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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 June 2019 (27.06.2019)

WIPO | PCT

(10) International Publication Number
WO 2019/125974 A1

(51) International Patent Classification:
A61K 31/7084 (2006.01) *C07H 21/00* (2006.01)
A61P 35/00 (2006.01)

(21) International Application Number:
PCT/US2018/065902

(22) International Filing Date:
17 December 2018 (17.12.2018)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/608,154 20 December 2017 (20.12.2017) US

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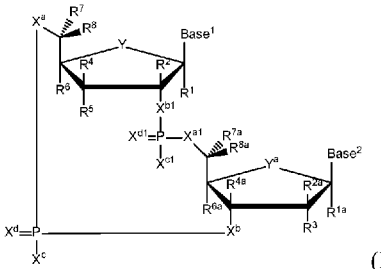
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS,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

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

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
— *with sequence listing part of description (Rule 5.2(a))*

(54) Title: CYCLIC DI-NUCLEOTIDE COMPOUNDS AS STING AGONISTS



(I)

(57) Abstract: A class of polycyclic compounds of general formula (I), wherein $Base^1$, $Base^2$, Y, Z^a, X^a, X^{a1}, X^b, X^{b1}, X^c, X^{c1}, X^d, X^{d1}, R^1, R^{1a}, R^2, R^{2a}, R^3, R^4, R^{4a}, R^5, R^6, R^{6a}, R^7, R^{7a}, R^8, R^{8a}, and R^9 are defined herein, that may be useful as inductors of type I interferon production, specifically as STING active agents, are provided. Also provided are processes for the synthesis and use of compounds.

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TITLE OF THE APPLICATION

CYCLIC DI-NUCLEOTIDE COMPOUNDS AS STING AGONISTS

FIELD OF THE INVENTION

[0001] The present disclosure relates to cyclic di-nucleotide compounds and derivatives thereof that may be useful as STING (Stimulator of Interferon Genes) agonists that activate the STING pathway. The present disclosure also relates to processes for the synthesis and to uses of such cyclic di-nucleotide compounds.

REFERENCE TO SEQUENCE LISTING SUBMITTED ELECTRONICALLY

[0002] The sequence listing of the present application is submitted electronically via EFS-Web as an ASCII-formatted sequence listing, with a file name of "24556_SEQLIST_14NOV2018", a creation date of November 14, 2018, and a size of 25KB. This sequence listing submitted via EFS-Web is part of the specification and is herein incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[0003] The immune system has evolved to recognize and neutralize different types of threats in order to maintain the homeostasis of the host, and it is generally broken down into two arms: adaptive and innate. The adaptive immune system is specialized to recognize as foreign those antigens not naturally expressed in the host and to mount an anti-antigen response through the coordinated actions of many leukocyte subsets. The hallmark of adaptive immune responses is their ability to provide "memory" or long-lasting immunity against the encountered antigen. While this specific and long-lasting effect is critical to host health and survival, the adaptive immune response requires time to generate a full-blown response.

[0004] The innate immune system compensates for this time delay and is specialized to act quickly against different insults or danger signals. It provides the first line of defense against bacteria, viruses, parasites and other infectious threats, but it also responds strongly to certain danger signals associated with cellular or tissue damage. The innate immune system has no antigen specificity but does respond to a variety of effector mechanisms. Opsonization, phagocytosis, activation of the complement system, and production of soluble bioactive molecules such as cytokines or chemokines are all mechanisms by which the innate immune

system mediates its response. By responding to these damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs) described above, the innate immune system is able to provide broad protection against a wide range of threats to the host.

[0005] Free cytosolic DNA and RNA are among these PAMPs and DAMPs. It has recently been demonstrated that the main sensor for cytosolic DNA is cGAS (cyclic GMP-AMP synthase). Upon recognition of cytosolic DNA, cGAS catalyzes the generation of the cyclic-dinucleotide 2'3'-cGAMP, an atypical second messenger that strongly binds to the ER-transmembrane adaptor protein STING. A conformational change is undergone by cGAMP-bound STING, which translocates to a perinuclear compartment and induces the activation of critical transcription factors IRF-3 and NF-κB. This leads to a strong induction of type I interferons and production of pro-inflammatory cytokines such as IL-6, TNF-α and IFN-γ.

[0006] The importance of type I interferons and pro-inflammatory cytokines on various cells of the immune system has been very well established. In particular, these molecules strongly potentiate T-cell activation by enhancing the ability of dendritic cells and macrophages to uptake, process, present and cross-present antigens to T-cells. The T-cell stimulatory capacity of these antigen-presenting cells is augmented by the up-regulation of critical co-stimulatory molecules, such as CD80 or CD86. Finally, type I interferons can rapidly engage their cognate receptors and trigger the activation of interferon-responsive genes that can significantly contribute to adaptive immune cell activation.

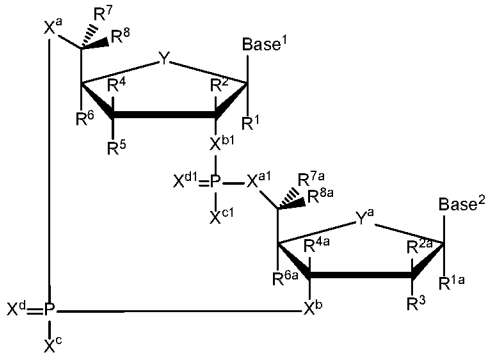
[0007] From a therapeutic perspective, type I interferons are shown to have antiviral activities by directly inhibiting human hepatitis B virus and hepatitis C virus replication, and by stimulating immune responses to virally infected cells. Compounds that can induce type I interferon production are used in vaccines, where they act as adjuvants, enhancing specific immune responses to antigens and minimizing side effects by reducing dosage and broadening the immune response.

[0008] In addition, interferons, and compounds that can induce interferon production, have potential use in the treatment of human cancers. Such molecules are potentially useful as anti-cancer agents with multiple pathways of activity. Interferons can inhibit human tumor cell proliferation directly and may be synergistic with various approved chemotherapeutic agents. Type I interferons can significantly enhance anti-tumor immune responses by inducing activation of both the adaptive and innate immune cells. Finally, tumor invasiveness may be inhibited by interferons by modulating enzyme expression related to tissue remodeling.

[0009] In view of the potential of type I interferons and type I interferon-inducing compounds as anti-viral and anti-cancer agents, there remains a need for new agents that can induce potent type I interferon production. With the growing body of data demonstrating that the cGAS-STING cytosolic DNA sensory pathway has a significant capacity to induce type I interferons, the development of STING activating agents is rapidly taking an important place in to day's anti-tumor therapy landscape.

SUMMARY OF THE INVENTION

[0010] The present disclosure relates to novel compounds of general formula (I). In particular, the present disclosure relates to compounds having the general structural formula (I):



(I)

or pharmaceutically acceptable salts, hydrates, solvates, or prodrugs thereof, as described herein. Embodiments of the disclosure include compounds of general formula (I), and pharmaceutically acceptable salts, hydrates, solvates, or prodrugs thereof, as well as synthesis and isolation of compounds of general formula (I), and pharmaceutically acceptable salts, hydrates, solvates, or prodrugs thereof. The compounds of general formula (I), and their pharmaceutically acceptable salts, hydrates, solvates, and/or prodrugs, may be useful as agents to induce immune responses, to induce STING-dependent type I interferon production, and/or to treat a cell proliferation disorders, such as cancers, in a subject. The compounds of general formula (I) could further be used in combination with other therapeutically effective agents, including but not limited to, other drugs useful for the treatment of cell proliferation disorders, such as cancers. The invention further relates to processes for preparing compounds of general formula (I), and pharmaceutical compositions that comprise compounds of general formula (I) and pharmaceutically acceptable salts thereof.

[0011] Other embodiments, aspects and features of the present invention are either further described in or will be apparent from the ensuing description, examples and appended claims.

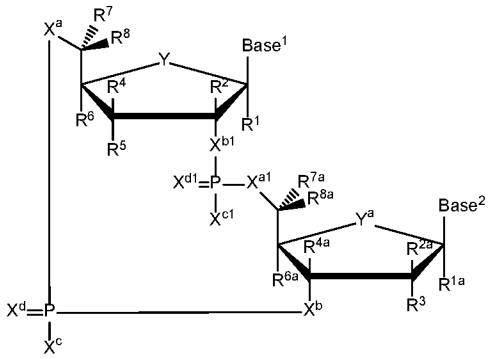
BRIEF DESCRIPTION OF THE DRAWINGS

[0012] Not Applicable

DETAILED DESCRIPTION OF THE INVENTION

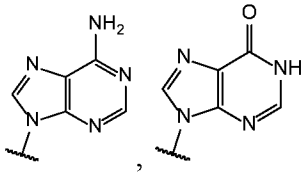
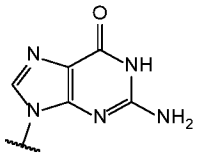
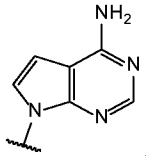
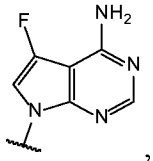
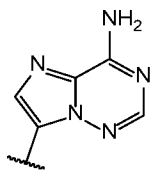
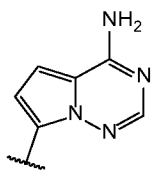
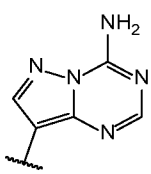
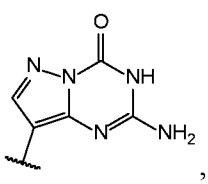
[0013] The present disclosure includes compounds of general formula (I), and pharmaceutically acceptable salts, hydrates, solvates, or prodrugs thereof. These compounds and their pharmaceutically acceptable salts, hydrates, solvates, and/or prodrugs may be useful as agents to induce immune responses, to induce STING-dependent type I interferon production, and/or to treat a cell proliferation disorder.

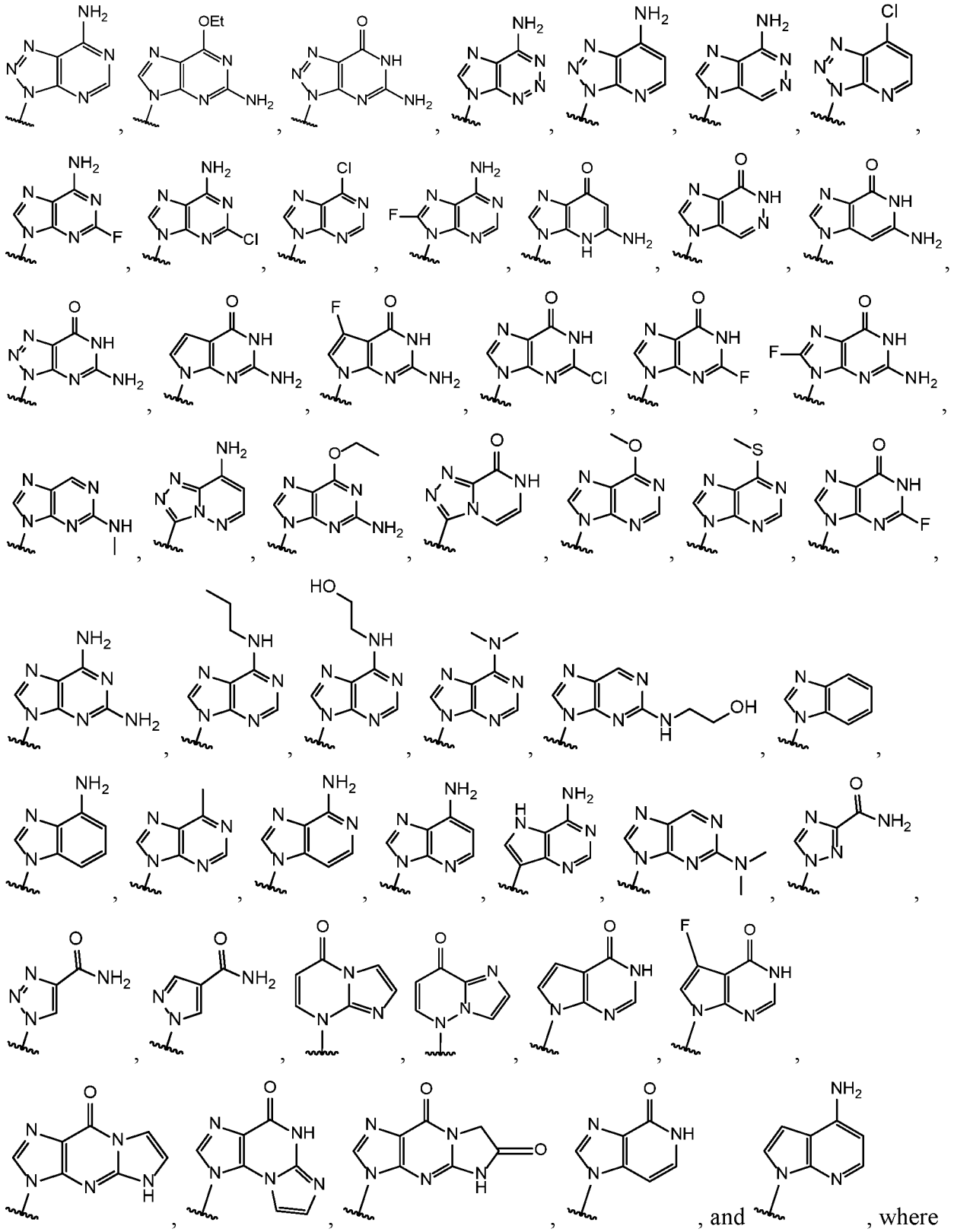
[0014] Embodiments disclosed herein relate to compounds of general formula (I):



(I)

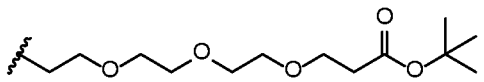
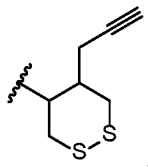
[0015] The present disclosure includes compounds of general formula (I), and pharmaceutically acceptable salts, hydrates, solvates, or prodrugs thereof. These compounds and their pharmaceutically acceptable salts, hydrates, solvates, and/or prodrugs may be useful as agents to induce immune responses, to induce STING-dependent type I interferon production, and/or to treat a cell proliferation disorder.

[0016] Embodiments disclosed herein relate to compounds of general formula (I) or pharmaceutically acceptable salts, hydrates, solvates, or prodrugs thereof, wherein $Base^1$ and $Base^2$ are each independently selected from the group consisting of  , ,  ,  ,  ,  ,  ,  ,  ,

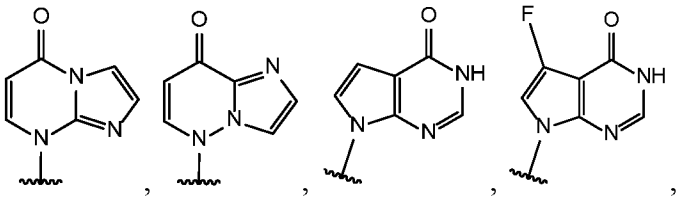
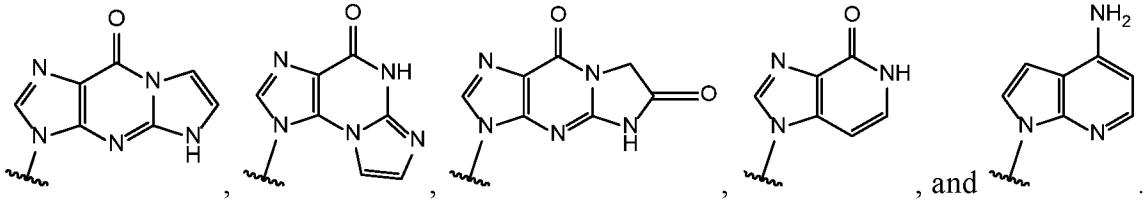


, and , where Base[1] and Base[2] each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6}

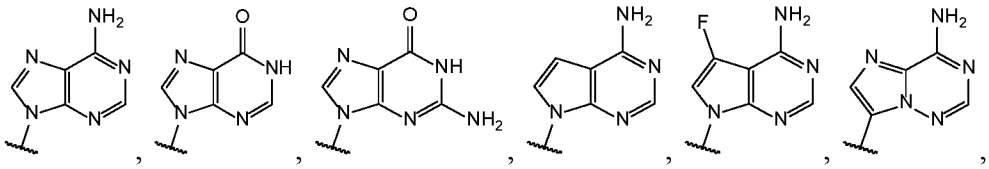
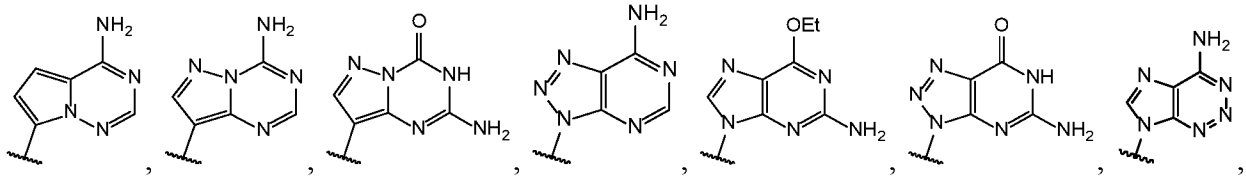
cycloalkyl, O(C_{1-3} alkyl), O(C_{3-6} cycloalkyl), S(C_{1-3} alkyl), S(C_{3-6} cycloalkyl), NH(C_{1-3} alkyl), NH(C_{3-6} cycloalkyl), N(C_{1-3} alkyl)$_2$, and N(C_{3-6} cycloalkyl)$_2$; Y and Y^a are each independently selected from the group consisting of -O-, -S-, -SO_2-, -CH_2-, and -CF_2-; X^a and X^{a1} are each independently selected from the group consisting of -O-, -S-, and -CH_2-; X^b and X^{b1} are each independently selected from the group consisting of -O-, -S-, and -CH_2-; X^c and X^{c1} are each independently selected from the group consisting of -SR^9, -OR^9, and -NR^9R^9; X^d and X^{d1} are each independently selected from the group consisting of O and S; R^1 and R^{1a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^1 and R^{1a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^2 and R^{2a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^2 and R^{2a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^3 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^3 C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^4 and R^{4a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^4 and R^{4a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^5 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^5 C_1-C_6 alkyl,

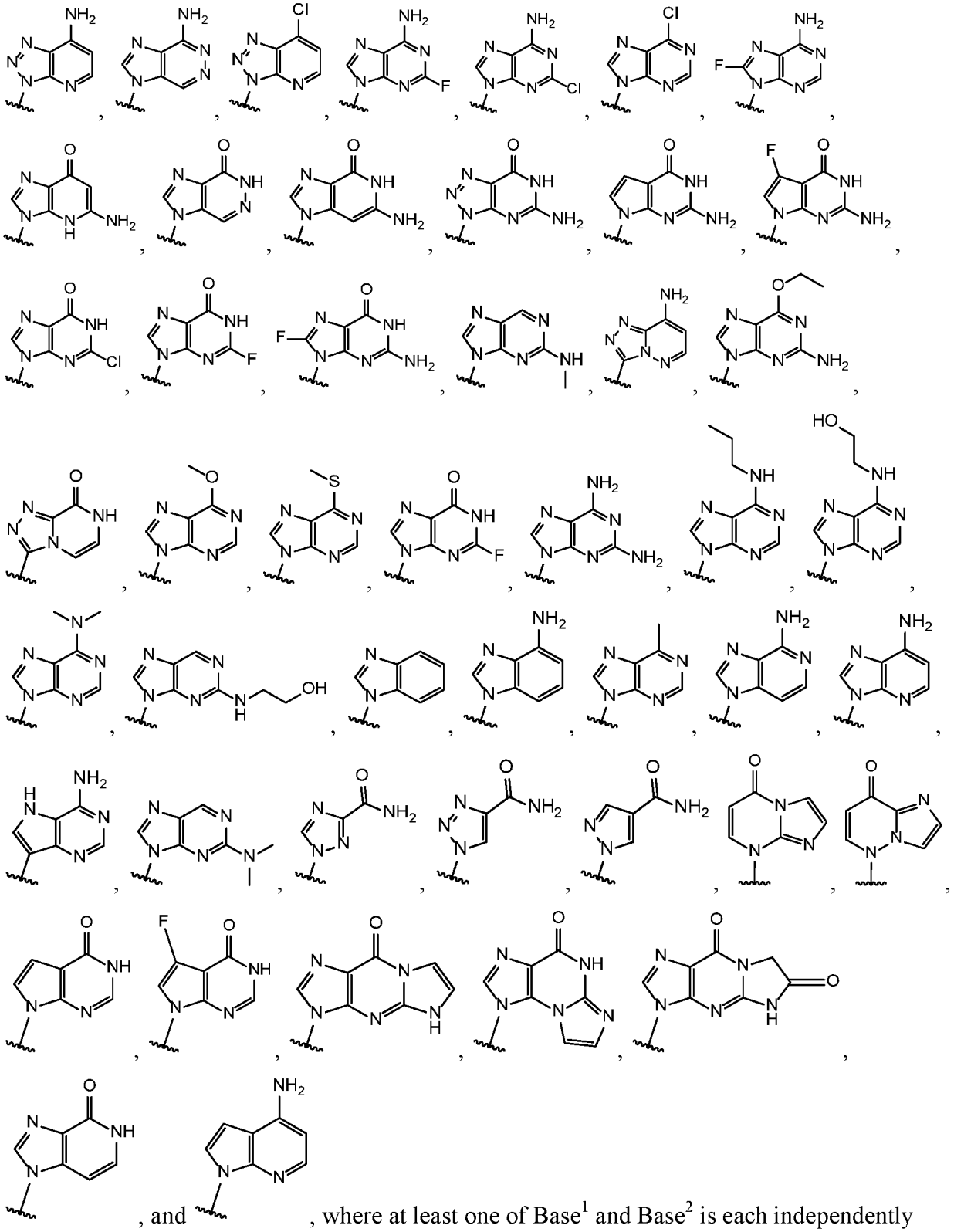
C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^6 and R^{6a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^6 and R^{6a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^7 and R^{7a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^7 and R^{7a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^8 and R^{8a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^8 and R^{8a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; each R^9 is independently selected from the group consisting of H, C_1-C_{20} alkyl,  , and  , where each R^9 C_1-C_{20} alkyl is optionally substituted by 0 to 3 substituents independently selected from the group consisting of OH, -O-C_1-C_{20} alkyl,-S-C(O)C_1-C_6 alkyl, and C(O)OC_1-C_6 alkyl; optionally R^{1a} and R^3 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, -O-C_1-C_6 alkylene, or -O-C_2-C_6 alkenylene, such that where R^{1a} and R^3 are connected to form -O-C_1-C_6 alkylene, or -O-C_2-C_6 alkenylene, said O is bound at the R^3 position; optionally R^{2a} and R^3 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, -O-C_1-C_6 alkylene, or -O-C_2-C_6 alkenylene, such that where R^{2a} and R^3 are connected to form -O-C_1-C_6 alkylene, or -O-C_2-C_6 alkenylene, said O is bound at the R^3 position; optionally R^3 and R^{6a} are

connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, -O-C_1-C_6 alkylene, or -O-C_2-C_6 alkenylene, such that where R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, or -O-C_2-C_6 alkenylene, said O is bound at the R^3 position; optionally R^4 and R^5 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, -O-C_1-C_6 alkylene, or -O-C_2-C_6 alkenylene, such that where R^4 and R^5 are connected to form -O-C_1-C_6 alkylene, or -O-C_2-C_6 alkenylene, said O is bound at the R^5 position; optionally R^5 and R^6 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^5 and R^6 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^5 position; optionally R^7 and R^8 are connected to form C_1-C_6 alkylene or C_2-C_6 alkenylene; and optionally R^{7a} and R^{8a} are connected to form C_1-C_6 alkylene or C_2-C_6 alkenylene.

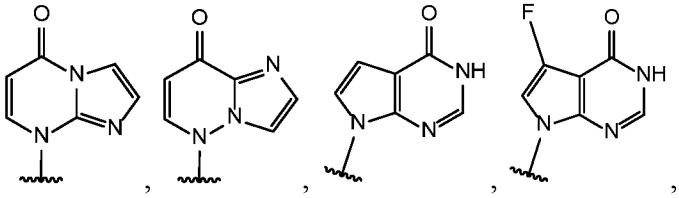
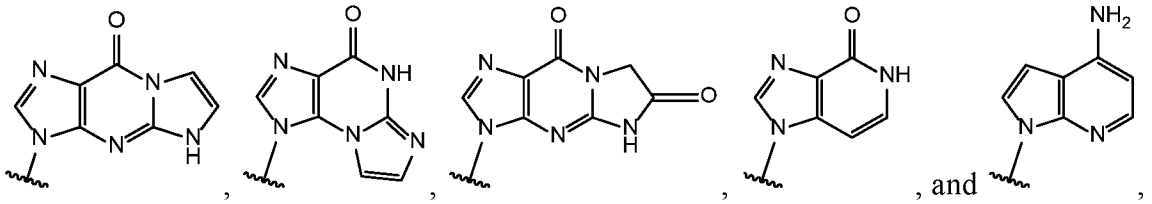
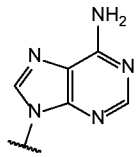
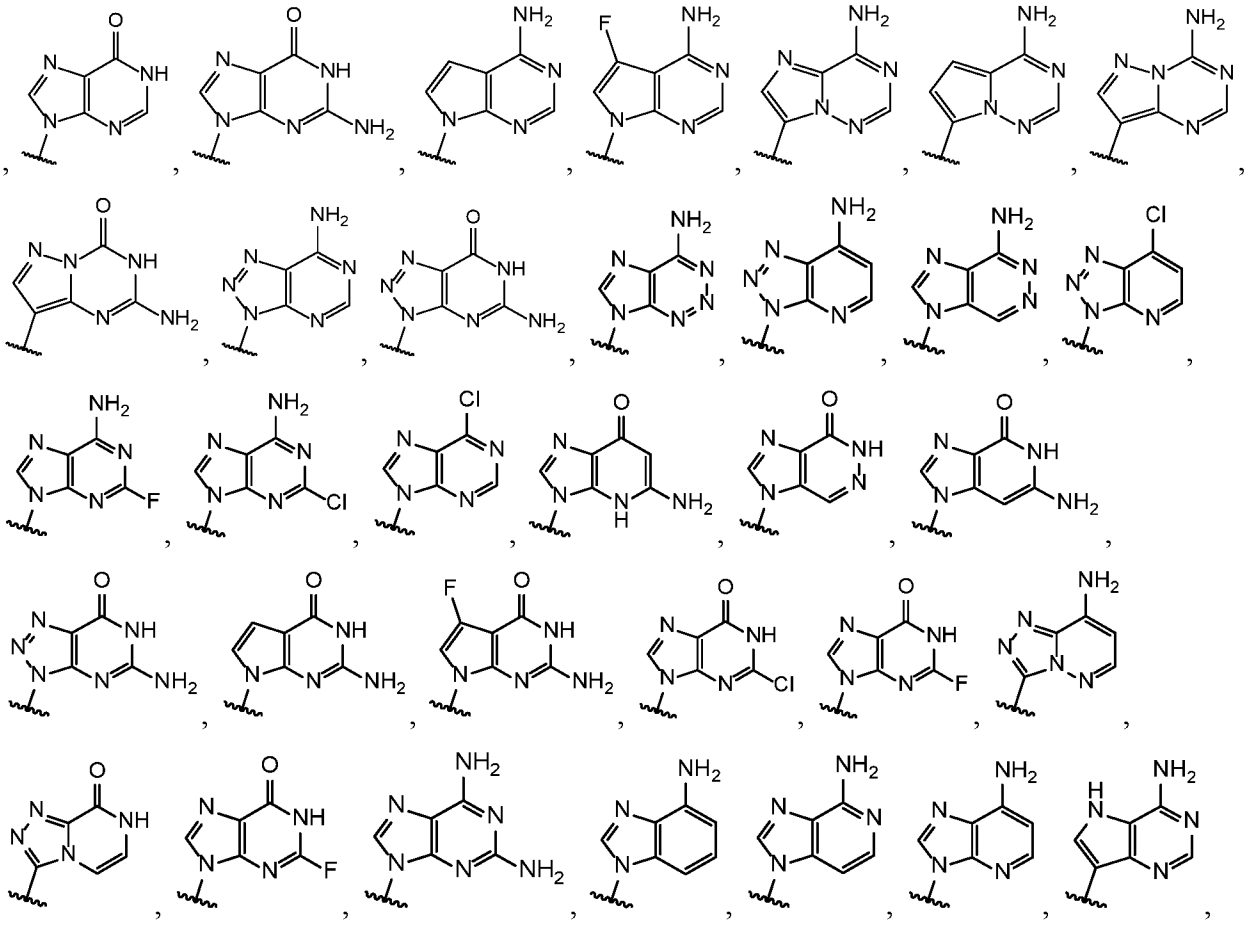
[0017] In embodiments, at least one of $Base^1$ and $Base^2$ is each independently selected from the group consisting of  ,  , and .

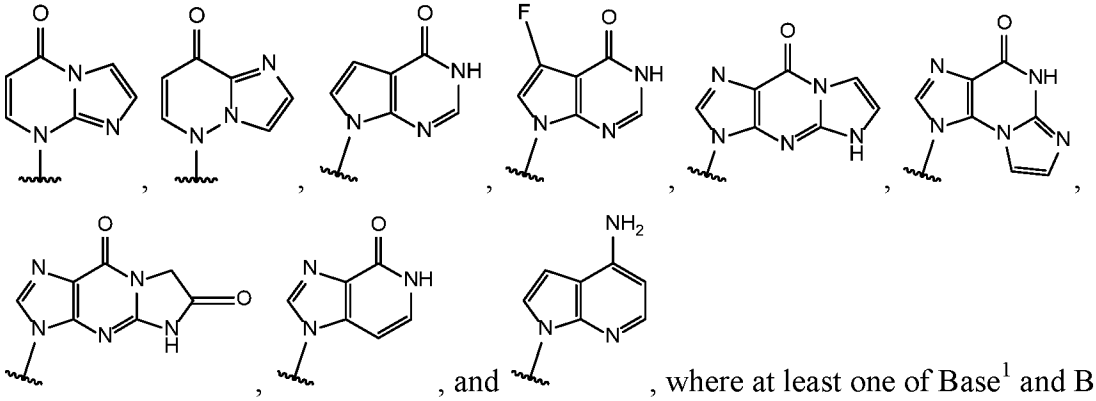
[0018] In each embodiment described herein, variables $Base^1$, $Base^2$, Y, Y^a, X^a, X^{a1}, X^b, X^{b1}, X^c, X^{c1}, X^d, X^{d1}, R^1, R^{1a}, R^2, R^{2a}, R^3, R^4, R^{4a}, R^5, R^6, R^{6a}, R^7, R^{7a}, R^8, R^{8a}, and R^9 of general formula (I), and the various aspects thereof, are each selected independently from each other.

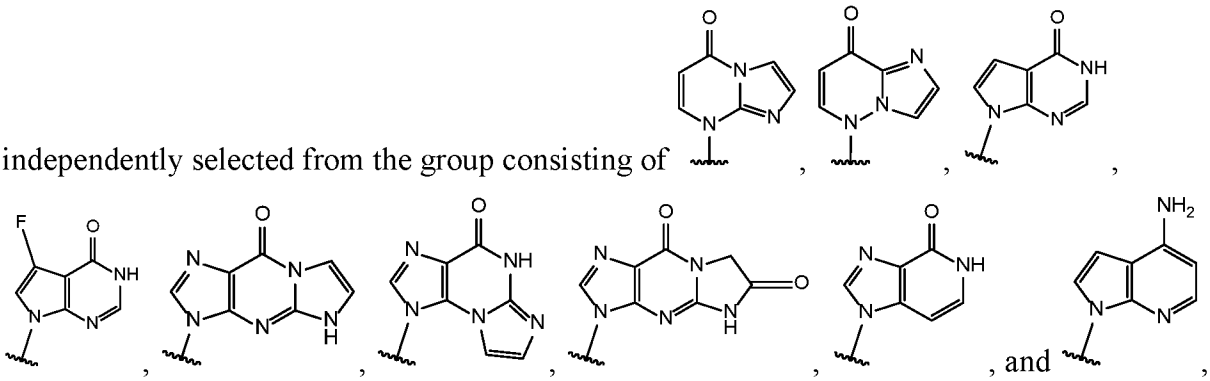
[0019] In a first embodiment, $Base^1$ and $Base^2$ are each independently selected from the group consisting of  ,  , .

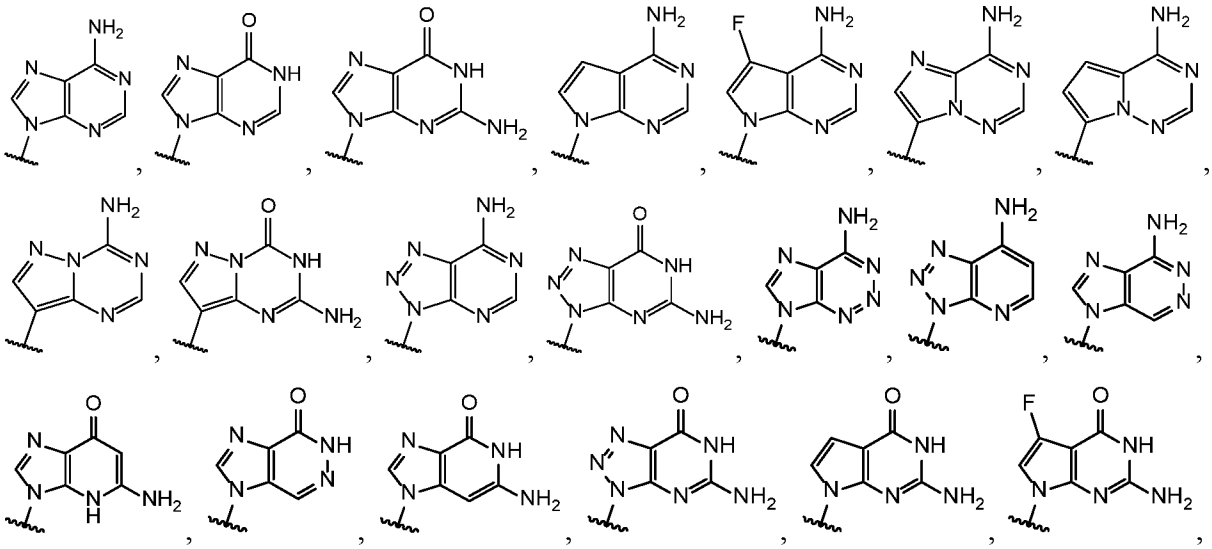


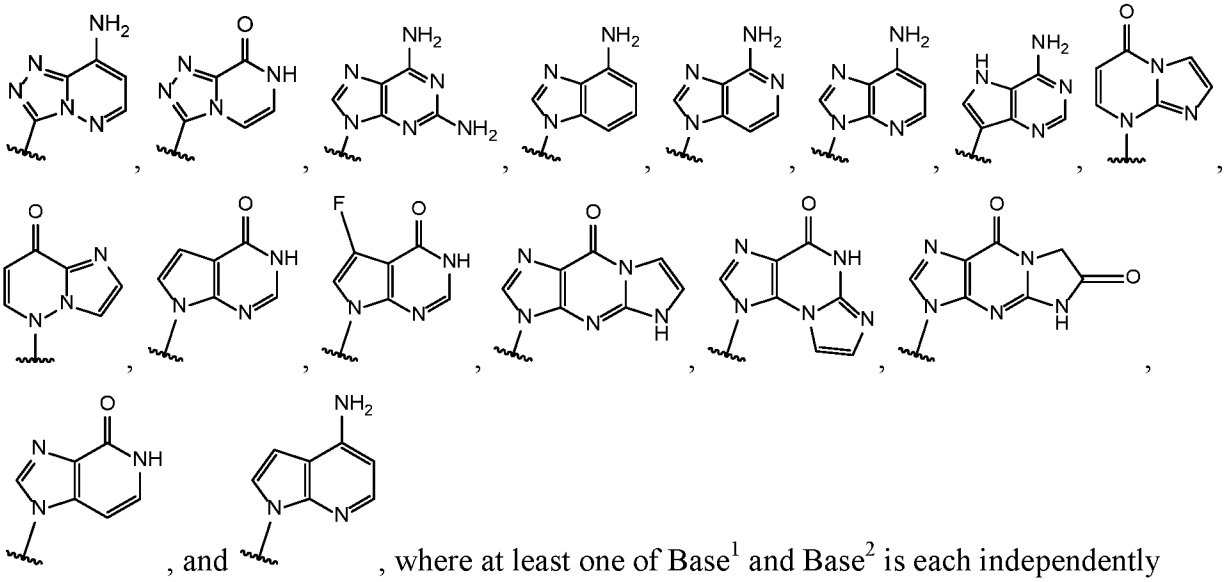
, and , where at least one of Base[1] and Base[2] is each independently

selected from the group consisting of  ,  , and , and where $Base^1$ and $Base^2$ each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl$)_2$, and $N(C_{3-6}$ cycloalkyl$)_2$. In particular aspects, $Base^1$ and $Base^2$ are each independently selected from the group consisting of  , 

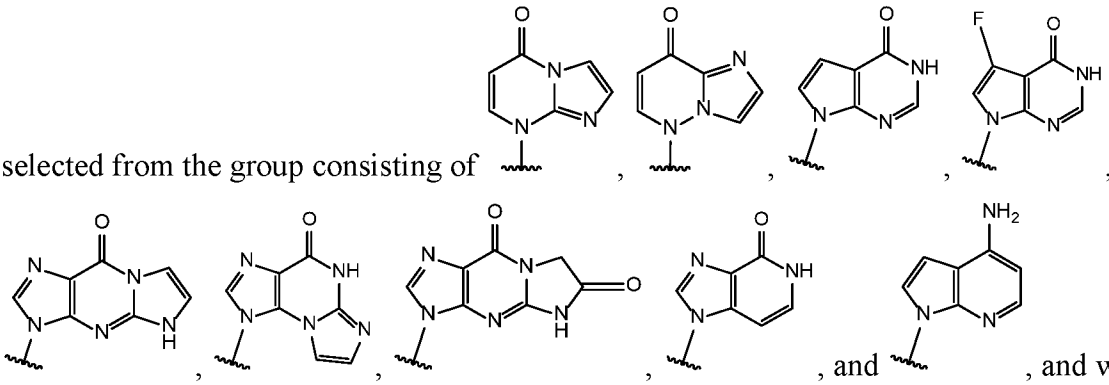

, and , where at least one of Base[1] and Base[2] is each independently selected from the group consisting of


, and , and where Base[1] and Base[2] each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl$)_2$, and $N(C_{3-6}$ cycloalkyl$)_2$. In even more particular aspects, Base[1] and Base[2] are each independently selected from the group consisting of

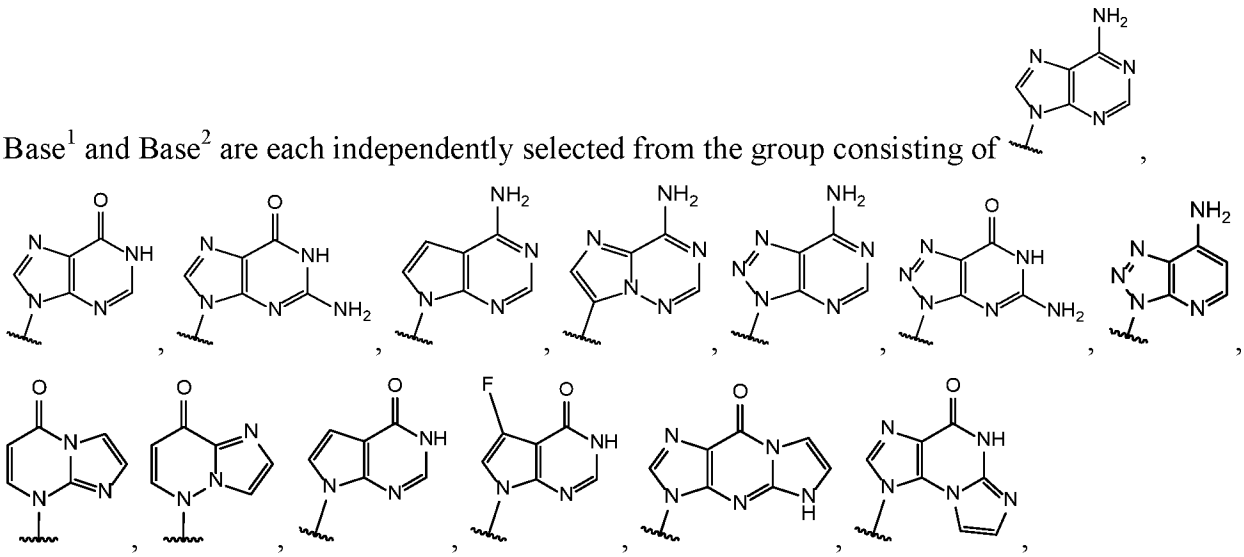


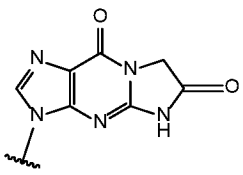
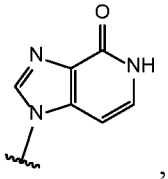
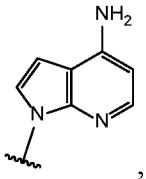


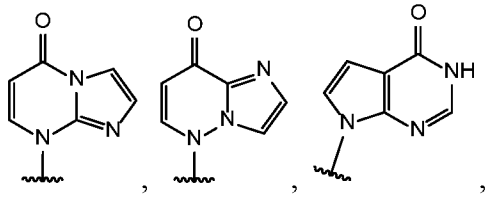
, where at least one of Base[1] and Base[2] is each independently selected from the group consisting of

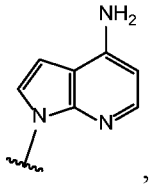


, and where Base[1] and Base[2] each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl$)_2$, and $N(C_{3-6}$ cycloalkyl$)_2$. In even more particular aspects, Base[1] and Base[2] are each independently selected from the group consisting of

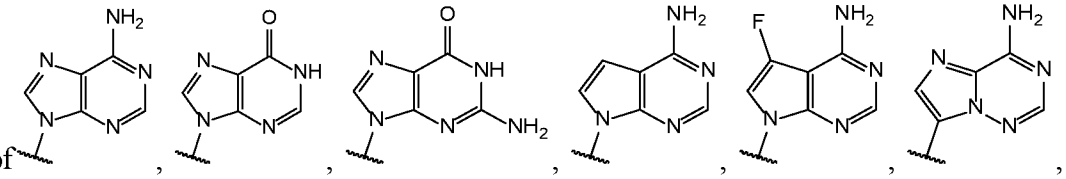





, and , where at least one of Base[1] and Base[2] is each independently selected from the group consisting of


, and


,

and where Base[1] and Base[2] each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl$)_2$, and $N(C_{3-6}$ cycloalkyl$)_2$. In still further instances of this embodiment, Base[1] and Base[2] are each independently selected from the group consisting of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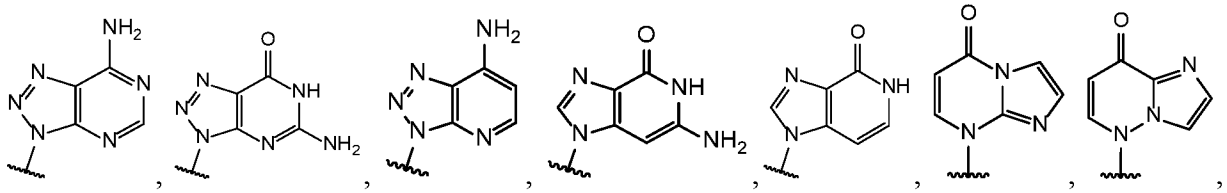
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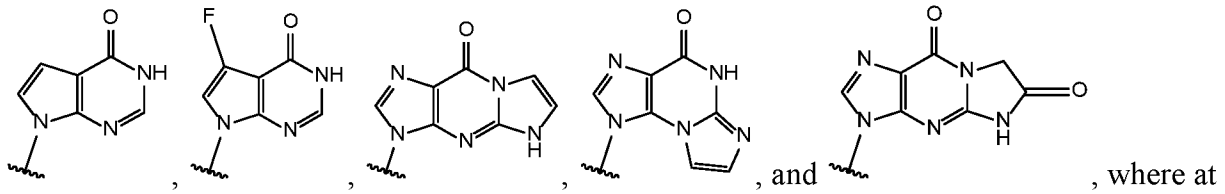
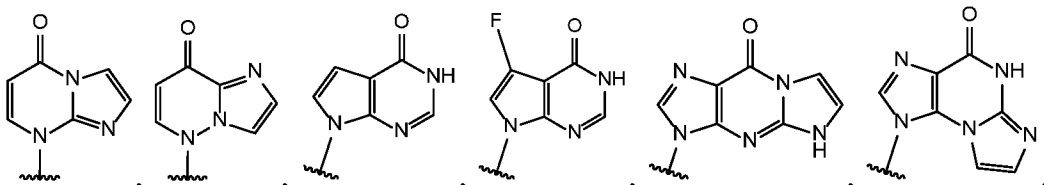
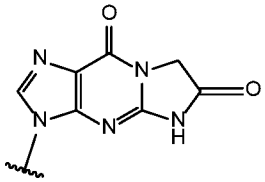
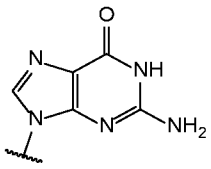
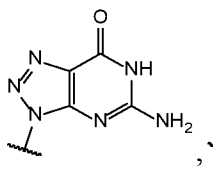
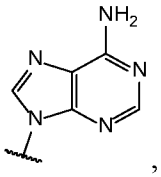
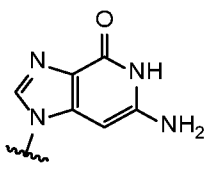
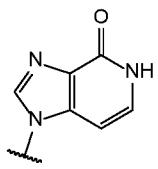
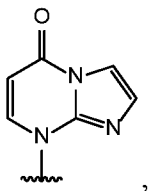
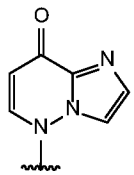
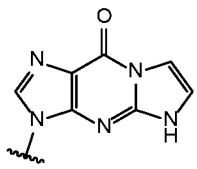
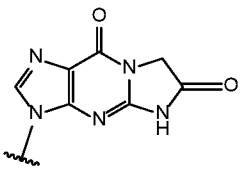
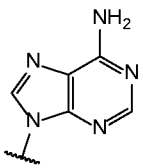
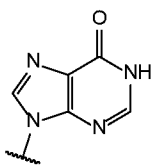
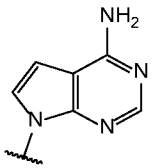
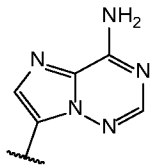
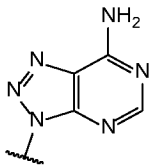
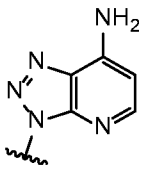
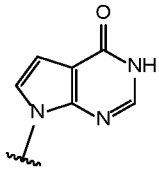
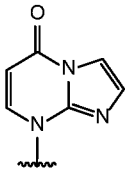
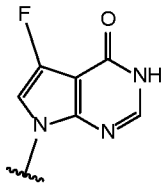
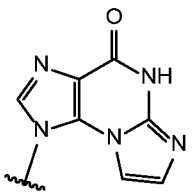
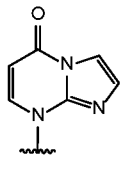
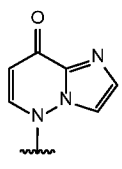
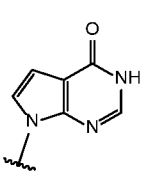
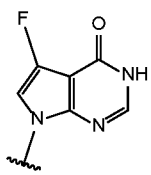
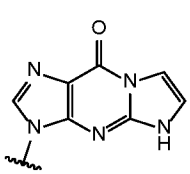
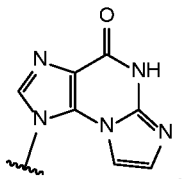
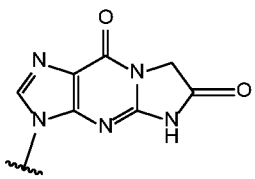
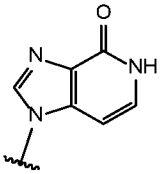

, and

, where at least one of Base[1] and Base[2] is each independently selected from the group consisting of


, and



, and where $Base^1$ and $Base^2$ each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl$)_2$, and $N(C_{3-6}$ cycloalkyl$)_2$.

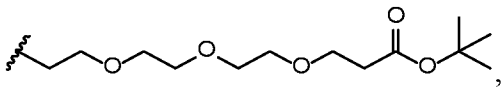
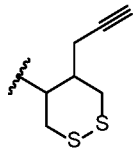
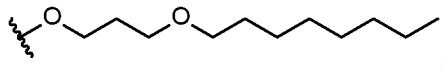
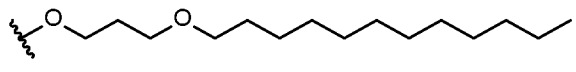
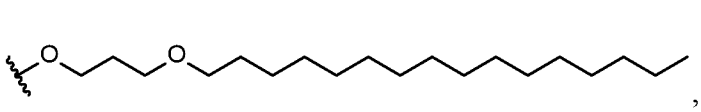
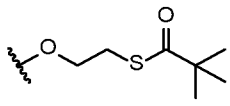
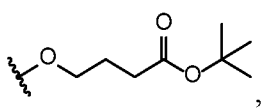
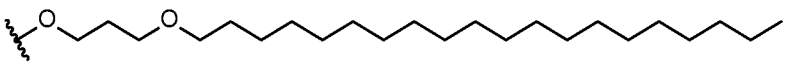
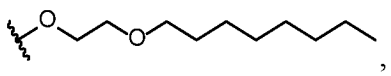
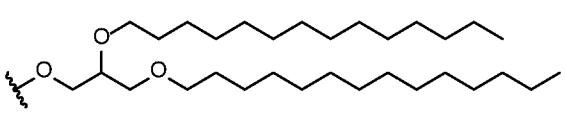
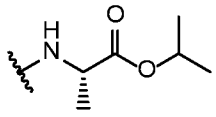
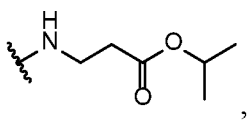
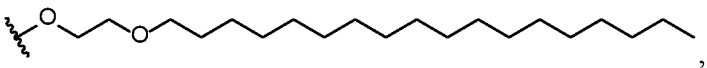
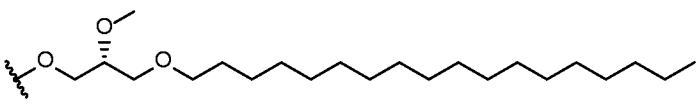
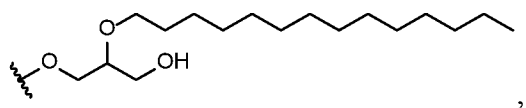
In even more particular instances of this embodiment, $Base^1$ is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  , and  ; $Base^2$ is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  , where at least one of $Base^1$ and $Base^2$ is each independently selected from the group consisting of  ,  ,  ,  ,  ,  ,  , and  , and where $Base^1$ and $Base^2$ each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl),

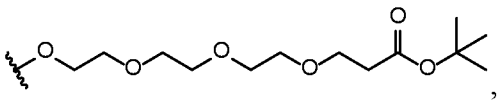
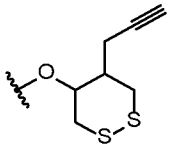
$NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl$)_2$, and $N(C_{3-6}$ cycloalkyl$)_2$. In this embodiment, all other groups are as provided in the general formula (I) above.

[0020] In a second embodiment, Y and Y^a are each independently selected from the group consisting of -O- and -S-. In this embodiment, all other groups are as provided in the general formula (I) above or in the first embodiment described above.

[0021] In a third embodiment, X^a and X^{a1} are each independently selected from the group consisting of -O- and -S-. In this embodiment, all other groups are as provided in the general formula (I) above or in the first through second embodiments described above.

[0022] In a fourth embodiment, X^b and X^{b1} are each independently selected from the group consisting of -O- and -S-. In this embodiment, all other groups are as provided in the general formula (I) above or in the first through third embodiments described above.

[0023] In a fifth embodiment, X^c and X^{c1} are each independently selected from the group consisting of $-OR^9$, $-SR^9$, and $-NR^9R^9$, where each R^9 is independently selected from the group consisting of H, C_1-C_{20} alkyl,  , and  , where each R^9 C_1-C_{20} alkyl is optionally substituted by 0 to 3 substituents independently selected from the group consisting of -OH, -O-C_1-C_{20} alkyl,-S-C(O)C_1-C_6 alkyl, and -C(O)OC_1-C_6 alkyl. In particular aspects, X^c and X^{c1} are each independently selected from the group consisting of -OH, -SH,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .

 , and  . In more particular aspects, X^c and X^{c1} are each independently selected from the group consisting of -OH and -SH. In all aspects of this embodiment, all other groups are as provided in the general formula (I) above or in the first through fourth embodiment described above.

[0024] In a sixth embodiment, X^d and X^{d1} are each independently selected from the group consisting of O and S. In this embodiment, all other groups are as provided in the general formula (I) above or in the first through fifth embodiments described above.

[0025] In a seventh embodiment, R^1 and R^{1a} are each H. In this embodiment, all other groups are as provided in the general formula (I) above or in the first through sixth embodiments described above.

[0026] In an eighth embodiment, R^2 and R^{2a} are each independently selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^2 and R^{2a} C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of OH, CN, and N_3. In particular aspects, R^2 and R^{2a} are each independently selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-CH_2CH_3$. In more particular aspects, R^2 and R^{2a} are each independently selected from the group consisting of H, F, Cl, OH, CN, N_3, and $-CH_3$. In even more particular aspects, R^2 and R^{2a} are each independently selected from the group consisting of H, F, and OH. In all aspects of this embodiment, all other groups are as provided in the general formula (I) above or in the first through seventh embodiments described above.

[0027] In a ninth embodiment, R^3 is selected from the group consisting H, F, Cl, I, Br, OH, CN, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^3 C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of OH, CN, and N_3. In particular aspects, R^3 is selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-CH_2CH_3$. In more particular aspects, R^3 is selected from the group consisting of H, F, Cl, OH, CN, N_3, and $-CH_3$. In even more particular aspects, R^3 is selected from the group consisting of H, F, and OH. In all aspects of this embodiment, all other groups are as provided in the general formula (I) above or in the first through eighth embodiments described above.

[0028] In a tenth embodiment, R^4 and R^{4a} are each independently selected from the group consisting of H, F, Cl, I, Br, CN, OH, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^4 and R^{4a} C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of OH, CN, and N_3. In particular aspects, R^4 and R^{4a} are each independently selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-CH_2CH_3$. In more particular aspects, R^4 and R^{4a} are each independently selected from the group consisting of H, F, Cl, OH, CN, N_3, and $-CH_3$. In even more particular aspects, R^4 and R^{4a} are each independently selected from the group consisting of H, F, and OH. In all aspects of this embodiment, all other groups are as provided in the general formula (I) above or in the first through ninth embodiments described above.

[0029] In an eleventh embodiment, R^5 is selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^5 C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of OH, CN, and N_3. In particular aspects, R^5 is selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-CH_2CH_3$. In more particular aspects, R^5 is selected from the group consisting of H, F, Cl, OH, CN, N_3, and CH_3. In even more particular aspects, R^5 is selected from the group consisting of H, F, and OH. In all aspects, all other groups are as provided in the general formula (I) above or in the first through tenth embodiments described above.

[0030] In a twelfth embodiment, R^6 and R^{6a} are each independently selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, where said R^6 and R^{6a} C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3. In particular aspects, R^6 and R^{6a} are each independently selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, $-CF_3$, $-CH_3$, $-CH_2OH$, CH_2CH_3, $-CH{=}CH_2$, $-C{\equiv}CH$, and $-C{\equiv}C-CH$. In more particular aspects, R^6 and R^{6a} are each independently selected from the group consisting of H, F, CN, N_3, $-CH_3$, $-CH{=}CH_2$, and $-C{\equiv}CH$. In even more particular aspects, R^6 and R^{6a} are each H. In all aspects of this embodiment, all other groups are as provided in the general formula (I) above or in the first through eleventh embodiments described above.

[0031] In a thirteenth embodiment, R^7 and R^{7a} are each independently selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^7 and R^{7a} C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of OH, CN, and N_3. In particular aspects, R^7 and R^{7a} are each independently selected from the group

consisting of H, -CF_3, -CH_3, and -CH_2CH_3. In more particular aspects, R^7 and R^{7a} are each H. In all aspects of this embodiment, all other groups are as provided in the general formula (I) above or in the first through twelfth embodiments described above.

[0032] In a fourteenth embodiment, R^8 and R^{8a} are each independently selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^8 and R^{8a} C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of OH, CN, and N_3. In particular aspects, R^8 and R^{8a} are each independently selected from the group consisting of H, -CF_3, -CH_3, and -CH_2CH_3. In more particular aspects, R^8 and R^{8a} are each H. In all aspects of this embodiment, all other groups are as provided in the general formula (I) above or in the first through thirteenth embodiments described above.

[0033] In a fifteenth embodiment, R^{1a} and R^3 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, -O-C_1-C_6 alkylene, or -O-C_2-C_6 alkenylene, such that where R^{1a} and R^3 are connected to form -O-C_1-C_6 alkylene or -O-C_2-C_6 alkenylene, said O is bound at the R^3 position. In this embodiment, all other groups are as provided in the general formula (I) above or in the first through fourteenth embodiments described above.

[0034] In a sixteenth embodiment, R^{2a} and R^3 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, -O-C_1-C_6 alkylene, or -O-C_2-C_6 alkenylene, such that where R^{2a} and R^3 are connected to form -O-C_1-C_6 alkylene or -O-C_2-C_6 alkenylene, said O is bound at the R^3 position. In this embodiment, all other groups are as provided in the general formula (I) above or in the first through fourteenth embodiments described above.

[0035] In a seventeenth embodiment, R^3 and R^{6a} are connected to form C_2-C_6 alkylene, C_2-C_6 alkenylene, -O-C_1-C_6 alkylene, or -O-C_2-C_6 alkenylene,, such that where R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene or -O-C_2-C_6 alkenylene, said O is bound at the R^3 position. In this embodiment, all other groups are as provided in the general formula (I) above or in the first through fourteenth embodiments described above.

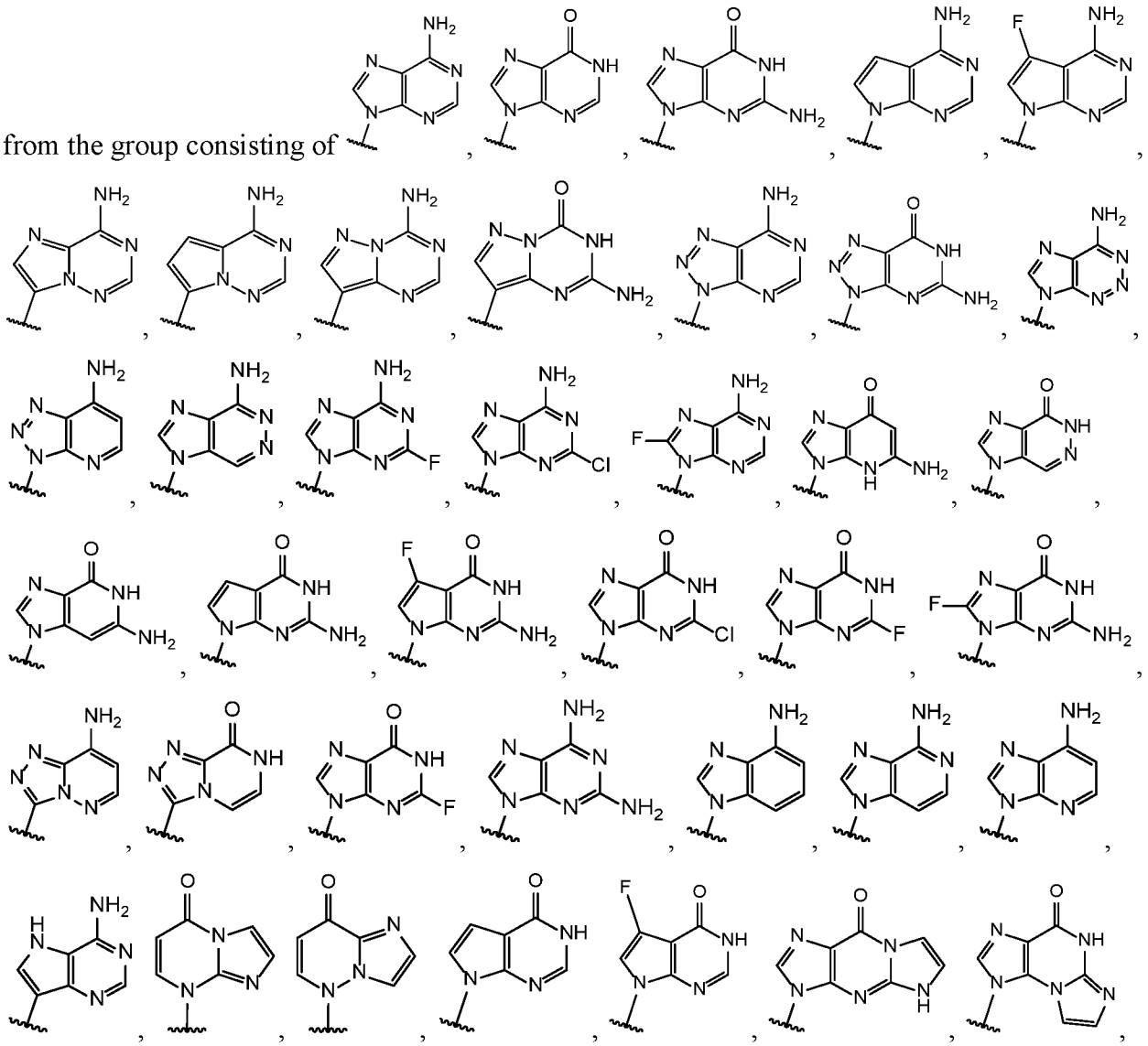
[0036] In an eighteenth embodiment, R^4 and R^5 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, -O-C_1-C_6 alkylene, or -O-C_2-C_6 alkenylene, such that where R^4 and R^5 are connected to form -O-C_1-C_6 alkylene or -O-C_2-C_6 alkenylene, said O is bound at the R^5 position. In this embodiment, all other groups are as provided in the general formula (I) above or in the first through fourteenth embodiments described above.

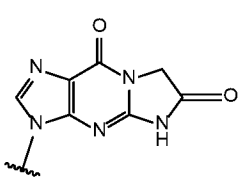
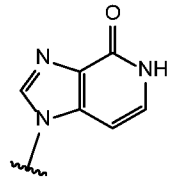
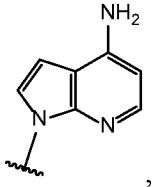
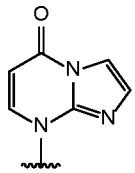
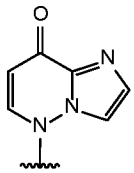
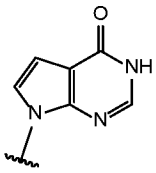
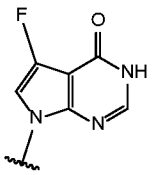
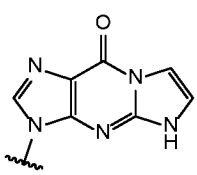
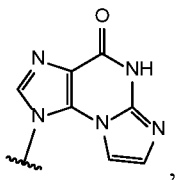
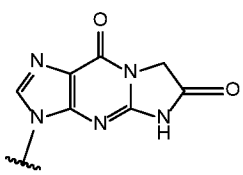
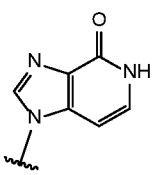
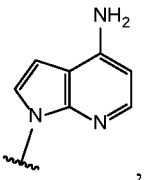
[0037] In a nineteenth embodiment, R^5 and R^6 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, -O-C_1-C_6 alkylene, or -O-C_2-C_6 alkenylene, such that where R^5 and R^6 are

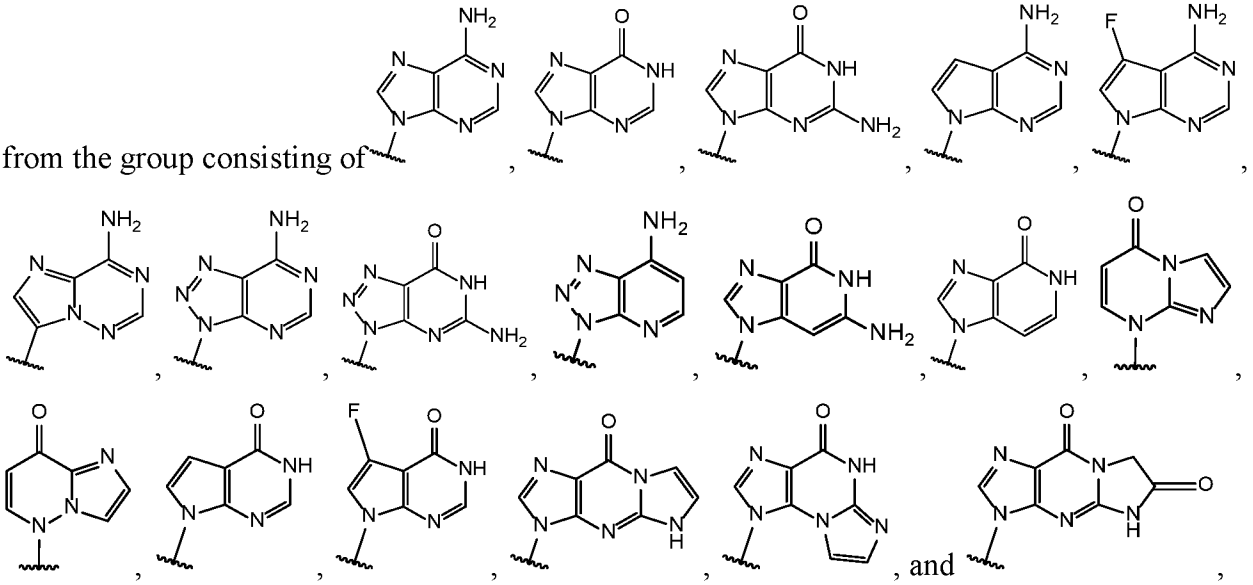
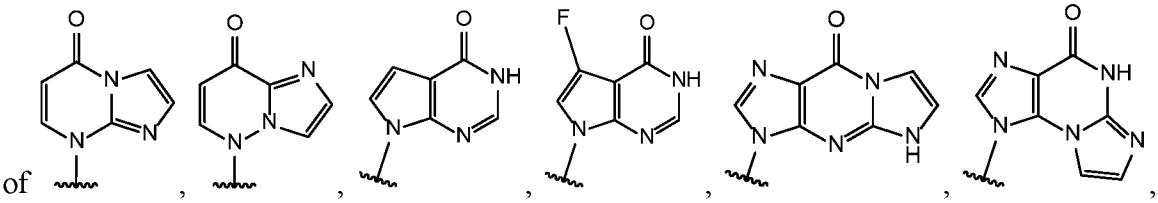
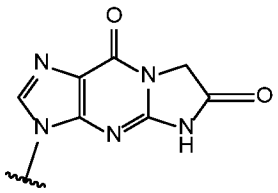
connected to form -O-C_1-C_6 alkylene or -O-C_2-C_6 alkenylene, said O is bound at the R^5 position. In this embodiment, all other groups are as provided in the general formula (I) above or in the first through fourteenth embodiments described above.

[0038] In a twentieth embodiment, R^7 and R^8 are connected to form C_1-C_6 alkylene or C_2-C_6 alkenylene. In this embodiment, all other groups are as provided in the general formula (I) above or in the first through fourteenth embodiments described above.

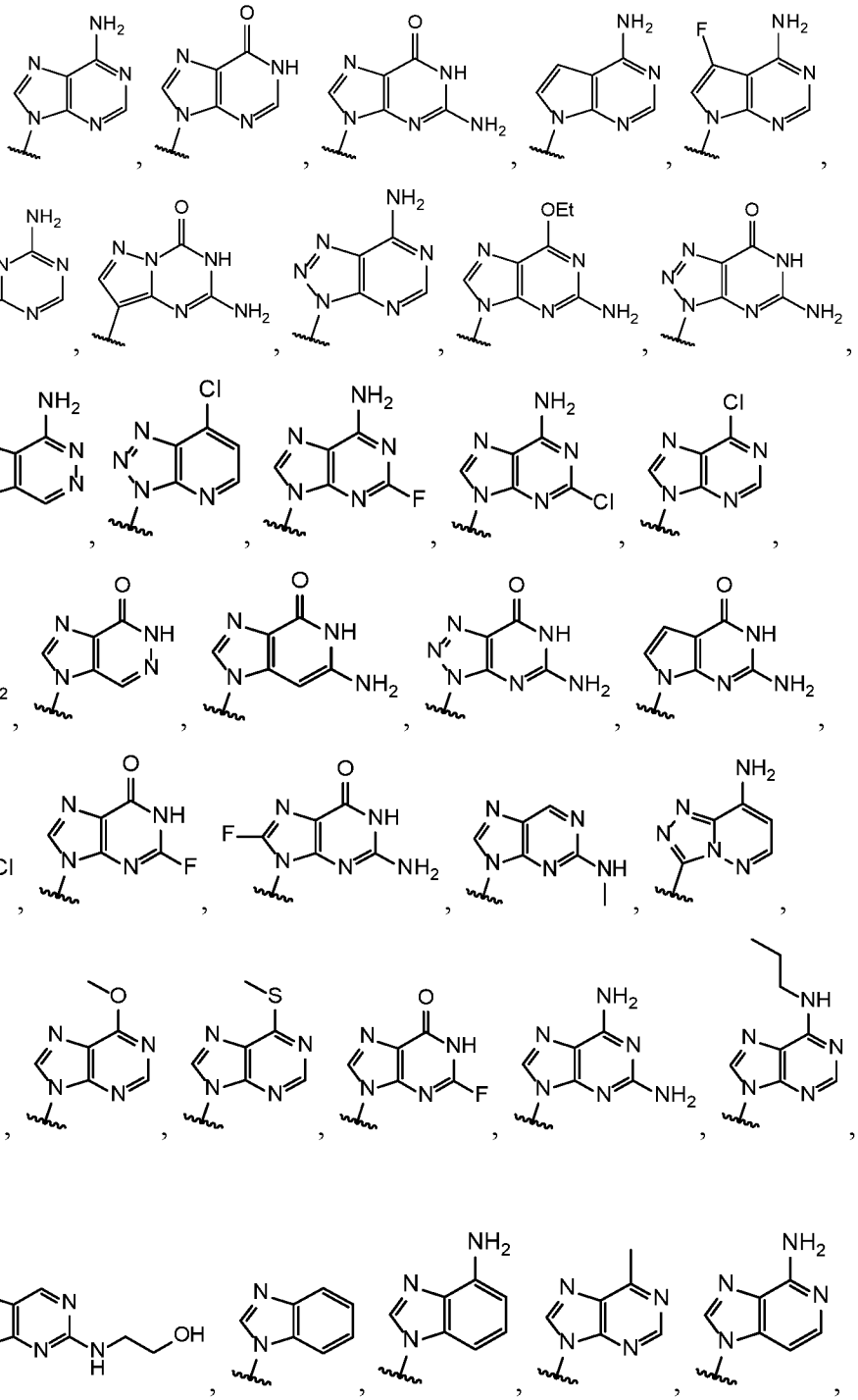
[0039] In a twenty-first embodiment, R^{7a} and R^{8a} are connected to form C_1-C_6 alkylene or C_2-C_6 alkenylene. In this embodiment, all other groups are as provided in the general formula (I) above or in the first through fourteenth embodiments described above.

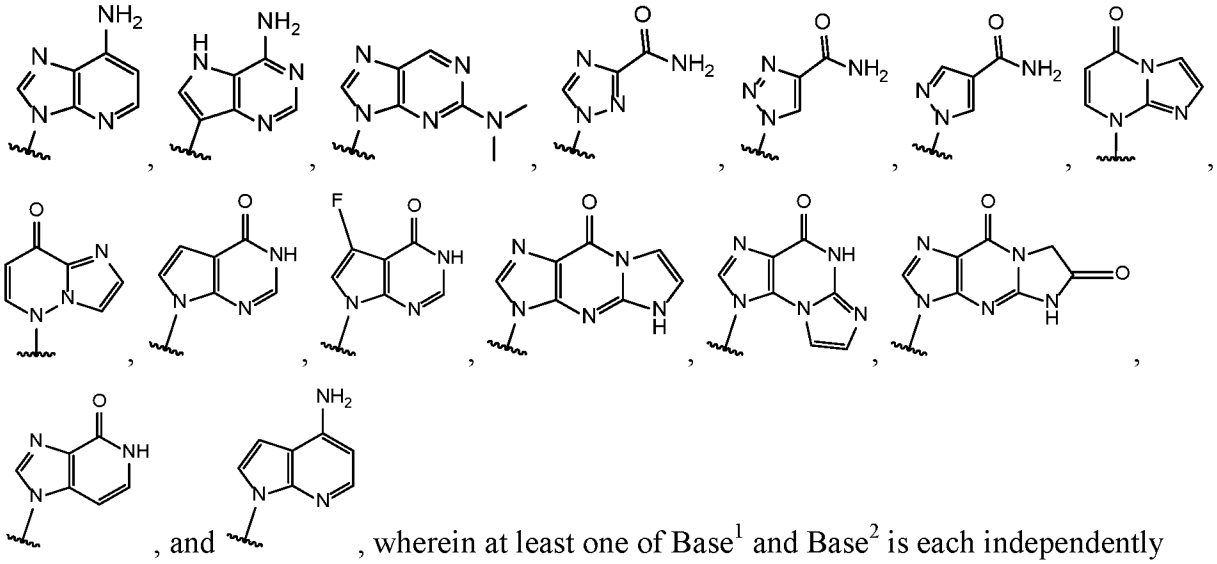
[0040] In a twenty-second embodiment, $Base^1$ and $Base^2$ are each independently selected from the group consisting of 

 ,  , and  , where at least one of Base[1] and Base[2] is each independently selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  , and  , and where Base[1] and Base[2] each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl)$_2$, and $N(C_{3-6}$ cycloalkyl)$_2$; Y and Y^a are each independently selected from the group consisting of -O- and -S-; X^a and X^{a1} are each -O-; X^b and X^{b1} are each -O-; X^c and X^{c1} are each independently selected from the group consisting of -OH and -SH; X^d and X^{d1} are each independently selected from the group consisting of O and S; R^1 and R^{1a} are each H; R^2 and R^{2a} are each independently selected from the group consisting of H, F, Cl, OH, CN, N_3, and $-CH_3$; R^3 is selected from the group consisting of H, F, Cl, OH, CN, N_3, and $-CH_3$; R^4 and R^{4a} are each independently selected from the group consisting of H, F, Cl, OH, CN, N_3, and $-CH_3$; R^5 is selected from the group consisting of H, F, Cl, OH, CN, N_3, and $-CH_3$; R^6 and R^{6a} are each independently selected from the group consisting of H, F, CN, N_3, $-CH_3$, $-CH=CH_2$, and -C≡CH; R^7 and R^{7a} are each H; R^8 and R^{8a} are each H; optionally R^3 and R^{6a} are connected to form $-O-C_1-C_6$ alkylene or $-O-C_2-C_6$ alkenylene, such that where R^3 and R^{6a} are connected to form $-O-C_1-C_6$ alkylene or $-O-C_2-C_6$ alkenylene, said O is bound at the R^3 position; and optionally R^5 and R^6 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, $-O-C_1-C_6$ alkylene, or $-O-C_2-C_6$ alkenylene, such that where R^5 and R^6 are connected to form $-O-C_1-C_6$ alkylene or $-O-C_2-C_6$ alkenylene, said O is bound at the R^5 position. In this embodiment, all other groups are as provided in the general formula (I) above or in the first through fourteenth embodiments described above.

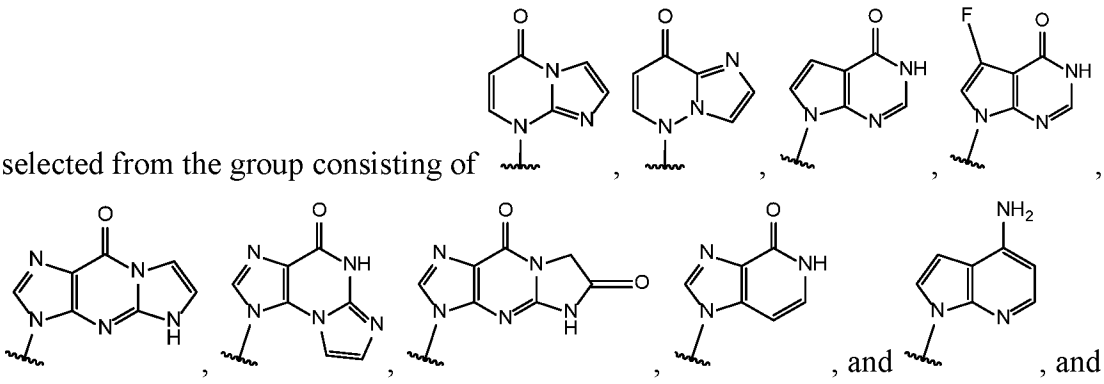
[0041] In a twenty-third embodiment, $Base^1$ and $Base^2$ are each independently selected from the group consisting of  , and , where at least one of $Base^1$ and $Base^2$ is each independently selected from the group consisting of  , and  , and where $Base^1$ and $Base^2$ each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl)$_2$, and $N(C_{3-6}$ cycloalkyl)$_2$; Y and Y^a are each independently selected from the group consisting of -O- and -S-; X^a and X^{a1} are each -O-; X^b and X^{b1} are each -O-; X^c and X^{c1} are each independently selected from the group consisting of -SH and -OH; X^d and X^{d1} are each independently selected from the group consisting of O and S; R^1 and R^{1a} are each H; R^2 is H; R^{2a} is selected from the group consisting of H, F, and OH; R^3 is selected from the group consisting of H, F, and OH; R^4 is selected from the group consisting of H, F, and OH; R^{4a} is H; R^5 is selected from the group consisting of H, F, and OH; R^6 and R^{6a} are each H; R^7 and R^{7a} are each H; and R^8 and R^{8a} are each H; and optionally R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, such that where R^3 and R^{6a} are connected to

form -O-C_1-C_6 alkylene, said O is bound at the R^3 position. In this embodiment, all other groups are as provided in the general formula (I) above or in the first through fourteenth embodiments described above.

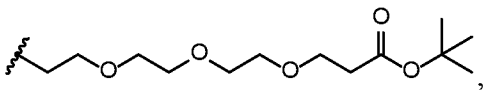
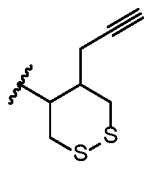
[0042] In a twenty-fourth embodiment, $Base^1$ and $Base^2$ are each independently selected from the group consisting of 

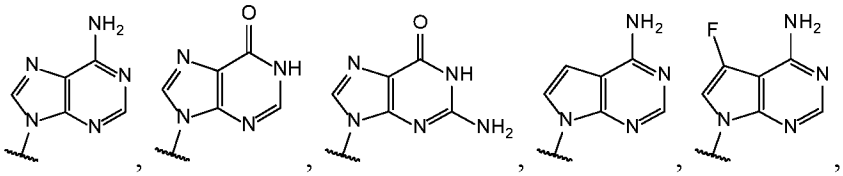


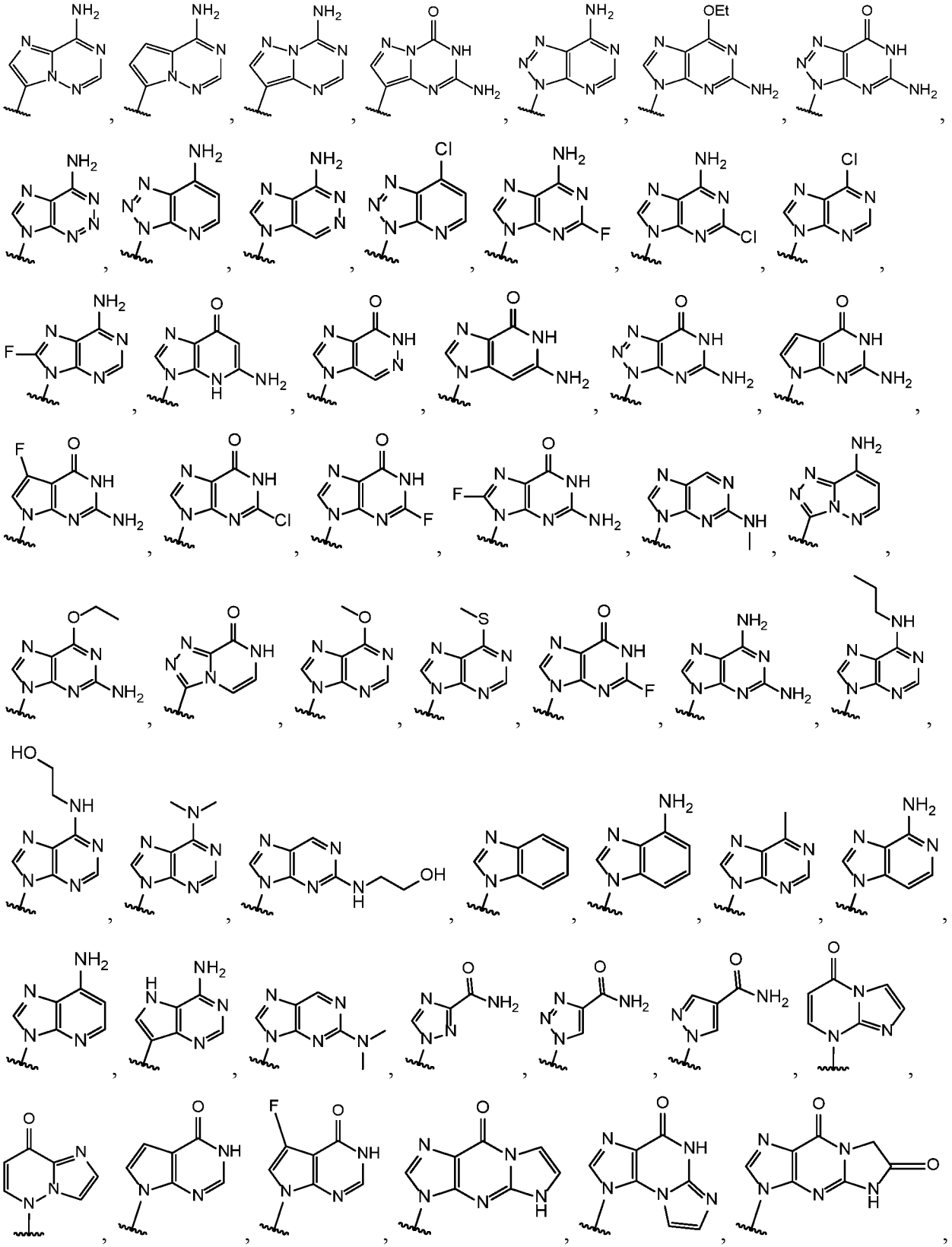
, and , wherein at least one of Base[1] and Base[2] is each independently selected from the group consisting of

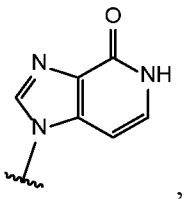
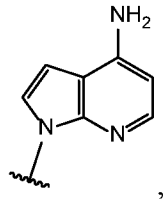


, and , and Base[1] and Base[2] each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl)$_2$, and $N(C_{3-6}$ cycloalkyl)$_2$; Y and Y^a are each independently selected from the group consisting of -O- and -S-; X^a and X^{a1} are each independently selected from the group consisting of -O- and -S-; X^b and X^{b1} are each independently selected from the group consisting of -O- and -S-; X^c and X^{c1} are each independently selected from the group consisting of $-SR^9$, $-OR^9$, and NR^9R^9; X^d and X^{d1} are each independently selected from the group consisting of O and S; R^1 and R^{1a} are each H; R^2 and R^{2a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^2 and R^{2a} C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of OH, CN, and N_3; R^3 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^3 C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of OH, CN, and N_3; R^4 and R^{4a} are each independently selected from the group consisting of H, F, Cl, I, Br, CN, OH, N_3,

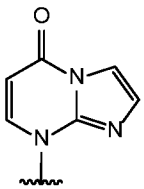
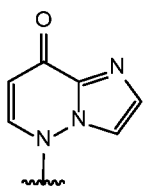
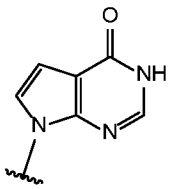
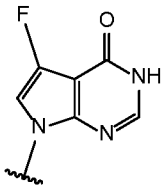
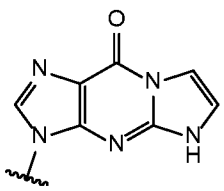
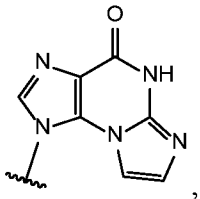
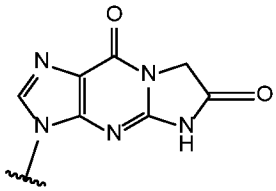
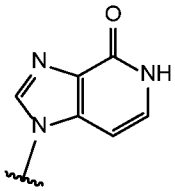
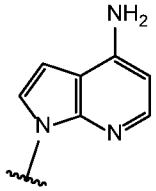
C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^4 and R^{4a} C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of OH, CN, and N_3; R^5 is selected from the group consisting of H, F, Cl, Br, I, OH, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^5 C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^6 and R^{6a} are each independently selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, where said R^6 and R^{6a} C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3; R^7 and R^{7a} are each independently selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^7 and R^{7a} C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of OH, CN, and N_3; R^8 and R^{8a} are each independently selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^8 and R^{8a} C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of OH, CN, and N_3; each R^9 is independently selected from the group consisting of H, C_1-C_6 alkyl,  , and  , where each R^9 C_1-C_6 alkyl is optionally substituted by 1 to 2 substituents independently selected from the group consisting of OH, -O-C_1-C_{20} alkyl,-S-C(O)C_1-C_6 alkyl, and -C(O)OC_1-C_6 alkyl; optionally R^3 and R^{6a} are connected to form C_2-C_6 alkylene, C_2-C_6 alkenylene,-O-C_1-C_6 alkylene, or -O-C_2-C_6 alkenylene, such that where R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene or -O-C_2-C_6 alkenylene, said O is bound at the R^3 position; and optionally R^5 and R^6 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, -O-C_1-C_6 alkylene, or -O-C_2-C_6 alkenylene, such that where R^5 and R^6 are connected to form -O-C_1-C_6 alkylene or -O-C_2-C_6 alkenylene, said O is bound at the R^5 position. In this embodiment, all other groups are as provided in the general formula (I) above or in the first through fourteenth embodiments described above.

[0043] In a twenty-fifth embodiment, $Base^1$ and $Base^2$ are each independently selected from the group consisting of  ,

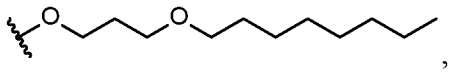
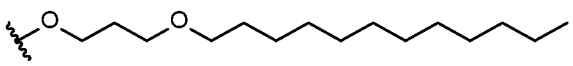
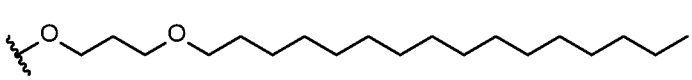
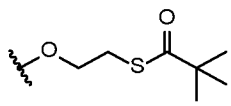
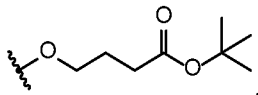
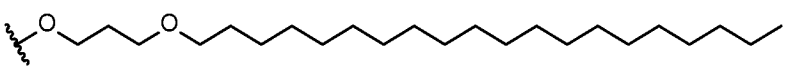
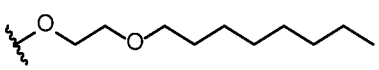
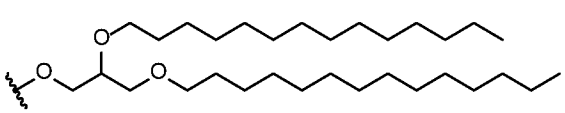
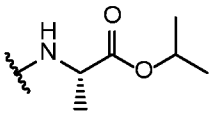
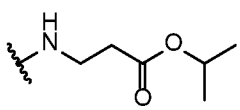
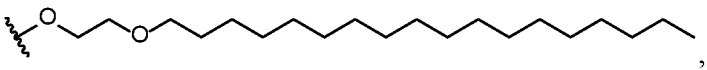
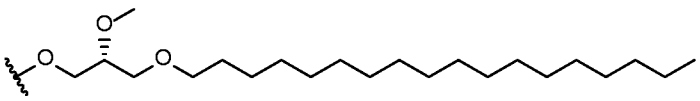
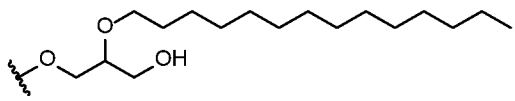


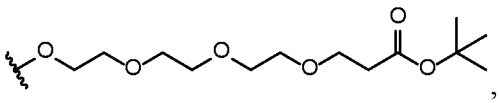
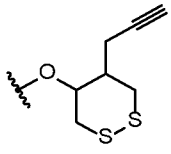



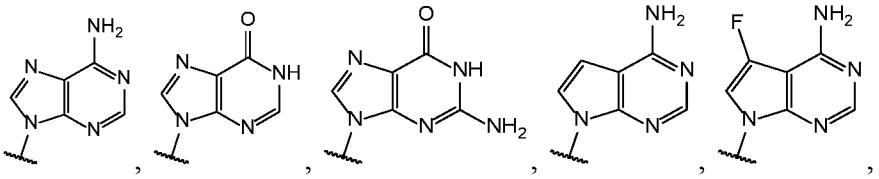
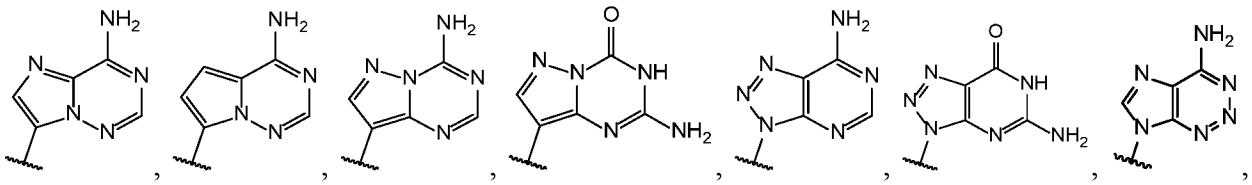
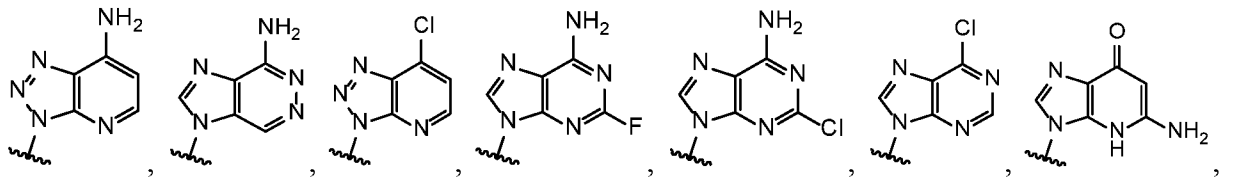
, and , wherein at least one of Base[1] and Base[2] is each independently selected from the group consisting of

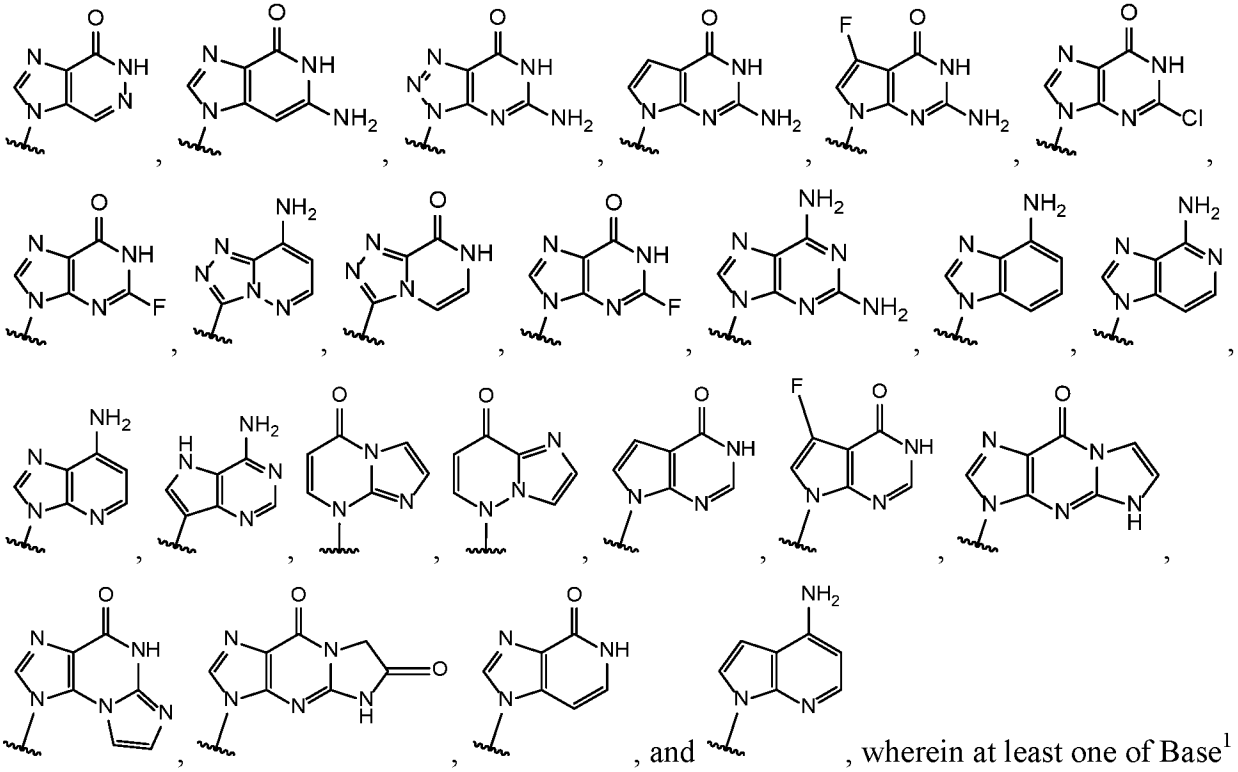










, and Base[1] and Base[2] each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl$)_2$, and $N(C_{3-6}$ cycloalkyl$)_2$; Y and Y^a are each independently selected from the group consisting of -O- and -S-; X^a and X^{a1} are each independently selected from the group consisting of -O- and -S-; X^b and X^{b1} are each independently selected from the group consisting of -O- and -S-; X^c and X^{c1} are each independently selected from the group consisting of -OH, -SH,

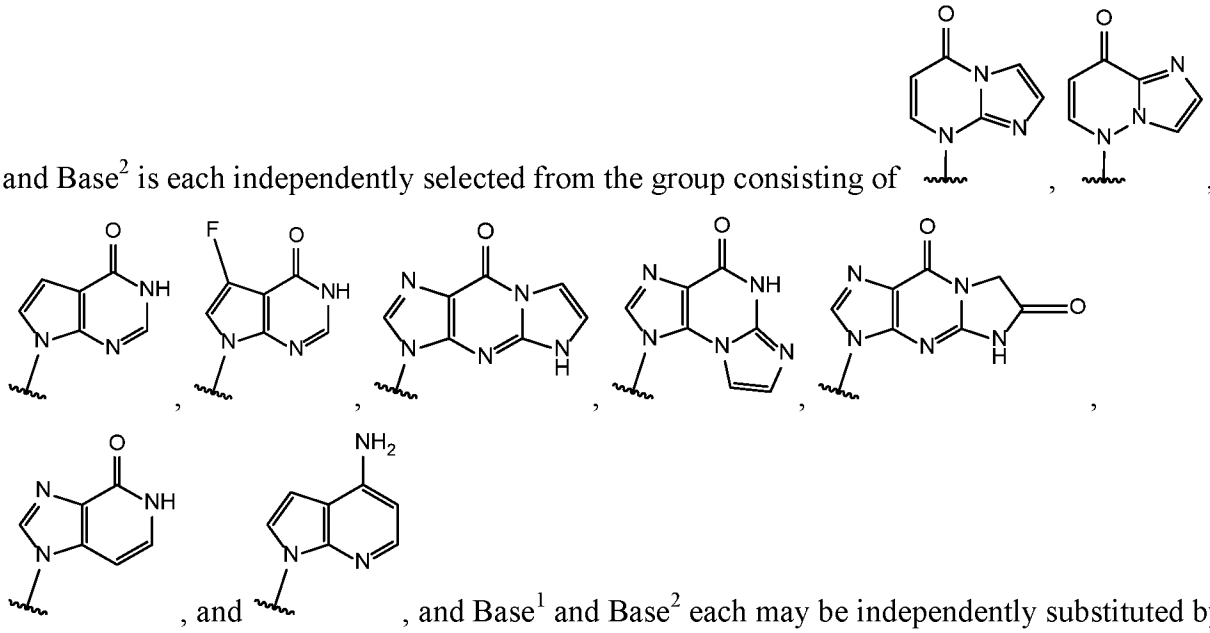














 , and  ; X^d and X^{d1} are each independently selected from the group consisting of O and S; R^1 and R^{1a} are each H; R^2 and R^{2a} are each independently selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-CH_2CH_3$; R^3 is selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-CH_2CH_3$; R^4 and R^{4a} are each independently selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-CH_2CH_3$; R^5 is selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-CH_2CH_3$; R^6 and R^{6a} are each independently selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, $-CF_3$, $-CH_3$, $-CH_2OH$, $-CH_2CH_3$, $-CH{=}CH_2$, $-C{\equiv}CH$, and $-C{\equiv}C-CH$; R^7 and R^{7a} are each independently selected from the group consisting of H, $-CF_3$, $-CH_3$, and $-CH_2CH_3$; R^8 and R^{8a} are each independently selected from the group consisting of H, $-CF_3$, $-CH_3$, and $-CH_2CH_3$; optionally R^3 and R^{6a} are connected to C_2-C_6 alkylene, C_2-C_6 alkenylene, -O-C_1-C_6 alkylene, or -O-C_2-C_6 alkenylene, such that where R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene or -O-C_2-C_6 alkenylene, said O is bound at the R^3 position; and optionally R^5 and R^6 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, -O-C_1-C_6 alkylene, or -O-C_2-C_6 alkenylene, such that where R^5 and R^6 are connected to form -O-C_1-C_6 alkylene or -O-C_2-C_6 alkenylene, said O is bound at the R^5 position. In this embodiment, all other groups are as provided in the general formula (I) above or in the first through fourteenth embodiments described above.

[0044] In a twenty-sixth embodiment, $Base^1$ and $Base^2$ are each independently selected from the group consisting of  ,  ,  , and  .

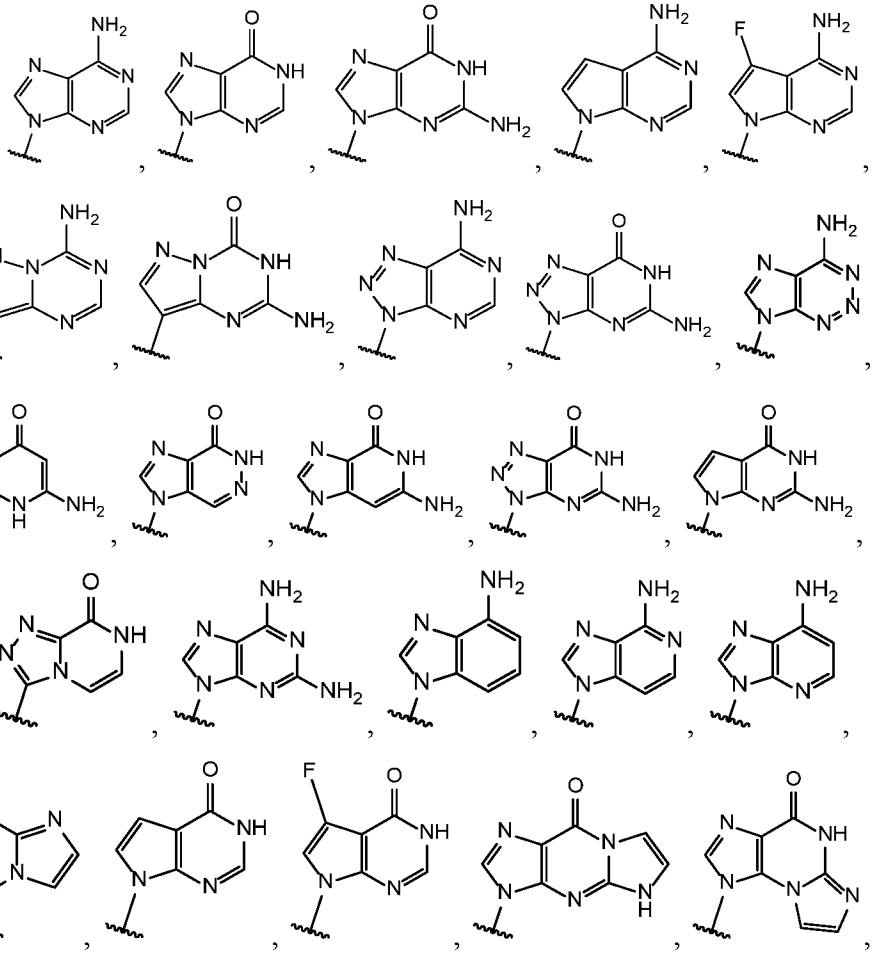


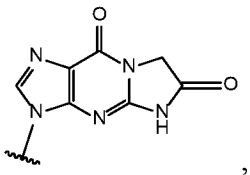
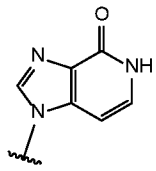
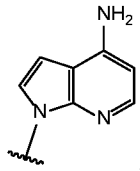
, and , wherein at least one of Base[1] and Base[2] is each independently selected from the group consisting of

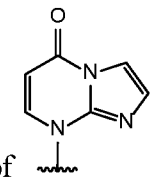
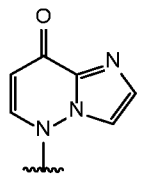
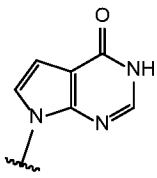
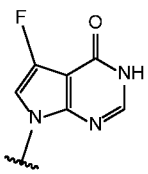
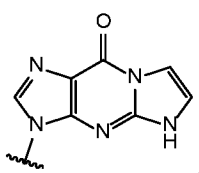
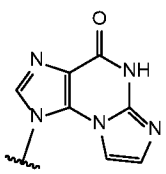
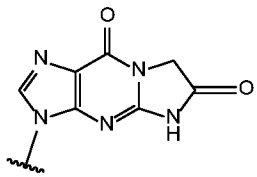
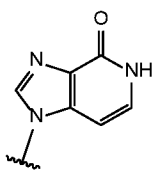
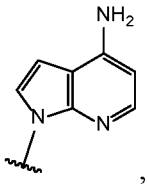


, and , and Base[1] and Base[2] each may be independently substituted by 0 to 3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl)$_2$, and $N(C_{3-6}$ cycloalkyl)$_2$; Y and Y^a are each independently selected from the group consisting of -O- and -S-; X^a and X^{a1} are each -O-; X^b and X^{b1} are each -O-; X^c and X^{c1} are each independently selected from the group consisting of -OH and -SH; X^d and X^{d1} are each independently selected from the

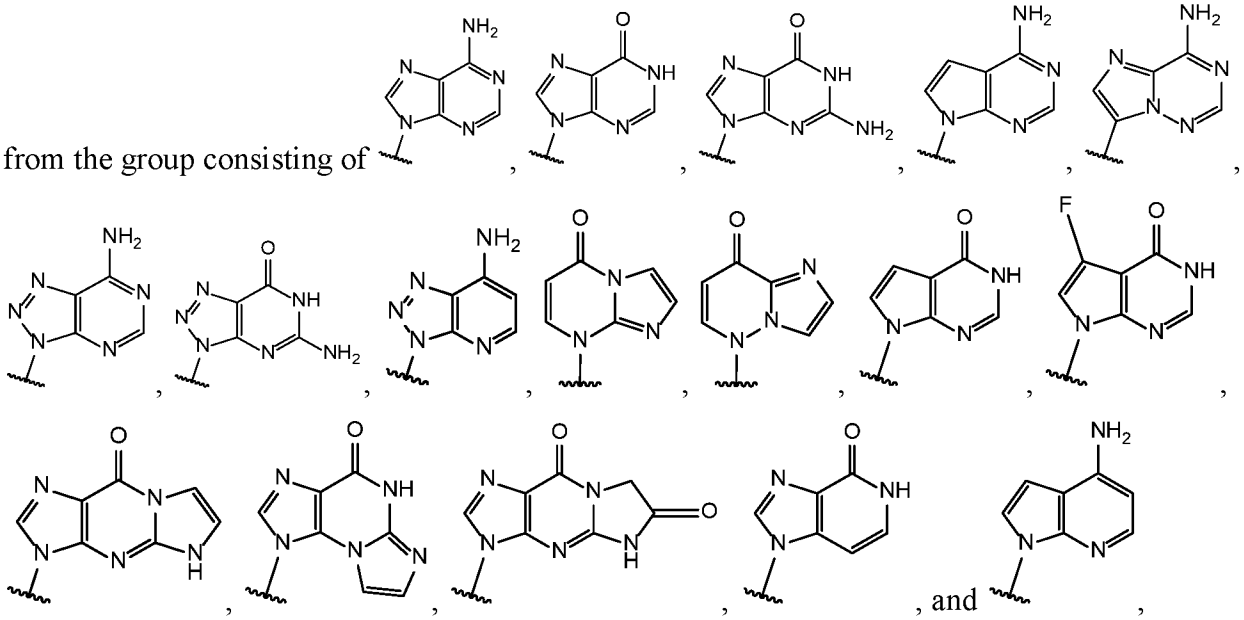
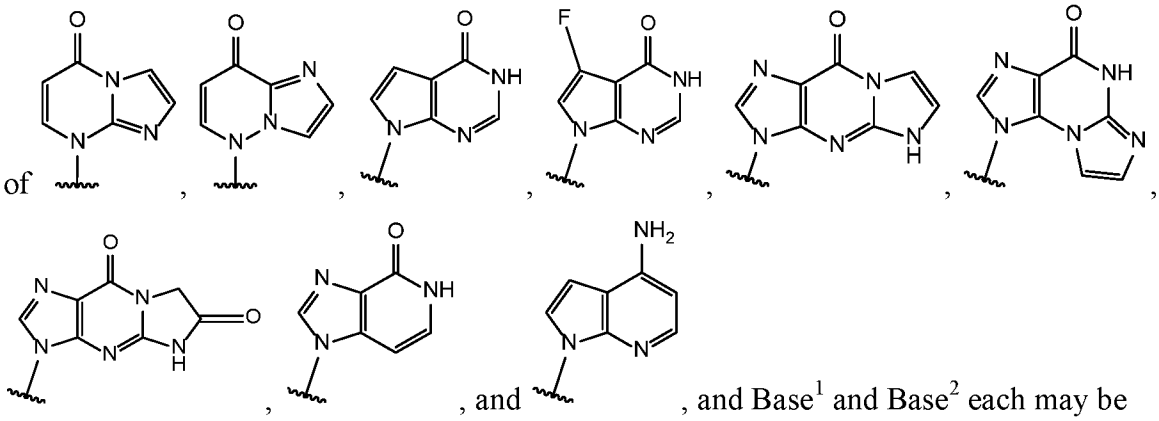
group consisting of O and S; R^1 and R^{1a} are each H; R^2 and R^{2a} are each independently selected from the group consisting of H, F, Cl, OH, CN, N_3, and $-CH_3$; R^3 is selected from the group consisting of H, F, Cl, OH, CN, N_3, and $-CH_3$; R^4 and R^{4a} are each independently selected from the group consisting of H, F, Cl, OH, CN, N_3, and $-CH_3$; R^5 is selected from the group consisting of H, F, Cl, OH, CN, N_3, and $-CH_3$; R^6 and R^{6a} are each independently selected from the group consisting of H, F, CN, N_3, $-CH_3$, $-CH=CH_2$, and $-C\equiv CH$; R^7 and R^{7a} are each H; R^8 and R^{8a} are each H; optionally R^3 and R^{6a} are connected to form $-O-C_1-C_6$ alkylene or $-O-C_2-C_6$ alkenylene, such that O is bound at the R^3 position; and optionally R^5 and R^6 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, $-O-C_1-C_6$ alkylene, or $-O-C_2-C_6$ alkenylene, such that where R^5 and R^6 are connected to form $-O-C_1-C_6$ alkylene or $-O-C_2-C_6$ alkenylene, said O is bound at the R^5 position. In this embodiment, all other groups are as provided in the general formula (I) above or in the first through fourteenth embodiments described above.

[0045] In a twenty-seventh embodiment, $Base^1$ and $Base^2$ are each independently selected from the group consisting of 

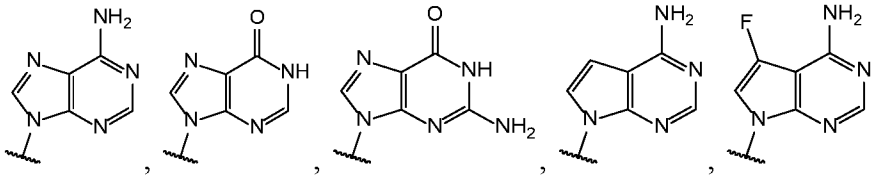
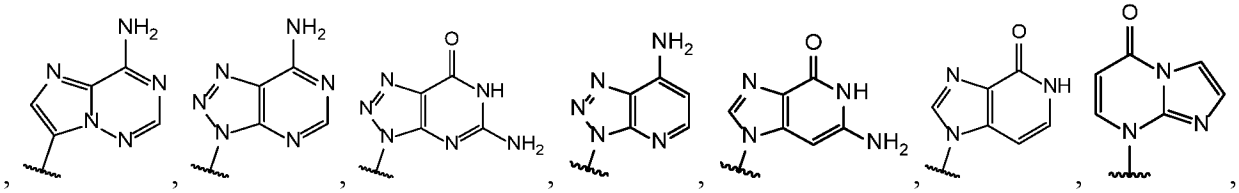
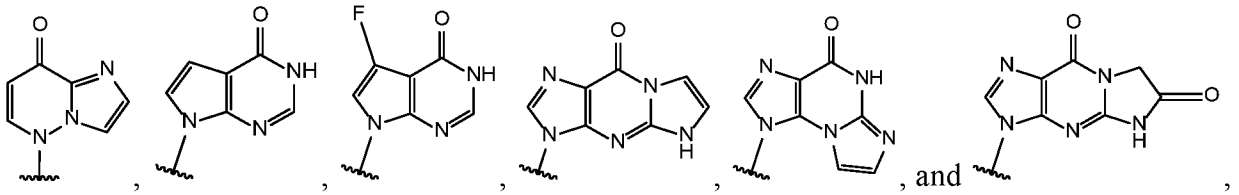
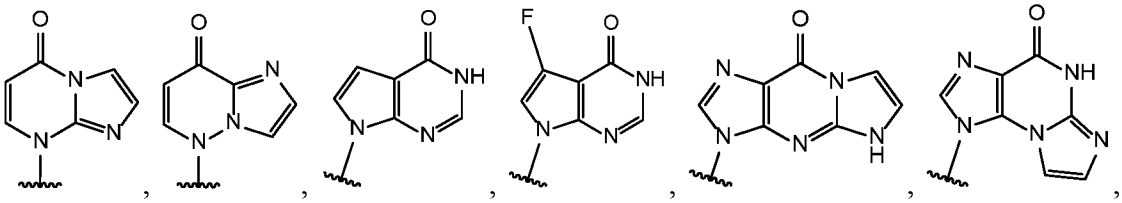
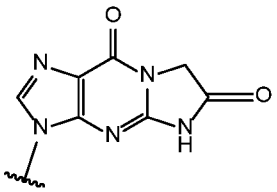



, and , wherein at least one of Base[1] and Base[2] is each independently selected from the group consisting of









, and 

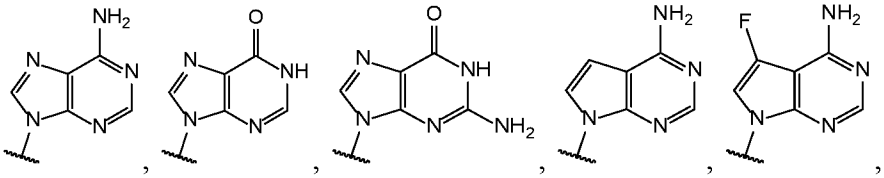
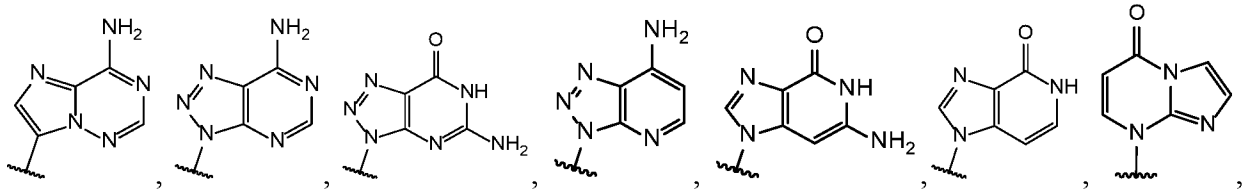
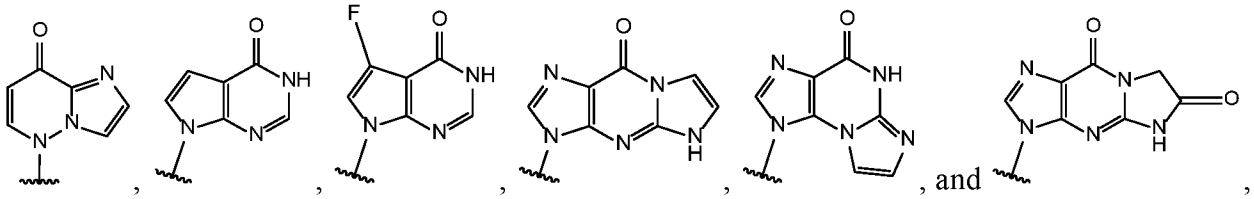
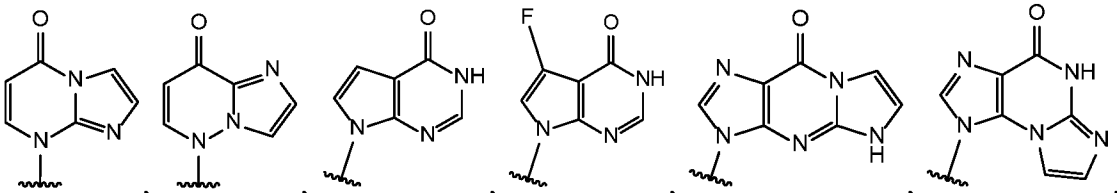
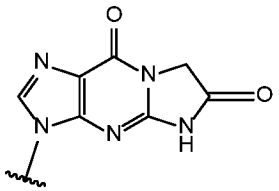
and Base[1] and Base[2] each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl)$_2$, and $N(C_{3-6}$ cycloalkyl)$_2$; Y and Y^a are each independently selected from the group consisting of -O- and -S-; X^a and X^{a1} are each -O-; X^b and X^{b1} are each -O-; X^c and X^{c1} are each independently selected from the group consisting of -OH and -SH; X^d and X^{d1} are each independently selected from the group consisting of O and S; R^1 and R^{1a} are each H; R^2 and R^{2a} are each independently selected from the group consisting of H, F, Cl, OH, CN, N_3, and $-CH_3$; R^3 is selected from the group consisting of H, F, Cl, OH, CN, N_3, and $-CH_3$; R^4 and R^{4a} are each independently selected from the group consisting of H, F, Cl, OH, CN, N_3, and CH_3; R^5 is selected from the group consisting of H, F, Cl, OH, CN, N_3, and $-CH_3$; R^6 and R^{6a} are each independently selected from the group consisting of H, F, CN, N_3, $-CH_3$, $-CH=CH_2$, and $-C\equiv CH$; R^7 and R^{7a} are each H; R^8 and R^{8a} are each H; optionally R^3 and R^{6a} are connected to form $-O-C_1-C_6$ alkylene or $-O-C_2-C_6$ alkenylene, such that where R^3 and R^{6a} are connected to form $-O-C_1-C_6$ alkylene or $-O-C_2-C_6$ alkenylene, said O is bound at the R^3 position; and optionally R^5 and R^6 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, $-O-C_1-C_6$ alkylene, or $-O-C_2-C_6$ alkenylene, such that where R^5 and R^6 are connected to form $-O-C_1-C_6$ alkylene or $-O-C_2-C_6$ alkenylene, said O is bound at the R^5 position. In this embodiment, all other groups are as provided in the general formula (I) above or in the first through fourteenth embodiments described above.

[0046] In a twenty-eighth embodiment, $Base^1$ and $Base^2$ are each independently selected from the group consisting of  , and , wherein at least one of $Base^1$ and $Base^2$ is each independently selected from the group consisting of  , and , and $Base^1$ and $Base^2$ each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl)$_2$, and $N(C_{3-6}$ cycloalkyl)$_2$; Y and Y^a are each independently selected from the group consisting of -O- and -S-; X^a and X^{a1} are each -O-; X^b and X^{b1} are each -O-; X^c and X^{c1} are each independently selected from the group consisting of -SH and -OH; X^d and X^{d1} are each independently selected from the group consisting of O and S; R^1 and R^{1a} are each H; R^2 and R^{2a} are each independently selected from the group consisting of H, F, and OH; R^3 is selected from the group consisting of H, F, and OH; R^4 and R^{4a} are each independently selected from the group consisting of H, F, and OH; R^5 is selected from the group consisting of H, F, and OH; R^6 and R^{6a} are each H; R^7 and R^{7a} are each H; R^8 and R^{8a} are each H; and optionally R^3 and R^{6a} are

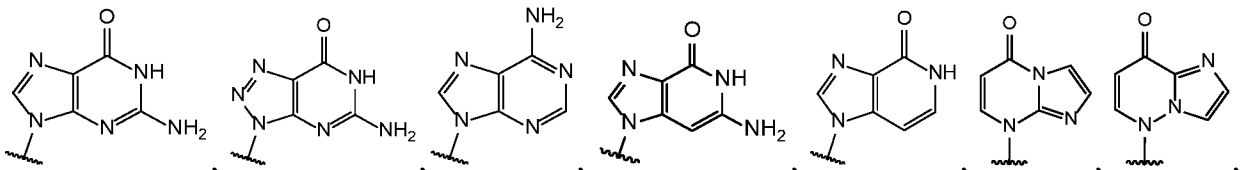
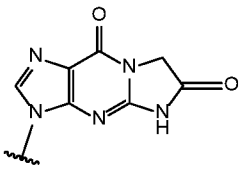
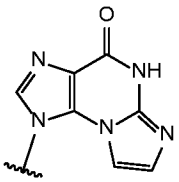
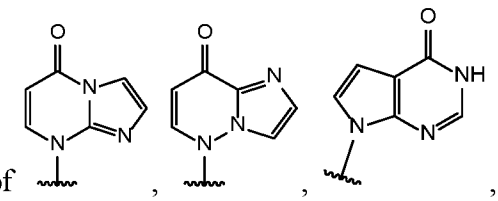
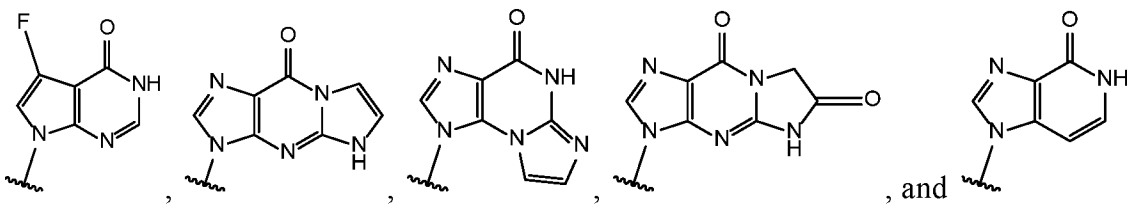
connected to form -O-C_1-C_6 alkylene or -O-C_2-C_6 alkenylene, such that where R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene or -O-C_2-C_6 alkenylene, said O is bound at the R^3 position. In this embodiment, all other groups are as provided in the general formula (I) above or in the first through fourteenth embodiments described above.

[0047] In a twenty-ninth embodiment, $Base^1$ and $Base^2$ are each independently selected from the group consisting of  ,  ,  , and , wherein at least one of $Base^1$ and $Base^2$ is each independently selected from the group consisting of  , and  , and $Base^1$ and $Base^2$ each may be independently substituted by 0 to 3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, O(C_{1-3} alkyl), O(C_{3-6} cycloalkyl), S(C_{1-3} alkyl), S(C_{3-6} cycloalkyl), NH(C_{1-3} alkyl), NH(C_{3-6} cycloalkyl), N(C_{1-3} alkyl)$_2$, and N(C_{3-6} cycloalkyl)$_2$; Y and Y^a are each independently selected from the group consisting of -O- and -S-; X^a and X^{a1} are each -O-; X^b and X^{b1} are each -O-; X^c and X^{c1} are each independently selected from the group consisting of -SH and -OH; X^d and X^{d1} are each independently selected from the group consisting of O and S; R^1 and R^{1a} are each H; R^2 is H; R^{2a} is selected from the group consisting

of H, F, and OH; R^3 is selected from the group consisting of H, F, and OH; R^4 is selected from the group consisting of H, F, and OH; R^{4a} is H; R^5 is selected from the group consisting of H, F, and OH; R^6 and R^{6a} are each H; R^7 and R^{7a} are each H; R^8 and R^{8a} are each H; and optionally R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, such that where R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, said O is bound at the R^3 position. In this embodiment, all other groups are as provided in the general formula (I) above or in the first through fourteenth embodiments described above.

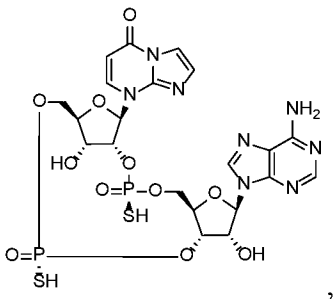
[0048] In a thirtieth embodiment, $Base^1$ and $Base^2$ are each independently selected from the group consisting of  ,  ,  , and , wherein at least one of $Base^1$ and $Base^2$ is each independently selected from the group consisting of  , and  , and $Base^1$ and $Base^2$ each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, O(C_{1-3} alkyl), O(C_{3-6} cycloalkyl), S(C_{1-3} alkyl), S(C_{3-6} cycloalkyl), NH(C_{1-3} alkyl), NH(C_{3-6} cycloalkyl), N(C_{1-3} alkyl)$_2$, and N(C_{3-6} cycloalkyl)$_2$; Y and Y^a are each independently selected from the group consisting of -O- and -S-; X^a and X^{a1}

are each -O-; X^b and X^{b1} are each -O-; X^c and X^{c1} are each independently selected from the group consisting of -SH and -OH; X^d and X^{d1} are each independently selected from the group consisting of O and S; R^1 and R^{1a} are each H; R^2 is H; R^{2a} is selected from the group consisting of H, F, and OH; R^3 is selected from the group consisting of H, F, and OH; R^4 is selected from the group consisting of H, F, and OH; R^{4a} is H; R^5 is selected from the group consisting of H, F, and OH; R^6 and R^{6a} are each H; R^7 and R^{7a} are each H; and R^8 and R^{8a} are each H. In this embodiment, all other groups are as provided in the general formula (I) above or in the first through fourteenth embodiments described above.

[0049] In a thirty-first embodiment, $Base^1$ is selected from the group consisting of  , and  ; $Base^2$ is selected from the group consisting of  , and  ; where at least one of $Base^1$ and $Base^2$ is each independently selected from the group consisting of  , and  , and where $Base^1$ and $Base^2$ each may be independently substituted by 0-3 substituents R^{10}, where

each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl)$_2$, and $N(C_{3-6}$ cycloalkyl)$_2$; Y and Y^a are each independently selected from the group consisting of -O- and -S-; X^a and X^{a1} are each -O-; X^b and X^{b1} are each -O-; X^c and X^{c1} are each independently selected from the group consisting of -SH and -OH; X^d and X^{d1} are each independently selected from the group consisting of O and S; R^1 and R^{1a} are each H; R^2 is H; R^{2a} is selected from the group consisting of H, F, and OH; R^4 is selected from the group consisting of H, F, and OH; R^{4a} is H; R^5 is selected from the group consisting of H, F, and OH; R^6 is H; R^7 and R^{7a} are each H; and R^8 and R^{8a} are each H; and optionally R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, such that where R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, said O is bound at the R^3 position. In this embodiment, all other groups are as provided in the general formula (I) above or in the first through fourteenth embodiments described above.

[0050] A thirty-second embodiment relates to a compound selected from the group consisting of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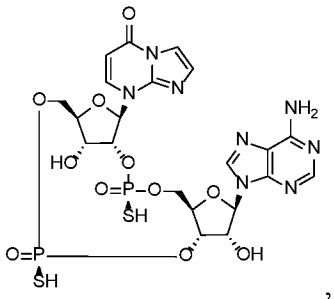
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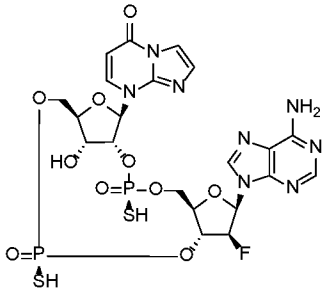
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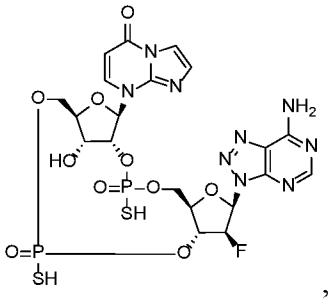
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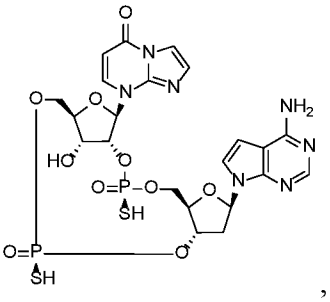
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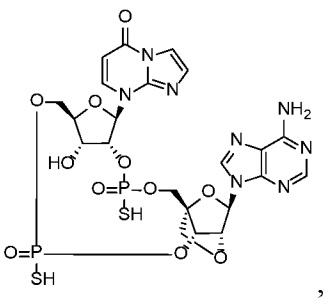
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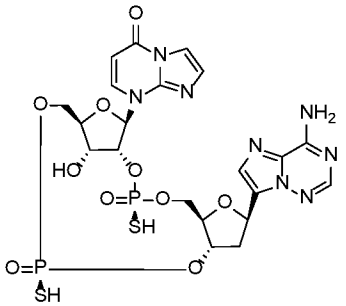
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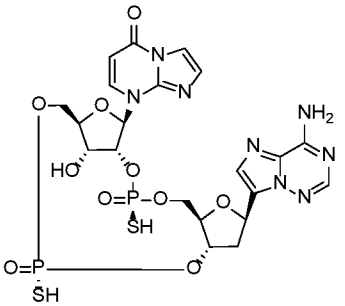
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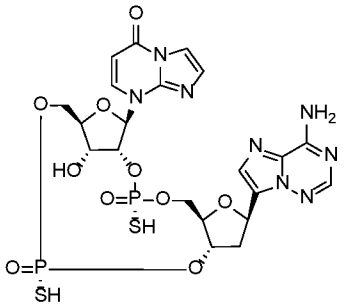
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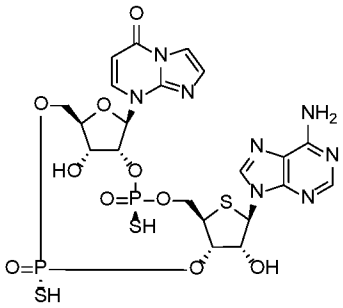
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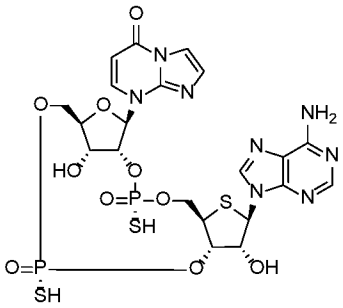
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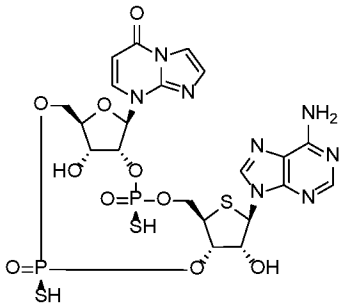
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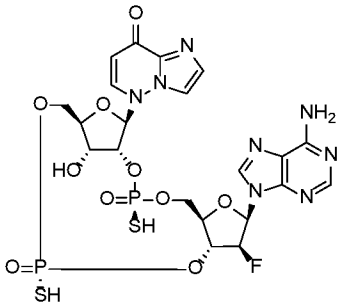
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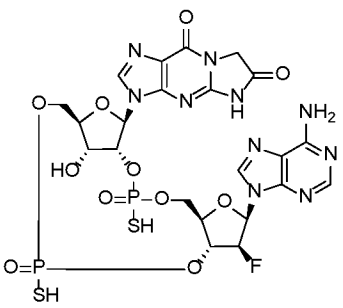
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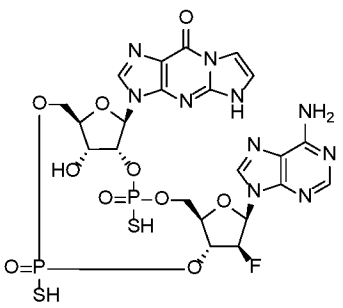
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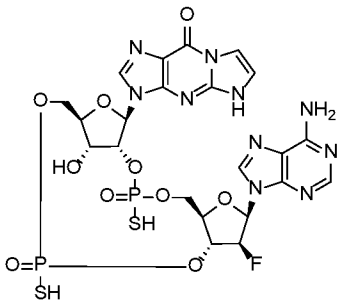
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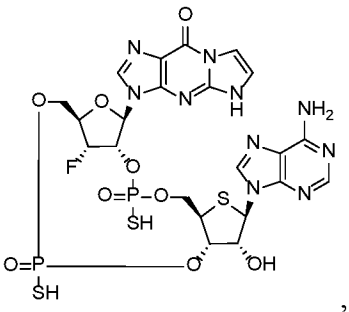
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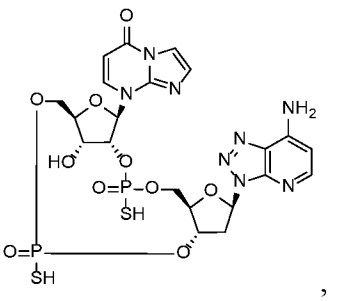
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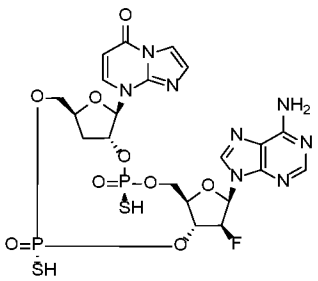
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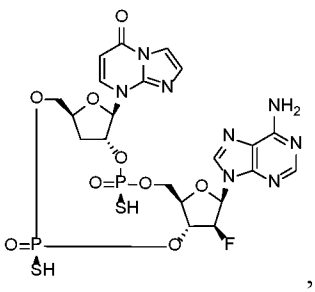
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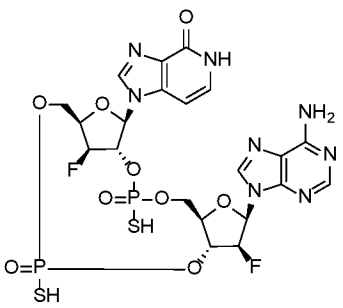
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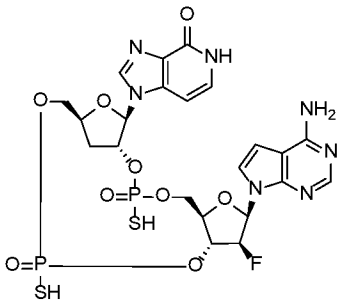
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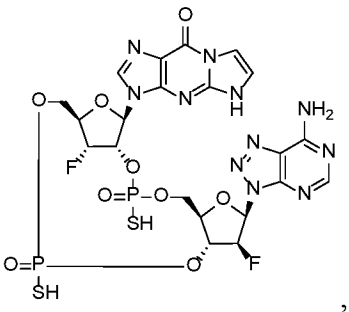
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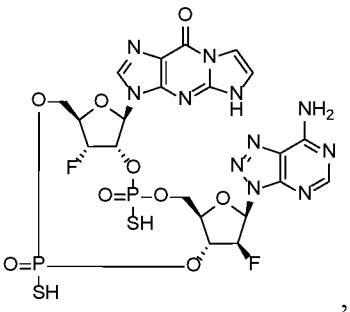
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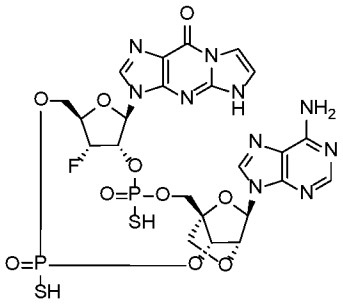
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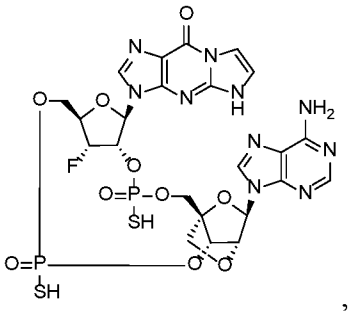
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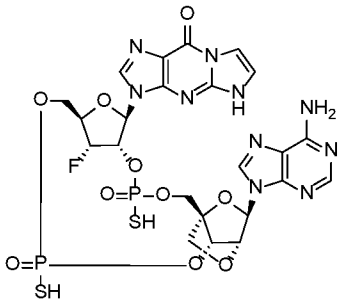
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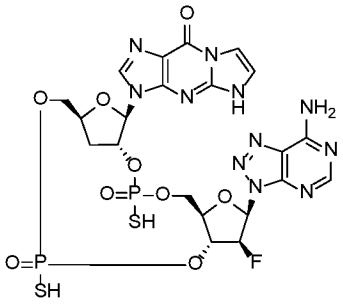
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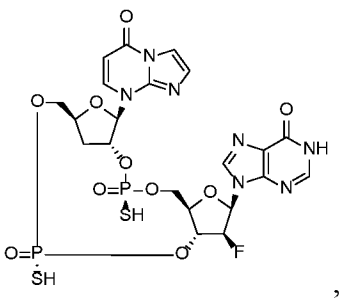
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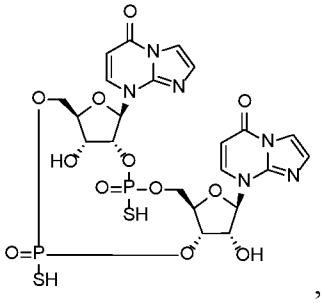
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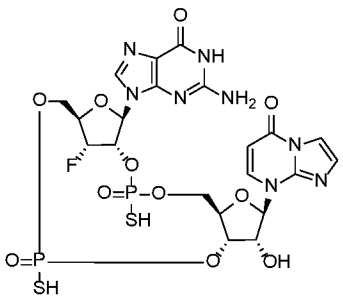
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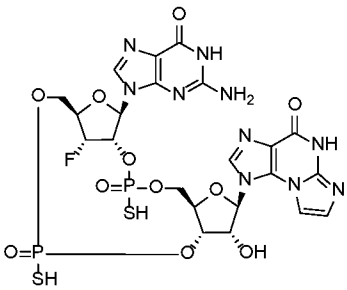
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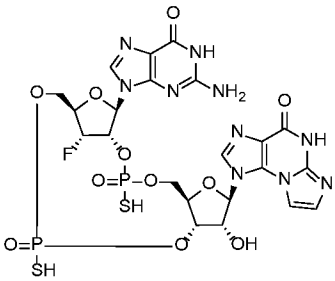
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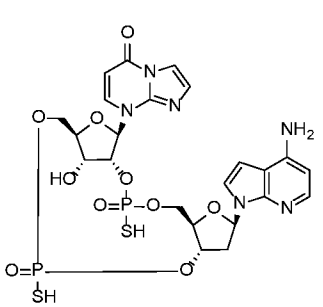
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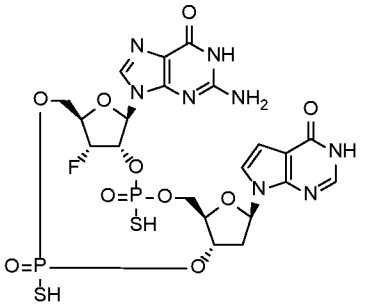
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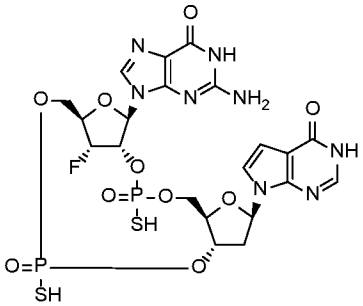
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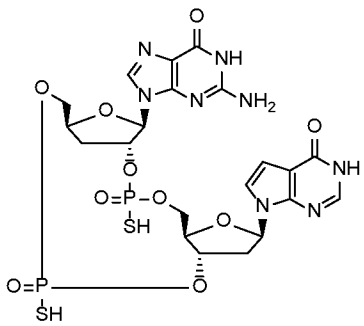
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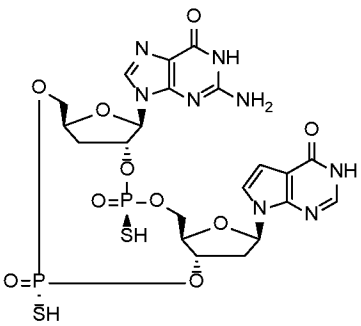
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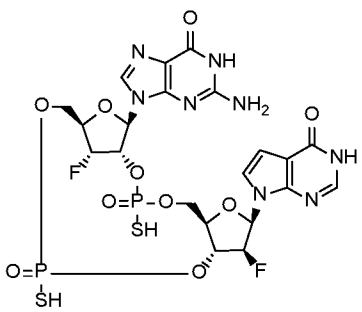
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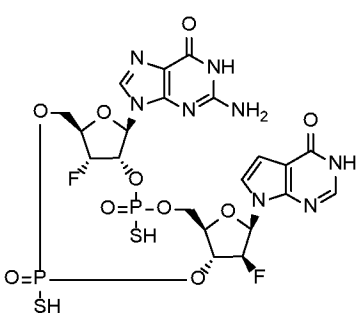
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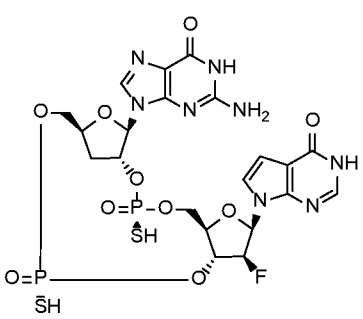
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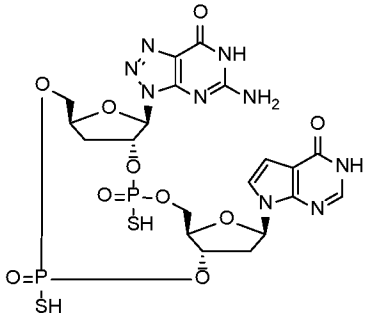
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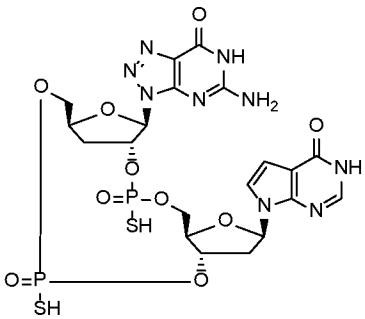
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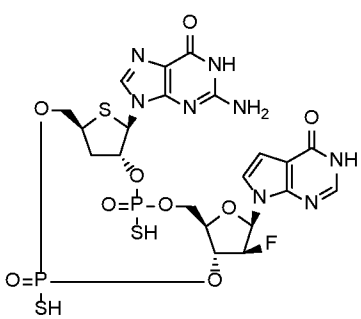
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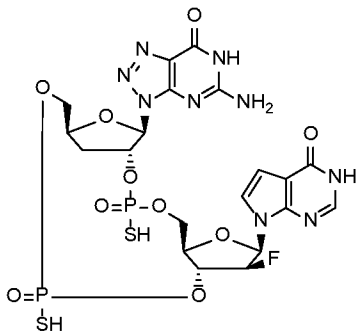
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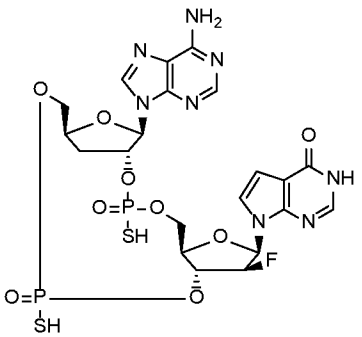
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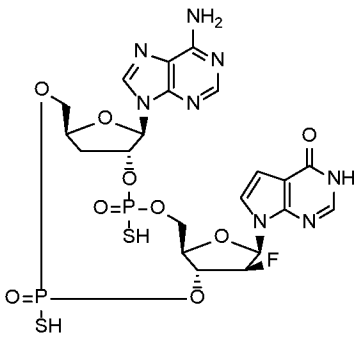
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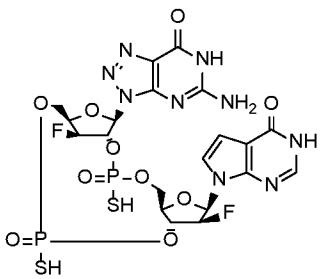
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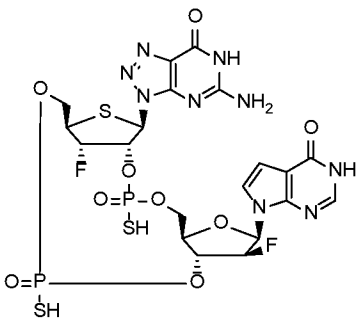
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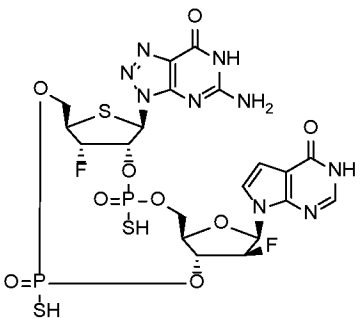
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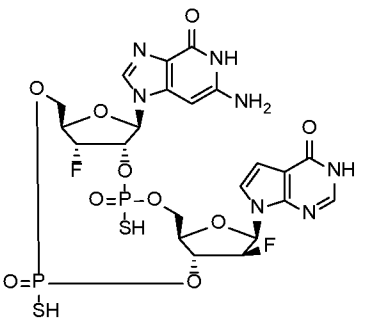
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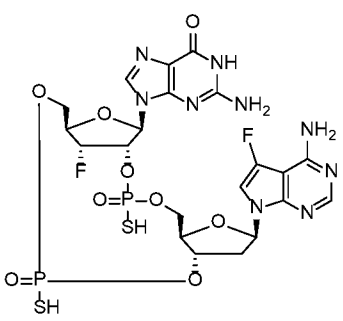
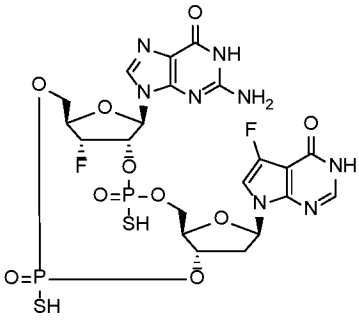
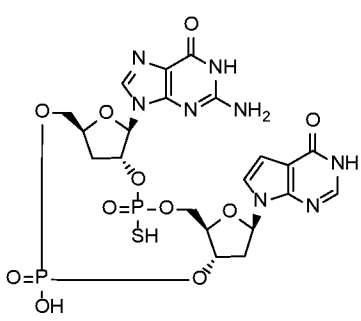




pharmaceutically acceptable salts thereof.

[0051] A thirty-third embodiment relates to a pharmaceutical composition, said pharmaceutical composition comprising (a) a compound according to any one of general formula (I) above or the first through thirty-second embodiments above or a pharmaceutically acceptable salt thereof; and (b) a pharmaceutically acceptable carrier.

[0052] A thirty-fourth embodiment relates to methods of inducing an immune response in a subject, comprising administering a therapeutically effective amount of a compound according to any one of general formula (I) above or the first through thirty-second embodiments above or a pharmaceutically acceptable salt thereof to the subject.

[0053] A thirty-fifth embodiment relates to methods of inducing an immune response in a subject, comprising administering a therapeutically effective amount of a composition according to the thirty-third embodiment above to the subject.

[0054] A thirty-sixth embodiment relates to methods of inducing STING-dependent type I interferon production in a subject, comprising administering a therapeutically effective amount of a compound according to any one of general formula (I) above or the first through thirty-second embodiments above or a pharmaceutically acceptable salt thereof to the subject.

[0055] A thirty-seventh embodiment relates to methods of inducing STING-dependent type I interferon production in a subject, comprising administering a therapeutically effective amount of a composition according to the thirty-third embodiment above to the subject.

[0056] A thirty-eighth embodiment relates to methods of inducing STING-dependent cytokine production in a subject, comprising administering a therapeutically effective amount of a compound according to any one of general formula (I) above or the first through thirty-second embodiments above or a pharmaceutically acceptable salt thereof to the subject.

[0057] A thirty-ninth embodiment relates to methods of inducing a STING-dependent cytokine production in a subject, comprising administering a therapeutically effective amount of a composition according to the thirty-third embodiment above to the subject.

[0058] A fortieth embodiment relates to a compound selected from the exemplary species depicted in Examples 1 through 54 shown below.

[0059] A forty-first embodiment relates to a pharmaceutical composition, said pharmaceutical composition comprising (a) a compound according to the fortieth embodiment above or a pharmaceutically acceptable salt thereof; and (b) a pharmaceutically acceptable carrier.

[0060] A forty-second embodiment relates to methods of inducing an immune response in a subject, comprising administering a therapeutically effective amount of a compound according to the fortieth embodiment above or a pharmaceutically acceptable salt thereof to the subject.

[0061] A forty-third embodiment relates to methods of inducing an immune response in a subject, comprising administering a therapeutically effective amount of a composition according to the forty-first embodiment above to the subject.

[0062] A forty-fourth embodiment relates to methods of inducing STING-dependent type I interferon production in a subject, comprising administering a therapeutically effective amount of a compound according to the fortieth embodiment above or a pharmaceutically acceptable salt thereof to the subject.

[0063] A forty-fifth embodiment relates to methods of inducing STING-dependent type I interferon production in a subject, comprising administering a therapeutically effective amount of a composition according to the forty-first embodiment above to the subject.

[0064] A forty-sixth embodiment relates to methods of inducing STING-dependent cytokine production in a subject, comprising administering a therapeutically effective amount of a compound according to the fortieth embodiment above or a pharmaceutically acceptable salt thereof to the subject.

[0065] A forty-seventh embodiment relates to methods of inducing STING-dependent cytokine production in a subject, comprising administering a therapeutically effective amount of a composition according to the forty-first embodiment above to the subject.

[0066] Other embodiments of the present disclosure include the following:

(a) A pharmaceutical composition comprising an effective amount of a compound of general formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

(b) The pharmaceutical composition of (a), further comprising an active agent selected from the group consisting of STING agonist compounds, anti-viral compounds,

antigens, adjuvants, CTLA-4 and PD-1 pathway antagonists and other immunomodulatory agents, lipids, liposomes, peptides, anti-cancer and chemotherapeutic agents.

(c) A pharmaceutical combination that is (i) a compound of general formula (I), or a pharmaceutically acceptable salt thereof, and (ii) an active agent selected from the group consisting of STING agonist compounds, anti-viral compounds, antigens, adjuvants, CTLA-4 and PD-1 pathway antagonists and other immunomodulatory agents, lipids, liposomes, peptides, anti-cancer and chemotherapeutic agents; wherein the compound of general formula (I), or pharmaceutically acceptable salt thereof, and the active agent are each employed in an amount that renders the combination effective for inducing an immune response in a patient.

(d) A method of inducing an immune response in a patient, which comprises administering to the subject a therapeutically effective amount of a compound of general formula (I), or a pharmaceutically acceptable salt thereof.

(e) A method of inducing an immune response in a patient, which comprises administering to the subject a therapeutically effective amount of a composition of (a), a composition of (b), or a combination of (c).

(f) A method of inducing STING-dependent type I interferon production in a patient, which comprises administering to the subject a therapeutically effective amount of a compound of general formula (I), or a pharmaceutically acceptable salt thereof.

(g) A method of inducing STING-dependent type I interferon production in a patient, which comprises administering to the subject a therapeutically effective amount of a composition of (a), a composition of (b), or a combination of (c).

(h) A method of inducing STING-dependent cytokine production in a patient, which comprises administering to the subject a therapeutically effective amount of a compound of general formula (I), or a pharmaceutically acceptable salt thereof.

(i) A method of inducing STING-dependent cytokine production in a patient, which comprises administering to the subject a therapeutically effective amount of a composition of (a), a composition of (b), or a combination of (c).

(j) A method of treating a cell proliferation disorder in a subject, said method comprising administering a therapeutically effective amount of a compound of general formula (I), or a pharmaceutically acceptable salt thereof to the subject;

(k) The method of (j), wherein the cell proliferation disorder is cancer.

(l) A method of treating a cell proliferation disorder in a subject, said method comprising administering a therapeutically effective amount of a composition of (a), a composition of (b), or a combination of (c) to the subject.

[0067] The present disclosure also includes a compound of the present disclosure for use (i) in, (ii) as a medicament for, or (iii) in the preparation of a medicament for: (a) inducing an immune response in a patient, or (b) inducing STING-dependent cytokine production in a patient. In these uses, the compounds of the present disclosure can optionally be employed in combination with one or more active agents selected from STING agonist compounds, anti-viral compounds, antigens, adjuvants, CTLA-4 and PD-1 pathway antagonists and other immunomodulatory agents, lipids, liposomes, peptides, anti-cancer agents, and chemotherapeutic agents.

[0068] Additional embodiments of the disclosure include the pharmaceutical compositions, combinations and methods set forth in (a) through (l) above and the uses set forth in the preceding paragraph, wherein the compound of the present disclosure employed therein is a compound of one of the embodiments, aspects, instances, occurrences, or features of the compounds described above. In all of these embodiments, the compound may optionally be used in the form of a pharmaceutically acceptable salt, as appropriate.

[0069] In the embodiments of the compound provided above, it is to be understood that each embodiment may be combined with one or more other embodiments, to the extent that such a combination provides a stable compound and is consistent with the description of the embodiments. It is further to be understood that the embodiments of compositions and methods provided as (a) through (l) above are understood to include all embodiments of the compounds, including such embodiments as result from combinations of embodiments.

[0070] The term “subject” (alternatively “patient”) as used herein refers to a mammal that has been the object of treatment, observation, or experiment. The mammal may be male or female. The mammal may be one or more selected from the group consisting of humans, bovine (*e.g.*, cows), porcine (*e.g.*, pigs), ovine (*e.g.*, sheep), capra (*e.g.*, goats), equine (*e.g.*, horses), canine (*e.g.*, domestic dogs), feline (*e.g.*, house cats), Lagomorpha (rabbits), rodents (*e.g.*, rats or mice), Procyon lotor (*e.g.*, raccoons). In particular embodiments, the subject is human.

[0071] As used herein, the term “immune response” relates to any one or more of the following: specific immune response, non-specific immune response, both specific and non-specific response, innate response, primary immune response, adaptive immunity, secondary

immune response, memory immune response, immune cell activation, immune cell proliferation, immune cell differentiation, and cytokine expression. In certain embodiments, a compound of general formula (I), or a pharmaceutically acceptable salt of the foregoing, is administered in conjunction with one or more additional therapeutic agents including anti-viral compounds, vaccines intended to stimulate an immune response to one or more predetermined antigens, adjuvants, CTLA-4 and PD-1 pathway antagonists and other immunomodulatory agents, lipids, liposomes, peptides, anti-cancer agents, and chemotherapeutic agents, etc. In certain embodiments, a compound of general formula (I), or a pharmaceutically acceptable salt of the foregoing, is administered in conjunction with one or more additional compositions including anti-viral compounds, vaccines intended to stimulate an immune response to one or more predetermined antigens, adjuvants, CTLA-4 and PD-1 pathway antagonists and other immunomodulatory agents, lipids, liposomes, peptides, anti-cancer agents, and chemotherapeutic agents, etc.

[0072] Compounds

[0073] The term "alkyl" refers to a monovalent straight or branched chain, saturated aliphatic hydrocarbon radical having a number of carbon atoms in the specified range. Thus, for example, "C_{1-6} alkyl" (or "C_1-C_6 alkyl") refers to any of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec- and *tert*-butyl, n- and iso-propyl, ethyl, and methyl. As another example, "C_{1-4} alkyl" refers to n-, iso-, sec- and *tert*-butyl, n- and isopropyl, ethyl, and methyl.

[0074] As used herein, the term "alkylene" refers to a bivalent straight chain, saturated aliphatic hydrocarbon radical having a number of carbon atoms in the specified range.

[0075] As used herein, the term "alkenyl" refers to a monovalent straight or branched chain, unsaturated aliphatic hydrocarbon radical having a number of carbon atoms in the specified range and including one or more double bond.

[0076] As used herein, the term "alkenylene" refers to a bivalent straight chain, unsaturated aliphatic hydrocarbon radical having a number of carbon atoms in the specified range and including one or more double bond.

[0077] As used herein, the term "alkynyl" refers to a monovalent straight or branched chain, unsaturated aliphatic hydrocarbon radical having a number of carbon atoms in the specified range and including one or more triple bond.

[0078] As used herein, the term "alkynylene" refers to a bivalent straight chain, unsaturated aliphatic hydrocarbon radical having a number of carbon atoms in the specified range and including one or more triple bond. The term "halogen" (or "halo") refers to fluorine, chlorine, bromine, and iodine (alternatively referred to as fluoro, chloro, bromo, and iodo or F, Cl, Br, and I).

[0079] The term "haloalkyl" refers to an alkyl group as defined above in which one or more of the hydrogen atoms have been replaced with a halogen. Thus, for example, "$C_{1\text{-}6}$ haloalkyl" (or "C_1-C_6 haloalkyl") refers to a C_1 to C_6 linear or branched alkyl group as defined above with one or more halogen substituents. The term "fluoroalkyl" has an analogous meaning except the halogen substituents are restricted to fluoro. Suitable fluoroalkyls include the series $(CH_2)_{0\text{-}4}CF_3$ (*i.e.*, trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoro-n-propyl, etc.).

[0080] As used herein, the term "haloalkenyl" refers to an alkenyl group as defined above in which one or more of the hydrogen atoms have been replaced with a halogen.

[0081] As used herein, the term "haloalkynyl" refers to an alkynyl group as defined above in which one or more of the hydrogen atoms have been replaced with a halogen.

[0082] As used herein, the term "alkoxy" as used herein, alone or in combination, includes an alkyl group connected to the oxy connecting atom. The term "alkoxy" also includes alkyl ether groups, where the term "alkyl" is defined above, and "ether" means two alkyl groups with an oxygen atom between them. Examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, methoxymethane (also referred to as "dimethyl ether"), and methoxyethane (also referred to as "ethyl methyl ether").

[0083] As used herein, the term "cycloalkyl" refers to a saturated hydrocarbon containing one ring having a specified number of carbon atoms. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0084] As used herein, the term "heterocycle", "heterocyclyl", or "heterocyclic", as used herein, represents a stable 3- to 6-membered monocyclic that is either saturated or unsaturated, and that consists of carbon atoms and from one to two heteroatoms selected from the group consisting of N, O, and S. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. The term includes heteroaryl moieties. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl,

dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, 1,3-dioxolanyl, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, triazolyl, and thienyl.

[0085] As used herein, the term "spirocycle" or "spirocyclic ring" refers to a pendant cyclic group formed by substituents on a single atom.

[0086] The term "compound" refers to the compound and, in certain embodiments, to the extent they are stable, any hydrate or solvate thereof. A hydrate is the compound complexed with water, and a solvate is the compound complexed with a solvent, which may be an organic solvent or an inorganic solvent.

[0087] A "stable" compound is a compound that can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a period of time sufficient to allow use of the compound for the purposes described herein (*e.g.*, therapeutic administration to a subject). The compounds of the present invention are limited to stable compounds embraced by general formula (I), or pharmaceutically acceptable salts thereof.

[0088] Unless expressly stated to the contrary, all ranges cited herein are inclusive; *i.e.*, the range includes the values for the upper and lower limits of the range as well as all values in between. As an example, temperature ranges, percentages, ranges of equivalents, and the like described herein include the upper and lower limits of the range and any value in the continuum there between. Numerical values provided herein, and the use of the term "about", may include variations of ± 1%, ± 2%, ±3%, ± 4%, ± 5%, ± 10%, ± 15%, and ± 20% and their numerical equivalents. As used herein, the term "one or more" item includes a single item selected from the list as well as mixtures of two or more items selected from the list.

[0089] In the compounds of general formula (I), and pharmaceutically acceptable salts of the foregoing, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present disclosure is meant to include all suitable isotopic variations of the

compounds of general formula (I), and pharmaceutically acceptable salts of the foregoing. For example, different isotopic forms of hydrogen (H) include protium (^{1}H), deuterium (^{2}H), and tritium (^{3}H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds within general formula (I), and the pharmaceutically acceptable salts of the foregoing, can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates.

[0090] In particular embodiments of the compounds of general formula (I), and/or pharmaceutically acceptable salts of the foregoing, the compounds are isotopically enriched with deuterium. In aspects of these embodiments, one or more of $Base^{1}$, $Base^{2}$, Y, Y^{a}, X^{a}, X^{a1}, X^{b}, X^{b1}, R^{1}, R^{1a}, R^{2}, R^{2a}, R^{3}, R^{4}, R^{4a}, R^{5}, R^{6}, R^{6a}, R^{7}, R^{7a}, R^{8}, R^{8a}, and R^{9} may include deuterium.

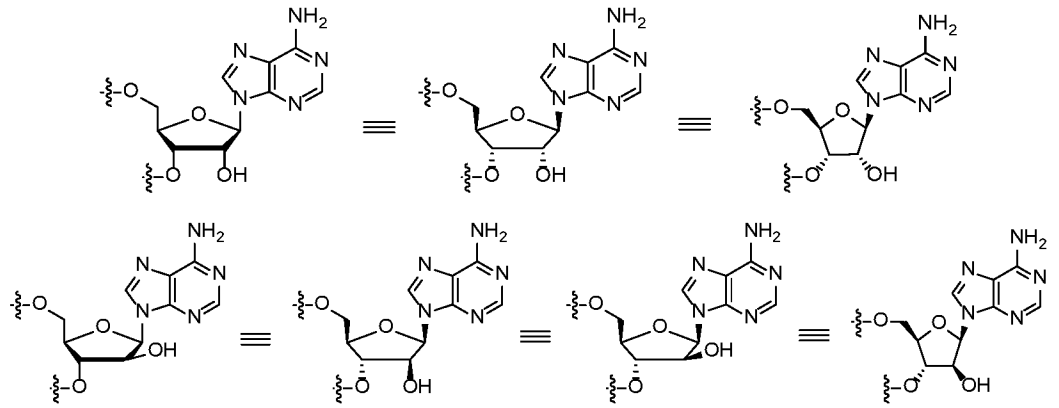
[0091] As shown in the general structural formulas and the structures of specific compounds as provided herein, a straight line at a chiral center includes both (R) and (S) stereoisomers and mixtures thereof.

[0092] Recitation or depiction of a specific compound in the claims (*i.e.*, a species) without a specific stereoconfiguration designation, or with such a designation for less than all chiral centers, is intended to encompass, for such undesignated chiral centers, the racemate, racemic mixtures, each individual enantiomer, a diastereoisomeric mixture and each individual diastereomer of the compound where such forms are possible due to the presence of one or more asymmetric centers.

[0093] The invention includes all possible enantiomers and diastereomers and mixtures of two or more stereoisomers, for example mixtures of enantiomers and/or diastereomers, in all ratios. Thus, enantiomers are a subject of the invention in enantiomerically pure form, both as levorotatory and as dextrorotatory antipodes, in the form of racemates and in the form of mixtures of the two enantiomers in all ratios. In the case of a cis/trans isomerism, the invention includes both the cis form and the trans form, as well as mixtures of these forms in all ratios. The preparation of individual stereoisomers can be carried out, if desired, by separation of a mixture by customary methods, for example by chromatography or crystallization, by the use of stereochemically uniform starting materials for the synthesis or by stereoselective synthesis.

Optionally a derivatization can be carried out before a separation of stereoisomers. The separation of a mixture of stereoisomers can be carried out at an intermediate step during the synthesis of a compound of general formula (I), or a pharmaceutically acceptable salt of the foregoing, or it can be done on a final racemic product. Absolute stereochemistry may be determined by X-ray crystallography of crystalline products or crystalline intermediates that are derivatized, if necessary, with a reagent containing a stereogenic center of known configuration. Unless a particular isomer, salt, solvate (including hydrates) or solvated salt of such racemate, enantiomer, or diastereomer is indicated, the present invention includes all such isomers, as well as salts, solvates (including hydrates), and solvated salts of such racemates, enantiomers, diastereomers, and mixtures thereof.

[0094] Those skilled in the art will recognize that chiral compounds, and in particular sugars, can be drawn in a number of different ways that are equivalent. Those skilled in the art will further recognize that the identity and regiochemical position of the substituents on ribose can vary widely and that the same prinicples of steroechemical equivalence apply regardless of substituent. Non-limiting examples of such equivalence include those exemplified below.



[0095] Salts

[0096] As indicated above, the compounds of the present invention can be employed in the form of pharmaceutically acceptable salts. Those skilled in the art will recognize those instances in which the compounds of the invention may form salts. Examples of such compounds are described herein by reference to possible salts. Such reference is for illustration only. Pharmaceutically acceptable salts can be used with compounds for treating patients. Non-pharmaceutical salts may, however, be useful in the preparation of intermediate compounds.

[0097] The term "pharmaceutically acceptable salt" refers to a salt (including an inner salt such as a zwitterion) that possesses effectiveness similar to the parent compound and that is not biologically or otherwise undesirable (*e.g.*, is neither toxic nor otherwise deleterious to the recipient thereof). Thus, an embodiment of the invention provides pharmaceutically acceptable salts of the compounds of the invention. The term "salt(s)", as employed herein, denotes any of the following: acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. Salts of compounds of the invention may be formed by methods known to those of ordinary skill in the art, for example, by reacting a compound of the invention with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in aqueous medium followed by lyophilization.

[0098] Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates ("mesylates"), naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates) and the like. Suitable salts include acid addition salts that may, for example, be formed by mixing a solution of a compound with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, acetic acid, trifluoroacetic acid, or benzoic acid. Additionally, acids that are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.), *Handbook of Pharmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

[0099] Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamine, *t*-butyl amine, choline, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (*e.g.*, methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (*e.g.*, dimethyl, diethyl, and

dibutyl sulfates), long chain halides (*e.g.*, decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (*e.g.*, benzyl and phenethyl bromides), and others. Compounds carrying an acidic moiety can be mixed with suitable pharmaceutically acceptable salts to provide, for example, alkali metal salts (*e.g.*, sodium or potassium salts), alkaline earth metal salts (*e.g.*, calcium or magnesium salts), and salts formed with suitable organic ligands such as quaternary ammonium salts. Also, in the case of an acid (such as -COOH) or alcohol group being present, pharmaceutically acceptable esters can be employed to modify the solubility or hydrolysis characteristics of the compound.

[0100] All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

[0101] In addition, when a compound of the invention contains both a basic moiety, such as, but not limited to an aliphatic primary, secondary, tertiary or cyclic amine, an aromatic or heteroaryl amine, pyridine or imidazole, and an acidic moiety, such as, but not limited to tetrazole or carboxylic acid, zwitterions ("inner salts") may be formed and are included within the terms "salt(s)" as used herein. It is understood that certain compounds of the invention may exist in zwitterionic form, having both anionic and cationic centers within the same compound and a net neutral charge. Such zwitterions are included within the invention.

[0102] Methods of Preparing Compounds

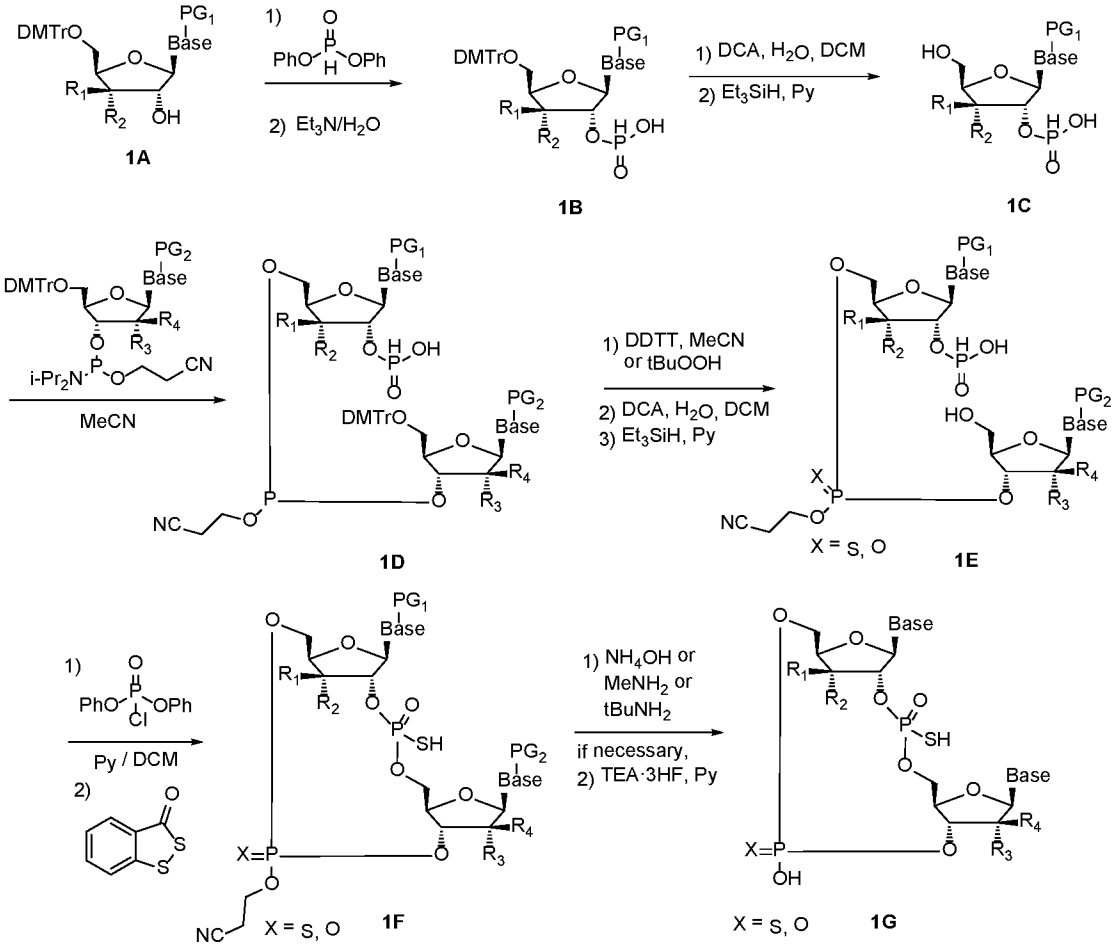
[0103] Several methods for preparing the compounds of general formula (I), and pharmaceutically acceptable salts of the foregoing, are described in the following Schemes and Examples. Starting materials and intermediates are purchased from commercial sources, made from known procedures, or are otherwise illustrated. In some cases the order of carrying out the steps of the reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products.

[0104] In the following Methods and Schemes, PG_1 or PG_2 represents a protecting group for an amino group in a nucleobase, which may be a phenyl carbonyl group including benzoyl group, an alkyl carbonyl group including isobutyl carbonyl group and 2-(4-(*tert*-butyl)phenoxy) acetyl group or a formamidine group including N,N-dimethyl-formamidine. All other variables have the same meaning as provided above.

[0105] *Method 1*

[0106] One method for the preparation of examples of Formula (I) of the instant invention is detailed in Scheme 1. This procedure was adequately modified from the previously reported procedure for cyclic dinucleotide synthesis (Barbara L. Gaffney *et al.*, *One-Flask Syntheses of c-di-GMP and the [Rp,Rp] and [Rp,Sp] Thiophosphate Analogues*, 12 ORG. LETT. 3269-3271 (2010)). The sequence starts with modified ribo-nucleoside with DMTr ether at 5'-O position and a nucleobase of which amino group was appropriately protected as described above if necessary. It was treated with diphenyl phosphite and then, aqueous trimethylamine to introduce an H-phosphonate group. Then, DMTr ether was removed under acidic condition. The resulting 5'-hydroxyl group was reacted with 3'-phosphoramidites of fully protected second modified ribo-nucleoside to give a linear dimer compound. It was immediately treated with (E)-*N,N*-dimethyl-N'-(3-thioxo-3H-1,2,4-dithiazol-5-yl)formimidamide or tert-butyl hydroperoxide. Then, the 5'-hydroxyl group of the second ribo-nucleoside was deprotected with dichloroacetic acid. Using diphenyl chlorophosphate as a coupling reagent, the H-phosphonate at 2'-O of the first ribo-nucleoside was reacted with 5'-OH of the second ribo-nucleoside to give a cyclic product. It was immediately sulfurized with 3H-1,2-benzodithiol-3-one. Treatment with ammonium hydroxide, t-butylamine, or methylamine plus fluoride anion in case silyl protection was used provided the desired cyclic dinucleotide 1G.

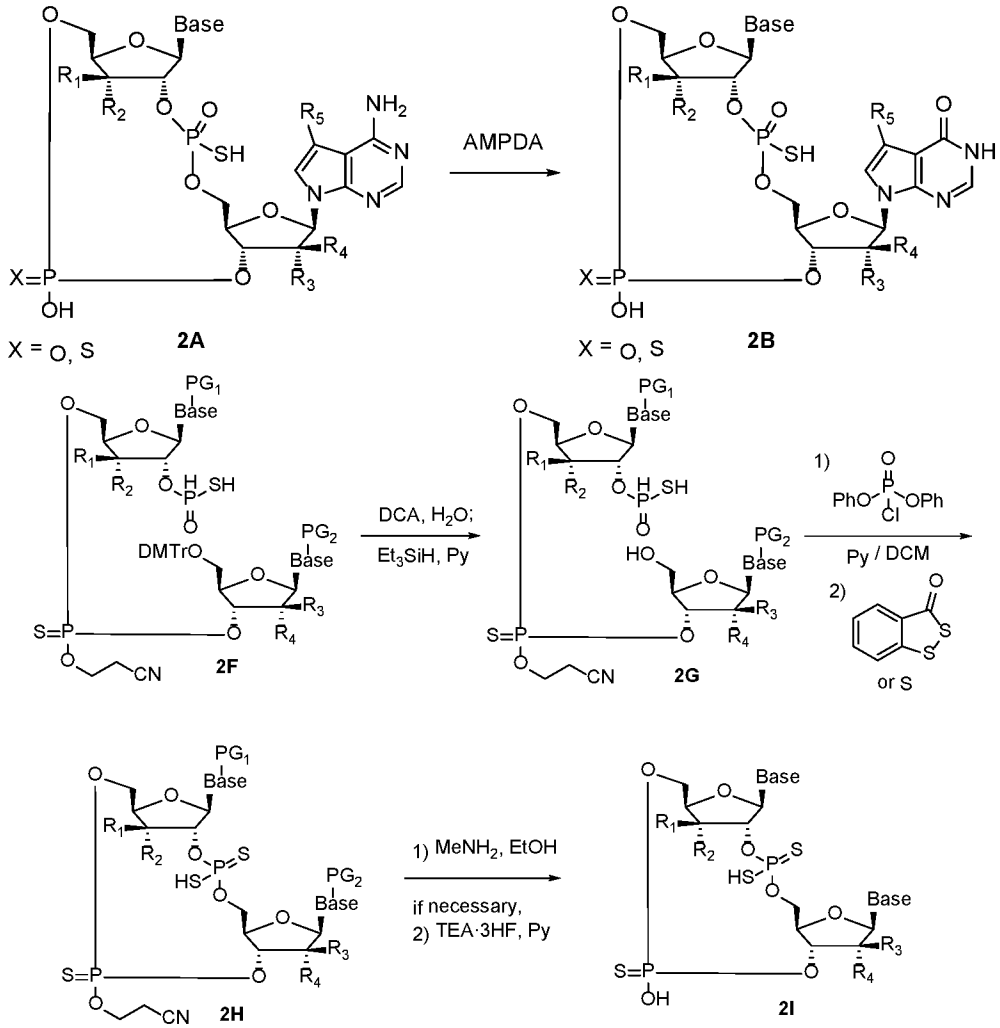
SCHEME 1



[0107] *Method 2*

[0108] One method for the preparation of examples of Formula (I) of the instant invention is detailed in Scheme 2. The sequence starts with a cyclic dinucleotide with 6-amino moiety in a nucleobase prepared from a sequence similar to Scheme 1. It was treated with adenosine monophosphate deaminase in an appropriate aqueous buffer solution to give cyclic dinucleotide 2B with 6-oxo moiety in the nucleobase.

SCHEME 2



[0109] Methods of Use

[0110] Compounds described herein having therapeutic applications, such as the compounds of general formula (I), the compounds of the Examples 1 through 54, and pharmaceutically acceptable salts of the foregoing, may be administered to a patient for the purpose of inducing an immune response, inducing STING-dependent cytokine production and/or inducing anti-tumor activity. The term "administration" and variants thereof (*e.g.*, "administering" a compound) means providing the compound to the individual in need of treatment. When a compound is provided in combination with one or more additional active agents (*e.g.*, antiviral agents useful for treating HCV infection or anti-tumor agents for treating cancers), "administration" and its variants are each understood to include concurrent and sequential provision of the compound or salt and other agents.

[0111] The compounds disclosed herein may be STING agonists. These compounds are potentially useful in treating diseases or disorders including, but not limited to, cell proliferation disorders. Cell-proliferation disorders include, but are not limited to, cancers, benign papillomatosis, gestational trophoblastic diseases, and benign neoplastic diseases, such as skin papilloma (warts) and genital papilloma.

[0112] In specific embodiments, the disease or disorder to be treated is a cell proliferation disorder. In certain embodiments, the cell proliferation disorder is cancer. In particular embodiments, the cancer is selected from brain and spinal cancers, cancers of the head and neck, leukemia and cancers of the blood, skin cancers, cancers of the reproductive system, cancers of the gastrointestinal system, liver and bile duct cancers, kidney and bladder cancers, bone cancers, lung cancers, malignant mesothelioma, sarcomas, lymphomas, glandular cancers, thyroid cancers, heart tumors, germ cell tumors, malignant neuroendocrine (carcinoid) tumors, midline tract cancers, and cancers of unknown primary (*i.e.*, cancers in which a metastasized cancer is found but the original cancer site is not known). In particular embodiments, the cancer is present in an adult patient; in additional embodiments, the cancer is present in a pediatric patient. In particular embodiments, the cancer is AIDS-related.

[0113] In specific embodiments, the cancer is selected from brain and spinal cancers. In particular embodiments, the cancer is selected from the group consisting of anaplastic astrocytomas, glioblastomas, astrocytomas, and estheosioneuroblastomas (also known as olfactory blastomas). In particular embodiments, the brain cancer is selected from the group consisting of astrocytic tumor (*e.g.*, pilocytic astrocytoma, subependymal giant-cell astrocytoma, diffuse astrocytoma, pleomorphic xanthoastrocytoma, anaplastic astrocytoma, astrocytoma, giant cell glioblastoma, glioblastoma, secondary glioblastoma, primary adult glioblastoma, and primary pediatric glioblastoma), oligodendroglial tumor (*e.g.*, oligodendroglioma, and anaplastic oligodendroglioma), oligoastrocytic tumor (*e.g.*, oligoastrocytoma, and anaplastic oligoastrocytoma), ependymoma (*e.g.*, myxopapillary ependymoma, and anaplastic ependymoma); medulloblastoma, primitive neuroectodermal tumor, schwannoma, meningioma, atypical meningioma, anaplastic meningioma, pituitary adenoma, brain stem glioma, cerebellar astrocytoma, cerebral astorcytoma/malignant glioma, visual pathway and hypothalmic glioma, and primary central nervous system lymphoma. In specific instances of these embodiments, the brain cancer is selected from the group consisting of glioma, glioblastoma multiforme, paraganglioma, and suprantentorial primordial neuroectodermal tumors (sPNET).

[0114] In specific embodiments, the cancer is selected from cancers of the head and neck, including nasopharyngeal cancers, nasal cavity and paranasal sinus cancers, hypopharyngeal cancers, oral cavity cancers (*e.g.*, squamous cell carcinomas, lymphomas, and sarcomas), lip cancers, oropharyngeal cancers, salivary gland tumors, cancers of the larynx (*e.g.*, laryngeal squamous cell carcinomas, rhabdomyosarcomas), and cancers of the eye or ocular cancers. In particular embodiments, the ocular cancer is selected from the group consisting of intraocular melanoma and retinoblastoma.

[0115] In specific embodiments, the cancer is selected from leukemia and cancers of the blood. In particular embodiments, the cancer is selected from the group consisting of myeloproliferative neoplasms, myelodysplastic syndromes, myelodysplastic/myeloproliferative neoplasms, acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), chronic myelogenous leukemia (CML), myeloproliferative neoplasm (MPN), post-MPN AML, post-MDS AML, del(5q)-associated high risk MDS or AML, blast-phase chronic myelogenous leukemia, angioimmunoblastic lymphoma, acute lymphoblastic leukemia, Langerans cell histiocytosis, hairy cell leukemia, and plasma cell neoplasms including plasmacytomas and multiple myelomas. Leukemias referenced herein may be acute or chronic.

[0116] In specific embodiments, the cancer is selected from skin cancers. In particular embodiments, the skin cancer is selected from the group consisting of melanoma, squamous cell cancers, and basal cell cancers.

[0117] In specific embodiments, the cancer is selected from cancers of the reproductive system. In particular embodiments, the cancer is selected from the group consisting of breast cancers, cervical cancers, vaginal cancers, ovarian cancers, prostate cancers, penile cancers, and testicular cancers. In specific instances of these embodiments, the cancer is a breast cancer selected from the group consisting of ductal carcinomas and phyllodes tumors. In specific instances of these embodiments, the breast cancer may be male breast cancer or female breast cancer. In specific instances of these embodiments, the cancer is a cervical cancer selected from the group consisting of squamous cell carcinomas and adenocarcinomas. In specific instances of these embodiments, the cancer is an ovarian cancer selected from the group consisting of epithelial cancers.

[0118] In specific embodiments, the cancer is selected from cancers of the gastrointestinal system. In particular embodiments, the cancer is selected from the group consisting of esophageal cancers, gastric cancers (also known as stomach cancers), gastrointestinal carcinoid

tumors, pancreatic cancers, gallbladder cancers, colorectal cancers, and anal cancer. In instances of these embodiments, the cancer is selected from the group consisting of esophageal squamous cell carcinomas, esophageal adenocarcinomas, gastric adenocarcinomas, gastrointestinal carcinoid tumors, gastrointestinal stromal tumors, gastric lymphomas, gastrointestinal lymphomas, solid pseudopapillary tumors of the pancreas, pancreatoblastoma, islet cell tumors, pancreatic carcinomas including acinar cell carcinomas and ductal adenocarcinomas, gallbladder adenocarcinomas, colorectal adenocarcinomas, and anal squamous cell carcinomas.

[0119] In specific embodiments, the cancer is selected from liver and bile duct cancers. In particular embodiments, the cancer is liver cancer (also known as hepatocellular carcinoma). In particular embodiments, the cancer is bile duct cancer (also known as cholangiocarcinoma); in instances of these embodiments, the bile duct cancer is selected from the group consisting of intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma.

[0120] In specific embodiments, the cancer is selected from kidney and bladder cancers. In particular embodiments, the cancer is a kidney cancer selected from the group consisting of renal cell cancer, Wilms tumors, and transitional cell cancers. In particular embodiments, the cancer is a bladder cancer selected from the group consisting of urethelial carcinoma (a transitional cell carcinoma), squamous cell carcinomas, and adenocarcinomas.

[0121] In specific embodiments, the cancer is selected from bone cancers. In particular embodiments, the bone cancer is selected from the group consisting of osteosarcoma, malignant fibrous histiocytoma of bone, Ewing sarcoma, chordoma (cancer of the bone along the spine).

[0122] In specific embodiments, the cancer is selected from lung cancers. In particular embodiments, the lung cancer is selected from the group consisting of non-small cell lung cancer, small cell lung cancers, bronchial tumors, and pleuropulmonary blastomas.

[0123] In specific embodiments, the cancer is selected from malignant mesothelioma. In particular embodiments, the cancer is selected from the group consisting of epithelial mesothelioma and sarcomatoids.

[0124] In specific embodiments, the cancer is selected from sarcomas. In particular embodiments, the sarcoma is selected from the group consisting of central chondrosarcoma, central and periosteal chondroma, fibrosarcoma, clear cell sarcoma of tendon sheaths, and Kaposi's sarcoma.

[0125] In specific embodiments, the cancer is selected from lymphomas. In particular embodiments, the cancer is selected from the group consisting of Hodgkin lymphoma (*e.g.*,

Reed-Sternberg cells), non-Hodgkin lymphoma (*e.g.*, diffuse large B-cell lymphoma, follicular lymphoma, mycosis fungoides, Sezary syndrome, primary central nervous system lymphoma), cutaneous T-cell lymphomas, primary central nervous system lymphomas. In specific embodiments, the cancer is selected from glandular cancers. In particular embodiments, the cancer is selected from the group consisting of adrenocortical cancer (also known as adrenocortical carcinoma or adrenal cortical carcinoma), pheochromocytomas, paragangliomas, pituitary tumors, thymoma, and thymic carcinomas.

[0126] In specific embodiments, the cancer is selected from thyroid cancers. In particular embodiments, the thyroid cancer is selected from the group consisting of medullary thyroid carcinomas, papillary thyroid carcinomas, and follicular thyroid carcinomas.

[0127] In specific embodiments, the cancer is selected from germ cell tumors. In particular embodiments, the cancer is selected from the group consisting of malignant extracranial germ cell tumors and malignant extragonadal germ cell tumors. In specific instances of these embodiments, the malignant extragonadal germ cell tumors are selected from the group consisting of nonseminomas and seminomas.

[0128] In specific embodiments, the cancer is selected from heart tumors. In particular embodiments, the heart tumor is selected from the group consisting of malignant teratoma, lymphoma, rhabdomyosacroma, angiosarcoma, chondrosarcoma, infantile fibrosarcoma, and synovial sarcoma.

[0129] In specific embodiments, the cell-proliferation disorder is selected from benign papillomatosis, benign neoplastic diseases and gestational trophoblastic diseases. In particular embodiments, the benign neoplastic disease is selected from skin papilloma (warts) and genital papilloma. In particular embodiments, the gestational trophoblastic disease is selected from the group consisting of hydatidiform moles, and gestational trophoblastic neoplasia (*e.g.*, invasive moles, choriocarcinomas, placental-site trophoblastic tumors, and epithelioid trophoblastic tumors).

[0130] As used herein, the terms “treatment” and “treating” refer to all processes in which there may be a slowing, interrupting, arresting, controlling, or stopping of the progression of a disease or disorder described herein. The terms do not necessarily indicate a total elimination of all disease or disorder symptoms.

[0131] The terms "administration of" and or "administering" a compound should be understood to include providing a compound described herein, or a pharmaceutically acceptable salt thereof, and compositions of the foregoing to a subject.

[0132] The amount of a compound administered to a subject is an amount sufficient to induce an immune response and/or to induce STING-dependent type I interferon production in the subject. In an embodiment, the amount of a compound can be an "effective amount" or "therapeutically effective amount," such that the subject compound is administered in an amount that will elicit, respectively, a biological or medical (*i.e.,* intended to treat) response of a tissue, system, animal, or human that is being sought by a researcher, veterinarian, medical doctor, or other clinician. An effective amount does not necessarily include considerations of toxicity and safety related to the administration of a compound.

[0133] An effective amount of a compound will vary with the particular compound chosen (*e.g.*, considering the potency, efficacy, and/or half-life of the compound); the route of administration chosen; the condition being treated; the severity of the condition being treated; the age, size, weight, and physical condition of the subject being treated; the medical history of the subject being treated; the duration of the treatment; the nature of a concurrent therapy; the desired therapeutic effect; and like factors and can be routinely determined by the skilled artisan.

[0134] The compounds disclosed herein may be administered by any suitable route including oral and parenteral administration. Parenteral administration is typically by injection or infusion and includes intravenous, intramuscular, intratumoral, and subcutaneous injection or infusion.

[0135] The compounds disclosed herein may be administered once or according to a dosing regimen where a number of doses are administered at varying intervals of time for a given period of time. For example, doses may be administered one, two, three, or four times per day. Doses may be administered until the desired therapeutic effect is achieved or indefinitely to maintain the desired therapeutic effect. Suitable dosing regimens for a compound disclosed herein depend on the pharmacokinetic properties of that compound, such as absorption, distribution and half-life, which can be determined by a skilled artisan. In addition, suitable dosing regimens, including the duration such regimens are administered, for a compound disclosed herein depend on the disease or condition being treated, the severity of the disease or condition, the age and physical condition of the subject being treated, the medical history of the subject being treated, the nature of concurrent therapy, the desired therapeutic effect, and like

factors within the knowledge and expertise of the skilled artisan. It will be further understood by such skilled artisans that suitable dosing regimens may require adjustment given an individual subject's response to the dosing regimen or over time as the individual subject needs change. Typical daily dosages may vary depending upon the particular route of administration chosen.

[0136] One embodiment of the present disclosure provides for a method of treating a cell proliferation disorder comprising administration of a therapeutically effective amount of a compound of general formula (I), or a pharmaceutically acceptable salt of the foregoing, to a subject in need of treatment thereof. In embodiments, the disease or disorder to be treated is a cell proliferation disorder. In aspects of these embodiments, the cell proliferation disorder is cancer. In further aspects of these embodiments, the cancer is selected from brain and spinal cancers, cancers of the head and neck, leukemia and cancers of the blood, skin cancers, cancers of the reproductive system, cancers of the gastrointestinal system, liver and bile duct cancers, kidney and bladder cancers, bone cancers, lung cancers, malignant mesothelioma, sarcomas, lymphomas, glandular cancers, thyroid cancers, heart tumors, germ cell tumors, malignant neuroendocrine (carcinoid) tumors, midline tract cancers, and cancers of unknown primary.

[0137] In one embodiment, disclosed herein is the use of a compound of general formula (I), or a pharmaceutically acceptable salt of the foregoing, in a therapy. The compound may be useful in a method of inducing an immune response and/or inducing STING-dependent type I interferon production in a subject, such as a mammal in need of such inhibition, comprising administering an effective amount of the compound to the subject.

[0138] In one embodiment, disclosed herein is a pharmaceutical composition comprising at least one compound of general formula (I), or at least one pharmaceutically acceptable salt of the foregoing, for use in potential treatment to induce an immune response and/or to induce STING-dependent type I interferon production.

[0139] One embodiment disclosed herein is the use of a compound of general formula (I), or a pharmaceutically acceptable salt of the foregoing, in the manufacture of a medicament to induce an immune response and/or to induce STING-dependent type I interferon production. In embodiments, the disease or disorder to be treated is a cell proliferation disorder. In aspects of these embodiments, the cell proliferation disorder is cancer. In further aspects of these embodiments, the cancer is selected from brain and spinal cancers, cancers of the head and neck, leukemia and cancers of the blood, skin cancers, cancers of the reproductive system, cancers of the gastrointestinal system, liver and bile duct cancers, kidney and bladder cancers, bone cancers,

lung cancers, malignant mesothelioma, sarcomas, lymphomas, glandular cancers, thyroid cancers, heart tumors, germ cell tumors, malignant neuroendocrine (carcinoid) tumors, midline tract cancers, and cancers of unknown primary.

[0140] Compositions

[0141] The term "composition" as used herein is intended to encompass a dosage form comprising a specified compound in a specified amount, as well as any dosage form that results, directly or indirectly, from combination of a specified compound in a specified amount. Such term is intended to encompass a dosage form comprising a compound of general formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug of the foregoing, and one or more pharmaceutically acceptable carriers or excipients. In embodiments, the dosage form comprises compounds of general structural formula (I), or a pharmaceutically acceptable salt, hydrate, or solvate thereof, and one or more pharmaceutically acceptable carriers or excipients. In specific embodiments, the dosage form comprises compounds of general structural formula (I), or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers or excipients. Accordingly, the compositions of the present disclosure encompass any composition made by admixing a compound of the present disclosure and one or more pharmaceutically acceptable carrier or excipients. By "pharmaceutically acceptable", it is meant the carriers or excipients are compatible with the compound disclosed herein and with other ingredients of the composition.

[0142] For the purpose of inducing an immune response and/or inducing STING-dependent type I interferon production, the compounds of general formula (I), or pharmaceutically acceptable salts of the foregoing, can be administered by means that produces contact of the active agent with the agent's site of action. The compounds can be administered by conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. The compounds can be administered alone, but typically are administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

[0143] In one embodiment, disclosed herein is a composition comprising a compound of general formula (I), or a pharmaceutically acceptable salt of the foregoing, and one or more pharmaceutically acceptable carriers or excipients. The composition may be prepared and packaged in bulk form in which a therapeutically effective amount of a compound of the

disclosure can be extracted and then given to a subject, such as with powders or syrups. Alternatively, the composition may be prepared and packaged in unit dosage form in which each physically discrete unit contains a therapeutically effective amount of a compound of general formula (I), or a pharmaceutically acceptable salt of the foregoing.

[0144] The compounds disclosed herein and a pharmaceutically acceptable carrier or excipient(s) will typically be formulated into a dosage form adapted for administration to a subject by a desired route of administration. For example, dosage forms include those adapted for (1) oral administration, such as tablets, capsules, caplets, pills, troches, powders, syrups, elixirs, suspensions, solutions, emulsions, sachets, and cachets; and (2) parenteral administration, such as sterile solutions, suspensions, and powders for reconstitution. Suitable pharmaceutically acceptable carriers or excipients will vary depending upon the particular dosage form chosen. In addition, suitable pharmaceutically acceptable carriers or excipients may be chosen for a particular function that they may serve in the composition. For example, certain pharmaceutically acceptable carriers or excipients may be chosen for their ability to facilitate the production of uniform dosage forms. Certain pharmaceutically acceptable carriers or excipients may be chosen for their ability to facilitate the production of stable dosage forms. Certain pharmaceutically acceptable carriers or excipients may be chosen for their ability to facilitate the carrying or transporting of a compound disclosed herein, once administered to the subject, from one organ or portion of the body to another organ or another portion of the body. Certain pharmaceutically acceptable carriers or excipients may be chosen for their ability to enhance patient compliance.

[0145] Suitable pharmaceutically acceptable excipients include the following types of excipients: diluents, lubricants, binders, disintegrants, fillers, glidants, granulating agents, coating agents, wetting agents, solvents, co-solvents, suspending agents, emulsifiers, sweeteners, flavoring agents, flavor masking agents, coloring agents, anti-caking agents, hemectants, chelating agents, plasticizers, viscosity increasing agents, antioxidants, preservatives, stabilizers, surfactants, and buffering agents.

[0146] A skilled artisan possesses the knowledge and skill in the art to select suitable pharmaceutically acceptable carriers and excipients in appropriate amounts for the use in the compositions of the disclosure. In addition, there are a number of resources available to the skilled artisan, which describe pharmaceutically acceptable carriers and excipients and may be useful in selecting suitable pharmaceutically acceptable carriers and excipients. Examples

include REMINGTON'S PHARMACEUTICAL SCIENCES (Mack Publishing Company), THE HANDBOOK OF PHARMACEUTICAL ADDITIVES (Gower Publishing Limited), and THE HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (the American Pharmaceutical Association and the Pharmaceutical Press).

[0147] The compositions of the disclosure are prepared using techniques and methods known to those skilled in the art. Some methods commonly used in the art are described in REMINGTON'S PHARMACEUTICAL SCIENCES (Mack Publishing Company).

[0148] In one embodiment, the disclosure is directed to a solid oral dosage form such as a tablet or capsule comprising a therapeutically effective amount of a compound of general formula (I), or a pharmaceutically acceptable salt of the foregoing, and a diluent or filler. Suitable diluents and fillers include lactose, sucrose, dextrose, mannitol, sorbitol, starch (*e.g.*, corn starch, potato starch, and pre-gelatinized starch), cellulose and its derivatives, (*e.g.*, microcrystalline cellulose), calcium sulfate, and dibasic calcium phosphate. The solid oral dosage form may further comprise a binder. Suitable binders include starch (*e.g.*, corn starch, potato starch, and pre-gelatinized starch) gelatin, acacia, sodium alginate, alginic acid, tragacanth, guar gum, povidone, and cellulose and its derivatives (*e.g.*, microcrystalline cellulose). The solid oral dosage form may further comprise a disintegrant. Suitable disintegrants include crospovidone, sodium starch glycolate, croscarmelose, alginic acid, and sodium carboxymethyl cellulose. The solid oral dosage form may further comprise a lubricant. Suitable lubricants include stearic acid, magnesium stearate, calcium stearate, and talc.

[0149] Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The composition can also be prepared to prolong or sustain the release as, for example, by coating or embedding particulate material in polymers, wax, or the like.

[0150] The compounds disclosed herein may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyrancopolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds of the disclosure may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanacrylates, and cross-linked or amphipathic block copolymers of hydrogels.

[0151] In one embodiment, the disclosure is directed to a liquid oral dosage form. Oral liquids such as solutions, syrups, and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of a compound or a pharmaceutically acceptable salt thereof disclosed herein. Syrups can be prepared by dissolving the compound of the disclosure in a suitably flavored aqueous solution; elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing a compound disclosed herein in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additives such as peppermint oil, or other natural sweeteners or saccharin or other artificial sweeteners and the like can also be added.

[0152] In one embodiment, the disclosure is directed to compositions for parenteral administration. Compositions adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions that may contain anti-oxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions that may include suspending agents and thickening agents. The compositions may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets.

[0153] Combinations

[0154] The compounds of general formula (I), and/or pharmaceutically acceptable salts of the foregoing, may be administered in combination with one or more additional active agents. In embodiments, one or more compounds of general formula (I), or one or more pharmaceutically acceptable salts of the foregoing, and the one or more additional active agents may be co-administered. The additional active agent(s) may be administered in a single dosage form with the compound of general formula (I), or pharmaceutically acceptable salt of the foregoing, or the additional active agent(s) may be administered in separate dosage form(s) from the dosage form containing the compound of general formula (I), or pharmaceutically acceptable salt of the foregoing. The additional active agent(s) may be one or more agents selected from the group consisting of STING agonist compounds, anti-viral compounds, antigens, adjuvants, anti-cancer agents, CTLA-4, LAG-3, and PD-1 pathway antagonists, lipids, liposomes, peptides, cytotoxic

agents, chemotherapeutic agents, immunomodulatory cell lines, checkpoint inhibitors, vascular endothelial growth factor (VEGF) receptor inhibitors, topoisomerase II inhibitors, smoothen inhibitors, alkylating agents, anti-tumor antibiotics, anti-metabolites, retinoids, and immunomodulatory agents including but not limited to anti-cancer vaccines. It will be understood the descriptions of the above additional active agents may be overlapping. It will also be understood that the treatment combinations are subject to optimization, and it is understood that the best combination to use of the compounds of general formula (I), or pharmaceutically acceptable salts of the foregoing, and one or more additional active agents will be determined based on the individual patient needs.

[0155] A compound disclosed herein may be used in combination with one or more other active agents, including but not limited to, other anti-cancer agents that are used in the prevention, treatment, control, amelioration, or reduction of risk of a particular disease or condition (*e.g.*, cell proliferation disorders). In one embodiment, a compound disclosed herein is combined with one or more other anti-cancer agents for use in the prevention, treatment, control amelioration, or reduction of risk of a particular disease or condition for which the compounds disclosed herein are useful. Such other active agents may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present disclosure.

[0156] When a compound disclosed herein is used contemporaneously with one or more other active agents, a composition containing such other active agents in addition to the compound disclosed herein is contemplated. Accordingly, the compositions of the present disclosure include those that also contain one or more other active ingredients, in addition to a compound disclosed herein. A compound disclosed herein may be administered either simultaneously with, or before or after, one or more other active agent(s). A compound disclosed herein may be administered separately, by the same or different route of administration, or together in the same pharmaceutical composition as the other agent(s).

[0157] Products provided as combinations may include a composition comprising a compound of general formula (I), or a pharmaceutically acceptable salt of the foregoing, and one or more other active agent(s) together in the same pharmaceutical composition, or may include a composition comprising a compound of general formula (I), or a pharmaceutically acceptable salt of the foregoing, and a composition comprising one or more other active agent(s) in separate

form, *e.g.* in the form of a kit or in any form designed to enable separate administration either concurrently or on separate dosing schedules.

[0158] The weight ratio of a compound of general formula (I), or a pharmaceutically acceptable salt of the foregoing, to a second active agent may be varied and will depend upon the therapeutically effective dose of each agent. Generally, a therapeutically effective dose of each will be used. Combinations of a compound disclosed herein and other active agents will generally also be within the aforementioned range, but in each case, a therapeutically effective dose of each active agent should be used. In such combinations, the compound disclosed herein and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

[0159] In one embodiment, this disclosure provides a composition comprising a compound of general formula (I), or a pharmaceutically acceptable salt thereof, and at least one other active agent as a combined preparation for simultaneous, separate or sequential use in therapy. In one embodiment, the therapy is the treatment of a cell proliferation disorder, such as cancer.

[0160] In one embodiment, the disclosure provides a kit comprising two or more separate pharmaceutical compositions, at least one of which contains a compound of general formula (I), or a pharmaceutically acceptable salt of the foregoing. In one embodiment, the kit comprises means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is a blister pack, as typically used for the packaging of tablets, capsules, and the like.

[0161] A kit of this disclosure may be used for administration of different dosage forms, for example, oral and parenteral, for administration of the separate compositions at different dosage intervals, or for titration of the separate compositions against one another. To assist with compliance, a kit of the disclosure typically comprises directions for administration.

[0162] Disclosed herein is a use of a compound of general formula (I), or a pharmaceutically acceptable salt of the foregoing, for treating a cell proliferation disorder, where the medicament is prepared for administration with another active agent. The disclosure also provides the use of another active agent for treating a cell proliferation disorder, where the medicament is administered with a compound of general formula (I), or a pharmaceutically acceptable salt of the foregoing.

[0163] The disclosure also provides the use of a compound of general formula (I), or a pharmaceutically acceptable salt of the foregoing, for treating a cell proliferation disorder, where the patient has previously (*e.g.*, within 24 hours) been treated with another active agent. The disclosure also provides the use of another active agent for treating a cell proliferation disorder, where the patient has previously (*e.g.*, within 24 hours) been treated with a compound of general formula (I), or a pharmaceutically acceptable salt of the foregoing. The second agent may be administered a week, several weeks, a month, or several months after the administration of a compound disclosed herein.

[0164] STING agonist compounds that may be used in combination with the compounds of general formula (I), or pharmaceutically acceptable salts of the foregoing, disclosed herein include but are not limited to cyclic di-nucleotide compounds.

[0165] Anti-viral compounds that may be used in combination with the compounds of general formula (I), or pharmaceutically acceptable salts of the foregoing, disclosed herein include hepatitis B virus (HBV) inhibitors, hepatitis C virus (HCV) protease inhibitors, HCV polymerase inhibitors, HCV NS4A inhibitors, HCV NS5A inhibitors, HCV NS5b inhibitors, and human immunodeficiency virus (HIV) inhibitors.

[0166] Antigens and adjuvants that may be used in combination with the compounds of general formula (I), or the pharmaceutically acceptable salts of the foregoing, include B7 costimulatory molecule, interleukin-2, interferon-y, GM-CSF, CTLA-4 antagonists, OX-40/0X-40 ligand, CD40/CD40 ligand, sargramostim, levamisol, vaccinia virus, Bacille Calmette-Guerin (BCG), liposomes, alum, Freund's complete or incomplete adjuvant, detoxified endotoxins, mineral oils, surface active substances such as lipolecithin, pluronic polyols, polyanions, peptides, and oil or hydrocarbon emulsions. Adjuvants, such as aluminum hydroxide or aluminum phosphate, can be added to increase the ability of the vaccine to trigger, enhance, or prolong an immune response. Additional materials, such as cytokines, chemokines, and bacterial nucleic acid sequences, like CpG, a toll-like receptor (TLR) 9 agonist as well as additional agonists for TLR 2, TLR 4, TLR 5, TLR 7, TLR 8, TLR9, including lipoprotein, LPS, monophosphoryllipid A, lipoteichoic acid, imiquimod, resiquimod, and in addition retinoic acid-inducible gene I (RIG-I) agonists such as poly I:C, used separately or in combination with the described compositions are also potential adjuvants.

[0167] CLTA-4 and PD-1 pathways are important negative regulators of immune response. Activated T-cells up-regulate CTLA-4, which binds on antigen-presenting cells and inhibits T-

cell stimulation, IL-2 gene expression, and T-cell proliferation; these anti-tumor effects have been observed in mouse models of colon carcinoma, metastatic prostate cancer, and metastatic melanoma. PD-1 binds to active T-cells and suppresses T-cell activation; PD-1 antagonists have demonstrated anti-tumor effects as well. CTLA-4 and PD-1 pathway antagonists that may be used in combination with the compounds of general formula (Ia), the compounds of general formula (Ib), the compounds of general formula (I), or the pharmaceutically acceptable salts of the foregoing, disclosed herein, include ipilimumab, tremelimumab, nivolumab, pembrolizumab, CT-011, AMP-224, and MDX-1106.

[0168] "PD-1 antagonist" or "PD-1 pathway antagonist" means any chemical compound or biological molecule that blocks binding of PD-L1 expressed on a cancer cell to PD-1 expressed on an immune cell (T-cell, B-cell, or NKT-cell) and preferably also blocks binding of PD-L2 expressed on a cancer cell to the immune-cell expressed PD-1. Alternative names or synonyms for PD-1 and its ligands include: PDCD1, PD1, CD279, and SLEB2 for PD-1; PDCD1L1, PDL1, B7H1, B7-4, CD274, and B7-H for PD-L1; and PDCD1L2, PDL2, B7-DC, Btdc, and CD273 for PD-L2. In any of the treatment method, medicaments and uses of the present disclosure in which a human individual is being treated, the PD-1 antagonist blocks binding of human PD-L1 to human PD-1, and preferably blocks binding of both human PD-L1 and PD-L2 to human PD-1. Human PD-1 amino acid sequences can be found in NCBI Locus No.: NP_005009. Human PD-L1 and PD-L2 amino acid sequences can be found in NCBI Locus No.: NP_054862 and NP_079515, respectively.

[0169] PD-1 antagonists useful in any of the treatment method, medicaments and uses of the present disclosure include a monoclonal antibody (mAb), or antigen binding fragment thereof, which specifically binds to PD-1 or PD-L1, and preferably specifically binds to human PD-1 or human PD-L1. The mAb may be a human antibody, a humanized antibody, or a chimeric antibody and may include a human constant region. In some embodiments, the human constant region is selected from the group consisting of IgG1, IgG2, IgG3, and IgG4 constant regions, and in preferred embodiments, the human constant region is an IgG1 or IgG4 constant region. In some embodiments, the antigen binding fragment is selected from the group consisting of Fab, Fab'-SH, $F(ab')_2$, scFv, and Fv fragments.

[0170] Examples of mAbs that bind to human PD-1, and useful in the treatment method, medicaments and uses of the present disclosure, are described in U.S. Patent Nos. US7488802, US7521051, US8008449, US8354509, and US8168757, PCT International Patent Application

Publication Nos. WO2004/004771, WO2004/072286, and WO2004/056875, and U.S. Patent Application Publication No. US2011/0271358.

[0171] Examples of mAbs that bind to human PD-L1, and useful in the treatment method, medicaments and uses of the present disclosure, are described in PCT International Patent Application Nos. WO2013/019906 and WO2010/077634 A1 and in U.S. Patent No. US8383796. Specific anti-human PD-L1 mAbs useful as the PD-1 antagonist in the treatment method, medicaments and uses of the present disclosure include MPDL3280A, BMS-936559, MEDI4736, MSB0010718C, and an antibody that comprises the heavy chain and light chain variable regions of SEQ ID NO:24 and SEQ ID NO:21, respectively, of WO2013/019906.

[0172] Other PD-1 antagonists useful in any of the treatment method, medicaments, and uses of the present disclosure include an immune-adhesion that specifically binds to PD-1 or PD-L1, and preferably specifically binds to human PD-1 or human PD-L1, *e.g.*, a fusion protein containing the extracellular or PD-1 binding portion of PD-L1 or PD-L2 fused to a constant region such as an Fc region of an immunoglobulin molecule. Examples of immune-adhesion molecules that specifically bind to PD-1 are described in PCT International Patent Application Publication Nos. WO2010/027827 and WO2011/066342. Specific fusion proteins useful as the PD-1 antagonist in the treatment method, medicaments, and uses of the present disclosure include AMP-224 (also known as B7-DCIg), which is a PD-L2-FC fusion protein and binds to human PD-1.

[0173] Examples of cytotoxic agents that may be used in combination with the compounds of general formula (I) or pharmaceutically acceptable salts thereof, include, but are not limited to, arsenic trioxide (sold under the tradename TRISENOX®), asparaginase (also known as L-asparaginase, and Erwinia L-asparaginase, sold under the tradenames ELSPAR® and KIDROLASE®).

[0174] Chemotherapeutic agents that may be used in combination with the compounds of general formula (I), or pharmaceutically acceptable salts of the foregoing, disclosed herein include abiraterone acetate, altretamine, anhydrovinblastine, auristatin, bexarotene, bicalutamide, BMS 184476, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl)benzene sulfonamide, bleomycin, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl- 1-Lproline-t-butylamide, cachectin, cemadotin, chlorambucil, cyclophosphamide, 3',4'-didehydro-4'deoxy-8'-norvin-caleukoblastine, docetaxol, doxetaxel, cyclophosphamide, carboplatin, carmustine, cisplatin, cryptophycin, cyclophosphamide, cytarabine, dacarbazine (DTIC), dactinomycin, daunorubicin,

decitabine dolastatin, doxorubicin (adriamycin), etoposide, 5-fluorouracil, finasteride, flutamide, hydroxyurea and hydroxyurea andtaxanes, ifosfamide, liarozole, lonidamine, lomustine (CCNU), MDV3100, mechlorethamine (nitrogen mustard), melphalan, mivobulin isethionate, rhizoxin, sertenef, streptozocin, mitomycin, methotrexate, taxanes, nilutamide, nivolumab, onapristone, paclitaxel, pembrolizumab, prednimustine, procarbazine, RPR109881, stramustine phosphate, tamoxifen, tasonermin, taxol, tretinoin, vinblastine, vincristine, vindesine sulfate, and vinflunine.

[0175] Examples of vascular endothelial growth factor (VEGF) receptor inhibitors include, but are not limited to, bevacizumab (sold under the trademark AVASTIN by Genentech/Roche), axitinib (described in PCT International Patent Publication No. WO01/002369), Brivanib Alaninate ((S)-((R)-1-(4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-5-methylpyrrolo[2,1-f][1,2,4]triazin-6-yloxy)propan-2-yl)2-aminopropanoate, also known as BMS-582664), motesanib (N-(2,3-dihydro-3,3-dimethyl-1H-indol-6-yl)-2-[(4-pyridinylmethyl)amino]-3-pyridinecarboxamide. and described in PCT International Patent Application Publication No. WO02/068470), pasireotide (also known as SO 230, and described in PCT International Patent Publication No. WO02/010192), and sorafenib (sold under the tradename NEXAVAR).

[0176] Examples of topoisomerase II inhibitors, include but are not limited to, etoposide (also known as VP-16 and Etoposide phosphate, sold under the tradenames TOPOSAR, VEPESID, and ETOPOPHOS), and teniposide (also known as VM-26, sold under the tradename VUMON).

[0177] Examples of alkylating agents, include but are not limited to, 5-azacytidine (sold under the trade name VIDAZA), decitabine (sold under the trade name of DECOGEN), temozolomide (sold under the trade names TEMODAR and TEMODAL by Schering-Plough/Merck), dactinomycin (also known as actinomycin-D and sold under the tradename COSMEGEN), melphalan (also known as L-PAM, L-sarcolysin, and phenylalanine mustard, sold under the tradename ALKERAN), altretamine (also known as hexamethylmelamine (HMM), sold under the tradename HEXALEN), carmustine (sold under the tradename BCNU), bendamustine (sold under the tradename TREANDA), busulfan (sold under the tradenames BUSULFEX® and MYLERAN®), carboplatin (sold under the tradename PARAPLATIN®), lomustine (also known as CCNU, sold under the tradename CEENU®), cisplatin (also known as CDDP, sold under the tradenames PLATINOL® and PLATINOL®-AQ), chlorambucil (sold under the tradename LEUKERAN®), cyclophosphamide (sold under the tradenames CYTOXAN® and NEOSAR®), dacarbazine (also known as DTIC, DIC and imidazole carboxamide, sold under the tradename

DTIC-DOME®), altretamine (also known as hexamethylmelamine (HMM) sold under the tradename HEXALEN®), ifosfamide (sold under the tradename IFEX®), procarbazine (sold under the tradename MATULANE®), mechlorethamine (also known as nitrogen mustard, mustine and mechloroethamine hydrochloride, sold under the tradename MUSTARGEN®), streptozocin (sold under the tradename ZANOSAR®), thiotepa (also known as thiophosphoamide, TESPA and TSPA, and sold under the tradename THIOPLEX®.

[0178] Examples of anti-tumor antibiotics include, but are not limited to, doxorubicin (sold under the tradenames ADRIAMYCIN® and RUBEX®), bleomycin (sold under the tradename LENOXANE®), daunorubicin (also known as dauorubicin hydrochloride, daunomycin, and rubidomycin hydrochloride, sold under the tradename CERUBIDINE®), daunorubicin liposomal (daunorubicin citrate liposome, sold under the tradename DAUNOXOME®), mitoxantrone (also known as DHAD, sold under the tradename NOVANTRONE®), epirubicin (sold under the tradename ELLENCE™), idarubicin (sold under the tradenames IDAMYCIN®, IDAMYCIN PFS®), and mitomycin C (sold under the tradename MUTAMYCIN®).

[0179] Examples of anti-metabolites include, but are not limited to, claribine (2-chlorodeoxyadenosine, sold under the tradename LEUSTATIN®), 5-fluorouracil (sold under the tradename ADRUCIL®), 6-thioguanine (sold under the tradename PURINETHOL®), pemetrexed (sold under the tradename ALIMTA®), cytarabine (also known as arabinosylcytosine (Ara-C), sold under the tradename CYTOSAR-U®), cytarabine liposomal (also known as Liposomal Ara-C, sold under the tradename DEPOCYT™), decitabine (sold under the tradename DACOGEN®), hydroxyurea and (sold under the tradenames HYDREA®, DROXIA™ and MYLOCEL™), fludarabine (sold under the tradename FLUDARA®), floxuridine (sold under the tradename FUDR®), cladribine (also known as 2-chlorodeoxyadenosine (2-CdA) sold under the tradename LEUSTATIN™), methotrexate (also known as amethopterin, methotrexate sodium (MTX), sold under the tradenames RHEUMATREX® and TREXALL™), and pentostatin (sold under the tradename NIPENT®).

[0180] Examples of retinoids include, but are not limited to, alitretinoin (sold under the tradename PANRETIN®), tretinoin (all-trans retinoic acid, also known as ATRA, sold under the tradename VESANOID®), Isotretinoin (13-c/s-retinoic acid, sold under the tradenames ACCUTANE®, AMNESTEEM®, CLARAVIS®, CLARUS®, DECUTAN®, ISOTANE®, IZOTECH®, ORATANE®, ISOTRET®, and SOTRET®), and bexarotene (sold under the tradename TARGRETIN®).

[0181] Activity: STING Biochemical [3H]cGAMP Competition Assay

[0182] The individual compounds described in the Examples herein are defined as STING agonists by (i) binding to the STING protein as evidenced by a reduction in binding of tritiated cGAMP ligand to the STING protein by at least 20% at 20uM (concentration of compound being tested) in a STING Biochemical [3H]cGAMP Competition Assay and (ii) demonstrating interferon production with a 6% or greater induction of IFN-β secretion at 30uM in the THP1 cell assay (where induction caused by cGAMP at 30uM was set at 100%).

[0183] The ability of compounds to bind STING is quantified by the ability to compete with tritiated cGAMP ligand for human STING receptor membrane using a radioactive filter-binding assay. The binding assay employs STING receptor obtained from Hi-Five cell membranes overexpressing full-length HAQ STING prepared in-house and tritiated cGAMP ligand also purified in-house.

[0184] The following experimental procedures detail the preparation of specific examples of the instant disclosure. The compounds of the examples are drawn in their neutral forms in the procedures and tables below. In some cases, the compounds were isolated as salts depending on the method used for their final purification and/or intrinsic molecular properties. The examples are for illustrative purposes only and are not intended to limit the scope of the instant disclosure in any way.

[0185] ABBREVIATIONS

A^{Bz}	6-*N*-benzoyladenine
AcOH	Acetic acid
AIBN	Azobisisobutyronitrile, 2,2'-azobis(2-methylpropionitrile)
AMPDA	Adenosine monophosphate deaminase
atm	Atmosphere, a unit of pressure defined as 101325Pa (1.01325 bar)
BCl_3	Boron trichloride
BF_3-OEt_2, BF_3-Et_2O	Boron trifluoride diethyl etherate
$BrCH_2CHO$	Bromoacetaldehyde
BSA	Trimethylsilyl *N*-(trimethylsilyl)acetimidate
Bz	Benzoyl
BzCl	Benzoyl chloride
CD_3OD	Deuterium-enriched methyl alcohol, deuterium-enriched methanol

Ci	Curie, a non-standard unit of radioactivity; 1Ci=3.7×10^{10}Bq, where Bq is Becquerel, the SI unit of radioactivity, equivalent to 1 disintegration per second (dps)
$ClCH_2CHO$	Chloroacetaldehyde
d	Doublet
D_2O	Deuterium-enriched water
DCA	Dichloroacetic acid
DCE	Dichloroethane
DCM, CH_2Cl_2	Dichloromethane
ddd	Doublet of doublet of doublet
ddt	Doublet of doublet of triplet
DDTT	(E)-N,N-dimethyl-N'-(3-thioxo-3H-1,2,4-dithiazol-5-yl)formimidamide, N'-(3-thioxo-3H-1,2,4-dithiazol-5-yl)-N,N-dimethylmethanimidamide
DEAD	Diethyl azodicarboxylate
DIEA	*N*-ethyl-*N*-isopropylpropan-2-amine
DIEA HCl	*N*-ethyl-*N*-isopropylpropan-2-amine hydrochloride
DiPEA	N,N-Diisopropylethylamine
DiPEA-HCl	2-chloro-N,N-diisopropylethylamine hydrochloride
DMA	N,N-dimethylacetamide
DMAP	Dimethylaminopyridine
DMF	N,N-dimethylformamide
DMF-DMA	N,N-Dimethylformamide dimethyl acetal
DMOCP	2-chloro-5,5-dimethyl-1,3,2-dioxaphosphineane 2-oxide
DMTr	4,4'-dimethoxytrityl
DMTrCl	4,4'-(chloro(phenyl)methylene)bis(methoxybenzene), 4,4'-dimethoxytrityl chloride
dq	Doublet of quartet
EC_{50}	half maximal effective concentration, concentration of a drug, antibody or toxicant that induces a response halfway between the baseline and maximum after a specified exposure time
eq	Equivalents

ES	Electron spray
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethyl alcohol, ethanol
g	Gram
h	Hour
H_2	Hydrogen (gas)
HEPES	2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid, a zwitterionic organic chemical buffering agent
hept	Heptet
Hex	Hexanes
HPLC	High performance liquid chromatography
Hz	Hertz
i-PrMgCl	Isopropylmagnesium chloride
i-PrMgCl-LiCl	Isopropylmagnesium chloride – lithium chloride
i-PrOH	Isopropanol, isopropyl alcohol
K_2CO_3	Potassium carbonate
LCMS	Liquid chromatography–mass spectroscopy
m	Multiplet
M	Molar, moles per liter
m/e	Mass/charge
mCi	Millicurie
Me	Methyl
MeCN, ACN	Acetonitrile
MeCOOH, CH_3COOH	Acetic acid
MeMgBr, CH_3MgBr	Methylmagnesium bromide
$MeNH_2$, CH_3NH_2	Methylamine
MeOH, CH_3OH	Methyl alcohol, methanol
$MgCl_2$	Magnesium chloride
$MgSO_4$	Magnesium sulfate
MOI	Multiplicity of infection
MPLC	Medium pressue liquid chromatography

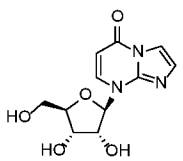
MTBE	Methyl t-butyl ether, methyl tertiary butyl ether
Na_2CO_3	Sodium carbonate
Na_2SO_4	Sodium sulfate
NaH	Sodium hydride
$NaHCO_3$	Sodium bicarbonate
$NaHSO_3$	Sodium bisulfite
NaOMe	Sodium methoxide
nBu_3SnH	Tri-n-butyltin hydride, tributyl stannane
NH_4HCO_3	Ammonium bicarbonate
NH_4OAc	Ammonium acetate
NMP	N-methyl-2-pyrrolidone
P_2O_5	Phosphorus pentoxide
$Pd(OH)_2/C$	Palladium hydroxide on carbon
Pd/C	Palladium on charcoal
PPh_3	Triphenylphosphine
Py	Pyridine
q	Quartet
RPM, rpm	Revolutions per minute
RT, rt	Room temperature, approximately 25°C
s	Singlet
sat	Saturated
$SnCl_4$	Tin(IV) chloride
t	Triplet
TBAF, Bu_4NF, $(CH_3CH_2CH_2CH_2)_4NF$	Tetra-n-butylammonium fluoride
TBDPSCl	*tert*-Butylchlorodiphenylsilane
TBS	t-Butyldimethylsilyl
TBSCl	t-Butyldimethylsilyl chloride
t-$BuNH_2$	*tert*-Butylamine
t-BuO_2H	*tert*-Butyl peroxide
TEA, Et_3N	Triethylamine
TEA·3HF, Et_3N·3HF	Triethylamine trihydrofluoride

TEA·HF	Triethylamine hydrofluoride
TEAA	Triethylammonium acetate
TES, Et_3SiH	Triethylsilane
TFA	Trifluoroacetic acid
TFA·Py	Pyridine 2,2,2-trifluoroacetate
THF	Tetrahydrofuran
TIPSOTf	Triisopropylsilyl trifluoromethanesulfonate
TLC	Thin layer chromatography
TMA	Trimethylamine
TMSCl	Trimethylsilyl chloride
$(TMS)_3SiH$	Tris(trimethylsilyl)silane
T_R	Retention time
TrisCl	Tris(hydroxymethyl)aminomethane hydrochloride
v/v	Volume/volume
λ_{em}	Emission wavelength
λ_{ex}	Excitation wavelength

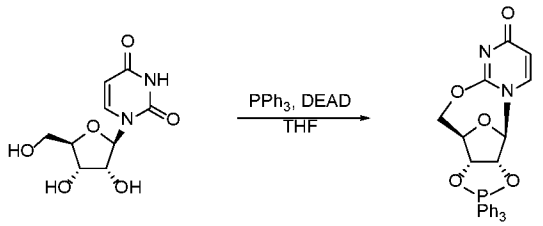
[0186] ***PREPARATIONS***

[0187] The following experimental procedures detail the preparation of specific examples of the instant disclosure. The compounds of the examples are drawn in their neutral forms in the procedures and tables below. In some cases, the compounds were isolated as salts depending on the method used for their final purification and/or intrinsic molecular properties. The examples are for illustrative purposes only and are not intended to limit the scope of the instant disclosure in any way.

[0188] **Preparation 1: 8-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl) tetrahydrofuran-2-yl)imidazo[1,2-a]pyrimidin-5(8H)-one**

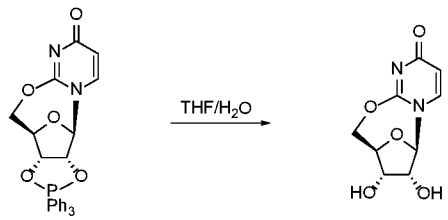


[0189] *Step 1: (3aR,4R,12R,12aR)-2,2,2-triphenyl-3a,4,12,12a-tetrahydro-5H,8H-2l5-4,12-epoxy[1,3,2]dioxaphospholo[4,5-e]pyrimido[2,1-b][1,3]oxazocin-8-one*



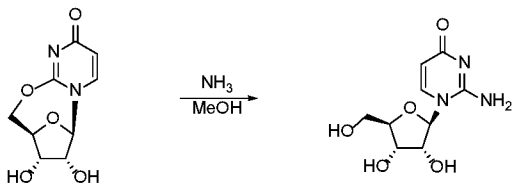
[0190] To a stirred solution of uridine (50g, 205mmol) in THF (500mL) was added PPh_3 (161g, 614mmol). DEAD (107g, 614mmol) was added to the mixture dropwise. The reaction mixture was left to stir for 12h and filtered. The product was recrystallized from DMF (2L) at 80°C. ^{1}H-NMR (400MHz, DMSO-d_6): δ 8.05 (br d, *J*=7.5Hz, 1H), 7.67-7.51 (m, 2H), 7.47-7.17 (m, 15H), 5.96-5.85 (m, 2H), 4.84 (br dd, *J*=6.6, 13.2Hz, 1H), 4.73 (s, 1H), 4.60-4.46 (m, 2H), 4.16 (br d, *J*=12.7Hz, 1H).

[0191] *Step 2: (6R,7R,8S,9R)-7,8-dihydroxy-7,8,9,10-tetrahydro-2H,6H-6,9-epoxypyrimido[2,1-b][1,3]oxazocin-2-one*



[0192] A mixture of (3aR,4R,12R,12aR)-2,2,2-triphenyl-3a,4,12,12a-tetrahydro-5H,8H-2l5-4,12-epoxy[1,3,2]dioxaphospholo[4,5-e]pyrimido[2,1-b][1,3]oxazocin-8-one (50g, 103mmol) in THF (500mL) and H_2O (500mL) was heated to 60°C for 12h. The mixture was cooled to RT and concentrated. To the residue was added acetone (200mL). The mixture was allowed to stir for 10min, filtered, and washed with acetone. The filter cake was dried *in vacuo* to give the product. ^{1}H-NMR (400MHz, DMSO-d_6): δ 8.02 (br d, *J*=7.0Hz, 1H), 5.93 (br d, *J*=7.0Hz, 1H), 5.58 (s, 1H), 5.42 (br s, 2H), 4.57-4.43 (m, 2H), 4.43-4.26 (m, 2H), 4.10 (br d, *J*=12.7Hz, 1H).

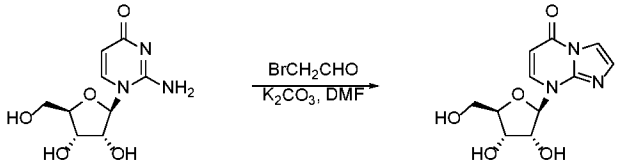
[0193] *Step 3: 2-amino-1-(β-D-ribofuranosyl)pyrimidin-4(1H)-one*



[0194] A mixture of (6*R*,7*R*,8*S*,9*R*)-7,8-dihydroxy-7,8,9,10-tetrahydro-2*H*,6*H*-6,9-epoxypyrimido[2,1-*b*][1,3]oxazocin-2-one (5.0g, 22mmol) in sat NH_3 in MeOH (60mL) in

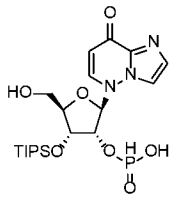
autoclave was heated to 60°C for 12h. The mixture was cooled to RT and concentrated to give the product. LCMS (ES, m/z): 244 $[M+H]^+$. ^{1}H-NMR (400MHz, DMSO-d_6): δ 7.62 (br d, *J*=7.1Hz, 1H), 6.95 (br s, 2H), 5.58 (br d, *J*=7.5Hz, 1H), 5.54-5.37 (m, 2H), 5.37-5.16 (m, 2H), 4.12 (br s, 2H), 4.04-3.89 (m, 2H), 3.60 (br s, 2H), 3.17 (br s, 3H).

[0195] *Step 4: 8-(β-D-ribofuranosyl)-8,8a-dihydroimidazo[1,2-a]pyrimidin-5(1H)-one*

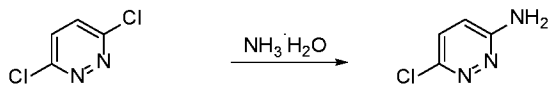


[0196] To a stirred solution of 2-amino-1-(β-D-ribofuranosyl)pyrimidin-4(1*H*)-one (8.0g, 33mmol) in DMF (80mL) were added K_2CO_3 (13.6g, 99mmol) and $BrCH_2CHO$ (32g, 260mmol). The reaction mixture was heated to 40°C for 4h, cooled to RT, and filtered. The filtrate was purified by reverse phase chromatography eluted with 1-25% ACN in aq NH_4OH (0.05% v/v) to give the product. LCMS (ES, m/z): 268 $[M+H]^+$. ^{1}H-NMR (400MHz, DMSO-d_6): δ 8.19 (br d, *J*=7.5Hz, 1H), 7.65 (br s, 1H), 7.26 (br s, 1H), 6.10 (br s, 1H), 6.02 (br d, *J*=7.5Hz, 1H), 4.59 (br s, 1H), 4.27 (br d, *J*=15.9Hz, 2H), 3.99-3.90 (m, 1H), 3.88-3.79 (m, 1H).

[0197] **Preparation 2: (2R,3R,4R,5R)-5-(hydroxymethyl)-2-(8-oxoimidazo[1,2-b]pyridazin-5(8H)-yl)-4-((triisopropylsilyl)oxy)tetrahydrofuran-3-yl hydrogen phosphonate**



[0198] *Step 1: 6-chloropyridazin-3-amine*

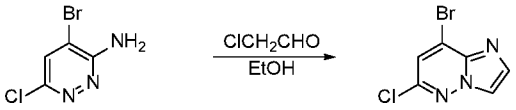


[0199] A mixture of 3,6-dichloropyridazine (100g, 671mmol) and NH_4OH (47g, 50%, 671mmol) was heated to 120°C for 16h, cooled to RT, and filtered to give the product. ^{1}H-NMR (400MHz, DMSO-d_6): δ 7.35 (s, 1H), 6.84 (s, 1H), 6.63 (s, 2H).

[0200] *Step 2: 4-bromo-6-chloropyridazin-3-amine*

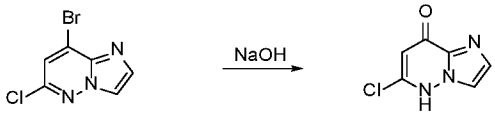
[0201] To a stirred solution of 6-chloropyridazin-3-amine (179g, 1.38mol) in MeOH (2L) was added $NaHCO_3$ (232g, 2.76mol). Br_2 (265g, 1.66mol) was added to the mixture dropwise. The reaction mixture was left to stir at RT for 16h and concentrated to give the crude product. The residue was used in the next step without further purification.

[0202] *Step 3: 8-bromo-6-chloroimidazo[1,2-b]pyridazine*



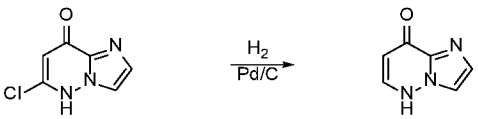
[0203] To the crude 4-bromo-6-chloropyridazin-3-amine (120g, 576mmol) was added EtOH (1.2L). $ClCH_2CHO$ (600g, 7.65mol) was added to the mixture over 30min. The reaction mixture was heated to 90°C for 3h, cooled to RT, and concentrated. The residue was purified by silica gel column chromatography eluted with 9-50% EtOAc in petroleum ether to give the product. ^{1}H-NMR (400MHz, DMSO-d_6): δ 8.01 (s, 1H), 7.68 (brs, 1H), 6.03 (s, 1H).

[0204] *Step 4: 6-chloroimidazo[1,2-b]pyridazin-8(5H)-one*



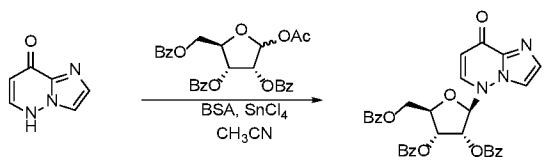
[0205] To 8-bromo-6-chloroimidazo[1,2-b]pyridazine (70g, 301mmol) were added H_2O (700mL) and NaOH (26g, 647mmol). The reaction mixture was heated to 100°C for 16h, cooled to RT, and neutralized to pH 6-7 with HCl. The product was collected by filtration.

[0206] *Step 5: imidazo[1,2-b]pyridazin-8(5H)-one*



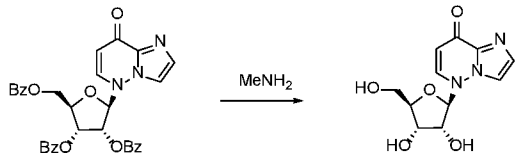
[0207] A flask containing 6-chloroimidazo[1,2-*b*]pyridazin-8(5*H*)-one (36g, 212mmol) and Pd/C (13g) in MeOH was degassed and purged with H_2 for three times. The reaction mixture was left to stir under H_2 (50psi) at 40°C for 16h, cooled to RT, and filtered. The filtrate was concentrated to give the product. ^{1}H-NMR (400MHz, DMSO-d_6): δ 8.60 (d, 1H), 8.57 (d, 1H), 8.23 (d, 1H), 7.17 (d, 1H).

[0208] *Step 6: 5-[2,3,5-tris-O-(phenylcarbonyl)-β-D-ribofuranosyl]imidazo[1,2-b]pyridazin-8(5H)-one*



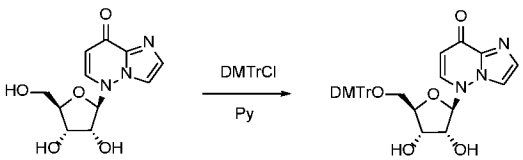
[0209] A mixture of imidazo[1,2-*b*]pyridazin-8(5*H*)-one (18g, 133mmol) and N,O-bis(trimethylsilyl)acetamide (108g, 532mmol) in MeCN (200mL) was heated to 70°C for 1h and cooled to RT. To the mixture were added 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribofuranose (45g, 89mmol), CH_3CN (200mL), and $SnCl_4$ (45.7g, 175mmol). The mixture was heated to 70°C for 3h, cooled to RT, and concentrated. The residue was purified by silica gel column chromatography eluted with 9-100% of EtOAc in petroleum ether to give the product. LCMS (ES, m/z): 580 $[M+H]^+$. ^{1}H-NMR (400MHz, DMSO-d_6): δ 8.26 (s, 1H), 8.18 (s, 1H), 8.01-8.03 (d, *J*=8Hz, 3H), 7.92-7.94 (d, *J*=8Hz, 2H), 7.84–7.85 (d, *J*=4Hz, 2H), 7.74 (s, 1H), 7.60-7.65 (m, 3H), 7.40-7.52 (m, 2H), 6.01-6.07 (m, 3H), 4.81-4.88 (m, 3H).

[0210] *Step 7: 5-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)imidazo[1,2-b]pyridazin-8(5H)-one*



[0211] (2R,3R,4R,5R)-2-((benzoyloxy)methyl)-5-(8-oxoimidazo[1,2-b]pyridazin-5(8H)-yl)tetrahydrofuran-3,4-diyl dibenzoate (3.9g, 5.38mmol) was dissolved in a solution of $MeNH_2$ in EtOH (30%, 60mL), and the resulting solution was stirred at RT for 6h. Then, the mixture was concentrated under reduced pressure, and the residue was purified by reverse phase (C18) chromatography eluted with 0 to 95% ACN in aq NH_4HCO_3 (0.04%) to give the product. LCMS (ES, m/z): 268.3 $[M+H]^+$. ^{1}H-NMR (400MHz, DMSO-d_6): δ 8.29 (d, *J*=2.3Hz, 1H), 8.21 (d, *J*=2.3Hz, 1H), 8.02 (d, *J*=6.4Hz, 1H), 7.14 (d, *J*=4.9Hz, 1H), 6.05 (d, *J*=6.4Hz, 1H), 5.61 (d, *J*=5.4Hz, 1H), 5.20 (t, *J*=5.1Hz, 1H), 5.15 (d, *J*=5.0Hz, 1H), 4.23 (q, *J*=5.0Hz, 1H), 4.11 (q, *J*=4.8Hz, 1H), 3.96 (q, *J*=3.6Hz, 1H), 3.73-3.68 (m, 1H), 3.63-3.58 (m, 1H).

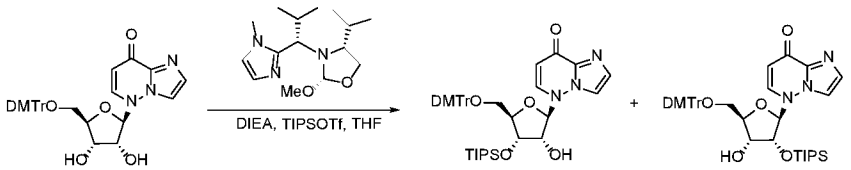
[0212] *Step 8: 5-((2R,3R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-3,4-dihydroxytetrahydrofuran-2-yl)imidazo[1,2-b]pyridazin-8(5H)-one*



[0213] To a solution of 5-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl) tetrahydrofuran-2-yl)imidazo[1,2-b]pyridazin-8(5H)-one (800mg, 2.99mmol) in Py (11mL) at 0°C was added 4,4'-(chloro(phenyl)methylene)bis (methoxybenzene) (0.112g, 3.29mmol). The mixture was stirred at RT for 2h. Then, the mixture was concentrated, and the residue was

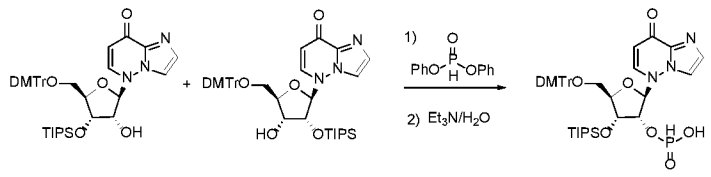
dissolved in CH_2Cl_2 (50mL). The solution was washed with sat aq $NaHCO_3$ (10mL), dried (Na_2SO_4) and concentrated. It was purified by silica gel column chromatography eluted with 0-10% MeOH in DCM (containing 1% Et_3N) to give the product. LCMS (ES, m/z): 568.2 $[M-H]^-$. ^{1}H-NMR (400MHz, DMSO-d_6): δ 8.17 (d, *J*=2.2Hz, 1H), 8.04 (d, *J*=6.4Hz, 1H), 7.99 (d, *J*=2.3Hz, 1H), 7.43-7.35 (m, 2H), 7.33-7.21 (m, 7H), 7.18 (d, *J*=4.0Hz, 1H), 6.93-6.84 (m, 4H), 6.08 (d, *J*=6.4Hz, 1H), 5.73 (d, *J*=5.3Hz, 1H), 5.20 (d, *J*=5.9Hz, 1H), 4.27 (q, *J*=4.9Hz, 1H), 4.16 (q, *J*=5.5Hz, 1H), 4.07 (dd, *J*=5.2, 3.5Hz, 1H), 3.73 (s, 6H), 3.26-3.24 (m, 2H).

[0214] *Step 9: 5-((2R,3R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-3-hydroxy-4-((triisopropylsilyl)oxy)tetrahydrofuran-2-yl)imidazo[1,2-b]pyridazin-8(5H)-one and 5-((2R,3R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxy-3-((triisopropylsilyl)oxy)tetrahydrofuran-2-yl)imidazo[1,2-b]pyridazin-8(5H)-one*



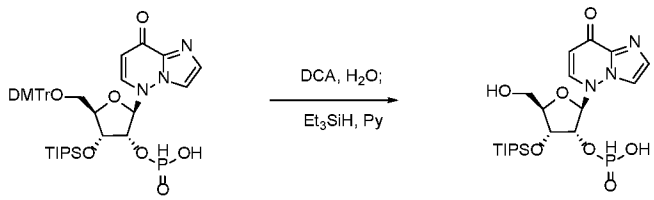
[0215] To a solution of 5-((2R,3R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy) methyl)-3,4-dihydroxytetrahydrofuran-2-yl)imidazo[1,2-b]pyridazin-8(5H)-one (1.00g, 1.76mmol) in THF (17mL) was added (2*S*,4*R*)-2-methoxy-3-[(1*S*)-2-methyl-1-(1-methyl-1*H*-imidazol-2-yl)propyl]-4-(propan-2-yl)-1,3-oxazolidine (42mg, 0.15mmol), *N*-ethyl-*N*-isopropylpropan-2-aminium chloride (6.8mg, 0.053mmol), and *N*-ethyl-*N*-isopropylpropan-2-amine (682mg, 5.28mmol). The resulting mixture was stirred at RT for 5min and then, cooled to 0°C. To the reaction was added TIPSOTf (1.62g, 5.28mmol) over 2min. It was stirred at RT for 4h. Then, EtOAc (100mL) and H_2O (50mL) were added. Layers were separated, and the aq layer was extracted with EtOAc (3×100mL). The combined organic layer was dried (Na_2SO_4), and concentrated to give a mixture containing the products. The crude was used for the next step without purification. LCMS (ES, m/z): 724.3 $[M-H]^-$.

[0216] *Step 10: (2R,3R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-2-(8-oxoimidazo[1,2-b]pyridazin-5(8H)-yl)-4-((triisopropylsilyl)oxy)tetrahydrofuran-3-yl hydrogen phosphonate*



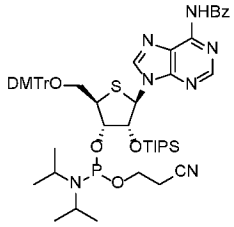
[0217] To a solution of the crude from Step 9 (3.5g, ~1.7mmol) in pyridine (9mL) at 0°C under Ar was added diphenyl phosphonate (2.06g, 8.80mmol) over 0.5min. The resulting mixture was warmed to RT for 20min. To the reaction mixture cooled at 0°C was added TEA (1.8mL) in H_2O (1.8mL) dropwise over 0.5min. It was warmed to RT for 30min. The mixture was concentrated and then, co-evaporated with toluene (3×20mL) to give a crude. It was partitioned between CH_2Cl_2 (300mL) and aq $NaHCO_3$ (5%, 80mL). The organic layer was washed with aq $NaHCO_3$ (2×80mL), dried (Na_2SO_4) and concentrated. The residue was purified by reverse phase (C18) chromatography eluted with 35 to 55% ACN in aq NH_4HCO_3 (10mM) to give the product. LCMS (ES, m/z): 788.3 $[M-H]^-$. ^{1}H-NMR (400MHz, DMSO-d_6): δ 8.25 (d, *J*=2.2Hz, 1H), 8.09–8.00 (m, 1H), 7.98 (d, *J*=2.3Hz, 1H), 7.49-7.35 (m, 3H), 7.34-7.21 (m, 8H), 6.89 (d, *J*=8.6Hz, 4H), 6.16–6.06 (m, 1H), 4.71-4.54 (m, 2H), 4.48-4.29 (m, 1H), 3.75 (d, *J*=2.5Hz, 6H), 3.72-3.64 (m, 1H), 3.36 (d, *J*=14.6Hz, 5H), 3.00 (q, *J*=7.3Hz, 2H), 1.34-1.19 (m, 5H), 1.03-0.87 (m, 12H), 0.81 (d, *J*=6.7Hz, 8H). ^{31}P-NMR: (162MHz, DMSO-d_6) δ 0.80 (s).

[0218] *Step 11: (2R,3R,4R,5R)-5-(hydroxymethyl)-2-(8-oxoimidazo[1,2-b]pyridazin-5(8H)-yl)-4-((triisopropylsilyl)oxy)tetrahydrofuran-3-yl hydrogen phosphonate*

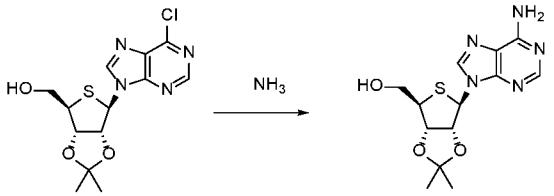


[0219] To a stirred solution of (2R,3R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl) methoxy)methyl)-2-(8-oxoimidazo[1,2-b]pyridazin-5(8H)-yl)-4-((triisopropylsilyl)oxy) tetrahydrofuran-3-yl hydrogen phosphonate (0.38g, 0.47mmol) in CH_2Cl_2 (6mL) was added H_2O (85mg, 4.7mmol), and DCA in CH_2Cl_2 (6%, 6.0mL, 4.2mmol). The mixture was stirred at RT for 15min, and then Et_3SiH (10mL) was added. After 40min, Py (0.66mL) was added to the reaction at 0°C, and the mixture was stirred for 5min. The reaction was concentrated to provide (2R,3R,4R,5R)-5-(hydroxymethyl)-2-(8-oxoimidazo[1,2-b]pyridazin-5(8H)-yl)-4-((triisopropyl-silyl)oxy)tetrahydrofuran-3-yl hydrogen phosphonate. LCMS (ES, m/z): 488.2 $[M+H]^+$.

[0220] **Preparation 3: (2R,3S,4R,5R)-5-(6-benzamido-9H-purin-9-yl)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-((triisopropylsilyl)oxy)tetrahydrothiophen-3-yl (2-cyanoethyl) diisopropylphosphoramidite**

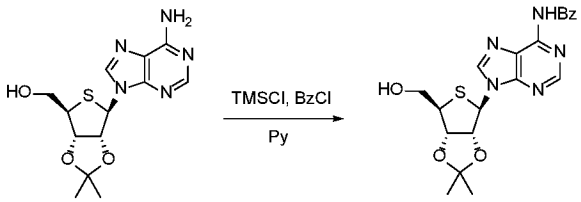


[0221] *Step 1: ((3aS,4R,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyltetrahydrothieno [3,4-d][1,3]dioxol-4-yl)methanol*



[0222] To a tube was added ((3aS,4R,6R,6aR)-6-(6-chloro-9H-purin-9-yl)-2,2-dimethyltetrahydrothieno[3,4-d][1,3]dioxol-4-yl)methanol (3.80g, 11.1mmol) in NH_3 in *i*-PrOH (2.0M, 200mL). The tube was sealed, and the reaction was stirred at 90°C for 16h. The mixture was concentrated. The residue was purified by a silica gel column, eluted with 0-20% MeOH in DCM to give the product. LCMS (ES, m/z): 324.1 $[M+H]^+$. ^{1}H-NMR (400MHz, DMSO-d_6): δ 8.41 (s, 1H), 8.18 (s, 1H), 7.32 (s, 2H), 6.08 (d, *J*=2.5Hz, 1H), 5.43-5.29 (m, 2H), 5.05 (dd, *J*=5.5, 1.5Hz, 1H), 3.73-3.55 (m, 3H), 1.54 (s, 3H), 1.31 (s, 3H).

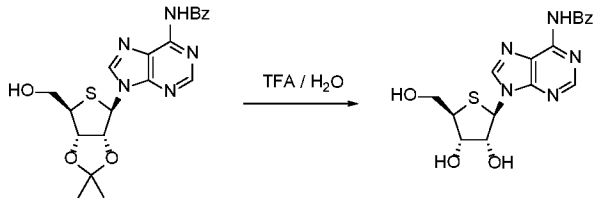
[0223] *Step 2: N-(9-((3aR,4R,6R,6aS)-6-(hydroxymethyl)-2,2-dimethyltetrahydrothieno [3,4-d][1,3]dioxol-4-yl)-9H-purin-6-yl)benzamide*



[0224] To a solution of ((3a*S*,4*R*,6*R*,6a*R*)-6-(6-amino-9*H*-purin-9-yl)-2,2-dimethyltetrahydrothieno[3,4-*d*][1,3]dioxol-4-yl)methanol (2.60g, 8.04mmol) in Py (30mL) at 0°C was added TMSCl (8.7g, 80mmol) dropwise. The mixture was warmed to RT and continued to stir for 2h. Then, BzCl (1.70g, 12.1mmol) was added, and the resulting mixture was stirred at RT for 2h. NH_4OH (28%, 2mL) was added to the mixture, and it was stirred for 2h. Then, the reaction was concentrated under reduced pressure, and the residue was purified by a silica gel column chromatography eluted with 0-20% MeOH in DCM to give the product. LCMS (ES, m/z): 428.1 $[M+H]^+$. ^{1}H-NMR (400MHz, DMSO-d_6): δ 11.22 (s, 1H), 8.79 (s, 1H), 8.76 (s, 1H), 8.10-8.02 (m, 2H), 7.80-7.70 (m, 1H), 7.71-7.50 (m, 3H), 6.21 (d, *J*=2.2Hz, 1H), 5.46 (dd, *J*=5.5,

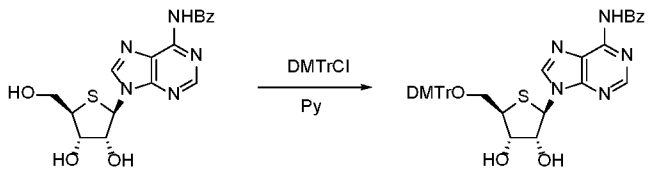
2.3Hz, 1H), 5.42-5.30 (m, 1H), 5.08 (dd, *J*=5.5, 1.4Hz, 1H), 3.74-3.58 (m, 2H), 1.57 (s, 3H), 1.33 (s, 3H).

[0225] *Step 3: N-(9-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrothiophen-2-yl)-9H-purin-6-yl)benzamide*



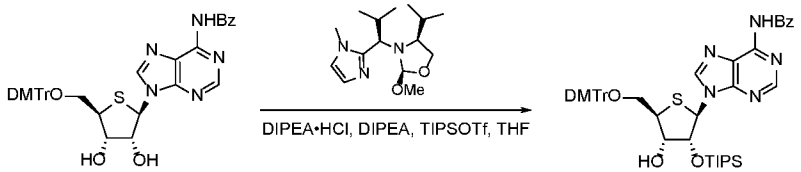
[0226] To a solution *N*-(9-((3a*R*,4*R*,6*R*,6a*S*)-6-(hydroxymethyl)-2,2-dimethyltetrahydrothieno[3,4-*d*][1,3]dioxol-4-yl)-9*H*-purin-6-yl)benzamide (2.7g, 6.3mmol) in H_2O (75mL) at 0°C was added TFA (75mL). The solution was stirred at RT for 30min. The mixture was concentrated and the, co-evaporated with toluene (4×100mL). The residue was purified by a silica gel column eluted with 0-20% MeOH in DCM to give the product. LCMS (ES, m/z): 388.2 $[M+H]^+$. ^{1}H-NMR (400MHz, DMSO-d_6): δ 11.16 (br, s, 1H), 8.78 (s, 1H), 8.72 (s, 1H), 8.07-7.97 (m, 2H), 7.68-7.46 (m, 3H), 5.97 (d, *J*=6.8Hz, 1H), 4.71 (dd, *J*=6.8, 3.4Hz, 1H), 4.21 (t, *J*=3.4Hz, 1H), 3.80 (dd, *J*=11.3, 6.9Hz, 1H), 3.62 (dd, *J*=11.4, 5.8Hz, 1H), 3.41-3.26 (m, 1H).

[0227] *Step 4: N-(9-((2R,3R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-3,4-dihydroxytetrahydrothiophen-2-yl)-9H-purin-6-yl)benzamide*



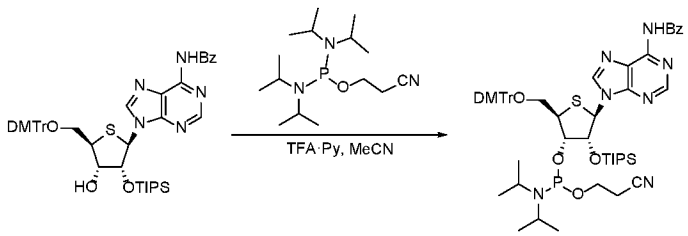
[0228] To a solution of *N*-(9-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl) tetrahydrothiophen-2-yl)-9*H*-purin-6-yl)benzamide (2g, 5.16mmol) in pyridine (5mL) at 0°C was added 4,4'-(chloro(phenyl)methylene)bis(methoxybenzene) (1.92g, 5.68mmol). The solution was stirred at RT for 3h. Then, MeOH (3mL) was added, and it was concentrated. The residue was purified by a silica gel column chromatography eluted with 0-20% MeOH in DCM to give the product. LCMS (ES, m/z): 690.2 $[M+H]^+$. ^{1}H-NMR (400MHz, DMSO-d_6): δ 11.23 (br, s, 1H), 8.64 (s, 1H), 8.58 (s, 1H), 8.09-8.02 (m, 2H), 7.71-7.61 (m, 1H), 7.61-7.52 (m, 2H), 7.51-7.38 (m, 2H), 7.38-7.22 (m, 7H), 6.97-6.82 (m, 4H), 5.99 (d, *J*=5.9Hz, 1H), 5.73 (d, *J*=5.6Hz, 1H), 5.43 (d, *J*=5.0Hz, 1H), 4.70 (q, *J*=4.9Hz, 1H), 4.28 (q, *J*=3.7Hz, 1H), 3.76-3.75 (m, 7H), 3.59-3.36 (m, 2H).

[0229] *Step 5: N-(9-((2R,3R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxy-3-((triisopropylsilyl)oxy)tetrahydrothiophen-2-yl)-9H-purin-6-yl)benzamide*



[0230] *N*-(9-((2*R*,3*R*,4*S*,5*R*)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-3,4-dihydroxytetrahydrothiophen-2-yl)-9*H*-purin-6-yl)benzamide (1.23g, 1.78mmol), (2*R*,4*S*)-4-isopropyl-2-methoxy-3-((*R*)-2-methyl-1-(1-methyl-1*H*-imidazol-2-yl)propyl)oxazolidine (0.753g, 2.67mmol), and *N*-ethyl-*N*-isopropylpropan-2-aminium chloride (8.9mg, 0.053mmol) were co-evaporated with THF (3×10mL) and then re-dissolved in THF (80mL) under Ar. To the mixture at 0°C was added *N*-ethyl-*N*-isopropylpropan-2-amine (0.691g, 5.35mmol). It was stirred at RT for 5min, and then TIPSOTf (1.64g, 5.35mmol) was added dropwise. The mixture was stirred at RT for 16h. Then, the solution was diluted with EtOAc (50mL) and washed with Na_2CO_3 (3×50mL). The organic layer was dried ($MgSO_4$) and concentrated to give a crude containing the product. The residue was used for the next reaction step without further purification. LCMS (ES, m/z): 846.3 $[M+H]^+$.

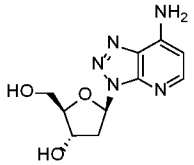
[0231] *Step 6: (2R,3S,4R,5R)-5-(6-benzamido-9H-purin-9-yl)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-((triisopropylsilyl)oxy)tetrahydrothiophen-3-yl (2-cyanoethyl) diisopropylphosphoramidite*



[0232] To a stirred solution of 3-((bis(diisopropylamino)phosphino)oxy)propanenitrile (1.43g, 4.76mmol) in MeCN (15mL) under Ar was added pyridin-1-ium 2,2,2-trifluoroacetate (688mg, 3.57mmol) and a solution of the crude from Step 5 (~2.0g, 2.4mmol) in MeCN (15mL) over 2min. It was stirred at RT for 1h. Then, it was concentrated, and the residue was dissolved in EtOAc (100mL). The solution was washed with aq $NaHCO_3$ (1%, 2×100mL), H_2O (100mL) and brine (100mL), dried (Na_2SO_4), and purified by reverse phase (C18) chromatography eluted with 40 to 100% ACN in H_2O to give the product. LCMS (ES, m/z): 1046.5 $[M+H]^+$. ^{1}H-NMR (400MHz, DMSO-d_6): δ 11.17 (s, 1H), 8.60 (d, *J*=1.5Hz, 1H), 8.50-8.43 (m, 1H), 8.09-7.99 (m,

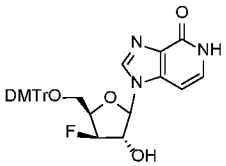
2H), 7.72-7.62 (m, 1H), 7.57-7.54 (m, 2H), 7.47-7.44 (m, 2H), 7.40-7.23 (m, 7H), 6.95-6.92 (m, 4H), 6.05-5.97 (m, 1H), 5.30-5.26 (m, 1H), 4.71-4.67 (m, 1H), 3.94-3.82 (m, 2H), 3.76 (d, *J*=1.5Hz, 6H), 3.70 (t, *J*=3.6Hz, 1H), 3.61-3.58 (m, 1H), 3.50-3.38 (m, 1H), 2.77-2.67 (m, 2H), 2.53-2.49 (m, 2H), 1.18 (dt, *J*=18.4, 6.9Hz, 12H), 0.94-0.72 (m, 21H). ^{31}P-NMR (162MHz, DMSO-d_6): δ 149.66, 149.23.

[0233] **Preparation 4: (2R,3S,5R)-5-(7-amino-3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-2-(hydroxymethyl)tetrahydrofuran-3-ol**

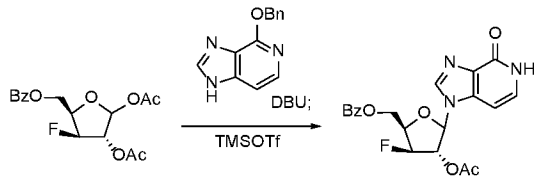


[0234] The title compound was prepared according to published procedure (*Nucleoside & Nucleotides* **1992**, *11*, 1059-1076).

[0235] **Preparation 5: 1-((3S,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)-1,5-dihydro-4H-imidazo[4,5-c]pyridin-4-one**



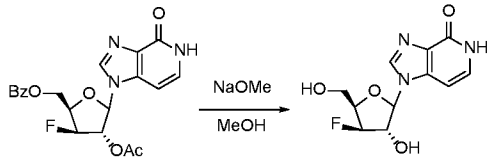
[0236] *Step 1: ((2R,3S,4S)-4-acetoxy-3-fluoro-5-(4-oxo-4,5-dihydro-1H-imidazo[4,5-c]pyridin-1-yl)tetrahydrofuran-2-yl)methyl benzoate*



[0237] To a suspension of 4-(benzyloxy)-1*H*-imidazo[4,5-*c*]pyridine (0.795g, 3.53mmol) and (3*S*,4*S*,5*R*)-5-((benzoyloxy)methyl)-4-fluorotetrahydrofuran-2,3-diyl diacetate (1.00g, 2.94mmol) in MeCN (20mL) and DCE (10mL) at 0°C under Ar was added 3,4,6,7,8,9,10-octahydropyrimido[1,2-*a*]azepine (1.34g, 8.82mmol). The resulting mixture was stirred at 0°C for 30min. Then, TIPSOTf (3.92g, 17.7mmol) was added to the solution, and it was stirred at 0°C for 30min. Then, the solution was heated to 80°C for 16h. Then, the reaction mixture was

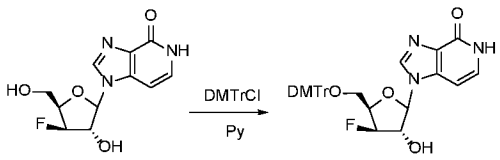
cooled to 0°C, and sat aq $NaHCO_3$ (10mL) and H_2O (30mL) were added. Layers were separated, and the aq layer was extracted with EtOAc (3×50mL). The combined organic layers were washed with brine (100mL), dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography, eluted with 1 to 10% MeOH in DCM to afford the product. LCMS (ES, m/z): 416.3 $[M+H]^+$.

[0238] *Step 2: 1-((3S,4R,5R)-4-fluoro-3-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-1,5-dihydro-4H-imidazo[4,5-c]pyridin-4-one*



[0239] To a stirred solution of ((2*R*,3*S*,4*S*)-4-acetoxy-3-fluoro-5-(4-oxo-4,5-dihydro-1*H*-imidazo[4,5-*c*]pyridin-1-yl)tetrahydrofuran-2-yl)methyl benzoate (2.5g, 5.3mmol) in MeOH (10mL) was added NaOMe (3.47g, 21.2mmol). The mixture was stirred at RT for 1h. Then, it was neutralized by addition of CH_3COOH. The solution was concentrated under reduced pressure, and the residue was purified by reverse phase (AQ-C18) chromatography eluted with 0 to 30% ACN in aq NH_4HCO_3 (5mM) to give the product. LCMS (ES, m/z): 270.0 $[M+H]^+$. ^{1}H-NMR (400MHz, DMSO-d_6): δ 11.31 (s, 1H), 8.06 (s, 1H), 7.23 (d, *J*=7.1Hz, 1H), 6.62 (d, *J*=7.1Hz, 1H), 6.37 (d, *J*=2.9Hz, 1H), 5.85 (d, *J*=2.8Hz, 1H), 5.22–4.98 (m, 2H), 4.54 (d, *J*=17.7Hz, 1H), 4.28 (dtd, *J*=29.6, 6.0, 3.1Hz, 1H), 3.93-3.62 (m, 2H).

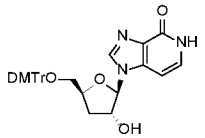
[0240] *Step 3: 1-((3S,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)-1,5-dihydro-4H-imidazo[4,5-c]pyridin-4-one*



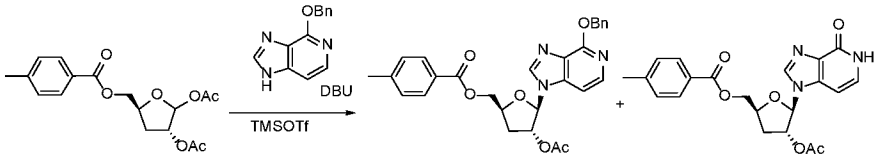
[0241] To a solution of 1-((3S,4R,5R)-4-fluoro-3-hydroxy-5-(hydroxymethyl) tetrahydrofuran-2-yl)-1,5-dihydro-4H-imidazo[4,5-c]pyridin-4-one (340mg, 1.26mmol) in Py (0.5mL) was added 4,4'-(chloro(phenyl)methylene)bis(methoxybenzene) (0.43g, 1.1mmol). The solution was stirred at RT for 4h. Then, the mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography eluted with 1 to 10% MeOH in DCM (0.5% Et_3N) to afford the product. LCMS (ES, m/z): 572.3 $[M+H]^+$. ^{1}H-NMR (400MHz, DMSO-d_6): δ δ 11.32 (d, *J*=5.9Hz, 1H), 7.95 (s, 1H), 7.41 (d, *J*=7.8Hz, 2H), 7.37–7.15 (m, 8H), 6.86 (dd, *J*=10.5, 8.6Hz, 4H), 6.60 (d, *J*=7.1Hz, 1H), 6.50–6.36 (m, 1H), 5.92 (d,

J=2.6Hz, 1H), 5.77 (s, 1H), 5.27-5.06 (m, 1H), 4.65–4.42 (m, 2H), 3.73 (d, *J*=2.6Hz, 6H), 3.30-3.24 (m, 1H).

[0242] **Preparation 6: 1-((2R,3R,5S)-5-((bis(4-methoxyphenyl)(phenyl)methoxy) methyl)-3-hydroxytetrahydrofuran-2-yl)-1,5-dihydro-4H-imidazo[4,5-c]pyridin-4-one**

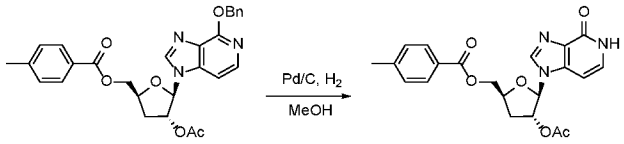


[0243] *Step 1: ((2S,4R,5R)-4-acetoxy-5-(4-(benzyloxy)-1H-imidazo[4,5-c]pyridin-1-yl)tetrahydrofuran-2-yl)methyl 4-methylbenzoate and ((2S,4R,5R)-4-acetoxy-5-(4-oxo-4,5-dihydro-1H-imidazo[4,5-c]pyridin-1-yl)tetrahydrofuran-2-yl)methyl 4-methylbenzoate*



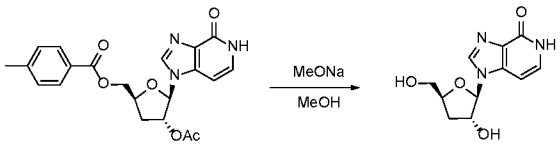
[0244] A mixture of (3*R*,5*S*)-5-(((4-methylbenzoyl)oxy)methyl)tetrahydrofuran-2,3-diyl diacetate (2.69g, 8.00mmol) and 4-(benzyloxy)-1*H*-imidazo[4,5-c]pyridine (1.98g, 8.80mmol) was co-evaporated with MeCN (5×15mL) and then, re-dissolved in MeCN (64mL) under Ar. To the mixture was added 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepine (1.32mL, 8.80mmol) and TIPSOTf (3.05mL, 16.8mmol). It was stirred at 80°C for 1h. Then, it was cooled to RT, and sat aq $NaHCO_3$ (40mL) and H_2O (150mL) were added. Layers were separated, and the aq layer was extracted with EtOAc (3×100mL). The combined organic phase was washed with brine (300mL), dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography eluted with 0-10% MeOH in DCM to give ((2S,4R,5R)-4-acetoxy-5-(4-(benzyloxy)-1H-imidazo[4,5-c]pyridin-1-yl)tetrahydrofuran-2-yl)methyl 4-methylbenzoate. LCMS (ES, m/z): 502.2 $[M+H]^+$. ^1H NMR (300MHz, DMSO-d_6): δ 8.41 (s, 1H), 7.88-7.75 (m, 3H), 7.56-7.45 (m, 2H), 7.42–7.28 (m, 6H), 6.26 (d, *J*=1.7Hz, 1H), 5.59-5.47 (m, 3H), 4.76-4.41 (m, 3H), 2.62–2.54 (m, 1H), 2.41–2.22 (m, 4H), 2.12 (s, 3H). Later fractions gave ((2S,4R,5R)-4-acetoxy-5-(4-oxo-4,5-dihydro-1H-imidazo[4,5-c]pyridin-1-yl)tetrahydrofuran-2-yl)methyl 4-methylbenzoate: LCMS (ES, m/z): 412.1 $[M+H]^+$. ^1H NMR (300MHz, DMSO-d_6): δ 11.23 (s, 1H), 8.20 (s, 1H), 7.81 (d, *J*=8.0Hz, 2H), 7.33 (d, *J*=7.9Hz, 2H), 7.12 (t, *J*=6.4Hz, 1H), 6.65 (d, *J*=7.1Hz, 1H), 6.16 (d, *J*=1.5Hz, 1H), 5.45 (d, *J*=5.8Hz, 1H), 4.75–4.39 (m, 3H), 2.39 (s, 3H), 2.33–2.22 (m, 2H), 2.11 (s, 3H).

[0245] *Step 2: ((2S,4R,5R)-4-acetoxy-5-(4-oxo-4,5-dihydro-1H-imidazo[4,5-c]pyridin-1-yl)tetrahydrofuran-2-yl)methyl 4-methylbenzoate*



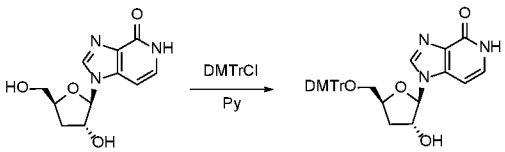
[0246] To a solution of ((2*S*,4*R*,5*R*)-4-acetoxy-5-(4-(benzyloxy)-1*H*-imidazo[4,5-c]pyridin-1-yl)tetrahydrofuran-2-yl)methyl 4-methylbenzoate (1.86g, 3.70mmol) in MeOH (40mL) was added Pd/C (10%, 0.80g). It was hydrogenated (1atm) at RT for 5h. Then, the mixture was filtered, and the filtrate was concentrated. The residue was purified by silica gel column chromatography eluted with 0-10% MeOH in DCM to give the product.

[0247] *Step 3: 1-((2R,3R,5S)-3-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-1,5-dihydro-4H-imidazo[4,5-c]pyridin-4-one*



[0248] To a solution of ((2*S*,4*R*,5*R*)-4-acetoxy-5-(4-oxo-4,5-dihydro-1*H*-imidazo[4,5-c]pyridin-1-yl)tetrahydrofuran-2-yl)methyl 4-methylbenzoate (1.60g, 3.88mmol) in MeOH (60mL) was added MeONa (0.52g, 9.7mmol). It was stirred at RT for 5h. Then, it was neutralized with diluted aq HCl. The resulting mixture was concentrated under reduced pressure, and the residue was purified by reverse phase (C18) chromatography eluted with 0 to 95% ACN in aq NH_4HCO_3 (5mM) to give the product. LCMS (ES, m/z): 251.9 $[M+H]^+$. ^{1}H-NMR (300MHz, DMSO-d_6): δ 8.25 (s, 1H), 7.15 (d, *J*=7.1Hz, 1H), 6.65 (d, *J*=7.1Hz, 1H), 5.72 (d, *J*=2.1Hz, 1H), 4.35-4.28 (m, 2H), 3.67 (dd, *J*=12.1, 3.2Hz, 1H), 3.50 (dd, *J*=12.0, 3.8Hz, 1H), 2.16–2.07 (m, 1H), 1.88-1.81 (m, 1H).

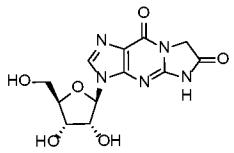
[0249] *Step 4: 1-((2R,3R,5S)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-3-hydroxytetrahydrofuran-2-yl)-1,5-dihydro-4H-imidazo[4,5-c]pyridin-4-one*



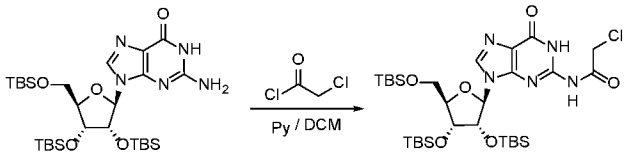
[0250] To a solution of 1-((2R,3R,5S)-3-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-1,5-dihydro-4H-imidazo[4,5-c]pyridin-4-one (0.90g, 3.6mmol) in pyridine (23mL) was added 4,4'-(chloro(phenyl)methylene)bis(methoxybenzene) (1.21g, 3.58mmol). The resulting mixture

was stirred at rt for 2h. Then, MeOH (8mL) was added, and the mixture was concentrated under reduced pressure. The residue was purified by reverse phase (C18) chromatography eluted with 0 to 95% ACN in aq NH_4HCO_3 (5mM) to give the product. LCMS (ES, m/z): 554.2 $[M+H]^+$. ^{1}H-NMR (300MHz, DMSO-d_6): δ 11.35-10.99 (m, 1H), 8.10 (s, 1H), 7.33-7.11 (m, 11H), 6.86-6.77 (m, 4H), 6.69 (d, *J*=7.0Hz, 1H), 5.81 (d, *J*=1.8Hz, 1H), 5.76 (d, *J*=3.8Hz, 1H), 3.72 (s, 6H), 3.23-3.02 (m, 2H), 2.27-2.17 (m, 1H), 1.98-1.91 (m, 1H).

[0251] **Preparation 7: 3-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-3,5-dihydro-9H-imidazo[1,2-a]purine-6,9(7H)-dione**

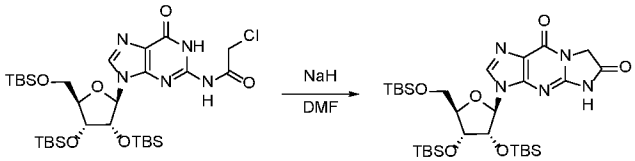


[0252] *Step 1: N-(9-((2R,3R,4R,5R)-3,4-bis((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)-2-chloroacetamide*



[0253] To a solution of 2-amino-9-((2R,3R,4R,5R)-3,4-bis((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-1,9-dihydro-6H-purin-6-one (19.0g, 30.4mmol) in DCM (190mL) at 0°C under Ar was added 2-chloroacetyl chloride (4.11g, 36.4mmol) and Py (5.8g, 73mmol). The mixture was stirred at 0°C for 2h. Then, the volatile components were removed under reduced pressure, and the residue was co-evaporated with toluene (3×50mL) to give the crude product. LCMS (ES, m/z): 702.3 $[M+H]^+$.

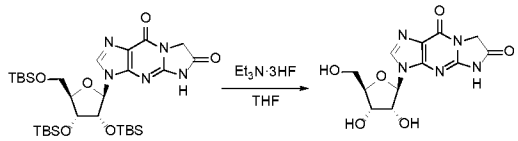
[0254] *Step 2: 3-((2R,3R,4R,5R)-3,4-bis((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-3,5-dihydro-9H-imidazo[1,2-a]purine-6,9(7H)-dione*



[0255] To a solution of the crude from Step 1 in DMF (350mL) at 0°C under Ar was added sodium hydride (60%, 2.2g, 91mmol), and the mixture was stirred at RT for 2h. Then, the

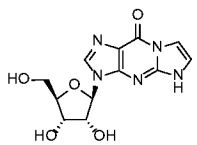
reaction was quenched with AcOH (25mL). After 30min, the reaction mixture was concentrated under reduced pressure. To the residue was added DCM (80mL) and H_2O (40mL). Layers were separated, and the aq layer was extracted with DCM (4×80mL). The combined organic solution was washed with brine (50mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with 0-10% MeOH in DCM to give the product. LCMS (ES, m/z): 666.3 $[M+H]^+$. ^{1}H-NMR: (400MHz, DMSO-d_6): δ 8.16 (s, 1H), 5.81 (d, *J*=6.6Hz, 1H), 4.62 (m, *J*=6.6, 4.4Hz, 1H), 4.51 (d, *J*=9.7Hz, 2H), 4.22 (m, *J*=4.5, 1.9Hz, 1H), 4.05-3.98 (m, 1H), 3.89 (m, *J*=11.3, 5.6Hz, 1H), 3.74 (dd, *J*=11.3, 3.7Hz, 1H), 3.33 (s, 2H), 2.51 (m, *J*=1.8Hz, 15H), 0.92 (d, *J*=1.9Hz, 21H), 0.17–0.06 (m, 14H).

[0256] *Step 3: 3-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-3,5-dihydro-9H-imidazo[1,2-a]purine-6,9(7H)-dione*

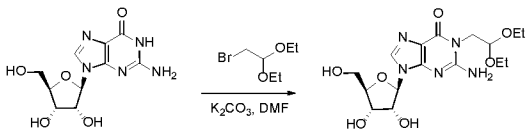


[0257] To a solution of 3-((2R,3R,4R,5R)-3,4-bis((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-3,5-dihydro-9H-imidazo[1,2-a]purine-6,9(7H)-dione (8.80g, 13.2mmol) in THF (88mL) was added $Et_3N·3HF$ (1.66g, 21.1mmol), and the mixture was stirred at RT for 24h. Then, it was concentrated, and the residue was purified by silica gel column chromatography using 0-20% MeOH in DCM to give the product. LCMS (ES, m/z): 324.0 $[M+H]^+$. ^{1}H NMR (400MHz, DMSO-d_6): δ 8.09 (s, 1H), 5.76 (d, *J*=5.9Hz, 1H), 4.45 (t, *J*=5.5Hz, 1H), 4.32 (s, 2H), 4.11 (t, *J*=4.2Hz, 1H), 3.92 (m, *J*=3.8Hz, 1H), 3.64 (dd, *J*=12.0, 4.0Hz, 1H), 3.54 (dd, *J*=12.0, 4.0Hz, 1H).

[0258] **Preparation 8: 3-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-3,5-dihydro-9H-imidazo[1,2-a]purin-9-one**

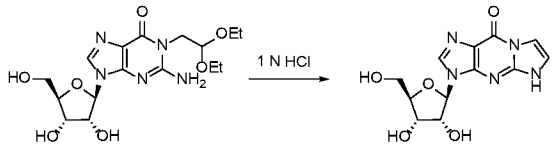


[0259] *Step 1: 2-amino-1-(2,2-diethoxyethyl)-9-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-1,9-dihydro-6H-purin-6-one*



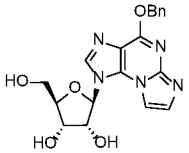
[0260] To a suspension of guanosine (15.0g, 53.0mmol) in DMF (150mL) was added K_2CO_3 (11.0g, 79.0mmol), and it was heated at 90°C. After 15min, 2-bromo-1,1-diethoxyethane (12.3mL, 79.0mmol) was added over 10min. The reaction was heated at 90°C for 72h. Then, additional K_2CO_3 (7.32g, 52.7mmol) and 2-bromo-1,1-diethoxyethane (8.22mL, 52.7mmol) were added. After 48h, the reaction mixture was filtered through a layer of CELITE, and the filtrate was concentrated. The residue was purified by silica column chromatography eluted with 0 to 5.2% MeOH in DCM to give the product. LCMS (ES, m/z): 400.2 $[M+H]^+$. ^{1}H-NMR (400MHz, DMSO-d_6): δ 7.97 (s, 1H), 6.85 (br s, 2H), 5.70 (d, *J*=6.1Hz, 1H), 5.40 (d, *J*=6.0Hz, 1H), 5.13 (d, *J*=4.6Hz, 1H), 5.01 (t, *J*=5.5Hz, 1H), 4.72 (t, *J*=5.3Hz, 1H), 4.41 (q, *J*=5.8Hz, 1H), 4.13-4.01 (m, 3H), 3.86 (q, *J*=4.0Hz, 1H), 3.74-3.56 (m, 3H), 3.56-3.40 (m, 3H), 1.07 (td, *J*=7.0, 1.9Hz, 6H).

[0261] *Step 2: 3-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-3,5-dihydro-9H-imidazo[1,2-a]purin-9-one*



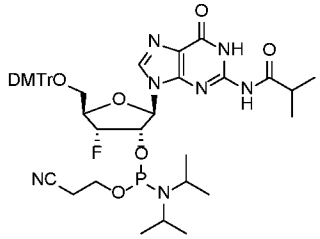
[0262] 2-amino-1-(2,2-diethoxyethyl)-9-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-1,9-dihydro-6H-purin-6-one (2.4g, 3.6mmol) was dissolved in aq HCl (1N, 24mL, 24mmol), and the mixture was stirred at RT for 24h. Then, it was neutralized with concentrated NH_4OH and concentrated. The crude was washed with cold H_2O and purified by reverse phase (C18) chromatography eluted with 0 to 95% ACN in aq NH_4HCO_3 (5mM) to give the product. LCMS (ES, m/z): 308.1 $[M+H]^+$. ^{1}H-NMR (300MHz, DMSO-d_6): δ 12.49 (s, 1H), 8.17 (s, 1H), 7.64 (t, *J*=2.2Hz, 1H), 7.45 (t, *J*=2.5Hz, 1H), 5.84 (d, *J*=5.7Hz, 1H), 5.44 (d, *J*=6.0Hz, 1H), 5.18 (d, *J*=4.8Hz, 1H), 5.07 (t, *J*=5.5Hz, 1H), 4.49 (q, *J*=5.5Hz, 1H), 4.14 (q, *J*=4.2Hz, 1H), 3.93 (q, *J*=3.9Hz, 1H), 3.67 (dt, *J*=11.8, 4.2Hz, 1H), 3.62-3.51 (m, 1H).

[0263] **Preparation 9: (2R,3R,4S,5R)-2-(4-(benzyloxy)-1H-imidazo[2,1-b]purin-1-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol**

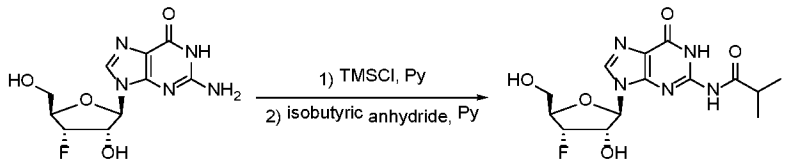


[0264] The title compound was prepared according to published procedure (*J. Org. Chem.* **1987**, *52*, 2374-2378).

[0265] **Preparation 10: (2R,3S,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl (2-cyanoethyl) diisopropylphosphoramidite**



[0266] *Step 1: N-(9-((2R,3S,4S,5R)-4-fluoro-3-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide*

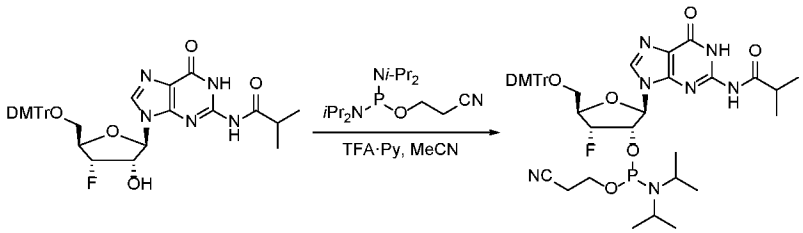


[0267] To a suspension of 2-amino-9-((2R,3S,4S,5R)-4-fluoro-3-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-1,9-dihydro-6H-purin-6-one (CARBOSYNTH catalog # ND10826, 1.50g, 5.26mmol) in Py (30mL) at 0-5°C was added TMSCl (2.86g, 26.3mmol), and the mixture was stirred at RT for 30min. Then, isobutyric anhydride (2.50g, 15.8mmol) was added dropwise, and it was stirred for an additional for 2h. Then, MeOH (5.3mL) was added. After 5min, NH_4OH (10.5mL) was added dropwise and stirring was continued for 30min. The reaction mixture was concentrated under reduced pressure, and MeOH (2mL) in CH_2Cl_2 (18mL) was added to the residue. Solids were filtered off, and the filtrate was concentrated and purified by flash column chromatography with 2-10% MeOH in CH_2Cl_2 to give the product. LCMS (ES, m/z): 356.1 $[M+H]^+$. ^{1}H-NMR: (400MHz, DMSO-d_6): δ 12.11 (s, 1H), 11.68 (s, 1H), 8.28 (s, 1H), 5.98 (d, *J*=6.1Hz, 1H), 5.85 (d, *J*=8.0Hz, 1H), 5.24 (t, *J*=5.4Hz, 1H), 5.14 (d, *J*=4.1Hz, 0.5H), 5.01 (d, *J*=4.2Hz, 0.5H), 4.87-4.69 (m, 1H), 4.26 (t, *J*=4.4Hz, 0.5H), 4.19 (t, *J*=4.4Hz, 0.5H), 3.61 (t, *J*=4.9Hz, 2H), 2.77 (hept, *J*=6.8Hz, 1H), 1.13 (d, *J*=6.7Hz, 6H). ^{19}F-NMR: (376MHz, DMSO-d_6): δ -197.5 (s).

[0268] *Step 2: N-(9-((2R,3S,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide*

[0269] N-(9-((2R,3S,4S,5R)-4-fluoro-3-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide (1.30g, 3.66mmol) was co-evaporated with Py (3×10mL) and re-dissolved in Py (26mL). To the solution at 0°C-5°C was added DMTrCl (1.36g, 4.02mmol). It was stirred at RT for 3h and then concentrated. CH_2Cl_2 (40mL, with 1% Et_3N) was added, and it was washed with sat aq $NaHCO_3$ (15mL), H_2O (10mL) and brine (10mL). The organic solution was dried (Na_2SO_4), concentrated and purified by silica gel column chromatography using 0-10% MeOH in CH_2Cl_2 (1% Et_3N) to give the product. LCMS (ES, m/z): 656.2 $[M-H]^-$. ^{1}H-NMR: (400MHz, DMSO-d_6): δ 12.10 (s, 1H), 11.61 (s, 1H), 8.14 (s, 1H), 7.40-7.31 (m, 2H), 7.31-7.19 (m, 7H), 6.89-6.78 (m, 4H), 6.08 (d, *J*=6.1Hz, 1H), 5.87 (d, *J*=7.3Hz, 1H), 5.23 (dd, *J*=4.1, 1.8Hz, 0.5H), 5.10 (d, *J*=4.4Hz, 0.5H), 4.96 (dq, *J*=22.4, 5.9Hz, 1H), 4.30 (dt, *J*=26.1, 4.6Hz, 1H), 3.74 (d, *J*=1.1Hz, 6H), 3.39 (dd, *J*=10.6, 5.7Hz, 1H), 3.22 (dd, *J*=10.6, 3.8Hz, 1H), 2.76 (p, *J*=6.8Hz, 1H), 1.13 (d, *J*=6.8Hz, 6H). ^{19}F-NMR: (376MHz, DMSO-d_6): δ -198.1 (s, 1F).

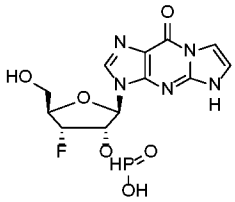
[0270] *Step 3: (2R,3S,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl (2-cyanoethyl) diisopropylphosphoramidite*



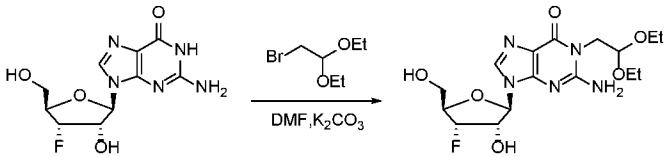
[0271] To a solution of N-(9-((2R,3S,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide (2.10g, 3.19mmol) in MeCN (30mL) at 0°C under Ar was added pyridin-1-ium 2,2,2-trifluoroacetate (0.678g, 3.51mmol) and 3-((bis(diisopropylamino)phosphino)oxy)-propanenitrile (1.16g, 3.83mmol) in MeCN (2mL) over 5min. The resulting mixture was stirred at RT for 5h. Then, TEA in CH_2Cl_2 (2%, 300mL) and H_2O (100mL) was added. Layers were separated, and the organic layer was washed with H_2O (3×100mL) and brine (2×100mL). The organic layer was dried (Na_2SO_4), concentrated, and purified by flash column chromatography

eluted with 10% DCM in EtOAc/Hex (2/3) to give the product. LCMS (ES, m/z): 858.3 $[M+H]^+$. ^{1}H-NMR: (400MHz, DMSO-d_6): δ 12.07 (s, 1H), 11.55 (s, 1H), 8.08 (d, J=4.2Hz, 1H), 7.44-7.08 (m, 9H), 6.83 (ddd, J=8.9, 6.2, 2.1Hz, 4H), 5.99 (t, J=6.8Hz, 1H), 5.42-5.03 (m, 2H), 4.48-4.22 (m, 1H), 3.71 (s, 7H), 3.59-3.35 (m, 3H), 3.28-3.24 (m, 3H), 2.83-2.61 (m, 2H), 1.09 (s, 12H), 1.03 (d, J=6.8Hz, 3H), 0.74 (d, J=6.7Hz, 3H). ^{19}F-NMR: (376MHz, DMSO-d_6): δ -195.8 (s), -197.1 (s). ^{31}P-NMR: (162MHz, DMSO-d_6): δ 151.55 (d), 151.35 (d).

[0272] **Preparation 11: (2R,3S,4R,5R)-4-fluoro-5-(hydroxymethyl)-2-(9-oxo-5,9-dihydro-3H-imidazo[1,2-a]purin-3-yl)tetrahydrofuran-3-yl hydrogen phosphonate**

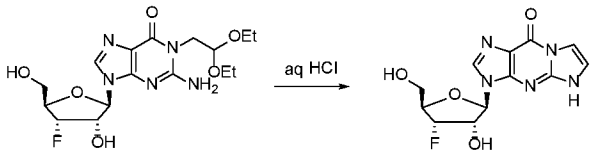


[0273] *Step 1: 2-amino-1-(2,2-diethoxyethyl)-9-((2R,3S,4S,5R)-4-fluoro-3-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-1,9-dihydro-6H-purin-6-one*



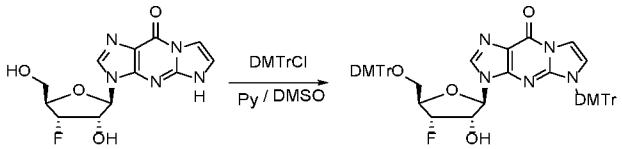
[0274] To a stirred suspension of 2-amino-9-((2R,3S,4S,5R)-4-fluoro-3-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-1,9-dihydro-6H-purin-6-one (2.36g, 8.19mmol) in DMF (50mL) was added K_2CO_3 (2.29g, 16.6mmol) and 2-bromo-1,1-diethoxyethane (3.26g, 16.6mmol). It was stirred at 90°C for 3 days. Then, additional K_2CO_3 (0.572g, 4.14mmol) and 2-bromo-1,1-diethoxyethane (0.815g, 4.14mmol) were added. After 48h, the reaction mixture was then filtered through a pad of CELITE. The filtrate was concentrated, and the residue was purified by reverse phase (C18) chromatography eluted with 0 to 95% ACN in aq NH_4HCO_3 (5mM) to give the product. LCMS (ES, m/z): 402.3 $[M+H]^+$. ^{1}H-NMR (400MHz, DMSO-d_6): δ 7.99 (s, 1H), 6.89 (s, 2H), 5.91 (d, *J*=6.4Hz, 1H), 5.76 (d, *J*=8.1Hz, 1H), 5.21 (t, *J*=5.5Hz, 1H), 5.11 (d, *J*=4.1Hz, 0.5H), 4.98 (d, *J*=4.2Hz, 0.5H), 4.84-4.68 (m, 2H), 4.23 (t, *J*=4.4Hz, 0.5H), 4.16 (t, *J*=4.4Hz, 0.5H), 4.07 (d, *J*=5.9Hz, 2H), 3.69 (dq, *J*=9.7, 7.0Hz, 2H), 3.60 (t, *J*=5.0Hz, 2H), 3.50 (dtd, *J*=9.4, 7.4, 6.5Hz, 2H), 1.09 (td, *J*=7.1, 1.7Hz, 6H).

[0275] *Step 2: 3-((2R,3S,4S,5R)-4-fluoro-3-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-3,5-dihydro-9H-imidazo[1,2-a]purin-9-one*



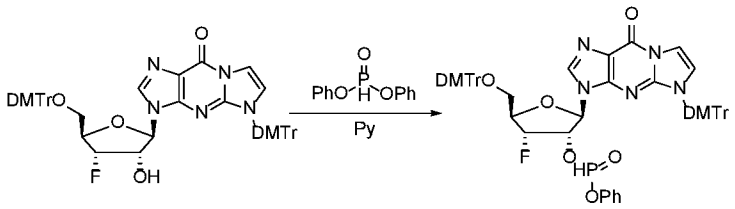
[0276] 2-amino-1-(2,2-diethoxyethyl)-9-((2R,3S,4S,5R)-4-fluoro-3-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-1,9-dihydro-6H-purin-6-one (1.10g, 2.74mmol) was dissolved in aq HCl (27.4mL, 54.8mmol), and it was stirred for 24h. Then, the solution was neutralized with concentrated NH_4OH and concentrated. The residue was purified by reverse phase (C18) chromatography eluted with 0 to 95% ACN in aq NH_4HCO_3 (5mM) to give the product. LCMS (ES, m/z): 310.2 $[M+H]^+$. ^{1}H-NMR (300MHz, DMSO-d_6): δ 8.13 (s, 1H), 7.60 (d, *J*=2.6Hz, 1H), 7.41 (d, *J*=2.6Hz, 1H), 5.86 (dd, *J*=12.3, 7.3Hz, 2H), 5.25 (t, *J*=5.6Hz, 1H), 5.13 (d, *J*=4.2Hz, 0.5H), 4.95 (d, *J*= 4.3Hz, 0.5H), 4.25 (t, *J*=4.5Hz, 0.5H), 4.16 (s, 0.5H), 3.60 (t, *J*=5.0Hz, 2H).

[0277] *Step 3: 3-((2R,3S,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)-5-(bis(4-methoxyphenyl)(phenyl)methyl)-3,5-dihydro-9H-imidazo[1,2-a]purin-9-one*



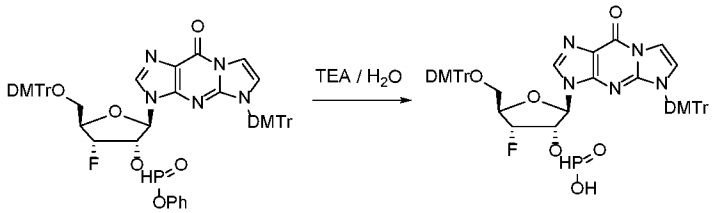
[0278] To a solution of 3-((2R,3S,4S,5R)-4-fluoro-3-hydroxy-5-(hydroxymethyl) tetrahydrofuran-2-yl)-3,5-dihydro-9H-imidazo[1,2-a]purin-9-one (600mg, 1.94mmol) in Py (12mL) and DMSO (24mL) was added a solution of 4,4'-(chloro(phenyl)methylene)bis (methoxybenzene) (1.64g, 4.85mmol) in Py (6mL) over 30min. It was stirred at RT for 4h. Then, the reaction mixture was concentrated under reduced pressure, and the residue was purified by reverse phase (C18) chromatography eluted with 0 to 95% ACN in aq NH_4HCO_3 (5mM) to give the product. LCMS (ES, m/z): 914.3 $[M+H]^+$. ^{1}H-NMR (400MHz, DMSO-d_6): δ 7.97 (s, 1H), 7.70 (d, *J*=2.9Hz, 1H), 7.34-7.08 (m, 19H), 6.83 (ddt, *J*=8.7, 6.9, 2.9Hz, 8H), 5.63 (d, *J*=4.9Hz, 1H), 5.45 (d, *J*=4.3Hz, 1H), 4.44 (t, *J*=5.1Hz, 1H), 4.32 (dd, *J*=9.4, 4.6Hz, 1H), 4.09-3.97 (m, 1H), 3.71 (d, *J*=7.3Hz, 6H), 3.65 (s, 6H), 3.03 (d, *J*=5.7Hz, 2H).

[0279] *Step 4: (2R,3S,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-2-(5-(bis(4-methoxyphenyl)(phenyl)methyl)-9-oxo-5,9-dihydro-3H-imidazo[1,2-a]purin-3-yl)-4-fluorotetrahydrofuran-3-yl phenyl phosphonate*



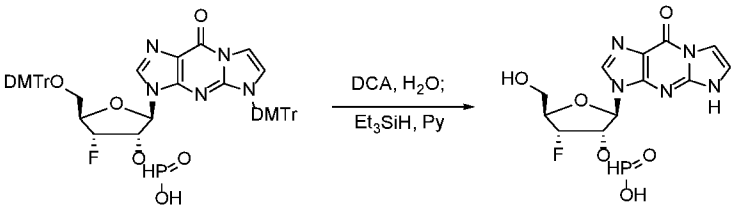
[0280] To a solution of 3-((2R,3S,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy) methyl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)-5-(bis(4-methoxyphenyl)(phenyl)methyl)-3,5-dihydro-9H-imidazo[1,2-a]purin-9-one (0.65g, 0.71mmol) in Py (3mL) under Ar was added diphenyl phosphonate (1.16g, 4.98mmol), and it was stirred at RT for 20min. The reaction mixture was used for the next step without purification. LCMS (ES, m/z): 1054.4 $[M+H]^+$.

[0281] *Step 5: (2R,3S,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-2-(5-(bis(4-methoxyphenyl)(phenyl)methyl)-9-oxo-5,9-dihydro-3H-imidazo[1,2-a]purin-3-yl)-4-fluorotetrahydrofuran-3-yl hydrogen phosphonate*



[0282] To the reaction mixture from Step 4 at 0°C was added H_2O (3.0mL, 0.17mol) and TEA (3.0mL, 33mmol). The mixture was stirred at RT for 20min. Then, it was concentrated and purified by reverse phase (C18) chromatography eluted with 0 to 95% ACN in aq NH_4HCO_3 (5mM) to give the product. LCMS (ES, m/z): 978.3 $[M+H]^+$. ^{31}P NMR (162MHz, DMSO): δ -0.07 (s).

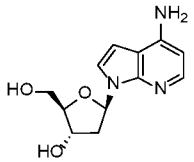
[0283] *Step 6: (2R,3S,4R,5R)-4-fluoro-5-(hydroxymethyl)-2-(9-oxo-5,9-dihydro-3H-imidazo[1,2-a]purin-3-yl)tetrahydrofuran-3-yl hydrogen phosphonate*



[0284] To the solution of (2R,3S,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy) methyl)-2-(5-(bis(4-methoxyphenyl)(phenyl)methyl)-9-oxo-5,9-dihydro-3H-imidazo[1,2-a]purin-3-yl)-4-fluorotetrahydrofuran-3-yl hydrogen phosphonate (0.60g, 0.60mmol) in DCM (17mL) were added DCA in DCM (17.4mL, 10.8mmol) and H_2O (0.20mL, 11mmol). It was

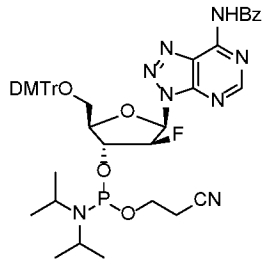
stirred at rt for 20min and then Et_3SiH (34.0mL, 212mmol) was added. The solution was stirred at rt for 60min. Py (6.4mL, 80mmol) was added, and the solution was stirred for 10min. The mixture was concentrated and co-evaporated with MeCN (3×15mL) to give the crude product, which was used for next step without purification. LCMS (ES, m/z): 374.0 $[M+H]^+$.

[0285] **Preparation 12: (2R,3S,5R)-5-(4-amino-1H-pyrrolo[2,3-b]pyridin-1-yl)-2-(hydroxymethyl)tetrahydrofuran-3-ol**

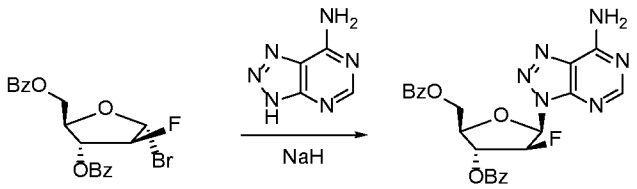


[0286] The title compound was prepared according to published procedure (*Heterocycles* **1989**, *29*, 795-805).

[0287] **Preparation 13: (2R,3R,4S,5R)-5-(7-benzamido-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-fluorotetrahydrofuran-3-yl (2-cyanoethyl) diisopropylphosphoramidite**



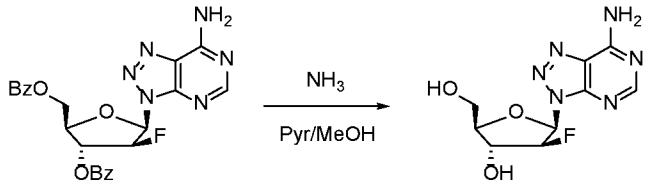
[0288] *Step 1: (2R,3R,4S,5R)-5-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-2-((benzoyloxy)methyl)-4-fluorotetrahydrofuran-3-yl benzoate*



[0289] To a mixture of 3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-amine (2.36g, 17.4mmol) in NMP (50mL) was added NaH (60%, 0.744g, 18.6 mmol). The mixture was vigorously stirred, and after 1h, generation of bubbles had completely ceased. The mixture was added to ((2R,3R,4S,5R)-3-(benzoyloxy)-5-bromo-4-fluorotetrahydrofuran-2-yl)methyl benzoate (neat, 5.25g, 12.4mmol) in one portion. It was stirred for 18h. LCMS showed several peaks with the

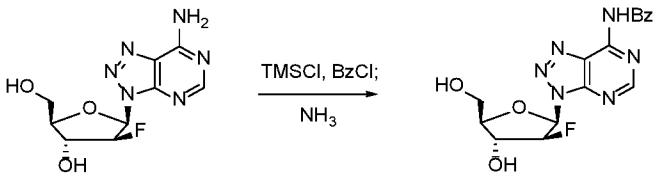
desired mass (m/e=479). EtOAc (70mL) and H_2O (70mL) were added to the reaction. Layers were separated, and the organic layer was washed with half saturated brine (3x10mL) and brine (1x10mL), dried ($MgSO_4$), and concentrated. The crude was purified via silica column eluting with 0 to 50% EtOAc in Hex to give the product. LCMS (ES, m/z): 479.3 $[M+H]^+$. ^{1}H-NMR (500MHz, DMSO-d_6): δ 8.62 (s, 1H), 8.34 (s, 1H), 8.28 (s, 1H), 8.10-8.04 (m, 2H), 7.97-7.90 (m, 2H), 7.77-7.69 (m, 1H), 7.67-7.55 (m, 3H), 7.49-7.42 (m, 2H), 6.97 (dd, *J*=6.5, 3.1Hz, 1H), 6.49 (dt, *J*=17.6, 6.9Hz, 1H), 6.16 (dt, *J*=56, 6.6Hz, 1H), 4.76-4.62 (m, 3H).

[0290] *Step 2: (2R,3R,4S,5R)-5-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-4-fluoro-2-(hydroxymethyl)tetrahydrofuran-3-ol*



[0291] To a solution of (2R,3R,4S,5R)-5-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-2-((benzoyloxy)methyl)-4-fluorotetrahydrofuran-3-yl benzoate (2.00g, 4.18mmol) in Py (10mL) at was added NH_3 in MeOH (7N, 20mL, 140mmol). It was stirred for 48h. LCMS showed completion of the reaction (m/e=271). It was concentrated and purified by silica column chromatography eluting with 10% MeOH in CH_2Cl_2 to give the desired product. LCMS (ES, m/z): 271.1 $[M+H]^+$. ^{1}H-NMR (500MHz, DMSO-d6): δ 8.54 (s, 1H), 8.33 (s, 1H), 8.22 (s, 1H), 6.73 (dd, *J*=6.5, 2.6Hz, 1H), 6.00 (d, *J*=5.4Hz, 1H), 5.51 (ddd, *J*=53, 7.2, 6.5Hz, 1H), 4.93 (t, *J*=5.8Hz, 1H), 4.86-4.74 (m, 1H), 3.91-3.83 (m, 1H), 3.77-3.61 (m, 2H).

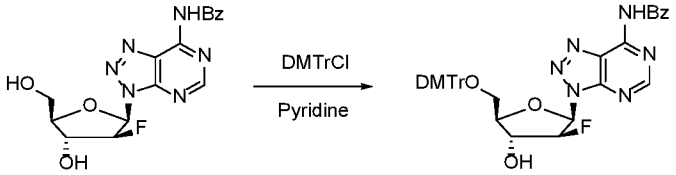
[0292] *Step 3: N-(3-((2R,3S,4R,5R)-3-fluoro-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl)benzamide*



[0293] To a solution of (2R,3R,4S,5R)-5-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-4-fluoro-2-(hydroxymethyl)tetrahydrofuran-3-ol (1.34g, 4.96mmol) in Py (30mL) at 0°C was added TMSCl (1.46mL, 11.4mmol). It was warmed to RT and stirred for 1h. Then, it was re-cooled to 0°C, and BzCl (0.921mL, 7.93mmol) was added dropwise. The reaction was slowly warmed to RT over 2h. LCMS showed completion of reaction (m/e=375, 479). H_2O (3mL) was added. It was cooled to 0°C, and NH_3 in MeOH (7N, 2.8mL, 20mmol) was added. After 1h, the

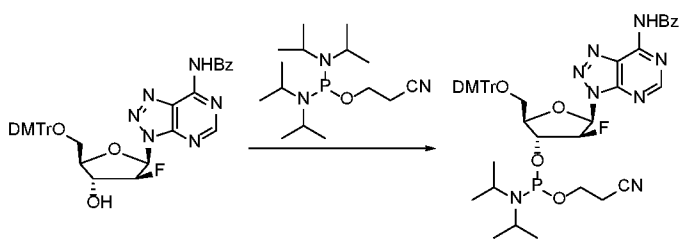
reaction mixture was concentrated. It was purified by silica column chromatography eluting with 0 to 10% MeOH in CH_2Cl_2 to give the product. LCMS (ES, m/z): 375.2 $[M+H]^+$. ^{1}H-NMR (500MHz, DMSO-d_6): δ 11.95 (s, 1H), 8.98 (s, 1H), 8.10 (d, *J*=7.6Hz, 2H), 7.73-7.66 (m, 1H), 7.59 (t, *J*=7.7Hz, 2H), 6.91 (d, *J*=6.2Hz, 1H), 6.06 (d, *J*=5.6Hz, 1H), 5.59 (t, *J*=53, 6.8Hz, 1H), 4.90 (t, *J*=5.8Hz, 1H), 4.82 (dq, *J*=19.8, 7.0Hz, 1H), 3.92 (td, *J*=7.6, 2.9Hz, 1H), 3.75 (ddd, *J*=12.1, 5.6, 3.0Hz, 1H), 3.66 (dt, *J*=12.0, 6.6Hz, 1H).

[0294] *Step 4: N-(3-((2R,3S,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-3-fluoro-4-hydroxytetrahydrofuran-2-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl)benzamide*



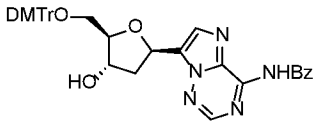
[0295] To a solution of N-(3-((2R,3S,4R,5R)-3-fluoro-4-hydroxy-5-(hydroxymethyl)-tetrahydrofuran-2-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl)benzamide (1.25g, 3.34mmol) in Py (15mL) at 0°C was added DMTrCl (1.58g, 4.68mmol). It was stirred at RT for 1h. LCMS showed a peak with the desired mass (m/e=677). It was partly concentrated (to 5mL), and EtOAc (20mL) and H_2O (10mL) were added. The layers were separated, and the aq layer was extracted with EtOAc (2×10mL). The combined organics were washed with brine (5mL), dried ($MgSO_4$), concentrated and purified by silica column chromatography eluting with 0 to 60% EtOAc in Hex to give the product. LCMS (ES, m/z): 675.5 $[M-H]^-$. ^{1}H-NMR (500MHz, DMSO-d_6): δ 8.13-8.07 (m, 2H), 7.69 (t, *J*=7.4Hz, 1H), 7.59 (t, *J*=7.6Hz, 2H), 7.35-7.29 (m, 2H), 7.23-7.10 (m, 6H), 6.97 (d, *J*=6.5Hz, 1H), 6.81-6.74 (m, 2H), 6.74-6.67 (m, 2H), 6.07 (d, *J*=5.7Hz, 1H), 5.62 (dt, *J*=53, 7.0Hz, 1H), 4.91-4.79 (m, 1H), 4.15-4.07 (m, 1H), 3.69 (s, 3H), 3.67 (s, 3H), 3.44 (dd, *J*=10.4, 8.0Hz, 1H), 3.21 (dd, *J*=10.3, 2.4Hz, 1H).

[0296] *Step 5: (2R,3R,4S,5R)-5-(7-benzamido-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-fluorotetrahydrofuran-3-yl (2-cyanoethyl) diisopropylphosphoramidite*

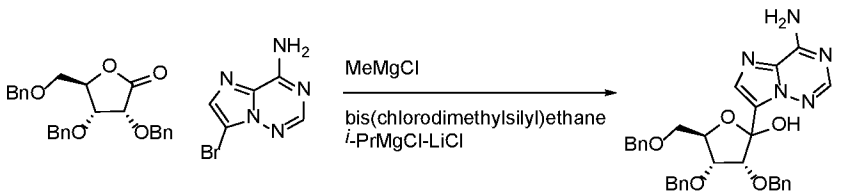


[0297] To a solution of 3-((bis(diisopropylamino)phosphino)oxy)propanenitrile (8.02g, 26.6mmol) in ACN (90mL) at RT was added pyridin-1-ium 2,2,2-trifluoroacetate (3.85g, 19.95mmol) and a solution of N-(3-((2R,3S,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy) methyl)-3-fluoro-4-hydroxytetrahydrofuran-2-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl) benzamide (9g, 13.30mmol) in ACN (90mL). The resulting mixture was stirred for 1h. Then, it was concentrated, and the residue was dissolved in CH_2Cl_2 (1000mL). It was washed with aq $NaHCO_3$ (1%, 2×300mL), H_2O (300mL) and brine (300mL), dried (Na_2SO_4), concentrated, and purified by reverse phase (C18) chromatography eluting with 0 to 95% ACN in H_2O to give the product. LCMS (ES, m/z): 877.5 $[M+H]^+$. ^{1}H-NMR: (400MHz, DMSO-d_6): δ 12.01 (s, 1H), 8.92 (s, 1H), 8.11 (d, *J*=7.6Hz, 2H), 7.66 (dt, *J*=42.3, 7.5Hz, 3H), 7.32 (td *J*=7.2, 6.6, 2.9Hz, 2H), 7.22-7.00 (m, 9H), 6.83-6.63 (m, 4H), 5.86 (ddt, *J*=52.8, 17.6, 6.9Hz, 1H), 5.16 (td, *J*=17.7, 17.2, 8.8Hz, 1H), 3.78-3.63 (m, 7H), 3.59-3.35 (m, 5H), 2.74 (t, *J*=5.9Hz, 1H), 2.63 (t, *J*=5.9Hz, 1H), 1.23-0.99 (m, 10H), 0.91 (d, *J*=6.7Hz, 2H). ^{31}P-NMR: (162MHz, DMSO-d_6): δ 150.26, 149.60 (2 s, 1P).

[0298] **Preparation 14: *N*-(7-((2*R*,4*S*,5*R*)-5-((bis(4-methoxyphenyl)(phenyl)methoxy) methyl)-4-hydroxytetrahydrofuran-2-yl)imidazo[2,1-*f*][1,2,4]triazin-4-yl)benzamide**



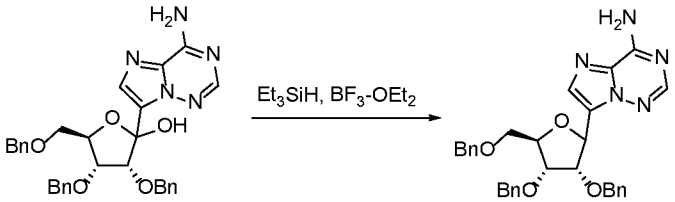
[0299] *Step 1: (3R,4R,5R)-2-(4-aminoimidazo[2,1-f][1,2,4]triazin-7-yl)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-ol*



[0300] To a stirring mixture of 7-bromoimidazo[2,1-*f*][1,2,4]triazin-4-amine (41g, 0.19mol) in THF (0.50L) at 0°C was added MeMgBr (3.0M in THF, 66mL, 0.19mol) dropwise to maintain the internal temperature below 10°C. Bis(chlorodimethylsilyl)ethane (41g, 190mmol) was added in one portion. MeMgBr (3.0M in diethyl ether, 66mL, 0.19mol) was then added dropwise to maintain the internal temperature below 10°C. *i*-PrMgCl-LiCl (1.3M in THF, 0.16L, 0.21mol) was added while maintaining the internal temperature below 10°C. A mixture of

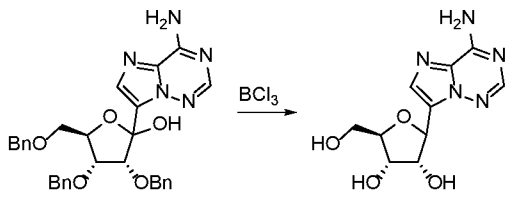
(3*R*,4*R*,5*R*)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)dihydrofuran-2(3*H*)-one (160g, 0.38mol) in THF was added dropwise at 0°C, and the mixture was then allowed to warm to RT and was stirred for 12h. The mixture was diluted with sat aq NH_4Cl (100mL) and extracted with EtOAc (3×1000mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by column chromatography (column height: 2500mm, diameter: 1000mm, 25-75% EtOAc in Hex) to afford (3*R*,4*R*,5*R*)-2-(4-aminoimidazo [2,1-*f*][1,2,4]triazin-7-yl)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)-tetrahydrofuran-2-ol.

[0301] *Step 2: 7-((3S,4R,5R)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-yl)imidazo[2,1-f][1,2,4]triazin-4-amine*



[0302] To a stirring mixture of (3*R*,4*R*,5*R*)-2-(4-aminoimidazo[2,1-*f*][1,2,4]triazin-7-yl)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-ol (64g, 0.12mmol) in DCM (1.3L) at 0°C was added TES (81g, 0.69mol), and then BF_3-OEt_2 (21g, 0.15mol). The mixture was then allowed to warm to 25°C, and the mixture was stirred for 1h. More BF_3-OEt_2 (57g, 0.40mol) was added, and the mixture was then heated to 35°C for 4h. Upon cooling to RT, the mixture was quenched with sat aq $NaHCO_3$ (200mL) and then extracted with EtOAc (3×300mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by column chromatography (15-75% EtOAc in Hex) to afford 7-((3*S*,4*R*,5*R*)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-yl)imidazo[2,1-*f*][1,2,4]triazin-4-amine. MS (ES, m/z)=538 [M+H]+.

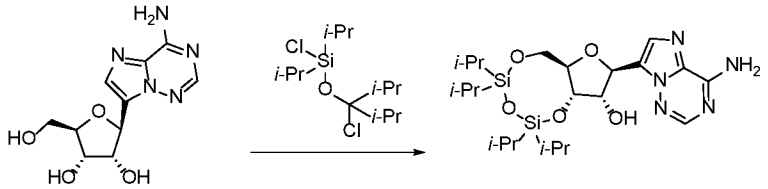
[0303] *Step 3: (3R,4S,5R)-2-(4-aminoimidazo[2,1-f][1,2,4]triazin-7-yl)-5-(hydroxymethyl)-tetrahydrofuran-3,4-diol*



[0304] To a stirring mixture of 7-((3*S*,4*R*,5*R*)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)-tetrahydrofuran-2-yl)imidazo[2,1-*f*][1,2,4]triazin-4-amine (12g, 22mmol) in DCM (850mL) at -78°C was added BCl_3 (18g, 0.16mol) dropwise. Upon completion, the mixture was stirred at

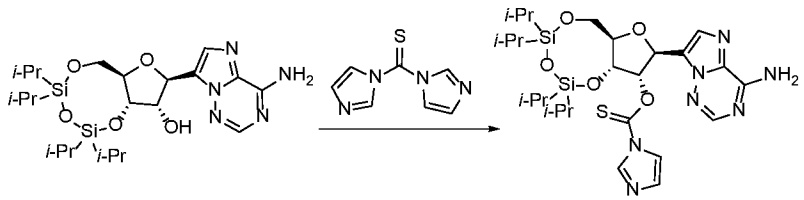
-78°C for 3h. After 3h, the mixture was quenched with MeOH (50mL) at -78°C, and the mixture was allowed to warm to 25°C. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography (9-25% MeOH in DCM) to afford (3*R*,4*S*,5*R*)-2-(4-aminoimidazo[2,1-*f*][1,2,4]triazin-7-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol.

[0305] *Step 4: (6aR,8S,9S,9aS)-8-(4-aminoimidazo[2,1-f][1,2,4]triazin-7-yl)-2,2,4,4-tetraisopropyltetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-9-ol*



[0306] To a stirred mixture of (2*S*,3*R*,4*S*,5*R*)-2-(4-aminoimidazo[2,1-*f*][1,2,4]triazin-7-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (4.0g, 15mmol) in Py (0.10L) was added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (5.8mL, 18mmol). After 3h, the mixture was diluted with toluene (50mL) and then concentrated. The resulting mixture was taken up in DCM and MeOH, and then silica gel (40g) was added. The mixture was concentrated, placed under vacuum for 1h and then purified by column chromatography (0-80% EtOAc in Hex) to afford (6a*R*,8*S*,9*S*,9a*S*)-8-(4-aminoimidazo[2,1-f][1,2,4]triazin-7-yl)-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4]trioxadisilocin-9-ol. MS (ES, m/z)=510 $[M+H]^+$.

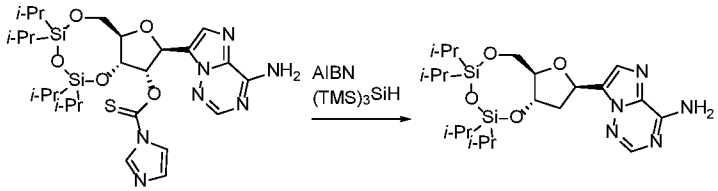
[0307] *Step 5: O-((6aR,8S,9S,9aR)-8-(4-aminoimidazo[2,1-f][1,2,4]triazin-7-yl)-2,2,4,4-tetraisopropyltetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-9-yl) 1H-imidazole-1-carbothioate*



[0308] To a mixture of (6a*R*,8*S*,9*S*,9a*S*)-8-(4-aminoimidazo[2,1-f][1,2,4]triazin-7-yl)-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4]trioxadisilocin-9-ol (6.45g, 12.7mmol) in MeCN (63.0mL) and Py (63.0mL) was added 1,1'-thiocarbonyldiimidazole (2.71g, 15.2mmol). After 90min, more 1,1'-thiocarbonyldiimidazole (2.71g, 15.2mmol) was added, and the mixture was stirred overnight. After stirring overnight, the mixture was concentrated and purified by column chromatography (0-100% EtOAc in Hex) to afford *O*-((6a*R*,8*S*,9*S*, 9a*R*)-8-(4-

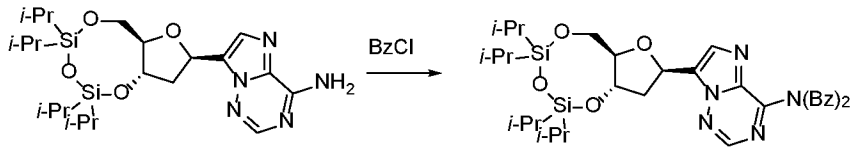
aminoimidazo[2,1-*f*][1,2,4]triazin-7-yl)-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4]trioxadisilocin-9-yl) 1H-imidazole-1-carbothioate. MS (ES, m/z)=620 $[M+H]^+$.

[0309] *Step 6: 7-((6aR,8R,9aS)-2,2,4,4-tetraisopropyltetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-8-yl)imidazo[2,1-f][1,2,4]triazin-4-amine*



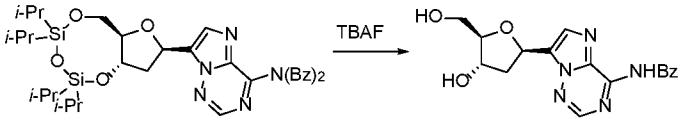
[0310] To a mixture of *O*-((6a*R*,8*S*,9*S*,9a*R*)-8-(4-aminoimidazo[2,1-*f*][1,2,4]triazin-7-yl)-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4]trioxadisilocin-9-yl) (5.65g, 9.11mmol) in toluene (91.0mL) was added 2,2'-azobis(2-methylpropionitrile (0.300g, 1.82mmol) and $(TMS)_3SiH$ (4.22mL, 13.7mmol). The mixture was heated to 85°C for 30min. After 30min, the mixture was allowed to cool to RT, placed directly on the column, and purified (0-80% EtOAc in Hex) to afford 7-((6a*R*,8*R*,9a*S*)-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4] trioxadisilocin-8-yl)imidazo[2,1-*f*][1,2,4]triazin-4-amine. MS (ES, m/z)=494 $[M+H]^+$.

[0311] *Step 7: N-benzoyl-N-(7-((6aR,8R,9aS)-2,2,4,4-tetraisopropyltetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-8-yl)imidazo[2,1-f][1,2,4]triazin-4-yl)benzamide*



[0312] To a mixture of 7-((6a*R*,8*R*,9a*S*)-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4]trioxadisilocin-8-yl)imidazo[2,1-*f*][1,2,4]triazin-4-amine (15.7g, 31.8mmol) in Py (64.0mL) was added BzCl (11.0mL, 95.0mmol), and the mixture was heated to 50°C for 45min. After 45min, the mixture was allowed to cool to RT. After cooling, a precipitate formed and was filtered off. The filtrate was diluted with DCM (50mL) and toluene (50mL). The mixture was concentrated to about 50mL. The mixture was filtered, and the solids were washed with DCM. The filtrate and washes were combined, loaded onto a column, and purified (0-50% EtOAc in Hex) to afford *N*-benzoyl-*N*-(7-((6a*R*,8*R*,9a*S*)-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4]trioxadisilocin-8-yl)imidazo[2,1-*f*][1,2,4]triazin-4-yl)benzamide. MS (ES, m/z)=702 $[M+H]^+$.

[0313] *Step 8: N-(7-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)imidazo[2,1-f][1,2,4]triazin-4-yl)benzamide*

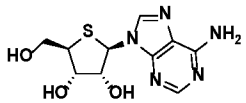


[0314] To a mixture of *N*-benzoyl-*N*-(7-((6a*R*,8*R*,9a*S*)-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4]trioxadisilocin-8-yl)imidazo[2,1-*f*][1,2,4]triazin-4-yl)benzamide (10g, 14mmol) in THF (0.14L) was added TBAF ((1.0M in THF, 29mL, 29mmol), and the mixture was stirred for 1h. After 1h, the mixture was concentrated and purified by column chromatography to afford *N*-(7-((2*R*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)tetrahydro-furan-2-yl)imidazo[2,1-f][1,2,4]triazin-4-yl)benzamide. MS (ES, m/z)=356 $[M+H]^+$.

[0315] *Step 9: N-(7-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-2-yl)imidazo[2,1-f][1,2,4]triazin-4-yl)benzamide*

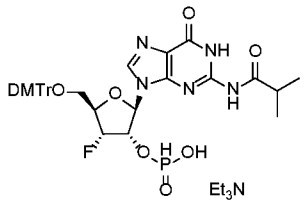
[0316] To a mixture of *N*-(7-((2*R*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)imidazo[2,1-f][1,2,4]triazin-4-yl)benzamide (6.1g, 17mmol) in Py (86mL) at 0°C was added DMTrCl (5.8g, 17mmol), and the mixture was allowed to warm to RT overnight. After stirring overnight, the mixture was diluted with toluene and then concentrated under reduced pressure to afford the crude product residue. The crude product residue was purified by silica gel chromatography (0-100% EtOAc in Hex) to afford *N*-(7-((2*R*,4*S*,5*R*)-5-((bis(4-methoxyphenyl)(phenyl)-methoxy)methyl)-4-hydroxytetrahydrofuran-2-yl)imidazo[2,1-*f*][1,2,4]triazin-4-yl) benzamide. MS (ES, m/z)=658 $[M+H]^+$.

[0317] **Preparation 15: 4'-thioadenosine**

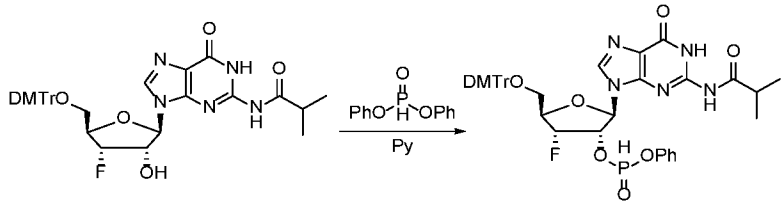


[0318] The title compound was prepared according to published procedures (*Journal of Medicinal Chemistry* **2006**, *49*(5), 1624-1634).

[0319] **Preparation 16: triethylammonium 5'-*O*-[bis(4-methoxyphenyl)(phenyl) methyl]-3'-deoxy-3'-fluoro-2'-*O*-[hydroxy(oxido)-λ^5-phosphanyl]-*N*-(2-methylpropanoyl)guanosine**

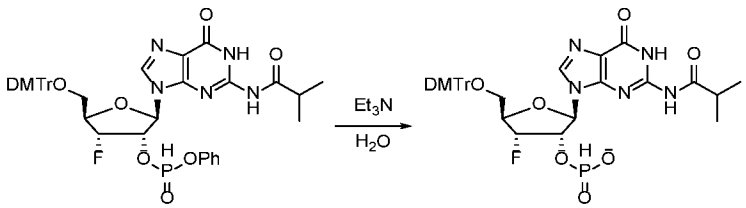


[0320] *Step 1: (2R,3S,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phenyl phosphonate*



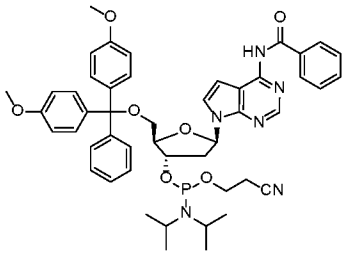
[0321] To a stirred solution of N-(9-((2R,3S,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl) methoxy) methyl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide (1g, 1.520mmol) in Py (7.6mL) under Ar was added diphenyl phosphonate (1.068g, 4.56mmol), and it was stirred at RT for 20min. The reaction mixture containing the product was used for the next reaction step without purification.

[0322] *Step 2: (2R,3S,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate*



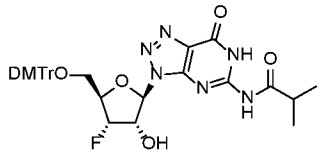
[0323] To the reaction mixture from Step 1 was added H_2O (1.5mL) and Et_3N (1.5mL). The mixture was stirred at RT for 20min. Then, it was concentrated, and the residue was partitioned between CH_2Cl_2 (50mL) and aq $NaHCO_3$ (5%, 20mL). Layers were separated. The organic layer was washed with aq $NaHCO_3$ (5%, 2x20mL), dried (Na_2SO_4), concentrated and purified by silica gel column chromatography using 0 to 7% MeOH in CH_2Cl_2 (1% Et_3N) to give the product. LCMS (ES, m/z): 722 $[M+H]^+$. ^{31}P-NMR: (162MHz, CD_3OD): δ 2.73 (s, 1P).

[0324] **Preparation 17: triethylammonium 5'-*O*-[bis(4-methoxyphenyl)(phenyl) methyl]-3'-deoxy-3'-fluoro-2'-*O*-[hydroxy(oxido)-λ^5-phosphanyl]-*N*-(2-methylpropanoyl)guanosine**

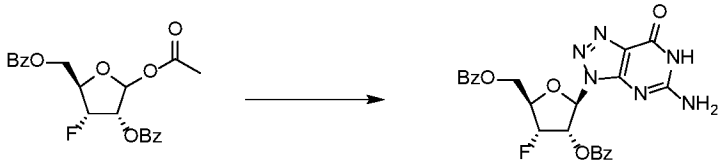


[0325] To a flask was added N-(7-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl) methoxy)methyl)-4-hydroxytetrahydrofuran-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzamide (4g, 6.09mmol), DCM (71.7mL), and 4,5-dicyanoimidazole (2.158g, 18.27mmol), and the solution was cooled to 0°C. 2-Cyanoethyl N,N,N',N'-tetraisopropylphosphorodiamidite (6.77mL, 21.32mmol) was added, and the mixture was stirred for 15min at 0°C, after which time the mixture was concentrated under reduced pressure and purified by silica gel chromatography using a gradient of 30-100% EtOAc in Hex to yield (2R,3S,5R)-5-(4-benzamido-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl) tetrahydrofuran-3-yl (2-cyanoethyl) diisopropylphosphoramidite. LCMS (ES, m/z): 857 $[M+H]^+$.

[0326] **Preparation 18: N-(3-((2R,3S,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl) methoxy)methyl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-yl)isobutyramide**



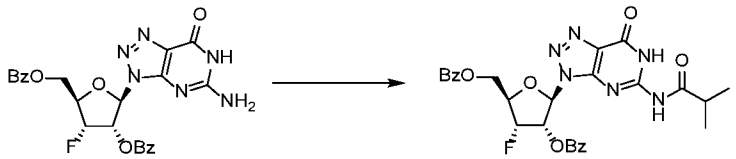
[0327] *Step 1: ((2R,3R,4S,5R)-5-(5-amino-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-4-(benzoyloxy)-3-fluorotetrahydrofuran-2-yl)methyl benzoate*



[0328] To a suspension of 8-azaguanine (5.14g, 33.8mmol) in anhydrous MeCN (100mL) at RT was added dropwise (E)-trimethylsilyl N-(trimethylsilyl)acetimidate (16.53mL, 67.6mmol) then the mixture was stirred at 70°C for 2h. The reaction was cooled to rt, and a solution of ((2R,3R,4S)-5-acetoxy-4-(benzoyloxy)-3-fluorotetrahydrofuran-2-yl)methyl benzoate (6.8g, 16.90mmol) in anhydrous MeCN (20mL) was added followed by dropwise addition of $SnCl_4$ (67.6mL, 67.6mmol). The homogeneous solution was stirred at 70°C for 2h. The reaction was

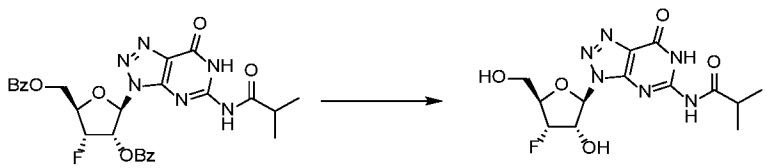
cooled to RT and concentrated. The residue was dissolved in EtOAc (1000mL) and neutralized by pouring into sat aq $NaHCO_3$ (500mL). The organic layer was separated, and the aq layer was extracted with EtOAc (4x500mL). The organic layers were combined and washed with H_2O (3×700 mL), brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to afford title compound without further purification. LCMS (ES, m/z): 495.3 $[M+H]^+$.

[0329] *Step 2: ((2R,3R,4S,5R)-4-(benzoyloxy)-3-fluoro-5-(5-isobutyramido-7-oxo-6,7-dihydro-3H- [1,2,3]triazolo[4,5-d]pyrimidin-3-yl)tetrahydrofuran-2-yl)methyl benzoate*



[0330] To a solution of ((2R,3R,4S,5R)-5-(5-amino-7-oxo-6,7-dihydro-3H-[1,2,3] triazolo[4,5-d]pyrimidin-3-yl)-4-(benzoyloxy)-3-fluorotetrahydrofuran-2-yl)methyl benzoate (8g, 16.18mmol) from Step 1 in anhydrous DMA (40mL) at RT was added dropwise isobutyric anhydride (4.02mL, 24.27mmol). The mixture was stirred at 140°C for 4h. The reaction was cooled and diluted with EtOAc (600mL), washed with sat aq NH_4Cl (4×500mL), brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by MPLC (220g silica gel, eluting with a gradient of 100% Hex to 100% EtOAc) to afford ((2R,3R,4S,5R)-4-(benzoyloxy)-3-fluoro-5-(5-isobutyramido-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)tetrahydrofuran-2-yl)methyl benzoate. LCMS (ES, m/z): 565.3 $[M+H]^+$.

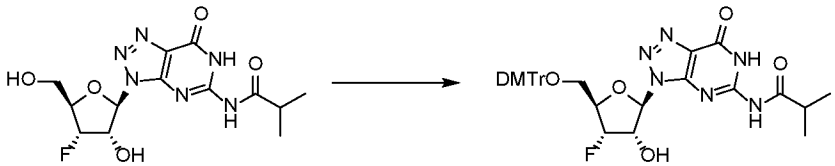
[0331] *Step 3: N-(3-((2R,3S,4S,5R)-4-fluoro-3-hydroxy-5-(hydroxymethyl) tetrahydrofuran-2-yl)-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-yl)isobutyramide*



[0332] To a solution of ((2R,3R,4S,5R)-4-(benzoyloxy)-3-fluoro-5-(5-isobutyramido-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)tetrahydrofuran-2-yl)methyl benzoate (6g, 10.63mmol) in THF (20mL), MeOH (16mL), and H_2O (4mL) at 0°C was added 5N aq NaOH (4.89mL, 24.45mmol) and stirred for 1h. The reaction was neutralized with formic acid (1.223mL, 31.9mmol). The solvent was removed, and the residue was purified by MPLC (120g, silica gel, eluting with a gradient of 100% CH_2Cl_2 to 20% MeOH/CH_2Cl_2) to afford N-(3-

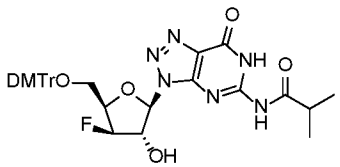
((2R,3S,4S,5R)-4-fluoro-3-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-yl)isobutyramide. LCMS (ES, m/z): 357.2 $[M+H]^+$.

[0333] *Step 4: N-(3-((2R,3S,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-yl)isobutyramide*



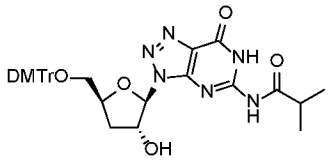
[0334] To a solution of N-(3-((2R,3S,4S,5R)-4-fluoro-3-hydroxy-5-(hydroxymethyl) tetrahydrofuran-2-yl)-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-yl)isobutyramide (3g, 8.42mmol) in anhydrous Py (40mL) at 0°C was added 4,4'-dimethoxytrityl chloride (3.42g, 10.10mmol). The ice bath was removed, and the reaction mixture was allowed to reach RT and was stirred for 2h. The mixture was diluted with EtOAc (400 mL), washed with sat aq $NaHCO_3$ (100mL), H_2O (3×100mL), brine, and dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by MPLC (120 g silica gel, eluting with a gradient of 100% DCM to 15% MeOH/DCM to afford N-(3-((2R,3S,4S,5R)-5-((bis(4-methoxyphenyl) (phenyl)methoxy)methyl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-yl)isobutyramide. LCMS (ES, m/z): 659.3 $[M+H]^+$.

[0335] **Preparation 19: N-(3-((2R,3S,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl) methoxy)methyl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-yl)isobutyramide**



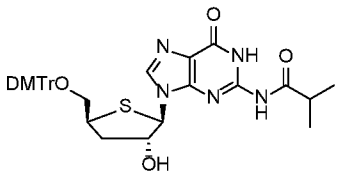
[0336] N-(3-((2R,3S,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-yl) isobutyramide was prepared according to procedures analogous to those described for Preparation **18** using the appropriately substituted ribose in Step 1. LCMS (ES, m/z): 659.4 $[M+H]^+$.

[0337] **Preparation 20: N-(3-((2R,3R,5S)-5-((bis(4-methoxyphenyl)(phenyl)methoxy) methyl)-3-hydroxytetrahydrofuran-2-yl)-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d] pyrimidin-5-yl)isobutyramide**

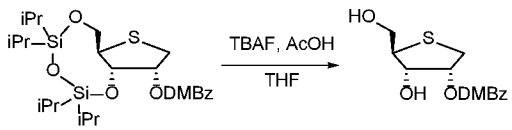


[0338] N-(3-((2R,3R,5S)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-3-hydroxy-tetrahydrofuran-2-yl)-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-yl)isobutyramide was prepared according to procedures analogous to those described for Preparation **18** using the appropriately substituted ribose in Step 1. LCMS (ES, m/z): 641.2 $[M+H]^+$.

[0339] **Preparation 21: N-(9-((2R,3R,5S)-5-((bis(4-methoxyphenyl)(phenyl)methoxy) methyl)-3-hydroxytetrahydrothiophen-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl) isobutyramide**

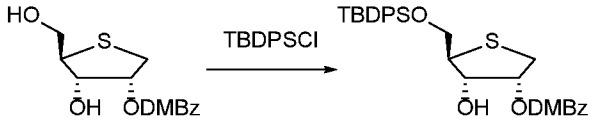


[0340] *Step 1: (3R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrothiophen-3-yl 2,4-dimethoxybenzoate*



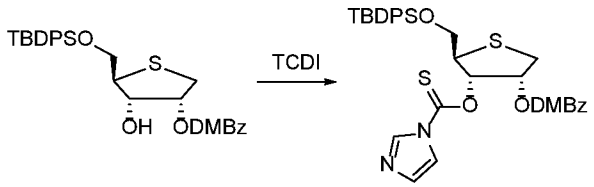
[0341] To a solution of (6aR,9R,9aS)-2,2,4,4-tetraisopropyltetrahydro-6H-thieno[3,2-f][1,3,5,2,4]trioxadisilocin-9-yl 2,4-dimethoxybenzoate (60g, 108mmol) in THF (500mL) were added AcOH (13.59g, 226mmol) and TBAF in THF (1M, 226mL, 226mmol). After 1h, it was concentrated under reduced pressure and purified by silica gel column chromatography eluting with 0-20% EtOAc in CH_2Cl_2 to give the product. LCMS (ES, m/z): 315.1 $[M+H]^+$. ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.87 (d, *J*=8.7Hz, 1H), 6.58-6.46 (m, 2H), 5.51 (dt, *J*=5.0, 3.7Hz, 1H), 4.31 (td, *J*=6.9, 3.7Hz, 1H), 3.88 (d, *J*=12.0Hz, 8H), 3.58 (dt, *J*=7.1, 4.7Hz, 1H), 3.26 (dd, *J*=12.2, 5.0Hz, 1H), 3.15-3.01 (m, 2H), 2.31 (s, 1H).

[0342] *Step 2: (3R,4S,5R)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-4-hydroxytetrahydrothiophen-3-yl 2,4-dimethoxybenzoate*



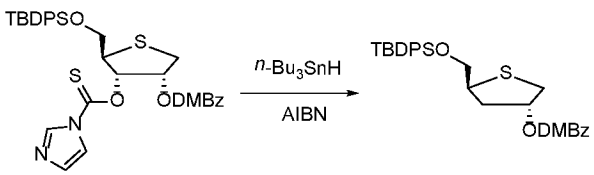
[0343] To a solution of (3R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrothiophen-3-yl 2,4-dimethoxybenzoate (33g, 105mmol) in Py (300mL) was added TBDPSCl (43.3g, 157mmol). It was stirred at RT for 4h. Then, H_2O (300mL) was added. Layers were separated, and the aq layer was extracted with CH_2Cl_2 (3x300mL). The combined organic layer was washed with brine (300mL), dried (Na_2SO_4), concentrated, and purified by silica gel column chromatography eluting with 1 to 10% EtOAc in petroleum ether to give the product. LCMS (ES, m/z): 575.3 $[M+Na]^+$. ^{1}H-NMR (400MHz, DMSO-d_6) δ 7.83 (d, *J*=8.7Hz, 1H), 7.68 (t, *J*=5.5Hz, 5H), 7.54-7.38 (m, 6H), 6.69-6.60 (m, 2H), 5.40 (d, *J*=5.6Hz, 1H), 5.35-5.29 (m, 1H), 4.12 (s, 1H), 4.05 (d, *J*=7.3Hz, 1H), 3.85 (d, *J*=7.2Hz, 6H), 3.78-3.66 (m, 1H), 3.55 (d, *J*=7.2Hz, 1H), 3.14 (dd, *J*=11.0, 5.0Hz, 1H), 2.86-2.77 (m, 1H), 1.03 (s, 9H).

[0344] *Step 3: (3R,4S,5R)-4-((1H-imidazole-1-carbonothioyl)oxy)-5-(((tert-butyldiphenylsilyl)oxy)methyl)tetrahydrothiophen-3-yl 2,4-dimethoxybenzoate*



[0345] To a solution of (3R,4S,5R)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-4-hydroxytetrahydrothiophen-3-yl 2,4-dimethoxybenzoate (48g, 87mmol) in DCE (500mL) was added di(1*H*-imidazol-1-yl)methanethione (20.12g, 113mmol). It was heated at 85°C under Ar for 1h. Then, it was concentrated and used in the next step without purification. LCMS (ES, m/z): 663.2 $[M+H]^+$.

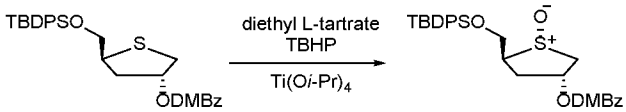
[0346] *Step 4: (3R,5S)-5-(((tert-butyldiphenylsilyl)oxy)methyl)tetrahydrothiophen-3-yl 2,4-dimethoxybenzoate*



[0347] To a solution of (3R,4S,5R)-4-((1H-imidazole-1-carbonothioyl)oxy)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)tetrahydrothiophen-3-yl 2,4-dimethoxybenzoate (crude, 57.6g, 87mmol) in THF (40mL) and toluene (200mL) was added n-Bu_3SnH (139g, 478mmol). It was

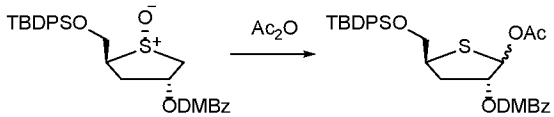
heated at 95°C, and 2, 2'-(diazene-1,2-diyl)bis(2-methylpropanenitrile) (1.427g, 8.69mmol) in toluene (200mL) was added over 30min. After 1h, the resulting mixture was concentrated and purified by silica gel column chromatography eluting with 0 to 10% EtOAc in petroleum ether to give the product. LCMS (ES, m/z): 537.3 $[M+H]^+$. ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.88 (d, *J*=8.6Hz, 1H), 7.77-7.67 (m, 4H), 7.50-7.36 (m, 6H), 6.58-6.48 (m, 2H), 5.70 (p, *J*=3.8Hz, 1H), 3.95-3.74 (m, 10H), 3.28 (dd, *J*=12.0, 4.6Hz, 1H), 3.10-3.02 (m, 1H), 2.49-2.39 (m, 1H), 1.92 (ddd, *J*=13.3, 8.6, 4.1Hz, 1H), 1.09 (s, 9H).

[0348] *Step 5: (1R,3R,5S)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-1-oxidotetrahydrothiophen-3-yl 2,4-dimethoxybenzoate*



[0349] To a solution of $Ti(OiPr)_4$ (23.29mL, 78mmol) in CH_2Cl_2 (130mL) under Ar was added diethyl (L)-tartrate (38.3mL, 224mmol) dropwise. After 10min, the mixture was cooled to -20°C, and then TBHP in decane (~5.5M, 27.1mL, 149mmol) was added dropwise. After 5min, a solution of (3R,5S)-5-(((tert-butyldiphenylsilyl)oxy)methyl)tetrahydrothiophen-3-yl 2,4-dimethoxybenzoate (40g, 74.5mmol) in CH_2Cl_2 (130mL) was added to the reaction at -20°C. The resulting mixture was stirred at -20°C for 16h. It was quenched by the addition of ice water (300mL) and allowed to warm up to RT. The precipitate was filtered off and washed with EtOAc (3×300mL). The filtrate was washed with H_2O (3×200mL). The aq layer was extracted with EtOAc (400mL). The combined organic layer was dried (Na_2SO_4), concentrated and purified by flash chromatography eluting with 0 to 70% EtOAc in petroleum ether to give the product (mixture of two isomers). LCMS (ES, m/z): 553.2 $[M+H]^+$. ^{1}H-NMR (400MHz, DMSO-d_6) δ 7.81 (d, *J*=8.7Hz, 1H), 7.75-7.61 (m, 4H), 7.54-7.39 (m, 6H), 6.67-6.56 (m, 2H), 5.66 (q, *J*=3.8Hz, 1H), 4.12 (dt, *J*=10.5, 4.4Hz, 1H), 3.92-3.79 (m, 8H), 3.58-3.42 (m, 1H), 3.20-3.09 (m, 1H), 2.97 (d, *J*=15.0Hz, 1H), 2.05 (ddd, *J*=14.5, 10.5, 4.3Hz, 1H), 1.02 (s, 9H).

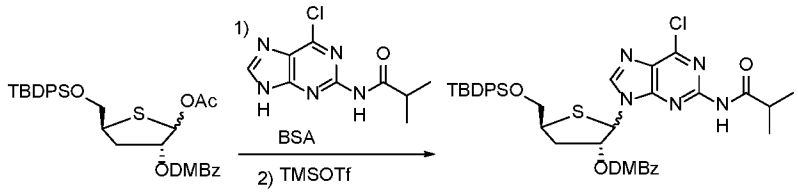
[0350] *Step 6: (3R,5S)-2-acetoxy-5-(((tert-butyldiphenylsilyl)oxy)methyl) tetrahydrothiophen-3-yl 2,4-dimethoxybenzoate*



[0351] A solution of (3R,5S)-2-acetoxy-5-(((tert-butyldiphenylsilyl)oxy)methyl)-tetrahydrothiophen-3-yl 2,4-dimethoxybenzoate (21g, 34.2mmol) in acetic anhydride (210mL)

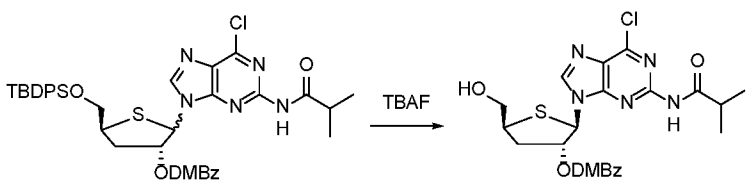
was heated at 110°C. After stirring of 3.5h, the reaction mixture was cooled to RT and concentrated. The residue was purified by silica gel column chromatography eluting with 0% to 20% EtOAc in petroleum ether to give the product. LCMS (ES, m/z): 535.3 $[M\text{-}OAc]^+$. ^{1}H-NMR (400MHz, DMSO-d_6) δ 7.76-7.61 (m, 5H), 7.46 (dq, *J*=7.6, 4.5, 3.7Hz, 6H), 6.68-6.58 (m, 2H), 6.22 (d, *J*=4.3Hz, 0.65H), 5.94 (s, 0.28H), 5.51-5.46 (m, 0.33H), 5.38 (ddd, *J*=11.1, 7.2, 4.3Hz, 0.65H), 3.96-3.61 (m, 9H), 2.40-2.21 (m, 2H), 2.03 (d, *J*=1.6Hz, 3H), 1.01 (s, 9H).

[0352] *Step 7: (3R,5S)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-2-(6-chloro-2-isobutyramido-9H-purin-9-yl)tetrahydrothiophen-3-yl 2,4-dimethoxybenzoate*



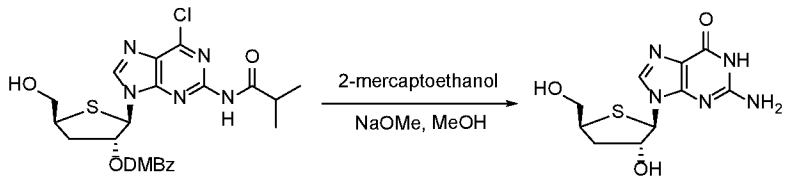
[0353] To a solution of *N*-(6-chloro-9*H*-purin-2-yl)isobutyramide (10.27g, 42.9mmol) in toluene (600mL) at 0°C was added trimethylsilyl *N*-(trimethylsilyl)acetimidate (23.26g, 114mmol). It was heated at 80°C for 1h and was cooled to 0°C again. To the reaction was then added a solution of (3*R*, 5*S*)-2-acetoxy-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-tetrahydro-thiophen-3-yl 2,4-dimethoxybenzoate (17g, 28.6mmol) in toluene (600mL) and TMSOTf (19.06g, 86mmol). It was heated to 80°C and stirred under Ar for 12h. At that time, the reaction was cooled to RT, and sat aq $NaHCO_3$ (400mL) was added. Layers were separated, and the aq layer was extracted with EtOAc (4×1000mL). The combined organic phase was dried (Na_2SO_4), concentrated and purified by silica gel column chromatography eluting with 10% to 40% EtOAc in petroleum ether to give the product (mixture of α and β isomers). LCMS (ES, m/z): 774.3 $[M+H]^+$. ^{1}H-NMR (400MHz, $CDCl_3$) δ 8.48 (s, 0.32H), 8.35 (s, 0.69H), 7.97-7.83 (m, 1.67H), 7.70 (dq, *J*=8.4, 1.5Hz, 4H), 7.54 (d, *J*=8.7Hz, 0.33H), 7.49-7.36 (m, 6H), 6.57-6.36 (m, 2.5H), 6.18 (d, *J*=2.4Hz, 0.7H), 5.87-5.80 (m, 0.35H), 5.73 (q, *J*=3.3Hz, 0.75H), 4.23-4.01 (m, 1.2H), 3.98-3.74 (m, 7.8H), 3.11 (s, 0.73H), 2.95 (s, 0.37H), 2.57-2.36 (m, 1.75H), 2.30-2.20 (m, 0.34H), 1.23 (d, *J*=6.8Hz, 2.19H), 1.19 (dd, *J*=6.8, 3.5Hz, 4.38H), 1.09 (d, *J*=1.7Hz, 9H).

[0354] *Step 8: (2R,3R,5S)-2-(6-chloro-2-isobutyramido-9H-purin-9-yl)-5-(hydroxymethyl)-tetrahydrothiophen-3-yl 2,4-dimethoxybenzoate*



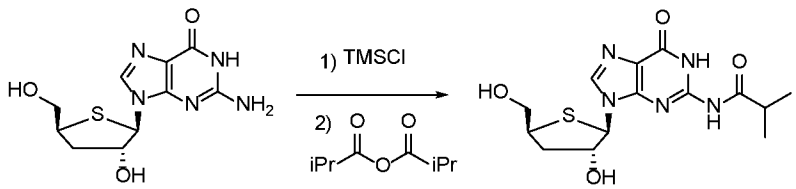
[0355] To a solution of (3R,5S)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-2-(6-chloro-2-isobutyramido-9H-purin-9-yl)tetrahydrothiophen-3-yl 2,4-dimethoxybenzoate (20g, 25.8mmol) in THF (135mL) was added TBAF in THF (1M, 31mL, 31mmol) dropwise. After 1h, the reaction mixture was concentrated and purified by column chromatography using 1% to 10% MeOH in CH_2Cl_2 as the eluent to give a mixture of two isomers. It was re-purified by reverse phase (C18) chromatography eluting with 10 to 45% ACN in aq NH_4CO_3 (5mM) to give the product. LCMS (ES, m/z): 536.2 $[M+H]^+$. ^{1}H-NMR (400MHz, DMSO-d_6) δ 10.80 (s, 1H), 8.83 (s, 1H), 7.72 (d, *J*=8.7Hz, 1H), 6.65-6.55 (m, 2H), 6.18 (d, *J*=2.5Hz, 1H), 5.80 (q, *J*=3.5Hz, 1H), 5.22 (t, *J*=5.1Hz, 1H), 3.93-3.67 (m, 9H), 2.85 (p, *J*=6.9Hz, 1H), 2.70 (ddd, *J*=13.4, 8.5, 4.5Hz, 1H), 2.36 (dt, *J*=14.1, 5.0Hz, 1H), 1.06 (dd, *J*=6.8, 3.3Hz, 6H).

[0356] *Step 9: 2-amino-9-((2R,3R,5S)-3-hydroxy-5-(hydroxymethyl)tetrahydrothiophen-2-yl)-1,9-dihydro-6H-purin-6-one*



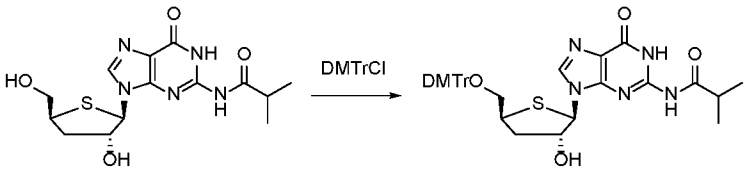
[0357] To a solution of (2R,3R,5S)-2-(6-chloro-2-isobutyramido-9H-purin-9-yl)-5-(hydroxymethyl)tetrahydrothiophen-3-yl 2,4-dimethoxybenzoate (6.0g, 11.19mmol) in MeOH (300mL) were added 2-mercaptoethanol (3.50g, 44.8mmol) and NaOMe (10.08g,56 mmol, 30% in MeOH). It was heated at 60°C for 16h, cooled to rt, and concentrated HCl (4mL) was added. The resulting mixture was concentrated, and H_2O (100mL) and EtOAc (100mL) were added. Layers were separated, and the aq layer was extracted with EtOAc (3x100mL). The aq layer was basified with $NaHCO_3$ (solid) to ~pH 8 and stirred at RT for 1h. The precipitate was filtered and kept under reduced pressure to give the product. LCMS (ES, m/z): 284.1 $[M+H]^+$. ^{1}H-NMR (400MHz, DMSO-d_6) δ 10.57 (s, 1H), 7.98 (s, 1H), 6.46 (s, 2H), 5.57 (dd, *J*=10.9, 3.9Hz, 2H), 5.12 (t, *J*=5.4Hz, 1H), 4.48 (p, *J*=4.1Hz, 1H), 3.78-3.53 (m, 3H), 2.11-1.99 (m, 2H).

[0358] *Step 10: N-(9-((2R,3R,5S)-3-hydroxy-5-(hydroxymethyl)tetrahydrothiophen-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide*



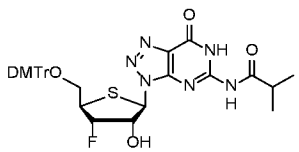
[0359] 2-amino-9-((2R,3R,5S)-3-hydroxy-5-(hydroxymethyl)tetrahydrothiophen-2-yl)-1,9-dihydro-6H-purin-6-one (580mg, 2.047mmol) was co-evaporated with Py (3x20mL) and then re-dissolved in Py (20mL). The mixture was cooled to 0°C and then treated with TMSCl (1557mg, 14.33mmol). It was warmed to RT and stirred for 2h. Then, the reaction was cooled to 0°C, and isobutyric anhydride (486mg, 3.07mmol) was added dropwise. It was warmed to RT and stirred for 2h. The reaction was quenched by the addition of MeOH (5mL). After 5min, NH_4OH (ca 29%, 10mL) was added. The mixture was stirred at RT for 30min. Then, it was concentrated and purified by column chromatography on silica gel eluting with 10% to 20% MeOH in CH_2Cl_2 to give the product. LCMS (ES, m/z): 354.1 $[M+H]^+$. ^{1}H-NMR (300MHz, CD_3OD) δ: 8.40 (s, 1H), 5.83-5.82 (m, 1H), 4.62-4.59 (m, 1H), 3.89-3.80 (m, 2H), 3.79-3.74 (m, 1H), 2.73-2.64 (m, 1H), 2.19-2.11(m, 2H), 1.20 (d, *J*=6.8Hz, 6H).

[0360] *Step 11: N-(9-((2R,3R,5S)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-3-hydroxytetrahydrothiophen-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide*

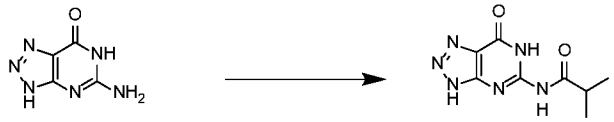


[0361] N-(9-((2R,3R,5S)-3-hydroxy-5-(hydroxymethyl)tetrahydrothiophen-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide (510mg, 1.443mmol) was co-evaporated with Py (3×5mL) and then re-suspended in Py (7mL). To the suspension was added DMTrCl (538mg, 1.587mmol), and the mixture was stirred at RT for 2h. At that time, the mixture was concentrated under reduced pressure, and residue was purified by column chromatography on silica gel eluting with 1% to 4% MeOH in CH_2Cl_2 (containing 1% Et_3N) to give the product. LCMS (ES, m/z): 656.0 $[M+H]^+$. ^{1}H-NMR (400MHz, CD_3OD) δ: 8.02 (s, 1H), 7.51- 7.43 (m, 2H), 7.40-7.17 (m, 7H), 6.91-6.82 (m, 4H), 5.85-5.84 (d, *J*=2.3Hz, 1H), 4.59-4.57 (m, 1H), 4.02-3.95 (m, 1H), 3.78(s, 6H), 3.52-3.34 (m, 3H), 2.72-2.68 (m, 1H), 1.95-191(m, 1H), 1.38 (d, *J*=6.8Hz, 6H).

[0362] **Preparation 22: N-(3-((2R,3R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)-methoxy)methyl)-4-fluoro-3-hydroxytetrahydrothiophen-2-yl)-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-yl)isobutyramide**

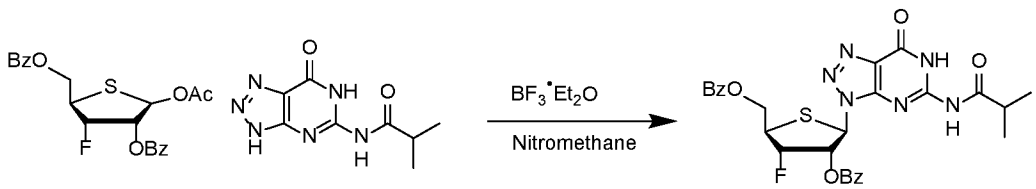


[0363] *Step 1: N-(7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-yl)isobutyramide*



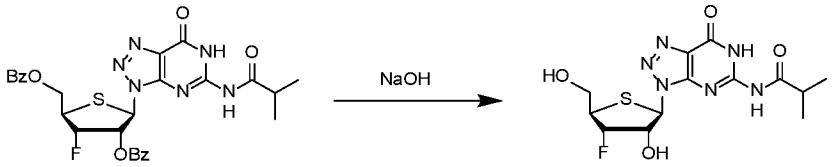
[0364] To a suspension of 5-amino-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (5.0g, 32.9mmol) in anhydrous DMF (60mL) was added isobutyric anhydride (12.5mL, 76.0mmol) dropwise. The reaction mixture was refluxed at 150°C for 1h. The reaction was quenched with MeOH (6.6mL, 164mmol) and concentrated *in vacuo*. The residue was taken up in DCM (50mL)/Hex (100mL) and was stirred at vigorously at RT for 15min. The product was collected by filtration. LCMS (ES, m/z): 223.2 $[M+H]^+$. ^{1}H NMR (500MHz, DMSO-d_6) δ 16.04 (s, 1H), 12.19 (s, 1H), 11.78 (s, 1H), 2.78 (hept, *J*=6.7Hz, 1H), 1.13 (d, *J*=6.8Hz, 6H).

[0365] *Step 2: ((2R,3S,4R,5R)-4-(benzoyloxy)-3-fluoro-5-(5-isobutyramido-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)tetrahydrothiophen-2-yl)methyl benzoate*



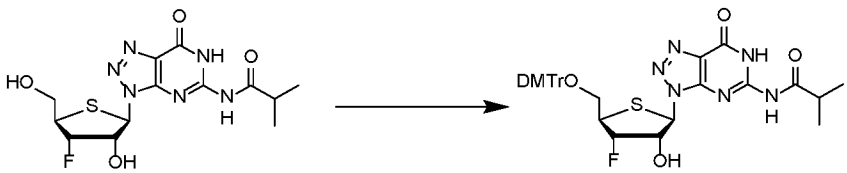
[0366] To a mixture of ((2R,3S,4R)-5-acetoxy-4-(benzoyloxy)-3-fluorotetrahydrothiophen-2-yl)methyl benzoate (1.5g, 3.6mmol) and N-(7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-yl)isobutyramide (0.96g, 4.3mmol) in nitromethane (20mL) was added $BF_3 \cdot Et_2O$ (0.54mL, 4.3mmol), and the resulting mixture was heated at 100°C under microwave irradiation for 1h. The reaction mixture was cooled, diluted in 100mL of EtOAc and washed with sat aq. $NaHCO_3$ (100mL) and brine (100mL). The organic portion was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by a silica gel column, eluting with 0-35% EtOAc/Hex. LCMS (ES, m/z): 581.4 $[M+H]^+$. ^{1}H NMR (500MHz, Chloroform-*d*) δ 12.24 (s, 1H), 9.70 (s, 1H), 8.06-8.03 (m, 2H), 7.99-7.96 (m, 2H), 7.67-7.62 (m, 1H), 7.61-7.56 (m, 1H), 7.53-7.46 (m, 2H), 7.46-7.40 (m, 2H), 6.73 (d, J=6.7Hz, 1H), 6.55-6.45 (m, 1H), 5.76 (t, J=2.9Hz, 0.5H), 5.66 (t, J=2.9Hz, 0.5H), 5.55 (dd, J=11.5, 8.8Hz, 1H), 4.86 (ddd, J=11.5, 7.8, 1.0Hz, 1H), 4.23 (dtd, J=15.0, 8.4, 2.5Hz, 1H), 2.93 (hept, J=6.9Hz, 1H), 1.41-1.32 (m, 6H).

[0367] *Step 3: N-(3-((2R,3R,4S,5R)-4-fluoro-3-hydroxy-5-(hydroxymethyl)tetrahydrothiophen-2-yl)-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-yl)isobutyramide*



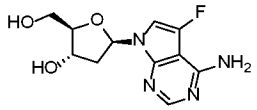
[0368] To a solution of ((2R,3S,4R,5R)-4-(benzoyloxy)-3-fluoro-5-(5-isobutyramido-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)tetrahydrothiophen-2-yl)methyl benzoate (4.5g, 7.8mmol) in THF (35mL)/MeOH (28mL)/H (7mL) at 0°C was added 2N NaOH (8.6mL, 17.2mmol). The reaction mixture was stirred at 0°C for 1h and then neutralized with AcOH (2.3mL, 39.0mmol). The product was collected by filtration and carried on to the next step without further purification. LCMS (ES, m/z): 373.3 $[M+H]^+$.

[0369] *Step 4: N-(3-((2R,3R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-fluoro-3-hydroxytetrahydrothiophen-2-yl)-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d] pyrimidin-5-yl)isobutyramide*



[0370] To a solution of N-(3-((2R,3R,4S,5R)-4-fluoro-3-hydroxy-5-(hydroxymethyl)-tetrahydrothiophen-2-yl)-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-yl) isobutyramide (1.8g, 4.8mmol) in Py (30mL) at 0°C was added DMTrCl(1.8g, 5.3mmol). The reaction mixture was stirred at 0°C for 1h. The reaction was quenched with H_2O (1mL), and the mixture was concentrated. The residue was diluted in 100mL of EtOAc and washed with sat aq. $NaHCO_3$ (100mL) and brine (100mL). The separated organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by a silica gel column, eluting with 0-100% EtOAc/Hex containing 0.1% Et_3N to give product. LCMS (ES, m/z): 675.5 $[M+H]^+$. ^1H NMR (500MHz, Chloroform-*d*) δ 12.13 (bs, 1H), 8.46 (bs, 1H), 7.54-7.48 (m, 2H), 7.38 (tt, J=6.8, 2.6Hz, 4H), 7.31-7.27 (m, 2H), 7.24-7.18 (m, 1H), 6.83 (dd, J=9.0, 1.0Hz, 4H), 6.16 (d, J=7.2Hz, 1H), 5.36 (m, 1H), 5.33-5.24 (m, 1H), 3.79-3.76 (m, 1H), 3.78 (s, 3H), 3.72 (d, J=1.8Hz, 1H), 3.70 (s, 3H), 3.43 (dd, J=10.2, 5.6Hz, 1H), 3.34 (dd, J=10.2, 5.4Hz, 1H), 2.14 (dt, J=13.7, 6.7Hz, 1H), 1.05 (d, J=6.9Hz, 3H), 1.00 (d, J=6.9Hz, 3H).

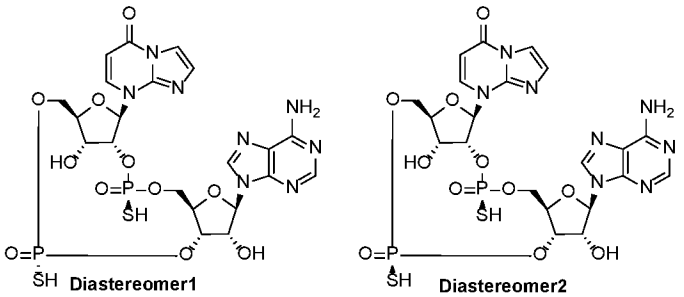
[0371] **Preparation 23: 7-(2-deoxy-β-D-erythro-pentofuranosyl)-5-fluoro-7*H*-pyrrolo[2,3-d]pyrimidin-4-amine**



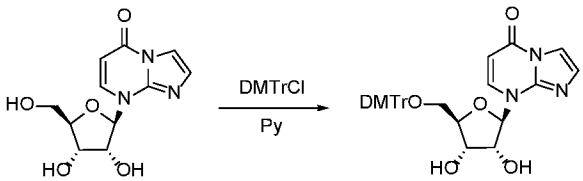
[0372] The title compound was prepared according to published procedures (*Synthesis* **2006** (12), 2005-2012).

[0373] **EXAMPLES**

[0374] **Examples 1 and 2: 8-[(2*R*,5*R*,7*R*,8*R*,10*R*,12a*R*,14*R*,15*R*,15a*S*,16*R*)-14-(6-amino-9*H*-purin-9-yl)-15,16-dihydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]imidazo[1,2-*a*]pyrimidin-5(8*H*)-one (Diastereomer 1) and 8-[(2*S*,5*R*,7*R*,8*R*,10*R*,12a*R*,14*R*,15*R*,15a*S*,16*R*)-14-(6-amino-9*H*-purin-9-yl)-15,16-dihydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,6,9,11,2,10]pentaoxadiphospha-cyclotetradecin-7-yl]imidazo[1,2-*a*]pyrimidin-5(8*H*)-one (Diastereomer 2)**



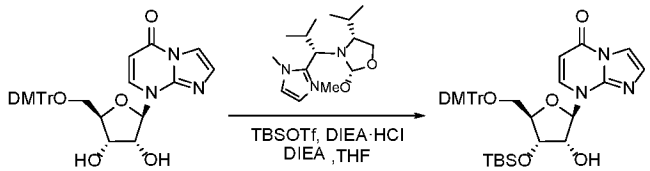
[0375] *Step 1: 8-((2R,3R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-3,4-dihydroxytetrahydrofuran-2-yl)imidazo[1,2-a]pyrimidin-5(8H)-one*



[0376] To a solution of 8-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl) tetrahydrofuran-2-yl)imidazo[1,2-a]pyrimidin-5(8H)-one (1.70g, 6.36mmol) in Py (25mL) was added DMTrCl (2.37g, 7.00mmol). The resulting mixture was stirred at RT for 4h. It was concentrated, and EtOAc (100mL) and H_2O (40mL) were added. Layers were separated, and the aq layer was extracted with EtOAc (2×50mL). The combined organics were washed with brine (50mL), dried ($MgSO_4$), and purified by column chromatography eluted with 0 to 10% MeOH in

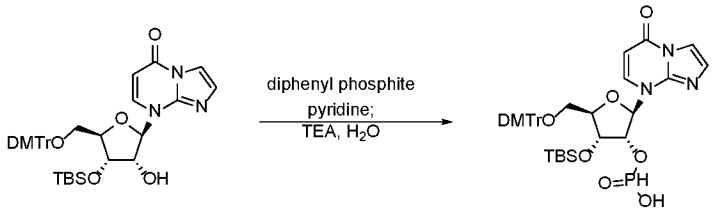
CH_2Cl_2 (0.2% of Et_3N) to give the product. LCMS (ES, m/z): 1137.5 $[2M-H]^-$. ^{1}H-NMR (300MHz, DMSO-d_6): δ 8.15 (d, *J*=7.9Hz, 1H), 7.64 (s, 1H), 7.43-7.17 (m, 10H), 6.92-6.81 (m, 4H), 6.09 (d, *J*=3.2Hz, 1H), 5.63 (d, *J*=5.1Hz, 1H), 5.50 (d, *J*=7.8Hz, 1H), 5.20 (d, *J*=6.2Hz, 1H), 4.39-4.17 (m, 2H), 4.06 (dt, *J*=6.8, 3.5Hz, 1H), 3.72 (s, 6H), 3.38 -3.23 (m, 2H).

[0377] *Step 2: 8-((2R,3R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-3-hydroxytetrahydrofuran-2-yl)imidazo[1,2-a]pyrimidin-5(8H)-one*



[0378] To a solution of 8-((2*R*,3*R*,4*S*,5*R*)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-3,4-dihydroxytetrahydrofuran-2-yl)imidazo[1,2-a]pyrimidin-5(8*H*)-one (5.0g, 8.8mmol), (2*S*,4*R*)-4-isopropyl-2-methoxy-3-((*S*)-2-methyl-1-(1-methyl-1*H*-imidazol-2-yl)propyl) oxazolidine (3.71g, 13.2mmol) and DIEA HCl (0.044g, 0.263mmol) in THF (90mL) at 0°C under Ar was added DIEA (3.40g, 26.3mmol) and TBSOTf (2.55g, 9.66mmol). The resulting mixture was stirred at RT for 1.5h. Then, it was concentrated, and the residue was partitioned between EtOAc (200mL) and H_2O (100mL). The aq layer was extracted with EtOAc (2×200mL), and the combined organic phase was dried (Na_2SO_4) and concentrated. The crude was purified by silica gel chromatography eluted with 0-40% EtOAc in Hex to give the product. LCMS (ES, m/z): 682.1 $[M-H]^-$. ^{1}H-NMR (400MHz, DMSO-d_6): δ 8.25 (d, *J*=7.9Hz, 1H), 7.67 (t, *J*=1.4Hz, 1H), 7.44-7.36 (m, 2H), 7.36-7.21 (m, 8H), 6.90 (dt, *J*=9.1, 1.2Hz, 4H), 6.09 (d, *J*=3.7Hz, 1H), 5.58 (dd, *J*=7.8, 1.0Hz, 1H), 5.50 (d, *J*=5.9Hz, 1H), 4.45 (q, *J*=4.9Hz, 1H), 4.34 (t, *J*=5.4Hz, 1H), 4.07 (dt, *J*=5.9, 4.1Hz, 1H), 3.75 (s, 6H), 3.47 (dd, *J*=10.9, 3.5Hz, 1H), 3.25 (dd, *J*=10.9, 4.3Hz, 1H), 0.80 (s, 9H), 0.05 (s, 3H), -0.00 (s, 3H).

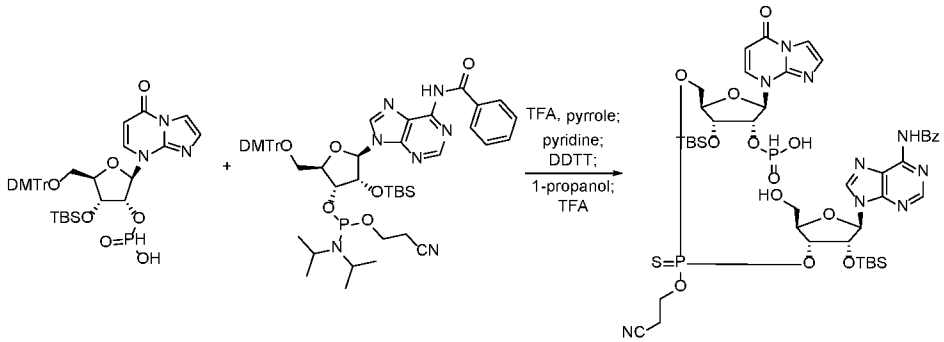
a. Step 3: 8-{5-O-[bis(4-methoxyphenyl)(phenyl)methyl]-3-O-[tert-butyl(dimethyl)silyl]-2-O-[hydroxy(oxido)-λ^5-phosphanyl]-β-D-ribofuranosyl}imidazo[1,2-a]pyrimidin-5(8H)-one



[0379] A solution of 8-((2R,3R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-3-hydroxytetrahydrofuran-2-yl)imidazo[1,2-a]

pyrimidin-5(8H)-one (1.0g, 1.46mmol) in Py (10mL) was concentrated *in vacuo*. To the residue was added Py (9.3mL) followed by dropwise addition of diphenyl phosphite (0.84mL, 4.4mmol). The mixture was left to stir for 5h, treated with TEA (0.61mL, 4.4mmol) and H_2O (0.61mL, 34mmol), and left to stir for 30min. The mixture was concentrated, and the residue was partitioned between DCM and 5% $NaHCO_3$ solution. The organic layer was separated, washed with 5% $NaHCO_3$ solution (2x), dried over Na_2SO_4, and purified by silica gel column chromatography eluted with 0-18% of MeOH in DCM with 0.5% TEA to afford the product as the triethylammonium salt. LCMS (ES, m/z): 746 $[M-H]^-$. ^{1}H-NMR (600MHz, DMSO-d_6): δ 9.94 (s, 1H), 8.21 (d, *J*=7.8Hz, 1H), 7.66 (s, 1H), 7.4-6.78 (m, 15H), 6.19 (s, 1H), 5.69 (d, *J*=7.8Hz, 1H), 5.07 (brs, 1H), 4.54 (s, 1H), 3.98 (m, 1H), 3.72 (s, 6H), 3.38 (m, 1H), 3.15 (m, 1H), 0.79 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H).

[0380] *Step 4: (2R,3R,4R,5R)-5-((((((2R,3R,4R,5R)-5-(6-benzamido-9H-purin-9-yl)-4-((tert-butyldimethylsilyl)oxy)-2-(hydroxymethyl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy) phosphorothioyl)oxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-2-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)tetrahydrofuran-3-yl hydrogen phosphonate*

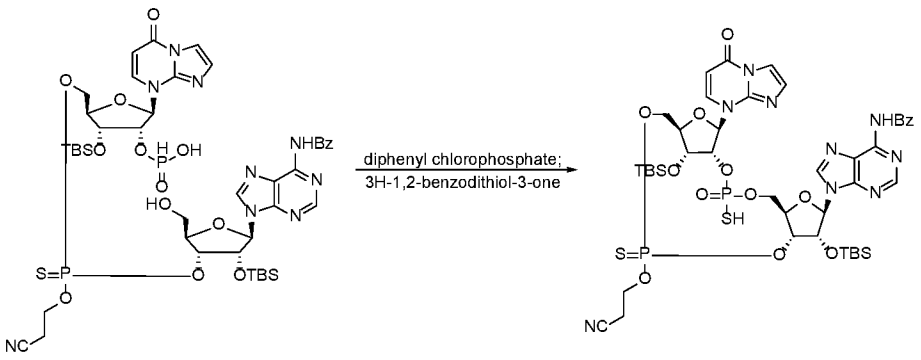


[0381] A solution of (2R,3R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-2-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)tetrahydrofuran-3-yl hydrogen phosphonate (0.64g, 0.67mmol) in MeCN (4.6 mL) was concentrated *in vacuo*. Addition of MeCN (4.6 mL) followed by concentration was repeated twice. The residue was taken up in MeCN (4.6mL), cooled to 0°C, and treated with pyrrole (0.14mL, 2.02mmol) and TFA (0.16mL, 2.02mmol) over 1min. The reaction mixture was allowed to warm to RT (1.5h) and left to stir at RT for 0.5h. The mixture was cooled to 0°C and treated with Py (0.22mL, 2.7mmol).

[0382] A solution of (2R,3R,4R,5R)-5-(6-benzamido-9H-purin-9-yl)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-((tert-butyldimethylsilyl)oxy)tetrahydrofuran-3-yl

(2-cyanoethyl) diisopropylphosphoramidite (0.886g, 0.896mmol) in ACN (4.6mL) in a separate flask was concentrated *in vacuo*. Addition of MeCN (4.6mL) followed by concentration was repeated twice. The residue was taken up in MeCN (1.6mL) and transferred to the H-phosphonate solution over 1min at 0°C. The mixture was left to stir at 0°C for 20min, treated with DDTT (0.166g, 0.809mmol), and left to stir at 0°C for 20min. The mixture was treated with 1-propanol (0.51mL, 6.7mmol), warmed to RT, and left to stir for 10min. TFA (0.519mL, 6.74mmol) was added to the reaction mixture; the mixture was left to stir for 1h and treated with pyridine (0.60mL, 7.4mmol). The mixture was concentrated to half the volume. The residue was added into rapidly stirring isopropyl acetate (46mL). The precipitate was filtered and dried under vacuum overnight to afford the crude products. LCMS (ES, m/z): 1060 $[M-H]^-$.

[0383] *Step 5: N-{9-[(5R,7R,8R,12aR,14R,15R,15aR,16R)-15,16-bis{[tert-butyl (dimethyl)silyl]oxy}-2-(2-cyanoethoxy)-10-oxido-7-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)-10-sulfanyl-2-sulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecin-14-yl]-9H-purin-6-yl}benzamide*

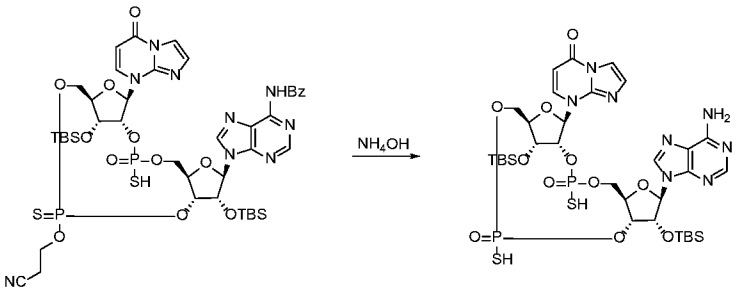


[0384] A solution of the crude (2R,3R,4R,5R)-5-((((((2R,3R,4R,5R)-5-(6-benzamido-9H-purin-9-yl)-4-((tert-butyldimethylsilyl)oxy)-2-(hydroxymethyl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphorothioyl)oxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-2-(5-oxoimidazo [1,2-a]pyrimidin-8(5H)-yl)tetrahydrofuran-3-yl hydrogen phosphonate in Py (4mL) was concentrated *in vacuo*. Addition of Py (4mL) followed by concentration was repeated once. The residue was taken up in Py (3.3mL).

[0385] Into a separate flask were added MeCN (32mL), Py (2.0mL), and diphenyl chlorophosphate (0.699mL, 3.37mmol). The solution was cooled to -20°C, and the solution of the hydrogen phosphonate in Py was added dropwise. The residue was rinsed with Py (0.6mL) and added to the reaction mixture. The mixture was left to stir at -23°C to -20°C for 20min. 3H-1,2-benzodithiol-3-one (0.136g, 0.809mmol) and H_2O (0.243mL, 13.5mmol) were added, and

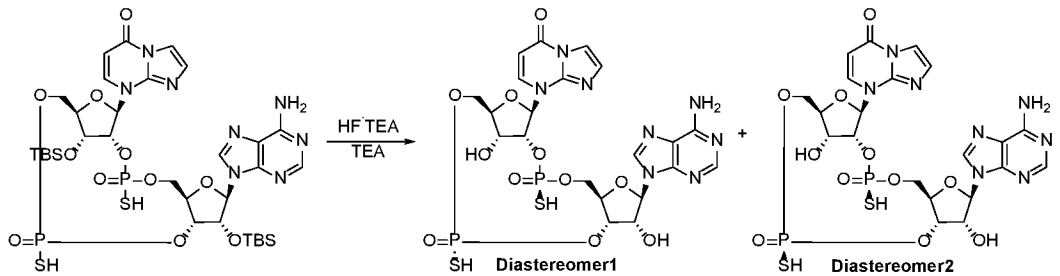
the cooling bath was removed. After the mixture was warmed to RT, it was concentrated and purified by silica gel column chromatography eluted with 100% EtOAc, then 5-20% MeOH in DCM to give the products. LCMS (ES, m/z): 1074 [M-H]$^-$.

[0386] *Step 6: 8-[(5R,7R,8R,12aR,14R,15R,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15,16-bis{[tert-butyl(dimethyl)silyl]oxy}-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]imidazo[1,2-a]pyrimidin-5(8H)-one*



[0387] To a stirred solution of *N*-{9-[(5*R*,7*R*,8*R*,12a*R*,14*R*,15*R*,15a*R*,16*R*)-15,16-bis {[*tert*-butyl(dimethyl)silyl]oxy}-2-(2-cyanoethoxy)-10-oxido-7-(5-oxoimidazo[1,2-*a*]pyrimidin-8(5*H*)-yl)-10-sulfanyl-2-sulfidooctahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecin-14-yl]-9*H*-purin-6-yl}benzamide (0.773g, 0.718mmol) in Py (8mL) were added H_2O (2mL) and NH_4OH (28%, 8mL). The mixture was left to stir for 5h, concentrated, and lyophilized to give the crude products. LCMS (ES, m/z): 917 [M-H]$^-$.

[0388] *Step 7: 8-[(2R,5R,7R,8R,10R,12aR,14R,15R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-15,16-dihydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]imidazo[1,2-a]pyrimidin-5(8H)-one (Diastereomer 1) and 8-[(2S,5R,7R,8R,10R,12aR,14R,15R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-15,16-dihydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]imidazo[1,2-a]pyrimidin-5(8H)-one (Diastereomer 2)*



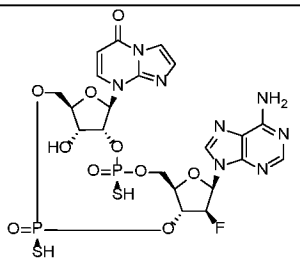
[0389] To a stirred solution of the crude 8-[(5*R*,7*R*,8*R*,12a*R*,14*R*,15*R*,15a*R*,16*R*)-14-(6-amino-9*H*-purin-9-yl)-15,16-bis{[*tert*-butyl(dimethyl)silyl]oxy}-2,10-dioxido-2,10-disulfanyloctahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]imidazo[1,2-*a*]pyrimidin-5(8*H*)-one (0.660g, 0.718mmol) in Py (1.5mL) were added TEA (2mL, 14.4mmol) and HF·TEA (0.1mL, 0.82mmol). The mixture was heated to 50°C for 6h, cooled to RT, diluted with H_2O, lyophilized, and purified by reverse phase HPLC (eluted MeCN/H_2O gradient with 100mM TEAA modifier, linear gradient) to afford two diastereomers of the title compounds.

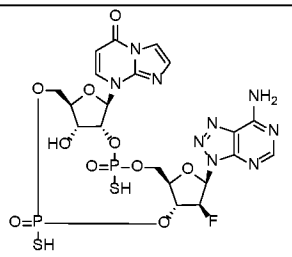
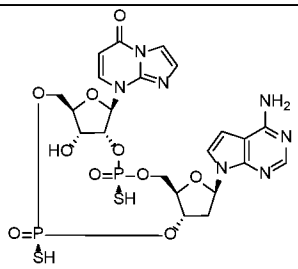
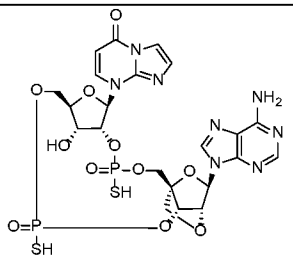
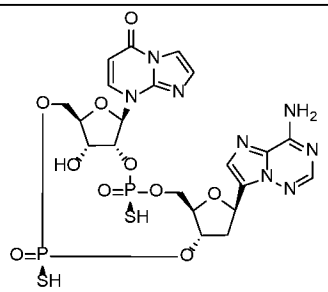
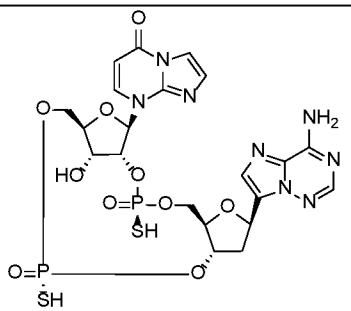
[0390] Example 1 (Diastereomer 1) (fast eluted): LCMS (ES, m/z): 689 $[M-H]^-$. ^{1}H-NMR (600MHz, D_2O): δ 8.48 (d, *J*=7.9Hz, 1H), 8.26 (s, 1H), 8.18 (s, 1H), 7.67 (s, 1H), 7.28 (s, 1H), 6.50 (d, *J*=8.2Hz, 1H), 6.12 (s, 1H), 5.41 (d, *J*=7.9Hz, 1H), 5.09-5.06 (m, 2H), 5.00 (d, *J*=3.6Hz, 1H), 4.76 (m, 1H), 4.56-4.46 (m, 3H), 4.32–4.20 (m, 3H).

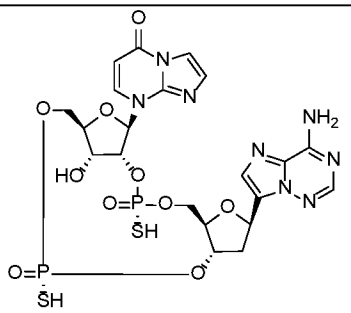
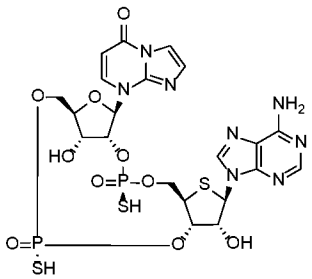
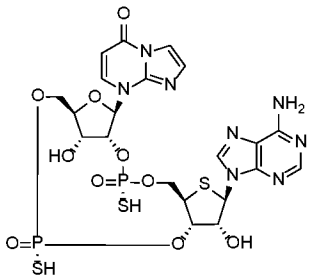
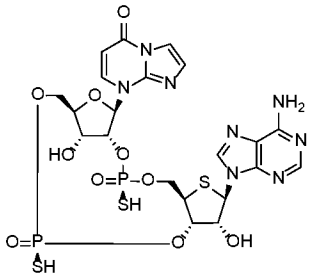
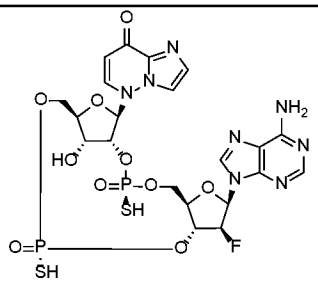
[0391] Example 2 (Diastereomer 2) (slow eluted): LCMS (ES, m/z): 689 $[M-H]^-$. ^{1}H-NMR (600MHz, D_2O): δ 8.30 (d, *J*=7.9Hz, 1H), 8.26 (s, 1H), 8.21 (s, 1H), 7.66 (s, 1H), 7.27 (s, 1H), 6.53 (d, *J*=8.2Hz, 1H), 6.13 (s, 1H), 5.56 (d, *J*=7.8Hz, 1H), 5.09 (td, *J*=8.7, 4.0Hz, 1H), 4.93-4.89 (m, 2H), 4.80 (m, 1H), 4.56-4.53 (m, 2H), 4.42–4.37 (m, 2H), 4.29 (m, 1H), 4.16 (dd, *J*=11.9, 5.0Hz, 1H).

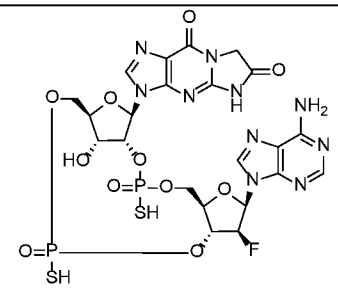
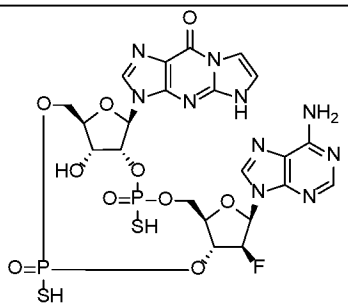
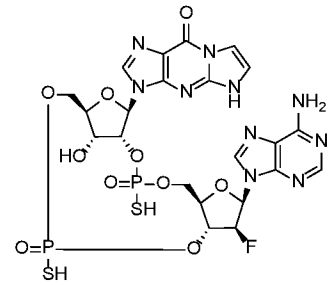
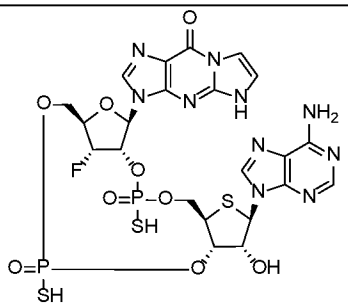
[0392] Examples **3** through **9**, as shown in Table 1 below, were prepared according to procedures analogous to those outlined in Examples **1** and **2** above using appropriate monomers, described as Preparations or as obtained from commercial sources, in the coupling step.

Table 1

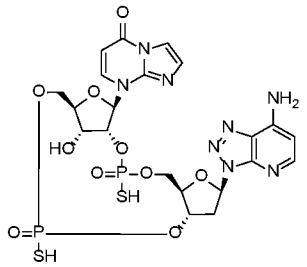
Ex.	Structure	Name	Mass $[M+H]^+$
3		8-[(2S,5R,7R,8R,10R,12aR,14R,15S,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15-fluoro-16-hydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]imidazo[1,2-a]pyrimidin-5(8H)-one	693

Ex.	Structure	Name	Mass $[M+H]^+$
4		8-[(5R,7R,8R,12aR,14R,15S,15aR,16R)-14-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-15-fluoro-16-hydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]imidazo[1,2-a]pyrimidin-5(8H)-one	694
5		8-[(2S,5R,7R,8R,10R,12aR,14R,15aS,16R)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-16-hydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]imidazo[1,2-a]pyrimidin-5(8H)-one	674
6		8-[(5R,7R,8R,12aR,14R,15R,15aS,18R)-14-(6-amino-9H-purin-9-yl)-18-hydroxy-2,10-dioxido-2,10-disulfanylhexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7(12H)-yl]imidazo[1,2-a]pyrimidin-5(8H)-one	703
7		8-[(2S,5R,7R,8R,10R,12aR,14R,15aS,16R)-14-(4-aminoimidazo[2,1-f][1,2,4]triazin-7-yl)-16-hydroxy-2,10-dioxido-2,10-disulfanyl-octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]imidazo[1,2-a]pyrimidin-5(8H)-one (Diastereomer 1)	675
8		8-[(2R,5R,7R,8R,10R,12aR,14R,15aS,16R)-14-(4-aminoimidazo[2,1-f][1,2,4]triazin-7-yl)-16-hydroxy-2,10-dioxido-2,10-disulfanyl-octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]imidazo[1,2-a]pyrimidin-5(8H)-one (Diastereomer 2)	675

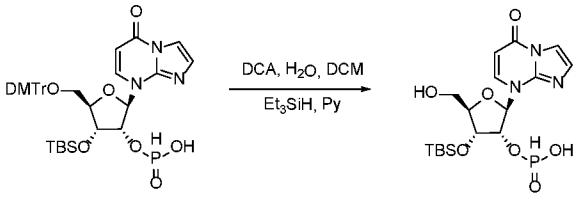
Ex.	Structure	Name	Mass $[M+H]^+$
9		8-[(2R,5R,7R,8R,10S,12aR,14R,15aS,16R)-14-(4-aminoimidazo[2,1-f][1,2,4]triazin-7-yl)-16-hydroxy-2,10-dioxido-2,10-disulfanyl-octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]imidazo[1,2-a]pyrimidin-5(8H)-one (Diastereomer 3)	675
10		8-[(2R,5R,7R,8R,10R,12aR,14R,15R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-15,16-dihydroxy-2,10-dioxido-2,10-disulfanyl-octahydro-12H-5,8-methanothieno[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]imidazo[1,2-a]pyrimidin-5(8H)-one (Diastereomer 1)	707
11		8-[(2R,5R,7R,8R,10S,12aR,14R,15R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-15,16-dihydroxy-2,10-dioxido-2,10-disulfanyl-octahydro-12H-5,8-methanothieno[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]imidazo[1,2-a]pyrimidin-5(8H)-one (Diastereomer 2)	707
12		8-[(2S,5R,7R,8R,10R,12aR,14R,15R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-15,16-dihydroxy-2,10-dioxido-2,10-disulfanyl-octahydro-12H-5,8-methanothieno[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]imidazo[1,2-a]pyrimidin-5(8H)-one (Diastereomer 3)	707
13		5-[(2R,5R,7R,8R,10R,12aR,14R,15S,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15-fluoro-16-hydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]imidazo[1,2-b]pyridazin-8(5H)-one	693

Ex.	Structure	Name	Mass $[M+H]^+$
14		3-[(5R,7R,8R,12aR,14R,15S,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15-fluoro-16-hydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3H-imidazo[1,2-a]purine-6,9(5H,7H)-dione	749
15		3-[(5R,7R,8R,12aR,14R,15S,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15-fluoro-16-hydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,5-dihydro-9H-imidazo[1,2-a]purin-9-one (Diastereomer 1)	733
16		3-[(5R,7R,8R,12aR,14R,15S,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15-fluoro-16-hydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,5-dihydro-9H-imidazo[1,2-a]purin-9-one (Diastereomer 2)	733
17		3-[(5R,7R,8S,12aR,14R,15R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-16-fluoro-15-hydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanothieno[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,5-dihydro-9H-imidazo[1,2-a]purin-9-one	749

[0393] **Example 18: 8-[(5R,7R,8R,12aR,14R,15aS,16R)-14-(7-amino-3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-16-hydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]imidazo[1,2-a]pyrimidin-5(8H)-one**

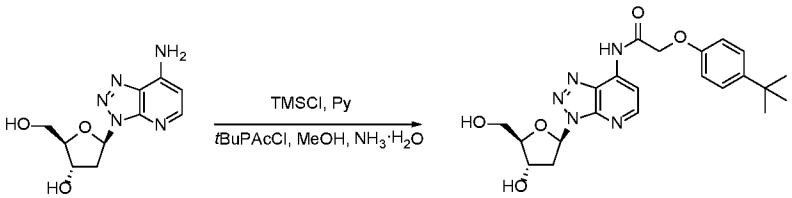


[0394] *Step 1: (2R,3R,4R,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(hydroxymethyl)-2-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)tetrahydrofuran-3-yl hydrogen phosphonate*



[0395] To a solution of (2R,3R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy) methyl)-4-((tert-butyldimethylsilyl)oxy)-2-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl) tetrahydrofuran-3-yl hydrogen phosphonate (0.76g, 0.9mmol) in CH_2Cl_2 (13mL) at RT was added H_2O (0.16mL), and DCA in CH_2Cl_2 (6%, 13mL, 8.1mmol). The mixture was stirred for 30min, and then Et_3SiH (16mL) was added. After 40min, Py (1.5mL) was added, and it was stirred for 10min. The solution was concentrated to give the crude product, which was used for the next reaction step without purification. LCMS (ES, m/z): 446.2 $[M+H]^+$.

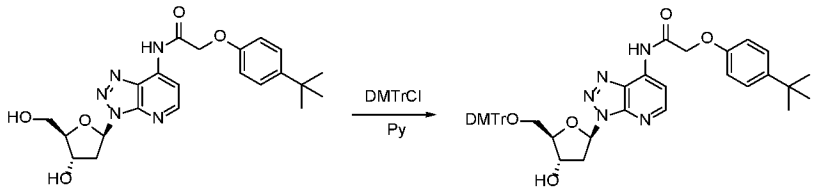
[0396] *Step 2: 2-(4-(tert-butyl)phenoxy)-N-(3-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl)acetamide*



[0397] (2R,3S,5R)-5-(7-amino-3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-2-(hydroxymethyl) tetrahydrofuran-3-ol (470mg, 1.87mmol) was co-evaporated with Py (3×5mL) and then re-suspended in Py (14mL). To the mixture under Ar at 0°C was added TMSCl (1.66mL, 13.1mmol), and it was stirred at RT for 2h. To the resulting mixture at 0°C was added 2-(4-(*tert*-butyl)phenoxy) acetyl chloride (0.576mL, 2.81mmol) over 1min. It was stirred at RT for 2h. Then, H_2O (3.5mL) was added, and it was stirred for 20min. Then, NH_4OH (7mL) was added, and it was stirred for 1h. It was concentrated and purified by preparative-TLC eluted with 3% MeOH in CH_2Cl_2 to give the product. LCMS (ES, m/z): 442.3 $[M+H]^+$. ^{1}H-NMR (400MHz,

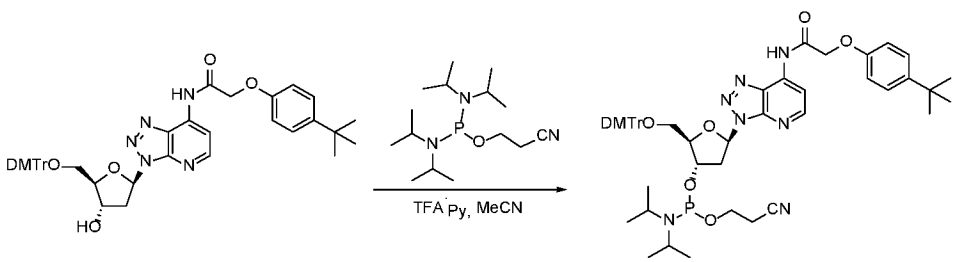
DMSO-d_6): δ 11.37 (s, 1H), 8.63 (d, *J*=5.4Hz, 1H), 8.21 (d, *J*=5.4Hz, 1H), 7.38-7.29 (m, 2H), 6.96-6.87 (m, 2H), 6.81 (t, *J*=6.4Hz, 1H), 5.42 (d, *J*=4.6Hz, 1H), 4.99 (s, 2H), 4.83 (t, *J*=5.8Hz, 1H), 4.66-4.55 (m, 1H), 3.96-3.92 (m, 1H), 3.60 (dt, *J*=11.1, 5.4Hz, 1H), 3.42 (dt, *J*=11.8, 6.0Hz, 1H), 3.18-3.10 (m, 1H), 2.51-2.45 (m, 1H), 1.26 (s, 9H).

[0398] *Step 3: N-(3-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-2-yl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl)-2-(4-(tert-butyl)phenoxy)acetamide*



[0399] To a solution of 2-(4-(*tert*-butyl)phenoxy)-*N*-(3-((2*R*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl) tetrahydrofuran-2-yl)-3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-7-yl)acetamide (467mg, 1.06mmol) in Py (5mL) at 0°C under Ar was added 4,4'-(chloro(phenyl)methylene)bis (methoxybenzene) (394mg, 1.16mmol), and the mixture was stirred at RT for 2h. Then, MeOH (3mL) was added, and the volatile components were removed under reduced pressure. The residue was purified by chromatography on silica gel eluted with 0-2.8% MeOH in CH_2Cl_2 to the product. LCMS (ES, m/z): 744.3 $[M+H]^+$. ^{1}H-NMR (300MHz, DMSO-d_6): δ 11.31 (s, 1H), 8.57 (d, *J*=5.4Hz, 1H), 8.18 (d, *J*=5.4Hz, 1H), 7.34–7.25 (m, 2H), 7.20 (dd, *J*=6.8, 3.0Hz, 2H), 7.11-7.06 (m, 7H), 6.92-6.78 (m, 3H), 6.73-6.65 (m, 2H), 6.65-6.58 (m, 2H), 5.42 (d, *J*=4.9Hz, 1H), 4.94 (s, 2H), 4.72-4.58 (m, 1H), 4.03 (q, *J*=5.3Hz, 1H), 3.65 (s, 3H), 3.63 (s, 3H), 3.18-2.93 (m, 3H), 2.56-2.48 (m, 1H), 1.22 (s, 9H).

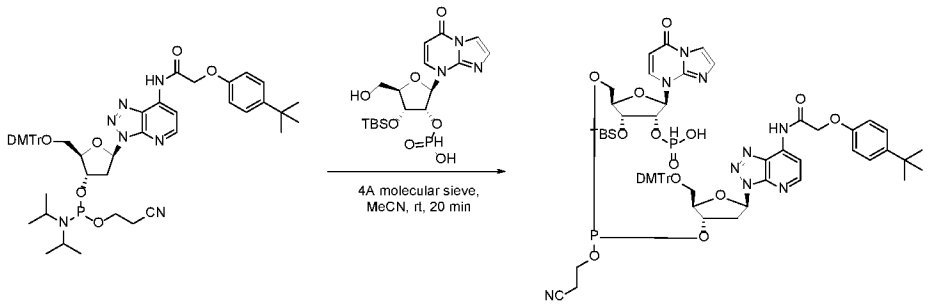
[0400] *Step 4: (2R,3S,5R)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-5-(7-(2-(4-(tert-butyl)phenoxy)acetamido)-3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)tetrahydrofuran-3-yl (2-cyanoethyl) diisopropylphosphoramidite*



[0401] To a solution of 3-((bis(diisopropylamino)phosphino)oxy)propanenitrile (477mg, 1.58 mol) in MeCN (8mL) at rt under Ar was added pyridin-1-ium 2,2,2-trifluoroacetate (229mg,

1.19mmol) and a solution of dry *N*-(3-((2*R*,4*S*,5*R*)-5-((bis(4-methoxyphenyl)(phenyl)methoxy) methyl)-4-hydroxytetrahydrofuran-2-yl)-3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-7-yl)-2-(4-(*tert*-butyl)phenoxy)acetamide (589mg, 0.792mmol) in MeCN (3.75mL) over 2min. After 1h, the residue was dissolved in EtOAc (60mL). It was washed with aq $NaHCO_3$ (1%, 2×40mL), H_2O (40mL), and brine (40mL), dried (Na_2SO_4), concentrated and purified by reverse phase (C18) chromatography eluted with 0 to 95% ACN in H_2O to give the product. LCMS (ES, m/z): 944.5 $[M+H]^+$. ^{1}H-NMR (300MHz, DMSO-d_6): δ 11.35 (s, 1H), 8.58 (dd, *J*=5.4, 1.4Hz, 1H), 8.18 (dd, *J*=5.4, 1.4Hz, 1H), 7.32-7.24 (m, 2H), 7.18 (dd, *J*=6.7, 3.0Hz, 2H), 7.14-7.00 (m, 7H), 6.91-6.80 (m, 3H), 6.72-6.57 (m, 4H), 5.03-4.89 (m, 3H), 4.17 (t, *J*=4.9Hz, 1H), 3.79-3.37 (m, 10H), 3.27–3.06 (m, 2H), 2.97 (dd, *J*=10.4, 6.1Hz, 1H), 2.78-2.58 (m, 3H), 1.21 (s, 9H), 1.14-1.06 (m, 9H), 0.98 (d, *J*=6.7Hz, 3H). ^{31}P NMR (121MHz, DMSO-d_6): δ 147.79, 147.14.

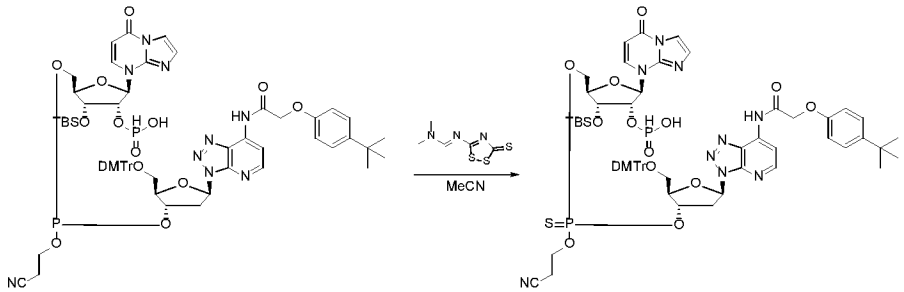
[0402] *Step 5: (2R,3R,4R,5R)-5-((((((2R,3S,5R)-2-((bis(4-methoxyphenyl)(phenyl) methoxy)methyl)-5-(7-(2-(4-(tert-butyl)phenoxy)acetamido)-3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphanyl)oxy)methyl)-4-((tert-butyldimethylsilyl) oxy)-2-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)tetrahydrofuran-3-yl hydrogen phosphonate*



[0403] (2*R*,3*R*,4*R*,5*R*)-4-((*tert*-butyldimethylsilyl)oxy)-5-(hydroxymethyl)-2-(5-oxoimidazo[1,2*a*]-pyrimidin-8(5*H*)-yl)tetrahydrofuran-3-yl phosphonate (~290mg, 0.56mmol) was co-evaporated with MeCN (3×3mL) and then re-dissolved in MeCN (2.5mL). Activated 4Å molecular sieve (200mg) was added to the solution under Ar. (2*R*,3*S*,5*R*)-2-((bis(4-methoxy-phenyl)(phenyl)methoxy)methyl)-5-(7-(2-(4-(*ter*t-butyl)phenoxy)acetamido)-3*H*[1,2,3]triazolo [4,5-*b*]pyridin-3-yl)tetrahydrofuran-3-yl(2-cyanoethyl)diisopropylphosphoramidite (480mg, 0.508mmol) was also co-evaporated with MeCN (3×3mL), and then re-dissolved in MeCN (2.5mL). Activated 4Å molecular sieve (200mg) was added to the solution under Ar. After 30min, it was added to the (2*R*,3*R*,4*R*,5*R*)-4-((*tert*-butyldimethylsilyl) oxy)-5-(hydroxymethyl)-2-(5-oxoimidazo[1,2*a*]-pyrimidin-8(5*H*)-yl)tetrahydrofuran-3-yl phosphonate solution. The

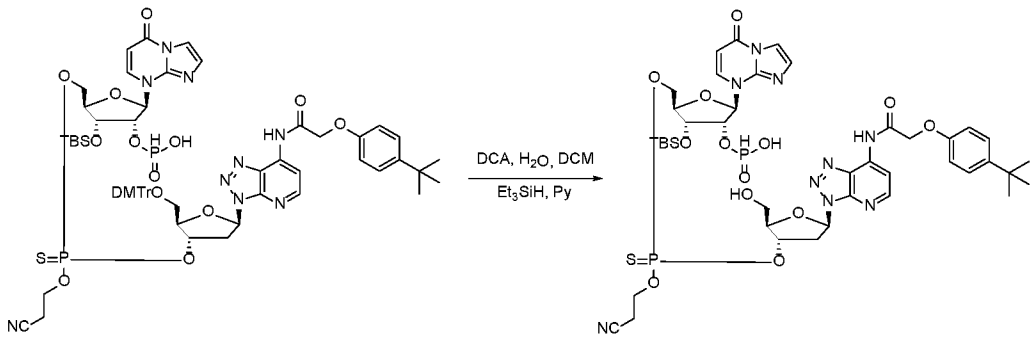
resulting mixture under Ar was stirred at RT for 30min. The reaction mixture was used for the next reaction step without purification. LCMS (ES, m/z): 1288.6 $[M+H]^+$.

[0404] *Step 6: (2R,3R,4R,5R)-5-((((((2R,3S,5R)-2-((bis(4-methoxyphenyl)(phenyl)methoxy) methyl)-5-(7-(2-(4-(tert-butyl)phenoxy)acetamido)-3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl) tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphorothioyl)oxy)methyl)-4-((tert-butyldimethyl-silyl)oxy)-2-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)tetrahydrofuran-3-yl hydrogen phosphonate*



[0405] To the reaction mixture from Step 5 at RT was added (*E*)-*N*,*N*-dimethyl-*N*'-(3-thioxo-3*H*-1,2,4-dithiazol-5-yl)formimidamide (0.115g, 0.560mmol), and the mixture was stirred for 1h. Then, it was filtered, and the filtrate was concentrated to give the crude product, which was used for the next step without purification. LCMS (ES, m/z): 1318.5 $[M-H]^-$.

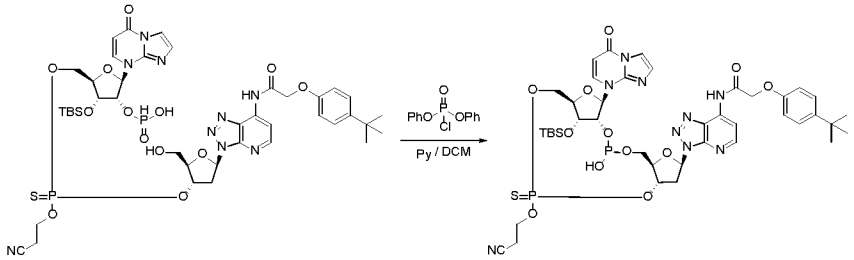
[0406] *Step 7: (2R,3R,4R,5R)-5-((((((2R,3S,5R)-5-(7-(2-(4-(tert-butyl)phenoxy) acetamido)-3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-2-(hydroxymethyl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphorothioyl)oxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-2-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)tetrahydrofuran-3-yl hydrogen phosphonate*



[0407] To a solution of the crude from Step 6 in CH_2Cl_2 (5.6mL) at RT was added H_2O (0.1mL) and DCA (6%, 7.3mL, 4.6mmol) in CH_2Cl_2. After 15min, TES (59mg, 0.51mmol) was added, and it was stirred for 40min. Then, Py (0.74mL, 9.2mmol) was added. After 5min, the mixture was concentrated, and the residue was purified by reverse phase (C18) chromatography

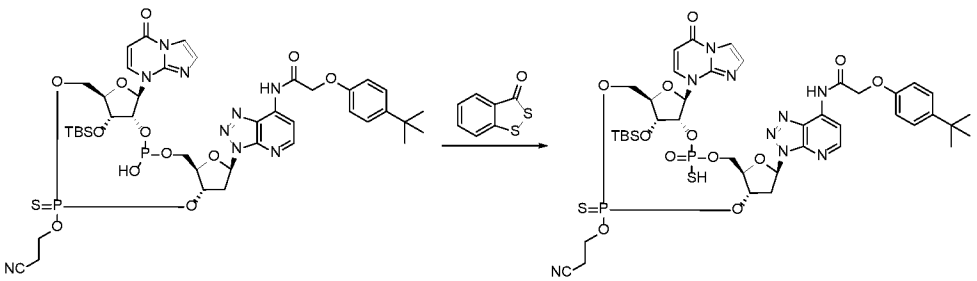
eluted with 0 to 95% ACN in aq NH_4HCO_3 (5mM) to give the product. LCMS (ES, m/z): 1018.3 $[M+H]^+$. ^{31}P NMR (121MHz, CD_3OD): δ 66.89(s), 66.81 (s); 2.96 (s), 2.87 (s).

[0408] *Step 8: N-{3-[(5R,7R,8R,12aR,14R,15aS,16R)-16-{[tert-butyl(dimethyl)silyl]oxy}-2-(2-cyanoethoxy)-10-hydroxy-7-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)-2-sulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl}-2-(4-tert-butylphenoxy)acetamide*



[0409] To a solution of (2*R*,3*R*,4*R*,5*R*)-5-((((((2*R*,3*S*,5*R*)-5-(7-(2-(4-(*tert*-butyl)phenoxy) acetamido)-3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-2-(hydroxymethyl)tetrahydrofuran-3-yl)oxy) (2-cyanoethoxy)phosphorothioyl)oxy)methyl)-4-((*tert*-butyldimethylsilyl)oxy)-2-(5-oxoimidazo [1,2-*a*]pyrimidin-8(5*H*)-yl)tetrahydrofuran-3-yl phosphonate (300mg, 0.290mmol) in DCM (29mL) and Py (29mL) at -40°C under Ar was added diphenyl phosphorochloridate (1.2mL, 5.80mmol) over 5min. It was stirred at -40°C for 20min. The reaction mixture was used for the next reaction step immediately without purification. LCMS (ES, m/z): 1000.1 $[M+H]^+$.

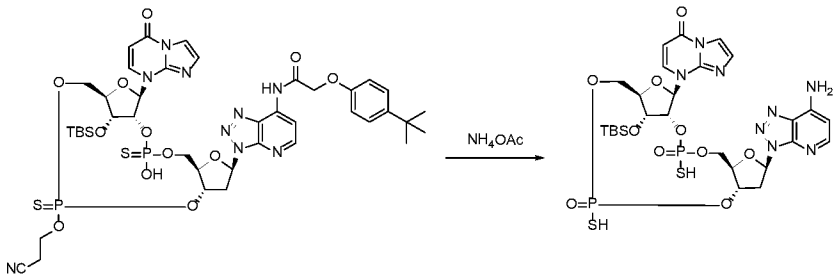
[0410] *Step 9: N-{3-[(5R,7R,8R,12aR,14R,15aS,16R)-16-{[tert-butyl(dimethyl)silyl]oxy}-2-(2-cyanoethoxy)-10-oxido-7-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)-10-sulfanyl-2-sulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl}-2-(4-tert-butylphenoxy)acetamide*



[0411] To the reaction mixture from Step 8 at -40°C was added 3*H*-benzo[*c*][1,2]dithiol-3-one (0.073g, 0.44mmol) and H_2O (0.3mL). It was stirred at RT for 40min, and the - mixture was concentrated under reduced pressure. The residue was purified by reverse phase (C18) chromatography eluted with 0 to 95% ACN in aq NH_4HCO_3 (5mM) to give the product. LCMS (ES, m/z): 1032.3 $[M+H]^+$. ^1H-NMR (300MHz, CD_3OD): δ 8.60-8.57 (m, 1H), 8.45 (d, *J*=8.0Hz,

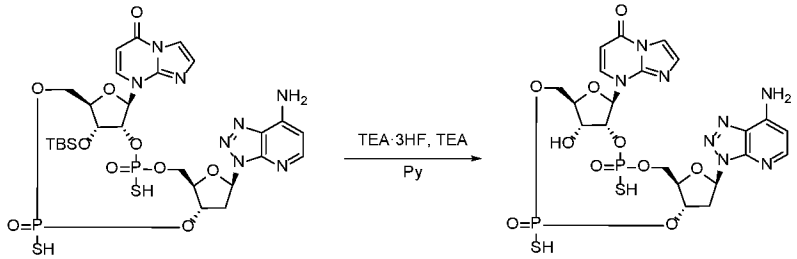
0.5H), 8.29-8.27 (m, 1H), 8.16 (d, *J*=8.0Hz, 0.5H), 7.62-7.61 (m, 1H), 7.41-7.29 (m, 2H), 7.27-7.13 (m, 1H), 7.09-6.90 (m, 3H), 6.56 (d, *J*=8.7Hz, 1H), 6.04 (dd, *J*=36.6, 7.9Hz, 1H), 5.76-5.74 (m, 1H), 5.17-5.13 (m, 1H), 4.82-4.79 (m, 2H), 4.68-4.63 (m, 1H), 4.60-4.11 (m, 5H), 3.97-3.70 (m, 2H), 3.00-2.94 (m, 3H), 1.27 (s, 9H), 0.97-0.96 (m, 9H), 0.28 (d, *J*=4.1Hz, 3H), 0.23 (d, *J*=2.3Hz, 3H). ^{31}P NMR (121MHz, CD_3OD): δ 66.05-64.43 (m, 1P), 57.93-57.39 (m, 1P).

[0412] *Step 10: 8-[(5R,7R,8R,12aR,14R,15aS,16R)-14-(7-amino-3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-16-{[tert-butyl(dimethyl)silyl]oxy}-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]imidazo[1,2-a]pyrimidin-5(8H)-one*



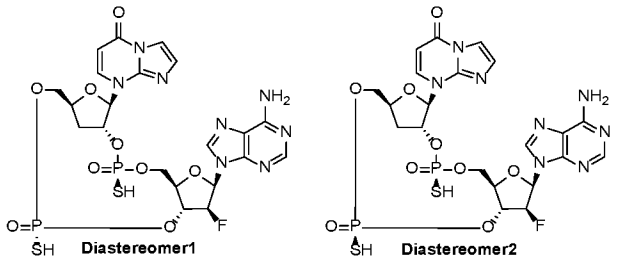
[0413] To a suspension of N-{3-[(5R,7R,8R,12aR,14R,15aS,16R)-16-{[*tert*-butyl(dimethyl)silyl]oxy}-2-(2-cyanoethoxy)-10-oxido-7-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)-10-sulfanyl-2-sulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphospha-cyclotetradecin-14-yl]-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl}-2-(4-*tert*-butylphenoxy)acetamide (118mg, 0.112mmol) in NH_4OH (9.9mL, 64mmol) was added NH_4OAc (1.0g, 13mmol). The resulting mixture was stirred at rt for 16h. Then, it was concentrated under reduced pressure, and the residue was purified by reverse phase (C18) chromatography eluted with 0 to 95% ACN in aq NH_4HCO_3 (5mM) to give the product. LCMS (ES, m/z): 789.2 $[M+H]^+$. ^{1}H-NMR (400MHz, CD_3OD): δ 8.98 (d, *J*=7.9Hz, 0.5H), 8.62 (dd, *J*=10.6, 7.9Hz, 0.5H), 8.09 (dd, *J*=5.6, 1.9Hz, 1H), 7.76-7.61 (m, 1H), 7.19 (d, *J*=1.7Hz, 1H), 6.89-6.81 (m, 1H), 6.67 (dd, *J*=8.6, 3.5Hz, 1H), 6.50 (dd, *J*=5.6, 1.3Hz, 1H), 6.22-6.02 (m, 1H), 5.59-5.41 (m, 1H), 5.30 (tdd, *J*=11.9, 8.4, 4.0Hz, 1H), 4.81-4.67 (m, 1.5H), 4.58-4.50 (m, 0.5H), 4.41-4.35 (m, 0.5H), 4.31-4.26 (m, 1.5H), 4.21-3.88 (m, 3H), 3.70-3.58 (m, 1H), 3.07–2.88 (m, 1H), 1.01 (s, 9H), 0.32 (d, *J*=5.5Hz, 3H), 0.26 (s, 3H). ^{31}P NMR (162MHz, CD_3OD): δ 57.05-56.52 (m).

[0414] *Step 11: 8-[(5R,7R,8R,12aR,14R,15aS,16R)-14-(7-amino-3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-16-hydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]imidazo[1,2-a]pyrimidin-5(8H)-one*

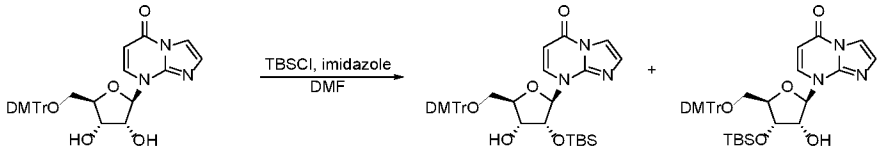


[0415] To a stirred suspension of 8-[(5R,7R,8R,12aR,14R,15aS,16R)-14-(7-amino-3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-16-{[tert-butyl(dimethyl)silyl]oxy}-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10] pentaoxadiphospha-cyclotetradecin-7-yl]imidazo[1,2-a]pyrimidin-5(8H)-one (68mg, 0.083mmol) in Py (0.22mL) at RT was added TEA (1.15mL, 8.26mmol) and TEA·3HF (0.674mL, 4.13mmol). The mixture was stirred at 50°C for 16h. Then, the mixture was concentrated under reduced pressure, and acetone (1.1mL) was added. Ethoxytrimethylsilane (3.9mL, 25mmol) was added to the mixture. The crude product crystallized out, and the mixture was maintained at 0°C. After 30min, the crude product was collected by filtration, and it was washed with acetone. The crude product was purified by reverse phase (C18) chromatography eluted with 0 to 15% ACN in aq NH_4HCO_3 (30mM) over 55min (T_R: 41.2 min) and then, prep-HPLC (XBridge Shield RP18 OBD Column, 19mm×250mm) eluted with 10 to 11% ACN in aq NH_4HCO_3 (10mM) over 11min to afford the product (T_R: 8.33 min). LCMS (ES, m/z): 674.9 $[M+H]^+$. ^{1}H-NMR (400MHz, D_2O): δ 8.38 (d, *J*=7.9Hz, 1H), 8.03 (d, *J*=5.7Hz, 1H), 7.61 (d, *J*=1.9Hz, 1H), 7.22 (d, *J*=1.9Hz, 1H), 6.73 (t, *J*=6.3Hz, 1H), 6.53 (d, *J*=8.2Hz, 1H), 6.49 (d, *J*=5.7Hz, 1H), 6.17 (d, *J*=7.9Hz, 1H), 5.34 (dq, *J*=8.7, 4.0Hz, 1H), 5.02 (ddd, *J*=10.0, 8.2, 4.3Hz, 1H), 4.64 (d, *J*=4.2Hz, 1H), 4.52-4.34 (m, 3H), 4.19-4.09 (m, 1H), 3.99-3.80 (m, 2H), 3.44 (dt, *J*=14.4, 6.0Hz, 1H), 2.93 (ddd, *J*=14.5, 7.0, 4.3Hz, 1H). ^{31}P NMR (162MHz, D_2O): δ 55.36 (s), 53.98 (s).

[0416] **Examples 19 and 20: 8-[(2*R*,5*S*,7*R*,8*R*,10*R*,12a*R*,14*R*,15*S*,15a*R*)-14-(6-amino-9*H*-purin-9-yl)-15-fluoro-2,10-dioxido-2,10-disulfanyloctahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]imidazo[1,2-*a*]pyrimidin-5(8*H*)-one (Diastereomer 1) and 8-[(2*S*,5*S*,7*R*,8*R*,10*R*,12a*R*,14*R*,15*S*,15a*R*)-14-(6-amino-9*H*-purin-9-yl)-15-fluoro-2,10-dioxido-2,10-disulfanyloctahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]imidazo[1,2-*a*]pyrimidin-5(8*H*)-one (Diastereomer 2**



[0417] *Step 1: 8-{5-O-[bis(4-methoxyphenyl)(phenyl)methyl]-2-O-[tert-butyl(dimethyl) silyl]-β-D-ribofuranosyl}imidazo[1,2-a]pyrimidin-5(8H)-one and 8-{5-O-[bis(4-methoxyphenyl) (phenyl)methyl]-3-O-[tert-butyl(dimethyl)silyl]-β-D-ribofuranosyl}imidazo[1,2-a]pyrimidin-5(8H)-one*

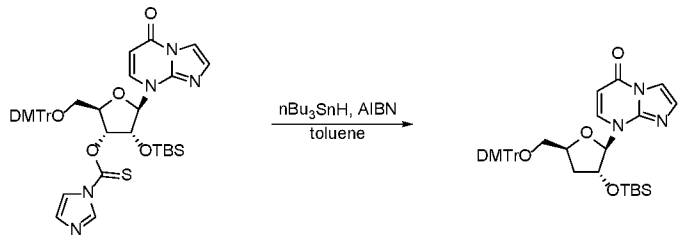


[0418] To a stirred solution of 8-{5-*O*-[bis(4-methoxyphenyl)(phenyl)methyl]-β-D-ribofuranosyl}imidazo[1,2-*a*]pyrimidin-5(8*H*)-one (1.64g, 2.88mmol) in DMF (6mL) were added imidazole (0.49g, 7.2mmol) and TBSCl (0.521g, 3.46mmol). The mixture was left to stir overnight. The mixture was concentrated, and purified by silica gel column chromatography eluting with 10-80% of EtOAc in Hex with 1% TEA to give the products. For 8-{5-*O*-[bis(4-methoxyphenyl)(phenyl)methyl]-2-*O*-[*tert*-butyl(dimethyl)silyl]-β-D-ribofuranosyl}imidazo[1,2-*a*]pyrimidin-5(8*H*)-one (fast eluting): LCMS (ES, m/z): 706 $[M+Na]^+$. ^{1}H-NMR (600MHz, DMSO-d_6): δ 8.19 (d, *J*=7.8Hz, 1H), 7.66 (s, 1H), 7.18–7.44 (m, 10H), 6.91 (d, *J*=8.5Hz, 4H), 6.10 (d, *J*=2.8Hz, 1H), 5.50 (d, *J*=7.8Hz, 1H), 5.26 (d, *J*=6.0Hz, 1H), 4.48 (brs, 1H), 4.22 (m, *J*=5.6Hz, 1H), 4.11 (brs, 1H), 3.74 (s, 6H), 3.31–3.42 (m, 2H), 0.81 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H). For 8-{5-*O*-[bis(4-methoxyphenyl)(phenyl)methyl]-3-*O*-[*tert*-butyl(dimethyl)silyl]-β-D-ribofuranosyl}imidazo[1,2-*a*]pyrimidin-5(8*H*)-one (slow eluting): LCMS (ES, m/z): 706 $[M+Na]^+$. ^{1}H-NMR (600MHz, DMSO-d_6): δ 8.25 (d, *J*=7.8Hz, 1H), 7.66 (s, 1H), 7.20-7.40 (m, 10H), 6.89 (d, *J*=7.5Hz, 4H), 6.08 (d, *J*=3.3Hz, 1H), 5.56 (d, *J*=7.8Hz, 1H), 5.52 (d, *J*=5.8Hz, 1H), 4.43 (m, *J*=4.8Hz, 1H), 4.33 (t, *J*=5.3Hz, 1H), 4.05 (m, 1H), 3.73 (s, 6H), 3.45 (dd, *J*=10.7, 2.8Hz, 1H), 3.22 (dd, *J*=10.7, 3.9Hz, 1H), 0.78 (s, 9H), 0.03 (s, 3H), -0.02 (s, 3H).

[0419] *Step 2: 8-{5-O-[bis(4-methoxyphenyl)(phenyl)methyl]-2-O-[tert-butyl(dimethyl)silyl]-3-O-(1H-imidazol-1-ylcarbonothioyl)-β-D-ribofuranosyl}imidazo[1,2-a]pyrimidin-5(8H)-one*

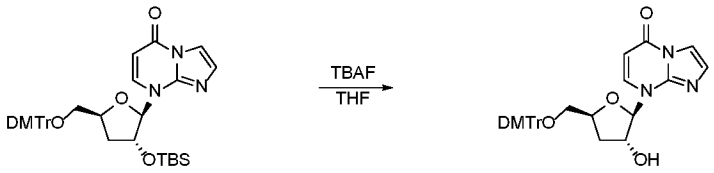
[0420] To a stirred solution of 8-{5-*O*-[bis(4-methoxyphenyl)(phenyl)methyl]-2-*O*-[*tert*-butyl(dimethyl)silyl]-β-D-ribofuranosyl}imidazo[1,2-*a*]pyrimidin-5(8*H*)-one (3.98g, 5.82mmol) in DCM (29mL) was added DMAP (71mg, 0.58mmol). 1,1'-Thiocarbonyldiimidazole (1.245g, 6.98mmol) was added to the mixture in small portions. The mixture was left to stir overnight. The mixture was purified by silica gel column chromatography eluting with 10-80% EtOAc in Hex with 1% TEA to give the product. LCMS (ES, m/z): 816 $[M+Na]^+$. ^{1}H-NMR (600MHz, DMSO-d_6): δ 8.58 (s, 1H), 8.21 (d, *J*=7.9Hz, 1H), 7.88 (s, 1H), 7.69 (s, 1H), 7.13-7.46 (m, 10H), 6.87 (m, 4H), 6.21 (d, *J*=5.9Hz, 1H), 6.12 (m, 1H), 5.89 (d, *J*=7.8Hz, 1H), 5.32 (t, *J*=5.6Hz, 1H), 4.62 (d, *J*=3.8Hz, 1H), 3.72 (s, 6H), 3.43-3.52 (m, 2H), 0.60 (s, 9H), -0.15 (s, 3H), -0.34 (s, 3H).

[0421] *Step 3: 8-((2R,3R,5S)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-3-((tert-butyldimethylsilyl)oxy)tetrahydrofuran-2-yl)imidazo[1,2-a]pyrimidin-5(8H)-one*



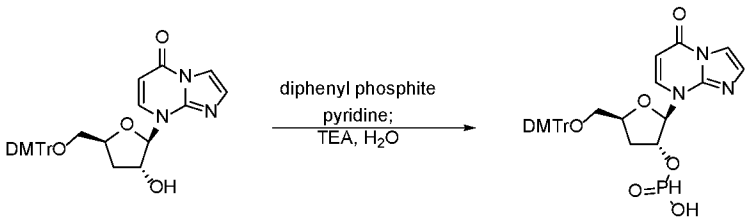
[0422] To a stirred solution of 8-{5-*O*-[bis(4-methoxyphenyl)(phenyl)methyl]-2-*O*-[*tert*-butyl(dimethyl)silyl]-3-*O*-(1*H*-imidazol-1-ylcarbonothioyl)-β-D-ribofuranosyl}imidazo[1,2-*a*]pyrimidin-5(8*H*)-one (4.23g, 5.33mmol) in toluene (152mL) were added AIBN (1.05g, 6.39mmol) and nBu_3SnH (2.82mL, 10.65mmol). The reaction mixture was heated to 95°C for 1h, cooled to RT, concentrated, and purified by silica gel column chromatography eluting with 5-80% EtOAc in Hex with 1% TEA to give the product. LCMS (ES, m/z): 690 $[M+Na]^+$. ^{1}H-NMR (600MHz, DMSO-d_6): δ 8.19 (d, *J*=7.8Hz, 1H), 7.65 (s, 1H), 7.44-6.87 (m, 14H), 6.03 (s, 1H), 5.37 (d, *J*=7.8Hz, 1H), 4.65 (d, *J*=3.5Hz, 1H), 4.52 (brs, 1H), 3.74 (s, 6H), 3.40 (m, 2H), 2.21 (m, 1H), 1.87 (dd, *J*=13.0, 4.8Hz, 1H), 0.86 (s, 9H), 0.12 (s, 3H), 0.07 (s, 3H).

[0423] *Step 4: 8-((2R,3R,5S)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-3-hydroxytetrahydrofuran-2-yl)imidazo[1,2-a]pyrimidin-5(8H)-one*



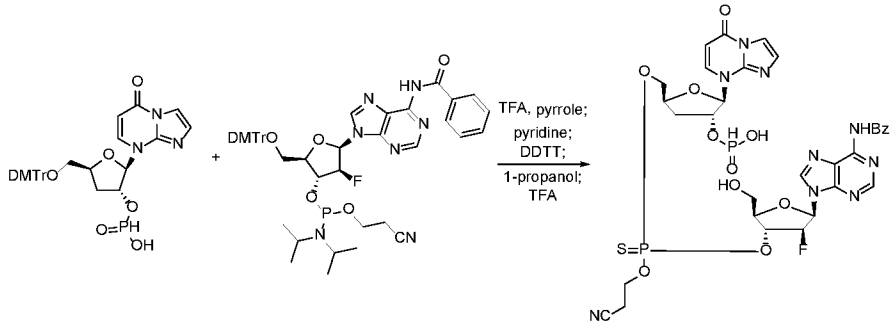
[0424] To a stirred solution of 8-((2R,3R,5S)-5-((bis(4-methoxyphenyl)(phenyl) methoxy)methyl)-3-((tert-butyldimethylsilyl)oxy)tetrahydrofuran-2-yl)imidazo[1,2-a]pyrimidin-5(8H)-one (2.54g, 3.80mmol) in THF (38mL) at 0°C was added TBAF (1.0M in THF, 7.61mL, 7.61mmol). The cooling bath was removed, and the mixture was left to stir at RT for 45min. The mixture was cooled to 0°C, diluted with EtOAc, and treated with sat $NaHCO_3$ solution. The aq layer was extracted with EtOAc (3x). The combined organics were dried (Na_2SO_4), concentrated, and purified by silica gel column chromatography eluting with 5-70% EtOAc:EtOH (3:1) in Hex with 0.5% TEA to give the product. LCMS (ES, m/z): 576 $[M+Na]^+$. ^{1}H-NMR (600MHz, DMSO-d_6): δ 8.19 (d, *J*=7.8Hz, 1H), 7.66 (s, 1H), 7.43-6.85 (m, 14H), 6.06 (s, 1H), 5.78 (d, *J*=3.5Hz, 1H), 5.38 (d, *J*=7.7Hz, 1H), 4.55 (brs, 1H), 4.49 (s, 1H), 3.74 (s, 6H), 3.36 (m, 2H), 2.20 (m, 1H), 1.88 (dd, *J*=13.0, 4.8Hz, 1H).

[0425] *Step 5: 8-{5-O-[bis(4-methoxyphenyl)(phenyl)methyl]-3-deoxy-2-O-[hydroxyl (oxido)-λ^5-phosphanyl]-β-D-erythro-pentofuranosyl}imidazo[1,2-a]pyrimidin-5(8H)-one*



[0426] A solution of 8-((2R,3R,5S)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-3-hydroxytetrahydrofuran-2-yl)imidazo[1,2-a]pyrimidin-5(8H)-one (546mg, 0.986mmol) in Py (5mL) was concentrated *in vacuo*. To the residue was added Py (6mL) followed by dropwise addition of diphenyl phosphite (567µL, 2.96mmol). The mixture was left to stir for 5h, treated with TEA (378µl, 2.71mmol) and H_2O (374µl, 20.8mmol), left to stir for 45min and concentrated. The residue was partitioned between DCM and sat $NaHCO_3$ solution. The organic layer was washed with sat aq $NaHCO_3$ (2x), dried over Na_2SO_4, and purified by silica gel column chromatography eluting with 0-18% of MeOH in DCM with 0.5% TEA to give the product. LCMS (ES, m/z): 616 $[M-H]^-$. ^{1}H-NMR (500MHz, DMSO-d_6): δ 9.85 (brs, 1H), 8.17 (d, *J*=7.8Hz, 1H), 7.65 (s, 1H), 7.42–6.81 (m, 14H), 6.14 (s, 1H), 5.47 (d, *J*=7.8Hz, 1H), 4.91 (m, 1H), 4.48 (m, 1H), 3.73 (s, 6H), 3.30 (m, 2H), 2.34 (m, 1H), 2.13 (dd, *J*=13.2, 5.2Hz, 1H).

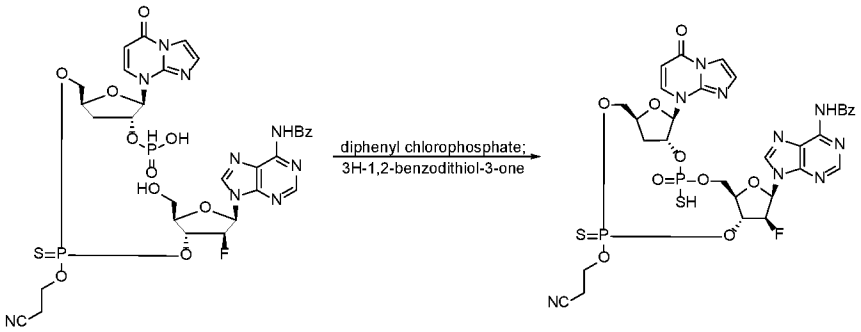
[0427] *Step 6: (2R,3R,5S)-5-((((((2R,3R,4S,5R)-5-(6-benzamido-9H-purin-9-yl)-4-fluoro-2-(hydroxymethyl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphorothioyl)oxy)methyl)-2-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)tetrahydrofuran-3-yl hydrogen phosphonate*



[0428] A solution of (2R,3R,5S)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-2-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)tetrahydrofuran-3-yl hydrogen phosphonate (520mg, 0.723mmol) in MeCN (3mL) was concentrated *in vacuo*. Addition of MeCN (3mL) followed by concentration was repeated twice. The residue was taken up in MeCN (2.5mL), cooled to 0°C, and treated with pyrrole (152µl, 2.17mmol) and TFA (167µl, 2.17mmol) over 1min. The reaction mixture was allowed to warm to RT over 1.5h. Then, the mixture was cooled to 0°C and treated with pyridine (234µl, 2.89mmol).

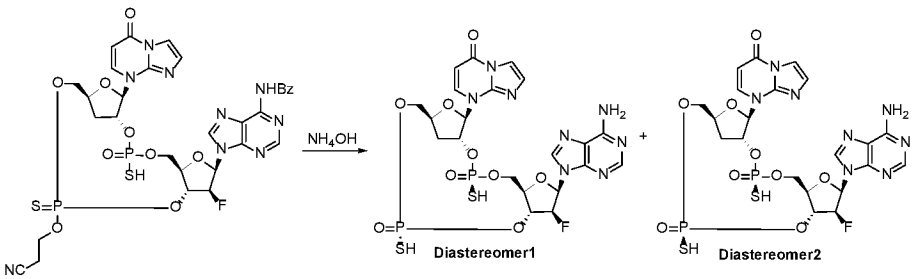
[0429] A solution of (2R,3R,4S,5R)-5-(6-benzamido-9H-purin-9-yl)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-fluorotetrahydrofuran-3-yl (2-cyanoethyl) diisopropylphosphoramidite (0.842g, 0.962mmol) in ACN (4mL) was concentrated *in vacuo*. The residue was taken up in ACN (1.6mL) and transferred to the H-phosphonate solution at 0°C over 1min. The mixture was left to stir at 0°C for 20min, treated with (E)-N,N-dimethyl-N'-(3-thioxo-3H-1,2,4-dithiazol-5-yl)formimidamide (0.178g, 0.868mmol), and left to stir at 0°C for 20min. The mixture was treated with 1-propanol (0.543mL, 7.23mmol), warmed to RT, and left to stir for 10min. TFA (0.557mL, 7.23mmol) was added to the mixture, and the reaction mixture was left to stir for 2h and treated with Py (0.643mL, 7.95mmol). The mixture was concentrated to half the volume. The residue was added into rapidly stirring isopropyl acetate (50mL). The precipitate was collected by filtration and kept under high vacuum overnight to give the crude products. LCMS (ES, m/z): 818 $[M-H]^-$.

[0430] *Step 7: N-{9-[(5S,7R,8R,12aR,14R,15S,15aR)-2-(2-cyanoethoxy)-15-fluoro-10-oxido-7-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)-10-sulfanyl-2-sulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]-9H-purin-6-yl}benzamide*



[0431] A solution of the crude (2R,3R,5S)-5-((((((2R,3R,4S,5R)-5-(6-benzamido-9H-purin-9-yl)-4-fluoro-2-(hydroxymethyl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy) phosphorothioyl)oxy)methyl)-2-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)tetrahydrofuran-3-yl hydrogen phosphonate from the previous step in Py (4mL) was concentrated *in vacuo*. Addition of Py (4mL) followed by concentration was repeated once. The residue was taken up in Py (3.6mL). Into a separate flask were added MeCN (34mL), Py (2.2mL), and diphenyl chlorophosphate (0.749mL, 3.62mmol). The solution was cooled to -20°C, and the solution of the hydrogen phosphonate in Py was added dropwise. The residue was rinsed with Py (0.7mL) and added to the reaction mixture. The mixture was left to stir at -23°C to -20°C for 20min. 3H-1,2-benzodithiol-3-one (0.146g, 0.868mmol) and H_2O (0.26mL, 14.5mmol) were added, and the cooling bath was removed. After the mixture was warmed to RT, it was concentrated and purified by silica gel column chromatography eluting with 100% EtOAc, then 5-20% MeOH in DCM to give the products. LCMS (ES, m/z): 832 $[M-H]^-$.

[0432] *Step 8: 8-[(2R,5S,7R,8R,10R,12aR,14R,15S,15aR)-14-(6-amino-9H-purin-9-yl)-15-fluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecin-7-yl]imidazo[1,2-a]pyrimidin-5(8H)-one (Diastereomers 1-2)*



[0433] To a stirred solution of *N*-{9-[(5*S*,7*R*,8*R*,12a*R*,14*R*,15*S*,15a*R*)-2-(2-cyanoethoxy)-15-fluoro-10-oxido-7-(5-oxoimidazo[1,2-*a*]pyrimidin-8(5*H*)-yl)-10-sulfanyl-2-sulfidooctahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]-9*H*-purin-

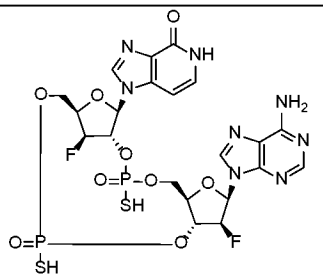
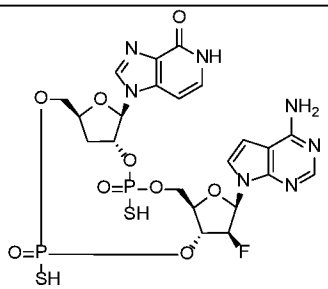
6-yl}benzamide (599mg, 0.718mmol) in Py (8mL) were added H_2O (2mL) and NH_4OH (28%, 8mL). The mixture was left to stir for 5h, concentrated, lyophilized, and purified by reverse phase HPLC (eluting MeCN/H_2O gradient with 100mM TEAA modifier, linear gradient) to afford the title compounds.

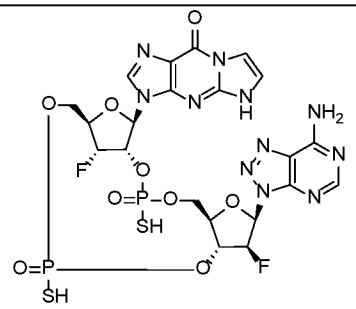
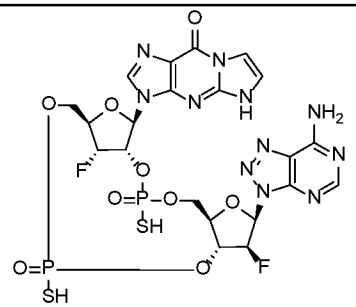
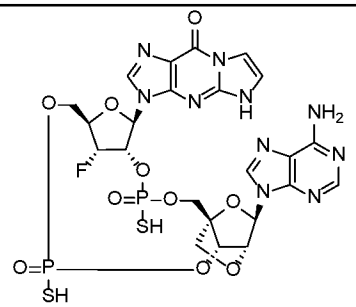
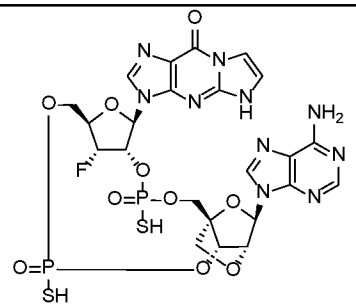
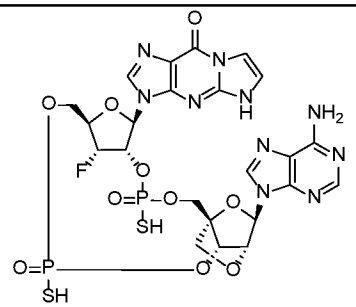
[0434] Example 19 (diastereomer 1) (fast eluted): LCMS (ES, m/z): 675 $[M-H]^-$. ^{1}H-NMR (600MHz, D_2O): δ 8.48 (d, *J*=7.9Hz, 1H), 8.31 (brs, 1H), 8.24 (s, 1H), 7.66 (s, 1H), 7.28 (s, 1H), 6.54 (dd, *J*=19.1, 3.0Hz, 1H), 6.37 (d, *J*=6.4Hz, 1H), 6.01 (d, *J*=7.9Hz, 1H), 5.71 (d, *J*=49.8Hz, 1H), 5.21-5.12 (m, 2H), 4.70 (d, *J*=7.7Hz, 1H), 4.54 (m, 1H), 4.32-4.16 (m, 4H), 2.72 (m, 1H), 2.56 (m, 1H).

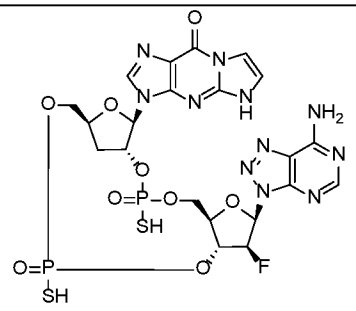
[0435] Example 20 (diastereomer 2) (slow eluted): LCMS (ES, m/z): 675 $[M-H]^-$. ^{1}H-NMR (600MHz, D_2O): δ 8.30 (s, 1H), 8.22 (s, 1H), 8.16 (d, *J*=7.8Hz, 1H), 7.65 (s, 1H), 7.26 (s, 1H), 6.54 (dd, *J*=16.2, 3.4Hz, 1H), 6.33 (d, *J*=4.6Hz, 1H), 5.93 (d, *J*=7.8Hz, 1H), 5.62 (d, *J*=50.3Hz, 1H), 5.09 (m, 2H), 4.66 (brs, 1H), 4.50 (t, *J*=11.3Hz, 1H), 4.41 (brs, 1H), 4.29 (m, 1H), 4.23 (m, 1H), 4.14 (m, 1H), 2.76 (m, 1H), 2.42 (m, 1H).

[0436] Examples **21** through **28**, as shown in Table 2 below, were prepared according to procedures analogous to those outlined in Examples **19** and **20** above using the appropriate monomers, described as Preparations or as obtained from commercial sources, in the coupling step.

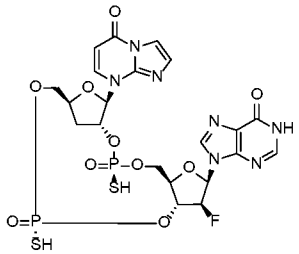
Table 2

Ex.	Structure	Name	Mass $[M+H]^+$
21		1-[(5R,7R,8S,12aR,14R,15S,15aR,16S)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecin-7-yl]-1,5-dihydro-4H-imidazo[4,5-c]pyridin-4-one	695
22		1-[(5S,7R,8R,12aR,14R,15S,15aR)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-15-fluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecin-7-yl]-1,5-dihydro-4H-imidazo[4,5-c]pyridin-4-one	676

Ex.	Structure	Name	Mass $[M+H]^+$
23		3-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-14-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-15,16-difluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,5-dihydro-9H-imidazo[1,2-a]purin-9-one (Diastereomer 1)	736
24		3-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-14-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-15,16-difluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,5-dihydro-9H-imidazo[1,2-a]purin-9-one (Diastereomer 2)	736
25		3-[(5R,7R,8S,12aR,14R,15R,15aS,18R)-14-(6-amino-9H-purin-9-yl)-18-fluoro-2,10-dioxido-2,10-disulfanylhexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7(12H)-yl]-3,5-dihydro-9H-imidazo[1,2-a]purin-9-one (Diastereomer 1)	745
26		3-[(5R,7R,8S,12aR,14R,15R,15aS,18R)-14-(6-amino-9H-purin-9-yl)-18-fluoro-2,10-dioxido-2,10-disulfanylhexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7(12H)-yl]-3,5-dihydro-9H-imidazo[1,2-a]purin-9-one (Diastereomer 2)	745
27		3-[(5R,7R,8S,12aR,14R,15R,15aS,18R)-14-(6-amino-9H-purin-9-yl)-18-fluoro-2,10-dioxido-2,10-disulfanylhexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7(12H)-yl]-3,5-dihydro-9H-imidazo[1,2-a]purin-9-one (Diastereomer 3)	745

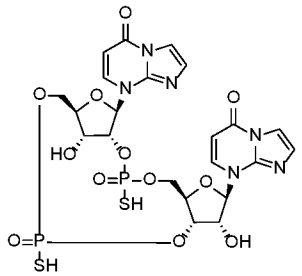
Ex.	Structure	Name	Mass $[M+H]^+$
28		3-[(5S,7R,8R,12aR,14R,15S,15aR)-14-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-15-fluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,5-dihydro-9H-imidazo[1,2-a]purin-9-one	718

[0437] **Examples 29: 9-[(2*R*,5*S*,7*R*,8*R*,10*R*,12a*R*,14*R*,15*S*,15a*R*)-15-fluoro-2,10-dioxido-7-(5-oxoimidazo[1,2-*a*]pyrimidin-8(5*H*)-yl)-2,10-disulfanyloctahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]-1,9-dihydro-6*H*-purin-6-one**

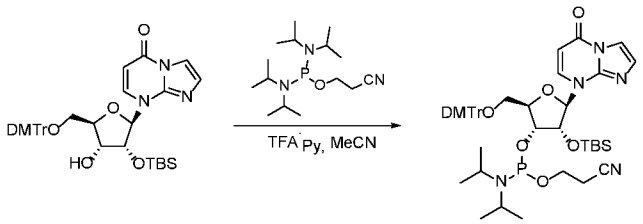


[0438] To 8-[(2*R*,5*S*,7*R*,8*R*,10*R*,12a*R*,14*R*,15*S*,15a*R*)-14-(6-amino-9*H*-purin-9-yl)-15-fluoro-2,10-dioxido-2,10-disulfanyloctahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecin-7-yl]imidazo[1,2-*a*]pyrimidin-5(8*H*)-one triethylammonium salt (16mg, 18μmol) were added sodium phosphate buffer (pH 6.8, 50mM, 1.5mL) and AMPDA (20mg). The reaction mixture was left to stir overnight, filtered, and purified by reverse phase HPLC (eluting MeCN/H_2O gradient with 100mM TEAA modifier, linear gradient) to afford the product. LCMS (ES, m/z): 676 $[M-H]^-$. ^1H NMR (600MHz, D_2O): δ 8.20 (m, 1H), 8.16 (d, *J*=7.9Hz, 1H), 8.14 (s, 1H), 7.63 (s, 1H), 7.25 (s, 1H), 6.51 (dd, *J*=18.9, 3.4Hz, 1H), 6.32 (d, *J*=4.4Hz, 1H), 6.03 (d, *J*=7.8Hz, 1H), 5.58 (d, *J*=50.2Hz, 1H), 5.11-5.03 (m, 2H), 4.65 (brs, 1H), 4.53 (t, *J*=11.2Hz, 1H), 4.39 (brs, 1H), 4.27 (m, 1H), 4.21-4.10 (m, 2H), 2.78 (dt, *J*=13.6, 7.0Hz, 1H), 2.35 (m, 1H).

[0439] **Example 30: 8,8'-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-15,16-dihydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10] pentaoxadiphosphacyclo-tetradecine-7,14-diyl]bisimidazo[1,2-a]pyrimidin-5(8H)-one**

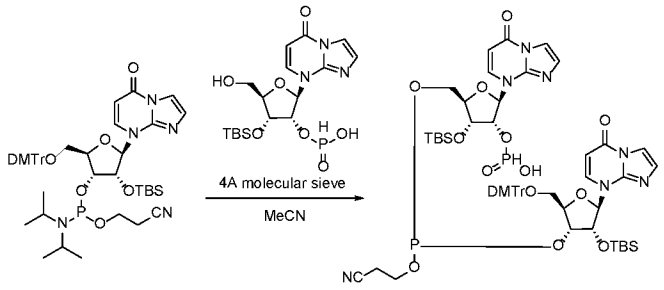


[0440] *Step 1: (2R,3R,4R,5R)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-5-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)tetrahydrofuran-3-yl (2-cyanoethyl) diisopropylphosphoramidite*



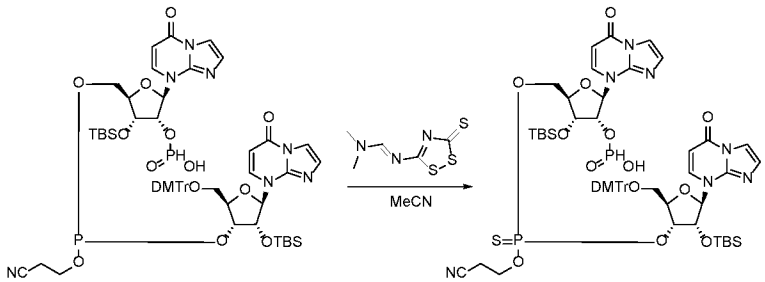
[0441] To a stirred solution of dry 3-((bis(diisopropylamino)phosphino)oxy) propanenitrile (643mg, 2.14mmol) in MeCN (4mL) under Ar was added pyridin-1-ium 2,2,2-trifluoroacetate (309mg, 1.60mmol) and 8-((2R,3R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl) methoxy)methyl)-3-((tert-butyldimethylsilyl)oxy)-4-hydroxytetrahydrofuran-2-yl)imidazo[1,2-a]pyrimidin-5(8H)-one (730 mg, 1.07 mmol) in MeCN (4mL). The resulting mixture was stirred at RT for 1h, then concentrated. The residue was dissolved in EtOAc (100mL), washed with aq $NaHCO_3$ (1%, 2×50mL), H_2O (50mL) and brine (50mL), dried (Na_2SO_4) and purified by reverse phase (C18) chromatography eluted with 60 to 95% ACN in aq NH_4HCO_3 (5mM) to give the product. LCMS (ES, m/z): 884.1 $[M+H]^+$. ^1H NMR (300MHz, DMSO-d_6): δ 8.14 (dd, *J*=7.9, 5.1Hz, 1H), 7.65-7.60 (m, 1H), 7.40-7.35 (m, 2H), 7.33-7.21 (m, 7H), 7.18-7.15(m, 1H), 6.99-6.77 (m, 4H), 6.13-5.93 (m, 1H), 5.58 (dd, *J*=12.2, 7.9Hz, 1H), 4.76 (dt, *J*=29.9, 4.6Hz, 1H), 4.39-4.15 (m, 2H), 3.74-3.69 (m, 7H), 3.66-3.31 (m, 5H), 2.73 (t, *J*=5.9Hz, 1H), 2.55 (t, *J*=5.9Hz, 1H), 1.15-0.92 (m, 12H), 0.73 (d, *J*=5.2Hz, 9H), 0.06~-0.34 (m, 6H). ^{31}P NMR: (121MHz, DMSO-d_6) δ 148.94(s), 148.68(s).

[0442] *Step 2: (2R,3R,4R,5R)-5-((((((2R,3R,4R,5R)-2-((bis(4-methoxyphenyl)(phenyl) methoxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-5-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphanyl)oxy)methyl)-4-((tert-butyldimethylsilyl) oxy)-2-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)tetrahydrofuran-3-yl hydrogen phosphonate*



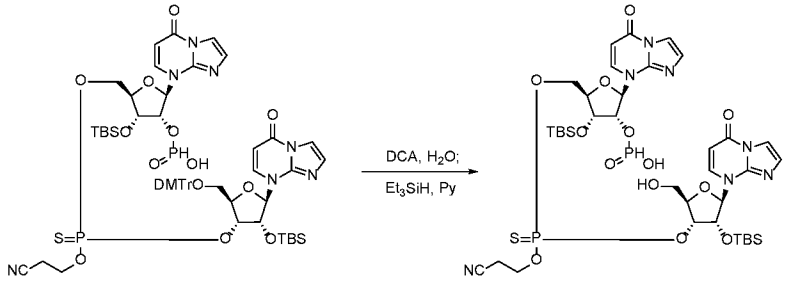
[0443] (2R,3R,4R,5R)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-((*tert*-butyldimethylsilyl)oxy)-5-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)tetrahydrofuran-3-yl (2-cyanoethyl)diisopropylphosphoramidite (540mg, 0.611mmol) was co-evaporated with MeCN (3×6mL) and re-dissolved in MeCN (5mL). Activated 4Å molecular sieve (300mg) was added. (2R,3R,4R,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(hydroxymethyl)-2-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)tetrahydrofuran-3-yl hydrogen phosphonate (crude, ~0.71 mmol) was co-evaporated with MeCN (3×8mL) and re-dissolved in MeCN (4mL) under Ar. Activated 4Å molecular sieve (300mg) was added. To this mixture was added the mixture containing (2R,3R,4R,5R)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-((tert-butyldimethylsilyl) oxy)-5-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)tetrahydrofuran-3-yl (2-cyanoethyl)diisopropyl-phosphoramidite dropwise, and it was stirred for 30min. The reaction mixture was used for the next reaction step directly without purification. LCMS (ES, m/z): 1228.4 $[M+H]^+$.

[0444] *Step 3: (2R,3R,4R,5R)-5-((((((2R,3R,4R,5R)-2-((bis(4-methoxyphenyl)(phenyl) methoxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-5-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphorothioyl)oxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-2-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)tetrahydrofuran-3-yl hydrogen phosphonate*



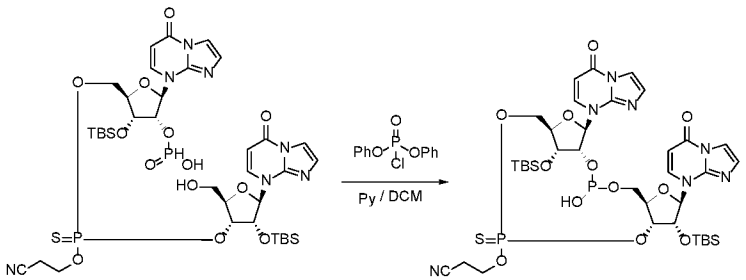
[0445] To the reaction mixture from Step 2 was added (*E*)-*N*,*N*-dimethyl-*N*'-(3-thioxo-3*H*-1,2,4-dithiazol-5-yl)formimidamide (138mg, 0.672mmol), and the mixture was stirred at rt for 1h. Then, it was concentrated to give the crude product, which was used for the next reaction step directly without purification. LCMS (ES, m/z): 1258.5 $[M-H]^-$.

[0446] *Step 4: (2R,3R,4R,5R)-4-((tert-butyldimethylsilyl)oxy)-5-((((((2R,3R,4R,5R)-4-((tert-butyldimethylsilyl)oxy)-2-(hydroxymethyl)-5-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphorothioyl)oxy)methyl)-2-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)tetrahydrofuran-3-yl hydrogen phosphonate*



[0447] To a solution of crude from Step 4 in DCM (9mL) was added H_2O (0.11mL, 6.1mmol) and DCA (8.8mL, 5.58mmol). The mixture was stirred at RT for 30min and then, Et_3SiH (20mL) was added. After 1h, Py (0.90mL, 11mmol) was added, and the mixture was stirred for 10min. It was concentrated, and the residue was purified by reverse phase (C18) chromatography eluted with 0 to 95% ACN in aq NH_4HCO_3 (5mM) to give the product. LCMS (ES, m/z): 958.3 $[M+H]^+$. ^1H NMR (300MHz, CD_3OD): δ 8.25-8.20 (m, 1H), 8.10-8.05 (m, 1H), 7.86-7.84 (m, 0.5H), 7.72-7.68 (m, 1H), 7.65-7.58 (m, 1H), 7.25-7.22 (m, 2H), 6.26-6.21 (m, 1H), 6.04-5.84 (m, 4H), 5.77-5.75 (m, 0.5H), 5.32-5.17 (m, 1H), 5.16-4.97 (m, 2H), 4.63-4.18 (m, 6H), 4.09-3.52 (m, 4H), 1.05-0.90 (m, 9H), 0.85-0.63 (m, 9H), 0.27-0.23 (m, 6H), -0.06 to -0.09 (m, 3H), -0.2 to -0.30 (m, 3H). ^{31}P-NMR: (121MHz, CD_3OD) δ 67.88 (s), 67.65 (s); 3.23 (s), 3.12 (s).

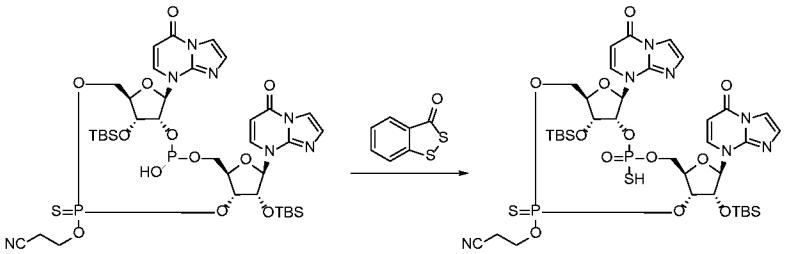
[0448] *Step 5: 3-{[(5R,7R,8R,12aR,14R,15R,15aR,16R)-15,16-bis{[tert-butyl(dimethyl)silyl]oxy}-10-hydroxy-7,14-bis(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)-2-sulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-2-yl]oxy}propanenitrile*



[0449] To Py (30mL) at -40°C under Ar was added diphenyl phosphorochloridate (1.65g, 6.15mmol) and a solution of (2R,3R,4R,5R)-4-((*tert*-butyldimethylsilyl)oxy)-5-((((((2R,3R,4R,

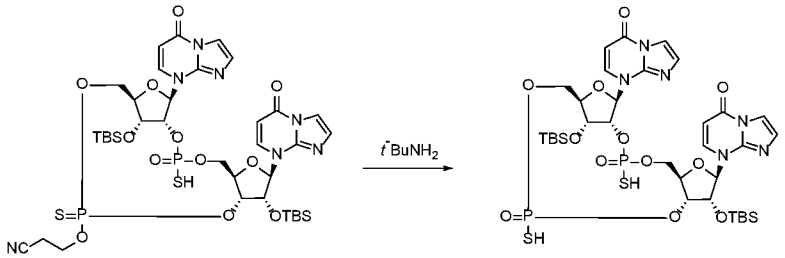
5R)-4-((*tert*-butyldimethylsilyl)oxy)-2-(hydroxymethyl)-5-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphorothioyl)oxy)methyl)-2-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)tetrahydrofuran-3-yl hydrogen phosphonate (0.30g, 0.31mmol) in DCM (30mL) drop-wise over 5min. It was stirred at -40°C for 30min. The reaction mixture was used for the next reaction step immediately without purification. LCMS (ES, m/z): 940.3 $[M+H]^+$.

[0450] *Step 6: 3-{[(5R,7R,8R,12aR,14R,15R,15aR,16R)-15,16-bis{[tert-butyl(dimethyl)silyl]oxy}-10-oxido-7,14-bis(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)-10-sulfanyl-2-sulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-2-yl]oxy}propanenitrile*



[0451] To the mixture from Step 5 at -40°C was added 3*H*-benzo[*c*][1,2]dithiol-3-one (78mg, 0.46mmol). It was warmed to RT and stirred for 40min. The mixture was concentrated and purified by reverse phase (C18) chromatography eluted with 0 to 95% ACN in aq NH_4HCO_3 (5mM) to give the product. LCMS (ES, m/z): 972.3 $[M+H]^+$. ^{31}P-NMR: (121MHz, CD_3OD) δ 67.71-64.65 (m), 62.22-53.56 (m).

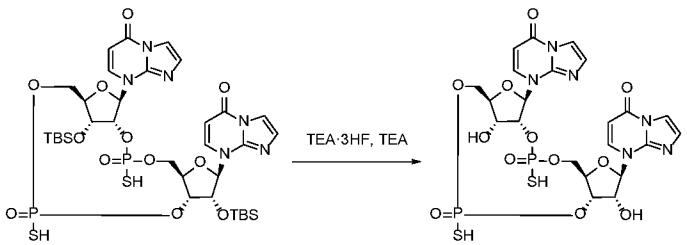
[0452] *Step 7: 8,8'-[(5R,7R,8R,12aR,14R,15R,15aR,16R)-15,16-bis{[tert-butyl(dimethyl)silyl]oxy}-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-7,14-diyl]bisimidazo[1,2-a]pyrimidin-5(8H)-one*



[0453] 3-{[(5R,7R,8R,12aR,14R,15R,15aR,16R)-15,16-bis{[tert-butyl(dimethyl)silyl]oxy}-10-oxido-7,14-bis(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)-10-sulfanyl-2-sulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetra-decin-2-yl]oxy}propanenitrile (0.25g, 0.21mmol) was dissolved in MeCN (5mL) and *t*-$BuNH_2$ (10mL,

94mmol) was added. It was stirred at RT for 1h. Then, the solution was concentrated and the residue was purified by reverse phase (C18) chromatography eluted with 0 to 95% ACN in aq NH_4HCO_3 (5mM) over 55min to give the product (T_R=43min). LCMS (ES, m/z): 919.3 $[M+H]^+$. ^1H NMR (400MHz, CD_3OD): δ 8.87 (d, *J*=7.9Hz, 1H), 8.51 (d, *J*=7.8Hz, 1H), 7.63 (dd, *J*=16.2, 1.7Hz, 2H), 7.20 (dd, *J*=28.2, 1.7Hz, 2H), 6.66 (d, *J*=8.3Hz, 1H), 6.16 (d, *J*=3.2Hz, 1H), 5.81 (dd, *J*=15.7, 7.9Hz, 2H), 5.31-5.07 (m, 2H), 4.95-4.91 (m, 1H), 4.75-4.72 (m, 1H), 4.57-4.53 (m, 1H), 4.45-4.41 (m, 1H), 4.32-4.21 (m, 2H), 4.18-4.14 (m, 1H), 3.95-3.91 (m, 1H), 1.05-0.91(m, 18H), 0.34- 0.11 (m, 12H). ^{31}P-NMR: (162MHz, CD_3OD) δ 57.80 (s), 57.12 (s).

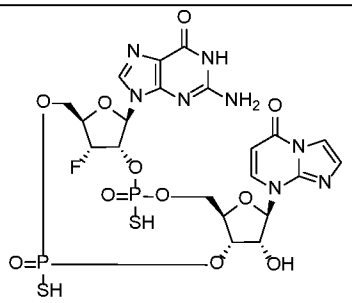
[0454] *Step 8: 8,8'-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-15,16-dihydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecine-7,14-diyl]bisimidazo[1,2-a]pyrimidin-5(8H)-one*



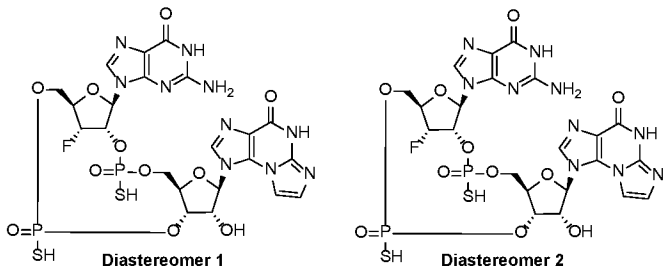
[0455] To a suspension of 8,8'-[(5R,7R,8R,12aR,14R,15R,15aR,16R)-15,16-bis{[tert-butyl(dimethyl)silyl]oxy}-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-7,14-diyl]bisimidazo[1,2-a]pyrimidin-5(8H)-one (38mg, 0.040mmol) in Py (0.2mL) was added $Et_3N{\cdot}3HF$ (0.64g, 4.0mmol) and TEA (0.83mL, 6.0mmol). The mixture was heated at 50°C for 3h. Then, it was concentrated, and acetone (0.6mL) and ethoxytrimethylsilane (3.7mL) were added. The mixture was stirred at 0°C for 30min, and the resulting solid was collected by filtration and purified by reverse phase (AQ C18) chromatography eluted with 0 to 95% ACN in aq NH_4HCO_3 (5mM) over 58min to give the product (T_R=36min). LCMS (ES, m/z): 690.8 $[M+H]^+$. ^1H NMR (400MHz, D_2O): δ 8.30 (d, *J*=7.9Hz, 1H), 8.13 (d, *J*=7.9Hz, 1H), 7.70-7.49 (m, 2H), 7.37-7.14 (m, 2H), 6.47 (d, *J*=8.1Hz, 1H), 6.02 (s, 1H), 5.45 (d, *J*=7.8Hz, 1H), 5.25 (d, *J*=7.9Hz, 1H), 5.08-4.91 (m, 2H), 4.70-4.65 (m, 2H), 4.55-4.39 (m, 3H), 4.33-4.28 (m, 2H), 4.13-4.06 (m, 1H). ^{31}P-NMR: (162MHz, D_2O) δ 55.16 (s), 52.14 (s).

[0456] Example **31**, as shown in Table 3 below, were prepared according to procedures analogous to those outlined in Example **30** above using the appropriate monomers, described as Preparations or as obtained from commercial sources, in the coupling step.

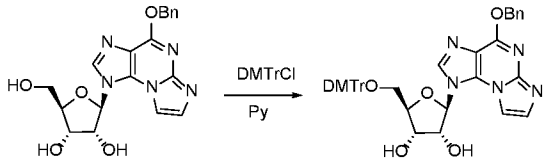
Table 3

Ex.	Structure	Name	Mass $[M+H]^+$
31		2-amino-9-[(5R,7R,8S,12aR,14R,15R,15aS,16R)-16-fluoro-15-hydroxy-2,10-dioxido-14-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	709

[0457] **Examples 32 and 33: 1-[(5R,7R,8S,12aR,14R,15R,15aS,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-16-fluoro-15-hydroxy-2,10-dioxido-2,10-disulfanyl-octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]-1H-imidazo[2,1-b]purin-4(5H)-one (Diastereomer 1) and 1-[(5R,7R,8S,12aR,14R,15R,15aS,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-16-fluoro-15-hydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxa-diphosphacyclotetradecin-14-yl]-1H-imidazo[2,1-b]purin-4(5H)-one (Diastereomer 2)**



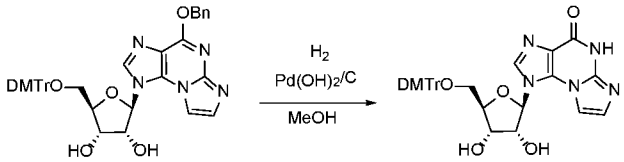
[0458] *Step 1: (2R,3R,4S,5R)-2-(4-(benzyloxy)-1H-imidazo[2,1-b]purin-1-yl)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)tetrahydrofuran-3,4-diol*



[0459] To a stirred solution of (2R,3R,4S,5R)-2-(4-(benzyloxy)-1H-imidazo[2,1-b]purin-1-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (1.27g, 3.20mmol) in Py (25mL) under Ar were

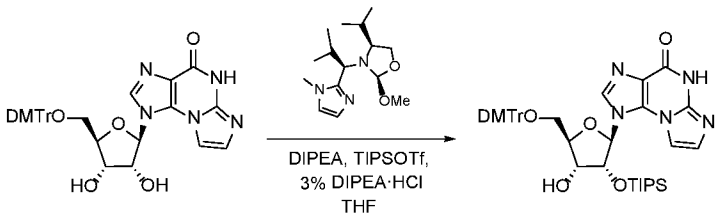
added *N*-ethyl-*N*-isopropylpropan-2-amine (1.06mL, 6.39mmol) and DMTrCl (1.62g, 4.79mmol). The resulting mixture was stirred at RT for 2h. Then, MeOH (2mL) was added. It was concentrated and purified by silica gel column chromatography eluted with 0 to 5.6% MeOH in DCM to give the product. LCMS (ES, m/z): 700.4 $[M+H]^+$. ^{1}H-NMR (400MHz, DMSO-d_6): δ 8.35 (s, 1H), 8.07 (d, *J*=1.7Hz, 1H), 7.58–7.48 (m, 3H), 7.45-7.33 (m, 3H), 7.14-7.06 (m, 5H), 7.04-6.95 (m, 4H), 6.73-6.62 (m, 4H), 6.30 (d, *J*=2.0Hz, 1H), 5.98 (d, *J*=5.0Hz, 1H), 5.61-5.47 (m, 2H), 5.28 (d, *J*=7.2Hz, 1H), 4.90-4.81 (m, 1H), 4.39 (td, *J*=7.2, 4.5Hz, 1H), 4.19 (dt, *J*=7.0, 3.3Hz, 1H), 3.68,3.67 (2 s, 6H), 3.25 (dd, *J*=11.1, 2.3Hz, 1H), 2.95 (dd, *J*=10.8, 3.8Hz, 1H).

[0460] *Step 2: 1-((2R,3R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-3,4-dihydroxytetrahydrofuran-2-yl)-1H-imidazo[2,1-b]purin-4(5H)-one*



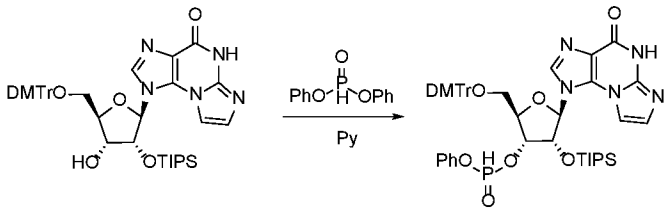
[0461] To a solution of (2R,3R,4S,5R)-2-(4-(benzyloxy)-1H-imidazo[2,1-b]purin-1-yl)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)tetrahydrofuran-3,4-diol (1.00g, 1.43mmol) in MeOH (20mL) and EtOAc (10mL) was added $Pd(OH)_2$/C (0.22g). The mixture was charged with H_2 (2atm) and stirred at 40°C for 30h. It was filtered, and the filtrate was concentrated. The crude was purified by reverse phase (AQ-C18) chromatography eluted with 0 to 95% ACN in aq NH_4HCO_3 (5mM) to give the product. LCMS (ES, m/z): 610.3 $[M+H]^+$. ^{1}H-NMR (400MHz, DMSO-d_6): δ 11.53 (br s, 1H), 8.22 (s, 1H), 7.79 (d, *J*=1.8Hz, 1H), 7.26–7.11 (m, 6H), 7.09-7.01 (m, 4H), 6.80-6.66 (m, 4H), 6.18 (d, *J*=2.0Hz, 1H), 5.99 (s, 1H), 5.29 (d, *J*=7.5Hz, 1H), 4.82 (d, *J*=4.5Hz, 1H), 4.38 (q, *J*=5.8, 5.3Hz, 1H), 4.18 (dt, *J*=6.8, 3.1Hz, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.27 (dd, *J*=10.9, 2.5Hz, 1H), 2.96 (dd, *J* =10.9, 3.8Hz, 1H).

[0462] *Step 3: 1-((2R,3R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxy-3-((triisopropylsilyl)oxy)tetrahydrofuran-2-yl)-1H-imidazo[2,1-b]purin-4(5H)-one*



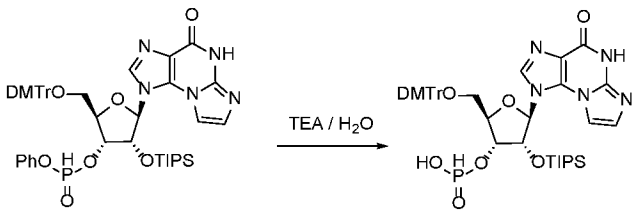
[0463] To a solution of 1-((2R,3R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy) methyl)-3,4-dihydroxytetrahydrofuran-2-yl)-1H-imidazo[2,1-b]purin-4(5H)-one (0.37g, 0.60mmol) in THF (6mL) were added (2*R*,4*S*)-4-isopropyl-2-methoxy-3-((*R*)-2-methyl-1-(1-methyl-1*H*-imidazol-2-yl)propyl)oxazolidine (0.068g, 0.240mmol), DiPEA·HCl (3.0mg, 0.018mmol), and DiPEA (0.491mL, 2.82mmol). The mixture was stirred at RT for 5min and then cooled to 0°C. To the mixture was added TIPSOTf (0.70mL, 2.6mmol) over 2min. It was stirred at RT for 2h. Then, the mixture was concentrated, and EtOAc (50 mL) and aq $NaHCO_3$ (5%, 30mL) were added. Layers were separated, and the organic layer was washed with aq $NaHCO_3$ (5%, 30mL), dried (Na_2SO_4) and concentrated. The crude product was used for next step directly. LCMS (ES, m/z): 766.3 $[M+H]^+$.

[0464] *Step 4: (2R,3R,4R,5R)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-5-(4-oxo-4,5-dihydro-1H-imidazo[2,1-b]purin-1-yl)-4-((triisopropylsilyl)oxy)tetrahydrofuran-3-yl phenyl phosphonate*



[0465] To a solution of crude from Step 3 in Py (4mL) under Ar was added diphenyl phosphonate (0.58mL, 3.0mmol), and the reaction was stirred at RT for 20min. It was used for the next reaction step without purification. LCMS (ES, m/z): 906.2 $[M+H]^+$.

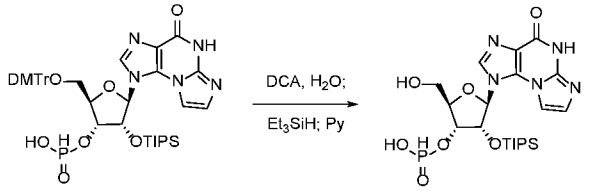
[0466] *Step 5: (2R,3R,4R,5R)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-5-(4-oxo-4,5-dihydro-1H-imidazo[2,1-b]purin-1-yl)-4-((triisopropylsilyl)oxy)tetrahydrofuran-3-yl hydrogen phosphonate*



[0467] To the reaction mixture from Step 4 at 0°C was added H_2O (2mL) and TEA (2mL). It was stirred at RT for 20min. Then, it was concentrated, and the residue was purified by reverse phase (AQ-C18) chromatography eluted with 0 to 95% ACN in aq NH_4HCO_3 (5mM) to give the product. LCMS (ES, m/z): 830.2 $[M+H]^+$. ^{1}H-NMR (400MHz, DMSO-d_6): δ 12.34 (br s, 1H), 7.99 (s, 1H), 7.69 (s, 1H), 7.34 (s, 0.5H), 7.20-7.12 (m, 6H), 7.06-7.02 (m, 4H), 6.75-6.71 (m,

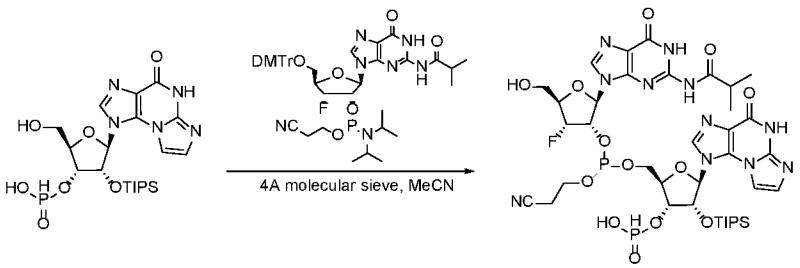
4H), 6.14 (d, *J*=3.7Hz, 1H), 5.88 (s, 0.5H), 4.99 (s, 1H), 4.89-4.74 (m, 1H), 4.37 (d, *J*=5.7Hz, 1H), 3.70-3.69 (m, 6H), 3.30-3.28 (m, 1H), 3.06-3.02 (m, 1H), 1.10–0.84 (m, 21H). ^{31}P-NMR: (162MHz, DMSO-d_6) δ 1.13 (s, 1P).

[0468] *Step 6: (2R,3R,4R,5R)-2-(hydroxymethyl)-5-(4-oxo-4,5-dihydro-1H-imidazo[2,1-b]purin-1-yl)-4-((triisopropylsilyl)oxy)tetrahydrofuran-3-yl hydrogen phosphonate*



[0469] To a solution of (2R,3R,4R,5R)-2-((bis(4-methoxyphenyl)(phenyl)methoxy) methyl)-5-(4-oxo-4,5-dihydro-1H-imidazo[2,1-b]purin-1-yl)-4-((triisopropylsilyl)oxy) tetrahydrofuran-3-yl hydrogen phosphonate (290mg, 0.342mmol) in DCM (5.1mL) at RT was added H_2O (62mg, 3.4mmol) and DCA in DCM (5%, 5.1mL, 3.1mmol). It was stirred for 15min, and then Et_3SiH (5mL) was added. After 1h, Py (0.2mL) was added, and the mixture was stirred for 5min. Then, it was concentrated, and the residue was used for the next reaction step without purification. LCMS (ES, m/z): 528.2 $[M+H]^+$.

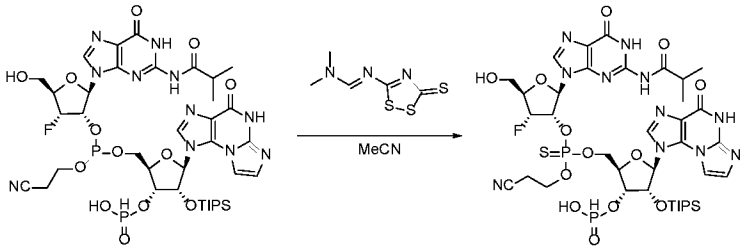
[0470] *Step 7: (2R,3R,4R,5R)-2-((((2-cyanoethoxy)(((2R,3S,4R,5R)-4-fluoro-5-(hydroxymethyl)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl)oxy)phosphanyl)oxy)methyl)-5-(4-oxo-4,5-dihydro-1H-imidazo[2,1-b]purin-1-yl)-4-((triisopropylsilyl)oxy)tetrahydrofuran-3-yl hydrogen phosphonate*



[0471] (2R,3S,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl (2-cyanoethyl)diisopropyl-phosphoramidite (0.32g, 0.38mmol) was co-evaporated with MeCN (3×3mL) and re-dissolved in MeCN (3mL). Activated 4Å molecular sieve (100mg) was added. (2R,3R,4R,5R)-2-(hydroxyl-methyl)-5-(4-oxo-4,5-dihydro-1H-imidazo[2,1-b]purin-1-yl)-4-((triisopropylsilyl)oxy) tetrahydrofuran-3-yl hydrogen phosphonate (crude, 0.89g, 0.34mmol) was co-evaporated with MeCN (3×5mL) and re-suspended in MeCN (8mL) under Ar. Activated 4Å molecular sieve

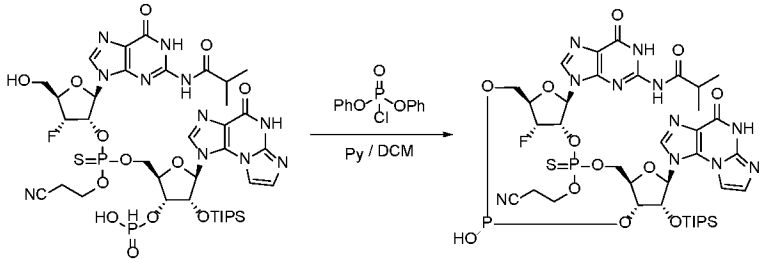
(100mg) was added. After 30min, to the mixture was added the mixture containing (2R,3S,4R, 5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl (2-cyanoethyl) diisopropylphosphoramidite, and it was stirred at RT for 15min. Then, the reaction mixture was used for the next reaction step without purification. LCMS (ES, m/z): 980.1 $[M-H]^-$.

[0472] *Step 8: (2R,3R,4R,5R)-2-((((2-cyanoethoxy)(((2R,3S,4R,5R)-4-fluoro-5-(hydroxymethyl)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl) oxy)phosphorothioyl)oxy)methyl)-5-(4-oxo-4,5-dihydro-1H-imidazo[2,1-b]purin-1-yl)-4-((triisopropylsilyl)oxy)tetrahydrofuran-3-yl hydrogen phosphonate*



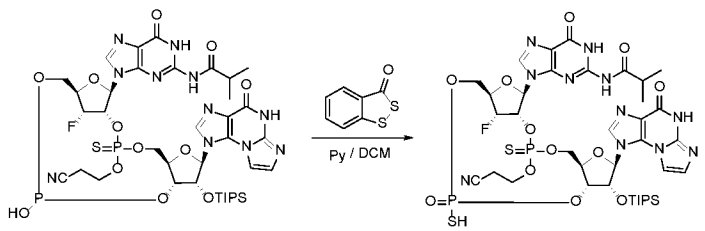
[0473] To the reaction mixture from Step 7 was added (E)-N,N-dimethyl-N'-(3-thioxo-3H-1,2,4-dithiazol-5-yl)formimidamide (77mg, 0.38mmol), and the mixture was stirred at RT for 1h. It was concentrated, and the residue was purified by reverse phase (C18) chromatography eluted with 0 to 95% ACN in aq NH_4HCO_3 (5mM) to give the product. LCMS (ES, m/z): 1014.3 $[M+H]^+$. ^{1}H-NMR (400MHz, CD_3OD): δ 8.35 (d, *J*=8.6Hz, 1H), 8.23-8.06 (m, 1H), 7.86 (s, 0.5H), 7.76 (d, *J*=14.0Hz, 1H), 7.23 (d, *J*=17.0Hz, 1H), 6.44-6.11 (m, 2.5H), 5.59-5.55 (m, 1H), 5.50-5.26 (m, 1H), 4.71 (d, *J*=5.5Hz, 1H), 4.62-4.17 (m, 5H), 4.12-3.75 (m, 3H), 3.08-2.51 (m, 3H), 1.29–1.13 (m, 6H), 0.98-0.88 (m, 21H). ^{31}P-NMR: (162MHz, CD_3OD) δ 67.45-66.89 (m); 3.97-3.90 (m).

[0474] *Step 9: N-(9-{(5R,7R,8S,12aR,14R,15R,15aR,16R)-10-(2-cyanoethoxy)-16-fluoro-2-hydroxy-14-(4-oxo-4,5-dihydro-1H-imidazo[2,1-b]purin-1-yl)-10-sulfido-15-[(tripropan-2-ylsilyl)oxy]octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclo-tetradecin-7-yl}-6-oxo-6,9-dihydro-1H-purin-2-yl)-2-methylpropanamide*



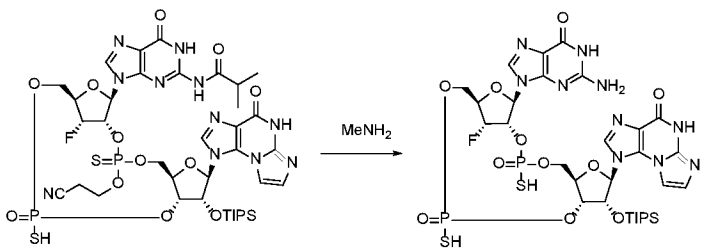
[0475] To Py (3.5mL) and DCM (3.5mL) at -40°C under Ar was added diphenyl phosphorochloridate (0.285mL, 1.38mmol), and a solution of (2R,3R,4R,5R)-2-((((2-cyanoethoxy)(((2R,3S,4R,5R)-4-fluoro-5-(hydroxymethyl)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl)oxy)phosphorothioyl)oxy)methyl)-5-(4-oxo-4,5-dihydro-1H-imidazo[2,1-b]purin-1-yl)-4-((triisopropylsilyl)oxy)tetrahydrofuran-3-yl hydrogen phosphonate (71mg, 0.069mmol) in Py (3.5mL) and DCM (3.5mL). It was stirred at -40°C for 30min. Then, the reaction mixture was used for the next step without purification. LCMS (ES, m/z): 996.4 $[M+H]^+$.

[0476] *Step 10: N-(9-{(5R,7R,8S,12aR,14R,15R,15aR,16R)-10-(2-cyanoethoxy)-16-fluoro-2-oxido-14-(4-oxo-4,5-dihydro-1H-imidazo[2,1-b]purin-1-yl)-2-sulfanyl-10-sulfido-15-[(tripropan-2-ylsilyl)oxy]octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl}-6-oxo-6,9-dihydro-1H-purin-2-yl)-2-methylpropanamide*



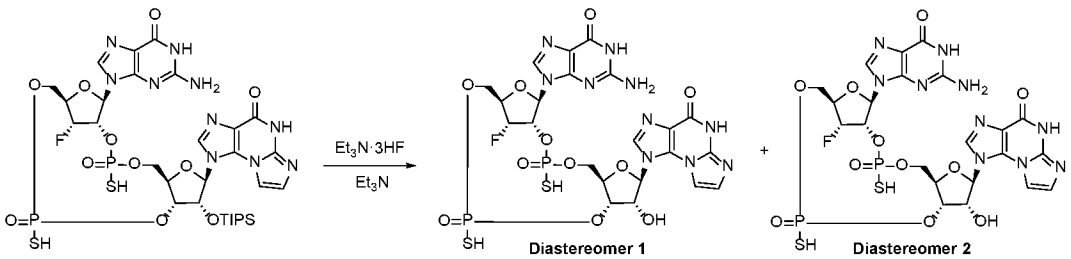
[0477] To the reaction mixture from Step 9 at -40°C was added 3*H*-benzo[c][1,2]dithiol-3-one (17.4mg, 0.104mmol). The reaction was stirred at rt for 2h, and then MeOH (1mL) was added. It was concentrated and purified by reverse phase (AQ-C18) chromatography eluted with 0 to 95% ACN in aq NH_4HCO_3 (5mM) to give the product. LCMS (ES, m/z): 1028.4 $[M+H]^+$. ^{1}H-NMR (400MHz, CD_3OD): δ 8.57-8.02 (m, 2H), 7.99-7.55 (m, 1H), 7.56-7.12 (m, 7H), 6.50-6.08 (m, 2H), 5.65-4.95 (m, 6H), 4.72-4.18 (m, 5H), 4.13-3.56 (m, 3H), 2.95-2.65 (m, 3H), 1.45-0.73 (m, 24H). ^{31}P-NMR: (162MHz, CD_3OD) δ 67.53-63.91 (m), 58.62-55.15 (m).

[0478] *Step 11: 1-{(5R,7R,8S,12aR,14R,15R,15aR,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-16-fluoro-2,10-dioxido-2,10-disulfanyl-15-[(tripropan-2-ylsilyl)oxy]octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl}-1H-imidazo[2,1-b]purin-4(5H)-one*



[0479] N-(9-{(5R,7R,8S,12aR,14R,15R,15aR,16R)-10-(2-cyanoethoxy)-16-fluoro-2-oxido-14-(4-oxo-4,5-dihydro-1H-imidazo[2,1-b]purin-1-yl)-2-sulfanyl-10-sulfido-15-[(tripropan-2-ylsilyl)oxy]octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl}-6-oxo-6,9-dihydro-1H-purin-2-yl)-2-methylpropanamide (57mg, 0.055mmol) was dissolved in $MeNH_2$ in EtOH (30%, 3.2mL, 22mmol), and it was stirred at RT for 3h. Then, it was concentrated, and the crude product was used for the next reaction step without purification. LCMS (ES, m/z): 905.3 $[M+H]^+$.

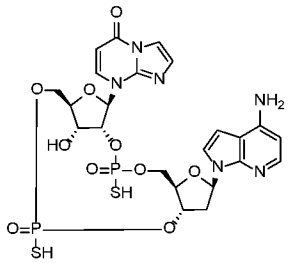
[0480] *Step 12: 1-[(5R,7R,8S,12aR,14R,15R,15aS,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-16-fluoro-15-hydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]-1H-imidazo[2,1-b]purin-4(5H)-one (Diastereomer 1-2)*



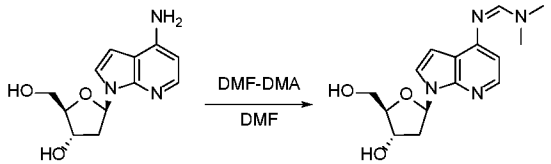
[0481] To a solution of the crude from Step 11 in Py (0.12mL) under Ar were added TEA (0.76mL, 5.5mmol) and TEA·3HF (0.45mL, 2.7mmol). The mixture was stirred at 50°C for 15h. Then, it was cooled to RT, and acetone (5.5mL) and ethoxytrimethylsilane (2.6mL, 17mmol) were added. After stirring for 30min, precipitates formed, and the reaction mixture was purified by prep-HPLC (XBridge Shield RP18 OBD Column, 19mm×250mm) eluted with 5 to 15% ACN in aq NH_4HCO_3 (10mM) over 20min to provide two peaks (T_R: 13.53 and 16.58min) with matching mass (LCMS (ES, m/z): 749.0 $[M+H]^+$). Fractions at T_R=13.53 were further purified by reverse phase chromatography (AQ-C18) eluted with 0 to 95% ACN in aq NH_4HCO_3 (5 mM) to give the product. Example 32 (diastereomer 1): LCMS (ES, m/z): 749.0 $[M+H]^+$. ^{1}H-NMR: (400MHz, D_2O): δ 8.12 (s, 1H), 7.86 (s, 1H), 7.61 (d, *J*=2.4Hz, 1H), 7.22 (d, *J*=2.3Hz, 1H), 6.35 (d, *J*=1.6Hz, 1H), 5.99 (d, *J*=8.6Hz, 1H), 5.88-5.72 (m, 1H), 5.46 (dd, *J*=53.5, 3.4Hz, 1H), 5.19 (td, *J*=8.6, 4.7Hz, 1H), 4.56-4.40 (m, 4H), 4.14-4.00 (m, 2H). ^{31}P-NMR: (162MHz, D_2O): δ 55.37 (s), 52.33 (s). Fractions at T_R=16.58 were further purified by reverse phase chromatography (AQ-C18) eluted with 0 to 95% ACN in aq NH_4HCO_3 (5 mM) to give the product. Example 33 (diastereomer 2): LCMS (ES, m/z): 749.0 $[M+H]^+$. ^{1}H-NMR: (400MHz, D_2O): δ 8.26 (s, 1H), 7.89 (s, 1H), 7.65 (d, *J*=2.4Hz, 1H), 7.26 (d, *J*=2.4Hz, 1H), 6.33 (d,

J=2.5Hz, 1H), 6.01 (d, *J*=8.5Hz, 1H), 5.93-5.72 (m, 1H), 5.44-5.20 (m, 2H), 4.81 (dd, *J*=4.7, 2.6Hz, 1H), 4.55-4.34 (m, 4H), 4.05 (t, *J*=12.7Hz, 2H). ^{31}P-NMR: (162MHz, D_2O): δ 55.75 (s), 55.64 (s).

[0482] **Example 34: 8-[(5*R*,7*R*,8*R*,12a*R*,14*R*,15a*S*,16*R*)-14-(4-amino-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-16-hydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]imidazo[1,2-*a*]pyrimidin-5(8*H*)-one**

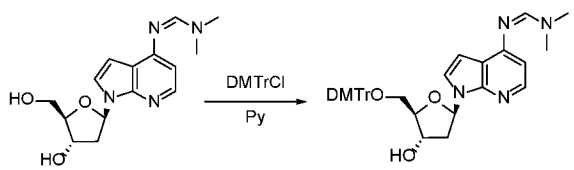


[0483] *Step 1: (Z)-N'-(1-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)-N,N-dimethylformimidamide*



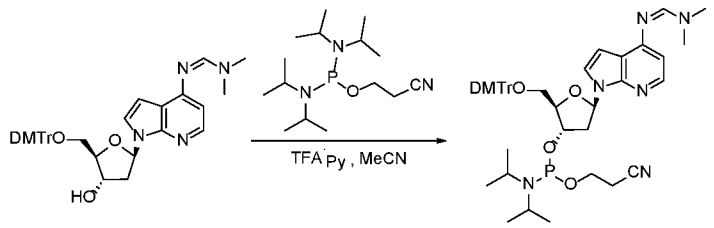
[0484] To a solution of (2R,3S,5R)-5-(4-amino-1H-pyrrolo[2,3-b]pyridin-1-yl)-2-(hydroxymethyl)tetrahydrofuran-3-ol (0.14mg, 0.56mmol) in DMF (2mL) was added DMF-DMA (1.0g, 8.4mmol). The resulting mixture was stirred at 40°C for 12h. Then, it was concentrated and the residue was purified by column chromatography eluted with 0% to 10% MeOH in DCM to give the product. LCMS (ES, m/z): 305.2 $[M+H]^+$. ^{1}H NMR (300MHz, DMSO-d_6): δ 8.04-7.90 (m, 2H), 7.46 (d, *J*=3.7Hz, 1H), 6.59 (dd, *J*=7.4, 5.5Hz, 2H), 6.46 (d, *J*=3.6Hz, 1H), 5.27 -5.15 (m, 2H), 4.35-4.30 (m, 1H), 3.83-3.80 (m, 1H), 3.62 -3.41 (m, 2H), 3.03 (d, *J*=17.3Hz, 6H), 2.62-2.49 (m, 1H), 2.18-2.14 (m, 1H).

[0485] *Step 2: (Z)-N'-(1-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-2-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)-N,N-dimethylformimidamide*



[0486] To a mixture of (Z)-N'-(1-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl) tetrahydrofuran-2-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)-N,N-dimethylformimidamide (100mg, 0.33mmol) in Py (1.8mL) was added DMTrCl (122mg, 0.361mmol). After stirring at RT for 2h, the mixture was concentrated, and the residue was purified by reverse phase chromatography (C18) eluted with 0 to 95% aq NH_4HCO_3 (5mM) in MeCN to give the product. LCMS (ES, m/z): 607.3 $[M+H]^+$. ^1H NMR (300MHz, DMSO-d_6): δ 8.03-7.92 (m, 2H), 7.41-7.12 (m, 9H), 6.85-6.80 (m, 4H), 6.72-6.54 (m, 2H), 6.46 (d, *J*=3.7Hz, 1H), 5.73 (s, 1H), 5.27 (d, *J*=4.4Hz, 1H), 4.33 (dt, *J*=6.7, 3.6Hz, 1H), 3.90 (q, *J*=4.4Hz, 1H), 3.72 (s, 6H), 3.18-3.15 (m, 2H), 3.06 (s, 3H), 3.00 (s, 3H), 2.51-2.48 (m, 1H), 2.26-2.13 (m, 1H).

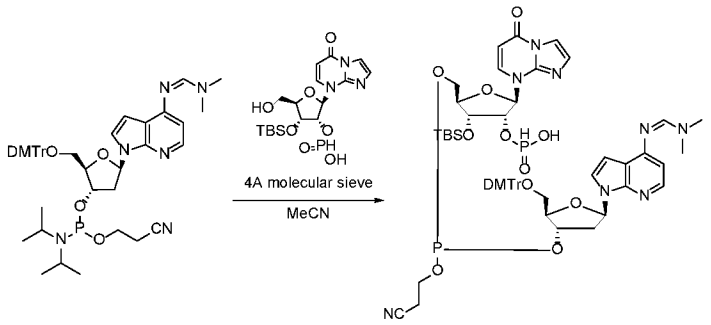
[0487] *Step 3: (2R,3S,5R)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-5-(4-(((Z)-(dimethylamino)methylene)amino)-1H-pyrrolo[2,3-b]pyridin-1-yl)tetrahydrofuran-3-yl (2-cyanoethyl) diisopropylphosphoramidite*



[0488] To a stirred solution of 3-((bis(diisopropylamino)phosphino)oxy)propanenitrile (129mg, 0.429mmol) in MeCN (2mL) under Ar was added TFA·Py (62mg, 0.32mmol) and a solution of (Z)-N'-(1-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy) methyl)-4-hydroxytetrahydrofuran-2-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)-N,N-dimethylformimidamide in MeCN (4mL) over 2min. The resulting mixture was stirred at RT for 1h. Then, it was concentrated, and DCM (40mL) was added. The solution was washed with aq $NaHCO_3$ (1%, 2×20mL), H_2O (20mL), and brine (20mL), dried (Na_2SO_4), and concentrated. The residue was purified by reverse phase chromatography (C18) eluted with 0 to 95% aq NH_4HCO_3 (5mM) in MeCN to give the product. LCMS (ES, m/z): 807.5 $[M+H]^+$. ^1H NMR (400MHz, DMSO-d_6): δ 8.06-7.95 (m, 2H), 7.42-7.37 (m, 3H), 7.33-7.25 (m,7H), 6.85-6.81 (m, 4H), 6.72-6.59 (m, 2H), 6.51 (dd, *J*=3.7,1.5Hz, 1H), 4.65 (m, 1H), 4.06 (dq, *J*=21.5, 4.3Hz, 1H), 3.83-3.51 (m, 10H), 3.29-3.12 (m, 2H), 3.06 (d, *J*=24.2Hz, 6H), 2.75-2.70 (m, 3H), 2.50-2.40 (m, 1H), 1.20-1.13 (m, 9H), 1.06 (d, *J*=6.7Hz, 3H). ^{31}P NMR (162MHz, DMSO-d_6): δ 147.54 (s), 146.94 (s).

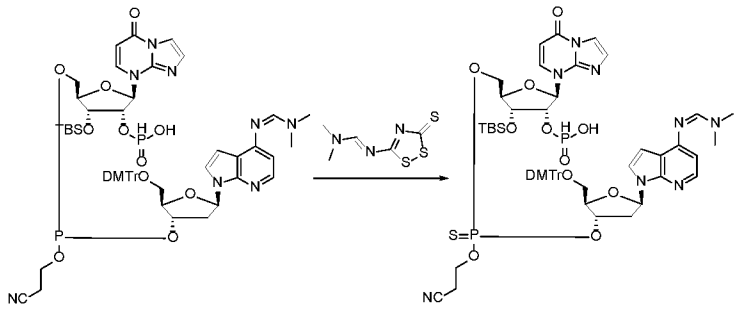
[0489] *Step 4: (2R,3R,4R,5R)-5-((((((2R,3S,5R)-2-((bis(4-methoxyphenyl)(phenyl) methoxy)methyl)-5-(4-(((Z)-(dimethylamino)methylene)amino)-1H-pyrrolo[2,3-b]pyridin-1-*

yl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphanyl)oxy)methyl)-4-((tert-butyldimethylsilyl) oxy)-2-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)tetrahydrofuran-3-yl hydrogen phosphonate



[0490] (2R,3R,4R,5R)-4-((*tert*-butyldimethylsilyl)oxy)-5-(hydroxymethyl)-2-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)tetrahydrofuran-3-yl hydrogen phosphonate (crude, 0.24g, ~0.130mmol) was also co-evaporated with MeCN (3×3mL), and then re-dissolved in MeCN (1mL). Activated 4Å molecular sieve (100mg) was added to the solution under Ar. (2R,3S,5R)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-5-(4-(((Z)-(dimethylamino)methylene) amino)-1H-pyrrolo[2,3-b]pyridin-1-yl)tetrahydrofuran-3-yl (2-cyanoethyl)diisopropyl-phosphoramidite (0.115g, 0.143mmol) was co-evaporated with MeCN (3×3mL) and re-dissolved in MeCN (1mL). Activated 4Å molecular sieve (100mg) was added to the solution under Ar. After 30min, it was added to the solution containing (2R,3R,4R,5R)-4-((*tert*-butyldimethylsilyl) oxy)-5-(hydroxymethyl)-2-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)tetrahydrofuran-3-yl hydrogen phosphonate. The resulting mixture under Ar was stirred at RT for 30min. It was used for the next reaction step without purification. LCMS (ES, m/z): 1151.5 $[M+H]^+$.

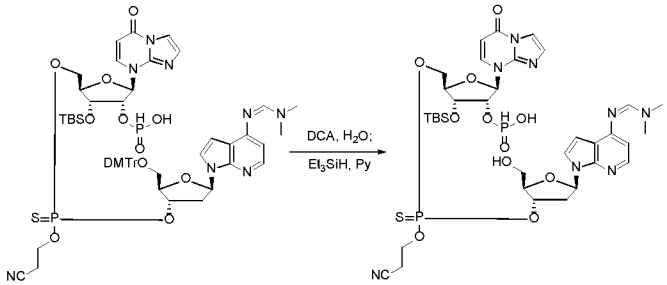
[0491] *Step 5: (2R,3R,4R,5R)-5-((((((2R,3S,5R)-2-((bis(4-methoxyphenyl)(phenyl)methoxy) methyl)-5-(4-(((Z)-(dimethylamino)methylene)amino)-1H-pyrrolo[2,3-b]pyridin-1-yl) tetra-hydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphorothioyl)oxy)methyl)-4-((tert-butyldimethylsilyl) oxy)-2-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)tetrahydrofuran-3-yl hydrogen phosphonate*



[0492] To the reaction mixture from Step 4 was added (*E*)-*N*,*N*-dimethyl-*N*'-(3-thioxo-3*H*-1,2,4-dithiazol-5-yl)formimidamide (0.029g, 0.14mmol), and it was stirred at RT for 30min.

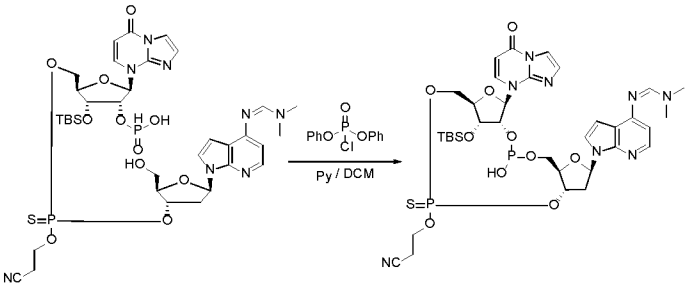
Then, it was concentrated to give a crude containing the product, and it was used for the next reaction step without purification. LCMS (ES, m/z): 1183.5 $[M+H]^+$.

[0493] *Step 6: (2R,3R,4R,5R)-4-((tert-butyldimethylsilyl)oxy)-5-((((2-cyanoethoxy)(((2R,3S,5R)-5-(4-(((Z)-(dimethylamino)methylene)amino)-1H-pyrrolo[2,3-b]pyridin-1-yl)-2-(hydroxymethyl)tetrahydrofuran-3-yl)oxy)phosphorothioyl)oxy)methyl)-2-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)tetrahydrofuran-3-yl hydrogen phosphonate*



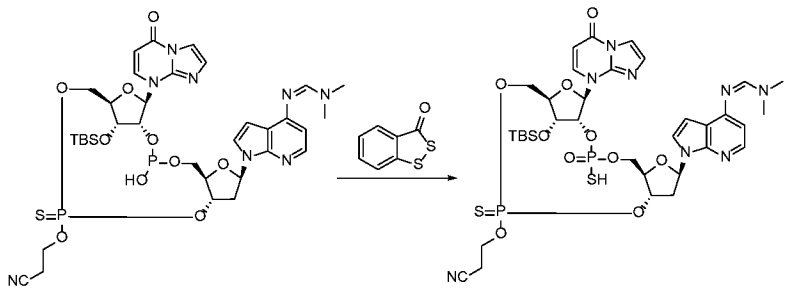
[0494] To a solution of the crude from Step 5 in DCM (1.8mL) was added H_2O (23mg, 1.3mmol) and DCA in DCM (6%, 1.87mL, 1.17mmol). The reaction was stirred at RT for 30min. Then, Et_3SiH (2.0mL) was added to the reaction, and it was stirred for 1h. Then, Py (185mg, 2.34mmol) was added, and the resulting solution was concentrated. The residue was purified by reverse phase chromatography (C18) eluted with 0 to 95% aq NH_4HCO_3 (5mM) in MeCN to give the product. LCMS (ES, m/z): 881.3 $[M+H]^+$. ^1H NMR (400MHz, CD_3OD): δ 8.10-7.94 (m, 3H), 7.68-7.51 (m, 2H), 7.41-7.34 (m, 1H), 7.23-7.15 (m, 1H), 6.75-6.65 (m, 1H), 6.63-6.44 (m, 1.5H), 6.32-6.23 (m, 1H), 6.06-5.88 (m, 0.5H), 5.80-5.74 (m, 1H), 5.35-5.30 (m, 1H), 5.24-5.19 (m, 1H), 4.86-4.77 (m, 2H), 4.57-4.22 (m, 6H), 3.79-3.76 (m, 2H), 3.22-3.05 (m, 5H), 3.05-2.78 (m, 3H), 2.64-2.42 (m, 1H), 1.00 (d, *J*=6.8Hz, 9H), 0.33-0.17 (m, 6H). ^{31}P NMR (162MHz, CD_3OD): δ 66.88 (s), 66.77 (s); 2.98 (s), 2.87 (s).

[0495] *Step 7: N'-{1-[(5R,7R,8R,12aR,14R,15aS,16R)-16-{[tert-butyl(dimethyl)silyl] oxy}-2-(2-cyanoethoxy)-10-hydroxy-7-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)-2-sulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclo-tetradecin-14-yl]-1H-pyrrolo[2,3-b]pyridin-4-yl}-N,N-dimethylimidoformamide*



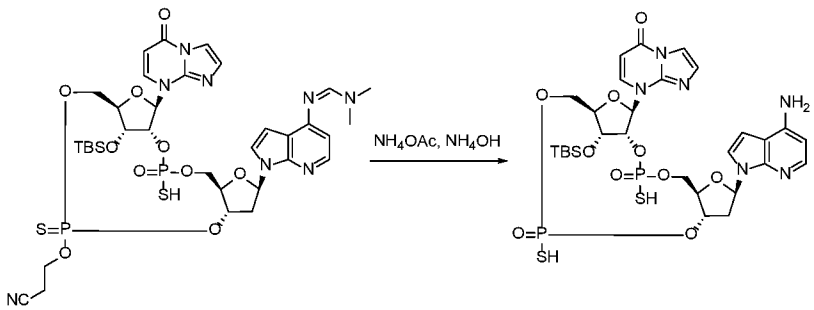
[0496] (2R,3R,4R,5R)-4-((*tert*-butyldimethylsilyl)oxy)-5-((((2-cyanoethoxy) (((2R,3S,5R)-5-(4-(((Z)-(dimethylamino)methylene)amino)-1H-pyrrolo[2,3-b]pyridin-1-yl)-2-(hydroxyl-methyl)tetrahydrofuran-3-yl)oxy)phosphorothioyl)oxy)methyl)-2-(5-oxoimidazo[1,2-a] pyrimidin-8(5H)-yl)tetrahydrofuran-3-yl hydrogen phosphonate (40mg, 0.045mmol) was co-evaporated with Py (3×2mL) and then dissolved in DCM (5mL). To this solution at -40°C was added a solution of diphenyl phosphorochloridate (239mg, 0.891mmol) in Py (5mL) over 10min. The resulting mixture was stirred at -40°C for 20min. Then, it was used for the next reaction step directly. LCMS (ES, m/z): 863.3 $[M+H]^+$.

[0497] *Step 8: N'-{1-[(5R,7R,8R,12aR,14R,15aS,16R)-16-{[tert-butyl(dimethyl)silyl] oxy}-2-(2-cyanoethoxy)-10-oxido-7-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)-10-sulfanyl-2-sulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]-1H-pyrrolo[2,3-b]pyridin-4-yl}-N,N-dimethylimidoformamide*



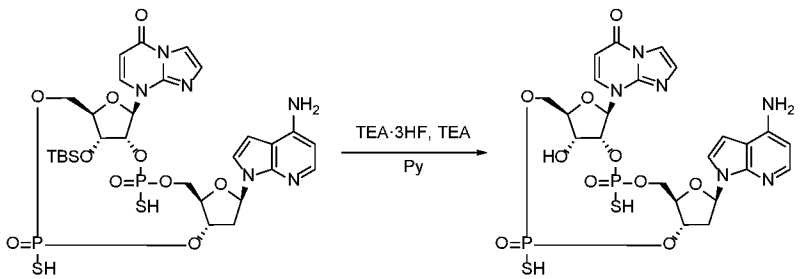
[0498] To the reaction mixture from Step 7 at -40°C was added 3*H*-benzo[*c*][1,2]dithiol-3-one (11mg, 0.068mmol) and H_2O (0.05mL). After stirring at RT for 40min, the mixture was concentrated under reduced pressure. The residue was purified by reverse phase chromatography (C18) eluted with 0 to 95% aq NH_4HCO_3 (5mM) in MeCN to give the product. LCMS (ES, m/z): 895.3 $[M+H]^+$. ^{31}P NMR (162MHz, CD_3OD): δ 65.78-65.36 (m), 58.29-57.20 (m).

[0499] *Step 9: 8-[(5R,7R,8R,12aR,14R,15aS,16R)-14-(4-amino-1H-pyrrolo[2,3-b]pyridin-1-yl)-16-{[tert-butyl(dimethyl)silyl]oxy}-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]imidazo[1,2-a]pyrimidin-5(8H)-one*



[0500] N'-{1-[(5R,7R,8R,12aR,14R,15aS,16R)-16-{[tert-butyl(dimethyl)silyl]oxy}-2-(2-cyanoethoxy)-10-oxido-7-(5-oxoimidazo[1,2-a]pyrimidin-8(5H)-yl)-10-sulfanyl-2-sulfido-octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10] pentaoxadiphosphacyclo-tetradecin-14-yl]-1H-pyrrolo[2,3-b]pyridin-4-yl}-N,N-dimethylimidoformamide (20mg, 0.022mmol) and NH_4OAc (1.0g, 13mmol) were dissolved in NH_4OH (10mL, 260mmol), and the resulting mixture was stirred at rt for 3h. Then, it was concentrated, and the residue was purified by reverse phase chromatography (C18) eluted with 0 to 95% aq NH_4HCO_3 (5mM) in MeCN over 51min to give the product (T_R=32.5min). LCMS (ES, m/z): 787.3 $[M+H]^+$.

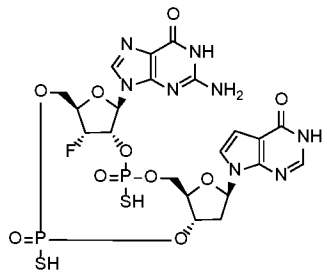
[0501] *Step 10: 8-[(5R,7R,8R,12aR,14R,15aS,16R)-14-(4-amino-1H-pyrrolo[2,3-b]pyridin-1-yl)-16-hydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]imidazo[1,2-a]pyrimidin-5(8H)-one*



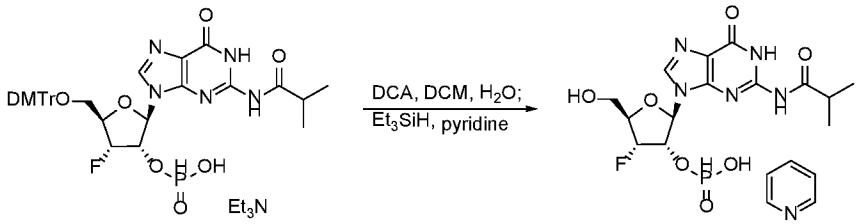
[0502] To a suspension of 8-[(5R,7R,8R,12aR,14R,15aS,16R)-14-(4-amino-1H-pyrrolo[2,3-b]pyridin-1-yl)-16-{[tert-butyl(dimethyl)silyl]oxy}-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10] pentaoxadiphosphacyclo-tetradecin-7-yl]imidazo[1,2-a]pyrimidin-5(8H)-one (10mg, ~0.012mmol) in Py (0.2mL) were added TEA (62mg, 0.61mmol) and TEA·3HF (49mg, 0.31mmol). The mixture was stirred at 50°C for 3h. Then, it was concentrated, and acetone (1.1mL) and ethoxytrimethylsilane (3.9mL, 25mmol) were added. After stirring for 30min, precipitates were formed. The precipitates were purified by reverse phase chromatography (C18) eluted with 0 to 95% aq NH_4HCO_3 (30mM) in MeCN to give the product. LCMS (ES, m/z): 672.9 $[M+H]^+$. ^1H NMR (400MHz, D_2O): δ 8.37 (d, *J*=7.9Hz, 1H), 7.86-7.83 (m, 1H), 7.65 (s, 1H), 7.32-7.28 (m, 2H), 6.67-6.63 (m, 1H), 6.56 (d, *J*=8.3Hz, 1H), 6.46-6.40 (m, 2H), 6.01 (d, *J*=7.9Hz, 1H), 5.19-4.99 (m, 2H), 4.88-4.82 (m, 2H), 4.53-4.48 (m, 1H), 4.41-4.28 (m, 2H), 4.19-4.02 (m, 1H), 3.97-3.73 (m, 1H), 2.96-2.73 (m, 2H). ^{31}P NMR (162MHz, D_2O): δ 55.28 (s), 53.94 (s).

[0503] **Example 35: 2-amino-9-[(5*R*,7*R*,8*S*,12a*R*,14*R*,15a*S*,16*R*)-16-fluoro-2,10-dioxido-14-(4-oxo-3,4-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-2,10-disulfanyloctahydro-**

12*H*-5,8-methanofuro[3,2-*l*][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6*H*-purin-6-one (Diastereomer 1)

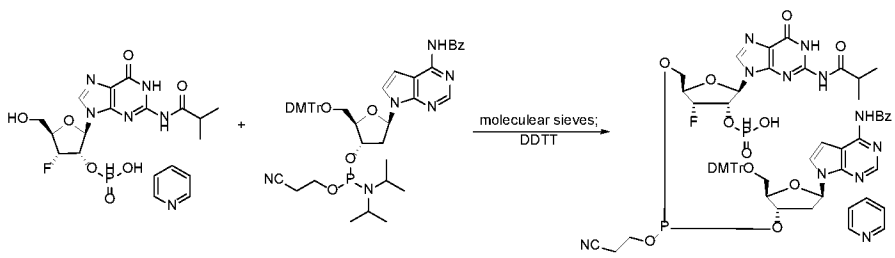


[0504] *Step 1 : 3'-deoxy-3'-fluoro-2'-O-[hydroxy(oxido)-λ^5-phosphanyl]-N-(2-methylpropanoyl)guanosine*



[0505] To a stirred solution of triethylammonium 5'-*O*-[bis(4-methoxyphenyl)(phenyl) methyl]-3'-deoxy-3'-fluoro-2'-*O*-[hydroxy(oxido)-λ^5-phosphanyl]-*N*-(2-methylpropanoyl) guanosine (1.35g, 1.50mmol) in DCM (22.5mL) were added H_2O (0.27mL, 15mmol) and 2,2-DCA in DCM solution (0.6M, 22.5mL, 13.5mmol) at RT. The mixture was stirred at RT for 15min, treated with Et_3SiH (5mL), and left to stir for 1.5h. Py (2.4mL, 30mmol) was added, and the mixture was stirred for 5min and concentrated under reduced pressure to give the crude product as the pyridinium salt. LCMS (ES, m/z): 420 $[M+H]^+$.

[0506] *Step 2 : (2R,3S,4R,5R)-5-((((((2R,3S,5R)-5-(4-benzamido-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphorothioyl)oxy)methyl)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl hydrogen phosphonate*

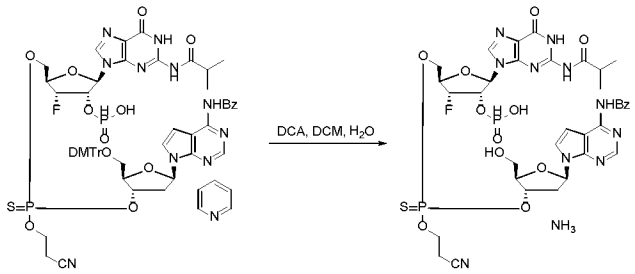


[0507] A solution of 7-{5-*O*-[bis(4-methoxyphenyl)(phenyl)methyl]-3-*O*-[(2-cyanoethoxy)(dipropan-2-ylamino)phosphanyl]-2-deoxy-β-D-*erythro*-pentofuranosyl}-*N*-

(phenylcarbonyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (1.41g, 1.65mmol) in MeCN (5mL) was concentrated *in vacuo*. Addition of MeCN (5mL) followed by concentration was repeated twice. To the residue were added MeCN (5mL) and activated 4Å molecular sieves (100mg).

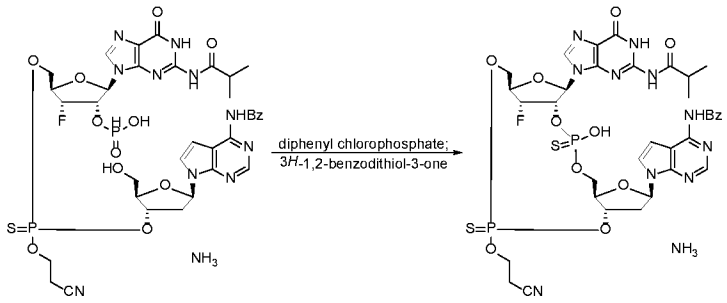
[0508] The crude pyridinium 3'-deoxy-3'-fluoro-2'-*O*-[hydroxy(oxido)-λ^5-phosphanyl]-*N*-(2-methylpropanoyl)guanosine was dissolved in MeCN (5m) and concentrated *in vacuo*. Addition of MeCN (5mL) followed by concentration was repeated twice. To the residue were added MeCN (5mL) and activated 4Å molecular sieves (100mg). After 30min, the phosphoramidite solution was added to the H-phosphonate solution over 5min. The flask was rinsed with MeCN (1mL), and the solution was transferred to the H-phosphonate solution (2x). The resulting mixture was charged with Ar and stirred at RT for 10min, treated with DDTT (0.339g, 1.65mmol), and left to stir for 45min. The mixture was concentrated to give the product as the pyridinium salt. LCMS (ES, m/z): 1205 $[M-H]^-$.

[0509] *Step 3 : (2R,3S,4R,5R)-5-((((((2R,3S,5R)-5-(4-benzamido-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-(hydroxymethyl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphorothioyl)oxy)methyl)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl hydrogen phosphonate*



[0510] The crude pyridinium (2R,3S,4R,5R)-5-((((((2R,3S,5R)-5-(4-benzamido-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphorothioyl)oxy)methyl)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl hydrogen phosphonate was dissolved in DCM (22.5mL) was treated with H_2O (0.27mL, 15mmol) and 2,2-DCA in DCM (0.6M, 22.5mL, 13.5mmol) at RT over 3min. The mixture was left to stir for 15min and cooled to 0°C. The mixture was treated with Hex (50mL) and left to stir for 30min. The supernatant was decanted, and DCM and Hex (30mL each) were added to the residue. The supernatant was decanted, and the residue was dried under vacuum and purified by reverse phase (C18) chromatography eluting with 0 to 95% MeCN in 5mM aq NH_4HCO_3 solution to give the product as the ammonium salt. LCMS (ES, m/z): 903 $[M-H]^-$.

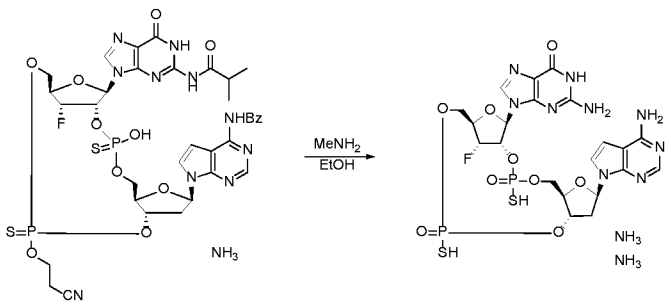
[0511] *Step 4 : N-{7-[(5R,7R,8S,12aR,14R,15aS,16R)-2-(2-cyanoethoxy)-16-fluoro-10-hydroxy-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-2,10-disulfido-octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecin-14-yl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}benzamide*



[0512] A solution of ammonium (2R,3S,4R,5R)-5-((((((2R,3S,5R)-5-(4-benzamido-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-(hydroxymethyl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy) phosphorothioyl)oxy)methyl)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl hydrogen phosphonate (850mg, 0.922mmol) in Py (10mL) was concentrated *in vacuo*. Addition of Py (10mL) followed by concentration was repeated twice. The residue was taken up in DCM (92mL) and Py (22mL).

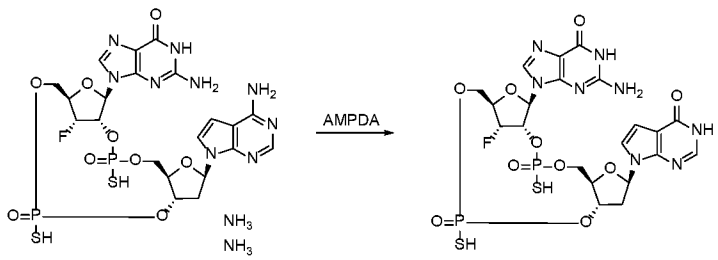
[0513] To a stirred Py (70mL) in a separate flask was added diphenyl chlorophosphate (4954mg, 18.44mmol) under Ar at -40°C over 5min. To the solution was added hydrogen phosphonate solution dropwise at -40°C over 20min. The resulting mixture was stirred at -40°C for 20min and treated with 3*H*-1,2-benzodithiol-3-one (233mg, 1.38mmol) in one portion and H_2O (332mg, 18.4mmol) at -40°C. After stirring at RT for 40min, the mixture was concentrated under reduced pressure. The residue was purified by reverse phase (C18) chromatography eluting with 0 to 95% MeCN in 5mM aq NH_4HCO_3 solution to give the product as the ammonium salt (800mg, 0.885mmol). LCMS (ES, m/z): 917 $[M-H]^-$.

[0514] *Step 5: 2-amino-9-[(5R,7R,8S,12aR,14R,15aS,16R)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-16-fluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one*



[0515] To ammonium *N*-{7-[(5*R*,7*R*,8*S*,12a*R*,14*R*,15a*S*,16*R*)-2-(2-cyanoethoxy)-16-fluoro-10-hydroxy-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9*H*-purin-9-yl}-2,10-disulfidooctahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecin-14-yl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}benzamide (800mg, 0.885mmol) was added $MeNH_2$ in EtOH (30% w/w, 47mL), and the resulting solution was left to stir at RT for 8h and concentrated. The residue was taken up in acetone (30mL), left to stir overnight, filtered, and washed with acetone (5mLx2). The filter cake was dissolved in DMSO (8mL) and then filtered. The filtrate was purified by reverse phase (C18) chromatography eluting with 0 to 100% MeCN in 30mM aq NH_4HCO_3 solution to give the four phosphorus diastereomers as the diammonium salts. The second fastest eluting peak fractions were collected and lyophilized to give the product as the diammonium salt. LCMS (ES, m/z): 692 $[M+H]^+$. ^{1}H-NMR: (400MHz, D_2O): δ 8.28 (s, 1H), 8.03 (s, 1H), 7.17 (d, *J*=3.7Hz, 1H), 6.33-6.32 (m, 2H), 5.97 (d, *J*=8.5Hz, 1H), 5.48 (d, *J*=55.6Hz, 1H), 5.26-5.14 (m, 1H), 4.91-4.87 (m, 1H), 4.66-4.64 (m, 1H), 4.19-4.13 (m, 4H), 4.02-3.99 (m, 1H), 2.71-2.68 (m, 2H). ^{31}P-NMR: (162MHz, D_2O): δ 54.14, 52.59.

[0516] *Step 6: 2-amino-9-[(5R,7R,8S,12aR,14R,15aS,16R)-16-fluoro-2,10-dioxido-14-(4-oxo-3,4-dihydro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one*

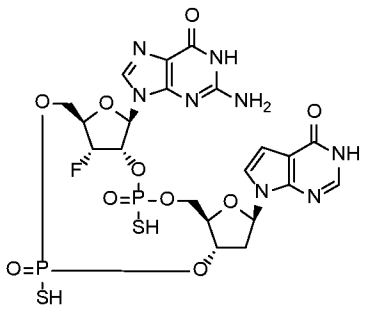
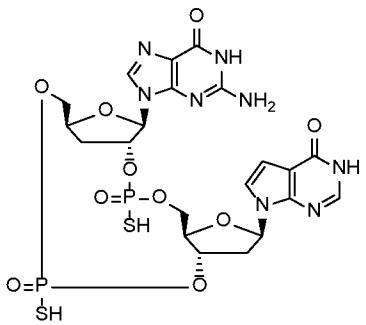
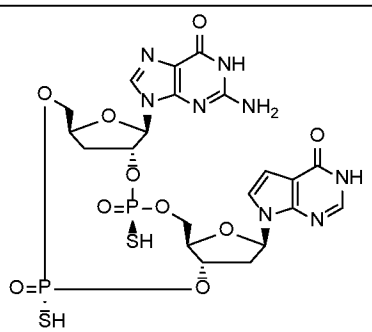


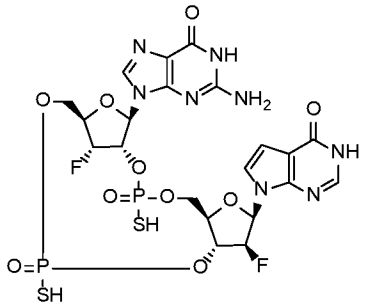
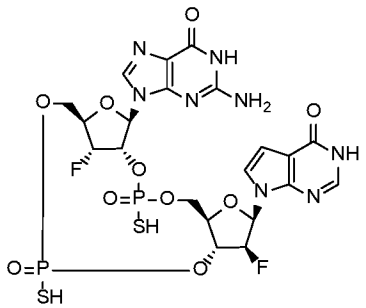
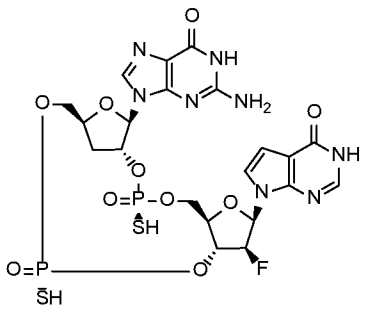
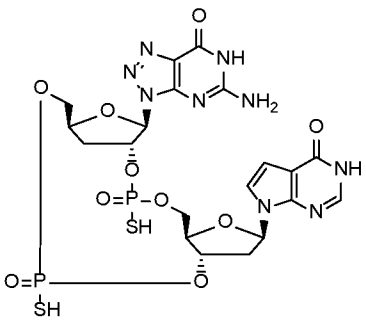
[0517] To diammonium 2-amino-9-[(5*R*,7*R*,8*S*,12a*R*,14*R*,15a*S*,16*R*)-14-(4-amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-16-fluoro-2,10-dioxido-2,10-disulfanyloctahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6*H*-purin-6-one (4.3mg, 6.1μmol) were added sodium phosphate buffer (pH 6.8, 50mM, 8mL) and AMPDA (200mg). The reaction mixture was left to stir for 11 days, filtered, and purified by reverse phase HPLC (eluting MeCN/H_2O gradient with 100mM TEAA modifier, linear gradient) to afford the product (Diastereomer 1) as the triethylammonium salt. LCMS (ES, m/z): 691 $[M-H]^-$. ^{1}H NMR (600MHz, D_2O): δ 8.39 (s, 1H), 8.07 (s, 1H), 7.28 (d, *J*=3.3Hz, 1H), 6.62 (m, 2H),

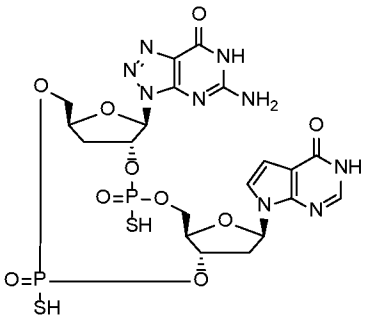
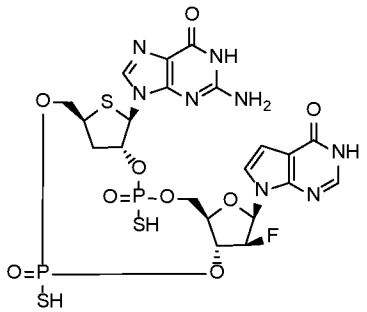
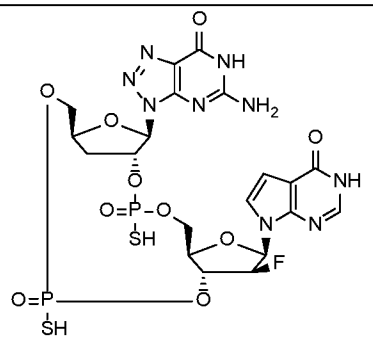
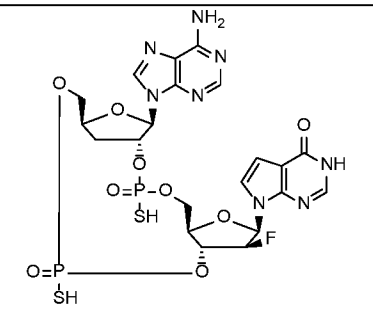
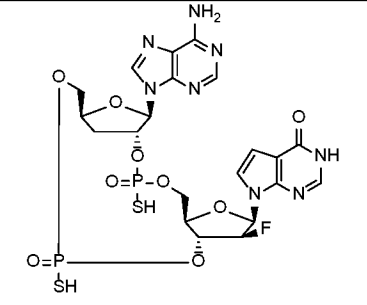
6.11 (d, *J*=8.6Hz, 1H), 5.58 (dd, *J*=53.1, 2.4Hz, 1H), 5.45 (m, 1H), 5.21 (m, 1H), 4.41 (brs, 1H), 4.23-4.30 (m, 2H), 4.10 (m, 2H), 2.95-3.08 (m, 2H), 2.86 (m, 1H).

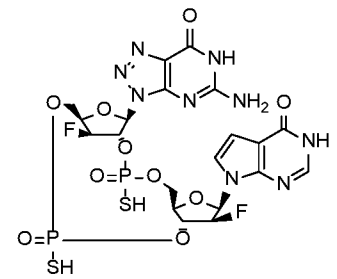
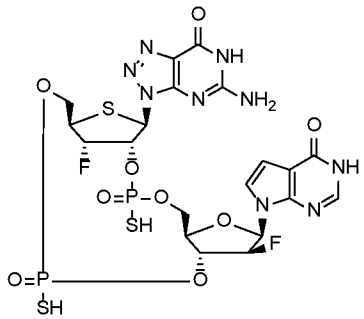
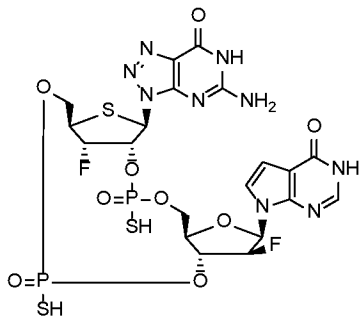
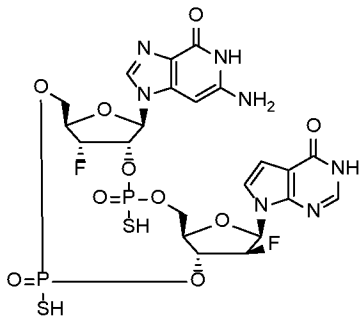
[0518] Examples **36** through **51**, as shown in Table 5 below, were prepared according to procedures analogous to those outlined in Example **35** above.

Table 5

Ex.	Structure	Name	Mass [M-H]$^-$
36		2-amino-9-[(5*R*,7*R*,8*S*,12a*R*,14*R*,15a*S*,16*R*)-16-fluoro-2,10-dioxido-14-(4-oxo-3,4-dihydro-7*H*-pyrrolo[2,3-*d*] pyrimidin-7-yl)-2,10-disulfanyl-octahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,6,9,11,2,10] pentaoxadiphospha-cyclotetradecin-7-yl]-1,9-dihydro-6*H*-purin-6-one (Diastereomer 2)	691
37		2-amino-9-[(5*S*,7*R*,8*R*,12a*R*,14*R*,15a*S*)-2,10-dioxido-14-(4-oxo-3,4-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-2,10-disulfanyloctahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6*H*-purin-6-one (Diastereomer 1)	673
38		2-amino-9-[(2*R*,5*S*,7*R*,8*R*,10*R*,12a*R*,14*R*,15a*S*)-2,10-dioxido-14-(4-oxo-3,4-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-2,10-disulfanyloctahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6*H*-purin-6-one (Diastereomer 2)	673

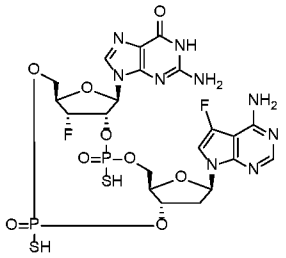
Ex.	Structure	Name	Mass [M-H]⁻
39		2-amino-9-[(5*R*,7*R*,8*S*,12a*R*,14*R*,15*S*,15a*R*,16*R*)-15,16-difluoro-2,10-dioxido-14-(4-oxo-3,4-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-2,10-disulfanyl-octahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6*H*-purin-6-one (Diastereomer 1)	709
40		2-amino-9-[(5*R*,7*R*,8*S*,12a*R*,14*R*,15*S*,15a*R*,16*R*)-15,16-difluoro-2,10-dioxido-14-(4-oxo-3,4-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-2,10-disulfanyl-octahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6*H*-purin-6-one (Diastereomer 2)	709
41		2-amino-9-[(2*R*,5*S*,7*R*,8*R*,10*R*,12a*R*,14*R*,15*S*,15a*R*)-15-fluoro-2,10-dioxido-14-(4-oxo-3,4-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-2,10-disulfanyl-octahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6*H*-purin-6-one	691
42		5-amino-3-[(5*S*,7*R*,8*R*,12a*R*,14*R*,15a*S*)-2,10-dioxido-14-(4-oxo-3,4-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-2,10-disulfanyloctahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-one (Diastereomer 1)	674

Ex.	Structure	Name	Mass [M-H]⁻
43		5-amino-3-[(5*S*,7*R*,8*R*,12a*R*,14*R*,15a*S*)-2,10-dioxido-14-(4-oxo-3,4-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-2,10-disulfanyloctahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-one (Diastereomer 2)	674
44		2-amino-9-[(5*S*,7*R*,8*R*,12a*R*,14*R*,15*S*,15a*R*)-15-fluoro-2,10-dioxido-14-(4-oxo-3,4-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-2,10-disulfanyl-octahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6*H*-purin-6-one	707
45		5-amino-3-[(5*S*,7*R*,8*R*,12a*R*,14*R*,15*S*,15a*R*)-15-fluoro-2,10-dioxido-14-(4-oxo-3,4-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-2,10-disulfanyl-octahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-one	692
46		7-[(5*S*,7*R*,8*R*,12a*R*,14*R*,15*S*,15a*R*)-7-(6-amino-9*H*-purin-9-yl)-15-fluoro-2,10-dioxido-2,10-disulfanyloctahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (Diastereomer 1)	675
47		7-[(5*S*,7*R*,8*R*,12a*R*,14*R*,15*S*,15a*R*)-7-(6-amino-9*H*-purin-9-yl)-15-fluoro-2,10-dioxido-2,10-disulfanyloctahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (Diastereomer 2)	675

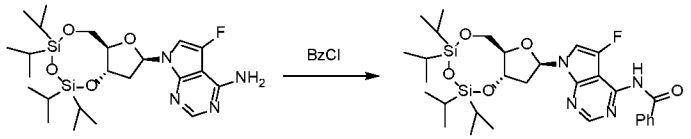
Ex.	Structure	Name	Mass [M-H]⁻
48		5-amino-3-[(5*R*,7*R*,8*S*,12a*R*,14*R*,15*S*,15a*R*,16*S*)-15,16-difluoro-2,10-dioxido-14-(4-oxo-3,4-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-2,10-disulfanyl-octahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-one	710
49		5-amino-3-[(5*R*,7*R*,8*R*,12a*R*,14*R*,15*S*,15a*R*,16*S*)-15,16-difluoro-2,10-dioxido-14-(4-oxo-3,4-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-2,10-disulfanyl-octahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-one (Diastereomer 1)	726
50		5-amino-3-[(5*R*,7*R*,8*R*,12a*R*,14*R*,15*S*,15a*R*,16*S*)-15,16-difluoro-2,10-dioxido-14-(4-oxo-3,4-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-2,10-disulfanyl-octahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-one (Diastereomer 2)	726
51		6-amino-1-[(5*R*,7*R*,8*S*,12a*R*,14*R*,15*S*,15a*R*,16*R*)-15,16-difluoro-2,10-dioxido-14-(4-oxo-3,4-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-2,10-disulfanyl-octahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,5-dihydro-4*H*-imidazo[4,5-*c*]pyridin-4-one	708

[0519] **Example 52: 2-amino-9-[(5*R*,7*R*,8*S*,12a*R*,14*R*,15a*S*,16*R*)-14-(4-amino-5-fluoro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-16-fluoro-2,10-dioxido-2,10-disulfanyloctahydro-12*H*-5,8-**

methanofuro[3,2-*l*][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6*H*-purin-6-one

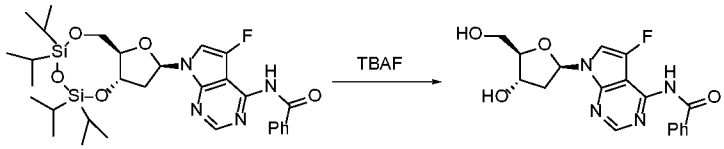


[0520] *Step 1: N-{5-fluoro-7-[(6aR,8R,9aS)-2,2,4,4-tetra(propan-2-yl)tetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-8-yl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}benzamide*



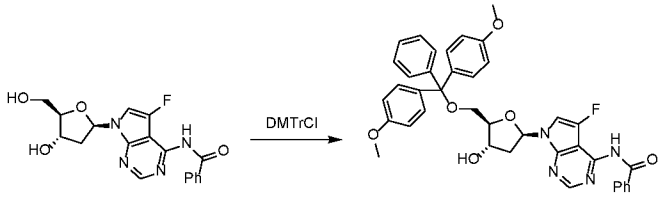
[0521] BzCl (1.2mL, 10.3mmol) was added to a stirring solution of 5-fluoro-7-[(6aR,8R,9aS)-2,2,4,4-tetra(propan-2-yl)tetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-8-yl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine (3.3g, 6.5mmol) in Py (32mL) at 0°C. The reaction mixture was allowed to warm to RT and stir for 1h. MeOH (10mL) was added, and the reaction mixture was allowed to stir for 30min. The reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica eluting with Hex, EtOAc, and EtOH to give the titled compound. LCMS (ES, m/z): 615 $[M+H]^+$.

[0522] *Step 2: 7-(2-deoxy-β-D-erythro-pentofuranosyl)-5-fluoro-N-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine*



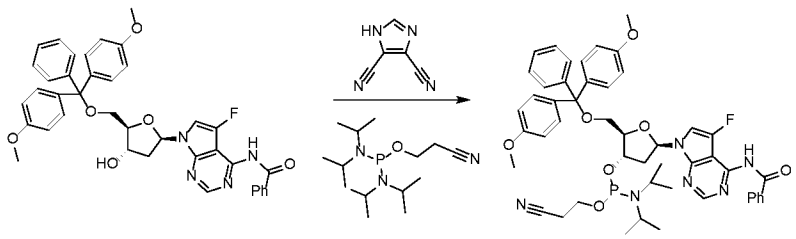
[0523] To N-{5-fluoro-7-[(6aR,8R,9aS)-2,2,4,4-tetra(propan-2-yl)tetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-8-yl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}benzamide (2.8g, 4.60mmol) in THF (46mL) at RT was added TBAF (1M, 14mL, 14mmol). The reaction mixture was stirred overnight. The reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica eluting with hexane, EtOAc, and EtOH to give the titled compound. LCMS (ES, m/z): 373 $[M+H]^+$.

[0524] *Step 3: 7-{5-O-[bis(4-methoxyphenyl)(phenyl)methyl]-2-deoxy-β-D-erythro-pentofuranosyl}-5-fluoro-N-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine*



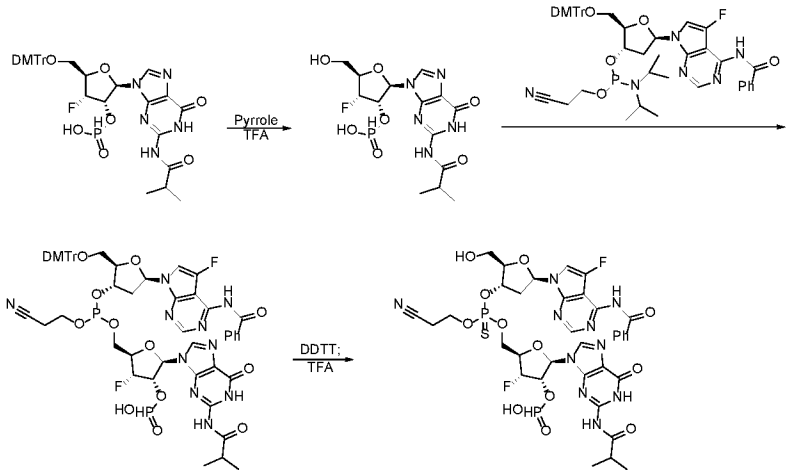
[0525] DMTrCl (1.33g, 3.93mmol) was added to 7-(2-deoxy-β-D-erythro-pentofuranosyl)-5-fluoro-N-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (1.2g, 3.3mmol) in Py (12mL) at 0°C. The reaction mixture was allowed to warm to RT and stir overnight. Additional DMTrCl (1.33g, 3.93mmol) was added, and the reaction mixture was stirred for 4h. DMAP (0.040g, 0.33mmol) was added, and the reaction mixture was stirred for 2h. The reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica eluting with MeOH and DCM with 1% TEA additive to give the title compound. LCMS (ES, m/z): 675 $[M+H]^+$.

[0526] *Step 4: 7-{5-O-[bis(4-methoxyphenyl)(phenyl)methyl]-3-O-[(2-cyanoethoxy)(dipropan-2-ylamino)phosphanyl]-2-deoxy-β-D-erythro-pentofuranosyl}-5-fluoro-N-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine*



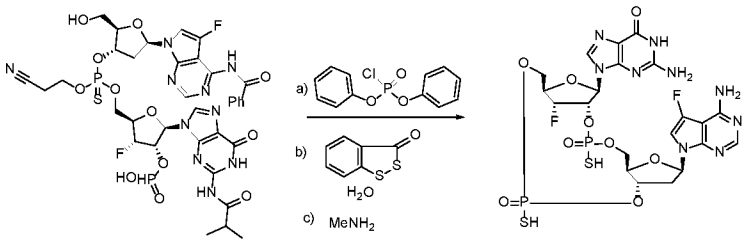
[0527] To 7-{5-O-[bis(4-methoxyphenyl)(phenyl)methyl]-2-deoxy-β-D-erythro-pentofuranosyl}-5-fluoro-N-(phenylcarbonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (1.5g, 2.2mmol) in DCM (22mL) was added 4,5-dicyanoimidazole (0.8g, 6.7mmol) followed by 2-cyanoethyl N,N,N',N'-tetraisopropylphosphorodiamidite (2.1mL, 6.7mmol) at 0°C. The reaction mixture was stirred overnight. The reaction mixture was concentrated *in vacuo*. The product was purified by flash column chromatography on silica eluting with EtOAc and Hex with 1% TEA additive to the title compound. LCMS (ES, m/z): 875 $[M+H]^+$.

[0528] *Step 5: (2R,3S,4R,5R)-5-((((((2R,3S,5R)-5-(4-benzamido-5-fluoro-7H-pyrrolo [2,3-d]pyrimidin-7-yl)-2-(hydroxymethyl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphorothioyl)oxy)methyl)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl hydrogen phosphonate*



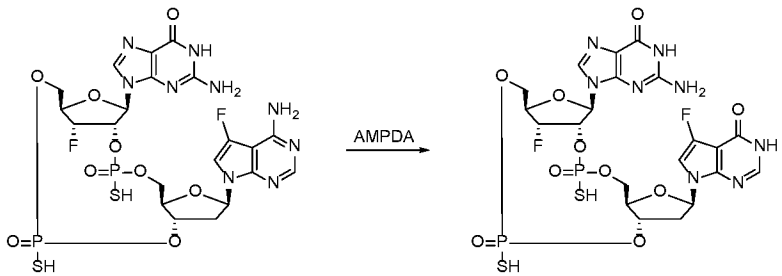
[0529] Pyrrole (0.277mL, 3.96mmol) was added to a stirring solution of 5'-O-[bis(4-methoxyphenyl)(phenyl)methyl]-3'-deoxy-3'-fluoro-2'-O-[hydroxy(oxido)-λ~5~-phosphanyl]-N-(2-methylpropanoyl)guanosine (1.2g, 1.3mmol) in MeCN (4.5mL) at 0°C followed by TFA (0.3mL, 4.0mmol). The reaction mixture was stirred at 0°C for 2h. 7-{5-O-[bis(4-methoxyphenyl)(phenyl)methyl]-3-O-[(2-cyanoethoxy)(dipropan-2-ylamino)phosphanyl]-2-deoxy-β-D-erythro-pentofuranosyl}-5-fluoro-N-(phenylcarbonyl)-7H-pyrrolo[2,3-d] pyrimidin-4-amine (1.2g, 1.3mmol) in MeCN (4.50mL) was added at 0°C. The reaction mixture was allowed to stir for 30min. (*E*)-*N*,*N*-dimethyl-*N*'-(3-thioxo-3*H*-1,2,4-dithiazol-5-yl) formimidamide (0.33g, 1.6mmol) was added at 0°C. The reaction mixture was allowed to stir for 30min. 1-propanol (1mL, 13mmol) was added at 0°C, and the reaction mixture was allowed to stir for 10min and warmed to RT. TFA (1.0mL, 13mmol) was added, and the reaction mixture stirred at RT for 30min. Py (1.3mL, 16mmol) was added, and the reaction mixture was stirred for 20min. The reaction mixture was concentrated to half volume, diluted with isopropyl acetate (15mL), and left to stir overnight. The precipitate was isolated by filtration to give the title compound that was used in the next step without further purification.

[0530] *Step 6: 2-amino-9-[(5R,7R,8S,12aR,14R,15aS,16R)-14-(4-amino-5-fluoro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-16-fluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one*



[0531] Diphenyl chlorophosphate (1.4mL, 6.6mmol) was added to degassed MeCN (60mL) and Py (5mL) at RT. A solution of the crude (2R,3S,4R,5R)-5-((((((2R,3S,5R)-5-(4-benzamido-5-fluoro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-(hydroxymethyl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphorothioyl)oxy)methyl)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl hydrogen phosphonate in Py (8mL) was added dropwise while maintaining the internal temperature below -20°C. The reaction mixture was stirred for 30min. 3*H*-1,2-Benzodithiol-3-one (0.3g, 1.6mmol) followed by H_2O (0.5mL, 26mmol) were added, and the reaction mixture was allowed to warm to RT and stir for 30min. The reaction mixture was concentrated *in vacuo* and azeotroped with Py. The residue was dissolved in Py (8mL) and cooled to 0°C. $MeNH_2$ (12.16mL, 98mmol, 33% v/v in EtOH) was added, and the reaction mixture was allowed to warm to RT and stir overnight. The reaction mixture was concentrated *in vacuo*, and purified by reverse phase HPLC (eluted MeCN/H_2O gradient with 100mM TEAA modifier, linear gradient) to give the four phosphorus diastereomers as triethylammonium salts. The slowest eluting peak fractions were collected and lyophilized to give the product as the triethylammonium salt. LCMS (ES, m/z): 708 $[M-H]^-$. ^1H NMR (600MHz, D_2O) δ 8.14 (s, 1H), 7.97 (s, 1H), 7.15 (s, 1H), 6.63 (m, 1H), 6.07 (d, *J*=8.5Hz, 1H), 5.77 (m, 1H), 5.53 (dd, *J*=53.3, 2.4Hz, 1H), 5.35 (m, 1H), 4.75 (m, 1H), 4.48 (m, 1H), 4.31–4.08 (m, 4H), 2.80 (m, 2H).

[0532] *Step 7: 2-amino-9-[(5R,7R,8S,12aR,14R,15aS,16R)-16-fluoro-14-(5-fluoro-4-oxo-3,4-dihydro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 1)*

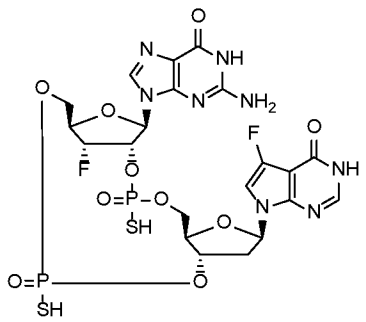


[0533] To triethylammonium 2-amino-9-[(5R,7R,8S,12aR,14R,15aS,16R)-14-(4-amino-5-fluoro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-16-fluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (4.6mg, 5.7μmol) were added sodium phosphate buffer (pH 6.8, 50mM, 8mL) and AMPDA (200mg). The reaction mixture was left to stir for 4 days, filtered, and purified by

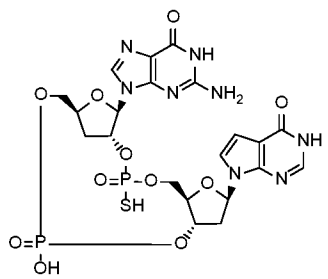
reverse phase HPLC (eluting MeCN/H_2O gradient with 100mM TEAA modifier, linear gradient) to afford the product (Diastereomer 1) as the triethylammonium salt. LCMS (ES, m/z): 709 [M-H]$^-$. ^{1}H NMR (600MHz, D_2O) δ 8.02 (s, 1H), 7.99 (s, 1H), 7.04 (s, 1H), 6.66 (m, 1H), 6.07 (d, *J*=8.5Hz, 1H), 5.76 (m, 1H), 5.49 (d, *J*=55.8Hz, 1H), 5.34 (m, 1H), 4.74 (m, 1H), 4.47 (m, 1H), 4.31 (brs, 1H), 4.22–4.13 (m, 2H), 4.06 (m, 1H), 2.80 (m, 3H).

[0534] Example **53**, as shown in Table 6 below, was prepared according to procedures analogous to those outlined in Example **52** above.

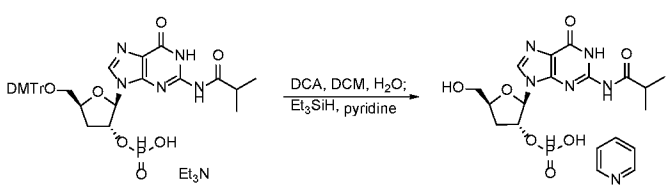
Table 6

Ex.	Structure	Name	Mass [M-H]$^-$
53		2-amino-9-[(5*R*,7*R*,8*S*,12a*R*,14*R*,15a*S*,16*R*)-16-fluoro-14-(5-fluoro-4-oxo-3,4-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-2,10-dioxido-2,10-disulfanyl-octahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6*H*-purin-6-one (Diastereomer 2)	709

[0535] **Example 54: 2-amino-9-[(5*S*,7*R*,8*R*,12a*R*,14*R*,15a*S*)-2-hydroxy-2,10-dioxido-14-(4-oxo-3,4-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-10-sulfanyloctahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6*H*-purin-6-one**

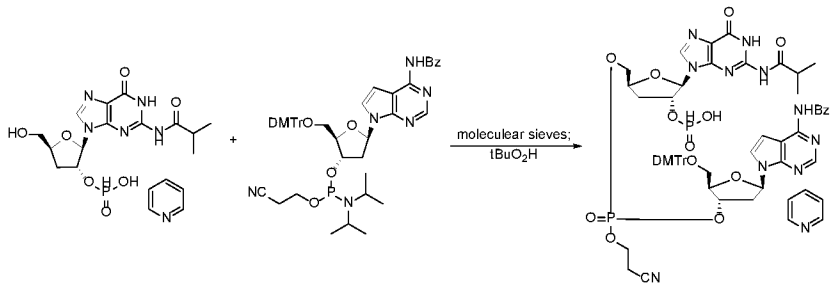


[0536] *Step 1: 3'-deoxy-2'-O-[hydroxy(oxido)-λ^5-phosphanyl]-N-(2-methylpropanoyl)guanosine*



[0537] To a stirred solution of triethylammonium 5'-*O*-[bis(4-methoxyphenyl)(phenyl) methyl]-3'-deoxy-2'-*O*-[hydroxy(oxido)-λ^5-phosphanyl]-*N*-(2-methylpropanoyl)guanosine (1.28g, 1.59mmol) in DCM (24mL) were added H_2O (0.287g, 15.9mmol) and DCA in DCM solution (0.6M, 23.85mL, 14.31mmol) at RT. The mixture was stirred at RT for 10min, treated with Et_3SiH (32mL), and left to stir for 1h. Py (2.264g, 28.6mmol) was added, and the mixture was concentrated under reduced pressure to give the crude product as the pyridinium salt. LCMS (ES, m/z): 402 $[M+H]^+$.

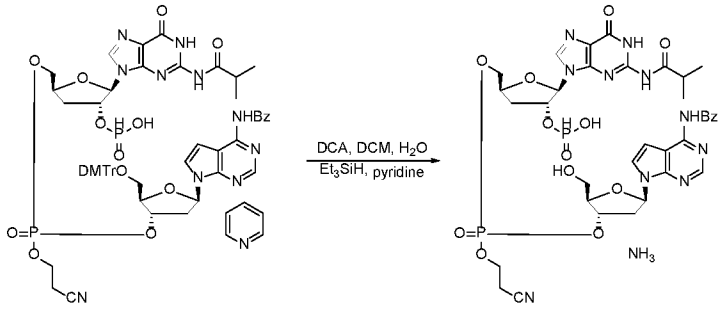
[0538] *Step 2: (2R,3R,5S)-5-((((((2R,3S,5R)-5-(4-benzamido-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphoryl)oxy)methyl)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl hydrogen phosphonate*



[0539] A solution of 7-{5-*O*-[bis(4-methoxyphenyl)(phenyl)methyl]-3-*O*-[(2-cyanoethoxy)(dipropan-2-ylamino)phosphanyl]-2-deoxy-β-D-*erythro*-pentofuranosyl}-*N*-(phenylcarbonyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (1.43g, 1.67mmol) in MeCN (5mL) was concentrated *in vacuo*. Addition of MeCN (5mL) followed by concentration was repeated twice. To the residue were added MeCN (12mL) and activated 4Å molecular sieves (150mg).

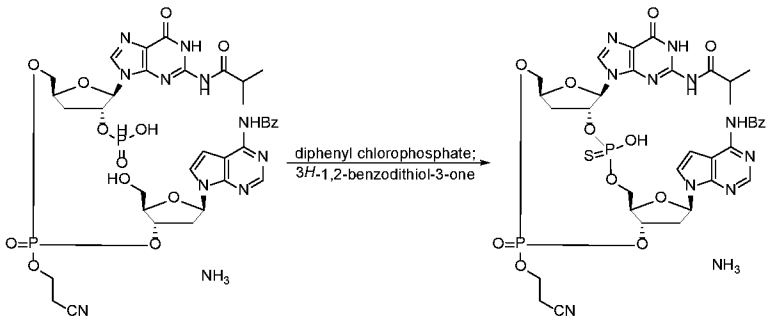
[0540] The crude pyridinium 3'-deoxy-3'-fluoro-2'-*O*-[hydroxy(oxido)-λ^5-phosphanyl]-*N*-(2-methylpropanoyl)guanosine was dissolved in MeCN (5m) and concentrated *in vacuo*. Addition of MeCN (5mL) followed by concentration was repeated twice. To the residue were added MeCN (12mL) and activated 4Å molecular sieves (150mg). After 30min, the phosphoramidite solution was added to the H-phosphonate solution. The flask was rinsed with MeCN (1mL), and the solution was transferred to the H-phosphonate solution (2x). The resulting mixture was charged with Ar and stirred at RT for 30min, treated with $tBuO_2H$ (5.5M in decane, 1.0mL, 5.5mmol) over 1min, and left to stir for 1h. The mixture was cooled to 0°C, treated with aq $Na_2S_2O_3$ solution (18g in 3mL H_2O) slowly. The mixture was left to stir at RT for 5min and concentrated to give the crude product as the pyridinium salt. LCMS (ES, m/z): 1171 $[M-H]^-$.

[0541] *Step 3: (2R,3R,5S)-5-((((((2R,3S,5R)-5-(4-benzamido-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-(hydroxymethyl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphoryl) oxy)methyl)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl hydrogen phosphonate*



[0542] The crude pyridinium (2R,3R,5S)-5-((((((2R,3S,5R)-5-(4-benzamido-7H-pyrrolo [2,3-d]pyrimidin-7-yl)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphoryl)oxy)methyl)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl hydrogen phosphonate was dissolved in DCM (24mL) was treated with H_2O (286mg, 15.9mmol) and DCA in DCM (0.6M, 23.9mL, 14.3mmol) at RT. The mixture was left to stir for 10min, treated with Et_3SiH (20mL), left to stir for 1h, and treated with Py (2.26g, 28.6mmol). The mixture was concentrated and purified by reverse phase (C18) chromatography eluting with 0 to 95% MeCN in 5mM aq NH_4HCO_3 solution to give the product as the ammonium salt. LCMS (ES, m/z): 871 $[M+H]^+$.

[0543] *Step 4: N-{7-[(5S,7R,8R,12aR,14R,15aS)-2-(2-cyanoethoxy)-10-hydroxy-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-2-oxido-10-sulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}benzamide*

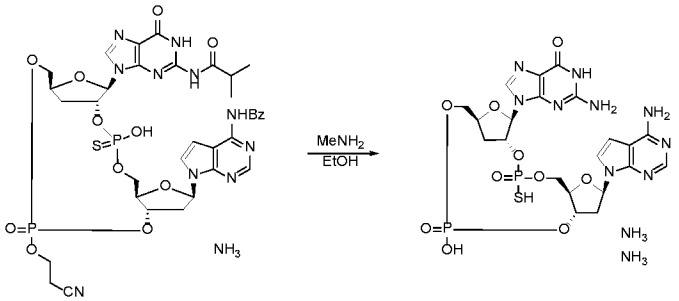


[0544] A solution of ammonium (2R,3R,5S)-5-((((((2R,3S,5R)-5-(4-benzamido-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-(hydroxymethyl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy) phosphoryl)oxy)methyl)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl hydrogen phosphonate (803mg, 0.923mmol) in Py (5mL) was concentrated *in vacuo*.

Addition of Py (5mL) followed by concentration was repeated twice. The residue was taken up in DCM (70mL) and Py (20mL).

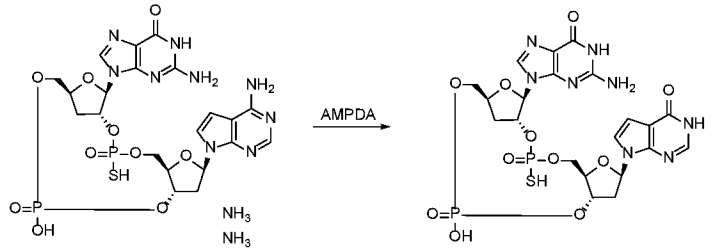
[0545] To a stirred Py (72mL) and DCM (20mL) in a separate flask was added diphenyl chlorophosphate (4961mg, 18.47mmol) under Ar at -40°C. To the solution was added the hydrogen phosphonate solution dropwise at -40°C over 30min. The resulting mixture was left to stir at -40°C for 40min and treated with 3*H*-1,2-benzodithiol-3-one (255mg, 1.384mmol) in one portion and H_2O (416mg, 23.1mmol) at -40°C. After stirring at RT for 1h, the mixture was concentrated under reduced pressure. The residue was purified by reverse phase (C18) chromatography eluting with 0 to 95% MeCN in 5mM aq NH_4HCO_3 solution to give the product as the ammonium salt. LCMS (ES, m/z): 885 $[M+H]^+$.

[0546] *Step 5: 2-amino-9-[(5S,7R,8R,12aR,14R,15aS)-14-(4-amino-7H-pyrrolo[2,3-d] pyrimidin-7-yl)-2-hydroxy-2,10-dioxido-10-sulfanyloctahydro-12H-5,8-methanofuro[3,2-l] [1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one*



[0547] To ammonium *N*-{7-[(5*S*,7*R*,8*R*,12a*R*,14*R*,15a*S*)-2-(2-cyanoethoxy)-10-hydroxy-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9*H*-purin-9-yl}-2-oxido-10-sulfidooctahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,6,9,11,2,10]pentaoxadiphospha-cyclotetradecin-14-yl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}benzamide (580mg, 0.656mmol) was added $MeNH_2$ in EtOH (33% w/w, 38 mL), and the resulting solution was left to stir at RT for 3h and concentrated. The residue was purified by Prep-HPLC (Atlantis Prep T3 OBD Column) eluting with 4 to 13% MeCN in 10mM aq NH_4HCO_3 solution to give the two phosphorus diastereomers as the diammonium salts. The slower eluting peak fractions were collected and lyophilized to give the product as the diammonium salt. LCMS (ES, m/z): 658 $[M+H]^+$. ^{1}H-NMR: (400MHz, D_2O): δ 8.07 (s, 1H), 7.86 (s, 1H), 7.35 (d, *J*=3.8Hz, 1H), 6.52 (dd, *J*=6.8, 4.4Hz, 1H), 6.48 (d, *J*=3.7Hz, 1H), 5.78 (d, *J*=6.0Hz, 1H), 5.47-5.37 (m, 1H), 5.10-5.04 (m, 1H), 4.56-48 (m, 1H), 4.23-4.21 (m, 1H), 4.15-4.00 (m, 4H), 2.83-2.76 (m, 1H), 2.74-2.67 (m, 1H), 2.63-2.55 (m, 1H), 2.47-2.41 (m, 1H). ^{31}P-NMR: (162MHz, D_2O): δ 53.18, -0.86.

[0548] *Step 6: 2-amino-9-[(5S,7R,8R,12aR,14R,15aS)-2-hydroxy-2,10-dioxido-14-(4-oxo-3,4-dihydro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-10-sulfanyloctahydro-12H-5,8-methanofuro [3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one*



[0549] To diammonium 2-amino-9-[(5*S*,7*R*,8*R*,12a*R*,14*R*,15a*S*)-14-(4-amino-7*H*-pyrrolo [2,3-*d*]pyrimidin-7-yl)-2-hydroxy-2,10-dioxido-10-sulfanyloctahydro-12*H*-5,8-methanofuro[3,2-*l*][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6*H*-purin-6-one (2.7mg, 4.0μmol) were added sodium phosphate buffer (pH 6.8, 50mM, 8mL) and AMPDA (200mg). The reaction mixture was left to stir for 11 days and filtered. The filtrate was treated with AMPDA (200mg) and left to stir for 2 weeks. The mixture was purified by reverse phase HPLC (eluting ACN/H_2O gradient with 100mM TEAA modifier, linear gradient) to afford the product as the triethylammonium salt. LCMS (ES, m/z): 657 $[M-H]^-$. ^1H NMR (500MHz, D_2O): δ 8.07 (s, 1H), 7.98 (s, 1H), 7.35 (s, 1H), 6.68-6.61 (m, 2H), 5.92 (d, *J*=4.6Hz, 1H), 5.45 (m, 1H), 5.13 (brs, 1H), 4.62 (brs, 1H), 4.33 (s, 1H), 4.23-4.08 (m, 4H), 3.08–2.66 (m, 3H), 2.53 (m, 1H).

[0550] BIOLOGICAL EVALUATION

[0551] The individual compounds described in the Examples herein are defined as STING agonists by (i) binding to the STING protein as evidenced by a reduction in binding of tritiated cGAMP ligand to the STING protein by at least 20% at 20uM (concentration of compound being tested) in a STING Biochemical [3H]cGAMP Competition Assay and (ii) demonstrating interferon production with a 6% or greater induction of IFN-β secretion at 30uM in the THP1 cell assay (where induction caused by cGAMP at 30uM was set at 100%).

[0552] [^{3}H]-cGAMP Synthesis

[0553] 2.3mL of buffer solution containing 80mM TrisCl, 200mM $MgCl_2$, and 20mM NaCl followed by 0.32mL of 10mM aq solution of GTP was added to a plastic 50mL AMICON tube. A solution of [^{3}H]ATP (21Ci/mmol, 45mCi) in 0.5mL H_2O was then added followed by 1mL of 1mg/mL solution of DNA (Herring testes activator DNA, Sigma, #D6898) and 53uL of 47mM solution of cGAS enzyme. Additional H_2O was added to bring the total volume to 10mL.

[0554] The reaction was stirred for 2h at 37°C and then added directly to an Amicon Ultra-15 10K centrifuge tube and spun for 1h at 4,000g. The collected solution was then purified on a semi-prep Mono Q column using the following mobile phases:

A: 0.05M TrisCl pH 8.5 adjusted with 1M NaOH

B: 0.05M TrisCl, 0.5M NaCl pH 8.5 adjusted with 1M NaOH

[0555] Gradient: 100% A for 5min followed by a linear gradient to 50:50 (A:B) over 25min, 3mL/min, 254nm.

[0556] The collected product fractions were pooled and adjusted to a total volume of 30mL with buffer A. A total yield of 15.5mCi of [^{3}H]cGAMP was isolated at a radiochemical purity of 98.0% at a specific activity of 21.5Ci/mmol.

[0557] cGAS Enzyme

[0558] A recombinant DNA vector was chemically synthesized to express the truncated human cGAS enzyme (residues 161-522). To aid in expression and purification, the amino terminus contains a hexahistidine tag, SUMO tag and TEV cleavage site. The recombinant enzyme was overexpressed in ROSETTA™ 2(DE3) Single Competent Cells (Novagen). Affinity purification was carried out using HIS-Select HF Nickel Affinity Gel (Sigma) followed by size exclusion chromatography using a Hi-Load 26/60 SUPERDEX200 prep grade column (GE Healthcare). Fractions were pooled, concentrated, flash-frozen in liquid nitrogen and stored at -80°C until needed.

[0559] **Example 55: ^{3}H-cGAMP filtration binding assay (HAQ STING)**

[0560] The ability of compounds to bind STING is quantified by their ability to compete with tritiated cGAMP ligand for human STING receptor membrane using a radioactive filter-binding assay. The binding assay employs STING receptor obtained from *Trichoplusia ni* cell membranes (*T.ni*; Expression Systems, cat # 94-002F, www.expressionsystems.com) overexpressing full-length HAQ STING and tritiated cGAMP ligand.

[0561] The basic HAQ STING filtration assay protocol is as follows:

[0562] The compounds were serially titrated by the Hamilton STARPlus CORE in a 96-well plate (Greiner, #651201) using a 1:3 ten-point dose response format. After compound preparation, a 2.2ug/ml working concentration of STING membrane (SEQ. ID. No. 1) was prepared by diluting concentrated membrane into assay buffer (1x PBS; Invitrogen #SH30028.02) and douncing 7x using a manual tissue homogenizer (Wheaton, #357546). 148uL

of prepared membrane was then manually added to each well of a 96-well deep-well polypropylene plate (Fisher Scientific, #12-566-121). Following membrane addition, 2uL of either titrated test compound, DMSO control (Sigma #276855), or cold cGAMP control was added to the appropriate wells using a BIOMEK FX. Compound and membrane then preincubated for 60min at RT to allow compound binding to equilibrate. Following equilibration, 8nM of [^{3}H] c-GAMP ligand was prepared by diluting into assay buffer, and 50uL of this working stock was then manually added to each well of the assay plate. Plates were then incubated at RT for 60min, and the contents of each assay plate were then filtered through a 96-well GF/B filter plate (PerkinElmer, #6005250) using a TOMTEC MACH III Cell Harvester equipped with 20mM HEPES buffer (Fisher Scientific, #BP299500). The filter plates were then dried at 55°C for 30min using a pressurized oven before 30uL of ULTIMA GOLD F scintillate was added to each well. Tritium levels for each reaction well were then measured using a PerkinElmer TopCount plate reader.

[0563] After normalization to controls, the percent activity for each compound concentration was calculated by measuring the amount of remaining radioactivity. The plot of percent activity versus the log of compound concentration was fit with a 4-parameter dose response equation to calculate EC_{50} values.

[0564] The final reaction conditions were:

Component	Volume (uL)	Final Concentration
STING membrane	148	1.5ug/ml
^{3}H-cGAMP	50	2.0nM
Low Control (cold cGAMP)	2	10uM
Test compound/DMSO	2	10uM

[0565] Compound concentrations tested were 20.000, 637.00, 2.200, 0.740, 0.247, 0.082, 0.027, 0.009, 0.003, and 0.001μM with 1.0% residual DMSO.

[0566] Full-Length STING (HAQ) Virus Generation

[0567] STING virus was generated using an insect cell baculovirus system. *Spodoptera frugiperda Sf21* cells (Kempbio, Inc.) were diluted to 5e5 cells/ml in Sf-900II SFM media (LifeTechnologies #10902088) without antibiotics. The cell suspension was added to each well of a treated 6-well plate (2mL per well, 1e6 cells total), and the cells were allowed to adhere for at least 30min. Meanwhile, a 1mL co-transfection mix was assembled by combining 500ng of HAQ STING [STING(1-379)R71H,G230A,H232R,R293Q-GG-AviTag-GS-HRV3C-

HIS8/pBAC1] DNA (Genewiz custom synthesis) with 1mL Sf-900II SFM media containing 10µL Cellfectin® II Reagent (Invitrogen #10362100) and 100ng viral backbone BestBac 2.0, v-cath/chiA Deleted Linearized Baculovirus DNA (Expression Systems #91-002). The transfection mixtures were allowed to incubate for 30min. After incubation, media was gently removed from the adhered cells in the 6-well plate, the 1mL transfection mixtures were added (1mL per well), and the plate was placed in a humidified incubator at 27°C. The following day, 1mL Sf-900II SFM media (no antibiotics) was added to each well of the 6-well plate. After media addition, the cells were allowed to incubate with DNA (SEQ. ID. No. 2) at 27°C for 5-7 days to generate the P0 viral stock. To generate P1 viral stocks, 0.5mL of P0 viral supernatant was added to 50mL uninfected *Sf21* cells (seeded the day prior to infection at a density of $5x10^5$ cells/mL to allow for one overnight doubling) in Sf-900II SFM media containing 5µg/mL gentamicin (Invitrogen #15710072). The infected cells were then incubated at 27°C for 3 days while shaking at 110rpm (ATR Biotech Multitron Infors HT #AJ118). On day 3, P1 cultures were counted using a ViCell XR (Beckman Coulter Life Sciences #383556) to confirm infection had occurred (cell size ≥3µm larger than uninfected cells and viability approximately 85-95%). Cultures were harvested in 50mL conical tubes and centrifuged at 2000xg for 10min at 4°C. The P1 viral supernatants were poured off into clean 50ml centrifuge tubes, and the remaining P1 cell pellets were used to generate Baculovirus Infected Insect Cells (BIICs). Cryopreservation media containing Sf-900II SFM media with 10% heat inactivated FBS, 10% DMSO (Sigma #D2650), and 5µg/ml gentamicin was prepared and sterilized through 0.22µM filter immediately prior to use. P1 cell pellets were resuspended to a density of 2e7 cells/ml and aliquoted into cryovials (1mL per vial). Cryovials were placed in MR. FROSTY™ cell freezers O/N at -80°C and transferred to liquid nitrogen for long term storage the following day. To generate P2 viral stock, 0.5mL of the P1 viral supernatant was added to 50mL uninfected *Sf21* cells (seeded the day prior to infection at a density of $5x10^5$ cells/mL to allow for one overnight doubling) in Sf-900II SFM media containing 5µg/mL gentamicin. These cells were incubated at 27°C for 3 days while shaking at 110rpm before harvesting P2 stock with centrifugation at 2000xg for 10min at 4°C. The P2 viral supernatants were poured off and discarded, while the P2 cell pellets were used to generate P2 BIICs following the same protocol described above. The baculovirus generation protocol has been validated to consistently produce P1/P2 BIICs with titers of 2e9 pfu/mL (2e7 cells/mLx100 pfu/cell).

[0568] Full-Length STING (HAQ) Expression

[0569] To generate STING membranes, P1/P2 BIICs were amplified overnight by adding thawed BIICs to *Sf21* cells seeded at a density of $1.0x10^6$cells/mL. The volume of BIIC used to infect the culture was calculated using an assumed BIIC titer of 2e9 pfu/ml to achieve an MOI of 10 in the overnight amplification. After culturing overnight, the cells were counted on a ViCell XR to confirm infection had occurred (cell size ≥3µm larger than uninfected cells and viability approximately 80-90%). The volume of infected *Sf21* cells from the overnight amplification used to infect the large-scale expression of *Trichoplusia ni* (*T.ni*; Expression Systems, cat # 94-002F, www.expressionsystems.com) seeded at a density of $1.0x10^6$ in cell media (ESF921 SFM containing 5µg/mL gentamicin) at MOI=2.0 was calculated based on (100 pfu/infected *Sf21* cell). The cells were allowed to express for 48h at 27°C before harvesting the cell pellet, by centrifugation at 3,400xg for 10min at 4°C. *T. ni* cells were counted on a ViCell XR to confirm infection had occurred (cell size ≥3µm larger than uninfected cells and viability approximately 80-90%) prior to harvest.

[0570] Full-Length STING (HAQ) Membrane Generation

[0571] Buffer stock reagents:

1) 1M HEPES pH 7.5, Teknova, Cat#H1035
2) 5M NaCl, Sigma Aldrich, Cat#S5150-1L
3) KCl, Sigma Aldrich, Cat#319309-500ML
4) Complete EDTA-free protease inhibitor tablets, Roche Diagnostics, Cat#11873580001
5) Benzonase, Universal Nuclease, Pierce, Cat#88702

[0572] Lysis buffer [25mM HEPES pH 7.5, 10mM $MgCl_2$, 20mM KCl, (Benzonase 1:5000, Complete Protease Inhibitor tab/50mL)] was added to the pellet of cells expressing full-length STING (HAQ) prepared above at 5mL Lysis buffer per g of cell pellet. The pellet was resuspended and dounced twenty times using a Wheaton Dounce Homogenizer to disrupt the cell membrane. Homogenized lysate was then passed through the EMULSIFLEX-C5 microfluidizer at a pressure close to 5000PSI. The resuspended pellet was centrifuged at 36,000rpm (100,000xg) in a 45Ti rotor ultra-high speed centrifuge for 45min, 4°C. The supernatant was removed. The pellet then was resuspended in wash buffer [(25mM HEPES pH7.5, 1mM $MgCl_2$, 20mM KCl, 1M NaCl (Complete Protease Inhibitor tab/50mL)] at a volume of 50mL pellet/centrifuge tube. The pellet/wash buffer mixture was then homogenized, using a glass homogenizer on ice (20 strokes), followed by centrifugation at 36,000rpm for 45min at 4°C. The supernatant was removed. The wash step was repeated once more. The resulting membrane was resuspended in

20mM HEPES pH 7.5, 500mM NaCl, 10% glycerol, EDTA-free Protease Inhibitors (1tablet/50mL). The protein concentration was measured by Bradford assay (Bio-Rad Protein Assay, Cat#500-0006), and protein enrichment was determined by SDS-PAGE and confirmed by Western blot. The resuspended membranes were stored at -80°C.

[0573] *Full-Length HAQ STING [STING(1-379)R71H,G230A,H232R,R293Q-GG-AviTag-GS-HRV3C-HIS8]Amino Acid Sequence:*

MPHSSLHPSIPCPRGHGAQKAALVLLSACLVTLWGLGEPPEHTLRYLVLHLASLQLGLL
LNGVCSLAEELHHIHSRYRGSYWRTVRACLGCPLRRGALLLLSIYFYYSLPNAVGPPFT
WMLALLGLSQALNILLGLKGLAPAEISAVCEKGNFNVAHGLAWSYYIGYLRLILPELQA
RIRTYNQHYNNLLRGAVSQRLYILLPLDCGVPDNLSMADPNIRFLDKLPQQTADRAGIK
DRVYSNSIYELLENGQRAGTCVLEYATPLQTLFAMSQYSQAGFSREDRLEQAKLFCQTL
EDILADAPESQNNCRLIAYQEPADDSSFSLSQEVLRHLRQEEKEEVTVGSLKTSAVPSTST
MSQEPELLISGMEKPLPLRTDFSGGGLNDIFEAQKIEWHEGSLEVLFQGPHHHHHHHH
(SEQ. ID. No. 1)

[0574] *Full-length HAQ [STING(1-379)R71H,G230A,H232R,R293Q-GG-AviTag-GS-HRV3C-HIS8/pBAC1] Plasmid DNA Sequence:*

GGAACGGCTCCGCCCACTATTAATGAAATTAAAAATTCCAATTTTAAAAAACGCAGC
AAGAGAAACATTTGTATGAAAGAATGCGTAGAAGGAAAGAAAAATGTCGTCGACAT
GCTGAACAACAAGATTAATATGCCTCCGTGTATAAAAAAAATATTGAACGATTTGA
AAGAAAACAATGTACCGCGCGGCGGTATGTACAGGAAGAGGTTTATACTAAACTGT
TACATTGCAAACGTGGTTTCGTGTGCCAAGTGTGAAAACCGATGTTTAATCAAGGCT
CTGACGCATTTCTACAACCACGACTCCAAGTGTGTGGGTGAAGTCATGCATCTTTTA
ATCAAATCCCAAGATGTGTATAAACCACCAAACTGCCAAAAAATGAAAACTGTCGA
CAAGCTCTGTCCGTTTGCTGGCAACTGCAAGGGTCTCAATCCTATTTGTAATTATTGA
ATAATAAAACAATTATAAATGCTAAATTTGTTTTTTATTAACGATACAAACCAAACG
CAACAAGAACATTTGTAGTATTATCTATAATTGAAAACGCGTAGTTATAATCGCTGA
GGTAATATTTAAAATCATTTTCAAATGATTCACAGTTAATTTGCGACAATATAATTTT
ATTTTCACATAAACTAGACGCCTTGTCGTCTTCTTCTTCGTATTCCTTCTCTTTTTCAT
TTTTCTCTTCATAAAAATTAACATAGTTATTATCGTATCCATATATGTATCTATCGTA
TAGAGTAAATTTTTTGTTGTCATAAATATATATGTCTTTTTTAATGGGGTGTATAGTA
CCGCTGCGCATAGTTTTTCTGTAATTTACAACAGTGCTATTTTCTGGTAGTTCTTCGG
AGTGTGTTGCTTTAATTATTAAATTTATATAATCAATGAATTTGGGATCGTCGGTTTT

GTACAATATGTTGCCGGCATAGTACGCAGCTTCTTCTAGTTCAATTACACCATTTTTT
AGCAGCACCGGATTAACATAACTTTCCAAAATGTTGTACGAACCGTTAAACAAAAA
CAGTTCACCTCCCTTTTCTATACTATTGTCTGCGAGCAGTTGTTTGTTGTTAAAAATA
ACAGCCATTGTAATGAGACGCACAAACTAATATCACAAACTGGAAATGTCTATCAA
TATATAGTTGCTGATCAGATCTGATCATGGAGATAATTAAAATGATAACCATCTCGC
AAATAAATAAGTATTTTACTGTTTTCGTAACAGTTTTGTAATAAAAAAACCTATAAA
TATAGGATCCATGCCCCACTCCAGCCTGCATCCATCCATCCCGTGTCCCAGGGGTCA
CGGGGCCCAGAAGGCAGCCTTGGTTCTGCTGAGTGCCTGCCTGGTGACCCTTTGGGG
GCTAGGAGAGCCACCAGAGCACACTCTCCGGTACCTGGTGCTCCACCTAGCCTCCCT
GCAGCTGGGACTGCTGTTAAACGGGGTCTGCAGCCTGGCTGAGGAGCTGCACCACA
TCCACTCCAGGTACCGGGGCAGCTACTGGAGGACTGTGCGGGCCTGCCTGGGCTGC
CCCCTCCGCCGTGGGGCCCTGTTGCTGCTGTCCATCTATTTCTACTACTCCCTCCCAA
ATGCGGTCGGCCCGCCCTTCACTTGGATGCTTGCCCTCCTGGGCCTCTCGCAGGCAC
TGAACATCCTCCTGGGCCTCAAGGGCCTGGCCCCAGCTGAGATCTCTGCAGTGTGTG
AAAAAGGGAATTTCAACGTGGCCCATGGGCTGGCATGGTCATATTACATCGGATATC
TGCGGCTGATCCTGCCAGAGCTCCAGGCCCGGATTCGAACTTACAATCAGCATTACA
ACAACCTGCTACGGGGTGCAGTGAGCCAGCGGCTGTATATTCTCCTCCCATTGGACT
GTGGGGTGCCTGATAACCTGAGTATGGCTGACCCCAACATTCGCTTCCTGGATAAAC
TGCCCCAGCAGACCGCTGACCGTGCTGGCATCAAGGATCGGGTTTACAGCAACAGC
ATCTATGAGCTTCTGGAGAACGGGCAGCGGGCGGGCACCTGTGTCCTGGAGTACGC
CACCCCCTTGCAGACTTTGTTTGCCATGTCACAATACAGTCAAGCTGGCTTTAGCCG
GGAGGATAGGCTTGAGCAGGCCAAACTCTTCTGCCAGACACTTGAGGACATCCTGG
CAGATGCCCCTGAGTCTCAGAACAACTGCCGCCTCATTGCCTACCAGGAACCTGCAG
ATGACAGCAGCTTCTCGCTGTCCCAGGAGGTTCTCCGGCACCTGCGGCAGGAGGAA
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GATGTCCCAAGAGCCTGAGCTCCTCATCAGTGGAATGGAAAAGCCCCTCCCTCTCCG
CACGGATTTCTCTGGCGGTGGCCTGAACGACATCTTCGAAGCCCAGAAAATCGAATG
GCATGAAGGCAGCCTGGAAGTGCTGTTCCAGGGCCCACACCACCATCATCACCATC
ACCATTAATGAGCGGCCGCACTCGAGCACCACCACCACCACCACTAACCTAGGTAG
CTGAGCGCATGCAAGCTGATCCGGGTTATTAGTACATTTATTAAGCGCTAGATTCTG
TGCGTTGTTGATTTACAGACAATTGTTGTACGTATTTTAATAATTCATTAAATTTATA
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GAATTTAAATATTAAATCCTCAATAGATTTGTAAAATAGGTTTCGATTAGTTTCAAA
CAAGGGTTGTTTTTCCGAACCGATGGCTGGACTATCTAATGGATTTTCGCTCAACGC
CACAAAACTTGCCAAATCTTGTAGCAGCAATCTAGCTTTGTCGATATTCGTTTGTGTT
TTGTTTTGTAATAAAGGTTCGACGTCGTTCAAAATATTATGCGCTTTTGTATTTCTTT
CATCACTGTCGTTAGTGTACAATTGACTCGACGTAAACACGTTAAATAGAGCTTGGA
CATATTTAACATCGGGCGTGTTAGCTTTATTAGGCCGATTATCGTCGTCGTCCCAACC
CTCGTCGTTAGAAGTTGCTTCCGAAGACGATTTTGCCATAGCCACACGACGCCTATT
AATTGTGTCGGCTAACACGTCCGCGATCAAATTTGTAGTTGAGCTTTTTGGAATTATT
TCTGATTGCGGGCGTTTTTGGGCGGGTTTCAATCTAACTGTGCCCGATTTTAATTCAG
ACAACACGTTAGAAAGCGATGGTGCAGGCGGTGGTAACATTTCAGACGGCAAATCT
ACTAATGGCGGCGGTGGTGGAGCTGATGATAAATCTACCATCGGTGGAGGCGCAGG
CGGGGCTGGCGGCGGAGGCGGAGGCGGAGGTGGTGGCGGTGATGCAGACGGCGGT
TTAGGCTCAAATGTCTCTTTAGGCAACACAGTCGGCACCTCAACTATTGTACTGGTTT
CGGGCGCCGTTTTTGGTTTGACCGGTCTGAGACGAGTGCGATTTTTTTCGTTTCTAAT
AGCTTCCAACAATTGTTGTCTGTCGTCTAAAGGTGCAGCGGGTTGAGGTTCCGTCGG
CATTGGTGGAGCGGGCGGCAATTCAGACATCGATGGTGGTGGTGGTGGTGGAGGCG
CTGGAATGTTAGGCACGGGAGAAGGTGGTGGCGGCGGTGCCGCCGGTATAATTTGT
TCTGGTTTAGTTTGTTCGCGCACGATTGTGGGCACCGGCGCAGGCGCCGCTGGCTGC
ACAACGGAAGGTCGTCTGCTTCGAGGCAGCGCTTGGGGTGGTGGCAATTCAATATTA
TAATTGGAATACAAATCGTAAAAATCTGCTATAAGCATTGTAATTTCGCTATCGTTT
ACCGTGCCGATATTTAACAACCGCTCAATGTAAGCAATTGTATTGTAAAGAGATTGT
CTCAAGCTCGGATCGATCCCGCACGCCGATAACAAGCCTTTTCATTTTTACTACAGC
ATTGTAGTGGCGAGACACTTCGCTGTCGTCGAGGTTTAAACGCTTCCTCGCTCACTG
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TAATACGGTTATCCACAGAATCAGGGGATAACGCAGGAAAGAACATGTGAGCAAAA
GGCCAGCAAAAGGCCAGGAACCGTAAAAAGGCCGCGTTGCTGGCGTTTTTCCATAG
GCTCCGCCCCCCTGACGAGCATCACAAAAATCGACGCTCAAGTCAGAGGTGGCGAA
ACCCGACAGGACTATAAAGATACCAGGCGTTTCCCCCTGGAAGCTCCCTCGTGCGCT
CTCCTGTTCCGACCCTGCCGCTTACCGGATACCTGTCCGCCTTTCTCCCTTCGGGAAG
CGTGGCGCTTTCTCATAGCTCACGCTGTAGGTATCTCAGTTCGGTGTAGGTCGTTCGC
TCCAAGCTGGGCTGTGTGCACGAACCCCCCGTTCAGCCCGACCGCTGCGCCTTATCC
GGTAACTATCGTCTTGAGTCCAACCCGGTAAGACACGACTTATCGCCACTGGCAGCA

GCCACTGGTAACAGGATTAGCAGAGCGAGGTATGTAGGCGGTGCTACAGAGTTCTT
GAAGTGGTGGCCTAACTACGGCTACACTAGAAGGACAGTATTTGGTATCTGCGCTCT
GCTGAAGCCAGTTACCTTCGGAAAAAGAGTTGGTAGCTCTTGATCCGGCAAACAAA
CCACCGCTGGTAGCGGTGGTTTTTTTGTTTGCAAGCAGCAGATTACGCGCAGAAAAA
AAGGATCTCAAGAAGATCCTTTGATCTTTTCTACGGGGTCTGACGCTCAGTGGAACG
AAAACTCACGTTAAGGGATTTTGGTCATGAGATTATCAAAAAGGATCTTCACCTAGA
TCCTTTTAAATTAAAAATGAAGTTTTAAATCAATCTAAAGTATATATGAGTAAACTT
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TATTGTCTCATGAGCGGATACATATTTGAATGTATTTAGAAAAATAAACAAATAGGG
GTTCCGCGCACATTTCCCCGAAAAGTGCCACCTGACGCGCCCTGTAGCGGCGCATTA
AGCGCGGCGGGTGTGGTGGTTACGCGCAGCGTGACCGCTACACTTGCCAGCGCCCT
AGCGCCCGCTCCTTTCGCTTTCTTCCCTTCCTTTCTCGCCACGTTCGCCGGCTTTCCCC
GTCAAGCTCTAAATCGGGGGCTCCCTTTAGGGTTCCGATTTAGTGCTTTACGGCACC
TCGACCCCAAAAAACTTGATTAGGGTGATGGTTCACGTAGTGGGCCATCGCCCTGAT
AGACGGTTTTTCGCCCTTTGACGTTGGAGTCCACGTTCTTTAATAGTGGACTCTTGTT
CCAAACTGGAACAACACTCAACCCTATCTCGGTCTATTCTTTTGATTTATAAGGGATT
TTGCCGATTTCGGCCTATTGGTTAAAAAATGAGCTGATTTAACAAAAATTTAACGCG

AATTTTAACAAAATATTAACGTTTACAATTTCCCATTCGCCATTCAGGCTGCGCAACT GTTGGGAAGGGCGATCGGTGCGGGCCTCTTCGCTATTACGCCA (SEQ. ID. No. 2)

[0575] Certain compounds of the disclosure were evaluated in HAQ STING *in vitro* binding assay as described above. Table 7 tabulates the biological data for these compounds as EC_{50} values.

Table 7: ^{3}H-cGAMP filtration binding assay for HAQ STING

Compound	EC_{50} (nM)	Compound	EC_{50} (nM)	Compound	EC_{50} (nM)
Example 1	77	Example 22	146	Example 39	1
Example 2	2	Example 23	28	Example 40	5
Example 3	140	Example 24	411	Example 41	2
Example 4	59	Example 25	1	Example 42	1
Example 5	563	Example 26	19	Example 43	37
Example 6	28	Example 27	61	Example 44	1
Example 7	2	Example 28	41	Example 45	3
Example 8	23	Example 29	45	Example 46	16
Example 9	23	Example 30	37	Example 47	460
Example 10	3	Example 31	16	Example 48	2
Example 11	1742	Example 32	14	Example 49	1
Example 12	156	Example 33	90	Example 50	4
Example 13	238	Example 34	1123	Example 51	13
Example 17	3	Example 35	11	Example 52	14
Example 18	126	Example 36	2	Example 53	167
Example 19	208	Example 37	49	Example 54	12
Example 20	15	Example 38	1		

[0576] **Example 56: ^{3}H-cGAMP filtration binding assay (WT STING)**

[0577] The ability of compounds to bind STING is quantified by their ability to compete with tritiated cGAMP ligand for human STING receptor membrane using a radioactive filter-binding assay. The binding assay employs STING receptor obtained from *Trichoplusia ni* cell membranes (*T.ni*; Expression Systems, cat #94-002F, www.expressionsystems.com) overexpressing full-length WT STING and tritiated cGAMP ligand.

[0578] The basic WT STING filtration assay protocol is as follows:

[0579] 16nM of [^{3}H] c-GAMP ligand was prepared by diluting into assay buffer, and 50uL of this working stock was manually added to each well of the assay plate. After ligand addition, 2uL of either titrated test compound, DMSO control (Sigma #276855), or cold cGAMP control was added to the appropriate wells using a BIOMEK FX. The serially titrated compound was prepared on a Hamilton STARPlus CORE in a 96-well plate (Greiner, #651201) using a 1:3 ten-point dose response format. Following compound addition, a 2.2ug/ml working concentration of STING membrane (SEQ. ID. No. 3) was prepared by diluting concentrated membrane into assay buffer (1x PBS; Invitrogen #SH30028.02) and douncing 7x using a manual tissue homogenizer (Wheaton, #357546). 148uL of this prepared membrane was then manually added to each well of a 96-well deep-well polypropylene plate (Fisher Scientific, #12-566-121). Compound, ligand, and membrane then incubated for 60min at RT before the contents of each assay plate were filtered through a 96-well GF/B filter plate (PerkinElmer, #6005250) using a TOMTEC MACH III Cell Harvester equipped with 20mM HEPES buffer (Fisher Scientific, #BP299500). The filter plates were then dried at 55°C for 30min using a pressurized VWR oven before 30uL of ULTIMA GOLD F scintillate was added to each well. Tritium levels for each reaction well were then measured using a PerkinElmer TopCount plate reader.

[0580] After normalization to controls, the percent activity for each compound concentration was calculated by measuring the amount of remaining radioactivity. The plot of percent activity versus the log of compound concentration was fit with a 4-parameter dose response equation to calculate EC_{50} values.

[0581] The final reaction conditions were:

Component	Volume (uL)	Final Concentration
STING membrane	148	1.5ug/ml
^{3}H-cGAMP	50	4.0nM
Low Control (cold cGAMP)	2	10uM
Test compound/DMSO	2	10uM

[0582] Compound concentrations tested were 20.000, 637.00, 2.200, 0.740, 0.247, 0.082, 0.027, 0.009, 0.003, and 0.001μM with 1.0% residual DMSO.

[0583] Full-Length STING (WT) Virus Generation

[0584] STING virus was generated using an insect cell baculovirus system. *Spodoptera frugiperda Sf21* cells (Kempbio, Inc.) were diluted to 5e5 cells/ml in Sf-900II SFM media (LifeTechnologies #10902088) without antibiotics. The cell suspension was added to each well

of a treated 6-well plate (2mL per well, 1e6 cells total), and the cells were allowed to adhere for at least 30min. Meanwhile, a 1mL co-transfection mix was assembled by combining 500ng of WT STING[STING(1-379)H232R-gg-AviTag-gs-HRV3C-HIS8/pBAC1] (Genewiz custom synthesis) with 1mL Sf-900II SFM media containing 10µL CELLFECTIN® II Reagent (Invitrogen #10362100) and 100ng viral backbone BestBac 2.0, v-cath/chiA Deleted Linearized Baculovirus DNA (Expression Systems #91-002). The transfection mixtures were allowed to incubate for 30min. After incubation, media was gently removed from the adhered cells in the 6-well plate, the 1mL transfection mixtures were added (1mL per well), and the plate was placed in a humidified incubator at 27°C. The following day, 1mL Sf-900II SFM media (no antibiotics) was added to each well of the 6-well plate. After media addition, the cells were allowed to incubate with DNA [(SEQ. ID. No. 4) and linearized viral backbone BestBac 2.0] at 27°C for 5-7 days to generate the P0 viral stock. To generate P1 viral stocks, 0.5mL of P0 viral supernatant was added to 50mL uninfected *Sf21* cells (seeded the day prior to infection at a density of $5x10^5$ cells/mL to allow for one overnight doubling) in Sf-900II SFM media containing 5µg/mL gentamicin (Invitrogen #15710072). The infected cells were then incubated at 27°C for 3 days while shaking at 110rpm (ATR Biotech Multitron Infors HT #AJ118). On day 3, P1 cultures were counted using a ViCell XR (Beckman Coulter Life Sciences #383556) to confirm infection had occurred (cell size ≥3µm larger than uninfected cells and viability approximately 85-95%). Cultures were harvested in 50mL conical tubes and centrifuged at 2000xg for 10min at 4°C. The P1 viral supernatants were poured off into clean 50ml centrifuge tubes, and the remaining P1 cell pellets were used to generate Baculovirus Infected Insect Cells (BIICs). Cryopreservation media containing Sf-900II SFM media with 10% heat inactivated FBS, 10% DMSO (Sigma #D2650), and 5µg/ml gentamicin was prepared and sterilized through 0.22µM filter immediately prior to use. P1 cell pellets were resuspended to a density of 2e7 cells/ml and aliquoted into cryovials (1mL per vial). Cryovials were placed in MR. FROSTY™ cell freezers O/N at -80°C and transferred to liquid nitrogen for long term storage the following day. To generate P2 viral stock, 0.5mL of the P1 viral supernatant was added to 50mL uninfected *Sf21* cells (seeded the day prior to infection at a density of $5x10^5$ cells/mL to allow for one overnight doubling) in Sf-900II SFM media containing 5µg/mL gentamicin. These cells were incubated at 27°C for 3 days while shaking at 110rpm before harvesting P2 stock with centrifugation at 2000xg for 10min at 4°C. The P2 viral supernatants were poured off and discarded, while the P2 cell pellets were used to generate P2 BIICs following the same protocol described above. The baculovirus generation

protocol has been validated to consistently produce P1/P2 BIICs with titers of 2e9 pfu/mL (2e7 cells/mLx100pfu/cell).

[0585] Full-Length STING (WT) Expression

[0586] To generate STING membranes, P1/P2 BIICs were amplified overnight by adding thawed BIICs to *Sf21* cells seeded at a density of $1.0x10^6$ cells/mL. The volume of BIIC used to infect the culture was calculated using an assumed BIIC titer of 2e9 pfu/ml to achieve an MOI of 10 in the overnight amplification. After culturing overnight, the cells were counted on a ViCell XR to confirm infection had occurred (cell size ≥3µm larger than uninfected cells and viability approximately 80-90%). The volume of infected *Sf21* cells from the overnight amplification used to infect the large-scale expression of *Trichoplusia ni* (*T.ni*; Expression Systems, cat # 94-002F, www.expressionsystems.com) seeded at a density of $1.0x10^6$ in cell media (ESF921 SFM containing 5µg/mL gentamicin) at MOI=2.0 was calculated based on (100pfu/infected *Sf21* cell). The cells were allowed to express for 48h at 27°C before harvesting the cell pellet, by centrifugation at 3,400xg for 10min at 4°C. *T. ni* cells were counted on a ViCell XR to confirm infection had occurred (cell size ≥3µm larger than uninfected cells and viability approximately 80-90%) prior to harvest.

[0587] Full-Length STING (WT) Membrane Generation

[0588] Buffer stock reagents:

1) 1 M HEPES pH 7.5, Teknova, Cat#H1035
2) 5 M NaCl, Sigma Aldrich, Cat#S5150-1L
3) KCl, Sigma Aldrich, Cat#319309-500ML
4) Complete EDTA-free protease inhibitor tablets, Roche Diagnostics, Cat#11873580001
5) Benzonase, Universal Nuclease, Pierce, Cat#88702

[0589] Lysis buffer [25mM HEPES pH 7.5, 10mM $MgCl_2$, 20mM KCl, (Benzonase 1:5000, Complete Protease Inhibitor tab/50mL)] was added to the pellet of cells expressing full-length STING (WT) prepared above at 5mL Lysis buffer per g of cell pellet. The pellet was resuspended and dounced twenty times using a Wheaton Dounce Homogenizer to disrupt the cell membrane. Homogenized lysate was then passed through the emulsiflex-C5 microfluidizer at a pressure close to 5000PSI. The resuspended pellet was centrifuged at 36,000rpm (100,000xg) in a 45Ti rotor ultra-high speed centrifuge for 45min, 4°C. The supernatant was removed. The pellet then was resuspended in wash buffer [(25mM HEPES pH 7.5, 1mM $MgCl_2$, 20mM KCl, 1M NaCl (Complete Protease Inhibitor tab/50mL)] at a volume of 50mL/pellet/centrifuge tube.

The pellet/wash buffer mixture was then homogenized, using a glass homogenizer on ice (20 strokes), followed by centrifugation at 36,000rpm for 45min at 4°C. The supernatant was removed. The wash step was repeated once more. The resulting membrane was resuspended in 20mM HEPES pH 7.5, 500mM NaCl, 10% glycerol, EDTA-free Protease Inhibitors (1tablet/50mL). The protein concentration was measured by Bradford assay (Bio-Rad Protein Assay, Cat#500-0006), and protein enrichment was determined by SDS-PAGE and confirmed by Western blot. The resuspended membranes were stored at -80°C.

[0590] *Full-Length STING WT [STING(1-379)H232R-gg-AviTag-gs-HRV3C-HIS8] Amino Acid Sequence:*

MPHSSLHPSIPCPRGHGAQKAALVLLSACLVTLWGLGEPPEHTLRYLVLHLASLQLGLL
LNGVCSLAEELRHIHSRYRGSYWRTVRACLGCPLRRGALLLLSIYFYYSLPNAVGPPFT
WMLALLGLSQALNILLGLKGLAPAEISAVCEKGNFNVAHGLAWSYYIGYLRLILPELQA
RIRTYNQHYNNLLRGAVSQRLYILLPLDCGVPDNLSMADPNIRFLDKLPQQTGDRAGIK
DRVYSNSIYELLENGQRAGTCVLEYATPLQTLFAMSQYSQAGFSREDRLEQAKLFCRTL
EDILADAPESQNNCRLIAYQEPADDSSFSLSQEVLRHLRQEEKEEVTVGSLKTSAVPSTST
MSQEPELLISGMEKPLPLRTDFSGGGLNDIFEAQKIEWHEGSLEVLFQGPHHHHHHHH
(SEQ. ID. No. 3)

[0591] *Full-length WT STING [STING(1-379)H232R-gg-AviTag-gs-HRV3C-HIS8/pBAC1] plasmid sequence:*

GGAACGGCTCCGCCCACTATTAATGAAATTAAAAATTCCAATTTTAAAAAACGCAGC
AAGAGAAACATTTGTATGAAAGAATGCGTAGAAGGAAAGAAAAATGTCGTCGACAT
GCTGAACAACAAGATTAATATGCCTCCGTGTATAAAAAAAATATTGAACGATTTGA
AAGAAAACAATGTACCGCGCGGCGGTATGTACAGGAAGAGGTTTATACTAAACTGT
TACATTGCAAACGTGGTTTCGTGTGCCAAGTGTGAAAACCGATGTTTAATCAAGGCT
CTGACGCATTTCTACAACCACGACTCCAAGTGTGTGGGTGAAGTCATGCATCTTTTA
ATCAAATCCCAAGATGTGTATAAACCACCAAACTGCCAAAAAATGAAAACTGTCGA
CAAGCTCTGTCCGTTTGCTGGCAACTGCAAGGGTCTCAATCCTATTTGTAATTATTGA
ATAATAAAACAATTATAAATGTCAAATTTGTTTTTTATTAACGATACAAACCAAACG
CAACAAGAACATTTGTAGTATTATCTATAATTGAAAACGCGTAGTTATAATCGCTGA
GGTAATATTTAAAATCATTTTCAAATGATTCACAGTTAATTTGCGACAATATAATTTT
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TTTTCTCTTCATAAAAATTAACATAGTTATTATCGTATCCATATATGTATCTATCGTA

TAGAGTAAATTTTTTGTTGTCATAAATATATATGTCTTTTTTAATGGGGTGTATAGTA
CCGCTGCGCATAGTTTTTCTGTAATTTACAACAGTGCTATTTTCTGGTAGTTCTTCGG
AGTGTGTTGCTTTAATTATTAAATTTATATAATCAATGAATTTGGGATCGTCGGTTTT
GTACAATATGTTGCCGGCATAGTACGCAGCTTCTTCTAGTTCAATTACACCATTTTTT
AGCAGCACCGGATTAACATAACTTTCCAAAATGTTGTACGAACCGTTAAACAAAAA
CAGTTCACCTCCCTTTTCTATACTATTGTCTGCGAGCAGTTGTTTGTTGTTAAAAATA
ACAGCCATTGTAATGAGACGCACAAACTAATATCACAAACTGGAAATGTCTATCAA
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AAATAAATAAGTATTTTACTGTTTTCGTAACAGTTTTGTAATAAAAAAACCTATAAA
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CGGGGCCCAGAAGGCAGCCTTGGTTCTGCTGAGTGCCTGCCTGGTGACCCTTTGGGG
GCTAGGAGAGCCACCAGAGCACACTCTCCGGTACCTGGTGCTCCACCTAGCCTCCCT
GCAGCTGGGACTGCTGTTAAACGGGGTCTGCAGCCTGGCTGAGGAGCTGCGCCACA
TCCACTCCAGGTACCGGGGCAGCTACTGGAGGACTGTGCGGGCCTGCCTGGGCTGC
CCCCTCCGCCGTGGGGCCCTGTTGCTGCTGTCCATCTATTTCTACTACTCCCTCCCAA
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TGAACATCCTCCTGGGCCTCAAGGGCCTGGCCCCAGCTGAGATCTCTGCAGTGTGTG
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ACAACCTGCTACGGGGTGCAGTGAGCCAGCGGCTGTATATTCTCCTCCCATTGGACT
GTGGGGTGCCTGATAACCTGAGTATGGCTGACCCCAACATTCGCTTCCTGGATAAAC
TGCCCCAGCAGACCGGTGACCGTGCTGGCATCAAGGATCGGGTTTACAGCAACAGC
ATCTATGAGCTTCTGGAGAACGGGCAGCGGGCGGGCACCTGTGTCCTGGAGTACGC
CACCCCCTTGCAGACTTTGTTTGCCATGTCACAATACAGTCAAGCTGGCTTTAGCCG
GGAGGATAGGCTTGAGCAGGCCAAACTCTTCTGCCGGACACTTGAGGACATCCTGG
CAGATGCCCCTGAGTCTCAGAACAACTGCCGCCTCATTGCCTACCAGGAACCTGCAG
ATGACAGCAGCTTCTCGCTGTCCCAGGAGGTTCTCCGGCACCTGCGGCAGGAGGAA
AAGGAAGAGGTTACTGTGGGCAGCTTGAAGACCTCAGCGGTGCCCAGTACCTCCAC
GATGTCCCAAGAGCCTGAGCTCCTCATCAGTGGAATGGAAAAGCCCCTCCCTCTCCG
CACGGATTTCTCTGGCGGTGGCCTGAACGACATCTTCGAAGCCCAGAAAATCGAATG
GCATGAAGGCAGCCTGGAAGTGCTGTTCCAGGGCCCACACCACCATCATCACCATC
ACCATTAATGAGCGGCCGCACTCGAGCACCACCACCACCACCACTAACCTAGGTAG

CTGAGCGCATGCAAGCTGATCCGGGTTATTAGTACATTTATTAAGCGCTAGATTCTG
TGCGTTGTTGATTTACAGACAATTGTTGTACGTATTTTAATAATTCATTAAATTTATA
ATCTTTAGGGTGGTATGTTAGAGCGAAAATCAAATGATTTTCAGCGTCTTTATATCT
GAATTTAAATATTAAATCCTCAATAGATTTGTAAAATAGGTTTCGATTAGTTTCAAA
CAAGGGTTGTTTTTCCGAACCGATGGCTGGACTATCTAATGGATTTTCGCTCAACGC
CACAAAACTTGCCAAATCTTGTAGCAGCAATCTAGCTTTGTCGATATTCGTTTGTGTT
TTGTTTTGTAATAAAGGTTCGACGTCGTTCAAAATATTATGCGCTTTTGTATTTCTTT
CATCACTGTCGTTAGTGTACAATTGACTCGACGTAAACACGTTAAATAGAGCTTGGA
CATATTTAACATCGGGCGTGTTAGCTTTATTAGGCCGATTATCGTCGTCGTCCCAACC
CTCGTCGTTAGAAGTTGCTTCCGAAGACGATTTTGCCATAGCCACACGACGCCTATT
AATTGTGTCGGCTAACACGTCCGCGATCAAATTTGTAGTTGAGCTTTTTGGAATTATT
TCTGATTGCGGGCGTTTTTGGGCGGGTTTCAATCTAACTGTGCCCGATTTTAATTCAG
ACAACACGTTAGAAAGCGATGGTGCAGGCGGTGGTAACATTTCAGACGGCAAATCT
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CGGGGCTGGCGGCGGAGGCGGAGGCGGAGGTGGTGGCGGTGATGCAGACGGCGGT
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CGGGCGCCGTTTTTGGTTTGACCGGTCTGAGACGAGTGCGATTTTTTTCGTTTCTAAT
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CATTGGTGGAGCGGGCGGCAATTCAGACATCGATGGTGGTGGTGGTGGTGGAGGCG
CTGGAATGTTAGGCACGGGAGAAGGTGGTGGCGGCGGTGCCGCCGGTATAATTTGT
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TTGCCGATTTCGGCCTATTGGTTAAAAAATGAGCTGATTTAACAAAAATTTAACGCG
AATTTTAACAAAATATTAACGTTTACAATTTCCCATTCGCCATTCAGGCTGCGCAACT
GTTGGGAAGGGCGATCGGTGCGGGCCTCTTCGCTATTACGCCA (SEQ. ID. No. 4)

[0592] Certain compounds of the disclosure were evaluated in WT STING *in vitro* binding assay as described above. The following table tabulates the biological data for these compounds as EC_{50} values.

Table 8: ^{3}H-cGAMP filtration binding assay for WT STING

Compound	EC_{50} (nM)	Compound	EC_{50} (nM)	Compound	EC_{50} (nM)
Example 1	1642	Example 19	902	Example 45	85
Example 2	32	Example 20	83	Example 46	2402
Example 3	1856	Example 21	832	Example 48	205
Example 4	1764	Example 29	136	Example 49	756
Example 5	10260	Example 38	393	Example 50	9133
Example 13	1960	Example 40	2830	Example 52	21
Example 14	433	Example 41	124	Example 53	253
Example 15	43	Example 42	46	Example 55	212
Example 16	90	Example 43	148	Example 56	1985

[0593] **Example 57: IFN-β secretion in THP1 cell culture (5h)**

[0594] The ability of compounds to stimulate the secretion of interferon-beta from THP1 cells was measured using a human IFN-β AlphaLISA kit (Perkin Elmer, Cat. No. AL265F). The basic protocol is as follows:

[0595] A Labcyte Echo 550 acoustic dispenser was used to transfer 120nL of compound dissolved in DMSO into the wells of an empty, sterile 384-well microplate, (Corning, Cat. No. 3712). THP1 cells (American Type Culture Collection, Cat. No. TIB202) previously frozen in Recovery Medium (Life Technologies, Cat. No. 12648-010) were thawed and immediately diluted 10-fold into 37°C assay medium (RPMI 1640+L-Glutamine & phenol red, Life Technologies, Cat. No. 11875-085; 0.5% heat inactivated fetal bovine serum, Sigma Aldrich, Cat. No. F4135; 1mM Sodium Pyruvate, Life Technologies, Cat. No. 11360-070; 1x non-

essential amino acids; Life Technologies, Cat. No. 11140-050). The cell viability and count was ascertained using a Beckman Coulter V-Cell XR cell counter. The cell suspension was centrifuged at 200xg for 5min at RT. Cells were resuspended to a density of $0.8x10^6$/mL in 37°C assay medium. Subsequent liquid transfers were performed using either a Matrix electronic multichannel pipette or an Agilent Bravo Automated Liquid Handling Platform.

[0596] The assay was started by dispensing 40µL of the previously prepared cell suspension into the wells of the plate containing compounds. After 5h incubation at 37°C, 5% CO_2 in a humidified atmosphere, the plate of cells and compounds was centrifuged at 200xg for 5min at RT. From each well, 5µL of supernatant was transferred into corresponding wells of a white 384-well plate (Perkin Elmer, Cat. No. 6005620). To these supernatant-containing wells was added 10µL of 5x Anti-Analyte Acceptor beads (50µg/mL of AlphaLISA HiBlock Buffer) and incubated for 30min at RT while shaking on an orbital plate shaker. To each well was added 10µL of 5x Biotinylated Antibody Anti-analyte (5nM in AlphaLISA HiBlock Buffer) and incubated on an orbital plate shaker for 60min at RT or overnight at 4°C. To each well was added 25µL of 2x SA-Donor beads (80µg/mL in AlphaLISA HiBlock Buffer) and incubated for 30-45min at RT in the dark while shaking on an orbital plate shaker. The plate was then read on a Perkin Elmer Envision (λ_{ex}=680nm, λ_{em}=570nm). The percent effect of the AlphaLISA signal at each compound concentration was calculated based on 30uM cGAMP positive controls and 0.3% DMSO negative controls. The plot of percent effect versus the log of compound concentration was fit with a 4-parameter concentration response equation to calculate EC_{50} values. The test compounds were tested at concentrations 30000, 10000, 3333, 1111, 370.4, 123.4, 41.2, 13.7, 4.6, and 1.5nM with 0.3% residual DMSO. The control compound, cGAMP was tested at concentrations 100000, 33333, 11111, 3704, 1235, 412, 137, 46, and 15nM with 0.3% residual DMSO.

[0597] Compounds of the disclosure were evaluated for IFN-β secretion in THP1 cell culture as described above. The following table tabulates the biological data for these compounds as percent activation relative to 2'3'-cGAMP at the 30µM concentration.

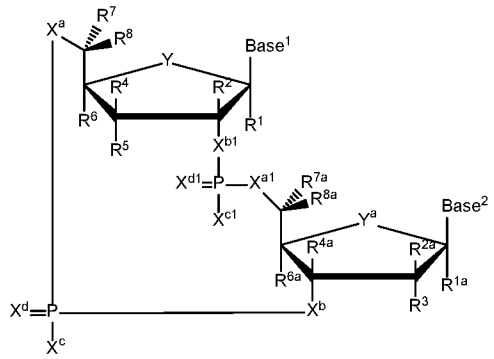
Table 9: IFN-β secretion in THP1 cell culture (5h)

Compound	% Effect at 30μM relative to 2'3'-cGAMP	Compound	% Effect at 30μM relative to 2'3'-cGAMP	Compound	% Effect at 30μM relative to 2'3'-cGAMP
Example 1	143	Example 19	7	Example 37	102
Example 2	44	Example 20	169	Example 38	109
Example 3	20	Example 21	143	Example 39	166
Example 4	139	Example 22	100	Example 40	150
Example 5	39	Example 23	123	Example 41	156
Example 6	145	Example 23	36	Example 42	72
Example 7	140	Example 25	131	Example 43	120
Example 8	128	Example 26	153	Example 44	164
Example 9	80	Example 27	143	Example 45	135
Example 10	183	Example 28	143	Example 46	166
Example 11	5	Example 29	150	Example 47	13
Example 12	123	Example 30	127	Example 48	159
Example 13	334	Example 31	28	Example 49	163
Example 14	12	Example 32	141	Example 50	109
Example 15	318	Example 33	83	Example 51	113
Example 16	281	Example 34	157	Example 52	53
Example 17	122	Example 35	98	Example 53	85
Example 18	124	Example 36	94	Example 54	68

[0598] It will be appreciated that various of the above-discussed and other features and functions, or alternatives thereof, may be desirably combined into many other different systems or applications. It also will be appreciated that various presently unforeseen or unanticipated alternatives, modifications, variations or improvements therein may be subsequently made by those skilled in the art and are also intended to be encompassed by the following claims.

WHAT IS CLAIMED IS:

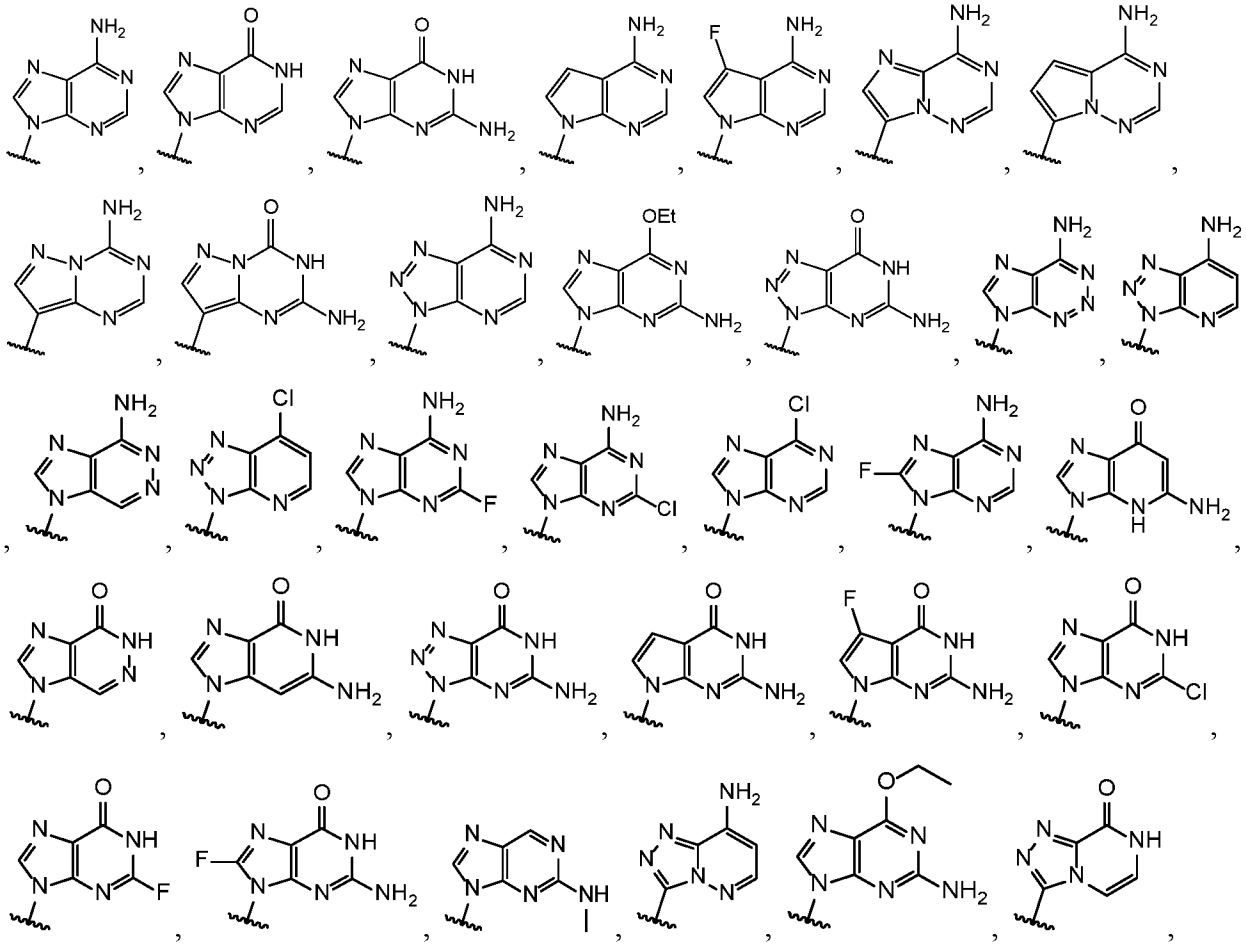
1. A compound of formula (I):

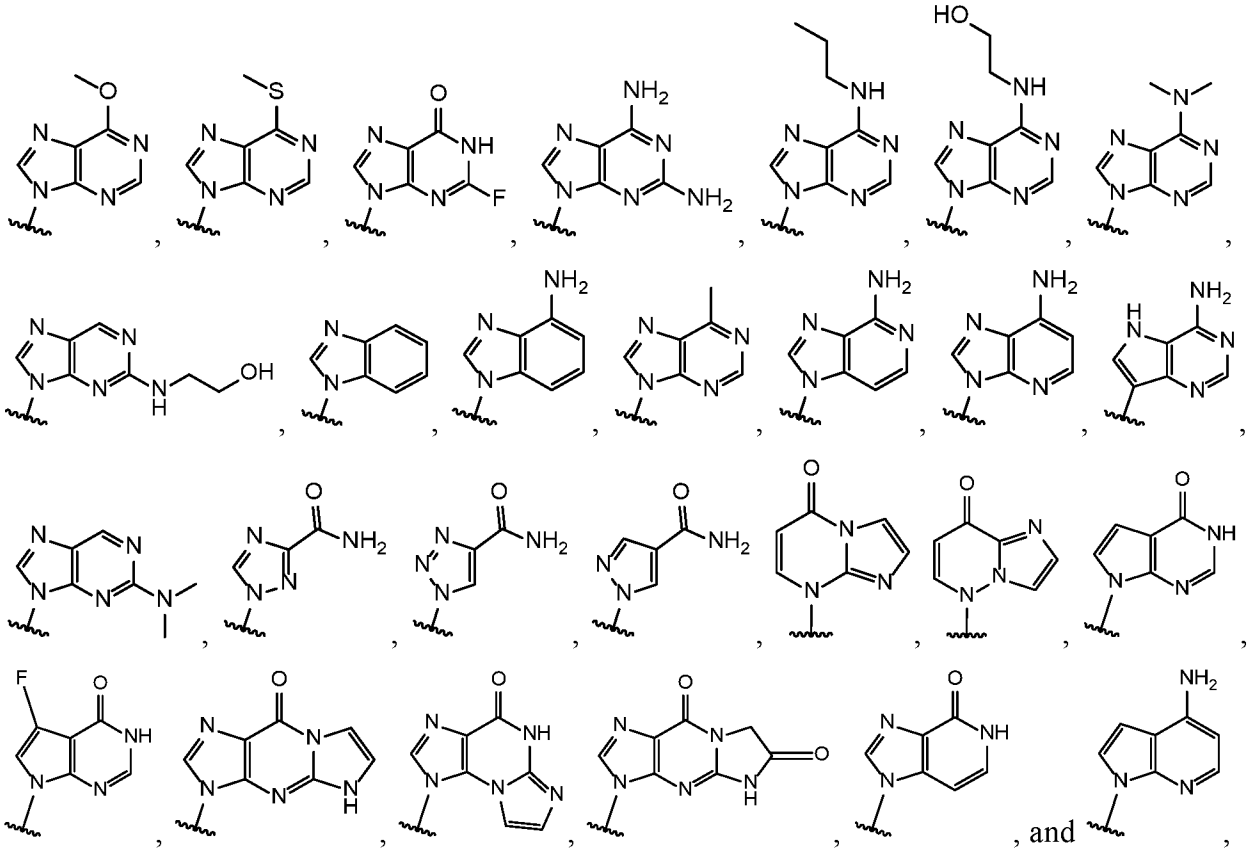


(I)

or a pharmaceutically acceptable salt thereof, wherein

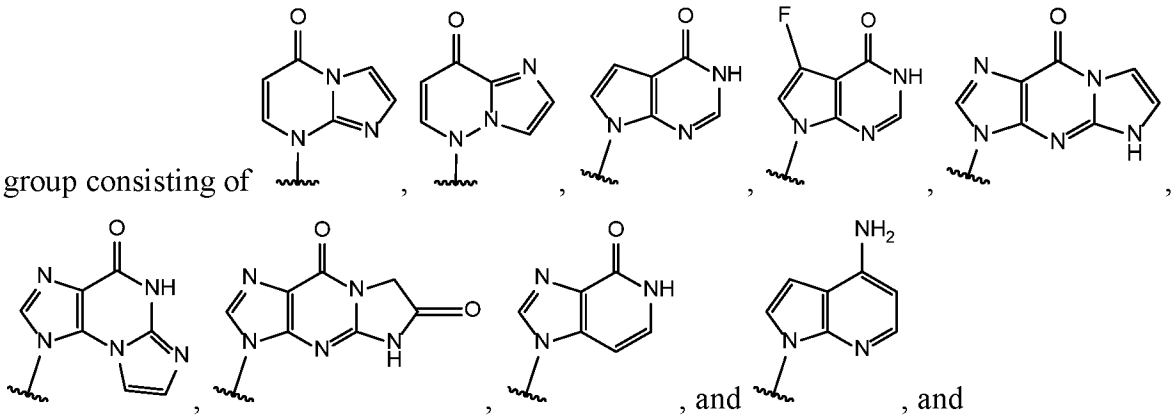
Base[1] and Base[2] are each independently selected from the group consisting of





wherein

at least one of $Base^1$ and $Base^2$ is each independently selected from the group consisting of



, and

$Base^1$ and $Base^2$ each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl)$_2$, and $N(C_{3-6}$ cycloalkyl)$_2$;

Y and Y^a are each independently selected from the group consisting of -O-, -S-, -SO_2-, -CH_2-, and -CF_2-;

X^a and X^{a1} are each independently selected from the group consisting of -O-, -S-, and $-CH_2-$;

X^b and X^{b1} are each independently selected from the group consisting of -O-, -S-, and $-CH_2-$;

X^c and X^{c1} are each independently selected from the group consisting of $-SR^9$, $-OR^9$, and $-NR^9R^9$;

X^d and X^{d1} are each independently selected from the group consisting of O and S;

R^1 and R^{1a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^1 and R^{1a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3;

R^2 and R^{2a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^2 and R^{2a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3;

R^3 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^3 C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3;

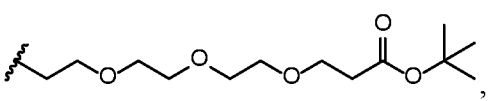
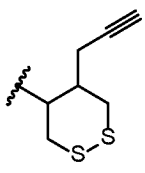
R^4 and R^{4a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^4 and R^{4a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3;

R^5 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^5 C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3;

R^6 and R^{6a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^6 and R^{6a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3;

R^7 and R^{7a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^7 and R^{7a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3;

R^8 and R^{8a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl, where said R^8 and R^{8a} C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -O-C_1-C_6 alkyl, -O-C_2-C_6 alkenyl, and -O-C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3;

each R^9 is independently selected from the group consisting of H, C_1-C_{20} alkyl,  , and  , where each R^9 C_1-C_{20} alkyl is optionally substituted by 0 to 3 substituents independently selected from the group consisting of OH, -O-C_1-C_{20} alkyl,-S-C(O)C_1-C_6 alkyl, and C(O)OC_1-C_6 alkyl;

optionally R^{1a} and R^3 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, -O-C_1-C_6 alkylene, or -O-C_2-C_6 alkenylene, such that where R^{1a} and R^3 are connected to form -O-C_1-C_6 alkylene, or -O-C_2-C_6 alkenylene, said O is bound at the R^3 position;

optionally R^{2a} and R^3 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, -O-C_1-C_6 alkylene, or -O-C_2-C_6 alkenylene, such that where R^{2a} and R^3 are connected to form -O-C_1-C_6 alkylene, or -O-C_2-C_6 alkenylene, said O is bound at the R^3 position;

optionally R^3 and R^{6a} are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, -O-C_1-C_6 alkylene, or -O-C_2-C_6 alkenylene, such that where R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, or -O-C_2-C_6 alkenylene, said O is bound at the R^3 position;

optionally R^4 and R^5 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, -O-C_1-C_6 alkylene, or -O-C_2-C_6 alkenylene, such that where R^4 and R^5 are connected to form -O-C_1-C_6 alkylene, or -O-C_2-C_6 alkenylene, said O is bound at the R^5 position;

optionally R^5 and R^6 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, such that where R^5 and R^6 are connected to form -O-C_1-C_6 alkylene, -O-C_2-C_6 alkenylene, or -O-C_2-C_6 alkynylene, said O is bound at the R^5 position;

optionally R^7 and R^8 are connected to form C_1-C_6 alkylene or C_2-C_6 alkenylene; and

optionally R^{7a} and R^{8a} are connected to form C_1-C_6 alkylene or C_2-C_6 alkenylene.

2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

Y and Y^a are each independently selected from the group consisting of -O- and -S-;

X^a and X^{a1} are each independently selected from the group consisting of -O- and -S-;

X^b and X^{b1} are each independently selected from the group consisting of -O and -S-;

X^c and X^{c1} are each independently selected from the group consisting of -SR^9, -OR^9, and -NR^9R^9;

X^d and X^{d1} are each independently selected from the group consisting of O and S;

R^1 and R^{1a} are each H;

R^2 and R^{2a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^2 and R^{2a} C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of OH, CN, and N_3;

R^3 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^3 C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of OH, CN, and N_3;

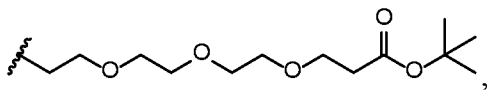
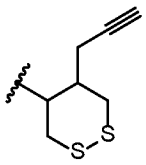
R^4 and R^{4a} are each independently selected from the group consisting of H, F, Cl, I, Br, CN, OH, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^4 and R^{4a} C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of OH, CN, and N_3;

R^5 is selected from the group consisting of H, F, Cl, Br, I, OH, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^5 C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3;

R^6 and R^{6a} are each independently selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, where said R^6 and R^{6a} C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I, OH, CN, and N_3;

R^7 and R^{7a} are each independently selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^7 and R^{7a} C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of OH, CN, and N_3;

R^8 and R^{8a} are each independently selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^8 and R^{8a} C_1-C_6 alkyl or C_1-C_6 haloalkyl are substituted by 0 to 3 substituents selected from the group consisting of OH, CN, and N_3;

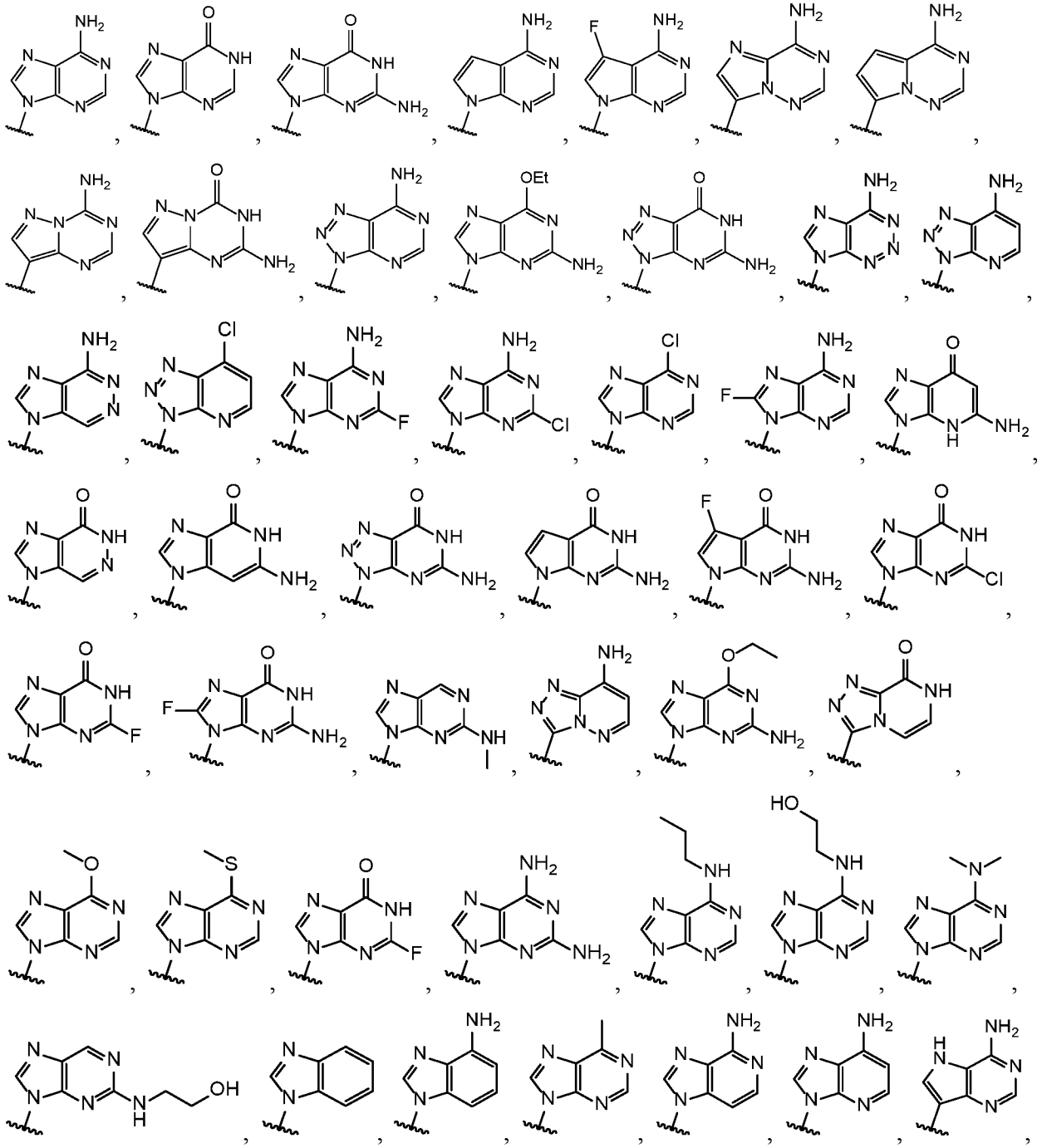
each R^9 is independently selected from the group consisting of H, C_1-C_6 alkyl,  , and  , where each R^9 C_1-C_6 alkyl is optionally substituted by 1 to 2 substituents independently selected from the group consisting of OH, -O-C_1-C_{20} alkyl,-S-C(O)C_1-C_6 alkyl, and -C(O)OC_1-C_6 alkyl;

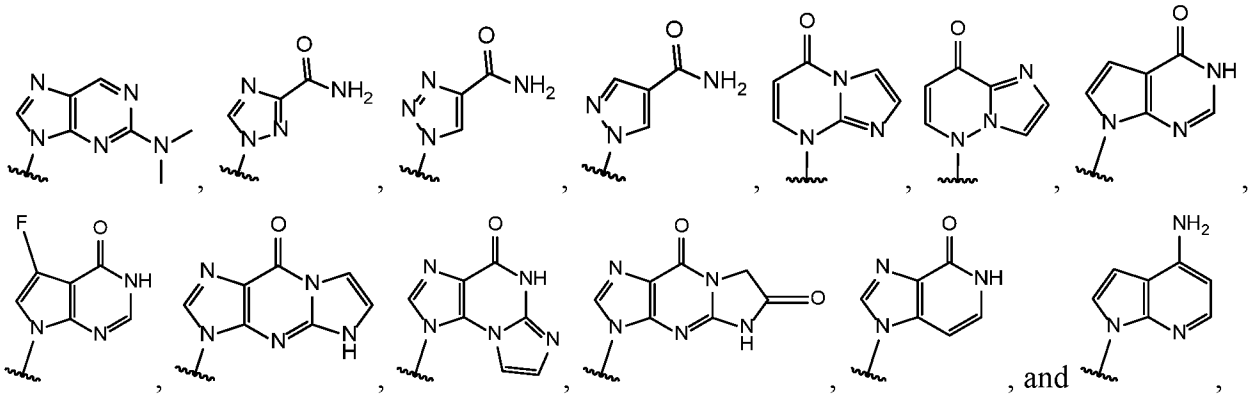
optionally R^3 and R^{6a} are connected to form C_2-C_6 alkylene, C_2-C_6 alkenylene, -O-C_1-C_6 alkylene, or -O-C_2-C_6 alkenylene, such that where R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene or -O-C_2-C_6 alkenylene, said O is bound at the R^3 position; and

optionally R^5 and R^6 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, -O-C_1-C_6 alkylene, or -O-C_2-C_6 alkenylene, such that where R^5 and R^6 are connected to form -O-C_1-C_6 alkylene or -O-C_2-C_6 alkenylene, said O is bound at the R^5 position.

3. The compound according to claim 1 or claim 2, or a pharmaceutically acceptable salt thereof, wherein

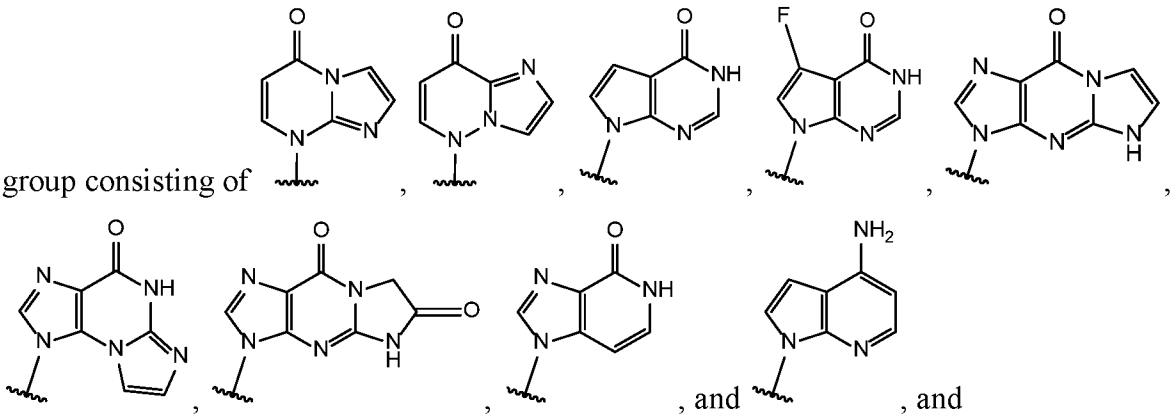
$Base^1$ and $Base^2$ are each independently selected from the group consisting of





wherein

at least one of $Base^1$ and $Base^2$ is each independently selected from the group consisting of



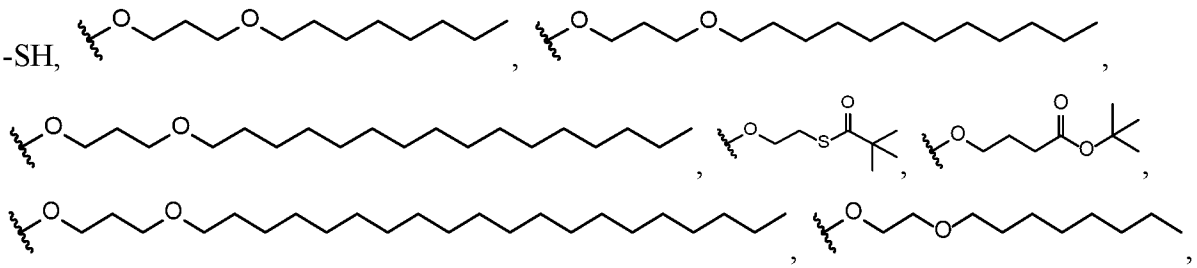
$Base^1$ and $Base^2$ each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl)$_2$, and $N(C_{3-6}$ cycloalkyl)$_2$;

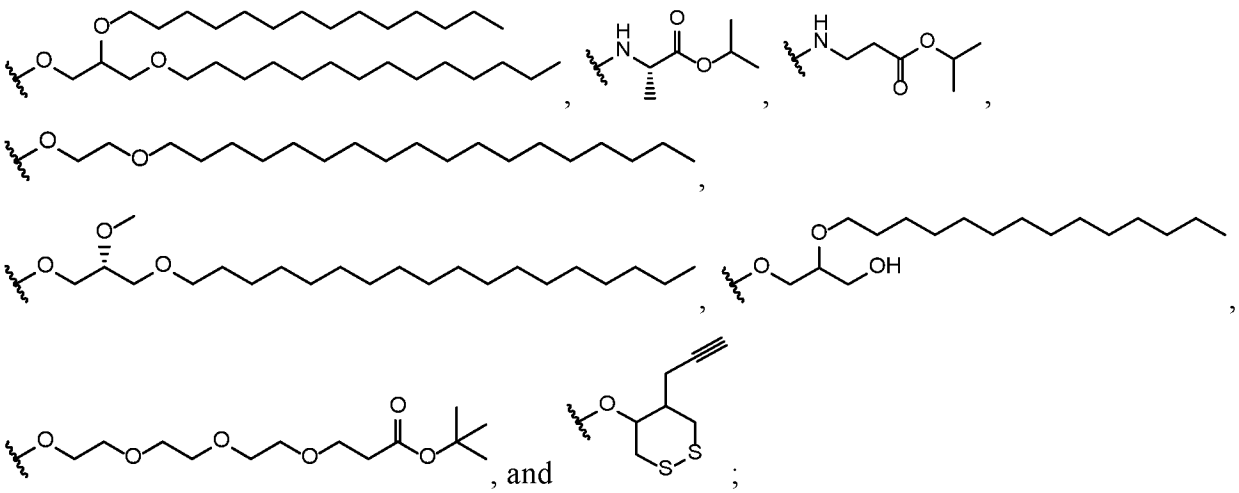
Y and Y^a are each independently selected from the group consisting of -O- and -S-;

X^a and X^{a1} are each independently selected from the group consisting of -O- and -S-;

X^b and X^{b1} are each independently selected from the group consisting of -O- and -S-;

X^c and X^{c1} are each independently selected from the group consisting of -OH, -SH,





X^d and X^{d1} are each independently selected from the group consisting of O and S;

R^1 and R^{1a} are each H;

R^2 and R^{2a} are each independently selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-CH_2CH_3$;

R^3 is selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-CH_2CH_3$;

R^4 and R^{4a} are each independently selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-CH_2CH_3$;

R^5 is selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-CH_2CH_3$;

R^6 and R^{6a} are each independently selected from the group consisting of H, F, Cl, I, Br, OH, CN, N_3, $-CF_3$, $-CH_3$, $-CH_2OH$, $-CH_2CH_3$, $-CH=CH_2$, $-C\equiv CH$, and $-C\equiv C-CH$;

R^7 and R^{7a} are each independently selected from the group consisting of H, $-CF_3$, $-CH_3$, and $-CH_2CH_3$;

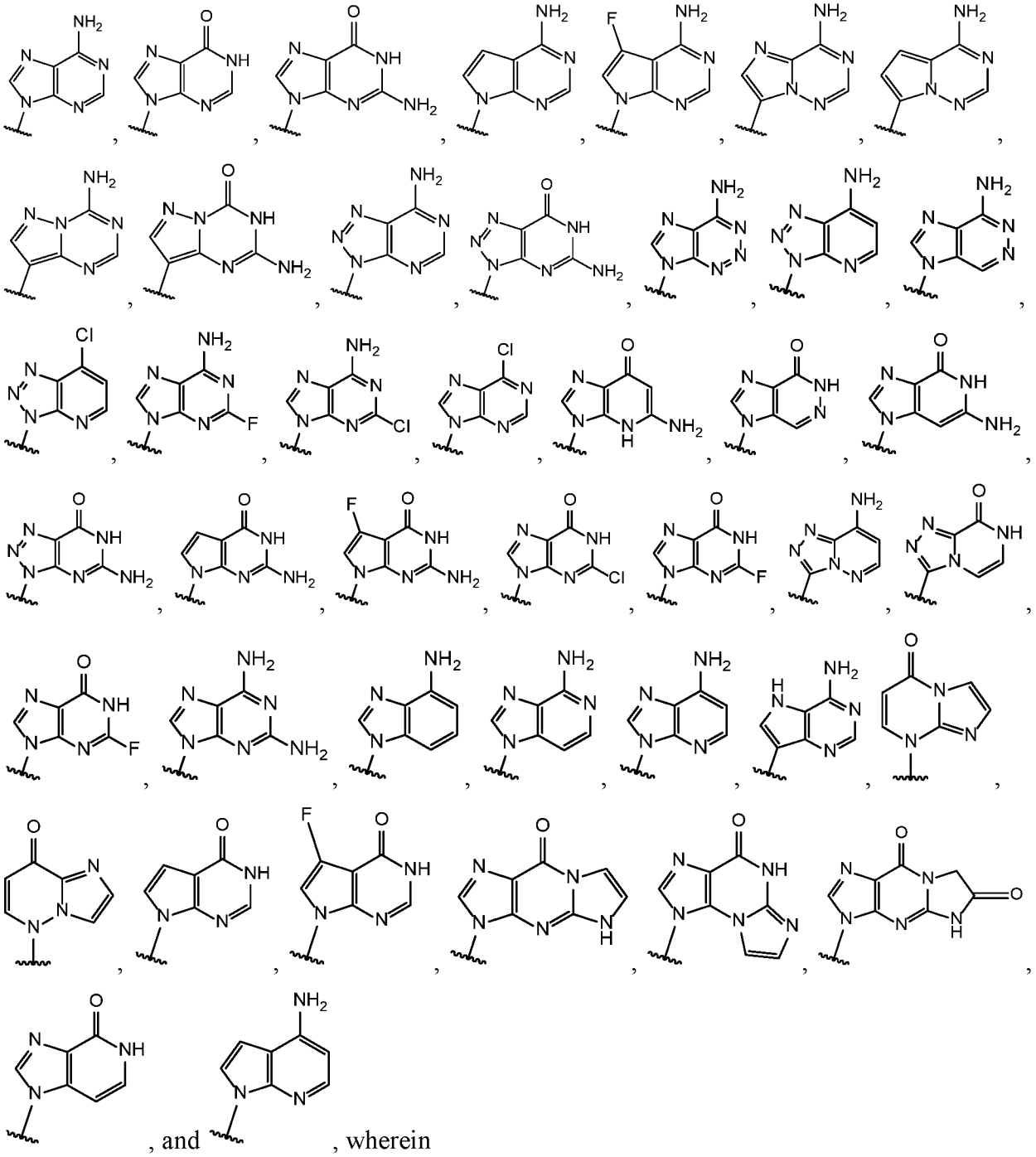
R^8 and R^{8a} are each independently selected from the group consisting of H, $-CF_3$, $-CH_3$, and $-CH_2CH_3$;

optionally R^3 and R^{6a} are connected to C_2-C_6 alkylene, C_2-C_6 alkenylene, -O-C_1-C_6 alkylene, or -O-C_2-C_6 alkenylene, such that where R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene or -O-C_2-C_6 alkenylene, said O is bound at the R^3 position; and

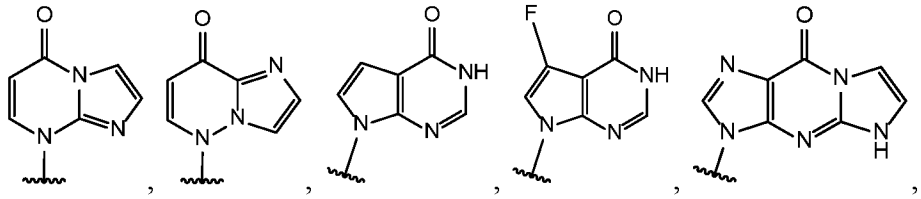
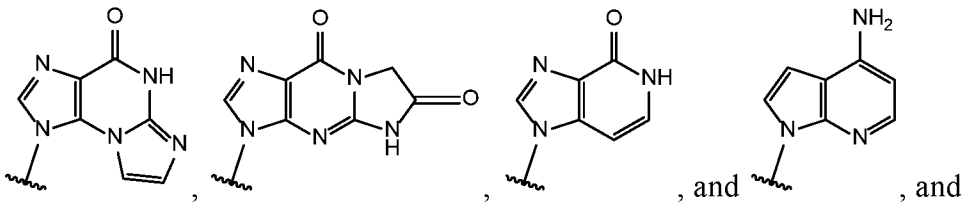
optionally R^5 and R^6 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, -O-C_1-C_6 alkylene, or -O-C_2-C_6 alkenylene, such that where R^5 and R^6 are connected to form -O-C_1-C_6 alkylene or -O-C_2-C_6 alkenylene, said O is bound at the R^5 position.

4. The compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein

$Base^1$ and $Base^2$ are each independently selected from the group consisting of



, and , wherein

at least one of $Base^1$ and $Base^2$ is each independently selected from the group consisting of  ,  , and , and

$Base^1$ and $Base^2$ each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl)$_2$, and $N(C_{3-6}$ cycloalkyl)$_2$;

Y and Y^a are each independently selected from the group consisting of -O- and -S-;

X^a and X^{a1} are each -O-;

X^b and X^{b1} are each -O-;

X^c and X^{c1} are each independently selected from the group consisting of -OH and -SH;

X^d and X^{d1} are each independently selected from the group consisting of O and S;

R^1 and R^{1a} are each H;

R^2 and R^{2a} are each independently selected from the group consisting of H, F, Cl, OH, CN, N_3, and $-CH_3$;

R^3 is selected from the group consisting of H, F, Cl, OH, CN, N_3, and $-CH_3$;

R^4 and R^{4a} are each independently selected from the group consisting of H, F, Cl, OH, CN, N_3, and $-CH_3$;

R^5 is selected from the group consisting of H, F, Cl, OH, CN, N_3, and $-CH_3$;

R^6 and R^{6a} are each independently selected from the group consisting of H, F, CN, N_3, $-CH_3$, $-CH=CH_2$, and $-C\equiv CH$;

R^7 and R^{7a} are each H;

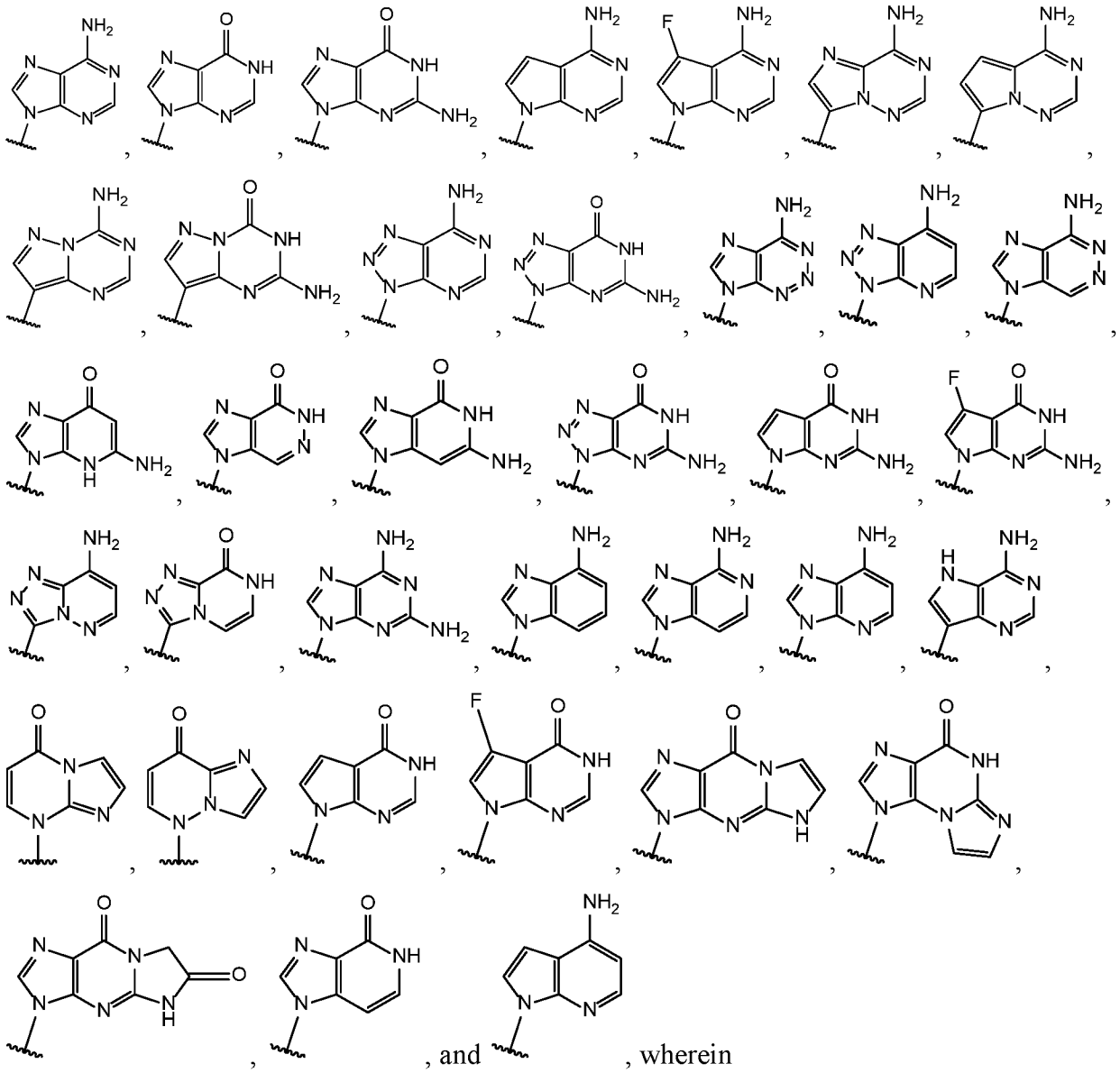
R^8 and R^{8a} are each H;

optionally R^3 and R^{6a} are connected to form $-O-C_1-C_6$ alkylene or $-O-C_2-C_6$ alkenylene, such that O is bound at the R^3 position; and

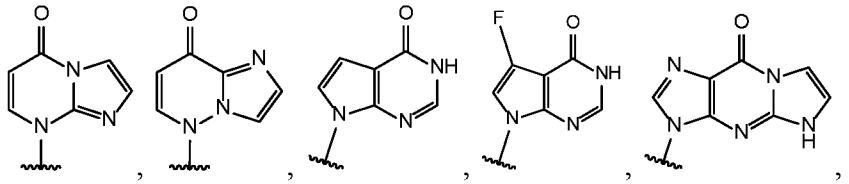
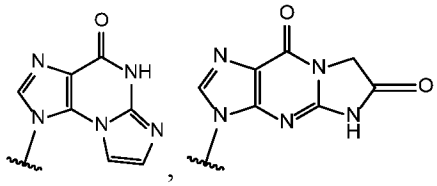
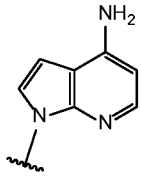
optionally R^5 and R^6 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, -O-C_1-C_6 alkylene, or -O-C_2-C_6 alkenylene, such that where R^5 and R^6 are connected to form -O-C_1-C_6 alkylene or -O-C_2-C_6 alkenylene, said O is bound at the R^5 position.

5. The compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein

$Base^1$ and $Base^2$ are each independently selected from the group consisting of



, and , wherein

at least one of $Base^1$ and $Base^2$ is each independently selected from the group consisting of  ,  , and  , and

$Base^1$ and $Base^2$ each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl)$_2$, and $N(C_{3-6}$ cycloalkyl)$_2$;

Y and Y^a are each independently selected from the group consisting of -O- and -S-;

X^a and X^{a1} are each O;

X^b and X^{b1} are each O;

X^c and X^{c1} are each independently selected from the group consisting of -OH and -SH;

X^d and X^{d1} are each independently selected from the group consisting of O and S;

R^1 and R^{1a} are each H;

R^2 and R^{2a} are each independently selected from the group consisting of H, F, Cl, OH, CN, N_3, and $-CH_3$;

R^3 is selected from the group consisting of H, F, Cl, OH, CN, N_3, and $-CH_3$;

R^4 and R^{4a} are each independently selected from the group consisting of H, F, Cl, OH, CN, N_3, and CH_3;

R^5 is selected from the group consisting of H, F, Cl, OH, CN, N_3, and $-CH_3$;

R^6 and R^{6a} are each independently selected from the group consisting of H, F, CN, N_3, $-CH_3$, $-CH=CH_2$, and $-C\equiv CH$;

R^7 and R^{7a} are each H;

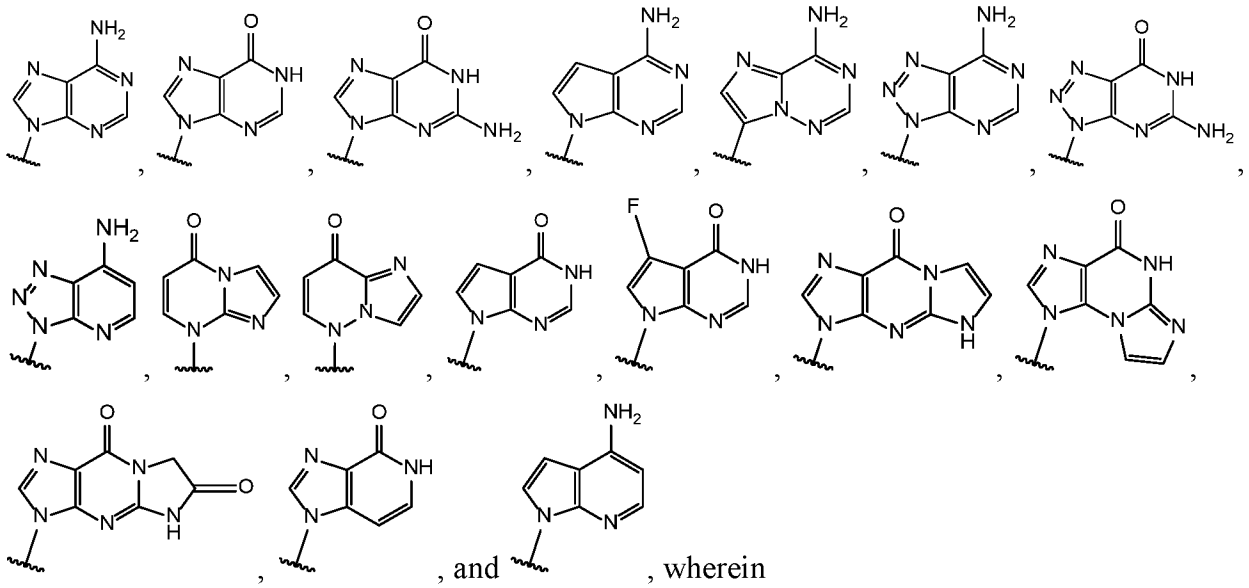
R^8 and R^{8a} are each H;

optionally R^3 and R^{6a} are connected to form $-O-C_1-C_6$ alkylene or $-O-C_2-C_6$ alkenylene, such that where R^3 and R^{6a} are connected to form $-O-C_1-C_6$ alkylene or $-O-C_2-C_6$ alkenylene, said O is bound at the R^3 position; and

optionally R^5 and R^6 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, -O-C_1-C_6 alkylene, or -O-C_2-C_6 alkenylene, such that where R^5 and R^6 are connected to form -O-C_1-C_6 alkylene or -O-C_2-C_6 alkenylene, said O is bound at the R^5 position.

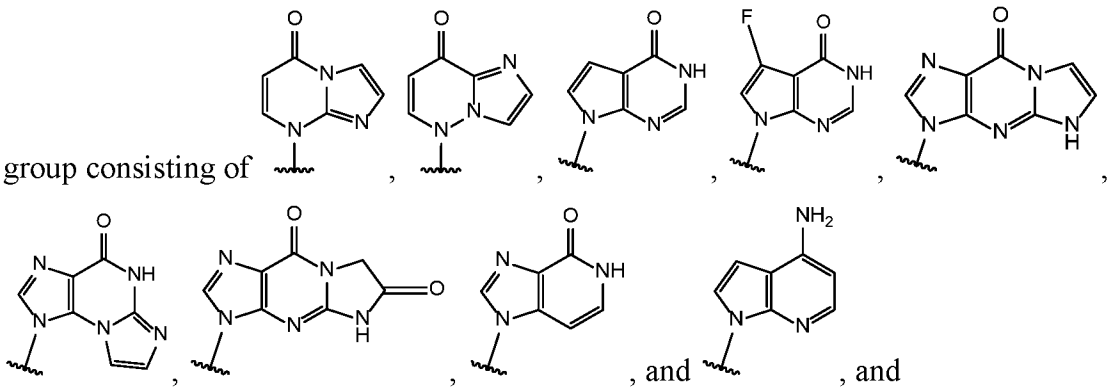
6. The compound according to any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein

$Base^1$ and $Base^2$ are each independently selected from the group consisting of



, and , wherein

at least one of $Base^1$ and $Base^2$ is each independently selected from the group consisting of



, and , and

$Base^1$ and $Base^2$ each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, O(C_{1-3} alkyl), O(C_{3-6} cycloalkyl), S(C_{1-3} alkyl), S(C_{3-6} cycloalkyl), NH(C_{1-3} alkyl), NH(C_{3-6} cycloalkyl), N(C_{1-3} alkyl)$_2$, and N(C_{3-6} cycloalkyl)$_2$;

Y and Y^a are each independently selected from the group consisting of -O- and -S-;

X^a and X^{a1} are each -O-;

X^b and X^{b1} are each -O-;

X^c and X^{c1} are each independently selected from the group consisting of -SH and -OH;

X^d and X^{d1} are each independently selected from the group consisting of O and S;

R^1 and R^{1a} are each H;

R^2 and R^{2a} are each independently selected from the group consisting of H, F, and OH;

R^3 is selected from the group consisting of H, F, and OH;

R^4 and R^{4a} are each independently selected from the group consisting of H, F, and OH;

R^5 is selected from the group consisting of H, F, and OH;

R^6 and R^{6a} are each H;

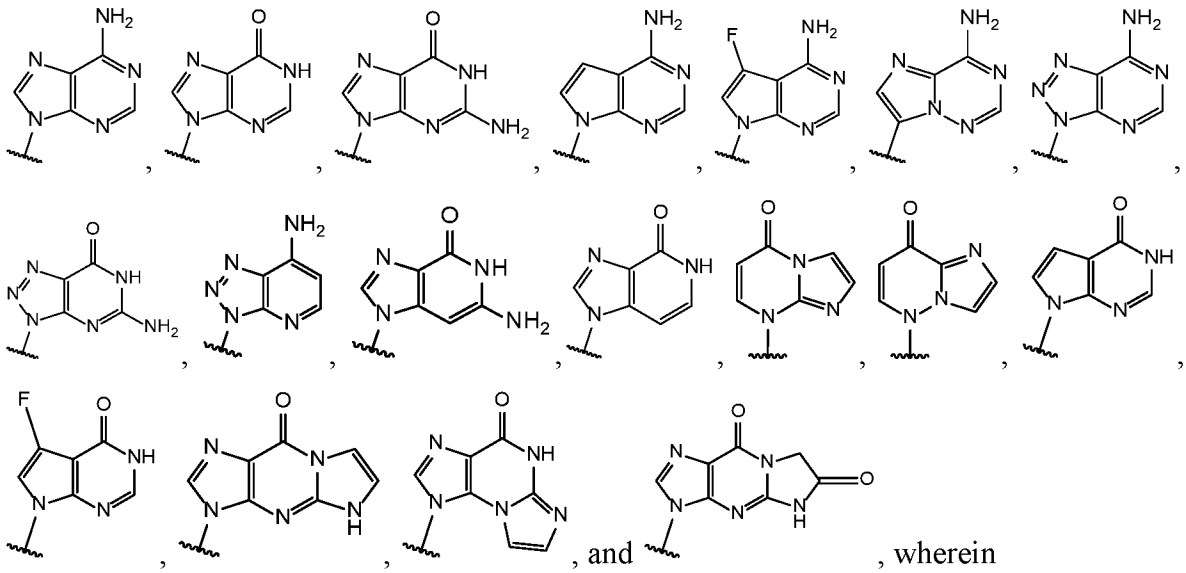
R^7 and R^{7a} are each H;

R^8 and R^{8a} are each H; and

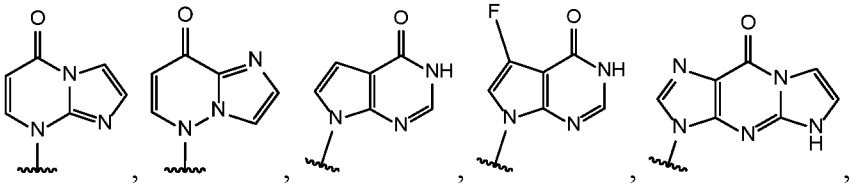
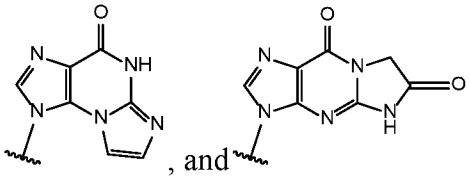
optionally R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene or -O-C_2-C_6 alkenylene, such that where R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene or -O-C_2-C_6 alkenylene, said O is bound at the R^3 position.

7. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

$Base^1$ and $Base^2$ are each independently selected from the group consisting of



, wherein

at least one of $Base^1$ and $Base^2$ is each independently selected from the group consisting of  ,  , and , and

$Base^1$ and $Base^2$ each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl)$_2$, and $N(C_{3-6}$ cycloalkyl)$_2$;

Y and Y^a are each independently selected from the group consisting of -O- and -S-;

X^a and X^{a1} are each -O-;

X^b and X^{b1} are each -O-;

X^c and X^{c1} are each independently selected from the group consisting of -SH and -OH;

X^d and X^{d1} are each independently selected from the group consisting of O and S;

R^1 and R^{1a} are each H;

R^2 is H;

R^{2a} is selected from the group consisting of H, F, and OH;

R^3 is selected from the group consisting of H, F, and OH;

R^4 is selected from the group consisting of H, F, and OH;

R^{4a} is H;

R^5 is selected from the group consisting of H, F, and OH;

R^6 and R^{6a} are each H;

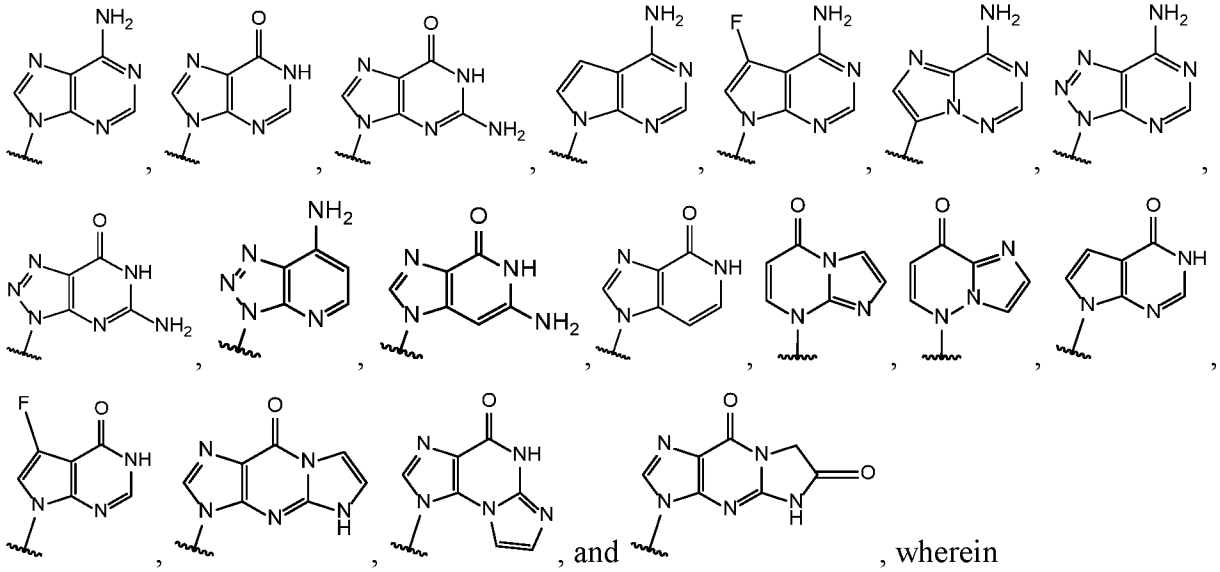
R^7 and R^{7a} are each H;

R^8 and R^{8a} are each H; and

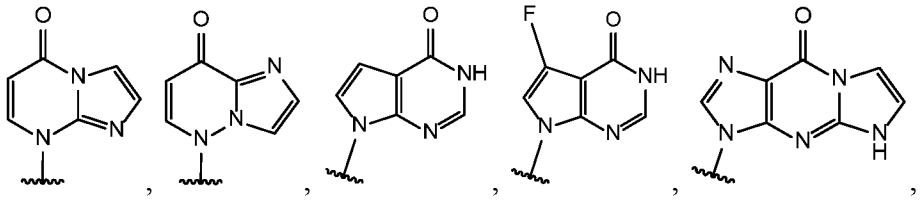
optionally R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, such that where R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, said O is bound at the R^3 position.

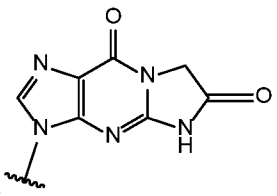
8. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

$Base^1$ and $Base^2$ are each independently selected from the group consisting of



, and , wherein at least one of $Base^1$ and $Base^2$ is each independently selected from the group consisting of



, and  , and

$Base^1$ and $Base^2$ each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl)$_2$, and $N(C_{3-6}$ cycloalkyl)$_2$;

Y and Y^a are each independently selected from the group consisting of -O- and -S-;

X^a and X^{a1} are each -O-;

X^b and X^{b1} are each -O-;

X^c and X^{c1} are each independently selected from the group consisting of -SH and -OH;

X^d and X^{d1} are each independently selected from the group consisting of O and S;

R^1 and R^{1a} are each H;

R^2 is H;

R^{2a} is selected from the group consisting of H, F, and OH;

R^3 is selected from the group consisting of H, F, and OH;

R^4 is selected from the group consisting of H, F, and OH;

R^{4a} is H;

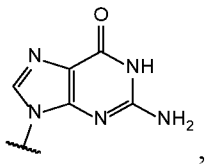
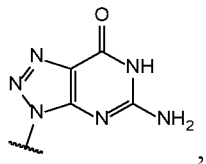
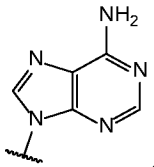
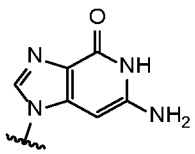
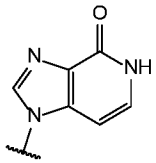
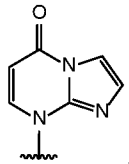
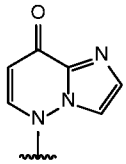
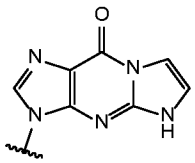
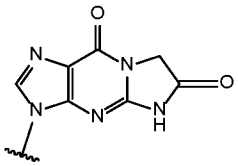
R^5 is selected from the group consisting of H, F, and OH;

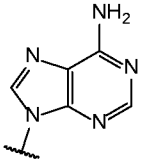
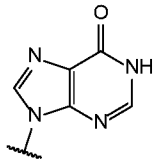
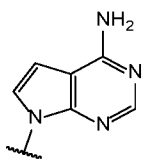
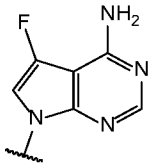
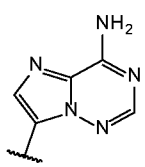
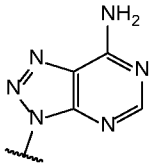
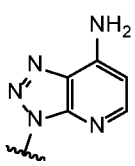
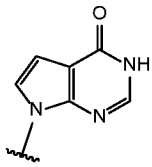
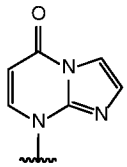
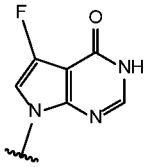
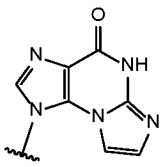
R^6 and R^{6a} are each H;

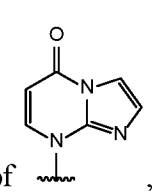
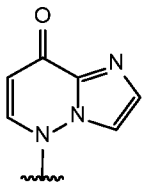
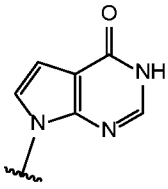
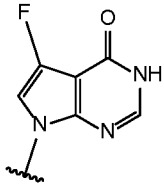
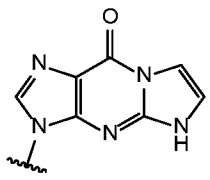
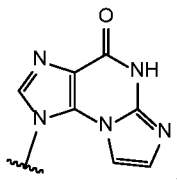
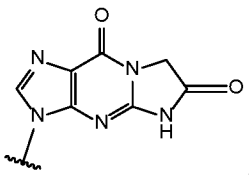
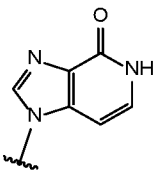
R^7 and R^{7a} are each H; and

R^8 and R^{8a} are each H.

9. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

$Base^1$ is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  , and  ;

Base^2 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  ;

at least one of Base^1 and Base^2 is each independently selected from the group consisting of  ,  ,  ,  ,  ,  ,  , and  , and Base^1 and Base^2 each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl)$_2$, and $N(C_{3-6}$ cycloalkyl)$_2$;

Y and Y^a are each independently selected from the group consisting of -O- and -S-;

X^a and X^{a1} are each -O-;

X^b and X^{b1} are each -O-;

X^c and X^{c1} are each independently selected from the group consisting of -SH and -OH;

X^d and X^{d1} are each independently selected from the group consisting of O and S;

R^1 and R^{1a} are each H;

R^2 is H;

R^{2a} is selected from the group consisting of H, F, and OH;

R^3 is selected from the group consisting of H, F, and OH;

R^4 is selected from the group consisting of H, F, and OH;

R^{4a} is H;

R^5 is selected from the group consisting of H, F, and OH;

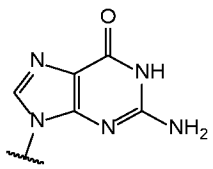
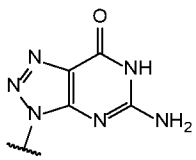
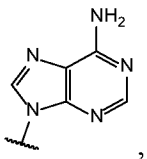
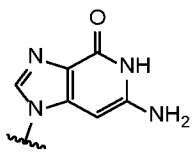
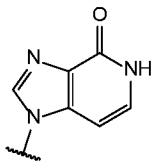
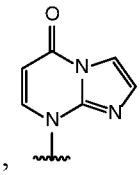
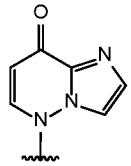
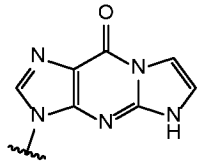
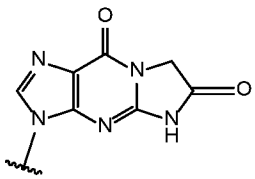
R^6 and R^{6a} are each H;

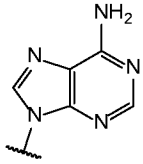
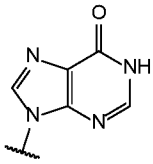
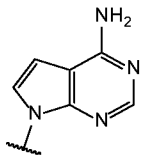
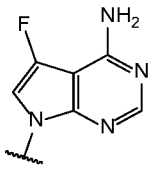
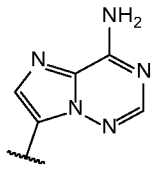
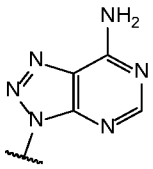
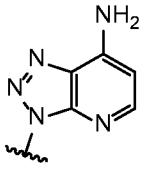
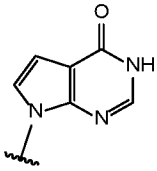
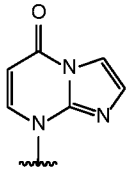
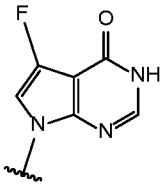
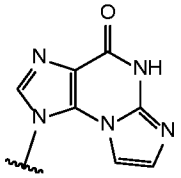
R^7 and R^{7a} are each H;

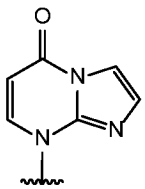
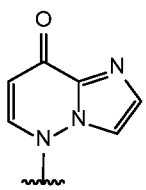
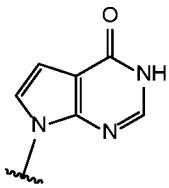
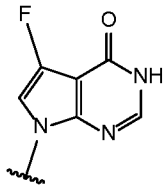
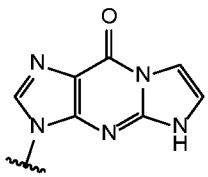
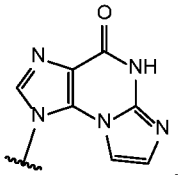
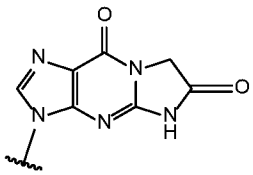
R^8 and R^{8a} are each H; and

R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, such that where R^3 and R^{6a} are connected to form -O-C_1-C_6 alkylene, said O is bound at the R^3 position.

10. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

$Base^1$ is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  , and  ;

Base^2 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  ;

at least one of Base^1 and Base^2 is each independently selected from the group consisting of  ,  ,  ,  ,  ,  ,  , and  , and Base^1 and Base^2 each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl)$_2$, and $N(C_{3-6}$ cycloalkyl)$_2$;

Y and Y^a are each independently selected from the group consisting of -O- and -S-;

X^a and X^{a1} are each -O-;

X^b and X^{b1} are each -O-;

X^c and X^{c1} are each independently selected from the group consisting of -SH and -OH;

X^d and X^{d1} are each independently selected from the group consisting of O and S;

R^1 and R^{1a} are each H;

R^2 is H;

R^{2a} is selected from the group consisting of H, F, and OH;

R^3 is selected from the group consisting of H, F, and OH;

R^4 is selected from the group consisting of H, F, and OH;

R^{4a} is H;

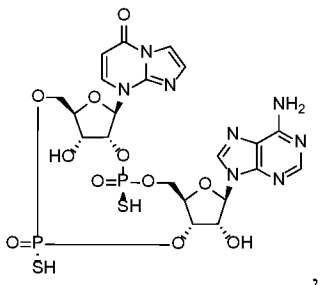
R^5 is selected from the group consisting of H, F, and OH;

R^6 and R^{6a} are each H;

R^7 and R^{7a} are each H; and

R^8 and R^{8a} are each H.

11. A compound selected from the group consisting of: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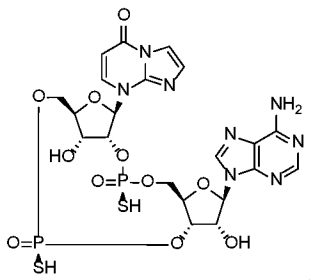
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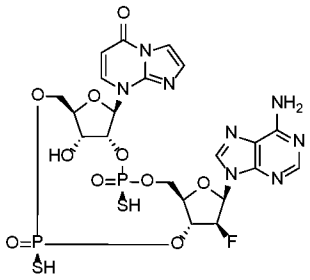
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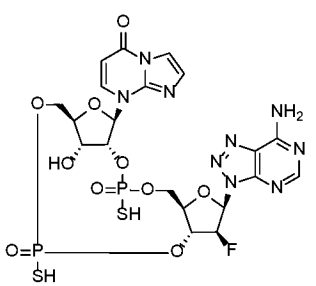
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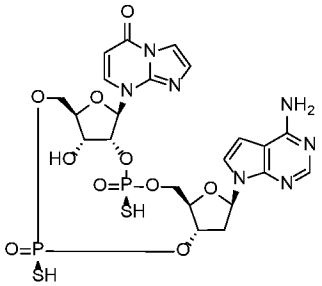
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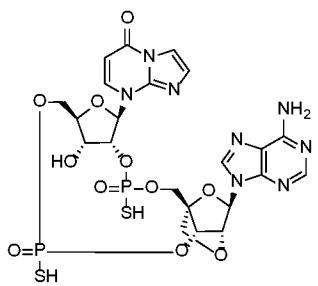
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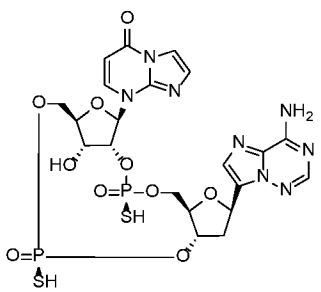
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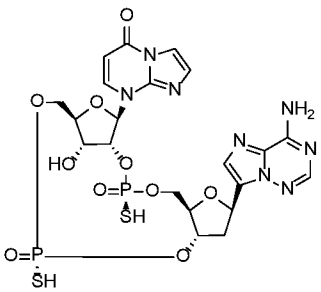
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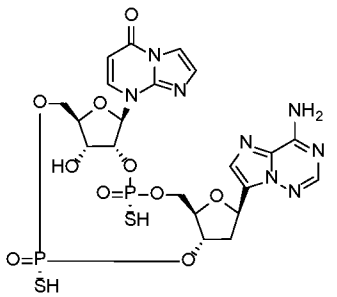
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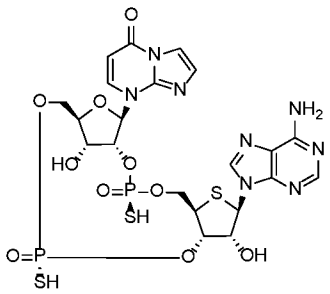
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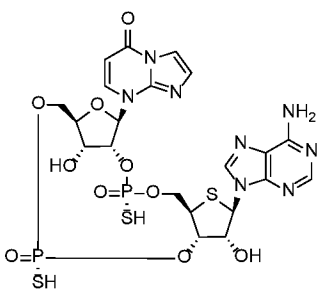
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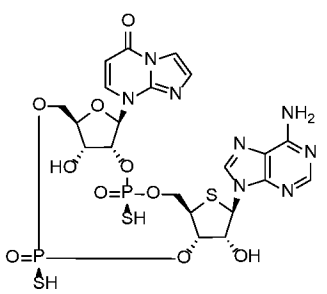
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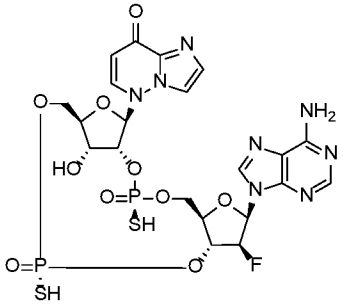
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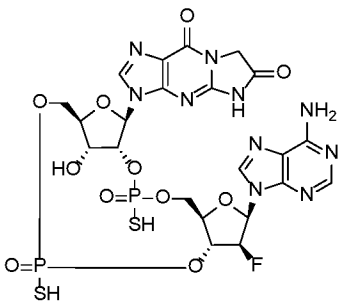
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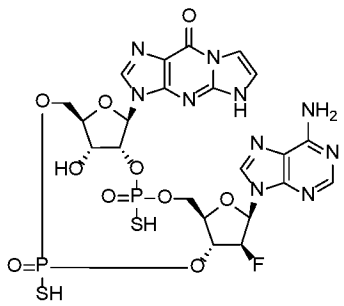
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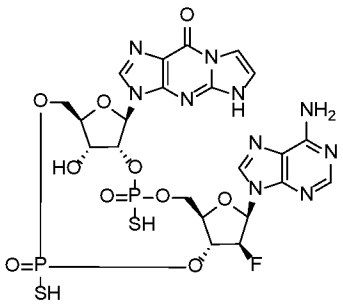
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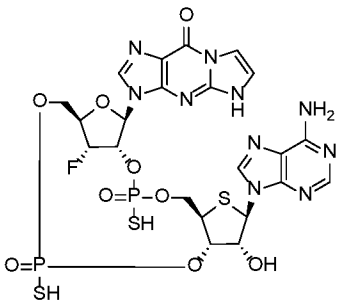
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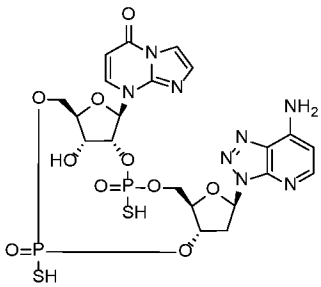
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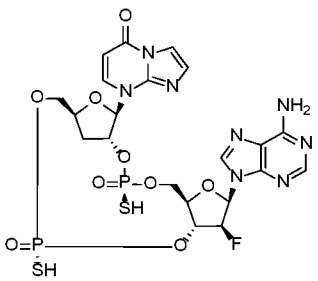
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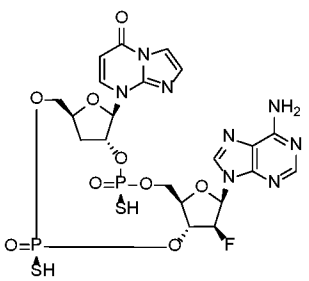
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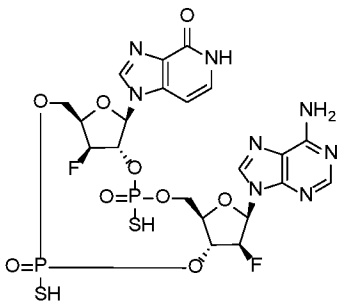
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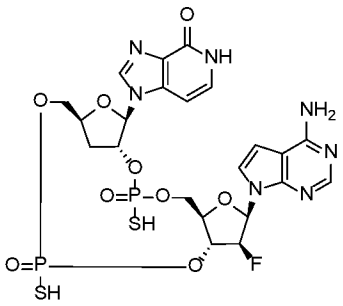
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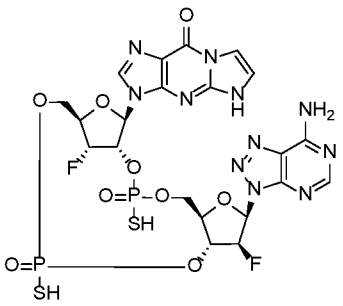
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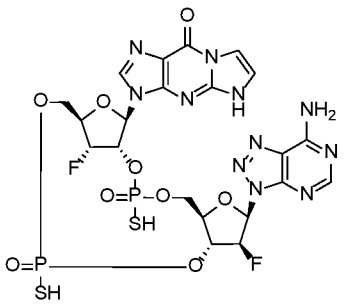
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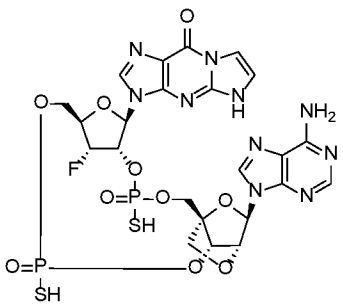
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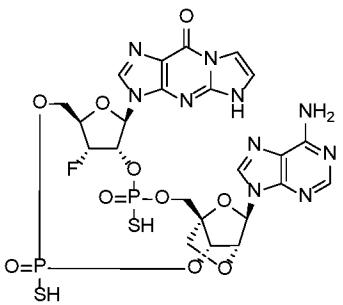
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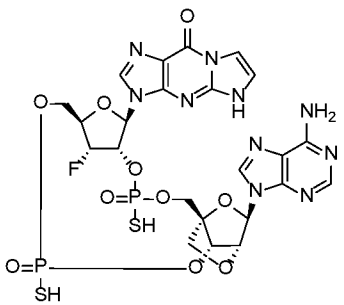
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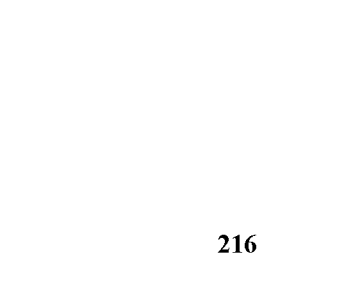
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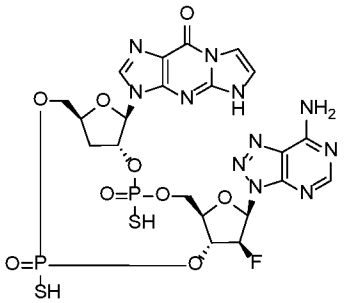
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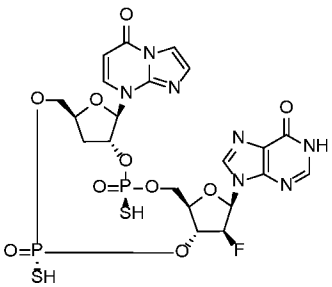
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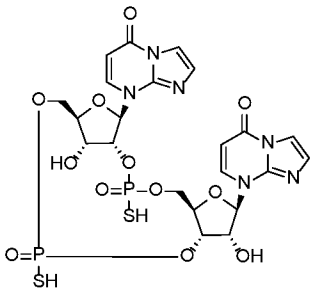
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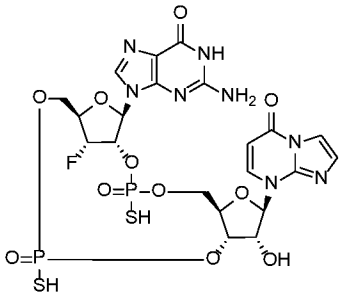
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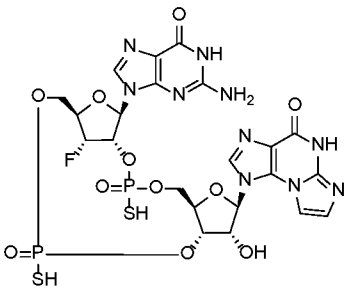
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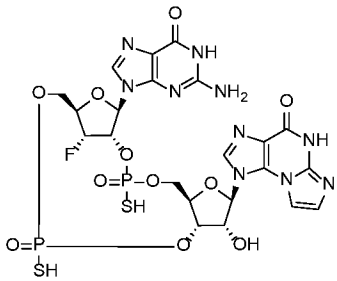
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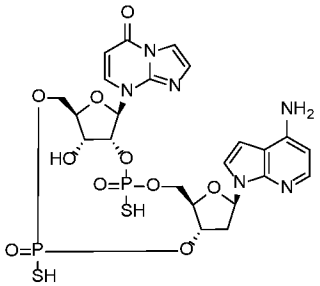
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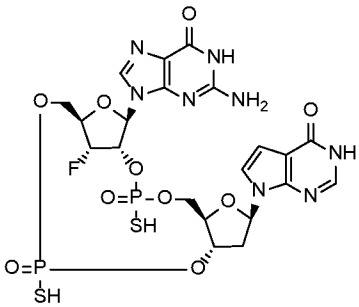
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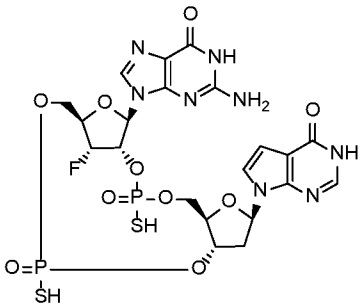
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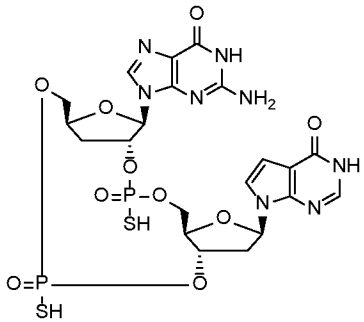
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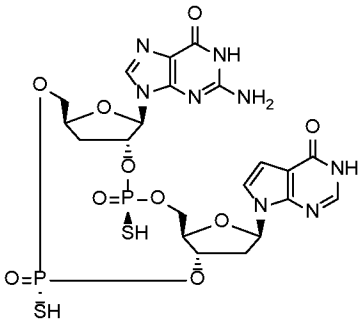
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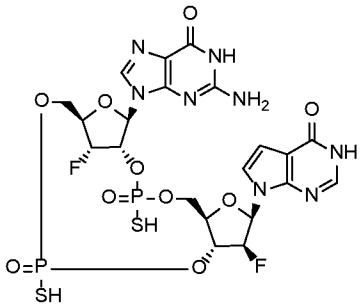
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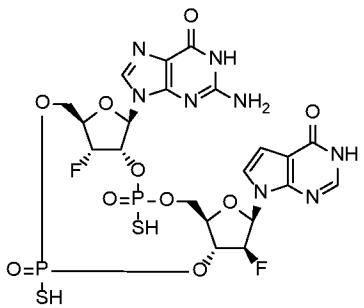
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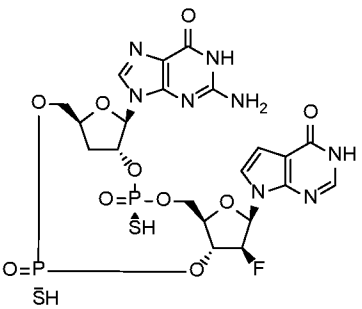
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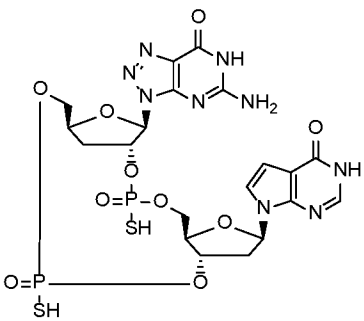
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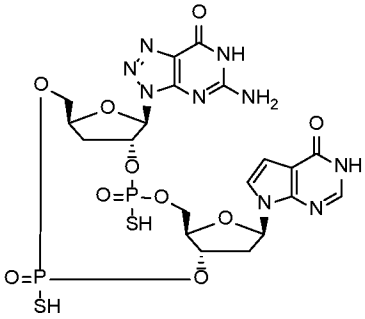
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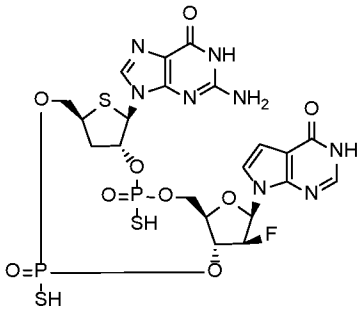
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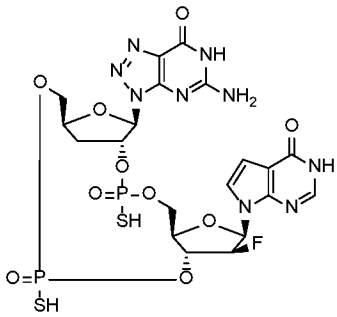
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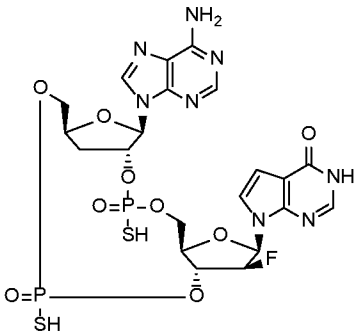
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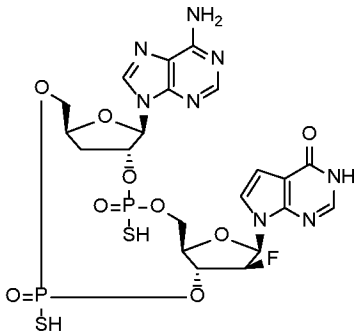
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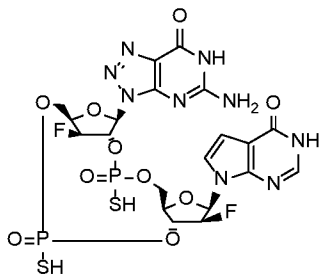
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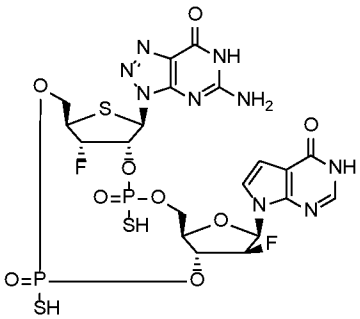
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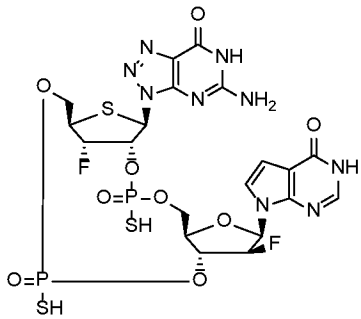
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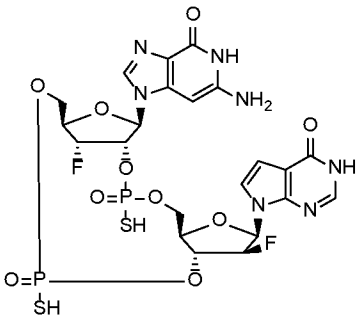
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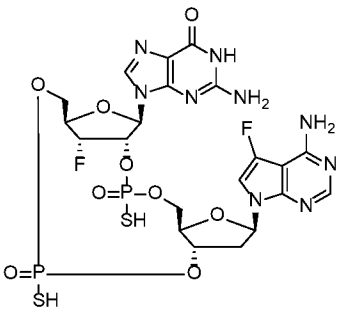
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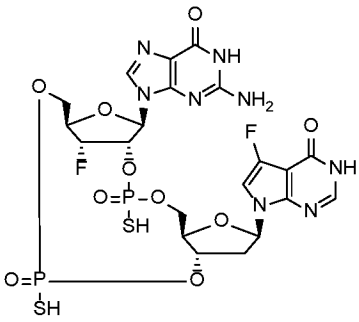
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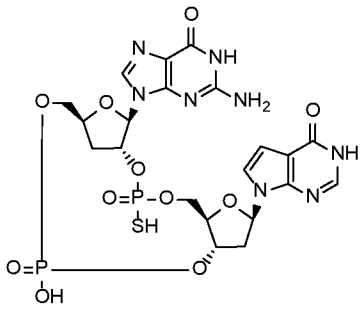
, and

pharmaceutically acceptable salts thereof.

12. A pharmaceutical composition, said pharmaceutical composition comprising:

(a) a compound according to any one of claims 1 to 11 or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof; and

(b) a pharmaceutically acceptable carrier.

13. A method of inducing an immune response in a subject, said method comprising administering a therapeutically effective amount of a compound according to any one of claims 1 to 11 to the subject.

14. A method of inducing an immune response in a subject, said method comprising administering a therapeutically effective amount of a pharmaceutical composition according to claim 12 to the subject.

15. A method of inducing a STING-dependent type I interferon production in a subject, said method comprising administering a therapeutically effective amount of a compound according to any one of claims 1 to 11 to the subject.

16. A method of inducing a STING-dependent type I interferon production in a subject, said method comprising administering a therapeutically effective amount of a pharmaceutical composition according to claim 12 to the subject.

17. A method of treating a cell proliferation disorder in a subject, said method comprising administering a therapeutically effective amount of a compound according to any one of claims 1 to 11 to the subject.

18. The method of claim 17, wherein the cell proliferation disorder is cancer.

19. A method of treating a cell proliferation disorder in a subject, said method comprising administering a therapeutically effective amount of a pharmaceutical composition according to claim 1 to the subject.

20. The method of claim 19, wherein the cell proliferation disorder is cancer.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/65902

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/7084, A61P 35/00, C07H 21/00 (2019.01)
CPC - A61K 31/706, A61K 31/7064, A61K 31/7076

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2017/161349 A1 (Immune Sensor, Llc) 21 September 2017 (21.09.2017); p15	1-3, 7-10
A	WO 2017/075477 A1 (Aduro Biotech, Inc.) 04 May 2017 (04.05.2017); p11	1-3, 7-10
A	US 2017/0044206 A1 (Merck Sharp & Dohme Corp.) 16 February 2017 (16.02.2017); p47	1-3, 7-10
A	WO 2017/093933 A1 (Glaxosmithkline Intellectual Property Development Limited) 08 June 2017 (08.06.2017); entire document	1-3, 7-10
A	WO 2017/186711 A1 (Invivogen) 02 November 2017 (02.11.2017); entire document	1-3, 7-10
A	PubChem CID 126584781, create date: 22 April 2017 (22.04.2017) page 4	1-3, 7-10
P/A	WO 2018/100558 A2 (Takeda Pharmaceutical Company Limited) 07 June 2018 (07.06.2018); entire document	1-3, 7-10
P/A	WO 2018/208667 A1 (Merck Sharp & Dohme Corp.) 15 November 2018 (15.11.2018); entire document	1-3, 7-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 February 2019	30 APR 2019
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/65902

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-6, 12-18
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Supplemental Box

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-3, 7-10

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 18/65902

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I+: Claims 1-3, and 7-11 directed to a compound of formula (I) or a pharmaceutically acceptable salt thereof. The compound of formula (I) will be searched to the extent that it encompasses the compound of formula (I), wherein Base1 is the 1st group of the 1st row in page 194 and Base2 is the 5th group of the 3rd row in page 195; at least one of Base1 and Base2 is the 1st group of the 1st row in page 195; Y and Ya are -O-; Xa and Xa1 are -O-; Xb and Xb1 are -O-; Xc and Xc1 are -SR9; Xd and Xd1 are O; R1 and R1a are H; R2 and R2a are H; R3 is H; R4 and R4a are H; R5 is H; R6 and R6a are H; R7 and R7a are H; R8 and R8a are H; and R9 is H. It is believed that claims 1-3(in part), and 7-10(in part) read on this first named invention, and thus these claims will be searched without fee. Applicant is invited to elect additional compounds of claim 1, wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be the compound of formula (I), wherein Base1 is the 5th group of the 3rd row in page 195 and Base2 is the 1st group of the 1st row in page 194; at least one of Base1 and Base2 is the 1st group of the 1st row in page 195; Y and Ya are -O-; Xa and Xa1 are -O-; Xb and Xb1 are -O-; Xc and Xc1 are -SR9; Xd and Xd1 are O; R1 and R1a are H; R2 and R2a are H; R3 is OH; R4 and R4a are H; R5 is OH; R6 and R6a are H; R7 and R7a are H; R8 and R8a are H; and R9 is H (i.e., claims 1-3(in part), and 7-11(in part)).

Group II: claims 19-20 directed to a method of treating a cell proliferation disorder in a subject, said method comprising administering a therapeutically effective amount of a pharmaceutical composition
according to claim 1 to the subject

The group of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I+ includes the technical feature of a unique compound of formula (I) in claim 1 containing the same, which is not required by any other invention of Group I+.

Group II includes the technical feature of a method of treating a cell proliferation disorder in a subject, said method comprising administering a therapeutically effective amount of a pharmaceutical composition, not required by Group I+.

Common technical features:

The inventions of Group I+ share the technical feature of a compound of formula (I) containing the same.

Groups I+ and II share the technical feature of a compound of formula (I) in claim 1.

These shared technical features, however, do not provide a contribution over the prior art, as being anticipated by PubChem CID 126584781 (hereinafter 'CID'). CID discloses a compound of formula (I) wherein Base1 is the 5th group of the 4th row in page 195 and Base2 is the 6th group of the 2nd row in page 195; at least one of Base1 and Base2 is the 3rd group of the 2nd row in page 195; Y and Ya are -O-; Xa and Xa1 are -O-; Xb and Xb1 are -O-; Xc and Xc1 are -OR9; Xd and Xd1 are O; R1 and R1a are H; R2 and R2a are H; R3 is OH; R4 is OH and R4a is H; R5 is H; R6 and R6a are H; R7 and R7a are H; R8 and R8a are H; and R9 is H (p4, "2D Structure").

As said compound and compositions were known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the inventions of Groups I+ and II. The inventions of Group I+ and II thus lack unity under PCT Rule 13.

Note:
claims 4-6, and 12-18 determined unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).