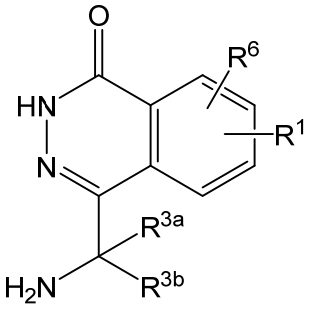
[0005] Cells lacking MTAP activity have elevated levels of the MTAP substrate, methylthioadenosine (MTA), which is a potent inhibitor of PRMT5. Inhibition of PRMT5 activity results in reduced methylation activity and increased sensitivity of cellular proliferation to PRMT5 depletion or loss of activity. Hence, the loss of MTAP activity reduces methylation activity of PRMT5 making the cells selectively dependent on PRMT5 activity.

SUMMARY

[0006] Thus, we realized that MTA-cooperative inhibition of PRMT5 activity in MTAP deleted cancers will provide therapeutic benefit for a wide range of cancers. The compounds of the present disclosure provide this therapeutic benefit as MTA-cooperative inhibitors of PRMT5 that negatively modulate the activity of MTA-bound PRMT5 in a cell, particularly an MTAP-deficient cell, or for treating various forms of MTAP-associated cancer.

[0007] There is a need to develop new MTA-cooperative PRMT5 inhibitors that are capable of inhibiting PRMT5 activity in the presence of elevated MTA concentrations, particularly in MTAP-deficient cells.

[0007a] In one aspect of the present disclosure, there is provided a compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof:

wherein:

R^1 is hydrogen, halogen, hydroxyalkyl, -L-CN, -Y-C1 – C5 alkyl, -Y-cycloalkyl, -Y-heterocyclyl, -Y-aryl, -Y-arC1-C3alkyl or -Y-heteroaryl, wherein the cycloalkyl, the heterocyclyl, the aryl, and the heteroaryl portions are each optionally substituted with one or more R^2;

each Y is independently a bond or -NR^4-;

each R^2 is independently hydroxy, halogen, cyano, cyanomethyl, -$(NR^4)_2$, hydroxyalkyl, alkoxy, -SO_2C1 – C3alkyl, -X-arC1-C3alkyl, heteroalkyl, C2- C4 alkynyl, -X-haloalkyl, -X-C1 – C5 alkyl, -Z-C1 – C5 alkyl, heterocyclyl, -X-L-cycloalkyl, -Z-cycloalkyl, -X-aryl, -Z-aryl, or -X-heteroaryl, wherein the heterocyclyl, the cycloalkyl, the aryl and the heteroaryl are optionally substituted with one or more R^5, or;

each X is independently a bond, O, S, -NR^4- or -NR^4C(O)-;

each Z is independently a bond, -SO-, -SO_2-, -CH(OH)- or -C(O)-;

each L is independently a bond or C1 – C3 alkylene;

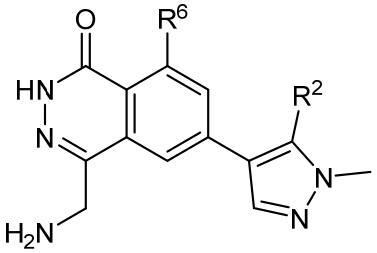
R^{3a} and R^{3b} are each independently hydrogen or deuterium, or R^{3a} and R^{3b} together are oxo;

each R^4 is independently hydrogen or C1 – C3 alkyl;

each R^5 is independently cyano, oxo, halogen, C1 – C3 alkyl, hydroxyalkyl, alkoxy, -X-haloalkyl, -Z-cycloalkyl, -X-arC1-C3alkyl, X-arC1-C3alkyl substituted with cyano, -X-L-cycloalkyl, -X-L-heteroaryl optionally substituted with one or more C1-C3alkyl or oxo, or -X-aryl; and

R^6 is hydrogen, halogen, C1-C3 alkyl, haloalkyl or alkoxy.

[0007b] In another aspect of the present disclosure, there is provided a compound of Formula (I-D):



Formula (I-D)

or a pharmaceutically acceptable salt thereof:

wherein:

each Y is independently a bond or -NR^4-;

each R^2 is independently hydroxy, halogen, cyano, cyanomethyl, -$(NR^4)_2$, hydroxyalkyl, alkoxy, -SO_2C1 – C3alkyl, -X-arC1-C3alkyl, heteroalkyl, C2- C4 alkynyl, -X-haloalkyl, -X-C1 – C5 alkyl, -Z-C1 – C5 alkyl, heterocyclyl, -X-L-cycloalkyl, -Z-cycloalkyl, -X-aryl, -Z-aryl, or -X-heteroaryl, wherein the heterocyclyl,

the cycloalkyl, the aryl and the heteroaryl are optionally substituted with one or more R^5, or;

each X is independently a bond, O, S, $-NR^4-$ or $-NR^4C(O)-$;

each Z is independently a bond, -SO-, $-SO_2-$, -CH(OH)- or -C(O)-;

each L is independently a bond or C1 – C3 alkylene;

each R^4 is independently hydrogen or C1 – C3 alkyl;

each R^5 is independently cyano, oxo, halogen, C1 – C3 alkyl, hydroxyalkyl, alkoxy, -X-haloalkyl, -Z-cycloalkyl, -X-arC1-C3alkyl, X-arC1-C3alkyl substituted with cyano, -X-L-cycloalkyl, -X-L-heteroaryl optionally substituted with one or more C1-C3alkyl or oxo, or -X-aryl; and

R^6 is hydrogen, halogen, C1-C3 alkyl, haloalkyl or alkoxy.

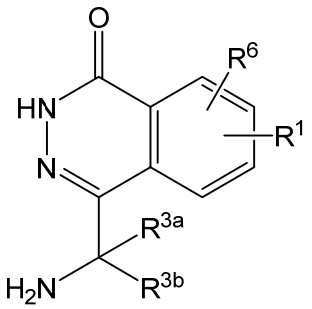
[0007c] In a further aspect of the present disclosure, there is provided a pharmaceutical composition, comprising a therapeutically effective amount of a compound of Formula (I) disclosed herein or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

[0007d] In another aspect of the present disclosure, there is provided a use of a compound of Formula (I) disclosed herein or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for inhibiting PRMT5 activity in a cell.

[0007e] In a further aspect of the present disclosure, there is provided a use of a therapeutically effective amount of a compound of Formula (I) disclosed herein or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutically acceptable salt or solvate thereof, alone or combined with a pharmaceutically acceptable carrier, excipient or diluents, in the manufacture of a medicament for treating cancer.

[0007f] In another aspect of the present disclosure, there is provided a compound of Formula (I) disclosed herein or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutically acceptable salt or solvate thereof, alone or combined with a pharmaceutically acceptable carrier, excipient or diluents, or a pharmaceutical composition disclosed herein, for use in therapy.

[0008] In one example of the present disclosure, compounds are provided that are represented by Formula (I):



Formula (I)

[0009] and pharmaceutically acceptable salts thereof:

[00010] wherein:

[0010] R^1 is hydrogen, halogen, hydroxyalkyl, -L-CN, -Y-C1 – C5 alkyl, -Y-cycloalkyl, -Y-heterocyclyl, -Y-aryl, -Y-arC1-C3alkyl or -Y-heteroaryl, wherein the cycloalkyl, the

heterocyclyl, the aryl, and the heteroaryl portions are each optionally substituted with one or more R^2;

[0011] each Y is independently a bond or -NR^4-;

[0012] each R^2 is independently hydroxy, halogen, cyano, cyanomethyl, -$(NR^4)_2$, hydroxyalkyl, alkoxy, -SO_2C1 – C3alkyl, -X-arC1-C3alkyl, heteroalkyl, C2- C4 alkynyl, -X-haloalkyl, -X-C1 – C5 alkyl, -Z-C1 – C5 alkyl, heterocyclyl, -X-L-cycloalkyl, -Z-cycloalkyl, -X-aryl, -Z-aryl, or -X-heteroaryl, wherein the heterocyclyl, the cycloalkyl, the aryl and the heteroaryl are optionally substituted with one or more R^5;

[0013] each X is independently a bond, O, S, -NR^4- or -NR^4C(O)-

[0014] each Z is independently a bond, -SO-, -SO_2-, -CH(OH)- or -C(O)-;

[0015] each L is independently a bond or C1 – C3 alkylene;

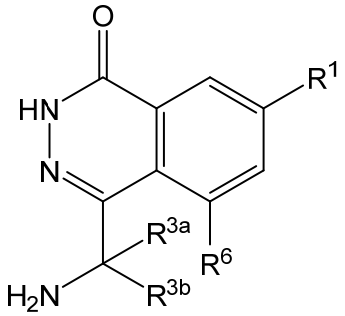
[0016] R^{3a} and R^{3b} are each independently hydrogen or deuterium, or R^{3a} and R^{3b} together are oxo;

[0017] each R^4 is independently hydrogen or C1 – C3 alkyl;

[0018] each R^5 is independently cyano, oxo, halogen, C1 – C3 alkyl, hydroxyalkyl, alkoxy, -X-haloalkyl, -Z-cycloalkyl, -X-arC1-C3alkyl, X-arC1-C3alkyl substituted with cyano -X-L-cycloalkyl, -X-L-heteroaryl optionally substituted with one or more C1-C3alkyl or oxo, or -X-aryl; and

[0019] R^6 is hydrogen, halogen, C1-C3 alkyl, haloalkyl or alkoxy.

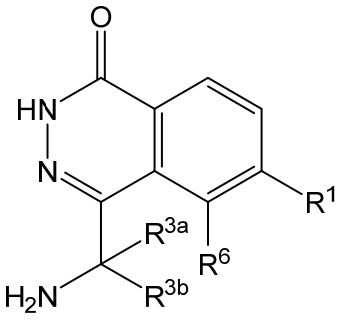
[0020] In one example of the present disclosure, compounds are provided that are represented by Formula (I-A):



Formula (I-A)

or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^{3a}, R^{3b}, R^4, R^5, R^6, Y, X, Z and L are as each defined for Formula I.

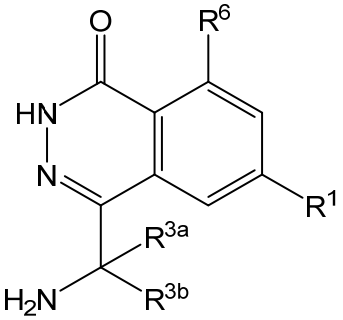
[0021] In one example of the present disclosure, compounds are provided that are represented by Formula (I-B):



Formula (I-B)

or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^{3a}, R^{3b}, R^4, R^5, R^6, Y, X, Z and L are as each defined for Formula I.

[0022] In one example of the present disclosure, compounds are provided that are represented by Formula (I-C):



Formula (I-C)

or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^{3a}, R^{3b}, R^4, R^5, R^6, Y, X, Z and L are as each defined for Formula I.

[0023] In another example of the present disclosure, compounds are provided that are represented by Formula (I-D):

R^6 is hydrogen, halogen, C1-C3 alkyl, haloalkyl or alkoxy.

[0024] In another example of the present disclosure, intermediates are provided that are useful for the preparation of compounds of Formula (I), Formula (I-A), Formula (I-B) and Formula (I-C).

[0025] In another example of the present disclosure, pharmaceutical compositions are provided comprising a therapeutically effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

[0026] In yet another example of the present disclosure, methods for inhibiting PRMT5 activity in a in a cell, comprising contacting the cell with a compound of Formula (I), Formula (I-A), Formula (I-B) and Formula (I-C). In one example, the contacting is in vitro. In one example, the contacting is in vivo.

[0027] Also provided herein is a method of inhibiting cell proliferation, in vitro or in vivo, the method comprising contacting a cell with an effective amount of a compound of Formula (I), Formula (I-A), Formula (I-B), Formula (I-C) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof as defined herein. In one example, the cell is an MTAP-deficient cell.

[0028] Also provided are methods for treating cancer in a patient comprising administering a therapeutically effective amount of a compound or pharmaceutical composition of the present disclosure or a pharmaceutically acceptable salt thereof to a patient in need thereof.

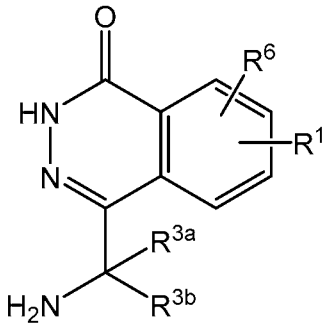
[0029] Also provided herein is a method for treating cancer in a patient in need thereof, the method comprising (a) determining that the cancer is associated with MTAP double deletion (e.g., an MTAP-associated cancer); and (b) administering to the patient a therapeutically effective amount of a compound of Formula (I), Formula (I-A), Formula (I-B), Formula (I-C) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

DETAILED DESCRIPTION OF THE INVENTION

[0030] The present invention relates to MTA-cooperative PRMT5 inhibitors. In particular, the present invention relates to compounds that inhibit PRMT5 activity in the presence of bound MTA, pharmaceutical compositions comprising a therapeutically effective amount of the compounds, and methods of use therefor.

WE CLAIM:

1. A compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof:

wherein:

R^1 is hydrogen, halogen, hydroxyalkyl, -L-CN, -Y-C1 – C5 alkyl, -Y-cycloalkyl, -Y-heterocyclyl, -Y-aryl, -Y-arC1-C3alkyl or -Y-heteroaryl, wherein the cycloalkyl, the heterocyclyl, the aryl, and the heteroaryl portions are each optionally substituted with one or more R^2;

each Y is independently a bond or $-NR^4-$;

each R^2 is independently hydroxy, halogen, cyano, cyanomethyl, $-(NR^4)_2$, hydroxyalkyl, alkoxy, $-SO_2$C1 – C3alkyl, -X-arC1-C3alkyl, heteroalkyl, C2- C4 alkynyl, -X-haloalkyl, -X-C1 – C5 alkyl, -Z-C1 – C5 alkyl, heterocyclyl, -X-L-cycloalkyl, -Z-cycloalkyl, -X-aryl, -Z-aryl, or -X-heteroaryl, wherein the heterocyclyl, the cycloalkyl, the aryl and the heteroaryl are optionally substituted with one or more R^5, or;

each X is independently a bond, O, S, $-NR^4-$ or $-NR^4C(O)-$;

each Z is independently a bond, -SO-, $-SO_2-$, -CH(OH)- or -C(O)-;

each L is independently a bond or C1 – C3 alkylene;

R^{3a} and R^{3b} are each independently hydrogen or deuterium, or R^{3a} and R^{3b} together are oxo;

each R^4 is independently hydrogen or C1 – C3 alkyl;

each R^5 is independently cyano, oxo, halogen, C1 – C3 alkyl, hydroxyalkyl, alkoxy, -X-haloalkyl, -Z-cycloalkyl, -X-arC1-C3alkyl, X-arC1-C3alkyl substituted with cyano, -X-L-cycloalkyl, -X-L-heteroaryl optionally substituted with one or more C1-C3alkyl or oxo, or -X-aryl; and

R^6 is hydrogen, halogen, C1-C3 alkyl, haloalkyl or alkoxy.

2. The compound according to claim 1, wherein R^1 is hydrogen.

3. The compound according to claim 1, wherein R^1 is halogen.

4. The compound according to claim 3, wherein the halogen is bromine.

5. The compound according to claim 1, wherein R^1 is -Y-C1 – C5 alkyl.

6. The compound of claim 5, wherein Y is a bond and the C1 – C5 alkyl is methyl.

7. The compound according to claim 1, wherein R^1 is hydroxyalkyl.

8. The compound according to claim 1, wherein R^1 is -L-CN.

9. The compound according to claim 8, wherein L is C1 – C3 alkylene.

10. The compound according to claim 1, wherein R^1 is -Y-heterocyclyl.

11. The compound according to claim 10, wherein Y is a bond and the heterocyclyl is azetidinyl, THFyl or morpholinyl.

12. The compound according to claim 1, wherein R^1 is -Y-aryl, wherein the aryl is optionally substituted with one or more R^2.

13. The compound according to claim 12, wherein Y is a bond and the aryl is phenyl optionally substituted with one or two R^2.

14. The compound according to claim 13, wherein the one or two R^2 groups are each independently cyano, halogen or -Y-C1 – C5 alkyl, wherein Y is a bond.

15. The compound according to claim 1, wherein R^1 is -Y-cycloalkyl.

16. The compound according to claim 15, wherein Y is a bond and the cycloalkyl is cyclopentyl.

17. The compound according to claim 1, wherein R^1 is -Y-heteroaryl optionally substituted with one or more R^2.

18. The compound according to claim 17, wherein Y is a bond and the heteroaryl is pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, triazolyl, oxidazolyl, pyridyl, pyridiazinyl, pyrimidinyl, quinolinyl, isoquinolinyl, phthalazinyl, pyrazolopyridinyl, 1*H*-pyrrolopyridyl, pyrazolopyrimidinyl, imidazopyridyl, tetrahydropyrazolopyrazinyl, 2*H*-4λ^4-imidazopyrimidinyl, 2*H*-4λ^4-imidazopyridazinyl, oxazolopyridyl or 5,6-dihydro-8H-imidazooxazinyl, each optionally substituted with one or more R^2.

19. The compound according to claim 18, wherein the heteroaryl is tetrahydropyrazolopyrazinyl, optionally substituted with one or more R^2.

20. The compound according to claim 19, wherein the tetrahydropyrazolopyrazinyl is substituted with one R^2 selected from the group consisting of -X-C1-C5 alkyl, arC1-C3alkyl, -Z-C1-C5 alkyl, -Z-cycloalkyl and -X-aryl.

21. The compound according to claim 20, wherein R^2 is -Z-cycloalkyl.

22. The compound according to claim 21, wherein Z is a bond and the cycloalkyl is cyclopropyl.

23. The compound according to claim 21, wherein Z is -C(O)- and the cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or bicyclo[1.1.1]pentyl.

24. The compound according to claim 17, wherein the heteroaryl is pyridyl, optionally substituted with one or two R^2.

25. The compound according to claim 24, wherein the pyridyl is substituted with one R^2.

26. The compound according to claim 25, wherein R^2 is hydroxy, halogen, cyano, $-(NR^4)_2$, hydroxyalkyl, alkoxy, $-SO_2$C1 – C3alkyl, arC1-C3alkyl, heteroalkyl, C2- C4 alkynyl, -X-haloalkyl, -X-C1 – C5 alkyl, -Z-C1 – C5 alkyl, heterocyclyl, -X-L-cycloalkyl, -Z-cycloalkyl, -X-aryl, -Z-aryl, or -X-heteroaryl, wherein the heterocyclyl, the cycloalkyl, the aryl and the heteroaryl are optionally substituted with one or more R^5.

27. The compound according to claim 26, wherein R^2 is -X-C1 – C5 alkyl, and X is a bond and the C1 – C5 alkyl is methyl, ethyl, propyl, or isopropyl.

28. The compound according to claim 26, wherein R^2 is -X-haloalkyl, and X is a bond and the haloalkyl is difluoromethyl or trifluoromethyl.

29. The compound according to claim 26, wherein R^2 is -X-haloalkyl, X is O and the haloalkyl is difluoromethyl or trifluoromethyl.

30. The compound according to claim 26, wherein R^2 is -X-L-cycloalkyl, wherein X is a bond, L is a bond and the cycloalkyl is cyclopropyl.

31. The compound according to claim 26, wherein R^2 is -X-L-cycloalkyl, wherein X is a bond, L is a methylene and the cycloalkyl is cyclopropyl or cyclohexyl.

32. The compound according to claim 26, wherein R^2 is -X-L-cycloalkyl, wherein X is O, L is methylene and the cycloalkyl is cyclopropyl.

33. The compound according to claim 26, wherein R^2 is C2- C4 alkynyl, wherein the C2-C4 alkynyl is ethynyl or prop-2-ynyl.

34. The compound according to claim 26, wherein R^2 is -SO_2C1 – C3 alkyl, wherein the C1 – C3 alkyl is methyl.

35. The compound according to claim 26, wherein R^2 is heterocyclyl, wherein the heterocyclyl is morpholinyl or tetrahydropryanyl.

36. The compound according to claim 26, wherein R^2 is -X-heteroaryl, wherein the heteroaryl is optionally substituted with one or more R^5.

37. The compound according to claim 36, wherein X is a bond, and the heteroaryl is pyrazolyl substituted with one R^5, wherein R^5 is C1 – C3 alkyl.

38. The compound according to claim 36, wherein the X is a bond, and the heteroaryl is pyridyl or pyrimidinyl, each optionally substituted with one or more R^5.

39. The compound according to claim 36, wherein the X is a bond or O, and the heteroaryl is quinolinyl optionally substituted with one or more R^5.

40. The compound according to claim 36, wherein the X is -NR^4-, and the heteroaryl is quinolinyl optionally substituted with one or more R^5.

41. The compound according to claim 36, wherein R^2 is -X-aryl, wherein the aryl is optionally substituted with one or more R^5.

42. The compound according to claim 41, wherein X is a bond and the aryl is phenyl or naphthyl substituted with one, two or three R^5.

43. The compound according to claim 42, wherein each R^5 is selected from the group consisting of cyano, halogen, -X-L-cycloalkyl, -X-haloalkyl, heterocyclyl, X-heteroaryl, C1 – C3 alkyl and alkoxy.

44. The compound according to claim 41, wherein X is O and the aryl is phenyl substituted with one or two R^5.

45. The compound according to claim 44, wherein each R^5 is cyano, halogen, C1 – C3 alkyl or alkoxy.

46. The compound according to claim 41, wherein X is S, the aryl is phenyl substituted with one R^5, wherein R^5 is halogen or C1 – C3 alkyl.

47. The compound according to claim 41, wherein the X is -NR^4-, and the aryl is phenyl optionally substituted with one or more R^5.

48. The compound according to claim 26, wherein R^2 is halogen, wherein the halogen is chlorine or fluorine.

49. The compound according to claim 18, wherein the heteroaryl is pyrazolopyridinyl, optionally substituted with one or more R^2.

50. The compound of claim 49, wherein the pyrazolylpyridinyl is substituted with one R^2, wherein the one R^2 is alkoxy or -X-aryl.

51. The compound of claim 45, wherein the alkoxy is methoxy or isopropyloxy.

52. The compound of claim 45, wherein the -X-aryl, the X is O and the aryl is phenyl.

53. The compound according to claim 1, wherein R^1 is -Y-aryl, wherein Y is -NR^4- and the aryl is phenyl optionally substituted with one or more R^5.

54. The compound according to claim 1, wherein R^1 is -Y-C1- C5 alkyl, wherein Y is -NR^4- and the C1 – C5 alkyl is methyl, ethyl or propyl.

55. The compound according to claim 1, wherein R^1 is -Y-arC1-C3alkyl, wherein Y is -NR^4- and the arC1-C3alkyl is benzyl.

56. The compound according to claim 24, wherein the pyridyl is substituted with two R^2.

57. The compound according to claim 56, wherein each R^2 is -X-C1 – C5 alkyl or one R^2 is halogen or -X-L-cycloalkyl and the second R^2 is -X-C1 – C5 alkyl, wherein each X is a bond.

58. The compound according to claim 18, wherein the heteroaryl is pyrimidinyl, optionally substituted with one or more R^2.

59. The compound according to claim 58, wherein the pyrimidinyl is substituted with one R^2.

60. The compound according to claim 59, wherein R^2 is -X-C1 – C5 alkyl or -X-haloalkyl.

61. The compound according to claim 18, wherein the heteroaryl is pyrazolyl, optionally substituted with one, two or three R^2 groups.

62. The compound according to claim 61, wherein the pyrazolyl is substituted with one R^2.

63. The compound according to claim 62, wherein R^2 is -X-C1 – C5 alkyl, hydroxyalkyl, arC1-C3alkyl, or -X-aryl optionally substituted with one or more R^5.

64. The compound according to claim 63, wherein R^2 is -X-C1 – C5 alkyl, wherein the X is a bond, and the C1 - C5 alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl or isopentyl.

65. The compound according to claim 61, wherein the pyrazolyl is substituted with two independently selected R^2.

66. The compound according to claim 65, wherein the two R^2 groups are (1) independently -t -X-C1 – C5 alkyl, (2) -X-C1 – C5 alkyl and halogen, (3) -X-C1 – C5 alkyl and alkoxy, (4) -X-C1 – C5 alkyl and $-N(R^4)_2$, -(5) X-C1 – C5 alkyl and -X-haloalkyl, (6) -X-C1 – C5 alkyl and arC1-C3alkyl, (7) -X-C1 – C5 alkyl and -X-L-cyclolalkyl, -(8) -X-C1 – C5 alkyl and -heterocyclyl, (9) -X-C1 – C5 alkyl and -X-aryl

optionally substituted with one or more R^5, (10) -X-C1 – C5 alkyl and -X-heteroaryl optionally substituted with one or more R^5, (11) -X-C1 – C5 alkyl and cyanomethyl, (12) -X-C1 – C5 alkyl and cyano, (13) cyano and halogen, wherein the halogen is chlorine or fluorine, (14) cyano and -X-L-cycloalkyl, (15) independently halogen, (16) cyano and alkoxy, wherein each X is a bond, (17) cyano and -X-aryl, (18) cyano and -X-heteroaryl, (19) cyano and heterocyclyl (20) halogen and -X-arC1-C3alkyl or X-arC1-C3alkyl substituted with cyano, and (21) halogen and -X-aryl.

67. The compound according to claim 66, wherein the pyrazolyl is substituted with -X-C1 – C5 alkyl and -X-aryl optionally substituted with one or more R^5, wherein the X is a bond and the aryl is phenyl substituted with two R^5, wherein each R^5 is independently -X-C1 – C5 alkyl, wherein each X is a bond; one R^5 is cyano and one R^5 is -X-C1 – C5 alkyl, wherein each X is a bond; one R^5 is cyano and one R^5 is -X-L-cycloalkyl, wherein X is a bond and L is a bond, methylene or ethylene; one R^5 is cyano and one R^5 is halogen; one R^5 is cyano and one R^5 is alkoxy; or each R^5 is independently halogen.

68. The compound according to claim 66, wherein the pyrazolyl is substituted with -X-C1 – C5 alkyl and -X-aryl optionally substituted with one or more R^5, wherein the X is a bond and the aryl is phenyl substituted with three R^5, wherein each R^5 is -X-C1 – C5 alkyl, wherein each X is a bond; one R^5 is cyano and two R^5 are-X-C1 – C5 alkyl, wherein each X is a bond; one R^5 is cyano, one R^5 is halogen, and one R^5 is -X-C1 – C5 alkyl, wherein X is a bond; one R^5 is cyano and two R^5 are alkoxy, one R^5 is cyano and two R^5 are halogens, one R^2 is cyano and two R^2 are halogen; one R^2 is cyano, one R^2 is halogen and one R^2 is alkoxy, or one R^2 is alkoxy, and two R^2 are independently halogen.

69. The compound according to claim 18, wherein the heteroaryl is imidazolyl, 1*H*-pyrrolopyridyl, tetrahydropyrazolopyrazinyl, 2*H*-4λ^4-imidazopyrimidinyl, 2*H*-4λ^4-imidazopyridazinyl, or oxazolopyridyl, each substituted with one R^2 group, wherein each R^2 is -X-C1 – C5 alkyl, wherein X is a bond.

70. The compound according to claim 18, wherein the heteroaryl is imidazopyridyl substituted with one R^2 group, wherein R^2 is cyano, alkoxy, halogen or -X-C1 – C5 alkyl and X is a bond.

71. The compound according to claim 18, wherein the heteroaryl is imidazopyridyl substituted with two R^2 groups, wherein one R^2 group is halogen and the second R^2 group is -X-C1 – C5 alkyl, wherein X is a bond, or halogen.

72. The compound according to any of claims 2-71, wherein R^{3a} and R^{3b} are each hydrogen.

73. The compound according to any of claims 2-71, wherein R^{3a} and R^{3b} are each deuterium.

74. The compound according to any of claims 2-71, wherein one of R^{3a} and R^{3b} is hydrogen and the other is deuterium.

75. The compound according to any of claims 2-71, wherein R^{3a} and R^{3b} together are oxo.

76. The compound according to any of claims 2-75, wherein R^4 is hydrogen.

77. The compound according to any of claims 2-75, wherein R^4 is methyl.

78. The compound according to any of claims 2-77, wherein R^6 is hydrogen.

79. The compound according to any of claims 2-77, wherein R^6 is halogen.

80. The compound of claim 79, wherein the halogen is chlorine or fluorine.

81. The compound according to any of claims 2-77, wherein R^6 is C1 – C3 alkyl.

82. The compound according to claim 81, wherein the C1 – C3 alkyl is methyl or ethyl.

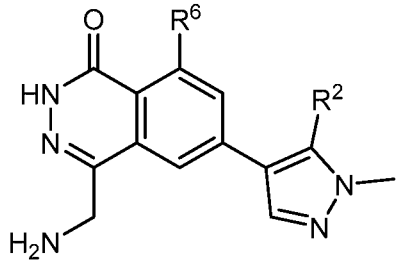
83. The compound according to any of claims 2-77, wherein R^6 is alkoxy.

84. The compound according to claim 83, wherein the alkoxy is methoxy.

85. The compound according to any of claims 2-77, wherein R^6 is haloalkyl.

86. The compound according to claim 85, wherein the haloalkyl is trifiuoromethyl.

87. A compound of Formula (I-D):



Formula (I-D)

or a pharmaceutically acceptable salt thereof:

wherein:

each Y is independently a bond or $-NR^4-$;

each R^2 is independently hydroxy, halogen, cyano, cyanomethyl, $-(NR^4)_2$, hydroxyalkyl, alkoxy, $-SO_2$C1 – C3alkyl, -X-arC1-C3alkyl, heteroalkyl, C2- C4 alkynyl, -X-haloalkyl, -X-C1 – C5 alkyl, -Z-C1 – C5 alkyl, heterocyclyl, -X-L-cycloalkyl, -Z-cycloalkyl, -X-aryl, -Z-aryl, or -X-heteroaryl, wherein the heterocyclyl, the cycloalkyl, the aryl and the heteroaryl are optionally substituted with one or more R^5, or;

each X is independently a bond, O, S, $-NR^4-$ or $-NR^4C(O)-$;

each Z is independently a bond, -SO-, $-SO_2-$, -CH(OH)- or -C(O)-;

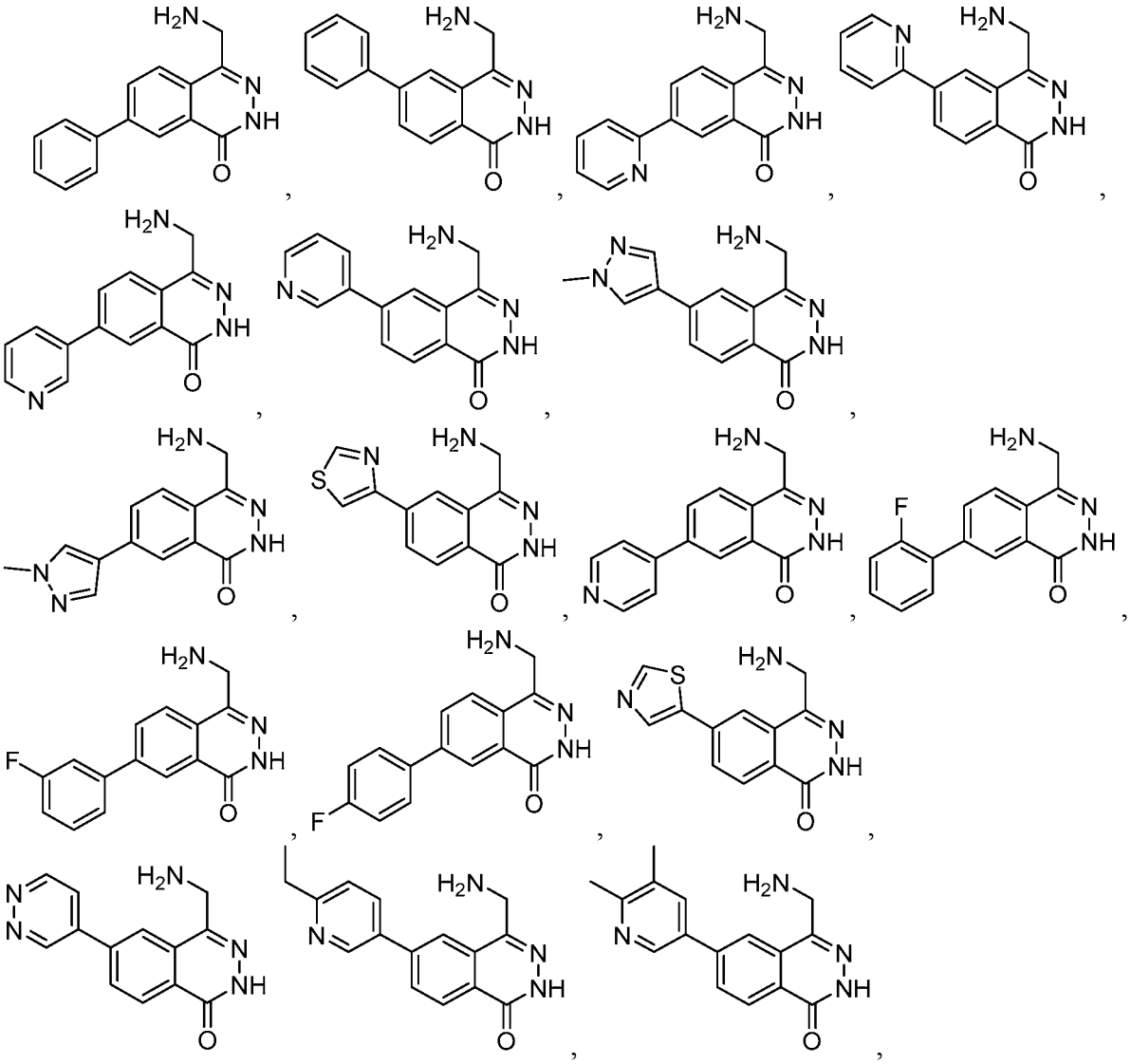
each L is independently a bond or C1 – C3 alkylene;

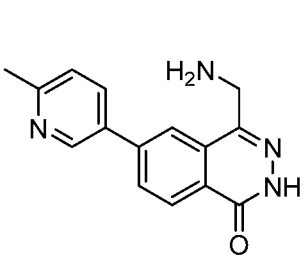
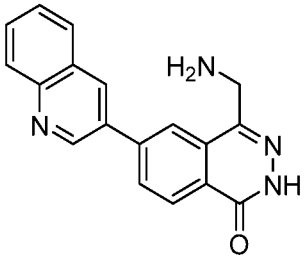
each R^4 is independently hydrogen or C1 – C3 alkyl;

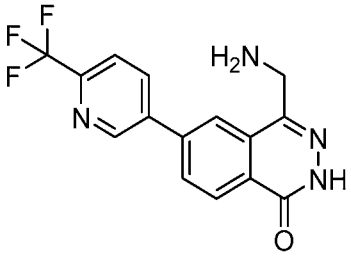
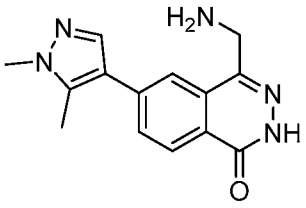
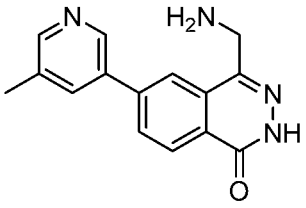
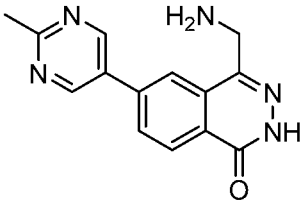
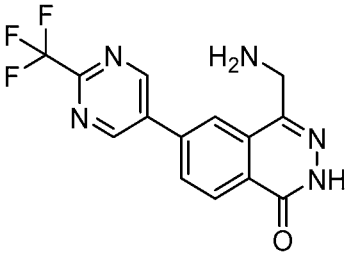
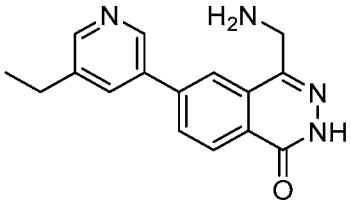
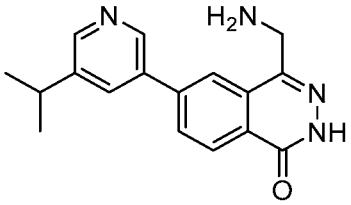
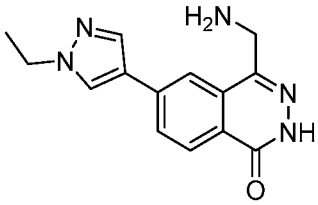
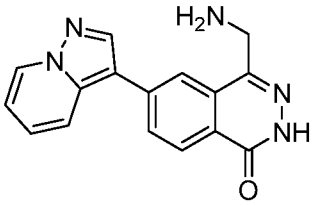
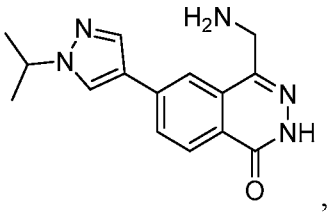
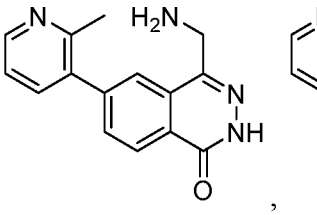
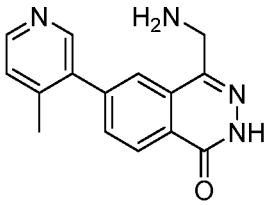
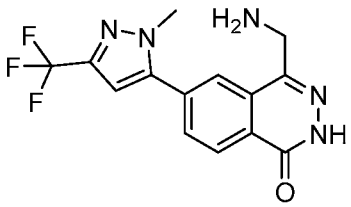
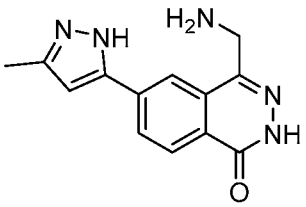
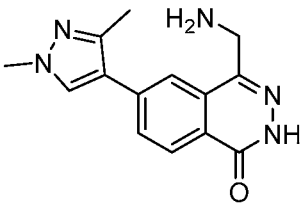
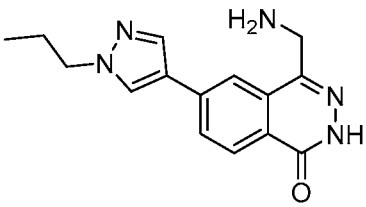
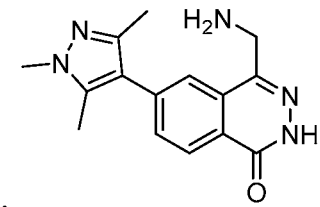
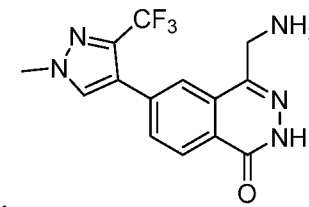
each R^5 is independently cyano, oxo, halogen, C1 – C3 alkyl, hydroxyalkyl, alkoxy, -X-haloalkyl, -Z-cycloalkyl, -X-arC1-C3alkyl, X-arC1-C3alkyl substituted with cyano, -X-L-cycloalkyl, -X-L-heteroaryl optionally substituted with one or more C1-C3alkyl or oxo, or -X-aryl; and

R^6 is hydrogen, halogen, C1-C3 alkyl, haloalkyl or alkoxy.

88. The compound of claim 1, wherein the compound is:



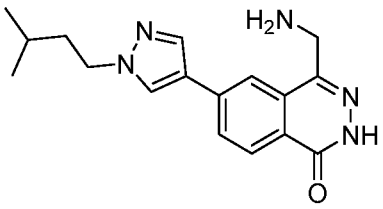
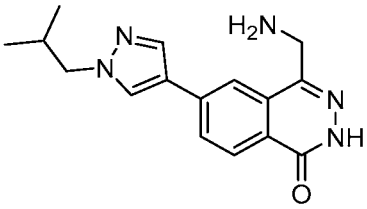
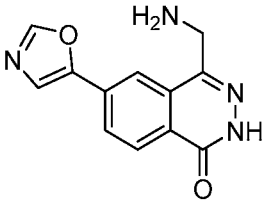
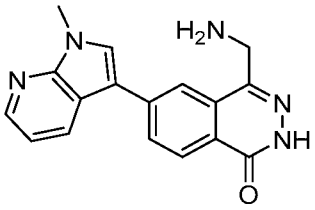
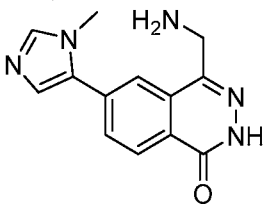
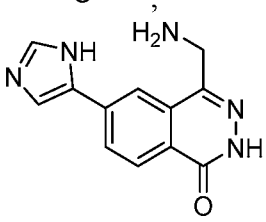
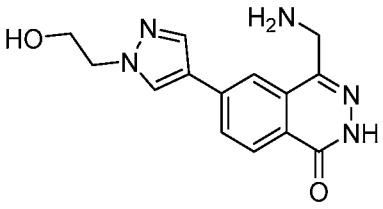
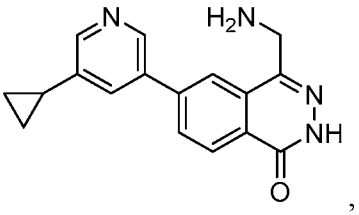
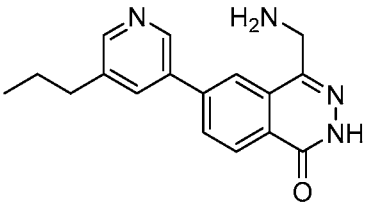
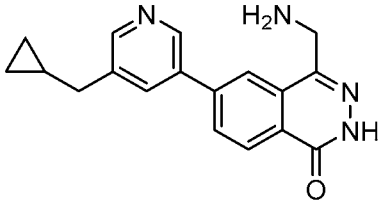
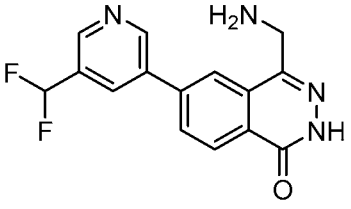
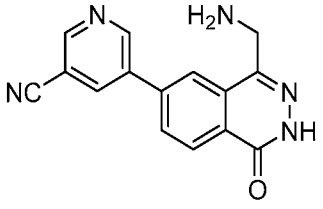
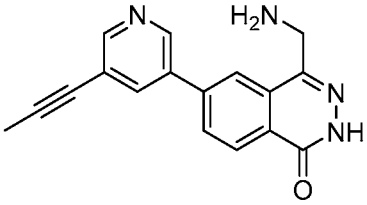
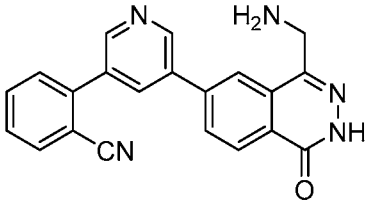
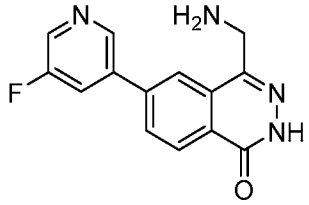
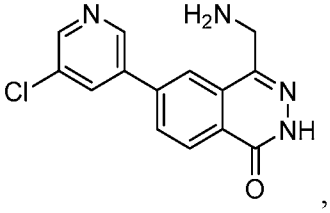
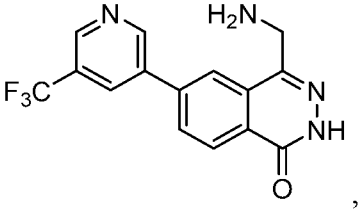
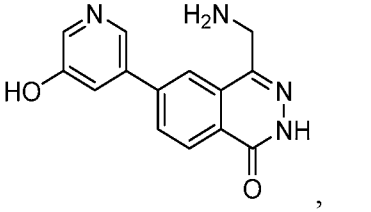
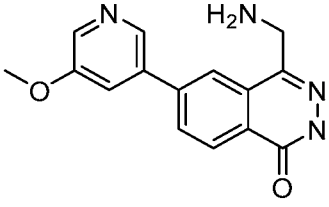
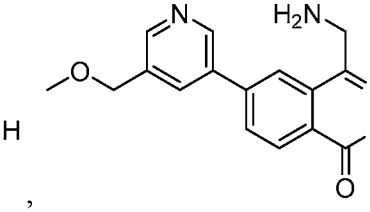
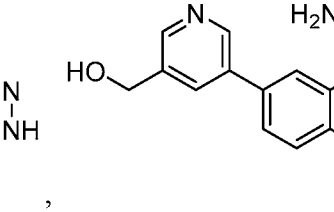
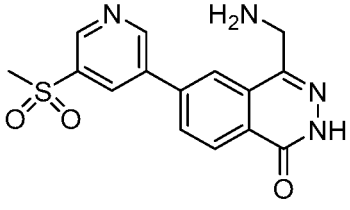
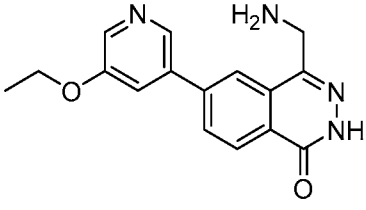
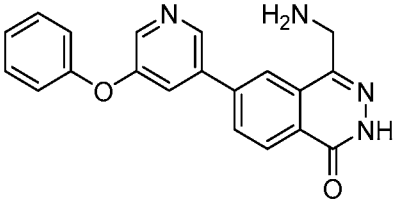

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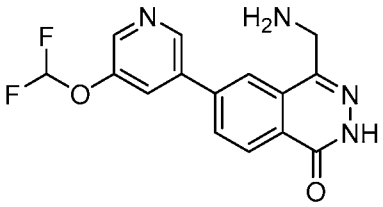
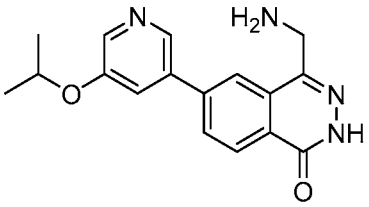
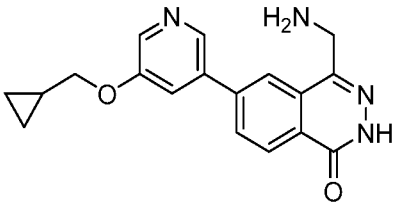
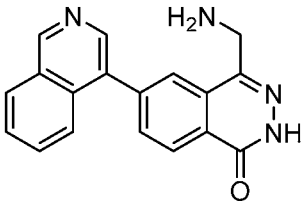
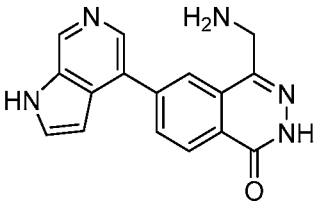
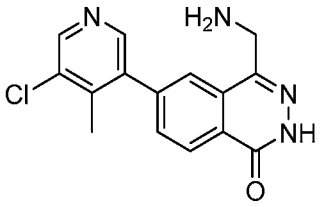
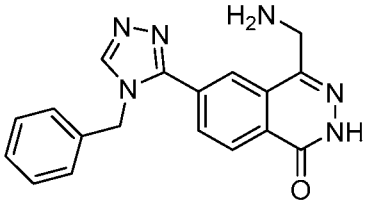
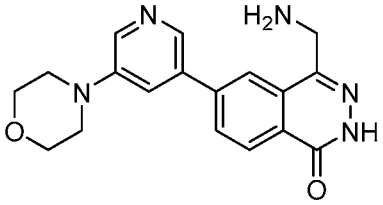
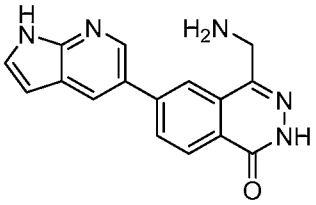
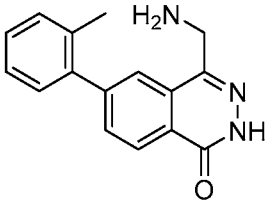
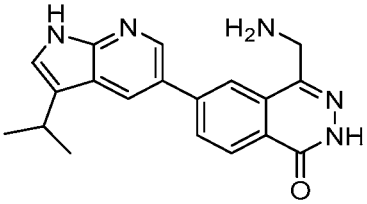
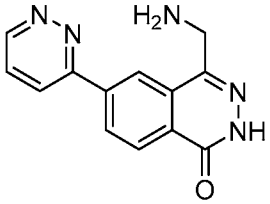
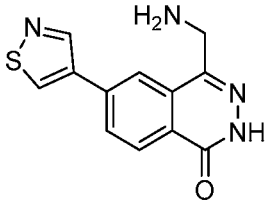
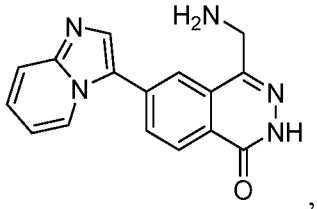
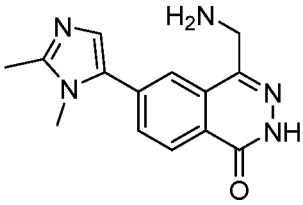
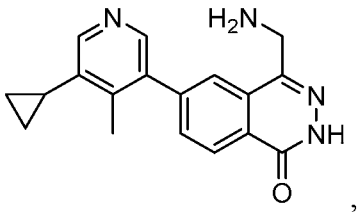
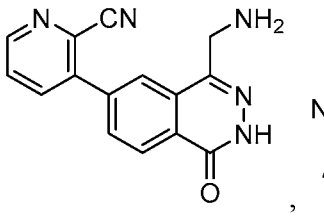
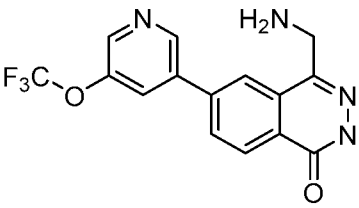
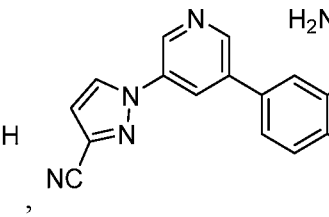
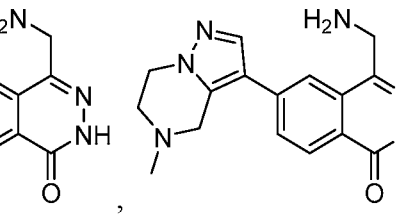
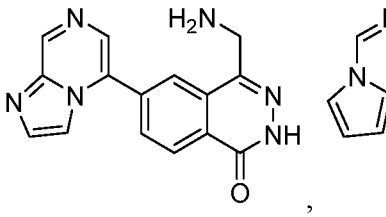
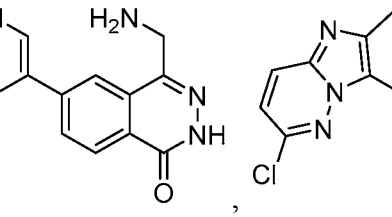
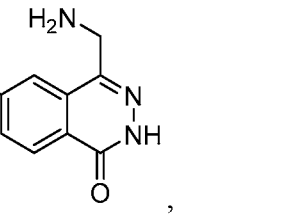
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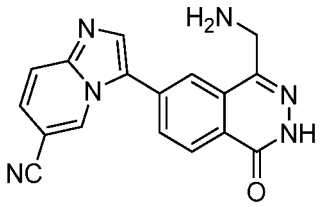
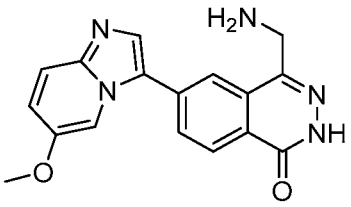
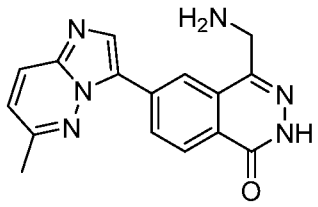
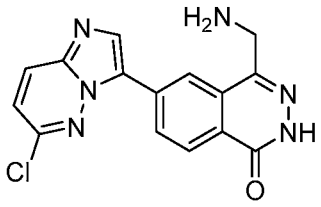
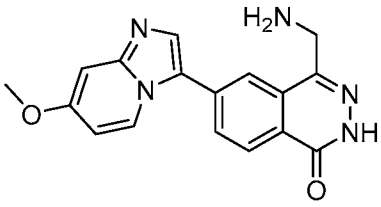
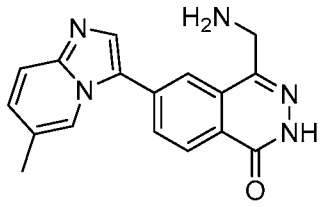
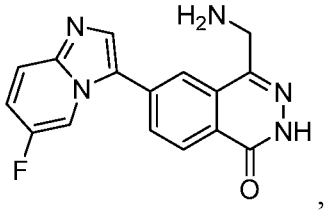
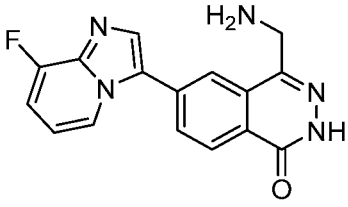
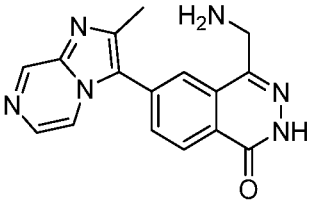
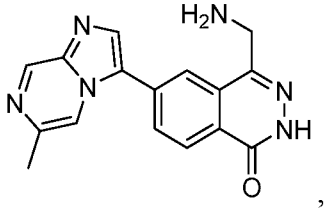
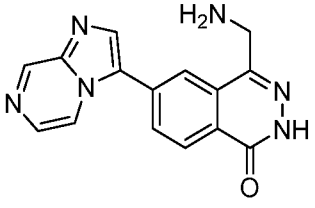
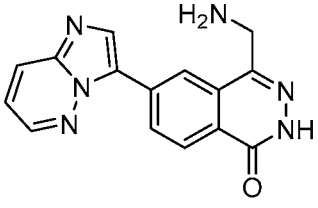
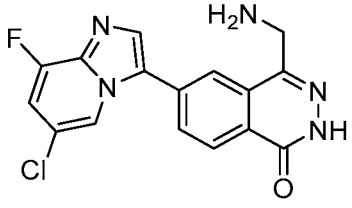
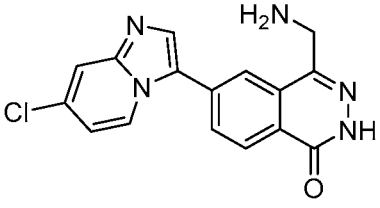
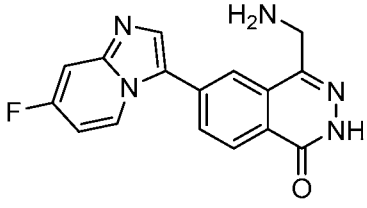
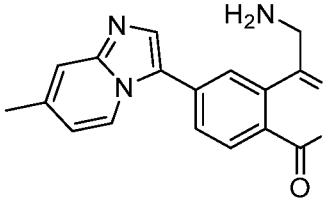
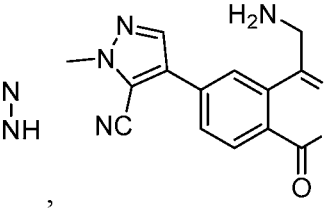
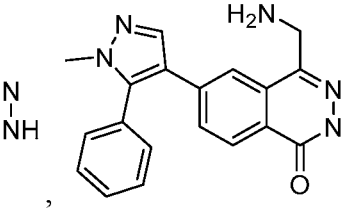
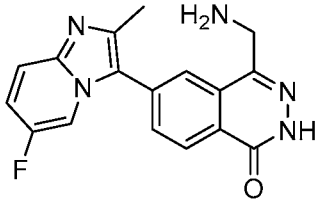
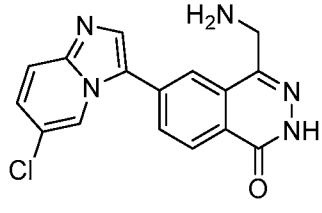
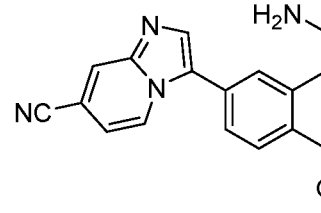
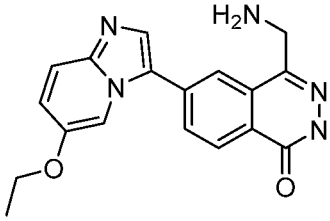
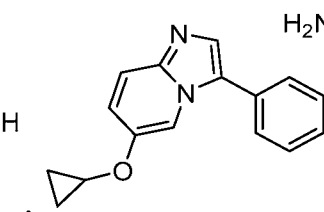
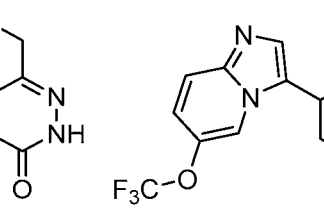
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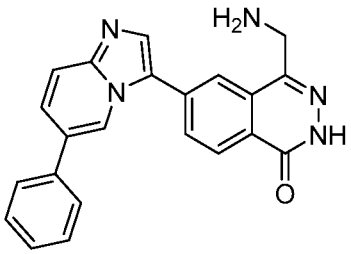
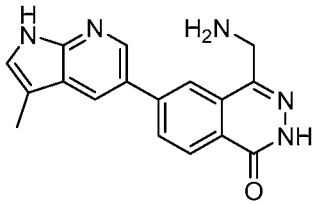
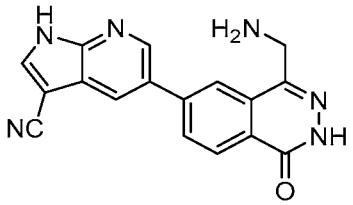
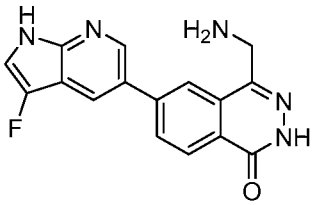
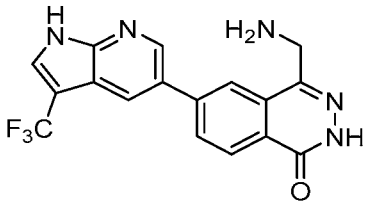
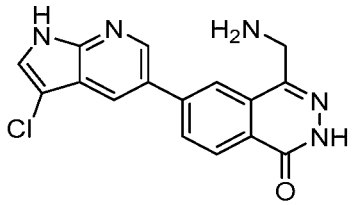
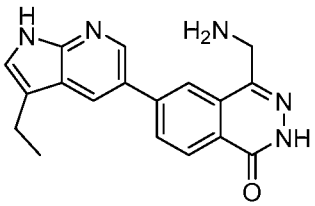
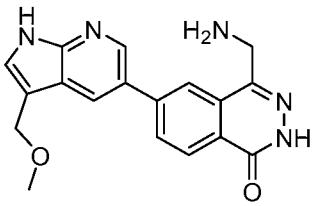
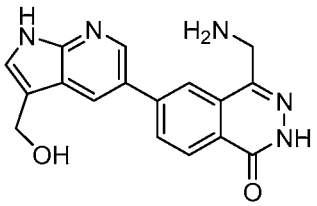
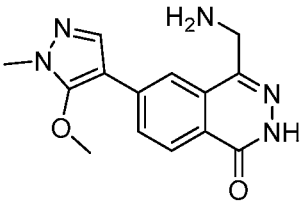
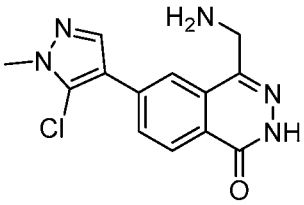
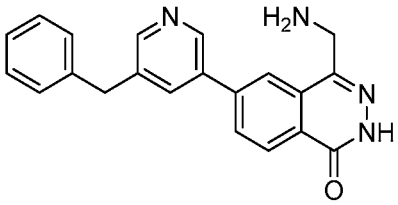
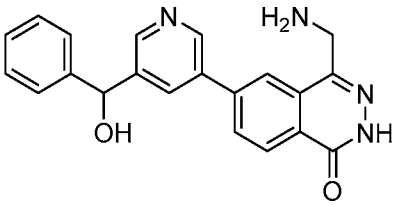
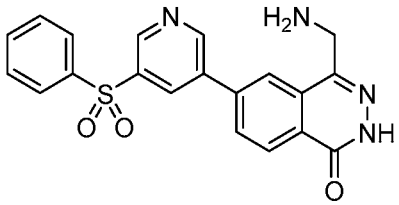
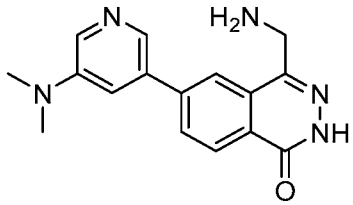
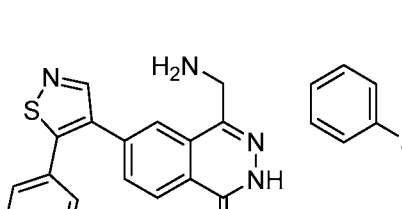
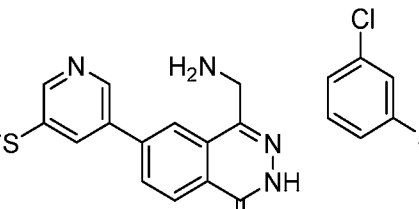
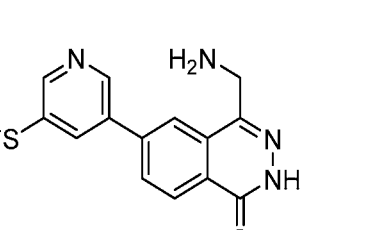
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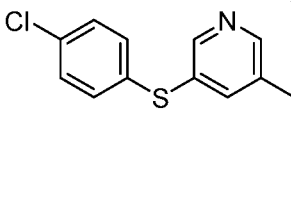
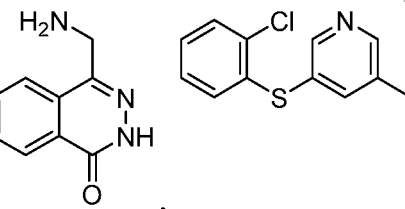
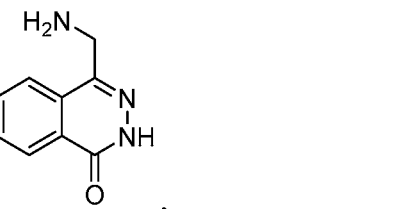
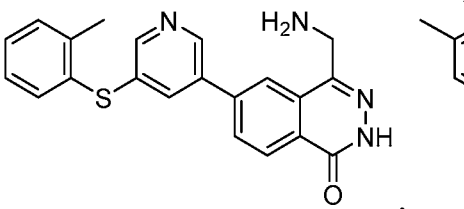
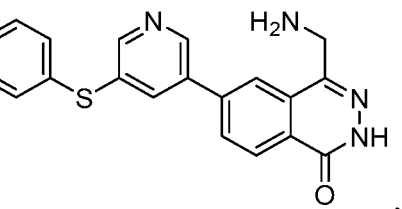
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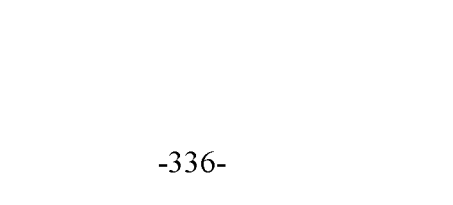
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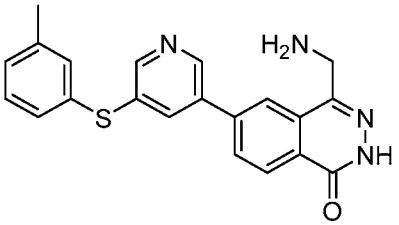
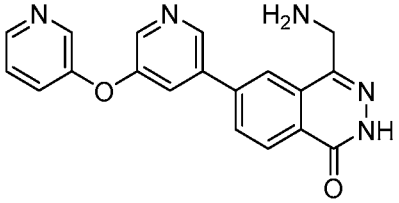
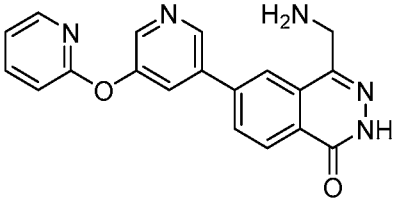
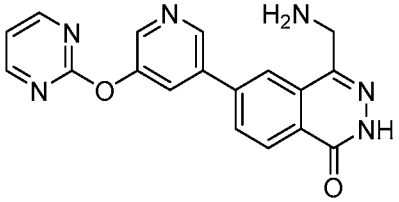
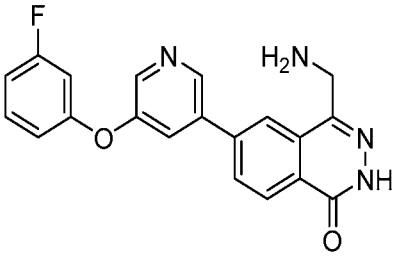
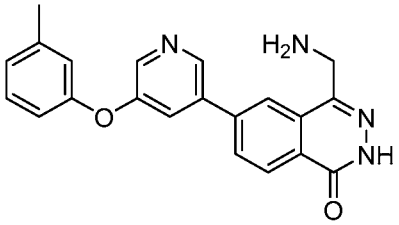
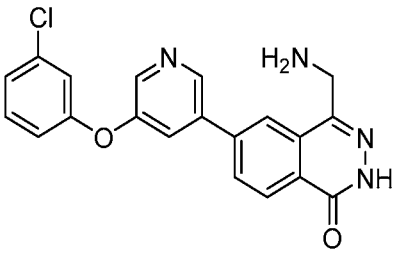
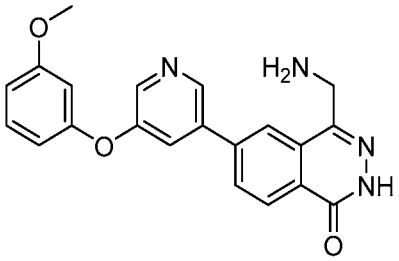
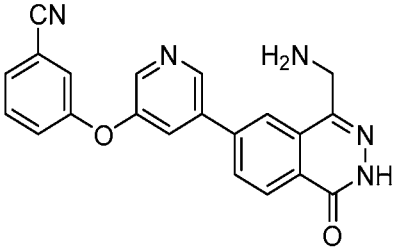
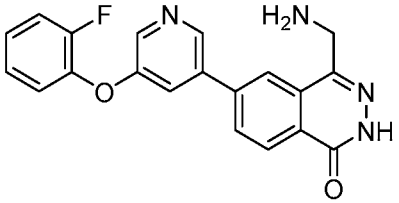
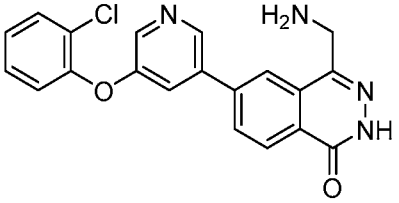
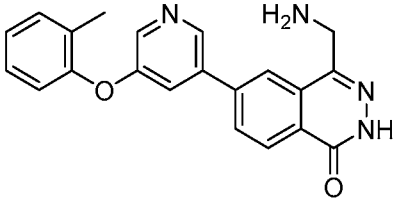
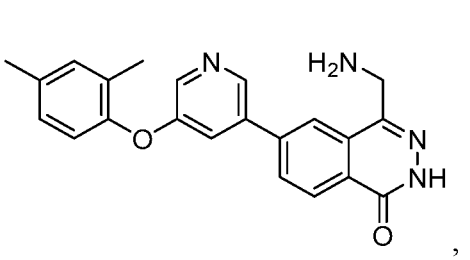
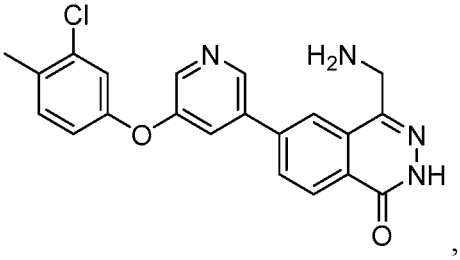

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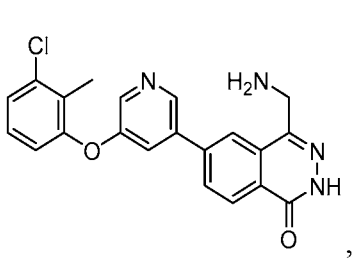
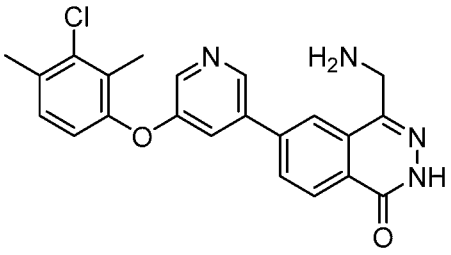
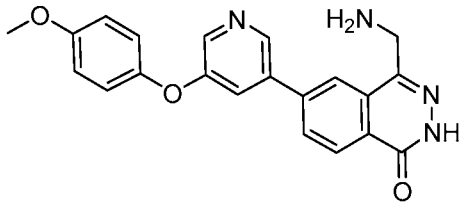
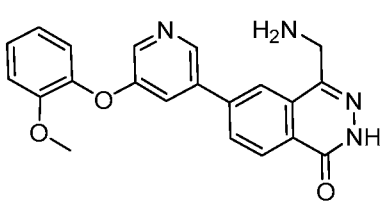
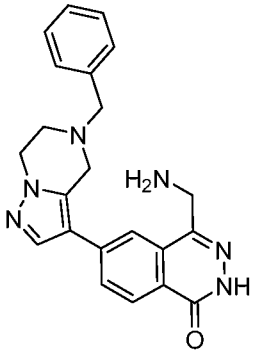
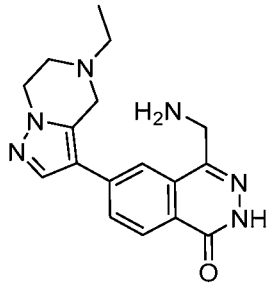
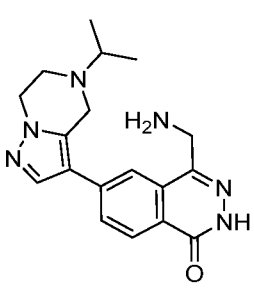
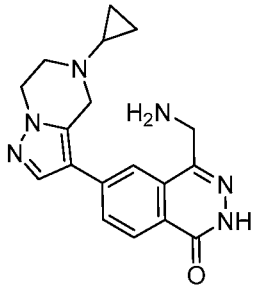
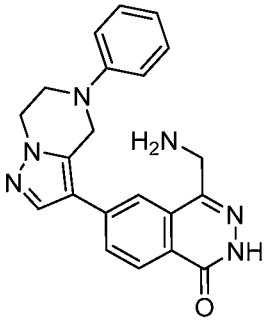
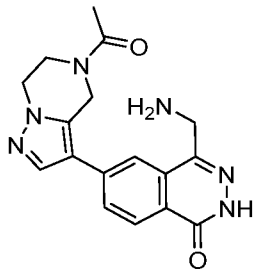
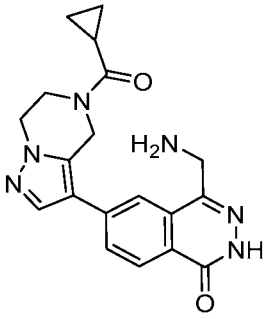
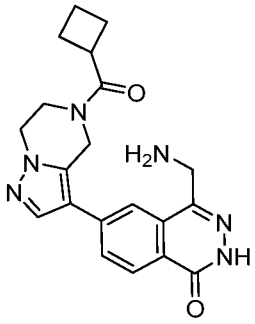
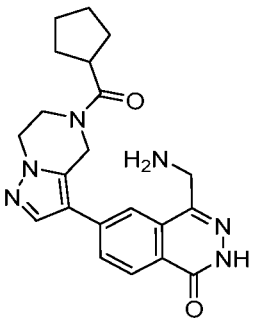
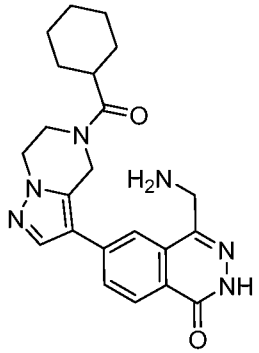
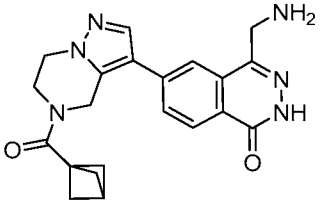
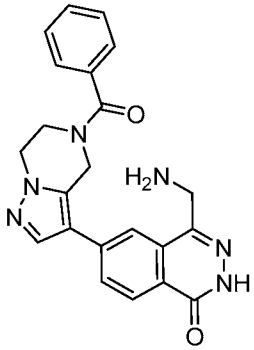
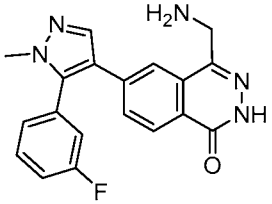
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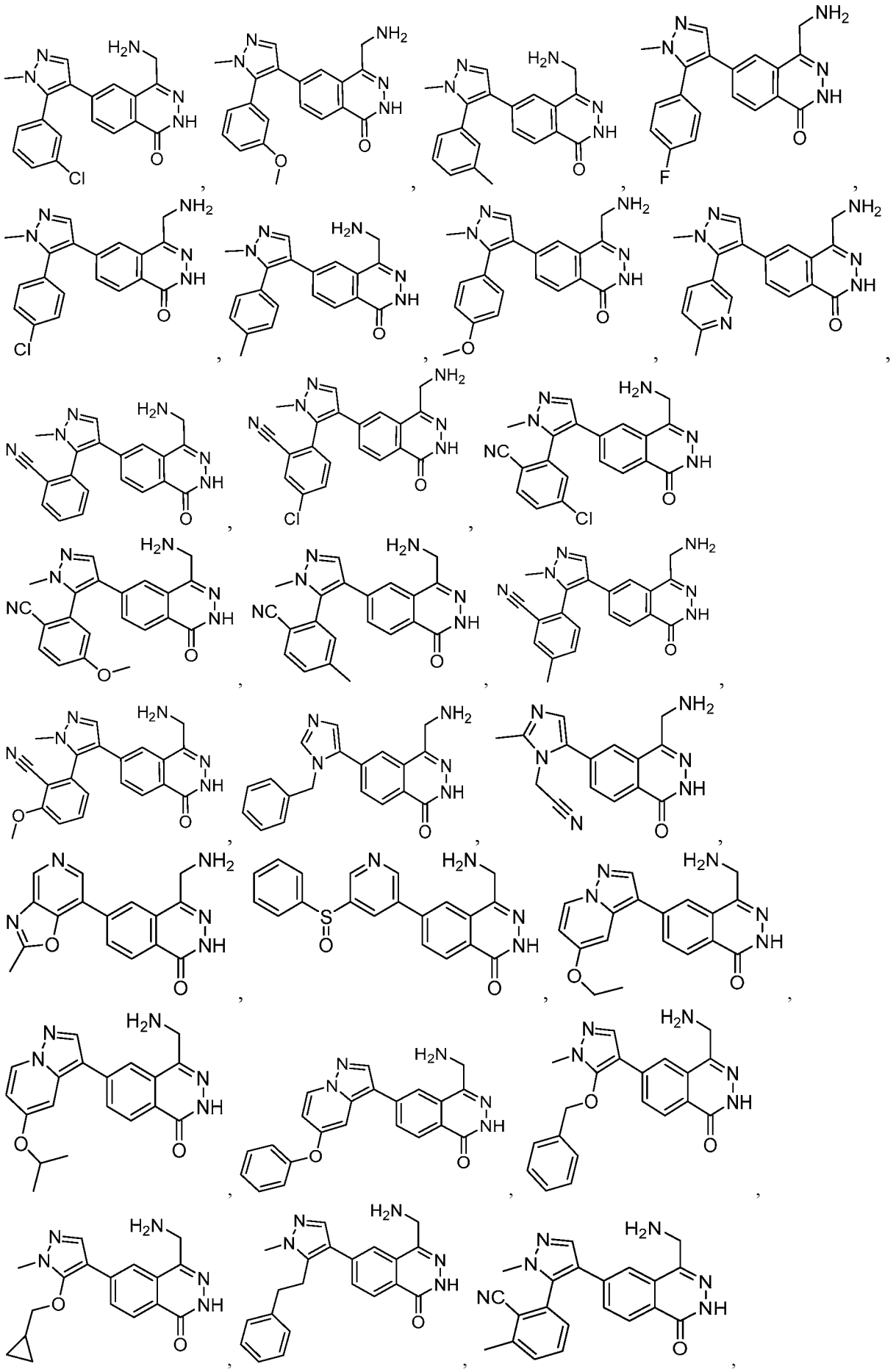
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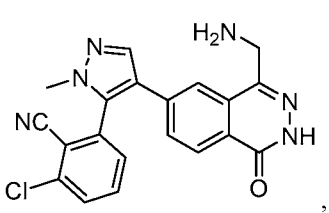
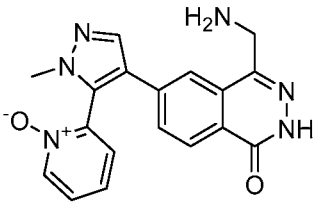
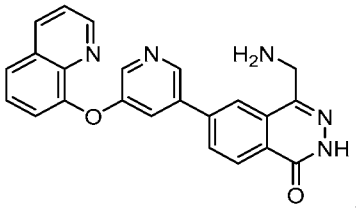
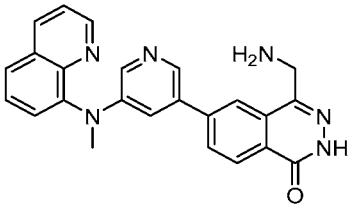
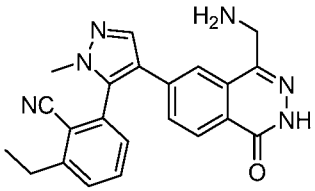
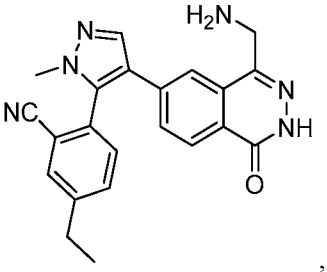
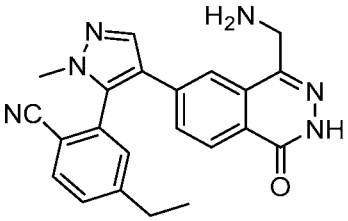
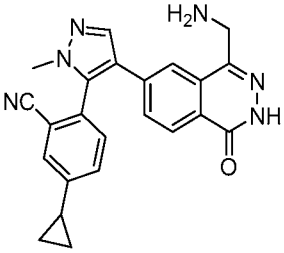
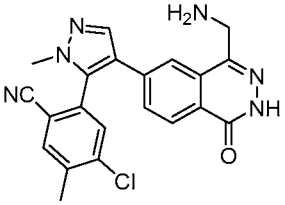
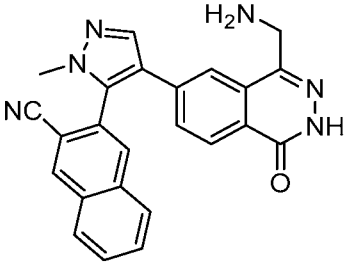
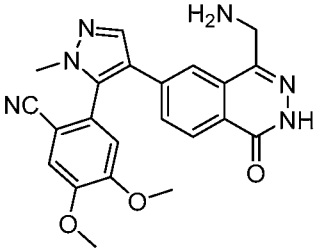
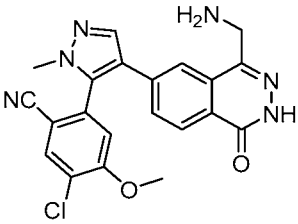
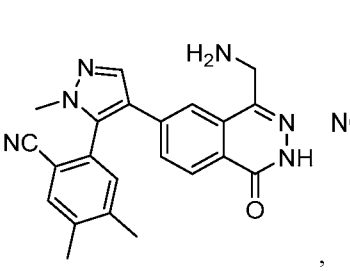
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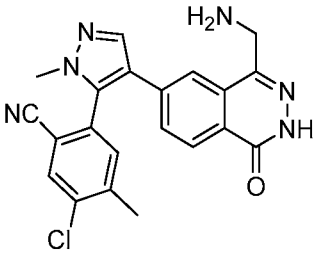
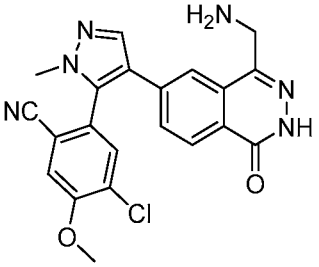
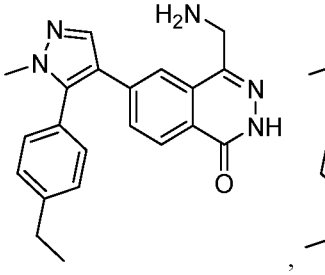
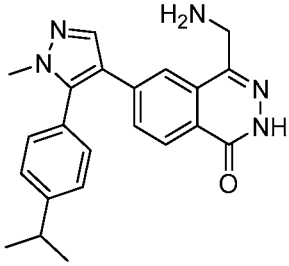
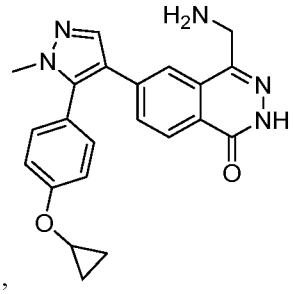

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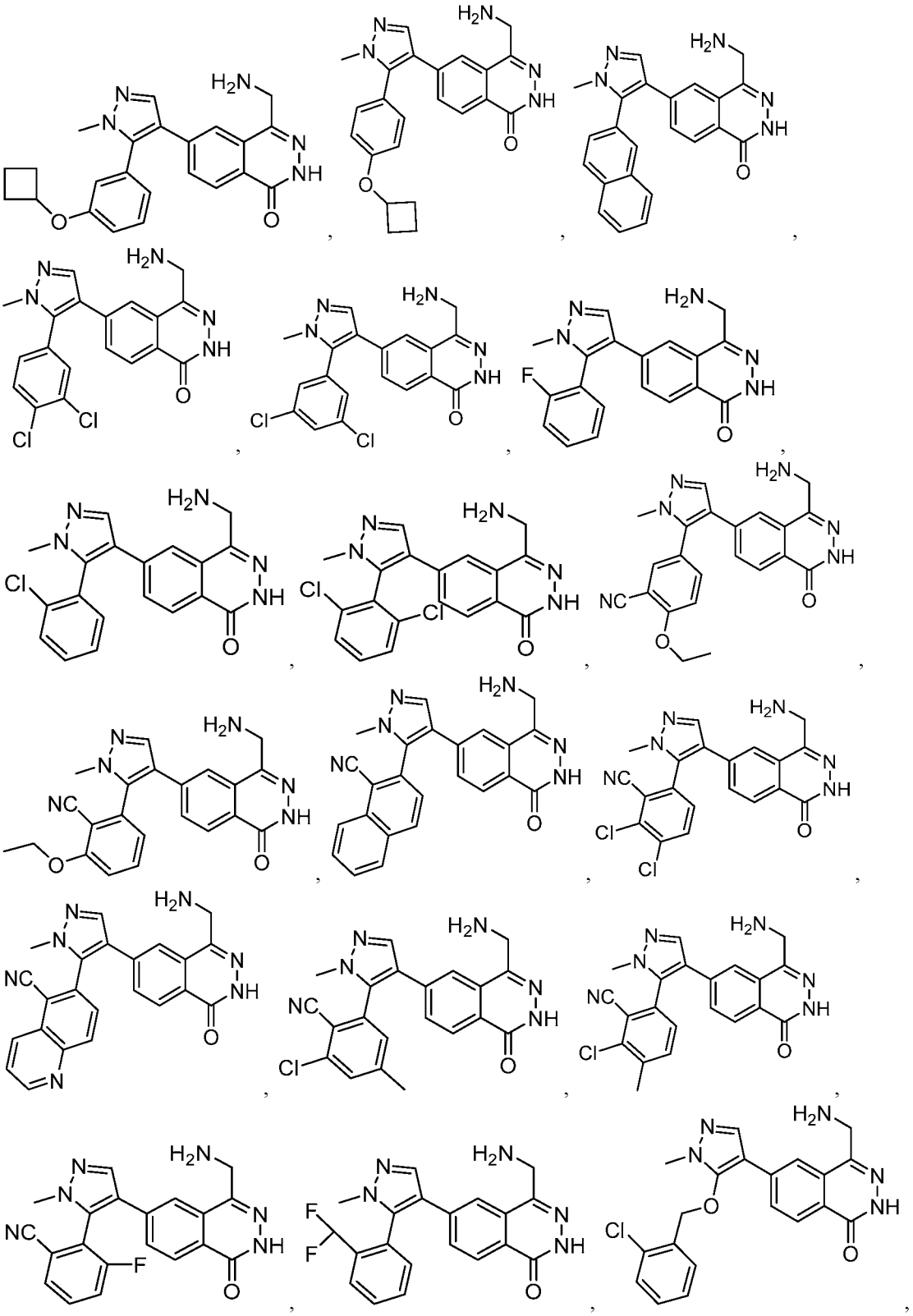
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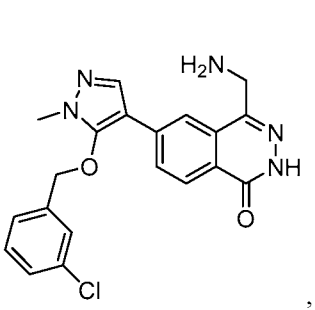
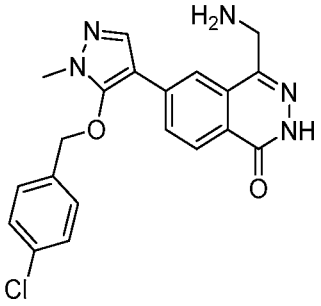
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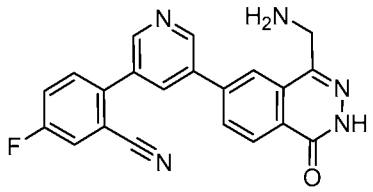
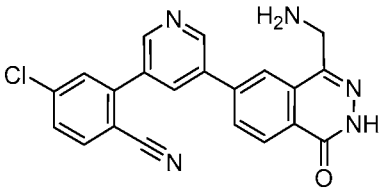
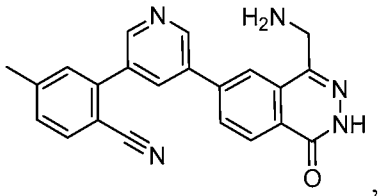
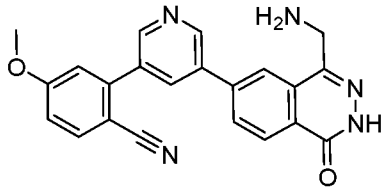
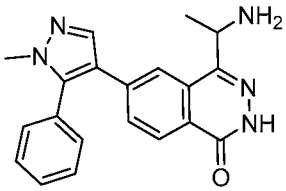
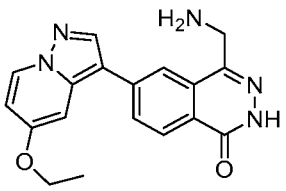
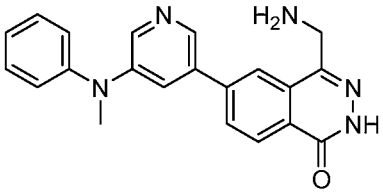
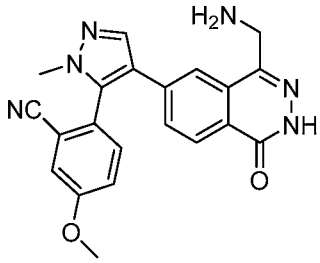
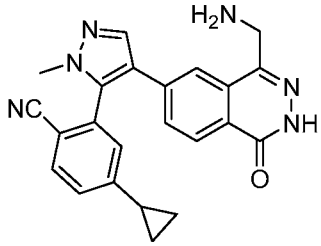
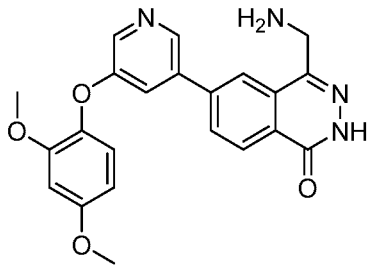
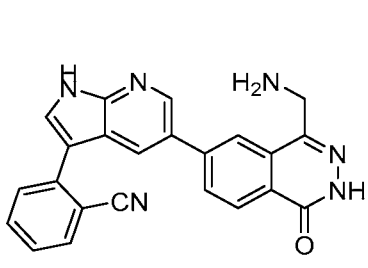
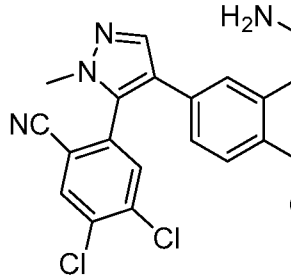
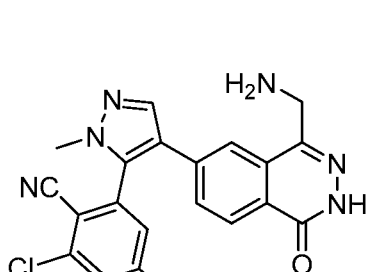
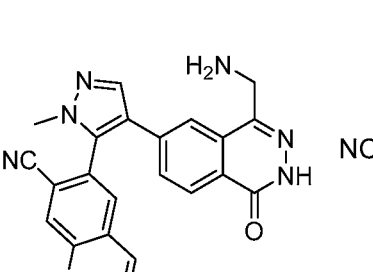
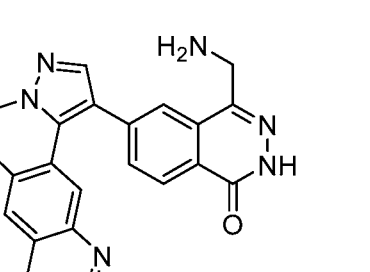
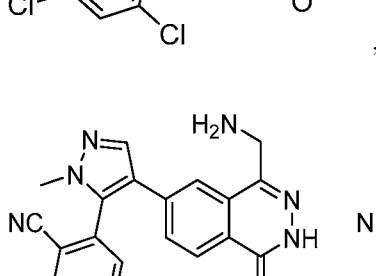
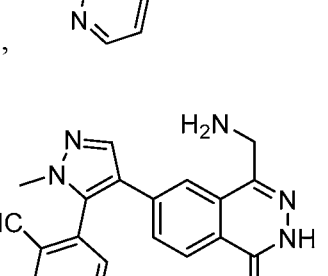
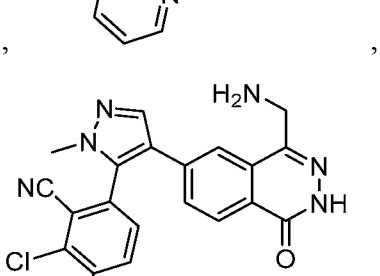
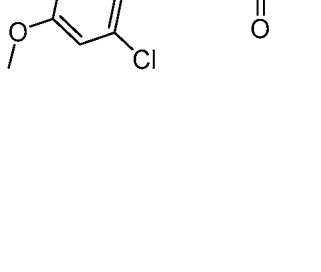
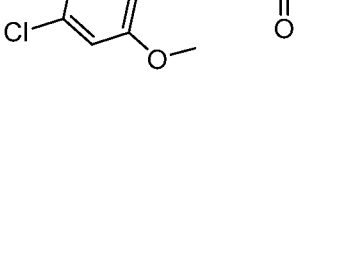
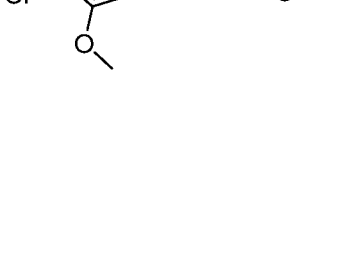
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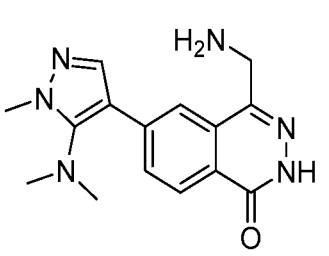
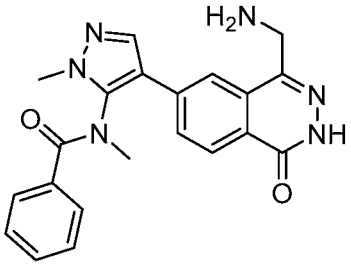
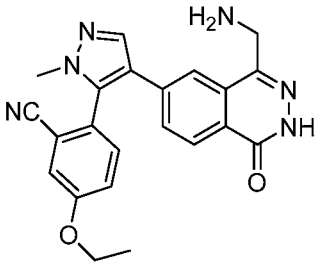
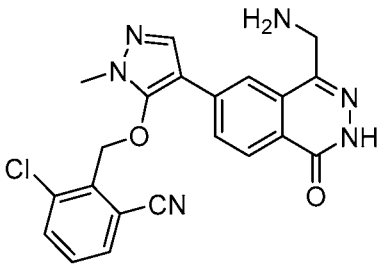
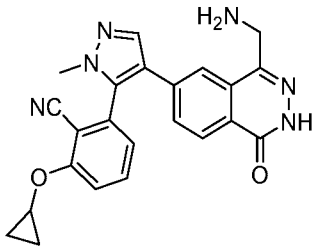
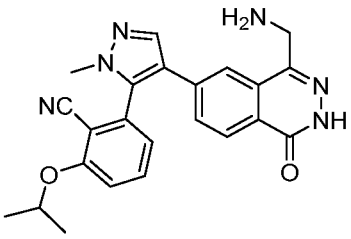
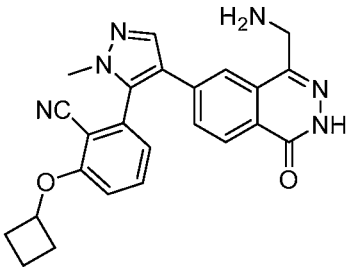
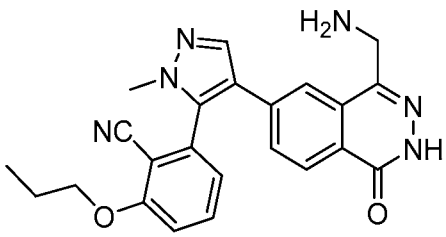
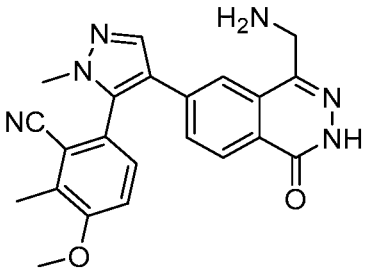
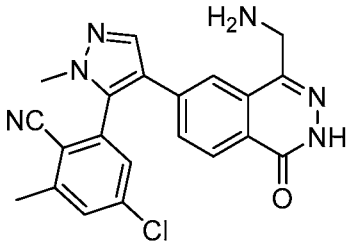
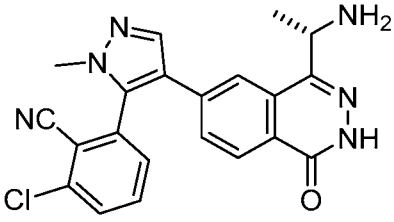
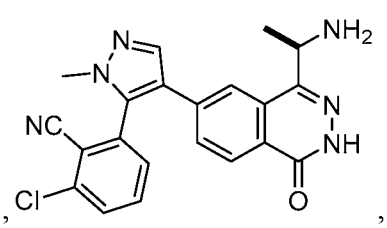
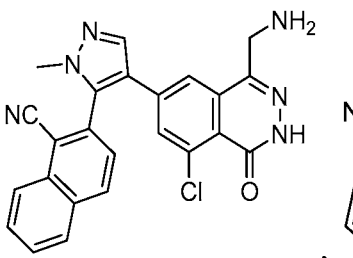
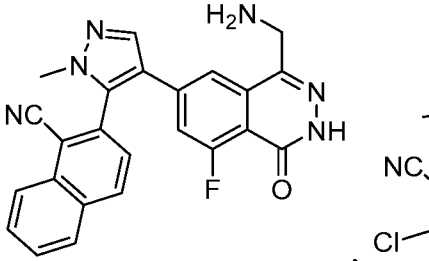
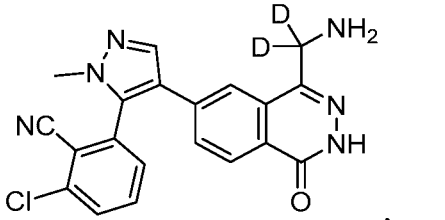
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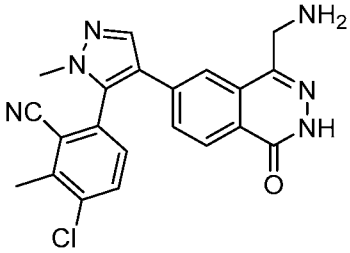
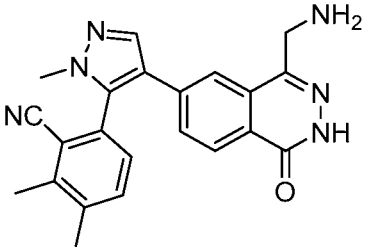
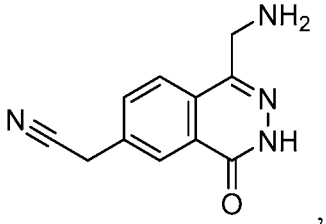



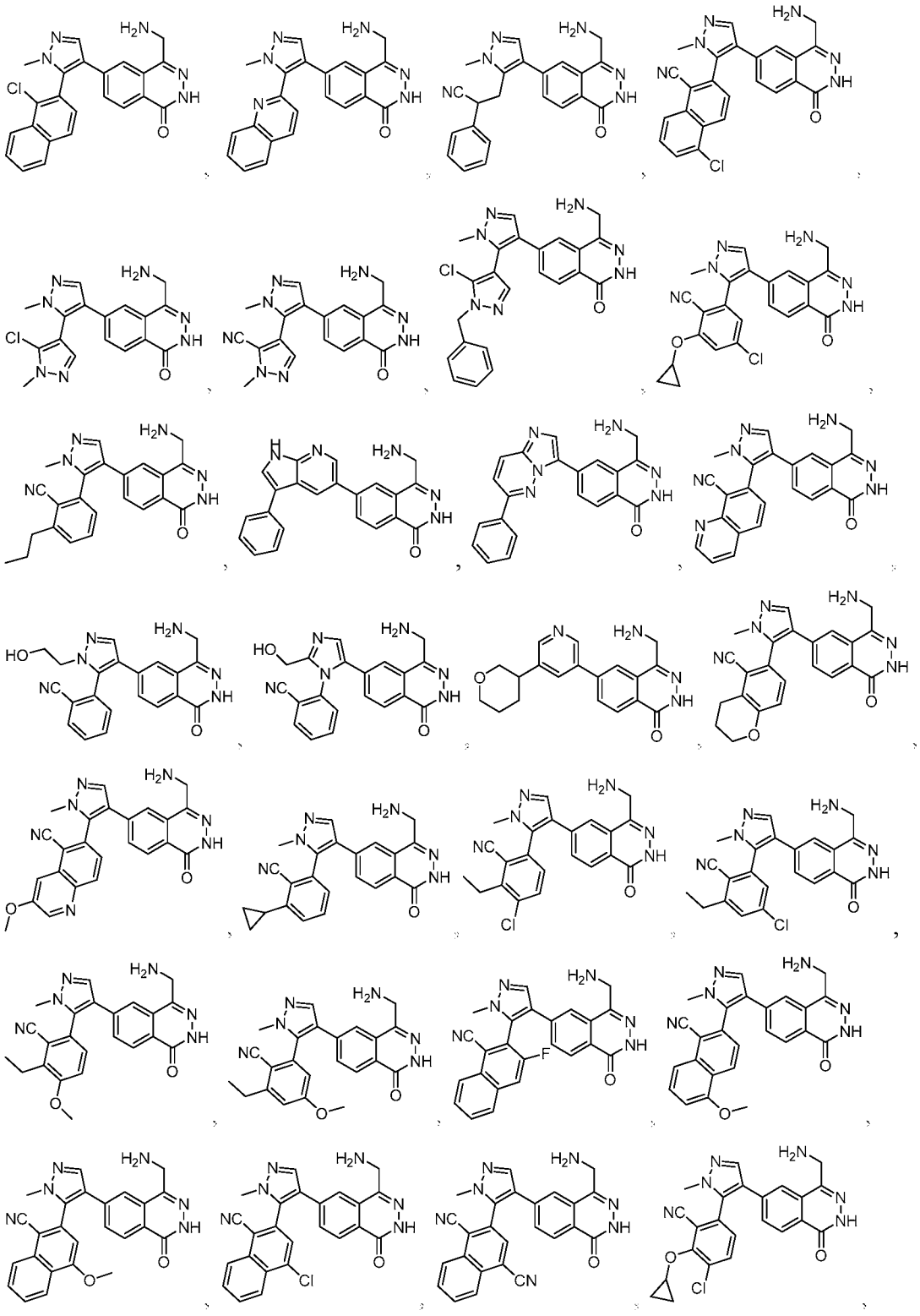






















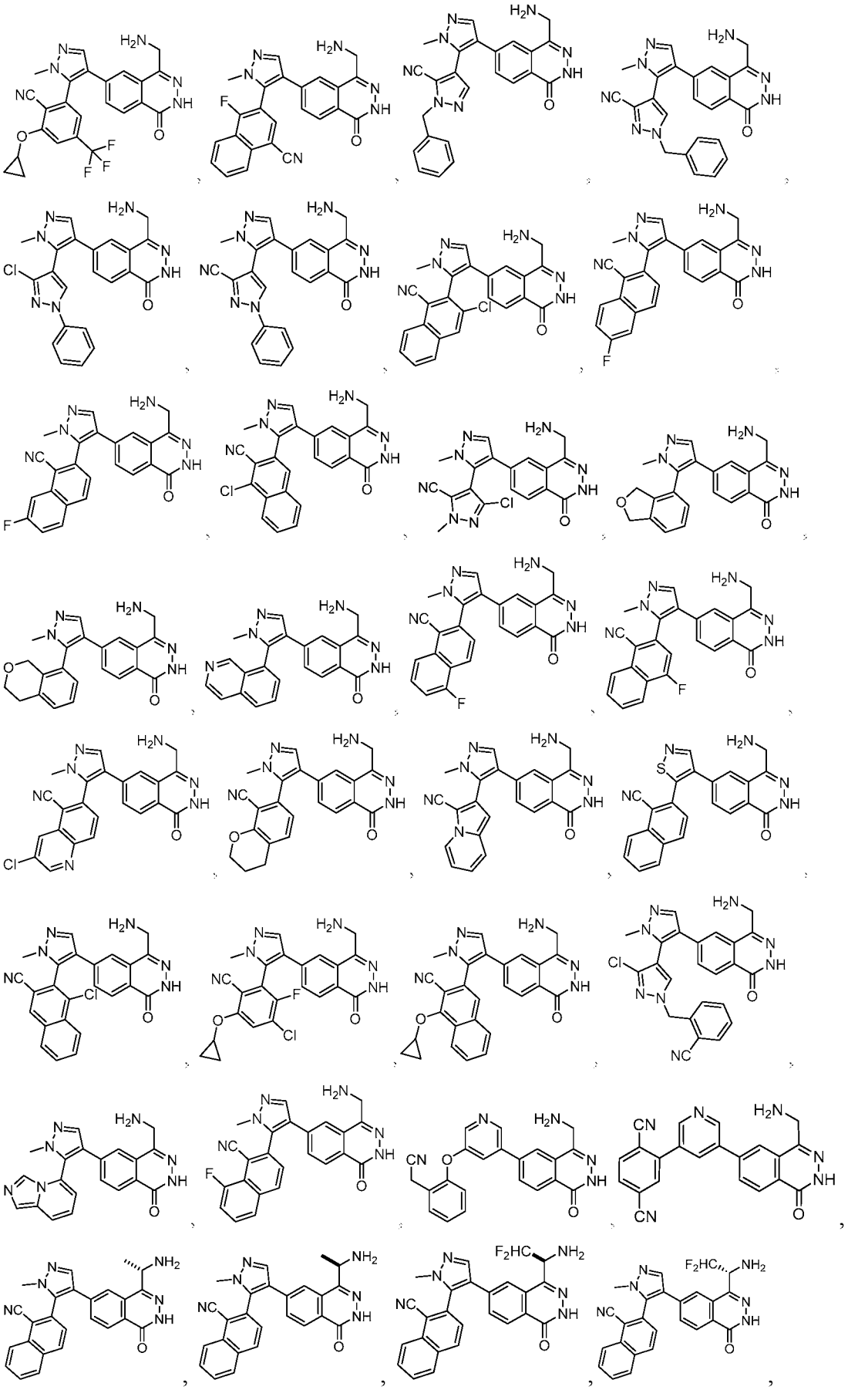

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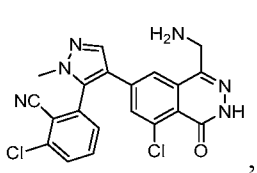
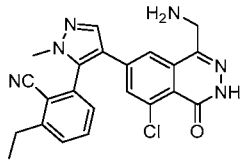
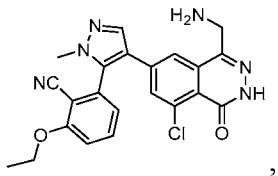
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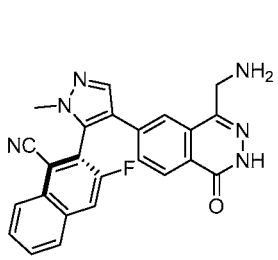
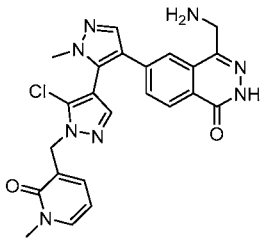
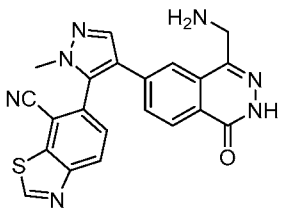
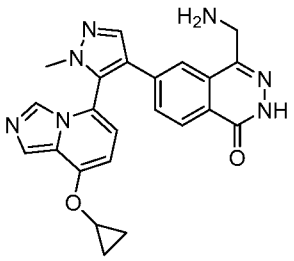
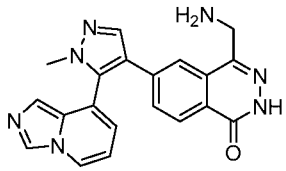
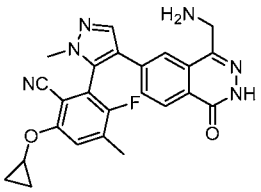
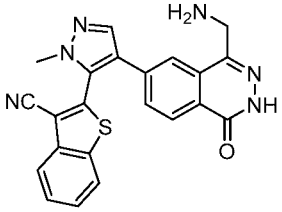
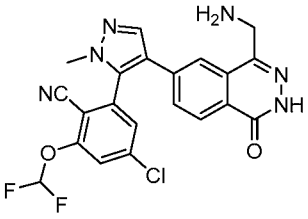
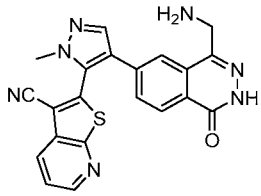
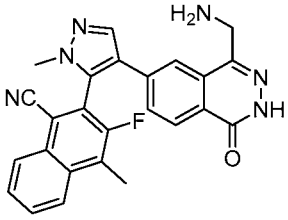
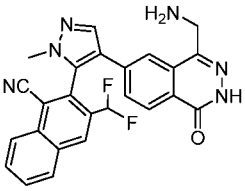
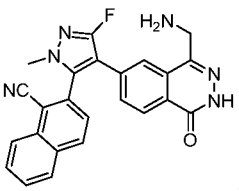
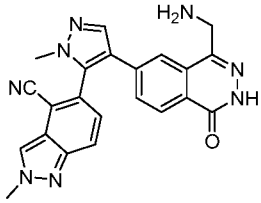
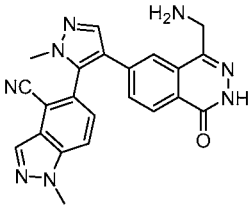
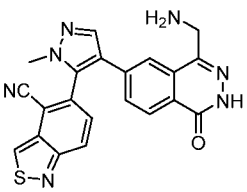
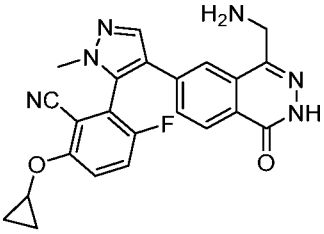
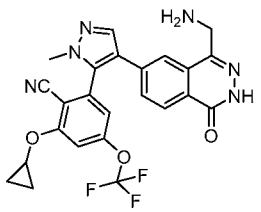
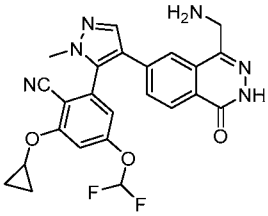
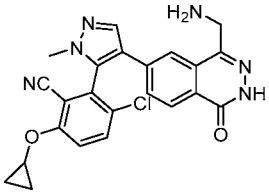
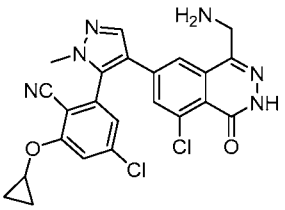
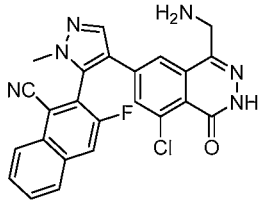
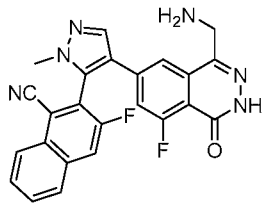
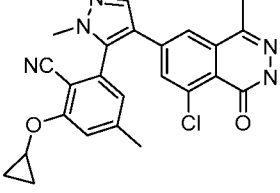
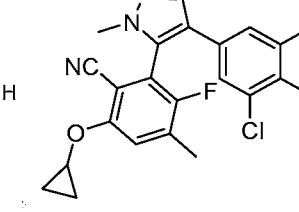
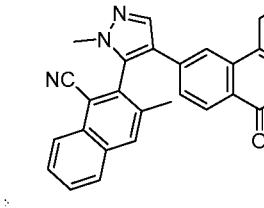
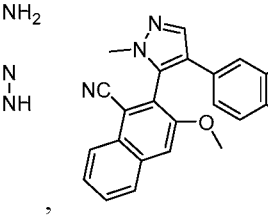
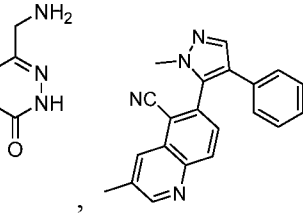
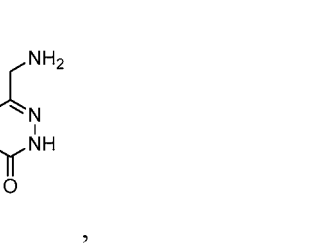
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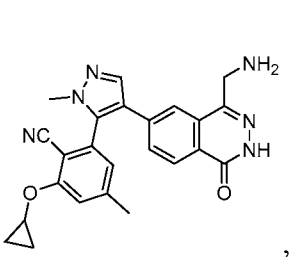
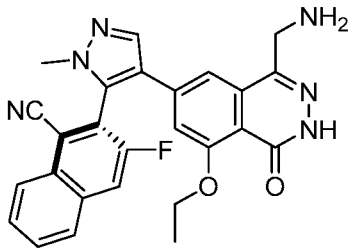
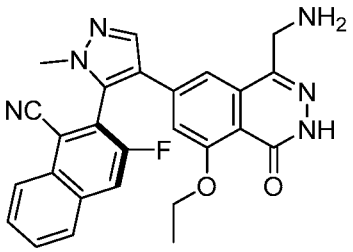
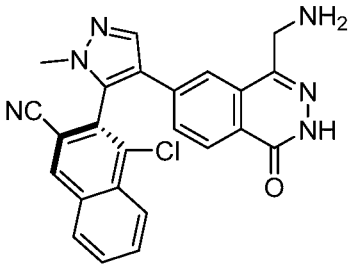
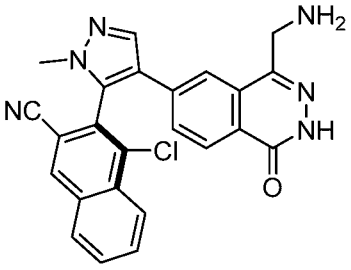
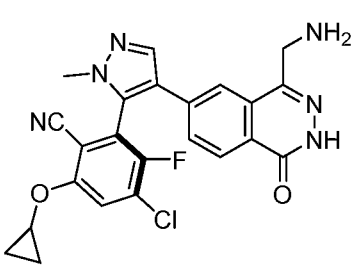
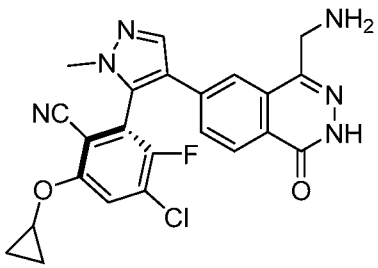

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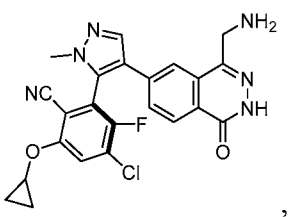
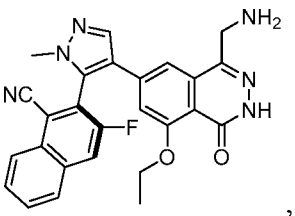
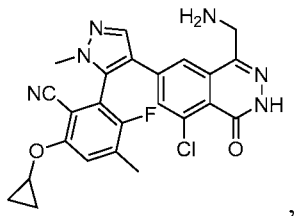
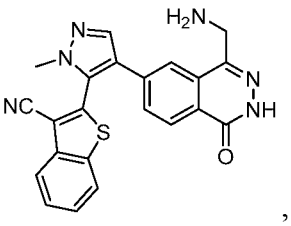
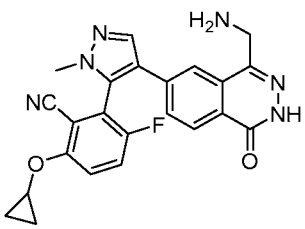
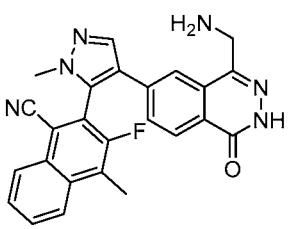
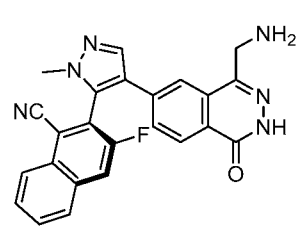
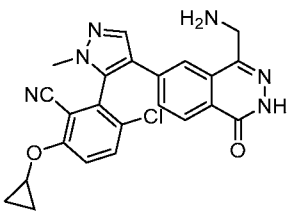
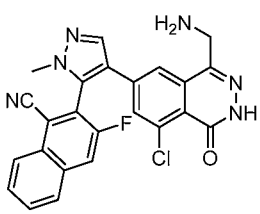
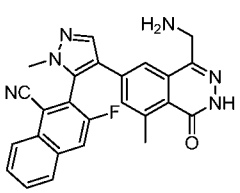
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or a pharmaceutically acceptable salt thereof.

89. The compound of claim 1, wherein the compound is:

or a pharmaceutically acceptable salt thereof.

90. A pharmaceutical composition, comprising a therapeutically effective amount of a compound of Formula (I) according to any one of claims 1-89 or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

91. Use of a compound of Formula (I) according to any one of claims 1-89 or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition according to claim 90, in the manufacture of a medicament for inhibiting PRMT5 activity in a cell.

92. Use of a therapeutically effective amount of a compound of Formula (I) according to any one of claims 1-89 or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutically acceptable salt or solvate thereof, alone or combined with a pharmaceutically acceptable carrier, excipient or diluents, in the manufacture of a medicament for treating cancer.

93. The use of claim 92, wherein the therapeutically effective amount of the compound is between about 0.01 to 300 mg/kg per day.

94. The use of claim 92, wherein the therapeutically effective amount of the compound is between about 0.1 to 100 g/kg per day.

95. The use according to any one of claims 92-94, wherein the cancer is selected from the group consisting of Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large

bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Biliary tract: gall bladder carcinoma, ampullary carcinoma, cholangiocarcinoma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial wcarcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma); Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma.

96. The use according to any one of claims 92-95, wherein the cancer is a MTAP-associated cancer.

97. The use of claim 95, wherein the cancer is hepatocellular carcinoma, breast cancer, skin cancer, bladder cancer, liver cancer, pancreatic cancer, or head and neck cancer.

98. A compound of Formula (I) according to any one of claims 1-89 or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutically acceptable salt or solvate thereof, alone or combined with a pharmaceutically acceptable carrier, excipient or diluents, or a pharmaceutical composition according to claim 90, for use in therapy.