US 20180244712A1

(19) **United States**

(12) **Patent Application Publication**

Altman et al.

(10) **Pub. No.: US 2018/0244712 A1**

(43) **Pub. Date: Aug. 30, 2018**

(54) **CYCLIC DI-NUCLEOTIDE COMPOUNDS AS STING AGONISTS**

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(21) Appl. No.: **15/886,568**

(22) Filed: **Feb. 1, 2018**

Related U.S. Application Data

(63) Continuation of application No. 15/234,182, filed on Aug. 11, 2016.

(60) Provisional application No. 62/356,125, filed on Jun. 29, 2016, provisional application No. 62/268,723, filed on Dec. 17, 2015, provisional application No. 62/204,677, filed on Aug. 13, 2015.

Publication Classification

(51) **Int. Cl.**

C07H 21/04	(2006.01)
C07H 21/02	(2006.01)
C07H 21/00	(2006.01)
C07H 19/23	(2006.01)
C07H 19/20	(2006.01)
A61K 39/39	(2006.01)
A61K 31/7084	(2006.01)
A61K 31/708	(2006.01)
A61K 31/7076	(2006.01)
A61K 31/7064	(2006.01)
A61K 31/706	(2006.01)

(52) **U.S. Cl.**

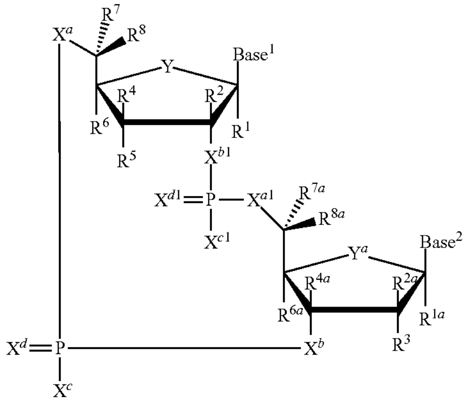
CPC ***C07H 21/04*** (2013.01); ***C07H 21/02*** (2013.01); ***C07H 21/00*** (2013.01); ***C07H 19/23*** (2013.01);

(Continued)

(57) **ABSTRACT**

A class of polycyclic compounds of general formula (I), of general formula (I'), or of general formula (I''), wherein $Base^1$, $Base^2$, 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, and R^{8a} 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.

(I)



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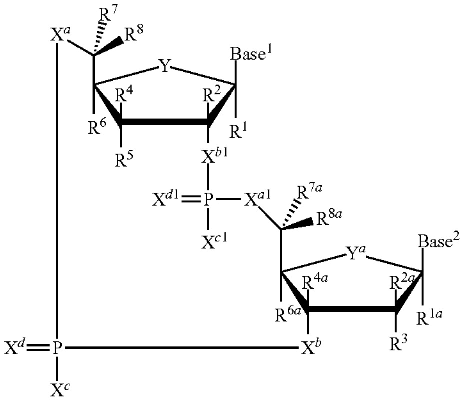

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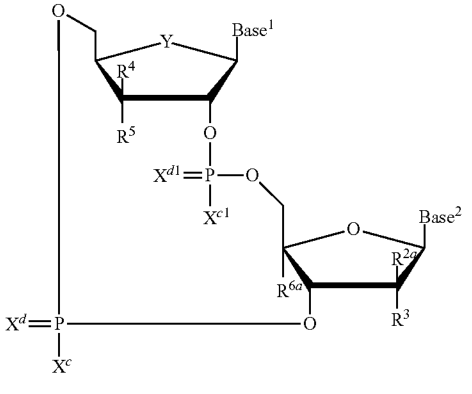


Specification includes a Sequence Listing.

(52) **U.S. Cl.**
CPC ***C07H 19/20*** (2013.01); *A61K 31/706* (2013.01); *A61K 31/7084* (2013.01); *A61K 31/708* (2013.01); *A61K 31/7076* (2013.01); *A61K 31/7064* (2013.01); ***A61K 39/39*** (2013.01)

CYCLIC DI-NUCLEOTIDE COMPOUNDS AS STING AGONISTS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/204,677, filed Aug. 13, 2015, U.S. Provisional Patent Application No. 62/268,723, filed Dec. 17, 2015, and U.S. Provisional Patent Application No. 62/356,125, filed Jun. 29, 2016.

FIELD OF THE INVENTION

[0002] 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.

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 antigens not naturally expressed in the host as foreign 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.

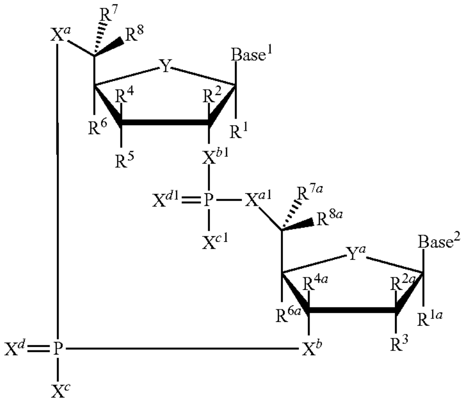
[0009] Type I interferons can significantly enhance anti-tumor immune responses by inducing activation of both the adaptive and innate immune cells. Finally, tumor invasiveness may be inhibited by interferons by modulating enzyme expression related to tissue remodeling.

[0010] 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 today's anti-tumor therapy landscape.

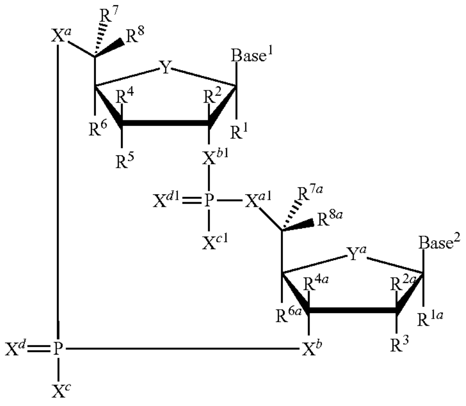
SUMMARY OF THE INVENTION

[0011] The present disclosure relates to novel cyclic di-nucleotide compounds of general formula (I), general formula (I'), and/or general formula (I"). In particular, the present disclosure relates to compounds having the general structural formula (I):

(I)

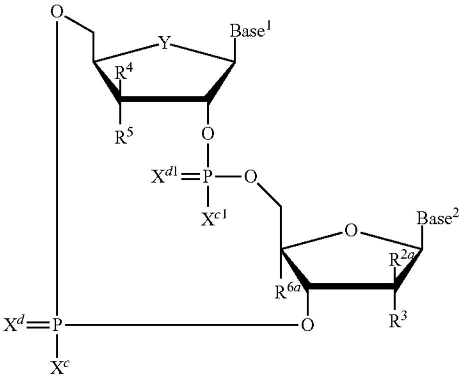


or pharmaceutically acceptable salts, hydrates, solvates, or prodrugs thereof, as described herein. The present disclosure also relates to compounds having general structural formula (I'):



(I')

or pharmaceutically acceptable salts, hydrates, solvates, or prodrugs thereof, as described herein. The present disclosure also relates to compounds having general structural formula (I''):



(I'')

or pharmaceutically acceptable salts, hydrates, solvates, or prodrugs thereof, as described herein.

[0012] Embodiments of the disclosure include compounds of general formula (I), compounds of general formula (I'), and/or 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), compounds of general formula (I'), and/or compounds of general formula (I''), and pharmaceutically acceptable salts, hydrates, solvates, or prodrugs thereof. Uses of compounds of general formula (I), compounds of general formula (I'), and/or compounds of general formula (I'') are also disclosed.

[0013] Other embodiments, aspects and features of the present disclosure are either further described in or will be apparent from the ensuing description, examples and appended claims.

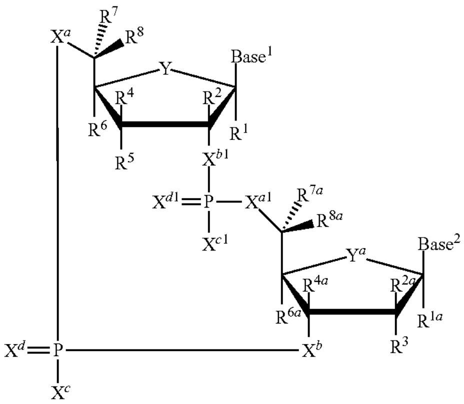
BRIEF DESCRIPTION OF THE DRAWINGS

[0014] Not Applicable

DETAILED DESCRIPTION OF THE INVENTION

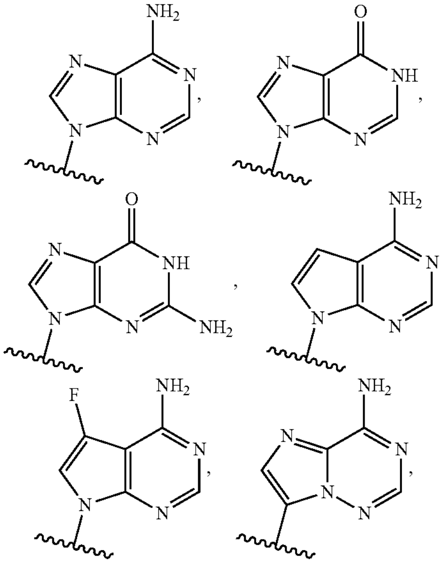
[0015] The present disclosure includes compounds of general formula (I), compounds of general formula (I'), and/or compounds of general formula (I'') above, and pharmaceutically acceptable salts, hydrates, solvates, or prodrugs thereof. These compounds and their pharmaceutically acceptable salts, hydrates, solvates, and/or prodrugs are useful as agents to induce interferon production.

[0016] A first embodiment of the disclosure relates to cyclic di-nucleotide compounds of general formula (I):



(I)

or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, wherein Base^1 and Base^2 are each independently selected from the group consisting of,



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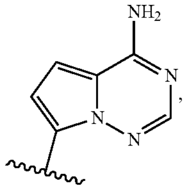
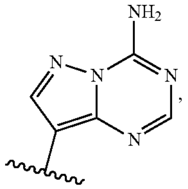
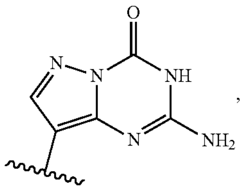
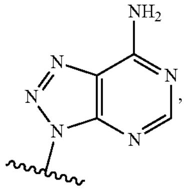
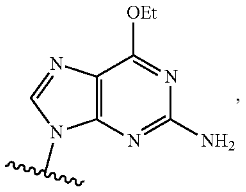
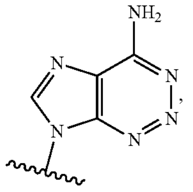
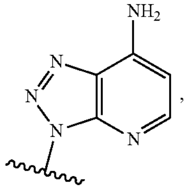
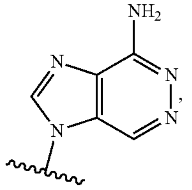
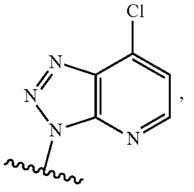
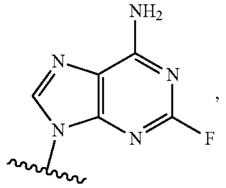
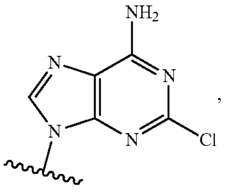
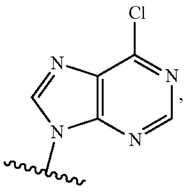
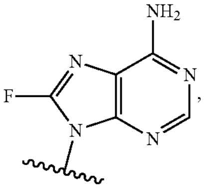
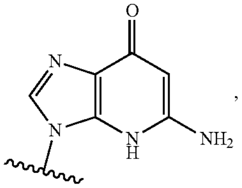
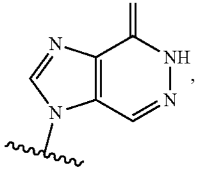
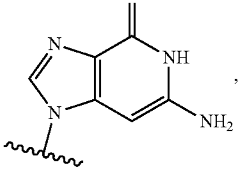

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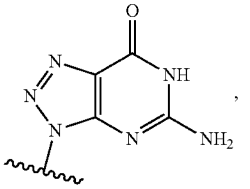
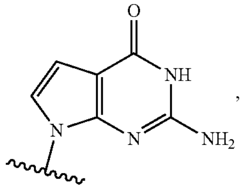
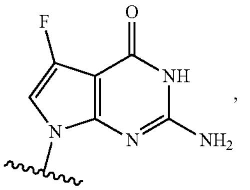
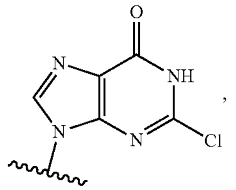
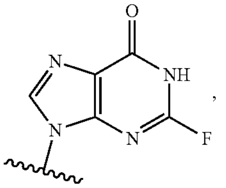
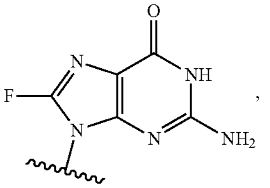
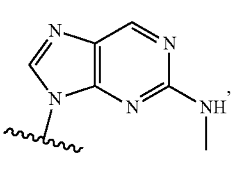
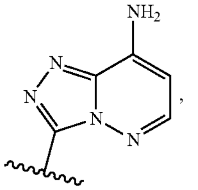
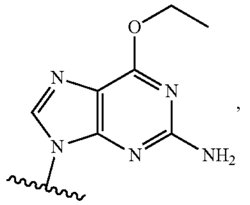
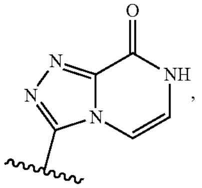
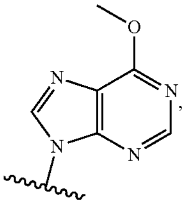
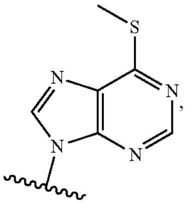
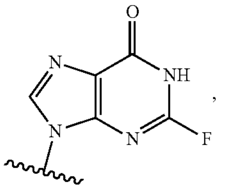
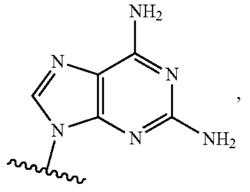
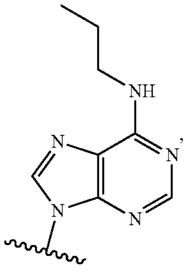
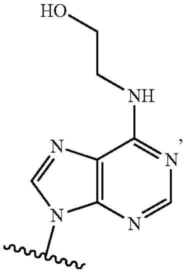
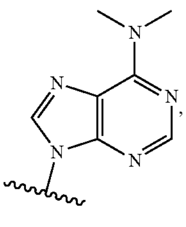

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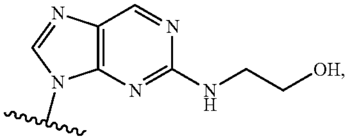

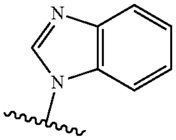

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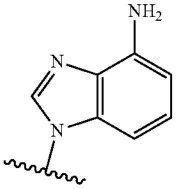

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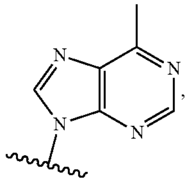

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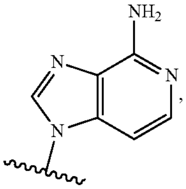

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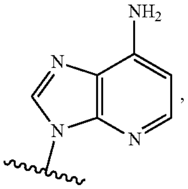

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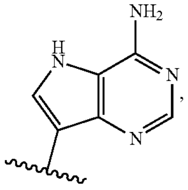

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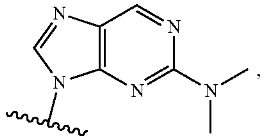

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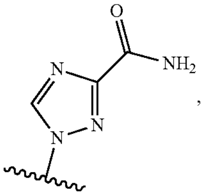

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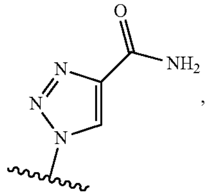

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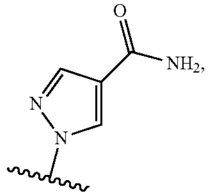
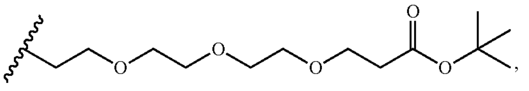


where Base^1 and Base^2 each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH$_2$, C$_{1-3}$ alkyl, C$_{3-6}$ cycloalkyl, O(C$_{1-3}$ alkyl), O(C$_{3-6}$ cycloalkyl), S(C$_{1-3}$ alkyl), S(C$_{3-6}$ 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, C, and S; X^b and X^{b1} are each independently selected from the group consisting of O, C, and S; X^c and X^{c1} are each independently selected from the group consisting of O$^-$, S$^-$, OR^9, and NR^{9}R^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,



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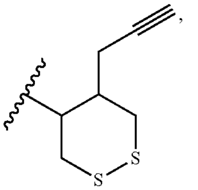
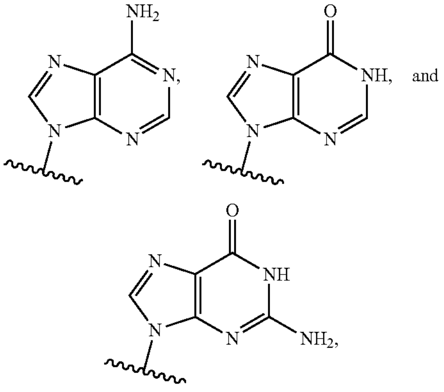
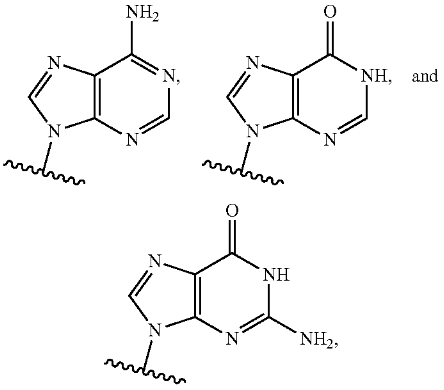


where each R^9 C_1-C_{20} alkyl is optionally substituted by 0 to 3 substituents independently selected from the group consisting of OH, —O—C_1-C_{20} alkyl, —S—C(O)C_1-C_6 alkyl, and C(O)OC_1-C_6 alkyl; optionally R^{1a} and R^3 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, —O—C_1-C_6 alkylene, —O—C_2-C_6 alkenylene, or —O—C_2-C_6 alkynylene, such that where R^{1a} and R^3 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^3 position; optionally R^{2a} and R^3 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, —O—C_1-C_6 alkylene, —O—C_2-C_6 alkenylene, or —O—C_2-C_6 alkynylene, such that where R^{2a} and R^3 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^3 position; optionally R^3 and R^{6a} 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^3 and R^{6a} 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^3 position; optionally R^4 and R^5 are connected to form are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, —O—C_1-C_6 alkylene, —O—C_2-C_6 alkenylene, or —O—C_2-C_6 alkynylene, such that where R^4 and R^5 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^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, C_2-C_6 alkenylene, or C_2-C_6 alkynylene; and optionally R^{7a} and R^{8a} are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene.

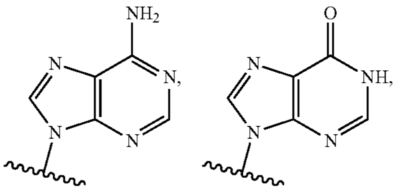
[0017] In specific aspects of this embodiment, when Y and Y^a are each O, X^a and X^{a1} are each O, X^b and X^{b1} are each O, and X^c and X^{c1} are each OH or SH, X^d and X^{d1} are each O, R^1 and R^{1a} are each H, R^2 is H, R^6 and R^{6a} are each H, R^7 and R^{7a} are each H, R^8 and R^{8a} are each H, and $Base^1$ and $Base^2$ are each selected from the group consisting of



R^5 and R^3 are not both selected from the group consisting of H, F and OH. That is, when Y and Y^a are each O, X^a and X^{a1} are each O, X^b and X^{b1} are each O, and X^c and X^{c1} are each OH or SH, X^d and X^{d1} are each O, R^1 and R^{1a} are each H, R^2 is H, 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 $Base^1$ and $Base^2$ are each selected from the group consisting of



either only one of R^5 and R^3 is selected from the group consisting of H, F, and OH, or neither R^5 and R^3 is selected from the group consisting of H, F, and OH. In further specific instances of this aspect, when Y and Y^a are each O, X^a and X^{a1} are each O, X^b and X^{b1} are each O, and X^c and X^{c1} are each OH, X^d and X^{d1} are each O or S, R^1 and R^{1a} are each H, R^2 is H, 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 $Base^1$ and $Base^2$ are each selected from the group consisting of



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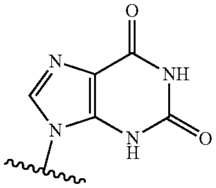

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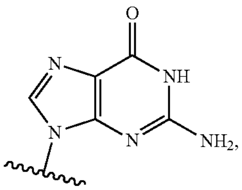
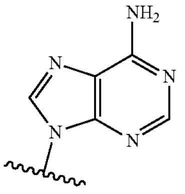


R^5 and R^3 are not both selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, where said C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I and OH.

[0018] In further specific aspects of this embodiment, when $Base^1$ and $Base^2$ are each selected from the group consisting of



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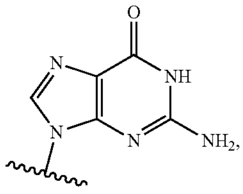
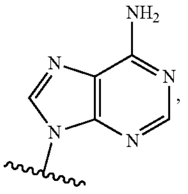
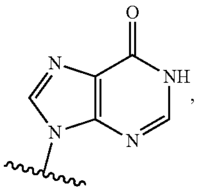
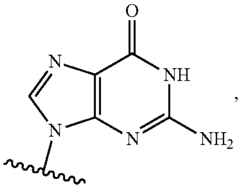


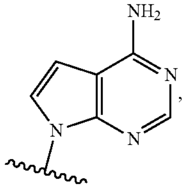
and R is F and R^5 is F, at least one of X^c and X^{c1} is SR^9.

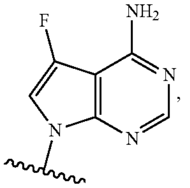
[0019] In a first aspect of the first embodiment, $Base^1$ and $Base^2$ are each independently selected from the group consisting of,

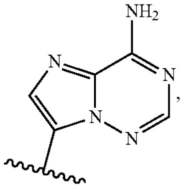


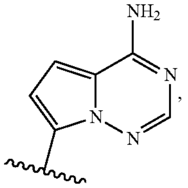


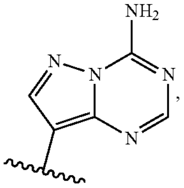


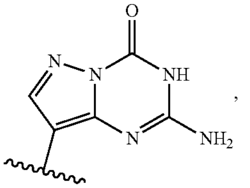












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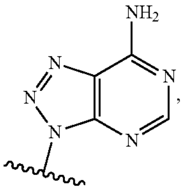

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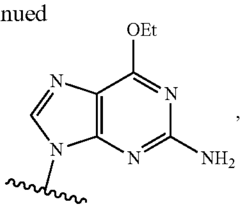
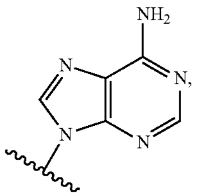
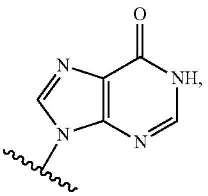
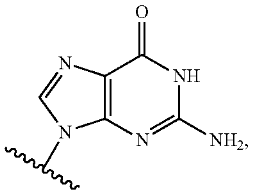
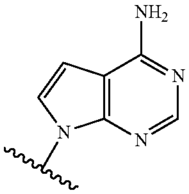


where $Base^1$ and $Base^2$ each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$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









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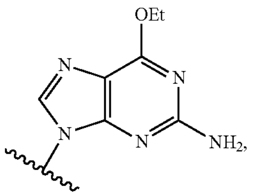
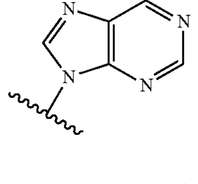


where $Base^1$ and $Base^2$ each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$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



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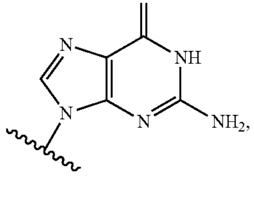


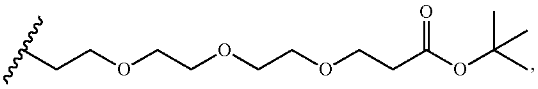
where $Base^1$ and $Base^2$ each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, O(C_{1-3} alkyl), O(C_{3-6} cycloalkyl), S(C_{1-3} alkyl), S(C_{3-6} cycloalkyl), 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 aspect, all other groups are as provided in the general formula (I) of the first embodiment above.

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

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

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

[0023] In a fifth aspect of the first embodiment, X^c and X^{c1} are each independently selected from the group consisting of O^-, S^-, OR^9, and NR^9R^9, where each R^9 is independently selected from the group consisting of H, C_1-C_{20} alkyl,



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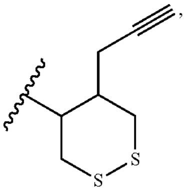

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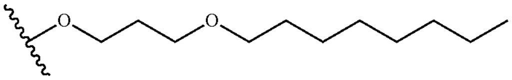
where each R^9 C_1-C_{20} alkyl is optionally substituted by 0 to 3 substituents independently selected from the group consisting of OH, —O—C_1-C_{20} alkyl, —S—C(O)C_1-C_6 alkyl, and C(O)OC_1-C_6 alkyl. In particular instances, X^c and X^{c1} are each independently selected from the group consisting of O^-, S^-,



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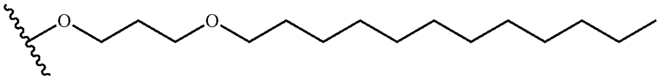

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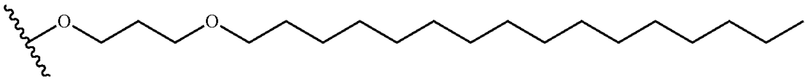

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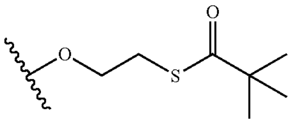

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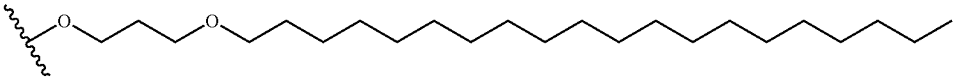

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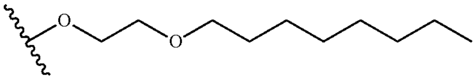

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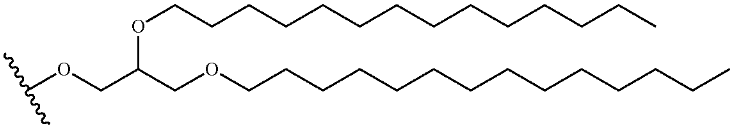

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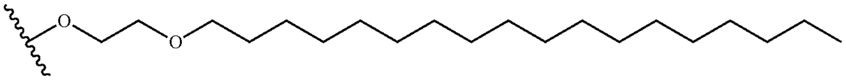

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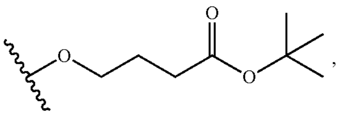

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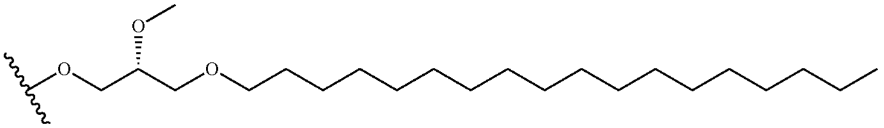

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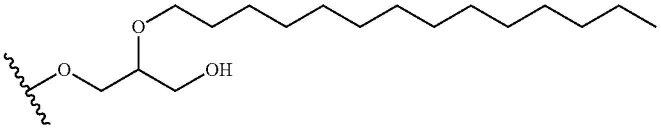

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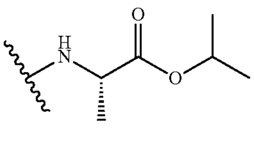

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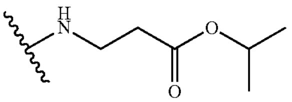

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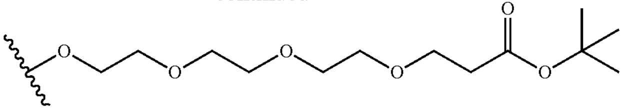

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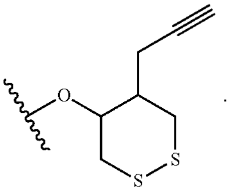

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In all instances of this aspect, all other groups are as provided in the general formula (I) of the first embodiment above or in the first through fourth aspects described above.

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

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

[0026] In an eighth aspect of the first embodiment, R^2 and R^{2a} are each independently selected from the group consisting of H, F, Cl, I, Br, OH, 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 F, Cl, Br, I, OH, CN, and N_3. In particular instances, 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 this aspect, all other groups are as provided in the general formula (I) of the first embodiment above or in the first through seventh aspects described above.

[0027] In a ninth aspect of the first embodiment, R^3 is selected from the group consisting H, F, Cl, I, Br, OH, 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 F, Cl, Br, I, OH, CN, and N_3. In particular instances, R^3 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 this aspect, all other groups are as provided in the general formula (I) of the first embodiment above or in the first through eighth aspects described above.

[0028] In a tenth aspect of the first embodiment, R^4 and R^{4a} are each independently selected from the group consisting of H, F, Cl, I, Br, 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 F, Cl, Br, I, OH, CN, and N_3. In particular instances, 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 this aspect, all other groups are as provided in the general formula (I) of the first embodiment above or in the first through ninth aspects described above.

[0029] In an eleventh aspect of the first embodiment, R^5 is selected from the group consisting of H, F, Cl, I, Br, 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. In particular instances, R^5 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 this aspect, all other groups are as provided in the general formula (I) of the first embodiment above or in the first through tenth aspects described above.

[0030] In a twelfth aspect of the first embodiment, R^6 and R^{6a} are each independently selected from the group consisting of H, F, Cl, I, Br, OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl. In this aspect, all other groups are as provided in the general formula (I) of the first embodiment above or in the first through eleventh aspects described above.

[0031] In a thirteenth aspect of the first embodiment, R^7 and R^{7a} are each H. In this aspect, all other groups are as provided in the general formula (I) of the first embodiment above or in the first through twelfth aspects described above.

[0032] In a fourteenth aspect of the first embodiment, R^8 and R^{8a} are each H. In this aspect, all other groups are as provided in the general formula (I) of the first embodiment above or in the first through thirteenth aspects described above.

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

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

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

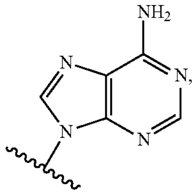
[0036] In an eighteenth aspect of the first embodiment, R^4 and R^5 are connected by C_1-C_6 alkylene, —O—C_1-C_6 alkylene, —O—C_2-C_6 alkenylene, or —O—C_2-C_6 alkynylene, such that where R^4 and R^5 are connected to form —O—C_1-C_6 alkylene, —O—C_2-C_6 alkenylene, or —O—C_2-C_6 alkynylene, said O is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

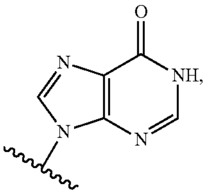
[0037] In a nineteenth aspect of the first embodiment, R^5 and R^6 are connected to form —O—C_1-C_6 alkylene, —O—C_2-C_6 alkenylene, or —O—C_2-C_6 alkynylene, such that where R^5 and R^6 are connected to form —O—C_1-C_6 alkylene, —O—C_2-C_6 alkenylene, or —O—C_2-C_6 alkynylene, said O is bound at the R^5 position. In this aspect, all other groups are as provided in the general formula (I) of the first embodiment above or in the first through fourteenth aspects described above.

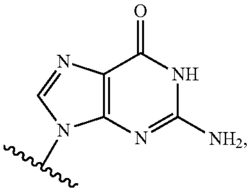
[0038] In a twentieth aspect of the first embodiment, R^7 and R^8 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene. In this aspect, all other groups are as provided in the general formula (I) of the first embodiment above or in the first through fourteenth aspects described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

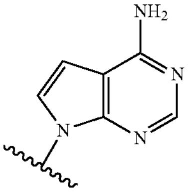
[0039] In a twenty-first aspect of the first embodiment, R^{7a} and R^{8a} are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene. In this aspect, all other groups are as provided in the general formula (I) of the first embodiment above or in the first through fourteenth aspects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

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









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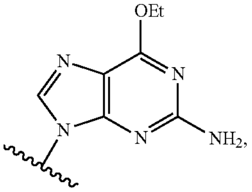
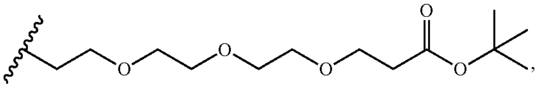


where $Base^1$ and $Base^2$ each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ 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 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 O^-, S^-, 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, I, Br, OH, 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 F, Cl, Br, I, OH, CN, and N_3; R^3 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^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 F, Cl, Br, I, OH, CN, and N_3; R^4 and R^{4a} are each independently selected from the group consisting of H, 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 F, Cl, Br, I, OH, CN, and N_3; R^5 is selected from the group consisting of H, F, Cl, I, Br, 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, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, and C_1-C_6 haloalkyl, where said R^6 and R^{6a} 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^7 and R^{7a} are each H; R^8 and R^{8a} are each H; each R^9 is independently selected from the group consisting of H, C_2-C_3 alkyl,



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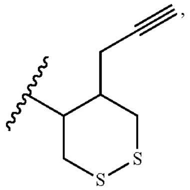
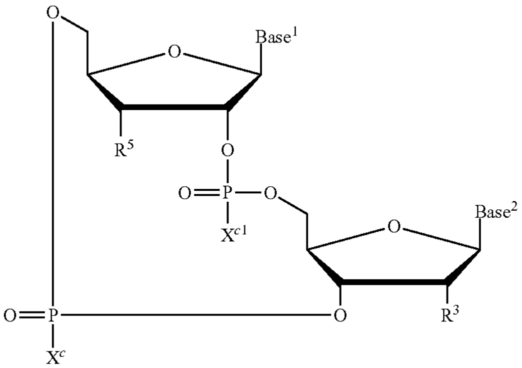


where each R^9 C_2-C_3 alkyl is optionally substituted by 1 to 2 substituents independently selected from the group consisting of OH, —O—C_1-C_{20} alkyl, —S—C(O)C_1-C_6 alkyl, and C(O)OC_1-C_6 alkyl; optionally R^3 and R^{6a} are connected to form —O—C_1-C_6 alkylene, —O—C_2-C_6 alkenylene, and —O—C_2-C_6 alkynylene, such that where R^3 and R^{6a} 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^3 position or optionally R^4 and R^5 are connected by C_1-C_6

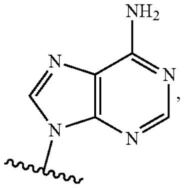
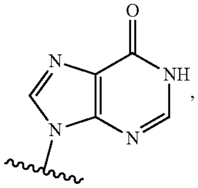
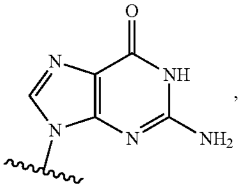
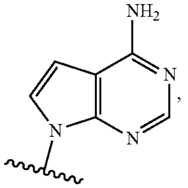
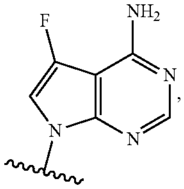
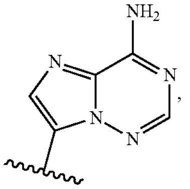
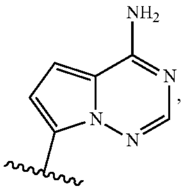
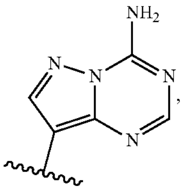
alkylene, —O—C_1-C_6 alkylene, —O—C_2-C_6 alkenylene, or —O—C_2-C_6 alkynylene, such that where R^4 and R^5 are connected to form —O—C_1-C_6 alkylene, —O—C_2-C_6 alkenylene, or —O—C_2-C_6 alkynylene, said O is bound at the R^5 position. In this aspect, all other groups are as provided in the general formula (I) of the first embodiment above.

[0041] In a twenty-third aspect of the first embodiment, the compound of formula (I) is a compound of formula (Ia):



(Ia)

or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, wherein Base^1 and Base^2 are each independently selected from the group consisting of

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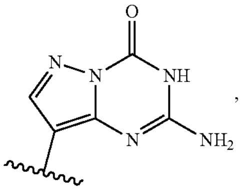
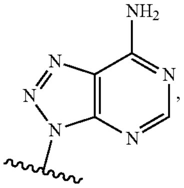
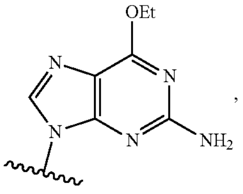
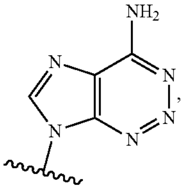
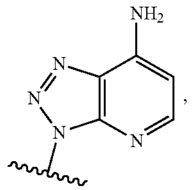
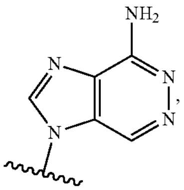
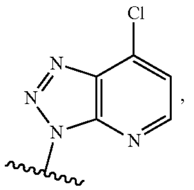
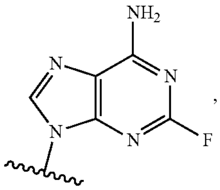
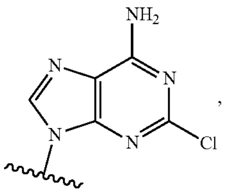
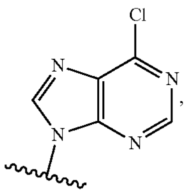
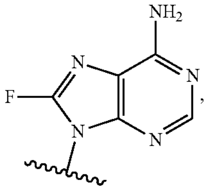
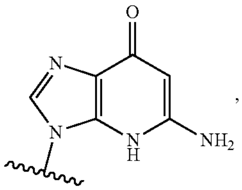
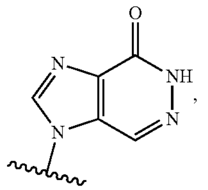
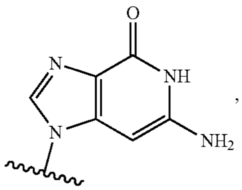
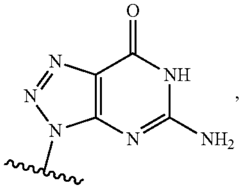
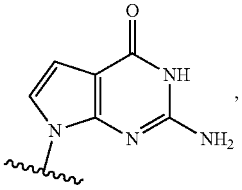

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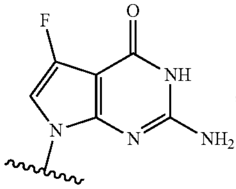
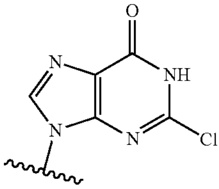
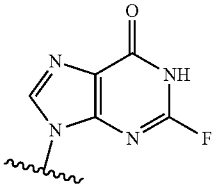
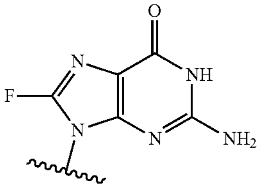
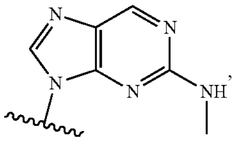
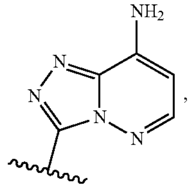
,

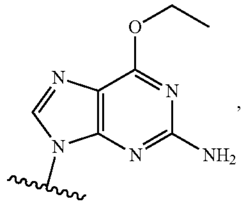
,

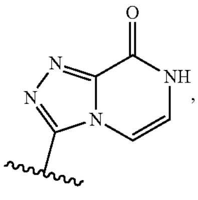
,

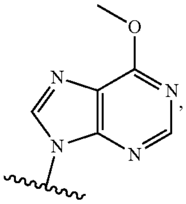
,

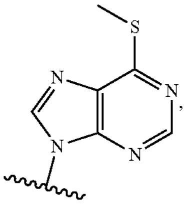
,

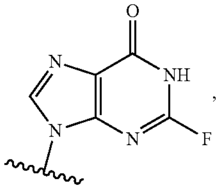
,

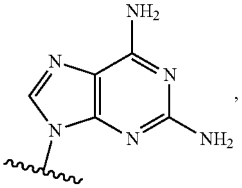
,

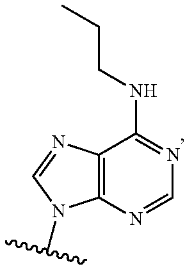
,

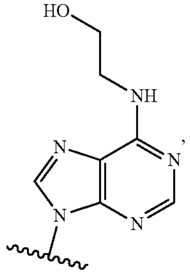
,

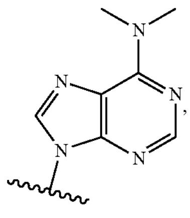


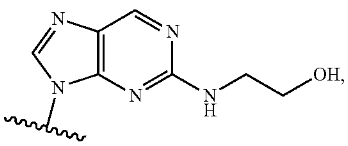
,

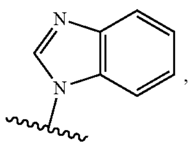
,











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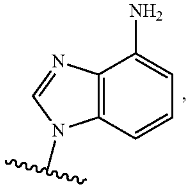
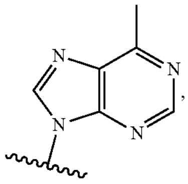
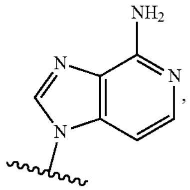
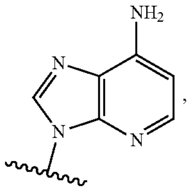
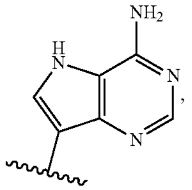
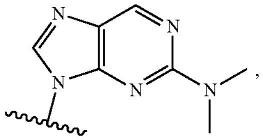


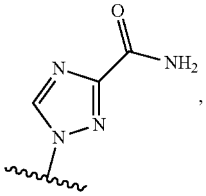


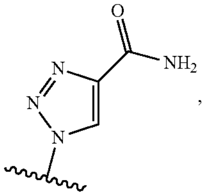


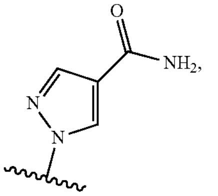




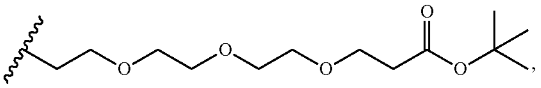


,

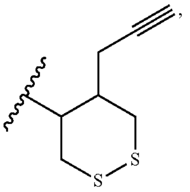
, and



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)$_2$; X^c and X^{c1} are each independently selected from the group consisting of O^-, S^-, OR^9, and NR^9R^9; R^3 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^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 F, Cl, I, Br, and OH; 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 F, Cl, I, Br, and OH; R^3 and R^5 are not both selected from the group consisting of OH, C_1-C_6 alkyl substituted with OH, and C_1-C_6 haloalkyl substituted with OH; and each R^9 is independently selected from the group consisting of H, C_2-C_3 alkyl,



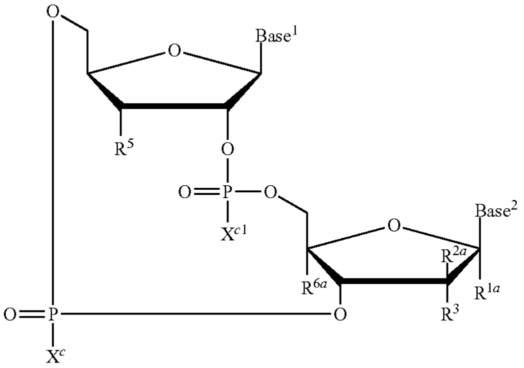
, and



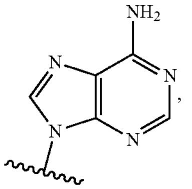
where each R^9 C_2-C_3 alkyl is optionally substituted by 1 to 2 substituents independently selected from the group consisting of OH, —O—C_1-C_{20} alkyl, —S—C(O)C_1-C_6 alkyl, and C(O)OC_1-C_6 alkyl. In this aspect, all other groups are as provided in the general formula (I) of the first embodiment above.

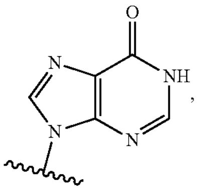
[0042] In a twenty-fourth aspect of the first embodiment, the compound of formula (I) is a compound of formula (Ib):

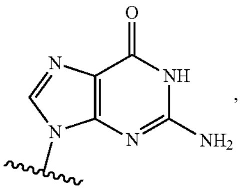
(Ib)

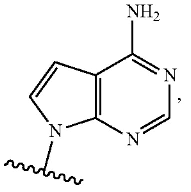


or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, wherein $Base^1$ and $Base^2$ are each independently selected from the group consisting of









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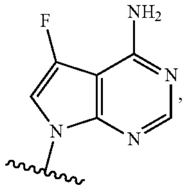

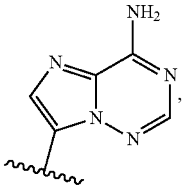

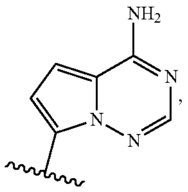

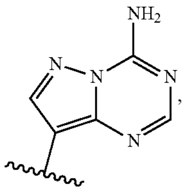

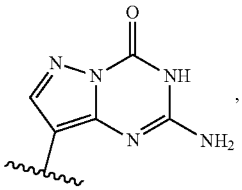

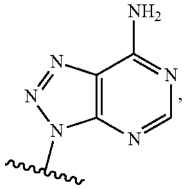

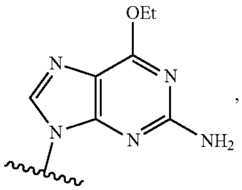

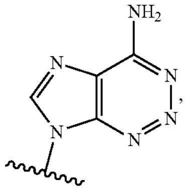

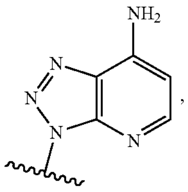

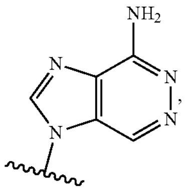

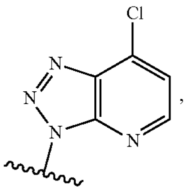

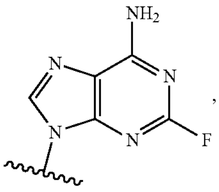

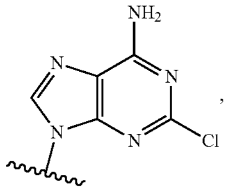

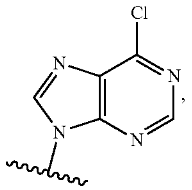

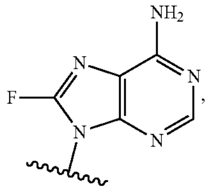

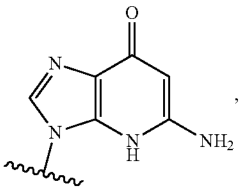

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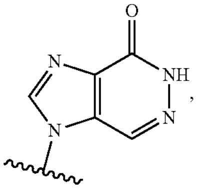
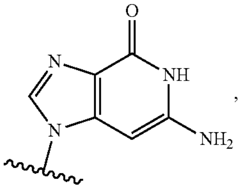
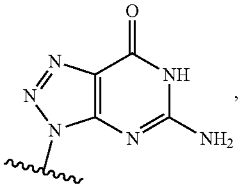
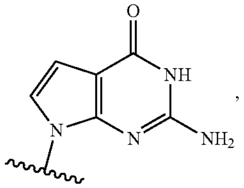
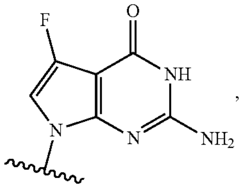
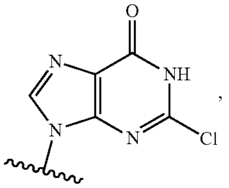
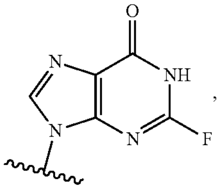
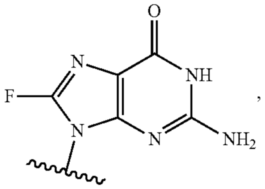
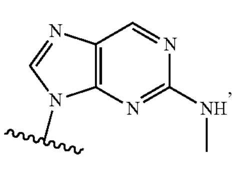
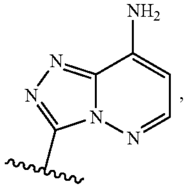
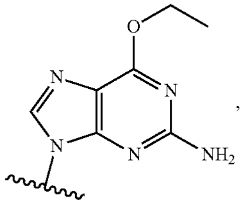
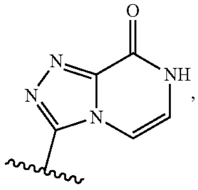
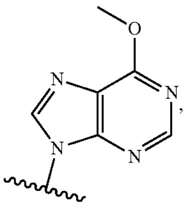
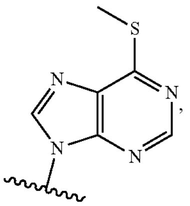
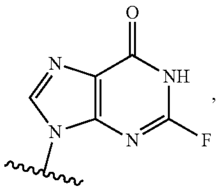
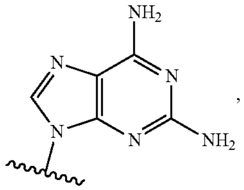

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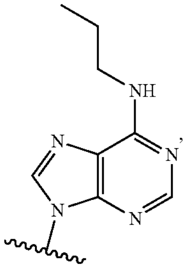
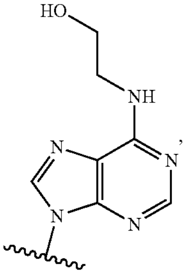
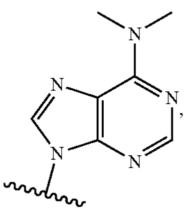
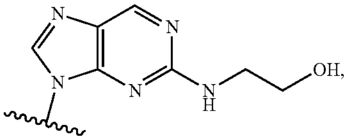
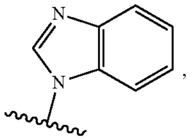
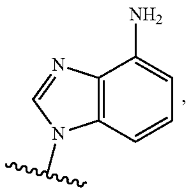
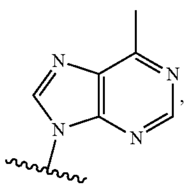
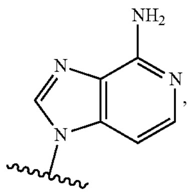
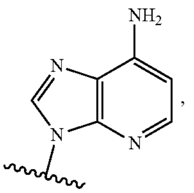
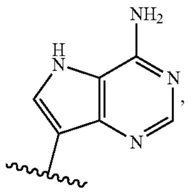
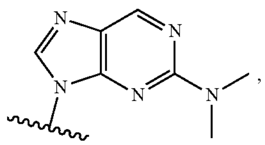
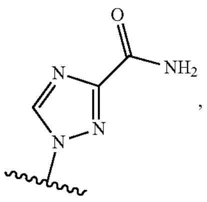
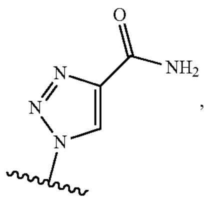

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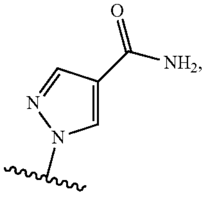
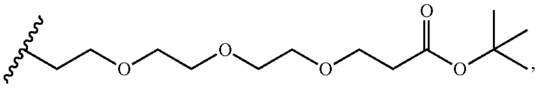
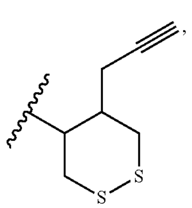


where Base^1 and Base^2 each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, $O(C_{1-3}$ alkyl), $O(C_{3-6}$ cycloalkyl), $S(C_{1-3}$ alkyl), $S(C_{3-6}$ cycloalkyl), $NH(C_{1-3}$ alkyl), $NH(C_{3-6}$ cycloalkyl), $N(C_{1-3}$ alkyl$)_2$, and $N(C_{3-6}$ cycloalkyl$)_2$; X^c and X^{c1} are each independently selected from the group consisting of O^-, S^-, OR^9, and NR^9R^9; R^{1a} 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^{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^{2a} 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^{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 F, Cl, I, Br, and OH; R^3 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^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 F, Cl, I, Br, and OH; 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 F, Cl, I, Br, and OH; R^3 and R^5 are not both selected from the group consisting of OH, C_1-C_6 alkyl substituted with OH, and C_1-C_6 haloalkyl substituted with OH; R^{6a} is selected from the group consisting of H, F, Cl, I, Br, OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl; each R^9 is independently selected from the group consisting of H, C_2-C_3 alkyl,

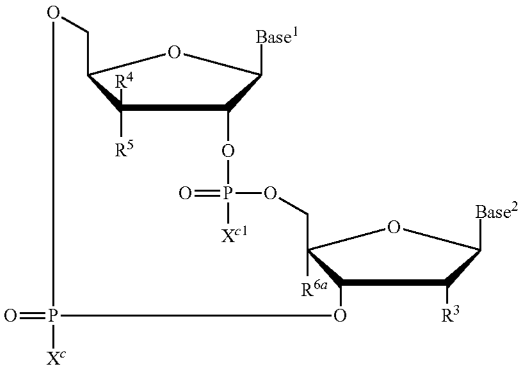

, and



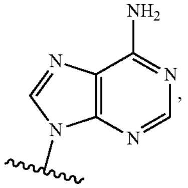
where each R^9 C_2-C_3 alkyl is optionally substituted by 1 to 2 substituents independently selected from the group consisting of OH, —O—C_1-C_{20} alkyl, —S—C(O)C_1-C_6 alkyl, and C(O)OC_1-C_6 alkyl; and optionally R^3 and R^{6a} are connected to form —O—C_1-C_6 alkylene, —O—C_2-C_6 alkenylene, and —O—C_2-C_6 alkynylene, such that where R^3 and R^{6a} 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^3 position. In this aspect, all other groups are as provided in the general formula (I) of the first embodiment above.

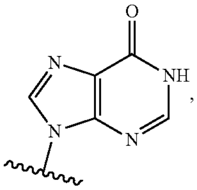
[0043] In a twenty-fifth aspect of the first embodiment, the compound of formula (I) is a compound of formula (Ic):

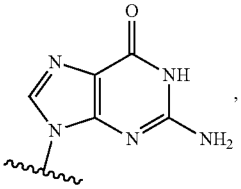
(Ic)

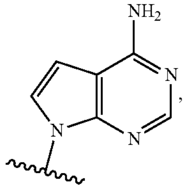


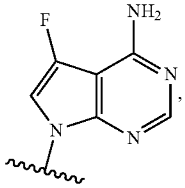
or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, wherein $Base^1$ and $Base^2$ are each independently selected from the group consisting of

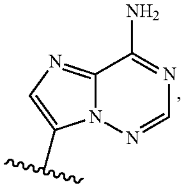


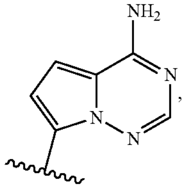


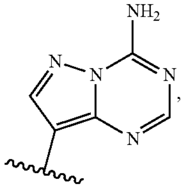


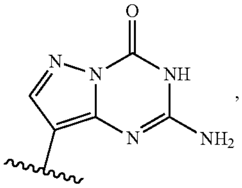


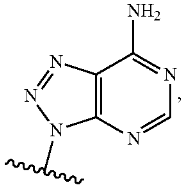












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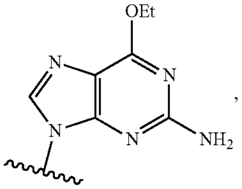
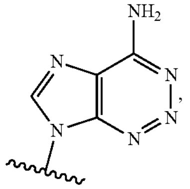
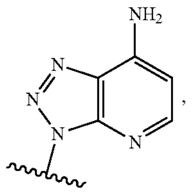
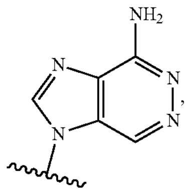
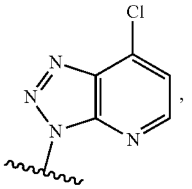
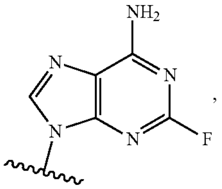
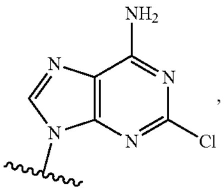
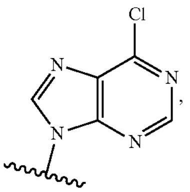
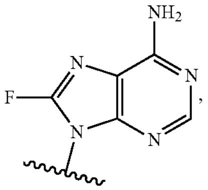
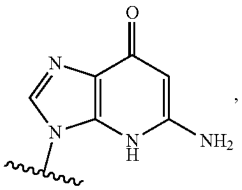
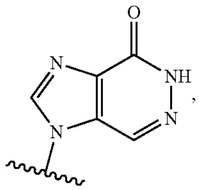
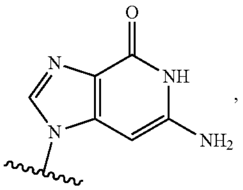
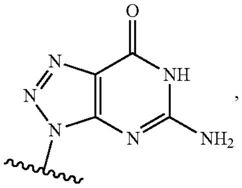
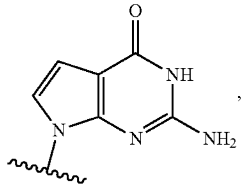
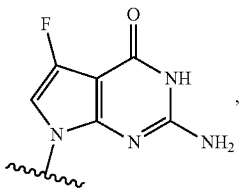
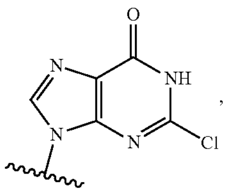

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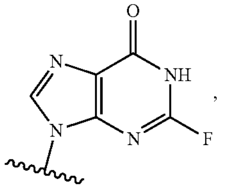
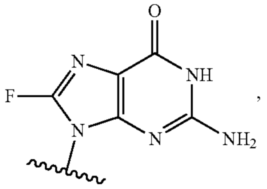
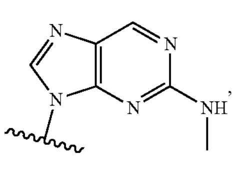
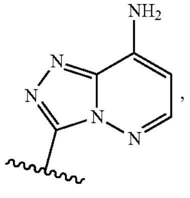
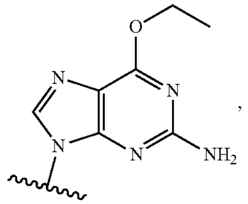
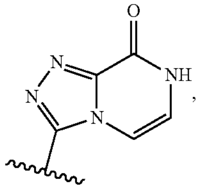
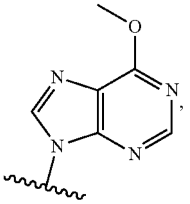
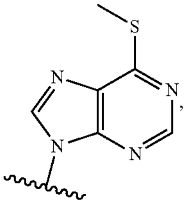
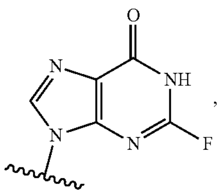
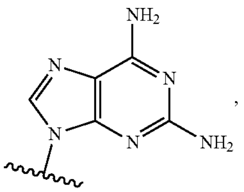
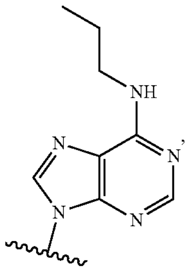
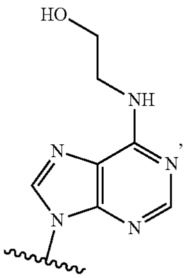
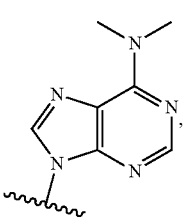
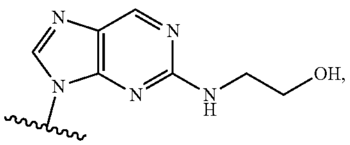
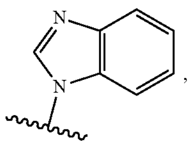
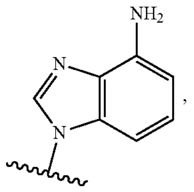
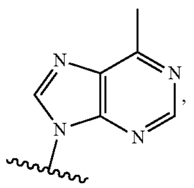

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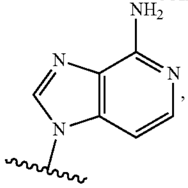

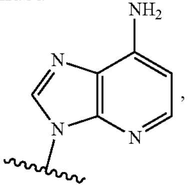

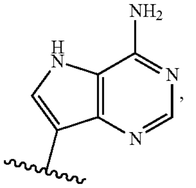

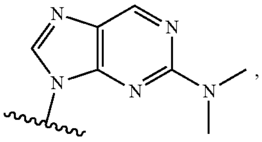

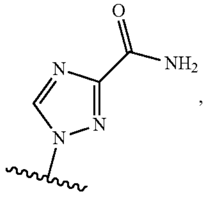

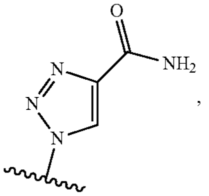

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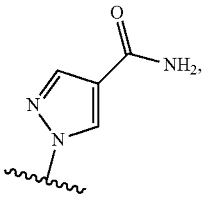
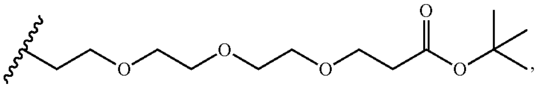


where Base¹ and Base² each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, O(C_{1-3} alkyl), O(C_{3-6} cycloalkyl), S(C_{1-3} alkyl), S(C_{3-6} cycloalkyl), NH(C_{1-3} alkyl), NH(C_{3-6} cycloalkyl), N(C_{1-3} alkyl)$_2$, and N(C_{3-6} cycloalkyl)$_2$; X^c and X^{c1} are each independently selected from the group consisting of O^-, S^-, OR^9, and NR^9R^9; R^3 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^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 F, Cl, I, Br, and OH; R^4 is selected from the group consisting of H, F, OH, CN, N_3, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, where said R^4 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, I, Br, and OH; 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 F, Cl, I, Br, and OH; R^3 and R^5 are not both selected from the group consisting of OH, C_1-C_6 alkyl substituted with OH, and C_1-C_6 haloalkyl substituted with OH; R^{6a} 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^{6a} 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, I, Br, and OH; each R^9 is independently selected from the group consisting of H, C_2-C_3 alkyl,



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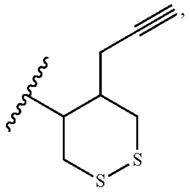


where each R^9 C_2-C_3 alkyl is optionally substituted by 1 to 2 substituents independently selected from the group consisting of OH, —O—C_1-C_{20} alkyl, —S—C(O)C_1-C_6 alkyl, and C(O)OC_1-C_6 alkyl; and optionally R^4 and R^5 are connected by C_1-C_6 alkylene, —O—C_1-C_6 alkylene, —O—C_2-C_6 alkenylene, or —O—C_2-C_6 alkynylene, such that where R^4 and R^5 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. In this aspect, all other groups are as provided in the general formula (I) of the first embodiment above.

[0044] A twenty-sixth aspect of the first embodiment relates to a pharmaceutical composition, said pharmaceutical composition comprising (a) a compound according to any one of general formula (I) of the first embodiment above or in the first through twenty-fifth aspects described above or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, and (b) a pharmaceutically acceptable carrier.

[0045] A twenty-seventh aspect of the first 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) of the first embodiment above or in the first through twenty-fifth aspects described above or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof to the subject.

[0046] A twenty-eighth aspect of the first embodiment relates to methods of inducing an immune response in a subject, comprising administering a therapeutically effective amount of a composition according to the twenty-sixth aspect described above to the subject.

[0047] A twenty-ninth aspect of the first embodiment relates to methods of inducing a 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) of the first embodiment above or in the first through twenty-fifth aspects described above or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof to the subject.

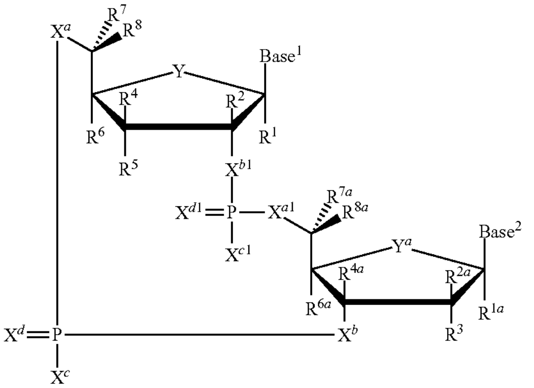
[0048] A thirtieth aspect of the first embodiment relates to methods of inducing a STING-dependent type I interferon production in a subject, comprising administering a therapeutically effective amount of a composition according to the twenty-sixth aspect described above to the subject.

[0049] A thirty-first aspect of the first embodiment relates to methods of inducing a STING-dependent cytokine production in a subject, comprising administering a therapeutically effective amount of a compound according to any one of general formula (I) of the first embodiment above or in the first through twenty-fifth aspects described above or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof to the subject.

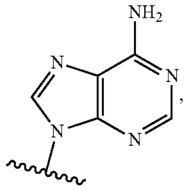
[0050] A thirty-second aspect of the first embodiment relates to methods of inducing a STING-dependent cytokine production in a subject, comprising administering a therapeutically effective amount of a composition according to the twenty-sixth aspect described above to the subject.

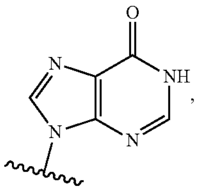
[0051] A second embodiment of the disclosure relates to cyclic di-nucleotide compounds of general formula (I'):

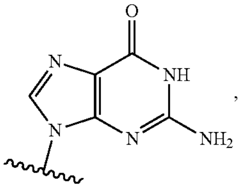
(I')

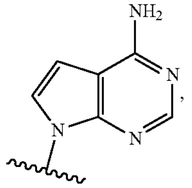


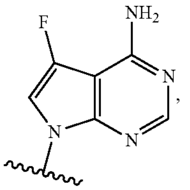
or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, wherein Base^1 and NH$_2$NH Base^2 are each independently selected from the group consisting of

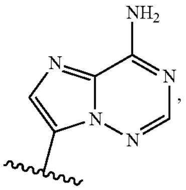


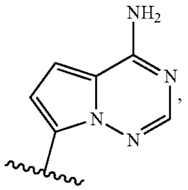


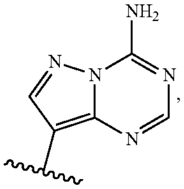


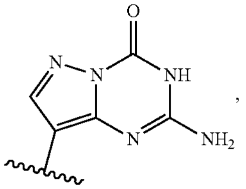












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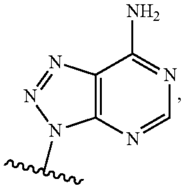

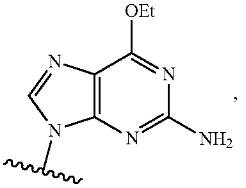

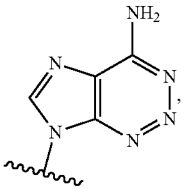

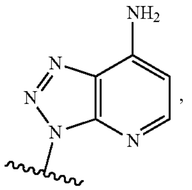

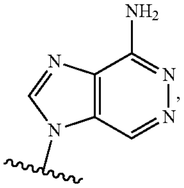

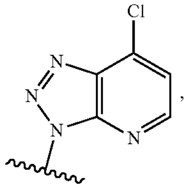

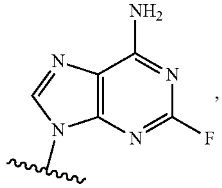

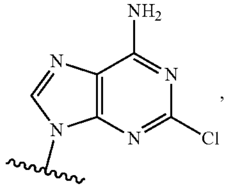

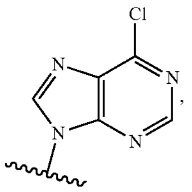

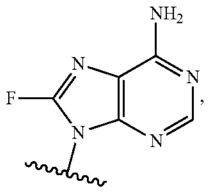

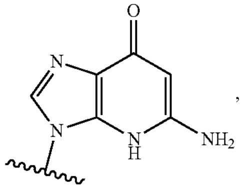

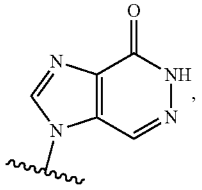

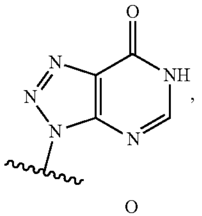

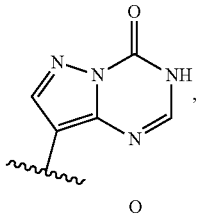

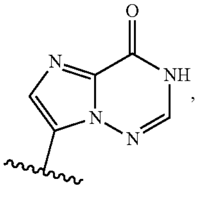

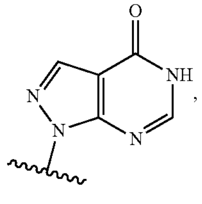

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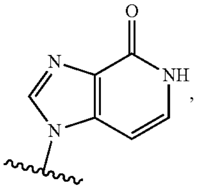
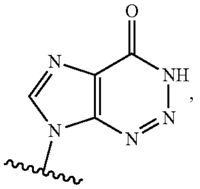
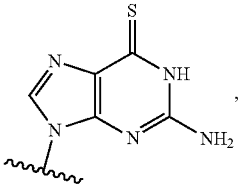
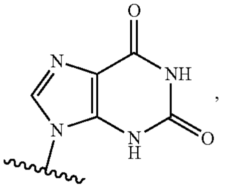
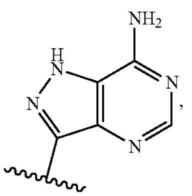
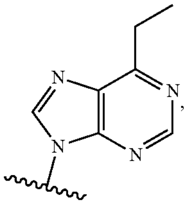
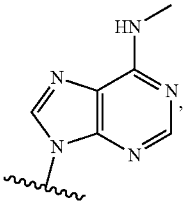
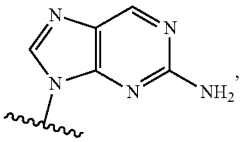
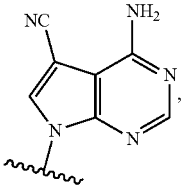
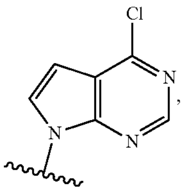
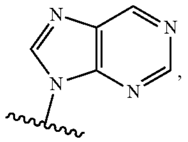
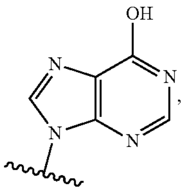
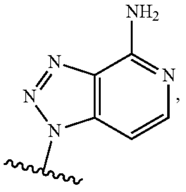
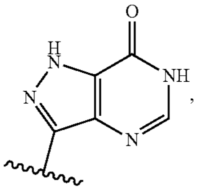
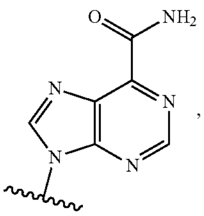
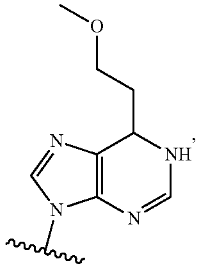
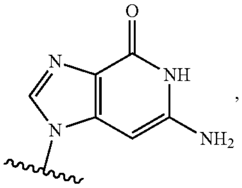
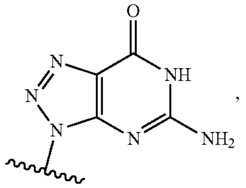

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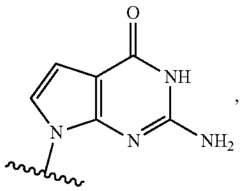
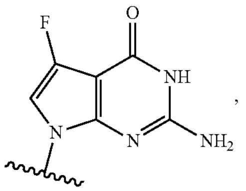
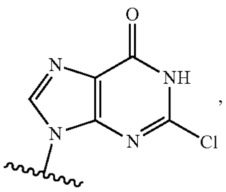
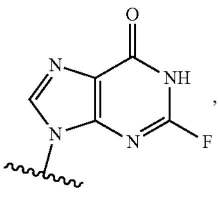
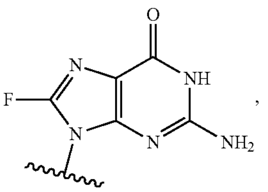
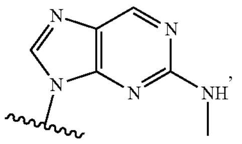
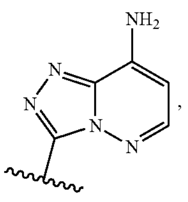
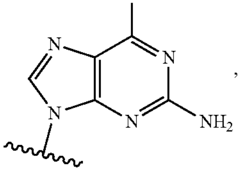
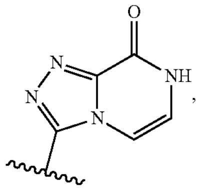
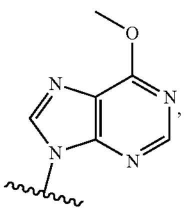
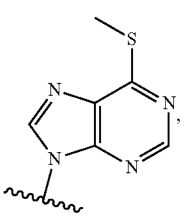
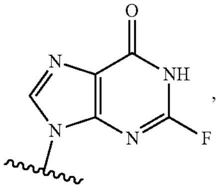
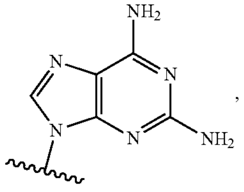
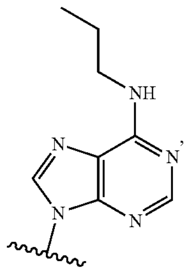

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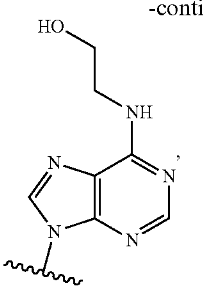
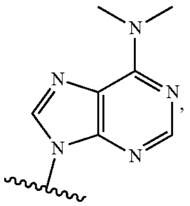
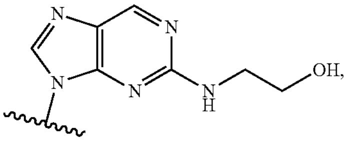
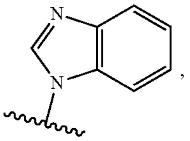
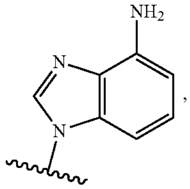
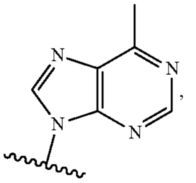
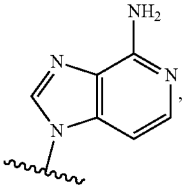
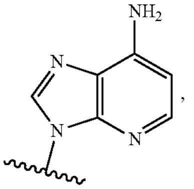
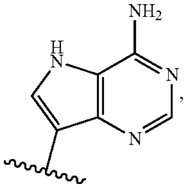
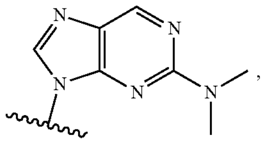
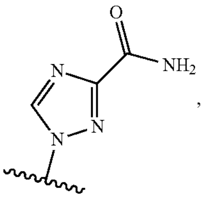
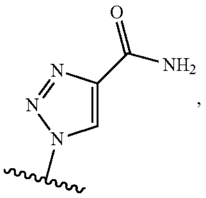

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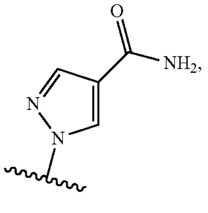
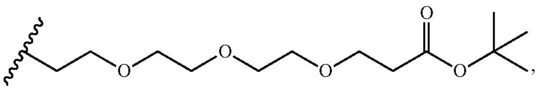


where Base^1 and Base^2 each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH$_2$, C$_{1-3}$ alkyl, C$_{3-6}$ cycloalkyl, O(C$_{1-3}$ alkyl), O(C$_{3-6}$ cycloalkyl), S(C$_{1-3}$ alkyl), S(C$_{3-6}$ 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 independently selected from the group consisting of 0, 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 OR^9, SR^9, and NR^{9}R^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, NH$_2$, 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, NR^{9}R^9, 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,



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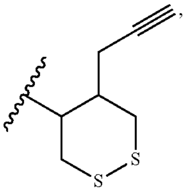
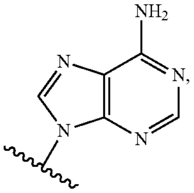
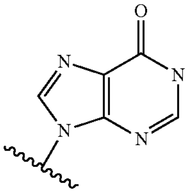


,

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, C_2-C_6 alkynylene, —O—C_1-C_6 alkylene, —O—C_2-C_6 alkenylene, or —O—C_2-C_6 alkynylene, such that where R^{1a} and R^3 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^3 position; optionally R^{2a} and R^3 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, —O—C_1-C_6 alkylene, —O—C_2-C_6 alkenylene, or —O—C_2-C_6 alkynylene, such that where R^{2a} and R^3 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^3 position; optionally R^3 and R^{6a} 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^3 and R^{6a} 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^3 position; optionally R^4 and R^5 are connected to form are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, —O—C_1-C_6 alkylene, —O—C_2-C_6 alkenylene, or —O—C_2-C_6 alkynylene, such that where R^4 and R^5 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^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, C_2-C_6 alkenylene, or C_2-C_6 alkynylene; and optionally R^{7a} and R^{8a} are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene.

[0052] In specific aspects of this embodiment, when Y and Y^a are each O, X^a and X^{a1} are each O, X^b and X^{b1} are each O, and X^c and X^{c1} are each OH or SH, X^d and X^{d1} are each O, R^1 and R^{1a} are each H, R^2 is H, 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 Base^1 and Base^2 are each selected from the group consisting of





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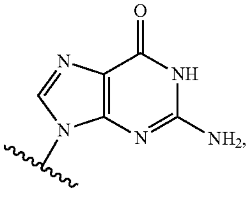
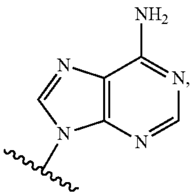
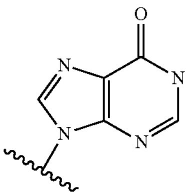


R^5 and R^3 are not both selected from the group consisting of H, F and OH. That is, when Y and Y^a are each O, X^a and X^{a1} are each O, X^b and X^{b1} are each O, and X^c and X^{c1} are each OH or SH, X^d and X^{d1} are each O, R^1 and R^{1a} are each H, R^2 is H, R^6 and R^{6a} are each H, R^7 and R^{7a} are each H, R^8 and R^{8a} are each H, and Base^1 and Base^2 are each selected from the group consisting of





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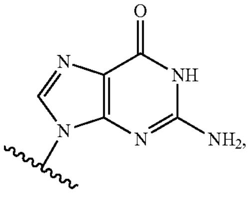
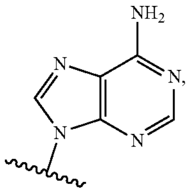
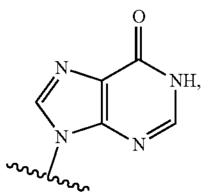
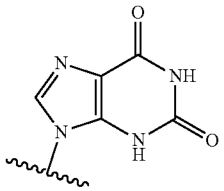


either only one of R^5 and R^3 is selected from the group consisting of H, F, and OH, or neither R^5 and R^3 is selected from the group consisting of H, F, and OH. In further specific instances of this aspect, when Y and Y^a are each O, X^a and X^{a1} are each O, X^b and X^{b1} are each O, and X^c and X^{c1} are each OH, X^d and X^{d1} are each O or S, R^1 and R^{1a} are each H, R^2 is H, 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 Base^1 and Base^2 are each selected from the group consisting of

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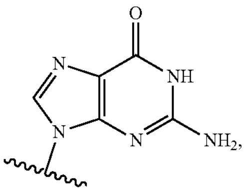
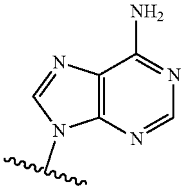


R^5 and R^3 are not both selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, where said C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I and OH.

[0053] In further specific aspects of this embodiment, when $Base^1$ and $Base^2$ are each selected from the group consisting of



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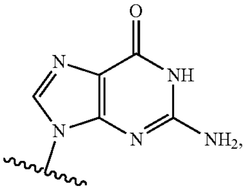
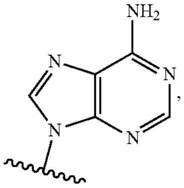
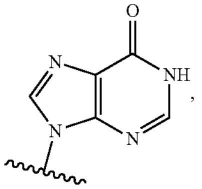
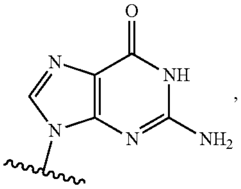
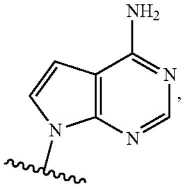
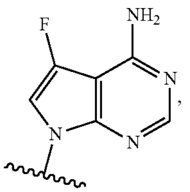
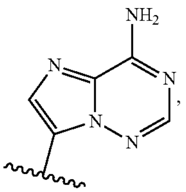
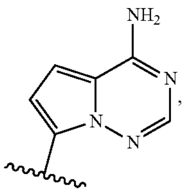


and R^{2a} is F and R^5 is F, at least one of X^c and X^{c1} is SR^9.

[0054] In a first aspect of the second embodiment, $Base^1$ and $Base^2$ are each independently selected from the group consisting of

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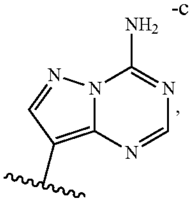
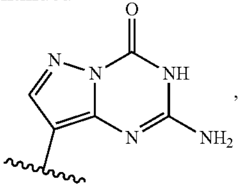
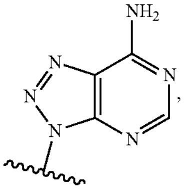

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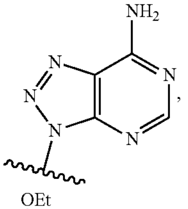
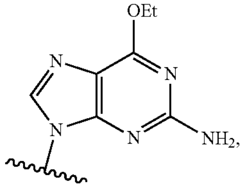
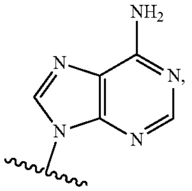
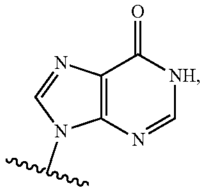
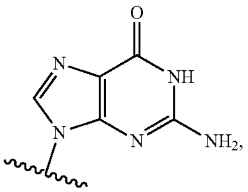
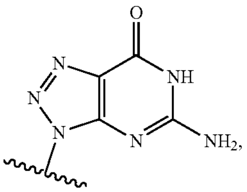
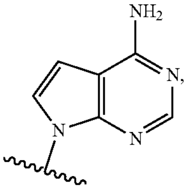
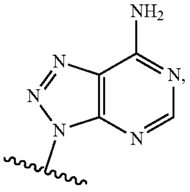



where $Base^1$ and $Base^2$ each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, O(C_{1-3} alkyl), O(C_{3-6} cycloalkyl), S(C_{1-3} alkyl), S(C_{3-6} cycloalkyl),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

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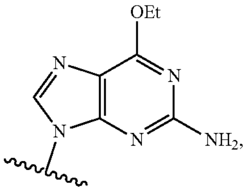
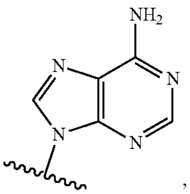


where Base^1 and Base^2 each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH$_2$, C$_{1-3}$ alkyl, C$_{3-6}$ cycloalkyl, O(C$_{1-3}$ alkyl), O(C$_{3-6}$ cycloalkyl), S(C$_{1-3}$ alkyl), S(C$_{3-6}$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



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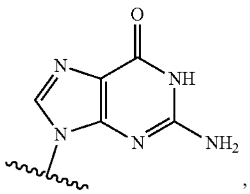

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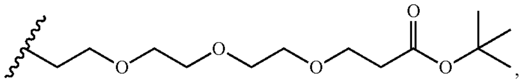
where Base^1 and Base^2 each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH$_2$, C$_{1-3}$ alkyl, C$_{3-6}$ cycloalkyl, O(C$_{1-3}$ alkyl), O(C$_{3-6}$ cycloalkyl), S(C$_{1-3}$ alkyl), S(C$_{3-6}$ 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 aspect, all other groups are as provided in the general formula (I') of the second embodiment above.

[0055] In a second aspect of the second embodiment, X^c and X^{c1} are each independently selected from the group consisting of OR^9, SR^9, and NR^{9}R^9, where each R^9 is independently selected from the group consisting of H, C$_1$-C$_{20}$ alkyl,



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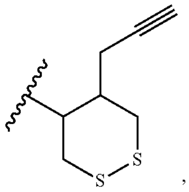

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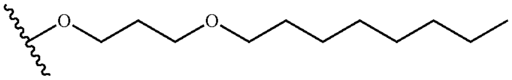
where each R^9 C$_1$-C$_{20}$ alkyl is optionally substituted by 0 to 3 substituents independently selected from the group consisting of OH, —O—C$_1$-C$_{20}$ alkyl, —S—C(O)C$_1$-C$_6$ alkyl, and C(O)OC$_1$-C$_6$ alkyl. In particular instances, X^c and X^{c1} are each independently selected from the group consisting of O$^-$, S$^-$,



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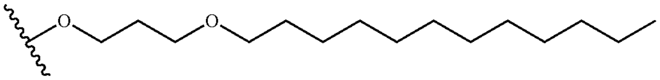

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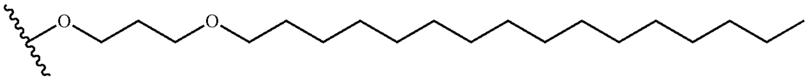

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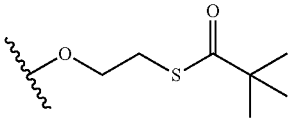

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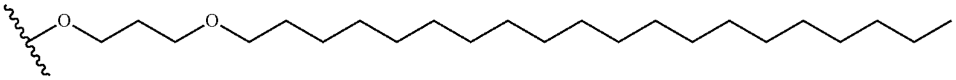

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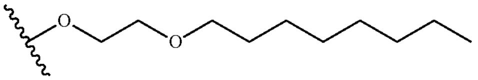

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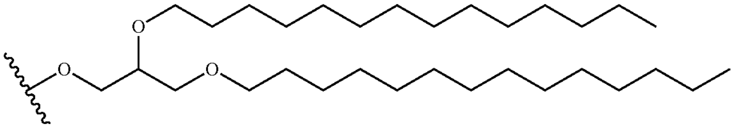

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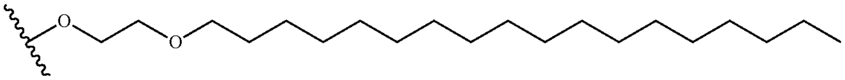

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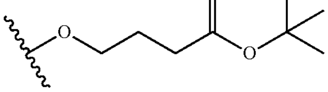

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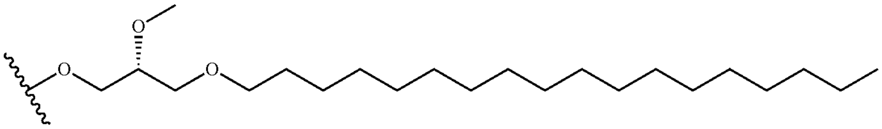

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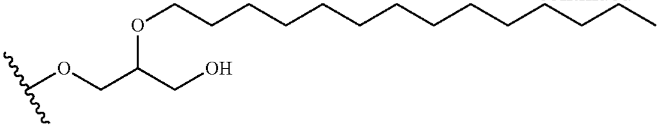

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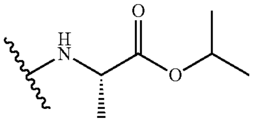

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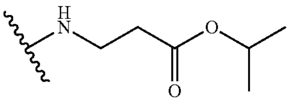

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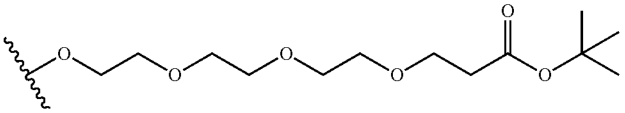

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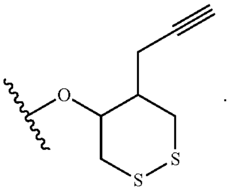


.

In all instances of this aspect, all other groups are as provided in the general formula (I') of the second embodiment above or in the first aspect described above.

[0056] In a third aspect of the second embodiment, R^1 and R^{1a} are each H. In this aspect, all other groups are as provided in the general formula (I') of the second embodiment above or in the first through second aspects described above.

[0057] In a fourth aspect of the second embodiment, R^2 and R^{2a} are each independently selected from the group consisting of H, F, Cl, I, Br, OH, 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 F, Cl, Br, I, OH, CN, and N_3. In particular instances, 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 this aspect, all other groups are as provided in the general formula (I') of the second embodiment above or in the first through third aspects described above.

[0058] In a fifth aspect of the second embodiment, R^3 is selected from the group consisting H, F, Cl, I, Br, OH, 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 F, Cl, Br, I, OH, CN, and N_3. In particular instances, R^3 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 even more particular instances, R^3 is selected from NH_2 and N_3. In this aspect, all other groups are as provided in the general formula (I') of the second embodiment above or in the first through fourth aspects described above.

[0059] In a sixth aspect of the second embodiment, R^4 and R^{4a} are each independently selected from the group consisting of H, F, Cl, I, Br, 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 F, Cl, Br, I, OH, CN, and N_3. In particular instances, 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 even more particular instances, R^4 and R^{4a} are each F. In this aspect, all other groups are as provided in the general formula (I') of the second embodiment above or in the first through fifth aspects described above.

[0060] In a seventh aspect of the second embodiment, R^5 is selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, 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, NR^9R^9, and N_3. In particular instances, R^5 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 even more particular instances, R^5 is selected from NH_2 and N_3. In this aspect, all other groups are as provided in the general formula (I') of the second embodiment above or in the first through sixth aspects described above.

[0061] In an eighth aspect of the second embodiment, R^6 and R^{6a} are each independently selected from the group consisting of H, F, Cl, I, Br, OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl. In this aspect, all other groups are as provided in the general formula (I') of the second embodiment above or in the first through seventh aspects described above.

[0062] In a ninth aspect of the second embodiment, R^7 and R^{7a} are each independently selected from the group consisting of H and C_1-C_6 alkyl. In particular instances, R^7 and R^{7a} are each independently selected from the group consisting of H and CH_3. In more particular instances, R^{7a} is CH_3. In additional instances, R^7 and R^{7a} are each H. In this aspect, all other groups are as provided in the general formula (I') of the second embodiment above or in the first through eighth aspects described above.

[0063] In a tenth aspect of the second embodiment, R^8 and R^{8a} are each independently selected from the group consisting of H and C_1-C_6 alkyl. In particular instances, R^8 and R^{8a} are each independently selected from the group consisting of H and CH_3. In more particular instances, R^{8a} is CH_3. In additional instances, R^8 and R^{8a} are each H. In this aspect, all other groups are as provided in the general formula (I') of the second embodiment above or in the first through ninth aspects described above.

[0064] In an eleventh aspect of the second embodiment, R^{1a} and R^3 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, —O—C_1-C_6 alkylene, —O—C_2-C_6 alkenylene, or —O—C_2-C_6 alkynylene, such that where R^{1a} and R^3 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^3 position. In this aspect, all other groups are as provided in the general formula (I') of the second embodiment above or in the first through tenth aspects described above.

[0065] In a twelfth aspect of the second embodiment, R^{2a} and R^3 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, —O—C_1-C_6 alkylene, —O—C_2-C_6 alkenylene, or —O—C_2-C_6 alkynylene, such that where R^{2a} and R^3 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^3 position. In this aspect, all other groups are as provided in the general formula (I') of the second embodiment above or in the first through eleventh aspects described above.

[0066] In a thirteenth aspect of the second embodiment, R^3 and R^{6a} are connected to form —O—C_1-C_6 alkylene, —O—C_2-C_6 alkenylene, and —O—C_2-C_6 alkynylene, such that where R^3 and R^{6a} 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^3 position. In this aspect, all other groups are as provided in the general formula (I') of the second embodiment above or in the first through eleventh aspects described above.

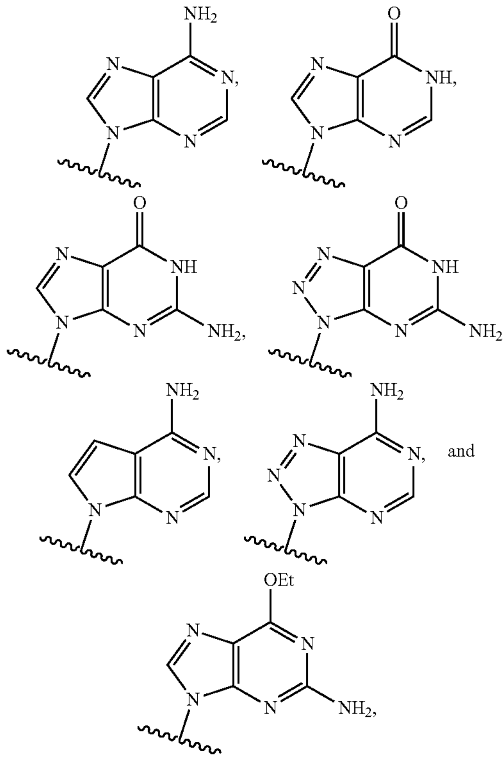
[0067] In a fourteenth aspect of the second embodiment, R^4 and R^5 are connected by C_1-C_6 alkylene, —O—C_1-C_6 alkylene, —O—C_2-C_6 alkenylene, or —O—C_2-C_6 alkynylene, such that where R^4 and R^5 are connected to form —O—C_1-C_6 alkylene, —O—C_2-C_6 alkenylene, or —O—C_2-C_6 alkynylene, said O is bound at the R^5 position. In this aspect, all other groups are as provided in the general formula (I') of the second embodiment above or in the first through eleventh aspects described above.

[0068] In a fifteenth aspect of the second embodiment, 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. In this aspect, all other groups are as provided in the general formula (I') of the second embodiment above or in the first through eleventh aspects described above.

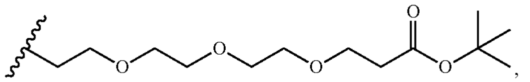
[0069] In a sixteenth aspect of the second embodiment, R^7 and R^8 are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene. In this aspect, all other groups are as provided in the general formula (I') of the second embodiment above or in the first through eleventh aspects described above.

[0070] In a seventeenth aspect of the second embodiment, R^{7a} and R^{8a} are connected to form C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene. In this aspect, all other groups are as provided in the general formula (I') of the second embodiment above or in the first through eleventh aspects described above.

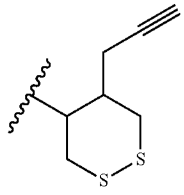
[0071] In an eighteenth aspect of the second embodiment, $Base^1$ and $Base^2$ are each independently selected from the group consisting of



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 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 OR^9, SR^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, 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 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, 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 F, Cl, Br, I, OH, CN, and N_3; R^4 and R^{4a} are each independently selected from the group consisting of H, 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 F, Cl, Br, I, OH, CN, and N_3; R^5 is selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, 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, NR^9R^9, and N_3; R^6 and R^{6a} are each independently selected from the group consisting of H, F, Cl, Br, I, OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, and C_1-C_6 haloalkyl, where said R^6 and R^{6a} 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^7 and R^{7a} are each H; R^8 and R^{8a} are each H; each R^9 is independently selected from the group consisting of H, C_2-C_3 alkyl,

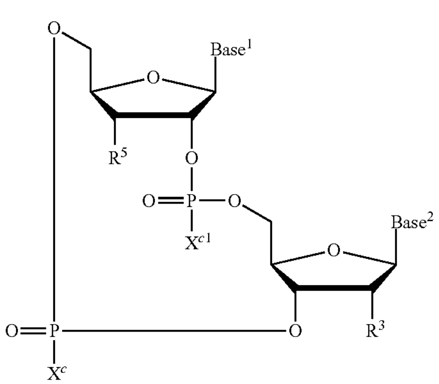


and



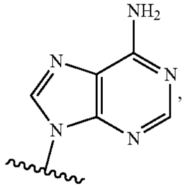
where each R^9 C_2-C_3 alkyl is optionally substituted by 1 to 2 substituents independently selected from the group consisting of OH, —O—C_1-C_{20} alkyl, —S—C(O)C_1-C_6 alkyl, and C(O)OC_1-C_6 alkyl; optionally R^3 and R^{6a} are connected to form —O—C_1-C_6 alkylene, —O—C_2-C_6 alkenylene, and —O—C_2-C_6 alkynylene, such that where R^3 and R^{6a} 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^3 position or optionally R^4 and R^5 are connected by C_1-C_6 alkylene, —O—C_1-C_6 alkylene, —O—C_2-C_6 alkenylene, or —O—C_2-C_6 alkynylene, such that where R^4 and R^5 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. In all instances of this aspect, all other groups are as provided in the general formula (I') of the second embodiment above.

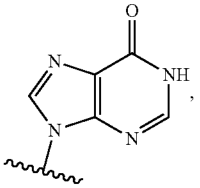
[0072] In a nineteenth aspect of the second embodiment, the compound of formula (I') is a compound of formula (I'a):

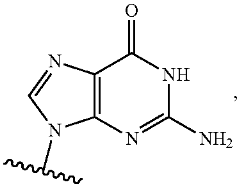


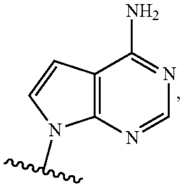
(I'a)

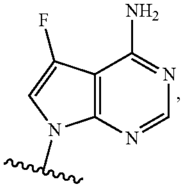
or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, wherein $Base^1$ and $Base^2$ are each independently selected from the group consisting of

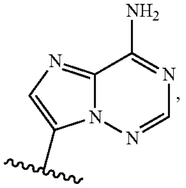


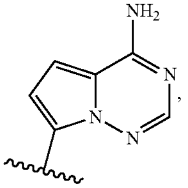


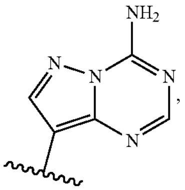


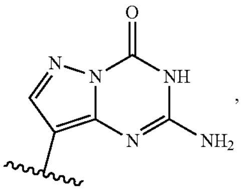


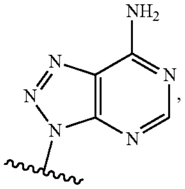


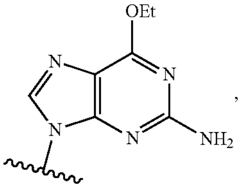


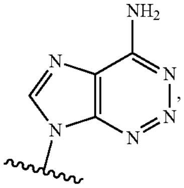


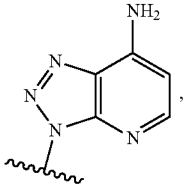


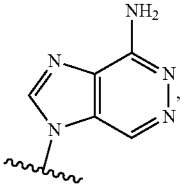


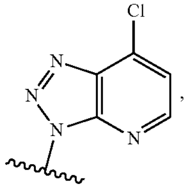


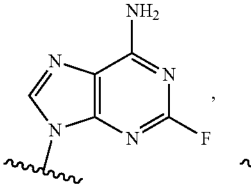


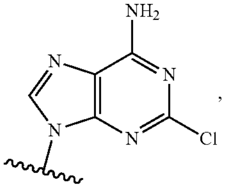












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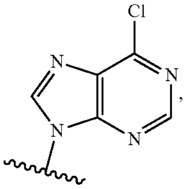

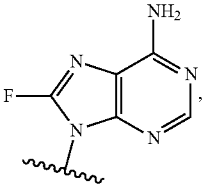

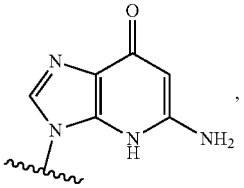

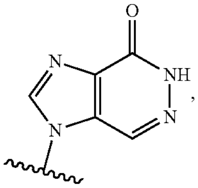

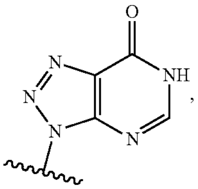

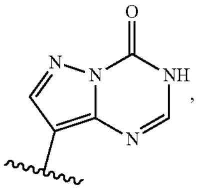

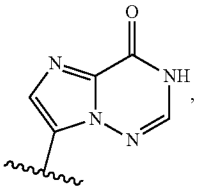

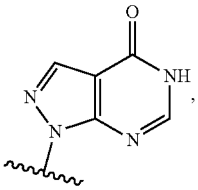

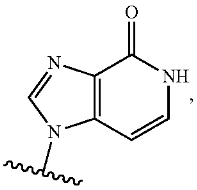

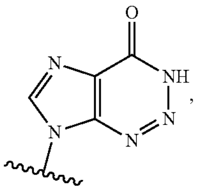

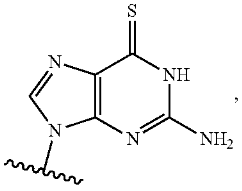

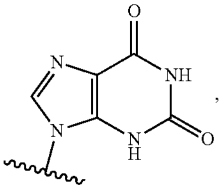

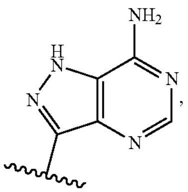

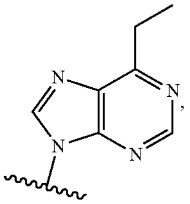

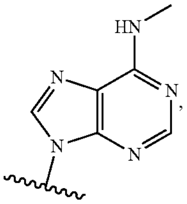

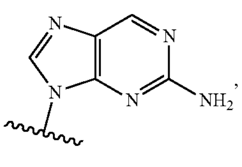

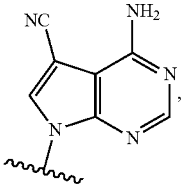

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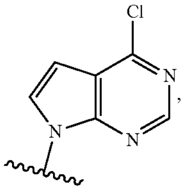

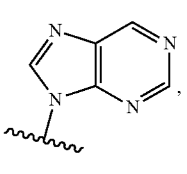

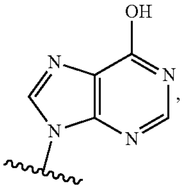

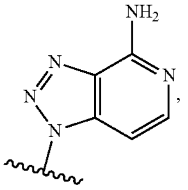

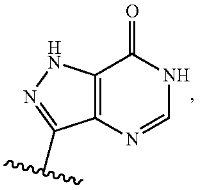

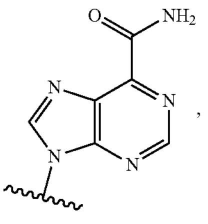

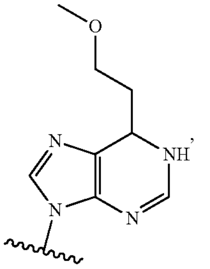

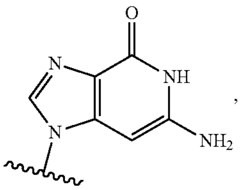

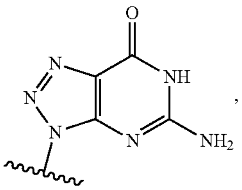

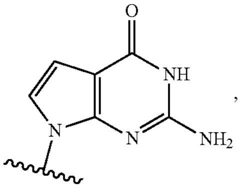

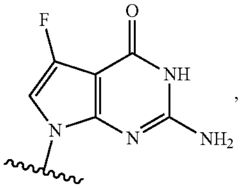

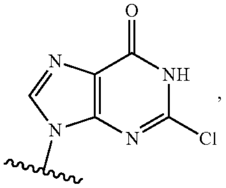

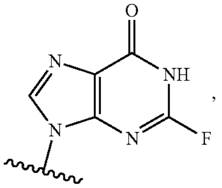

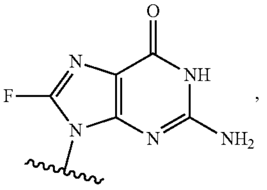

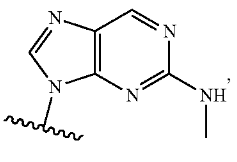

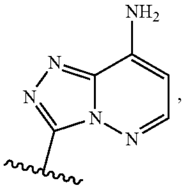

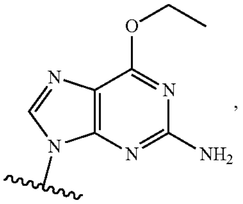

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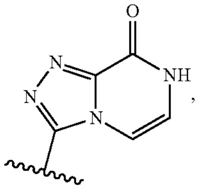
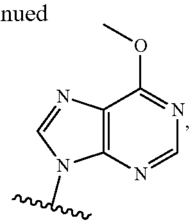
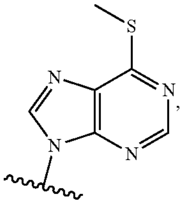
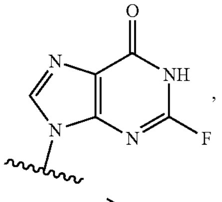
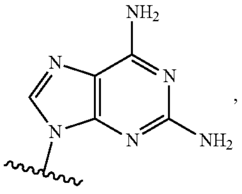
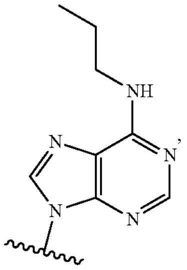
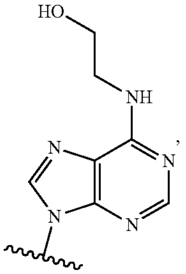
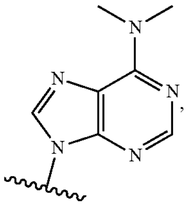
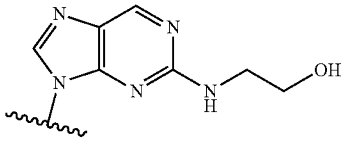
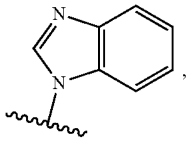
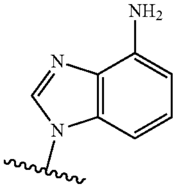
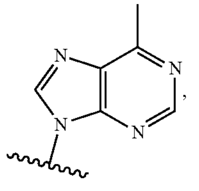
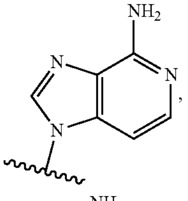
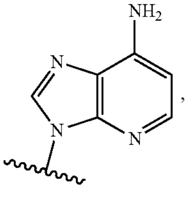
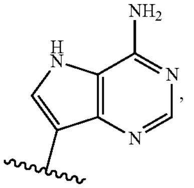
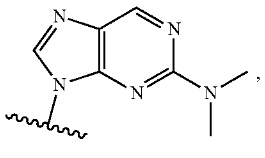

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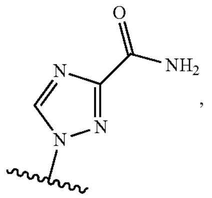
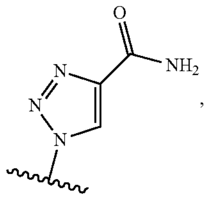

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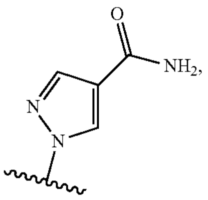
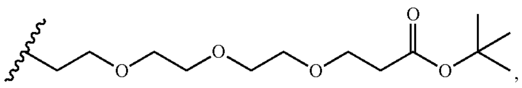


where Base^1 and Base^2 each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH$_2$, C$_{1-3}$ alkyl, C$_{3-6}$ cycloalkyl, O(C$_{1-3}$ alkyl), O(C$_{3-6}$ cycloalkyl), S(C$_{1-3}$ alkyl), S(C$_{3-6}$ cycloalkyl), NH(C$_{1-3}$ alkyl), NH(C$_{3-6}$ cycloalkyl), N(C$_{1-3}$ alkyl)$_2$, and N(C$_{3-6}$ cycloalkyl)$_2$; X^c and X^{c1} are each independently selected from the group consisting of OR^9, SR^9, and NR^{9}R^9; 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 F, Cl, Br, I, and OH; R^5 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, NH$_2$, 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, and OH; R^3 and R^5 are not both selected from the group consisting of: OH, R^5 C$_1$-C$_6$ alkyl substituted with OH, or C$_1$-C$_6$ haloalkyl substituted with OH; and each R^9 is independently selected from the group consisting of H, C$_2$-C$_3$ alkyl,



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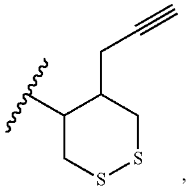
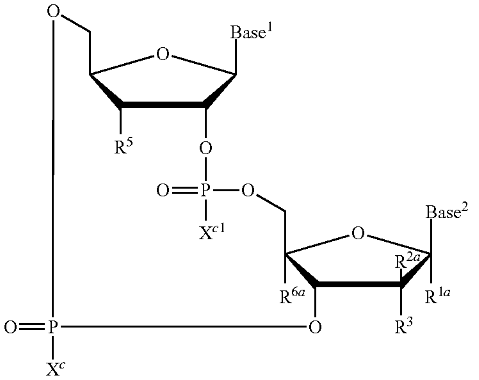


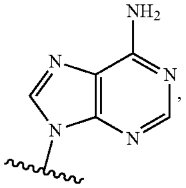
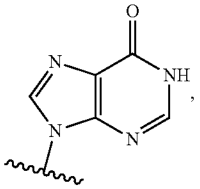
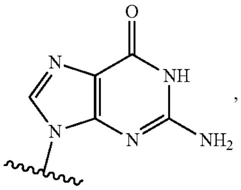
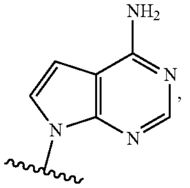
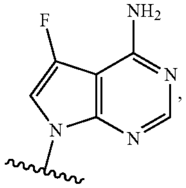
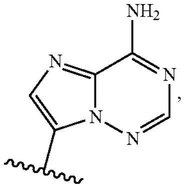
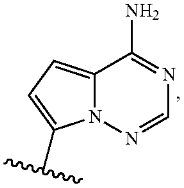
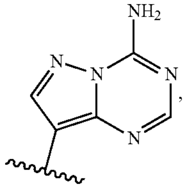
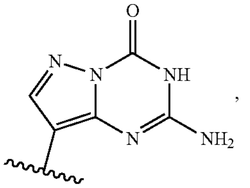
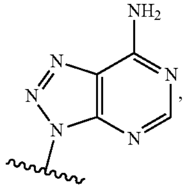
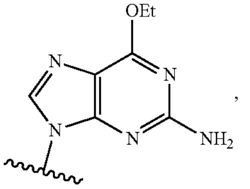
where each R^9 C$_2$-C$_3$ alkyl is optionally substituted by 1 to 2 substituents independently selected from the group consisting of OH, —O—C$_1$-C$_{20}$ alkyl, —S—C(O)C$_1$-C$_6$ alkyl, and C(O)OC$_1$-C$_6$ alkyl. In all instances of this aspect, all other groups are as provided in the general formula (I') of the second embodiment above.

[0073] In a twentieth aspect of the second embodiment, the compound of formula (I') is a compound of formula (I'b):



(I'b)

or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, wherein Base^1 and Base^2 are each independently selected from the group consisting of

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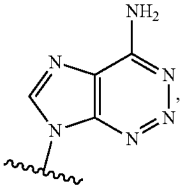
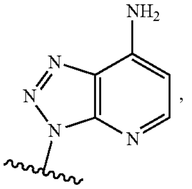
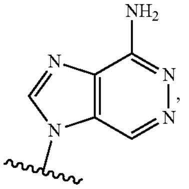
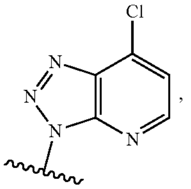
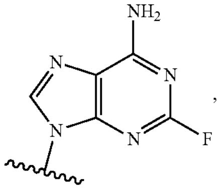
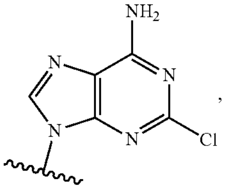
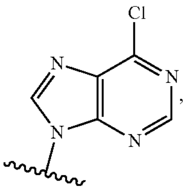
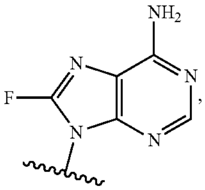
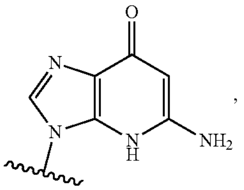
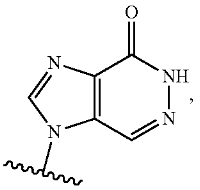
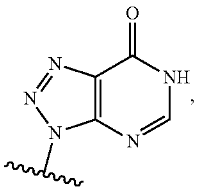
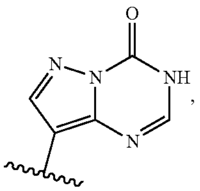
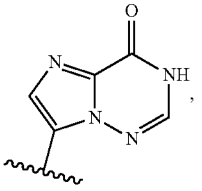
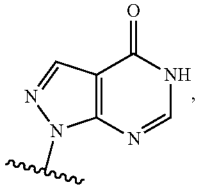
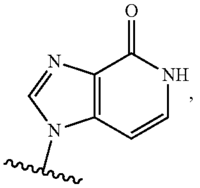
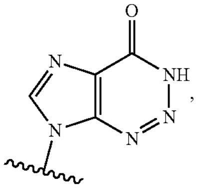

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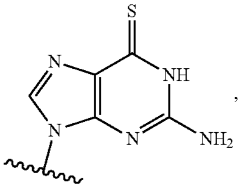
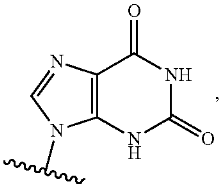
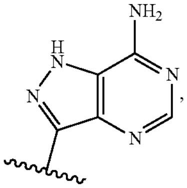
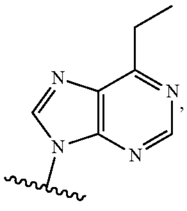
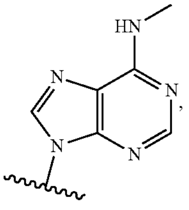
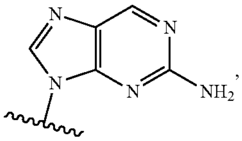
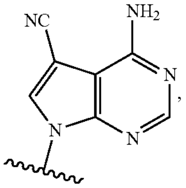
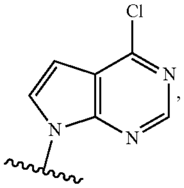
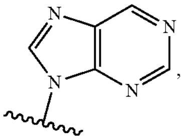
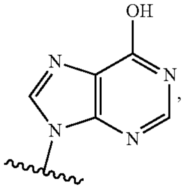
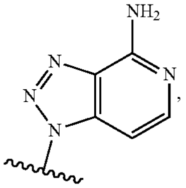
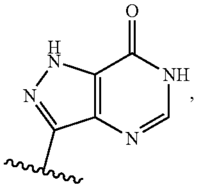
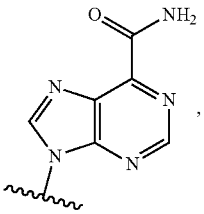
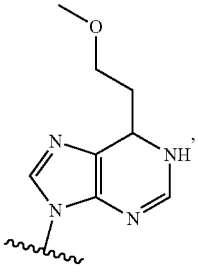
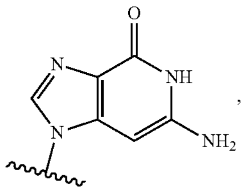
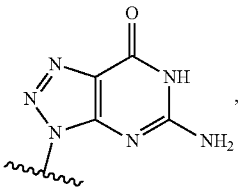
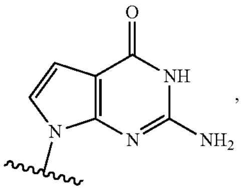
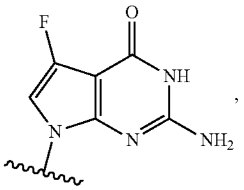

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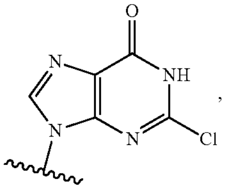
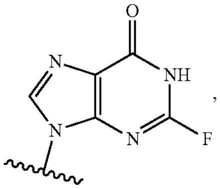
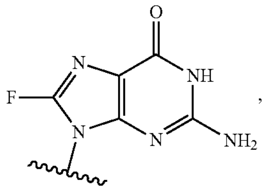
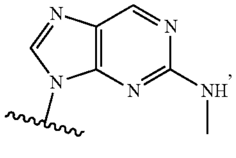
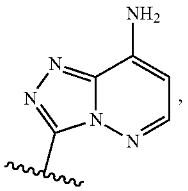
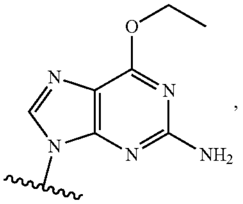
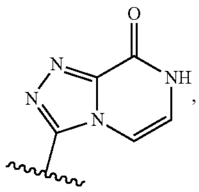
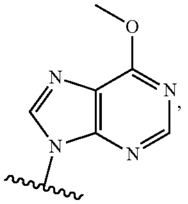
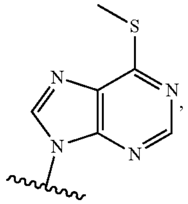
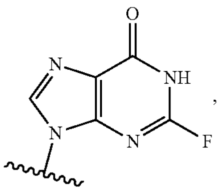
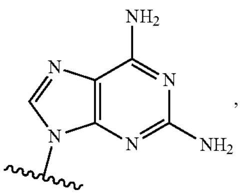
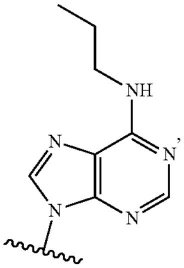
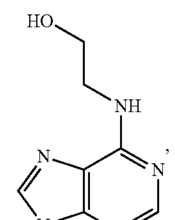
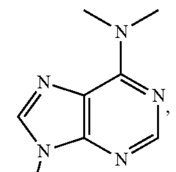

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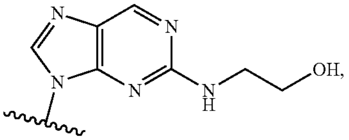

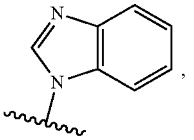

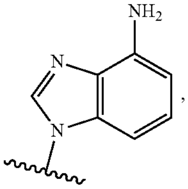

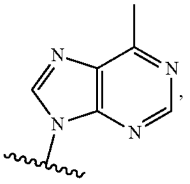

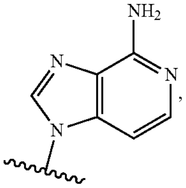

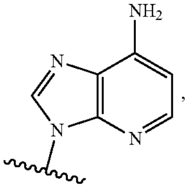

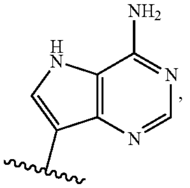

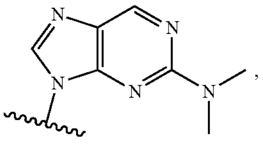

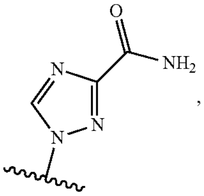

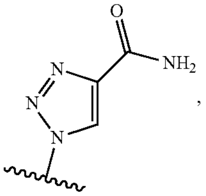

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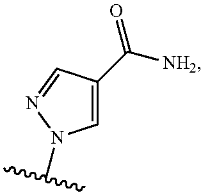
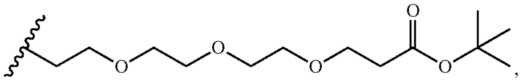


where Base^1 and Base^2 each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH$_2$, C$_{1-3}$ alkyl, C$_{3-6}$ cycloalkyl, O(C$_{1-3}$ alkyl), O(C$_{3-6}$ cycloalkyl), S(C$_{1-3}$ alkyl), S(C$_{3-6}$ cycloalkyl), NH(C$_{1-3}$ alkyl), NH(C$_{3-6}$ cycloalkyl), N(C$_{1-3}$ alkyl)$_2$, and N(C$_{3-6}$ cycloalkyl)$_2$; X^c and X^{c1} are each independently selected from the group consisting of OR^9, SR^9, and NR^{9}R^9; R^{1a} 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^{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^{2a} 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^{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 F, Cl, Br, I, and OH; 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 F, Cl, Br, I, and OH; R^5 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, NH$_2$, 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, and OH; R^3 and R^5 are not both selected from the group consisting of OH, C$_1$-C$_6$ alkyl substituted with OH, and C$_1$-C$_6$ haloalkyl substituted with OH; R^{6a} is selected from the group consisting of H, F, Cl, Br, I, OH, C$_1$-C$_6$ alkyl, C$_2$-C$_6$ alkenyl, and C$_2$-C$_6$ alkynyl; each R^9 is independently selected from the group consisting of H, C$_2$-C$_3$ alkyl,



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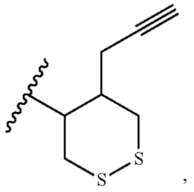
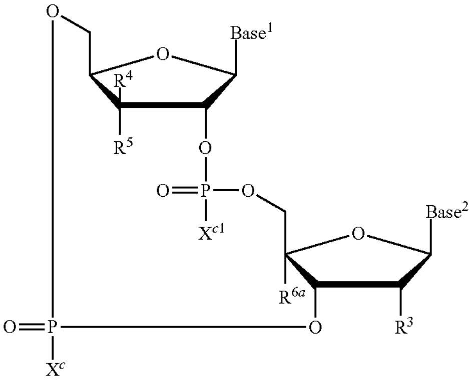


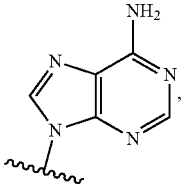
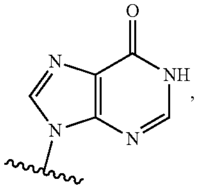
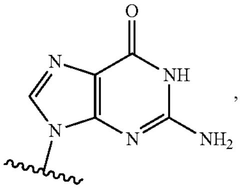
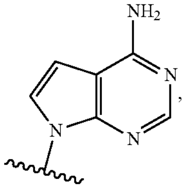
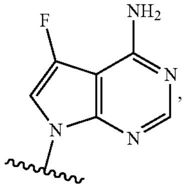
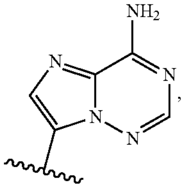
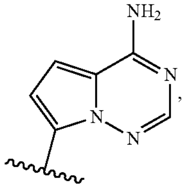
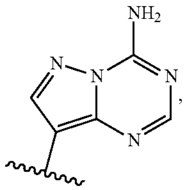
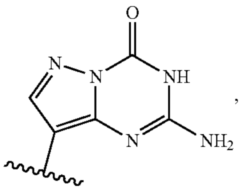
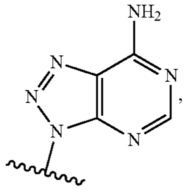
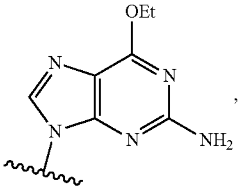
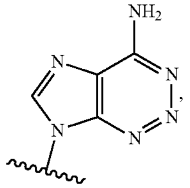
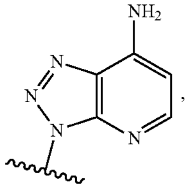
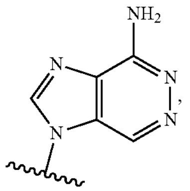
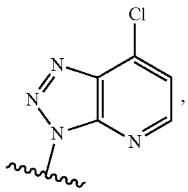
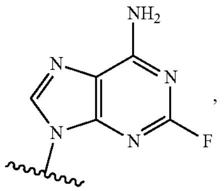
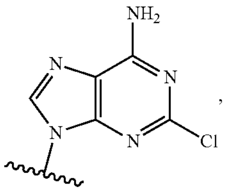
where each R^9 C$_2$-C$_3$ alkyl is optionally substituted by 1 to 2 substituents independently selected from the group consisting of OH, —O—C$_1$-C$_{20}$ alkyl, —S—C(O)C$_1$-C$_6$ alkyl, and C(O)OC$_1$-C$_6$ alkyl; and optionally R^3 and R^{6a} are connected to form —O—C$_1$-C$_6$ alkylene, —O—C$_2$-C$_6$ alkenylene, and —O—C$_2$-C$_6$ alkynylene, such that where R^3 and R^{6a} 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^3 position. In this aspect, all other groups are as provided in the general formula (I') of the second embodiment above.

[0074] In a twenty-first aspect of the second embodiment, the compound of formula (I') is a compound of formula (I'c):



(I'c)

or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, wherein Base^1 and Base^2 are each independently selected from the group consisting of

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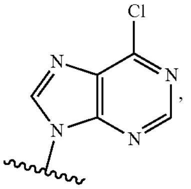
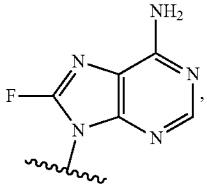
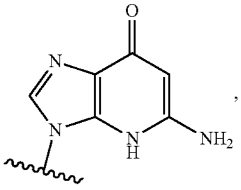
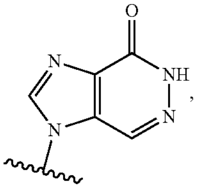
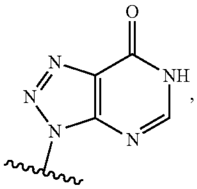
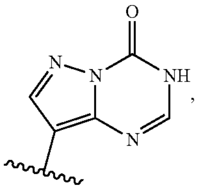
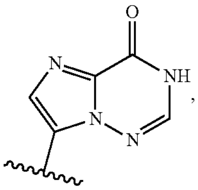
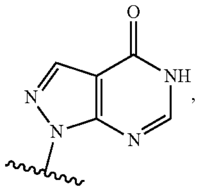
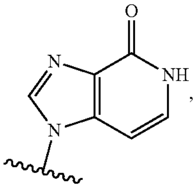
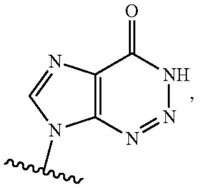
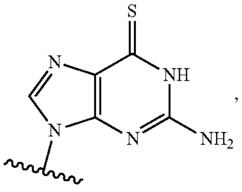
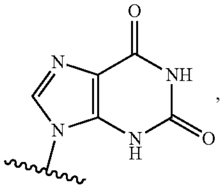
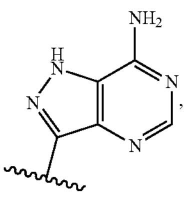
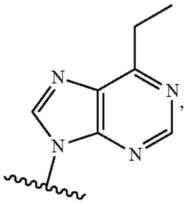
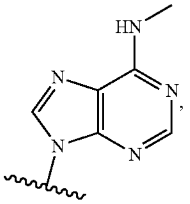
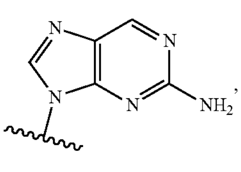
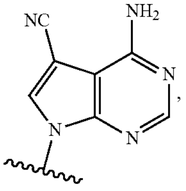

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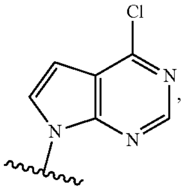
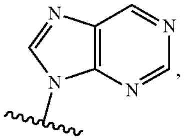
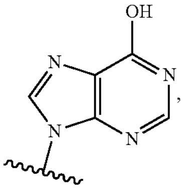
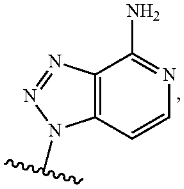
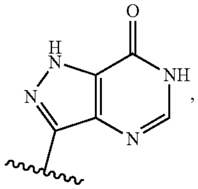
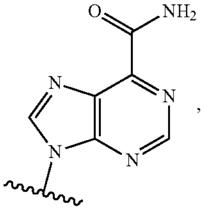
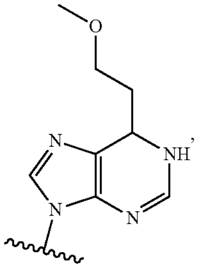
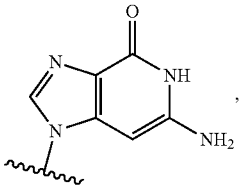
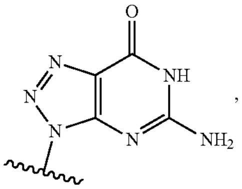
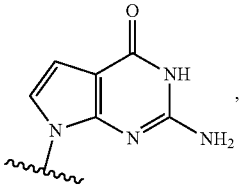
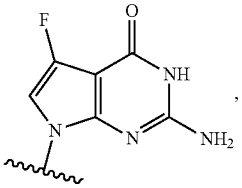
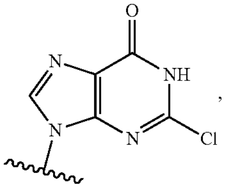
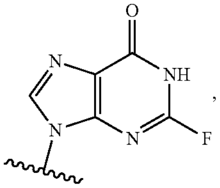
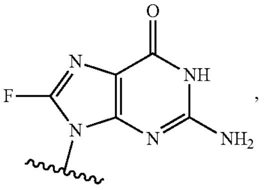
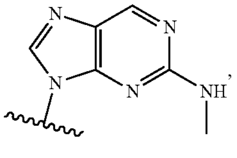
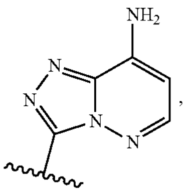
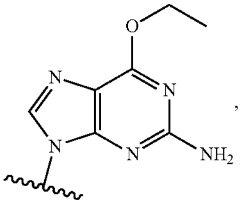

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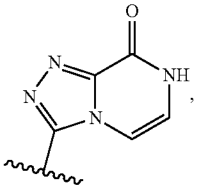
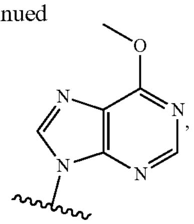
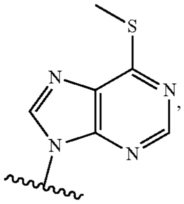
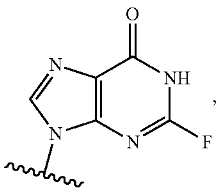
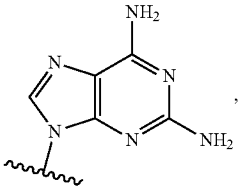
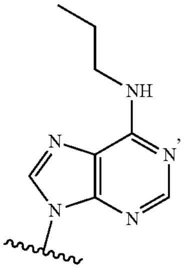
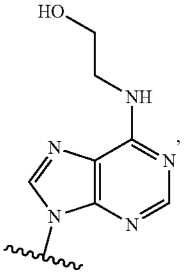
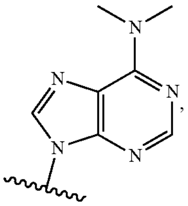
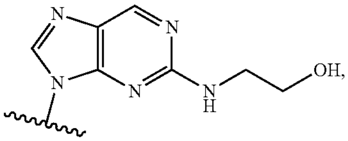
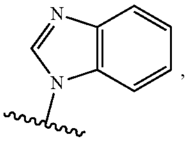
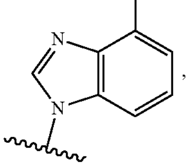
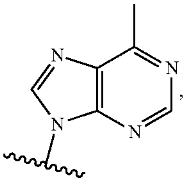
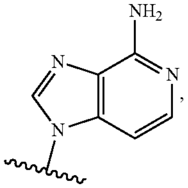
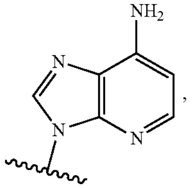
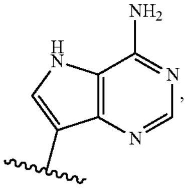
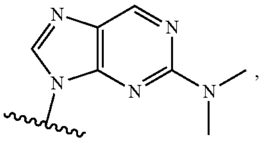

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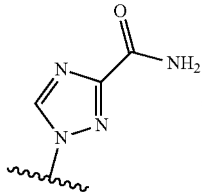

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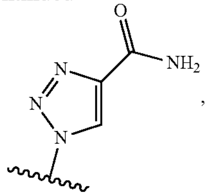

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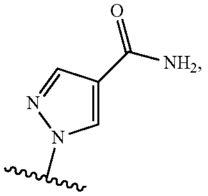
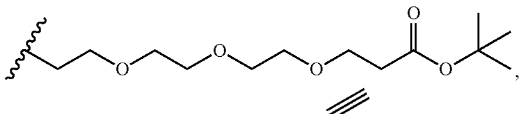


where Base^1 and Base^2 each may be independently substituted by 0-3 substituents R^{10}, where each R^{10} is independently selected from the group consisting of F, Cl, I, Br, OH, SH, NH_2, C_{1-3} alkyl, C_{3-6} cycloalkyl, O(C_{1-3} alkyl), O(C_{3-6} cycloalkyl), S(C_{1-3} alkyl), S(C_{3-6} cycloalkyl), NH(C_{1-3} alkyl), NH(C_{3-6} cycloalkyl), N(C_{1-3} alkyl)$_2$, and N(C_{3-6} cycloalkyl)$_2$; X^c and X^{c1} are each independently selected from the group consisting of OR^9, SR^9, and NR^9R^9; 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 F, Cl, Br, I, and OH; R^4 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^4 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, and OH; R^5 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, NH_2, 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, and OH; R^{6a} 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^{6a} 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, and OH; each R^9 is independently selected from the group consisting of H, C_2-C_3 alkyl,



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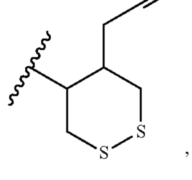

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where each R^9 C_2-C_3 alkyl is optionally substituted by 1 to 2 substituents independently selected from the group consisting of OH, —O—C_1-C_{20} alkyl, —S—C(O)C_1-C_6 alkyl, and C(O)OC_1-C_6 alkyl; and optionally R^4 and R^5 are connected by C_1-C_6 alkylene, —O—C_1-C_6 alkylene, —O—C_2-C_6 alkenylene, or —O—C_2-C_6 alkynylene, such that where R^4 and R^5 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. In this aspect, all other groups are as provided in the general formula (I') of the second embodiment above.

[0075] A twenty-second aspect of the second embodiment relates to a pharmaceutical composition, said pharmaceutically acceptable composition comprising (a) a compound according to any one of general formula (I') of the second embodiment above or in the first through twenty-first aspects described above or a pharmaceutically acceptable salt, hydrate, solvate or prodrug thereof, and (b) a pharmaceutically acceptable carrier.

[0076] A twenty-third aspect of the second 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') of the second embodiment above or in the first through twenty-first aspects described above or a pharmaceutically acceptable salt, hydrate, solvate or prodrug thereof to the subject.

[0077] A twenty-fourth aspect of the second embodiment relates to methods of inducing an immune response in a subject, comprising administering a therapeutically effective amount of a composition according to the twenty-second aspect described above or a pharmaceutically acceptable salt, hydrate, solvate or prodrug thereof to the subject.

[0078] A twenty-fifth aspect of the second embodiment relates to methods of inducing a STING-dependent type I interferon production in a subject, comprising administering a therapeutically effective amount of a compound according to any one of general (I') of the second embodiment above or in the first through twenty-first aspects described above or a pharmaceutically acceptable salt, hydrate, solvate or prodrug thereof to the subject.

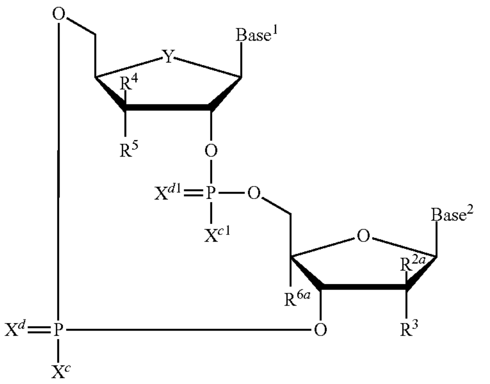
[0079] A twenty-sixth aspect of the second embodiment relates to methods of inducing a STING-dependent type I interferon production in a subject, comprising administering a therapeutically effective amount of a composition according to the twenty-second aspect described above to the subject.

[0080] A twenty-seventh aspect of the second embodiment relates to methods of inducing a STING-dependent cytokine production in a subject, comprising administering a therapeutically effective amount of a compound according to any one of general (I') of the second embodiment above or in the first through twenty-first aspects described above or a pharmaceutically acceptable salt, hydrate, solvate or prodrug thereof to the subject.

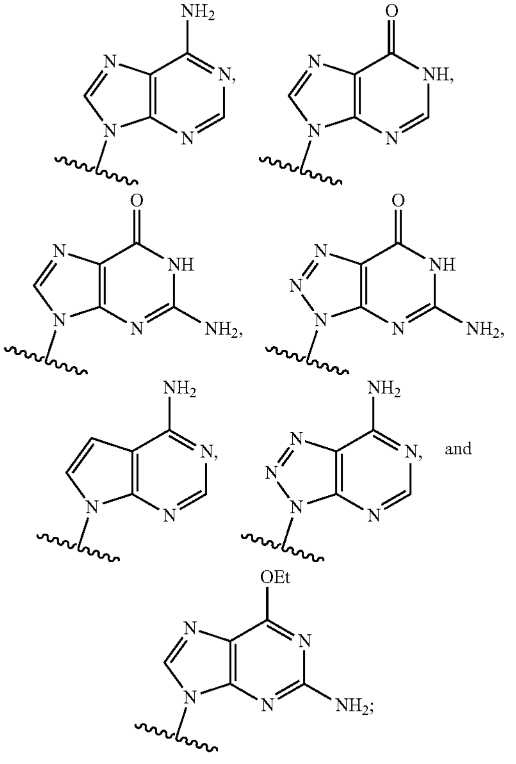
[0081] A thirty-third aspect of the second embodiment relates to methods of inducing a STING-dependent cytokine production in a subject, comprising administering a therapeutically effective amount of a composition according to the twenty-second aspect described above to the subject.

[0082] A third embodiment of the disclosure relates to cyclic di-nucleotide compounds of general formula (I''):

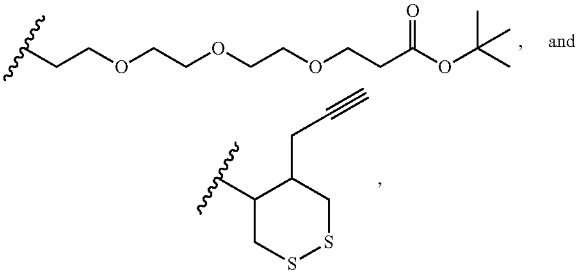
(I'')



or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, wherein Base^1 and Base^2 are each independently selected from the group consisting of

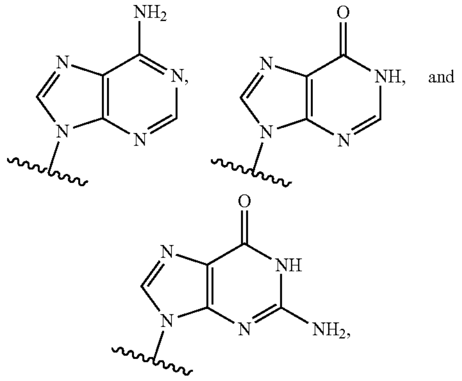


Y is selected from the group consisting of —O— and —S—; X^c and X^{c1} are each independently selected from the group consisting of OR^9 and SR^9; X^d and X^{d1} are each independently selected from the group consisting of O and S; R^{2a} is selected from the group consisting of H, F, Cl, Br, I, OH, 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; 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; R^4 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; R^5 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, NH$_2$, 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; R^{6a} 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; each R^9 is independently selected from the group consisting of H, C$_1$-C$_{20}$ alkyl,

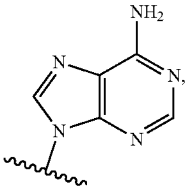


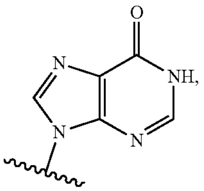
where each R^9 C$_1$-C$_{20}$ alkyl is optionally substituted by 0 to 3 substituents independently selected from the group consisting of OH, —O—C$_1$-C$_{20}$ alkyl, —S—C(O)C$_1$-C$_6$ alkyl, and C(O)OC$_1$-C$_6$ alkyl; and optionally R^3 and R^{6a} are connected to form —O—C$_1$-C$_6$ alkylene, —O—C$_2$-C$_6$ alkenylene, or —O—C$_2$-C$_6$ alkynylene, such that where R^3 and R^{6a} 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^3 position.

[0083] In specific aspects of this embodiment, when Y and Y^a are each O, X^a and X^{a1} are each O, X^b and X^{b1} are each O, and X^c and X^{c1} are each OH or SH, X^d and X^{d1} are each O, R^1 and R^{1a} are each H, R^2 is H, 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 Base^1 and Base^2 are each selected from the group consisting of



R^5 and R^3 are not both selected from the group consisting of H, F and OH. That is, when Y and Y^a are each O, X^a and X^{a1} are each O, X^b and X^{b1} are each O, and X^c and X^{c1} are each OH or SH, X^d and X^{d1} are each O, R^1 and R^{1a} are each H, R^2 is H, 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 $Base^1$ and $Base^2$ are each selected from the group consisting of





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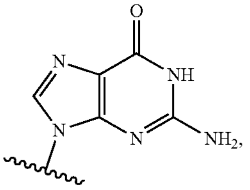
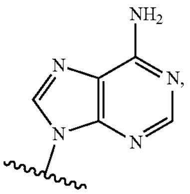
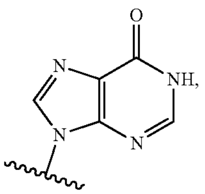
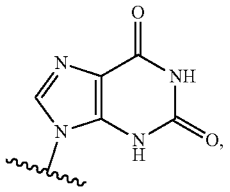


either only one of R^5 and R^3 is selected from the group consisting of H, F, and OH, or neither R^5 and R^3 is selected from the group consisting of H, F, and OH. In further specific instances of this aspect, when Y and Y^a are each O, X^a and X^{a1} are each O, X^b and X^{b1} are each O, and X^c and X^{c1} are each OH, X^d and X^{d1} are each O or S, R^1 and R^{1a} are each H, R^2 is H, 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 $Base^1$ and $Base^2$ are each selected from the group consisting of







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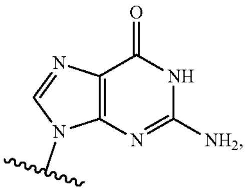
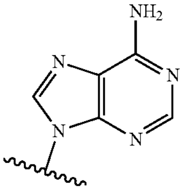


R^5 and R^3 are not both selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, where said C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl are substituted by 0 to 3 substituents selected from the group consisting of F, Cl, Br, I and OH.

[0084] In further specific aspects of this embodiment, when $Base^1$ and $Base^2$ are each selected from the group consisting of



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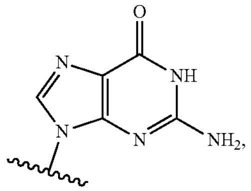
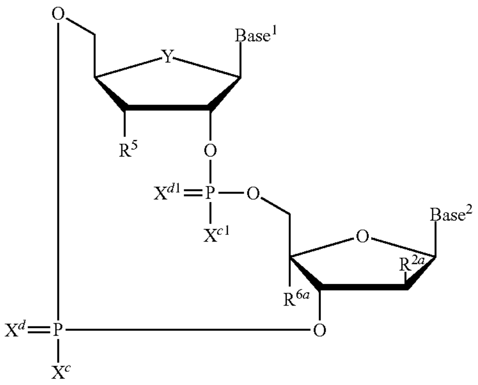


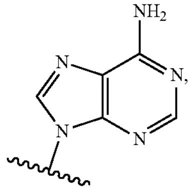
and R^{2a} is F and R^5 is F, at least one of X^c and X^{c1} is SR^9.

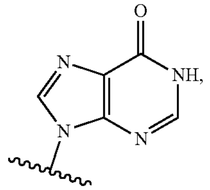
[0085] In a first aspect of the third embodiment, the compound of formula (I") is a compound of formula (I"a):

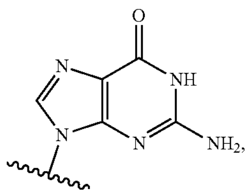


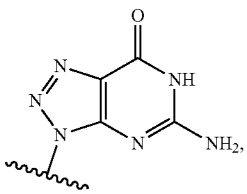
(I"a)

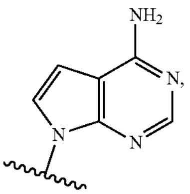
or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, wherein $Base^1$ and $Base^2$ are each independently selected from the group consisting of

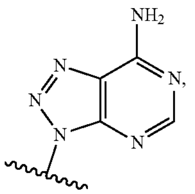












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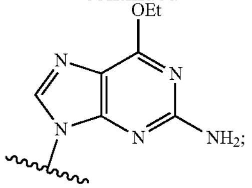
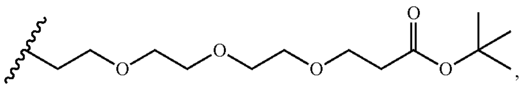


Y is selected from the group consisting of —O— and —S—; X^c and X^{c1} are each independently selected from the group consisting of OR^9 and SR^9; X^d and X^{d1} are each independently selected from the group consisting of O and S; R^{2a} is selected from the group consisting of H, F, Cl, Br, I, OH, 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; R^5 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, NH_2, 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; R^{6a} 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; and each R^9 is independently selected from the group consisting of H, C_1-C_{20} alkyl,



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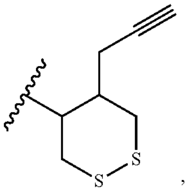

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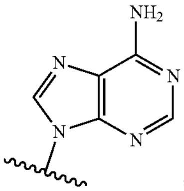
where each R^9 C_1-C_{20} alkyl is optionally substituted by 0 to 3 substituents independently selected from the group consisting of OH, —O—C_1-C_{20} alkyl, —S—C(O)C_1-C_6 alkyl, and C(O)OC_1-C_6 alkyl. In instances of this aspect, $Base^1$ and $Base^2$ are each independently selected from the group consisting of



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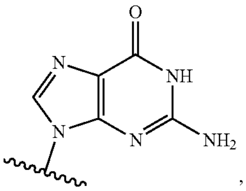

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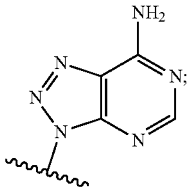
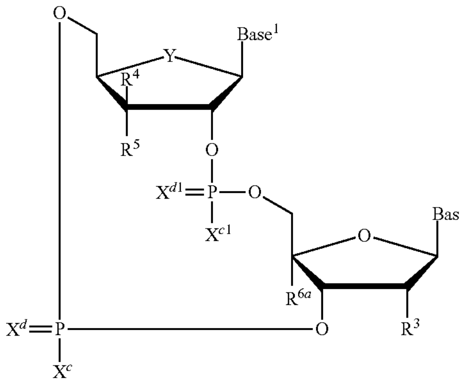


Y is selected from the group consisting of —O— and —S—; X^c and X^{c1} are each independently selected from the group consisting of OR^9 and SR^9; X^d and X^{d1} are each independently selected from the group consisting of O and S; R^{2a} is F; R^5 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, NH_2, 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; R^{6a} 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; and each R^9 is independently H.

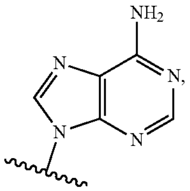
[0086] In a second aspect of the third embodiment, the compound of formula (I") is a compound wherein R^3 and R^{6a} are connected to form —O—C_1-C_6 alkylene, —O—C_2-C_6 alkenylene, or —O—C_2-C_6 alkynylene, such that where R^3 and R^{6a} are connected to form —O—C_1-C_6 alkylene, —O—C_2-C_6 alkenylene, or —O—C_2-C_6 alkynylene, said O is bound at the R^3 position.

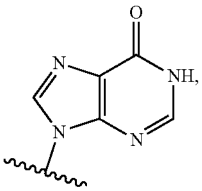
[0087] In a third aspect of the third embodiment, the compound of formula (I") is a compound of formula (I"b):

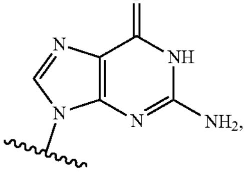
(I"b)

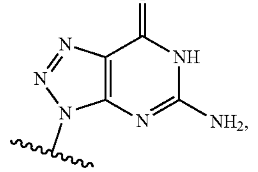


or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, wherein $Base^1$ and $Base^2$ are each independently selected from the group consisting of









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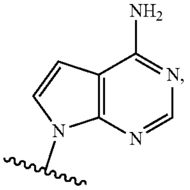

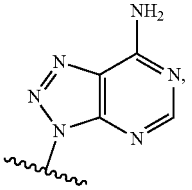

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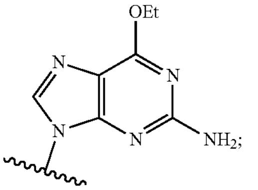
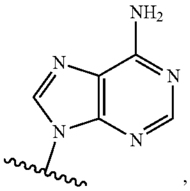


Y is selected from the group consisting of —O— and —S—; X^c and X^{c1} are each independently selected from the group consisting of OR^9 and SR^9; X^d and X^{d1} are each independently selected from the group consisting of O and S; R^3 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, 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; R^4 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; R^5 is selected from the group consisting of H, F, Cl, Br, I, OH, CN, NH_2, 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; R^{6a} 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; each R^9 is independently H; and R^3 and R^{6a} 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^3 and R^{6a} 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^3 position. In instances of this aspect, $Base^1$ and $Base^2$ are each independently selected from the group consisting of



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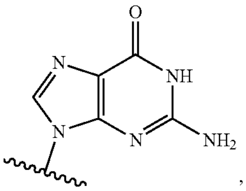

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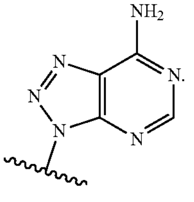
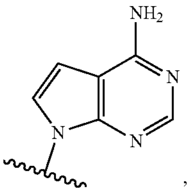


[0088] In a fourth aspect of the third embodiment, the compound of formula (I") is a compound wherein at least one of $Base^1$ and $Base^2$ are each independently selected from the group consisting of



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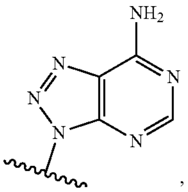

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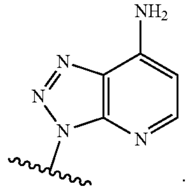

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[0089] A fifth aspect of the third embodiment relates to a pharmaceutical composition, said pharmaceutical composition comprising (a) a compound according to any one of general formula (I") of the third embodiment or a pharmaceutically acceptable salt, hydrate, solvate or prodrug thereof; and (b) a pharmaceutically acceptable carrier.

[0090] A sixth aspect of the third embodiment relates to methods of inducing an immune response in a subject, comprising administering a therapeutically effective amount of a compound according to general formula (I") of the third embodiment above or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof to the subject.

[0091] A seventh aspect of the 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 fifth aspect described above to the subject.

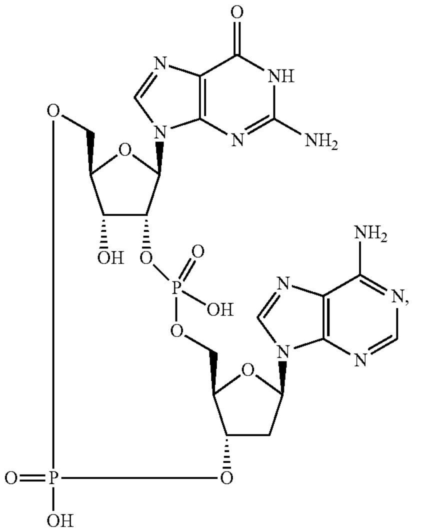
[0092] An eighth aspect of the third embodiment relates to methods of inducing a STING-dependent type I interferon production in a subject, comprising administering a therapeutically effective amount of a compound according general formula (I") of the third embodiment above or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof to the subject.

[0093] A ninth aspect of the third embodiment relates to methods of inducing a STING-dependent type I interferon production in a subject, comprising administering a therapeutically effective amount of a composition according to the fifth aspect described above to the subject.

[0094] A tenth aspect of the third embodiment relates to methods of inducing a STING-dependent cytokine production in a subject, comprising administering a therapeutically effective amount of a compound according to general formula (I") of the third embodiment above or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof to the subject.

[0095] An eleventh aspect of the third 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 fifth aspect described above to the subject.

[0096] In an additional embodiment, the compound is selected from the group consisting of



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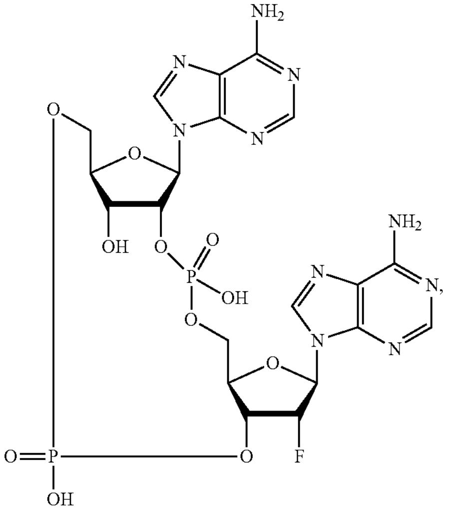

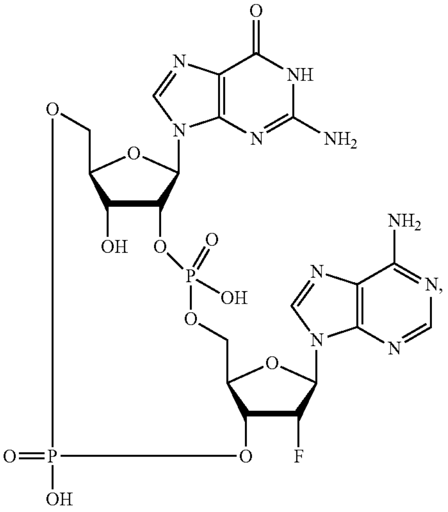

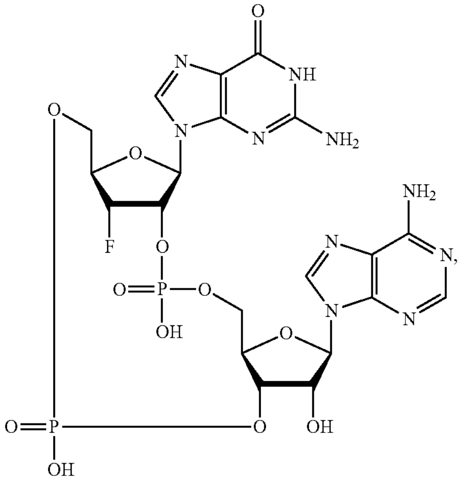

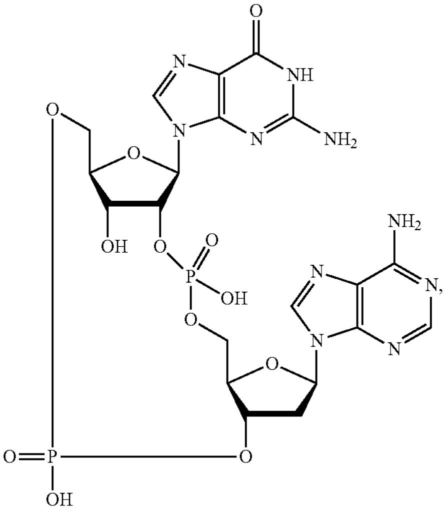

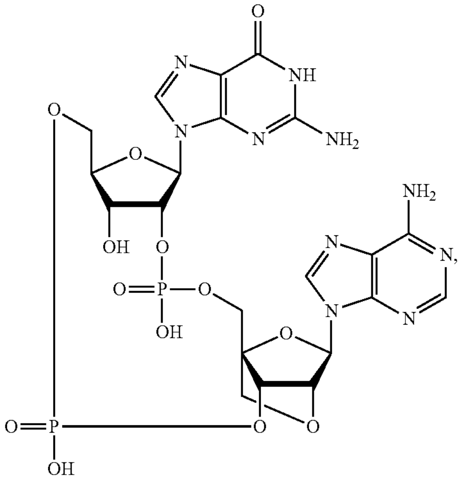

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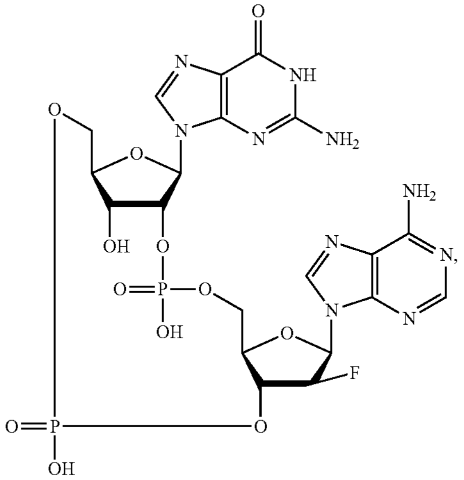

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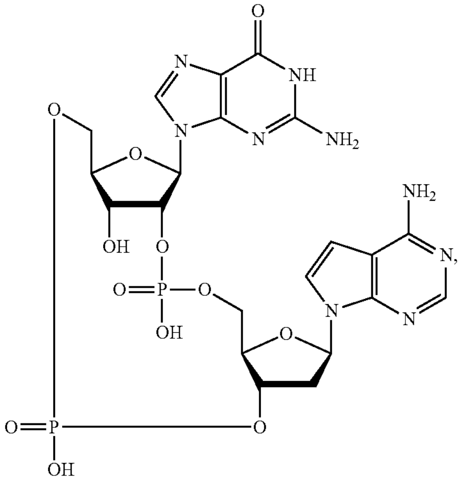

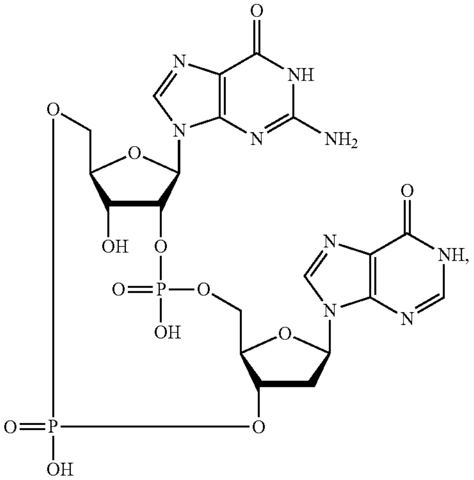

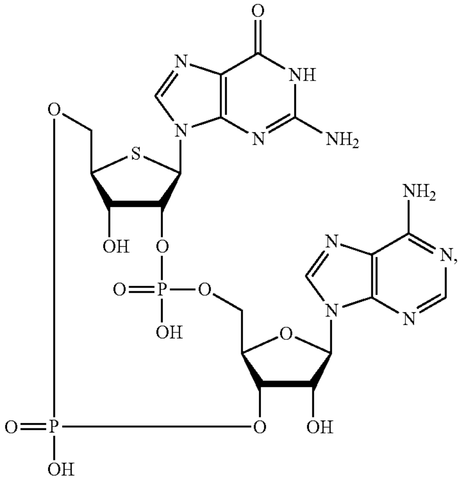

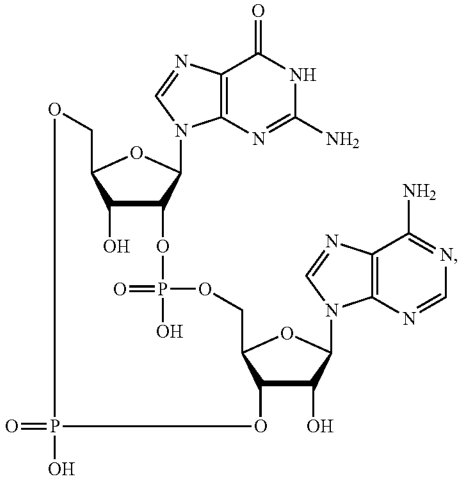

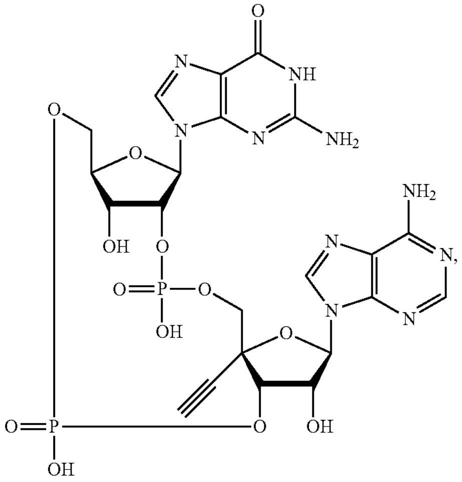

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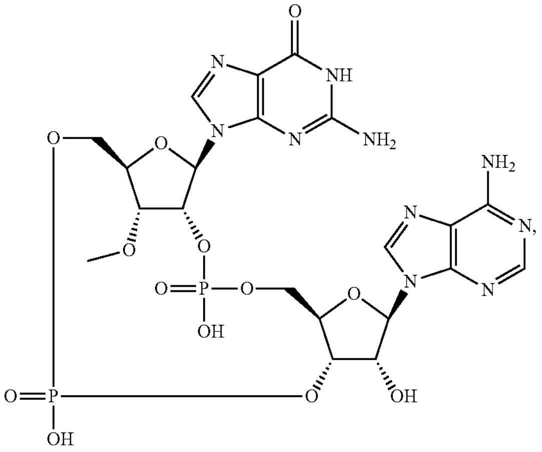

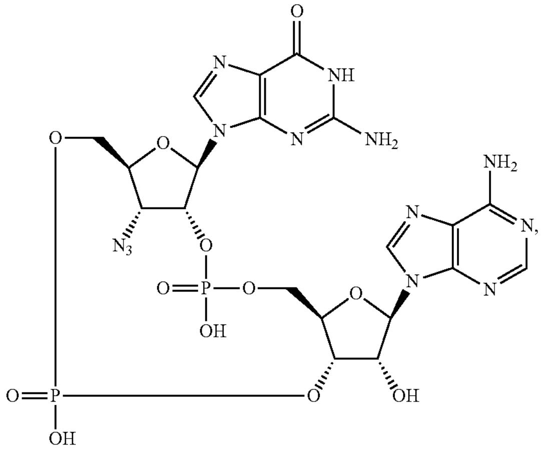

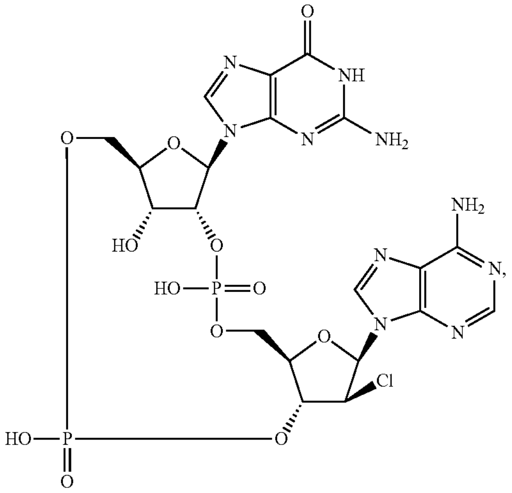

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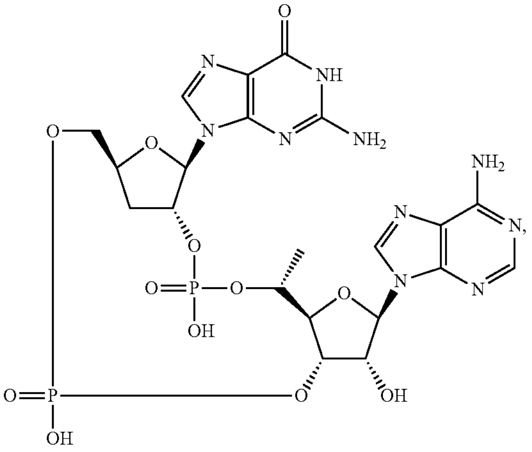

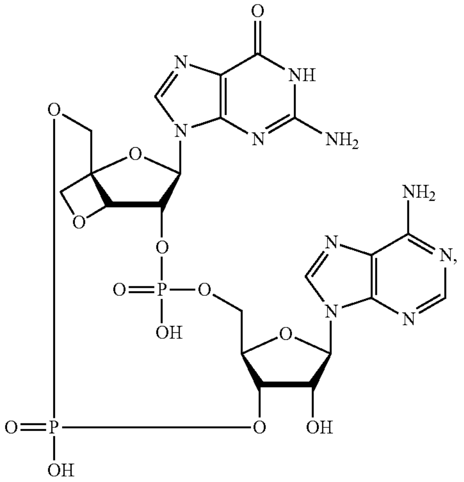

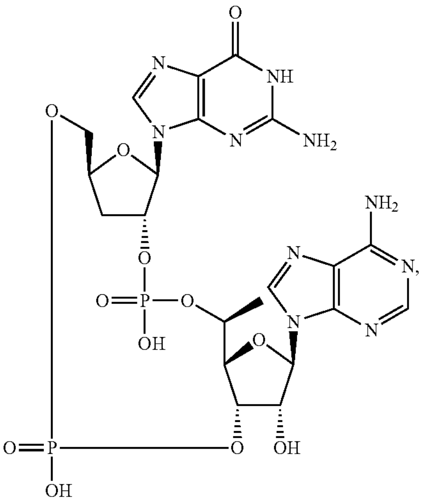

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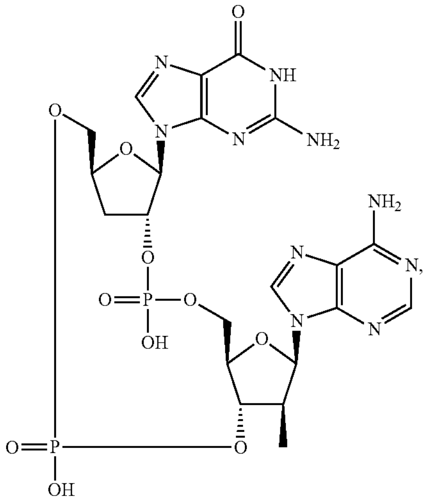

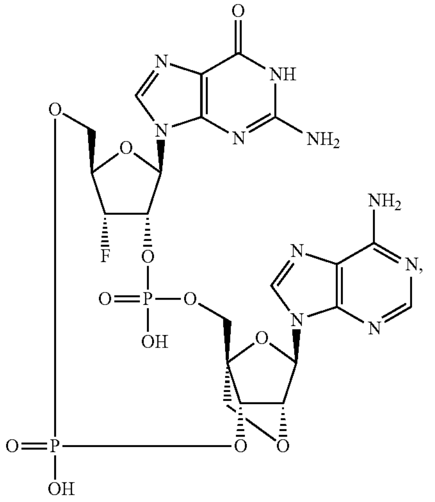

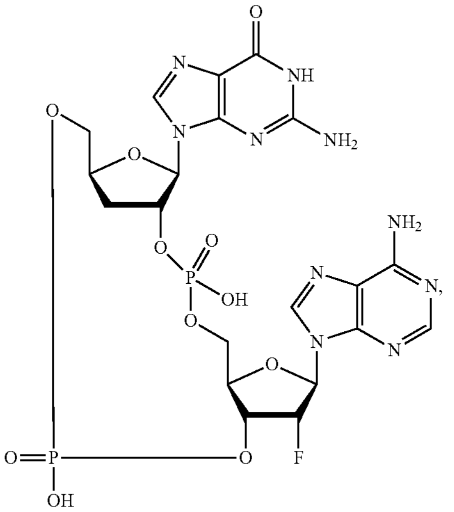

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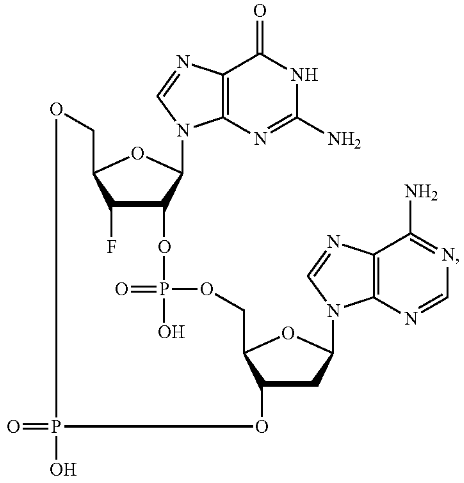

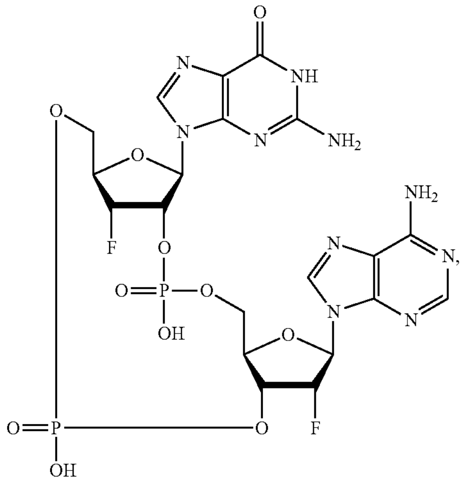

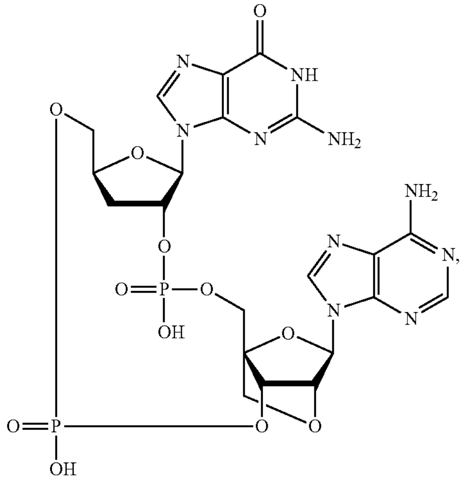

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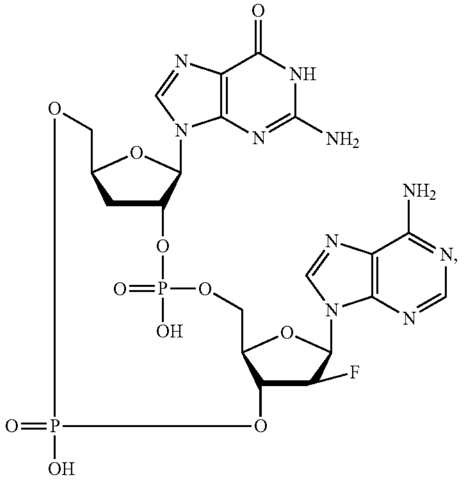

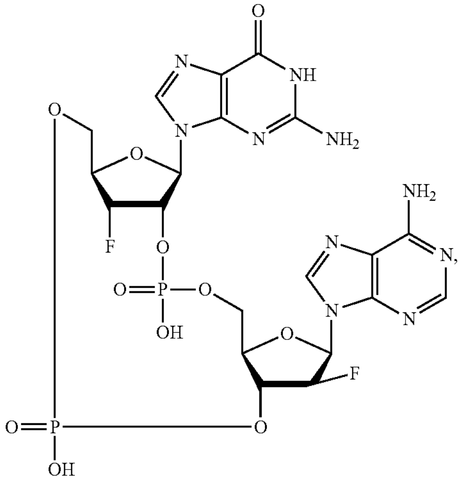

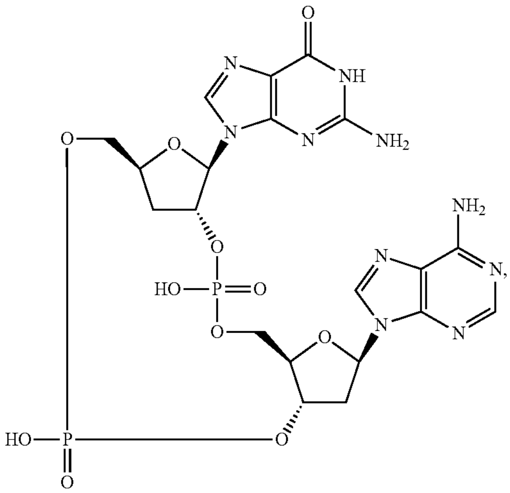

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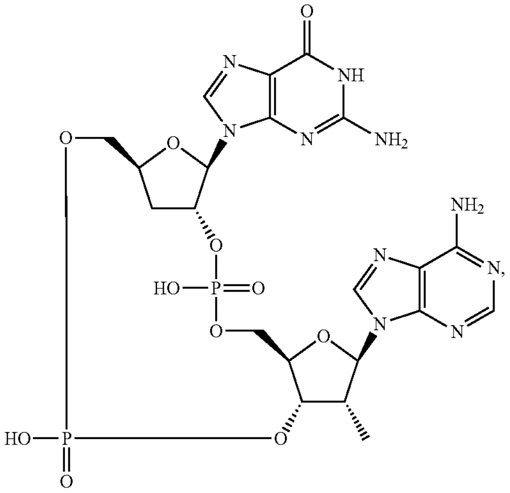

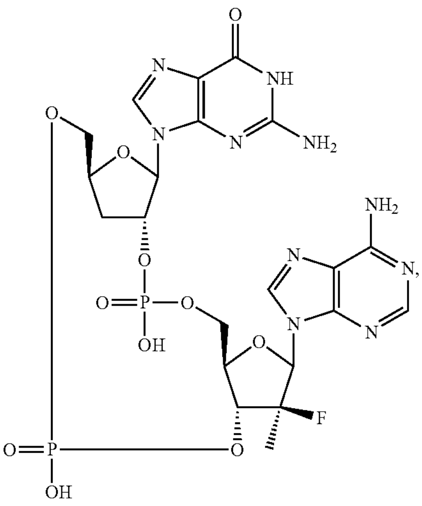

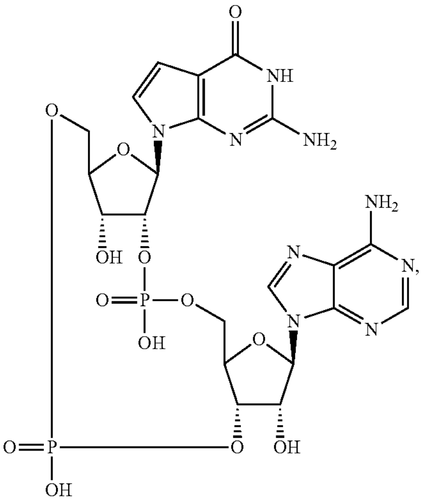

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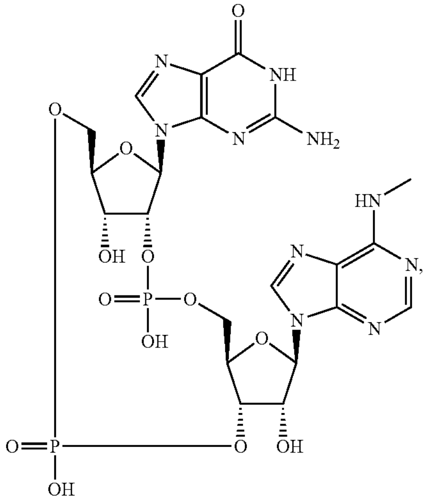

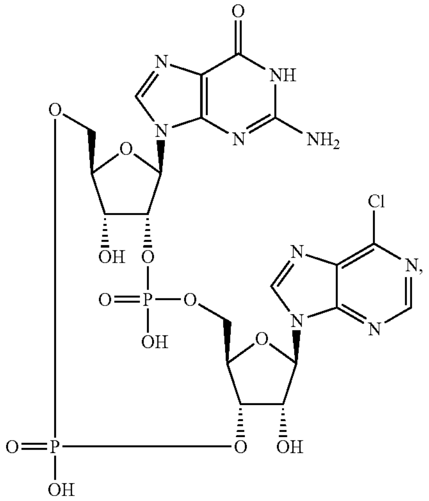

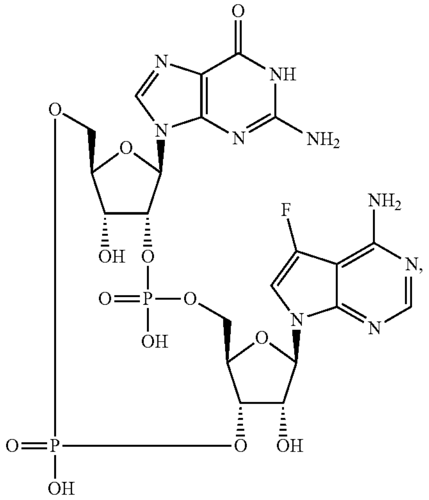

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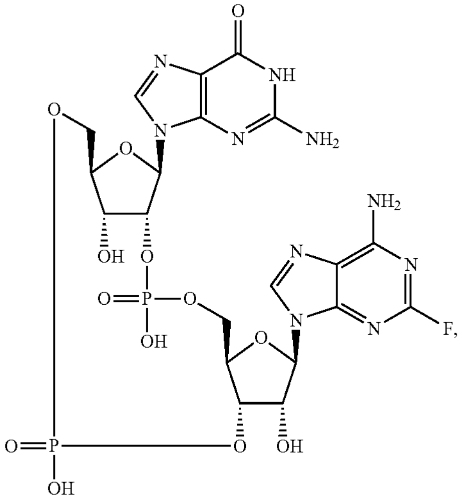

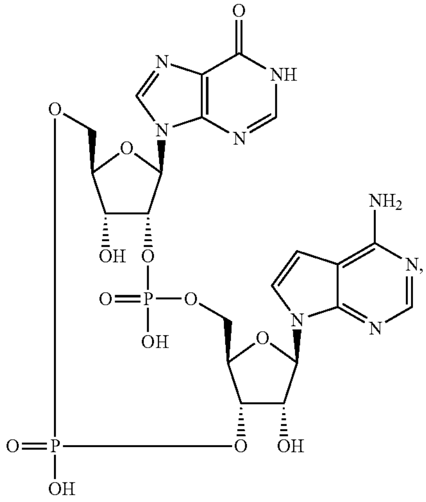

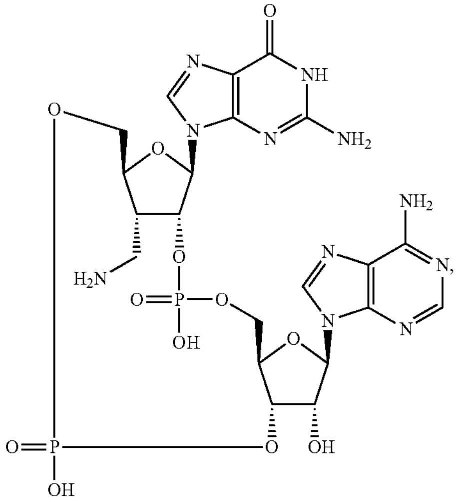

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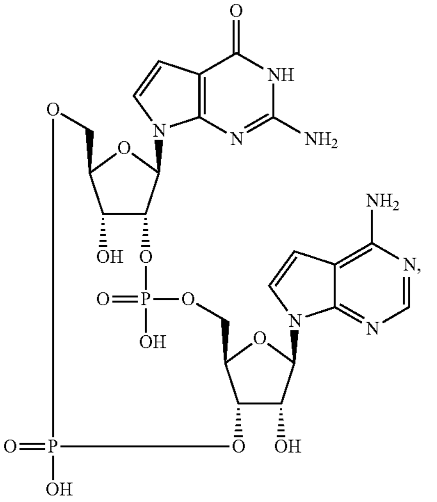

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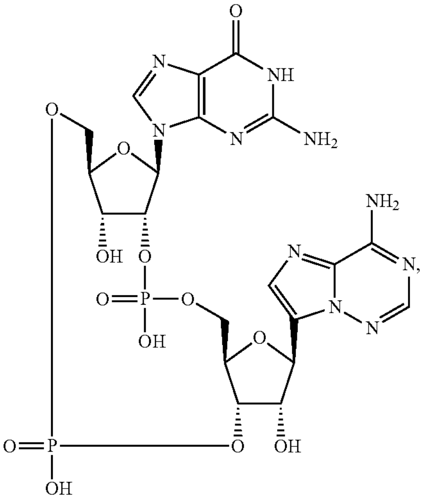

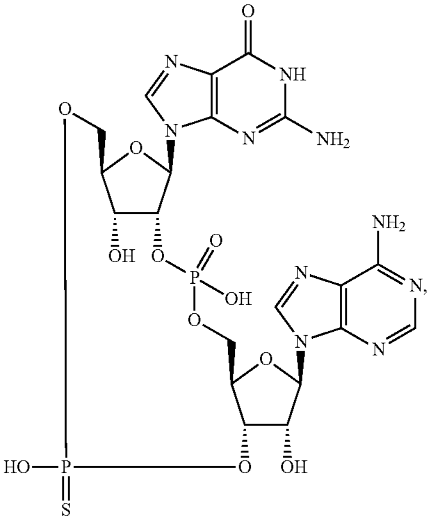

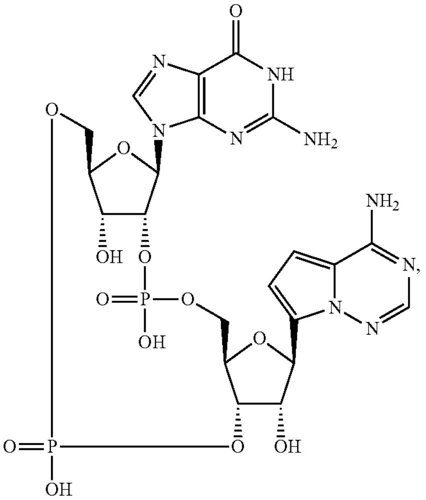

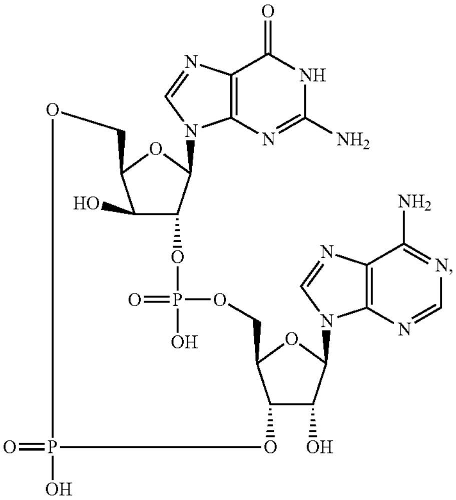

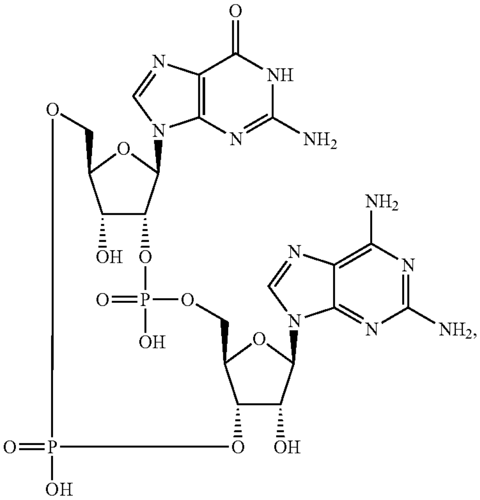

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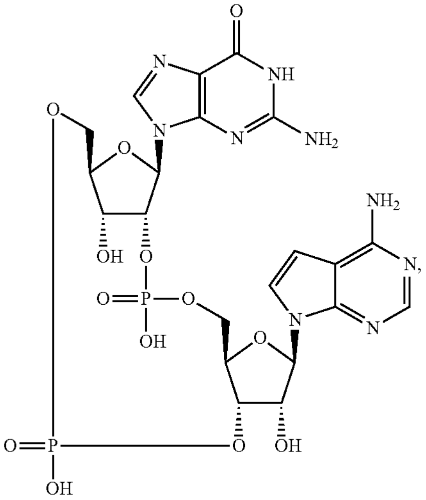

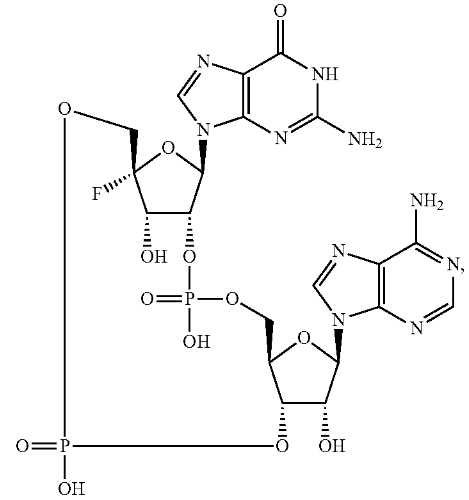

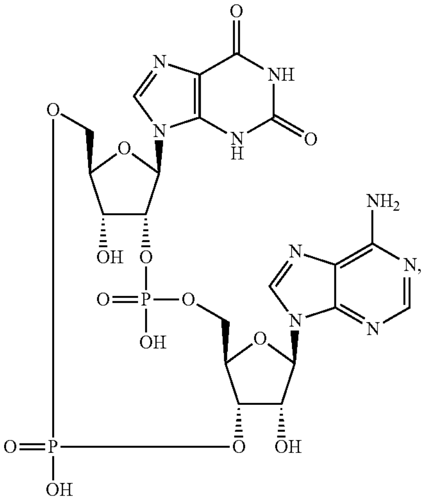

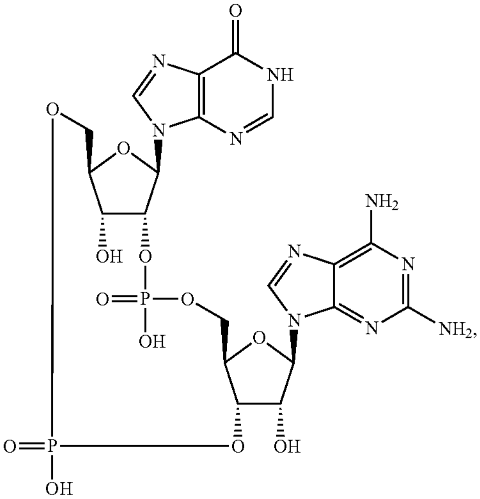

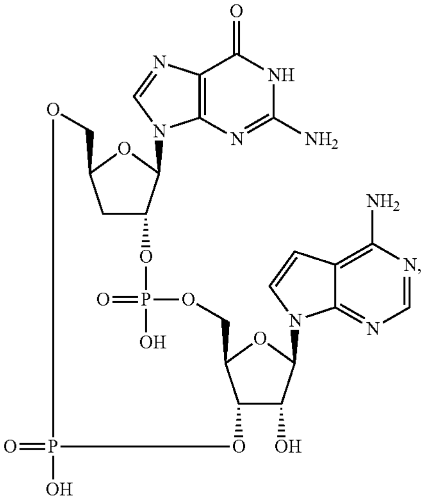

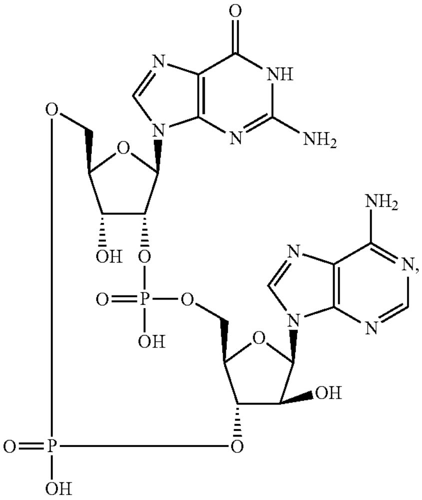

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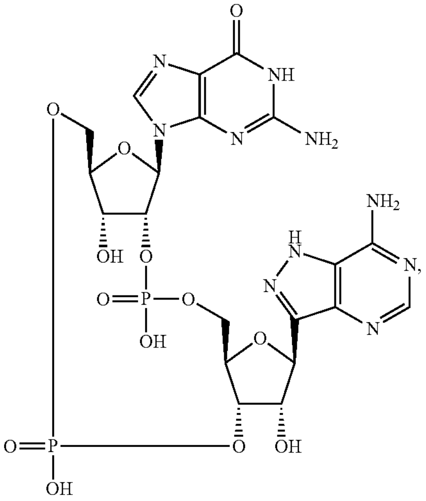

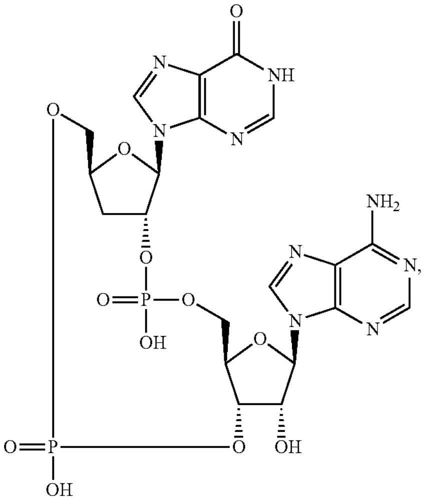

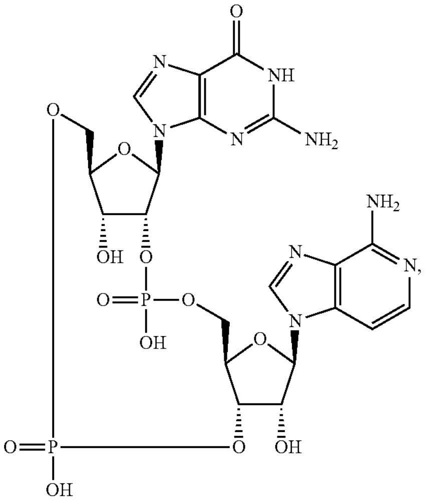

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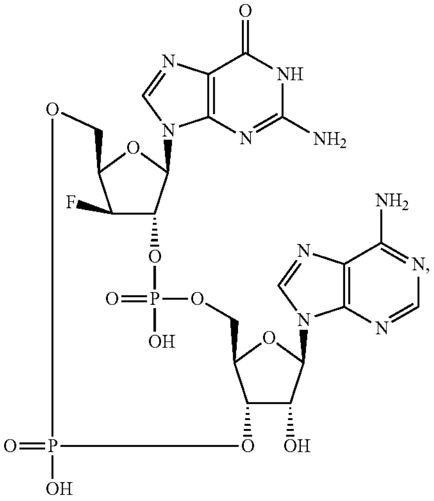

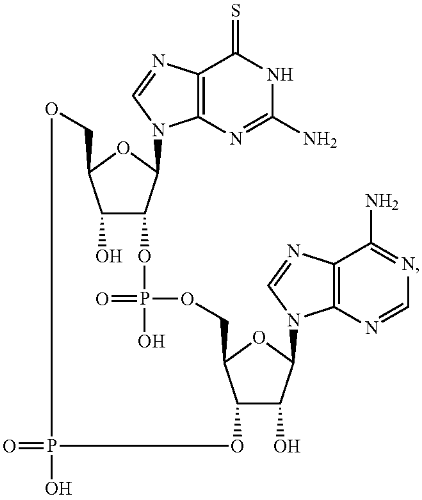

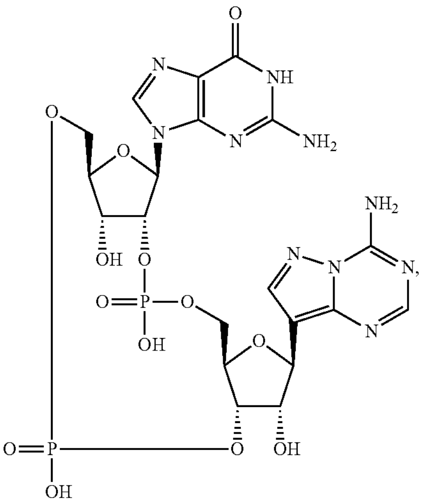

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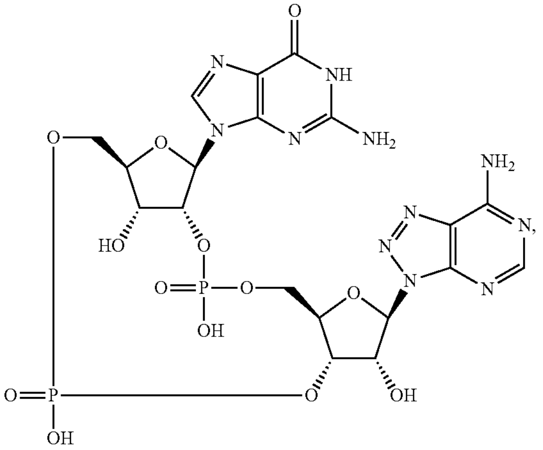

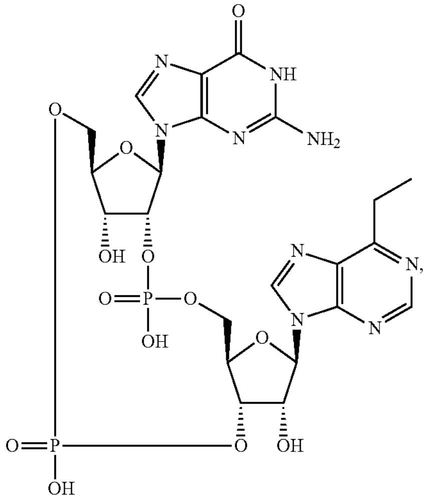

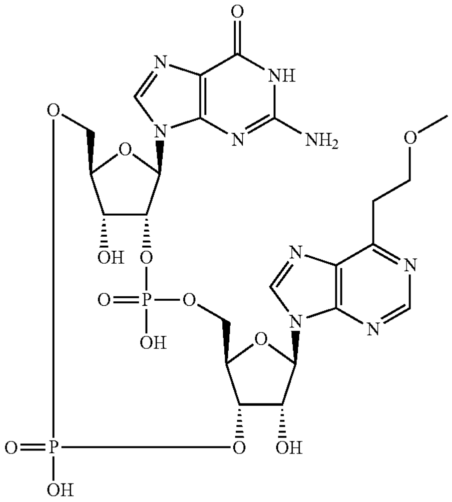

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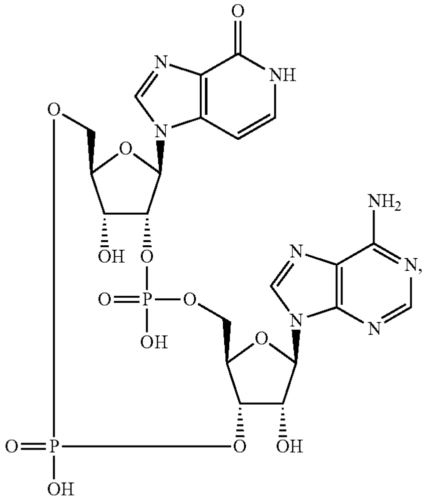

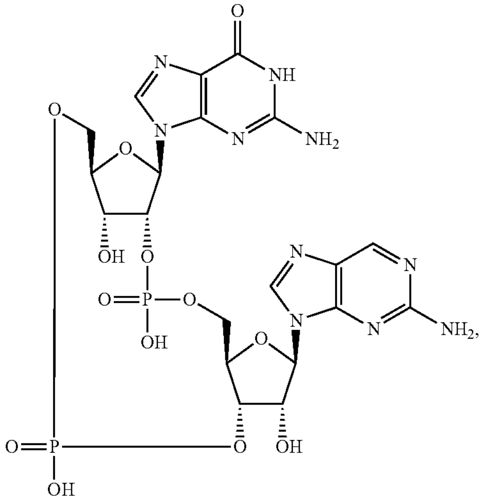

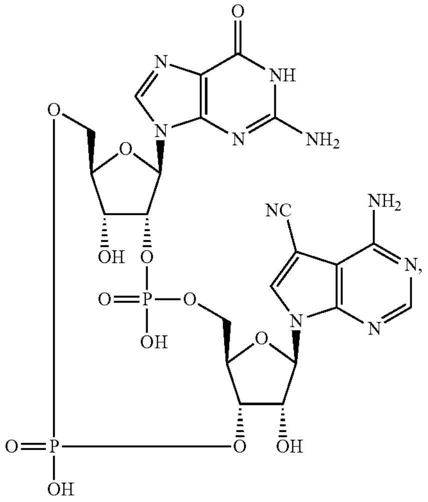

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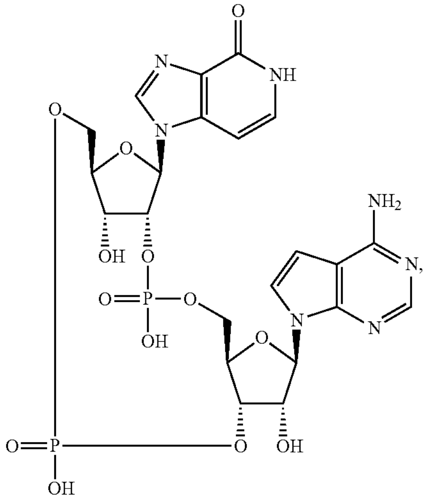

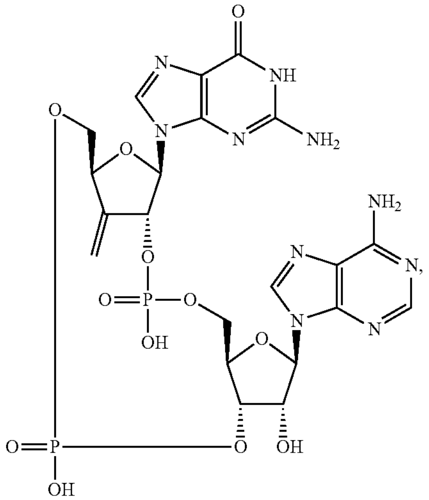

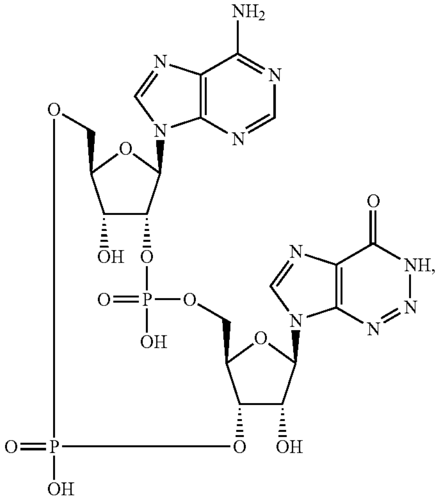

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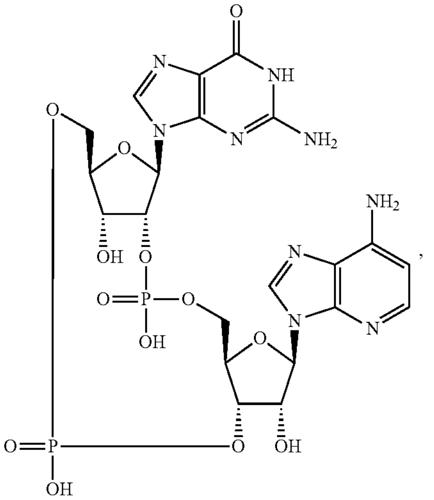

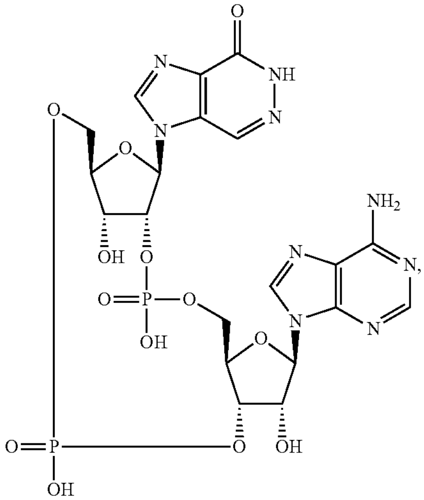

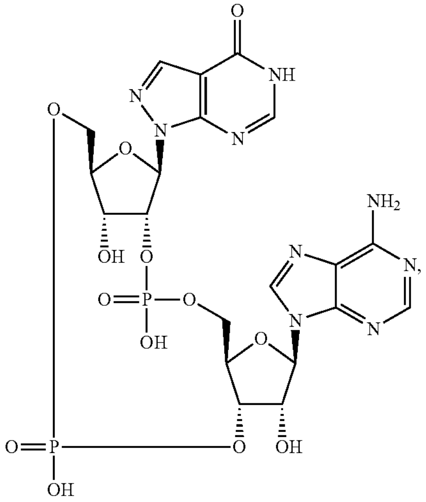

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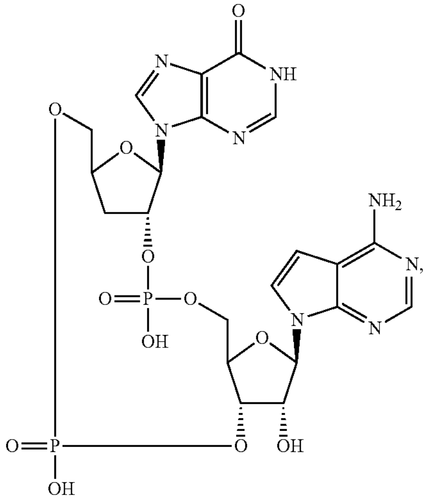

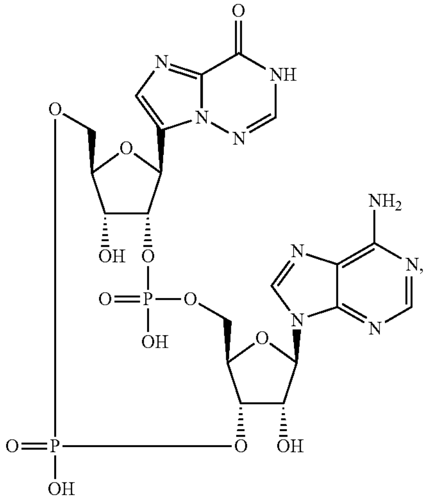

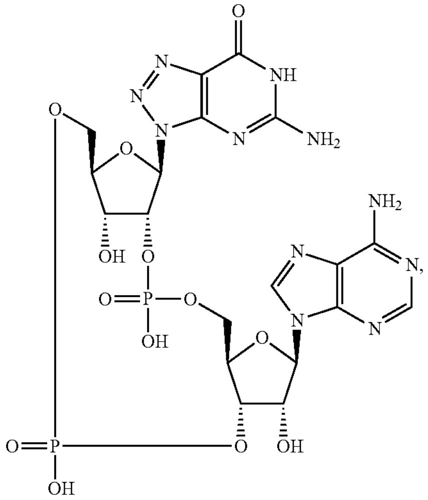

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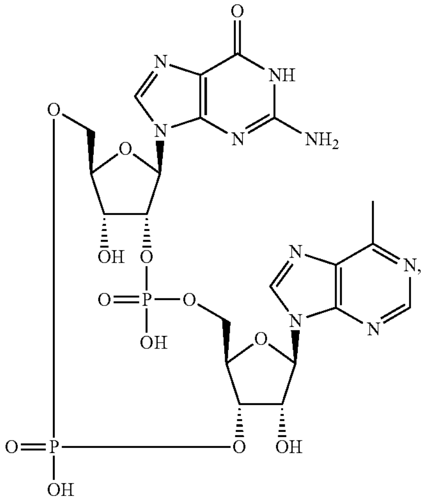

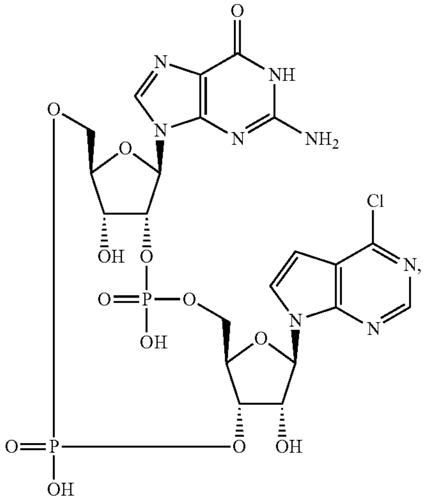

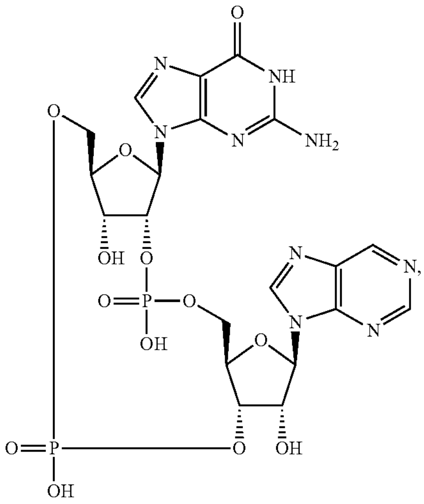

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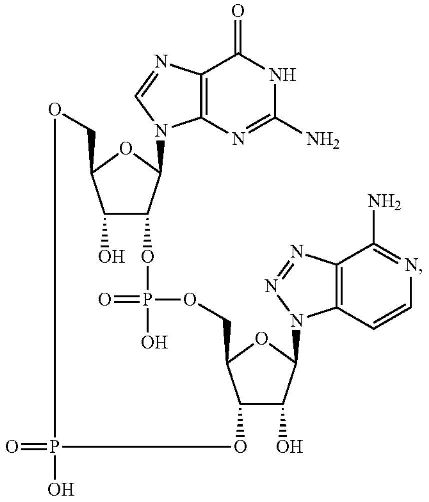

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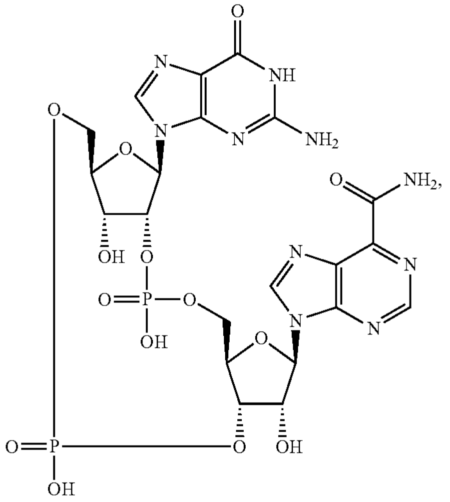

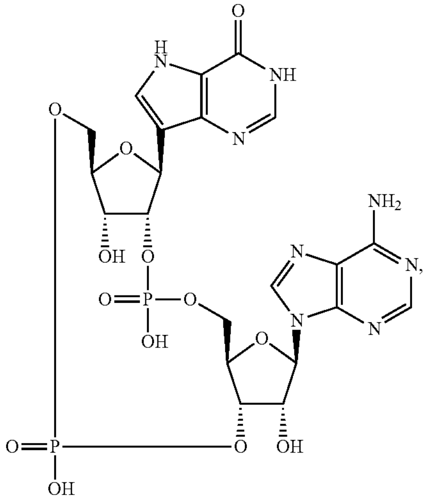

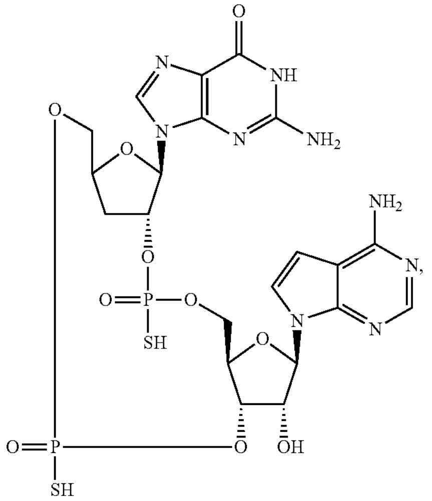

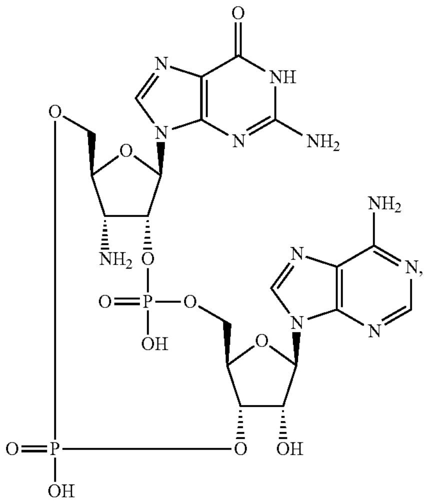

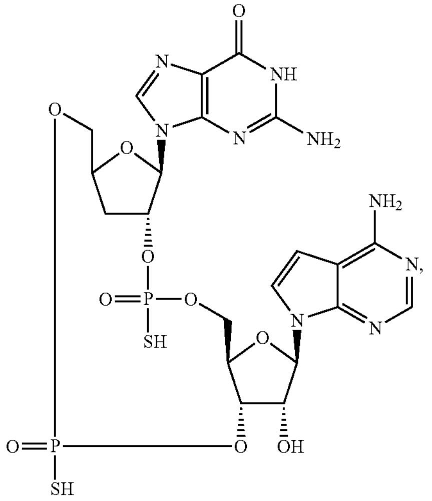

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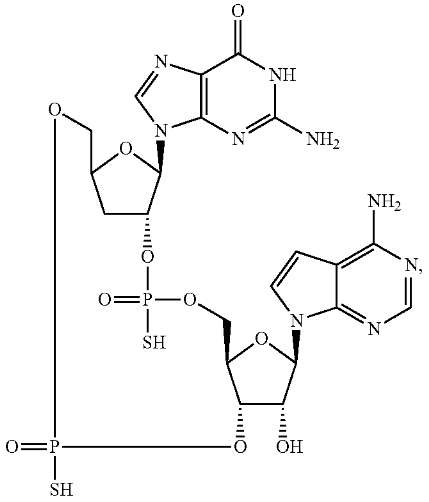

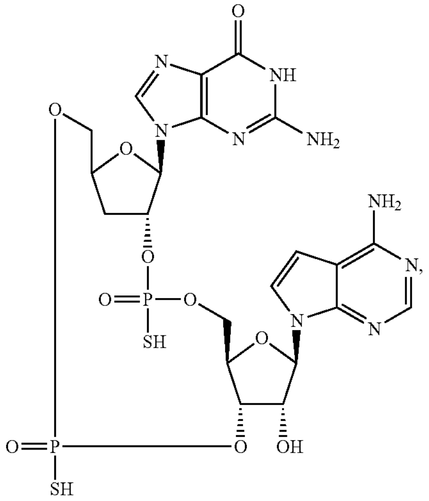

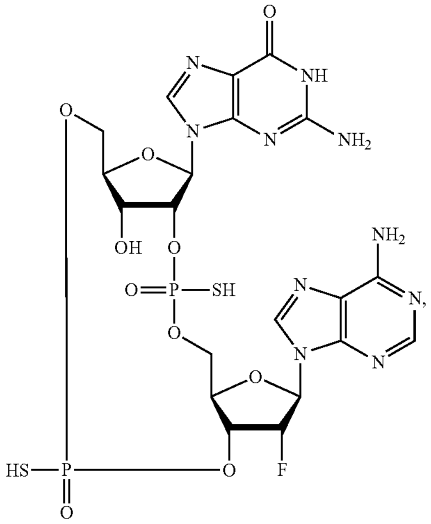

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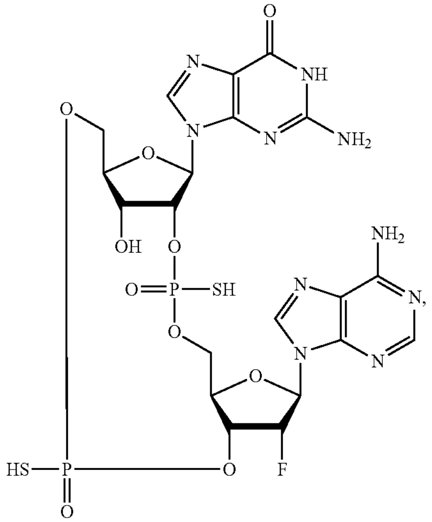

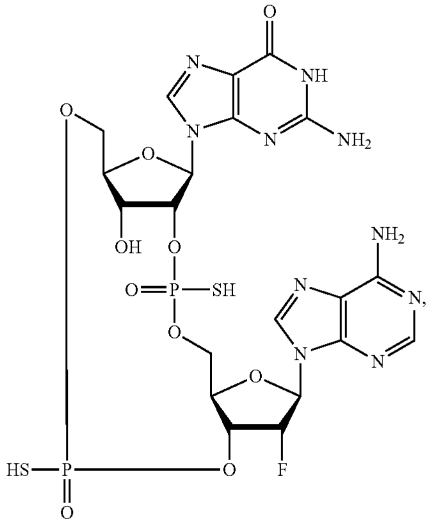

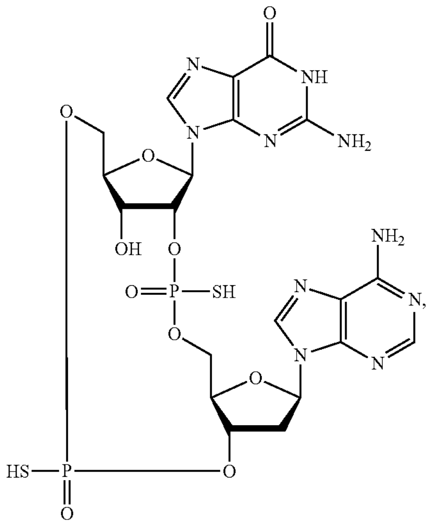

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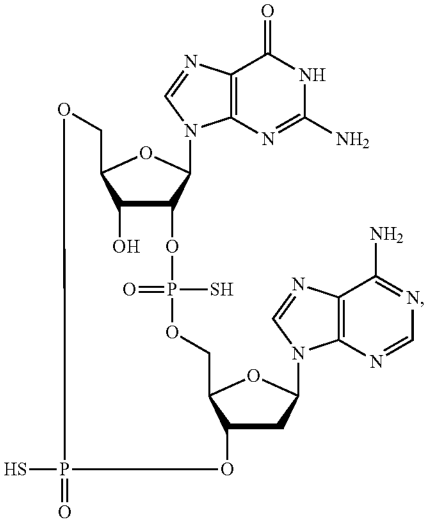

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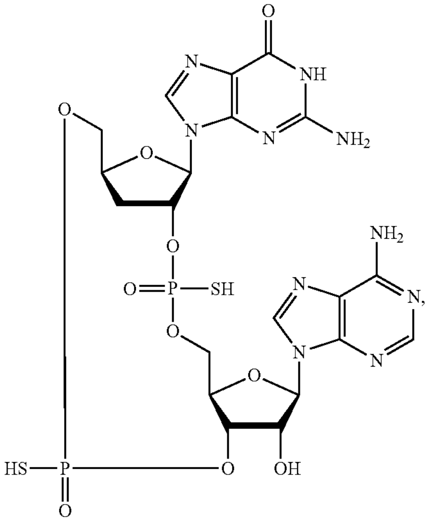

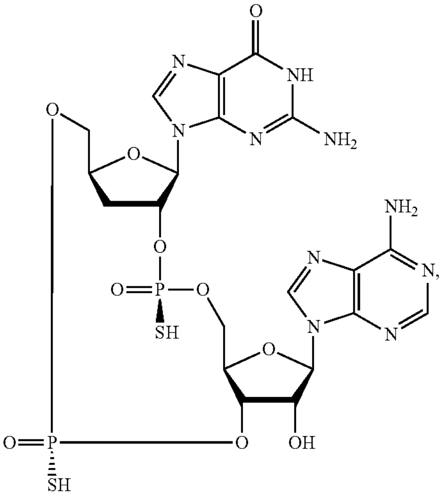

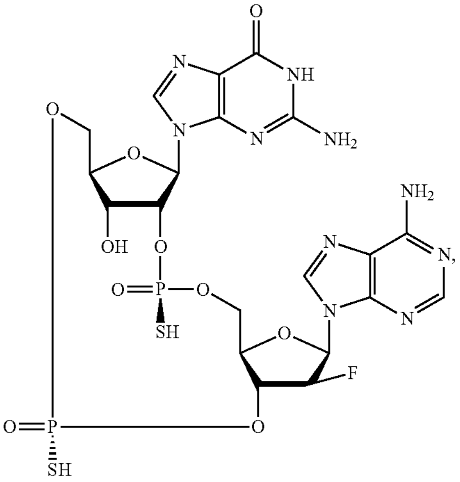

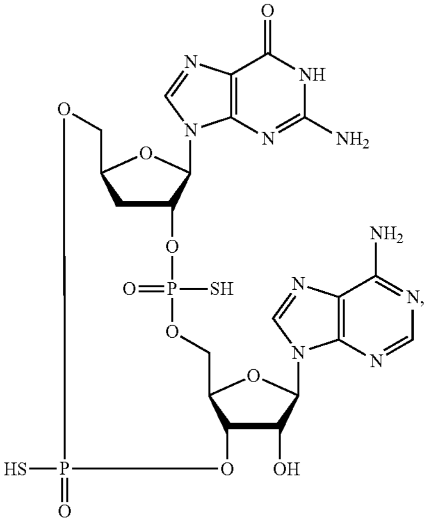

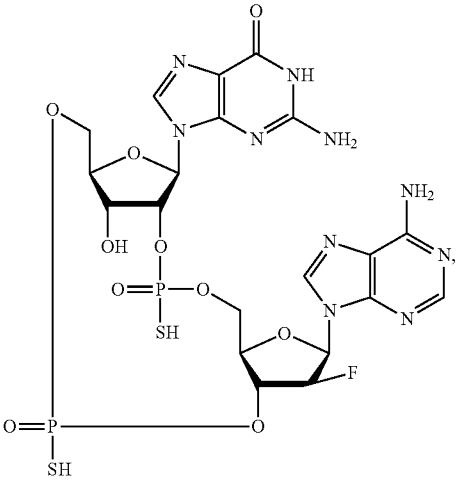

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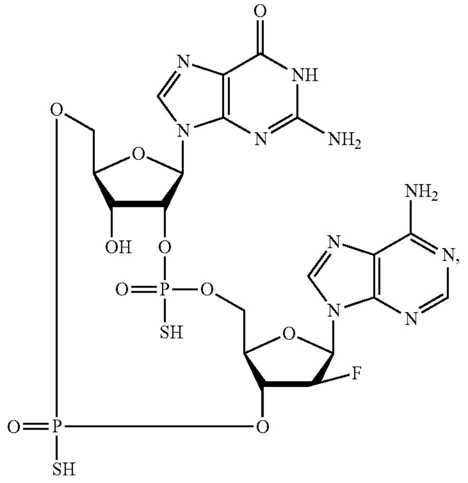

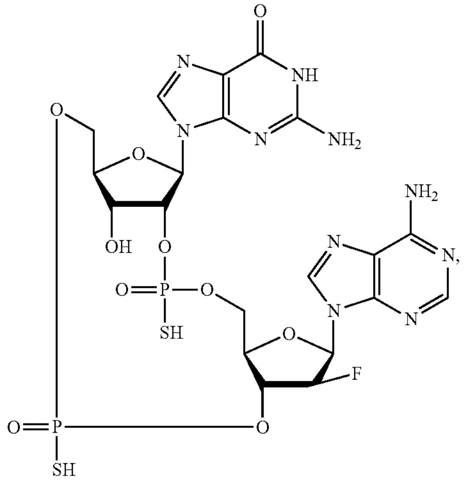

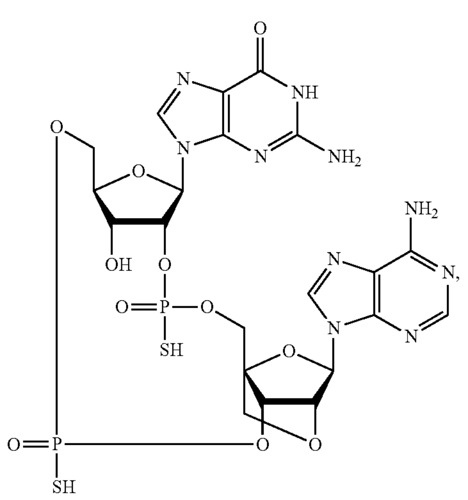

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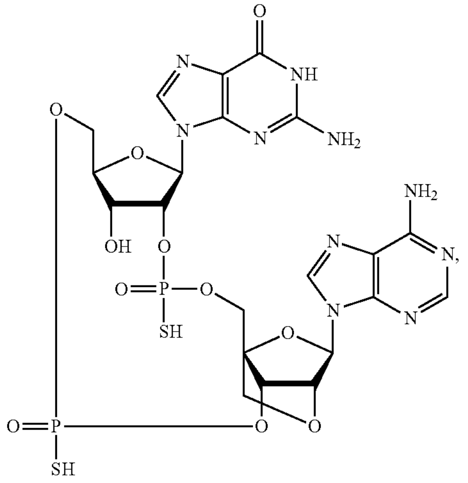

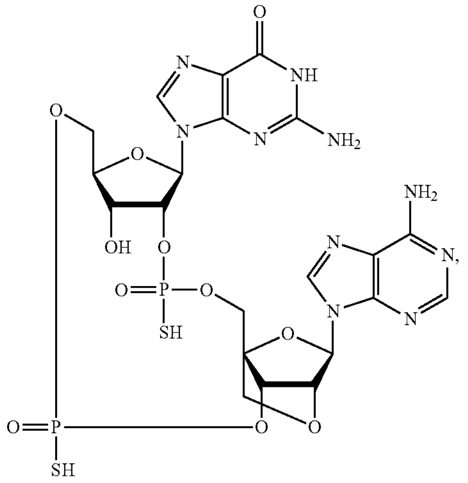

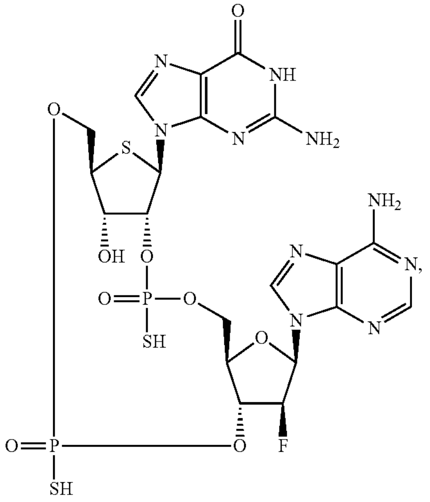

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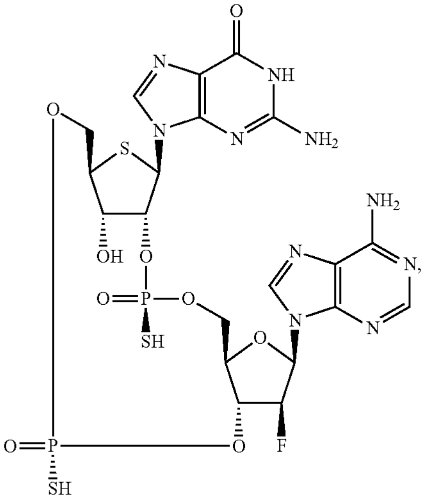

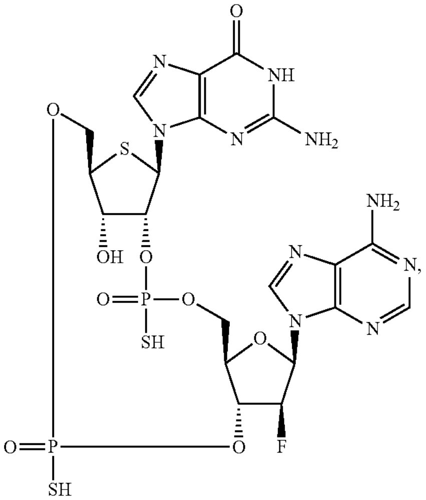

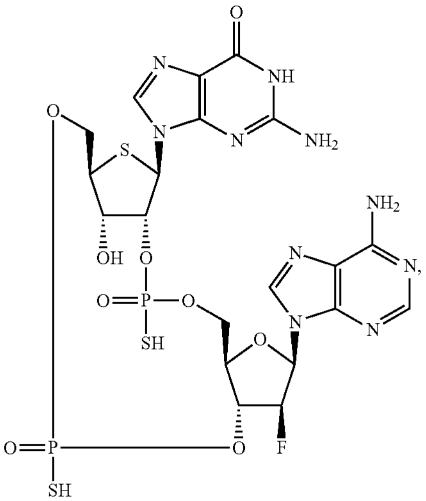

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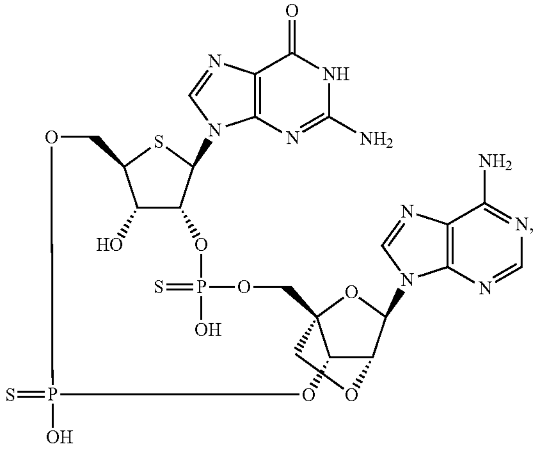

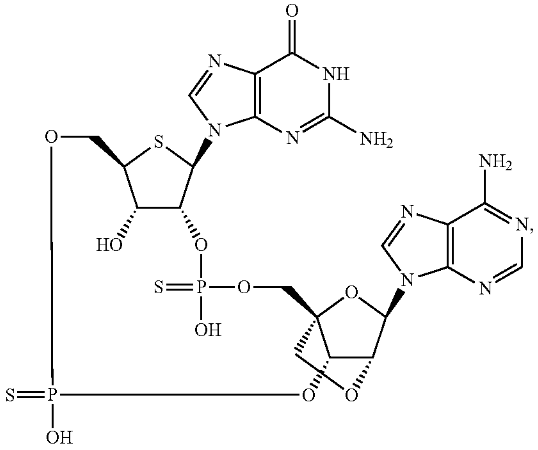

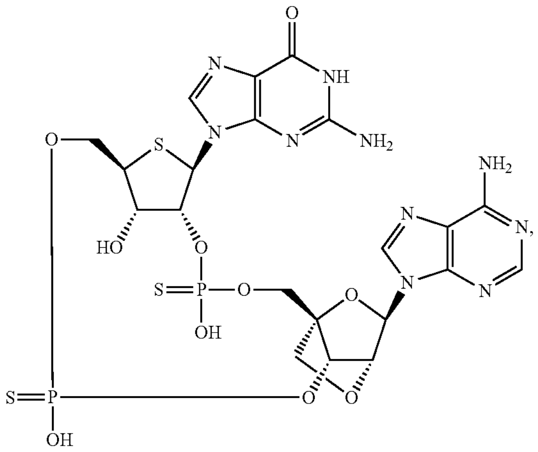

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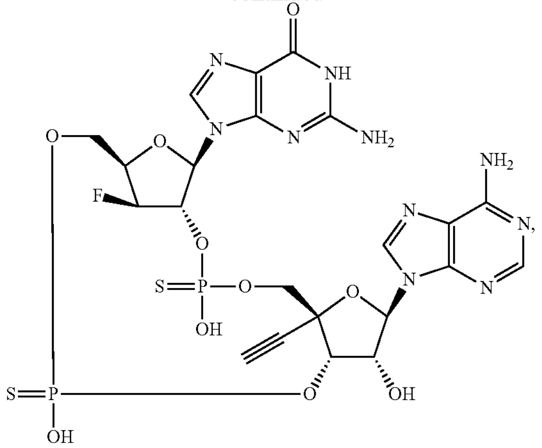

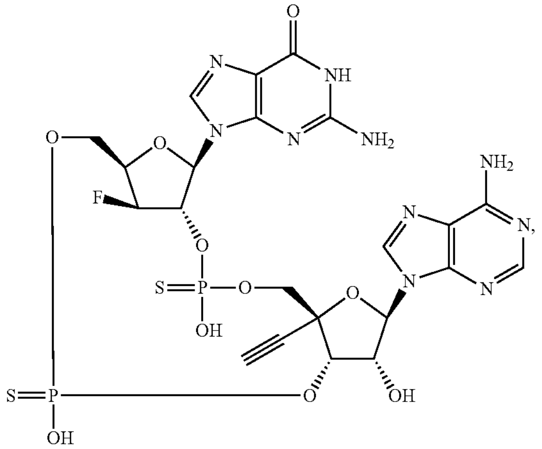

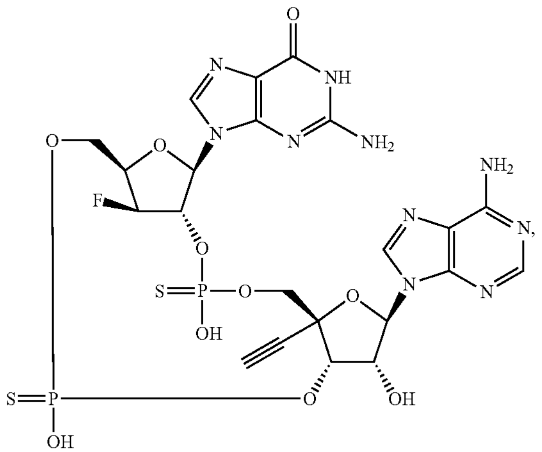

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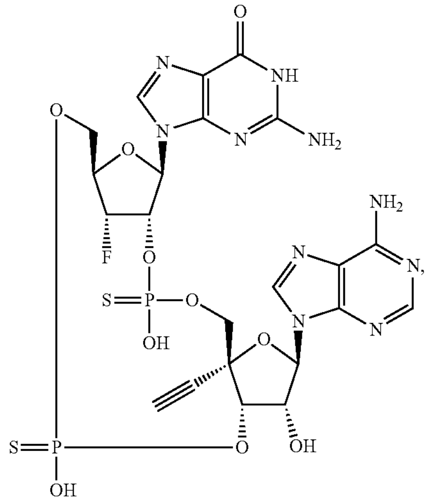

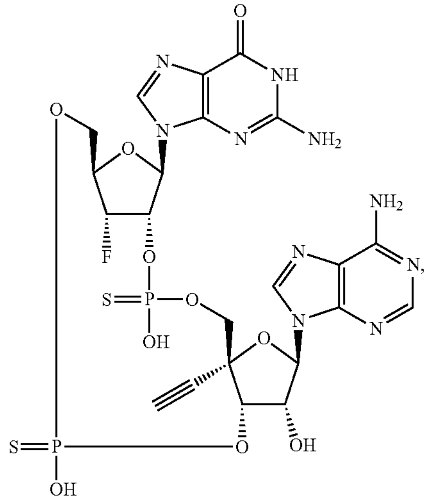

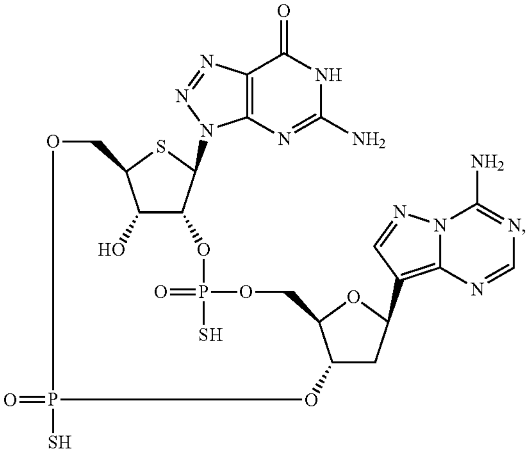

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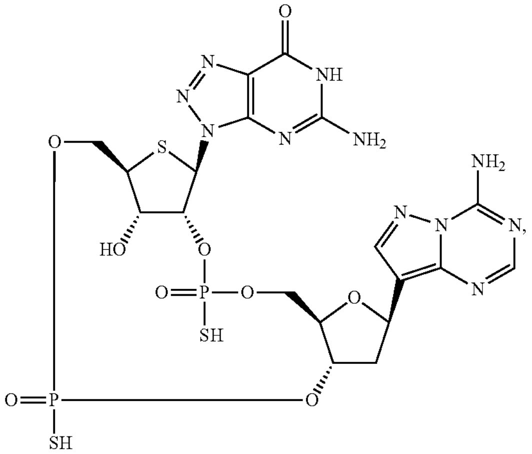

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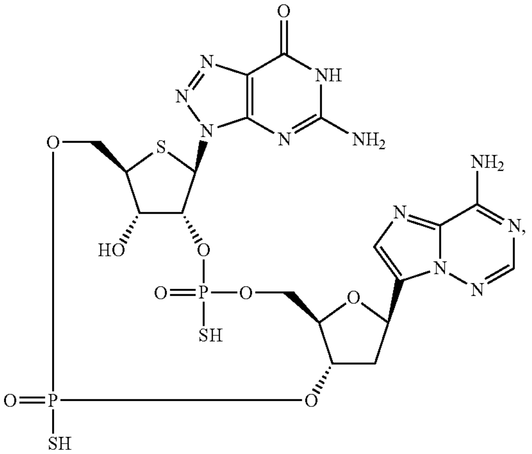

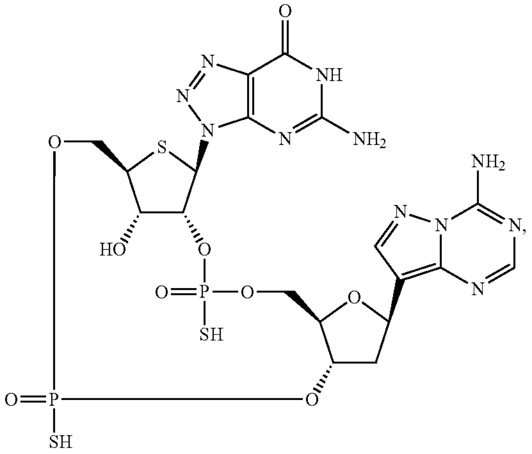

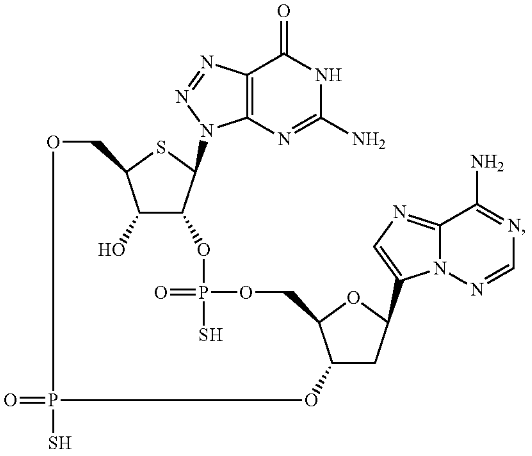

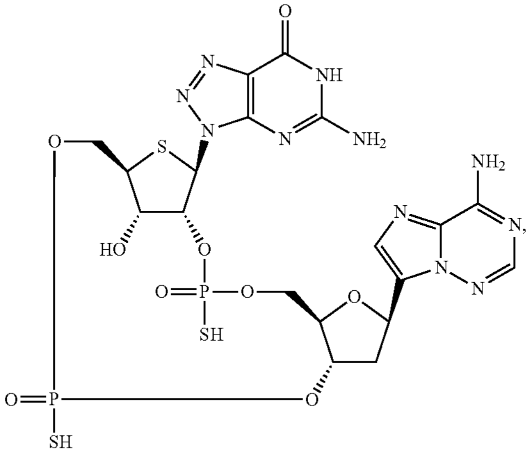

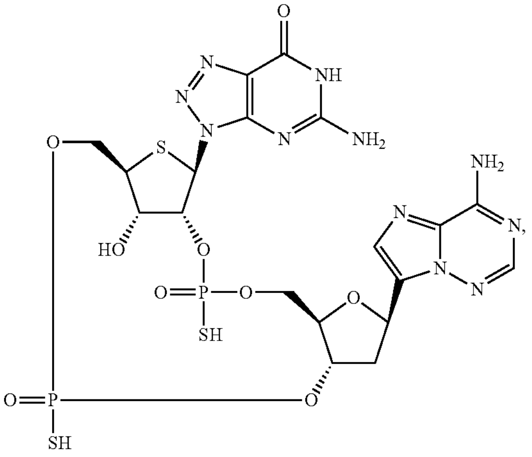

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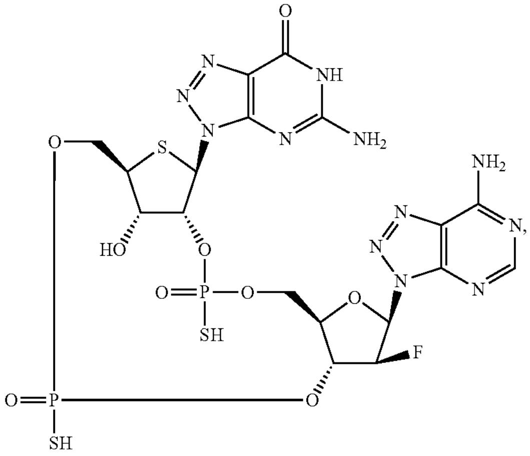

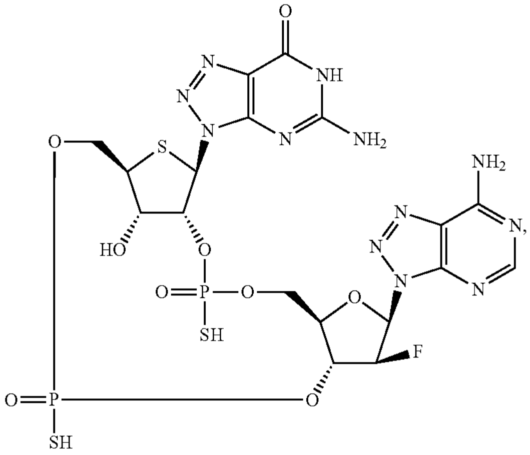

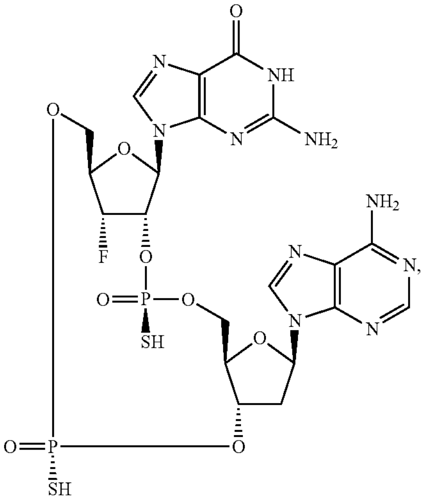

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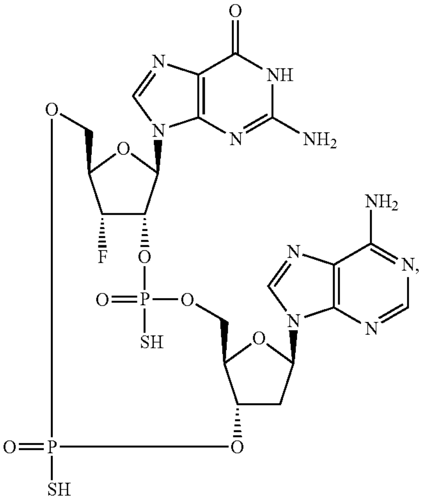

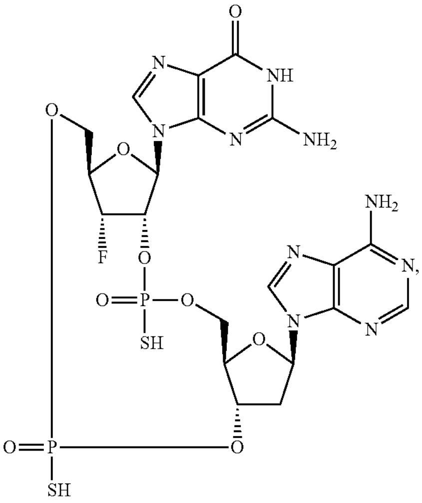

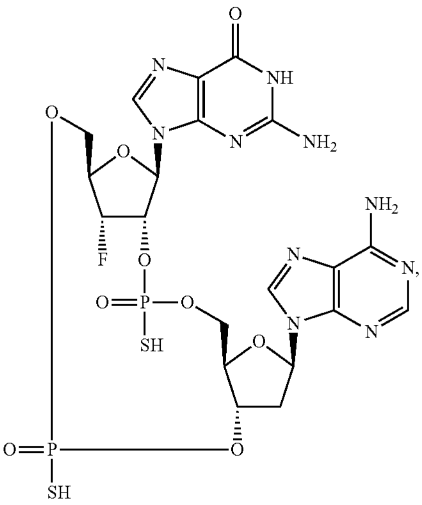

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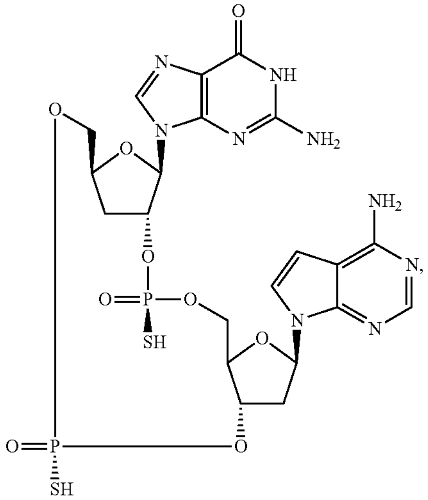

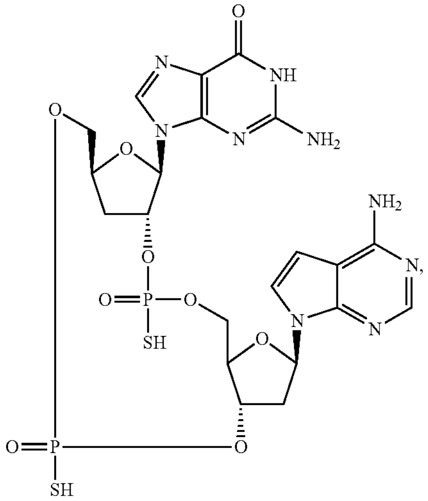

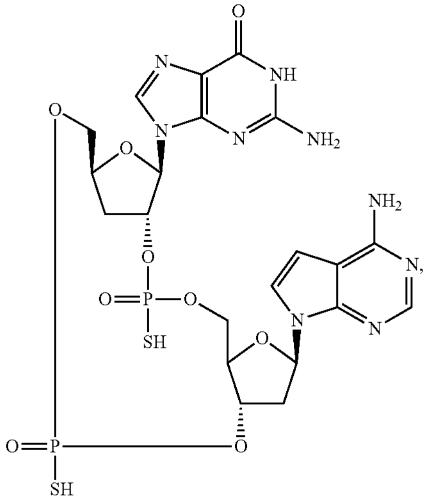

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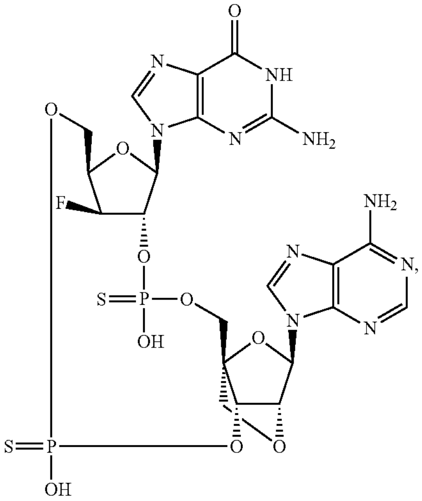

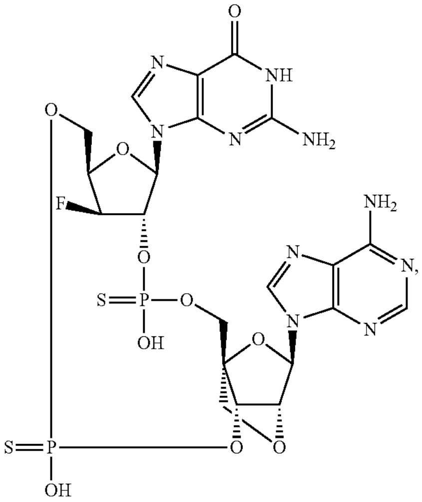

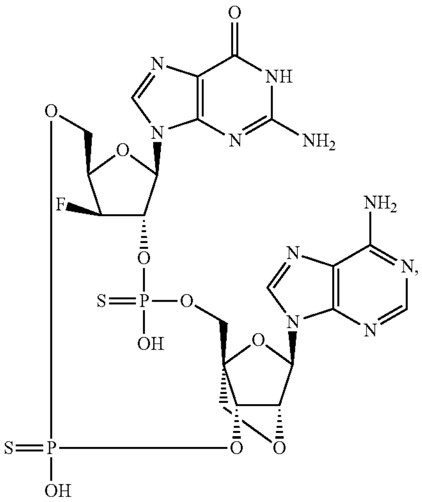

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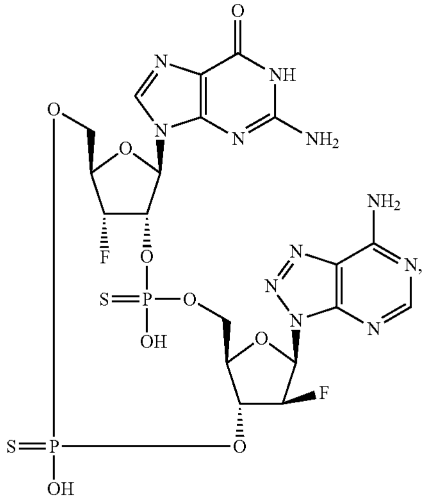

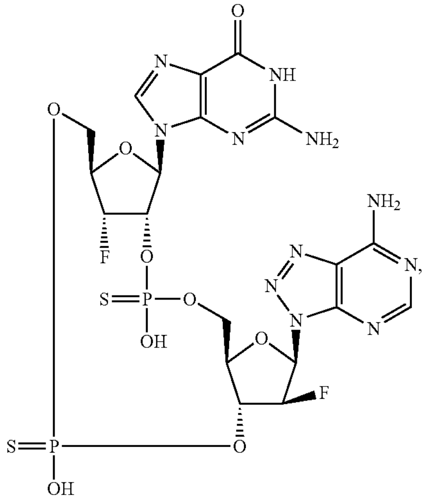

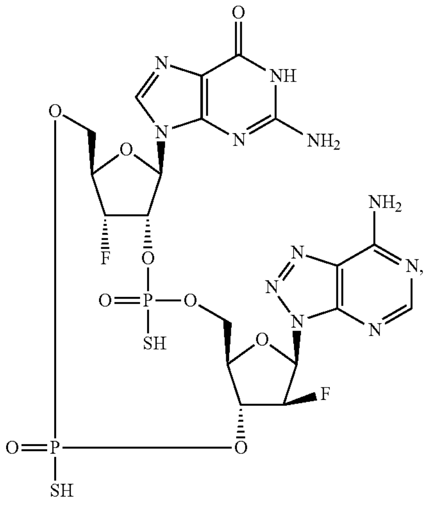

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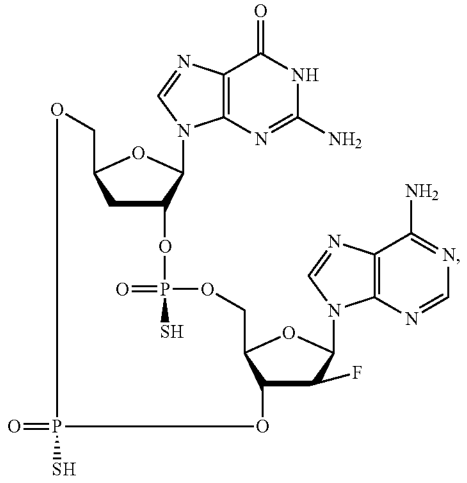

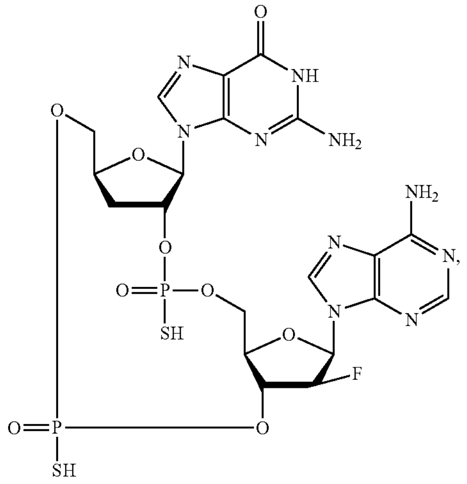

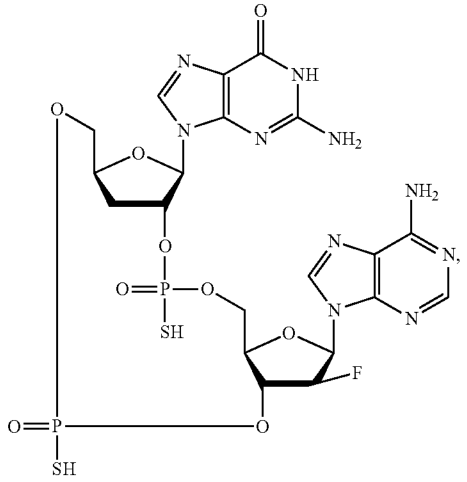

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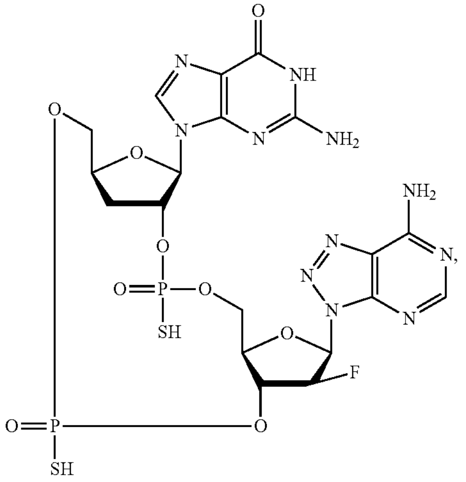

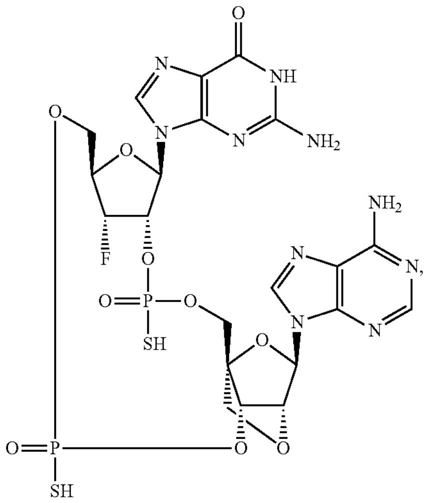

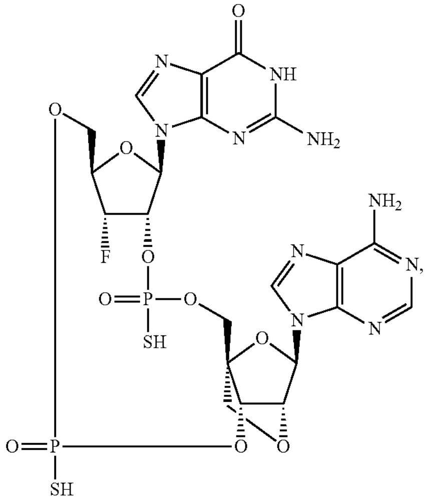

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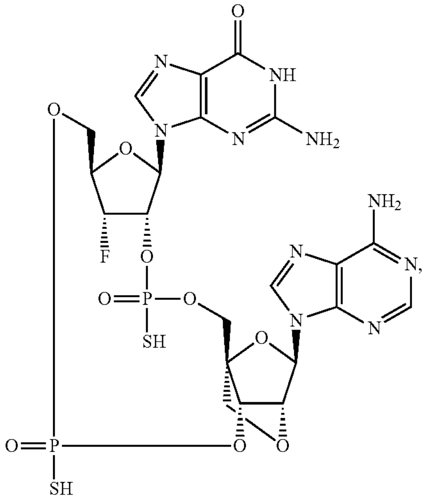

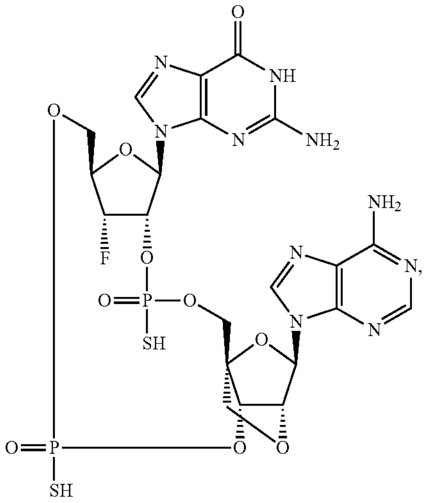

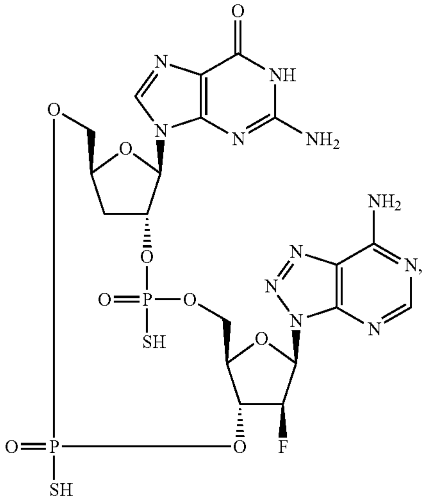

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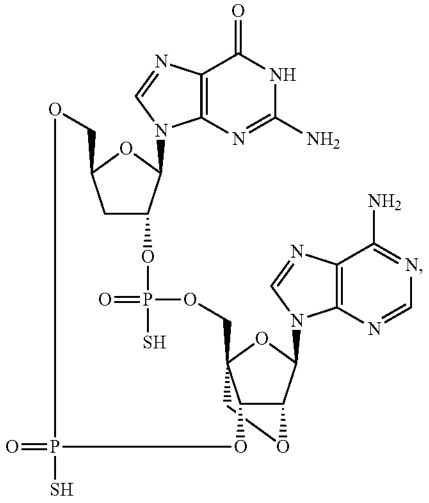

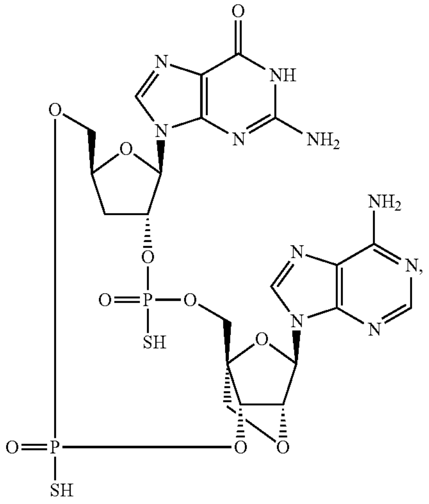

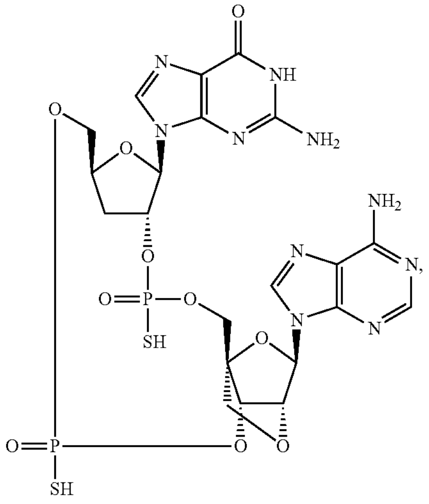

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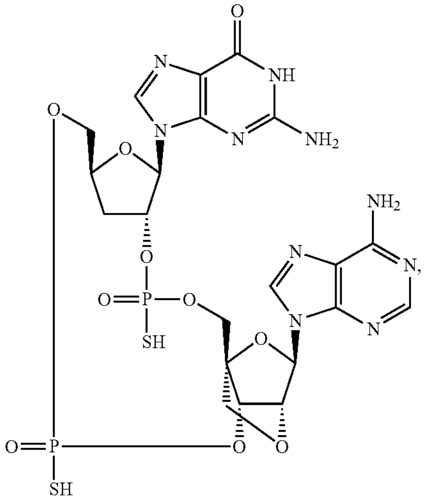

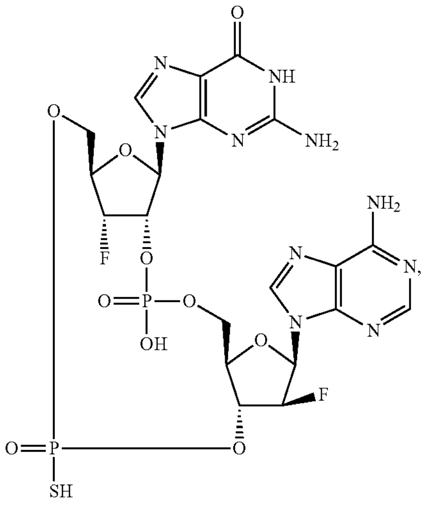

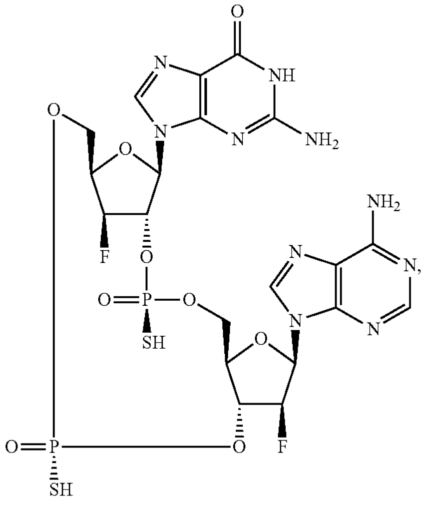

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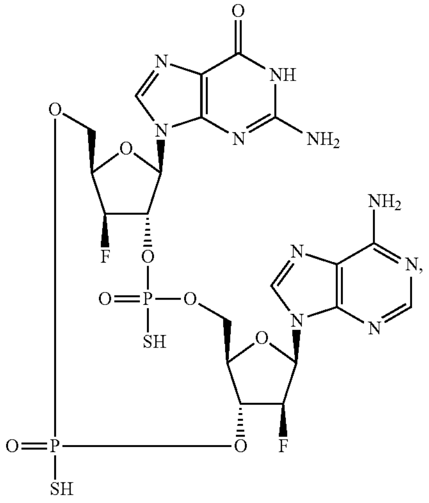

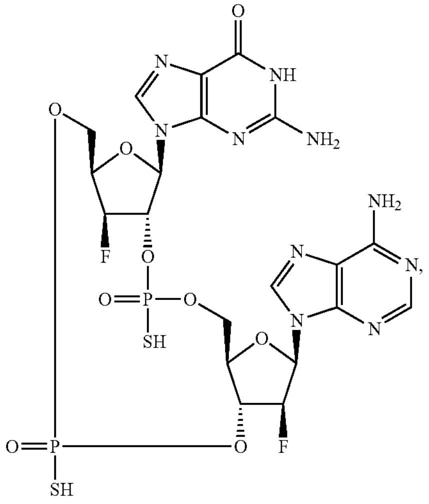

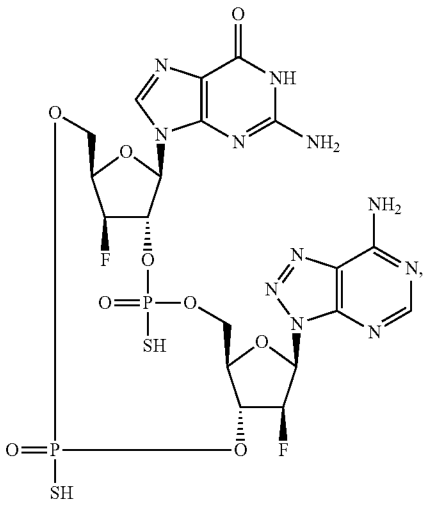

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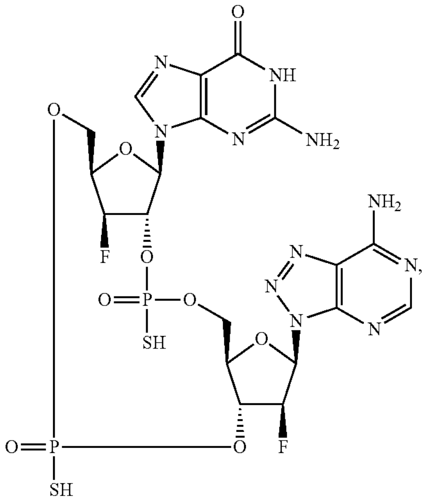

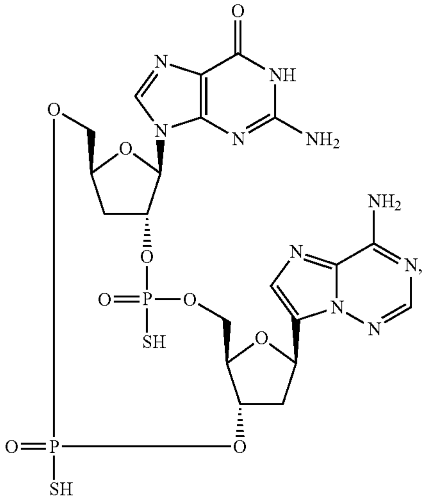

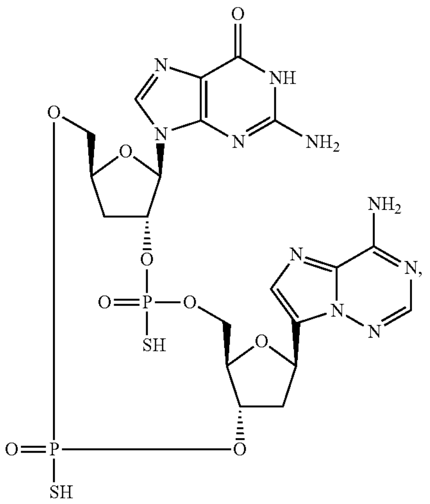

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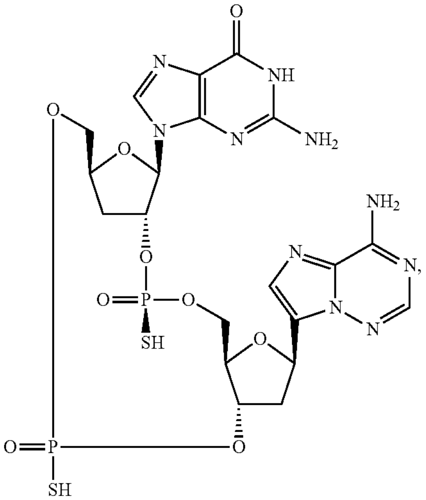

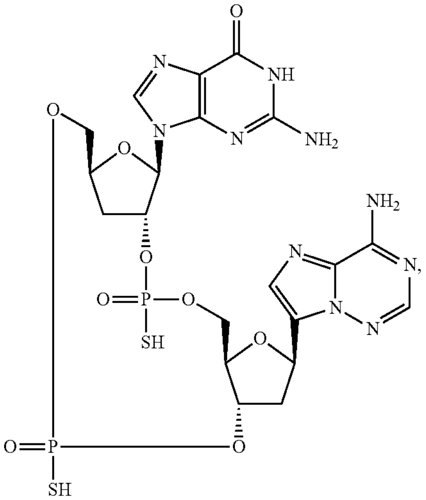

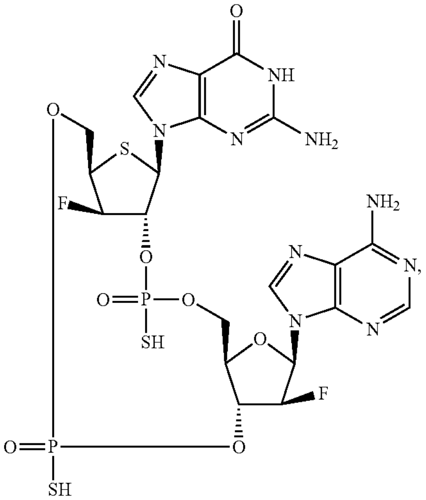

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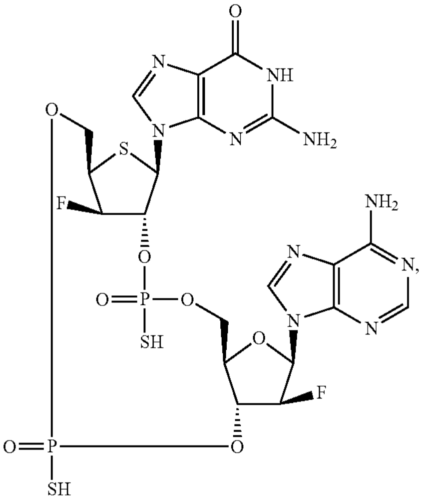

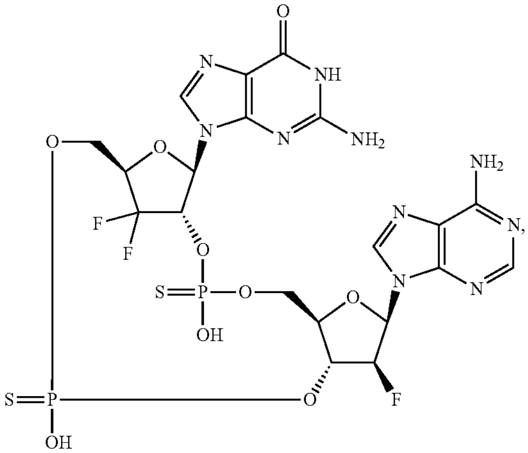

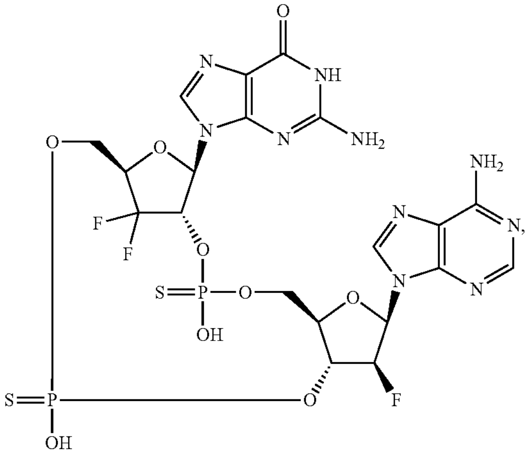

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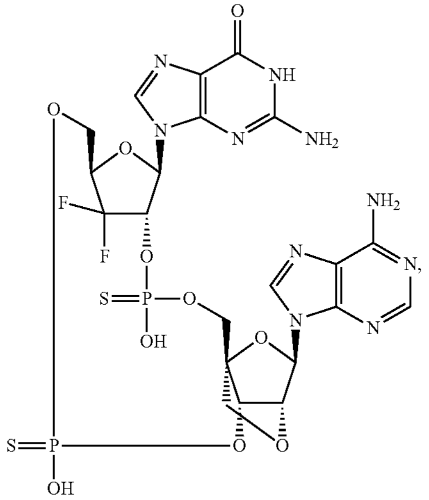

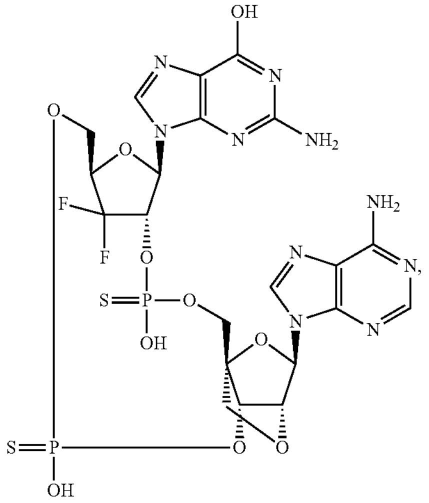

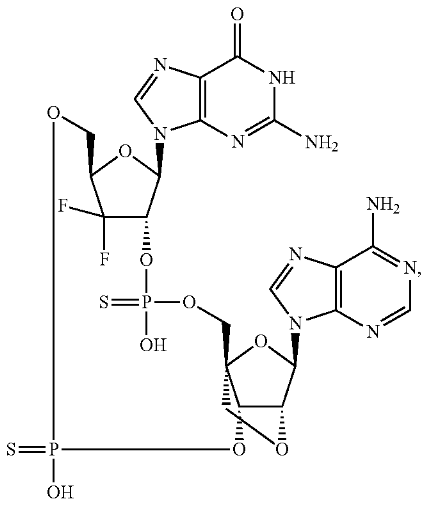

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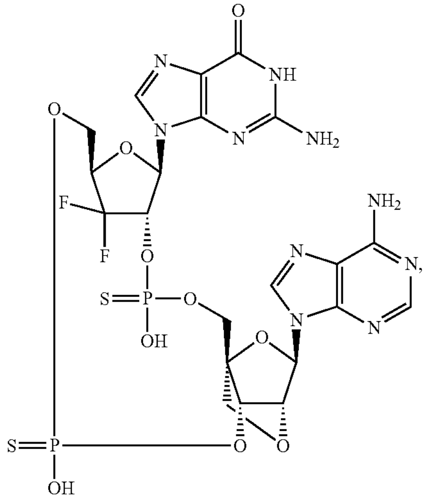

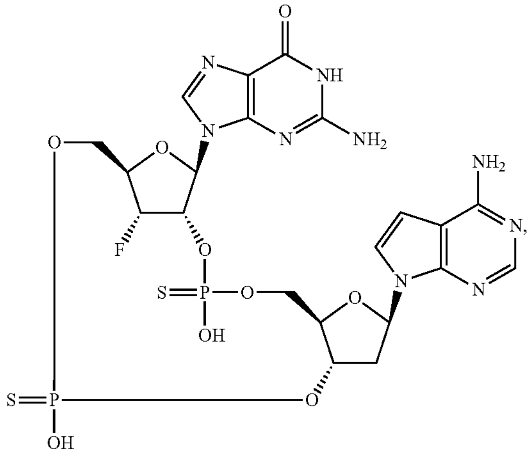

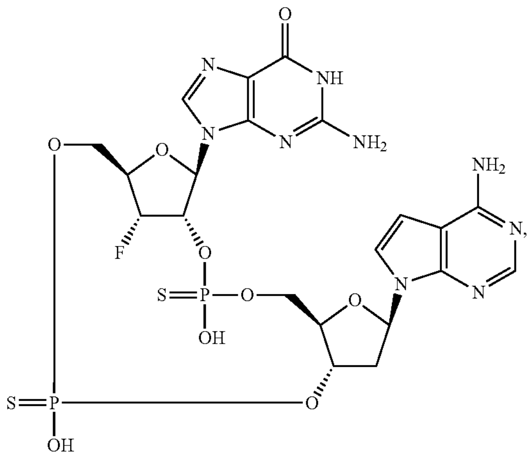

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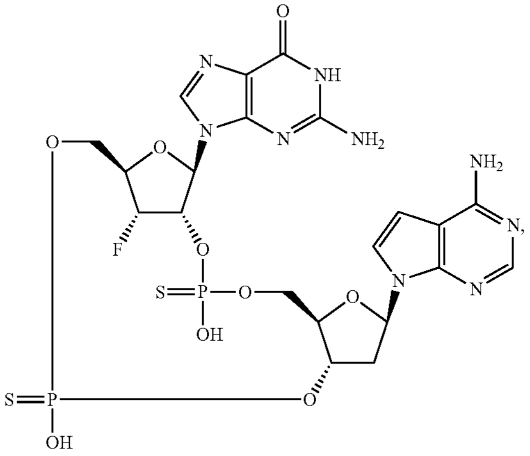

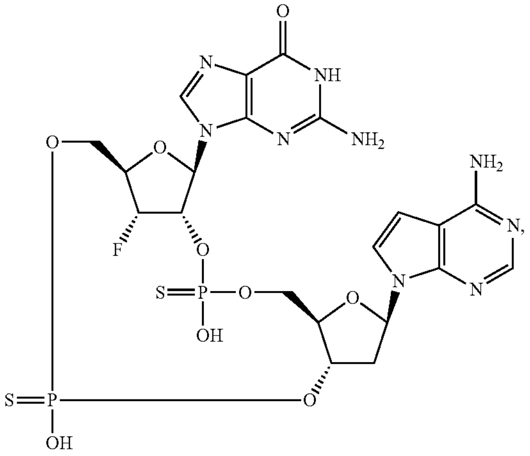

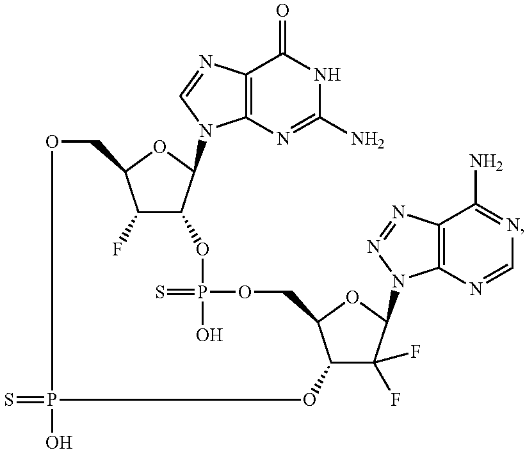

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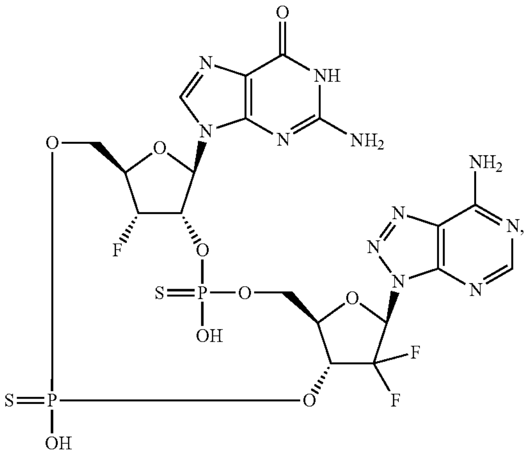

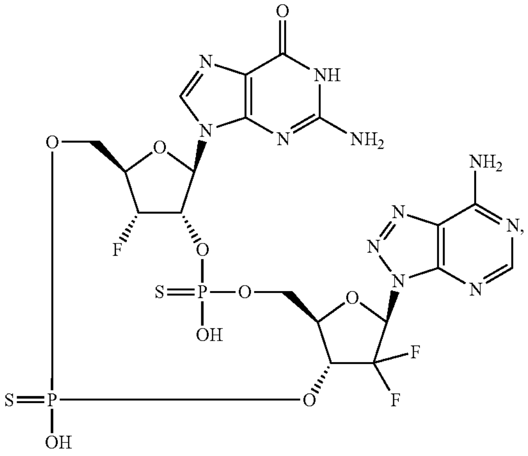

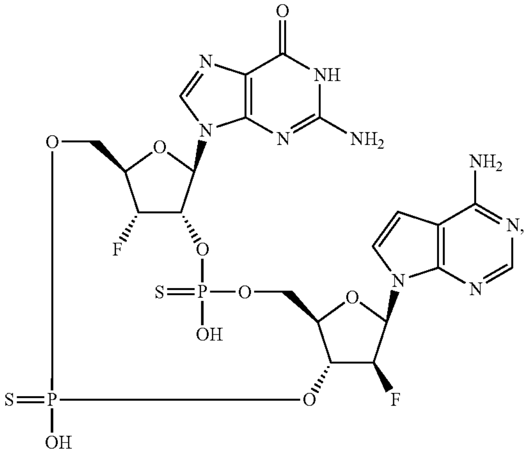

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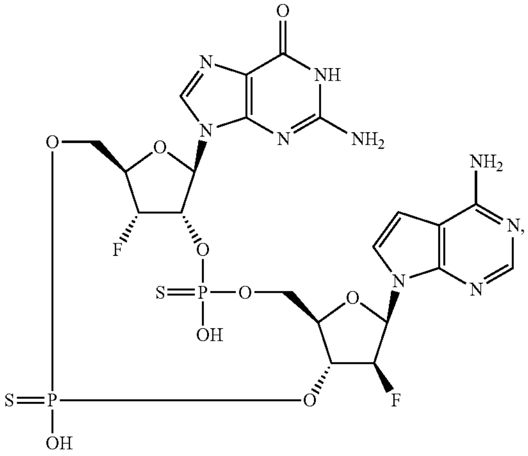

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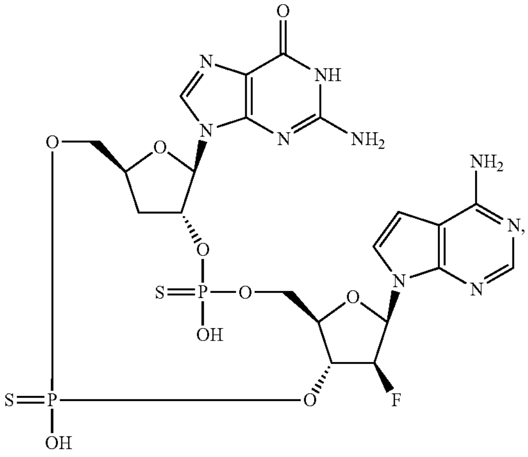

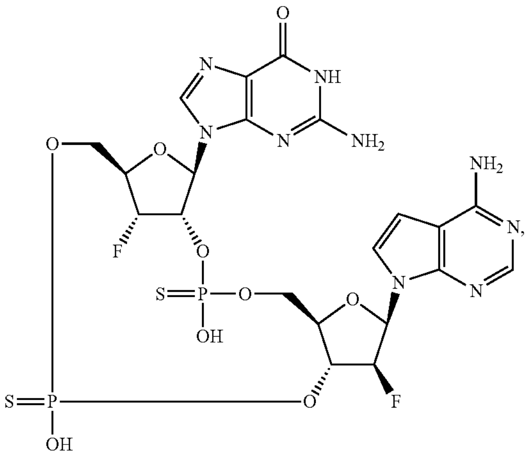

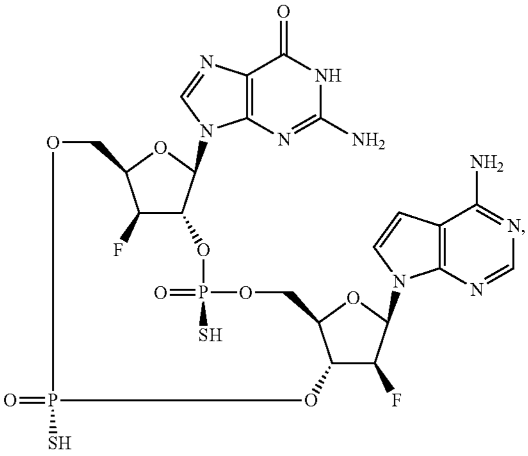

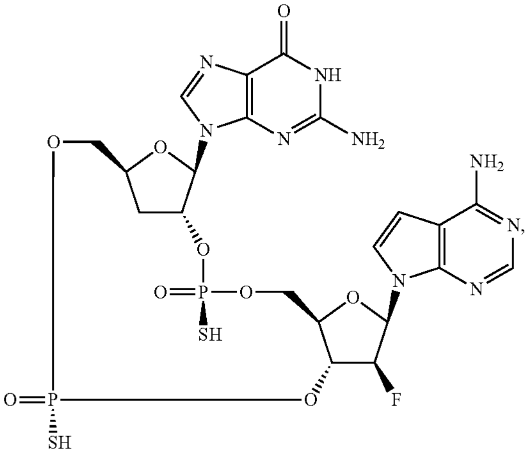

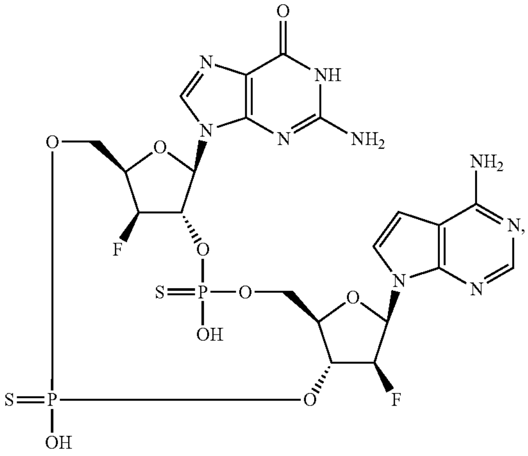

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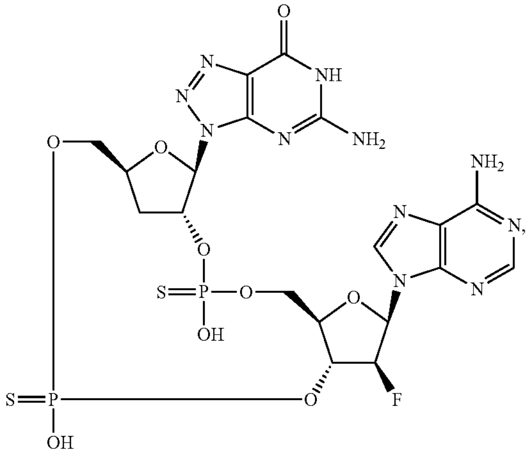

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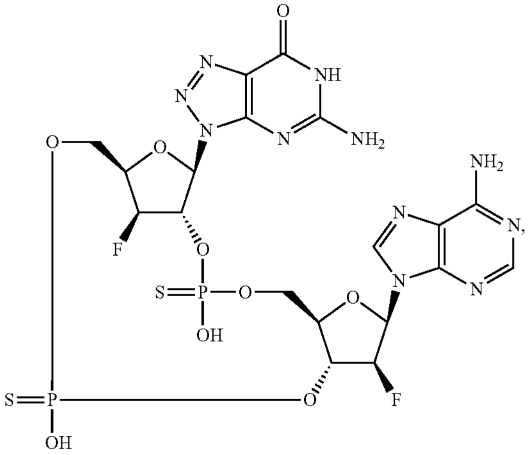

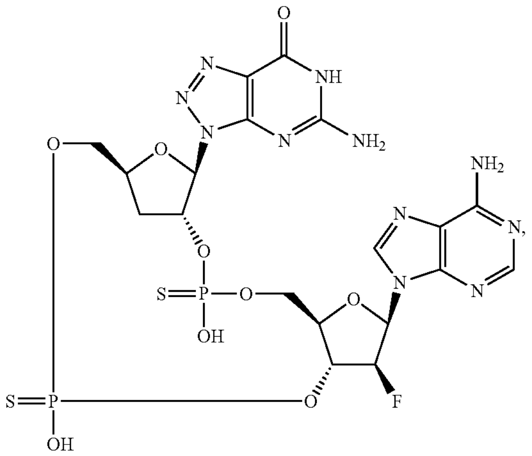

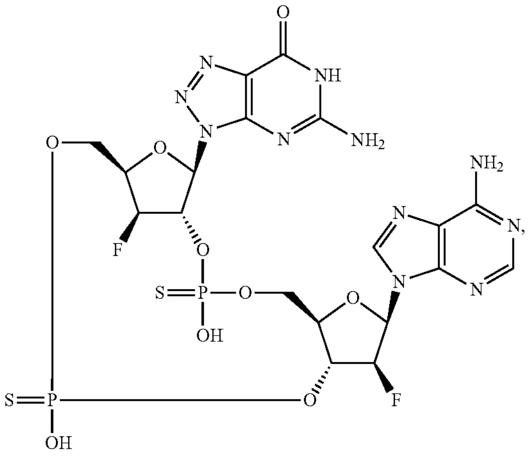

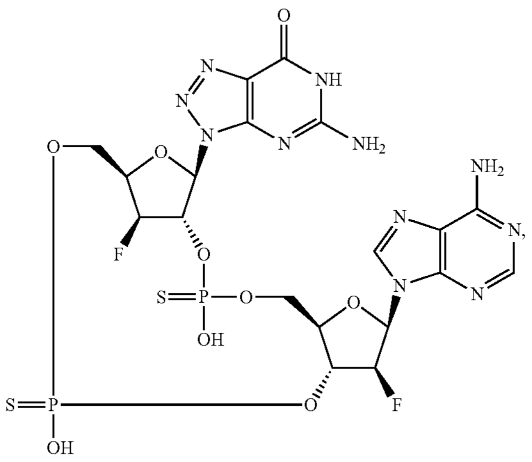

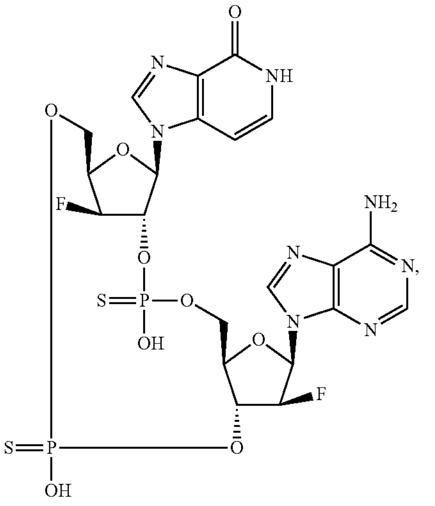

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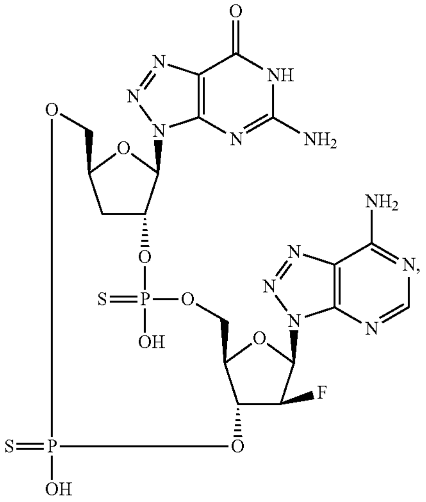

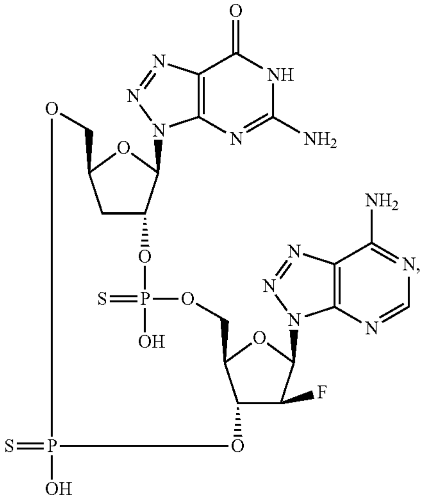

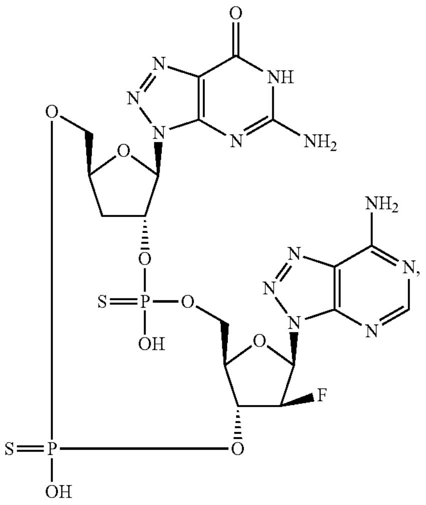

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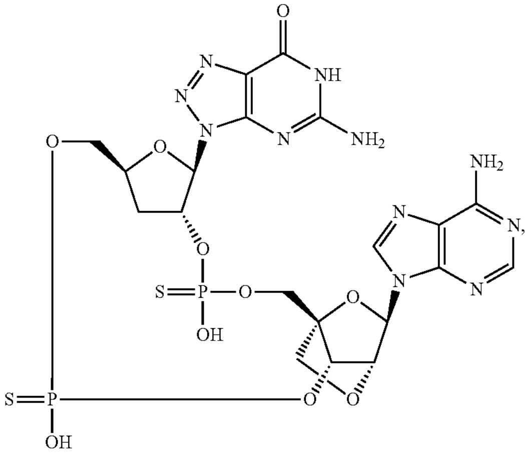

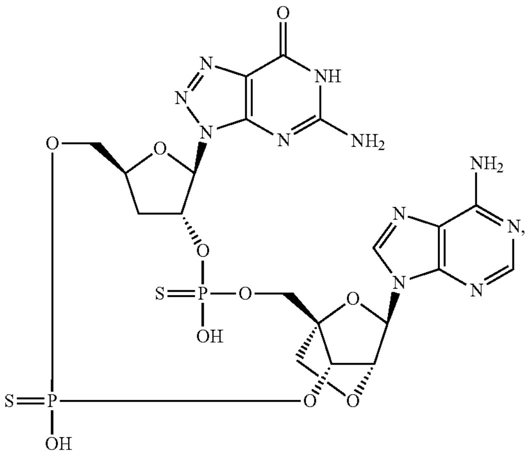

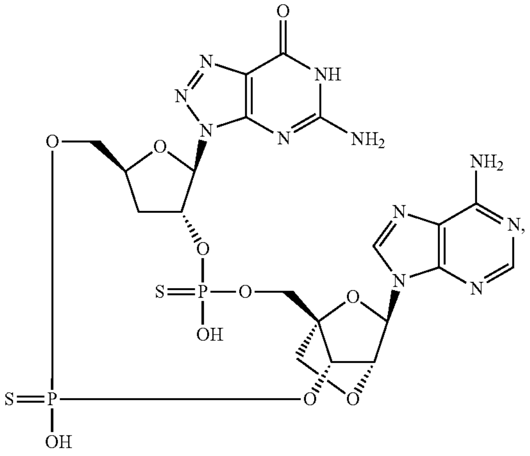

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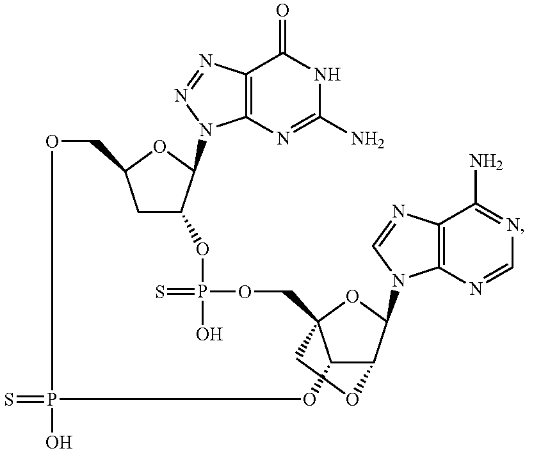

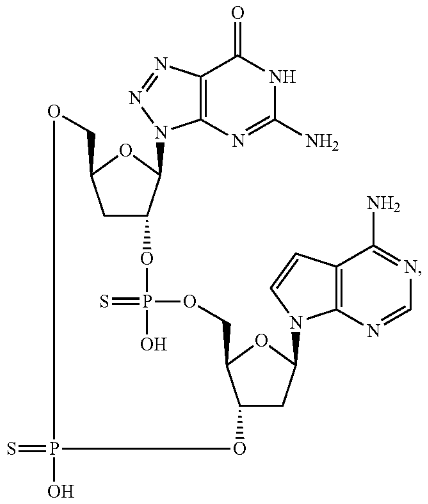

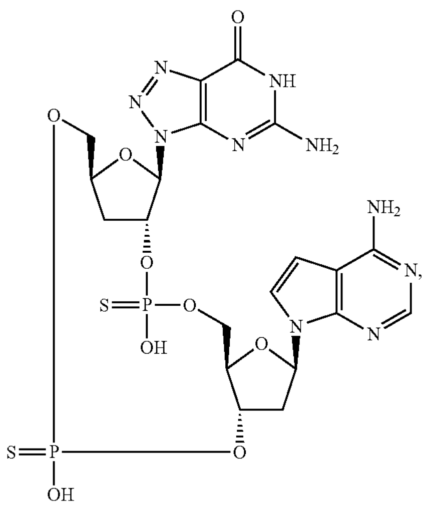

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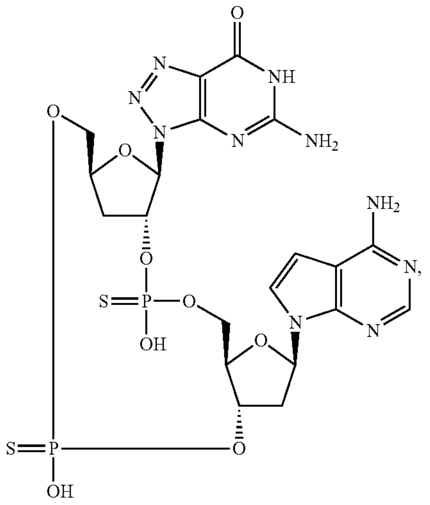

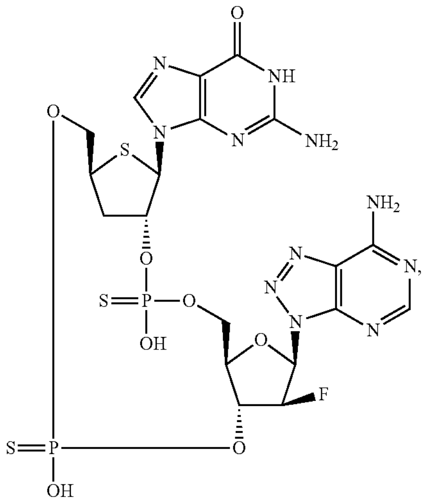

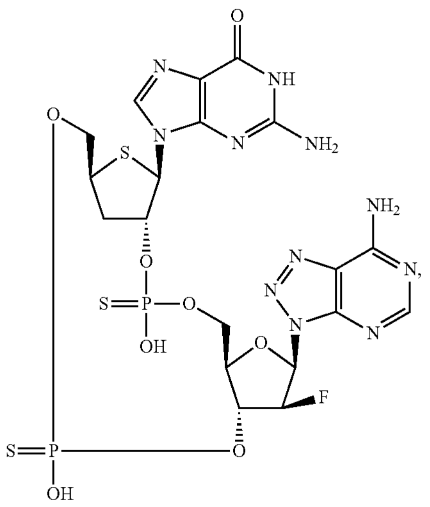

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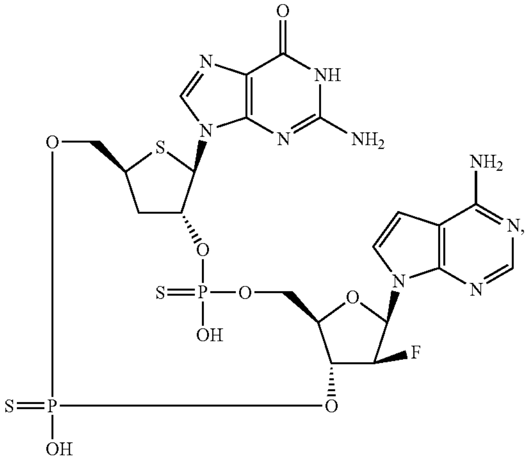

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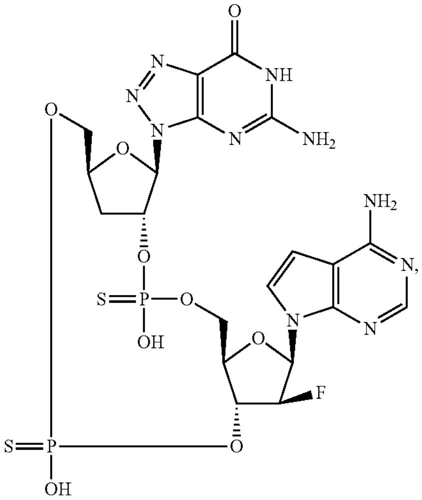

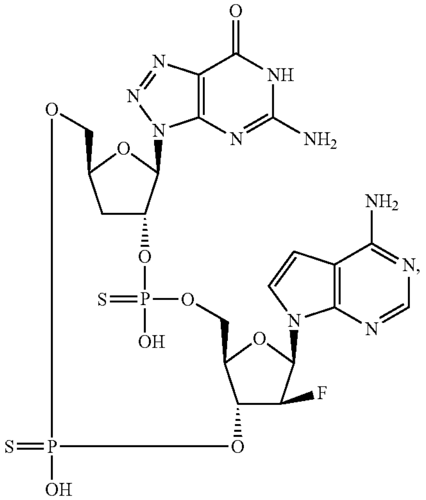

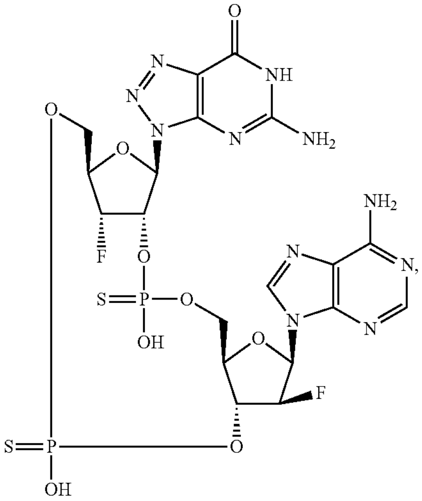

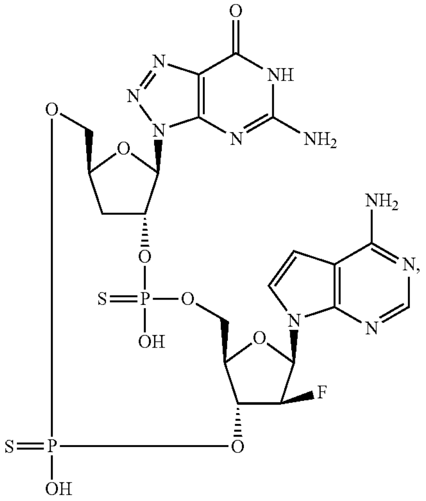

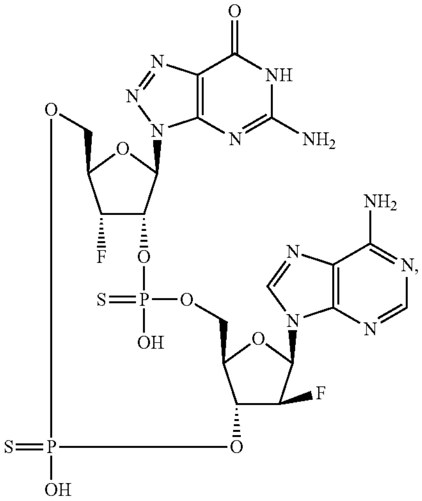

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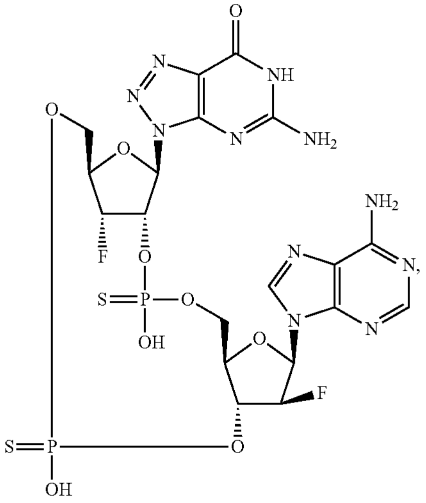

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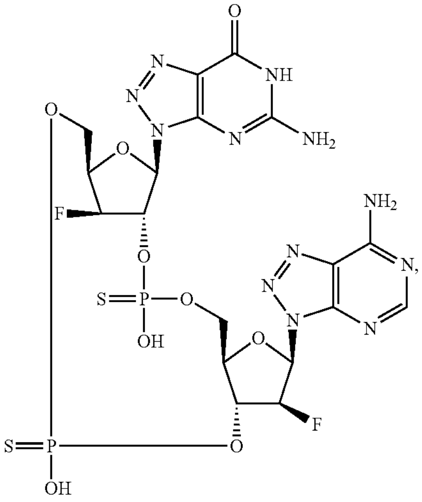

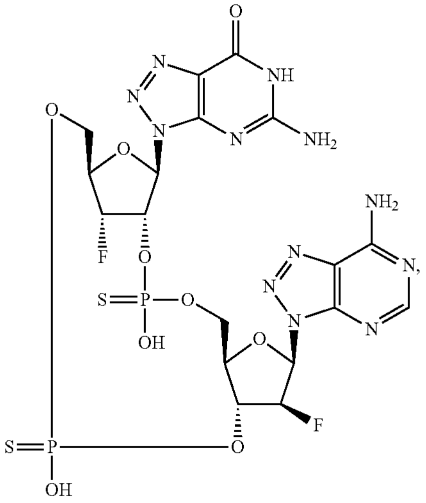

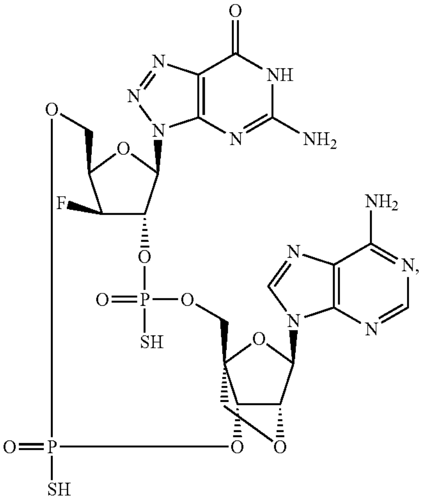

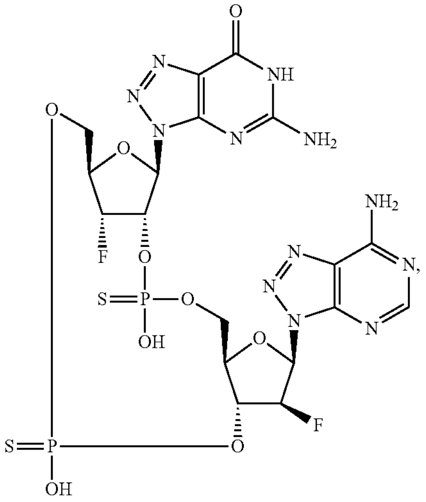

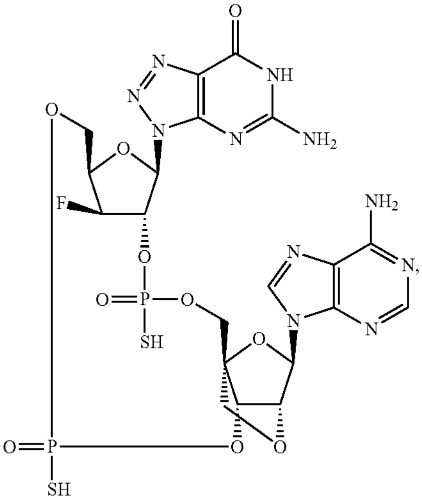

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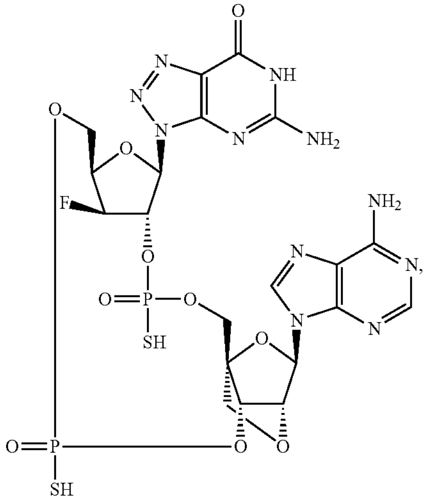

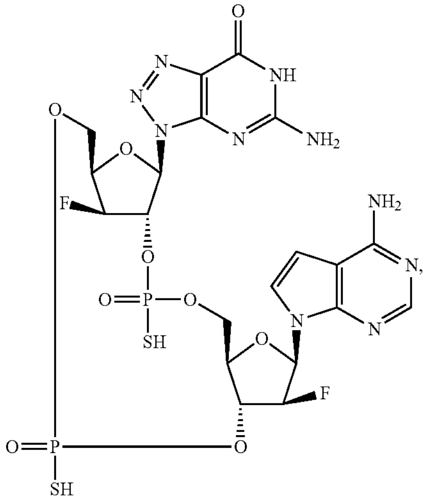

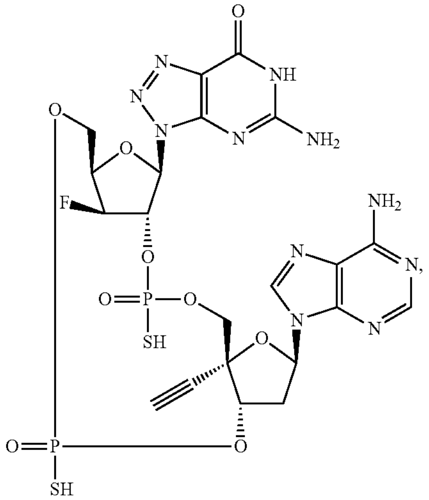

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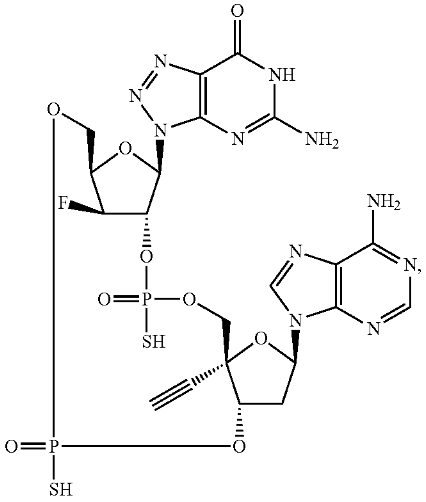

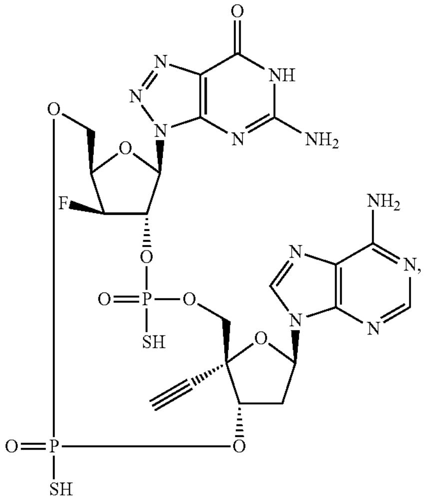

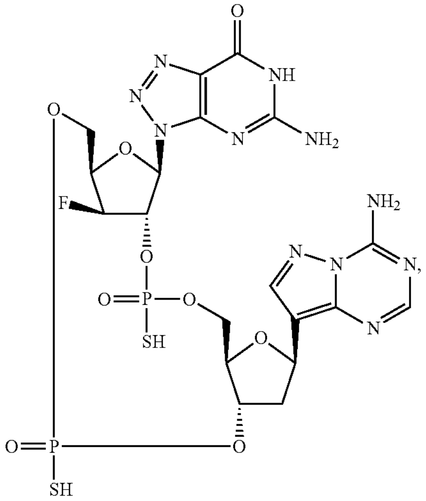

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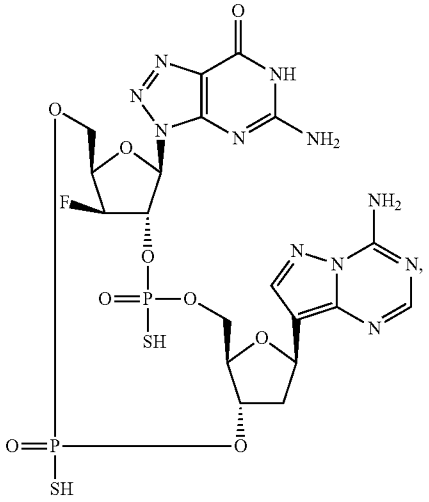

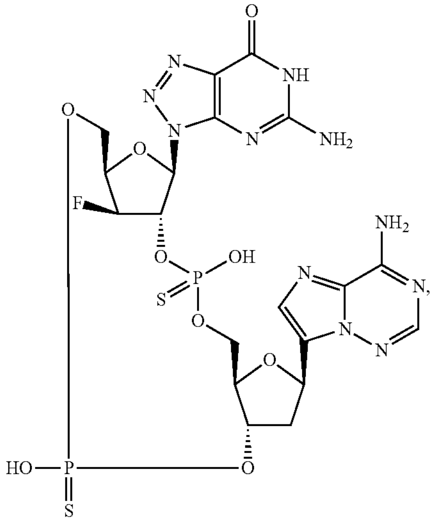

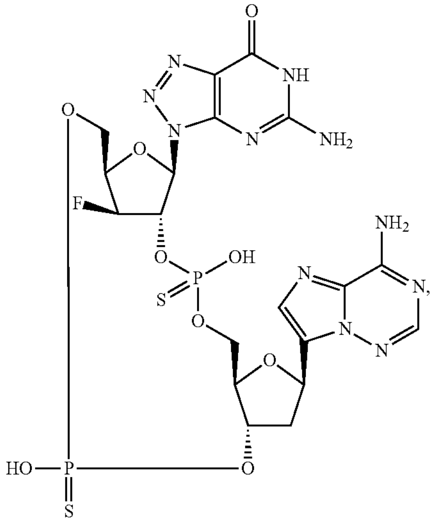

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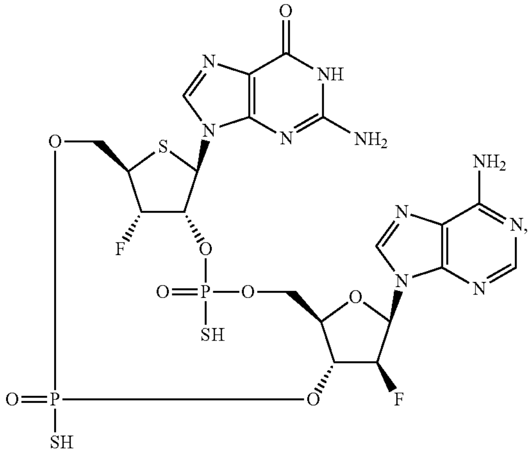

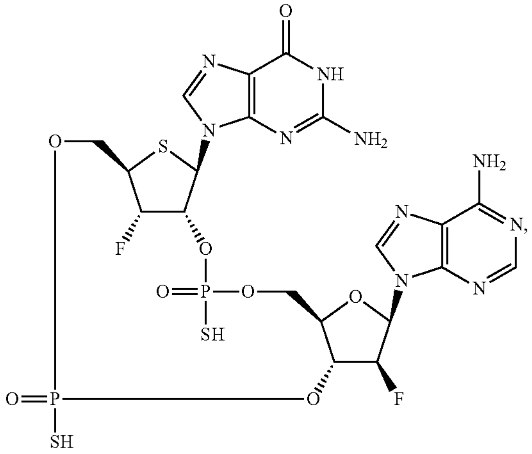

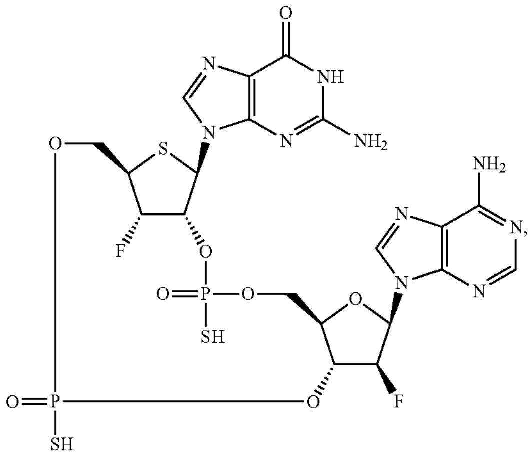

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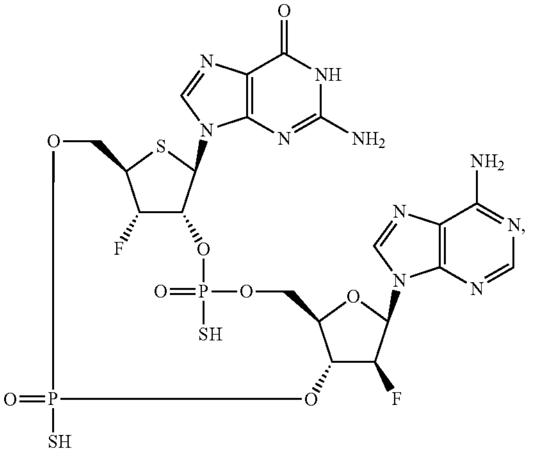

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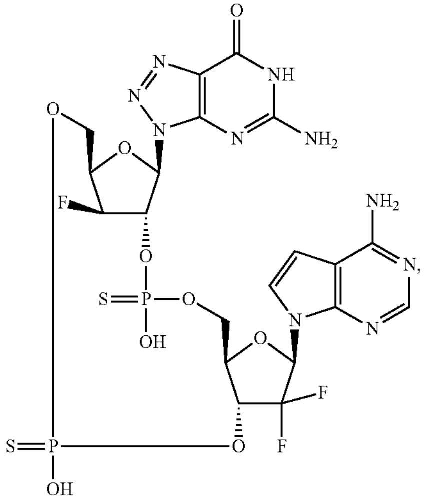

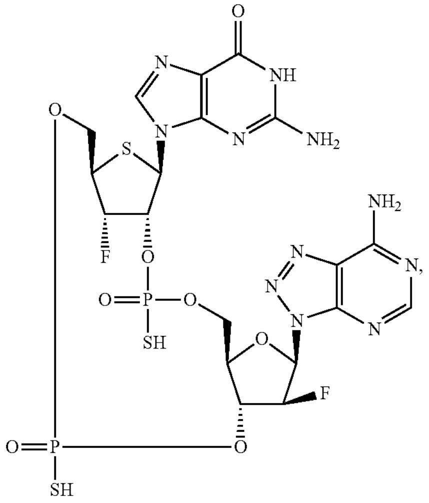

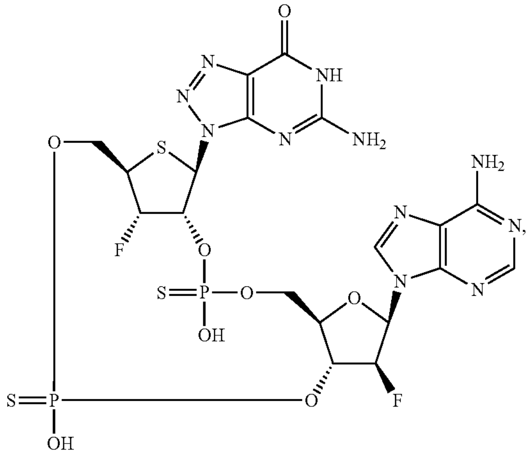

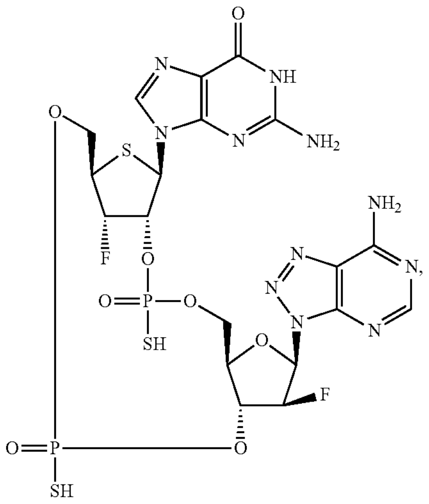

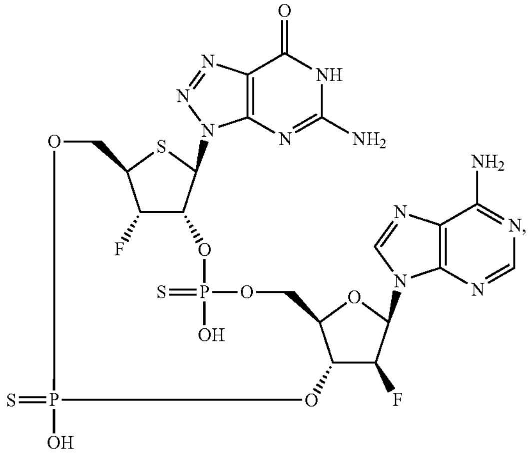

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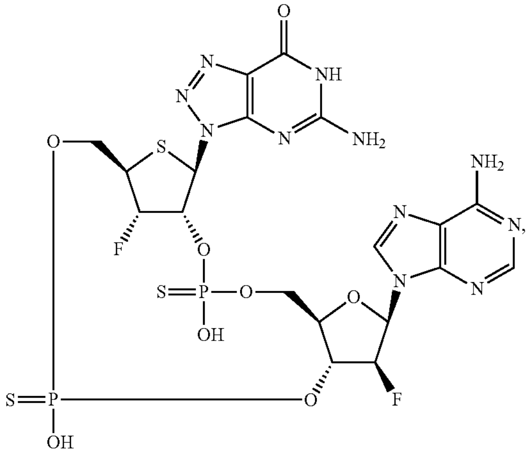

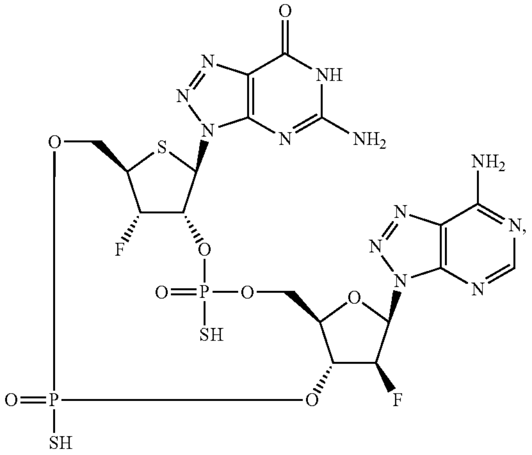

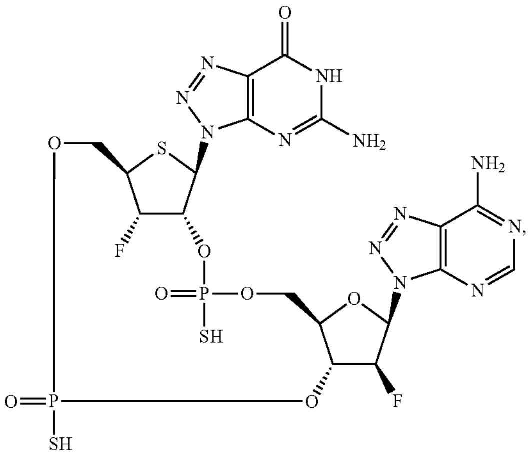

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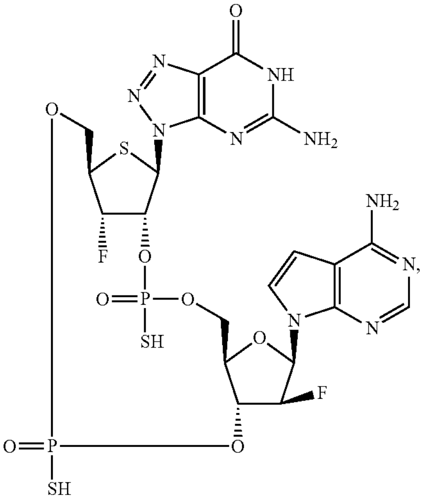

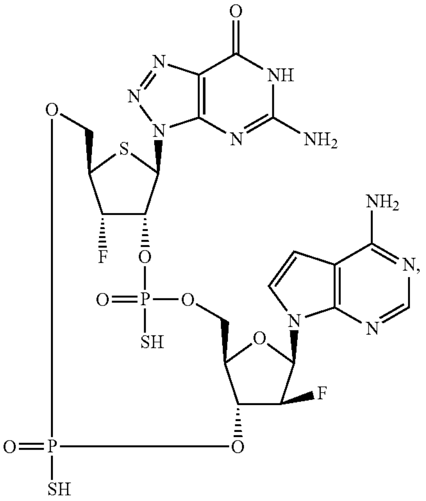

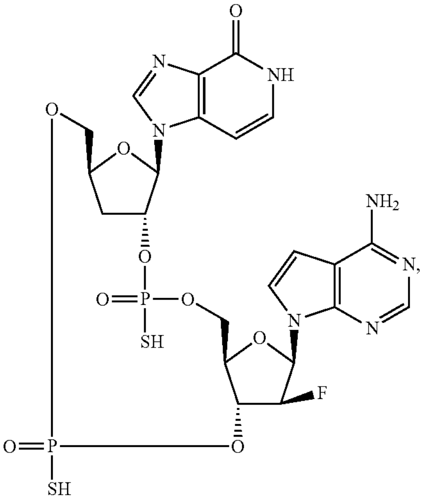

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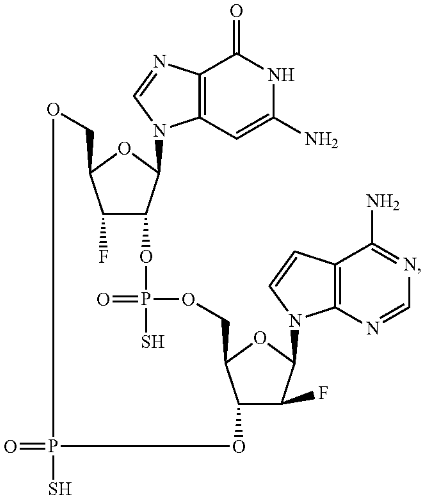

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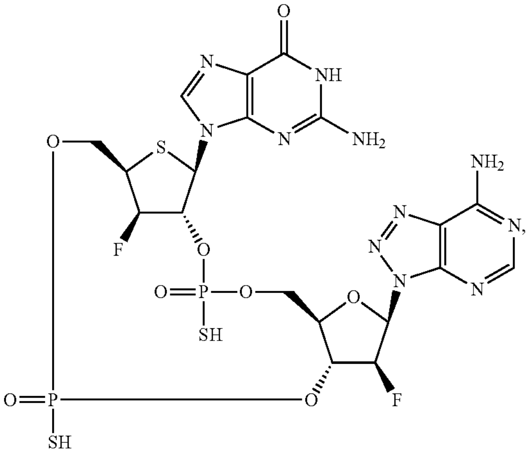

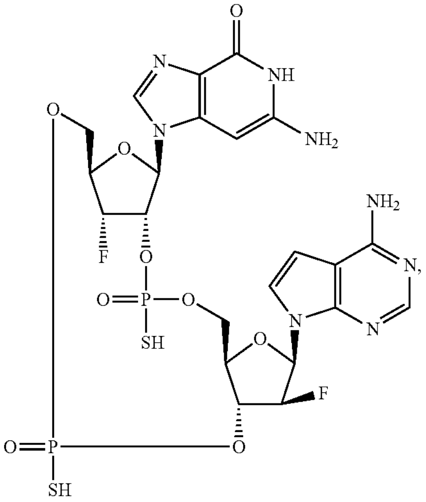

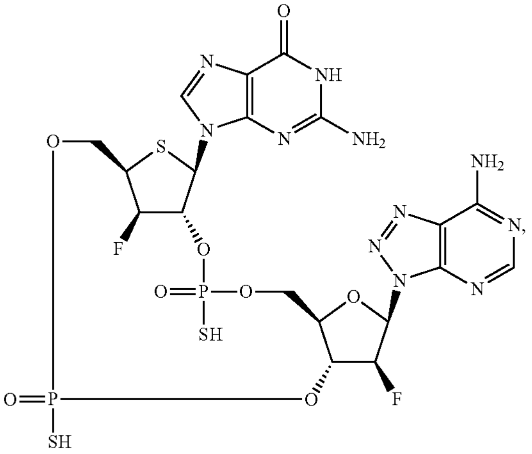

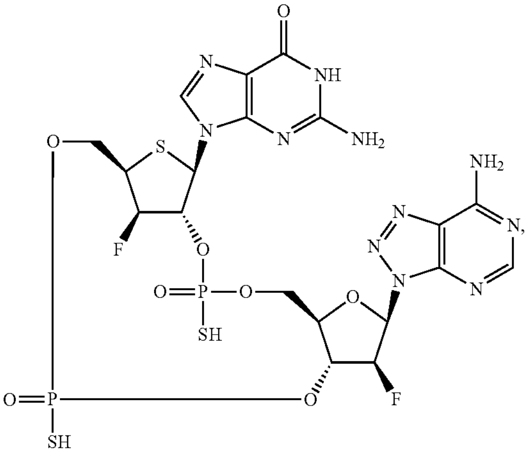

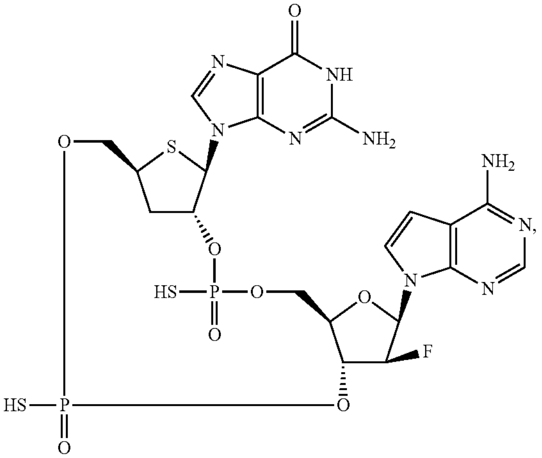

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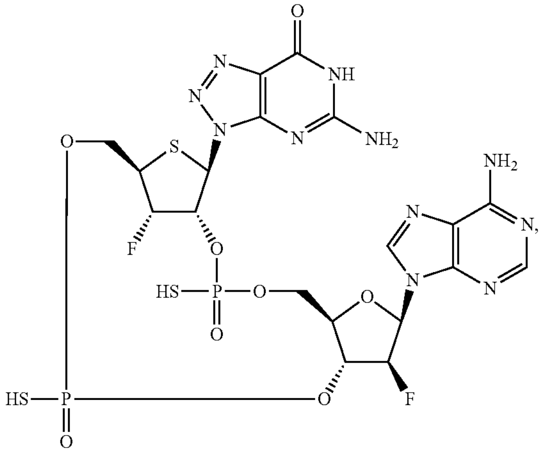

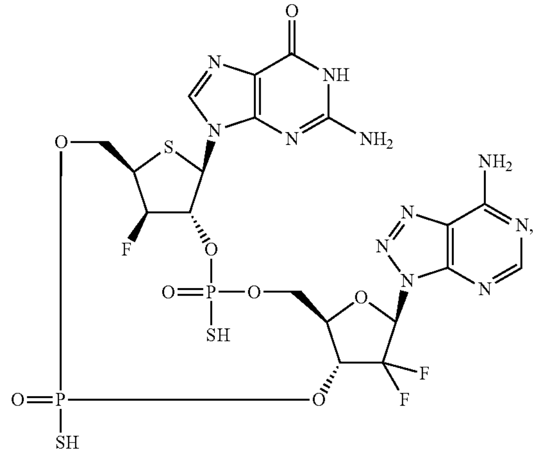

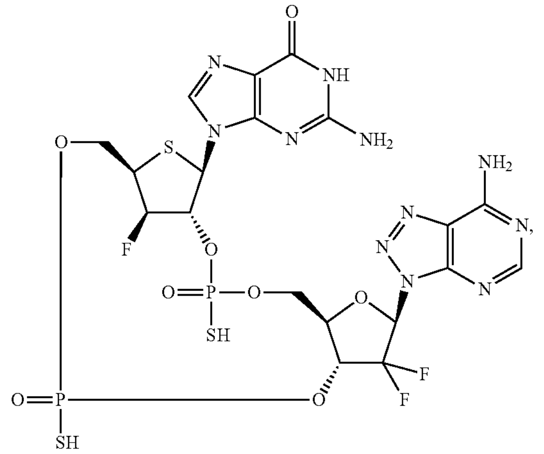

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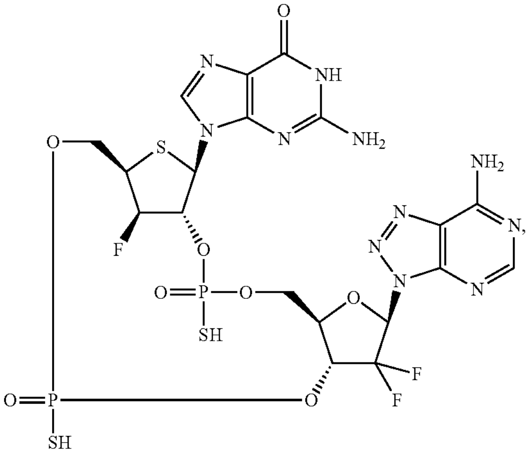

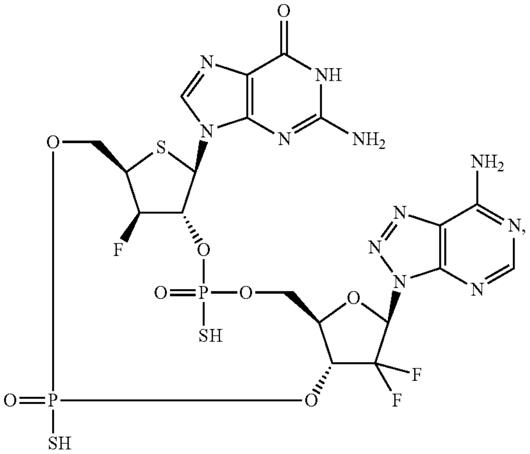

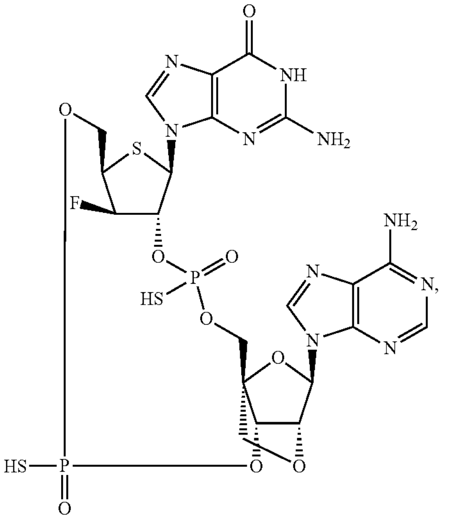

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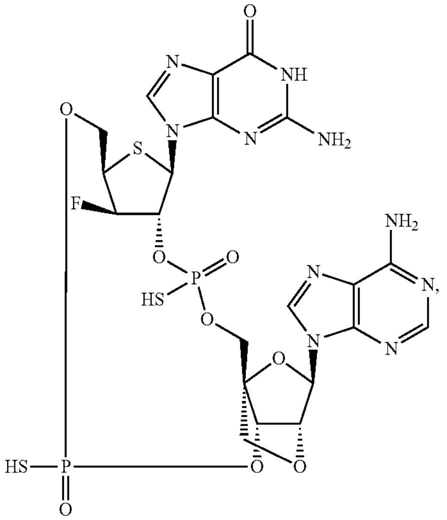

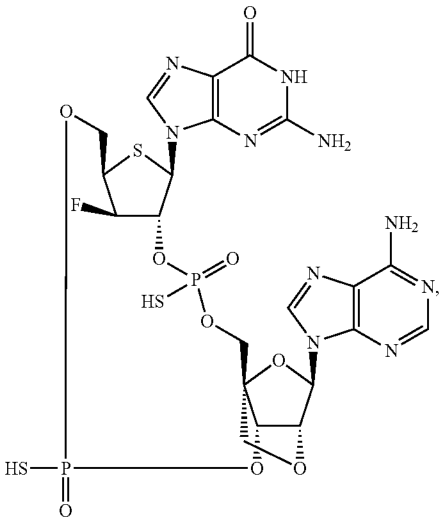

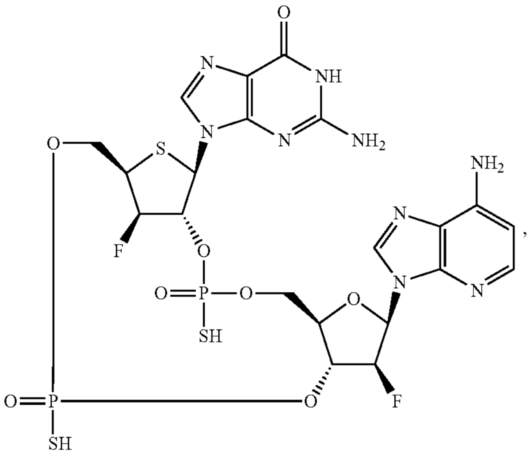

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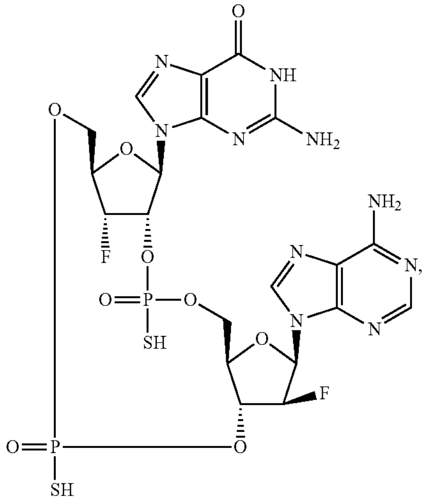

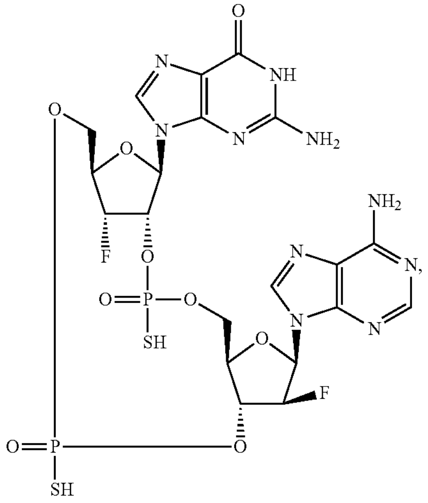

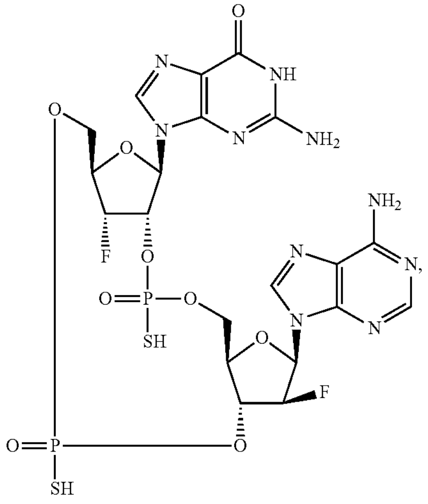

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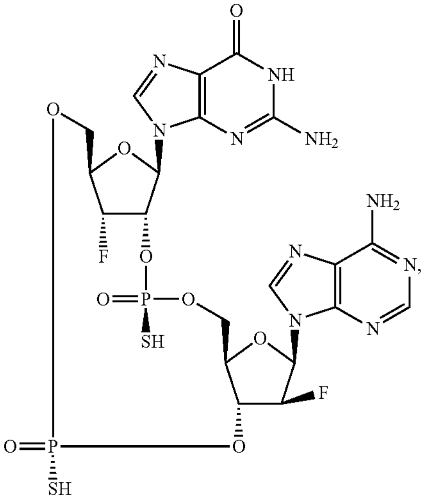

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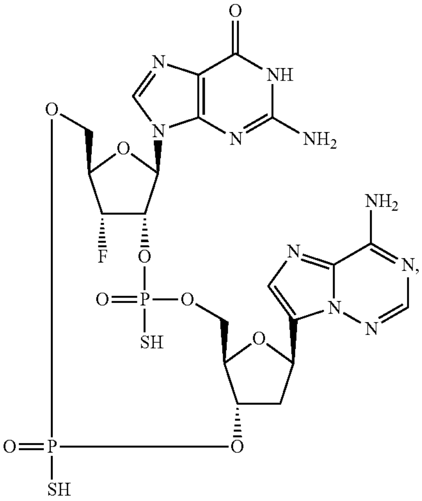

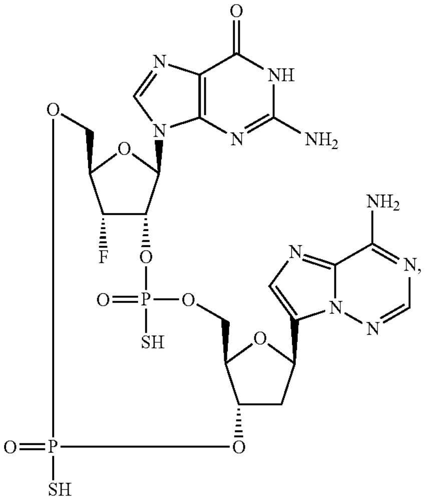

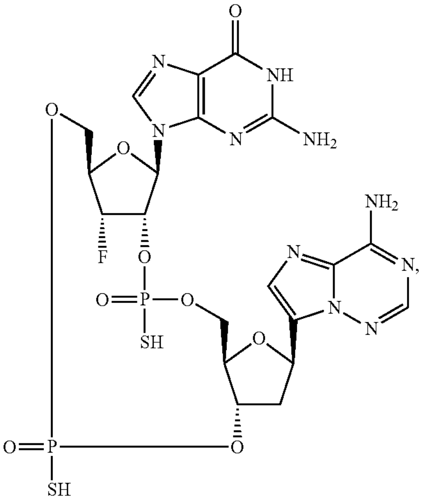

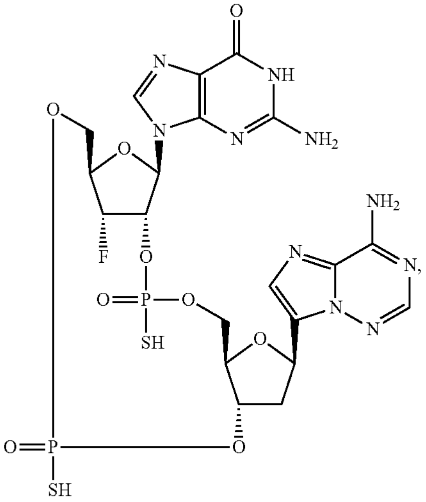

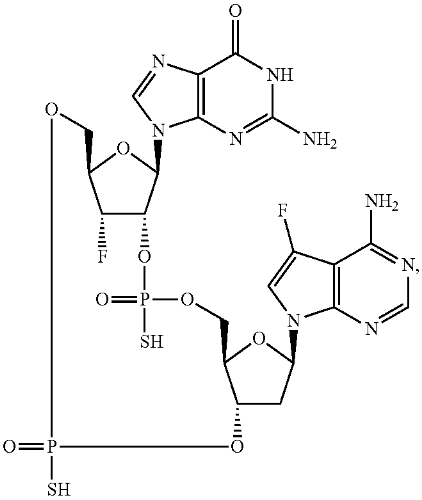

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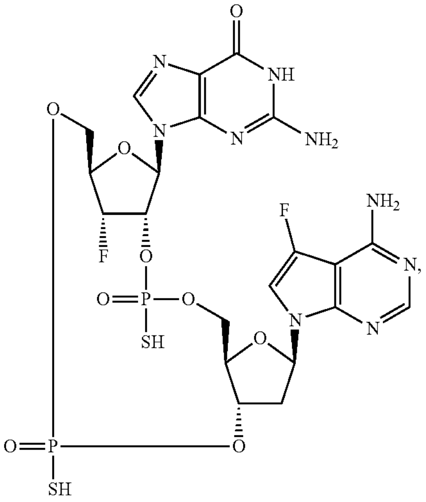

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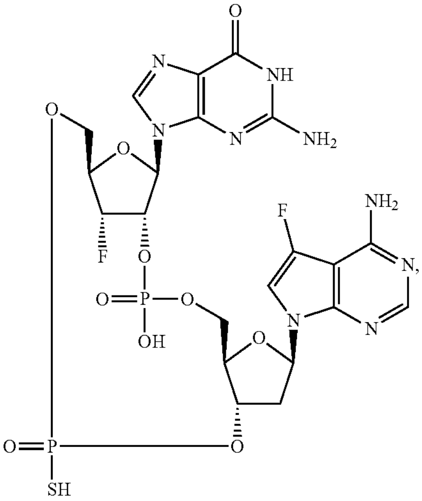

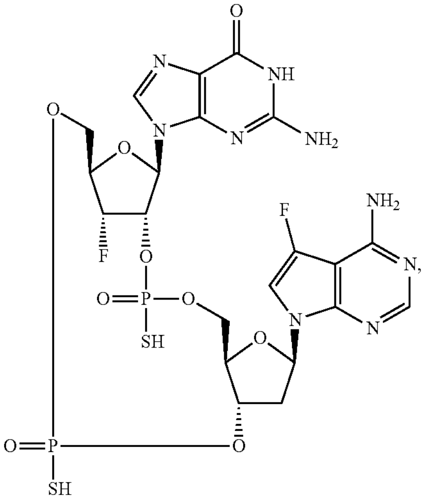

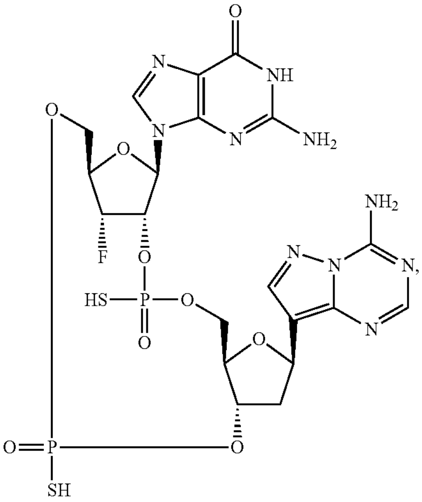

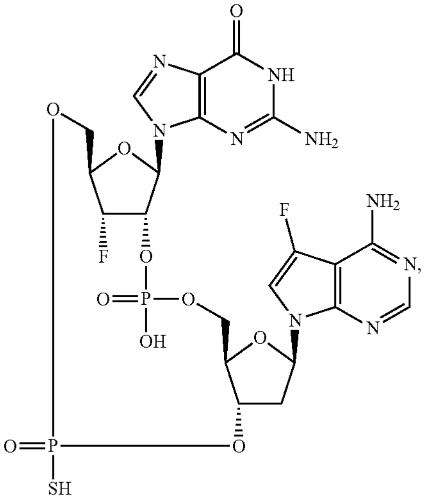

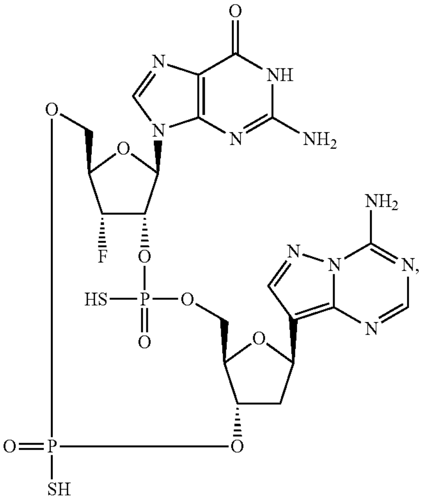

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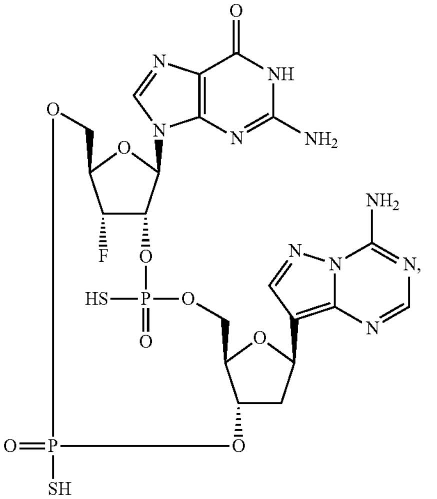

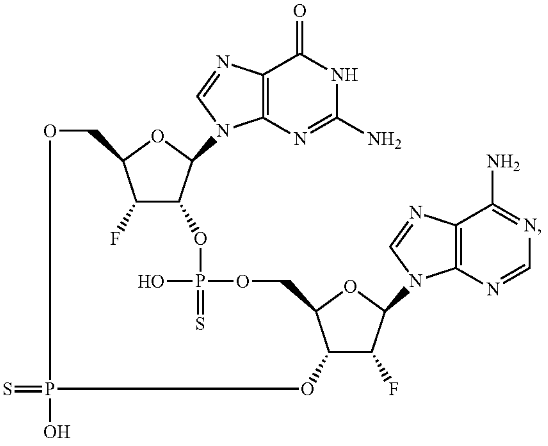

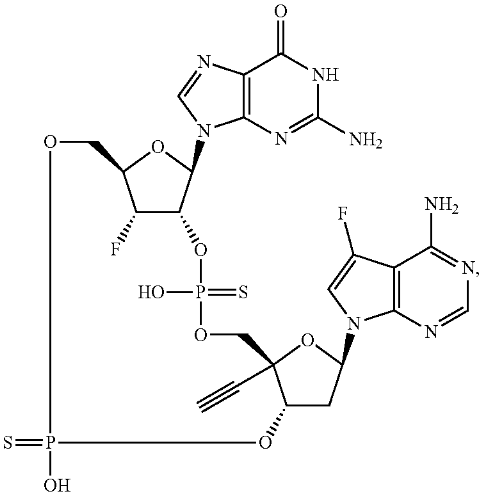

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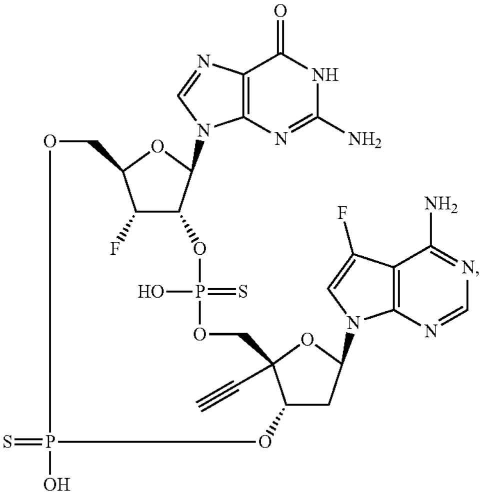

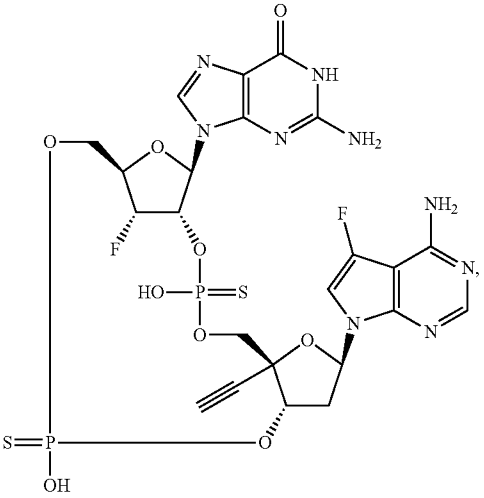

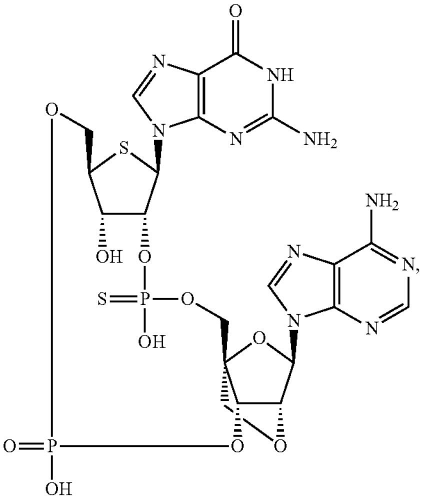

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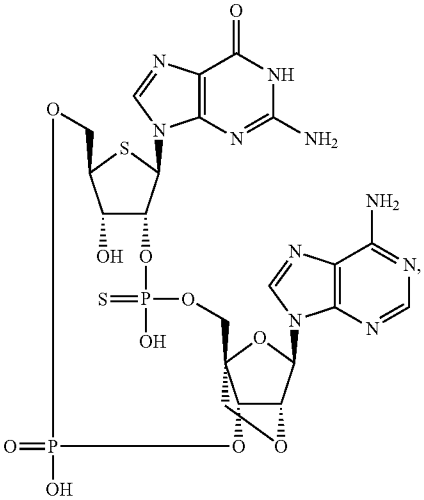

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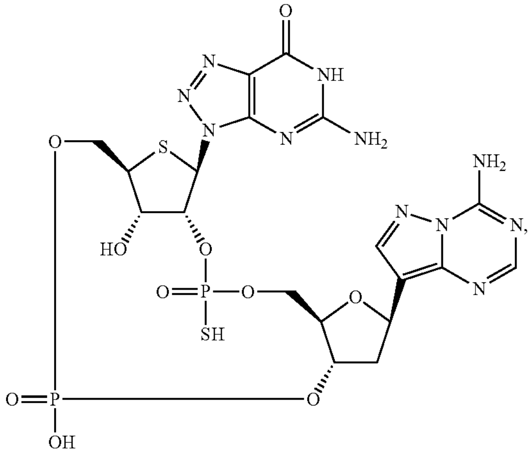

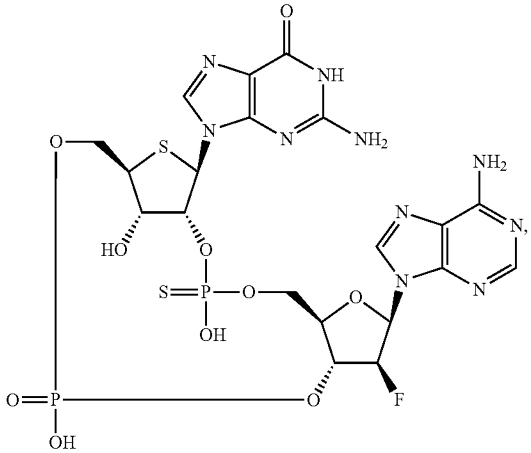

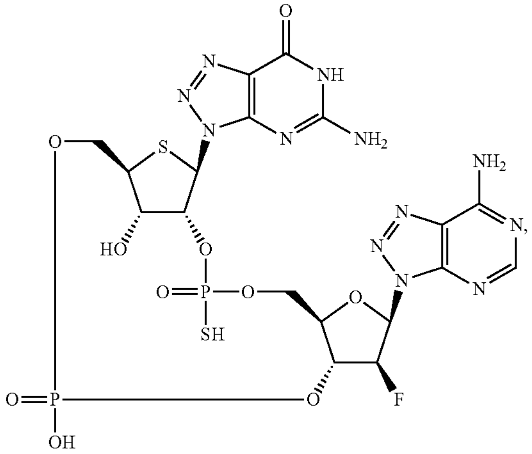

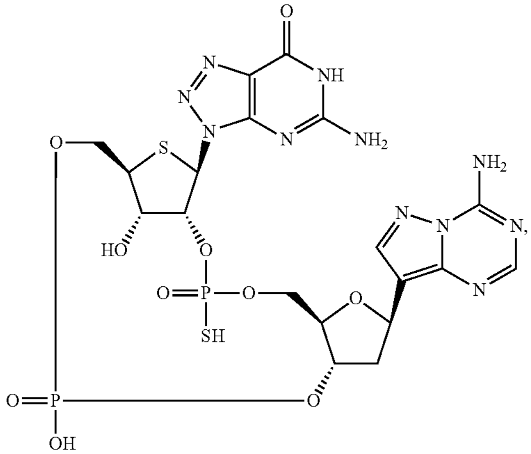

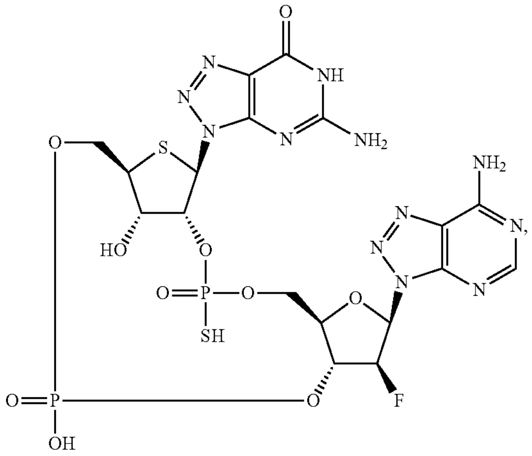

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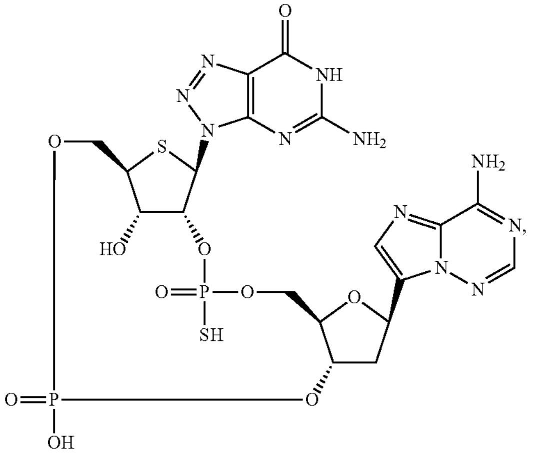

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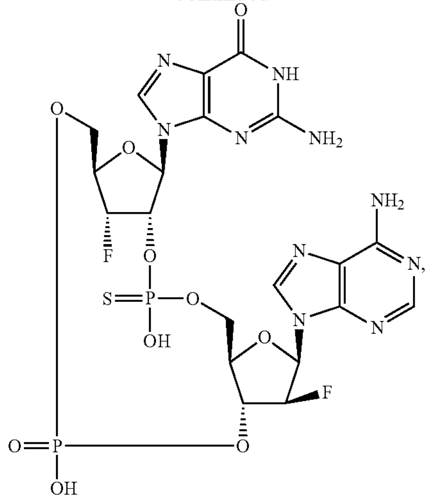

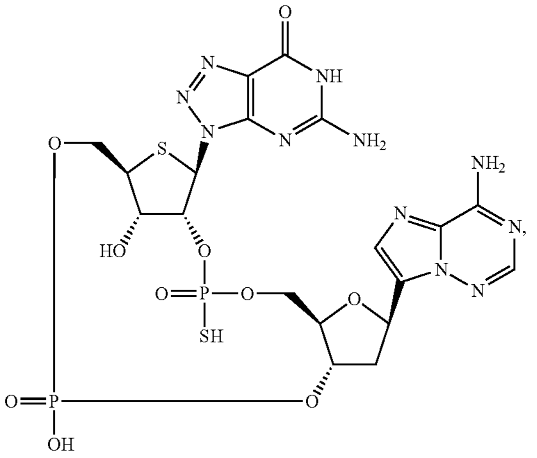

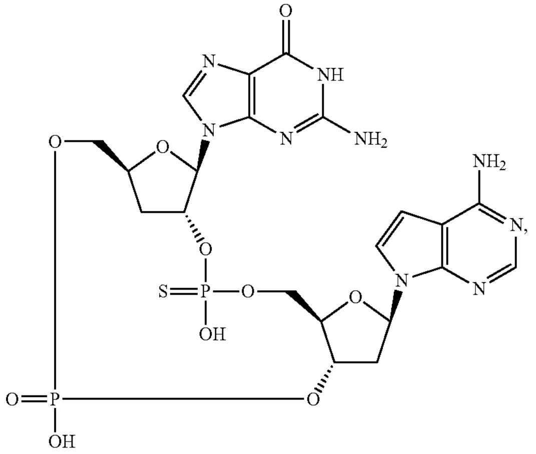

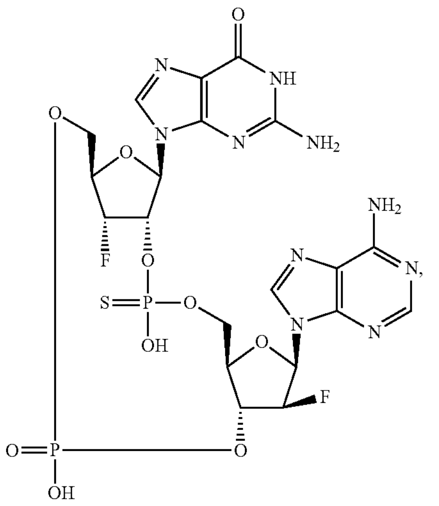

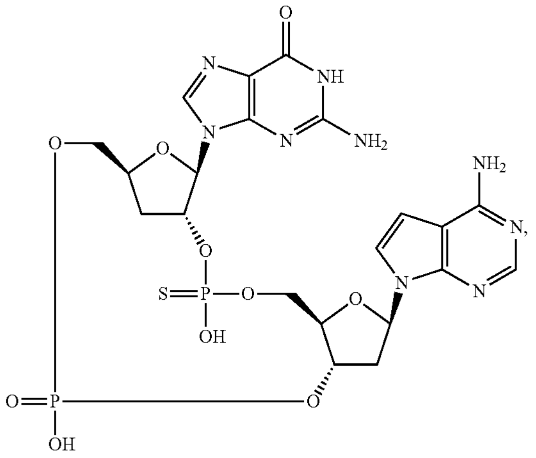

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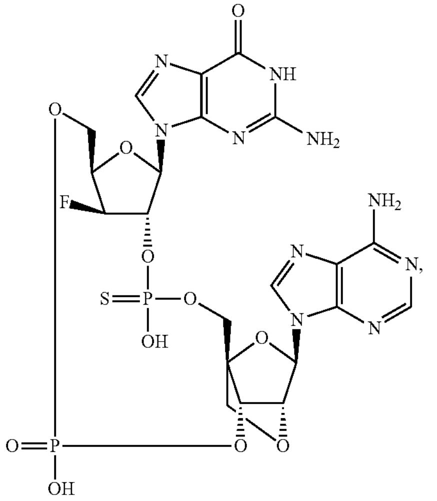

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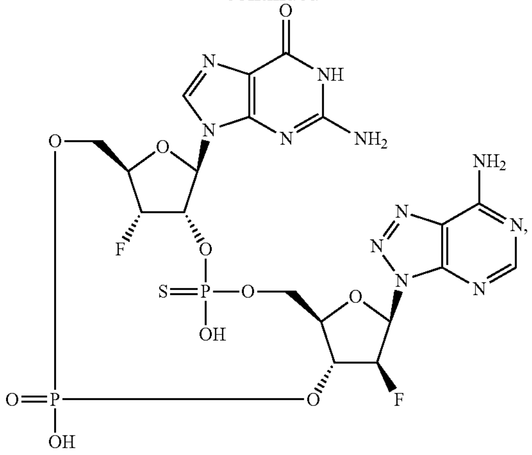

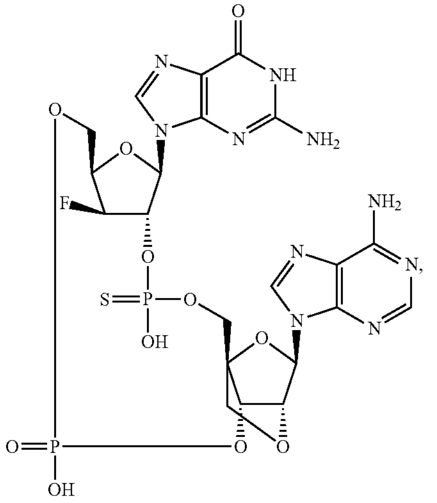

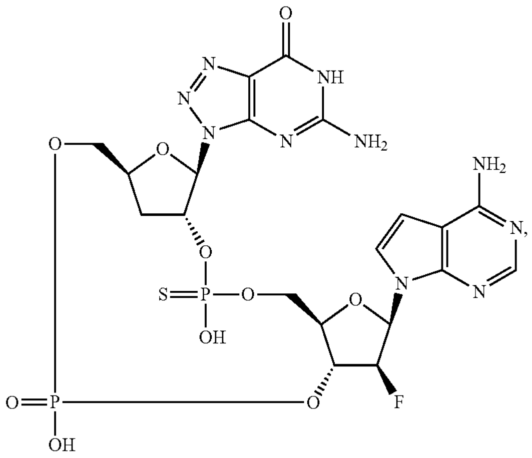

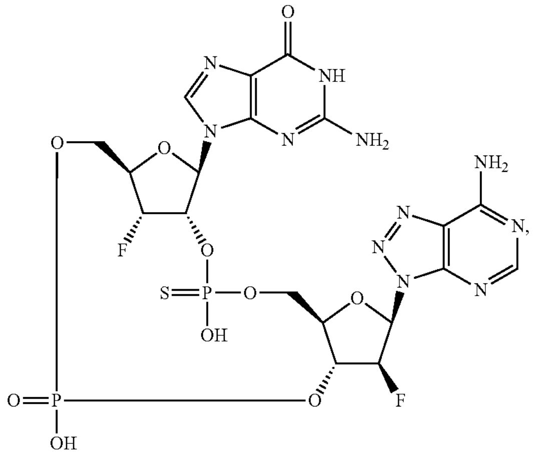

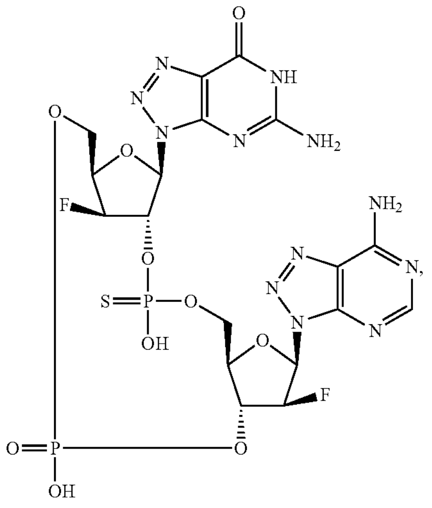

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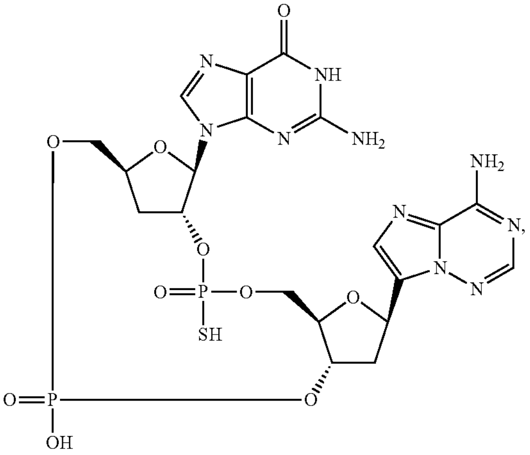

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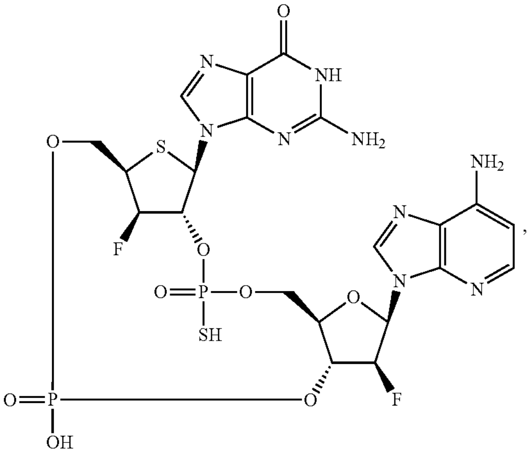

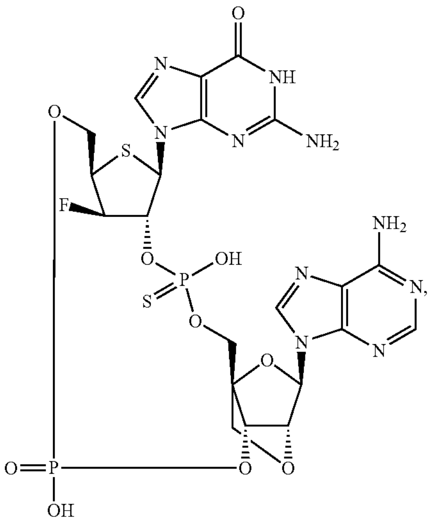

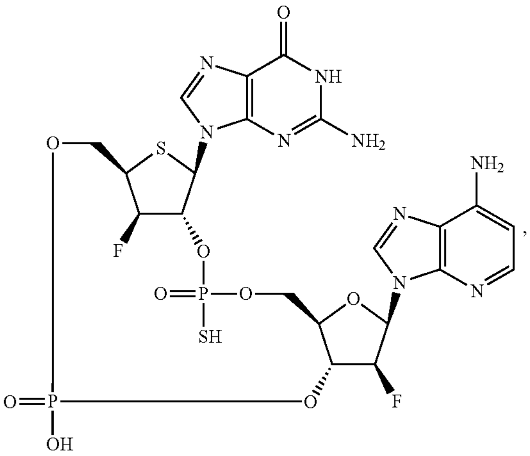

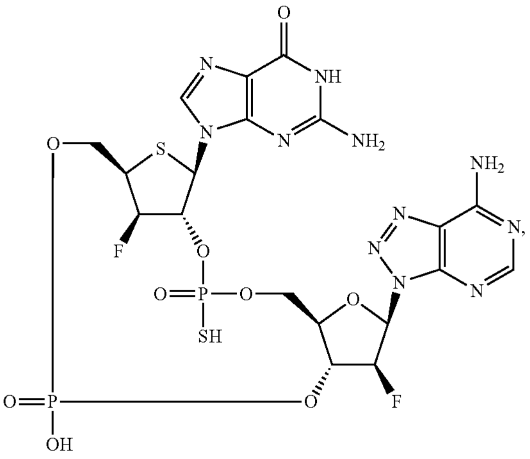

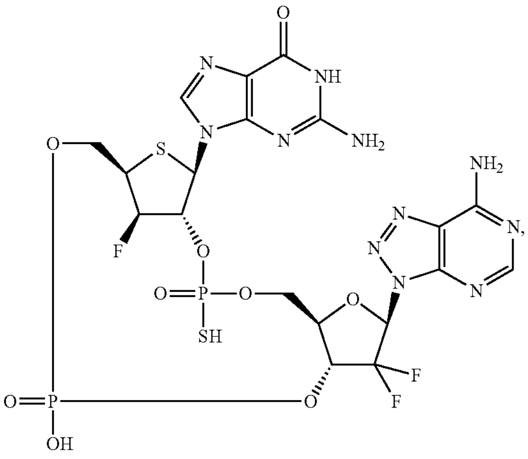

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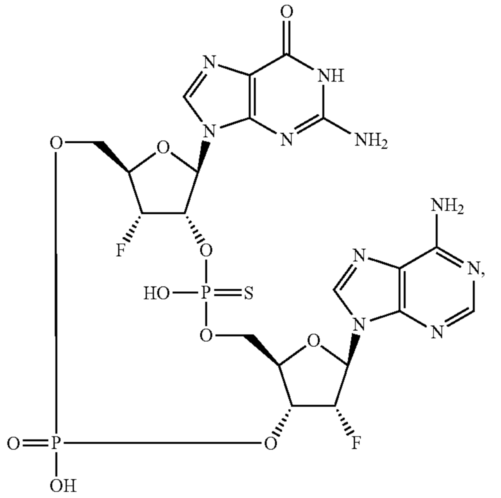

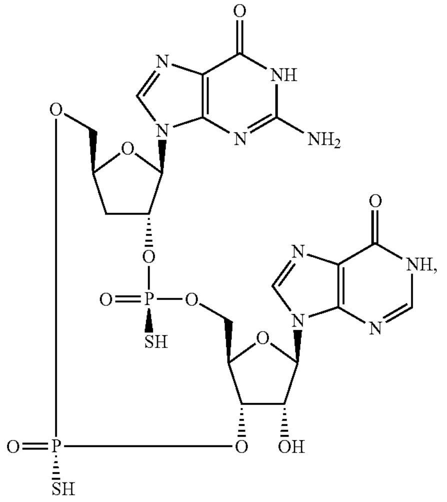

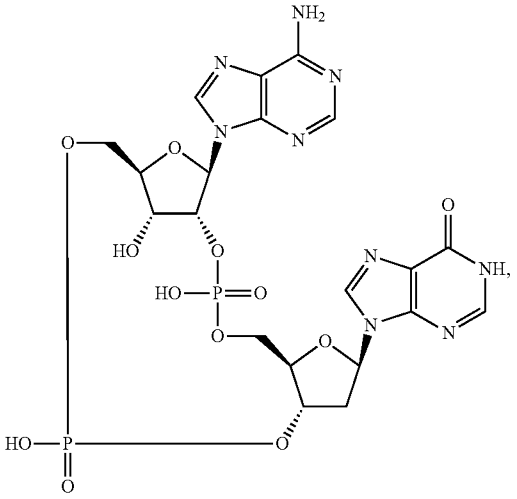

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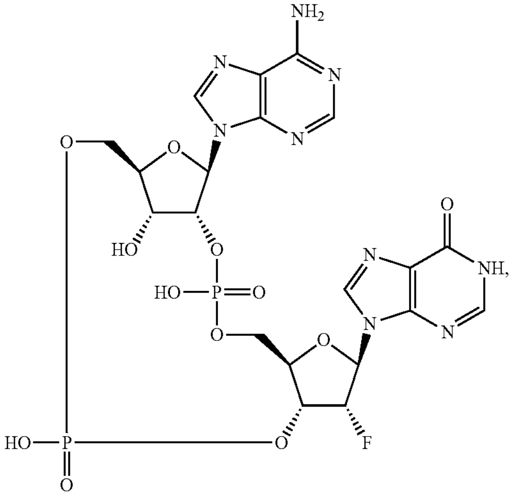

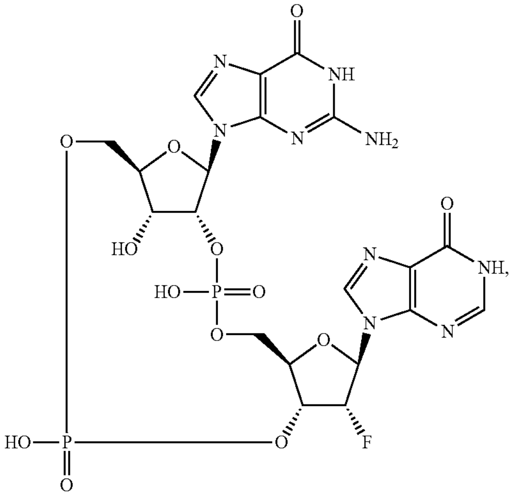

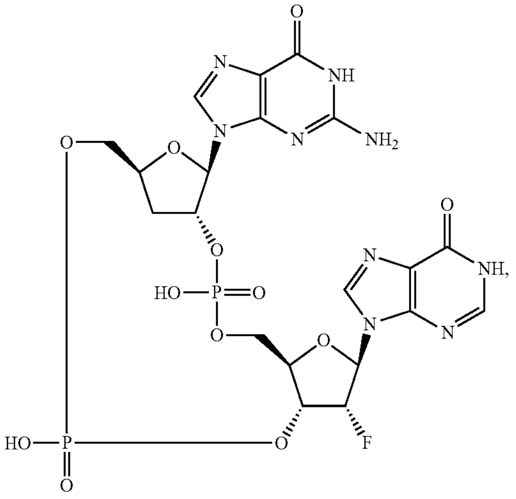

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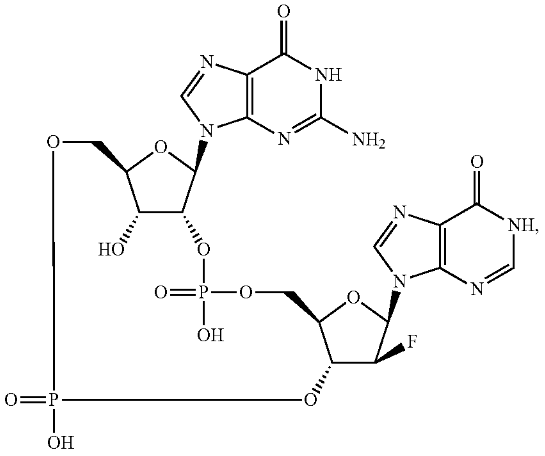

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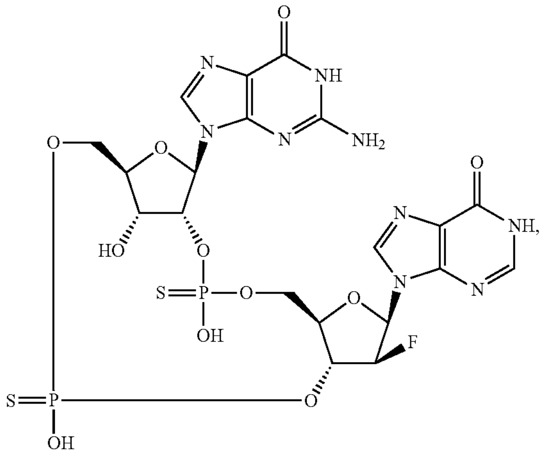

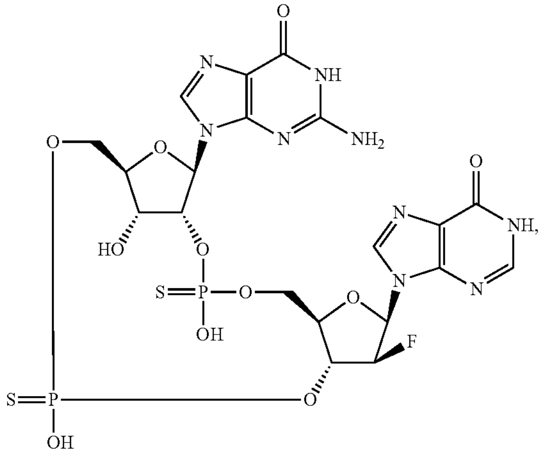

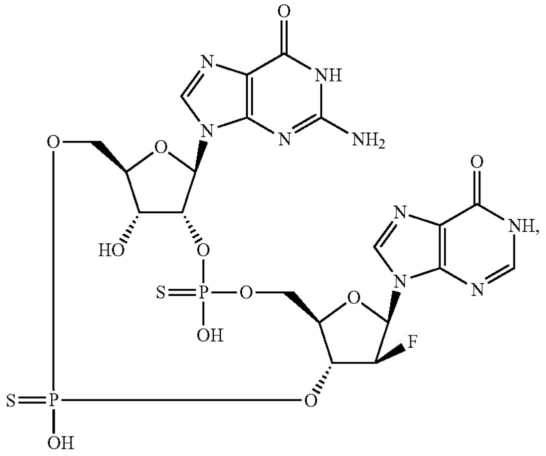

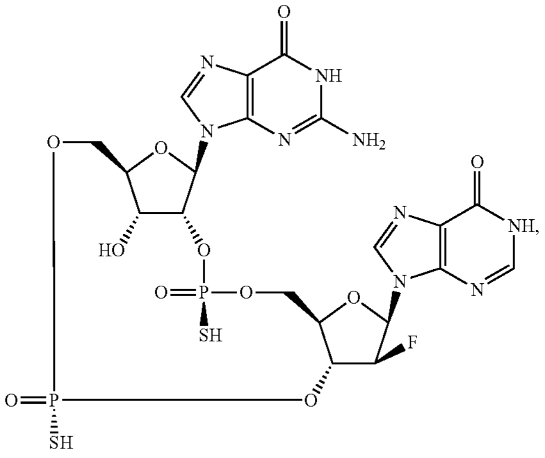

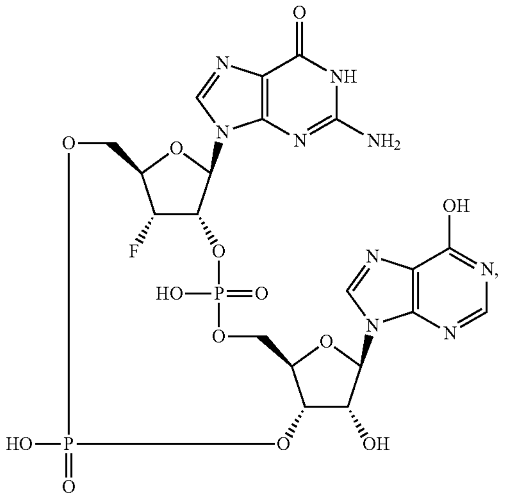

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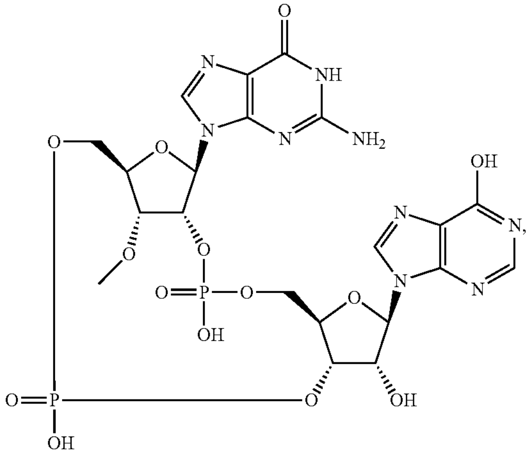

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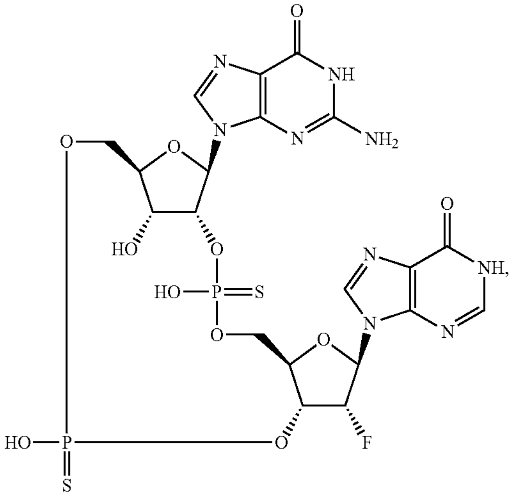

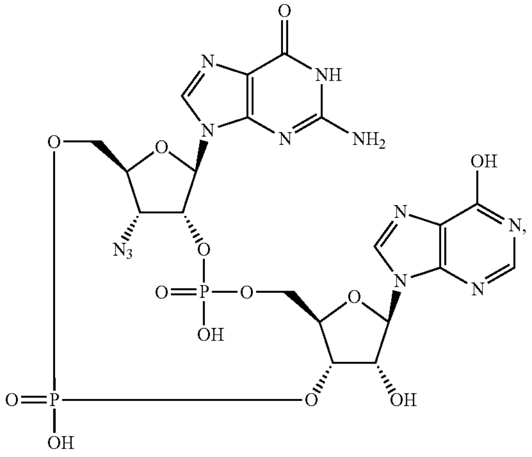

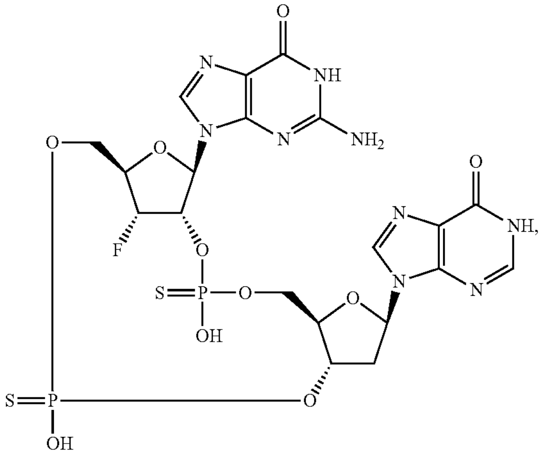

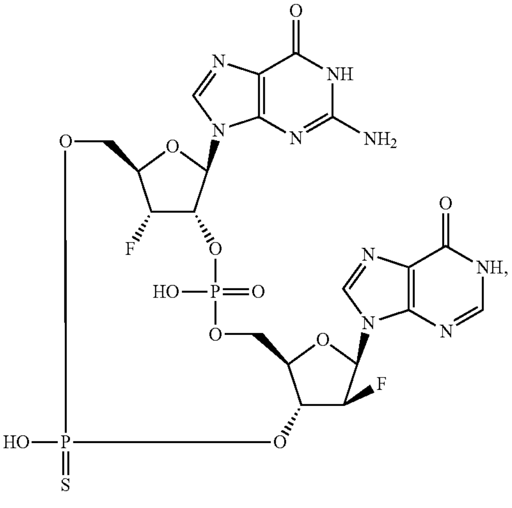

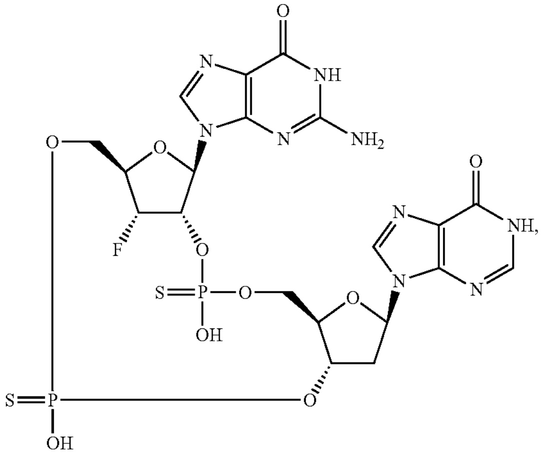

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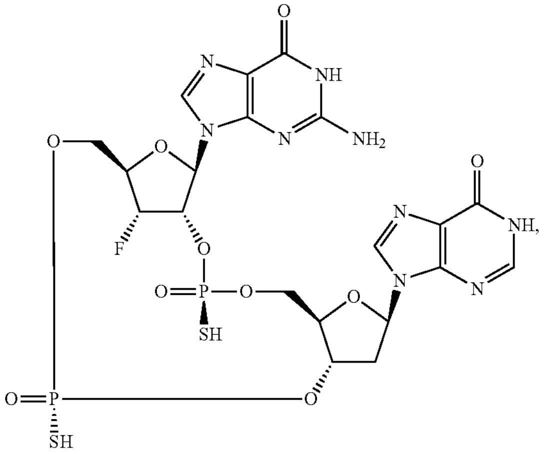

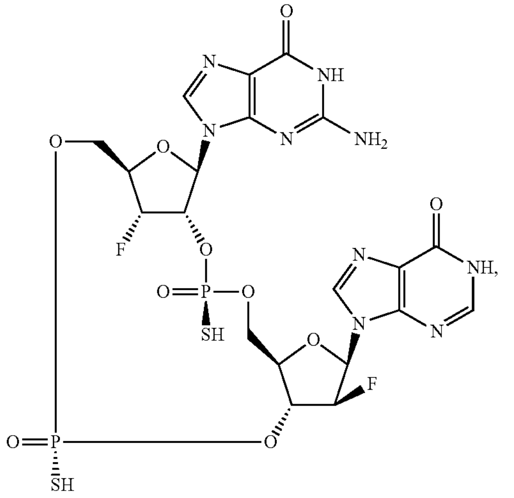

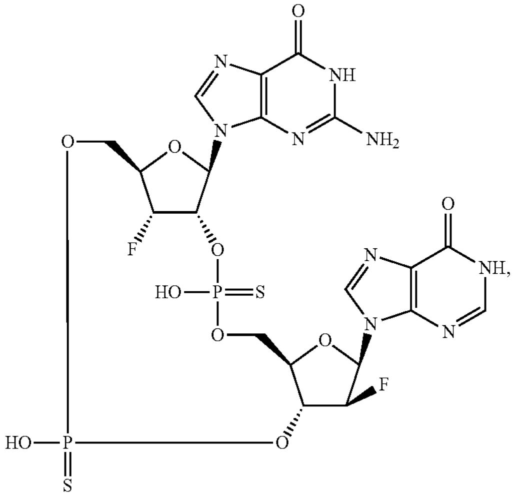

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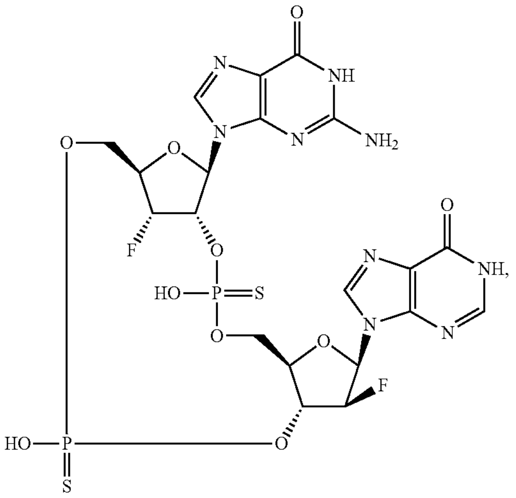

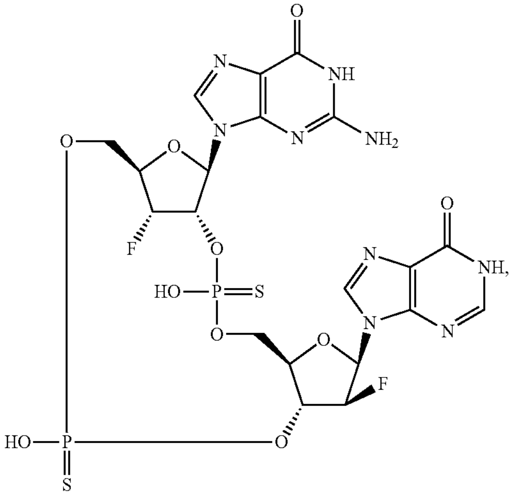

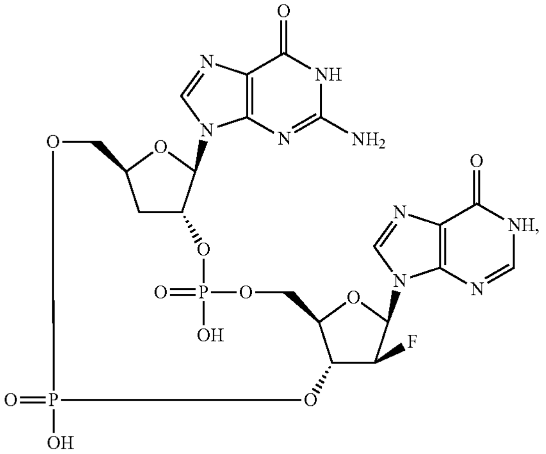

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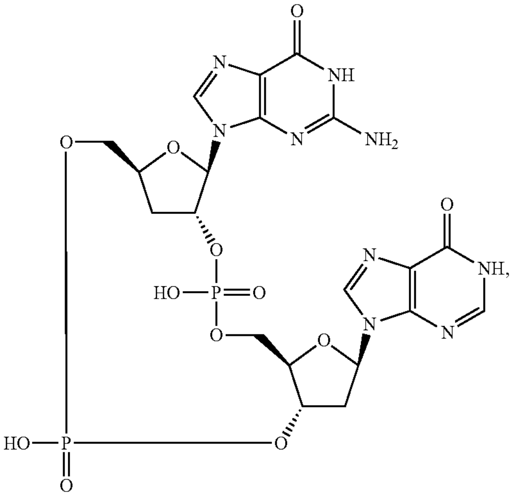

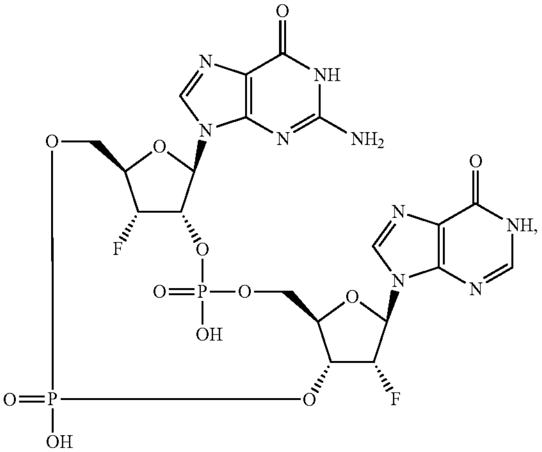

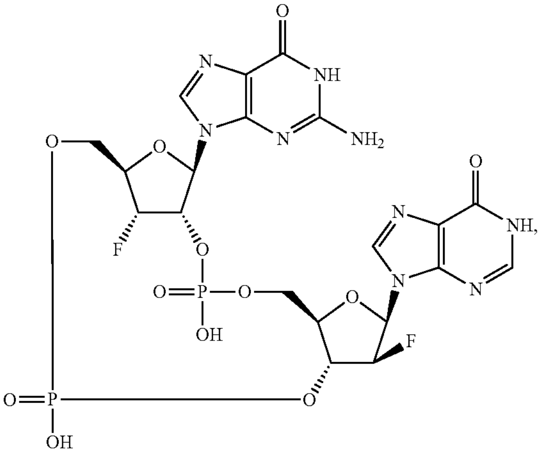

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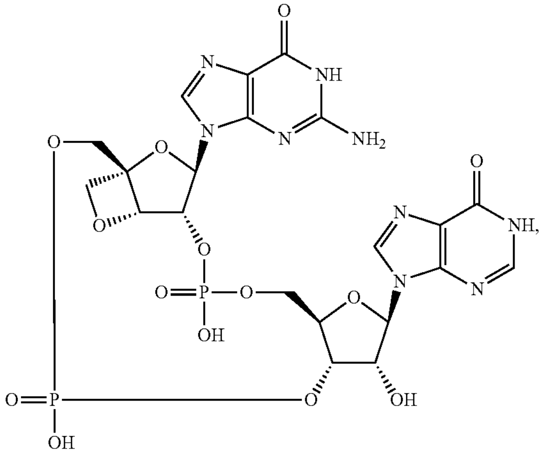

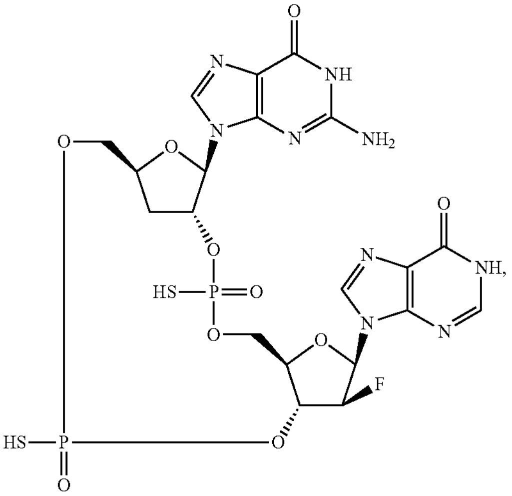

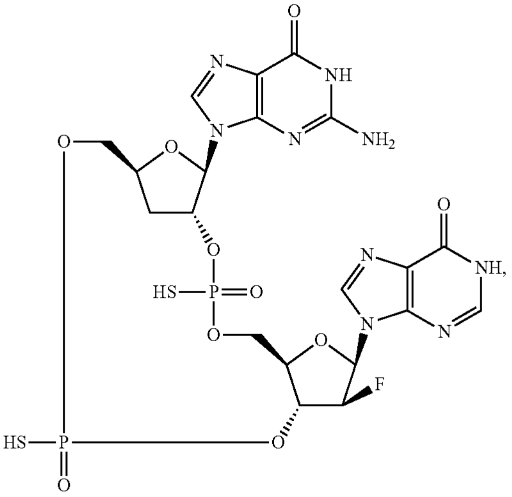

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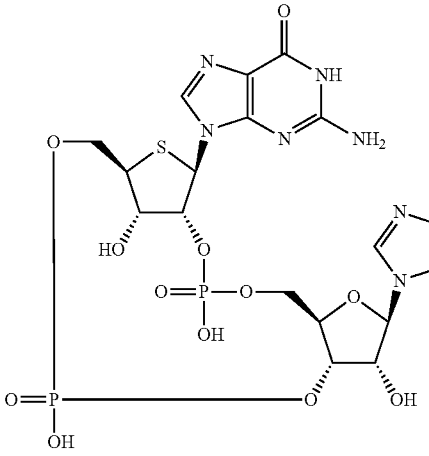

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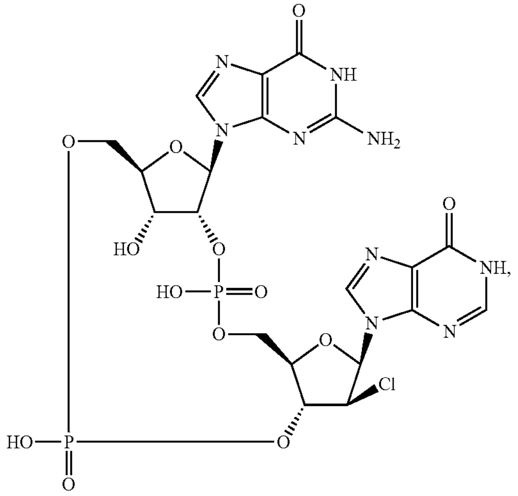

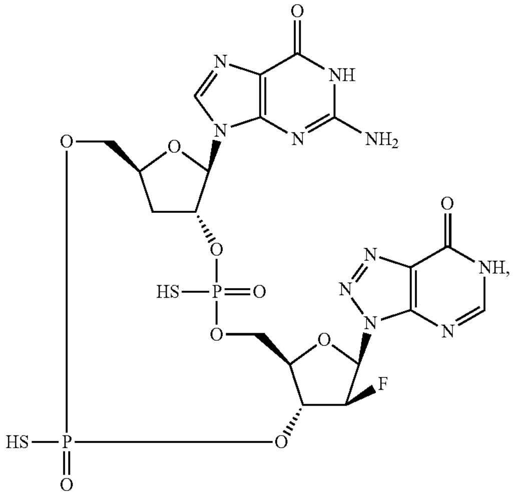

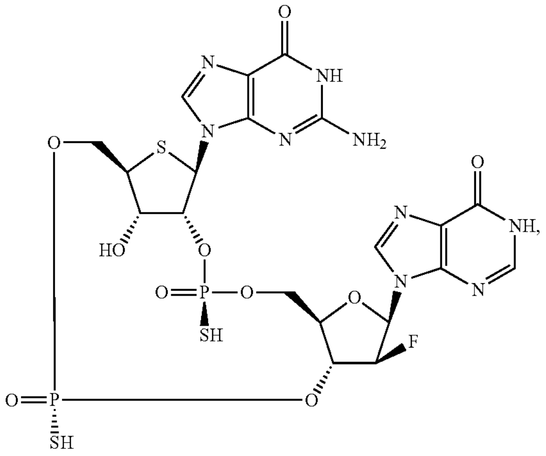

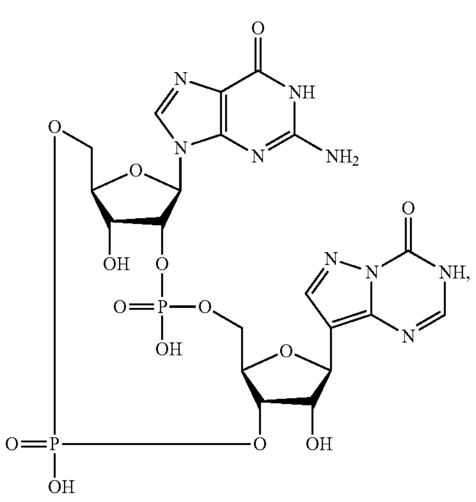

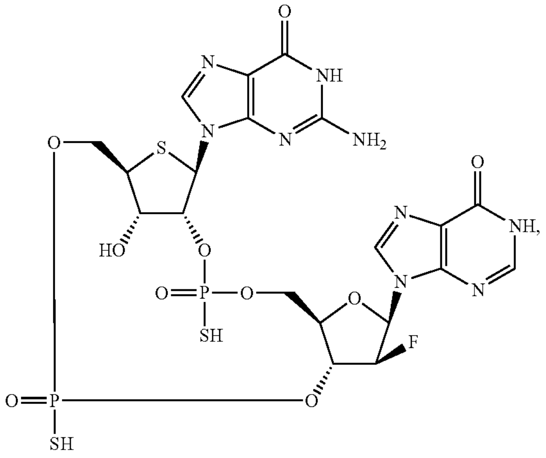

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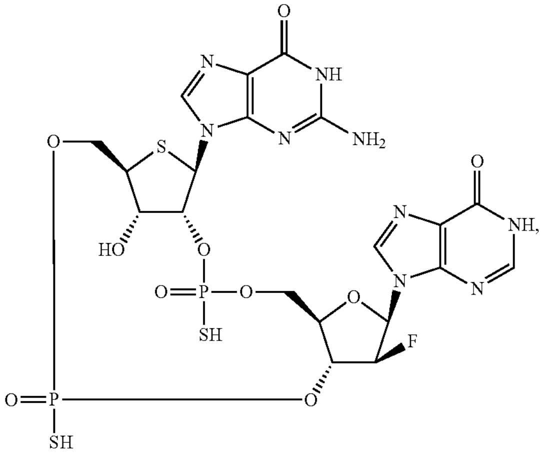

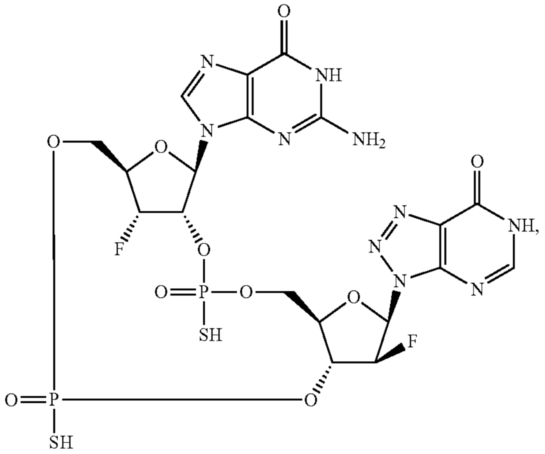

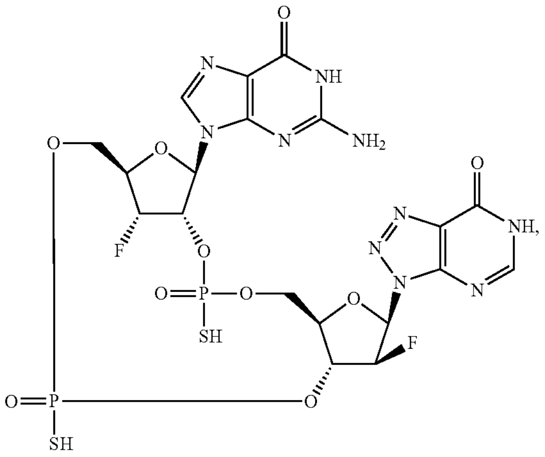

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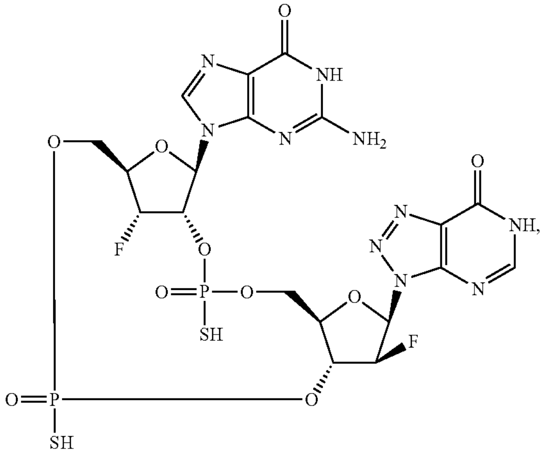

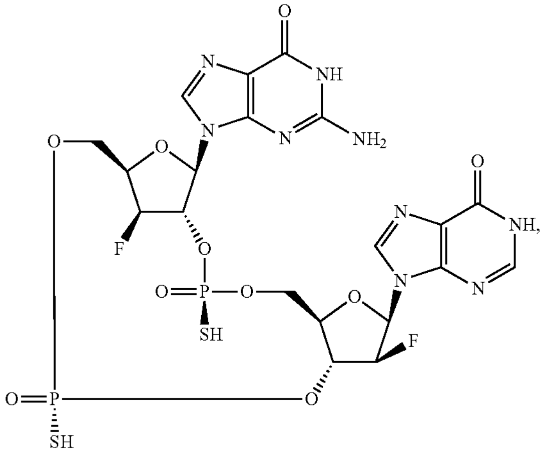

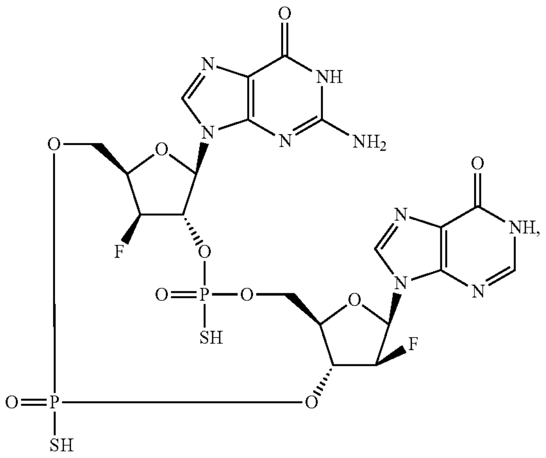

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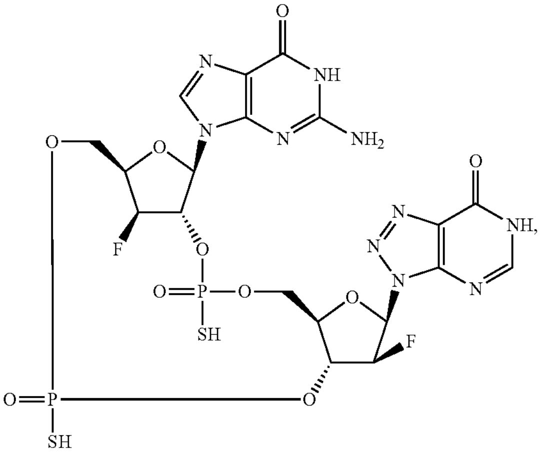

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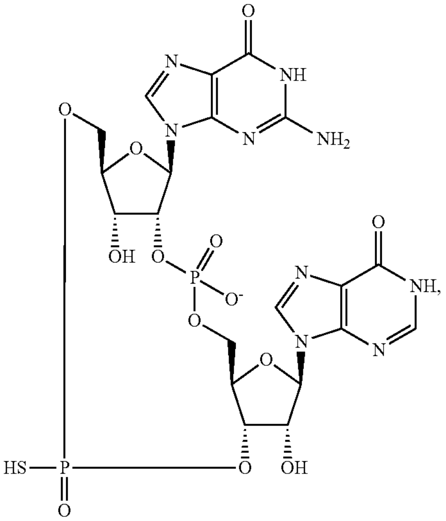

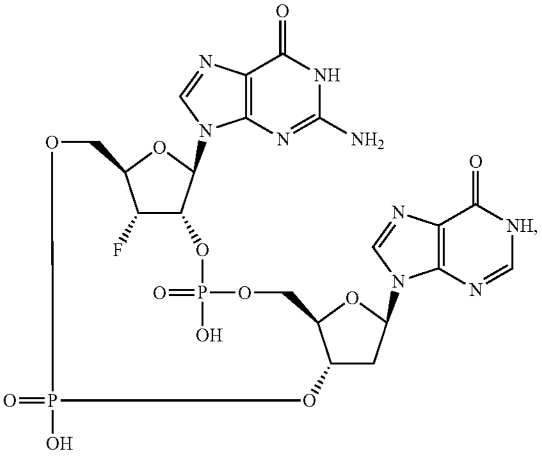

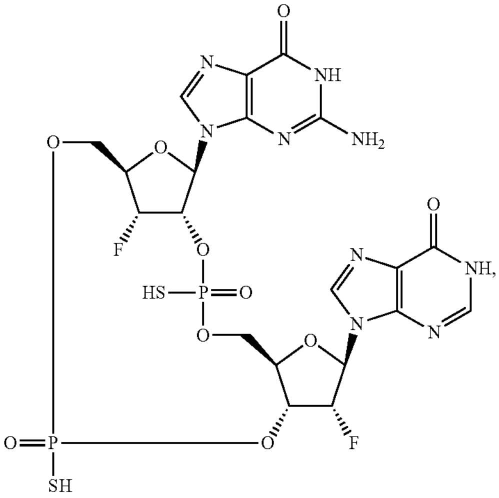

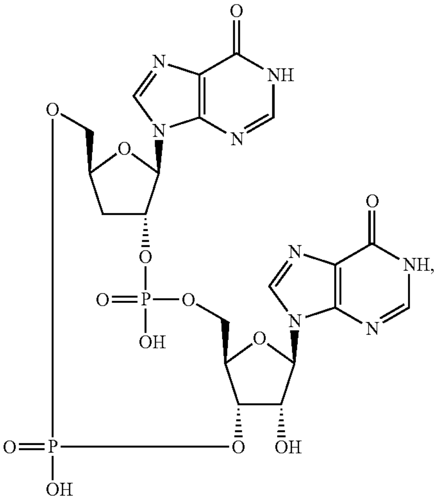

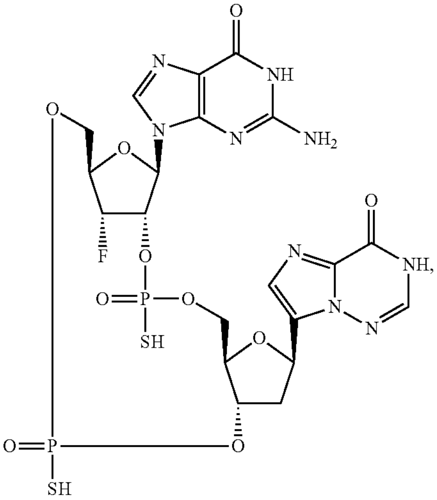

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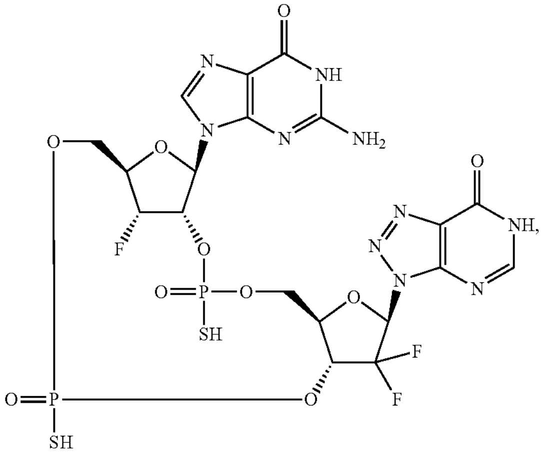

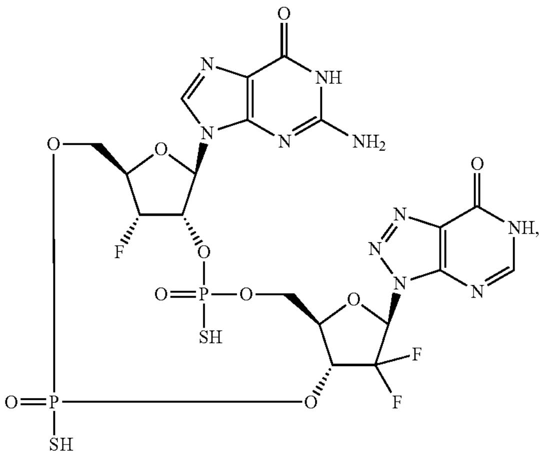

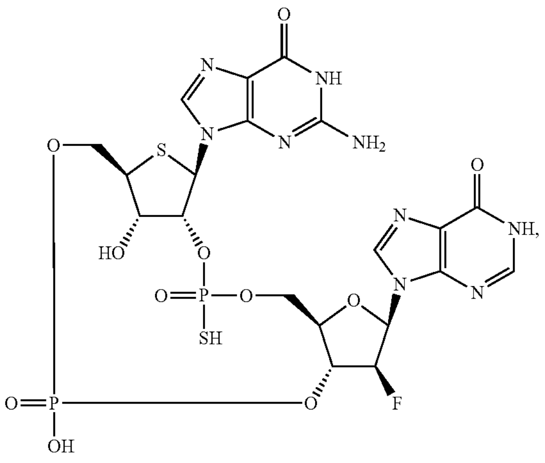

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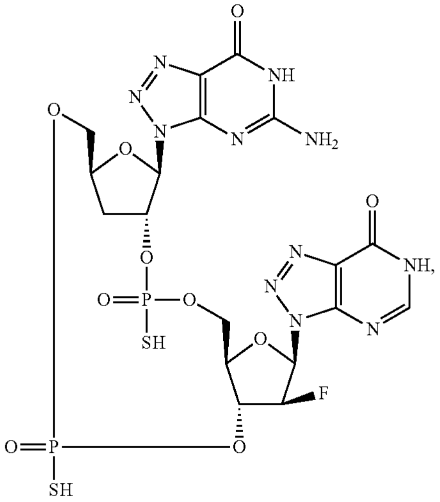

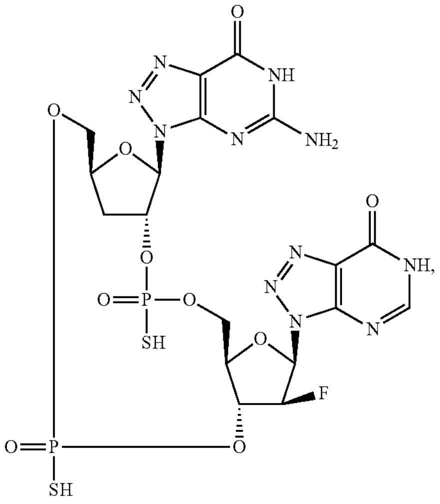

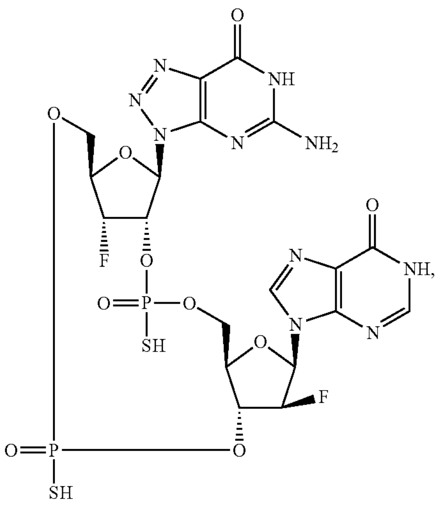

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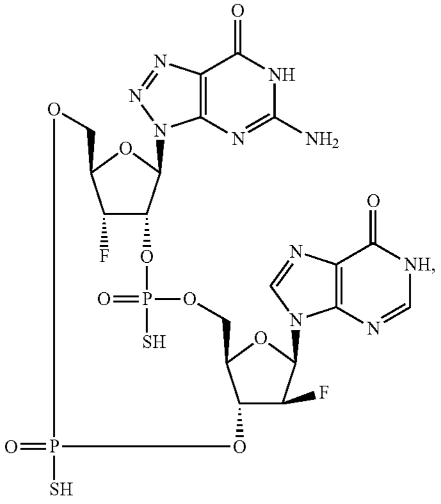

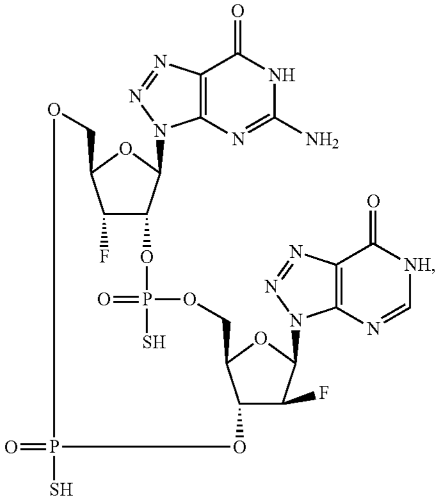

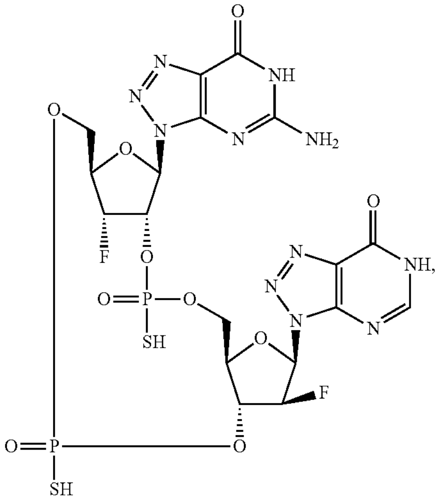

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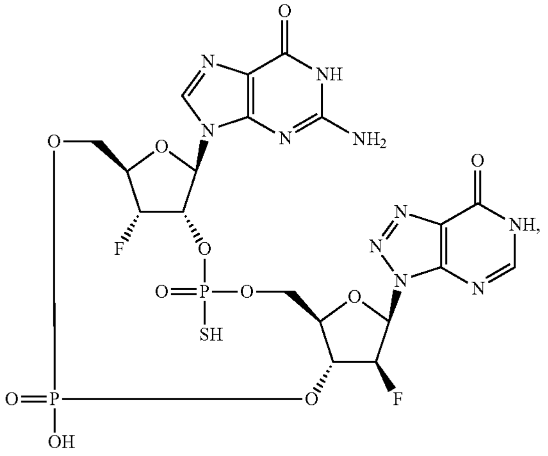

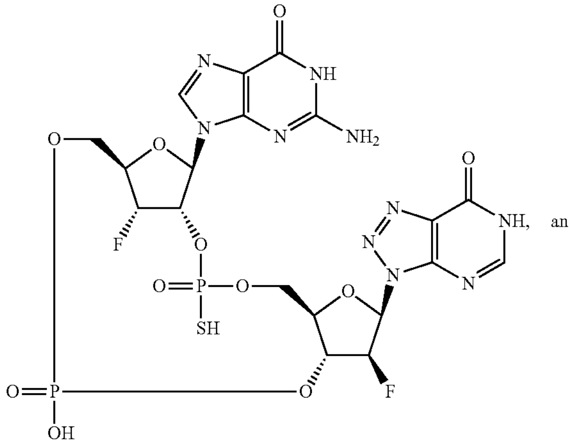

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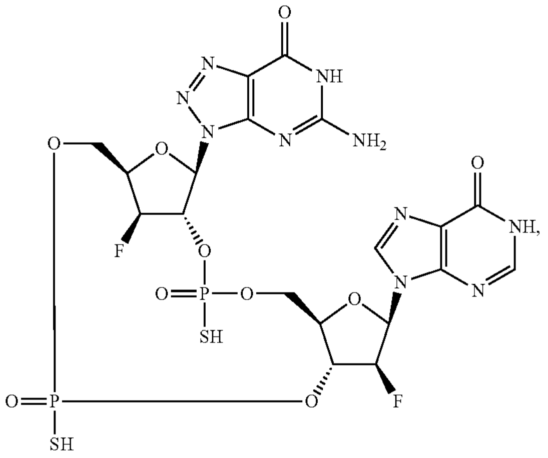

and pharmaceutically acceptable salts, hydrates, solvates, or prodrugs thereof. In aspects of this embodiment, the compound is selected from the group consisting of

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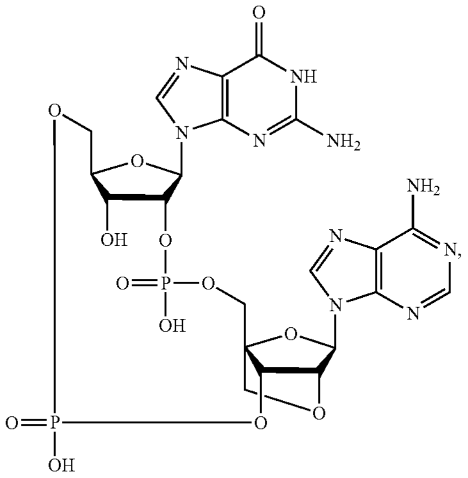

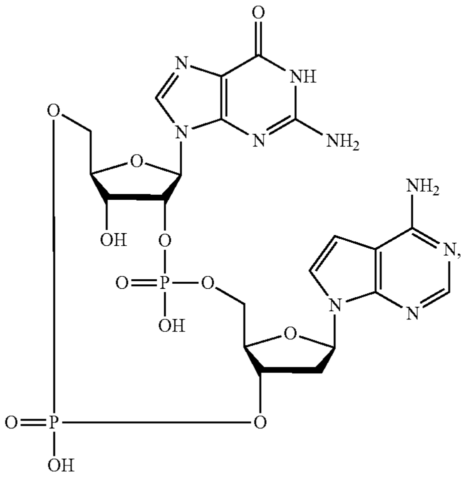

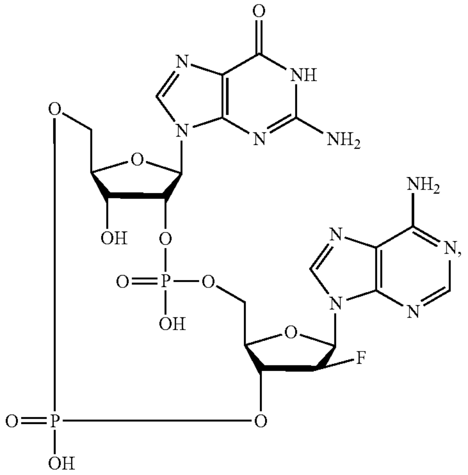

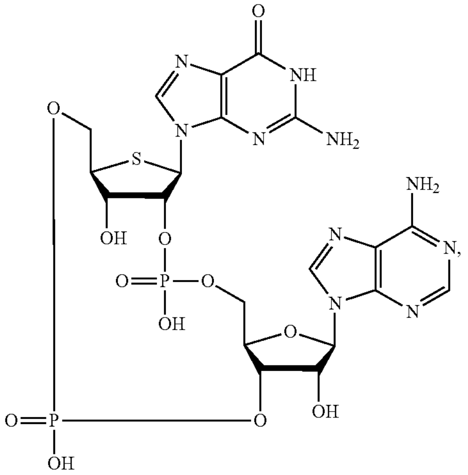

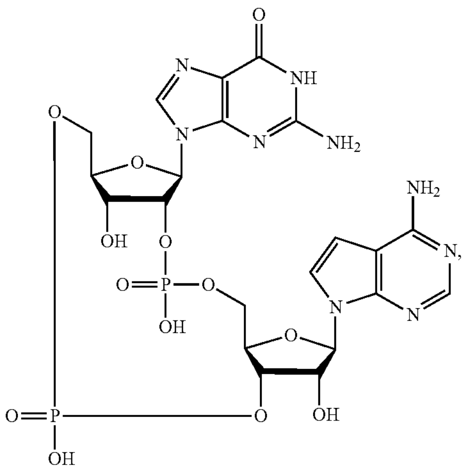

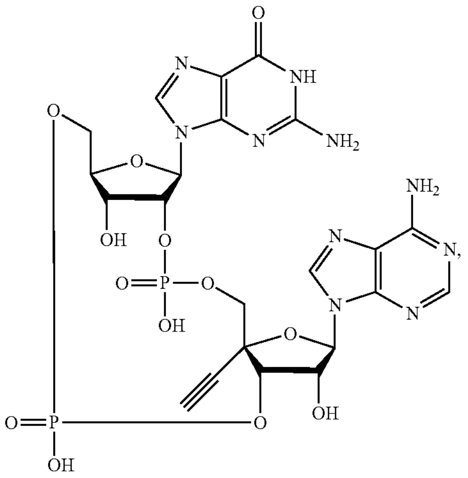

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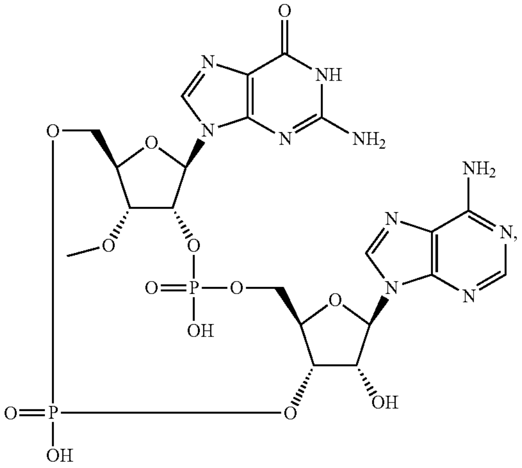

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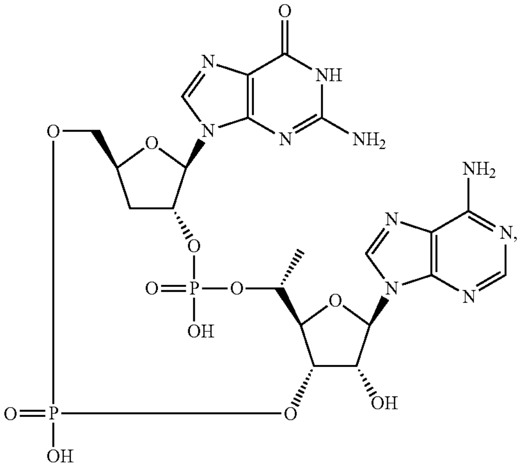

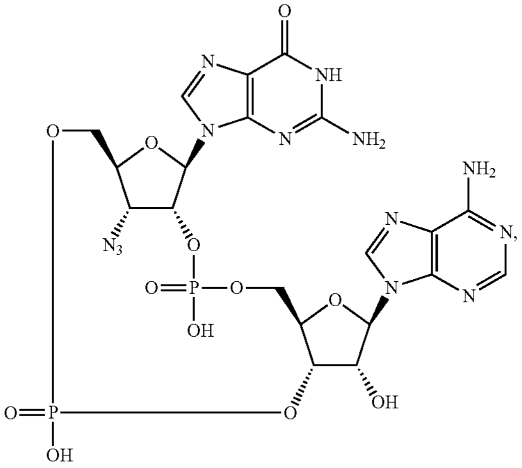

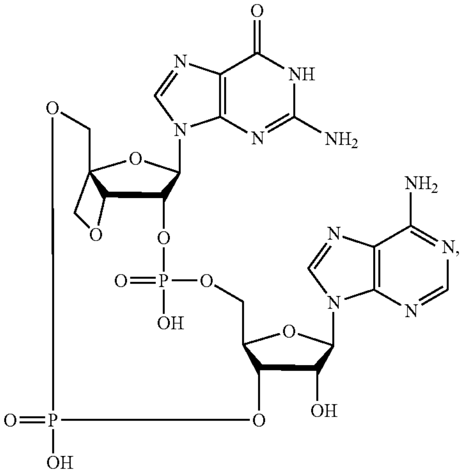

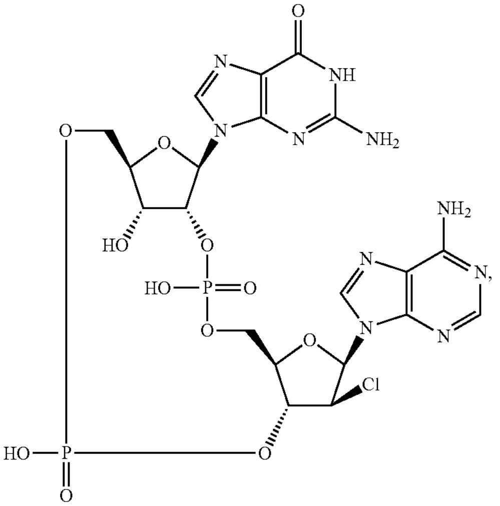

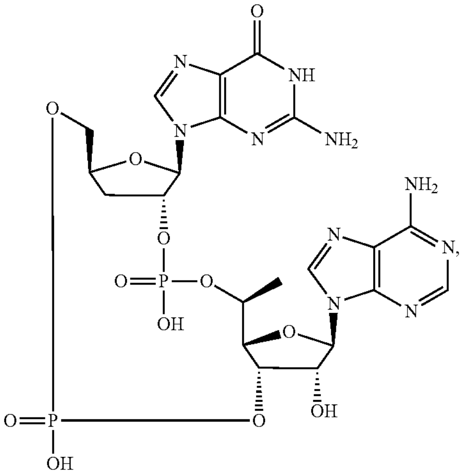

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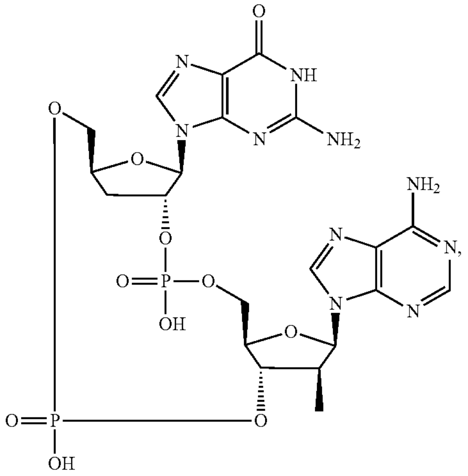

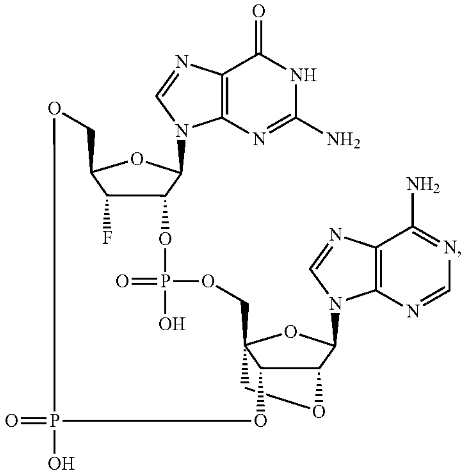

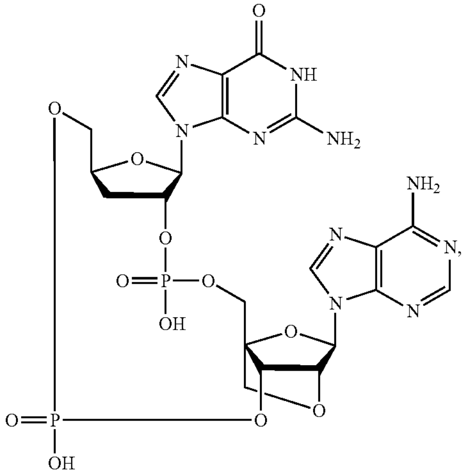

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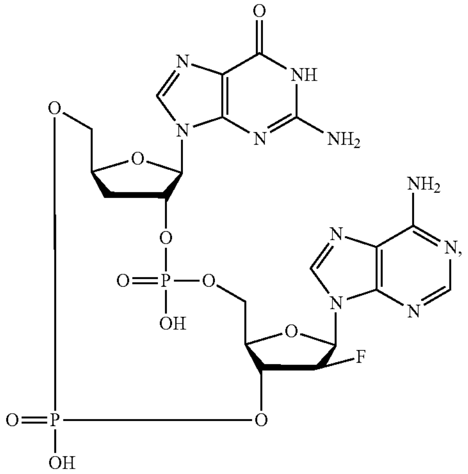

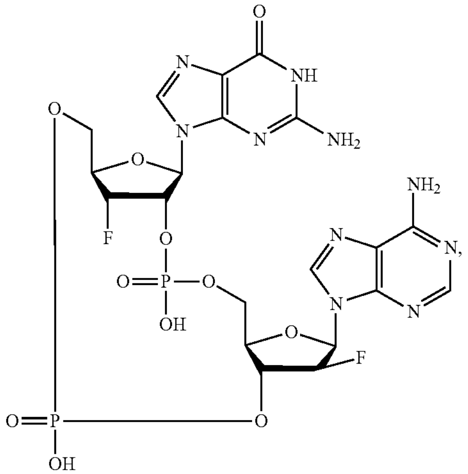

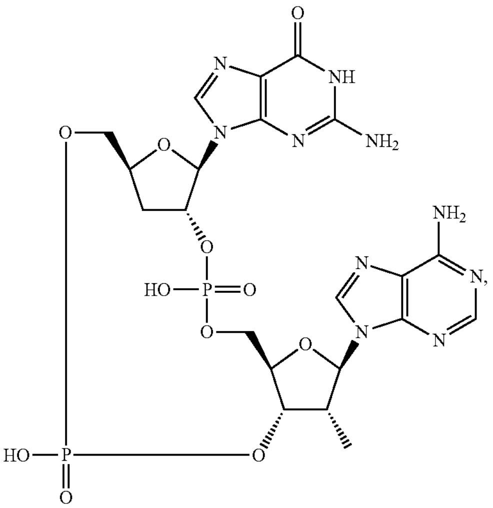

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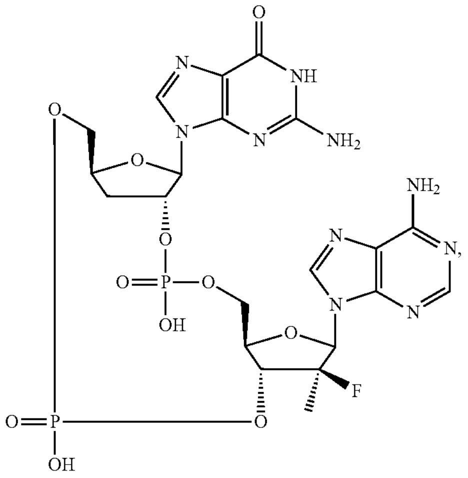

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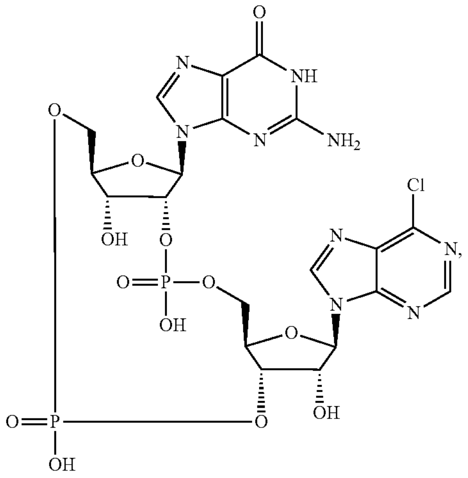

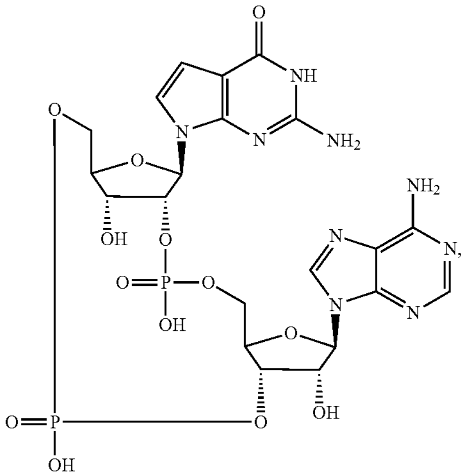

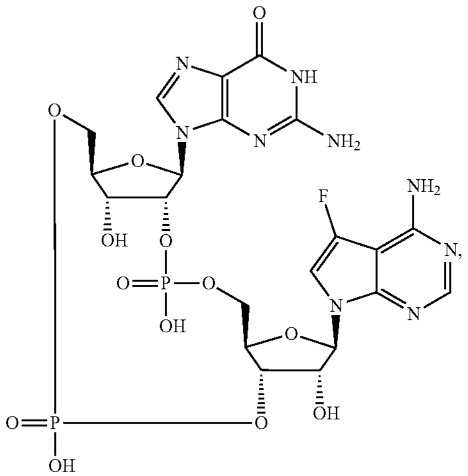

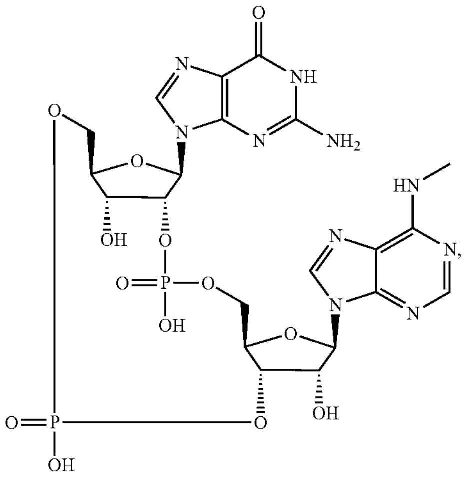

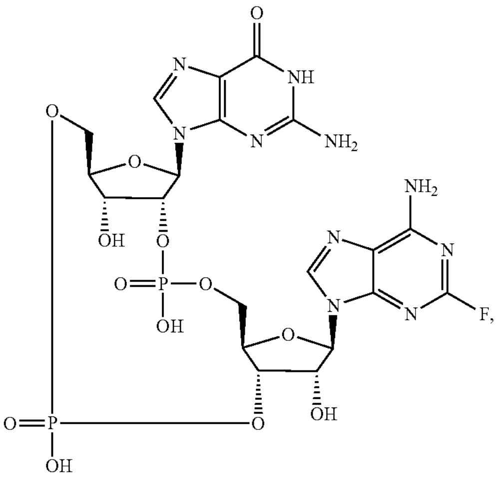

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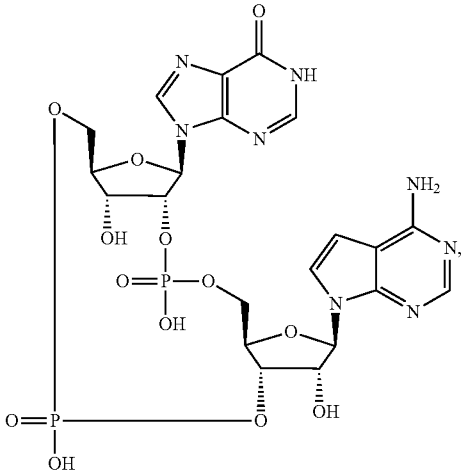

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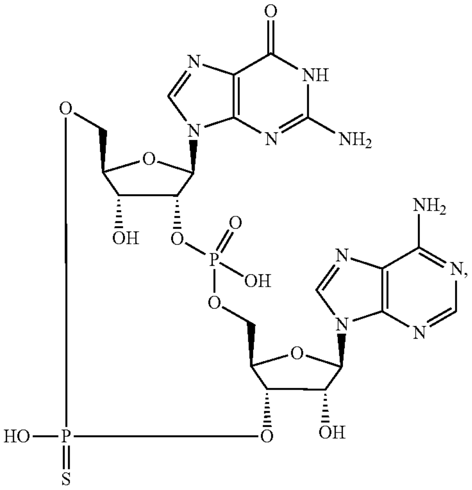

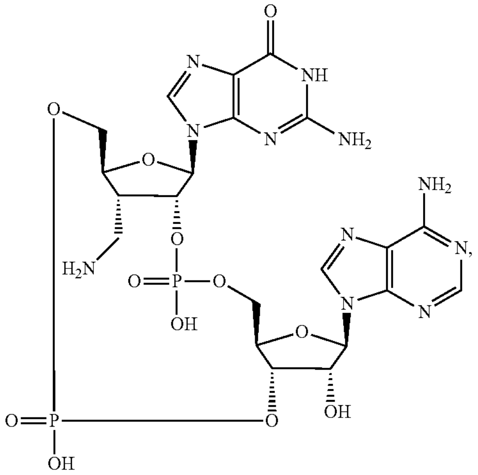

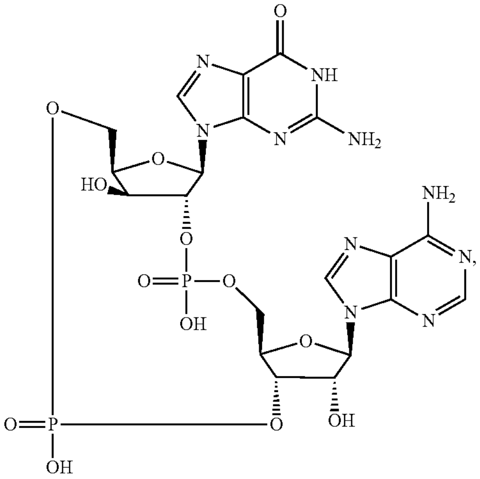

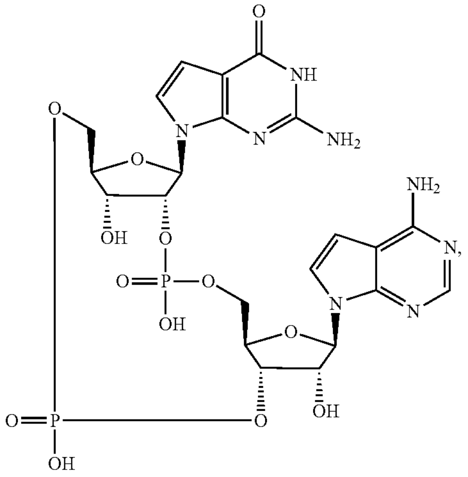

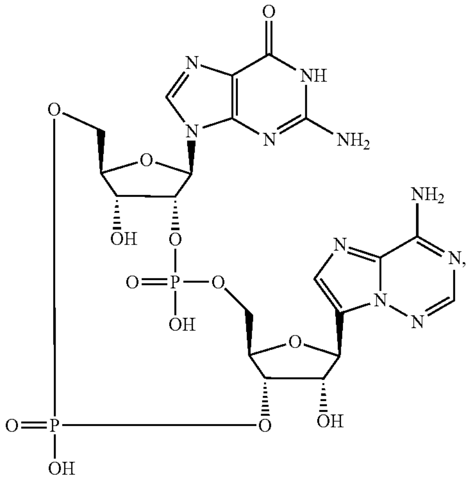

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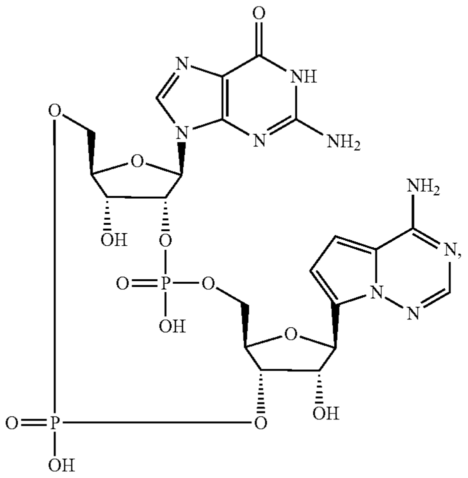

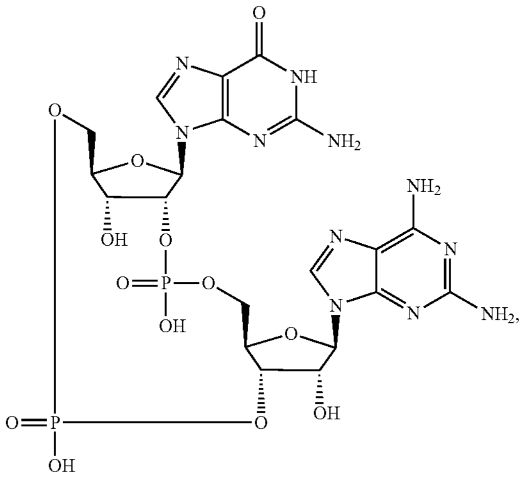

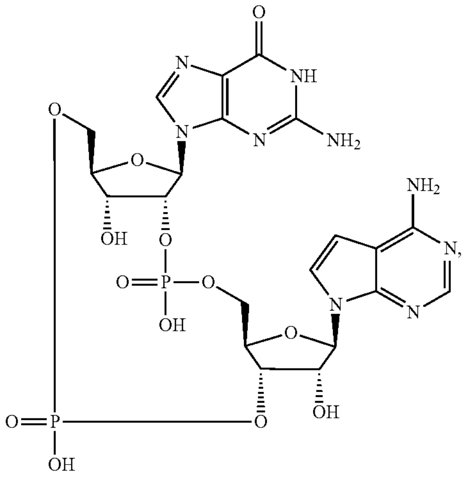

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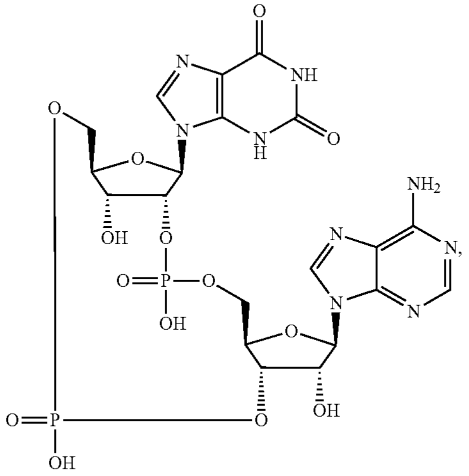

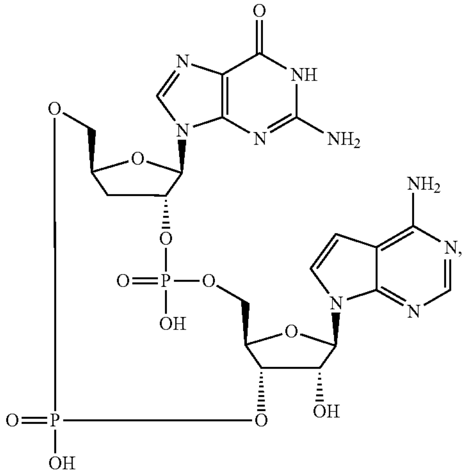

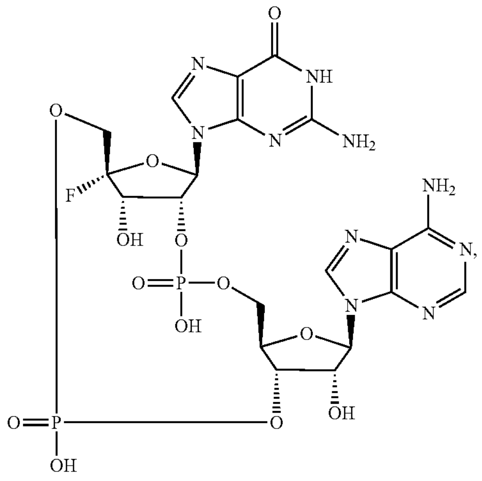

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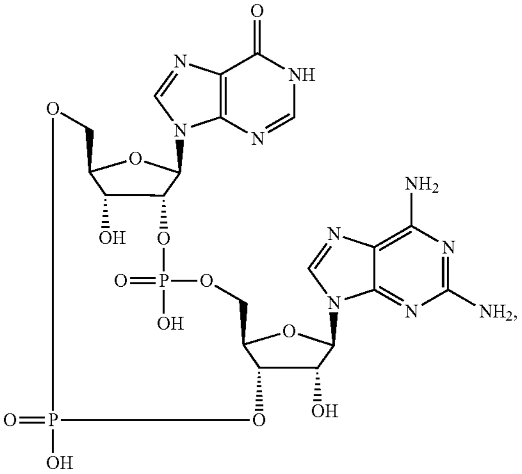

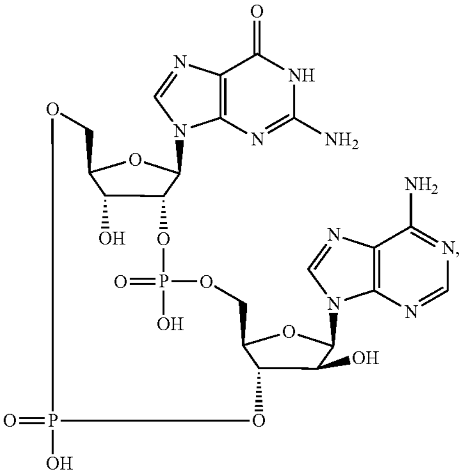

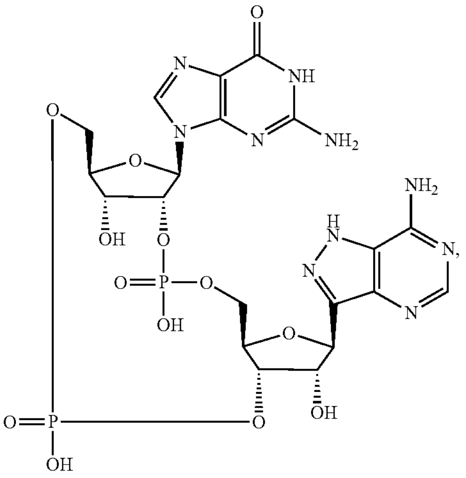

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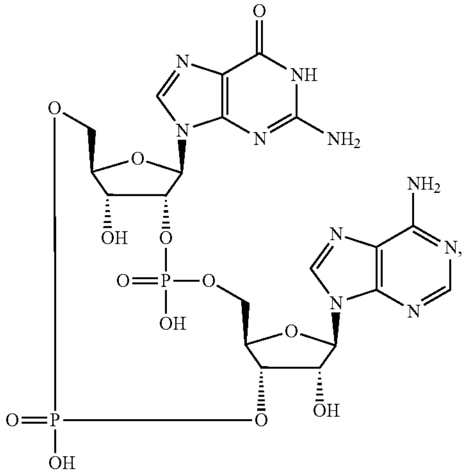

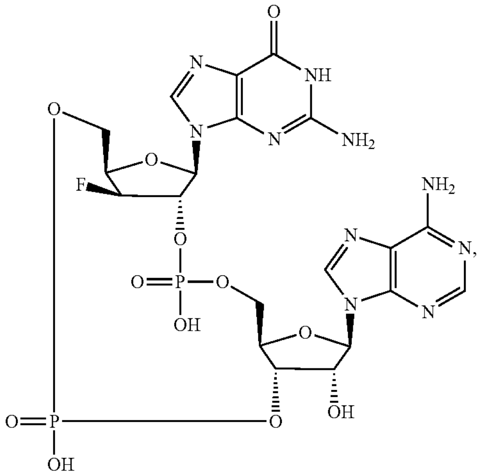

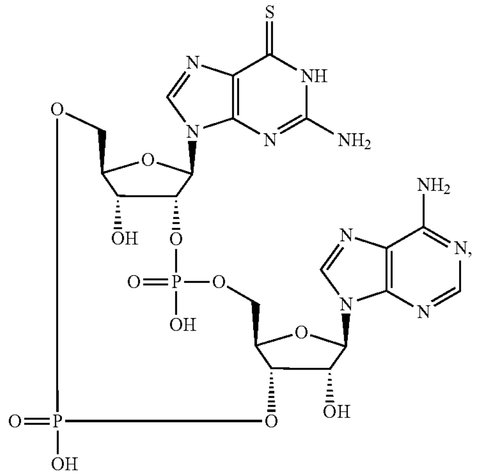

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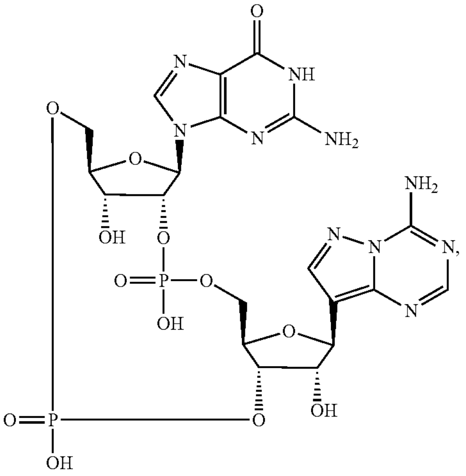

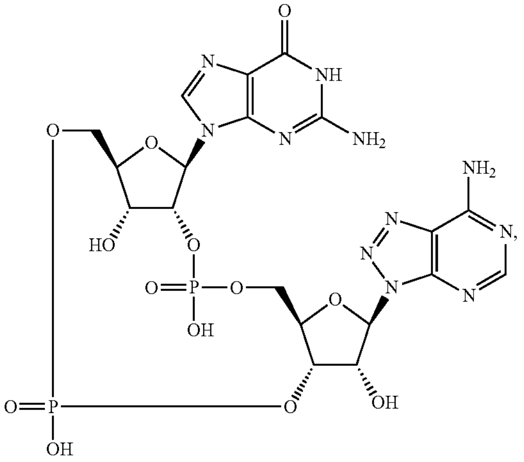

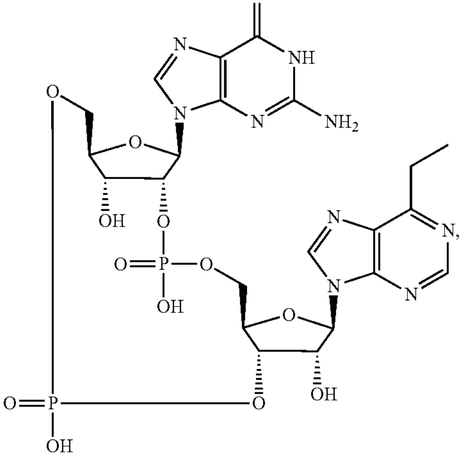

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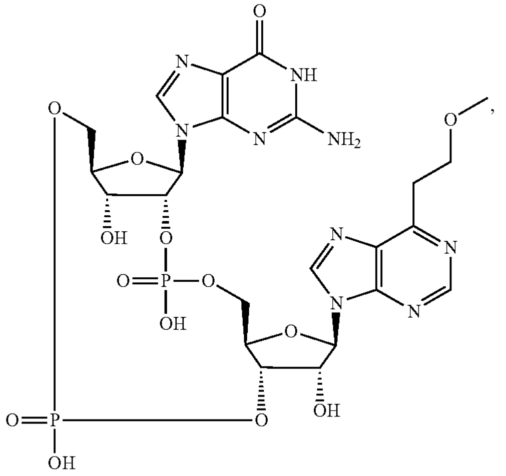

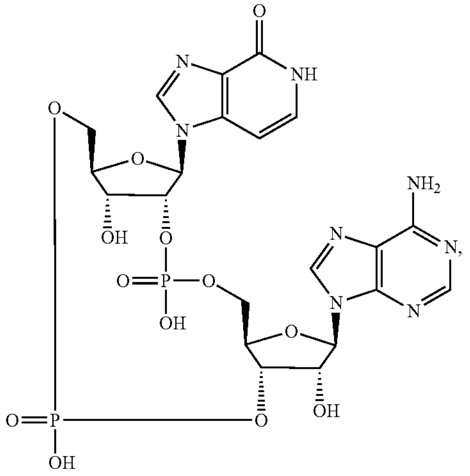

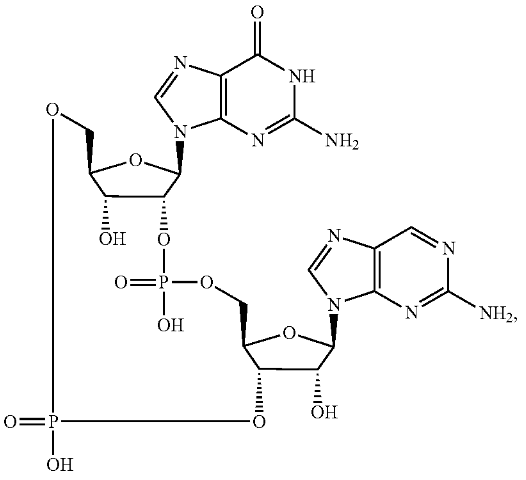

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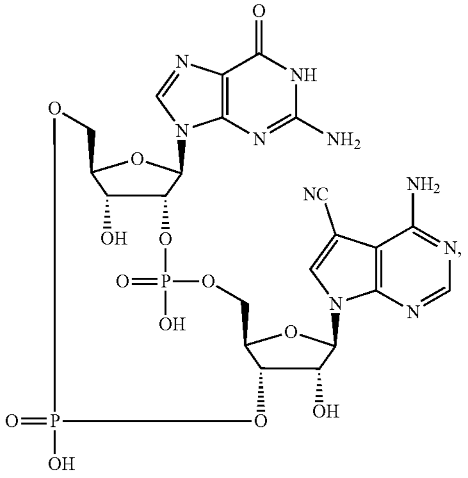

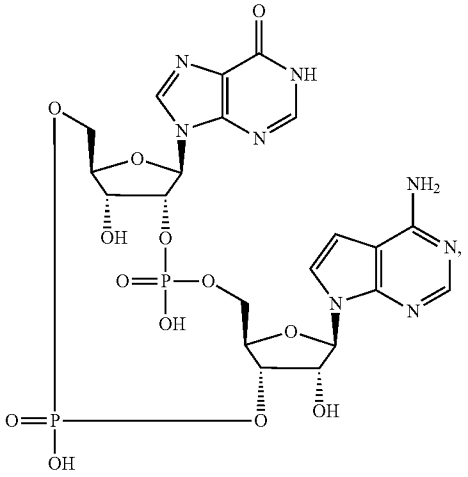

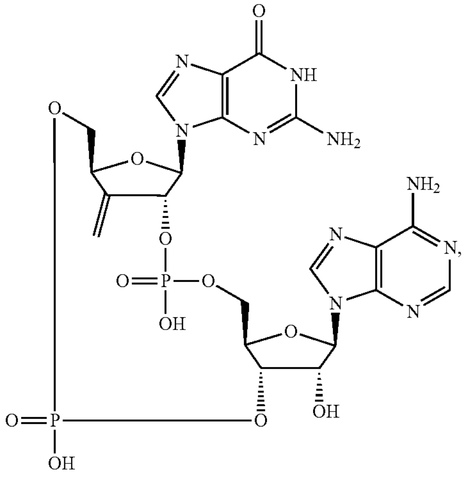

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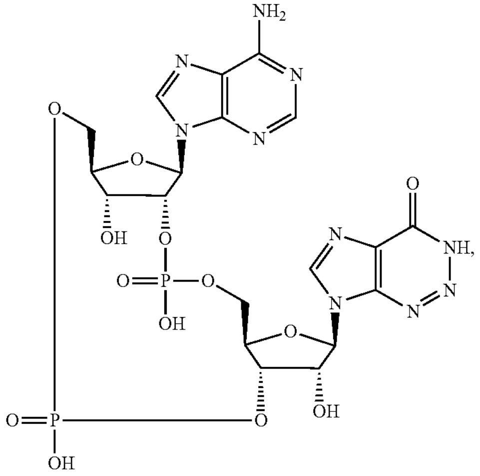

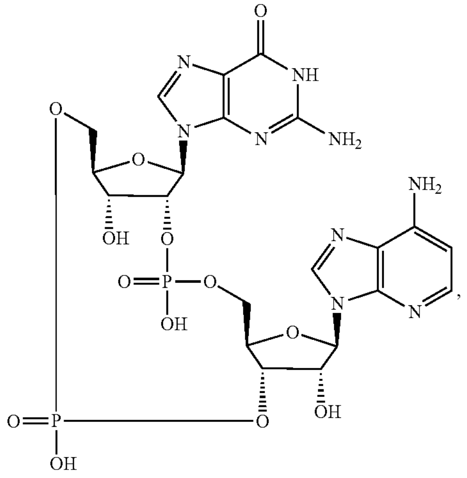

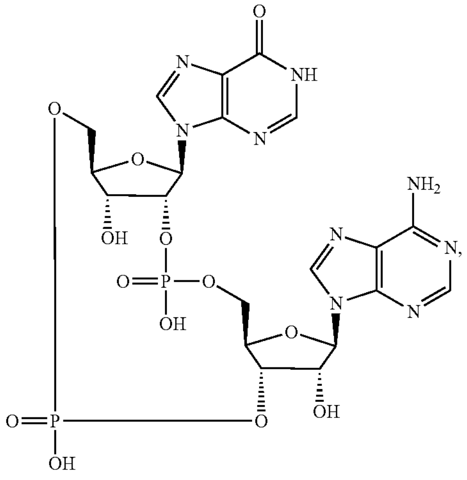

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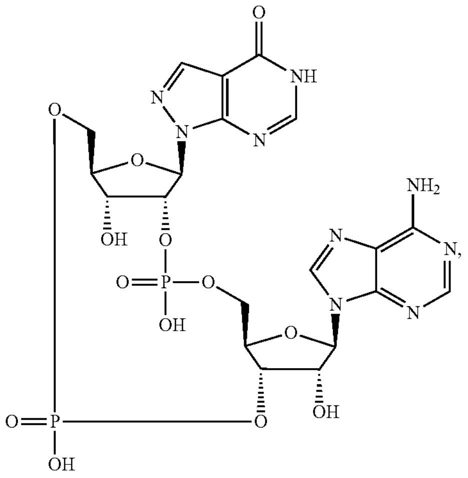

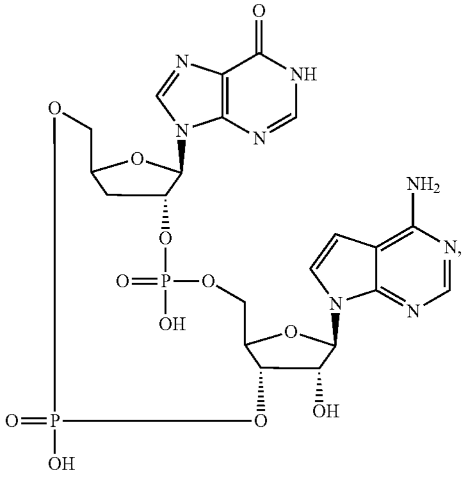

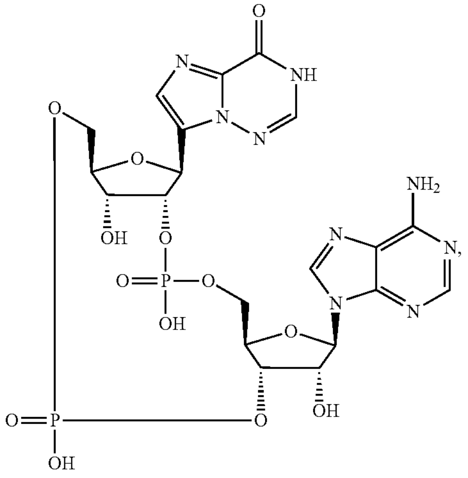

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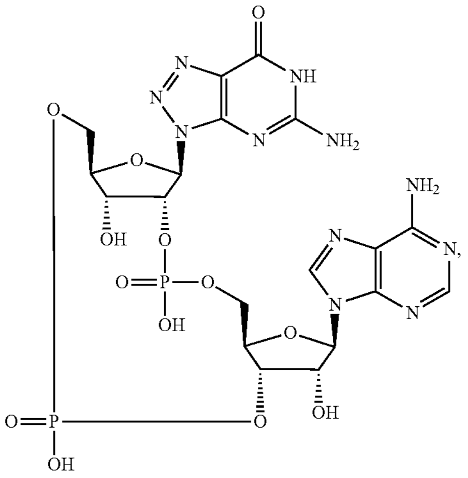

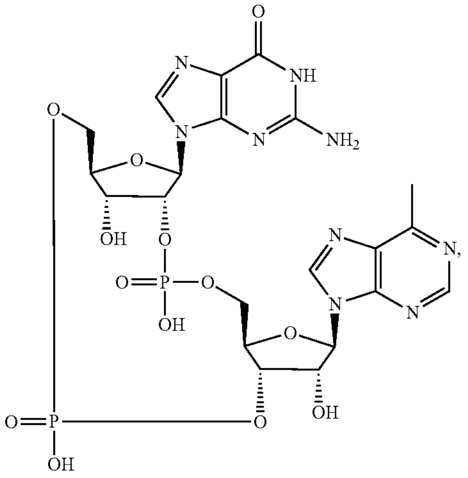

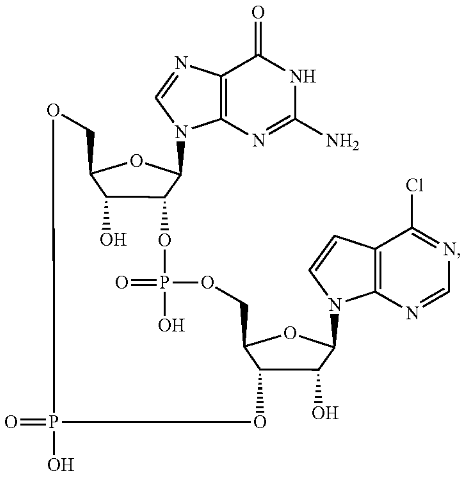

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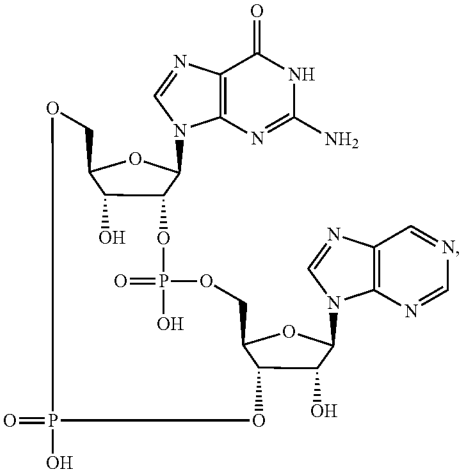

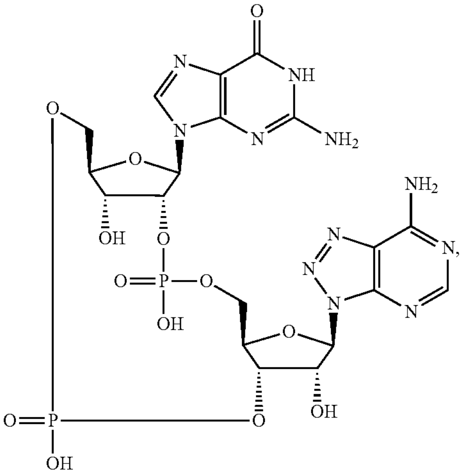

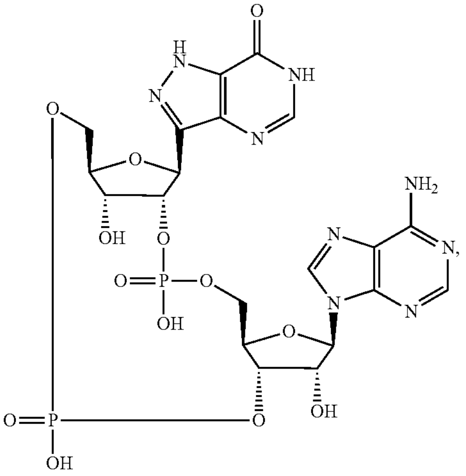

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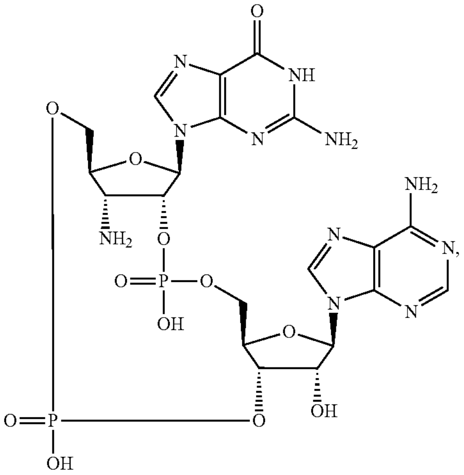

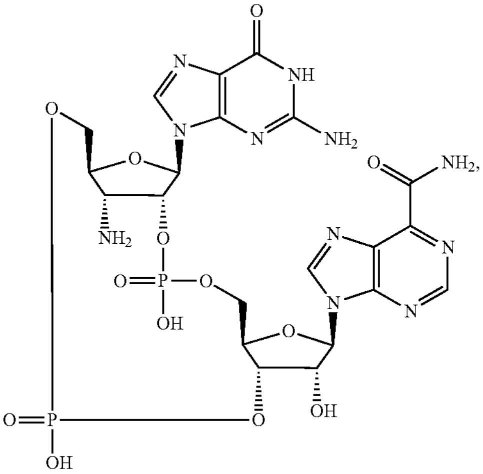

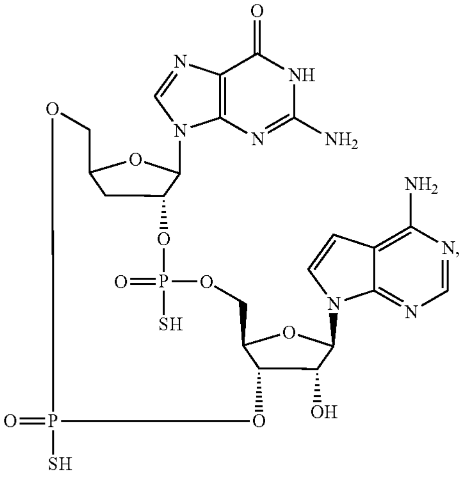

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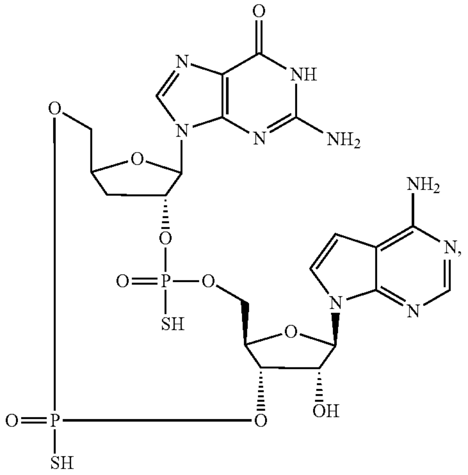

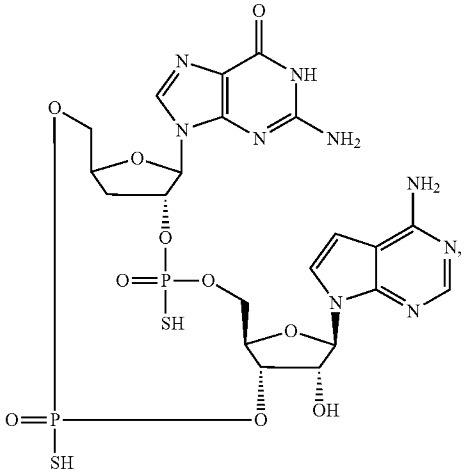

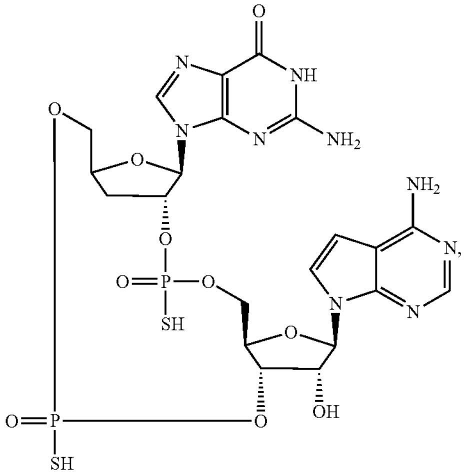

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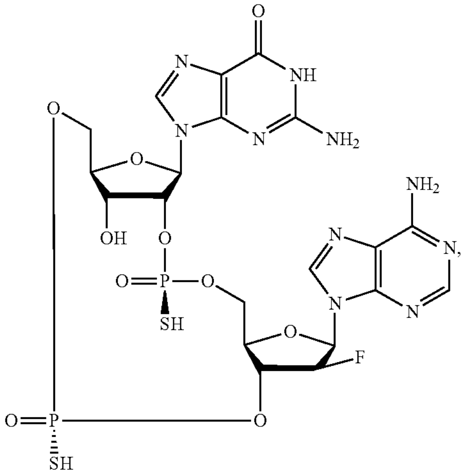

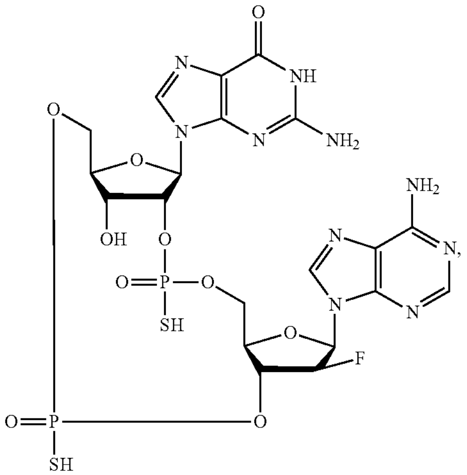

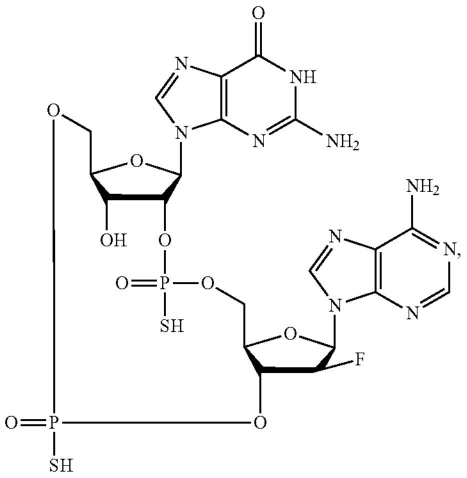

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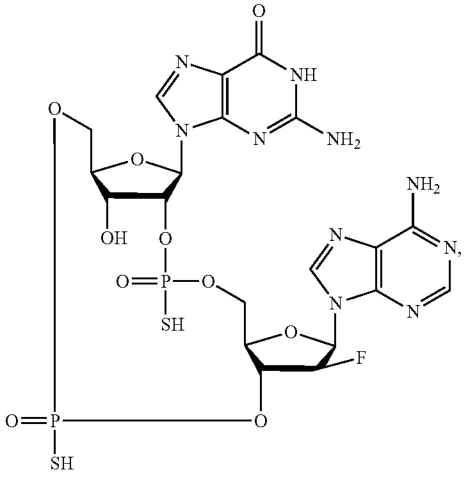

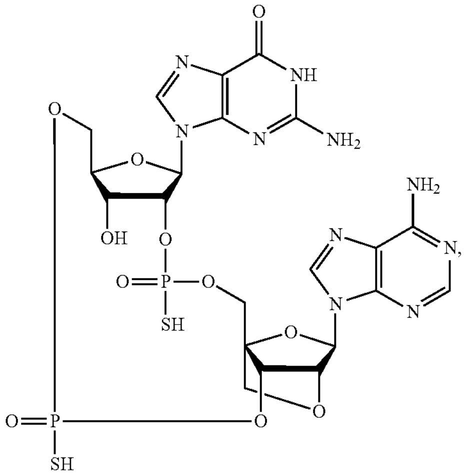

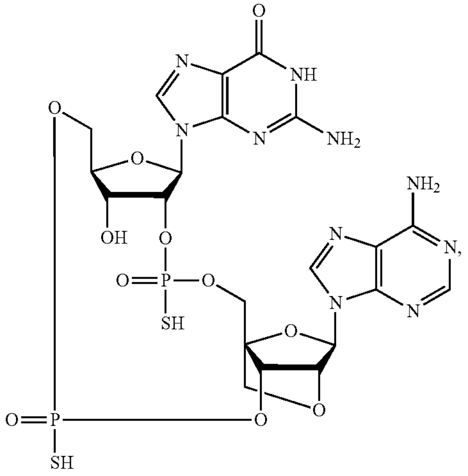

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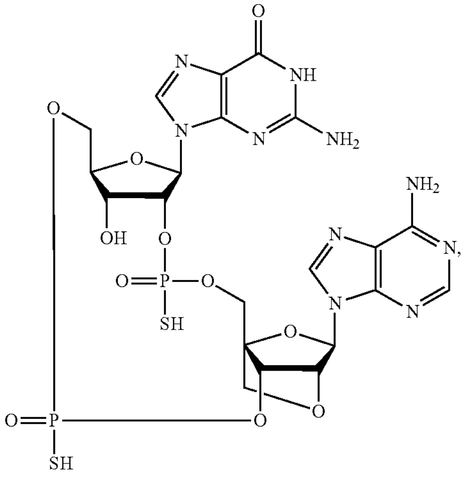

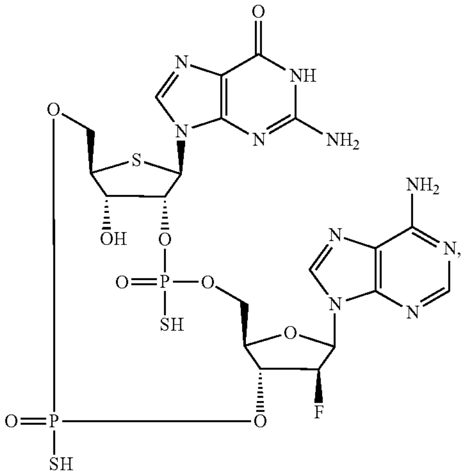

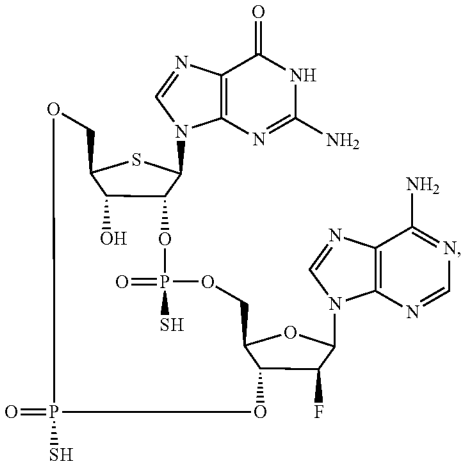

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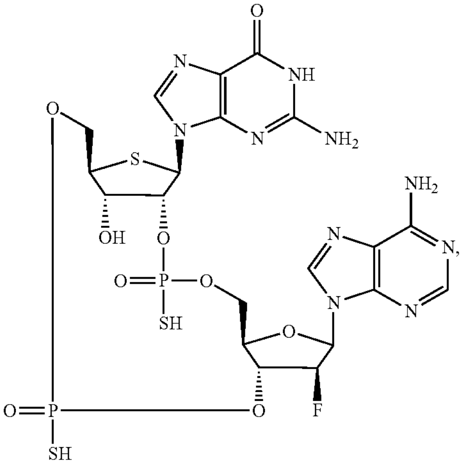

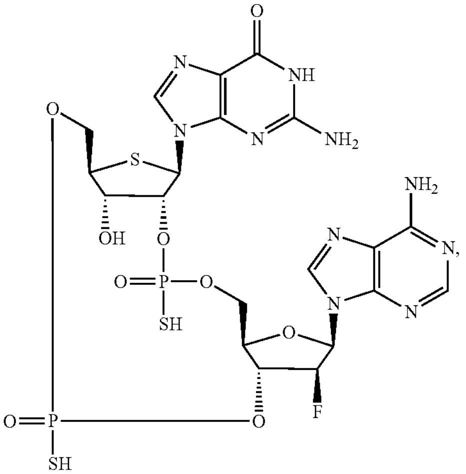

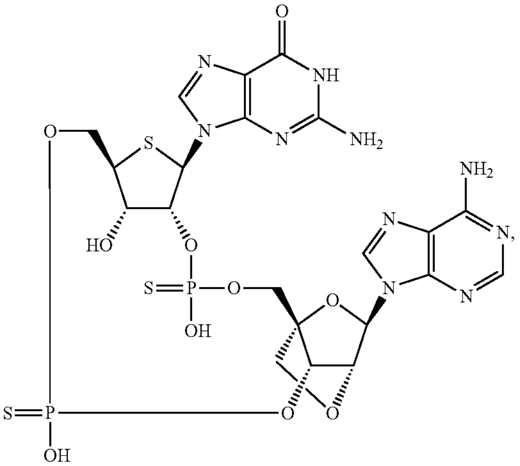

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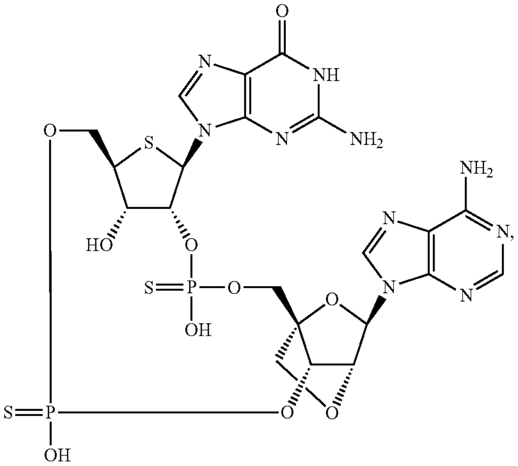

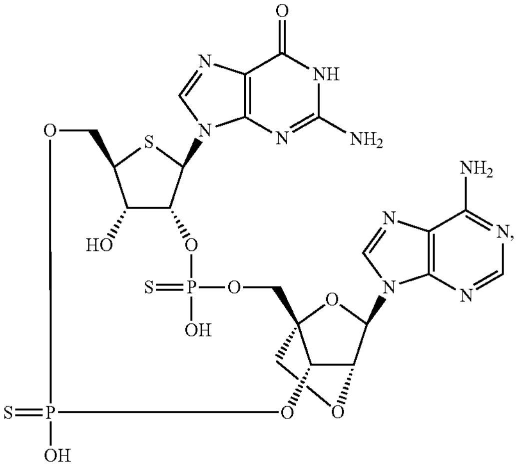

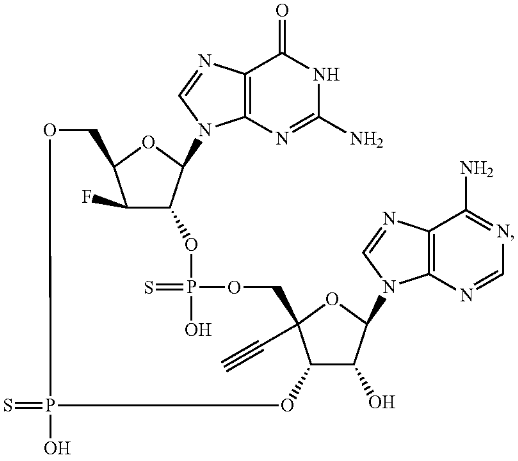

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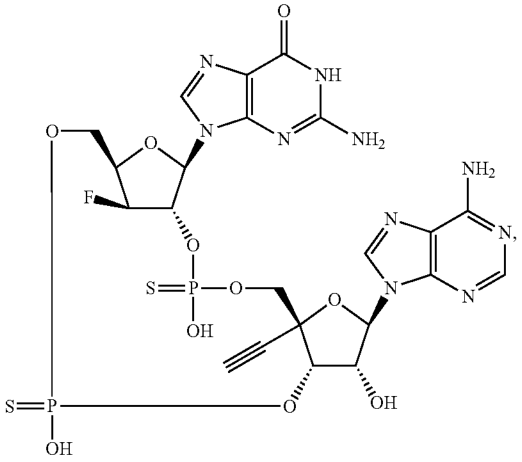

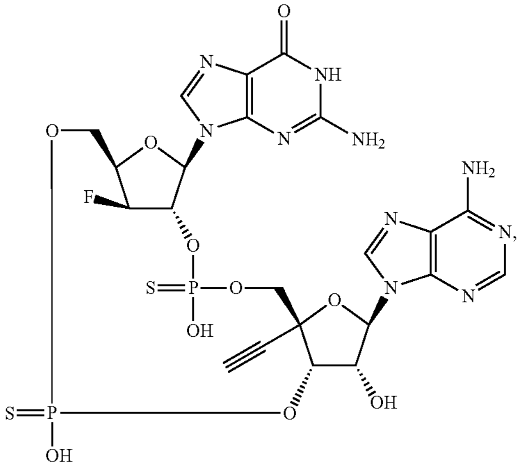

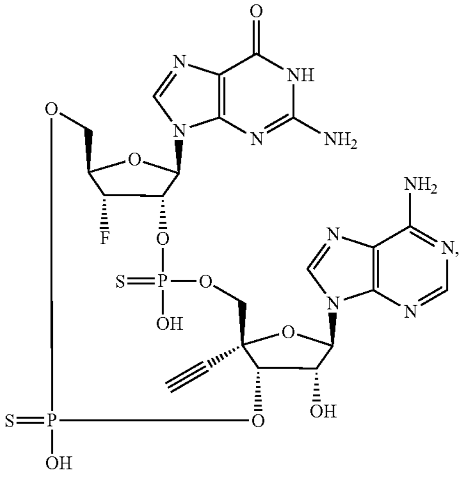

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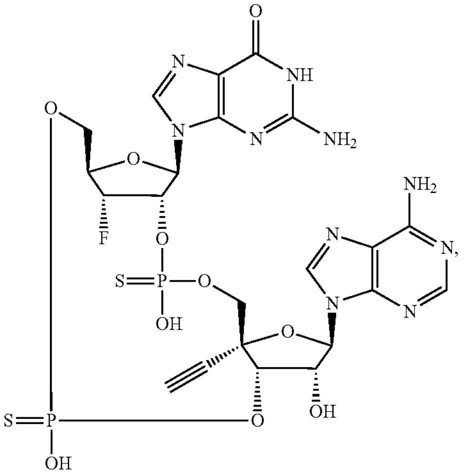

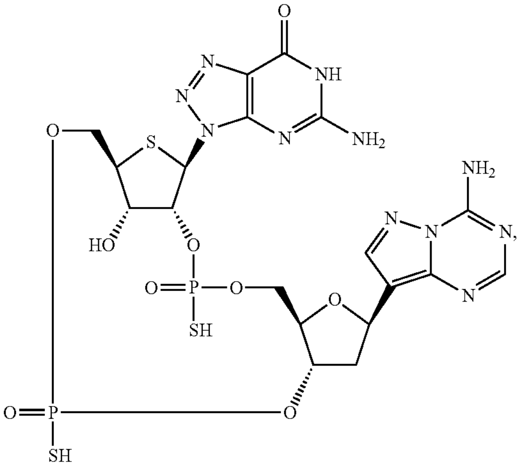

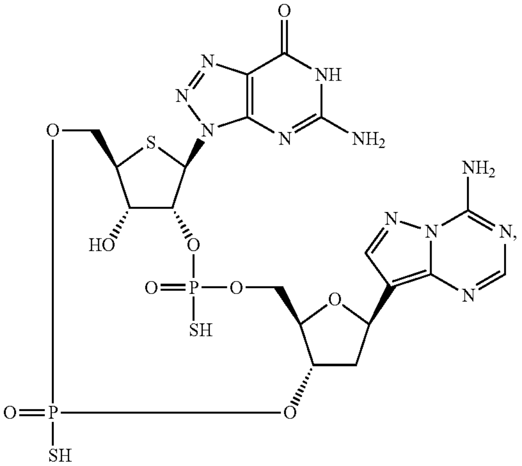

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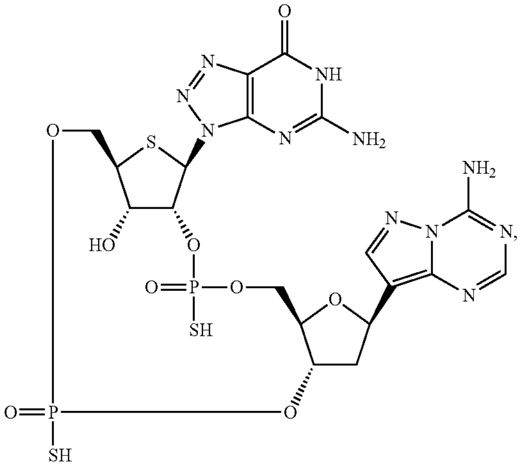

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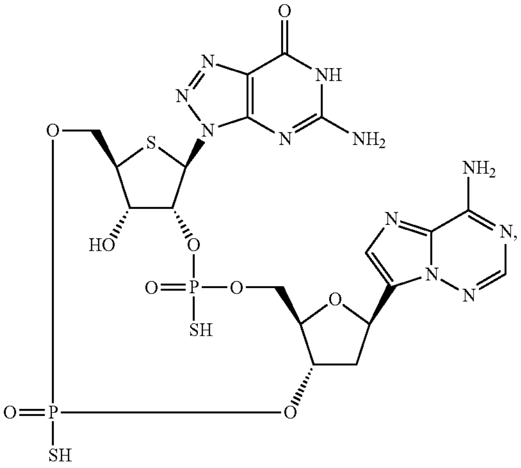

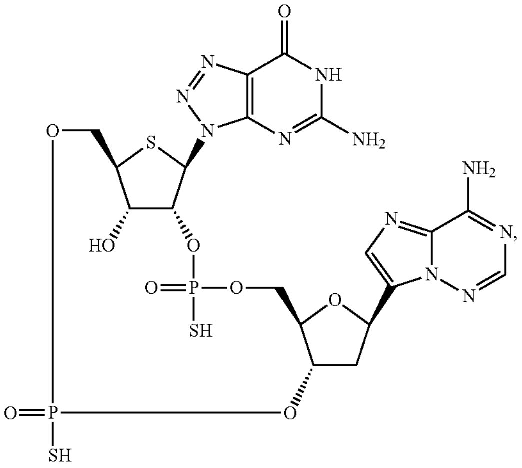

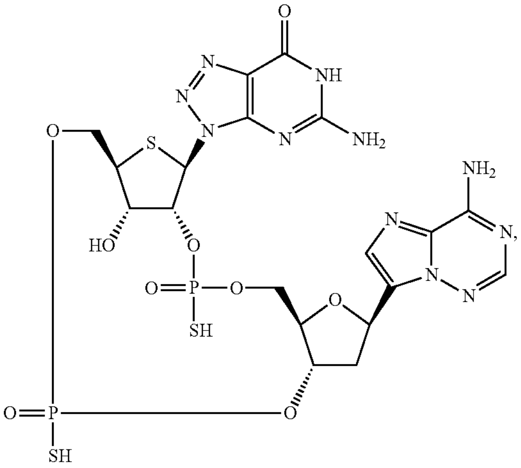

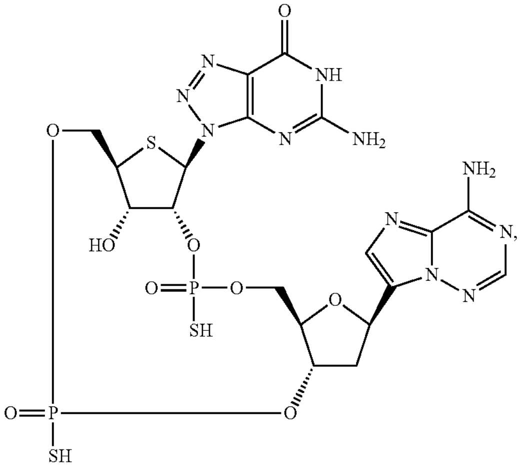

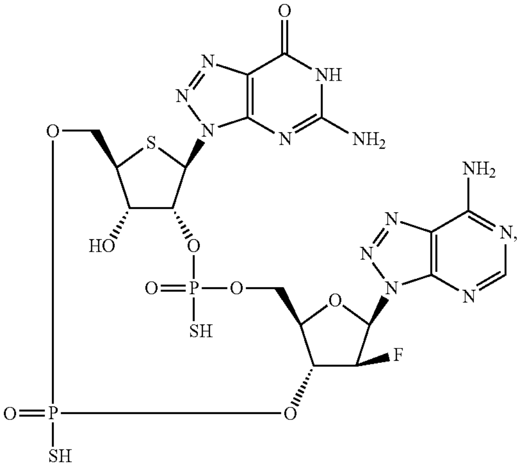

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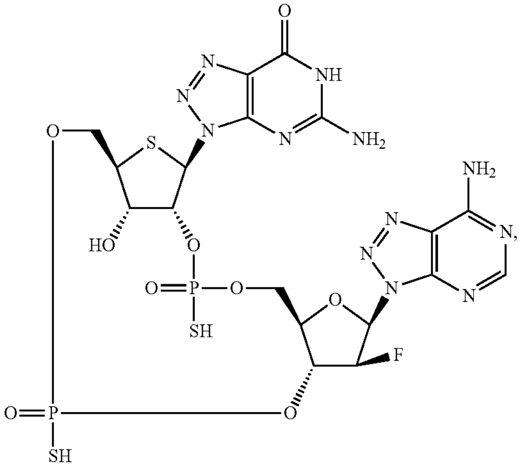

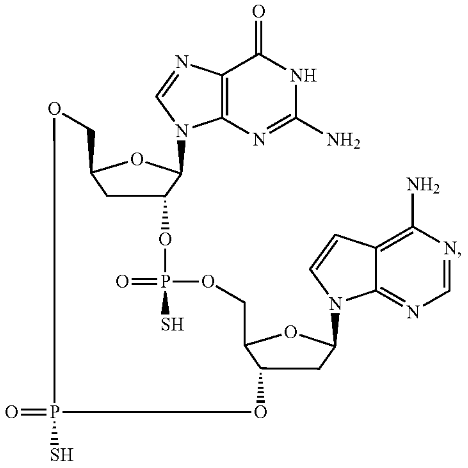

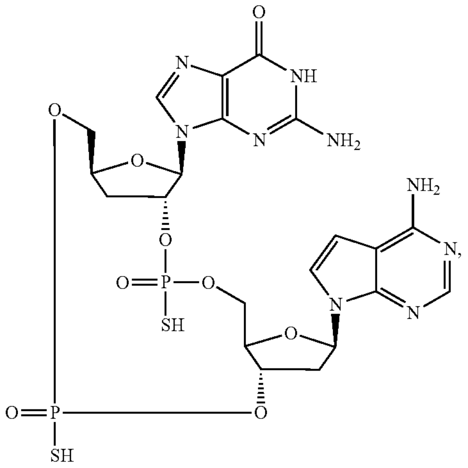

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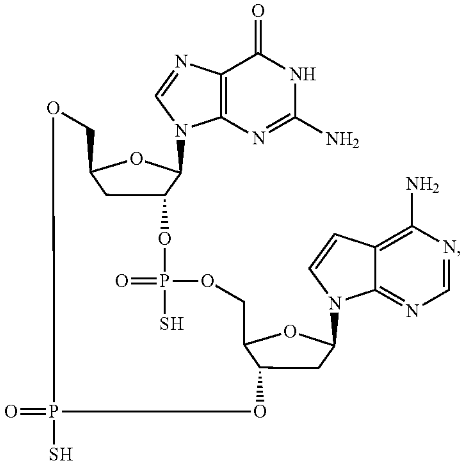

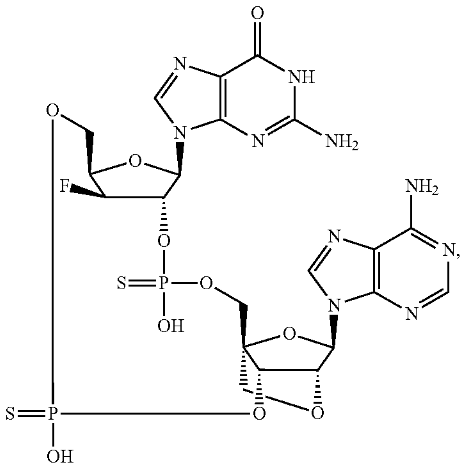

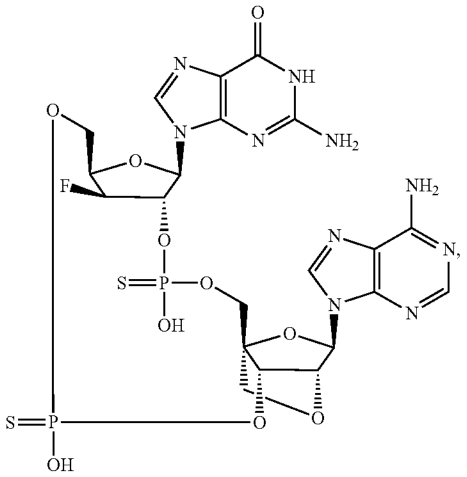

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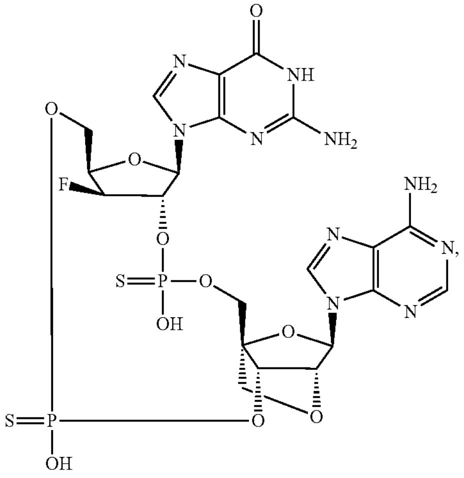

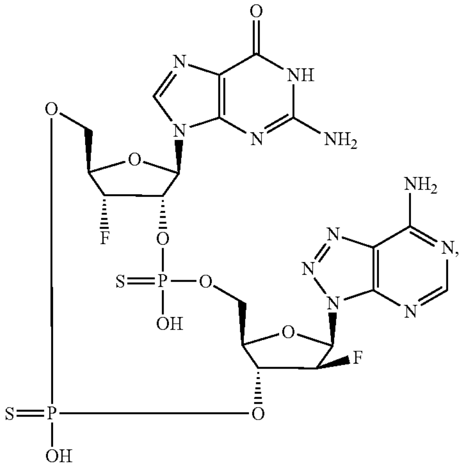

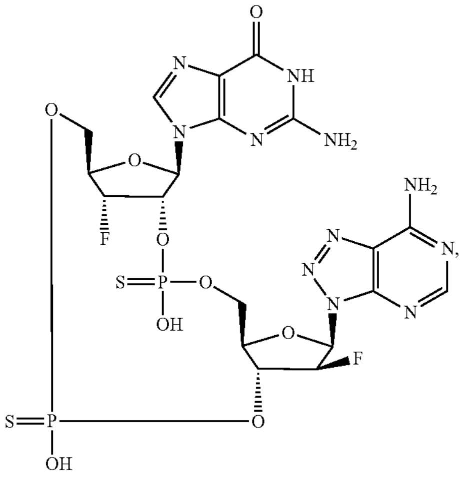

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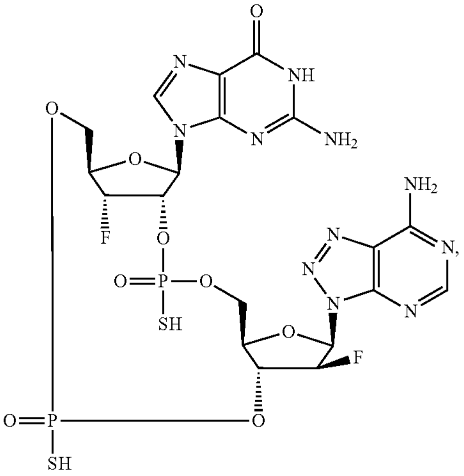

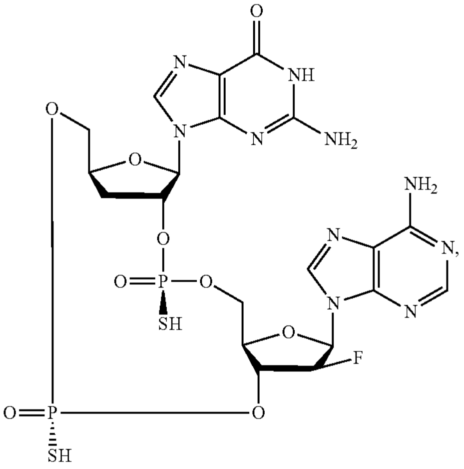

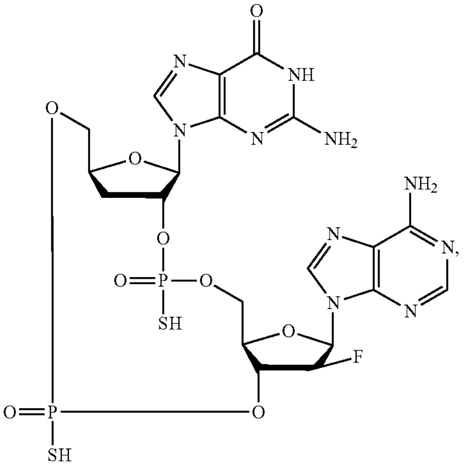

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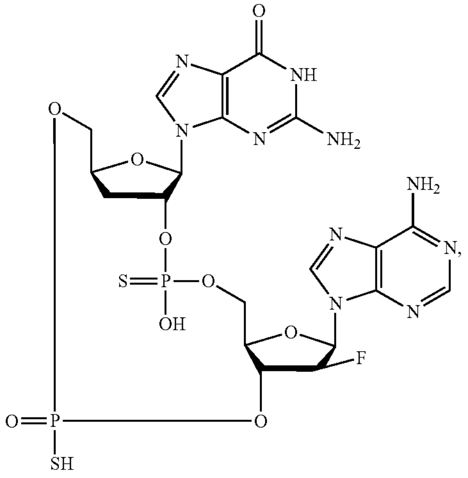

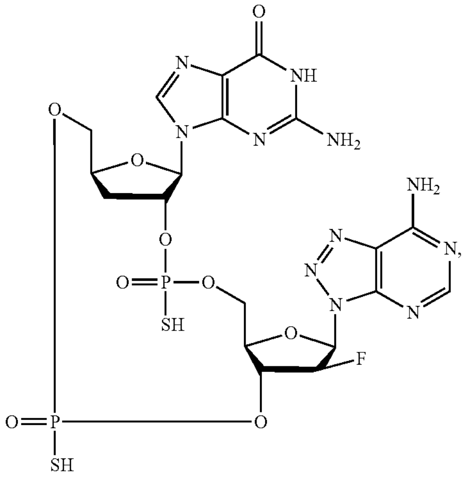

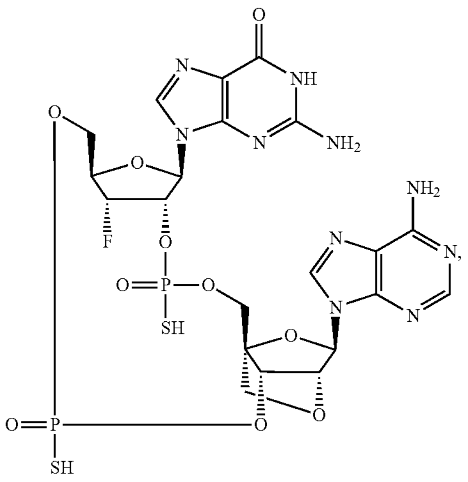

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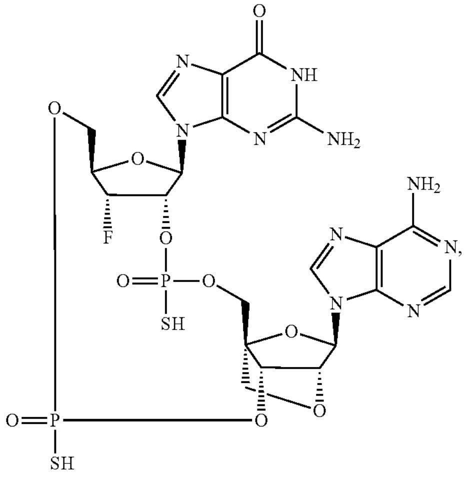

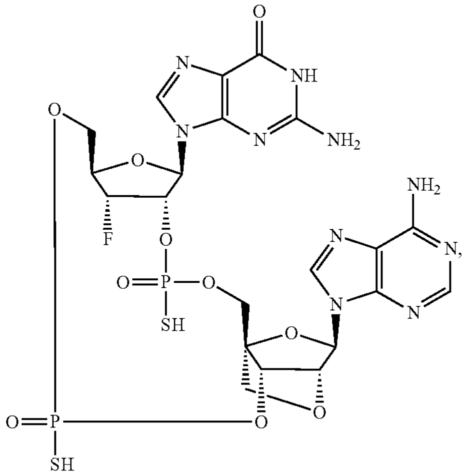

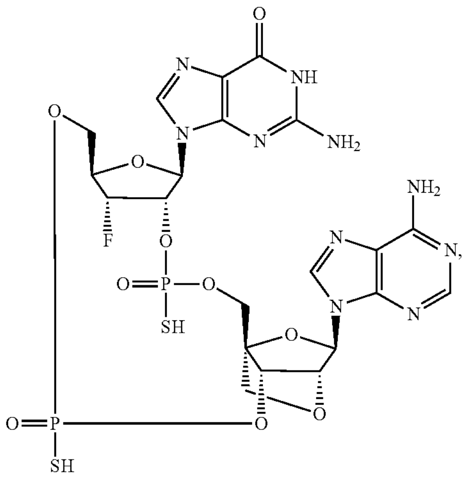

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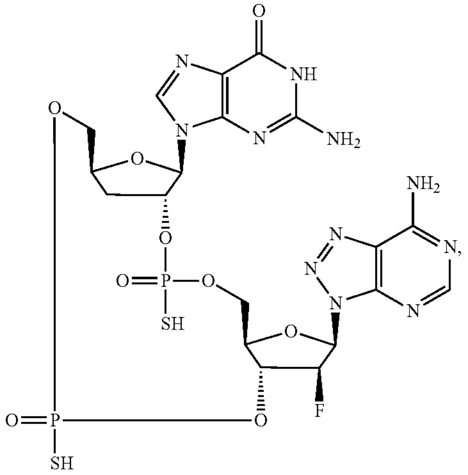

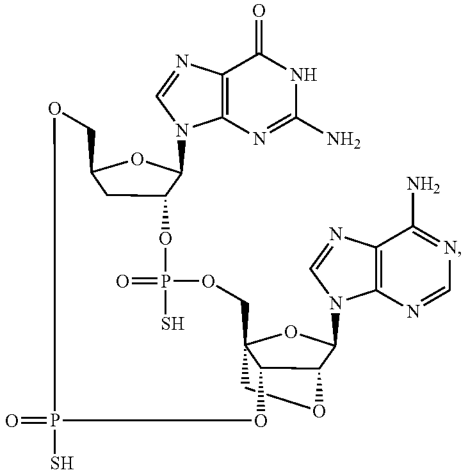

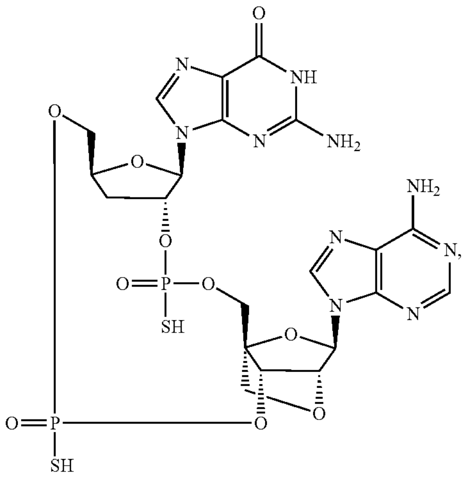

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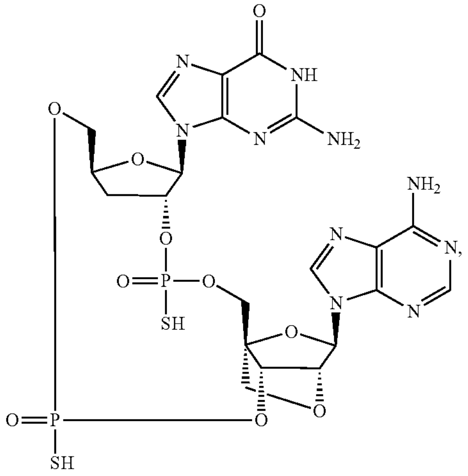

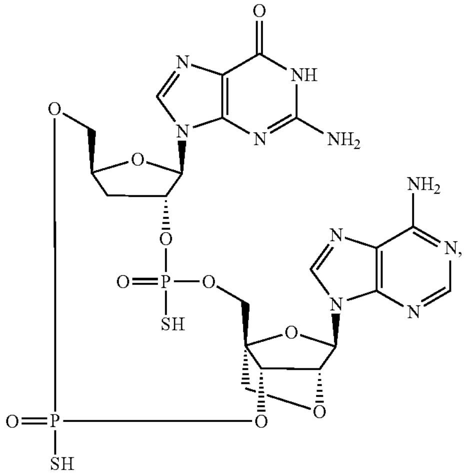

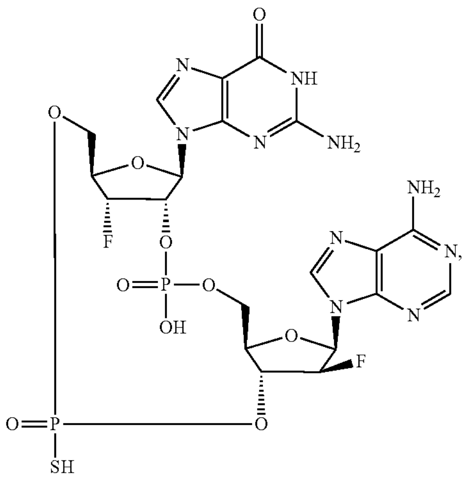

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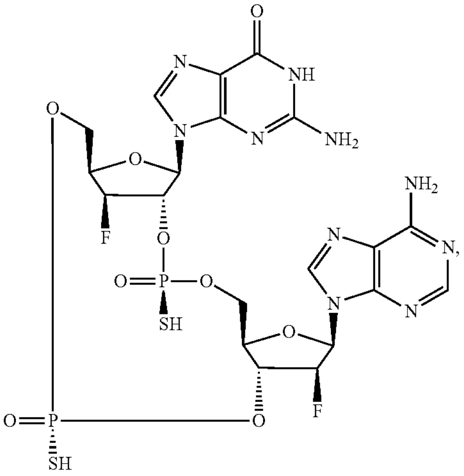

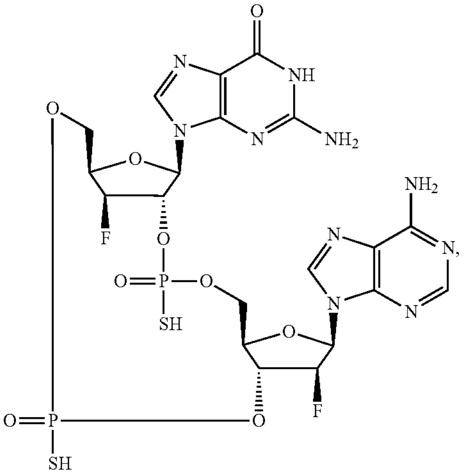

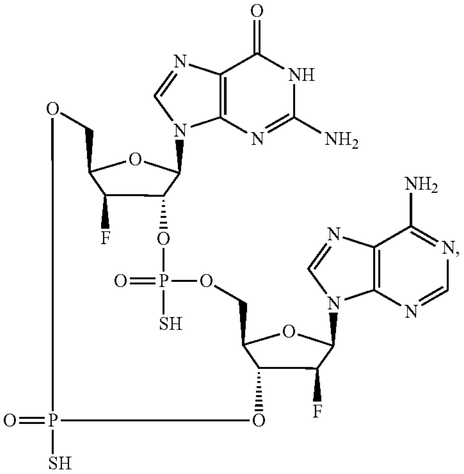

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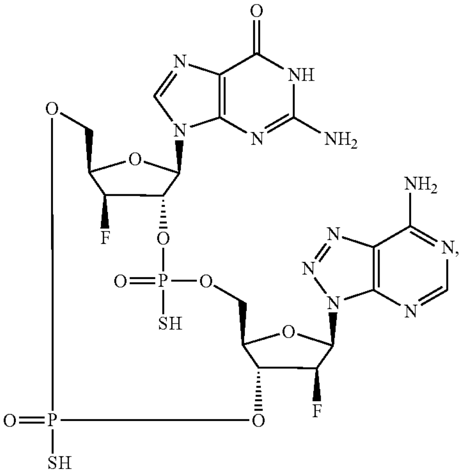

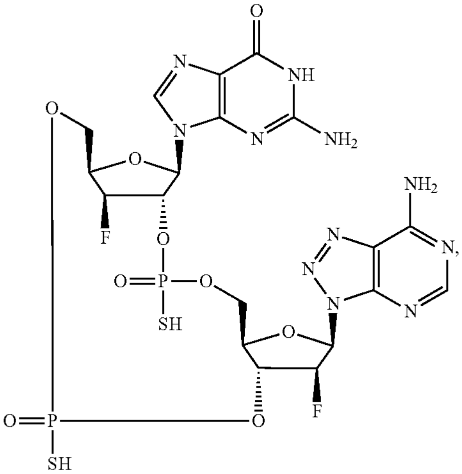

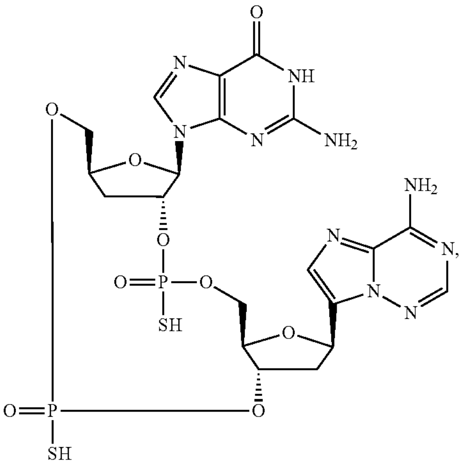

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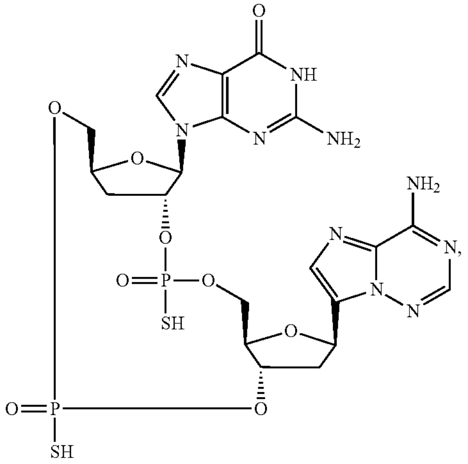

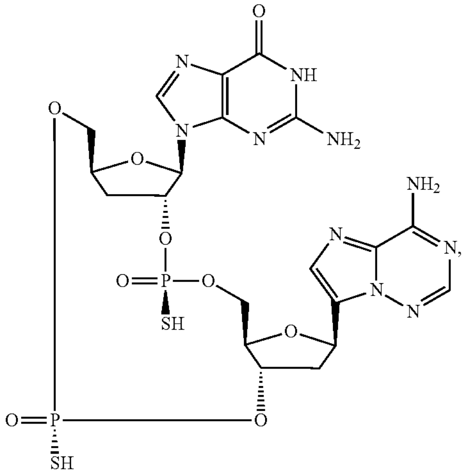

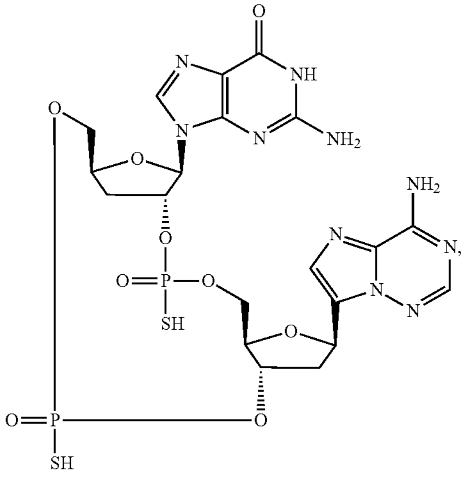

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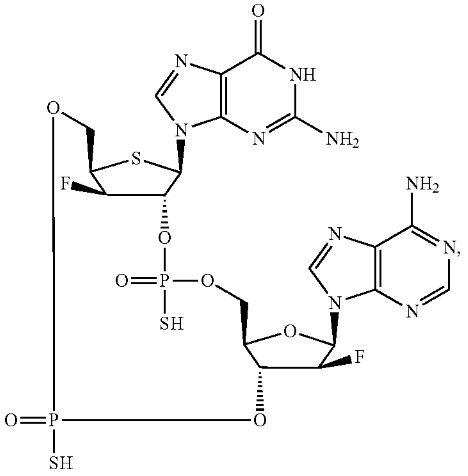

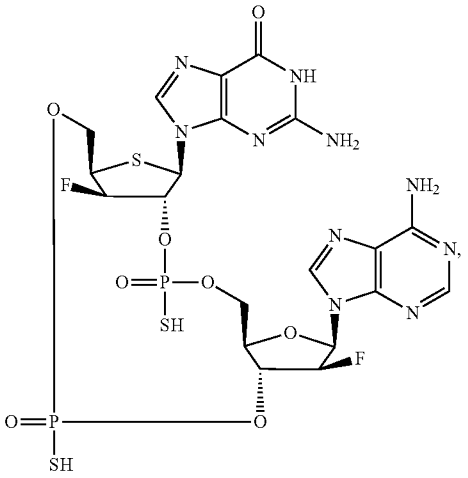

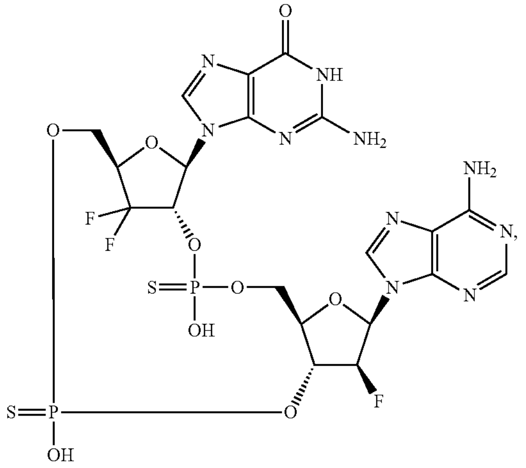

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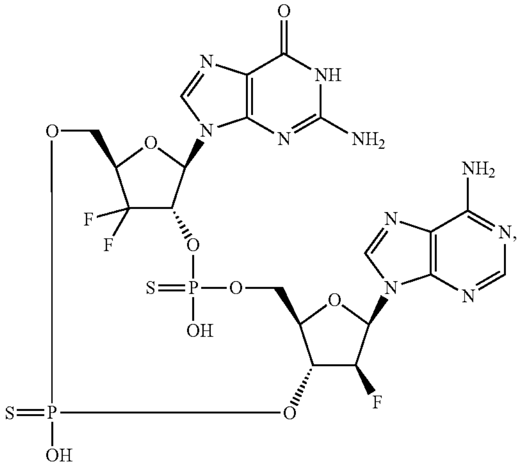

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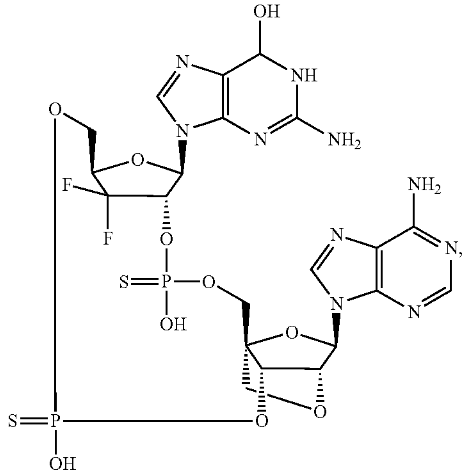

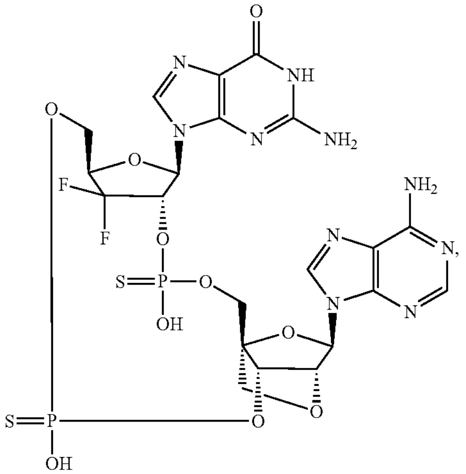

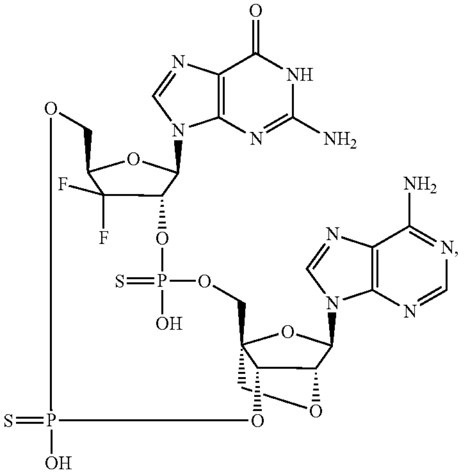

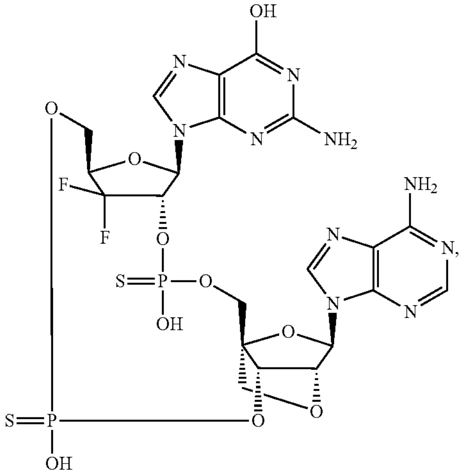

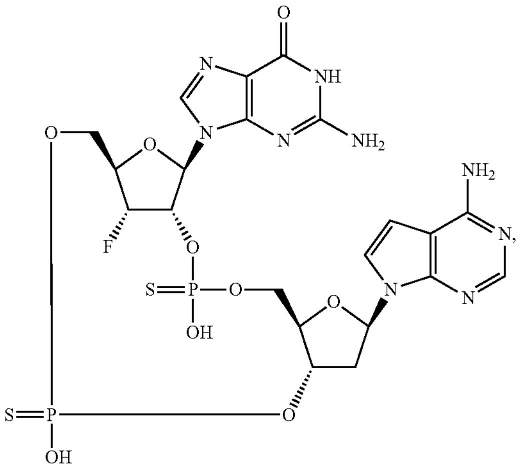

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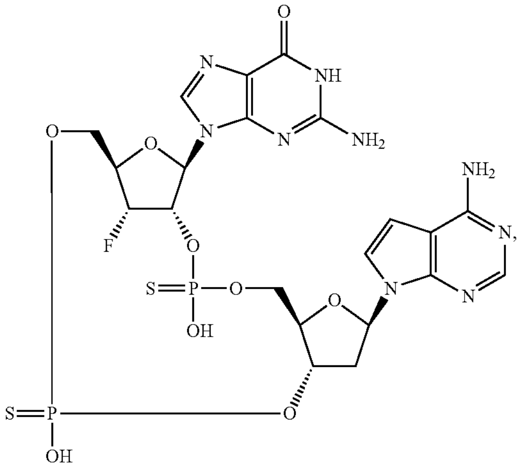

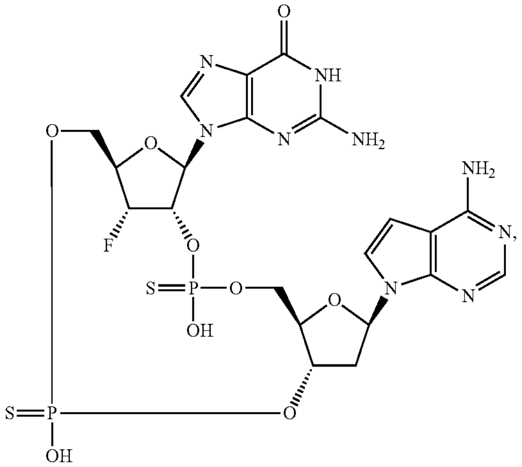

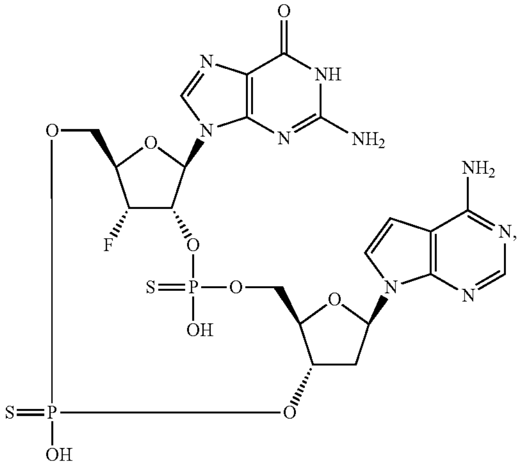

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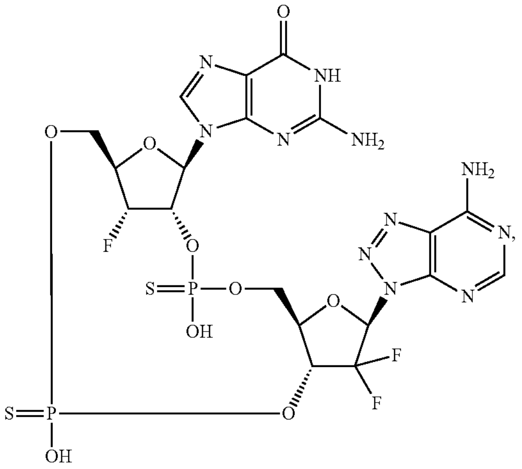

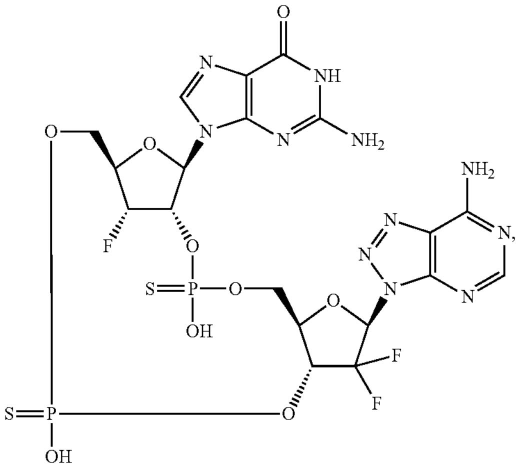

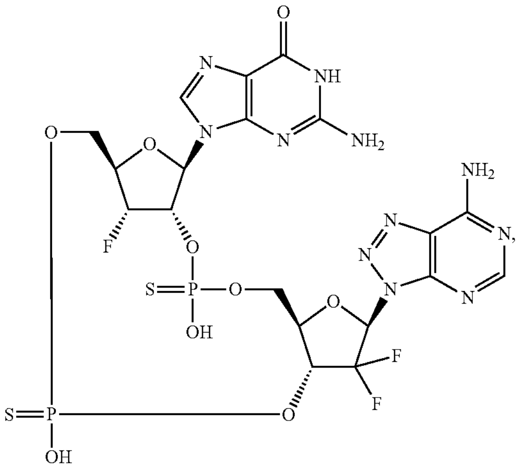

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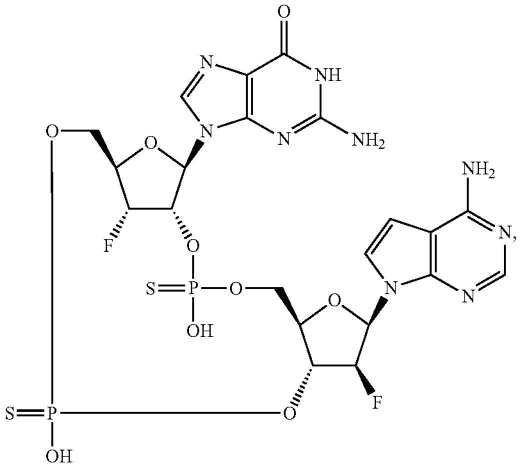

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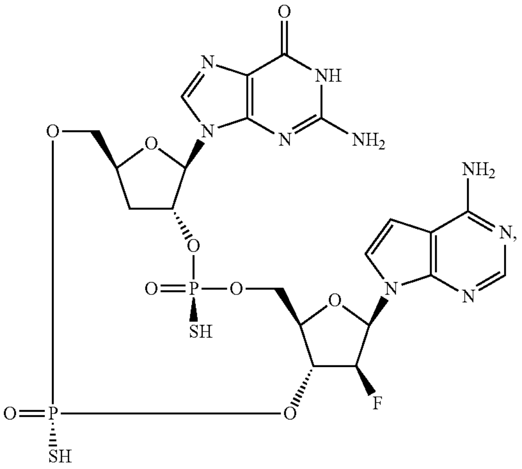

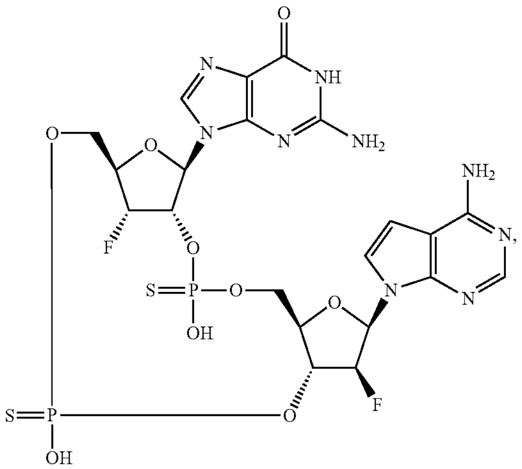

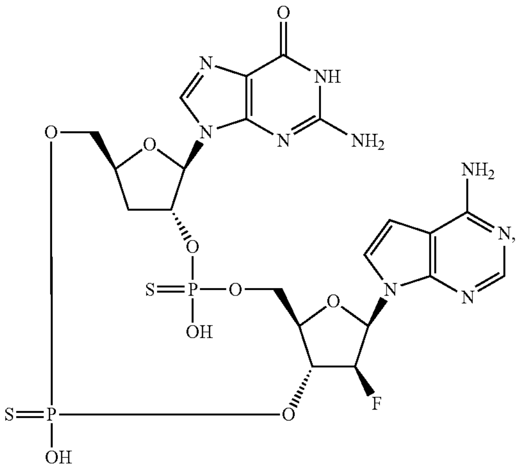

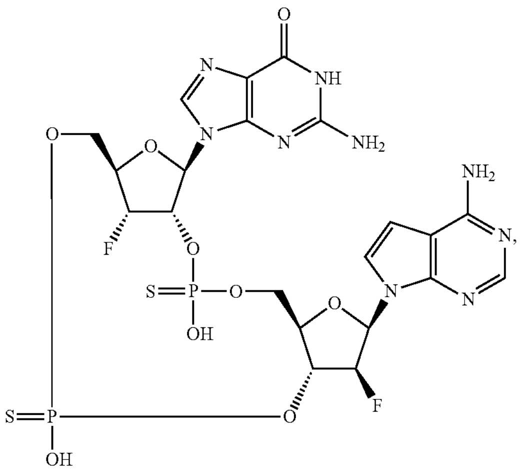

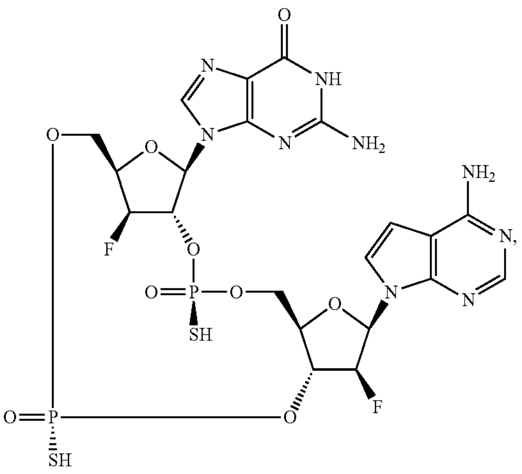

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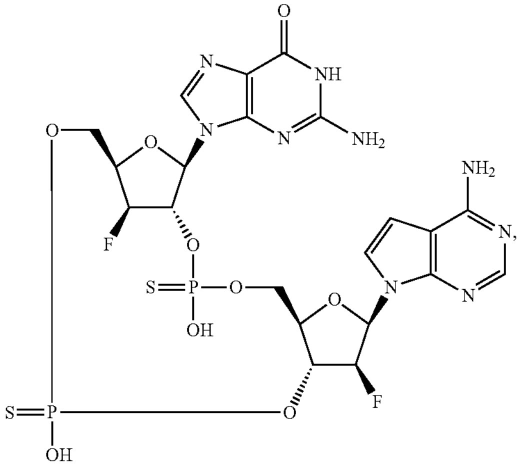

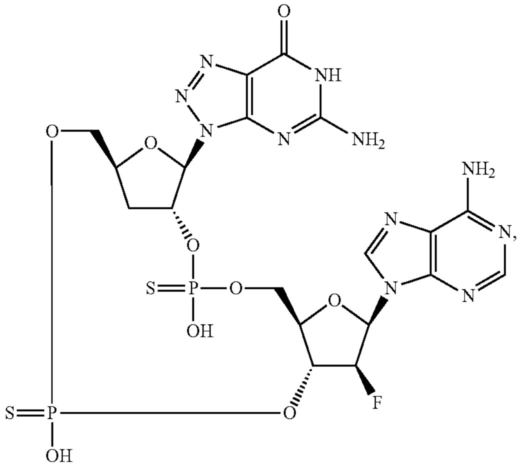

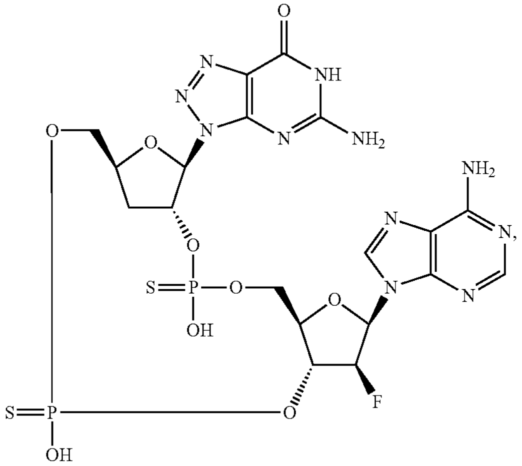

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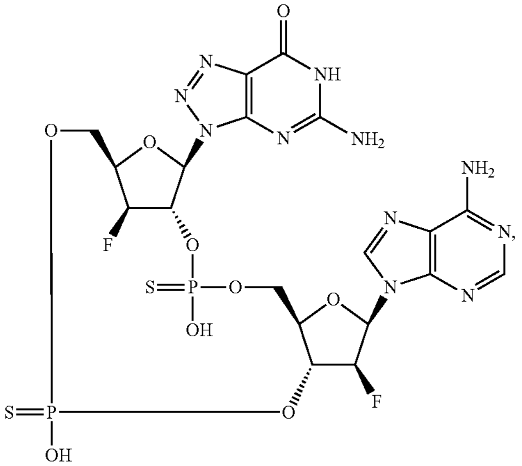

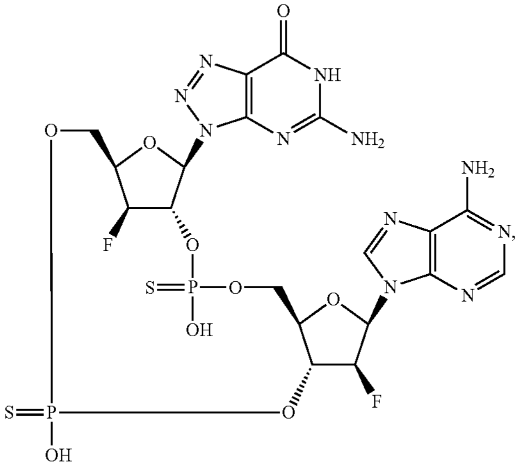

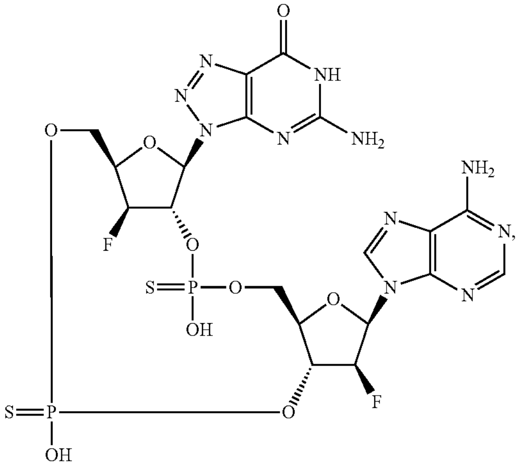

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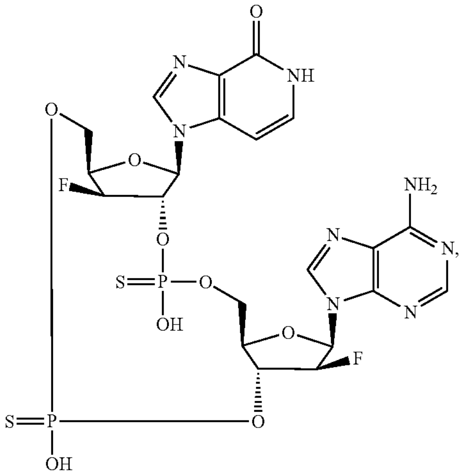

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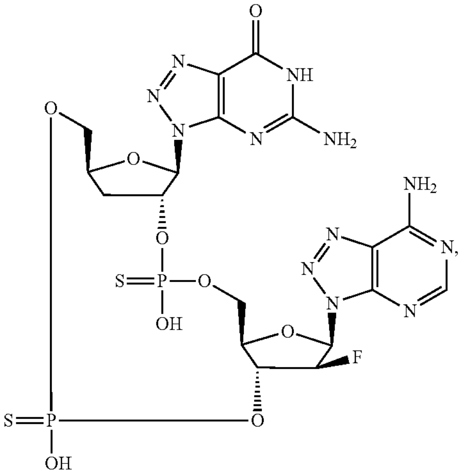

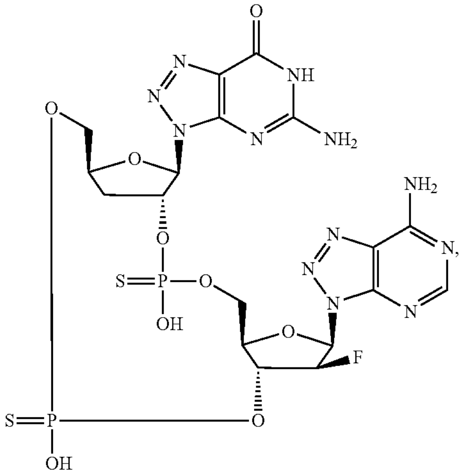

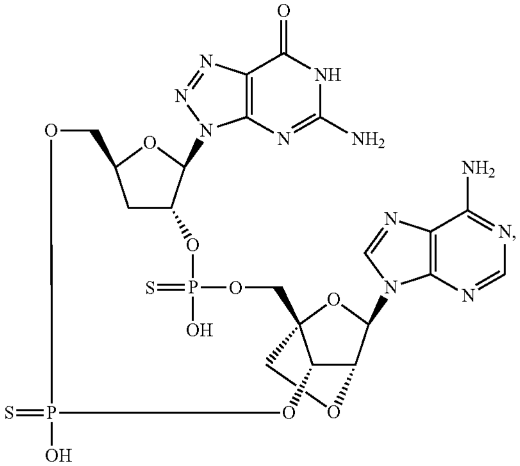

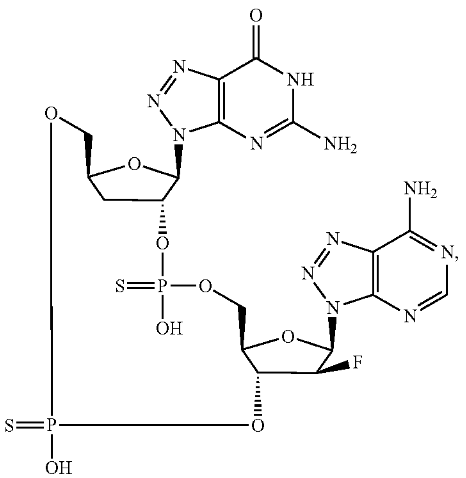

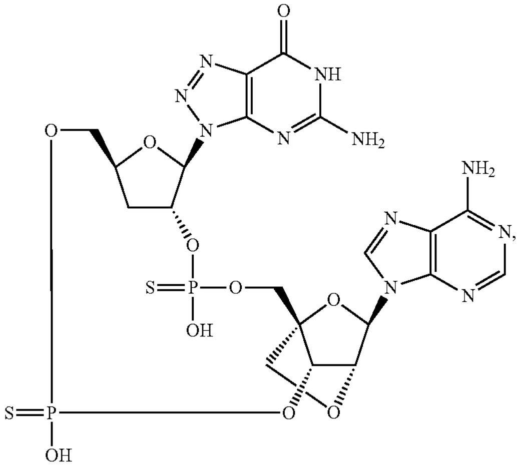

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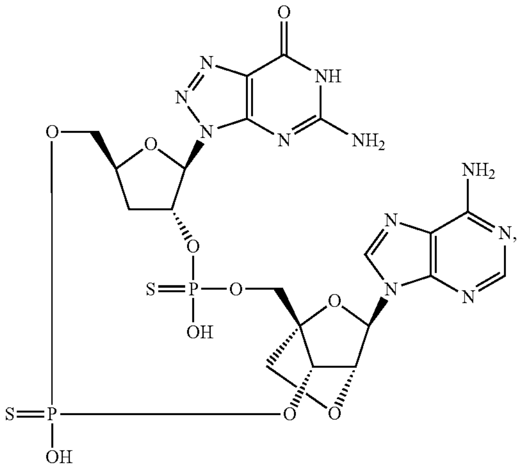

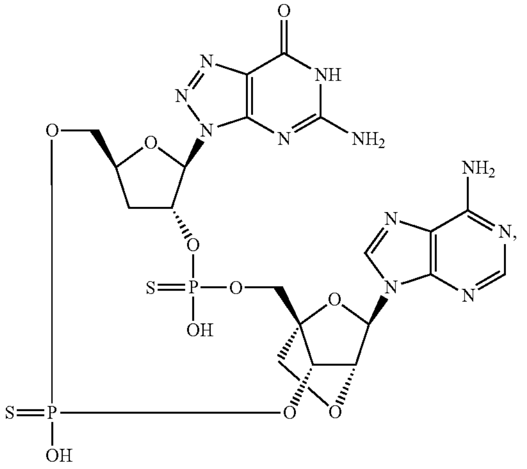

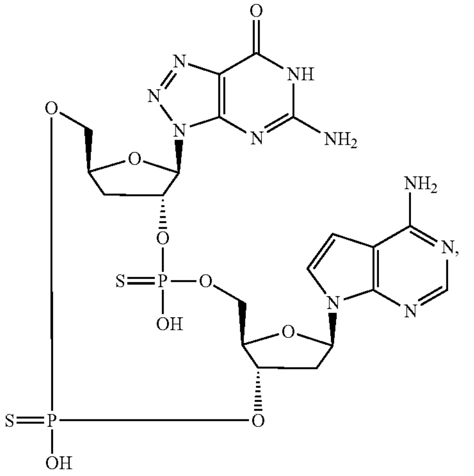

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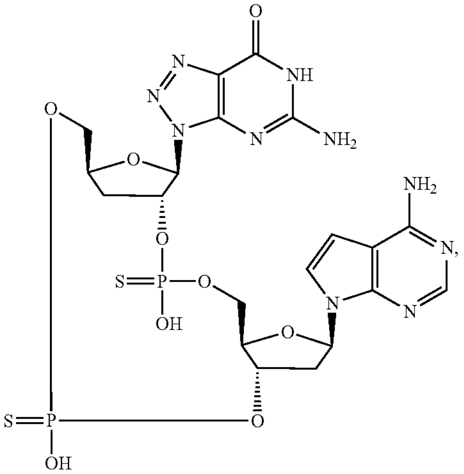

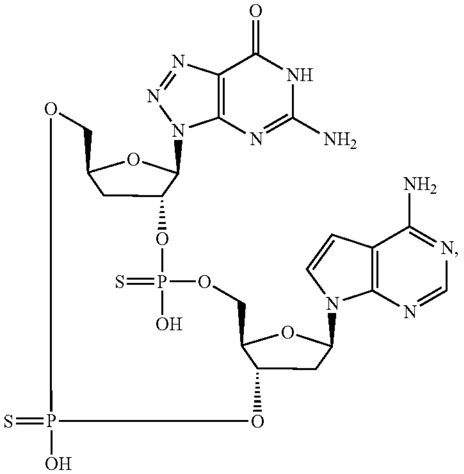

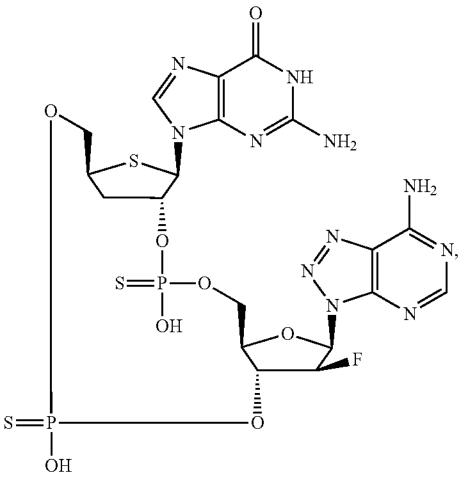

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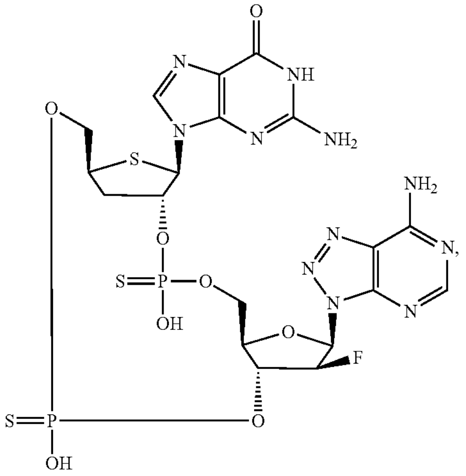

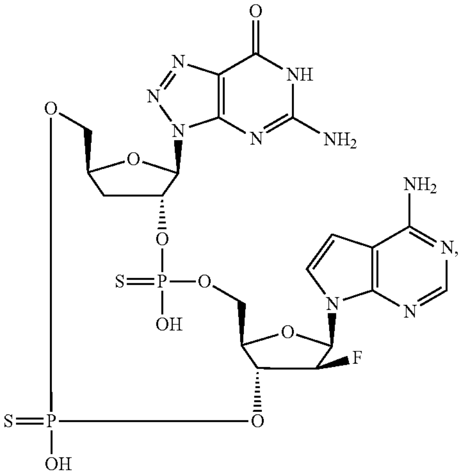

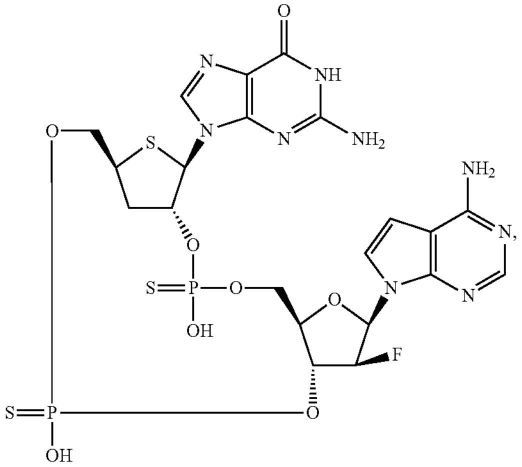

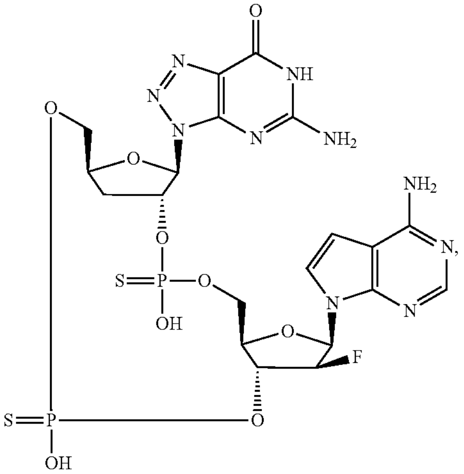

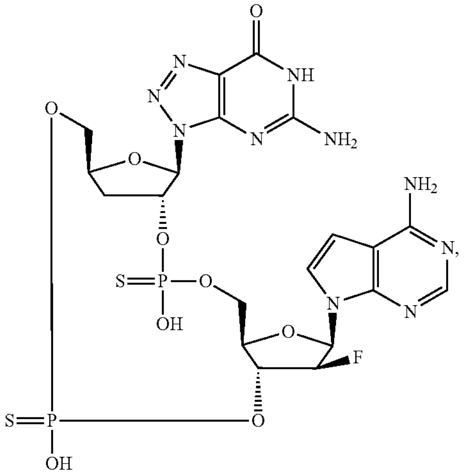

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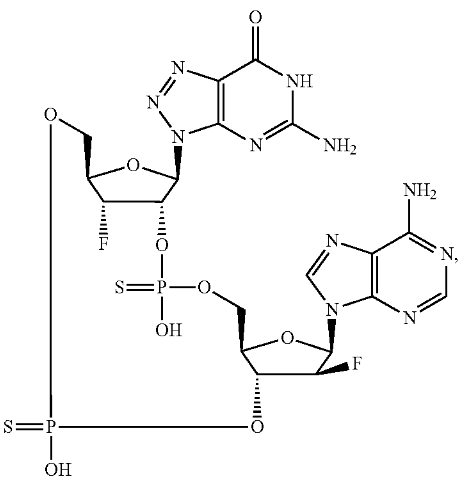

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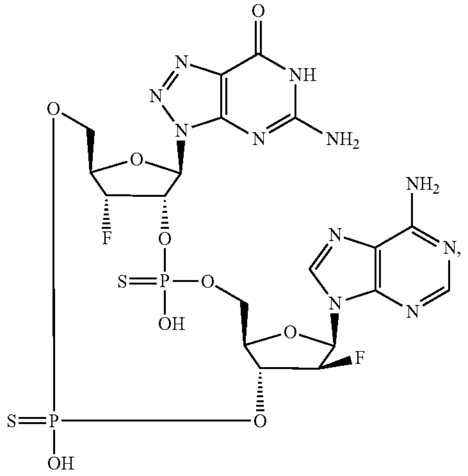

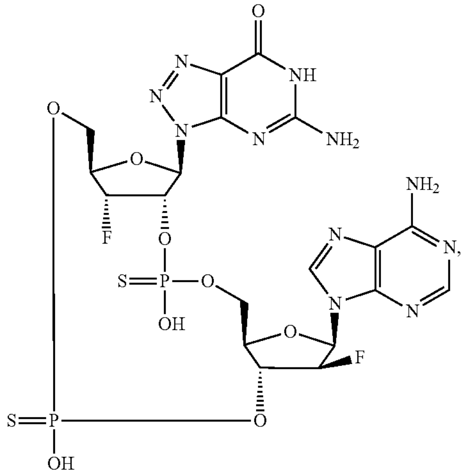

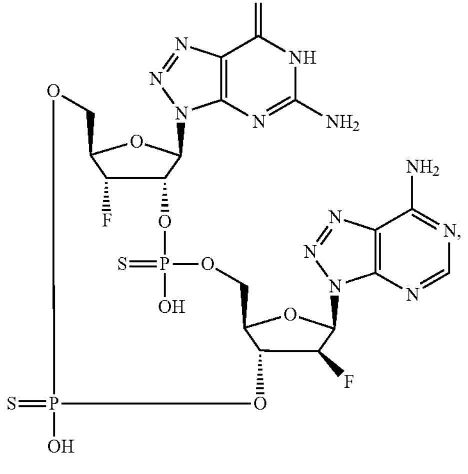

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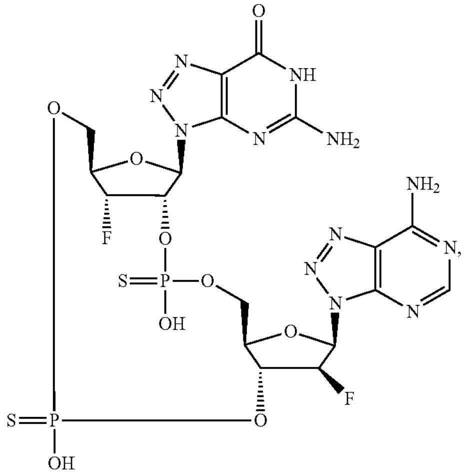

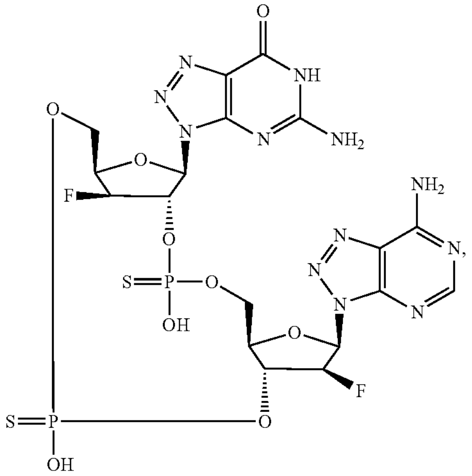

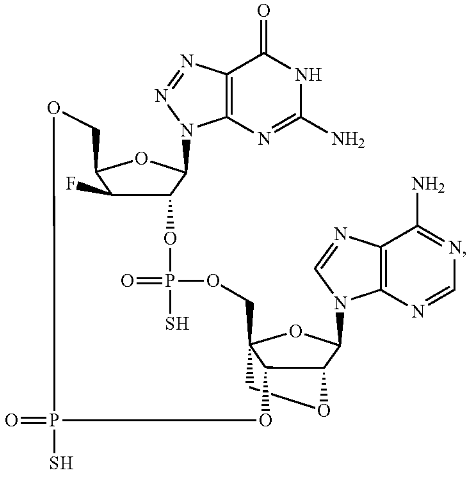

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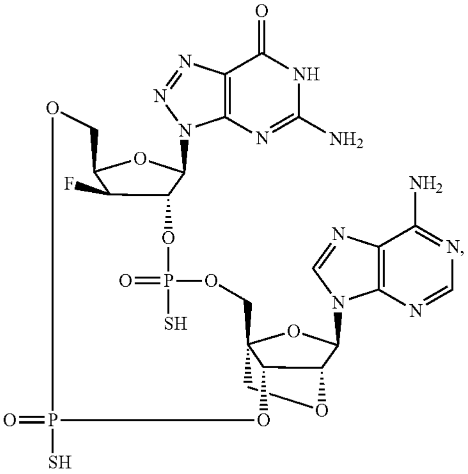

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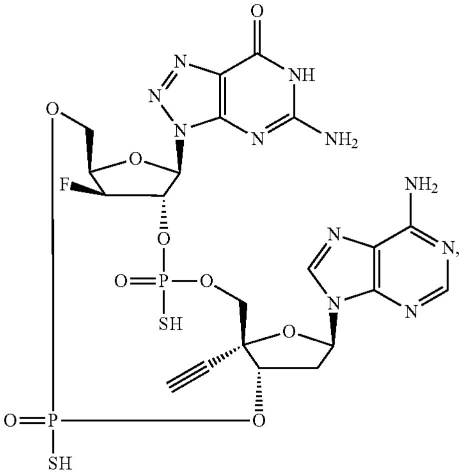

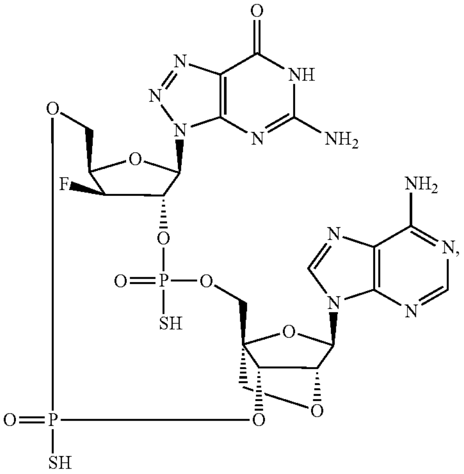

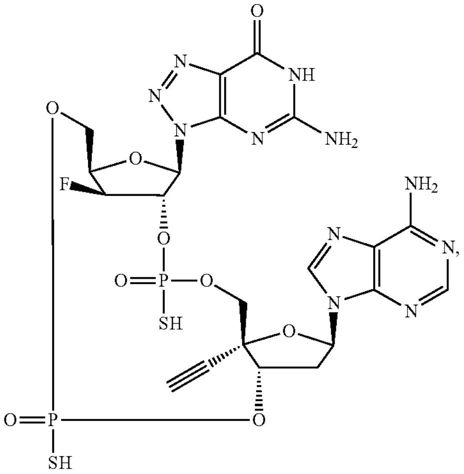

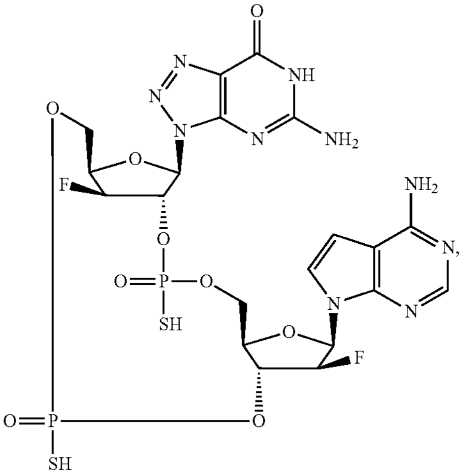

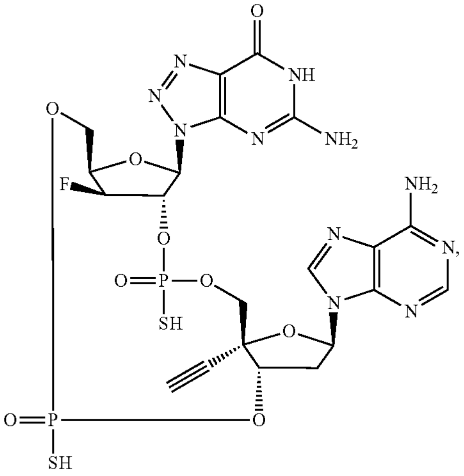

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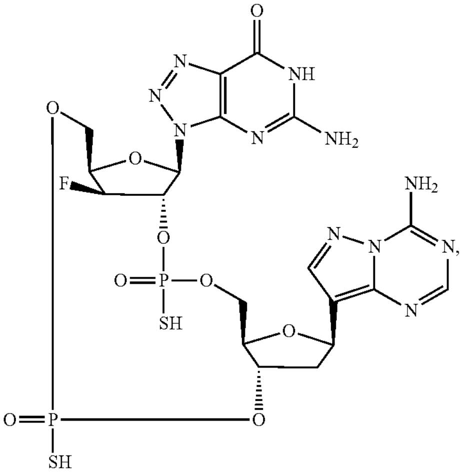

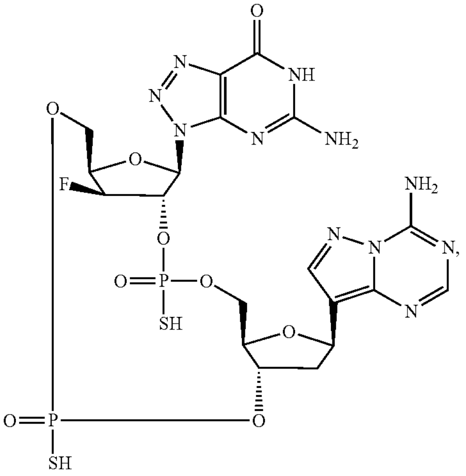

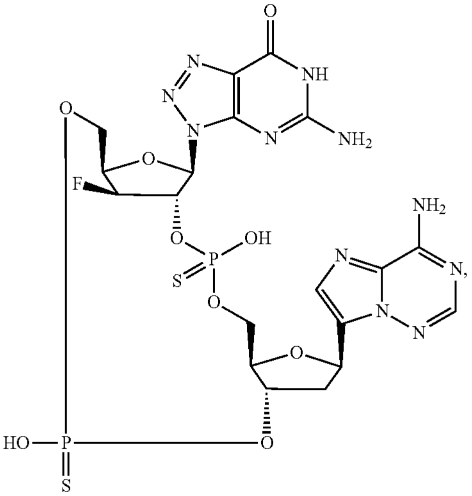

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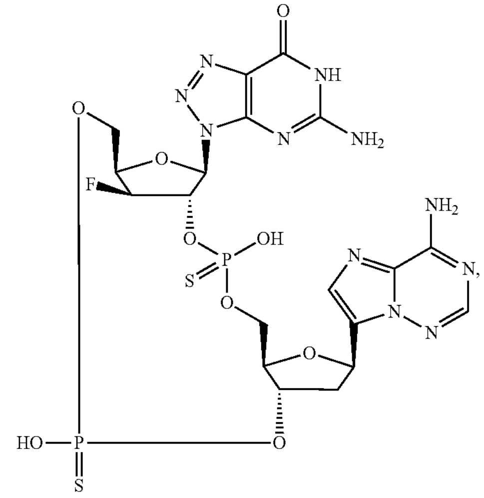

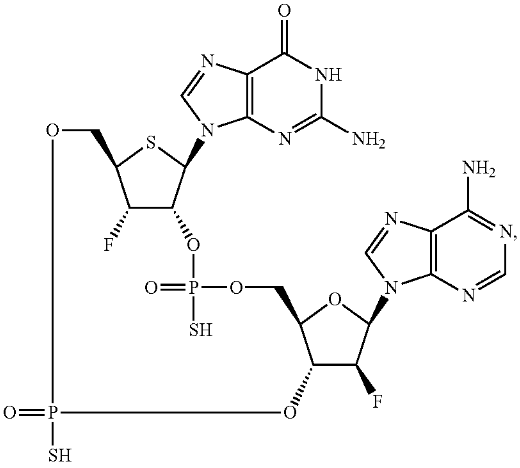

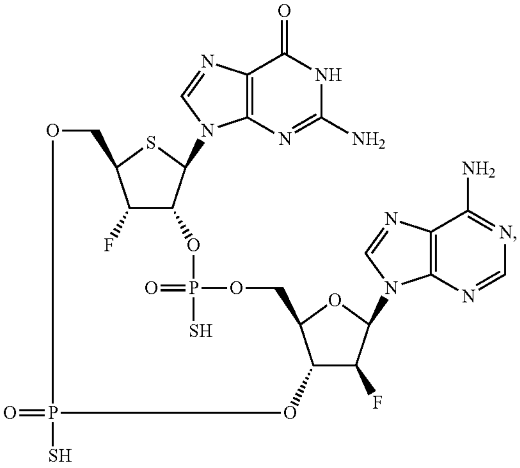

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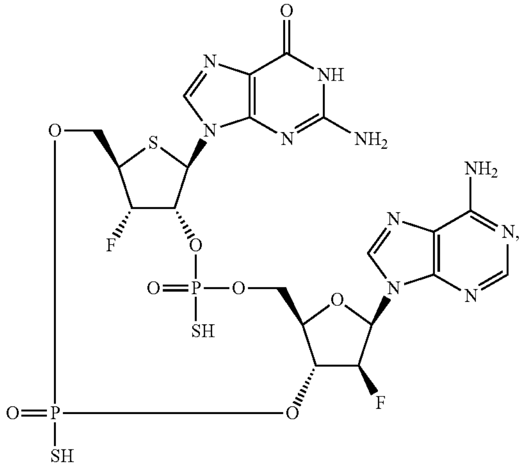

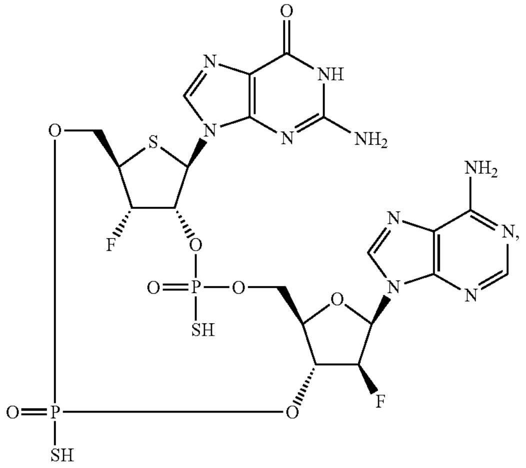

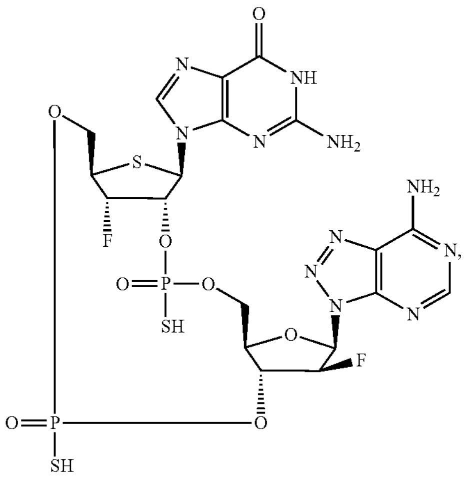

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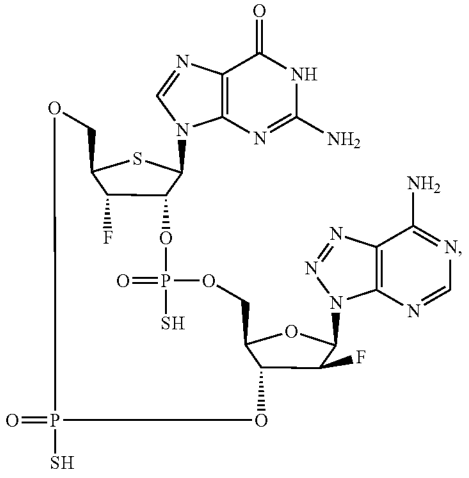

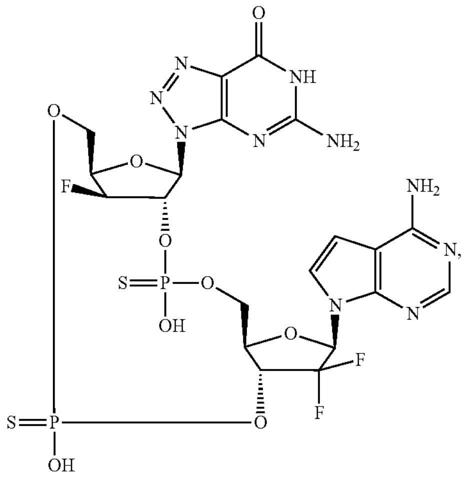

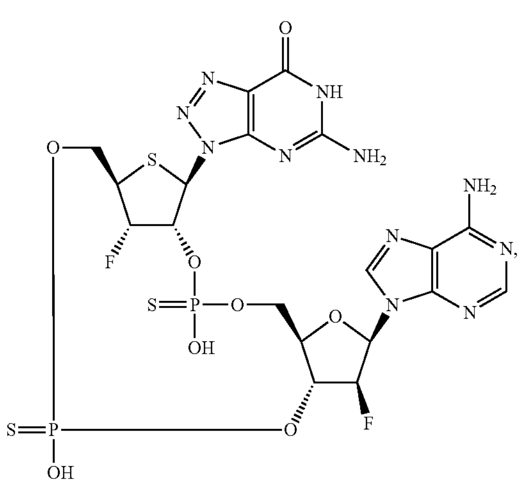

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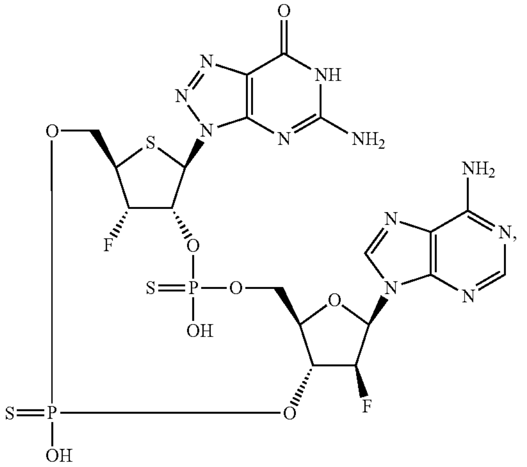

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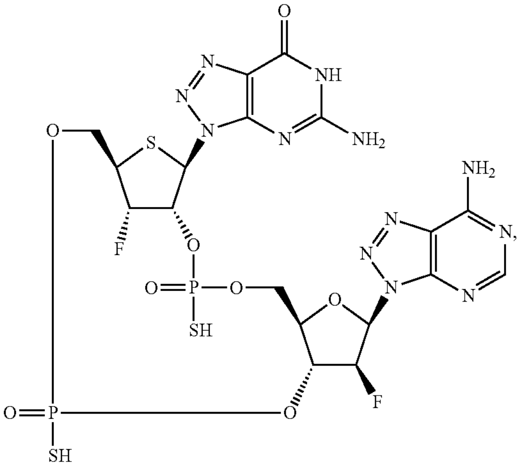

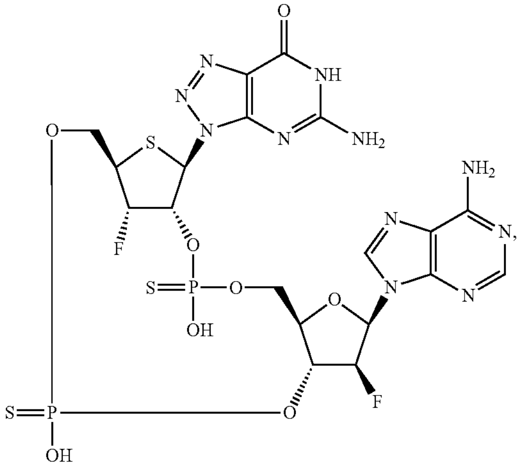

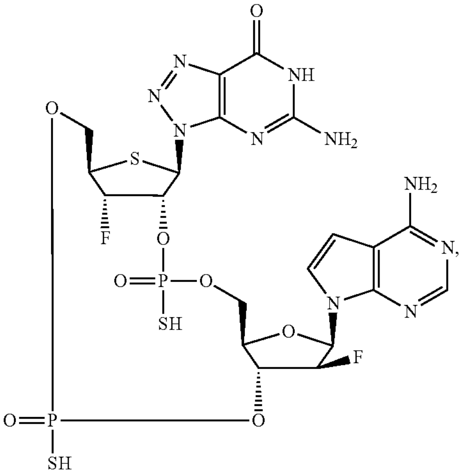

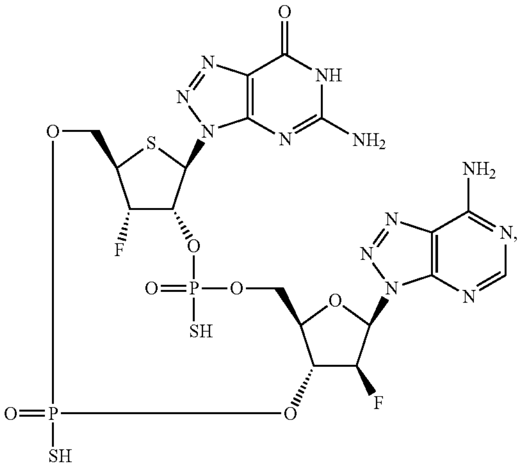

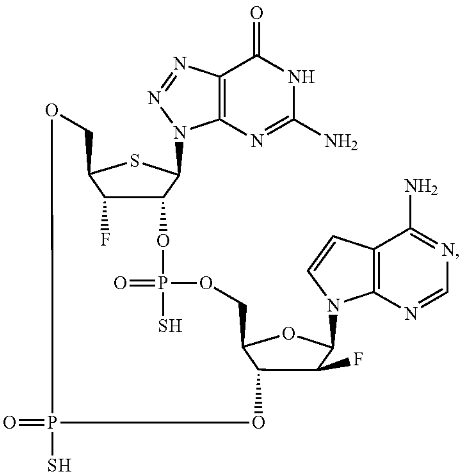

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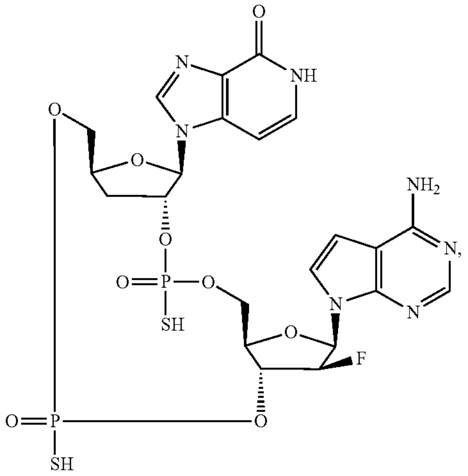

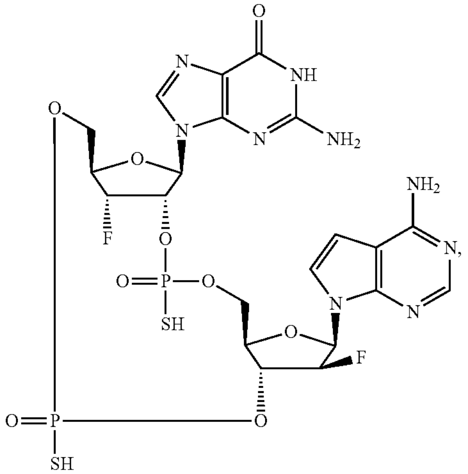

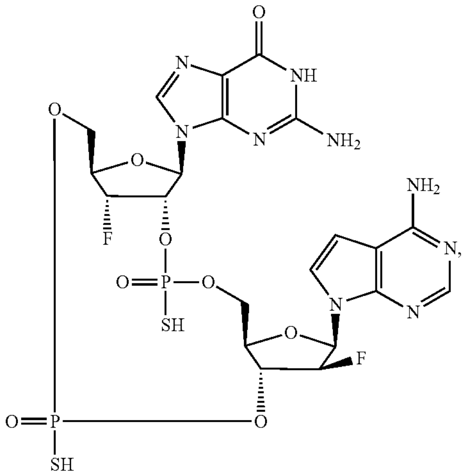

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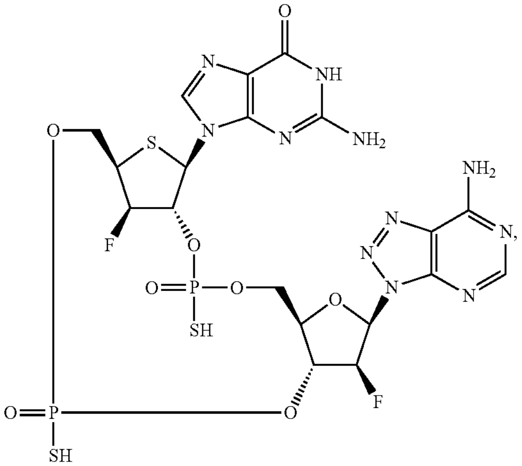

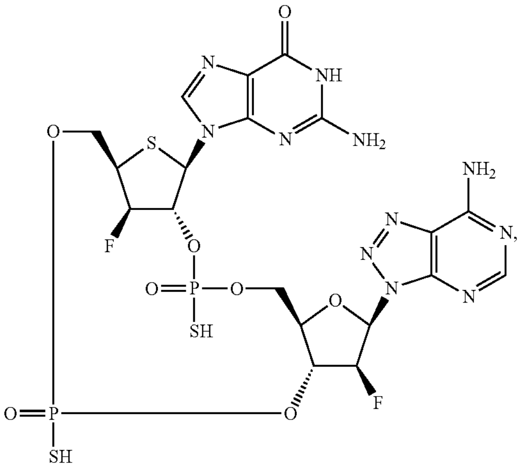

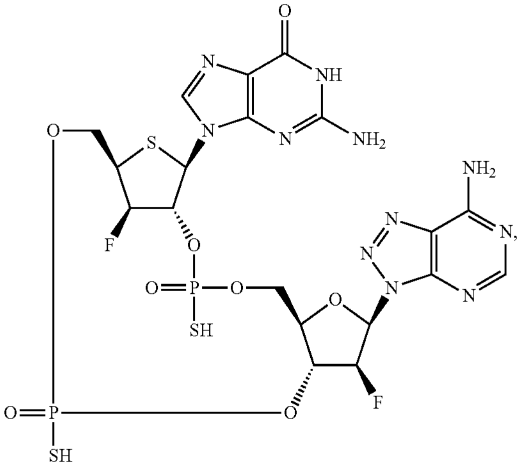

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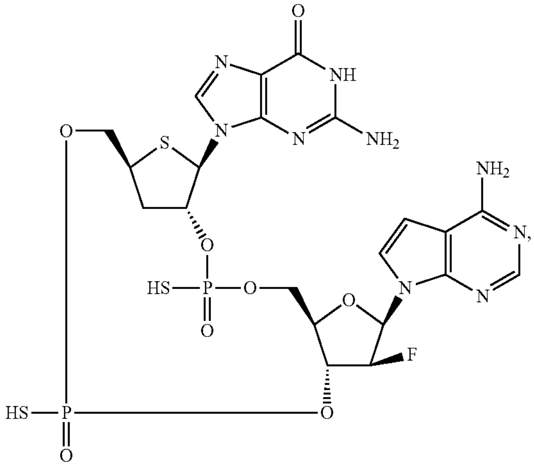

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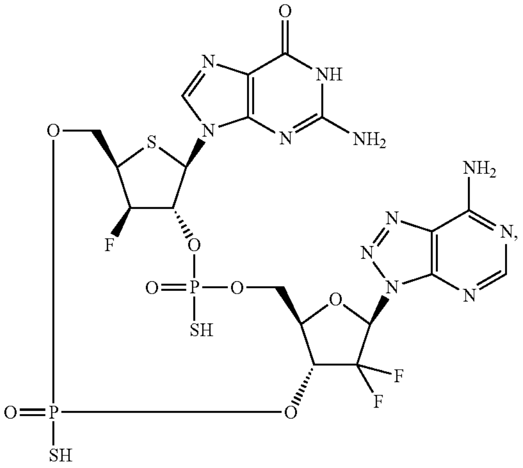

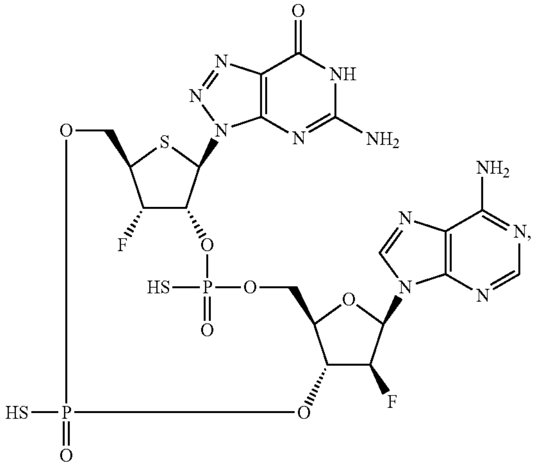

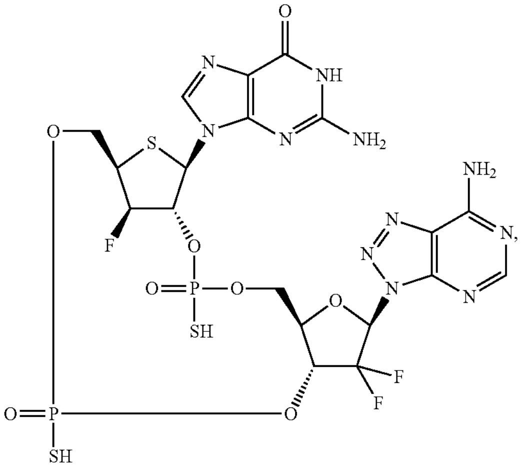

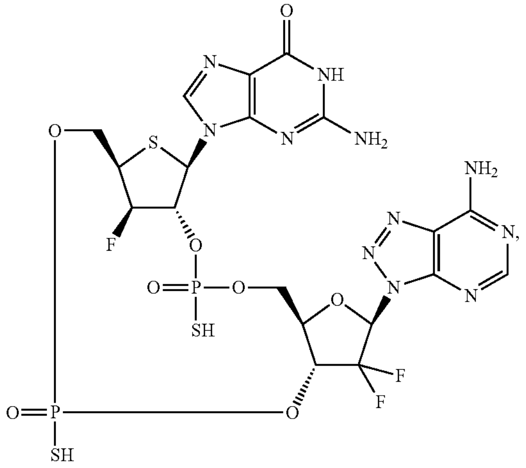

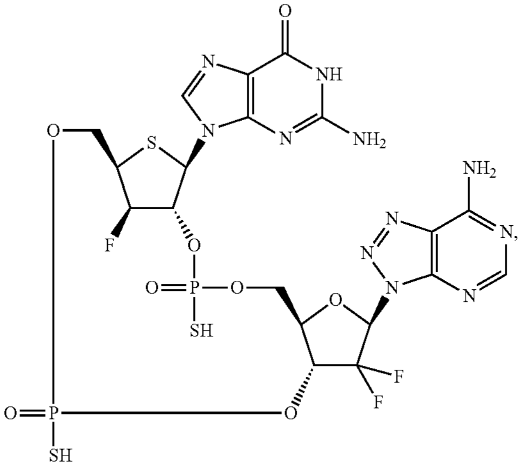

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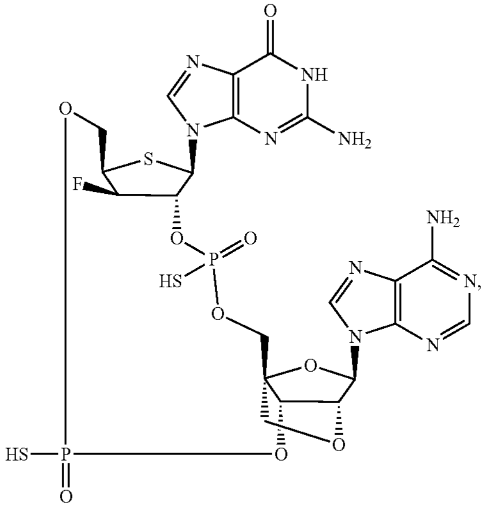

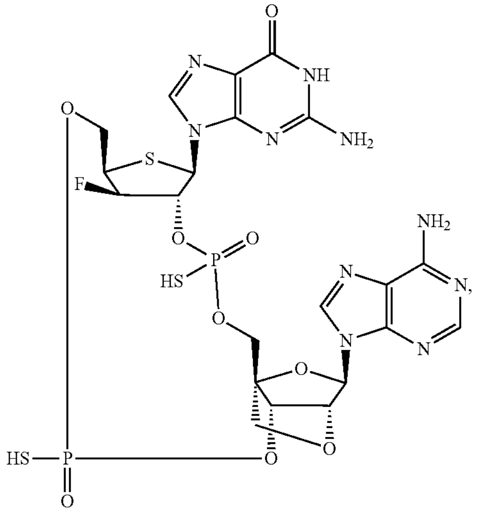

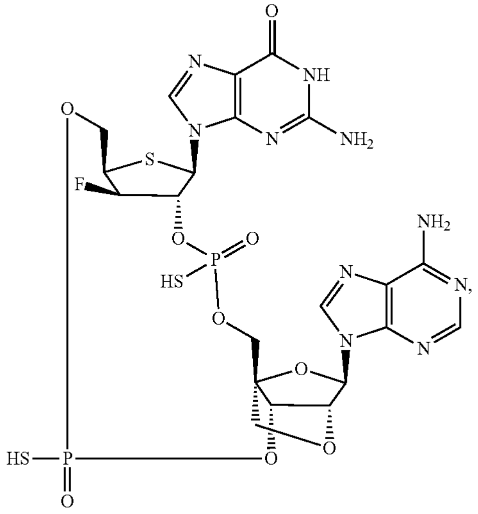

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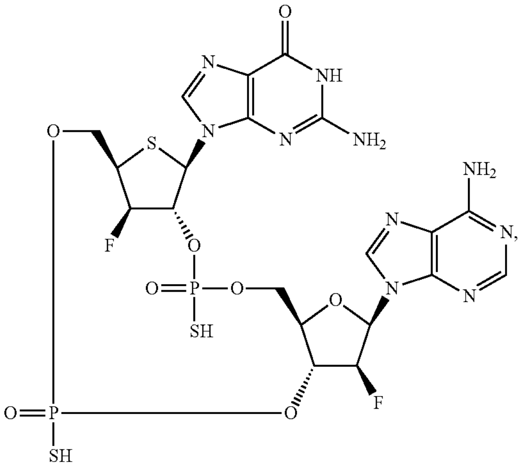

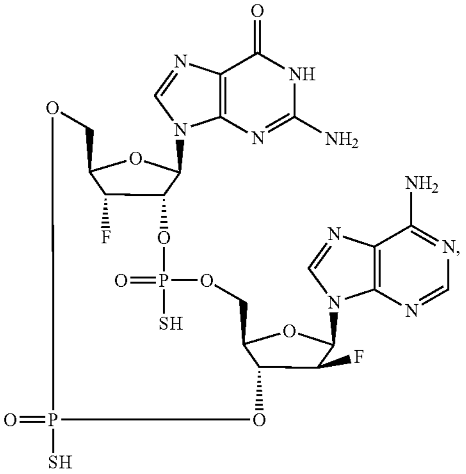

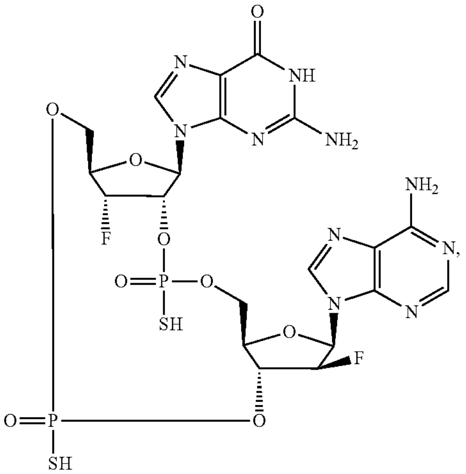

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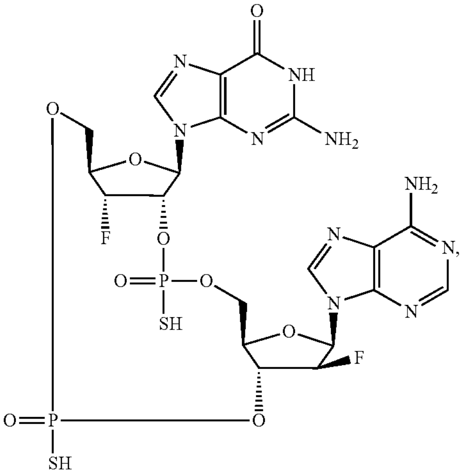

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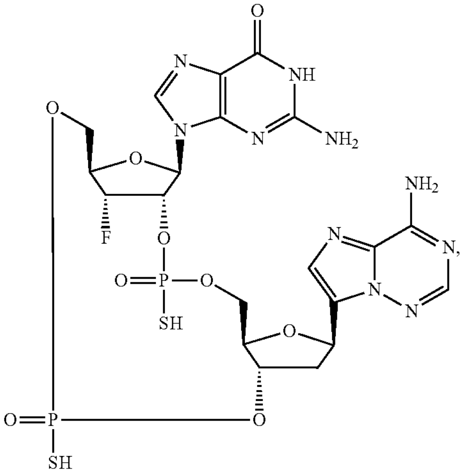

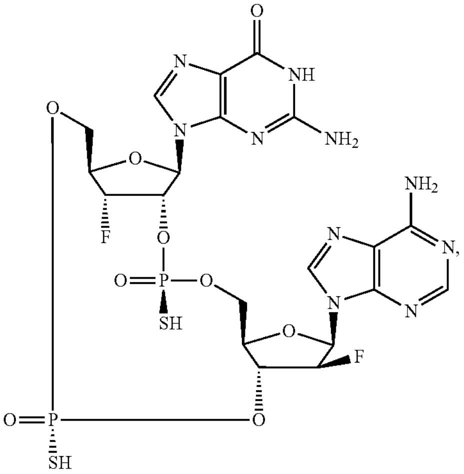

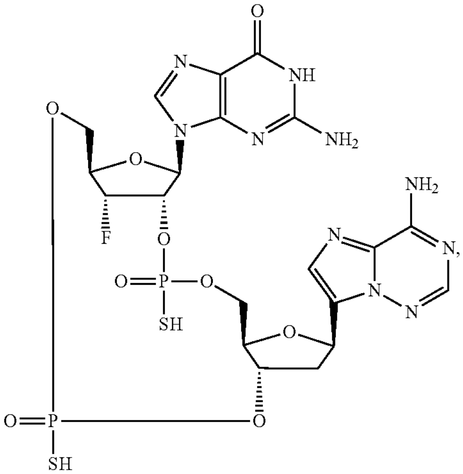

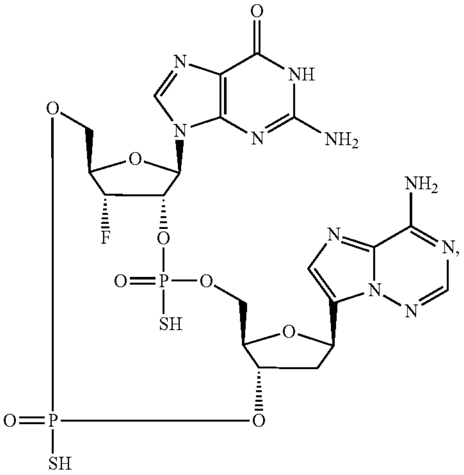

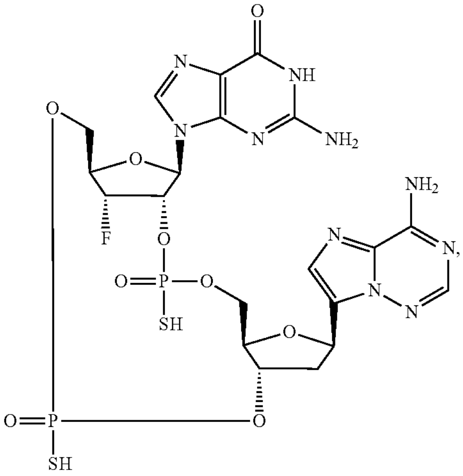

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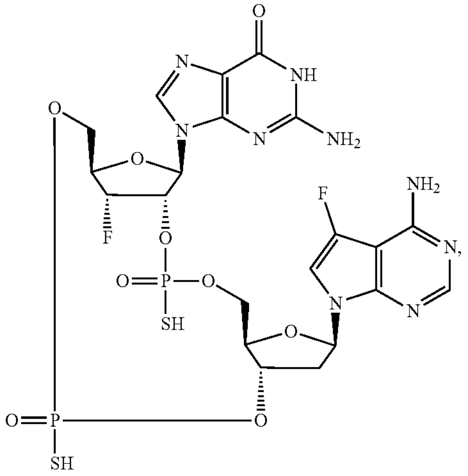

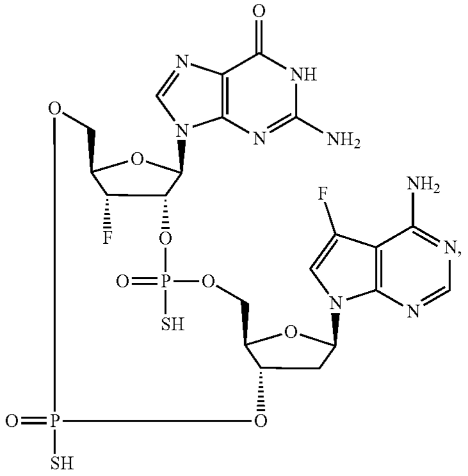

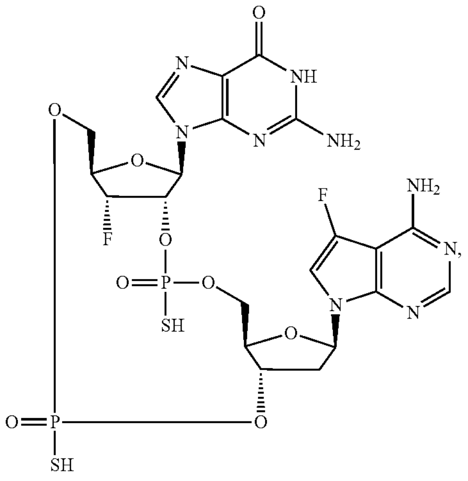

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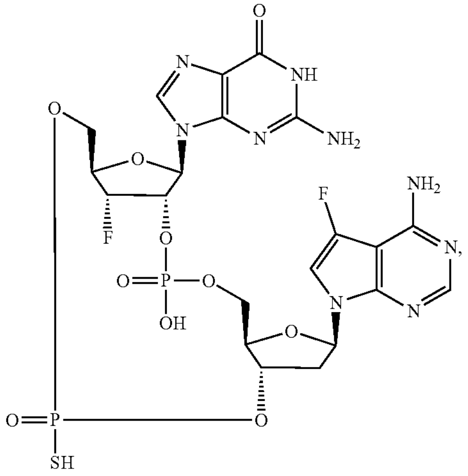

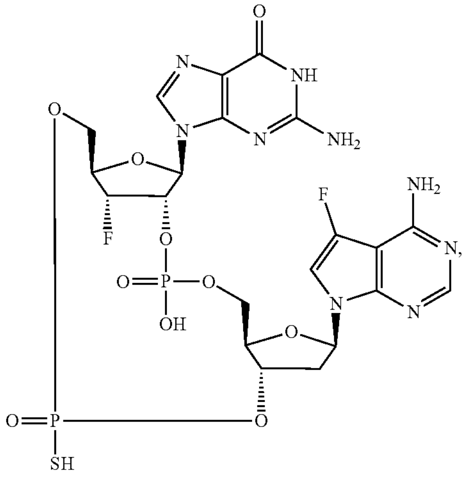

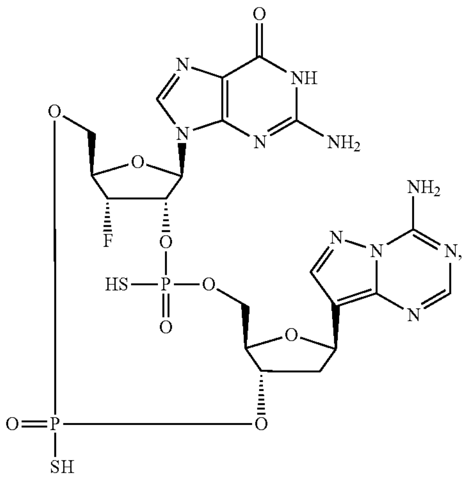

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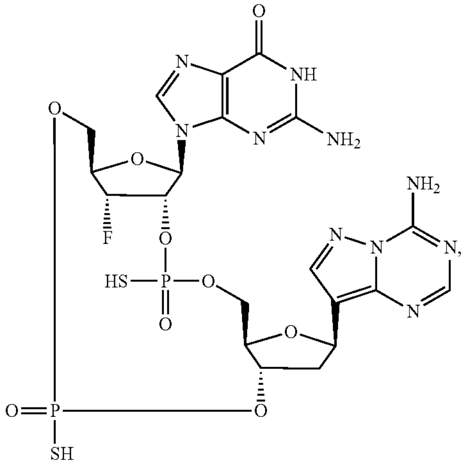

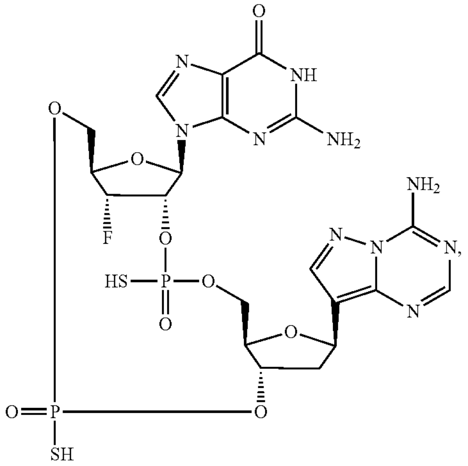

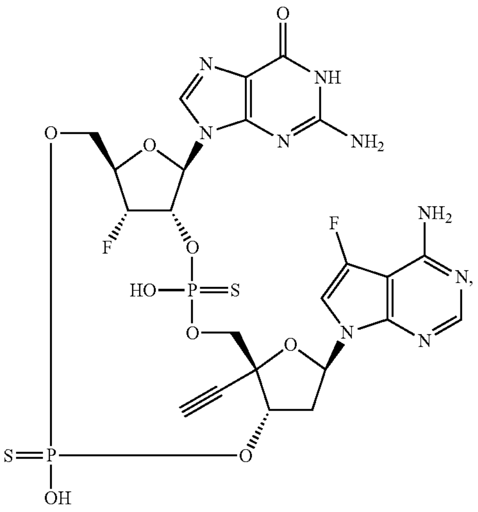

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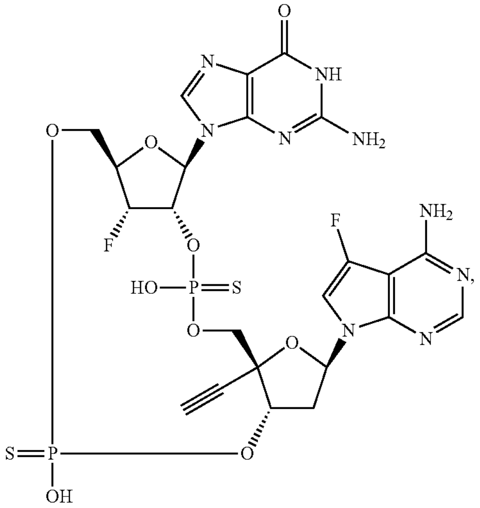

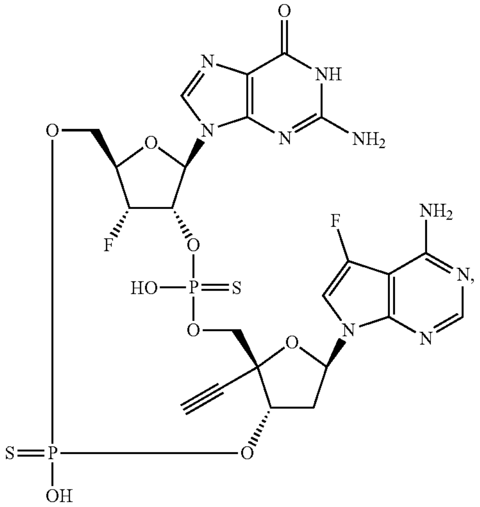

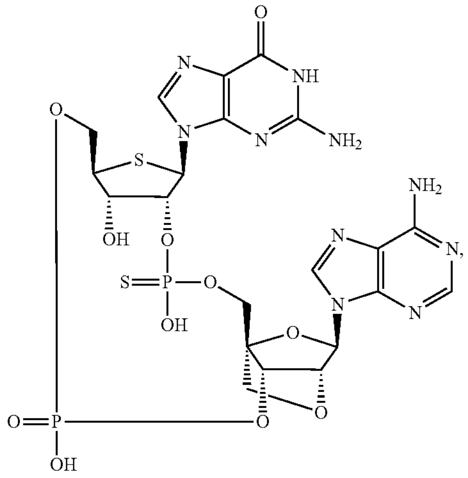

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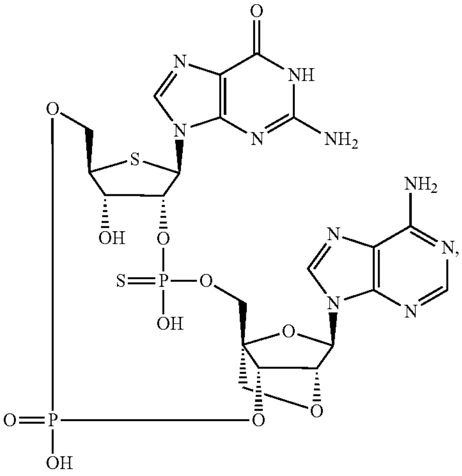

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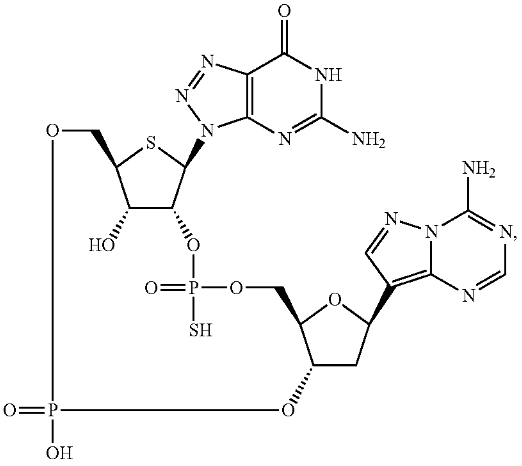

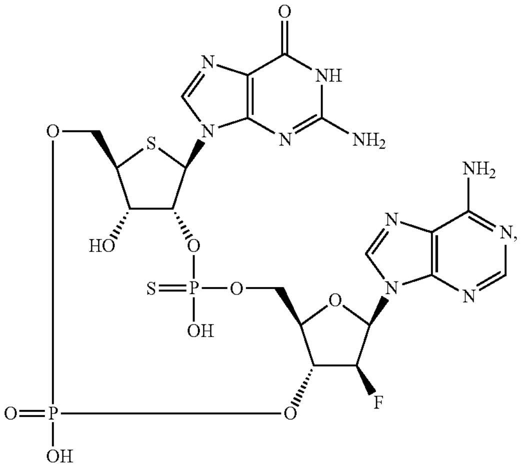

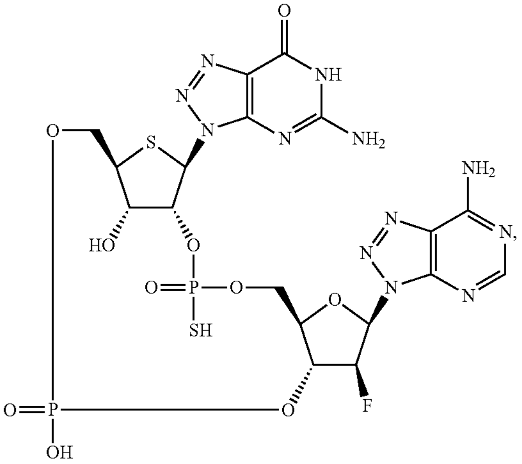

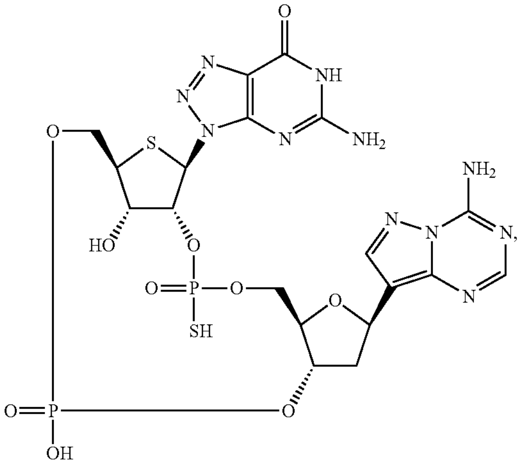

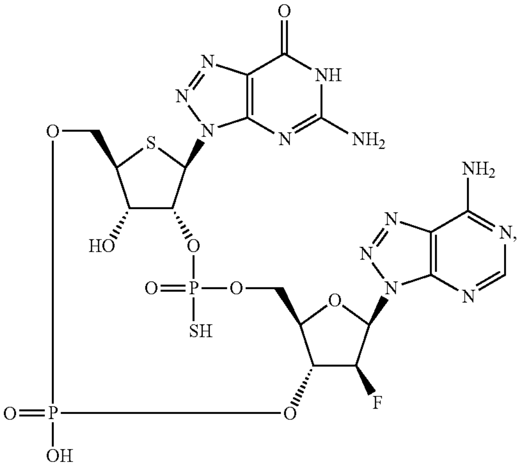

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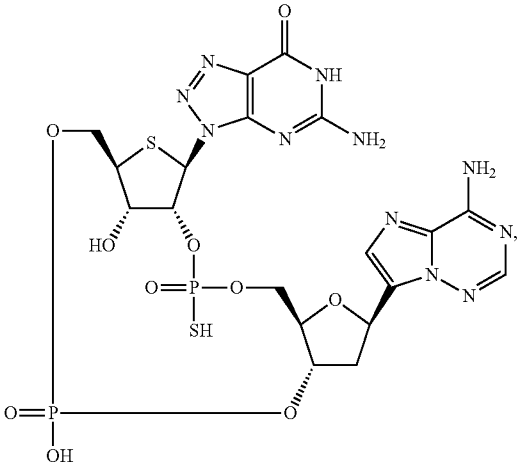

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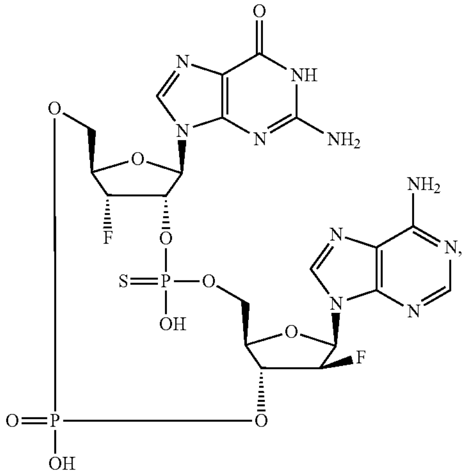

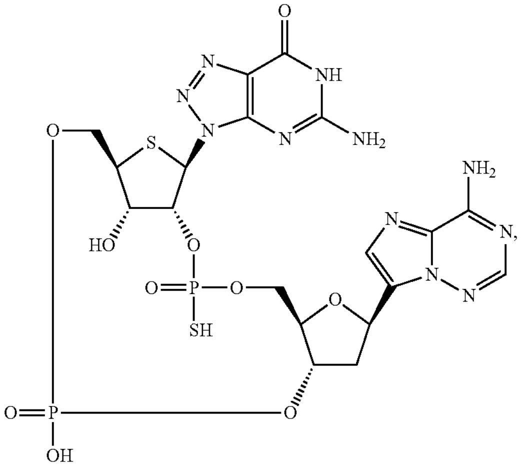

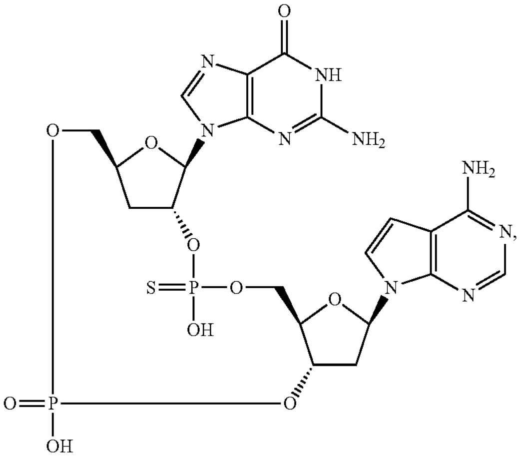

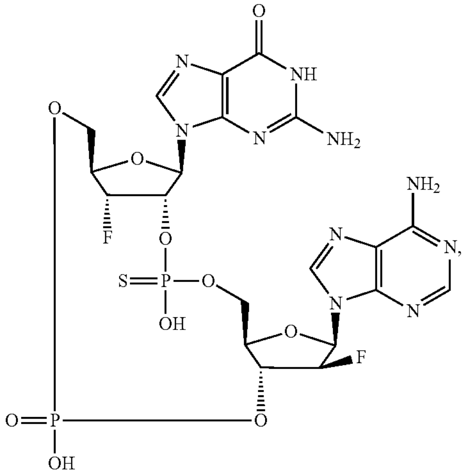

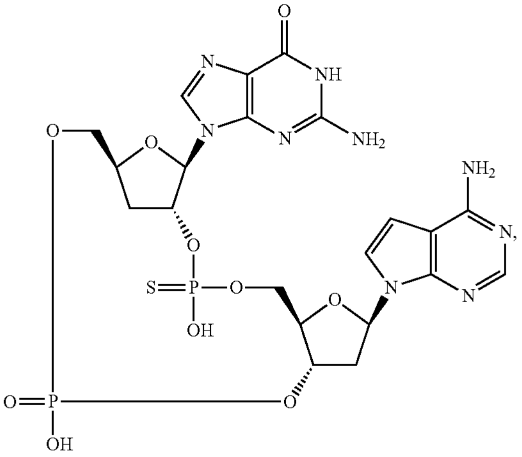

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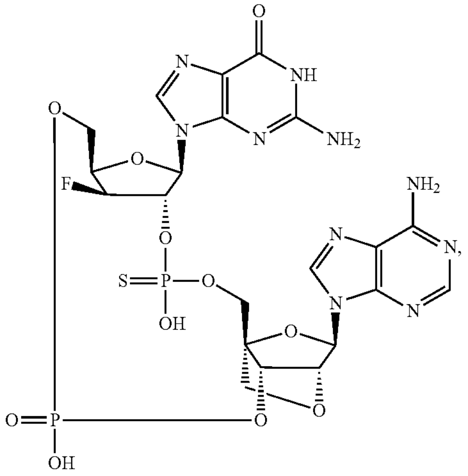

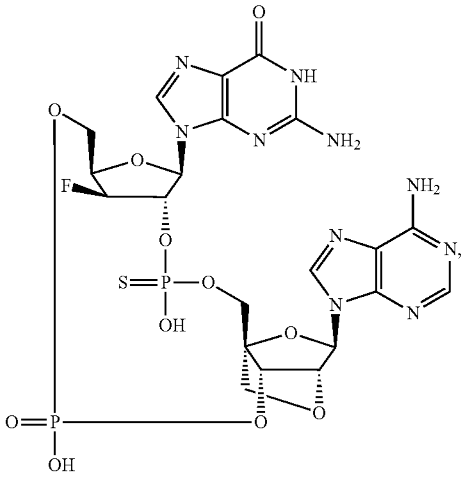

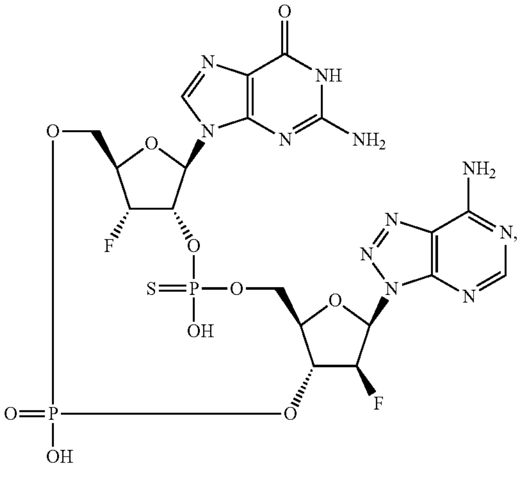

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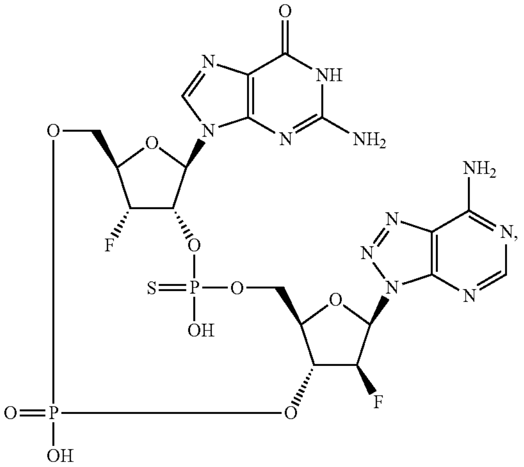

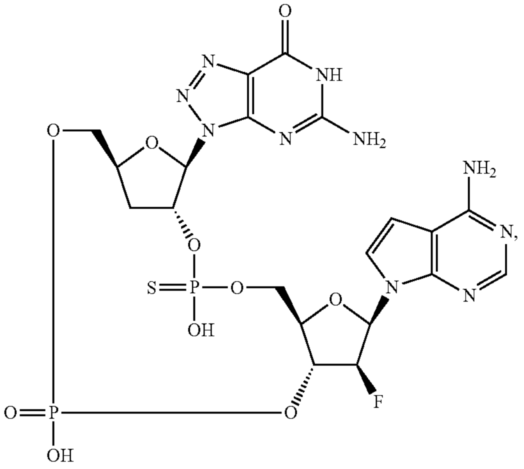

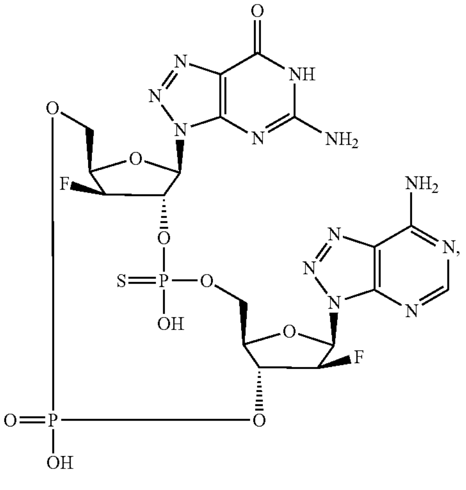

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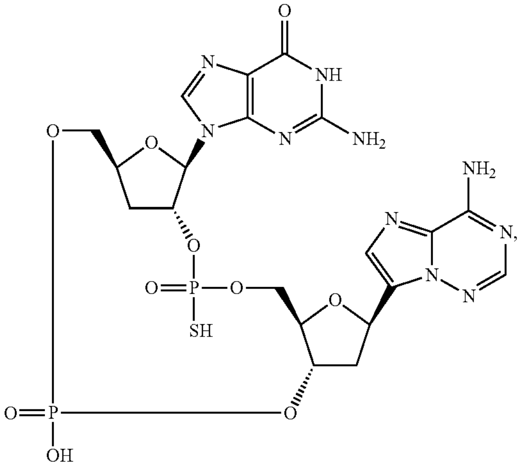

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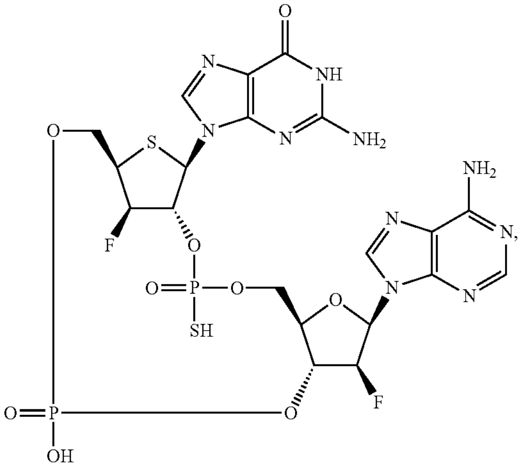

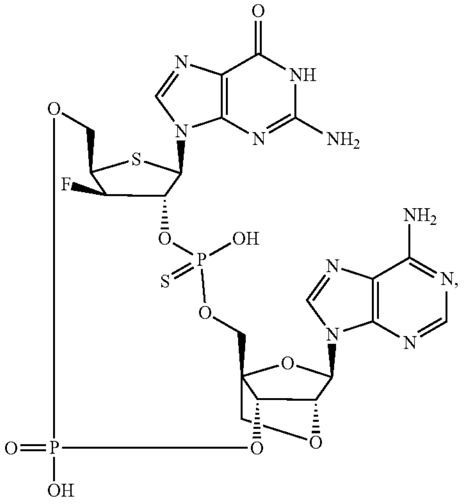

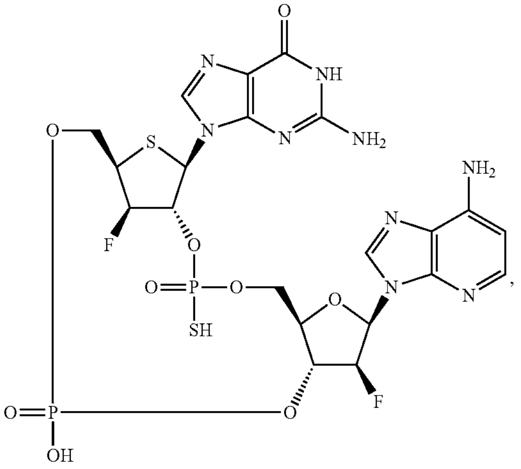

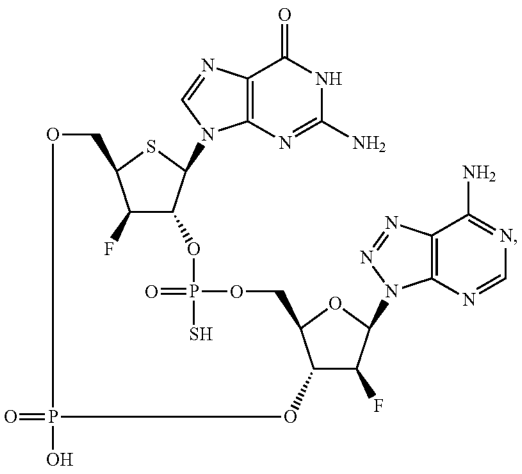

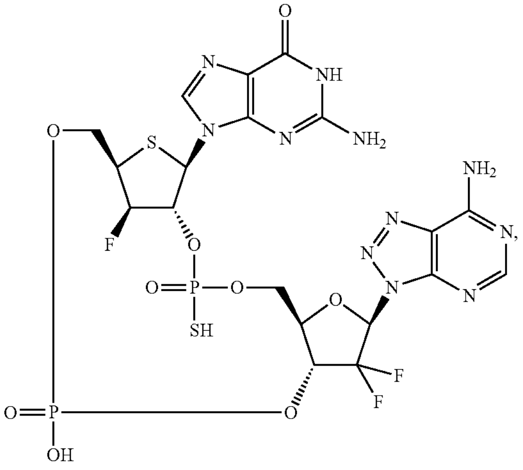

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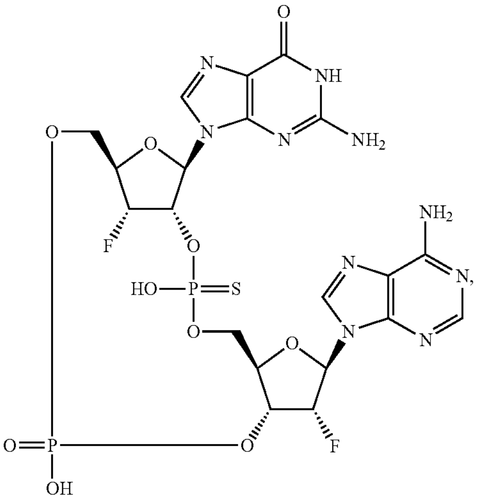

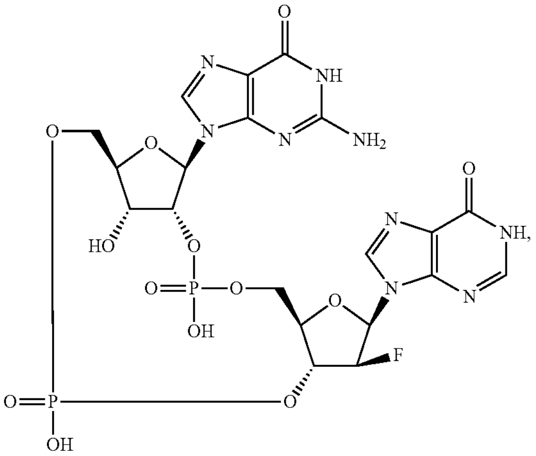

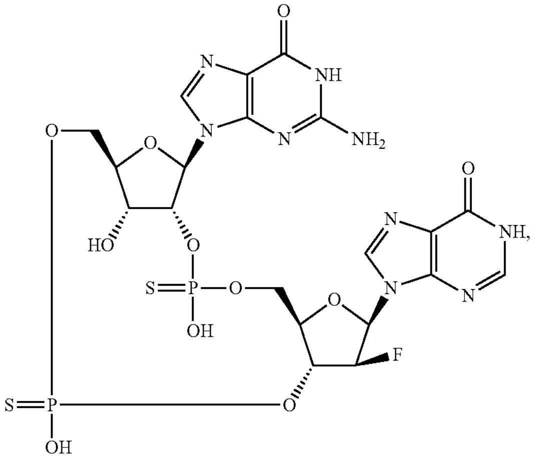

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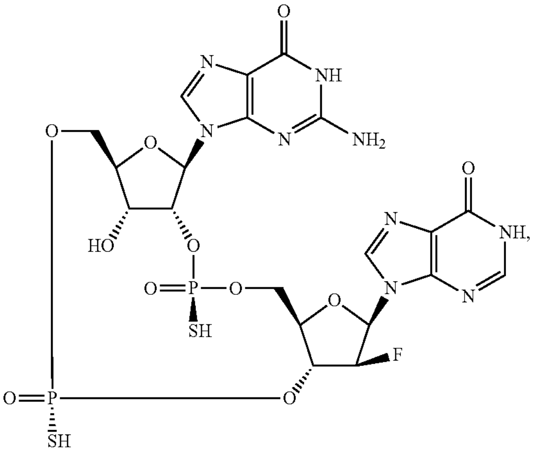

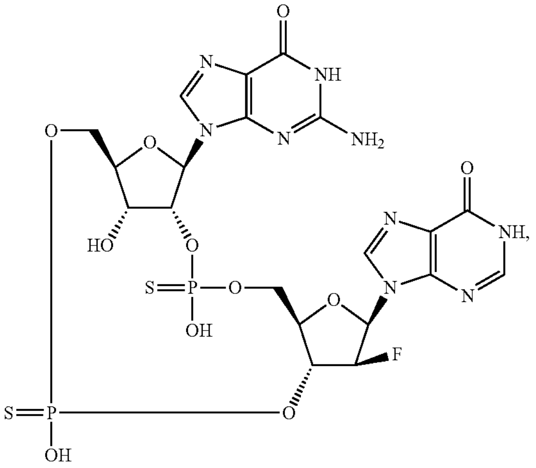

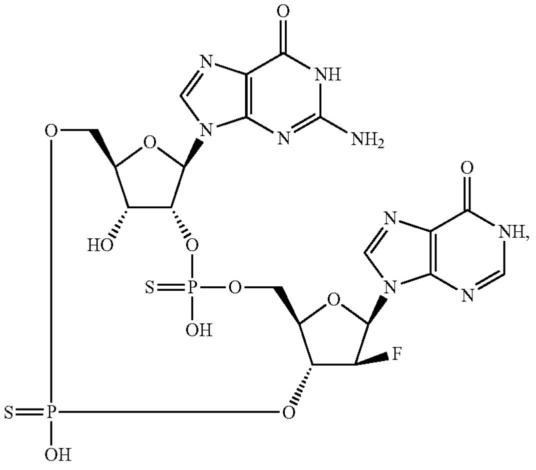

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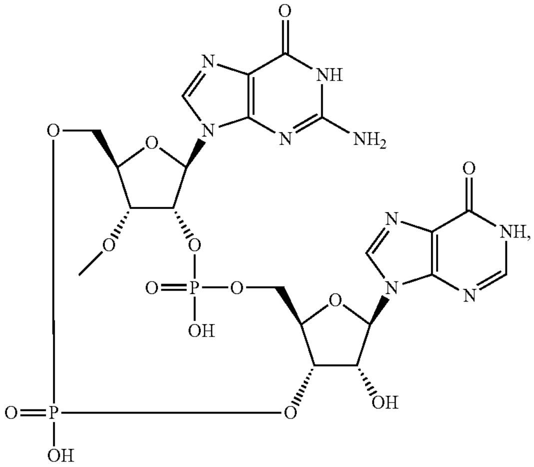

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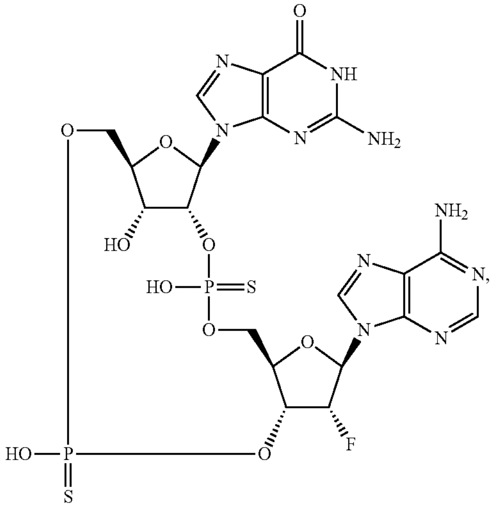

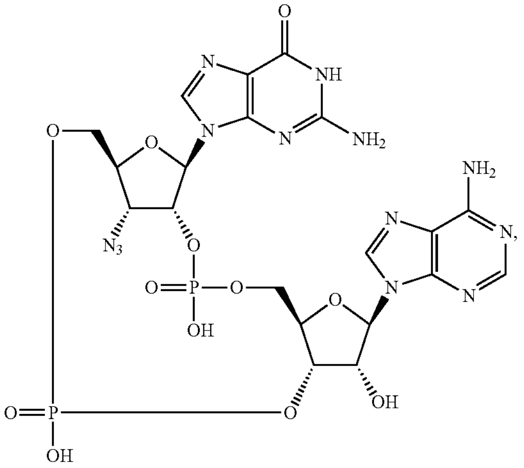

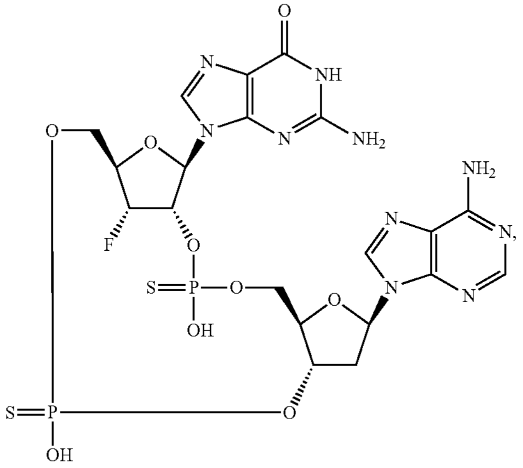

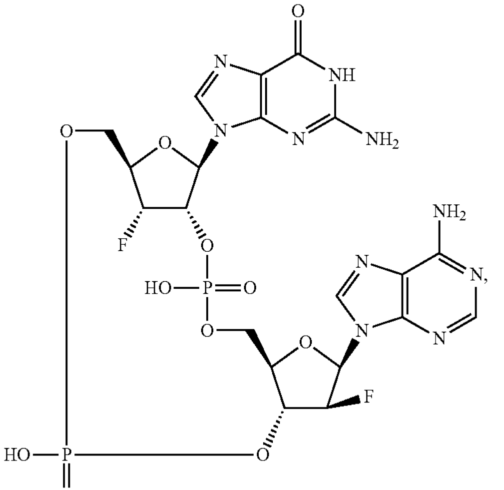

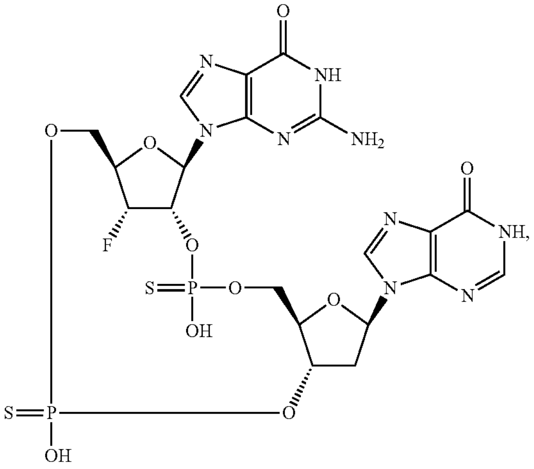

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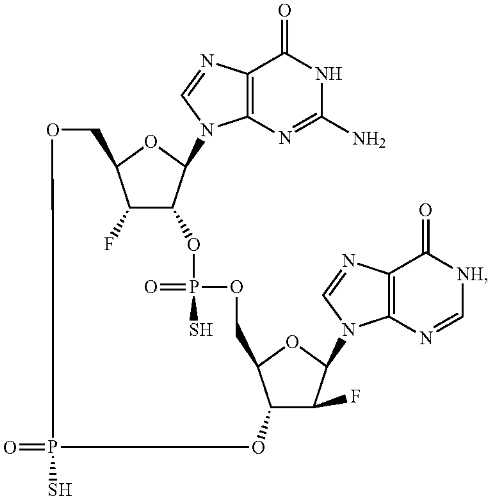

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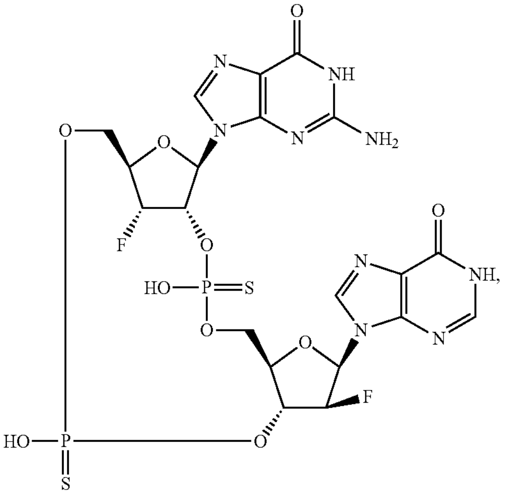

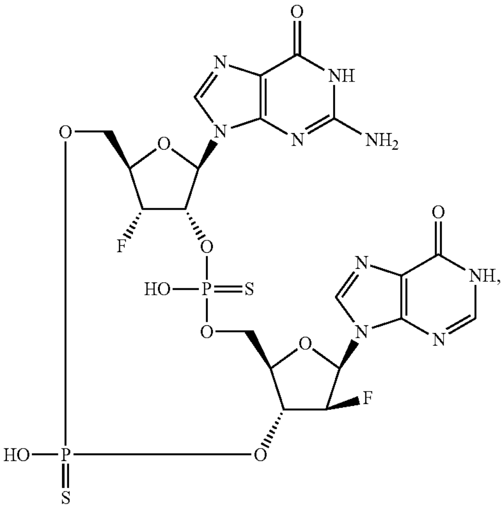

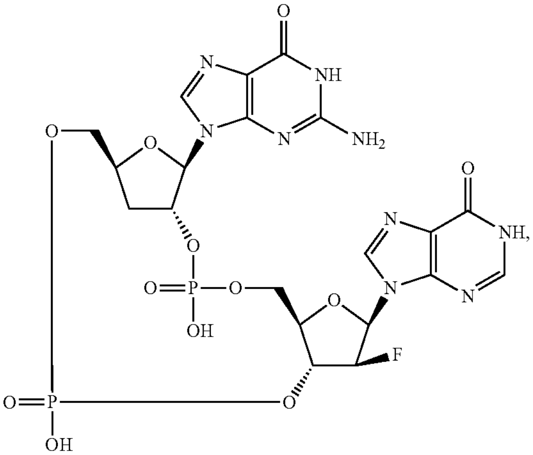

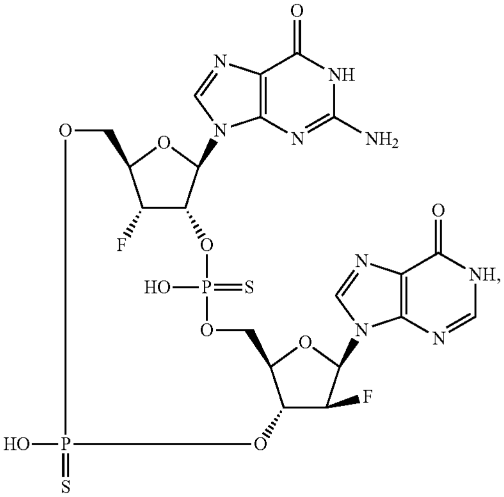

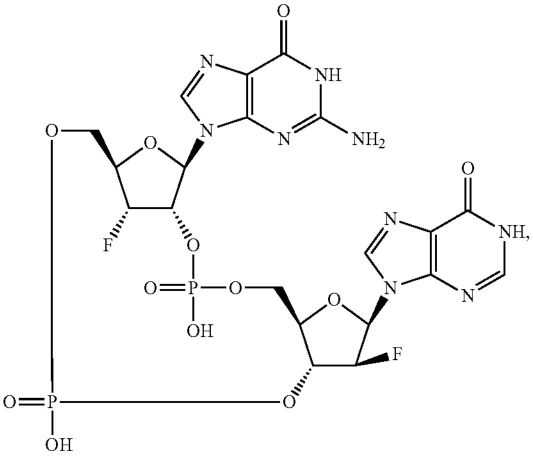

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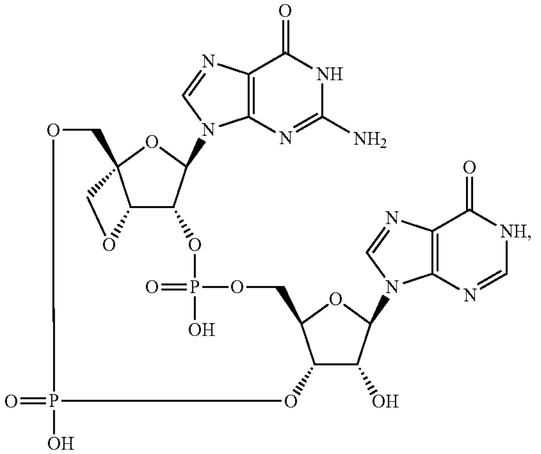

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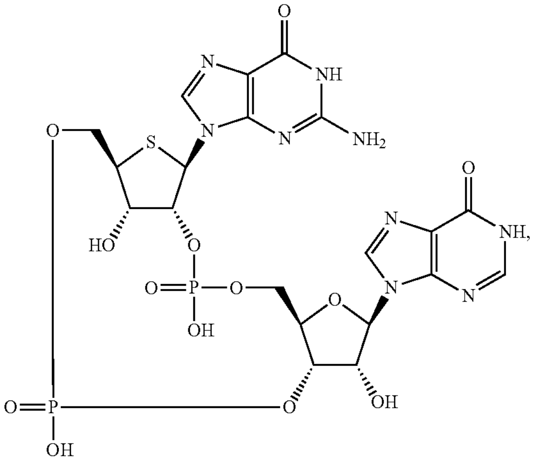

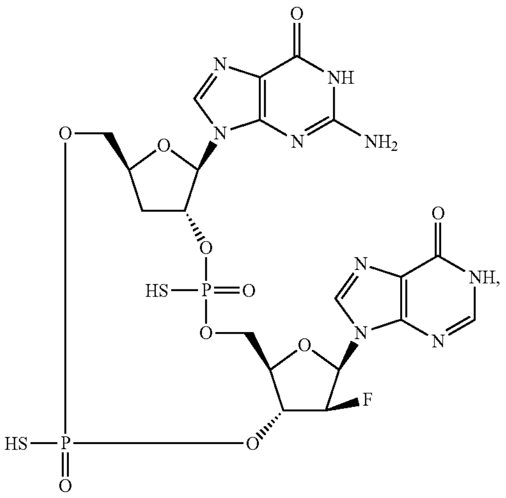

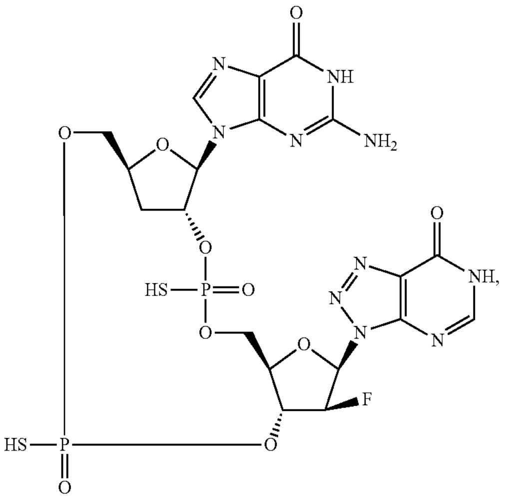

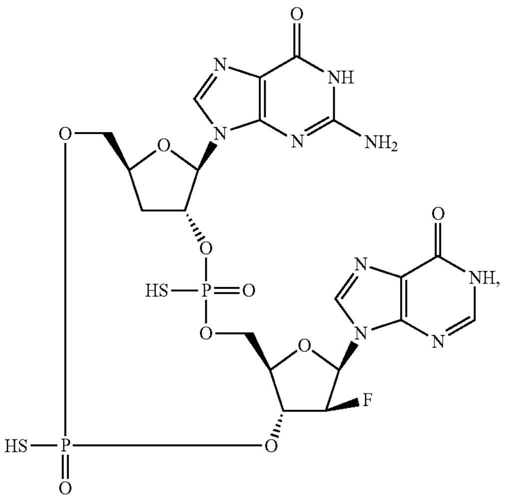

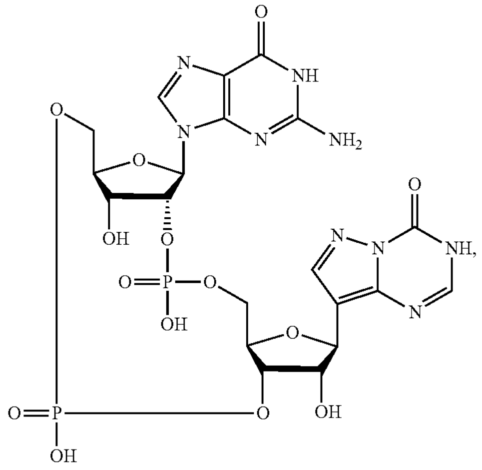

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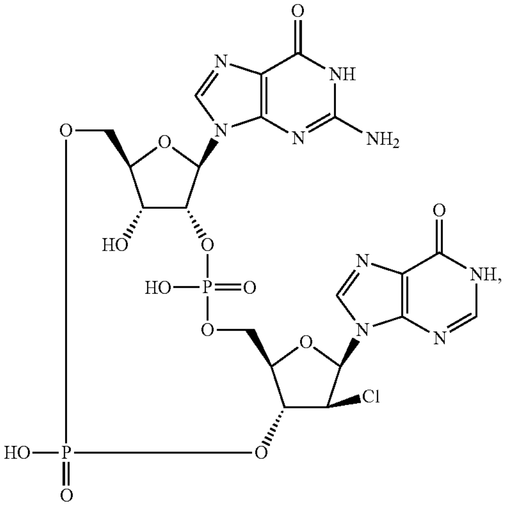

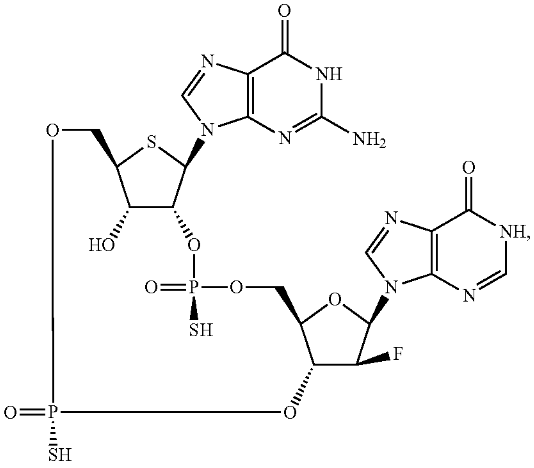

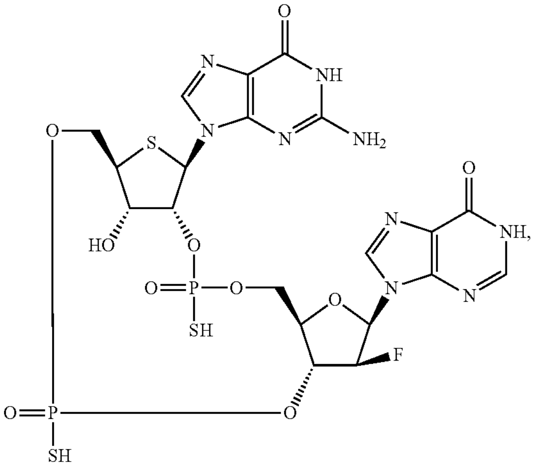

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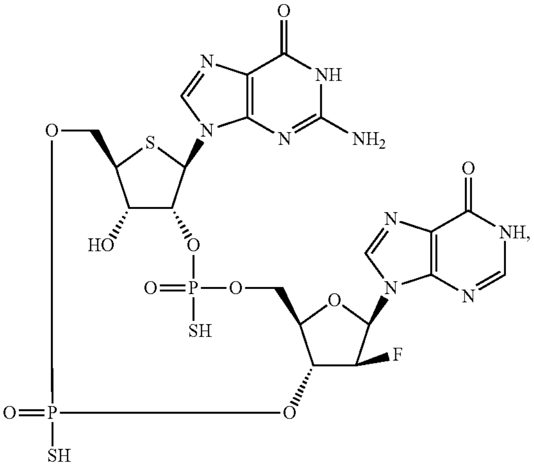

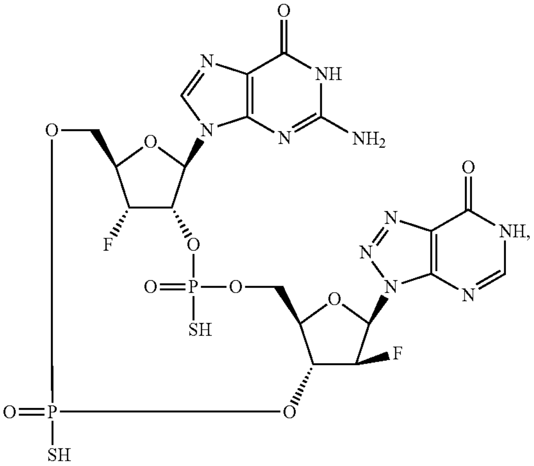

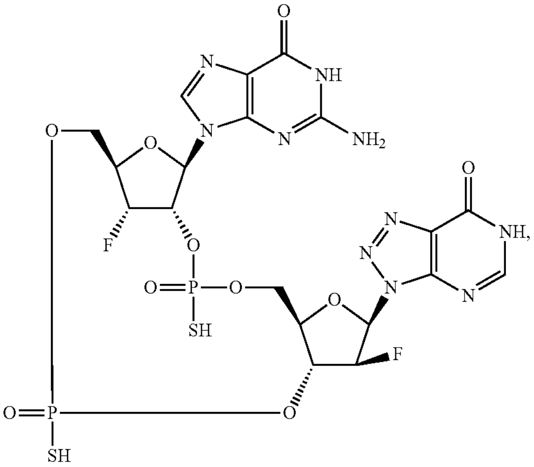

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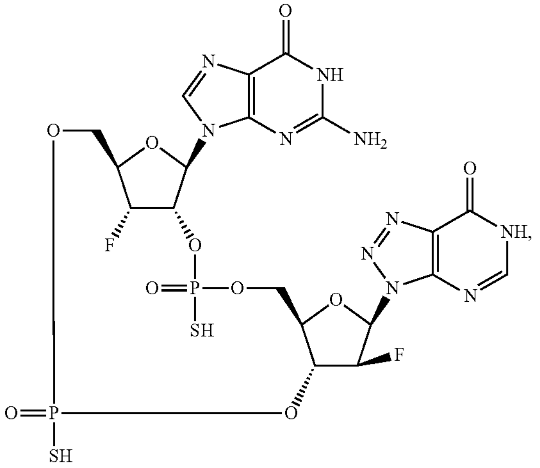

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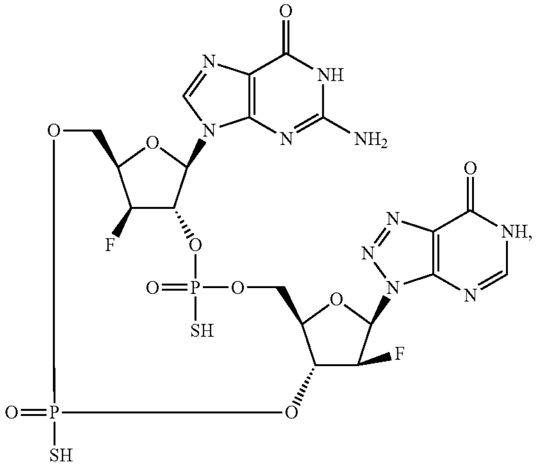

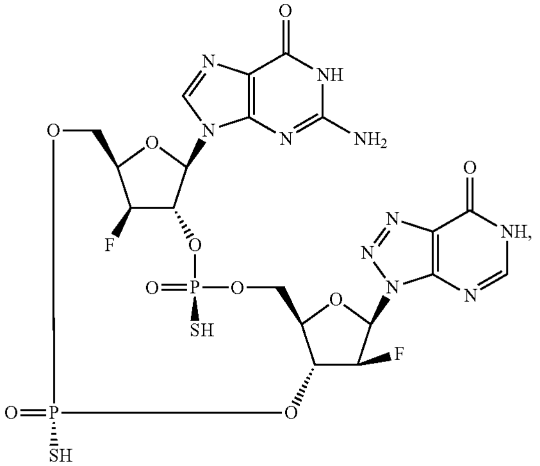

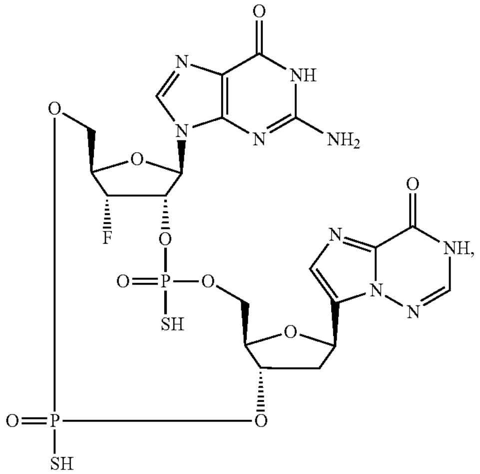

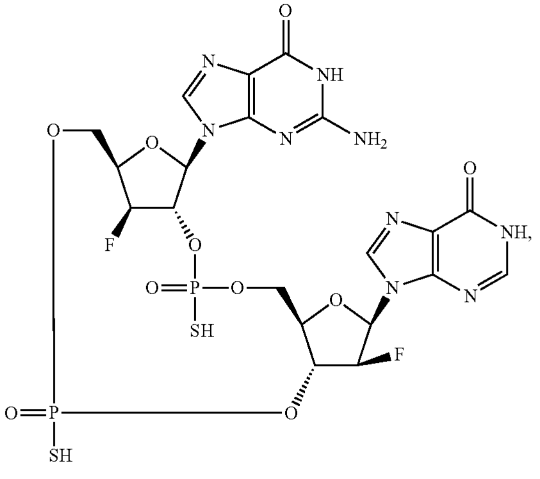

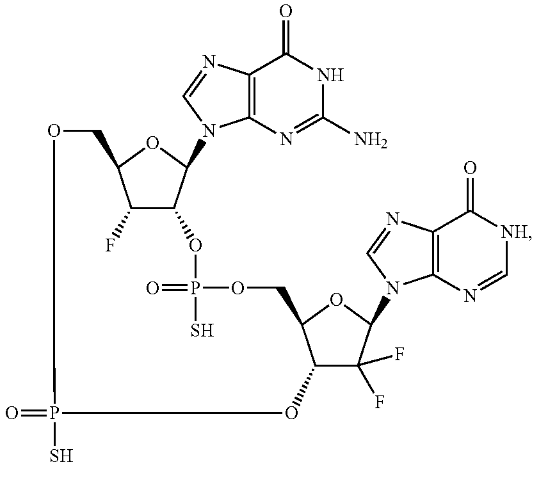

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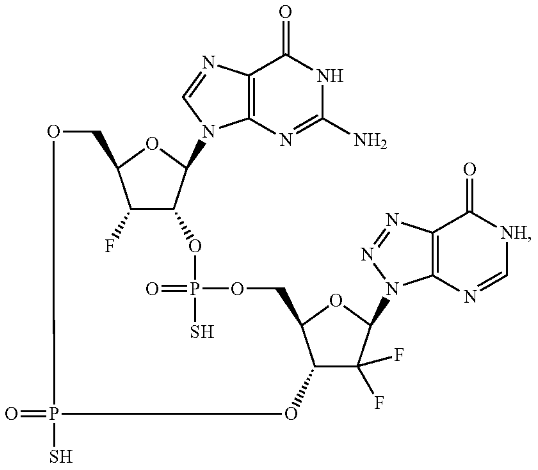

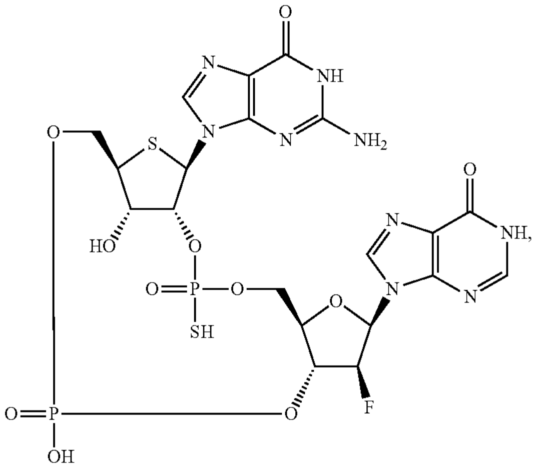

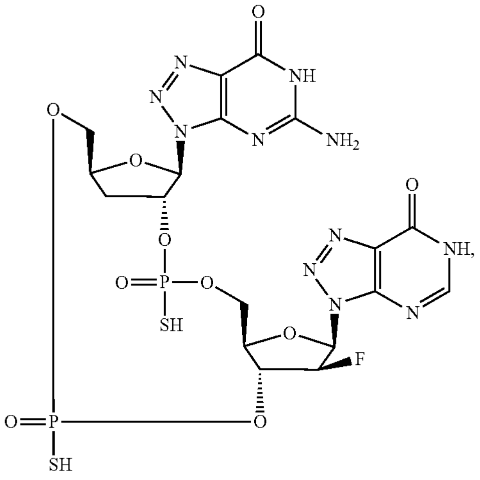

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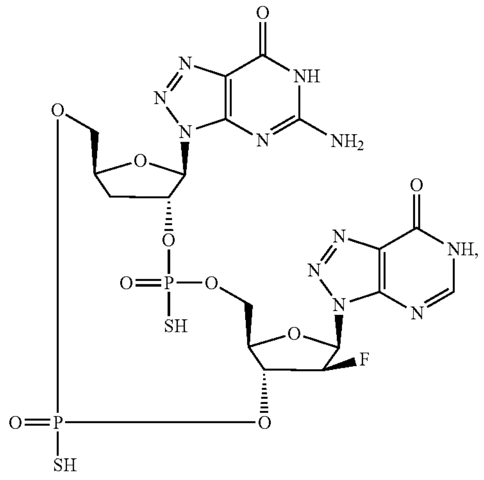

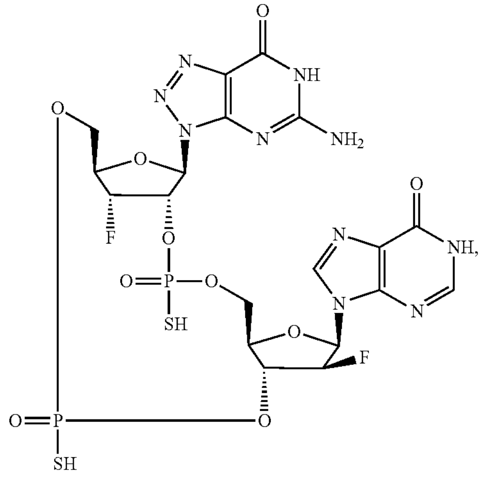

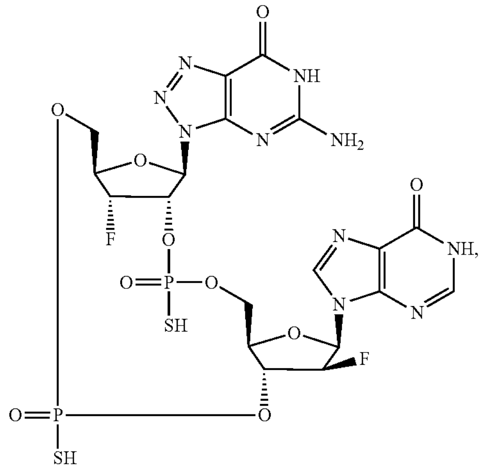

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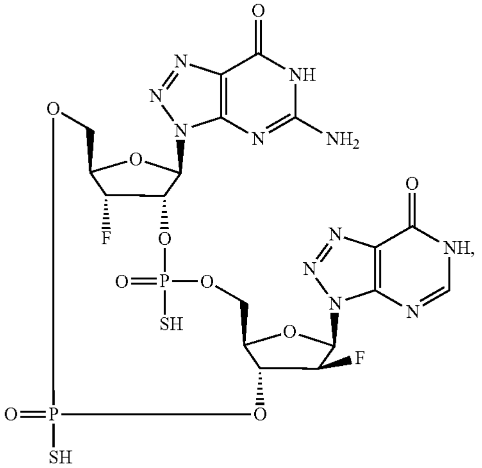

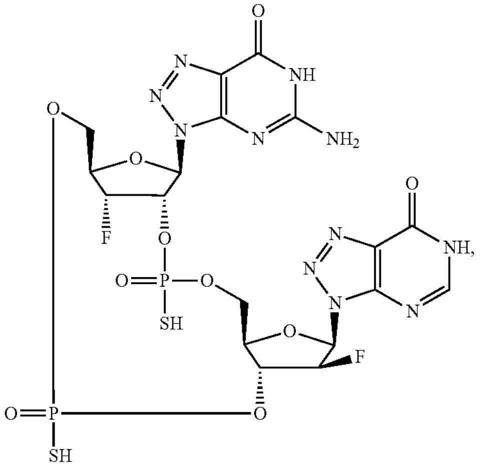

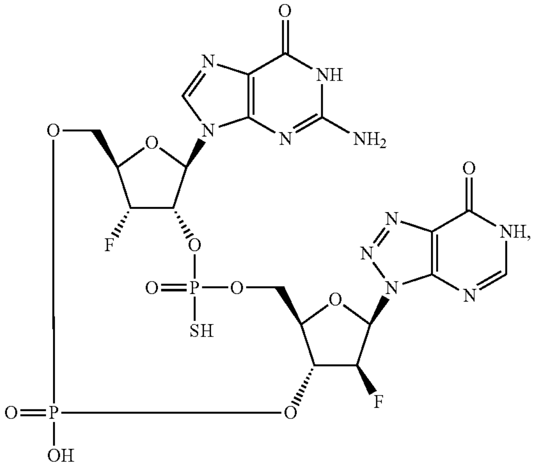

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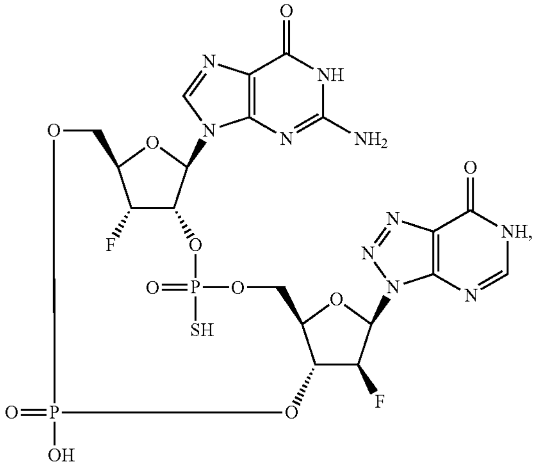

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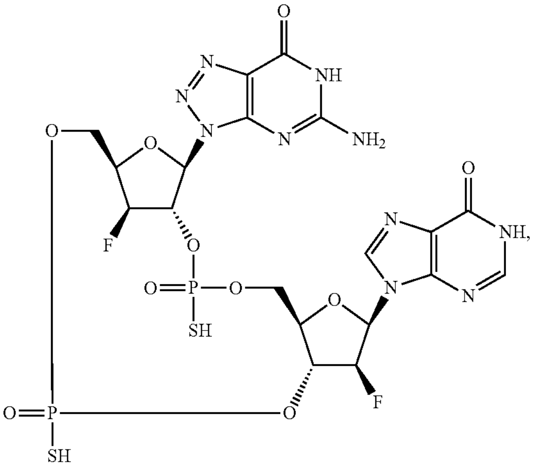
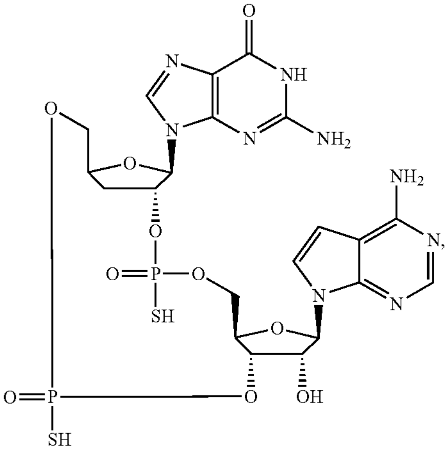


and pharmaceutically acceptable salts, hydrates, solvates, or prodrugs thereof. In particular aspects, the compound is selected from the group consisting of



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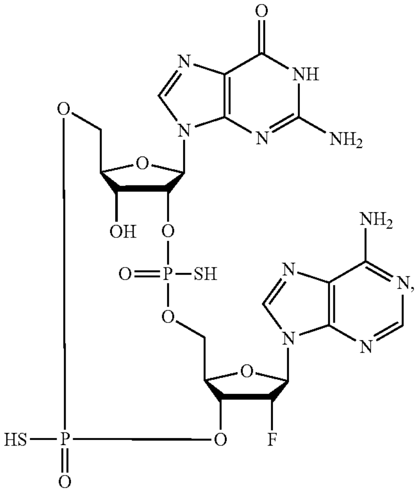

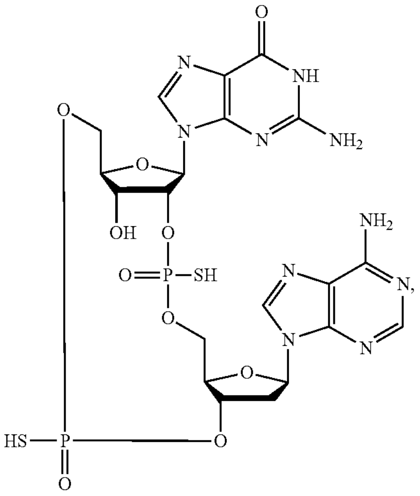

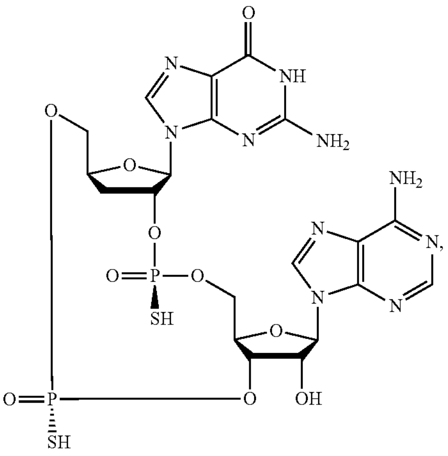

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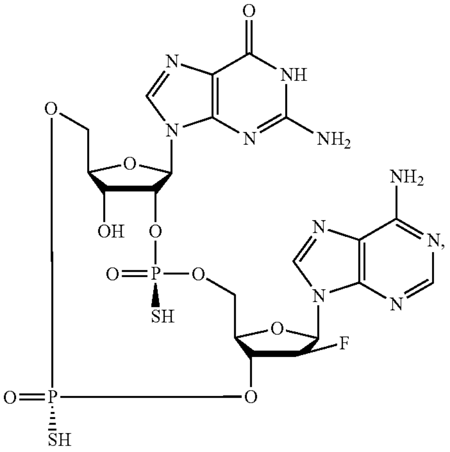

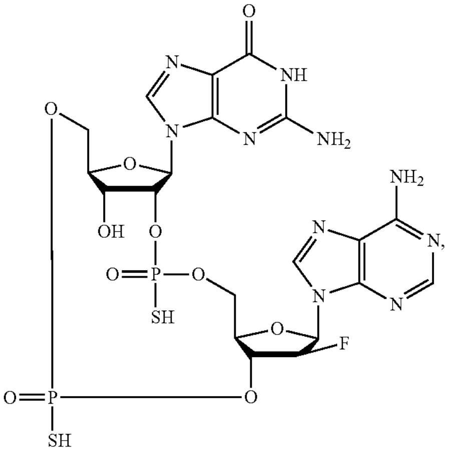

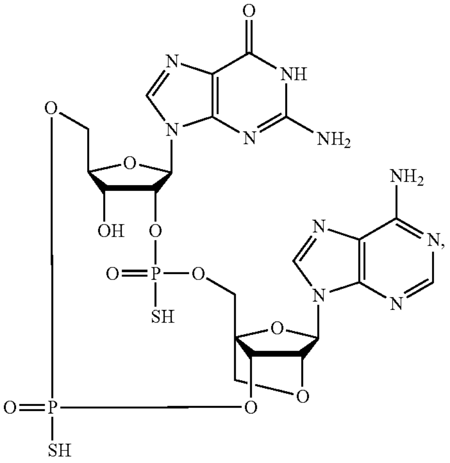

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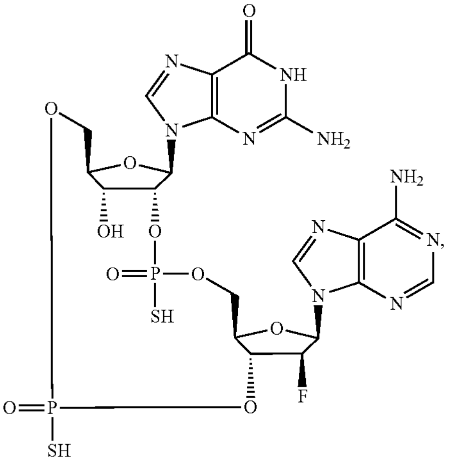

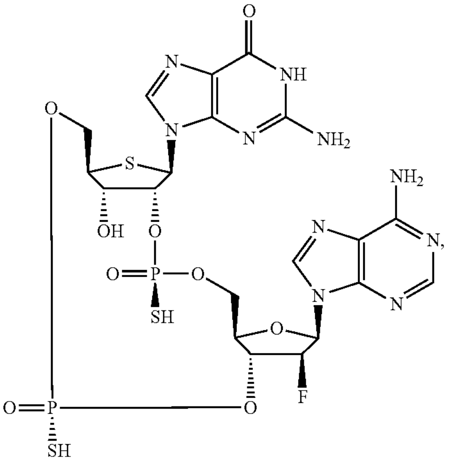

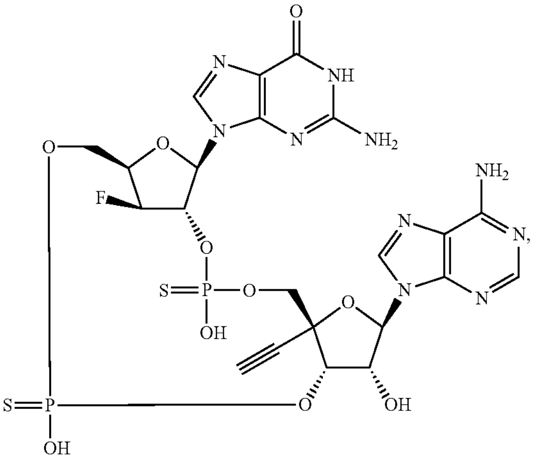

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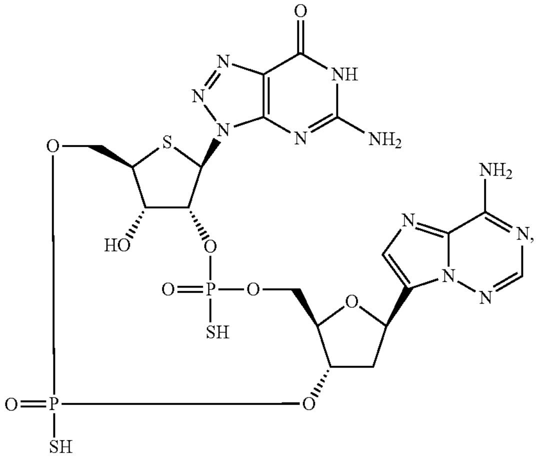

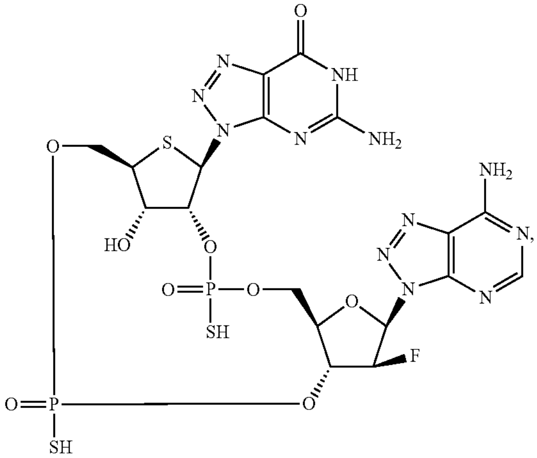

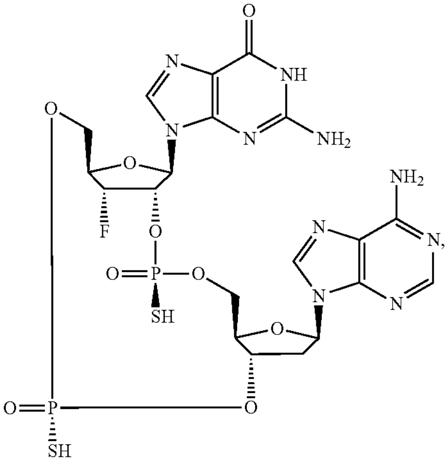

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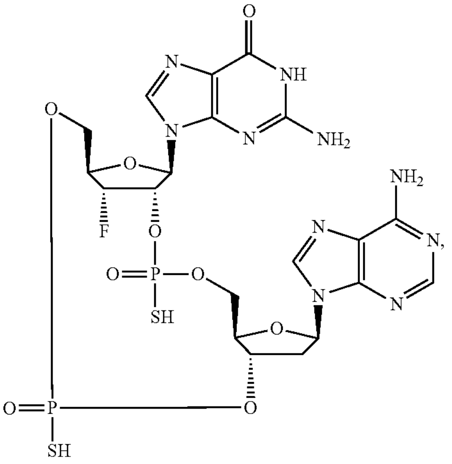

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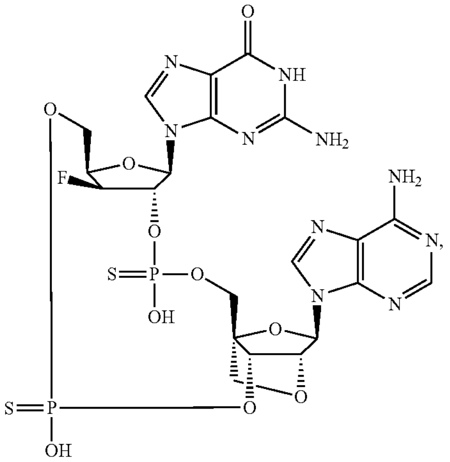

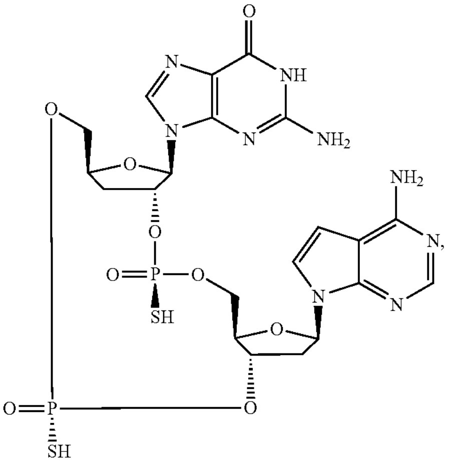

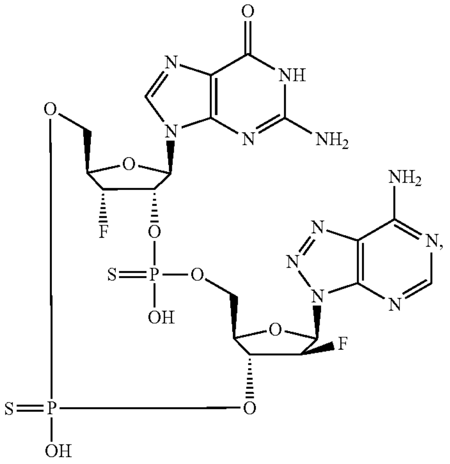

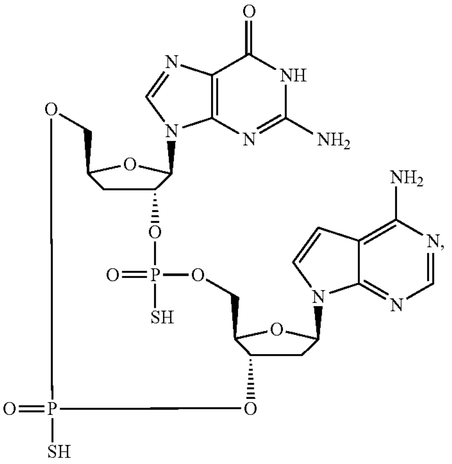

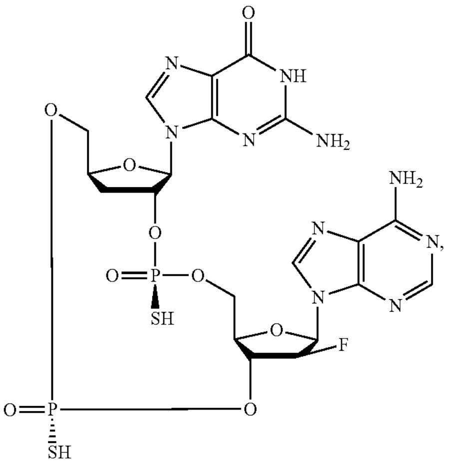

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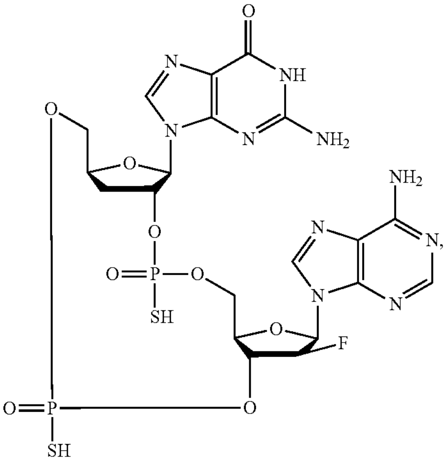

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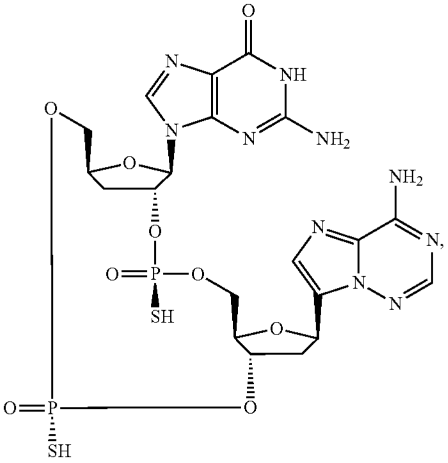

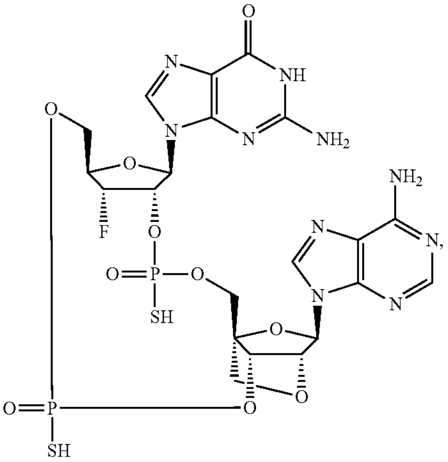

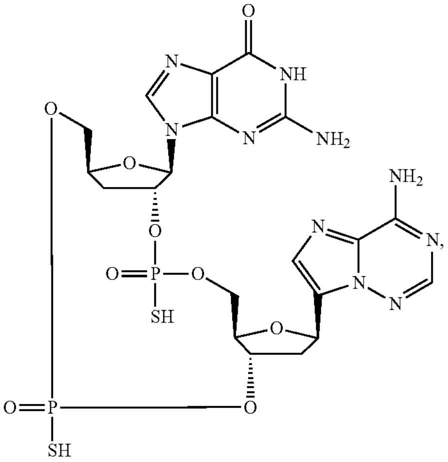

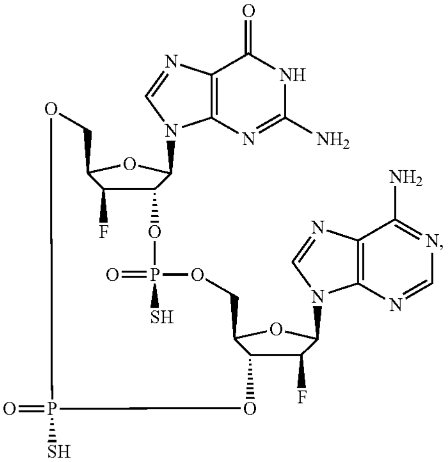

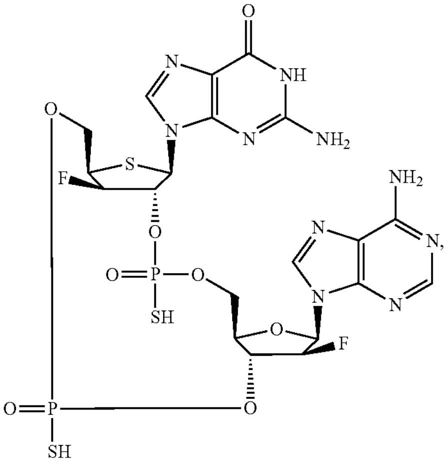

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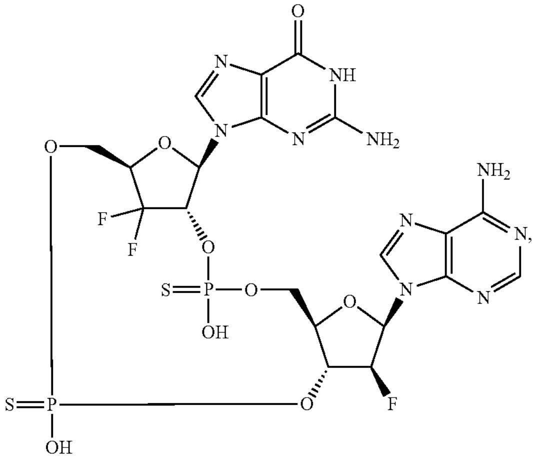

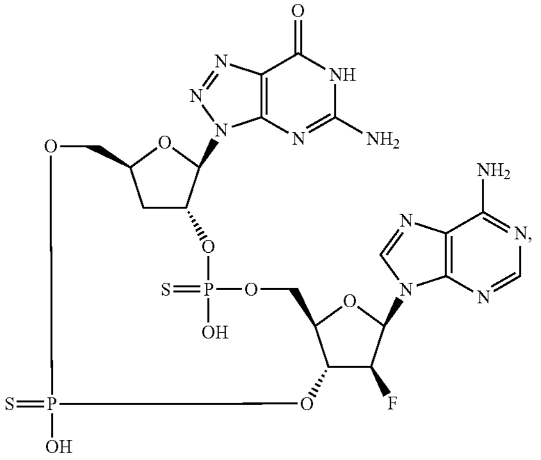

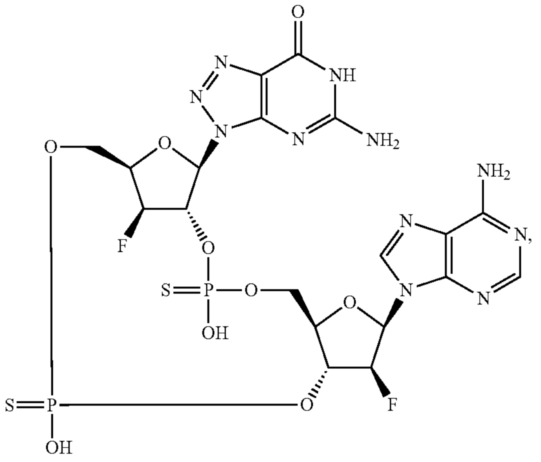

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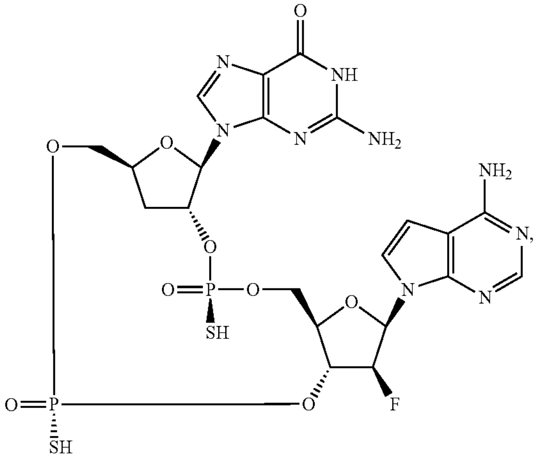

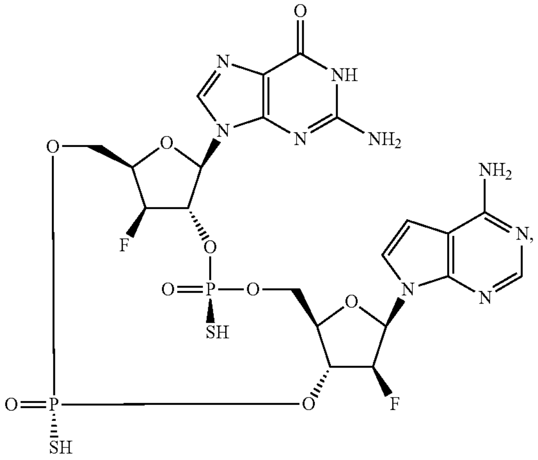

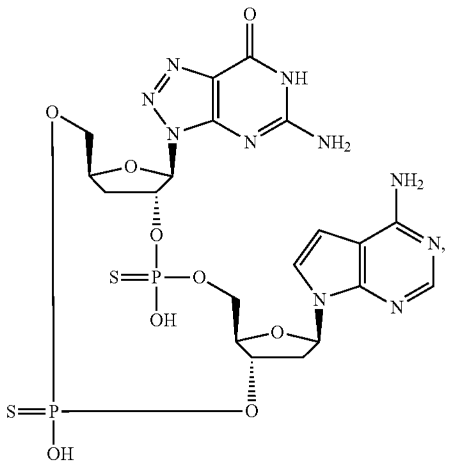

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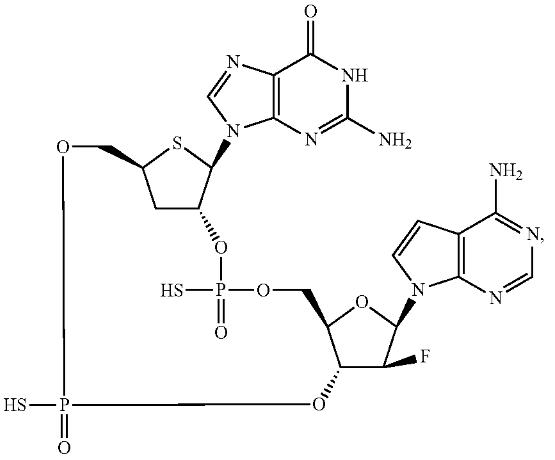

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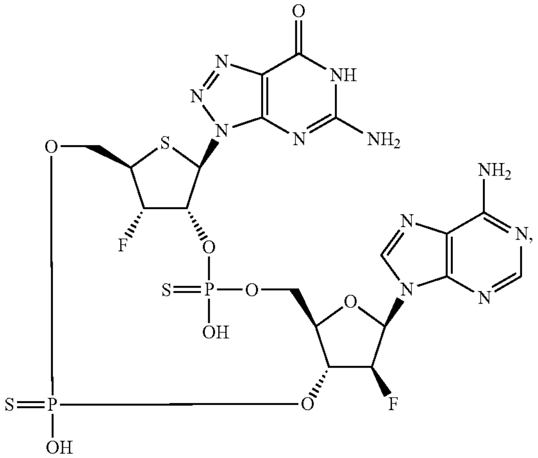

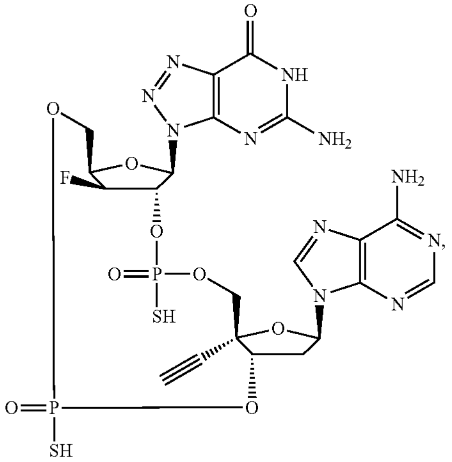

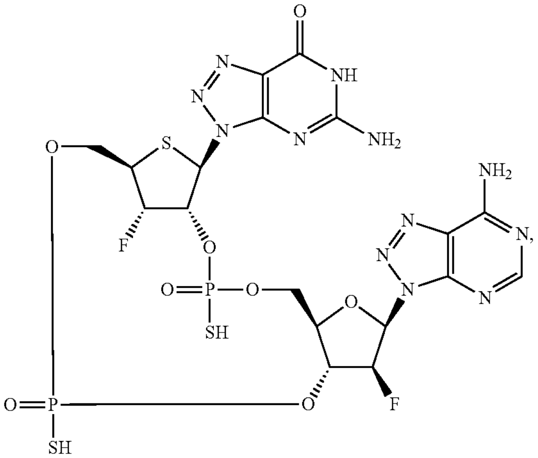

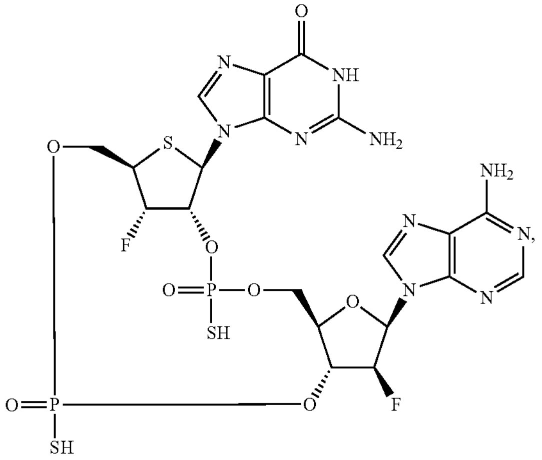

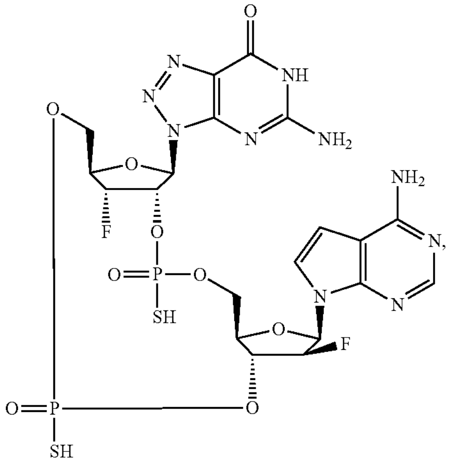

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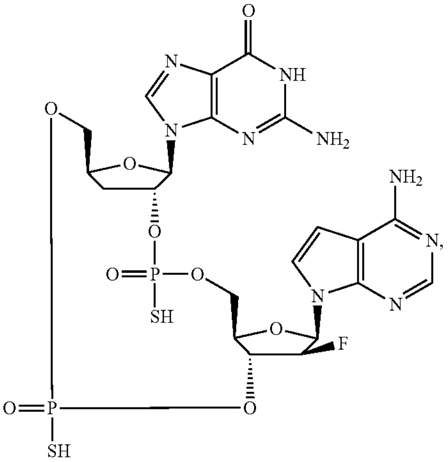

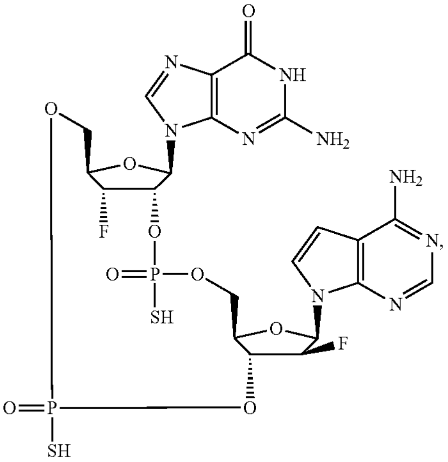

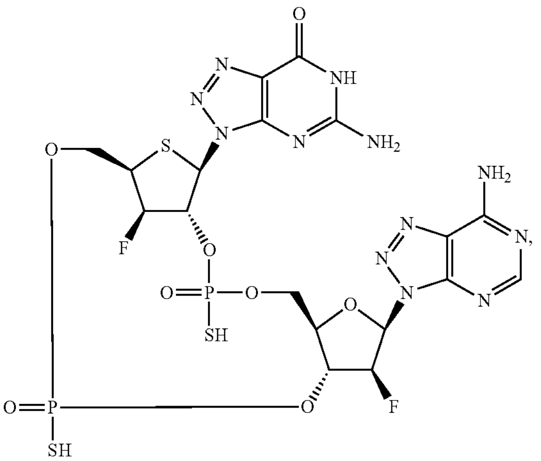

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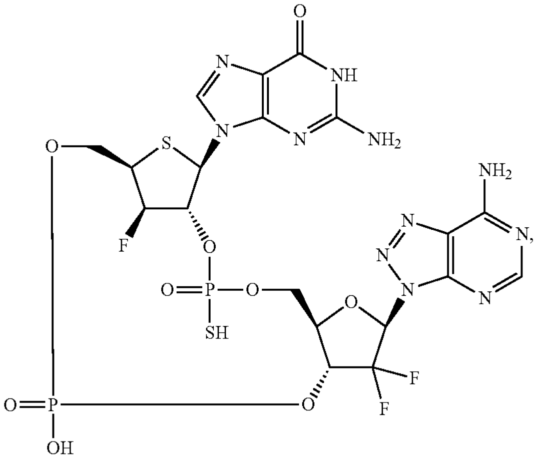

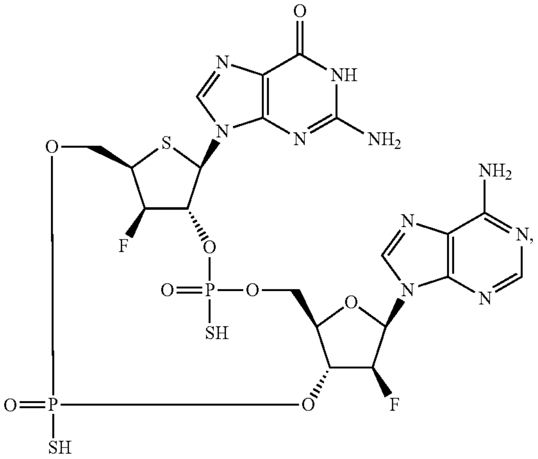

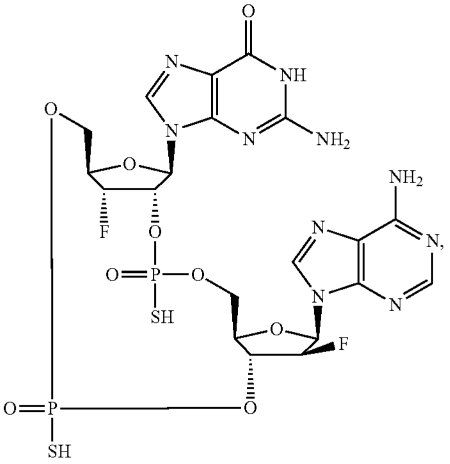

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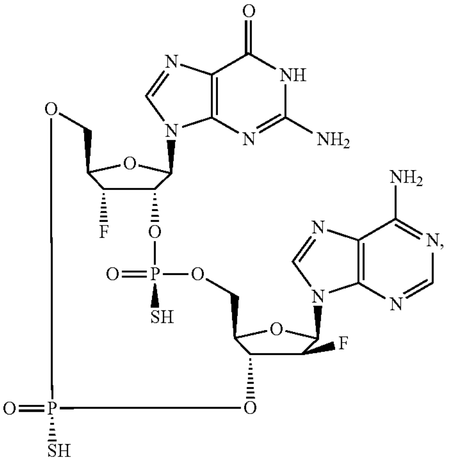

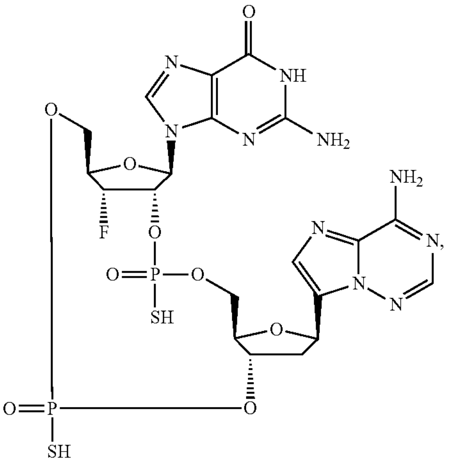

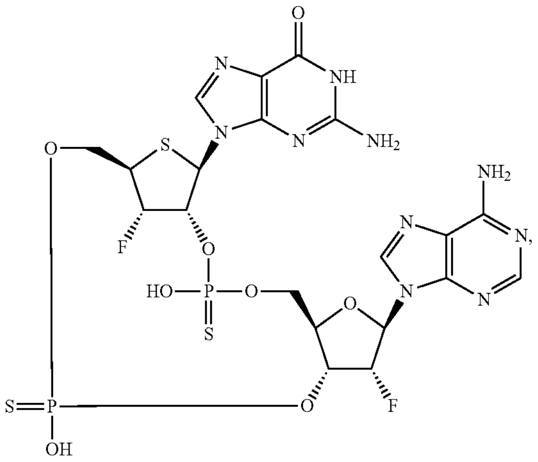

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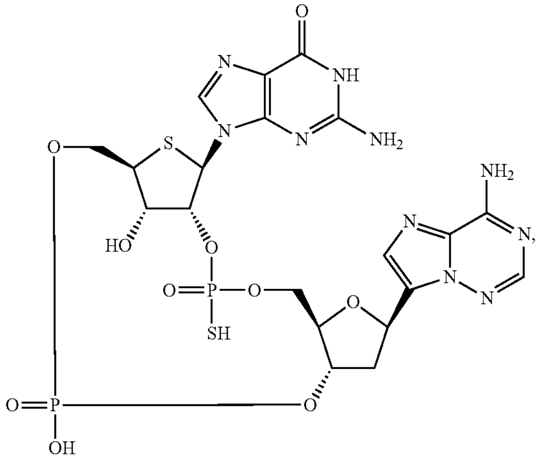

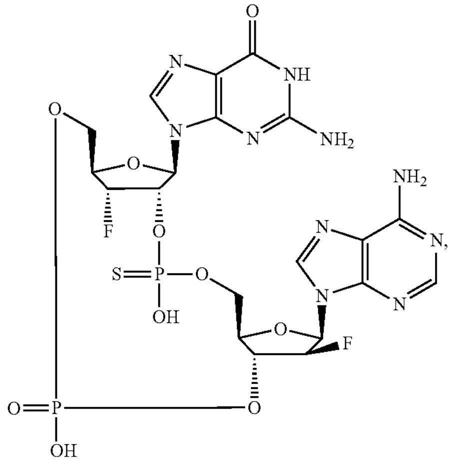

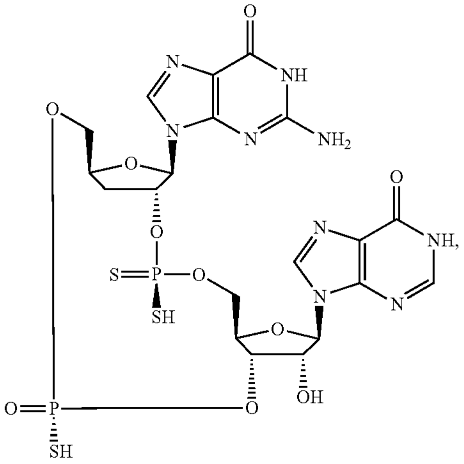

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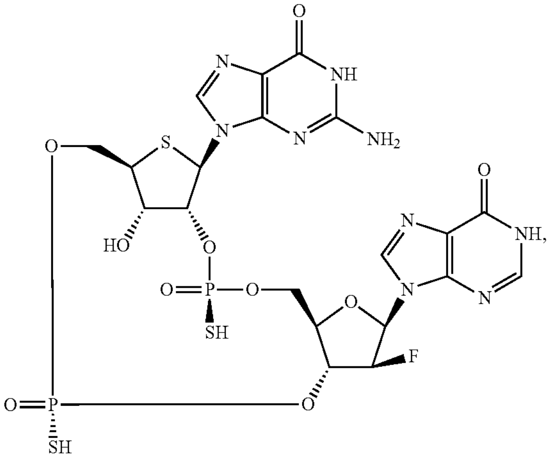

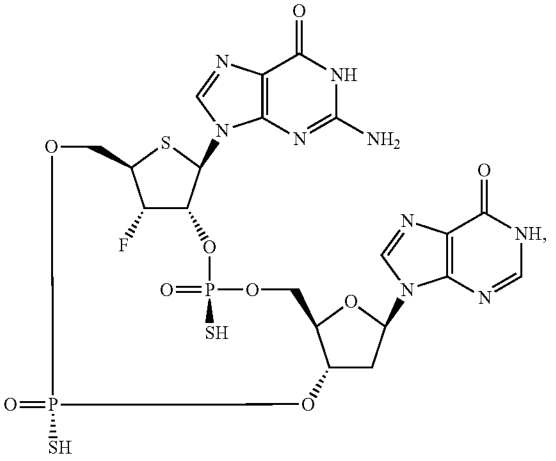

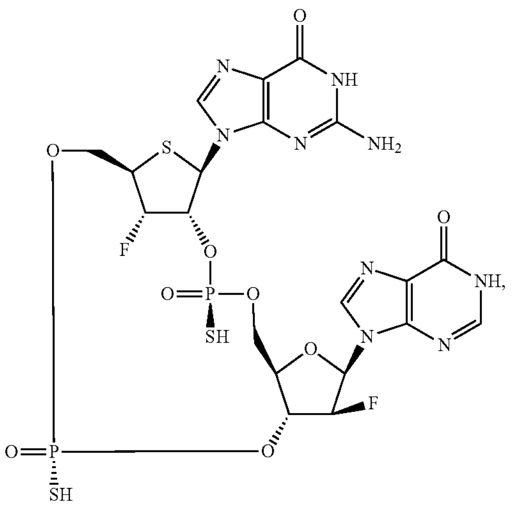

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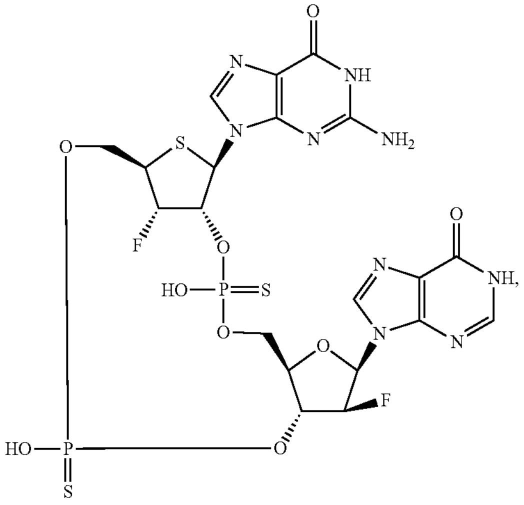

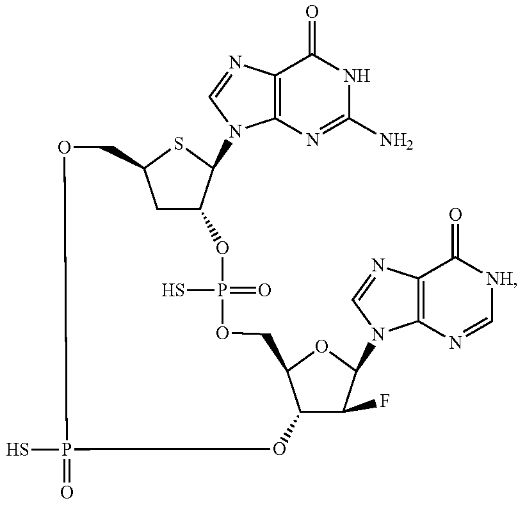

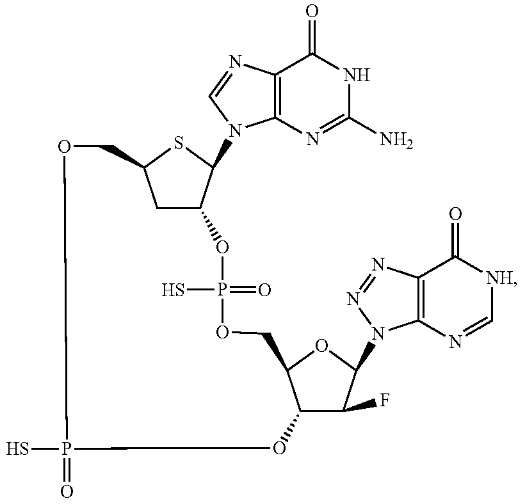

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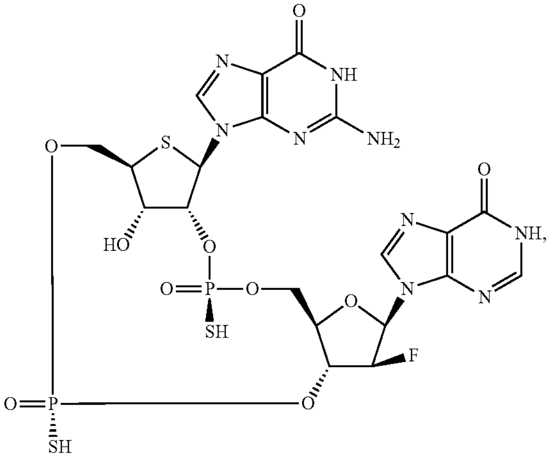

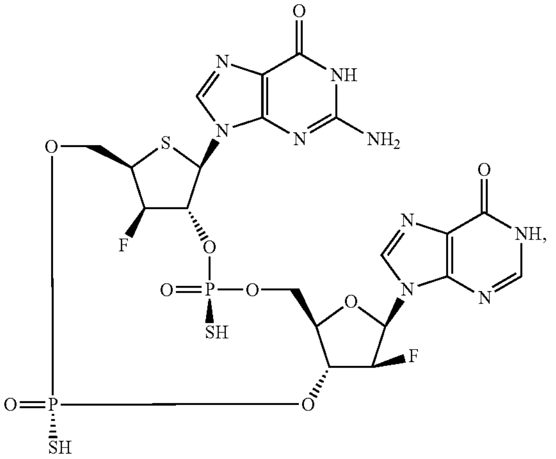

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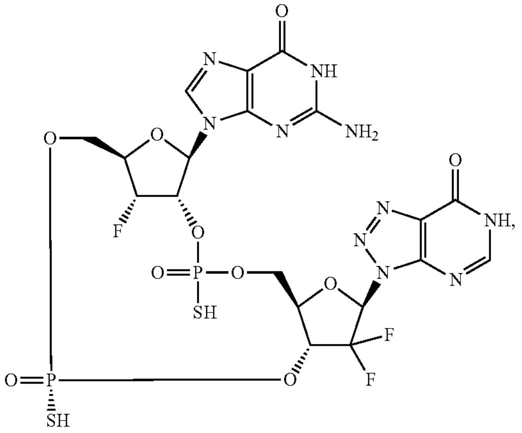

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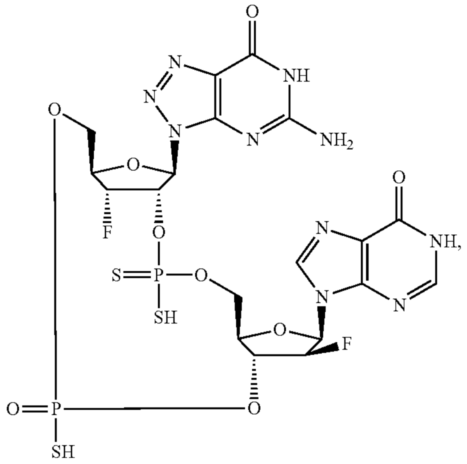
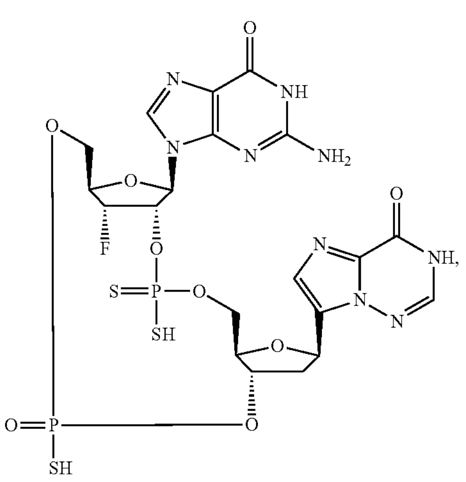
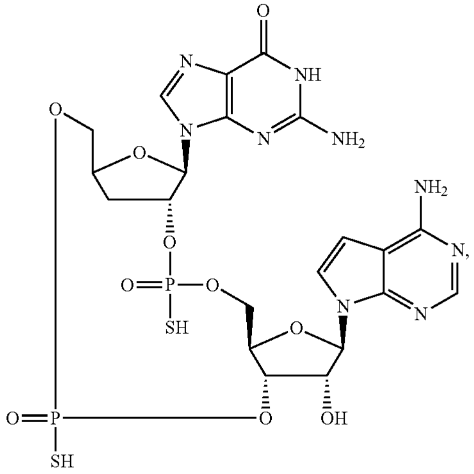


and pharmaceutically acceptable salts, hydrates, solvates, or prodrugs thereof. In more particular aspects of this embodiment, the compound is selected from the group consisting of





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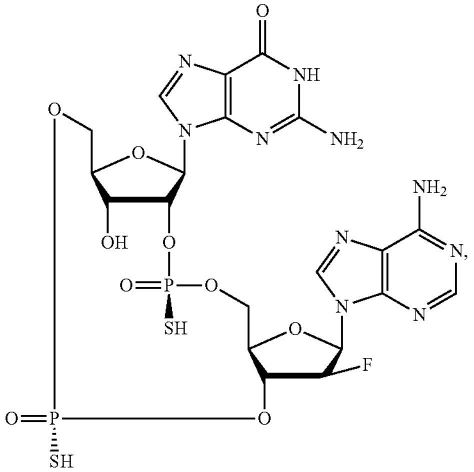

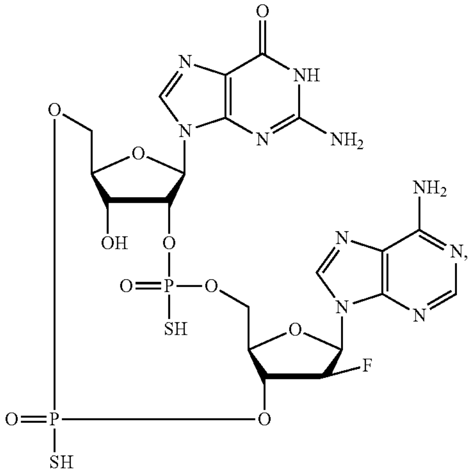

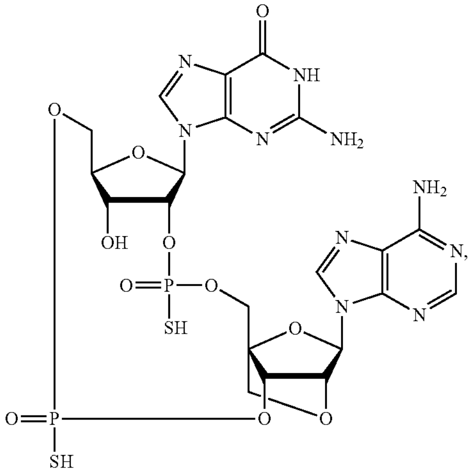

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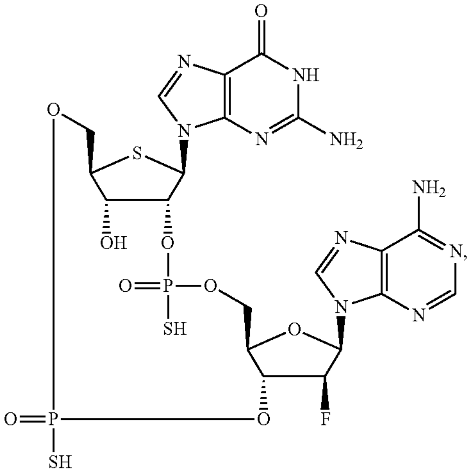

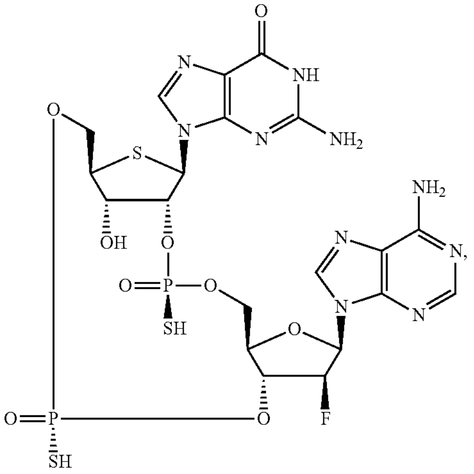

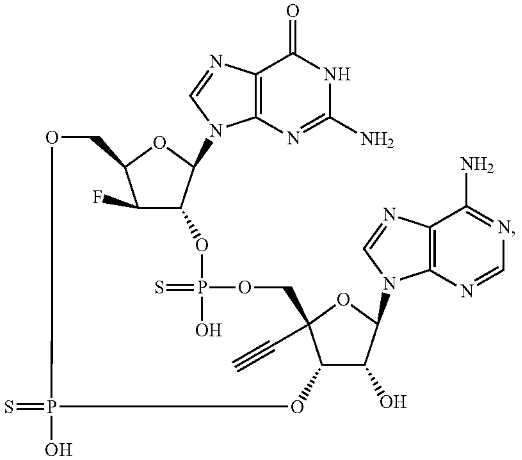

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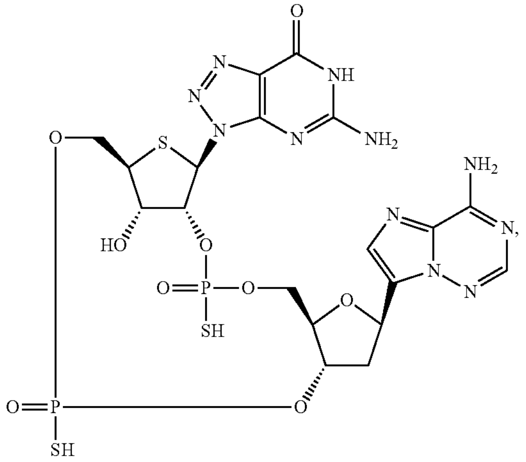

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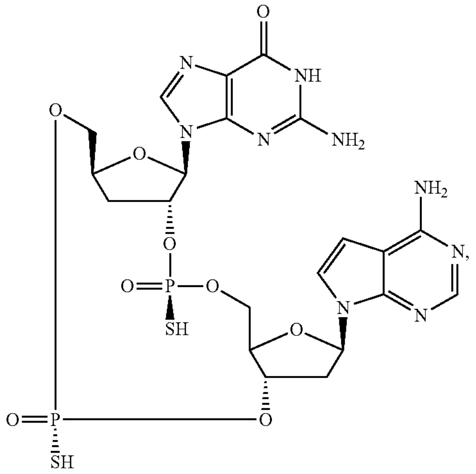

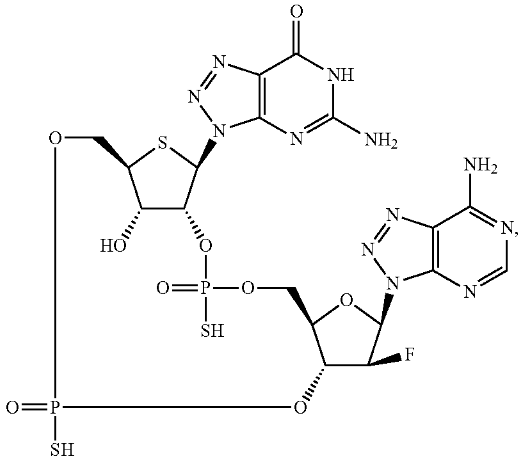

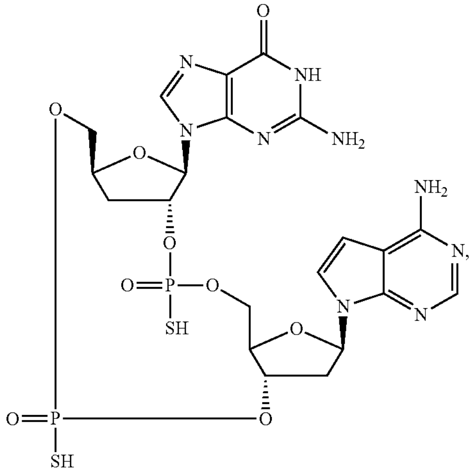

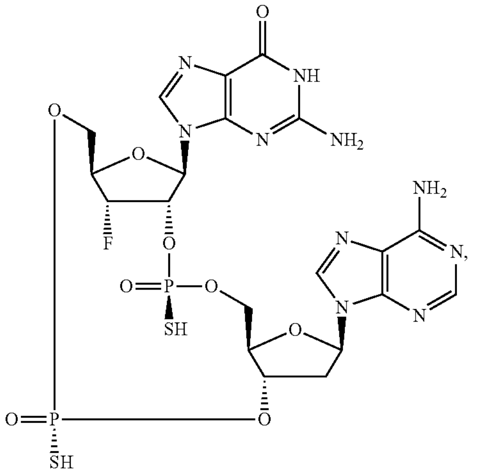

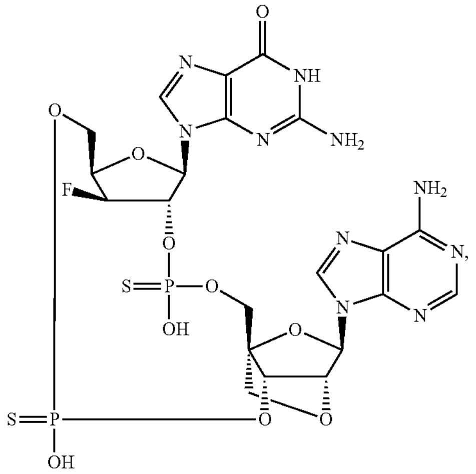

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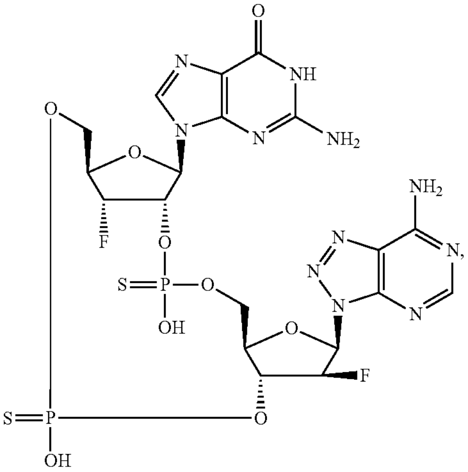

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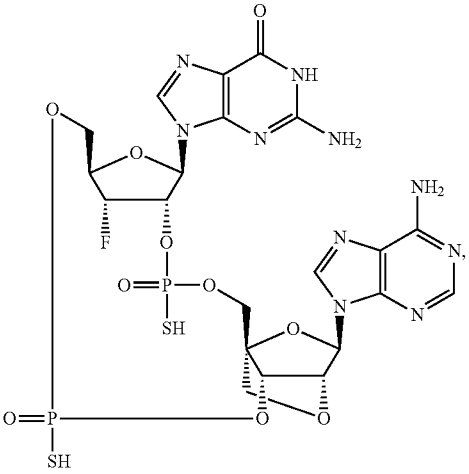

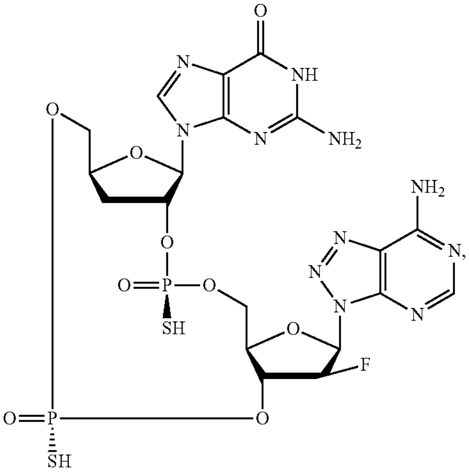

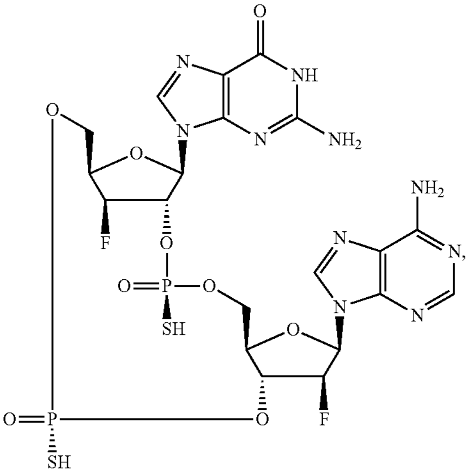

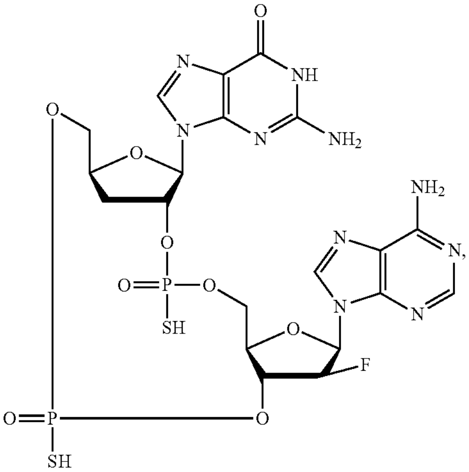

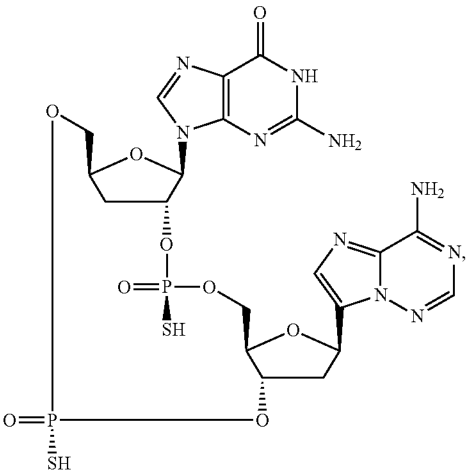

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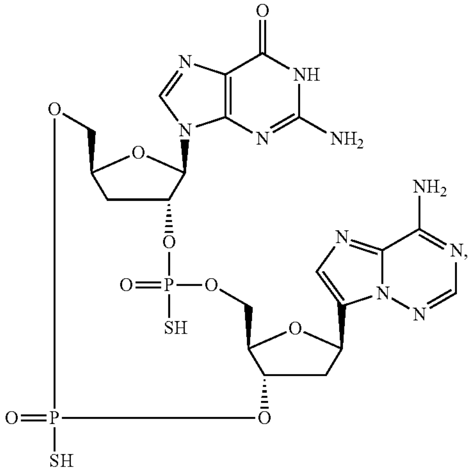

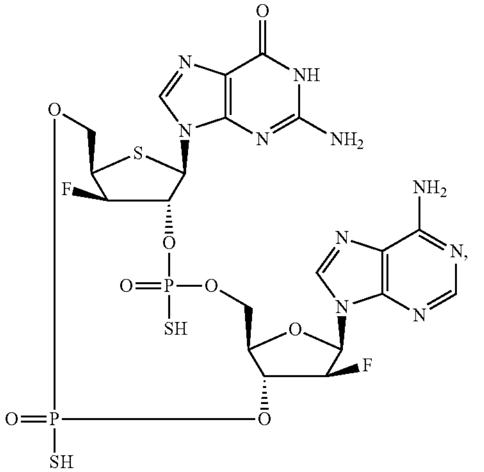

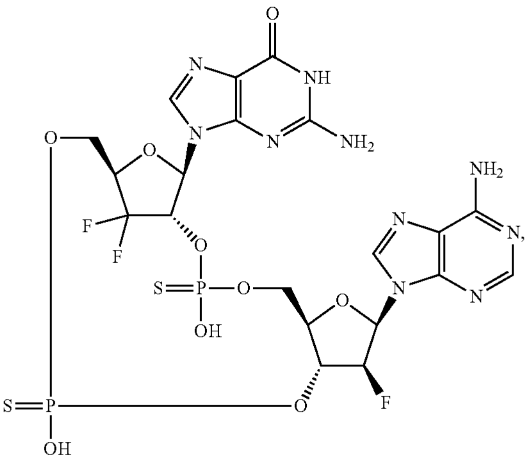

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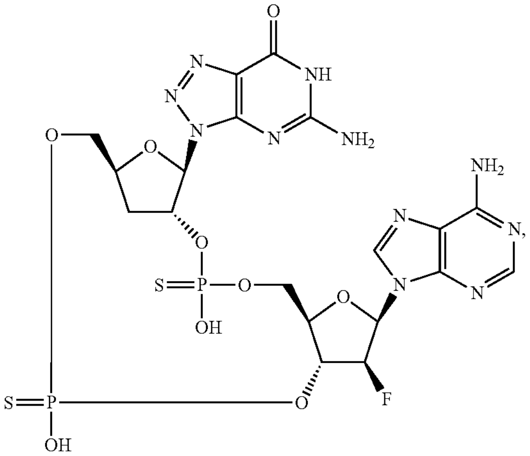

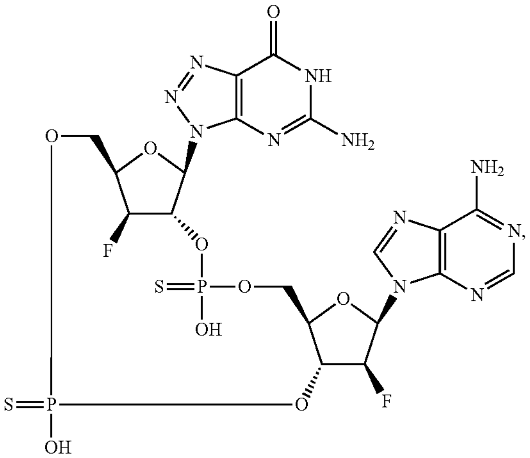

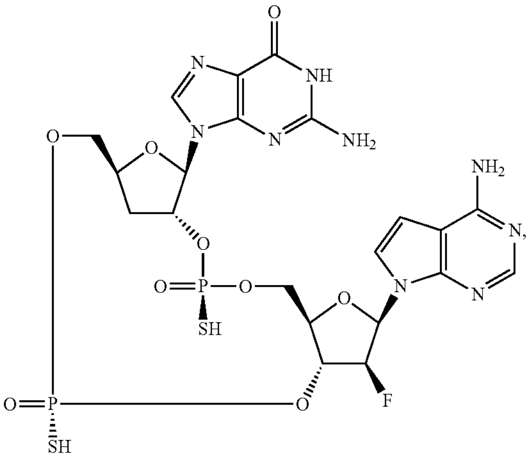

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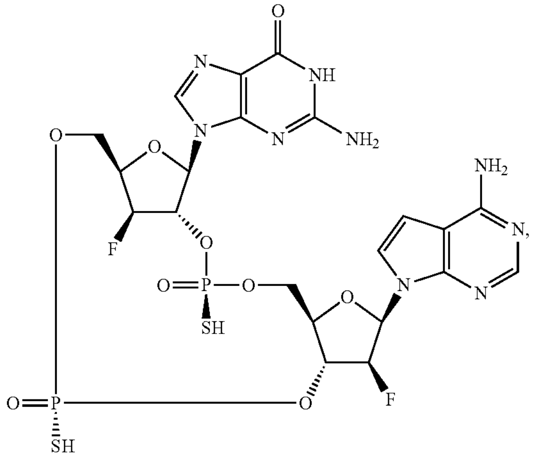

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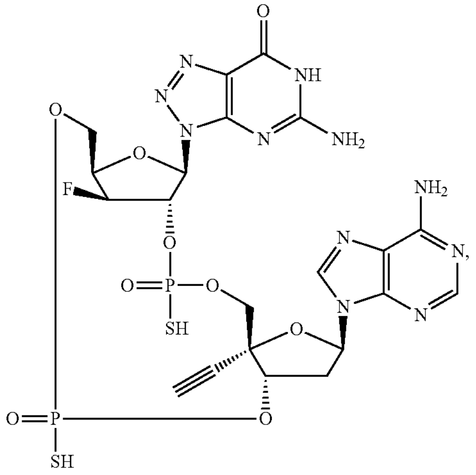

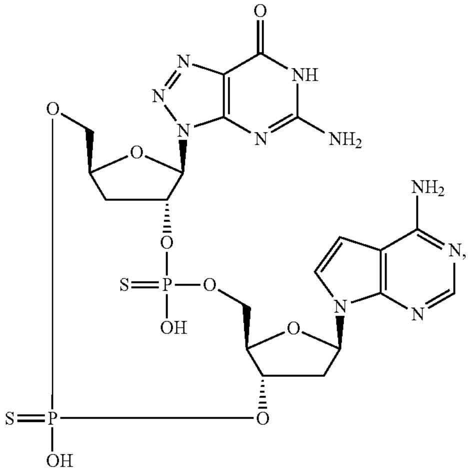

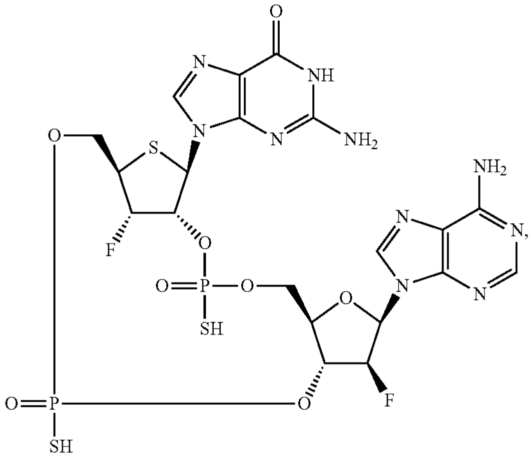

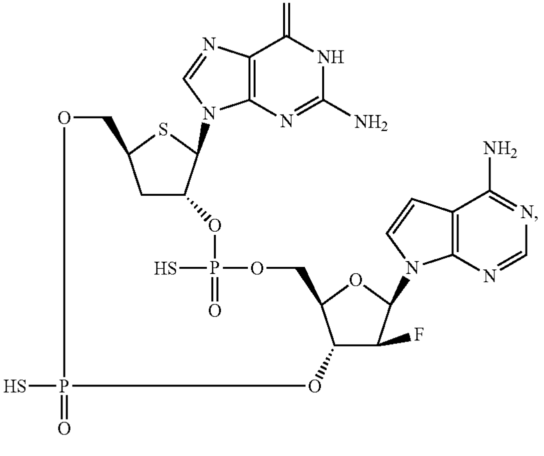

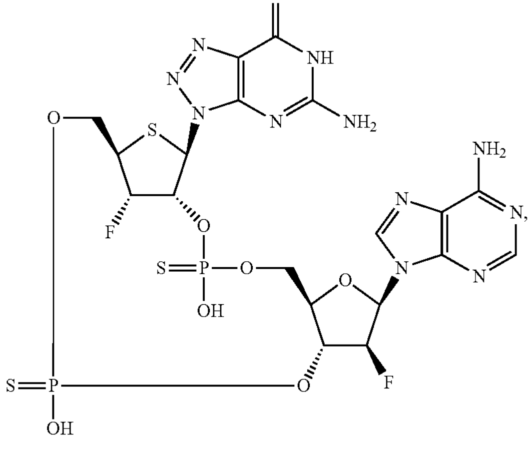

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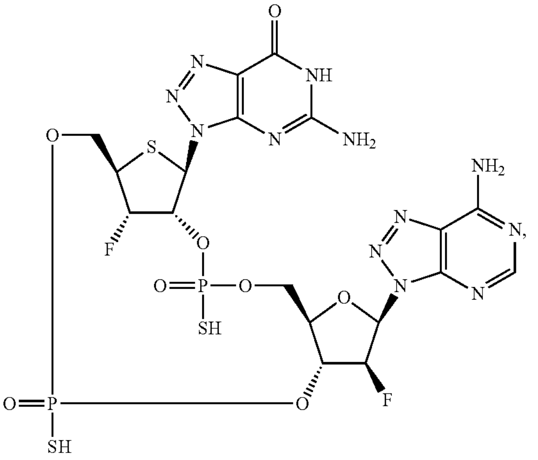

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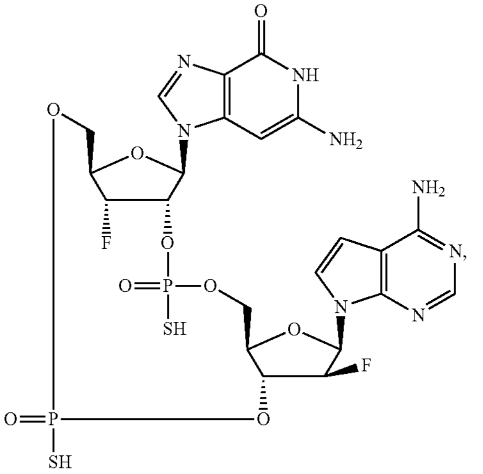

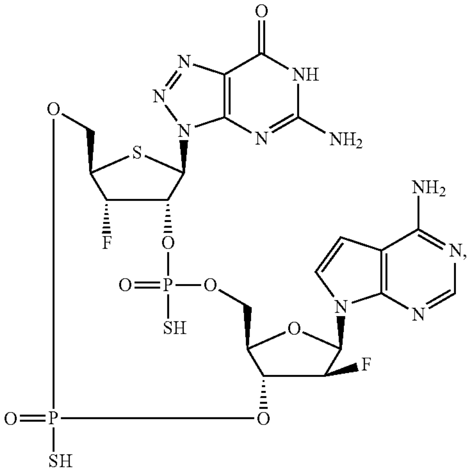

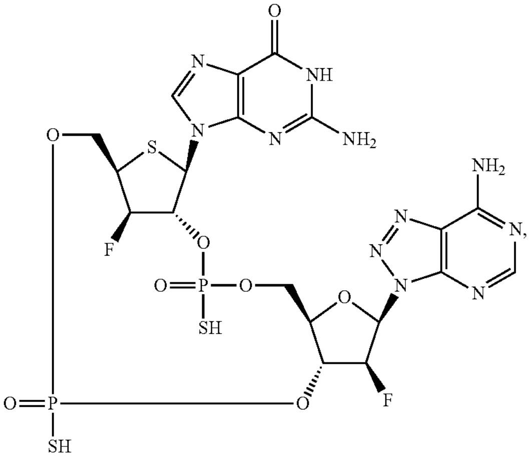

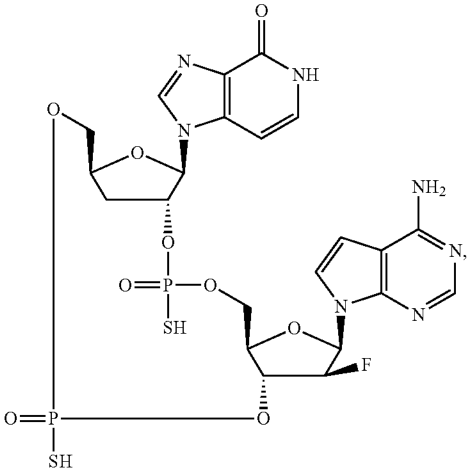

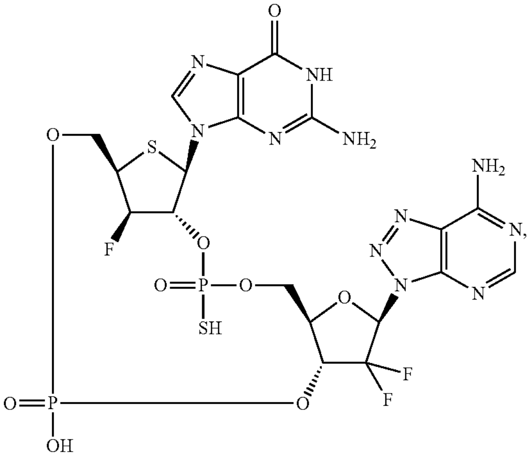

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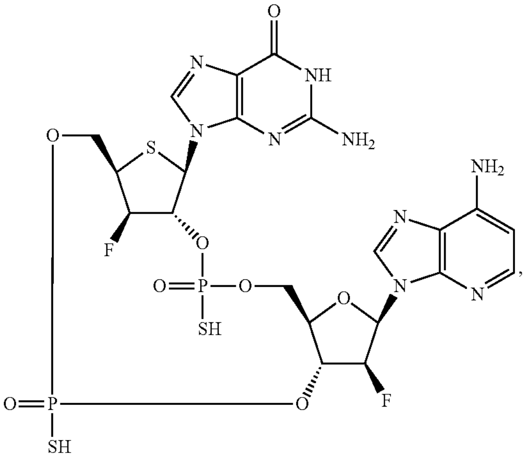

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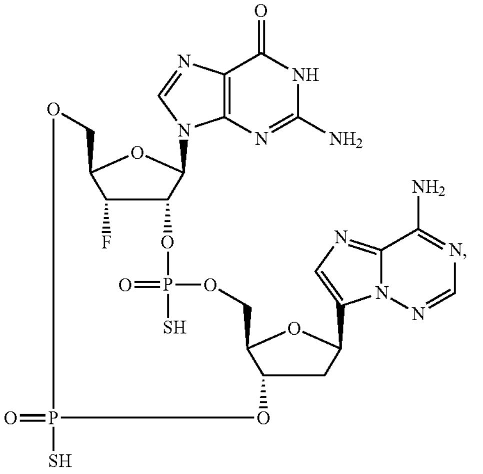

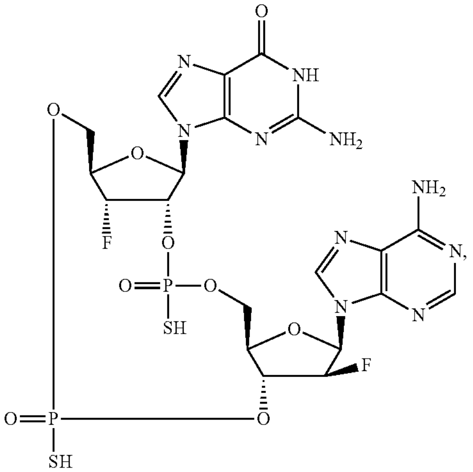

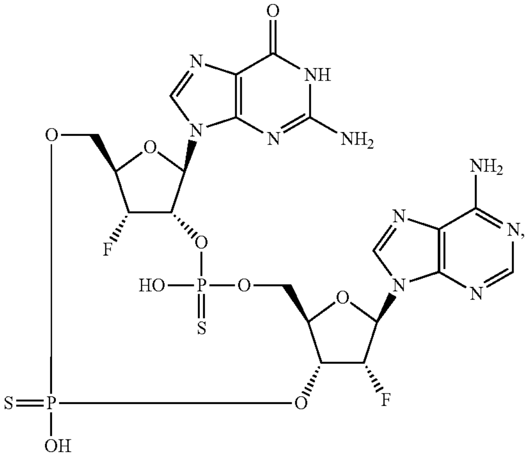

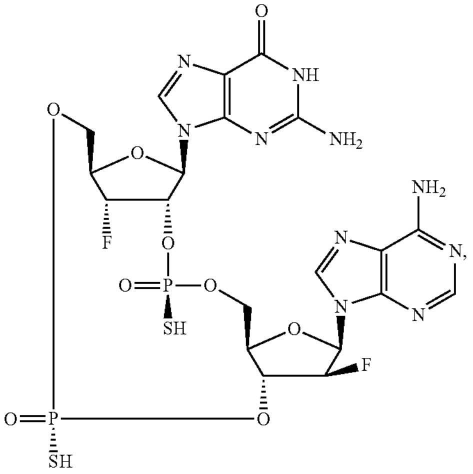

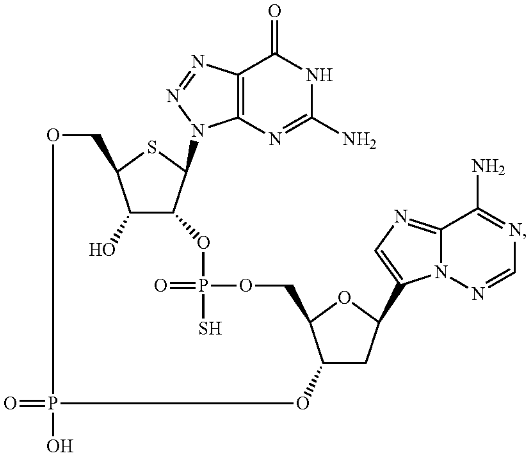

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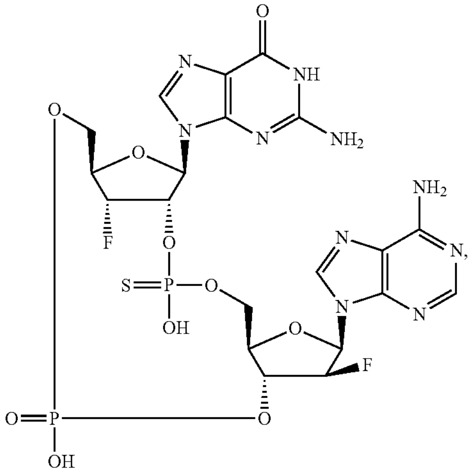

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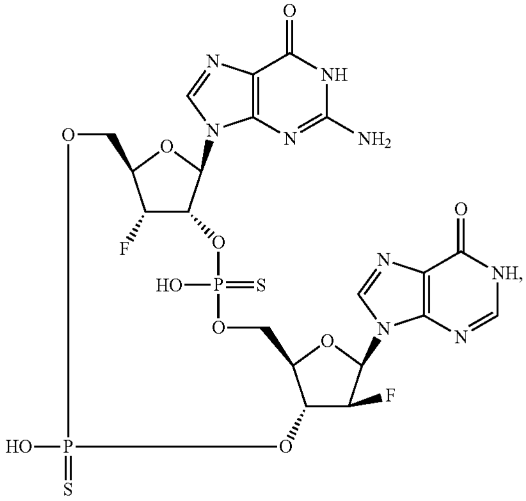

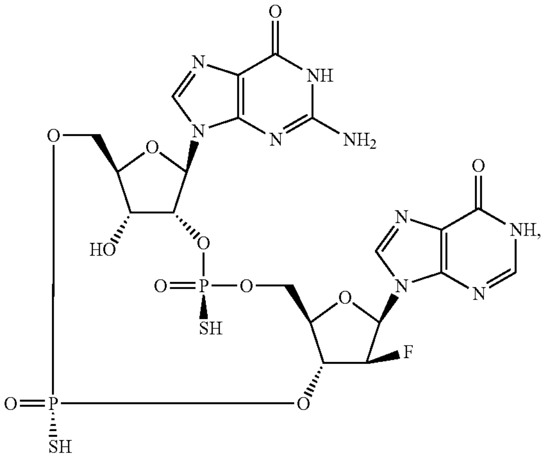

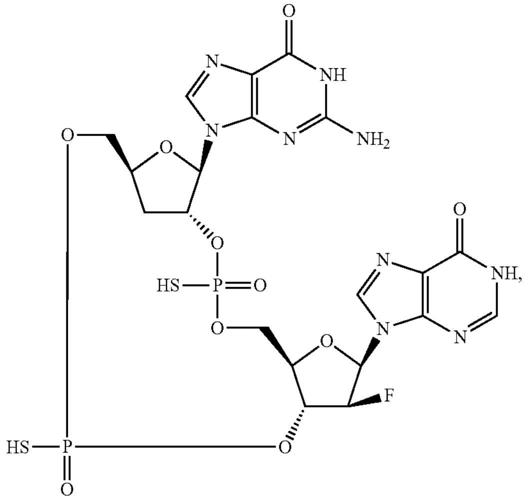

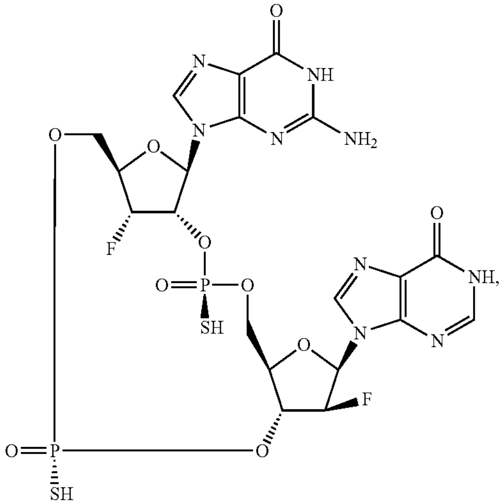

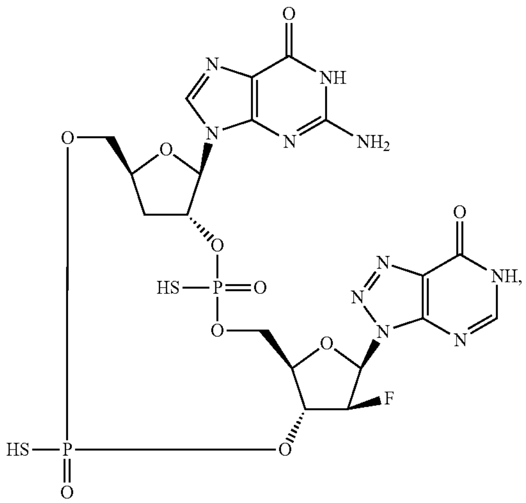

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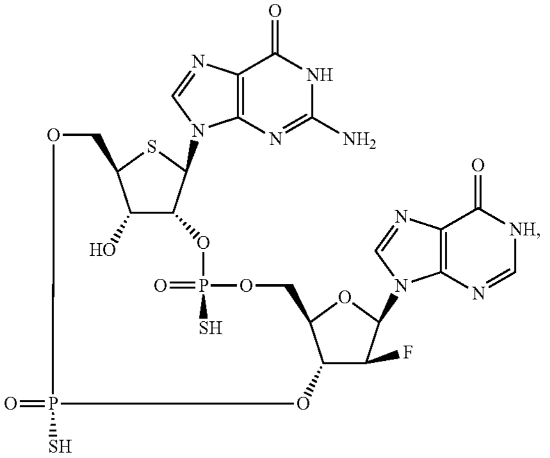

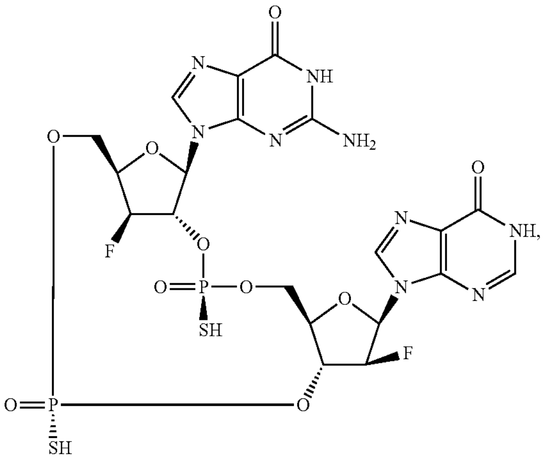

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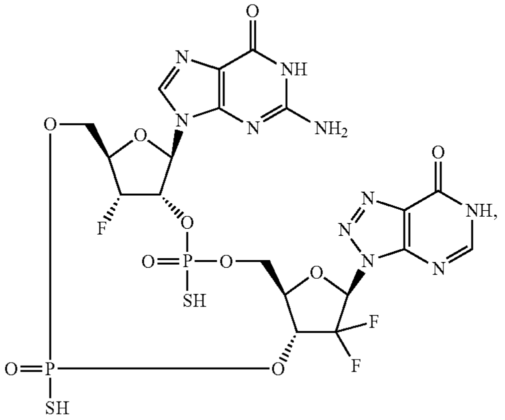

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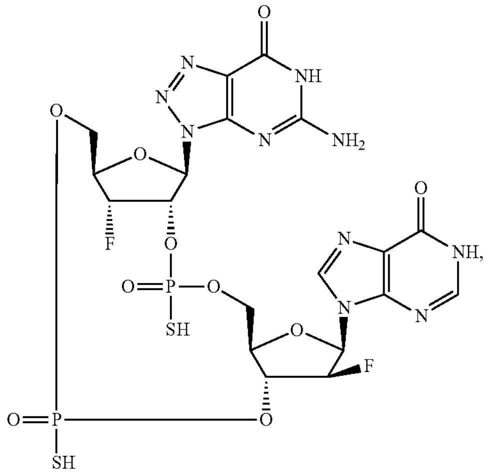
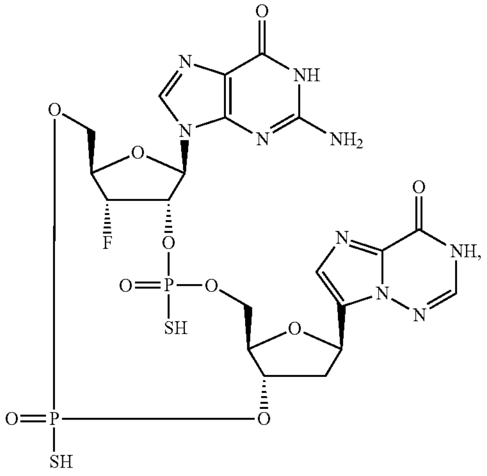
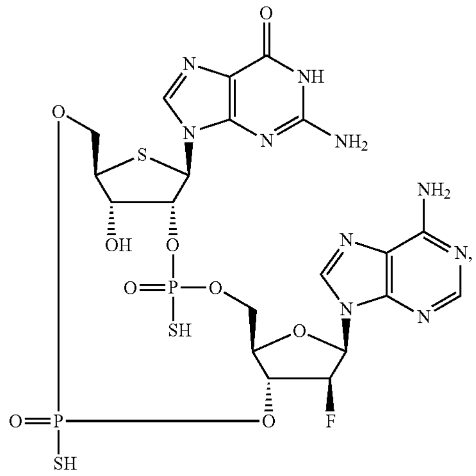


and pharmaceutically acceptable salts, hydrates, solvates, or prodrugs thereof. In still more particular aspects, the compound is selected from the group consisting of





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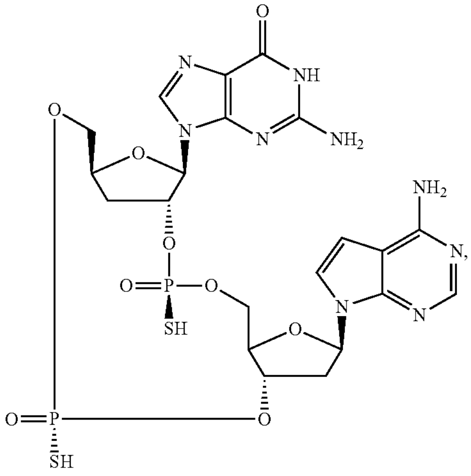

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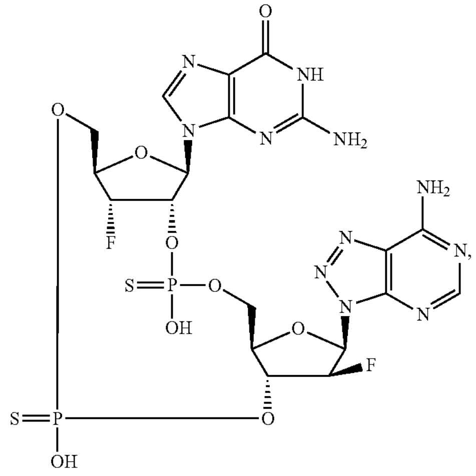

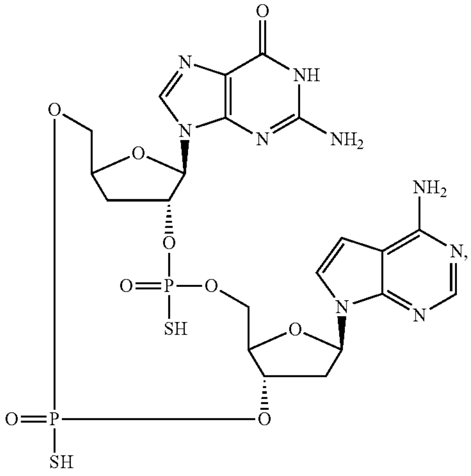

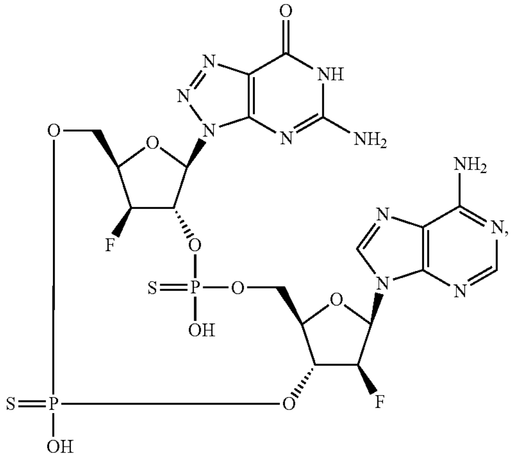

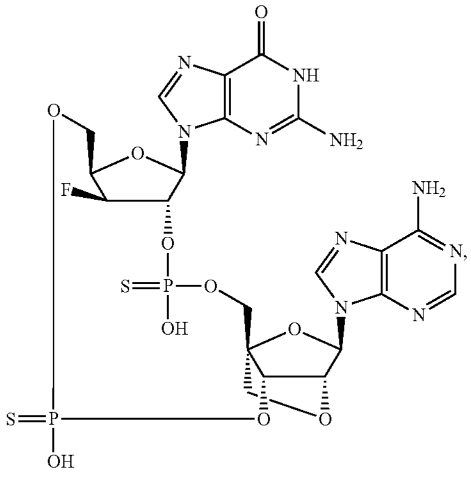

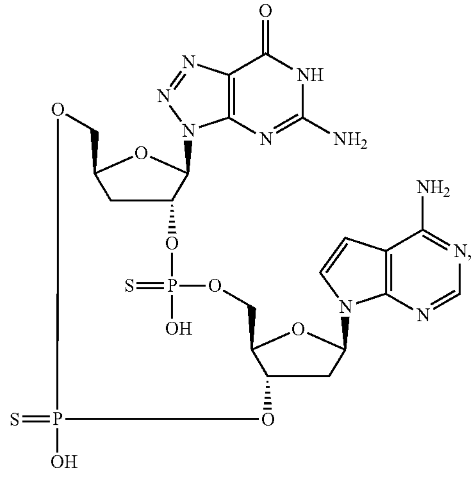

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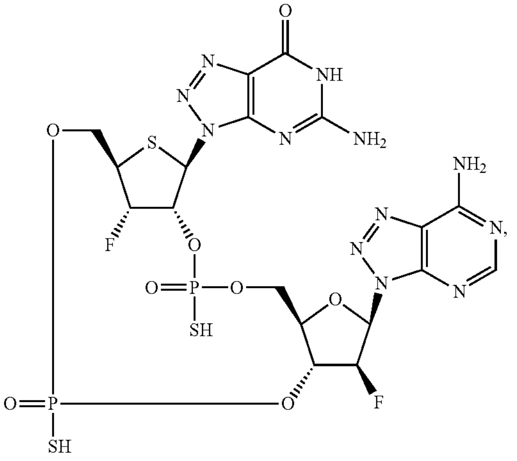

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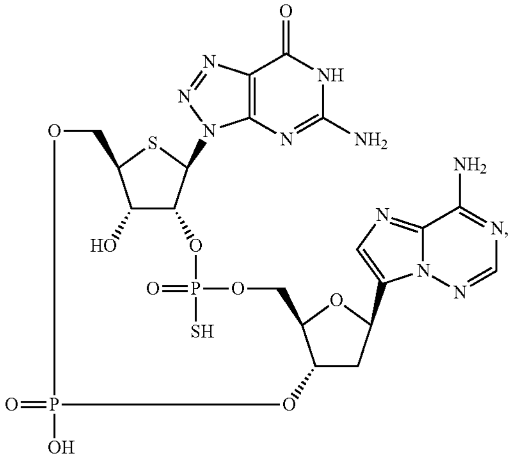

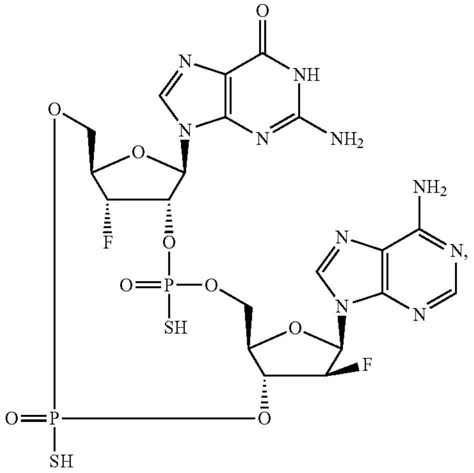

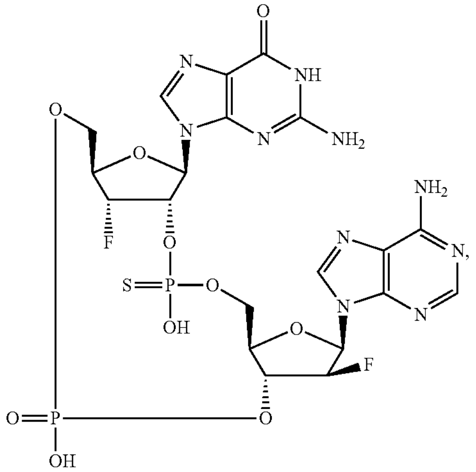

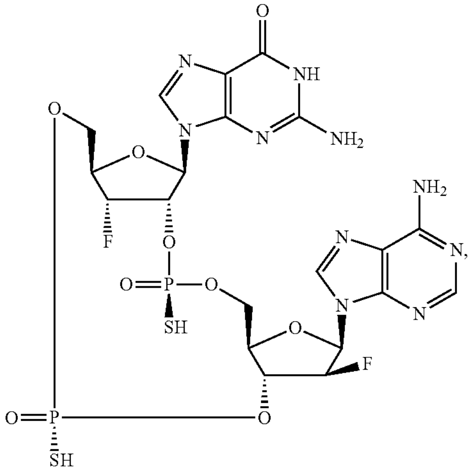

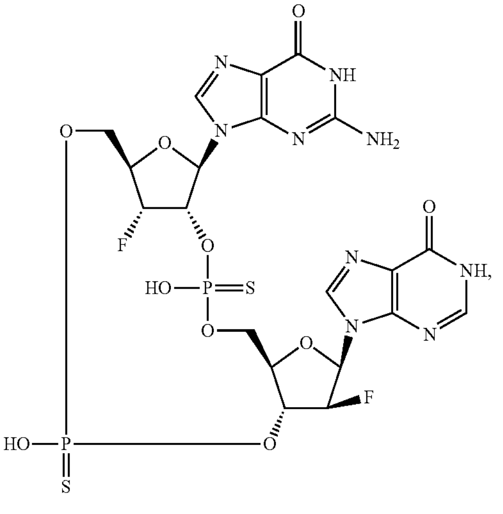

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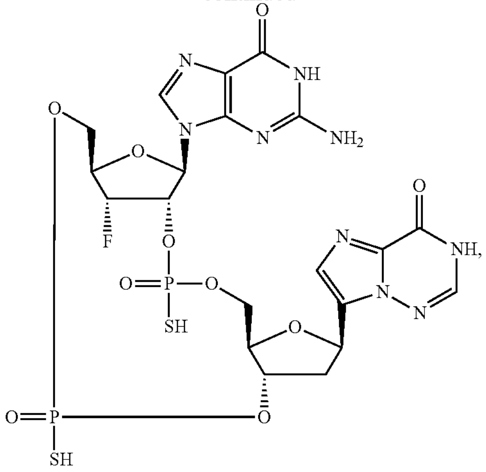


and pharmaceutically acceptable salts, hydrates, solvates, or prodrugs thereof.

[0097] In another embodiment, for the compounds of general formula (I), compounds of general formula (I') and compounds of general formula (I"), 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}, R^9, and R^{10} are each selected independently from each other.

[0098] In another embodiment of the disclosure, the compound of the disclosure is selected from the exemplary species depicted in Examples 1 through 348 shown below.

[0099] Other embodiments of the present disclosure include the following:

[0100] (a) A pharmaceutical composition comprising an effective amount of a compound of general formula (I) or a compound of general formula (I'), or a compound of general formula (I"), or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, and a pharmaceutically acceptable carrier.

[0101] (b) The pharmaceutical composition of (a), further comprising a second therapeutic 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.

[0102] (c) A pharmaceutical combination that is (i) a compound of general formula (I) or a compound of general formula (I'), or a compound of general formula (I"), or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, and (ii) a second therapeutic 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 a compound of general formula (I) or compound of general formula (I'), or compound of general formula (I"), or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, and the second therapeutic agent are each employed in an amount that renders the combination effective for inducing an immune response in a patient.

[0103] (e) A method of inducing an immune response in a patient, which comprises administering to the subject an effective amount of a compound of general formula (I) or a compound of general formula (I'), or a compound of general formula (I"), or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof.

[0104] (f) A method of inducing an immune response in a patient, which comprises administering to the subject an effective amount of a composition of (a), a composition of (b) or a combination of (c).

[0105] (g) A method of inducing STING-dependent type I interferon production in a patient, which comprises administering to the subject an effective amount of a compound of general formula (I) or a compound of general formula (I'), or a compound of general formula (I").

[0106] (h) A method of inducing STING-dependent type I interferon production in a patient, which comprises administering to the subject an effective amount of a composition of (a), a composition of (b) or a combination of (c).

[0107] (i) A method of inducing STING-dependent cytokine production in a patient, which comprises administering to the subject an effective amount of a compound of general formula (I) or a compound of general formula (I'), or a compound of general formula (I"), or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof.

[0108] (j) A method of inducing STING-dependent cytokine production in a patient, which comprises administering to the subject an effective amount of a composition of (a), a composition of (b) or a combination of (c).

[0109] (k) 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 compound of general formula (I'), or a compound of general formula (I"), or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof to the subject;

[0110] (l) The method of (k), wherein the cell proliferation disorder is cancer.

[0111] (m). A method of treating a cell proliferation disorder in a subject, said method comprising administering a therapeutically effective amount of a pharmaceutical composition of (a), a composition of (b) or a combination of (c) to the subject.

[0112] (n) The method of (m), wherein the cell proliferation disorder is cancer.

[0113] 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 a 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 second therapeutic 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 and chemotherapeutic agents.

[0114] Additional embodiments of the disclosure include the pharmaceutical compositions, combinations and methods set forth in (a)-(n) 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, classes, sub-classes, 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, hydrate, solvate or prodrug as appropriate.

[0115] 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 (n) above are understood to include all embodiments of the compounds, including such embodiments as result from combinations of embodiments.

[0116] The term "subject" (alternatively referred to herein as "patient") as used herein refers to an animal, preferably a mammal, such as a human being, male or female, that has been the object of treatment, observation, or experiment. A subject also refers to one or more of cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, and birds. In embodiments, the subject is human.

[0117] 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, the compound of general formula (I), compound of general formula (I'), or compound of general formula (I"), or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, is administered in conjunction with one or more additional therapeutic agents including vaccines intended to stimulate an immune response to one or more predetermined anti-viral compounds, antigens, adjuvants, CTLA-4 and PD-1 pathway antagonists and other immunomodulatory agents, lipids, liposomes, peptides, anti-cancer and chemotherapeutic agents, etc. In certain embodiments, the compound of general formula (I), compound of general formula (I'), or compound of general formula (I"), or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, is administered in conjunction with one or more additional compositions including vaccines intended to stimulate an immune response to one or more predetermined anti-viral compounds, antigens, adjuvants, CTLA-4 and PD-1 pathway antagonists and other immunomodulatory agents, lipids, liposomes, peptides, anti-cancer and chemotherapeutic agents, etc.

Compounds

[0118] 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.

[0119] 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.

[0120] 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.

[0121] 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.

[0122] 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.

[0123] 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.

[0124] 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).

[0125] 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_{1-6} 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 $(CH_2)_{0-4}CF_3$ (i.e., trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoro-n-propyl, etc.).

[0126] 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.

[0127] 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.

[0128] As used herein, the term "spirocycle" or "spirocyclic ring" refers to a pendant cyclic group formed by substituents on a single atom. For example, in general formula (I), a spirocycle may be formed by R^{2a} and R^3.

[0129] 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.

[0130] 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.

[0131] 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.

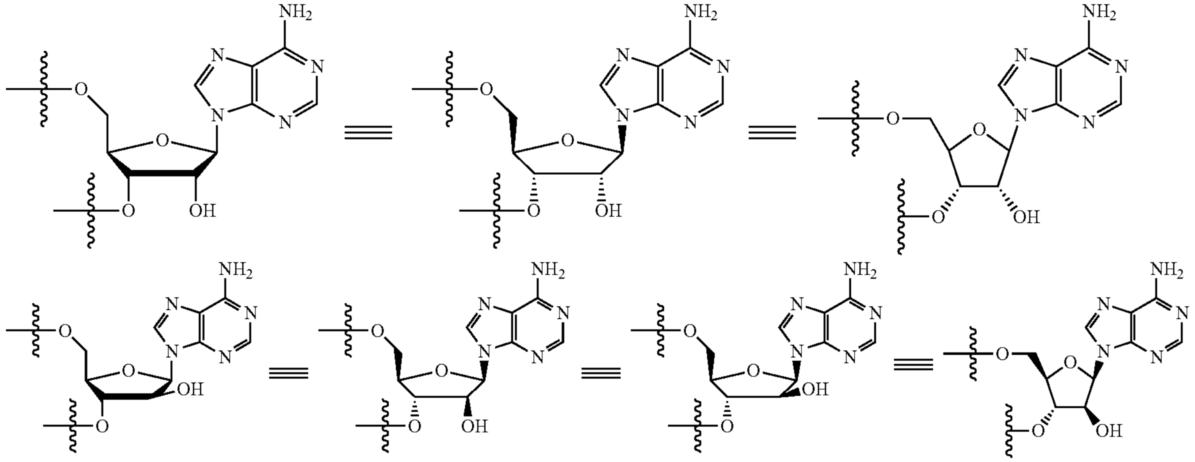
[0132] In the compounds of general formula (I), compounds of general formula (I'), and compounds of general formula (I"), the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic 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), compounds of general formula (I'), and compounds of general formula (I"). For example, different isotopic forms of hydrogen (H) include protium (^1H) and deuterium (^2H). 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) 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.

[0133] In particular embodiments of the compounds of general formula (I), compounds of general formula (I'), and compounds of general formula (I"), the compounds are isotopically enriched with deuterium. In aspects of these embodiments, one or more of 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}, R^9, and R^{10} may be deuterium.

[0134] 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. Also, unless otherwise specified (e.g., 100% purified compound), reference to a particular stereochemistry at a position provides a compound having the indicated stereochemistry, but does not exclude the presence of stereoisomers having different stereochemistry at the indicated position.

[0135] 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 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. 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), a compound of general formula (I'), and/or a compound of general formula (I"), 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, which are derivatized, if necessary, with a reagent containing a stereogenic center of known configuration. Alternatively, absolute stereochemistry may be determined by Vibrational Circular Dichroism (VCD) spectroscopy analysis. The present invention includes all such isomers, as well as salts, solvates (which includes hydrates) and solvated salts of such racemates, enantiomers, diastereomers and tautomers and mixtures thereof.

[0136] 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 principles of stereochemical equivalence apply regardless of substituent. Non-limiting examples of such equivalence include those exemplified below.



Salts

[0137] Compounds described herein having appropriate functional groups can be provided as salts. Examples of such compounds are described herein by reference to possible salts. Such reference is for illustration only. Additional embodiments include salts of any compounds described herein having suitable groups.

[0138] Pharmaceutically acceptable salts can be used with compounds for treating patients. Non-pharmaceutical salts may, however, be useful in the preparation of intermediate compounds.

[0139] Pharmaceutically acceptable salts are suitable for administration to a patient, preferably, a human. 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. 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 (—COOH) or alcohol group being present, pharmaceutically acceptable esters can be employed to modify the solubility or hydrolysis characteristics of the compound.

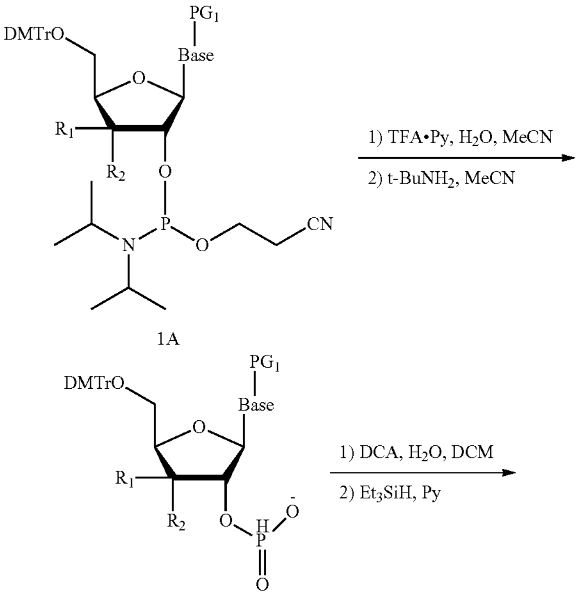
Methods of Preparing Compounds

[0140] Several methods for preparing the compounds of general formula (I), compounds of general formula (I'), and compounds of general formula (I''), or pharmaceutically acceptable salts, hydrates, solvates, or prodrugs thereof, 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.

Method 1

[0141] One method for the preparation of examples of the disclosure 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 a nucleobase of which amino group was appropriately protected with an alkyl or phenyl carbonyl group, a phosphoramidite functionality at 2'-O position, and DMTr ether at 5'-O position. It was treated with aqueous TFA/pyridine condition and subsequently t-butylamine to convert the 2'-phosphoramidite moiety to an H-phosphonate. 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 cyclized compound. It was immediately oxidized with t-butyl hydroperoxide. Then, the 5'-hydroxyl group of the second ribo-nucleoside was deprotected with dichloroacetic acid. Using 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxide 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 oxidized with aqueous iodine. Treatment with t-butylamine and methylamine plus fluoride anion in case silyl protection was used provided the desired cyclic dinucleotide 1G.

SCHEME 1



1A

1B

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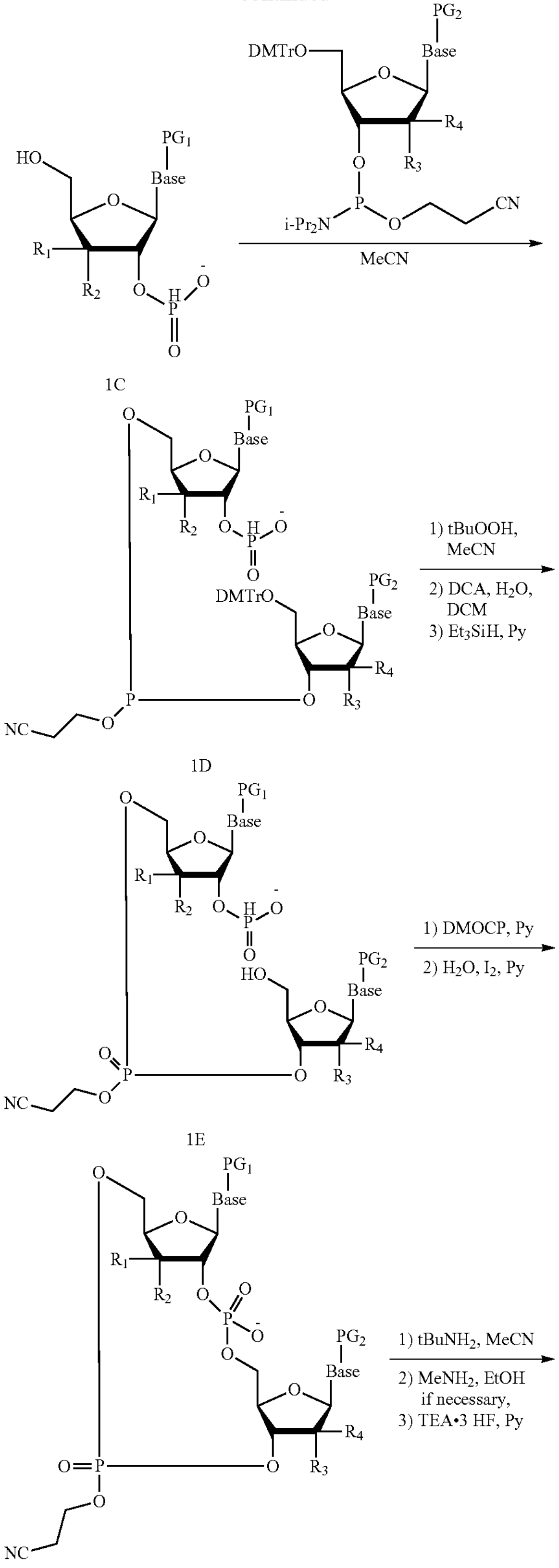

1C

1D

1E

1F

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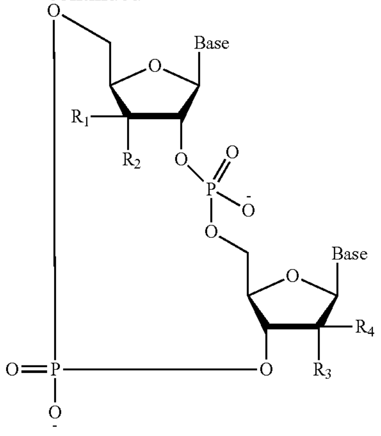
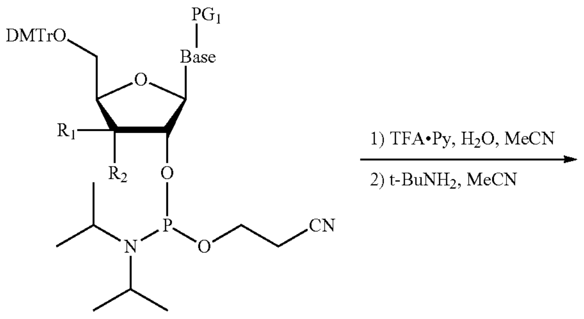


1G

Method 2

[0142] Another method for the preparation of examples of the disclosure is detailed in Scheme 2. This procedure was modified from Scheme 1. The sequence starts with modified ribo-nucleoside with a nucleobase of which amino group was appropriately protected with an alkyl or phenyl carbonyl group, a phosphoramidite functionality at 2'-O position, and DMTr ether at 5'-O position. It was treated with aqueous TFA/pyridine condition and subsequently t-butylamine to convert the 2'-phosphoramidite moiety to an H-phosphonate. 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 cyclized compound. It was immediately thioated with (E)-N,N-dimethyl-N'-(3-thioxo-3H-1,2,4-dithiazol-5-yl)formimidamide. Then, the 5'-hydroxyl group of the second ribo-nucleoside was deprotected with dichloroacetic acid. Using 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxide 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 thioated with 3H-benzo[c][1,2]dithiol-3-one. Treatment with t-butylamine and methylamine plus fluoride anion in case silyl protection was used provided the desired cyclic dinucleotide diphosphorothioate 2G.

SCHEME 2



2A

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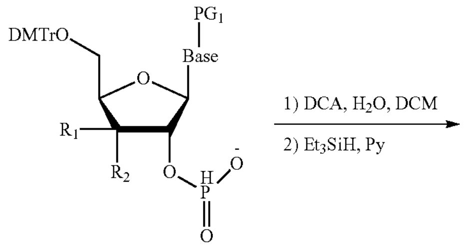
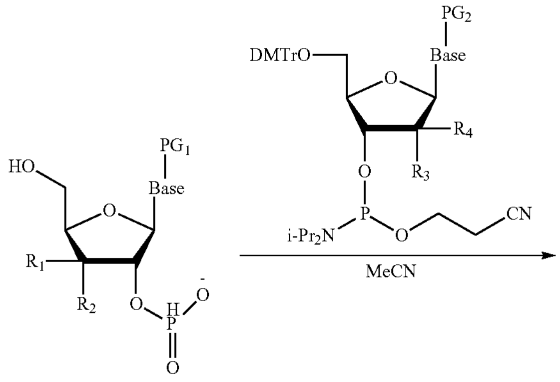
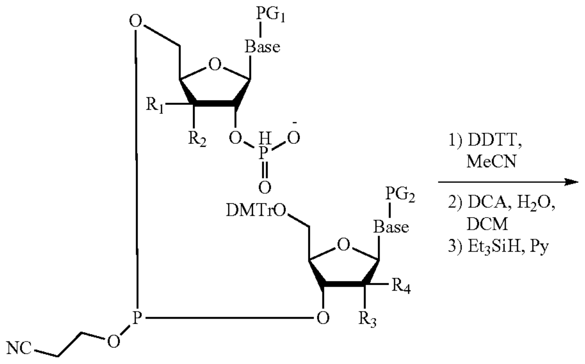


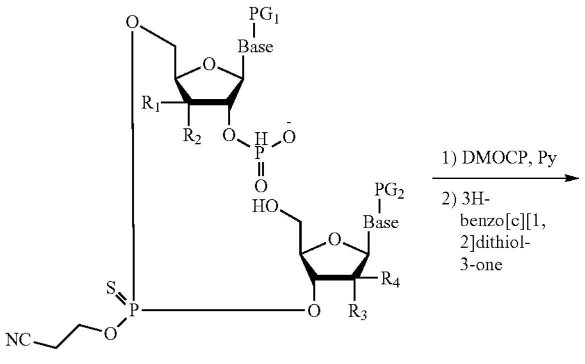
2B



2C



2D



2E

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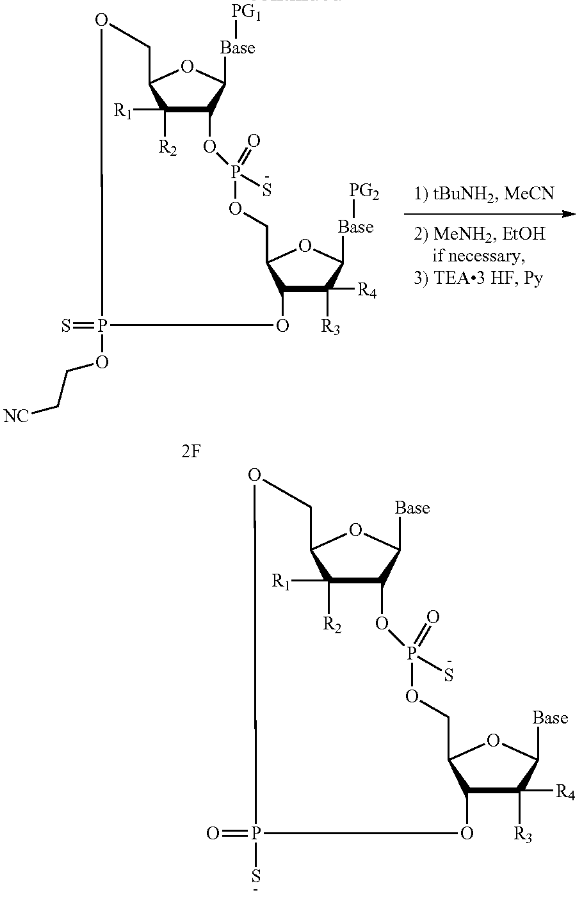


2F

2G

Methods of Use

[0143] Compounds described herein having therapeutic applications, such as the compounds of general formula (I), compounds of general formula (I'), and compounds of general formula (I"), and the compounds of the Examples 1 through 348, can be administered to a patient for the purpose of inducing an immune response, inducing a 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 other 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.

[0144] The compounds disclosed herein are STING agonists and inhibitors of viral replication. These compounds are potentially useful in treating diseases or disorders including, but not limited to, cell proliferation disorders, such as cancer.

[0145] Cell-proliferation disorders include, but are not limited to, cancer. Examples of such cancers include, but are not limited to, Acute Lymphoblastic Leukemia; Acute Myeloid Leukemia; Adrenocortical Carcinoma; AIDS-Related Lymphoma; AIDS-Related Malignancies; Anal Cancer; Astrocytoma; Bile Duct Cancer; Bladder Cancer; Bone Cancer, Osteosarcoma/Malignant Fibrous Histiocytoma; Brain Stem Glioma; Brain Tumor, Cerebellar Astrocytoma; Brain Tumor, Cerebral Astrocytoma/Malignant Glioma; Brain Tumor, Ependymoma; Brain Tumor, Medulloblastoma; Brain Tumor, Supratentorial Primitive Neuroectodermal Tumors; Brain Tumor, Visual Pathway and Hypothalamic Glioma; Breast Cancer; Bronchial Adenomas/Carcinoids; Carcinoid Tumor; Carcinoid Tumor, Gastrointestinal; Carcinoma, Adrenocortical; Carcinoma, Islet Cell; Central Nervous System Lymphoma, Primary; Cerebral Astrocytoma/Malignant Glioma; Cervical Cancer; Chronic Lymphocytic Leukemia; Chronic Myelogenous Leukemia; Chronic Myeloproliferative Disorders; Clear Cell Sarcoma of Tendon Sheaths; Colon Cancer; Colorectal Cancer; Cutaneous T-Cell Lymphoma; Endometrial Cancer; Ependymoma; Epithelial Cancer, Ovarian; Esophageal Cancer; Esophageal Cancer; Ewing’s Family of Tumors; Extracranial Germ Cell Tumor; Extrahepatic Bile Duct Cancer; Eye Cancer, Intraocular Melanoma; Eye Cancer, Retinoblastoma; Gallbladder Cancer; Gastric (Stomach) Cancer; Gastrointestinal Carcinoid Tumor; Germ Cell Tumor, Extracranial, Childhood; Germ Cell Tumor, Extragonadal; Germ Cell Tumor, Ovarian; Gestational Trophoblastic Tumor; Glioma, Childhood Brain Stem; Glioma, Childhood Visual Pathway and Hypothalamic; Hairy Cell Leukemia; Head and Neck Cancer; Hepatocellular (Liver) Cancer; Hodgkin’s Lymphoma; Hypopharyngeal Cancer; Hypothalamic and Visual Pathway Glioma; Intraocular Melanoma; Islet Cell Carcinoma (Endocrine Pancreas); Kaposi’s Sarcoma; Kidney Cancer; Laryngeal Cancer; Leukemia, Acute Lymphoblastic; Leukemia, Acute Myeloid; Leukemia, Chronic Lymphocytic; Leukemia, Chronic Myelogenous; Leukemia, Hairy Cell; Lip and Oral Cavity Cancer; Liver Cancer; Lung Cancer, Non-Small Cell; Lung Cancer, Small Cell; Lymphoblastic Leukemia; Lymphoma, AIDS-Related; Lymphoma, Central Nervous System (Primary); Lymphoma, Cutaneous T-Cell; Lymphoma, Hodgkin’s; Lymphoma, Hodgkin’s During Pregnancy; Lymphoma, Non-Hodgkin’s; Lymphoma, Primary Central Nervous System; Macroglobulinemia, Waldenstrom’s; Male Breast Cancer; Malignant Mesothelioma; Malignant Thymoma; Medulloblastoma, Childhood; Melanoma; Melanoma, Intraocular; Merkel Cell Carcinoma; Mesothelioma, Malignant; Metastatic Squamous Neck Cancer with Occult Primary; Multiple Endocrine Neoplasia Syndrome, Childhood; Multiple Myeloma/Plasma Cell Neoplasm; Mycosis Fungoides; Myelodysplastic Syndromes; Myelogenous Leukemia, Chronic; Myeloid Leukemia; Myeloma, Multiple; Myeloproliferative Disorders, Chronic; Nasal Cavity and Paranasal Sinus Cancer; Nasopharyngeal Cancer; Neuroblastoma; Non-Hodgkin’s Lymphoma; Non-Small Cell Lung Cancer; Oral Cancer; Oral Cavity and Lip Cancer; Oropharyngeal Cancer; steosarcoma/Malignant Fibrous Histiocytoma of Bone; Ovarian Epithelial Cancer; Ovarian Germ Cell Tumor; Ovarian Low Malignant Potential Tumor; Pancreatic Cancer; Paranasal Sinus and Nasal Cavity Cancer; Parathyroid Cancer; Penile Cancer; Pheochromocytoma; Pineal and Supratentorial Primitive Neuroectodermal Tumors; Pituitary Tumor; Plasma Cell Neoplasm/Multiple Myeloma; Pleuropulmonary Blastoma; Pregnancy and Breast Cancer; Pregnancy and Hodgkin’s Lymphoma; Pregnancy and Non-Hodgkin's Lymphoma; Primary Central Nervous System Lymphoma; Primary Liver Cancer; Prostate Cancer; Rectal Cancer; Renal Cell (Kidney) Cancer; Renal Pelvis and Ureter, Transitional Cell Cancer; Retinoblastoma; Rhabdomyosarcoma; Salivary Gland Cancer; Sarcoma, Ewing's Family of Tumors; Sarcoma, Kaposi's; Sarcoma (Osteosarcoma)/Malignant Fibrous Histiocytoma of Bone; Sarcoma, Soft Tissue; Sezary Syndrome; Skin Cancer; Skin Cancer (Melanoma); Skin Carcinoma, Merkel Cell; Small Cell Lung Cancer; Small Intestine Cancer; Soft Tissue Sarcoma; Squamous Neck Cancer with Occult Primary, Metastatic; Stomach (Gastric) Cancer; Supratentorial Primitive Neuroectodermal Tumors; T-Cell Lymphoma, Cutaneous; Testicular Cancer; Thymoma, Malignant; Thyroid Cancer; Transitional Cell Cancer of the Renal Pelvis and Ureter; Trophoblastic Tumor, Gestational; Ureter and Renal Pelvis, Transitional Cell Cancer; Urethral Cancer; Uterine Sarcoma; Vaginal Cancer; Visual Pathway and Hypothalamic Glioma; Vulvar Cancer; Waldenstrom's Macro globulinemia; and Wilms' Tumor.

[0146] In one embodiment, the cancer is brain cancer, such as an 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; and pituitary adenoma. In another embodiment, the brain cancer is glioma, glioblastoma multiforme, paraganglioma, or suprantentorial primordial neuroectodermal tumors (sP-NET).

[0147] In another embodiment, the cancer is leukemia, such as 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, and acute lymphoblastic leukemia.

[0148] In one embodiment, the cancer is skin cancer, including melanoma. In another embodiment, the cancer is prostate cancer, breast cancer, thyroid cancer, colon cancer, or lung cancer. In another embodiment, the cancer is sarcoma, including central chondrosarcoma, central and periosteal chondroma, and fibrosarcoma. In another embodiment, the cancer is cholangiocarcinoma.

[0149] As used herein, the terms "treatment" and "treating" refer to all processes wherein 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.

[0150] The terms "administration of" and or "administering" a compound should be understood to include providing a compound described herein, or a pharmaceutically acceptable salt, hydrate, solvate or prodrug thereof, and compositions of the foregoing to a subject.

[0151] 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.

[0152] In an embodiment, the amount of a compound can be an "effective amount" or "therapeutically effective amount," wherein 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.

[0153] 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.

[0154] 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, and subcutaneous injection or infusion.

[0155] The compounds disclosed herein may be administered once or according to a dosing regimen wherein 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.

[0156] 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.

[0157] 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), a compound of general formula (I'), or a compound of general formula (I") to a subject in need of treatment thereof. In one embodiment, the cell proliferation disorder is cancer.

[0158] In one embodiment, the cancer is brain cancer, leukemia, skin cancer, prostate cancer, thyroid cancer, colon cancer, lung cancer or sarcoma. In another embodiment the cancer is selected from the group consisting of glioma, glioblastoma multiforme, paraganglioma, suprantentorial primordial neuroectodermal tumors, acute myeloid leukemia, myelodysplastic syndrome, chronic myelogenous leukemia, melanoma, breast, prostate, thyroid, colon, lung, central chondrosarcoma, central and periosteal chondroma tumors, fibrosarcoma, and cholangiocarcinoma.

[0159] In one embodiment, disclosed herein is the use of a compound of general formula (I), compound of general formula (I'), and/or compound of general formula (I''), or a pharmaceutically acceptable salt, hydrate, solvate or prodrug thereof, 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.

[0160] In one embodiment, disclosed herein is a pharmaceutical composition comprising at least one compound of general formula (I), compound of general formula (I'), and/or compound of general formula (I''), or a pharmaceutically acceptable salt, hydrate, solvate or prodrug thereof, for use in potential treatment to induce an immune response and/or to induce STING-dependent type I interferon production.

[0161] In one embodiment, disclosed herein is the use of a compound of general formula (I), compound of general formula (I'), and/or compound of general formula (I''), or a pharmaceutically acceptable salt, hydrate, solvate or prodrug thereof, in the manufacture of a medicament for the treatment to induce an immune response and/or to induce STING-dependent type I interferon production. In one embodiment, the disease or disorder to be treated is a cell proliferation disorder. In another embodiment, the cell proliferation disorder is cancer. In another embodiment, the cancer is brain cancer, leukemia, skin cancer, breast, prostate cancer, thyroid cancer, colon cancer, lung cancer, or sarcoma. In another embodiment, the cancer is glioma, glioblastoma multiforme, paraganglioma, suprantentorial primordial neuroectodermal tumors, acute myeloid leukemia, myelodysplastic syndrome, chronic myelogenous leukemia, melanoma, breast, prostate, thyroid, colon, lung, central chondrosarcoma, central and periosteal chondroma tumors, fibrosarcoma, and/or cholangiocarcinoma.

Compositions

[0162] 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 which 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), a compound of general formula (I'), and/or a compound of general formula (I''), or a pharmaceutically acceptable salt, hydrate, solvate, or prodrug 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.

[0163] For the purpose of inducing an immune response and/or inducing a STING-dependent type I interferon production, the compounds, optionally in the form of a salt, hydrate, solvate or prodrug, can be administered by means that produces contact of the active agent with the agent's site of action. They 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. They 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.

[0164] In one embodiment, disclosed herein is a composition comprising a compound of general formula (I), a compound of general formula (I'), and/or a compound of general formula (I''), or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers or excipients. The composition may be prepared and packaged in bulk form wherein an 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 wherein each physically discrete unit contains an effective amount of a compound of general formula (I), a compound of general formula (I'), and/or a compound of general formula (I'').

[0165] 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.

[0166] 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.

[0167] 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 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).

[0168] 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).

[0169] In one embodiment, the disclosure is directed to a solid oral dosage form such as a tablet or capsule comprising an effective amount of a compound of the disclosure 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 oral solid 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 oral solid dosage form may further comprise a disintegrant. Suitable disintegrants include crospovidone, sodium starch glycolate, croscarmelose, alginic acid, and sodium carboxymethyl cellulose. The oral solid dosage form may further comprise a lubricant. Suitable lubricants include stearic acid, magnesium stearate, calcium stearate, and talc.

[0170] 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.

[0171] The compounds disclosed herein may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyrancopolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine 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.

[0172] In one embodiment, the disclosure is directed to a liquid oral dosage form. Oral liquids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of a compound disclosed herein. Syrups can be prepared by dissolving the compound of the disclosure in a suitably flavored aqueous solution; while 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.

[0173] 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 which 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.

Combinations

[0174] The compounds of general formula (I), compounds of general formula (I'), and/or compounds of general formula (I"), or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, may be administered in combination with one or more additional therapeutic agents. In embodiments, one or more a compound of general formula (I), compound of general formula (I'), or compound of general formula (I"), or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, and the one or more additional therapeutic agents may be co-adminstered. The additional therapeutic agent(s) may be administered in a single dosage form with the compound of general formula (I), compound of general formula (I'), or compound of general formula (I"), or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, or the additional therapeutic agent(s) may be administered in separate dosage form(s) from the dosage form containing the compound of general formula (I), compound of general formula (I'), or compound of general formula (I"), or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof. The additional therapeutic 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, 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 therapeutic 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), compounds of general formula (I'), or compounds of general formula (I") and one or more additional therapeutic agents will be determined based on the individual patient needs.

[0175] 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.

[0176] 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 therapeutic 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).

[0177] Products provided as combinations may include a composition comprising a compound of general formula (I), compound of general formula (I'), or compound of general formula (I"), or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, 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), compound of general formula (I'), or compound of general formula (I"), or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, and a composition comprising one or more other therapeutic 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.

[0178] The weight ratio of a compound disclosed herein to a second active agent may be varied and will depend upon the effective dose of each agent. Generally, an 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, an 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).

[0179] In one embodiment, this disclosure provides a composition comprising a compound of general formula (I), compound of general formula (I'), or compound of general formula (I"), or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, and at least one other therapeutic 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.

[0180] 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), compound of general formula (I'), or compound of general formula (I"), or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof. 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.

[0181] 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.

[0182] Disclosed herein is a use of a compound of general formula (I), compound of general formula (I'), or compound of general formula (I"), or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, for treating a cell proliferation disorder, wherein 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, wherein the medicament is administered with a compound of general formula (I).

[0183] The disclosure also provides the use of a compound of general formula (I), compound of general formula (I'), or compound of general formula (I"), or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, for treating a cell proliferation disorder, wherein the patient has previously (e.g., within 24 hours) been treated with another active agent. The disclosure also provides the use of another therapeutic agent for treating a cell proliferation disorder, wherein the patient has previously (e.g., within 24 hours) been treated with a compound of general formula (I), compound of general formula (I'), or compound of general formula (I"), or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof. The second agent may be applied a week, several weeks, a month, or several months after the administration of a compound disclosed herein.

[0184] STING agonist compounds that may be used in combination with the compounds of general formula (I), compounds of general formula (I'), and compounds of general formula (I") disclosed herein include but are not limited to cyclic di-nucleotide compounds.

[0185] Anti-viral compounds that may be used in combination with the compounds of general formula (I), compounds of general formula (I'), and compounds of general formula (I") disclosed herein include hepatitis B virus (HBV) inhibitors, hepatitis C virus (HCV) protease inhibitors, HCV polymerase inhibitors, HCV NS4 Å inhibitors, HCV NS5A inhibitors, HCV NS5b inhibitors, and human immunodeficiency virus (HIV) inhibitors.

[0186] Antigens and adjuvants that may be used in combination with the compounds of general formula (I), compounds of general formula (I'), and compounds of general formula (I") disclosed herein include B7 costimulatory molecule, interleukin-2, interferon-y, GM-CSF, CTLA-4 antagonists, OX-40/OX-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.

[0187] CLTA-4 and PD-1 pathways are important negative regulators of immune response. Activated T-cells upregulate 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 (I) disclosed herein include ipilimumab, tremelimumab, nivolumab, pembrolizumab, CT-011, AMP-224, and MDX-1106.

[0188] "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.

[0189] 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.

[0190] 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. Pat. No. 7,488,802, U.S. Pat. No. 7,521,051, U.S. Pat. No. 8,008,449, U.S. Pat. No. 8,354,509, and U.S. Pat. No. 8,168,757, PCT International Patent Application Publication Nos. WO2004/004771, WO2004/072286, and WO2004/056875, and U.S. Patent Application Publication No. US2011/0271358.

[0191] 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. Pat. No. 8,383,796. 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.

[0192] 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.

[0193] Examples of cytotoxic agents that may be used in combination with the compounds of general formula (I), compounds of general formula (I'), and compounds of general formula (I''), or pharmaceutically acceptable salts, hydrates, solvates, or prodrugs thereof, disclosed herein 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®).

[0194] Chemotherapeutic agents that may be used in combination with the compounds of general formula (I), compounds of general formula (I'), and compounds of general formula (I''), or pharmaceutically acceptable salts, hydrates, solvates, or prodrugs thereof, 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-proly-1-Lproline-tbutylamide, 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 hydroxyureataxanes, 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.

[0195] 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).

[0196] 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).

[0197] 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®.

[0198] 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®).

[0199] 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 (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®).

[0200] 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®).

Activity: STING Biochemical [3H]cGAMP Competition Assay

[0201] The individual compounds described in the Examples herein are defined as STING agonists by demonstrating binding to the STING protein with an EC_{50} of 20 uM or less in the STING Biochemical [3H]cGAMP Competition Assay and demonstrating interferon production with a 20% or greater luminescence induction at 30 uM in the IFN-β secretion in the THP1 cell assay.

[0202] 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.

Abbreviations

[0203] ^{1}H-NMR Proton nuclear magnetic resonance spectroscopy
[0204] ^{19}F-NMR ^{19}F nuclear magnetic resonance spectroscopy
[0205] ^{31}P-NMR ^{31}P nuclear magnetic resonance spectroscopy
[0206] Å Angstrom
[0207] A^{Bz} 6-N-benzoyladenine
[0208] aq Aqueous
[0209] Ar Argon
[0210] ATP Adenosine 5'-triphosphate
[0211] Bz Benzoyl
[0212] CD_3OD Deuterium-enriched methyl alcohol, deuterium-enriched methanol
[0213] $CHCl_3$ Trichloromethane
[0214] Ci Curie, a non-standard unit of radioactivity; $1Ci=3.7\times10^{10}Bq$, where Bq is Becquerel, the SI unit of radioactivity, equivalent to 1 disintegration per second (dps)
[0215] CO_2 Carbon dioxide
[0216] d Doublet
[0217] d Day(s)
[0218] D_2O Deuterium-enriched water
[0219] DCA Dichloroacetic acid
[0220] DCM, CH_2Cl_2 Dichloromethane
[0221] ddd Doublet of doublet of doublet
[0222] ddt Doublet of doublet of triplet
[0223] DDTT (E)-N,N-dimethyl-N'-(3-thioxo-3H-1,2,4-dithiazol-5-yl)formimidamide
[0224] DMF N,N-dimethylformamide

[0225] DMOCP 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphineane 2-oxide

[0226] DMSO Dimethyl sulfoxide

[0227] DMTr 4,4'-dimethoxytrityl

[0228] DMTrCl 4,4'-dimethoxytrityl chloride

[0229] dq Doublet of quartet

[0230] 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

[0231] eq Equivalents

[0232] ES Electron spray

[0233] Et Ethyl

[0234] Et_2O Diethyl ether

[0235] Et_3 SiH Triethylsilane

[0236] EtOAc Ethyl acetate

[0237] EtOH Ethyl alcohol, ethanol

[0238] g Gram

[0239] GTP Guanosine 5'-triphosphate

[0240] h Hour

[0241] H_2O Water

[0242] HEPES 2-[4-(2-hydroxyethyl)piperazin 1-yl]ethanesulfonic acid, a zwitterionic organic chemical buffering agent

[0243] hept Heptet

[0244] Hex Hexanes

[0245] HF-Pyr Hydrogen fluoride-pyridine complex

[0246] HPLC High performance liquid chromatography

[0247] Hz Hertz

[0248] ITP Inosine 5'-triphosphate

[0249] J NMR Coupling constant

[0250] LCMS Liquid chromatography-mass spectroscopy

[0251] m Multiplet

[0252] M Molar, moles per liter

[0253] mCi Millicurie

[0254] Me Methyl

[0255] MeCN Acetonitrile

[0256] $MeNH_2$ Methylamine

[0257] mg Milligram

[0258] $MgCl_2$ Magnesium chloride

[0259] MHz Megahertz

[0260] min Minute(s)

[0261] mL, ml Milliliter

[0262] mM Millimole per liter

[0263] mmol Millimole

[0264] MOI Multiplicity of infection

[0265] MPLC Medium pressure liquid chromatography

[0266] MTBE Methyl t-butyl ether, methyl tertiary butyl ether

[0267] Na_2SO_4 Sodium sulfate

[0268] NaCl Sodium chloride

[0269] $NaHCO_3$ Sodium bicarbonate

[0270] $NaHSO_3$ Sodium bisulfite

[0271] NaOH Sodium hydroxide

[0272] ng Nanogram(s)

[0273] NH_4HCO_3 Ammonium bicarbonate

[0274] NH_4OH Ammonium hydroxide

[0275] nL Nanoliter

[0276] nm Nanometer

[0277] nM Nanomolar

[0278] P_2O_5 Phosphorus pentoxide

[0279] Py Pyridine

[0280] q Quartet

[0281] RPM, rpm Revolutions per minute

[0282] RT, rt Room temperature, approximately 25° C.

[0283] s Singlet

[0284] sat Saturated

[0285] t Triplet

[0286] TB S t-Butyldimethylsilyl

[0287] TMA Trimethylamine

[0288] TEA, Et_3N Triethylamine

[0289] TFA Trifluoroacetic acid

[0290] TLC Thin layer chromatography

[0291] TMSCl Trimethylsilyl chloride

[0292] T_R Retention time

[0293] TrisCl Tris(hydroxymethyl)aminomethane hydrochloride

[0294] v/v Volume/volume

[0295] λ_{em} Emission wavelength

[0296] λ_{ex} Excitation wavelength

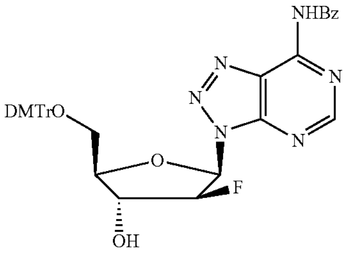
[0297] μg Microgram

[0298] μL, uL Microliter

[0299] μM, uM Micromolar

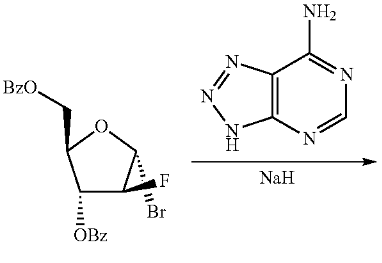
Preparation 1: N-(3-((2R,3S,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)-methyl)-3-fluoro-4-hydroxytetrahydrofuran-2-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl)benzamide

[0300]



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

[0301]



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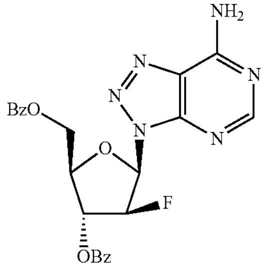
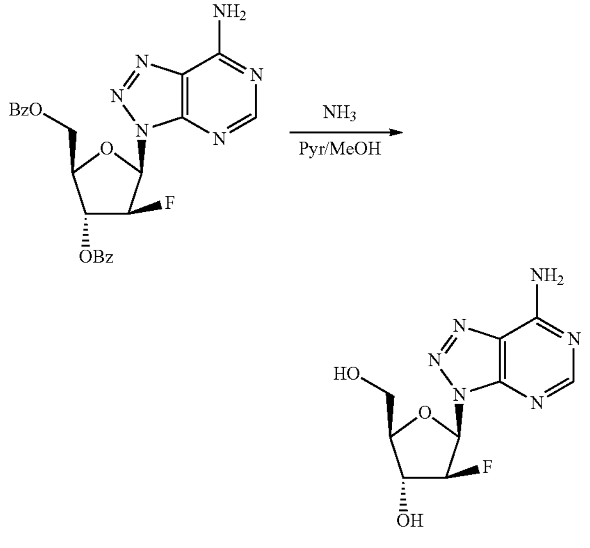


[0302] To a mixture of 3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-amine (2.36 g, 17.4 mmol) in NMP (50 ml) was added NaH (60%, 0.744 g, 18.6 mmol). The mixture was vigorously stirred and after 1 h, generation of bubbles had completely ceased. The mixture was added to ((2R,3R,4S,5R)-3-(benzoyloxy)-5-bromo-4-fluorotetrahydrofuran-2-yl)methyl benzoate (neat, 5.25 g, 12.4 mmol) in one portion. The reaction was stirred for 18 h. LCMS showed several peaks with the desired mass (m/e=479). EtOAc (70 mL) and water (70 mL) were added to the reaction. Layers were separated, and the organic layer was washed with half saturated brine (3x10 mL) and brine (1x10 mL), 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 (500 MHz, 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, 3.1 Hz, 1H), 6.49 (dt, J=17.6, 6.9 Hz, 1H), 6.16 (dt, J=56, 6.6 Hz, 1H), 4.76-4.62 (m, 3H).

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

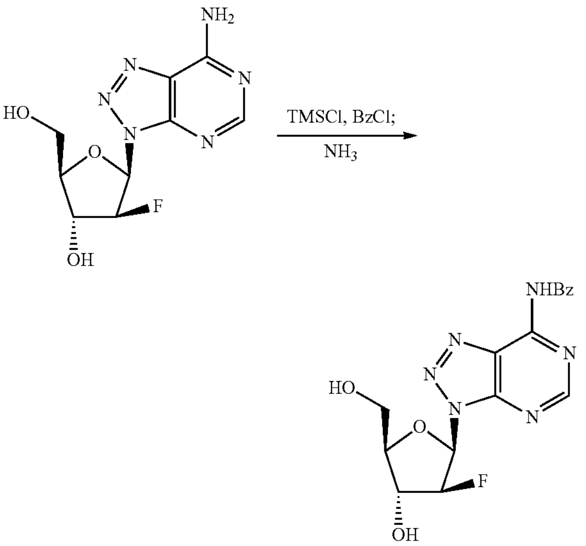
[0303]



[0304] 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 (2.00 g, 4.18 mmol) in pyridine (10 mL) at was added NH_3 in MeOH (7N, 20 mL, 140 mmol). It was stirred for 48 h. 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 (500 MHz, DMSO-d6): δ 8.54 (s, 1H), 8.33 (s, 1H), 8.22 (s, 1H), 6.73 (dd, J=6.5, 2.6 Hz, 1H), 6.00 (d, J=5.4 Hz, 1H), 5.51 (ddd, J=53, 7.2, 6.5 Hz, 1H), 4.93 (t, J=5.8 Hz, 1H), 4.86-4.74 (m, 1H), 3.91-3.83 (m, 1H), 3.77-3.61 (m, 2H).

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

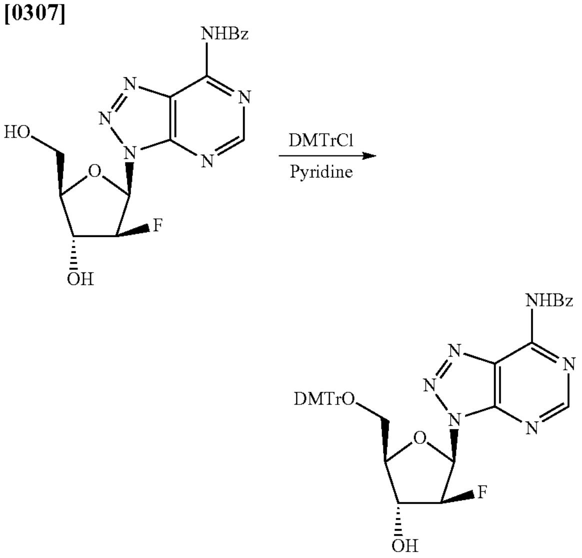
[0305]



[0306] 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 (1.34 g, 4.96 mmol) in pyridine (30 mL) at 0° C. was added TMSCl (1.46 mL, 11.4 mmol). It was warmed to rt and stirred for 1 h. Then, it was recooled to 0° C. and BzCl (0.921 mL, 7.93 mmol) was added dropwise. The reaction was slowly warmed to rt over 2 h. LCMS showed completion of reaction (m/e=375, 479). Water (3 mL) was added. It was cooled to 0° C. and NH_3 in MeOH (7N, 2.8 mL, 20 mmol) was added. After 1 h, 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 (500 MHz, DMSO-d_6): δ 11.95 (s, 1H), 8.98 (s, 1H), 8.10 (d, J=7.6 Hz, 2H), 7.73-7.66 (m, 1H), 7.59 (t, J=7.7 Hz, 2H), 6.91 (d, J=6.2 Hz, 1H), 6.06 (d, J=5.6 Hz, 1H), 5.59 (t, J=53, 6.8 Hz, 1H), 4.90 (t, J=5.8 Hz, 1H), 4.82 (dq, J=19.8, 7.0 Hz, 1H), 3.92 (td, J=7.6, 2.9 Hz, 1H), 3.75 (ddd, J=12.1, 5.6, 3.0 Hz, 1H), 3.66 (dt, J=12.0, 6.6 Hz, 1H).

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

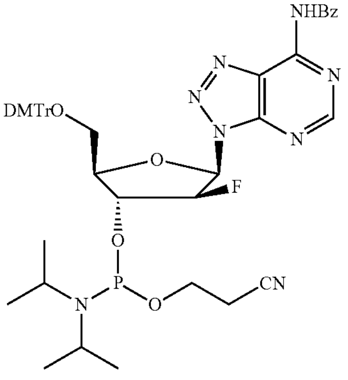
[0307]



[0308] 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 (1.25 g, 3.34 mmol) in pyridine (15 mL) at 0° C. was added DMTrCl (1.58 g, 4.68 mmol). It was stirred at rt for 1 h. LCMS showed a peak with the desired mass (m/e=677). It was partly concentrated (to 5 mL), and EtOAc (20 mL) and water (10 mL) were added. Layers were separated, and the aq layer was extracted with EtOAc (2×10 mL). The combined organics were washed with brine (5 mL), 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 (500 MHz, DMSO-d_6): δ 8.13-8.07 (m, 2H), 7.69 (t, J=7.4 Hz, 1H), 7.59 (t, J=7.6 Hz, 2H), 7.35-7.29 (m, 2H), 7.23-7.10 (m, 6H), 6.97 (d, J=6.5 Hz, 1H), 6.81-6.74 (m, 2H), 6.74-6.67 (m, 2H), 6.07 (d, J=5.7 Hz, 1H), 5.62 (dt, J=53, 7.0 Hz, 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, 8.0 Hz, 1H), 3.21 (dd, J=10.3, 2.4 Hz, 1H).

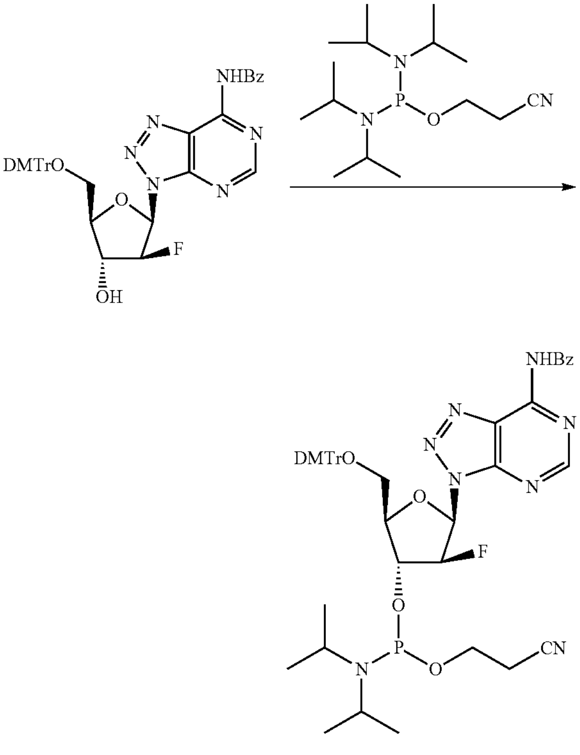
Preparation 2: (2R,3R,4S,5R)-5-(7-benzamido-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-fluorotetrahydrofuran-3-yl (2-cyanoethyl) diisopropylphosphoramidite

[0309]



Step 1: (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

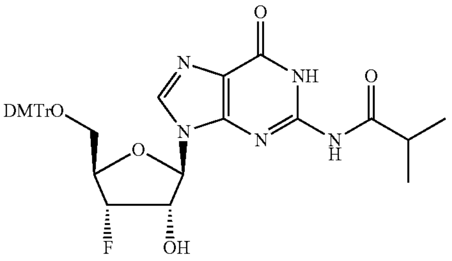
[0310]



[0311] To a solution of 3-((bis(diisopropylamino)phosphino)oxy)propanenitrile (8.02 g, 26.6 mmol) in ACN (90 mL) at rt was added pyridin-1-ium 2,2,2-trifluoroacetate (3.85 g, 19.95 mmol) and a solution of N-(3-((2R,3 S,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 (9 g, 13.30 mmol) in ACN (90 mL). The resulting mixture was stirred for 1 h. Then, it was concentrated and the residue was dissolved in CH_2Cl_2 (1000 mL). It was washed with aq $NaHCO_3$ (1%, 2×300 mL), water (300 mL) and brine (300 mL), dried (Na_2SO_4), concentrated, and purified by reverse phase (C18) chromatography eluting with 0 to 95% ACN in water to give the product. LCMS (ES, m/z): 877.5 $[M+H]^+$. ^{1}H-NMR: (400 MHz, DMSO-d_6): δ 12.01 (s, 1H), 8.92 (s, 1H), 8.11 (d, J=7.6 Hz, 2H), 7.66 (dt, J=42.3, 7.5 Hz, 3H), 7.32 (td J=7.2, 6.6, 2.9 Hz, 2H), 7.22-7.00 (m, 9H), 6.83-6.63 (m, 4H), 5.86 (ddt, J=52.8, 17.6, 6.9 Hz, 1H), 5.16 (td, J=17.7, 17.2, 8.8 Hz, 1H), 3.78-3.63 (m, 7H), 3.59-3.35 (m, 5H), 2.74 (t, J=5.9 Hz, 1H), 2.63 (t, J=5.9 Hz, 1H), 1.23-0.99 (m, 10H), 0.91 (d, J=6.7 Hz, 2H). ^{31}P-NMR: (162 MHz, DMSO-d_6): δ 150.26, 149.60 (2 s, 1P).

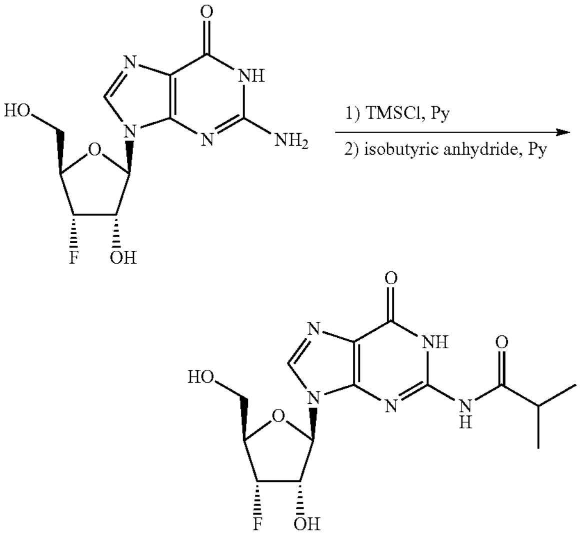
Preparation 3. N-(9-((2R,3S,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide

[0312]



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

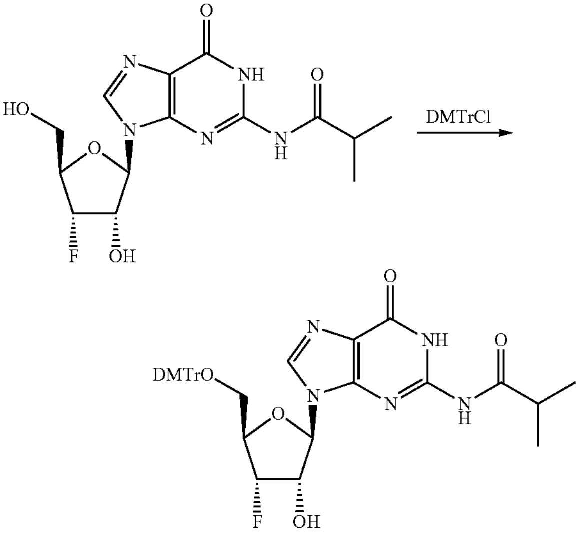
[0313]



[0314] To a suspension of 2-amino-9-((2R,3 S,4S,5R)-4-fluoro-3-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-1,9-dihydro-6H-purin-6-one (Carbosynth catalog #ND10826, 1.50 g, 5.26 mmol) in pyridine (30 mL) at 0-5° C. was added TMSCl (2.86 g, 26.3 mmol), and the mixture was stirred at rt for 30 min. Then, isobutyric anhydride (2.50 g, 15.8 mmol) was added dropwise, and it was stirred for an additional for 2 h. Then, MeOH (5.3 mL) was added. After 5 min, NH_4OH (10.5 mL) was added dropwise and stirring was continued for 30 min. The reaction mixture was concentrated under reduced pressure, and MeOH (2 mL) in CH_2Cl_2 (18 mL) was added to the residue. Insolubles 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: (400 MHz, DMSO-d_6): δ 12.11 (s, 1H), 11.68 (s, 1H), 8.28 (s, 1H), 5.98 (d, J=6.1 Hz, 1H), 5.85 (d, J=8.0 Hz, 1H), 5.24 (t, J=5.4 Hz, 1H), 5.14 (d, J=4.1 Hz, 0.5H), 5.01 (d, J=4.2 Hz, 0.5H), 4.87-4.69 (m, 1H), 4.26 (t, J=4.4 Hz, 0.5H), 4.19 (t, J=4.4 Hz, 0.5H), 3.61 (t, J=4.9 Hz, 2H), 2.77 (hept, J=6.8 Hz, 1H), 1.13 (d, J=6.7 Hz, 6H). ^{19}F-NMR: (376 MHz, DMSO-d_6): δ −197.5 (s).

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

[0315]

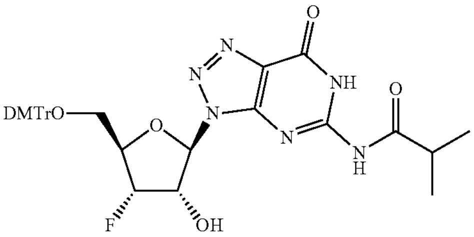


[0316] N-(9-((2R,3 S,4S,5R)-4-fluoro-3-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide (1.30 g, 3.66 mmol) was co-evaporated with pyridine (3×10 mL) and re-dissolved in pyridine (26 mL). To the solution at 0-5° C. was added DMTrCl (1.36 g, 4.02 mmol). It was stirred at rt for 3 h and then, concentrated. CH_2Cl_2 (40 mL, with 1% Et_3N) was added, and it was washed with sat aq $NaHCO_3$ (15 mL), water (10 mL) and brine (10 mL). 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: (400 MHz, 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=6.1 Hz, 1H), 5.87 (d, J=7.3 Hz, 1H), 5.23 (dd, J=4.1, 1.8 Hz, 0H), 5.10 (d, J=4.4 Hz, 0H), 4.96 (dq, J=22.4, 5.9 Hz, 1H), 4.30 (dt, J=26.1, 4.6 Hz, 1H), 3.74 (d, J=1.1 Hz, 6H), 3.39 (dd, J=10.6, 5.7 Hz, 1H), 3.22 (dd, J=10.6, 3.8 Hz, 1H), 2.76 (p, J=6.8 Hz, 1H), 1.13 (d, J=6.8 Hz, 6H). ^{19}F-NMR: (376 MHz, DMSO-d_6): δ −198.1 (s, 1F).

[0317] The product of Preparation 3 may optionally be treated according to the procedures of Preparation 22, Steps 4 and 5 (below), to afford (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 hydrogen phosphonate. LCMS (ES, m/z): 720 $[M-H]^-$.

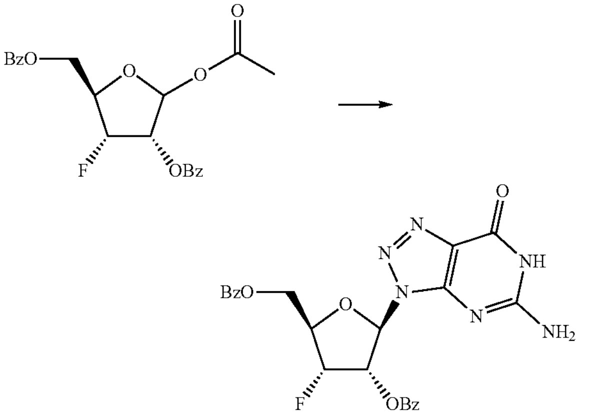
Preparation 4: N-(3-((2R,3S,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-yl) isobutyramide

[0318]



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

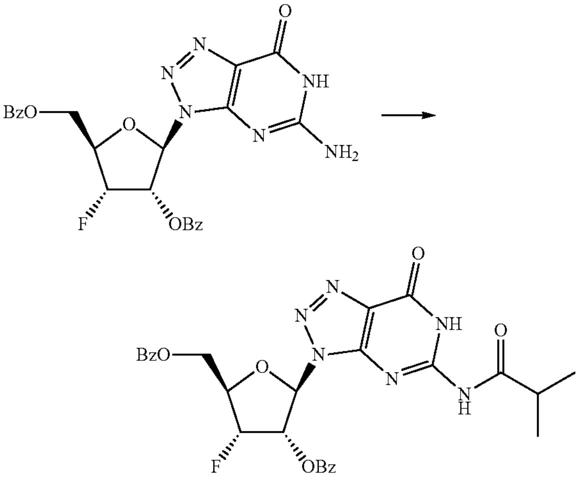
[0319]



[0320] To a suspension of 8-azaguanine (5.14 g, 33.8 mmol) in anhydrous CH_3CN (100 mL) at rt was added dropwise (E)-trimethylsilyl N-(trimethylsilyl)acetimidate (16.53 mL, 67.6 mmol), then the mixture was stirred at 70° C. for 2 h. The reaction was cooled to rt, and a solution of ((2R,3R,4S)-5-acetoxy-4-(benzoyloxy)-3-fluorotetrahydrofuran-2-yl)methyl benzoate (6.8 g, 16.90 mmol) in anhydrous CH_3CN (20 mL) was added followed by dropwise addition of tin(IV) chloride (67.6 mL, 67.6 mmol). The homogeneous solution was stirred at 70° C. for 2 h. The reaction was cooled to rt and concentrated. The residue was dissolved in EtOAc (1000 mL) and neutralized by pouring into sat aq $NaHCO_3$ (500 mL). The organic layer was separated, and the aq layer was extracted with EtOAc (4×500 mL). The organic layers were combined and washed with water (3×700 mL), brine, dried over anhydrous sodium sulfate, filtered, and concentrated to afford title compound without further purification. LCMS (ES, m/z): 495.3 $[M+H]^+$.

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

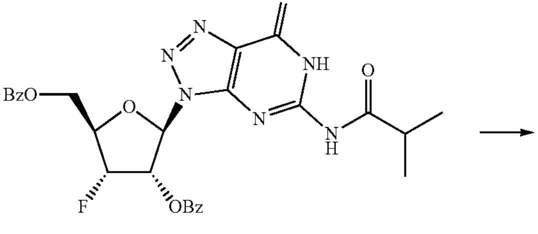
[0321]



[0322] 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 (8 g, 16.18 mmol) from Step 1 in anhydrous DMA (40 mL) at rt was added dropwise isobutyric anhydride (4.02 mL, 24.27 mmol). The mixture was stirred at 140° C. for 4 h. The reaction was cooled and diluted with EtOAc (600 mL), washed with sat aq NH_4Cl (4×500 mL), brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by MPLC (220 g silica gel, eluting with a gradient of 100% hexanes to 100% ethyl acetate) 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 $[M+H]^+$.

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

[0323]



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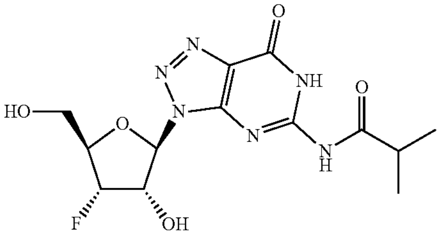
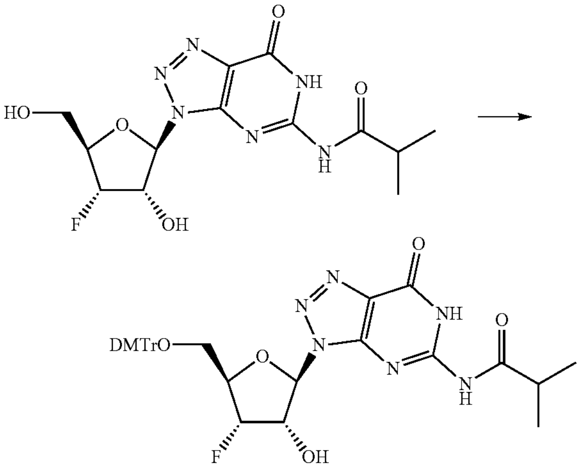


[0324] To a solution of ((2R,3R,4S,5R)-4-(benzoyloxy)-3-fluoro-5-(5-isobutyramido-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)tetrahydrofuran-2-yl)methyl benzoate (6 g, 10.63 mmol) in THF (20 mL), CH_3OH (16 mL), and water (4 mL) at 0° C. was added 5N aqueous NaOH (4.89 mL, 24.45 mmol) and stirred for 1 h. The reaction was neutralized with formic acid (1.223 mL, 31.9 mmol). The solvent was removed, and the residue was purified by MPLC (120 g, silica gel, eluting with a gradient of 100% CH_2Cl_2 to 20% CH_3OH/CH_2Cl_2) to afford N-(3-((2R,3 S,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 $[M+H]^+$.

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

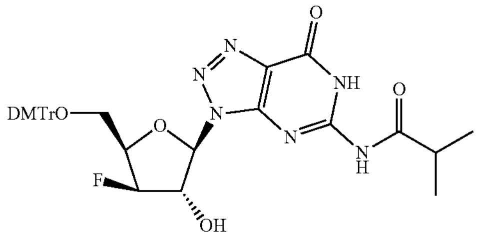
[0325]



[0326] 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 (3 g, 8.42 mmol) in anhydrous pyridine (40 mL) at 0° C. was added 4,4'-dimethoxytrityl chloride (3.42 g, 10.10 mmol). The ice bath was removed, and the reaction mixture was allowed to reach RT and was stirred for 2 h. The mixture was diluted with EtOAc (400 mL), washed with sat aq $NaHCO_3$ (100 mL), water (3×100 mL), brine, and dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by MPLC (120 g silica gel, eluting with a gradient of 100% CH_2Cl_2 to 15% CH_3OH/CH_2CH_2 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 $[M+H]^+$.

Preparation 5: 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

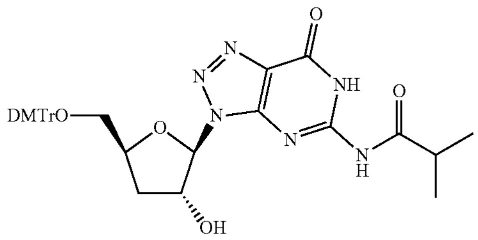
[0327]



[0328] N-(3-((2R,3 S,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 4 using the appropriately substituted ribose in Step 1. LCMS (ES, m/z): 659.4 [M+H]+.

Preparation 6: 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

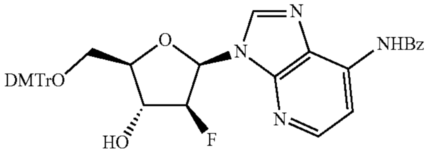
[0329]



[0330] N-(3-((2R,3R,5 S)-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 was prepared according to procedures analogous to those described for Preparation 4 using the appropriately substituted ribose in Step 1. LCMS (ES, m/z): 641.2 [M+H]+.

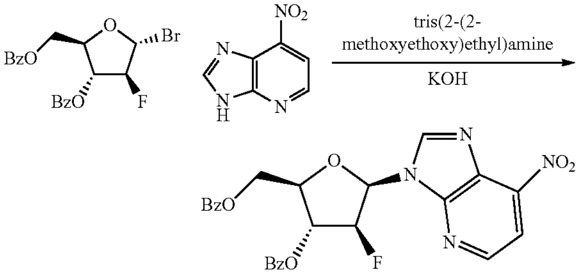
Preparation 7: 3-{5-O-[bis(4-methoxyphenyl)(phenyl)methyl]-2-deoxy-2-fluoro-3-D-arabinofuranosyl}-N-(phenylcarbonyl)-3H-imidazo[4,5-b]pyridin-7-amine

[0331]



Step 1: 3-[2-deoxy-2-fluoro-3,5-bis-O-(phenylcarbonyl)-β-D-arabinofuranosyl]-7-nitro-3H-imidazo[4,5-b]pyridine

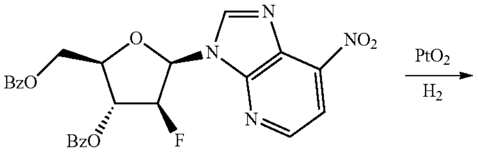
[0332]



[0333] To a stirred mixture of freshly ground KOH (308 mg, 5.48 mmol) in acetonitrile (50 mL) was added tris(2-(2-methoxyethoxy)ethyl)amine (0.070 mL, 0.219 mmol). The reaction mixture was aged for 15 min at ambient temperature followed by addition of 7-nitro-3H-imidazo[4,5-b]pyridine (600 mg, 3.66 mmol) in a single portion. The resulting mixture was stirred at ambient temperature for 15 min. A solution of 2-deoxy-2-fluoro-3,5-bis-O-(phenylcarbonyl)-α-D-arabinofuranosyl bromide (1700 mg, 4.02 mmol) in acetonitrile (10 mL) was added dropwise and the resulting mixture was vigorously stirred at RT for 17 h. The reaction mixture was diluted with sat aq ammonium chloride (80 mL) and extracted with DCM (3×150 mL). The organic extracts were combined, dried over sodium sulphate and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel; 120 g prepacked, (0-70% ethyl acetate/hexanes) to afford 3-[2-deoxy-2-fluoro-3,5-bis-O-(phenylcarbonyl)-3-D-arabinofuranosyl]-7-nitro-3H-imidazo[4,5-b]pyridine. MS: 507 $(M+H)^+$.

Step 2: 3-[2-deoxy-2-fluoro-3,5-bis-O-(phenylcarbonyl)-β-D-arabinofuranosyl]-3H-imidazo[4,5-b]pyridin-7-amine

[0334]



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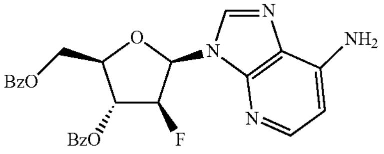
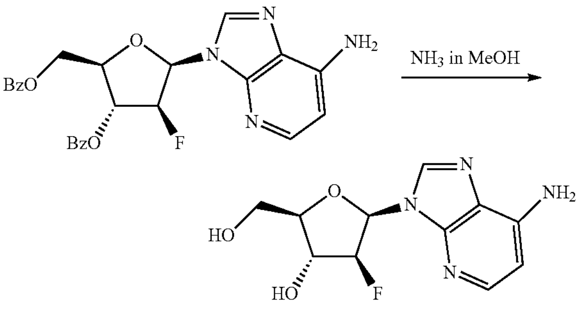


[0335] To a stirred solution of 3-[2-deoxy-2-fluoro-3,5-bis-O-(phenylcarbonyl)-3-D-arabinofuranosyl]-7-nitro-3H-imidazo[4,5-b]pyridine (1380 mg, 2.72 mmol) in methanol (55 mL) at RT was added platinum(IV) oxide (61.9 mg, 0.272 mmol). The reaction mixture was placed under an atmosphere of hydrogen and stirred at RT for 72 h. The catalyst was removed by filtration through a plug of CELITE. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel; 80 g prepacked, ((0-40% (3:1, ethyl acetate:ethanol)/hexanes) to afford 3-[2-deoxy-2-fluoro-3,5-bis-O-(phenylcarbonyl)-3-D-arabinofuranosyl]-3H-imidazo[4,5-b]pyridin-7-amine. MS: 477 $(M+H)^+$.

Step 3: 3-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-3H-imidazo[4,5-b]pyridin-7-amine

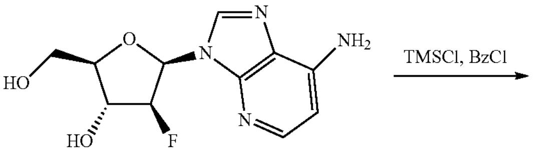
[0336]



[0337] To a stirred solution of 3-[2-deoxy-2-fluoro-3,5-bis-O-(phenylcarbonyl)-3-D-arabinofuranosyl]-3H-imidazo[4,5-b]pyridin-7-amine (995 mg, 2.09 mmol) in methanol (36 mL) at ambient temperature was added ammonia (7N in methanol, 12 mL, 84.0 mmol). The resulting solution was brought to 80° C. and stirred for 5 h. The reaction mixture was cooled to RT and concentrated under reduced pressure. The resulting residue was suspended in methanol/dichloromethane and sonicated until a solid precipitated out of solution. Solid was collected by filtering through a glass frit affording 3-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-3H-imidazo[4,5-b]pyridin-7-amine. MS: 269 $(M+H)^+$.

Step 4: 3-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-N-(phenylcarbonyl)-3H-imidazo[4,5-b]pyridin-7-amine

[0338]



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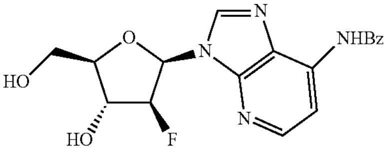
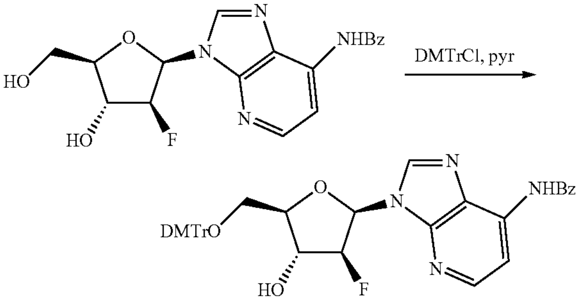


[0339] To a stirred solution of 3-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-3H-imidazo[4,5-b]pyridin-7-amine (550 mg, 2.05 mmol) in pyridine (6.5 mL) at RT was added TMSCl (2.62 mL, 20.5 mmol). The resulting solution was stirred for 1.5 h followed by addition of benzoyl chloride (0.357 mL, 3.08 mmol). After stirring for an additional hour, water (2.15 mL) was added to the reaction mixture, which was then stirred for 45 min. The reaction mixture was cooled to 0° C. and aqueous ammonia (28% w/w) (0.370 mL, 4.79 mmol) was added. The reaction mixture was returned to RT and stirred for 45 min and then concentrated under reduced pressure. The resulting residue was taken up in water (20 mL) and extracted with ethyl acetate (3×40 mL). The organic extracts were combined washed with brine, dried over sodium sulphate and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel; 120 g prepacked, (0-7% methanol/dichloromethane) to afford 3-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-N-(phenylcarbonyl)-3H-imidazo[4,5-b]pyridin-7-amine. MS: 373 $(M+H)^+$.

Step 5: 3-{5-O-[bis(4-methoxyphenyl)(phenyl)methyl]-2-deoxy-2-fluoro-β-D-arabinofuranosyl}-N-(phenylcarbonyl)-3H-imidazo[4,5-b]pyridin-7-amine

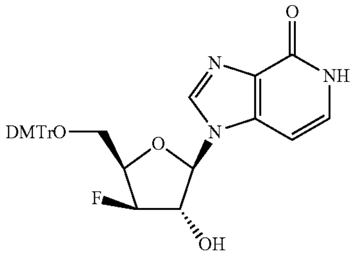
[0340]



[0341] To a stirred mixture of 3-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-N-(phenylcarbonyl)-3H-imidazo[4,5-b]pyridin-7-amine (185 mg, 0.497 mmol) and 4 Å molecular sieves in pyridine (3 mL) at 0° C. was added 4,4'-dimethoxytrityl chloride (253 mg, 0.745 mmol) in a single portion. The reaction mixture was allowed to warm to RT and was stirred for 18 h. Sieves were removed by filtration and the filtrate was concentrated under reduced pressure. The resulting residue was taken up in a mixture of methanol/ether and added to water. The phases were separated, and the aqueous layer was extracted with ether (3 times). The organic extracts were combined, washed with brine, dried over sodium sulphate and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel; 40 g prepacked, ((0-40% (3:1, ethyl acetate:ethanol)/hexanes) to afford 3-{5-O-[bis(4-methoxyphenyl)(phenyl)methyl]-2-deoxy-2-fluoro-β-D-arabinofuranosyl}-N-(phenylcarbonyl)-3H-imidazo[4,5-b]pyridin-7-amine. MS: 675 $(M+H)^+$.

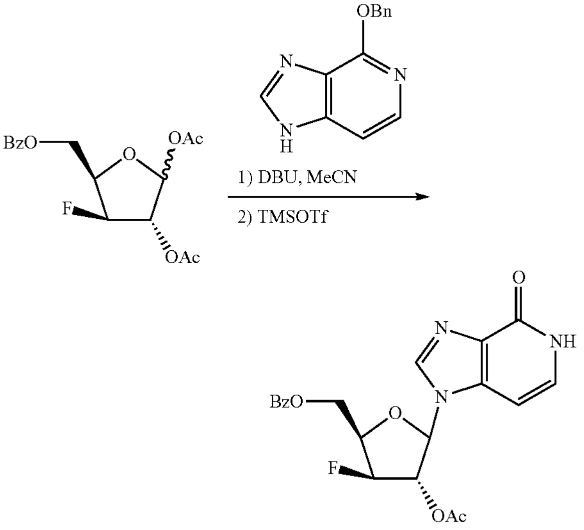
Preparation 8: 1-((2R,3S,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)-1,5-dihydro-4H-imidazo[4,5-c]pyridin-4-one

[0342]



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

[0343]

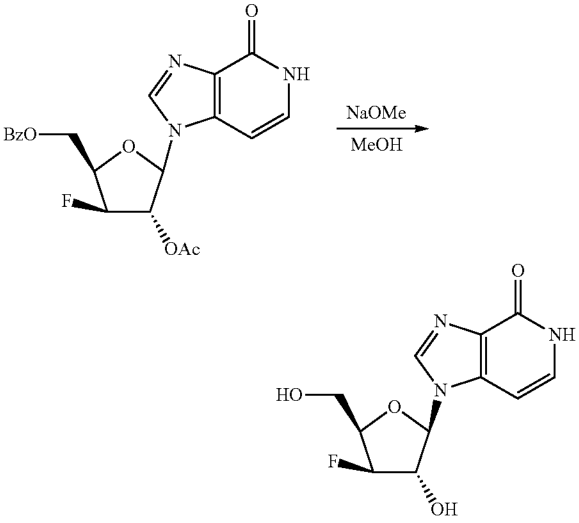


[0344] To a suspension of 4-(benzyloxy)-1H-imidazo[4,5-c]pyridine (0.795 g, 3.53 mmol) and (3S,4S,5R)-5-((benzoyloxy)methyl)-4-fluorotetrahydrofuran-2,3-diyl diacetate (1 g, 2.94 mmol) in ACN (20 mL) and CH_2Cl_2 (10 mL) at 0° C. under Ar was added 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepine (1.34 g, 8.815 mmol). The resulting mixture was stirred at 0° C. for 30 min. Then, trimethylsilyl trifluoromethanesulfonate (3.92 g, 17.65 mmol) was added to the solution, and it was stirred at 0° C. for 30 min. Then, it was heated to 80° C. for 16 h. The reaction was cooled to rt and sat aq $NaHCO_3$ (10 mL) and water (30 mL) were added. It was extracted with EtOAc (3×50 mL). The combined organic layers was washed with brine, dried over

(Na_2SO_4), concentrated, and the residue was purified by silica gel column chromatography, eluted with 1 to 10% MeOH in CH_2Cl_2 to give the product. LCMS (ES, m/z): 416.3 $[M+H]^+$.

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

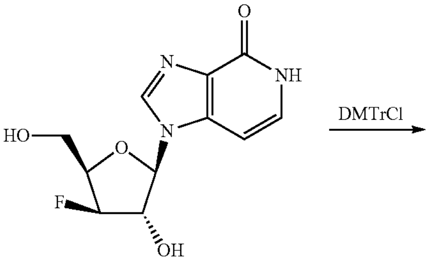
[0345]



[0346] To a solution of ((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 (2.5 g, 5.3 mmol) in MeOH (10 mL) was added sodium methanolate (3.47 g, 21.2 mmol). The solution was stirred at rt for 1 h. It was neutralized with AcOH, and the solution was concentrated. The residue was purified by reverse phase (AQ C18) chromatography eluted with 0 to 30% ACN in aq NH_4HCO_3 (5 mM) to give the product. LCMS (ES, m/z): 270.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.31 (s, 1H), 8.06 (s, 1H), 7.23 (d, J=7.1 Hz, 1H), 6.62 (d, J=7.1 Hz, 1H), 6.37 (d, J=2.9 Hz, 1H), 5.85 (d, J=2.8 Hz, 1H), 5.22-4.98 (m, 2H), 4.54 (d, J=17.7 Hz, 1H), 4.28 (dtd, J=29.6, 6.0, 3.1 Hz, 1H), 3.93-3.62 (m, 2H).

Step 3: 1-((2R,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

[0347]



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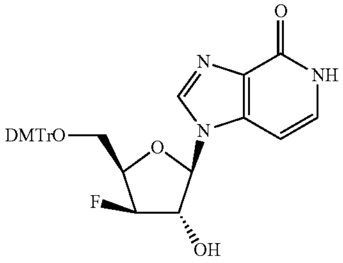
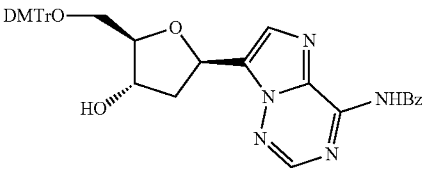


[0348] To a stirred solution of 1-((2R,3S,4R,5R)-4-fluoro-3-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-1H-imidazo[4,5-c]pyridin-4(5H)-one (340 mg, 1.26 mmol) in pyridine (3 mL) at rt was added 4,4'-(chloro(phenyl)methylene)bis(methoxybenzene) (426 mg, 1.1 mmol).

[0349] It was stirred for 4 h. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography eluted with 1 to 10% MeOH in CH_2Cl_2 (0.5% Et_3N) to give the product. LCMS (ES, m/z): 572.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.32 (d, J=5.9 Hz, 1H), 7.95 (s, 1H), 7.41 (d, J=7.8 Hz, 2H), 7.37-7.15 (m, 8H), 6.86 (dd, J=10.5, 8.6 Hz, 4H), 6.60 (d, J=7.1 Hz, 1H), 6.50-6.36 (m, 1H), 5.92 (d, J=2.6 Hz, 1H), 5.77 (s, 1H), 5.27-5.06 (m, 1H), 4.65-4.42 (m, 2H), 3.73 (d, J=2.6 Hz, 6H), 3.30-3.24 (m, 1H).

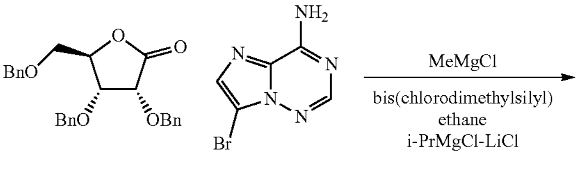
Preparation 9: N-(7-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-2-yl)imidazo[2,1-f][1,2,4]triazin-4-yl)benzamide

[0350]



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

[0351]



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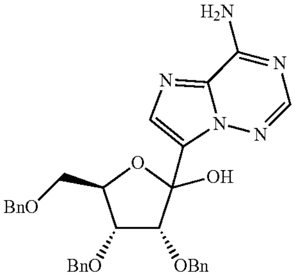
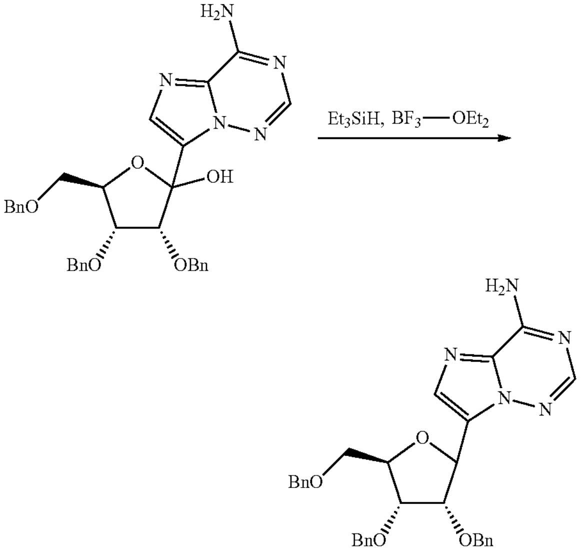


[0352] To a stirring mixture of 7-bromoimidazo[2,1-f][1,2,4]triazin-4-amine (41 g, 0.19 mol) in THF (0.50 L) at 0° C. was added MeMgBr (3.0M in THF, 66 mL, 0.19 mol) dropwise to maintain the internal temperature below 10° C. Bis(chlorodimethylsilyl)ethane (41 g, 190 mmol) was added in one portion. MeMgBr (3.0M in diethyl ether, 66 mL, 0.19 mol) was then added dropwise to maintain the internal temperature below 10° C. i-PrMgCl—LiCl (1.3 M in THF, 0.16 L, 0.21 mol) was added while maintaining the internal temperature below 10° C. A mixture of (3R,4R,5R)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)dihydrofuran-2(3H)-one (160 g, 0.38 mol) in THF was added dropwise at 0° C., and the mixture was then allowed to warm to rt and was stirred for 12 h. The mixture was diluted with saturated aqueous ammonium chloride (100 mL) and extracted with ethyl acetate (3×1000 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by column chromatography (column height: 2500 mm, diameter: 1000 mm, 25% to 75% ethyl acetate gradient in hexanes) to afford (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.

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

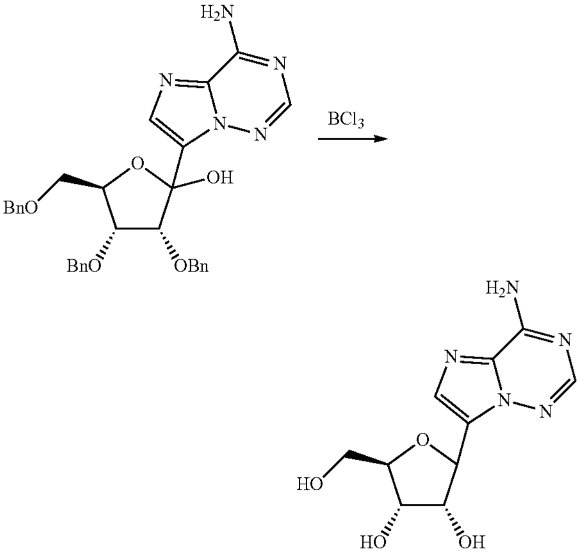
[0353]



[0354] To a stirring mixture of (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 (64 g, 0.12 mmol) in DCM (1.3 L) at 0° C. was added triethylsilane (81 g, 0.69 mol), and then boron trifluoride diethyl etherate (21 g, 0.15 mol). The mixture was then allowed to warm to 25° C., and the mixture was stirred for 1 h. More boron trifluoride diethyl etherate (57 g, 0.40 mol) was added, and the mixture was then heated to 35° C. for 4 h. Upon cooling to rt, the mixture was quenched with saturated aqueous sodium bicarbonate (200 mL) and then extracted with ethyl acetate (3×300 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by column chromatography (15-75% ethyl acetate gradient in hexanes) to afford 7-((3S,4R,5R)-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]+.

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

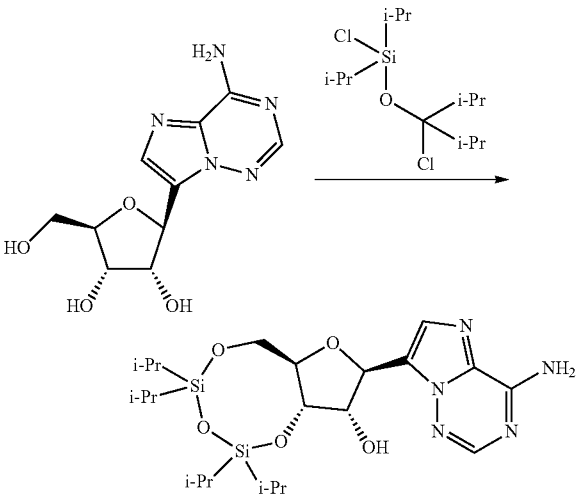
[0355]



[0356] To a stirring mixture of 7-((3S,4R,5R)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)-tetrahydrofuran-2-yl)imidazo[2, 1-f][1,2,4]triazin-4-amine (12 g, 22 mmol) in DCM (850 mL) at −78° C. was added boron trichloride (18 g, 0.16 mol) dropwise. Upon completion, the mixture was stirred at −78° C. for 3 h. After 3 h, the mixture was quenched with methanol (50 mL) 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% methanol gradient in dichloromethane) to afford (3R,4S,5R)-2-(4-aminoimidazo[2,1-f][1,2,4]triazin-7-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol.

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

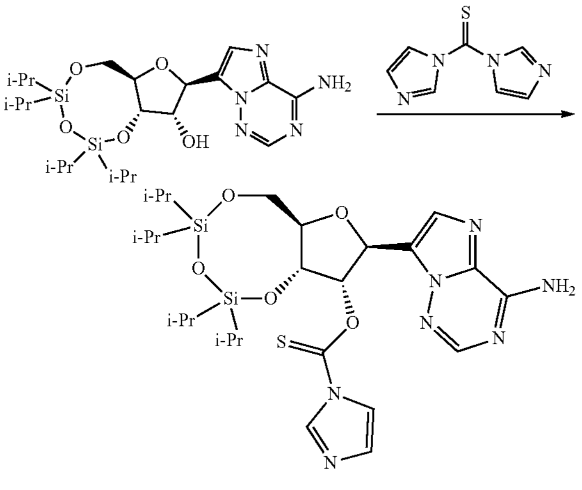
[0357]



[0358] To a stirred mixture of (2S,3R,4S,5R)-2-(4-aminoimidazo[2,1-f][1,2,4]triazin-7-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (4.0 g, 15 mmol) in pyridine (0.10 L) was added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (5.8 mL, 18 mmol). After 3 h, the mixture was diluted with toluene (50 mL) and then concentrated. The resulting mixture was taken up in DCM and methanol and then silica gel (40 g) was added. The mixture was concentrated, placed under vacuum for 1 h and then purified by column chromatography (0-80% ethyl acetate gradient in hexanes) to afford (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. MS (ES, m/z)=510 [M+H]+.

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

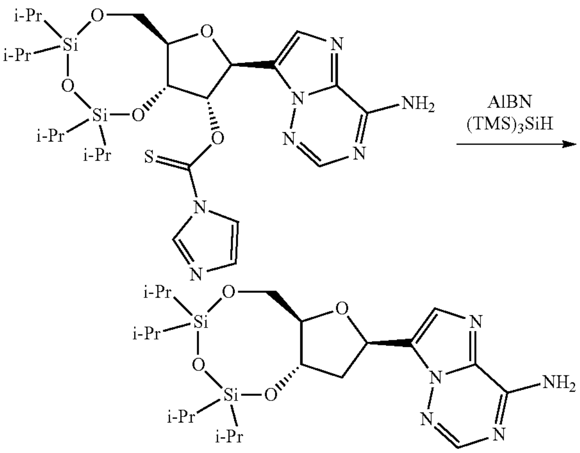
[0359]



[0360] To a mixture of (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 (6.45 g, 12.7 mmol) in acetonitrile (63.0 mL) and pyridine (63.0 mL) was added 1,1'-thiocarbonyldiimidazole (2.71 g, 15.2 mmol). After 90 min, more 1,1'-thiocarbonyldiimidazole (2.71 g, 15.2 mmol) was added, and the mixture was stirred overnight. After stirring overnight, the mixture was concentrated and purified by column chromatography (0-100% ethyl acetate gradient in hexanes) to afford 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-][1,3,5,2,4]trioxadisilocin-9-yl) 1H-imidazole-1-carbothioate. MS (ES, m/z) =620 [M+H]+.

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

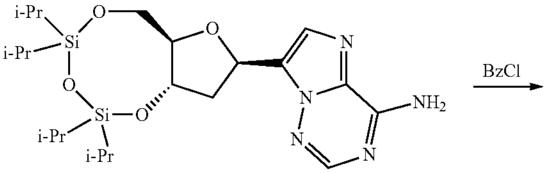
[0361]



[0362] To a mixture of 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-][1,3,5,2,4]trioxadisilocin-9-yl) (5.65 g, 9.11 mmol) in toluene (91.0 mL) was added 2,2'-azobis(2-methylpropionitrile) (0.300 g, 1.82 mmol) and tris(trimethylsilyl)silane (4.22 mL, 13.7 mmol). The mixture was heated to 85° C. for 30 min. After 30 min, the mixture was allowed to cool to rt and placed directly on the column and purified (0-80% ethyl acetate gradient in hexanes) to afford 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. MS (ES, m/z)=494 [M+H]+ 494.

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

[0363]



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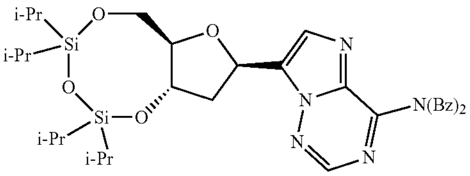
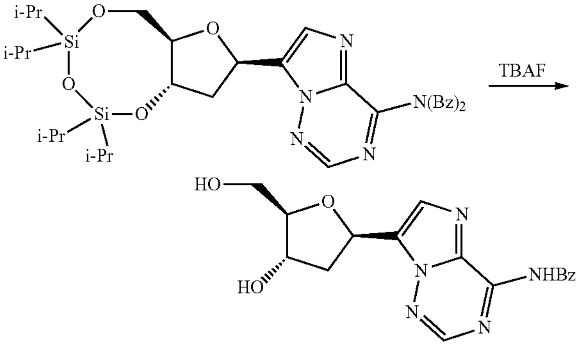


[0364] To a mixture of 7-((6aR,8R,9aS)-2,2,4,4-tetraisopropyltetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-8-yl)imidazo[2,1-f][1,2,4]triazin-4-amine (15.7 g, 31.8 mmol) in pyridine (64.0 mL) was added benzoyl chloride (11.0 mL, 95.0 mmol), and the mixture was heated to 50° C. for 45 min. After 45 min, the mixture was allowed to cool to rt. After cooling, a precipitate formed and was filtered off. The filtrate was diluted with DCM (50 mL) and toluene (50 mL). The mixture was concentrated to about 50 mL. The mixture was filtered, and the solids washed with DCM. The filtrate and washes were combined, loaded onto a column, and purified (0-50% ethyl acetate gradient in hexanes) to afford 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. MS (ES, m/z)=702 [M+H]+.

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

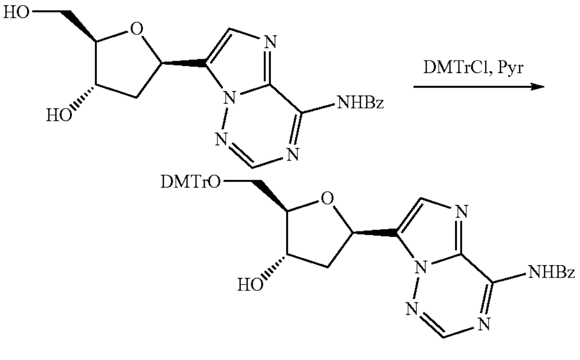
[0365]



[0366] To a mixture of 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 (10 g, 14 mmol) in tetrahydrofuran (0.14 L) was added TBAF ((1.0M in THF, 29 mL, 29 mmol), and the mixture was stirred for 1 h. After 1 h, the mixture was concentrated and purified by column chromatography to afford N-(7-((2R,4S,5R)-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]+.

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

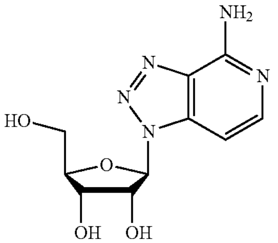
[0367]



[0368] To a mixture of N-(7-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)imidazo[2,1-f][1,2,4]triazin-4-yl)benzamide (6.1 g, 17 mmol) in pyridine (86 mL) at 0° C. was added 4,4'-(chloro(phenyl)methylene)bis(methoxybenzene) (5.8 g, 17 mmol), 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. The crude product was purified by silica gel chromatography (0-100% ethyl acetate gradient in hexanes) to afford 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. MS (ES, m/z)=658 [M+H]+.

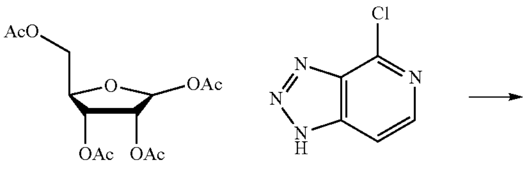
Preparation 10: (2R,3R,4S,5R)-2-(4-amino-1H-[1,2,3]triazolo[4,5-c]pyridin-1-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol

[0369]



Step 1: (2R,3R,4R,5R)-2-(acetoxymethyl)-5-(4-chloro-1H-[1,2,3]triazolo[4,5-c]pyridin-1-yl)tetrahydrofuran-3,4-diyl diacetate

[0370]



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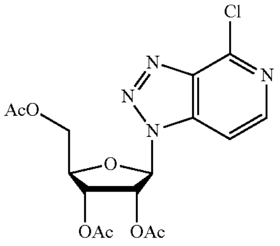
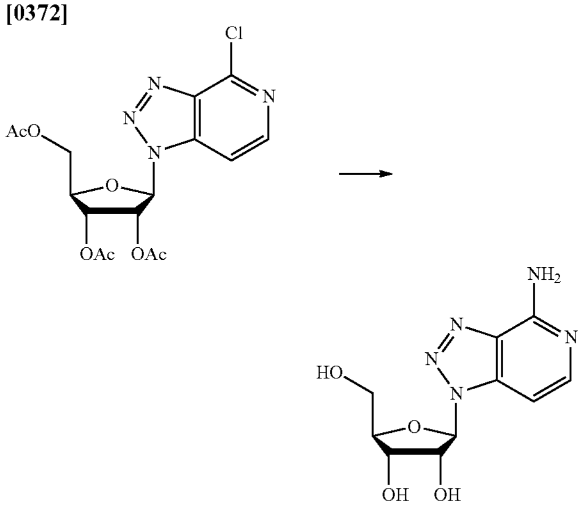


[0371] To a suspension of 4-chloro-1H-[1,2,3]triazolo[4,5-c]pyridine (1.0 g, 6.5 mmol) and (3R,4R,5R)-5-(acetoxymethyl)tetrahydrofuran-2,3,4-triyl triacetate (3.1 g, 9.7 mmol) in nitromethane (50 mL) was added $BF_3.Et_2O$ (1.23 mL, 9.7 mmol), and the resulting mixture was heated at 50° C. for 2 h. The reaction mixture was cooled to rt, diluted with 100 mL of DCM and washed with sat aq. $NaHCO_3$ (100 mL) and brine (100 mL). The separated organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by a silica gel column, eluting with 0-100% EtOAc:EtOH (3:1)/Hexane. LCMS (ES, m/z): 413.07 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d) δ 8.40 (d, J=5.8 Hz, 1H), 7.56 (d, J=5.8 Hz, 1H), 6.43 (d, J=4.1 Hz, 1H), 6.17 (dd, J=5.3, 4.1 Hz, 1H), 5.74 (t, J=5.3 Hz, 1H), 5.32 (s, 1H), 4.58 (ddd, J=5.3, 3.9, 2.9 Hz, 1H), 4.42 (dd, J=12.5, 3.0 Hz, 1H), 4.25 (dd, J=12.5, 3.9 Hz, 1H), 2.17 (d, J=18.8 Hz, 6H), 2.03 (s, 3H).

Step 2: (2R,3R,4S,5R)-2-(4-amino-1H-[1,2,3]triazolo[4,5-c]pyridin-1-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol

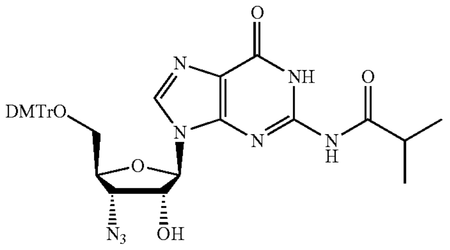
[0372]



[0373] To a solution of (2R,3R,4R,5R)-2-(acetoxymethyl)-5-(4-chloro-1H-[1,2,3]triazolo[4,5-c]pyridin-1-yl) tetrahydrofuran-3,4-diyl diacetate (1.2 g, 2.9 mmol) in MeOH (8.3 mL) was added a 7N solution of ammonia in MeOH (8.3 mmol, 58.1 mmol). The reaction mixture was stirred at 150° C. in a sealed Q-Tube™ Pressure Tube Reactor for 18 h. Excess solvent was removed under reduced pressure, and the residue was purified by a reverse phase silica gel column, eluting with 0-10% Acetonitrile/H_2O containing 0.05% TFA. LCMS (ES, m/z): 268.17 $[M+H]^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 13.87 (s, 2H), 9.34 (s, 4H), 7.89 (d, J=7.1 Hz, 2H), 7.51 (d, J=7.0 Hz, 2H), 7.42 (s, 4H), 7.32 (s, 6H), 7.22 (s, 5H), 6.69 (s, 2H), 6.30 (d, J=4.9 Hz, 2H), 5.72 (s, 2H), 5.41 (s, 2H), 4.75-4.67 (m, 0H), 4.65 (t, J=5.0 Hz, 2H), 4.27 (t, J=4.6 Hz, 2H), 4.07 (q, J=4.2 Hz, 2H), 3.86-3.67 (m, 2H), 3.69-3.58 (m, 2H), 3.54 (dd, J=12.0, 4.7 Hz, 2H), 3.48-3.38 (m, 1H), 3.28 (s, 1H), 3.23 (s, 0H), 1.76 (d, J=0.5 Hz, 5H), 1.11 (dt, J=26.0, 7.1 Hz, 1H).

Preparation 11: 9-{3-azido-5-O-[bis(4-methoxyphenyl)(phenyl)methyl]-3-deoxy-β-D-ribofuranosyl}-2-[(2-methylpropanoyl)amino]-1,9-dihydro-6H-purin-6-one

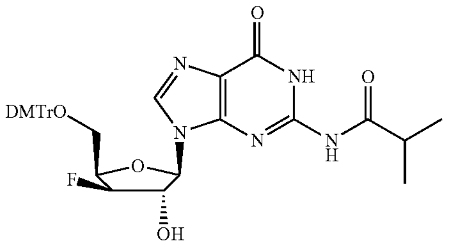
[0374]



[0375] The title compound was prepared according to published procedures (*Nucleosides, Nucleotides & Nucleic Acids* 2005, 24(10-12), 1707-1727).

Preparation 12: 9-{5-O-[bis(4-methoxyphenyl)(phenyl)methyl]-3-deoxy-3-fluoro-β-D-xylofuranosyl}-2-[(2-methylpropanoyl)amino]-1,9-dihydro-6H-purin-6-one

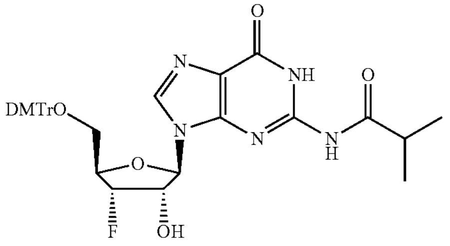
[0376]



[0377] The title compound was prepared according to published procedures (*Tetrahedron Letters,* 1989, 30(24), 3171-3174).

Preparation 13: 1-{5-O-[bis(4-methoxyphenyl)(phenyl)methyl]-3-deoxy-3-fluoro-β-D-ribofuranosyl}-6-[(2-methylpropanoyl)amino]-1,5-dihydro-4H-imidazo[4,5-c]pyridin-4-one

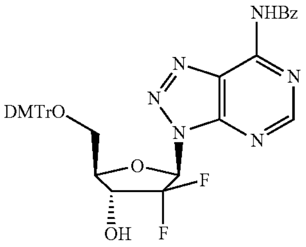
[0378]



[0379] The title compound was prepared according to published procedures (WO2002057425).

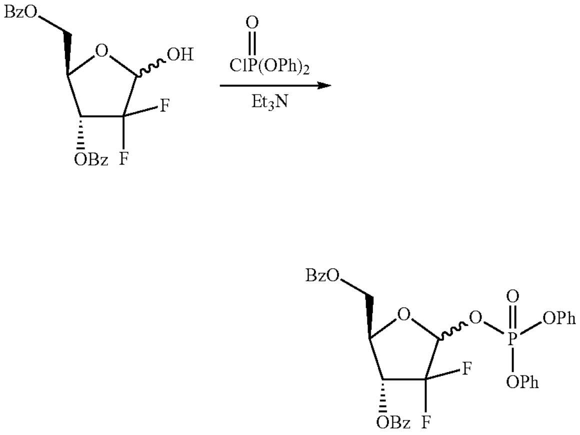
Preparation 14: N-(3-((2R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-3,3-difluoro-4-hydroxytetrahydrofuran-2-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl)benzamide

[0380]



Step 1: (((2R,3R)-3-(benzoyloxy)-5-((diphenoxyphosphoryl)oxy)-4,4-difluorotetrahydrofuran-2-yl)methyl benzoate

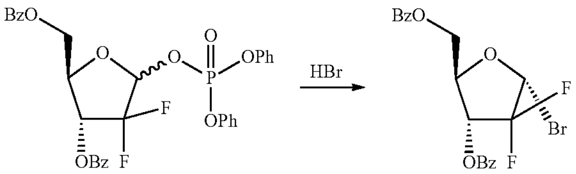
[0381]



[0382] To ((2R,3R)-3-(benzoyloxy)-4,4-difluoro-5-hydroxytetrahydrofuran-2-yl)methyl benzoate (20.0 g, 52.9 mmol) in toluene (150 mL) at 0° C. were added Et_3N (7.74 mL, 55.5 mmol) and diphenyl phosphoryl chloride (12.1 mL, 58.2 mmol) in toluene (20 mL) dropwise. The reaction was warmed to rt and stirred for 3 h. LCMS showed completion of the reaction (m/e=611). Water (30 mL) and aq HCl (1 M, 5 mL) were added. Layers were separated, and the aq layer was extracted with CH_2Cl_2 (2×30 mL). The combined organic solution was washed with sat aq $NaHCO_3$ (20 mL), and Brine (20 mL), dried ($MgSO_4$), and concentrated. It was purified by silica column chromatography eluting with 0 to 30% EtOAc in Hex to give the product. LCMS (ES, m/z): 611.3 $[M+H]^+$.

Step 2: ((2R,3R,5R)-3-(benzoyloxy)-5-bromo-4,4-difluorotetrahydrofuran-2-yl)methyl benzoate

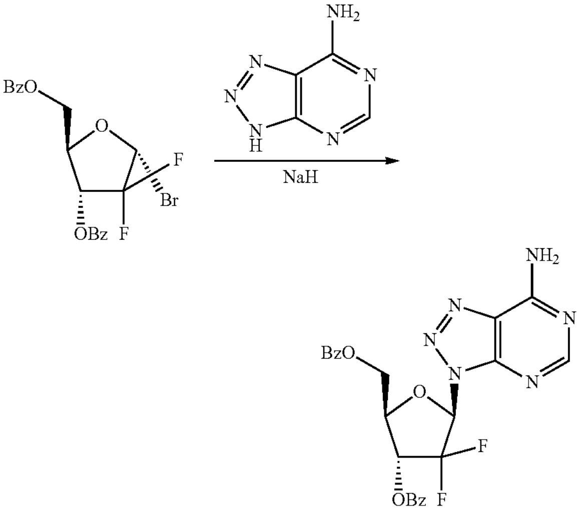
[0383]



[0384] To ((2R,3R)-3-(benzoyloxy)-5-((diphenoxyphosphoryl)oxy)-4,4-difluorotetrahydrofuran-2-yl)methyl benzoate (23.8 g, 39.0 mmol) at 0° C. was added HBr in acetic acid (33%, 51.2 mL, 292 mmol). It was stirred as it warmed to rt. After 6 h, LCMS showed completion of the reaction (m/e=441 and 443). CH_2Cl_2 (200 mL) was added, and the organic layer was washed with water (2×50 mL), sat aq $NaHCO_3$ (2×50 mL) and brine (50 mL). It was dried ($MgSO_4$) and concentrated to give the crude product. It was used in the next step without purification. LCMS (ES, m/z): 441.1, 443.1 $[M+H]^+$.

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

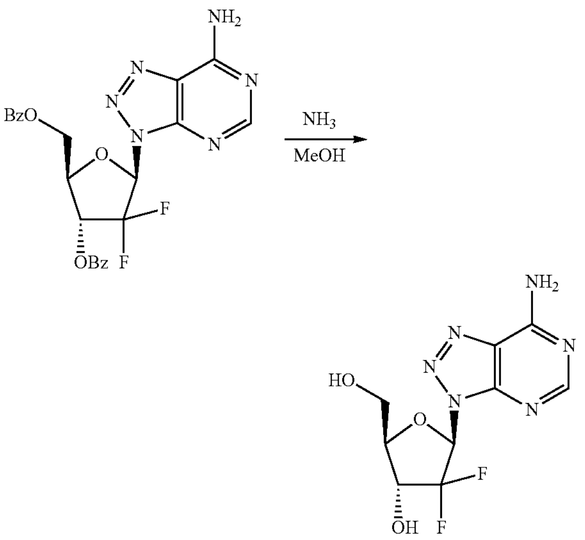
[0385]



[0386] To a mixture of 3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-amine (3.21 g, 23.6 mmol) in NMP (60 mL) was added NaH (60%, 0.979 g, 24.5 mmol). The mixture was vigorously stirred, and after 1 h, generation of bubbles had completely ceased. To the mixture was added to ((2R,3R,5R)-3-(benzoyloxy)-5-bromo-4,4-difluorotetrahydrofuran-2-yl)methyl benzoate (neat, 8.00 g, 18.1 mmol). The mixture was stirred vigorously for 30 min. Then, it was heated to 90° C. for 5 h. It was cooled to rt, and CH_2Cl_2 (300 mL) and water (150 mL) were added. The phases were separated, and the organic layer was washed with water (8×150 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated. The residue was purified by silica column chromatography eluting with 0% to 30% EtOAc to give the desired product. LCMS (ES, m/z): 497.1 $[M+H]^+$. ^{1}H NMR (500 MHz, Chloroform-d) δ 8.44 (s, 1H), 8.15-8.08 (m, 2H), 8.08-7.99 (m, 2H), 7.63 (ddt, J=8.7, 7.1, 1.3 Hz, 1H), 7.56-7.44 (m, 3H), 7.40-7.32 (m, 2H), 6.79-6.68 (m, 2H), 6.04 (bs, 2H), 4.92-4.84 (m, 1H), 4.80-4.72 (m, 2H).

Step 4. (2R,3R,5R)-5-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-4,4-difluoro-2-(hydroxymethyl)tetrahydrofuran-3-ol

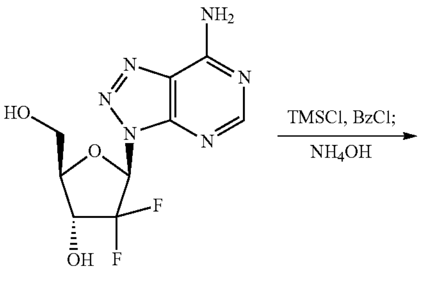
[0387]



[0388] To (2R,3R,5R)-5-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-2-((benzoyloxy) methyl)-4,4-difluorotetrahydrofuran-3-yl benzoate (1.05 g, 2.11 mmol) was added ammonia in MeOH (7N, 9.0 mL, 63 mmol), and the mixture was stirred for 24 h. LCMS showed completion of reaction (m/e=289). It was concentrated and purified by silica column chromatography eluting with 0 to 15% MeOH in CH_2Cl_2 to give the desired product. LCMS (ES, m/z): 289.1 $[M+H]^+$. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 8.65 (s, 1H), 8.36 (s, 1H), 8.32 (s, 1H), 6.65 (d, J=12.4 Hz, 1H), 6.40 (d, J=6.7 Hz, 1H), 5.03 (dd, J=6.4, 5.3 Hz, 1H), 4.83 (dq, J=16.5, 8.9 Hz, 1H), 4.00 (t, J=6.7 Hz, 1H), 3.77 (ddd, J=12.3, 5.2, 2.5 Hz, 1H), 3.68 (dt, J=12.5, 6.3 Hz, 1H).

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

[0389]



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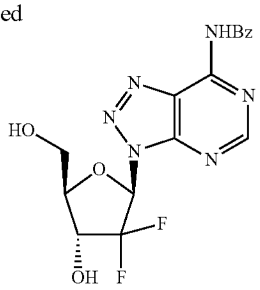
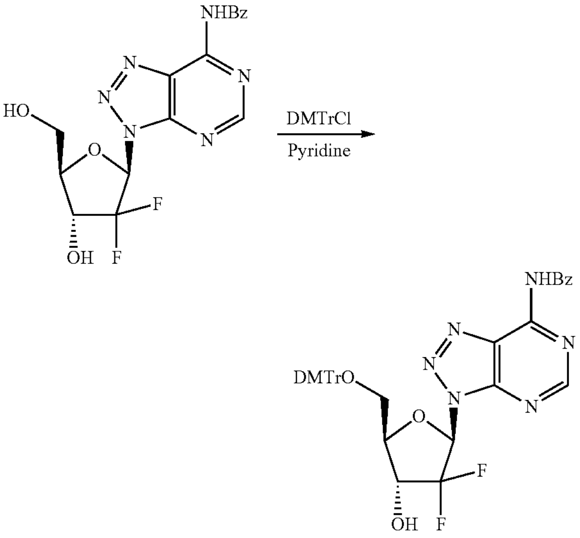


[0390] To a solution of (2R,3R,5R)-5-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-4,4-difluoro-2-(hydroxymethyl)tetrahydrofuran-3-ol (0.57 g, 2.0 mmol) in pyridine (15 mL) at 0° C. was added TMSCl (0.55 mL, 4.3 mmol). It was warmed to rt and stirred for 1 h. Then, it was recooled to 0° C. and BzCl (0.34 mL, 2.9 mmol) was added dropwise. The reaction was slowly warmed rt over 2 h. LCMS showed completion of reaction (m/e=393,497). It was cooled to 0° C., and ammonium hydroxide (28%, 1.1 mL, 7.9 mmol) was added. After 30 min, it was concentrated and purified by silica column chromatography eluting with 0 to 10% MeOH in CH_2Cl_2 to give the product. LCMS (ES, m/z): 393.3 $[M+H]^+$. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 12.02 (s, 1H), 9.01 (s, 1H), 8.13-8.07 (m, 2H), 7.73-7.66 (m, 1H), 7.64-7.55 (m, 2H), 6.86 (d, J=11.6 Hz, 1H), 6.46 (d, J=6.7 Hz, 1H), 5.01 (dd, J=6.3, 5.4 Hz, 1H), 4.86 (dt, J=16.7, 8.3 Hz, 1H), 4.04 (ddd, J=8.8, 6.2, 2.6 Hz, 1H), 3.78 (ddd, J=12.3, 5.4, 2.7 Hz, 1H), 3.68 (dt, J=12.4, 6.2 Hz, 1H).

Step 6: N-(3-((2R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-3,3-difluoro-4-hydroxytetrahydrofuran-2-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl)benzamide

[0391]

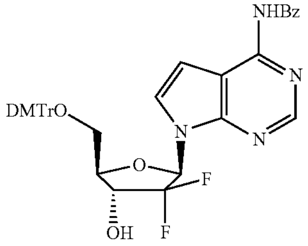


[0392] To a solution of N-(3-((2R,4R,5R)-3,3-difluoro-4-hydroxy-5-(hydroxymethyl)-tetrahydrofuran-2-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl)benzamide (0.68 g, 1.7 mmol) in pyridine (15 mL) at 0° C. was added DMTrCl

(0.65 g, 1.9 mmol). It was stirred at rt for 1 h. LCMS showed a peak with the desired mass (m/e=695). It was partly concentrated (to 5 mL), and EtOAc (20 mL) and water (10 mL) were added. The phases were separated, and the aqueous layer was extracted with EtOAc (2×10 mL). The combined organic portions were washed with brine, 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): 695.2 $[M+H]^+$. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 12.05 (s, 1H), 8.93 (s, 1H), 8.11 (d, J=7.6 Hz, 2H), 7.70 (m, 1H), 7.60 (t, J=7.7 Hz, 2H), 7.38-7.32 (m, 2H), 7.25-7.13 (m, 7H), 6.96 (d, J=11.9 Hz, 1H), 6.84-6.73 (m, 4H), 6.48 (d, J=6.9 Hz, 1H), 4.97 (dq, J=16.7, 8.3 Hz, 1H), 4.23 (m, 1H), 3.70 (s, 3H), 3.69 (s, 3H), 3.42-3.36 (m, 1H), 3.32-3.28 (m, 1H).

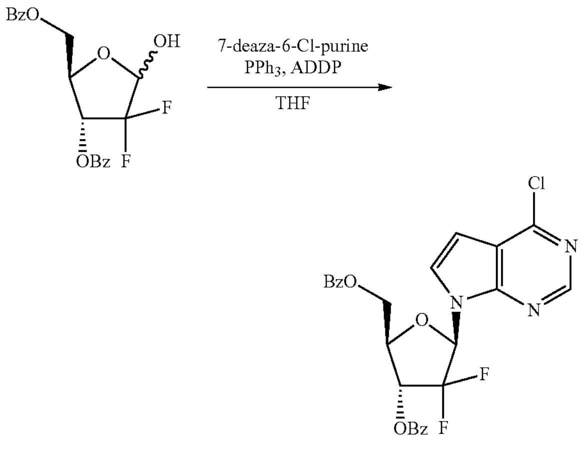
Preparation 15: N-(7-((2R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-3,3-difluoro-4-hydroxytetrahydrofuran-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzamide

[0393]



Step 1: ((2R,3R,5R)-3-(benzoyloxy)-5-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-4,4-difluorotetrahydrofuran-2-yl)methyl benzoate

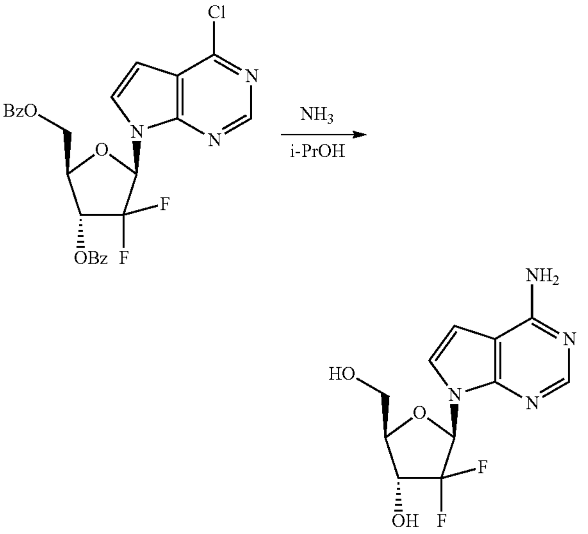
[0394]



[0395] To a solution of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (4.06 g, 26.4 mmol) and ((2R,3R)-3-(benzoyloxy)-4,4-difluoro-5-hydroxytetrahydrofuran-2-yl)methyl benzoate (10.0 g, 26.4 mmol) and triphenylphosphine (20.80 g, 79 mmol) in THF (100 mL) was added (E)-diazene-1,2-diylbis(piperidin-1-ylmethanone) (20.01 g, 79 mmol) dropwise. It was slowly warmed to rt. After stirring for 2 h, the mixture was concentrated. The residue was purified by silica gel column chromatography using 0-20% EtOAc in Petroleum Ether to give the product. LCMS (ES, m/z): 514.3 $[M+H]^+$. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.71 (s, 1H), 8.08-7.87 (m, 5H), 7.76-7.42 (m, 6H), 6.98 (dd, J=10.3, 7.9 Hz, 1H), 6.84 (d, J=3.8 Hz, 1H), 6.29 (ddd, J=10.0, 6.0, 3.8 Hz, 1H), 5.44 (q, J=5.5 Hz, 1H), 4.79-4.60 (m, 2H).

Step 2. (2R,3R,5R)-5-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-4,4-difluoro-2-(hydroxymethyl)tetrahydrofuran-3-ol

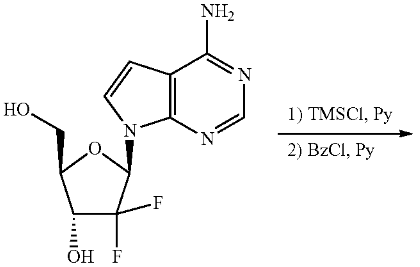
[0396]



[0397] A solution of ((2R,3R,5R)-3-(benzoyloxy)-5-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-4,4-difluorotetrahydrofuran-2-yl)methyl benzoate (1.9 g, 3.70 mmol) in NH_3/2-propanol (saturated at −78° C., 100 mL) was stirred at 90° C. for 16 h. It was cooled to rt, concentrated, and purified by silica gel column chromatography using 0-10% MeOH in CH_2Cl_2 to give the product. LCMS (ES, m/z): 287.1 $[M+H]^+$. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.06 (s, 1H), 7.40-7.25 (m, 1H), 7.14 (s, 2H), 6.82 (d, J=5.9 Hz, 1H), 6.60 (d, J=3.7 Hz, 1H), 6.34 (dd, J=16.2, 2.1 Hz, 1H), 4.88 (t, J=5.7 Hz, 1H), 4.27 (ddd, J=9.9, 6.2, 3.6 Hz, 1H), 4.08 (dq, J=6.8, 4.1, 3.5 Hz, 1H), 3.78 (dt, J=11.1, 5.4 Hz, 1H), 3.62 (dt, J=11.4, 5.8 Hz, 1H).

Step 3: N-(7-((2R,4R,5R)-3,3-difluoro-4-hydroxy-5-hydroxymethyl)tetrahydrofuran-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzamide

[0398]



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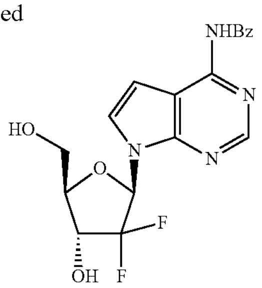
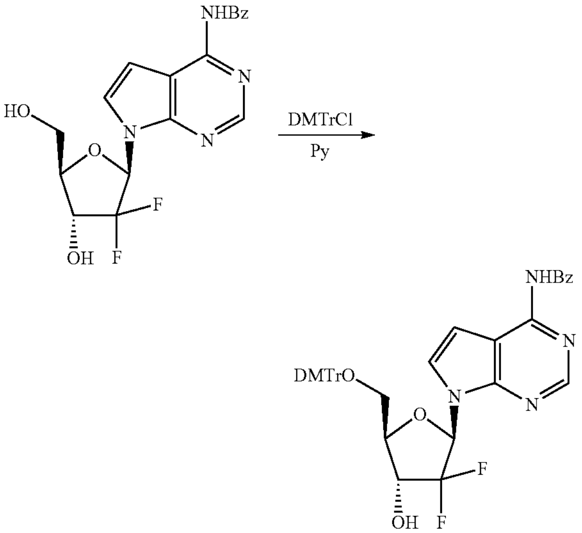


[0399] To a solution of (2R,3R,5R)-5-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-4,4-difluoro-2-(hydroxymethyl)tetrahydrofuran-3-ol (900 mg, 3.14 mmol) in pyridine (15 mL) at 0° C. was added chlorotrimethylsilane (3.42 g, 31.4 mmol). It was warmed to rt over 1 h and benzoyl chloride (663 mg, 4.72 mmol) was added dropwise. After 2 h, NH_4OH (28%, 15.00 mL) was added, and it was stirred for 0.5 h. The resulting mixture was concentrated, and the residue was purified by silica gel column chromatography using 0-10% MeOH in CH_2Cl_2 to give the product. LCMS (ES, m/z): 391.1 $[M+H]^+$. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.61 (s, 1H), 8.08-7.98 (m, 2H), 7.97-7.91 (m, 1H), 7.67-7.51 (m, 2H), 7.50-7.47 (m, 1H), 6.70 (d, J=3.9 Hz, 1H), 6.56 (dd, J=15.6, 1.5 Hz, 1H), 4.32 (dd, J=9.4, 3.6 Hz, 1H), 4.16 (d, J=5.6 Hz, 1H), 3.80 (dd, J=11.5, 5.2 Hz, 1H), 3.66 (dd, J=11.5, 6.5 Hz, 1H), 3.12 (s, 2H).

Step 4: N-(7-((2R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-3,3-difluoro-4-hydroxytetrahydrofuran-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzamide

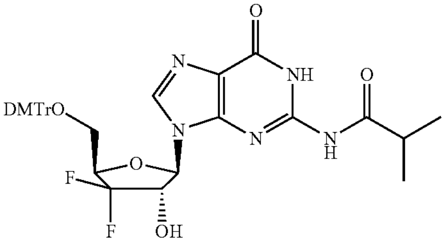
[0400]



[0401] To a solution of N-(7-((2S,4R,5R)-3,3-difluoro-4-hydroxy-5-(hydroxymethyl)-tetrahydrofuran-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzamide (1.1 g, 2.82 mmol) in pyridine (12 mL) at 0° C. was added 4,4'-(chloro(phenyl)methylene)-bis(methoxybenzene) (0.955 g, 2.82 mmol). It was warmed to RT and stirred for 3 h. The mixture was concentrated. The product was purified by silica gel column chromatography using 0-10% MeOH in CH_2Cl_2 to give the product. LCMS (ES, m/z): 693.3 $[M+H]^+$. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 11.25 (s, 1H), 8.67 (s, 1H), 8.09-8.01 (m, 2H), 7.60-7.48 (m, 2H), 7.47-7.36 (m, 3H), 7.33-7.18 (m, 7H), 6.91-6.78 (m, 4H), 6.75-6.57 (m, 3H), 5.76 (s, 1H), 4.55-4.33 (m, 2H), 3.74 (s, 6H), 3.44 (t, J=8.7 Hz, 1H), 3.35 (s, 1H).

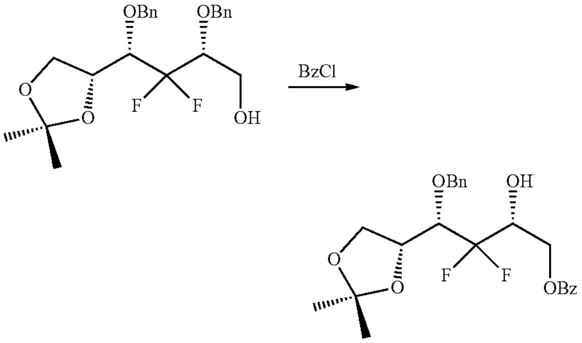
Preparation 16: N-(9-((2R,3S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4,4-difluoro-3-hydroxytetrahydrofuran-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide

[0402]



Step 1: (2R,4S)-4-(benzyloxy)-4-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3,3-difluoro-2-hydroxybutyl benzoate

[0403]

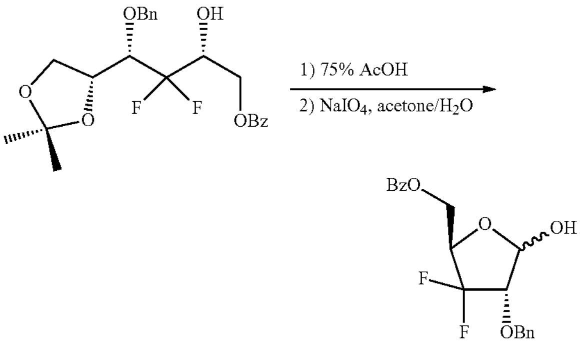


[0404] To a solution of (2R,4S)-4-(benzyloxy)-4-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3,3-difluorobutane-1,2-diol (3.50 g, 10.5 mmol) in CH_2Cl_2 (52 mL) and pyridine (26 mL) at −70° C. was added benzoyl chloride (1.48 g, 10.5 mmol) in CH_2Cl_2 (11 mL) dropwise over 50 min. After 2 h, methanol (150 mL) was added. The mixture was stirred at RT for 0.5 h. Water (200 mL) was added. Layers were separated, and the aq layer was extracted with ether (4×150 mL). The combined organic layers were washed with aq HCl (1 N, 2×150 mL), sat aq $NaHCO_3$ (2×150 mL) and brine (2×150 mL). It was dried (Na_2SO_4), concentrated and purified by silica gel column chromatography (EtOAc/petroleum ether=1/10) to give the product. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.11-8.01 (m, 2H), 7.61-7.55 (m, 1H), 7.48-7.31 (m, 7H), 4.89-4.53 (m, 4H), 4.46-4.41 (m, 1H), 4.40-4.29 (m, 1H), 4.17-4.02 (m, 2H), 3.98-3.84 (m, 0.5H), 3.74-3.66

(m, 0.5H), 1.46 (s, 3H), 1.28 (s, 3H). ^{19}F-NMR: (376 MHz, $CDCl_3$): δ −106.8 (d, J=270.7 Hz, 1F), −119.2 (d, J=270.7 Hz, 1F).

Step 2: ((2R,4S)-4-(benzyloxy)-3,3-difluoro-5-hydroxytetrahydrofuran-2-yl)methyl benzoate

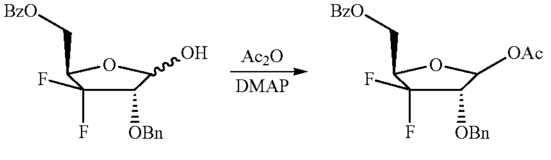
[0405]



[0406] (2R,4 S)-4-(benzyloxy)-4-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3,3-difluoro-2-hydroxybutyl benzoate (3.00 g, 6.87 mmol) was dissolved in aq AcOH (75%, 66 mL). It was stirred at 50° C. for 3 h. It was partly concentrated. The residue was redissolved in acetone (33 mL). To the solution at rt was added sodium periodate (1.20 g, 5.61 mmol) in water (33 mL). After 1.5 h, the solid formed was filtered off and washed with acetone. The filtrate was concentrated. Water and CH_2Cl_2 were added, and layers were separated. The aq layer was extracted with CH_2Cl_2 (4×150 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by silica gel column chromatography (ethyl acetate/petroleum ether=1/5) to give the product. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.05-8.01 (m, 2H), 7.59-7.52 (m, 1H), 7.46-7.35 (m, 7H), 5.49-5.42 (m, 1H), 4.99-4.72 (m, 1H), 4.67-4.47 (m, 4H), 4.11-3.80 (m, 1H). ^{19}F-NMR: (376 MHz, $CDCl_3$): δ −117.1 (d, J=240.6 Hz, 1F), −117.9 (d, J=251.9 Hz, 1F).

Step 3: ((2R,4S)-5-acetoxy-4-(benzyloxy)-3,3-difluorotetrahydrofuran-2-yl)methyl benzoate

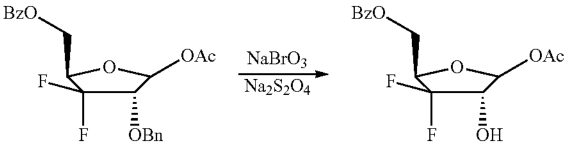
[0407]



[0408] To a solution of ((2R,4S)-4-(benzyloxy)-3,3-difluoro-5-hydroxytetrahydrofuran-2-yl)methyl benzoate (2.40 g, 6.59 mmol) in CH_2Cl_2 (66 mL) at rt was added N,N-dimethylpyridin-4-amine (0.080 g, 0.659 mmol) and acetic anhydride (4.03 g, 39.5 mmol) dropwise. After 6 h, it was quenched by addition of sat aq $NaHCO_3$ (30 mL). Layers were separated, and the aq layer was extracted with CH_2Cl_2 (3×150 mL). The combined organic layers were washed with water (2×150 mL) and brine (2×100 mL), dried (Na_2SO_4), concentrated and purified by silica gel column chromatography (ethyl acetate/petroleum ether=1/7) to give the product. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.08-7.89 (m, 2H), 7.61-7.48 (m, 1H), 7.47-7.25 (m, 7H), 6.15 (d, J=6.0 Hz, 1H), 4.89-4.75 (m, 1H), 4.73-4.40 (m, 4H), 4.18-4.02 (m, 1H), 1.98 (s, 3H). ^{19}F-NMR: (282 MHz, $CDCl_3$): δ −116.5 (d, J=248.2 Hz, 1F), −120.9 (d, J=248.2 Hz, 1F).

Step 4. ((2R,4S)-5-acetoxy-3,3-difluoro-4-hydroxytetrahydrofuran-2-yl)methyl benzoate

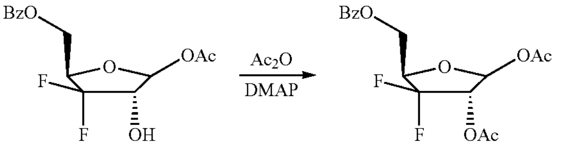
[0409]



[0410] To a solution of ((2R,4S)-5-acetoxy-4-(benzyloxy)-3,3-difluorotetrahydrofuran-2-yl)methyl benzoate (2.50 g, 6.15 mmol) in EtOAc (60 mL) was added sodium bromate (5.57 g, 36.9 mmol) in water (46 mL). The mixture was stirred vigorously, and to it was added sodium dithionite (6.43 g, 36.9 mmol) in water (92 mL) dropwise over 1 h. After 5 h, layers were separated, and the aq layer was extracted with EtOAc (5×150 mL). The combined organic layers were washed with sat aq $Na_2S_2O_3$ (2×150 mL) and brine (2×150 mL), dried (Na_2SO_4), concentrated, and purified by silica gel column chromatography (ethyl acetate/petroleum ether=1/5) to give the product. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.10-7.89 (m, 2H), 7.63-7.50 (m, 1H), 7.48-7.30 (m, 2H), 6.09 (d, J=6.0 Hz, 1H), 4.71-4.42 (m, 3H), 4.36-4.26 (m, 1H), 2.04 (s, 3H). ^{19}F-NMR: (282 MHz, $CDCl_3$): δ −119.5 (d, J=248.2 Hz, 1F), −122.0 (d, J=248.2 Hz, 1F).

Step 5: (3S,5R)-5-((benzoyloxy)methyl)-4,4-difluorotetrahydrofuran-2,3-diyl diacetate

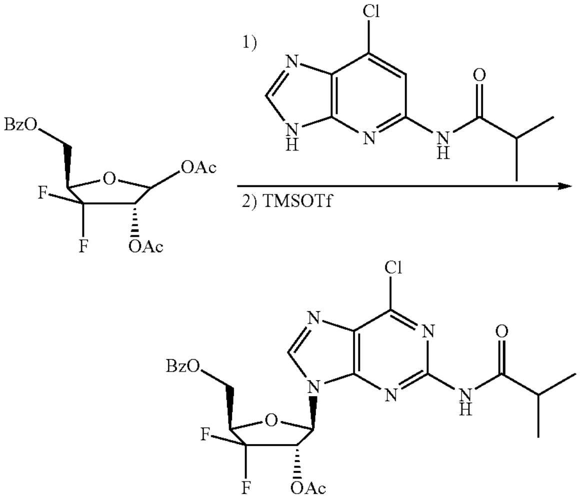
[0411]



[0412] To a solution of ((2R,4S)-5-acetoxy-3,3-difluoro-4-hydroxytetrahydrofuran-2-yl)methyl benzoate (2.00 g, 6.32 mmol) in CH_2Cl_2 (84 mL) at rt was added DMAP (0.08 g, 0.632 mmol) and acetic anhydride (3.87 g, 37.9 mmol) dropwise. After 6 h, it was quenched by addition of sat aq $NaHCO_3$ (30 mL). Layers were separated, and the aq layer was extracted with CH_2Cl_2 (3×140 mL). The combined organic layers were washed with water (2×140 mL) and brine (2×140 mL), dried (Na_2SO_4), concentrated and purified by silica gel column chromatography (ethyl acetate/petroleum ether=1/6) to give the product. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.11-8.01 (m, 2H), 7.63-7.54 (m, 1H), 7.50-7.41 (m, 2H), 6.20 (d, J=4.0 Hz, 1H), 5.39 (d, J=8.0 Hz, 1H), 4.69-4.48 (m, 3H), 2.23 (s, 3H), 2.08 (s, 3H). ^{19}F-NMR: (376 MHz, $CDCl_3$): δ −117.6 (d, J=251.9 Hz, 1F), −119.5 (d, J=251.9 Hz, 1F).

Step 6. ((2R,4S,5R)-4-acetoxy-5-(6-chloro-2-isobutyramido-9H-purin-9-yl)-3,3-difluorotetrahydrofuran-2-yl)methyl benzoate

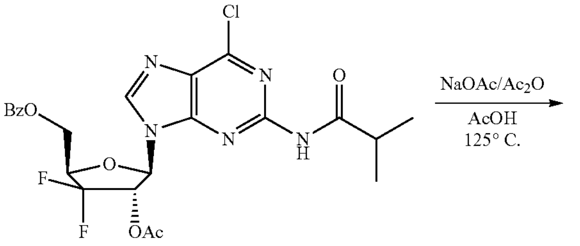
[0413]



[0414] To a solution of (3 S,5R)-5-((benzoyloxy)methyl)-4,4-difluorotetrahydrofuran-2,3-diyl diacetate (2.20 g, 6.14 mmol) and N-(6-chloro-9H-purin-2-yl)isobutyramide (1.77 g, 7.37 mmol) in ACN (80 mL) at 0° C. was added 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepine (2.80 mL, 18.4 mmol). After 0.5 h, trimethylsilyl trifluoromethanesulfonate (6.82 mL, 36.8 mmol) was added dropwise to the reaction at 0° C. After 0.5 h, it was heated at 80° C. for 16 h. The reaction was then quenched by the addition of water (150 mL). Layers were separated, and the aq layer was extracted with EtOAc (3×150 mL). The combined organic layers were washed with sat aq $NaHCO_3$ (2×150 mL) and brine (2×150 mL), dried (Na_2SO_4), concentrated and purified by silica gel column chromatography (ethyl acetate/petroleum ether=1/1) to give the product. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 8.08-7.98 (m, 2H), 7.64-7.53 (m, 1H), 7.51-7.40 (m, 2H), 6.25 (d, J=4.0 Hz, 1H), 5.98-5.93 (m, 1H), 4.85-4.53 (m, 3H), 2.92-2.80 (m, 1H), 2.22 (s, 3H) 1.28 (d, J=4.0 Hz, 6H). ^{19}F-NMR: (376 MHz, $CDCl_3$): δ −116.7 (d, J=248.2 Hz, 1F), −118.1 (d, J=248.2 Hz, 1F).

Step 7: ((2R,4S,5R)-5-(2-acetamido-6-oxo-1,6-dihydro-9H-purin-9-yl)-4-acetoxy-3,3-difluorotetrahydrofuran-2-yl)methyl benzoate

[0415]



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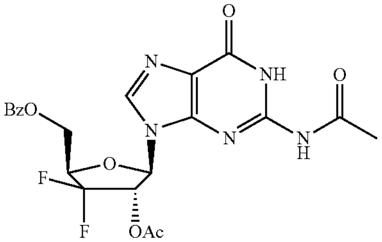
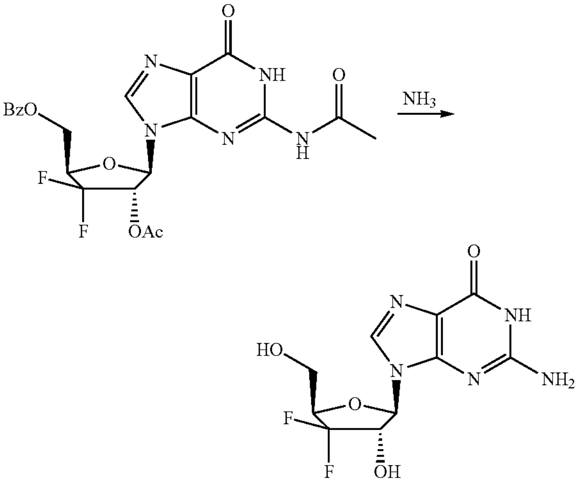


[0416] To a solution of ((2R,4S,5R)-4-acetoxy-5-(6-chloro-2-isobutyramido-9H-purin-9-yl)-3,3-difluorotetrahydrofuran-2-yl)methyl benzoate (1.80 g, 3.35 mmol) in AcOH (29 mL) was added Sodium acetate (1.37 g, 16.7 mmol) and acetic anhydride (29 mL). The reaction was stirred at 125° C. for 2.5 h. It was cooled to rt, and MeOH (50 mL) was added. The mixture was concentrated under reduced pressure, and the residue was coevaporated with ethanol (2×50 mL). DCM (150 mL) and water (150 mL) were added, and layers were separated. The organic phase was washed with sat aq $NaHCO_3$ (2×150 mL), dried (Na_2SO_4), and concentrated to give the product. LCMS (ES, m/z): 492.1 $[M+H]^+$.

Step 8: 2-amino-9-((2R,3S,5R)-4,4-difluoro-3-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-1,9-dihydro-6H-purin-6-one

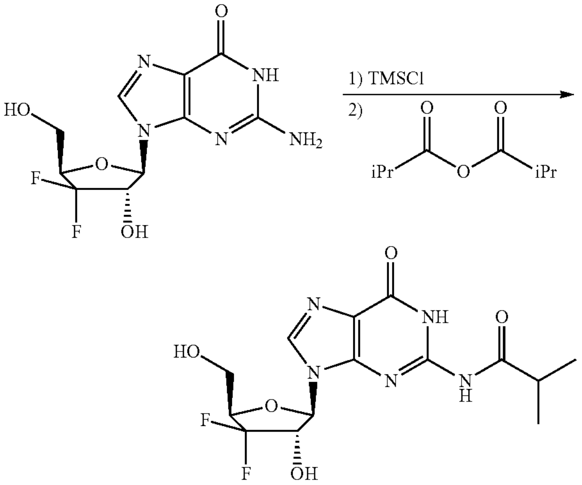
[0417]



[0418] To ((2R,4S,5R)-5-(2-acetamido-6-oxo-1,6-dihydro-9H-purin-9-yl)-4-acetoxy-3,3-difluorotetrahydrofuran-2-yl)methyl benzoate (neat, 1.80 g, 3.66 mmol) was added NH_3 in MeOH (7 M, 90 mL, MeOH). It was stirred at rt for 60 h. It was concentrated and purified by reverse phase (C18) chromatography eluting with 5-20% MeCN in aq NH_4HCO_3 (5 mM) to give the product. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 10.7 (s, 1H), 7.95 (s, 1H), 6.56-6.44 (m, 3H), 5.62 (d, J=6.0 Hz, 1H), 5.32 (t, J=5.4 Hz, 1H), 4.90-4.77 (m, 1H), 4.23-4.08 (m, 1H), 3.68-3.52 (m, 2H). ^{19}F-NMR: (282 MHz, DMSO-d_6): δ −113.1 (d, J=234.1 Hz, 1F), −121.8 (d, J=234.1 Hz, 1F).

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

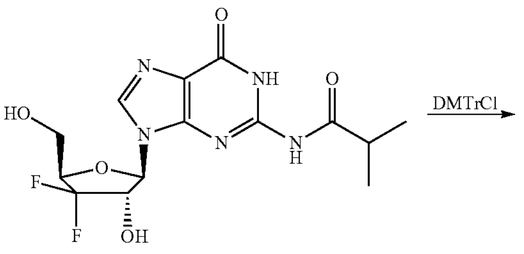
[0419]



[0420] 2-amino-9-((2R,3 S,5R)-4,4-difluoro-3-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-1,9-dihydro-6H-purin-6-one (800 mg, 2.64 mmol) was co-evaporated with pyridine (3×3 mL). It was re-suspended in pyridine (13 mL). To the mixture at 0° C. was added chlorotrimethylsilane (1.686 mL, 13.19 mmol) dropwise. It was warmed to rt and stirred for 2 h. The reaction was cooled to 0° C., and isobutyric anhydride (0.656 mL, 3.96 mmol) was added dropwise. It was warmed to rt, stirred for 2 h, and then water (4 mL) and NH_4OH (8 mL) were added to the reaction. After 30 min, it was concentrated. The residue was purified by flash column chromatography with 0-10% MeOH in CH_2Cl_2 to give the product. LCMS (ES, m/z): 374.1 $[M+H]^+$. ^{1}H-NMR: (300 MHz, DMSO-d_6) δ 12.11 (s, 1H), 11.69 (s, 1H), 8.30 (s, 1H), 6.58 (d, J=6.0 Hz, 1H), 5.74 (dd, J=9.0, 3.0 Hz, 1H), 5.33 (t, J=6.0 Hz, 1H), 4.96-4.83 (m, 1H), 4.26-4.17 (m, 1H), 3.72-3.62 (m, 2H), 2.80-2.71 (m, 1H), 1.11 (d, J=9.0 Hz, 6H).

Step 10: N-(9-((2R,3S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4,4-difluoro-3-hydroxytetrahydrofuran-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide

[0421]



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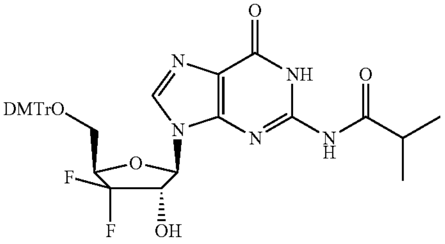
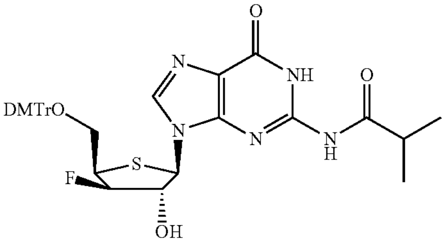


[0422] N-(9-((2R,3 S,5R)-4,4-difluoro-3-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide (640 mg, 1.714 mmol) was co-evaporated with pyridine (3×3 mL) and then re-suspended in pyridine (5.7 mL). To the suspension was added 4,4'-(chloro(phenyl)methylene)bis(methoxybenzene) (639 mg, 1.886 mmol), and it was stirred for 16 h. Then, it was concentrated and then, co-evaporated with toluene (3×20 mL). The crude was purified by silica column chromatography eluting with 1 to 30% MeOH in CH_2Cl_2 (containing 1% Et_3N) to give the product. LCMS (ES, m/z): 676.3 $[M+H]^+$. ^{1}H-NMR: (300 MHz, DMSO-d_6) δ 12.11 (s, 1H), 11.61 (s, 1H), 8.15 (s, 1H), 7.34 (J=6.0, 3.0 Hz, 2H), 7.28-7.19 (m, 7H), 6.85-6.80 (m, 4H), 6.71 (d, J=6.0 Hz, 1H), 5.78 (d, J=6.0 Hz, 1H), 5.13-5.05 (m, 1H), 4.46-4.39 (m, 1H), 3.71 (s, 6H), 3.46-3.40 (m, 1H), 3.22-3.18 (m, 1H), 2.78-2.70 (m, 1H), 1.11 (d, J=9.0 Hz, 6H).

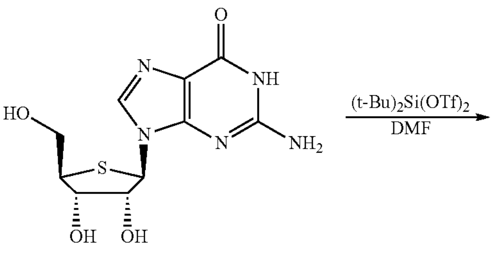
Preparation 17: N-(9-((2R,3R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)-methoxy)methyl)-4-fluoro-3-hydroxytetrahydrothiophen-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide

[0423]



Step 1: 2-amino-9-((4aR,6R,7R,7aR)-2,2-di-tert-butyl-7-hydroxytetrahydro-4H-thieno[3,2-d][1,3,2]dioxasilin-6-yl)-1,9-dihydro-6H-purin-6-one

[0424]



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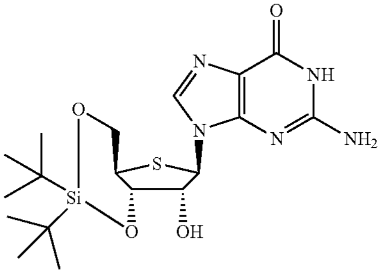
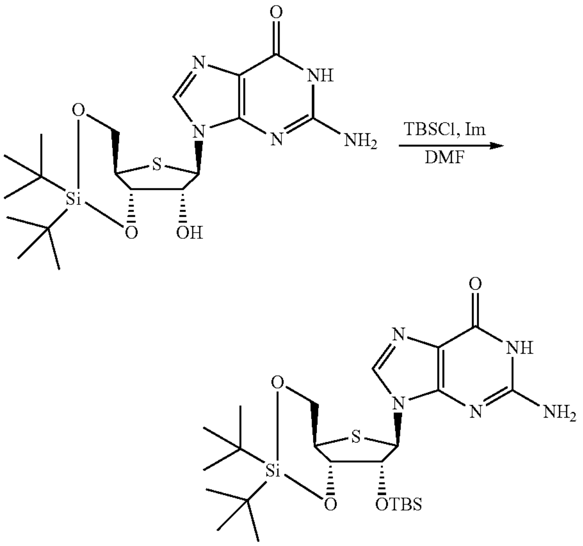


[0425] To a stirred suspension of 2-amino-9-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrothiophen-2-yl)-1H-purin-6(9H)-one (15 g, 50.1 mmol) in DMF (150 mL) at 0° C. under Ar was injected di-tert-butylsilanediyl bis(trifluoromethanesulfonate) (26.5 g, 60.1 mmol). The resulting solution was stirred at rt for 1 h. It was used for the next reaction step directly without purification. LCMS (ES, m/z): 440.2 $[M+H]^+$.

Step 2: 2-amino-9-((4aR,6R,7R,7aR)-2,2-di-tert-butyl-7-((tert-butyldimethylsilyl)oxy) tetrahydro-4H-thieno[3,2-d][1,3,2]dioxasilin-6-yl)-1,9-dihydro-6H-purin-6-one

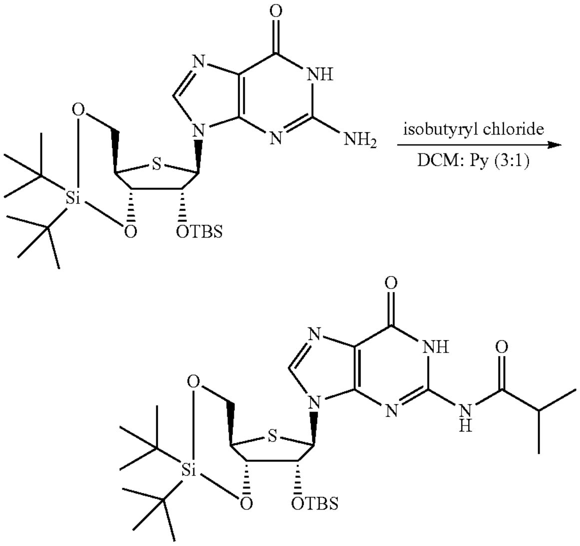
[0426]



[0427] To the reaction mixture from the previous step at 0° C. was added 1H-imidazole (17.05 g, 251 mmol) in one portion. The mixture was stirred rt for 0.5 h. tert-butylchlorodimethylsilane (15.10 g, 100 mmol) was added to the mixture, and it was stirred at 60° C. for 16 h. Then, the volatile components were removed under reduced pressure. The solid was suspended in cold methanol (75 mL), filtered, and washed with cold methanol (2×30 mL). The solid was kept under reduced pressure to give the product. LCMS (ES, m/z): 554.4 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.80 (s, 1H), 7.98 (s, 1H), 6.49 (s, 2H), 5.53 (s, 1H), 4.46 (d, J=3.2 Hz, 1H), 4.42 (d, J=9.9 Hz, 1H), 4.34 (dd, J=9.9, 4.7 Hz, 1H), 4.21 (t, J=10.5 Hz, 1H), 3.70-3.64 (m, 1H), 1.04 (s, 9H), 1.00 (s, 9H), 0.92 (s, 9H), 0.19 (s, 3H), 0.11 (s, 3H).

Step 3: N-(9-((4aR,6R,7R,7aR)-2,2-di-tert-butyl-7-((tert-butyldimethylsilyl)oxy)tetrahydro-4H-thieno[3,2-d][1,3,2]dioxasilin-6-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide

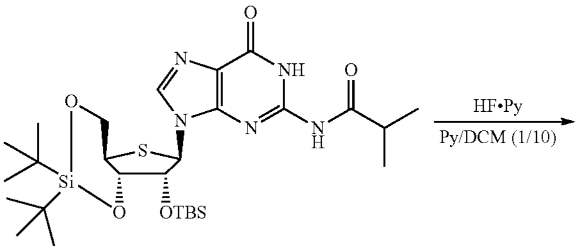
[0428]



[0429] 2-amino-9-((4aR,6R,7R,7aS)-2,2-di-tert-butyl-7-((tert-butyldimethylsilyl)oxy)tetrahydro-4H-thieno[3,2-d][1,3,2]dioxasilin-6-yl)-1H-purin-6(9H)-one (29.1 g, 52.5 mmol) was co-evaporated with dry pyridine (3×50 mL) and re-dissolved in pyridine (70 mL) and dichloromethane (210 mL). The mixture was charged with Ar and cooled to 0° C. To the mixture was added isobutyryl chloride (11.20 g, 105 mmol). It was stirred at rt for 4 h. It was concentrated under reduced pressure. The solid was suspended in cold methanol (100 mL), filtered, and washed with cold methanol (3×50 mL). The solid was kept under reduced pressure to give the product. LCMS (ES, m/z): 624.1 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.13 (s, 1H), 11.39 (s, 1H), 8.32 (s, 1H), 5.61 (s, 1H), 4.66 (d, J=3.4 Hz, 1H), 4.48 (d, J=9.9 Hz, 1H), 4.38-4.33 (m, 1H), 4.21 (t, J=9.9 Hz, 1H), 3.76-3.70 (m, 1H), 2.84-2.80 (m, 1H), 1.13 (d, J=6.7 Hz, 6H), 1.06 (s, 9H), 1.01 (s, 9H), 0.91 (s, 9H), 0.16 (s, 3H), 0.11 (s, 3H).

Step 4. N-(9-((2R,3R,4S,5R)-3-((tert-butyldimethylsilyl)oxy)-4-hydroxy-5-(hydroxymethyl)tetrahydrothiophen-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl) isobutyramide

[0430]



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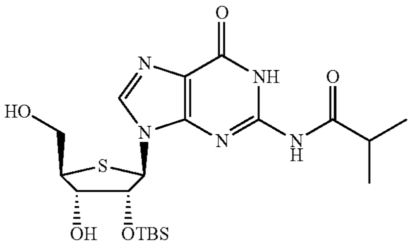
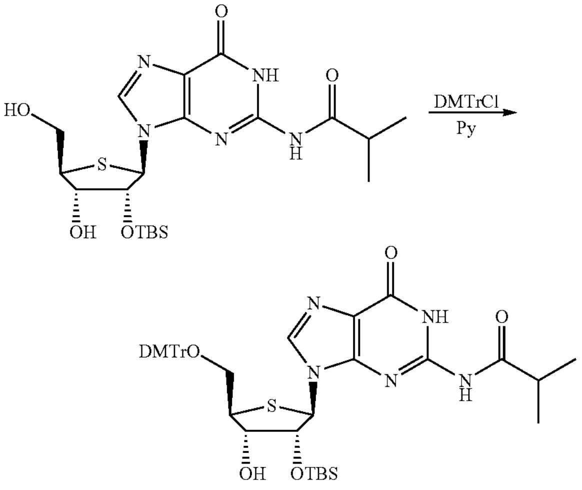


[0431] HF-Pyridine (26.6 g, 188 mmol) at 0° C. was diluted with pyridine (29 mL). The resulting solution was added slowly to a stirred suspension of N-(9-((4aR,6R,7R,7aS)-2,2-di-tert-butyl-7-((tert-butyldimethylsilyl)oxy)tetrahydro-4H-thieno[3,2-d][1,3,2]dioxasilin-6-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide (29.3 g, 47.0 mmol) in CH_2Cl_2 (290 mL) at 0° C. It was stirred at 0° C. for 2 h. The reaction mixture was diluted with CH_2Cl_2 (500 mL). It was washed with water (500 mL) and sat aq $NaHCO_3$ (500 mL). The organic layer was dried (Na_2SO_4) and concentrated to give the product. LCMS (ES, m/z): 484.4 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.05 (s, 1H), 11.73 (s, 1H), 8.43 (s, 1H), 5.89 (d, J=7.9 Hz, 1H), 5.34 (d, J=3.9 Hz, 1H), 5.27 (t, J=5.6 Hz, 1H), 4.60 (dd, J=8.1, 3.2 Hz, 1H), 4.19-4.17 (m, 1H), 3.80-3.74 (m, 1H), 3.66-3.60 (m, 1H), 3.30 (t, J=8.0 Hz, 1H), 2.80-2.73 (m, 1H), 1.12 (d, J=6.7 Hz, 6H), 0.68 (s, 9H), −0.06 (s, 3H), −0.29 (s, 3H).

Step 5. N-(9-((2R,3R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-3-((tert-butyldimethylsilyl)oxy)-4-hydroxytetrahydrothiophen-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide

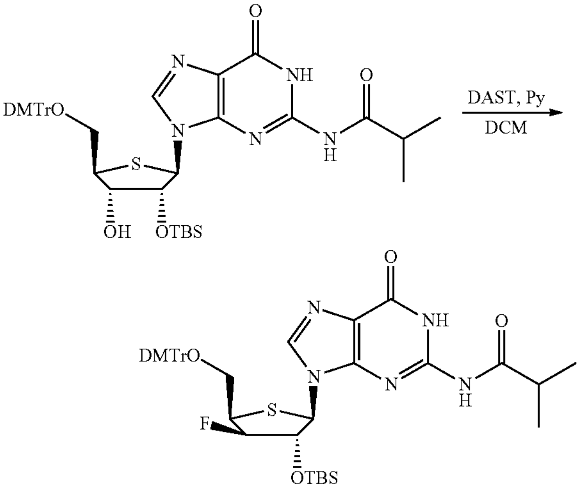
[0432]



[0433] N-(9-((2R,3R,4S,5R)-3-((tert-butyldimethylsilyl)oxy)-4-hydroxy-5-(hydroxymethyl)tetrahydrothiophen-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide (21 g, 43.4 mmol) was co-evaporated with pyridine (3×50 mL) and dissolved in pyridine (210 mL). 4,4'-(chloro(phenyl)methylene)bis(methoxybenzene) (16.2 g, 47.8 mmol) was added, and it was stirred at rt for 3 h and then concentrated under reduced pressure and co-evaporated with toluene (3×50 mL). The crude was purified by silica gel chromatography eluting with 0-40% EtOAc in CH_2Cl_2 (containing 0.1% Et_3N) to give the product. LCMS (ES, m/z): 786.4 $[M+H]^+$. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 12.06 (s, 1H), 11.71 (s, 1H), 8.19 (s, 1H), 7.44-7.42 (m, 2H), 7.37-7.22 (m, 7H), 6.92 (d, J=8.5 Hz, 4H), 5.87 (d, J=7.2 Hz, 1H), 5.44 (d, J=4.4 Hz, 1H), 4.40 (dd, J=7.3, 3.3 Hz, 1H), 4.19 (d, J=5.9 Hz, 1H), 3.75 (s, 6H), 3.54-3.35 (m, 2H), 3.34-3.28 (m, 1H), 2.83-2.71 (m, 1H), 1.11 (d, J=6.7 Hz, 6H), 0.70 (s, 9H), −0.08 (s, 3H), −0.29 (s, 3H).

Step 6: N-(9-((2R,3R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-3-((tert-butyldimethylsilyl)oxy)-4-fluorotetrahydrothiophen-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide

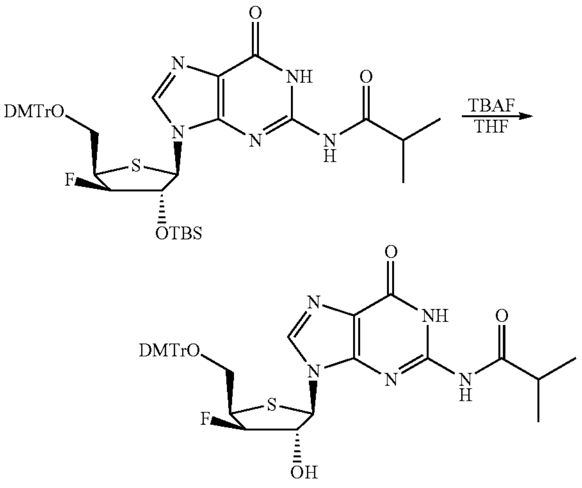
[0434]



[0435] To a solution of N-(9-((2R,3R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)-methyl)-3-((tert-butyldimethylsilyl)oxy)-4-hydroxytetrahydrothiophen-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide (22 g, 28.0 mmol) in CH_2Cl_2 (220 mL) at 0° C. was added pyridine (18.11 mL, 224 mmol) and DAST (14.79 mL, 112 mmol) dropwise. The reaction was allowed to warm to rt and stirred for 7 h. It was then cooled to 0° C. and quenched by slow addition of sat aq $NaHCO_3$ (500 mL). More CH_2Cl_2 (500 mL) was added, and the phases were separated. The organic phase was washed with sat aq $NaHCO_3$ (3×200 mL) and brine (300 mL), dried (Na_2SO_4), concentrated, and purified by reverse phase (C18) chromatography eluting with 45-95% of ACN in aq NH_4HCO_3 (5 mM) to give the product. LCMS (ES, m/z): 788.2 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.06 (s, 1H), 11.56 (s, 1H), 8.02 (s, 1H), 7.44-7.42 (m, 2H), 7.34-7.23 (m, 7H), 6.92-6.89 (m, 4H), 5.71 (d, J=4.9 Hz, 1H), 5.14 (dt, J=51.0, 5.6 Hz, 1H), 5.01-4.96 (m, 1H), 3.88-3.85 (m, 1H), 3.75 (s, 6H), 3.57 (t, J=8.8 Hz, 1H), 3.50 (dd, J=10.0, 5.3 Hz, 1H), 2.81-2.74 (m, 1H), 1.12 (d, J=6.8 Hz, 6H), 0.77 (s, 9H), 0.00 (s, 3H), −0.16 (s, 3H). F-NMR: (376 MHz, DMSO-d_6, ppm) δ −193.99 (s, 1F).

Step 7: N-(9-((2R,3R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-fluoro-3-hydroxytetrahydrothiophen-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide

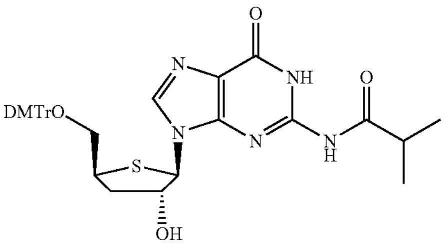
[0436]



[0437] To a solution of N-(9-((2R,3R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)-methoxy) methyl)-3-((tert-butyldimethylsilyl)oxy)-4-fluorotetrahydrothiophen-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide (7.2 g, 6.85 mmol) in THF (70 mL) at rt was added TBAF (1.0M in THF, 8.22 mL, 8.22 mmol) dropwise. It was stirred at rt for 30 min, the solution was concentrated, and CH_2Cl_2 (300 mL) was added. The mixture was washed with $NaHCO_3$ (3×200 mL) and brine (200 mL), and the organic phase was separated, dried (Na_2SO_4), concentrated and purified by reverse phase (C18) chromatography eluting with 0-95% of ACN in aq NH_4HCO_3 (5 mM) to give the product. LCMS (ES, m/z): 674.3 $[M+H]^+$. ^1H-NMR (400 MHz, DMSO-d_6): δ 12.02 (br, 1H), 7.85 (s, 1H), 7.44-7.41 (m, 2H), 7.36-7.24 (m, 7H), 6.94-6.90 (m, 4H), 6.33 (bs, 1H), 5.78 (d, J=2.7 Hz, 1H), 5.19 (dt, J=50.2, 4.0 Hz, 1H), 4.80-4.75 (m, 1H), 4.10-4.02 (m, 1H), 3.76 (s, 6H), 3.55 (dd, J=9.3, 5.6 Hz, 1H), 3.44 (t, J=8.9 Hz, 1H), 2.79-2.71 (m, 1H), 1.12 (d, J=6.8 Hz, 6H). F-NMR: (376 MHz, DMSO-d_6) δ −194.75 (s).

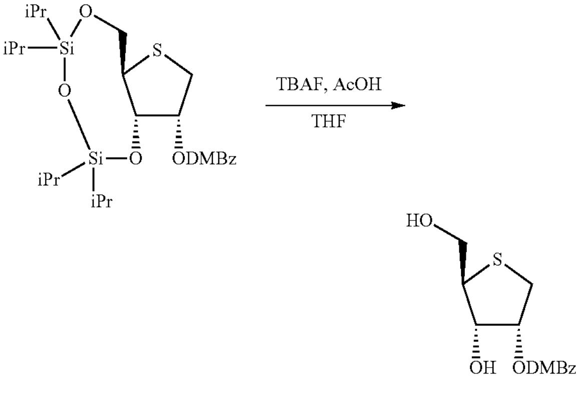
Preparation 18: N-(9-((2R,3R,5S)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-3-hydroxytetrahydrothiophen-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide

[0438]



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

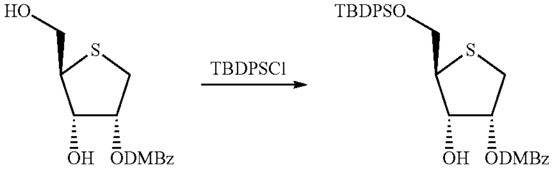
[0439]



[0440] 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 (60 g, 108 mmol) in THF (500 mL) were added AcOH (13.59 g, 226 mmol) and TBAF in THF (1 M, 226 mL, 226 mmol). After 1 h, 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 $[M+H]^+$. 1H-NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J=8.7 Hz, 1H), 6.58-6.46 (m, 2H), 5.51 (dt, J=5.0, 3.7 Hz, 1H), 4.31 (td, J=6.9, 3.7 Hz, 1H), 3.88 (d, J=12.0 Hz, 8H), 3.58 (dt, J=7.1, 4.7 Hz, 1H), 3.26 (dd, J=12.2, 5.0 Hz, 1H), 3.15-3.01 (m, 2H), 2.31 (s, 1H).

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

[0441]

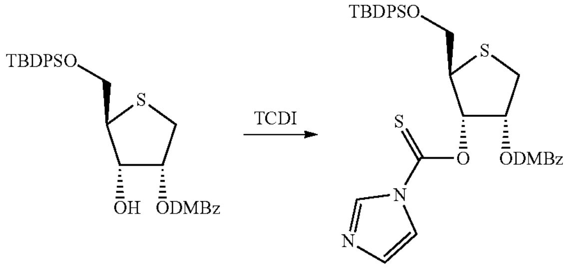


[0442] To a solution of (3R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrothiophen-3-yl 2,4-dimethoxybenzoate (33 g, 105 mmol) in pyridine (300 mL) was added tert-butylchlorodiphenylsilane (43.3 g, 157 mmol). It was stirred at rt for 4 h. Then, water (300 mL) was added. Layers were separated, and the aq layer was extracted with CH_2Cl_2 (3×300 mL). The combined organic layer was washed with brine (300 mL), 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 $[M+Na]^+$. ^1H-NMR (400 MHz, DMSO-d_6) δ 7.83 (d, J=8.7 Hz, 1H), 7.68 (t, J=5.5 Hz, 5H), 7.54-7.38 (m, 6H), 6.69-6.60 (m, 2H), 5.40 (d, J=5.6 Hz, 1H), 5.35-5.29 (m, 1H), 4.12 (s, 1H), 4.05 (d, J=7.3 Hz, 1H), 3.85 (d, J=7.2

Hz, 6H), 3.78-3.66 (m, 1H), 3.55 (d, J=7.2 Hz, 1H), 3.14 (dd, J=11.0, 5.0 Hz, 1H), 2.86-2.77 (m, 1H), 1.03 (s, 9H).

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

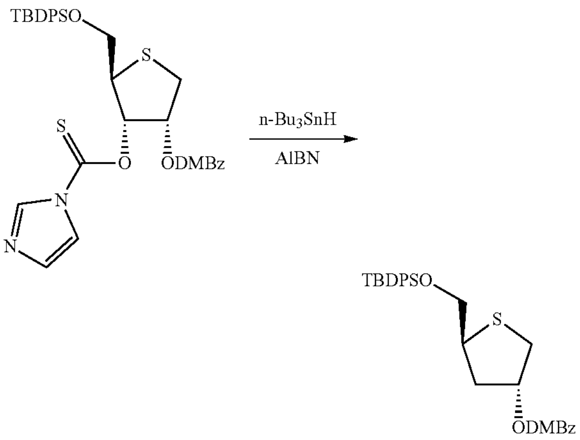
[0443]



[0444] To a solution of (3R,4S,5R)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-4-hydroxytetrahydrothiophen-3-yl 2,4-dimethoxybenzoate (48 g, 87 mmol) in dichloroethane (500 mL) was added di(1H-imidazol-1-yl)methanethione (20.12 g, 113 mmol). It was heated at 85° C. under Ar for 1 h. Then, it was concentrated and used in the next step without purification. LCMS (ES, m/z): 663.2 $[M+H]^+$.

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

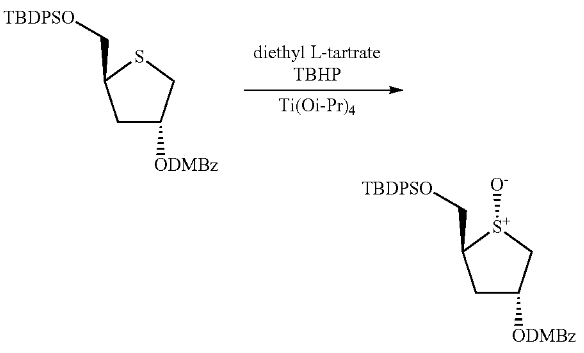
[0445]



[0446] 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, 57.6 g, 87 mmol) in THF (40 mL) and toluene (200 mL) was added tributylstannane (139 g, 478 mmol). It was heated at 95° C., and 2,2'-(diazene-1,2-diyl)bis(2-methylpropanenitrile) (1.427 g, 8.69 mmol) in toluene (200 mL) was added over 30 min. After 1 h, 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 (400 MHz, $CDCl_3$) δ 7.88 (d, J=8.6 Hz, 1H), 7.77-7.67 (m, 4H), 7.50-7.36 (m, 6H), 6.58-6.48 (m, 2H), 5.70 (p, J=3.8 Hz, 1H), 3.95-3.74 (m, 10H), 3.28 (dd, J=12.0, 4.6 Hz, 1H), 3.10-3.02 (m, 1H), 2.49-2.39 (m, 1H), 1.92 (ddd, J=13.3, 8.6, 4.1 Hz, 1H), 1.09 (s, 9H).

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

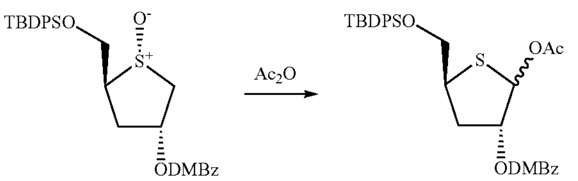
[0447]



[0448] To a solution of $Ti(OiPr)_4$ (23.29 mL, 78 mmol) in CH_2Cl_2 (130 mL) under Ar was added diethyl (L)-tartrate (38.3 mL, 224 mmol) dropwise. After 10 min, the mixture was cooled to −20° C., and then TBHP in decane (~5.5M, 27.1 mL, 149 mmol) was added dropwise. After 5 min, a solution of (3R,5S)-5-(((tert-butyldiphenylsilyl)oxy)methyl) tetrahydrothiophen-3-yl 2,4-dimethoxybenzoate (40 g, 74.5 mmol) in CH_2Cl_2 (130 mL) was added to the reaction at −20° C. The resulting mixture was stirred at −20° C. for 16 h. It was quenched by the addition of ice water (300 mL) and allowed to warm up to rt. The precipitate was filtered off and washed with EtOAc (3×300 mL). The filtrate was washed with water (3×200 mL). The aq layer was extracted with EtOAc (400 mL). 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 (400 MHz, DMSO-d_6) δ 7.81 (d, J=8.7 Hz, 1H), 7.75-7.61 (m, 4H), 7.54-7.39 (m, 6H), 6.67-6.56 (m, 2H), 5.66 (q, J=3.8 Hz, 1H), 4.12 (dt, J=10.5, 4.4 Hz, 1H), 3.92-3.79 (m, 8H), 3.58-3.42 (m, 1H), 3.20-3.09 (m, 1H), 2.97 (d, J=15.0 Hz, 1H), 2.05 (ddd, J=14.5, 10.5, 4.3 Hz, 1H), 1.02 (s, 9H).

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

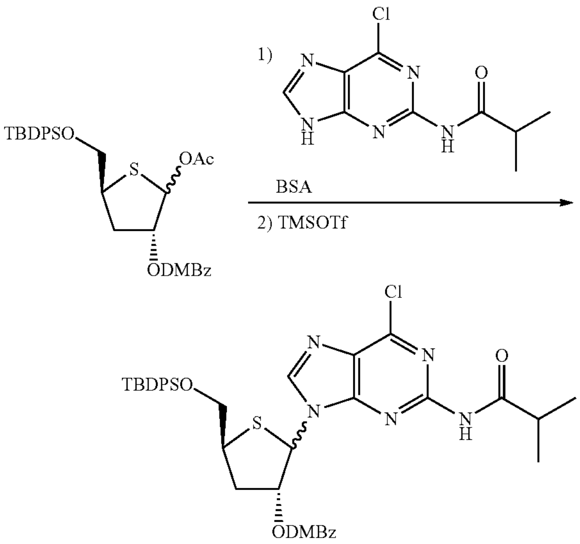
[0449]



[0450] A solution of (3R,5S)-2-acetoxy-5-(((tert-butyldiphenylsilyl)oxy)methyl)-tetrahydrothiophen-3-yl 2,4-dimethoxybenzoate (21 g, 34.2 mmol) in acetic anhydride (210 mL) was heated at 110° C. After stirring of 3.5 h, 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–OAc]$^+$. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.76-7.61 (m, 5H), 7.46 (dq, J=7.6, 4.5, 3.7 Hz, 6H), 6.68-6.58 (m, 2H), 6.22 (d, J=4.3 Hz, 0.65H), 5.94 (s, 0.28H), 5.51-5.46 (m, 0.33H), 5.38 (ddd, J=11.1, 7.2, 4.3 Hz, 0.65H), 3.96-3.61 (m, 9H), 2.40-2.21 (m, 2H), 2.03 (d, J=1.6 Hz, 3H), 1.01 (s, 9H).

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

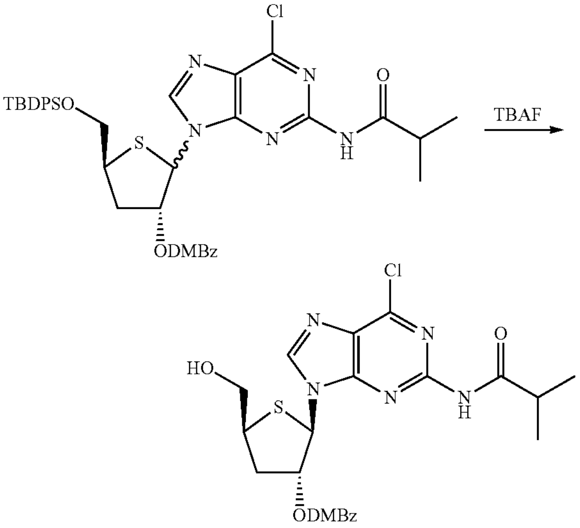
[0451]



[0452] To a solution of N-(6-chloro-9H-purin-2-yl)isobutyramide (10.27 g, 42.9 mmol) in toluene (600 mL) at 0° C. was added trimethylsilyl N-(trimethylsilyl)acetimidate (23.26 g, 114 mmol). It was heated at 80° C. for 1 h and was cooled to 0° C. again. To the reaction was then added a solution of (3R,5S)-2-acetoxy-5-(((tert-butyldiphenylsilyl) oxy)methyl)-tetrahydrothiophen-3-yl 2,4-dimethoxybenzoate (17 g, 28.6 mmol) in toluene (600 mL) and trimethylsilyl trifluoromethanesulfonate (19.06 g, 86 mmol). It was heated to 80° C. and stirred under Ar for 12 h. At that time, the reaction was cooled to rt, and sat aq NaHCO$_3$ (400 mL) was added. Layers were separated, and the aq layer was extracted with EtOAc (4×1000 mL). The combined organic phase was dried (Na$_2$SO$_4$), concentrated and purified by silica gel column chromatography eluting with 10% to 40% EtOAc in petroleum ether to give the product (mixture of a and 3 isomers). LCMS (ES, m/z): 774.3 [M+H]$^+$. ^{1}H-NMR (400 MHz, 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, 1.5 Hz, 4H), 7.54 (d, J=8.7 Hz, 0.33H), 7.49-7.36 (m, 6H), 6.57-6.36 (m, 2.5H), 6.18 (d, J=2.4 Hz, 0.7H), 5.87-5.80 (m, 0.35H), 5.73 (q, J=3.3 Hz, 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=6.8 Hz, 2.19H), 1.19 (dd, J=6.8, 3.5 Hz, 4.38H), 1.09 (d, J=1.7 Hz, 9H).

Step 8. (2R,3R,5S)-2-(6-chloro-2-isobutyramido-9H-purin-9-yl)-5-(hydroxymethyl)-tetrahydrothiophen-3-yl 2,4-dimethoxybenzoate

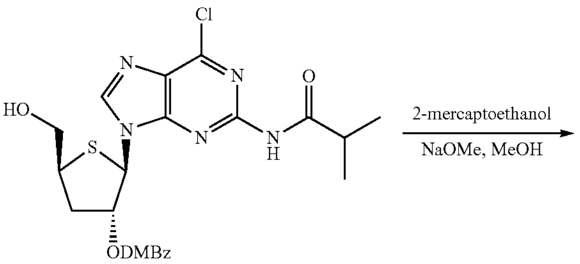
[0453]



[0454] To a solution of (3R,5 S)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-2-(6-chloro-2-isobutyramido-9H-purin-9-yl)tetrahydrothiophen-3-yl 2,4-dimethoxybenzoate (20 g, 25.8 mmol) in THF (135 mL) was added TBAF in THF (1 M, 31 mL, 31 mmol) dropwise. After 1 h, the reaction mixture was concentrated and purified by column chromatography using 1% to 10% MeOH in CH$_2$Cl$_2$ 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$_4$CO$_3$ (5 mM) to give the product. LCMS (ES, m/z): 536.2 [M+H]$^+$. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.80 (s, 1H), 8.83 (s, 1H), 7.72 (d, J=8.7 Hz, 1H), 6.65-6.55 (m, 2H), 6.18 (d, J=2.5 Hz, 1H), 5.80 (q, J=3.5 Hz, 1H), 5.22 (t, J=5.1 Hz, 1H), 3.93-3.67 (m, 9H), 2.85 (p, J=6.9 Hz, 1H), 2.70 (ddd, J=13.4, 8.5, 4.5 Hz, 1H), 2.36 (dt, J=14.1, 5.0 Hz, 1H), 1.06 (dd, J=6.8, 3.3 Hz, 6H).

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

[0455]



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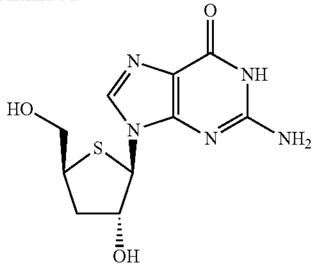
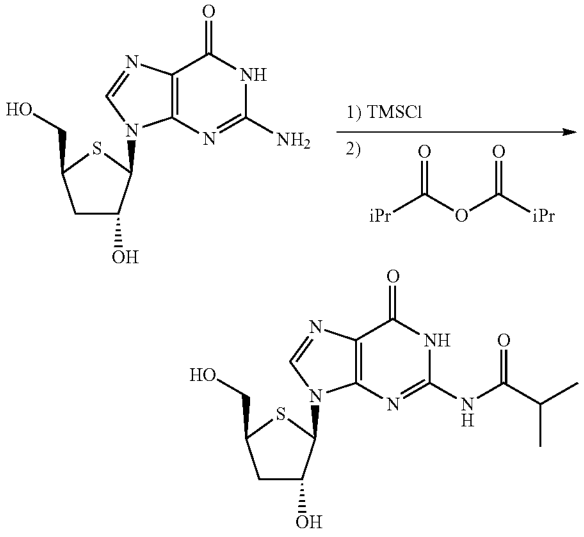


[0456] To a solution of (2R,3R,5 S)-2-(6-chloro-2-isobutyramido-9H-purin-9-yl)-5-(hydroxymethyl)tetrahydrothiophen-3-yl 2,4-dimethoxybenzoate (6.0 g, 11.19 mmol) in MeOH (300 mL) were added 2-mercaptoethanol (3.50 g, 44.8 mmol) and NaOMe (10.08 g, 56 mmol, 30% in MeOH). It was heated at 60° C. for 16 h, cooled to rt, and conc. HCl (4 mL) was added. The resulting mixture was concentrated, and water (100 mL) and EtOAc (100 mL) were added. Layers were separated, and the aq layer was extracted with EtOAc (3×100 mL). The aq layer was basified with $NaHCO_3$ (solid) to ~pH 8 and stirred at rt for 1 h. The precipitate was filtered and kept under reduced pressure to give the product. LCMS (ES, m/z): 284.1 $[M+H]^+$. ^1H-NMR (400 MHz, DMSO-d_6) δ 10.57 (s, 1H), 7.98 (s, 1H), 6.46 (s, 2H), 5.57 (dd, J=10.9, 3.9 Hz, 2H), 5.12 (t, J=5.4 Hz, 1H), 4.48 (p, J=4.1 Hz, 1H), 3.78-3.53 (m, 3H), 2.11-1.99 (m, 2H).

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

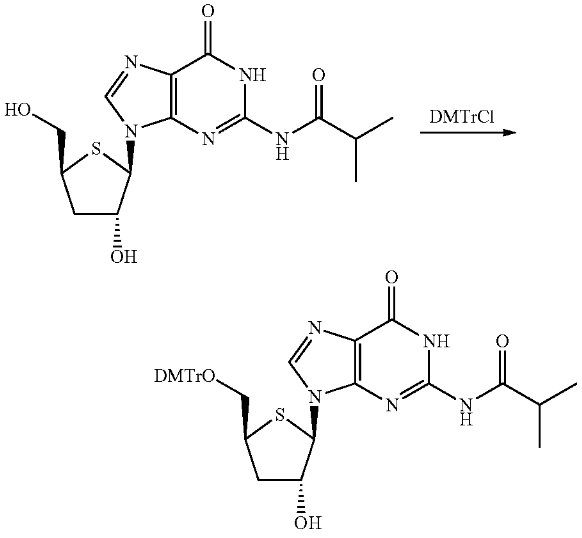
[0457]



[0458] 2-amino-9-((2R,3R,5S)-3-hydroxy-5-(hydroxymethyl)tetrahydrothiophen-2-yl)-1,9-dihydro-6H-purin-6-one (580 mg, 2.047 mmol) was co-evaporated with pyridine (3×20 mL) and then re-dissolved in pyridine (20 mL). The mixture was cooled to 0° C. and then treated with chlorotrimethylsilane (1557 mg, 14.33 mmol). It was warmed to rt and stirred for 2 h. Then, the reaction was cooled to 0° C. again, and isobutyric anhydride (486 mg, 3.07 mmol) was added dropwise. It was warmed to rt and stirred for 2 h. The reaction was quenched by the addition of methanol (5 mL). After 5 min, NH_4OH (ca 29%, 10 mL) was added. The mixture was stirred at rt for 30 min. 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 $[M+H]^+$. ^1H-NMR (300 MHz, 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=6.8 Hz, 6H).

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

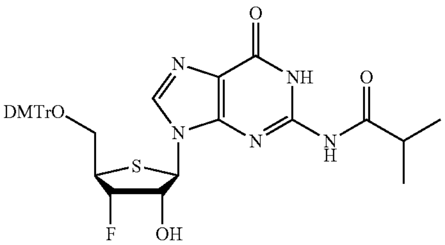
[0459]



[0460] N-(9-((2R,3R,5 S)-3-hydroxy-5-(hydroxymethyl)tetrahydrothiophen-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide (510 mg, 1.443 mmol) was co-evaporated with pyridine (3×5 mL) and then re-suspended in pyridine (7 mL). To the suspension was added 4,4'-(chloro(phenyl)methylene)bis(methoxybenzene) (538 mg, 1.587 mmol), and the mixture was stirred at rt for 2 h. At that time the mixture was concentrated under reduced pressure, and the 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 $[M+H]^+$. ^1H-NMR (400 MHz, 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=2.3 Hz, 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=6.8 Hz, 6H).

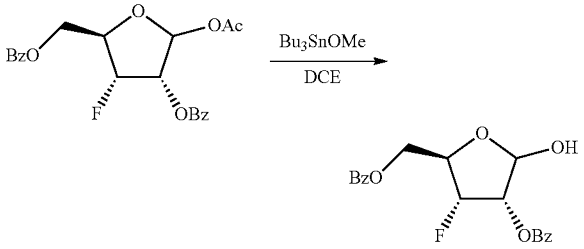
Preparation 19: N-(9-((2R,3R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)-methoxy)methyl)-4-fluoro-3-hydroxytetrahydrothiophen-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide

[0461]



Step 1: ((2R,3R,4S)-4-(benzoyloxy)-3-fluoro-5-hydroxytetrahydrofuran-2-yl)methyl benzoate

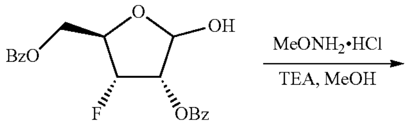
[0462]



[0463] To a stirred solution of ((2R,3R,4S)-5-acetoxy-4-(benzoyloxy)-3-fluorotetrahydrofuran-2-yl)methyl benzoate (20.0 g, 49.7 mmol) in dry 1,2-dichloroethane (200 mL) was added tri-N-butyltin methoxide (28.8 mL, 99 mmol). The resulting mixture was stirred at 80° C. for 3 h and then concentrated in vacuo. The residue was diluted in 500 mL of ethyl acetate and washed with sat aq. NH_4Cl (500 mL) and brine (500 mL). 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 0-40% EtOAc/Hexane. LCMS (ES, m/z): 343.2 $[M+H-H_2O]^+$. ^1H NMR (500 MHz, Chloroform-d) δ 8.18-8.00 (m, 7H), 7.68-7.57 (m, 3H), 7.61-7.35 (m, 7H), 5.73 (dd, J=8.3, 4.6 Hz, 1H), 5.65 (dt, J=3.9, 2.0 Hz, 1H), 5.54 (t, J=4.7 Hz, 0H), 5.50-5.40 (m, 2H), 5.36-5.24 (m, 1H), 4.87 (dtd, J=25.5, 4.0, 1.5 Hz, 1H), 4.74-4.46 (m, 4H), 4.15 (q, J=7.2 Hz, 1H), 3.39 (d, J=4.1 Hz, 1H), 3.30 (dd, J=8.6, 3.4 Hz, 1H), 2.07 (s, 2H), 1.41-1.23 (m, 3H).

Step 2. (2R,3R,4S)-3-fluoro-2-hydroxy-5-(methoxyimino)pentane-1,4-diyl dibenzoate

[0464]



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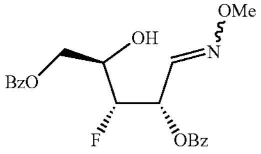
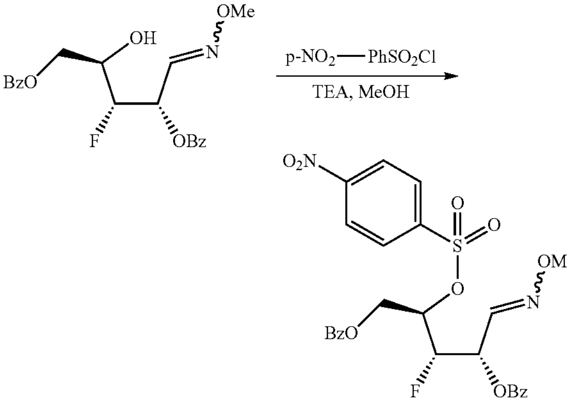


[0465] To a stirred solution of ((2R,3R,4S)-4-(benzoyloxy)-3-fluoro-5-hydroxytetrahydrofuran-2-yl)methyl benzoate (17.9 g, 49.7 mmol) in dry MeOH (100 mL) was added O-methylhydroxylamine hydrochloride (6.23 g, 74.6 mmol), followed by triethylamine (10.39 mL, 74.6 mmol). The reaction mixture was stirred at rt for 2 h and then concentrated in vacuo. The residue was diluted in 500 mL of ethyl acetate and washed with sat aq. NH_4Cl (500 mL) and brine (500 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was used for the next step directly without further purification. LCMS (ES, m/z): 390.2 $[M+H]^+$.

Step 3: (2R,3S,4S)-3-fluoro-5-(methoxyimino)-2-(((4-nitrophenyl)sulfonyl)oxy)pentane-1,4-diyl dibenzoate

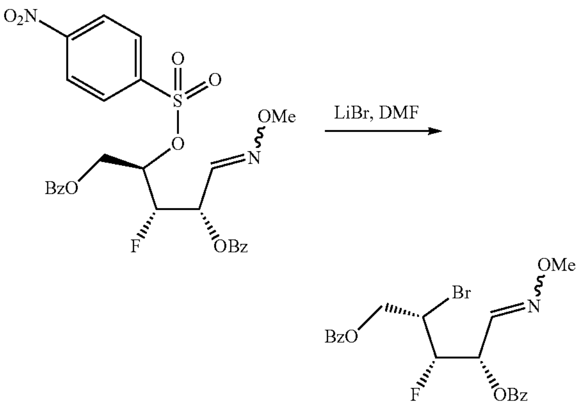
[0466]



[0467] To a stirred solution of (2R,3R,4S)-3-fluoro-2-hydroxy-5-(methoxyimino)pentane-1,4-diyl dibenzoate (19.4 g, 49.7 mmol) in dry EtOAc (100 mL) was added 4-nitrobenzenesulfonyl chloride (16.5 g, 74.6 mmol), followed by triethylamine (10.4 mL, 74.6 mmol). The reaction mixture was stirred at rt for 18 h and was then diluted with 200 mL of ethyl acetate, washed with water (300 mL) and brine (300 mL). 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 0-30% EtOAc/Hexane. LCMS (ES, m/z): 575.3 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d) δ 8.25-7.99 (m, 7H), 7.94-7.80 (m, 2H), 7.68-7.55 (m, 2H), 7.57-7.46 (m, 3H), 7.50-7.38 (m, 3H), 6.55 (ddd, J=17.2, 5.3, 2.8 Hz, 0H), 5.89 (ddd, J=17.7, 6.2, 4.1 Hz, 1H), 5.46-5.37 (m, 1H), 5.40-5.28 (m, 1H), 5.21 (t, J=4.3 Hz, 0H), 4.84 (tdd, J=12.8, 2.6, 1.5 Hz, 1H), 4.53 (dddd, J=23.1, 13.0, 7.0, 1.8 Hz, 1H), 4.14 (q, J=7.2 Hz, 1H), 3.99 (d, J=36.3 Hz, 4H), 2.06 (s, 2H), 1.44-1.23 (m, 2H).

Step 4: (2S,3S,4S)-2-bromo-3-fluoro-5-(methoxyimino)pentane-1,4-diyl dibenzoate

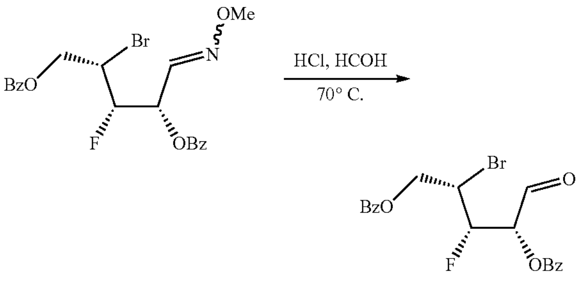
[0468]



[0469] To a stirred solution of (2R,3 S,4S)-3-fluoro-5-(methoxyimino)-2-(((4-nitrophenyl)sulfonyl)oxy)pentane-1,4-diyl dibenzoate (21.3 g, 37.1 mmol) in dry DMF (100 mL) was added freshly opened lithium bromide powder (16.1 g, 185 mmol). The resulting mixture was stirred at 60° C. for 18 h. The reaction mixture was diluted in 300 mL of ethyl acetate and washed with water (500 mL) and brine (500 mL). 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 0-25% EtOAc/Hexane to give product. LCMS (ES, m/z): 452.1 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d) δ 8.15-8.03 (m, 11H), 7.69-7.56 (m, 8H), 7.56-7.41 (m, 12H), 6.93-6.86 (m, 1H), 6.45 (ddd, J=14.7, 5.9, 4.7 Hz, 0H), 5.93 (ddd, J=11.8, 6.7, 5.9 Hz, 2H), 5.32 (s, 1H), 5.29-5.10 (m, 3H), 4.89-4.77 (m, 3H), 4.80-4.67 (m, 3H), 4.60-4.40 (m, 3H), 3.95 (d, J=16.9 Hz, 2H), 3.89 (s, 6H), 1.32-1.22 (m, 1H).

Step 5: (2S,3S,4S)-2-bromo-3-fluoro-5-oxopentane-1,4-diyl dibenzoate

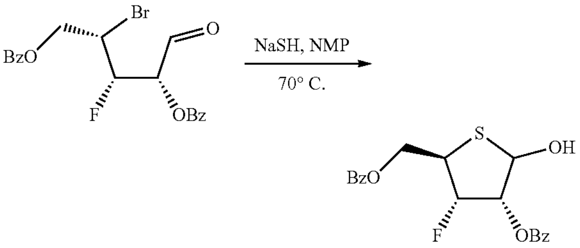
[0470]



[0471] To a stirred solution of (2S,3S,4S)-2-bromo-3-fluoro-5-(methoxyimino)pentane-1,4-diyl dibenzoate (20.0 g, 44.2 mmol) in THF (200 mL) was added 37% aqueous solution of formaldehyde (32.9 mL, 442 mmol) and 1N HCl (44.2 mL, 44.2 mmol). The resulting mixture was stirred at 55° C. for 5 h. The reaction mixture was concentrated in vacuo to remove most of the THF. The residue was diluted in 300 mL of ethyl acetate and washed with water (300 mL) and brine (300 mL). The separated organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was used for the next step without further purification. LCMS (ES, m/z): 423.2 $[M+H]^+$.

Step 6: ((2R,3S,4R)-4-(benzoyloxy)-3-fluoro-5-hydroxytetrahydrothiophen-2-yl)methyl benzoate

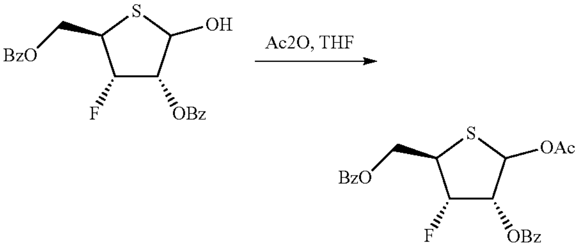
[0472]



[0473] To a stirred solution of (2S,3S,4S)-2-bromo-3-fluoro-5-oxopentane-1,4-diyl dibenzoate (18.7 g, 44.2 mmol) in NMP (150 mL) at 0° C. was added sodium hydrosulfide (5.0 g, 89.0 mmol). The resulting mixture was stirred at 0° C. for 30 min and then at rt for 30 min. The reaction mixture was diluted in 300 mL of ethyl acetate and washed with water (300 mL) and brine (300 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was used for the next step without further purification. LCMS (ES, m/z): 359.2 $[M+H-H_2O]^+$.

Step 6: ((2R,3S,4R)-5-acetoxy-4-(benzoyloxy)-3-fluorotetrahydrothiophen-2-yl)methyl benzoate

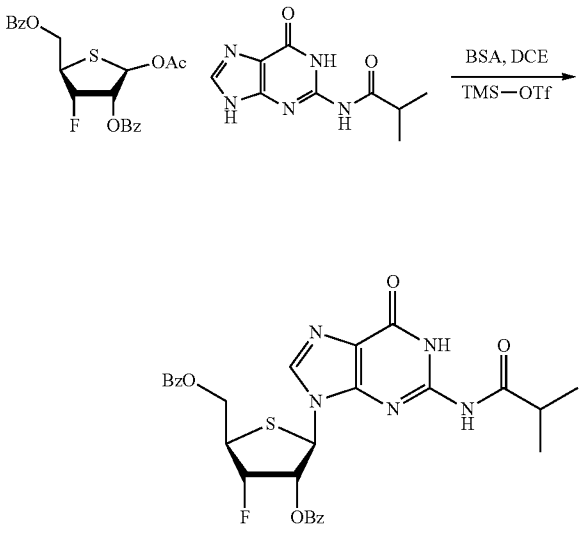
[0474]



[0475] To a stirred solution of ((2R,3 S,4R)-4-(benzoyloxy)-3-fluoro-5-hydroxytetrahydrothiophen-2-yl)methyl benzoate (16.6 g, 44.2 mmol) in dry THF (150 mL) at 0° C. was added acetic anhydride (8.3 mL, 133 mmol) and triethylamine (18.5 mL, 133 mmol). The resulting mixture was stirred at 0° C. for 30 min and then at rt for 2 h. The reaction was quenched by addition of MeOH, and the reaction mixture was concentrated in vacuo to remove most of the THF. The residue was diluted in 300 mL of ethyl acetate and washed with water (300 mL) and brine (300 mL). 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 0-25% EtOAc/Hexane to give product. LCMS (ES, m/z): 441.2 [M+Na]$^+$. ^{1}H NMR (500 MHz, Chloroform-d) δ 8.15-8.02 (m, 4H), 7.68-7.57 (m, 2H), 7.55-7.42 (m, 4H), 6.02 (t, J=2.4 Hz, 1H), 5.88 (ddd, J=6.1, 3.6, 2.4 Hz, 1H), 5.50-5.42 (m, 0H), 5.35 (dd, J=7.3, 3.6 Hz, 0H), 5.32 (s, 0H), 4.80-4.69 (m, 1H), 4.56 (dd, J=11.6, 5.9 Hz, 1H), 4.26-4.10 (m, 2H), 2.25-2.11 (m, 1H), 2.08 (d, J=10.0 Hz, 3H), 1.29 (t, J=7.1 Hz, 1H).

Step 7: ((2R,3S,4R,5R)-4-(benzoyloxy)-3-fluoro-5-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl) tetrahydrothiophen-2-yl)methyl benzoate

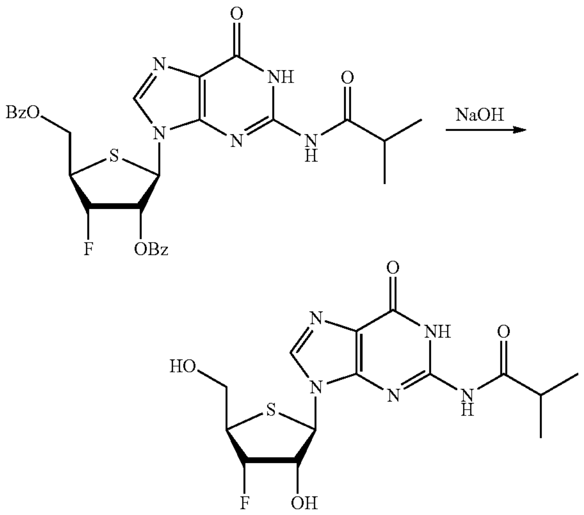
[0476]



[0477] To a suspension of N-(6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide (15.86 g, 71.7 mmol) in ClCH$_2$CH$_2$C$_1$ (300 mL) was added (Z)-trimethylsilyl N-(trimethylsilyl)acetimidate (35.1 mL, 143 mmol). The suspension was stirred at 70° C. overnight and was then cooled to −15° C. To this mixture was added ((2R,3S,4R)-5-acetoxy-4-(benzoyloxy)-3-fluorotetrahydrothiophen-2-yl) methyl benzoate (10 g, 23.90 mmol), followed by TMS-OTf (8.64 mL, 47.8 mmol). The reaction mixture was stirred at −15° C. for 2 h, then at rt for 5 h and finally at 70° C. for 5 d. The reaction mixture was allowed to cool to RT and was then filtered. The filtrate was washed with sat. aq. NaHCO$_3$, brine and then dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by silica gel column, eluting with 0-60% EtOAc/Hexane. Subsequent recrystallization from EtOAc gave product. LCMS (ES, m/z): 580.5 [M+H]$^+$. ^{1}H NMR (500 MHz, Chloroform-d) δ 12.19 (s, 0H), 9.56 (s, 1H), 8.12-8.06 (m, 1H), 8.02-7.96 (m, 1H), 7.66 (s, 0H), 7.71-7.58 (m, 1H), 7.57-7.50 (m, 1H), 7.54-7.42 (m, 1H), 6.59 (ddd, J=25.3, 7.4, 3.1 Hz, 1H), 6.20 (d, J=7.4 Hz, 0H), 5.68-5.59 (m, 1H), 4.87 (ddd, J=11.7, 7.7, 1.5 Hz, 1H), 4.26-4.11 (m, 1H), 2.96 (hept, J=6.8 Hz, 1H), 1.38 (dd, J=19.0, 6.9 Hz, 3H).

Step 8: N-(9-((2R,3R,4S,5R)-4-fluoro-3-hydroxy-5-(hydroxymethyl)tetrahydrothiophen-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide

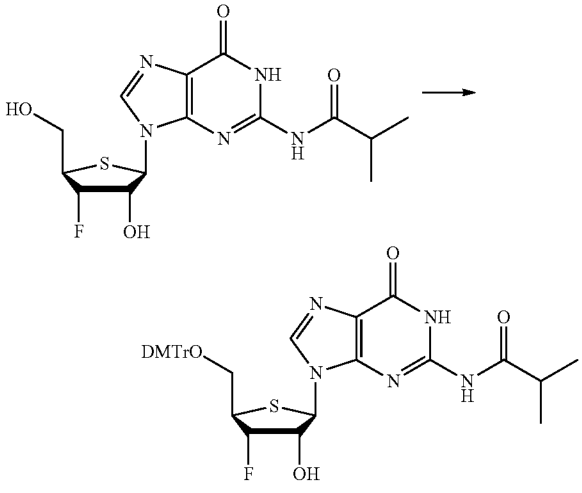
[0478]



[0479] To a solution of ((2R,3 S,4R,5R)-4-(benzoyloxy)-3-fluoro-5-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrothiophen-2-yl)methyl benzoate (0.96 g, 1.66 mmol) in THF (5 mL)/MeOH (4 mL)/H$_2$O (1 mL) at 0° C. was added 2N sodium hydroxide (1.8 mL, 3.6 mmol). The reaction mixture was stirred at 0° C. for 30 min and then neutralized with acetic acid (0.38 mL, 6.6 mmol). The product was collected by filtration and carried on to the next step without further purification. LCMS (ES, m/z): 372.3 [M+H]$^+$.

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

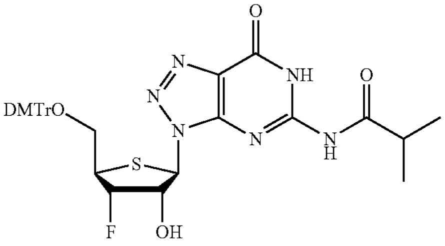
[0480]



[0481] To a solution of N-(9-((2R,3R,4S,5R)-4-fluoro-3-hydroxy-5-(hydroxymethyl)-tetrahydrothiophen-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide (0.62 g, 1.66 mmol) in pyridine (25 mL) at 0° C. was added 4,4'-dimethoxytrityl chloride (0.84 g, 2.48 mmol). The reaction mixture was stirred at 0° C. for 3 h. The reaction was quenched with H_2O (1 mL), and the mixture was concentrated. The residue was diluted in 100 mL of ethyl acetate and washed with saturated aq. $NaHCO_3$ (100 mL) and brine (100 mL). 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/Hexane containing 0.1% Et_3N to give product. LCMS (ES, m/z): 674.6 $[M+H]^-$. ^1H NMR (500 MHz, Chloroform-d) δ 11.96 (s, 0H), 8.35 (s, 0H), 7.70 (s, OH), 7.63-7.56 (m, 1H), 7.50-7.43 (m, 2H), 7.38-7.24 (m, 1H), 6.93-6.85 (m, 2H), 5.92 (d, J=8.3 Hz, 0H), 5.35-5.23 (m, 1H), 4.15 (q, J=7.1 Hz, 1H), 3.85-3.69 (m, 3H), 3.46 (dd, J=10.2, 5.4 Hz, 0H), 3.35 (dd, J=10.2, 5.2 Hz, 0H), 2.09 (d, J=19.4 Hz, 2H), 1.34-1.22 (m, 2H), 1.01 (d, J=6.8 Hz, 1H), 0.91 (d, J=6.9 Hz, 1H).

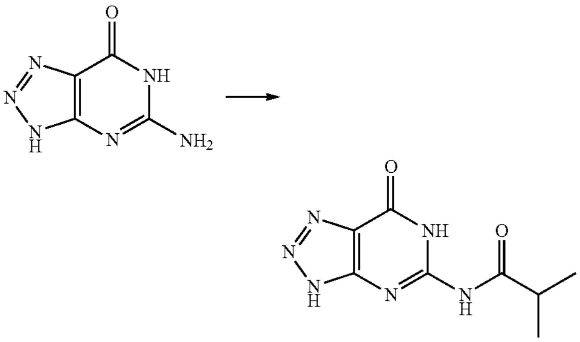
Preparation 20: N-(3-((2R,3R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)-methoxy)methyl)-4-fluoro-3-hydroxytetrahydrothiophen-2-yl)-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-yl) isobutyramide

[0482]



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

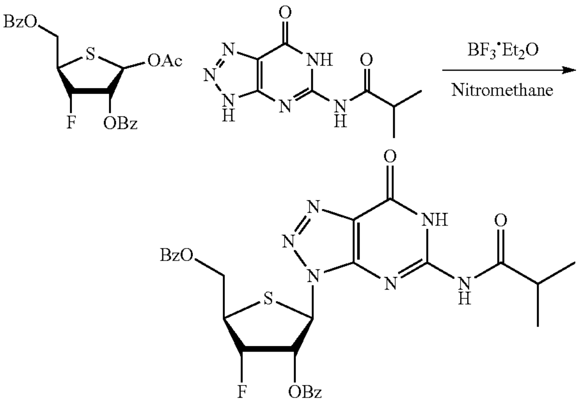
[0483]



[0484] To a suspension of 5-amino-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (5.0 g, 32.9 mmol) in anhydrous DMF (60 mL) was added isobutyric anhydride (12.5 mL, 76.0 mmol) dropwise. The reaction mixture was refluxed at 150° C. for 1 h. The reaction was quenched with MeOH (6.6 mL, 164 mmol) and concentrated in vacuo. The residue was taken up in DCM (50 mL)/Hexane (100 mL) and was stirred at vigorously at rt for 15 min. The product was collected by filtration. LCMS (ES, m/z): 223.2 $[M+H]^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 16.04 (s, 1H), 12.19 (s, 1H), 11.78 (s, 1H), 2.78 (hept, J=6.7 Hz, 1H), 1.13 (d, J=6.8 Hz, 6H).

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

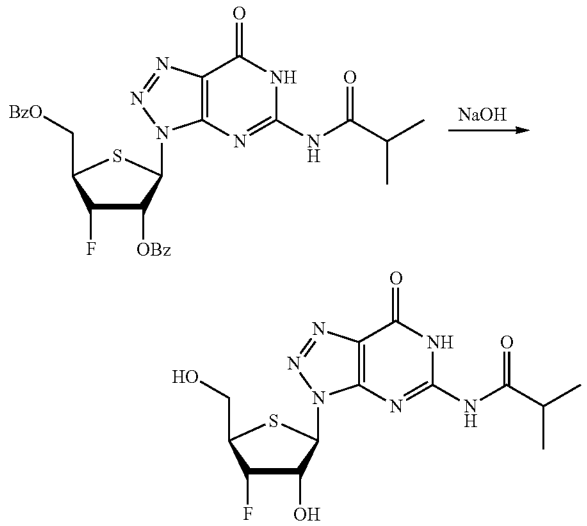
[0485]



[0486] To a mixture of ((2R,3 S,4R)-5-acetoxy-4-(benzoyloxy)-3-fluorotetrahydrothiophen-2-yl)methyl benzoate (1.5 g, 3.6 mmol) and N-(7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-yl)isobutyramide (0.96 g, 4.3 mmol) in nitromethane (20 mL) was added $BF_3.Et_2O$ (0.54 mL, 4.3 mmol) and the resulting mixture was heated at 100° C. under microwave irradiation for 1 h. The reaction mixture was cooled, diluted in 100 mL of ethyl acetate and washed with saturated aq. $NaHCO_3$ (100 mL) and brine (100 mL). 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/Hexane. LCMS (ES, m/z): 581.4 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d) δ 12.27 (s, 2H), 9.73 (s, 2H), 8.19-7.93 (m, 8H), 7.86-7.80 (m, 0H), 7.71-7.55 (m, 4H), 7.57-7.39 (m, 8H), 7.40-7.33 (m, 0H), 6.76 (d, J=6.7 Hz, 2H), 6.62-6.48 (m, 2H), 5.79 (t, J=2.9 Hz, 1H), 5.69 (t, J=2.9 Hz, 1H), 5.62-5.54 (m, 2H), 4.89 (ddd, J=11.6, 7.8, 1.3 Hz, 2H), 4.78-4.65 (m, 1H), 4.31-4.18 (m, 2H), 4.15 (q, J=7.1 Hz, 3H), 2.95 (hept, J=6.9 Hz, 2H), 2.81-2.68 (m, 1H), 2.07 (s, 4H), 1.39 (dd, J=17.5, 6.9 Hz, 10H), 1.34-1.24 (m, 8H).

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

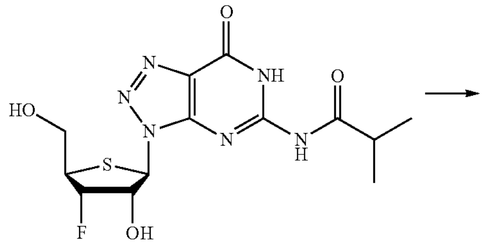
[0487]



[0488] To a solution of ((2R,3 S,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 (4.5 g, 7.8 mmol) in THF (35 mL)/MeOH (28 mL)/H (7 mL) at 0° C. was added 2N sodium hydroxide (8.6 mL, 17.2 mmol). The reaction mixture was stirred at 0° C. for 1 h and then neutralized with acetic acid (2.3 mL, 39.0 mmol). Product was collected by filtration and carried on to the next step without further purification. LCMS (ES, m/z): 373.3 $[M+H]^+$.

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

[0489]



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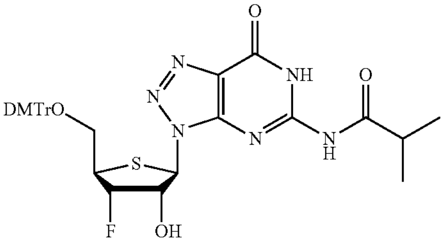
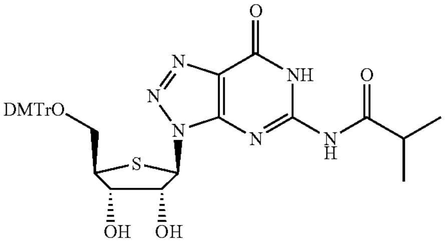


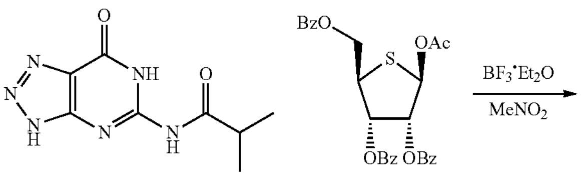
[0490] To a solution of N-(3-((2R,3R,4S,5R)-4-fluoro-3-hydroxy-5-(hydroxymethyl)-tetrahydrothiophen-2-yl)-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-yl) isobutyramide (1.8 g, 4.8 mmol) in pyridine (30 mL) at 0° C. was added 4,4'-dimethoxytrityl chloride (1.8 g, 5.3 mmol). The reaction mixture was stirred at 0° C. for 1 h. The reaction was quenched with H_2O (1 mL), and the mixture was concentrated. The residue was diluted in 100 mL of ethyl acetate and washed with saturated aq. $NaHCO_3$ (100 mL) and brine (100 mL). 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/Hexane containing 0.1% Et_3N to give product. LCMS (ES, m/z): 675.5 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d) δ 12.16 (s, 1H), 8.48 (s, 0H), 7.57-7.50 (m, 1H), 7.49-7.37 (m, 2H), 7.39-7.29 (m, 0H), 7.31 (s, 1H), 7.32-7.14 (m, 1H), 6.91-6.81 (m, 2H), 6.22-6.16 (m, 0H), 5.42-5.31 (m, 1H), 3.77 (d, J=36.0 Hz, 7H), 3.46 (dd, J=10.2, 5.6 Hz, 0H), 3.36 (dd, J=10.2, 5.4 Hz, 0H), 2.17 (p, J=6.9 Hz, 0H), 1.06 (dd, J=26.1, 6.9 Hz, 3H).

Preparation 21: N-(3-((2R,3R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)-methoxy)methyl)-3,4-dihydroxytetrahydrothiophen-2-yl)-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-yl) isobutyramide

[0491]



[0492] Step 1: (2R,3S,4R,5R)-2-((benzoyloxy)methyl)-5-(5-isobutyramido-7-oxo-6,7-dihydro-3H-1,2,3 triazolo[4,5-d]pyrimidin-3-yl)tetrahydrothiophene-3,4-diyl dibenzoate



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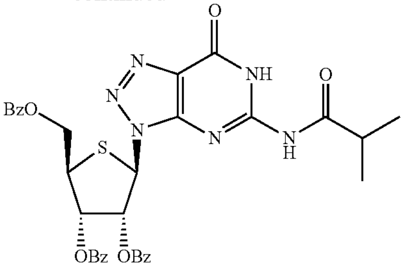
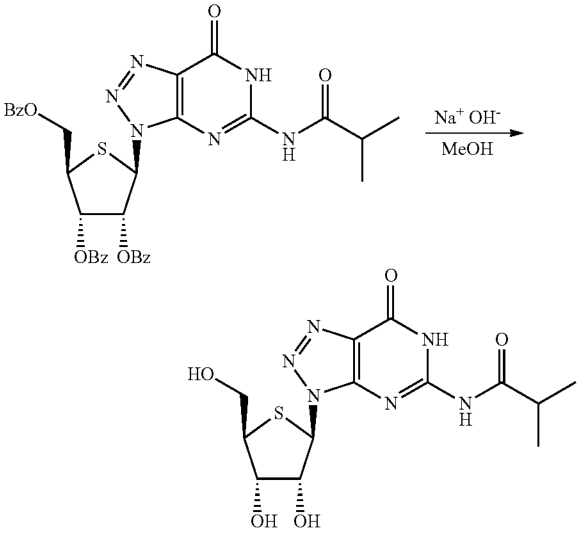


[0493] $BF_3.OEt_2$ (3.65 mL, 28.8 mmol) was added dropwise to a mixture of (2R,3R,4S,5R)-2-acetoxy-5-((benzoyloxy)methyl)tetrahydrothiophene-3,4-diyl dibenzoate (10.0 g, 19.2 mmol) and N-(7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5 yl)isobutyramide (5.98 g, 26.9 mmol) in $MeNO_2$ (180 mL) at ambient temperature. Upon completion of addition, the mixture was heated at 120° C. in a microwave reactor for 45 min. The sample was cooled to rt and concentrated in vacuo. The residue was purified by flash column chromatography eluting with EtOAc/isohexane (10-90%) to give desired product. LCMS (ES, m/z): 683.5 $[M+H]^+$.H NMR (500 MHz, Chloroform-d) δ 12.24 (s, 1H), 9.77 (s, 1H), 8.08-7.95 (m, 4H), 7.94-7.87 (m, 2H), 7.70-7.35 (m, 9H), 6.84 (d, J=5.9 Hz, 1H), 6.67 (dd, J=5.9, 3.9 Hz, 1H), 6.49 (t, J=3.7 Hz, 1H), 5.52 (dd, J=11.4, 7.8 Hz, 1H), 5.04 (dd, J=11.4, 7.8 Hz, 1H), 4.28 (m, 1H), 2.97 (hept, J=6.9 Hz, 1H), 1.42 (dd, 6.9 Hz, 6H).

Step 2. N-(3-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrothiophen-2-yl)-7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-yl) isobutyramide

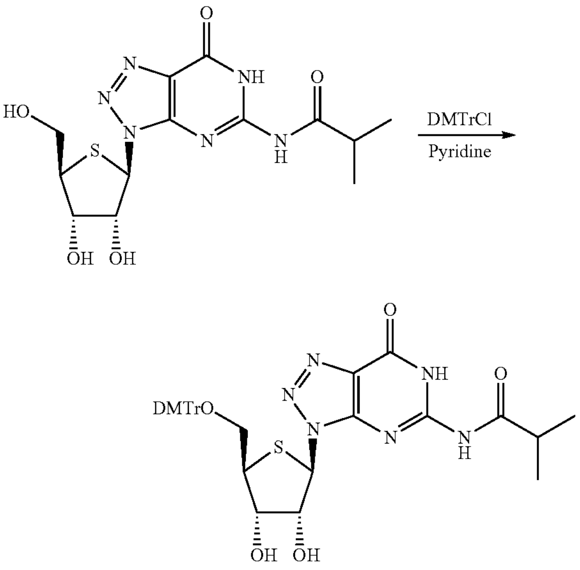
[0494]



[0495] To a stirred solution of the product from Step 1 (5.3 g, 7.8 mmol) dissolved in Pyridine (8 mL) and MeOH (32 mL) at 25° C. was added sodium hydroxide (1.24 g, 31.1 mmol) in one portion. The mixture was stirred at 25° C. for 15 min before the addition of acetic acid (1.8 mL, 31.1 mmol). The mixture was concentrated in vacuo, and the residue was purified by flash column chromatography eluting with EtOAc/isohexane (70-100%) to give the desired product. LCMS (ES, m/z): 371.3 $[M+H]^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 12.24 (s, 1H), 11.96 (s, 1H), 5.91 (d, J=5.6 Hz, 1H), 5.73 (d, J=5.5 Hz, 1H), 5.43 (d, J=5.0 Hz, 1H), 5.12 (m, 1H), 4.81 (m, br, 1H), 4.40 (m, 1H), 3.89-3.77 (m, 1H), 3.53 (m, 1H), 3.46-3.36 (m, 1H), 2.79 (m, 1H), 1.14 (dd, J=6.7, 1.2 Hz, 6H).

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

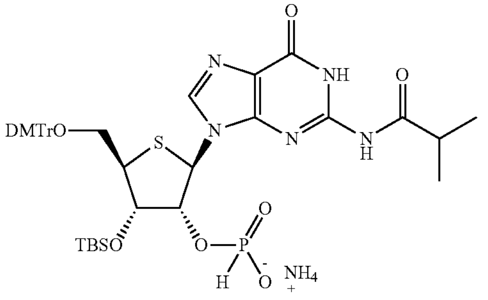
[0496]



[0497] To the product from step 2 (2.3 g, 6.2 mmol) was added pyridine (62 mL) at ambient temperature. To this mixture was added DMTrCl (2.3 g, 6.8 mmol). After 1 h, water (2 mL) was added, and it was concentrated in vacuo. Ethyl acetate (15 mL), water (5 mL) and brine (1 mL) were added. Layers were separated, and the aqueous layer was extracted with ethyl acetate twice (20 mL×2). The combined organics were dried over $MgSO_4$, concentrated in vacuo and purified by flash column chromatography, eluting with 0 to 80% EtOAc in Hexane to give the desired product. LCMS (ES, m/z): 673.4 $[M+H]^+$ 0.1H NMR (500 MHz, DMSO-d_6) δ 12.24 (s, 1H), 11.96 (s, 1H), 7.50-7.36 (m, 2H), 7.35-7.10 (m, 9H), 6.96-6.82 (m, 4H), 5.88 (d, J=4.1 Hz, 1H), 5.83 (d, J=5.1 Hz, 1H), 5.42 (d, J=5.7 Hz, 1H), 4.66 (q, J=4.1 Hz, 1H), 4.45 (td, J=5.9, 3.5 Hz, 1H), 3.81-3.69 (6H), 3.65 (ddd, J=8.4, 6.0, 4.3 Hz, 1H), 3.46-3.35 (m, 1H), 3.19 (dd, J=9.4, 7.9 Hz, 1H), 2.78 (h, J=6.8 Hz, 1H), 1.22-1.05 (m, 6H).

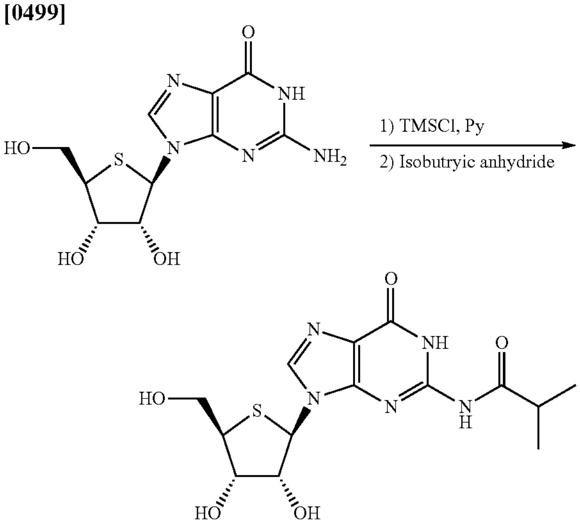
Preparation 22: ammonium (2R,3R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrothiophen-3-yl phosphonate

[0498]



Step 1: N-(9-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrothiophen-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide

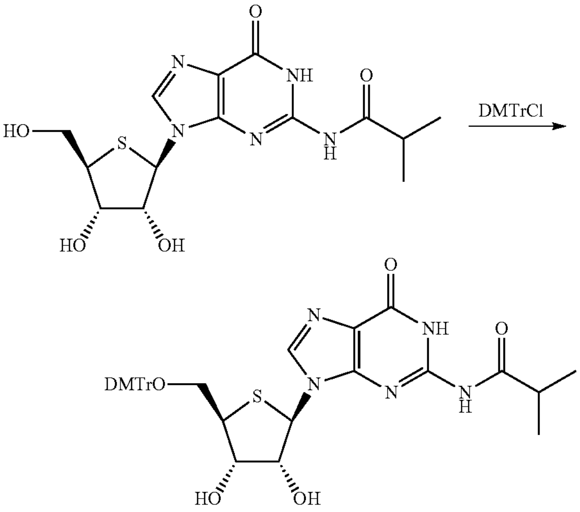
[0499]



[0500] 2-amino-9-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrothiophen-2-yl)-1,9-dihydro-6H-purin-6-one (1.7 g, 5.7 mmol) was co-evaporated with pyridine (3×5 mL) and then, re-dissolved in pyridine (34 mL). To the mixture at 0° C. was added chlorotrimethylsilane (4.32 g, 39.8 mmol) dropwise. It was stirred at rt for 1 h and then, cooled to 0° C. again. Isobutyric anhydride (1.348 g, 8.52 mmol) was added dropwise, and it was stirred at rt for 3 h. It was quenched by the addition of water (8.5 mL). After 5 min, NH_4OH (ca. 29%, 17 mL) was added, and the mixture was stirred for 30 min. It was concentrated and purified by column chromatography eluted with 1 to 30% MeOH in CH_2Cl_2 to give the product. LCMS (ES, m/z): 396.9 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.52 (br s, 2H), 8.39 (s, 1H), 5.79 (d, J=7.1 Hz, 1H), 5.59 (s, 1H), 5.40 (s, 1H), 5.22 (s, 1H), 4.55 (d, J=6.7 Hz, 1H), 4.21 (s, 1H), 3.77 (t, J=9.3 Hz, 1H), 3.61 (s, 1H), 3.30 (dt, J=6.4, 3.3 Hz, 1H), 2.78 (p, J=6.9 Hz, 1H), 1.13 (d, J=6.8 Hz, 6H).

Step 2: N-(9-((2R,3R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-3,4-dihydroxytetrahydrothiophen-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide

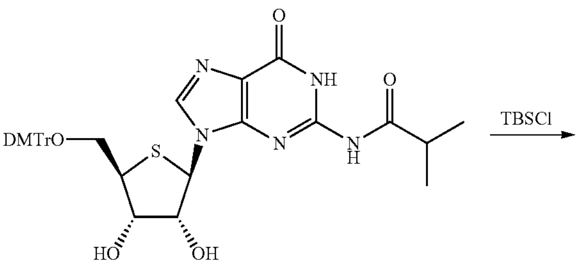
[0501]



[0502] To a mixture of N-(9-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)-tetrahydrothiophen-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide (480 mg, 1.299 mmol) in pyridine (10 mL) was added 4,4'-(chloro(phenyl)methylene)-bis(methoxybenzene) (484 mg, 1.43 mmol). It was stirred at rt for 16 h and then, concentrated. The crude was purified by column chromatography on silica gel eluted with 1 to 30% MeOH in CH_2Cl_2 (containing 1% Et_3N) to give the product. LCMS (ES, m/z): 672.2 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6+D_2O): δ 8.08 (s, 1H), 7.39 (d, J=7.2 Hz, 2H), 7.32 (t, J=7.6 Hz, 2H), 7.26 (dt, J=9.1, 3.3 Hz, 5H), 6.94-6.87 (m, 4H), 5.75 (d, J=5.9 Hz, 1H), 4.39 (dd, J=5.9, 3.5 Hz, 1H), 4.14 (t, J=3.9 Hz, 1H), 3.74 (s, 6H), 3.49-3.37 (m, 2H), 3.33 (dd, J=14.5, 7.3 Hz, 1H), 2.87-2.67 (m, 1H), 1.11 (dd, J=6.8, 1.6 Hz, 6H).

Step 3: N-(9-((2R,3R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-3-hydroxytetrahydrothiophen-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide and N-(9-((2R,3R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-3-((tert-butyldimethylsilyl)oxy)-4-hydroxytetrahydrothiophen-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide

[0503]



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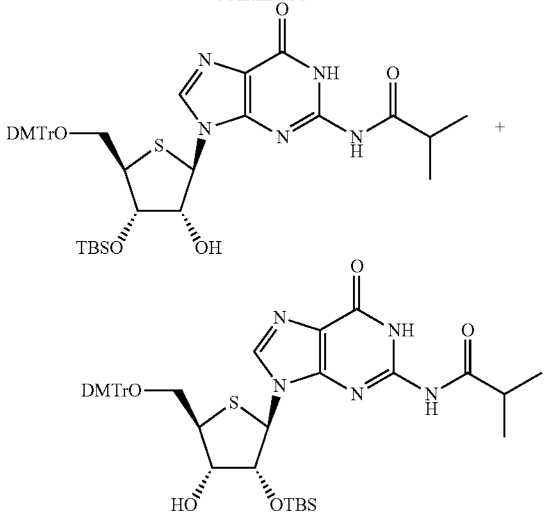
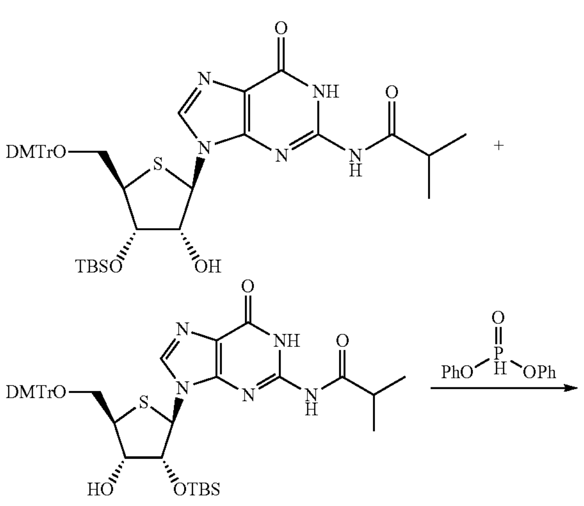


[0504] To a solution of N-(9-((2R,3R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)-methoxy)methyl)-3,4-dihydroxytetrahydrothiophen-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide (580 mg, 0.863 mmol) in DMF (5 mL) at rt was added 1H-imidazole (147 mg, 2.16 mmol) and tert-butylchlorodimethylsilane (156 mg, 1.04 mmol). After 6 h, the mixture was diluted with EtOAc (50 mL) and washed with sat aq $NaHCO_3$ (2×20 mL) and brine (20 mL). It was dried (Na_2SO_4), concentrated, and purified by reverse phase (C18) chromatography eluted with 0 to 95% ACN in water to give the products. LCMS (ES, m/z): 786.3 $[M+H]^+$.

Step 4. (2R,3R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrothiophen-3-yl phenyl phosphonate and (2R,3S,4R,5R)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-5-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrothiophen-3-yl phenyl phosphonate

[0505]



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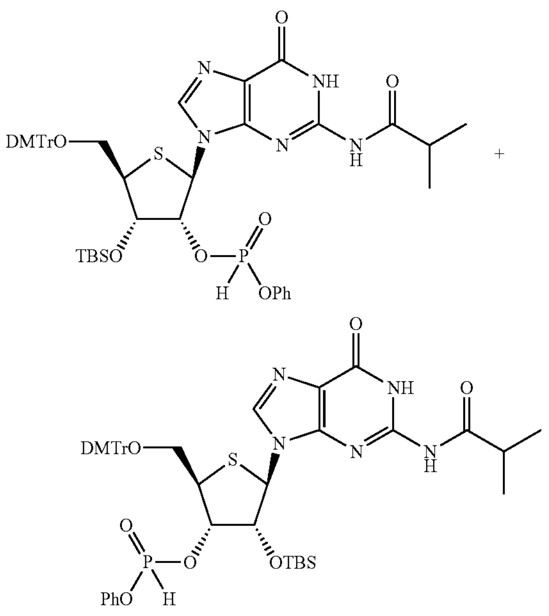
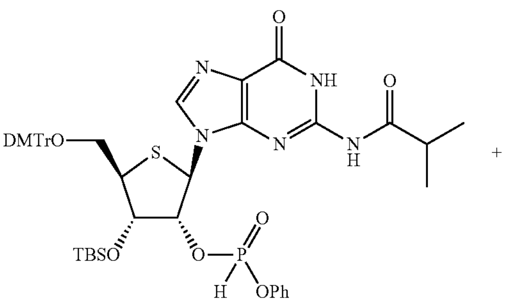


[0506] To a solution of a mixture of N-(9-((2R,3R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)-methoxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-3-hydroxytetrahydrothiophen-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide and N-(9-((2R,3R,4S,5R)-5-((bis(4-methoxyphenyl) (phenyl)methoxy)methyl)-3-((tert-butyldimethylsilyl)oxy)-4-hydroxytetrahydrothiophen-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide (220 mg, 0.280 mmol) in pyridine (2 mL) at 0° C. was added diphenyl phosphonate (98 mg, 0.420 mmol). The resulting mixture was stirred at rt for 20 min. It was used in the next reaction step without purification. LCMS (ES, m/z): 926.2 $[M+H]^+$.

Step 5: ammonium (2R,3R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrothiophen-3-yl phosphonate

[0507]



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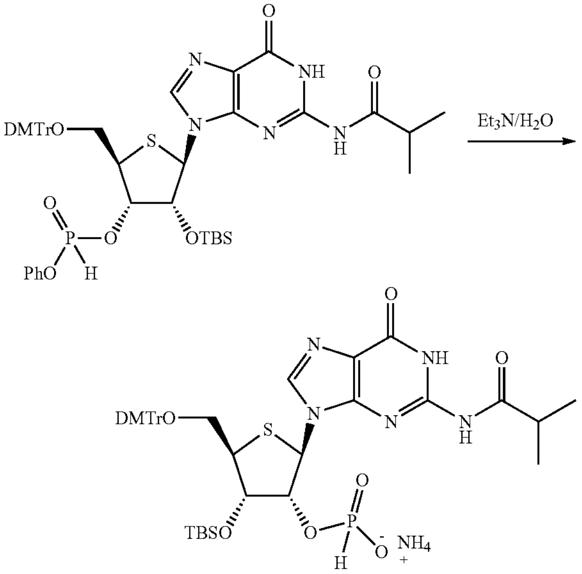
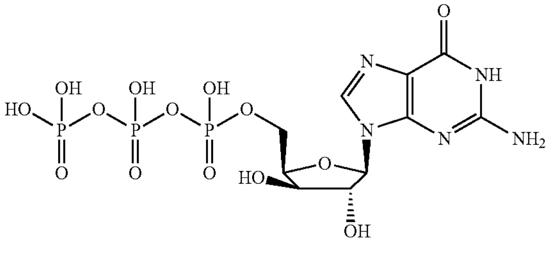


[0508] To the reaction mixture from Step 4 at 0° C. was added Et_3N (0.28 mL, 2.0 mmol) and water (0.28 mL). It was stirred at rt for 30 min. It was concentrated, and the residue was partitioned between CH_2Cl_2 (40 mL) and aq $NaHCO_3$ (5%, 30 mL). The organic layer was washed with aq $NaHCO_3$ (5%, 2×30 mL), dried (Na_2SO_4), concentrated and purified by silica gel column chromatography using 0-10% MeOH in $CHCl_3$ containing 1% Et_3N to give a mixture. The mixture was further purified by prep-HPLC Prep-HPLC (XBridge Shield RP18 OBD Column, 19×150 mm) eluted with 46 to 79% ACN in aq NH_4HCO_3 (10 mM) over 7 min to give the product. LCMS (ES, m/z): 850.2 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD): δ 8.18 (s, 1H), 7.68 (s, 0.5H), 7.59-7.49 (m, 2H), 7.45-7.36 (m, 4H), 7.37-7.30 (m, 2H), 7.28-7.22 (m, 1H), 6.95-6.87 (m, 4H), 6.16-6.07 (m, 2H), 4.88-4.87 (m, 1H), 4.69 (dd, J=7.3, 3.3 Hz, 1H), 3.81 (s, 6H), 3.51 (dd, J=4.9, 1.9 Hz, 2H), 3.37 (s, 1H), 2.67 (p, J=6.9 Hz, 1H), 1.21 (dd, J=6.9, 0.9 Hz, 6H), 0.77 (s, 9H), 0.01 (s, 3H), −0.28 (s, 3H). ^{31}P-NMR (162 MHz, DMSO-d_6): δ −0.74 (s, 1P).

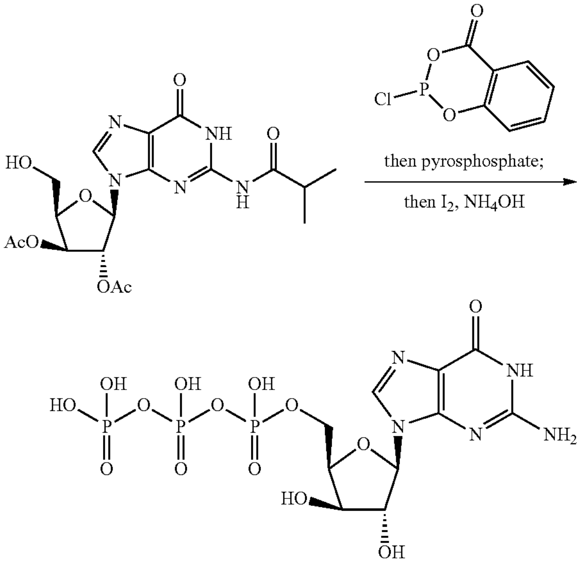
Preparation 23: 2-amino-9-[5-O-(hydroxy{[hydroxy (phosphonooxy)phosphoryl]oxy]-phosphoryl)-β-D-xylofuranosyl}-1,9-dihydro-6H-purin-6-one

[0509]



Step 1: 2-amino-9-[5-O-(hydroxy{[hydroxy (phosphonooxy)phosphoryl]oxy}-phosphoryl)-β-D-xylofuranosyl]-1,9-dihydro-6H-purin-6-one

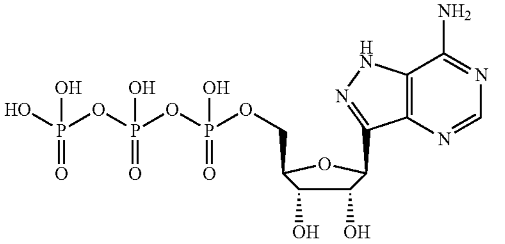
[0510]



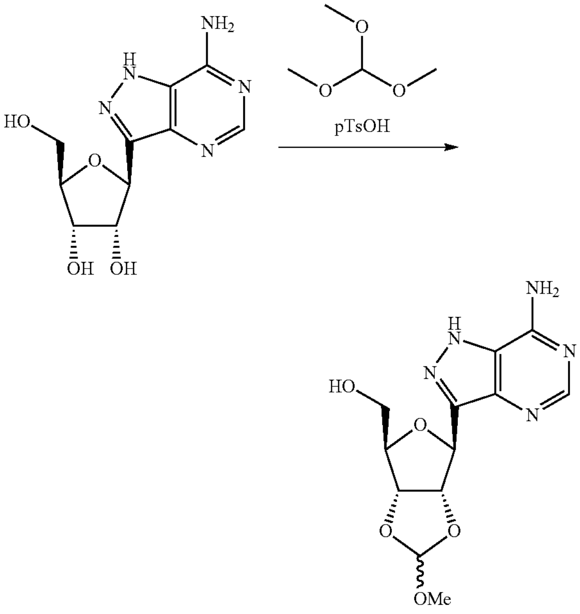
[0511] To a stirred solution of 9-(2,3-di-O-acetyl-β-D-xylofuranosyl)-2-[(2-methylpropanoyl)-amino]-1,9-dihydro-6H-purin-6-one (100 mg, 0.229 mmol) in pyridine (0.25 mL) and 1,4-dioxane (0.75 mL) was added a freshly prepared solution of 2-chloro-4H-1,3,2-benzodioxaphosphorin-4-one (50 mg, 0.247 mmol) in 1,4-dioxane (0.25 mL). The reaction mixture was stirred at ambient temperature for 10 min, and then a solution of tributylammonium pyrophosphate (189 mg, 0.344 mmol) in DMF (0.69 mL) was added, followed by addition of tributylamine (0.23 mL, 0.968 mmol) in one portion at ambient temperature. The reaction mixture was stirred for 10 min at ambient temperature, and then a solution of iodine (29.0 mg, 0.114 mmol) in pyridine (0.50 mL) and water (0.05 mL) was added. The reaction mixture was stirred for 15 min, excess iodine was quenched with 5% aq $NaHSO_3$ (3 mL), and the reaction mixture was evaporated to dryness. The residue was dissolved in 10 mL H_2O, and after standing at rt for 30 min, 28% aq ammonium hydroxide (5 mL) was added. The reaction mixture was stirred at 50° C. for 5 h. LCMS indicated full conversion to desired product, and the mixture was filtered and lyophilyzed. The product was purified using mass-directed reverse phase HPLC with a Waters SunFire C18 OBD Prep Column, 100 Å, 5 μm, 19 mm×150 mm, [Waters Part#186002568] using a gradient solvent system with MeCN and 100 mM aq triethylammonium acetate. Lyophilization of the product fractions furnished 2-amino-9-[5-O-(hydroxy{[hydroxy(phosphonooxy)phosphoryl] oxy}phosphoryl)-3-D-xylofuranosyl]-1,9-dihydro-6H-purin-6-one as the tetra-triethylamine salt. LCMS (ES, m/z): 522 $[M-H]^-$.

Preparation 24: ((2R,3S,4R,5S)-5-(7-amino-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl tetrahydrogen triphosphate

[0512]



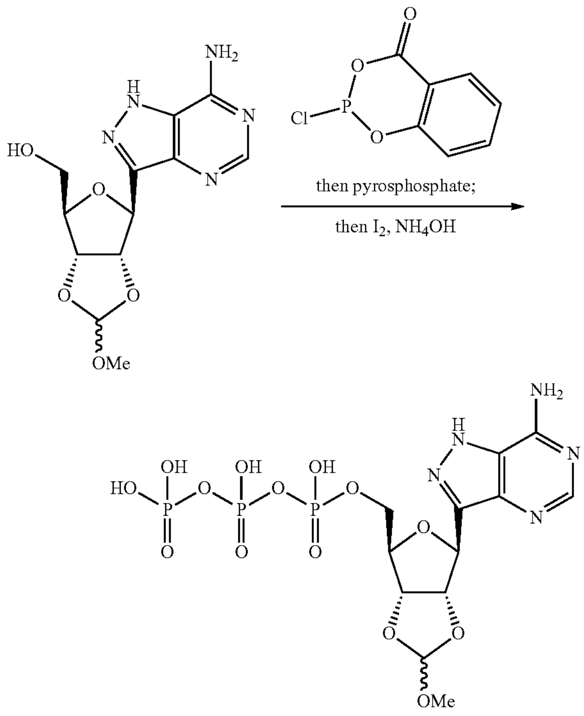
[0513] Step 1: ((3aR,4R,6S,6aS)-6-(7-amino-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-2-methoxytetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methanol



[0514] To the stirred suspension of (2S,3R,4S,5R)-2-(7-amino-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (30 mg, 0.105 mmol) in 1,4-dioxane (0.3 mL) was added trimethyl orthoformate (0.22 mL, 2.011 mmol) in one portion at ambient temperature, followed by p-toluenesulfonic acid monohydrate (22 mg, 0.116 mmol). The reaction mixture was stirred at ambient temperature for 16 h. LCMS indicated significant conversion to desired product, and the crude mixture was carefully quenched by adding triethylamine (0.05 mL) at 0° C. Following concentration, the residue was purified by flash column chromatography on 12 gram silica gel using a gradient solvent system with MeOH and CH_2Cl_2. Concentration of the product fractions furnished ((3aR,4R,6S,6aS)-6-(7-amino-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-2-methoxytetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methanol. LCMS (ES, m/z): 310 $[M+H]^+$.

Step 2: ((3aR,4R,6S,6aS)-6-(7-amino-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-2-methoxytetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl tetrahydrogen triphosphate

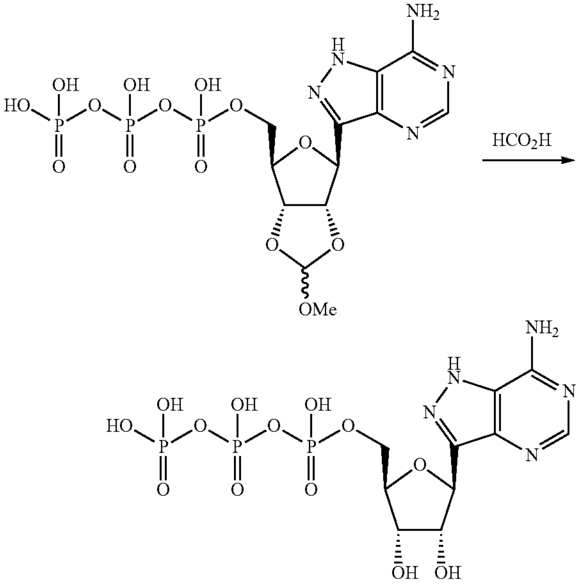
[0515]



[0516] To the stirred suspension of ((3aR,4R,6S,6aS)-6-(7-amino-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-2-methoxytetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methanol (16 mg, 0.052 mmol) in pyridine (0.05 mL) and 1,4-dioxane (0.15 mL) was added DMF (0.05 mL) to form a homogeneous solution. To this solution was added a freshly prepared solution of 2-chloro-4H-1,3,2-benzodioxaphosphorin-4-one (12 mg, 0.059 mmol) in 1,4-dioxane (0.05 mL) at ambient temperature. The reaction mixture was stirred at ambient temperature for 15 min, and then a solution of tributylammonium pyrophosphate (43 mg, 0.078 mmol) in DMF (0.10 mL) was added, followed by tributylamine (0.052 mL, 0.219 mmol). The reaction mixture was stirred at ambient temperature for 15 min, and then a solution of iodine (6.58 mg, 0.026 mmol) in pyridine (0.10 mL) and water (0.01 mL) was added. The reaction mixture was stirred at ambient temperature for 15 min and excess iodine was quenched with 5% aqueous $NaHSO_3$ (0.5 mL). LCMS indicated significant conversion to desired product, and the reaction mixture was concentrated to yield ((3 aR,4R,6S,6aS)-6-(7-amino-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-2-methoxytetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl tetrahydrogen triphosphate, which was used directly in the next reaction step without additional purification. LCMS (ES, m/z): 548 $[M-H]^-$.

Step 3. ((2R,3S,4R,5S)-5-(7-amino-H-pyrazolo[4,3-d]pyrimidin-3-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl tetrahydrogen triphosphate

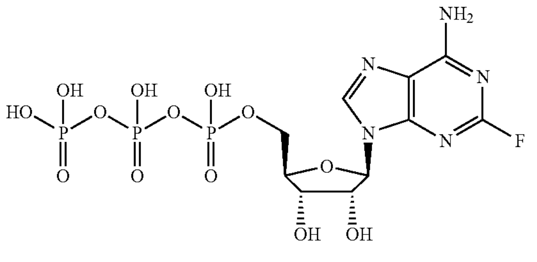
[0517]



[0518] To the stirred solution of crude ((3aR,4R,6S,6aS)-6-(7-amino-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-2-methoxytetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl tetrahydrogen triphosphate (49.4 mg, 0.090 mmol) in water (0.15 mL) and DMF (0.15 mL) was added formic acid (0.4 mL, 10.60 mmol) in one portion. The reaction mixture was stirred at ambient temperature for 18 h. LCMS indicated significant conversion to desired product, and the mixture was filtered and lyophilyzed. The product was purified using mass-directed reverse phase HPLC with a Waters SunFire C18 OBD Prep Column, 100 Å, 5 μm, 19 mm×150 mm, [Waters Part#186002568] using a gradient solvent system with MeCN and 100 mM aqueous triethylammonium acetate. Lyophilization of the product fractions furnished ((2R,3 S,4R,5 S)-5-(7-amino-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl tetrahydrogen triphosphate. LCMS (ES, m/z): 506 [M−H]$^-$.

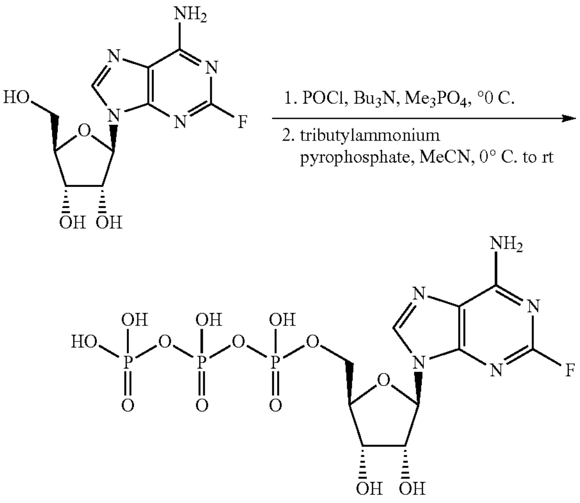
Preparation 25: ((2R,3S,4R,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl tetrahydrogen triphosphate

[0519]



Step 1: ((2R,3S,4R,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl) methyl tetrahydrogen triphosphate

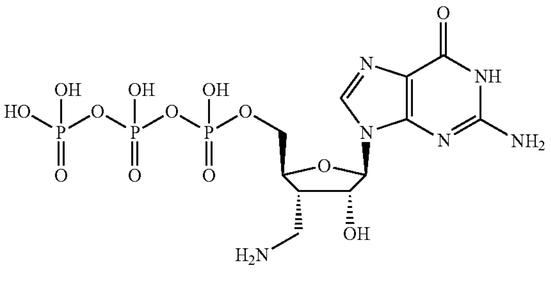
[0520]



[0521] To a mixture of 2-fluoroadenosine (200 mg, 0.701 mmol) in trimethylphosphate (1.948 mL, 16.83 mmol) was added tributylamine (0.500 mL, 2.104 mmol), and the mixture was stirred 15 min at rt and then cooled in an ice/brine bath. Then POCl$_3$ (0.137 mL, 1.472 mmol) was added dropwise with bath temperature maintained at −5 to 0° C. After 1.25 h, a 0° C. mixture of tributylammonium pyrophosphate (327 mg, 0.596 mmol), MeCN (2.8 mL) and tributylamine (1.000 mL, 4.21 mmol) were added, and the mixture was allowed to warm to rt, followed by 16 h stirring at rt. The mixture was purified directly by reverse phase HPLC using a gradient of 1-20% MeCN with 100 mM aqueous triethylammonium acetate to furnish ((2R,3 S,4R, 5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl tetrahydrogen triphosphatemg. LCMS (ES, m/z): 524 [M−H]$^-$.

Preparation 26: 3'-(aminomethyl)-3'-deoxyguanosine 5'-(tetrahydrogen triphosphate)

[0522]

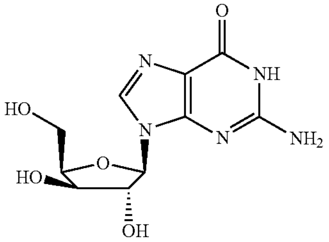


[0523] The title compound was prepared according to published procedures (WO2015161137).

[0524] The Preparations below were used as shown or were further modified through additional synthetic manipulations analogous to those described in Preparations 1-26.

Preparation 27: 2-amino-9-((β-D-xylofuranosyl)-1,9-dihydro-6H-purin-6-one

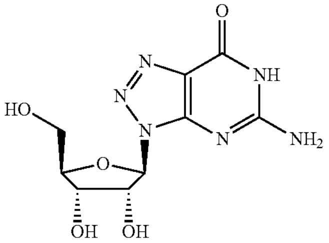
[0525]



[0526] The title compound was prepared according to published procedures (*Journal of Medicinal Chemistry* 1987, 30(6), 982-991).

Preparation 28: 5-amino-3-(β-D-ribofuranosyl)-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one

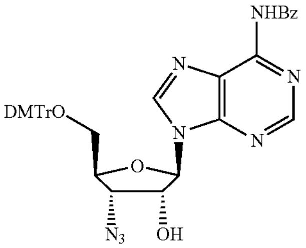
[0527]



[0528] The title compound was prepared according to published procedures (*Journal of Organic Chemistry* 2007, 72(1), 173-179).

Preparation 29: 9-{3-azido-5-O-[bis(4-methoxyphenyl)(phenyl)methyl]-3-deoxy-β-D-ribofuranosyl}-N-(phenylcarbonyl)-9H-purin-6-amine

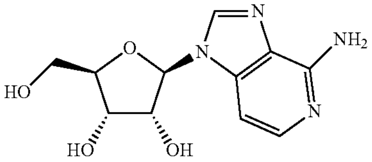
[0529]



[0530] The title compound was prepared according to published procedures (*Bulletin of the Korean Chemical Society* 2004, 25(2), 243-248 and *Nucleosides, Nucleotides & Nucleic Acids* 2005 24(10-12), 1707-1727).

Preparation 30: 1-(β-D-ribofuranosyl)-1H-imidazo[4,5-c]pyridin-4-amine

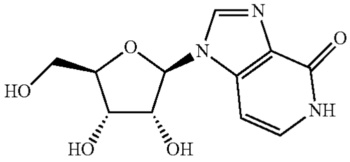
[0531]



[0532] The title compound was prepared according to published procedures (*Tetrahedron* 1993, 49(3), 557-570).

Preparation 31: 1-(β-D-ribofuranosyl)-1,5-dihydro-4H-imidazo[4,5-c]pyridin-4-one

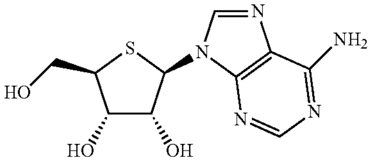
[0533]



[0534] The title compound was prepared according to published procedures (*Tetrahedron* 1993, 49(3), 557-570)

Preparation 32: 4'-thioadenosine

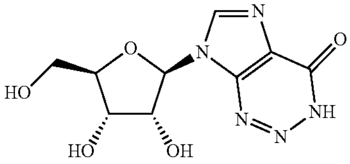
[0535]



[0536] The title compound was prepared according to published procedures (*Journal of Medicinal Chemistry* 2006, 49(5), 1624-1634).

Preparation 33: 7-(β-D-ribofuranosyl)-3,7-dihydro-4H-imidazo[4,5-d][1,2,3]triazin-4-one

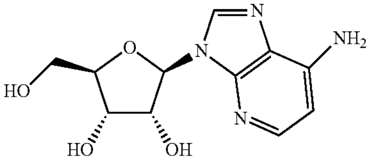
[0537]



[0538] The title compound was prepared according to published procedures (*Organic & Biomolecular Chemistry* 2014, 12(23), 3813-3815).

Preparation 34: 3-(β-D-ribofuranosyl)-3H-imidazo[4,5-b]pyridin-7-amine

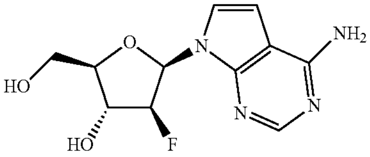
[0539]



[0540] The title compound was prepared according to published procedures (*Biochemistry* 2005, 44(37), 12445-12453).

Preparation 35: 7-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine

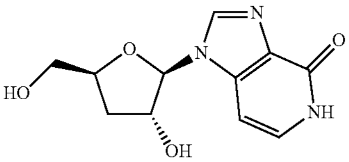
[0541]



[0542] The title compound was prepared according to published procedures (*Journal of the Chemical Society, Perkin Transactions* 1*: Organic and Bio-Organic Chemistry* 1995 (12), 1543-50).

Preparation 36: 1-(3-deoxy-β-D-erythro-pentofuranosyl)-1,5-dihydro-4H-imidazo[4,5-c]pyridin-4-one

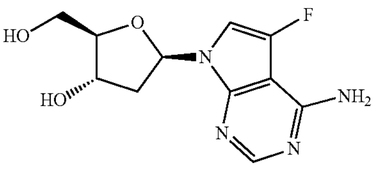
[0543]



[0544] The title compound was prepared according to published procedures (*Chemical & Pharmaceutical Bulletin* 1996, 44(2), 288-295).

Preparation 37: 7-(2-deoxy-β-D-erythro-pentofuranosyl)-5-fluoro-7H-pyrrolo[2,3-d]pyrimidin-4-amine

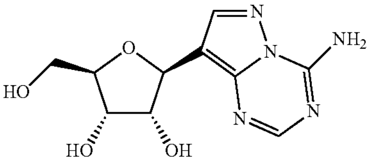
[0545]



[0546] The title compound was prepared according to published procedures (*Synthesis* 2006 (12), 2005-2012).

Preparation 38: (2S,3R,4S,5R)-2-(4-aminopyrazolo[1,5-a][1,3,5]triazin-8-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol

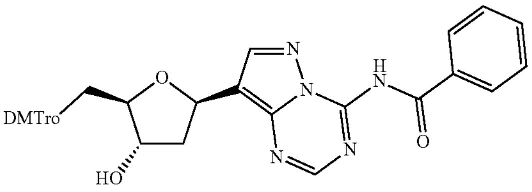
[0547]



[0548] The title compound was prepared according to published procedures (WO2015148746).

Preparation 39: N-(8-((2R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-2-yl)pyrazolo[1,5-a][1,3,5]triazin-4-yl)benzamide

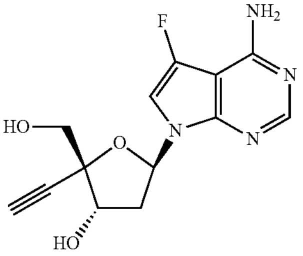
[0549]



[0550] The title compound was prepared according to published procedures (WO2015148746).

Preparation 40: 7-(2-deoxy-4-ethynyl-β-D-erythro-pentofuranosyl)-5-fluoro-7H-pyrrolo[2,3-d]pyrimidin-4-amine

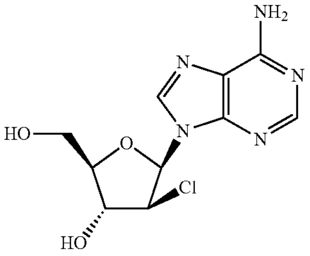
[0551]



[0552] The title compound was prepared according to published procedures (WO2015148746).

Preparation 41: 9-(2-chloro-2-deoxy-(β-D-arabinofuranosyl)-9H-purin-6-amine

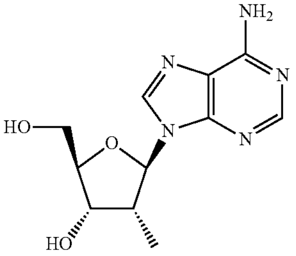
[0553]



[0554] The title compound was prepared according to published procedures (*Journal of the American Chemical Society* 1996, 118(46), 11341-11348).

Preparation 42: 2'-deoxy-2'-methyladenosine

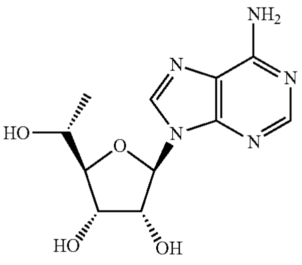
[0555]



[0556] The title compound was prepared according to published procedures (*Synthesis* 2005 (17), 2865-2870).

Preparation 43: (2R,3R,4S,5R)-2-(6-amino-9H-purin-9-yl)-5-((R)-1-hydroxyethyl)tetrahydrofuran-3,4-diol

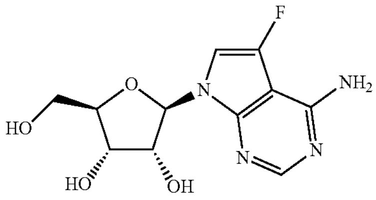
[0557]



[0558] The title compound was prepared according to published procedures (*Bioorganicheskaya Khimiya* 1989, 15(7), 969-975).

Preparation 44: 5-fluoro-7-(B3-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine

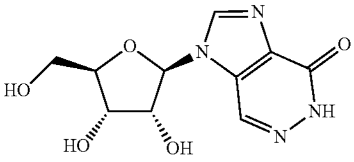
[0559]



[0560] The title compound was prepared according to published procedures (*Nucleosides, Nucleotides, & Nucleic Acids* 2004, 23(1-2), 161-170).

Preparation 45: 1-(β-D-ribofuranosyl)-1,5-dihydro-4H-imidazo[4,5-d]pyridazin-4-one

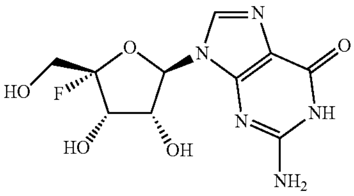
[0561]



[0562] The title compound was prepared according to published procedures (*Journal of the Chemical Society, Perkin Transactions* 1*: Organic and Bio-Organic Chemistry* (1972-1999), 1989 (10), 1769-1774).

Preparation 46: 2-amino-9-1(2R,3R,4S,5S)-5-fluoro-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-1,9-dihydro-6H-purin-6-one

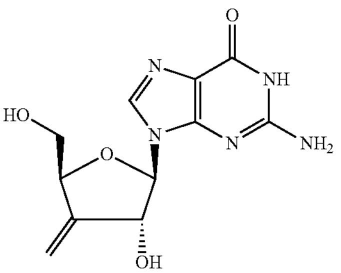
[0563]



[0564] The title compound was prepared according to published procedures (WO2014099941)

Preparation 47: 2-amino-9-((2R,3R,5S)-3-hydroxy-5-(hydroxymethyl)-4-methylenetetrahydrofuran-2-yl)-1,9-dihydro-6H-purin-6-one

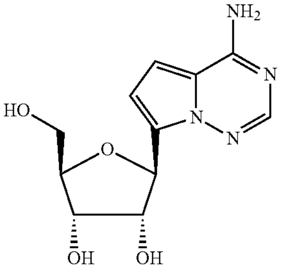
[0565]



[0566] The title compound was prepared according to published procedures (*Journal of Medicinal Chemistry* 1992, 35, 2283-2293).

Preparation 48: (2S,3R,4S,5R)-2-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol

[0567]



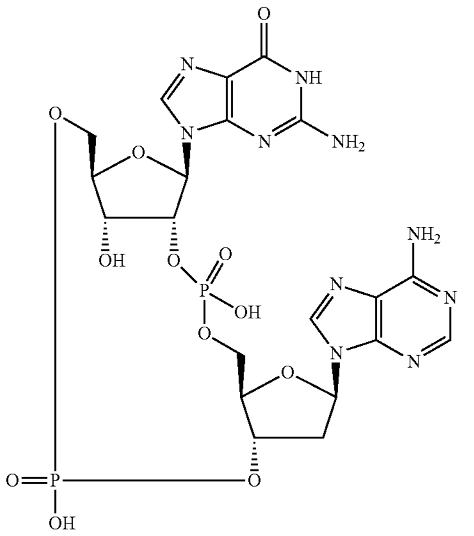
[0568] The title compound was prepared according to published procedures (*Tetrahedron Letters* 1994, 35(30), 5339).

[0569] 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.

EXAMPLES

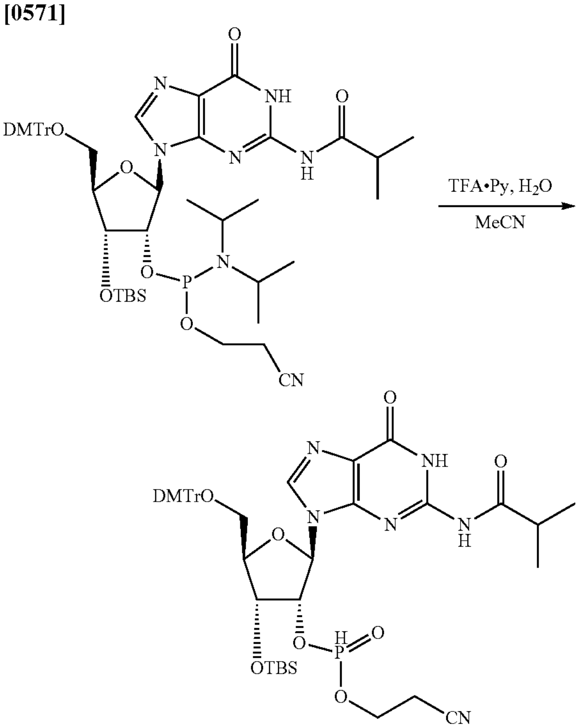
Example 1: (5R,7R,8R,12aR,14R,15aS,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-14-(6-amino-9H-purin-9-yl)-16-hydroxyoctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-2,10-diolate 2,10-dioxide

[0570]



Step 1: (2R,3R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl (2-cyanoethyl) phosphonate

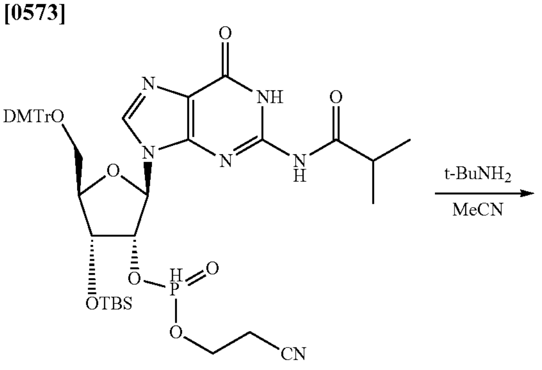
[0571]



[0572] To a solution of (2R,3R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl (2-cyanoethyl) diisopropylphosphoramidite (3 g, 3.09 mmol) in ACN (15 mL) was added water (0.111 mL, 6.18 mmol) and pyridin-1-ium 2,2,2-trifluoroacetate (0.717, 3.71 mmol). The resulting mixture was stirred at RT, and the reaction progress was monitored by LCMS/TLC. After the phosphoramidite was consumed, the reaction mixture containing the product was used in the next step without purification. LCMS (ES, m/z): 887.4 $[M+H]^+$.

Step 2: 2-methylpropan-2-aminium (2R,3R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl) methoxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate

[0573]



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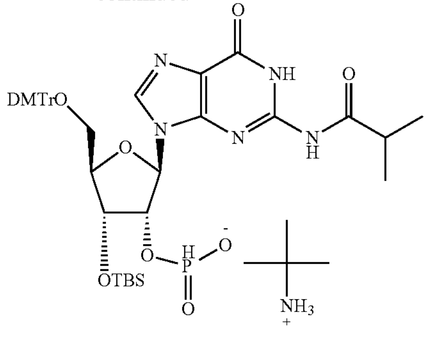
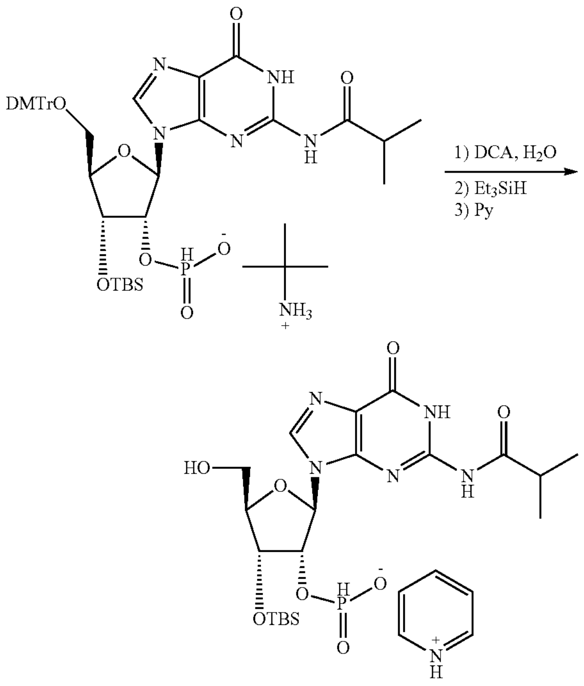


[0574] To the reaction mixture from Step 1 (assumed to contain 3.09 mmol of (2R,3S,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-(tert-butyldimethylsilyloxy)-2-(2-isobutyramido-6-oxo-1,6-dihydropurin-9-yl)-tetrahydrofuran-3-yl 2-cyanoethyl phosphonate) was added tert-butylamine (15.0 mL, 142 mmol) in one portion, and the resulting solution was stirred at rt for 40 min. It was concentrated, and the residue was co-evaporated with ACN (2×15 mL) to give the product, which was used for the next step without further purification. LCMS (ES, m/z): 832.3 $[M-H]^-$.

Step 3: pyridin-1-ium (2R,3R,4R,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(hydroxymethyl)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate

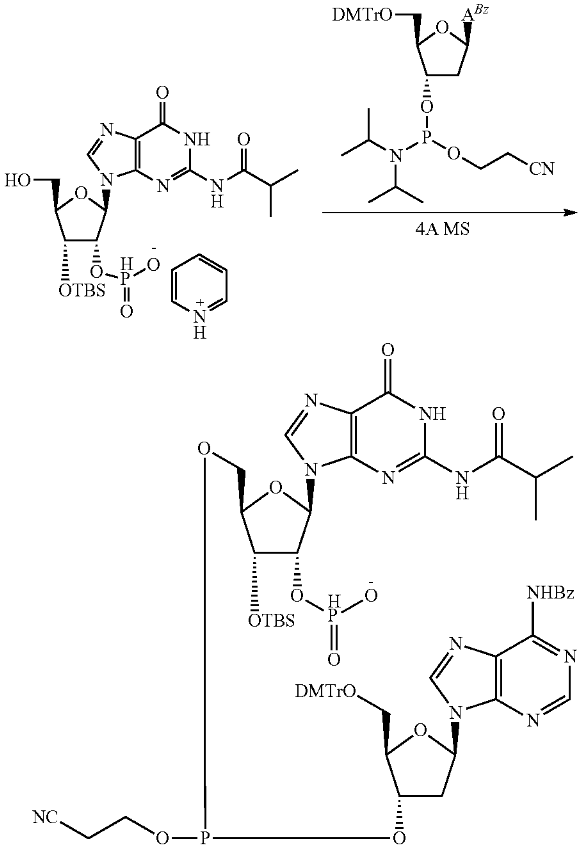
[0575]



[0576] To a stirred solution of crude 2-methylpropan-2-aminium (2R,3R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-((tert-butyldimethyl silyl)oxy)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate (~4.2 g, ~3.09 mmol, from step 2) in CH_2Cl_2 (37 mL) were added water (0.558 mL, 31.0 mmol) and dichloroacetic acid in CH_2Cl_2 (6%, 37 mL, 31.5 mmol). It was stirred for 40 min. Then, triethylsilane (60 mL) was added, and the solution was stirred for 1.5 h. Pyridine (4.5 mL) was added to the reaction. It was concentrated. The residue was triturated with MTBE (50 ml) and Hexane (50 mL), and the supernatant was decanted. This process was repeated twice. The crude mixture was kept over P_2O_5 under reduced pressure for 20 h to give a crude mixture containing the product. LCMS (ES, m/z): 532.2 $[M+H]^+$.

Step 4. (2R,3R,4R,5R)-5-((((((2R,3S,5R)-5-(6-benzamido-9H-purin-9-yl)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphanyl)oxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate

[0577]

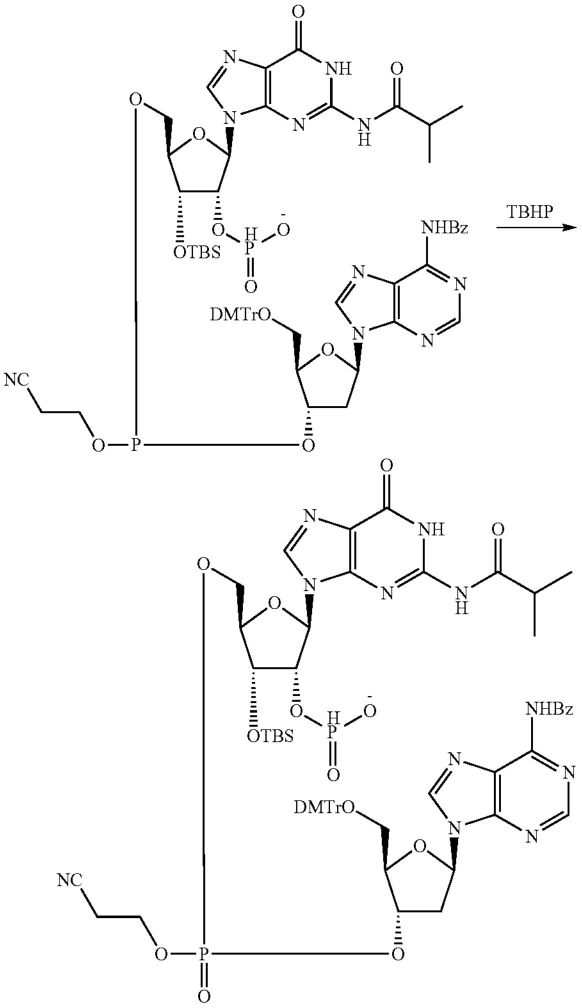


[0578] To a stirred solution of pyridin-1-ium (2R,3R,4R,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(hydroxymethyl)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate (680 mg, crude, –0.722 mmol) in ACN (5 mL) under Ar was added activated 4 Å molecular sieves (100 mg). The resulting mixture was stirred at rt over

30 min. (2R,3S,5R)-5-(6-benzamido-9H-purin-9-yl)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)tetrahydrofuran-3-yl (2-cyanoethyl) diisopropylphosphoramidite (0.805 g, 0.939 mmol) was co-evaporated with ACN (3×1 mL), re-dissolved in ACN (5 mL), and dried by adding activated 4 Å molecular sieve (100 mg). After 30 min, it was added to the previously prepared mixture containing pyridin-1-ium (2R,3R,4R,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(hydroxymethyl)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate. The mixture was stirred at rt for 1 h. The reaction mixture containing the product was used in the next reaction step immediately without purification. LCMS (ES, m/z): 1288.4 $[M+H]^+$.

Step 5. (2R,3R,4R,5R)-5-((((((2R,3S,5R)-5-(6-benzamido-9H-purin-9-yl)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphoryl) oxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate

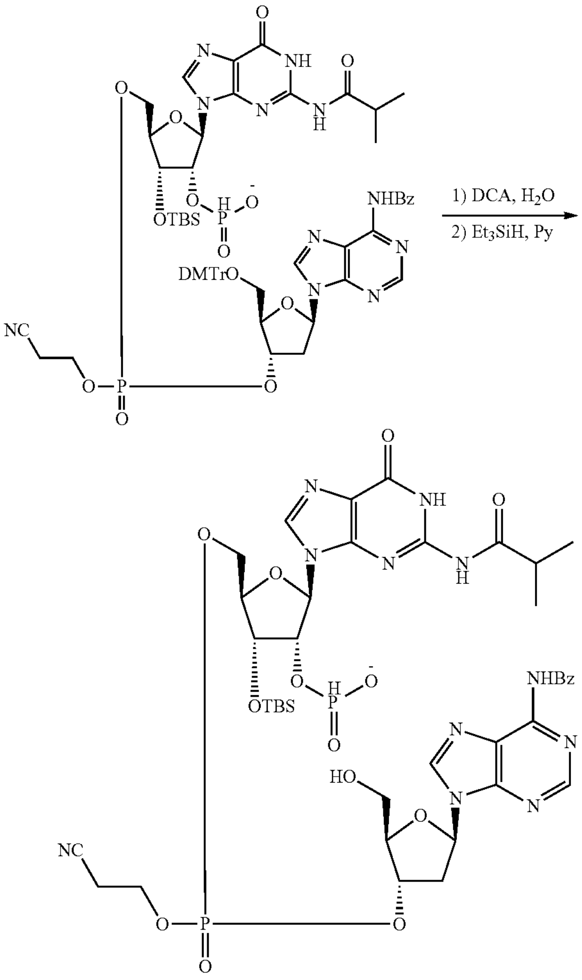
[0579]



[0580] To the reaction mixture containing the crude (2R,3R,4R,5R)-5-((((((2R,3S,5R)-5-(6-benzamido-9H-purin-9-yl)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphanyl)oxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate (~1 mmol, with excess pyridinium 2,2-dichloroacetate) was added tert-butyl hydroperoxide in decane (5.5M, 0.64 mL, 3.5 mmol) dropwise. It was stirred at rt for 1 h. Then, the solution was cooled to 0° C., and $NaHSO_3$ (250 mg) in water (5 mL) was added slowly. After 5 min, the mixture was concentrated, and the residue was purified by reverse phase (C18) chromatography eluted with 5 to 45% ACN in aq NH_4HCO_3 (0.04%) to give the product. LCMS (ES, m/z): 1305.6 $[M+H]^+$.

Step 6. (2R,3R,4R,5R)-5-((((((2R,3S,5R)-5-(6-benzamido-9H-purin-9-yl)-2-(hydroxymethyl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphoryl)oxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate

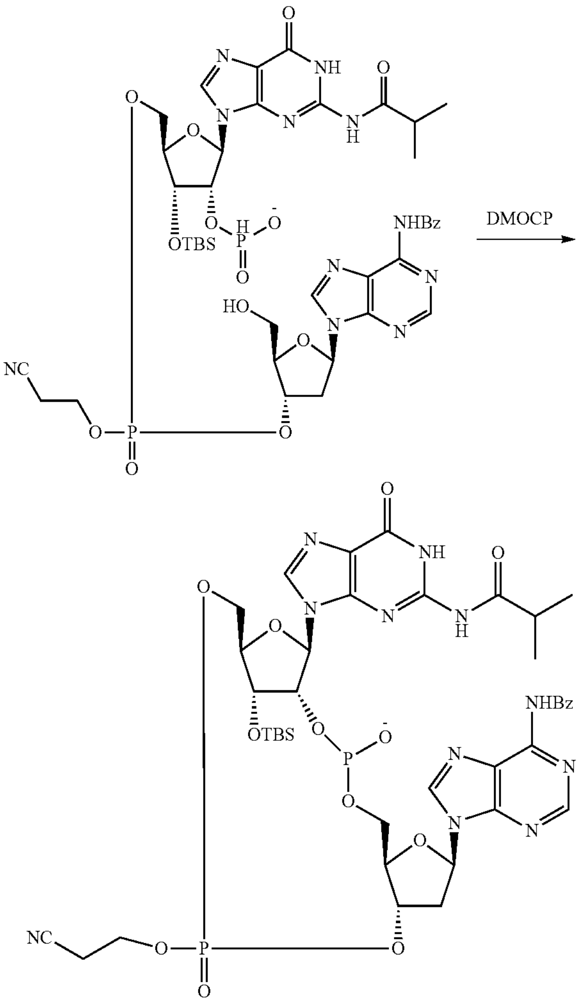
[0581]



[0582] To a stirred solution of (2R,3R,4R,5R)-5-((((((2R,3S,5R)-5-(6-benzamido-9H-purin-9-yl)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphoryl)oxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate (340 mg, 0.239 mmol) in CH_2Cl_2 (4 mL) were added water (44.5 mg, 2.468 mmol) and dichloroacetic acid (0.280 g, 2.17 mmol) in CH_2C_1 (5 ml). It was stirred at rt for 30 min. Et_3SiH (4 mL) was then added, and the mixture was stirred for 1.5 h. Pyridine (3 mL) was added to the reaction, and it was concentrated to give a crude product, which was used for the next step without purification. LCMS (ES, m/z): 1002.4 $[M+H]^+$.

Step 7: (5R,7R,8R,12aR,14R,15aS,16R)-16-{[tert-butyl(dimethyl)silyl]oxy}-2-(2-cyanoethoxy)-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl) amino]-9H-purin-9-yl}octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-10-olate 2-oxide

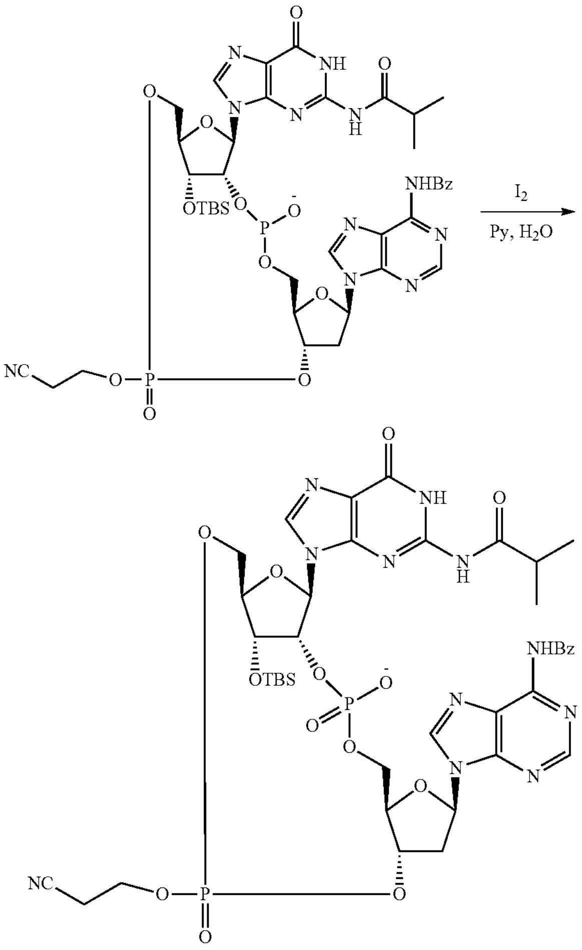
[0583]



[0584] Crude (2R,3R,4R,5R)-5-((((((2R,3S,5R)-5-(6-benzamido-9H-purin-9-yl)-2-(hydroxymethyl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphoryl)oxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate (1.5 g, –0.24 mmol) was co-evaporated with pyridine (3×5 mL) and then re-dissolved in pyridine (4 mL). To the reaction was added 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxide (160 mg, 0.865 mmol) in one portion. The resulting mixture was stirred at rt for 1 h. It was used for the next reaction step directly without purification. LCMS (ES, m/z): 984.3 $[M+H]^+$.

Step 8. (5R,7R,8R,12aR,14R,15aS,16R)-16-{[tert-butyl(dimethyl)silyl]oxy}-2-(2-cyanoethoxy)-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-10-olate 2,10-dioxide

[0585]

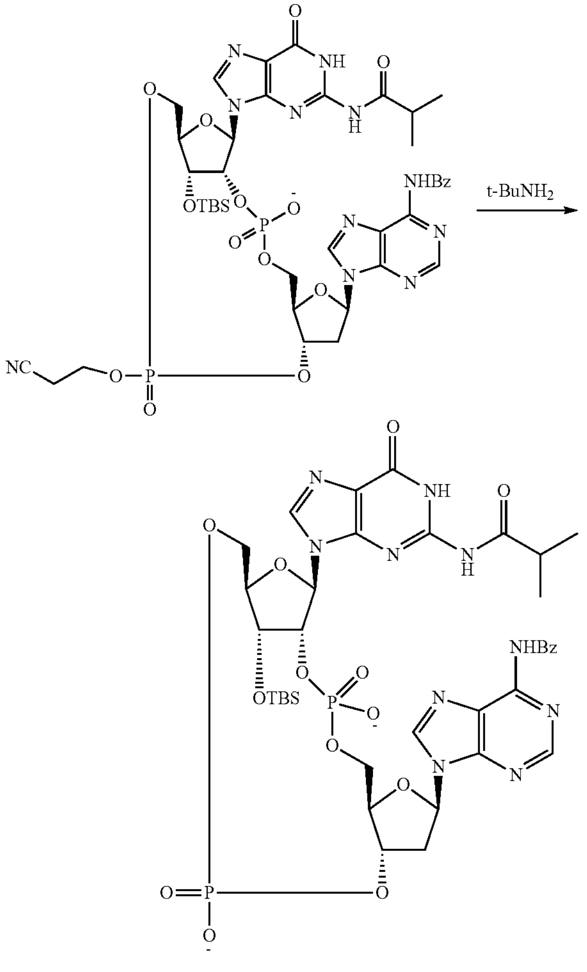


[0586] To the stirred mixture containing (5R,8R,12aR,14R,15aS,16R)-16-{[tert-butyl(dimethyl)silyl]oxy}-2-(2-cyanoethoxy)-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-

9H-purin-9-yl}octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-10-olate 2-oxide was added water (156 mg, 8.65 mmol) and iodine (81 mg, 0.321 mmol). After 10 min, the mixture was poured into a solution of $NaHSO_3$ (52 mg) in water (36 ml), and it was stirred for 5 min. It was cooled to 0° C., and $NaHCO_3$ (1.04 g) was slowly added. After 5 min, EtOAc (50 mL) and Et_2O (50 ml) were added. Layers were separated, and the aq layer was extracted with EtOAc (1×30 ml). The organic layers were combined, concentrated, and purified by silica gel column chromatography eluted with 0-20% MeOH in CH_2Cl_2 to give the product. LCMS (ES, m/z): 998.3 $[M+H]^+$.

Step 9. (5R,7R,8R,12aR,14R,15aS,16R)-16-{[tert-butyl(dimethyl)silyl]oxy}-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino-9H-purin-9-yl}octahydro-12H-5,8-methanofuro 3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-2,10-diolate 2,10-dioxide

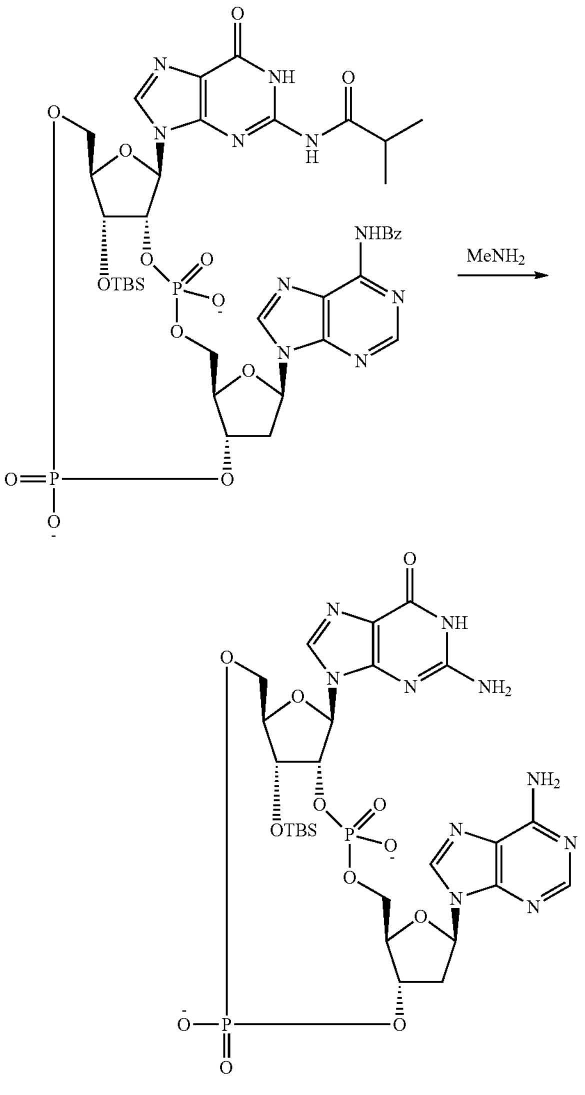
[0587]



[0588] To a stirred solution of (5R,7R,8R,12aR,14R,15aS,16R)-16-{[tert-butyl(dimethyl)silyl]oxy}-2-(2-cyanoethoxy)-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-10-olate 2,10-dioxide (160 mg) in ACN (2 mL) was added tert-butylamine (2 mL) at rt. After 30 min, it was concentrated to give the crude product, which was used for the next step without purification. LCMS (ES, m/z): 945.2 $[M+H]^+$.

Step 10: (5R,7R,8R,12aR,14R,15aS,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-14-(6-amino-9H-purin-9-yl)-16-{[tert-butyl(dimethyl)silyl]oxy}octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-2,10-diolate 2,10-dioxide

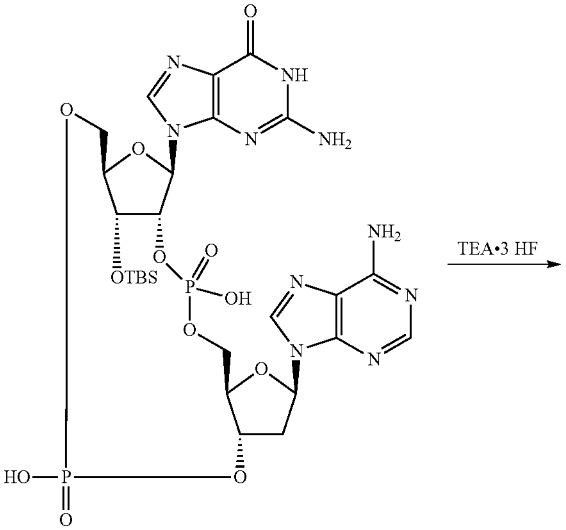
[0589]



[0590] Crude (5R,7R,8R,12aR,14R,15aS,16R)-16-{[tert-butyl(dimethyl)silyl]oxy}-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecine-2,10-diolate 2,10-dioxide (220 mg) was dissolved in a solution of $MeNH_2$ in EtOH (30%, 4 mL), and it was stirred at rt for 5 h. Then, the volatile component was removed under reduced pressure to give a crude product, which was used for the next reaction step without purification. LCMS (ES, m/z): 773.2 $[M+H]^+$ and 771.3 $[M-H]^-$.

Step 11: (5R,7R,8R,12aR,14R,15aS,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-14-(6-amino-9H-purin-9-yl)-16-hydroxyoctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-2,10-diolate 2,10-dioxide

[0591]



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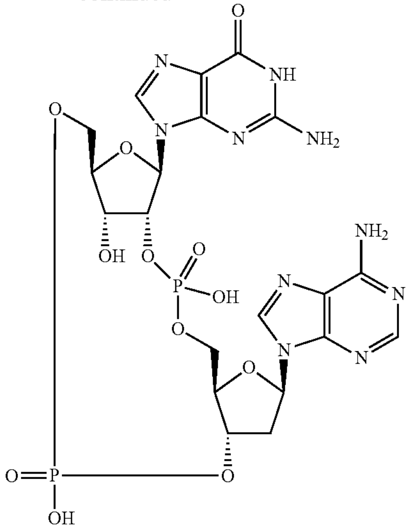


[0592] The crude from Step 10 was co-evaporated with pyridine (2.5 ml) and Et_3N (2.5 mL) three times. It was dissolved in pyridine (2 mL). To the solution was added Et_3N (1.51 g, 14.9 mmol) and triethylamine trihydrofluoride (1.2 g, 7.45 mmol) dropwise. The mixture was heated at 50° C. for 5 h. Then, it was concentrated and purified by preparative-HPLC (T3 Prep Column, 100 Å, 5 μm, 19 mm×250 mm) eluted with 0 to 10% ACN in aq NH_4HCO_3 (50 mM) to give the product. LCMS (ES, m/z): 657.1 $[M-H]^-$. ^{1}H-NMR: (300 MHz, DMSO-d_6+D_2O): δ 8.35 (s, 1H), 8.16 (s, 1H), 8.03 (s, 1H), 6.34 (dd, J=8.8, 5.9 Hz, 1H), 5.85 (d, J=8.3 Hz, 1H), 5.12-4.98 (m, 2H), 4.36 (d, J=3.9 Hz, 1H), 4.22 (t, J=7.2 Hz, 1H), 4.09 (s, 1H), 3.96-3.79 (m, 4H), 3.09-2.99 (m, 1H), 2.64-2.51 (m, 1H). ^{31}P-NMR: (121 MHz, DMSO-d_6+D_2O): δ −1.65 (s), −2.36 (s).

[0593] Examples 2 through 19, shown in Table 1 below, were prepared according to procedures analogous to those outlined in Example 1 above using the appropriate nucleoside monomers, described as Preparations or as obtained from commercial sources.

TABLE 1

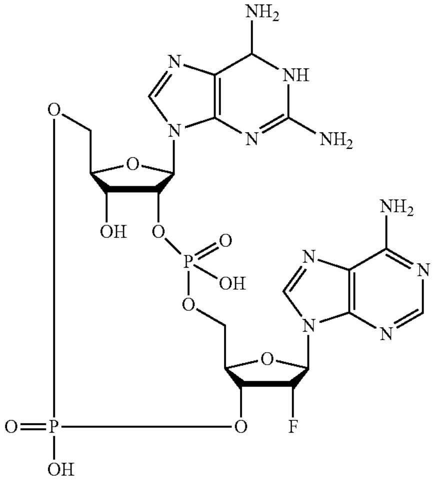
Ex.	Structure	Name	Mass $[M-H]^-$
2		(5R,7R,8R,12aR,14R,15R,15aR,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-14-(6-amino-9H-purin-9-yl)-15-fluoro-16-hydroxyoctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-2,10-diolate 2,10-dioxide	675

TABLE 1-continued

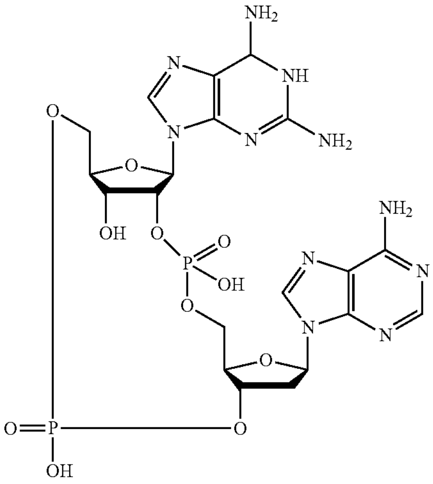
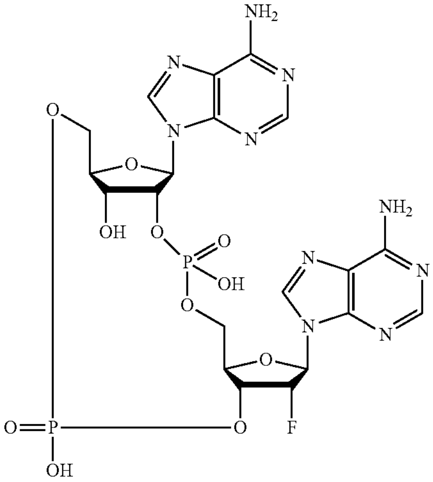
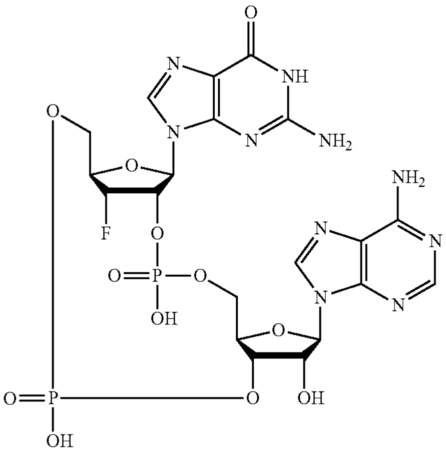
Ex.	Structure	Name	Mass [M − H]⁻
3		(5R,7R,8R,12aR,14R,15aS,16R)-7,14-bis(6-amino-9H-purin-9-yl)-16-hydroxyoctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-2,10-diolate 2,10-dioxide	657
4		(5R,7R,8R,12aR,14R,15R,15aR,16R)-7,14-bis(6-amino-9H-purin-9-yl)-15-fluoro-16-hydroxyoctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-2,10-diolate 2,10-dioxide	659
5		(5R,7R,8S,12aR,14R,15R,15aS,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-14-(6-amino-9H-purin-9-yl)-16-fluoro-15-hydroxyoctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-2,10-diolate 2,10-dioxide	675

TABLE 1-continued

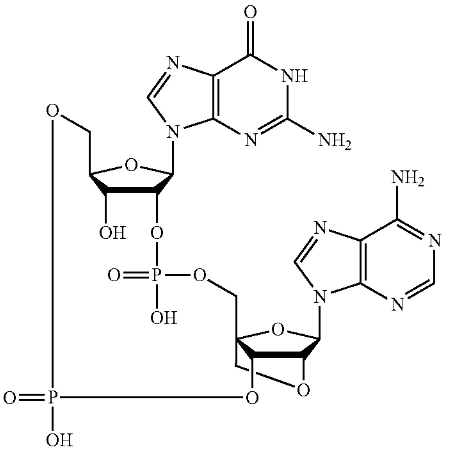
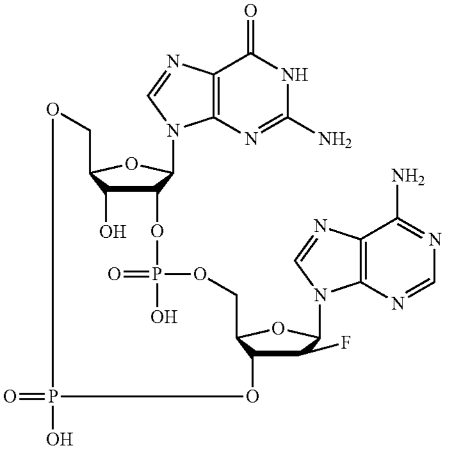
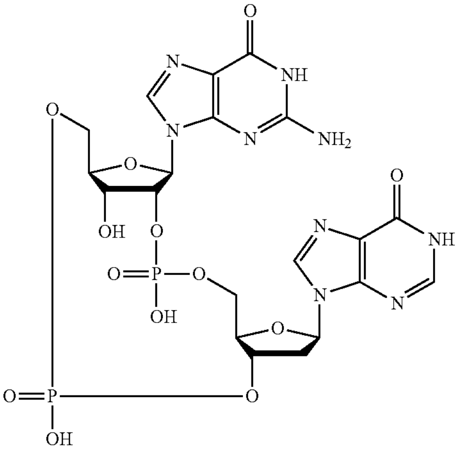
Ex.	Structure	Name	Mass $[M-H]^-$
6		(5R,7R,8R,12aR,14R,15R,15aS,18R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-14-(6-amino-9H-purin-9-yl)-18-hydroxyhexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-2,10(12H)-diolate 2,10-dioxide	685
7		(5R,7R,8R,12aR,14R,15S,15aR,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-14-(6-amino-9H-purin-9-yl)-15-fluoro-16-hydroxyoctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-2,10-diolate 2,10-dioxide	675
8		(5R,7R,8R,12aR,14R,15aS,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-16-hydroxy-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-2,10-diolate 2,10-dioxide	660 $[M + H]^+$

TABLE 1-continued

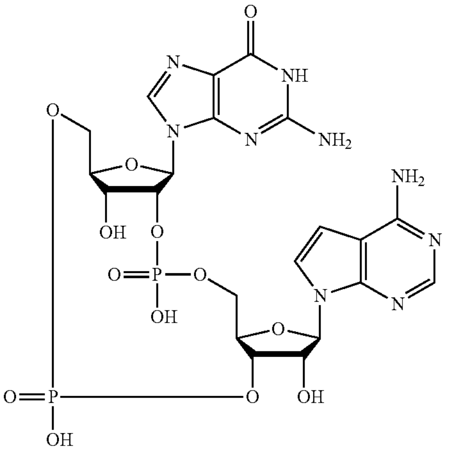
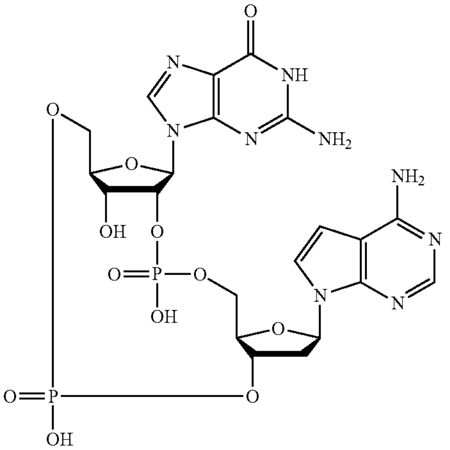
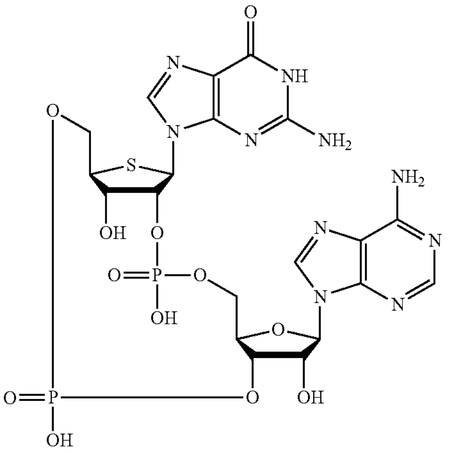
Ex.	Structure	Name	Mass [M − H]⁻
9		(5R,7R,8R,12aR,14R,15R,15aS,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-15,16-dihydroxyoctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-2,10-diolate 2,10-dioxide	672
10		(5R,7R,8R,12aR,14R,15aS,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-16-hydroxyoctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-2,10-diolate 2,10-dioxide	656
11		(5R,7R,8R,12aR,14R,15R,15aS,16S)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-14-(6-amino-9H-purin-9-yl)-15,16-dihydroxyoctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecine-2,10-diolate 2,10-dioxide	689

TABLE 1-continued

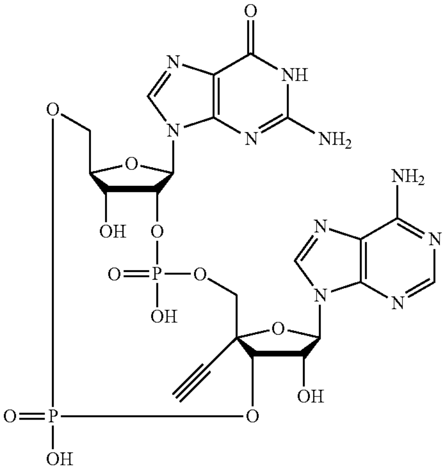
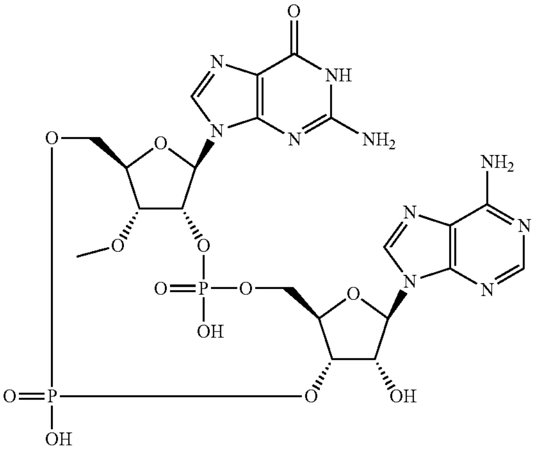
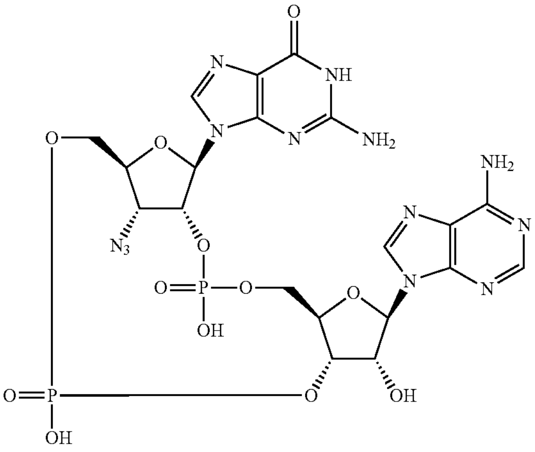
Ex.	Structure	Name	Mass $[M - H]^-$
12		(5R,7R,8R,12aR,14R,15R,15aS,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-14-(6-amino-9H-purin-9-yl)-12a-ethynyl-15,16-dihydroxyoctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-2,10-diolate 2,10-dioxide	699 $[M + H]^+$
13		2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-2,10,15-trihydroxy-16-methoxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	687
14		2-amino-9-[(5S,7R,8R,12aR,14R,15R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-16-azido-2,10,15-trihydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	698

TABLE 1-continued

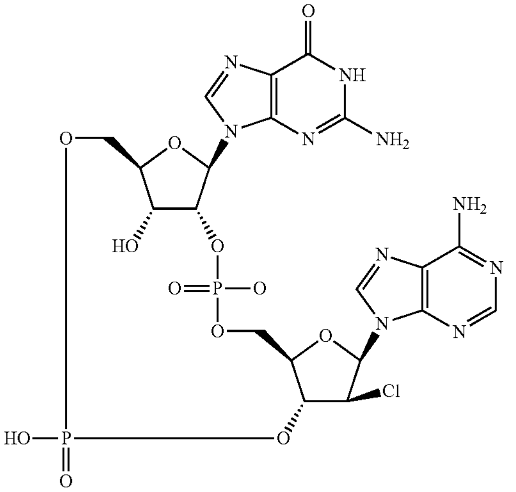
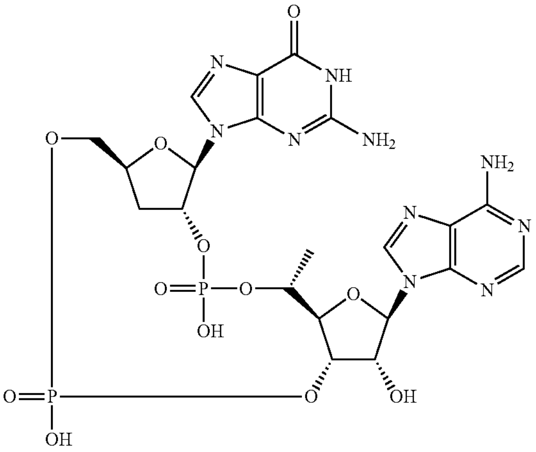
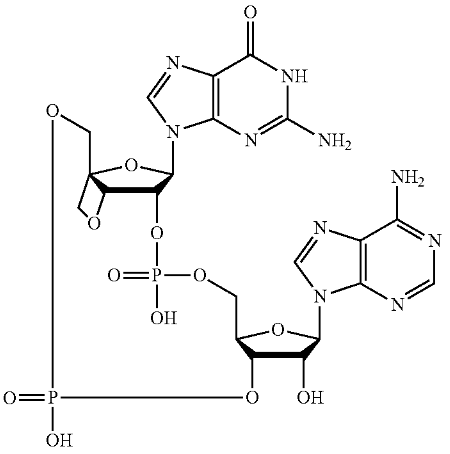
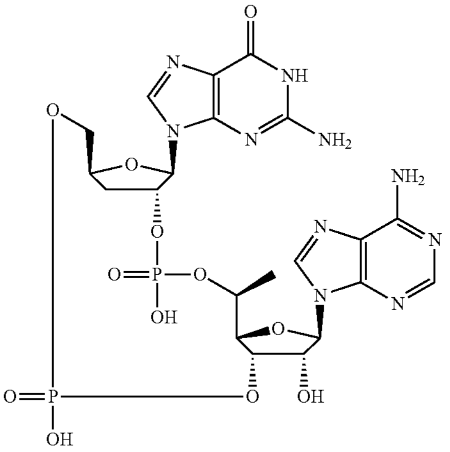
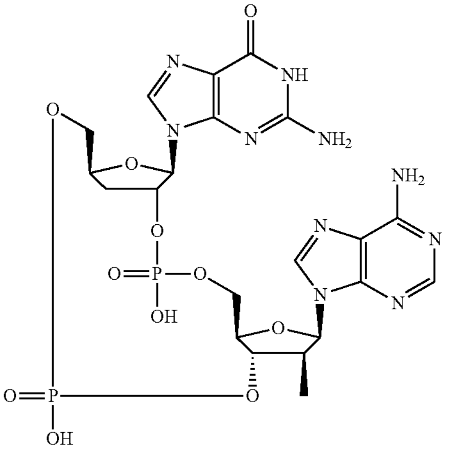
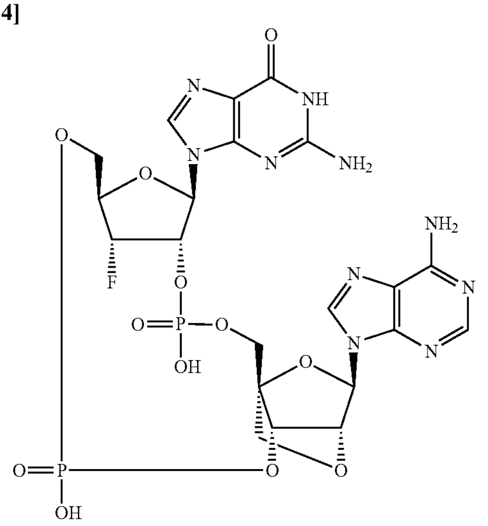
Ex.	Structure	Name	Mass [M − H]⁻
15		2-amino-9-[(5R,7R,8R,12aR,14R,15S,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15-chloro-2,10,16-trihydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	691
16		2-amino-9-[(5S,7R,8R,12R,12aR,14R,15R,15aS)-14-(6-amino-9H-purin-9-yl)-2,10,15-trihydroxy-12-methyl-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	671

TABLE 1-continued

Ex.	Structure	Name	Mass [M − H]$^-$
17		2-amino-9-[(2aR,5S,6aS,7R,8R,9aR,12S,14R,14aS,15R)-8-(6-amino-9H-purin-9-yl)-5,7,12-trihydroxy-5,12-dioxidohexahydro-6aH-2a,14-(epoxymethano)furo[3,2-d]oxeto[2,3-k][1,3,7,9,2,8]tetraoxadiphosphacyclotridecin-15(2H,3H)-yl]-1,9-dihydro-6H-purin-6-one	685
18		2-amino-9-[(5S,7R,8R,12S,12aS,14R,15R,15aS)-14-(6-amino-9H-purin-9-yl)-2,10,15-trihydroxy-12-methyl-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	671
19		2-amino-9-[(5S,7R,8R,12aR,14R,15S,15aS)-14-(6-amino-9H-purin-9-yl)-2,10-dihydroxy-15-methyl-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	655

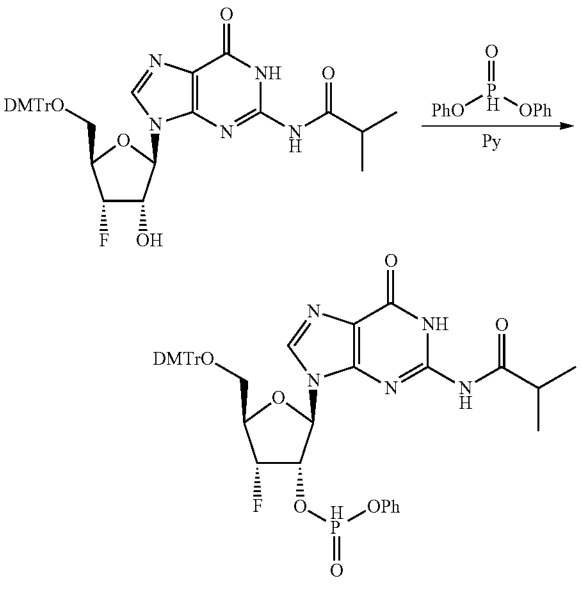
Example 20: (5R,7R,8S,12aR,14R,15R,15aS,18R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-14-(6-amino-9H-purin-9-yl)-18-fluorohexahydro-14H-15,12a-(enoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-2,10(12H)-diolate

[0594]



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

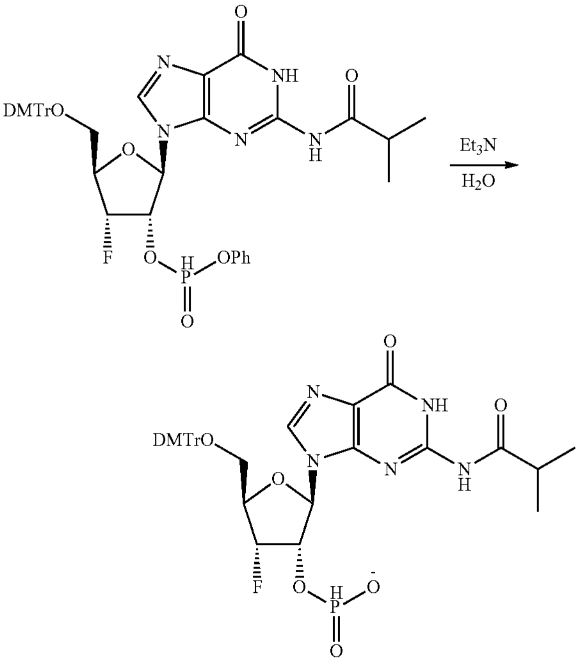
[0595]



[0596] To a stirred solution of N-(9-((2R,3 S,4 S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy) methyl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide (1 g, 1.520 mmol) in pyridine (7.6 mL) under Ar was added diphenyl phosphonate (1.068 g, 4.56 mmol), and it was stirred at rt for 20 min. The reaction mixture containing the product was used for the next reaction step without purification.

Step 2. (2R,3,4R,5R)-5-((bis(4-m ethoxyphenyl)(phenyl)methoxy)methyl)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate

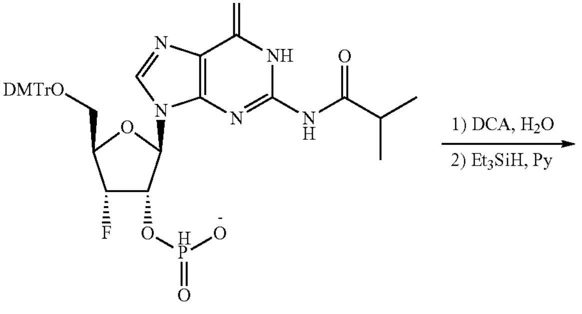
[0597]



[0598] To the reaction mixture from Step 1 was added water (1.5 ml) and Et_3N (1.5 mL). The mixture was stirred at rt for 20 min. Then, it was concentrated, and the residue was partitioned between CH_2Cl_2 (50 mL) and aq $NaHCO_3$ (5%, 20 mL). Layers were separated. The organic layer was washed with aq $NaHCO_3$ (5%, 2×20 mL), 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: (162 MHz, CD_3OD): δ 2.73 (s, 1P).

Step 3. (2R,3S,4R,5R)-4-fluoro-5-(hydroxymethyl)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate

[0599]



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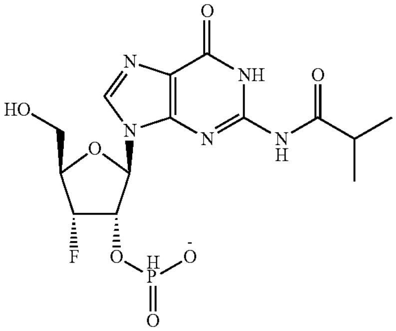
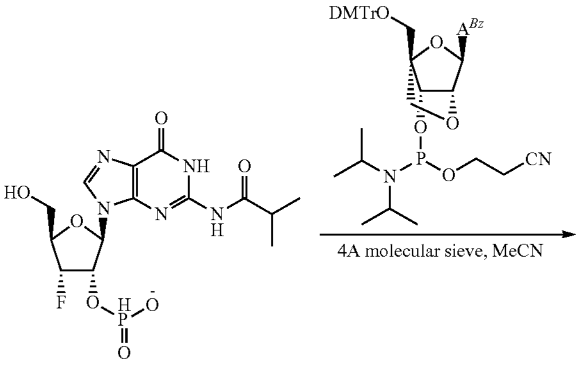


[0600] To a stirred solution of the product of Step 2 (0.9 g, 0.999 mmol) in CH_2Cl_2 (6 mL) were added water (0.180 g, 9.99 mmol) and 2,2-dichloroacetic acid (1.16 g, 8.99 mmol) in CH_2Cl_2 (10 ml). The mixture was stirred at rt for 15 min. Et_3SiH (10 mL) was added, and it was stirred for 1 h. Then, pyridine (2 mL) was added, and it was concentrated. The residue was purified by reverse phase (C18) chromatography eluted with 0 to 30% ACN in aq NH_4HCO_3 (0.04%) to give the product. LCMS (ES, m/z): 722 $[M-H]^-$. 417.9. ^{1}H-NMR: (400 MHz, CD_3OD): δ 8.31 (s, 1H), 7.49 (d, J=1.6 Hz, 0.5H), 6.15 (d, J=6.8 Hz, 1H), 5.91 (d, J=1.6 Hz, 0.5H), 5.42-5.32 (m, 1.5H), 5.21 (dd, J=4.5, 1.9 Hz, 0.5H), 4.45-4.32 (m, 1H), 3.81 (d, J=3.5 Hz, 2H), 3.20 (q, J=7.4 Hz, 1H), 2.73 (p, J=6.9 Hz, 1H), 1.30 (t, J=7.3 Hz, 1.5H), 1.23 (d, J=6.9 Hz, 6H). ^{19}F-NMR: (376 MHz, CD_3OD): δ −200.96 (s, 1F). ^{31}P-NMR: (162 MHz, CD_3OD): δ 2.41 (s, 1P).

Step 4: (2R,3S,4R,5R)-5-((((((1R,3R,4R,7S)-3-(6-benzamido-9H-purin-9-yl)-1-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-2,5-dioxabicyclo[2.2.1]heptan-7-yl)oxy)(2-cyanoethoxy)phosphanyl)oxy)methyl)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate

[0601]



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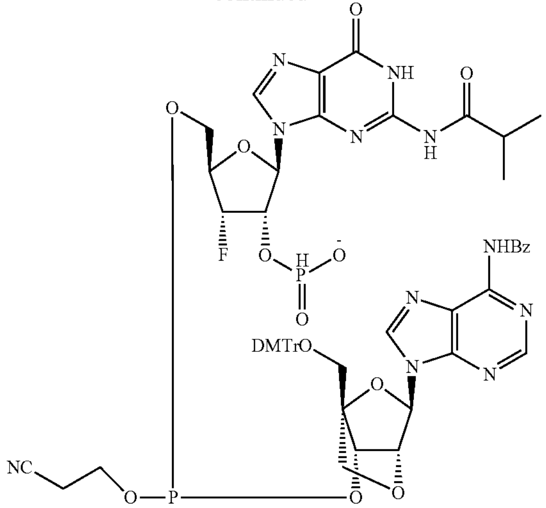
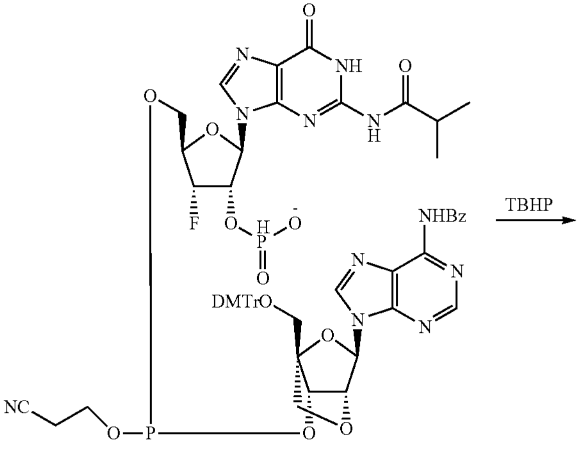


[0602] (2R,3 S,4R,5R)-4-fluoro-5-(hydroxymethyl)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate (600 mg, 0.676 mmol) was co-evaporated with ACN (3×5 mL), re-dissolved in ACN (3 mL), dried by addition of activated 4 Å molecular sieves (150 mg) and kept under Ar. (1R,3R,4R,7S)-3-(6-benzamido-9H-purin-9-yl)-1-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-2,5-dioxabicyclo[2.2.1]heptan-7-yl (2-cyanoethyl) diisopropylphosphoramidite (available from Exiqon (EQ-0063-1000), 235.5 mg, 0.56 mmol) and pyridinium 2,2,2-trifluoroacetate (162 mg, 0.84 mmol) were co-evaporated with ACN (3×5 mL), re-dissolved in ACN (5 mL), and dried by addition activated 4 Å molecular sieve (150 mg). After 30 min, it was added to the previously prepared mixture containing (2R,3S,4R,5R)-4-fluoro-5-(hydroxymethyl)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate. The mixture was stirred at rt for 1 h. The reaction mixture containing the product was used in the next reaction step immediately without purification. LCMS (ES, m/z): 1202.3 $[M-H]^-$.

Step 5. (2R,3S,4R,5R)-5-((((((R,3R,4R,7S)-3-(6-benzamido-9H-purin-9-yl)-1-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-2,5-dioxabicyclo[2.2.1]heptan-7-yl)oxy)(2-cyanoethoxy)phosphoryl)oxy)methyl)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate

[0603]



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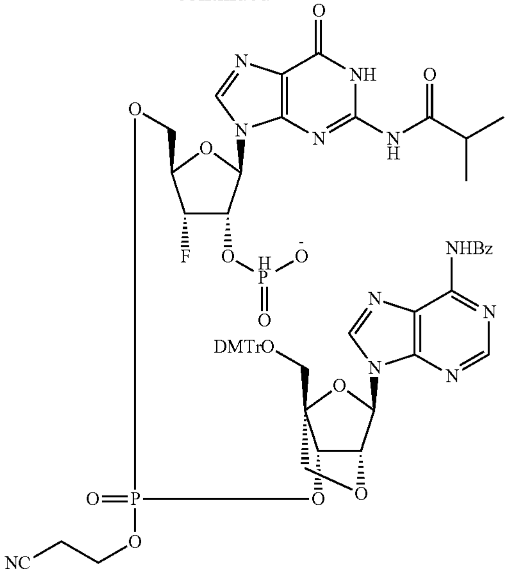
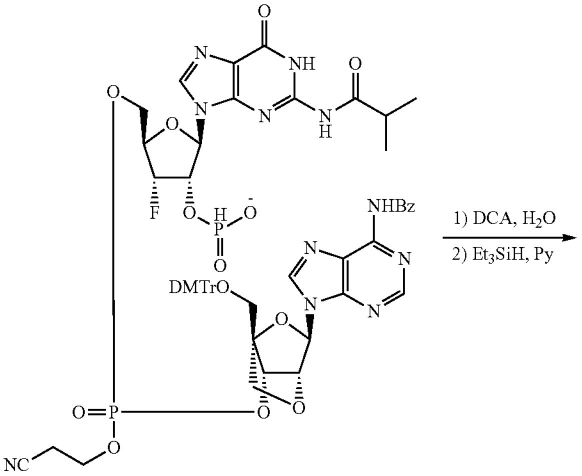


[0604] To the stirred reaction mixture from Step 4 was added tert-butyl hydroperoxide in decane (5.5M, 0.31 mL, 1.71 mmol) dropwise. The resulting mixture was stirred at rt for 1 h. After 30 min, the solution was cooled to 0° C., and $NaHSO_3$ (150 mg) in water (5 mL) was added slowly. After 5 min, the mixture was concentrated, and the residue was purified by reverse phase (C18) chromatography eluted with 0 to 75% ACN in aq NH_4HCO_3 (5 mM) to give the product. LCMS (ES, m/z): 1220.1 $[M+H]^+$. ^{19}F-NMR (376 MHz, CD_3OD): δ −200.38, −202.45 (2s, 1F). ^{31}P-NMR: (162 MHz, CD_3OD): δ 2.57, 2.49 (2s, 1P); −3.52, −4.21 (2s, 1P).

Step 6. (2R,3S,4R,5R)-5-((((((S,3R,4R,7S)-3-(6-benzamido-9H-purin-9-yl)-1-(hydroxymethyl)-2,5-dioxabicyclo[2.2.1]heptan-7-yl)oxy)(2-cyanoethoxy)phosphoryl)oxy)methyl)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate

[0605]



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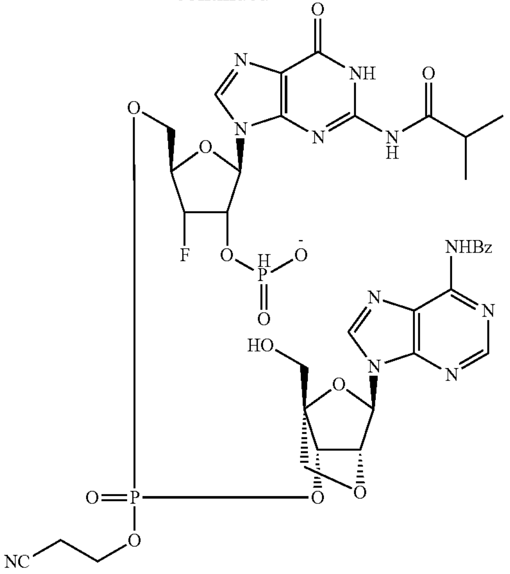
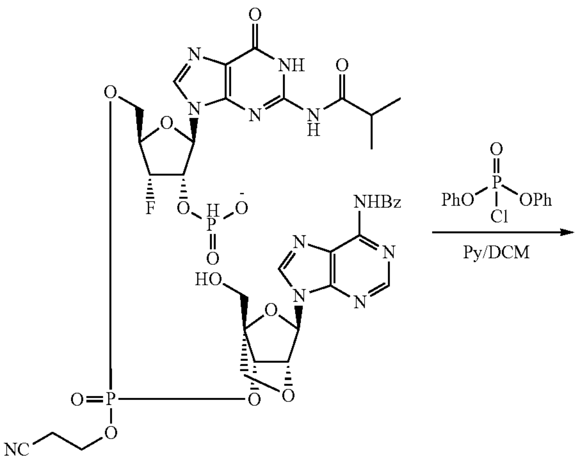


[0606] To a solution of (2R,3S,4R,5R)-5-((((((1R,3R,4R,7S)-3-(6-benzamido-9H-purin-9-yl)-1-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-2,5-dioxabicyclo[2.2.1]heptan-7-yl)oxy)(2-cyanoethoxy)phosphoryl)oxy)methyl)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate (190 mg, 0.16 mmol) in CH_2Cl_2 (2.5 mL) was added water (28.8 mg, 1.6 mmol) and dichloroacetic acid in CH_2Cl_2 (0.6M, 2.5 mL). The mixture was stirred at rt for 10 min, and then Et_3SiH (4.5 mL) was added. After 1 h, pyridine (0.5 mL) was added. After 10 min, the resulting mixture was concentrated to give the product, which was used for the next reaction step without purification. LCMS (ES, m/z): 917.9 $[M+H]^+$. ^{31}P-NMR: (162 MHz, CD_3OD): δ 2.51, 2.34 (2s, 1P); −3.46, −3.82 (2s, 1P).

Step 7: (5R,7R,8S,12aR,14R,15R,15aS,18R)-2-(2-cyanoethoxy)-18-fluoro-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}hexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-10 (12H)-olate 2,10-dioxide

[0607]



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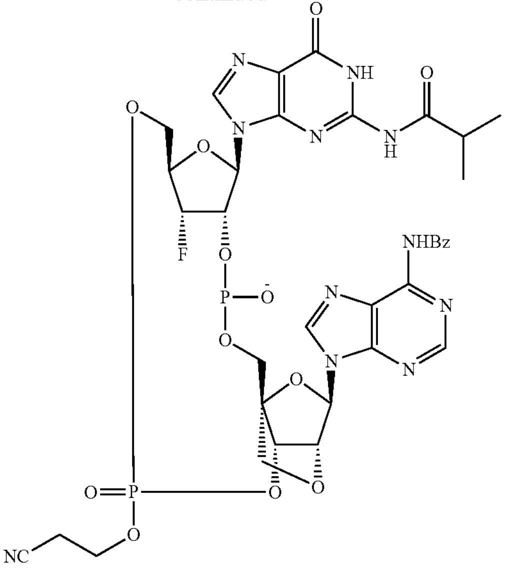

[0608] To pyridine (16 mL) under Ar was added diphenyl chlorophosphate (0.66 mL, 3.2 mmol). It was cooled at −40° C. and then, a solution of crude from Step 6 in CH_2Cl_2 (16 mL) was added dropwise over 20 min. The resulting mixture was stirred at −40° C. for 40 min. The reaction mixture was used in the next step without purification. LCMS (ES, m/z): 898.2 $[M-H]^-$.

Step 8. (5R,7R,8S,12aR,14R,15R,15aS,18R)-2-(2-cyanoethoxy)-18-fluoro-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}hexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-10(12H)-olate 2,10-dioxide [3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-2,10 (12H)-diolate 2,10-dioxide

[0609]

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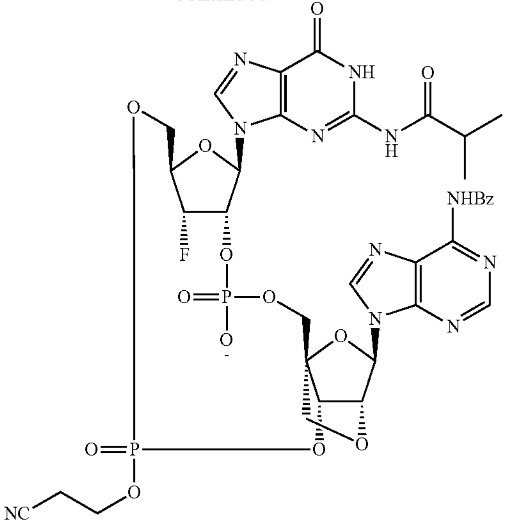
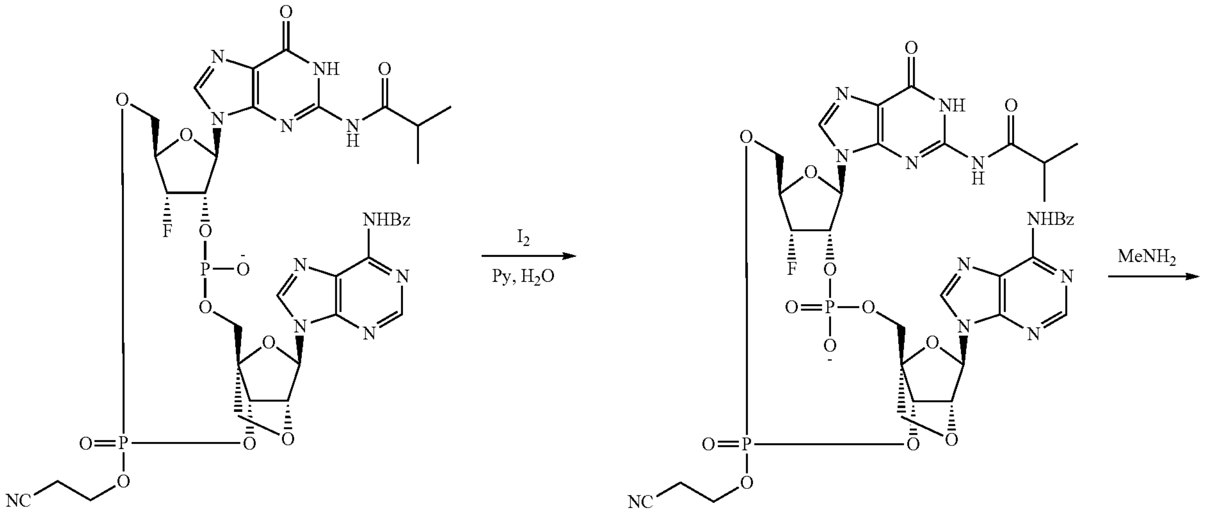


[0610] To the solution from Step 7 at 0° C. was added I_2 in pyridine/water (9/1) (3%, 1.76 mL) over 5 min. The mixture was stirred at rt for 40 min. Then, it was treated with a solution of $Na_2S_2O_3.5H_2O$ (150 mg) in water (2 mL). After 5 min, the mixture was concentrated under reduced pressure. The residue was purified by reverse phase (C18) chromatography eluted with 0 to 45% ACN in aq NH_4HCO_3 (0.04%) to give the product. LCMS (ES, m/z): 915.8 $[M+H]^+$. ^{19}F-NMR (376 MHz, CD_3OD): δ −198.70, −203.36 (2s, 1F). ^{31}P-NMR (162 MHz, CD_3OD): δ −0.96, −1.75 (2s, 1P); −3.64, −4.71 (2s, 1P).

Step 9: (5R,7R,8S,12aR,14R,15R,15aS,18R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-14-(6-amino-9H-purin-9-yl)-18-fluorohexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro [3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-2,10 (12H)-diolate 2,10-dioxide

[0611]



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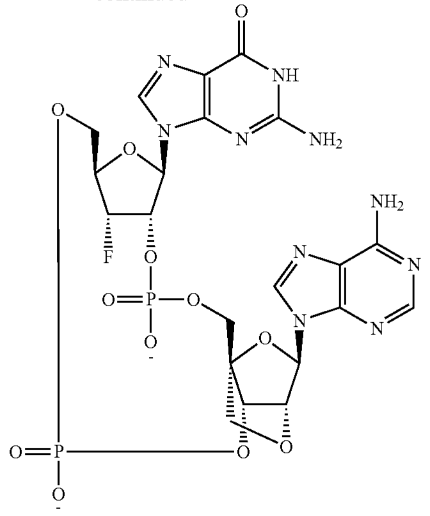


[0612] (5R,7R,8S,12aR,14R,15R,15aS,18R)-2-(2-cyanoethoxy)-18-fluoro-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}hexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-10(12H)-olate 2,10-dioxide (110 mg, 0.12 mmol) was dissolved in a solution of $MeNH_2$ in EtOH (30%, 15 mL), and the resulting solution was stirred at rt for 3 h. Then, it was concentrated, and the residue was purified by preparative-HPLC (Atlantis Prep T3 Column, 19×250 mm) eluted with 0 to 9% ACN in aq NH_4HCO_3 (50 mM) to give the product. LCMS (ES, m/z): 686.9 $[M-H]^-$. ^{1}H-NMR (400 MHz, D_2O): δ 8.14 (s, 1H), 7.85 (s, 1H), 7.80 (s, 1H), 6.01 (s, 1H), 5.99 (d, J=8.5 Hz, 1H), 5.84-5.66 (m, 1H), 5.44 (d, J=3.6 Hz, 0.5H), 5.31 (d, J=3.6 Hz, 0.5H), 4.96 (d, J=3.9 Hz, 1H), 4.84 (s, 1H), 4.65-4.53 (m, 1H), 4.33-4.15 (m, 4H), 4.10 (d, J=8.2 Hz, 1H), 3.96 (d, J=8.2 Hz, 1H). ^{19}F-NMR (376 MHz, D_2O): δ −199.02 (s, 1F). ^{31}P-NMR (162 MHz, D_2O): δ −1.89 (s, 1P), −2.49 (s, 1P).

[0613] Examples 21 through 29, as shown in Table 2 below, were prepared according to procedures analogous to those outlined in Example 20 above using the appropriate monomers, described as Preparations or as obtained from commercial sources, in the coupling step.

TABLE 2

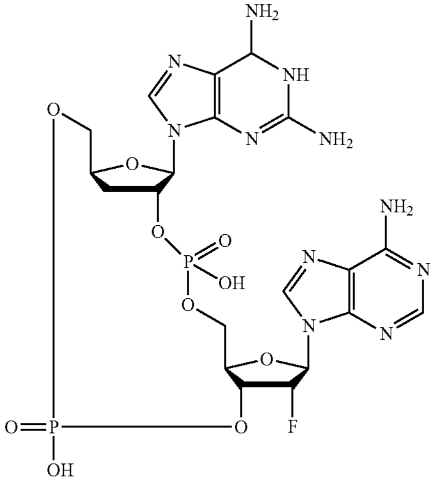
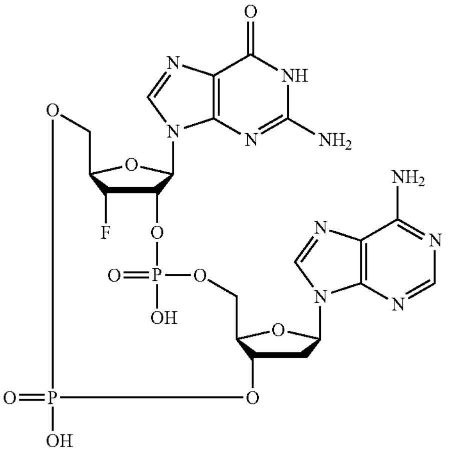
Ex.	Structure	Name	Mass [M − H]
21		2-amino-9-[(5S,7R,8R,12aR,14R,15R,15aR)-14-(6-amino-9H-purin-9-yl)-15-fluoro-2,10-dihydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	659
22		2-amino-9-[(5R,7R,8S,12aR,14R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-16-fluoro-2,10-dihydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	659

TABLE 2-continued

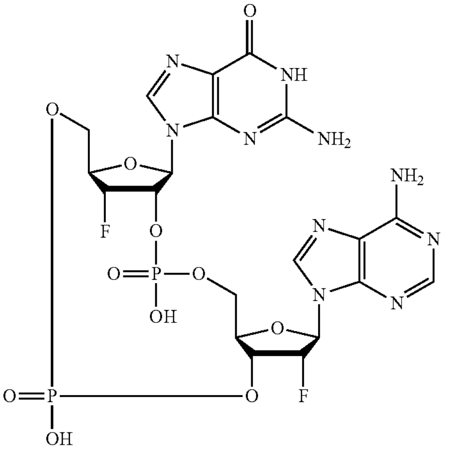
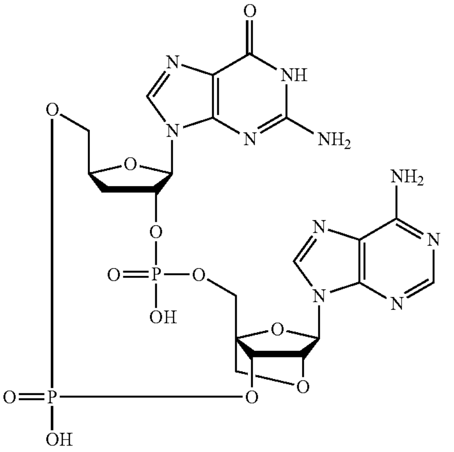
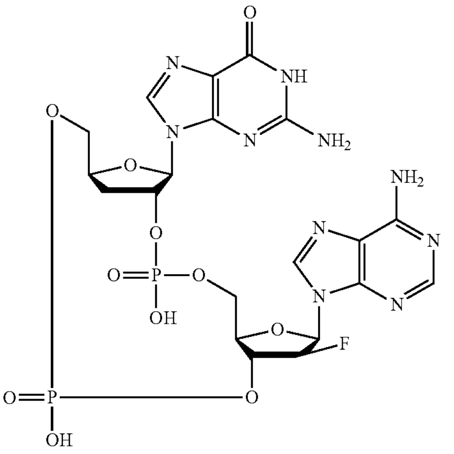
Ex.	Structure	Name	Mass [M − H]
23		2-amino-9-[(5R,7R,8S,12aR,14R,15R,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	677
24		2-amino-9-[(5S,7R,8R,12aR,14R,15R,15aS)-14-(6-amino-9H-purin-9-yl)-2,10-dihydroxy-2,10-dioxidohexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7(12H)-yl]-1,9-dihydro-6H-purin-6-one	669
25		2-amino-9-[(5S,7R,8R,12aR,14R,15S,15aR)-14-(6-amino-9H-purin-9-yl)-15-fluoro-2,10-dihydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	659

TABLE 2-continued

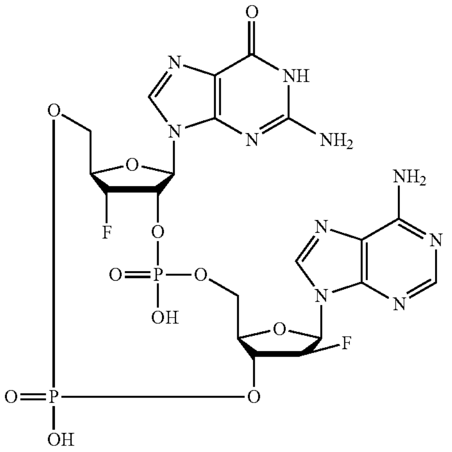
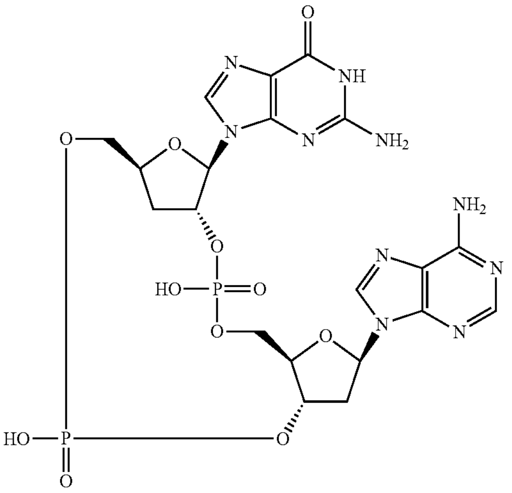
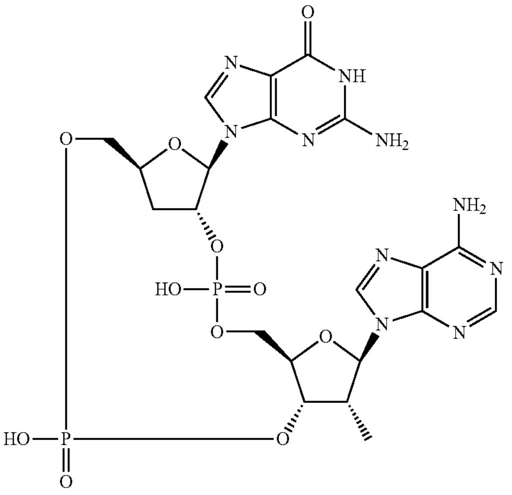
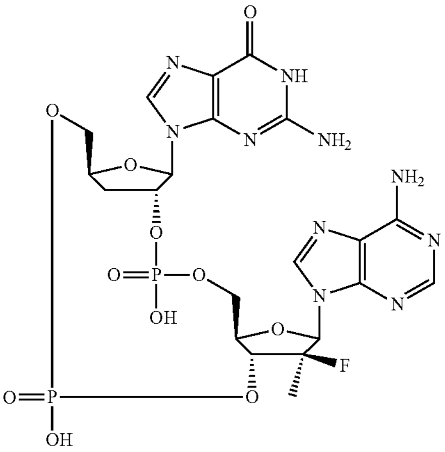
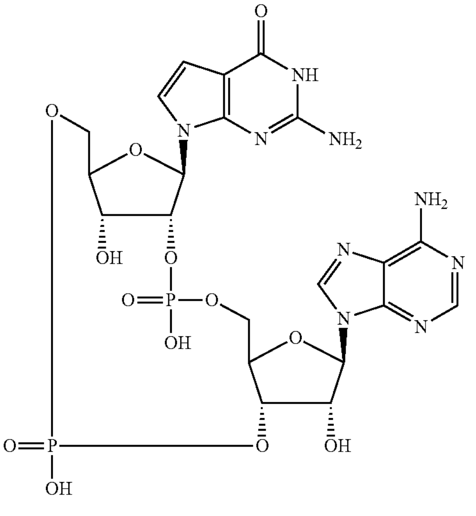
Ex.	Structure	Name	Mass [M − H]
26		2-amino-9-[(2S,5R,7R,8S,10S,12aR,14R,15S,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	677
27		2-amino-9-[(5S,7R,8R,12aR,14R,15aS)-14-(6-amino-9H-purin-9-yl)-2,10-dihydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	641
28		2-amino-9-[(5S,7R,8R,12aR,14R,15R,15aS)-14-(6-amino-9H-purin-9-yl)-2,10-dihydroxy-15-methyl-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	655

TABLE 2-continued

Ex.	Structure	Name	Mass [M − H]
29		2-amino-9-[(5S,8R,12aR,15S,15aR)-14-(6-amino-9H-purin-9-yl)-15-fluoro-2,10-dihydroxy-15-methyl-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	673

Example 30: 2-amino-7-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one

[0614]



[0615] cGAS buffer consisted of 40 mM Tris-HCL, pH 7.5, 100 uM NaCl, 10 mM $MgCl_2$. cGAS enzyme was purchased from Novoprotein (Novoprotein code: SGCAS), having been expressed in *E. coli* and purified using a HIS tag. The calculated molecular weight was 55.3 kDa, and the sequence was:

(SEQ. ID. NO. 1)

MAHHEIHHHGSDSEVNQEAKPEVKPEVKPETHINLKVSDGSSEIFFKIKK

TTPLRRLMEAFAKRQGKEMDSLTFLYDGIEIQADQTPEDLDMEDNDIIEA

-continued

HREQIGGENLYFQGGASKLRAVLEKLKLSRDDISTAAGMVKGVVDHLLLR

LKCDSAFRGVGLLNTGSYYEHVKISAPNEFDVMFKLEVPRIQLEEYSNTR

AYYFVKFKRNPKENPLSQFLEGEILSASKMLSKFRKIIKEEINDIKDTDV

IMKRKRGGSPAVTLLISEKISVDITLALESKSSWPASTQEGLRIQNWLSA

KVRKQLRLKPFYLVPKHAKEGNGFQEETWRLSFSHIEKEILNNHGKSKTC

CENKEEKCCRKDCLKLMKYLLEQLKERFKDKKHLDKFSSYHVKTAFFHVC

TQNPQDSQWDRKDLGLCFDNCVTYFLQCLRTEKLENYFIPEFNLFSSNLI

DKRSKEFLTKQIEYERNNEFPVFDEF

[0616] To a vial were added Herring DNA (CAS#9007-49-2, 0.3 mg/mL in cGAS buffer; 14.8 mL) and cGAS enzyme (3.1 mg/mL in cGAS buffer; 0.78 mL), and the mixture was incubated at RT for 15 min. 7-Deaza-GTP (TriLink catalog # N-1044; 5 mM in cGAS buffer, 1.95 mL, 9.75 μmol) and ATP (5 mM in cGAS buffer, 1.95 mL, 9.75 μmol) were added, and the mixture was incubated on a Radleys Metz heater shaker set to maintain 37° C. while shaking at 250 rpm for 16 h, after which the mixture was filtered and lyopholyzed. The product was purified using mass-directed reverse phase HPLC with a Waters SunFire C18 OBD Prep Column, 100 Å, 5 μm, 19 mm×150 mm, [Waters Part#186002568] using a gradient solvent system with MeCN and 100 mM aqueous triethylammonium acetate. Lyophilization of the product fractions furnished the title compound. LCMS (ES, m/z): 672 $[M-H]^-$. ^1H NMR (600 MHz, DMSO-d_6) δ 10.33 (s, 1H), 8.37 (s, 1H), 8.10 (s, 1H), 7.56 (s, 1H), 7.24 (s, 2H), 6.94 (d, J=3.4 Hz, 1H), 6.28-6.24 (m, 3H), 6.01 (d, J=8.1 Hz, 1H), 5.86 (d, J=7.9 Hz, 1H), 5.61 (s, 1H), 5.01-4.97 (m, 1H), 4.86-4.83 (m, 1H), 4.70 (s, 1H), 4.25 (s, 1H), 4.21 (dd, J=10.4, 4.8 Hz, 1H), 4.03-3.92 (4, 3H), 3.80-3.75 (m, 1H), 3.69 (d, J=12.1 Hz, 1H), 2.76 (s, 12H), 1.02 (S, 18H).

[0617] Examples 31 to 65 in Table 3 below were made using procedures analogous to those described above for Example 30 using the appropriate nucleoside triphosphate monomers. Where necessary, the triphosphates were formed according to methods similar to those described for Preparations 23 to 26 or by submission of the requisite 5'-OH nucleoside monomer to NuBlocks LLC (Oceanside, Calif.). Example 38 was made using ATP and α-thio-GTP (BIOLOG Life Science Institute, catalog # G014/G015).

TABLE 3

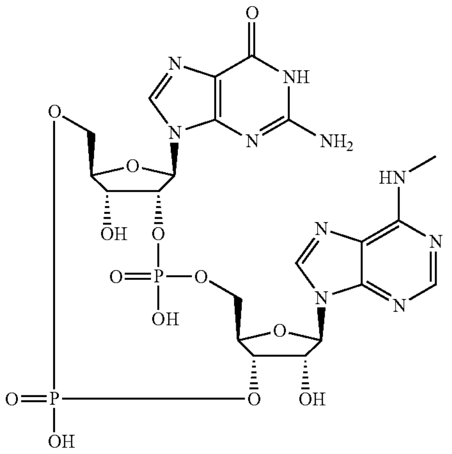
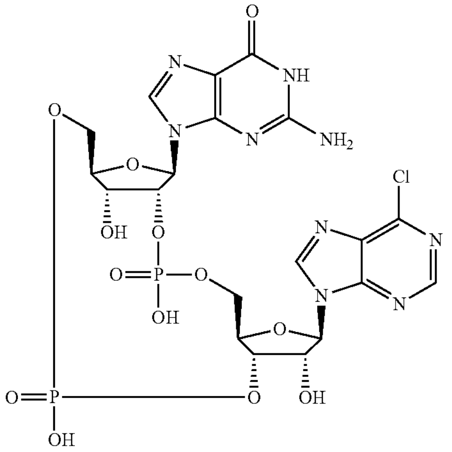
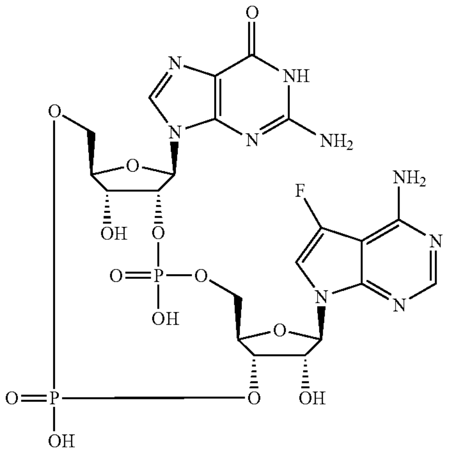
Ex.	Structure	Name	Mass $[M-H]^-$
31		2-amino-9-{(5R,7R,8R,12aR,14R,15R,15aS,16R)-2,10,15,16-tetrahydroxy-14-[6-(methylamino)-9H-purin-9-yl]-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl}-1,9-dihydro-6H-purin-6-one	687
32		2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-14-(6-chloro-9H-purin-9-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	692
33		2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-14-(4-amino-5-fluoro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	690

TABLE 3-continued

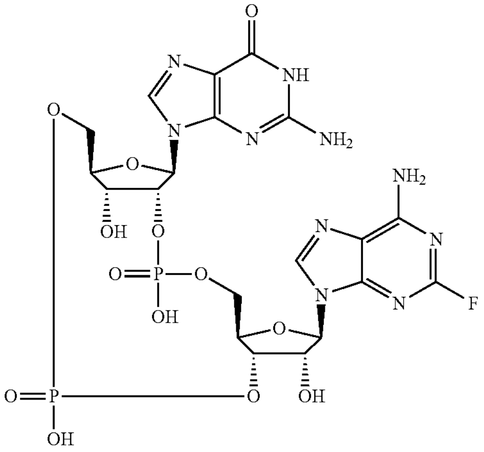
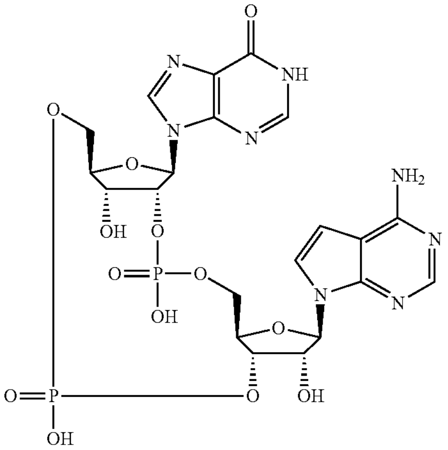
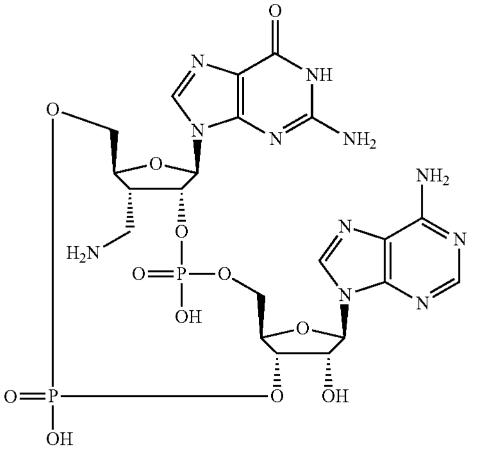
Ex.	Structure	Name	Mass [M − H]⁻
34		2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-14-(6-amino-2-fluoro-9H-purin-9-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	691
35		9-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	657
36		2-amino-9-[(5S,7R,8R,12aR,14R,15R,15aS,16R)-16-(aminomethyl)-14-(6-amino-9H-purin-9-yl)-2,10,15-trihydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	686

TABLE 3-continued

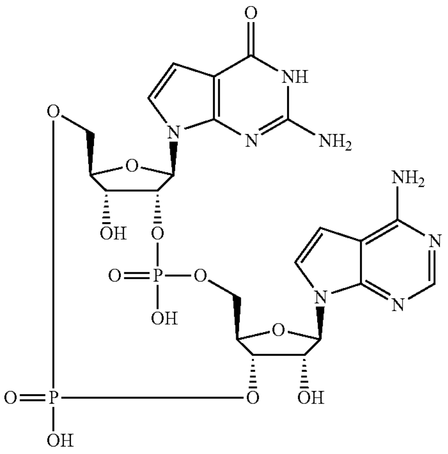
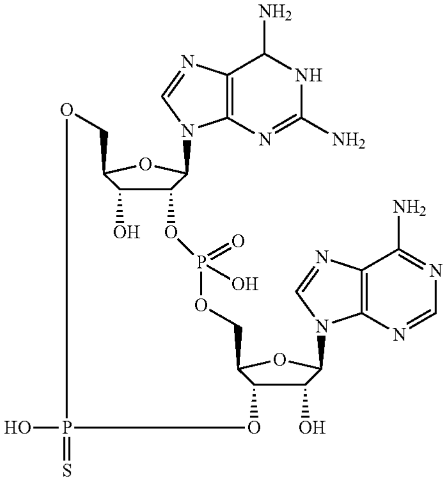
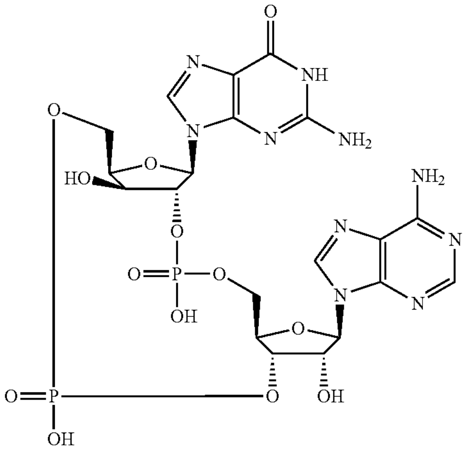
Ex.	Structure	Name	Mass $[M-H]^-$
37		2-amino-7-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one	671
38		2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-2,10,15,16-tetrahydroxy-10-oxido-2-sulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	689
39		2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,16S)-14-(6-amino-9H-purin-9-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	673

TABLE 3-continued

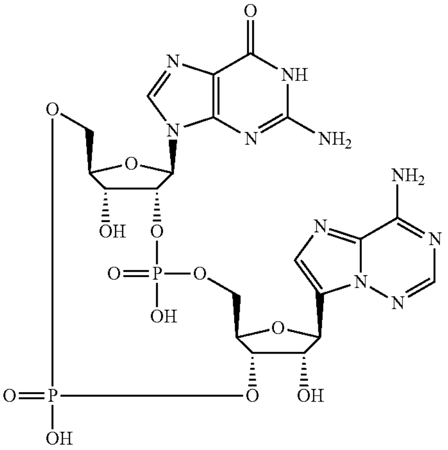
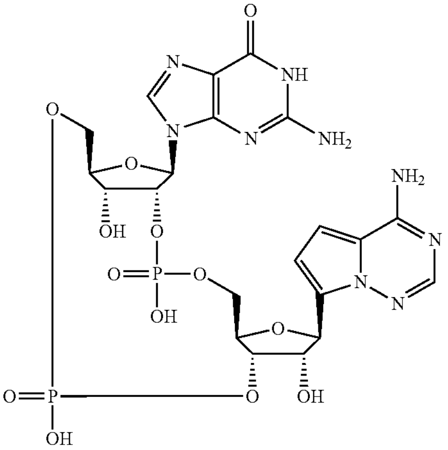
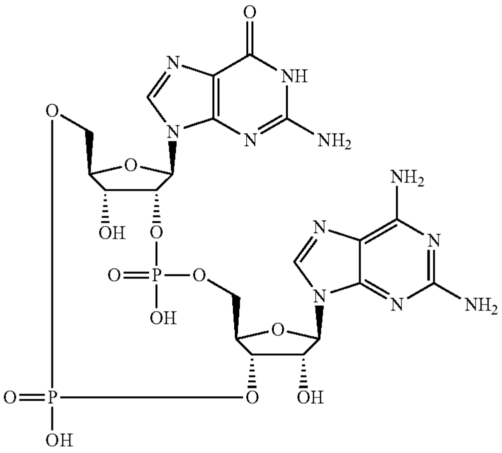
Ex.	Structure	Name	Mass [M − H]⁻
40		2-amino-9-[(5R,7R,8R,12aR,14S,15S,15aS,16R)-14-(4-aminoimidazo[2,1-f][1,2,4]triazin-7-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	673
41		2-amino-9-[(5R,7R,8R,12aR,14S,15S,15aS,16R)-14-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	672
42		2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-14-(2,6-diamino-9H-purin-9-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	688

TABLE 3-continued

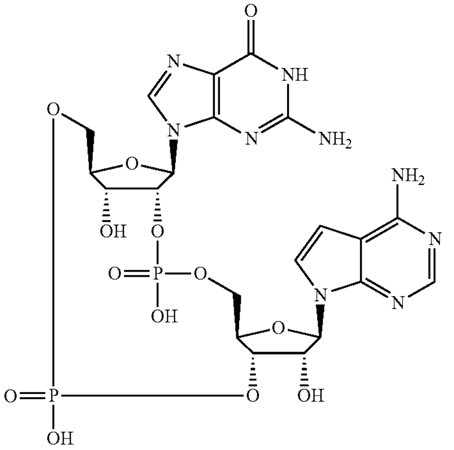
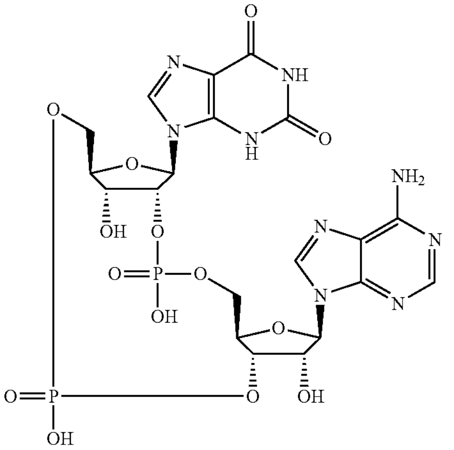
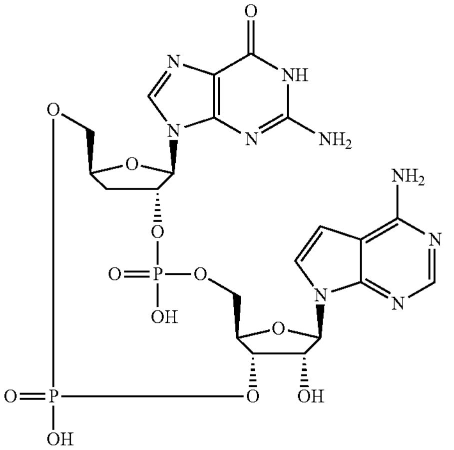
Ex.	Structure	Name	Mass [M − H]⁻
43		2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-10,15,16-trihydroxy-2,10-dioxido-2-sulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	688
44		9-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,9-dihydro-1H-purine-2,6-dione	674
45		2-amino-9-[(5S,7R,8R,12aR,14R,15R,15aS)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2,10,15-trihydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	656

TABLE 3-continued

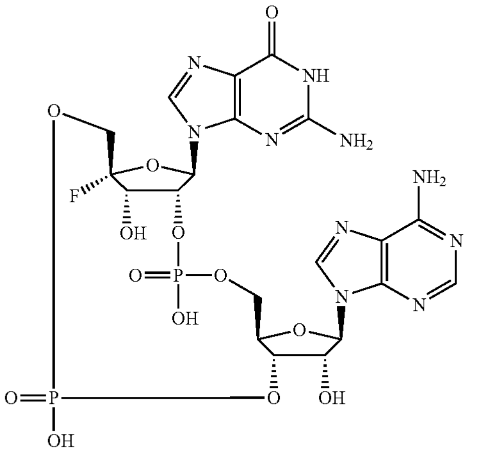
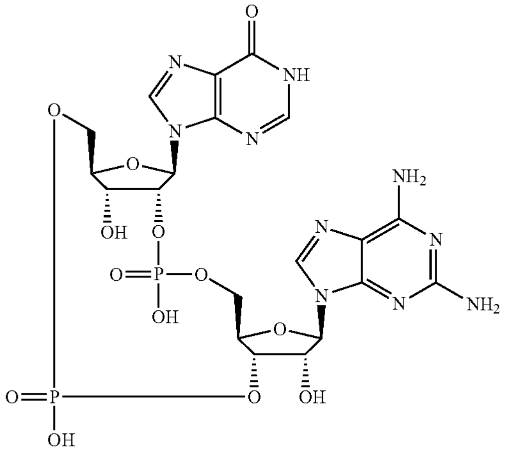
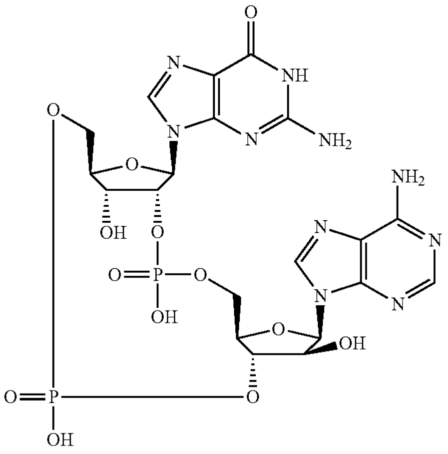
Ex.	Structure	Name	Mass $[M - H]^-$
46		2-amino-9-[(5S,7R,8R,12aR,14R,15R,15aS,16S)-14-(6-amino-9H-purin-9-yl)-5-fluoro-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	691
47		9-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-14-(2,6-diamino-9H-purin-9-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	673
48		2-amino-9-[(5R,7R,8R,12aR,14R,15S,15aS,16R)-14-(6-amino-9H-purin-9-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	673

TABLE 3-continued

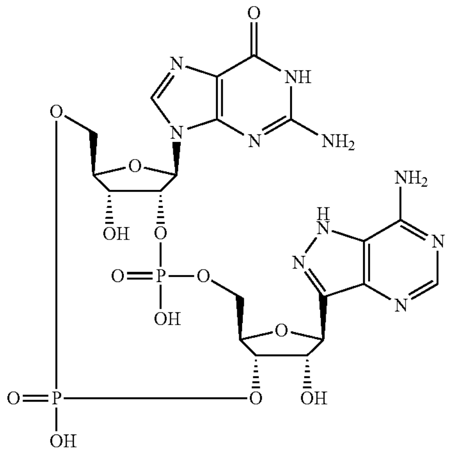
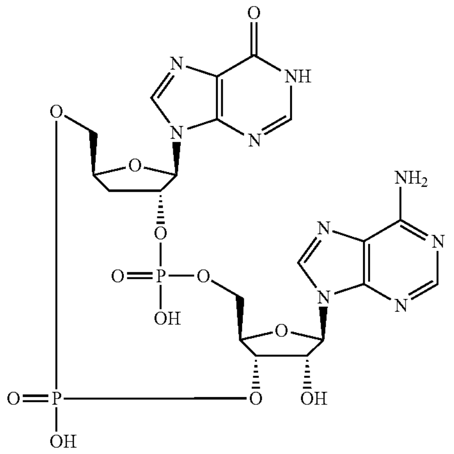
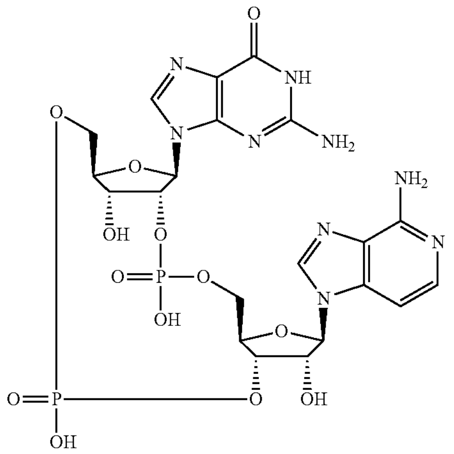
Ex.	Structure	Name	Mass $[M - H]^-$
49		2-amino-9-[(5R,7R,8R,12aR,14S,15S,15aS,16R)-14-(7-amino-1H-pyrazolo[4,3-d]pyrimidin-3-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	673
50		9-[(5S,7R,8R,12aR,14R,15R,15aS)-14-(6-amino-9H-purin-9-yl)-2,10,15-trihydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	642
51		2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-14-(4-amino-1H-imidazo[4,5-c]pyridin-1-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	672

TABLE 3-continued

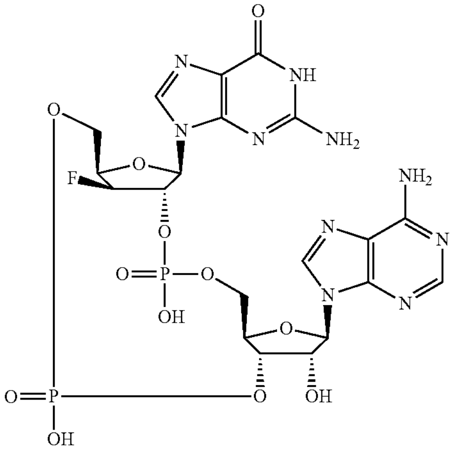
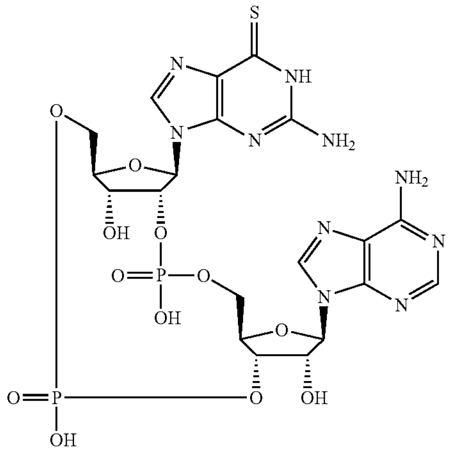
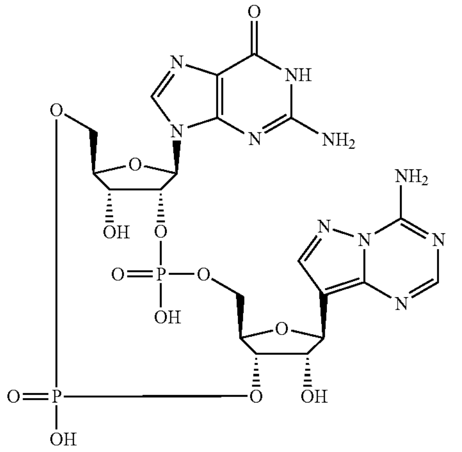
Ex.	Structure	Name	Mass [M − H]⁻
52		2-amino-9-[(5R,7R,8S,12aR,14R,15R,15aS,16S)-14-(6-amino-9H-purin-9-yl)-16-fluoro-2,10,15-trihydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	675
53		2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purine-6-thione	689
54		2-amino-9-[(5R,7R,8R,12aR,14S,15S,15aS,16R)-14-(4-aminopyrazolo[1,5-a][1,3,5]triazin-8-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	673

TABLE 3-continued

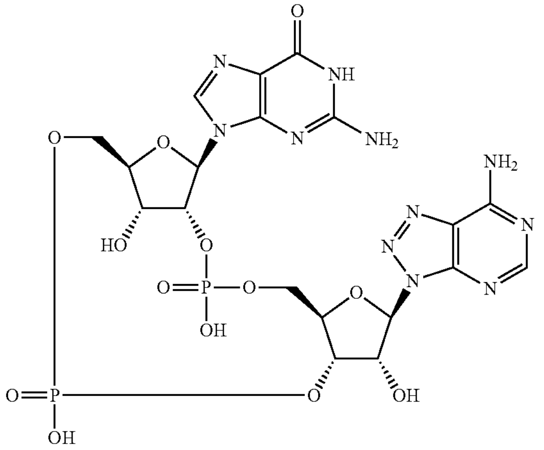
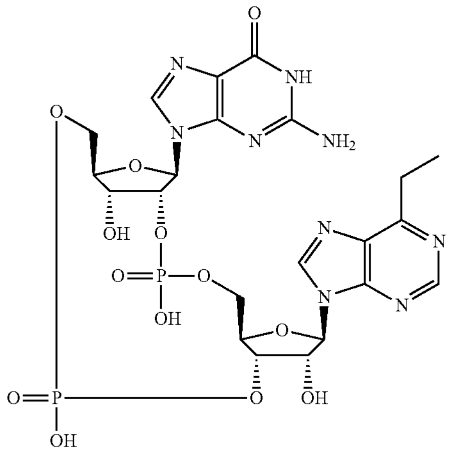
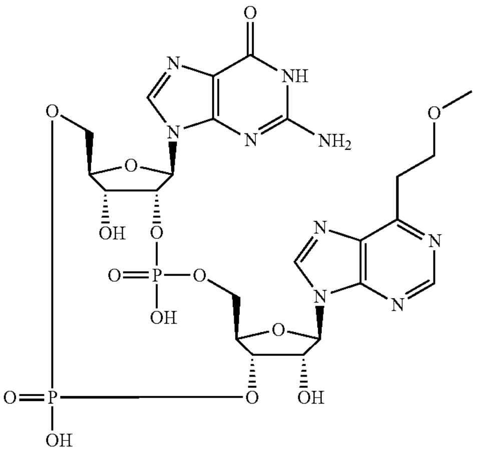
Ex.	Structure	Name	Mass [M − H]⁻
55		2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-14-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	674
56		2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-14-(6-ethyl-9H-purin-9-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	686
57		2-amino-9-{(5R,7R,8R,12aR,14R,15R,15aS,16R)-2,10,15,16-tetrahydroxy-14-[6-(2-methoxyethyl)-9H-purin-9-yl]-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl}-1,9-dihydro-6H-purin-6-one	716

TABLE 3-continued

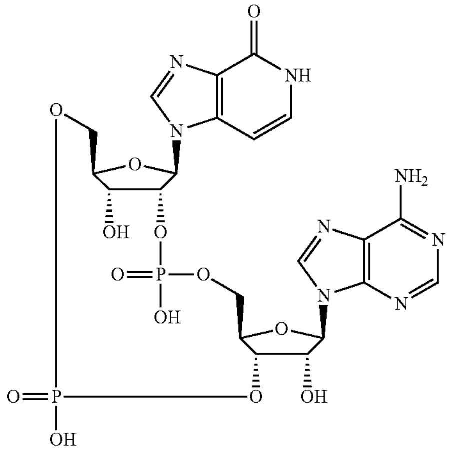
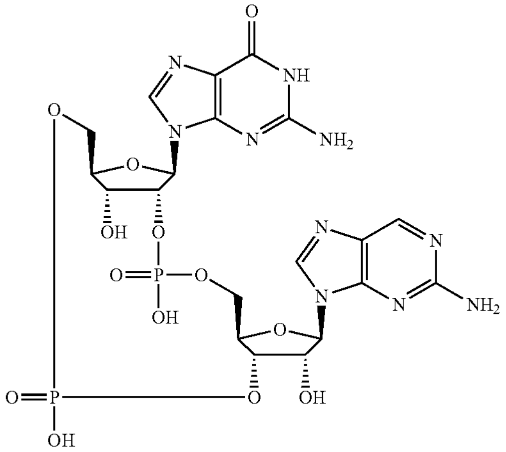
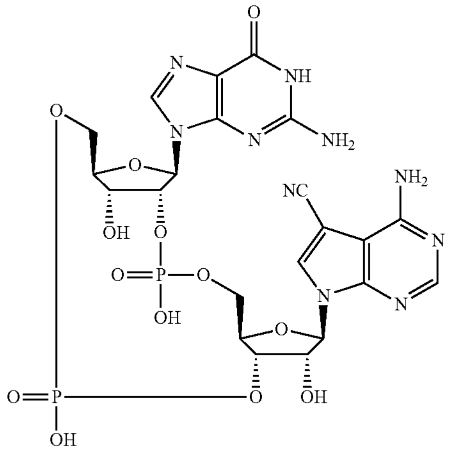
Ex.	Structure	Name	Mass $[M - H]^-$
58		1-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,5-dihydro-4H-imidazo[4,5-c]pyridin-4-one	657
59		2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-14-(2-amino-9H-purin-9-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	673
60		4-amino-7-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile	697

TABLE 3-continued

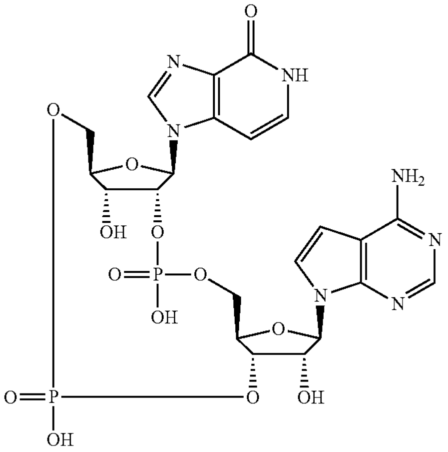
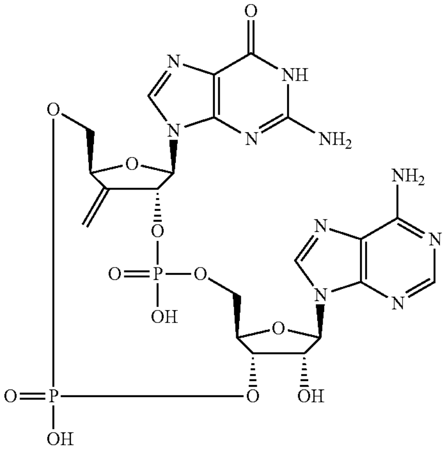
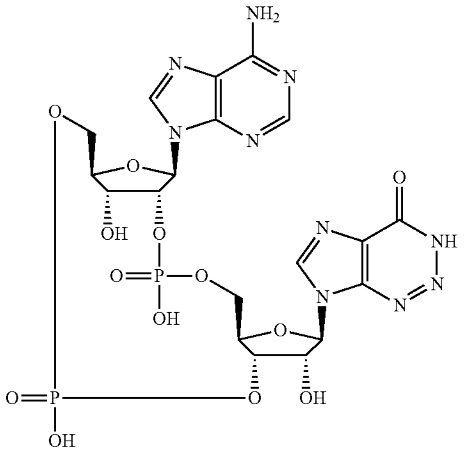
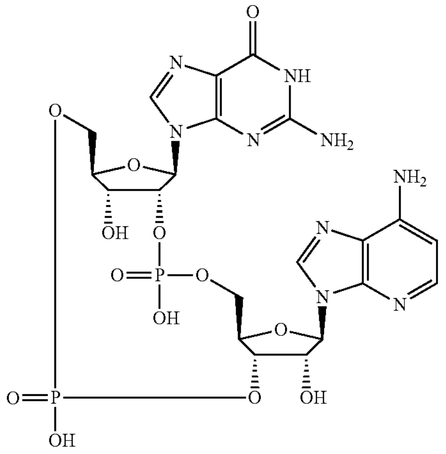
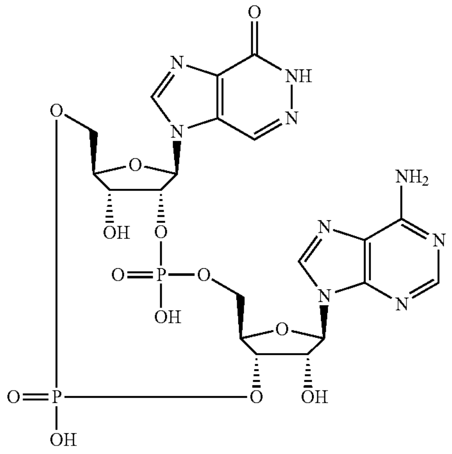
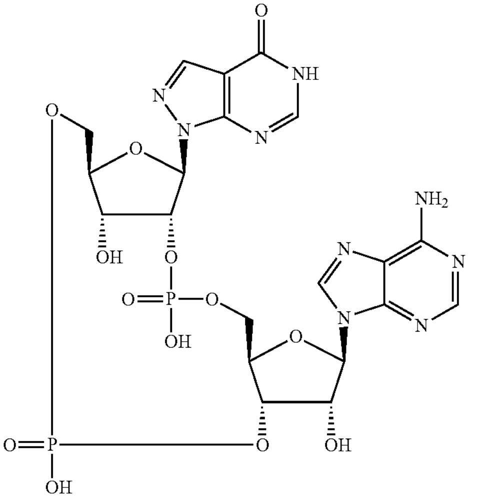
Ex.	Structure	Name	Mass [M − H]⁻
61		1-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,5-dihydro-4H-imidazo[4,5-c]pyridin-4-one	656
62		2-amino-9-[(5S,7R,8R,12aR,14R,15R,15aS)-14-(6-amino-9H-purin-9-yl)-2,10,15-trihydroxy-16-methylidene-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]/pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	669

TABLE 3-continued

Ex.	Structure	Name	Mass [M − H]⁻
63		7-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-7-(6-amino-9H-purin-9-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]-3,7-dihydro-4H-imidazo[4,5-d][1,2,3]triazin-4-one	659
64		2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-14-(7-amino-3H-imidazo[4,5-b]pyridin-3-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	672
65		1-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,5-dihydro-4H-imidazo[4,5-d]pyridazin-4-one	658

Example 66: 1-[(5R,7R,8R,12aR,14R,15R,15aS, 16R)-14-(6-amino-9H-purin-9-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecin-7-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

[0618]



[0619] cGAS buffer consisted of 40 mM Tris-HCL, pH 7.5, 100 uM NaCl, 10 mM $MgCl_2$. cGAS enzyme was purchased from Novoprotein (Novoprotein code: SGCAS), having been expressed in *E. coli* and purified using a HIS tag. The calculated molecular weight was 55.3 kDa, and the sequence was:

(SEQ. ID. NO. 1)

MAHHEIHHHGSDSEVNQEAKPEVKPEVKPETHINLKVSDGSSEIFFKIKK

TTPLRRLMEAFAKRQGKEMDSLTFLYDGIEIQADQTPEDLDMEDNDIIEA

-continued

HREQIGGENLYFQGGASKLRAVLEKLKLSRDDISTAAGMVKGVVDHLLLR

LKCDSAFRGVGLLNTGSYYEHVKISAPNEFDVMFKLEVPRIQLEEYSNTR

AYYFVKFKRNPKENPLSQFLEGEILSASKMLSKFRKIIKEEINDIKDTDV

IMKRKRGGSPAVTLLISEKISVDITLALESKSSWPASTQEGLRIQNWLSA

KVRKQLRLKPFYLVPKHAKEGNGFQEETWRLSFSHIEKEILNNHGKSKTC

CENKEEKCCRKDCLKLMKYLLEQLKERFKDKKHLDKFSSYHVKTAFFHVC

TQNPQDSQWDRKDLGLCFDNCVTYFLQCLRTEKLENYFIPEFNLFSSNLI

DKRSKEFLTKQIEYERNNEFPVFDEF

[0620] To a vial were added Herring DNA (CAS#9007-49-2, 0.3 mg/mL in cGAS buffer; 15.2 mL) and cGAS enzyme (3.1 mg/mL in cGAS buffer; 0.8 mL), and the mixture was incubated at RT for 15 min. ATP (5 mM in cGAS buffer, 2.0 mL, 10 μmol), 7-deaza-8-aza-ITP (5 mM in cGAS buffer, 2.0 mL, 10 μmol), and DMSO (5 mL) were added, and the mixture was incubated on a Radleys Metz heater shaker set to maintain 37° C. while shaking at 250 rpm for 3 d. The mixture was filtered, lyopholyzed, and purified by reverse phase HPLC (eluting acetonitrile/water gradient with 100 mM TEAA modifier, linear gradient) to afford the title compound as the TEA salt. LCMS (ES, m/z): 658 $[M-H]^-$. ^1H NMR (600 MHz, D_2O): δ 8.36 (s, 1H), 8.34 (s, 1H), 8.13 (s, 1H), 7.51 (s, 1H), 6.41 (d, J=8.2 Hz, 1H), 6.24 (s, 1H), 5.69 (m, 1H), 5.42 (m, 1H), 4.88 (d, J=4.4 Hz, 1H), 4.66 (d, J=4.1 Hz, 1H), 4.51 (m, 1H), 4.43 (m, 2H), 4.23 (m, 2H), 4.01 (m, 1H).

[0621] Examples 67 to 74 in Table 4 below were made using procedures analogous to those described above for Example 66 using the appropriate nucleoside triphosphate monomers. Where necessary, the triphosphates were formed according to methods similar to those described for Preparations 23 to 26 or by submission of the requisite 5'-OH nucleoside monomer to NuBlocks LLC (Oceanside, Calif.).

TABLE 4

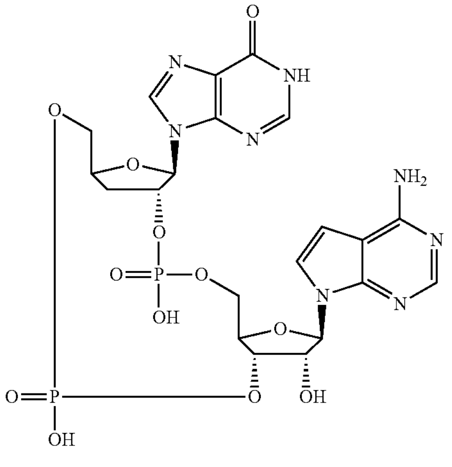
Ex.	Structure	Name	Mass $[M-H]^-$
67		9-[(5S,7R,8R,12aR,14R,15R,15aS)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2,10,15-trihydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro [3,2-l][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	641

TABLE 4-continued

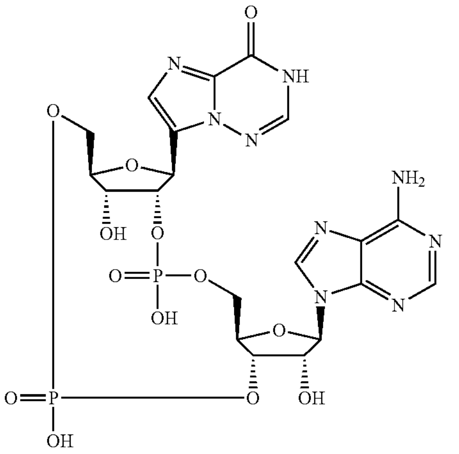
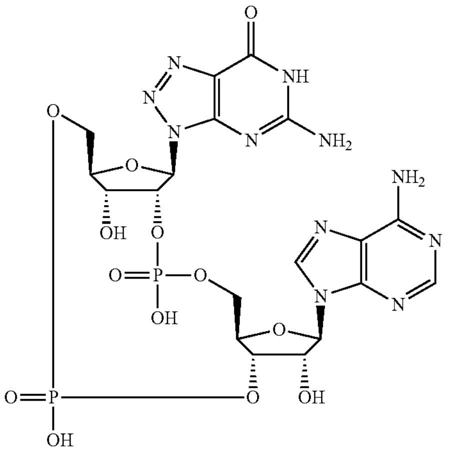
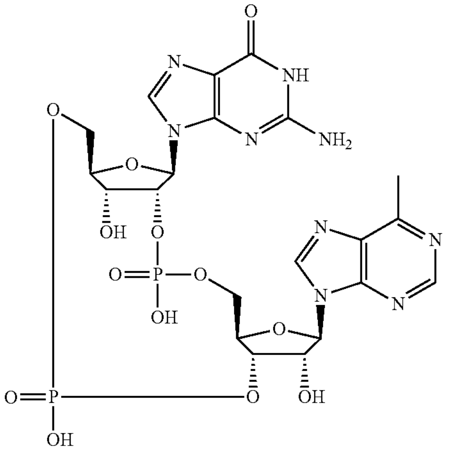
Ex.	Structure	Name	Mass [M − H]⁻
68		7-[(5R,7S,8R,12aR,14R,15R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]imidazo[2,1-f][1,2,4]triazin-4(3H)-one	658
69		5-amino-3-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one	674
70		2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-2,10,15,16-tetrahydroxy-14-(6-methyl-9H-purin-9-yl)-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	672

TABLE 4-continued

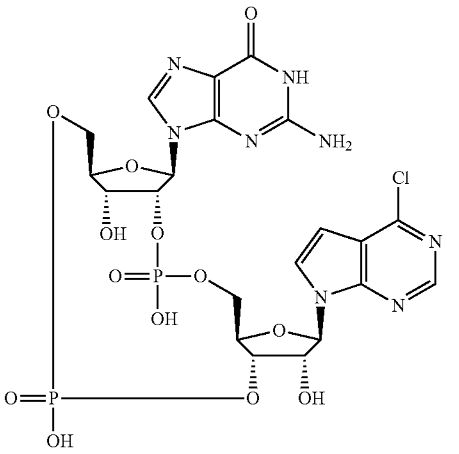
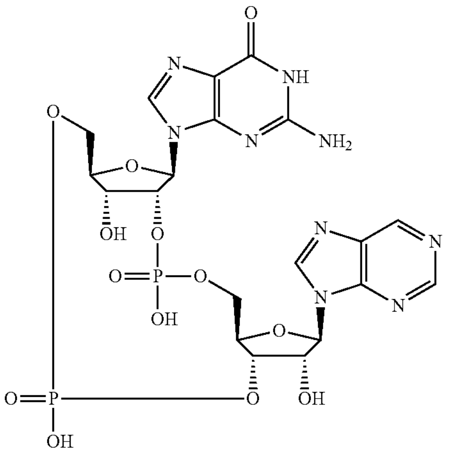
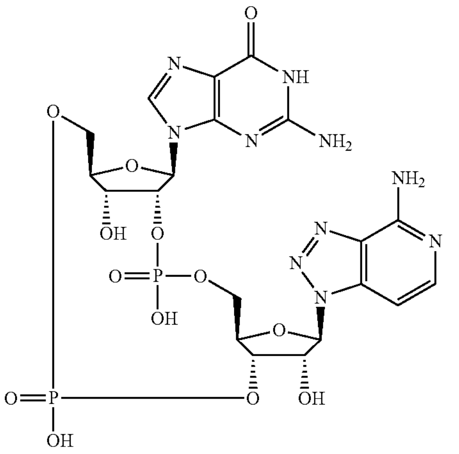
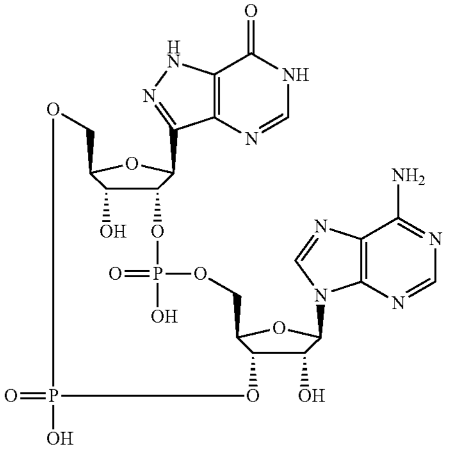
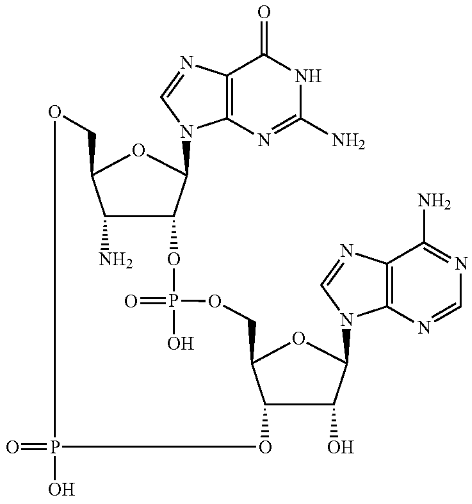
Ex.	Structure	Name	Mass [M − H]$^-$
71		2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-14-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	691
72		2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-2,10,15,16-tetrahydroxy-2,10-dioxido-14-(9H-purin-9-yl)octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	658
73		2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-14-(4-amino-1H-[1,2,3]triazolo[4,5-c]pyridin-1-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	673

TABLE 4-continued

Ex.	Structure	Name	Mass [M − H]⁻
74		3-[(5R,7S,8R,12aR,14R,15R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one	658

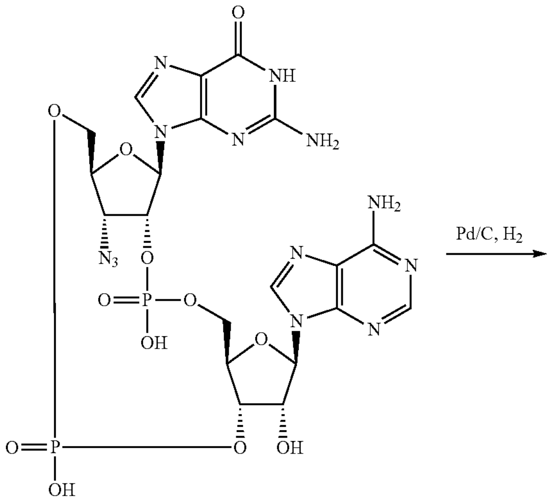
Example 75: 2-Amino-9-[(5S,7R,8R,12aR,14R,15R,15aS,16R)-16-amino-14-(6-amino-9H-purin-9-yl)-2,10,15-trihydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one

[0622]



Step 1: 2-Amino-9-[(5S,7R,8R,12aR,14R,15R,15aS,16R)-16-amino-14-(6-amino-9H-purin-9-yl)-2,10,15-trihydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one

[0623]



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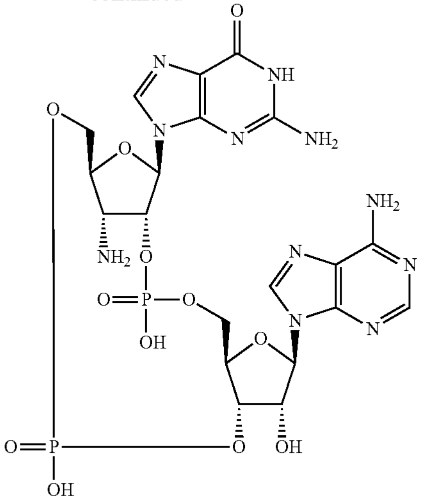
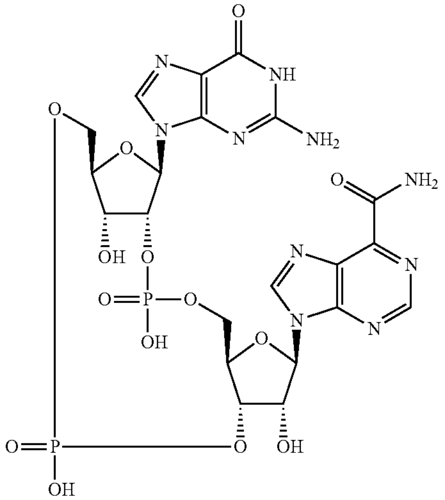


[0624] To a stirred solution of 2-amino-9-[(5 S,7R,8R, 12aR,14R,15R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-16-azido-2,10,15-trihydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Example 14, 4.0 mg, 0.0055 mmol) in absolute EtOH (1.0 mL) and deionized water (1.0 mL) was added palladium on carbon (1.0 mg, 10 wt. % loading) in one portion under Ar at RT. The reaction vessel was then flushed with hydrogen gas and attached to a hydrogen gas balloon. The reaction mixture was left to stir for 48 h, filtered, and concentrated to afford the title compound. LCMS (ES, m/z): 672 [M−H]$^-$. (600 MHz, DMSO-d$_6$) δ 10.70 (s, 1H), 8.42 (s, 1H), 8.12 (s, 1H), 7.96 (s, 1H), 7.70 (s, 1H), 7.29 (br, 2H), 6.56 (br, 2H), 6.00 (d, J=8.3 Hz, 1H), 5.89 (d, J=8.5 Hz, 1H), 5.21 (s, 1H), 5.04 (t, J=6.0 Hz, 1H), 4.16 (s, 1H), 4.05 (dd, J=10.5, 5.0 Hz, 1H), 4.00 (s, 1H), 3.77 (d, J=4.1 Hz, 1H), 3.67 (m, 2H). ^{31}P NMR: (202 MHz, DMSO-d$_6$): δ −0.4 (s), 2.0 (s).

[0625] Alternatively, Example 75 may be prepared from the requisite monomers, according to a method similar to that described above for Example 30.

Example 76: 9-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]-9H-purine-6-carboxamide

[0626]



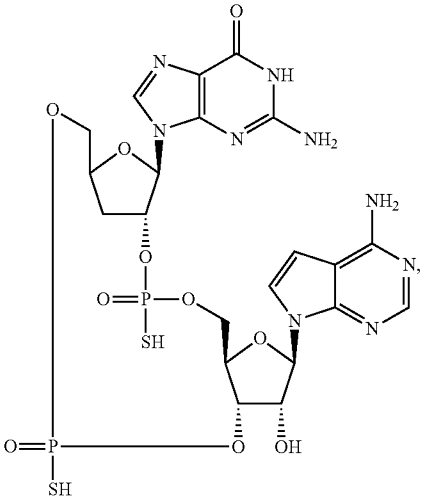
[0627] To a stirred solution of 2-amino-9-[(5R,7R,8R, 12aR,14R,15R,15aS,16R)-14-(6-chloro-9H-purin-9-yl)-2, 10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one, (Example 32, 16 mg, 0.018 mmol) in DMSO (1.7 mL) was added sodium cyanide (8.0 mg, 0.16 mmol) in one portion under Ar at RT. The reaction mixture was heated to 80° C. and left to stir at the same temperature for 3 h, cooled to ambient temperature, then quenched with cold acetic acid (15 uL). The mixture was filtered and lyophilyzed. The product was purified using mass-directed reverse phase HPLC with a Waters SunFire C18 OBD Prep Column, 100 Å, 5 μm, 19 mm×150 mm, [Waters Part#186002568] using a gradient solvent system with MeCN and 100 mM aqueous triethylammonium acetate. Lyophilization of the product fractions furnished 9-[(5R,7R,8R,12aR,14R,15R, 15aS,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]-9H-purine-6-carbonitrile. LCMS (ES, m/z): 683 [M−H]$^-$.

[0628] To a stirred suspension of 9-[(5R,7R,8R,12aR,14R, 15R,15aS,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5, 8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]-9H-purine-6-carbonitrile (3.0 mg, 0.003 mmol) in deionized water (338 uL) was added Hydrido(dimethylphosphinous acid-kP)[hydrogen bis(dimethylphosphinito-kP)]platinum(II) (1.0 mg, 0.002 mmol). The reaction mixture was heated to 85° C. and left to stir at the same temperature for 6 h, cooled to ambient temperature, filtered and lyopholyzed. The product was purified using mass-directed reverse phase HPLC with a Waters SunFire C18 OBD Prep Column, 100 Å, 5 μm, 19 mm×150 mm, [Waters Part#186002568] using a gradient solvent system with MeCN and 100 mM aqueous triethylammonium acetate. Lyopholization of the product fractions furnished 9-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]-9H-purine-6-carboxamide. LCMS (ES, m/z): 701 [M−H]$^-$. ^{1}H NMR (500 MHz, DMSO): δ 10.58 (s, 1H), 9.06 (s, 1H), 8.36 (s, 1H), 8.05 (s, 1H), 7.91 (s, 1H), 7.74 (s, 1H), 6.55 (br, 4H), 6.07 (d, J=7.7 Hz, 1H), 5.81 (d, J=6.0 Hz, 1H), 5.77 (m, 1H), 5.04 (m, 1H), 4.96 (d, J=4.5 Hz, 1H), 4.60 (m, 1H), 4.27 (m, 1H), 4.07-4.04 (m, 2H), 3.99-3.75 (m, 2H). ^{31}P NMR: (202 MHz, DMSO): δ 1.9 (s), −0.8 (s).

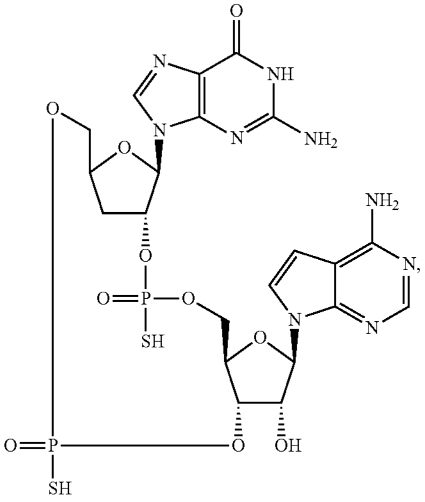
Examples 77, 78, 79, 80: 2-amino-9-[(5S,7R,8R,12aR,14R,15R,15aS)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-15-hydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomers 1-4)

[0629]

Diastereomer 1



Diastereomer 2



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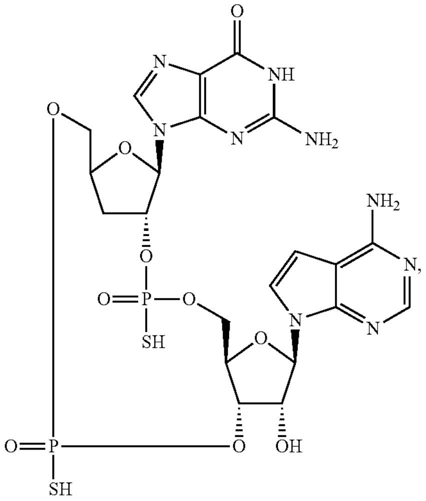
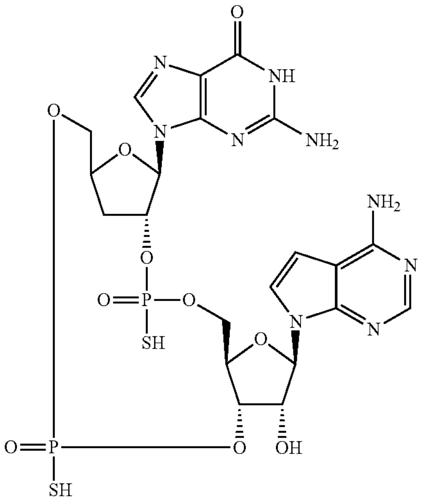
Diastereomer 3

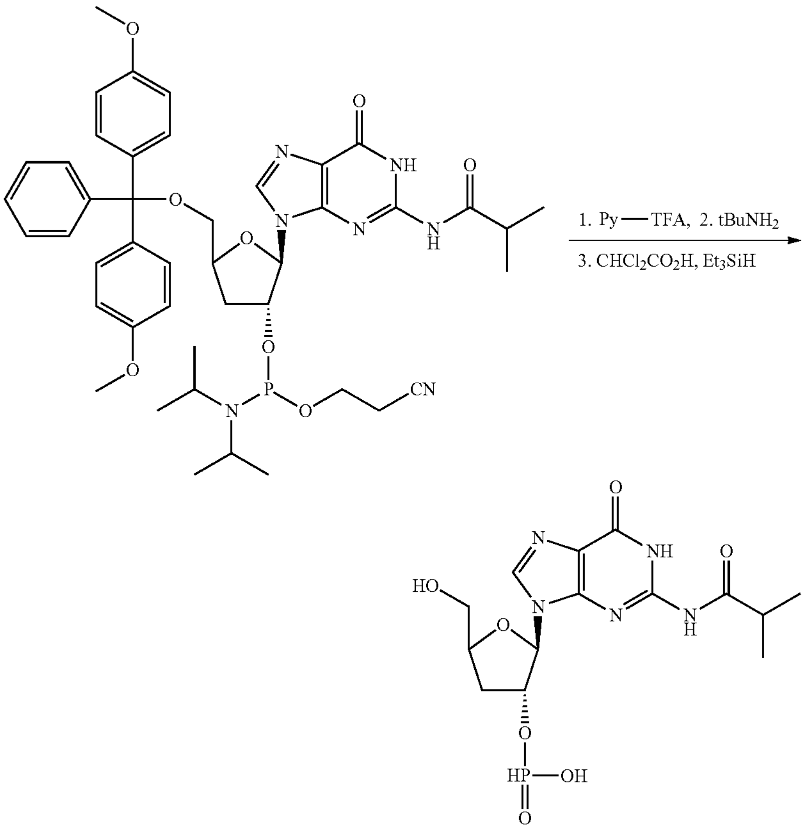


Diastereomer 4



Step 1: (2R,3R)-5-(hydroxymethyl)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl hydrogen phosphonate

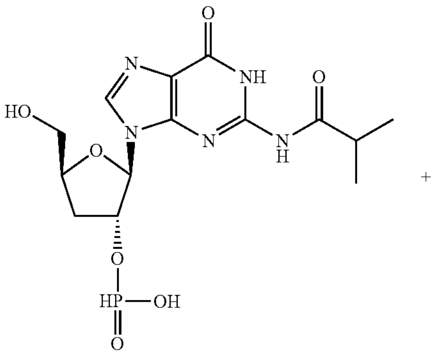
[0630]



[0631] To a flask was added (2R,3R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl (2-cyanoethyl) diisopropylphosphoramidite (4.00 g, 4.76 mmol), MeCN (23.65 ml), and water (0.158 ml). Pyridine trifluoroacetate (1.104 g, 5.71 mmol) was added, and the reaction was stirred at rt for 1 h. Tert-butylamine (20.02 ml, 190 mmol) was then added, and stirring was continued at rt for 1 h, after which time the reaction was partitioned between hexanes and acetonitrile. The acetonitrile layer was collected and concentrated under vacuum. DCM (39.9 ml) and water (0.798 ml) were added, followed by dichloroacetic acid (55.1 ml, 33.3 mmol), and the solution was stirred for 20 min at rt, after which time triethylsilane (133 ml, 833 mmol) was added, and the reaction was stirred for a further 2 h at rt. The reaction was cooled to 0° C., and pyridine (5.39 mL 66.6 mmol) was added. Then the mixture was concentrated under reduced pressure to give the title compound, which was not purified further. LCMS (ES, m/z): 400 $[M-H]^-$.

Step 2: O-((2R,3R,4R,5R)-5-(4-benzamido-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-((tert-butyldimethylsilyl)oxy)tetrahydrofuran-3-yl) 0-(((2S,4R,5R)-4-((hydroxyhydrophosphoryl)oxy)-5-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-2-yl)methyl)O-hydrogen phosphorothioate

[0632]



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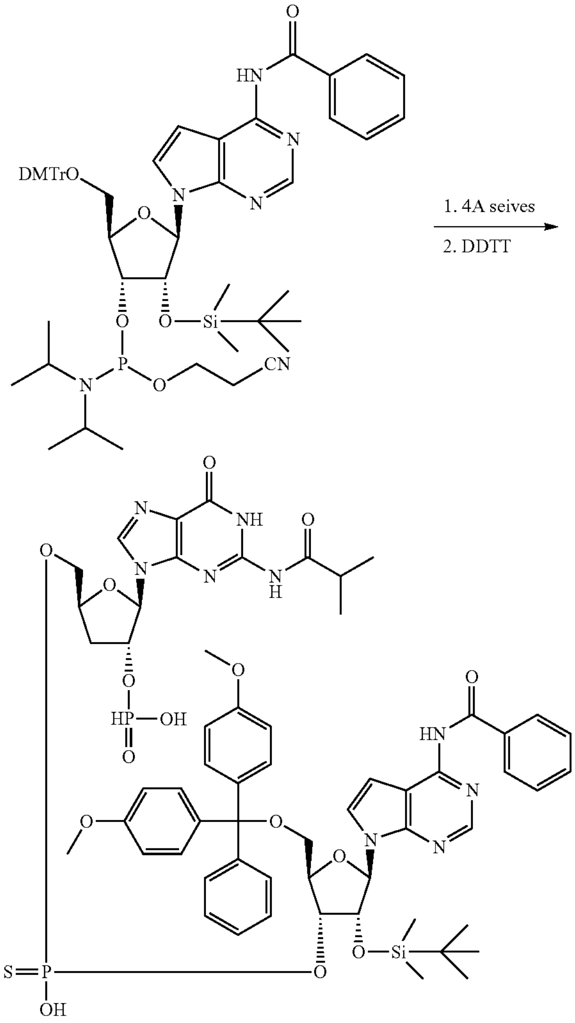
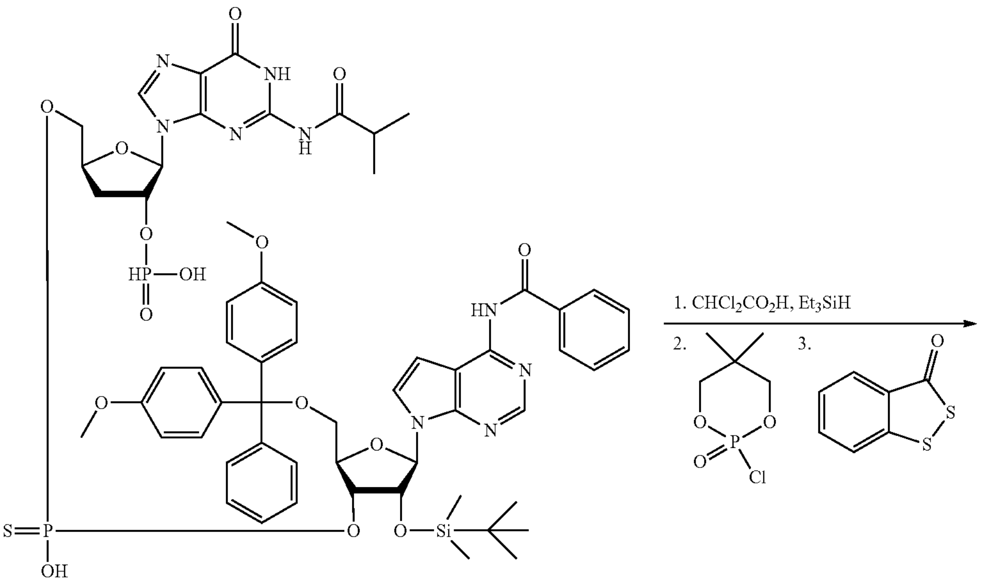


[0633] To a flask was added (2R,3R,5S)-5-(hydroxymethyl)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl hydrogen phosphonate (335 mg, 0.836 mmol) and MeCN (20 mL), and then the solution was concentrated under reduced pressure. This process was repeated 2×, and then MeCN (8 mL) was added, followed by activated 4 Å sieves. The mixture was stirred for 20 min at rt. (2R,3R,4R,5R)-5-(4-benzamido-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-((tert-butyldimethylsilyl)oxy)tetrahydrofuran-3-yl (2-cyanoethyl) diisopropylphosphoramidite (825 mg, 0.836 mmol) was dissolved in MeCN (5 mL). Molecular sieves (4 Å) were added, and the mixture was stirred for 30 min at rt, after which time this solution was transferred to the hydrogen phosphonate solution and 2×1.5 mL portions of MeCN were used to complete the transfer. After stirring 30 min at rt, ((dimethylamino-methylidine)amino)-3H-1,2,4-dithiazoline-3-thione (189 mg, 0.919 mmol) was added. After stirring 5 min at rt, the mixture was concentrated under reduced pressure and purified using reverse phase HPLC with a 10-100% gradient of MeCN and 100 mM aqueous triethylammonium acetate. The product-containing fractions were collected and lyophilized, during which time the cyanoethyl protecting group was cleaved, to furnish O-((2R,3R,4R,5R)-5-(4-benzamido-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-((bis(4-methoxyphenyl)(phenyl)methoxy) methyl)-4-((tert-butyldimethylsilyl)oxy)tetrahydrofuran-3-yl)O-(((2S,4R,5R)-4-((hydroxyhydrophosphoryl)oxy)-5-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl) tetrahydrofuran-2-yl)methyl)O-hydrogen phosphorothioate. LCMS (ES, m/z): 1264 [M−H]$^-$.

Step 3: N-{7-[(5S,7R,8R,12aR,14R,15R,15aR)-15-{[tert-butyl(dimethyl)silyl]oxy}-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-2,10-dioxido-2,10-disulfanyl}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 (Diastereomers 1-4)

[0634]



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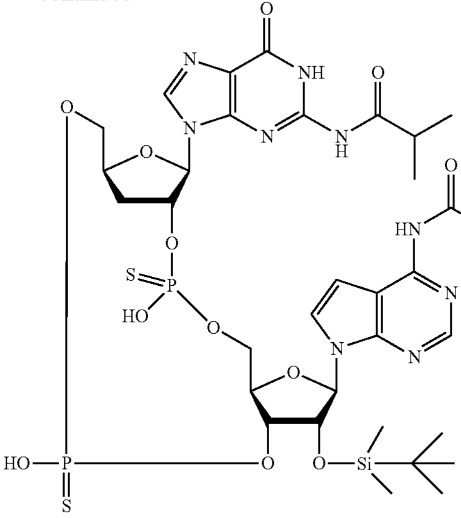
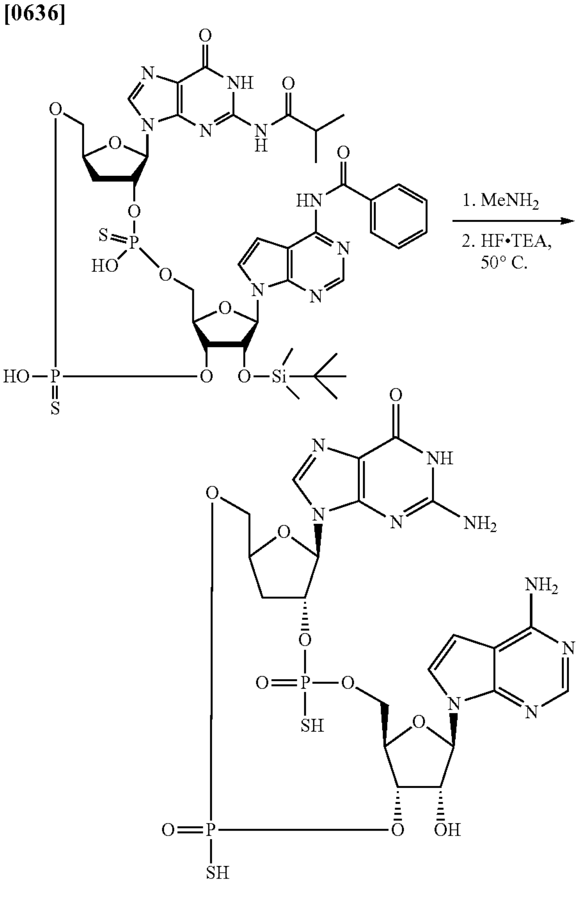


[0635] To a flask containing O-((2R,3R,4R,5R)-5-(4-benzamido-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-((tert-butyldimethylsilyl)oxy) tetrahydrofuran-3-yl)O-(((2 S,4R,5R)-4-((hydroxyhydrophosphoryl)oxy)-5-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-2-yl) methyl)O-hydrogen phosphorothioate (581 mg, 0.440 mmol) was added DCM (8.81 mL), water (0.079 mL, 4.40 mmol) and then dichloroacetic acid (8.74 mL, 5.28 mmol). The mixture was stirred for 15 min at rt, and then triethylsilane (10.97 mL, 68.7 mmol) was added. The mixture was stirred at rt for 1.5 h and then concentrated under reduced pressure. The mixture was dissolved in pyridine (10 mL) and then concentrated under reduced pressure. This process was repeated 2×, and then the resulting sample was dissolved in pyridine (17 ml) and 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinan-2-one (81 mg, 0.440 mmol) was added in 1 portion at rt. After stirring for 30 min at rt, additional 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinan-2-one (81 mg, 0.440 mmol) was added. This sequence was repeated twice, and then water (238 μl, 13.19 mmol) and 3H-1,2-benzodithiol-3-one (111 mg, 0.660 mmol) were added. The mixture was stirred for 1 h at rt and then partitioned between water (10 mL) and 1:1 EtOAc/ether (10 mL). The layers were separated, and the aqueous phase was extracted with 1:1 EtOAc/ether (3×10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Reverse phase HPLC purification (gradient of 30-100% MeCN and 100 mM aqueous triethylammonium acetate) furnished 4 diastereomers of N-{7-[(5S,7R,8R,12aR,14R,15R,15aR)-15-{[tert-butyl(dimethyl)silyl]oxy}-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-2,10-dioxido-2,10-disulfanyl}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, all of which showed LCMS (ES, m/z): 976 [M−H]⁻.

Step 4: 2-amino-9-[(5S,7R,8R,12aR,14R,15R,15aS)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-15-hydroxy-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 (Diastereomers 1-4)

[0636]



Diastereomer 1

[0637] To a flask containing N-{7-[(5 S,7R,8R,12aR,14R,15R,15aR)-15-{[tert-butyl(dimethyl)silyl]oxy}-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-2,10-dioxido-2,10-disulfanyl}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 (fastest eluting peak, 7.4 mg, 7.57 μmol) was added methylamine (33% in EtOH) (1 mL, 8.03 mmol), and the mixture was stirred at rt for 4 h, after which time the mixture was concentrated under reduced pressure. Pyridine (1 mL) was added, and the mixture was concentrated under reduced pressure. Then, pyridine (0.5 ml), triethylamine (0.104 ml, 0.746 mmol) and triethylamine trihydrofluoride (0.030 ml, 0.187 mmol) were added, and the mixture was stirred at 50° C. for 16 h, after which time the mixture was cooled to rt and concentrated under reduced pressure. Purification by reverse phase HPLC (gradient of acetonitrile and 100 mM aqueous triethylammonium acetate) furnished Example 77, 2-amino-9-[(5S,7R,8R,12aR,14R,15R,15aS)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-15-hydroxy-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). LCMS (ES, m/z): 688 [M−H]$^-$. ^{1}H NMR (600 MHz, Deuterium Oxide) δ 8.06 (s, 1H), 8.03 (s, 1H), 7.41 (d, J=3.8 Hz, 1H), 6.25 (d, J=3.7 Hz, 1H), 6.17 (d, J=2.6 Hz, 1H), 5.68 (d, J=7.5 Hz, 1H), 5.42-5.36 (m, 2H), 5.10-5.06 (m, 1H), 4.83-4.81 (m, 1H), 4.51-4.48 (m, 1H), 4.36-4.33 (m, 1H), 4.28 (dt, J=10.1, 4.9 Hz, 1H), 4.06-3.94 (m, 2H), 3.03 (q, J=7.3 Hz, 12H), 2.44-2.40 (m, 2H), 1.11 (t, J=7.3 Hz, 18H).

[0638] The other diastereomers from Step 3 were individually processed in an analogous manner to afford three additional diastereomeric products:

[0639] Example 78: 2-Amino-9-[(5 S,7R,8R,12aR,14R,15R,15aS)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-15-hydroxy-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 2). LCMS (ES, m/z): 688 [M−H]$^-$. ^{1}H NMR (600 MHz, Deuterium Oxide) δ 8.04 (s, 1H), 7.75 (s, 1H), 7.50 (d, J=3.6 Hz, 1H), 6.19-6.17 (m, 1H), 6.16 (d, J=3.7 Hz, 1H), 5.65 (d, J=7.4 Hz, 1H), 5.63-5.57 (m, 1H), 5.14 (td, J=7.8, 4.4 Hz, 1H), 4.54 (d, J=4.2 Hz, 1H), 4.52-4.46 (m, 1H), 4.33 (d, J=8.9 Hz, 1H), 4.27 (dd, J=11.9, 3.1 Hz, 1H), 4.18-4.15 (m, 1H), 3.96 (dd, J=11.4, 3.6 Hz, 2H), 3.04 (q, J=7.3 Hz, 12H), 2.44-2.36 (m, 2H), 1.11 (t, J=7.3 Hz, 18H).

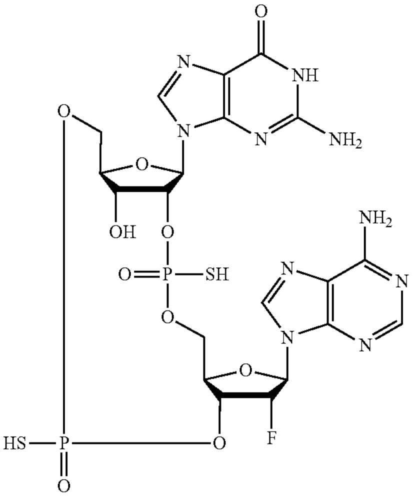
[0640] Example 79: 2-Amino-9-[(5 S,7R,8R,12aR,14R,15R,15aS)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-15-hydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 3). LCMS (ES, m/z): 688 [M−H]$^-$. ^{1}H NMR (600 MHz, Deuterium Oxide) δ 8.00 (s, 1H), 7.97 (s, 1H), 7.19 (d, J=3.8 Hz, 1H), 6.15 (d, J=3.8 Hz, 2H), 5.66 (d, J=7.3 Hz, 1H), 5.32 (dq, J=9.9, 7.2 Hz, 1H), 4.95 (td, J=8.6, 4.6 Hz, 1H), 4.81 (d, J=4.4 Hz, 1H), 4.50 (d, J=8.0 Hz, 1H), 4.32 (d, J=7.8 Hz, 1H), 4.25 (dt, J=12.0, 3.6 Hz, 1H), 4.05-3.97 (m, 3H), 3.03 (q, J=7.3 Hz, 12H), 2.51-2.41 (m, 2H), 1.11 (t, J=7.3 Hz, 18H).

[0641] Example 80: 2-Amino-9-[(5 S,7R,8R,12aR,14R,15R,15aS)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-15-hydroxy-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 4). LCMS (ES, m/z): 688 [M−H]$^-$. ^{1}H NMR (600 MHz, Deuterium Oxide) δ 8.00 (s, 1H), 7.72 (s, 1H), 7.23 (d, J=3.8 Hz, 1H), 6.14 (s, 1H), 6.12 (d, J=3.7 Hz, 1H), 5.64 (d, J=6.9 Hz, 1H), 5.47 (dq, J=14.2, 7.0 Hz, 1H), 5.05 (td, J=8.0, 4.5 Hz, 1H), 4.52 (d, J=4.4 Hz, 1H), 4.49 (dt, J=7.4, 2.7 Hz, 1H), 4.33-4.27 (m, 2H), 4.19 (ddd, J=11.5, 8.5, 3.0 Hz, 1H), 4.00 (dd, J=11.5, 3.9 Hz, 1H), 3.94 (ddd, J=11.6, 5.6, 2.2 Hz, 1H), 3.01 (q, J=7.3 Hz, 12H), 2.49-2.40 (m, 2H), 1.10 (t, J=7.3 Hz, 18H).

Example 81: 2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15-fluoro-2,10,16-trihydroxy-2,10-disulfidooctahydro-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)

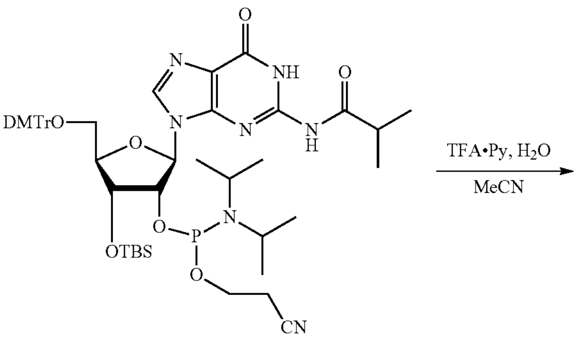
[0642]

Diastereomer 1



Step 1: (2R,3R,4R,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(hydroxymethyl)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate

[0643]



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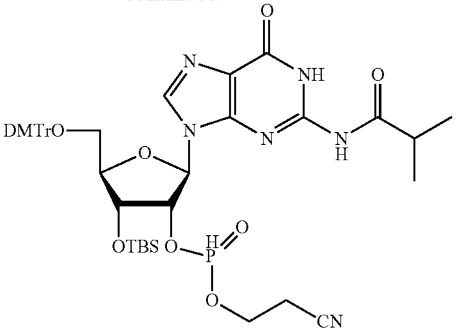
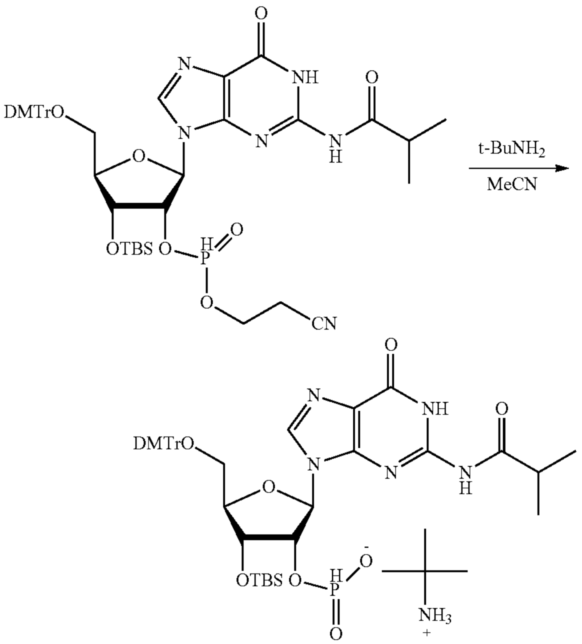


[0644] To a stirred solution of (2R,3R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl) methoxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl (2-cyanoethyl) diisopropylphosphoramidite (3 g, 3.09 mmol) in MeCN (15 mL) at 25° C. was added H_2O (0.111 mL, 6.18 mmol) and pyridin-1-ium 2,2,2-trifluoroacetate (0.717 g, 3.71 mmol). The resulting mixture was stirred at 25° C. for 20 min. The reaction progress was monitored by LCMS/TLC. After the phosphoramidite starting material was consumed, the reaction mixture that containing the desired product (major) was used for the next step without any after-treatment. LCMS (ES, m/z): 887.4 $[M+H]^+$.

Step 2: (2R,3R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate

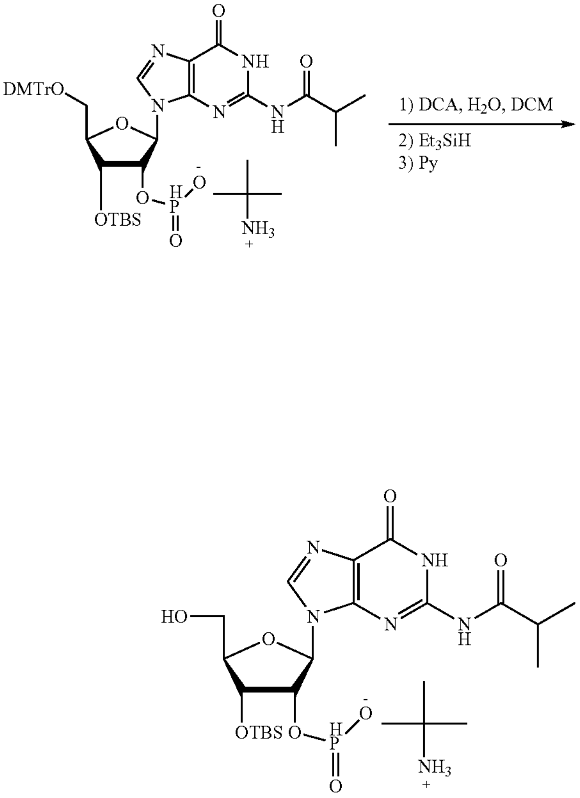
[0645]



[0646] To a stirred solution of the product of Step 1 (15.0 mL, 142 mmol) from the previous reaction was added tert-butylamine in one portion, and it was stirred at 25° C. for 40 min. The resulting solution was concentrated in vacuo. The residue was co-evaporated with dry MeCN (two times, 15 mL each), used for the next step without purification. LCMS (ES, m/z): 832.3 $[M-H]^-$.

Step 3: (2R,3R,4R,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(hydroxymethyl)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate

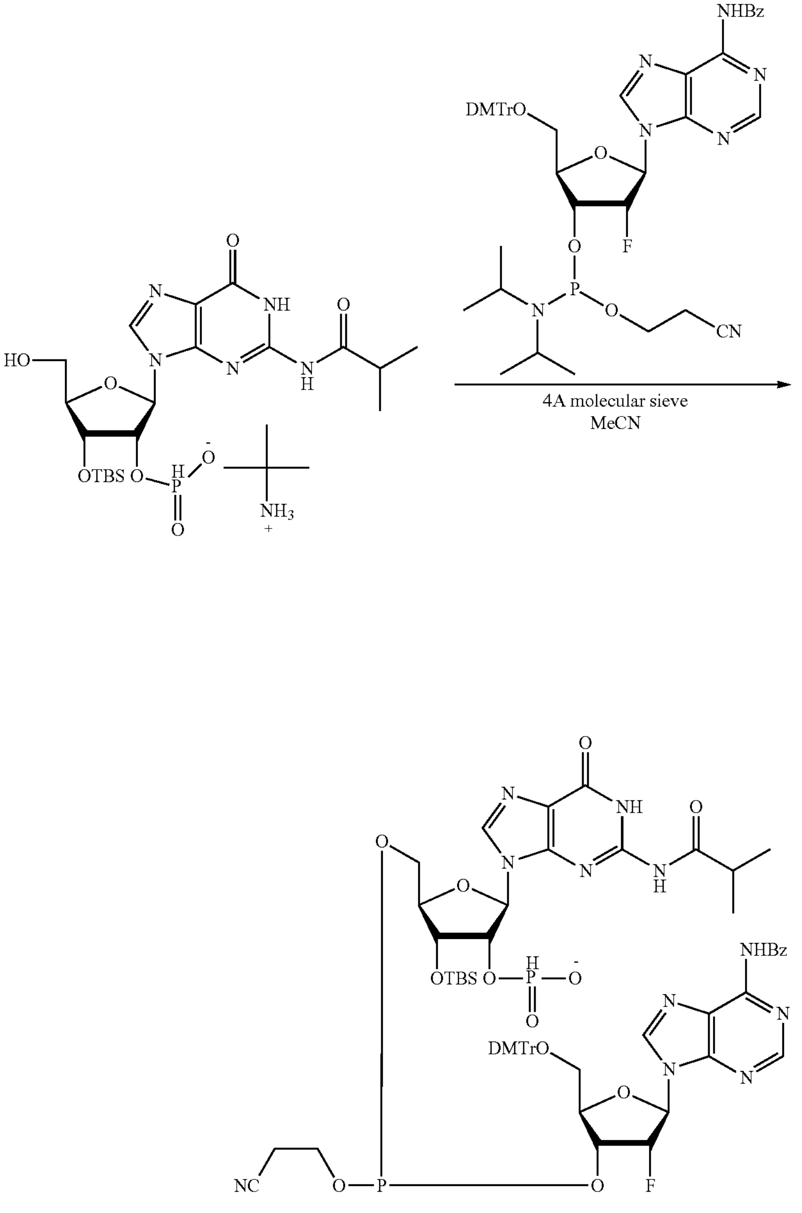
[0647]



[0648] To a stirred solution of the product of Step 2 in CH_2Cl_2 (37 mL) was added H_2O (0.558 mL, 31.0 mmol) and 6% DCA in CH_2Cl_2 (37 mL, 31.5 mmol) dropwise. The resulting mixture was stirred at 25° C. for 40 min, then Et_3SiH (60 mL) was added, and the reaction mixture was stirred for 1.5 h. Pyridine (4.5 mL, 2 eq to DCA) was added to the reaction. The resulting solution was stirred at 25° C. for 5 min and then concentrated in vacuo. The residue was triturated with MTBE/hexane (100 mL, v/v, 1/1), and the supernatant was decanted. This process was repeated two more times. The final residue was concentrated at reduced pressure and was used for the next step without purification. LCMS (ES, m/z): 532.18 $[M+H]^+$.

Step 4. (2R,3R,4R,5R)-5-((((((2R,3R,4R,5R)-5-(6-benzamido-9H-purin-9-yl)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-fluorotetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphanyl)oxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate

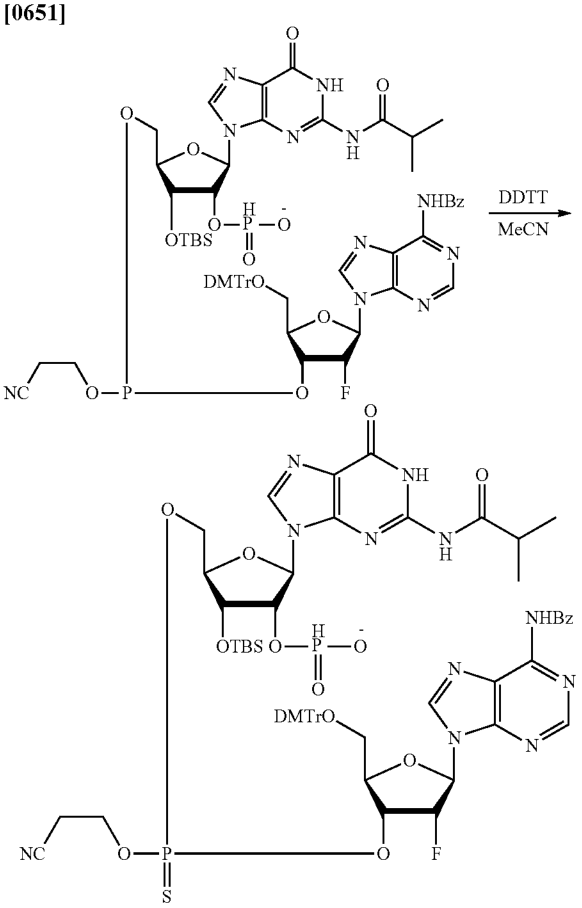
[0649]



[0650] To a stirred solution of the product of Step 3 (0.704 g, 0.722 mmol) in MeCN (5 mL) under Ar was added activated 4 Å molecular sieve (200 mg), and the mixture was stirred at RT over 30 min. (2R,3R,4R,5R)-5-(6-benzamido-9H-purin-9-yl)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-fluorotetrahydrofuran-3-yl (2-cyanoethyl) diisopropylphosphoramidite (0.822 g, 0.939 mmol) was twice co-evaporated with dry MeCN (3 mL). Activated 4 Å molecular sieve (200 mg) was added. After 30 min, the phosphoramidite solution was transferred into the solution of the product of Step 3 by syringe. The resulting mixture was stirred at RT for 20 min. The desired product was detected by TLC/LCMS, and the reaction solution was used for the next reaction without purification. LCMS (ES, m/z): 1306.7 $[M+H]^+$.

Step 5. (2R,3R,4R,5R)-5-((((((2R,3R,4R,5R)-5-(6-benzamido-9H-purin-9-yl)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-fluorotetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphorothioyl)oxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate

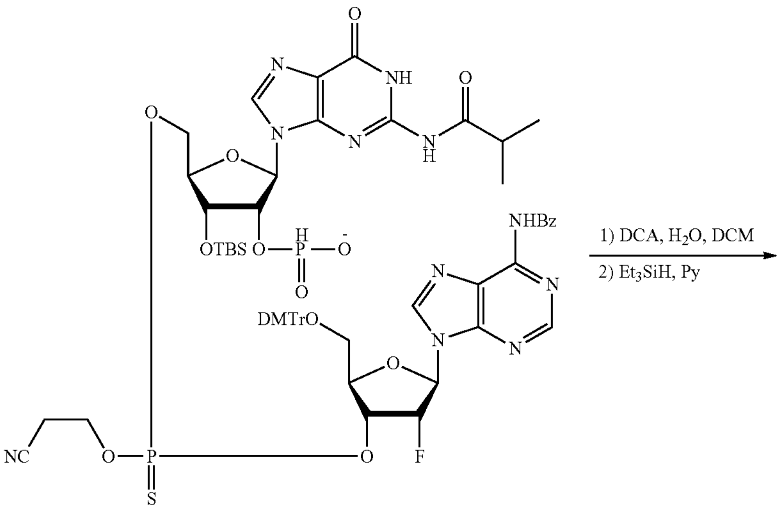
[0651]



[0652] To the reaction mixture containing the product of Step 4 (~0.722 mmol) under Ar was added (E)-N,N-dimethyl-N'-(3-thioxo-3H-1,2,4-dithiazol-5-yl)formimidamide (163 mg, 0.794 mmol) in one portion, and the mixture was stirred at RT for 30 min. The reaction progress was monitored by TLC/LCMS. After the consumption of the starting phosphite, the reaction mixture was concentrated in vacuo, and the residue was purified by reverse phase chromatography (X-Bridge BEH130 Prep C18) eluting with 5 to 95% MeCN in H_2O (0.04% NH_4HCO_3). The product-containing fractions were combined and concentrated under reduced pressure to 2/3 volume. NaCl (10 g) was added, and the aqueous mixture was extracted with EtOAc/Et_2O (v/v, 1/1, 3×80 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. LCMS (ES, m/z): 1339.5 $[M+H]^+$. ^{31}P-NMR (162 MHz, CD_3OD): δ 67.83 (d, J=43.9 Hz), 2.81 (d, J=15.7 Hz).

Step 6. (2R,3R,4R,5R)-5-((((((2R,3R,4R,5R)-5-(6-benzamido-9H-purin-9-yl)-4-fluoro-2-(hydroxymethyl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphorothioyl)oxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate

[0653]



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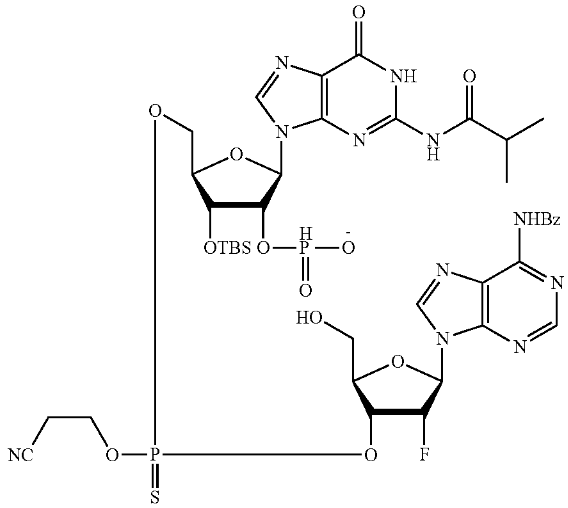
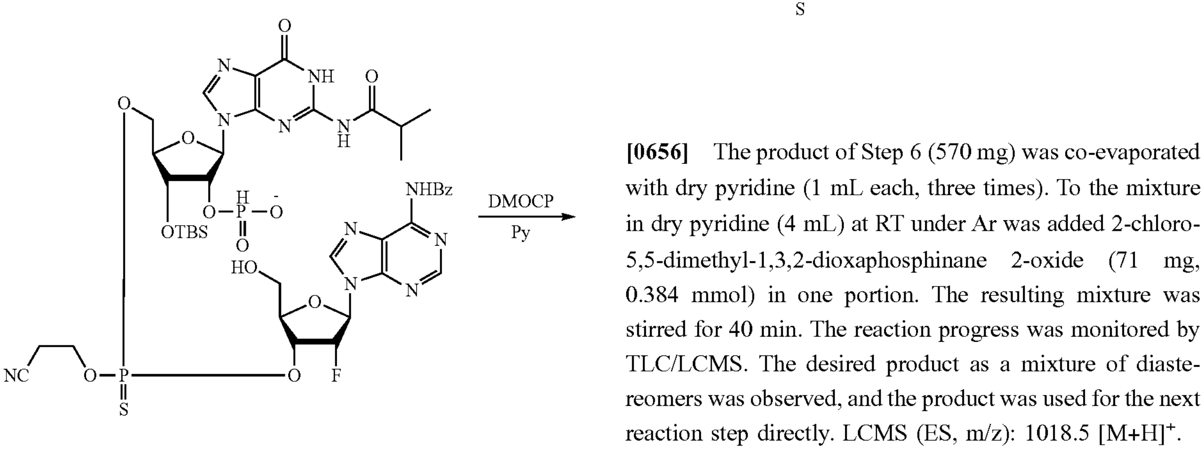


[0654] To a stirred solution of the product of Step 5 (180 mg, 0.128 mmol) in CH_2Cl_2 (7 mL) was added 2,2-dichloroacetic acid in CH_2Cl_2 (2.47 mg, 1.15 mmol) and H_2O (22.97 mg, 1.28 mmol). After stirring at RT for 20 min, Et_3SiH (4.5 mL) was added. After 2 h, pyridine (1 mL) was added, and the mixture was stirred for 10 min. After removal of volatiles, the product was used for the next reaction step without purification. LCMS (ES, m/z): 1036.4 $[M+H]^+$.

Step 7: (5R,7R,8R,12aR,14R,15R,15aR,16R)-16-{[tert-butyl(dimethyl)silyl]oxy}-2-(2-cyanoethoxy)-15-fluoro-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-10-olate 2-sulfide

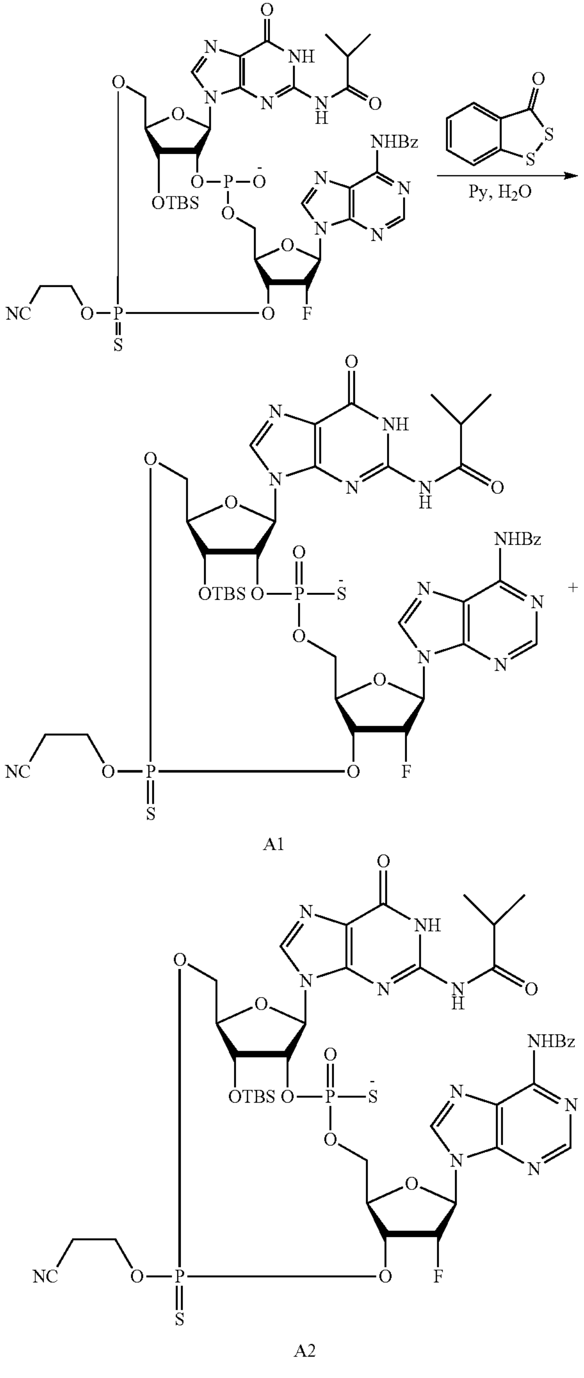
[0655]



[0656] The product of Step 6 (570 mg) was co-evaporated with dry pyridine (1 mL each, three times). To the mixture in dry pyridine (4 mL) at RT under Ar was added 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxide (71 mg, 0.384 mmol) in one portion. The resulting mixture was stirred for 40 min. The reaction progress was monitored by TLC/LCMS. The desired product as a mixture of diastereomers was observed, and the product was used for the next reaction step directly. LCMS (ES, m/z): 1018.5 $[M+H]^+$.

Step 8: Diastereomeric mixtures (5R,7R,8R,12aR,14R,15R,15aR,16R)-16-{[tert-butyl(dimethyl)silyl]oxy}-2-(2-cyanoethoxy)-15-fluoro-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-O-thiolate 10-oxide 2-sulfide (A1) and (5R,7R,8R,12aR,14R,15R,15aR,16R)-16-{[tert-butyl(dimethyl)silyl]oxy}-2-(2-cyanoethoxy)-15-fluoro-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-10-thiolate 10-oxide 2-sulfide (A2)

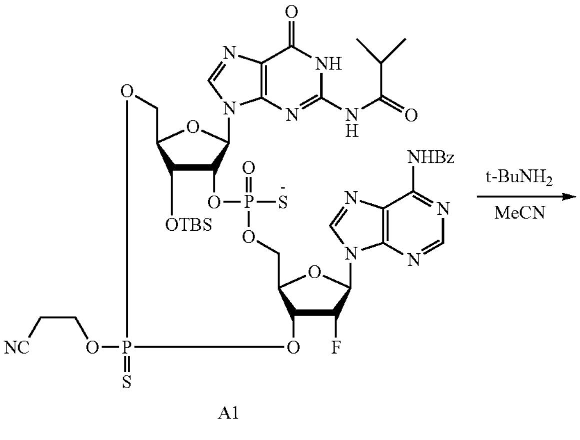
[0657]



[0658] To the stirred mixture of the product of Step 7 was added H_2O (69.2 mg, 3.84 mmol) and 3H-benzo[c][1,2]dithiol-3-one (32.3 mg, 0.192 mmol). The mixture was stirred at RT for 40 min. The reaction progress was monitored by TLC/LCMS. After the reaction completed, the reaction mixture was poured into aq $NaHCO_3$ (0.14 g $NaHCO_3$ in 5 mL H_2O) and stirred for 5 min. The resulting mixture was extracted with EtOAc/ether (v/v, 1/1, 3×15 mL). The combined organic layers were dried (Na_2SO_4), and purified by silica gel chromatography eluted with 0 to 15% MeOH in CH_2Cl_2 to give products: mixture of diastereomers A1 (eluted out at 5.5% MeOH in CH_2Cl_2); mixture of diastereomers A2 (eluted out at 9.8% MeOH in CH_2Cl_2); (2R,3R,4R,5R)-5-((((((2R,3R,4R,5R)-5-(6-benzamido-9H-purin-9-yl)-4-fluoro-2-(hydroxymethyl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphorothioyl)oxy)methyl)-4-((tert-butyldimethyl silyl)oxy)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate (eluted out at 12.6% MeOH in CH_2Cl_2). Mixture A1: LCMS (ES, m/z): 1050.30 $[M+H]^+$. ^{31}P-NMR (162 MHz, CD_3OD): δ 66.34 (s), 64.63 (s). Mixture A2: LCMS (ES, m/z): 1050.30 $[M+H]^+$. ^{31}P-NMR (162 MHz, CD_3OD): δ 65.94, 64.17, 62.55, 61.28.

Step 9: Diastereomers (5R,7R,8R,12aR,14R,15R,15aR,16R)-16-{[tert-butyl(dimethyl)silyl]oxy}-15-fluoro-7-{2-[(2-methylpropanoyl)amino-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-2,10-bis(thiolate) 2,10-dioxide (B1) and (5R,7R,8R,12aR,14R,15R,15aR,16R)-16-{[tert-butyl(dimethyl)silyl]oxy}-15-fluoro-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}octahydro-12H-5,8-methanofuro[3,2-l]1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-2,10-bis(thiolate) 2,10-dioxide (B2)

[0659]



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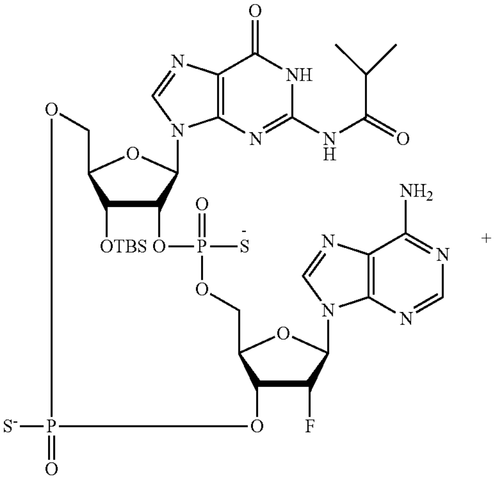
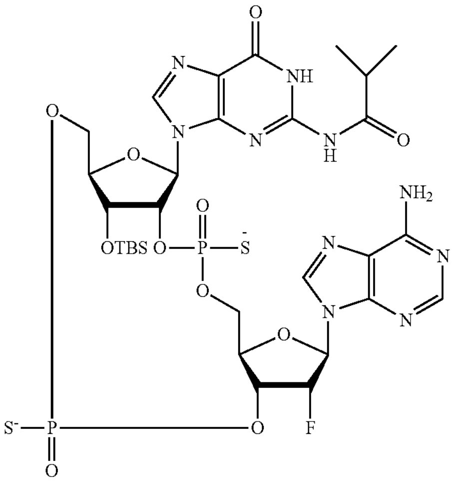


B1

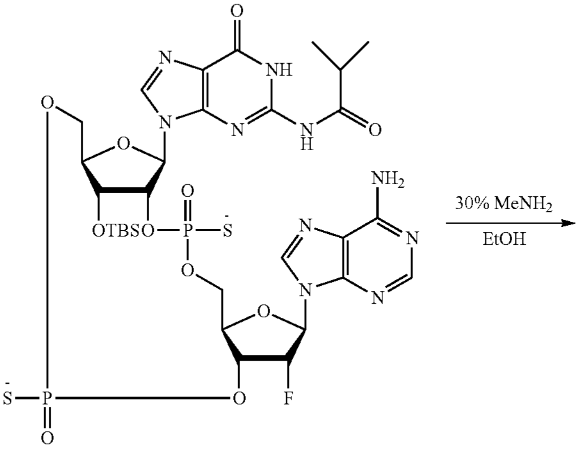


B2

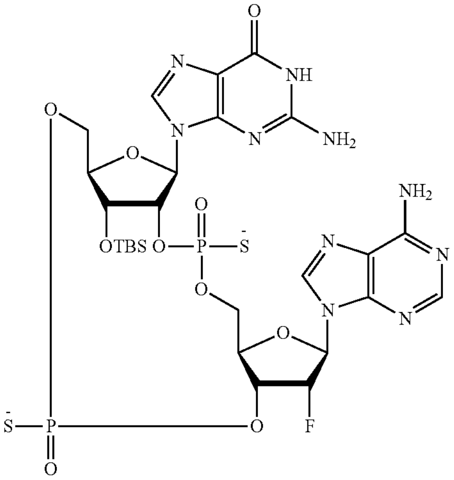
[0660] To a stirred suspension of crude A1 (95 mg, ~0.09 mmol) from the previous step in MeCN (1 mL) at RT under Ar was added tert-butylamine (1.5 mL). After 30 min, volatile components were removed in vacuo. The residue was purified by reverse phase prep-HPLC (X-Bridge BEH130 Prep C18) eluted with 25 to 45% MeCN in aq NH_4HCO_3 (10 mM) over 8 min to give compound B2 as a single diastereomer (T_R=5.97 min). LCMS (ES, m/z): 891.4 $[M-H]^-$. H-NMR (300 MHz, CD_3OD): δ 8.44 (s, 1H), 8.22 (s, 1H), 8.09 (s, 1H), 6.37 (d, J=14.0 Hz, 1H), 5.95 (d, J=8.0 Hz, 1H), 5.65-5.54 (m, 1H), 5.26-5.10 (m, 2H), 4.57-4.41 (m, 4H), 4.24 (s, 1H), 4.01 (d, J=11.5 Hz, 1H), 3.89 (d, J=11.8 Hz, 1H), 2.75-2.63 (m, 1H), 1.04-0.91 (m, 15H), 0.28-0.24 (m, 6H). ^{31}P-NMR (121 MHz, CD_3OD): δ 57.10 (s), 53.1 (s).

Step 10: (5R,7R,8R,12aR,14R,15R,15aR,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-14-(6-amino-9H-purin-9-yl)-16-{[tert-butyl(dimethyl)silyl]oxy}-15-fluorooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-2,10-bis(thiolate) 2,10-dioxide

[0661]



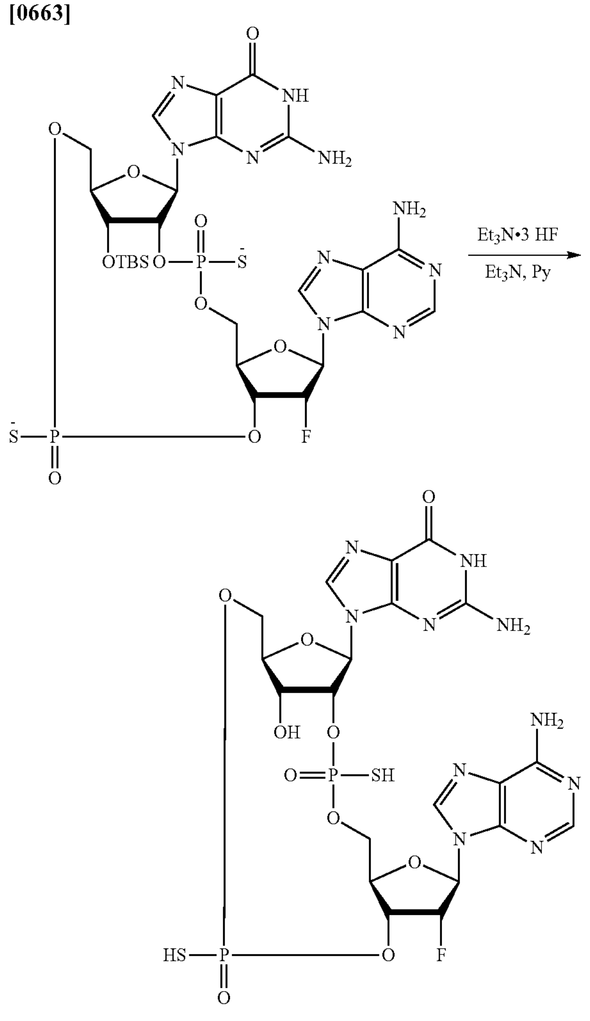
B2



[0662] To a stirred solution of compound B2 (13 mg, 0.013 mmol) from the previous step was added a solution of $MeNH_2$ in EtOH (0.6 mL, 30% by weight). The mixture was stirred at RT for 12 h. The volatile components were removed under reduced pressure, and the residue containing product compound was used for the next reaction step without purification. LCMS (ES, m/z): 823.15 $[M+H]^+$.

Step 11: 2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15-fluoro-2,10,16-trihydroxy-2,10-disulfidooctahydro-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)

[0663]



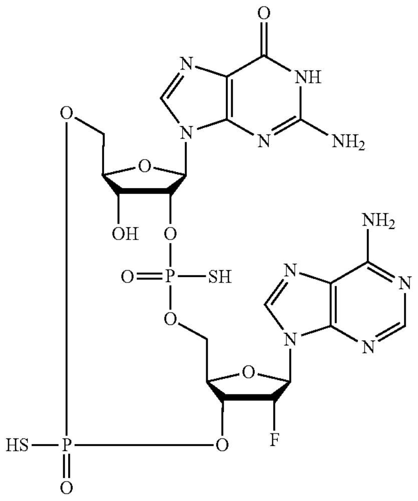
Diastereomer 1

[0664] The crude product from Step 10 (25 mg) was co-evaporated with pyridine/Et_3N (v/v, 3/1, 1 mL each, three times) and then dissolved in pyridine (0.15 mL). The mixture was charged with Ar and Et_3N (0.20 mL) and triethylamine trihydrofluoride (56.4 mg, 0.350 mmol) were added. The resulting solution was warmed at 50° C. for 6 h. The reaction progress was monitored by TLC/LCMS. After completion of the reaction, the mixture was concentrated in vacuo and then, co-evaporated with MeCN (three times, 1 mL each). The residue was purified by reverse phase prep-HPLC (X-Bridge BEH130 Prep C18) eluted with 0 to 22% MeCN in aq NH_4HCO_3 (50 mM) over 15 min to give the product compound (T_R=8.3 min). LCMS (ES, m/z): 708.95 $[M+H]^+$. ^{1}H-NMR (400 MHz, D_2O): δ 8.18 (s, 1H), 8.16 (s, 1H), 7.77 (s, 1H), 6.37 (d, J=14.3 Hz, 1H), 5.86 (d, J=8.4 Hz, 1H), 5.61-5.54 (m, 1.5H), 5.43 (s, 0.5H), 5.27-5.12 (m, 2H), 4.59 (d, J=3.6 Hz, 1H), 4.47 (t, J=12.9 Hz, 2H), 4.36 (d, J=4.8 Hz, 1H), 4.04 (dd, J=23.2, 12.0 Hz, 2H). ^{31}P-NMR (162 MHz, D_2O): δ 55.63 (s), 51.55 (s).

Example 82: 2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15-fluoro-2,10,16-trihydroxy-2,10-disulfidooctahydro-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 2)

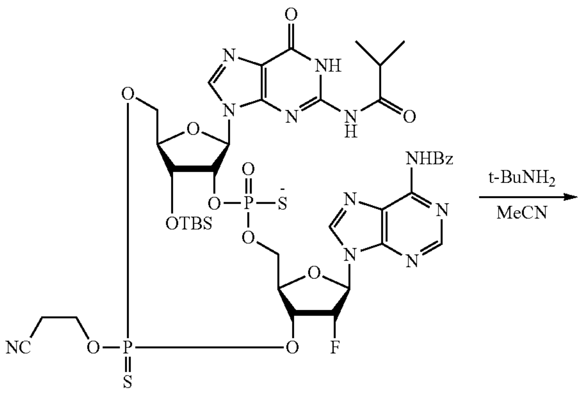
[0665]

Diastereomer 2



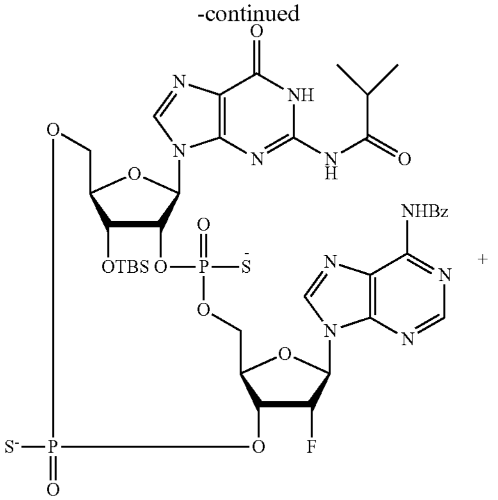
Step 1: Diastereomers (5R,7R,8R,12aR,14R,15R,15aR,16R)-16-{[tert-butyl(dimethyl)silyl]oxy}-15-fluoro-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-2,10-bis(thiolate) 2,10-dioxide (B3) and (5R,7R,8R,12aR,14R,15R,15aR,16R)-16-{[tert-butyl(dimethyl)silyl]oxy}-15-fluoro-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-2,10-bis(thiolate) 2,10-dioxide (B4)

[0666]

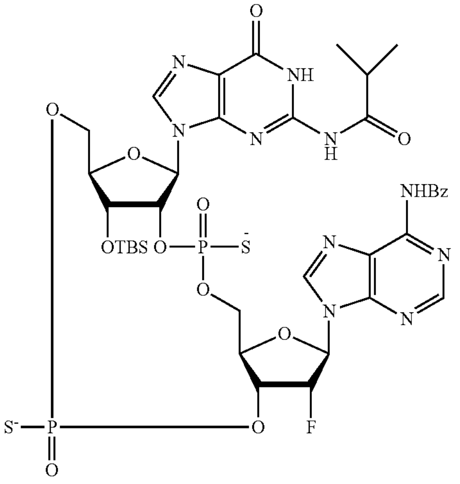


A2

-continued



B3



B4

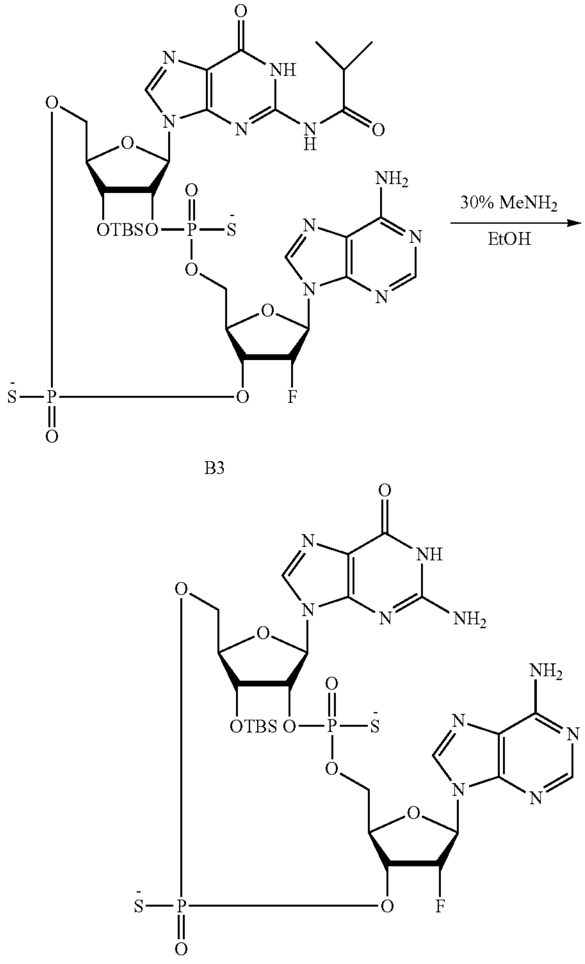
[0667] To a stirred suspension of crude A2 (105 mg, -0.1 mmol) from Example 81, Step 8 in MeCN (1 mL) under Ar was added tert-butylamine (1.5 mL), and the mixture was stirred at RT for 30 min. The volatile components were removed in vacuo. The residue was purified by reverse phase prep-HPLC (X-Bridge BEH130 Prep C18) eluted with 25 to 40% MeCN in aq NH_4HCO_3 (10 mM) over 10 min to give two diastereomeric compounds, B3 (T_R=6.12 min, 0.025 mmol) and B4 (T_R=7.45 min, 0.021 mmol).

[0668] Compound B3: LCMS (ES, m/z): 995.3 $[M-H]^-$. H-NMR (300 MHz, CD_3OD): δ 8.82 (s, 1H), 8.72 (s, 1H), 8.65 (s, 1H), 8.20-8.13 (m, 2H), 7.66-7.54 (m, 3H), 6.47 (d, J=14.0 Hz, 1H), 6.09 (d, J=8.4 Hz, 1H), 5.96-5.95 (m, 0.5H), 5.81-5.78 (m, 0.5H), 5.52-5.36 (m, 2H), 4.64-4.56 (m, 2H), 4.48-4.43 (m, 1H), 4.37-4.30 (m, 1H), 4.25-4.22 (m, 1H), 4.17-4.10 (m, 1H), 3.98 (d, J=11.7 Hz, 1H), 2.65 (p, J=6.8 Hz, 1H), 1.12 (d, J=6.8 Hz, 3H), 0.98-0.95 (m, 12H), 0.22 (d, J=8.0 Hz, 6H). ^{31}P-NMR (121 MHz, CD_3OD): δ 56.96 (s), 55.90 (s).

[0669] Compound B4: LCMS (ES, m/z): 995.4 $[M-H]^-$. H-NMR (300 MHz, CD_3OD): δ 8.97 (s, 1H), 8.68 (s, 1H), 8.24-8.22 (m, 3H), 7.59 (ddd, J=14.5, 7.9, 6.2 Hz, 3H), 6.46 (d, J=13.0 Hz, 1H), 5.99 (d, J=8.3 Hz, 1H), 5.67-5.57 (m, 1H), 5.45-5.33 (m, 2H), 4.56 (dd, J=13.5, 4.9 Hz, 2H), 4.47-4.38 (m, 2H), 4.25 (t, J=3.5 Hz, 1H), 4.07 (d, J=11.3 Hz, 1H), 3.94 (d, J=11.0 Hz, 1H), 2.75 (p, J=6.8 Hz, 1H), 1.04 (d, J=6.8 Hz, 3H), 0.95 (s, 12H), 0.23 (d, J=5.2 Hz, 6H). ^{31}P-NMR (121 MHz, CD_3OD): δ 56.81 (s), 54.76 (s).

Step 2. (5R,7R,8R,12aR,14R,15R,15aR,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-14-(6-amino-9H-purin-9-yl)-16-{[tert-butyl(dimethyl)silyl]oxy}-15-fluorooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-2,10-bis(thiolate) 2,10-dioxide

[0670]

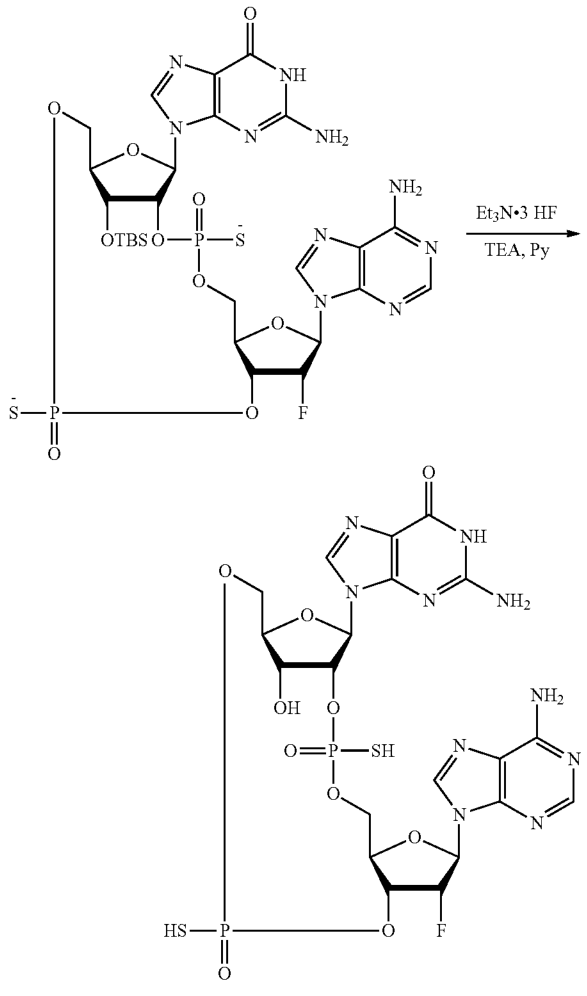


B3

[0671] Compound B3 from Step 1 (25 mg, 0.025 mmol) was dissolved in a solution of $MeNH_2$ in EtOH (1 mL, 30% by weight), and the mixture was stirred at RT for 12 h. The reaction progress was monitored by TLC/LCMS. After the reaction was complete, the volatile components were removed in vacuo, and the residue containing the crude product was used for the next reaction step without purification. LCMS (ES, m/z): 823.25 $[M+H]^+$.

Step 3: 2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15-fluoro-2,10,16-trihydroxy-2,10-disulfidooctahydro-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 2)

[0672]



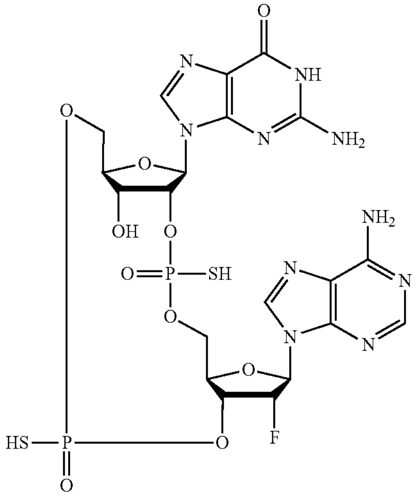
Diastereomer 2

[0673] The crude product of Step 2 (35 mg) was co-evaporated with pyridine/Et_3N (v/v, 3/1, 1 mL each, three times) and then re-dissolved in pyridine (0.4 mL). The mixture was charged with Ar and Et_3N (0.34 mL, 2.4 mmol), and triethylamine trihydrofluoride (97 mg, 0.6 mmol) were added. The resulting solution was warmed at 50° C. for 6 h. Then, the mixture was concentrated at reduced pressure and then co-evaporated with MeCN (3×1 mL). The residue was purified by reverse phase prep-HPLC (X-Bridge BEH130 Prep C18) eluted with 0 to 10% MeCN in aq NH_4HCO_3 (50 mM) over 14 min to give the product compound (T_R=9.2 min). LCMS (ES, m/z): 709.00 $[M+H]^+$. H-NMR (400 MHz, DMF-d_7+D_2O): δ 8.68 (s, 1H), 8.61 (s, 1H), 8.45 (s, 1H), 6.57 (d, J=14.8 Hz, 1H), 6.27-6.25 (m, 1.5H), 6.15-6.13 (m, 0.5H), 5.72-5.68 (m, 1H), 5.56-5.54 (m, 1H), 4.85-4.83 (m, 1H), 4.71-4.69 (m, 1H), 4.52-4.43 (m, 4H), 4.27-4.24 (m, 1H). ^{31}P-NMR (162 MHz, DMF-d_7+D_2O): δ 56.03 (s), 53.37 (s). ^{19}F-NMR (376 MHz, DMF-d_7+D_2O): δ −205.44 (s).

Example 83: 2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15-fluoro-2,10,16-trihydroxy-2,10-disulfidooctahydro-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 3)

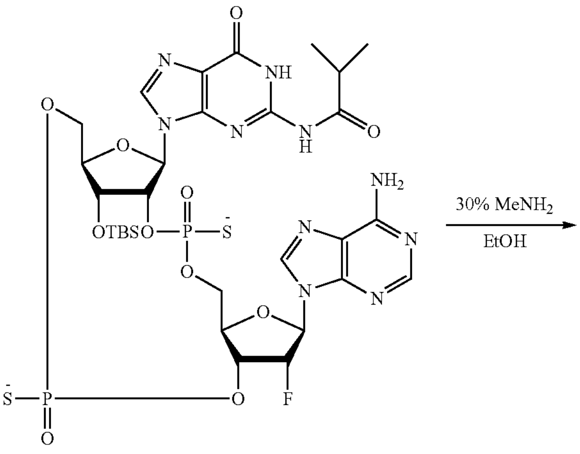
[0674]

Diastereomer 3



Step 1: (5R,7R,8R,12aR,14R,15R,15aR,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-14-(6-amino-9H-purin-9-yl)-16-{[tert-butyl(dimethyl)silyl]oxy}-15-fluorooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-2,10-bis(thiolate) 2,10-dioxide

[0675]



B4

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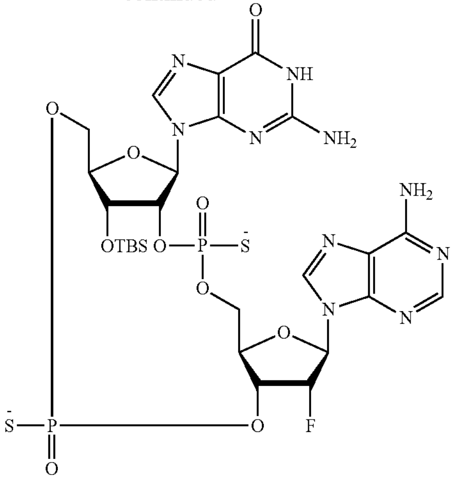
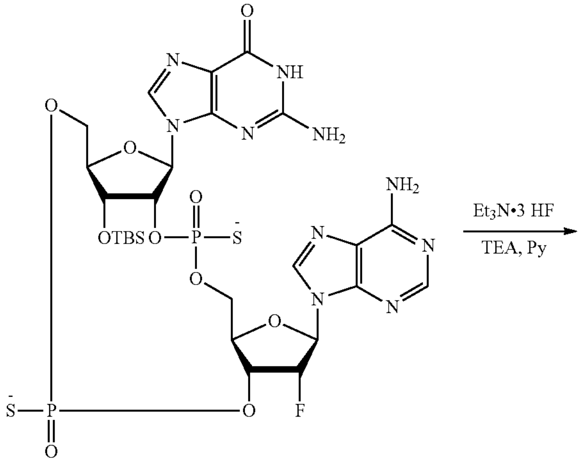


[0676] Compound B4 ((5R,7R,8R,12aR,14R,15R,15aR,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-14-(6-amino-9H-purin-9-yl)-16-{[tert-butyl(dimethyl)silyl]oxy}-15-fluorooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-2,10-bis(thiolate) 2,10-dioxide, 21 mg, 0.021 mmol) from Example 82, Step 1 was dissolved in a solution of $MeNH_2$ in EtOH (1 mL, 30% by weight), and the mixture was stirred at RT for 12 h. The reaction progress was monitored by TLC/LCMS. After the reaction was complete, the volatile components were removed in vacuo, and the product was used for the next reaction step without purification. LCMS (ES, m/z): 823.25 $[M+H]^+$.

Step 2: 2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15-fluoro-2,10,16-trihydroxy-2,10-disulfidooctahydro-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 3)

[0677]



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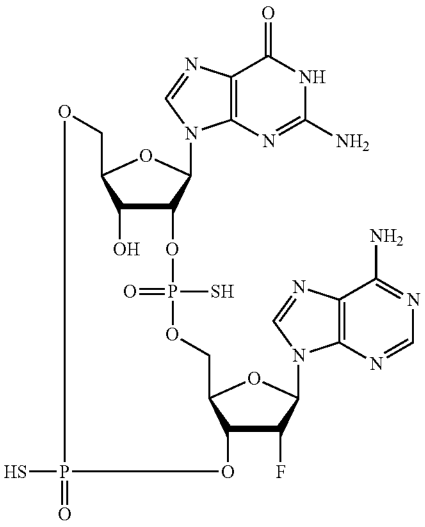


Diastereomer 3

[0678] The crude product of Step 1 (31 mg) was co-evaporated with pyridine/Et_3N (v/v, 3/1, 3×1 mL) and then, re-dissolved in pyridine (0.4 mL). The mixture was charged with Ar and Et_3N (0.28 mL, 2.0 mmol) and triethylamine trihydrofluoride (81 mg, 0.5 mmol) were added. The resulting solution was warmed at 50° C. for 6 h. The mixture was concentrated at reduced pressure and then co-evaporated with MeCN (3×1 mL). The residue was purified by reverse phase prep-HPLC (X-Bridge BEH130 Prep C18) eluting with 0 to 10% MeCN in aq NH_4HCO_3 (50 mM) over 14 min to give the product compound (T_R=10.1 min). LCMS (ES, m/z): 709.00 $[M+H]^+$. H-NMR (400 MHz, DMF-d_7+D_2O): δ 8.73 (s, 1H), 8.28-8.20 (m, 2H), 6.55 (d, J=14.8 Hz, 1H), 6.25-5.85 (m, 3H), 5.62-5.56 (m, 1H), 4.76 (s, 1H), 4.62-4.60 (m, 2H), 4.49-4.41 (m, 3H), 4.18-4.15 (m, 1H). ^{31}P-NMR (162 MHz, DMF-d_7+D_2O): δ 56.09 (s), 54.75 (s). ^{19}F-NMR (376 MHz, DMF-d_7+D_2O): δ −203.33 (s).

[0679] Examples 84 through 116, shown in Table 5 below, were prepared according to procedures analogous to those outlined in Examples 77 through 83 above using the appropriate monomers, described as Preparations or as obtained from commercial sources, in the coupling step.

TABLE 5

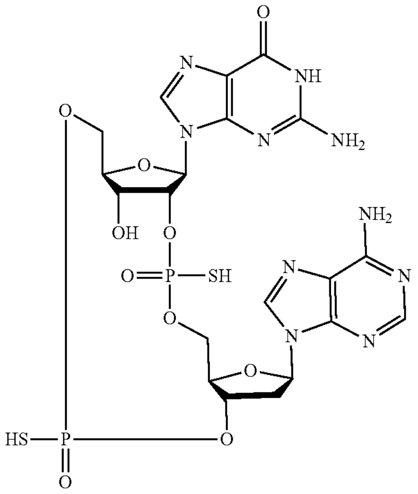
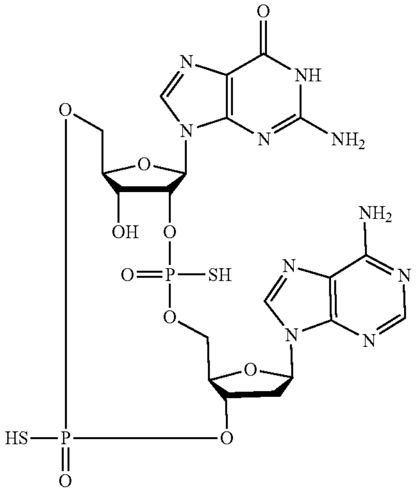
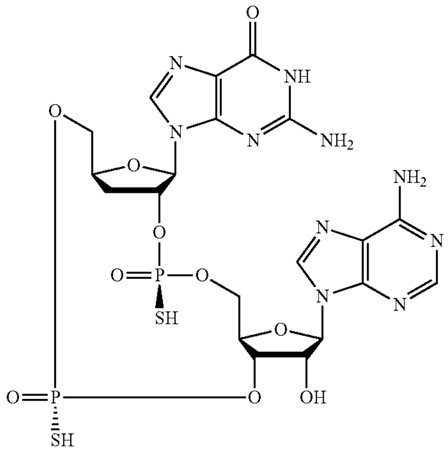
Ex.	Structure	Name	Mass [M − H]⁻
84		2-amino-9-[(5R,7R,8R,12aR,14R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-2,10,16-trihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 1)	691 [M + H]⁺
85		2-amino-9-[(5R,7R,8R,12aR,14R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-2,10,16-trihydroxy-2,10-disulfidooctahydro-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 2)	691 [M + H]⁺
86		2-amino-9-[(2R,5S,7R,8R,10R,12aR,14R,15R,15aS)-14-(6-amino-9H-purin-9-yl)-2,10,15-trihydroxy-2,10-disulfidooctahydro-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)	689

TABLE 5-continued

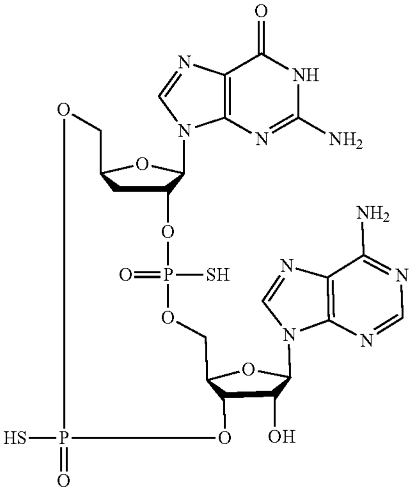
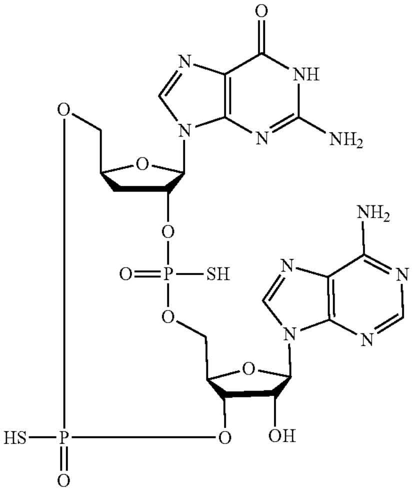
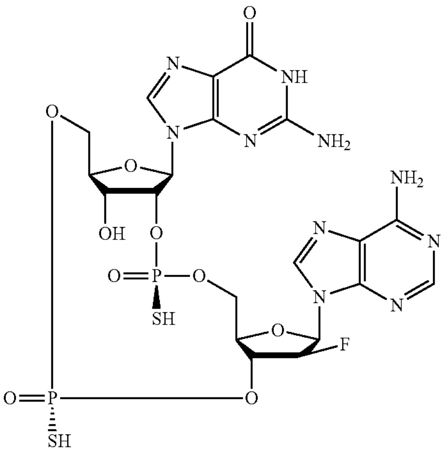
Ex.	Structure	Name	Mass [M − H]⁻
87		2-amino-9-[(5S,7R,8R,12aR,14R,15R,15aS)-14-(6-amino-9H-purin-9-yl)-2,10,15-trihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 2)	689
88		2-amino-9-[(5S,7R,8R,12aR,14R,15R,15aS)-14-(6-amino-9H-purin-9-yl)-2,10,15-trihydroxy-2,10-disulfidooctahydro-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 3)	689
89		2-amino-9-[(2R,5R,7R,8R,10,R,12aR,14R,15S,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15-fluoro-2,10,16-trihydroxy-2,10-disulfidooctahydro-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)	707

TABLE 5-continued

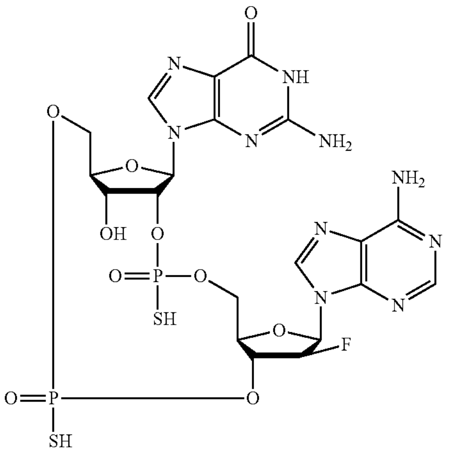
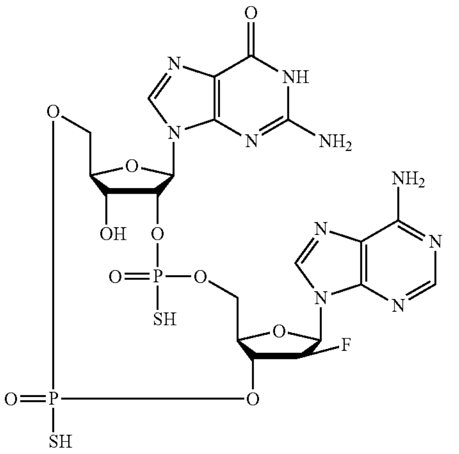
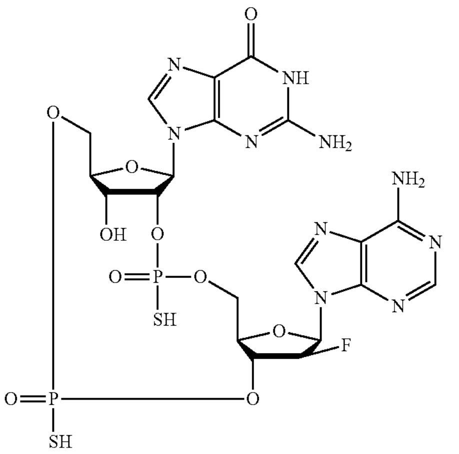
Ex.	Structure	Name	Mass [M − H]⁻
90		2-amino-9-[(5R,7R,8R,12aR,14R,15S,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15-fluoro-2,10,16-trihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 2)	707
91		2-amino-9-[(5R,7R,8R,12aR,14R,15S,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15-fluoro-2,10,16-trihydroxy-2,10-disulfidooctahydro-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 3)	707
92		2-amino-9-[(5R,7R,8R,12aR,14R,15S,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15-fluoro-2,10,16-trihydroxy-2,10-disulfidooctahydro-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 4)	707

TABLE 5-continued

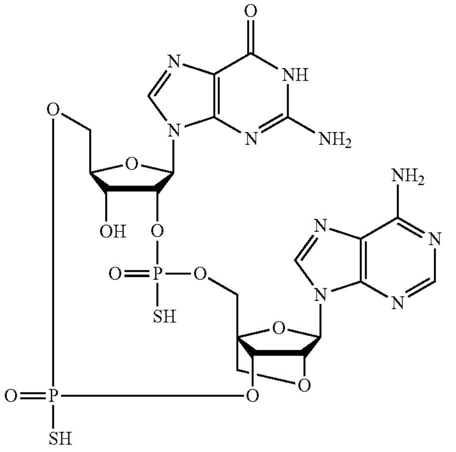
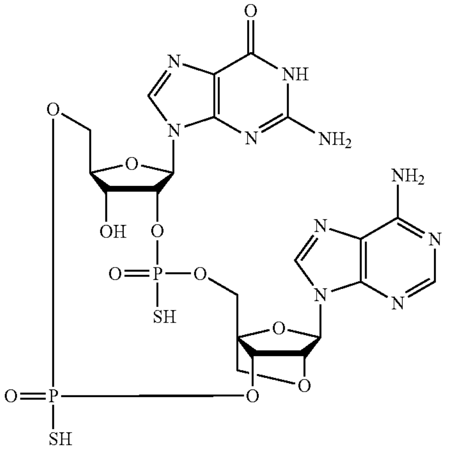
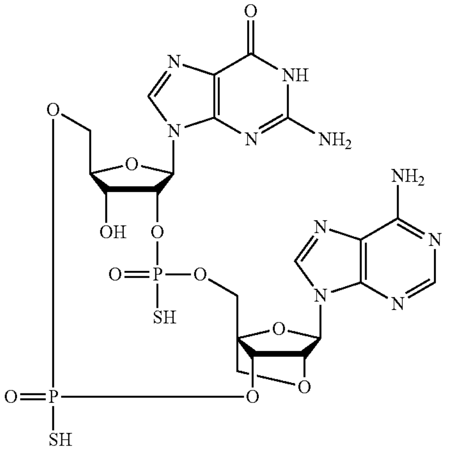
Ex.	Structure	Name	Mass $[M - H]^-$
93		2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,18R)-14-(6-amino-9H-purin-9-yl)-2,10,18-trihydroxy-2,10-disulfidohexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7(12H)-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 1)	717
94		2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,18R)-14-(6-amino-9H-purin-9-yl)-2,10,18-trihydroxy-2,10-disulfidohexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7(12H)-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 2)	717
95		2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,18R)-14-(6-amino-9H-purin-9-yl)-2,10,18-trihydroxy-2,10-disulfidohexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7(12H)-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 3)	719 $[M + H]^+$

TABLE 5-continued

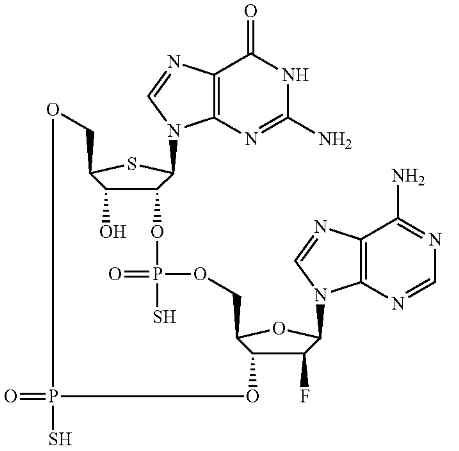
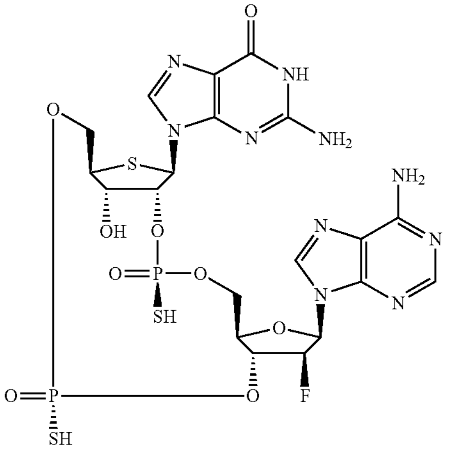
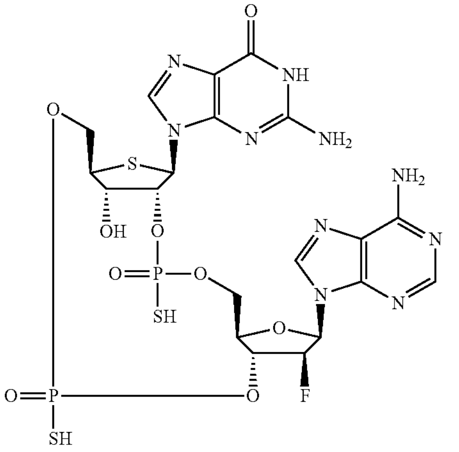
Ex.	Structure	Name	Mass [M − H]⁻
96		2-amino-9-[(5R,7R,8R,12aR,14R,15S,15aR,16S)-14-(6-amino-9H-purin-9-yl)-15-fluoro-16-hydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 1)	723
97		2-amino-9-[(2R,5R,7R,8R,10R,12aR,14R,15S,15aR,16S)-14-(6-amino-9H-purin-9-yl)-15-fluoro-16-hydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 2)	723
98		2-amino-9-[(5R,7R,8R,12aR,14R,15S,15aR,16S)-14-(6-amino-9H-purin-9-yl)-15-fluoro-16-hydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 3)	723

TABLE 5-continued

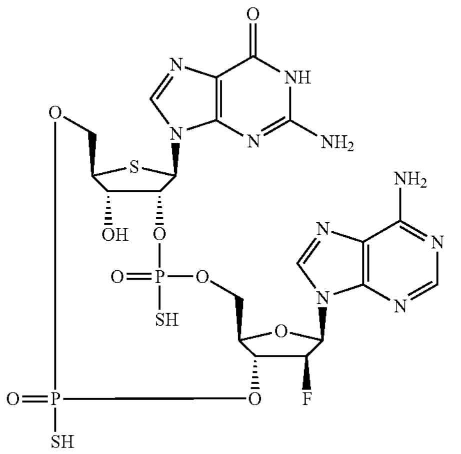
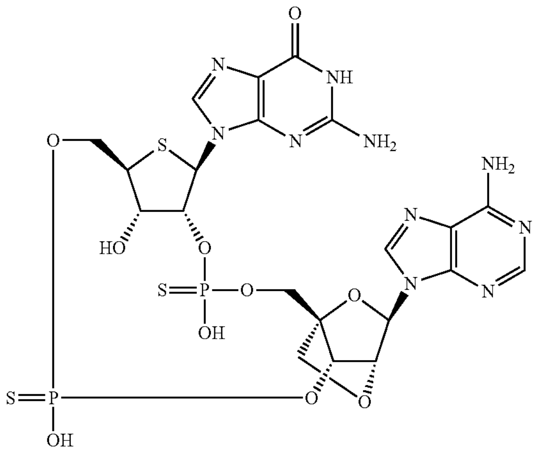
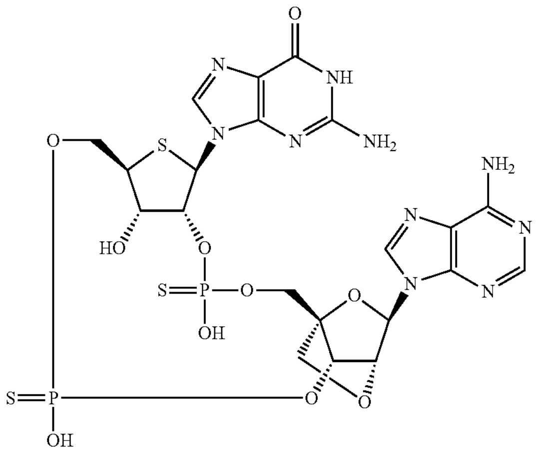
Ex.	Structure	Name	Mass [M − H]⁻
99		2-amino-9-[(5R,7R,8R,12aR,14R,15S,15aR,16S)-14-(6-amino-9H-purin-9-yl)-15-fluoro-16-hydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 4)	723
100		2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,18S)-14-(6-amino-9H-purin-9-yl)-2,10,18-trihydroxy-2,10-disulfidohexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7(12H)-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 1)	733
101		2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,18S)-14-(6-amino-9H-purin-9-yl)-2,10,18-trihydroxy-2,10-disulfidohexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7(12H)-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 2)	733

TABLE 5-continued

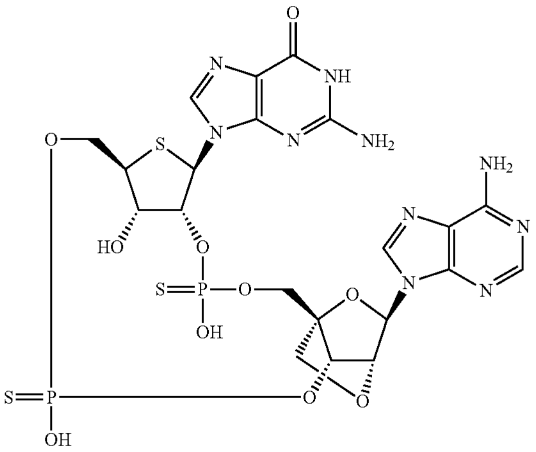
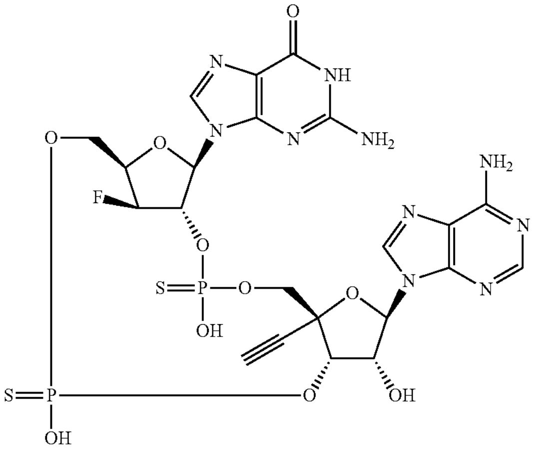
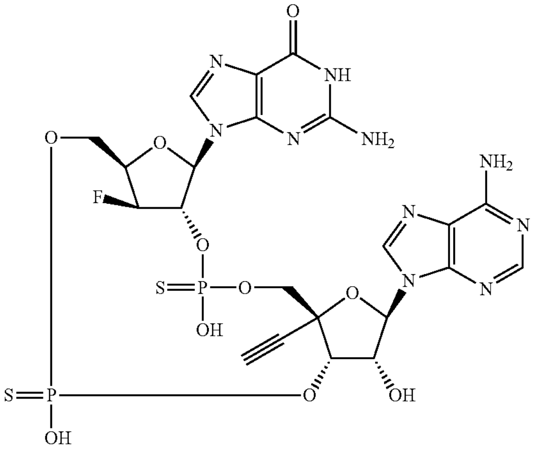
Ex.	Structure	Name	Mass [M − H]⁻
102		2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,18S)-14-(6-amino-9H-purin-9-yl)-2,10,18-trihydroxy-2,10-disulfidohexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7(12H)-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 3)	733
103		2-amino-9-[(5R,7R,8S,12aR,14R,15R,15aS,16S)-14-(6-amino-9H-purin-9-yl)-12a-ethynyl-16-fluoro-2,10,15-trihydroxy-2,10-disulfidooctahydro-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)	731
104		2-amino-9-[(5R,7R,8S,12aR,14R,15R,15aS,16S)-14-(6-amino-9H-purin-9-yl)-12a-ethynyl-16-fluoro-2,10,15-trihydroxy-2,10-disulfidooctahydro-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 2)	731

TABLE 5-continued

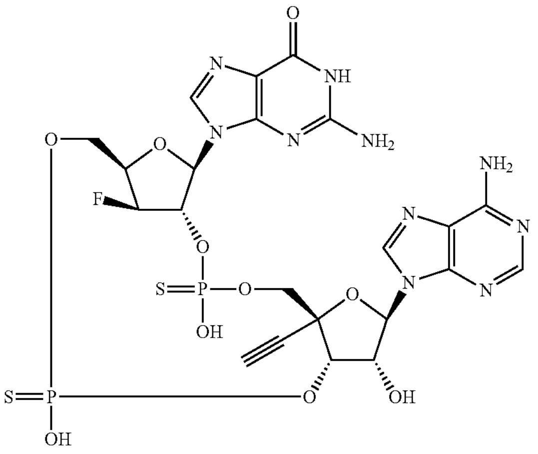
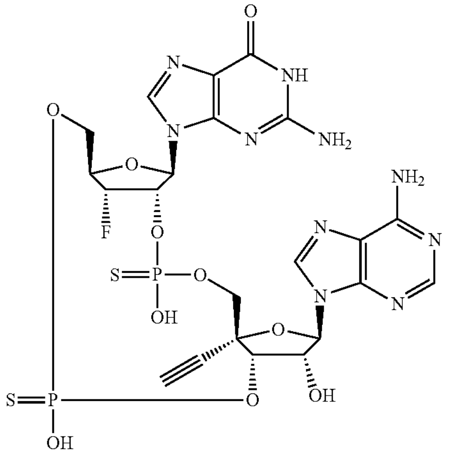
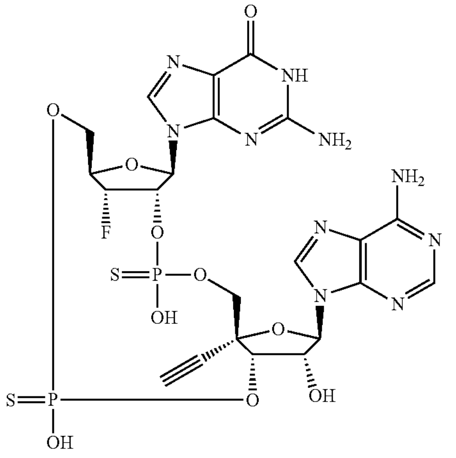
Ex.	Structure	Name	Mass [M − H]⁻
105		2-amino-9-[(5R,7R,8S,12aR,14R,15R,15aS,16S)-14-(6-amino-9H-purin-9-yl)-12a-ethynyl-16-fluoro-2,10,15-trihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 3)	731
106		2-amino-9-[(5R,7R,8S,12aR,14R,15R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-12a-ethynyl-16-fluoro-2,10,15-trihydroxy-2,10-disulfidooctahydro-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)	731
107		2-amino-9-[(5R,7R,8S,12aR,14R,15R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-12a-ethynyl-16-fluoro-2,10,15-trihydroxy-2,10-disulfidooctahydro-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 2)	731

TABLE 5-continued

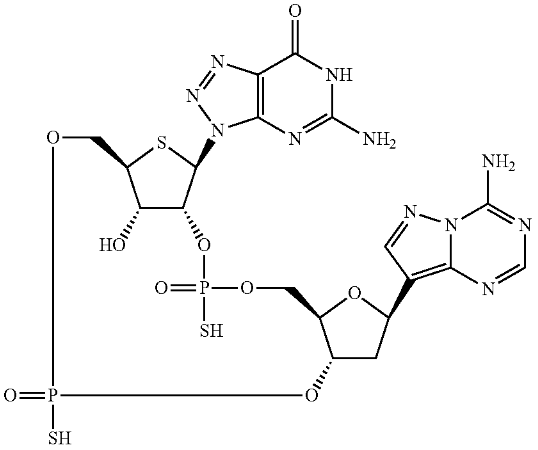
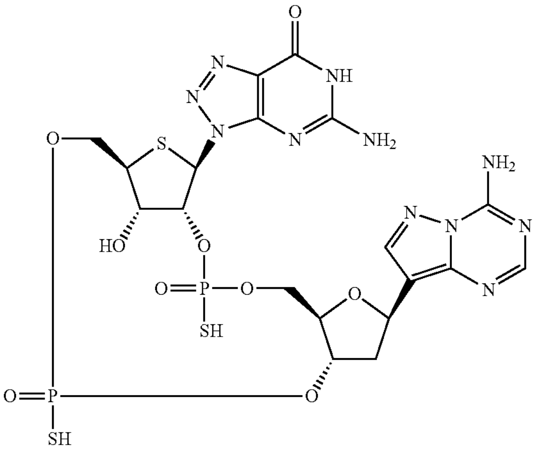
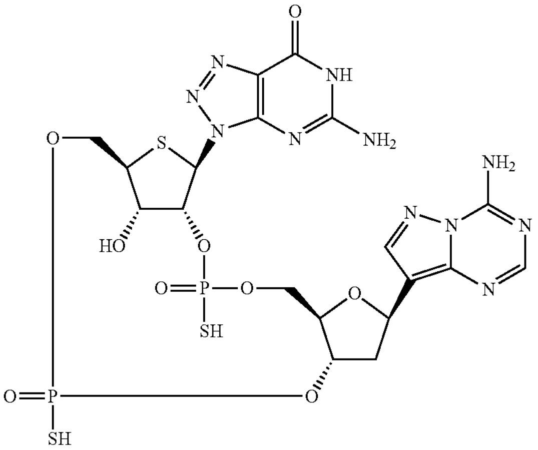
Ex.	Structure	Name	Mass [M − H]⁻
108		5-amino-3-[(5R,7R,8R,12aR,14R,15aS,16S)-14-(4-aminopyrazolo[1,5-a][1,3,5]triazin-8-yl)-16-hydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 1)	706
109		5-amino-3-[(5R,7R,8R,12aR,14R,15aS,16S)-14-(4-aminopyrazolo[1,5-a][1,3,5]triazin-8-yl)-16-hydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 2)	706
110		5-amino-3-[(5R,7R,8R,12aR,14R,15aS,16S)-14-(4-aminopyrazolo[1,5-a][1,3,5]triazin-8-yl)-16-hydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 3)	706

TABLE 5-continued

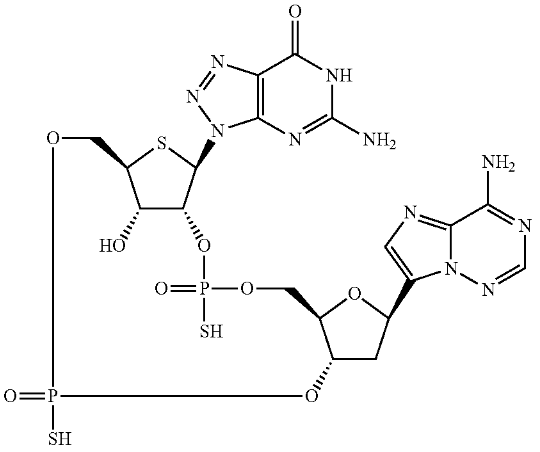
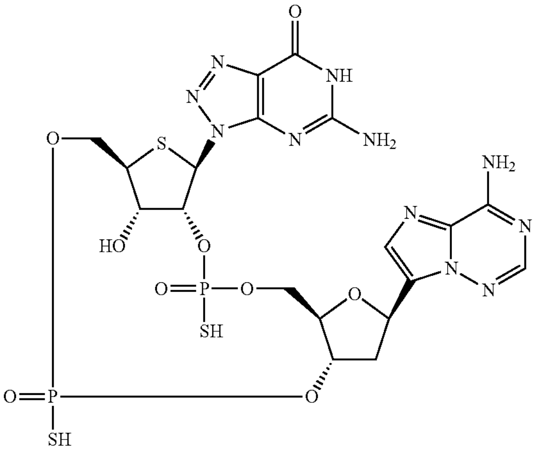
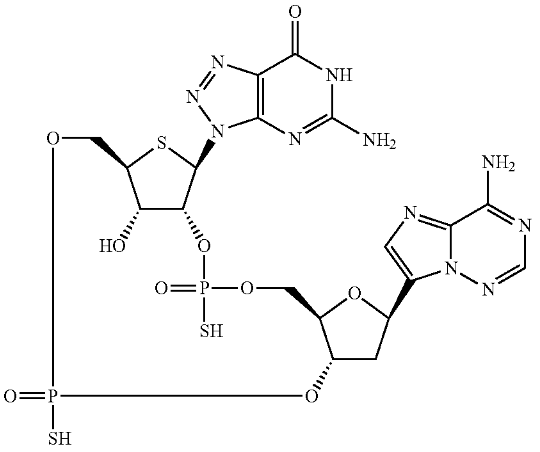
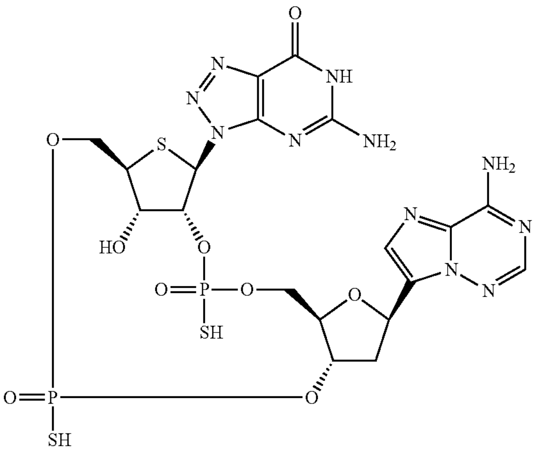
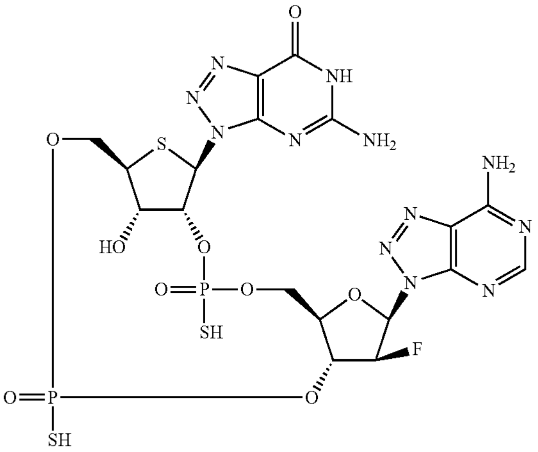
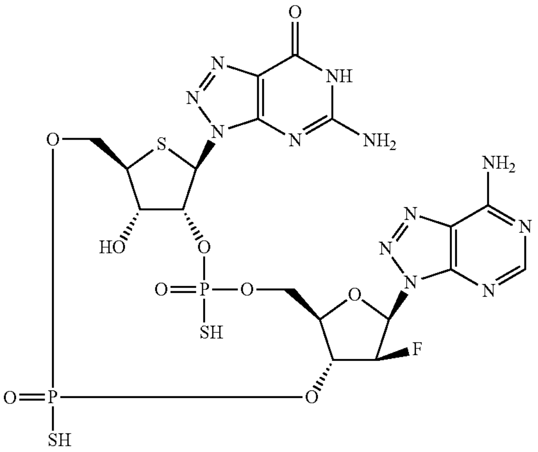
Ex.	Structure	Name	Mass [M − H]$^-$
111		5-amino-3-[(5R,7R,8R,12aR,14R,15aS,16S)-14-(4-aminoimidazo[2,1-f][1,2,4]triazin-7-yl)-16-hydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 1)	706
112		5-amino-3-[(5R,7R,8R,12aR,14R,15aS,16S)-14-(4-aminoimidazo[2,1-f][1,2,4]triazin-7-yl)-16-hydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 2)	706
113		5-amino-3-[(5R,7R,8R,12aR,14R,15aS,16S)-14-(4-aminoimidazo[2,1-f][1,2,4]triazin-7-yl)-16-hydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 3)	706

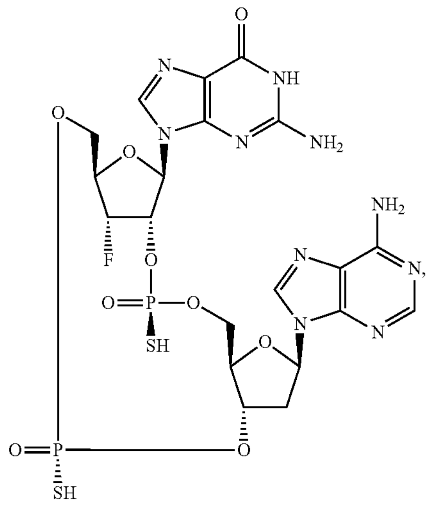
TABLE 5-continued

Ex.	Structure	Name	Mass [M − H]$^-$
114		5-amino-3-[(5R,7R,8R,12aR,14R,15aS,16S)-14-(4-aminoimidazo[2,1-f][1,2,4]triazin-7-yl)-16-hydroxy-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 4)	706
115		5-amino-3-[(5R,7R,8R,12aR,14R,15S,15aR,16S)-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][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 1)	725
116		5-amino-3-[(5R,7R,8R,12aR,14R,15S,15aR,16S)-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][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 2)	725

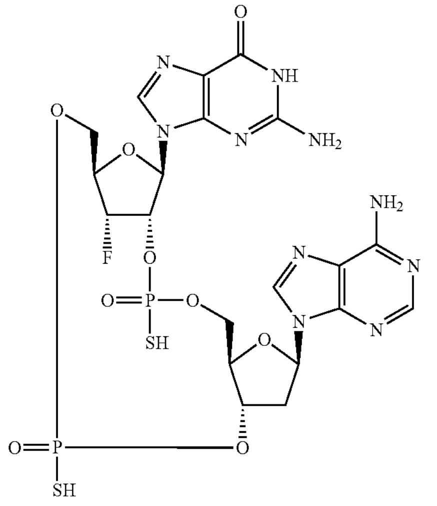
Examples 117 and 118: 2-amino-9-[(2R,5R,7R,8S,10R,12aR,14R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-16-fluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro [3,2-l][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 1) and 2-amino-9-[(5R,7R,8S,12aR,14R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-16-fluoro-2,10-dihydroxy-2,10-disulfidooctahydro-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 2)

[0680]

Diastereomer 1

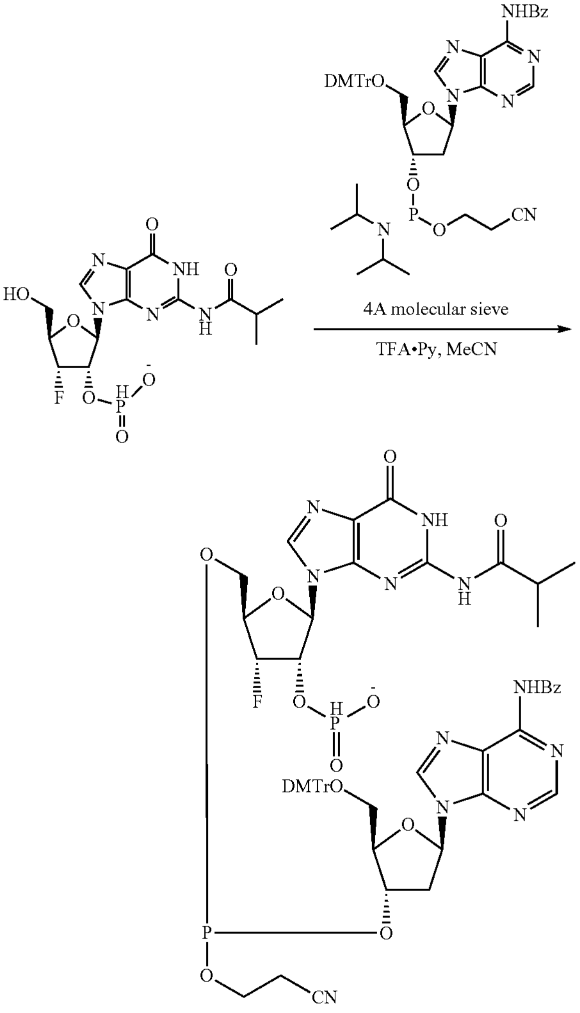


Diastereomer 2



Step 1: 2R,3S,4R,5R)-5-((((((2R,3S,5R)-5-(6-benzamido-9H-purin-9-yl)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphanyl)oxy)methyl)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate

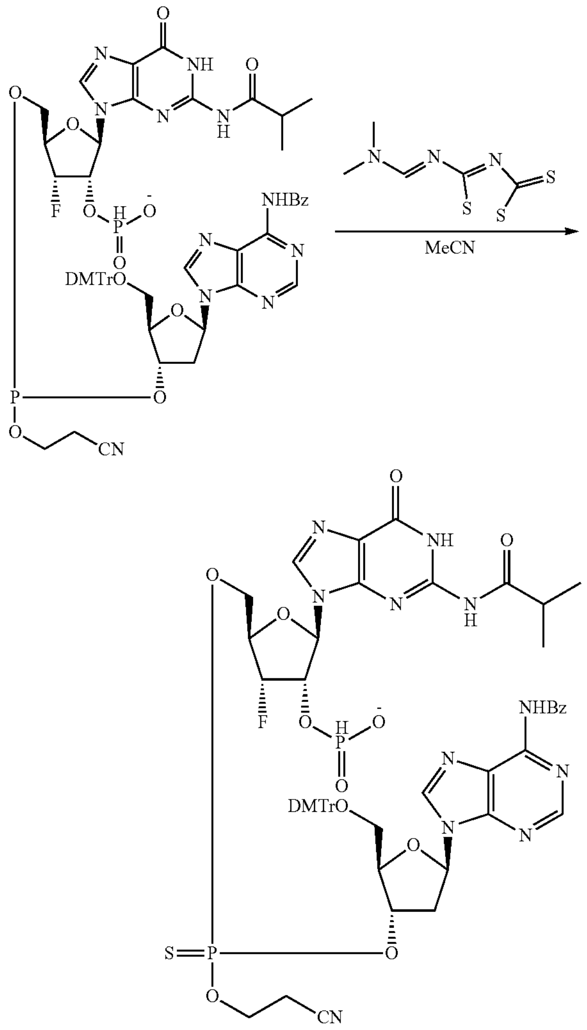
[0681]



[0682] ((2R,3 S,5R)-5-(6-benzamido-9H-purin-9-yl)-2-((bis(4-methoxyphenyl)(phenyl)methoxy) methyl)tetrahydrofuran-3-yl (2-cyanoethyl) diisopropylphosphoramidite (1058 mg, 1.234 mmol) was co-evaporated with dry ACN (3×5 mL), re-dissolved in ACN (10 mL) under Ar, and dried by adding activated 4 Å molecular sieve (200 mg). (2R,3S,4R,5R)-4-fluoro-5-(hydroxymethyl)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate (430 mg, 1.03 mmol) and pyridinium 2,2,2-trifluoroacetate (298 mg, 1.54 mmol) were co-evaporated with ACN (3×5 mL) and then re-dissolved in ACN (10 mL), and dried by adding activated 4 Å molecular sieve (200 mg). After 30 min, it was added to the previously prepared mixture containing ((2R,3S,5R)-5-(6-benzamido-9H-purin-9-yl)-2-((bis(4-methoxyphenyl)(phenyl) methoxy)methyl) tetrahydrofuran-3-yl (2-cyanoethyl) diisopropylphosphoramidite. It was stirred at rt for 30 min. The reaction mixture was used for the next reaction step without purification. LCMS (ES, m/z): 1173.8 $[M-H]^-$.

Step 2. (2R,3S,4R,5R)-5-((((((2R,3S,5R)-5-(6-benzamido-9H-purin-9-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 phosphonate

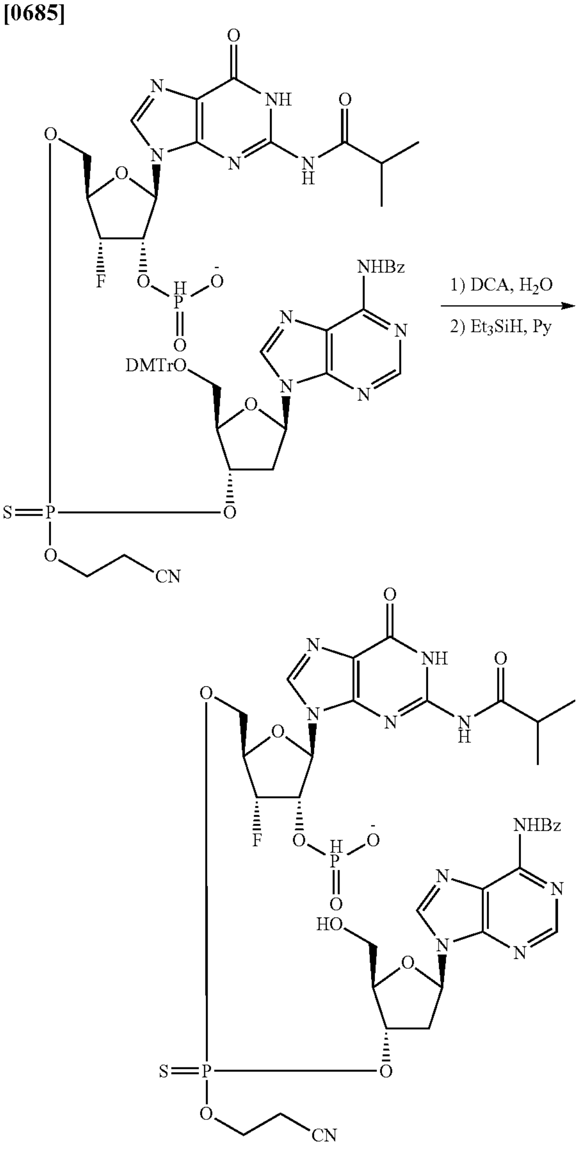
[0683]



[0684] To the reaction mixture from Step 1 was added (E)-N,N-dimethyl-N'-(3-thioxo-3H-1,2,4-dithiazol-5-yl)formimidamide (DDTT, 0.232 g, 1.13 mmol) in one portion. The mixture was stirred at rt for 1 h. It was concentrated to give a crude sample containing the product, which was used for the next reaction step without purification. LCMS (ES, m/z): 1205.8 $[M-H]^-$.

Step 3. (2R,3S,4R,5R)-5-((((((2R,3S,5R)-5-(6-benzamido-9H-purin-9-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 phosphonate

[0685]

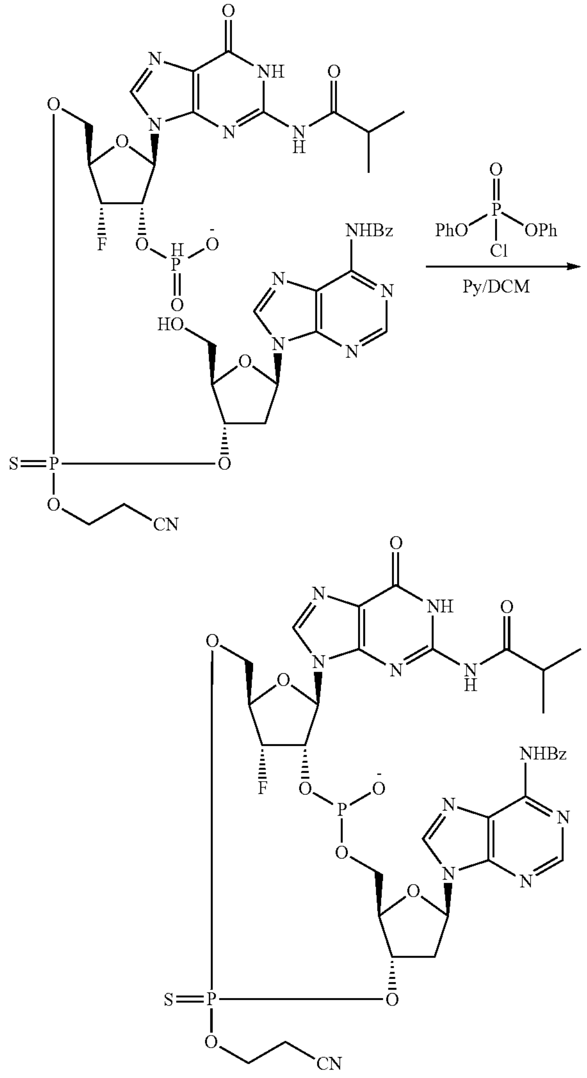


[0686] To a solution of the crude from Step 2 in CH_2Cl_2 (15 mL) was added water (0.2 mL, 10 mmol) and 2,2-dichloroacetic acid in CH_2Cl_2 (0.6M, 15 mL, 9 mmol). After 30 min, triethylsilane (28 mL) was added, and it was stirred for 1.5 h. Then, pyridine (1.4 mL) was added. It was concentrated, and the residue was purified by reverse phase (C18) chromatography eluted with 0 to 43% ACN in aq NH_4HCO_3 (5 mM) to give the product. LCMS (ES, m/z): 905.8 $[M+H]^+$. ^{1}H-NMR (300 MHz, CD_3OD): δ 8.71-8.44 (m, 2H), 8.21-8.03 (m, 3H), 7.80 (d, J=10.4 Hz, 0.5H), 7.66-7.61 (m, 1H), 7.54 (t, J=7.6 Hz, 2H), 6.61-6.42 (m, 1H), 6.14 (dd, J=13.2, 6.0 Hz, 1H), 5.68 (d, J=9.9 Hz, 0.5H), 5.60-5.19 (m, 3H), 4.69-4.36 (m, 3H), 4.36-4.17 (m, 3H), 3.92-3.64 (m, 2H), 3.13-2.55 (m, 5H), 1.19 (dd, J=6.9, 2.1

Hz, 6H). ^{19}F-NMR (282 MHz, CD_3OD): δ −202.55, −202.75 (d, 1F). ^{31}P-NMR (121 MHz, CD_3OD): δ 66.91, 66.69 (2s, 1P); 2.66, 2.60 (2s, 1P).

Step 4: (5R,7R,8S,12aR,14R,15aS,16R)-2-(2-cyanoethoxy)-16-fluoro-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-10-olate 2-sulfide

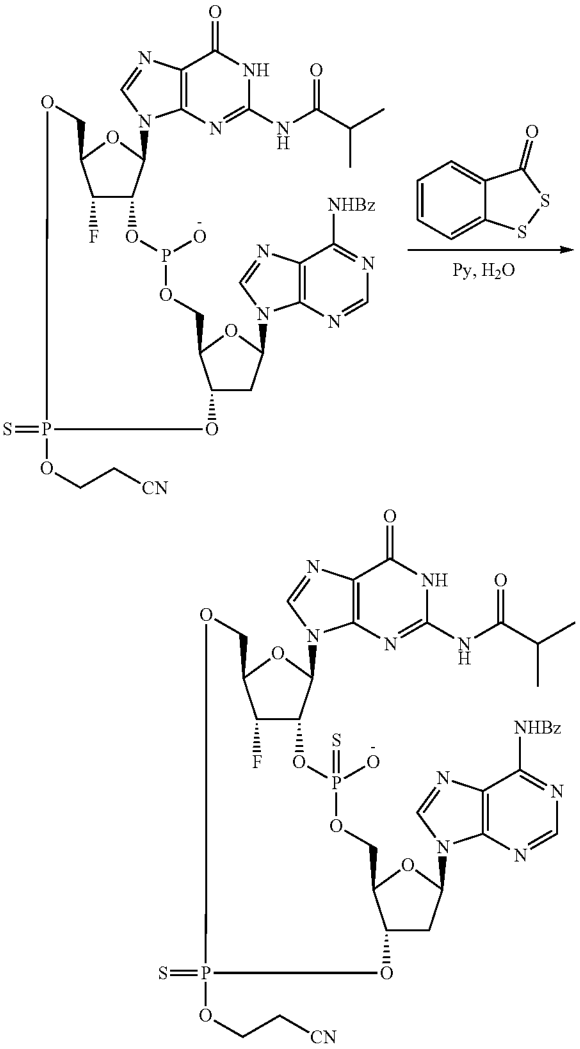
[0687]



[0688] Diphenyl phosphorochloridate (2375 mg, 8.84 mmol) was added to pyridine (45 ml) at −30° C. To the solution at −30° C. was added (2R,3S,4R,5R)-5-((((((2R,3S,5R)-5-(6-benzamido-9H-purin-9-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 phosphonate (400 mg, 0.44 mmol) in CH_2Cl_2 (45 mL) dropwise over 20 min. The resulting mixture was stirred at −30° C. for 40 min. The reaction mixture was used for the next reaction step immediately without purification. LCMS (ES, m/z): 887.8 $[M+H]^+$.

Step 5: (5R,7R,8S,12aR,14R,15aS,16R)-2-(2-cyanoethoxy)-16-fluoro-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-10-olate 2,10-disulfide

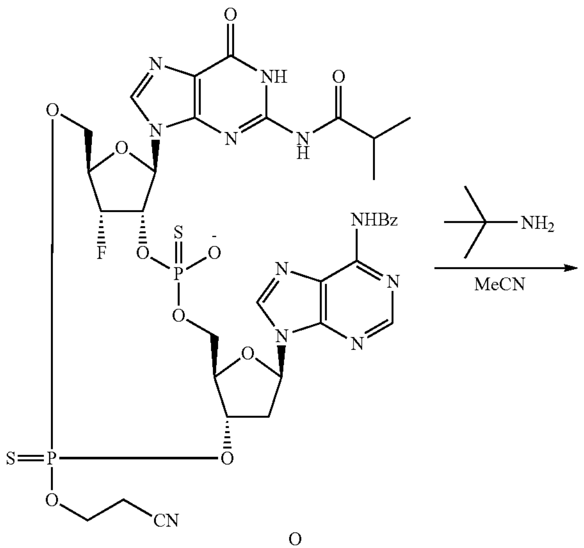
[0689]

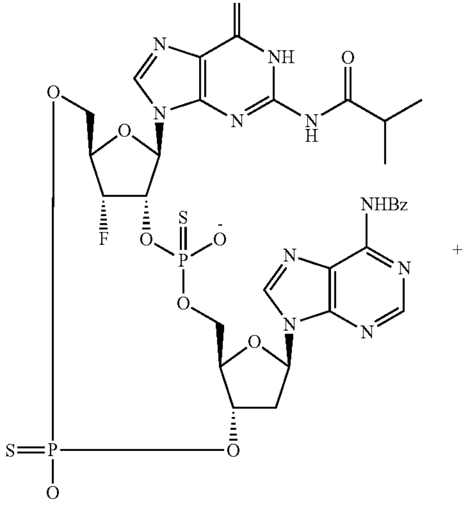


[0690] To the mixture from Step 4 at −30° C. was added 3H-benzo[c][1,2]dithiol-3-one (112 mg, 0.663 mmol) and water (279 μL, 15.5 mmol). After stirring at rt for 1 h, the mixture was poured into a solution of $Na_2S_2O_3.5H_2O$ (280 mg) in water (10 mL) at 0° C. It was stirred at rt for 5 min, and the mixture was concentrated under reduced pressure. The residue was purified by reverse phase (C18) chromatography eluted with 0 to 28% ACN in aq NH_4HCO_3 (5 mM) to give the product. LCMS (ES, m/z): 919.8 $[M+H]^+$. ^{19}F-NMR (376 MHz, CD_3OD): δ −198.51, −198.98,-200.16 (3s, 1F).]$^+$. ^{31}P-NMR (162 MHz, CD_3OD): δ 65.90, 65.09, 63.64, 62.95, 57.26, 56.50 (6s, 2P).

Step 6. Diastereomers (5R,7R,8S,12aR,14R,15aS,16R)-16-fluoro-7-{2-[(2-methylpropanoyl) amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-2,10-diolate 2,10-disulfide (28-6-A), (5R,7R,8S,12aR,14R,15aS,16R)-16-fluoro-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}octahydro-12H-5,8-methanofuro[3,2-l]1,3,6,9,11,2,10 pentaoxadiphosphacyclotetradecine-2,10-diolate 2,10-disulfide (28-6-B), and (5R,7R,8S,12aR,14R,15aS,16R)-16-fluoro-7-{2-[(2-methylpropanoyl) amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecine-2,10-diolate 2,10-disulfide (28-6-C)

[0691]





28-6-A

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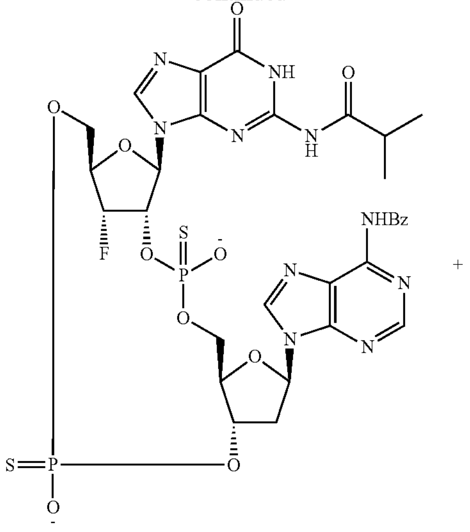
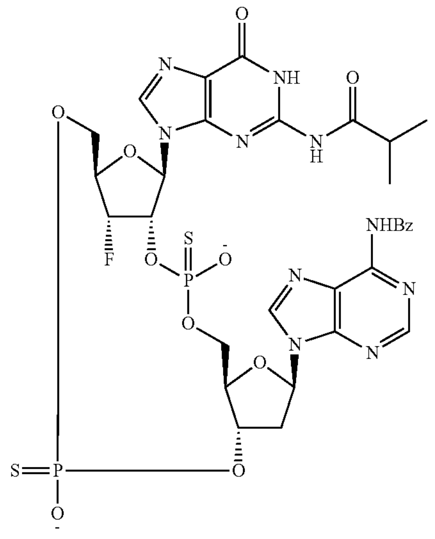


28-6-B



28-6-C

[0692] To a solution of (5R,7R,8 S,12aR,14R,15aS,16R)-2-(2-cyanoethoxy)-16-fluoro-7-{2-[(2-methylpropanoyl) amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecin-10-olate 2,10-disulfide (265 mg, 0.288 mmol) in ACN (5 mL) at rt was added tert-butylamine (5 mL, 0.29 mmol). The reaction mixture was stirred for 10 min. Then, volatile components were removed under reduced pressure. The residue was purified by preparative-HPLC (T3 Prep Column, 19 mm×250 mm) eluted with 5 to 20% ACN in aq NH_4HCO_3 (50 mM) over 21 min.

[0693] The first fractions (T_R: 8.95 min) gave (5R,7R,8S,12aR,14R,15aS,16R)-16-fluoro-7-{2-[(2-methylpropanoyl) amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecine-2,10-diolate 2,10-

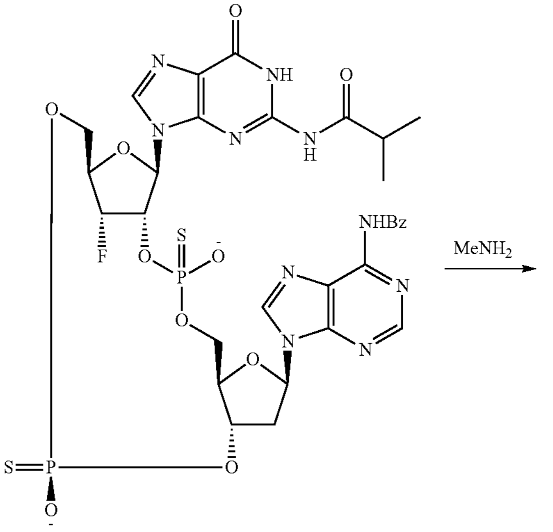
disulfide (28-6-A). LCMS (ES, m/z): 866.7 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.74 (s, 1H), 8.71 (s, 1H), 8.26 (s, 1H), 8.07 (d, J=7.5 Hz, 1H), 7.65 (d, J=7.7 Hz, 1H), 7.57 (t, J=7.5 Hz, 2H), 6.60-6.34 (m, 1H), 5.94 (d, J=8.6 Hz, 1H), 5.91-5.66 (m, 1H), 5.46-5.16 (m, 2H), 4.50 (d, J=27.0 Hz, 1H), 4.27 (d, J=9.8 Hz, 1H), 4.16 (t, J=10.1 Hz, 1H), 3.98 (q, J=11.0 Hz, 1H), 3.86 (d, J=11.9 Hz, 1H), 3.72-3.69 (m, 1H), 3.10-3.06 (m, 1H), 3.00-2.82 (m, 1H), 2.74-2.70 (m, 1H), 1.06 (dd, J=27.2, 6.8 Hz, 6H). ^{31}P-NMR (162 MHz, DMSO-d_6): δ 53.92 (s, 1P), 52.99 (s, 1P).

[0694] The second fractions (T_R: 10.00 min) gave (5R,7R,8S,12aR,14R,15aS,16R)-16-fluoro-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl) amino]-9H-purin-9-yl}octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecine-2,10-diolate 2,10-disulfide (28-6-B). LCMS (ES, m/z): 866.7 $[M+H]^+$.

[0695] The third fractions (T_R: 11.27-12.16 min) gave (5R,7R,8S,12aR,14R,15aS,16R)-16-fluoro-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecine-2,10-diolate 2,10-disulfide (28-6-C), a mixture of two diastereomers, which was used in next step. LCMS (ES, m/z): 866.7 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.77 (s, 1H), 8.74 (s, 1H), 8.72 (s, 1H), 8.12-8.02 (m, 2H), 7.66-7.64 (m, 1H), 7.56 (t, J=7.5 Hz, 2H), 6.47-6.44 (m, 1H), 5.99 (d, J=8.6 Hz, 1H), 5.55-5.33 (m, 2H), 5.22 (d, J=11.6 Hz, 1H), 4.47 (d, J=25.7 Hz, 1H), 4.43-4.40 (m, 1H), 4.03-3.98 (m, 2H), 3.84 (d, J=11.8 Hz, 1H), 3.75-3.72 (m, 1H), 3.18-3.15 (m, 1H), 2.82-2.73 (m, 2H), 1.13 (dd, J=6.9, 2.5 Hz, 6H). ^{31}P-NMR (162 MHz, DMSO): δ 53.42 (s, 1P), 52.16 (s, 1P).

Step 7: 2-amino-9-[(5R,7R,8S,12aR,14R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-16-fluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomers 1 and 2)

[0696]



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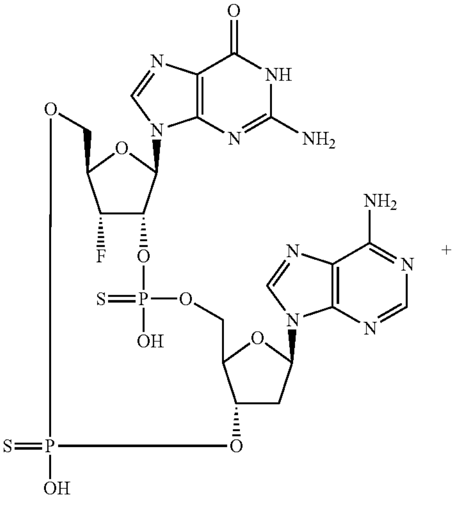
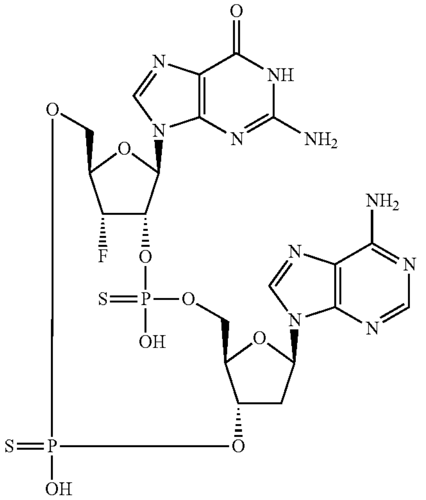


Diastereomer 1



Diastereomer 2

[0697] (5R,7R,8S,12aR,14R,15aS,16R)-16-fluoro-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecine-2,10-diolate 2,10-disulfide (28-6-C) (180 mg, 0.208 mmol) was dissolved in a solution of $MeNH_2$ in EtOH (30%, 5.0 mL, 42 mmol), and the resulting solution was stirred at rt for 1 h. The volatile components were removed under reduced pressure to give a crude sample that was purified by Prep-HPLC (Atlantis Prep T3 OBD Column, 19 mm×250 mm) eluted with 5 to 19.5% ACN in aq NH_4HCO_3 (50 mM) over 19 min to give, after concentration:

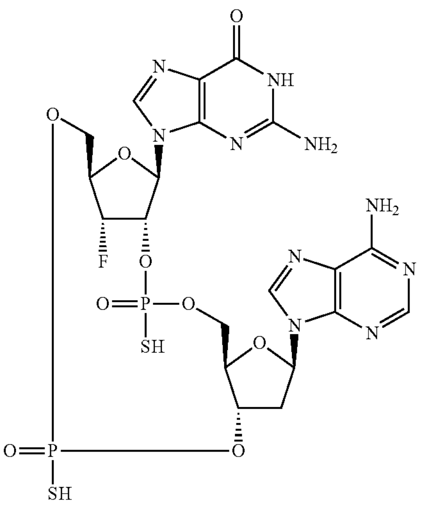
[0698] Example 117 (T_R: 14.82 min): 2-amino-9-[(2R,5R,7R,8S,10R,12aR,14R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-16-fluoro-2,10-dihydroxy-2,10-disulfidooctahydro-

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). LCMS (ES, m/z): 690.8 $[M-H]^-$. ^{1}H-NMR (400 MHz, D_2O): δ 8.14 (s, 1H), 8.13 (s, 1H), 8.11 (s, 1H), 6.37 (t, J=5.5 Hz, 1H), 5.99 (d, J=8.7 Hz, 1H), 5.54 (d, J=3.3 Hz, 0.5H), 5.48-5.30 (m, 1.5H), 5.12 (dd, J=10.2, 5.5 Hz, 1H), 4.66 (d, J=34.1 Hz, 1H), 4.36 (s, 1H), 4.24-4.01 (m, 4H), 3.04 (dt, J=14.1, 5.6 Hz, 1H), 2.79 (dt, J=13.5, 6.4 Hz, 1H). ^{19}F-NMR (376 MHz, D_2O): δ −198.66 (s, 1F). ^{31}P-NMR (162 MHz, D_2O): δ 53.97 (s, 1P), 53.46 (s, 1P).

[0699] Example 118 (T_R: 15.93 min): 2-amino-9-[(5R,7R,8 S,12aR,14R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-16-fluoro-2,10-dihydroxy-2,10-disulfidooctahydro-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 2). LCMS (ES, m/z): 690.8 $[M-H]^-$. ^{1}H-NMR (400 MHz, D_2O): δ 8.16 (s, 1H), 8.11 (s, 1H), 7.83 (s, 1H), 6.34 (dd, J=6.5, 3.0 Hz, 1H), 5.95 (d, J=8.6 Hz, 1H), 5.69-5.53 (m, 1H), 5.47 (d, J=3.4 Hz, 0.5H), 5.33 (d, J=3.4 Hz, 0.5H), 5.23 (p, J=7.3 Hz, 1H), 4.64 (d, J=26.7 Hz, 1H), 4.35 (ddd, J=10.6, 6.9, 3.2 Hz, 1H), 4.31-4.17 (m, 2H), 4.05-3.95 (m, 2H), 2.94-2.85 (m, 1H), 2.74 (dt, J=14.0, 7.2 Hz, 1H). ^{19}F-NMR (376 MHz, D_2O): δ −198.74 (s, 1F). ^{31}P-NMR (162 MHz, D_2O): δ 55.05 (s, 1P), 52.87 (s, 1P).

Example 119: 2-amino-9-[1(5R,7R,8S,12aR,14R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-16-fluoro-2,10-dihydroxy-2,10-disulfidooctahydro-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 3)

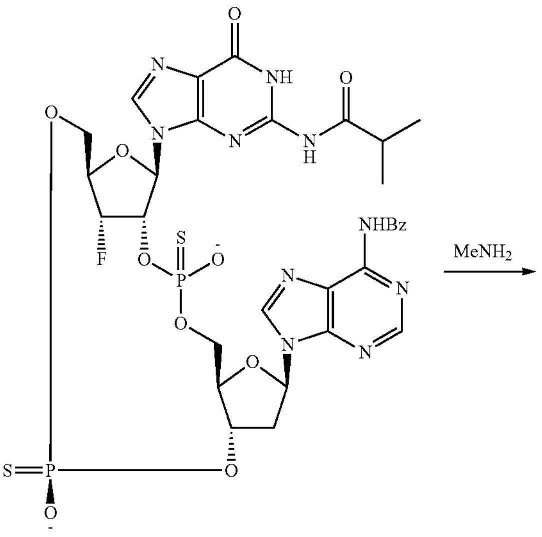
[0700]



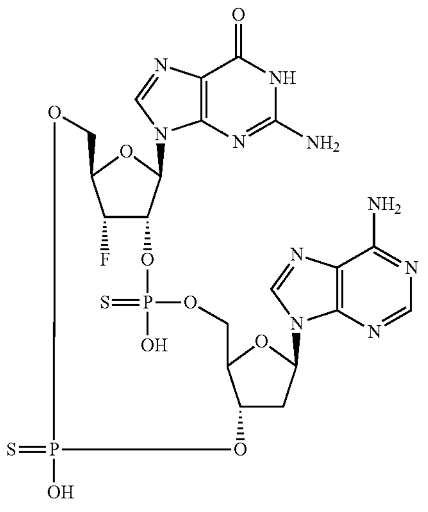
Diastereomer 3

Step 1: 2-amino-9-[(5R,7R,8S,12aR,14R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-16-fluoro-2,10-dihydroxy-2,1-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one

[0701]



28-6-B



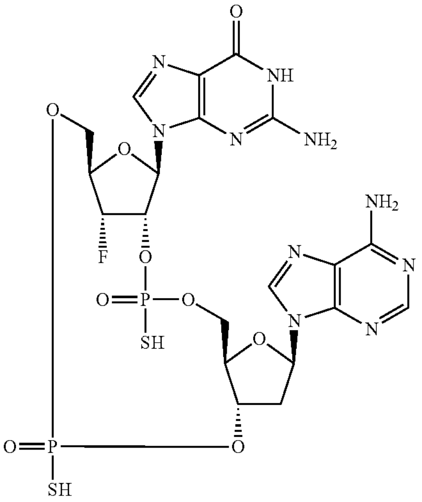
Diastereomer 3

[0702] (5R,7R,8S,12aR,14R,15aS,16R)-16-fluoro-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-2,10-diolate 2,10-disulfide (28-6-B) (45 mg, 0.053 mmol) was dissolved in a solution of $MeNH_2$ in EtOH (30%, 1.5 mL, 11 mmol), and the resulting solution was stirred at rt for 1 h. The volatile components were removed under reduced pressure, and the residue was purified by Prep-HPLC (Atlantis Prep T3 OBD Column, 19 mm×250 mm) eluted with 18 to 19.5% ACN in aq NH_4HCO_3 (50 mM) over 16 min to give the product (T_R: 11.22 min). LCMS (ES, m/z): 690.8 $[M-H]^-$. ^{1}H-NMR (400 MHz, D_2O): δ 8.32 (s, 1H), 8.15 (s, 1H), 7.96 (s, 1H), 6.41 (t, J=5.7 Hz, 1H), 6.00 (d, J=8.6 Hz, 1H), 5.56 (dt, J=22.9, 10.4 Hz, 1H), 5.40-5.30 (m, 1.5H), 5.19 (d, J=3.6 Hz, 0.5H), 4.64 (d, J=28.3 Hz, 1H), 4.40-4.27 (m, 2H), 4.27-4.17 (m, 1H), 4.02 (d, J=11.9 Hz, 1H), 3.95-3.85 (m, 1H), 2.92 (dt, J=14.1, 5.6 Hz, 1H), 2.79 (td, J=13.8, 13.1, 6.1 Hz, 1H). ^{19}F-NMR (376 MHz, D_2O): δ −198.02 (s, 1F). ^{31}P-NMR (162 MHz, D_2O): δ 57.89 (s, 1P), 55.05 (s, 1P).

Example 120: 2-amino-9-[(5R,7R,8S,12aR,14R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-16-fluoro-2,10-dihydroxy-2,10-disulfidooctahydro-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 4)

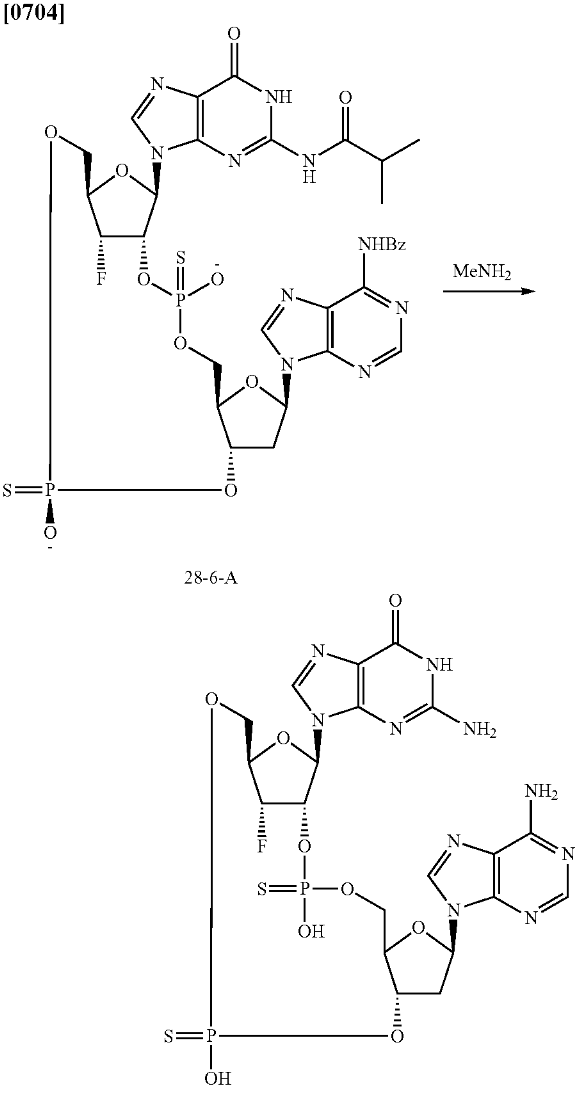
[0703]

Diastereomer 4



Step 1: 2-amino-9-[(5R,7R,8S,12aR,14R,15aS,16R)-14-(6-amino-9H-purin-9-yl)-16-fluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one

[0704]



28-6-A

Diastereomer 4

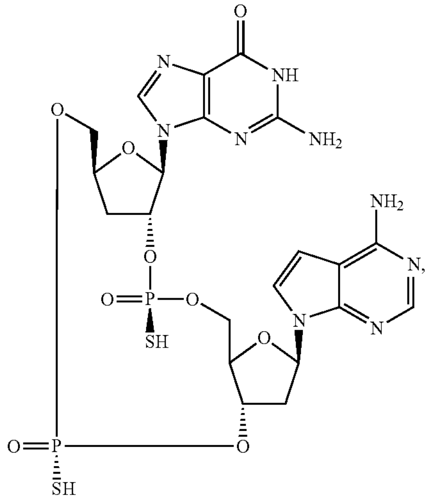
[0705] (5R,7R,8S,12aR,14R,15aS,16R)-16-fluoro-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-2,10-diolate 2,10-disulfide (28-6-A) (45 mg, 0.053 mmol) was dissolved in a solution of $MeNH_2$ in EtOH (30%, 1.5 mL, 11 mmol), and the resulting solution was stirred at rt for 1 h. The volatile components were removed under reduced pressure, and the residue was purified by Prep-HPLC (Atlantis Prep T3 OBD Column, 19 mm×250 mm) eluted with 4 to 11% ACN in aq NH_4HCO_3 (50 mM) over 17 min to give the product (T_R: 11.72 min). LCMS (ES, m/z): 690.8 $[M-H]^-$. ^{1}H-NMR (400 MHz, D_2O): δ 8.33 (s, 1H), 8.29 (s, 1H), 8.16 (s, 1H), 6.41 (t, J=6.5 Hz, 1H), 6.05 (d, J=8.6 Hz, 1H), 5.49-5.32 (m, 1.5H), 5.23 (d, J=3.5 Hz, 0.5H), 4.79-4.73 (m, 1H), 4.69-

4.59 (m, 1H), 4.40-4.32 (m, 1H), 4.23 (q, J=8.9, 7.5 Hz, 2H), 4.07 (d, J=11.8 Hz, 1H), 3.94-3.84 (m, 1H), 3.00 (dt, J=12.7, 6.2 Hz, 1H), 2.94-2.84 (m, 1H). ^{19}F-NMR (376 MHz, D_2O): δ −197.92 (s, 1F). ^{31}P-NMR (162 MHz, D_2O): δ 59.46 (s, 1P), 54.42 (s, 1P).

Example 121, 122,123: 2-amino-9-[(2R,5S,7R,8R,10R,12aR,14R,15aS)-14-(4-amino-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) and 2-amino-9-[(5S,7R,8R,12aR,14R,15aS)-14-(4-amino-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 (Diastereomers 2 and 3)

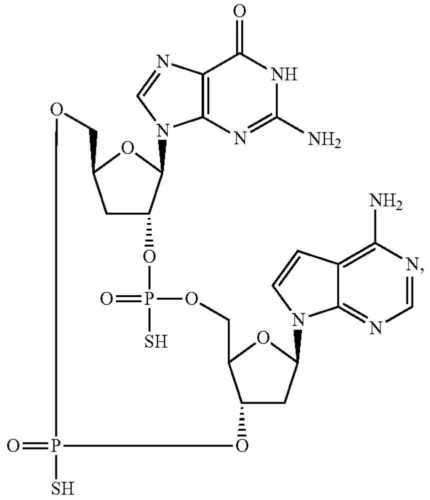
[0706]

Diastereomer 1

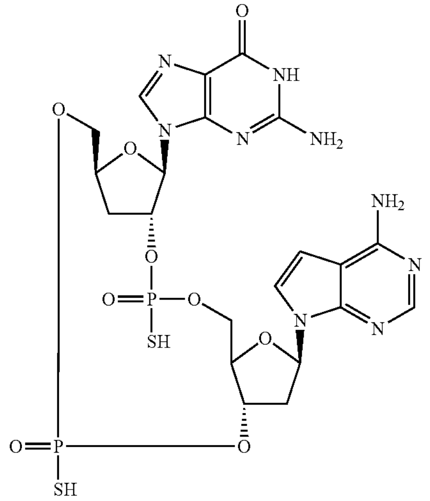


-continued

Diastereomer 2

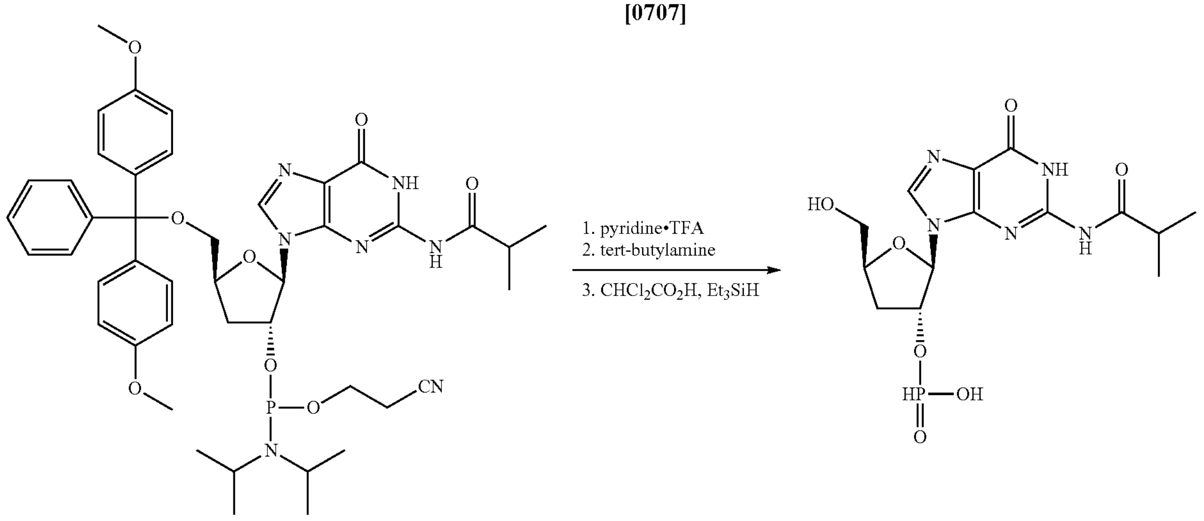


Diastereomer 3



Step 1: (2R,3R,5S)-5-(hydroxymethyl)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl hydrogen phosphonate

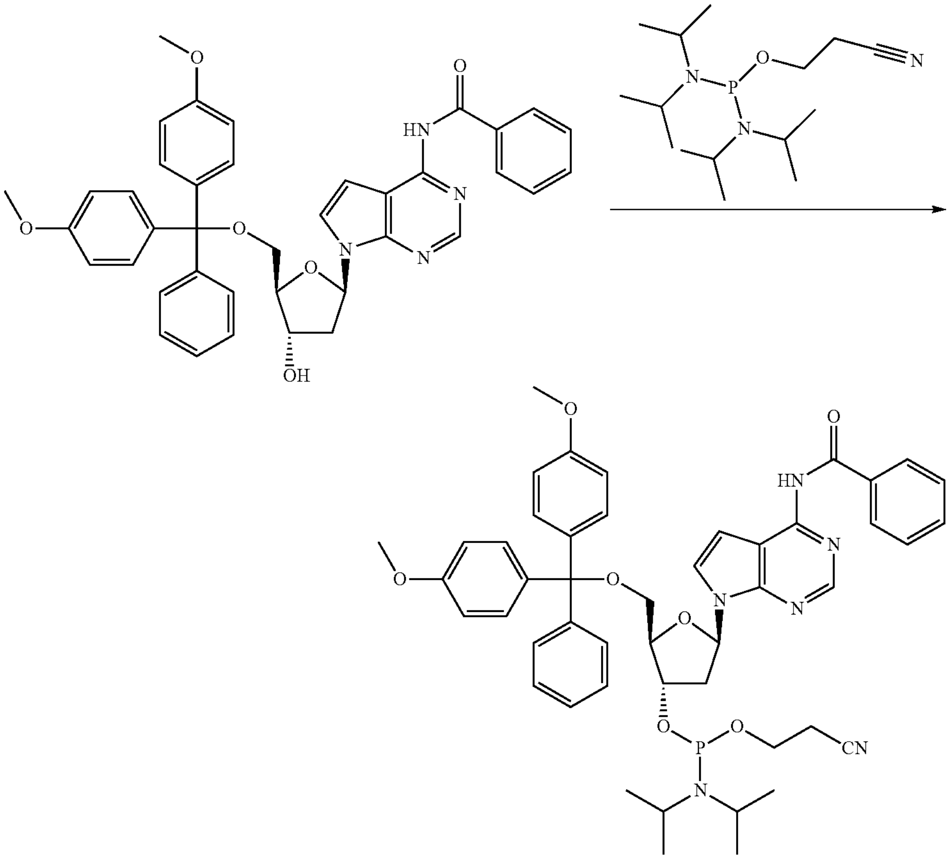
[0707]



[0708] To a flask was added (2R,3R,5 S)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl (2-cyanoethyl) diisopropylphosphoramidite (4 g, 4.76 mmol), MeCN (23.65 ml), and water (0.158 ml). Pyridine trifluoroacetate (1.104 g, 5.71 mmol) was then added, and the mixture was stirred 1 h at rt, after which time tert-butylamine (20.02 ml, 190 mmol) was added. After stirring 1 h at rt, the mixture was concentrated under reduced pressure. The resulting mixture was dissolved in DCM (39.9 ml), and then water (0.798 ml) was added, followed by dichloroacetic acid (2.75 ml, 33.3 mmol). The solution was stirred for 20 min at rt, and then triethylsilane (133 ml, 833 mmol) was added, and the reaction was stirred for a further 2 h at rt. After cooling to 0° C., pyridine was added, and the mixture was concentrated under reduced pressure. The resulting sample was partitioned between hexanes (100 mL) and water (20 mL). The layers were separated, and the aqueous phase was purified by reverse phase HPLC using a gradient solvent system of 0-35% MeCN in 0.04% aq ammonium bicarbonate. The product-containing fractions were collected and lyophilized to give (2R,3R,5S)-5-(hydroxymethyl)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl hydrogen phosphonate. LCMS (ES, m/z): 400 $[M-H]^-$.

Step 2: (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

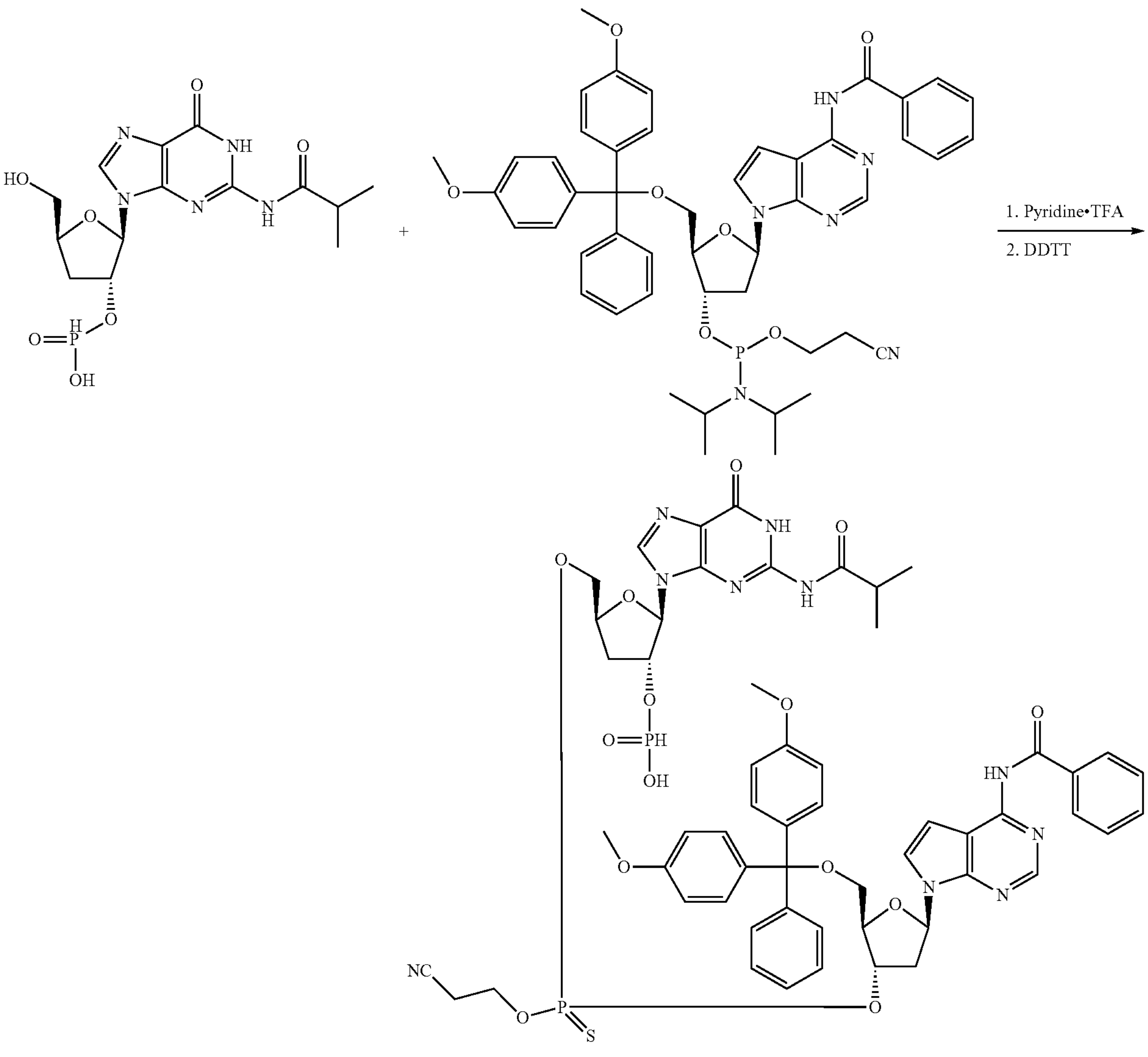
[0709]



[0710] 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 (4 g, 6.09 mmol), DCM (71.7 ml), and 4,5-dicyanoimidazole (2.158 g, 18.27 mmol), and the solution was cooled to 0° C. 2-Cyanoethyl N,N,N',N'-tetraisopropylphosphorodiamidite (6.77 ml, 21.32 mmol) was added, and the mixture was stirred for 15 min 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 hexanes 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 $[M+H]^-$.

Step 3: (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)phosphorothioyl) oxy)methyl)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl hydrogen phosphonate

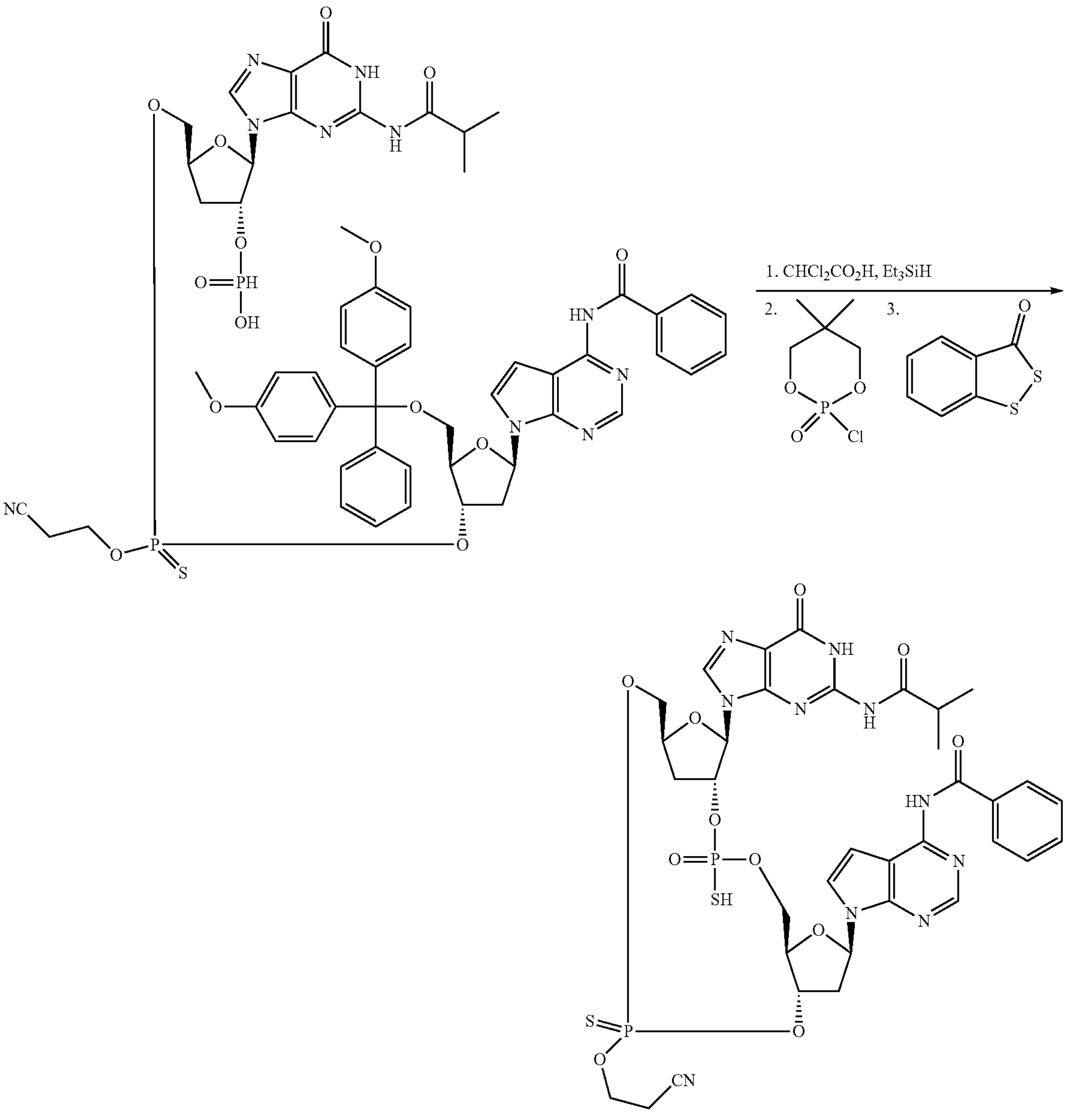
[0711]



[0712] To a flask containing (2R,3R,5S)-5-(hydroxymethyl)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl hydrogen phosphonate (1.62 g, 2.81 mmol) was added pyridine trifluoroacetate (0.543 g, 2.81 mmol), activated 4 Å sieves and MeCN (10 mL), and the mixture was stirred 20 min at rt. To a separate flask containing (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 (2.408 g, 2.81 mmol) was added MeCN (10 mL) and activated 4 Å sieves, and the mixture was stirred 20 min at rt, after which time the hydrogen phosphonate solution was added, and MeCN (2×4 mL) was used to complete the transfer. The mixture was stirred 1 h at rt, and then ((dimethylamino-methylidene)amino)-3H-1,2,4-dithiazoline-3-thione (0.634 g, 3.09 mmol) was added. The resulting mixture was stirred 30 min at rt and then concentrated under reduced pressure. Reverse phase HPLC purification using a gradient solvent system of 5-100% MeCN in 0.04% aqueous ammonium bicarbonate yielded (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) phosphorothioyl)oxy)methyl)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl) tetrahydrofuran-3-yl hydrogen phosphonate. LCMS (ES, m/z): 1187 $[M-H]^-$.

Step 4: N-{7-[(5S,7R,8R,12aR,14R,15aS)-2-(2-cyanoethoxy)-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-10-oxido-10-sulfanyl-2-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

[0713]

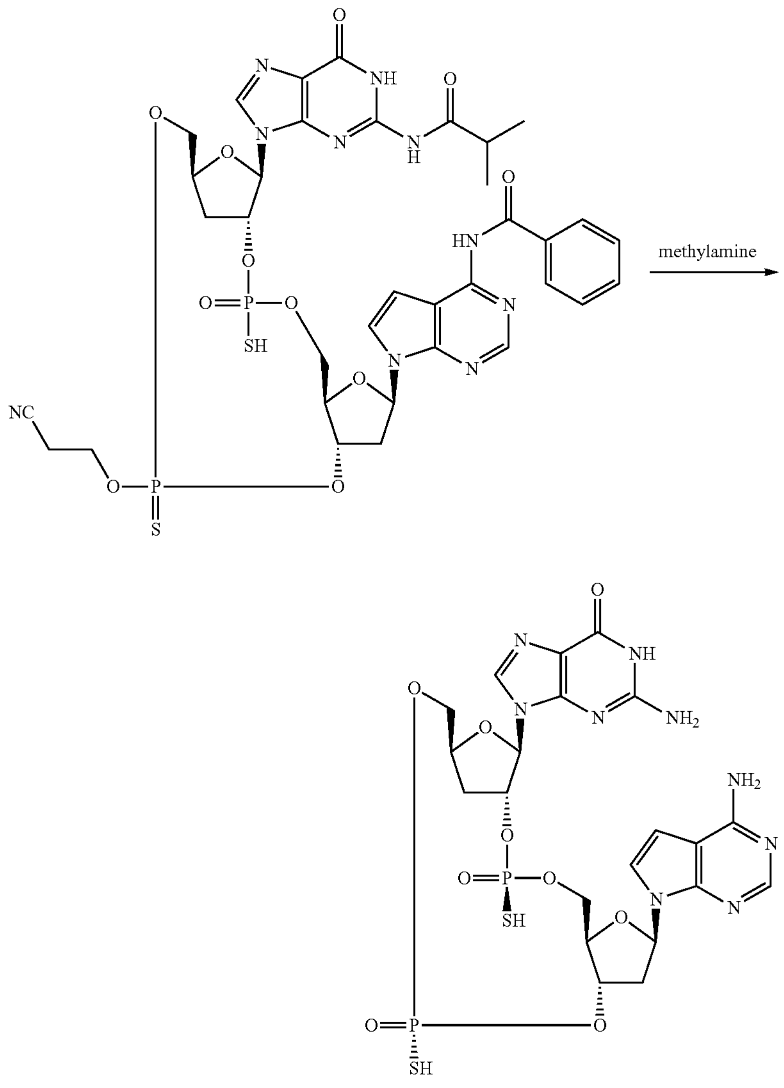


[0714] To a flask containing (2R,3R,5S)-5-((((((2R,3S,5R)-5-(4-benzamido-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphorothioyl)oxy)methyl)-2-(2-isobutyramido-6-oxo-1H-purin-9(6H)-yl)tetrahydrofuran-3-yl hydrogen phosphonate (1.34 g, 1.127 mmol) was added DCM (22.54 ml) and water (0.203 ml, 11.27 mmol), and then dichloroacetic acid (1.116 ml, 13.52 mmol) was added. The solution was stirred for 20 min at rt, and then triethylsilane (28.1 ml, 176 mmol) was added. After stirring 3 h at rt, the mixture was concentrated under reduced pressure. Pyridine (50 mL) was added, and then the mixture was concentrated under reduced pressure. This process was repeated 2×, and then pyridine (37.6 ml) was added, followed by 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane 2-oxide (0.624 g, 3.38 mmol). The resulting mixture was stirred for 1 h at rt, after which time water (610 μl, 33.8 mmol) was added, followed by 3H-1,2-benzodithiol-3-one

(285 mg, 1.692 mmol). The resulting mixture was stirred 30 min at rt and then concentrated under reduced pressure. HPLC purification using a gradient solvent system of MeCN in 100 mM aqueous triethylammonium acetate yielded 3 separate diastereomers of N-{7-[(5 S,7R,8R,12aR,14R,15aS)-2-(2-cyanoethoxy)-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl})-10-oxido-10-sulfanyl-2-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 after lyopholization, all of which showed LCMS (ES, m/z): 899 $[M-H]^-$.

Step 5: 2-amino-9-[(5S,7R,8R,12aR,14R,15aS)-14-(4-amino-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

[0715]



[0716] To a vial containing one diastereomer (slowest eluting) of N-{7-[(5 S,7R,8R,12aR,14R,15aS)-2-(2-cyanoethoxy)-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-10-oxido-10-sulfanyl-2-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 (122 mg, 0.135 mmol) was added methylamine (33% in EtOH) (2 mL, 16.07 mmol) and the resulting solution was stirred for 4 h at rt, after which time it was concentrated under reduced pressure. Purification by reverse phase HPLC using a gradient solvent system of MeCN in 100 mM aqueous triethylammonium acetate yielded Example 121, 2-amino-9-[(2R,5 S,7R,8R,10R,12aR,14R,15aS)-14-(4-amino-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). LCMS (ES, m/z): 672 $[M-H]^-$. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.54 (s, 1H), 8.01 (s, 1H), 7.86 (s, 1H), 7.29 (d, J=2.7 Hz, 1H), 6.97 (s, 2H), 6.60-6.53 (m, 3H), 6.44 (t, J=6.9 Hz, 1H), 5.73 (d, J=2.7 Hz, 1H), 4.95 (s, 1H), 4.80 (s, 1H), 4.38-4.27 (m, 2H), 3.97-3.91 (m, 2H), 3.90-3.82 (m, 1H), 3.64 (dt, J=16.1, 9.3 Hz, 1H), 2.69-2.63 (m, 1H), 2.63 (s, 12H), 2.60-2.54 (m, 3H), 2.22-2.13 (m, 1H), 1.01-0.94 (m, 18H).

[0717] The other diastereomers from Step 4 were treated in an analogous manner to produce two additional diastereomers of 2-amino-9-[(5 S,7R,8R,12aR,14R,15aS)-14-(4-amino-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:

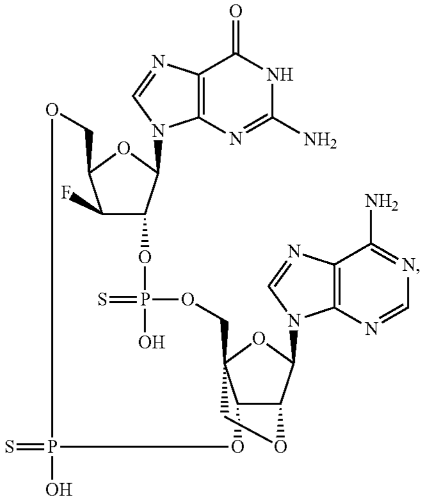
[0718] Example 122 (Diastereomer 2): LCMS (ES, m/z): 672 $[M-H]^-$. ^1H NMR (600 MHz, DMSO-d_6) δ 10.57 (s, 1H), 9.55 (s, 2H), 8.10 (s, 1H), 7.95 (s, 1H), 7.47 (s, 1H), 7.42 (d, J=3.2 Hz, 1H), 6.66 (d, J=3.4 Hz, 1H), 6.51 (s, 2H), 6.49-6.44 (m, 1H), 5.73 (d, J=4.0 Hz, 1H), 5.08-5.00 (m, 2H), 4.31-4.27 (m, 1H), 4.22 (t, J=11.3 Hz, 1H), 4.07 (q, J=10.6 Hz, 1H), 4.00-3.95 (m, 1H), 3.76-3.71 (m, 1H), 3.65 (td, J=11.6, 6.1 Hz, 1H), 3.02 (d, J=4.2 Hz, 12H), 2.67-2.61 (m, 1H), 2.61-2.53 (m, 2H), 2.18 (dt, J=11.7, 5.3 Hz, 1H), 1.12 (t, J=7.3 Hz, 18H).

[0719] Example 123 (Diastereomer 3): LCMS (ES, m/z): 672 $[M-H]^-$. ^1H NMR (600 MHz, DMSO-d_6) δ 10.53 (s, 1H), 8.01 (s, 3H), 7.28 (d, J=3.4 Hz, 1H), 6.97 (s, 2H), 6.56 (d, J=3.5 Hz, 1H), 6.49 (s, 2H), 6.44 (dd, J=8.6, 5.8 Hz, 1H), 5.70 (d, J=3.9 Hz, 1H), 5.00-4.92 (m, 1H), 4.90-4.83 (m, 1H), 4.33-4.27 (m, 1H), 4.12-3.96 (m, 4H), 3.81 (q, J=12.8, 11.6 Hz, 1H), 3.69 (dd, J=12.0, 6.0 Hz, 2H), 2.83-2.77 (m, 1H), 2.65 (d, J=37.6 Hz, 12H), 2.23 (dt, J=12.8, 6.7 Hz, 1H), 1.03-0.92 (m, 18H).

Examples 124, 125, and 126: 2-amino-9-[(5R,7R,8S,12aR,14R,15R,15aS,18S)-14-(6-amino-9H-purin-9-yl)-18-fluoro-2,10-dihydroxy-2,10-disulfidohexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7(12H)-yl]-1,9-dihydro-6H-purin-6-one (Diastereomers 1-3)

[0720]

Diastereomer 1



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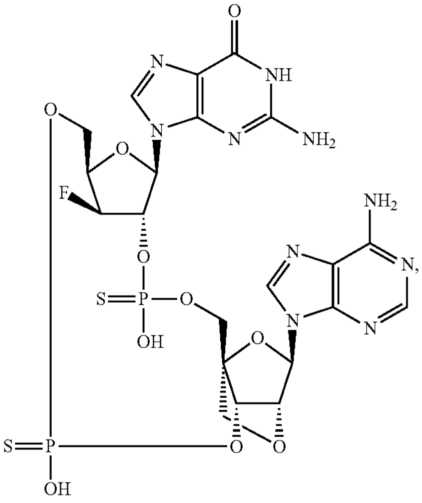
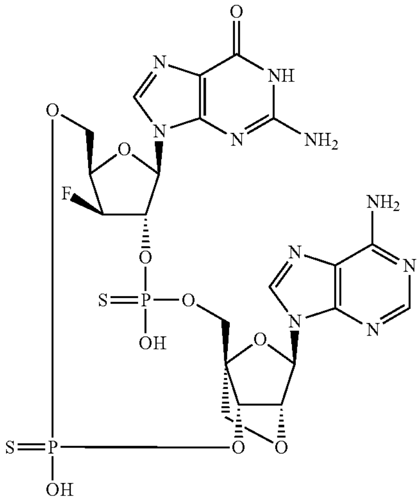
Diastereomer 2

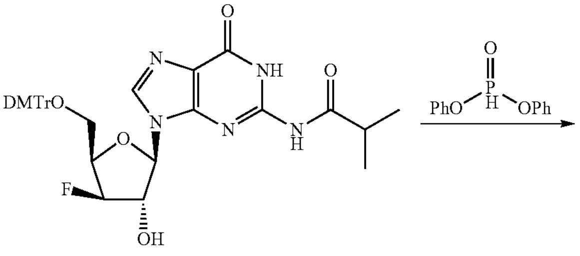


Diastereomer 3



Step 1: (2R,3S,4S,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

[0721]



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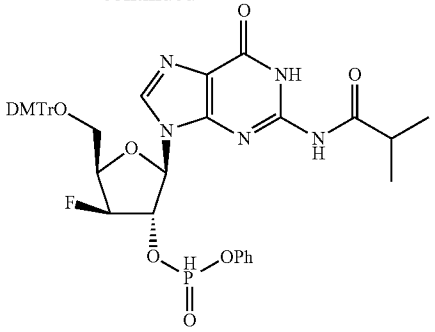
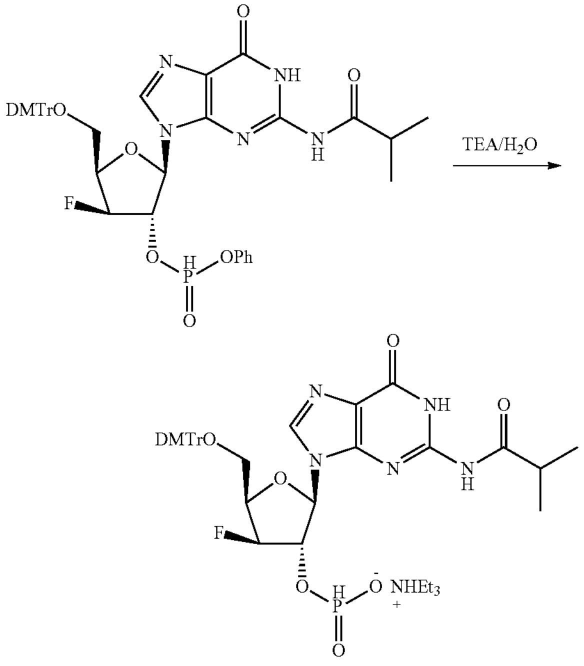


[0722] To a solution of N-(9-((2R,3 S,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy) methyl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide (630 mg, 0.96 mmol) in pyridine (5 mL) under Ar was added diphenyl phosphonate (1.07 g, 4.56 mmol), and the mixture was stirred at rt for 20 min. It was used for the next reaction step without purification. LCMS (ES, m/z): 798.3 [M+H]$^+$.

Step 2. t (2R,3S,4S,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

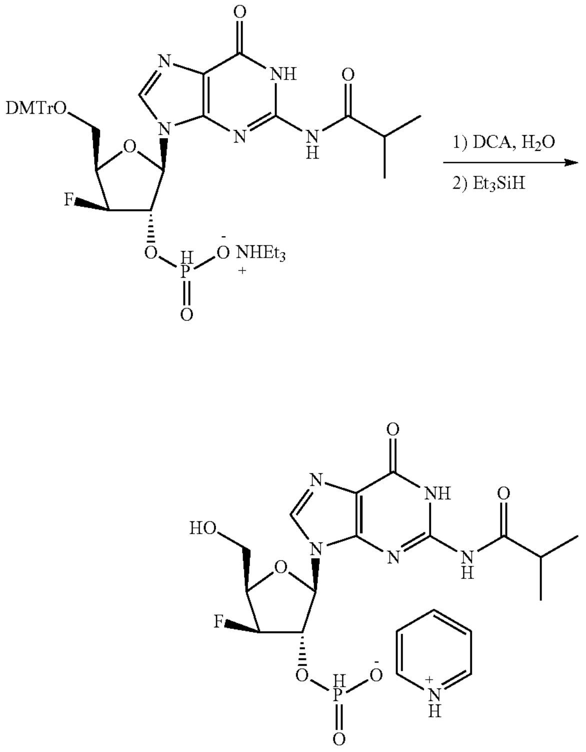
[0723]



[0724] To the reaction mixture from Step 1 at 0° C. was added water (1 mL), triethylamine (1 mL). The resulting mixture was stirred at rt for 20 min. Then, it was concentrated, and the residue was partitioned between CH_2Cl_2 (50 mL) and aq $NaHCO_3$ (5%, 20 mL). The organic layer was washed with aq $NaHCO_3$ (5%, 20 mL), dried ($Na_2S_2O_4$), concentrated and purified by silica gel column chromatography using 0-7% MeOH in CH_2Cl_2 (1% Et_3N) to give the product. LCMS (ES, m/z): 722.2 [M+H]$^+$. ^{1}H-NMR (400 MHz, CD_3OD): δ 7.76 (s, 1H), 7.74 (s, 0.5H), 7.51 (d, J=1.5 Hz, 1H), 7.48 (q, J=2.4, 1.9 Hz, 1H), 7.41-7.34 (m, 4H), 7.34-7.27 (m, 2H), 7.26-7.21 (m, 1H), 6.92-6.85 (m, 4H), 6.22 (s, 1H), 6.15 (s, 0.5H), 5.37 (d, J=2.7 Hz, 0.5H), 5.28-5.19 (m, 1.5H), 4.73-4.69 (m, 0.5H), 4.66-4.62 (m, 1H), 3.80 (s, 6H), 3.65-3.55 (m, 1H), 3.53-3.44 (m, 1H), 3.12 (q, J=7.3 Hz, 8H), 2.75 (p, J=6.8 Hz, 1H), 1.33-1.22 (m, 18H). ^{31}P-NMR: (162 MHz, CD_3OD): δ 2.67 (s, 1P).

Step 3. (2R,3S,4S,5R)-4-fluoro-5-(hydroxymethyl)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate

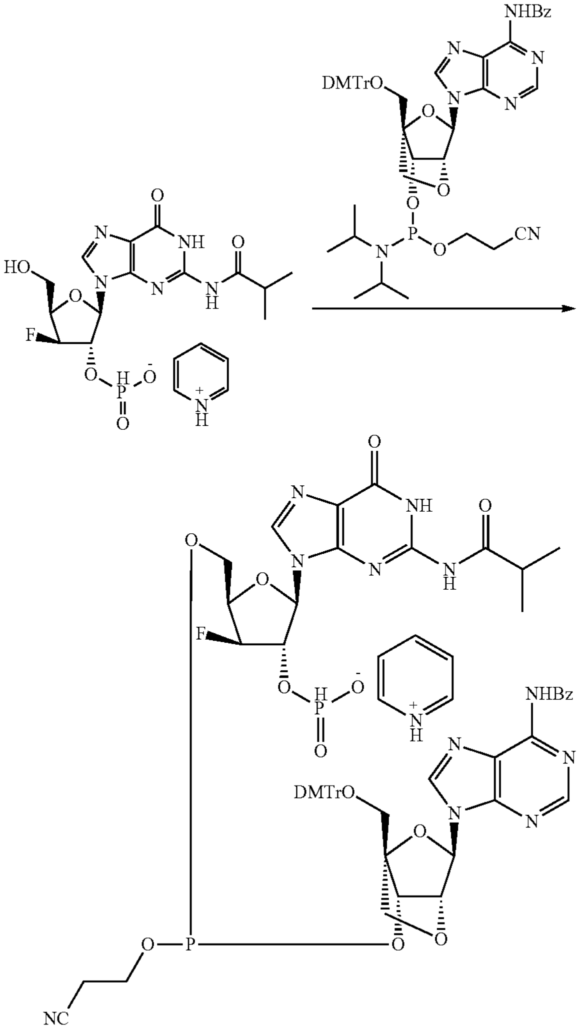
[0725]



[0726] To a stirred solution of (2R,3 S,4S,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 (540 mg, 0.64 mmol) in CH_2Cl_2 (7 mL) at rt was added water (0.115 g, 6.4 mmol) and 2,2-dichloroacetic acid in CH_2Cl_2 (6%, 7 mL, 5.76 mmol). The mixture was stirred at rt for 15 min, and then Et_3SiH (15 mL) was added. After 40 min, pyridine (0.90 mL) was added, and the mixture was stirred for 5 min. It was concentrated, and the residue was used for next reaction step without purification. LCMS (ES, m/z): 419.9 [M+H]$^+$.

Step 4. (2R,3S,4S,5R)-5-((((((1R,3R,4R,7S)-3-(6-benzamido-9H-purin-9-yl)-1-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-2,5-dioxabicyclo[2.2.2.1]heptan-7-yl)oxy)(2-cyanoethoxy)phosphanyl)oxy)methyl)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate

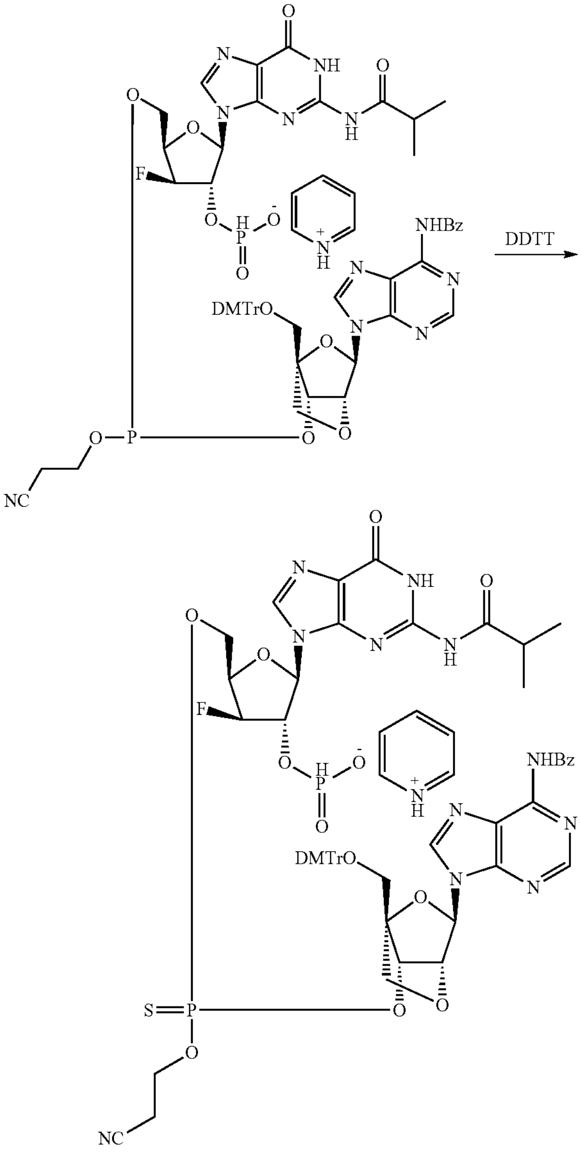
[0727]



[0728] The crude from Step 3 was co-evaporated with ACN (3×5 mL), re-dissolved in ACN (3 mL) under Ar, and dried by adding activated 4 Å molecular sieve (100 mg). (1R,3R,4R,7S)-3-(6-benzamido-9H-purin-9-yl)-1-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-2,5-dioxabicyclo[2.2.1]heptan-7-yl (2-cyanoethyl) diisopropylphosphoramidite (684.84 mg, 0.774 mmol) was co-evaporated with ACN (3×5 mL), re-dissolved in ACN (3 mL), and dried by adding activated 4 Å molecular sieve (100 mg). After 30 min, it was added to the previously prepared mixture containing pyridin-1-ium (2R,3 S,4S,5R)-4-fluoro-5-(hydroxymethyl)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate. The resulting mixture was stirred at rt for 30 min. Then it was used in the next reaction step without purification. LCMS (ES, m/z): 1202.1 $[M+H]^+$.

Step 5. (2R,3S,4S,5R)-5-((((((1R,3R,4R,7S)-3-(6-benzamido-9H-purin-9-yl)-1-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-2,5-dioxabicyclo[2.2.1]heptan-7-yl)oxy)(2-cyanoethoxy)phosphorothioyl)oxy)methyl)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate

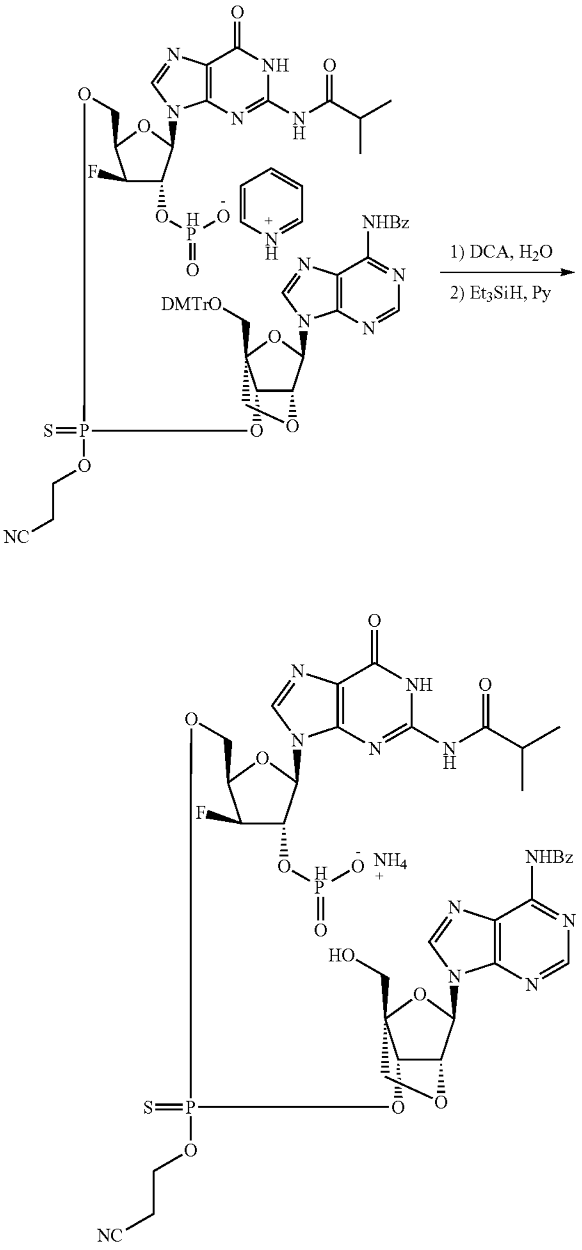
[0729]



[0730] To the mixture from Step 4 was added (E)-N,N-dimethyl-N'-(3-thioxo-3H-1,2,4-dithiazol-5-yl)formimidamide (144.32 mg, 0.704 mmol), and the mixture was stirred at rt for 30 min. Then, it was concentrated, and the crude was used for the next step without purification. LCMS (ES, m/z): 1234.3 $[M+H]^+$.

Step 6. (2R,3S,4S,5R)-5-((((((1S,3R,4R,7S)-3-(6-benzamido-9H-purin-9-yl)-1-(hydroxymethyl)-2,5-dioxabicyclo[2.2.1]heptan-7-yl)oxy)(2-cyanoethoxy)phosphorothioyl)oxy)methyl)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate

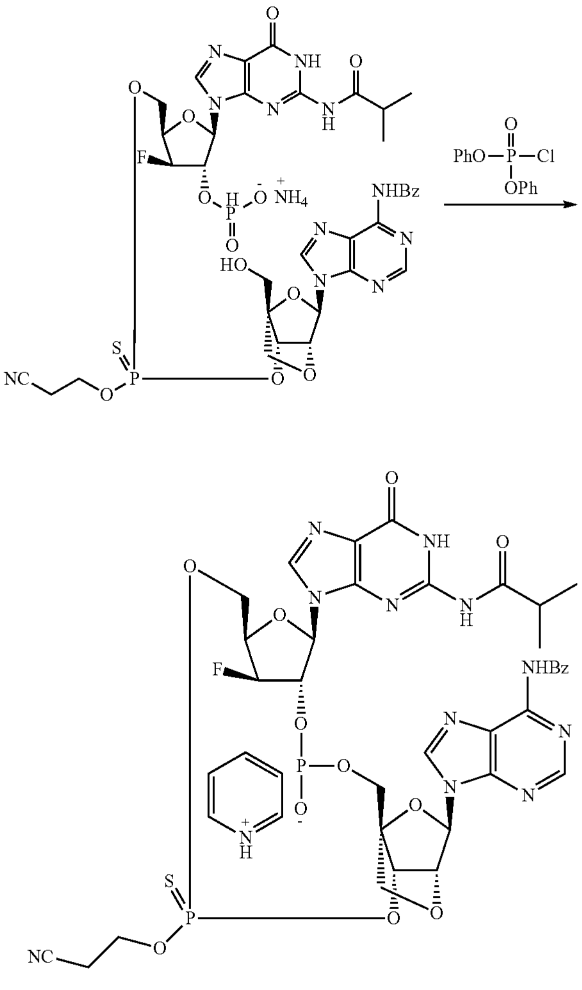
[0731]



[0732] To a solution of the crude from Step 5 in CH_2Cl_2 (7 mL) at rt was added water (120 mg, 6.4 mmol) and 2,2-dichloroacetic acid in CH_2Cl_2 (6%, 7 mL, 6 mmol). After 5 min, triethylsilane (15 mL) was added, and it was stirred for additional 2 h. Then, pyridine (0.9 mL) was added, and it was concentrated. 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): 933.9 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD): δ 8.74-8.64 (m, 1H), 8.58-8.52 (m, 1H), 8.16-8.06 (m, 2H), 7.98-7.88 (m, 1H), 7.75 (d, J=4.6 Hz, 0.5H), 7.67 (t, J=7.3 Hz, 1H), 7.60-7.56 (m, 2H), 6.25-6.22 (m, 1H), 6.19-6.10 (m, 1H), 5.91 (s, 0.5H), 5.46-5.22 (m, 3H), 5.12 (d, J=12.4 Hz, 1H), 4.84-4.49 (m, 3H), 4.35 (tdd, J=13.2, 6.1, 3.0 Hz, 2H), 4.14 (d, J=8.5 Hz, 1H), 4.11-3.96 (m, 3H), 2.91 (dt, J=16.4, 6.0 Hz, 2H), 2.81-2.68 (m, 1H), 1.29-1.21 (m, 6H). ^{31}P-NMR: (162 MHz, CD_3OD): δ 67.84, 66.33 (2 s, 1P); 2.65, 2.52 (2 s, 1P).

Step 7: (5R,7R,8S,12aR,14R,15R,15aS,18S)-2-(2-cyanoethoxy)-18-fluoro-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}hexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-10 (12H)-olate 2-sulfide

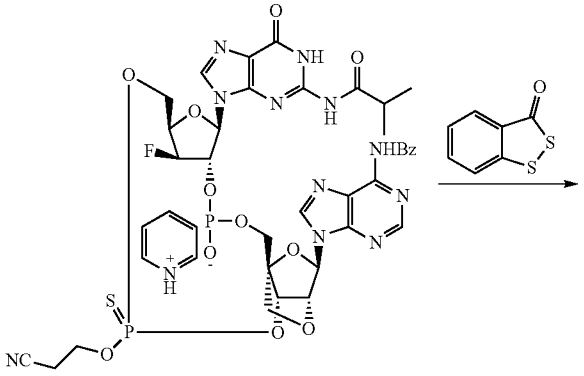
[0733]



[0734] To pyridine (30 mL) at −40° C. under Ar was added diphenyl phosphorochloridate (1783.7 mg, 6.64 mmol) and then, a solution of (2R,3 S,4S,5R)-5-((((((1S,3R,4R,7S)-3-(6-benzamido-9H-purin-9-yl)-1-(hydroxymethyl)-2,5-dioxabicyclo[2.2.1]heptan-7-yl)oxy)(2-cyanoethoxy)phosphorothioyl)oxy)methyl)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate (310 mg, 0.33 mmol, co-evaporated with pyridine 3x5 mL) in CH_2Cl_2 (30 mL) over 20 min. The resulting mixture was stirred at −40° C. for 20 min. It was used in the next step immediately without purification. LCMS (ES, m/z): 916.1 $[M+H]^+$.

Step 8. (5R,7R,8S,12aR,14R,15R,15aS,18S)-2-(2-cyanoethoxy)-18-fluoro-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}hexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-10(12H)-olate 2,10-disulfide

[0735]



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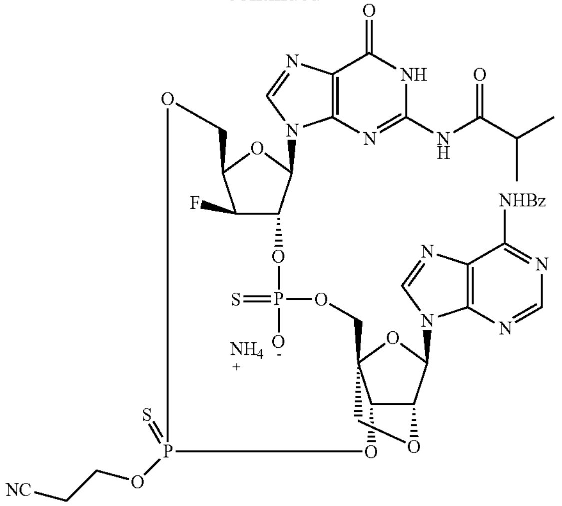
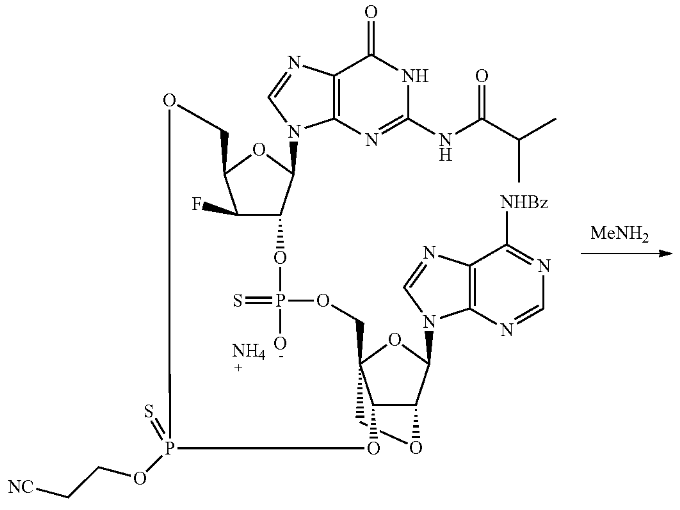


[0736] To the solution from Step 7 at −40° C. was added 3H-benzo[c][1,2]dithiol-3-one (83.6 mg, 0.498 mmol) and water (179 mg, 9.92 mmol). The mixture was stirred at rt for 40 min. Then, it was concentrated, and the residue was purified by reverse phase (C18) chromatography eluted with 0 to 95% ACN in aq NH_4HCO_3 (0.04%) to give the product. LCMS (ES, m/z): 947.8 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD): δ 8.79-8.58 (m, 2H), 8.18-8.06 (m, 2H), 7.92 (d, J=13.5 Hz, 1H), 7.69-7.66 (m, 1H), 7.63-7.54 (m, 2H), 6.40-6.14 (m, 2H), 6.03-5.56 (m, 1.5H), 5.39-5.10 (m, 2.5H), 4.93-4.85 (m, 2H), 4.84-4.43 (m, 3H), 4.43-3.98 (m, 3H), 2.95 (t, J=5.9 Hz, 1H), 2.84-2.66 (m, 2H), 1.30-1.19 (m, 6H). ^{31}P-NMR (162 MHz, CD_3OD): δ 66.60-64.98 (m, 1P), 56.95-55.65 (m, 1P).

Step 9: 2-amino-9-[(5R,7R,8S,12aR,14R,15R,15aS,18S)-14-(6-amino-9H-purin-9-yl)-18-fluoro-2,10-dihydroxy-2,10-disulfidohexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7(12H)-yl]-1,9-dihydro-6H-purin-6-one (Diastereomers 13)

[0737]



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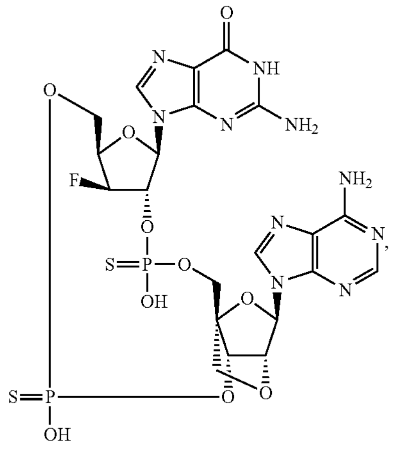
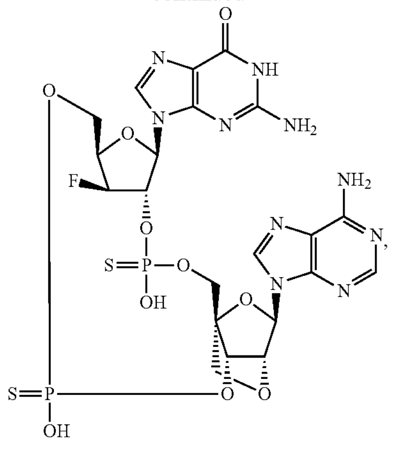
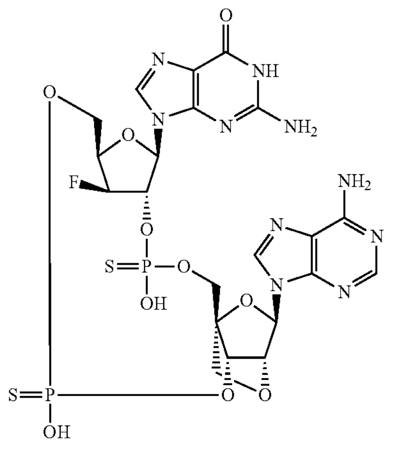


Diastereomer 1



Diastereomer 2



Diastereomer 3

[0738] (5R,7R,8S,12aR,14R,15R,15aS,18 S)-2-(2-cyanoethoxy)-18-fluoro-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}hexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-10(12H)-olate 2,10-disulfide (260 mg, 0.27 mmol) was dissolved in a solution of $MeNH_2$ in EtOH (30%, 20 mL), and the resulting solution was stirred at rt for 3 h. Then, it was concentrated, and the residue was purified by Prep-HPLC (Atlantis Prep RP C18 OBD Column, 19 mm×250 mm) eluted with 0 to 14% ACN in aq NH_4HCO_3 (50 mM) over 25 min to afford the diastereomers of 2-amino-9-[(5R,7R,8S,12aR,14R,15R,15aS,18S)-14-(6-amino-9H-purin-9-yl)-18-fluoro-2,10-dihydroxy-2,10-disulfidohexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7(12H)-yl]-1,9-dihydro-6H-purin-6-one:

[0739] Example 124 (T_R: 22.52 min): LCMS (ES, m/z): 719.0 $[M-H]^-$. ^1H-NMR: (400 MHz, D_2O+DCl): δ 8.71 (s, 1H), 8.26 (s, 1H), 8.09 (s, 1H), 5.73 (s, 1H), 5.65 (s, 1H), 5.22-5.10 (m, 1H), 4.74-4.72 (m, 2H), 4.45 (d, J=4.1 Hz, 1H), 4.21-4.11 (m, 1H), 4.05-3.94 (m, 2H), 3.83-3.56 (m, 2H), 3.46 (s, 2H). ^{31}P-NMR: (162 MHz, D_2O+DCl): δ 60.35 (s, 1P), 56.87 (s, 1P).

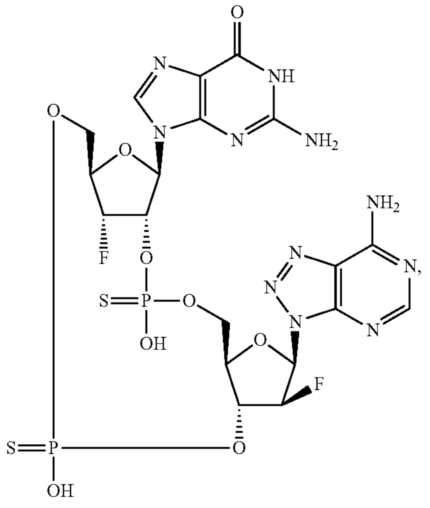
[0740] Example 125 (T_R: 15.75 min): LCMS (ES, m/z): 719.0 $[M-H]^-$. ^1H-NMR: (400 MHz, D_2O): δ 8.31 (s, 1H), 8.14 (s, 1H), 7.74 (s, 1H), 6.11 (s, 1H), 6.06 (s, 1H), 5.61-5.49 (m, 1H), 5.35 (s, 1H), 5.10 (d, J=9.8 Hz, 1H), 4.71-4.55 (m, 1H), 4.51-4.20 (m, 3H), 4.18-3.95 (m, 4H). ^{31}P-NMR: (162 MHz, D_2O): δ 54.87-51.81 (m, 2P).

[0741] Example 126 (T_R: 13.17 min): LCMS (ES, m/z): 718.8 $[M-H]^-$. ^1H-NMR: (300 MHz, D_2O+DCl): δ 8.89 (s, 1H), 8.46 (s, 1H), 8.29 (s, 1H), 5.95 (s, 1H), 5.88 (s, 1H), 5.30-5.14 (m, 1H), 4.98 (t, J=5.2 Hz, 1H), 4.89 (s, 1H), 4.60 (s, 1H), 4.35-4.14 (m, 2H), 4.07 (d, J=11.4 Hz, 1H), 4.01-3.85 (m, 2H), 3.68-3.62 (m, 2H). ^{31}P-NMR: (121 MHz, D_2O+DCl): δ 60.15 (s, 1P), 56.60 (s, 1P).

Examples 127 and 128: 2-amino-9-[(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-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-611-purin-6-one (Diastereomer1), and 2-amino-9-[(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-dihydroxy-2,10-disulfidooctahydro-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 2)

[0742]

Diastereomer 1



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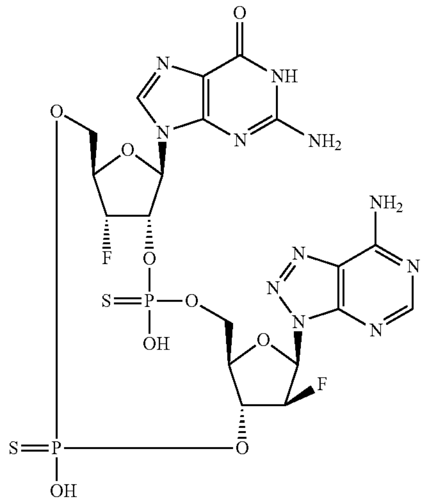
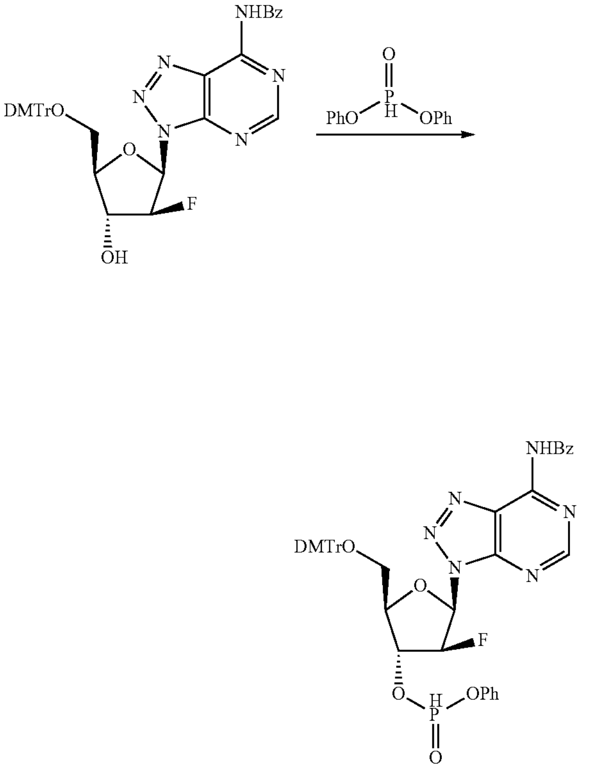
Diastereomer 2



Step 1. (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 phenyl phosphate

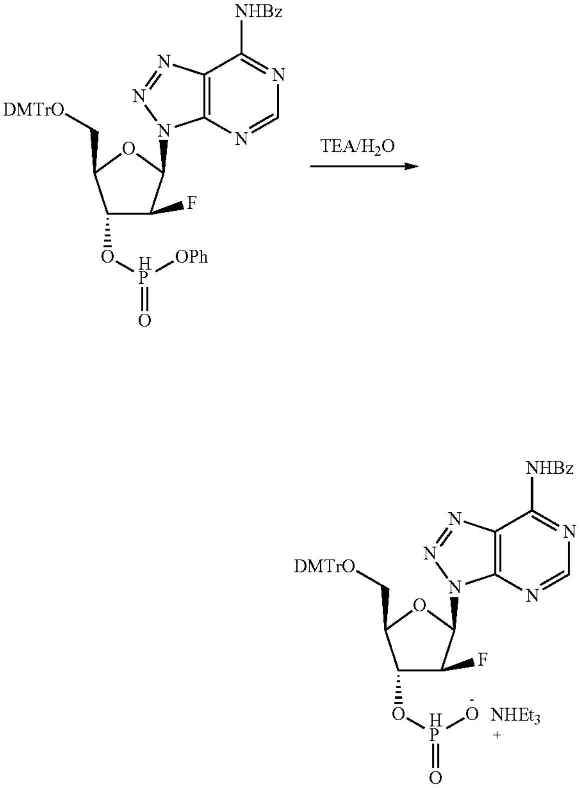
[0743]



[0744] To a stirred solution of N-(3-((2R,3 S,4R,5SR)-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 (770 mg, 1.138 mmol) in pyridine (5 ml) at 0° C. under Ar was added diphenyl phosphonate (1.33 g, 5.69 mmol) over 2 min. The resulting mixture was stirred at rt for 20 min. It was used for the next reaction step directly without purification.

Step 2: (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 phosphonate

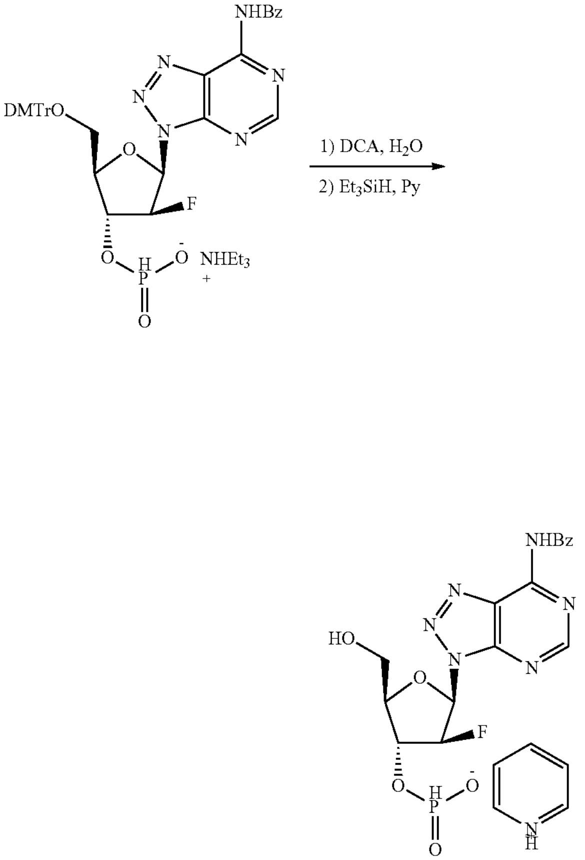
[0745]



[0746] To the reaction mixture from Step 1 at 0° C. was added Et_3N (0.56 mL) in water (0.56 mL) over 5 min. The resulting mixture was stirred at rt for 30 min. It was concentrated, and the residue was partitioned between CH_2Cl_2 (60 mL) and aq $NaHCO_3$ (5%, 24 mL). The organic layer was washed with aq $NaHCO_3$ (5%, 2×24 mL), dried (Na_2SO_4), concentrated, and purified by chromatography on silica gel using 0-10% MeOH in CH_2Cl_2 (0.5% Et_3N) to give the product. LCMS (ES, m/z): 741.2 $[M+H]^+$. ^{1}H-NMR (400 MHz, CD_3OD): δ 8.79 (s, 1H), 8.21-8.11 (m, 2H), 7.71 (t, J=7.4 Hz, 1H), 7.67-7.58 (m, 2.5H), 7.46-7.37 (m, 2H), 7.30-7.23 (m, 4H), 7.18-7.13 (m, 2H), 7.03 (dd, J=6.4, 2.8 Hz, 1H), 6.76-6.73 (m, 2H), 6.69-6.65 (m, 2H), 6.04 (s, 0.5H), 5.85 (t, J=6.4 Hz, 0.5H), 5.72 (t, J=6.4 Hz, 0.5H), 5.60 (td, J=16.9, 6.9 Hz, 1H), 4.44-4.40 (m, 1H), 3.77-3.68 (m, 8H), 3.57 (dd, J=10.6, 2.9 Hz, 1H), 2.91 (q, J=7.3 Hz, 18H), 1.20 (t, J=7.3 Hz, 27H). ^{31}P-NMR: (162 MHz, CD_3OD): δ 2.48 (s, 1P).

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

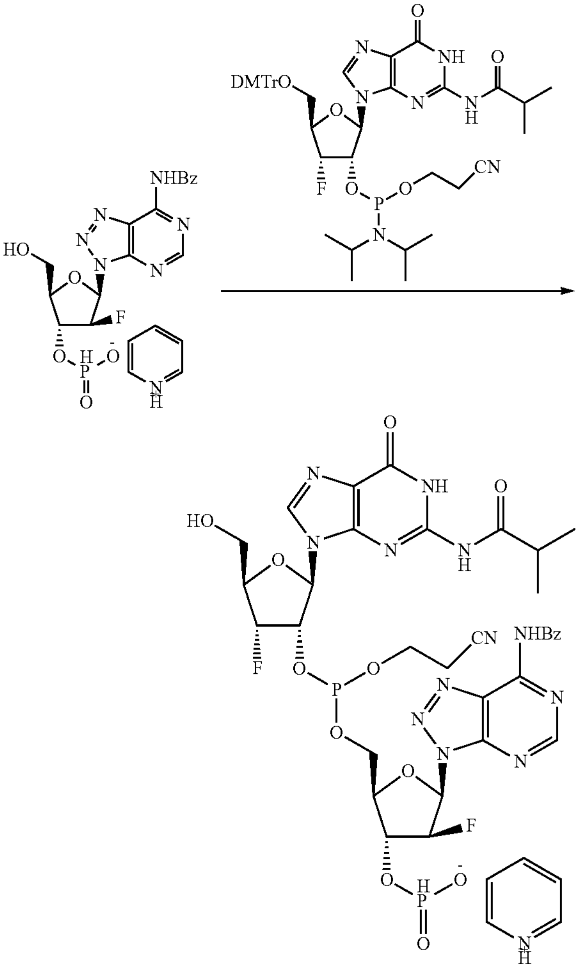
[0747]



[0748] To a solution of (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 phosphonate (610 mg, 0.65 mmol) in CH_2Cl_2 (9.8 mL) was added water (0.12 g, 6.5 mmol) and dichloroacetic acid in CH_2Cl_2 (0.6M, 9.8 mL, 5.9 mmol). After 30 in, triethylsilane (20 mL) was added and stirring was continued for additional 2 h. Then, pyridine (5 mL) was added, and it was concentrated. The crude was used for the next reaction step without purification. LCMS (ES, m/z): 439.1 [M+H]$^+$.

Step 4: (2R,3R,4S,5R)-5-(7-benzamido-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-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)-4-fluorotetrahydrofuran-3-yl phosphonate

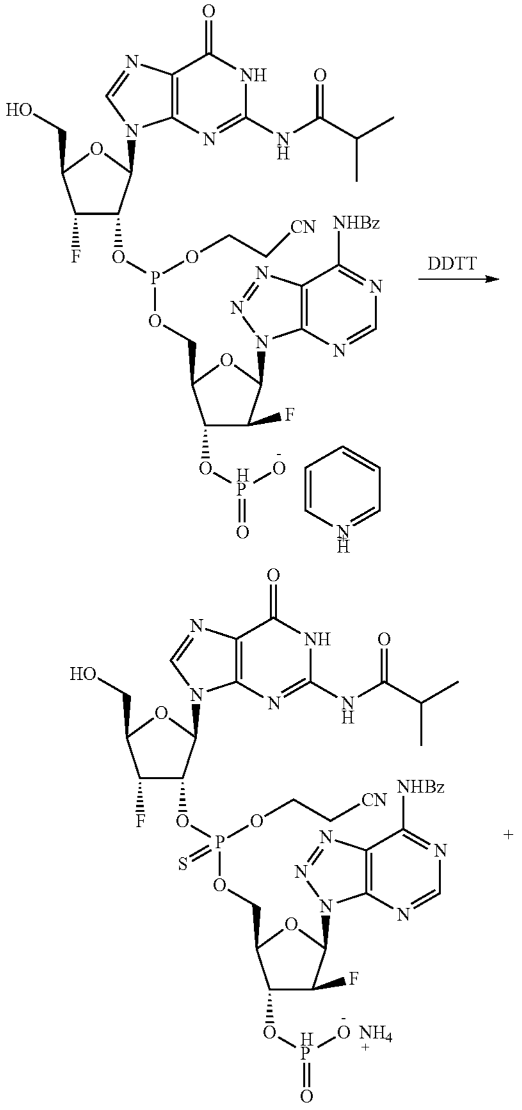
[0749]



[0750] The crude product of Step 3 was co-evaporated with dry ACN (3x3 mL), re-dissolved in ACN (3 mL), and dried by adding activated 4 Å molecular sieve (200 mg). (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 (0.824 g, 0.960 mmol) was co-evaporated with dry ACN (3x3 mL), re-dissolved in ACN (5 mL), and dried by adding activated 4 Å molecular sieve (200 mg). After 30 min, it was added to the previously prepared mixture containing pyridin-1-ium (2R,3R,4S,5R)-5-(7-benzamido-3H-[1,2,3]triazolo [4,5-d]pyrimidin-3-yl)-4-fluoro-2-(hydroxymethyl)tetrahydrofuran-3-yl phosphonate. It was stirred at rt for 30 min, and the reaction mixture was used in the next reaction step directly without purification. LCMS (ES, m/z): 893.2 [M+H]$^+$.

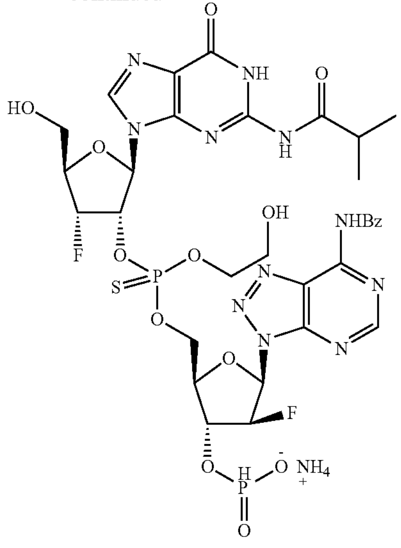
Step 5: Diastereomers (2R,3R,4S,5R)-5-(7-benzamido-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-2-((((2-cyanoethoxy) (((2R,3S,4R,5R)-4-fluoro-5-(hydroxymethyl)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl)oxy) phosphorothioyl)oxy)methyl)-4-fluorotetrahydrofuran-3-yl phosphonate (116-5-A) and (2R,3R,4S,5R)-5-(7-benzamido-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-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)-4-fluorotetrahydrofuran-3-yl phosphonate (116-5-B)

[0751]



116-5-A

-continued



116-5-B

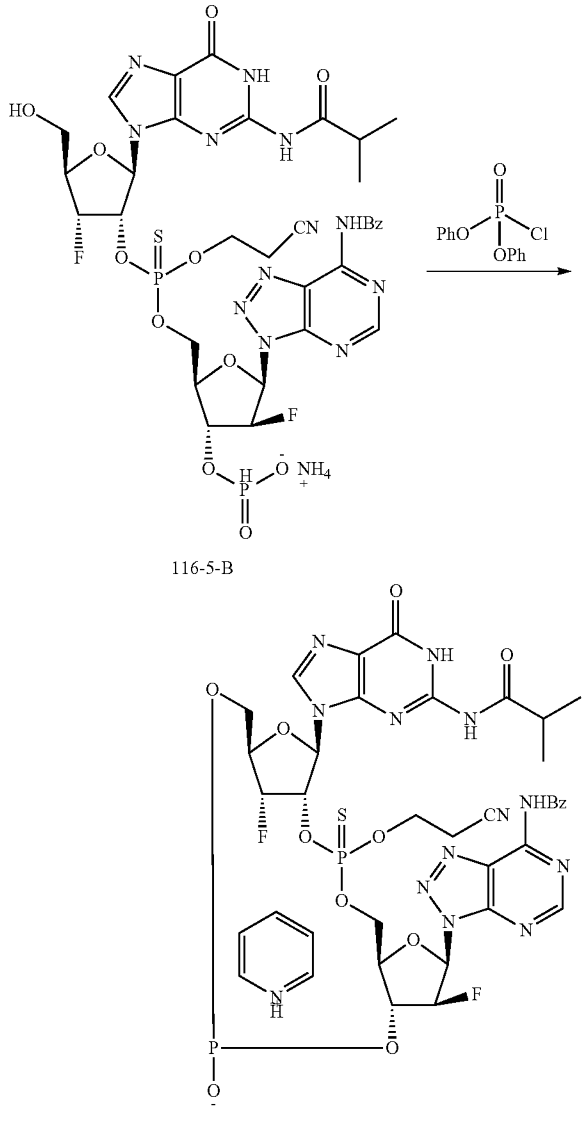
[0752] To the reaction mixture from Step 4 at rt, was added (E)-N,N-dimethyl-N-(3-thioxo-3H-1,2,4-dithiazol-5-yl) formimidamide (181 mg, 0.880 mmol), and the mixture was stirred for 1 h. Then, it was concentrated, and the residue was purified by reverse phase (AQ-C18) chromatography eluted with 0 to 28% ACN in aq NH_4HCO_3 (5 mM) over 88 min.

[0753] The first fractions with desired mass (T_R=50 min) gave (2R,3R,4S,5R)-5-(7-benzamido-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-2-((((2-cyanoethoxy)(((2R,3 S,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)-4-fluorotetrahydrofuran-3-yl phosphonate (116-5-A). LCMS (ES, m/z): 924.9 $[M+H]^+$. ^{1}H-NMR: (400 MHz, CD_3OD): δ 8.90 (s, 1H), 8.31 (s, 1H), 8.10 (d, J=7.8 Hz, 2H), 7.75 (s, 0.5H), 7.69 (t, J=7.4 Hz, 1H), 7.57 (t, J=7.7 Hz, 2H), 7.02 (dd, J=6.5, 2.6 Hz, 1H), 6.27-6.13 (m, 1.5H), 5.79-5.51 (m, 3H), 5.47-5.21 (m, 12H), 4.58 (dd, J=15.4, 7.6 Hz, 2H), 4.50-4.25 (m, 3H), 4.05 (ddd, J=24.7, 13.2, 6.1 Hz, 2H), 3.90-3.76 (m, 4H), 2.85-2.56 (m, 3H), 1.34 (d, J=6.5 Hz, 3H), 1.25-1.19 (m, 3H). ^{31}P-NMR (162 MHz, CD_3OD): δ 67.56 (s, 1P), 3.09 (s, 1P).

[0754] The second fractions with desired mass (T_R=55 min) gave (2R,3R,4S,5R)-5-(7-benzamido-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-2-((((2-cyanoethoxy)(((2R,3 S,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)-4-fluorotetrahydrofuran-3-yl phosphonate (116-5-B). LCMS (ES, m/z): 925.1 $[M+H]^+$. ^{1}H-NMR: (400 MHz, CD_3OD): δ 8.87 (s, 1H), 8.33 (s, 1H), 8.16 (d, J=7.8 Hz, 2H), 7.75 (s, 0.5H), 7.70 (t, J=7.4 Hz, 1H), 7.61 (t, J=7.7 Hz, 2H), 6.91 (dd, J=6.2, 3.4 Hz, 1H), 6.23 (d, J=7.1 Hz, 1H), 6.17 (s, 0.5H), 5.74-5.54 (m, 3H), 5.46 (d, J=4.6 Hz, 0.5H), 5.33 (d, J=4.6 Hz, 0.5H), 4.65-4.24 (m, 4H), 4.15 (dt, J=13.0, 5.8 Hz, 2H), 3.95-3.75 (m, 2H), 2.90-2.67 (m, 3H), 1.36-1.31 (m, 3H), 1.19 (d, J=6.8 Hz, 3H). ^{31}P-NMR: (162 MHz, CD_3OD): δ 67.29 (s, 1P), 3.07 (s, 1P).

Step 6: (5R,7R,8S,12aR,14R,15S,15aR,16R)-10-(2-cyanoethoxy)-15,16-difluoro-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{7-[(phenylcarbonyl)amino]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-2-olate 10-sulfide

[0755]

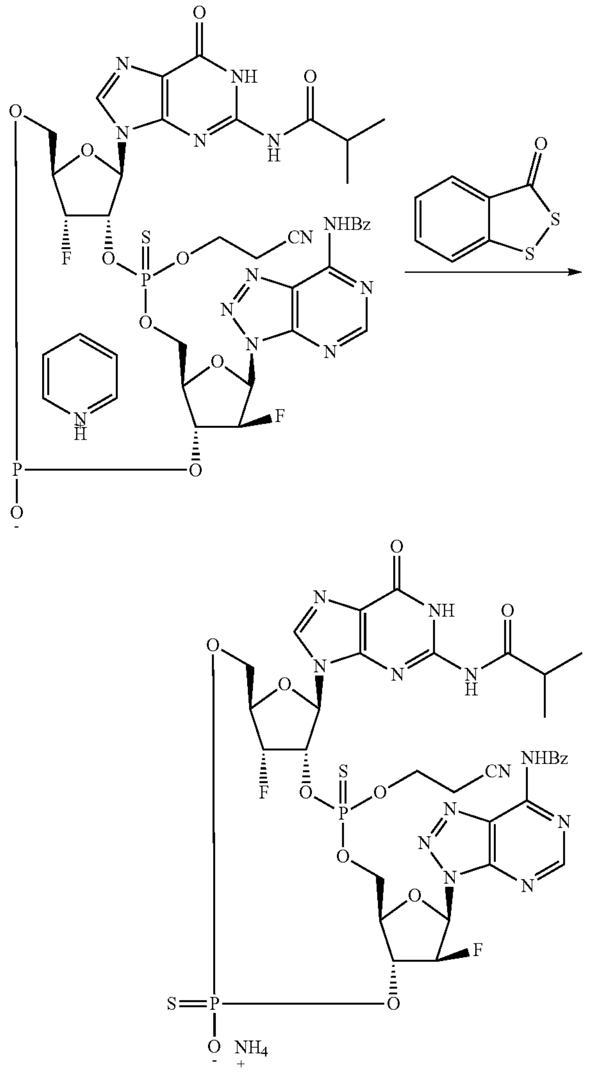


116-5-B

[0756] To pyridine (10 mL) at −40° C. under Ar was added diphenyl phosphorochloridate (628 mg, 2.34 mmol), and then, a solution of (2R,3R,4S,5R)-5-(7-benzamido-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-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)-4-fluorotetrahydrofuran-3-yl phosphonate (116-5-B) (110 mg, 0.105 mmol, co-evaporated with pyridine 3×5 mL) in CH_2Cl_2 (10 mL) over 20 min. It was stirred at −40° C. for 20 min. The reaction mixture was used in the next step immediately without purification.

Step 7: (5R,7R,8S,12aR,14R,15S,15aR,16R)-10-(2-cyanoethoxy)-15,16-difluoro-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{7-[(phenylcarbonyl)amino]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-2-olate 2,10-disulfide

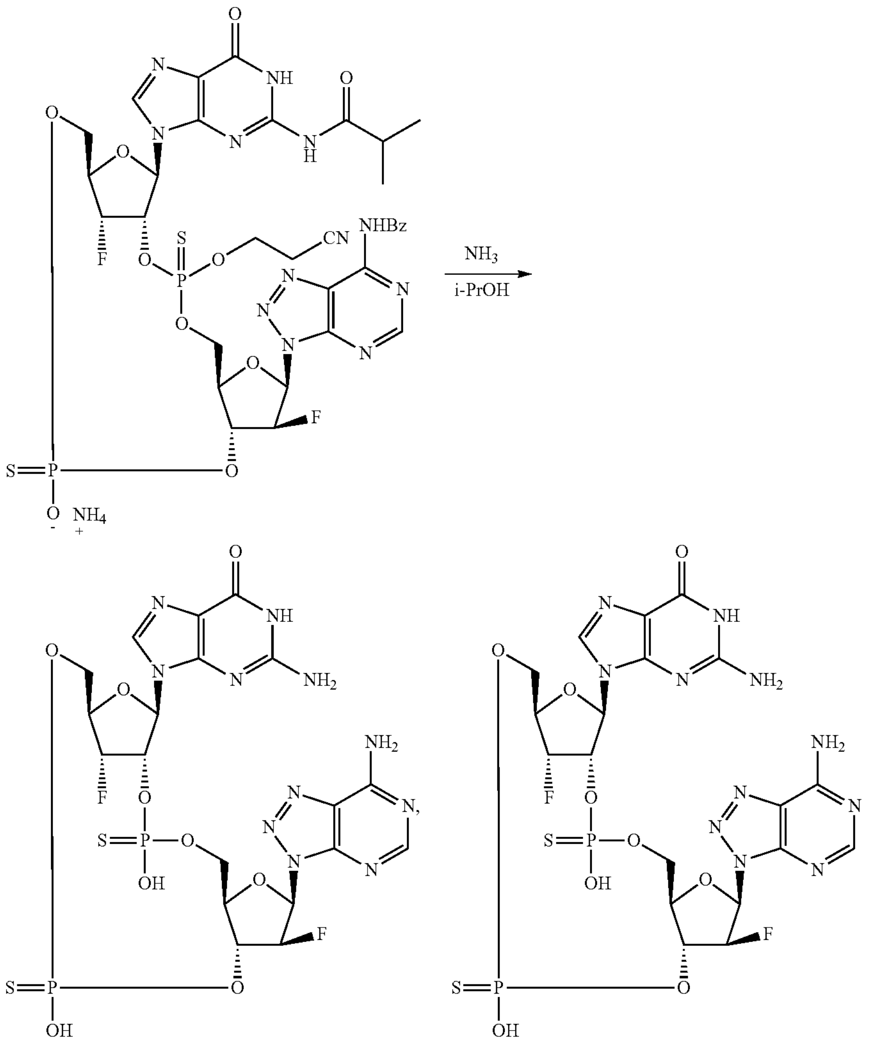
[0757]



[0758] To the mixture from Step 6 at −20° C. was added 3H-benzo[c][1,2]dithiol-3-one (27.8 mg, 0.165 mmol) and water (42 mg, 2.3 mmol). The resulting mixture was stirred at rt for 30 min. It was concentrated, and the residue was purified by reverse phase (AQ-C18) chromatography eluted with 0 to 28% ACN in aq NH_4HCO_3 (5 mM) to give the product. LCMS (ES, m/z): 938.9 $[M+H]^+$. ^{1}H-NMR: (400 MHz, CD_3OD): δ 8.94-8.71 (m, 2H), 8.23-8.06 (m, 2H), 7.75-7.67 (m, 1H), 7.64 (t, J=7.5 Hz, 2H), 7.11-6.97 (m, 1H), 6.32-6.17 (m, 2H), 6.02-5.73 (m, 2H), 5.68-5.38 (m, 1H), 4.73 (d, J=24.3 Hz, 1H), 4.68-4.42 (m, 4H), 4.39-4.19 (m, 2H), 4.06-3.66 (m, 2H), 2.99-2.62 (m, 2H), 2.61-2.37 (m, 1H), 1.20 (d, J=6.8 Hz, 3H), 1.12 (d, J=6.7 Hz, 3H). ^{31}P-NMR: (162 MHz, CD_3OD): δ 64.05, 63.79 (2 s, 1P); 56.67, 56.27 (2 s, 1P).

Step 8: 2-amino-9-[(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-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-9-dihydro-6H-purin-6-one (Diastereomers 1 and 2)

[0759]



Diastereomer 1

Diastereomer 2

[0760] To pyridinium (5R,7R,8S,12aR,14R,15S,15aR,16R)-10-(2-cyanoethoxy)-15,16-difluoro-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{7-[(phenylcarbonyl) amino]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-2-olate 2,10-disulfide in a steel tank (150 mL) at −60° C. was added ammonia in isopropanol (50 mL) at −60° C. The reactor was tightly sealed and then, heated at 50° C. for 16 h. Then, the volatile components were removed under reduced pressure, and the residue was purified by prep-HPLC (Atlantis Prep T3 OBD Column, 19×250 mm) eluted with 0 to 5% ACN in aq NH_4HCO_3 (50 mM) over 25 min.

[0761] Example 127 (T_R=17.32 min): 2-amino-9-[(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-dihydroxy-2,10-disulfidooctahydro-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). LCMS (ES, m/z): 709.8 $[M-H]^-$. ^{1}H-NMR: (400 MHz, D_2O): δ 8.32 (s, 1H), 8.27 (s, 1H), 6.78 (dd, J=11.1, 4.9 Hz, 1H), 6.07 (d, J=8.6 Hz, 1H), 5.81 (t, J=4.6 Hz, 0.5H), 5.68 (t, J=4.7 Hz, 0.5H), 5.63 (dq, J=9.8, 5.0 Hz, 1H), 5.58 (d, J=3.5 Hz, 0.5H), 5.45 (d, J=3.4 Hz, 0.5H), 5.43-5.26 (m, 1H), 4.65-

4.63 (m, 1H), 4.56 (q, J=5.6 Hz, 1H), 4.31-4.23 (m, 3H), 4.12-4.05 (m, 1H). ^{31}P-NMR: (162 MHz, D_2O): δ 55.76 (s, 1P), 54.26 (s, 1P).

[0762] Example 128 (T_R=21.10 min): 2-amino-9-[(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-dihydroxy-2,10-disulfidooctahydro-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 2). LCMS (ES, m/z): 709.8 [M−H]$^-$. ^{1}H-NMR: (400 MHz, D_2O): δ 8.26 (s, 1H), 8.01 (s, 1H), 6.79 (dd, J=9.4, 5.3 Hz, 1H), 6.05 (d, J=8.6 Hz, 1H), 5.85 (t, J=5.0 Hz, 0.5H), 5.72 (t, J=5.0 Hz, 0.5H), 5.65-5.35 (m, 3H), 4.69-4.62 (m, 1H), 4.48 (d, J=5.5 Hz, 1H), 4.42 (t, J=11.1 Hz, 1H), 4.18 (t, J=6.2 Hz, 2H), 4.09-4.06 (m, 1H). ^{31}P-NMR (162 MHz, D_2O): δ 54.74 (s, 1P), 53.84 (s, 1P).

[0763] Examples 129 through 243, as shown in Table 6 below, were or may be prepared according to procedures analogous to those outlined in Examples 116 through 128 above using the appropriate monomers, described as Preparations or as obtained from commercial sources, in the coupling step.

TABLE 6

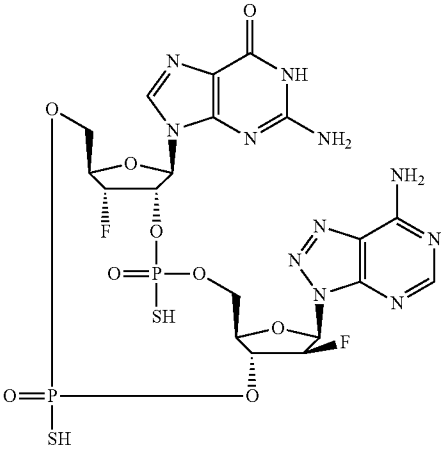
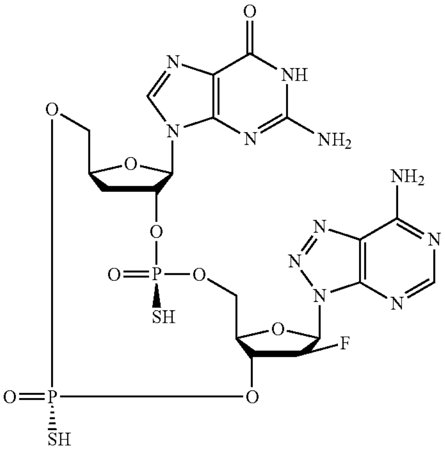
Ex.	Structure	Name	Mass [M − H]$^-$
129		2-amino-9-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-14-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-15,16-difluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 3)	710
130		2-amino-9-[(2R,5S,7R,8R,10R,12aR,14R,15S,15aR)-14-(6-amino-9H-purin-9-yl)-15-fluoro-2,10-dihydroxy-2,10-disulfidooctahydro-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)	691

TABLE 6-continued

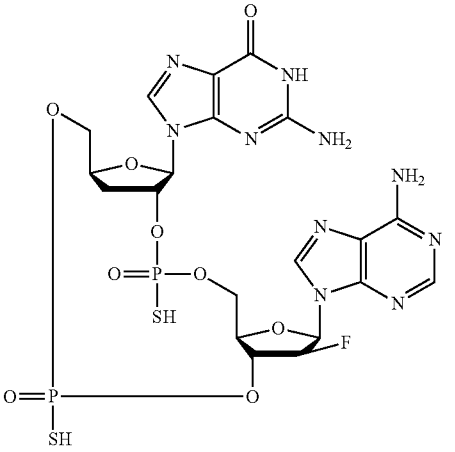
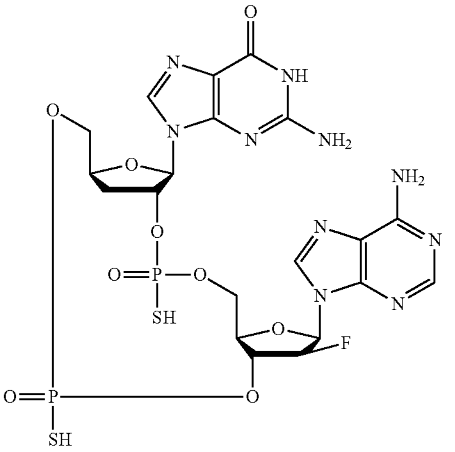
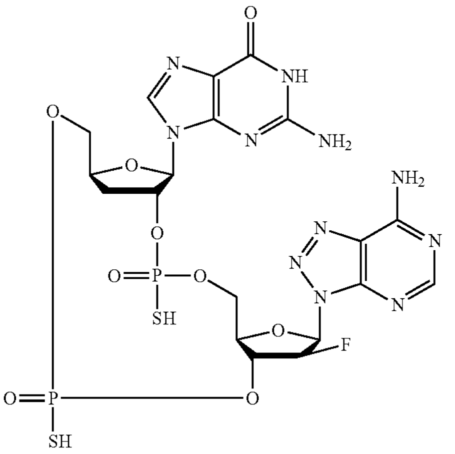
Ex.	Structure	Name	Mass [M − H]⁻
131		2-amino-9-[(5S,7R,8R,12aR,14R,15S,15aR)-14-(6-amino-9H-purin-9-yl)-15-fluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 2)	691
132		2-amino-9-[(5S,7R,8R,12aR,14R,15S,15aR)-14-(6-amino-9H-purin-9-yl)-15-fluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-oe (Diastereomer 3)	691
133		2-amino-9-[(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-dihydroxy-2,10-disulfidooctahydro-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)	694

TABLE 6-continued

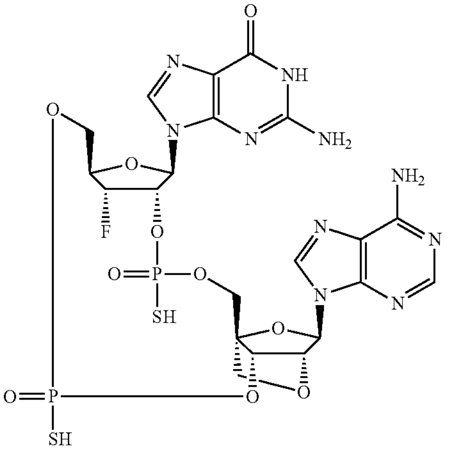
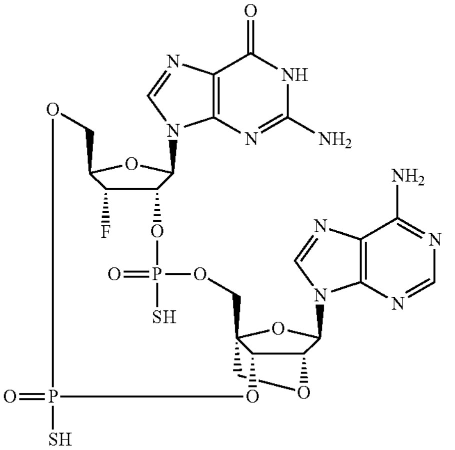
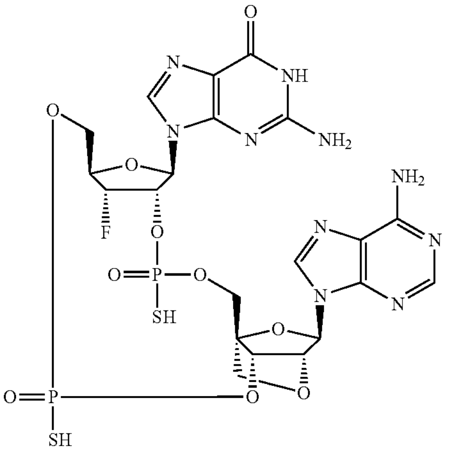
Ex.	Structure	Name	Mass [M − H]⁻
134		2-amino-9-[(5R,7R,8S,12aR,14R,15R,15aS,18R)-14-(6-amino-9H-purin-9-yl)-18-fluoro-2,10-dioxido-2,10-disulfanylhexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7(12H)-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 1)	719
135		2-amino-9-[(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]-1,9-dihydro-6H-purin-6-one (Diastereomer 2)	719
136		2-amino-9-[(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]-1,9-dihydro-6H-purin-6-one (Diastereomer 3)	719

TABLE 6-continued

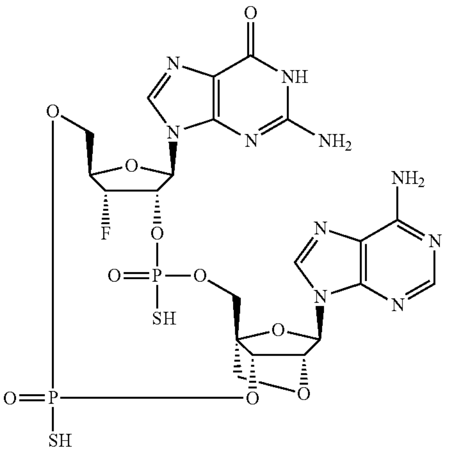
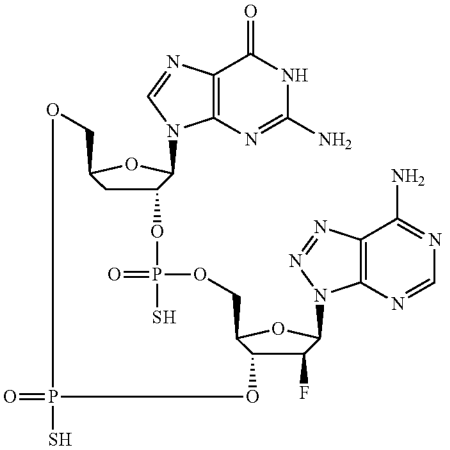
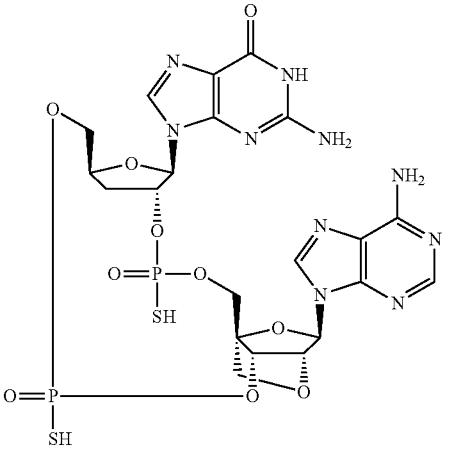
Ex.	Structure	Name	Mass [M − H]⁻
137		2-amino-9-[(5R,7R,8S,12aR,14R,15R,15aS,18R)-14-(6-amino-9H-purin-9-yl)-18-fluoro-2,10-dioxido-2,10-disulfanylhexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7(12H)-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 4)	719
138		2-amino-9-[(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]-1,9-dihydro-6H-purin-6-one	692
139		2-amino-9-[(5S,7R,8R,12aR,14R,15R,15aS)-14-(6-amino-9H-purin-9-yl)-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]-1,9-dihydro-6H-purin-6-one (Diastereomer 1)	701

TABLE 6-continued

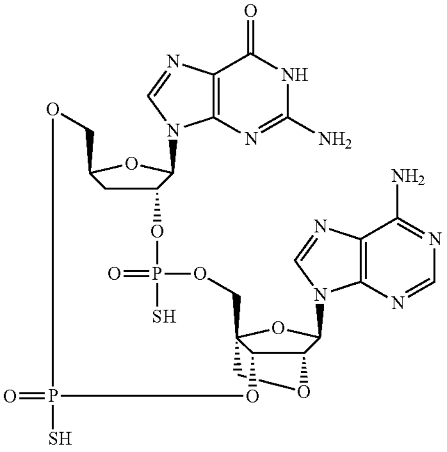
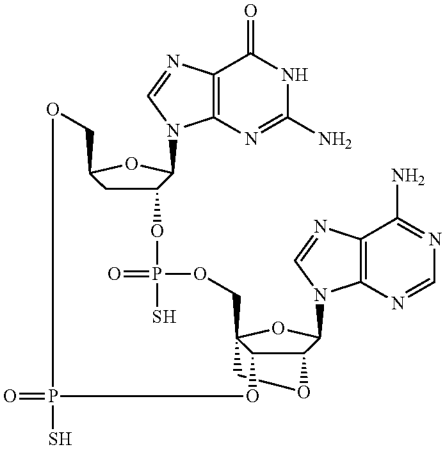
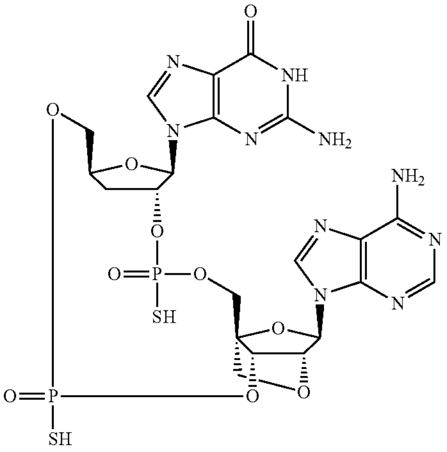
Ex.	Structure	Name	Mass [M − H]⁻
140		2-amino-9-[(5S,7R,8R,12aR,14R,15R,15aS)-14-(6-amino-9H-purin-9-yl)-2,10-dioxido-2,10-disulfanylhexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7(12H)-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 2)	701
141		2-amino-9-[(5S,7R,8R,12aR,14R,15R,15aS)-14-(6-amino-9H-purin-9-yl)-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]-1,9-dihydro-6H-purin-6-one (Diasteroemer 3)	701
142		2-amino-9-[(5S,7R,8R,12aR,14R,15R,15aS)-14-(6-amino-9H-purin-9-yl)-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]-1,9-dihydro-6H-purin-6-one (Diastereomer 4)	701

TABLE 6-continued

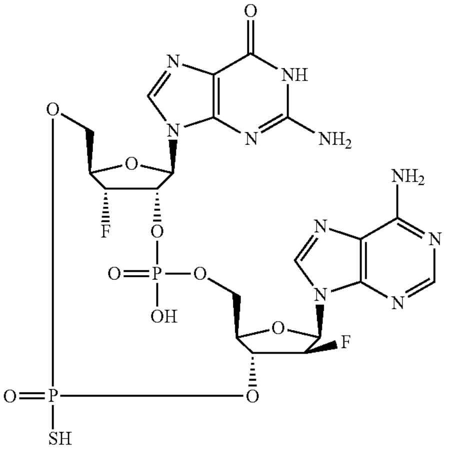
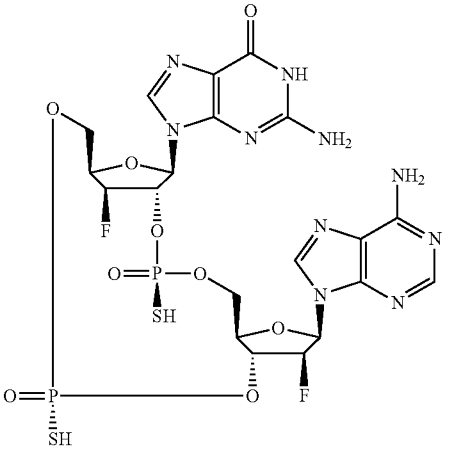
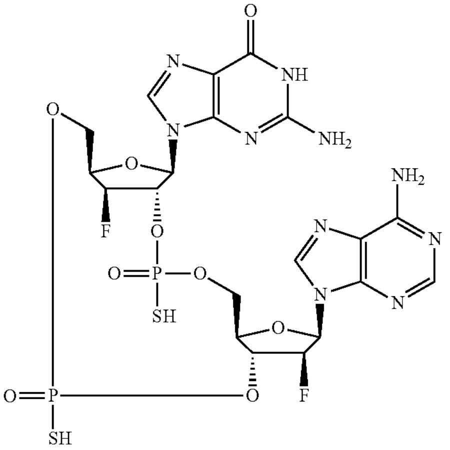
Ex.	Structure	Name	Mass [M − H]⁻
143		2-amino-9-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-10-oxido-2-sulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	694
144		2-amino-9-[(2R,5R,7R,8S,10R,12aR,14R,15S,15aR,16S)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 1)	709
145		2-amino-9-[(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]-1,9-dihydro-6H-purin-6-one (Diastereomer 2)	709

TABLE 6-continued

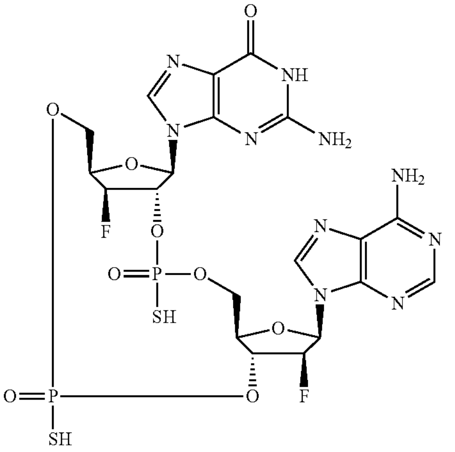
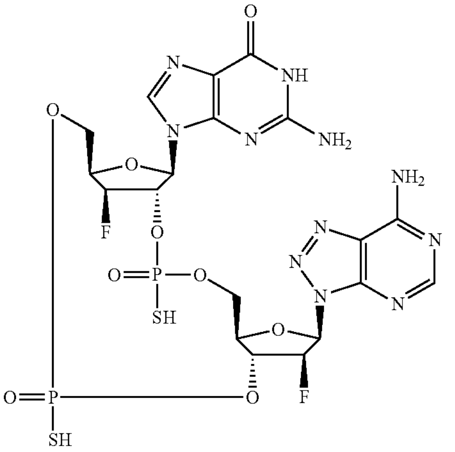
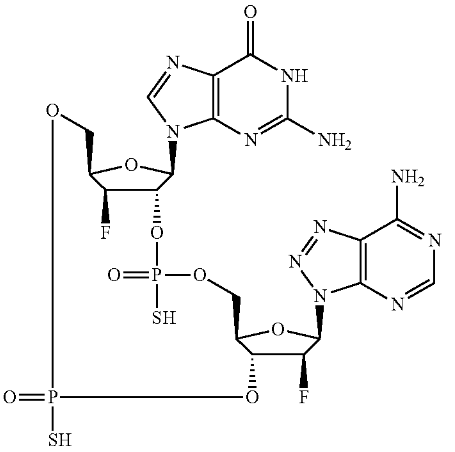
Ex.	Structure	Name	Mass [M − H]⁻
146		2-amino-9-[(5R,7R,8S,12aR,14R,15S,15aR,16S)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 3)	709
147		2-amino-9-[(5R,7R,8S,12aR,14R,15S,15aR,16S)-14-(7-amino-3H-[1,2,3]triazolo[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]-1,9-dihydro-6H-purin-6-one (Diastereomer 1)	710
148		2-amino-9-[(5R,7R,8S,12aR,14R,15S,15aR,16S)-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]-1,9-dihydro-6H-purin-6-one (Diastereomer 2)	710

TABLE 6-continued

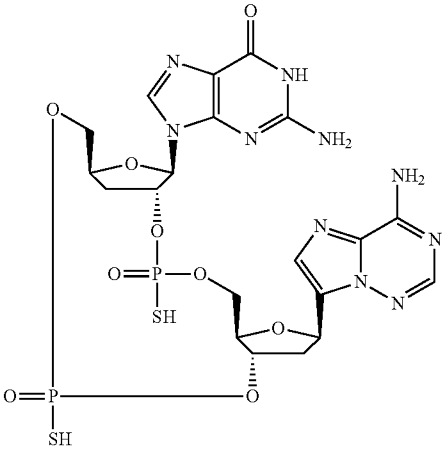
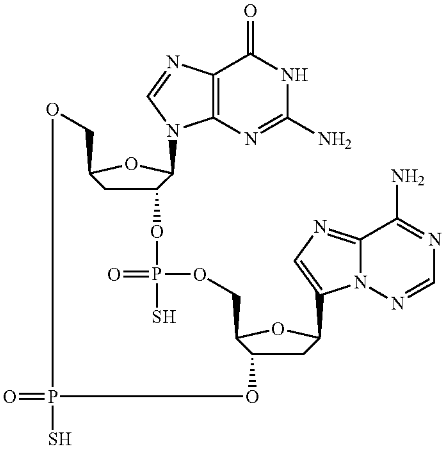
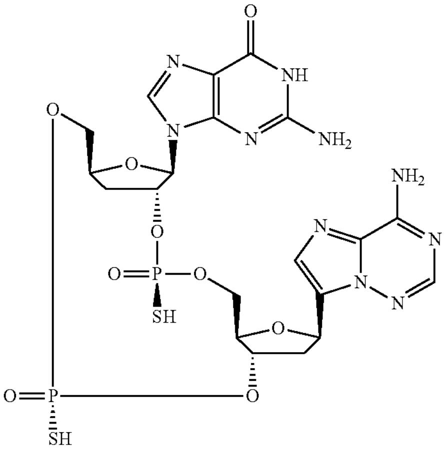
Ex.	Structure	Name	Mass [M − H]⁻
149		2-amino-9-[(5S,7R,8R,12aR,14R,15aS)-14-(4-aminoimidazo[2,1-f][1,2,4]triazin-7-yl)-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 1)	673
150		2-amino-9-[(5S,7R,8R,12aR,14R,15aS)-14-(4-aminoimidazo[2,1-f][1,2,4]triazin-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 2)	673
151		2-amino-9-[(2R,5S,7R,8R,10R,12aR,14R,15aS)-14-(4-aminoimidazo[2,1-f][1,2,4]triazin-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 3)	673

TABLE 6-continued

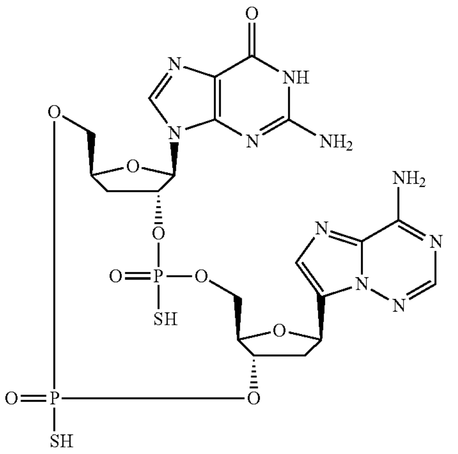
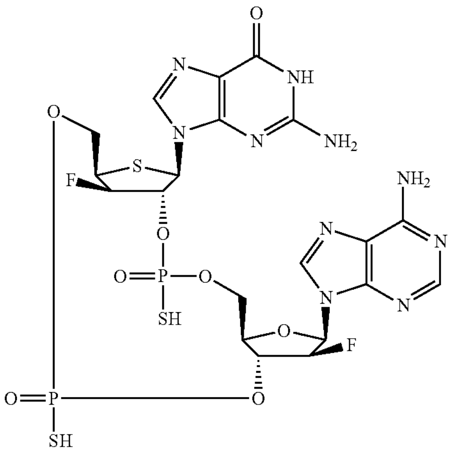
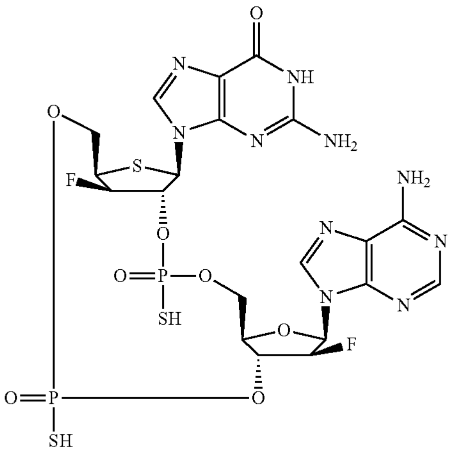
Ex.	Structure	Name	Mass [M − H]⁻
152		2-amino-9-[(5S,7R,8R,12aR,14R,15aS)-14-(4-aminoimidazo[2,1-f][1,2,4]triazin-7-yl)-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 4)	673
153		(5R,7R,8R,12aR,14R,15S,15aR,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-14-(6-amino-9H-purin-9-yl)-15,16-difluorooctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecine-2,10-bis(thiolate) 2,10-dioxide (Diastereomer 1)	725
154		(5R,7R,8R,12aR,14R,15S,15aR,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-14-(6-amino-9H-purin-9-yl)-15,16-difluorooctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecine-2,10-bis(thiolate) 2,10-dioxide (Diastereomer 2)	725

TABLE 6-continued

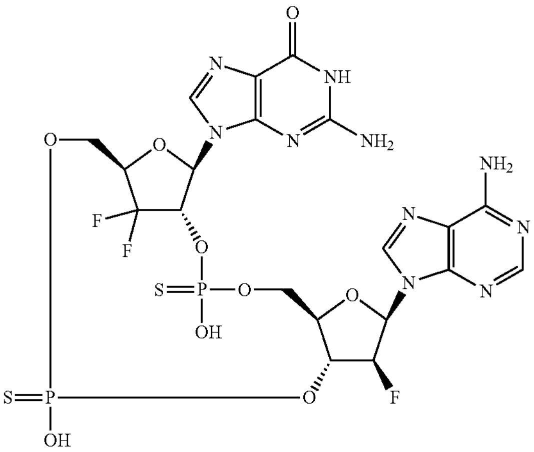
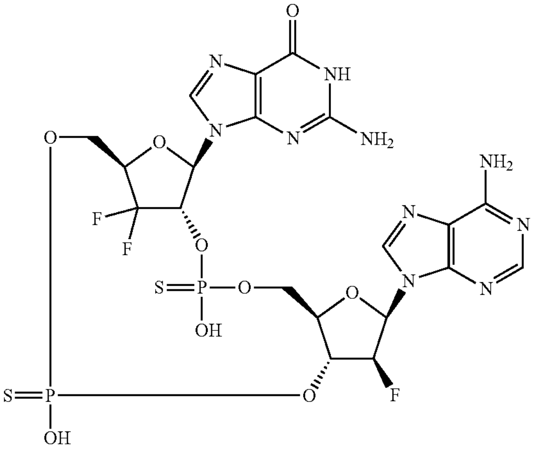
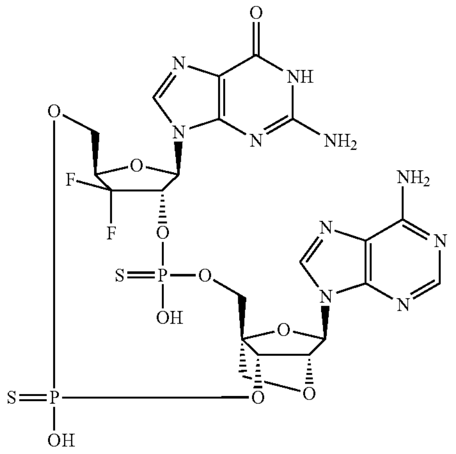
Ex.	Structure	Name	Mass $[M - H]^-$
155		2-amino-9-[(5R,7R,8S,12aR,14R,15S,15aR)-14-(6-amino-9H-purin-9-yl)-15,16,16-trifluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 1)	727
156		2-amino-9-[(5R,7R,8S,12aR,14R,15S,15aR)-14-(6-amino-9H-purin-9-yl)-15,16,16-trifluoro-2,10-dihydroxy-2,10-disulfidooctahydro-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 2)	727
157		2-amino-9-[(5R,7R,8S,12aR,14R,15R,15aS)-14-(6-amino-9H-purin-9-yl)-18,18-difluoro-2,10-dihydroxy-2,10-disulfidohexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecin-7(12H)-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 1)	737

TABLE 6-continued

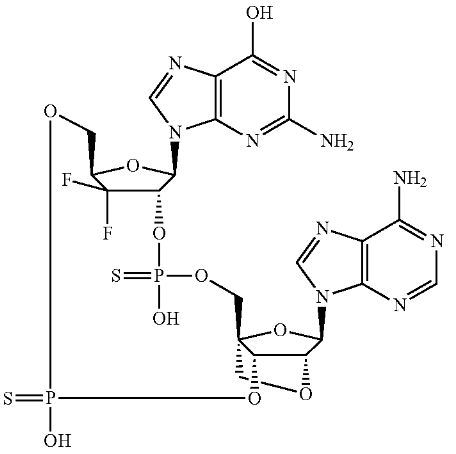
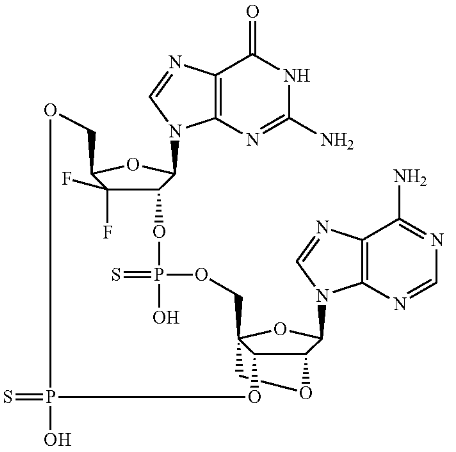
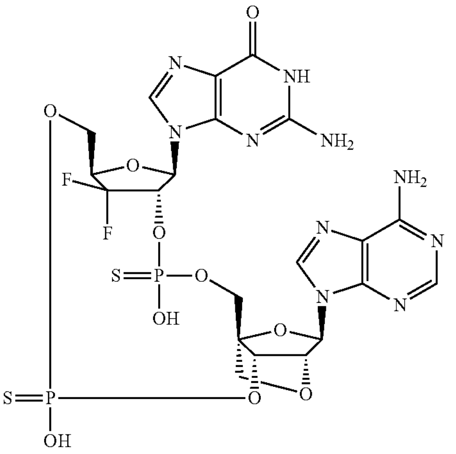
Ex.	Structure	Name	Mass [M − H]⁻
158		2-amino-9-[(5R,7R,8S,12aR,14R,15R,15aS)-14-(6-amino-9H-purin-9-yl)-18,18-difluoro-2,10-dihydroxy-2,10-disulfidohexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7(12H)-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 2)	737
159		2-amino-9-[(5R,7R,8S,12aR,14R,15R,15aS)-14-(6-amino-9H-purin-9-yl)-18,18-difluoro-2,10-dihydroxy-2,10-disulfidohexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7(12H)-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 3)	737
160		2-amino-9-[(5R,7R,8S,12aR,14R,15R,15aS)-14-(6-amino-9H-purin-9-yl)-18,18-difluoro-2,10-dihydroxy-2,10-disulfidohexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7(12H)-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 4)	737

TABLE 6-continued

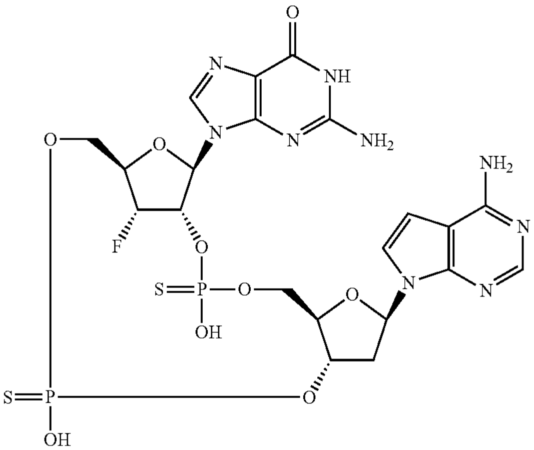
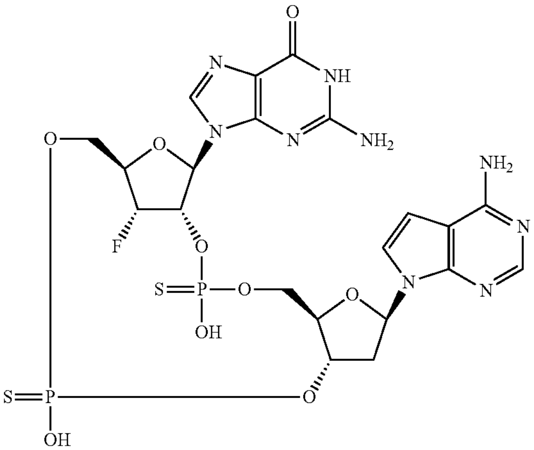
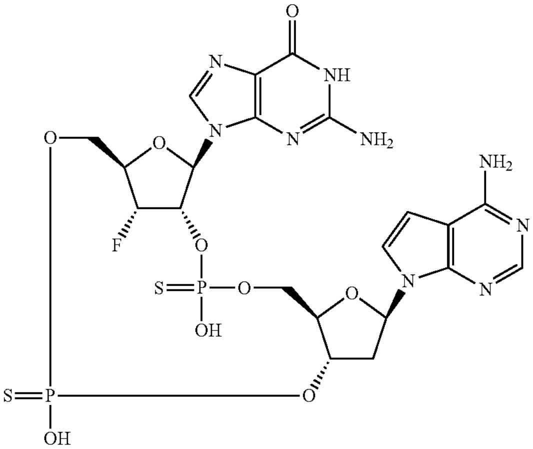
Ex.	Structure	Name	Mass $[M - H]^-$
161		2-amino-9-[(5R,7R,8S,12aR,14R,15aS,16R)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-16-fluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6, 9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 1)	690
162		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-dihydroxy-2,10-disulfidooctahydro-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 2)	690
163		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-dihydroxy-2,10-disulfidooctahydro-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 3)	690

TABLE 6-continued

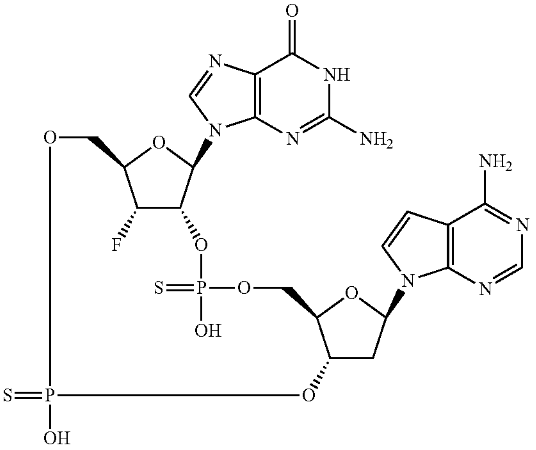
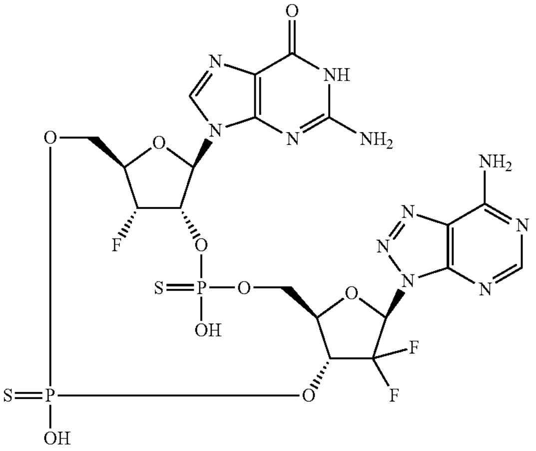
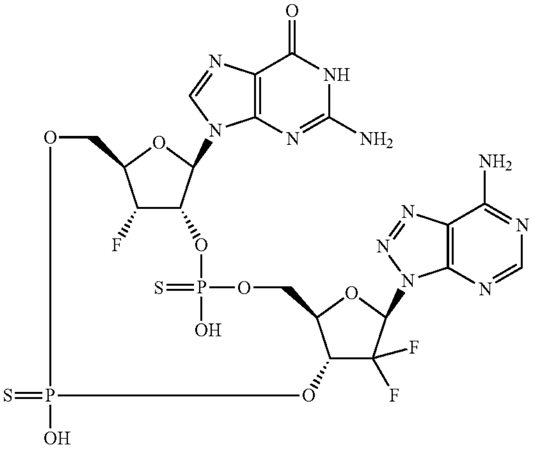
Ex.	Structure	Name	Mass [M − H]$^-$
164		2-amino-9-[(5R,7R,8S,12aR,14R,15aS,16R)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-16-fluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 4)	690
165		2-amino-9-[(5R,7R,8S,12aR,14R,15aR,16R)-14-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-15,15,16-trifluoro-2,10-dihydroxy-2,10-disulfidooctahydro-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)	728
166		2-amino-9-[(5R,7R,8S,12aR,14R,15aR,16R)-14-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-15,15,16-trifluoro-2,10-dihydroxy-2,10-disulfidooctahydro-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 2)	728

TABLE 6-continued

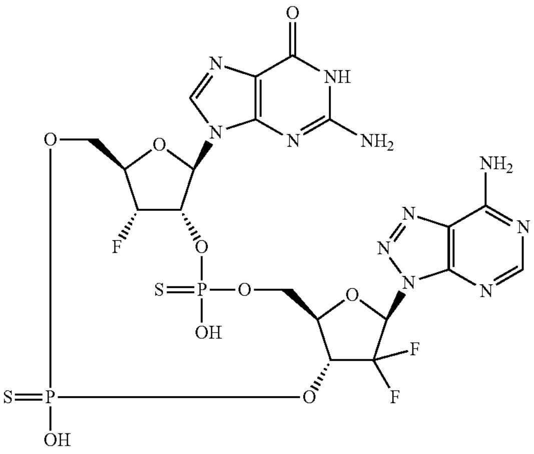
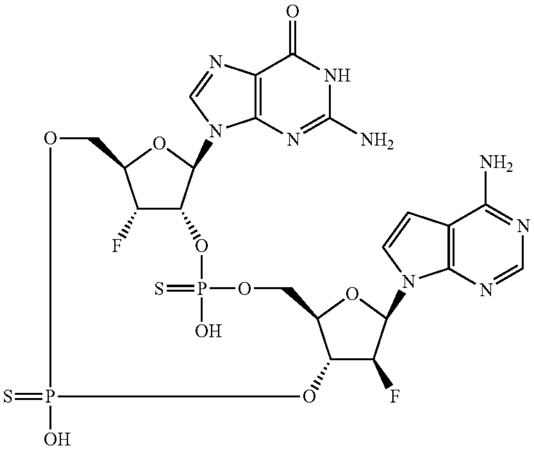
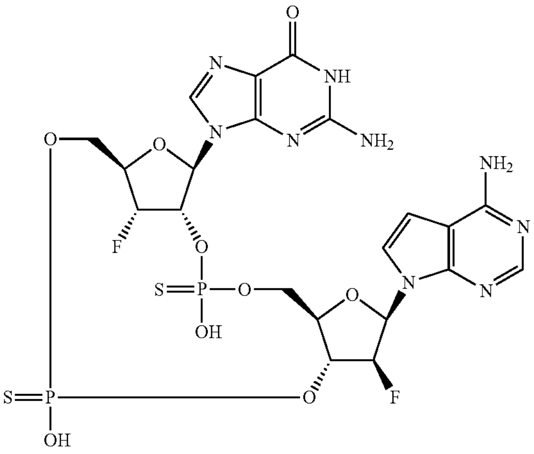
Ex.	Structure	Name	Mass [M − H]⁻
167		2-amino-9-[(5R,7R,8S,12aR,14R,15aR,16R)-14-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-15,15,16-trifluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 3)	728
168		2-amino-9-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-15,16-difluoro-2,10-dihydroxy-2,10-disulfidooctahydro-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)	708
169		2-amino-9-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-15,16-difluoro-2,10-dihydroxy-2,10-disulfidooctahydro-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 2)	708

TABLE 6-continued

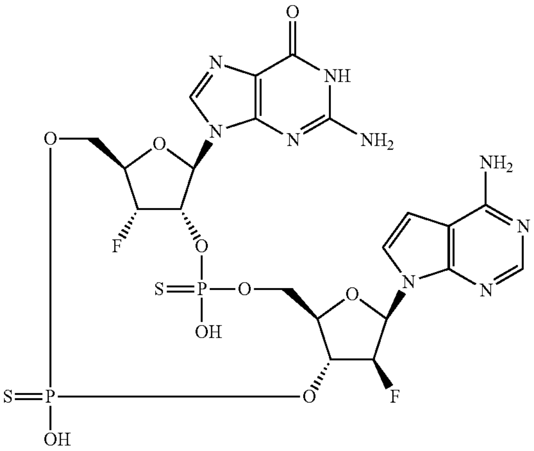
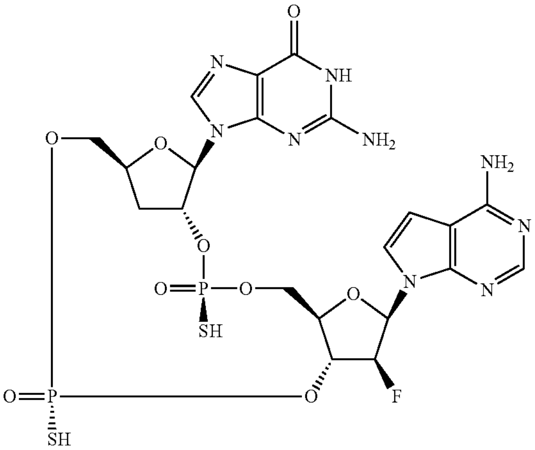
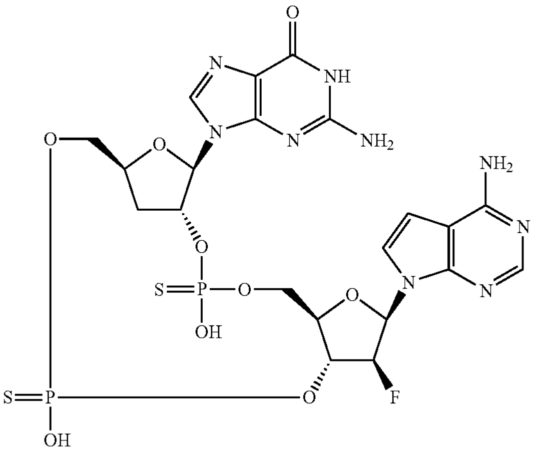
Ex.	Structure	Name	Mass [M − H]$^-$
170		2-amino-9-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-15,16-difluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 3)	708
171		2-amino-9-[(2R,5S,7R,8R,10R,12aR,14R,15S,15aR)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-15-fluoro-2,10-dihydroxy-2,10-disulfidooctahydro-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)	690
172		2-amino-9-[(5S,7R,8R,12aR,14R,15S,15aR)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-15-fluoro-2,10-dihydroxy-2,10-disulfidooctahydro-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 2)	690

TABLE 6-continued

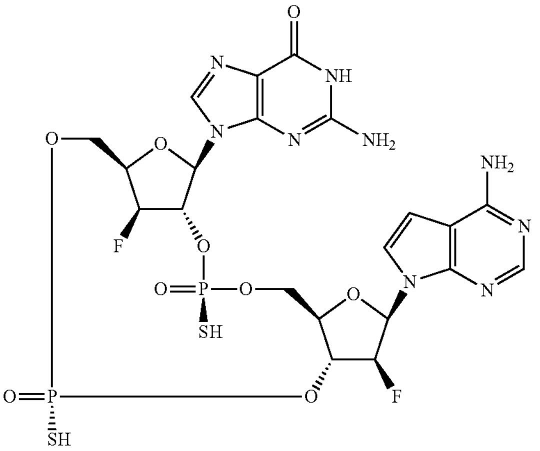
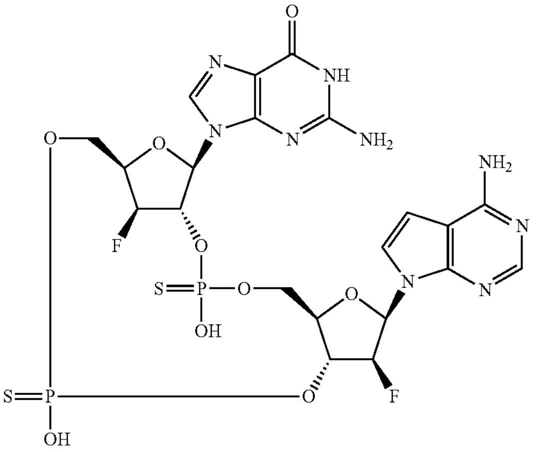
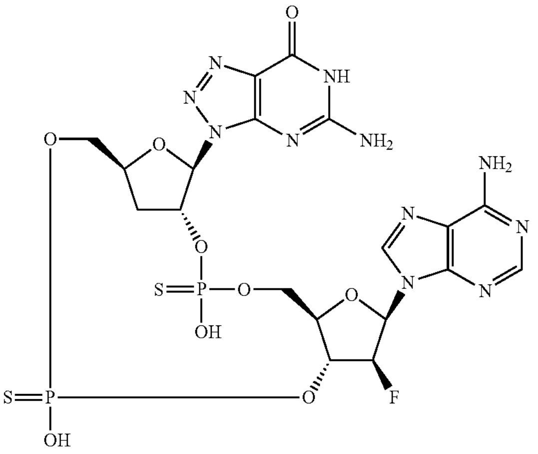
Ex.	Structure	Name	Mass $[M-H]^-$
173		2-amino-9-[(2R,5R,7R,8S,10R,12aR,14R,15S,15aR,16S)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-15,16-difluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 1)	708
174		2-amino-9-[(5R,7R,8S,12aR,14R,15S,15aR,16S)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-15,16-difluoro-2,10-dihydroxy-2,10-disulfidooctahydro-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 2)	708
175		5-amino-3-[(5S,7R,8R,12aR,14R,15S,15aR)-14-(6-amino-9H-purin-9-yl)-15-fluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 1)	692

TABLE 6-continued

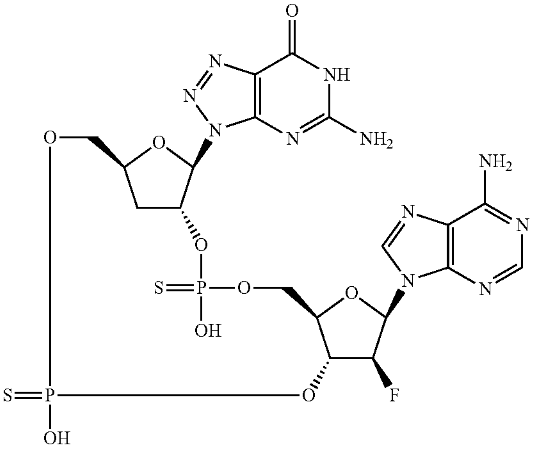
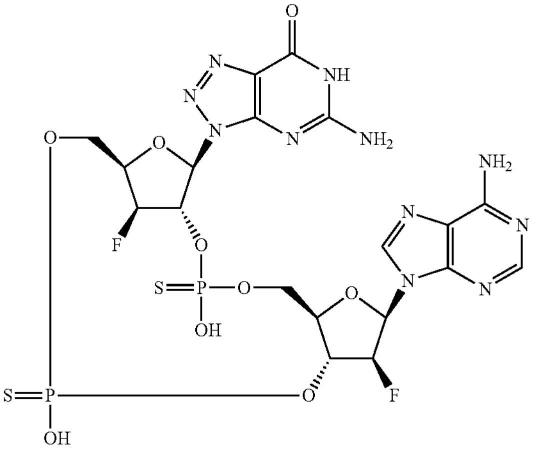
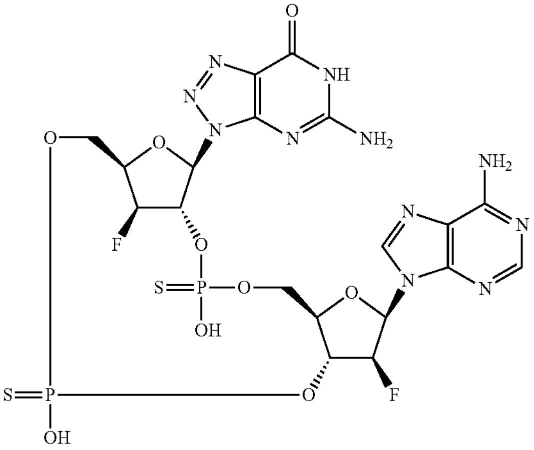
Ex.	Structure	Name	Mass [M − H]⁻
176		5-amino-3-[(5S,7R,8R,12aR,14R,15S,15aR)-14-(6-amino-9H-purin-9-yl)-15-fluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 2)	692
177		5-amino-3-[(5R,7R,8S,12aR,14R,15S,15aR,16S)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 1)	710
178		5-amino-3-[(5R,7R,8S,12aR,14R,15S,15aR,16S)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 2)	710

TABLE 6-continued

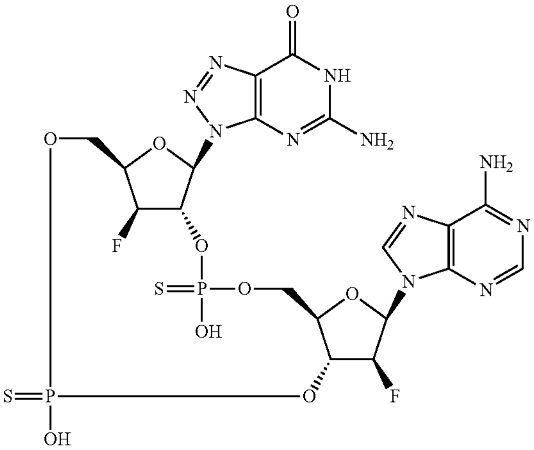
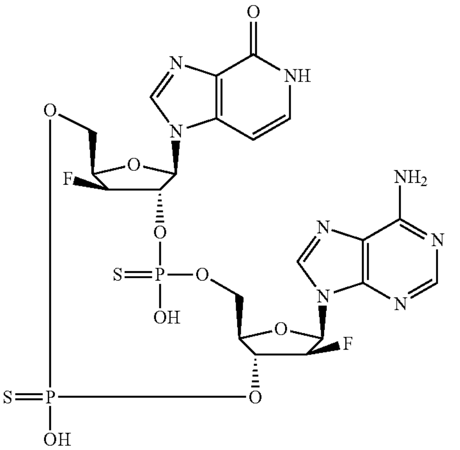
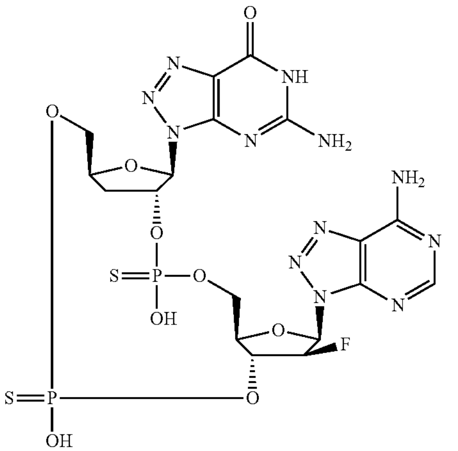
Ex.	Structure	Name	Mass [M − H]$^-$
179		5-amino-3-[(5R,7R,8S,12aR,14R,15S,15aR,16S)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 3)	710
180		1-[(5R,7R,8S,12aR,14R,15S,15aR,16S)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-2,10-disulfidooctahydro-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	693
181		5-amino-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-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 1)	693

TABLE 6-continued

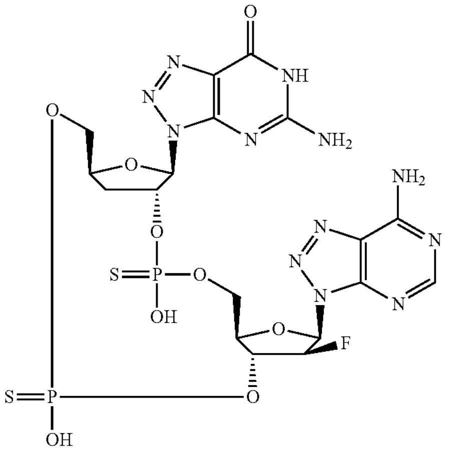
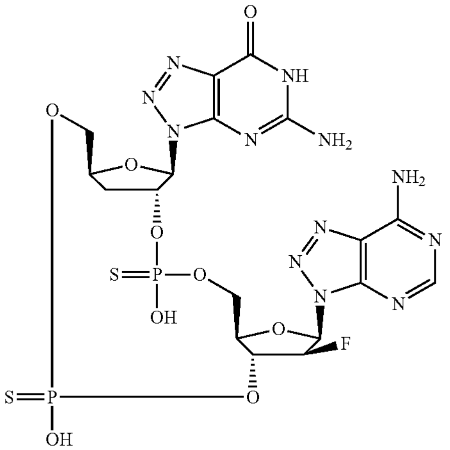
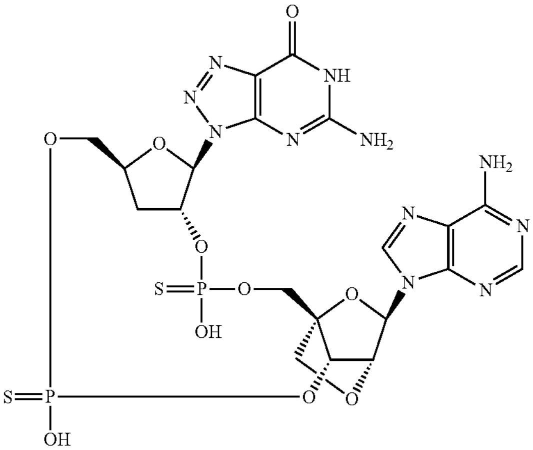
Ex.	Structure	Name	Mass [M − H]⁻
182		5-amino-3-[(5S,7R,8R,12aR,14R,15S,15aR)-14-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-15-fluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 2)	693
183		5-amino-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-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 3)	693
184		5-amino-3-[(5S,7R,8R,12aR,14R,15R,15aS)-14-(6-amino-9H-purin-9-yl)-2,10-dihydroxy-2,10-disulfidohexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7(12H)-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 1)	702

TABLE 6-continued

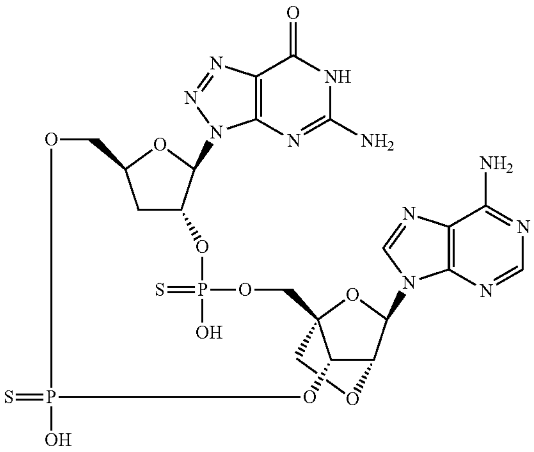
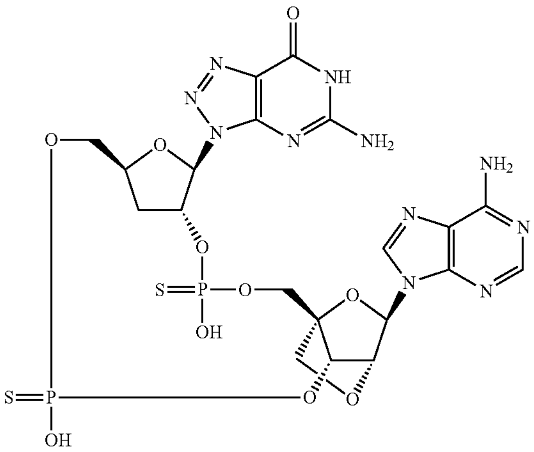
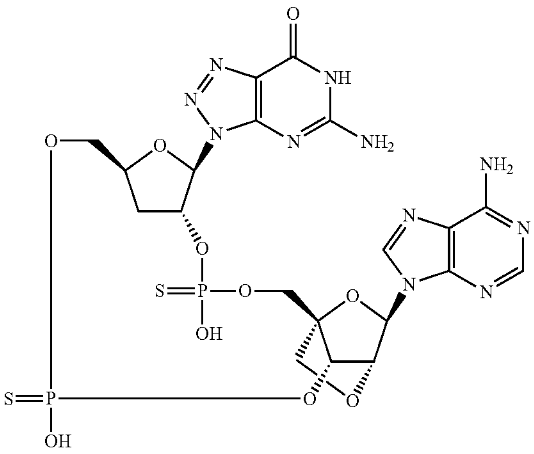
Ex.	Structure	Name	Mass [M − H]⁻
185		5-amino-3-[(5S,7R,8R,12aR,14R,15R,15aS)-14-(6-amino-9H-purin-9-yl)-2,10-dihydroxy-2,10-disulfidohexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7(12H)-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 2)	702
186		5-amino-3-[(5S,7R,8R,12aR,14R,15R,15aS)-14-(6-amino-9H-purin-9-yl)-2,10-dihydroxy-2,10-disulfidohexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3 ,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7(12H)-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 3)	702
187		5-amino-3-[(5S,7R,8R,12aR,14R,15R,15aS)-14-(6-amino-9H-purin-9-yl)-2,10-dihydroxy-2,10-disulfidohexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7(12H)-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 4)	702

TABLE 6-continued

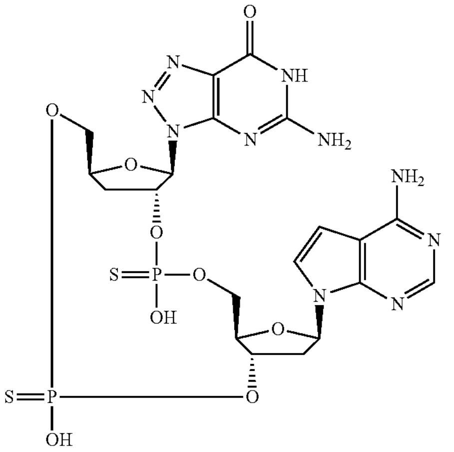
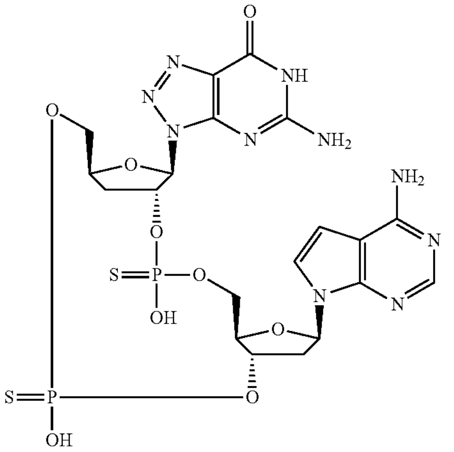
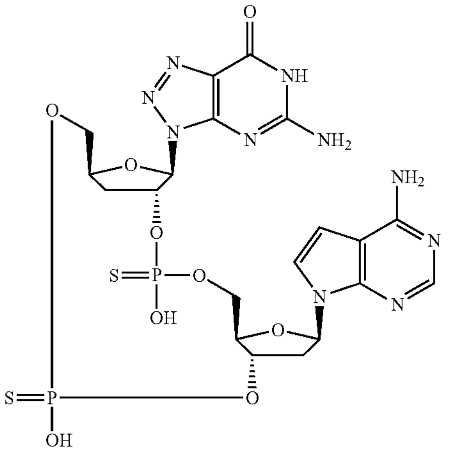
Ex.	Structure	Name	Mass [M − H]⁻
188		5-amino-3-[(5S,7R,8R,12aR,14R,15aS)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 1)	673
189		5-amino-3-[(5S,7R,8R,12aR,14R,15aS)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 2)	673
190		5-amino-3-[(5S,7R,8R,12aR,14R,15aS)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 3)	673

TABLE 6-continued

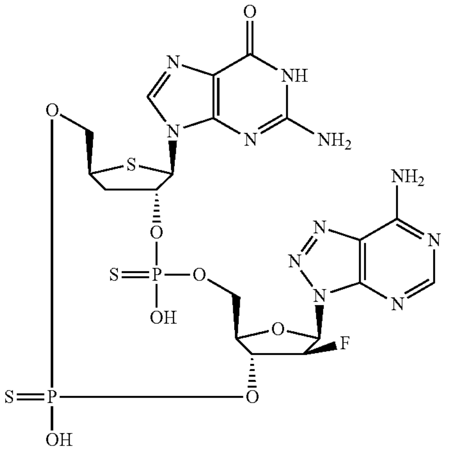
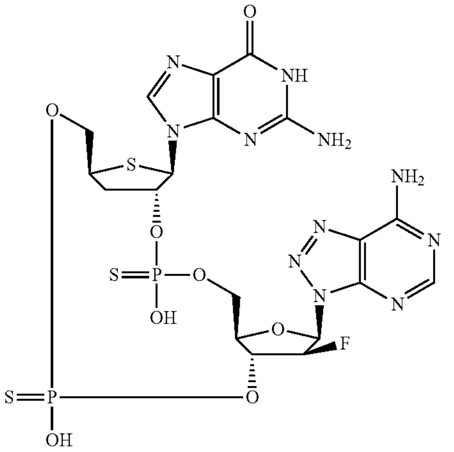
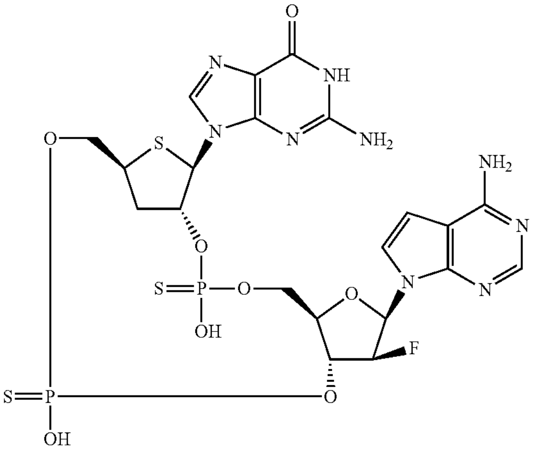
Ex.	Structure	Name	Mass [M − H]⁻
191		2-amino-9-[(5S,7R,8R,12aR,14R,15S,15aR)-14-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-15-fluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 1)	708
192		2-amino-9-[(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-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 2)	708
193		2-amino-9-[(5S,7R,8R,12aR,14R,15S,15aR)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-15-fluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	706

TABLE 6-continued

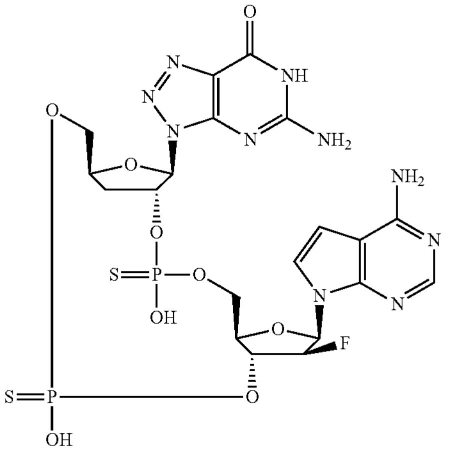
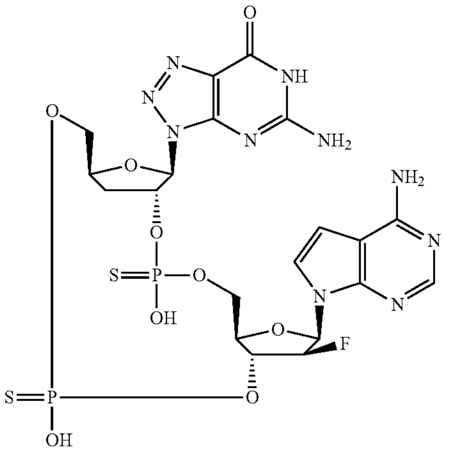
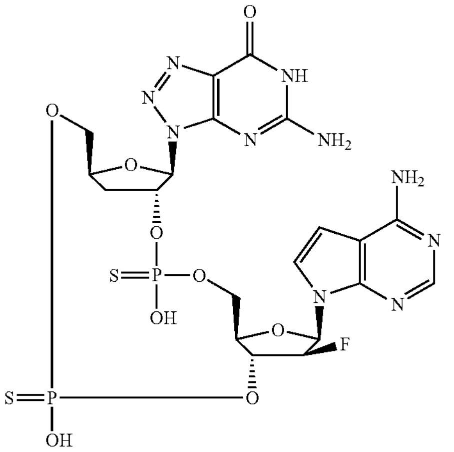
Ex.	Structure	Name	Mass $[M - H]^-$
194		5-amino-3-[(5S,7R,8R,12aR,14R,15S,15aR)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-15-fluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 1)	691
195		5-amino-3-[(5S,7R,8R,12aR,14R,15S,15aR)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-15-fluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 2)	691
196		5-amino-3-[(5S,7R,8R,12aR,14R,15S,15aR)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-15-fluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 3)	691

TABLE 6-continued

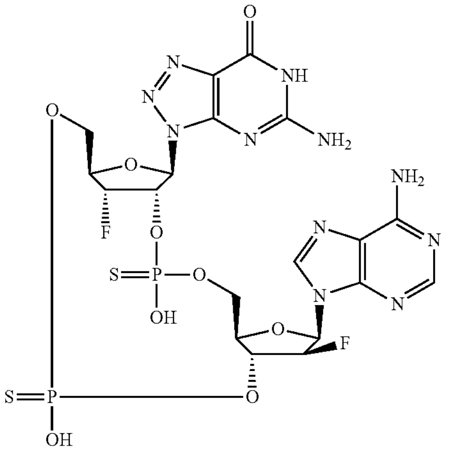
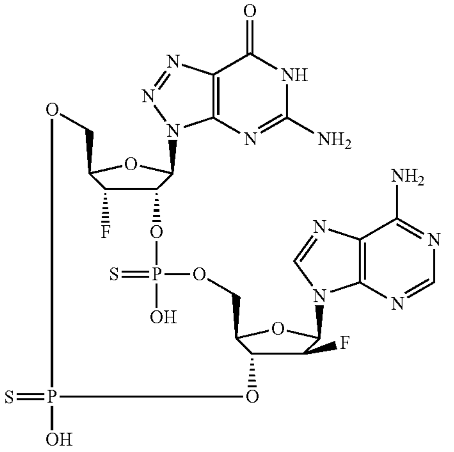
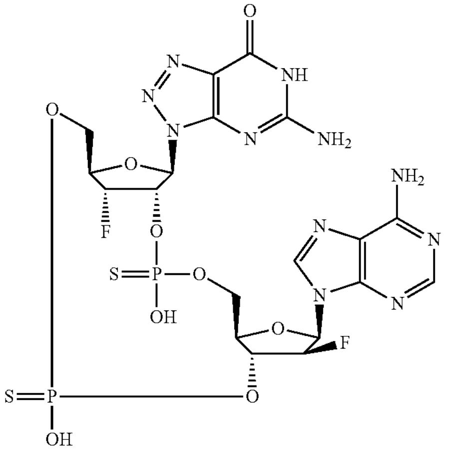
Ex.	Structure	Name	Mass [M − H]⁻
197		5-amino-3-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 1)	710
198		5-amino-3-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 2)	710
199		5-amino-3-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 3)	710

TABLE 6-continued

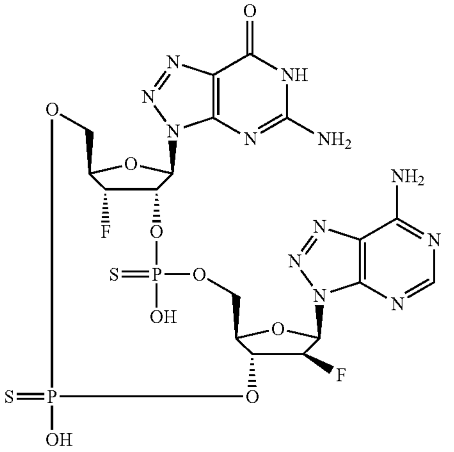
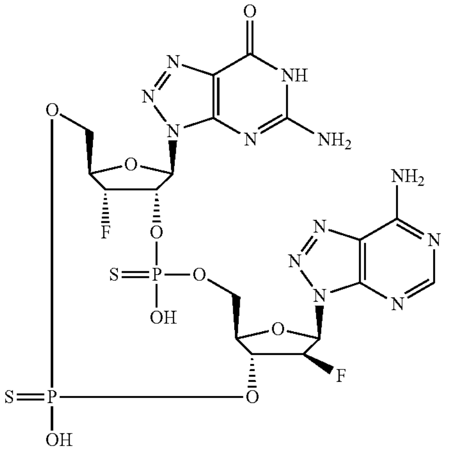
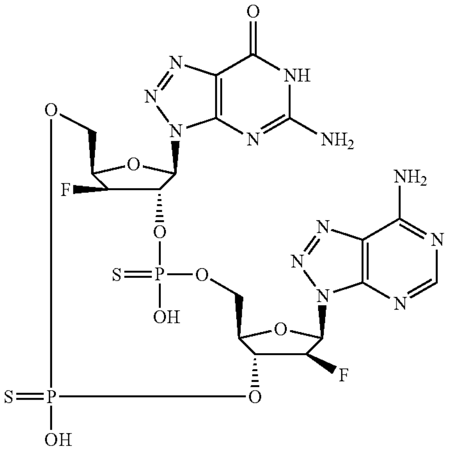
Ex.	Structure	Name	Mass $[M - H]^-$
200		5-amino-3-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-14-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-15,16-difluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 1)	711
201		5-amino-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-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 2)	711
202		5-amino-3-[(5R,7R,8S,12aR,14R,15S,15aR,16S)-14-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-15,16-difluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one	711

TABLE 6-continued

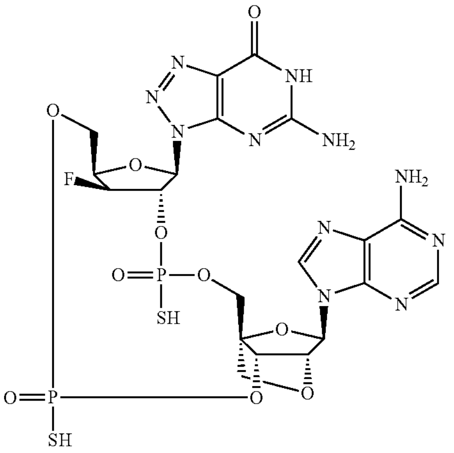
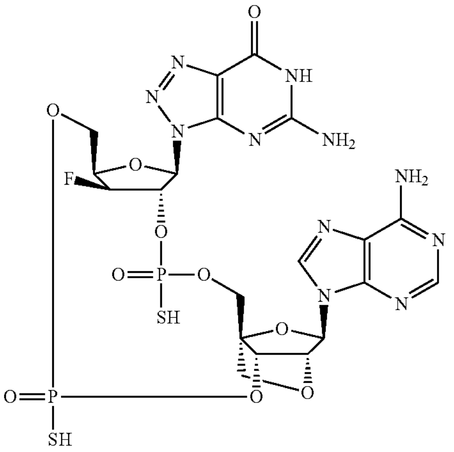
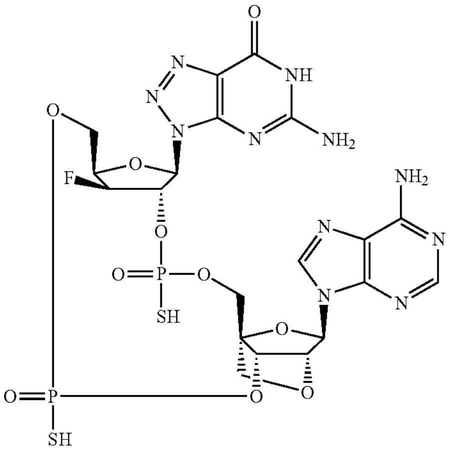
Ex.	Structure	Name	Mass [M − H]$^-$
203		5-amino-3-[(5R,7R,8S,12aR,14R,15R,15aS,18S)-14-(6-amino-9H-purin-9-yl)-18-fluoro-2,10-dioxido-2,10-disulfanylhexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7(12H)-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 1)	720
204		5-amino-3-[(5R,7R,8S,12aR,14R,15R,15aS,18S)-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]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 2)	720
205		5-amino-3-[(5R,7R,8S,12aR,14R,15R,15aS,18S)-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]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 3)	720

TABLE 6-continued

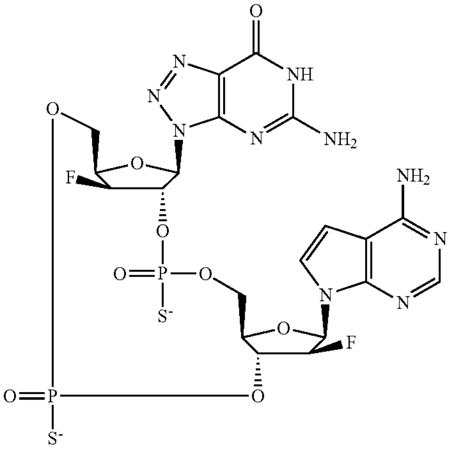
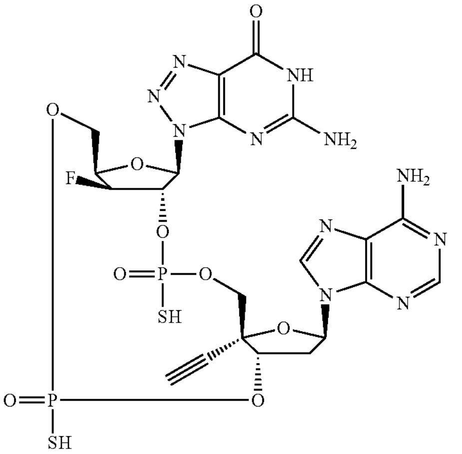
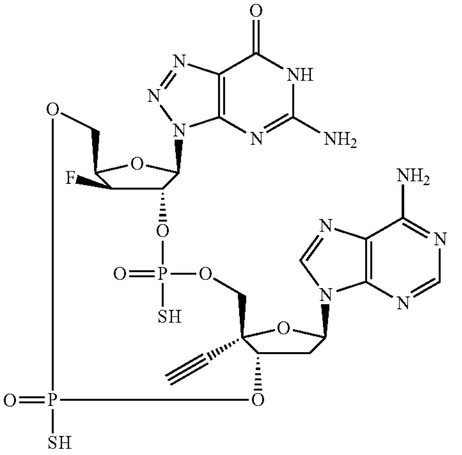
Ex.	Structure	Name	Mass [M − H]⁻
206		5-amino-3-[(5R,7R,8S,12aR,14R,15S,15aR,16S)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-15,16-difluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one	709
207		5-amino-3-[(5R,7R,8S,112aR,14R,15aS,16S)-14-(6-amino-9H-purin-9-yl)-12a-ethynyl-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]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 1)	716
208		5-amino-3-[(5R,7R,8S,112aR,14R,15aS,16S)-14-(6-amino-9H-purin-9-yl)-12a-ethynyl-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]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 2)	716

TABLE 6-continued

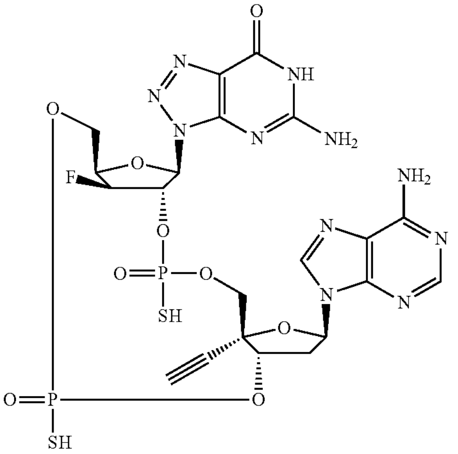
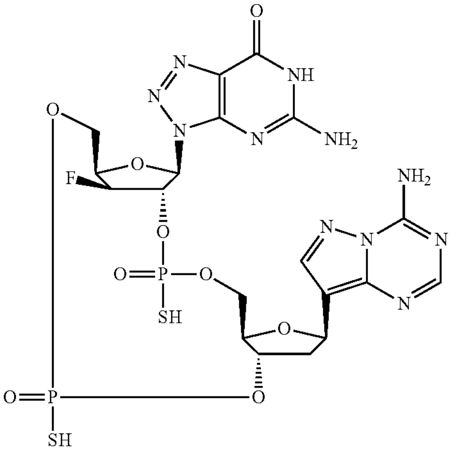
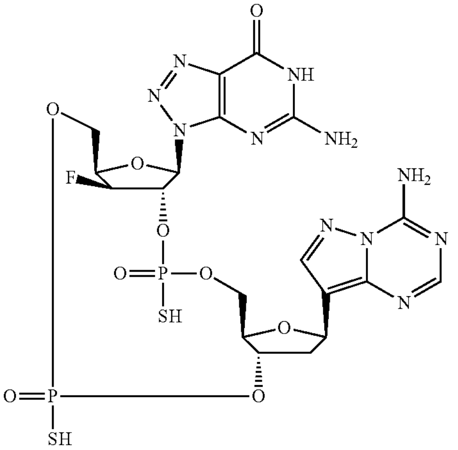
Ex.	Structure	Name	Mass [M − H]⁻
209		5-amino-3-[(5R,7R,8S,112aR,14R,15aS,16S)-14-(6-amino-9H-purin-9-yl)-12a-ethynyl-16-fluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 3)	716
210		5-amino-3-[(5R,7R,8S,12aR,14R,15aS,16S)-14-(4-aminopyrazolo[1,5-a][1,3,5]triazin-8-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]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 1)	692
211		5-amino-3-[(5R,7R,8S,12aR,14R,15aS,16S)-14-(4-aminopyrazolo[1,5-a][1,3,5]triazin-8-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]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 2)	692

TABLE 6-continued

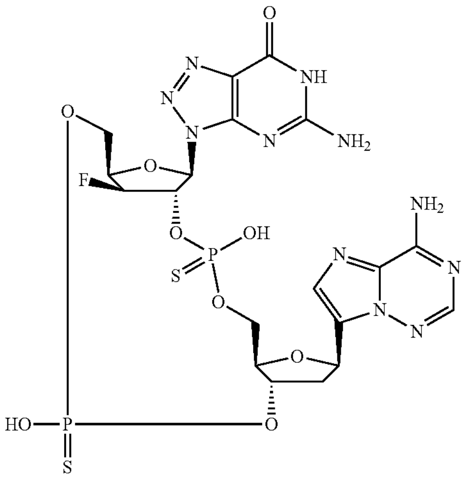
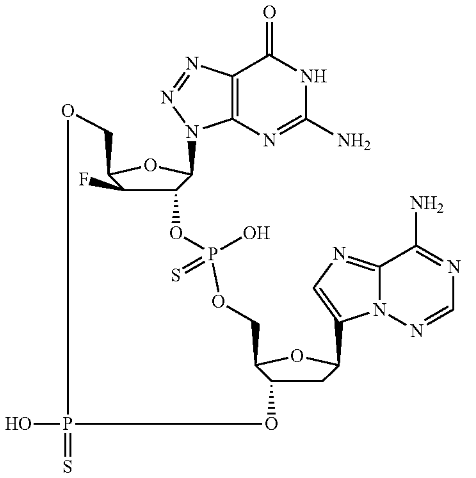
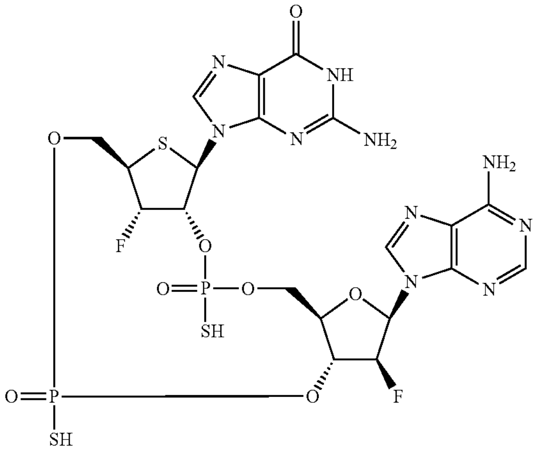
Ex.	Structure	Name	Mass $[M-H]^-$
212		5-amino-3-[(5R,7R,8S,12aR,14R,15aS,16S)-14-(4-aminoimidazo[2,1-f][1,2,4]triazin-7-yl)-16-fluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 1)	692
213		5-amino-3-[(5R,7R,8S,12aR,14R,15aS,16S)-14-(4-aminoimidazo[2,1-f][1,2,4]triazin-7-yl)-16-fluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 2)	692
214		2-amino-9-[(5R,7R,8R,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]tetraoxathiadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 1)	725

TABLE 6-continued

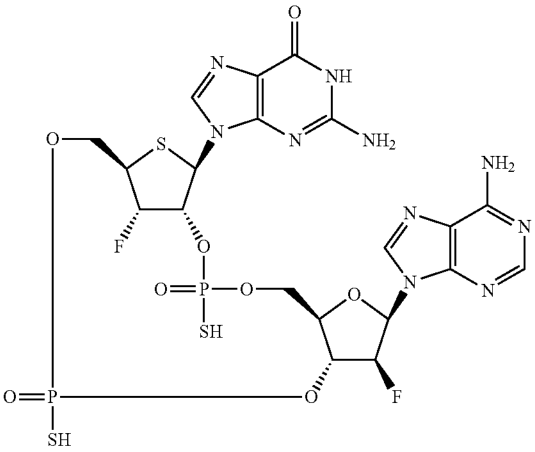
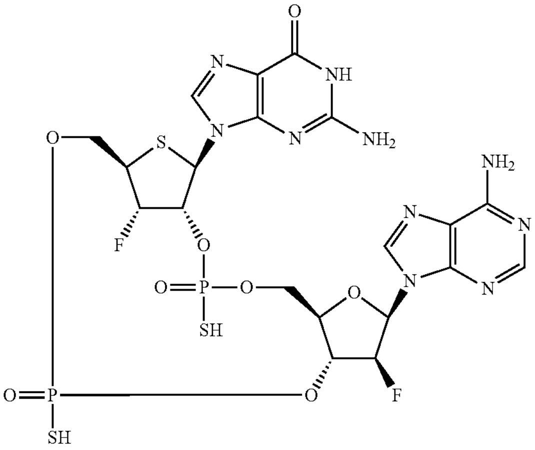
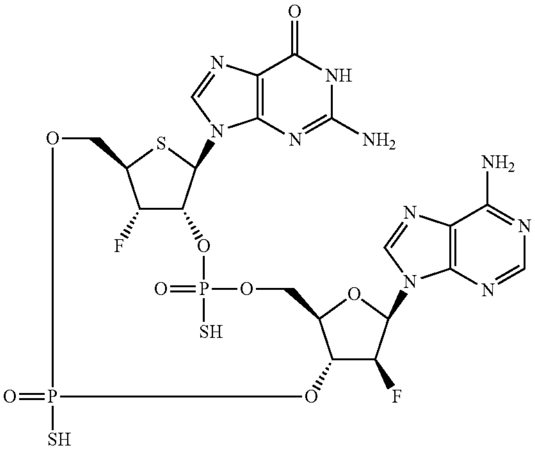
Ex.	Structure	Name	Mass $[M - H]^-$
215		2-amino-9-[(5R,7R,8R,12aR,14R,15S,15aR,16S)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 2)	725
216		2-amino-9-[(5R,7R,8R,12aR,14R,15S,15aR,16S)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 3)	725
217		2-amino-9-[(2R,5R,7R,8R,10R,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][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 4)	725

TABLE 6-continued

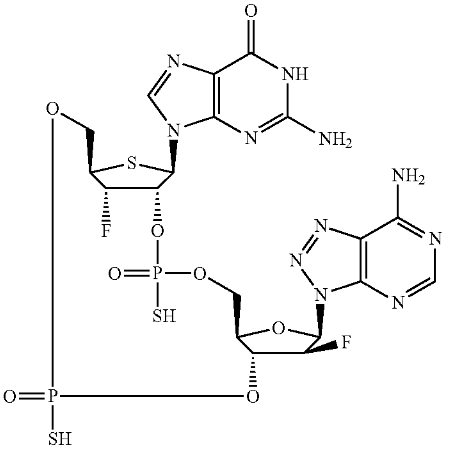
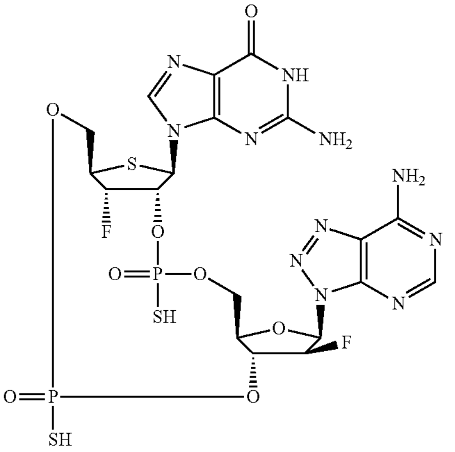
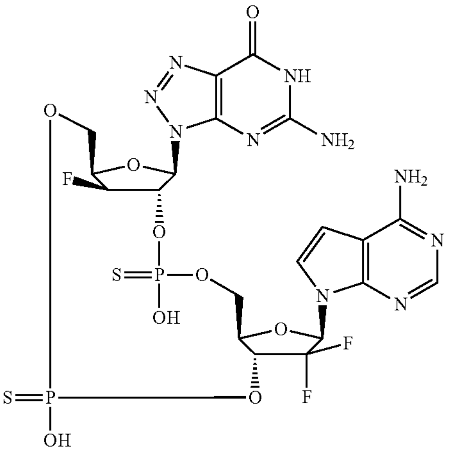
Ex.	Structure	Name	Mass [M − H]$^-$
218		2-amino-9-[(5R,7R,8R,12aR,14R,15S,15aR,16S)-14-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-15,16-difluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 1)	726
219		2-amino-9-[(5R,7R,8R,12aR,14R,15S,15aR,16S)-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][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 2)	726
220		5-amino-3-[(5R,7R,8S,12aR,14R,15aR,16S)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-15,15,16-trifluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one	727

TABLE 6-continued

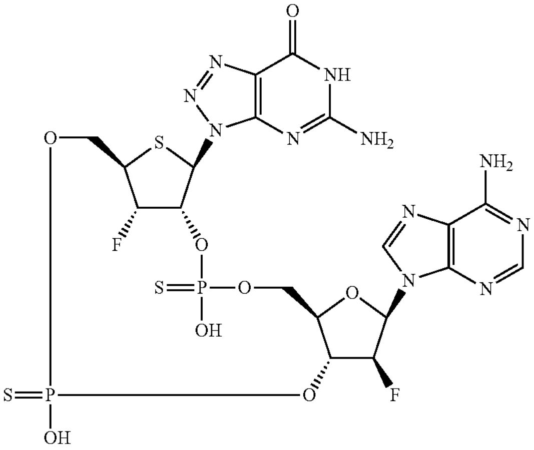
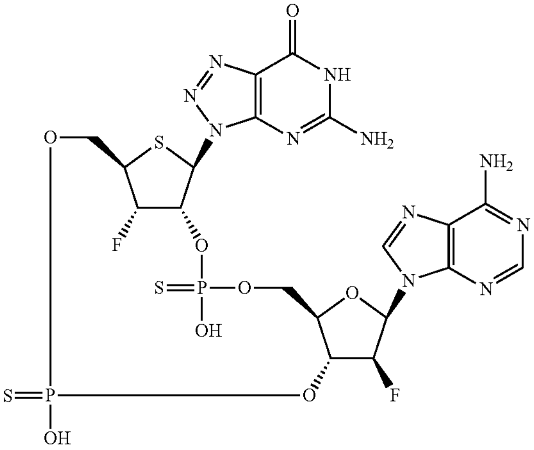
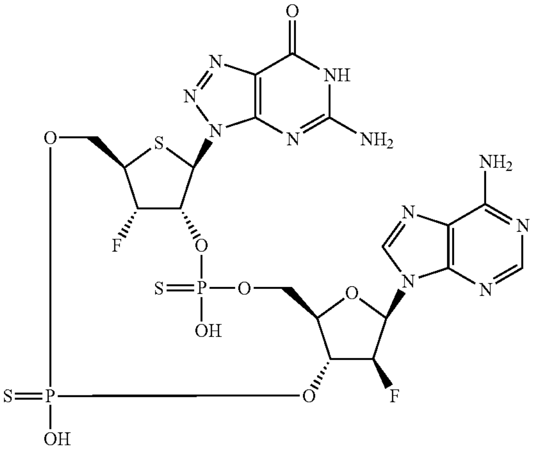
Ex.	Structure	Name	Mass [M − H]⁻
221		5-amino-3-[(5R,7R,8R,12aR,14R,15S,15aR,16S)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H41,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 1)	726
222		5-amino-3-[(5R,7R,8R,12aR,14R,15S,15aR,16S)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 2)	726
223		5-amino-3-[(5R,7R,8R,12aR,14R,15S,15aR,16S)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 3)	726

TABLE 6-continued

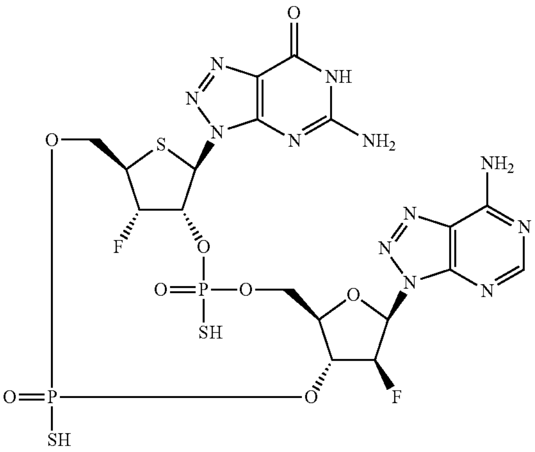
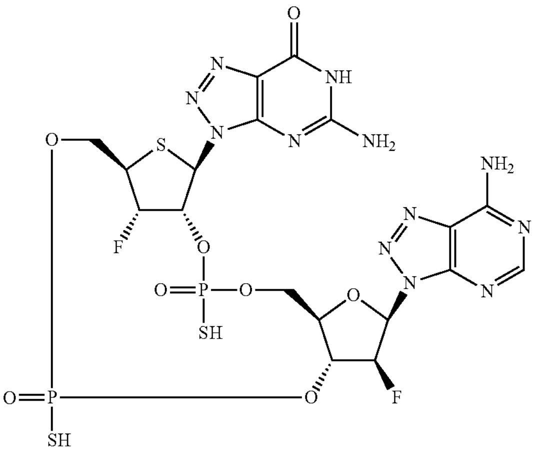
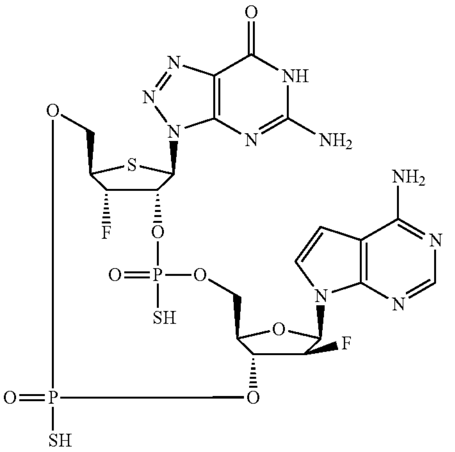
Ex.	Structure	Name	Mass [M − H]⁻
224		5-amino-3-[(5R,7R,8R,12aR,14R,15S,15aR,16S)-14-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-15,16-difluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathi adiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 1)	727
225		5-amino-3-[(5R,7R,8R,12aR,14R,15S,15aR,16S)-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][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 2)	727
226		5-amino-3-[(5R,7R,8R,12aR,14R,15S,15aR,16S)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-15,16-difluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 1)	725

TABLE 6-continued

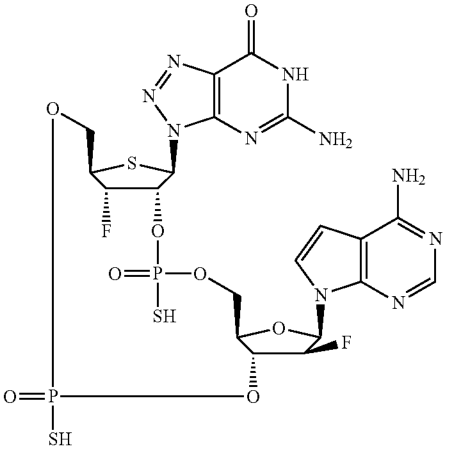
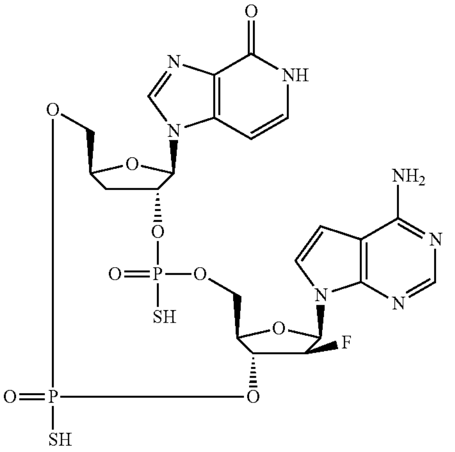
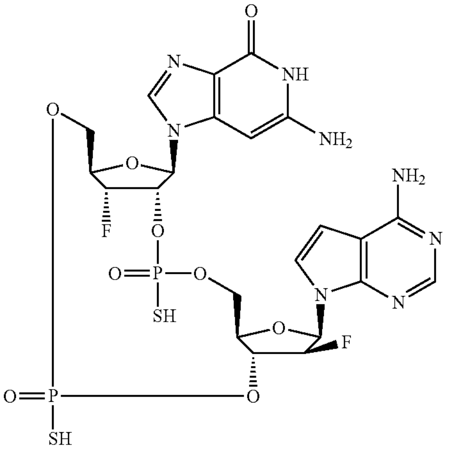
Ex.	Structure	Name	Mass [M − H]⁻
227		5-amino-3-[(5R,7R,8R,12aR,14R,15S,15aR,16S)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-15,16-difluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 2)	725
228		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	674
229		6-amino-1-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-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 (Diastereomer 1)	707

TABLE 6-continued

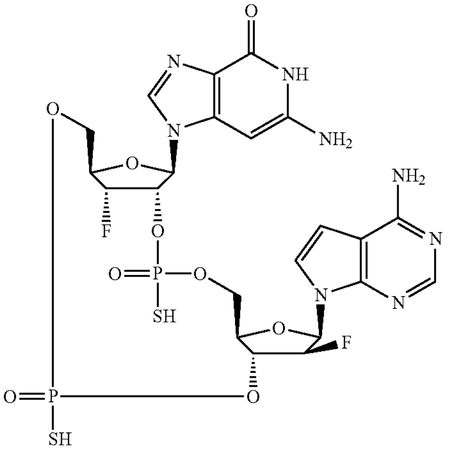
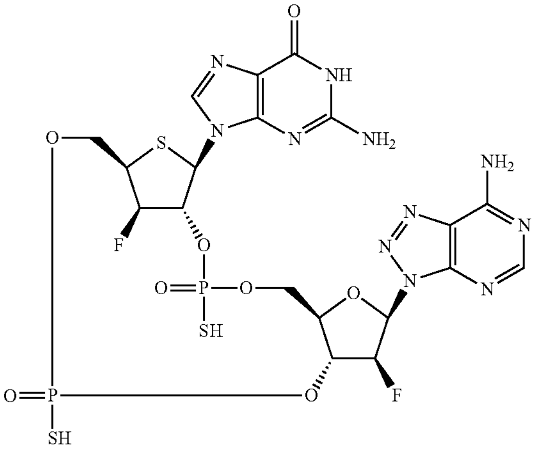
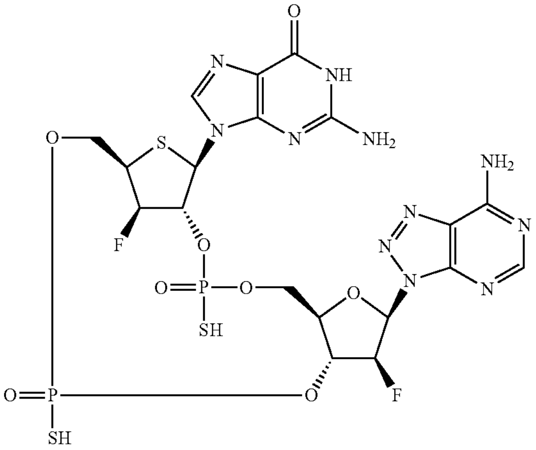
Ex.	Structure	Name	Mass [M − H]⁻
230		6-amino-1-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-15,16-difluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,5-dihydro-4H-imidazo[4,5-c]pyridin-4-one (Diastereomer 2)	707
231		2-amino-9-[(5R,7R,8R,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][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 1)	726
232		2-amino-9-[(5R,7R,8R,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][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 2)	726

TABLE 6-continued

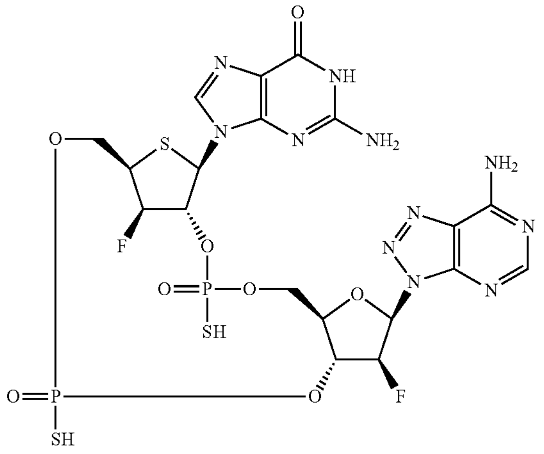
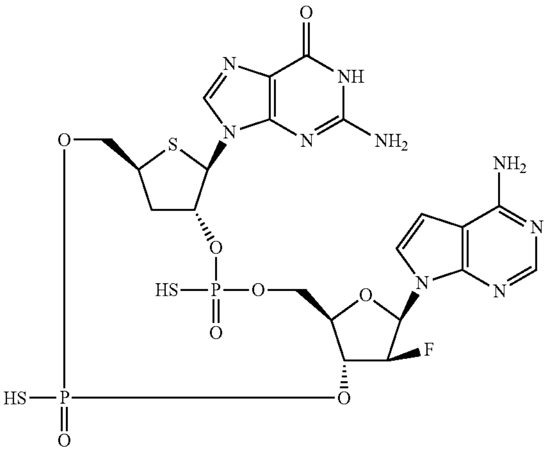
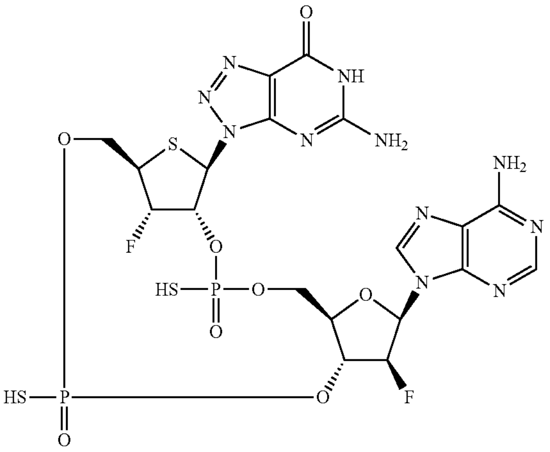
Ex.	Structure	Name	Mass [M − H]⁻
233		2-amino-9-[(5R,7R,8R,12aR,14R,15S,15aR,16R)-14-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-15,16-difluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 3)	726
234		2-amino-9-[(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][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	706
235		5-amino-3-[(5R,7R,8R,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][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclodecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one	726

TABLE 6-continued

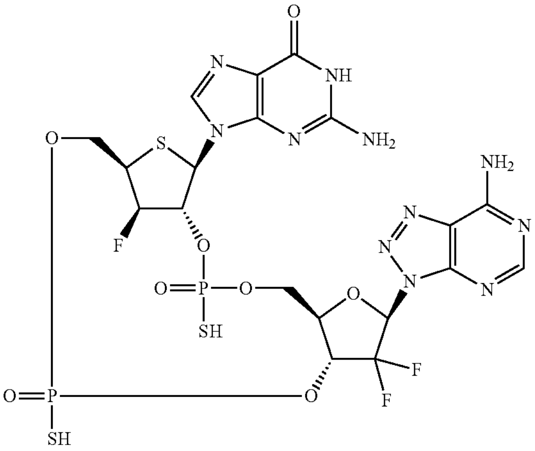
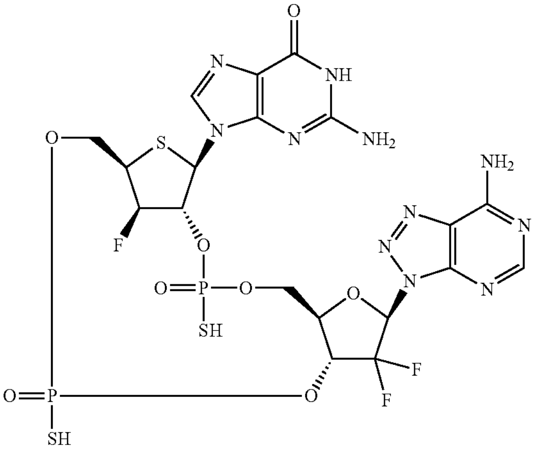
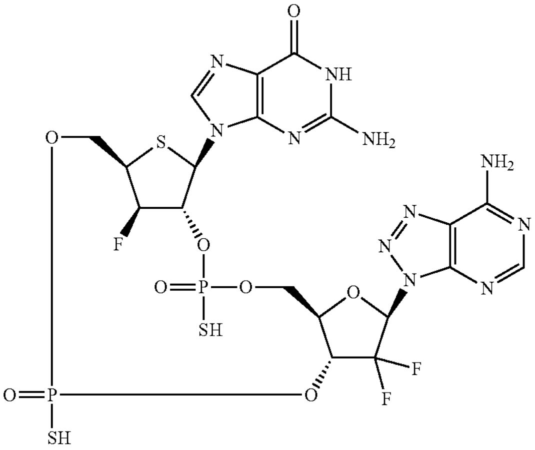
Ex.	Structure	Name	Mass [M − H]⁻
236		2-amino-9-[(5R,7R,8R,12aR,14R,15aR,16R)-14-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-15,15,16-trifluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 1)	744
237		2-amino-9-[(5R,7R,8R,12aR,14R,15aR,16R)-14-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-15,15,16-trifluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 2)	744
238		2-amino-9-[(5R,7R,8R,12aR,14R,15aR,16R)-14-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-15,15,16-trifluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 3)	744

TABLE 6-continued

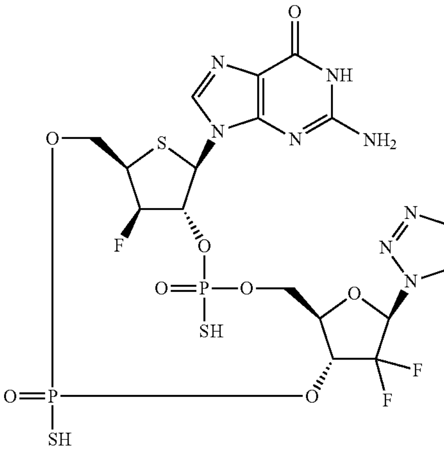
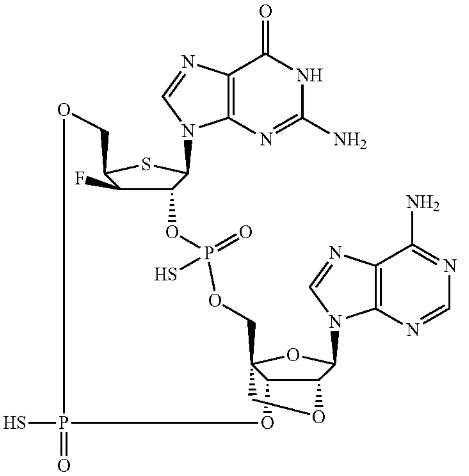
Ex.	Structure	Name	Mass [M − H]⁻
239		2-amino-9-[(5R,7R,8R,12aR,14R,15aR,16R)-14-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-15,15,16-trifluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 4)	744
240		2-amino-9-[(5R,7R,8R,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][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7(12H)-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 1)	735

TABLE 6-continued

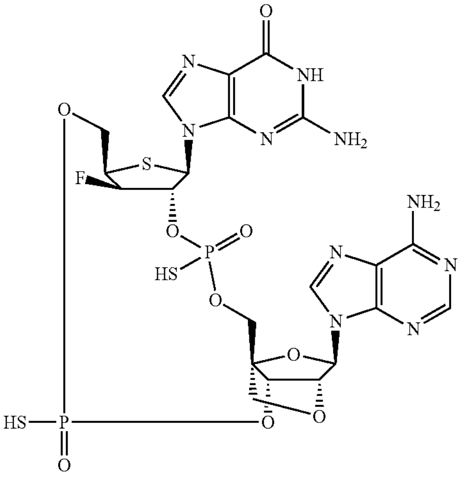
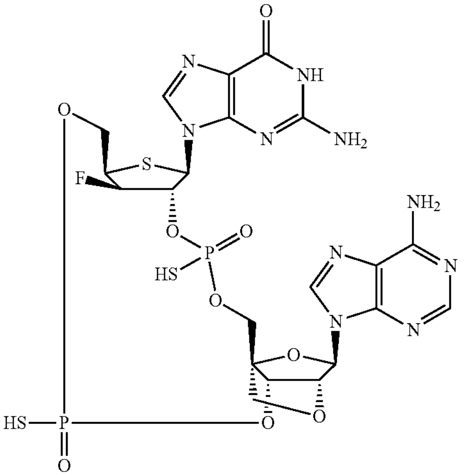
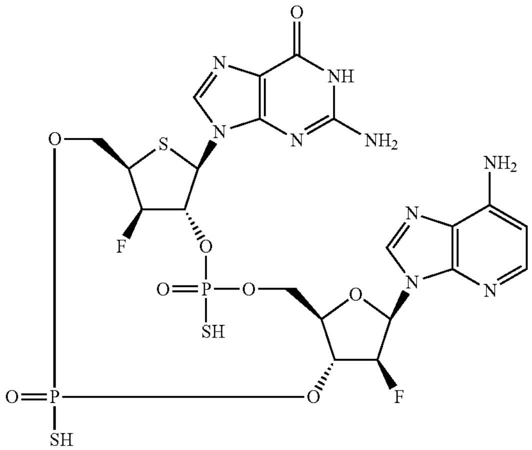
Ex.	Structure	Name	Mass [M − H]$^-$
241		2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,18R)-14-(6-amino-9H-purin-9-yl)-18-fluoro-2,10-dioxido-2,10-disulfanylhexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7(12H)-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 2)	735
242		2-amino-9-[(5R,7R,8R,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][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7(12H)-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 3)	735

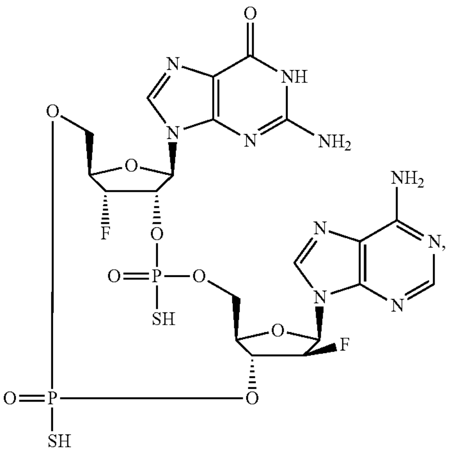
TABLE 6-continued

Ex.	Structure	Name	Mass $[M-H]^-$
243		2-amino-9-[(5R,7R,8R,12aR,14R,15S,15aR,16R)-14-(7-amino-3H-imidazo[4,5-b]pyridin-3-yl)-15,16-difluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	724

Examples 244, 245, 246, and 247: 2-amino-9-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomers 1-3) and 2-amino-9-[(2R,5R,7R,8S,10R,12aR,14R,15S,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-2,10-disulfidooctahydro-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 4)

[0764]

Diastereomer 1



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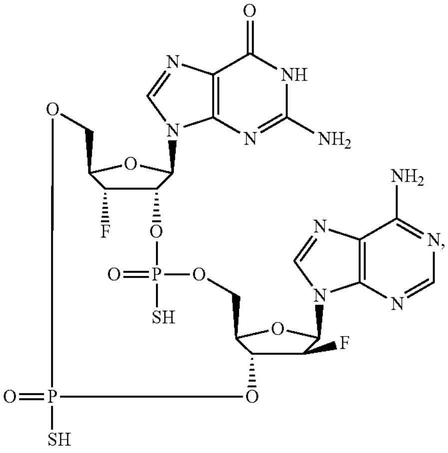
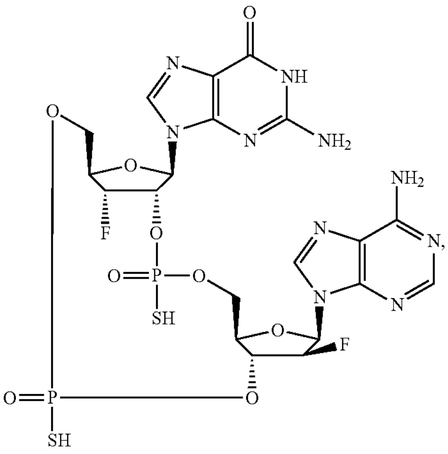
Diastereomer 2

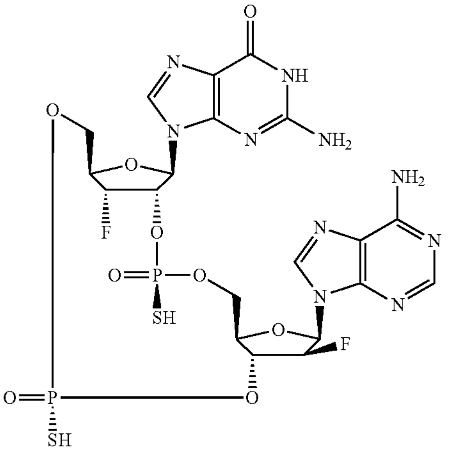


Diastereomer 3



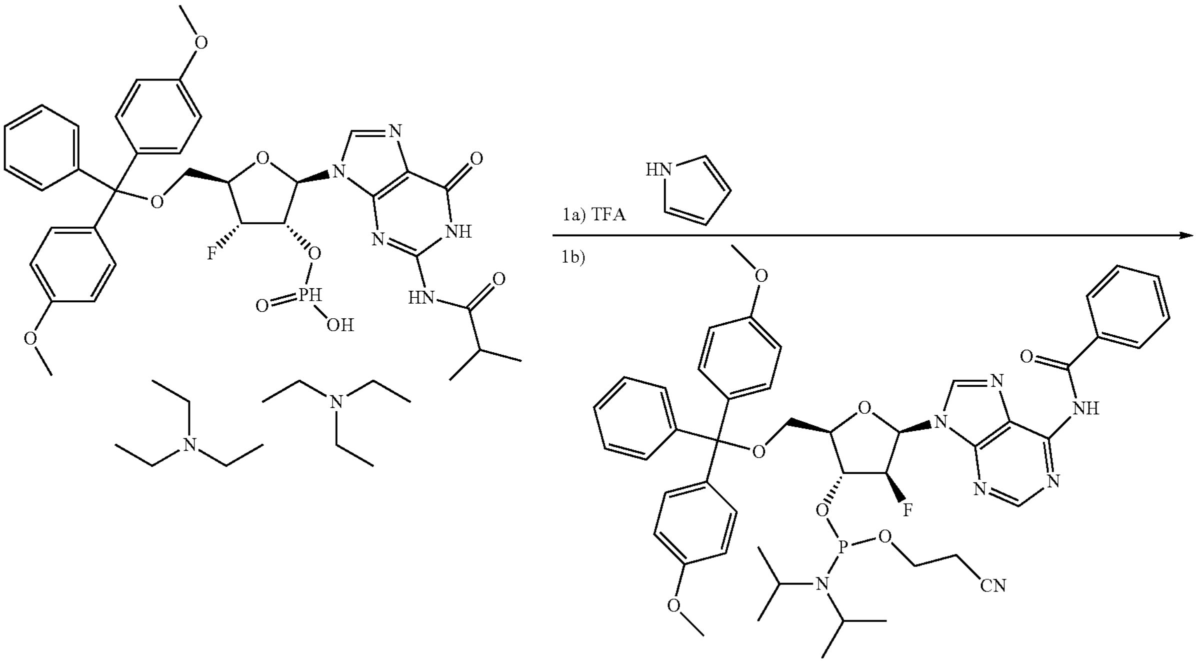
-continued

Diastereomer 4



Step 1. (2R,3S,4R,5R)-5-((((((2R,3R,4S,5R)-5-(6-benzamido-9H-purin-9-yl)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-fluorotetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphanyl)oxy)methyl)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl hydrogen phosphonate

[0765]



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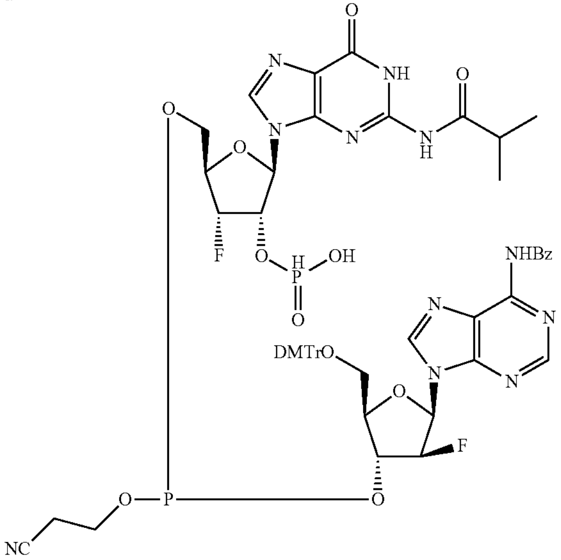
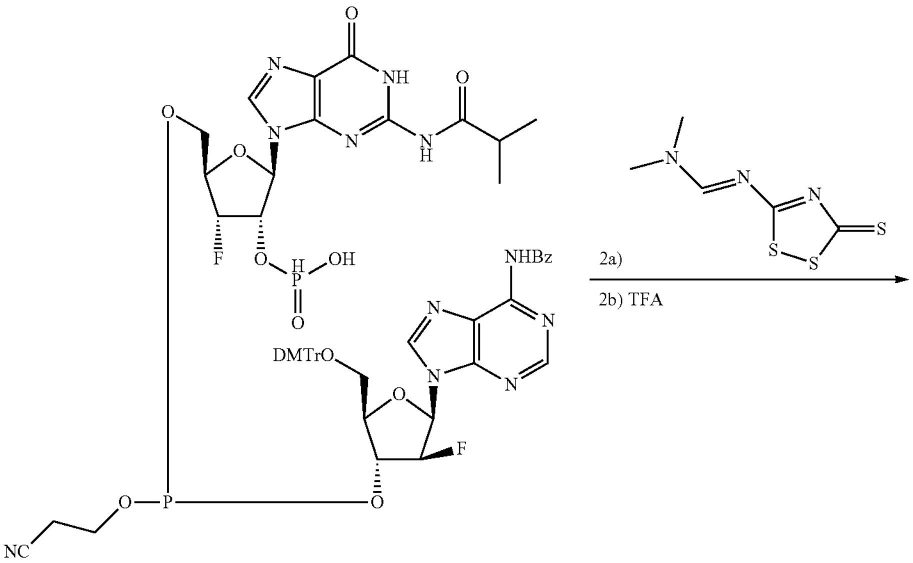


[0766] Pyrrole (0.087 mL, 1.2 mmol) was added to a solution of (2R,3S,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl hydrogen phosphonate triethylamine salt (1:2) (0.34 g, 0.41 mmol) in acetonitrile (3.0 mL) under an argon atmosphere at 0° C. After 5 min, TFA (0.096 mL, 0.14 mmol) was added, and the reaction mixture was stirred at 0° C. for 30 min. Pyridine (0.13 mL, 1.7 mmol) was added drop wise at 0° C. The reaction mixture was then stirred for 10 min at 0° C. At that time, a mixture 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 (0.48 g, 0.55 mmol) in acetonitrile (3.0 mL) was added drop wise over 5 min to the reaction mixture under an argon atmosphere at 0° C. The reaction mixture was stirred at 0° C. for 20 min and immediately used in the next step without further manipulation.

Step 2. (2R,3S,4R,5R)-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)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl hydrogen phosphonate

[0767]



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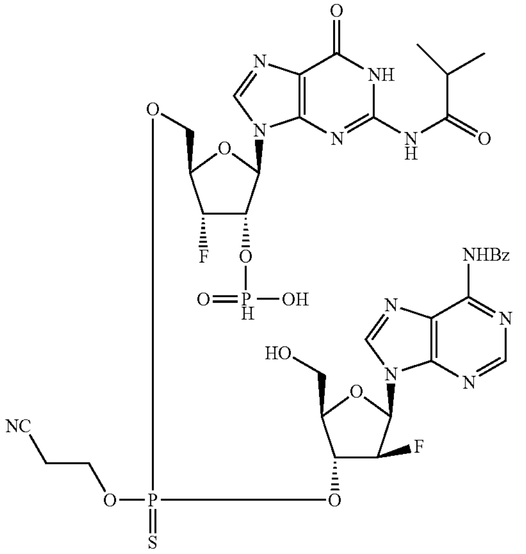
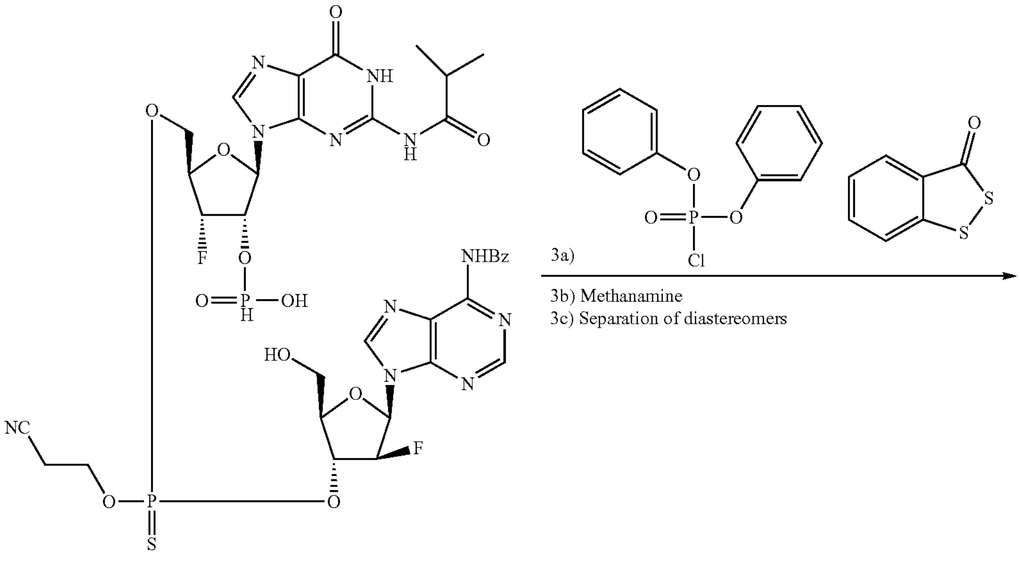


[0768] To the crude reaction mixture from Step 1 was added (E)-N,N-dimethyl-N'-(3-thioxo-3H-1,2,4-dithiazol-5-yl)formimidamide (0.10 g, 0.50 mmol) under an argon atmosphere at 0° C. The reaction mixture was stirred for 45 minutes at 0° C. At that time, 1-propanol (0.31 mL, 4.13 mmol) was added to the reaction mixture under an argon atmosphere at 0° C. The reaction mixture was then allowed to warm to ambient temperature and stirred for 10 min. TFA (0.32 mL, 4.1 mmol) was added to the reaction mixture, and the reaction mixture was stirred for 30 min at ambient temperature. Pyridine (0.37 mL, 4.6 mmol) was added at ambient temperature, and the reaction mixture was stirred for 10 min. The reaction mixture was concentrated under reduced pressure to approximately one-half volume. The mixture was then diluted with isopropyl acetate (20 mL) and stirred for 30 min at ambient temperature. The resulting suspension was filtered. The collected solids were dried overnight under high vacuum to afford (2R,3 S,4R,5R)-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)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl) tetrahydrofuran-3-yl hydrogen phosphonate. LCMS (ES, m/z): 922 [M−H]$^-$.

Step 3: 2-amino-9-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one

[0769]



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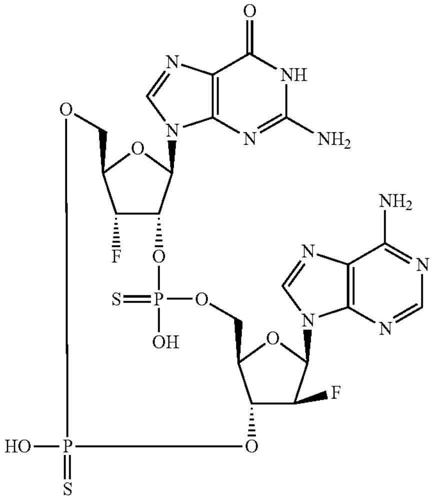


Diastereomers 1-4

[0770] (2R,3 S,4R,5R)-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)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl hydrogen phosphonate (0.30 g, 0.33 mmol) was azeotroped with dry pyridine (2×10 mL) and then dried under high vacuum for 1 h. In a separate flask, diphenyl phosphorochloridate (0.34 mL, 1.6 mmol) was added to a mixture of acetonitrile (15 mL) and pyridine (1.0 mL). The resulting solution was then cooled to −20° C. To this mixture was added drop wise over a period of 5 min a mixture of (2R,3 S,4R,5R)-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)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl hydrogen phosphonate (0.30 g, 0.33 mmol) in pyridine (4.0 mL) at −20° C. The reaction mixture was then stirred at −20° C. for 15 min post-addition. 3H-benzo[c][1,2]dithiol-3-one (0.066 g, 0.39 mmol) and water (0.12 mL, 6.5 mmol) were then added to the reaction mixture at −20° C. The reaction mixture was allowed to gradually warm to ambient temperature. The reaction mixture was stirred for 30 min at ambient temperature. The reaction mixture was then concentrated under reduced pressure to approximately one quarter volume. The reaction mixture was cooled to 0° C., and methanamine (33% in ethanol) (2.63 mL, 24 mmol) was added drop wise. After the addition was complete, the reaction mixture was allowed to warm to ambient temperature. The reaction mixture was stirred at ambient temperature for 18 h. The reaction mixture was concentrated under reduced pressure to afford the crude product residue. The crude product residue was azeotroped (3×30 mL ethanol) to afford the crude product. This material was dissolved in water (5 mL) and acetonitrile (1 mL). The resulting mixture was purified by mass-directed reverse phase HPLC (Waters Sunfire 19×250 mm, UV 215/254 nm, fraction trigger by SIM negative MS monitoring mass 709; mobile phase=100 mM triethylammonium acetate in water/acetonitrile gradient, 2-30% acetonitrile over 40 min) to afford the 4 diastereomers of 2-amino-9-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one.

[0771] Example 244: 2-amino-9-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-2,10-disulfidooctahydro-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): T_R=17.7 min. LCMS (ES, m/z): 709 $[M-H]^-$.

[0772] Example 245: 2-amino-9-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-2,10-disulfidooctahydro-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 2): T_R=21.9 min. LCMS (ES, m/z): 709 $[M-H]^-$. 1H NMR (500 MHz, DMSO-d_6) δ 8.32 (s, 1H), 8.21-8.09 (m, 2H), 7.46-7.29 (m, 2H), 6.59-6.43 (m, 2H), 6.40-6.29 (m, 1H), 5.88 (d, J=8.8 Hz, 1H), 5.49-5.19 (m, 4H), 4.45-4.32 (m, 2H), 4.10-3.93 (m, 2H), 3.94-3.82 (m, 1H), 3.80-3.68 (m, 1H).

[0773] Example 246: 2-amino-9-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-2,10-disulfidooctahydro-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 3): T_R=23.8 min. LCMS (ES, m/z): 709 $[M-H]^-$. 1H NMR (500 MHz, DMSO-d_6) δ 8.18-8.08 (m, 3H), 7.41-7.33 (m, 2H), 6.59-6.47 (m, 2H), 6.37-6.27 (m, 1H), 5.84 (d, J=8.7 Hz, 1H), 5.52-5.26 (m, 2H), 5.21-5.11 (m, 1H), 4.46-4.35 (m, 2H), 4.19-4.02 (m, 2H), 3.83-3.65 (m, 2H).

[0774] Example 247: 2-amino-9-[(2R,5R,7R,8S,10R,12aR,14R,15S,15 aR,16R)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-2,10-disulfidooctahydro-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 4): T_R=26.4 min. LCMS (ES, m/z): 709 $[M-H]^-$. ^1H NMR (500 MHz, DMSO-d_6) δ 8.19-8.07 (m, 3H), 7.41-7.32 (m, 2H), 6.70-6.50 (m, 2H), 6.40-6.29 (m, 1H), 5.85 (d, J=8.7 Hz, 1H), 5.33-5.25 (m, 2H), 5.23-5.12 (m, 1H), 4.48-4.35 (m, 1H), 4.33-4.24 (m, 1H), 4.09-3.93 (m, 2H), 3.92-3.81 (m, 1H), 3.83-3.70 (m, 1H).

[0775] Examples 248 through 256, as shown in Table 7 below, were prepared according to procedures analogous to those outlined in Examples 244 through 247 above using the appropriate monomers, described as Preparations or as obtained from commercial sources, in the coupling step.

TABLE 7

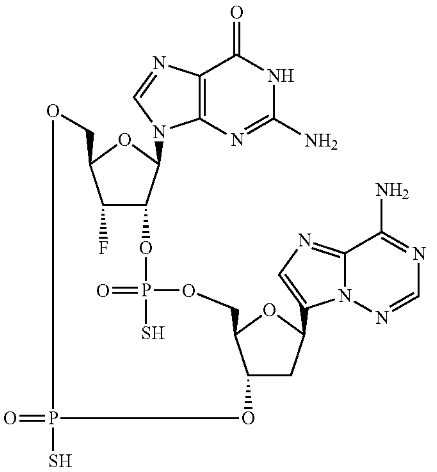
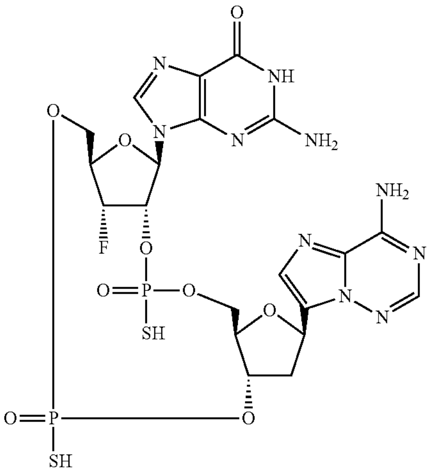
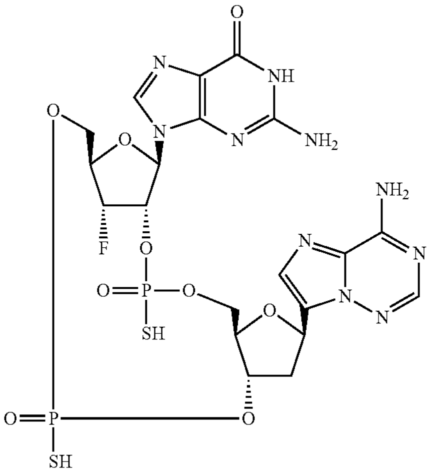
Ex.	Structure	Name	Mass [M − H]⁻
248		2-amino-9-[(5R,7R,8S,12aR,14R,15aS,16R)-14-(4-aminoimidazo[2,1-f][1,2,4]triazin-7-yl)-16-fluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-1][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 1)	691
249		2-amino-9-[(5R,7R,8S,12aR,14R,15aS,16R)-14-(4-aminoimidazo[2,1-f][1,2,4]triazin-7-yl)-16-fluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-1][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 2)	691
250		2-amino-9-[(5R,7R,8S,12aR,14R,15aS,16R)-14-(4-aminoimidazo[2,1-f][1,2,4]triazin-7-yl)-16-fluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-1][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 3)	691

TABLE 7-continued

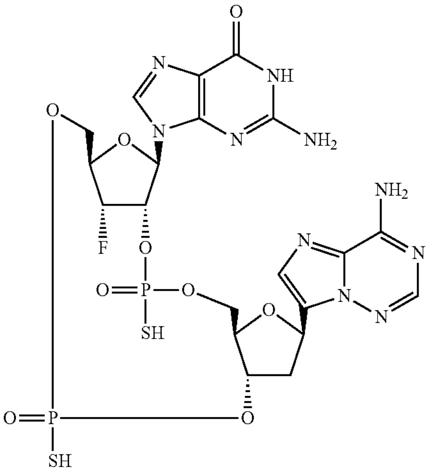
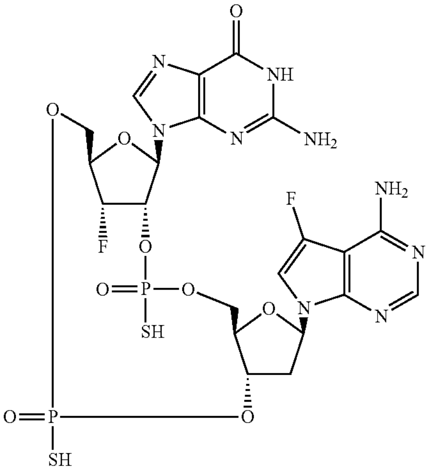
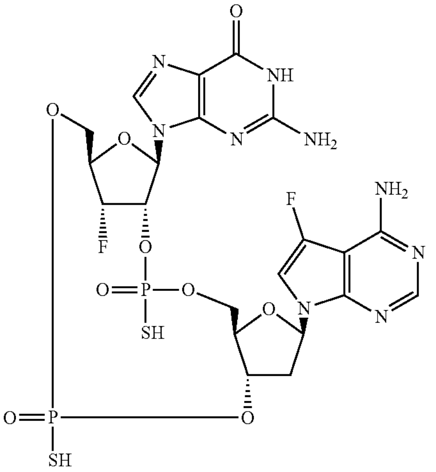
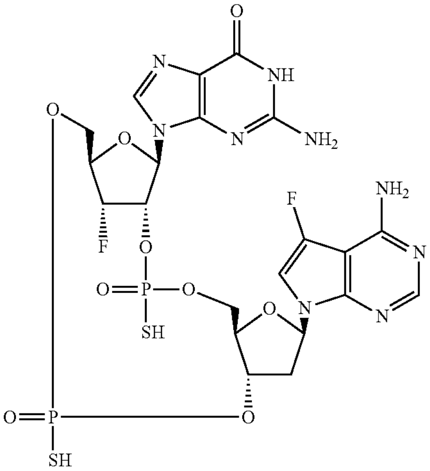
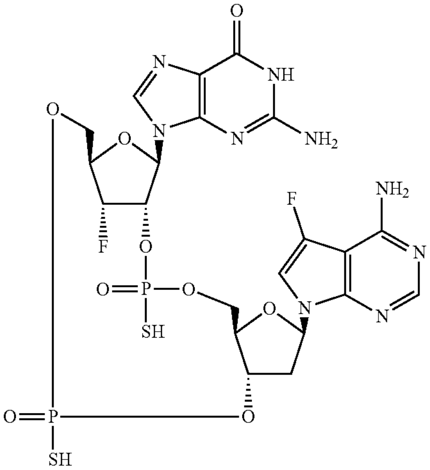
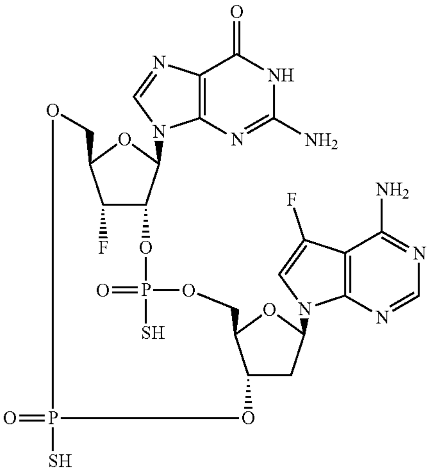
Ex.	Structure	Name	Mass [M − H]⁻
251		2-amino-9-[(5R,7R,8S,12aR,14R,15aS,16R)-14-(4-aminoimidazo[2,1-f][1,2,4]triazin-7-yl)-16-fluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-1][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 4)	691
252		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[3,2-1][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 1)	708
253		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[3,2-1][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 2)	708

TABLE 7-continued

Ex.	Structure	Name	Mass [M − H]⁻
254		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[3,2-1][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 3)	708
255		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-10-hydroxy-2,10-dioxido-2-sulfanyloctahydro-12H-5,8-methanofuro[3,2-1][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 1)	692
256		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-10-hydroxy-2,10-dioxido-2-sulfanyloctahydro-12H-5,8-methanofuro[3,2-1][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 2)	692

[0776] Examples 257 through 259 in Table 8 were made according to procedures analogous to those described above for Examples 244 through 247 using the appropriate monomeric nucleosides, described as Preparations or as obtained from commercial sources, with the following additional representative treatment as a final step: A sample (0.12 mmol) was dissolved in water (6 mL), and the resulting mixture was applied to ion exchange resin in a column (DOWEX 50WX2 hydrogen form, 100-200 mesh, 1.5 g, pre-washed with 10 mL water, and then packed in column before compound loading occurred). After loading mixture had completely absorbed to column, the column was then washed with additional water (10 mL). The eluent was lyophilized to afford product.

TABLE 8

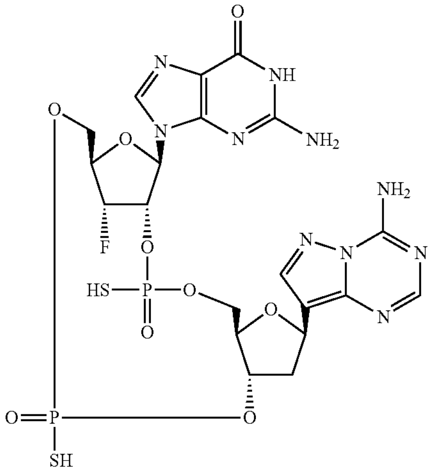
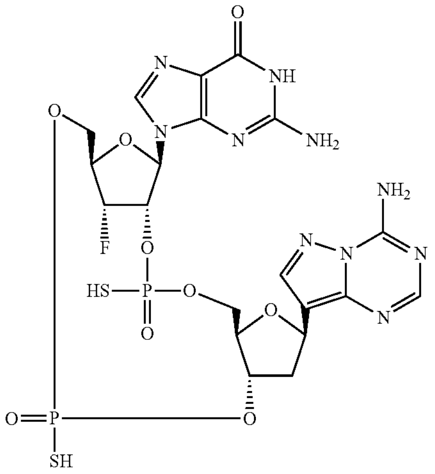
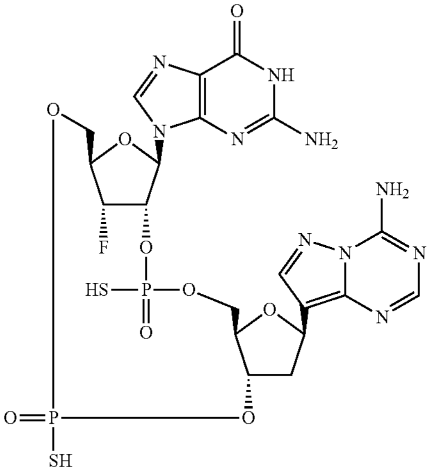
Ex.	Structure	Name	Mass [M − H]−
257		2-amino-9-[(5R,7R,8S,12aR,14R,15aS,16R)-14-(4-aminopyrazolo[1,5-a][1,3,5]triazin-8-yl)-16-fluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 1)	691
258		2-amino-9-[(5R,7R,8S,12aR,14R,15aS,16R)-14-(4-aminopyrazolo[1,5-a][1,3,5]triazin-8-yl)-16-fluoro-2,10-dihydroxy-2,10-disulfidooctahydro-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 2)	691

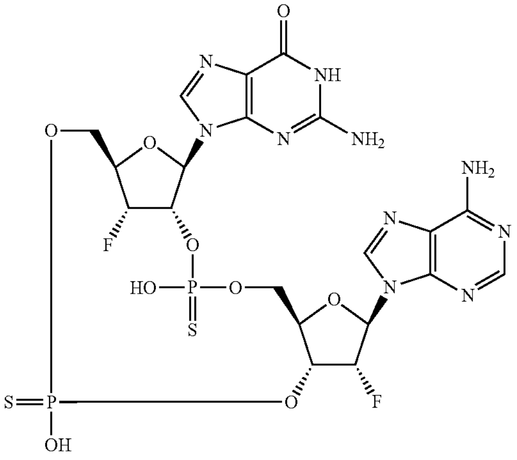
TABLE 8-continued

Ex.	Structure	Name	Mass [M − H]−
259		2-amino-9-[(5R,7R,8S,12aR,14R,15aS,16R)-14-(4-aminopyrazolo[1,5-a][1,3,5]triazin-8-yl)-16-fluoro-2,10-dihydroxy-2,10-disulfidooctahydro-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 3)	691

[0777] Alternatively, Examples 117-142, 144-152, 172, 174, and 244-247, above were made using procedures similar to those described for Examples 81 through 83 above.

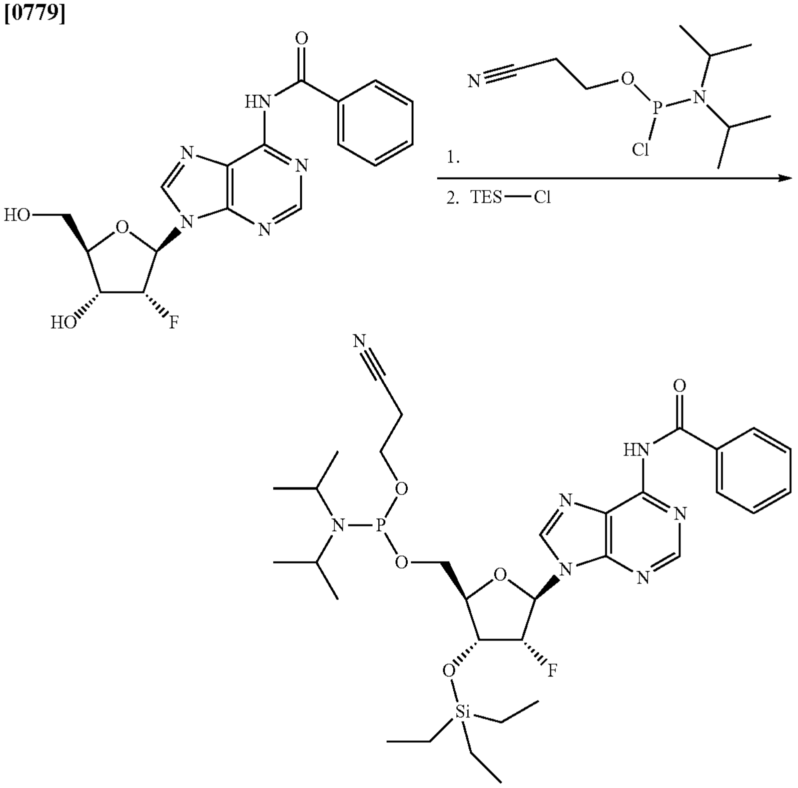
Example 260: 2-amino-9-[(5R,7R,8S,12aR,14R,15R,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one

[0778]



Step 1. ((2R,3R,4R,5R)-5-(6-benzamido-9H-purin-9-yl)-4-fluoro-3-((triethylsilyl)oxy)tetrahydrofuran-2-yl)methyl (2-cyanoethyl) diisopropylphosphoramidite

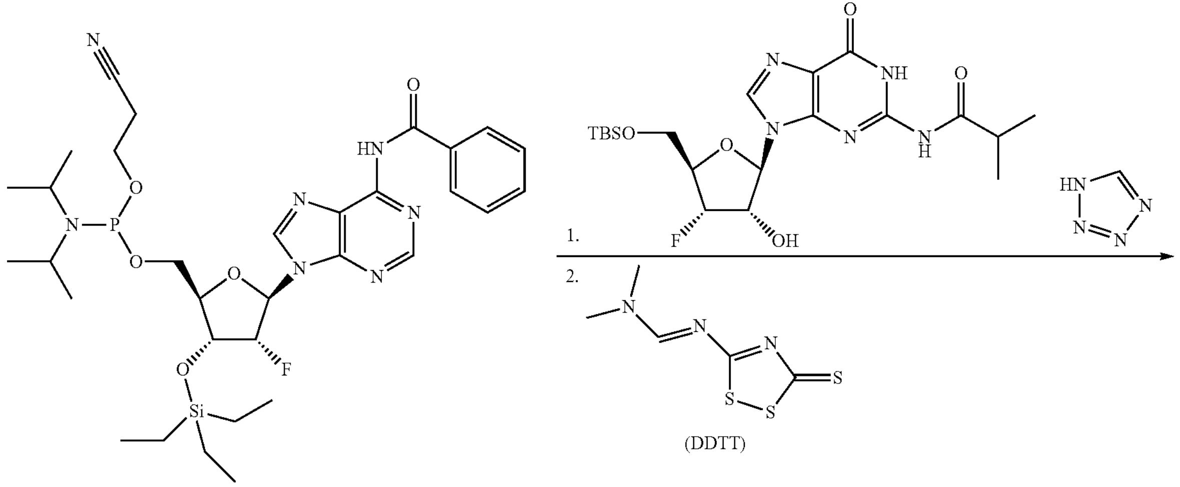
[0779]



[0780] To a solution of N-(9-((2R,3R,4R,5R)-3-fluoro-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-9H-purin-6-yl)benzamide (780 mg, 2.089 mmol) in DMF (8 mL) and DIPEA (1.116 mL, 6.39 mmol) at 0° C. was added 200 mg activated molecular sieve 4 Å and 2-cyanoethyl N,N-diisopropylchlorophosphoramidite (572 mg, 2.343 mmol) in 1 ml dry CH_3CN. The resulting mixture was stirred at 0° C. for 5 h; chlorotriethylsilane (401 mg, 2.66 mmol) was added dropwise. The resulting mixture was stirred at rt overnight. The reaction carried directly to next step. LCMS (ES, m/z): 686 $[M-H]^-$.

Step 2: O-(((2R,3R,4R,5R)-5-(6-benzamido-9H-purin-9-yl)-4-fluoro-3-((triethylsilyl)oxy) tetrahydrofuran-2-yl)methyl)O-((2R,3S,4R,5R)-5-(((tert-butyldimethylsilyl)oxy)methyl)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl) tetrahydrofuran-3-yl)O-(2-cyanoethyl) phosphorothioate

[0781]



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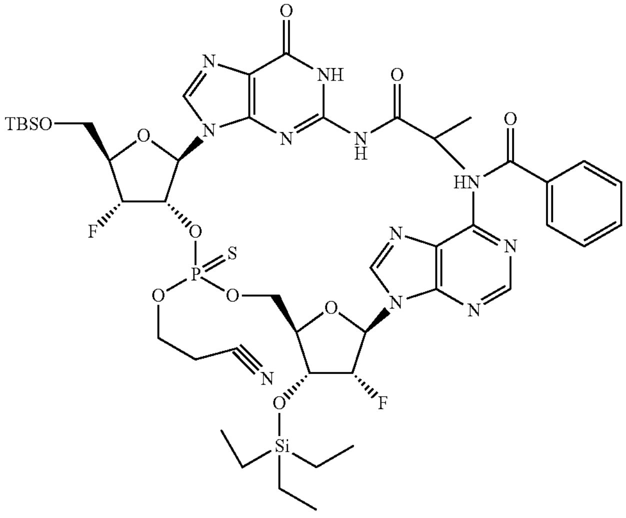
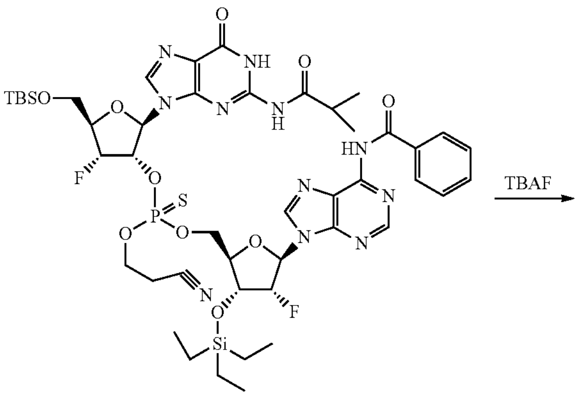


[0782] To a solution of the product of step 1 was added N-(9-((2R,3 S,4S,5R)-5-(((tert-butyldimethylsilyl)oxy)methyl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide (500 mg, 1.065 mmol) and 1H-tetrazole (895 mg, 12.78 mmol). The mixture was stirred at RT for 2 h, and DDTT (568 g, 2.77 mmol) was added. The mixture was stirred for 1 h, then partitioned between ethyl acetate and H_2O, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting with 0-6% MeOH/DCM to give O-(((2R,3R,4R,5R)-5-(6-benzamido-9H-purin-9-yl)-4-fluoro-3-((triethyl silyl)oxy)tetrahydrofuran-2-yl)methyl)O-((2R,3 S,4R,5R)-5-(((tert-butyldimethylsilyl)oxy)methyl)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl)O-(2-cyanoethyl) phosphorothioate. LCMS (ES, m/z): 1088 $[M+H]^+$

Step 3: O-(((2R,3R,4R,5R)-5-(6-benzamido-9H-purin-9-yl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)methyl)O-((2R,3S,4R,5R)-4-fluoro-5-(hydroxymethyl)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl)O-hydrogen phosphorothioate

[0783]



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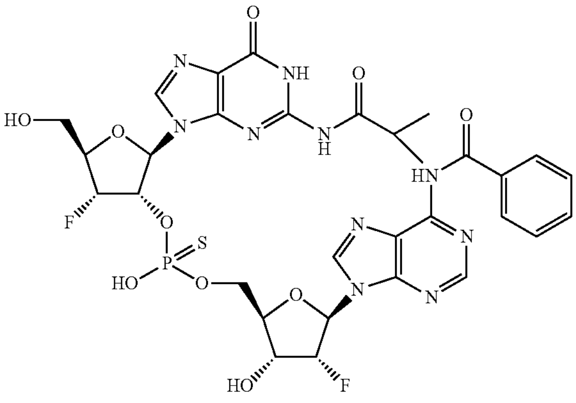
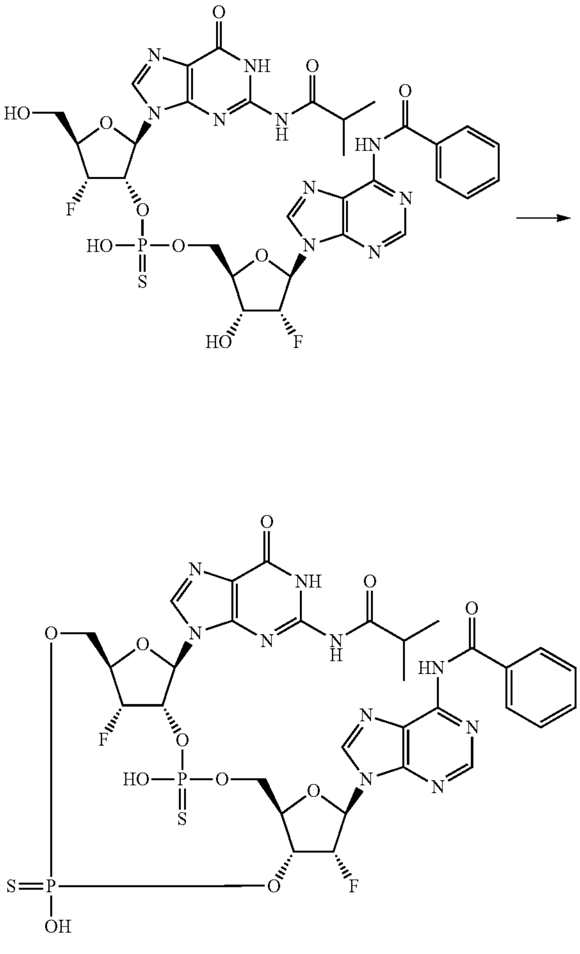


[0784] To a solution of the mixture (520 mg) from step 3 in THE (5 mL) was added TBAF (1.0M in THF) (1.140 mL, 1.140 mmol). The resulting mixture was stirred at RT for 2 h and concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting with 0-8% MeOH/DCM to give O-(((2R,3R,4R,5R)-5-(6-benzamido-9H-purin-9-yl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)methyl)O-((2R,3 S,4R,5R)-4-fluoro-5-(hydroxymethyl)-2-(2-isobutyramido-6-oxo-1H-purin-9(6H)-yl)tetrahydrofuran-3-yl)O-hydrogen phosphorothioate. LCMS (ES, m/z): 807 $[M+H]^+$

Step 4. N-{9-[(5R,7R,8S,12aR,14R,15R,15aR,16R)-15,16-difluoro-2,10-dihydroxy-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]-9H-purin-6-yl}benzamide

[0785]

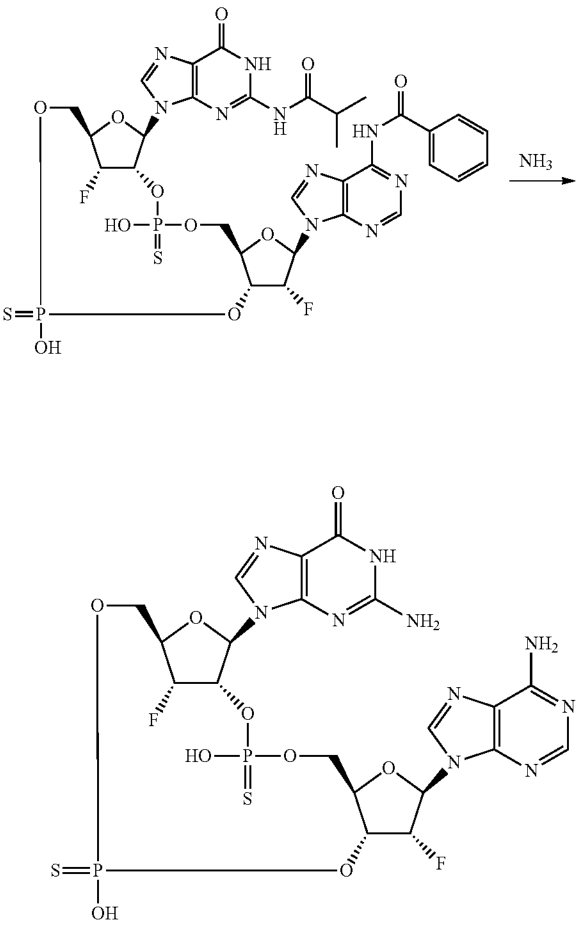


[0786] O-(((2R,3R,4R,5R)-5-(6-benzamido-9H-purin-9-yl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)methyl)O-((2R,3S,4R,5R)-4-fluoro-5-(hydroxymethyl)-2-(2-isobutyramido-6-oxo-1H-purin-9(6H)-yl)tetrahydrofuran-3-yl)O-hydrogen phosphorothioate (250 mg, 0.310 mmol) and diisopropylammonium tetrazolide (80 mg, 0.465 mmol) were azeotrope with dry CH_3CN (3×10 ml) and dried under high vacuum for 30 min.

[0787] The above mixture was dissolved in DMF (1 mL) and acetonitrile (7 mL) and added 200 mg active molecular sieve 4 Å and a solution of 2-cyanoethyl N,N,N',N'-tetraisopropylphosphorodiamidite (128 mg, 0.403 mmol) in 1 ml dry CH_3CN. The resulting mixture was stirred at rt for 30 min, followed by addition of 1H-tetrazole (109 mg, 1.550 mmol). The reaction stayed at rt for 1 h and added DDTT (95 mg, 0.465 mmol). The stirring continued for 1 h and concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting with 0-10% MeOH/DCM with 1% ET3N to give the desired product. LCMS (ES, m/z): 883 $[M-H]^-$.

Step 5: 2-amino-9-[(5R,7R,8S,12aR,14R,15R,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l]1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl-1,9-dihydro-6H-purin-6-one

[0788]

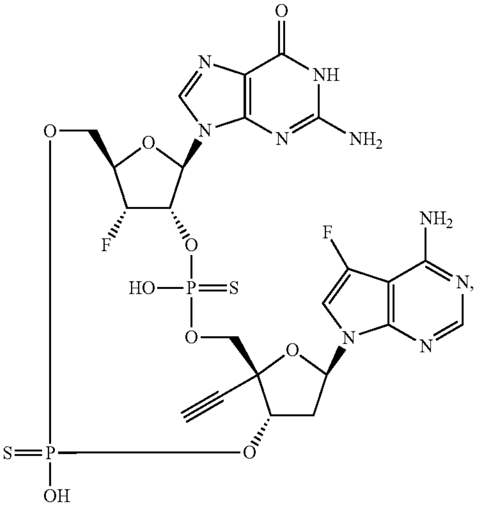


[0789] N-{9-[(5R,7R,8S,12aR,14R,15R,15aR,16R)-15,16-difluoro-2,10-dihydroxy-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]-9H-purin-6-yl}benzamide (120 mg, 0.136 mmol) and ammonia (7.0M in MeOH) (2 ml, 14.00 mmol) were sealed in a microwave tube. The reaction mixture was heated to 50° C. and stirred for 4 h. The reaction mixture was concentrated, and purified using mass-directed reverse phase HPLC (X-Bridge BEH 150 Prep C18) using a gradient solvent system with MeCN and 100 mM aqueous triethylammonium acetate to give desired product. Lyopholization of the product fractions furnished 2-amino-9-[(5R,7R,8S,12aR,14R,15R,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]-pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one. LCMS (ES, m/z): 709 $[M-H]^-$. ^{1}H NMR (H_2O-d2, 500 MHz): δ_H 8.23 (1H, s), 8.17 (1H, s), 7.93 (1H, s), 6.43 (1H, d, J=15.0 Hz), 6.00 (1H, d, J=8.7 Hz), 5.75 (1H, m), 5.58 (2H, m), 5.15 (1H, m), 4.65 (2H, m), 4.54 (1H, m), 4.15-4.30 (3H, m). ^{31}P NMR: (H_2O-d_2, 202 MHz): δ 52.1, 52.2.

Examples 261, 262, 263: 2-amino-9-[(5R,7R,8S,12aR,14R,15aS,16R)-14-(4-amino-5-fluoro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-12a-ethynyl-16-fluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomers 1-3)

[0790]

Diastereomer 1



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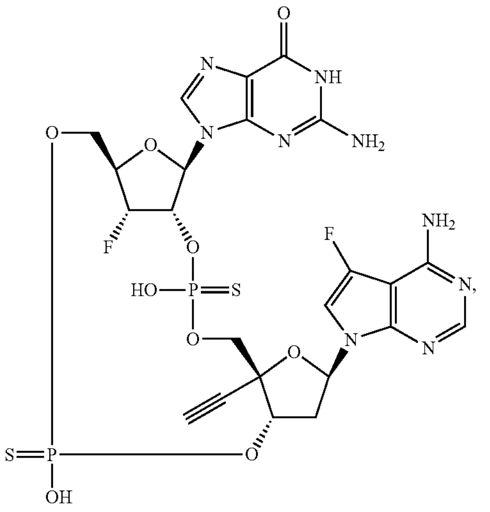
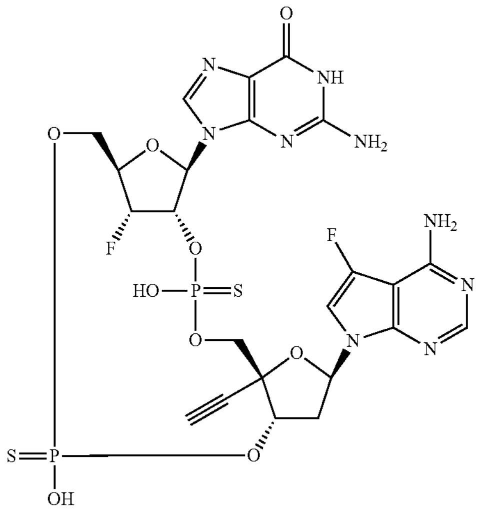
Diastereomer 2

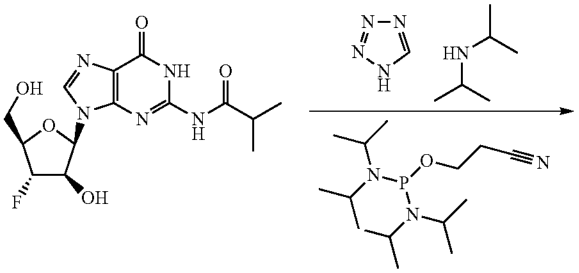


Diastereomer 3



Step 1: ((2R,3R,4S,5R)-4-(((2-cyanoethoxy)(diisopropylamino)phosphanyl)oxy)-3-fluoro-5-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-2-yl)methyl (2-cyanoethyl) diisopropylphosphoramidite

[0791]



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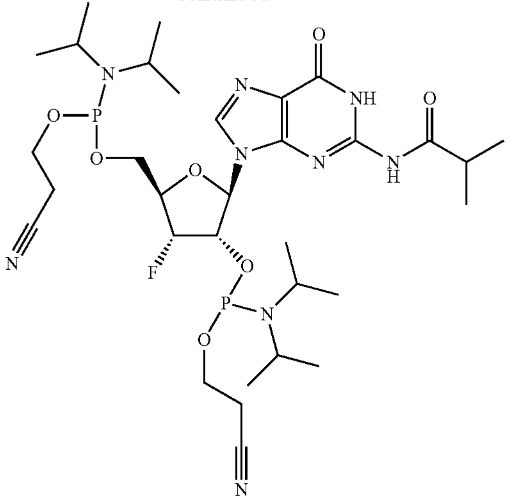
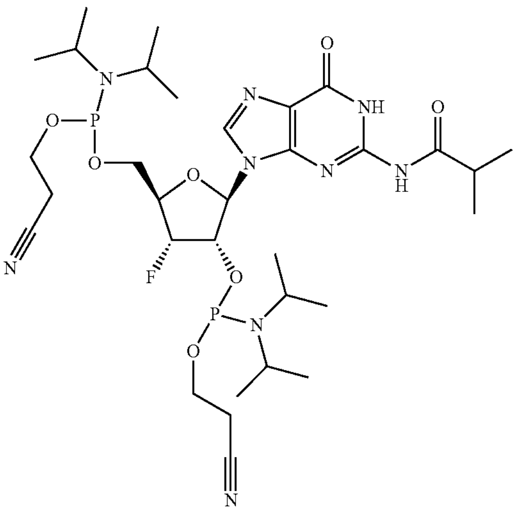


[0792] To a solution of N-(9-((2R,3R,4S,5R)-4-fluoro-3-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide (190 mg, 0.535 mmol) and 3-((bis(diisopropylamino)phosphino)oxy)propanenitrile (95%) (373 mg, 1.176 mmol) in DMF (5 ml) was added diisopropylammonium tetrazolide (137 mg, 0.802 mmol). The mixture was stirred at RT for 2 h, then added 1H-tetrazole (15.77 mg, 0.225 mmol) and continued for 2 h. 300 mg activated molecular sieve 4A was added and continued stirring at RT for 2 h. The reaction carried directly to next step. LCMS (ES, m/z): 754 [M−H]$^-$.

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

[0793]



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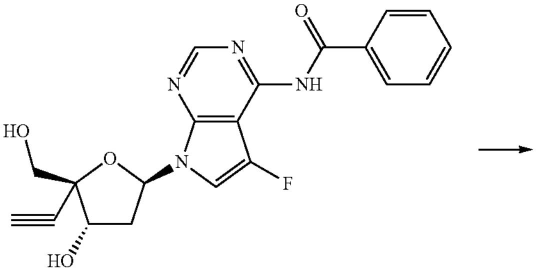
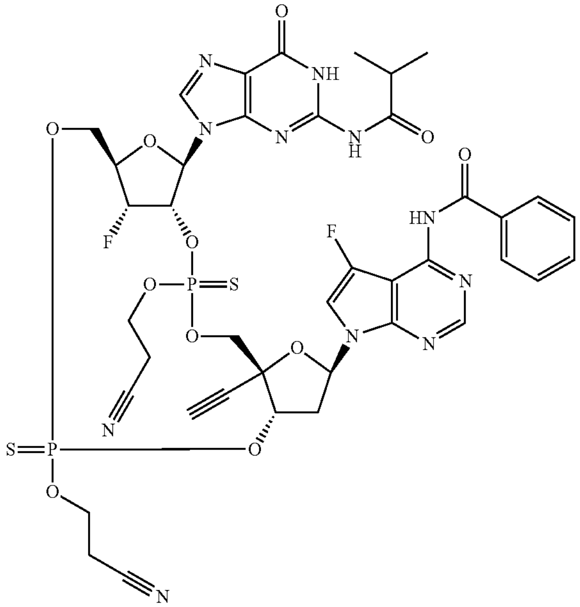


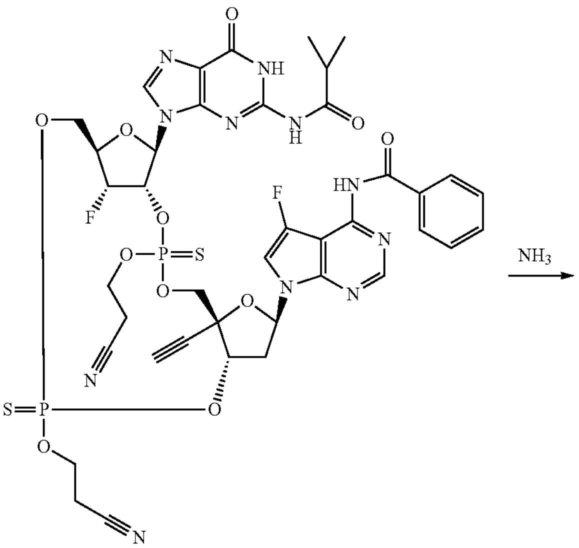


[0794] To a solution of N-(7-((2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-5-fluoro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)benzamide (180 mg, 0.454 mmol) and Et$_3$N (0.114 mL, 0.817 mmol) in DMF (4 mL) at −78° C. was added a solution of TMS-C$_1$ (0.070 mL, 0.545 mmol) in CH$_2$Cl$_2$ (1 mL) dropwise. The mixture was stirred at −78° C. for 20 min and warmed to 0° C. within 1 h, then added 200 mg activated molecular sieve 4 Å and continued stirring at RT for 2 h. The mixture was cooled to 0° C. and transferred to a stirred solution of the product of Step 1 (394 mg, 0.454 mmol) (precooled to −0° C.), followed by addition of 1H-tetrazole (191 mg, 2.72 mmol). The mixture was gradually warmed to RT and stirred at RT for 2 h. The filtration removed the solids. After washed with 3 ml DMF, the combined filtrate was added additional 1H-tetrazole (191 mg, 2.72 mmol) and stirred at RT overnight.

[0795] After completion of reaction, the reaction mixture was diluted with ethyl acetate and washed successively with H_2O and brine. The organic layer was dried over anhydrous Na_2SO_4 and purified by a silica gel chromatography, eluting with 0-8% MeOH/DCM to give two desired fractions with the same molecular weight. LCMS (ES, m/z): 1014 $[M+H]^+$

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

[0796]



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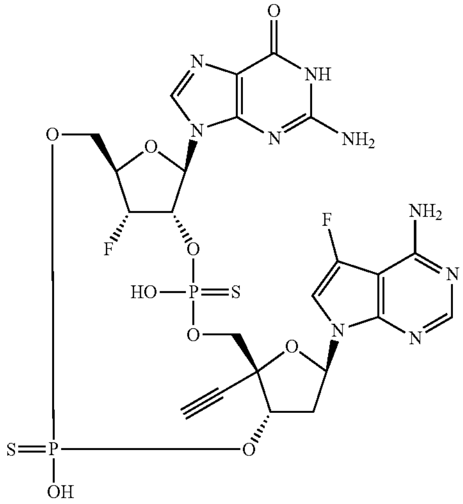


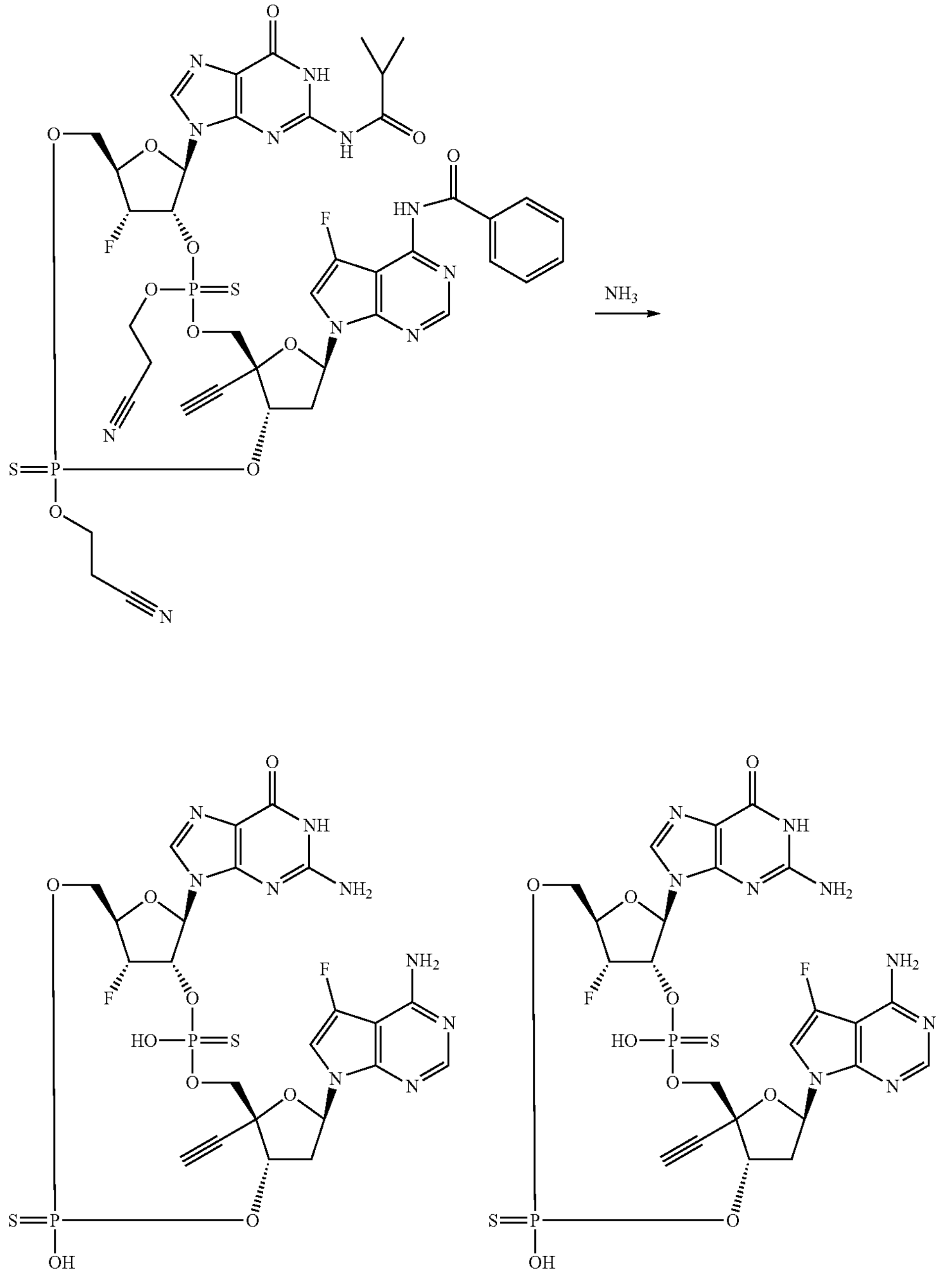
Diastereomer 1

[0797] N-{7-[(5R,7R,8S,12aR,14R,15aS,16R)-2,10-bis(2-cyanoethoxy)-12a-ethynyl-16-fluoro-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]-5-fluoro-7H-pyrrolo[2,3-d]pyrimidin-4-yl}benzamide (faster fraction from step 2) (30 mg, 0.030 mmol) and 7.0M ammonia in MeOH (2 ml, 14.00 mmol) were sealed in a microwave tube. The mixture was heated to 50° C. and stirred for 8 h. The reaction mixture was concentrated, and the product was purified using mass-directed reverse phase HPLC (X-Bridge BEH 150 Prep C18) using a gradient solvent system with MeCN and 100 mM aqueous triethylammonium acetate. Lyophilization of the product fractions furnished 2-amino-9-[(5R,7R,8S,12aR,14R,15aS,16R)-14-(4-amino-5-fluoro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-12a-ethynyl-16-fluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one as the bis-triethylamine salt.

[0798] Example 261 (Diastereomer 1): LCMS (ES, m/z): 732 $[M-H]^-$. ^1H NMR (H_2O-d_2, 500 MHz): δ_H 8.32 (1H, s), 8.08 (1H, s), 7.05 (1H, s), 6.70 (1H, t, J=6.1 Hz), 6.08 (1H, d, J=8.7 Hz), 5.71 (1H, d, J=53.2 Hz), 5.47-5.40 (1H, m), 5.14-5.10 (1H, m), 4.65 (2H, m), 4.28 (1H, t, J=8.7 Hz), 4.14-4.02 (3H, m), 2.85 (2H, d, J=6.4 Hz). ^{31}P NMR: (H_2O-d_2, 202 MHz): δ 53.7, 54.0.

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

[0799]



Diastereomer 2

Diastereomer 3

[0800] N-{7-[(5R,7R,8S,12aR,14R,15aS,16R)-2,10-bis(2-cyanoethoxy)-12a-ethynyl-16-fluoro-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]-5-fluoro-7H-pyrrolo[2,3-d]pyrimidin-4-yl}benzamide (slow fraction from Step 2, 65 mg, 0.064 mmol) and 7.0M ammonia in MeOH (2 ml, 14.00 mmol) were sealed in a microwave tube and heated to 50° C. and stirred for 8 h. The reaction mixture was concentrated and purified using mass-directed reverse phase HPLC (X-Bridge BEH 150 Prep C18) using a gradient solvent system with MeCN and 100 mM aqueous triethylammonium acetate to give two additional diastereomers after lyopholization of the product fractions.

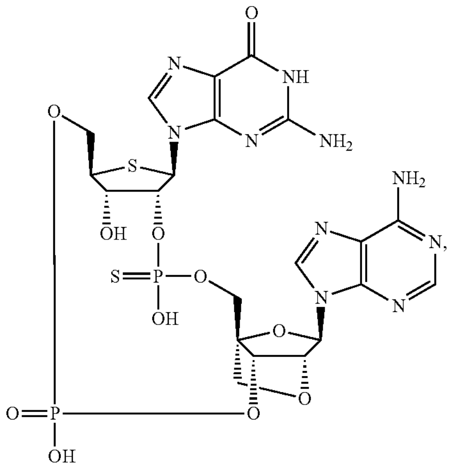
[0801] Example 262 (Diastereomer 2): LCMS (ES, m/z): 732 $[M-H]^-$. ^1H NMR (H_2O-d_2, 500 MHz): δ_H 8.09 (2H, d, J=3.0 Hz), 7.19 (1H, s), 6.74 (1H, s), 6.08 (1H, d, J=8.3 Hz), 5.63 (1H, s), 5.53 (1H, s), 5.35-5.33 (1H, m), 4.65 (2H, m), 4.34 (1H, d, J=8.8 Hz), 4.28 (1H, t, J=10.3 Hz), 4.11 (1H, d, J=12.1 Hz), 3.89 (1H, dd, J=10.6, 4.0 Hz), 2.85 (2H, d, J=6.4 Hz). ^{31}P NMR: (H_2O-d_2, 202 MHz): δ 54.7, 59.8.

[0802] Example 263 (Diastereomer 3): LCMS (ES, m/z): 732 $[M-H]^-$. ^1H NMR (H_2O-d_2, 500 MHz): δ_H 8.08 (1H, s), 7.94 (1H, s), 7.04 (1H, s), 6.68 (1H, s), 6.04 (1H, d, J=8.6 Hz), 5.64 (1H, s), 5.54 (1H, d, J=3.3 Hz), 5.24 (1H, d, J=7.7 Hz), 4.65 (2H, m), 4.40 (1H, d, J=8.2 Hz), 4.18 (1H, dd, J=11.0, 5.5 Hz), 4.09-4.00 (2H, m), 2.93-2.89 (1H, m), 2.82 (1H, d, J=7.1 Hz). ^{31}P NMR: (H_2O-d_2, 202 MHz): δ 53.1, 54.9.

Examples 264 and 265: 2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,18S)-14-(6-amino-9H-purin-9-yl)-2,10,18-trihydroxy-2-oxido-10-sulfidohexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7(12H)-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 1) and 2-amino-9-[(5R,7R,8R,12aR,14R,15R, 15aS,18S)-14-(6-amino-9H-purin-9-yl)-2,10,18-trihydroxy-2-oxido-10-sulfidohexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7(12H)-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 2)

[0803]

Diastereomer 1



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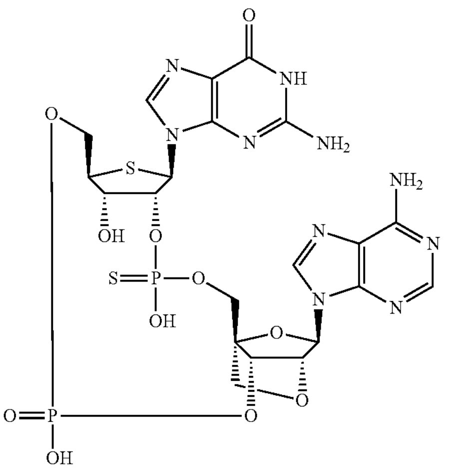
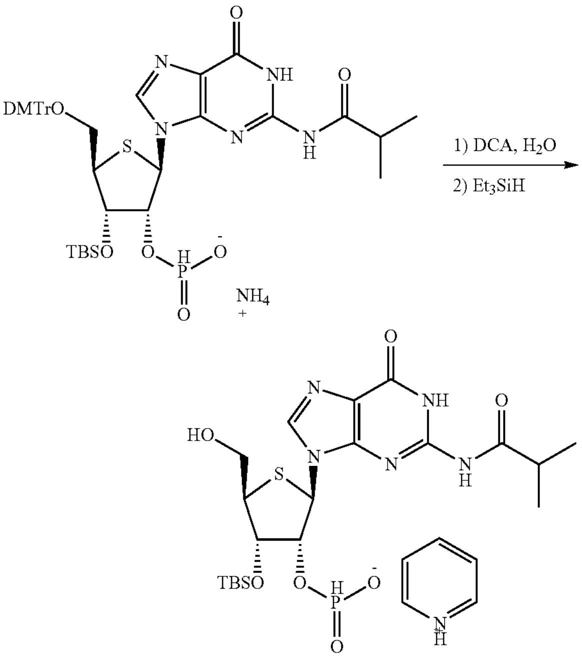
Diastereomer 2



Step 1: (2R,3R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(hydroxymethyl)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrothiophen-3-yl phosphonate

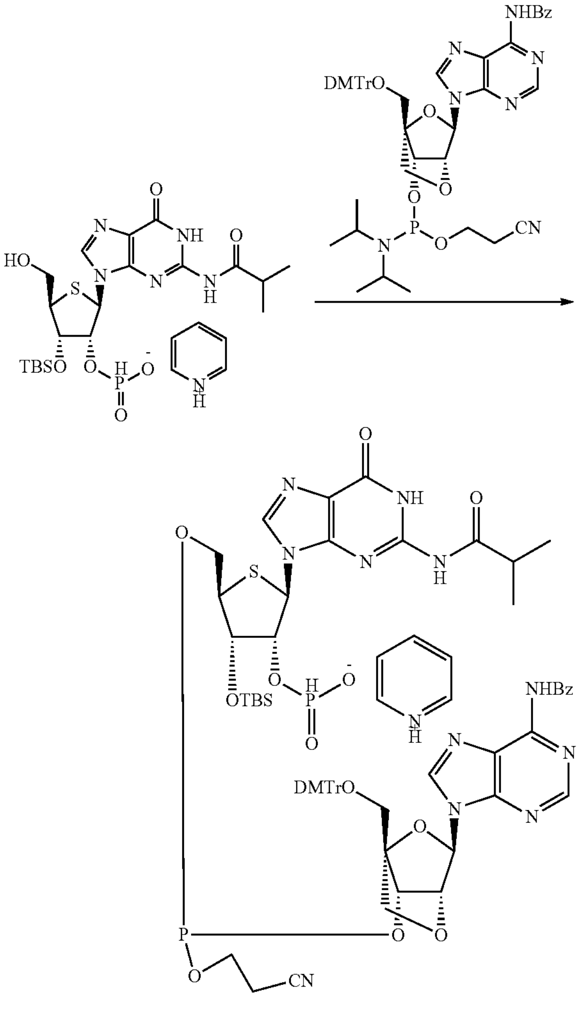
[0804]



[0805] To a solution of (2R,3R,4S,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrothiophen-3-yl phosphonate (750 mg, 0.865 mmol) in CH_2Cl_2 (9 mL) was added water (156 mg, 8.65 mmol) and 2,2-dichloroacetic acid in CH_2Cl_2 (0.6M, 11 mL, 6.6 mmol). The mixture was stirred at rt for 15 min, and then, Et_3SiH (4.00 mL) was added. After 1 h, pyridine (1232 mg, 15.57 mmol) was added, and it was concentrated to give a crude sample that was used for next reaction step without purification. LCMS (ES, m/z): 548.1 $[M+H]^+$.

Step 2. (2R,3R,4S,5R)-5-((((((R,3R,4R,7S)-3-(6-benzamido-9H-purin-9-yl)-1-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-2,5-dioxabicyclo[2.2.1]heptan-7-yl)oxy)(2-cyanoethoxy)phosphanyl)oxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrothiophen-3-yl phosphonate

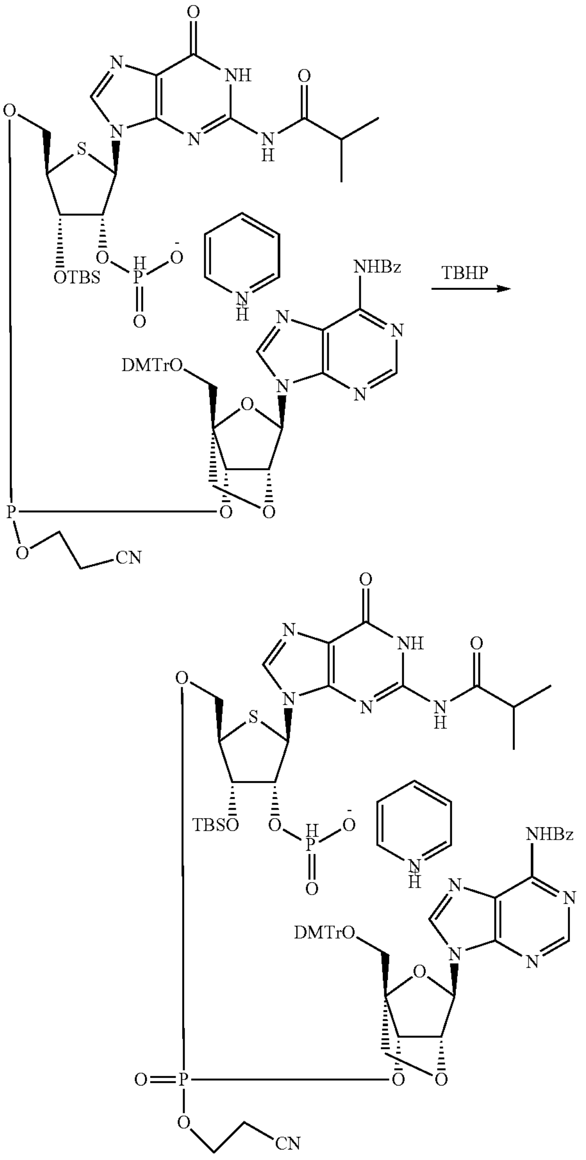
[0806]



[0807] The crude sample from Step 1 was co-evaporated with ACN (3×2 mL), re-dissolved in ACN (3 mL), and dried by adding activated 4 Å molecular sieve (150 mg). (1R,3R,4R,7S)-3-(6-benzamido-9H-purin-9-yl)-1-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-2,5-dioxabicyclo[2.2.1]heptan-7-yl (2-cyanoethyl) diisopropylphosphoramidite (0.843 g, 0.952 mmol) was also co-evaporated with ACN (3×1 mL), re-dissolved in ACN (3 mL), and dried by adding activated 4 Å molecular sieve (150 mg). After 30 min, it was added to the previously prepared mixture containing pyridin-1-ium (2R,3R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(hydroxymethyl)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrothiophen-3-yl phosphonate. The reaction mixture was used in the next reaction step without purification. LCMS (ES, m/z): 1332.1 $[M+H]^+$.

Step 3. (2R,3R,4S,5R)-5-((((((R,3R,4R,7S)-3-(6-benzamido-9H-purin-9-yl)-1-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-2,5-dioxabicyclo[2.2.1]heptan-7-yl)oxy)(2-cyanoethoxy)phosphoryl)oxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrothiophen-3-yl phosphonate

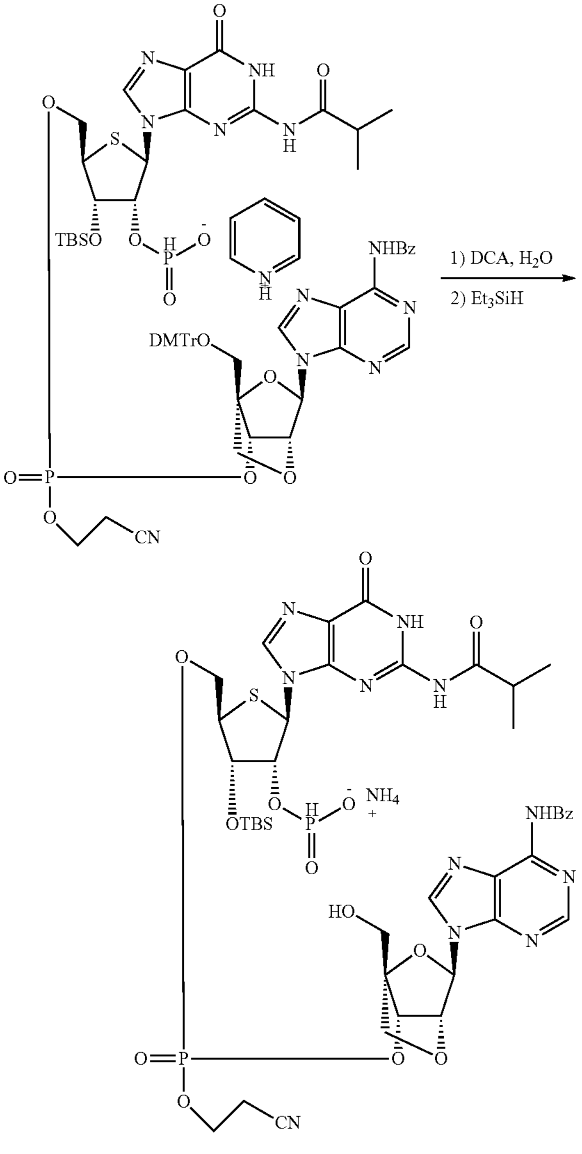
[0808]



[0809] To a reaction mixture from Step 2 at rt was added 2-hydroperoxy-2-methylpropane (0.234 g, 2.60 mmol), and it was stirred for 40 min. It was concentrated to give a crude product, which was used for the next step without purification. LCMS (ES, m/z): 1347.1 $[M+H]^+$.

Step 4: (2R,3R,4S,5R)-5-((((((1S,3R,4R,7S)-3-(6-benzamido-9H-purin-9-yl)-1-(hydroxymethyl)-2,5-dioxabicyclo[2.2.1]heptan-7-yl)oxy)(2-cyanoethoxy)phosphoryl)oxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrothiophen-3-yl phosphonate

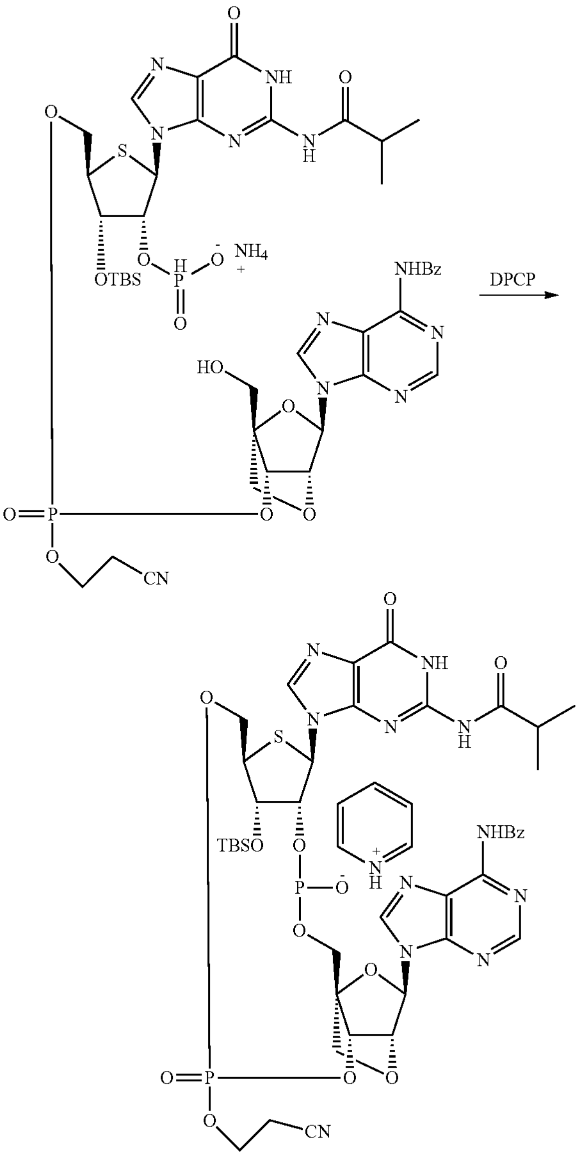
[0810]



[0811] To the crude from Step 3 in CH_2Cl_2 (9 mL) was added water (156 mg, 8.65 mmol) and 2,2-dichloroacetic acid in CH_2Cl_2 (0.6N, 10 mL, 6 mmol). The resulting mixture was stirred at rt for 15 min. Then, triethylsilane (4 mL, 0.21 mmol) was added, and the stirring was continued for 40 min. Pyridine (1232 mg, 15.57 mmol) was added. 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 (5 mM) to give the product. LCMS (ES, m/z): 1046.3 $[M+H]^+$.

Step 5. (5R,7R,8R,12aR,14R,15R,15aS,18S)-18-{[tert-butyl(dimethyl)silyl]oxy}-2-(2-cyanoethoxy)-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}hexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-10(12H)-olate 2-oxide

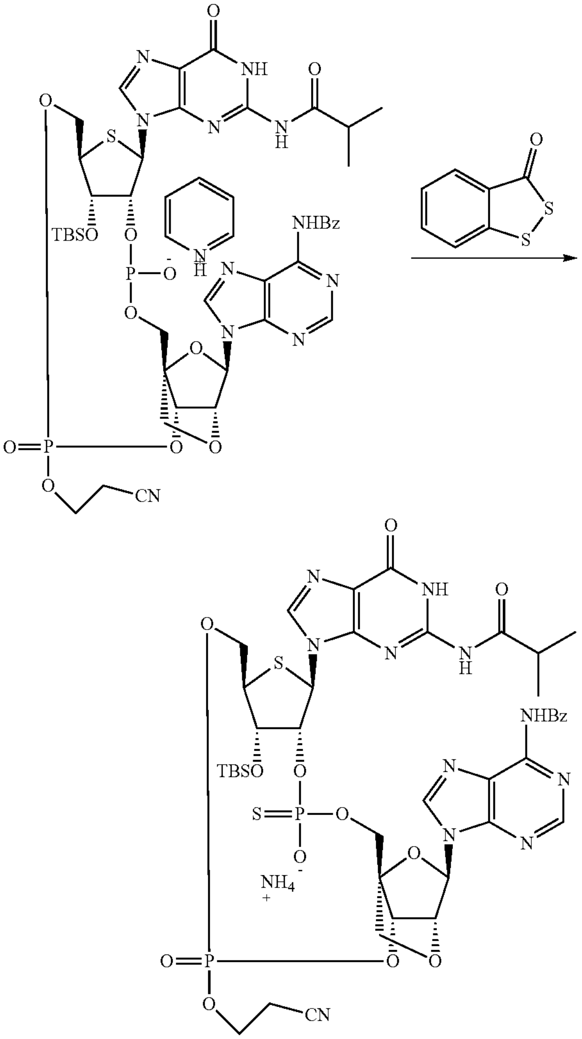
[0812]



[0813] To pyridine (20 mL) at −40° C. under Ar was added diphenyl phosphorochloridate (1.28 g, 4.78 mmol) over 5 min. To the solution at −40° C. was added a solution of (2R,3R,4S,5R)-5-((((((1 S,3R,4R,7S)-3-(6-benzamido-9H-purin-9-yl)-1-(hydroxymethyl)-2,5-dioxabicyclo [2.2.1] heptan-7-yl)oxy)(2-cyanoethoxy)phosphoryl)oxy)methyl)-4-((tert-butyldimethylsilyl)oxy)-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrothiophen-3-yl phosphonate (250 mg, 0.239 mmol, co-evaporated with pyridine, 3x10 mL) in CH_2Cl_2 (20 mL) dropwise. The resulting mixture was stirred at −40° C. for 30 min. The reaction mixture was used for the next reaction step immediately without purification. LCMS (ES, m/z): 1028.4 $[M+H]^+$.

Step 6: (5R,7R,8R,12aR,14R,15R,15aS,18S)-18-{[tert-butyl(dimethyl)silyl]oxy}-2-(2-cyanoethoxy)-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}hexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-10(12H)-olate 2-oxide 10-sulfide

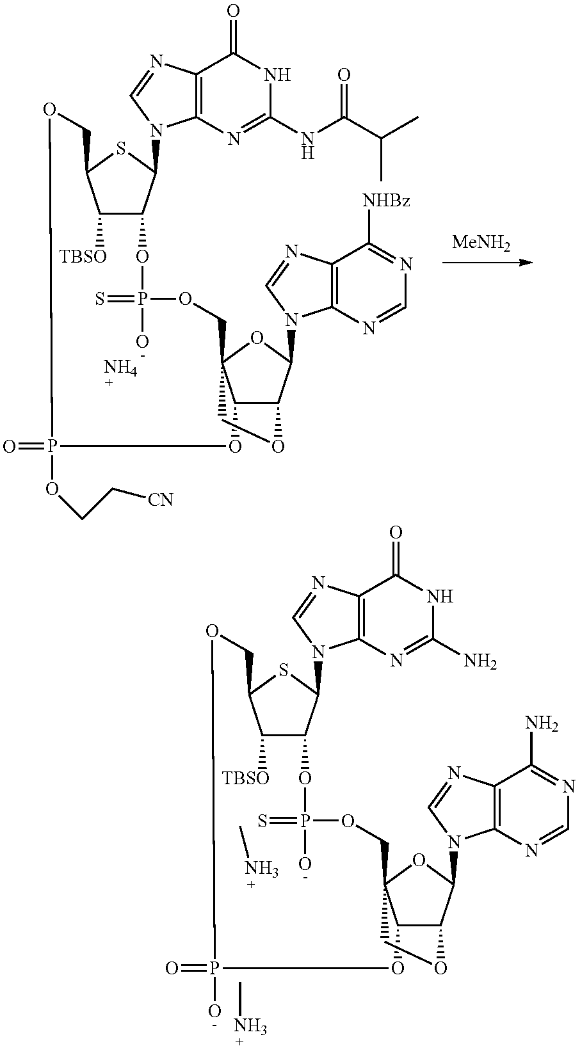
[0814]



[0815] To the reaction mixture at rt from Step 5 was added 3H-benzo[c][1,2]dithiol-3-one (121 mg, 0.717 mmol). After stirring at 25° C. for 40 min, water (431 mg, 23.9 mmol) was added. 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 (5 mM) to give the product. LCMS (ES, m/z): 1060.3 $[M+H]^+$. ^{31}P-NMR: (121 MHz, D_2O) δ 54.91, 54.61 (m, 1P), 6-6.08, −6.48 (m, 1P).

Step 7: (5R,7R,8R,12aR,14R,15R,15aS,18S)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-14-(6-amino-9H-purin-9-yl)-18-{[tert-butyl(dimethyl)silyl]oxy}hexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecine-2,10(12H)-diolate 2-oxide 10-sulfide

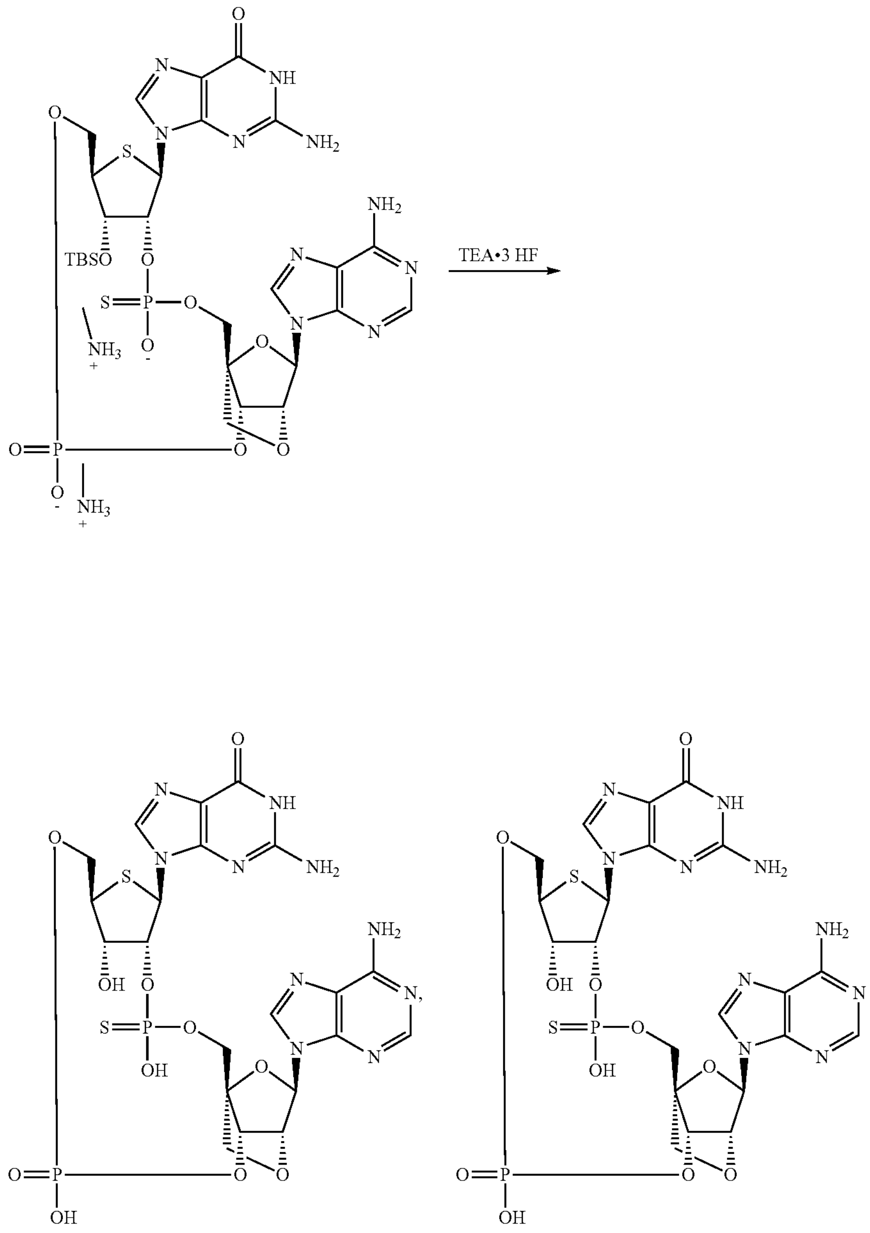
[0816]



[0817] (5R,7R,8R,12aR,14R,15R,15aS,18S)-18-{[tert-butyl(dimethyl)silyl]oxy}-2-(2-cyanoethoxy)-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}hexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-10(12H)-olate 2-oxide 10-sulfide (190 mg, 0.178 mmol) was dissolved in a solution of methylamine in EtOH (30%, 1 mL), and the resulting solution was stirred at rt for 2 h. Then, it was concentrated to give a crude sample containing the product. LCMS (ES, m/z): 833.2 $[M+H]^+$.

Step 8: 2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,18S)-14-(6-amino-9H-purin-9-yl)-2,10,18-trihydroxy-2-oxido-10-sulfidohexahydro-14H-15,2a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7(12H)-yl]-1,9-dihydro-6H-purin-6-one

[0818]



Diastereomer 1

Diastereomer 2

[0819] The crude from Step 7 was suspended in pyridine (5 mL) under Ar. To the mixture was added Et_3N (1864 mg, 18.42 mmol) and triethylamine trihydrofluoride (742 mg, 4.60 mmol) dropwise. The mixture was heated to 50° C. for 16 h. Then, it was concentrated, and the residue was purified by preparative-HPLC (XBridge Shield RP18 OBD Column, 19×150 mm) eluted with 0 to 14% ACN in aq NH_4HCO_3 (10 mM) over 16 min to give two products after concentration.

[0820] Example 264: 2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,18S)-14-(6-amino-9H-purin-9-yl)-2,10,18-trihydroxy-2-oxido-10-sulfidohexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10] tetraoxathiadiphosphacyclotetradecin-7(12H)-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 1): T_R: 11.00 min. LCMS (ES, m/z): 719.0 $[M+H]^+$. ^{1}H-NMR: (300 MHz, D_2O): δ 8.13 (s, 1H), 7.94 (s, 1H), 7.64 (s, 1H), 6.11-5.97 (m, 2H), 5.92-5.85 (m, 1H), 5.25-5.05 (m, 1H), 4.87 (s, 1H), 4.75 (s, 2H), 4.30-4.21 (m, 1H), 4.12-3.78 (m, 4H), 3.50-3.45 (m, 1H). ^{31}P-NMR: (121 MHz, D_2O) δ 52.06 (s, 1P), 6-0.86 (s, 1P)

[0821] Example 265: 2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,18S)-14-(6-amino-9H-purin-9-yl)-2,10,18-trihydroxy-2-oxido-10-sulfidohexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7(12H)-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 2): T_R: 12.32 min. LCMS (ES, m/z): 719.0 $[M+H]^+$. ^{1}H-NMR: (300 MHz, D_2O): δ 8.13-8.03 (m, 2H), 7.64 (s, 1H), 6.11-5.97 (m, 2H), 5.92-5.90 (m, 1H), 5.20-5.15 (m, 1H), 4.87-4.75 (m, 3H), 4.33-4.20 (m, 1H), 4.12-4.00 (m, 2H), 3.90-3.78 (m, 2H), 3.45-3.40 (m, 1H). ^{31}P-NMR: (121 MHz, D_2O) δ 54.88 (s, 1P), 6-0.97 (s, 1P).

[0822] Examples 266 through 272, as shown in Table 9 below, were prepared according to procedures analogous to those outlined for Examples 264 and 265 above using the appropriate monomeric nucleosides, described as Preparations or as obtained from commercial sources.

TABLE 9

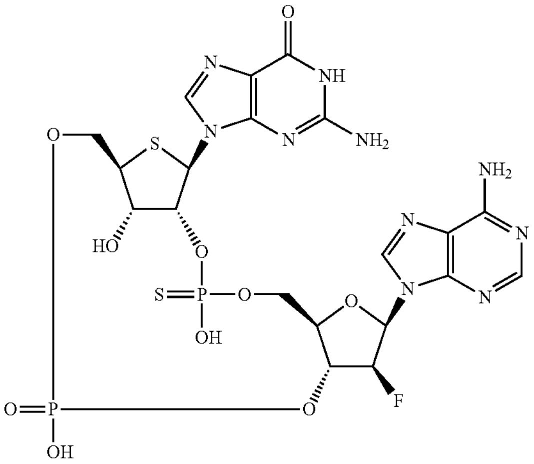
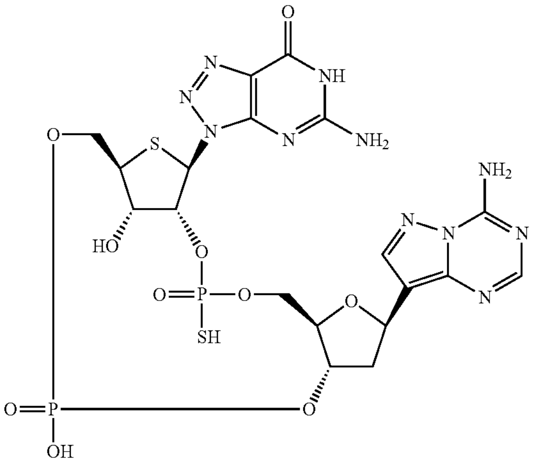
Ex.	Structure	Name	Mass $[M-H]^-$
266		2-amino-9-[(5R,7R,8R,12aR,14R,15S,15aR,16S)-14-(6-amino-9H-purin-9-yl)-15-fluoro-2,10,16-trihydroxy-2-oxido-10-sulfidooctahydro-12H-5,8-methanofuro[3,2-1][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	707
267		5-amino-3-[(5R,7R,8R,12aR,14R,15aS,16S)-14-(4-aminopyrazolo[1,5-a][1,3,5]triazin-8-yl)-2,16-dihydroxy-2,10-dioxido-10-sulfanyloctahydro-12H-5,8-methanofuro[3,2-1][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 1)	690

TABLE 9-continued

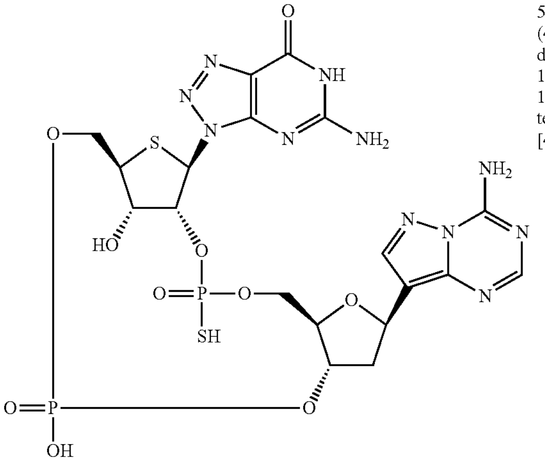
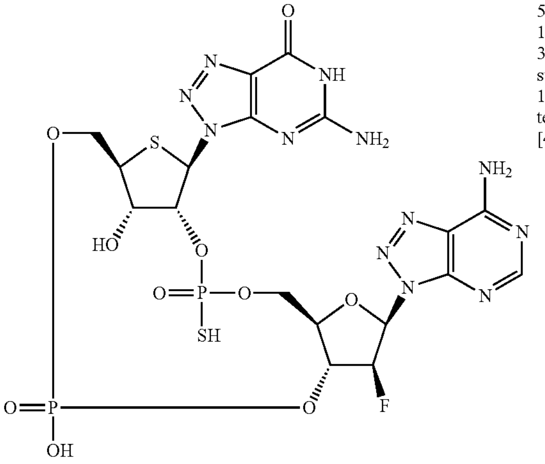
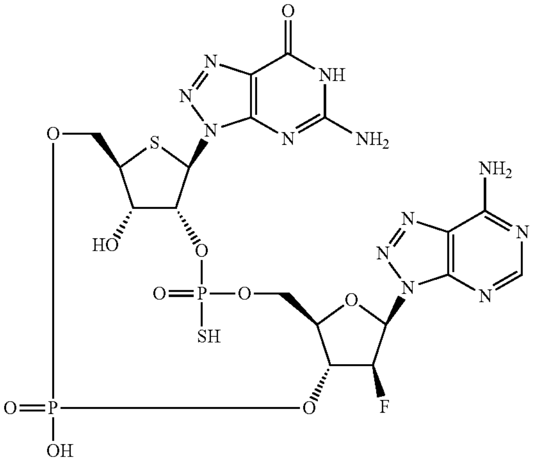
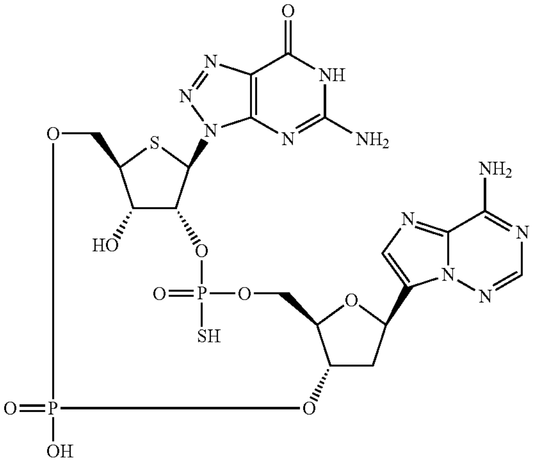
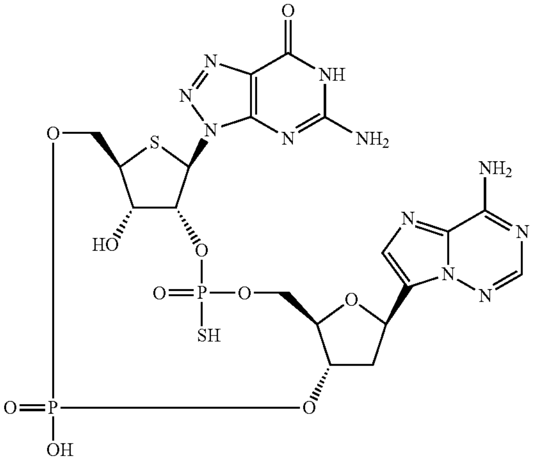
Ex.	Structure	Name	Mass $[M - H]^-$
268		5-amino-3-[(5R,7R,8R,12aR,14R,15aS,16S)-14-(4-aminopyrazolo[1,5-a][1,3,5]triazin-8-yl)-2,16-dihydroxy-2,10-dioxido-10-sulfanyloctahydro-12H-5,8-methanofuro[3,2-1][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclo-tetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 2)	690
269		5-amino-3-[(5R,7R,8R,12aR,14R,15S,15aR,16S)-14-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-15-fluoro-2,16-dihydroxy-2,10-dioxido-10-sulfanyloctahydro-12H-5,8-methanofuro[3,2-1][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclo-tetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 1)	709

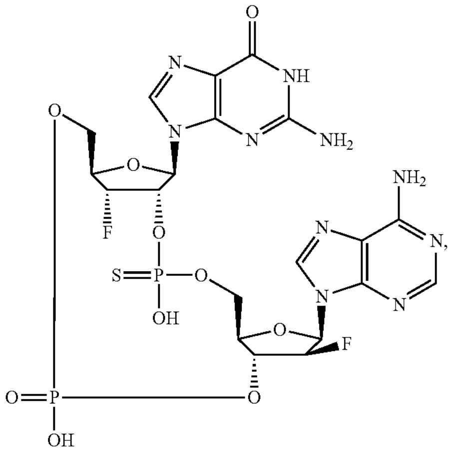
TABLE 9-continued

Ex.	Structure	Name	Mass [M − H]⁻
270		5-amino-3-[(5R,7R,8R,12aR,14R,15S,15aR,16S)-14-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-15-fluoro-2,16-dihydroxy-2,10-dioxido-10-sulfanyloctahydro-12H-5,8-methanofuro[3,2-1][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 2)	709
271		5-amino-3-[(5R,7R,8R,12aR,14R,15aS,16S)-14-(4-aminoimidazo[2,1-f][1,2,4]triazin-7-yl)-2,16-dihydroxy-2,10-dioxido-10-sulfanyloctahydro-12H-5,8-methanofuro[3,2-1][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 1)	690
272		5-amino-3-[(5R,7R,8R,12aR,14R,15aS,16S)-14-(4-aminoimidazo[2,1-f][1,2,4]triazin-7-yl)-2,16-dihydroxy-2,10-dioxido-10-sulfanyloctahydro-12H-5,8-methanofuro[3,2-1][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 2)	690

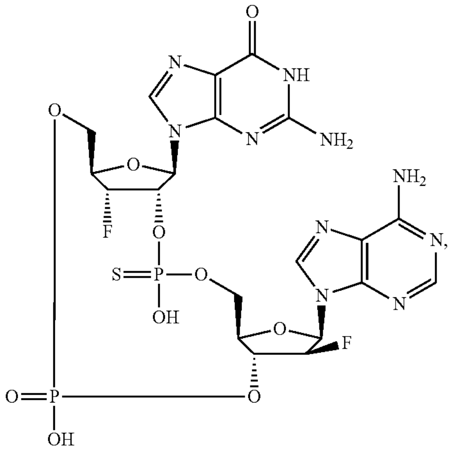
Examples 273 and 274: 2-amino-9-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-2-oxido-10-sulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 1) and 2-amino-9-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-14-(6-amino-911-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-2-oxido-10-sulfidooctahydro-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 2)

[0823]

Diastereomer 1

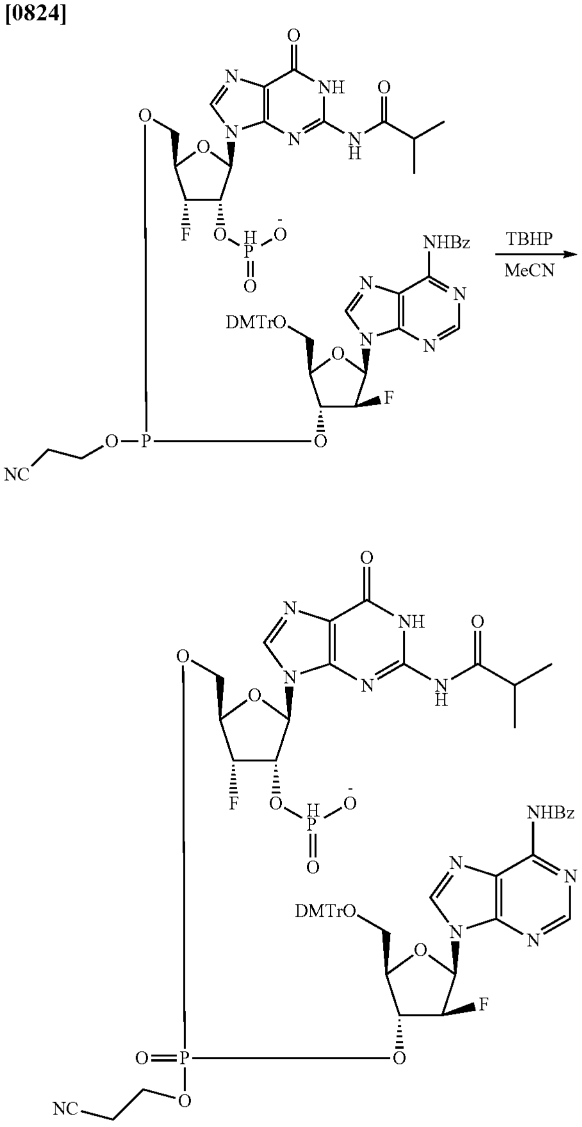


Diastereomer 2



Step 1. (2R,3S,4R,5R)-5-((((((2R,3R,4S,5R)-5-(6-benzamido-9H-purin-9-yl)-2-(bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-fluorotetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphoryl)oxy)methyl)-4-fluoro-2-(2-isobutyramido-6-oxo-, 6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate

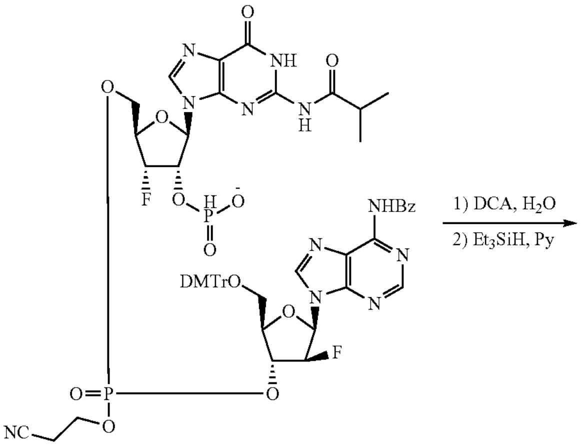
[0824]



[0825] To a mixture containing the crude (2R,3S,4R,5R)-5-((((((2R,3R,4S,5R)-5-(6-benzamido-9H-purin-9-yl)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-fluorotetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphanyl)oxy)methyl)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate (product of Step 1, Examples 244-247, crude, assumed 0.75 mmol) was added tert-butyl hydroperoxide in decane (5.5M, 0.48 mL, 2.6 mmol) dropwise, and the mixture was stirred at rt for 1 h. Then, it was cooled to 0° C., and a solution of $Na_2S_2O_3$ (553 mg) in water (2 mL) was added slowly. The mixture was stirred at rt for 5 min and then, concentrated to give the product. LCMS (ES, m/z): 1208.5 $[M-H]^-$.

Step 2. (2R,3S,4R,5R)-5-((((((2R,3R,4S,5R)-5-(6-benzamido-9H-purin-9-yl)-4-fluoro-2-(hydroxymethyl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy)phosphoryl)oxy)methyl)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate

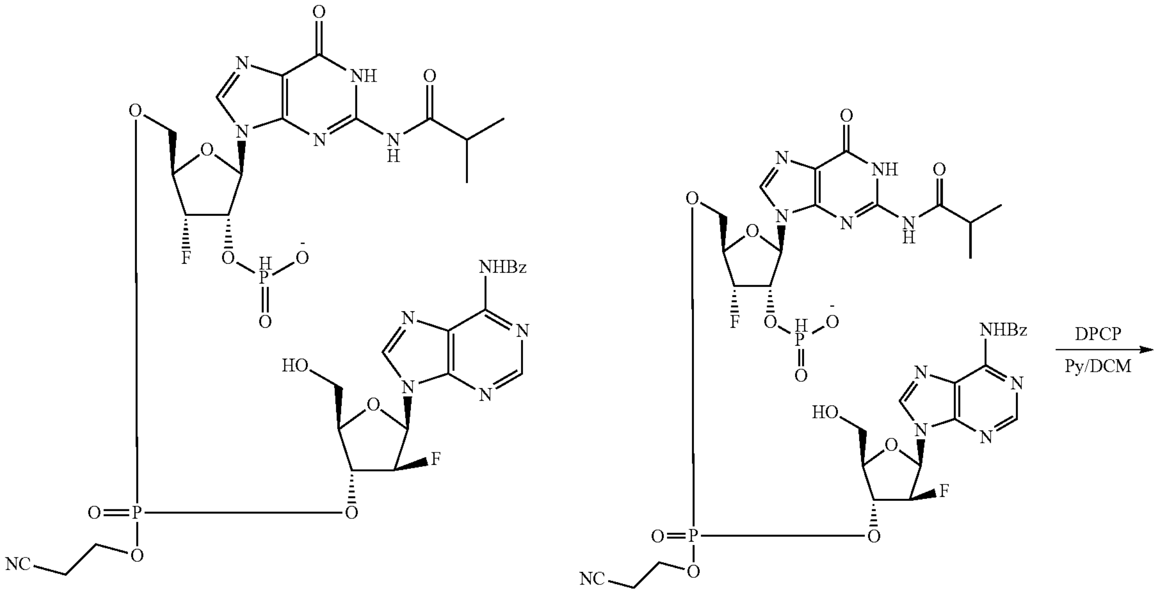
[0826]



[0827] To a solution of the crude from Step 1 in CH_2Cl_2 (10 mL) was added water (130 mg, 7.5 mmol) and 2,2-dichloroacetic acid (0.77 g, 6 mmol) in CH_2Cl_2 (10 mL). After 20 min, triethylsilane (20 mL) was added, and stirring was continued for 2 h. Pyridine (1 mL) was added, and the reaction mixture was concentrated. 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): 908.2 $[M+H]^+$. ^{1}H-NMR: (400 MHz, CD_3OD) δ 8.76 (d, J=7.7 Hz, 2H), 8.65 (s, 1H), 8.56 (s, 1H), 8.21-8.08 (m, 6H), 7.69 (t, J=7.4 Hz, 2H), 7.64-7.50 (m, 5H), 6.67 (ddd, J=32.7, 14.9, 4.4 Hz, 2H), 6.21-6.10 (m, 2H), 5.99-5.91 (m, 1H), 5.64-5.57 (m, 1H), 5.56-5.45 (m, 3H), 5.38 (s, 3H), 4.71-4.54 (m, 6H), 4.47-4.23 (m, 5H), 3.92 (d, J=3.8 Hz, 1H), 3.89-3.80 (m, 2H), 2.94 (dt, J=31.1, 5.9 Hz, 4H), 2.83-2.74 (m, 2H), 1.36-1.19 (m, 13H), 1.12 (s, 2H). ^{31}P-NMR: (162 MHz, CD_3OD) δ 2.55, −1.33, −3.09, −3.11, −155.89.

Step 3. (5R,7R,8S,12aR,14R,15S,15aR,16R)-2-(2-cyanoethoxy)-15,16-difluoro-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-10-olate 2-oxide

[0828]



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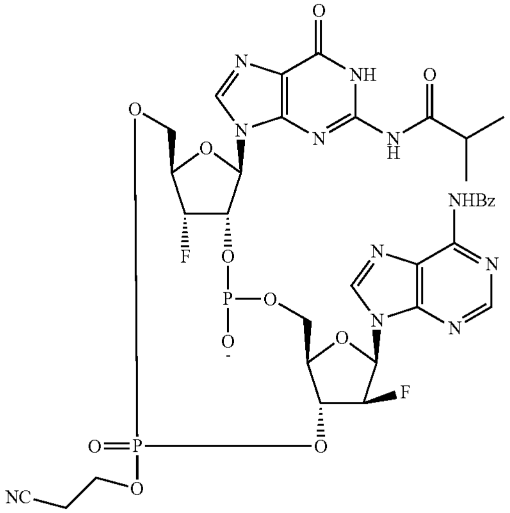
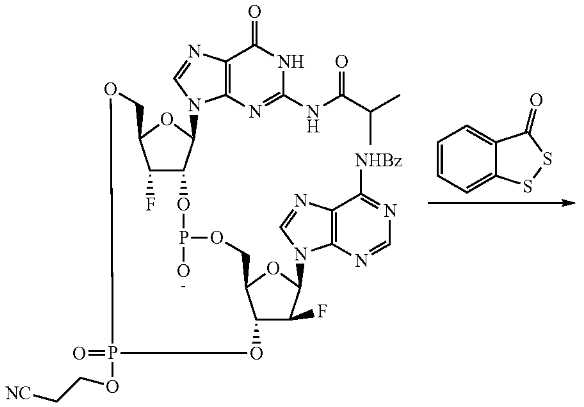


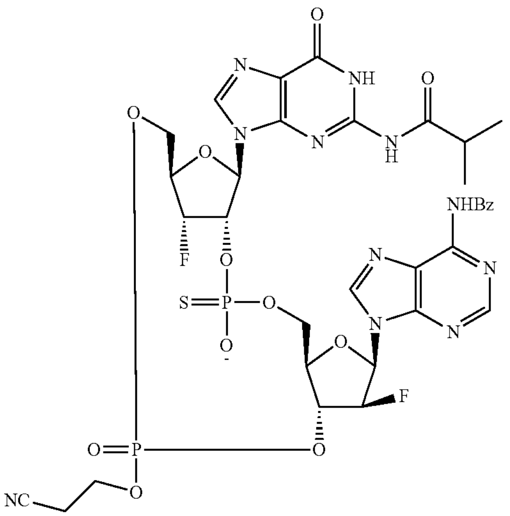
[0829] To pyridine (50 mL) under Ar was added diphenyl chlorophosphate (2.66 g, 9.92 mmol). It was cooled at −40° C., and then, a solution of (2R,3 S,4R,5R)-5-((((((2R,3R, 4S,5R)-5-(6-benzamido-9H-purin-9-yl)-4-fluoro-2-(hydroxymethyl)tetrahydrofuran-3-yl)oxy)(2-cyanoethoxy) phosphoryl)oxy)methyl)-4-fluoro-2-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3-yl phosphonate (450 mg, 496 mmol, co-evaporated with pyridine 3×5 mL) in CH_2Cl_2 (50 mL) was added dropwise over 20 min. The resulting mixture was stirred at −40° C. for 20 min. The reaction mixture was immediately used in the next step without purification. LCMS (ES, m/z): 891.1 $[M+H]^+$.

Step 4: (5R,7R,8S,12aR,14R,15S,15aR,16R)-2-(2-cyanoethoxy)-15,16-difluoro-7-{2-[(2-methylpropanoyl)amino-6-oxo-1,6-dihydro-9H-purin-9-yl}-14-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}octahydro-12H-5,8-methanofuro[3,2-l]1,3,6,9,11, 2,10]pentaoxadiphosphacyclotetradecin-10-olate 2-oxide 10-sulfide

[0830]



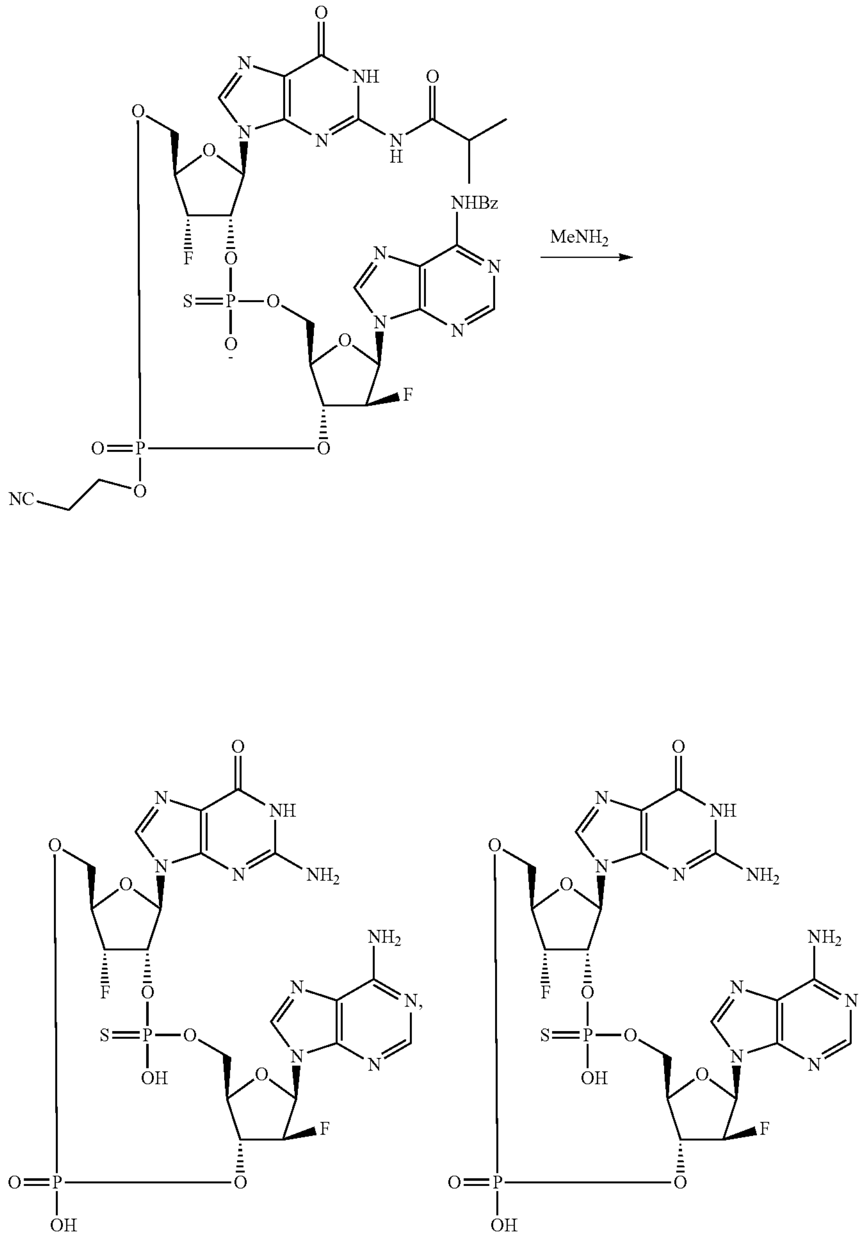
-continued



[0831] To the reaction mixture of Step 3 at −40° C. was added 3H-benzo[c][1,2]dithiol-3-one (32.76 mg, 0.195 mmol) and water (125 mg, 0.744 mmol). After stirring at rt for 40 min, the reaction 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 (0.04%) to give the product. LCMS (ES, m/z): 922.1 $[M+H]^+$. ^{1}H-NMR: (400 MHz, CD_3OD) δ 8.81-8.73 (m, 2H), 8.63-8.48 (m, 2H), 8.24 (s, 1H), 8.21-8.10 (m, 5H), 7.73-7.56 (m, 7H), 6.83-6.72 (m, 2H), 6.28 (d, J=8.6 Hz, 1H), 6.14 (d, J=8.5 Hz, 1H), 5.83-5.56 (m, 4H), 5.49 (d, J=11.1 Hz, 1H), 4.76-4.46 (m, 11H), 4.37 (s, 1H), 4.29 (d, J=6.8 Hz, 1H), 4.18 (d, J=10.2 Hz, 1H), 3.04 (dd, J=6.5, 5.1 Hz, 4H), 2.83-2.68 (m, 1H), 2.06 (s, 2H), 1.23 (dd, J=22.5, 6.9 Hz, 9H), 1.14-1.05 (m, 3H). ^{31}P-NMR: (162 MHz, CD_3OD) δ62.41, 56.84, 56.29, −3.14, −3.35, −4.77, −5.06, −60.84.

Step 5: 2-amino-9-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-2-oxido-10-sulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomers 1 and 2)

[0832]



Diastereomer 1

Diastereomer 2

[0833] The (5R,7R,8S,12aR,14R,15S,15aR,16R)-2-(2-cyanoethoxy)-15,16-difluoro-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-4-{6-[(phenylcarbonyl)amino]-9H-purin-9-yl}octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-10-olate 2-oxide 10-sulfide (380 mg, 0.377 mmol) was dissolved in a solution of $MeNH_2$ in EtOH (30%, 30 mL), and the resulting solution was stirred at rt for 2 h. Then, it was concentrated, and the residue was purified by Prep-HPLC (XBridge Shield RP18 OBD Column, 19×150 mm) eluted with 4 to 10% ACN in aq NH_4HCO_3 (10 mM) over 20 min.

[0834] Example 273: 2-amino-9-[(5R,7R,8 S,12aR,14R, 15S,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-2-oxido-10-sulfidooctahydro-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): T_R=10.10 min. LCMS (ES, m/z): 693.0 $[M-H]^-$. ^{1}H-NMR: (400 MHz, CDCl$_3$) δ 10.84 (d, J=2.4 Hz, 1H), 10.72 (s, 1H), 10.59 (d, J=3.9 Hz, 1H), 9.01 (dd, J=19.4, 3.0 Hz, 1H), 8.56 (d, J=8.5 Hz, 1H), 8.14-7.96 (m, 2H), 7.93-7.82 (m, 1H), 7.73 (dd, J=12.0, 6.5 Hz, 2H), 7.31-7.19 (m, 2H), 7.15 (d, J=2.8 Hz, 1H), 6.94-6.74 (m, 3H), 6.71-6.53 (m, 2H). ^{31}P-NMR: (162 MHz, D$_2$O): δ 62.301 (s, 1P), 0.976 (s, 1P).

[0835] Example 274: 2-amino-9-[(5R,7R,8 S,12aR,14R, 15S,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-2-oxido-10-sulfidooctahydro-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 2): T_R: 14.27 min. LCMS (ES, m/z): 692.9 $[M-H]^-$. ^{1}H-NMR: (400 MHz, DMSO-d6) δ 8.31 (d, J=11.0 Hz, 2H), 8.18 (s, 1H), 6.40 (dd, J=22.6, 2.6 Hz, 1H), 5.88 (d, J=8.8 Hz, 1H), 5.44 (d, J=33.7 Hz, 2H), 5.35-5.23 (m, 1H), 5.24-5.05 (m, 2H), 4.48-4.34 (m, 1H), 4.31 (dd, J=10.6, 4.5 Hz, 1H), 4.16-3.87 (m, 3H). ^{31}P-NMR: (162 MHz, DMSO-d6): δ 55.096 (s, 1P), −2.731 (s, 1P).

[0836] Examples 275 through 288, as shown in Table 10 below, were prepared according to procedures analogous to those outlined in Examples 274 and 275 above using the appropriate monomeric nucleosides, described as Preparations or as obtained from commercial sources.

TABLE 10

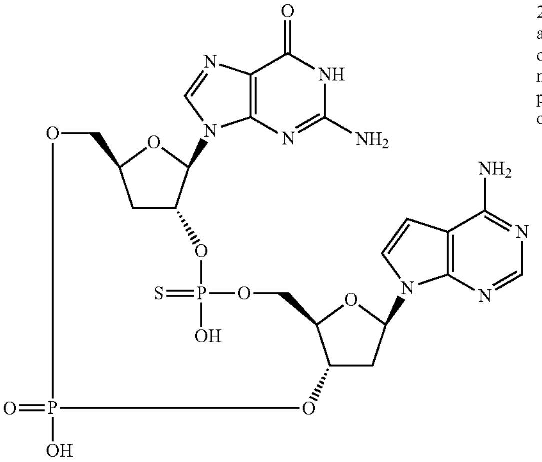
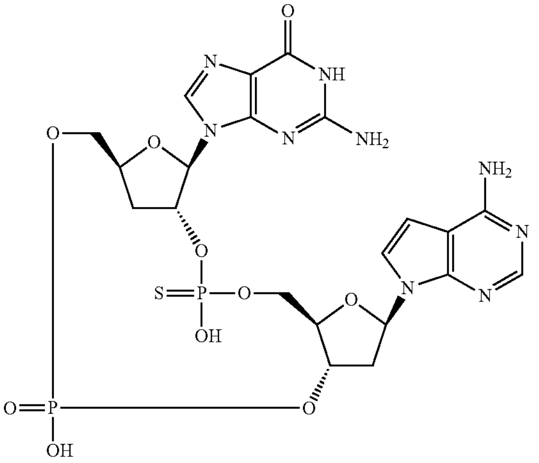
Ex.	Structure	Name	Mass [M − H]
275		2-amino-9-[(5S,7R,8R,12aR,14R,15aS)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2,10-dihydroxy-2-oxido-10-sulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10] pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 1)	656
276		2-amino-9-[(5S,7R,8R,12aR,14R,15aS)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2,10-dihydroxy-2-oxido-10-sulfidooctahydro-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 2)	656

TABLE 10-continued

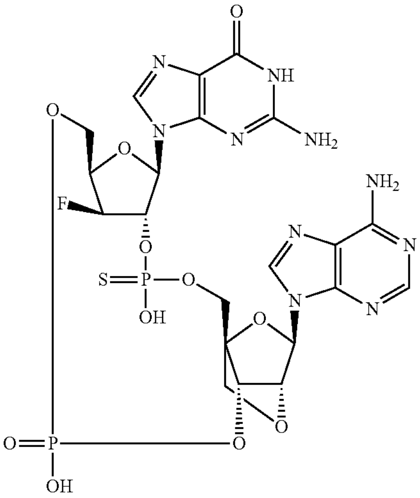
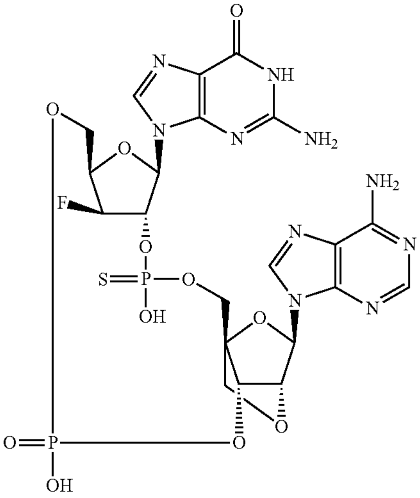
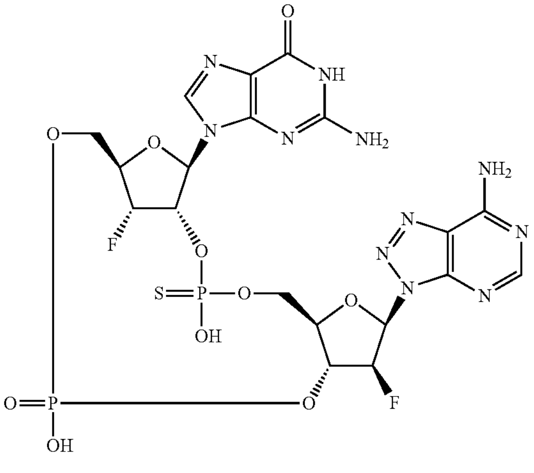
Ex.	Structure	Name	Mass [M − H]
277		2-amino-9-[(5R,7R,8S,12aR,14R,15R,15aS,18S)-14-(6-amino-9H-purin-9-yl)-18-fluoro-2,10-dihydroxy-2-oxido-10-sulfidohexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7(12H)-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 1)	703
278		2-amino-9-[(5R,7R,8S,12aR,14R,15R,15aS,18S)-14-(6-amino-9H-purin-9-yl)-18-fluoro-2,10-dihydroxy-2-oxido-10-sulfidohexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7(12H)-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 2)	703
279		2-amino-9-[(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-dihydroxy-2-oxido-10-sulfidooctahydro-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)	694

TABLE 10-continued

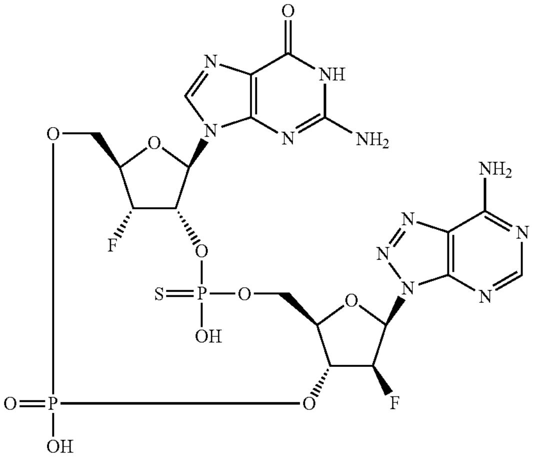
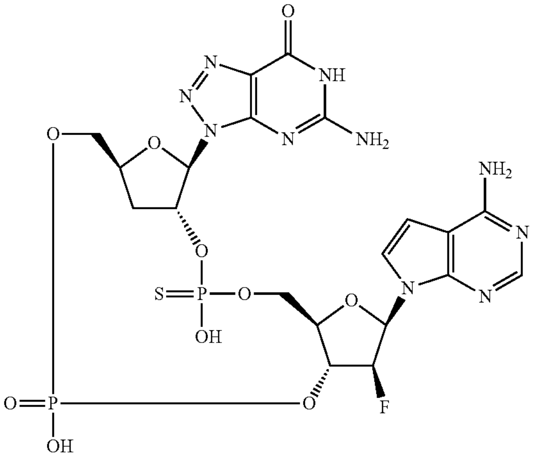
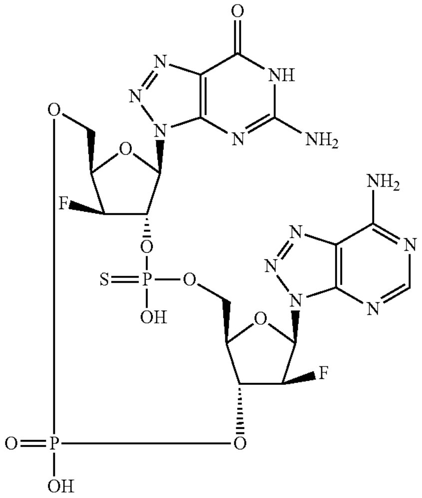
Ex.	Structure	Name	Mass [M − H]
280		2-amino-9-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-14-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-15,16-difluoro-2,10-dihydroxy-2-oxido-10-sulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 2)	694
281		5-amino-3-[(5S,7R,8R,12aR,14R,15S,15aR)-14-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-15-fluoro-2,10-dihydroxy-2-oxido-10-sulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one	675
282		5-amino-3-[(5R,7R,8S,12aR,14R,15S,15aR,16S)-14-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-15,16-difluoro-2,10-dihydroxy-2-oxido-10-sulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one	695

TABLE 10-continued

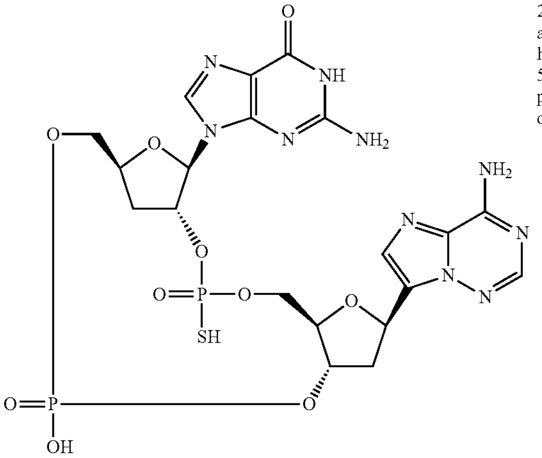
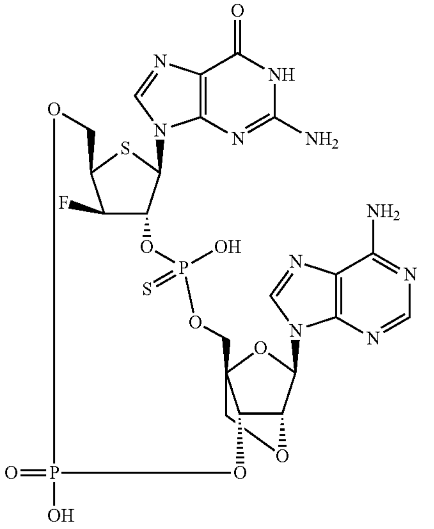
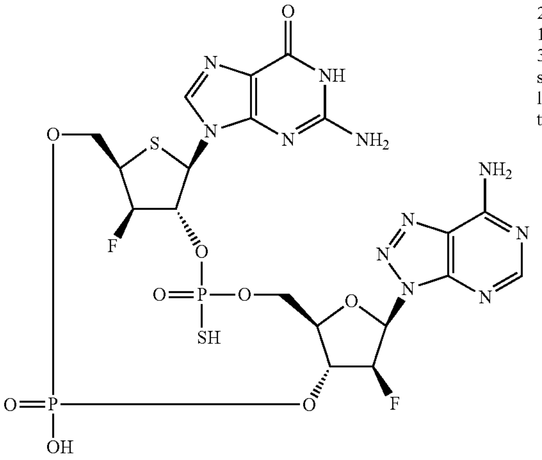
Ex.	Structure	Name	Mass [M − H]
283		2-amino-9-[(5S,7R,8R,12aR,14R,15aS)-14-(4-aminoimidazo[2,1-f][1,2,4]triazin-7-yl)-2-hydroxy-2,10-dioxido-10-sulfanyloctahydro-12H-5,8-methanofuro[3,2-1][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	657
284		2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,18R)-14-(6-amino-9H-purin-9-yl)-18-fluoro-2,10-dihydroxy-2-oxido-10-sulfidohexahydro-14H-15,12a-(epoxymethano)-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7(12H)-yl]-1,9-dihydro-6H-purin-6-one	719
285		2-amino-9-[(5R,7R,8R,12aR,14R,15S,15aR,16R)-14-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-15,16-difluoro-2-hydroxy-2,10-dioxido-10-sulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	710

TABLE 10-continued

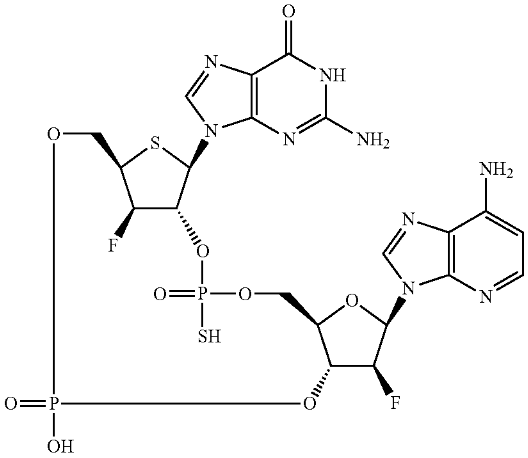
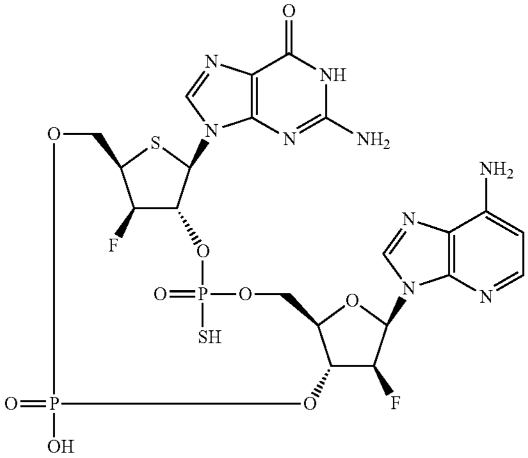
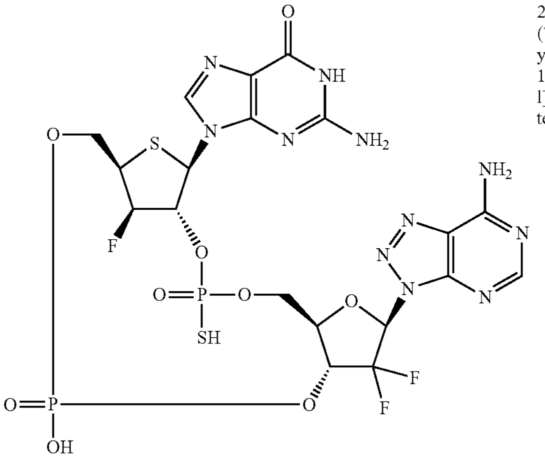
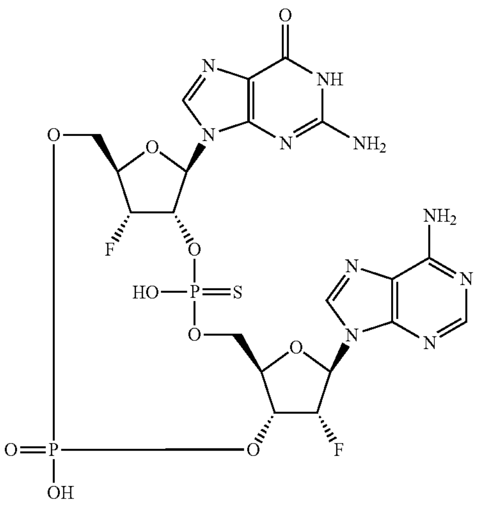
Ex.	Structure	Name	Mass [M − H]
286		2-amino-9-[(5R,7R,8R,12aR,14R,15S,15aR,16R)-14-(7-amino-3H-imidazo[4,5-b]pyridin-3-yl)-15,16-difluoro-2-hydroxy-2,10-dioxido-10-sulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclo-tetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 1)	708
287		2-amino-9-[(5R,7R,8R,12aR,14R,15S,15aR,16R)-14-(7-amino-3H-imidazo[4,5-b]pyridin-3-yl)-15,16-difluoro-2-hydroxy-2,10-dioxido-10-sulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclo-tetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 2)	708

TABLE 10-continued

Ex.	Structure	Name	Mass [M − H]
288		2-amino-9-[(5R,7R,8R,12aR,14R,15aR,16R)-14-(7-amino-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-15,15,16-trifluoro-2-hydroxy-2,10-dioxido-10-sulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	728

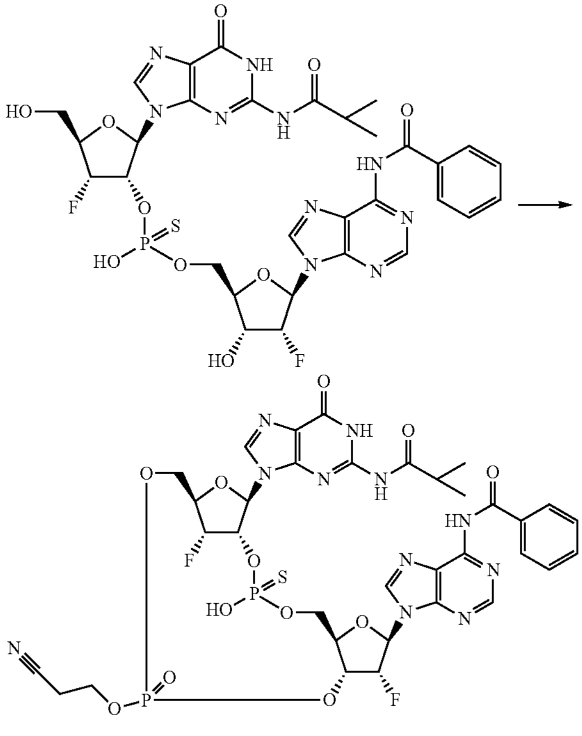
Example 289: 2-amino-9-[(5R,7R,8S,12aR,14R,15R,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one

[0837]



Step 1: N-{9-[(5R,7R,8S,12aR,14R,15R,15aR,16R)-2-(2-cyanoethoxy)-15,16-difluoro-10-hydroxy-7-{2-[(2-methylpropanoyl)amino]-6-oxo-1,6-dihydro-9H-purin-9-yl}-2-oxido-10-sulfidooctahydro-12H-5,8-methanofuro[3,2-1][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]-9H-purin-6-yl}benzamide

[0838]



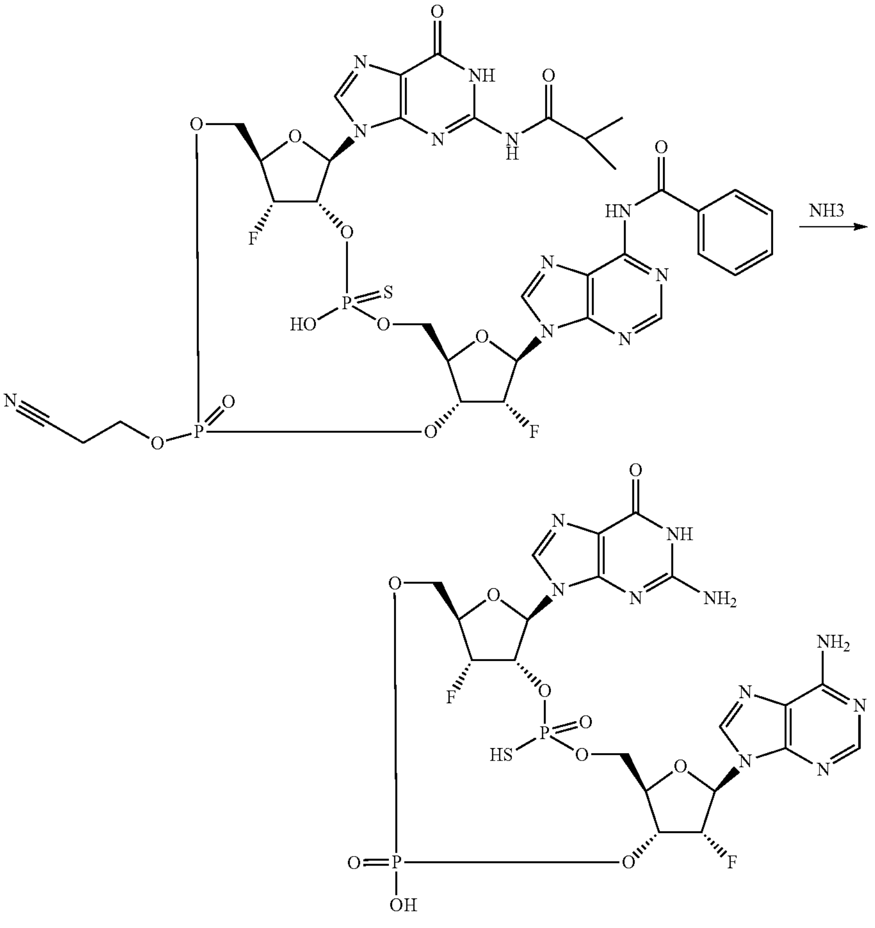
[0839] O-(((2R,3R,4R,5R)-5-(6-benzamido-9H-purin-9-yl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)methyl)O-((2R, 3S,4R,5R)-4-fluoro-5-(hydroxymethyl)-2-(2-isobutyramido-6-oxo-1H-purin-9(6H)-yl)tetrahydrofuran-3-yl)O-hydrogen phosphorothioate (product of Step 3, Example 261, 100 mg, 0.124 mmol) and diisopropylammonium tetrazolide (31.8 mg, 0.186 mmol) were azeotrope with dry CH_3CN (3×10 ml) and dried under high vacuum for 30 min.

[0840] The above mixture was dissolved in DMF (1 mL) and acetonitrile (7 mL) and added 200 mg active MS 4 Å and a solution of 2-cyanoethyl N,N,N',N'-tetraisopropylphosphorodiamidite (51.1 mg, 0.161 mmol) in 1 ml dry CH_3CN. The resulting mixture was stirred at rt for 30 min, followed by addition of 1H-tetrazole (43.4 mg, 0.620 mmol). The reaction stayed at rt for 1 h and added tert-butyl hydroperoxide (5.0M in Decane)(0.074 mL, 0.372 mmol). The stirring continued for 1 h and concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting with 0-8% MeOH/DCM to give the desired product. LCMS (ES, m/z): 922 $[M+H]^+$

Step 2: 2-amino-9-[(5R,7R,8S,12aR,14R,15R,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-2-oxido-10-sulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one

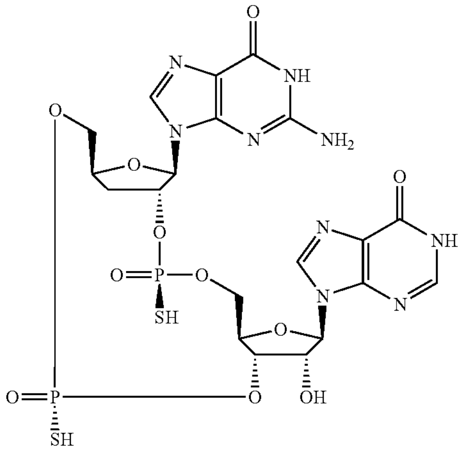
[0841]

[0842] N-{9-[(5R,7R,8S,12aR,14R,15R,15aR,16R)-2-(2-cyanoethoxy)-15,16-difluoro-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]-9H-purin-6-yl}benzamide (90 mg, 0.098 mmol) and ammonia (7.0M in MeOH) (2 ml, 14.00 mmol) were sealed in a microwave tube. The mixture was heated to 50° C. and stirred for 4 h. The reaction mixture was concentrated, and purified using mass-directed reverse phase HPLC (X-Bridge BEH 150 Prep C18) using a gradient solvent system with MeCN and 100 mM aqueous triethylammonium acetate to give three desired diastereomers. Lyophilization of the product fractions furnished 2-amino-9-[(5R,7R,8S,12aR,14R,15R,15aR,16R)-14-(6-amino-9H-purin-9-yl)-15,16-difluoro-2,10-dihydroxy-2-oxido-10-sulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one. LCMS (ES, m/z): 693 $[M-H]^-$. ^{1}H NMR (H2O-d2, 500 MHz): δ_H 8.23 (2H, d, J=5.2 Hz), 7.81 (1H, s), 6.42 (1H, d, J=14.2 Hz), 5.99 (1H, d, J=8.6 Hz), 5.70 (1H, m), 5.40 (2H, m), 5.20 (1H, m), 4.62 (2H, m), 4.54 (1H, s), 4.15-4.30 (3H, m). ^{31}P NMR: (H_2O-d_2, 202 MHz): δ −1.6, 52.1.



Example 290: 2-amino-9-[(2R,5S,7R,8R,10R,12aR,14R,15R,15aS)-15-hydroxy-2,10-dioxido-14-(6-oxo-1,6-dihydro-9H-purin-9-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

[0843]



[0844] To (2R,5 S,7R,8R,10R,12aR,14R,15R,15aS)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-14-(6-amino-9H-purin-9-yl)-15-hydroxyoctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecine-2,10-bis(thiolate) 2,10-dioxide (Example 86, 5.0 mg, 0.0071 mmol) were added sodium phosphate buffer (pH 6.8, 50 mM, 0.5 mL) and adenosine monophosphate deaminase (3 mg). The reaction mixture was left to stir overnight, filtered, and purified by reverse phase HPLC (1-10% MeCN in aq NH_4HCO_3 (100 mM)) to afford the title compound as a diammonium salt. LCMS (ES, m/z): 690 $[M-H]^-$. ^{1}H NMR (500 MHz, D_2O): δ 8.30 (s, 1H), 8.20 (s, 1H), 7.95 (s, 1H), 6.19 (s, 1H), 5.82 (d, J=6.0 Hz, 1H), 5.64 (m, 1H), 5.15 (m, 1H), 4.86 (d, J=4.5 Hz, 1H), 4.60 (m, 1H), 4.48-4.53 (m, 2H), 4.38 (m, 1H), 4.11 (dd, J=11.5, 4.0 Hz, 1H), 4.05 (m, 1H), 2.63 (m, 1H), 2.52 (m, 1H). ^{31}P NMR: (202 MHz, D_2O): δ 55.78 (s), 52.44 (s).

[0845] Examples 291 through 348 as shown in Table 11 below, were prepared according to procedures analogous to those outlined in Example 290 above, from the starting compound ("St. Cmpd.") indicated.

TABLE 11

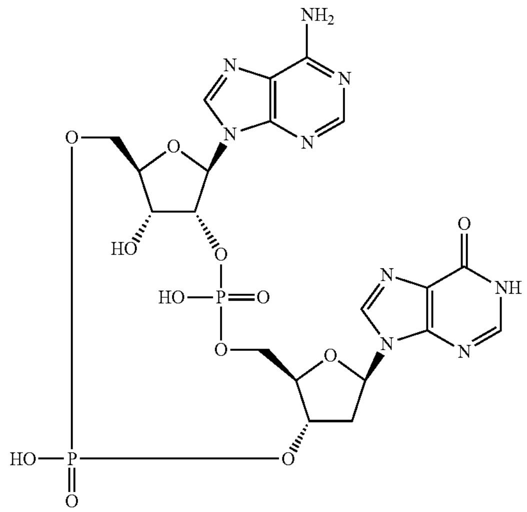
Ex.	Structure	Name	Mass $[M - H]^-$	St. Cmpd.
291		9-[(5R,7R,8R,12aR,14R,15aS,16R)-7-(6-amino-9H-purin-9-yl)-2,10,16-trihydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]-1,9-dihydro-6H-purin-6-one	642	3

TABLE 11-continued

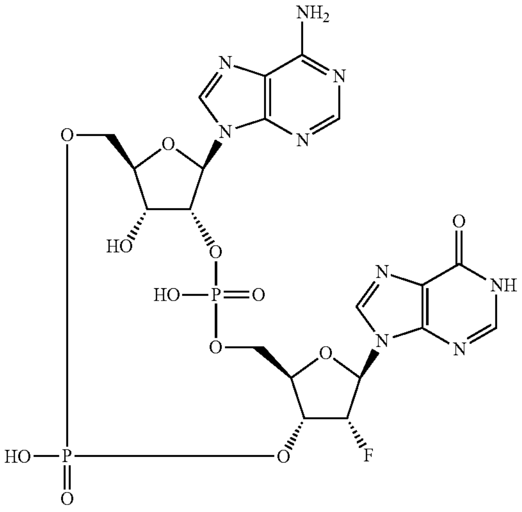
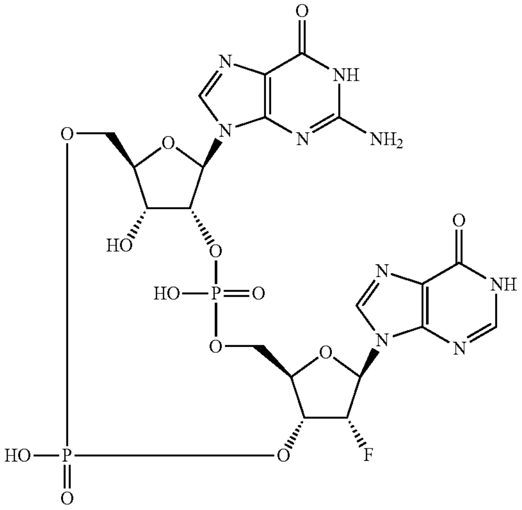
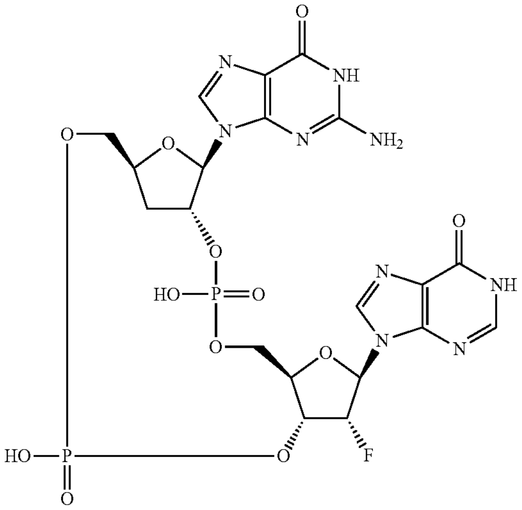
Ex.	Structure	Name	Mass [M − H]⁻	St. Cmpd.
292		9-[(5R,7R,8R,12aR,14R,15R,15aR,16R)-7-(6-amino-9H-purin-9-yl)-15-fluoro-2,10,16-trihydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]-1,9-dihydro-6H-purin-6-one	660	4
293		2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aR,16R)-15-fluoro-2,10,16-trihydroxy-2,10-dioxido-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	676	2
294		2-amino-9-[(5S,7R,8R,12aR,14R,15R,15aR)-15-fluoro-2,10-dihydroxy-2,10-dioxido-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	660	21

TABLE 11-continued

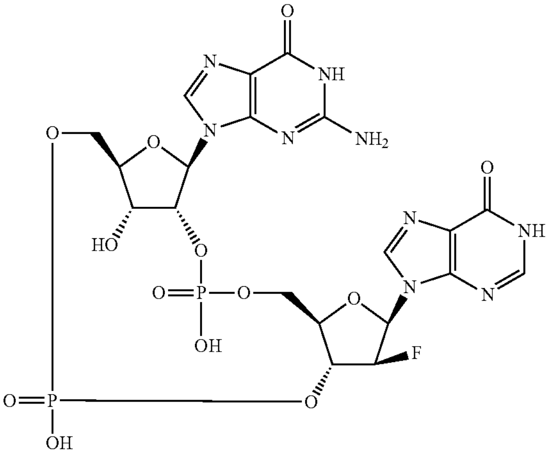
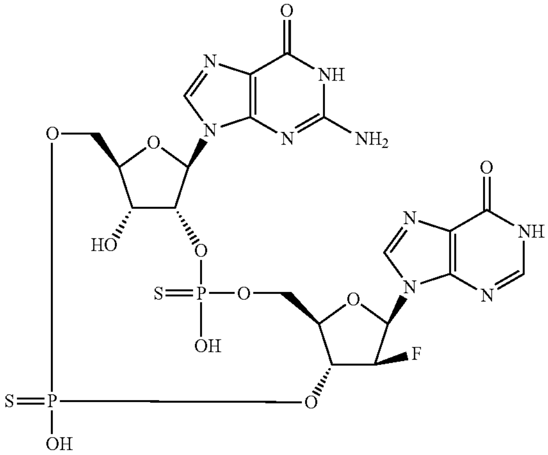
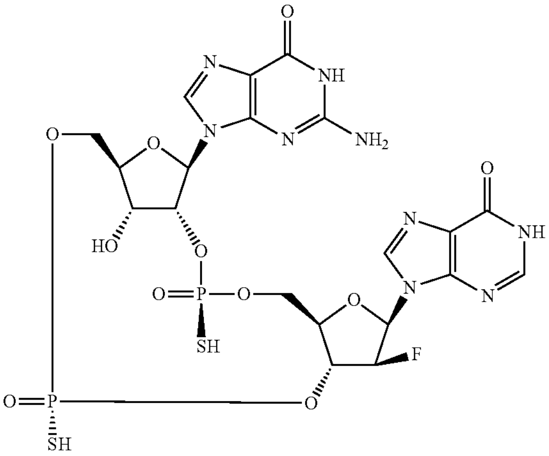
Ex.	Structure	Name	Mass [M − H]⁻	St. Cmpd.
295		2-amino-9-[(5R,7R,8R,12aR,14R,15S,15aR,16R)-15-fluoro-2,10,16-trihydroxy-2,10-dioxido-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	676	7
296		2-amino-9-[(5R,7R,8R,12aR,14R,15S,15aR,16R)-15-fluoro-2,10,16-trihydroxy-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)-2,10-disulfidooctahydro-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)	708	90
297		2-amino-9-[(2R,5R,7R,8R,10R,12aR,14R,15S,15aR,16R)-15-fluoro-2,10,16-trihydroxy-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)-2,10-disulfidooctahydro-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 2)	708	89

TABLE 11-continued

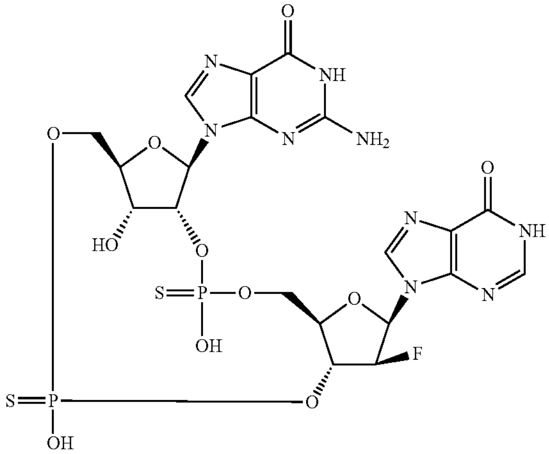
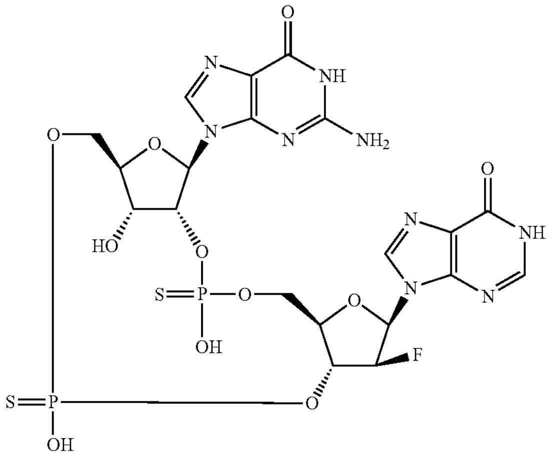
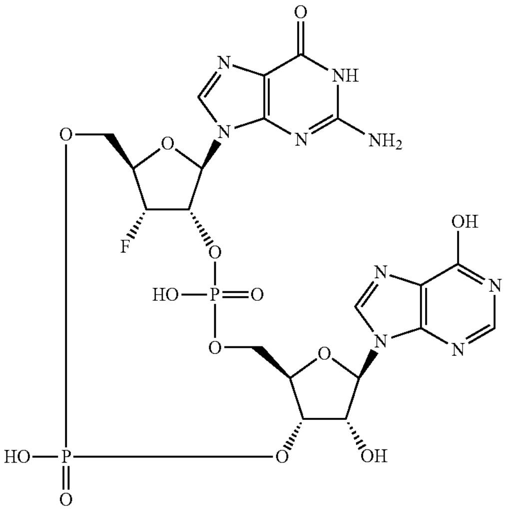
Ex.	Structure	Name	Mass [M − H]⁻	St. Cmpd.
298		2-amino-9-[(5R,7R,8R,12aR,14R,15S,15aR,16R)-15-fluoro-2,10,16-trihydroxy-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 3)	708	91
299		2-amino-9-[(5R,7R,8R,12aR,14R,15S,15aR,16R)-15-fluoro-2,10,16-trihydroxy-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)-2,10-disulfidooctahydro-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 4)	708	92
300		2-amino-9-[(5R,7R,8S,12aR,14R,15R,15aS,16R)-16-fluoro-2,10,15-trihydroxy-14-(6-hydroxy-9H-purin-9-yl)-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	676	5

TABLE 11-continued

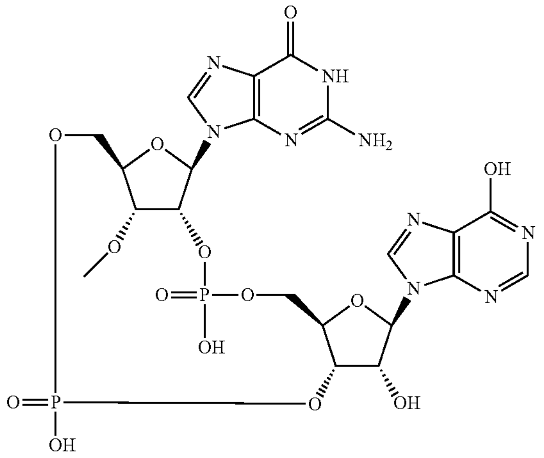
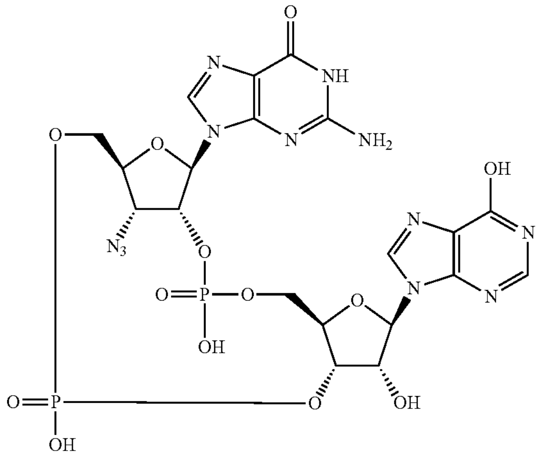
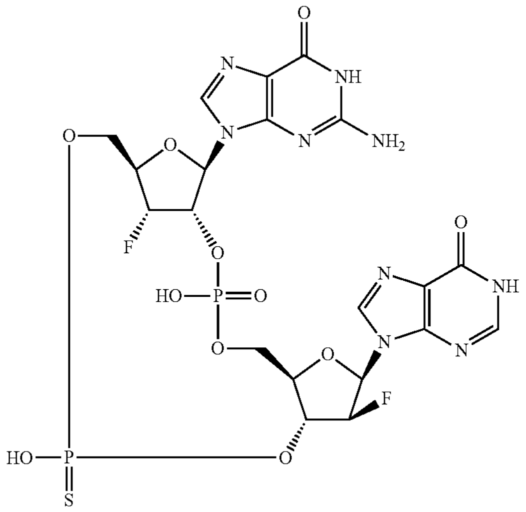
Ex.	Structure	Name	Mass [M − H]⁻	St. Cmpd.
301		2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,16R)-2,10,15-trihydroxy-14-(6-hydroxy-9H-purin-9-yl)-16-methoxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	688	13
302		2-amino-9-[(5S,7R,8R,12aR,14R,15R,15aS,16R)-16-azido-2,10,15-trihydroxy-14-(6-hydroxy-9H-purin-9-yl)-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	699	14
303		2-amino-9-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-15,16-difluoro-2,10-dihydroxy-10-oxido-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)-2-sulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	694	143

TABLE 11-continued

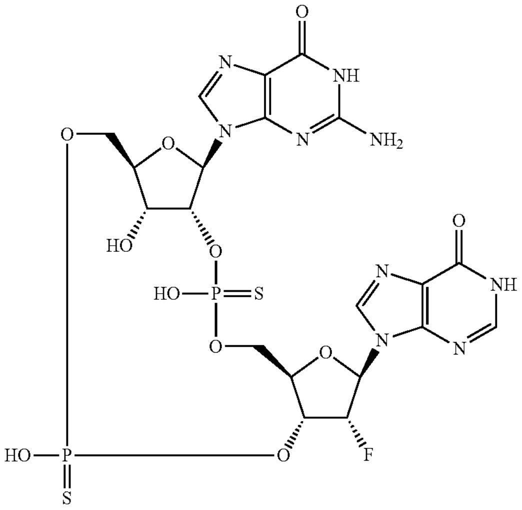
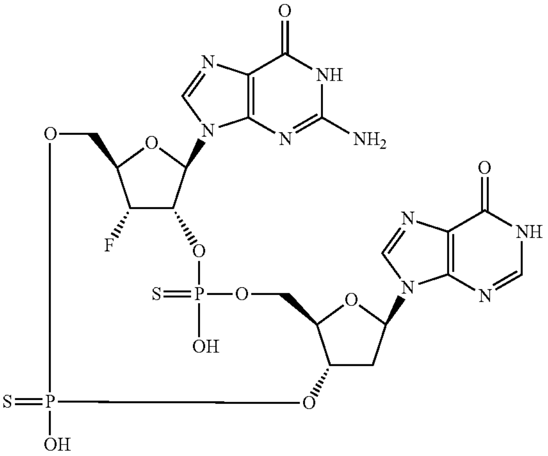
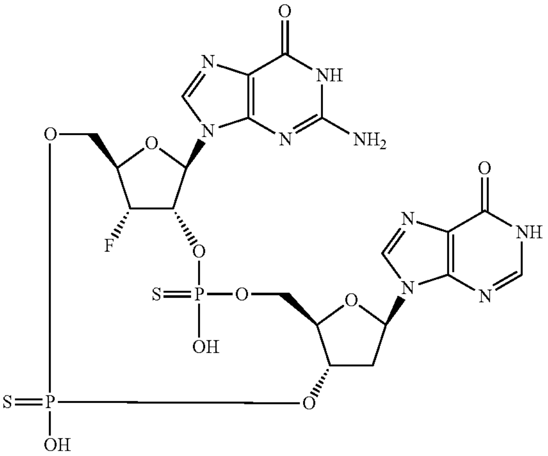
Ex.	Structure	Name	Mass [M − H]⁻	St. Cmpd.
304		2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aR,16R)-15-fluoro-2,10,16-trihydroxy-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	708	81
305		2-amino-9-[(5R,7R,8S,12aR,14R,15aS,16R)-16-fluoro-2,10-dihydroxy-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)-2,10-disulfidooctahydro-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)	692	120
306		2-amino-9-[(5R,7R,8S,12aR,14R,15aS,16R)-16-fluoro-2,10-dihydroxy-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)-2,10-disulfidooctahydro-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 2)	692	118

TABLE 11-continued

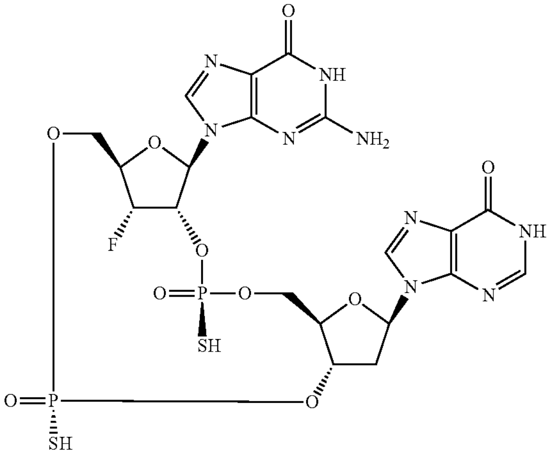
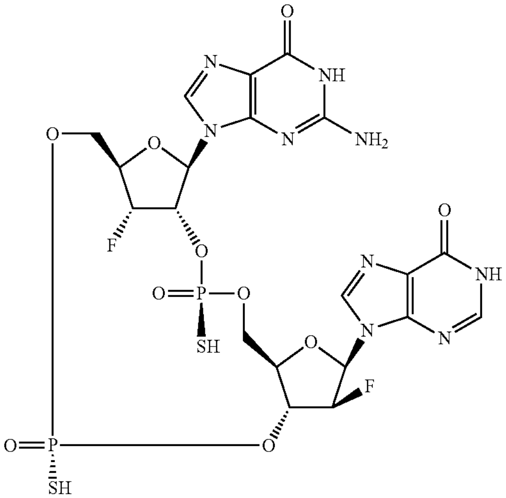
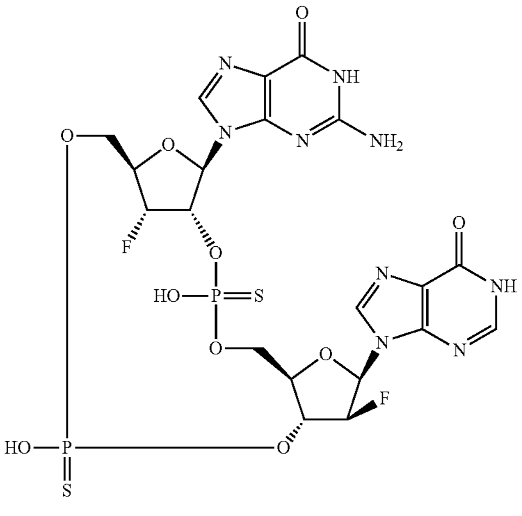
Ex.	Structure	Name	Mass $[M - H]^-$	St. Cmpd.
307		2-amino-9-[(2R,5R,7R,8S,10R,12aR,14R,15aS,16R)-16-fluoro-2,10-dihydroxy-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 3)	692	117
308		2-amino-9-[(2R,5R,7R,8S,10R,12aR,14R,15S,15aR,16R)-15,16-difluoro-2,10-dihydroxy-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)-2,10-disulfidooctahydro-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)	710	247
309		2-amino-9-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-15,16-difluoro-2,10-dihydroxy-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)-2,10-disulfidooctahydro-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 2)	710	245

TABLE 11-continued

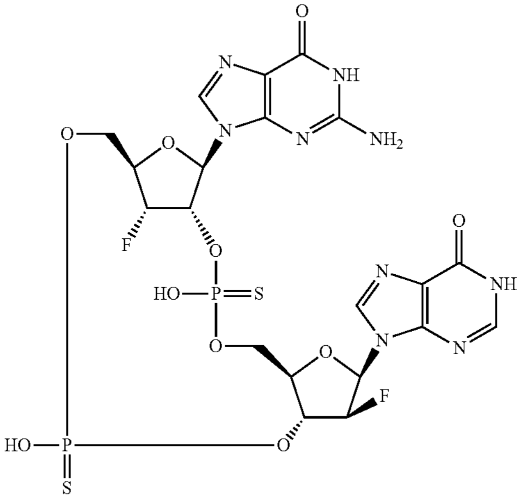
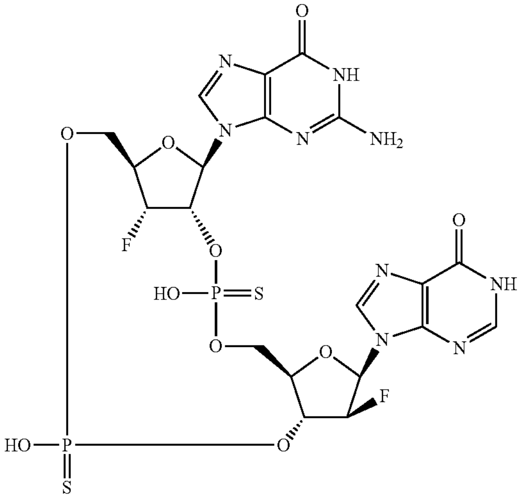
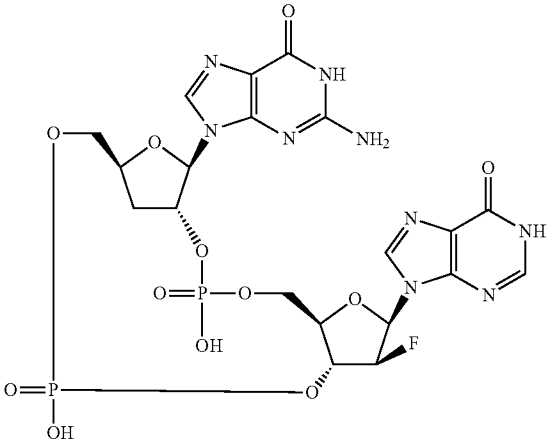
Ex.	Structure	Name	Mass [M − H]⁻	St. Cmpd.
310		2-amino-9-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-15,16-difluoro-2,10-dihydroxy-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)-2,10-disulfidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 3)	710	246
311		2-amino-9-[(5R,7R,8S,12aR,15S,15aR,16R)-15,16-difluoro-2,10-dihydroxy-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)-2,10-disulfidooctahydro-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 4)	710	244
312		2-amino-9-[(5S,7R,8R,12aR,14R,15S,15aR)-15-fluoro-2,10-dihydroxy-2,10-dioxido-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	660	25

TABLE 11-continued

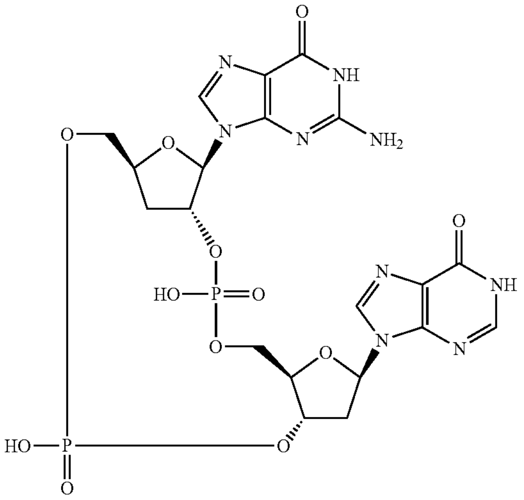
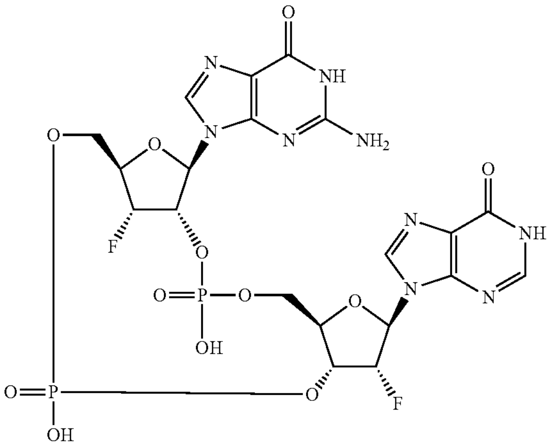
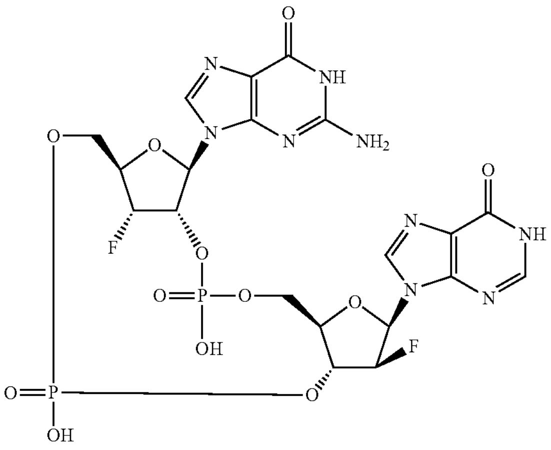
Ex.	Structure	Name	Mass [M − H]$^-$	St. Cmpd.
313		2-amino-9-[(5S,7R,8R,12aR,14R,15aS)-2,10-dihydroxy-2,10-dioxido-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	642	27
314		2-amino-9-[(5R,7R,8S,12aR,14R,15R,15aR,16R)-15,16-difluoro-2,10-dihydroxy-2,10-dioxido-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	678	23
315		2-amino-9-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-15,16-difluoro-2,10-dihydroxy-2,10-dioxido-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	678	26

TABLE 11-continued

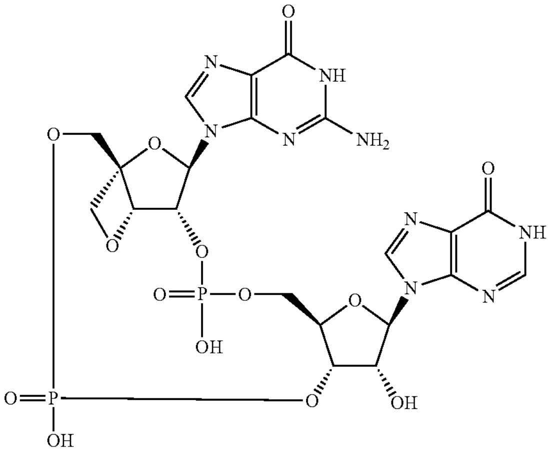
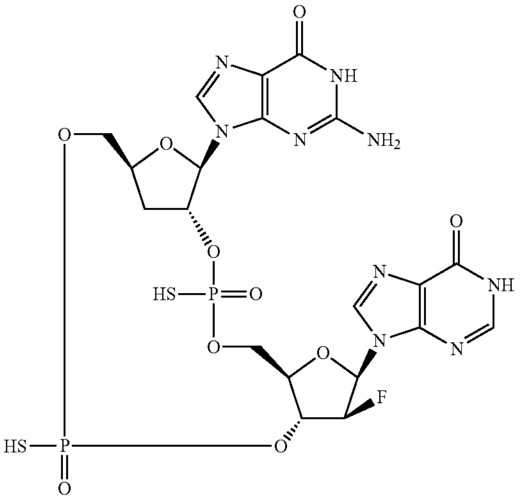
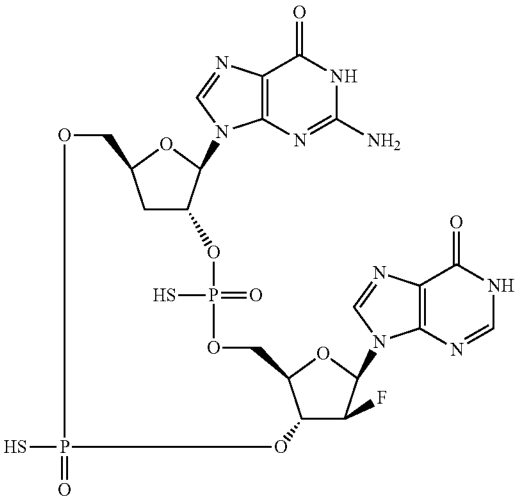
Ex.	Structure	Name	Mass [M − H]⁻	St. Cmpd.
316		2-amino-9-[(2aR,6aS,7R,8R,9aR,14R,14aS,15R)-5,7,12-trihydroxy-5,12-dioxido-8-(6-oxo-1,6-dihydro-9H-purin-9-yl)hexahydro-6aH,2a,14-(epoxymethano)furo[3,2-d]oxeto[2,3-k][1,3,7,9,2,8]tetraoxadiphosphacyclotridecin-15(2H,3H)-yl]-1,9-dihydro-6H-purin-6-one	686	17
317		2-amino-9-[(2R,5S,7R,8R,10R,12aR,14R,15S,15aR)-15-fluoro-2,10-dioxido-14-(6-oxo-1,6-dihydro-9H-purin-9-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 (Diastereomer 1)	692	130
318		2-amino-9-[(5S,7R,8R,12aR,14R,15S,15aR)-15-fluoro-2,10-dioxido-14-(6-oxo-1,6-dihydro-9H-purin-9-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 (Diastereomer 2)	692	131

TABLE 11-continued

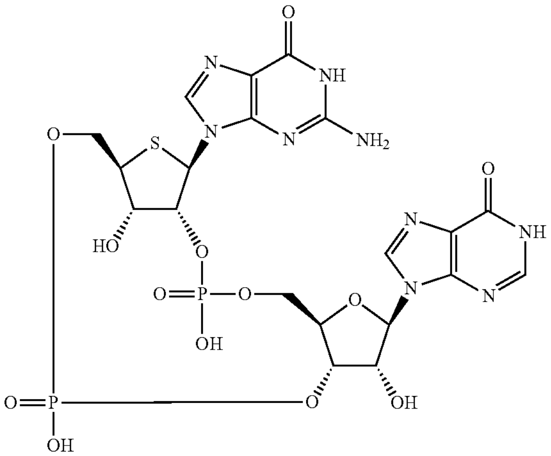
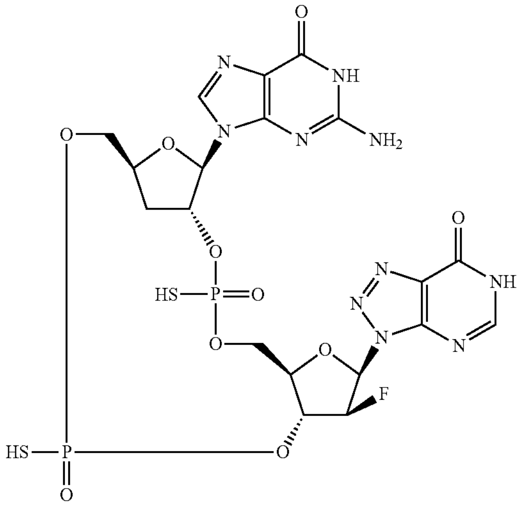
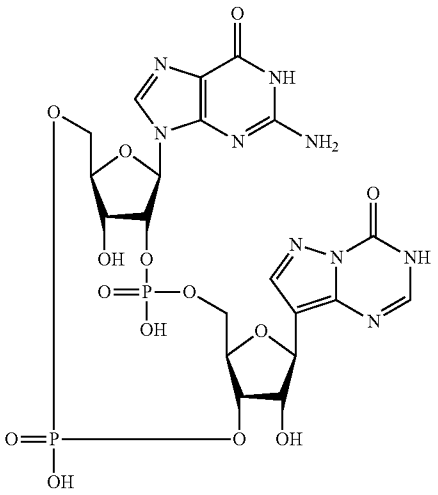
Ex.	Structure	Name	Mass [M − H]⁻	St. Cmpd.
319		2-amino-9-[(5R,7R,8R,12aR,14R,15R,15aS,16S)-2,10,15,16-tetrahydroxy-2,10-dioxido-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	690	11
320		3-[(5S,7R,8R,12aR,14R,15S,15aR)-7-(2-amino-6-oxo-1,6-dihydro-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-14-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one	693	133
321		8-[(5R,7R,8R,12aR,14S,15S,15aS,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-2,10,15,16-tetrahydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]pyrazolo[1,5-a][1,3,5]triazin-4(3H)-one	674	54

TABLE 11-continued

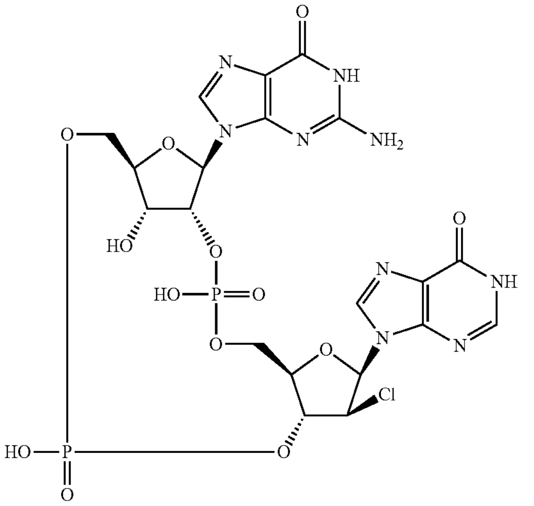
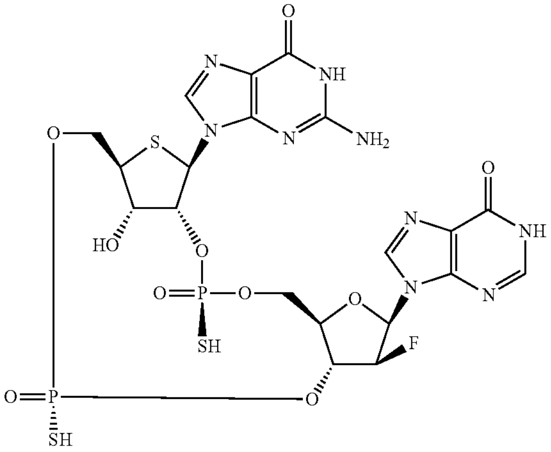
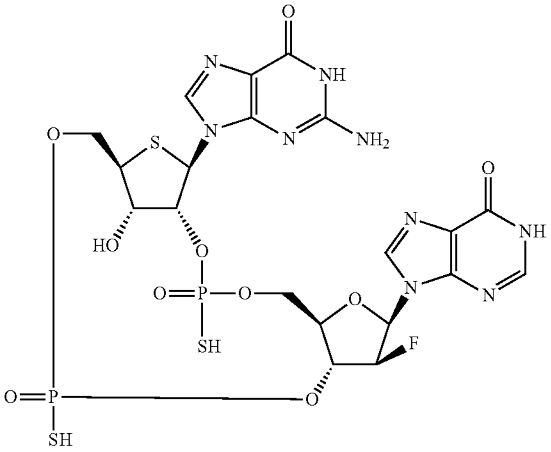
Ex.	Structure	Name	Mass $[M-H]^-$	St. Cmpd.
322		2-amino-9-[(5R,7R,8R,12aR,14R,15S,15aR,16R)-15-chloro-2,10,16-trihydroxy-2,10-dioxido-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	692	15
323		2-amino-9-[(2R,5R,7R,8R,10R,12aR,14R,15S,15aR,16S)-15-fluoro-16-hydroxy-2,10-dioxido-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 1)	724	97
324		2-amino-9-[(5R,7R,8R,12aR,14R,15S,15aR,16S)-15-fluoro-16-hydroxy-2,10-dioxido-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 2)	724	99

TABLE 11-continued

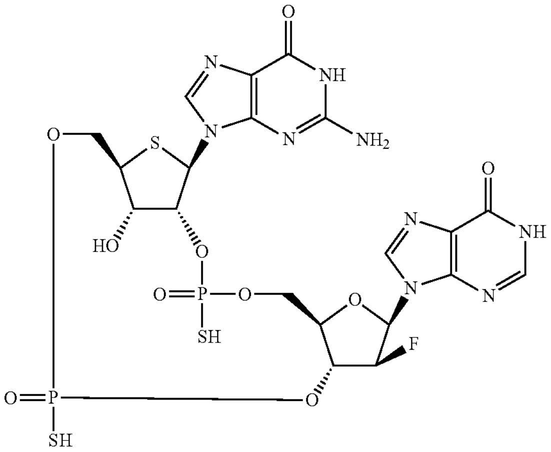
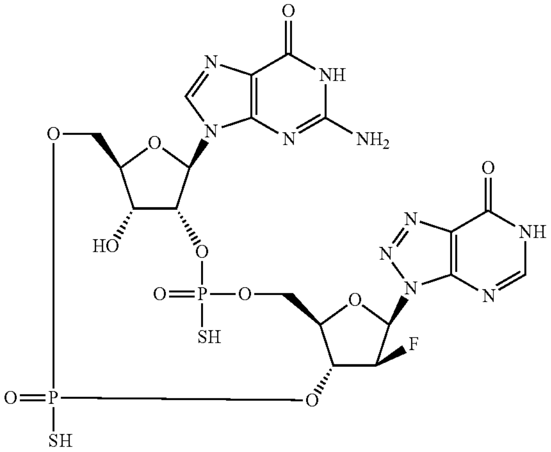
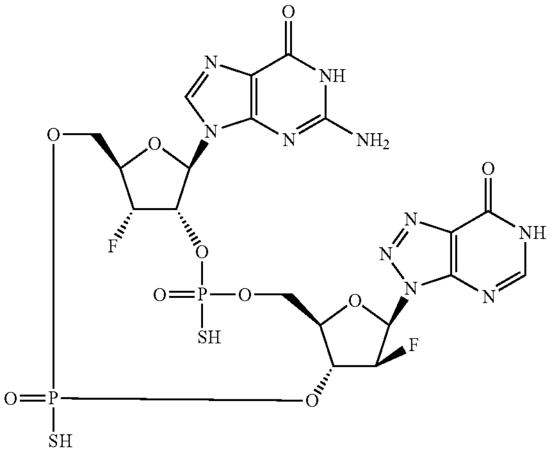
Ex.	Structure	Name	Mass $[M - H]^-$	St. Cmpd.
325		2-amino-9-[(5R,7R,8R,12aR,14R,15S,15aR,16S)-15-fluoro-16-hydroxy-2,10-dioxido-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one (Diastereomer 3)	724	96
326		3-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-7-(2-amino-6-oxo-1,6-dihydro-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-14-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 1)	711	130
327		3-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-7-(2-amino-6-oxo-1,6-dihydro-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-14-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 2)	711	128

TABLE 11-continued

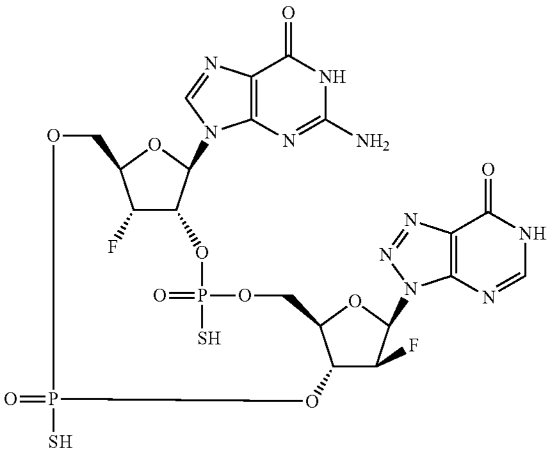
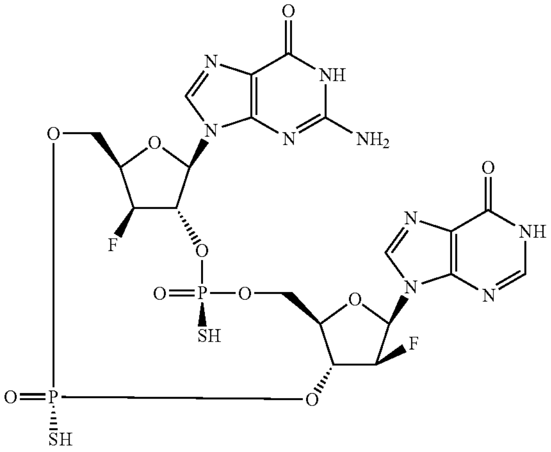
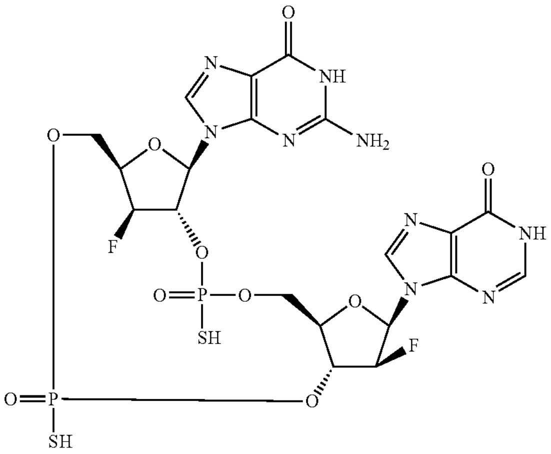
Ex.	Structure	Name	Mass [M − H]⁻	St. Cmpd.
328		3-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-15,16-difluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 3)	711	127
329		2-amino-9-[(2R,5R,7R,8S,10R,12aR,14R,15S,15aR,16S)-15,16-difluoro-2,10-dioxido-14-(6-oxo-1,6-dihydro-9H-purin-9-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 (Diastereomer 1)	710	144
330		2-amino-9-[(5R,7R,8S,12aR,14R,15S,15aR,16S)-15,16-difluoro-2,10-dioxido-14-(6-oxo-1,6-dihydro-9H-purin-9-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 (Diastereomer 2)	710	145

TABLE 11-continued

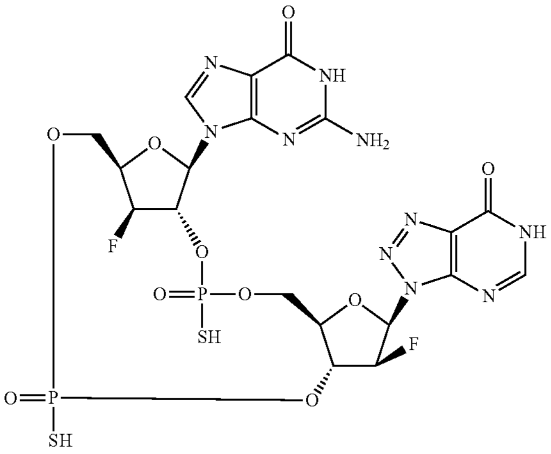
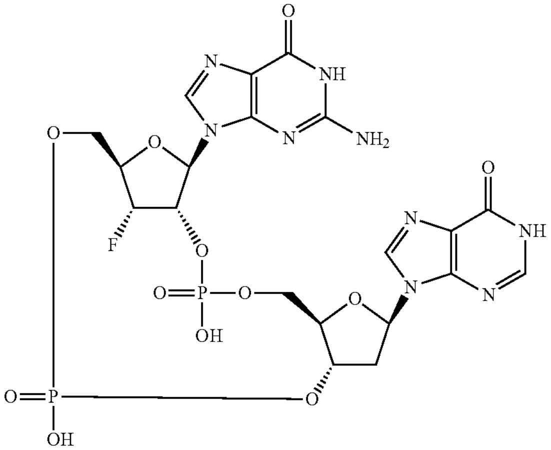
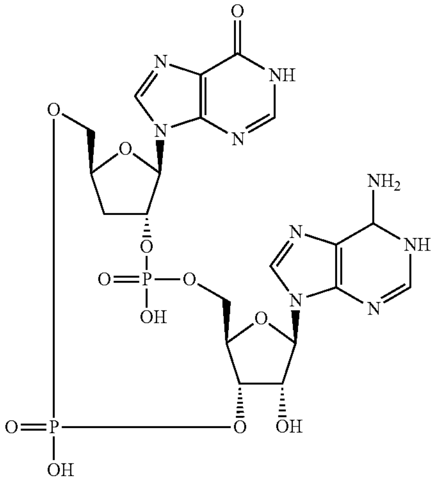
Ex.	Structure	Name	Mass [M − H]⁻	St. Cmpd.
331		3-[(5R,7R,8S,12aR,14R,15S,15aR,16S)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-15,16-difluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one	711	147
332		2-amino-9-[(5R,7R,8S,12aR,14R,15aS,16R)-16-fluoro-2,10-dihydroxy-2,10-dioxido-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)octahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	660	22
333		9,9'-[(5S,7R,8R,12aR,14R,15R,15aS)-2,10,15-trihydroxy-2,10-dioxidooctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxaciphosphacyclotetradecine-7,14-diyl]bis(1,9-dihydro-6H-purin-6-one	643	50

TABLE 11-continued

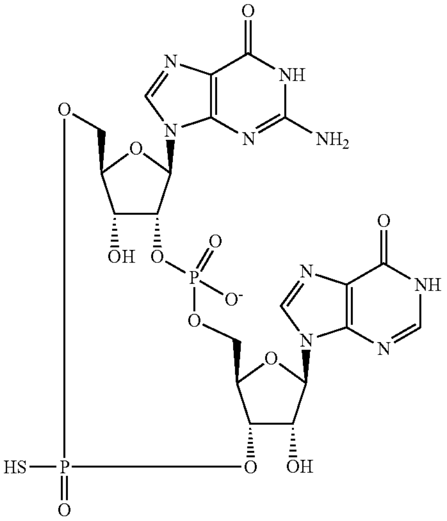
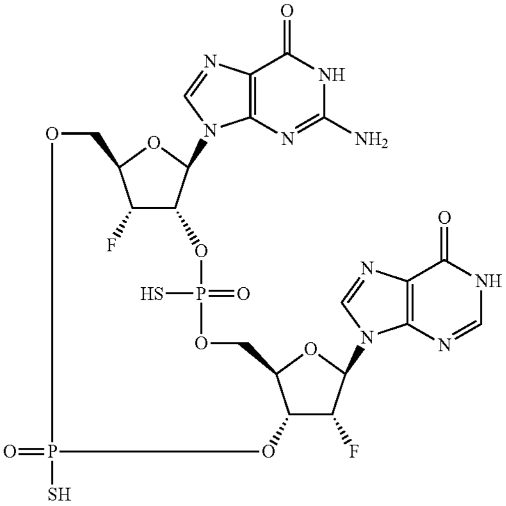
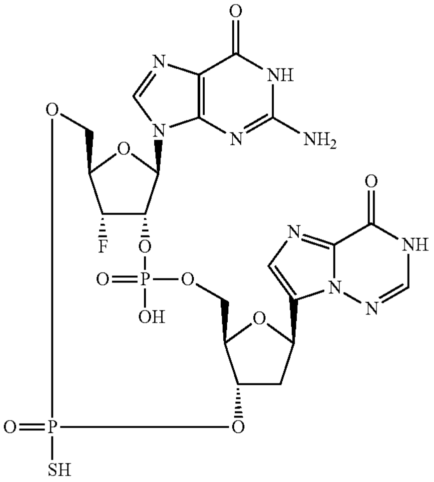
Ex.	Structure	Name	Mass [M − H]⁻	St. Cmpd.
334		2-amino-9-[(5R,7R,8R,12ar,14R,15R,15aS,16R)-10,15,16-trihydroxy-2,10-dioxido-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)-2-sulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	690	38
335		2-amino-9-[(5R,7R,8S,12aR,14R,15R,15aR,16R)-15,16-difluoro-2,10-dioxido-14-(6-oxo-1,6-dihydro-9H-purin-9-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	710	260
336		7-[(5R,7R,8S,12aR,14R,15aS,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-16-fluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]imidazo[2,1-f][1,2,4]triazin-4(3H)-one (Diastereomer 1)	692	249

TABLE 11-continued

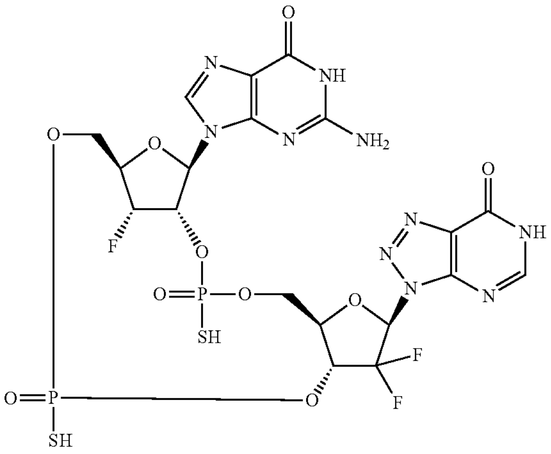
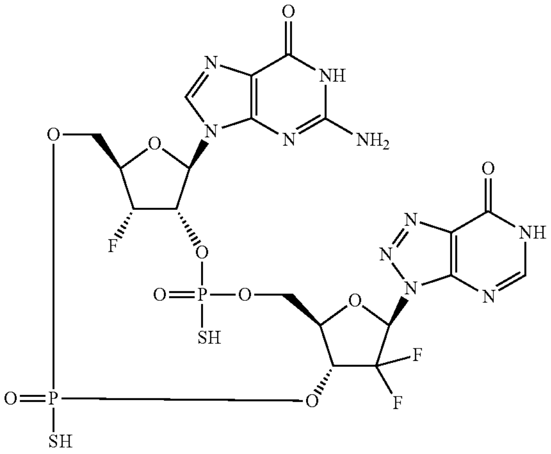
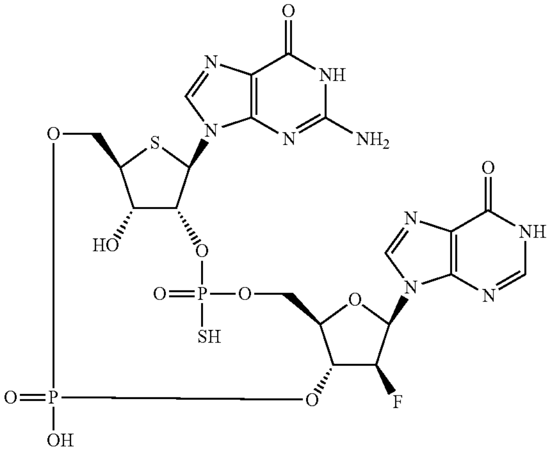
Ex.	Structure	Name	Mass [M − H]$^-$	St. Cmpd.
337		3-[5R,7R,8S,12aR,14R,15aR,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-15,15,16-trifluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 1)	729	165
338		3-[(5R,7R,8S,12aR,14R,15aR,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-15,15,16-trifluoro-2,10-dioxido-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 2)	729	167
339		2-amino-9-[(5R,7R,8R,12aR,14R,15S,15aR,16S)-15-fluoro-2,16-dihydroxy-2,10-dioxido-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)-10-sulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,9,11,6,2,10]tetraoxathiadiphosphacyclotetradecin-7-yl]-1,9-dihydro-6H-purin-6-one	708	266

TABLE 11-continued

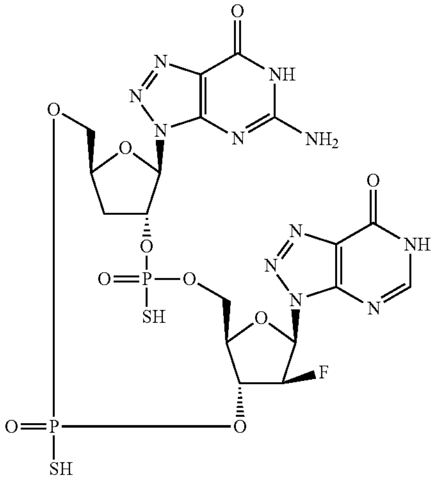
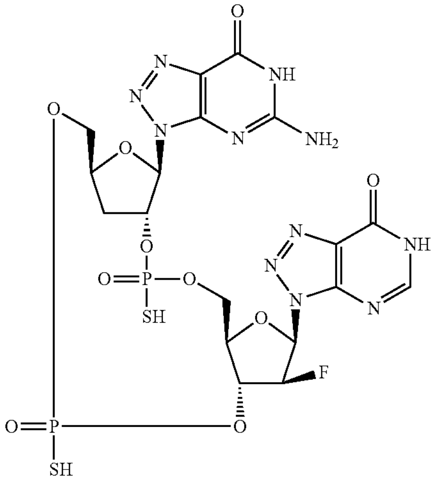
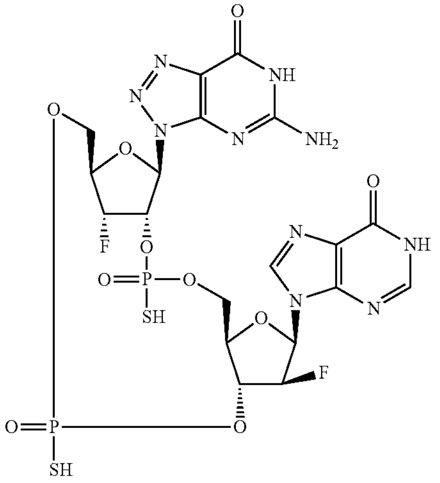
Ex.	Structure	Name	Mass [M − H]⁻	St. Cmpd.
340		5-amino-3-[(5S,7R,8R,12aR,14R,15S,15aR)-15-fluoro-2,10-dioxido-14-(7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-c]pyrimidin-3-yl)-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 1)	694	181
341		5-amino-3-[(5S,7R,8R,12aR,14R,15S,15aR)-15-fluoro-2,10-dioxido-14-(7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-c][pyrimidin-3-yl)-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 2)	694	182
342		5-amino-3-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-15,16-difluoro-2,10-dioxido-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 1)	711	199

TABLE 11-continued

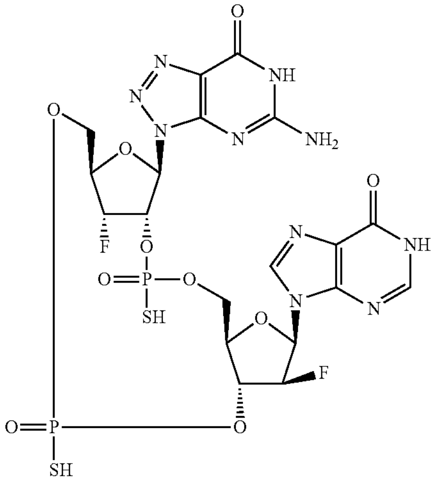
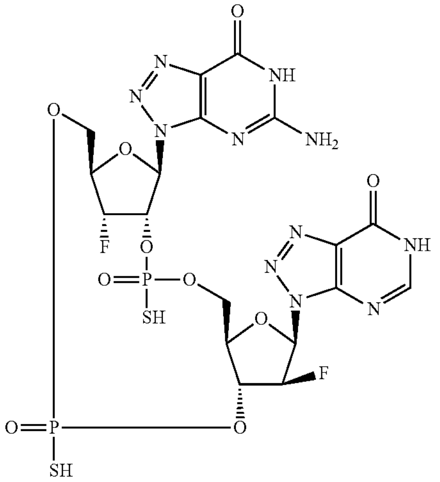
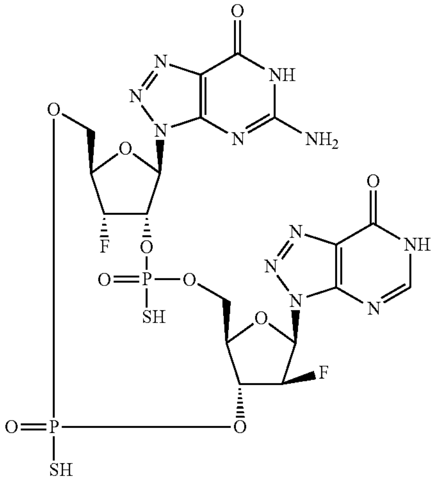
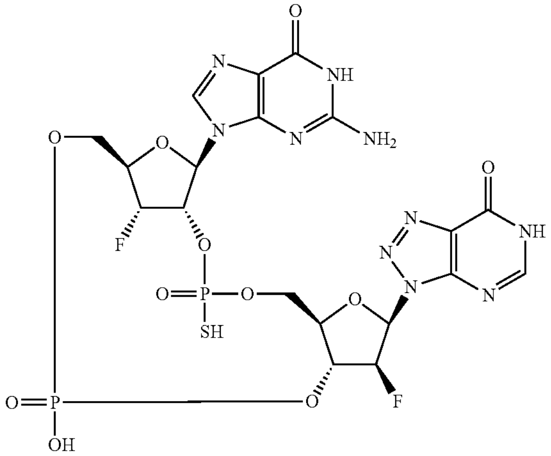
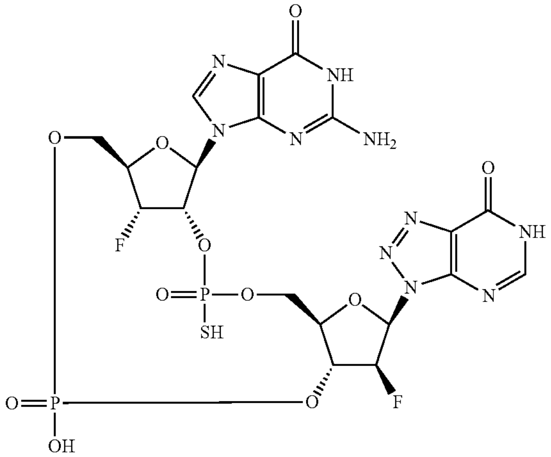
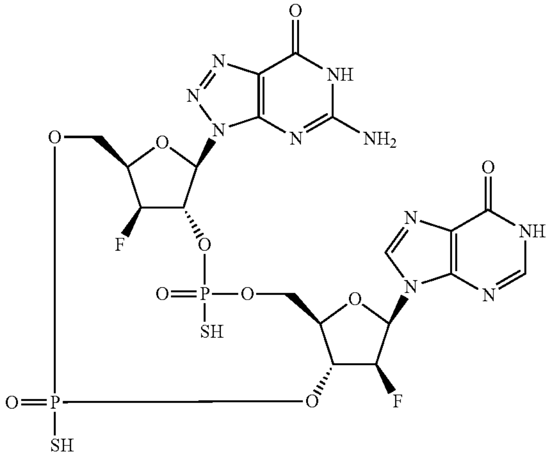
Ex.	Structure	Name	Mass [M − H]⁻	St. Cmpd.
343		5-amino-3-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-15,16-difluoro-2,10-dioxido-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 2)	711	197
344		5-amino-3-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-15,16-difluoro-2,10-dioxido-14-(7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-c]pyrimidin-3-yl)-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 1)	712	200
345		5-amino-3-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-15,16-difluoro-2,10-dioxido-14-(7-oxo-6,7-dihydro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 2)	712	201

TABLE 11-continued

Ex.	Structure	Name	Mass [M − H]⁻	St. Cmpd.
346		3-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-15,16-difluoro-2-hydroxy-2,10-dioxido-10-sulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 1)	695	279
347		3-[(5R,7R,8S,12aR,14R,15S,15aR,16R)-7-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-15,16-difluoro-2-hydroxy-2,10-dioxido-10-sulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-14-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one (Diastereomer 2)	695	280
348		5-amino-3-[(5R,7R,8S,12aR,14R,15S,15aR,16S)-15,16-difluoro-2,10-dioxido-14-(6-oxo-1,6-dihydro-9H-purin-9-yl)-2,10-disulfanyloctahydro-12H-5,8-methanofuro[3,2-l][1,3,6,9,11,2,10]pentaoxadiphosphacyclotetradecin-7-yl]-3,6-dihydro-7H-[1,2,3]triazolo[4,5-d]pyrimidin-7-one	711	179

Biological Evaluation

[0846] The individual compounds described in the Examples are defined as STING agonists by demonstrating binding to the STING protein with an EC_{50} of 20 uM or less in the STING Biochemical [^{3}H]cGAMP Competition Assay (using either HAQ or wild type (WT) STING) and demonstrating interferon production with a 5% or greater luminescence induction at 30 uM in the INF-β secretion in the THP1 cell assay. The methods below describe each of these assays.

$[^3H]$-cGAMP Synthesis

[0847] 2.3 mL of buffer solution containing 80 mM tris Cl, 200 mM $MgCl_2$ and 20 mM NaCl followed by 0.32 mL of a 10 mM aq solution of GTP was added to a plastic 50 mL AMICON tube. A solution of $[^3H]$ATP (21Ci/mmol, 45 mCi) in 0.5 mL H_2O was then added followed by 1 mL of a 1 mg/mL solution of DNA (Herring testes activator DNA, Sigma, #D6898) and 53 uL of a 47 mM solution of cGAS enzyme. Additional H_2O was added to bring the total volume to 10 mL.

[0848] The reaction was stirred for 2 h at 37° C. and then added directly to an Amicon Ultra-15 10K centrifuge tube and spun for 1 h at 4,000 g. The collected solution was then purified on a semi-prep Mono Q column using the following mobile phases:

[0849] A: 0.05M TrisCl pH 8.5 adjusted with 1M NaOH

[0850] B: 0.05M TrisCl, 0.5M NaCl pH 8.5 adjusted with 1M NaOH

[0851] Gradient: 100% A for 5 min followed by a linear gradient to 50:50 (A:B) over 25 min, 3 mL/min, 254 nm.

[0852] The collected product fractions were pooled and adjusted to a total volume of 30 mL with buffer A. A total yield of 15.5 mCi of $[^3H]$cGAMP was isolated at a radiochemical purity of 98.0% at a specific activity of 21.5Ci/mmol.

cGAS Enzyme

[0853] 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).

[0854] Fractions were pooled, concentrated, flash frozen in liquid nitrogen and stored at −80° C. until needed for research applications.

Example 349: ^3H-cGAMP Filtration Binding Assay (HAQ STING)

[0855] 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, wwwv.expressionsystems.com) overexpressing full-length HAQ STING prepared in-house and tritiated cGAMP ligand also purified in-house.

[0856] The basic HAQ STING filtration assay protocol is as follows:

[0857] 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 2.2 ug/ml working concentration of STING membrane (SEQ. ID. No. 2) was prepared by diluting concentrated membrane into assay buffer (1×PBS; Invitrogen #SH30028.02) and douncing 7× using a manual tissue homogenizer (Wheaton, #357546). 148 uL 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, 2 uL of either titrated test compound, DMSO control (Sigma #276855), or cold cGAMP control (prepared in-house) was added to the appropriate wells using a Biomek FX. Compound and membrane then preincubated for 60 min at RT to allow compound binding to equilibrate. Following equilibration, 8 nM of $[^3H]$ c-GAMP ligand was prepared by diluting into assay buffer, and 50 uL of this working stock was then manually added to each well of the assay plate. Plates were then incubated at RT for 60 min, and the contents of each assay plate were then filtered through a 96-well GF/B filter plate (PerkinElmer, #6005250) using a TomTec MachIII Cell Harvester equipped with 20 mM HEPES buffer (Fisher Scientific, # BP299500). The filter plates were then dried at 55° C. for 30 min using a pressurized VWR oven before 30 uL of Ultima GoldF scintillate was added to each well. Tritium levels for each reaction well were then measured using a PerkinElmer TopCount plate reader.

[0858] 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.

[0859] The final reaction conditions were:

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

[0860] Compound concentrations tested were 20.000, 637.00, 2.200, 0.740, 0.247, 0.082, 0.027, 0.009, 0.003, and 0.001M with 1.0% residual DMSO.

Full-Length STING (HAQ) Virus Generation

[0861] 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 (2 mL per well, 1e6 cells total), and the cells were allowed to adhere for at least 30 min. Meanwhile, a 1 mL co-transfection mix was assembled by combining 500 ng of HAQ STING [STING(1-379)R^{71}H,G230A,H232R,R^{293}Q-GG-AviTag-GS-HRV3C-HIS8/pBAC1] DNA (Genewiz custom synthesis) with 1 mL Sf-900II SFM media containing 10 μL Cellfectin® II Reagent (Invitrogen #10362100) and 100 ng viral backbone BestBac 2.0, v-cath/chiA Deleted Linearized Baculovirus DNA (Expression Systems #91-002). The transfection mixtures were allowed to incubate for 30 min. After incubation, media was gently removed from the adhered cells in the 6-well plate, the 1 mL transfection mixtures were added (1 mL per well), and the plate was placed in a humidified incubator at 27° C. The following day, 1 mL 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. 3) at 27° C. for 5-7 days to generate the P0 viral stock. To generate P1 viral stocks, 0.5 mL of P0 viral supernatant was added to 50 mL uninfected Sf21 cells (seeded the day prior to infection at a density of 5×10^5

cells/mL to allow for one overnight doubling) in Sf-900II SFM media containing 5 g/mL gentamicin (Invitrogen #15710072). The infected cells were then incubated at 27° C. for 3 d while shaking at 110 rpm (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 ≥3 μm larger than uninfected cells and viability approximately 85-95%). Cultures were harvested in 50 mL conical tubes and centrifuged at 2000×g for 10 min at 4° C. The P1 viral supernatants were poured off into clean 50 ml centrifuge tubes, and the remaining P1 cell pellets were used to generate Baculovirus Infected Insect Cells (BIICs) according to in-house validated SOP. Cryopreservation media containing Sf-900II SFM media with 10% heat inactivated FBS, 10% DMSO (Sigma #D2650), and 5 μg/ml gentamicin was prepared in-house and sterilized through 0.22 μM filter immediately prior to use. P1 cell pellets were resuspended to a density of 2e7 cells/ml and aliquoted into cryovials (1 mL 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, 0.5 mL of the P1 viral supernatant was added to 50 mL uninfected Sf21 cells (seeded the day prior to infection at a density of 5×10^5 cells/mL to allow for one overnight doubling) in Sf-900II SFM media containing 5 μg/mL gentamicin. These cells were incubated at 27° C. for 3 d while shaking at 110 rpm before harvesting P2 stock with centrifugation at 2000×g for 10 min 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/mLx 100 pfu/cell).

Full-Length STING (HAQ) Expression

[0862] To generate STING membranes, P1/P2 BIICs were amplified overnight by adding thawed BIICs to Sf21 cells seeded at a density of 1.0×10^6 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 ≥3 μm 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 1.0×10^6 in cell media (ESF921 SFM containing 5 μg/mL gentamicin) at MOI=2.0 was calculated based on (100 pfu/infected Sf21 cell). The cells were allowed to express for 48 h at 27° C. before harvesting the cell pellet, by centrifugation at 3,400×g for 10 min at 4° C. *T. ni* cells were counted on a ViCell XR to confirm infection had occurred (cell size ≥3 μm larger than uninfected cells and viability approximately 80-90%) prior to harvest.

Full-Length STING (HAQ) Membrane Generation

[0863] Buffer stock reagents:

[0864] 1) 1 M HEPES pH 7.5, Teknova, Cat#H1035

[0865] 2) 5 M NaCl, Sigma Aldrich, Cat#S5150-1L

[0866] 3) KCl, Sigma Aldrich, Cat#319309-500ML

[0867] 4) Complete EDTA-free protease inhibitor tablets, Roche Diagnostics, Cat#11873580001

[0868] 5) Benzonase, Universal Nuclease, Pierce, Cat#88702

[0869] Lysis buffer [25 mM HEPES pH 7.5, 10 mM $MgCl_2$, 20 mM KCl, (Benzonase 1:5000, Complete Protease Inhibitor tab/50 mL)] was added to the pellet of cells expressing full-length STING (HAQ) prepared above at 5 mL Lysis buffer/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-C_5 microfluidizer at a pressure close to 5000 PSI. The resuspended pellet was centrifuged at 36,000 rpm (100,000×g) in a 45Ti rotor in the ultra-high speed centrifuge for 45 min, 4° C. The supernatant was removed. The pellet then was resuspended in wash buffer [(25 mM HEPES pH7.5, 1 mM $MgCl_2$, 20 mM KCl, 1M NaCl (Complete Protease Inhibitor tab/50 mL)] at a volume of 50 mL pellet/centrifuge tube. The pellet/wash buffer mixture was then homogenized, using a glass homogenizer on ice (20 strokes), followed by centrifugation at 36,000 rpm for 45 min at 4° C. The supernatant was removed. The wash step was repeated once more. The resulting membrane was resuspended in 20 mM HEPES pH 7.5, 500 mM NaCl, 10% glycerol, EDTA-free Protease Inhibitors (1 tablet/50 mL). 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.

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

[0870]

(SEQ. ID. No. 2)
MPHSSLHPSIPCPRGHGAQKAALVLLSACLVTLWGLGEPPEHTLRYLVLH

LASLQLGLLLNGVCSLAEELHHIHSRYRGSYWRTVRACLGCPLRRGALLL

LSIYFYYSLPNAVGPPFTWMLALLGLSQALNILLGLKGLAPAEISAVCEK

GNFNVAHGLAWSYYIGYLRLILPELQARIRTYNQHYNNLLRGAVSQRLYI

LLPLDCGVPDNLSMADPNIRFLDKLPQQTADRAGIKDRVYSNSIYELLEN

GQRAGTCVLEYATPLQTLFAMSQYSQAGFSREDRLEQAKLFCQTLEDILA

DAPESQNNCRLIAYQEPADDSSFSLSQEVLRHLRQEEKEEVTVGSLKTSA

VPSTSTMSQEPELLISGMEKPLPLRTDFSGGGLNDIFEAQKIEWHEGSLE

VLFQGPHHHHHHHH

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

(SEQ. ID. No. 3)
GGAACGGCTCCGCCCACTATTAATGAAATTAAAAATTCCAATTTTAAAAA

ACGCAGCAAGAGAAACATTTGTATGAAAGAATGCGTAGAAGGAAAGAAAA

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CACGACTCCAAGTGTGTGGGTGAAGTCATGCATCTTTTAATCAAATCCCA

AGATGTGTATAAACCACCAAACTGCCAAAAAATGAAAACTGTCGACAAGC

TCTGTCCGTTTGCTGGCAACTGCAAGGGTCTCAATCCTATTTGTAATTAT

TGAATAATAAAACAATTATAAATGCTAAATTTGTTTTTTATTAACGATAC

AAACCAAACGCAACAAGAACATTTGTAGTATTATCTATAATTGAAAACGC

GTAGTTATAATCGCTGAGGTAATATTTAAAATCATTTTCAAATGATTCAC

AGTTAATTTGCGACAATATAATTTTATTTTCACATAAACTAGACGCCTTG

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ATTTTTTGTTGTCATAAATATATATGTCTTTTTTAATGGGGTGTATAGTA

CCGCTGCGCATAGTTTTTCTGTAATTTACAACAGTGCTATTTTCTGGTAG

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TCTAGTTCAATTACACCATTTTTTAGCAGCACCGGATTAACATAACTTTC

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ATGAGACGCACAAACTAATATCACAAACTGGAAATGTCTATCAATATATA

GTTGCTGATCAGATCTGATCATGGAGATAATTAAAATGATAACCATCTCG

CAAATAAATAAGTATTTTACTGTTTTCGTAACAGTTTTGTAATAAAAAAA

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CCTGCCTGGTGACCCTTTGGGGGCTAGGAGAGCCACCAGAGCACACTCTC

CGGTACCTGGTGCTCCACCTAGCCTCCCTGCAGCTGGGACTGCTGTTAAA

CGGGGTCTGCAGCCTGGCTGAGGAGCTGCACCACATCCACTCCAGGTACC

GGGGCAGCTACTGGAGGACTGTGCGGGCCTGCCTGGGCTGCCCCCTCCGC

CGTGGGGCCCTGTTGCTGCTGTCCATCTATTTCTACTACTCCCTCCCAAA

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AGGCACTGAACATCCTCCTGGGCCTCAAGGGCCTGGCCCCAGCTGAGATC

TCTGCAGTGTGTGAAAAAGGGAATTTCAACGTGGCCCATGGGCTGGCATG

GTCATATTACATCGGATATCTGCGGCTGATCCTGCCAGAGCTCCAGGCCC

GGATTCGAACTTACAATCAGCATTACAACAACCTGCTACGGGGTGCAGTG

AGCCAGCGGCTGTATATTCTCCTCCCATTGGACTGTGGGGTGCCTGATAA

CCTGAGTATGGCTGACCCCAACATTCGCTTCCTGGATAAACTGCCCCAGC

AGACCGCTGACCGTGCTGGCATCAAGGATCGGGTTTACAGCAACAGCATC

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AGCTTGAAGACCTCAGCGGTGCCCAGTACCTCCACGATGTCCCAAGAGCC

TGAGCTCCTCATCAGTGGAATGGAAAAGCCCCTCCCTCTCCGCACGGATT

TCTCTGGCGGTGGCCTGAACGACATCTTCGAAGCCCAGAAAATCGAATGG

CATGAAGGCAGCCTGGAAGTGCTGTTCCAGGGCCCACACCACCATCATCA

CCATCACCATTAATGAGCGGCCGCACTCGAGCACCACCACCACCACCACT

AACCTAGGTAGCTGAGCGCATGCAAGCTGATCCGGGTTATTAGTACATTT

ATTAAGCGCTAGATTCTGTGCGTTGTTGATTTACAGACAATTGTTGTACG

TATTTTAATAATTCATTAAATTTATAATCTTTAGGGTGGTATGTTAGAGC

GAAAATCAAATGATTTTCAGCGTCTTTATATCTGAATTTAAATATTAAAT

CCTCAATAGATTTGTAAAATAGGTTTCGATTAGTTTCAAACAAGGGTTGT

TTTTCCGAACCGATGGCTGGACTATCTAATGGATTTTCGCTCAACGCCAC

AAAACTTGCCAAATCTTGTAGCAGCAATCTAGCTTTGTCGATATTCGTTT

GTGTTTTGTTTTGTAATAAAGGTTCGACGTCGTTCAAAATATTATGCGCT

TTTGTATTTCTTTCATCACTGTCGTTAGTGTACAATTGACTCGACGTAAA

CACGTTAAATAGAGCTTGGACATATTTAACATCGGGCGTGTTAGCTTTAT

TAGGCCGATTATCGTCGTCGTCCCAACCCTCGTCGTTAGAAGTTGCTTCC

GAAGACGATTTTGCCATAGCCACACGACGCCTATTAATTGTGTCGGCTAA

CACGTCCGCGATCAAATTTGTAGTTGAGCTTTTTGGAATTATTTCTGATT

GCGGGCGTTTTTGGGCGGGTTTCAATCTAACTGTGCCCGATTTTAATTCA

GACAACACGTTAGAAAGCGATGGTGCAGGCGGTGGTAACATTTCAGACGG

CAAATCTACTAATGGCGGCGGTGGTGGAGCTGATGATAAATCTACCATCG

GTGGAGGCGCAGGCGGGGCTGGCGGCGGAGGCGGAGGCGGAGGTGGTGGC

GGTGATGCAGACGGCGGTTTAGGCTCAAATGTCTCTTTAGGCAACACAGT

CGGCACCTCAACTATTGTACTGGTTTCGGGCGCCGTTTTTGGTTTGACCG

GTCTGAGACGAGTGCGATTTTTTTCGTTTCTAATAGCTTCCAACAATTGT

TGTCTGTCGTCTAAAGGTGCAGCGGGTTGAGGTTCCGTCGGCATTGGTGG

AGCGGGCGGCAATTCAGACATCGATGGTGGTGGTGGTGGTGGAGGCGCTG

GAATGTTAGGCACGGGAGAAGGTGGTGGCGGCGGTGCCGCCGGTATAATT

TGTTCTGGTTTAGTTTGTTCGCGCACGATTGTGGGCACCGGCGCAGGCGC

CGCTGGCTGCACAACGGAAGGTCGTCTGCTTCGAGGCAGCGCTTGGGGTG

GTGGCAATTCAATATTATAATTGGAATACAAATCGTAAAAATCTGCTATA

AGCATTGTAATTTCGCTATCGTTTACCGTGCCGATATTTAACAACCGCTC

AATGTAAGCAATTGTATTGTAAAGAGATTGTCTCAAGCTCGGATCGATCC

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GCGTTTTTCCATAGGCTCCGCCCCCCTGACGAGCATCACAAAAATCGACG

CTCAAGTCAGAGGTGGCGAAACCCGACAGGACTATAAAGATACCAGGCGT

TTCCCCCTGGAAGCTCCCTCGTGCGCTCTCCTGTTCCGACCCTGCCGCTT

ACCGGATACCTGTCCGCCTTTCTCCCTTCGGGAAGCGTGGCGCTTTCTCA

TAGCTCACGCTGTAGGTATCTCAGTTCGGTGTAGGTCGTTCGCTCCAAGC

TGGGCTGTGTGCACGAACCCCCCGTTCAGCCCGACCGCTGCGCCTTATCC

GGTAACTATCGTCTTGAGTCCAACCCGGTAAGACACGACTTATCGCCACT

GGCAGCAGCCACTGGTAACAGGATTAGCAGAGCGAGGTATGTAGGCGGTG

CTACAGAGTTCTTGAAGTGGTGGCCTAACTACGGCTACACTAGAAGGACA

GTATTTGGTATCTGCGCTCTGCTGAAGCCAGTTACCTTCGGAAAAAGAGT

TGGTAGCTCTTGATCCGGCAAACAAACCACCGCTGGTAGCGGTGGTTTTT

TTGTTTGCAAGCAGCAGATTACGCGCAGAAAAAAAGGATCTCAAGAAGAT

CCTTTGATCTTTTCTACGGGGTCTGACGCTCAGTGGAACGAAAACTCACG

TTAAGGGATTTTGGTCATGAGATTATCAAAAAGGATCTTCACCTAGATCC

TTTTAAATTAAAAATGAAGTTTTAAATCAATCTAAAGTATATATGAGTAA

ACTTGGTCTGACAGTTACCAATGCTTAATCAGTGAGGCACCTATCTCAGC

GATCTGTCTATTTCGTTCATCCATAGTTGCCTGACTCCCCGTCGTGTAGA

TAACTACGATACGGGAGGGCTTACCATCTGGCCCCAGTGCTGCAATGATA

CCGCGAGACCCACGCTCACCGGCTCCAGATTTATCAGCAATAAACCAGCC

AGCCGGAAGGGCCGAGCGCAGAAGTGGTCCTGCAACTTTATCCGCCTCCA

TCCAGTCTATTAATTGTTGCCGGGAAGCTAGAGTAAGTAGTTCGCCAGTT

AATAGTTTGCGCAACGTTGTTGCCATTGCTACAGGCATCGTGGTGTCACG

CTCGTCGTTTGGTATGGCTTCATTCAGCTCCGGTTCCCAACGATCAAGGC

GAGTTACATGATCCCCCATGTTGTGCAAAAAAGCGGTTAGCTCCTTCGGT

CCTCCGATCGTTGTCAGAAGTAAGTTGGCCGCAGTGTTATCACTCATGGT

TATGGCAGCACTGCATAATTCTCTTACTGTCATGCCATCCGTAAGATGCT

TTTCTGTGACTGGTGAGTACTCAACCAAGTCATTCTGAGAATAGTGTATG

CGGCGACCGAGTTGCTCTTGCCCGGCGTCAATACGGGATAATACCGCGCC

ACATAGCAGAACTTTAAAAGTGCTCATCATTGGAAAACGTTCTTCGGGGC

GAAAACTCTCAAGGATCTTACCGCTGTTGAGATCCAGTTCGATGTAACCC

ACTCGTGCACCCAACTGATCTTCAGCATCTTTTACTTTCACCAGCGTTTC

TGGGTGAGCAAAAACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAAGGG

CGACACGGAAATGTTGAATACTCATACTCTTCCTTTTTCAATATTATTGA

AGCATTTATCAGGGTTATTGTCTCATGAGCGGATACATATTTGAATGTAT

TTAGAAAAATAAACAAATAGGGGTTCCGCGCACATTTCCCCGAAAAGTGC

CACCTGACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGGTT

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ACGCGCAGCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTT

CGCTTTCTTCCCTTCCTTTCTCGCCACGTTCGCCGGCTTTCCCCGTCAAG

CTCTAAATCGGGGGCTCCCTTTAGGGTTCCGATTTAGTGCTTTACGGCAC

CTCGACCCCAAAAAACTTGATTAGGGTGATGGTTCACGTAGTGGGCCATC

GCCCTGATAGACGGTTTTTCGCCCTTTGACGTTGGAGTCCACGTTCTTTA

ATAGTGGACTCTTGTTCCAAACTGGAACAACACTCAACCCTATCTCGGTC

TATTCTTTTGATTTATAAGGGATTTTGCCGATTTCGGCCTATTGGTTAAA

AAATGAGCTGATTTAACAAAAATTTAACGCGAATTTTAACAAAATATTAA

CGTTTACAATTTCCCATTCGCCATTCAGGCTGCGCAACTGTTGGGAAGGG

CGATCGGTGCGGGCCTCTTCGCTATTACGCCA

[0871] Certain compounds of the disclosure were evaluated in HAQ STING in vitro binding assay as described above. The following table tabulates the biological data for these compounds as EC$_{50}$ values.

TABLE 12

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

Compound	EC$_{50}$ (nM)
Example 1	<1
Example 2	1.3
Example 3	257.1
Example 4	22
Example 5	1.1
Example 6	<1
Example 7	1.2
Example 8	13.6
Example 9	7.2
Example 10	4.9
Example 11	1.2
Example 12	<1
Example 13	1.5
Example 14	<1
Example 15	378.1
Example 16	12.4
Example 17	121
Example 18	53.9
Example 19	173
Example 20	<1
Example 21	1.3
Example 22	4822
Example 23	<1
Example 24	2.4
Example 25	3.4
Example 26	<1
Example 27	1.3
Example 28	18.7
Example 30	91
Example 31	94
Example 32	11.1
Example 33	11.9
Example 34	24.6
Example 35	7.9
Example 36	21.5
Example 37	619.6
Example 38	3
Example 69	<1
Example 70	2
Example 71	<1
Example 72	<1
Example 73	834
Example 74	5.8
Example 39	24.4
Example 40	3.2

TABLE 12-continued

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

Compound	EC$_{50}$ (nM)
Example 41	11.8
Example 42	15.2
Example 43	162.2
Example 44	17.1
Example 45	24.8
Example 46	11.7
Example 47	39.2
Example 48	1.2
Example 49	30
Example 50	2.7
Example 51	287.1
Example 52	1.5
Example 53	1.7
Example 54	<1
Example 55	55.3
Example 56	89.4
Example 57	437.9
Example 58	3.1
Example 59	11.8
Example 60	42.5
Example 61	18.2
Example 66	117.1
Example 67	6.4
Example 68	63.8
Example 69	<1
Example 70	2
Example 71	<1
Example 72	<1
Example 73	834
Example 74	5.8
Example 75	2.6
Example 76	75.4
Example 77	160.5
Example 78	14.6
Example 79	103.2
Example 80	1.3
Example 81	<1
Example 82	21.5
Example 83	3.7
Example 85	<1
Example 86	<1
Example 87	<1
Example 88	<1
Example 89	8272
Example 90	1.7
Example 91	15.8
Example 92	114
Example 93	<1
Example 94	24.6
Example 95	13.9
Example 96	5.3
Example 97	<1
Example 98	1.8
Example 99	<1
Example 100	16.7
Example 101	8
Example 102	<1
Example 117	1
Example 118	1.4
Example 119	17.8
Example 120	45.1
Example 121	<1
Example 123	5.1
Example 124	<1
Example 125	21.7
Example 126	9.7
Example 127	24.4
Example 128	<1
Example 129	88.6
Example 130	<1
Example 131	2.4
Example 132	25.9
Example 133	61.4
Example 134	<1
Example 135	253.4
Example 136	3.7
Example 137	11.4
Example 138	738.8
Example 139	<1
Example 140	12.9
Example 141	<1
Example 142	6.2
Example 143	1.05
Example 144	<1
Example 145	<1
Example 146	5.6
Example 147	1.4
Example 148	33.3
Example 149	8.4
Example 150	<1
Example 151	<1
Example 152	<1
Example 244	156.6
Example 245	2.7
Example 246	21.3
Example 247	<1
Example 290	2.5
Example 291	64.7
Example 292	2.6
Example 293	1.9
Example 294	6.6
Example 295	29.6
Example 296	4.1
Example 297	<1
Example 298	52.9
Example 299	1325
Example 300	5.1
Example 301	4.8
Example 302	2.3
Example 303	<1
Example 304	3.3
Example 305	326.2
Example 306	3.6
Example 307	<1
Example 308	1.6
Example 309	4
Example 310	27.6
Example 311	1595
Example 312	122.5
Example 313	210.6
Example 314	<1
Example 315	49.9
Example 316	2324
Example 317	<1
Example 318	6.2
Example 319	7.3
Example 320	6.3
Example 321	112.2
Example 322	68.8
Example 332	8.2
Example 333	45.9

Example 350: ^{3}H-cGAMP Filtration Binding Assay (WT STING)

[0872] 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 prepared in-house and tritiated cGAMP ligand also purified in-house.

[0873] The basic WT STING filtration assay protocol is as follows:

[0874] 16 nM of [^{3}H] c-GAMP ligand was prepared by diluting into assay buffer, and 50 uL of this working stock was manually added to each well of the assay plate. After ligand addition, 2 uL of either titrated test compound, DMSO control (Sigma #276855), or cold cGAMP control (prepared in-house) 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 2.2 ug/ml working concentration of STING membrane (SEQ. ID. No. 4) was prepared by diluting concentrated membrane into assay buffer (1×PBS; Invitrogen # SH30028.02) and douncing 7× using a manual tissue homogenizer (Wheaton, #357546). 148 uL 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 60 min at RT before the contents of each assay plate were filtered through a 96-well GF/B filter plate (PerkinElmer, #6005250) using a TomTec MachIII Cell Harvester equipped with 20 mM HEPES buffer (Fisher Scientific, # BP299500). The filter plates were then dried at 55° C. for 30 min using a pressurized VWR oven before 30 uL of Ultima GoldF scintillate was added to each well. Tritium levels for each reaction well were then measured using a PerkinElmer TopCount plate reader.

[0875] 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.

[0876] The final reaction conditions were:

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

[0877] Compound concentrations tested were 20.000, 637.00, 2.200, 0.740, 0.247, 0.082, 0.027, 0.009, 0.003, and 0.001 μM with 1.0% residual DMSO.

Full-Length STING (WT) Virus Generation

[0878] 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 (2 mL per well, 1e6 cells total), and the cells were allowed to adhere for at least 30 min. Meanwhile, a 1 mL co-transfection mix was assembled by combining 500 ng of WT STING[STING(1-379)H232R-gg-AviTag-gs-HRV3C-HIS8/pBAC1] (Genewiz custom synthesis) with 1 mL Sf-900II SFM media containing 10 μL Cellfectin® II Reagent (Invitrogen #10362100) and 100 ng viral backbone BestBac 2.0, v-cath/chiA Deleted Linearized Baculovirus DNA (Expression Systems #91-002). The transfection mixtures were allowed to incubate for 30 min. After incubation, media was gently removed from the adhered cells in the 6-well plate, the 1 mL transfection mixtures were added (1 mL per well), and the plate was placed in a humidified incubator at 27° C. The following day, 1 mL 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. 5) 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, 0.5 mL of P0 viral supernatant was added to 50 mL uninfected Sf21 cells (seeded the day prior to infection at a density of 5×10^5 cells/mL to allow for one overnight doubling) in Sf-900II SFM media containing 5 g/mL gentamicin (Invitrogen #15710072). The infected cells were then incubated at 27° C. for 3 d while shaking at 110 rpm (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 ≥3 μm larger than uninfected cells and viability approximately 85-95%). Cultures were harvested in 50 mL conical tubes and centrifuged at 2000×g for 10 min at 4° C. The P1 viral supernatants were poured off into clean 50 ml centrifuge tubes, and the remaining P1 cell pellets were used to generate Baculovirus Infected Insect Cells (BIICs) according to in-house validated SOP. Cryopreservation media containing Sf-900II SFM media with 10% heat inactivated FBS, 10% DMSO (Sigma #D2650), and 5 μg/ml gentamicin was prepared in-house and sterilized through 0.22 μM filter immediately prior to use. P1 cell pellets were resuspended to a density of 2e7 cells/ml and aliquoted into cryovials (1 mL 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, 0.5 mL of the P1 viral supernatant was added to 50 mL uninfected Sf21 cells (seeded the day prior to infection at a density of 5×10^5 cells/mL to allow for one overnight doubling) in Sf-900II SFM media containing 5 μg/mL gentamicin. These cells were incubated at 27° C. for 3 d while shaking at 110 rpm before harvesting P2 stock with centrifugation at 2000×g for 10 min 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/mLx 100 pfu/cell).

Full-Length STING (WT) Expression

[0879] To generate STING membranes, P1/P2 BIICs were amplified overnight by adding thawed BIICs to Sf21 cells seeded at a density of 1.0×10^6 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 ≥3 μm 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 1.0×10^6 in cell media (ESF921 SFM containing 5 μg/mL gentamicin) at MOI=2.0 was calculated based on (100 pfu/infected Sf21 cell). The cells were allowed to express for 48 h at 27° C. before harvesting the cell pellet, by centrifugation at 3,400×g for 10 min at 4° C.

T. ni cells were counted on a ViCell XR to confirm infection had occurred (cell size ≥3 μm larger than uninfected cells and viability approximately 80-90%) prior to harvest.

Full-Length STING (WT) Membrane Generation

[0880] Buffer stock reagents:

[0881] 1) 1 M HEPES pH 7.5, Teknova, Cat#H1035

[0882] 2) 5 M NaCl, Sigma Aldrich, Cat#S5150-1L

[0883] 3) KCl, Sigma Aldrich, Cat#319309-500ML

[0884] 4) Complete EDTA-free protease inhibitor tablets, Roche Diagnostics, Cat#11873580001

[0885] 5) Benzonase, Universal Nuclease, Pierce, Cat#88702

[0886] Lysis buffer [25 mM HEPES pH 7.5, 10 mM $MgCl_2$, 20 mM KCl, (Benzonase 1:5000, Complete Protease Inhibitor tab/50 mL)] was added to the pellet of cells expressing full-length STING (WT) prepared above at 5 mL Lysis buffer/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-C_5 microfluidizer at a pressure close to 5000 PSI. The resuspended pellet was centrifuged at 36,000 rpm (100,000×g) in a 45Ti rotor in the ultra-high speed centrifuge for 45 min, 4° C. The supernatant was removed. The pellet then was resuspended in wash buffer [(25 mM HEPES pH 7.5, 1 mM $MgCl_2$, 20 mM KCl, 1M NaCl (Complete Protease Inhibitor tab/50 mL)] at a volume of 50 mL/pellet/centrifuge tube. The pellet/Wash buffer mixture was then homogenized, using a glass homogenizer on ice (20 strokes), followed by centrifugation at 36,000 rpm for 45 min at 4° C. The supernatant was removed. The wash step was repeated once more. The resulting membrane was resuspended in 20 mM HEPES pH 7.5, 500 mM NaCl, 10% glycerol, EDTA-free Protease Inhibitors (1 tablet/50 mL). 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.

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

[0887]

(SEQ. ID. No. 4)
MPHSSLHPSIPCPRGHGAQKAALVLLSACLVTLWGLGEPPEHTLRYLVLH

LASLQLGLLLNGVCSLAEELRHIHSRYRGSYWRTVRACLGCPLRRGALLL

LSIYFYYSLPNAVGPPFTWMLALLGLSQALNILLGLKGLAPAEISAVCEK

GNFNVAHGLAWSYYIGYLRLILPELQARIRTYNQHYNNLLRGAVSQRLYI

LLPLDCGVPDNLSMADPNIRFLDKLPQQTGDRAGIKDRVYSNSIYELLEN

GQRAGTCVLEYATPLQTLFAMSQYSQAGFSREDRLEQAKLFCRTLEDILA

DAPESQNNCRLIAYQEPADDSSFSLSQEVLRHLRQEEKEEVTVGSLKTSA

VPSTSTMSQEPELLISGMEKPLPLRTDFSGGGLNDIFEAQKIEWHEGSLE

VLFQGPHHHHHHHH

Full-length WT STING [STING(1-379)H232R-gg-AviTag-gs-HRV3C-HIS8/pBAC$_1$] plasmid sequence:

(SEQ. ID. No. 5)
GGAACGGCTCCGCCCACTATTAATGAAATTAAAAATTCCAATTTTAAAAA

ACGCAGCAAGAGAAACATTTGTATGAAAGAATGCGTAGAAGGAAAGAAAA

ATGTCGTCGACATGCTGAACAACAAGATTAATATGCCTCCGTGTATAAAA

AAAATATTGAACGATTTGAAAGAAAACAATGTACCGCGCGGCGGTATGTA

CAGGAAGAGGTTTATACTAAACTGTTACATTGCAAACGTGGTTTCGTGTG

CCAAGTGTGAAAACCGATGTTTAATCAAGGCTCTGACGCATTTCTACAAC

CACGACTCCAAGTGTGTGGGTGAAGTCATGCATCTTTTAATCAAATCCCA

AGATGTGTATAAACCACCAAACTGCCAAAAAATGAAAACTGTCGACAAGC

TCTGTCCGTTTGCTGGCAACTGCAAGGGTCTCAATCCTATTTGTAATTAT

TGAATAATAAAACAATTATAAATGTCAAATTTGTTTTTTATTAACGATAC

AAACCAAACGCAACAAGAACATTTGTAGTATTATCTATAATTGAAAACGC

GTAGTTATAATCGCTGAGGTAATATTTAAAATCATTTTCAAATGATTCAC

AGTTAATTTGCGACAATATAATTTTATTTTCACATAAACTAGACGCCTTG

TCGTCTTCTTCTTCGTATTCCTTCTCTTTTTCATTTTTCTCTTCATAAAA

ATTAACATAGTTATTATCGTATCCATATATGTATCTATCGTATAGAGTAA

ATTTTTTGTTGTCATAAATATATATGTCTTTTTTAATGGGGTGTATAGTA

CCGCTGCGCATAGTTTTTCTGTAATTTACAACAGTGCTATTTTCTGGTAG

TTCTTCGGAGTGTGTTGCTTTAATTATTAAATTTATATAATCAATGAATT

TGGGATCGTCGGTTTTGTACAATATGTTGCCGGCATAGTACGCAGCTTCT

TCTAGTTCAATTACACCATTTTTTAGCAGCACCGGATTAACATAACTTTC

CAAAATGTTGTACGAACCGTTAAACAAAAACAGTTCACCTCCCTTTTCTA

TACTATTGTCTGCGAGCAGTTGTTTGTTGTTAAAAATAACAGCCATTGTA

ATGAGACGCACAAACTAATATCACAAACTGGAAATGTCTATCAATATATA

GTTGCTGATCAGATCTGATCATGGAGATAATTAAAATGATAACCATCTCG

CAAATAAATAAGTATTTTACTGTTTTCGTAACAGTTTTGTAATAAAAAAA

CCTATAAATATAGGATCCATGCCCCACTCCAGCCTGCATCCATCCATCCC

GTGTCCCAGGGGTCACGGGGCCCAGAAGGCAGCCTTGGTTCTGCTGAGTG

CCTGCCTGGTGACCCTTTGGGGGCTAGGAGAGCCACCAGAGCACACTCTC

CGGTACCTGGTGCTCCACCTAGCCTCCCTGCAGCTGGGACTGCTGTTAAA

CGGGGTCTGCAGCCTGGCTGAGGAGCTGCGCCACATCCACTCCAGGTACC

GGGGCAGCTACTGGAGGACTGTGCGGGCCTGCCTGGGCTGCCCCCTCCGC

CGTGGGGCCCTGTTGCTGCTGTCCATCTATTTCTACTACTCCCTCCCAAA

TGCGGTCGGCCCGCCCTTCACTTGGATGCTTGCCCTCCTGGGCCTCTCGC

AGGCACTGAACATCCTCCTGGGCCTCAAGGGCCTGGCCCCAGCTGAGATC

TCTGCAGTGTGTGAAAAAGGGAATTTCAACGTGGCCCATGGGCTGGCATG

GTCATATTACATCGGATATCTGCGGCTGATCCTGCCAGAGCTCCAGGCCC

GGATTCGAACTTACAATCAGCATTACAACAACCTGCTACGGGGTGCAGTG

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AGCCAGCGGCTGTATATTCTCCTCCCATTGGACTGTGGGGTGCCTGATAA
CCTGAGTATGGCTGACCCCAACATTCGCTTCCTGGATAAACTGCCCCAGC
AGACCGGTGACCGTGCTGGCATCAAGGATCGGGTTTACAGCAACAGCATC
TATGAGCTTCTGGAGAACGGGCAGCGGGCGGGCACCTGTGTCCTGGAGTA
CGCCACCCCCTTGCAGACTTTGTTTGCCATGTCACAATACAGTCAAGCTG
GCTTTAGCCGGGAGGATAGGCTTGAGCAGGCCAAACTCTTCTGCCGGACA
CTTGAGGACATCCTGGCAGATGCCCCTGAGTCTCAGAACAACTGCCGCCT
CATTGCCTACCAGGAACCTGCAGATGACAGCAGCTTCTCGCTGTCCCAGG
AGGTTCTCCGGCACCTGCGGCAGGAGGAAAAGGAAGAGGTTACTGTGGGC
AGCTTGAAGACCTCAGCGGTGCCCAGTACCTCCACGATGTCCCAAGAGCC
TGAGCTCCTCATCAGTGGAATGGAAAAGCCCCTCCCTCTCCGCACGGATT
TCTCTGGCGGTGGCCTGAACGACATCTTCGAAGCCCAGAAAATCGAATGG
CATGAAGGCAGCCTGGAAGTGCTGTTCCAGGGCCCACACCACCATCATCA
CCATCACCATTAATGAGCGGCCGCACTCGAGCACCACCACCACCACCACT
AACCTAGGTAGCTGAGCGCATGCAAGCTGATCCGGGTTATTAGTACATTT
ATTAAGCGCTAGATTCTGTGCGTTGTTGATTTACAGACAATTGTTGTACG
TATTTTAATAATTCATTAAATTTATAATCTTTAGGGTGGTATGTTAGAGC
GAAAATCAAATGATTTTCAGCGTCTTTATATCTGAATTTAAATATTAAAT
CCTCAATAGATTTGTAAAATAGGTTTCGATTAGTTTCAAACAAGGGTTGT
TTTTCCGAACCGATGGCTGGACTATCTAATGGATTTTCGCTCAACGCCAC
AAAACTTGCCAAATCTTGTAGCAGCAATCTAGCTTTGTCGATATTCGTTT
GTGTTTTGTTTTGTAATAAAGGTTCGACGTCGTTCAAAATATTATGCGCT
TTTGTATTTCTTTCATCACTGTCGTTAGTGTACAATTGACTCGACGTAAA
CACGTTAAATAGAGCTTGGACATATTTAACATCGGGCGTGTTAGCTTTAT
TAGGCCGATTATCGTCGTCGTCCCAACCCTCGTCGTTAGAAGTTGCTTCC
GAAGACGATTTTGCCATAGCCACACGACGCCTATTAATTGTGTCGGCTAA
CACGTCCGCGATCAAATTTGTAGTTGAGCTTTTTGGAATTATTTCTGATT
GCGGGCGTTTTTGGGCGGGTTTCAATCTAACTGTGCCCGATTTTAATTCA
GACAACACGTTAGAAAGCGATGGTGCAGGCGGTGGTAACATTTCAGACGG
CAAATCTACTAATGGCGGCGGTGGTGGAGCTGATGATAAATCTACCATCG
GTGGAGGCGCAGGCGGGGCTGGCGGCGGAGGCGGAGGCGGAGGTGGTGGC
GGTGATGCAGACGGCGGTTTAGGCTCAAATGTCTCTTTAGGCAACACAGT
CGGCACCTCAACTATTGTACTGGTTTCGGGCGCCGTTTTTGGTTTGACCG
GTCTGAGACGAGTGCGATTTTTTTCGTTTCTAATAGCTTCCAACAATTGT
TGTCTGTCGTCTAAAGGTGCAGCGGGTTGAGGTTCCGTCGGCATTGGTGG
AGCGGGCGGCAATTCAGACATCGATGGTGGTGGTGGTGGAGGCGCTG
GAATGTTAGGCACGGGAGAAGGTGGTGGCGGCGGTGCCGCCGGTATATTT
GTTCTGGTTTAGTTTGTTCGCGCACGATTGTGGGCACCGGCGCAGGCGCC
GCTGGCTGCACAACGGAAGGTCGTCTGCTTCGAGGCAGCGCTTGGGGTGG

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TGGCAATTCAATATTATAATTGGAATACAAATCGTAAAAATCTGCTATAA
GCATTGTAATTTCGCTATCGTTTACCGTGCCGATATTTAACAACCGCTCA
ATGTAAGCAATTGTATTGTAAAGAGATTGTCTCAAGCTCGGATCGATCCC
GCACGCCGATAACAAGCCTTTTCATTTTTACTACAGCATTGTAGTGGCGA
GACACTTCGCTGTCGTCGAGGTTTAAACGCTTCCTCGCCACTGACTCGCT
GCGCTCGGTCGTTCGGCTGCGGCGAGCGGTATCAGCTCACTCAAAGGCGG
TAATACGGTTATCCACAGAATCAGGGGATAACGCAGGAAAGAACATGTGA
GCAAAAGGCCAGCAAAAGGCCAGGAACCGTAAAAAGGCCGCGTTGCTGGC
GTTTTTCATAGGCTCCGCCCCCCTGACGAGCATCACAAAAATCGACGCTC
AAGTCAGAGGTGGCGAAACCCGACAGGACTATAAAGATACCAGGCGTTTC
CCCCTGGAAGCTCCCTCGTGCGCTCTCCTGTTCCGACCCTGCCGCTTACC
GGATACCTGTCCGCCTTTCTCCCTTGGGAAGCGTGGCGCTTTCTCATAGC
TCACGCTGTAGGTATCTCAGTTCGGTGTAGGTCGTTCGCTCCAAGCTGGG
CTGTGTGCACGAACCCCCCGTTCAGCCCGACCGCTGCGCCTTATCCGGTA
ACTATCGTCTTGAGTCCAACCCGGTAAGACACGACTTATCGCCACTGGCA
GCAGCCACTGGTAACAGGATTAGCAGAGCGAGGTATGTAGGCGGTGCTAC
AGAGTTCTTGAAGTGGTGGCCTAACTACGGCTACACTAGAAGGACAGTAT
TTGGTATCTGCGCTCTGCTGAAGCCAGTTACCTTCGGAAAAAGAGTTGGT
AGCTCTTGATCCGGCAAACAAACCACCGCTGGTAGCGGTGGTTTTTTTGT
TTGCAAGCAGCAGATTACGCGCAGAAAAAAAGGATCTCAAGAAGATCCTT
TGATCTTTTCTACGGGGTCTGACGCTCAGTGGAACGAAAACTCACGTTAA
GGGATTTTGGTCATGAGATTATCAAAAAGGATCTTCACCTAGATCCTTTT
AAATTAAAAATGAAGTTTTAAATCAATCTAAAGTATATATGAGTAAACTT
GGTCTGACAGTTACCAATGCTTAATCAGTGAGGCACCTATCTCAGCGATC
TGTCTATTTCGTTCATCCATAGTTGCCTGACTCCCCGTCGTGTAGATAAC
TACGATACGGGAGGGCTTACCATCTGGCCCCAGTGCTGCAATGATACCGC
GAGACCCACGCTCACCGGCTCCAGATTTATCAGCAATAAACCAGCCAGCC
GGAAGGGCCGAGCGCAGAAGTGGTCCTGCAACTTTATCCGCCTCCATCCA
GTCTATTAATTGTTGCCGGGAAGCTAGAGTAAGTAGTTCGCCAGTTAATA
GTTTGCGCAACGTTGTTGCCATTGCTACAGGCATCGTGGTGTCACGCTCG
TCGTTTGGTATGGCTTCATTCAGCTCCGGTTCCCAACGATCAAGGCGAGT
TACATGATCCCCCATGTTGTGCAAAAAAGCGGTTAGCTCCTTCGGTCCTC
CGATCGTTGTCAGAAGTAAGTTGGCCGCAGTGTTATCACTCATGGTTATG
GCAGCACTGCATAATTCTCTTACTGTCATGCCATCCGTAAGATGCTTTTC
TGTGACTGGTGAGTACTCAACCAAGTCATTCTGAGAATAGTGTATGCGGC
GACCGAGTTGCTCTTGCCCGGCGTCAATACGGGATAATACCGCGCCACAT
AGCAGAACTTTAAAAGTGCTCATCATTGGAAAACGTTCTTCGGGGCGAAA
ACTCTCAAGGATCTTACCGCTGTTGAGATCCAGTTCGATGTAACCCACTC
GTGCACCCAACTGATCTTCAGCATCTTTTACTTTCACCAGCGTTTCTGGG

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TGAGCAAAAACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAAGGGCGAC

ACGGAAATGTTGAATACTCATACTCTTCCTTTTTCAATATTATTGAAGCA

TTTATCAGGGTTATTGTCTCATGAGCGGATACATATTTGAATGTATTTAG

AAAAATAAACAAATAGGGGTTCCGCGCACATTTCCCCGAAAAGTGCCACC

TGACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGGTTACGC

GCAGCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTCGCT

TTCTTCCCTTCCTTTCTCGCCACGTTCGCCGGCTTTCCCCGTCAAGCTCT

AAATCGGGGGCTCCCTTTAGGGTTCCGATTTAGTGCTTTACGGCACCTCG

ACCCCAAAAAACTTGATTAGGGTGATGGTTCACGTAGTGGGCCATCGCCC

TGATAGACGGTTTTTCGCCCTTTGACGTTGGAGTCCACGTTCTTTAATAG

TGGACTCTTGTTCCAAACTGGAACAACACTCAACCCTATCTCGGTCTATT

CTTTTGATTTATAAGGGATTTTGCCGATTTCGGCCTATTGGTTAAAAAAT

GAGCTGATTTAACAAAAATTTAACGCGAATTTTAACAAAATATTAACGTT

TACAATTTCCCATTCGCCATTCAGGCTGCGCAACTGTTGGGAAGGGCGAT

CGGTGCGGGCCTCTTCGCTATTACGCCA

[0888] 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 13

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

Compound	EC_{50} (nM)
Example 1	3.5
Example 2	0.7
Example 3	574.3
Example 4	43.5
Example 5	1.5
Example 6	2.9
Example 7	<1
Example 8	81.4
Example 9	12.4
Example 10	23.2
Example 13	0.7
Example 14	1.4
Example 20	1.4
Example 21	1.4
Example 25	16.1
Example 26	3.7
Example 27	10
Example 28	264.9
Example 29	5835
Example 32	25
Example 38	24.9
Example 41	505.9
Example 42	219
Example 43	1015
Example 44	1363
Example 45	104.8
Example 46	337
Example 47	444.1
Example 51	995.8
Example 61	378.7
Example 62	2.6
Example 63	68.8
Example 64	61.6
Example 65	249.6
Example 70	19.4
Example 71	4.4
Example 72	<1
Example 81	3.1
Example 82	14.6
Example 84	6.3
Example 86	2
Example 89	<1
Example 90	4.4
Example 93	1.9
Example 94	523.8
Example 95	64
Example 96	57.8
Example 97	0.4
Example 98	151.7
Example 99	1.8
Example 100	552
Example 101	74.4
Example 84	6.3
Example 86	2
Example 102	1
Example 103	<1
Example 104	11.6
Example 105	3.9
Example 106	<1
Example 107	17.9
Example 108	1784
Example 109	1393
Example 110	141.4
Example 111	155.1
Example 112	1279
Example 113	44.2
Example 114	3.3
Example 115	67.9
Example 116	1624
Example 117	1.7
Example 118	1.6
Example 119	40
Example 120	393.7
Example 122	179.2
Example 124	4
Example 126	447.4
Example 128	19.5
Example 129	973.3
Example 139	1.2
Example 141	<1
Example 142	174.8
Example 144	4.6
Example 145	14
Example 148	1932
Example 149	110.8
Example 152	5.7
Example 153	6.5
Example 154	60
Example 155	<1
Example 156	<1
Example 157	<1
Example 158	40
Example 159	7.1
Example 160	10.3
Example 161	6.2
Example 162	100.7
Example 163	14.3
Example 164	312.4
Example 165	2.9
Example 166	463.2
Example 167	87.7
Example 168	8.6
Example 169	186.6
Example 170	25.5
Example 171	18.7
Example 172	105.9
Example 176	16.2

TABLE 13-continued

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

Compound	EC_{50} (nM)
Example 177	7.9
Example 178	37.4
Example 179	111.7
Example 180	832.1
Example 181	459.2
Example 182	3276
Example 183	3180
Example 184	<1
Example 185	201.1
Example 186	30.2
Example 187	6.5
Example 188	47.6
Example 189	423.9
Example 190	408.7
Example 191	281.2
Example 192	3867
Example 193	190.5
Example 194	159.2
Example 195	1855
Example 196	1033
Example 197	1.2
Example 198	19.1
Example 199	72
Example 200	15
Example 201	649.5
Example 202	813.5
Example 203	7.3
Example 204	1233
Example 205	42.7
Example 206	259.7
Example 207	1.4
Example 208	23.3
Example 209	9.5
Example 210	28.5
Example 211	1045
Example 212	11.8
Example 213	135
Example 214	2.1
Example 215	33.1
Example 216	3.4
Example 217	66.2
Example 218	13.8
Example 219	530.5
Example 220	29% Inh @ 20 uM
Example 221	<1
Example 222	60
Example 223	302.5
Example 224	37.4
Example 225	779.3
Example 226	27.8
Example 227	260.6
Example 228	1005
Example 229	31% Inh @ 20 uM
Example 230	382.4
Example 231	540.4
Example 232	3283
Example 233	33.8
Example 234	275.2
Example 235	14.9
Example 236	6963
Example 237	307.2
Example 238	66.3
Example 239	3.2
Example 240	73.6
Example 241	471.8
Example 242	1.1
Example 243	26.3
Example 247	1.1
Example 248	31.7
Example 249	<1
Example 250	17.3
Example 251	<1
Example 252	768.4
Example 253	54.5
Example 254	39.7
Example 255	301.9
Example 256	93.5
Example 257	135.9
Example 258	5
Example 259	1.5
Example 260	7.2
Example 261	21.8
Example 262	57.3
Example 263	4.8
Example 264	177.5
Example 265	5473
Example 266	1.9
Example 267	6267
Example 268	77
Example 269	4837
Example 270	4383
Example 271	12.8
Example 272	749.6
Example 273	216.4
Example 274	2.3
Example 275	21.8
Example 276	321.5
Example 277	28.7
Example 278	477.9
Example 279	1235
Example 280	1186
Example 281	2485
Example 282	12190
Example 283	17.2
Example 284	128.3
Example 285	277.1
Example 286	4010
Example 287	80.2
Example 288	24.9
Example 289	5.3
Example 308	3.3
Example 323	3.7
Example 324	10.7
Example 325	866.1
Example 326	89.7
Example 327	14
Example 328	74.4
Example 329	31.7
Example 330	204
Example 331	182.9
Example 334	110.5
Example 335	5.2
Example 336	422.2
Example 337	29.2
Example 338	441.7

Example 351: IFN-β Secretion in THP1 Cell Culture (5 h)

[0889] 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:

[0890] A Labcyte Echo 550 acoustic dispenser was used to transfer 120 nL 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; 1 mM Sodium Pyruvate, Life Technologies, Cat. No. 11360-070; 1× 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 cells suspension was centrifuged at 200×g for 5 min at RT. Cells were resuspended to a density of 0.8×10^6/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.

[0891] The assay was started by dispensing 40 μL of the previously prepared cell suspension into the wells of the plate containing compounds. After 5 h incubation at 37° C., 5% CO_2 in a humidified atmosphere, the plate of cells and compounds was centrifuged at 200×g for 5 min at RT. From each well, 5 μL 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 10 μL of 5× Anti-Analyte Acceptor beads (50 μg/mL of AlphaLISA HiBlock Buffer) and incubated for 30 min at RT while shaking on an orbital plate shaker. To each well was added 10 μL of 5× Biotinylated Antibody Anti-analyte (5 nM in AlphaLISA HiBlock Buffer) and incubated on an orbital plate shaker for 60 min at RT or overnight at 4° C. To each well was added 25 μL of 2× SA-Donor beads (80 μg/mL in AlphaLISA HiBlock Buffer) and incubated for 30-45 min at RT in the dark while shaking on an orbital plate shaker. The plate was then read on a Perkin Elmer Envision (λ_{ex}=680 nm, λ_{em}=570 nm). The percent effect of the AlphaLISA signal at each compound concentration was calculated based on 30 uM 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 1.5 nM with 0.3% residual DMSO. The control compound, cGAMP was tested at concentrations 100000, 33333, 11111, 3704, 1235, 412, 137, 46, and 15 nM with 0.3% residual DMSO.

[0892] 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 30 μM concentration.

TABLE 14

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

Compound	% Effect at 30 μM relative to 2'3'-cGAMP
Example 1	154
Example 2	148
Example 3	149
Example 4	171
Example 5	152
Example 6	114
Example 7	112
Example 8	98
Example 9	143
Example 10	126
Example 11	169
Example 12	89
Example 13	39
Example 14	139
Example 15	39
Example 16	57
Example 17	81
Example 18	74
Example 19	49
Example 20	159
Example 21	142
Example 22	109
Example 23	125
Example 24	90
Example 25	145
Example 26	150
Example 27	164
Example 28	60
Example 29	25
Example 30	131
Example 31	100
Example 32	125
Example 33	200
Example 34	125
Example 35	51
Example 36	120
Example 37	57
Example 38	123
Example 39	74
Example 40	77
Example 41	8
Example 42	101
Example 43	130
Example 44	135
Example 45	161
Example 46	143
Example 47	141
Example 48	104
Example 49	74
Example 50	85
Example 51	36
Example 52	143
Example 53	127
Example 54	83
Example 55	83
Example 56	64
Example 57	7
Example 58	92
Example 59	76
Example 60	12
Example 61	34
Example 62	68
Example 63	83
Example 64	93
Example 65	87
Example 66	54
Example 67	111
Example 68	72
Example 69	31
Example 70	100
Example 71	113
Example 72	102
Example 73	5
Example 74	57
Example 75	96
Example 76	39
Example 77	39
Example 78	162
Example 79	145
Example 80	234
Example 81	138

TABLE 14-continued

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

Compound	% Effect at 30 μM relative to 2'3'-cGAMP
Example 82	111
Example 83	133
Example 84	128
Example 85	154
Example 86	137
Example 87	99
Example 88	54
Example 89	119
Example 90	117
Example 91	106
Example 92	62
Example 93	155
Example 94	138
Example 95	118
Example 96	67
Example 97	113
Example 98	54
Example 99	135
Example 100	35
Example 101	129
Example 102	132
Example 103	114
Example 104	154
Example 105	137
Example 106	208
Example 107	171
Example 108	15
Example 109	151
Example 110	181
Example 111	200
Example 112	33
Example 113	154
Example 114	163
Example 115	177
Example 116	149
Example 117	211
Example 118	174
Example 119	151
Example 120	72
Example 121	108
Example 122	75
Example 123	128
Example 124	128
Example 125	138
Example 126	167
Example 127	145
Example 128	146
Example 129	33
Example 130	215
Example 131	238
Example 132	150
Example 133	117
Example 134	138
Example 135	43
Example 136	131
Example 137	124
Example 138	51
Example 139	110
Example 140	96
Example 141	111
Example 142	111
Example 143	157
Example 144	114
Example 145	141
Example 146	59
Example 147	146
Example 148	13
Example 149	8
Example 150	89
Example 151	57

TABLE 14-continued

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

Compound	% Effect at 30 μM relative to 2'3'-cGAMP
Example 152	16
Example 153	234
Example 154	198
Example 155	139
Example 156	119
Example 157	151
Example 158	123
Example 159	140
Example 160	12
Example 161	130
Example 162	116
Example 163	127
Example 164	41
Example 165	245
Example 166	143
Example 167	278
Example 168	164
Example 169	117
Example 170	134
Example 171	142
Example 172	26
Example 173	142
Example 174	5
Example 175	120
Example 176	114
Example 177	180
Example 178	111
Example 179	66
Example 180	143
Example 181	178
Example 182	47
Example 183	23
Example 184	108
Example 185	61
Example 186	179
Example 187	134
Example 188	251
Example 189	93
Example 190	200
Example 191	516
Example 192	50
Example 193	399
Example 194	258
Example 195	61
Example 196	14
Example 197	237
Example 198	205
Example 199	139
Example 200	219
Example 201	222
Example 202	171
Example 203	194
Example 204	101
Example 205	132
Example 206	166
Example 207	189
Example 208	163
Example 209	170
Example 210	178
Example 211	114
Example 212	285
Example 213	255
Example 214	224
Example 215	277
Example 216	170
Example 217	70
Example 218	152
Example 219	142
Example 220	6
Example 221	405

TABLE 14-continued

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

Compound	% Effect at 30 μM relative to 2'3'-cGAMP
Example 222	171
Example 223	11
Example 224	288
Example 225	467
Example 226	439
Example 227	290
Example 228	6
Example 229	6
Example 230	116
Example 231	189
Example 232	21
Example 233	254
Example 234	75
Example 235	262
Example 236	5
Example 237	222
Example 238	183
Example 239	164
Example 240	141
Example 241	300
Example 242	156
Example 243	165
Example 244	96
Example 245	234
Example 246	217
Example 247	166
Example 248	42
Example 249	106
Example 250	6
Example 251	175
Example 252	23
Example 253	73
Example 254	131
Example 255	49
Example 256	149
Example 257	8
Example 258	120
Example 259	91
Example 260	113
Example 261	90
Example 262	108
Example 263	114
Example 264	123
Example 265	25
Example 266	168
Example 267	5
Example 268	181
Example 269	109
Example 270	235
Example 271	229
Example 272	44
Example 273	85
Example 274	124
Example 275	157
Example 276	45
Example 277	174
Example 278	68
Example 279	160
Example 280	191
Example 281	8
Example 282	39
Example 283	288
Example 284	260
Example 285	195
Example 286	16
Example 287	202
Example 288	153
Example 289	58
Example 290	90
Example 291	98
Example 292	114
Example 293	86
Example 294	84
Example 295	70
Example 296	92
Example 297	176
Example 298	121
Example 299	5
Example 300	86
Example 301	107
Example 302	103
Example 303	106
Example 304	104
Example 305	50
Example 306	153
Example 307	174
Example 308	132
Example 309	232
Example 310	117
Example 311	9
Example 312	90
Example 313	117
Example 314	143
Example 315	92
Example 316	12
Example 317	107
Example 318	150
Example 319	143
Example 320	115
Example 321	36
Example 322	41
Example 323	92
Example 324	99
Example 325	10
Example 326	34
Example 327	126
Example 328	99
Example 329	105
Example 330	67
Example 331	116
Example 332	113
Example 333	10
Example 334	66
Example 335	60
Example 336	85
Example 337	204
Example 338	219
Example 339	175
Example 340	306
Example 341	7
Example 342	23
Example 343	255
Example 344	337
Example 345	144
Example 346	182
Example 347	225
Example 348	8

[0893] 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. Also that various presently unforeseen or unanticipated alternatives, modifications, variations or improvements therein may be subsequently made by those skilled in the art which are also intended to be encompassed by the following claims.

SEQUENCE LISTING

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Asn Leu Lys Val Ser Asp Gly Ser Ser Glu Ile Phe Phe Lys Ile Lys
        35                  40                  45

Lys Thr Thr Pro Leu Arg Arg Leu Met Glu Ala Phe Ala Lys Arg Gln
    50                  55                  60

Gly Lys Glu Met Asp Ser Leu Thr Phe Leu Tyr Asp Gly Ile Glu Ile
65                  70                  75                  80

Gln Ala Asp Gln Thr Pro Glu Asp Leu Asp Met Glu Asp Asn Asp Ile
                85                  90                  95

Ile Glu Ala His Arg Glu Gln Ile Gly Gly Glu Asn Leu Tyr Phe Gln
            100                 105                 110

Gly Gly Ala Ser Lys Leu Arg Ala Val Leu Glu Lys Leu Lys Leu Ser
        115                 120                 125

Arg Asp Asp Ile Ser Thr Ala Ala Gly Met Val Lys Gly Val Val Asp
    130                 135                 140

His Leu Leu Leu Arg Leu Lys Cys Asp Ser Ala Phe Arg Gly Val Gly
145                 150                 155                 160

Leu Leu Asn Thr Gly Ser Tyr Tyr Glu His Val Lys Ile Ser Ala Pro
                165                 170                 175

Asn Glu Phe Asp Val Met Phe Lys Leu Glu Val Pro Arg Ile Gln Leu
            180                 185                 190

Glu Glu Tyr Ser Asn Thr Arg Ala Tyr Tyr Phe Val Lys Phe Lys Arg
        195                 200                 205

Asn Pro Lys Glu Asn Pro Leu Ser Gln Phe Leu Glu Gly Glu Ile Leu
    210                 215                 220

Ser Ala Ser Lys Met Leu Ser Lys Phe Arg Lys Ile Ile Lys Glu Glu
225                 230                 235                 240

Ile Asn Asp Ile Lys Asp Thr Asp Val Ile Met Lys Arg Lys Arg Gly
                245                 250                 255

Gly Ser Pro Ala Val Thr Leu Leu Ile Ser Glu Lys Ile Ser Val Asp
            260                 265                 270

Ile Thr Leu Ala Leu Glu Ser Lys Ser Ser Trp Pro Ala Ser Thr Gln
        275                 280                 285

Glu Gly Leu Arg Ile Gln Asn Trp Leu Ser Ala Lys Val Arg Lys Gln
    290                 295                 300

Leu Arg Leu Lys Pro Phe Tyr Leu Val Pro Lys His Ala Lys Glu Gly
305                 310                 315                 320

Asn Gly Phe Gln Glu Glu Thr Trp Arg Leu Ser Phe Ser His Ile Glu
                325                 330                 335

Lys Glu Ile Leu Asn Asn His Gly Lys Ser Lys Thr Cys Cys Glu Asn
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            340                 345                 350

Lys Glu Glu Lys Cys Cys Arg Lys Asp Cys Leu Lys Leu Met Lys Tyr
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Leu Leu Glu Gln Leu Lys Glu Arg Phe Lys Asp Lys Lys His Leu Asp
    370                 375                 380

Lys Phe Ser Ser Tyr His Val Lys Thr Ala Phe Phe His Val Cys Thr
385                 390                 395                 400

Gln Asn Pro Gln Asp Ser Gln Trp Asp Arg Lys Asp Leu Gly Leu Cys
                405                 410                 415

Phe Asp Asn Cys Val Thr Tyr Phe Leu Gln Cys Leu Arg Thr Glu Lys
            420                 425                 430

Leu Glu Asn Tyr Phe Ile Pro Glu Phe Asn Leu Phe Ser Ser Asn Leu
        435                 440                 445

Ile Asp Lys Arg Ser Lys Glu Phe Leu Thr Lys Gln Ile Glu Tyr Glu
    450                 455                 460

Arg Asn Asn Glu Phe Pro Val Phe Asp Glu Phe
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            20                  25                  30

Leu Trp Gly Leu Gly Glu Pro Pro Glu His Thr Leu Arg Tyr Leu Val
        35                  40                  45

Leu His Leu Ala Ser Leu Gln Leu Gly Leu Leu Leu Asn Gly Val Cys
    50                  55                  60

Ser Leu Ala Glu Glu Leu His His Ile His Ser Arg Tyr Arg Gly Ser
65                  70                  75                  80

Tyr Trp Arg Thr Val Arg Ala Cys Leu Gly Cys Pro Leu Arg Arg Gly
                85                  90                  95

Ala Leu Leu Leu Leu Ser Ile Tyr Phe Tyr Tyr Ser Leu Pro Asn Ala
            100                 105                 110

Val Gly Pro Pro Phe Thr Trp Met Leu Ala Leu Leu Gly Leu Ser Gln
        115                 120                 125

Ala Leu Asn Ile Leu Leu Gly Leu Lys Gly Leu Ala Pro Ala Glu Ile
    130                 135                 140

Ser Ala Val Cys Glu Lys Gly Asn Phe Asn Val Ala His Gly Leu Ala
145                 150                 155                 160

Trp Ser Tyr Tyr Ile Gly Tyr Leu Arg Leu Ile Leu Pro Glu Leu Gln
                165                 170                 175

Ala Arg Ile Arg Thr Tyr Asn Gln His Tyr Asn Asn Leu Leu Arg Gly
            180                 185                 190

Ala Val Ser Gln Arg Leu Tyr Ile Leu Leu Pro Leu Asp Cys Gly Val
        195                 200                 205

Pro Asp Asn Leu Ser Met Ala Asp Pro Asn Ile Arg Phe Leu Asp Lys
    210                 215                 220
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Leu Pro Gln Gln Thr Ala Asp Arg Ala Gly Ile Lys Asp Arg Val Tyr
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Ser Asn Ser Ile Tyr Glu Leu Leu Glu Asn Gly Gln Arg Ala Gly Thr
                245                 250                 255

Cys Val Leu Glu Tyr Ala Thr Pro Leu Gln Thr Leu Phe Ala Met Ser
            260                 265                 270

Gln Tyr Ser Gln Ala Gly Phe Ser Arg Glu Asp Arg Leu Glu Gln Ala
        275                 280                 285

Lys Leu Phe Cys Gln Thr Leu Glu Asp Ile Leu Ala Asp Ala Pro Glu
    290                 295                 300

Ser Gln Asn Asn Cys Arg Leu Ile Ala Tyr Gln Glu Pro Ala Asp Asp
305                 310                 315                 320

Ser Ser Phe Ser Leu Ser Gln Glu Val Leu Arg His Leu Arg Gln Glu
                325                 330                 335

Glu Lys Glu Glu Val Thr Val Gly Ser Leu Lys Thr Ser Ala Val Pro
            340                 345                 350

Ser Thr Ser Thr Met Ser Gln Glu Pro Glu Leu Leu Ile Ser Gly Met
        355                 360                 365

Glu Lys Pro Leu Pro Leu Arg Thr Asp Phe Ser Gly Gly Gly Leu Asn
    370                 375                 380

Asp Ile Phe Glu Ala Gln Lys Ile Glu Trp His Glu Gly Ser Leu Glu
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Val Leu Phe Gln Gly Pro His His His His His His His His
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aacaagatta atatgcctcc gtgtataaaa aaaatattga acgatttgaa agaaaacaat     180

gtaccgcgcg gcggtatgta caggaagagg tttatactaa actgttacat tgcaaacgtg     240

gtttcgtgtg ccaagtgtga aaaccgatgt ttaatcaagg ctctgacgca tttctacaac     300

cacgactcca agtgtgtggg tgaagtcatg catcttttaa tcaaatccca agatgtgtat     360

aaaccaccaa actgccaaaa aatgaaaact gtcgacaagc tctgtccgtt tgctggcaac     420

tgcaagggtc tcaatcctat ttgtaattat tgaataataa aacaattata aatgctaaat     480

ttgtttttta ttaacgatac aaaccaaacg caacaagaac atttgtagta ttatctataa     540

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atccatatat gtatctatcg tatagagtaa atttttgtt gtcataaata tatatgtctt      780

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<212> TYPE: PRT
<213> ORGANISM: Homo Sapien

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Leu Trp Gly Leu Gly Glu Pro Pro Glu His Thr Leu Arg Tyr Leu Val
        35                  40                  45

Leu His Leu Ala Ser Leu Gln Leu Gly Leu Leu Leu Asn Gly Val Cys
    50                  55                  60

Ser Leu Ala Glu Glu Leu Arg His Ile His Ser Arg Tyr Arg Gly Ser
65                  70                  75                  80

Tyr Trp Arg Thr Val Arg Ala Cys Leu Gly Cys Pro Leu Arg Arg Gly
                85                  90                  95

Ala Leu Leu Leu Leu Ser Ile Tyr Phe Tyr Tyr Ser Leu Pro Asn Ala
            100                 105                 110

Val Gly Pro Pro Phe Thr Trp Met Leu Ala Leu Leu Gly Leu Ser Gln
        115                 120                 125

Ala Leu Asn Ile Leu Leu Gly Leu Lys Gly Leu Ala Pro Ala Glu Ile
    130                 135                 140

Ser Ala Val Cys Glu Lys Gly Asn Phe Asn Val Ala His Gly Leu Ala
145                 150                 155                 160

Trp Ser Tyr Tyr Ile Gly Tyr Leu Arg Leu Ile Leu Pro Glu Leu Gln
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Ala Arg Ile Arg Thr Tyr Asn Gln His Tyr Asn Asn Leu Leu Arg Gly
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Ala Val Ser Gln Arg Leu Tyr Ile Leu Leu Pro Leu Asp Cys Gly Val
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Pro Asp Asn Leu Ser Met Ala Asp Pro Asn Ile Arg Phe Leu Asp Lys
    210                 215                 220

Leu Pro Gln Gln Thr Gly Asp Arg Ala Gly Ile Lys Asp Arg Val Tyr
225                 230                 235                 240

Ser Asn Ser Ile Tyr Glu Leu Leu Glu Asn Gly Gln Arg Ala Gly Thr
                245                 250                 255

Cys Val Leu Glu Tyr Ala Thr Pro Leu Gln Thr Leu Phe Ala Met Ser
            260                 265                 270

Gln Tyr Ser Gln Ala Gly Phe Ser Arg Glu Asp Arg Leu Glu Gln Ala
        275                 280                 285

Lys Leu Phe Cys Arg Thr Leu Glu Asp Ile Leu Ala Asp Ala Pro Glu
    290                 295                 300

Ser Gln Asn Asn Cys Arg Leu Ile Ala Tyr Gln Glu Pro Ala Asp Asp
305                 310                 315                 320

Ser Ser Phe Ser Leu Ser Gln Glu Val Leu Arg His Leu Arg Gln Glu
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Glu Lys Glu Glu Val Thr Val Gly Ser Leu Lys Thr Ser Ala Val Pro
            340                 345                 350

Ser Thr Ser Thr Met Ser Gln Glu Pro Glu Leu Leu Ile Ser Gly Met
        355                 360                 365

Glu Lys Pro Leu Pro Leu Arg Thr Asp Phe Ser Gly Gly Gly Leu Asn
    370                 375                 380

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<212> TYPE: DNA
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<400> SEQUENCE: 5

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1-21. (canceled)

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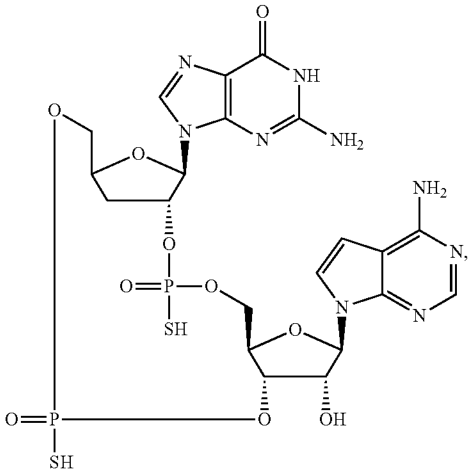

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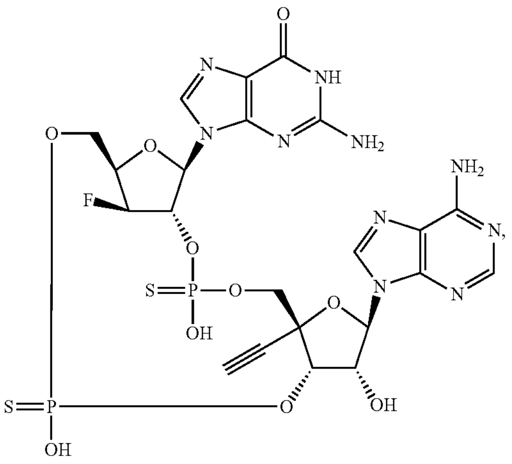

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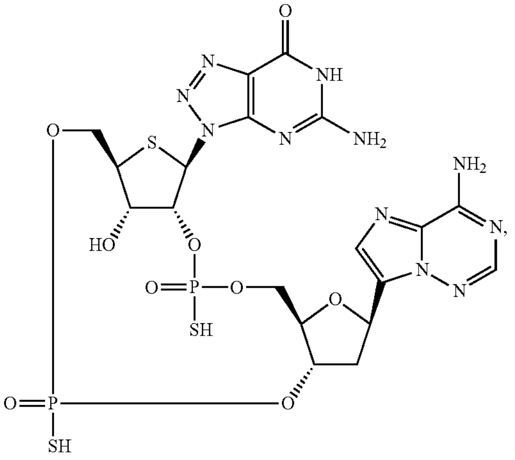

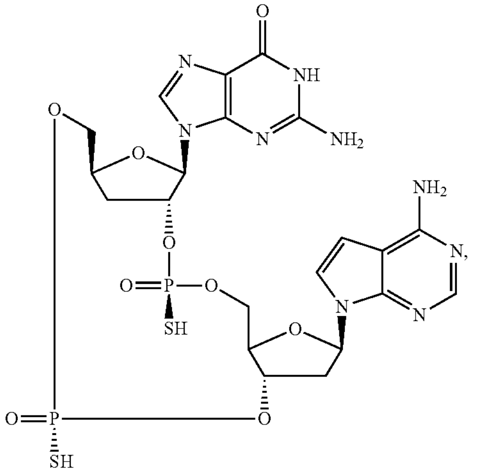

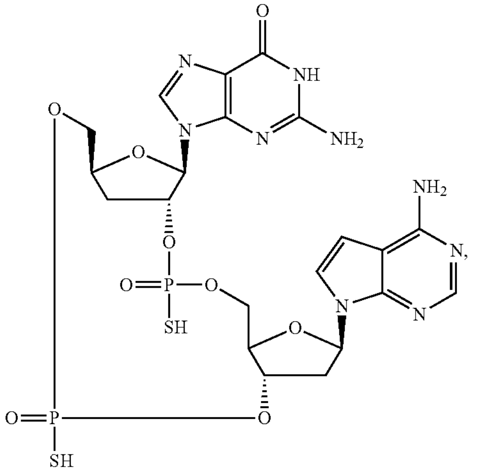

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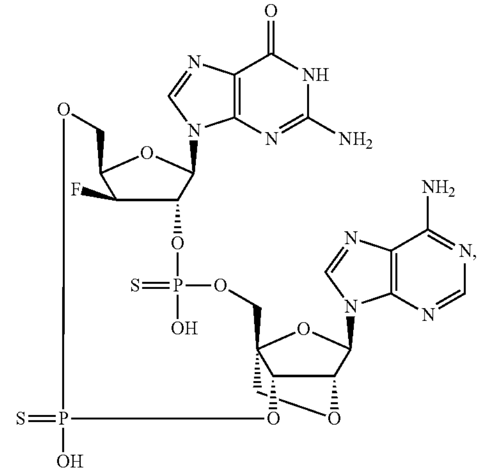

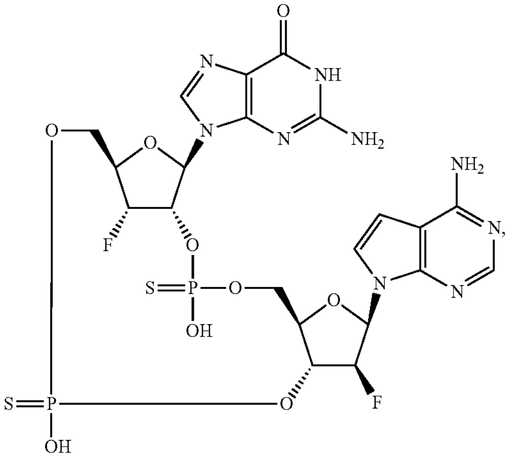

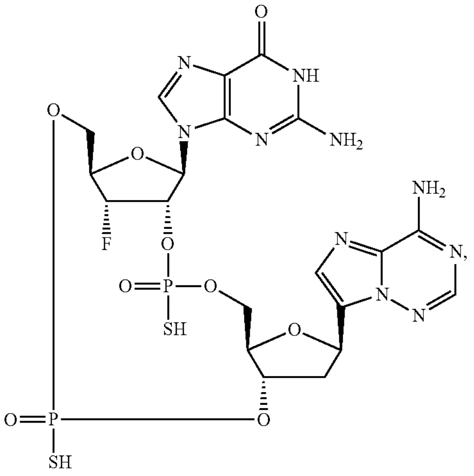

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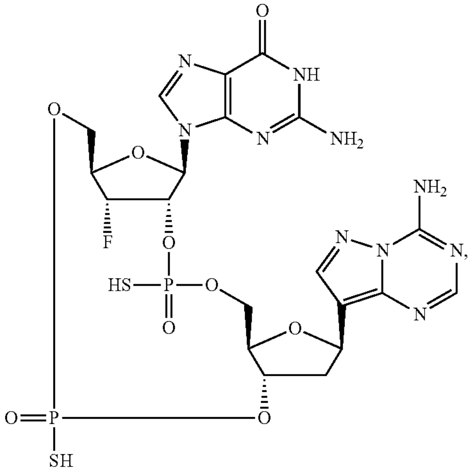
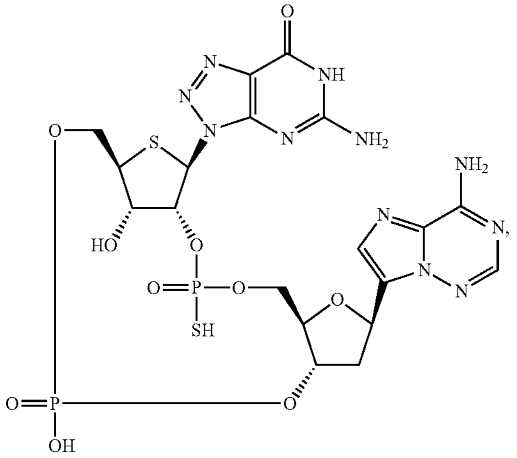
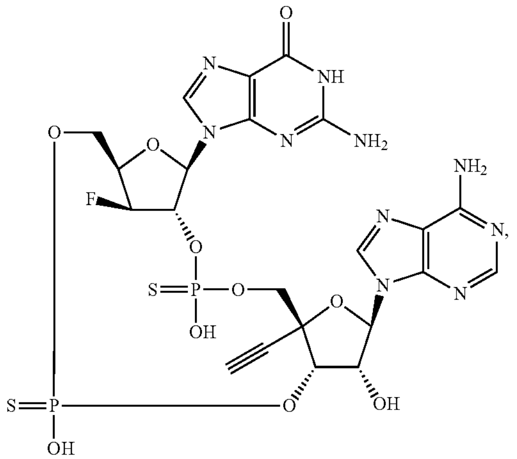


and



and pharmaceutically acceptable salts thereof.

23. The compound according to claim **22**, wherein the compound is selected from the group consisting of:



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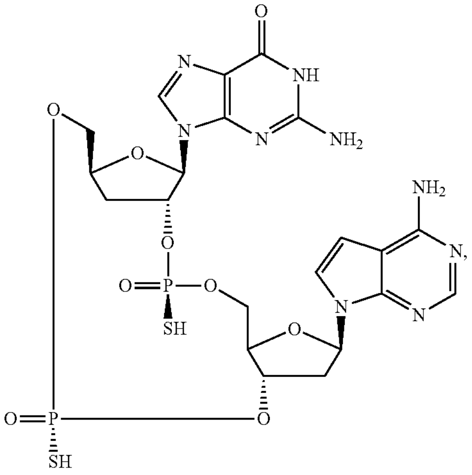

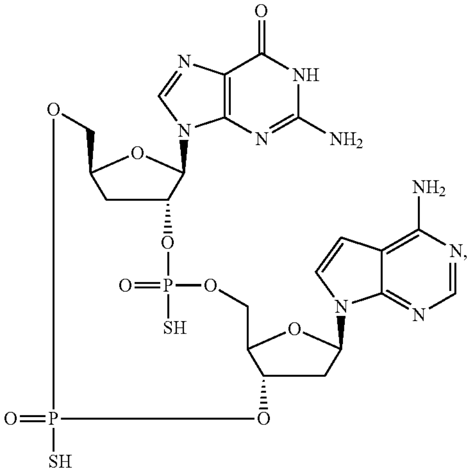

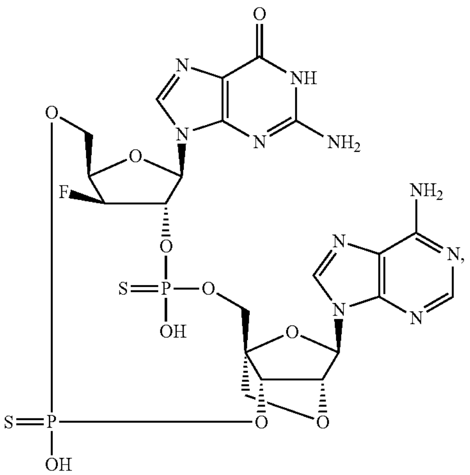

and

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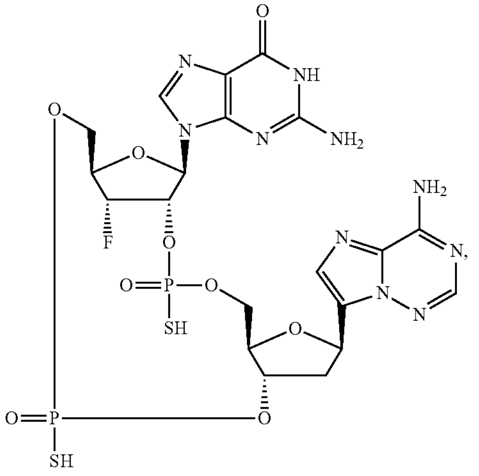
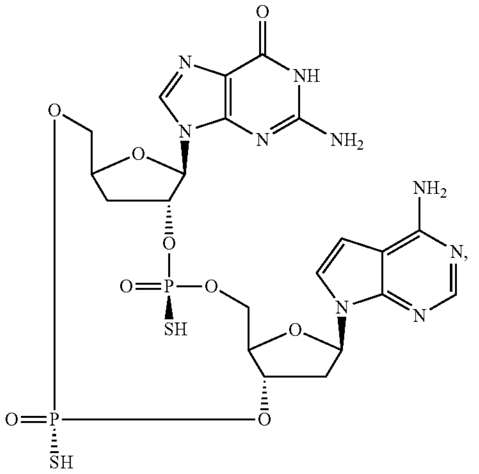
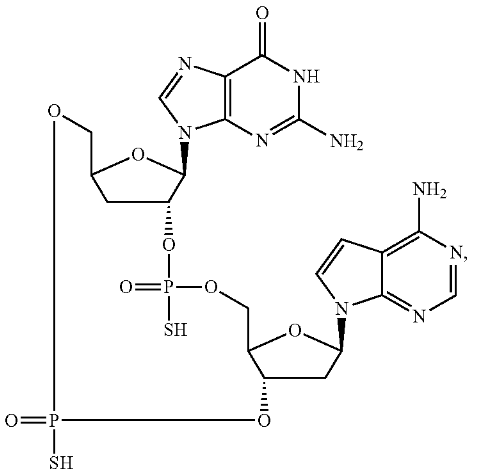


and pharmaceutically acceptable salts thereof.

24. The compound according to claim **22**, wherein the compound is selected from the group consisting of:





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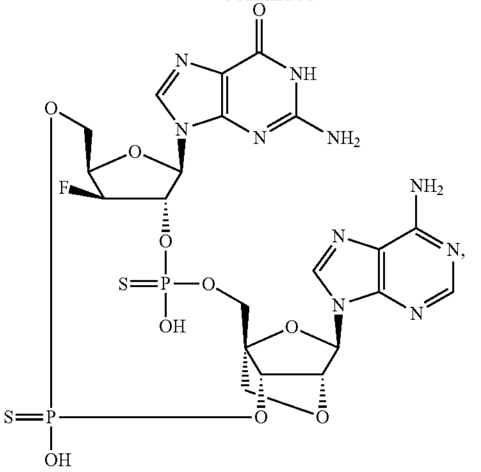
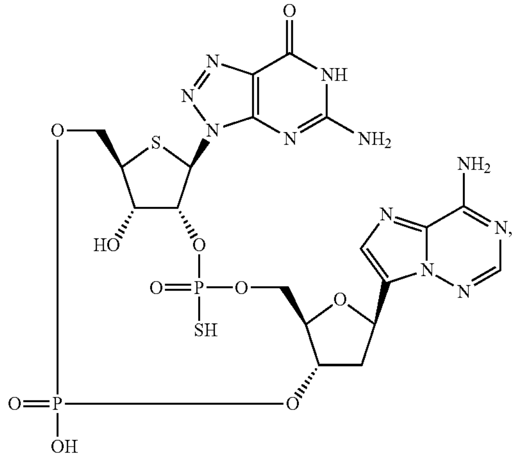


and



and pharmaceutically acceptable salts thereof.

25. A pharmaceutical composition, said pharmaceutical composition comprising:

(a) a compound selected from the group consisting of a compound according to claim **22** and pharmaceutically acceptable salts thereof; and

(b) a pharmaceutically acceptable carrier.

26. A method of inducing an immune response in a subject, said method comprising administering a therapeutically effective amount of a compound selected from the group consisting of a compound according to claim **22** and pharmaceutically acceptable salts thereof to the subject.

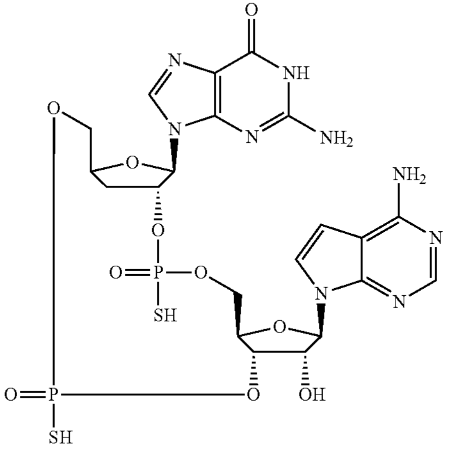
27. A method of inducing an immune response in a subject, said method comprising administering a therapeutically effective amount of a pharmaceutical composition according to claim **25** to the subject.

28. 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 selected from the group consisting of a compound according to claim **22** and pharmaceutically acceptable salts thereof to the subject.

29. 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 **25** to the subject.

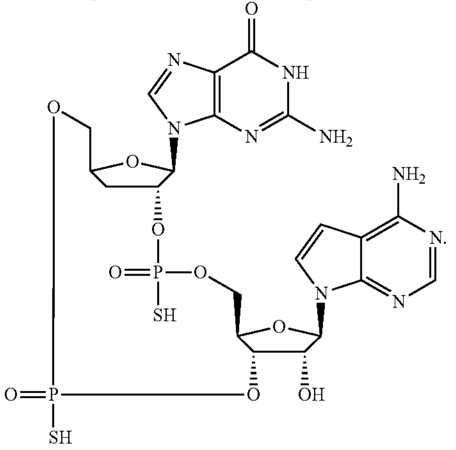
30-33. (canceled)

34. A compound, wherein the compound is selected from the group consisting of

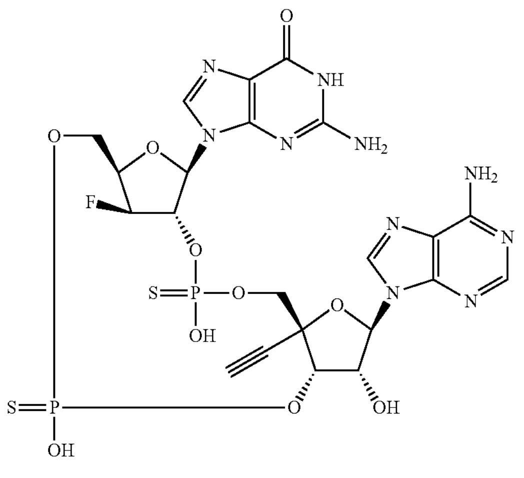


and pharmaceutically acceptable salts thereof.

35. The compound according to claim **34**, wherein the compound is a pharmaceutically acceptable salt of

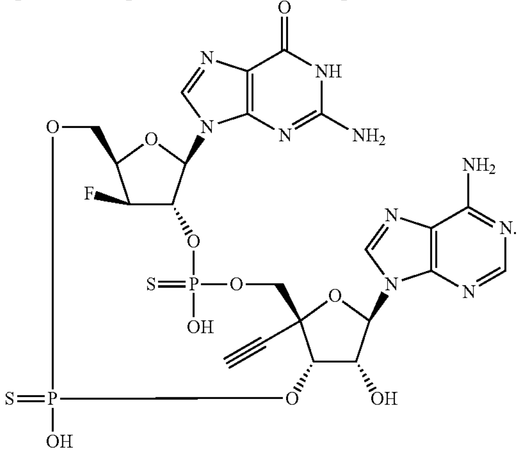


36. A compound, wherein the compound is selected from the group consisting of

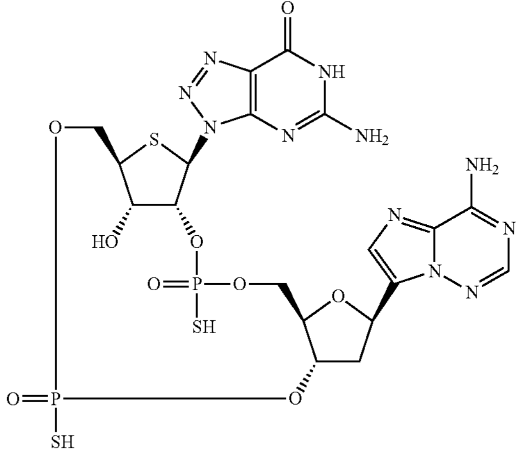


and pharmaceutically acceptable salts thereof.

37. The compound according to claim **36**, wherein the compound is a pharmaceutically acceptable salt of

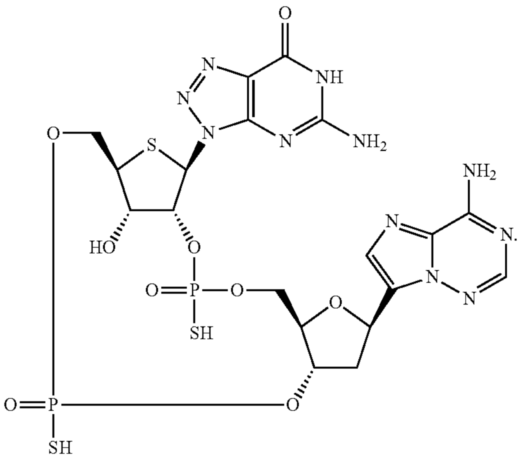


38. A compound, wherein the compound is selected from the group consisting of

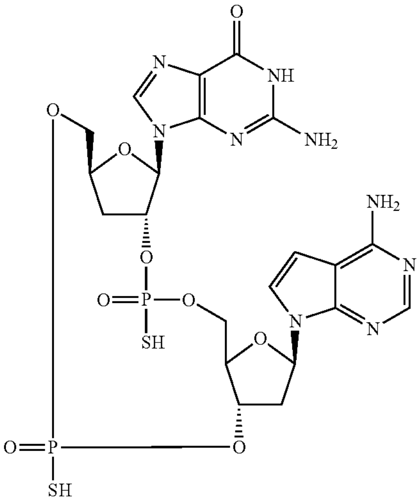


and pharmaceutically acceptable salts thereof.

39. The compound according to claim **38**, wherein the compound is a pharmaceutically acceptable salt of

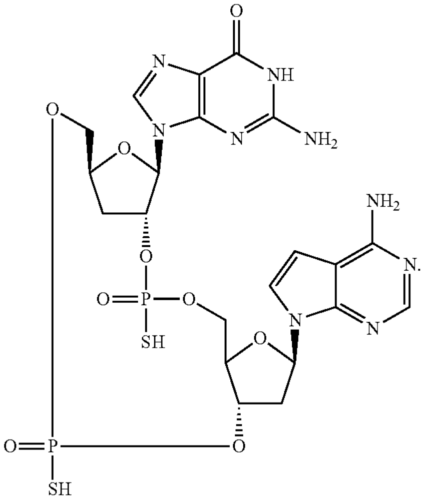


40. A compound, wherein the compound is selected from the group consisting of

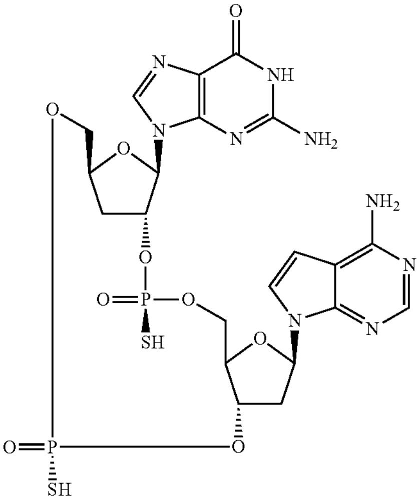


and pharmaceutically acceptable salts thereof.

41. The compound according to claim **40**, wherein the compound is a pharmaceutically acceptable salt of

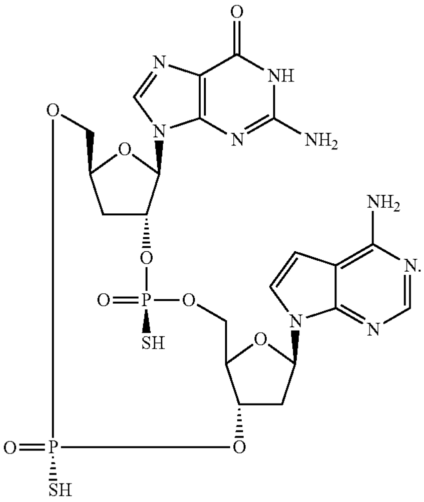


42. The compound according to claim **40**, wherein the compound is selected from the group consisting of

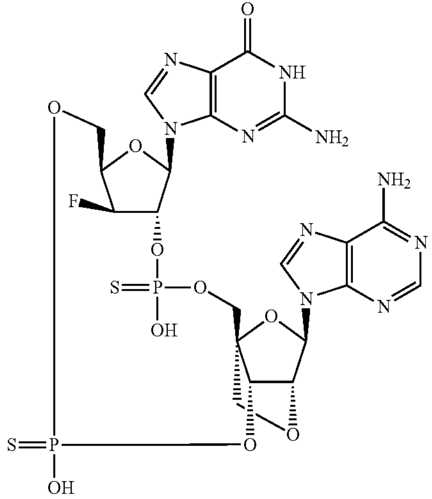


and pharmaceutically acceptable salts thereof.

43. The compound according to claim **42**, wherein the compound is a pharmaceutically acceptable salt of

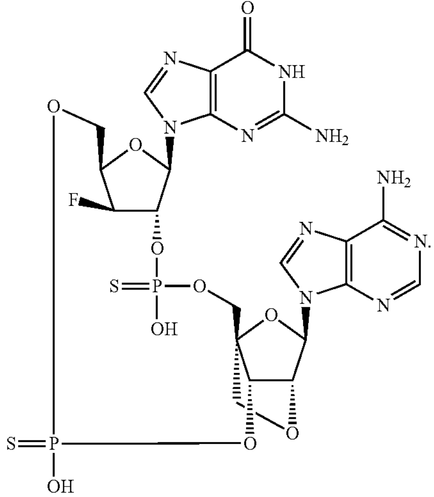


44. A compound, wherein the compound is selected from the group consisting of

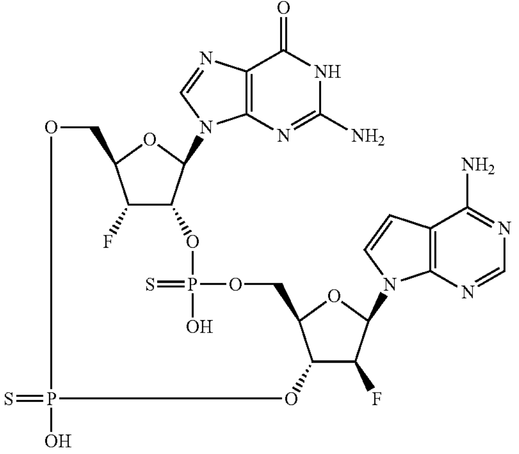


and pharmaceutically acceptable salts thereof.

45. The compound according to claim **44**, wherein the compound is a pharmaceutically acceptable salt of

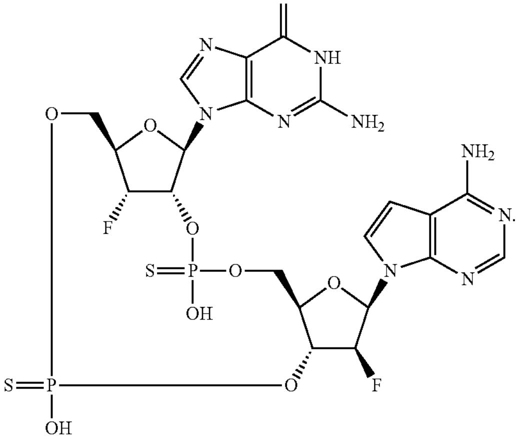


46. A compound, wherein the compound is selected from the group consisting of

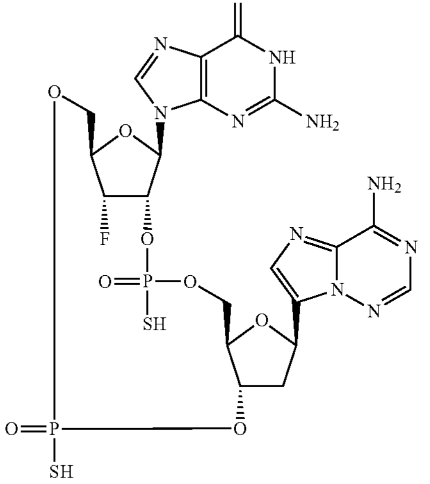


and pharmaceutically acceptable salts thereof.

47. The compound according to claim **46**, wherein the compound is a pharmaceutically acceptable salt of

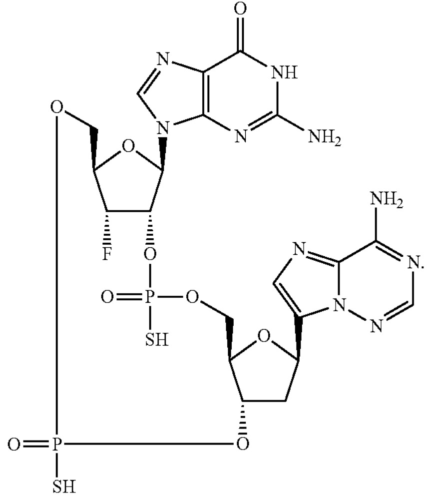


48. A compound, wherein the compound is selected from the group consisting of

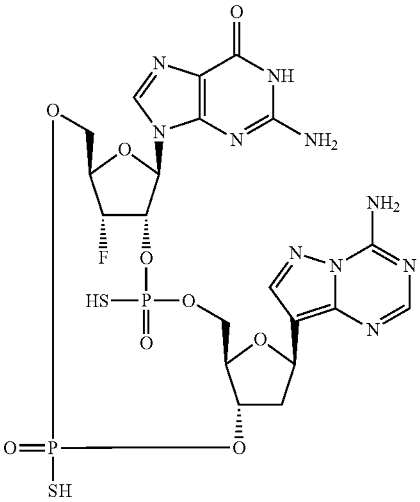


and pharmaceutically acceptable salts thereof.

49. The compound according to claim **48**, wherein the compound is a pharmaceutically acceptable salt of

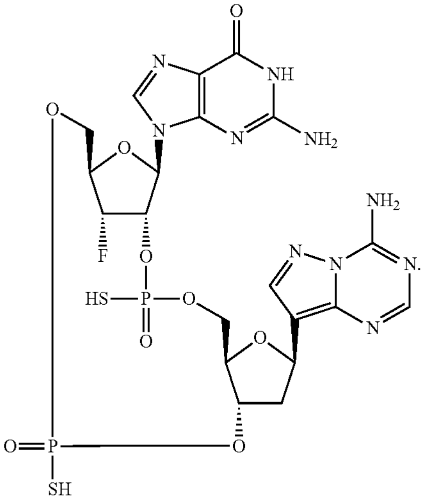


50. A compound, wherein the compound is selected from the group consisting of

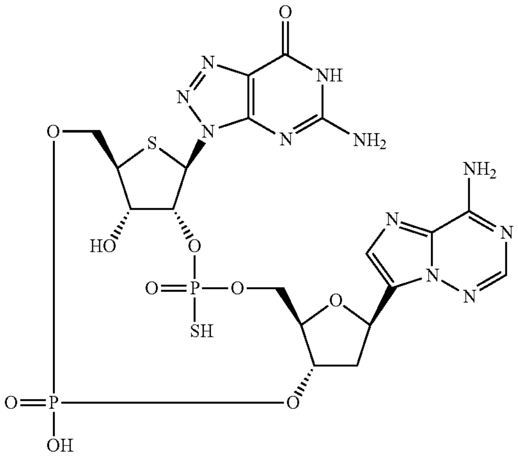


and pharmaceutically acceptable salt thereof.

51. The compound according to claim **50**, wherein the compound is a pharmaceutically acceptable salt of

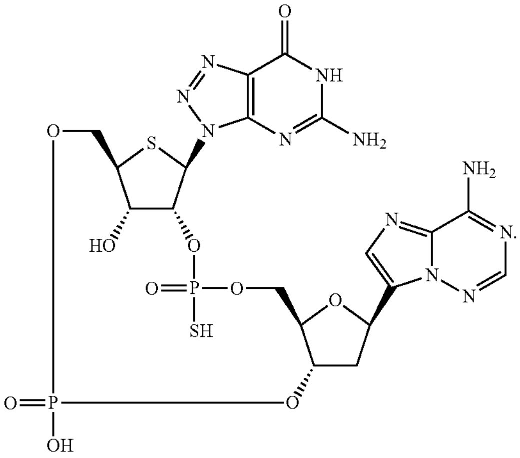


52. A compound, wherein the compound is selected from the group consisting of



and pharmaceutically acceptable salts thereof.

53. The compound according to claim **52**, wherein the compound is a pharmaceutically acceptable salt of



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