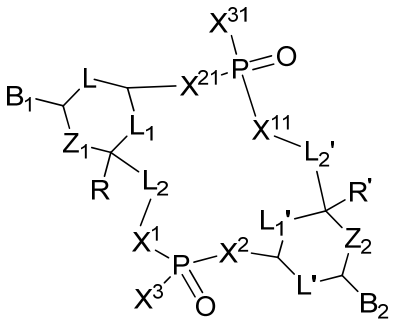
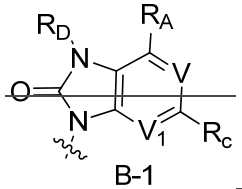
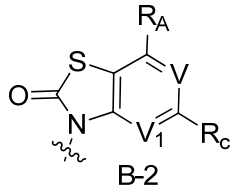
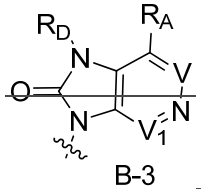
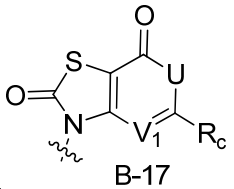
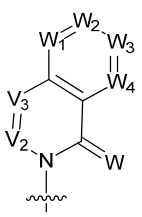
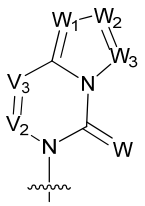
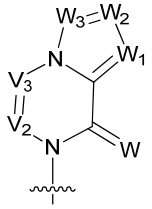
~~What is claimed is~~Claims:

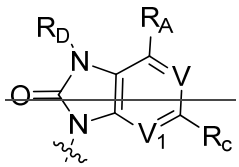
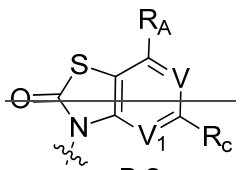
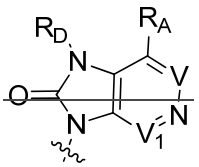
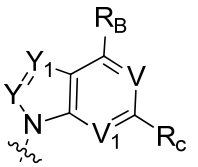
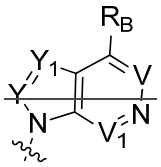
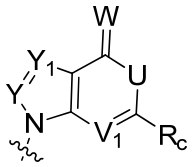
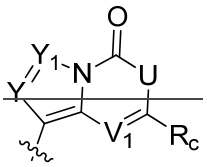
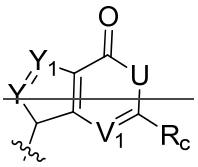
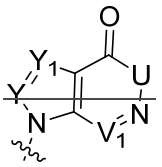
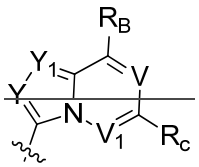
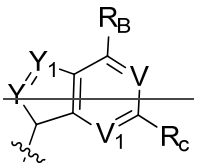
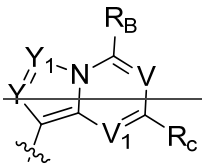
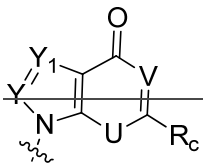
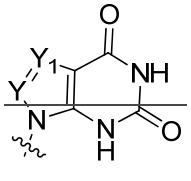
1. A cyclic di-nucleotide analogue (I), a~~n~~ stereoisomer, ~~prodrug,~~ stable isotope derivative or pharmaceutically acceptable salt thereof;

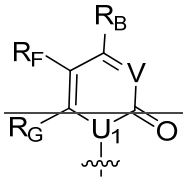


(I)

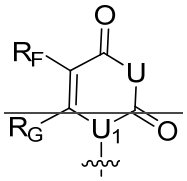
wherein each of Z_1, Z_2 is independently O~~, S, SO_2, CH_2, CF_2 or Se~~;

B_1 is  B-1,  B-2,  B-3,  B-17,  B-18,  B-19 or  B-20;

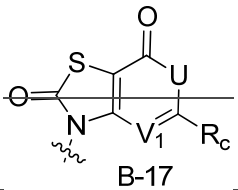
B_2 is  B-1,  B-2,  B-3,  B-4,  B-5, or  B-6,  B-7,  B-8,  B-9,  B-10,  B-11,  B-12,  B-13,  B-14;



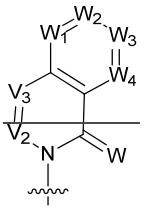
B-15 ,



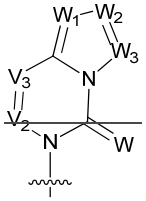
B-16 ,



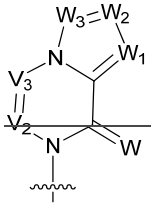
B-17 ,



B-18 ,



B-19 ~~or~~



B-20 ;

L, L_1, L' and L_1' are as defined in the following combinations:

1) L is a connecting bond, L_1 is CR^1R^2, L' is $CR^{11}R^{21}$, L_1' is a connecting bond, or

2) L is CR^1R^2, L_1 is a connecting bond, L' is a connecting bond, L_1' is $CR^{11}R^{21}$;

~~L and L_1 are each independently a connecting bond or CR^1R^2;~~

~~L' and L_1' are each independently a connecting bond or $CR^{11}R^{21}$;~~

L_2 is CH_2~~O, S or CR^3R^4~~; L_2' is CH_2~~O, S or $CR^{31}R^{41}$~~;

X^1 is O~~, S or CR^5R^6~~; X^{11} is O~~, S or $CR^{51}R^{61}$~~;

X^2 is O~~, S or CR^7R^8~~; and X^{21} is O~~, S or $CR^{71}R^{81}$~~;

X^3 and X^{31} are each independently OH, SH or BH_3^-;

R and R' are each independently hydrogen~~, C_{2-6} alkenyl, C_{2-6} alkynyl or C_{1-6} alkyl; the C_{2-6} alkenyl, C_{2-6} alkynyl or C_{1-6} alkyl is unsubstituted or selectively substituted at any position by 1 to 3 substituents selected from halogen, hydroxyl, amino, azido and cyano~~;

R^1 and R^2 are each independently hydrogen, halogen, cyano, hydroxyl, thiol, amino, azido, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkyl, halo-C_{1-6} alkyl, halo-C_{1-6} alkoxy, halo-C_{1-6} alkylthio, C_{1-6} alkylamino, $OC(O)R^a$ or OR^a; the C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkyl is unsubstituted or selectively substituted at any position by 1 to 3 substituents selected from halogen, hydroxyl, amino, azido, and cyano;

R^{11} and R^{21} are each independently hydrogen, halogen, cyano, hydroxyl, thiol, amino, azido, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkyl, halo-C_{1-6} alkyl, halo-C_{1-6} alkoxy, halo-C_{1-6} alkylthio, C_{1-6} alkylamino, $OC(O)R^a$, or OR^a; the C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkyl

is unsubstituted or selectively substituted at any position by 1 to 3 substituents selected from halogen, hydroxyl, amino, azido, and cyano;

~~alternatively, R^1 and R^2 together form carbonyl;~~

~~alternatively, R^{11} and R^{21} together form carbonyl;~~

~~alternatively, R is $-CH_2-$, R^1 is $-O-$, R and R^1 are interconnected to form heterocycloalkyl;~~

~~alternatively, R' is $-CH_2-$, R^{11} is $-O-$, R' and R^{11} are interconnected to form heterocycloalkyl;~~

~~R^3 and R^4 are each independently hydrogen, deuterium, halogen or C_{1-6} alkyl;~~

~~R^{31} and R^{41} are each independently hydrogen, deuterium, halogen or C_{1-6} alkyl;~~

~~R^5 and R^6 are each independently hydrogen, deuterium, halogen or C_{1-6} alkyl;~~

~~R^{51} and R^{61} are each independently hydrogen, deuterium, halogen or C_{1-6} alkyl;~~

~~R^7 and R^8 are each independently hydrogen, deuterium, halogen or C_{1-6} alkyl;~~

~~R^{71} and R^{81} are each independently hydrogen, deuterium, halogen or C_{1-6} alkyl;~~

Y and Y_1 are independently CR_E or N;

U is CHR_E' or NR_D';

~~U_1 is CH or N;~~

V, V_1, V_2 and V_3 are each independently CR_E'' or N;

W is O or S;

W_1, W_2, W_3 and W_4 are each independently N or CR_F';

each of R_A, R_B, R_C, R_E, R_E', R_E''~~, R_F~~, and R_F' ~~and R_G~~ are independently H, halogen, -CN, $-NO_2$, $-N_3$, R^c, $-SR^c$, $-OR^c$, $-OC(O)R^c$, $-OC(O)OR^c$, $-OC(O)NR^bR^c$, $-C(O)OR^c$, $-C(O)R^c$, $-C(O)NR^bR^c$, $-NR^bR^c$, $-NR^bC(O)R^c$, $-N(R^b)C(O)OR^c$, $-N(R^a)C(O)NR^bR^c$, $-NR^bS(O)_2R^c$, $-NR^bC(=NH)R^c$, $-NR^bC(=NR^c)NH_2$, $-S(O)_{1-2}R^c$, $-S(O)_2NR^bR^c$ or $-NR^aS(O)_2NR^bR^c$;

~~each of R_D and~~ R_D' is independently H or R^c;

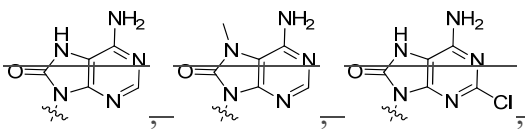
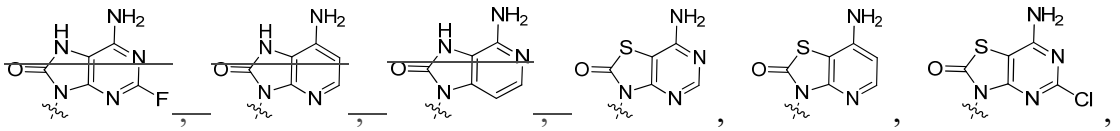
each of R^a and R^b is independently H, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-10} alkyl, halo- C_{1-6} alkyl~~, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aryl-C_{1-6} alkyl, heteroaryl-C_{1-6} alkyl, cycloalkyl-C_{1-6} alkyl, or heterocycloalkyl-C_{1-6} alkyl~~;

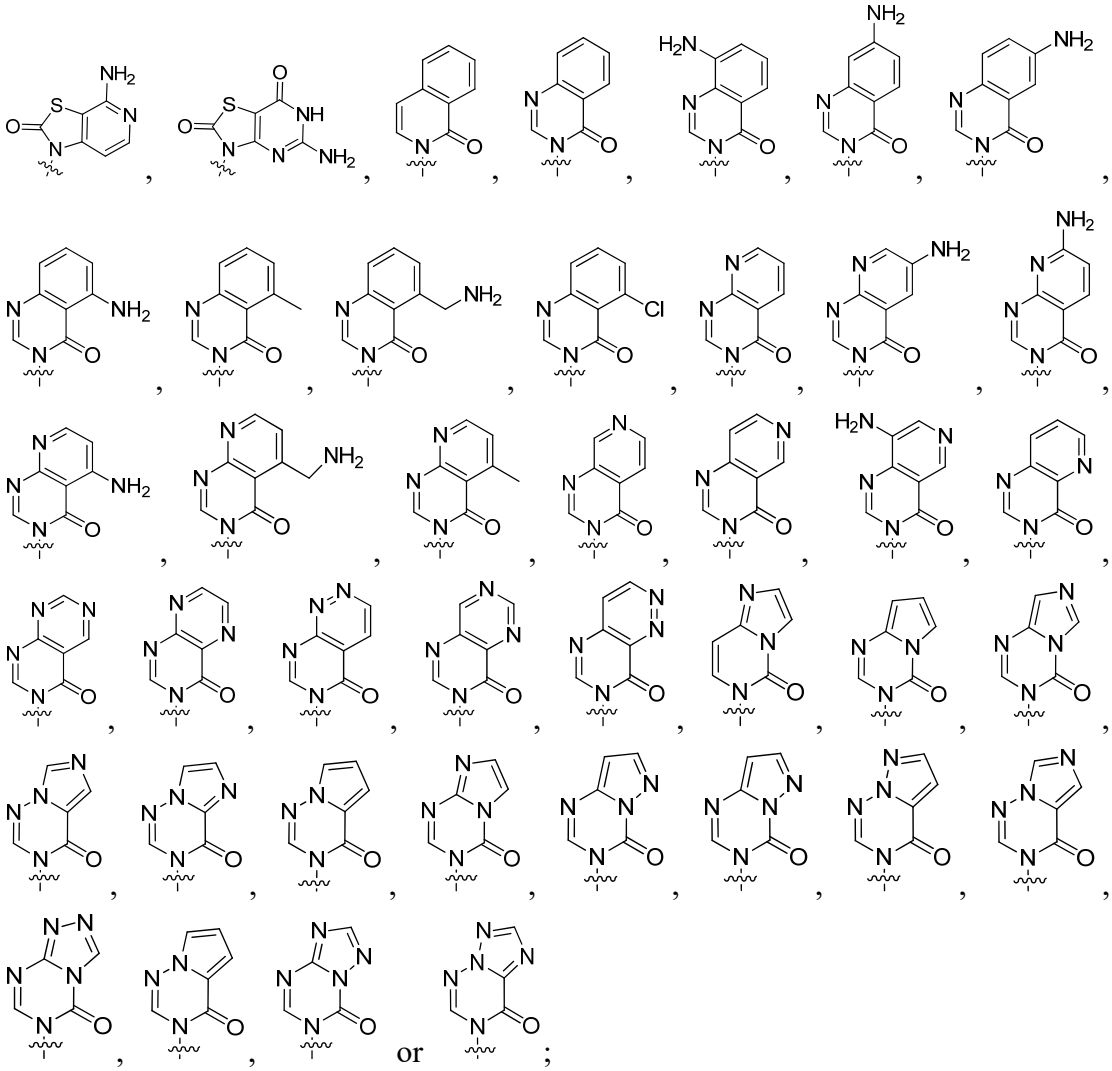
each R^c is independently H, substituted or unsubstituted C_{1-10} alkyl, substituted or

unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted C_{3-10} cycloalkyl, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted 3-10 membered heterocycloalkyl, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted C_{6-10} aryl-C_{1-6} alkyl, substituted or unsubstituted C_{3-10} cycloalkyl-C_{1-6} alkyl, substituted or unsubstituted 3-10 membered heterocycloalkyl-C_{1-6} alkyl, substituted or unsubstituted 5-10 membered heteroaryl-C_{1-6} alkyl; the C_{1-10} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 3-10 membered heterocycloalkyl, 5-10 membered heteroaryl, C_{6-10} aryl-C_{1-6} alkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, 3-10 membered heterocycloalkyl-C_{1-6} alkyl, or 5-10 membered heteroaryl-C_{1-6} alkyl is unsubstituted or selectively substituted at any position by one or more R^d;

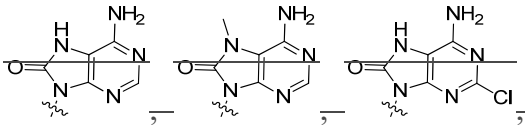
each R^d is independently halogen, halo-C_{1-6} alkyl, halo-C_{1-6} alkoxy, C_{1-6} alkyl, -CN, -N_3, -SR^e, -OR^e, -$C(O)R^e$, -$NR^eR^{e'}$, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted C_{3-10} cycloalkyl, or substituted or unsubstituted 3-10 membered heterocycloalkyl; the C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl or 3-10 membered heterocycloalkyl is unsubstituted or selectively substituted at any position by one or more substituents selected from halogen, hydroxyl, cyano, amino, C_{1-4} alkyl, halo-C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylamino and halo-C_{1-4} alkoxy;

each of R^e and $R^{e'}$ is independently C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-10} alkyl, halo- C_{1-6} alkyl~~, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aryl-C_{1-6} alkyl, heteroaryl-C_{1-6} alkyl, cycloalkyl-C_{1-6} alkyl, or heterocycloalkyl-C_{1-6} alkyl~~.

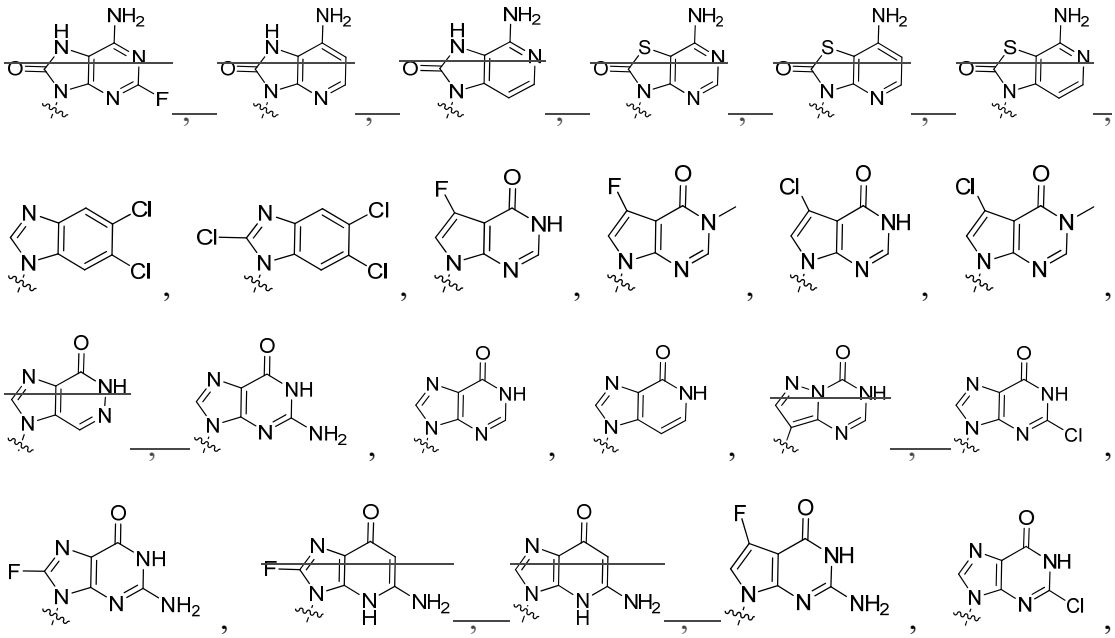
2. The cyclic di-nucleotide analogue of formula (I), the stereoisomer, ~~prodrug,~~ stable isotope derivative or pharmaceutically acceptable salt thereof according to claim 1, wherein B_1 is any of the following structures:  

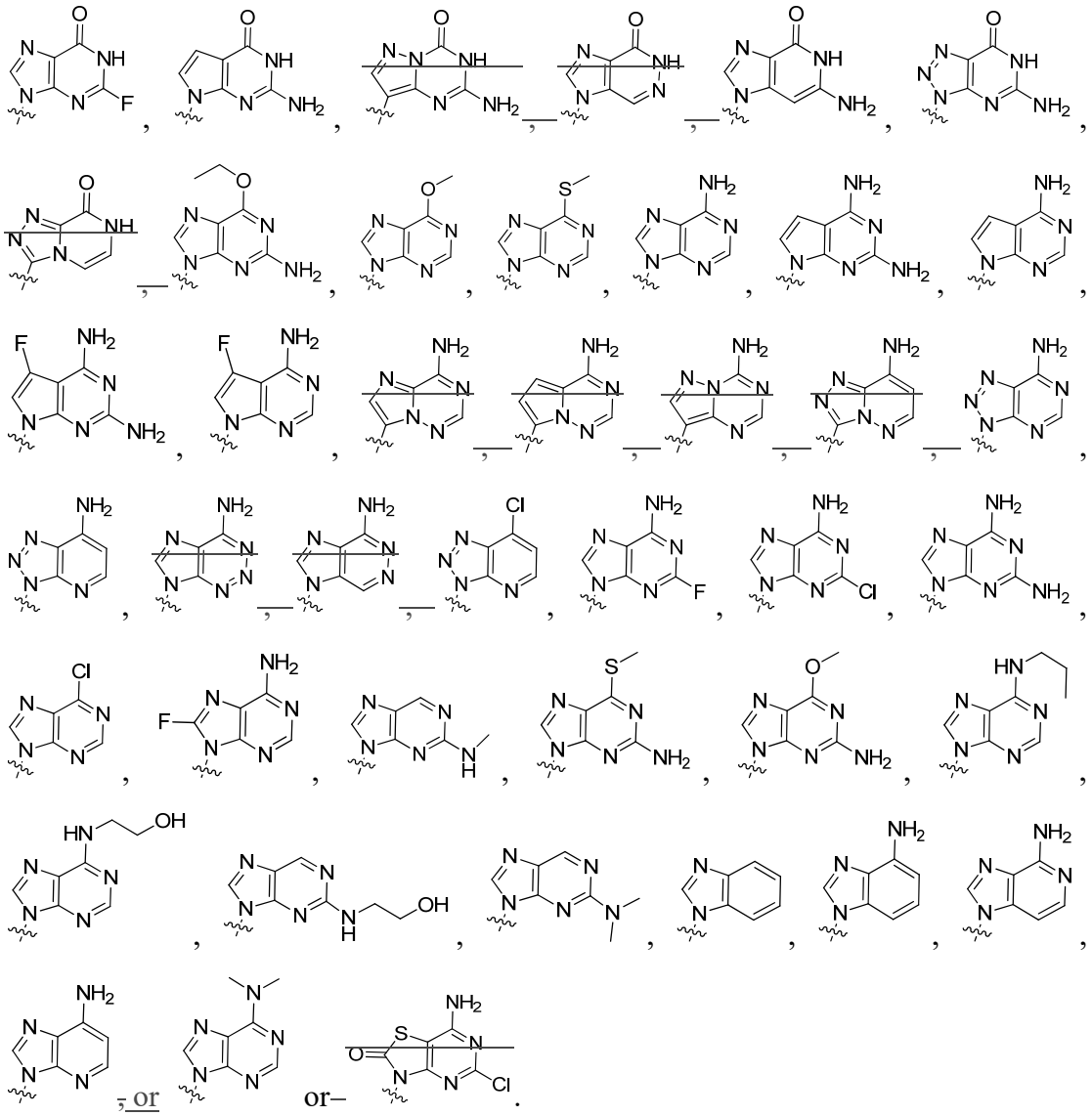


or



and/or, B_2 is any of the following structures:





3. ~~The cyclic di-nucleotide analogue of formula (I), the isomer, prodrug, stable isotope derivative or pharmaceutically acceptable salt thereof according to claim 1, wherein L_2 is CH_2;~~

~~and/or, L_2' is CH_2;~~

~~and/or, X^1 is O;~~

~~and/or, X^{11} is O;~~

~~and/or, X^2 is O;~~

~~and/or, X^{21} is O;~~

~~and/or, L, L_1, L' and L_1' are as defined in the following combinations:~~

~~1) L is a connecting bond, L_1 is CR^1R^2, L' is $CR^{11}R^{21}$, L_1' is a connecting bond, or~~

~~2) L is C R^1R^2, L_1 is a connecting bond, L' is a connecting bond, L_1' is $CR^{11}R^{21}$.~~

~~4.~~3. The cyclic di-nucleotide analogue of formula (I), the stereoisomer, ~~prodrug,~~ stable isotope derivative or pharmaceutically acceptable salt thereof according to claim 1, ~~wherein R and R' are each independently hydrogen;~~

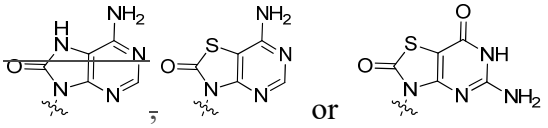
~~and/or,~~ R^1 and R^2 are each independently hydrogen, halogen, hydroxyl, or OR^a;

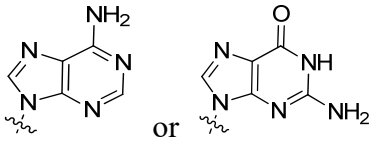
and/or, R^{11} and R^{21} are each independently hydrogen, halogen, hydroxyl, or OR^a;

and/or, each R^a is independently C_{1-4} alkyl or halo-C_{1-4} alkyl.

~~5.~~4. The cyclic di-nucleotide analogue of formula (I), the stereoisomer, ~~prodrug,~~ stable isotope derivative or pharmaceutically acceptable salt thereof according to claim 1, wherein Z_1 is O;

Z_2 is O;

B_1 is  ;

B_2 is  ;

L and L_1 are each independently a connecting bond or CR^1R^2;

L' and L_1' are each independently a connecting bond or $CR^{11}R^{21}$; and, L, L_1, L' and L_1' are as defined in the following combinations:

1) L is a connecting bond, L_1 is CR^1R^2, L' is $CR^{11}R^{21}$, L_1' is a connecting bond, or

2) L is CR^1R^2, L_1 is a connecting bond, L' is a connecting bond, L_1' is $CR^{11}R^{21}$;

L_2 is CH_2;

L_2' is CH_2;

X^1 is O;

X^{11} is O;

X^2 is O;

X^{21} is O;

X^3 and X^{31} are each independently OH or SH;

R and R' are each independently hydrogen;

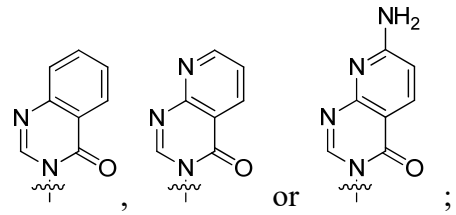
R^1 and R^2 are each independently hydrogen, halogen, hydroxyl or OR^a;

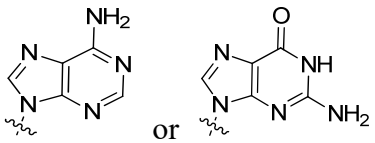
R^{11} and R^{21} are each independently hydrogen, halogen, hydroxyl or OR^a;

each R^a is independently C_{1-4} alkyl or halo-C_{1-4} alkyl.

~~6.~~5. The cyclic di-nucleotide analogue for formula (I), the stereoisomer, ~~prodrug,~~ stable isotope derivative or pharmaceutically acceptable salt thereof according to claim 1, wherein Z_1 is O;

Z_2 is O;

B_1 is ;

B_2 is ;

L and L_1 are each independently a connecting bond or CR^1R^2;

L' and L_1' are each independently a connecting bond or $CR^{11}R^{21}$; and, L, L_1, L' and L_1' are as defined in the following combinations:

1) L is a connecting bond, L_1 is CR^1R^2, L' is $CR^{11}R^{21}$, L_1' is a connecting bond, or

2) L is CR^1R^2, L_1 is a connecting bond, L' is a connecting bond, L_1' is $CR^{11}R^{21}$;

L_2 is CH_2;

L_2' is CH_2;

X^1 is O;

X^{11} is O;

X^2 is O;

X^{21} is O;

X^3 and X^{31} are each independently OH or SH;

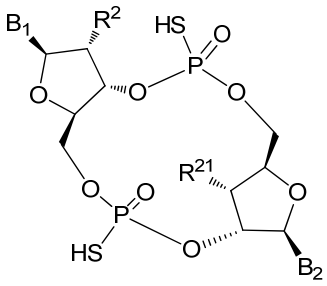
R and R' are each independently hydrogen;

R^1 and R^2 are each independently hydrogen, halogen, hydroxyl or OR^a;

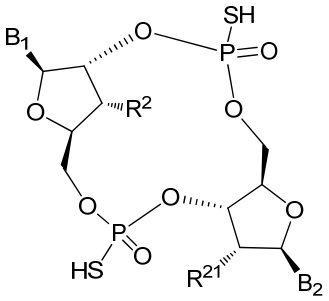
R^{11} and R^{21} are each independently hydrogen, halogen, hydroxyl or OR^a;

each R^a is independently C_{1-4} alkyl or halo-C_{1-4} alkyl.

~~7.~~6. The cyclic di-nucleotide analogue of formula (I), the stereoisomer, ~~prodrug,~~ stable isotope derivative or pharmaceutically acceptable salt thereof according to any one of claims 1 to ~~6~~5, wherein, which is shown as the compound of formula (VI) or (VII), the stereoisomer, ~~prodrug,~~ stable isotope derivative or pharmaceutically acceptable salt thereof:



(VI)

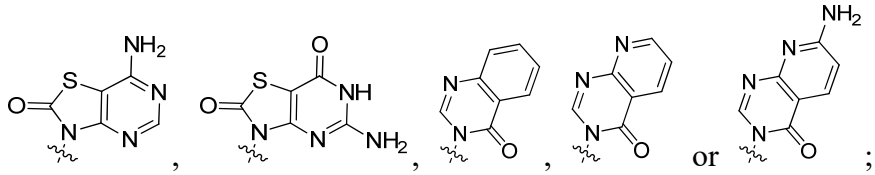


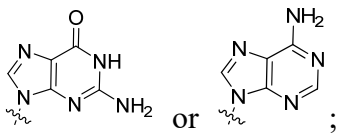
(VII)

wherein,B_1, B_2, R^2 and R^{21} are as defined in any one of claims 1 to ~~6~~5.

~~8.~~7. The cyclic di-nucleotide analogue of formula (I), the stereoisomer, ~~prodrug,~~ stable isotope derivative or pharmaceutically acceptable salt thereof according to claim ~~7~~6, wherein the stereo-configuration of P is (Sp, Sp), (Sp, Rp), (Rp, Rp) or (Rp, Sp).

~~9.~~8. The cyclic di-nucleotide analogue of formula (I), the stereoisomer, ~~prodrug,~~ stable isotope derivative or pharmaceutically acceptable salt thereof according to claim ~~7~~6,

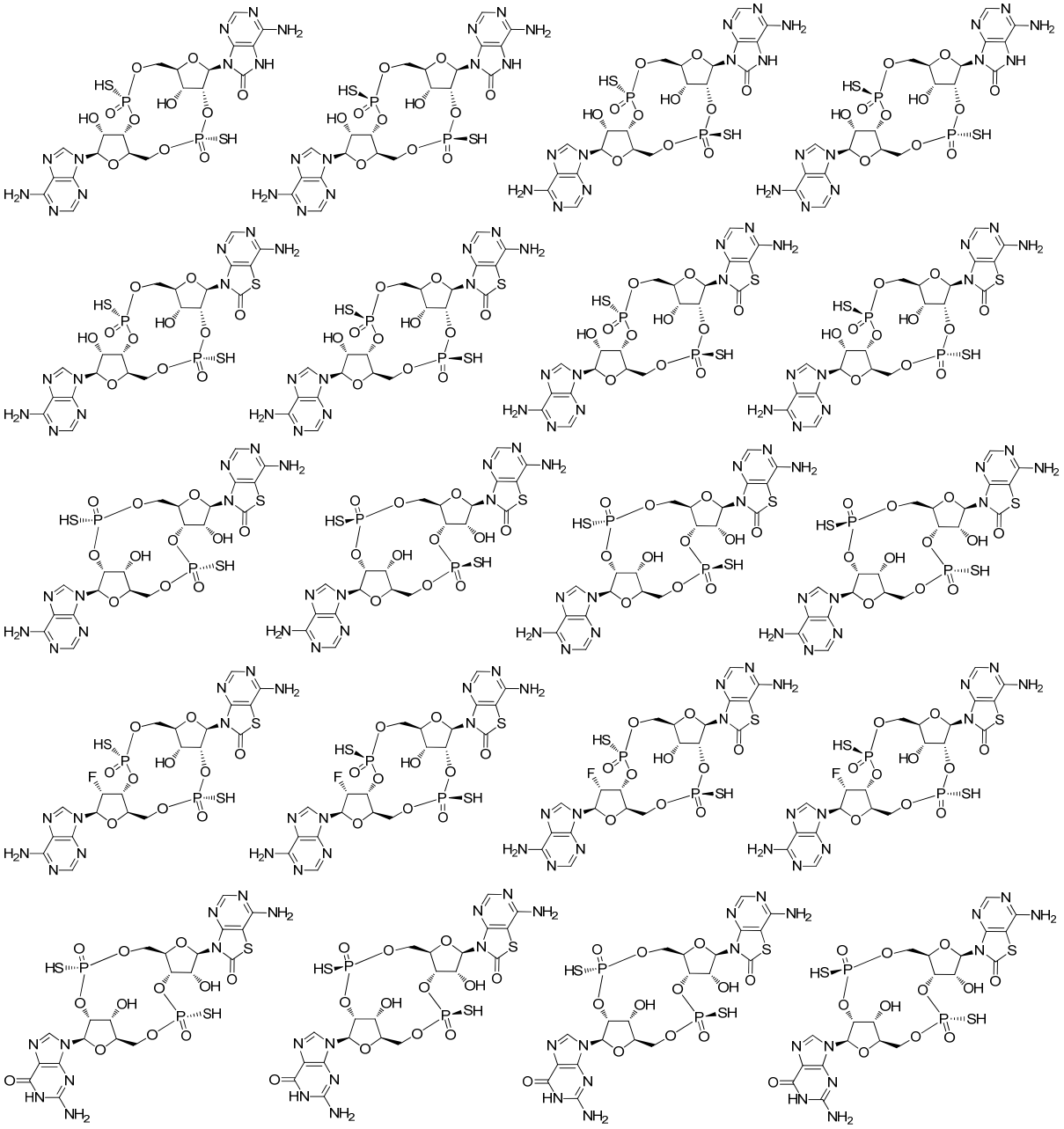
wherein B_1 is  ;

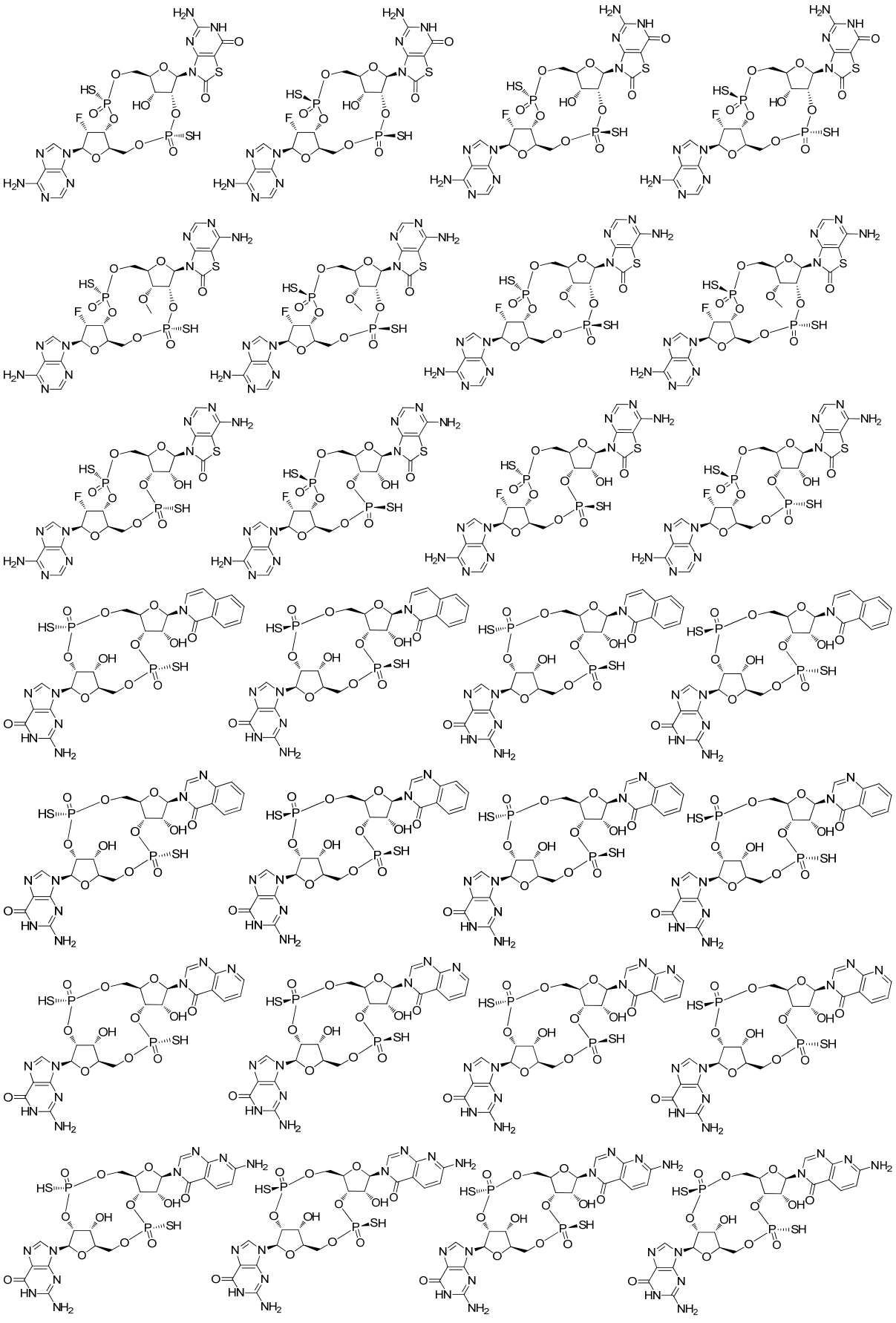
and/or, B_2 is  ;

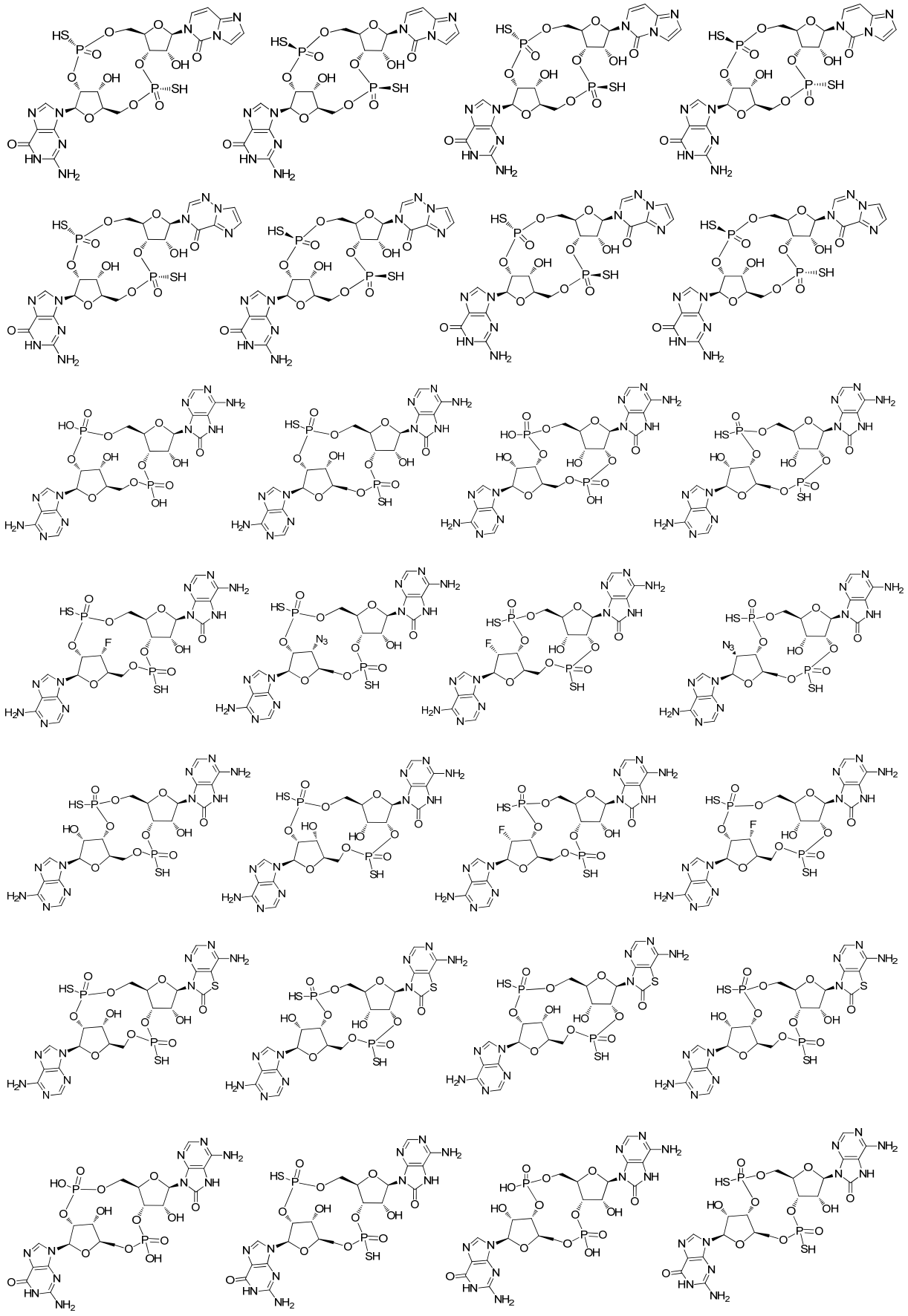
in Formula VI, R^2 is -OH; R^{21} is -OH;

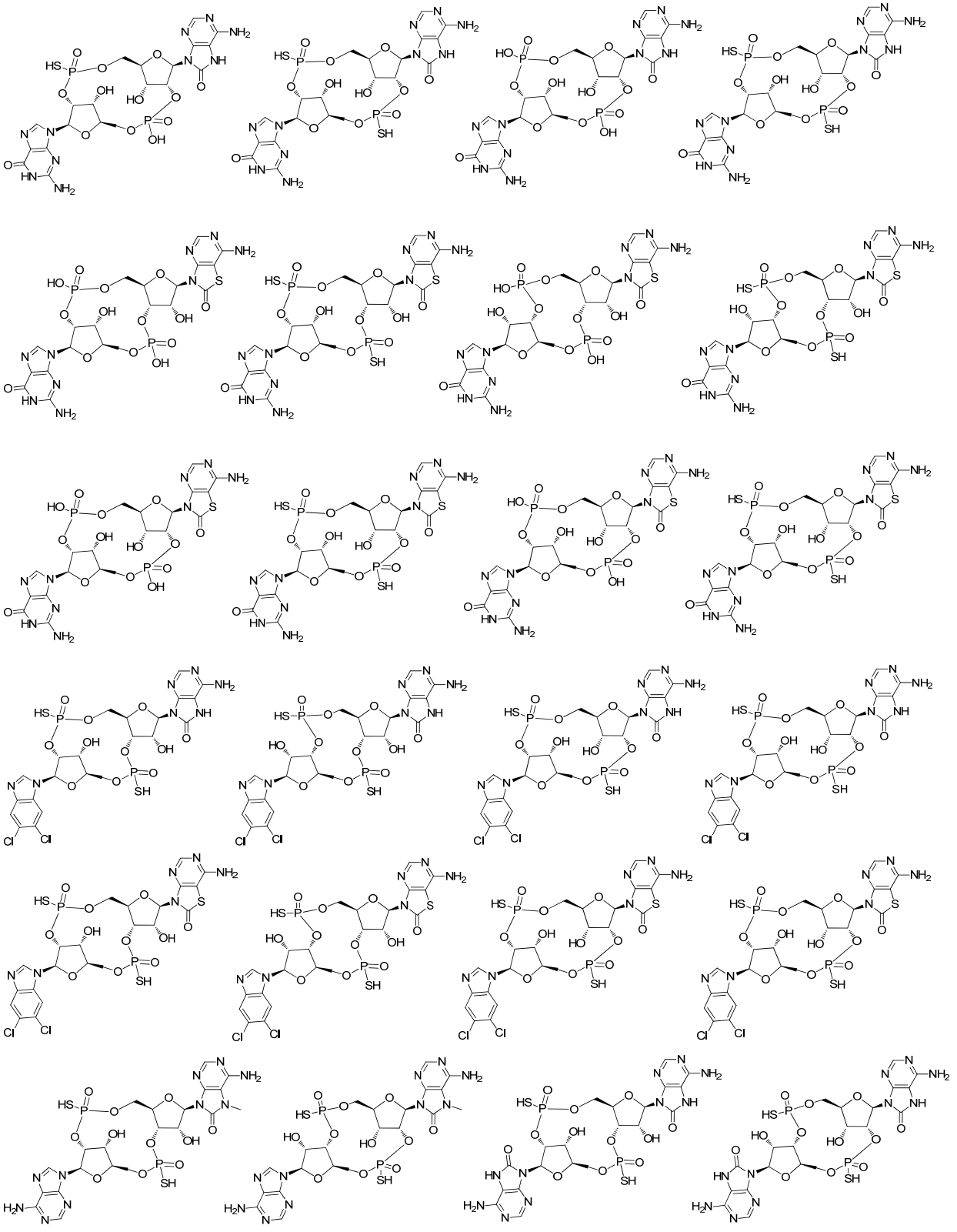
in Formula VII, R^2 is -OH or $-OCH_3$; R^{21} is -OH or F.

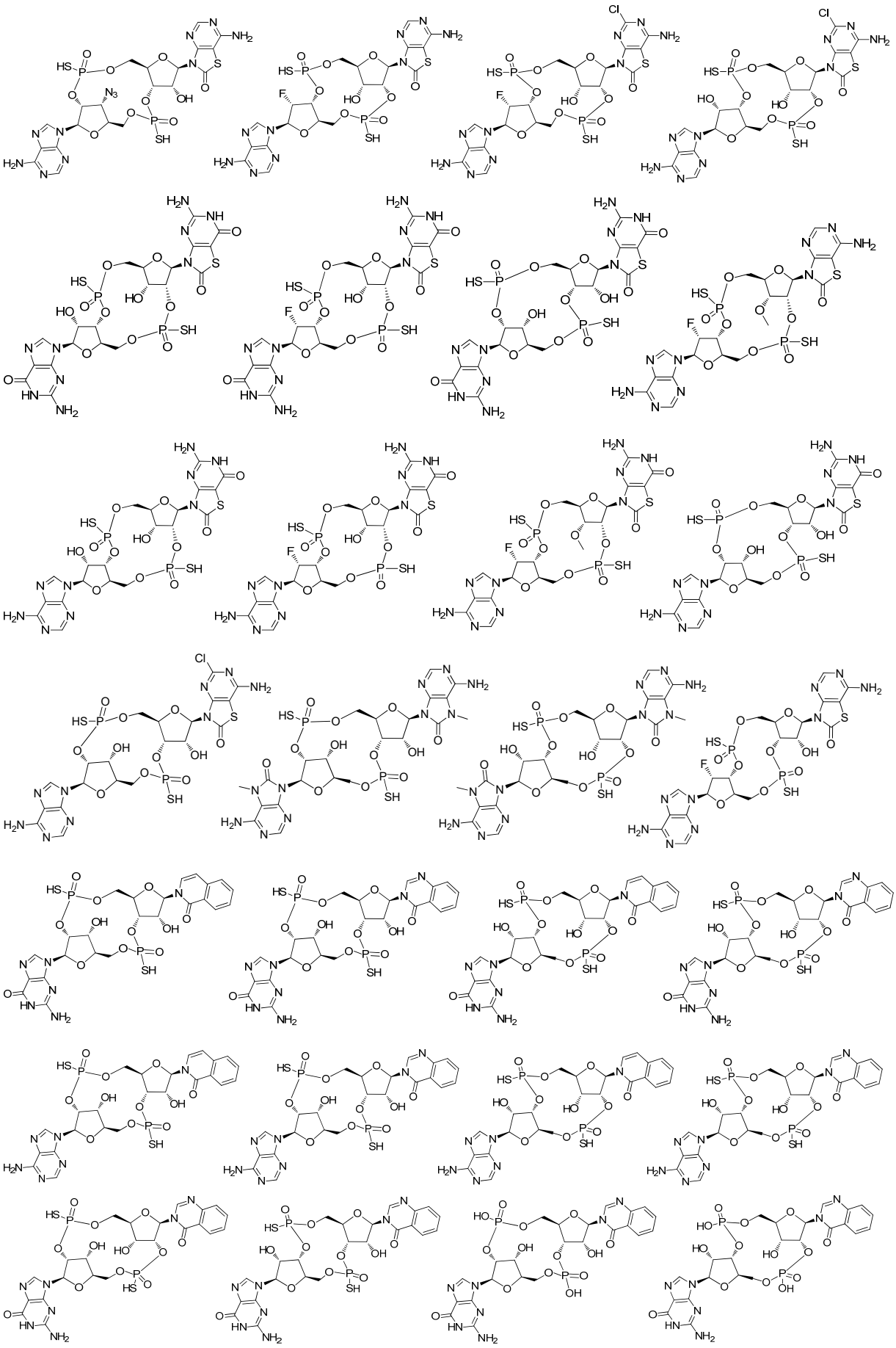
~~10.~~9. ~~The~~ A cyclic di-nucleotide analogue of formula (I), the stereoisomer, ~~prodrug,~~ stable isotope derivative or pharmaceutically acceptable salt thereof ~~according to claim 1~~, which is any of the following structures:

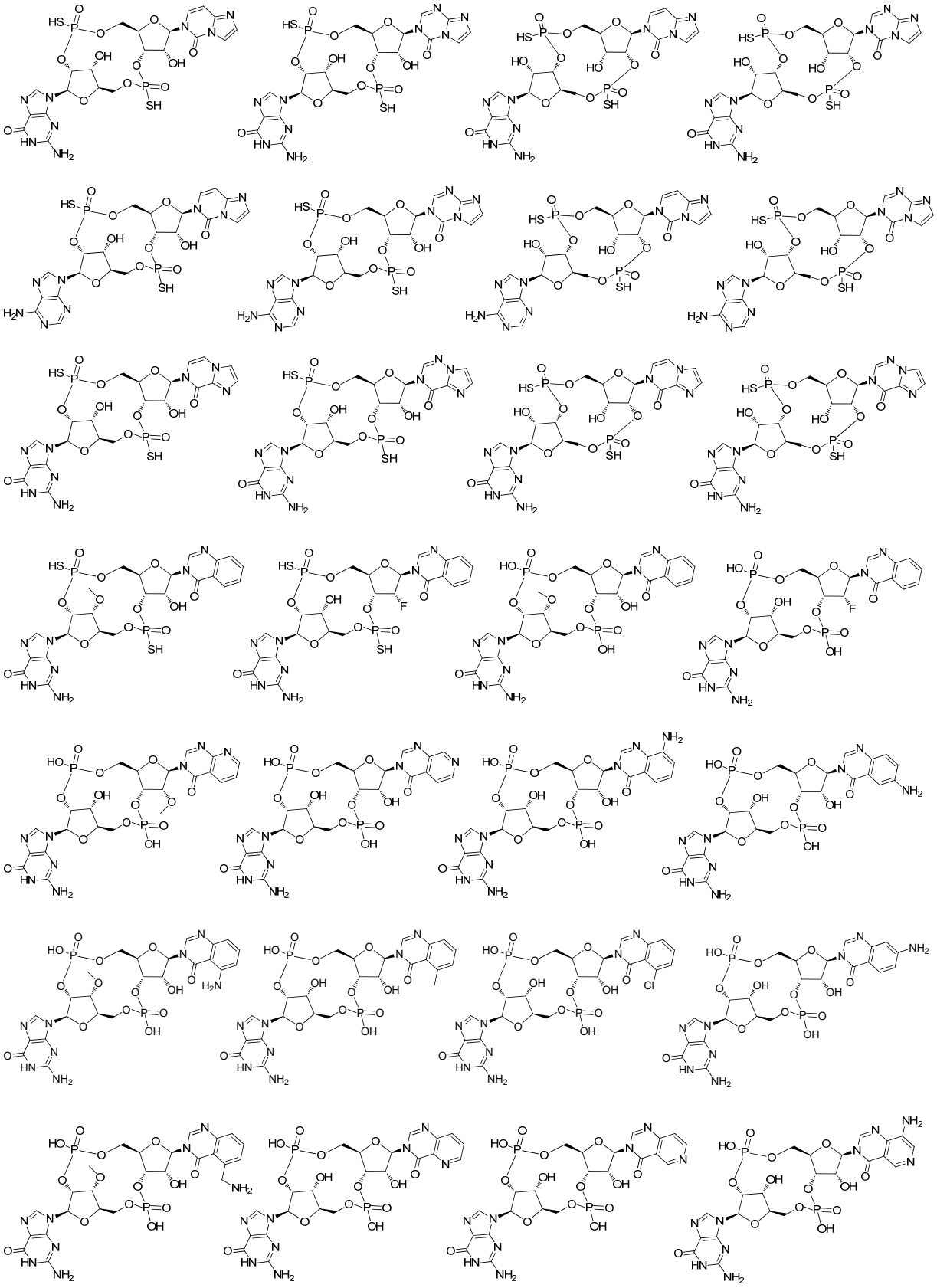


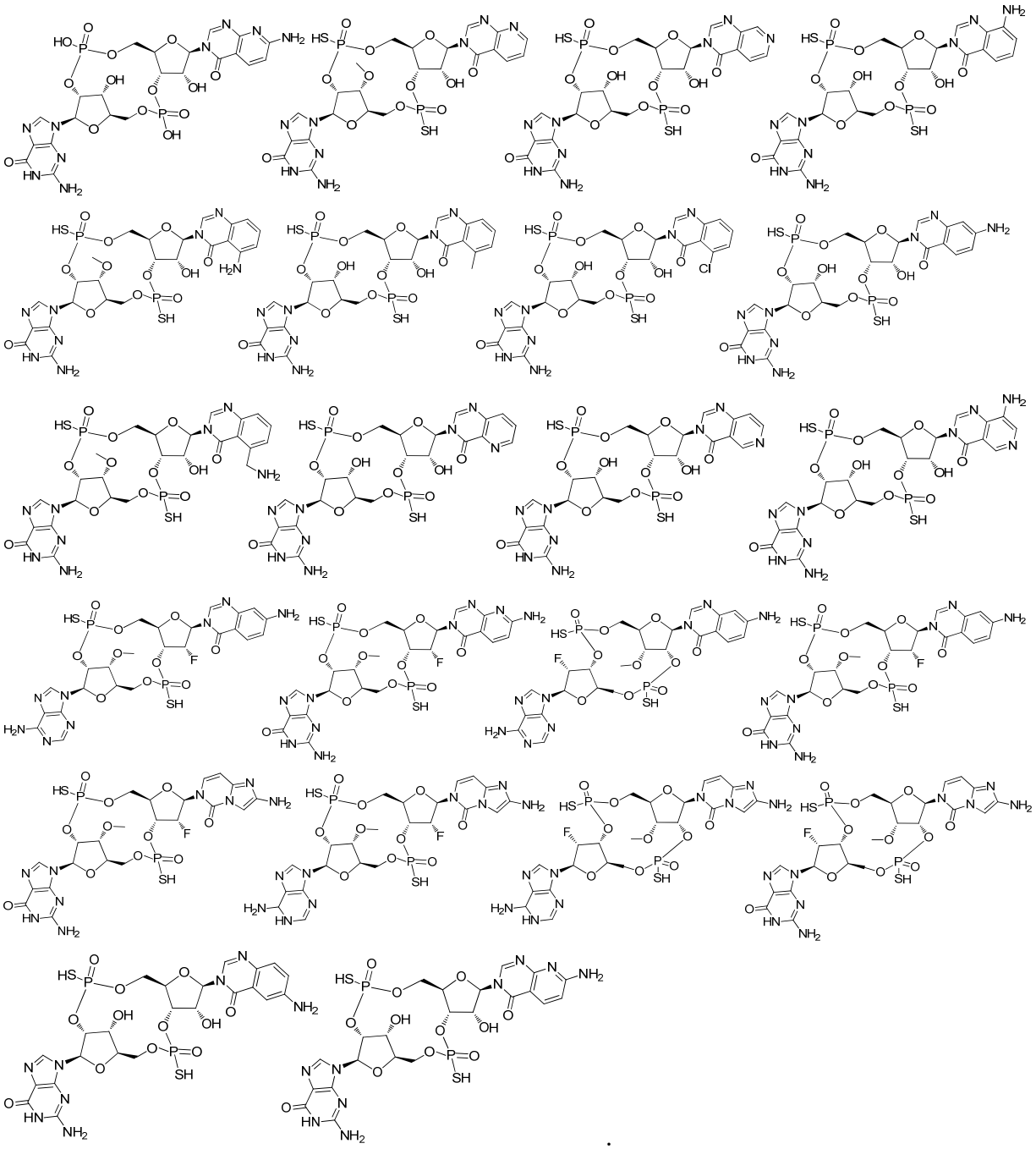












~~11.~~10. A pharmaceutical composition comprising a therapeutically effective amount of the compound of formula (I), the stereoisomer, ~~prodrug,~~ stable isotope derivative or pharmaceutically acceptable salt thereof according to at least one of claims 1 to ~~10~~9, and a pharmaceutical acceptable excipient.

~~12.~~11. ~~A use of the compound of formula (I), the isomer, prodrug, stable isotope derivative or pharmaceutically acceptable salt thereof according to at least one of claims~~

~~1 to 10~~The compound of formula (I), the stereoisomer, stable isotope derivative or pharmaceutically acceptable salt thereof according to any of claims 1 to 9 or the pharmaceutical composition according to claim ~~11~~10, comprised in ~~the preparation of~~ a STING modulator.

~~14.~~12. The compound of formula (I), the stereoisomer, stable isotope derivative or pharmaceutically acceptable salt thereof according to claim 11 or the pharmaceutical composition ~~use~~ according to claim ~~12~~11, wherein the STING modulator is a STING agonist.

~~15.~~13. A use of the compound of formula (I), the stereoisomer, ~~prodrug,~~ stable isotope derivative or pharmaceutically acceptable salt thereof according to at least one of claims 1 to ~~10~~ 9 or the pharmaceutical composition according to claim ~~11~~10, in the preparation of a medicament for the treatment, alleviation and/or prevention of a STING-mediated disease, wherein the STING-mediated disease is viral infection or other infectious diseases, autoimmune diseases, or malignancies.

~~15. The use according to claim 14, wherein the STING-mediated disease is viral infection or other infectious diseases, autoimmune diseases, or malignancies.~~

~~15. A use of the compound of formula (I), the isomer, prodrug, stable isotope derivative or pharmaceutically acceptable salt thereof according to at least one of claims 1 to 10 or the pharmaceutical composition according to claim 11, in the preparation of medicament for regulating the proliferation of T cells or other immune cells.~~

~~16.~~14. A use of the compound of formula (I), the stereoisomer, ~~prodrug,~~ stable isotope derivative or pharmaceutically acceptable salt thereof according to at least one of claims 1 to ~~10~~ 9 or the pharmaceutical composition according to claim ~~11~~ 10 in the preparation of medicament for the treatment and/or alleviation of malignancies.

~~17.~~15. ~~A use of t~~The compound of formula (I), the stereoisomer, ~~prodrug,~~ stable isotope derivative or pharmaceutically acceptable salt thereof according to at least one of claims 1 to ~~10~~9 or the pharmaceutical composition according to claim ~~11~~10~~in the preparation of~~ comprised in a vaccine adjuvant.

~~18.~~16. Use of ~~A~~a combination formulation, wherein the combination formulation comprises a compound of formula (I), the stereoisomer, ~~prodrug,~~ stable isotope derivative or pharmaceutically acceptable salt thereof according to at least one of claims 1 to ~~10~~ 9 or the pharmaceutical composition according to claim ~~11~~ 10 is ~~used~~ in combination with other kinds of therapeutic agents, ~~and/or therapeutic methods~~ in the manufacture of a medicament for the treatment of cancer.