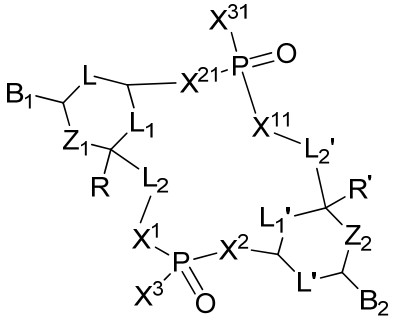
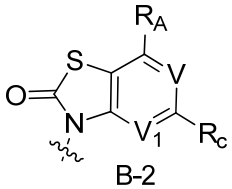
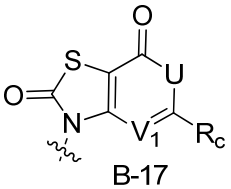
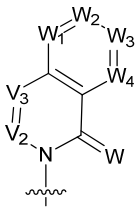
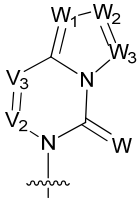
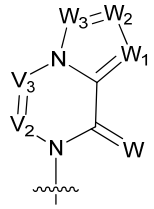
Claims:

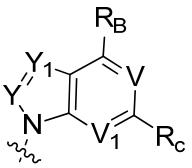
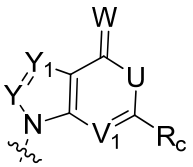
1. A cyclic di-nucleotide analogue (I), a stereoisomer, stable isotope derivative or pharmaceutically acceptable salt thereof;



(I)

wherein each of Z_1, Z_2 is independently O;

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

B_2 is  B-4 , or  B-6 ;

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; and X^{21} is O;

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

R and R' are each independently hydrogen;

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;

Y and Y_1 are independently CR_E or N;

U is CHR_E' or NR_D';

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'' and R_F' 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 $-NR^aS(O)_2NR^bR^c$;

R_D' is independently H or R^c;

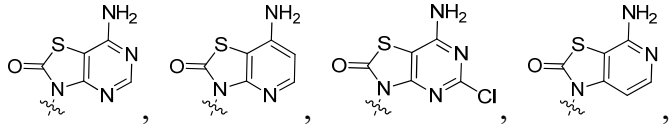
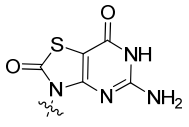
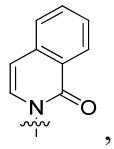
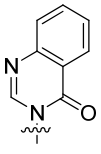
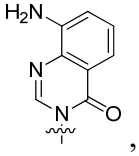
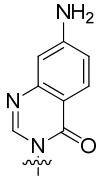
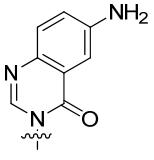
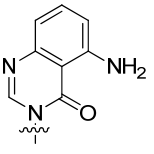
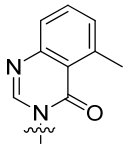
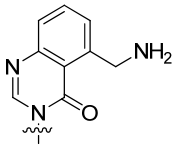
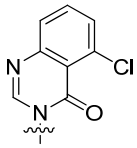
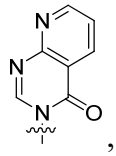
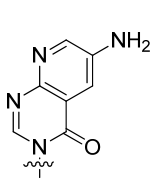
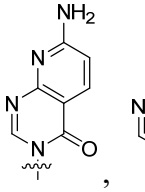
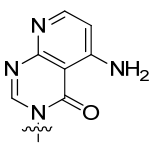
each of R^a and R^b is independently H, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-10} alkyl, halo- C_{1-6} alkyl;

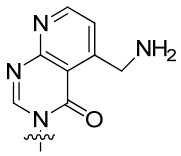
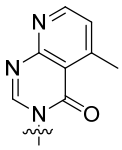
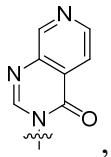
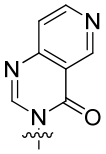
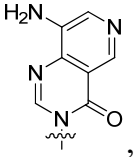
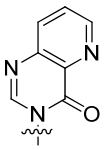
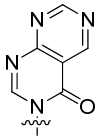
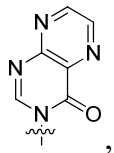
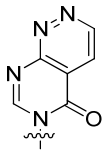
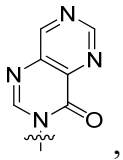
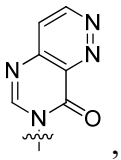
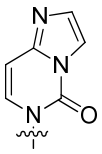
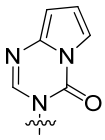
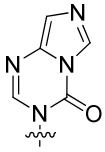
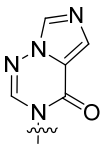
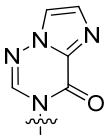
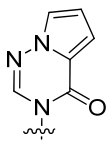
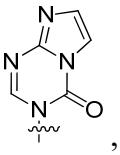
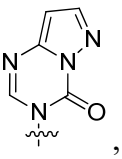
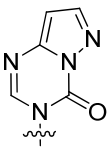
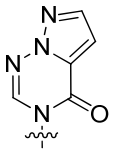
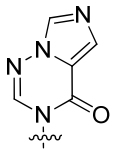
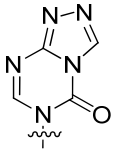
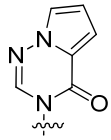
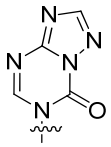
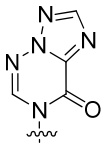
each R^c is independently H, substituted or unsubstituted C_{1-10} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted C_{3-10} cycloalkyl, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted 3-10 membered 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;

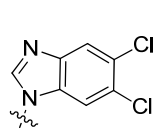
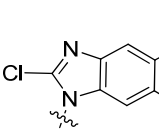
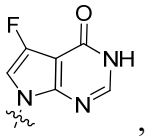
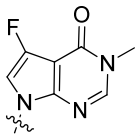
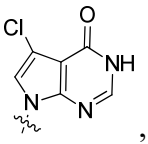
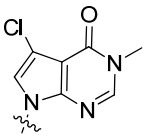
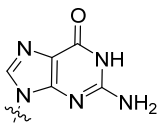
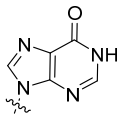
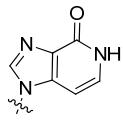
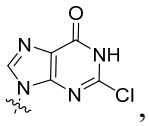
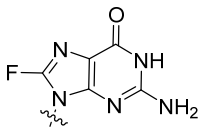
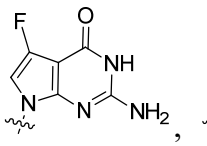
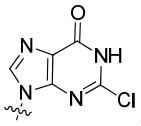
each R^d is independently halogen, halo-C_{1-6} alkyl, halo-C_{1-6} alkoxy, C_{1-6} alkyl, -CN, -N_3, -SR^e, -OR^e, -$C(O)R^e$, -$NR^eR^{e'}$, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted C_{3-10} cycloalkyl, or substituted 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.

2. The cyclic di-nucleotide analogue of formula (I), the stereoisomer, 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:

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

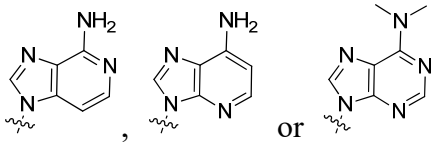
,

,

,

,

,



3. The cyclic di-nucleotide analogue of formula (I), the stereoisomer, stable isotope derivative or pharmaceutically acceptable salt thereof according to claim 1,

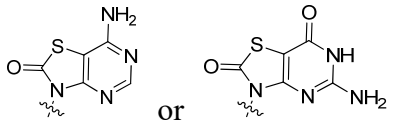
R^1 and R^2 are each independently hydrogen, halogen, hydroxyl, or OR^a;

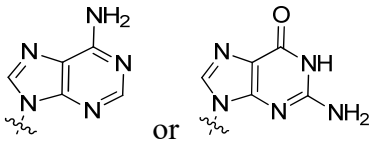
and/or, R^{11} and R^{21} are each independently hydrogen, halogen, hydroxyl, or OR^a;

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

4. The cyclic di-nucleotide analogue of formula (I), the stereoisomer, 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;

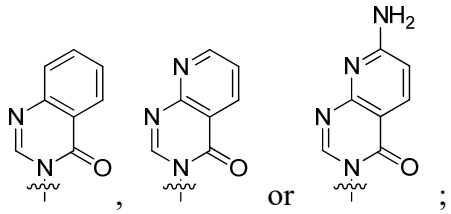
R^1 and R^2 are each independently hydrogen, halogen, hydroxyl or OR^a;

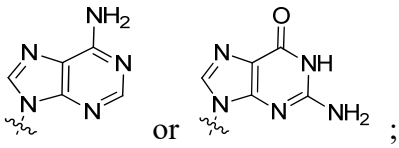
R^{11} and R^{21} are each independently hydrogen, halogen, hydroxyl or OR^a;

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

5. The cyclic di-nucleotide analogue for formula (I), the stereoisomer, 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;

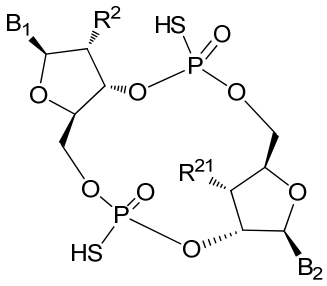
R and R' are each independently hydrogen;

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

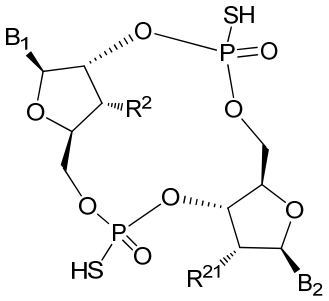
R^{11} and R^{21} are each independently hydrogen, halogen, hydroxyl or OR^a;

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

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



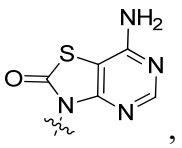
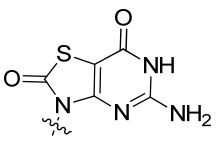
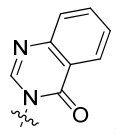
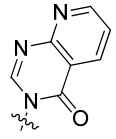
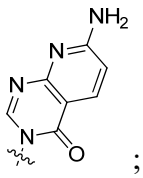
(VI)

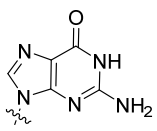
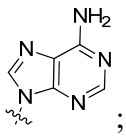


(VII)

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

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

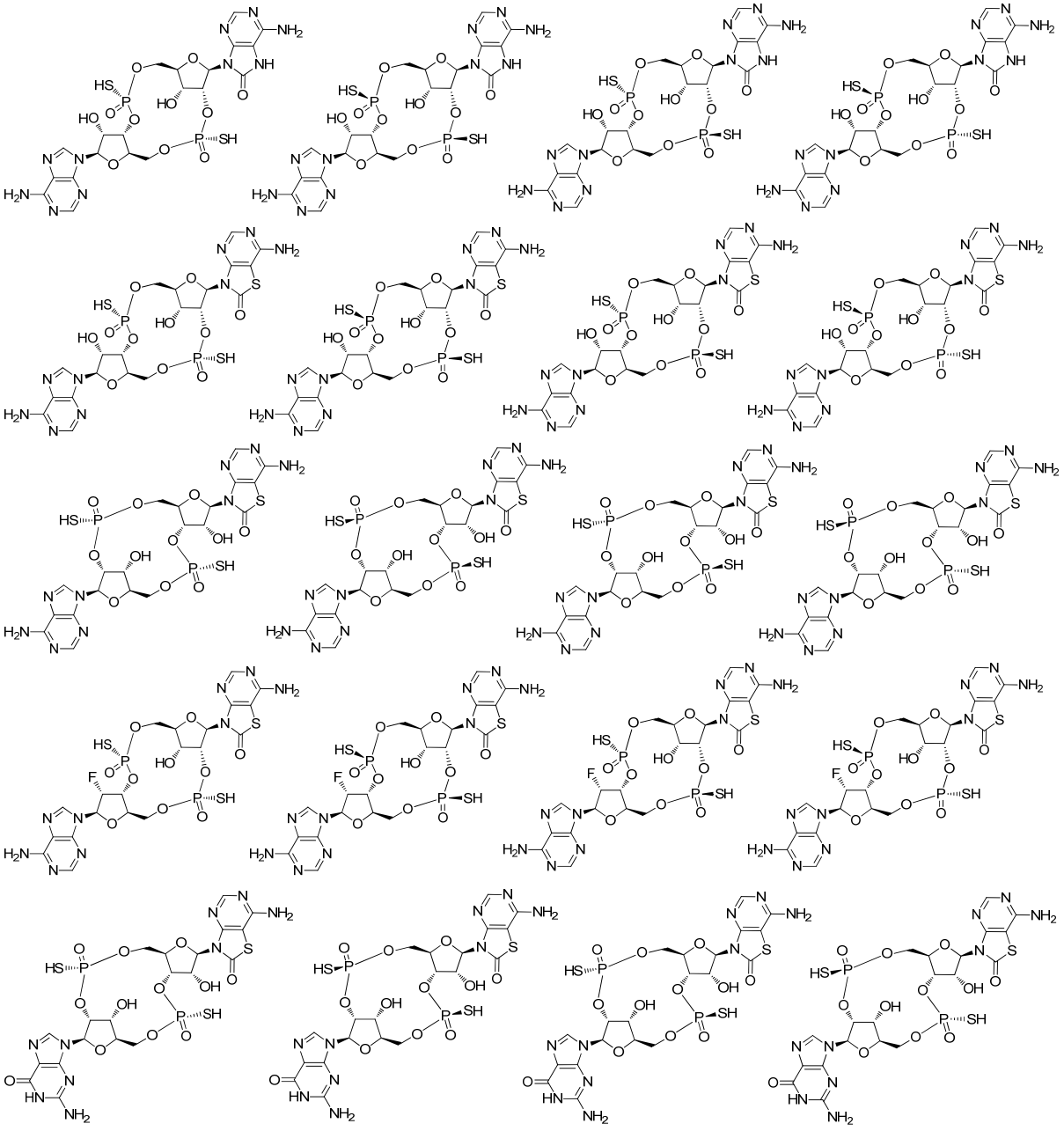
8. The cyclic di-nucleotide analogue of formula (I), the stereoisomer, stable isotope derivative or pharmaceutically acceptable salt thereof according to claim 6, wherein B_1 is , , ,  or ;

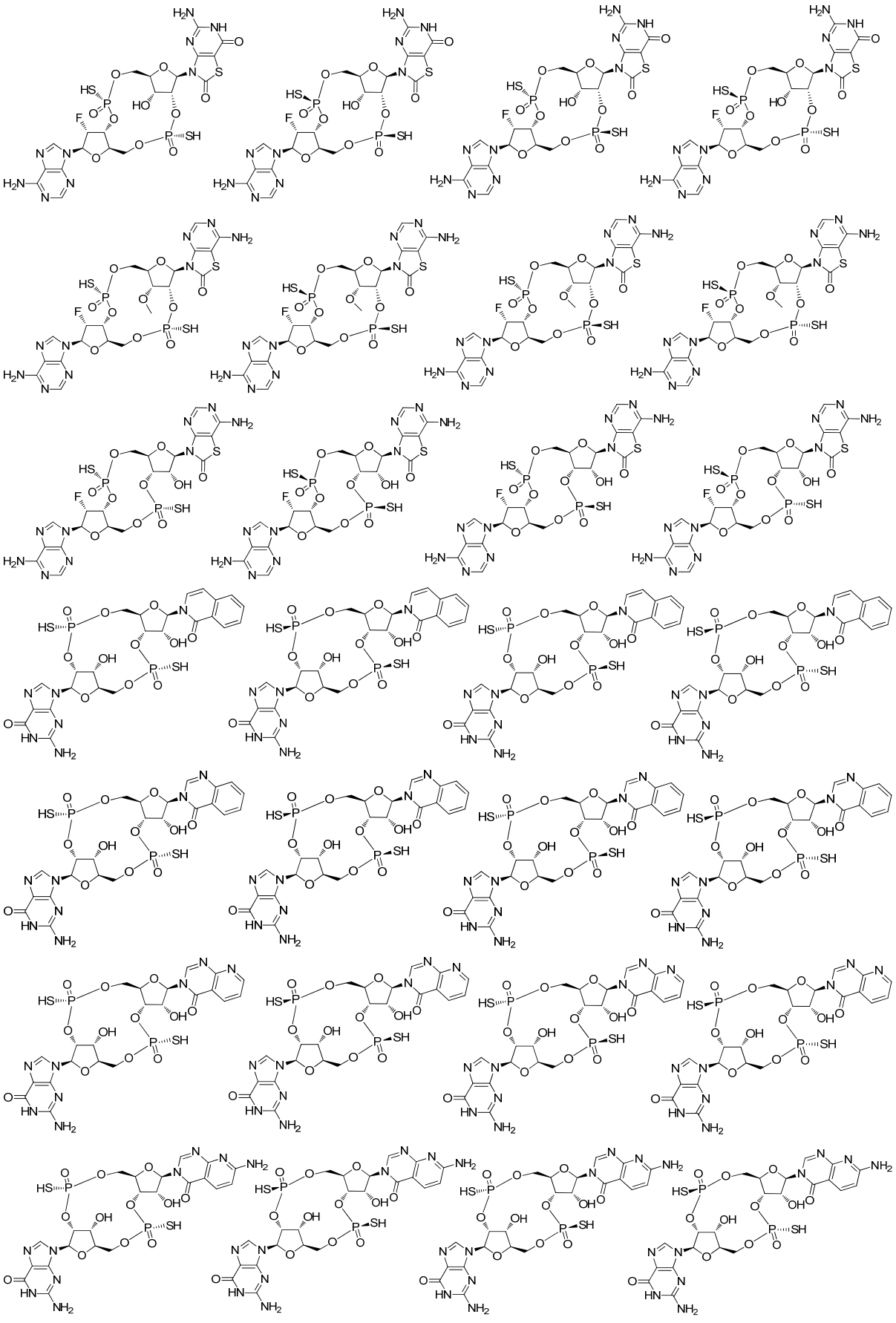
and/or, B_2 is  or ;

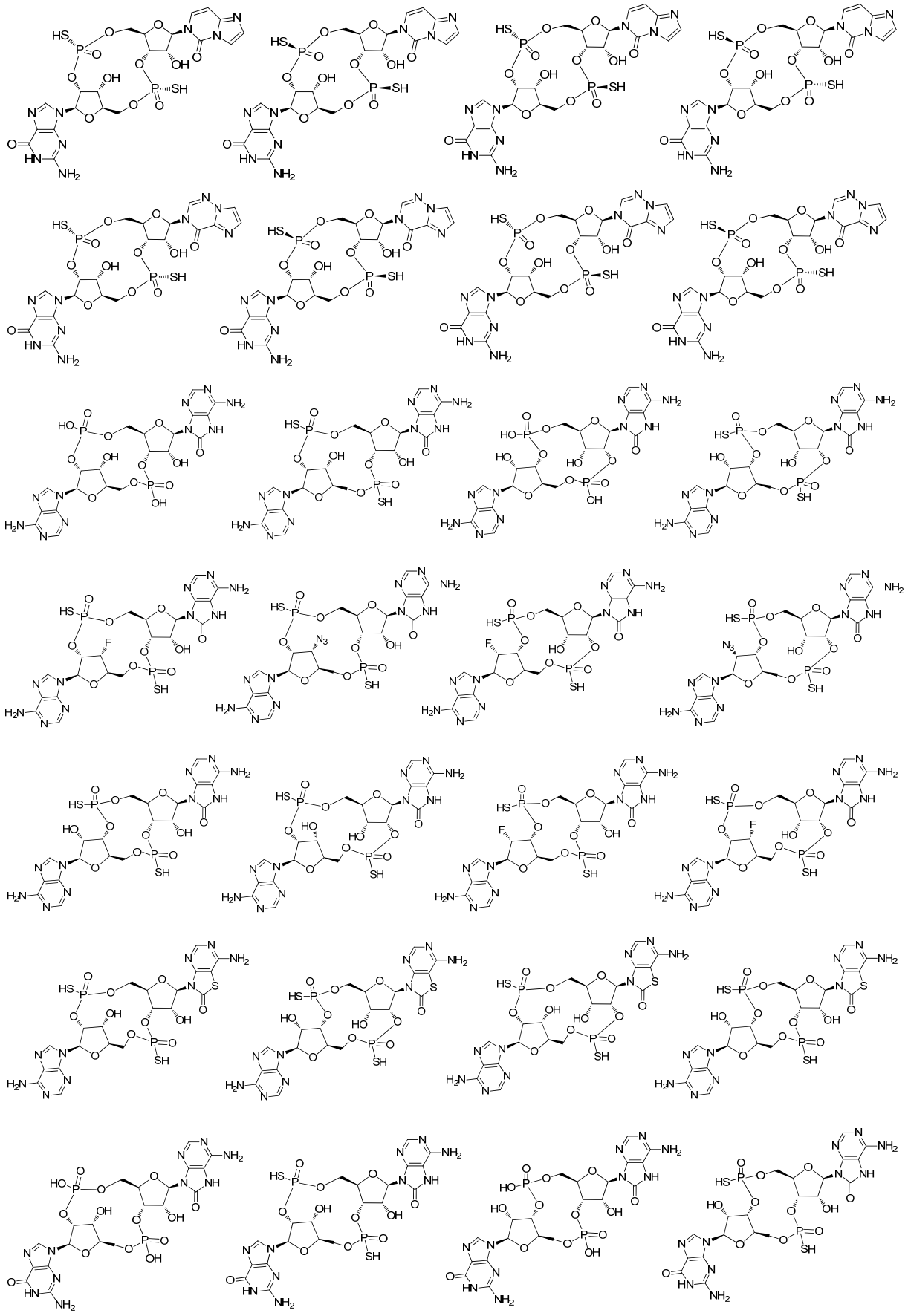
in Formula VI, R^2 is -OH; R^{21} is -OH;

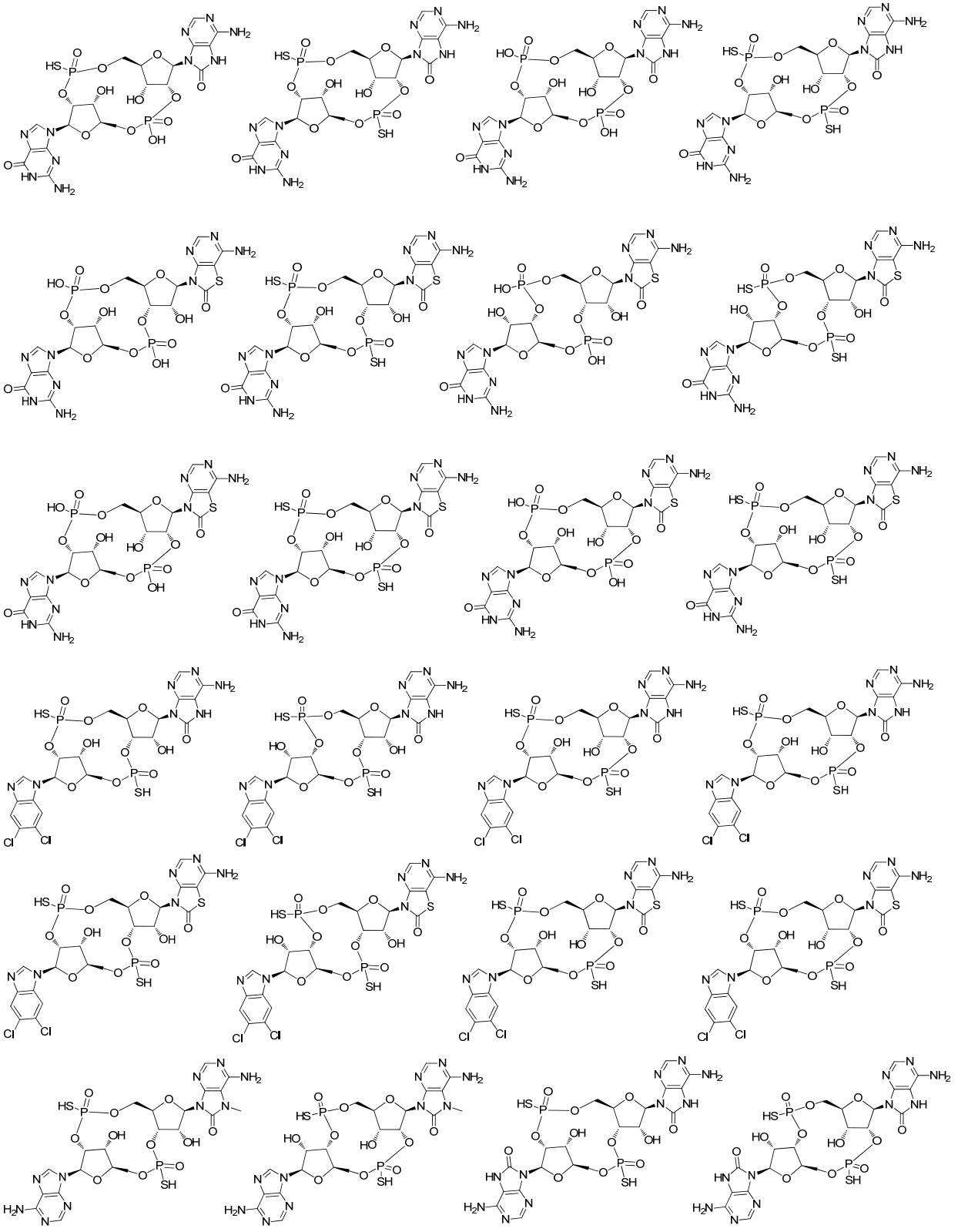
in Formula VII, R^2 is -OH or $-OCH_3$; R^{21} is -OH or F.

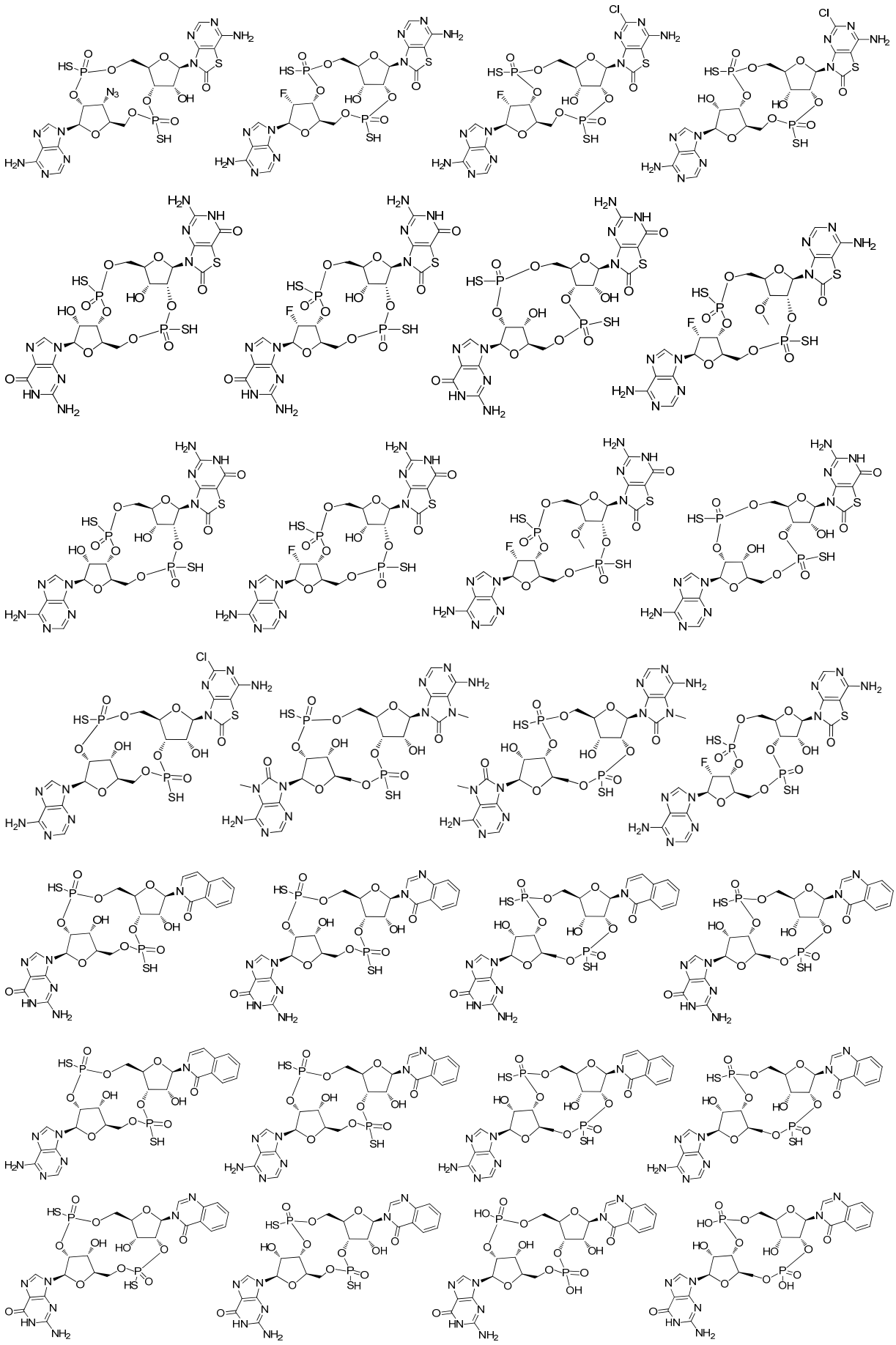
9. A cyclic di-nucleotide analogue of formula (I), the stereoisomer, stable isotope derivative or pharmaceutically acceptable salt thereof, which is any of the following structures:

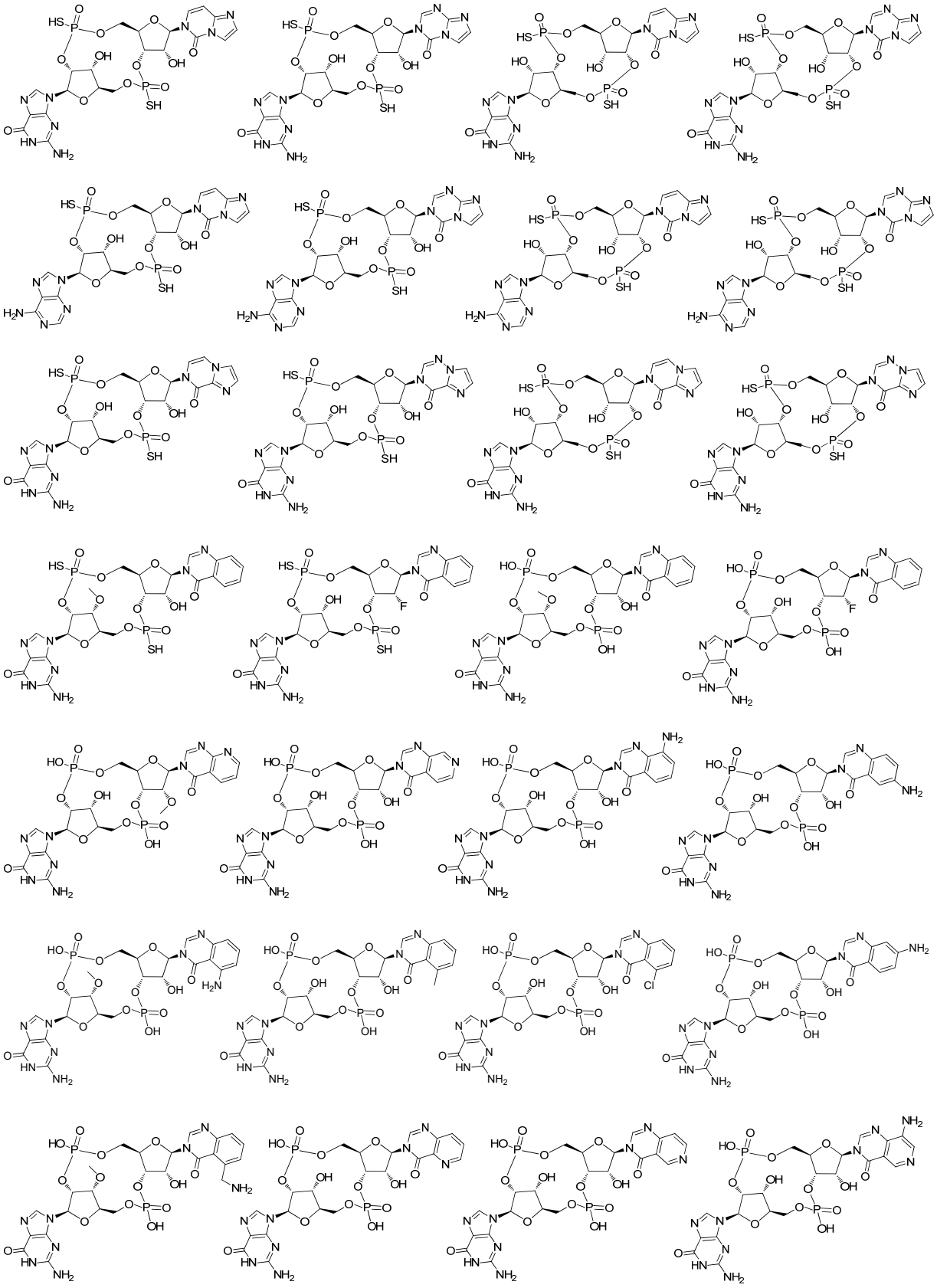


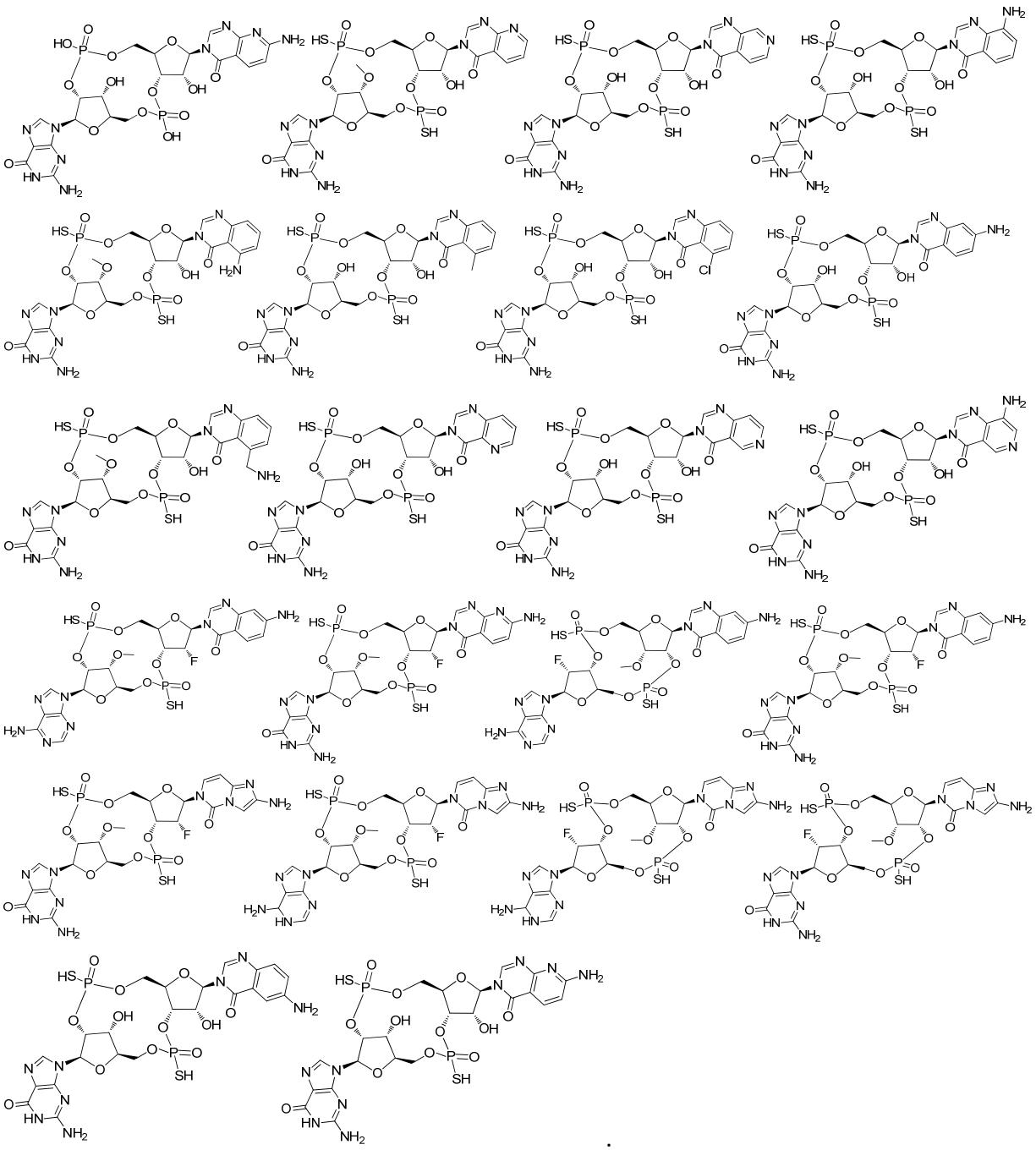












10. A pharmaceutical composition comprising a therapeutically effective amount of the compound of formula (I), the stereoisomer, stable isotope derivative or pharmaceutically acceptable salt thereof according to at least one of claims 1 to 9, and a pharmaceutically acceptable excipient.

11. 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 10, comprised in a STING modulator.

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

13. A use of the compound of formula (I), the stereoisomer, stable isotope derivative or pharmaceutically acceptable salt thereof according to at least one of claims 1 to 9 or the pharmaceutical composition according to claim 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.

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

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

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