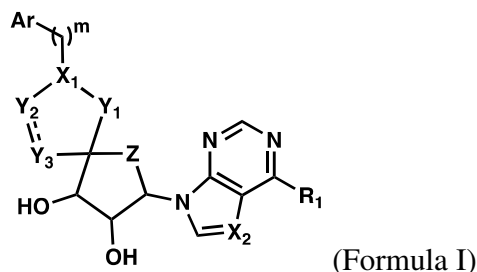


CLAIMS

1. A compound having the structure of Formula I:



or a pharmaceutically acceptable salt thereof,

wherein:

--- is a double bond or a single bond;

Ar is an optionally substituted aryl or heteroaryl, wherein one, two, or three optional substituents are independently selected from halogen, hydroxyl, cyano, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{N}(\text{R}_a)_2$, $-\text{C}(\text{O})\text{O}(\text{R}_a)$, $-\text{C}(\text{O})\text{R}_a$, $-\text{N}(\text{R}_a)_2$, $-\text{O}(\text{R}_a)$, $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_3\text{-C}_7$ heterocyclyl, optionally substituted $\text{C}_1\text{-C}_4$ alkyl and optionally substituted $\text{C}_2\text{-C}_6$ alkenyl;

R_1 is H, halogen, $\text{C}_1\text{-C}_4$ alkyl, $-\text{NH}_2$, or $-\text{NH}(\text{C}_1\text{-C}_4 \text{ alkyl})$, $\text{C}_2\text{-C}_4$ alkenyl, $\text{O}(\text{R}_a)$, $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_3\text{-C}_7$ heterocyclyl or $\text{N}(\text{R}_a)_2$;

X_1 and X_2 are each independently CH or N;

Y_1 is $(\text{CH}_2)_n$ or $\text{C}(\text{O})$, with the proviso that Y_1 cannot be $\text{C}(\text{O})$ when Y_2 or Y_3 is $\text{C}(\text{O})$;

Y_2 is CH_2 , $\text{C}(\text{O})$, S, SO_2 , O or NR_a , with the provisos that:

Y_2 cannot be $\text{C}(\text{O})$ when Y_1 or Y_3 is $\text{C}(\text{O})$; and

--- is a single bond;

Y_3 is CH_2 or $\text{C}(\text{O})$, with the provisos that:

Y_3 cannot be $\text{C}(\text{O})$ when Y_1 or Y_2 is $\text{C}(\text{O})$; and

--- is a single bond; or

Y_2 and Y_3 are CH and --- is a double bond;

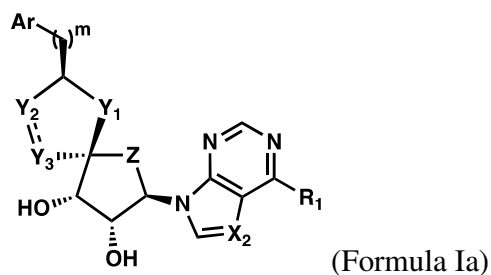
Z is CH_2 , O, S or NH;

R_a in each instance is independently H, $\text{C}_1\text{-C}_4$ alkyl or $\text{C}_3\text{-C}_6$ cycloalkyl;

m is 0, 1, 2 or 3; and

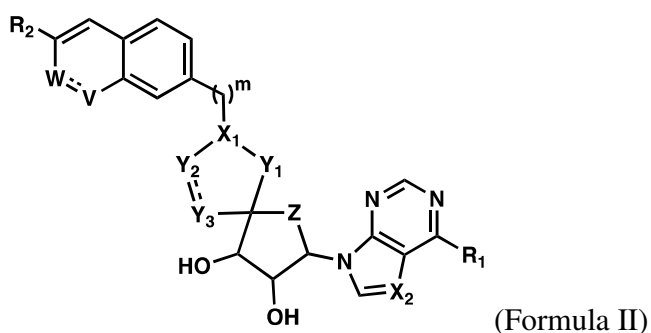
n is 1 or 2.

2. The compound of claim 1 having the structure of Formula Ia:



or a pharmaceutically acceptable salt thereof.

3. A compound having the structure of Formula II:



or a pharmaceutically acceptable salt thereof,

wherein:

$\equiv$ in each instance is independently a double bond or a single bond;

R_1 is H, halogen, C_1 - C_4 alkyl, $-NH_2$, or $-NH(C_1-C_4 \text{ alkyl})$; ~~C_2 - C_4 alkenyl, $O(R_a)$, C_3 - C_6 cycloalkyl, C_3 - C_7 heterocyclyl or $N(R_a)_2$;~~

R_2 is H, halogen, hydroxyl, cyano, $-C(O)NH_2$, $-C(O)N(R_a)_2$, $-C(O)O(R_a)$, $-C(O)R_a$, $-N(R_a)_2$, $-O(R_a)$, C_3 - C_6 cycloalkyl, C_3 - C_7 heterocyclyl, optionally substituted C_1 - C_4 alkyl or optionally substituted C_2 - C_6 alkenyl;

W is $C(R_b)$ or $C(O)$, with the proviso that V is NH and the $\equiv$ between W and V is a single bond when W is $C(O)$;

V is CH, NH or N, with the proviso that W is $C(R_b)$ and the $\equiv$ between W and V is a double bond when V is CH or N;

X_1 and X_2 are each independently CH or N;

Y_1 is $(CH_2)_n$ or $C(O)$, with the proviso that Y_1 cannot be $C(O)$ when Y_2 or Y_3 is $C(O)$;

Y_2 is CH_2 , $C(O)$, S , SO_2 , O or NR_a , with the provisos that:

Y_2 cannot be $C(O)$ when Y_1 or Y_3 is $C(O)$; and

the --- between Y_2 and Y_3 is a single bond;

Y_3 is CH_2 or $C(O)$, with the provisos that:

Y_3 cannot be $C(O)$ when Y_1 or Y_2 is $C(O)$; and

the --- between Y_2 and Y_3 is a single bond; or

Y_2 and Y_3 are CH and the = between Y_2 and Y_3 is a double bond;

Z is CH_2 , O , S or NH ;

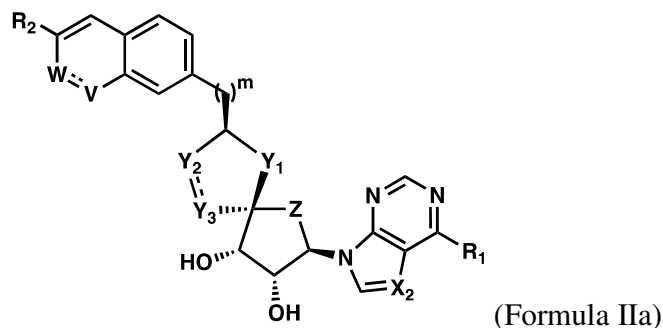
R_a in each instance is independently H , C_1 - C_4 alkyl or C_3 - C_6 cycloalkyl;

R_b is H , halogen, hydroxyl, cyano, $-C(O)NH_2$, $-C(O)N(R_a)_2$, $-C(O)O(R_a)$, $-C(O)R_a$, $-N(R_a)_2$, $-O(R_a)$, C_3 - C_6 cycloalkyl, C_3 - C_7 heterocyclyl, optionally substituted C_1 - C_4 alkyl or optionally substituted C_2 - C_6 alkenyl;

m is 0, 1, 2 or 3; and

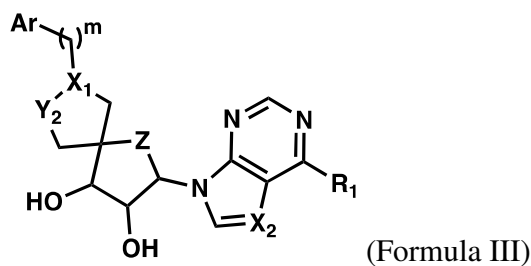
n is 1 or 2.

4. The compound of claim 3 having the structure of Formula IIa:



or a pharmaceutically acceptable salt thereof.

5. A compound having the structure of Formula III:



or a pharmaceutically acceptable salt thereof,

wherein:

Ar is an optionally substituted aryl or heteroaryl, wherein one, two, or three optional substituents are independently selected from halogen, hydroxyl, cyano, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{N}(\text{R}_a)_2$, $-\text{C}(\text{O})\text{O}(\text{R}_a)$, $-\text{C}(\text{O})\text{R}_a$, $-\text{N}(\text{R}_a)_2$, $-\text{O}(\text{R}_a)$, $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_3\text{-C}_7$ heterocyclyl, optionally substituted $\text{C}_1\text{-C}_4$ alkyl and optionally substituted $\text{C}_2\text{-C}_6$ alkenyl;

R_1 is H, halogen, $\text{C}_1\text{-C}_4$ alkyl, $-\text{NH}_2$, or $-\text{NH}(\text{C}_1\text{-C}_4 \text{ alkyl})$, ~~$\text{C}_2\text{-C}_4$ alkenyl, $\text{O}(\text{R}_a)$, $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_3\text{-C}_7$ heterocyclyl or $\text{N}(\text{R}_a)_2$;~~

X_1 and X_2 are each independently CH or N;

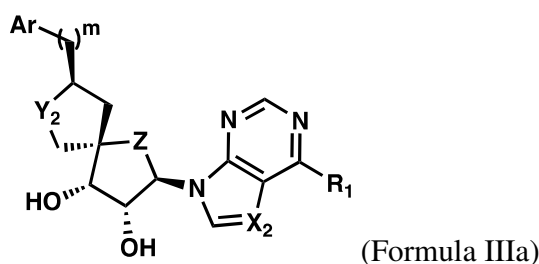
Y_2 is CH_2 , S, O or $\text{N}(\text{R}_a)$;

Z is CH_2 , O, S or NH;

R_a in each instance is independently H, $\text{C}_1\text{-C}_4$ alkyl or $\text{C}_3\text{-C}_6$ cycloalkyl; and

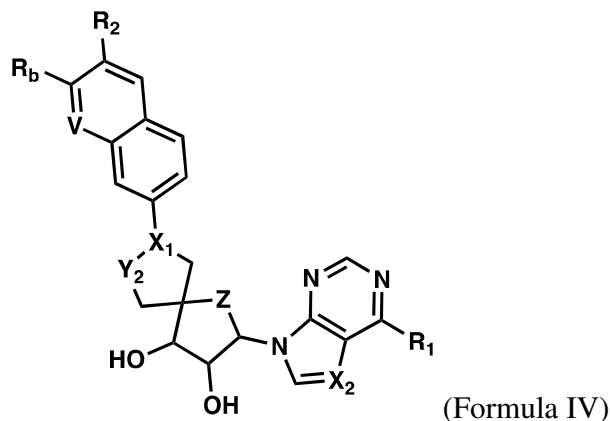
m is 0, 1, 2 or 3.

6. The compound of claim 5 having the structure of Formula IIIa:



or a pharmaceutically acceptable salt thereof.

7. A compound having the structure of Formula IV:



or a pharmaceutically acceptable salt thereof,

wherein:

R_1 is H, halogen, C_1 - C_4 alkyl, $-NH_2$, or $-NH(C_1$ - C_4 alkyl) C_2 - C_6 alkenyl, $-O(R_a)$, C_3 - C_6 cycloalkyl, C_3 - C_7 heterocyclyl or $N(R_a)_2$;

R_2 is H, halogen, hydroxyl, cyano, $-C(O)NH_2$, $-C(O)N(R_a)_2$, $-C(O)O(R_a)$, $-C(O)R_a$, $-N(R_a)_2$, $-O(R_a)$, C_3 - C_6 cycloalkyl, C_3 - C_7 heterocyclyl, optionally substituted C_1 - C_4 alkyl or optionally substituted C_2 - C_6 alkenyl;

X_1 and X_2 are each independently CH or N;

V is CH or N;

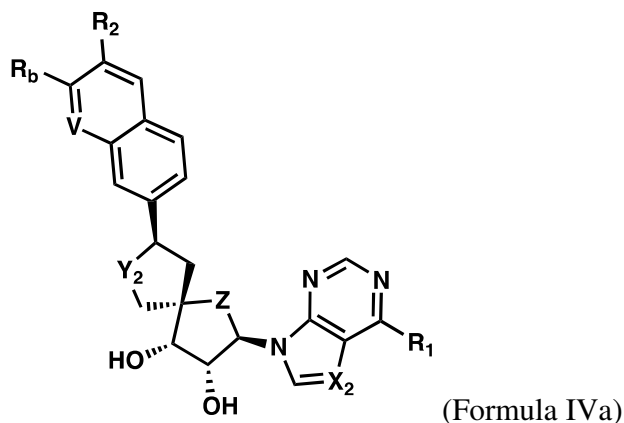
Y_2 is CH_2 , S, O or $N(R_a)$;

Z is CH_2 , O, S or NH;

R_a in each instance is independently H, C_1 - C_4 alkyl or C_3 - C_6 cycloalkyl; and

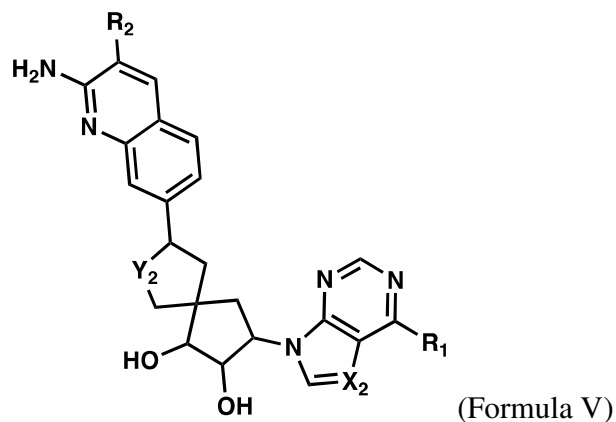
R_b is H, halogen, hydroxyl, cyano, $-C(O)NH_2$, $-C(O)N(R_a)_2$, $-C(O)O(R_a)$, $-C(O)R_a$, $-N(R_a)_2$, $-O(R_a)$, C_3 - C_6 cycloalkyl, C_3 - C_7 heterocyclyl, optionally substituted C_1 - C_4 alkyl or optionally substituted C_2 - C_6 alkenyl.

8. The compound of claim 7 having the structure of Formula IVa:



or a pharmaceutically acceptable salt thereof.

9. A compound having the structure of Formula V:



or a pharmaceutically acceptable salt thereof,

wherein:

R₁ is H, halogen, C₁-C₄ alkyl, ~~-NH₂, or -NH(C₁-C₄ alkyl)C₂-C₄ alkenyl, O(R_a), C₃-C₆ cycloalkyl, C₃-C₇ heterocyclyl or N(R_a)₂;~~

R₂ is H, halogen, hydroxyl, cyano, -C(O)NH₂, -C(O)N(R_a)₂, -C(O)O(R_a), -C(O)R_a, -N(R_a)₂, -O(R_a), C₃-C₆ cycloalkyl, C₃-C₇ heterocyclyl, optionally substituted C₁-C₄ alkyl or optionally substituted C₂-C₆ alkenyl;

X₂ is CH or N;

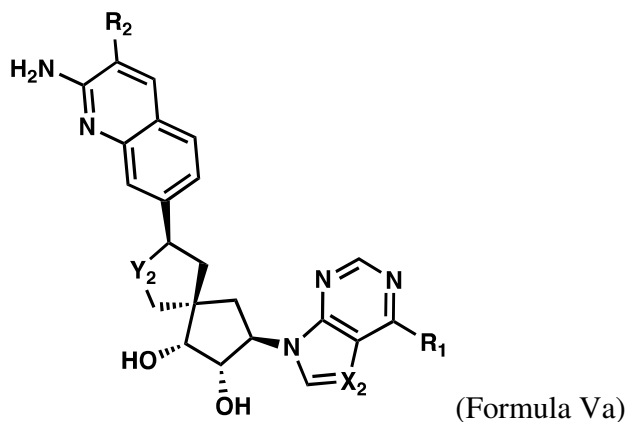
Y₂ is CH₂, S, O or N(R_a);

R_a in each instance is independently H, C₁-C₄ alkyl or C₃-C₆ cycloalkyl; and

wherein the compound has a PRMT5 IC₅₀ of about 100 nM or lower.

10. The compound of claim 9, wherein the compound has an average percent of maximum effect of about 60% or lower for the drug-resistant cell lines of Table 4 and/or the compound has an average percent of maximum effect of about 60% or greater for the drug-sensitive cell lines of Table 4.

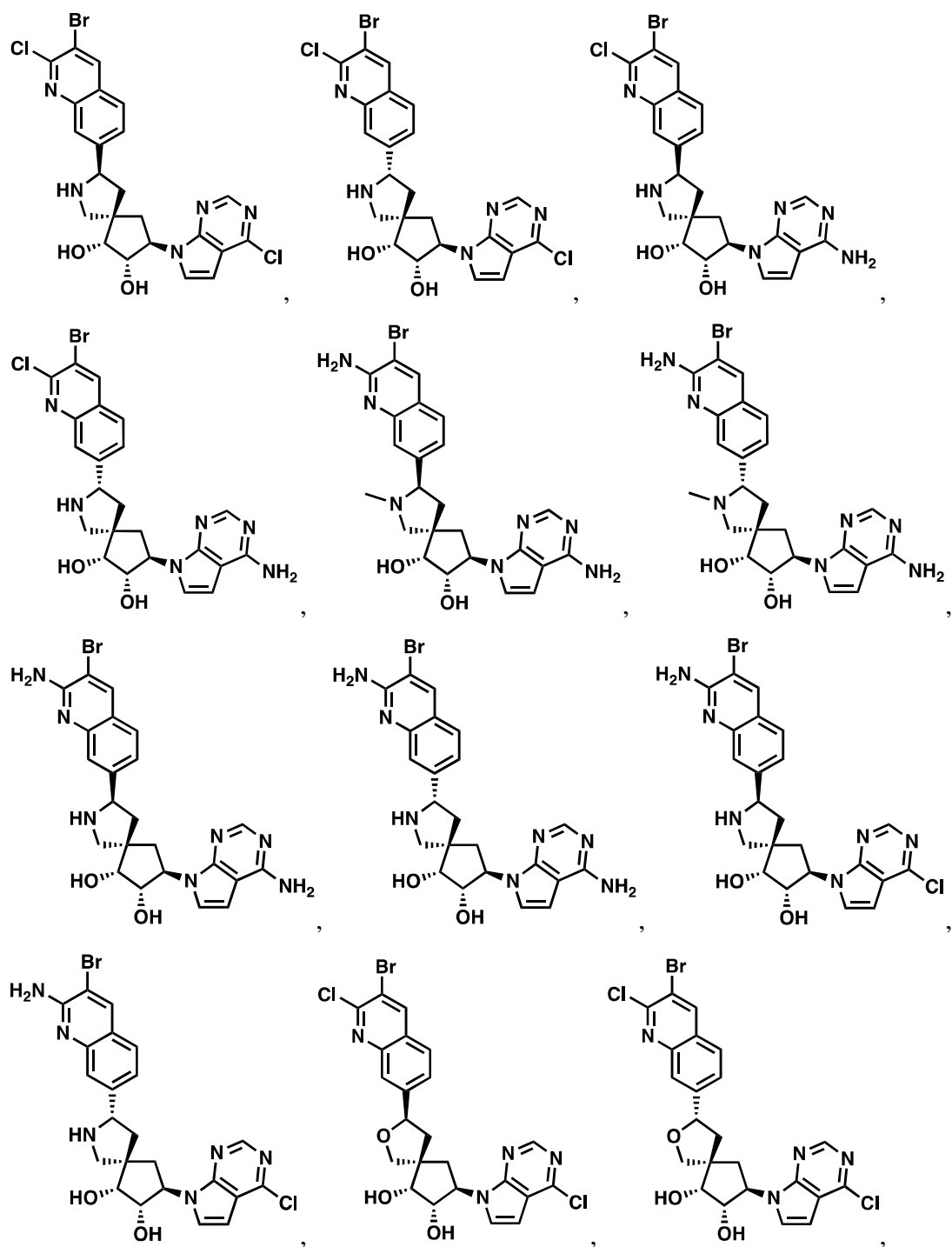
11. The compound of claim 9 having the structure of Formula Va:

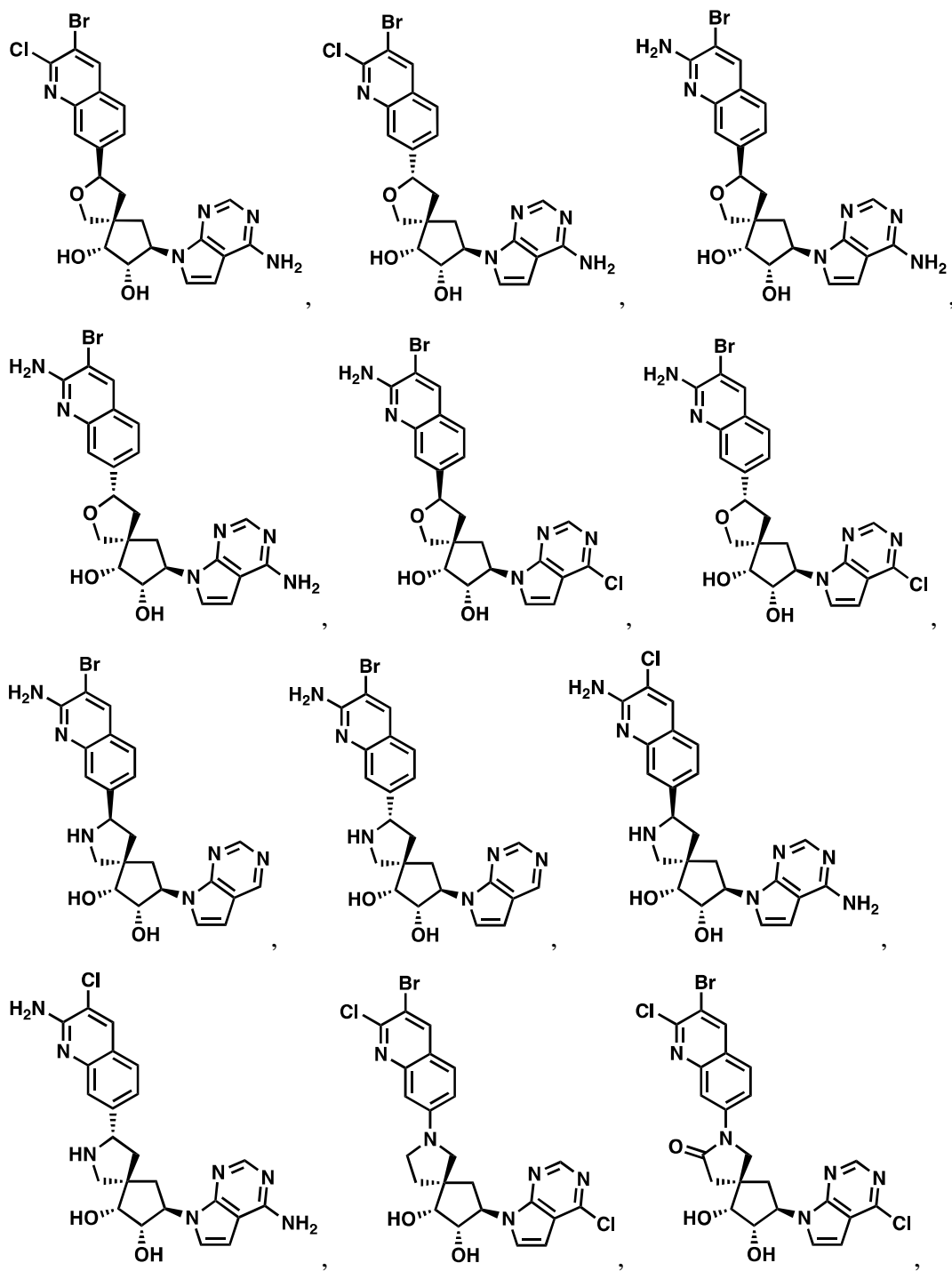


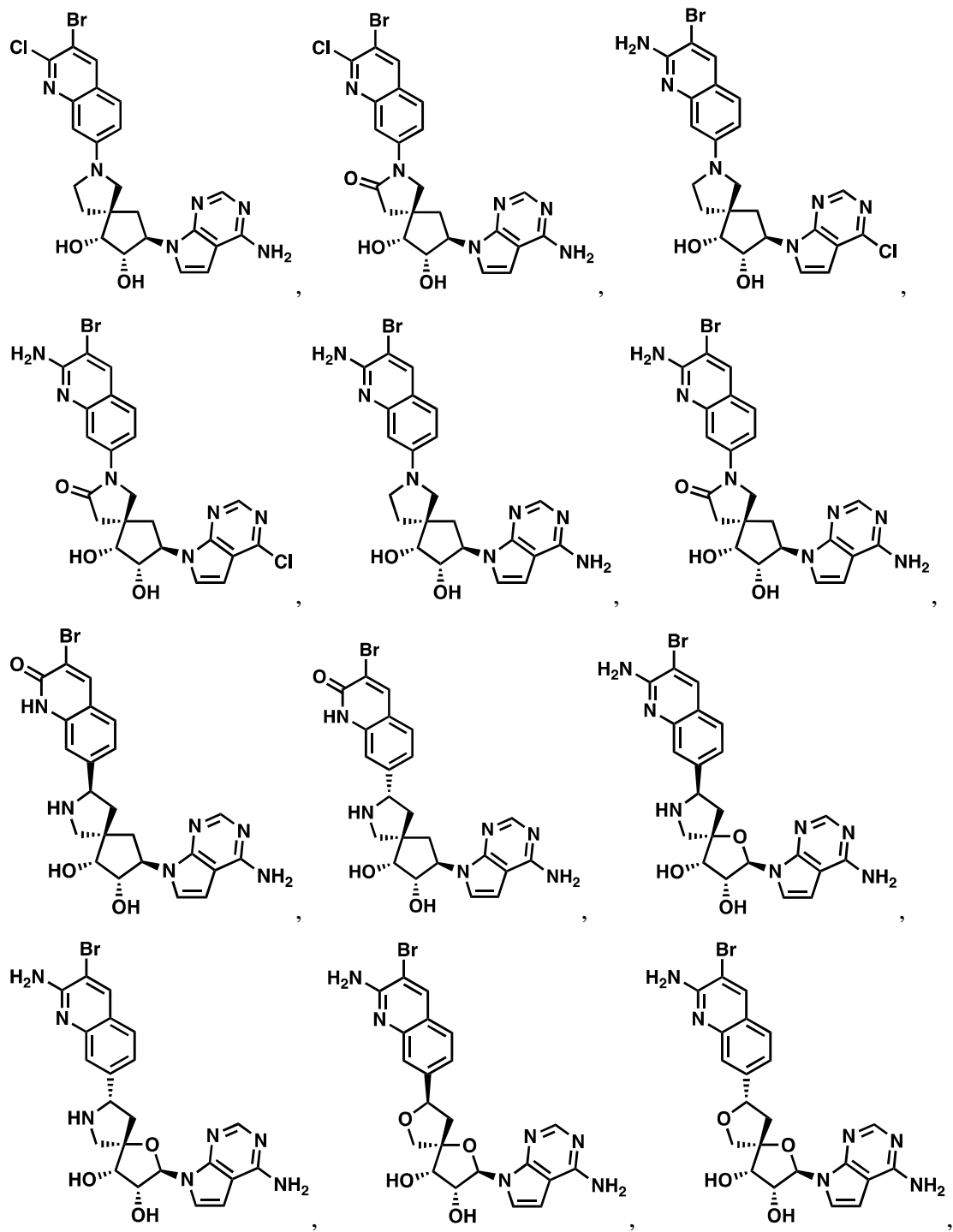
or a pharmaceutically acceptable salt thereof.

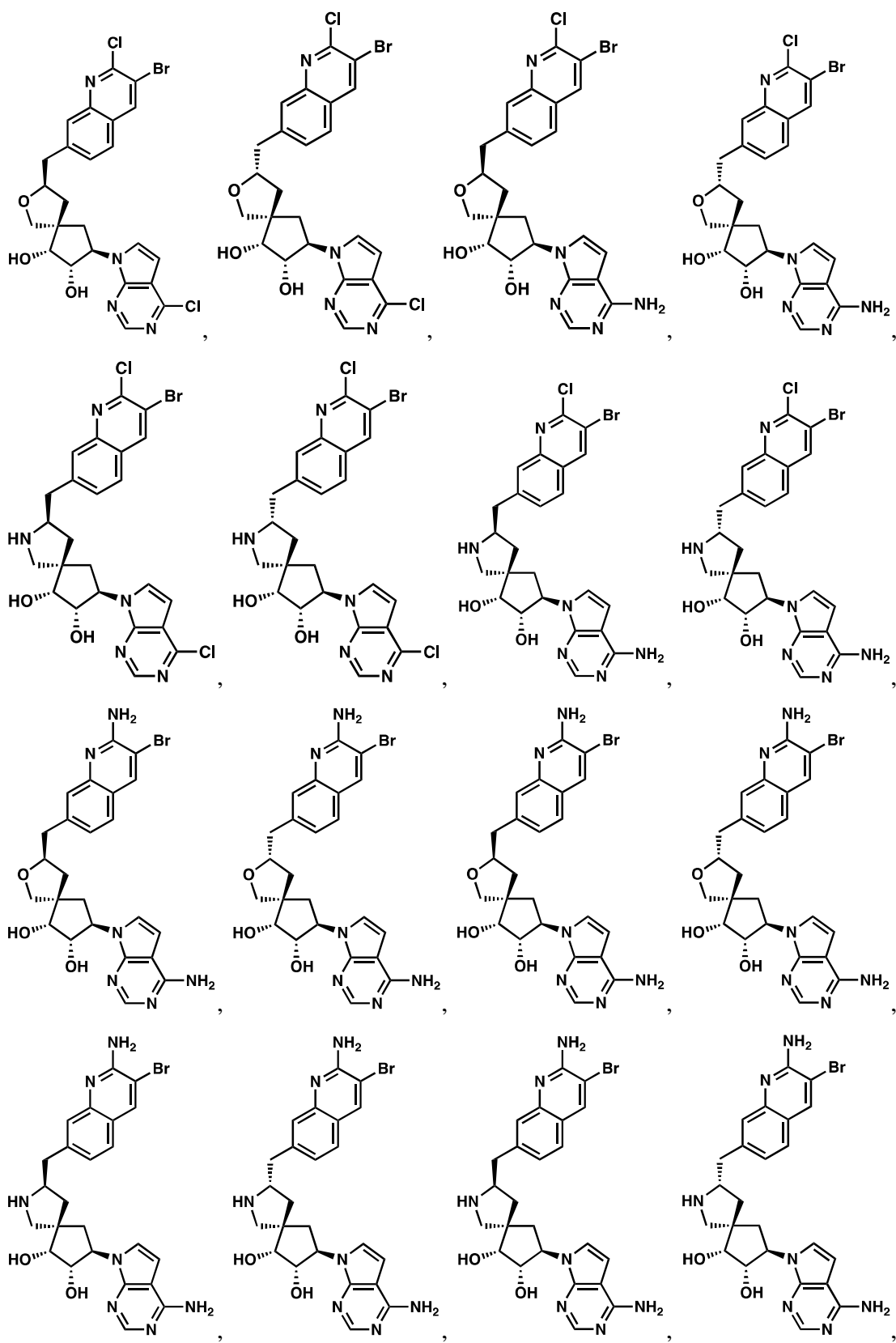
12. The compound of any one of claims 1, 3, 5, or 7, wherein X_1 is CH.
13. The compound of any one of claims 1-11, wherein X_2 is CH.
14. The compound of any one of claims 3, 4, 7, or 8, wherein V is N.
15. The compound of any one of claims 3, 4, 7, or 8, wherein R_b is NH_2 .
16. The compound of any one of claims 1-8, or 12-15, wherein Z is CH_2 .
17. The compound of any one of claims 1-16, wherein Y_2 is N(H).
18. The compound of any one of claims 1-16, wherein Y_2 is O.
19. The compound of any one of claims 1-18, wherein R_1 is Cl or NH_2 .
20. The compound of any one of claims 3, 4, or 7-19, wherein R_2 is Br.

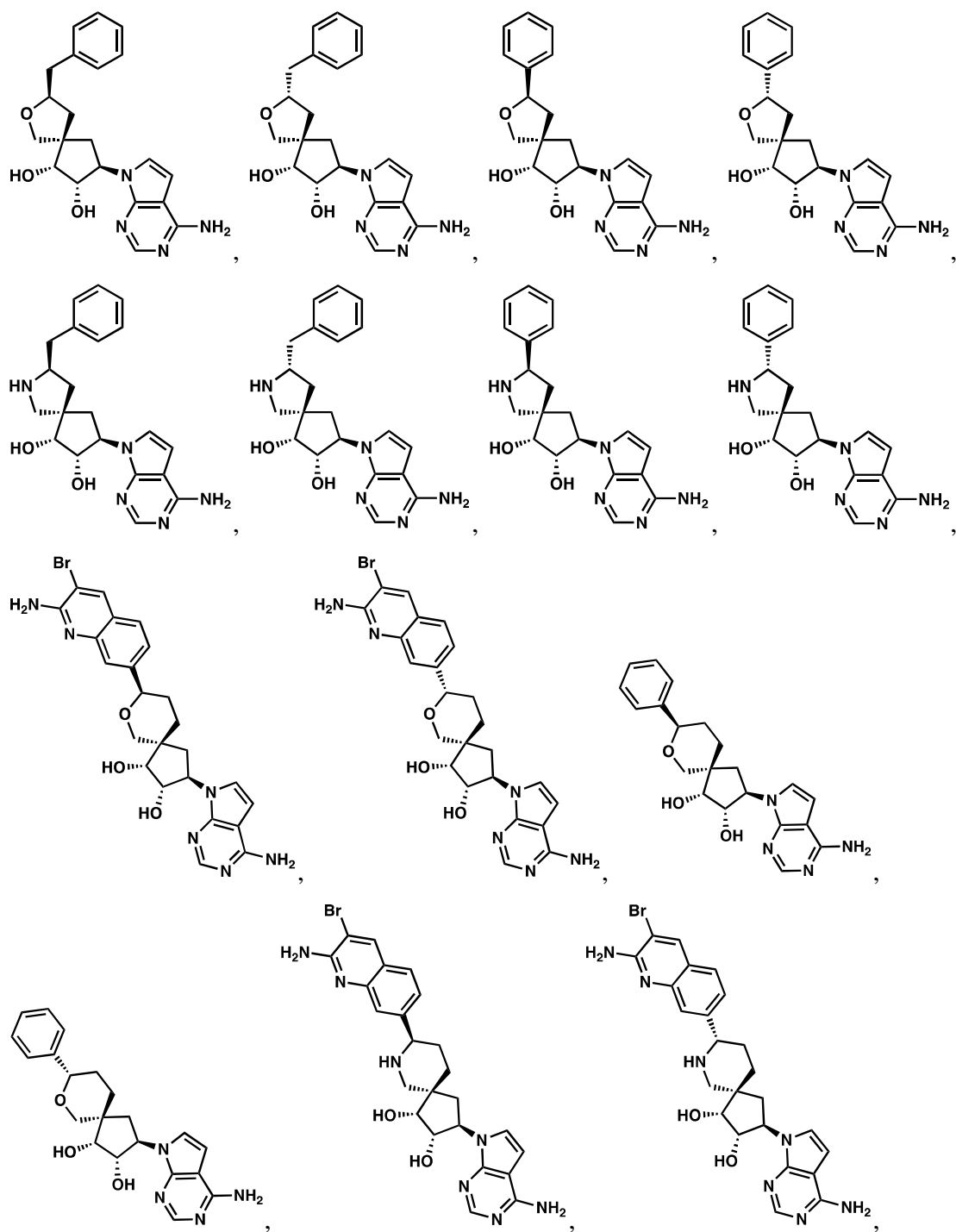
21. A compound selected from:

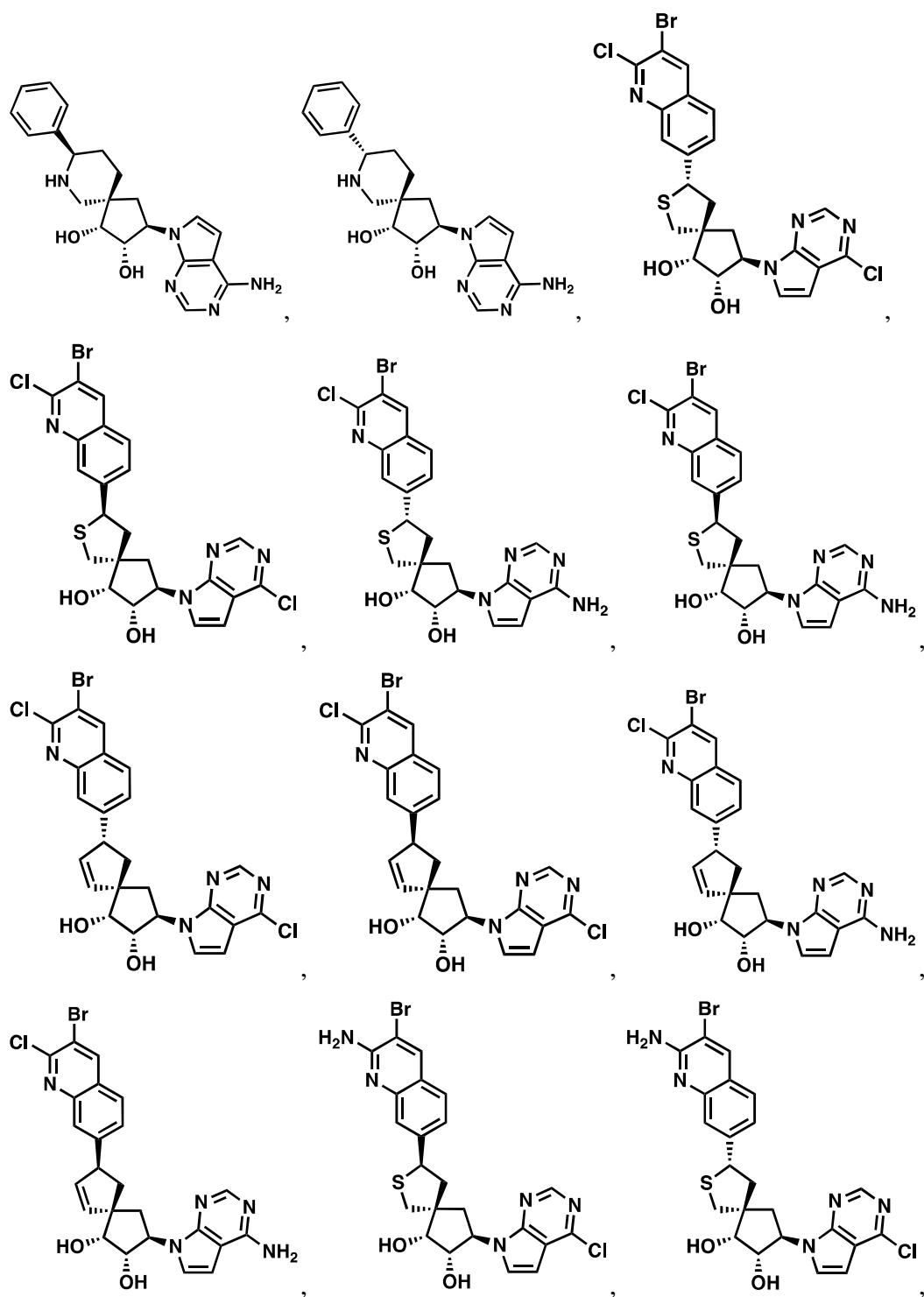


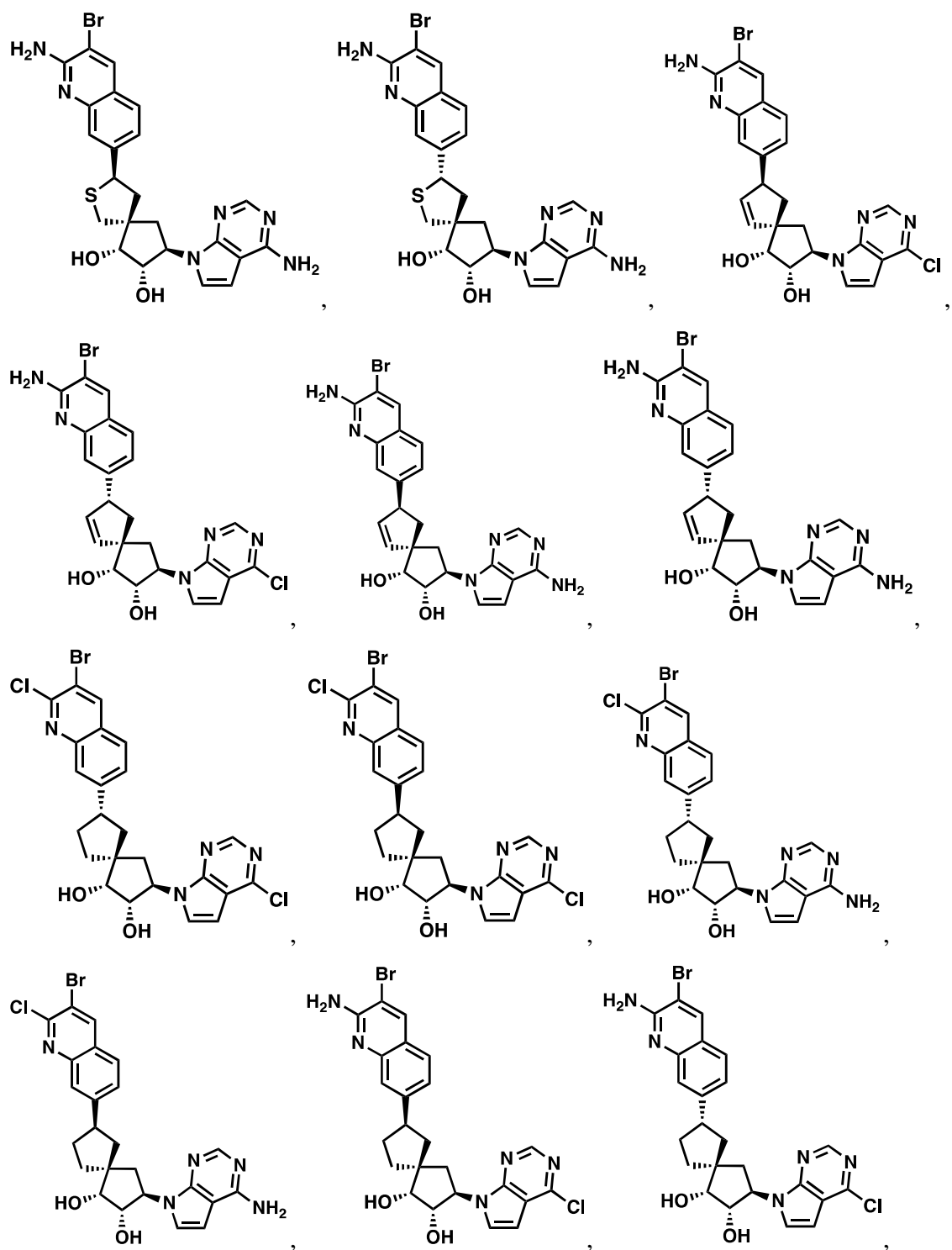


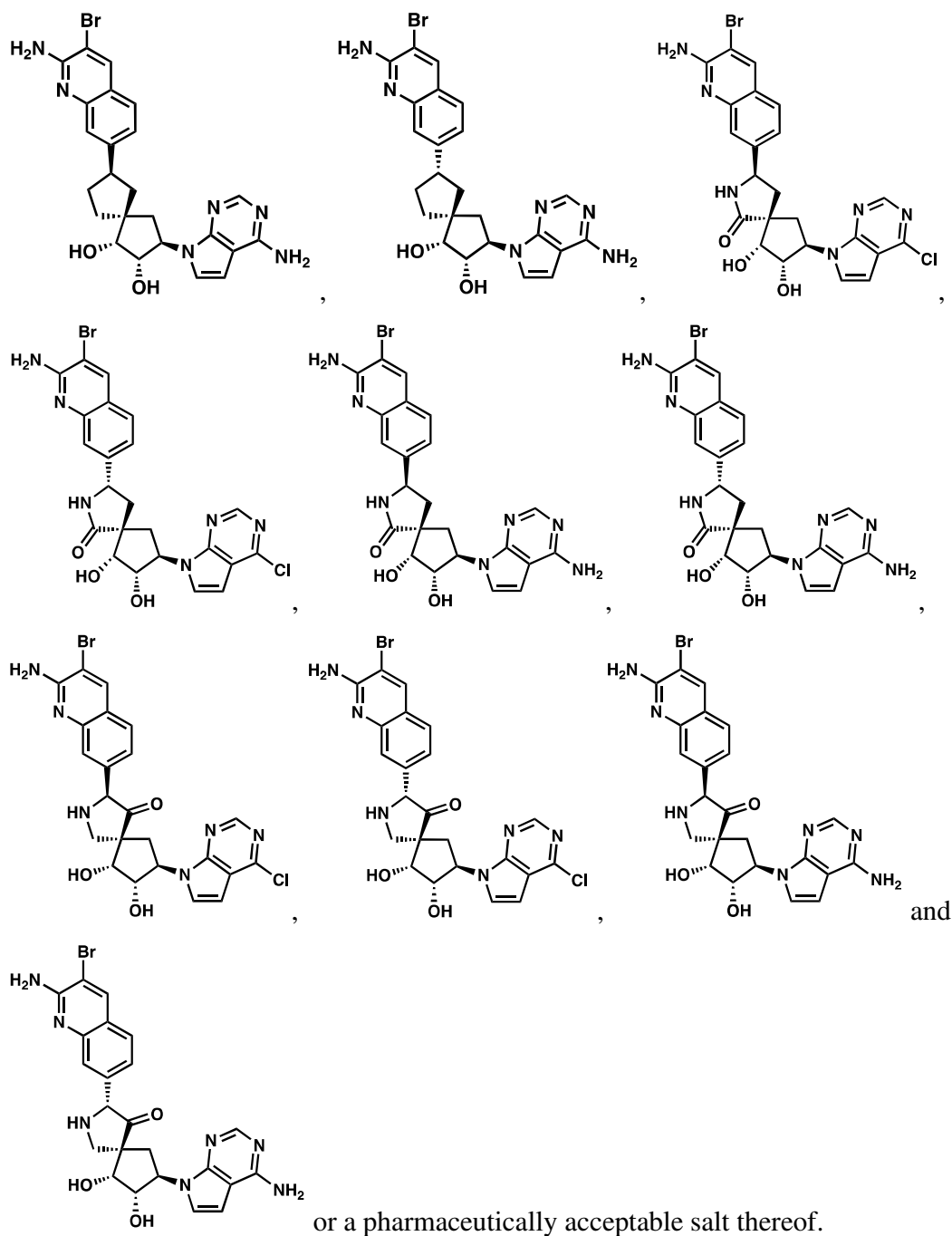




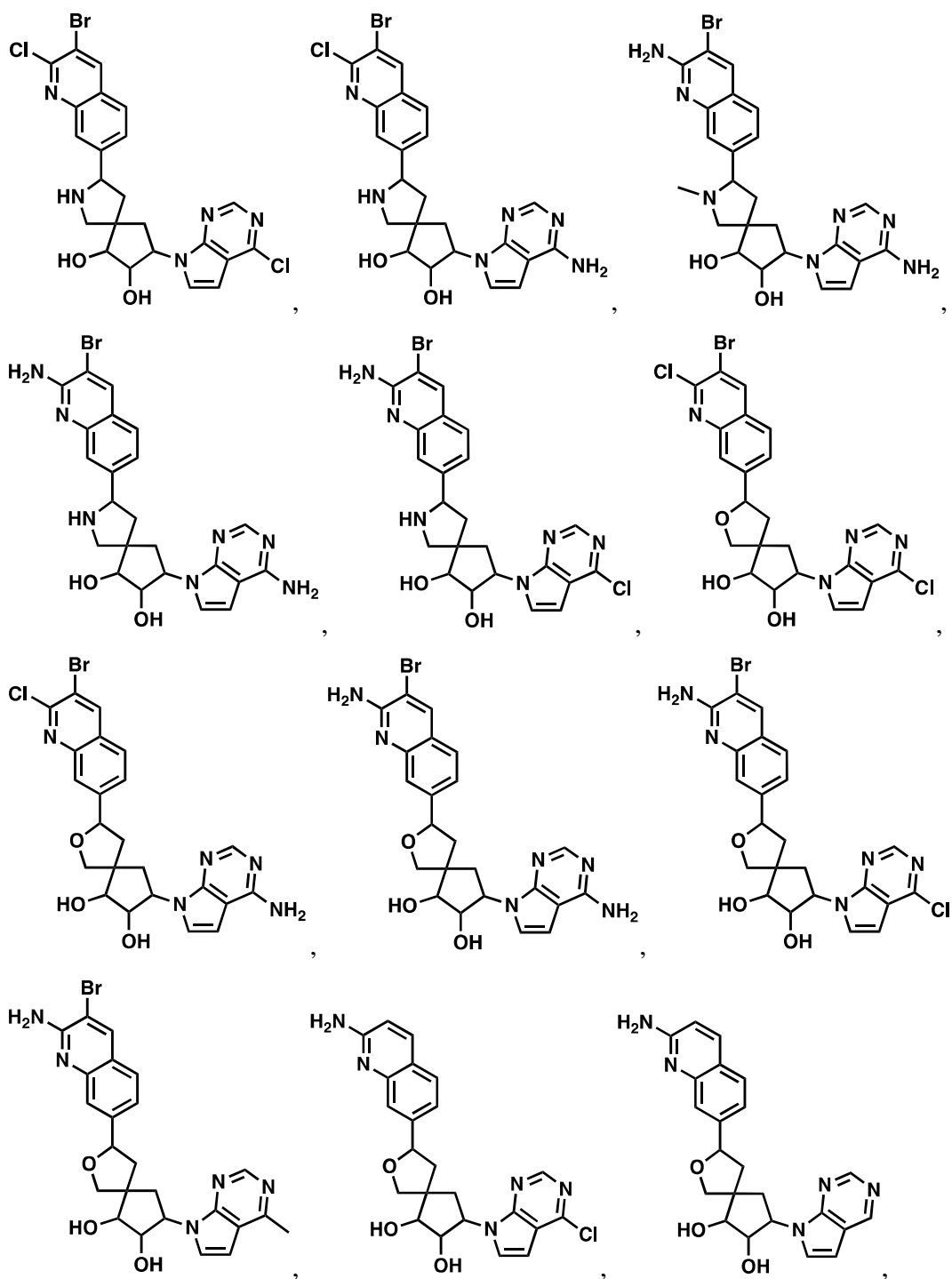


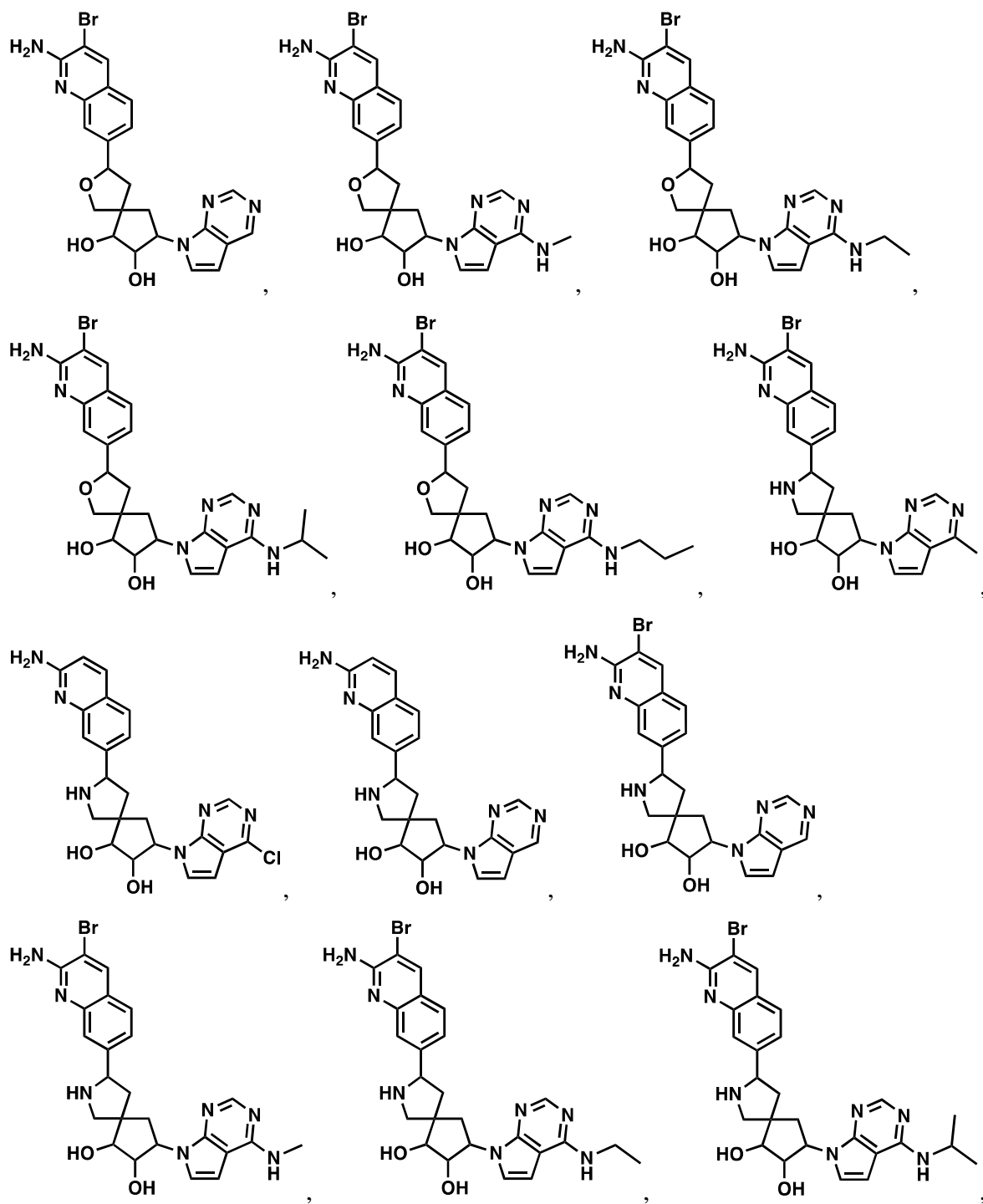


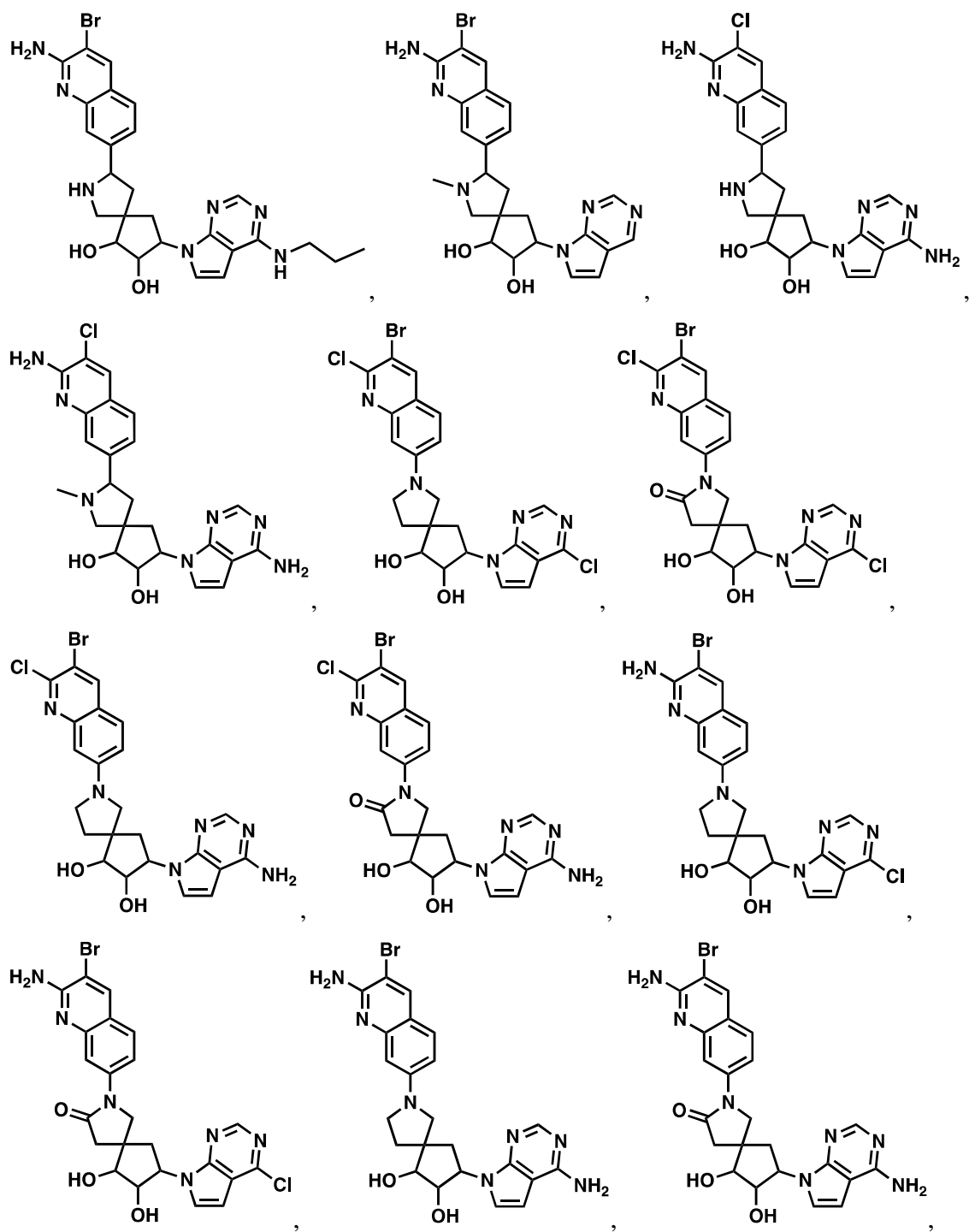


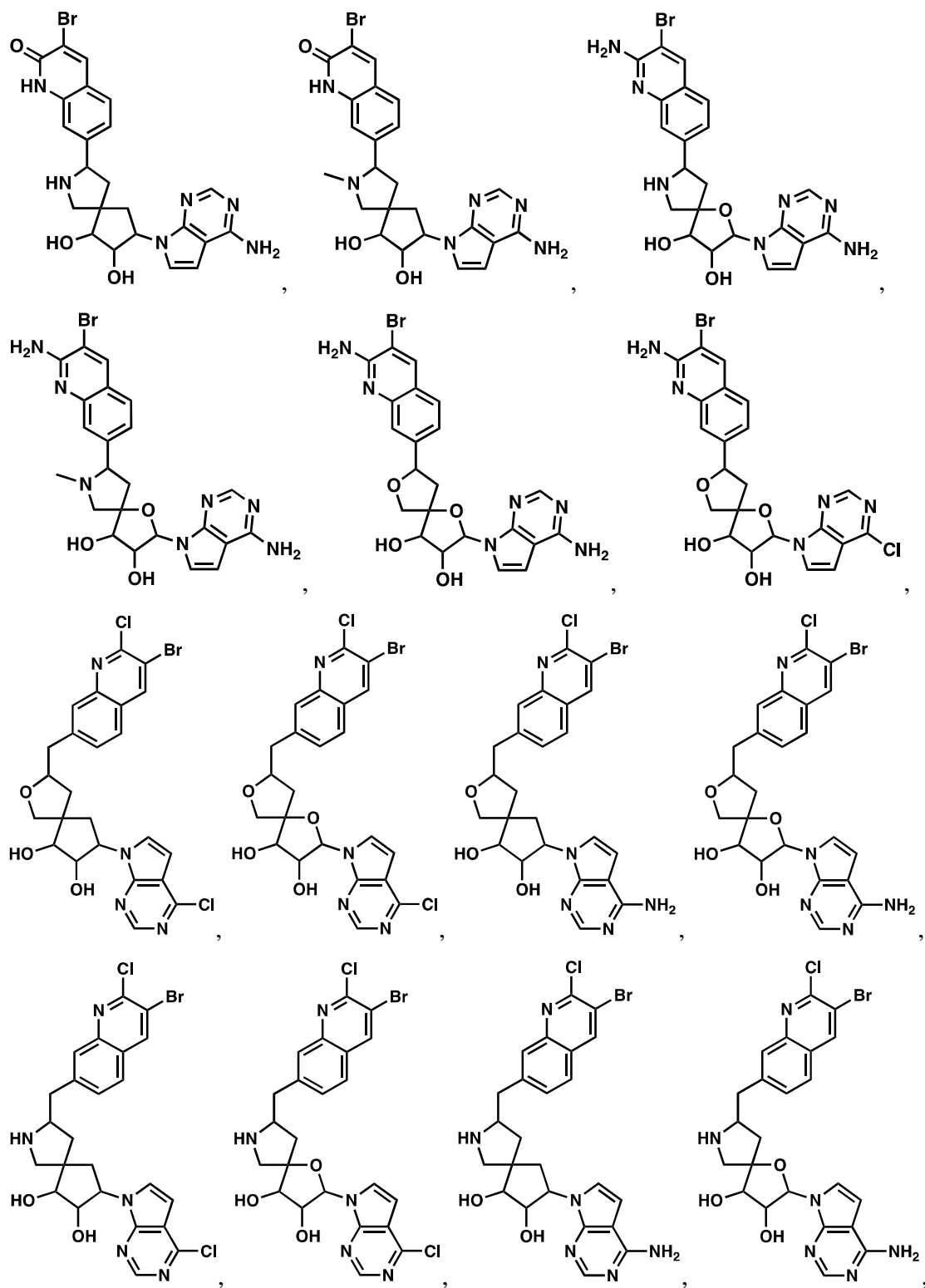


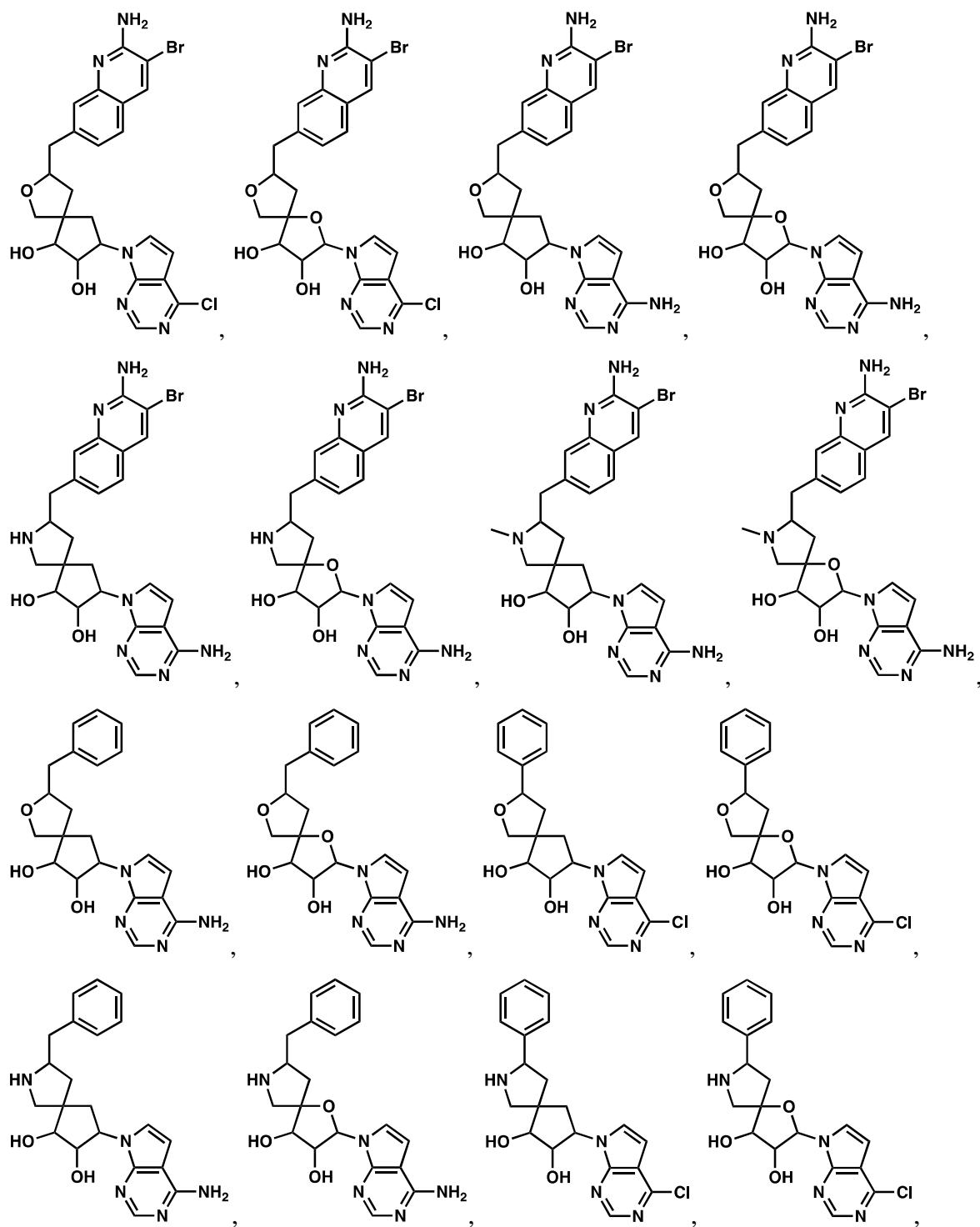
22. A compound selected from:

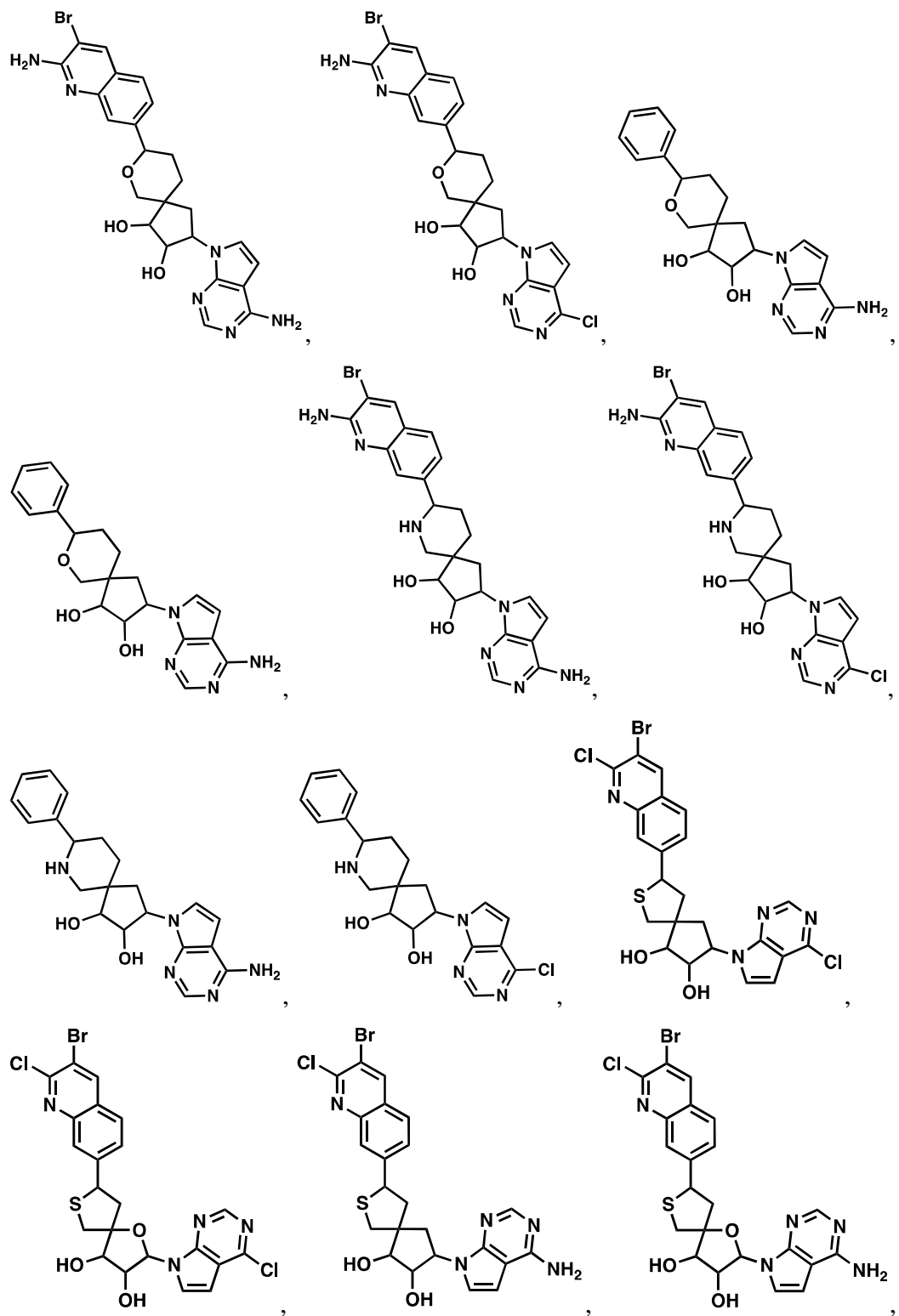


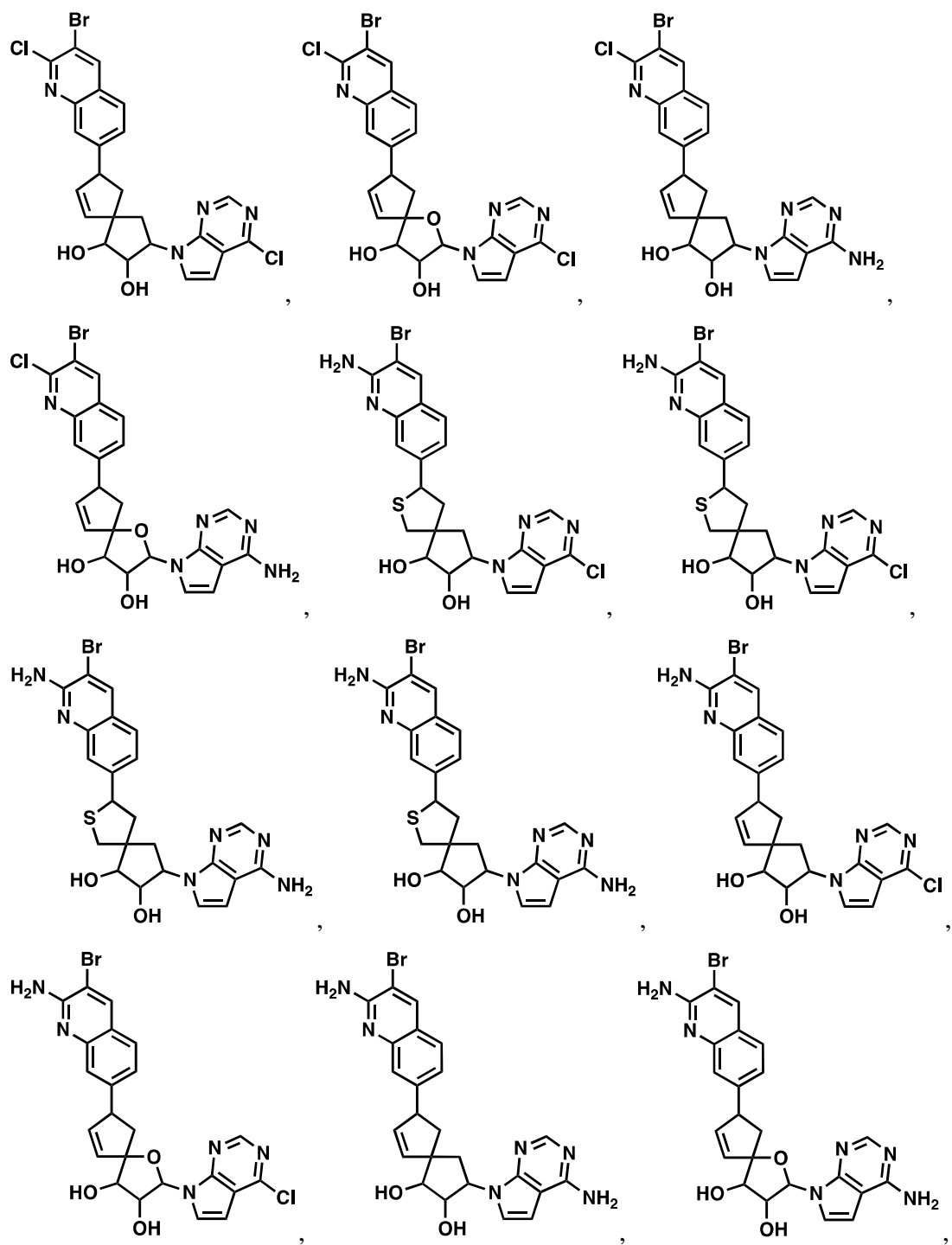


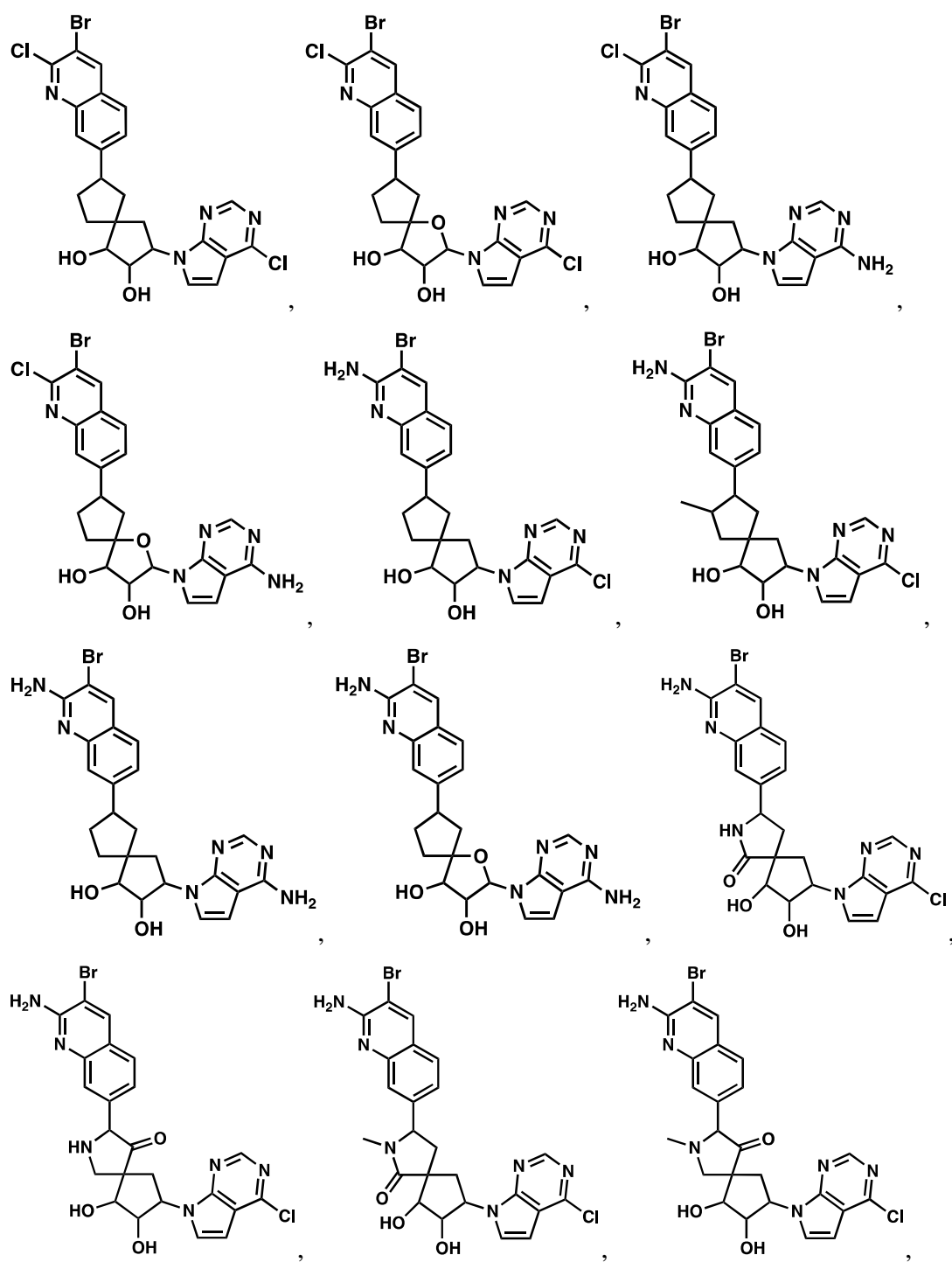


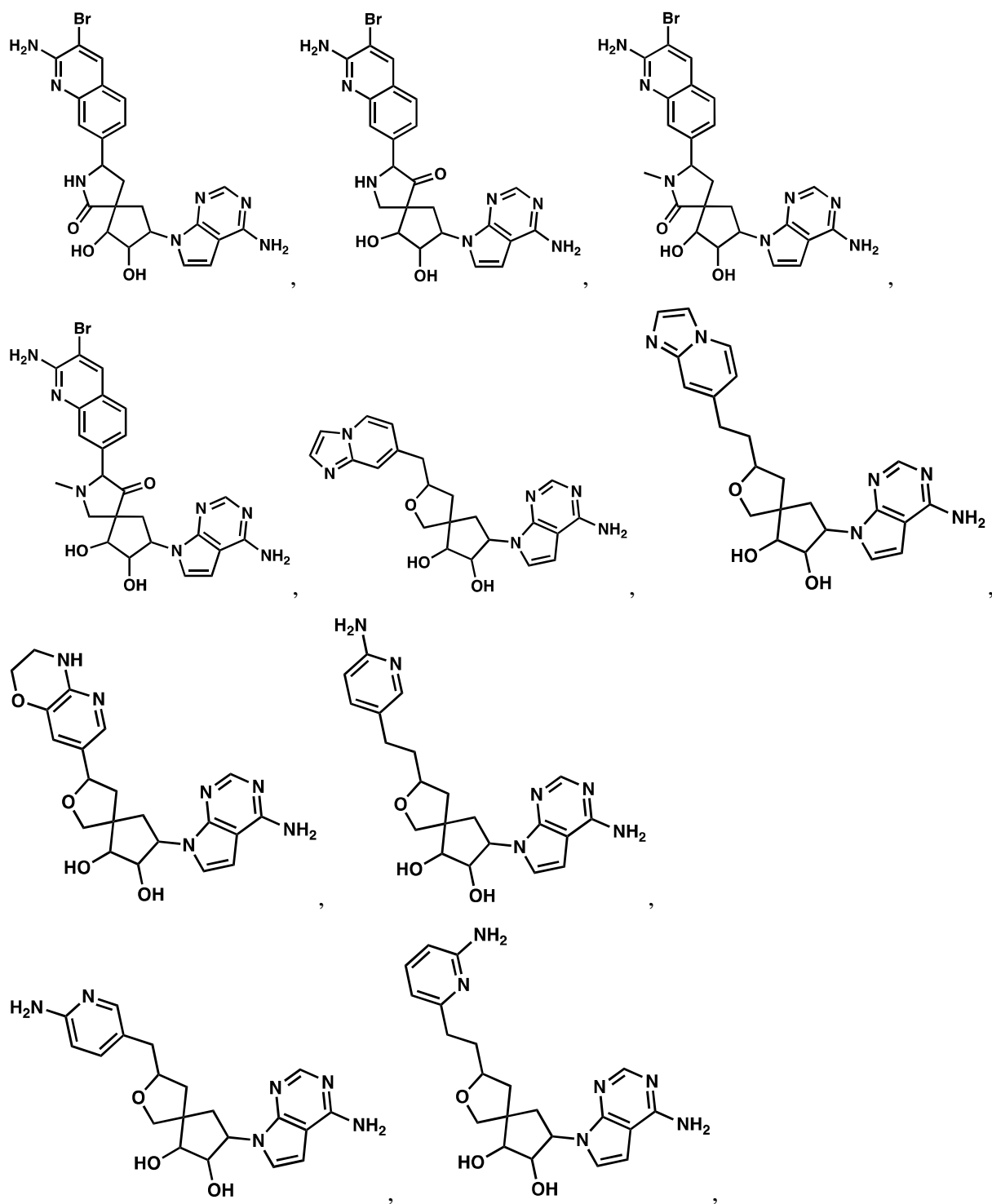


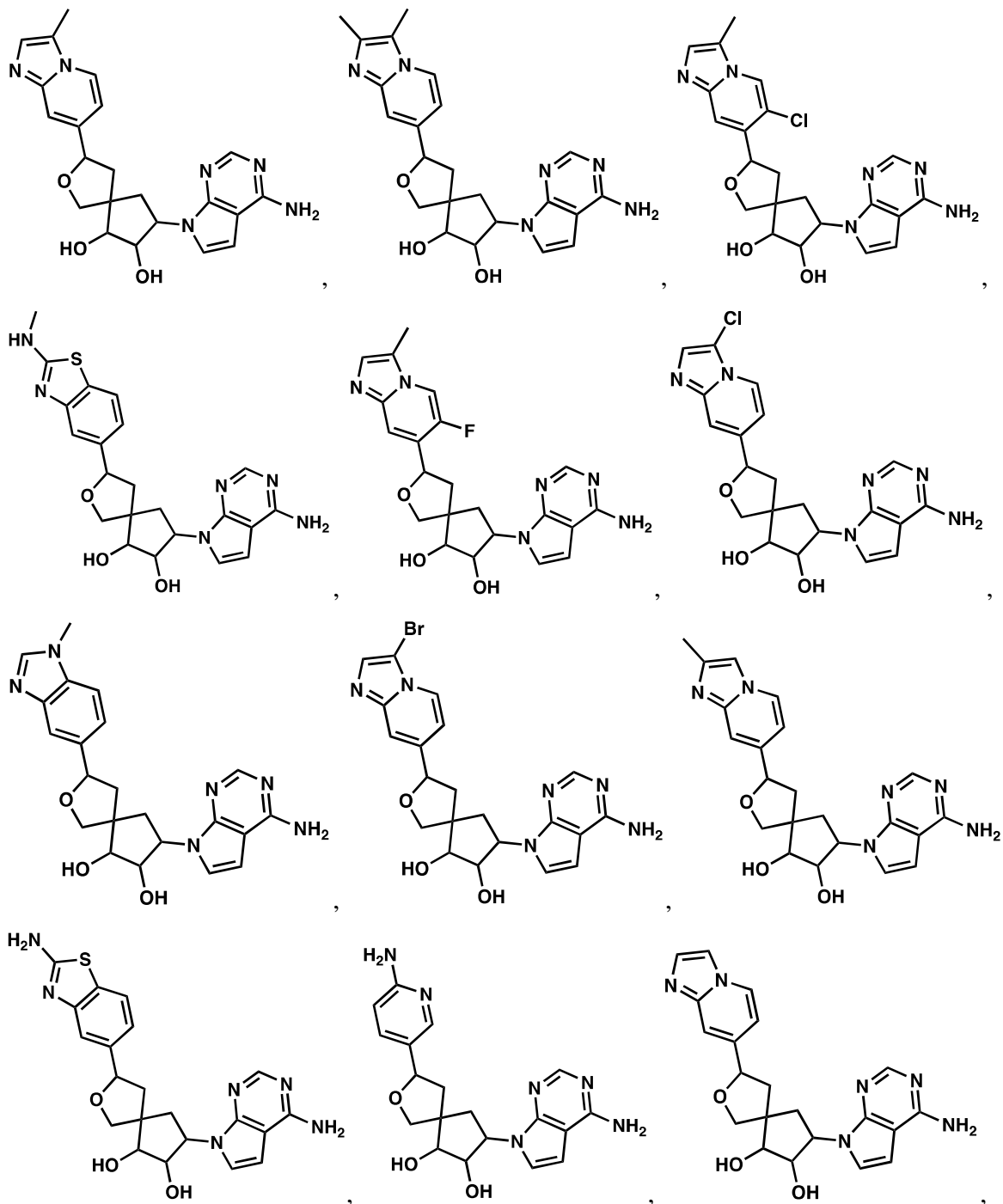


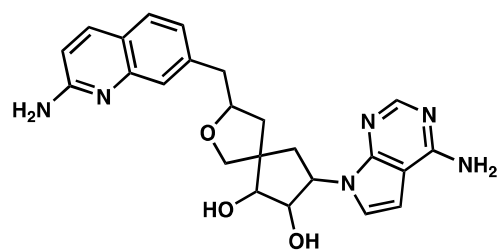
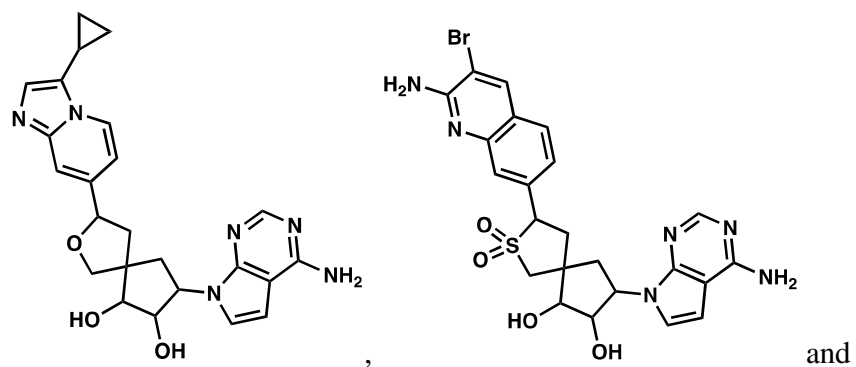
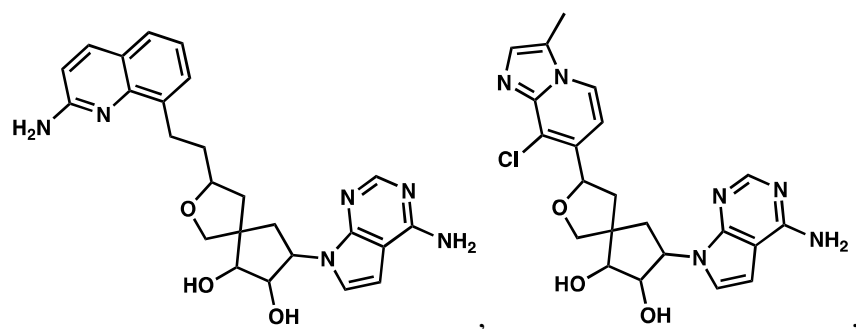




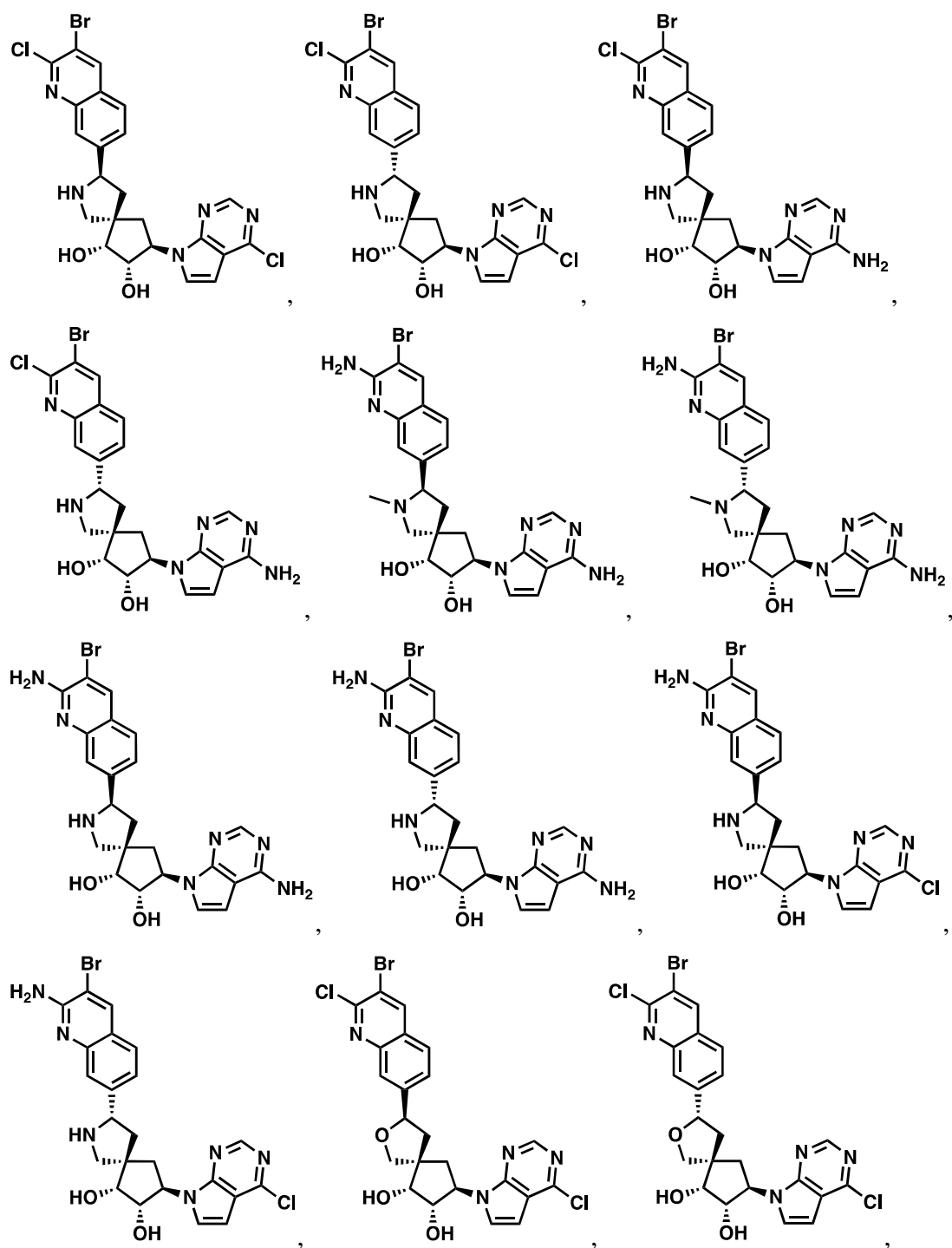


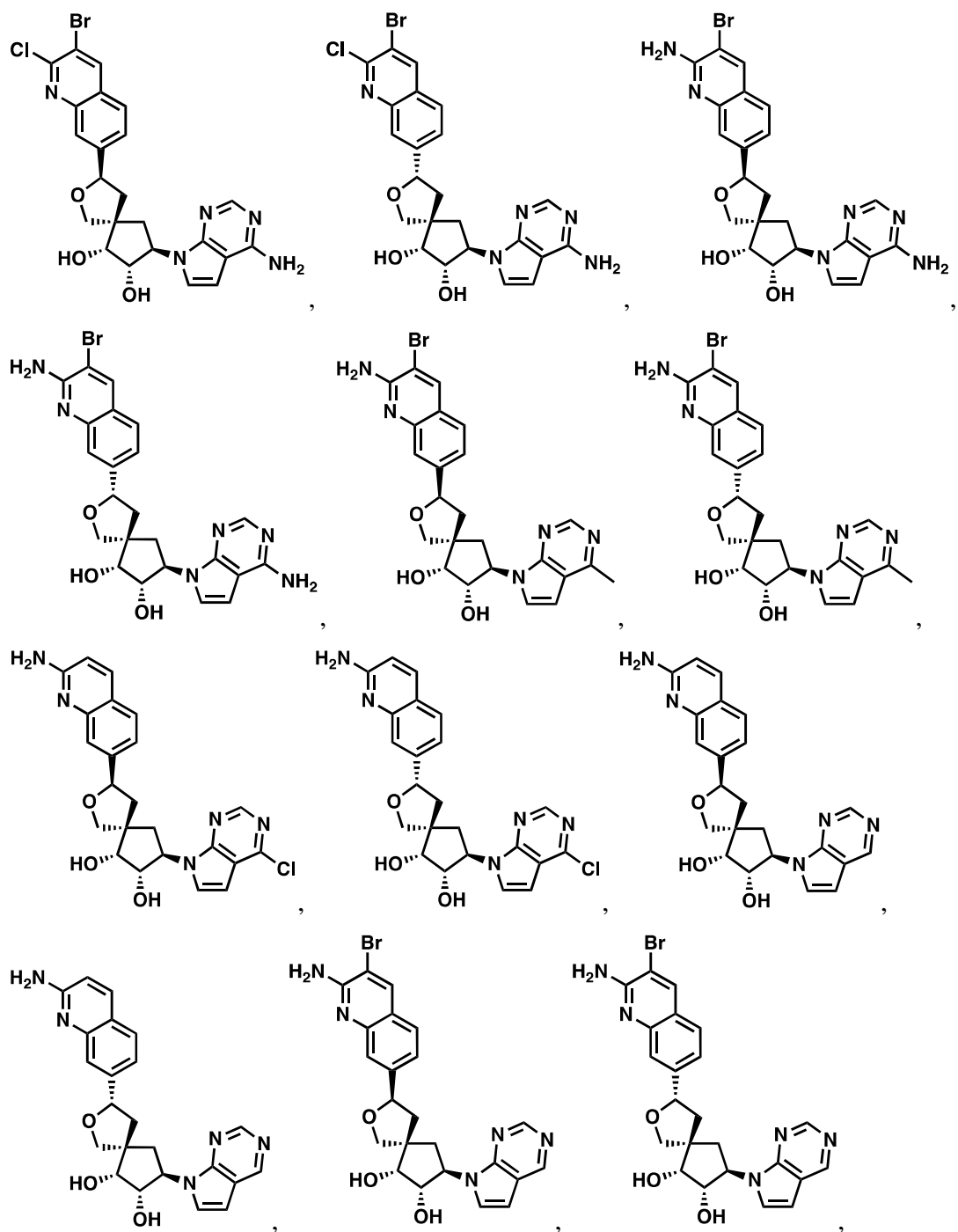


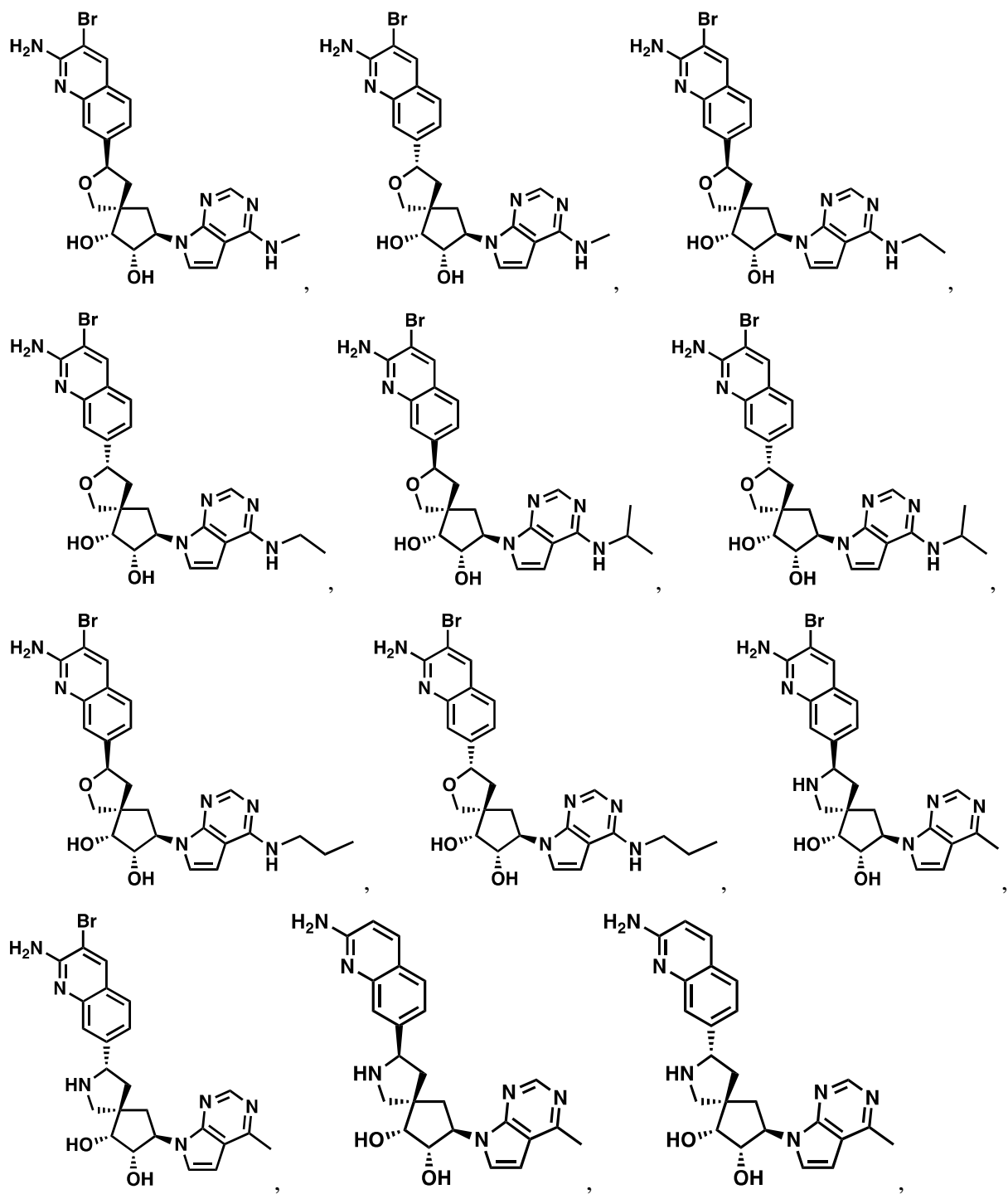


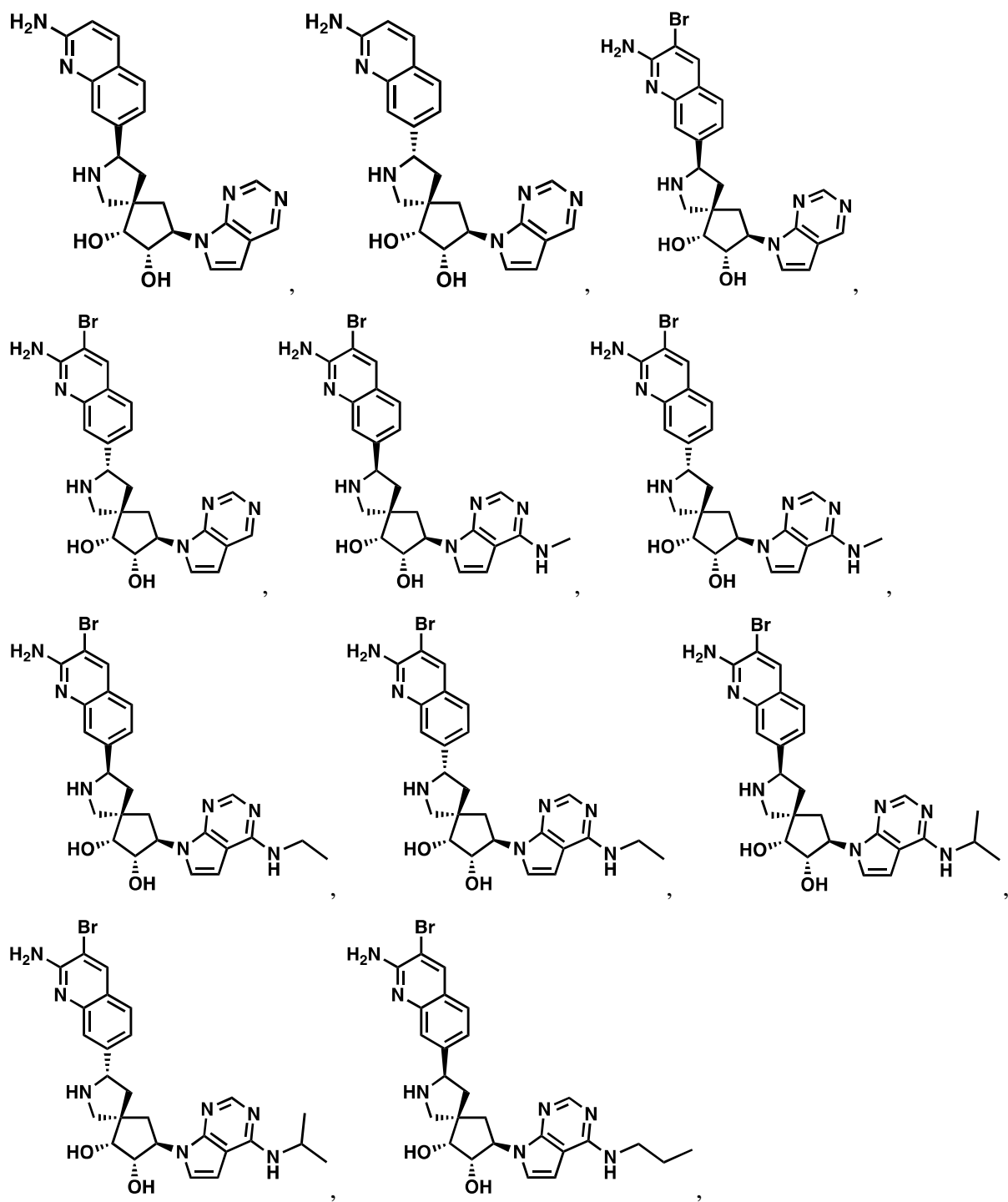


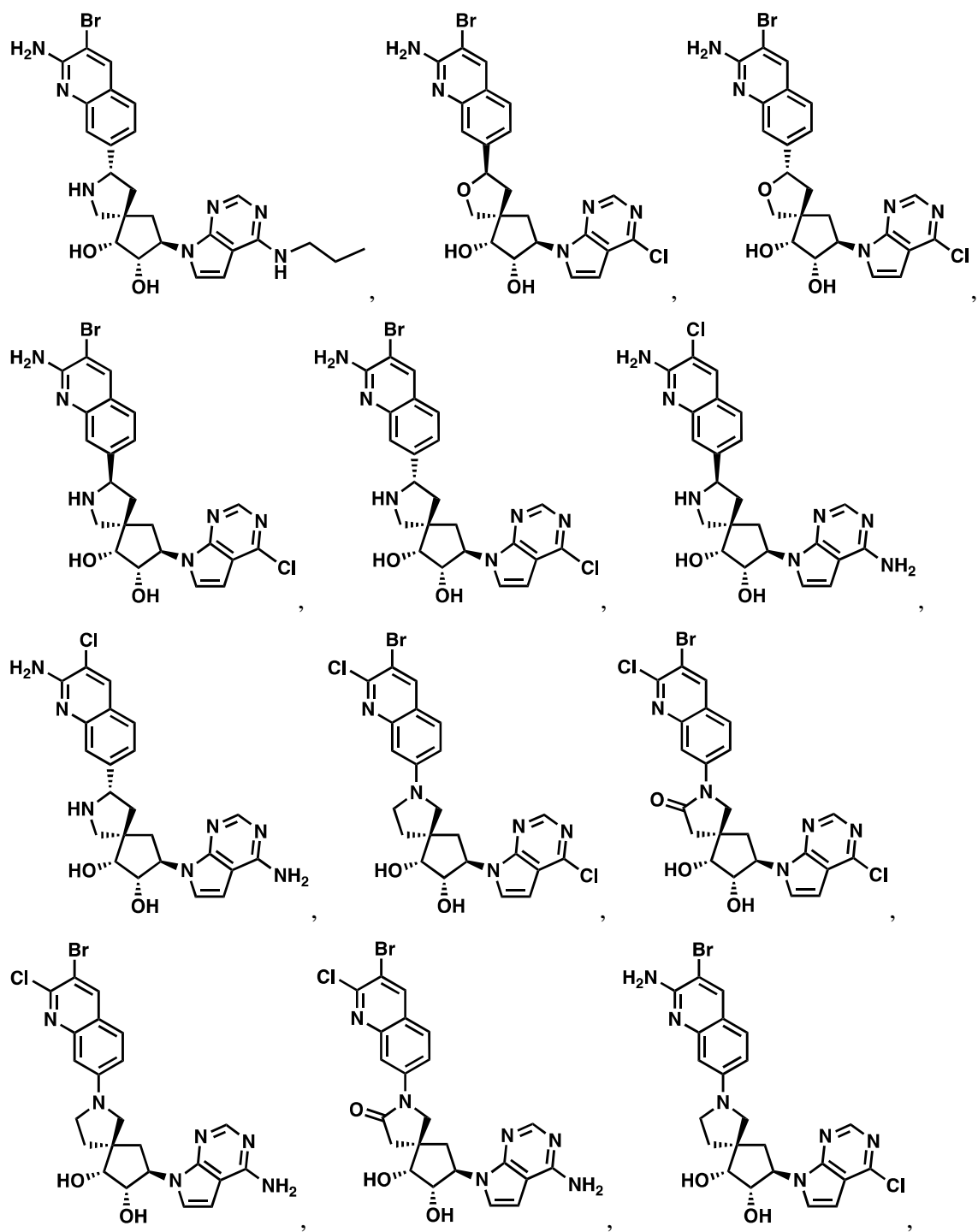
23. A compound selected from:

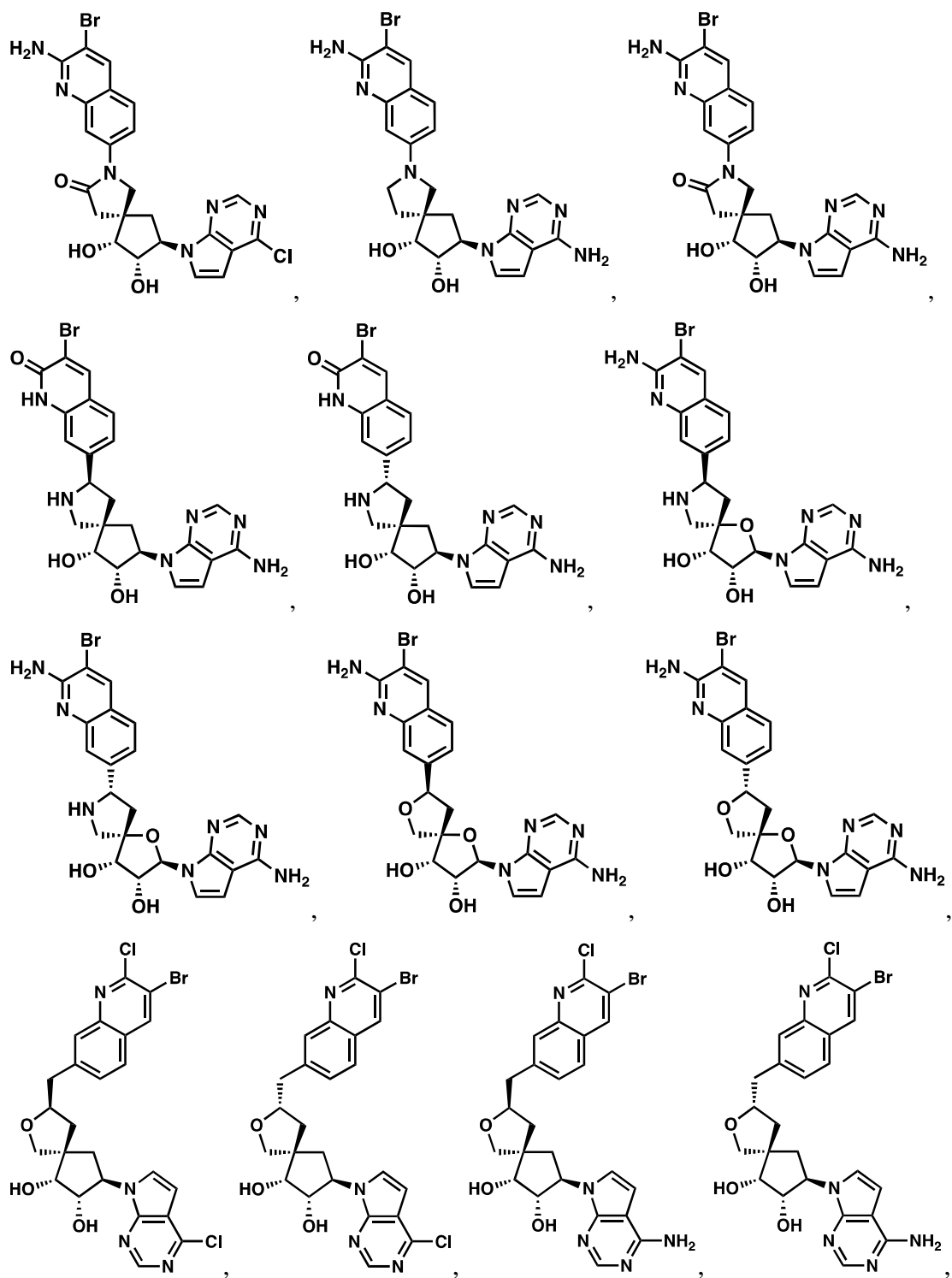


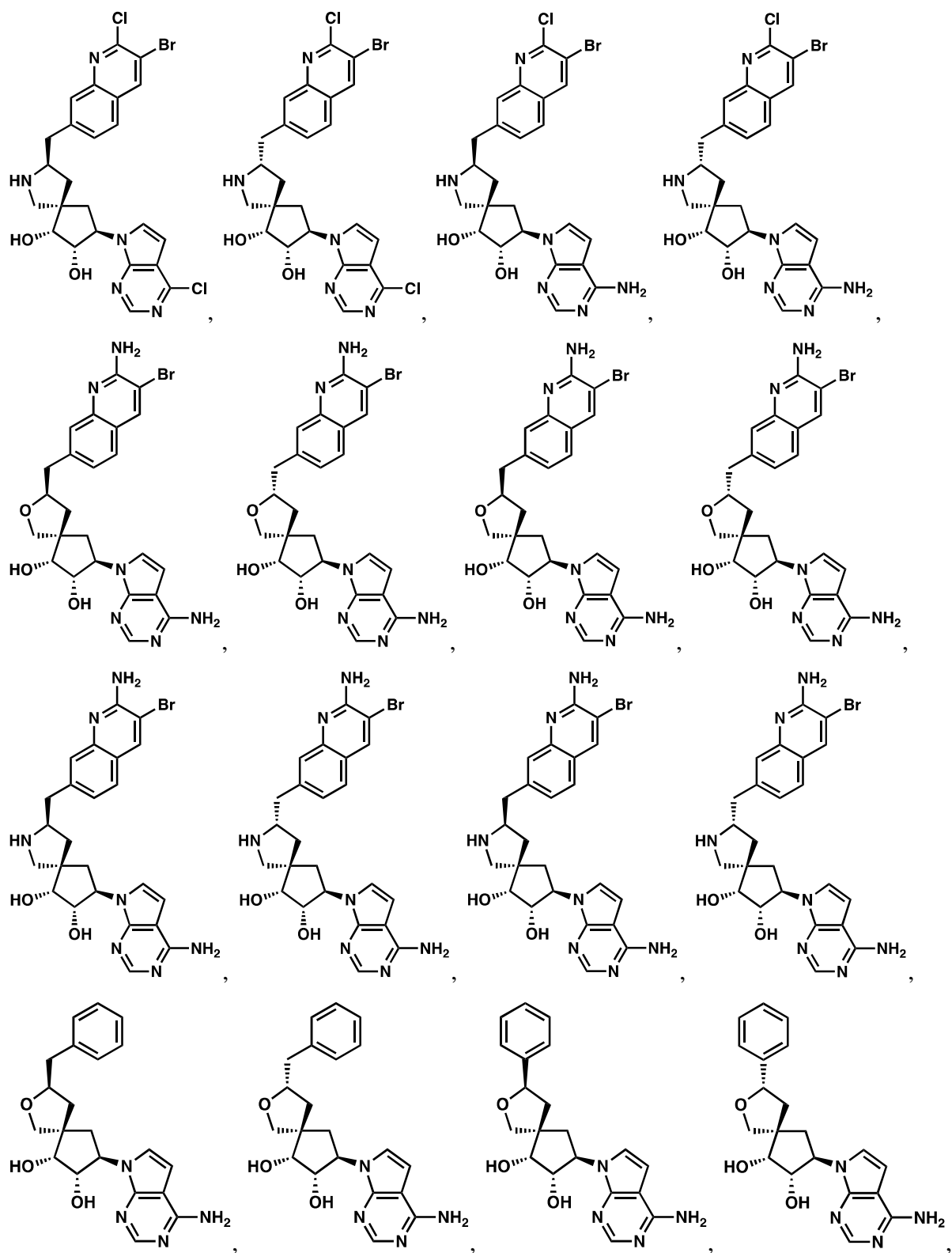


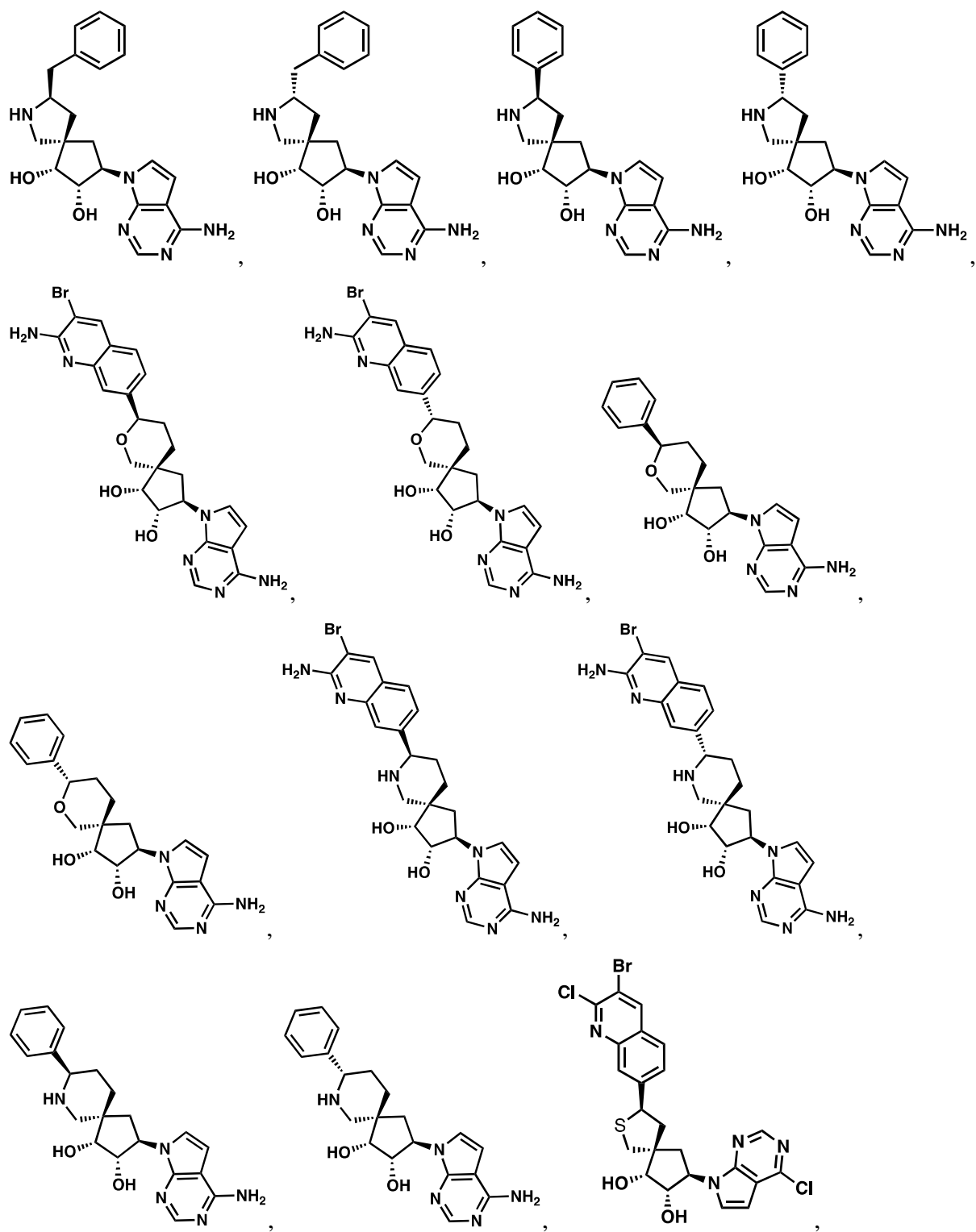


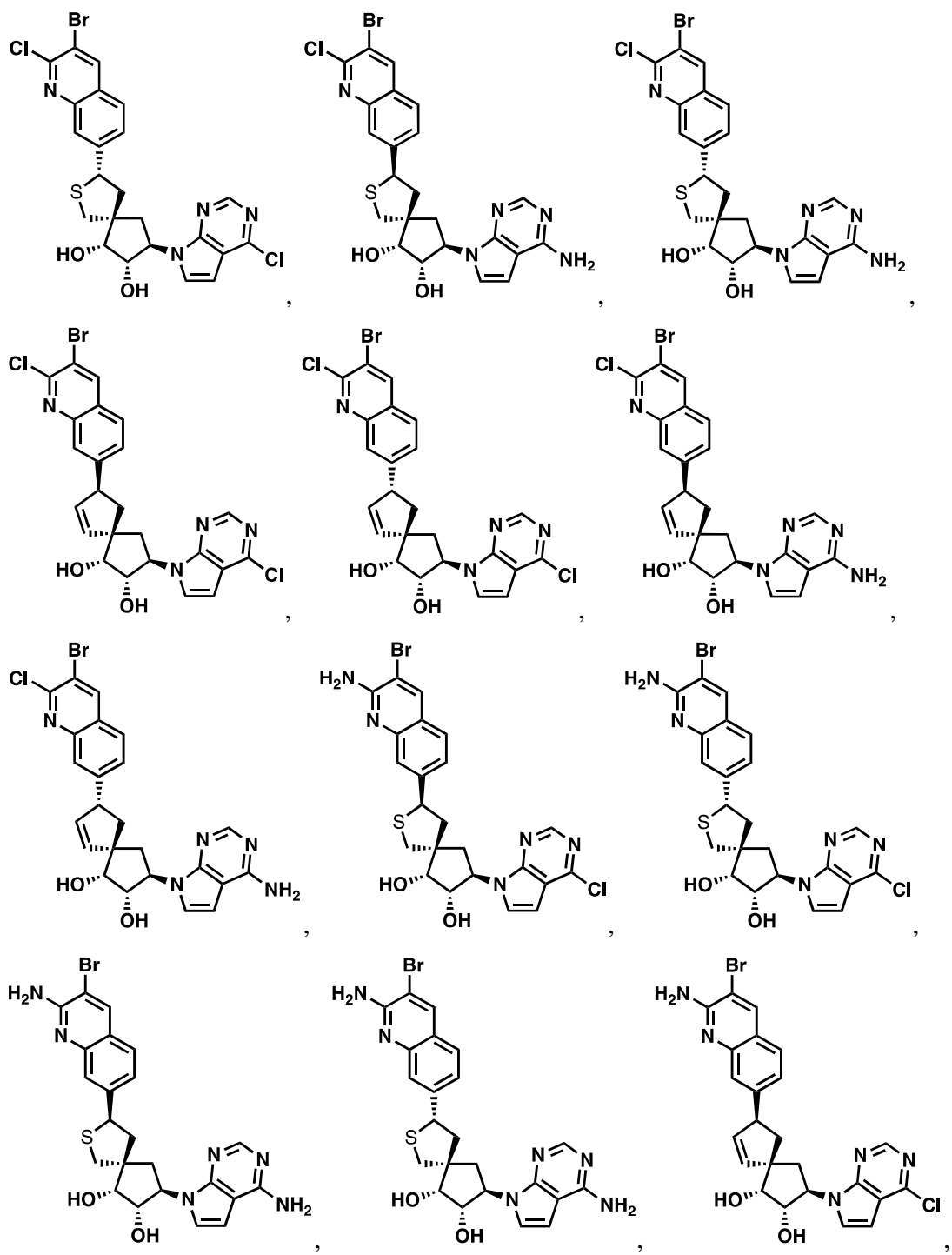


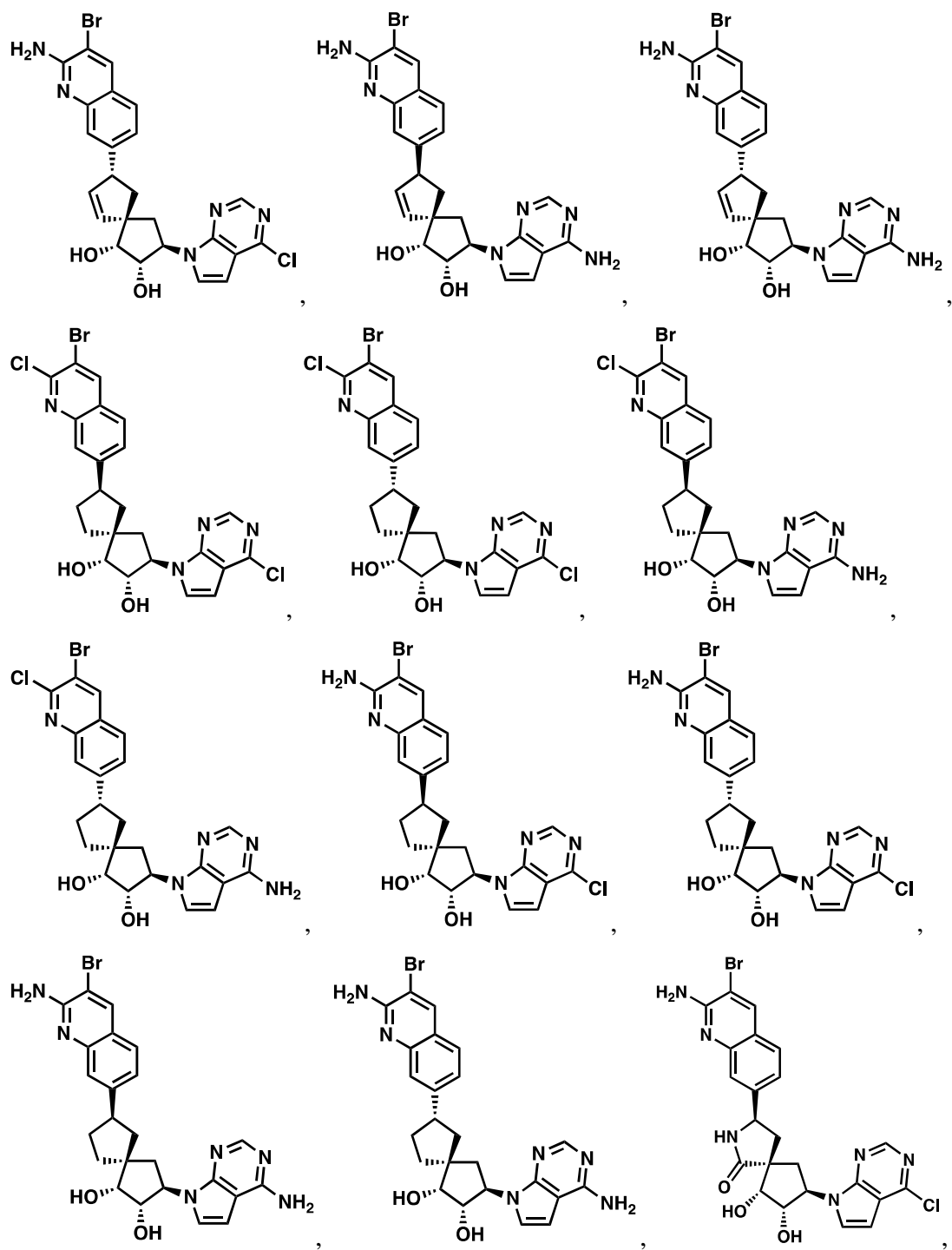


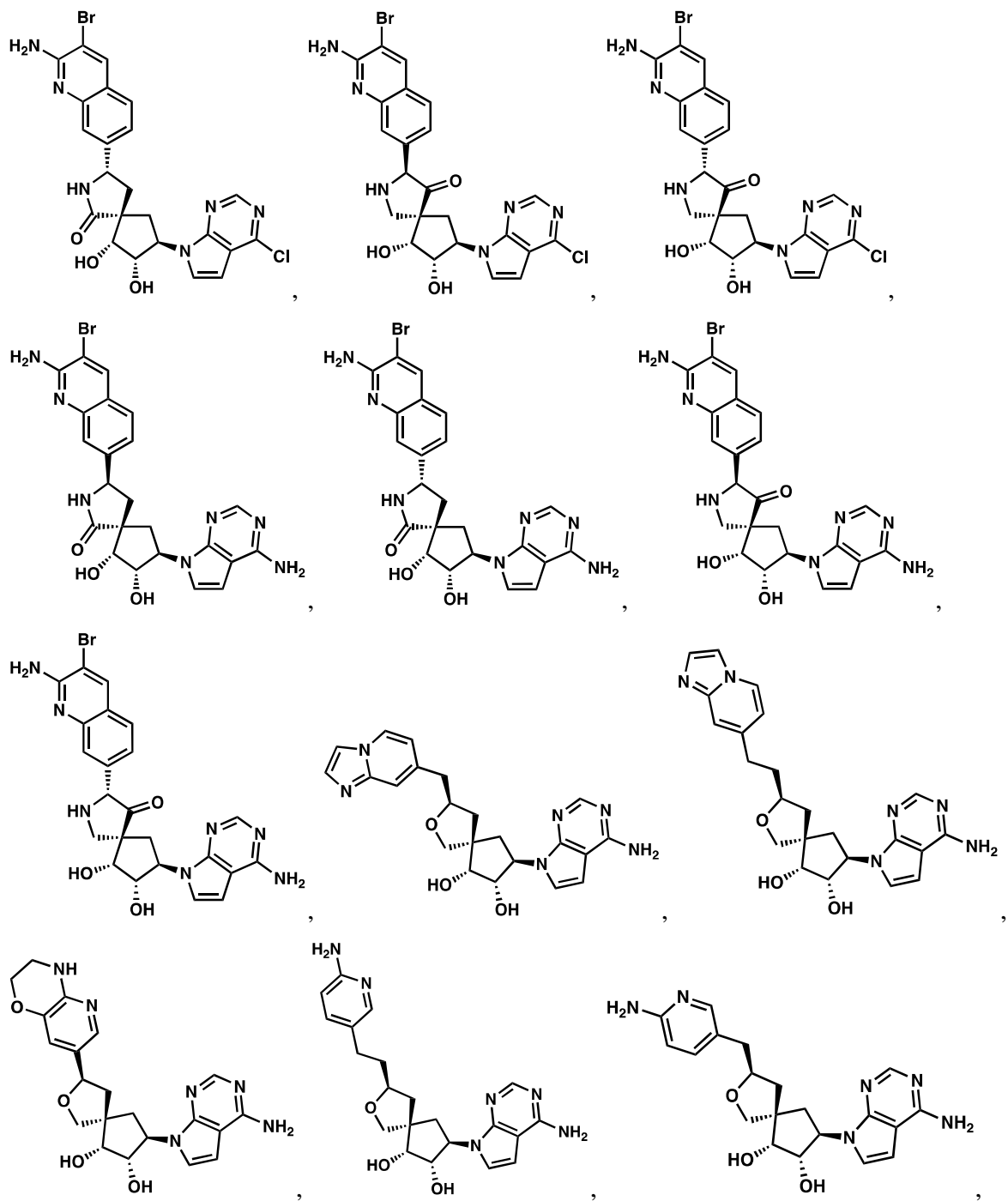


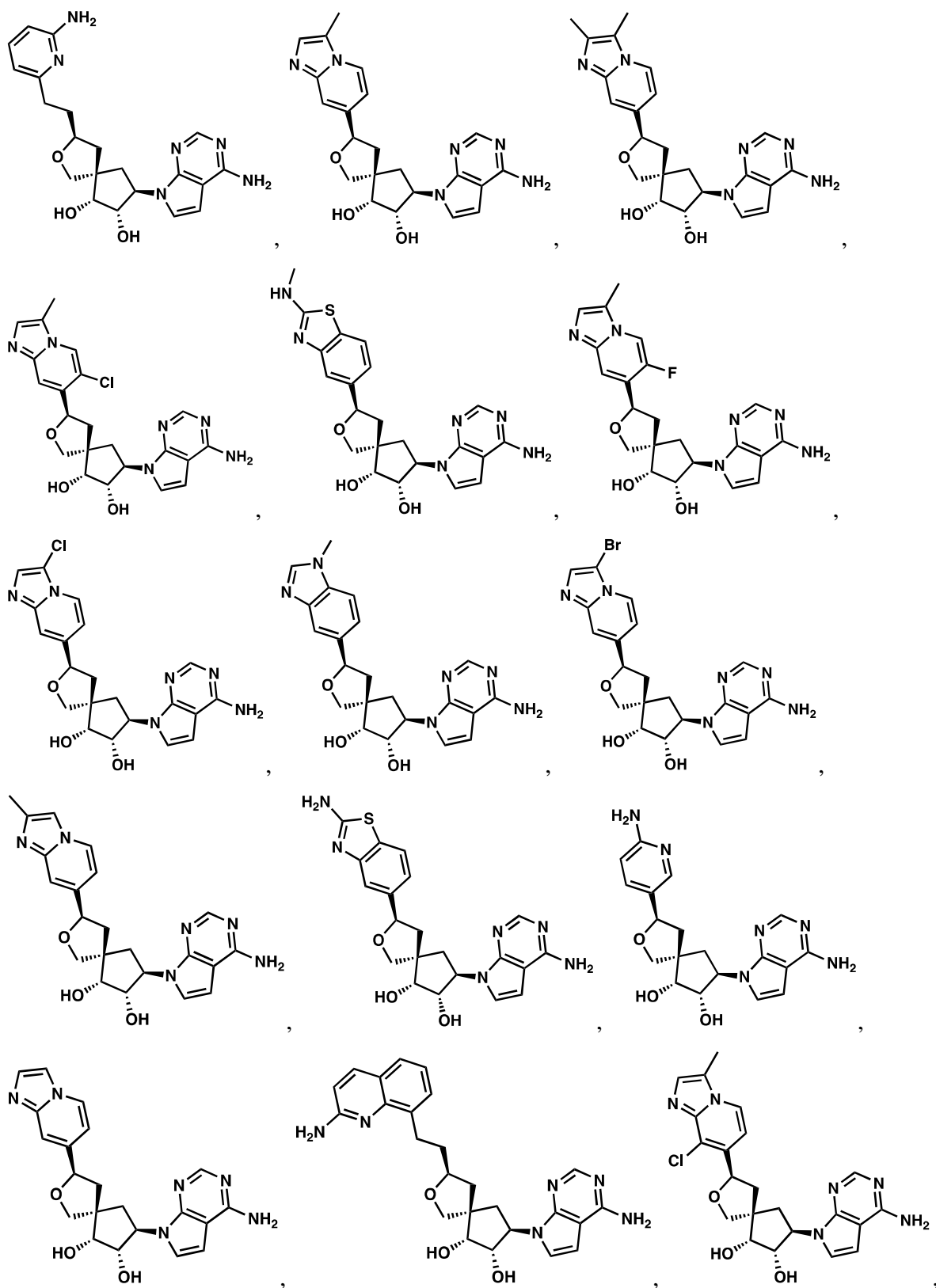


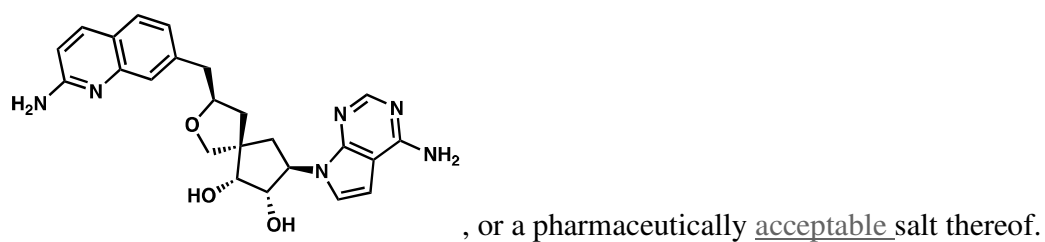
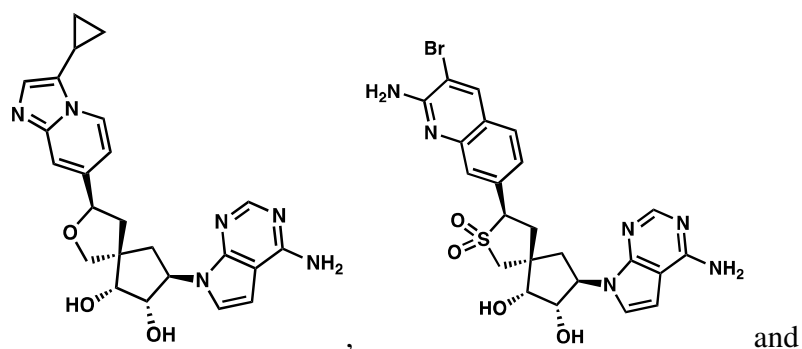




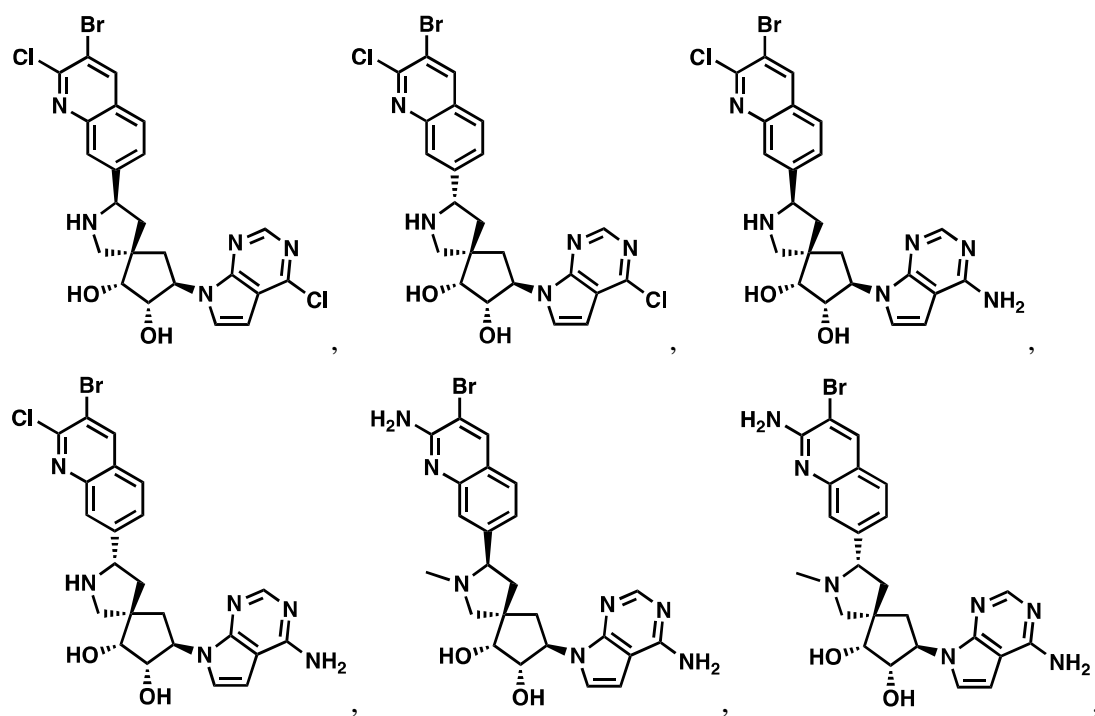


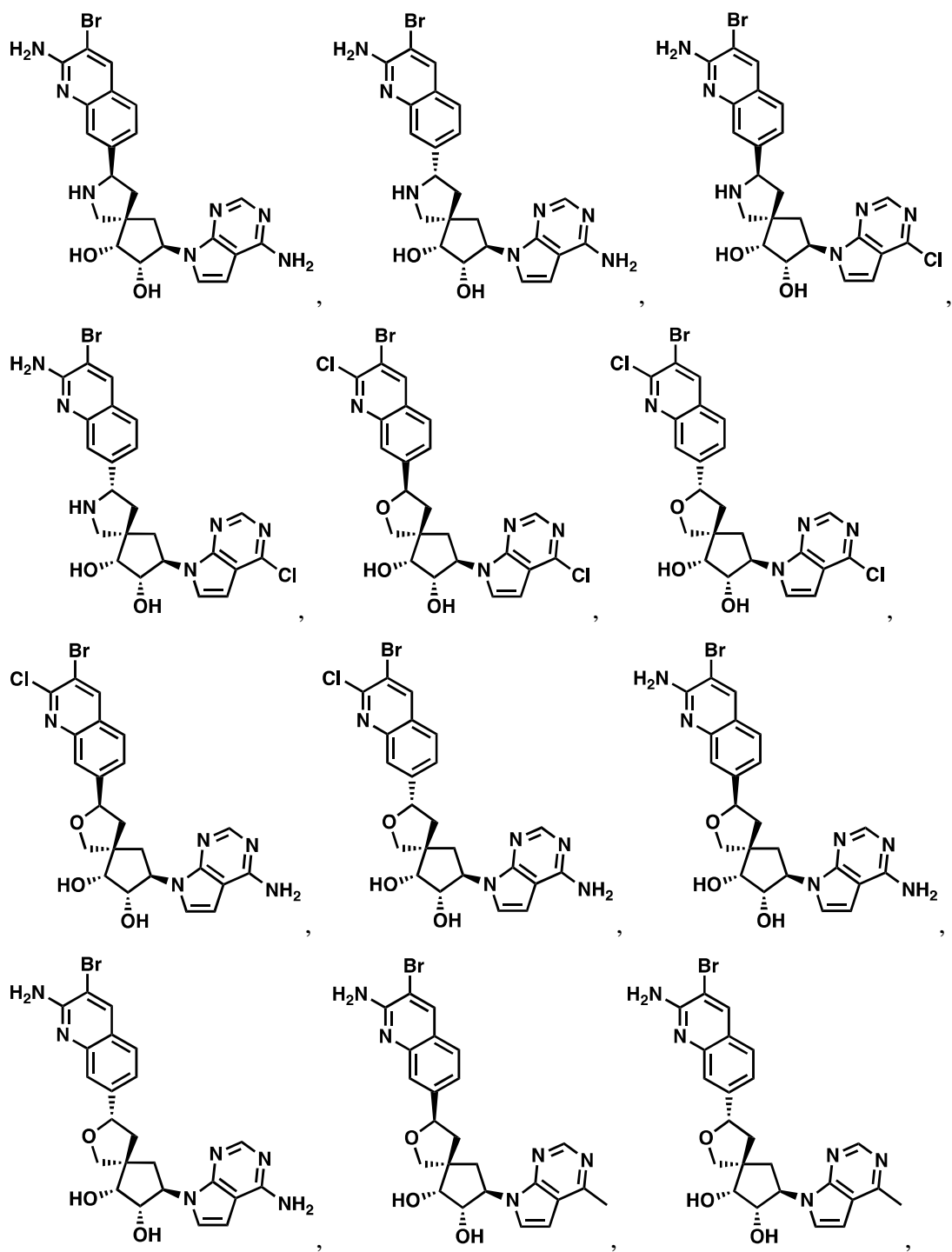


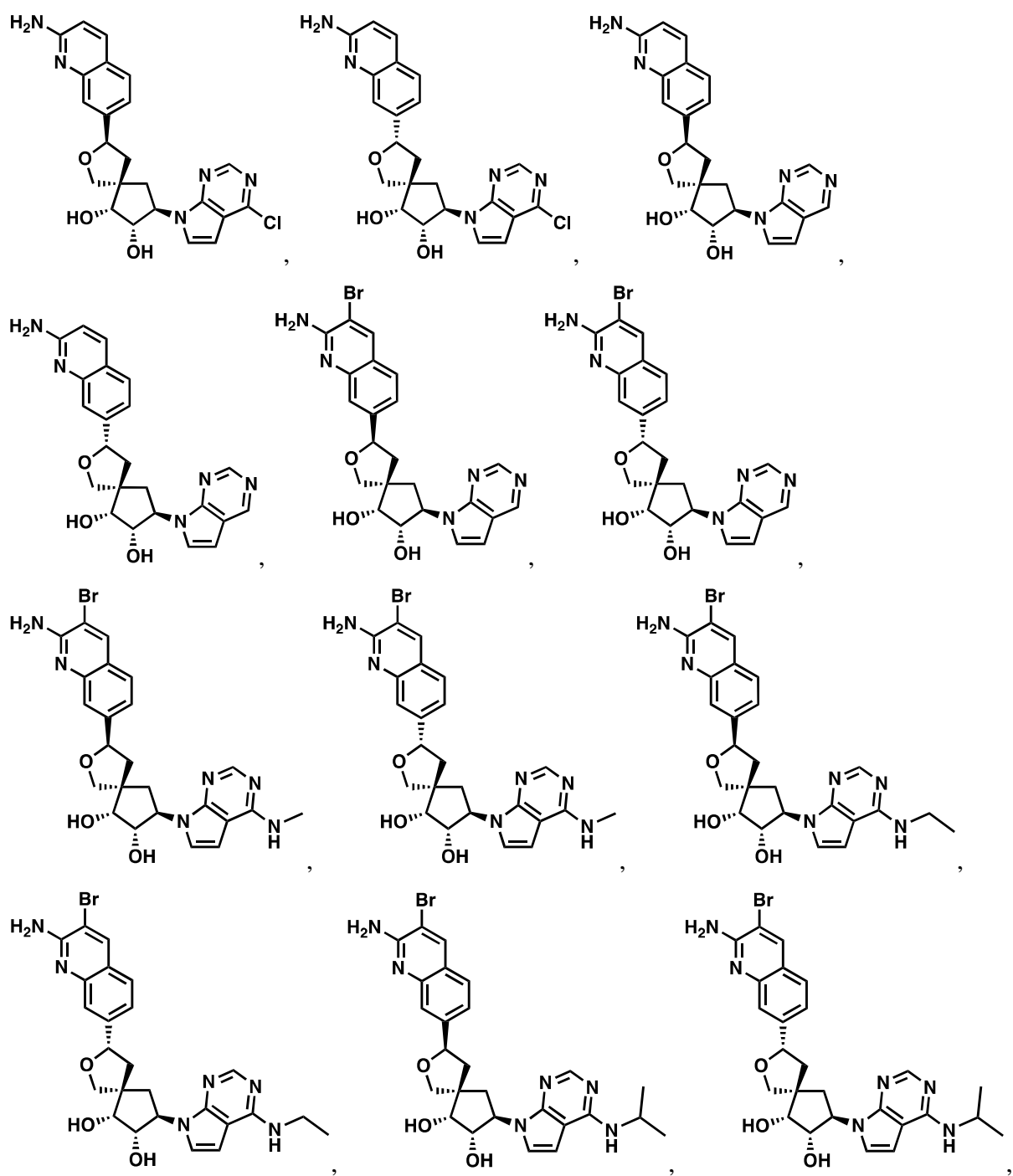


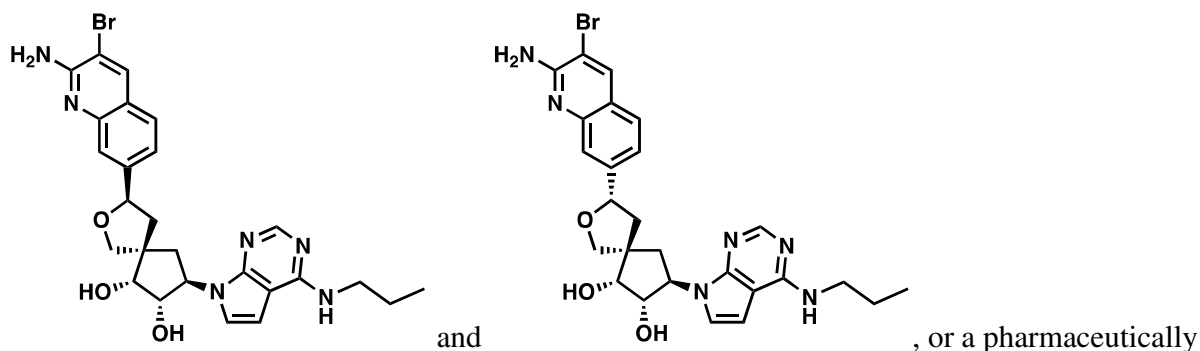


24. A compound selected from:









acceptable salt thereof.

25. A pharmaceutical composition comprising a compound of any one of claims 1-24 and a pharmaceutically acceptable diluent or excipient.

26. A compound of any one of claims 1-24 or a pharmaceutically acceptable salt thereof for use in the treatment of cancers, metabolic diseases, or blood diseases~~a disease characterized by increased expression of PRMT5,~~

wherein the cancers are selected from carcinoma (e.g., a carcinoma of the endometrium, bladder, breast, colon (e.g., colorectal carcinomas such as colon adenocarcinoma and colon adenoma)); sarcoma (e.g., a sarcoma such as Kaposi's, osteosarcoma, tumor of mesenchymal origin, for example fibrosarcoma or habdomyosarcoma); kidney; epidermis; liver; lung (e.g., adenocarcinoma, small cell lung cancer and non-small cell lung carcinomas); oesophagus; gall bladder; ovary; pancreas (e.g., exocrine pancreatic carcinoma); stomach; cervix; thyroid; nose; head and neck; prostate; and skin (e.g., squamous cell carcinoma); human breast cancers (e.g., primary breast tumors, node-negative breast cancer, invasive duct adenocarcinomas of the breast, non- endometrioid breast cancers); familial melanoma; melanoma; hematopoietic tumors of lymphoid lineage (e.g. leukemia, acute lymphocytic leukemia, mantle cell lymphoma, chronic lymphocytic leukaemia, B-cell lymphoma (such as diffuse large B cell lymphoma), T-cell lymphoma, multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, and Burkett's lymphoma); and hematopoietic tumors of myeloid lineage, for example acute and chronic myelogenous leukemias, myelodysplastic syndrome, promyelocytic leukemia; a tumor of the central or peripheral nervous system, for example astrocytoma,

neuroblastoma, glioma or schwannoma; seminoma; teratocarcinoma; xeroderma pigmentosum; retinoblastoma; keratoctanthoma; and thyroid follicular cancer.

27. Use of a compound of any one of claims 1-24 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancers, metabolic diseases, or blood diseases~~a disease characterized by increased expression of PRMT5,~~

wherein the cancers are selected from carcinoma (e.g., a carcinoma of the endometrium, bladder, breast, colon (e.g., colorectal carcinomas such as colon adenocarcinoma and colon adenoma)); sarcoma (e.g., a sarcoma such as Kaposi's, osteosarcoma, tumor of mesenchymal origin, for example fibrosarcoma or habdomyosarcoma); kidney; epidermis; liver; lung (e.g., adenocarcinoma, small cell lung cancer and non-small cell lung carcinomas); oesophagus; gall bladder; ovary; pancreas (e.g., exocrine pancreatic carcinoma); stomach; cervix; thyroid; nose; head and neck; prostate; and skin (e.g., squamous cell carcinoma); human breast cancers (e.g., primary breast tumors, node-negative breast cancer, invasive duct adenocarcinomas of the breast, non- endometrioid breast cancers); familial melanoma; melanoma; hematopoietic tumors of lymphoid lineage (e.g. leukemia, acute lymphocytic leukemia, mantle cell lymphoma, chronic lymphocytic leukaemia, B-cell lymphoma (such as diffuse large B cell lymphoma), T-cell lymphoma, multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, and Burkett's lymphoma); and hematopoietic tumors of myeloid lineage, for example acute and chronic myelogenous leukemias, myelodysplastic syndrome, promyelocytic leukemia; a tumor of the central or peripheral nervous system, for example astrocytoma, neuroblastoma, glioma or schwannoma; seminoma; teratocarcinoma; xeroderma pigmentosum; retinoblastoma; keratoctanthoma; and thyroid follicular cancer.

28. — ~~The use of claim 27, wherein the disease is selected from cancers, metabolic diseases, and blood diseases;~~

~~wherein the cancers are selected from carcinoma (e.g., a carcinoma of the endometrium, bladder, breast, colon (e.g., colorectal carcinomas such as colon adenocarcinoma and colon adenoma)); sarcoma (e.g., a sarcoma such as Kaposi's, osteosarcoma, tumor of mesenchymal origin, for example fibrosarcoma or habdomyosarcoma); kidney; epidermis; liver; lung (e.g., adenocarcinoma, small cell lung cancer and non-small cell lung carcinomas); oesophagus; gall~~

bladder; ovary; pancreas (*e.g.*, exocrine pancreatic carcinoma); stomach; cervix; thyroid; nose; head and neck; prostate; and skin (*e.g.*, squamous cell carcinoma); human breast cancers (*e.g.*, primary breast tumors, node-negative breast cancer, invasive duct adenocarcinomas of the breast, non-endometrioid breast cancers); familial melanoma; melanoma; hematopoietic tumors of lymphoid lineage (*e.g.*, leukemia, acute lymphocytic leukemia, mantle cell lymphoma, chronic lymphocytic leukaemia, B-cell lymphoma (such as diffuse large B-cell lymphoma), T-cell lymphoma, multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, and Burkett's lymphoma); and hematopoietic tumors of myeloid lineage, for example acute and chronic myelogenous leukemias, myelodysplastic syndrome, promyelocytic leukemia; a tumor of the central or peripheral nervous system, for example astrocytoma, neuroblastoma, glioma or schwannoma; seminoma; teratocarcinoma; xeroderma pigmentosum; retinoblastoma; keratocanthoma; and thyroid follicular cancer.