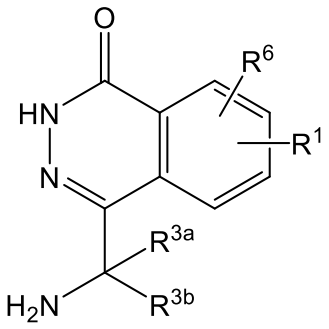
[0005] Cells lacking MTAP activity have elevated levels of the MTAP substrate, methylthioadenosine (MTA), which is a potent inhibitor of PRMT5. Inhibition of PRMT5 activity results in reduced methylation activity and increased sensitivity of cellular proliferation to PRMT5 depletion or loss of activity. 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 (C3-C12cycloalkyl)-Y-, (3-12 membered heterocyclyl)-Y-, (C6-C14aryl)-Y-, (C6-C14arylC1-C3alkyl)-Y- or (5-14 membered heteroaryl)-Y-, 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, -$(NR^4)_2$, hydroxy(C1-C12)alkyl, C1-C6alkoxy, -SO_2(C1 – C3alkyl), -(C6-C14arylC1-C3alkyl)-X-, hetero(C3-C12)alkyl, C2- C4 alkynyl, -halo(C1-C12alkyl)-X-, (C1 – C5 alkyl)-X-, (C1 – C5 alkyl)-Z-, 3-12 membered heterocyclyl, (C3-C12cycloalkyl)-L-X-, (C3-C12cycloalkyl)-Z-, (C6-C14aryl)-X-, (C6-C14aryl)-Z-, or (5-14 membered heteroaryl)-X-, wherein the heterocyclyl, the cycloalkyl, the aryl and the heteroaryl are optionally substituted with one or more R^5;
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, hydroxy(C1-C12)alkyl, C1-C6alkoxy, halo(C1-C12alkyl)-X-, (C3-C12cycloalkyl)-Z-, (C6-C14arylC1-C3alkyl)-X-,(C6-C14arylC1-C3alkyl)-X-, wherein the aryl is substituted with cyano, (C3-C12cycloalkyl)-L-X, (5-14 membered heteroaryl)-L-X-, and the heteroaryl is optionally substituted with one or more C1-C3alkyl or oxo, or (C6-C14aryl)-X-; and
R^6 is hydrogen, halogen, C1-C3 alkyl, halo(C1-C12alkyl) or C1-C6alkoxy.

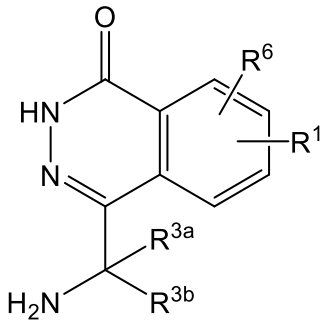
[0007b] In another aspect of the present disclosure, there is provided a pharmaceutical composition, comprising a compound of Formula (I) disclosed herein or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0007c] 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 thereofin the manufacture of a medicament for the treatment of cancer.

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

WE CLAIM:

1. A compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof:

wherein:

R^1 is (C3-C12cycloalkyl)-Y-, (3-12 membered heterocyclyl)-Y-, (C6-C14aryl)-Y-, (C6-C14arylC1-C3alkyl)-Y- or (5-14 membered heteroaryl)-Y-, 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, -$(NR^4)_2$, hydroxy(C1-C12)alkyl, C1-C6alkoxy, -SO_2(C1 – C3alkyl), (C6-C14arylC1-C3alkyl)-X-, hetero(C3-C12alkyl), C2- C4 alkynyl, halo(C1-C12alkyl)-X-, (C1 – C5 alkyl)-X-, (C1 – C5 alkyl)-Z-, 3-12 membered heterocyclyl, (C3-C12cycloalkyl)-L-X-, (C3-C12cycloalkyl)-Z-, (C6-C14aryl)-X-, (C6-C14aryl)-Z-, or (5-14 membered heteroaryl)-X-, wherein the heterocyclyl, the cycloalkyl, the aryl and the heteroaryl are optionally substituted with one or more R^5;

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, hydroxy(C1-C12)alkyl, C1-C6alkoxy, halo(C1-C12alkyl)-X-, (C3-C12cycloalkyl)-Z-, (C6-C14arylC1-C3alkyl)-X-, (C6-C14arylC1-C3alkyl)-X-, wherein the aryl is substituted with cyano, (C3-C12cycloalkyl)-L-X-, (5-14 membered heteroaryl)-L-X, and the heteroaryl is optionally substituted with one or more C1-C3alkyl or oxo, or (C6-C14aryl)-X-; and

R^6 is hydrogen, halogen, C1-C3 alkyl, halo(C1-C12alkyl) or C1-C6alkoxy.

2. The compound according to claim 1, wherein R^1 is (5-14 membered heteroaryl)-Y-, wherein the heteroaryl is optionally substituted with one or more R^2, and wherein Y is a bond and the 5-14 membered heteroaryl is pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, triazolyl, oxidazolyl, pyridyl, pyridiazinyl, pyrimidinyl, quinolinyl, isoquinolinyl, phthalazinyl, pyrazolopyridinyl, 1*H*-pyrrolopyridyl, pyrazolopyrimidinyl, imidazopyridyl, tetrahydropyrazolopyrazinyl, imidazopyrimidinyl, imidazopyridazinyl, oxazolopyridyl or 5,6-dihydro-8H-imidazooxazinyl, each of which is optionally substituted with one or more R^2.

3. The compound according to claim 2, wherein the 5-14 membered heteroaryl is pyrazolyl, optionally substituted with one, two or three R^2 groups.

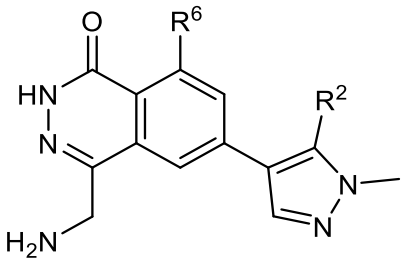
4. The compound according to claim 3, wherein the pyrazolyl is substituted with one R^2.

5. The compound according to claim 3, wherein the pyrazolyl is substituted with two independently selected R^2.

6. The compound according to claim 5, wherein the two R^2 groups are (1) independently (C1 – C5 alkyl)-X-, (2) (C1 – C5 alkyl)-X- and halogen, (3) (C1 – C5 alkyl)-X- and C1-C6alkoxy, (4) (C1 – C5 alkyl)-X- and -$N(R^4)_2$, (5) (C1 – C5 alkyl)-X- and halo(C1-C12alkyl)-X-, (6) (C1 – C5 alkyl)-X- and C6-C14arylC1-C3alkyl, (7) (C1 – C5 alkyl)-X- and (C3-C12cyclolalkyl)-L-X-, (8) (C1 – C5 alkyl)-X- and 3-12 membered heterocyclyl, (9) (C1 – C5 alkyl)-X- and (C6-C14aryl)-X- optionally substituted with one or more R^5, (10) (C1 – C5 alkyl)-X- and -(5-14 membered heteroaryl)-X-, wherein the heteroaryl is optionally substituted with one or more R^5, (11) (C1 – C5 alkyl)-X- and cyanomethyl, (12) (C1 – C5 alkyl)-X- and cyano, (13) cyano and halogen, wherein the halogen is chlorine or fluorine, (14) cyano and (C3-C12cycloalkyl)-L-X-, (15) independently halogen, (16) cyano and C1-C6alkoxy, (17) cyano and (C6-C14aryl)-X-, (18) cyano and (5-14 membered heteroaryl)-X-, (19) cyano and 5-14 membered heterocyclyl, (20) halogen and (C6-C14arylC1-C3alkyl)-X- or (C6-C14arylC1-C3alkyl)-X- substituted with cyano, and (21) halogen and (C6-C14aryl)-X-.

7. 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.

8. A compound of claim 1 which has Formula (I-D):



Formula (I-D)

or a pharmaceutically acceptable salt thereof:

wherein:

R^2 is hydroxy, halogen, cyano, cyanomethyl, -$(NR^4)_2$, hydroxy(C1-C12)alkyl, C1-C6alkoxy, -SO_2(C1 – C3alkyl), (C6-C14arylC1-C3alkyl)-X-, hetero(C3-C12alkyl), C2- C4 alkynyl, halo(C1-C12alkyl)-X-, (C1 – C5 alkyl)-X-, (C1 – C5 alkyl)-Z-, 5-10 membered heterocyclyl, (C3-C12cycloalkyl)-L-X-, (C3-C12cycloalkyl)-Z-, (C6-C14aryl)-X-, (C6-C14 aryl)-Z-, or (5-14 membered heteroaryl)-X-, wherein the heterocyclyl, the cycloalkyl, the aryl and the heteroaryl are optionally substituted with one or more R^5;

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)-;

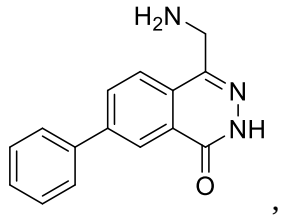
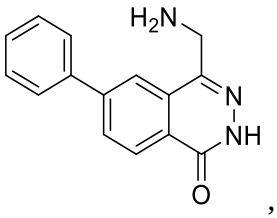
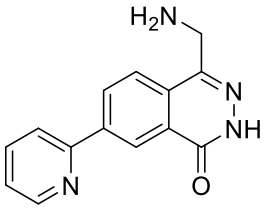
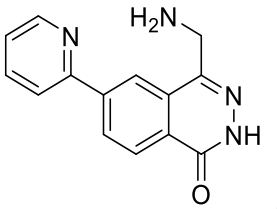
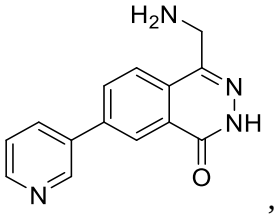
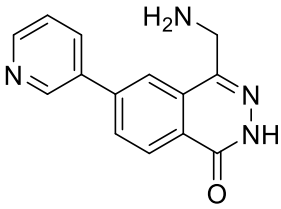
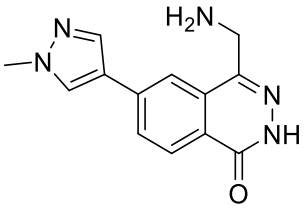
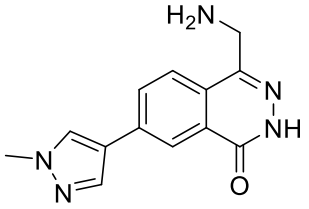
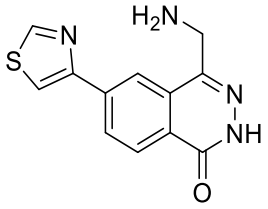
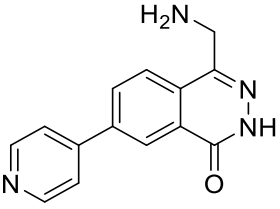
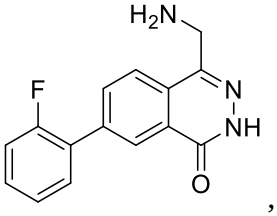
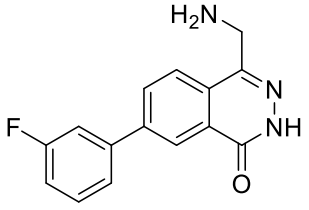
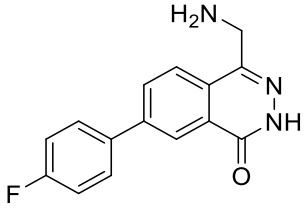
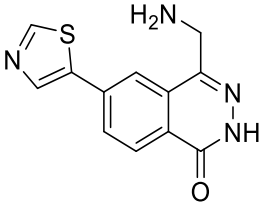
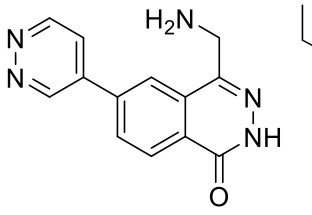
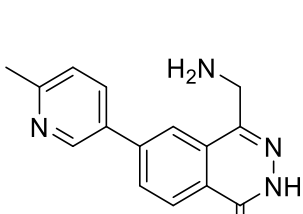
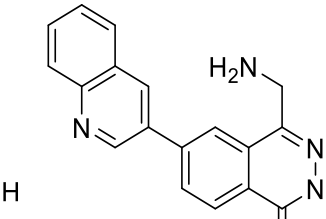
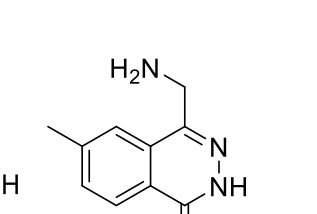
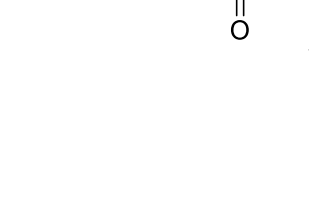
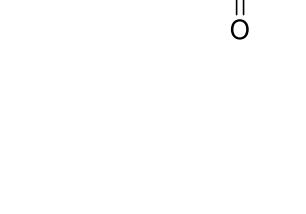
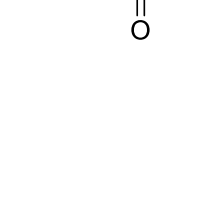
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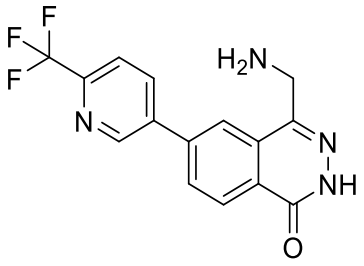
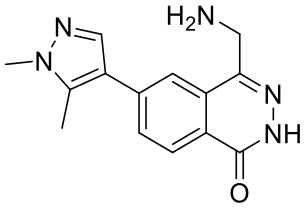
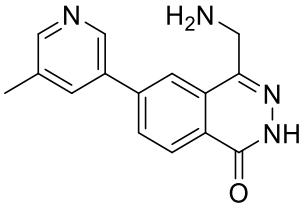
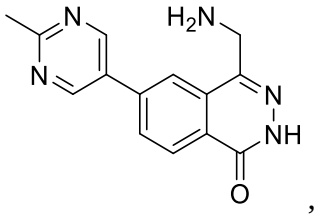
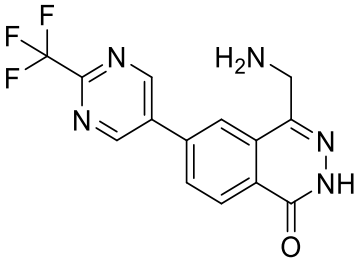
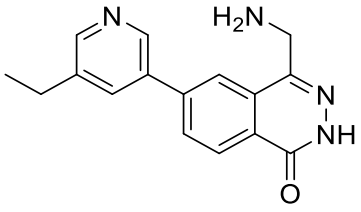
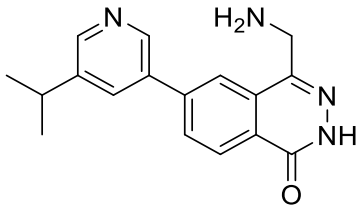
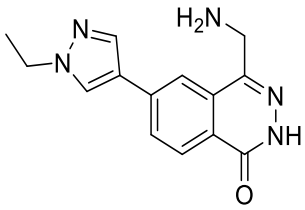
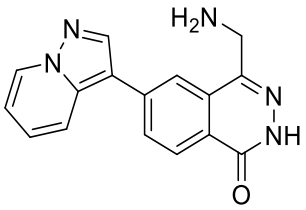
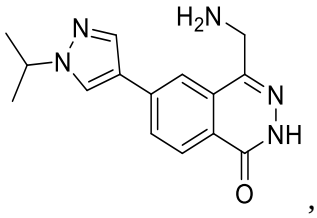
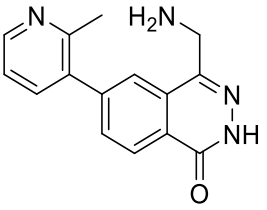
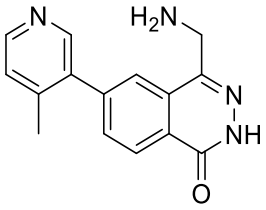
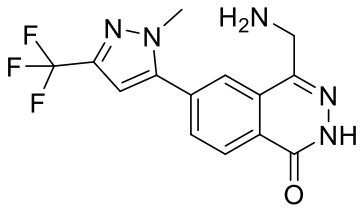
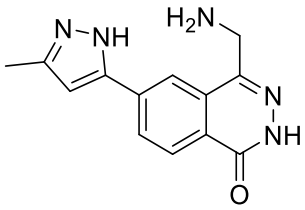
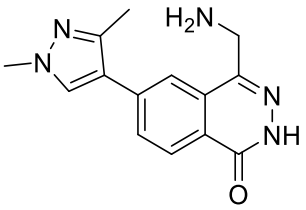
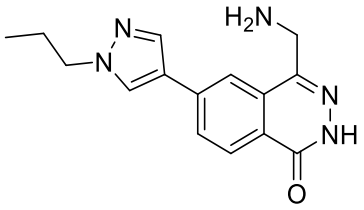
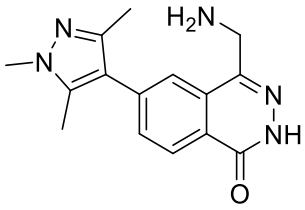
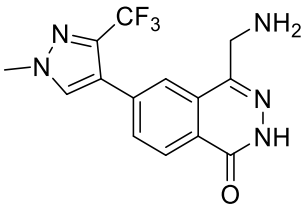
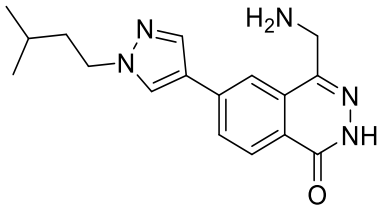
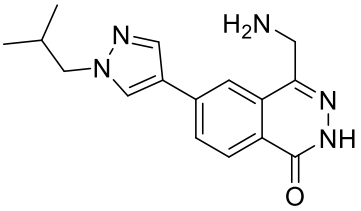
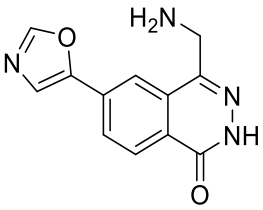
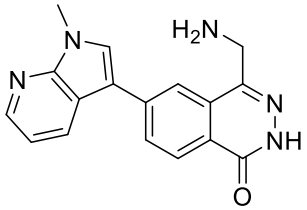
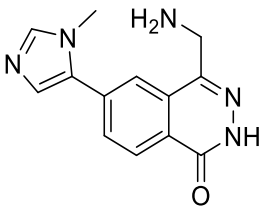
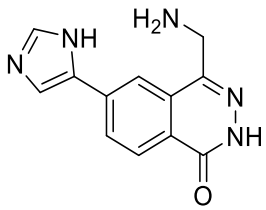
each R^4 is independently hydrogen or C1 – C3 alkyl;

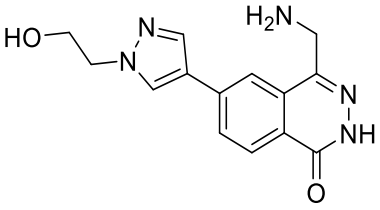
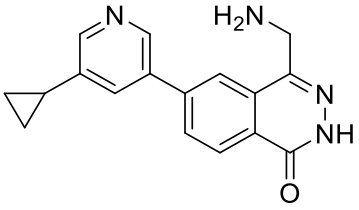
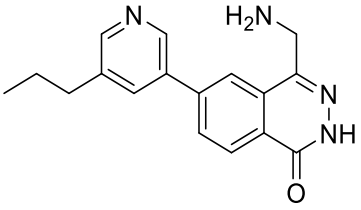
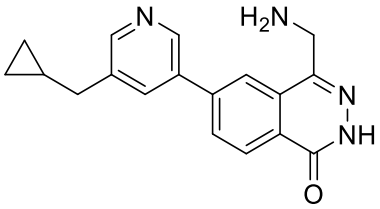
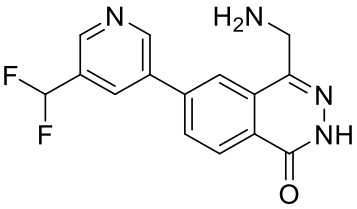
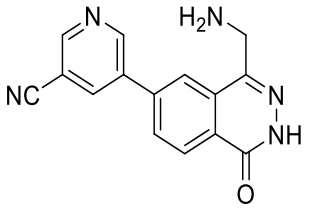
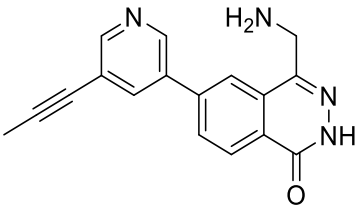
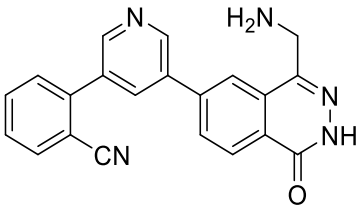
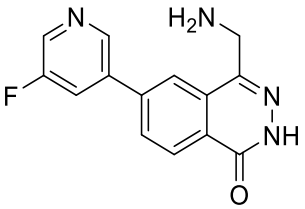
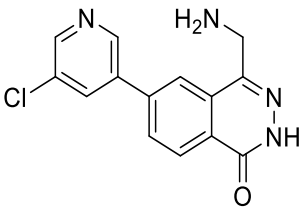
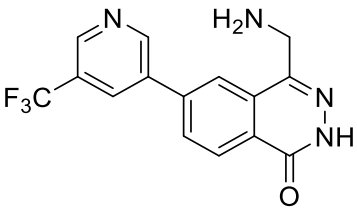
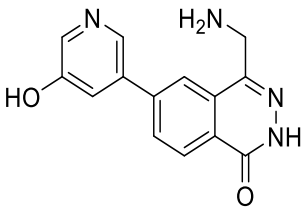
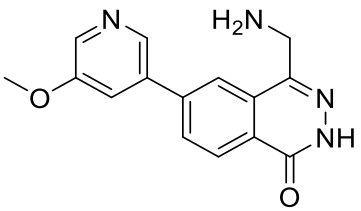
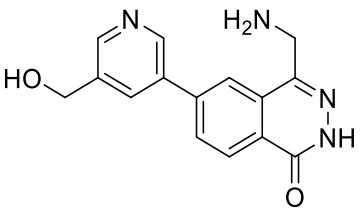
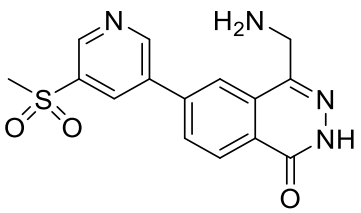
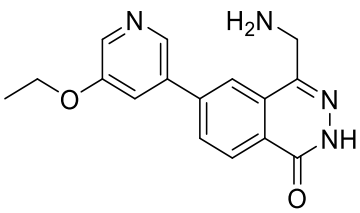
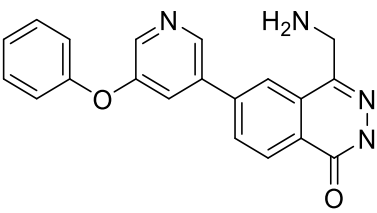
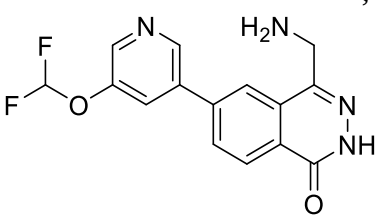
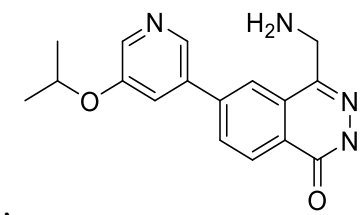
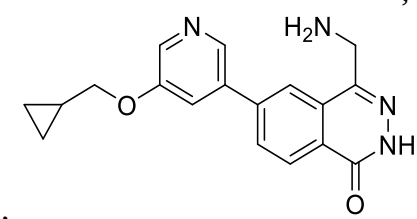
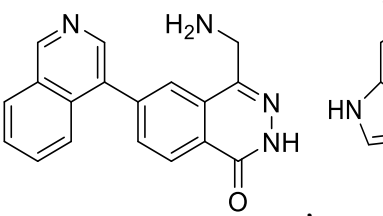
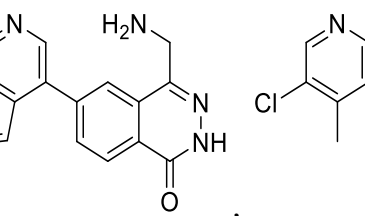
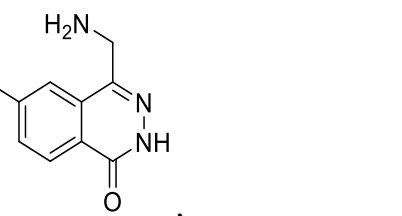
each R^5 is independently cyano, oxo, halogen, C1 – C3 alkyl, hydroxy(C1-C12alkyl), C1-C6alkoxy, halo(C1-C12alkyl)-X-, (C3-C12cycloalkyl)-Z-, (C6-C14arylC1-C3alkyl)-X-, (C6-C14arylC1-C3alkyl)-X-, wherein the aryl is substituted with cyano, (C3-C12cycloalkyl)-L-X-, (5-14 membered heteroaryl)-L-X-, and the heteroaryl is optionally substituted with one or more C1-C3alkyl or oxo, or (C6-C14aryl)-X-; and

R^6 is hydrogen, halogen, C1-C3 alkyl, halo(C1-C12alkyl) or C1-C6alkoxy.

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


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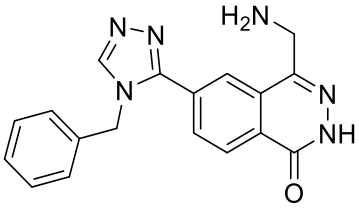
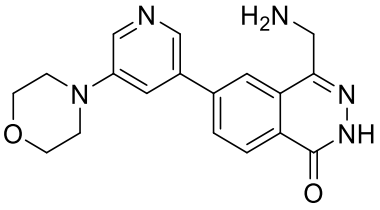
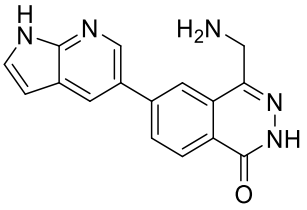
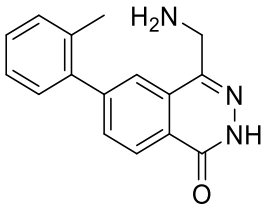
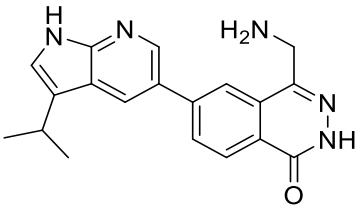
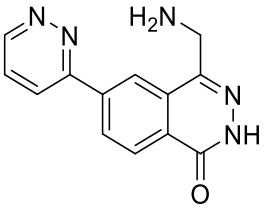
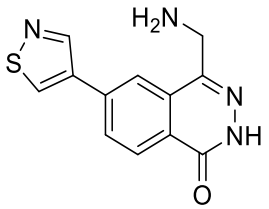
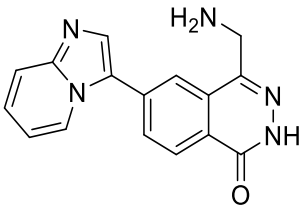
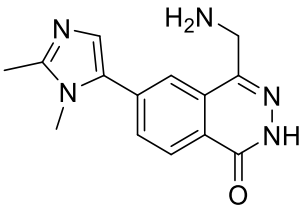
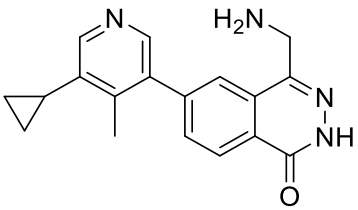
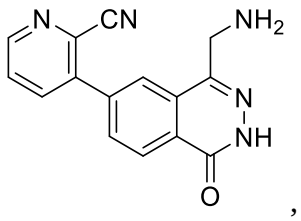
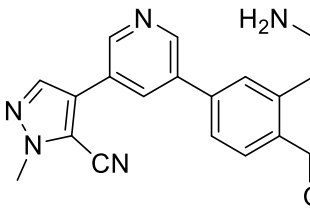
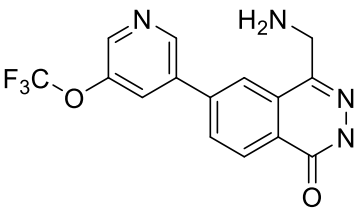
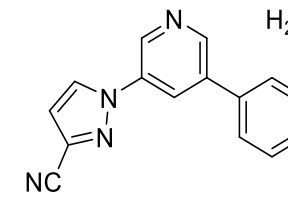
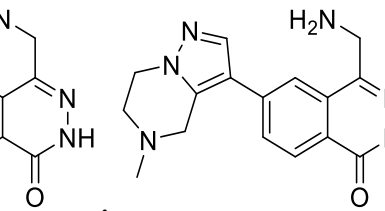
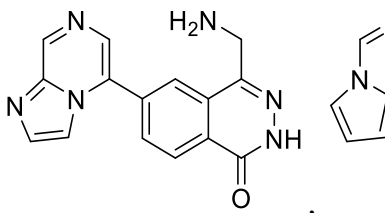
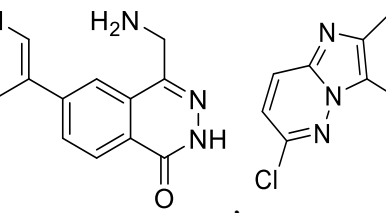
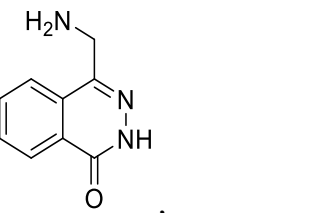
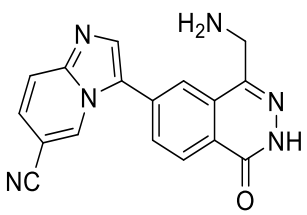
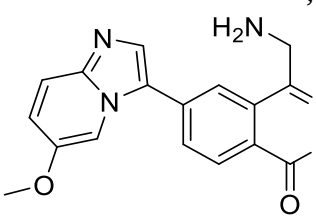
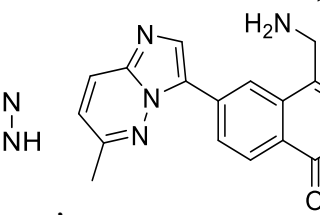
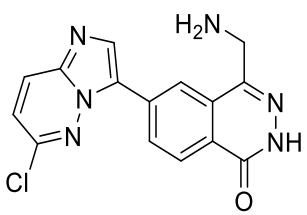
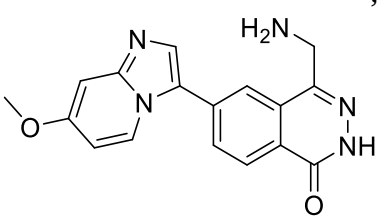
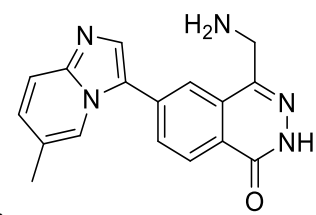

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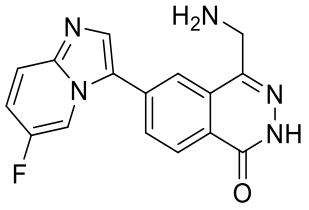
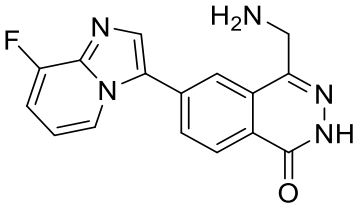
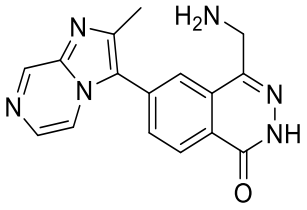
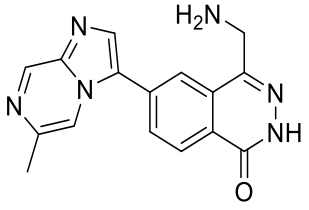
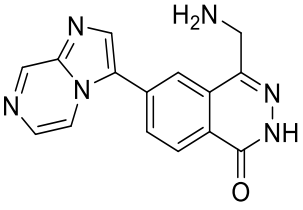
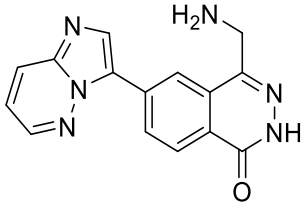
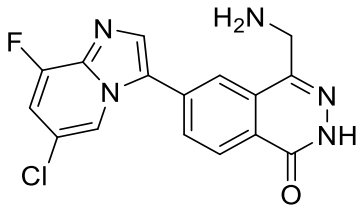
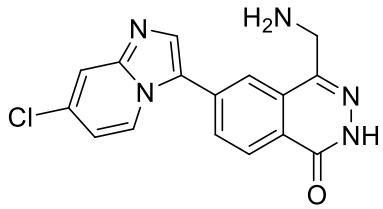
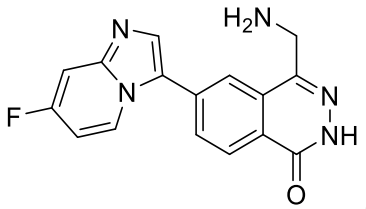
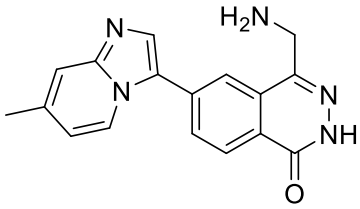
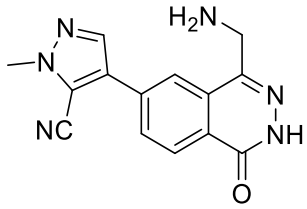
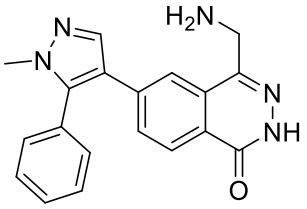
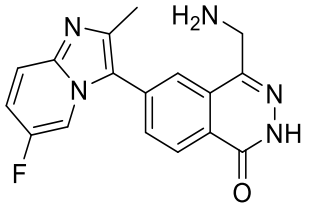
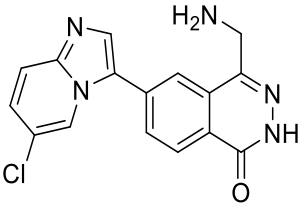
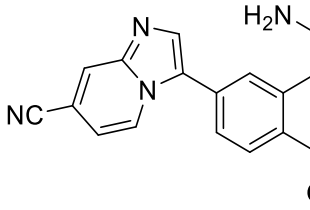
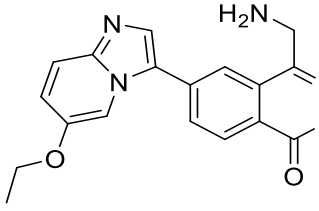
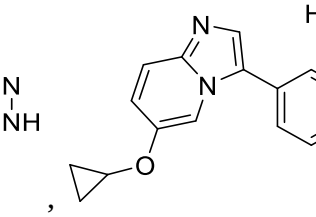
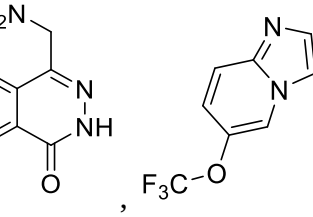
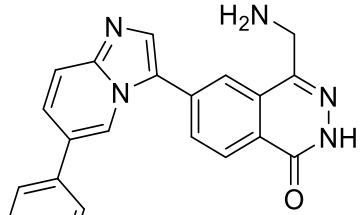
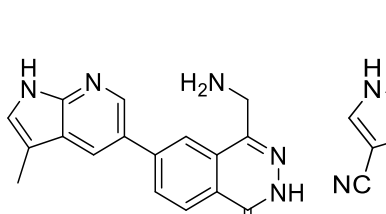
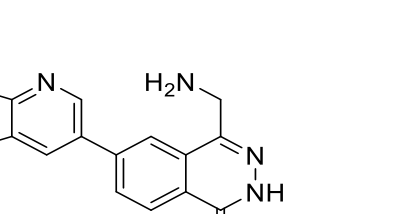
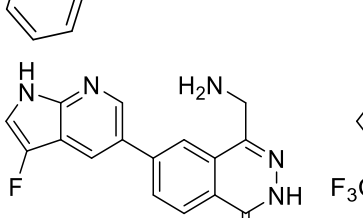
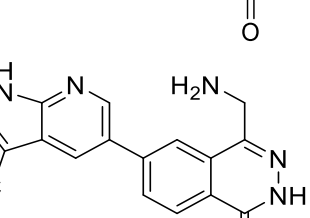
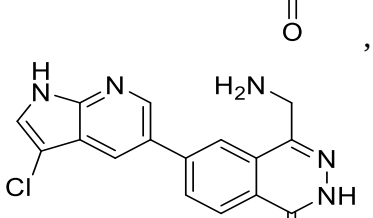
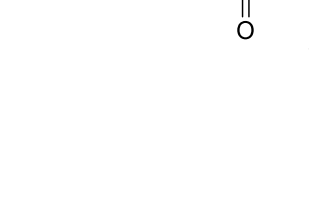
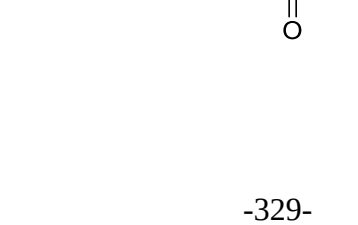
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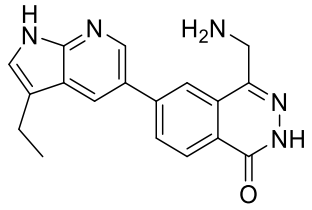
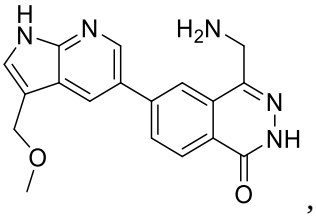
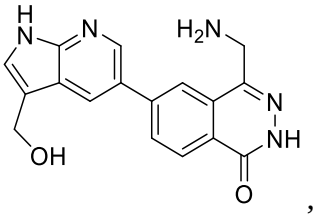
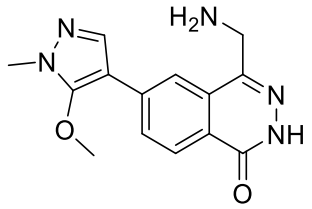
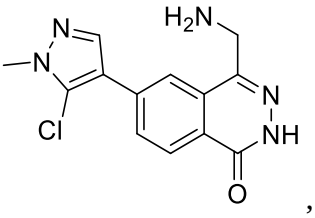
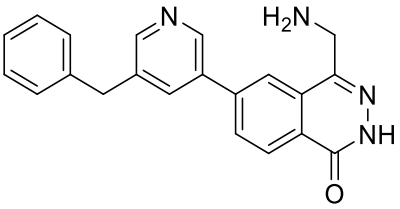
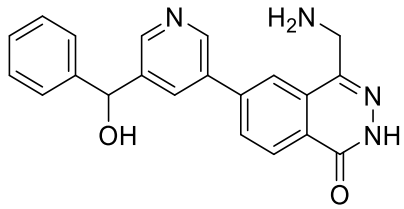
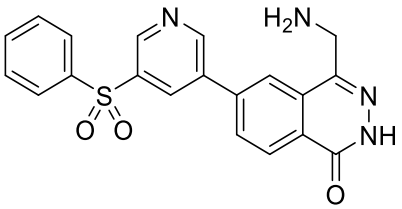
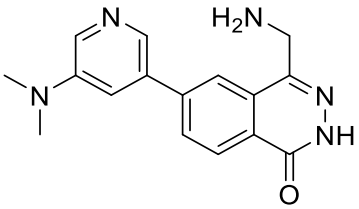
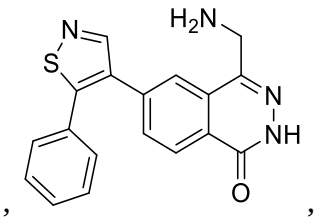
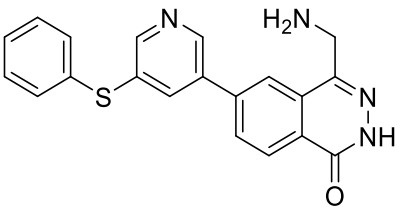
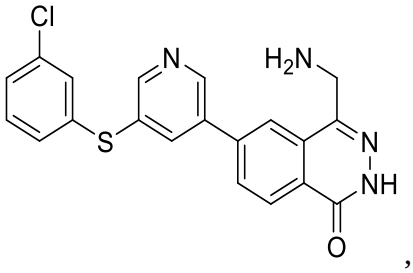
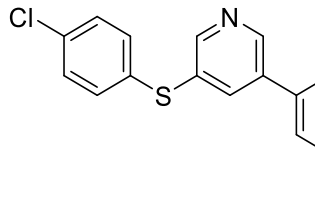
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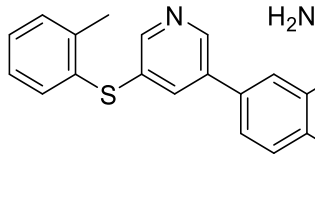
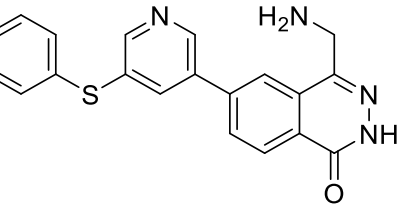
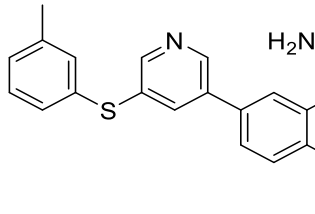
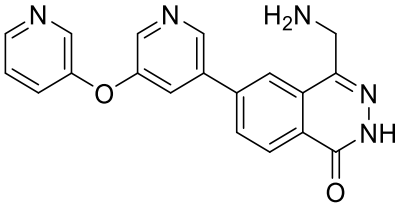
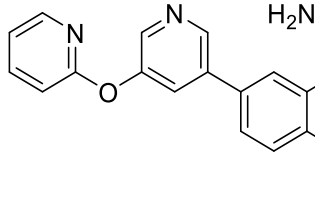
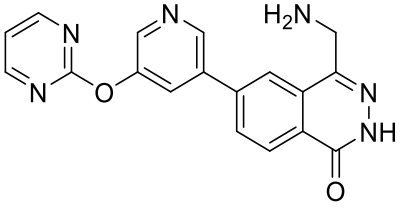

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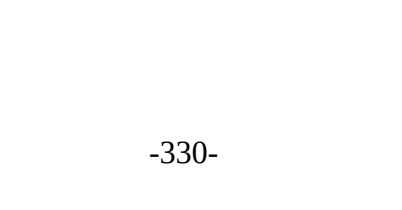
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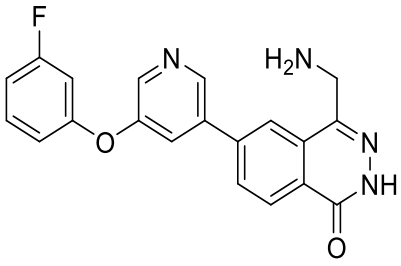
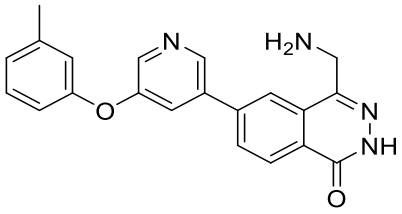
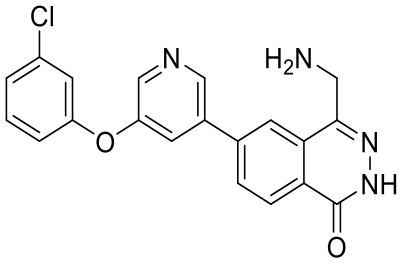
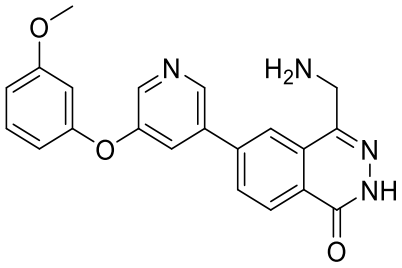
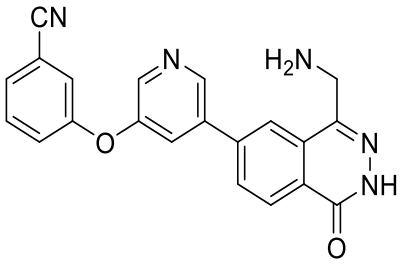
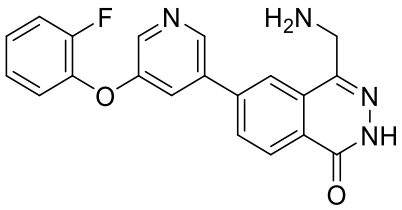
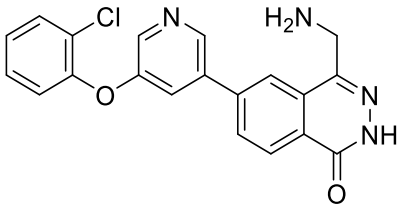
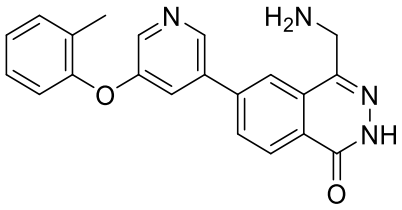
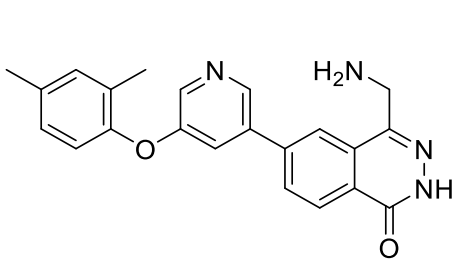
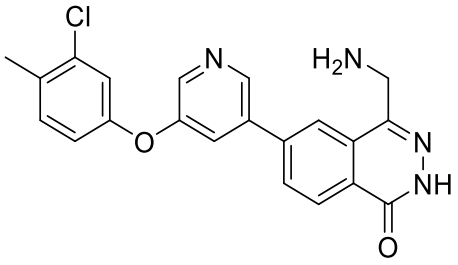
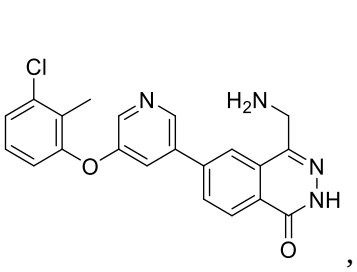
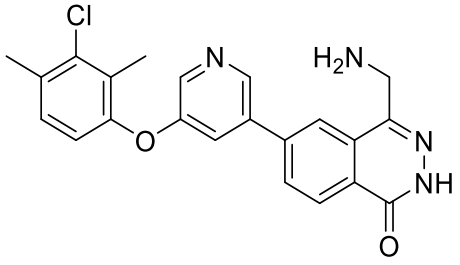
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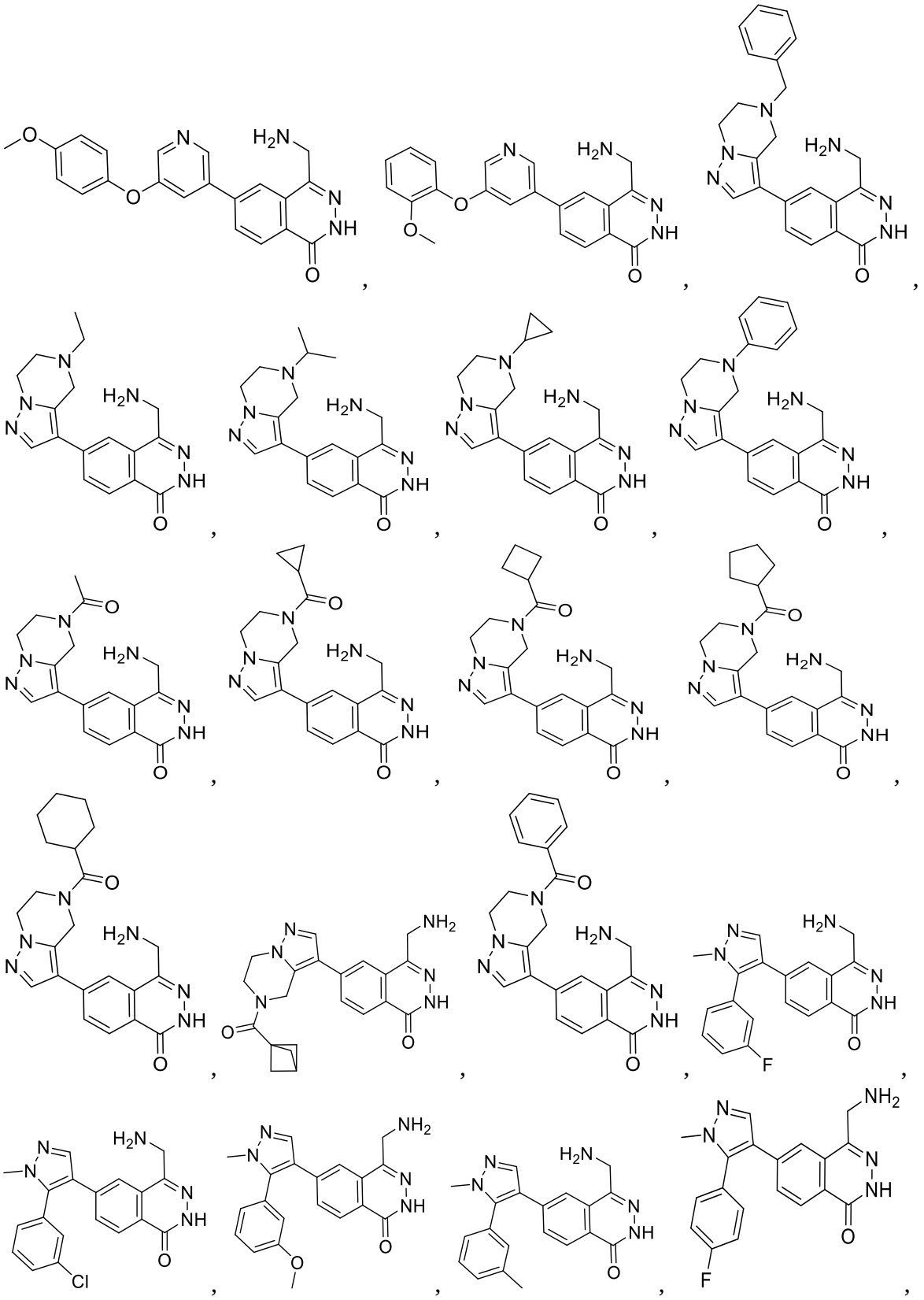
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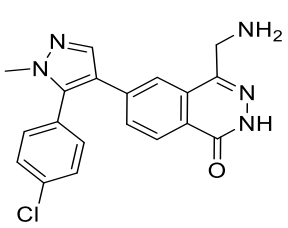
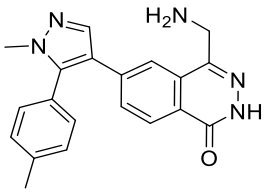
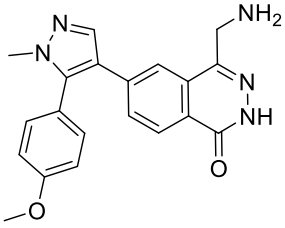
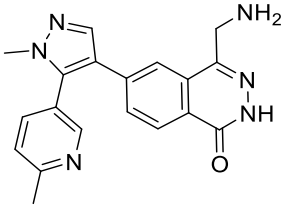
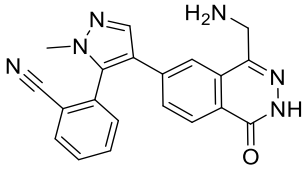
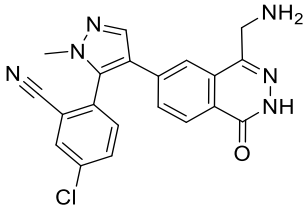
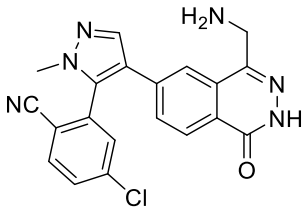
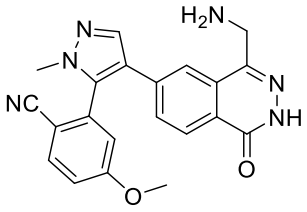
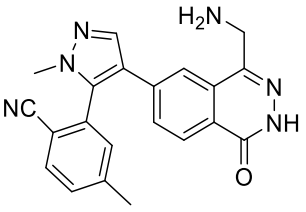
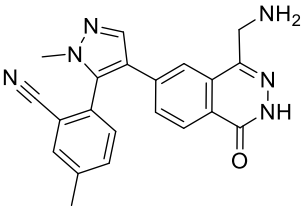
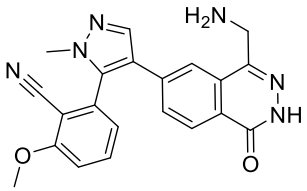
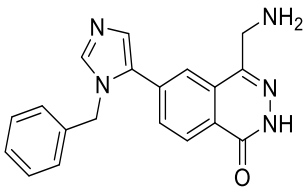
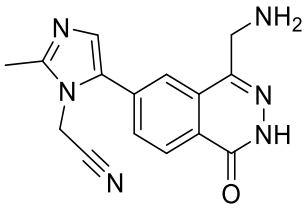
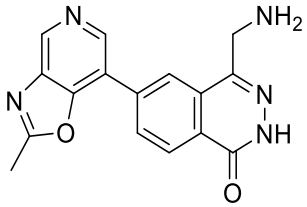
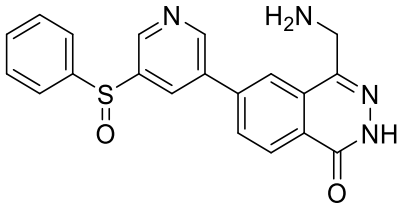
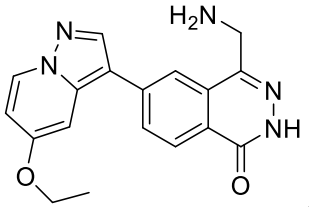
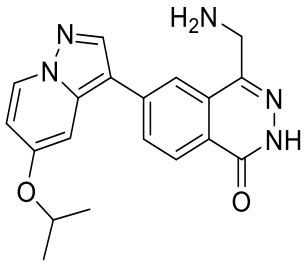
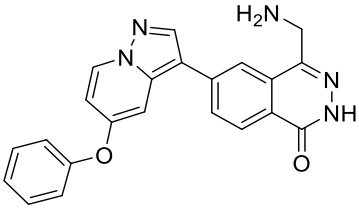
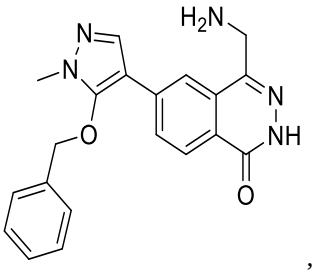
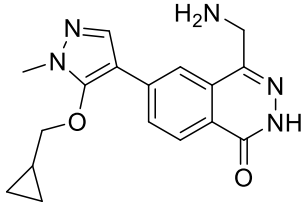
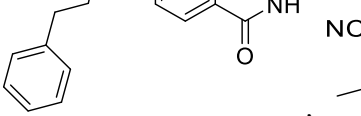
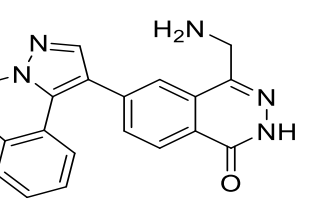
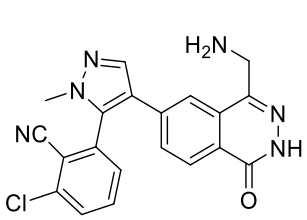
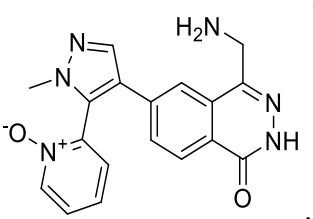
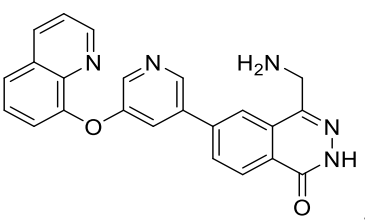
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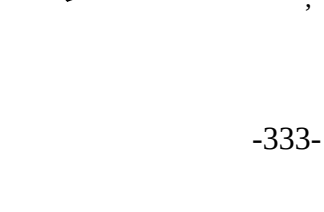
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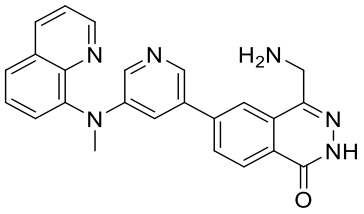
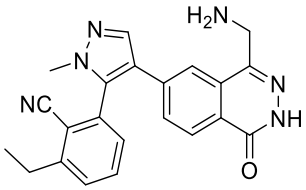
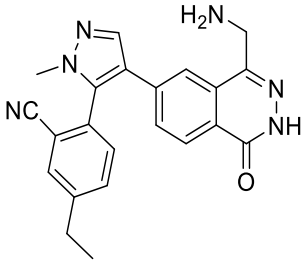
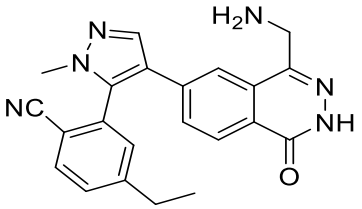
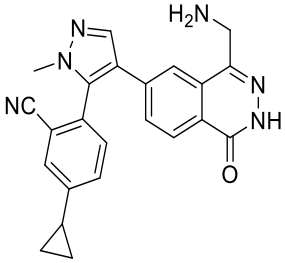
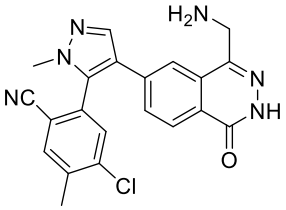
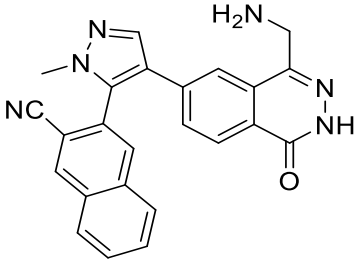
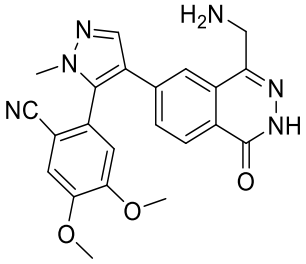
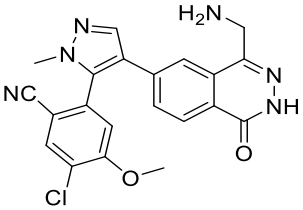
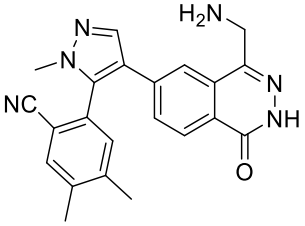
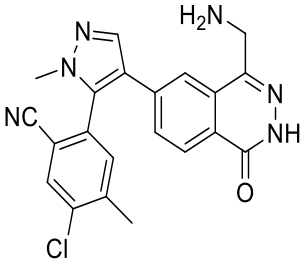
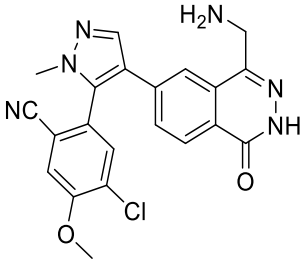
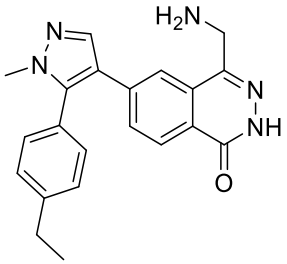
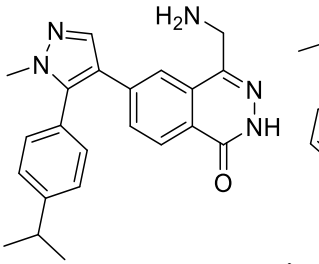
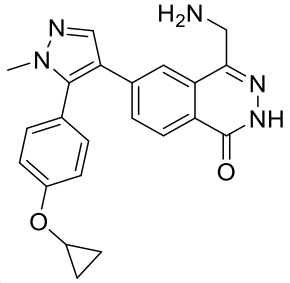
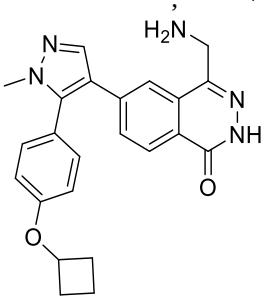
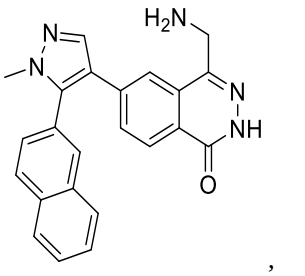
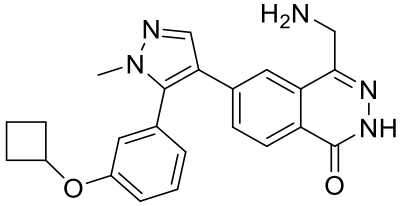

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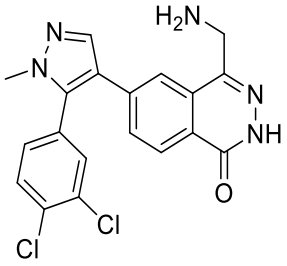
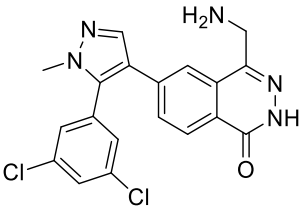
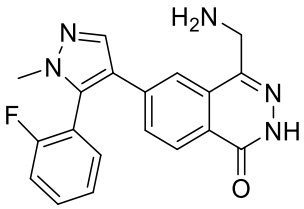
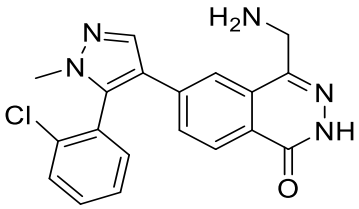
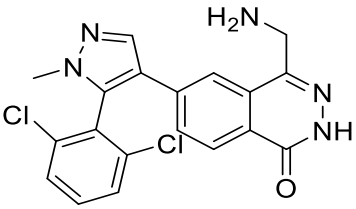
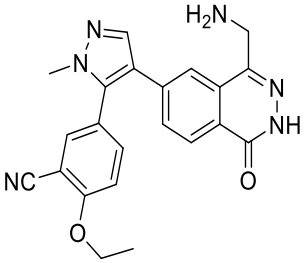
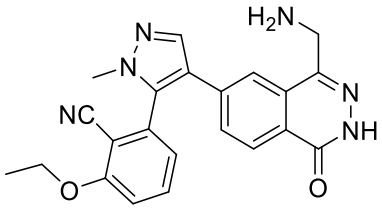
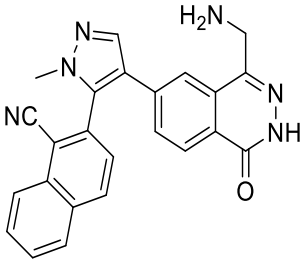
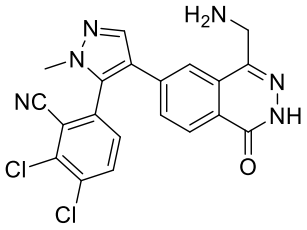
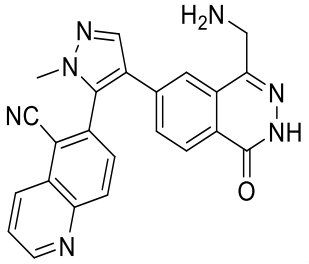
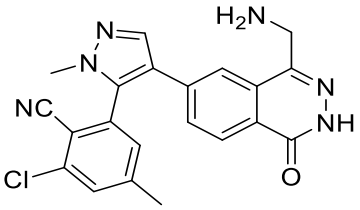
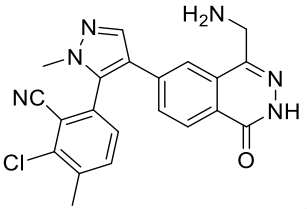
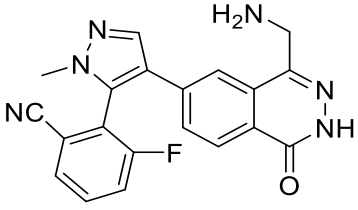
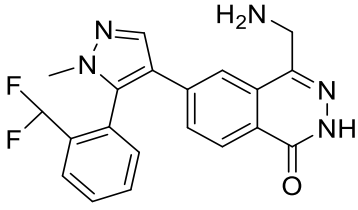
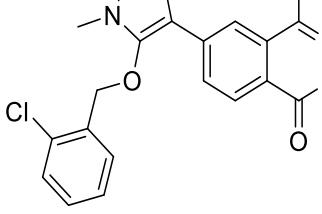

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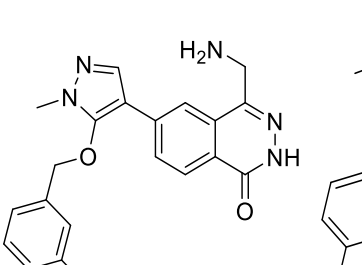
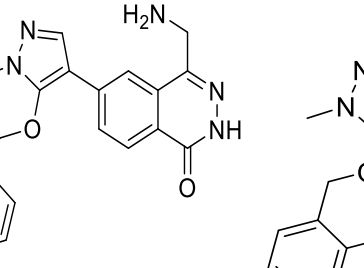
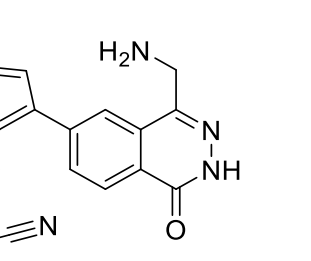
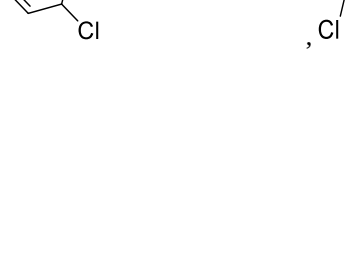
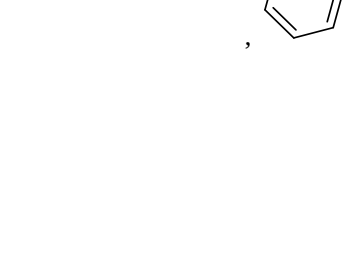

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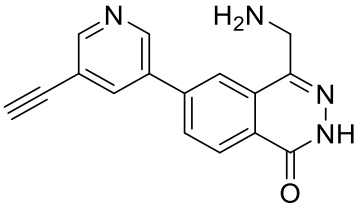
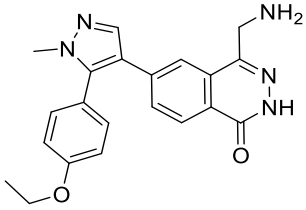
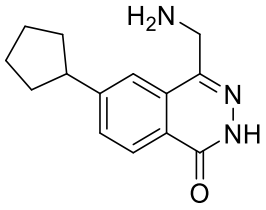
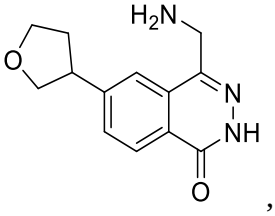
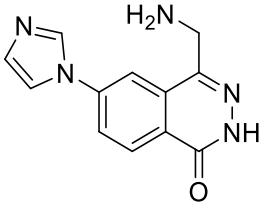
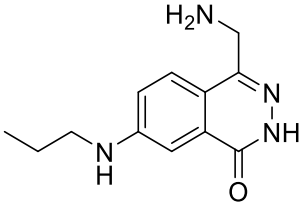
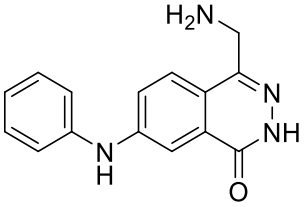
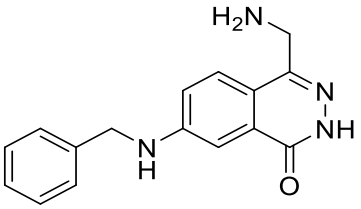
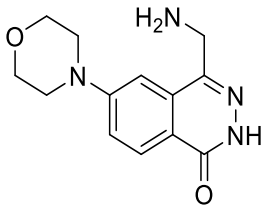
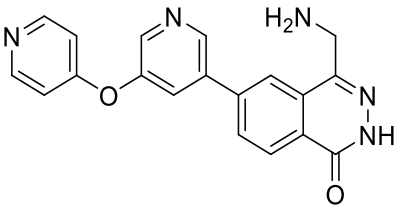
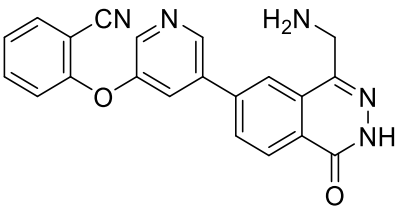
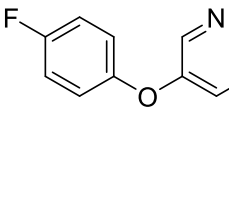
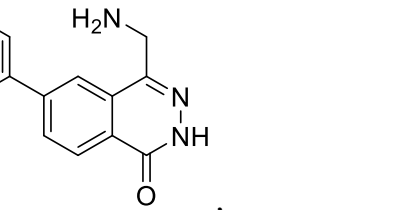
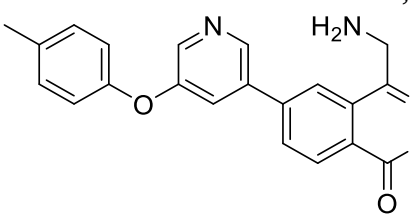
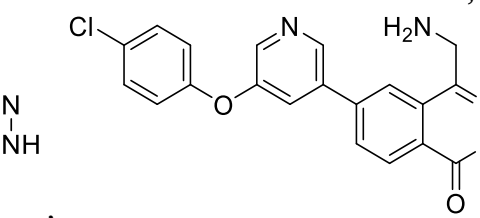
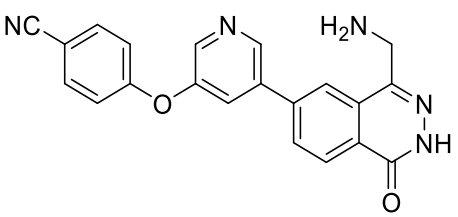
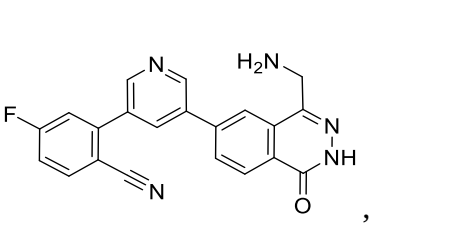
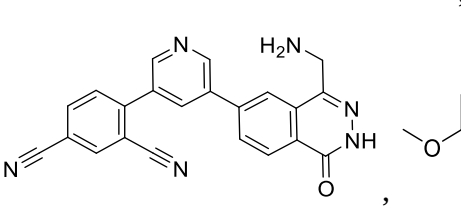
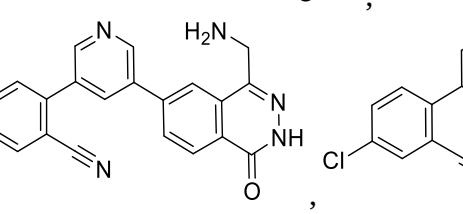
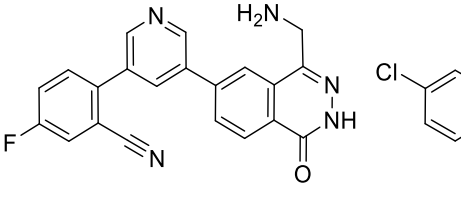
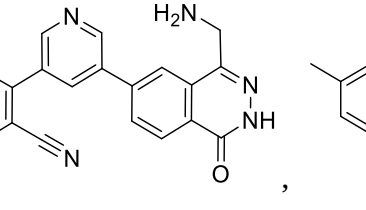

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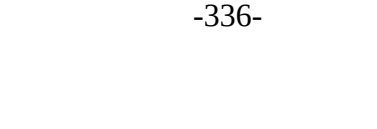
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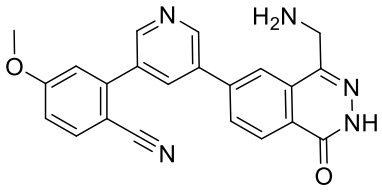
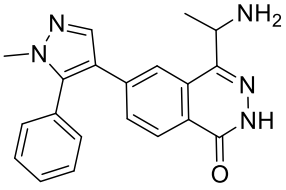
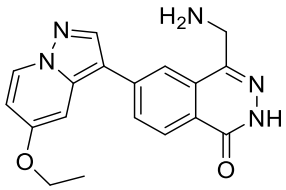
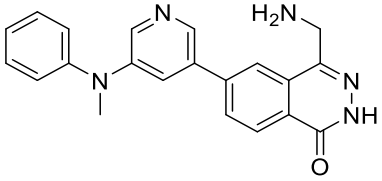
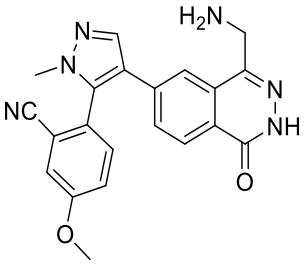
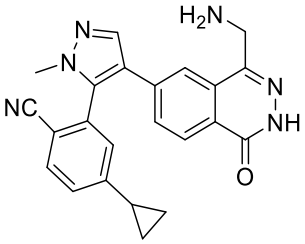
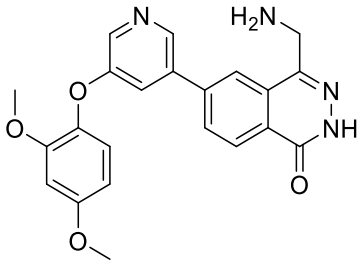
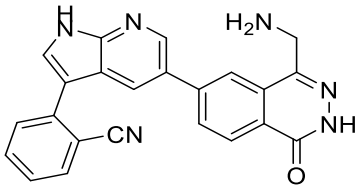
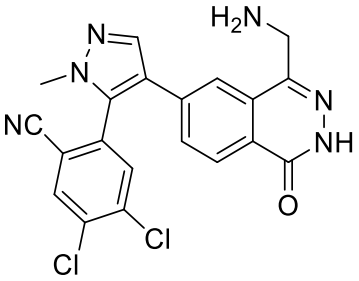
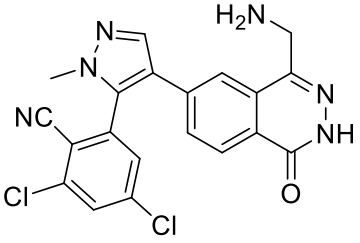
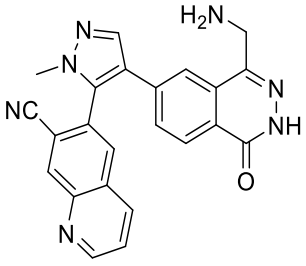
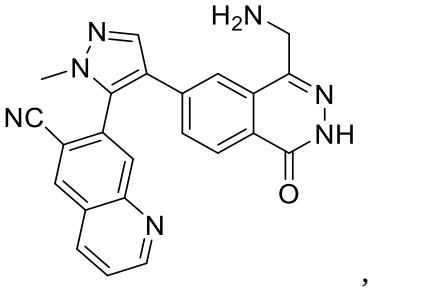
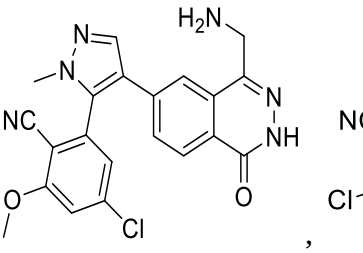

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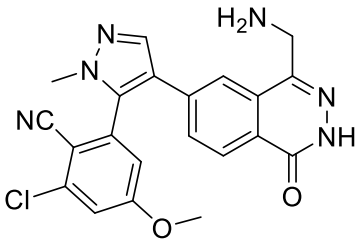
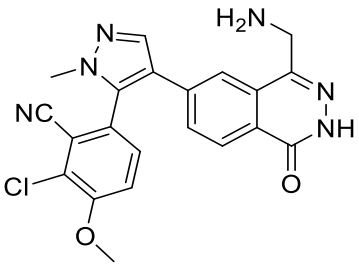
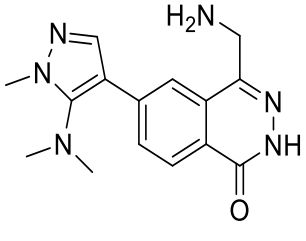
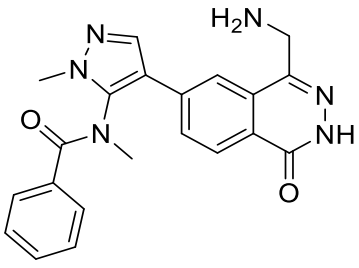
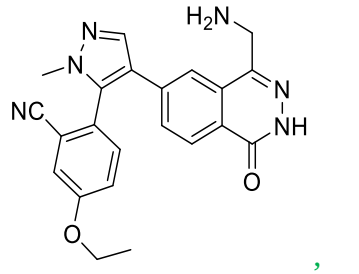
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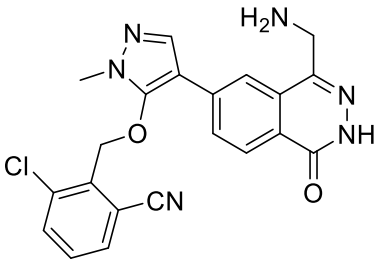
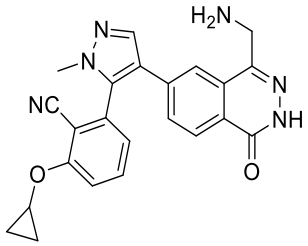
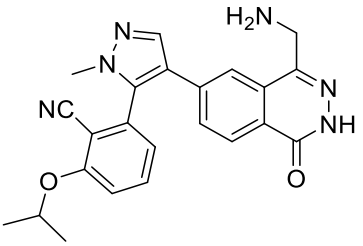
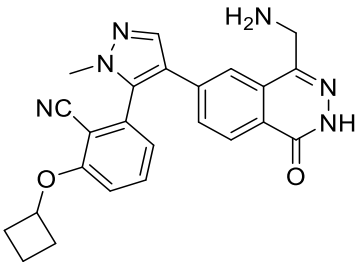
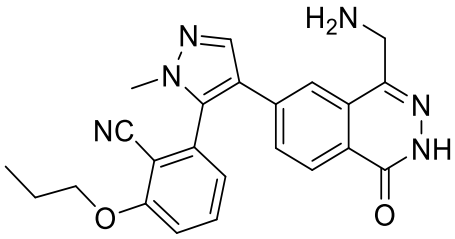
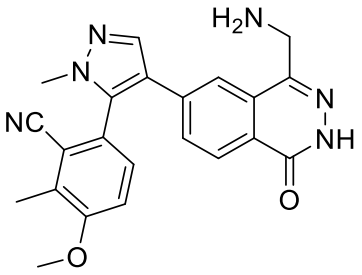
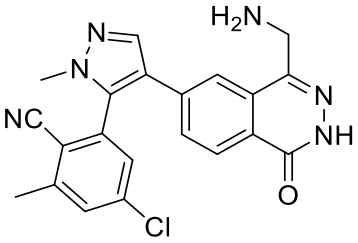
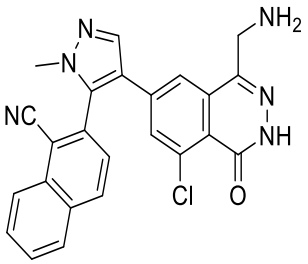
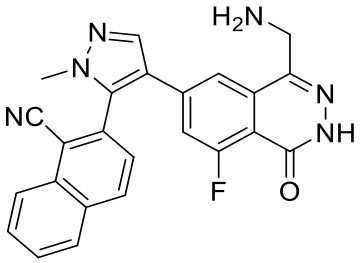
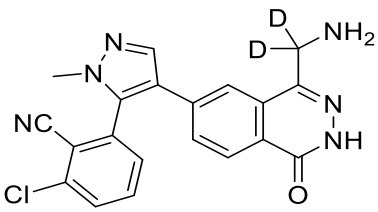
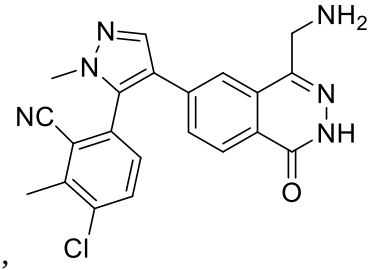
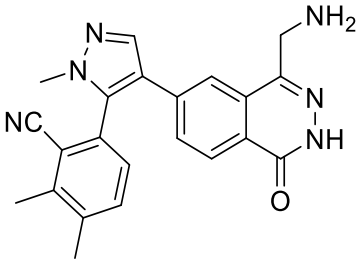
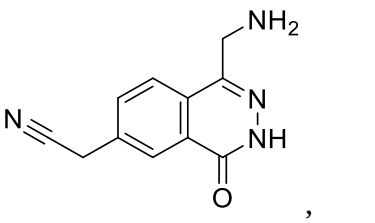
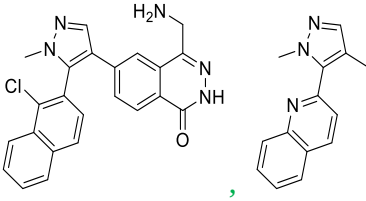
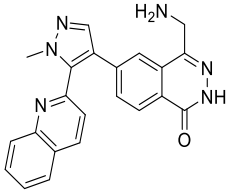
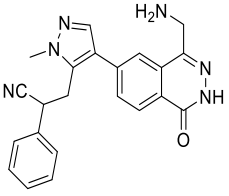
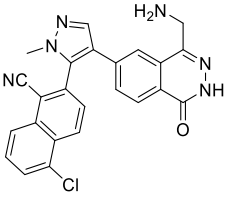
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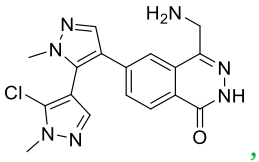
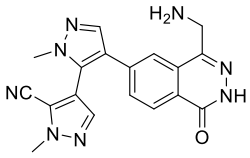
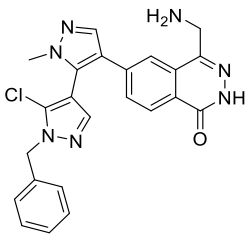
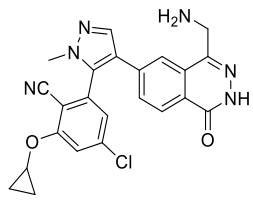
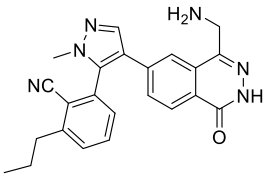
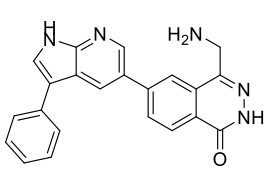
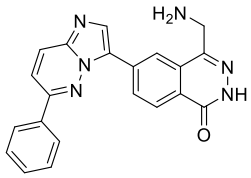
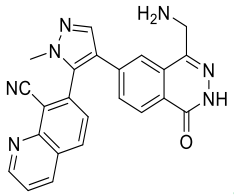
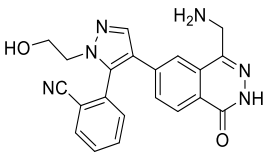
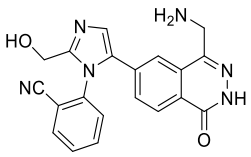
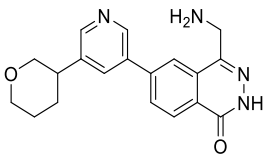
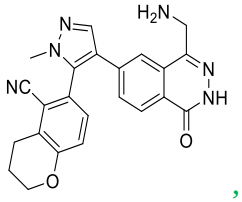
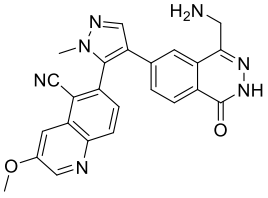
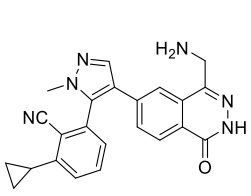
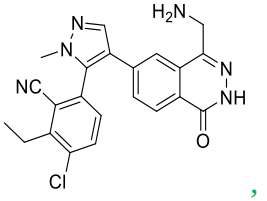
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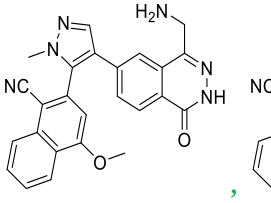
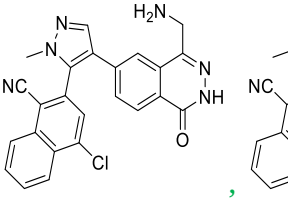
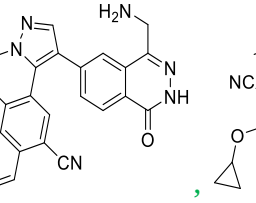
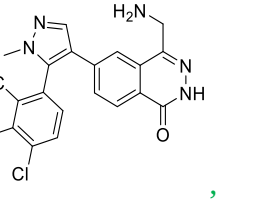

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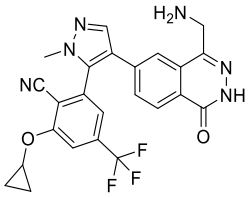
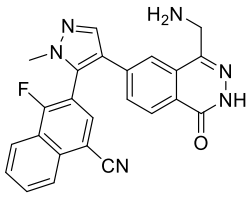
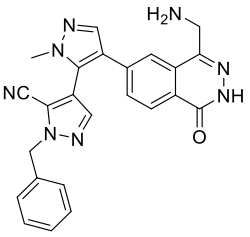
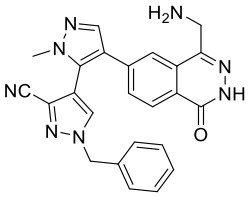
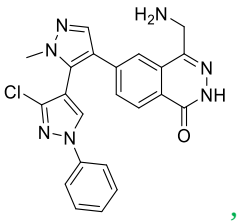
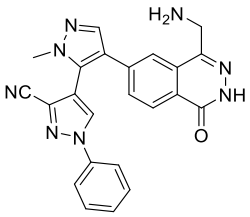
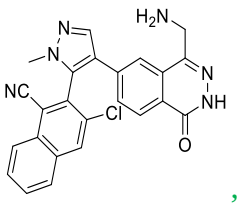
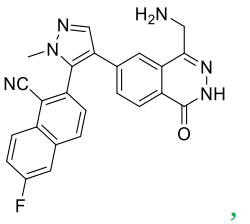
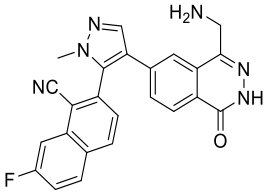
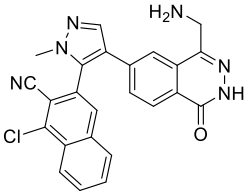
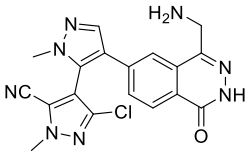
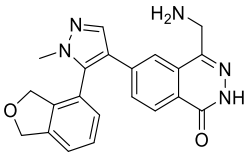
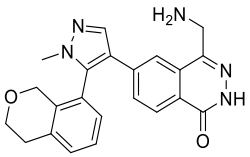
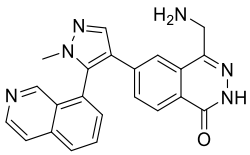
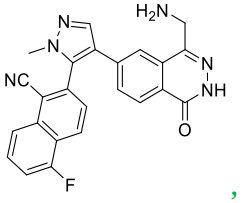
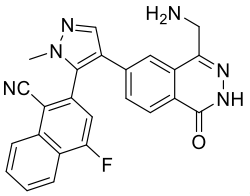
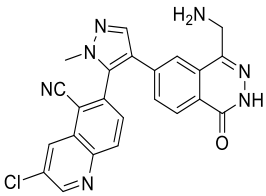
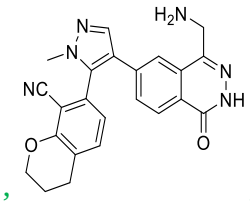
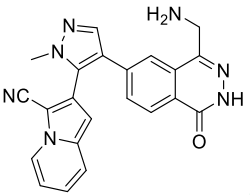
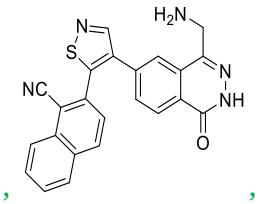
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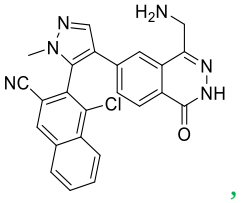
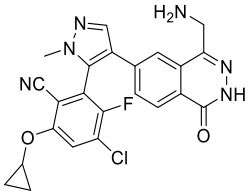
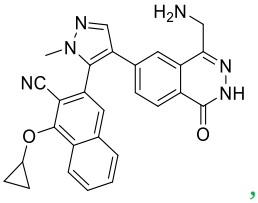
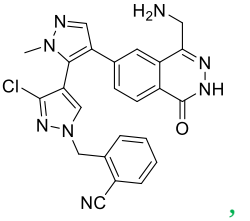
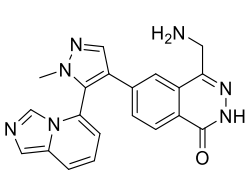
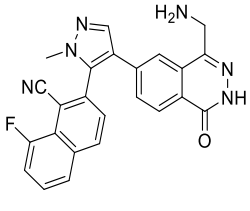
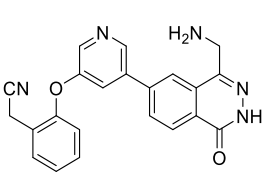
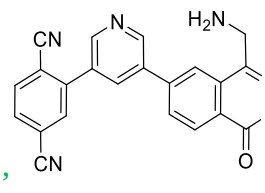
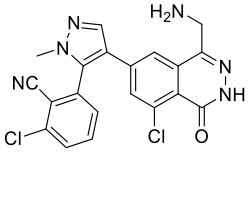
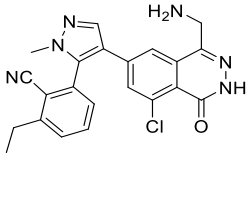
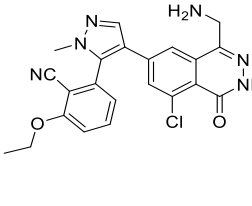
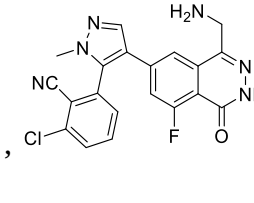
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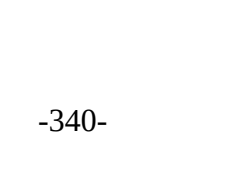
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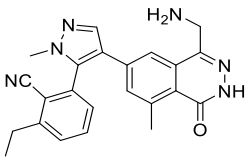
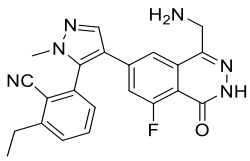
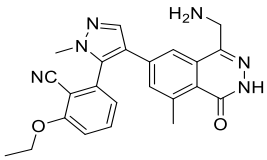
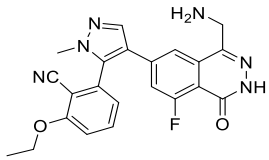
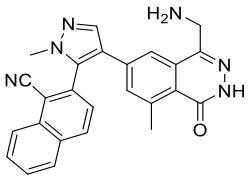
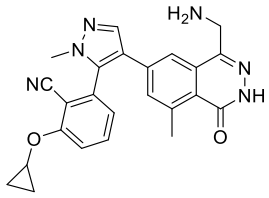
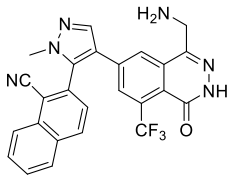
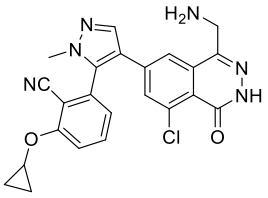
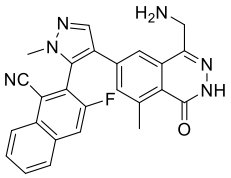
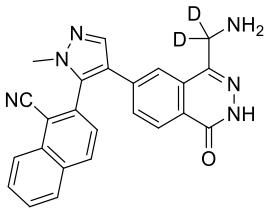
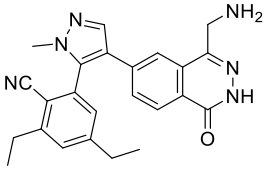
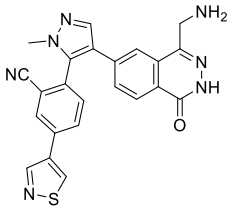
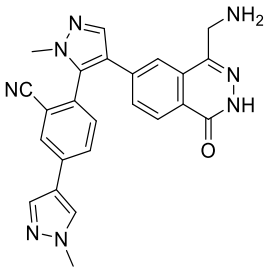
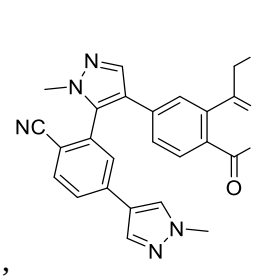
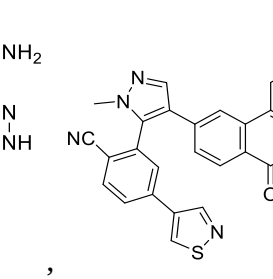
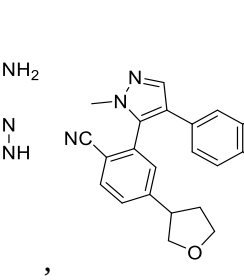
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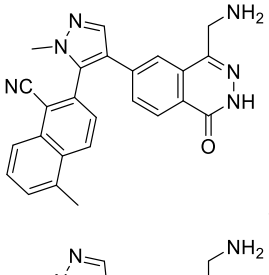
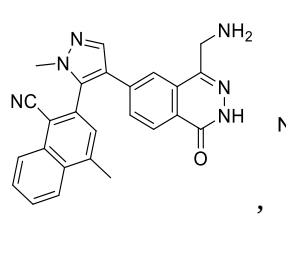
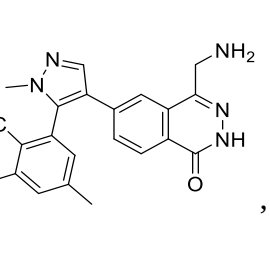
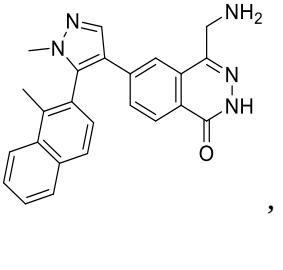
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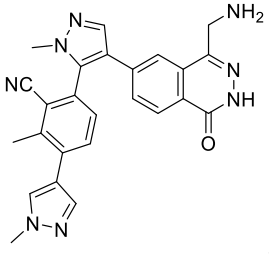
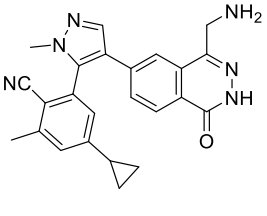
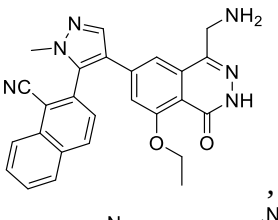
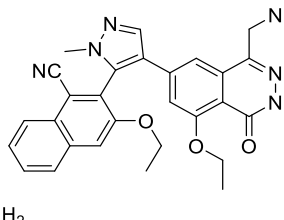
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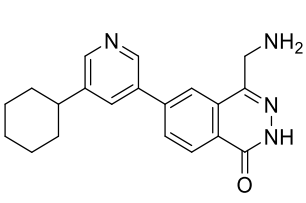
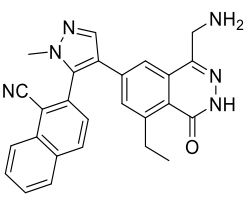
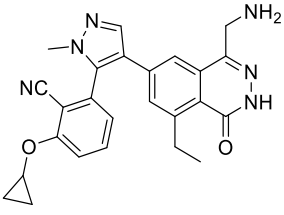
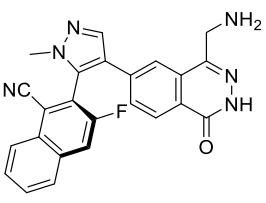
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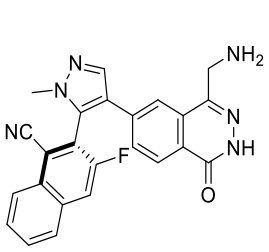
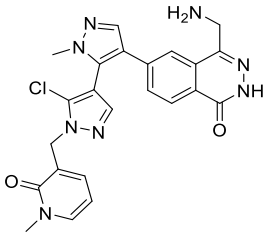
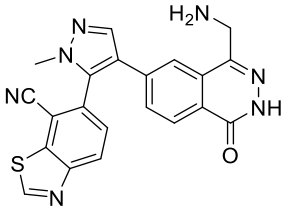
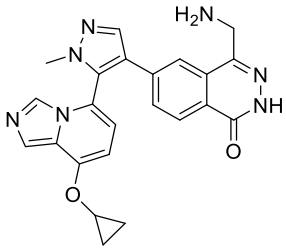
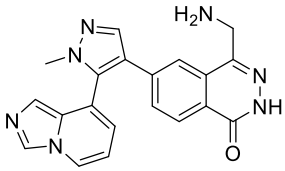
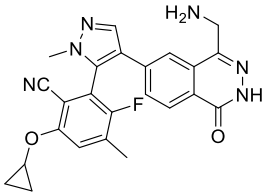
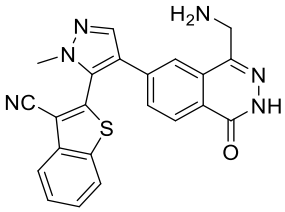
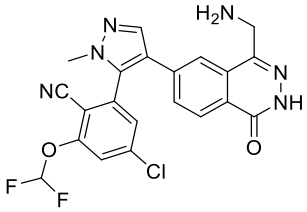
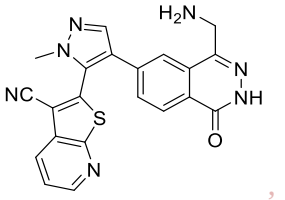
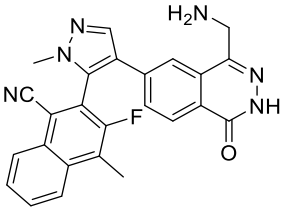
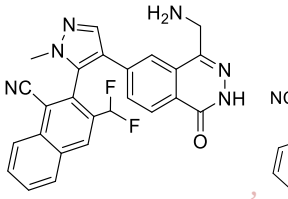
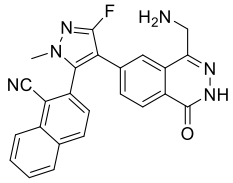
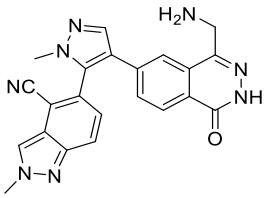
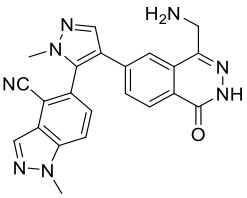
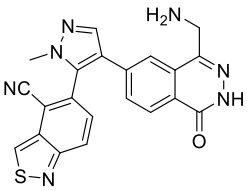
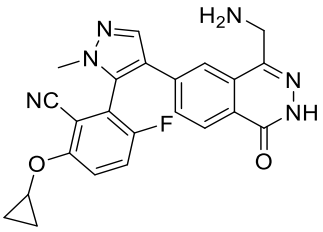
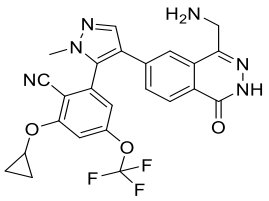
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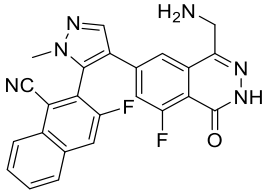
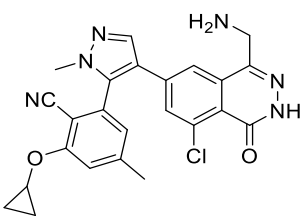
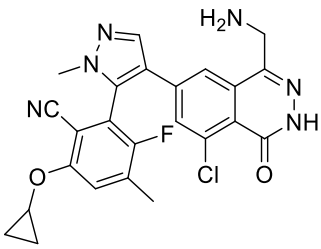
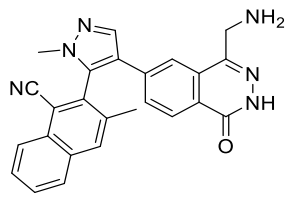
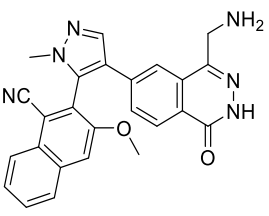
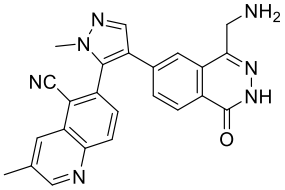
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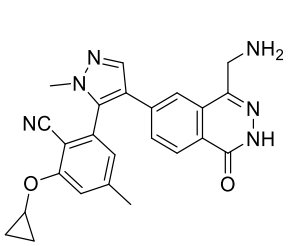
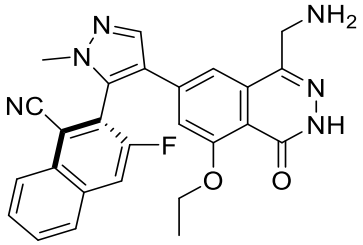
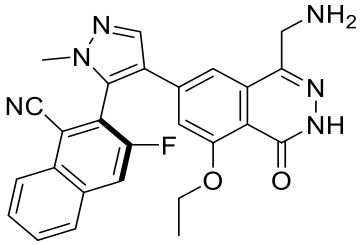
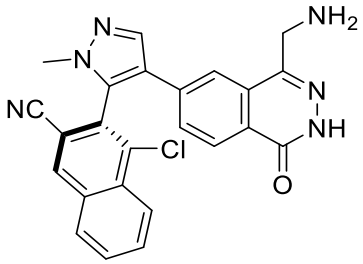
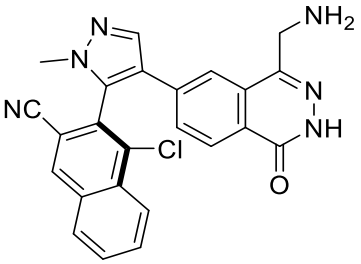
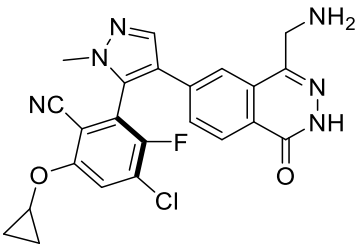
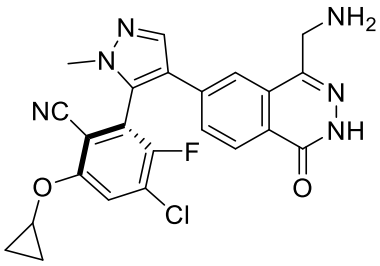
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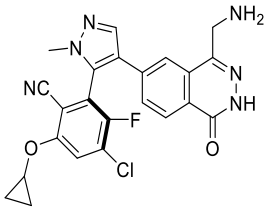



















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or a pharmaceutically acceptable salt thereof.

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


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or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition, comprising a compound of Formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

12. Use of a therapeutically effective amount of a compound of Formula (I) according to any one of claims 1-10 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cancer.

13. The use of claim 12, wherein the therapeutically effective amount of the compound is between about 0.01 to 300 mg/kg per day.

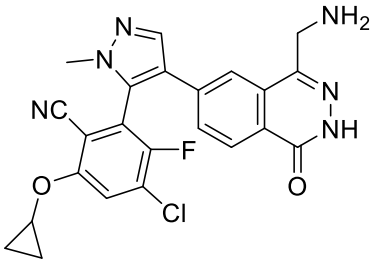
14. The use of claim 12, wherein the therapeutically effective amount of the compound is between about 0.1 to 100 g/kg per day.

15. The use according to any one of claims 12-14, wherein the cancer is selected from the group consisting of Cardiac; Lung; Gastrointestinal; Genitourinary tract; Liver; Biliary tract; Bone; Nervous system; Gynecological; Hematologic; Skin; and Adrenal glands.

16. The use according to any one of claims 12-14, wherein the cancer is a MTAP-associated cancer.

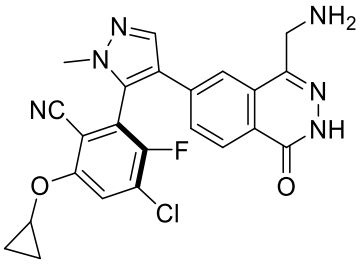
17. The use of claim 13, wherein the cancer is hepatocellular carcinoma, breast cancer, skin cancer, bladder cancer, liver cancer, pancreatic cancer, or head and neck cancer.

18. The compound of claim 1, wherein the compound is



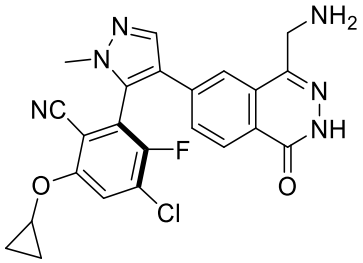
or a pharmaceutically acceptable salt thereof.

19. A pharmaceutically acceptable salt of the compound of claim 1, wherein the compound is



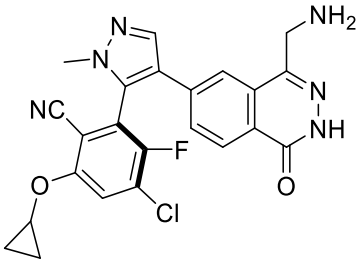
.

20. The use of claim 12, wherein the compound of Formula (I) is



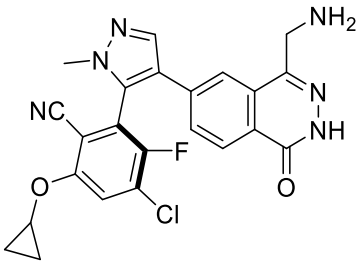
or a pharmaceutically acceptable salt thereof.

21. The use of claim 12, wherein the compound of Formula (I) is



.

22. The use of claim 12, wherein the compound of Formula (I) is a pharmaceutically acceptable salt of a compound of the formula



.

23. The use of claim 12, wherein the cancer is selected from the group consisting of sarcoma, myxoma, rhabdomyoma, fibroma, lipoma and teratoma, bronchogenic carcinoma, alveolar carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma, esophagus, stomach, pancreas, small bowel, large bowel, kidney, bladder and urethra, prostate, testis, hepatoma, cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma, gall bladder carcinoma, ampullary carcinoma, cholangiocarcinoma, osteogenic sarcoma, fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma, multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma, benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors, skull, meninges, brain,

uterus, vulva, vagina, fallopian tubes, blood, Hodgkin's disease, non-Hodgkin's lymphoma, malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis, and neuroblastoma.