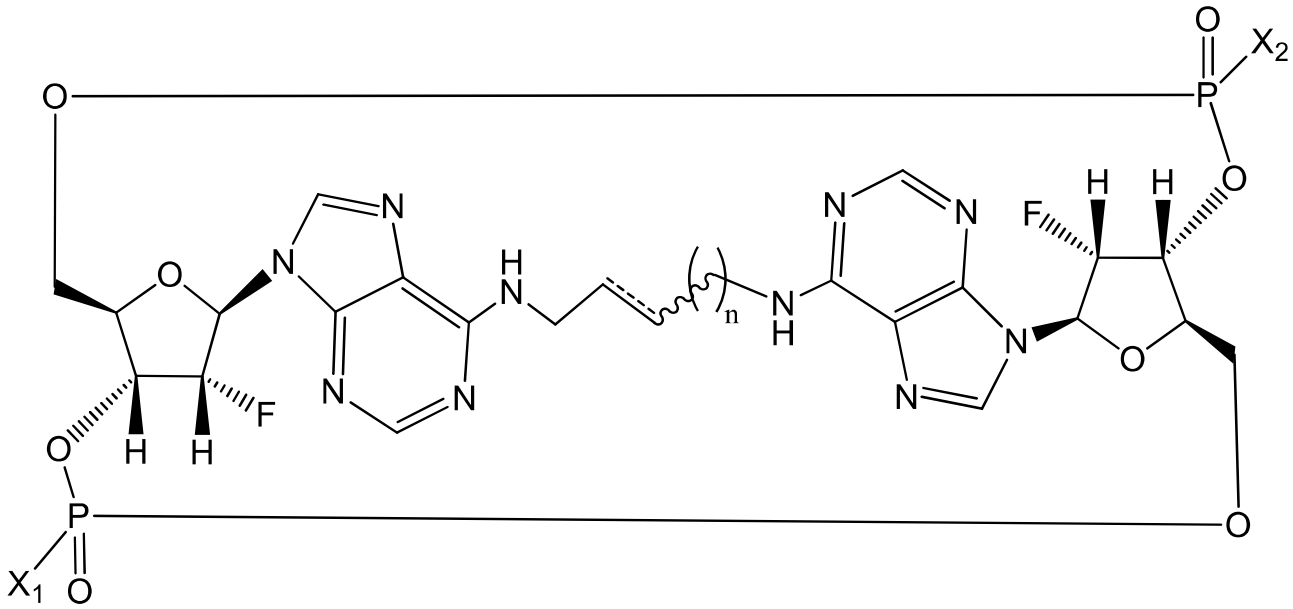
breast cancer" *Cancer Immunol Res.* 2014;2:901-10; Corrales L, *et al.*, "Direct Activation of STING in the Tumor Microenvironment Leads to Potent and Systemic Tumor Regression and Immunity" *Cell Rep*. 2015;11:1018-30; Curran E, *et al*. "STING Pathway Activation Stimulates Potent Immunity against Acute Myeloid Leukemia" *Cell Rep*. 2016;15:2357-66; Tang CH, *et al*. "Agonist-Mediated Activation of STING Induces Apoptosis in Malignant B Cells" *Cancer Res*. 2016;76:2137-52). This anti-tumor activity is likely due to disruption of tumor vasculature and followed by induction of adaptive immune response. (Corrales L, et al., "The host STING pathway at the interface of cancer and immunity" *J. Clin. Invest.* 2016;126:2404-11). Accordingly, direct stimulation of STING in a tumor microenvironment by an agonist may represent a novel approach for treating multiple cancer types.

BRIEF SUMMARY

Examples may provide a Compound of Formula (I):



(I)

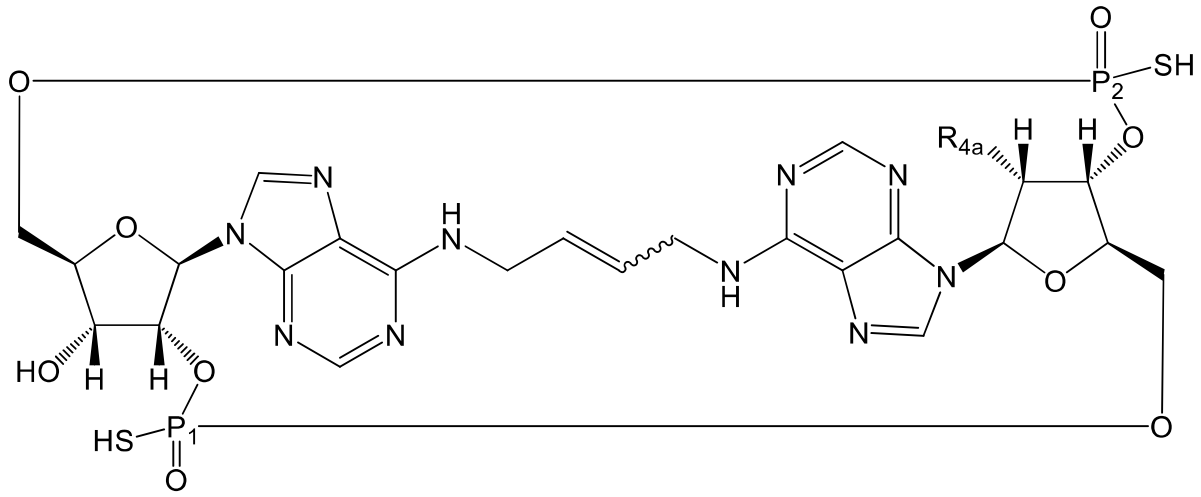
(where P_1 is the lower-left phosphorus and P_2 the upper right phosphorus as depicted above) having substituents and stereochemistry as indicated in Table 1, below, or a pharmaceutically acceptable salt thereof. The ------ indicates a single bond or double bond.

Where a phosphorous atom has four substituents that differ, that phosphorous atom will be a stereocenter. SpSp/RpRp/SpRp/RpSp refers to the phosphorous stereochemisty as indicated.

TABLE 1

Compound #	n	Geometry (Trans, Cis, or Saturated)	X_1	X_2	stereochemical configuration (P_1)	stereochemical configuration (P_2)
1	1	Trans	SH	SH	S	R
2	1	Trans	SH	SH	R	R
3	1	Trans	SH	SH	S	S
4	1	Cis	SH	SH	R	R
5	1	Cis	SH	SH	S	R
6	1	Saturated	SH	SH	S	R
8	2	Trans	SH	SH	Undetermined	Undetermined
9	1	Trans	OH	OH	n/a	n/a
11	2	Trans	SH	SH	Undetermined	Undetermined
12	2	Trans	SH	SH	Undetermined	Undetermined

Examples may further provide a Compound of Formula (II):



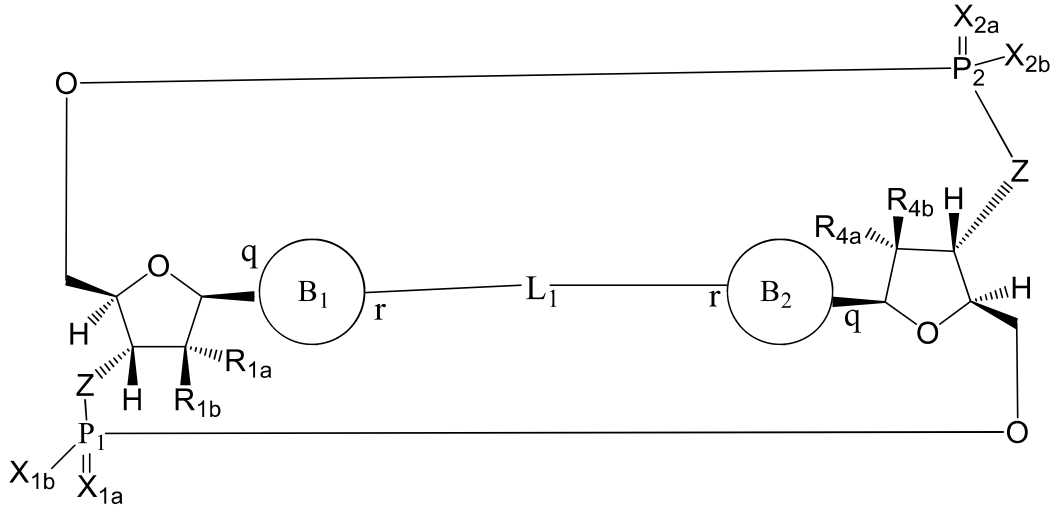
(II)

having substituents and stereochemistry as indicated in Table 2, below, or a pharmaceutically acceptable salt thereof. Where a phosphorous atom has four substituents that differ, that phosphorous atom will be a stereocenter.

TABLE 2

Compound #	R_{4a}	Geometric configuration	stereochemical configuration (P_1, P_2)
13	-OH	trans	S,R
14	-OH	trans	R,R
15	-F	trans	S,R
16	-F	trans	R,R

In one aspect, the present disclosure provides a compound of Formula (III):



(III)

or a pharmaceutically acceptable salt thereof, wherein

R_{1a} is selected from the group consisting of –H, -OH, and -F;

R_{1b} is selected from the group consisting of –H, -OH, and –F, wherein at least one of R_{1a} and R_{1b} is -H;

R_{4a} is selected from the group consisting of –H, –OH, and –F;

R_{4b} is selected from the group consisting of –H, –OH, and –F, wherein at least one of R_{4a} and R_{4b} is -H;

P_1 and P_2 each independently has an S or R stereochemical configuration;

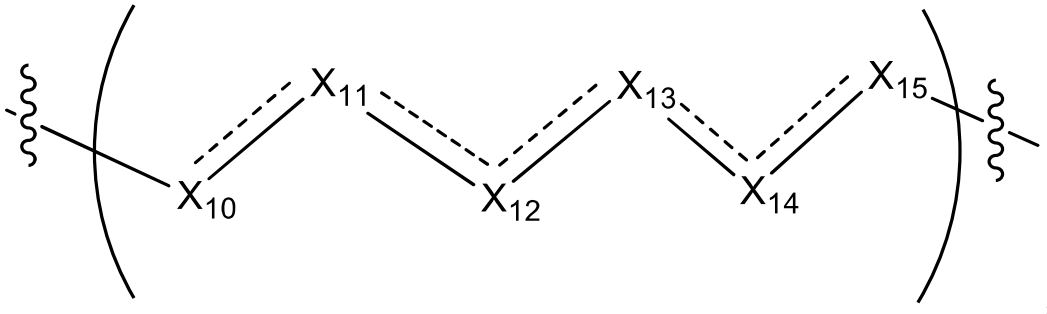
Z is –O– or –NH–;

X_{1a} and X_{2a} are the same or different and are independently selected from =O or =S;

X_{1b} and X_{2b} are the same or different and are independently selected from -OR_5 and -SR_5;

wherein R_5 is selected from the group consisting of –H, $C_{1\text{-}6}$alkyl, -C(O)$C_{1\text{-}6}$alkyl, and -$CH_2OC(O)OC_{1\text{-}6}$alkyl;

L_1 in formula (III) is four, five, or six carbons in length, and is



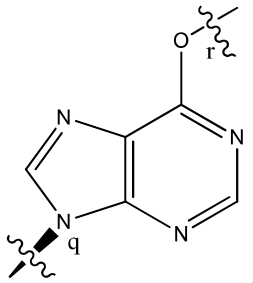
,

wherein ------ indicates a single bond, a double bond, or a triple bond and wherein (i) either 0 or 1 occurrence of ------ in L_1 indicates a triple bond; or (ii) 0, 1, or 2 occurrences of ------ in L_1 indicates a double bond, wherein geometry about each double bond is cis or trans; and (iii) wherein when 1 occurrence of ------ in L_1 indicates a triple bond, 0 occurrences of ------ in L_1 indicates a double bond; and (iv) wherein, when 2 occurrences of ------ in L_1 indicate a double bond, those double bonds are either adjacent bonds or alternating bonds;

wherein X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, and X_{15} are independently selected from a bond, $–CH_2–$, or –CH–, wherein the $–CH_2–$ or –CH– is unsubstituted or substituted by (i) –OH, (ii) –F, (iii) –Cl, (iv) $–NH_2$, or (v) -D, and when X_{10} or X_{15} is a bond, that bond is not a double bond or triple bond;

and wherein any two adjacent members of the group including X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, and X_{15} may optionally form, with additional atoms, a C_3 cycloalkyl or a C_3 heterocycloalkyl, said C_3 heterocycloalkyl including an N or O atom;

wherein B_1 and B_2 are independently selected from:



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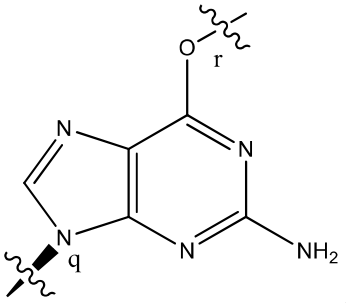

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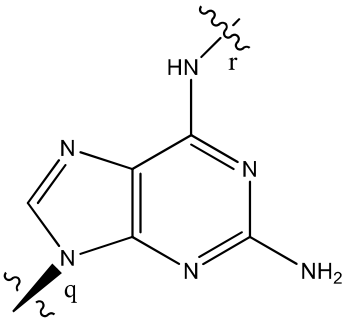

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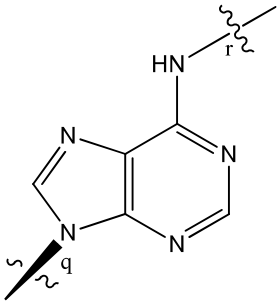

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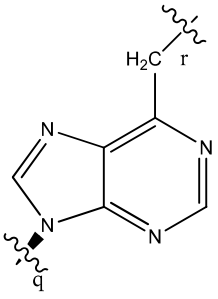
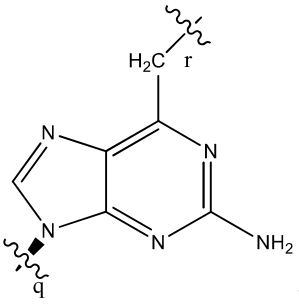
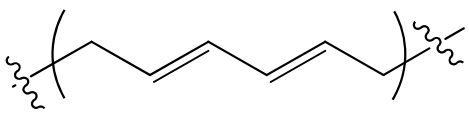
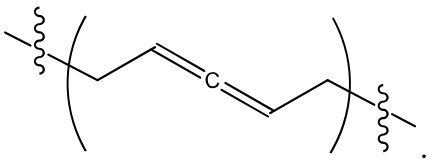


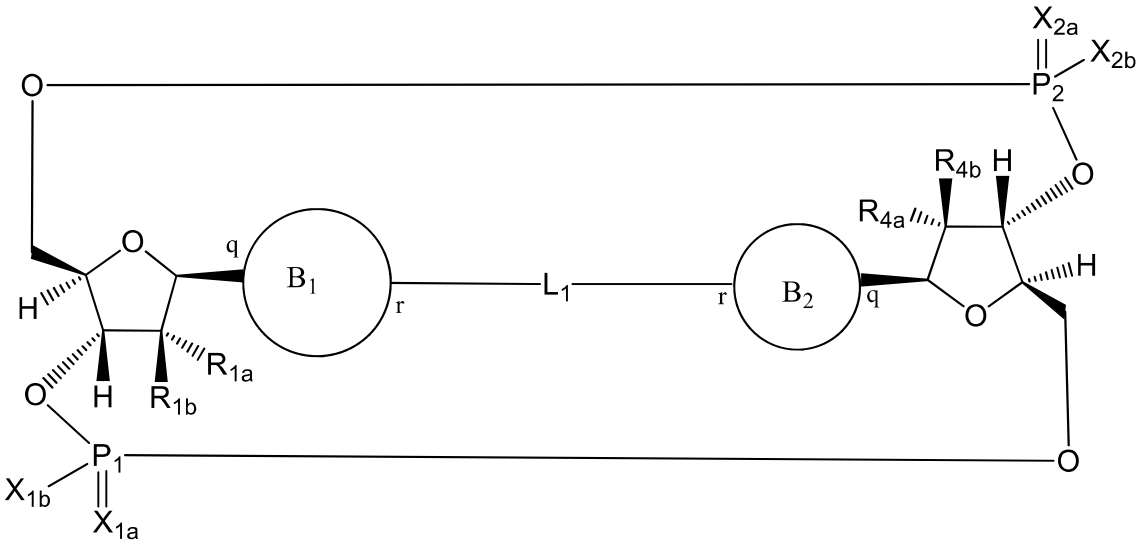
, and


where the bonds at points q and r on B_1 and B_2 are attached at points q and r on Formula (III).

In some examples where L_1 includes a triple bond or more than one double bond, L_1 may be, for example,

or



Examples may also provide a compound of Formula (III):



(III)

or a pharmaceutically acceptable salt thereof, wherein

R_{1a} is selected from the group consisting of –H and -F;

R_{1b} is selected from the group consisting of –H and –F, wherein R_{1a} and R_{1b} may not both be -F;

R_{4a} is selected from the group consisting of –H and -F;

R_{4b} is selected from the group consisting of –H and –F, wherein R_{4a} and R_{4b} may not both be –F;

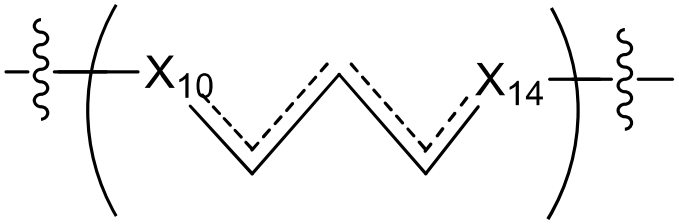
P_1 and P_2 each independently has an S or R stereochemical configuration;

X_{1a} and X_{2a} are the same or different and are independently selected from =O or =S;

X_{1b} and X_{2b} are the same or different and are independently selected from -OR_5 and -SR_5;

wherein R_5 is selected from the group consisting of –H, $C_{1\text{-}6}$alkyl, and -C(O)$C_{1\text{-}6}$alkyl;

L_1 in formula (III) is four or five carbons in length, and is

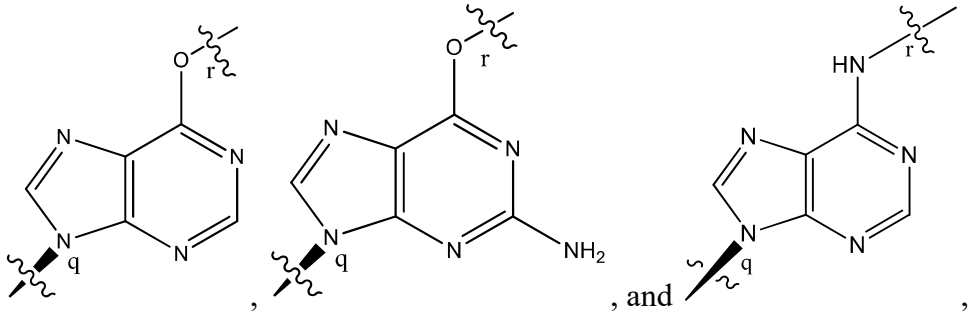


,

wherein ------ indicates a single bond or a double bond, and wherein either 0 or 1 occurrence of ------ in L_1 indicates a double bond, wherein geometry about the double bond is cis or trans;

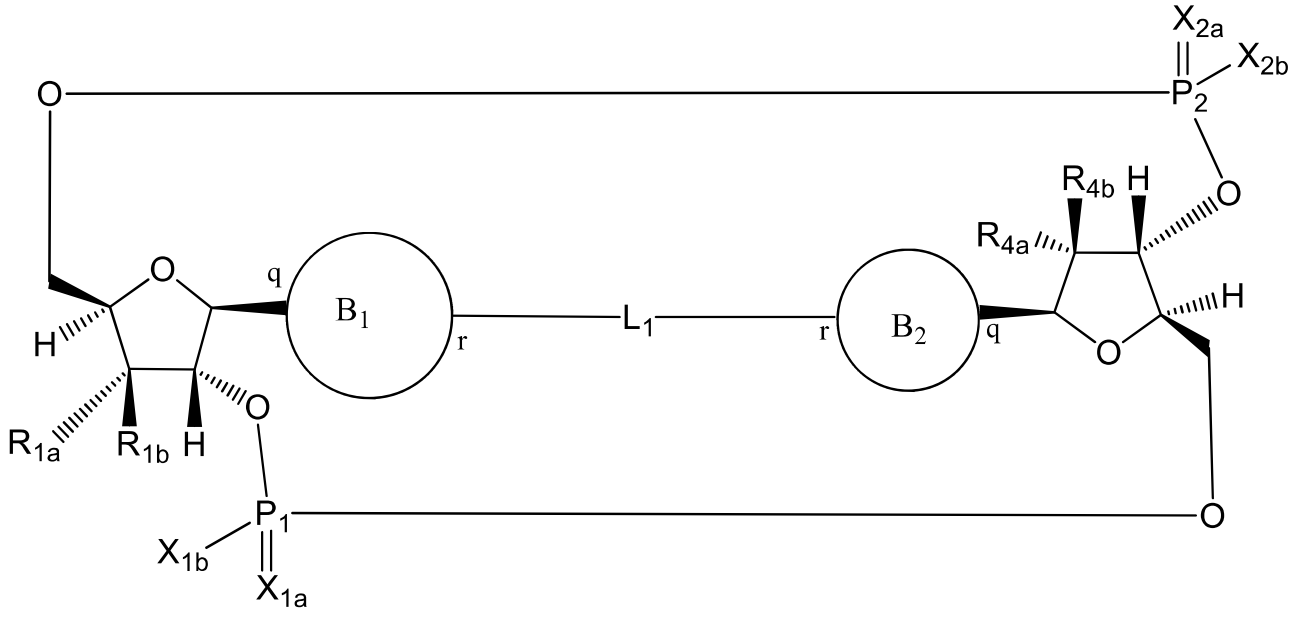
wherein X_{10} and X_{14} are independently selected from a bond, -CH-, or $–CH_2-$, and wherein, when X_{10} or X_{14} is a bond, that bond is not a double bond;

wherein B_1 and B_2 are independently selected from:



, , and , where the bonds at points q and r on B_1 and B_2 are attached at points q and r on Formula (III).

In another aspect, the present disclosure provides a compound of Formula (IV):



(IV)

or a pharmaceutically acceptable salt thereof, wherein

R_{1a} is selected from the group consisting of –H, -OH, and -F;

R_{1b} is selected from the group consisting of –H, -OH, and –F, wherein at least one of R_{1a} and R_{1b} is -H;

R_{4a} is selected from the group consisting of –H, -OH, and -F;

R_{4b} is selected from the group consisting of –H, -OH, and –F, wherein at least one of R_{4a} and R_{4b} is –H;

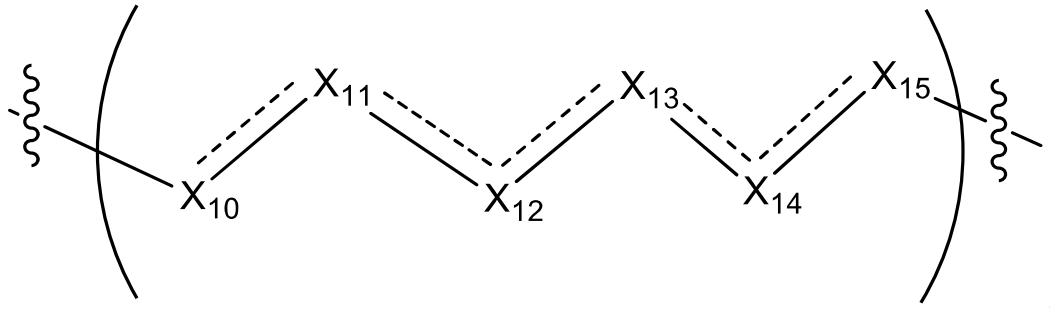
P_1 and P_2 each independently has an S or R stereochemical configuration;

X_{1a} and X_{2a} are the same or different and are independently selected from =O or =S;

X_{1b} and X_{2b} are the same or different and are independently selected from $-OR_5$ and $-SR_5$;

wherein R_5 is selected from the group consisting of –H, $C_{1\text{-}6}$alkyl, $-C(O)C_{1\text{-}6}$alkyl, and $-CH_2OC(O)OC_{1\text{-}6}$alkyl;

L_1 in formula (IV) is four, five, or six carbons in length, and is



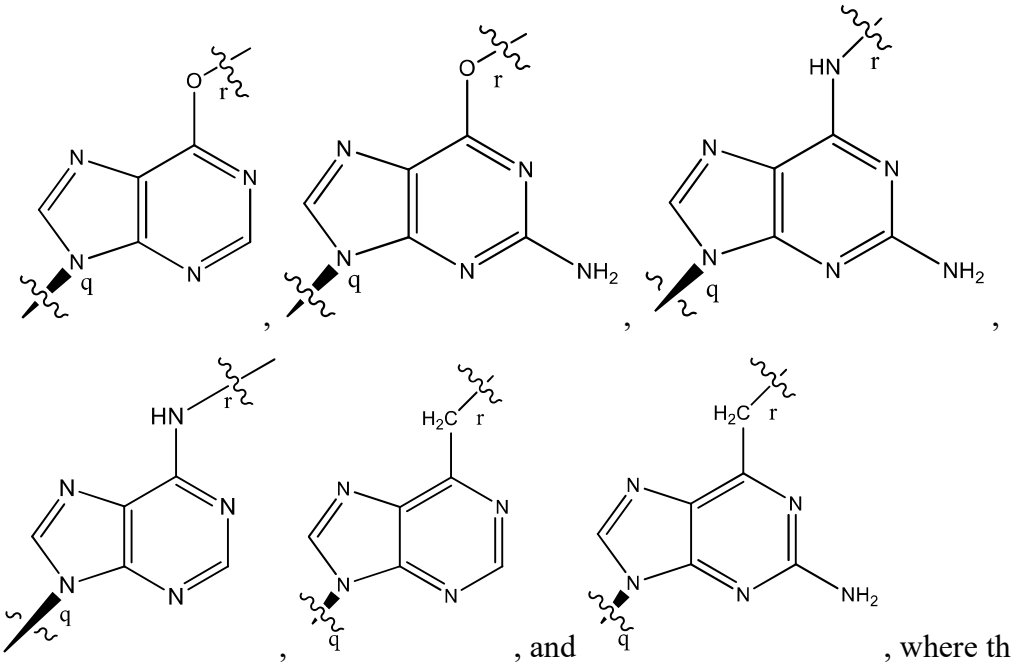
,

wherein ------ indicates a single bond, a double bond, or a triple bond and wherein (i) either 0 or 1 occurrence of ------ in L_1 indicates a triple bond; or (ii) 0, 1, or 2 occurrences of ------ in L_1 indicates a double bond, wherein geometry about each double bond is cis or trans; and (iii) wherein when 1 occurrence of ------ in L_1 indicates a triple bond, 0 occurrences of ------ in L_1 indicates a double bond; and (iv) wherein, when 2 occurrences of ------ in L_1 indicate a double bond, those double bonds are either adjacent bonds or alternating bonds;

wherein X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, and X_{15} are independently selected from a bond, $–CH_2–$, or –CH–, wherein the $–CH_2–$ or –CH– is unsubstituted or substituted by (i) –OH, (ii) –F, (iii) –Cl, (iv) $–NH_2$, or (v) -D, and when X_{10} or X_{15} is a bond, that bond is not a double bond or triple bond;

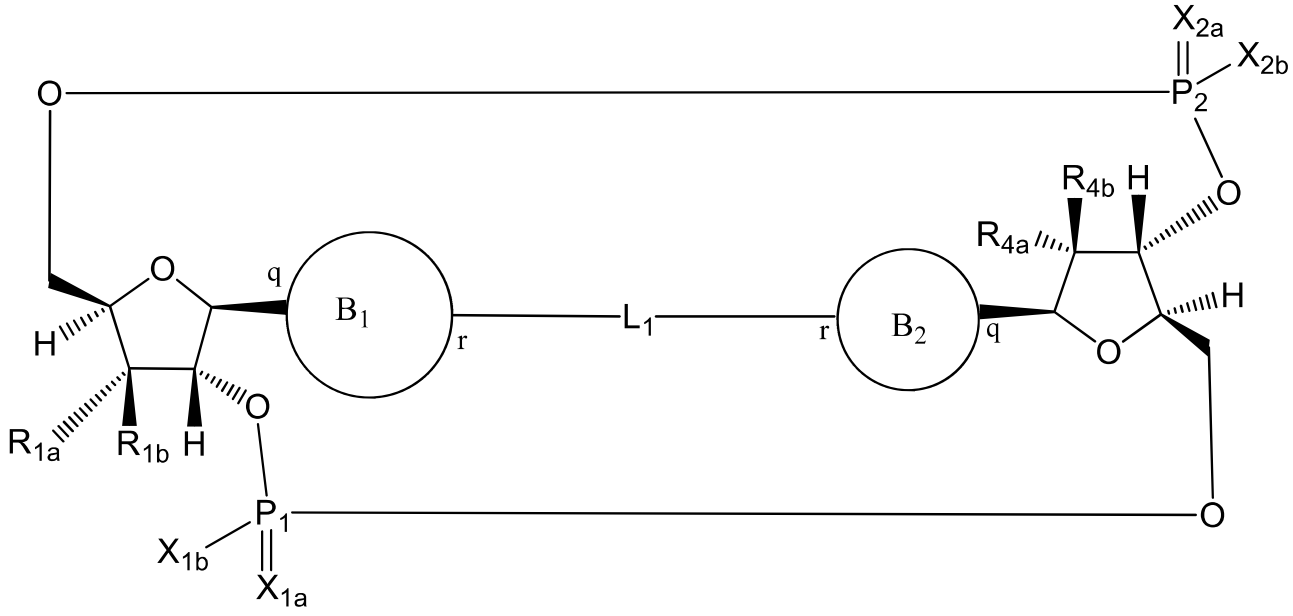
and wherein any two adjacent members of the group including X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, and X_{15} may optionally form, with additional atoms, a C_3 cycloalkyl or a C_3 heterocycloalkyl, said C_3 heterocycloalkyl including an N or O atom;

wherein B_1 and B_2 are independently selected from:



, and , where the bonds at points q and r on B_1 and B_2 are attached at points q and r on Formula (IV).

In another aspect, the present disclosur provides a compound of Formula (IV):



(IV)

or a pharmaceutically acceptable salt thereof, wherein

R_{1a} is selected from the group consisting of –H and -F;

R_{1b} is selected from the group consisting of –H and –F, wherein R_{1a} and R_{1b} may not both be -F;

R_{4a} is selected from the group consisting of –H and -F;

R_{4b} is selected from the group consisting of –H and –F, wherein R_{4a} and R_{4b} may not both be –F;

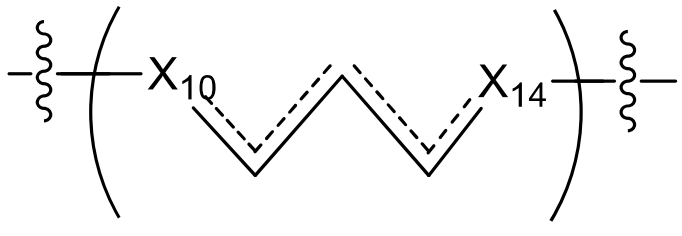
P_1 and P_2 each independently has an S or R stereochemical configuration;

X_{1a} and X_{2a} are the same or different and are independently selected from =O or =S;

X_{1b} and X_{2b} are the same or different and are independently selected from $-OR_5$ and $-SR_5$;

wherein R_5 is selected from the group consisting of –H, $C_{1\text{-}6}$alkyl, and $-C(O)C_{1\text{-}6}$alkyl;

L_1 in formula (IV) is four or five carbons in length, and is

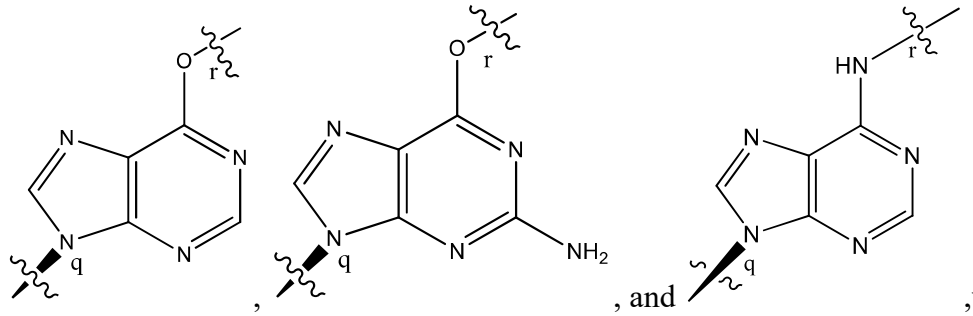


,

wherein ------ indicates a single bond or a double bond, and wherein either 0 or 1 occurrence of ------ in L_1 indicates a double bond, wherein geometry about the double bond is cis or trans;

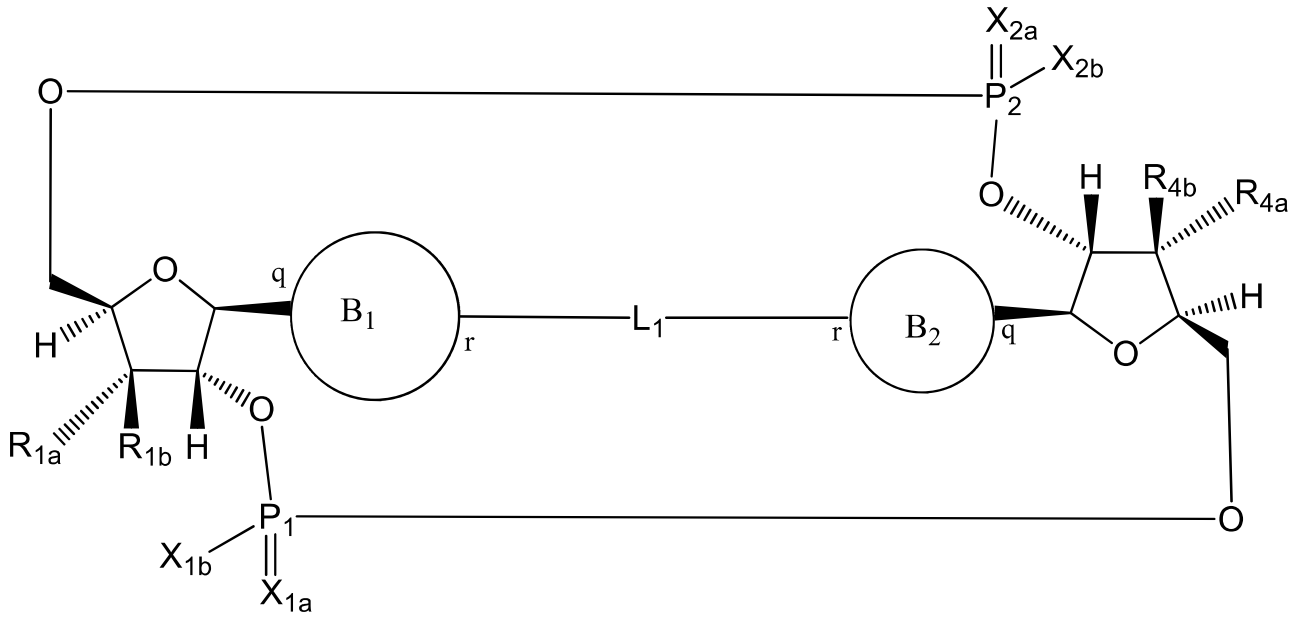
wherein X_{10} and X_{14} are independently selected from a bond, -CH-, or $–CH_2-$, and wherein, when X_{10} or X_{14} is a bond, that bond is not a double bond;

wherein B_1 and B_2 are independently selected from:



, , and ,where the bonds at points q and r on B_1 and B_2 are attached at points q and r on Formula (IV).

In another aspect, the present disclosure provides a compound of Formula (V):



(V)

or a pharmaceutically acceptable salt thereof, wherein

R_{1a} is selected from the group consisting of –H, -OH, and -F;

R_{1b} is selected from the group consisting of –H, -OH, and –F, wherein at least one of R_{1a} and R_{1b} is -H;

R_{4a} is selected from the group consisting of –H, -OH and -F;

R_{4b} is selected from the group consisting of –H, -OH, and –F, and wherein at least one of R_{4a} and R_{4b} is –H;

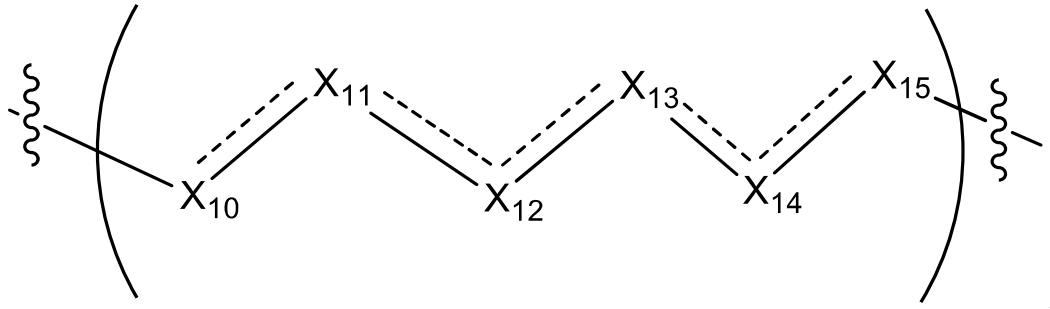
P_1 and P_2 each independently has an S or R stereochemical configuration;

X_{1a} and X_{2a} are the same or different and are independently selected from =O or =S;

X_{1b} and X_{2b} are the same or different and are independently selected from -OR_5 and -SR_5;

wherein R_5 is selected from the group consisting of –H, $C_{1\text{-}6}$alkyl, -C(O)$C_{1\text{-}6}$alkyl, and -$CH_2OC(O)OC_{1\text{-}6}$alkyl;

L_1 in formula (V) is four, five, or six carbons in length, and is

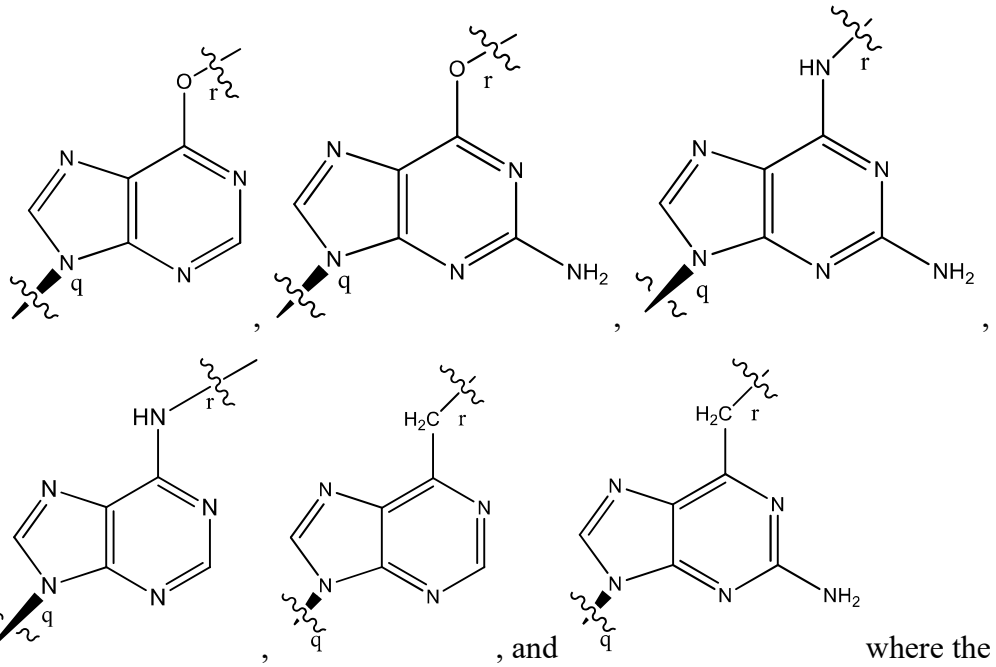


,

wherein ------ indicates a single bond, a double bond, or a triple bond and wherein (i) either 0 or 1 occurrence of ------ in L_1 indicates a triple bond; or (ii) 0, 1, or 2 occurrences of ------ in L_1 indicates a double bond, wherein geometry about each double bond is cis or trans; and (iii) wherein when 1 occurrence of ------ in L_1 indicates a triple bond, 0 occurrences of ------ in L_1 indicates a double bond; and (iv) wherein, when 2 occurrences of ------ in L_1 indicate a double bond, those double bonds are either adjacent bonds or alternating bonds;

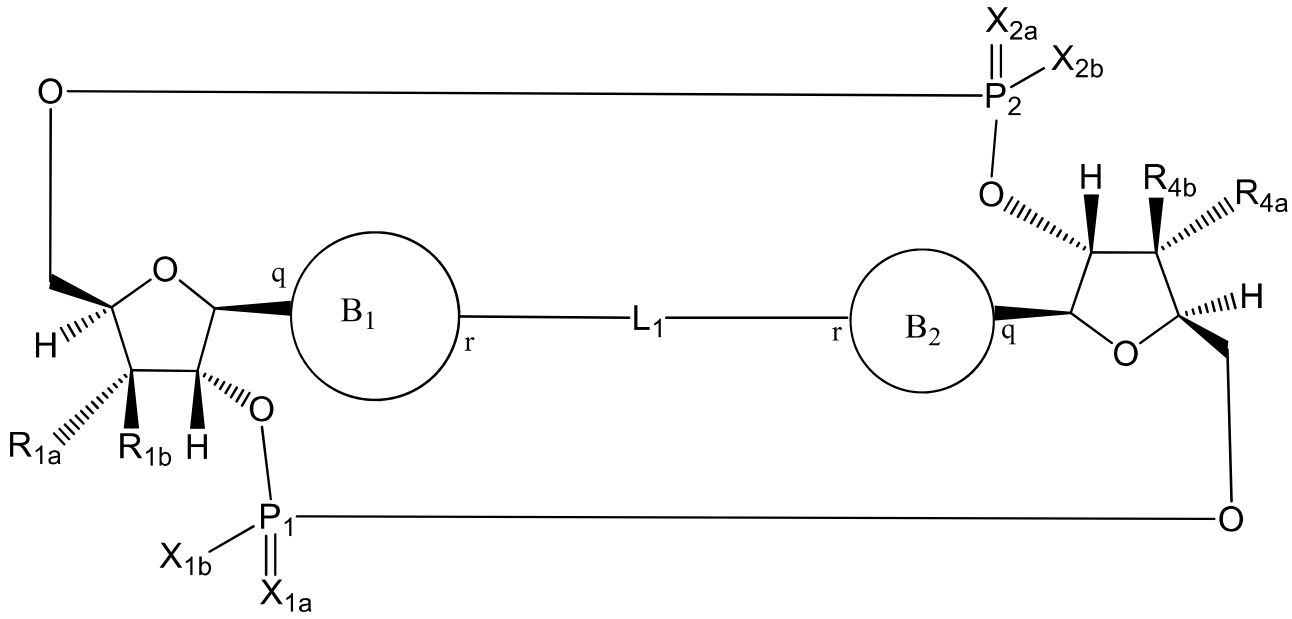
wherein X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, and X_{15} are independently selected from a bond, $–CH_2–$, or –CH–, wherein the $–CH_2–$ or –CH– is unsubstituted or substituted by (i) –OH, (ii) –F, (iii) –Cl, (iv) $–NH_2$, or (v) -D, and when X_{10} or X_{15} is a bond, that bond is not a double bond or triple bond;

and wherein any two adjacent members of the group including X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, and X_{15} may optionally form, with additional atoms, a C_3 cycloalkyl or a C_3 heterocycloalkyl, said C_3 heterocycloalkyl including an N or O atom;
wherein B_1 and B_2 are independently selected from:



, and where the bonds at points q and r on B_1 and B_2 are attached at points q and r on Formula (V).

In another aspect, the present disclosure provides a compound of Formula (V):



(V)

or a pharmaceutically acceptable salt thereof, wherein

R_{1a} is selected from the group consisting of –H and -F;

R_{1b} is selected from the group consisting of –H and –F, wherein R_{1a} and R_{1b} may not both be -F;

R_{4a} is selected from the group consisting of –H and -F;

R_{4b} is selected from the group consisting of –H and –F, wherein R_{4a} and R_{4b} may not both be –F;

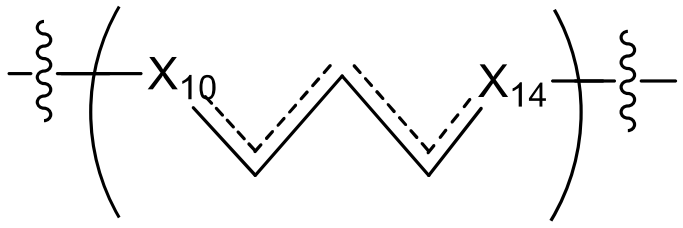
P_1 and P_2 each independently has an S or R stereochemical configuration;

X_{1a} and X_{2a} are the same or different and are independently selected from =O or =S;

X_{1b} and X_{2b} are the same or different and are independently selected from -OR_5 and -SR_5;

wherein R_5 is selected from the group consisting of –H, $C_{1\text{-}6}$alkyl, and -C(O)$C_{1\text{-}6}$alkyl;

L_1 in formula (V) is four or five carbons in length, and is

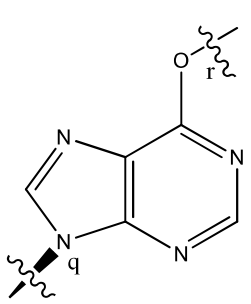


,

wherein ------ indicates a single bond or a double bond, and wherein either 0 or 1 occurrence of ------ in L_1 indicates a double bond, wherein geometry about the double bond is cis or trans;

wherein X_{10} and X_{14} are independently selected from a bond, -CH-, or $–CH_2-$, and wherein, when X_{10} or X_{14} is a bond, that bond is not a double bond;

wherein B_1 and B_2 are independently selected from:



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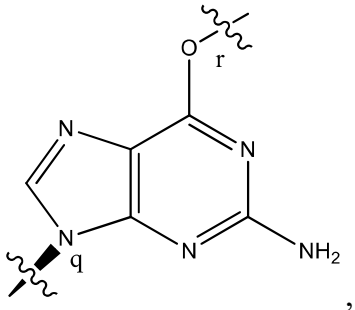

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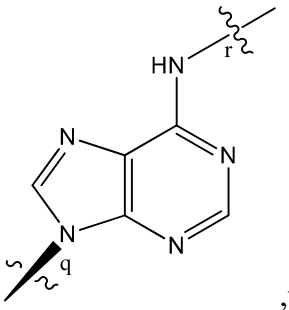
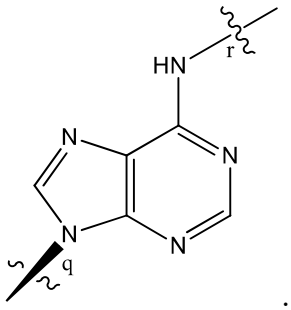
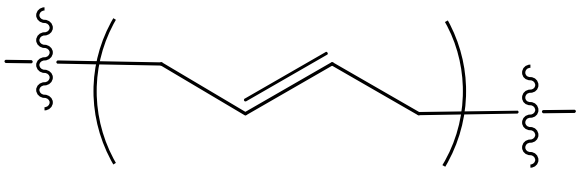


,where the bonds at points q and r on B_1 and B_2 are attached at points q and r on Formula (V).

In some examples of compounds and/or salts as reported in the Formulas above, (i) the stereochemical configuration of P_1 and P_2 are both R, the stereochemical configuration of P_1 is R and and P_2 is S, or the stereochemical configuration of P_1 is S and P_2 is R; (ii) one occurrence of ------ in L_1 indicates a double bond, wherein geometry about the double bond is trans; and (iii) Z is –O–.

Further examples of compounds and/or salts as reported in the Formulas above may be found in other aspects herein. For example, some examples provide a compound or pharmaceutically acceptable salt wherein R_{1a} and R_{4a} are each –F. In some examples R_{1b} and R_{4b} are each –F. In some examples B_1 and B_2 are each


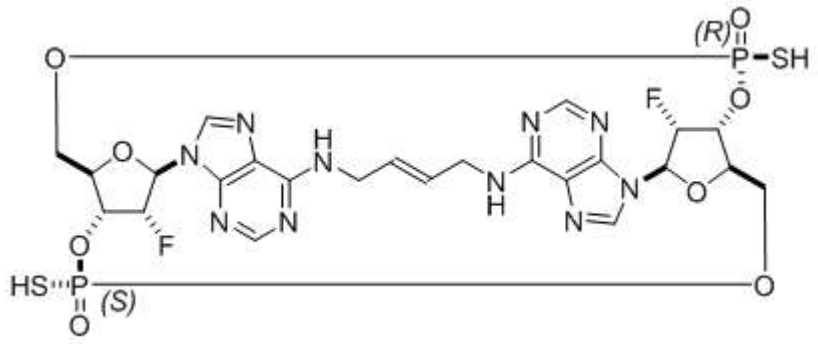
. In some examples X_{1a} and X_{2a} are both =O, and X_{1b} and X_{2b} are both –SH. In some examples L_1 is


.

In some examples the linker is four carbons long. In some examples the linker is five carbons long.

In another aspect, the present disclosure provides a compound selected from the group

consisting of: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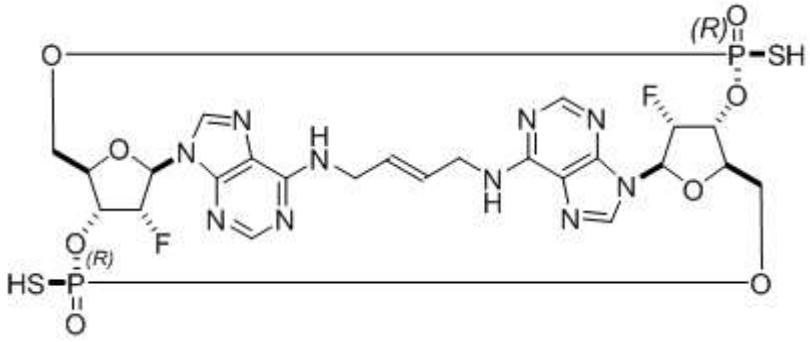
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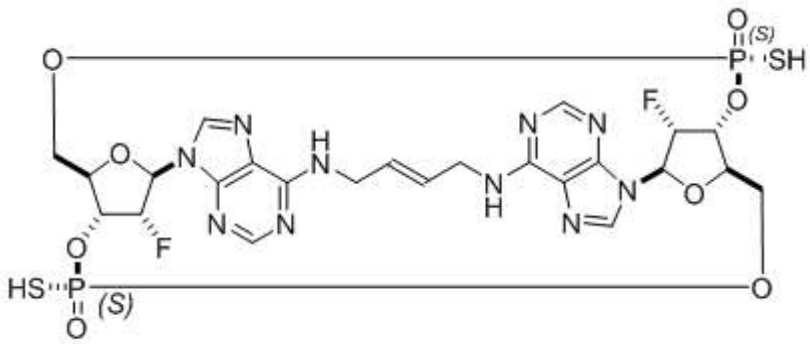
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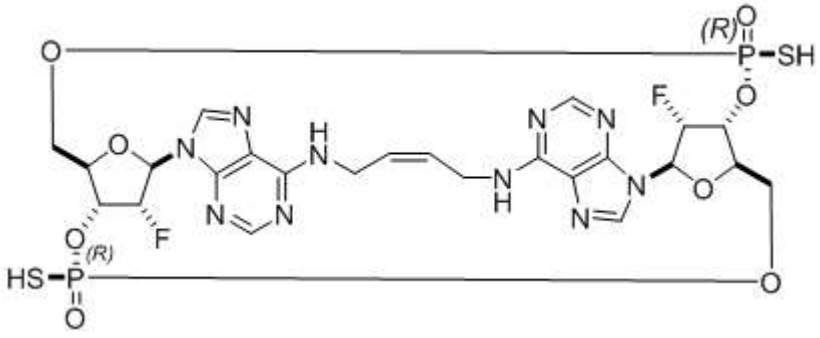
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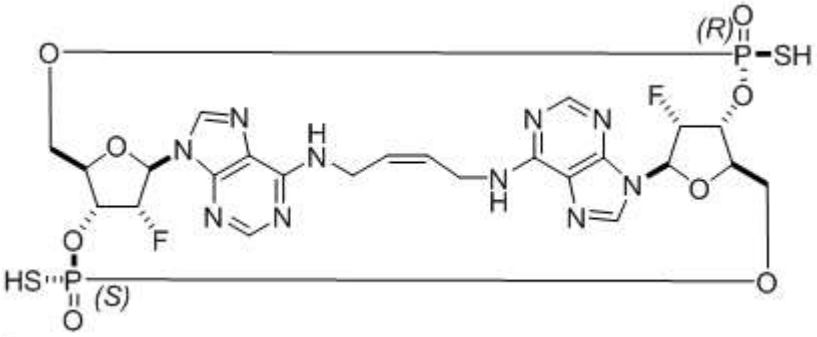
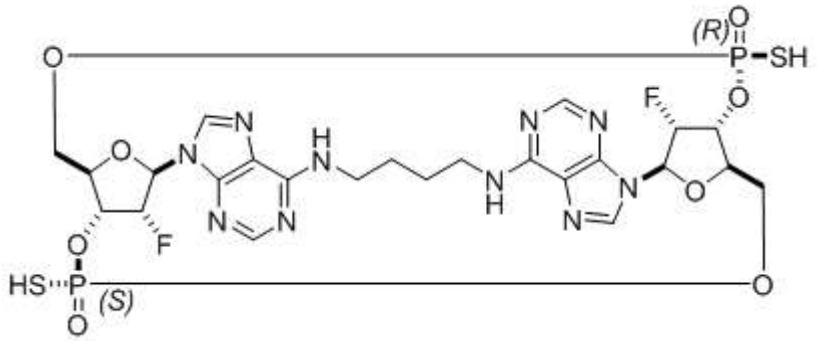
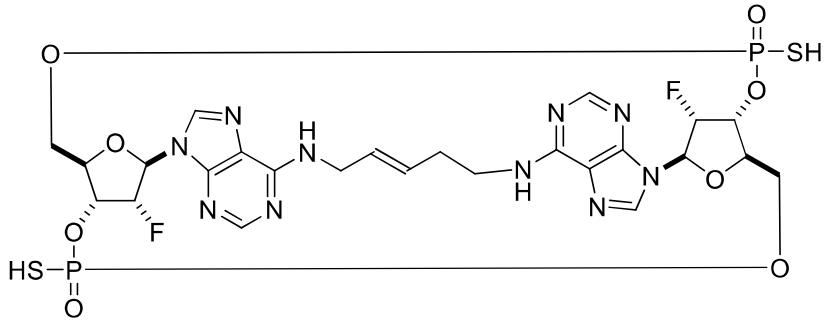
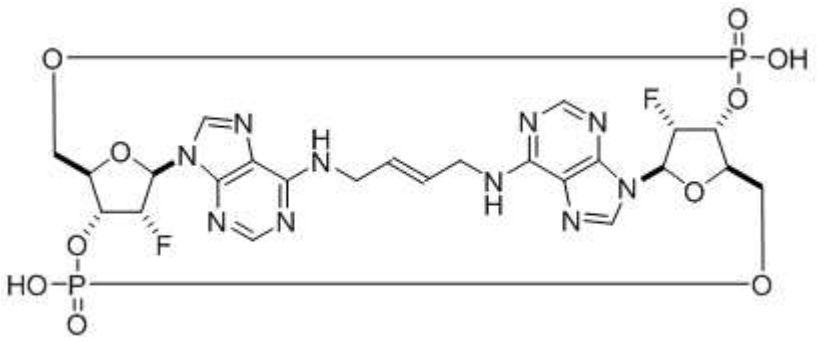
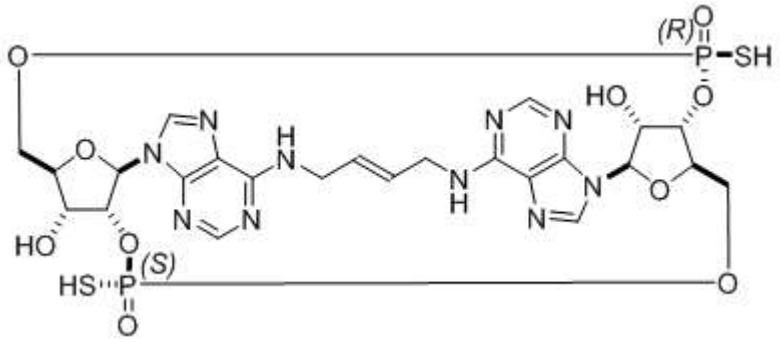

(R)
SH
HS
(S)
,


(R)
SH
HS
(S)
,


SH
HS
,


OH
HO
,



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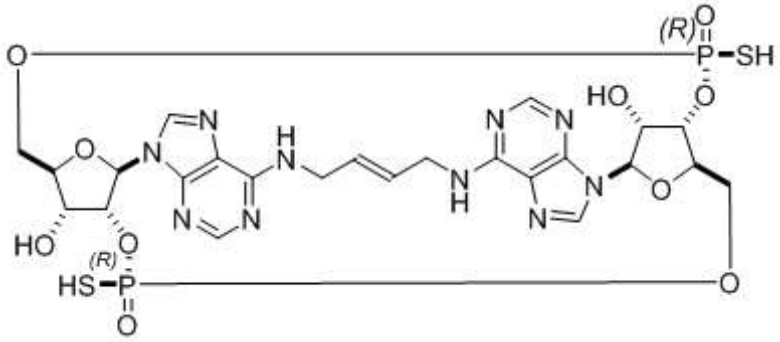

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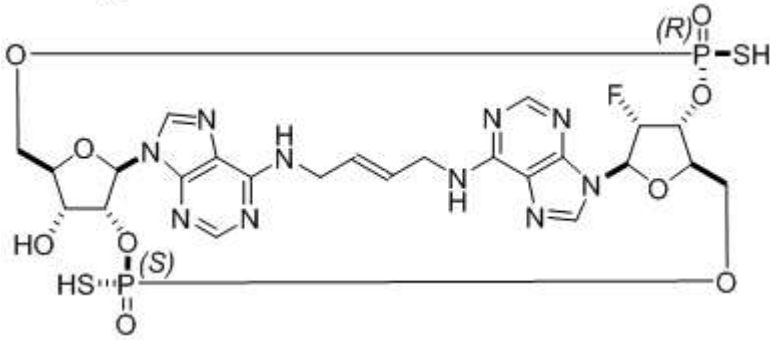

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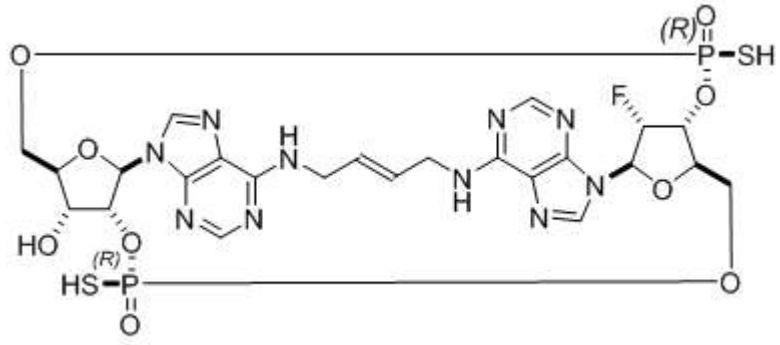

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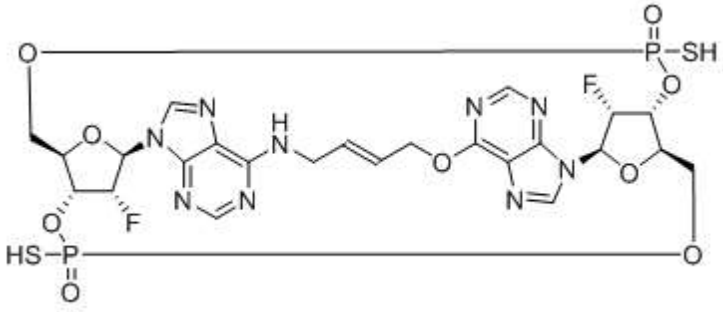

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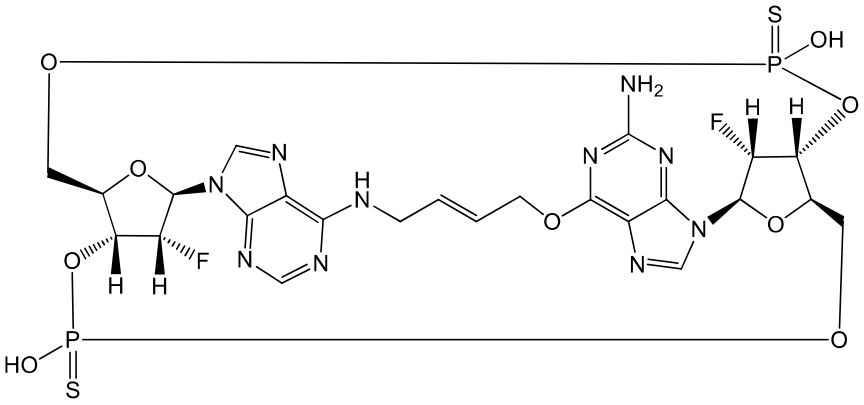

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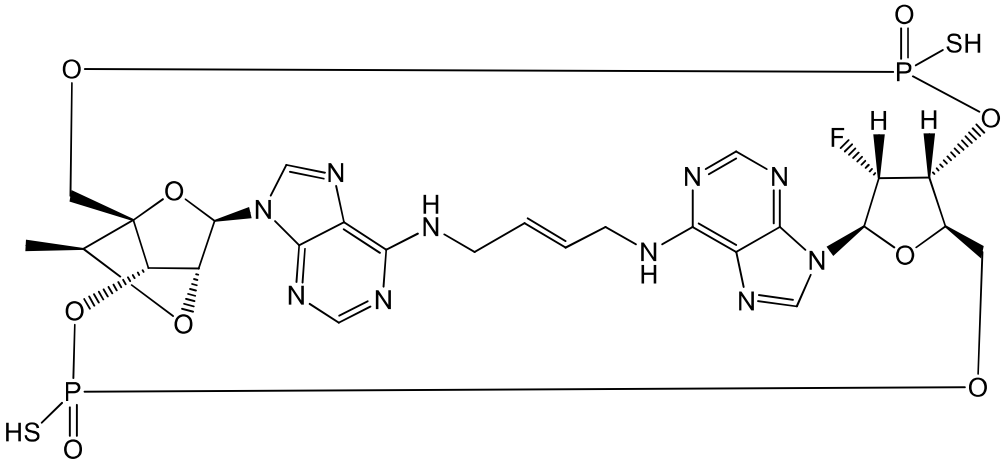

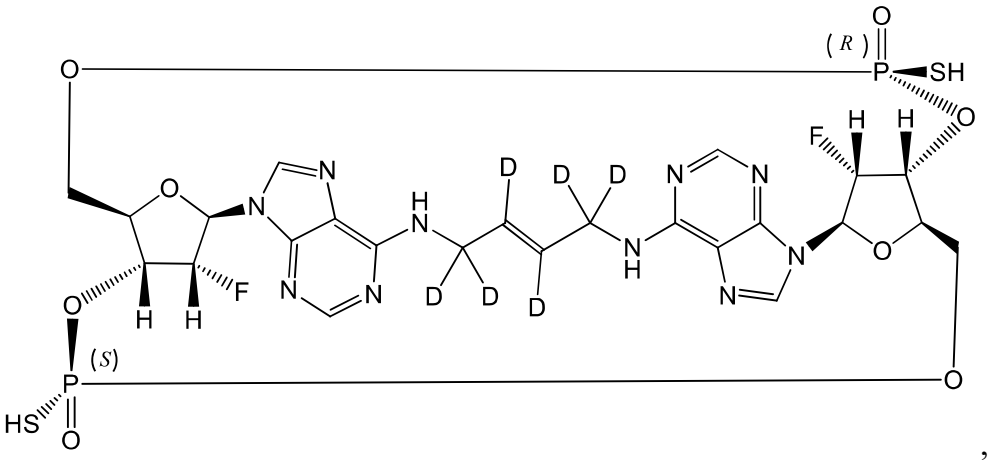

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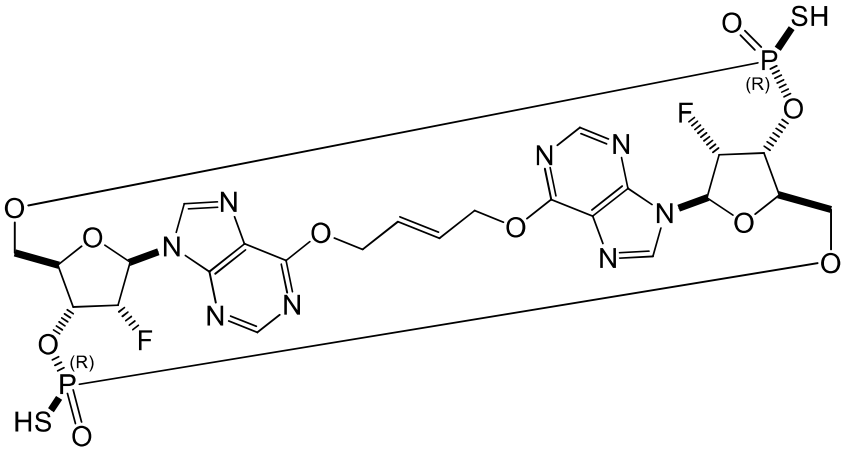

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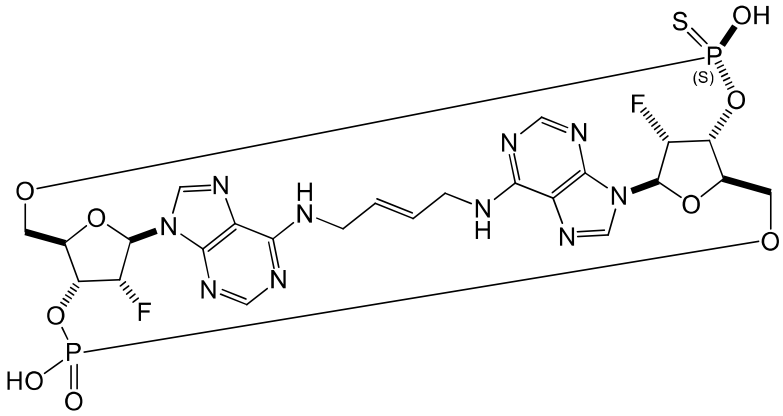

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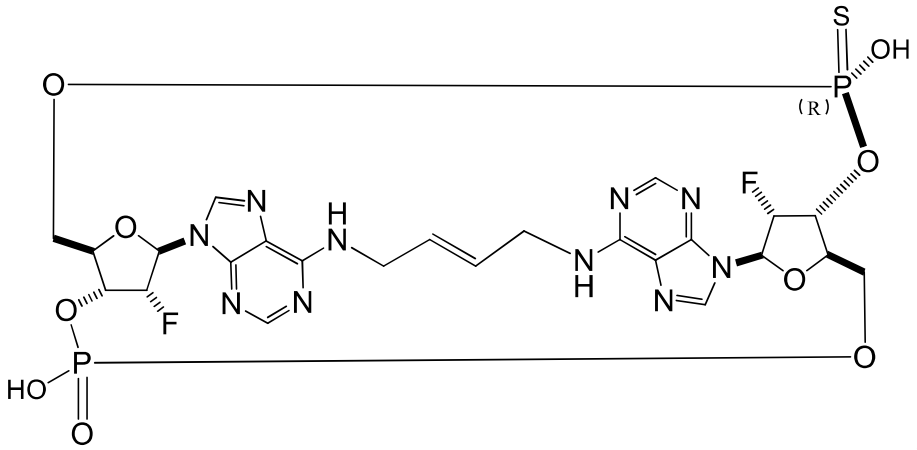

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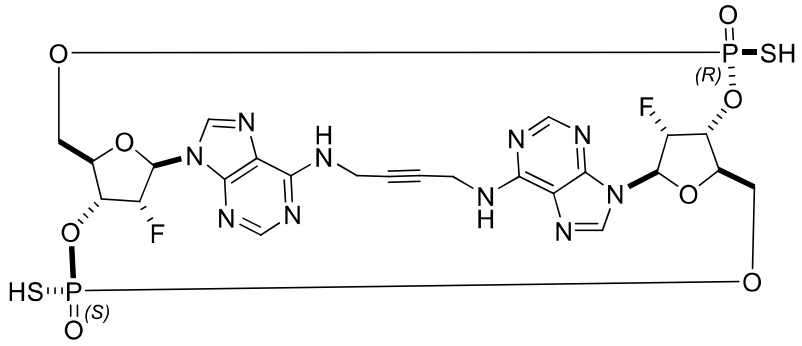

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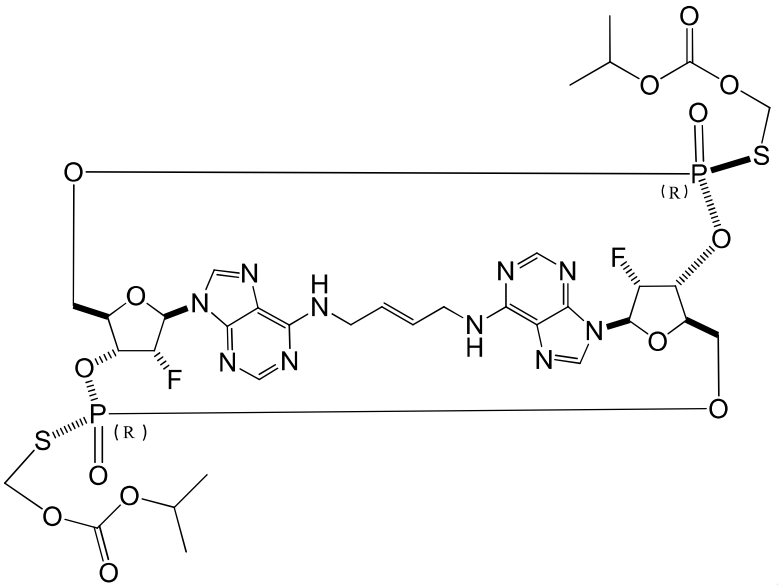

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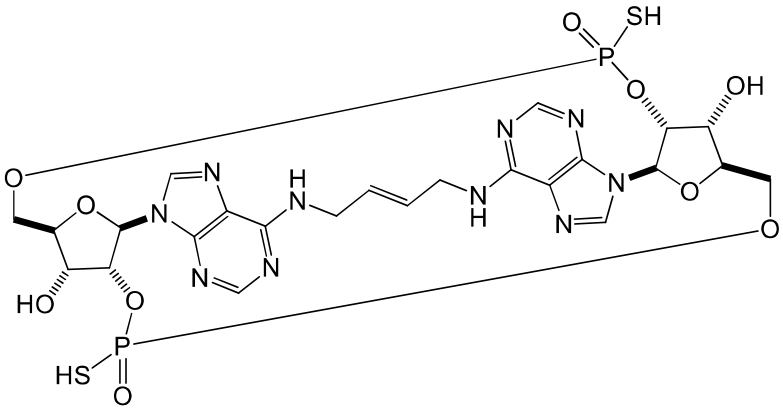

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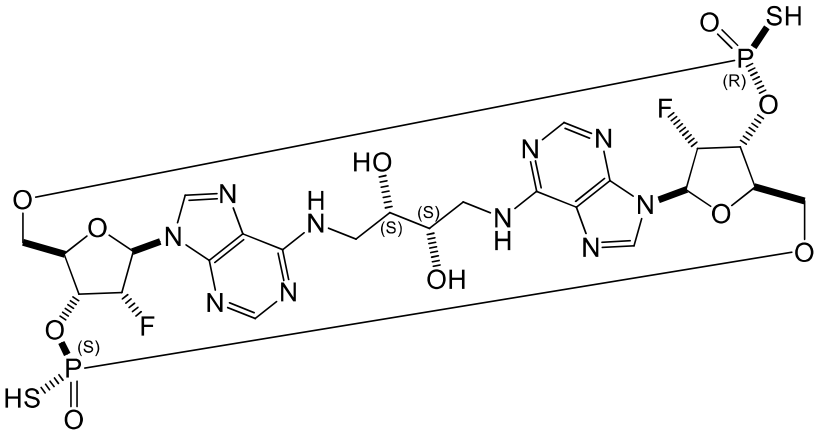

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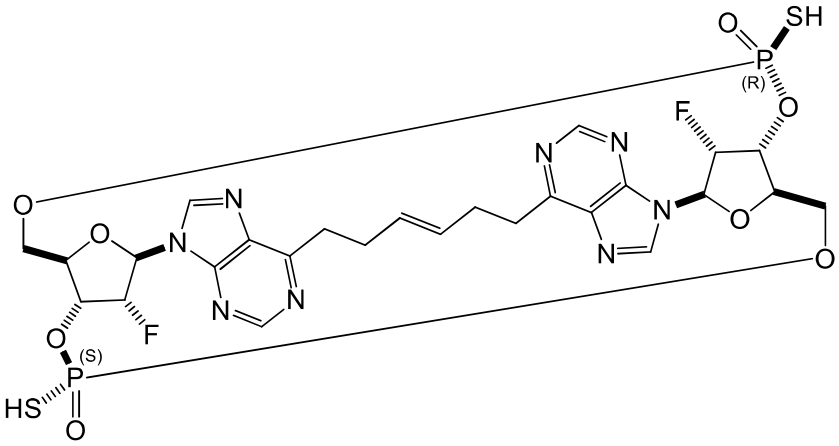

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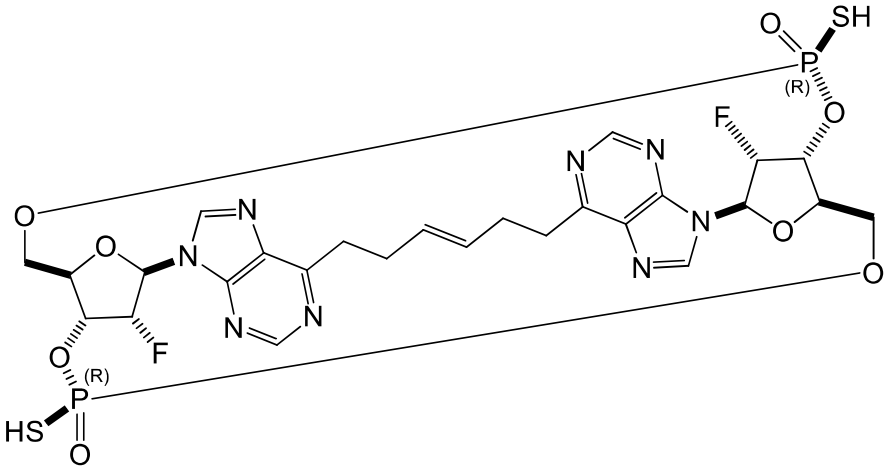

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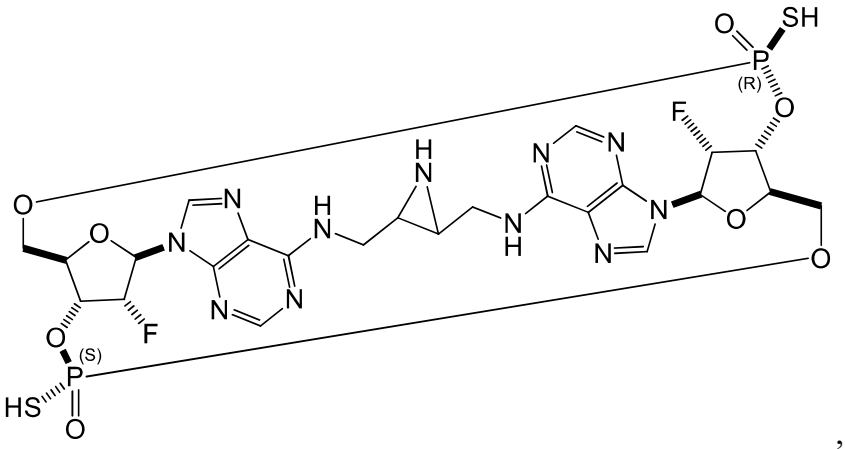

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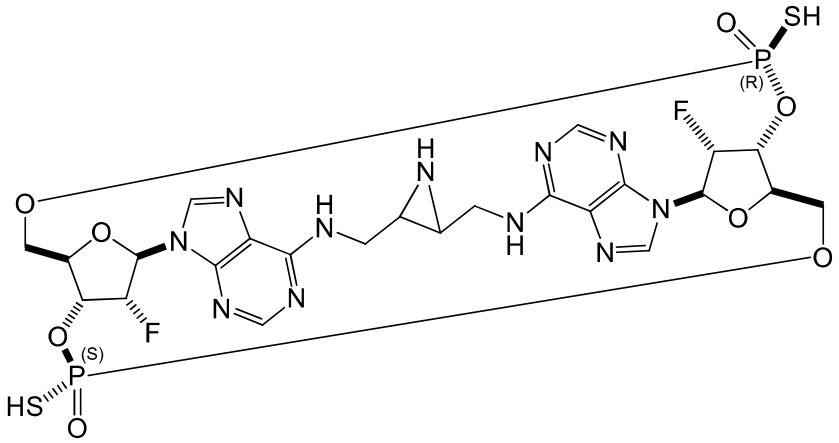

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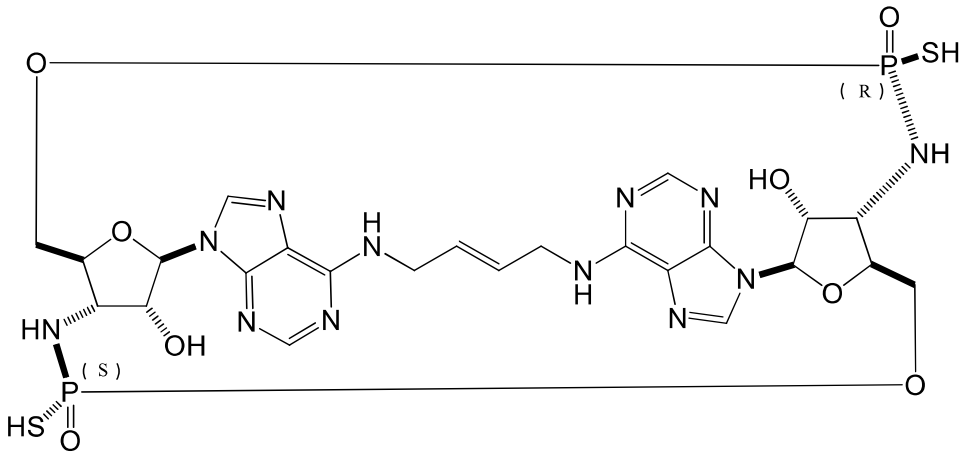

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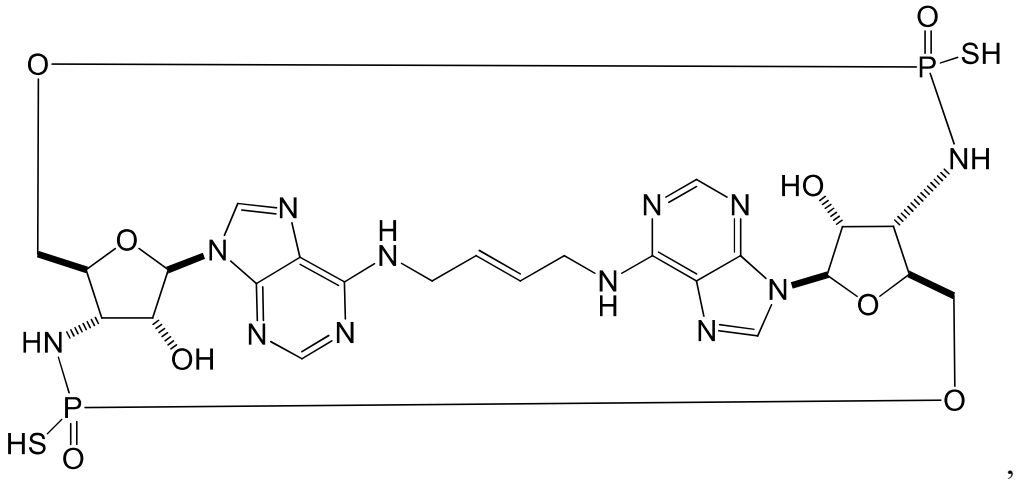
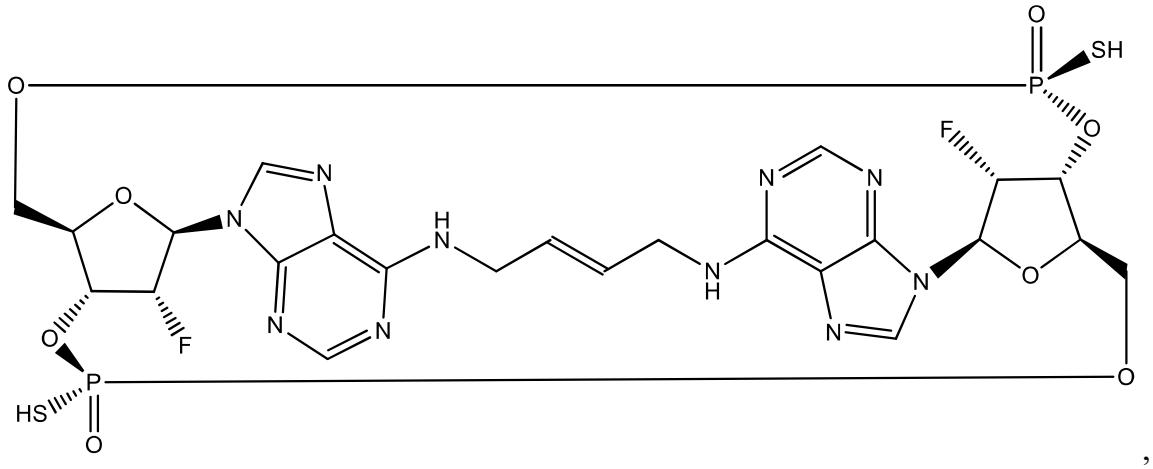


,

or a pharmaceutically acceptable salt thereof.

Examples may provide a compound or pharmaceutically acceptable salt with one or more of (i) an EC_{50} value below 100 micromolar in a cell reporter assay expressing STING HAQ genetic variant; (ii) an EC_{50} value below 100 micromolar in reporter cells expressing human STING AQ variant; (iii) an EC_{50} value below 100 micromolar in reporter cells expressing human STING WT variant; and (iv) an EC_{50} value below 100 micromolar in reporter cells expressing human STING REF variant. Another aspect of the disclosure

provides a compound having the following structure:



,

or a pharmaceutically acceptable salt thereof.

In yet another aspect, the present disclosure refers to a pharmaceutical composition comprising a compound as described herein or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In yet another aspect, the present disclosure refers to a compound or pharmaceutically acceptable salt as described herein, or pharmaceutical composition as described herein for use in therapy. In yet another aspect, the present disclosure refers to use of a compound or pharmaceutically acceptable salt as described herein for preparation of a pharmaceutical composition for treating cancer. In yet another aspect, the present disclosure refers to use of a compound or pharmaceutically acceptable salt as described herein, or pharmaceutical composition as described herein, in a treatment for cancer.

In yet another aspect, the present disclosure refers to use of a compound, a pharmaceutically acceptable salt, or a pharmaceutical composition as described herein in the manufacture of a medicament for treating cancer, the use comprising that the compound, pharmaceutically acceptable salt or pharmaceutical composition is to be administered to an individual identified as having a cancer treatable by the compound, pharmaceutically acceptable salt or pharmaceutical composition.

In yet another aspect, the present disclosure refers to use of a compound, pharmaceutically acceptable salt or pharmaceutical composition as described herein in the manufacture of a medicament for treating cancer in a patient having REF STING allele. In yet another aspect, the present disclosure refers to use of a compound, pharmaceutically acceptable salt or pharmaceutical composition as described herein in the manufacture of a medicament for treating cancer in a patient having WT STING allele. In yet another aspect, the present disclosure refers to use of a compound, pharmaceutically acceptable salt or

pharmaceutical composition as described herein in the manufacture of a medicament for treating cancer in a patient having AQ STING allele. In yet another aspect, the present disclosure refers to use of a compound, pharmaceutically acceptable salt or pharmaceutical composition as described herein in the manufacture of a medicament for treating cancer in a patient having HAQ STING allele.

Further examples may provide a pharmaceutically acceptable salt of a compound reported herein, wherein the salt is a diammonium salt. Further examples may provide compounds reported herein as a triethyl amine (TEA) salt. Further examples may provide a pharmaceutical composition including a compound or salt as reported herein and a pharmaceutically acceptable excipient.

Examples may provide a method of treating cancer comprising administering to a patient a compound, pharmaceutically acceptable salt, or pharmaceutical composition as reported herein.

Use of a compound or pharmaceutically acceptable salt thereof as reported herein for preparation of a pharmaceutical composition for treating cancer.

Examples may provide use of a compound, pharmaceutically acceptable salt, or pharmaceutical composition reported herein in a treatment for cancer.

Examples may provide a method of treating cancer comprising identifying an individual having a cancer treatable by a compound, a pharmaceutically acceptable salt, or a pharmaceutical composition reported herein; and administering to said individual a pharmaceutically effective amount of the compound, pharmaceutically acceptable salt or pharmaceutical composition by which the cancer has been identified as treatable.

In some examples the individual is identified as having a cancer treatable by a compound, pharmaceutically acceptable salt or pharmaceutical composition reported herein by a presence of a REF STING variant allele in the patient.

Some examples provide a method of treating cancer in a patient having REF STING allele comprising administering to said patient a compound, pharmaceutically acceptable salt or pharmaceutical composition as reported herein.

Some examples provide a method of treating cancer in a patient having WT STING allele comprising administering to said patient a compound, pharmaceutically acceptable salt or pharmaceutical composition as reported herein.

Some examples provide a method of treating cancer in a patient having AQ STING allele comprising administering to said patient a compound, pharmaceutically acceptable salt or pharmaceutical composition as reported herein.

Some examples provide a method of treating cancer in a patient having HAQ STING allele comprising administering to said patient a compound, pharmaceutically acceptable salt or pharmaceutical composition as reported herein.

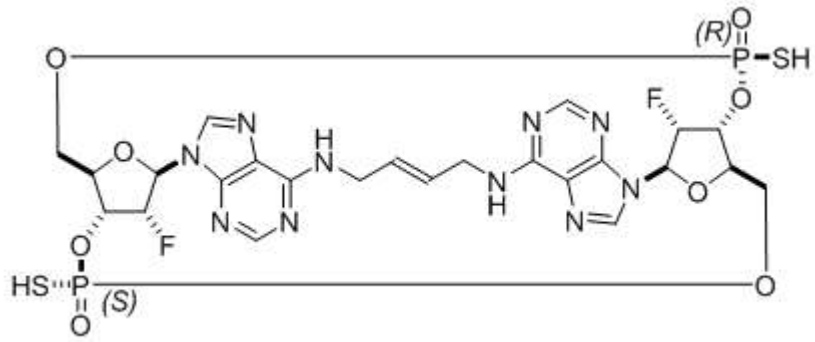
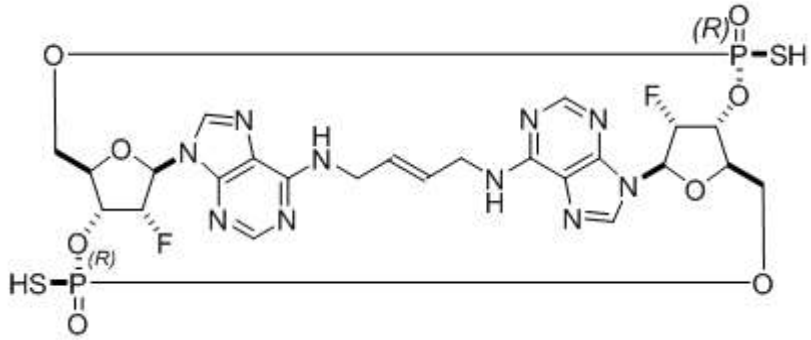
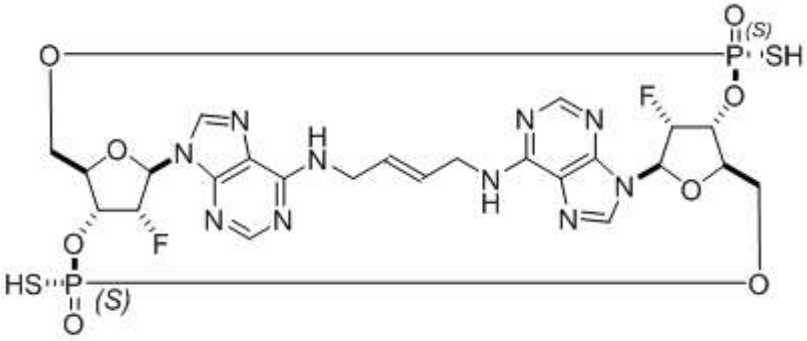
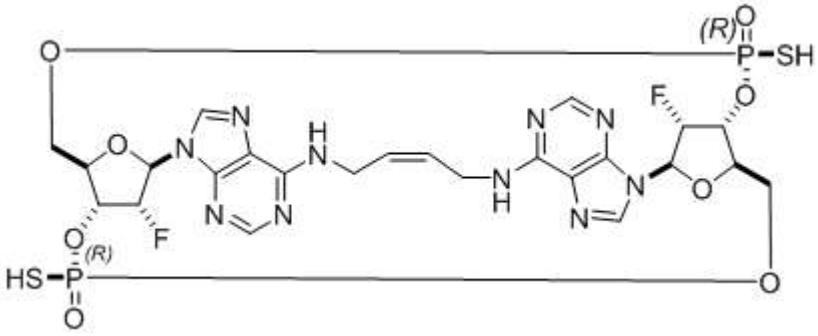
In some examples the cancer is selected from the group consisting of lymphoma, melanoma, colorectal cancer, breast cancer, acute myeloid leukemia, colon cancer, liver cancer, prostate cancer, pancreatic cancer, renal cancer, and glioma. In some examples the cancer is metastatic.

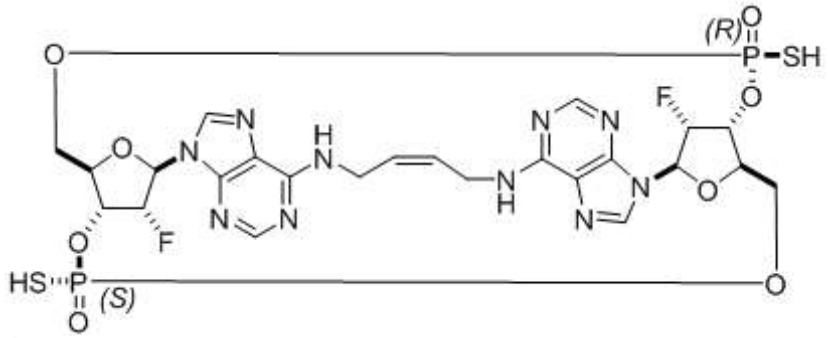
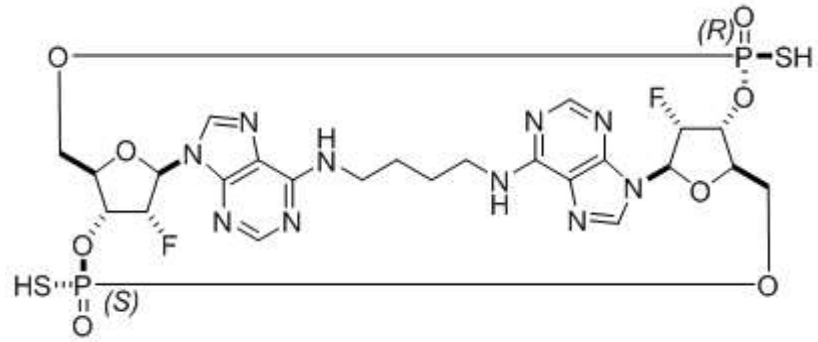
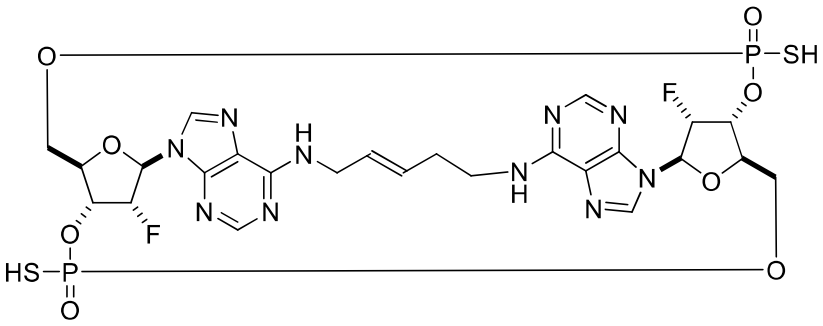
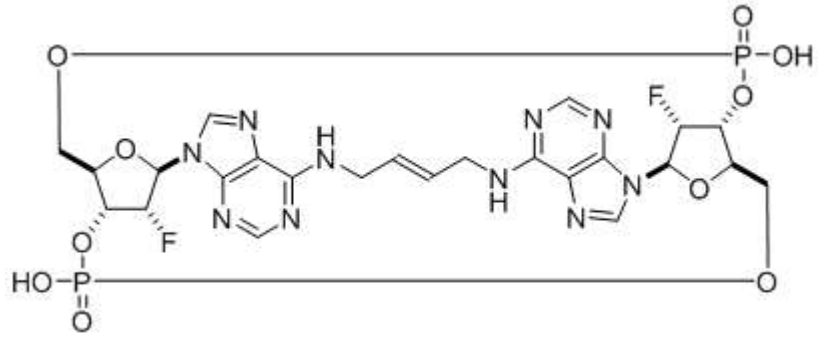
In some examples of compounds of formulas presented herein, one of the bonds in L_1 is a double bond. In further examples that double bond has a trans geometry. In further examples L_1 is saturated. In certain examples L_1 includes five carbon atoms. In other examples L_1 includes 4 carbon atoms.

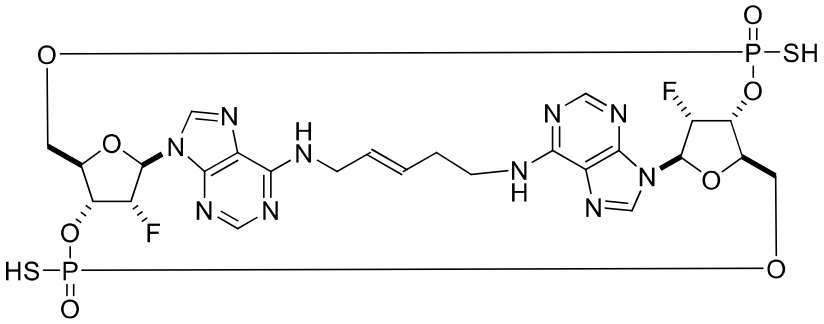
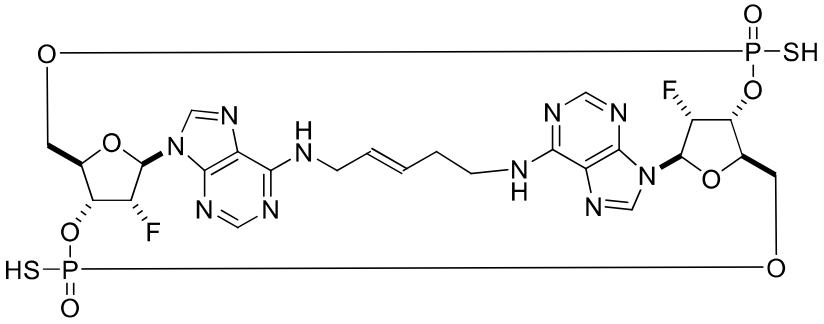
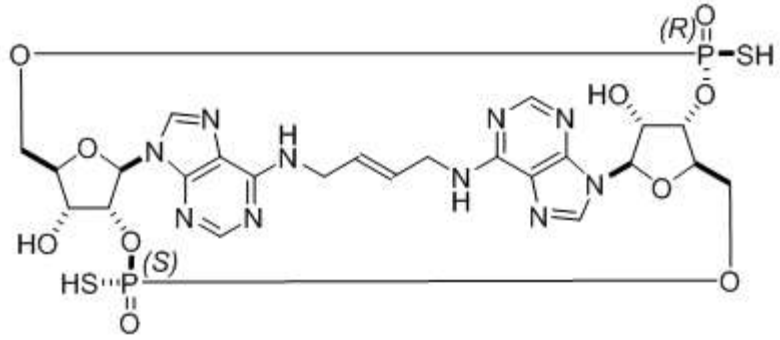
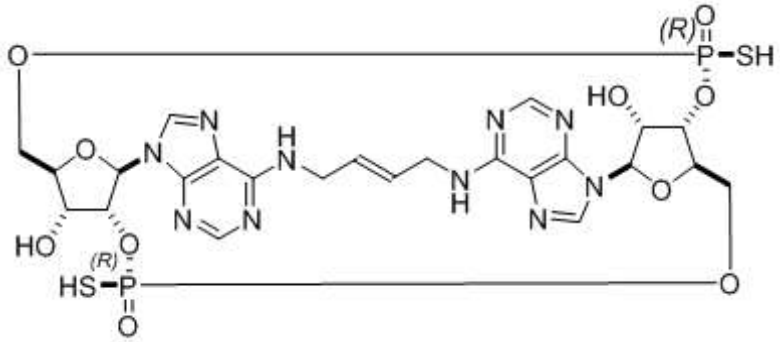
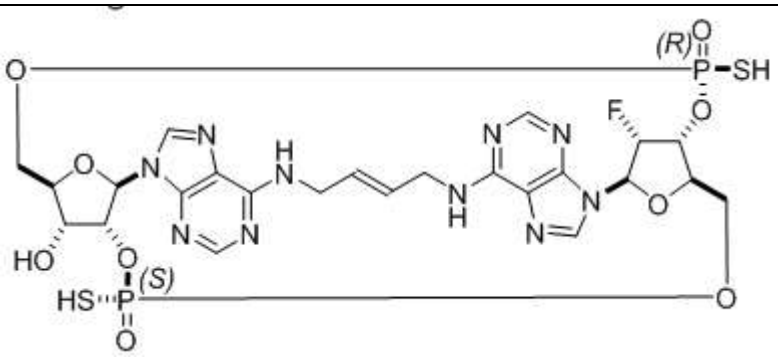
Examples may further provide mixtures of compounds as reported herein, including mixtures of stereoisomers of these compounds. For example, a mixture may be provided of Compound 11 and Compound 12, or a mixture may be provided of Compound 2 and Compound 4. Of course, these are not limiting examples and other mixtures are possible.

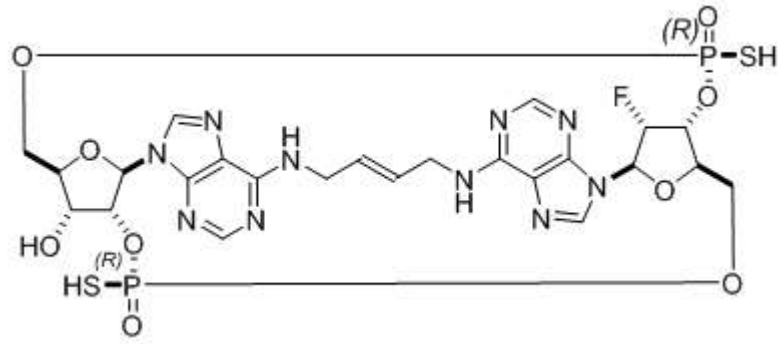
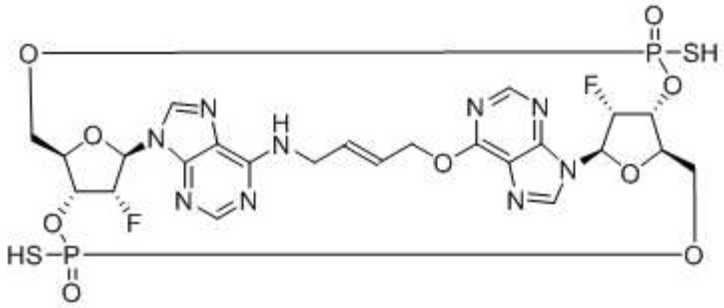
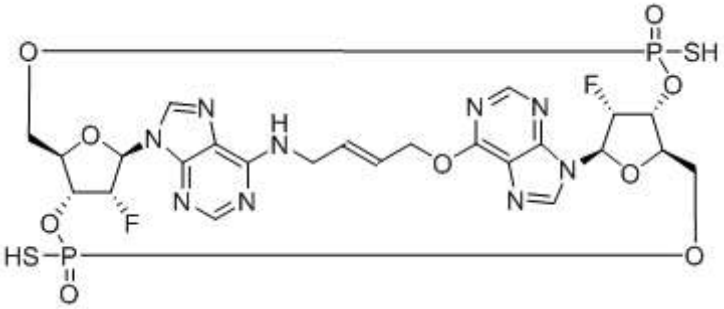
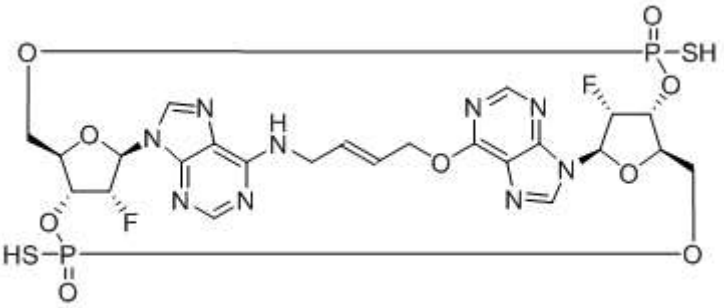
Particular examples are set forth in Table 3 below.

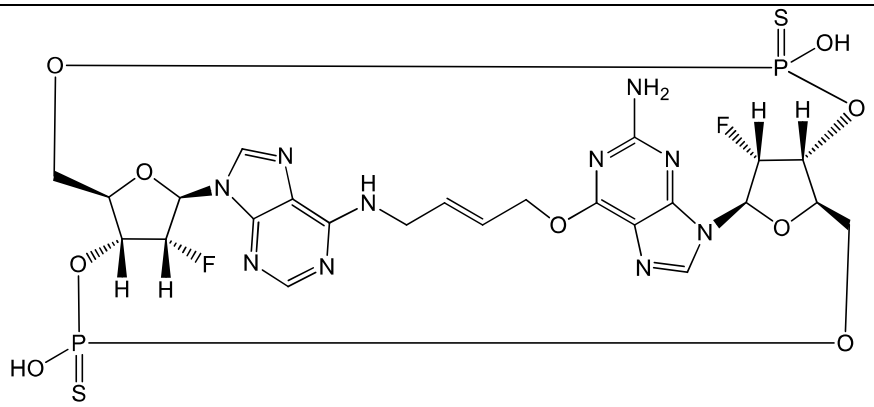
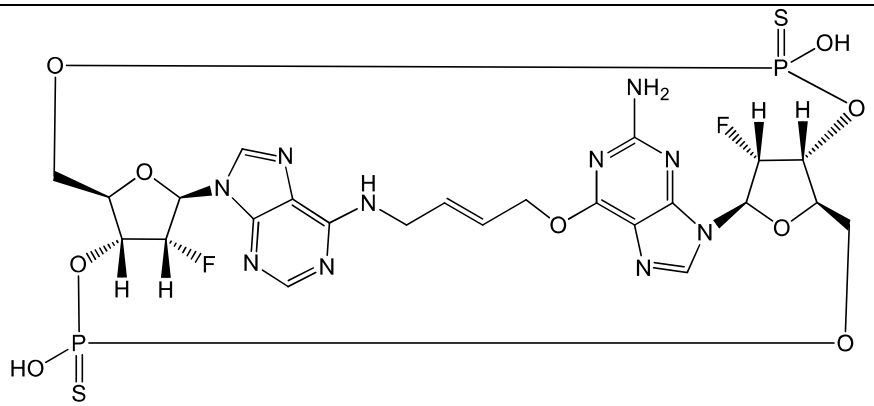
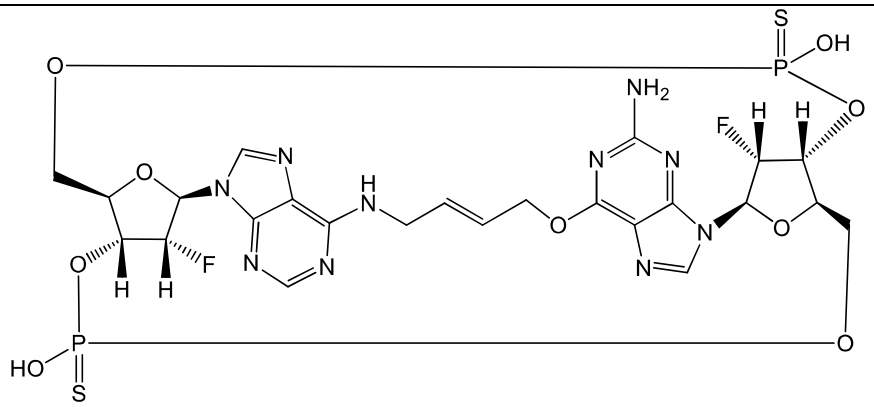
TABLE 3

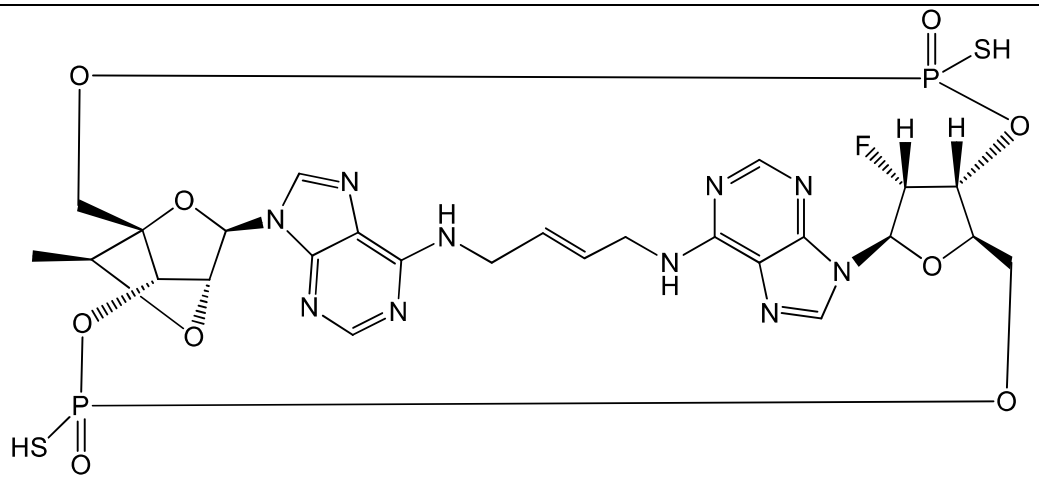
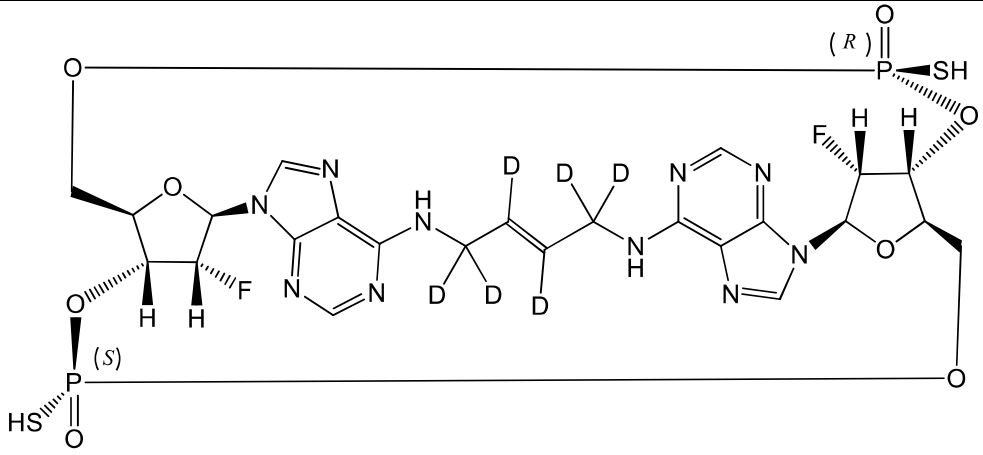
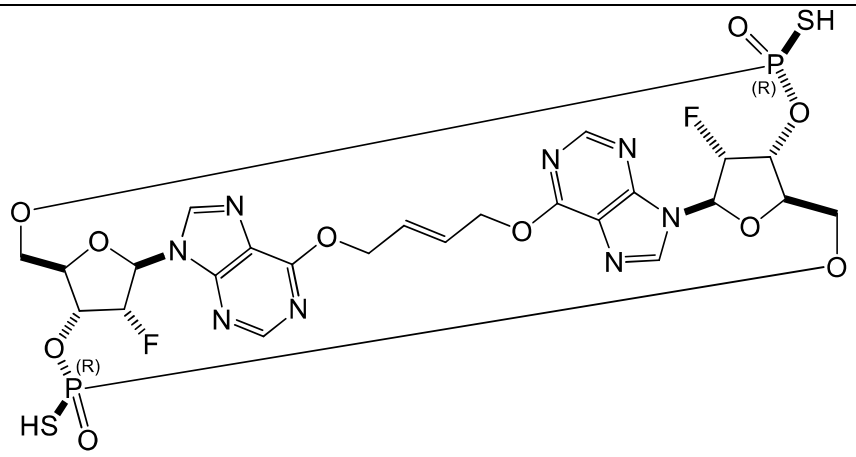
Compound No.	Structure
1	
2	
3	
4	

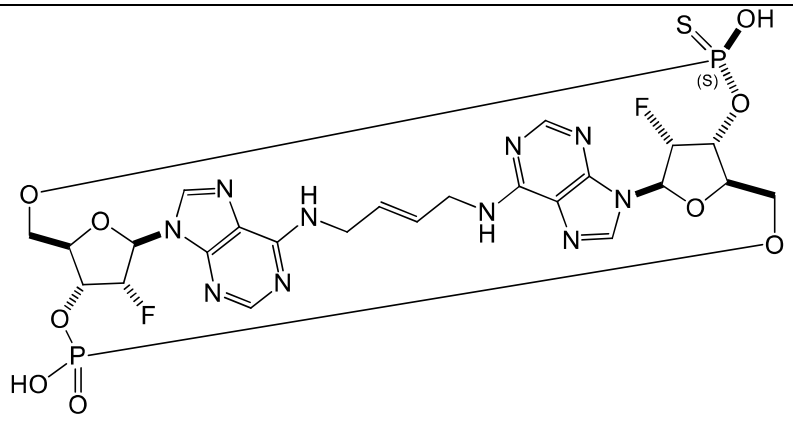
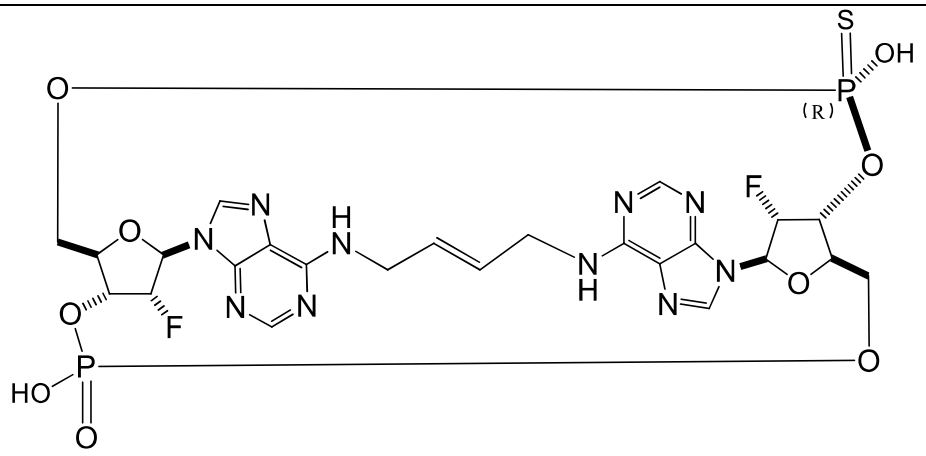
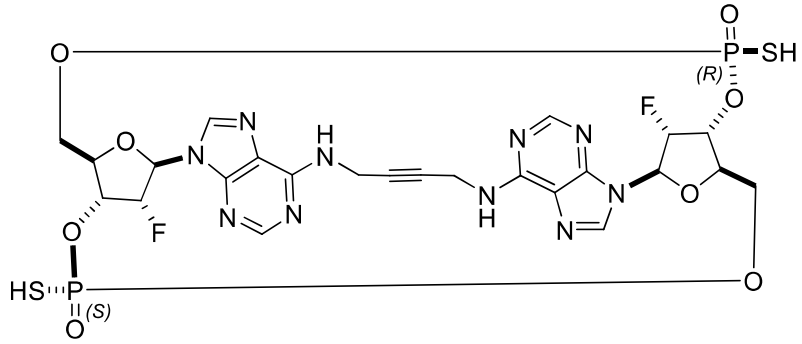
5	
6	
8	 (Stereoisomer 1)
9	

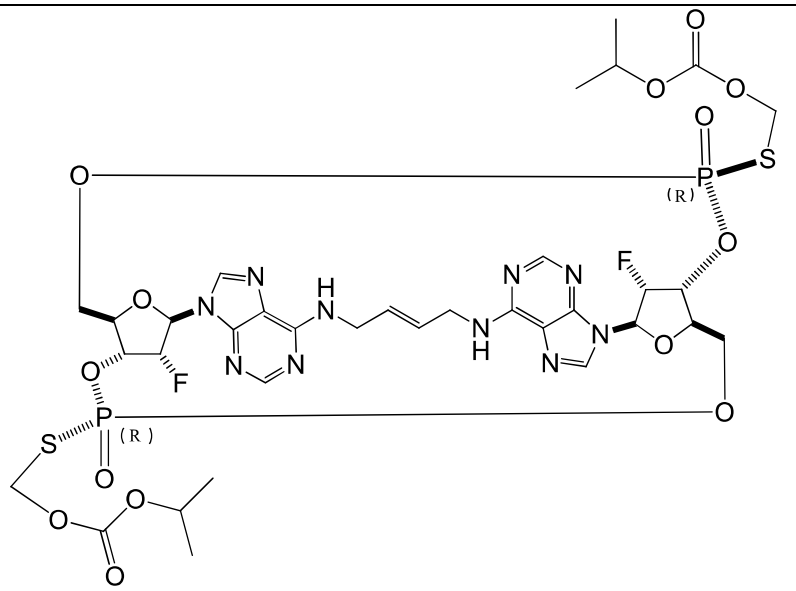
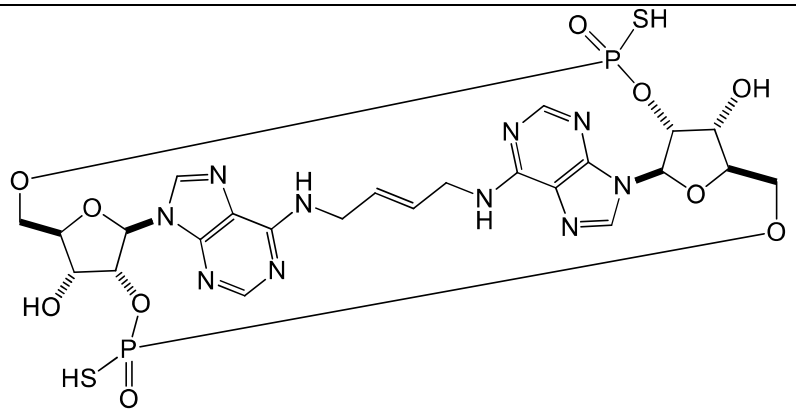
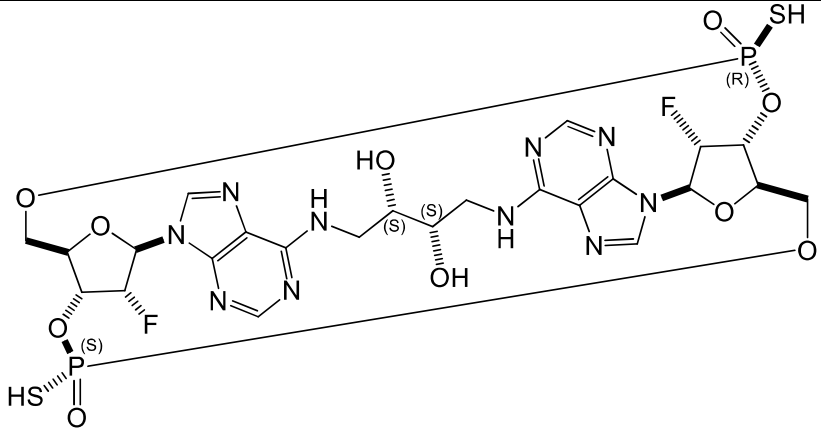
11	 (Stereoisomer 2)
12	 (Stereoisomer 3)
13	
14	
15	

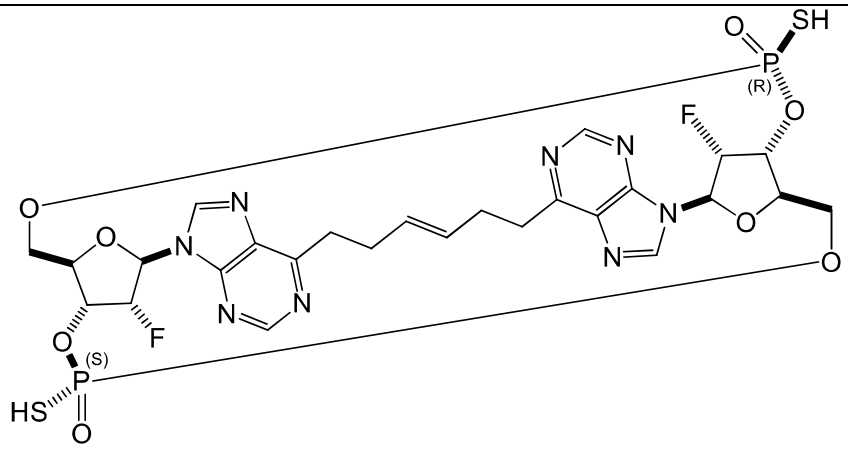
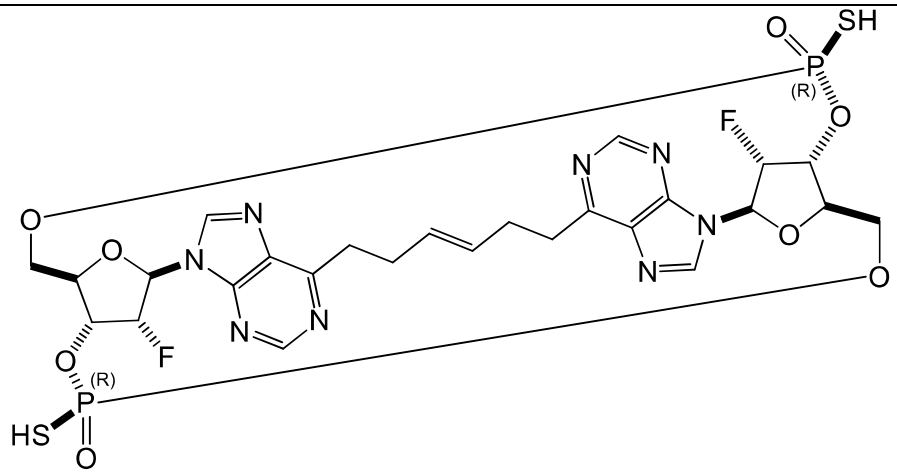
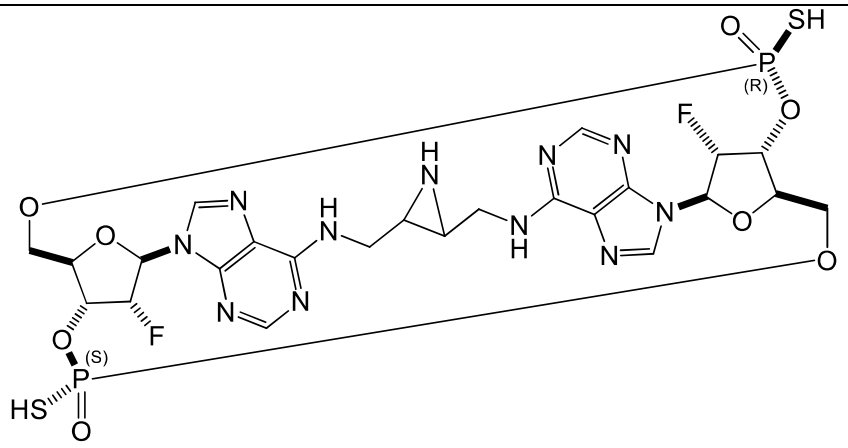
16	
18	 (Stereoisomer 1)
19	 (Stereoisomer 2)
20	 (Stereoisomer 3)

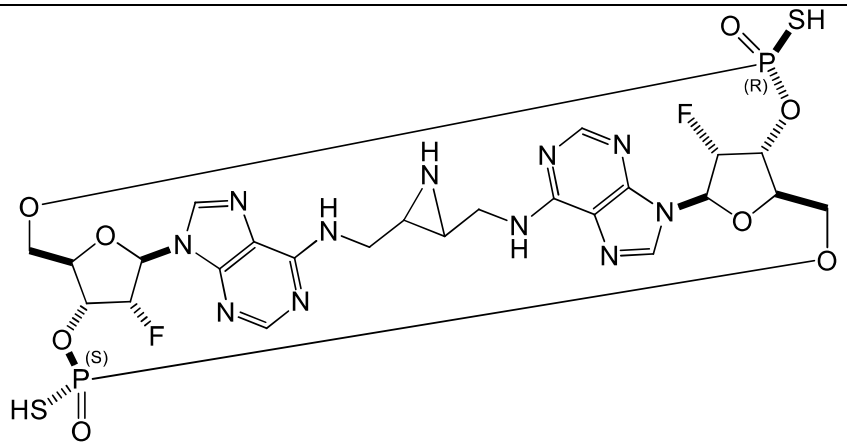
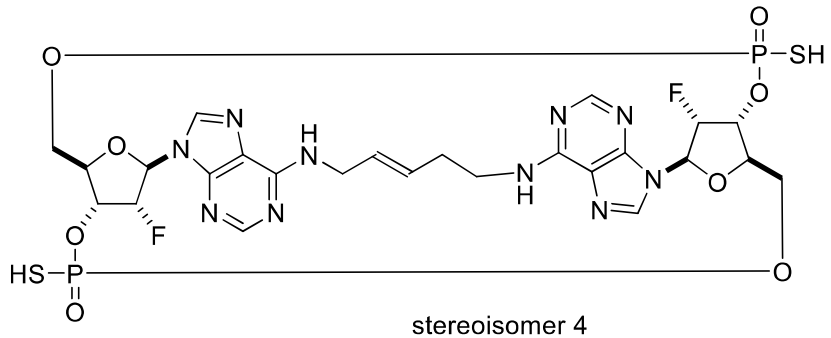
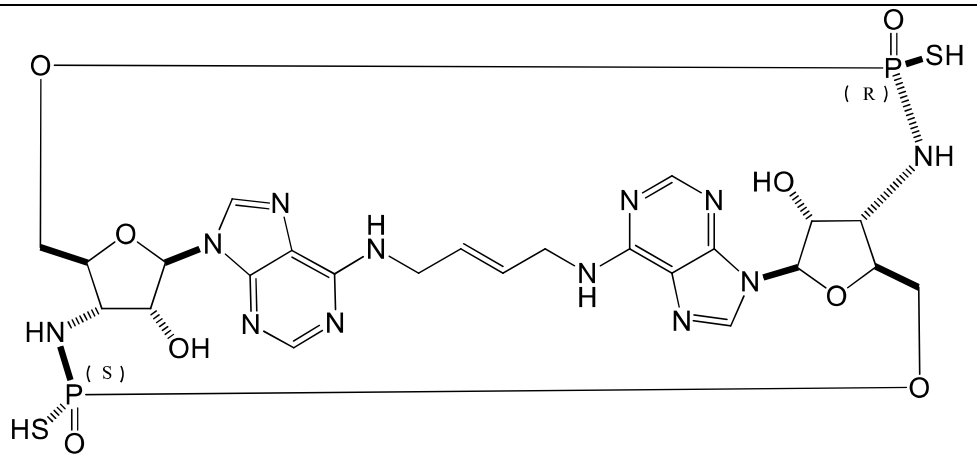
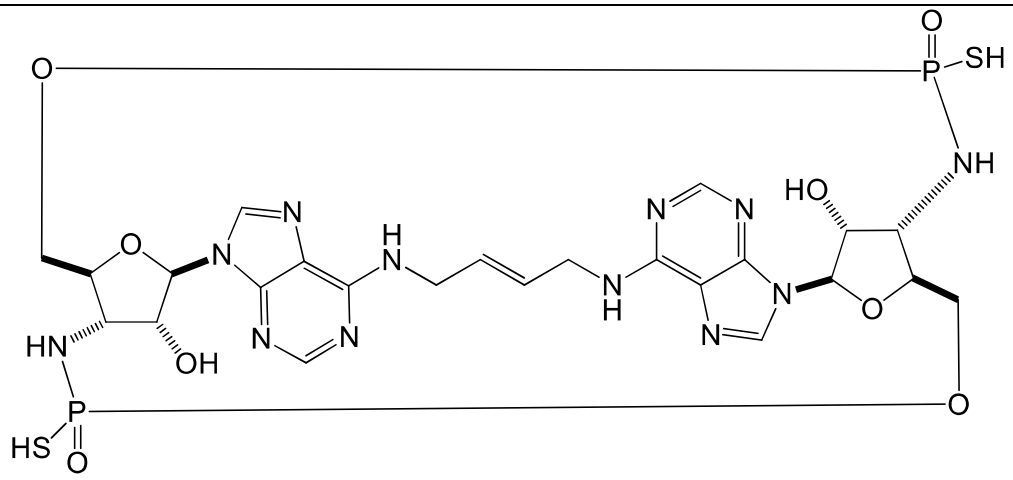
21	 (Stereoisomer 1)
22	 (Stereoisomer 2)
23	 (Stereoisomer 3)

24	
25	
26	

27	
28	
29	

30	
31	
32	

33	
34	
35	 (Stereoisomer 1)

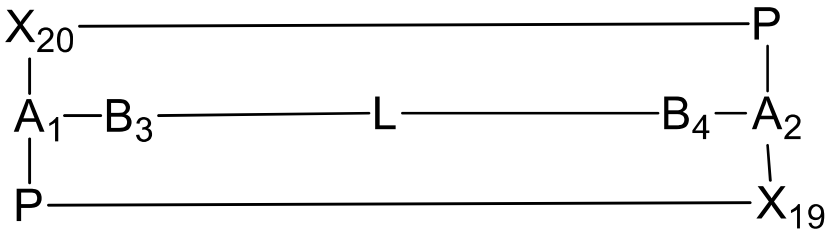
36	 (Stereoisomer 2)
37	 stereoisomer 4
38	
39	

In the table above, Compounds 8, 11, and 12 are drawn with the same structural formula and relate to three separate stereoisomers. The applicant notes, however, that the phosphorous chirality of Compound 8 is not necessarily the same as the phosphorous chirality for other compounds labeled "Stereoisomer 1," such as, for example, Compound 21. The same holds true for the other stereoisomers.

Examples may relate to C_4-C_6 linkers that may be covalently bound at either end to purine or pyrimidine bases that form part of a cyclic dinucleotide. In an example, the linkers are butene, pentene or hexene linkers bound at either end to purine bases. In another example, the linkers are butene linkers bound at either end to purine bases; in another example, the linkers are transbutene linkers with the double bond located between the center two carbons.

The following numbered examples are illustrative of use of these C_4-C_6 linkers:

1. A compound of Formula (X):



(X)

or a pharmaceutically acceptable salt thereof, wherein:

A_1 and A_2 are sugar moieties and may be the same or different;

B_3 and B_4 are purine or pyrimidine bases that may be the same or different and that form nucleotides with, respectively, A_1 and A_2;

L is a alkyl linker;

X_{19} and X_{20} are the same or different and are selected from the group consisting of –O–, -CH–, -NH–, and –S–, wherein –CH- and –NH- may be substituted or unsubstituted.

2. The compound or pharmaceutically acceptable salt of numbered example 1, wherein –CH- and –NH- of X_{19} and X_{20} may be substituted with $C_{1\text{-}6}$ alkyl.

3. The compound or pharmaceutically acceptable salt of numbered example 1, wherein L is butene, pentene, or hexane.

4. The compound or pharmaceutically acceptable salt of numbered example 3, wherein L is a transbutene linker with a double bond at its center.

Compounds or pharmaceutically acceptable salts of the numbered examples may be useful, for example, for treating cancer. A_1, A_2, B_3, and B_4 may be further substituted with,

for example, hydroxyl, halogen, or methoxy. Each phosphorous in Formula (X) may be substituted, for example, with –SH, -OH, =O, or =S until its valence has been satisfied.

Examples of cyclic dinucleotide analogs that may benefit from linkers of the present disclosure include but are not limited to those identified in US 2014/0205653 A1; US 2014/0329889 A1 ; US 2014/0341976 A1; US 2015/0056224 A1; US 2016/0362441 A1; US 2017/0158724 A1; US 2017/044206 A1; US 5,547,941; US 7,569,555 B2; US 7,592,326 B2; US 7,709,458 B2; US 9,549,944 B2; WO 2009/133560 A1; WO 2015/074145 A1; WO 2015/077354 A1; WO 2015/185565 A1; WO 2016/100261 A1; WO 2016/120305 A1;WO 2016/145102 A1; WO 2017/027645 A1; WO 2017/027646 A1; WO 2017/075477 A1; WO 2017/093933 A1;WO 2017/123657 A1; WO 2017/175156 A1; EP 1740,192 B1; CN 102199183 A; Corrales, L. *et al*., "Direct Activation of STING in the Tumor Microenvironment Leads to Potent and Systemic Tumor Regression and Immunity," *Cell Reports*, **11**: 1018-1030 (2015); and Lioux, T. *et al.*, "Design, Synthesis, and Biological Evaluation of Novel Cyclic Adenosine-Inosine Monophosphate (cAIMP) Analogs That Activate Stimulator of Interferon Genes (STING)," *J. Med. Chem.*, **59**: 10253-10267 (2016). All of those documents, including the compounds therein, are incorporated by reference herein; if any component of any of those documents contradicts or is otherwise inconsistent with anything in this specification, then this specification controls.

In some examples, a compound as reported herein is provided as a free acid. In some examples, the compound is provided as an NH_4 salt or as a triethyl amine (TEA) salt.

Examples may provide a method of treating cancer in a patient in need thereof, including administering to the patient a therapeutically effective amount of a compound reported herein, or a pharmaceutically acceptable salt thereof, as recited above.

In some examples, the compound is administered as a free acid. In some examples, the compound is administered as a diammonium salt (NH_4). Pharmaceutical compositions including a Compound of Formula I, Formula II, Formula III, Formula IV, Formula V, Table 3, or a pharmaceutically acceptable salt thereof, as well as a pharmaceutically acceptable excipient, are contemplated. Examples may provide a compound according to Formula I in which n is 1; geometry about the double bond is trans; X_1 and X_2 are each SH; stereochemistry at P_1 is S; and stereochemistry at P_2 is R; or a pharmaceutically acceptable salt thereof.

Examples may provide a method of treating cancer in a patient comprising administering to said patient a compound or pharmaceutically acceptable salt thereof, or a pharmaceutical composition, as reported herein. Cancers treated as reported herein may be

metastatic cancers. They may be selected from, for example, lymphoma, melanoma, colorectal cancer, breast cancer, acute myeloid leukemia, colon cancer, liver cancer, prostate cancer, pancreatic cancer, renal cancer, and glioma. Uses of compounds, salts, and pharmaceutical compositions for treatment of cancer and/or preparation of a medicament for treatment of cancer are also contemplated.

Examples may provide a method of treating cancer including identifying an individual having a cancer treatable by a compound, pharmaceutically acceptable salt, or pharmaceutical composition as reported herein, and administering to the individual a compound, pharmaceutically acceptable salt, or pharmaceutical composition by which the patient has been identified as treatable. In some examples the individual is identified as having a cancer treatable by a compound, pharmaceutically acceptable salt, or pharmaceutical composition as reported herein by presence of a human REF STING variant allele in the patient.

Examples may provide a method of treating cancer in a patient having REF STING allele comprising administering to said patient a compound or pharmaceutically acceptable salt thereof, or pharmaceutical composition as reported herein.

Examples may provide a method of treating cancer in a patient having WT STING allele comprising administering to said patient a compound or pharmaceutically acceptable salt thereof, or pharmaceutical composition as reported herein.

Examples may provide a method of treating cancer in a patient having AQ STING allele comprising administering to said patient a compound or pharmaceutically acceptable salt thereof, or pharmaceutical composition as reported herein.

Examples may provide a method of treating cancer in a patient having HAQ STING allele comprising administering to said patient a compound or pharmaceutically acceptable salt thereof, or pharmaceutical composition as reported herein.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 shows a synthesis of Compound 1a and Compound 2a.

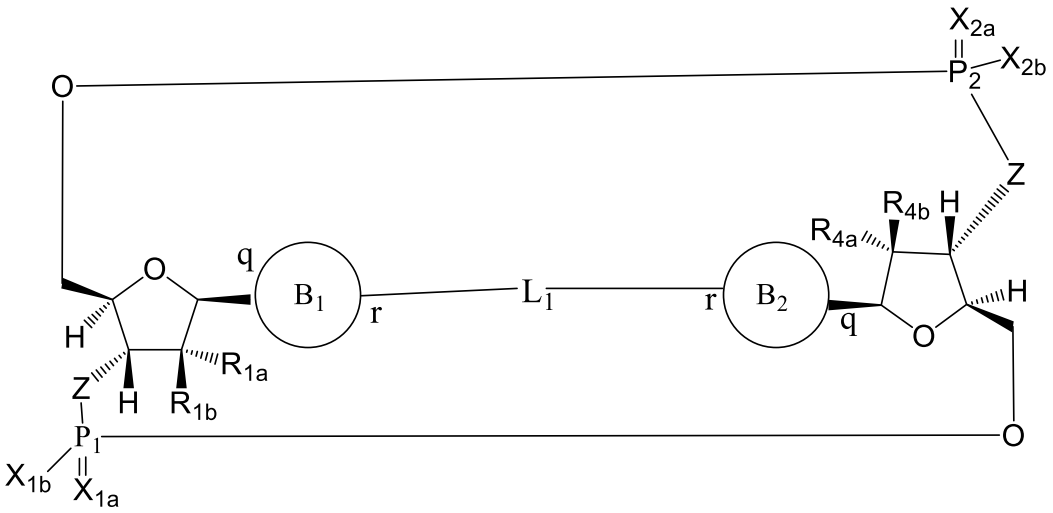
FIG. 2A and FIG. 2B show an alternate synthesis of Compound 1 and Compound 1a. That alternate synthesis is also shown in FIG. 2C through FIG. 2E.

FIG. 3 shows an ^{1}H NMR spectrograph for Compound 1.

FIG. 4A, FIG. 4B, and FIG. 4C, show X-ray crystallography results (ORTEP drawings) for, respectively, an asymmetric crystal of Compound 1, a first molecule from the

We claim:

1. A compound of Formula (III):



(III)

or a pharmaceutically acceptable salt thereof, wherein

R_{1a} is selected from the group consisting of –H, -OH, and -F;

R_{1b} is selected from the group consisting of –H, -OH, and –F, wherein at least one of R_{1a} and R_{1b} is -H;

R_{4a} is selected from the group consisting of –H, –OH, and –F;

R_{4b} is selected from the group consisting of –H, –OH, and –F, wherein at least one of R_{4a} and R_{4b} is -H;

P_1 and P_2 each independently has an S or R stereochemical configuration;

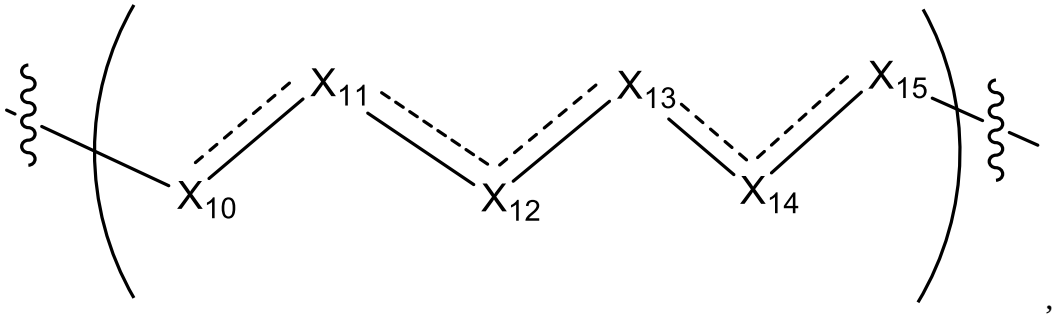
Z is –O– or –NH–;

X_{1a} and X_{2a} are the same or different and are independently selected from =O or =S;

X_{1b} and X_{2b} are the same or different and are independently selected from -OR_5 and -SR_5;

wherein R_5 is selected from the group consisting of –H, -$C_{1\text{-}6}$alkyl, -C(O)$C_{1\text{-}6}$alkyl, and -CH_2OC(O)$OC_{1\text{-}6}$alkyl;

L_1 in formula (III) is four, five, or six carbons in length, and is



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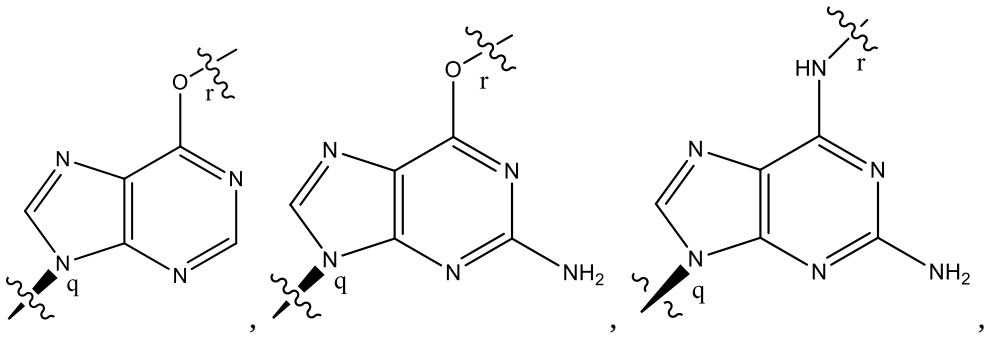
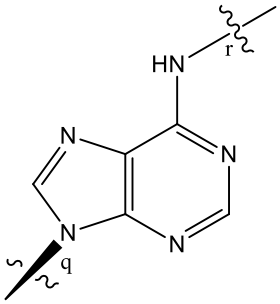
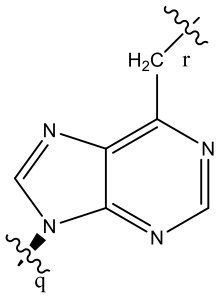
wherein ------ indicates a single bond, a double bond, or a triple bond and wherein (i) either 0 or 1 occurrence of ------ in L_1 indicates a triple bond; or (ii) 0, 1, or 2 occurrences of ------ in L_1 indicates a double bond, wherein geometry about each double bond is cis or trans; and (iii) wherein when 1 occurrence of ------ in L_1 indicates a triple bond, 0 occurrences of ------ in L_1 indicates a double bond; and (iv) wherein, when 2 occurrences of ------ in L_1 indicate a double bond, those double bonds are either adjacent bonds or alternating bonds;

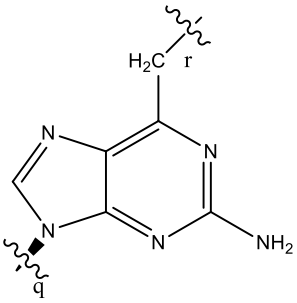
wherein X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, and X_{15} are independently selected from a bond, –CH_2–, or –CH–, wherein the –CH_2– or –CH– is unsubstituted or substituted by (i) –OH, (ii) –F, (iii) –Cl, (iv) –NH_2, or (v) -D, and when X_{10} or X_{15} is a bond, that bond is not a double bond or triple bond;

and wherein any two adjacent members of the group including X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, and X_{15} may optionally form, with additional atoms, a C_3 cycloalkyl or a C_3 heterocycloalkyl, said C_3 heterocycloalkyl including an N or O atom;
wherein B_1 and B_2 are independently selected from:





, 

, and 

where the bonds at points q and r on B_1 and B_2 are attached at points q and r on Formula (III).

2. A compound or pharmaceutically acceptable salt of claim 1, wherein:

R_{1a} is selected from the group consisting of –H and -F;

R_{1b} is selected from the group consisting of –H and –F, wherein R_{1a} and R_{1b} may not both be -F;

R_{4a} is selected from the group consisting of –H and -F;

R_{4b} is selected from the group consisting of –H and –F, wherein R_{4a} and R_{4b} may not both be –F;

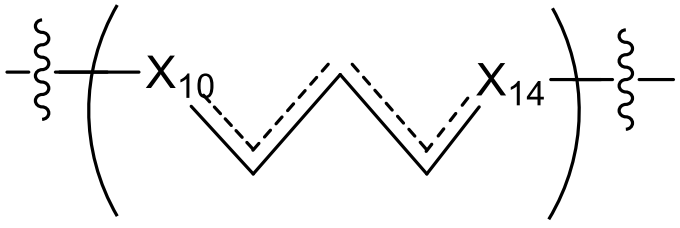
P_1 and P_2 each independently has an S or R stereochemical configuration;

X_{1a} and X_{2a} are the same or different and are independently selected from =O or =S;

X_{1b} and X_{2b} are the same or different and are independently selected from -OR_5 and -SR_5;

wherein R_5 is selected from the group consisting of –H, $C_{1\text{-}6}$alkyl, and -C(O)$C_{1\text{-}6}$alkyl;

L_1 in formula (III) is four or five carbons in length, and is



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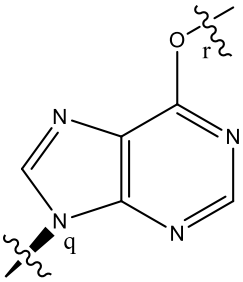
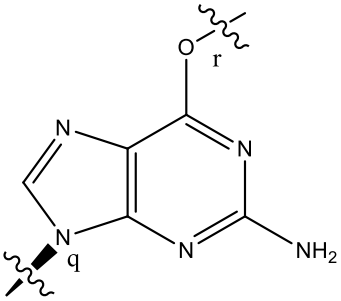
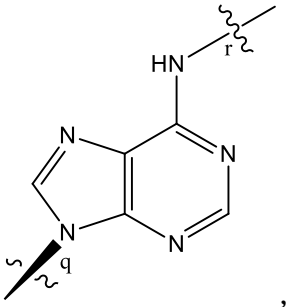
wherein ------ indicates a single bond or a double bond, and wherein either 0 or 1 occurrence of ------ in L_1 indicates a double bond, wherein geometry about the double bond is cis or trans;

wherein X_{10} and X_{14} are independently selected from a bond, -CH-, or –CH_2- , and wherein, when X_{10} or X_{14} is a bond, that bond is not a double bond;

wherein B_1 and B_2 are independently selected from:

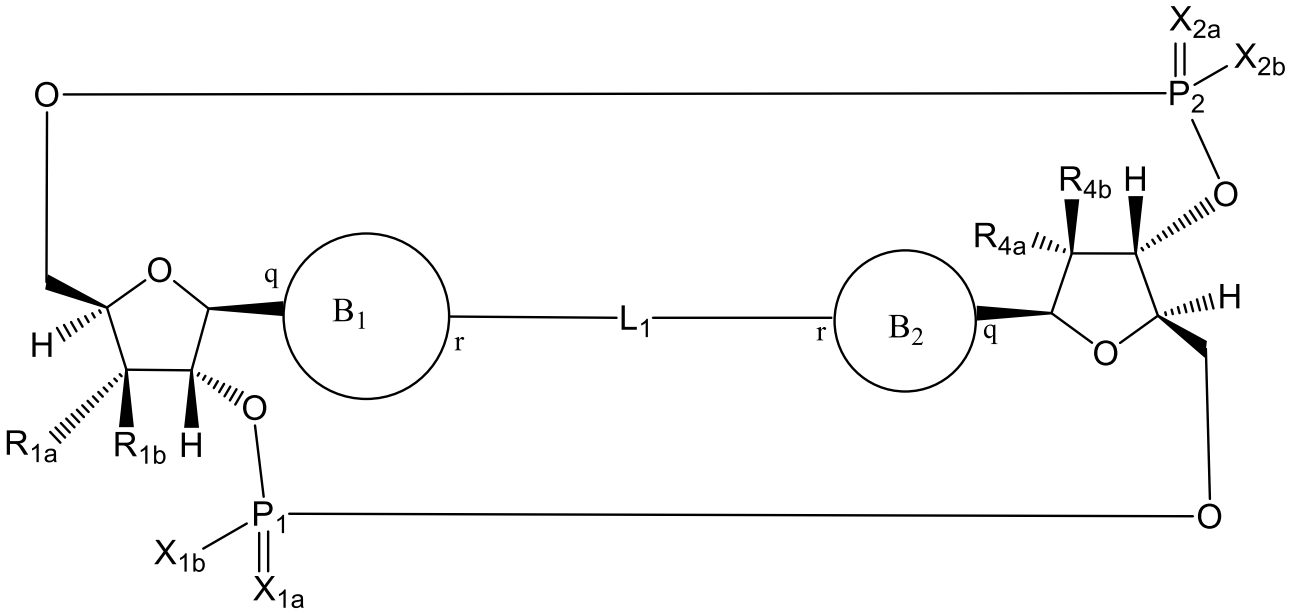


, 

, and 

, where the bonds at points q and r on B_1 and B_2 are attached at points q and r on Formula (III).

3. A compound of Formula (IV):



(IV)

or a pharmaceutically acceptable salt thereof, wherein

R_{1a} is selected from the group consisting of –H, -OH, and -F;

R_{1b} is selected from the group consisting of –H, -OH, and –F, wherein at least one of R_{1a} and R_{1b} is -H;

R_{4a} is selected from the group consisting of –H, -OH, and -F;

R_{4b} is selected from the group consisting of –H, -OH, and –F, wherein at least one of R_{4a} and R_{4b} is –H;

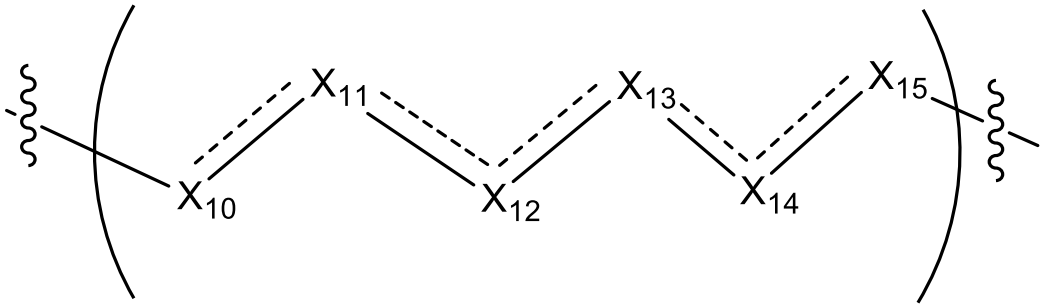
P_1 and P_2 each independently has an S or R stereochemical configuration;

X_{1a} and X_{2a} are the same or different and are independently selected from =O or =S;

X_{1b} and X_{2b} are the same or different and are independently selected from $-OR_5$ and $-SR_5$;

wherein R_5 is selected from the group consisting of –H, $C_{1\text{-}6}$alkyl, -C(O)$C_{1\text{-}6}$alkyl, and -$CH_2OC(O)OC_{1\text{-}6}$alkyl;

L_1 in formula (IV) is four, five, or six carbons in length, and is



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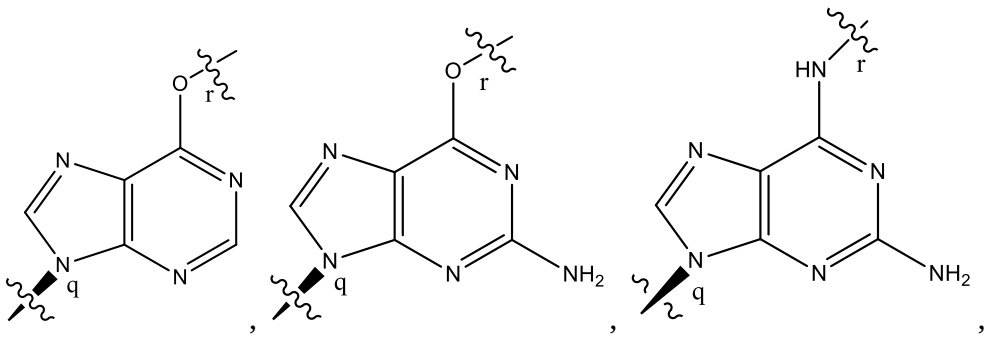
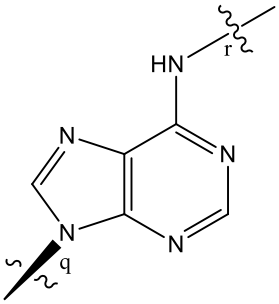
wherein ------ indicates a single bond, a double bond, or a triple bond and wherein (i) either 0 or 1 occurrence of ------ in L_1 indicates a triple bond; or (ii) 0, 1, or 2 occurrences of ------ in L_1 indicates a double bond, wherein geometry about each double bond is cis or trans; and (iii) wherein when 1 occurrence of ------ in L_1 indicates a triple bond, 0 occurrences of ------ in L_1 indicates a double bond; and (iv) wherein, when 2 occurrences of ------ in L_1 indicate a double bond, those double bonds are either adjacent bonds or alternating bonds;

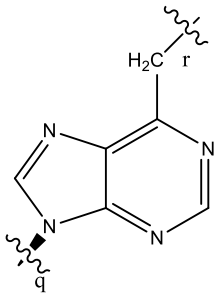
wherein X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, and X_{15} are independently selected from a bond, –CH_2–, or –CH–, wherein the –CH_2– or –CH– is unsubstituted or substituted by (i) –OH, (ii) –F, (iii) –Cl, (iv) –NH_2, or (v) -D, and when X_{10} or X_{15} is a bond, that bond is not a double bond or triple bond;

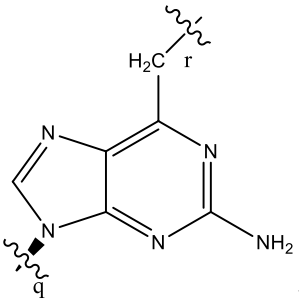
and wherein any two adjacent members of the group including X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, and X_{15} may optionally form, with additional atoms, a C_3 cycloalkyl or a C_3 heterocycloalkyl, said C_3 heterocycloalkyl including an N or O atom;

wherein B_1 and B_2 are independently selected from:



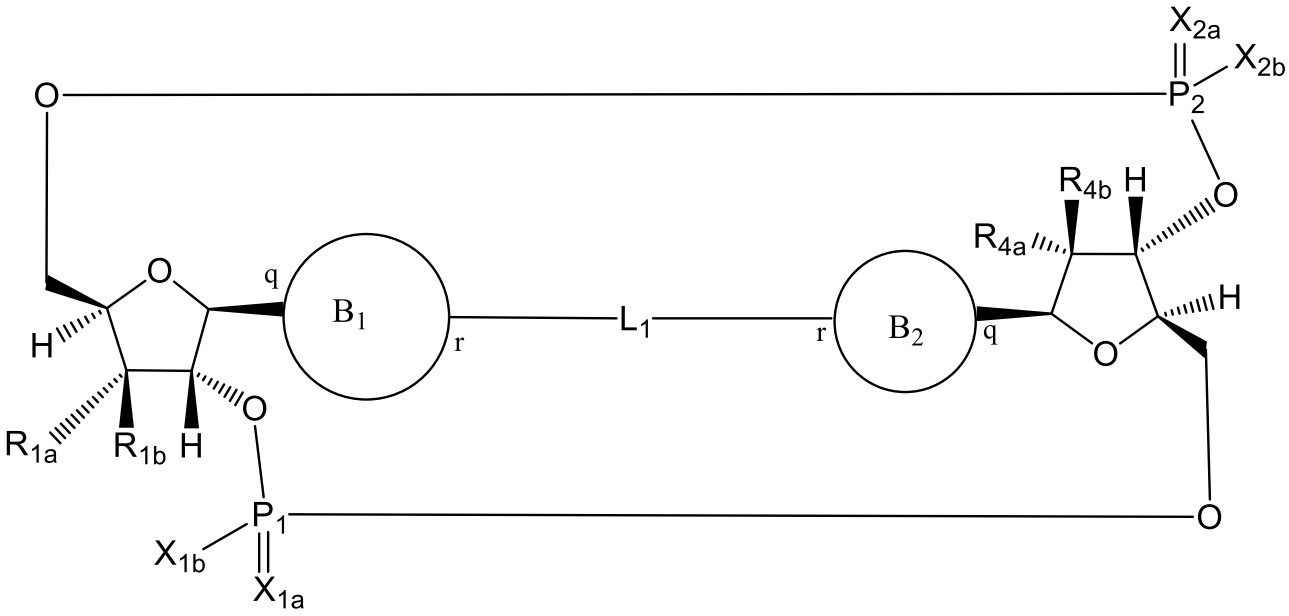


, 

, and 

where the bonds at points q and r on B_1 and B_2 are attached at points q and r on Formula (IV).

4. A compound of Formula (IV):



(IV)

or a pharmaceutically acceptable salt thereof, wherein

R_{1a} is selected from the group consisting of –H and -F;

R_{1b} is selected from the group consisting of –H and –F, wherein R_{1a} and R_{1b} may not both be -F;

R_{4a} is selected from the group consisting of –H and -F;

R_{4b} is selected from the group consisting of –H and –F, wherein R_{4a} and R_{4b} may not both be –F;

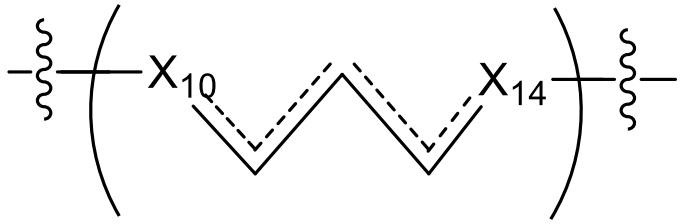
P_1 and P_2 each independently has an S or R stereochemical configuration;

X_{1a} and X_{2a} are the same or different and are independently selected from =O or =S;

X_{1b} and X_{2b} are the same or different and are independently selected from -OR_5 and -SR_5;

wherein R_5 is selected from the group consisting of –H, $C_{1\text{-}6}$alkyl, and -C(O)$C_{1\text{-}6}$alkyl;

L_1 in formula (IV) is four or five carbons in length, and is

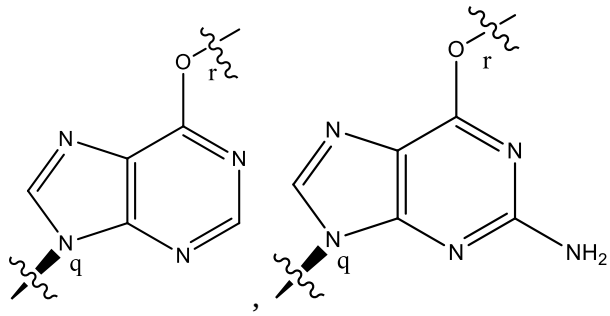


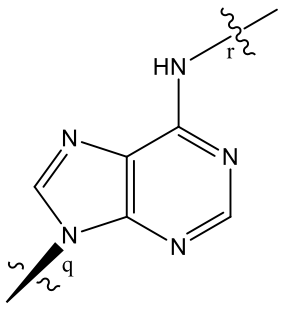
,

wherein ------ indicates a single bond or a double bond, and wherein either 0 or 1 occurrence of ------ in L_1 indicates a double bond, wherein geometry about the double bond is cis or trans;

wherein X_{10} and X_{14} are independently selected from a bond, -CH-, or $–CH_2-$, and wherein, when X_{10} or X_{14} is a bond, that bond is not a double bond;

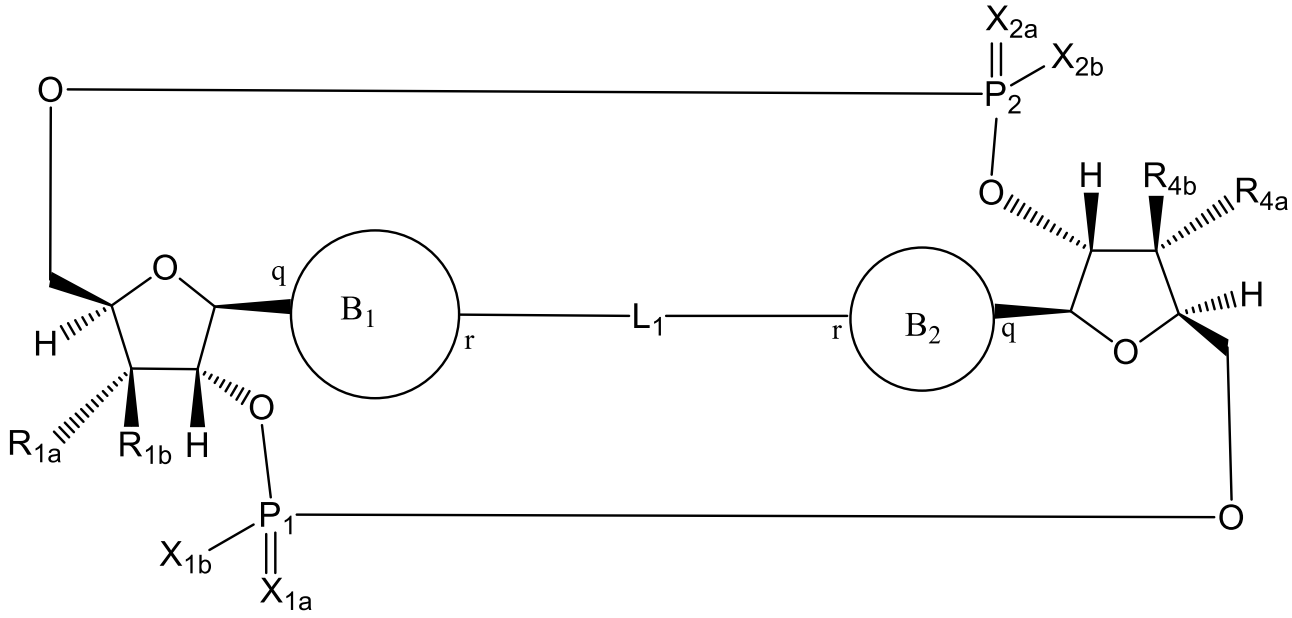
wherein B_1 and B_2 are independently selected from:



, 

, and ,where the bonds at points q and r on B_1 and B_2 are attached at points q and r on Formula (IV).

5. A compound of Formula (V):



(V)

or a pharmaceutically acceptable salt thereof, wherein

R_{1a} is selected from the group consisting of –H, -OH, and -F;

R_{1b} is selected from the group consisting of –H, -OH, and –F, wherein at least one of R_{1a} and R_{1b} is -H;

R_{4a} is selected from the group consisting of –H, -OH and -F;

R_{4b} is selected from the group consisting of –H, -OH, and –F, and wherein at least one of R_{4a} and R_{4b} is –H;

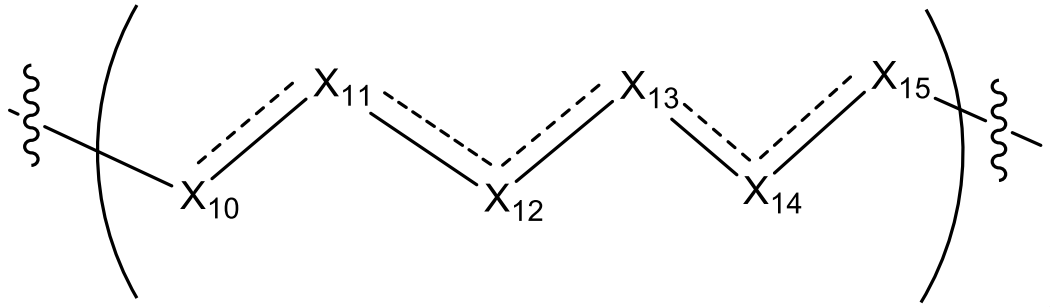
P_1 and P_2 each independently has an S or R stereochemical configuration;

X_{1a} and X_{2a} are the same or different and are independently selected from =O or =S;

X_{1b} and X_{2b} are the same or different and are independently selected from $-OR_5$ and $-SR_5$;

wherein R_5 is selected from the group consisting of –H, $C_{1\text{-}6}$alkyl, $-C(O)C_{1\text{-}6}$alkyl, and $-CH_2OC(O)OC_{1\text{-}6}$alkyl;

L_1 in formula (V) is four, five, or six carbons in length, and is

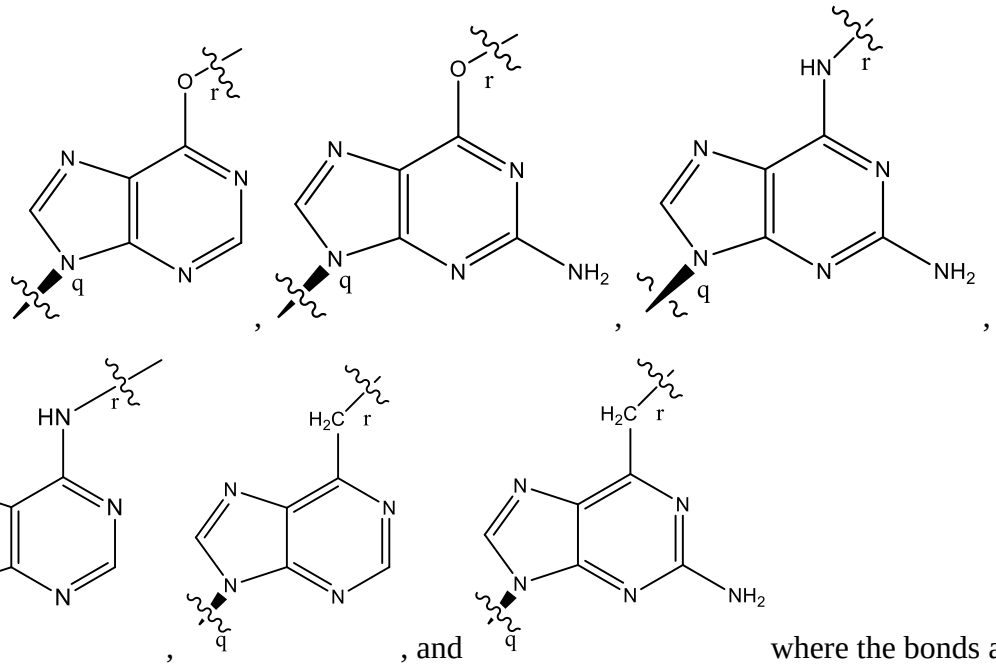


,

wherein ------ indicates a single bond, a double bond, or a triple bond and wherein (i) either 0 or 1 occurrence of ------ in L_1 indicates a triple bond; or (ii) 0, 1, or 2 occurrences of ------ in L_1 indicates a double bond, wherein geometry about each double bond is cis or trans; and (iii) wherein when 1 occurrence of ------ in L_1 indicates a triple bond, 0 occurrences of ------ in L_1 indicates a double bond; and (iv) wherein, when 2 occurrences of ------ in L_1 indicate a double bond, those double bonds are either adjacent bonds or alternating bonds;

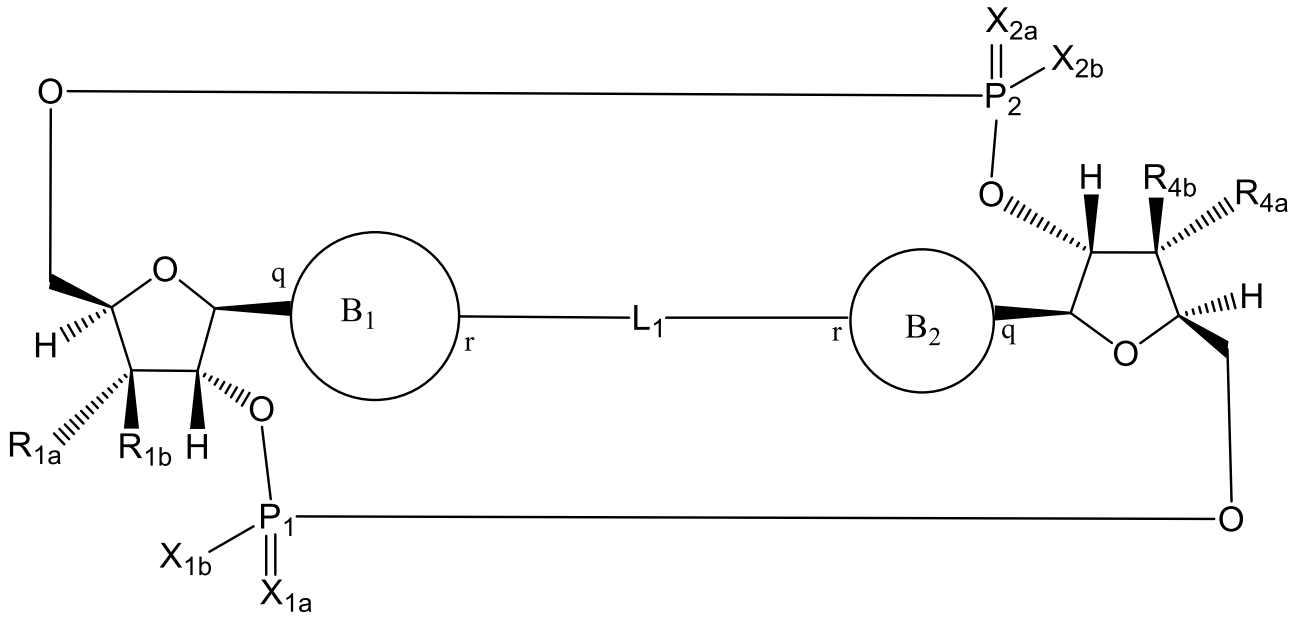
wherein X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, and X_{15} are independently selected from a bond, –CH_2–, or –CH–, wherein the –CH_2– or –CH– is unsubstituted or substituted by (i) –OH, (ii) –F, (iii) –Cl, (iv) –NH_2, or (v) -D, and when X_{10} or X_{15} is a bond, that bond is not a double bond or triple bond;

and wherein any two adjacent members of the group including X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, and X_{15} may optionally form, with additional atoms, a C_3 cycloalkyl or a C_3 heterocycloalkyl, said C_3 heterocycloalkyl including an N or O atom;
wherein B_1 and B_2 are independently selected from:



where the bonds at points q and r on B_1 and B_2 are attached at points q and r on Formula (V).

6. A compound of Formula (V):



(V)

or a pharmaceutically acceptable salt thereof, wherein

R_{1a} is selected from the group consisting of –H and -F;

R_{1b} is selected from the group consisting of –H and –F, wherein R_{1a} and R_{1b} may not both be -F;

R_{4a} is selected from the group consisting of –H and -F;

R_{4b} is selected from the group consisting of –H and –F, wherein R_{4a} and R_{4b} may not both be –F;

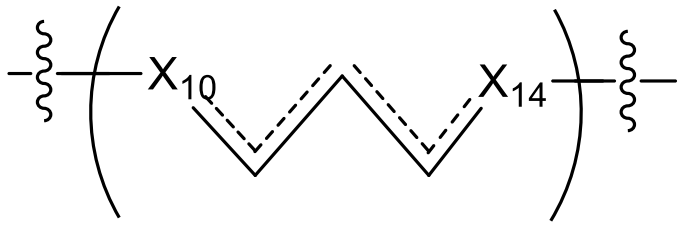
P_1 and P_2 each independently has an S or R stereochemical configuration;

X_{1a} and X_{2a} are the same or different and are independently selected from =O or =S;

X_{1b} and X_{2b} are the same or different and are independently selected from -OR_5 and -SR_5;

wherein R_5 is selected from the group consisting of –H, $C_{1\text{-}6}$alkyl, and -C(O)$C_{1\text{-}6}$alkyl;

L_1 in formula (V) is four or five carbons in length, and is



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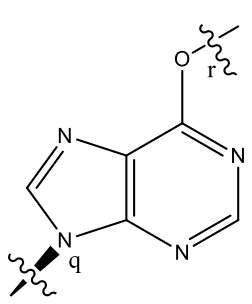
wherein ------ indicates a single bond or a double bond, and wherein either 0 or 1 occurrence of ------ in L_1 indicates a double bond, wherein geometry about the double bond is cis or trans;

wherein X_{10} and X_{14} are independently selected from a bond, -CH-, or $–CH_2-$, and wherein, when X_{10} or X_{14} is a bond, that bond is not a double bond;

wherein B_1 and B_2 are independently selected from:



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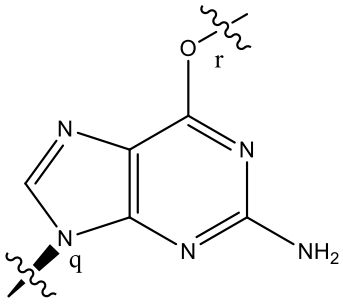

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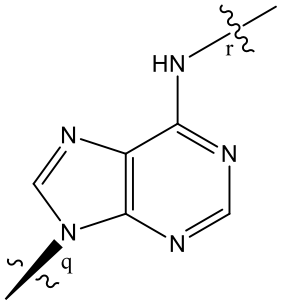


, where the bonds at points q and r on B_1 and B_2 are attached at points q and r on Formula (V).

7. A compound or pharmaceutically acceptable salt of any one of claims 1-6, wherein

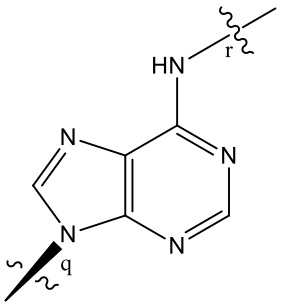
(i) stereochemical configuration of P_1 and P_2 are both R, stereochemical configuration of P_1 is R and and P_2 is S, or stereochemical configuration of P_1 is S and P_2 is R;

(ii) one occurrence of ------ in L_1 indicates a double bond, wherein geometry about the double bond is trans; and

(iii) Z is –O–.

8. A compound or pharmaceutically acceptable salt of any one of claims 1-7, wherein R_{1a} and R_{4a} are each –F.

9. A compound or pharmaceutically acceptable salt of any one of claims 1-7, wherein R_{1b} and R_{4b} are each –F.

10. A compound or pharmaceutically acceptable salt of any one of claims 1-9, wherein B_1 and B_2 are each


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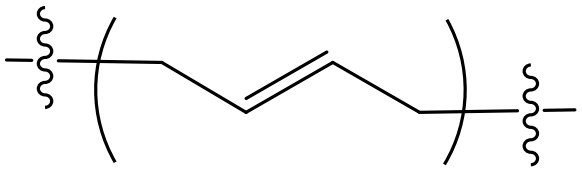
11. A compound or pharmaceutically acceptable salt of any one of claims 1-10, wherein X_{1a} and X_{2a} are both =O, and wherein X_{1b} and X_{2b} are both –SH.

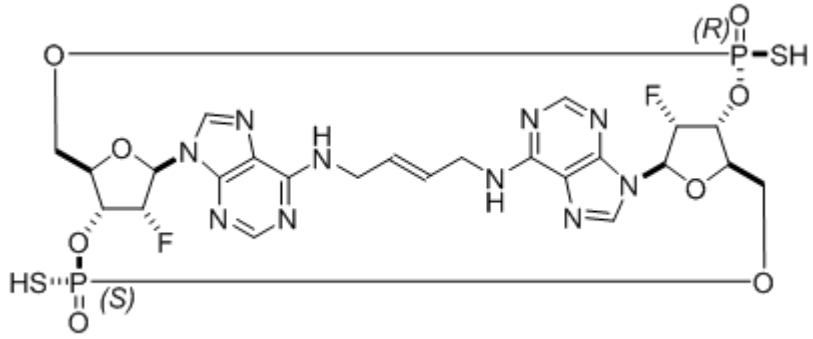
12. A compound or pharmaceutically acceptable salt of any one of claims 1-11, wherein

L_1 is  .

13. A compound or pharmaceutically acceptable salt of claim 1 or claim 2, wherein L_1 is five carbons in length.

14. A compound or pharmaceutically acceptable salt of any one of claims 1-11, wherein L_1 is four carbons in length.

15. A compound or pharmaceutically acceptable salt thereof, selected from the group consisting of:



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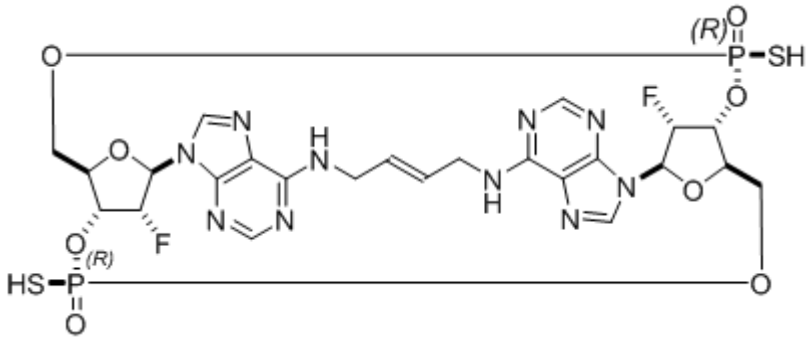

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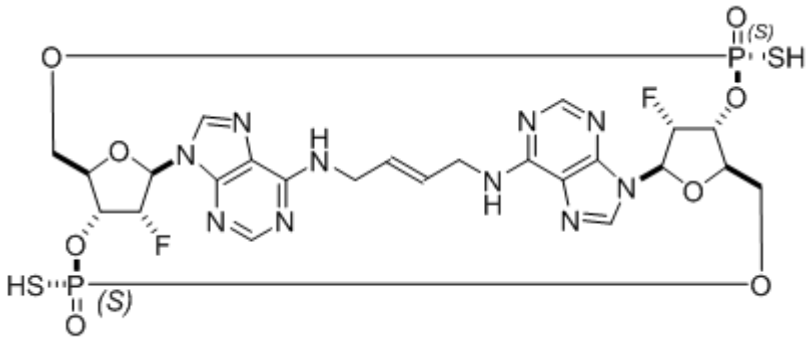

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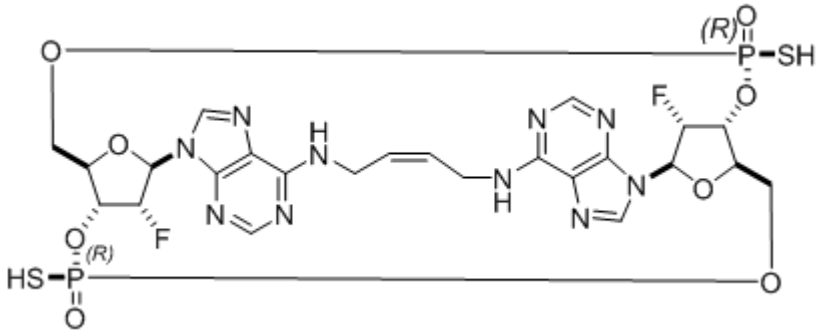

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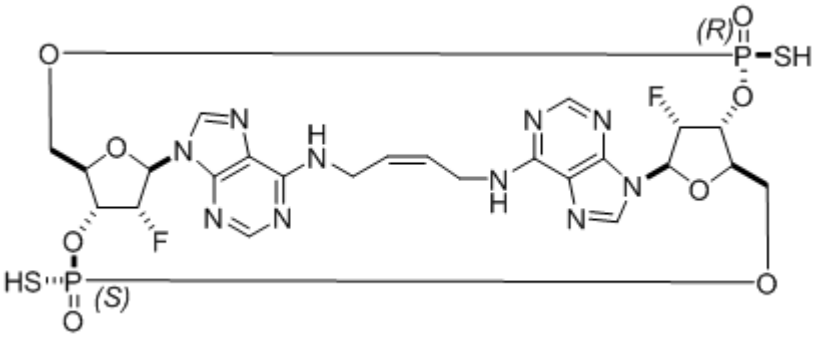

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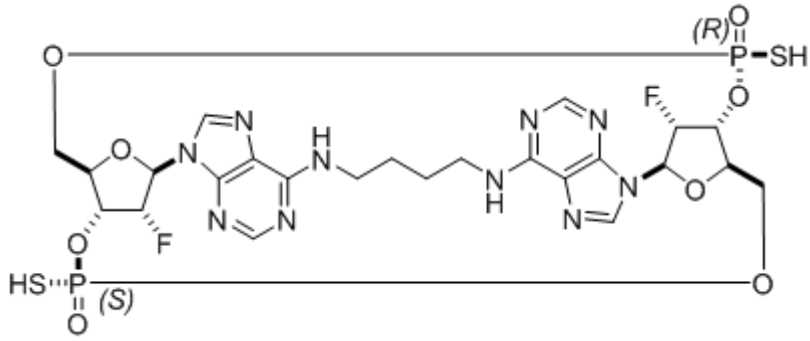

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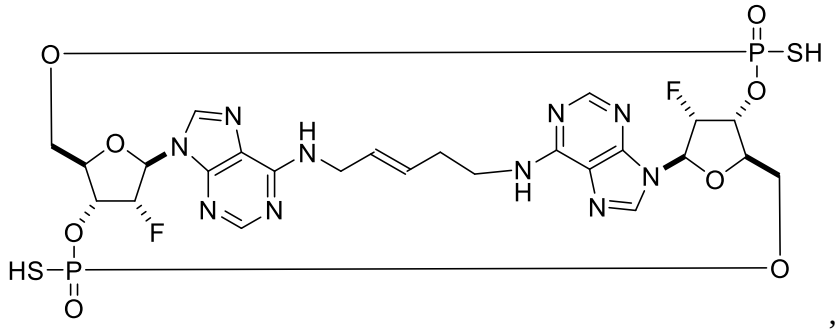

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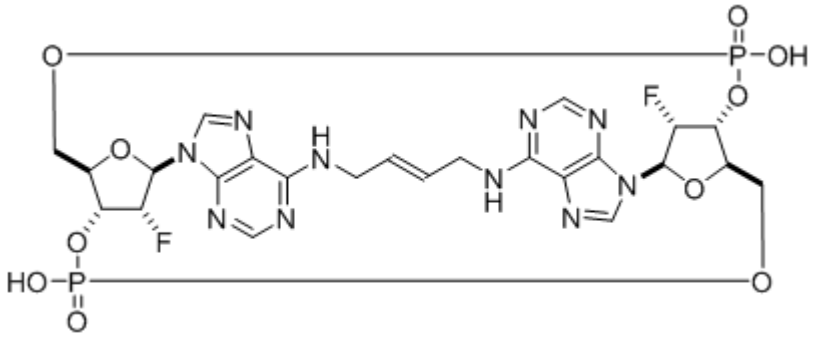

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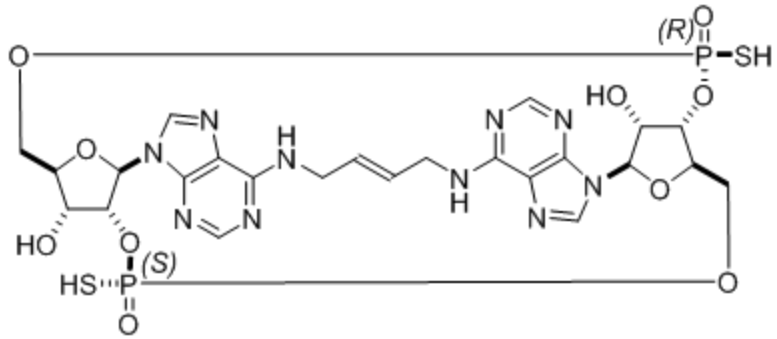

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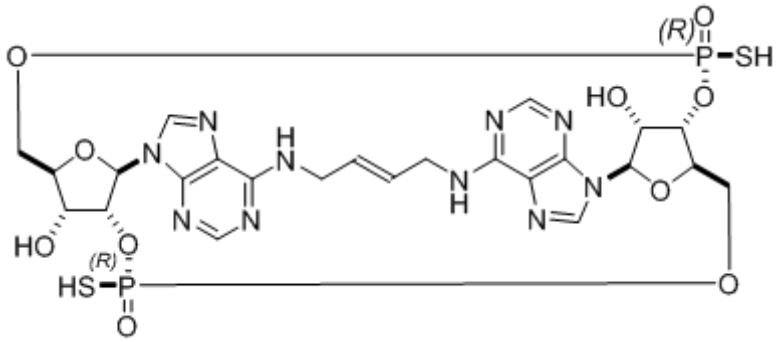

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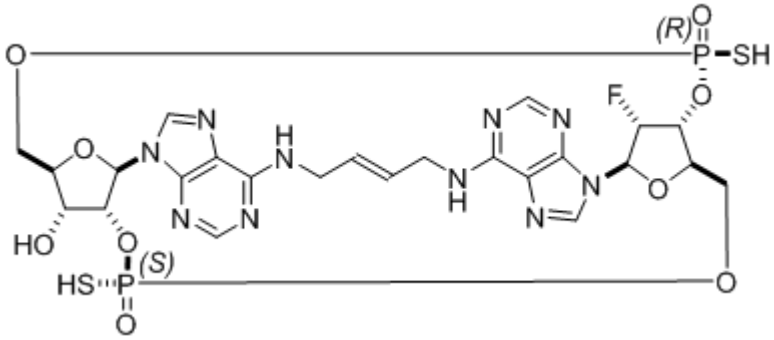

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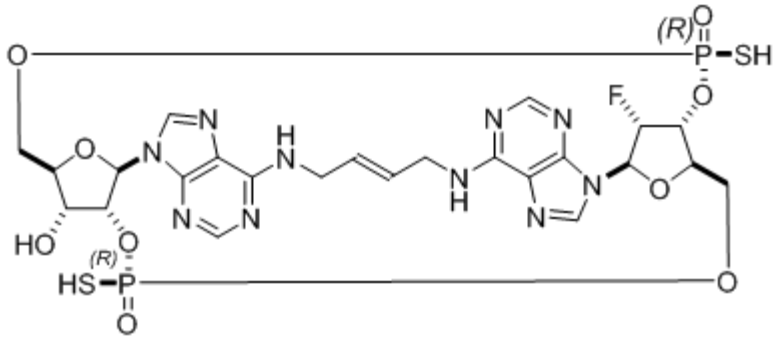

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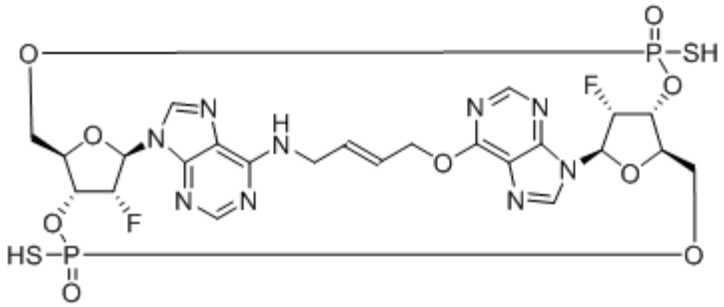

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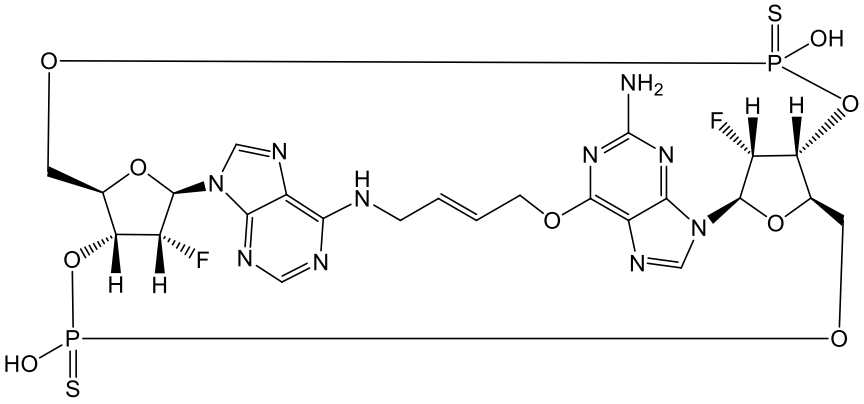

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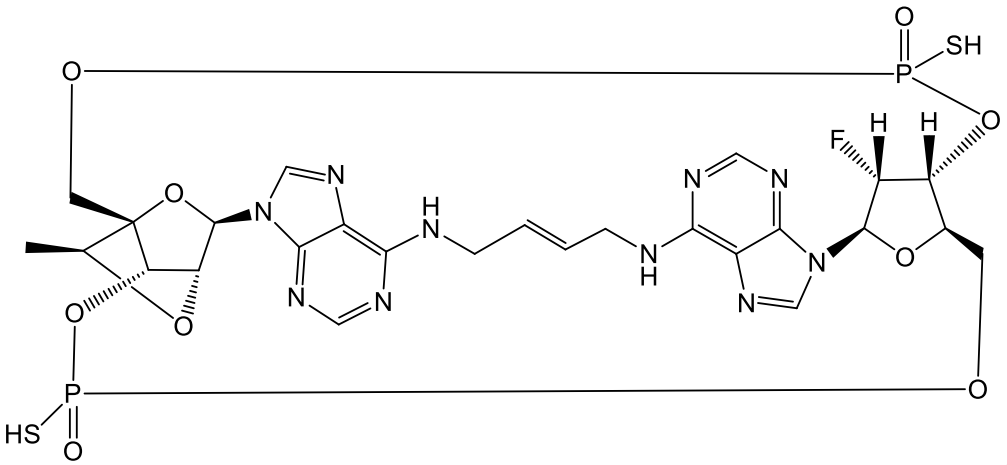

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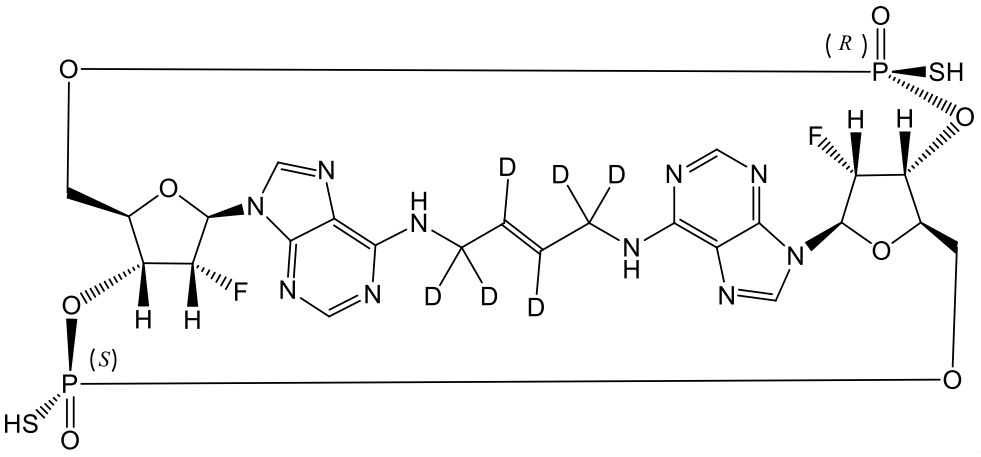

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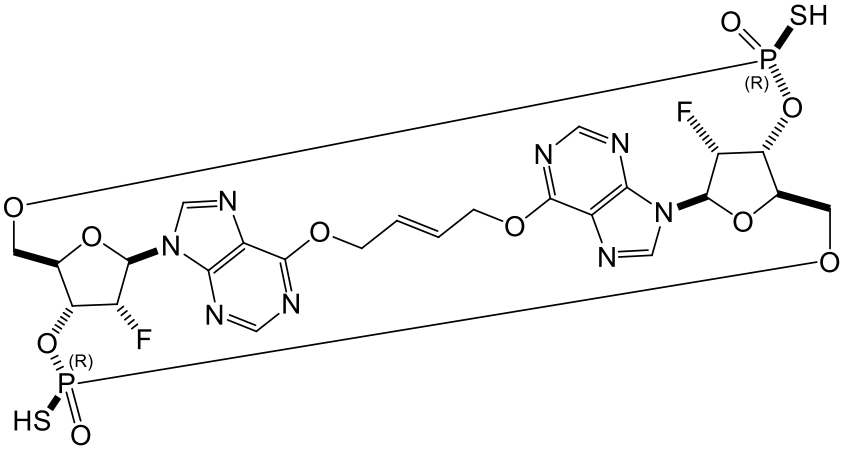

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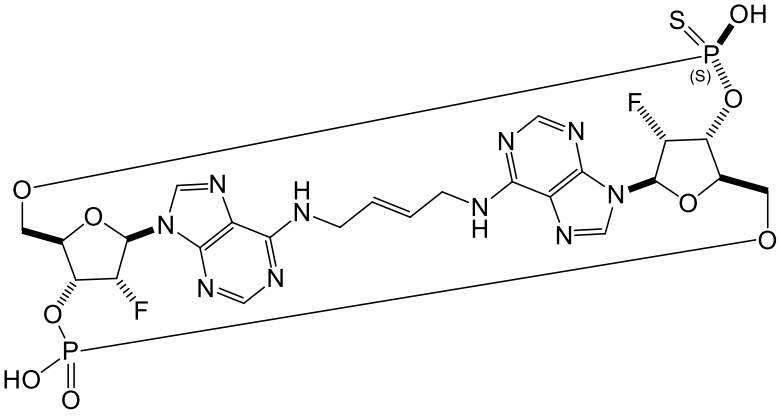

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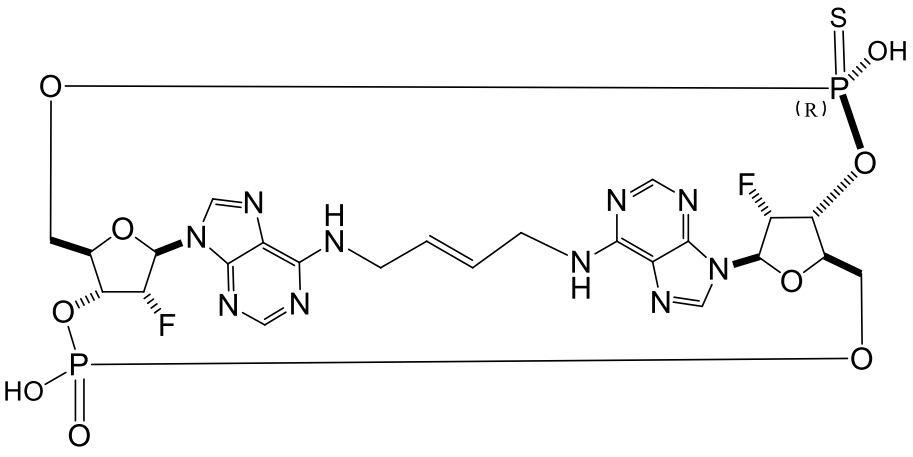

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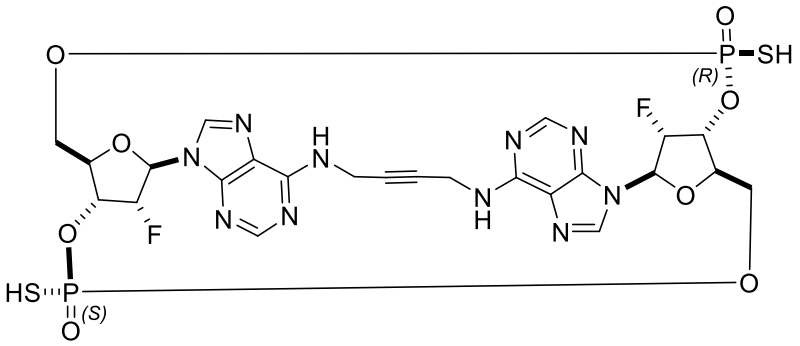

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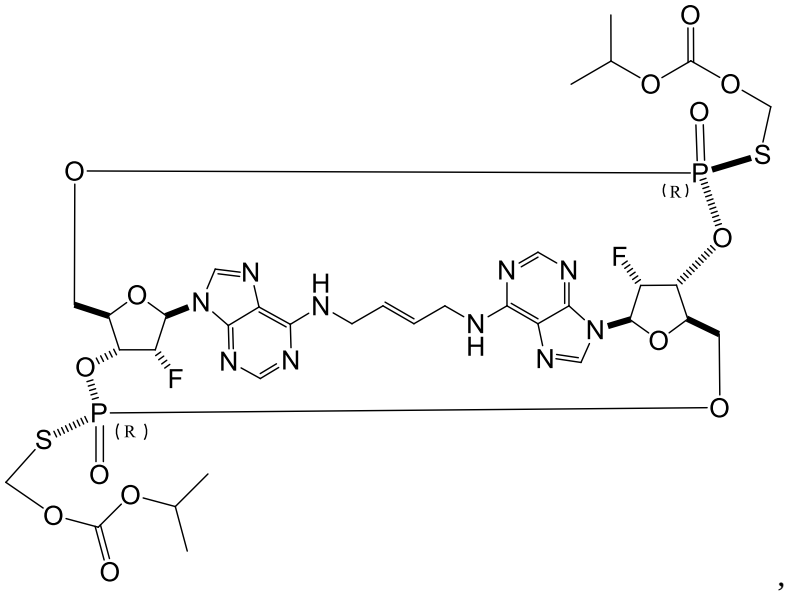

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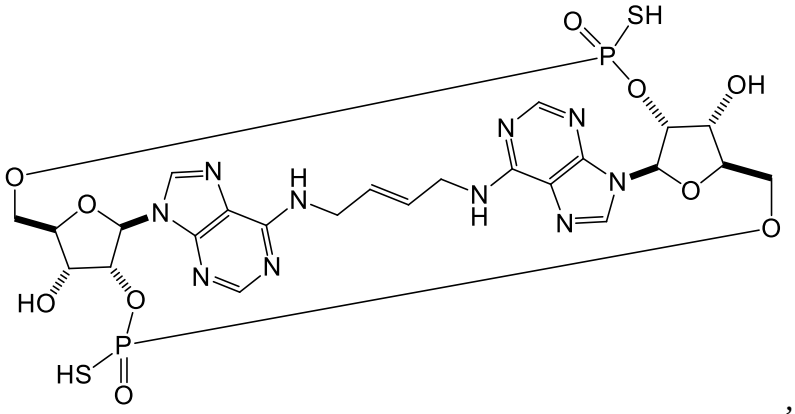

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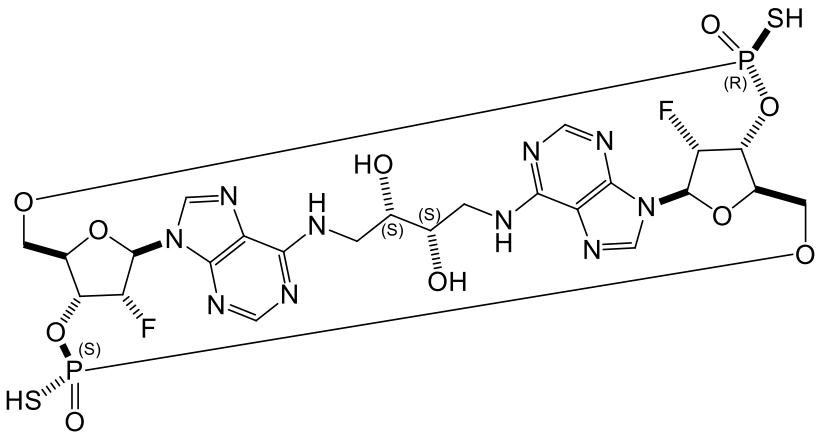

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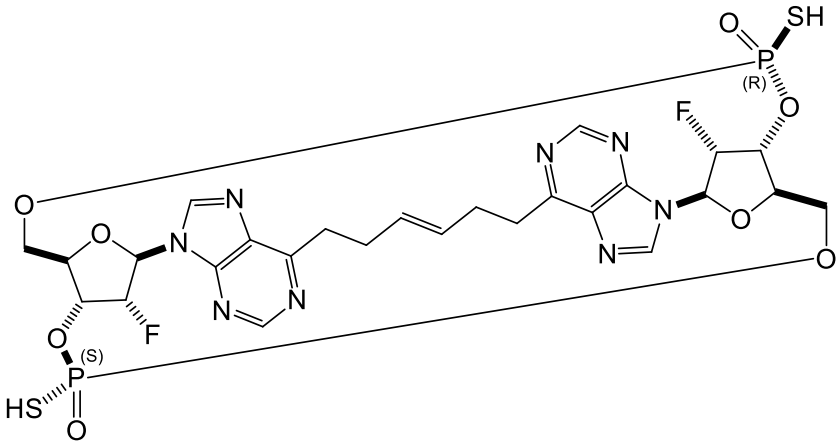

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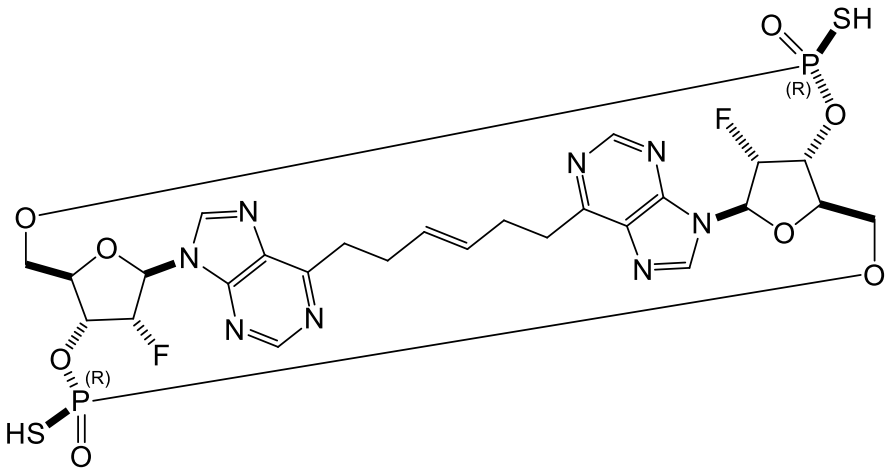

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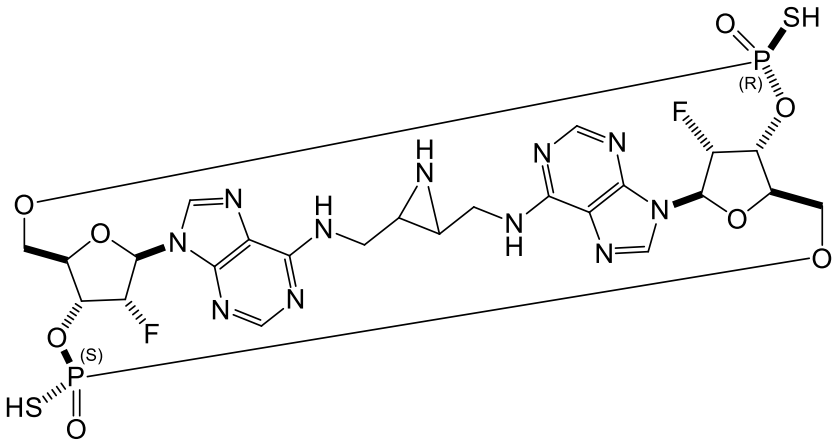

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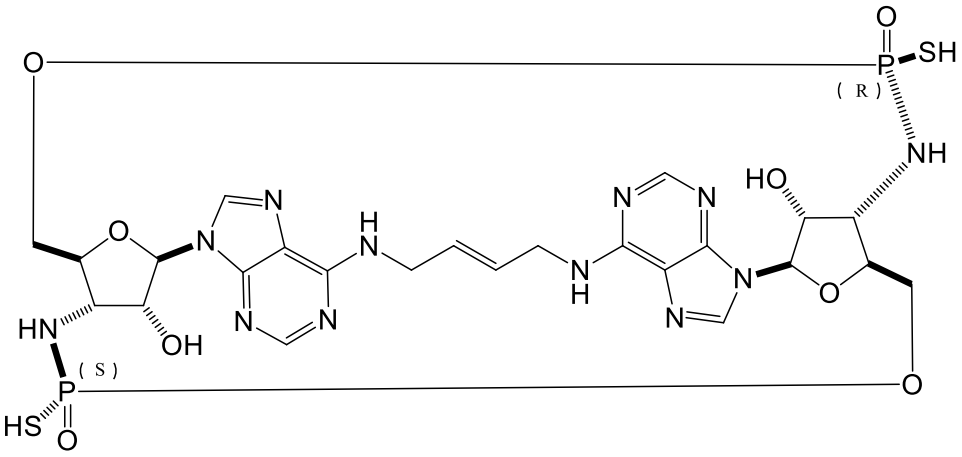

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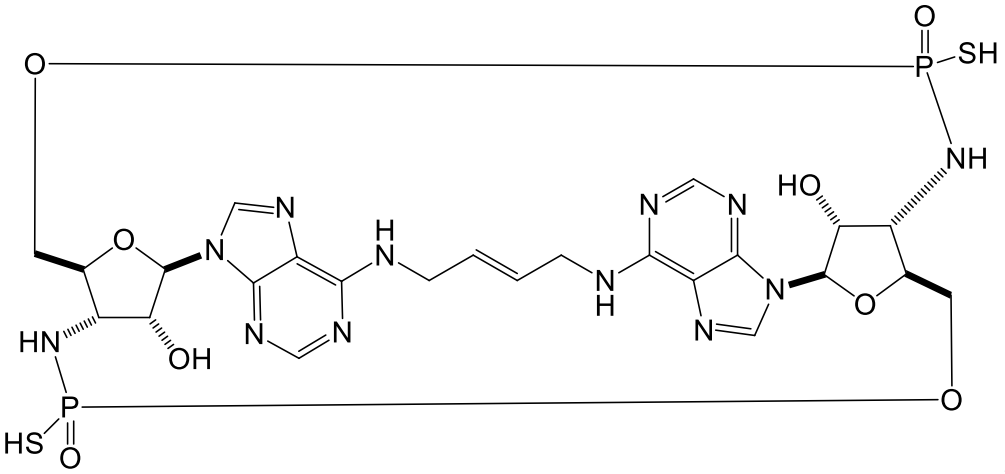

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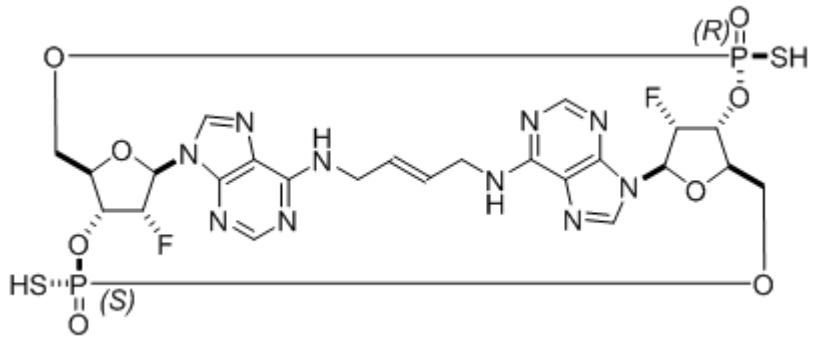
or a pharmaceutically acceptable salt thereof.

16. A compound or pharmaceutically acceptable salt thereof of claim 15, selected from the group consisting of:



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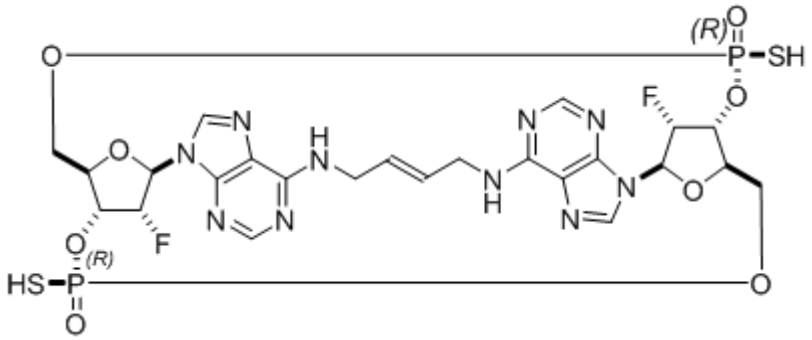
(R)
SH
F
HS
(R)

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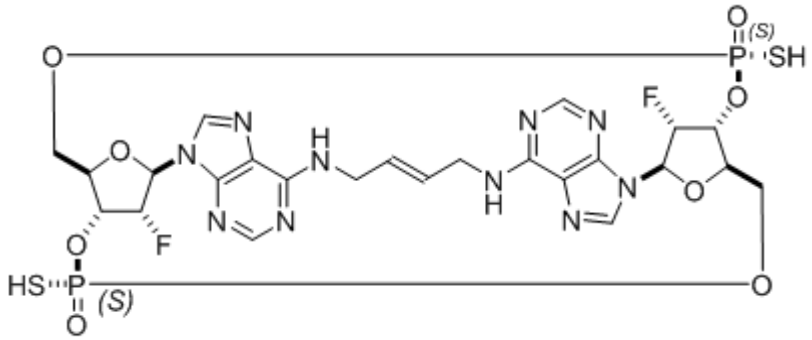
(S)
SH
F
HS
(S)

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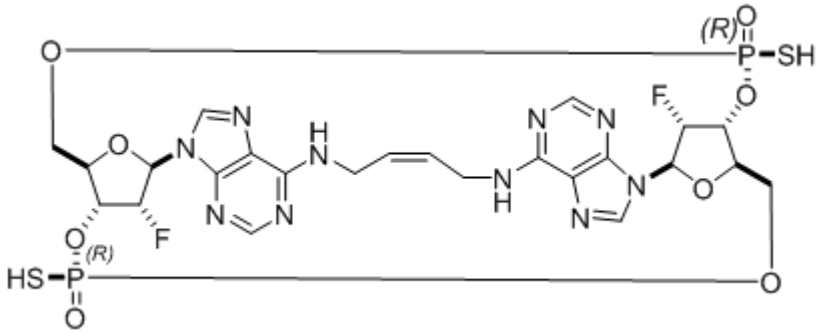
(R)
SH
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HS
(R)

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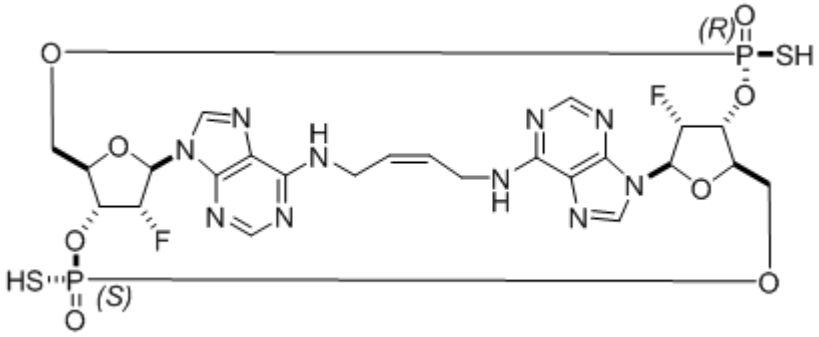
(R)
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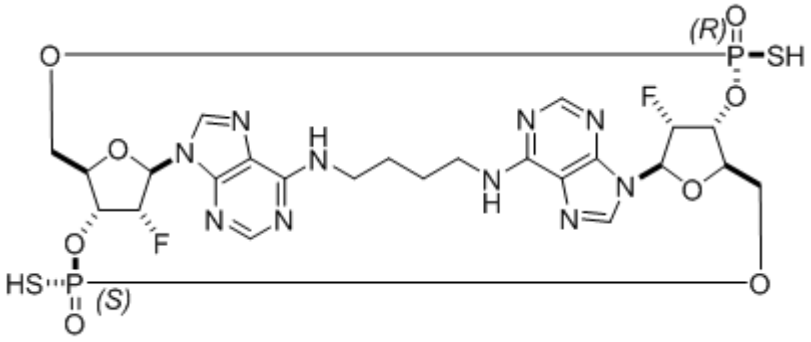
(R)
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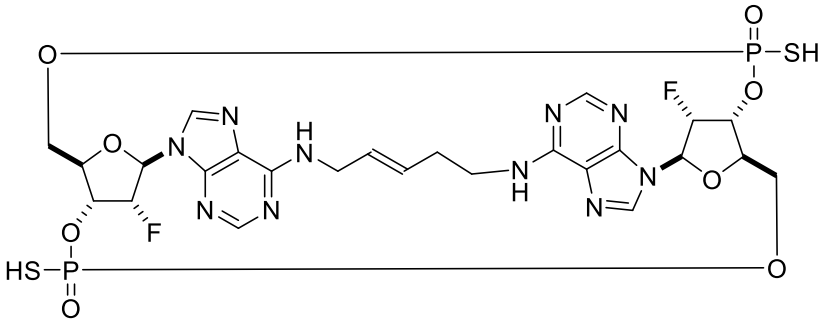
SH
F
HS

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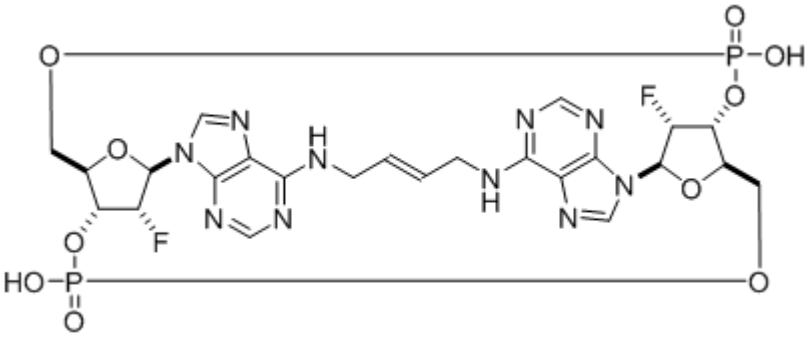
OH
F
HO

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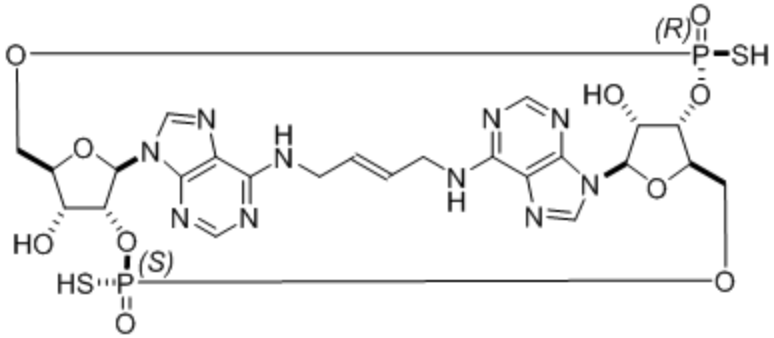
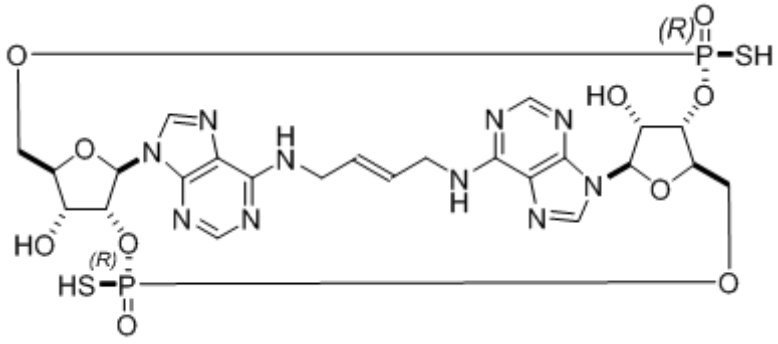

(R)
SH
HO
HO
(S)
HS

,



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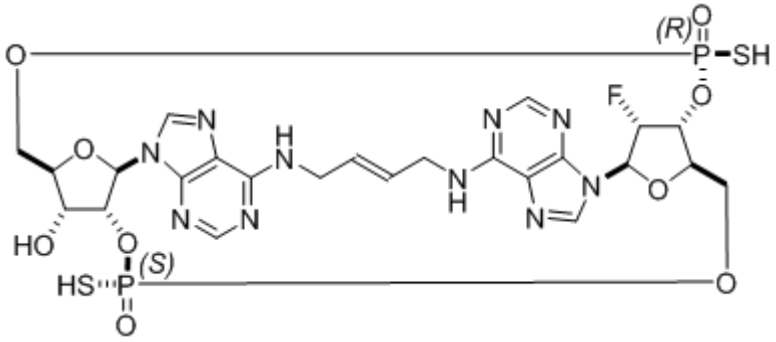

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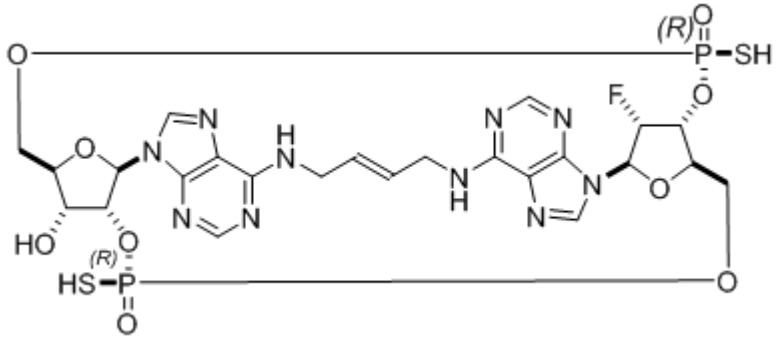

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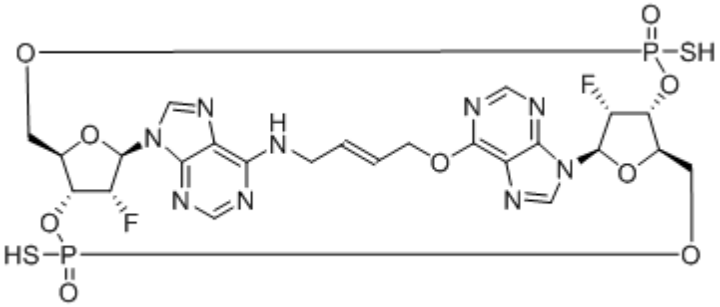

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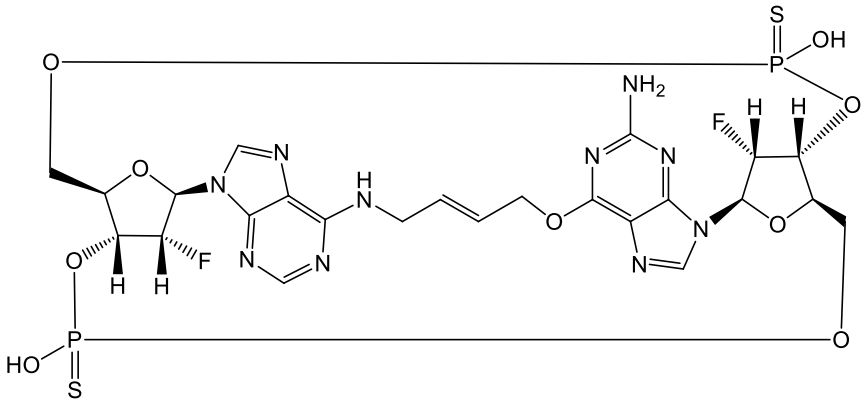

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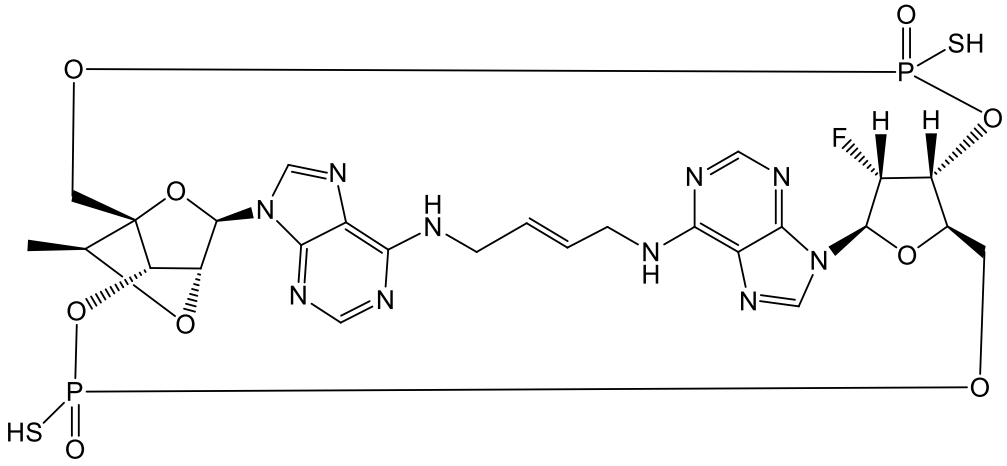
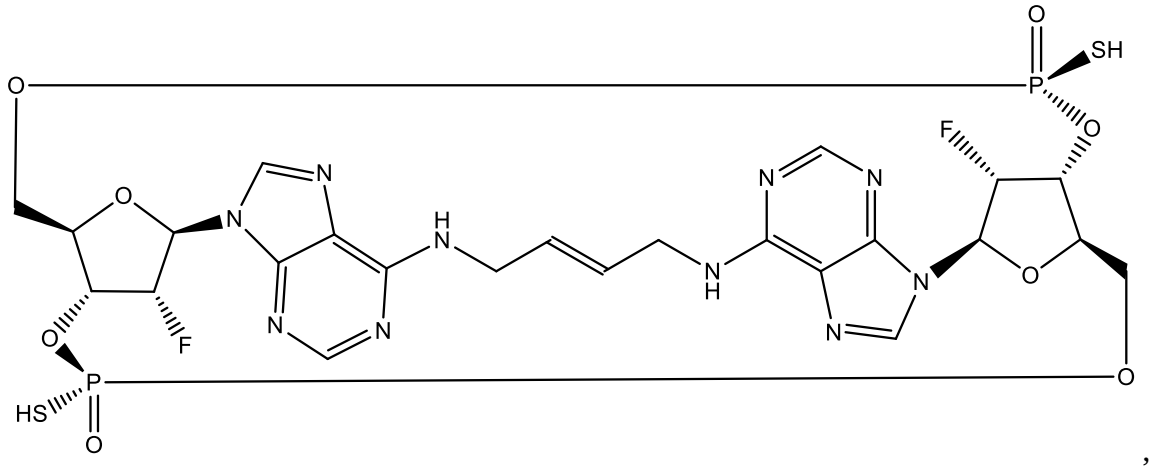


or a pharmaceutically acceptable salt thereof.

17. A compound or pharmaceutically acceptable salt of any one of claims 1-16, wherein the compound or pharmaceutically acceptable salt has (i) an EC_{50} value below 100 micromolar in reporter cells expressing human STING HAQ variant; (ii) an EC_{50} value below 100 micromolar in reporter cells expressing human STING AQ variant; (iii) an EC_{50} value below 100 micromolar in reporter cells expressing human STING WT variant; or (iv) an EC_{50} value below 100 micromolar in reporter cells expressing human STING REF variant.

18. A compound or pharmaceutically acceptable salt wherein the compound is:



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or a pharmaceutically acceptable salt thereof.

19. A pharmaceutically acceptable salt of any one of claims 1-18, wherein the salt is a diammonium salt.

20. A pharmaceutical composition comprising a compound according to any one of claims 1-18 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

21. A compound or pharmaceutically acceptable salt of any one of claims 1-19, or pharmaceutical composition according to claim 20 for use in therapy.

22. Use of a compound or pharmaceutically acceptable salt according to any one of claims 1-19 for preparation of a pharmaceutical composition for treating cancer.

23. Use of a compound or pharmaceutically acceptable salt of any one of claims 1-19, or pharmaceutical composition according to claim 20, in a treatment for cancer.

24. Use of a compound, a pharmaceutically acceptable salt, or a pharmaceutical composition of any one of claims 1-20 in the manufacture of a medicament for treating cancer, the use comprising thatthe compound, pharmaceutically acceptable salt or pharmaceutical composition is to be administered to an individual identified as having a cancer treatable by the compound, pharmaceutically acceptable salt or pharmaceutical composition.

25. The use of claim 24, wherein said individual is identified as having a cancer treatable by a compound, pharmaceutically acceptable salt or pharmaceutical composition of any one of claims 1-19 by a presence of a REF STING variant allele in the patient.

26. The compound or pharmaceutically acceptable salt or pharmaceutical composition of claim 21 or the use of claim 24, wherein the cancer is selected from the group consisting of lymphoma, melanoma, colorectal cancer, breast cancer, acute myeloid leukemia, colon cancer, liver cancer, prostate cancer, pancreatic cancer, renal cancer, and glioma.

27. Use of a compound, pharmaceutically acceptable salt or pharmaceutical composition of any one of claims 1-20 in the manufacture of a medicament for treating cancer in a patient having REF STING allele.

28. Use of a compound, pharmaceutically acceptable salt or pharmaceutical composition of any one of claims 1-20 in the manufacture of a medicament for treating cancer in a patient having WT STING allele.

29. Use of a compound, pharmaceutically acceptable salt or pharmaceutical composition of any one of claims 1-20 in the manufacture of a medicament for treating cancer in a patient having AQ STING allele.

30. Use of a compound, pharmaceutically acceptable salt or pharmaceutical composition of any one of claims 1-20 in the manufacture of a medicament for treating cancer in a patient having HAQ STING allele.

31. The use of any one of claims 27-30, wherein the cancer is selected from the group consisting of melanoma, colorectal cancer, breast cancer, acute myeloid leukemia, colon cancer, liver cancer, and glioma.

32. The compound or pharmaceutically acceptable salt or pharmaceutical composition of claim 21 or 26 or the use of any one of claims 24-31, wherein said cancer is metastatic.