	7.0± 3.45	23.80± 19.52	26
ODE-(3-F-4-OMe-Bn)-PMEG	0.18± 0.04	0.99± 0.13	14.25± 9.48	79
ODE-(3-Cl-4-OMe Bn)-PMEG	0.68± 0.62	1.34± 0.78	8.31± 1.83	12
ODE-(3-F-Bn)-PMEG	0.26± 0	1.59± 0.57	1.74± 0.03	7
PMEG bisamidate Reference Example 11	5.04± 7.01	>100± 0	>100± 0	>20
PMEG phenoxy amidate Reference Example 10	7.56± 0.63	>100± 0	>100± 0	>13
ODE-(3-Cl-Bn)-PMEG	0.22± 0.19	>0.4± 0	1.11± 0.27	5
Cidofovir	41.71 ± 12	>300± 0	>300± 0	>7

Reference Example 22. Cytotoxicity Assay

[0173] Cytotoxicity Assays in HEK-293 cells. Cytotoxicity assays are performed in concurrently with every antiviral assay using the same cell line and media to ensure the same compound exposure. For the antiviral studies against HPV11 in HEK-293 cells, transfected cells are seeded in duplicate plates. Following a 2 h exposure, compound dilutions are prepared in both the antiviral plate and the duplicate cytotoxicity plate. At 48 h following compound addition, CELL-TITER-GLO® (Promega) is added to each well and luminescence is determined on a luminometer. Concentrations of compounds sufficient to reduce cell viability by 50% are calculated from the experimental data (CC_{50} values).

[0174] Cytotoxicity Assays in Primary Human Foreskin Fibroblast Cells. Cytotoxicity was also evaluated in human foreskin fibroblast (HFF) cells as they are a highly sensitive indicator of toxicity in a standard assay with 7 d of compound exposure. A total of 4000 cells/well are seeded in 384-well plates in cell culture media containing 2% fetal bovine serum and antibiotics. Following a 24h incubation, 5-fold compound dilutions are performed in duplicate wells directly in the plates containing monolayers of HFF cells. At 7 d following compound addition, CELLTITER-GLO® reagent is added to each well and resulting luminescence is measured on a luminometer to assess the number of viable cells in each well. Data are then used to calculate CC_{50} values. The data is disclosed in Table 3 below.

Table 3. Cytotoxicity Results (CELLTITER-GLO®)

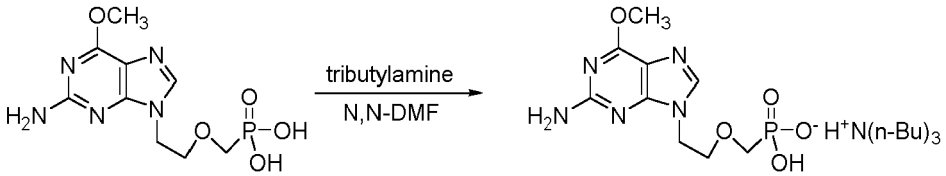
	(CC_{50}, μM)	
Compound	HEK 293 (2d incubation)	HFF (7d incubation)
ODE-(4-Me-Bn)-PMEG	32.01 ± 8.14	6.02 ± 3.79
ODE-(3-F-4-OMe-Bn)-PMEG	13.08 ± 5.17	1.72 ± 0.66
ODE-(3-Cl-4-OMe-Bn)-PMEG	8.87 ± 1.20	2.27 ± 0.51
ODE-(3-F-Bn)-PMEG	2.16 ± 0.36	6.88 ± 4.92
PMEG bisamidate Reference Example 11	>100 ± 0	>100 ± 0
PMEG phenoxy amidate Reference Example 10	>100 ± 0	70.93 ± 4.07

(continued)

	(CC_{50}, μM)	
Compound	HEK 293 (2d incubation)	HFF (7d incubation)
ODE-(3-Cl-Bn)-PMEG	1.0 ± 0.16	4.65 ± 1.73
Cidofovir	>300 ± 0	>300 ± 0

Reference Example 23. Synthesis of 9-[(2-phosphonomethoxy)ethyl]-2-amino-6-methoxypurine, tributylamine salt, 1, alternate name: ((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)phosphonic acid, tributylamine salt

[0175]

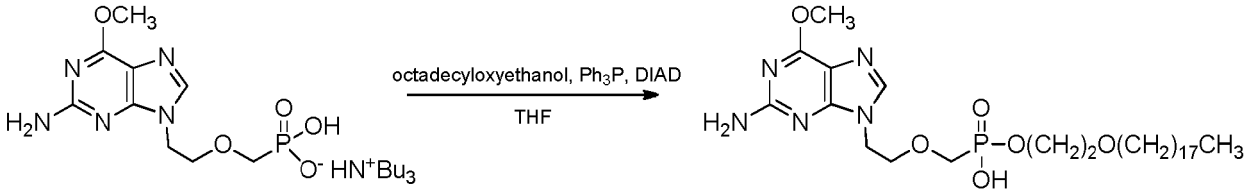


1 2

[0176] The scheme above provides a chemical synthetic scheme to afford 9-[(2-phosphonomethoxy)ethyl]-2-amino-6-methoxypurine, tributylamine salt.

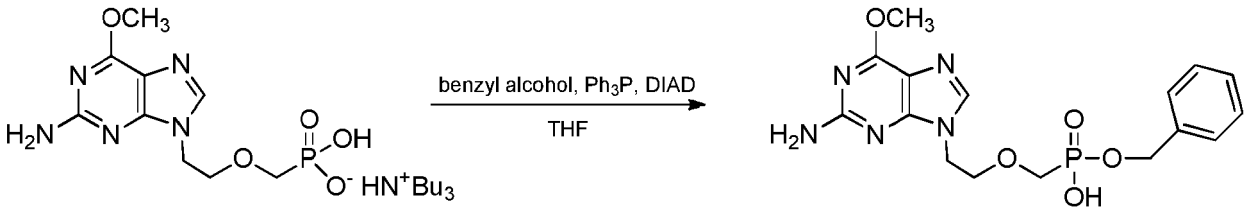
Reference Example 24. Synthesis of octadecyloxyethyl 9-[(2-phosphonomethoxy)ethyl]6-O-Me-guanine

[0177]



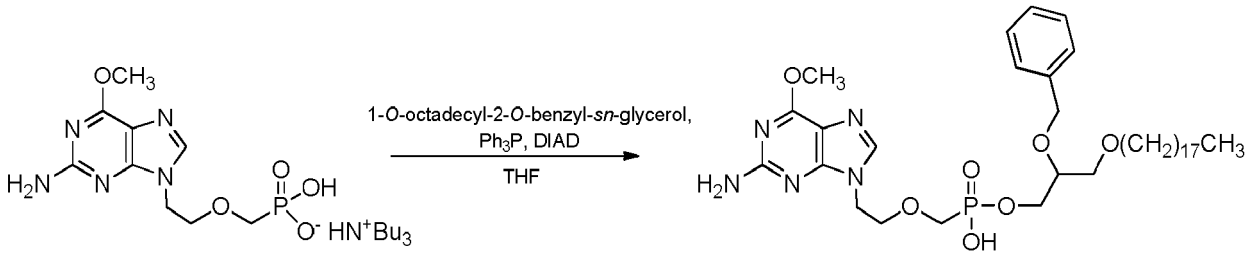
Reference Example 25. Synthesis of benzyl 9-[(2-phosphonomethoxy)ethyl]6-O-Me-guanine

[0178]



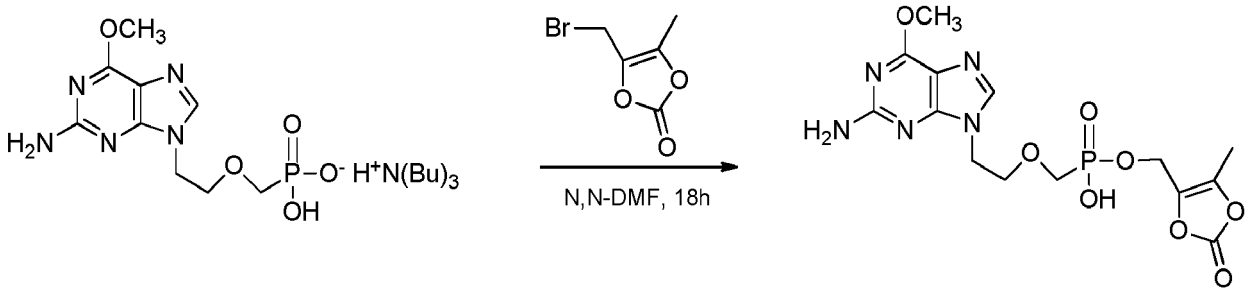
Reference Example 26. Synthesis of 1-O-octadecyl-2-O-benzyl-sn-glyceryl 9-[(2-phosphono-methoxy)ethyl]6-O-Me-guanine

[0179]



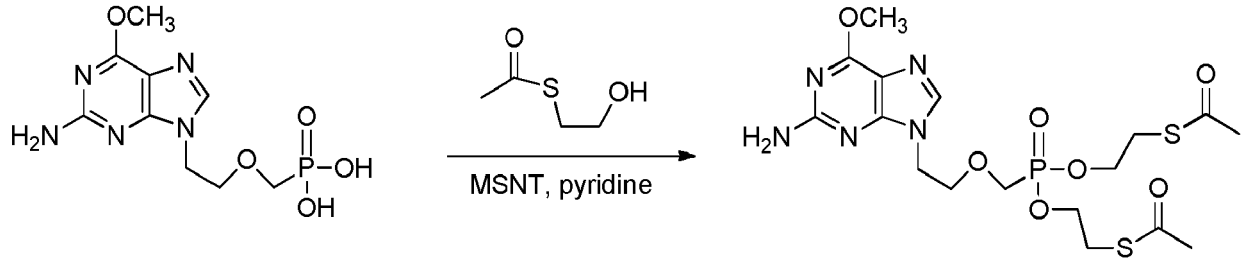
Reference Example 27. Synthesis of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl hydrogen ((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)phosphonate

[0180]



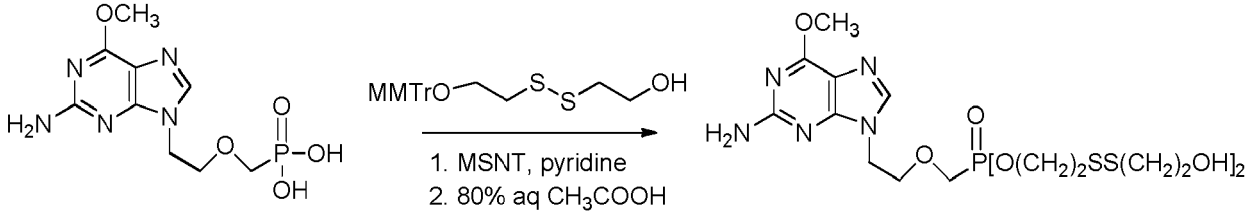
Reference Example 28. Synthesis of S,S'-(((((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)phosphoryl)bis(oxy))bis(ethane-2,1-diyl)) diethanethioate

[0181]



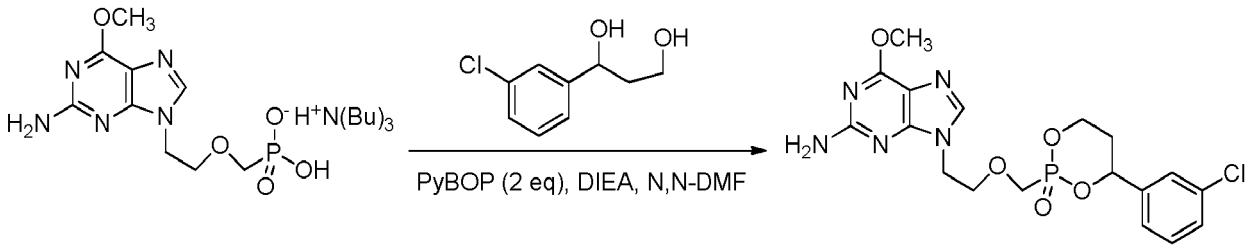
Reference Example 29. Synthesis of bis(2-((2-hydroxyethyl)sulfinothioyl)ethyl) ((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy) methyl)phosphonate

[0182]



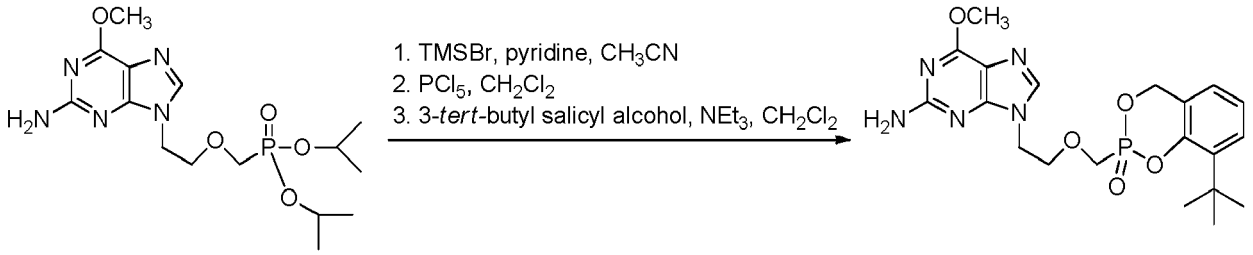
Reference Example 30. Synthesis of 2-amino-9-(2-((4-(3-chlorophenyl)-2-oxido-1,3,2-dioxaphosphinan-2-yl)methoxy)ethyl)-1,9-dihydro-6H-purin-6-one

[0183]



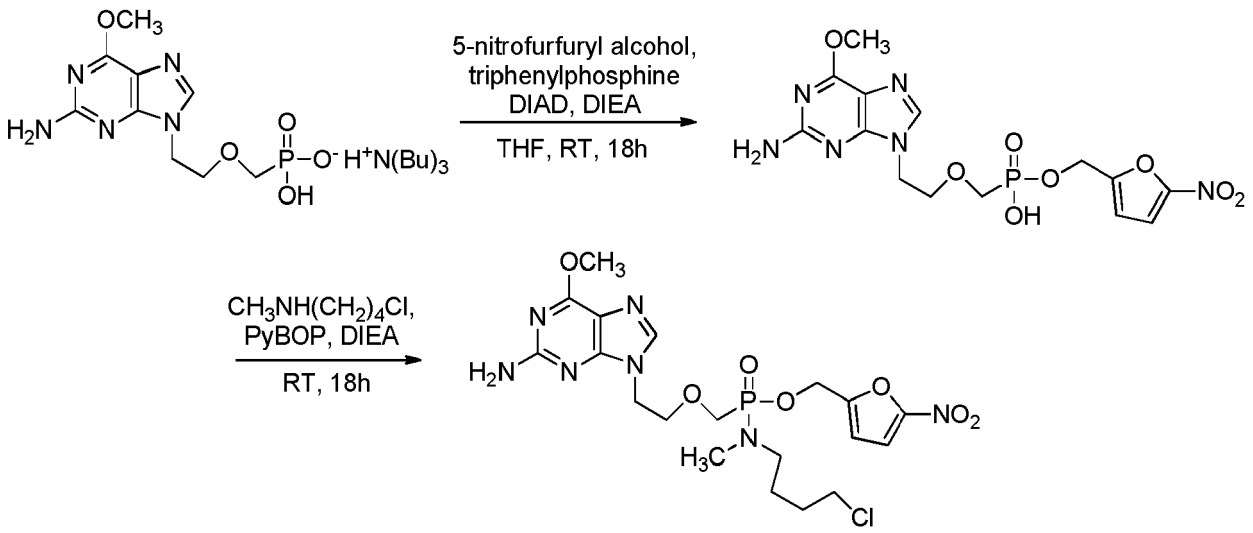
Reference Example 31. Synthesis of 2-((2-(2-amino-6-hydroxy-9H-purin-9-yl)ethoxy)methyl)-8-(tert-butyl)-4H-benzo[d][1,3,2]dioxaphosphinine 2-oxide

[0184]



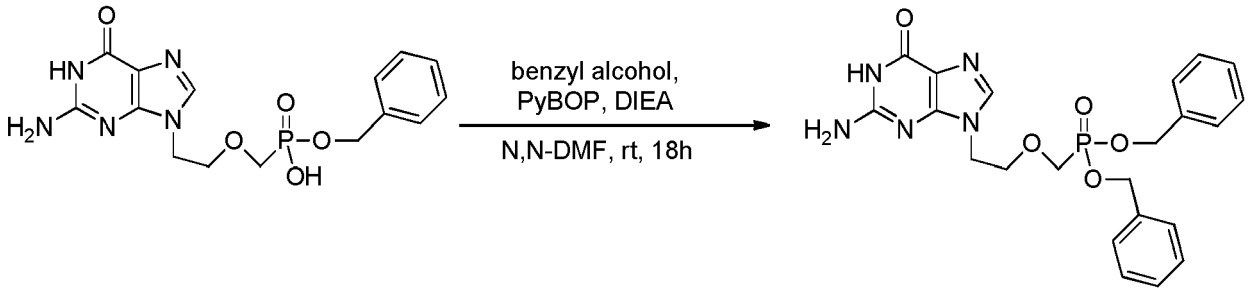
Reference Example 32. Synthesis of (5-nitrofuran-2-yl)methyl P-((2-(2-amino-6-methoxy-9H-purin-9-yl)ethoxy)methyl)-N-(4-chlorobutyl)-N-methylphosphonamidate

[0185]



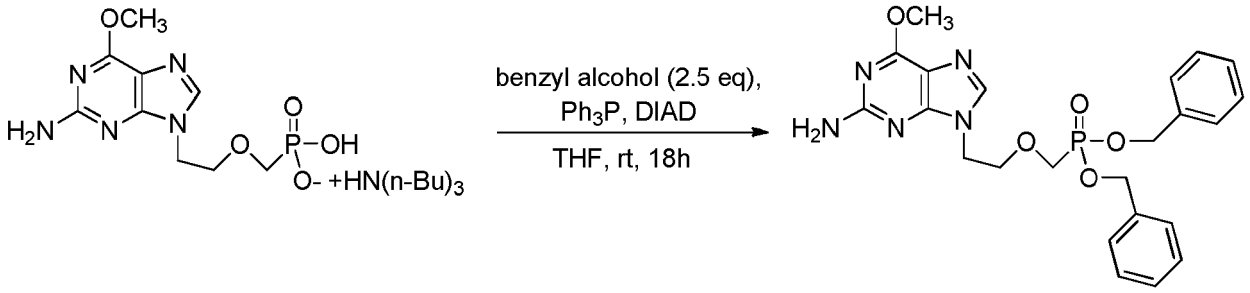
Reference Example 33. Synthesis of dibenzyl PMEG

[0186] Dibenzyl PMEG can be prepared from benzyl PMEG, Example 4, as illustrated below.



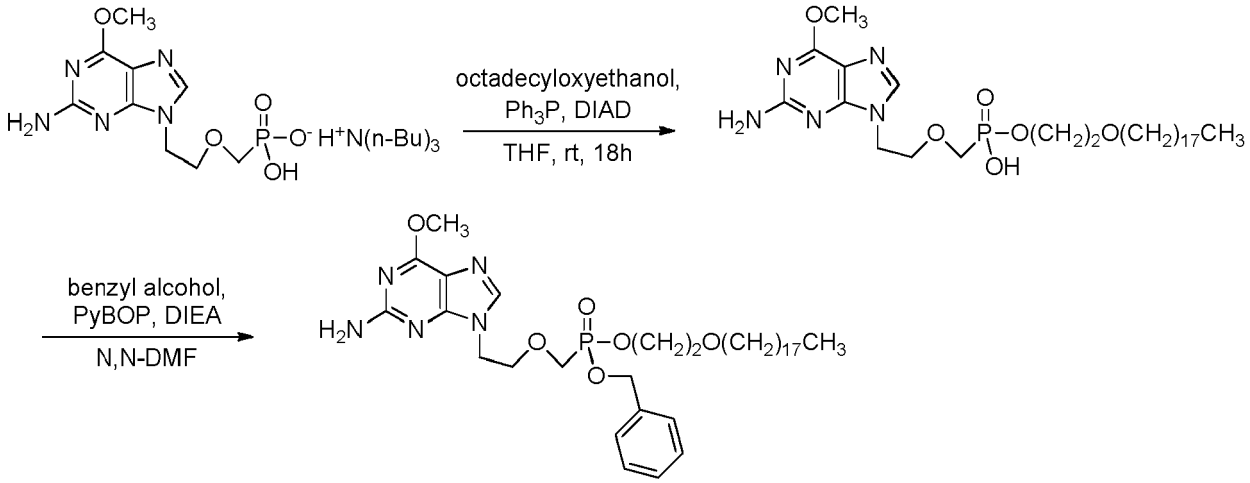
Reference Example 34. Synthesis of dibenzyl 9-[(2-phosphonomethoxyl)ethyl]6-OMe-guanine

[0187] Dibenzyl 9-[(2-phosphonomethoxyl)ethyl] 6-OMe-guanine can be prepared from 9-[(2-phosphonomethoxy)ethyl]-2-amino-6-methoxypurine, tributylamine salt (Example 23).



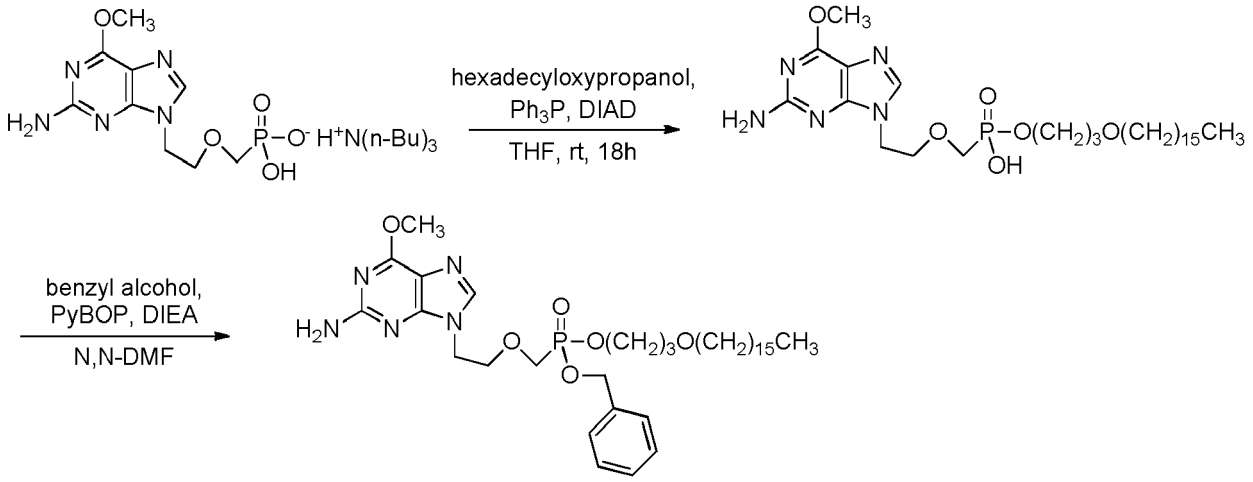
Reference Example 35. Synthesis of octadecyloxyethyl benzyl 9-[(2-phosphonomethoxyl)ethyl]6-OMe-guanine

[0188] The compound octadecyloxyethyl benzyl 9-[(2-phosphonomethoxyl)ethyl] 6-OMe-guanine can be prepared from 9-[(2-phosphonomethoxy)ethyl]-2-amino-6-methoxypurine, tributylamine salt (Example 23) as illustrated below.



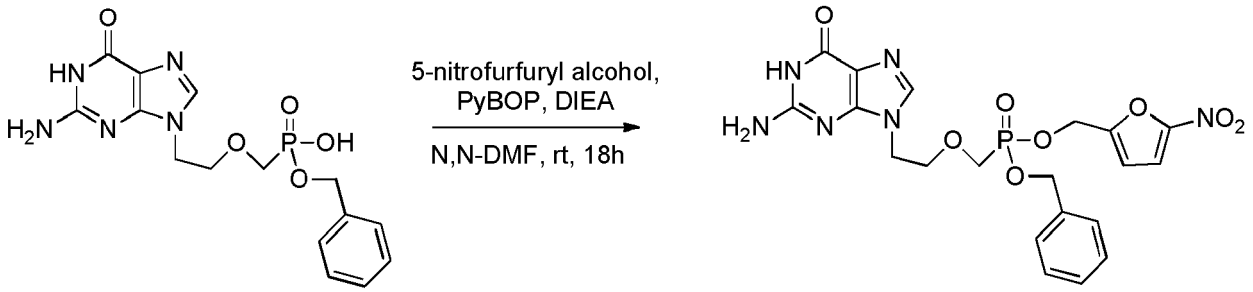
Reference Example 36. Synthesis of hexadecyloxypropyl benzyl 9-[(2-phosphonomethoxyl)ethyl] 6-OMe-guanine

[0189] The compound hexadecyloxypropyl benzyl 9-[(2-phosphonomethoxyl)ethyl] 6-OMe-guanine can be prepared from 9-[(2-phosphonomethoxy)ethyl]-2-amino-6-methoxypurine, tributylamine salt (Example 23) as illustrated below.



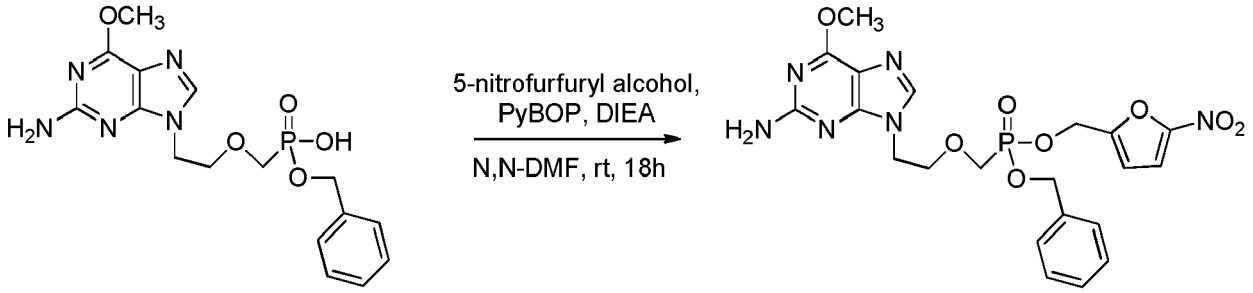
Reference Example 37. Synthesis of a nitrofuranylmethyl PMEG prodrug

[0190] Benzyl PMEG is treated with 5-nitrofurfuryl alcohol, ByBOP, diisopropylethylamine, and N,N-dimethylformamide for 18 hours at room temperature as illustrated below.



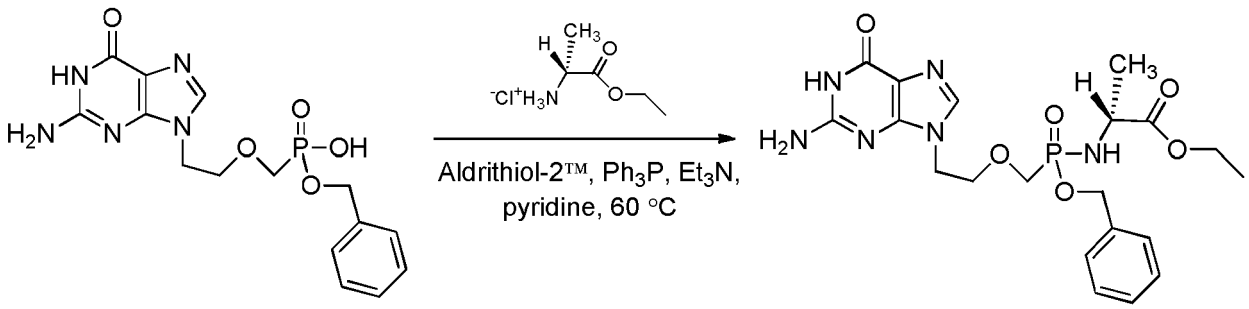
Reference Example 38. Synthesis of a nitrofuranylmethyl benzyl prodrug

[0191] The compound benzyl 9-[(2-phosphonomethoxyl)ethyl] 6-OMe-guanine is treated with 5-nitrofurfuryl alcohol, ByBOP, diisopropylethylamine, and N,N-dimethylformamide for 18 hours at room temperature as illustrated below.



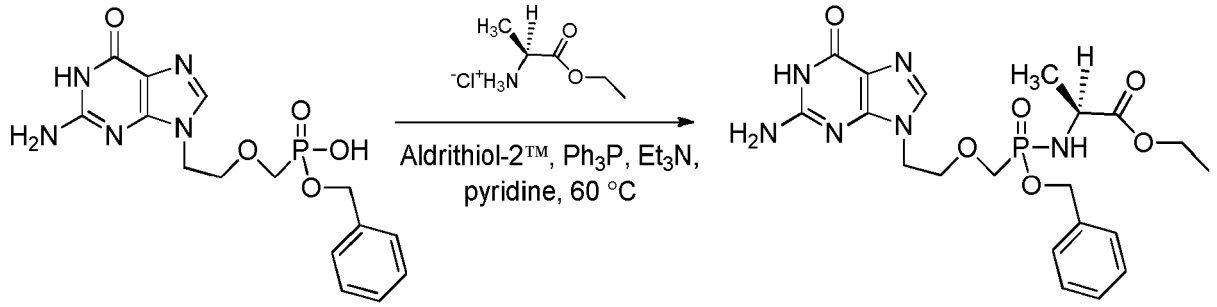
Example 39. Synthesis of 9-[2-(benzyloxy-(ethoxy-D-alanyl)-phosphonomethoxyl)ethyl]guanine

[0192] The compound 9-[2-(benzyloxy-(ethoxy-D-alanyl)-phosphonomethoxyl)ethyl]guanine is synthesized as illustrated below.



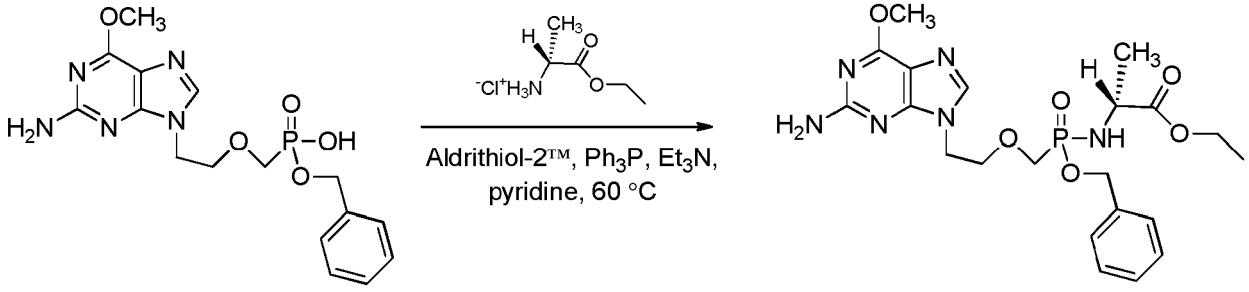
Example 40. Synthesis of 9-[2-(benzyloxy-(ethoxy-L-alanyl)-phosphonomethoxyl)ethyl]guanine

[0193] The compound 9-[2-(benzyloxy-(ethoxy-L-alanyl)-phosphonomethoxyl)ethyl]guanine is synthesized as illustrated below.



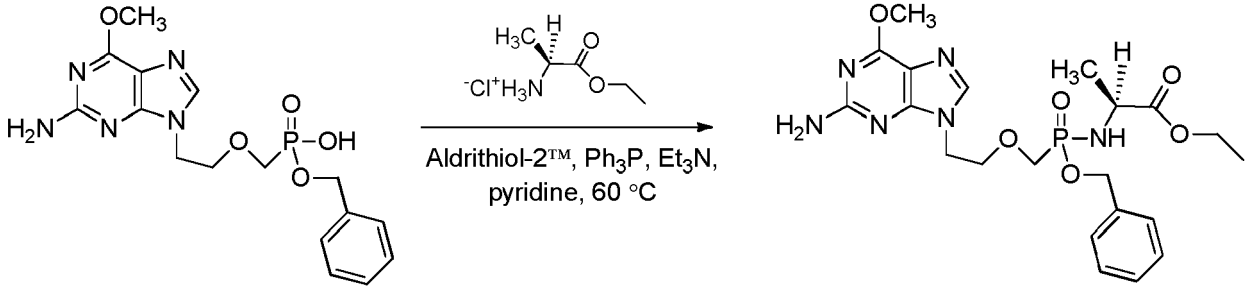
Example 41. Synthesis of 9-[2-(benzyloxy-(ethoxy-D-alanyl)-phosphonomethoxyl)ethyl]6-OMe guanine

[0194] The compound 9-[2-(phenoxy-(ethoxy-D-alanyl)-phosphonomethoxyl)ethyl] 6-OMe guanine is synthesized as illustrated below.



Example 42. Synthesis of 9-[2-(benzyloxy-(ethoxy-L-alanyl)-phosphonomethoxyl)ethyl]6-OMe guanine

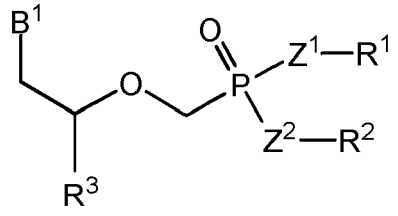
[0195] The compound 9-[2-(phenoxy-(benzyloxy-L-alanyl)-phosphonomethoxyl)ethyl] 6-OMe guanine is synthesized as illustrated below.



Additional Embodiments, disclosed but not claimed.

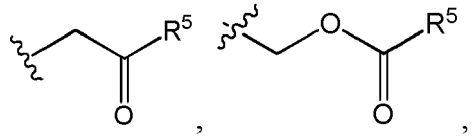
[0196]

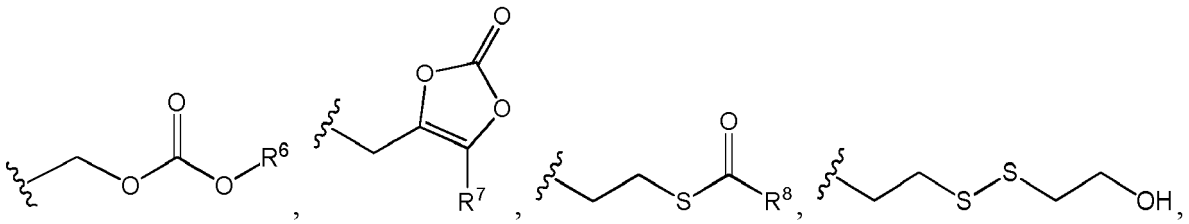
Embodiment P1. A compound of the structure of Formula (I), or a pharmaceutically acceptable salt thereof:

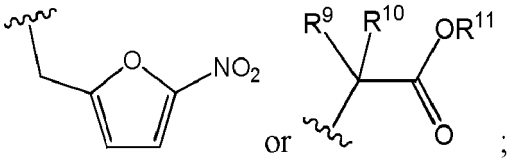


(I),

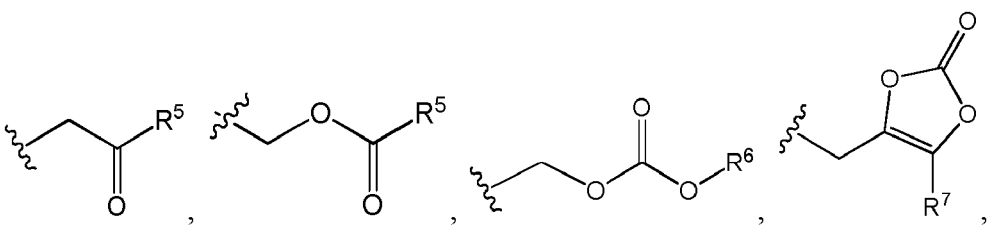
wherein: B^1 is a naturally occurring purine, a naturally occurring pyrimidine, a non-naturally occurring purine or a non-naturally occurring pyrimidine; Z^1 and Z^2 are independently O or NR^Z; R^Z is hydrogen or an optionally substituted C_{1-4} alkyl; R^1 is an optionally substituted -C_{2-24} alkenyl, an optionally substituted -C_{2-24} alkynyl, an optionally substituted -$(CHR^4)_a$-O-C_{2-24} alkenyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkyl(C_1-C_4 alkyl)-, an optionally substituted cycloalkenyl, an optionally substituted cycloalkenyl(C_1-C_4 alkyl)-, an optionally substituted aryl, an optionally substituted aryl(C_{1-4} alkyl), an optionally substituted heteroaryl, an optionally substituted heteroaryl(C_1-C_4 alkyl)-, an optionally substituted heterocyclyl, an optionally substituted heterocyclyl(C_1-C_4 alkyl)-,

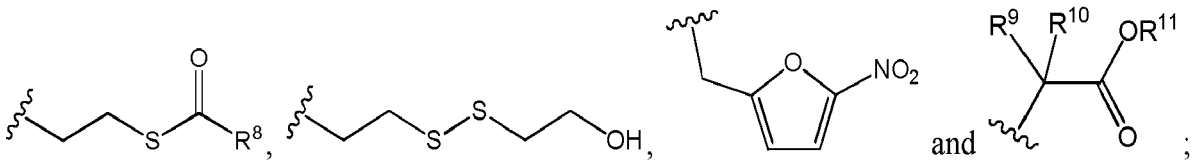




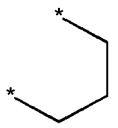


and R^2 is an optionally substituted -C_{2-24} alkenyl, an optionally substituted -C_{2-24} alkynyl, an optionally substituted -$(CHR^4)_b$-O-C_{2-24} alkenyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkyl(C_{1-4} alkyl)-, an optionally substituted cycloalkenyl, an optionally substituted cycloalkenyl(C_{1-4} alkyl)-, substituted aryl(C_{1-4} alkyl)-,

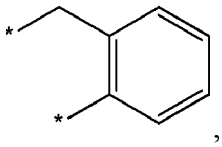




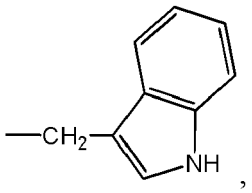
or R^1 and R^2 can be taken together to form a moiety selected from an optionally substituted



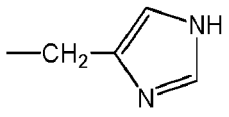
or an optionally substituted



wherein Z^1, Z^2, R^1 and R^2, the phosphorus and the moiety form a six-membered to ten-membered ring system; R^3 is hydrogen, optionally substituted alkyl or optionally substituted heteroalkyl; each R^4 is independently hydrogen, -$(CH_2)_c$-S-C_{1-24} alkyl or -O-$(CH_2)_d$-R^{4A}; each R^{4A} is independently hydrogen, an optionally substituted C_{1-24} alkyl or an optionally substituted aryl; each R^5, each R^6 and each R^8 are independently an optionally substituted C_{1-8} alkyl, an optionally substituted C_{2-8} alkenyl, an optionally substituted C_{2-8} alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkyl(C_1-C_4 alkyl)-, an optionally substituted cycloalkenyl, an optionally substituted cycloalkenyl(C_1-C_4 alkyl)-, an optionally substituted aryl, an optionally substituted aryl(C_{1-4} alkyl)-, an optionally substituted heteroaryl, an optionally substituted heteroaryl(C_1-C_4 alkyl)-, an optionally substituted heterocyclyl, or an optionally substituted heterocyclyl(C_1-C_4 alkyl)-; each R^7 is independently hydrogen, an optionally substituted C_{1-8} alkyl, an optionally substituted C_{2-8} alkenyl, an optionally substituted C_{2-8} alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkyl(C_1-C_4 alkyl)-, an optionally substituted cycloalkenyl, an optionally substituted cycloalkenyl(C_1-C_4 alkyl)-, an optionally substituted aryl, an optionally substituted aryl(C_{1-4} alkyl)-, an optionally substituted heteroaryl, an optionally substituted heteroaryl(C_1-C_4 alkyl)-, an optionally substituted heterocyclyl, or an optionally substituted heterocyclyl(C_1-C_4 alkyl)-; each R^9 and each R^{10} are independently hydrogen or an optionally substituted C_{1-6} alkyl; -CH_2SH, -$CH_2(C{=}O)NH_2$, -$CH_2CH_2(C{=}O)NH_2$, -CH_2CH_2S CH_3, CH_2-an optionally substituted phenyl, -CH_2OH, -$CH(OH)CH_3$,



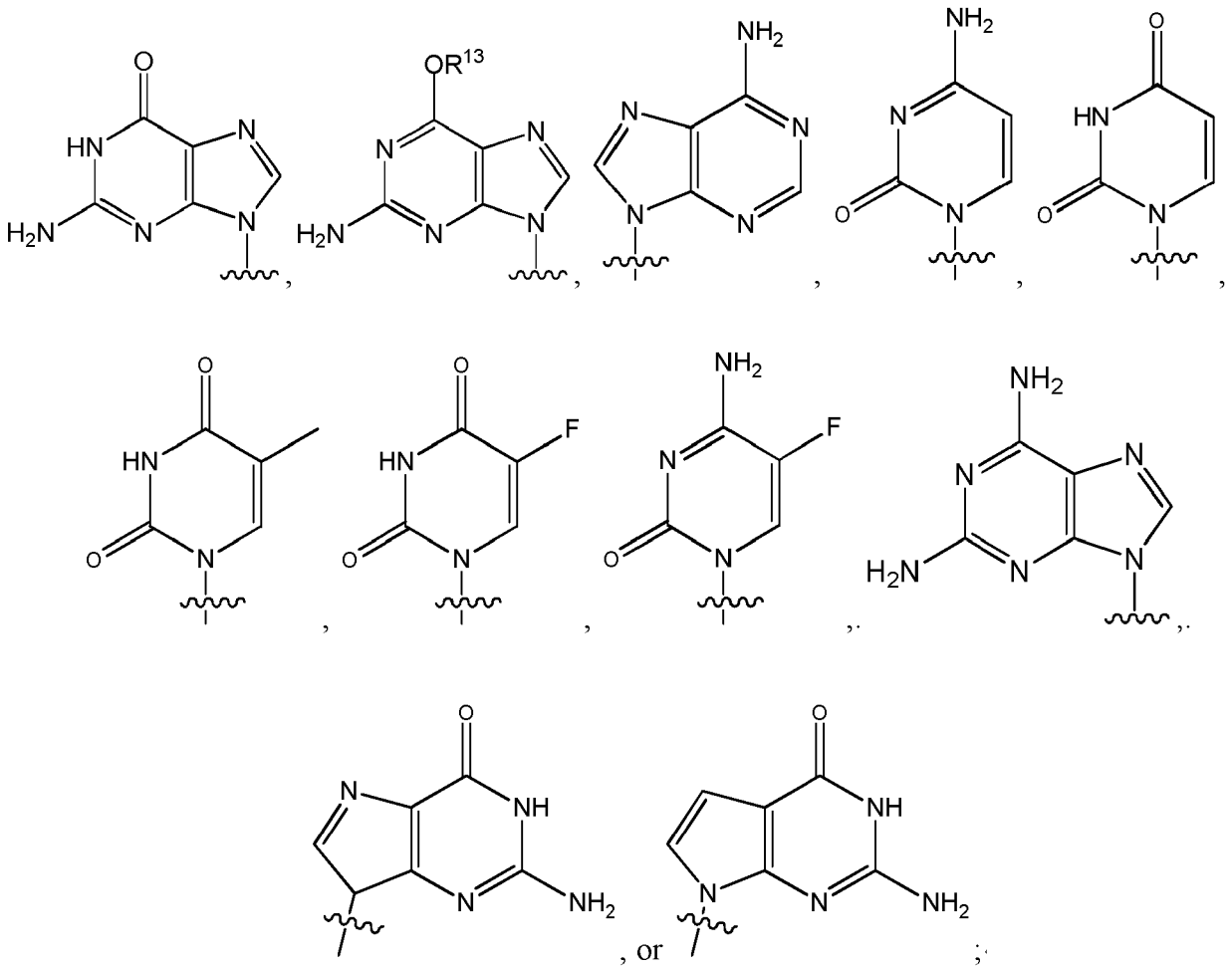
-$CH_2(C{=}O)OH$, -$CH_2CH_2(C{=}O)OH$, - $(CH_2)_3NH(C{=}NH)NH_2$,



and -$(CH_2)_4NH_2$; each R^{11} is independently hydrogen, an optionally substituted C_{1-8} alkyl, an optionally substituted C_{2-8} alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkyl(C_1-C_4 alkyl)-, an optionally substituted cycloalkenyl, an optionally substituted cycloalkenyl(C_1-C_4 alkyl)-, an

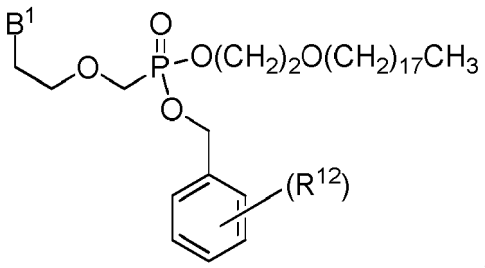
optionally substituted aryl, an optionally substituted aryl(C_{1-4} alkyl)-, an optionally substituted heteroaryl, an optionally substituted heteroaryl(C_1-C_4 alkyl)-, an optionally substituted heterocyclyl, or an optionally substituted heterocyclyl(C_1-C_4 alkyl)-; each a and each b are independently 1, 2, 3 or 4; and each c and each d are independently 0, 1, 2 or 3.

Embodiment P2. The compound of embodiment P1, wherein B^1 is:



wherein: R^{13} is unsubstituted C_{1-6} alkyl or an unsubstituted C_{3-6} cycloalkyl.

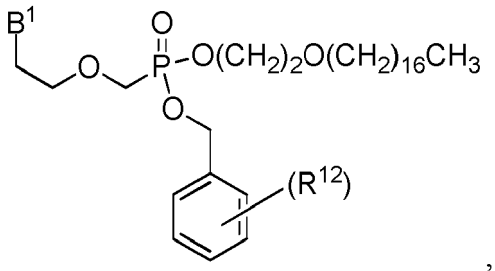
Embodiment P3. A compound of the formula:



wherein B^1 is adenine, hypoxanthine, xanthine, theobromine, caffeine, uric acid, isoguanine, 2,6-diaminopurine, cytosine, thymine or uracil, 5-fluorouracil, 5-fluorocytosine, 7-deazaguanine or 9-deazaguanine; and R^{12} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl), (heterocyclyl)alkyl, hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thio-

carbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, azido, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, amino, mono-substituted amino group or a di-substituted amino group, and wherein the phenyl ring can be substituted by R^{12} 1, 2 or 3 times, or its pharmaceutically acceptable salt.

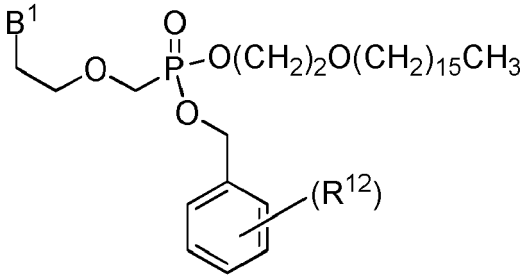
Embodiment P4. A compound of the formula:



,

wherein B^1 is adenine, hypoxanthine, xanthine, theobromine, caffeine, uric acid, isoguanine, 2,6-diaminopurine, cytosine, thymine or uracil, 5-fluorouracil, 5-fluorocytosine, 7-deazaguanine or 9-deazaguanine; and R^{12} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl), (heterocyclyl)alkyl, hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, azido, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, amino, mono-substituted amino group or a di-substituted amino group, and wherein the phenyl ring can be substituted by R^{12} 1, 2 or 3 times, or its pharmaceutically acceptable salt.

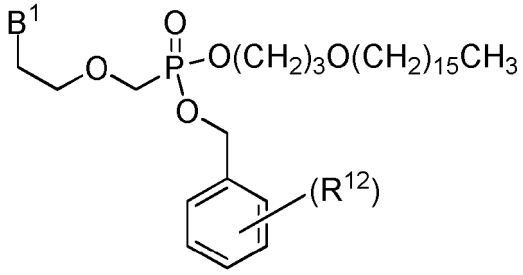
Embodiment P5. A compound of the formula:



,

wherein B^1 is adenine, hypoxanthine, xanthine, theobromine, caffeine, uric acid, isoguanine, 2,6-diaminopurine, cytosine, thymine or uracil, 5-fluorouracil, 5-fluorocytosine, 7-deazaguanine or 9-deazaguanine; and R^{12} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl), (heterocyclyl)alkyl, hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, azido, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, amino, mono-substituted amino group or a di-substituted amino group, and wherein the phenyl ring can be substituted by R^{12} 1, 2 or 3 times, or its pharmaceutically acceptable salt.

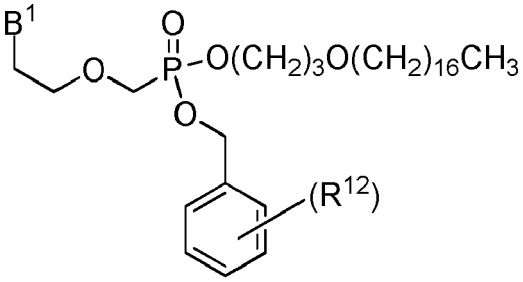
Embodiment P6. A compound of the formula:



,

wherein B^1 is adenine, hypoxanthine, xanthine, theobromine, caffeine, uric acid, isoguanine, 2,6-diaminopurine, cytosine, thymine or uracil, 5-fluorouracil, 5-fluorocytosine, 7-deazaguanine or 9-deazaguanine; and R^{12} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl), (heterocyclyl)alkyl, hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, azido, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, amino, mono-substituted amino group or a di-substituted amino group, and wherein the phenyl ring can be substituted by R^{12} 1, 2 or 3 times, or its pharmaceutically acceptable salt.

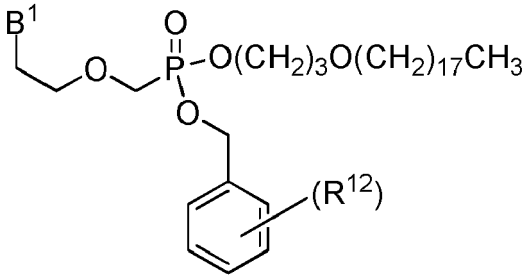
Embodiment P7. A compound of the formula:



,

wherein B^1 is adenine, hypoxanthine, xanthine, theobromine, caffeine, uric acid, isoguanine, 2,6-diaminopurine, cytosine, thymine or uracil, 5-fluorouracil, 5-fluorocytosine, 7-deazaguanine or 9-deazaguanine; and R^{12} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl), (heterocyclyl)alkyl, hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, azido, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, amino, mono-substituted amino group or a di-substituted amino group, and wherein the phenyl ring can be substituted by R^{12} 1, 2 or 3 times, or its pharmaceutically acceptable salt.

Embodiment P8. A compound of the formula:



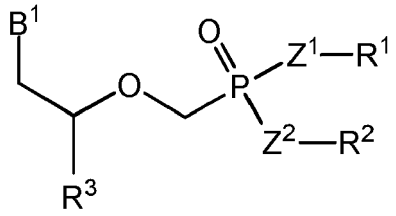
,

wherein B^1 is adenine, hypoxanthine, xanthine, theobromine, caffeine, uric acid, isoguanine, 2,6-diaminopurine, cytosine, thymine or uracil, 5-fluorouracil, 5-fluorocytosine, 7-deazaguanine or 9-deazaguanine; and R^{12} is alkyl,

alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl), (heterocyclyl)alkyl, hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, azido, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, amino, mono-substituted amino group or a di-substituted amino group, and wherein the phenyl ring can be substituted by R^{12} 1, 2 or 3 times, or its pharmaceutically acceptable salt.

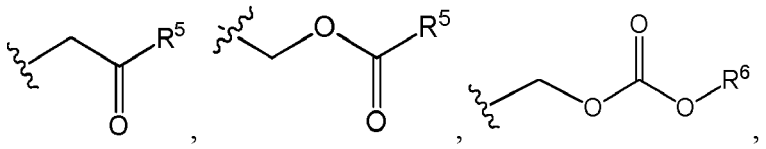
[0197] Further embodiments include Embodiments 1 to 24 following.

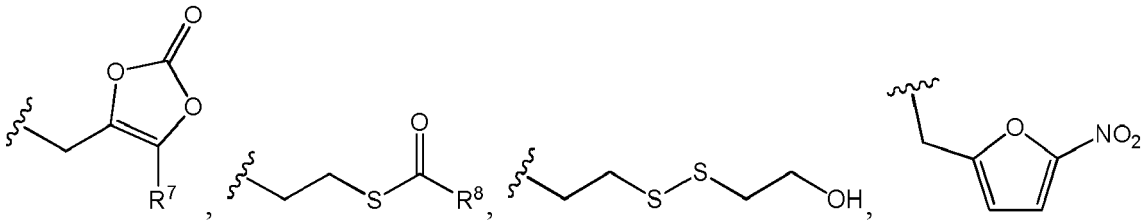
Embodiment 1. A compound of the structure of Formula (I), or a pharmaceutically acceptable salt thereof:



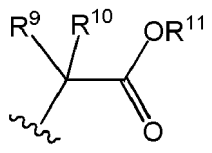
(I),

wherein: B^1 is selected from adenine, hypoxanthine, xanthine, theobromine, caffeine, uric acid, isoguanine, 2,6-diaminopurine, cytosine, thymine or uracil, guanine-7-yl, adenine-9-yl, cytosine-1-yl, thymin-1-yl, uracil-1-yl, 2,6-diaminopurin-9-yl, 5-fluorouracil, 5-fluorocytosine, 7-deazaguanine or 9-deazaguanine; Z^1 and Z^2 are independently O or NR^Z; R^Z is hydrogen or an optionally substituted C_{1-4} alkyl; R^1 is an optionally substituted -C_{2-24} alkenyl, an optionally substituted -C_{2-24} alkynyl, an optionally substituted -$(CHR^4)_a$-O-C_{2-24} alkenyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkyl(C_1-C_4 alkyl)-, an optionally substituted cycloalkenyl, an optionally substituted cycloalkenyl(C_1-C_4 alkyl)-, an optionally substituted aryl, an optionally substituted aryl(C_{1-4} alkyl), an optionally substituted heteroaryl, an optionally substituted heteroaryl(C_1-C_4 alkyl)-, an optionally substituted heterocyclyl, an optionally substituted heterocyclyl(C_1-C_4 alkyl)-,



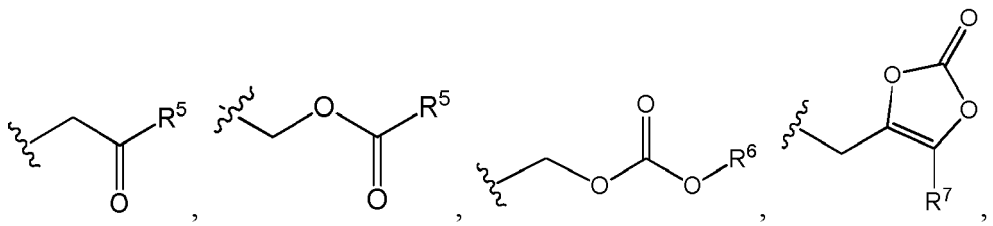


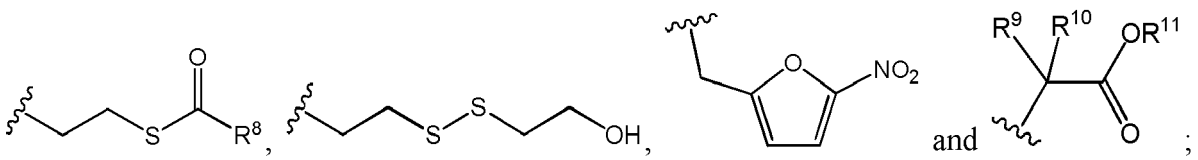
or



;

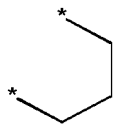
and R^2 is an optionally substituted -C_{2-24} alkenyl, an optionally substituted -C_{2-24} alkynyl, an optionally substituted -$(CHR^4)_b$-O-C_{2-24} alkenyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkyl(C_{1-4} alkyl)-, an optionally substituted cycloalkenyl, an optionally substituted cycloalkenyl(C_{1-4} alkyl)-, substituted aryl(C_{1-4} alkyl)-,



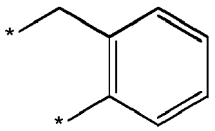


and ;

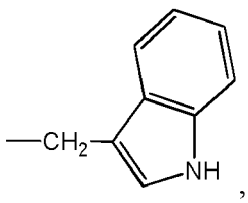
or R^1 and R^2 can be taken together to form a moiety selected from an optionally substituted



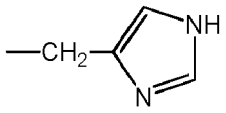
or an optionally substituted



wherein Z^1, Z^2, R^1 and R^2, the phosphorus and the moiety form a six-membered to ten-membered ring system; R^3 is hydrogen, optionally substituted alkyl or optionally substituted heteroalkyl; each R^4 is independently hydrogen, $-(CH_2)_c$-S-C_{1-24} alkyl or -O-$(CH_2)_d$-R^{4A}; each R^{4A} is independently hydrogen, an optionally substituted C_{1-24} alkyl or an optionally substituted aryl; each R^5, each R^6 and each R^8 are independently an optionally substituted C_{1-8} alkyl, an optionally substituted C_{2-8} alkenyl, an optionally substituted C_{2-8} alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkyl(C_1-C_4 alkyl)-, an optionally substituted cycloalkenyl, an optionally substituted cycloalkenyl(C_1-C_4 alkyl)-, an optionally substituted aryl, an optionally substituted aryl(C_{1-4} alkyl)-, an optionally substituted heteroaryl, an optionally substituted heteroaryl(C_1-C_4 alkyl)-, an optionally substituted heterocyclyl, or an optionally substituted heterocyclyl(C_1-C_4 alkyl)-; each R^7 is independently hydrogen, an optionally substituted C_{1-8} alkyl, an optionally substituted C_{2-8} alkenyl, an optionally substituted C_{2-8} alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkyl(C_1-C_4 alkyl)-, an optionally substituted cycloalkenyl, an optionally substituted cycloalkenyl(C_1-C_4 alkyl)-, an optionally substituted aryl, an optionally substituted aryl(C_{1-4} alkyl)-, an optionally substituted heteroaryl, an optionally substituted heteroaryl(C_1-C_4 alkyl)-, an optionally substituted heterocyclyl, or an optionally substituted heterocyclyl(C_1-C_4 alkyl)-; each R^9 and each R^{10} are independently hydrogen or an optionally substituted C_{1-6} alkyl; $-CH_2SH$, $-CH_2(C=O)NH_2$, $-CH_2CH_2(C=O)NH_2$, $-CH_2CH_2S\ CH_3$, CH_2-an optionally substituted phenyl, $-CH_2OH$, $-CH(OH)CH_3$,

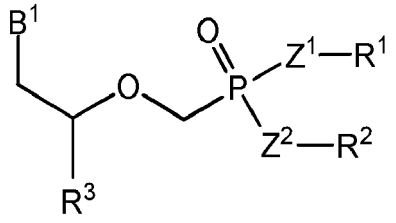


$-CH_2(C=O)OH$, $-CH_2CH_2(C=O)OH$, $-(CH_2)_3NH(C=NH)NH_2$,



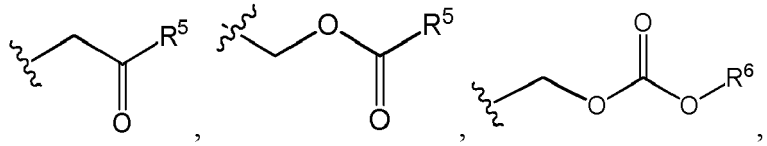
and -$(CH_2)_4NH_2$; each R^{11} is independently hydrogen, an optionally substituted C_{1-8} alkyl, an optionally substituted C_{2-8} alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkyl(C_1-C_4 alkyl)-, an optionally substituted cycloalkenyl, an optionally substituted cycloalkenyl(C_1-C_4 alkyl)-, an optionally substituted aryl, an optionally substituted aryl(C_{1-4} alkyl)-, an optionally substituted heteroaryl, an optionally substituted heteroaryl(C_1-C_4 alkyl)-, an optionally substituted heterocyclyl, or an optionally substituted heterocyclyl(C_1-C_4 alkyl)-; each a and each b are independently 1, 2, 3 or 4; and each c and each d are independently 0, 1, 2 or 3.

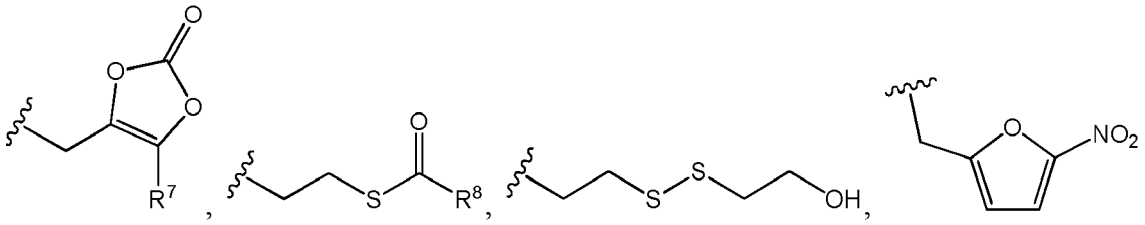
Embodiment 2. A compound of the structure of Formula (I), or a pharmaceutically acceptable salt thereof:



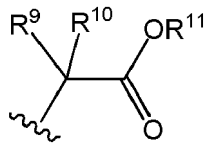
(I),

wherein: B^1 is guanine; Z^1 and Z^2 are independently O or NR^Z; R^Z is hydrogen or an optionally substituted C_{1-4} alkyl; R^1 is an optionally substituted -C_{2-24} alkenyl, an optionally substituted -C_{2-24} alkynyl, an optionally substituted -$(CHR^4)_a$-O-C_{2-24} alkenyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkyl(C_1-C_4 alkyl)-, an optionally substituted cycloalkenyl, an optionally substituted cycloalkenyl(C_1-C_4 alkyl)-, an optionally substituted aryl, an optionally substituted aryl(C_{1-4} alkyl), an optionally substituted heteroaryl, an optionally substituted heteroaryl(C_1-C_4 alkyl)-, an optionally substituted heterocyclyl, an optionally substituted heterocyclyl(C_1-C_4 alkyl)-,



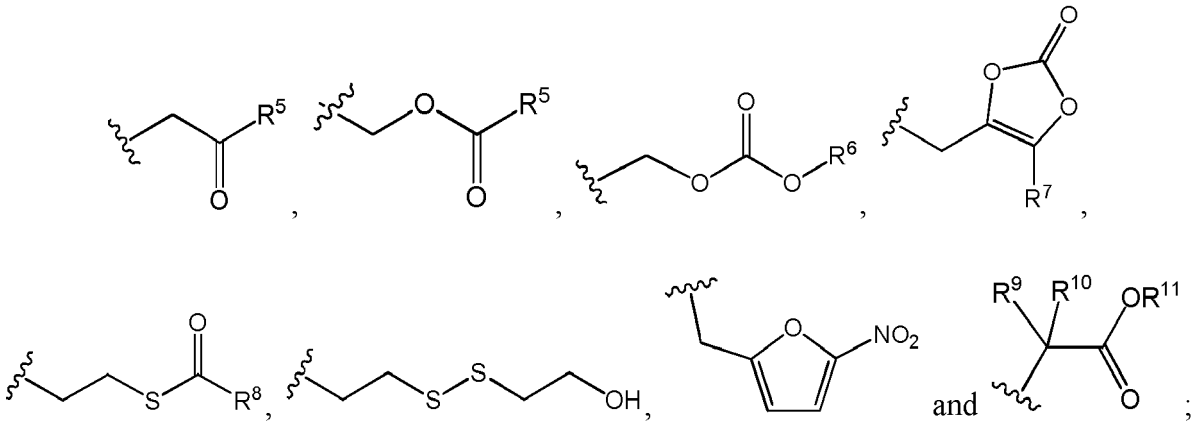


or

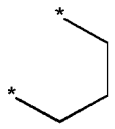


;

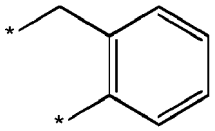
and R^2 is an optionally substituted -C_{2-24} alkenyl, an optionally substituted -C_{2-24} alkynyl, an optionally substituted -$(CHR^4)_b$-O-C_{2-24} alkenyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkyl(C_{1-4} alkyl)-, an optionally substituted cycloalkenyl, an optionally substituted cycloalkenyl(C_{1-4} alkyl)-, substituted aryl(C_{1-4} alkyl)-,



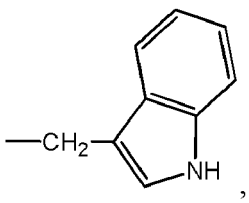
or R^1 and R^2 can be taken together to form a moiety selected from an optionally substituted



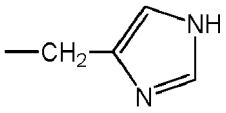
or an optionally substituted



wherein Z^1, Z^2, R^1 and R^2, the phosphorus and the moiety form a six-membered to ten-membered ring system; R^3 is optionally substituted alkyl or optionally substituted heteroalkyl; each R^4 is independently hydrogen, $-(CH_2)_c$-S-C_{1-24} alkyl or - O-$(CH_2)_d$-R^{4A}; each R^{4A} is independently hydrogen, an optionally substituted C_{1-24} alkyl or an optionally substituted aryl; each R^5, each R^6 and each R^8 are independently an optionally substituted C_{1-8} alkyl, an optionally substituted C_{2-8} alkenyl, an optionally substituted C_{2-8} alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkyl(C_1-C_4 alkyl)-, an optionally substituted cycloalkenyl, an optionally substituted cycloalkenyl(C_1-C_4 alkyl)-, an optionally substituted aryl, an optionally substituted aryl(C_{1-4} alkyl)-, an optionally substituted heteroaryl, an optionally substituted heteroaryl(C_1-C_4 alkyl)-, an optionally substituted heterocyclyl, or an optionally substituted heterocyclyl(C_1-C_4 alkyl)-; each R^7 is independently hydrogen, an optionally substituted C_{1-8} alkyl, an optionally substituted C_{2-8} alkenyl, an optionally substituted C_{2-8} alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkyl(C_1-C_4 alkyl)-, an optionally substituted cycloalkenyl, an optionally substituted cycloalkenyl(C_1-C_4 alkyl)-, an optionally substituted aryl, an optionally substituted aryl(C_{1-4} alkyl)-, an optionally substituted heteroaryl, an optionally substituted heteroaryl(C_1-C_4 alkyl)-, an optionally substituted heterocyclyl, or an optionally substituted heterocyclyl(C_1-C_4 alkyl)-; each R^9 and each R^{10} are independently hydrogen or an optionally substituted C_{1-6} alkyl; $-CH_2SH$, - $CH_2(C=O)NH_2$, $-CH_2CH_2(C=O)NH_2$, $-CH_2CH_2S\ CH_3$, CH_2-an optionally substituted phenyl, - CH_2OH, $-CH(OH)CH_3$,

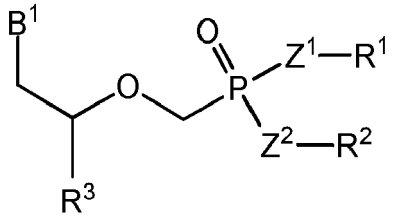


$-CH_2(C=O)OH$, $-CH_2CH_2(C=O)OH$, $-(CH_2)_3NH(C=NH)NH_2$,



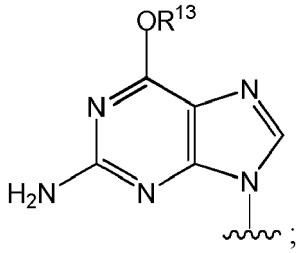
and -$(CH_2)_4NH_2$; each R^{11} is independently hydrogen, an optionally substituted C_{1-8} alkyl, an optionally substituted C_{2-8} alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkyl(C_1-C_4 alkyl)-, an optionally substituted cycloalkenyl, an optionally substituted cycloalkenyl(C_1-C_4 alkyl)-, an optionally substituted aryl, an optionally substituted aryl(C_{1-4} alkyl)-, an optionally substituted heteroaryl, an optionally substituted heteroaryl(C_1-C_4 alkyl)-, an optionally substituted heterocyclyl, or an optionally substituted heterocyclyl(C_1-C_4 alkyl)-; each a and each b are independently 1, 2, 3 or 4; and each c and each d are independently 0, 1, 2 or 3.

Embodiment 3. A compound of the structure of Formula (I), or a pharmaceutically acceptable salt thereof:



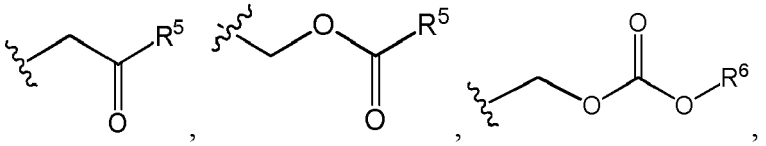
(I),

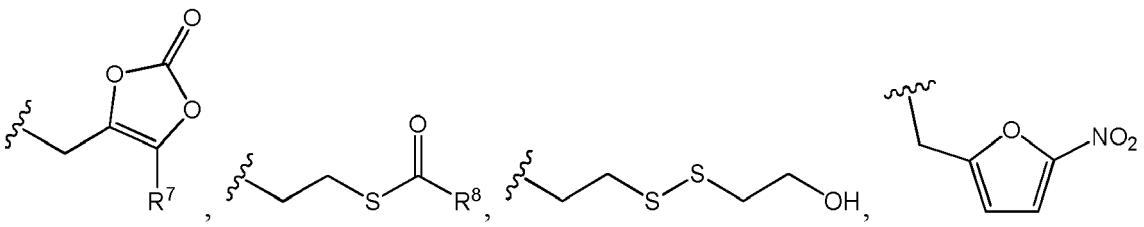
wherein: B^1 is



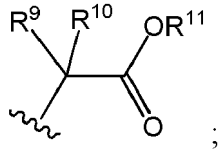
;

Z^1 and Z^2 are independently O or NR^Z; R^Z is hydrogen or an optionally substituted C_{1-4} alkyl; R^1 is an optionally substituted -C_{2-24} alkenyl, an optionally substituted -C_{2-24} alkynyl, an optionally substituted -$(CHR^4)_a$-O-C_{2-24} alkenyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkyl(C_1-C_4 alkyl)-, an optionally substituted cycloalkenyl, an optionally substituted cycloalkenyl(C_1-C_4 alkyl)-, an optionally substituted aryl, an optionally substituted aryl(C_{1-4} alkyl), an optionally substituted heteroaryl, an optionally substituted heteroaryl(C_1-C_4 alkyl)-, an optionally substituted heterocyclyl, an optionally substituted heterocyclyl(C_1-C_4 alkyl)-,



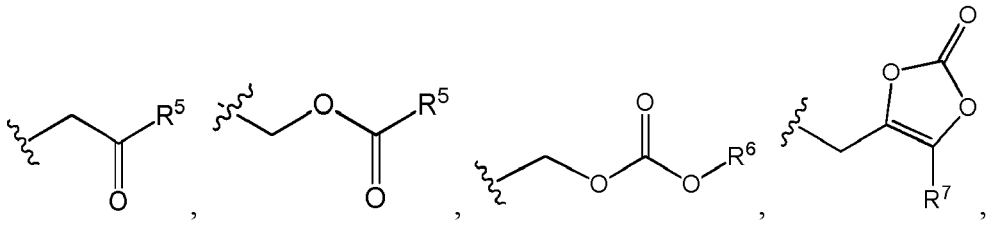


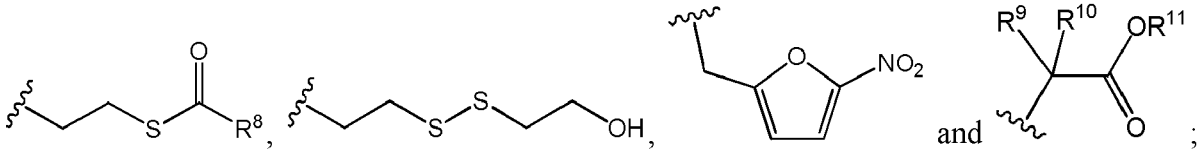
or



;

and R^2 is an optionally substituted -C_{2-24} alkenyl, an optionally substituted -C_{2-24} alkynyl, an optionally substituted -$(CHR^4)_b$-O-C_{2-24} alkenyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkyl(C_{1-4} alkyl)-, an optionally substituted cycloalkenyl, an optionally substituted cycloalkenyl(C_{1-4} alkyl)-, substituted aryl(C_{1-4} alkyl)-,

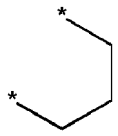




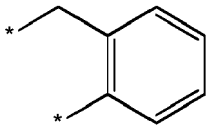
and

;

or R^1 and R^2 can be taken together to form a moiety selected from an optionally substituted



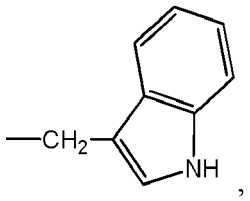
or an optionally substituted



,

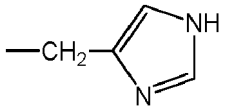
wherein Z^1, Z^2, R^1 and R^2, the phosphorus and the moiety form a six-membered to ten-membered ring system; R^3 is optionally substituted alkyl or optionally substituted heteroalkyl; each R^4 is independently hydrogen, -$(CH_2)_c$-S-C_{1-24} alkyl or - O-$(CH_2)_d$-R^{4A}; each R^{4A} is independently hydrogen, an optionally substituted C_{1-24} alkyl or an optionally substituted aryl; each R^5, each R^6 and each R^8 are independently an optionally substituted C_{1-8} alkyl, an optionally substituted C_{2-8} alkenyl, an optionally substituted C_{2-8} alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkyl(C_1-C_4 alkyl)-, an optionally substituted cycloalkenyl, an optionally substituted cycloalkenyl(C_1-C_4 alkyl)-, an optionally substituted aryl, an optionally substituted aryl(C_{1-4} alkyl)-, an optionally substituted heteroaryl, an optionally substituted heteroaryl(C_1-C_4 alkyl)-, an optionally substituted heterocyclyl, or an optionally substituted heterocyclyl(C_1-C_4 alkyl)-; each R^7 is independently hydrogen, an optionally substituted C_{1-8} alkyl, an optionally substituted C_{2-8} alkenyl, an optionally substituted C_{2-8} alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkyl(C_1-C_4 alkyl)-, an optionally substituted cycloalkenyl, an optionally substituted cycloalkenyl(C_1-C_4 alkyl)-, an optionally substituted aryl, an optionally substituted aryl(C_{1-4} alkyl)-, an optionally substituted heteroaryl, an optionally substituted heteroaryl(C_1-C_4 alkyl)-, an optionally substituted heterocyclyl, or an optionally substituted heterocyclyl(C_1-C_4 alkyl)-; each R^9 and each R^{10} are independently hydrogen or an optionally substituted C_{1-6} alkyl; -CH_2SH, - $CH_2(C=O)NH_2$, -$CH_2CH_2(C=O)NH_2$, -CH_2CH_2S CH_3, CH_2-an optionally

substituted phenyl, - CH_2OH, -$CH(OH)CH_3$,



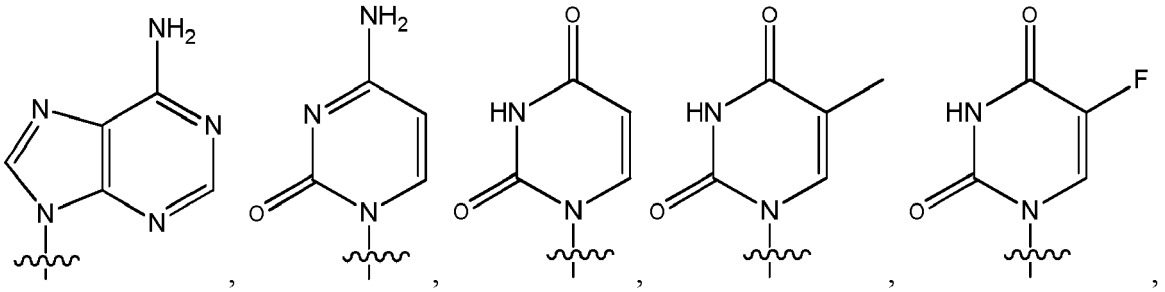
,

-$CH_2(C=O)OH$, -$CH_2CH_2(C=O)OH$, -$(CH_2)_3NH(C=NH)NH_2$,



and -$(CH_2)_4NH_2$; each R^{11} is independently hydrogen, an optionally substituted C_{1-8} alkyl, an optionally substituted C_{2-8} alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkyl(C_1-C_4 alkyl)-, an optionally substituted cycloalkenyl, an optionally substituted cycloalkenyl(C_1-C_4 alkyl)-, an optionally substituted aryl, an optionally substituted aryl(C_{1-4} alkyl)-, an optionally substituted heteroaryl, an optionally substituted heteroaryl(C_1-C_4 alkyl)-, an optionally substituted heterocyclyl, or an optionally substituted heterocyclyl(C_1-C_4 alkyl)-; R^{13} is unsubstituted C_{1-6} alkyl or an unsubstituted C_{3-6} cycloalkyl; each a and each b are independently 1, 2, 3 or 4; and each c and each d are independently 0, 1, 2 or 3.

Embodiment 4. The compound of embodiment 1, wherein B^1 is:



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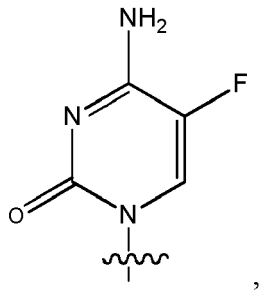

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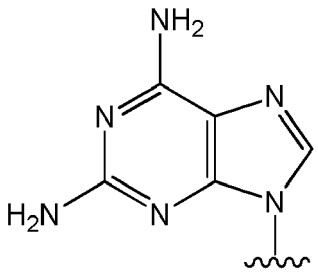

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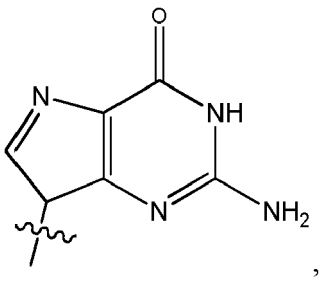
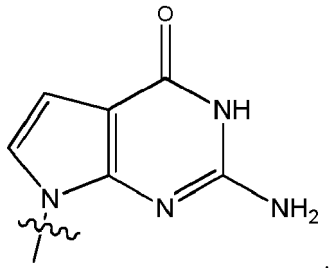
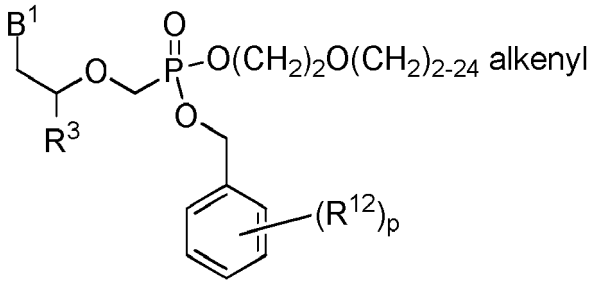


,

or

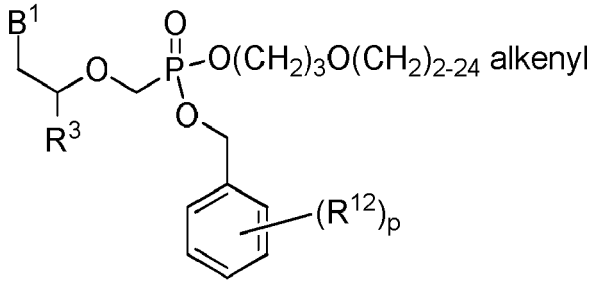


Embodiment 5. A compound of the formula:



wherein: R^{12} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl(alkyl), cycloalkenyl, cycloalkenyl(alkyl), aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl), (heterocyclyl)alkyl, hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, azido, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, amino, a mono-substituted amino group or a di-substituted amino group; p = 1, 2, 3, 4 or 5; and B^1 and R^3 are as defined in embodiment 1; or its pharmaceutically acceptable salt.

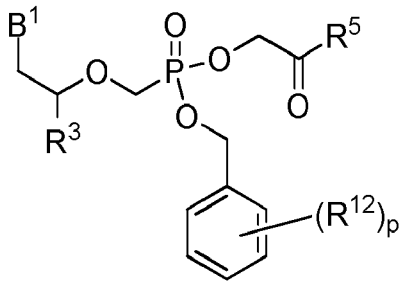
Embodiment 6. A compound of the formula:



(Ib)

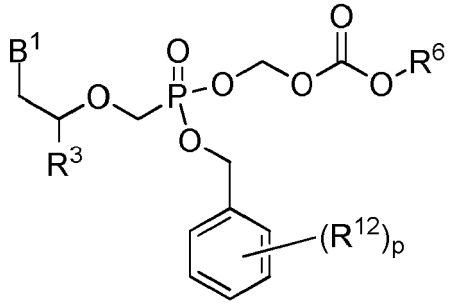
wherein: p = 1, 2, 3, 4 or 5; R^{12} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl(alkyl), cycloalkenyl, cycloalkenyl(alkyl), aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl), (heterocyclyl)alkyl, hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, azido, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, amino, a mono-substituted amino group or a di-substituted amino group; and B^1 and R^3 are as defined in embodiment 1; or its pharmaceutically acceptable salt.

Embodiment 7. A compound of the formula:



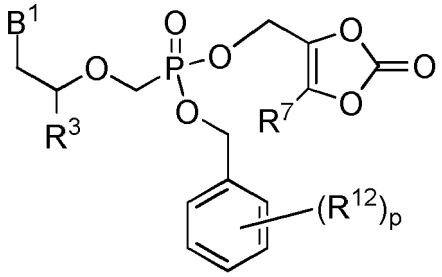
wherein: p = 1, 2, 3, 4 or 5; R^5 is an optionally substituted C_{1-8} alkyl, an optionally substituted C_{2-8} alkenyl, an optionally substituted C_{2-8} alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkyl(C_1-C_4 alkyl)-, an optionally substituted cycloalkenyl, an optionally substituted cycloalkenyl(C_1-C_4 alkyl)-, an optionally substituted aryl, an optionally substituted aryl(C_{1-4} alkyl)-, an optionally substituted heteroaryl, an optionally substituted heteroaryl(C_1-C_4 alkyl)-, an optionally substituted heterocyclyl, or an optionally substituted heterocyclyl(C_1-C_4 alkyl)-; R^{12} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl(alkyl), cycloalkenyl, cycloalkenyl(alkyl), aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl), (heterocyclyl)alkyl, hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, azido, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, amino, a mono-substituted amino group or a di-substituted amino group; and B^1 and R^3 are as defined in embodiment 1; or its pharmaceutically acceptable salt.

Embodiment 8. A compound of the formula:



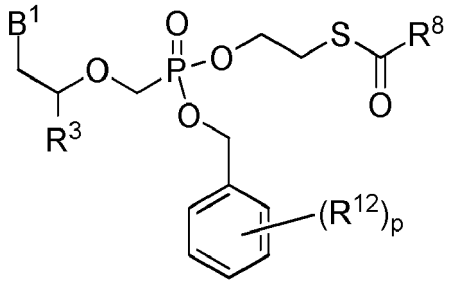
wherein: p = 1, 2, 3, 4 or 5; R^6 is an optionally substituted C_{1-8} alkyl, an optionally substituted C_{2-8} alkenyl, an optionally substituted C_{2-8} alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkyl(C_1-C_4 alkyl)-, an optionally substituted cycloalkenyl, an optionally substituted cycloalkenyl(C_1-C_4 alkyl)-, an optionally substituted aryl, an optionally substituted aryl(C_{1-4} alkyl)-, an optionally substituted heteroaryl, an optionally substituted heteroaryl(C_1-C_4 alkyl)-, an optionally substituted heterocyclyl, or an optionally substituted heterocyclyl(C_1-C_4 alkyl)-; R^{12} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl(alkyl), cycloalkenyl, cycloalkenyl(alkyl), aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl), (heterocyclyl)alkyl, hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, azido, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, amino, a mono-substituted amino group or a di-substituted amino group; and B^1 and R^3 are as defined in embodiment 1; or its pharmaceutically acceptable salt.

Embodiment 9. A compound of the formula:



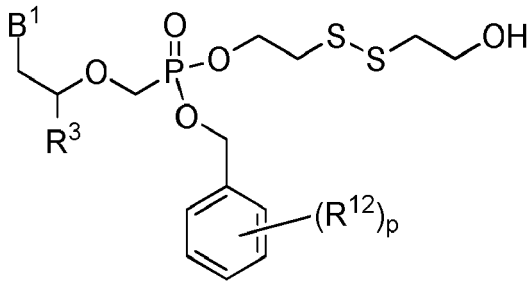
wherein: p = 1, 2, 3, 4 or 5; R^7 is independently hydrogen, an optionally substituted C_{1-8} alkyl, an optionally substituted C_{2-8} alkenyl, an optionally substituted C_{2-8} alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkyl(C_1-C_4 alkyl)-, an optionally substituted cycloalkenyl, an optionally substituted cycloalkenyl(C_1-C_4 alkyl)-, an optionally substituted aryl, an optionally substituted aryl(C_{1-4} alkyl)-, an optionally substituted heteroaryl, an optionally substituted heteroaryl(C_1-C_4 alkyl)-, an optionally substituted heterocyclyl, or an optionally substituted heterocyclyl(C_1-C_4 alkyl)-; R^{12} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl(alkyl), cycloalkenyl, cycloalkenyl(alkyl), aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl), (heterocyclyl)alkyl, hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, azido, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, amino, a mono-substituted amino group or a di-substituted amino group; and B^1 and R^3 are as defined in embodiment 1; or its pharmaceutically acceptable salt.

Embodiment 10. A compound of the formula:



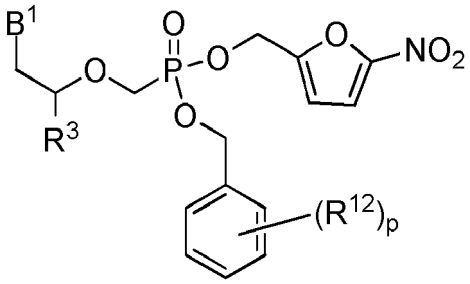
wherein: p = 1, 2, 3, 4 or 5; R^8 is an optionally substituted C_{1-8} alkyl, an optionally substituted C_{2-8} alkenyl, an optionally substituted C_{2-8} alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkyl(C_1-C_4 alkyl)-, an optionally substituted cycloalkenyl, an optionally substituted cycloalkenyl(C_1-C_4 alkyl)-, an optionally substituted aryl, an optionally substituted aryl(C_{1-4} alkyl)-, an optionally substituted heteroaryl, an optionally substituted heteroaryl(C_1-C_4 alkyl)-, an optionally substituted heterocyclyl, or an optionally substituted heterocyclyl(C_1-C_4 alkyl)-; R^{12} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl(alkyl), cycloalkenyl, cycloalkenyl(alkyl), aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl), (heterocyclyl)alkyl, hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, azido, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, amino, a mono-substituted amino group or a di-substituted amino group; and B^1 and R^3 are as defined in embodiment 1; or its pharmaceutically acceptable salt.

Embodiment 11. A compound of the formula:



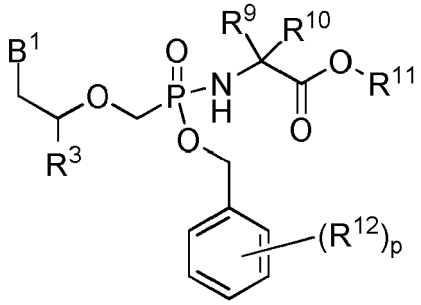
wherein: p = 1, 2, 3, 4 or 5; R^{12} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl(alkyl), cycloalkenyl, cycloalkenyl(alkyl), aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl), (heterocyclyl)alkyl, hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, azido, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, amino, a mono-substituted amino group or a di-substituted amino group; and B^1 and R^3 are as defined in embodiment 1; or its pharmaceutically acceptable salt.

Embodiment 12. A compound of the formula:

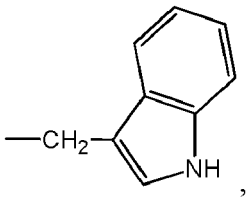


wherein: p = 1, 2, 3, 4 or 5; R^{12} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl(alkyl), cycloalkenyl, cycloalkenyl(alkyl), aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl), (heterocyclyl)alkyl, hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, azido, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, amino, a mono-substituted amino group or a di-substituted amino group; and B^1 and R^3 are as defined in embodiment 1; or its pharmaceutically acceptable salt.

Embodiment 13. A compound of the formula:

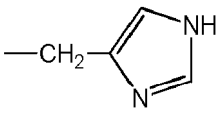


wherein: p = 1, 2, 3, 4 or 5; each R^9 and each R^{10} are independently hydrogen or an optionally substituted C_{1-6} alkyl; $-CH_2SH$, $-CH_2(C=O)NH_2$, $-CH_2CH_2(C=O)NH_2$, $-CH_2CH_2S\,CH_3$, CH_2-an optionally substituted phenyl, $-CH_2OH$, $-CH(OH)CH_3$,



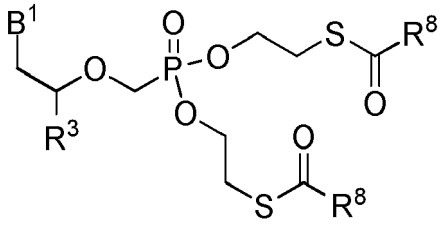
,

$-CH_2(C=O)OH$, $-CH_2CH_2(C=O)OH$, $-(CH_2)_3NH(C=NH)NH_2$,



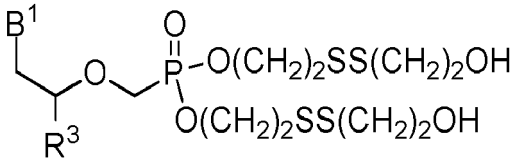
and $-(CH_2)_4NH_2$; R^{11} is independently hydrogen, an optionally substituted C_{1-8} alkyl, an optionally substituted C_{2-8} alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkyl(C_1-C_4 alkyl)-, an optionally substituted cycloalkenyl, an optionally substituted cycloalkenyl(C_1-C_4 alkyl)-, an optionally substituted aryl, an optionally substituted aryl(C_{1-4} alkyl)-, an optionally substituted heteroaryl, an optionally substituted heteroaryl(C_1-C_4 alkyl)-, an optionally substituted heterocyclyl, or an optionally substituted heterocyclyl(C_1-C_4 alkyl)-; R^{12} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl(alkyl), cycloalkenyl, cycloalkenyl(alkyl), aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl), (heterocyclyl)alkyl, hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, azido, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, amino, a mono-substituted amino group or a di-substituted amino group; and B^1 and R^3 are as defined in embodiment 1; or its pharmaceutically acceptable salt.

Embodiment 14. A compound of the formula:



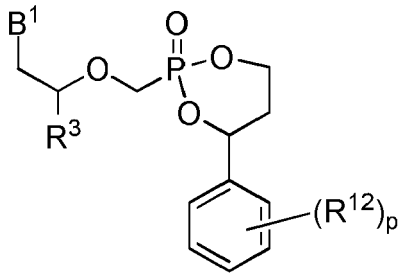
wherein: p = 1, 2, 3, 4 or 5; R^8 is an optionally substituted C_{1-8} alkyl, an optionally substituted C_{2-8} alkenyl, an optionally substituted C_{2-8} alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkyl(C_1-C_4 alkyl)-, an optionally substituted cycloalkenyl, an optionally substituted cycloalkenyl(C_1-C_4 alkyl)-, an optionally substituted aryl, an optionally substituted aryl(C_{1-4} alkyl)-, an optionally substituted heteroaryl, an optionally substituted heteroaryl(C_1-C_4 alkyl)-, an optionally substituted heterocyclyl, or an optionally substituted heterocyclyl(C_1-C_4 alkyl)-; and B^1 and R^3 are as defined in embodiment 1; or its pharmaceutically acceptable salt.

Embodiment 15. A compound of the formula:



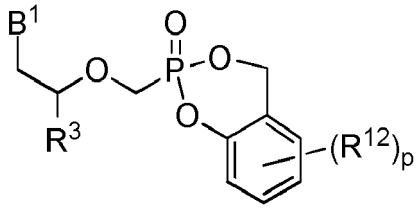
wherein: B^1 and R^3 are as defined in embodiment 1; or its pharmaceutically acceptable salt.

Embodiment 16. A compound of the formula:



wherein: p = 1, 2, 3, 4 or 5; R^{12} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl(alkyl), cycloalkenyl, cycloalkenyl(alkyl), aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl), (heterocyclyl)alkyl, hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, azido, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, amino, a mono-substituted amino group or a di-substituted amino group; and B^1 and R^3 are as defined in embodiment 1; or its pharmaceutically acceptable salt.

Embodiment 17. A compound of the formula:



wherein: p = 1, 2, 3, 4 or 5; R^{12} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl(alkyl), cycloalkenyl, cycloalkenyl(alkyl), aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl), (heterocyclyl)alkyl, hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, azido, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, amino, a mono-substituted amino group or a di-substituted amino group; and B^1 and R^3 are as defined in embodiment 1; or its pharmaceutically acceptable salt.

Embodiment 18. A pharmaceutical composition comprising an effective amount of a compound of any one of embodiments 1-17, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

Embodiment 19. The pharmaceutical composition of embodiment 18, wherein the pharmaceutical composition is in the form of a cream, a gel or an ointment.

Embodiment 20. The pharmaceutical composition of embodiment 18 or 19, wherein the pharmaceutical composition is a topical formulation.

Embodiment 21. Use of a compound of any one of embodiments 1-17, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for treating a viral disease in a subject in need thereof, wherein the viral disease is human papilloma virus.

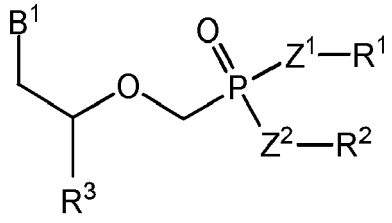
Embodiment 22. The use of embodiment 21, said compound, or a pharmaceutically acceptable salt thereof, for use in treating a plurality of types of human papilloma virus.

Embodiment 23. The use of embodiment 21, wherein the human papilloma virus is selected from the group consisting human papilloma virus HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, HPV-59, HPV-68, HPV-73 and HPV-82.

Embodiment 24. Use of a compound of any one of embodiments 1-17, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for treating cancer of the cervix in a subject in need thereof.

Claims

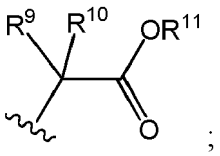
1. A compound of the structure of Formula (I), or a pharmaceutically acceptable salt thereof:



(I),

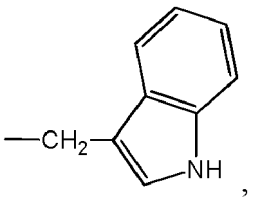
wherein:

B^1 is selected from adenine, hypoxanthine, xanthine, theobromine, caffeine, uric acid, isoguanine, 2,6-diaminopurine, cytosine, thymine or uracil, guanine-7-yl, adenine-9-yl, cytosine-1-yl, thymin-1-yl, uracil-1-yl, 2,6-diaminopurin-9-yl, 5-fluorouracil, 5-fluorocytosine, 7-deazaguanine and 9-deazaguanine;
Z^1 is NH;
Z^2 is O or NR^Z;
R^Z is hydrogen or $C_{1\text{-}4}$ alkyl;
R^1 is



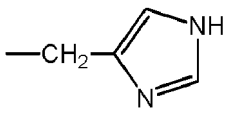
;

R^2 is aryl($C_{1\text{-}4}$ alkyl)-;
R^3 is hydrogen, alkyl or heteroalkyl;
each R^9 and each R^{10} are independently selected from hydrogen, $C_{1\text{-}6}$ alkyl, $-CH_2SH$, $-CH_2(C{=}O)NH_2$, $-CH_2CH_2(C{=}O)NH_2$, $-CH_2CH_2S\,CH_3$, CH_2- phenyl, $-CH_2OH$, $-CH(OH)CH_3$,



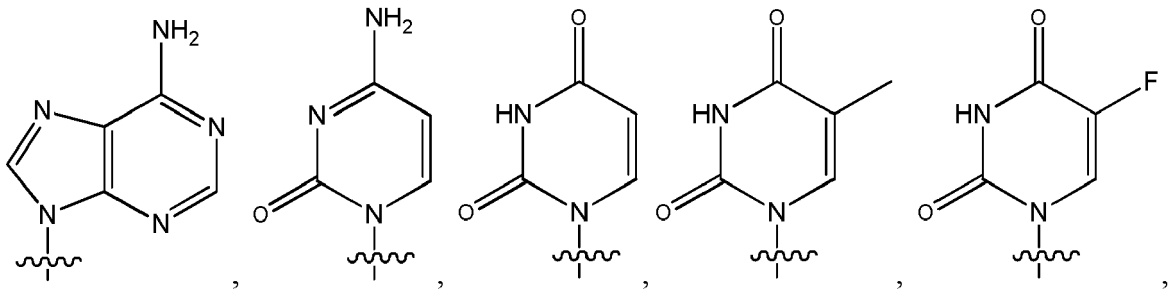
,

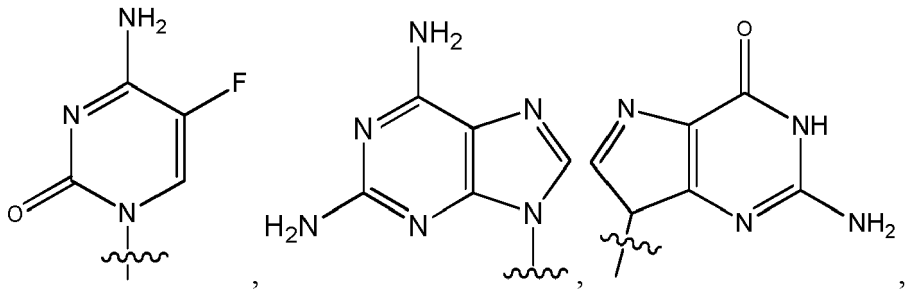
$-CH_2(C{=}O)OH$, $-CH_2CH_2(C{=}O)OH$, $-(CH_2)_3NH(C{=}NH)NH_2$,



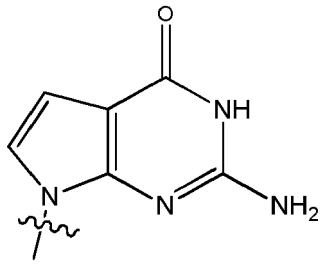
and $-(CH_2)_4NH_2$; and
each R^{11} is independently selected from hydrogen, $C_{1\text{-}8}$ alkyl, $C_{2\text{-}8}$ alkenyl, alkynyl, cycloalkyl, cycloalkyl(C_1-C_4 alkyl)-, cycloalkenyl, cycloalkenyl(C_1-C_4 alkyl)-, aryl, aryl($C_{1\text{-}4}$ alkyl)-, heteroaryl, heteroaryl(C_1-C_4 alkyl)-, heterocyclyl, and heterocyclyl(C_1-C_4 alkyl)-.

2. The compound of claim 1, wherein B^1 is:



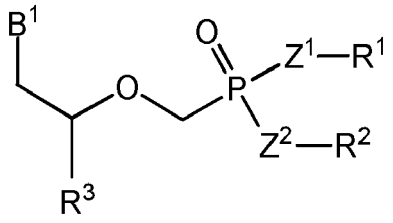


or



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

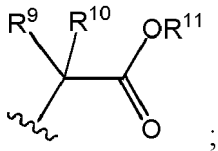
4. A compound of the structure of Formula (I), or a pharmaceutically acceptable salt thereof:



(I),

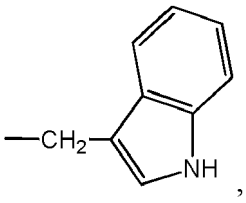
wherein:

B^1 is guanine;
Z^1 is NH;
Z^2 is O or NR^Z;
R^Z is hydrogen or C_{1-4} alkyl;
R^1 is



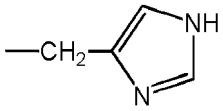
;

R^2 is aryl(C_{1-4} alkyl)-;
R^3 is alkyl or heteroalkyl;
each R^9 and each R^{10} are independently selected from hydrogen, C_{1-6} alkyl, $-CH_2SH$, $-CH_2(C=O)NH_2$, $-CH_2CH_2(C=O)NH_2$, $-CH_2CH_2S\ CH_3$, CH_2-phenyl, $-CH_2OH$, $-CH(OH)CH_3$,



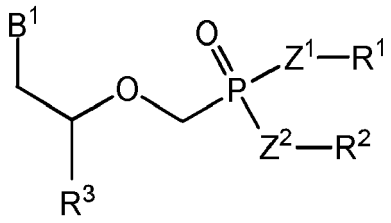
,

$-CH_2(C=O)OH$, $-CH_2CH_2(C=O)OH$, $-(CH_2)_3NH(C=NH)NH_2$,



and $-(CH_2)_4NH_2$; and
each R^{11} is independently selected from hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, alkynyl, cycloalkyl, cycloalkyl(C_1-C_4 alkyl)-, cycloalkenyl, cycloalkenyl(C_1-C_4 alkyl)-, aryl, aryl(C_{1-4} alkyl)-, heteroaryl, heteroaryl(C_1-C_4 alkyl)-, heterocyclyl, and heterocyclyl(C_1-C_4 alkyl)-.

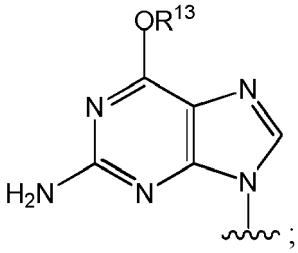
5. A compound of the structure of Formula (I), or a pharmaceutically acceptable salt thereof:



(I),

wherein:

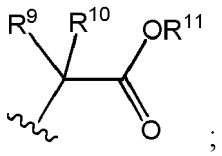
B^1 is



;

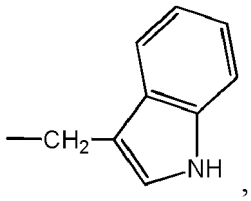
Z^1 is NH;
Z^2 is O or NR^Z;

R^Z is hydrogen or C_{1-4} alkyl;
R^1 is



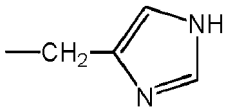
;

R^2 is aryl(C_{1-4} alkyl)-;
R^3 is alkyl or heteroalkyl;
each R^9 and each R^{10} are independently selected from hydrogen, C_{1-6} alkyl, $-CH_2SH$, $-CH_2(C=O)NH_2$, $-CH_2CH_2(C=O)NH_2$, $-CH_2CH_2S\ CH_3$, CH_2-phenyl, $-CH_2OH$, $-CH(OH)CH_3$,



,

$-CH_2(C=O)OH$, $-CH_2CH_2(C=O)OH$, $-(CH_2)_3NH(C=NH)NH_2$,



and $-(CH_2)_4NH_2$; and
each R^{11} is independently selected from hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, alkynyl, cycloalkyl, cycloalkyl(C_1-C_4 alkyl)-, cycloalkenyl, cycloalkenyl(C_1-C_4 alkyl)-, aryl, aryl(C_{1-4} alkyl)-, heteroaryl, heteroaryl(C_1-C_4 alkyl)-, heterocyclyl, and heterocyclyl(C_1-C_4 alkyl)-; and
R^{13} is unsubstituted C_{1-6} alkyl or an unsubstituted C_{3-6} cycloalkyl.

6. The compound of claim 5, wherein R^{13} is methyl.

7. The compound of any one of claims 1-5, wherein R^3 is CH_3, CH_2OH, or CH_2F.

8. The compound of any one of claims 1-5, wherein R^3 is CHF_2, CF_3, or OCH_3.

9. The compound of any one of claims 1-8, wherein Z^2 is O.

10. The compound of any one of claims 1-8, wherein Z^2 is NR^Z.

11. The compound of claim 10 wherein Z^2 is N-methyl, N-ethyl, N-(n-propyl), N-(isopropyl), N-(n-butyl), N-(iso-butyl) or N-(t-butyl).

12. The compound of any one of claims 1-11, wherein R^2 is benzyl.

13. The compound of any one of claims 1-12, wherein R^9 is C_{1-6} alkyl.

14. The compound of any one of claims 1-12, wherein R^{10} is hydrogen.

15. The compound of any one of claims 1-14, wherein R^{11} is C_{1-8} alkyl.

16. A pharmaceutical composition comprising an effective amount of a compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

17. The pharmaceutical composition of claim 16, wherein the pharmaceutical composition is in the form of a cream, a gel or an ointment.

18. The pharmaceutical composition of claim 16 or 17, wherein the pharmaceutical composition is a topical formulation.

19. A compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, for use in treating a viral disease in a subject in need thereof, wherein the viral disease is human papilloma virus.

20. The compound of claim 19, wherein the human papilloma virus is HPV-18.

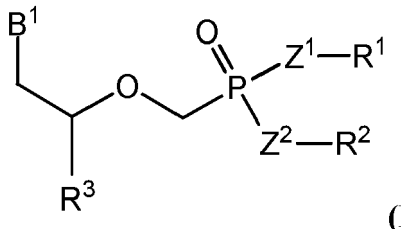
21. The compound of claim 19, wherein the human papilloma virus is selected from the group consisting human papilloma virus HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, HPV-59, HPV-68, HPV-73 and HPV-82.

22. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, for use in treating cancer of the cervix in a subject in need thereof.

23. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, for use in treating cervical intraepithelial neoplasia, vaginal intraepithelial neoplasia, and anal intraepithelial neoplasia in a subject in need thereof.

Patentansprüche

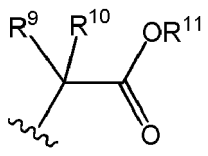
1. Verbindung mit der Struktur der Formel (I) oder ein pharmazeutisch unbedenkliches Salz davon:



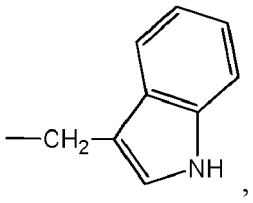
(I),

wobei:

B^1 ausgewählt ist aus Adenin, Hypoxanthin, Xanthin, Theobromin, Koffein, Harnsäure, Isoguanin, 2,6-Diaminopurin, Cytosin, Thymin oder Uracil, Guanin-7-yl, Adenin-9-yl, Cytosin-1-yl, Thymin-1-yl, Uracil-1-yl, 2,6-Diaminopurin-9-yl, 5-Fluoruracil, 5-Fluorcytosin, 7-Deazaguanin und 9-Deazaguanin;
Z^1 NH ist;
Z^2 O oder NR^Z ist;
R^Z Wasserstoff oder C_{1-4}-Alkyl ist;
R^1

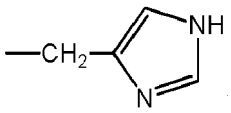


ist;
R^2 Aryl(C_{1-4}-Alkyl)- ist;
R^3 Wasserstoff, Alkyl oder Heteroalkyl ist;
jedes R^9 und jedes R^{10} unabhängig ausgewählt sind aus Wasserstoff, C_{1-6}-Alkyl, $-CH_2SH$, $-CH_2(C=O)NH_2$, $-CH_2CH_2(C=O)NH_2$, $-CH_2CH_2S\,CH_3$, CH_2-Phenyl, $-CH_2OH$, $-CH(OH)CH_3$,



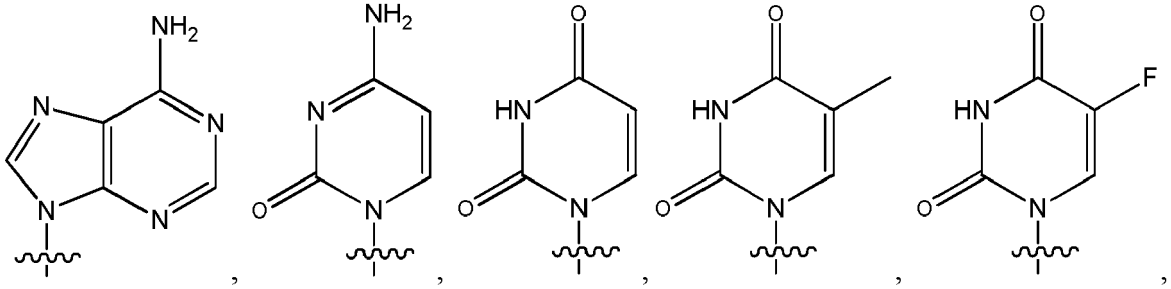
,

$-CH_2(C=O)OH$ $-CH_2CH_2(C=O)OH$, $-(CH_2)_3NH(C=NH)NH_2$,

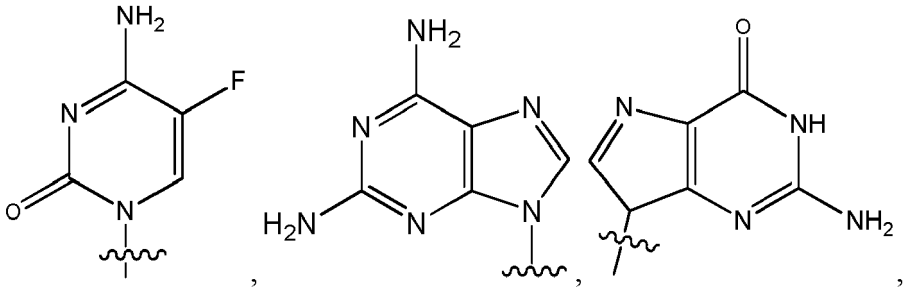


und $-(CH_2)_4NH_2$; und
jedes R^{11} unabhängig ausgewählt ist aus Wasserstoff, C_{1-8}-Alkyl, C_{2-8}-Alkenyl, Alkinyl, Cycloalkyl, Cycloalkyl(C_1-C_4-Alkyl)-, Cycloalkenyl, Cycloalkenyl(C_1-C_4-Alkyl)-, Aryl, Aryl(C_1-$_4$-Alkyl)-, Heteroaryl, Heteroaryl(C_1-C_4-Alkyl)-, Heterocyclyl und Heterocyclyl(C_1-C_4-Alkyl)-.

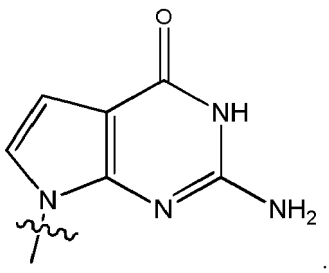
2. Verbindung nach Anspruch 1, wobei B^1 Folgendes ist.



,



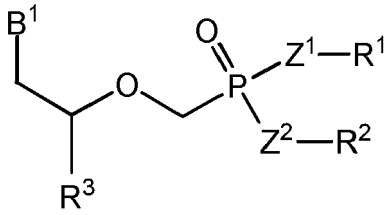
oder



.

3. Verbindung nach Anspruch 1 oder Anspruch 2, wobei R^3 Wasserstoff ist.

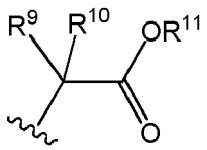
4. Verbindung mit der Struktur der Formel (I) oder ein pharmazeutisch unbedenkliches Salz davon:



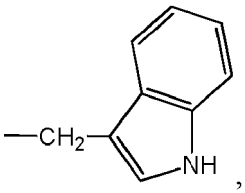
(I),

wobei:

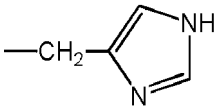
B^1 Guanin ist;
Z^1 NH ist;
Z^2 O oder NR^Z ist;
R^Z Wasserstoff oder C_{1-4}-Alkyl ist;
R^1



ist;
R^2 Aryl(C_{1-4}-Alkyl)- ist;
R^3 Alkyl oder Heteroalkyl ist;
jedes R^9 und jedes R^{10} unabhängig ausgewählt sind aus Wasserstoff, C_{1-6}-Alkyl, $-CH_2SH$, $-CH_2(C=O)NH_2$, $-CH_2CH_2(C=O)NH_2$, $-CH_2CH_2S\ CH_3$, CH_2-Phenyl, $-CH_2OH$, $-CH(OH)CH_3$,

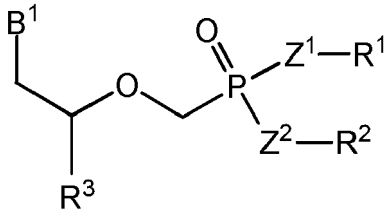


$-CH_2(C=O)OH$, $-CH_2CH_2(C=O)OH$, $-(CH_2)_3NH(C=NH)NH_2$,



und $-(CH_2)_4NH_2$; und
jedes R^{11} unabhängig ausgewählt ist aus Wasserstoff, C_{1-8}-Alkyl, C_{2-8}-Alkenyl, Alkinyl, Cycloalkyl, Cycloalkyl(C_1-C_4-Alkyl)-, Cycloalkenyl, Cycloalkenyl(C_1-C_4-Alkyl)-, Aryl, Aryl(C_{1-4}-Alkyl)-, Heteroaryl, Heteroaryl(C_1-C_4-Alkyl)-, Heterocyclyl und Heterocyclyl(C_1-C_4-Alkyl)-.

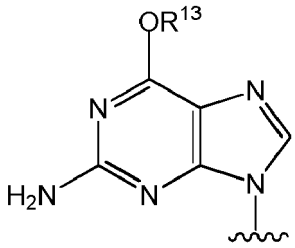
5. Verbindung mit der Struktur der Formel (I) oder ein pharmazeutisch unbedenkliches Salz davon:



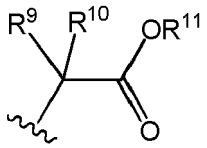
(I),

wobei:

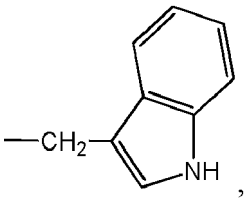
B^1



ist;
Z^1 NH ist;
Z^2 O oder NR^Z ist;
R^Z Wasserstoff oder C_{1-4}-Alkyl ist;
R^1

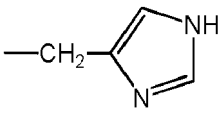


ist;
R^2 Aryl(C_{1-4}-Alkyl)- ist;
R^3 Alkyl oder Heteroalkyl ist;
jedes R^9 und jedes R^{10} unabhängig ausgewählt sind aus Wasserstoff, C_{1-6}-Alkyl, $-CH_2SH$, $-CH_2(C=O)NH_2$, $-CH_2CH_2(C=O)NH_2$, $-CH_2CH_2S\ CH_3$, CH_2-Phenyl, $-CH_2OH$, $-CH(OH)CH_3$,



,

$-CH_2(C=O)OH$, $-CH_2CH_2(C=O)OH$, $-(CH_2)_3NH(C=NH)NH_2$,



und $-(CH_2)_4NH_2$; und
jedes R^{11} unabhängig ausgewählt ist aus Wasserstoff, C_{1-8}-Alkyl, C_{2-8}-Alkenyl, Alkinyl, Cycloalkyl, Cycloalkyl(C_1-C_4-Alkyl)-, Cycloalkenyl, Cycloalkenyl(C_1-C_4-Alkyl)-, Aryl, Aryl(C_{1-4}-Alkyl)-, Heteroaryl, Heteroa-

ryl(C_1-C_4-Alkyl)-, -Heterocyclyl und Heterocyclyl(C_1-C_4-Alkyl)-; und
R^{13} unsubstituiertes C_{1-6}-Alkyl oder ein unsubstituiertes C_{3-6}-Cycloalkyl ist.

6. Verbindung nach Anspruch 5, wobei R^{13} Methyl ist.

7. Verbindung nach einem der Ansprüche 1-5, wobei R^3 CH_3, CH_2OH oder CH_2F ist.

8. Verbindung nach einem der Ansprüche 1-5, wobei R^3 CHF_2, CF_3 oder OCH_3 ist.

9. Verbindung nach einem der Ansprüche 1-8, wobei Z^2 O ist.

10. Verbindung nach einem der Ansprüche 1-8, wobei Z^2 NR^z ist.

11. Verbindung nach Anspruch 10, wobei Z^2 N-Methyl, N-Ethyl, N-(n-Propyl), N-(Isopropyl), N-(n-Butyl), N-(Isobutyl) oder N-(t-Butyl) ist.

12. Verbindung nach einem der Ansprüche 1-11, wobei R^2 Benzyl ist.

13. Verbindung nach einem der Ansprüche 1-12, wobei R^9 C_{1-6}-Alkyl ist.

14. Verbindung nach einem der Ansprüche 1-12, wobei R^{10} Wasserstoff ist.

15. Verbindung nach einem der Ansprüche 1-14, wobei R^{11} C_{1-8}-Alkyl ist.

16. Pharmazeutische Zusammensetzung, umfassend eine wirksame Menge einer Verbindung nach einem der Ansprüche 1-15 oder eines pharmazeutisch unbedenklichen Salzes davon und einen pharmazeutisch unbedenklichen Träger.

17. Pharmazeutische Zusammensetzung nach Anspruch 16, wobei die pharmazeutische Zusammensetzung in Form einer Creme, eines Gels oder einer Salbe vorliegt.

18. Pharmazeutische Zusammensetzung nach Anspruch 16 oder 17, wobei die pharmazeutische Zusammensetzung eine topische Formulierung ist.

19. Verbindung nach einem der Ansprüche 1-15 oder ein pharmazeutisch unbedenkliches Salz davon zur Verwendung bei der Behandlung einer Viruserkrankung bei einem Lebewesen, das dessen bedarf, wobei die Viruserkrankung das humane Papillomavirus ist.

20. Verbindung nach Anspruch 19, wobei das humane Papillomavirus HPV-18 ist.

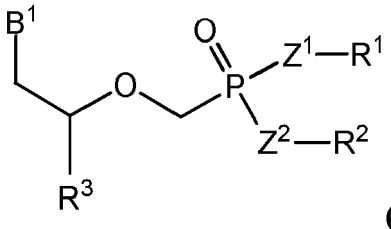
21. Verbindung nach Anspruch 19, wobei das humane Papillomavirus ausgewählt ist aus der Gruppe, bestehend aus dem humanen Papillomavirus HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, HPV-59, HPV-68, HPV-73 und HPV-82.

22. Verbindung nach einem der Ansprüche 1-15 oder ein pharmazeutisch unbedenkliches Salz davon zur Verwendung bei der Behandlung von Gebärmutterhalskrebs bei einem Lebewesen, das dessen bedarf.

23. Verbindung nach einem der Ansprüche 1-15 oder ein pharmazeutisch unbedenkliches Salz davon zur Verwendung bei der Behandlung von zervikaler intraepithelialer Neoplasie, vaginaler intraepithelialer Neoplasie und analer intraepithelialer Neoplasie bei einem Lebewesen, das dessen bedarf.

Revendications

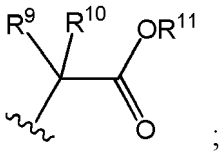
1. Composé de structure de Formule (I), ou sel pharmaceutiquement acceptable de celui-ci :



(I),

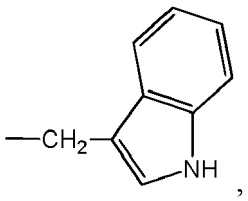
dans lequel :

B^1 est choisi parmi adénine, hypoxanthine, xanthine, théobromine, caféine, acide urique, isoguanine, 2,6-diaminopurine, cytosine, thymine ou uracile, guanine-7-yle, adénine-9- yle, cytosine-1-yle, thymin-1-yle, uracil-1-yle, 2,6-diaminopurin-9-yle, 5-fluorouracile, 5-fluorocytosine, 7-deazaguanine et 9-deazaguanine ;
Z^1 est NH,
Z^2 est O ou NR^Z ;
R^Z est hydrogène ou alkyle C_{1-4} ;
R^1 est



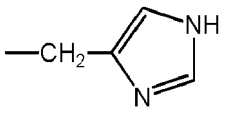
;

R^2 est aryl(alkyle C_{1-4})- ;
R^3 est hydrogène, alkyle ou hétéroalkyle ;
chaque R^9 et chaque R^{10} est indépendamment choisi parmi hydrogène, alkyle C_{1-6}, $-CH_2SH$, $-CH_2(C=O)NH_2$, $-CH_2CH_2(C=O)NH_2$, $-CH_2CH_2S\ CH_3$, CH_2- phényle, $-CH_2OH$, $-CH(OH)CH_3$,



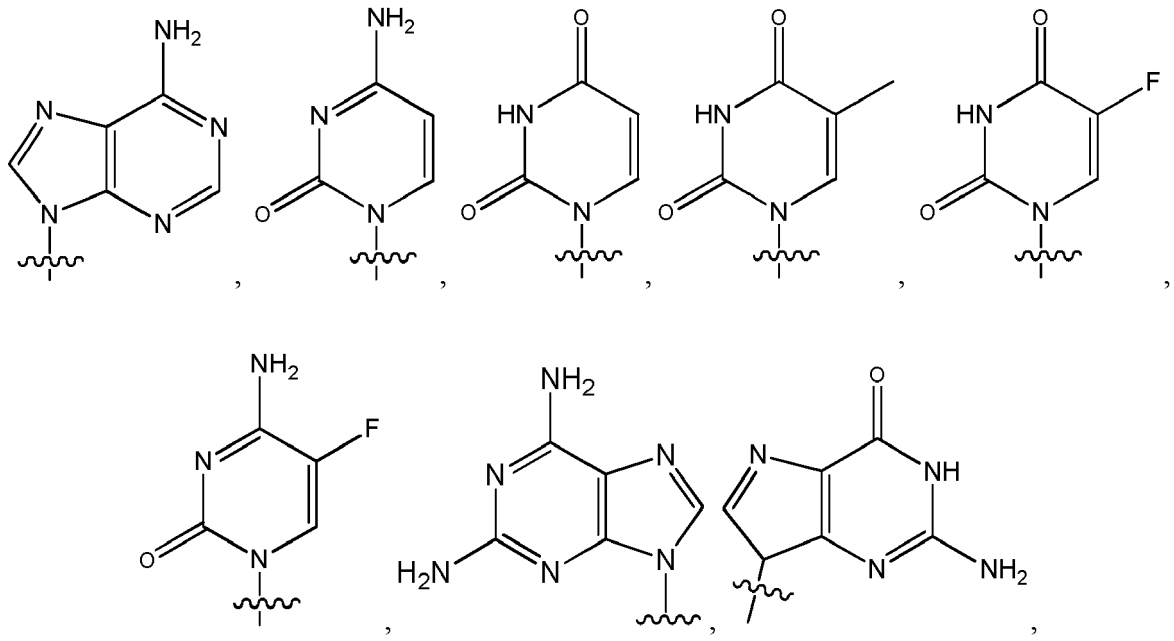
,

$-CH_2(C=O)OH$ $-CH_2CH_2(C=O)OH$, $-(CH_2)_3NH(C=NH)NH_2$,

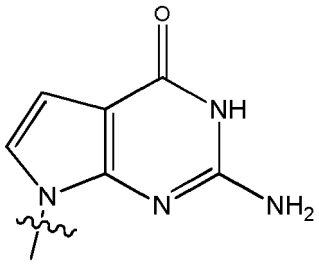


et -(CH2)4NH2 ; et
chaque R^{11} est indépendamment choisi parmi hydrogène, alkyle C_{1-8}, alkényle C_{2-8}, alkynyle, cycloalkyle, cycloalkyl(alkyle C_1-C_4)-, cycloalkényle, cycloalkényl(alkyle C_1-C_4)-, aryle, aryl(alkyle C_{1-4})-, hétéroaryle, hétéroaryl(alkyle C_1-C_4)-, hétérocyclyle et hétérocyclyl(alkyle C_1-C_4)-.

2. Composé selon la revendication 1, où B^1 est :

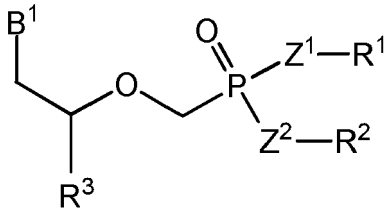


ou



3. Composé selon la revendication 1 ou 2, dans lequel R^3 est hydrogène.

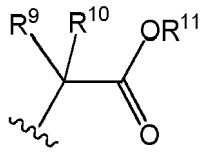
4. Composé de la structure de Formule (I), ou sel pharmaceutiquement acceptable de celui-ci



(I),

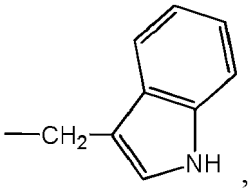
dans lequel :

B^1 est guanine ;
Z^1 est NH ;
Z^2 est O ou NR^Z ;
R^Z est hydrogène ou alkyle C_{1-4} ;
R^1 est



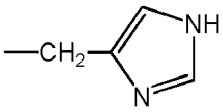
;

R^2 est aryl(alkyle C_{1-4})- ;
R^3 est alkyle ou hétéroalkyle ;
chaque R^9 et chaque R^{10} est indépendamment choisi parmi hydrogène, alkyle C_{1-6}, $-CH_2SH$, $-CH_2(C=O)NH_2$, $-CH_2CH_2(C=O)NH_2$, $-CH_2CH_2S\ CH_3$, CH_2- phényle, $-CH_2OH$, $-CH(OH)CH_3$,



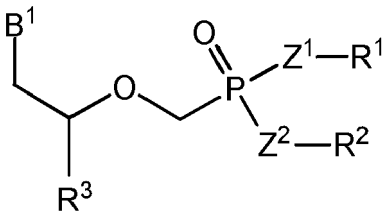
,

$-CH_2(C=O)OH$ $-CH_2CH_2(C=O)OH$, $-(CH_2)_3NH(C=NH)NH_2$,



et $-(CH_2)_4NH_2$; et
chaque R^{11} est indépendamment choisi parmi hydrogène, alkyle C_{1-8}, alkényle C_{2-8}, alkynyle, cycloalkyle, cycloalkyl(alkyle C_1-C_4)-, cycloalkényle, cycloalkényl(alkyle C_1-C_4)-, aryle, aryl(alkyle C_{1-4})-, hétéroaryle, hétéroaryl(alkyle C_1-C_4)-, hétérocyclyle et hétérocyclyl(alkyle C_1-C_4)-.

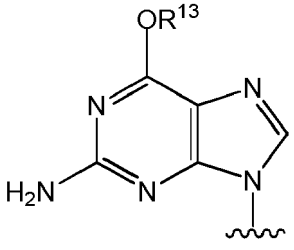
5. Composé de la structure de Formule (I), ou sel pharmaceutiquement acceptable de celui-ci



(I),

dans lequel :

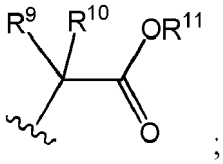
B^1 est



;

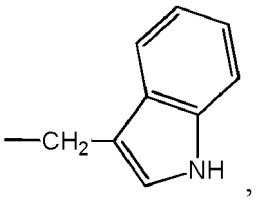
Z^1 est NH ;

Z^2 est O ou NR^Z ;
R^Z est hydrogène ou alkyle C_{1-4} ;
R^1 est



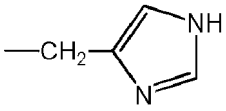
;

R^2 est aryl(alkyle C_{1-4})- ;
R^3 est alkyle ou hétéroalkyle ; chaque R^9 et chaque R^{10} est indépendamment choisi parmi hydrogène, alkyle C_{1-6}, $-CH_2SH$, $-CH_2(C=O)NH_2$, $-CH_2CH_2(C=O)NH_2$, $-CH_2CH_2S\ CH_3$, CH_2- phényle, $-CH_2OH$, $-CH(OH)CH_3$,



,

$-CH_2(C=O)OH$ $-CH_2CH_2(C=O)OH$, $-(CH_2)_3NH(C=NH)NH_2$,



et -(CH2)4NH2 ; et
chaque R^{11} est indépendamment choisi parmi hydrogène, alkyle C_{1-8}, alkényle C_{2-8}, alkynyle, cycloalkyle, cycloalkyl(alkyle C_1-C_4)-, cycloalkényle, cycloalkényl(alkyle C_1-C_4)-, aryle, aryl(alkyle C_{1-4})-, hétéroaryle, hétéroaryl(alkyle C_1-C_4)-, hétérocyclyle et hétérocyclyl(alkyle C_1-C_4)- ; et
R^{13} est alkyle C_{1-6} non substitué ou cycloalkyle C_{3-6} non substitué.

6. Composé selon la revendication 5, où R^{13} est méthyle.

7. Composé selon l'une quelconque des revendications 1 à 5, dans lequel R^3 est CH_3, CH_2OH ou CH_2F.

8. Composé selon l'une quelconque des revendications 1 à 5, dans lequel R^3 est CHF_2, CF_3 ou OCH_3.

9. Composé selon l'une quelconque des revendications 1 à 8, dans lequel Z^2 est O.

10. Composé selon l'une quelconque des revendications 1 à 8, dans lequel Z^2 est NR^Z.

11. Composé selon la revendication 10 dans lequel Z^2 est N-méthyle, N-éthyle, N-(n-propyl), N-(iso- propyl), N-(n-butyl), N-(iso-butyl) ou N-(t-butyl).

12. Composé selon l'une quelconque des revendications 1 à 11, dans lequel R^2 est benzyle.

13. Composé selon l'une quelconque des revendications 1 à 12, dans lequel R^9 est alkyle C_{1-6}.

14. Composé selon l'une quelconque des revendications 1 à 12, dans lequel R^{10} est hydrogène.

15. Composé selon l'une quelconque des revendications 1 à 14, dans lequel R^{11} est alkyle C_{1-8}.

16. Composition pharmaceutique comprenant une quantité efficace d'un composé selon l'une quelconque des reven-

dications 1 à 15, ou sel pharmaceutiquement acceptable de celui-ci, et un excipient pharmaceutiquement acceptable.

17. Composition pharmaceutique selon la revendication 16, dans laquelle la composition pharmaceutique se présente sous la forme d'une crème, d'un gel ou d'un onguent.

18. Composition pharmaceutique selon la revendication 16 ou 17, dans laquelle la composition pharmaceutique est une formulation topique.

19. Composé selon l'une quelconque des revendications 1 à 15, ou sel pharmaceutiquement acceptable de celui-ci, pour utilisation dans le traitement d'une maladie virale chez un sujet en ayant besoin, la maladie virale étant un papillomavirus humain.

20. Composé selon la revendication 19, dans lequel le papillomavirus humain est HPV-18.

21. Composé selon la revendication 19, dans lequel le papillomavirus humain est choisi dans le groupe constitué de papillomavirus humain HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, HPV-59, HPV-68, HPV-73 et HPV-82.

22. Composé selon l'une quelconque des revendications 1 à 15, ou sel pharmaceutiquement acceptable de celui-ci, pour utilisation dans le traitement du cancer du col de l'utérus chez un sujet en ayant besoin.

23. Composé selon l'une quelconque des revendications 1 à 15, ou sel pharmaceutiquement acceptable de celui-ci, pour utilisation dans le traitement de la néoplasie intra-épithéliale cervicale, de la néoplasie intra-épithéliale vaginale et de la néoplasie intra-épithéliale anale chez un sujet en ayant besoin.

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