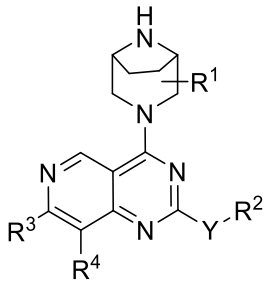
CLAIMS

WHAT IS CLAIMED IS:

1. Use of a therapeutically effective amount of a combination of a pan ErbB family inhibitor and a KRAS G12D inhibitor of formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is hydrogen, hydroxy, halogen, C1 – C3 alkyl, C1 - C3 cyanoalkyl, C1 - C3 hydroxyalkyl, HC(=O)-, $-CO_2R^5$, $-CO_2N(R^5)_2$ or a 5-6 membered heteroaryl;

Y is a bond, O or NR^5;

R^2 is hydrogen, $-N(R^5)_2$, heterocyclyl, C1 – C6 alkyl, -L-heterocyclyl, -L-aryl, -L-heteroaryl, -L-cycloalkyl, $-L-N(R^5)_2$, -L-$NHC(=NH)NH_2$, $-L-C(O)N(R^5)_2$, -L-C1-C6 haloalkyl, $-L-OR^5$, $-L-(CH_2OR^5)(CH_2)_nOR^5$, $-L-NR^5C(O)$-aryl, -L-COOH, or -LC(=O)OC1-C6 alkyl, wherein the heterocyclyl and the aryl portion of $-L-NR^5C(O)$-aryl and the heterocyclyl portion of -L-heterocyclyl and the cycloalkyl portion of the -L-cycloalkyl may be optionally substituted with one or more R^6, and wherein the aryl or heteroaryl of the -L-aryl and the -L-heteroaryl may be optionally substituted with one or more R^7;

each L is independently a C1 – C4 alkylene optionally substituted with hydroxy, C1 – C4 hydroxyalkyl or heteroaryl;

R^3 is aryl or heteroaryl, wherein the aryl or the heteroaryl is optionally substituted with one or more R^8;

R^4 is hydrogen, halogen or C1 – C3 alkyl;

each R^5 is independently hydrogen or C1 – C3 alkyl;

each R^6 is independently halogen, hydroxy, C1 - C3 hydroxyalkyl, C1 – C3 alkyl, C1 - C3 haloalkyl, C1-C3 alkoxy, cyano, -Q-phenyl, -Q-phenylSO_2F, -NHC(O)phenyl, -NHC(O)phenylSO_2F, C1-C3 alkyl substituted pyrazolyl, araC1-C3 alkyl-, tert-butyldimethylsilyloxyCH_2- , -$N(R^5)_2$, (C1-C3 alkoxy)C1-C3 alkyl-, (C1-C3 alkyl)C(=O), oxo, (C1-C3 haloalkyl)C(=O)-, -SO_2F, (C1-C3 alkoxy)C1-C3 alkoxy, -$CH_2OC(O)N(R^5)_2$, -CH_2NHC(O)OC1-C6 alkyl, -$CH_2NHC(O)N(R^5)_2$, -CH_2NHC(O)C1-C6 alkyl, -CH_2(pyrazolyl), -CH_2NHSO_2C1-C6 alkyl, -CH_2OC(O)heterocyclyl, -$OC(O)N(R^5)_2$, -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl), -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl(C1-C3 alkyl)$N(CH_3)_2$, -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl or -OC(O)heterocyclyl, -CH_2heterocyclyl, wherein the phenyl of -NHC(O)phenyl or -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl is optionally substituted with -C(O)H or OH and wherein the heterocyclyl of -CH_2heterocyclyl is optionally substituted with oxo;

Q is a bond or O;

each R^7 is independently halogen, hydroxy, HC(=O)-, C1 – C4 alkyl, C1 – C4 alkoxy, C1 – C4 haloalkyl, C1 – C4 hydroxyalkyl, or -$N(R^5)_2$; and

each R^8 is independently halogen, cyano, hydroxy, C1 - C4 alkyl, -S-C1 - C3 alkyl, C2 – C4 alkenyl, C2 – C4 alkynyl, C2 – C4 hydroxyalkynyl, C1-C3 cyanoalkyl , triazolyl, C1 - C3 haloalkyl, -O- C1 - C3 haloalkyl, -S- C1 - C3 haloalkyl, C1-C3 alkoxy, hydroxyC1-C3 alkyl, -$CH_2C(=O)N(R^5)_2$, -C3-C4 alkynyl$(NR^5)_2$, -$N(R^5)_2$, deuteroC2-C4 alkynyl, (C1-C3 alkoxy)haloC1-C3 alkyl-, or C3-C6 cycloalkyl wherein said C3-C6 cycloalkyl is optionally substituted with halogen or C1-C3 alkyl, in the manufacture of a medicament for treating cancer in a subject in need thereof.

2. The use of claim 1, wherein R^1 is hydrogen, halogen, hydroxy, C1 – C3 alkyl, C1- C3 cyanoalkyl, hydroxyalkyl, HC(=O)-, -CO_2R^5, or -$CO_2N(R^5)_2$.

3. The use of claim 2, wherein R^5 is hydrogen, C1 – C3 alkyl or C1 - C3 cyanoalkyl.

4. The use of claim 2, wherein Y is O and R^2 is C1 – C6 alkyl or -L-heterocyclyl optionally substituted with one or more R^6.

5. The use of claim 4, wherein the C1 – C6 alkyl is methyl, ethyl, isopropyl or isobutyl.

6. The use of claim 4, wherein L is methylene and the heterocyclyl is hexahydro-1*H*-pyrrolizinyl, hexahydro-3H-pyrrolizin-3-one, hexahydro-1H-pyrrolo[2,1-c][1,4]oxazinyl, octahydroindolizinyl, hexahydropyrrolizine 4(1H)-oxide, azetidinyl, pyrrolidinyl, pyrrolidin-2-one, oxetanyl, piperidinyl, 1-azabicyclo[2.2.1]heptanyl, morpholinyl, oxa-5-azabicyclo[2.2.1]heptan-5-yl, thiopyranyl, 6-oxa-2λ^2-azaspiro[3.4]octanyl, 7-oxa-2λ^2-azaspiro[3.5]nonanyl, 2',3'-dihydrospiro[cyclopropane-1,1'-indenyl], (2S)-1-azabicyclo[2.2.1]heptan-2-yl, or tetrahydrofuranyl, each optionally substituted with one or more R^6.

7. The use of claim 6, wherein heterocyclyl is:

hexahydro-1*H*-pyrrolizinyl, preferably wherein heterocyclyl is hexahydro-1*H*-pyrrolizinyl substituted with one R^6, wherein R^6 is halogen, hydroxy, C1 - C3 hydroxyalkyl, C1 - C3 haloalkyl, C1 – C3 alkyl, C1 - C3 alkoxy, phenyl or pyrazolyl, preferably wherein the halogen is fluorine;

hexahydro-1*H*-pyrrolizinyl further substituted with two additional R^6 groups, wherein the two additional R^6 groups are independently C1 – C3 alkyl;

azetidinyl substituted with one R6, wherein R6 is C1 – C3 alkyl;

pyrrolidinyl substituted with one R^6, wherein R^6 is hydroxalkyl, haloalkyl, C1 – C3 alkyl, alkoxy, araC1-C3 alkyl, -Q-phenyl and -NHC(O)phenyl, and wherein the aryl portion of the araC1-C3 alkyl or the phenyl portion of the -Q-phenyl and -NHC(O)phenyl are each optionally substituted with one or more R^6, preferably wherein the phenyl group of the -Q-phenyl or the -NHC(O)phenyl is substituted with SO_2F;

pyrrolidinyl substituted with two R^6 groups wherein one R^6 is C1 – C3 alkyl and the other R^6 is C1-C3 alkoxy or halogen;

pyrrolidin-2-one substituted with one R^6, wherein R^6 is C1 – C3 alkyl; or

piperidinyl substituted with one R^6, wherein R^6 is acetyl, (C1-C3 alkoxy)C1-C3 alkoxy, or -C(O)CH_2Cl.

8. The use of claim 4, wherein Y is O, L is ethylene or propylene and the heterocyclyl is morpholinyl or oxa-5-azabicyclo[2.2.1]heptan-5-yl.

9. The use of claim 2, wherein Y is O and R^2 is:

-L-heteroaryl, wherein the heteroaryl portion is optionally substituted with one or more R^7, preferably wherein L is methylene or ethylene and the heteroaryl is pyridyl, pyrazolyl, imidazolyl, triazolyl, 4,5,6,7-tetrahydro-1*H*-indazolyl, benzimidazolyl, imidazo[1,2-a]pyridinyl, or pyrimidinyl, each optionally substituted with one or more R^7, preferably wherein the heteroaryl is:

pyridyl substituted with one R^7, wherein R^7 is halogen, C1 – C4 alkyl, -N(R^5)$_2$, or C1-C4 alkoxy;

pyrazolyl substituted with one R^7, wherein R^7 is C1 – C4 alkyl or -N(R^5)$_2$;

imidazolyl substituted with one R^7, wherein R^7 is C1 – C4 alkyl, C1 – C4 haloalkyl, or C1 – C4 hydroxyalkyl; or

triazolyl substituted with one R^7, wherein R^7 is C1 – C4 alkyl;

-L-aryl, wherein the aryl portion is optionally substituted with one or more R^7;

-L-cycloalkyl, wherein the cycloalkyl portion is optionally substituted with one or more R^7;

-L-N(R^5)$_2$, preferably wherein L is ethylene and each R^5 is an independently selected C1 – C3 alkyl;

-L-NC(=NH)-NH_2, preferably L is ethylene or propylene;

-L-C1-C6 haloalkyl;

-L-OR^5;

-L-$(CH_2OR^5)(CH_2)_nOR^5$; or

-L-$NR^5C(O)$-aryl.

10. The use of claim 2, wherein R^3 is:

aryl optionally substituted with one or more R^8, preferably wherein the aryl is phenyl, naphthyl, 1,2,3,4-tetrahydronaphthalenyl and 2,3-dihydro-1H-indenyl, each optionally substituted with one or more R^8; or

heteroaryl optionally substituted with one or more R^8, preferably wherein the heteroaryl is isoquinolinyl, indazolyl, or benzo[d][1,3]dioxolyl optionally substituted with one or more R^8, more preferably wherein the heteroaryl is:

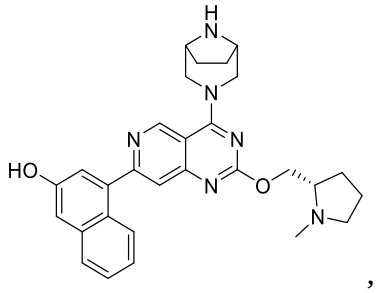
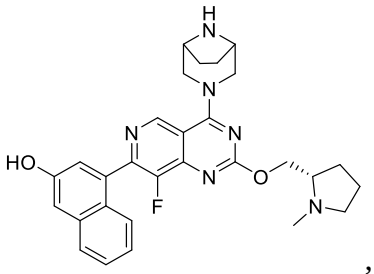
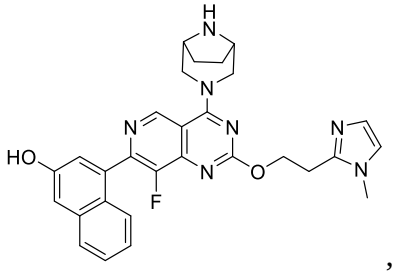
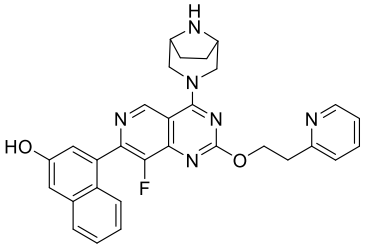
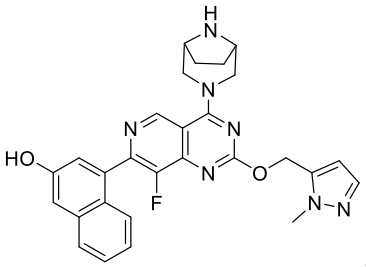
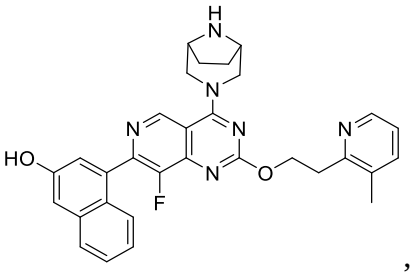
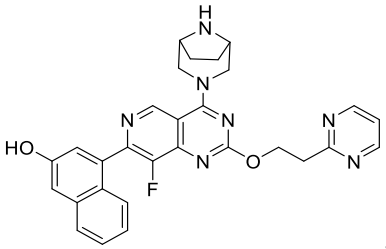
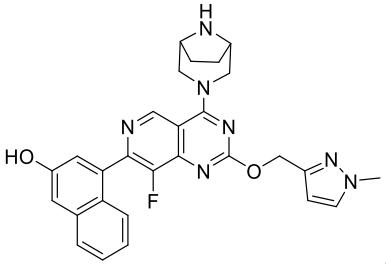
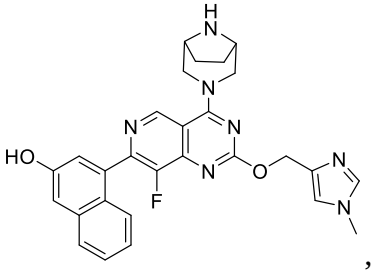
isoquinolinyl substituted with one or more R^8, wherein R^8 is halogen or C2 - C4 alkynyl;
indazolyl substituted with one R^8, wherein R^8 is C1 - C3 alkyl; or
benzo[d][1,3]dioxolyl substituted with two R^8 groups, wherein the R^8 groups are independently selected halogens.

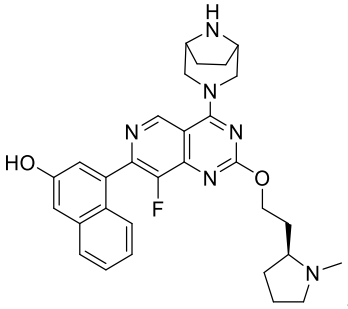
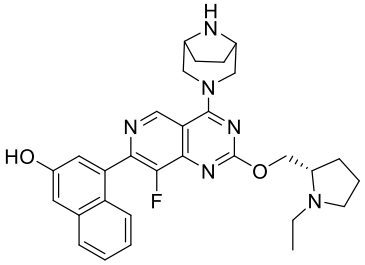
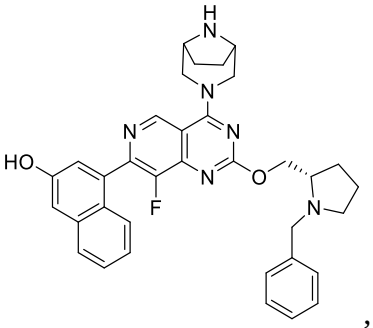
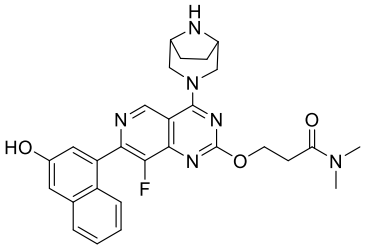
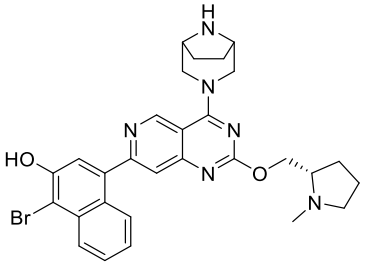
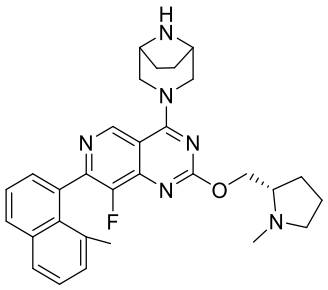
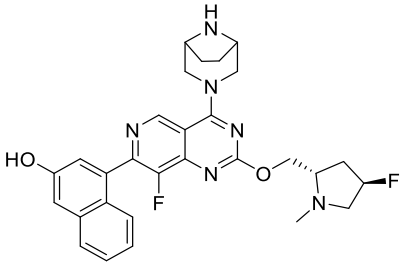
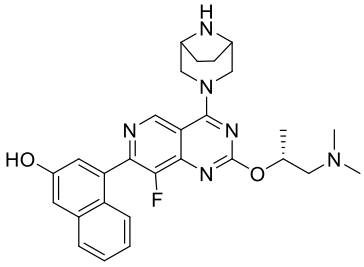
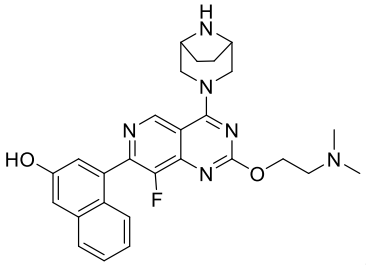
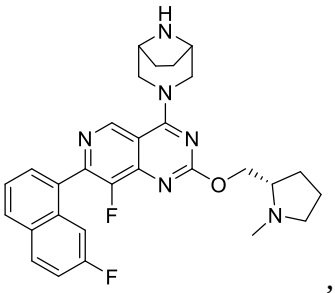
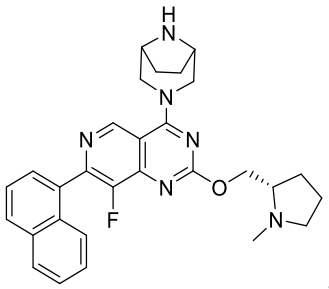
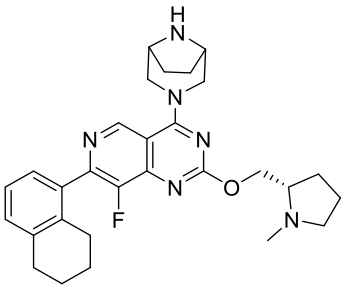
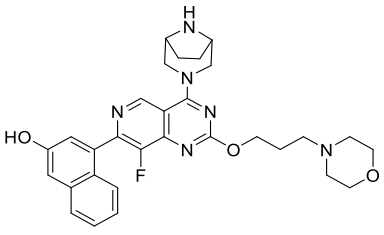
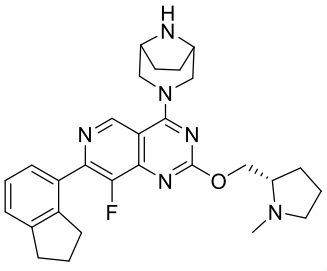
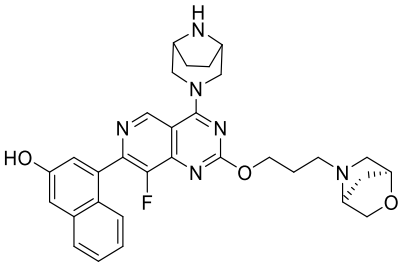
11. The use of claim 2, wherein R^4 is:

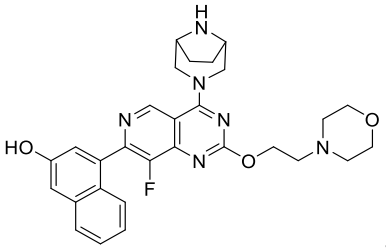
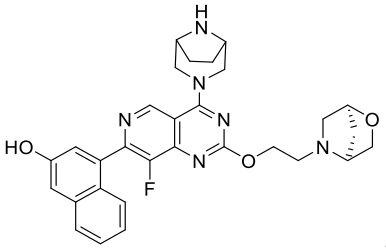
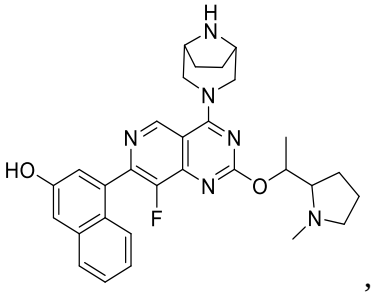
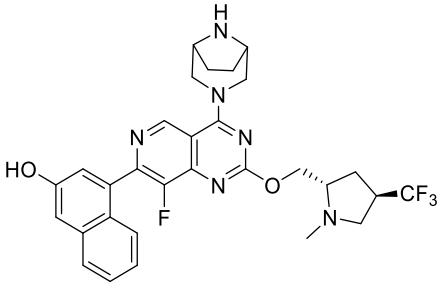
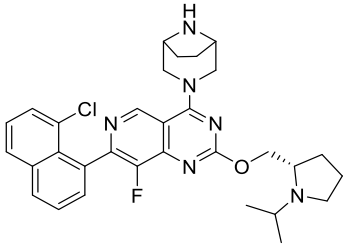
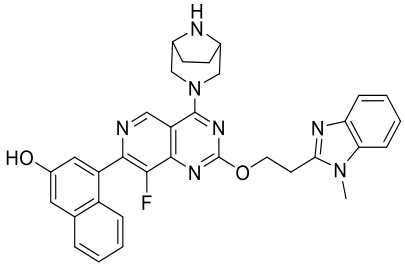
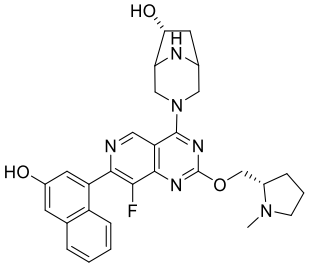
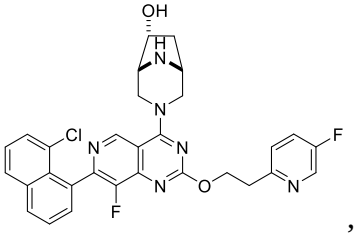
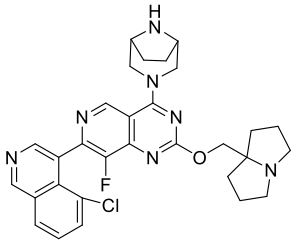
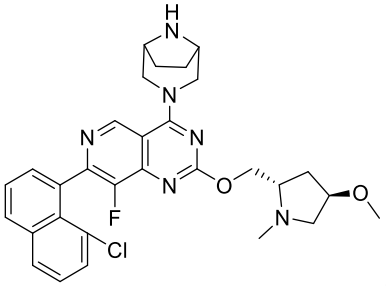
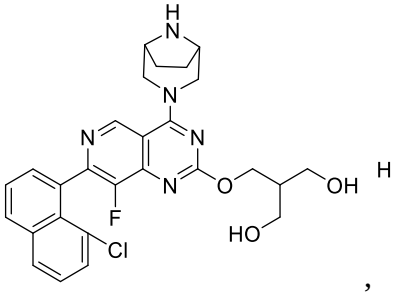
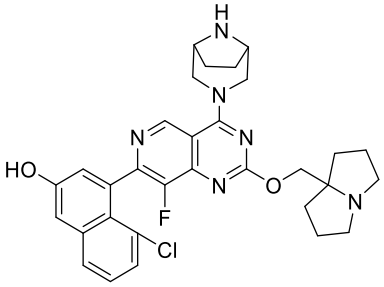
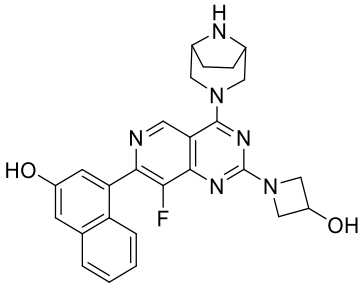
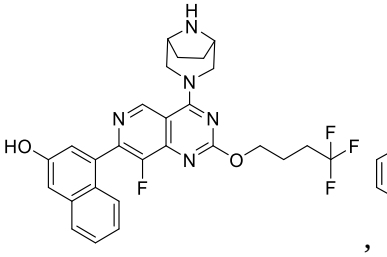
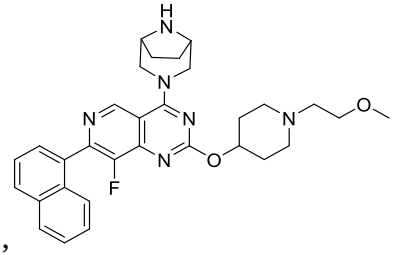
halogen preferably wherein the halogen is fluorine; or
C1 – C3 alkyl, preferably wherein the C1 – C3 alkyl is methyl.

12. The use of claim 1, wherein R^1 is hydrogen.

13. The use of claim 1, wherein the KRas G12D inhibitor is selected from the group consisting of:


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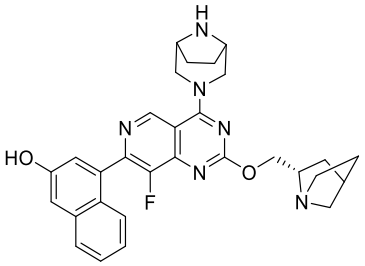
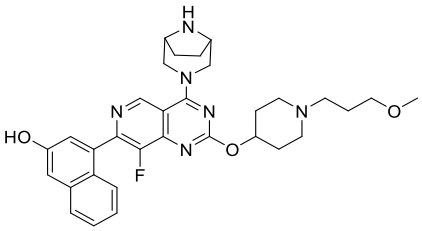
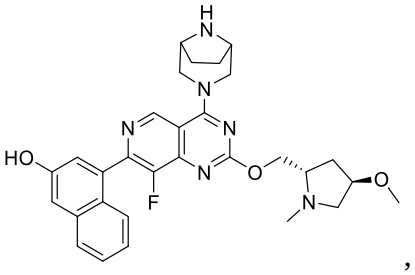
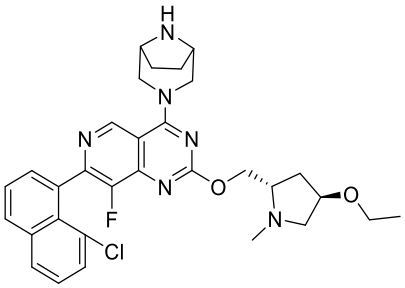
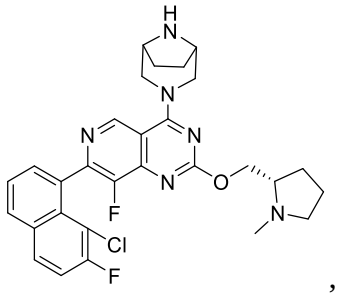
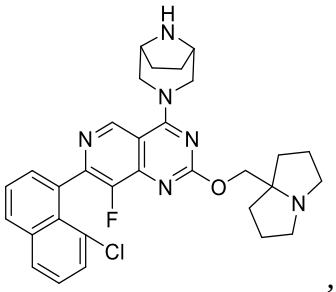
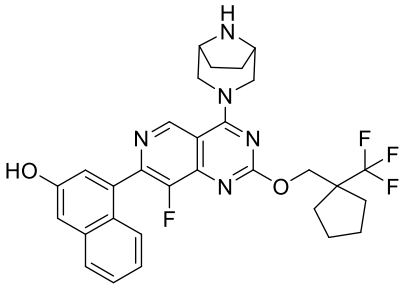
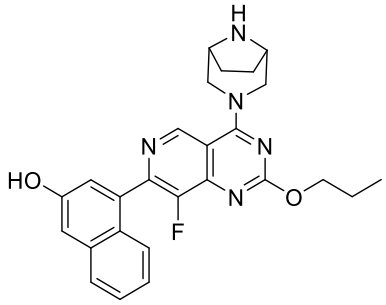
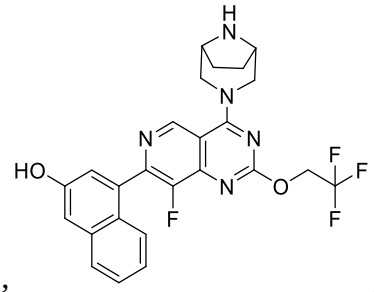
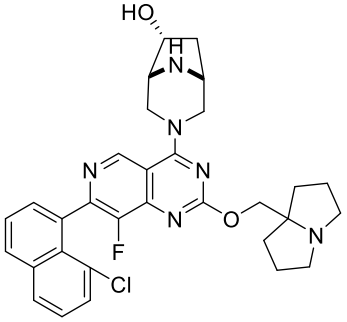
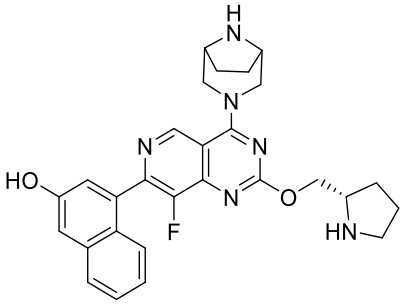
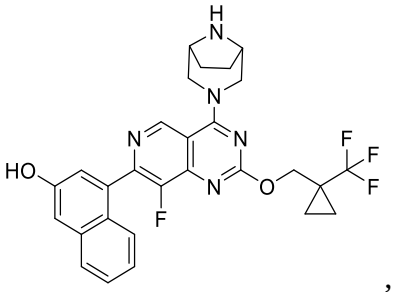
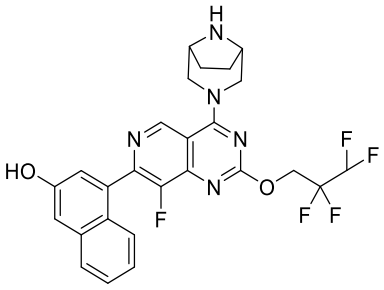
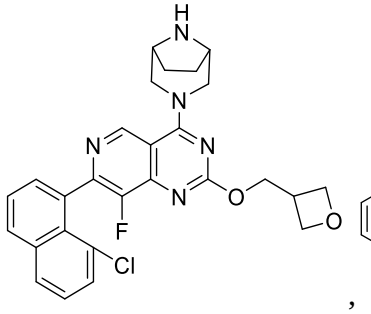
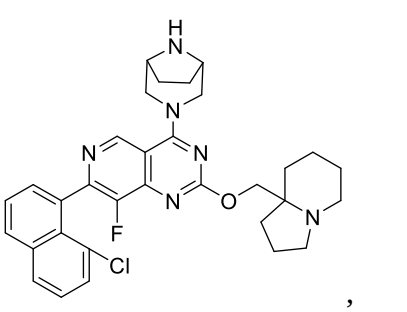

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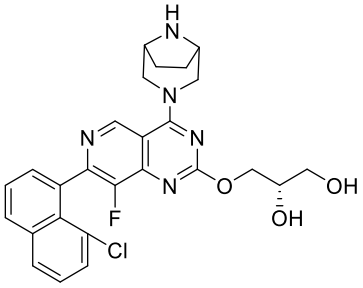
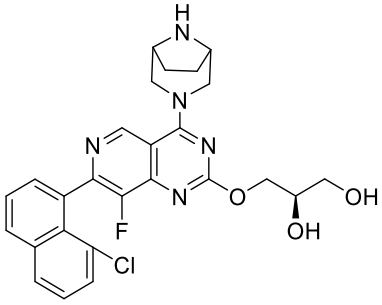
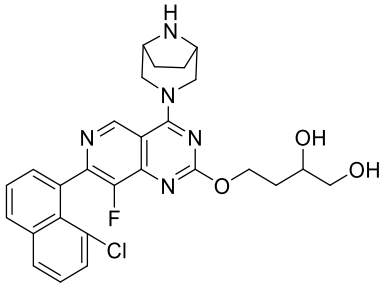
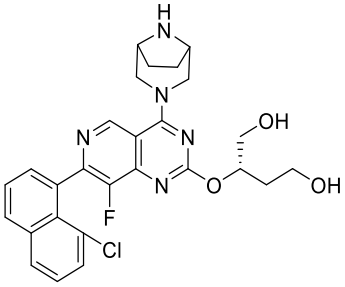
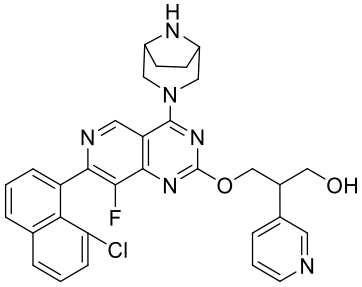
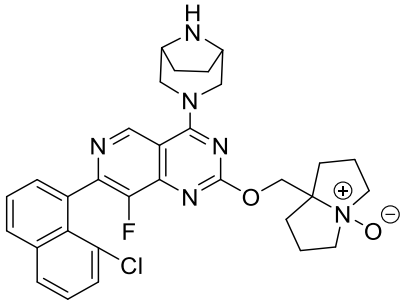
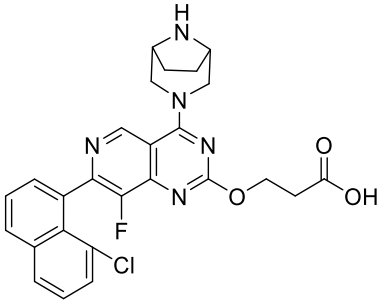
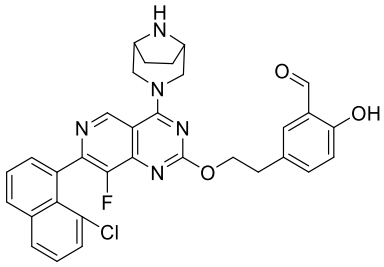
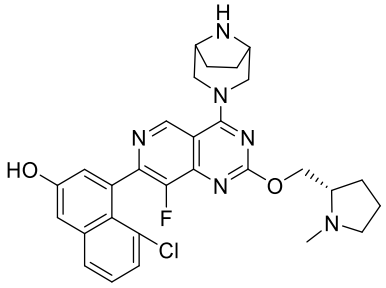
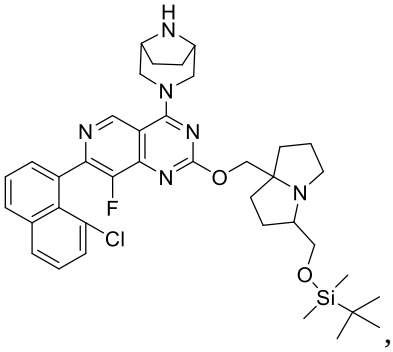
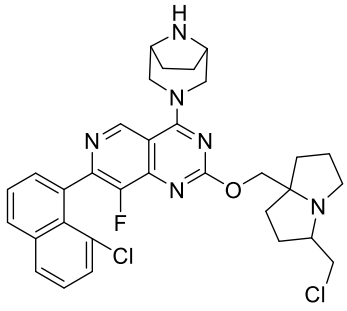
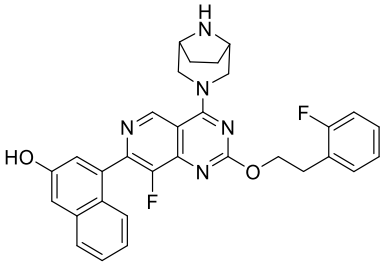
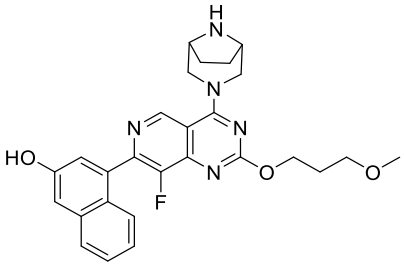
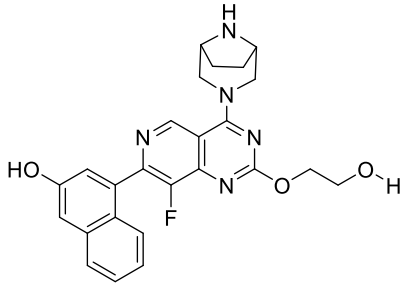
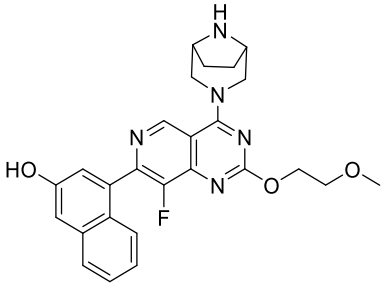
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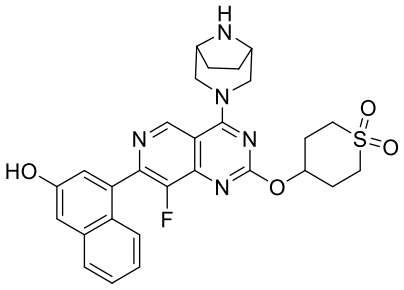
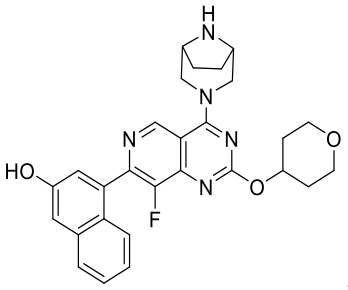
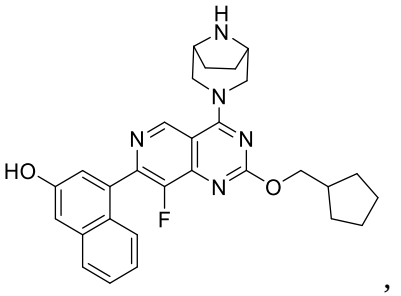
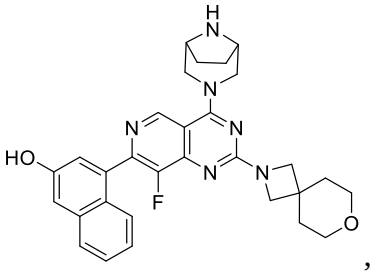
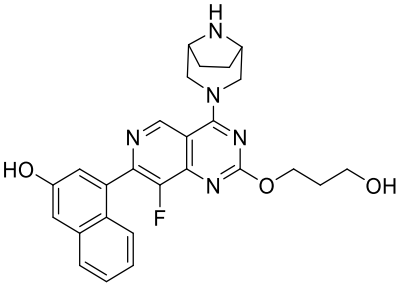
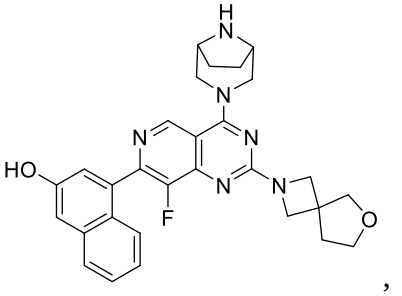
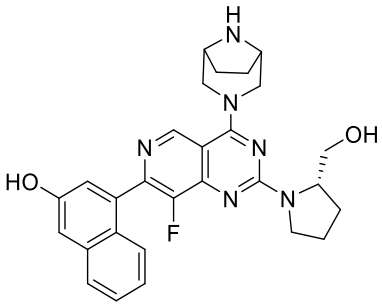
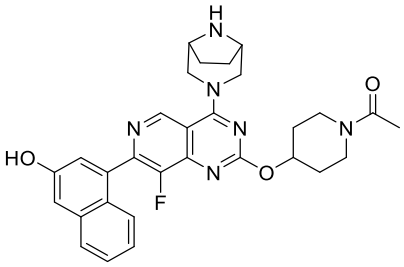
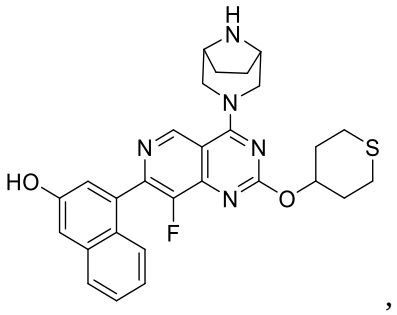
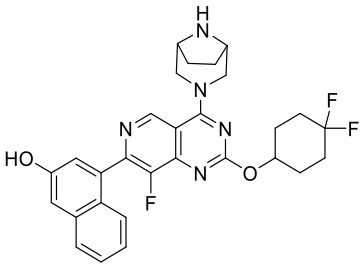
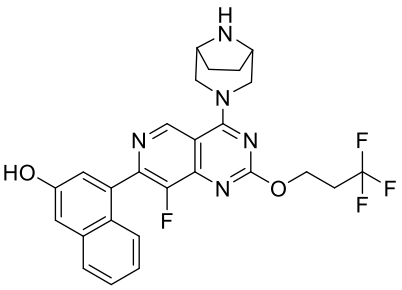
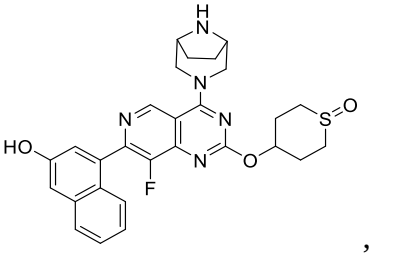
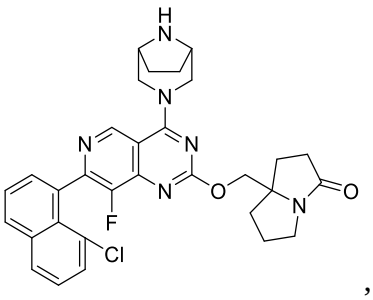
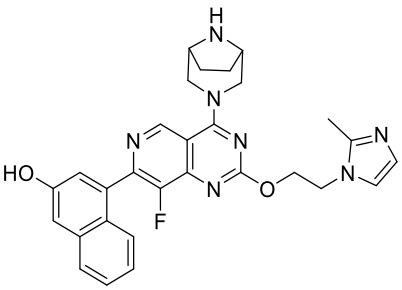
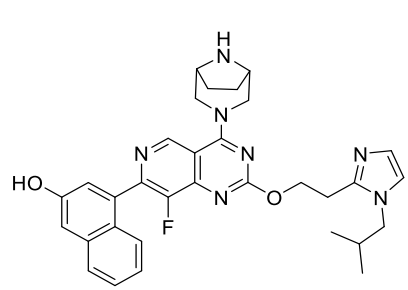

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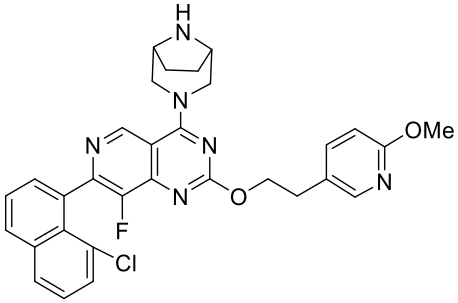
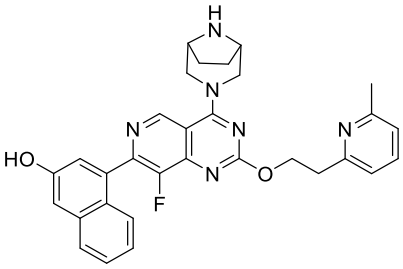
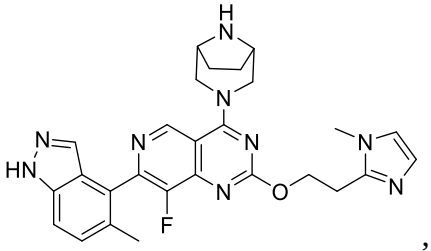
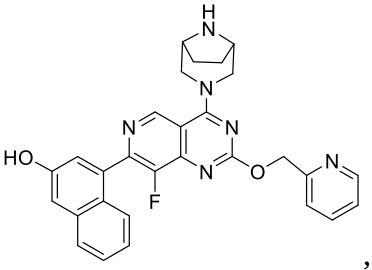
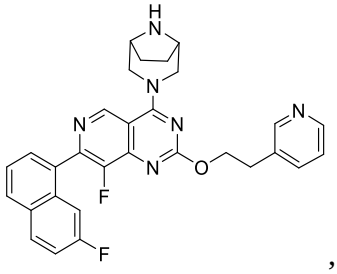
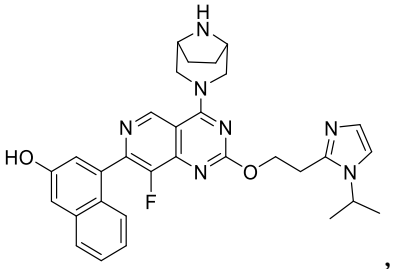
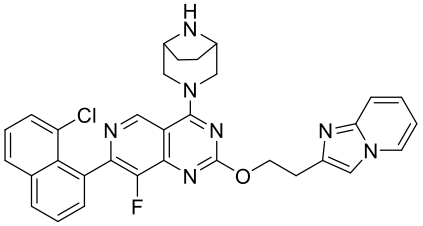
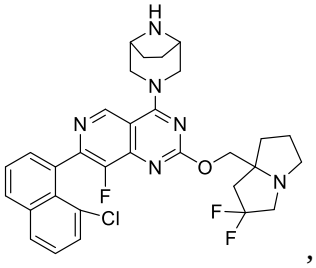
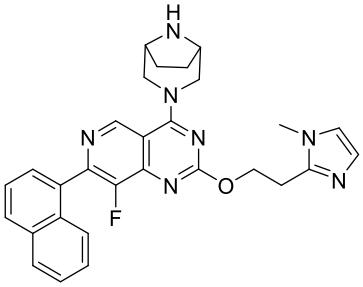
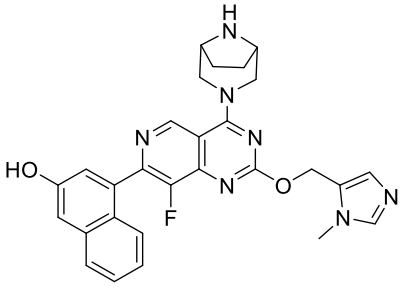
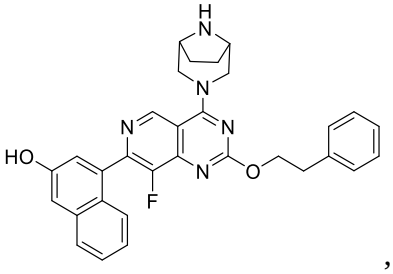
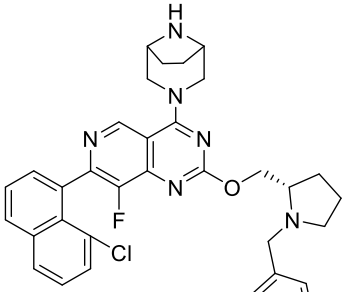
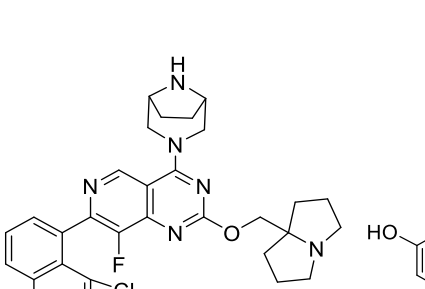
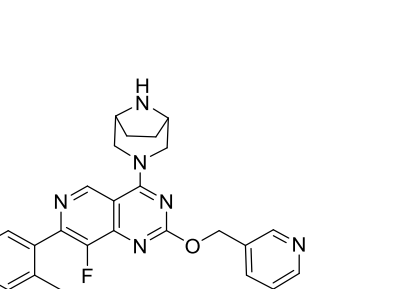

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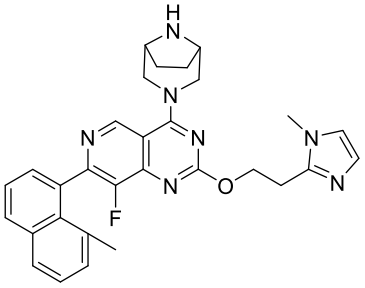
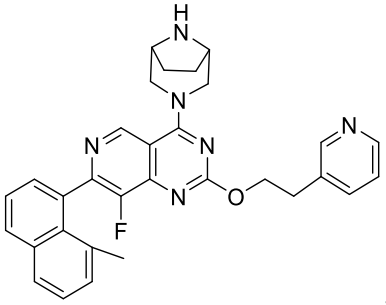
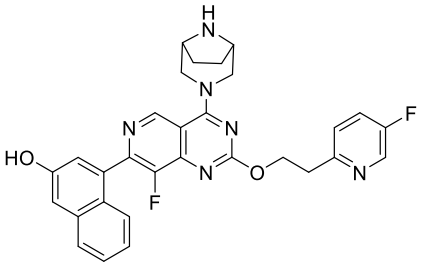
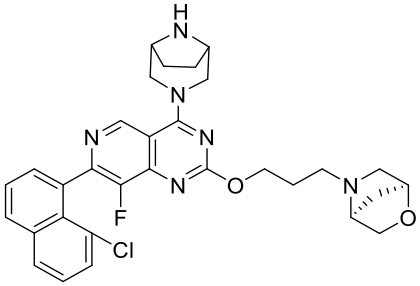
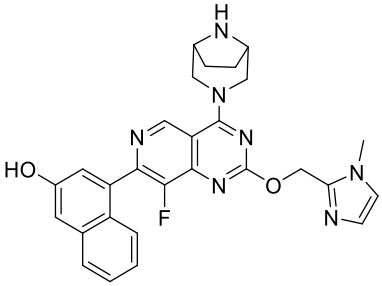
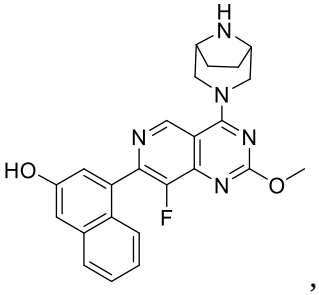
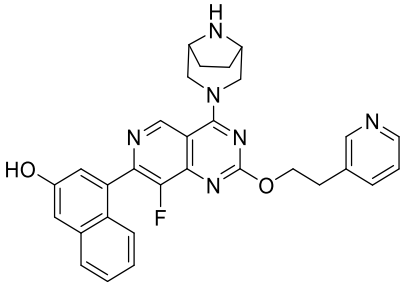
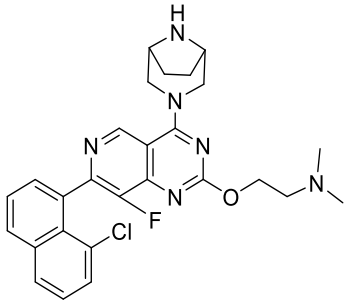
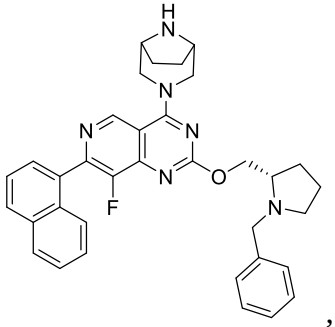
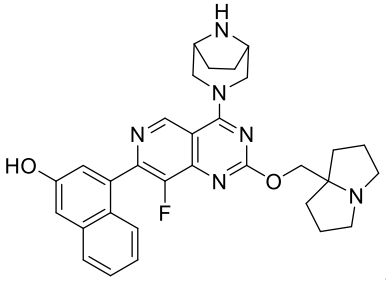
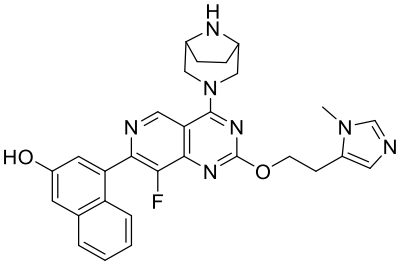
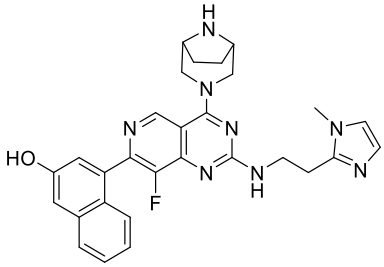
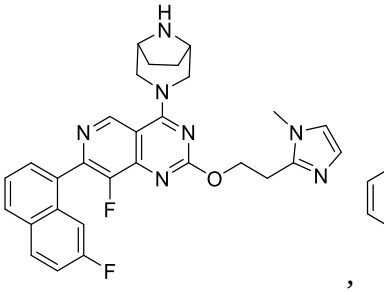
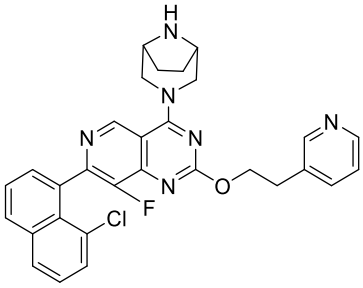
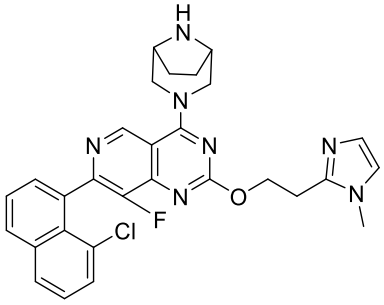
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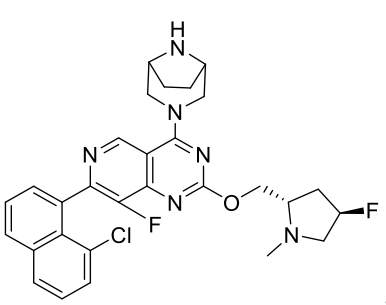
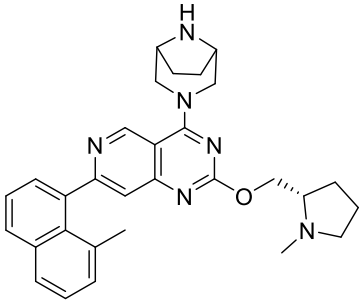
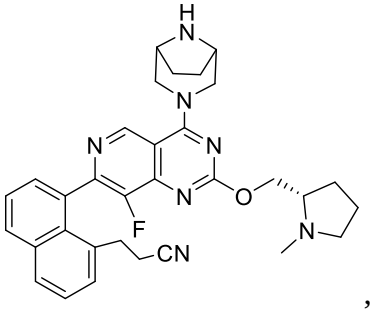
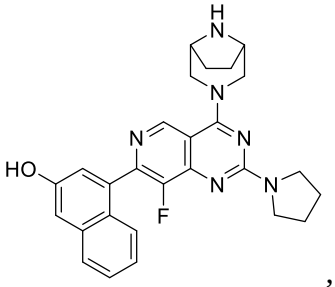
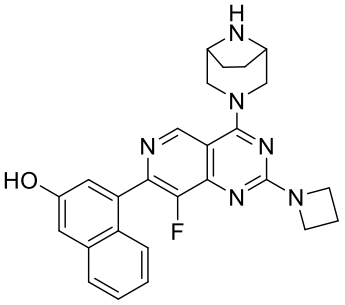
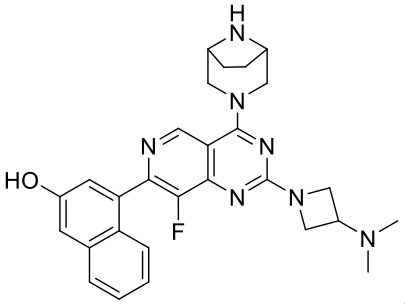
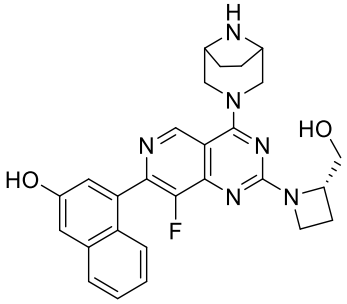
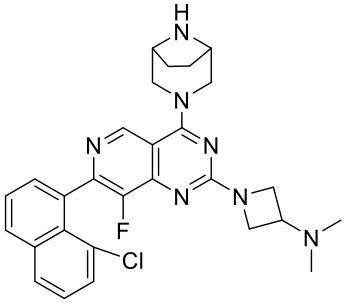
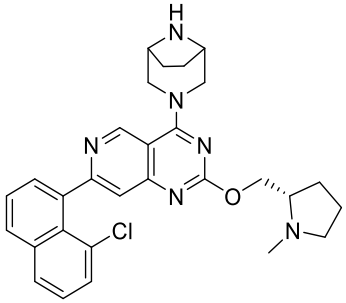
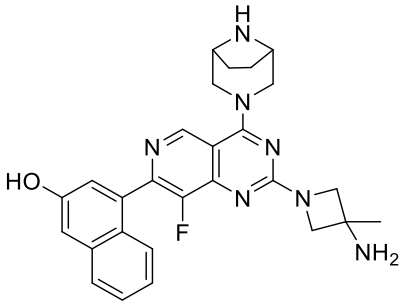
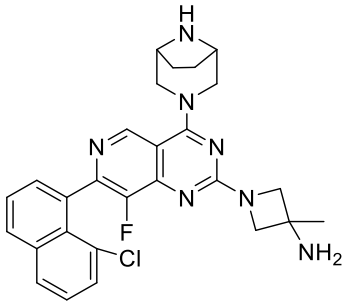
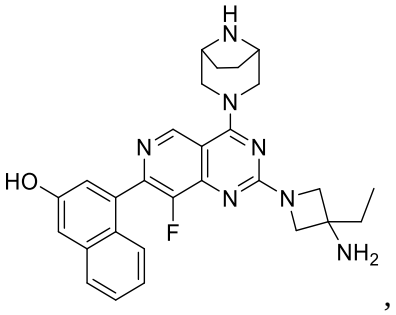
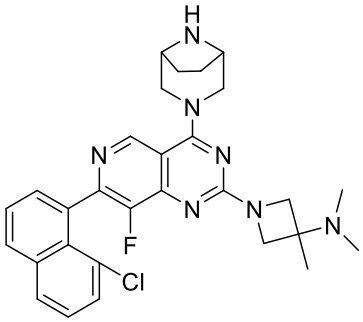
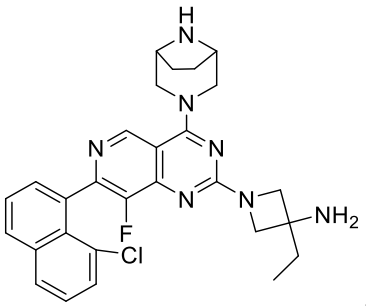
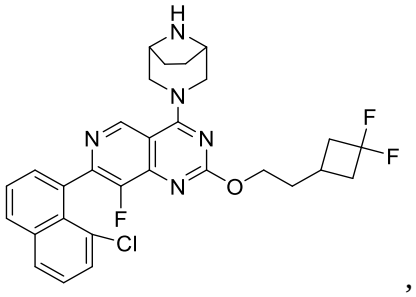

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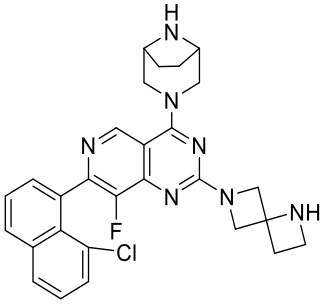
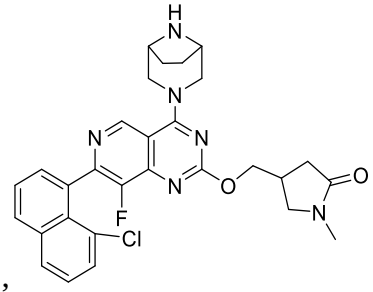
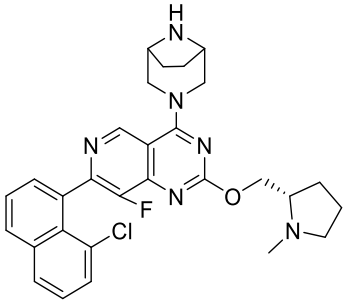
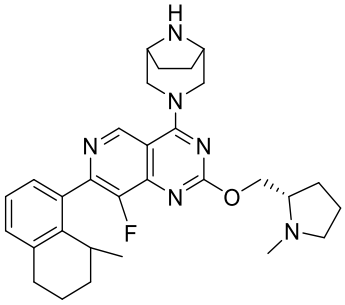
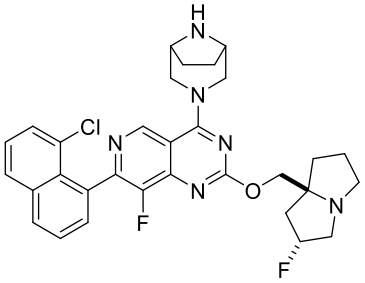
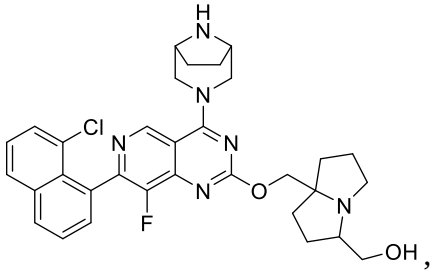
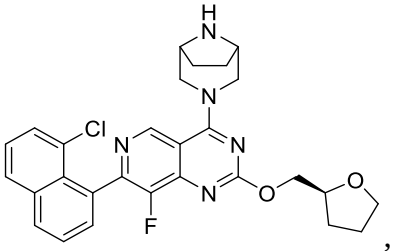
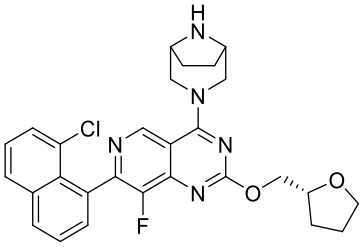
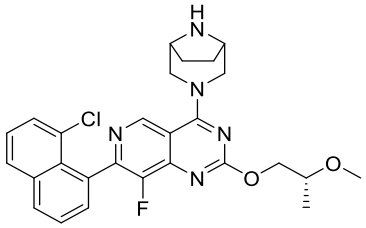
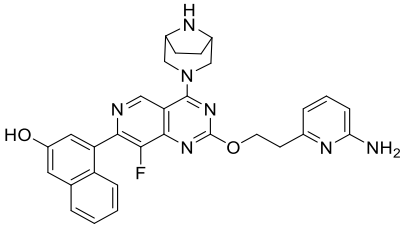
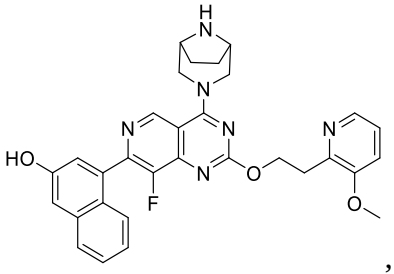
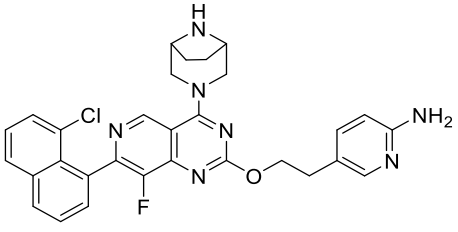
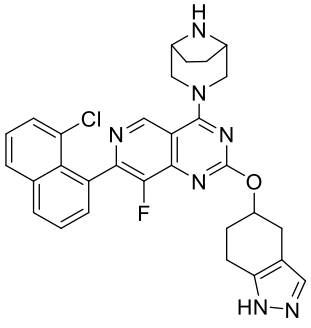
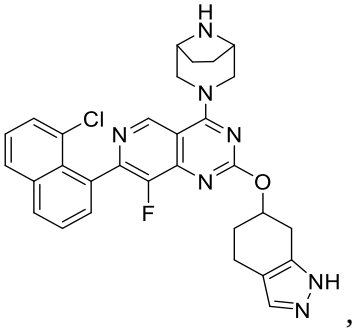
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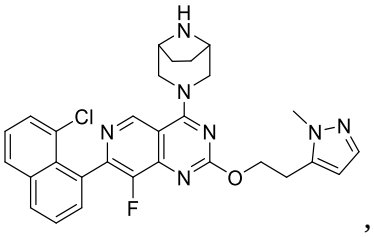
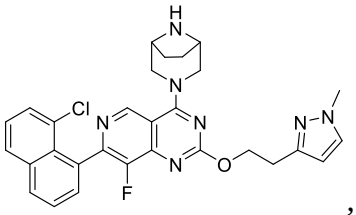
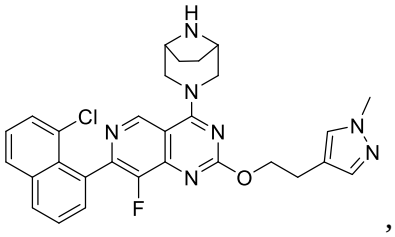
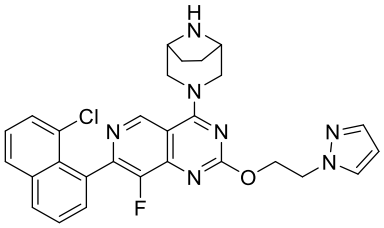
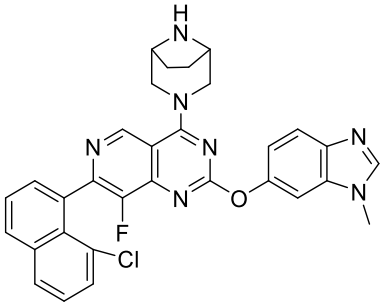
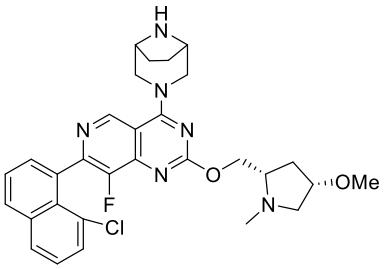
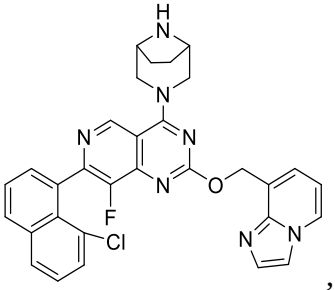
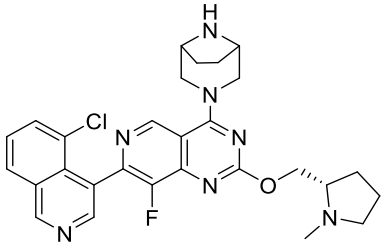
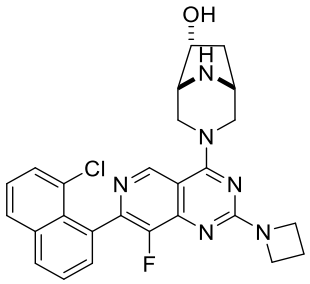
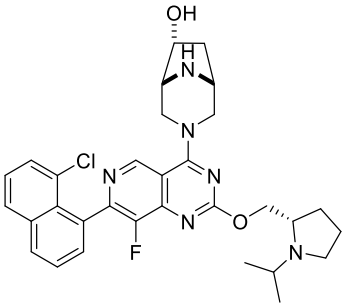
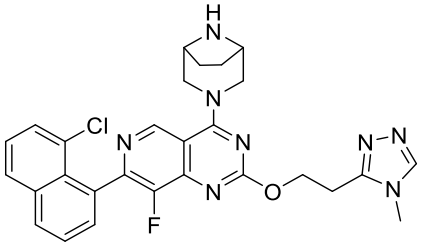
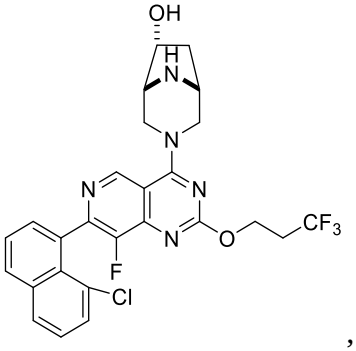
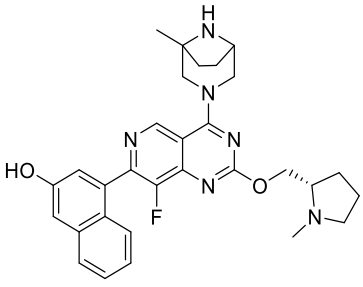
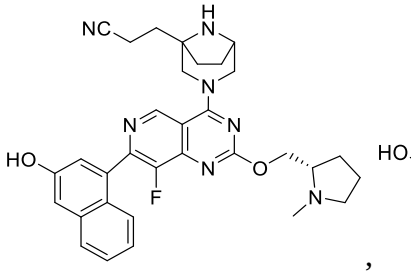
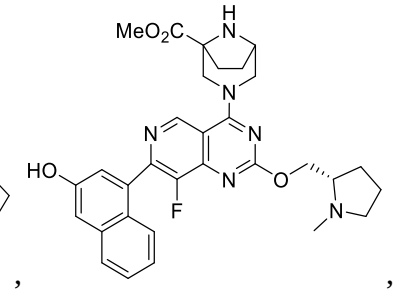
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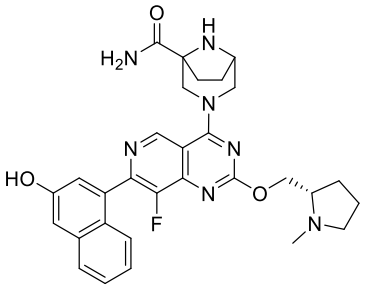
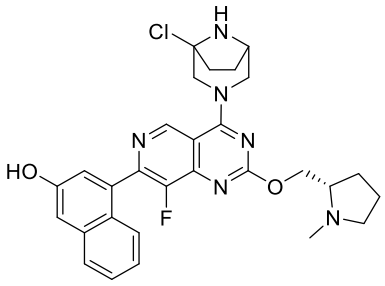
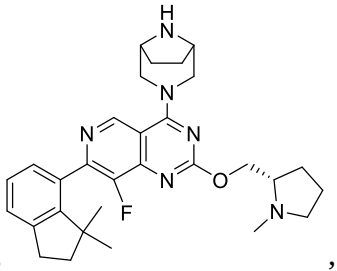
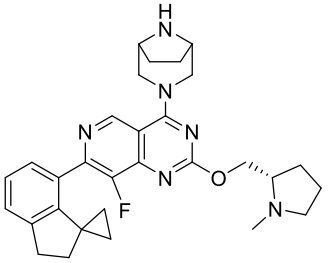
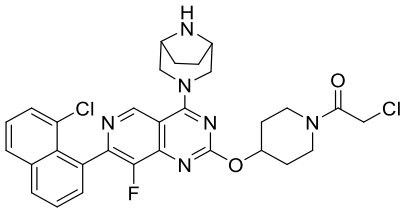
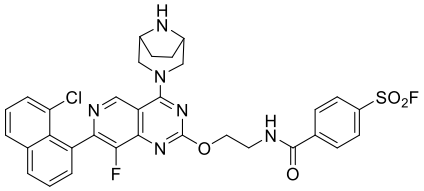
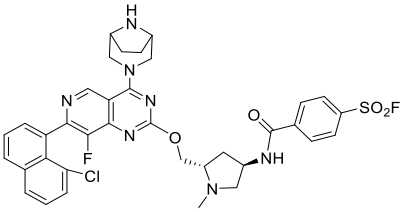
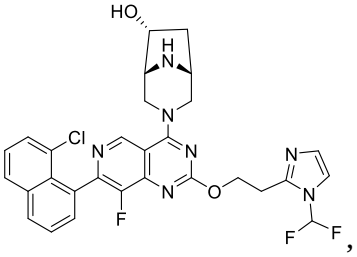
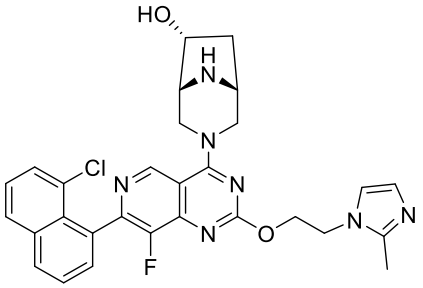
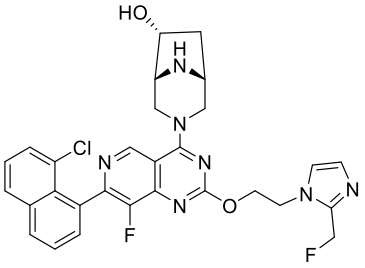
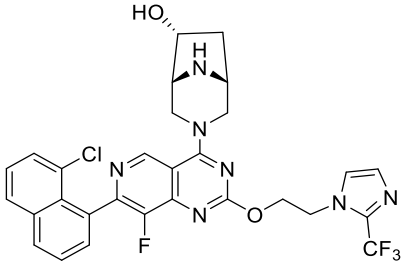
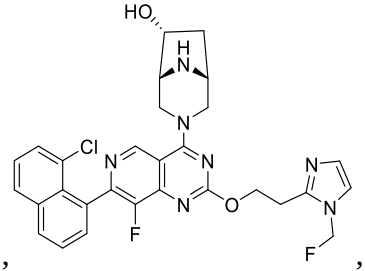
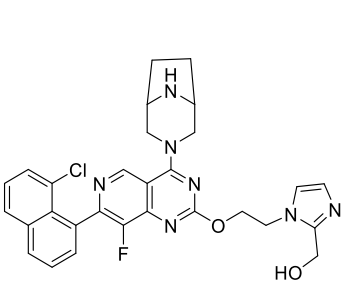
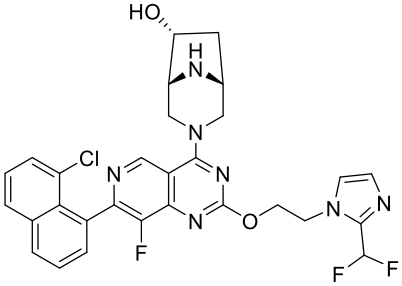
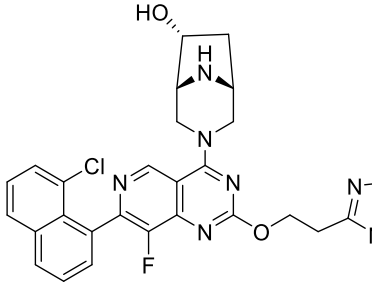

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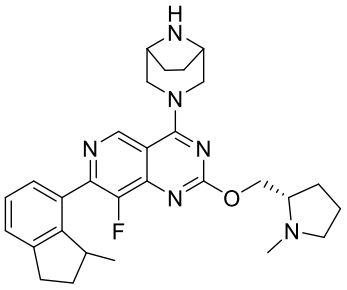
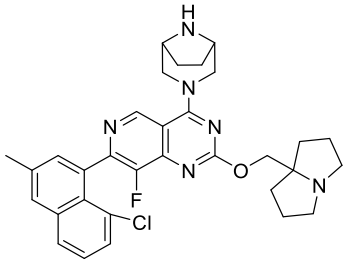
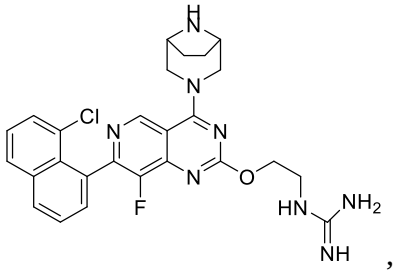
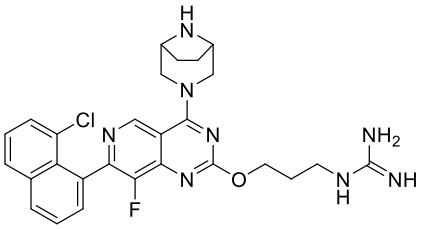
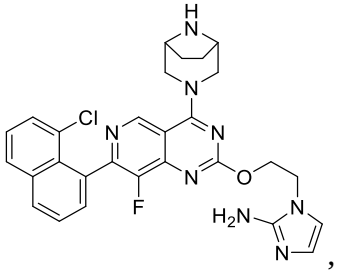
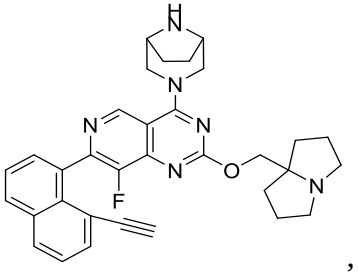
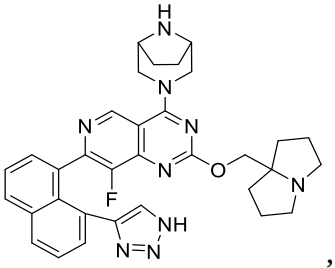
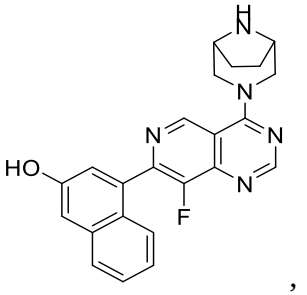
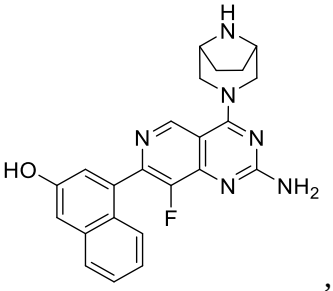
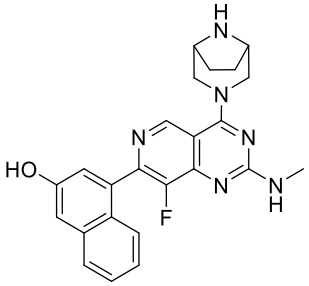
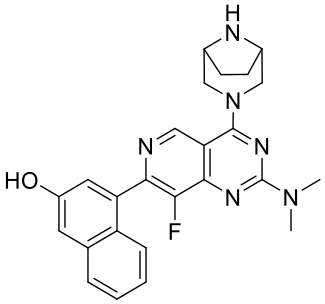
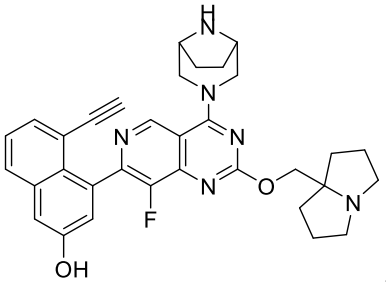
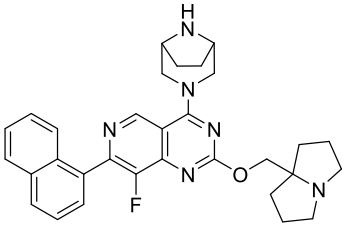
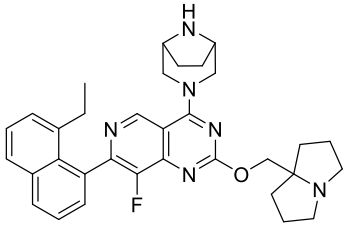
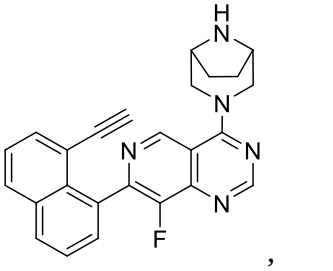
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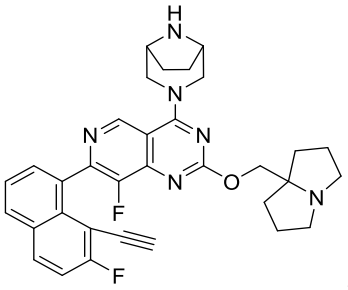
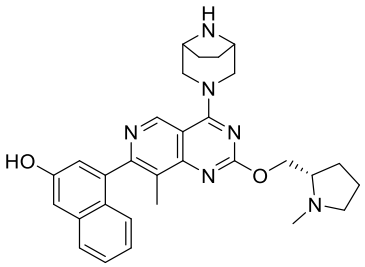
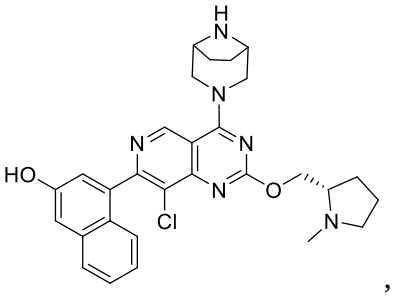
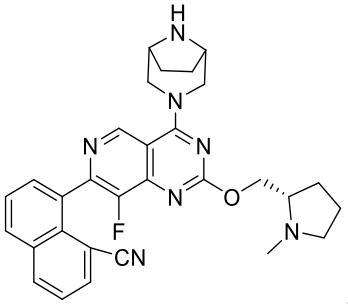
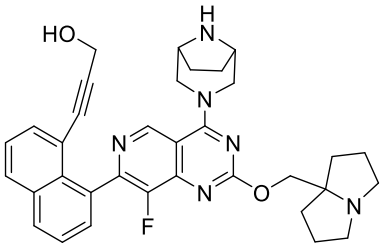
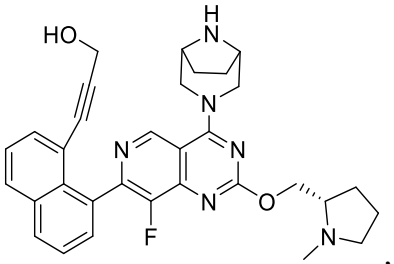
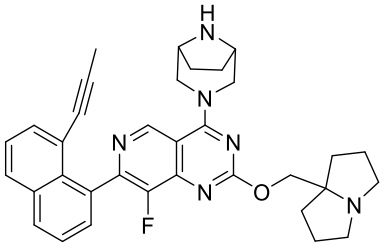
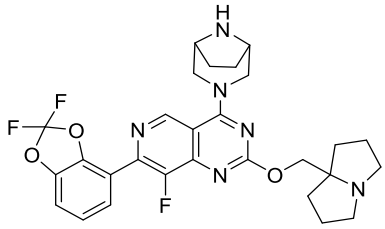
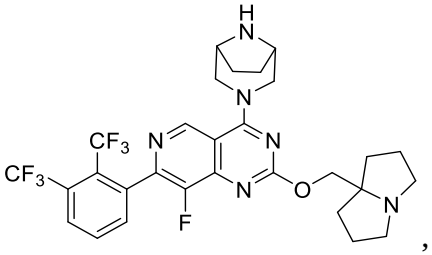
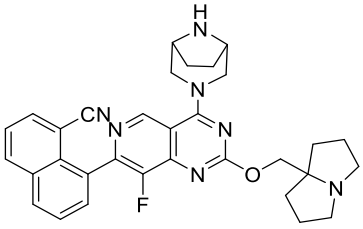
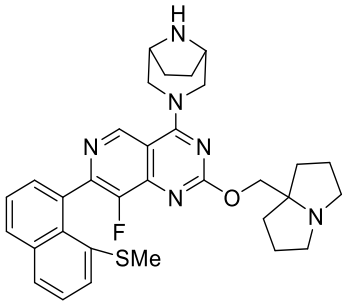
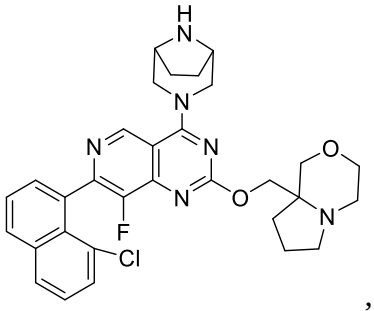
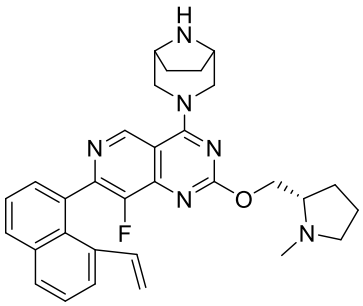
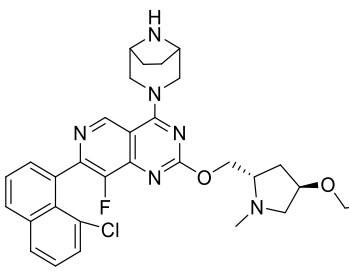
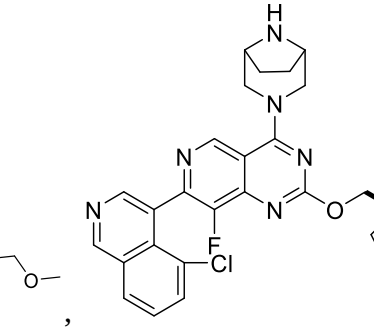

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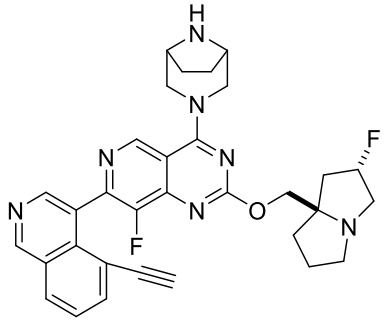
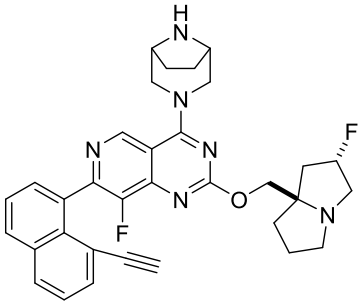
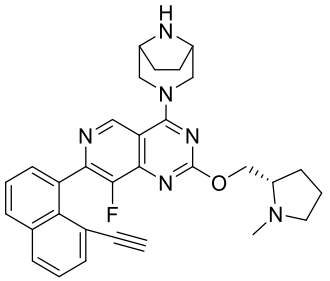
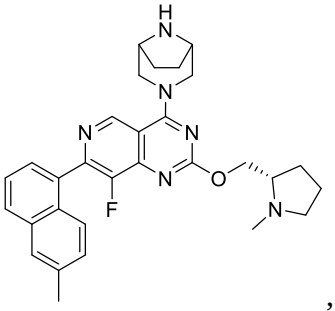
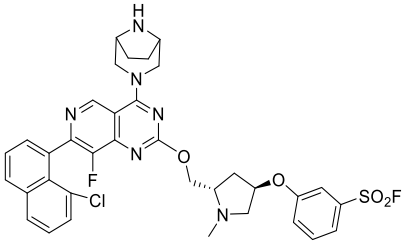
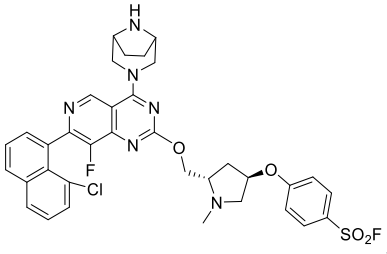
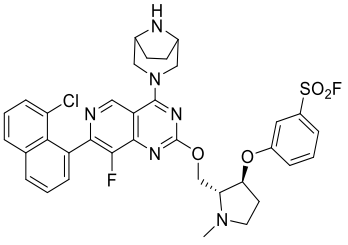
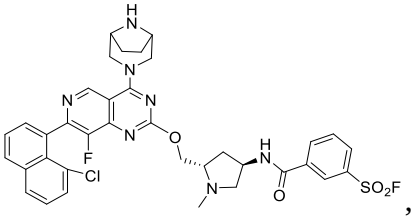
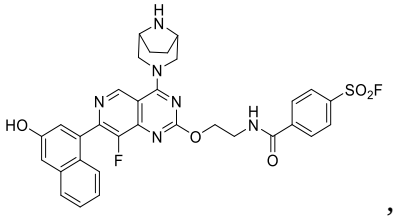
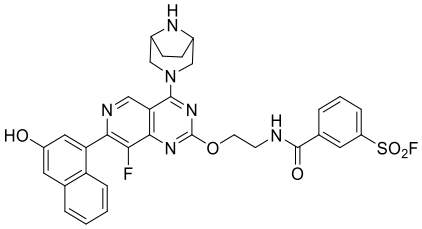
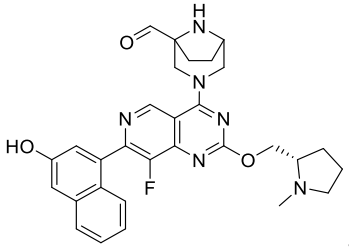
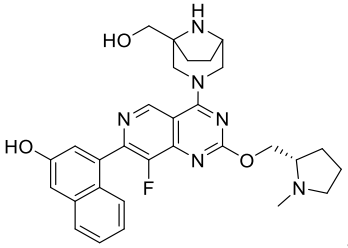
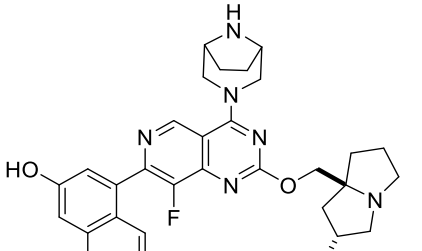
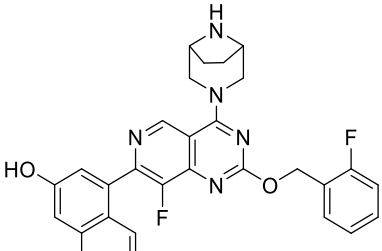
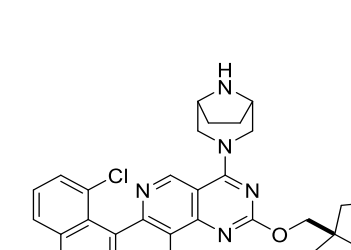
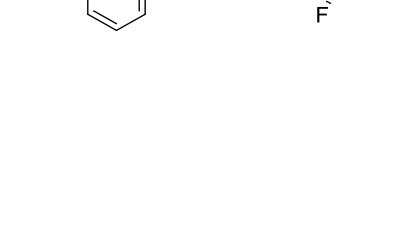
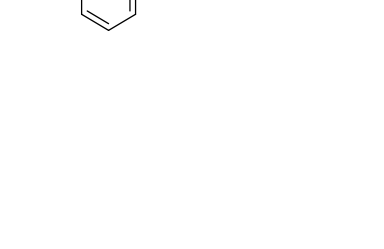
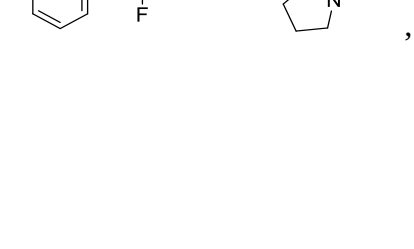

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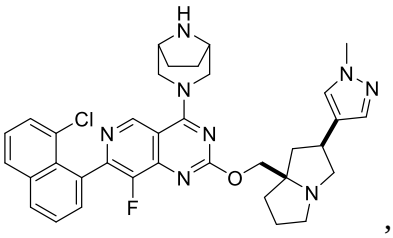
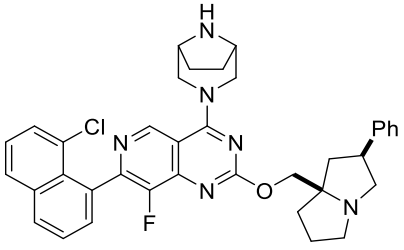
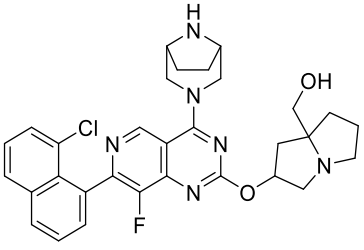

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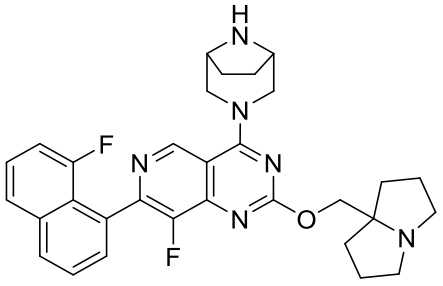
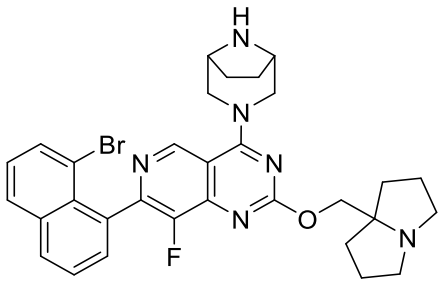
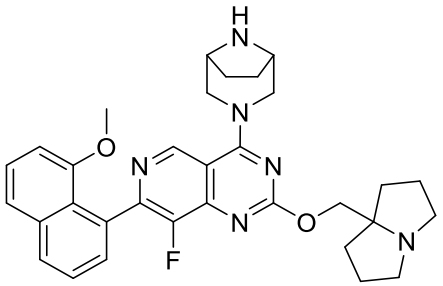
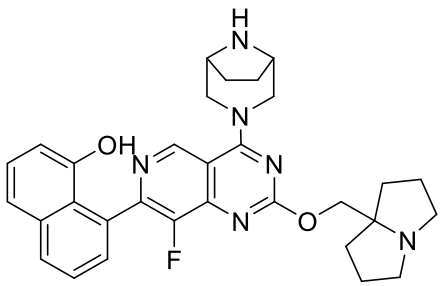
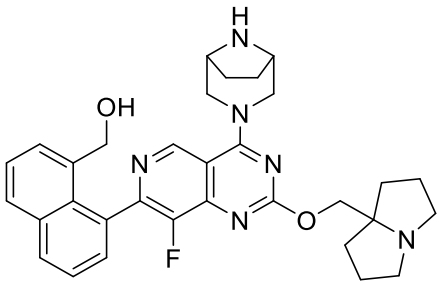
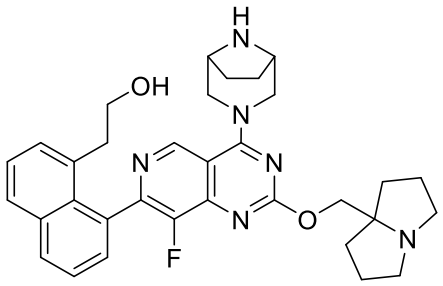
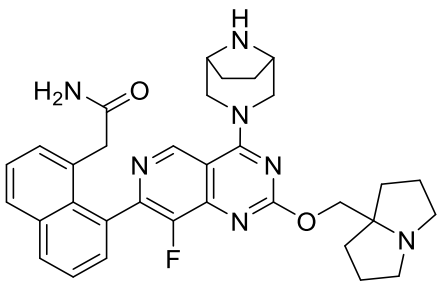
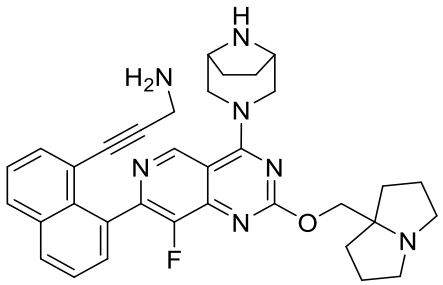
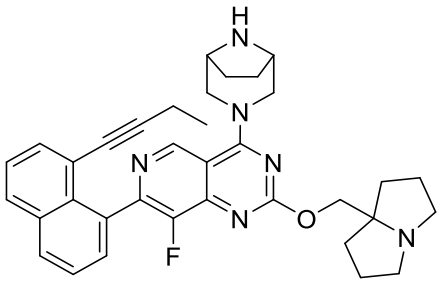
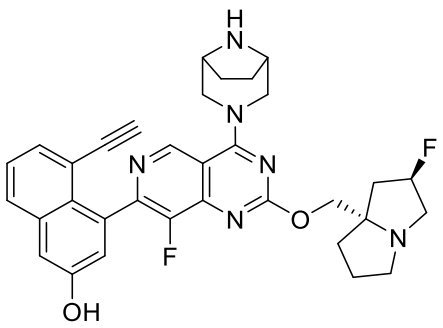
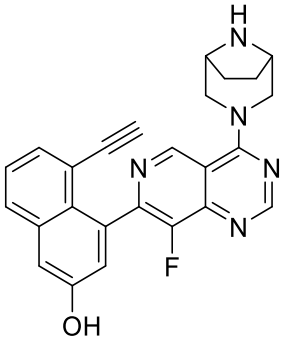
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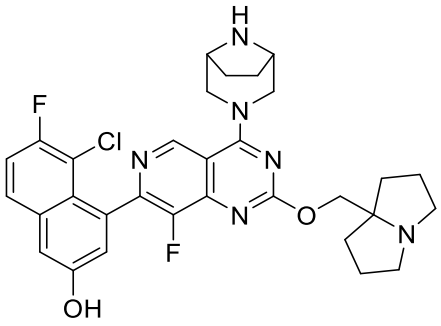
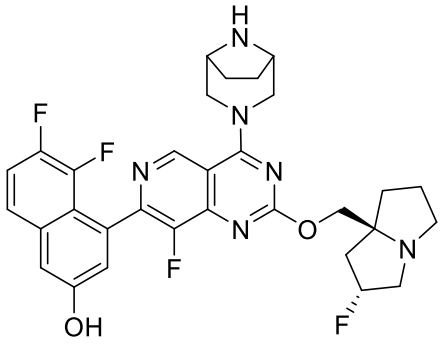
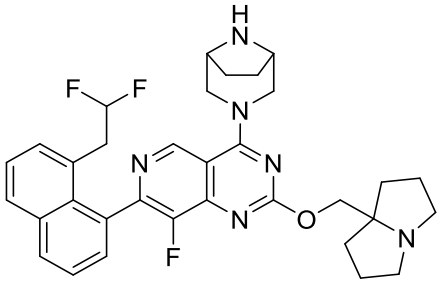
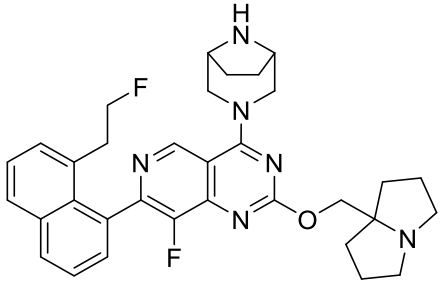
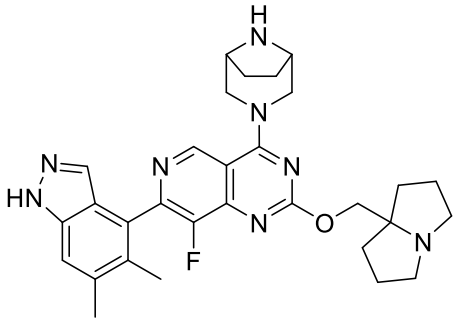
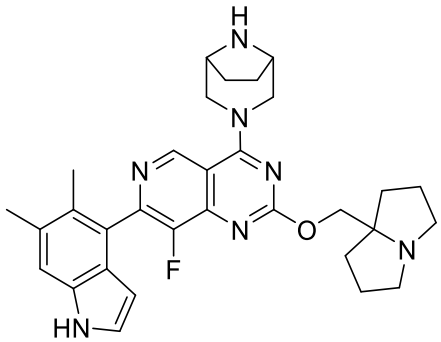
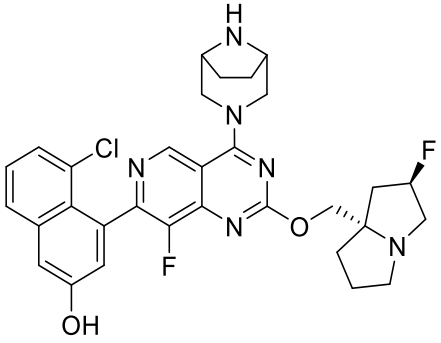
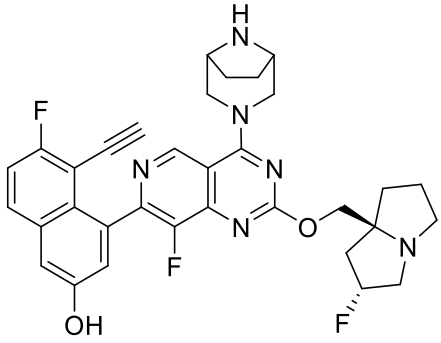
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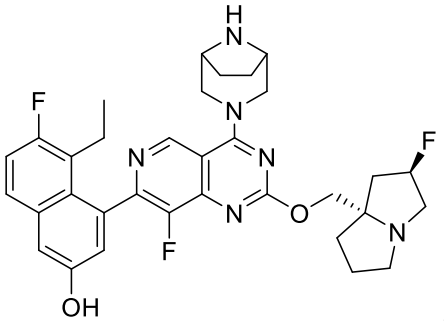
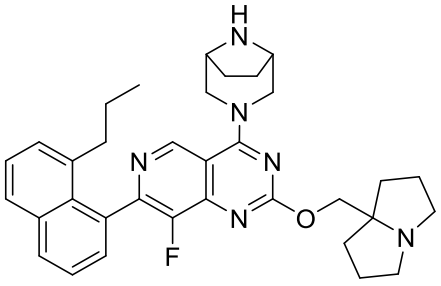
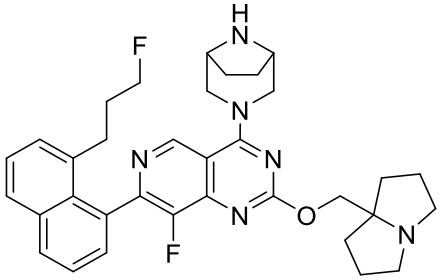
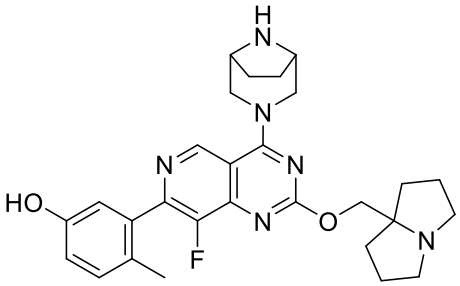
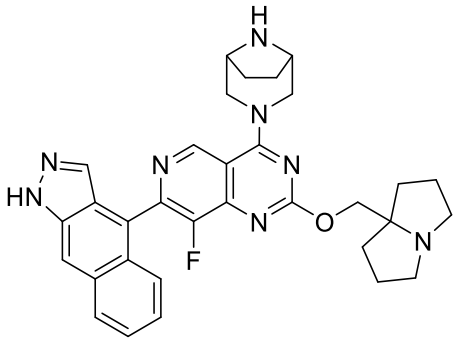
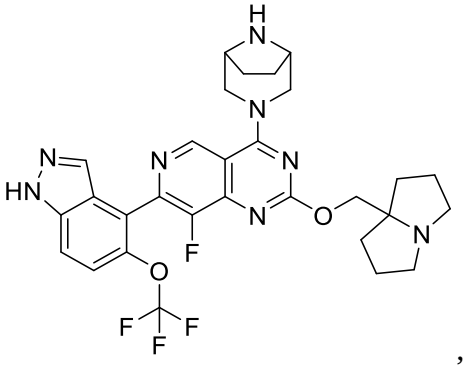
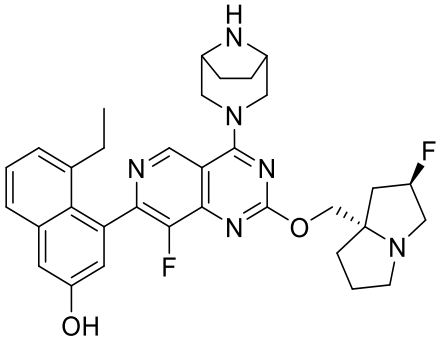
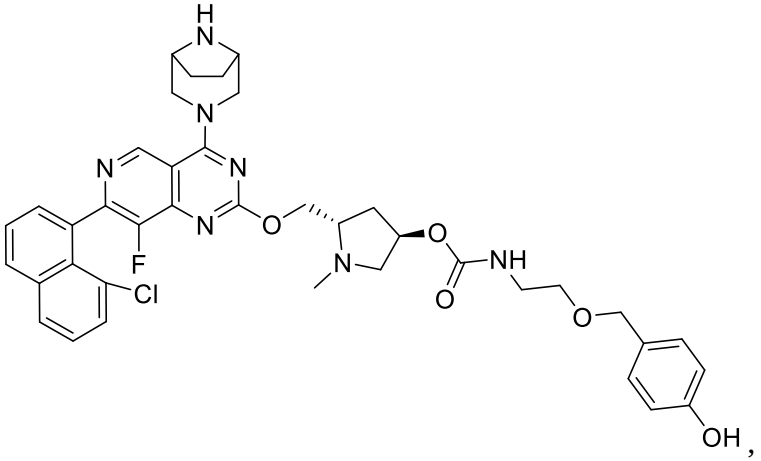
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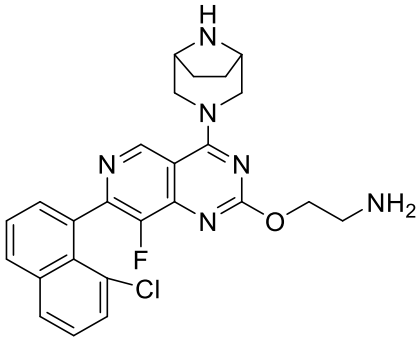
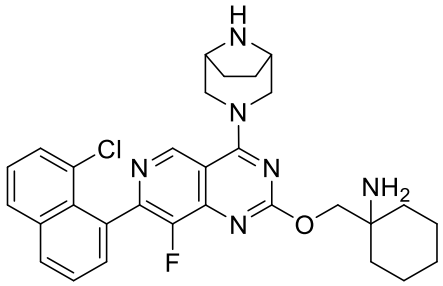
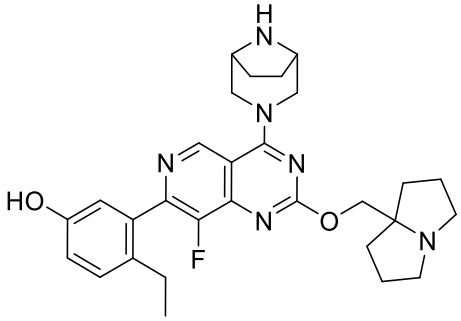
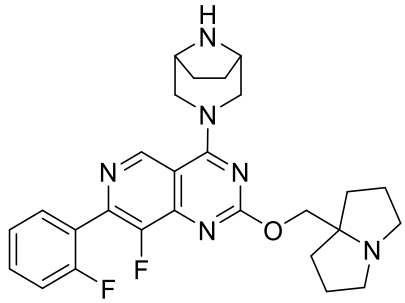
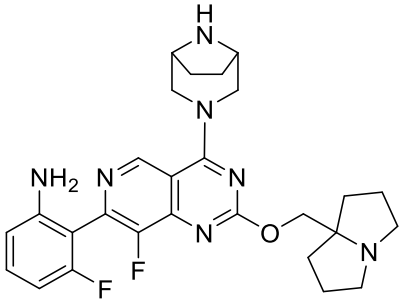
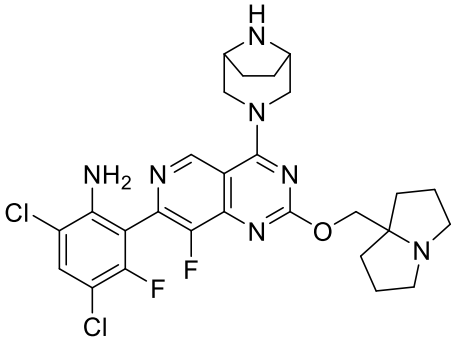
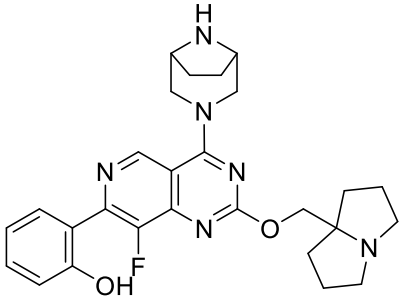
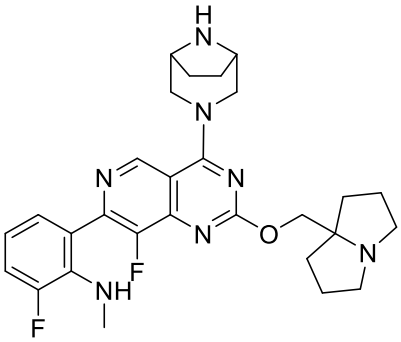
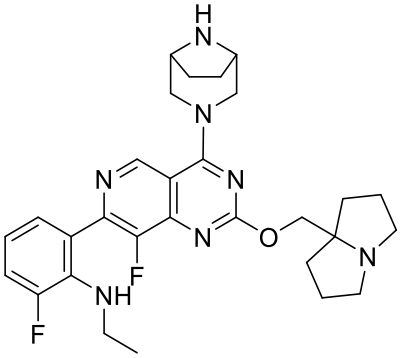

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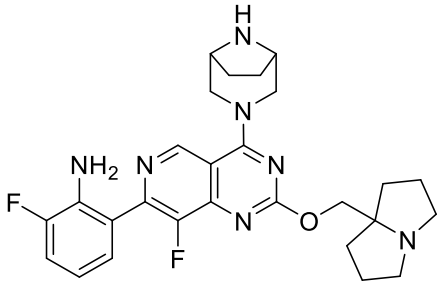
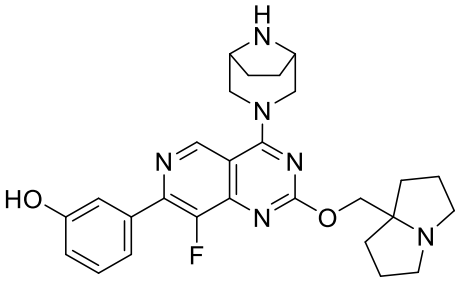
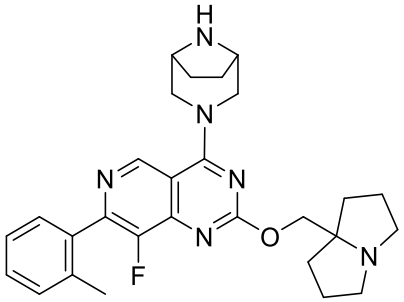
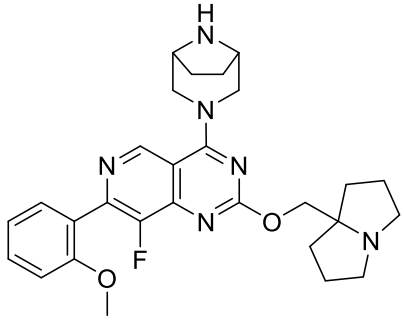
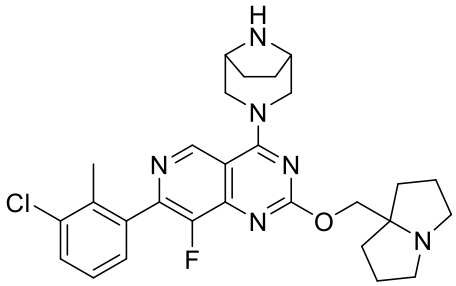
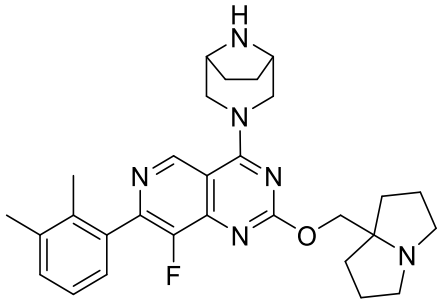
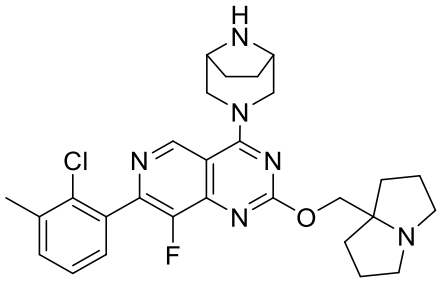
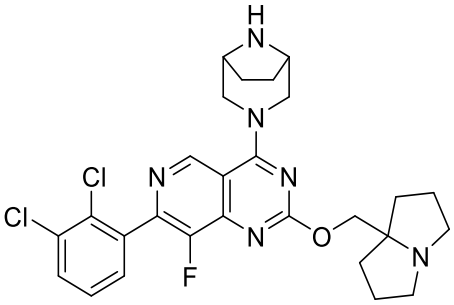
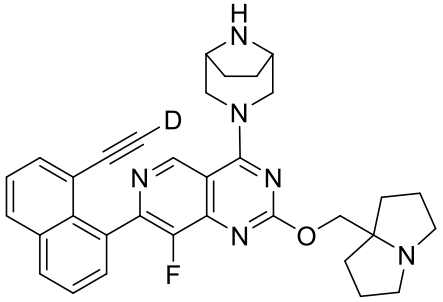
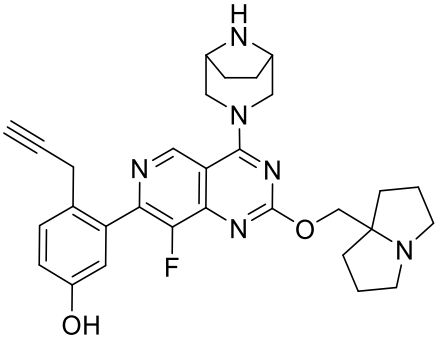

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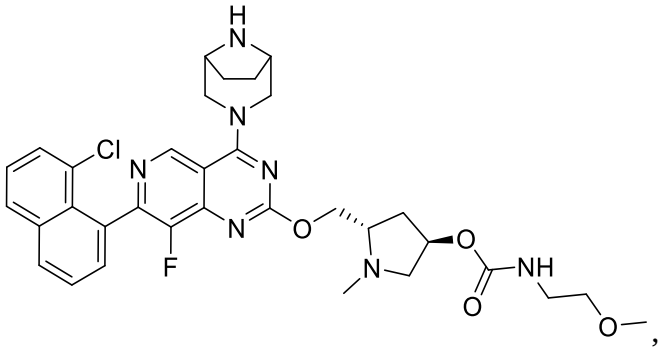
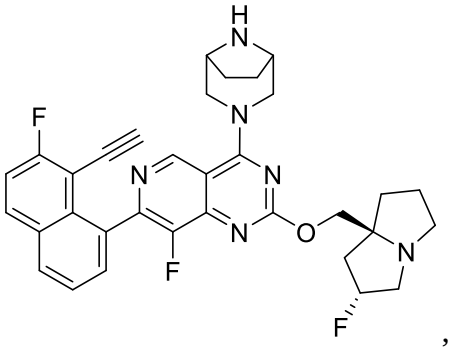
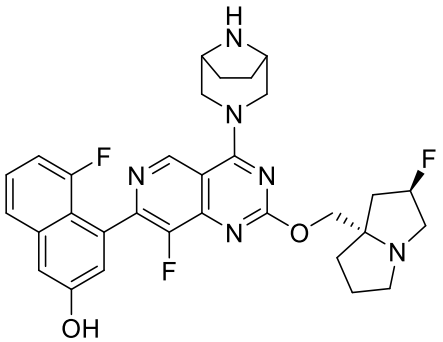
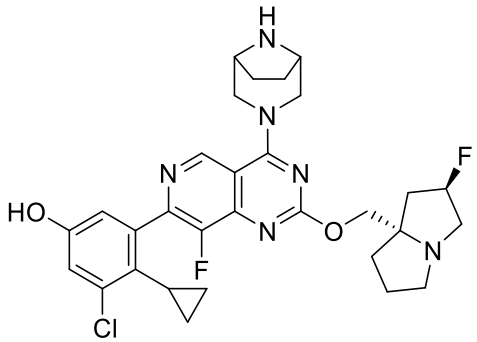
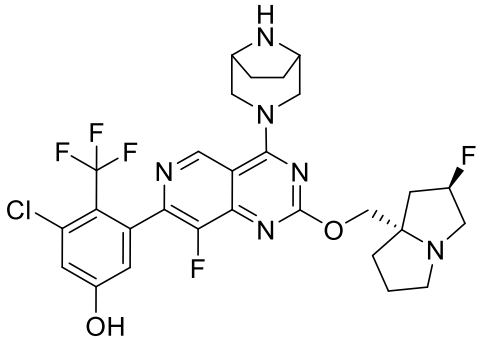
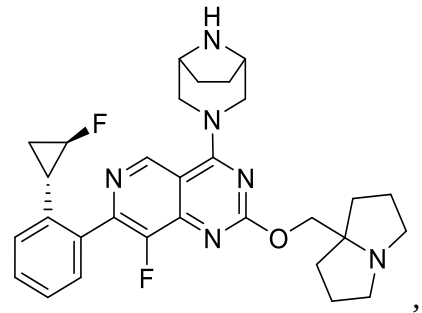
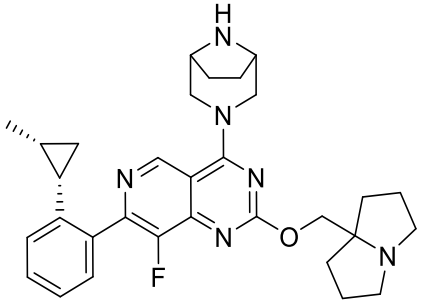
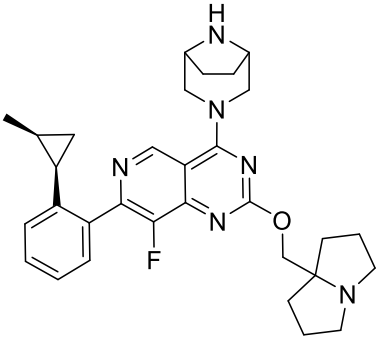
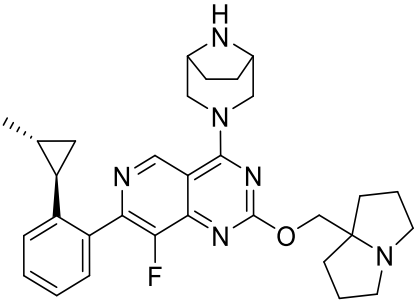

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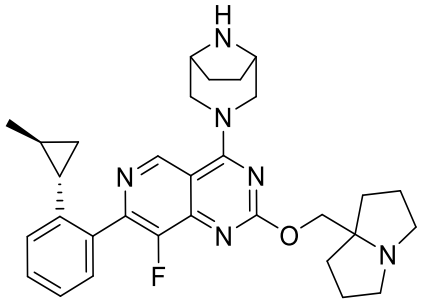
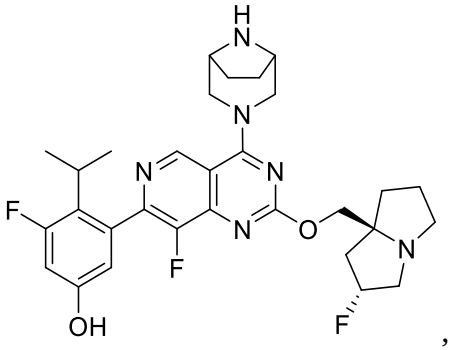
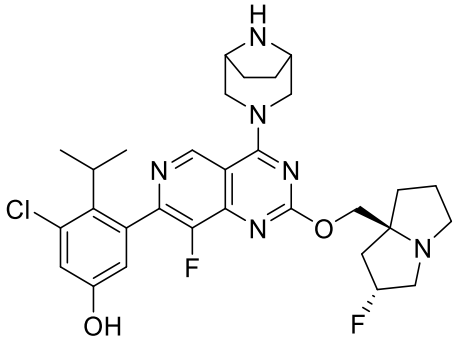
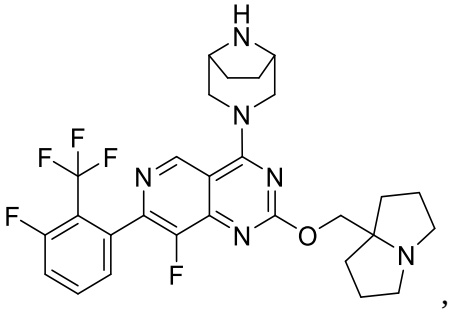
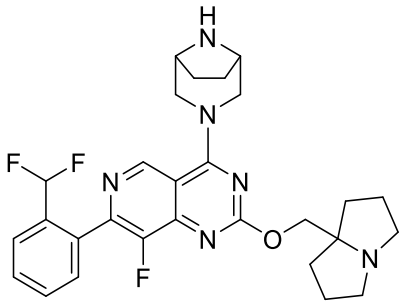
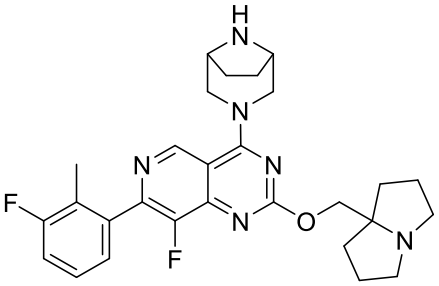
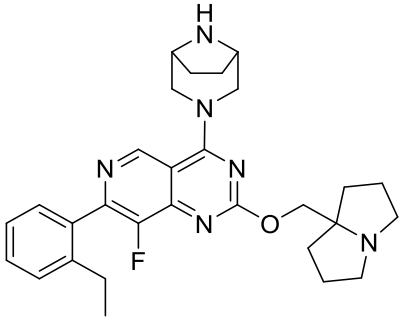
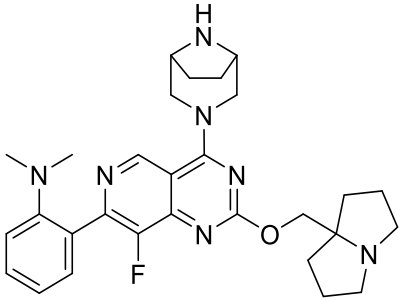
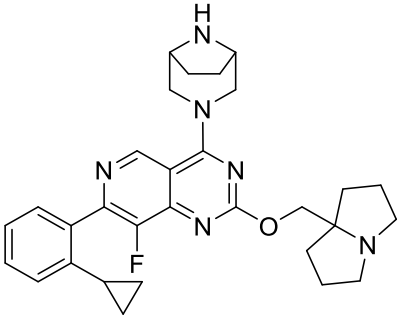

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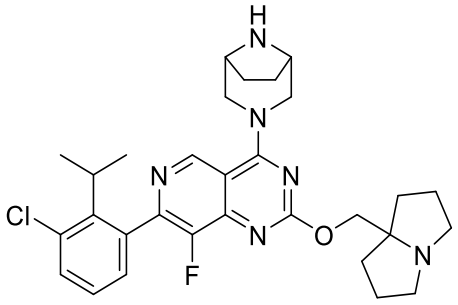
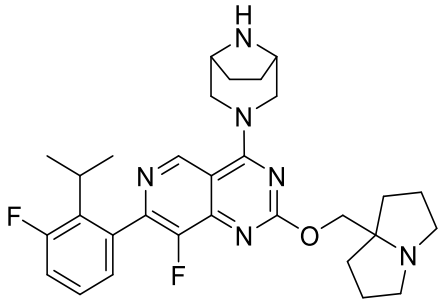
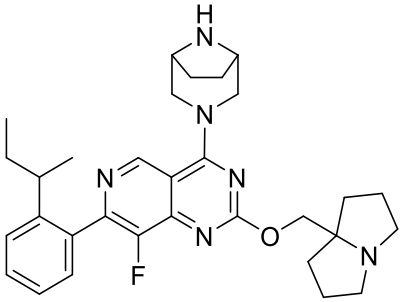
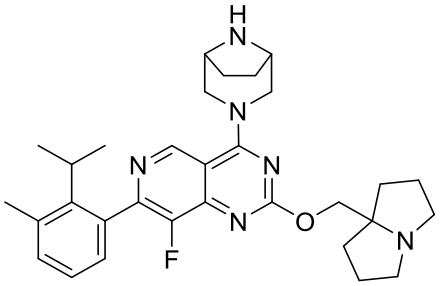
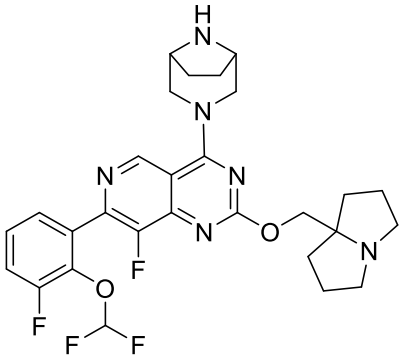
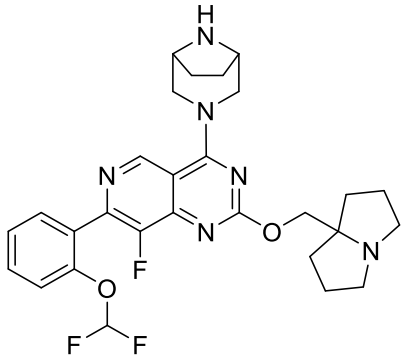
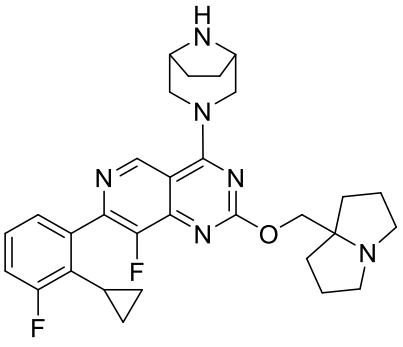
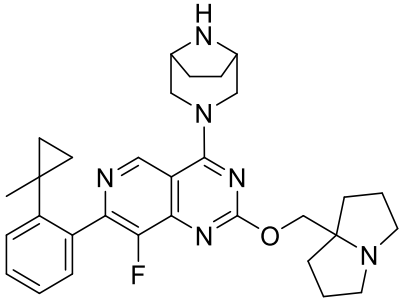
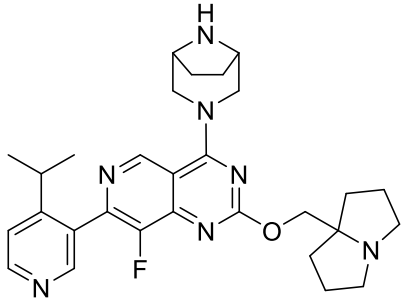
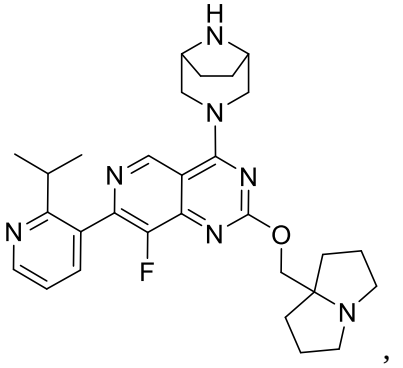

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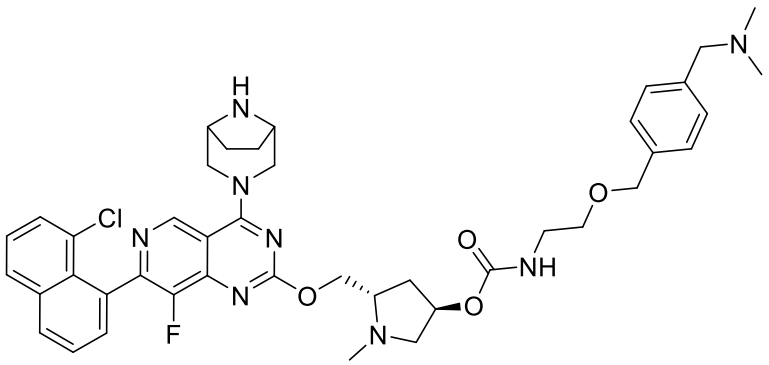
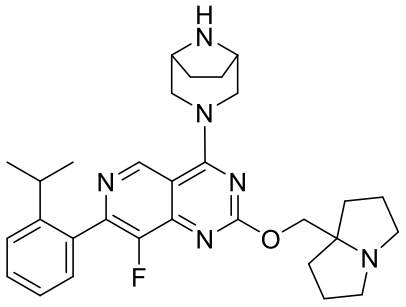
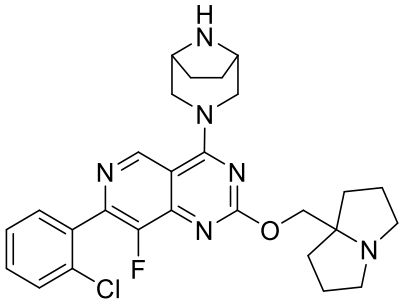
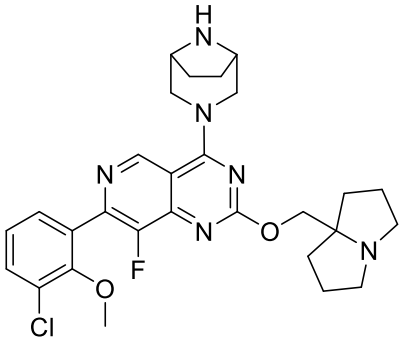
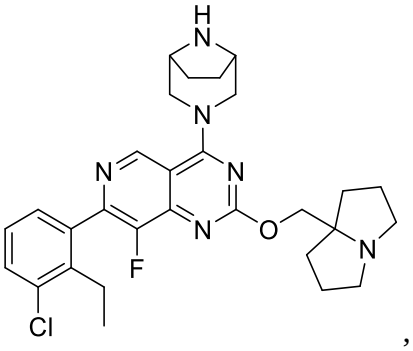
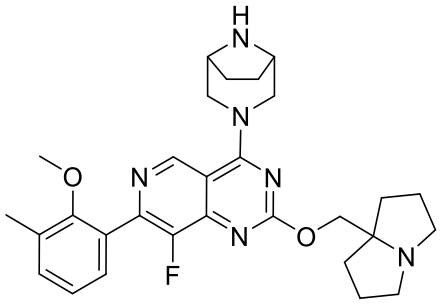
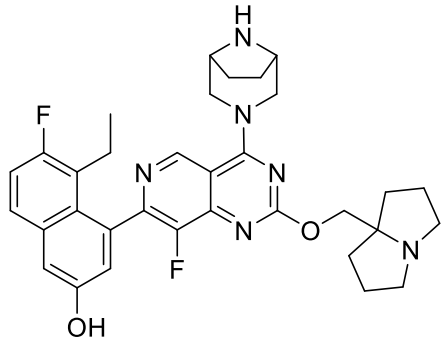
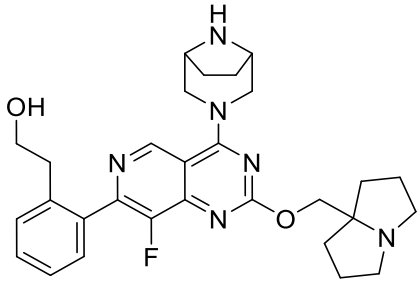
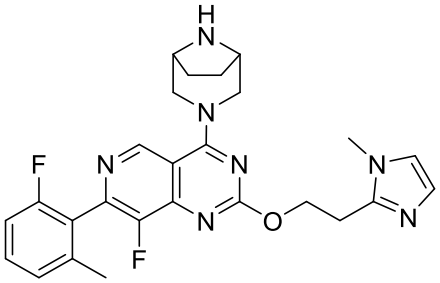
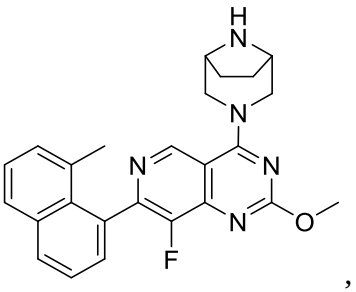

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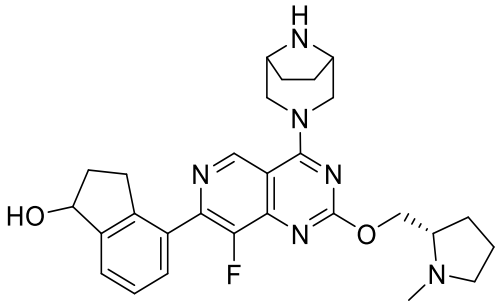
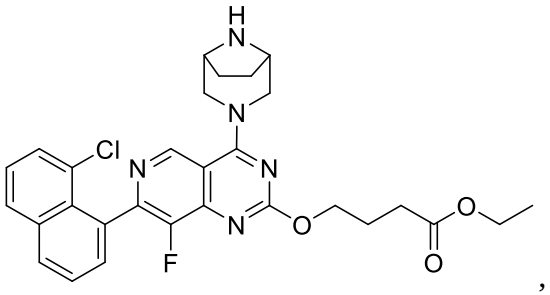
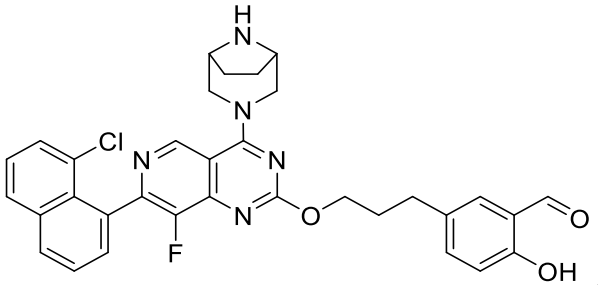
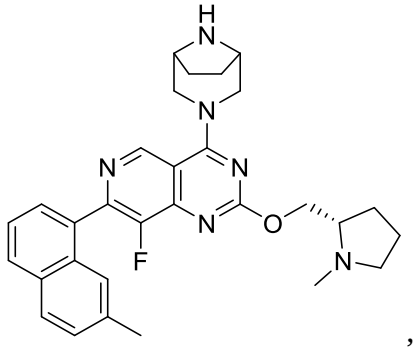
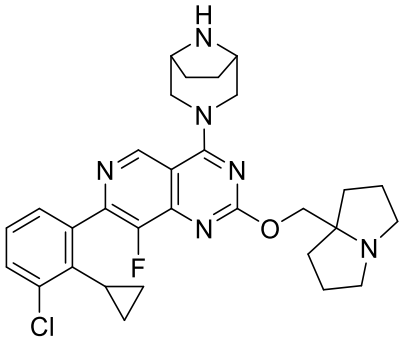
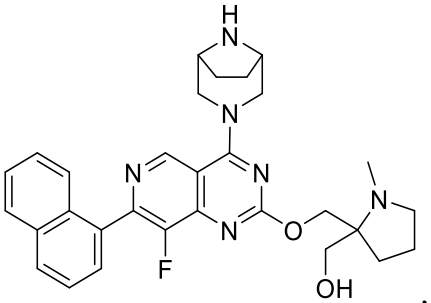
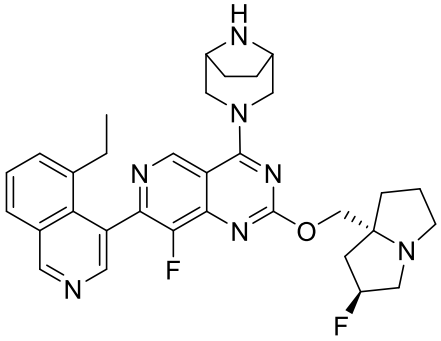
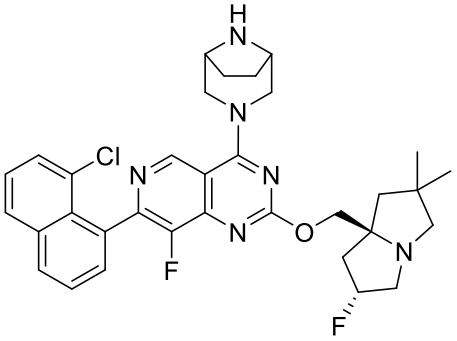

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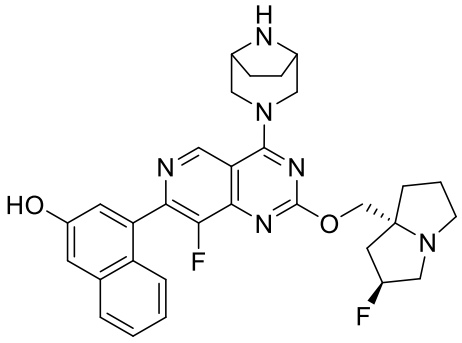
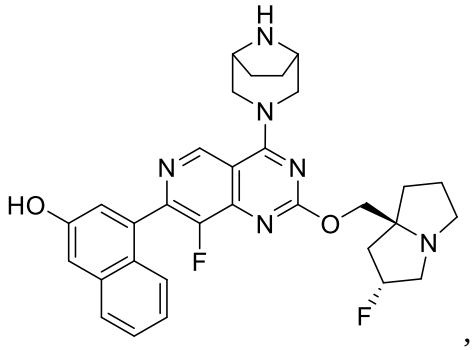
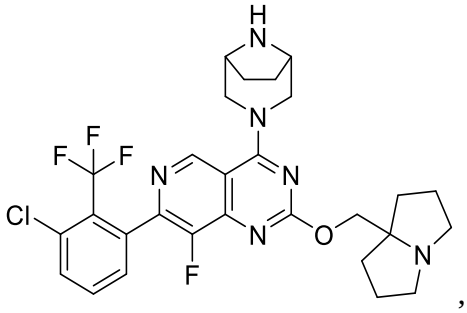
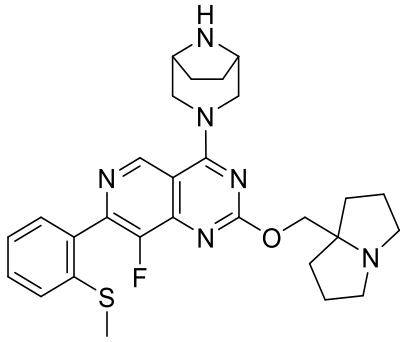
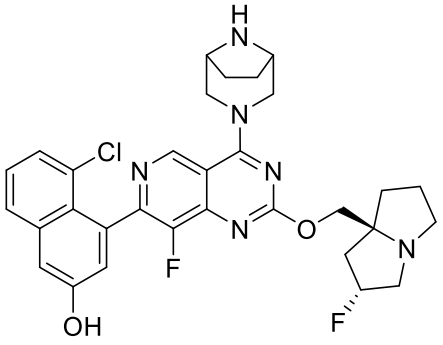
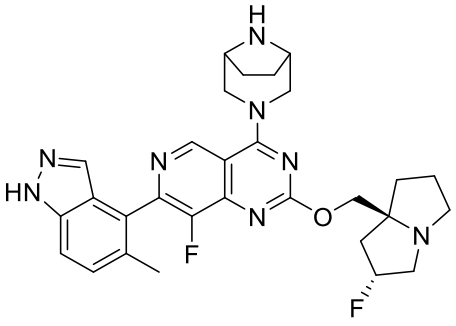
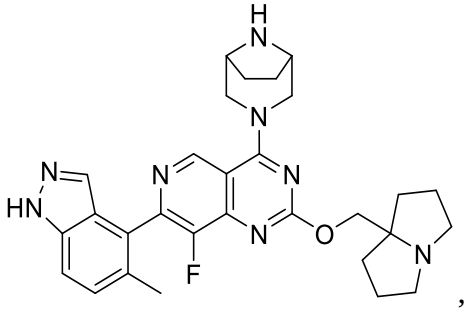
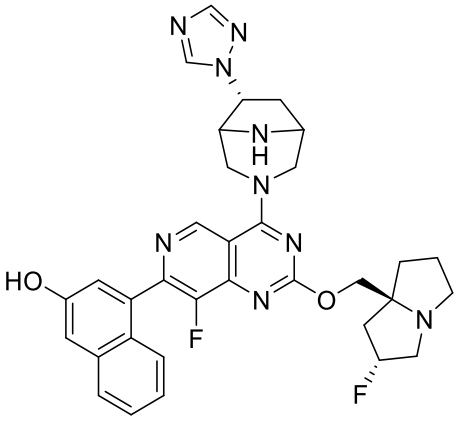

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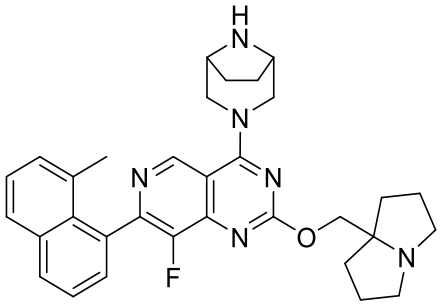
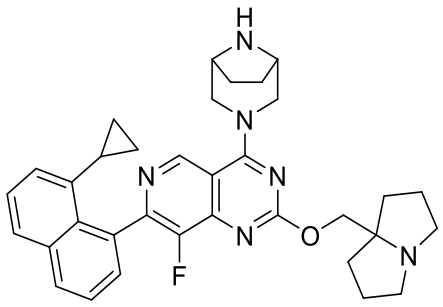
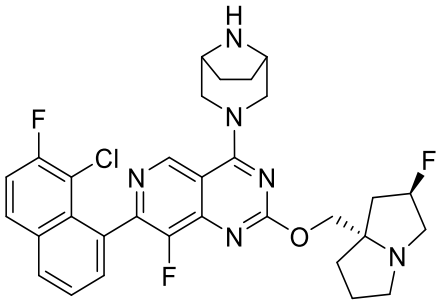
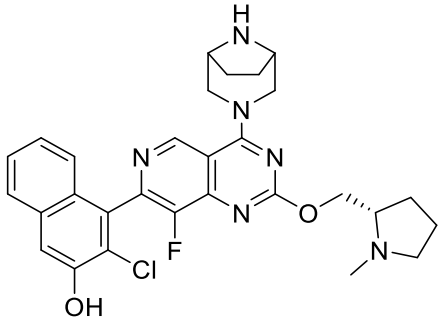
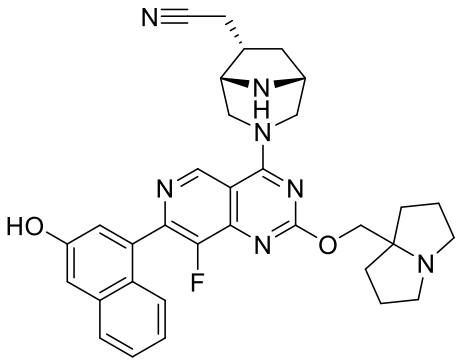
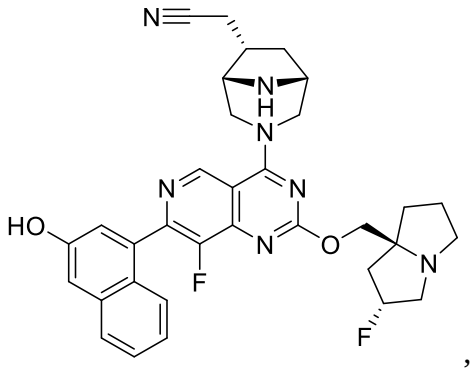
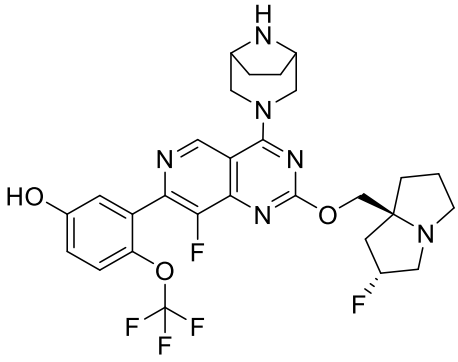
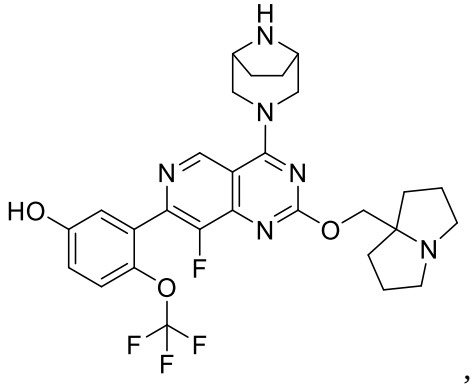

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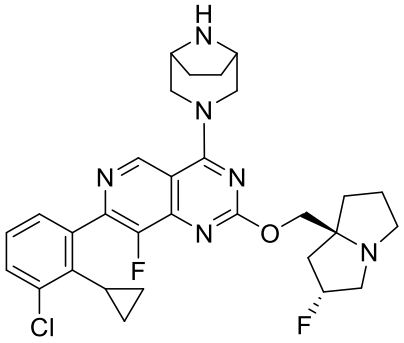
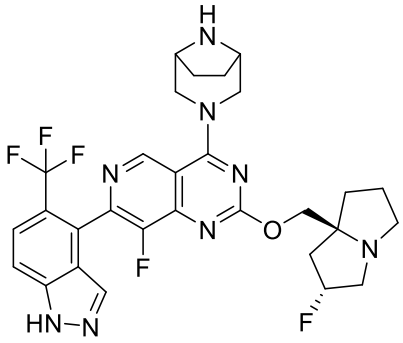
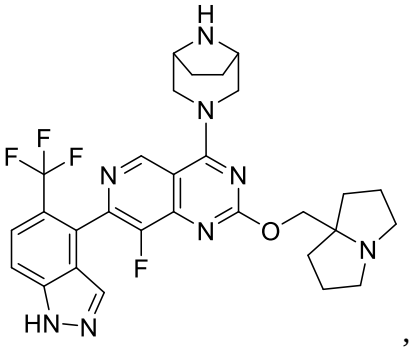
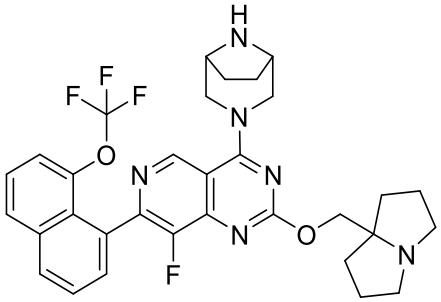
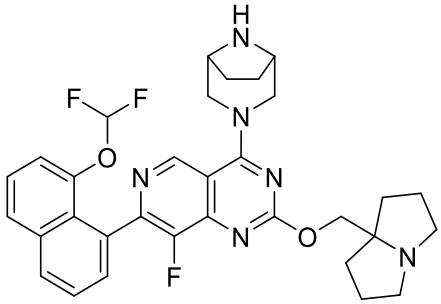
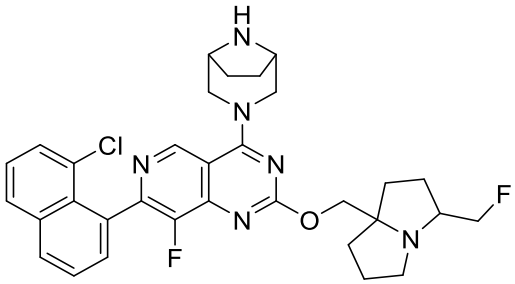
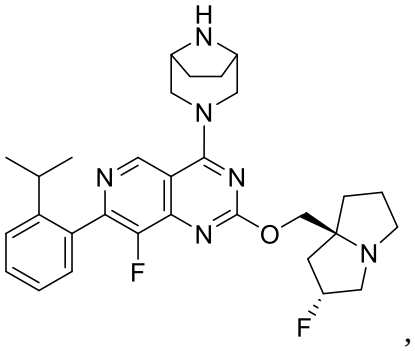
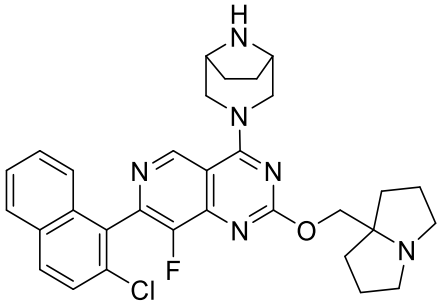
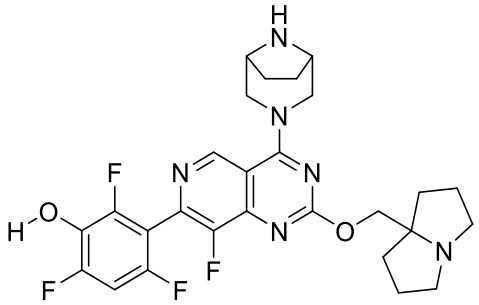

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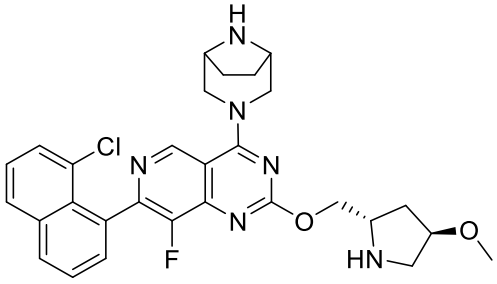
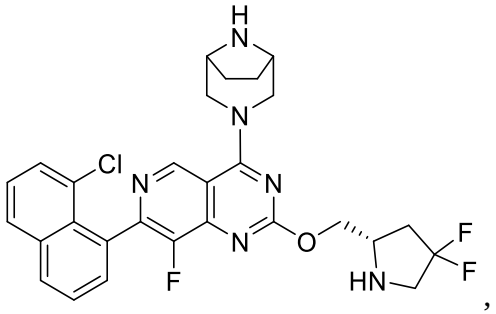
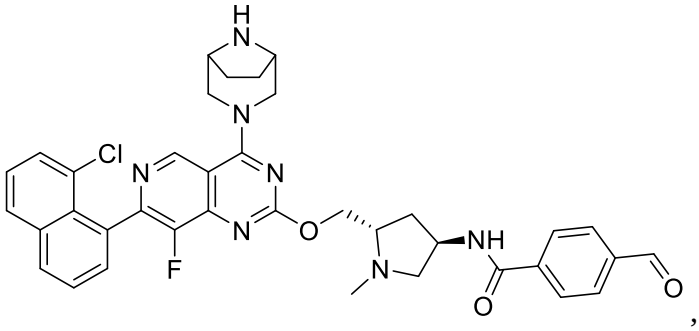
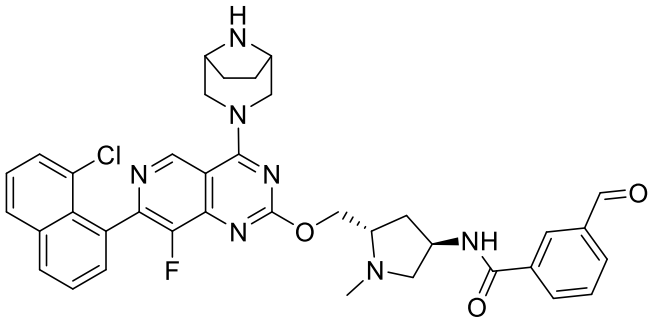
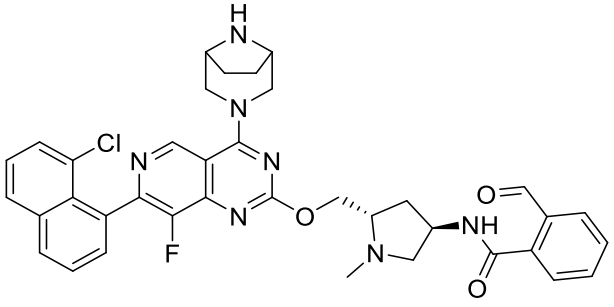
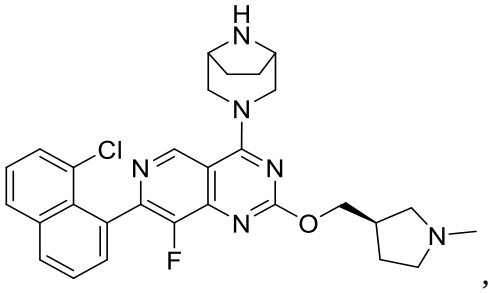
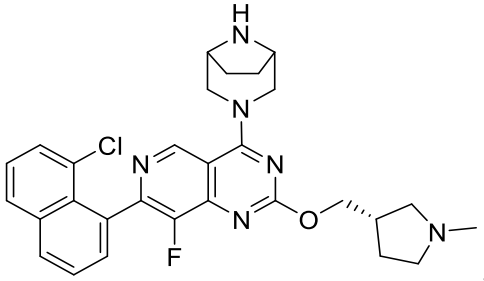
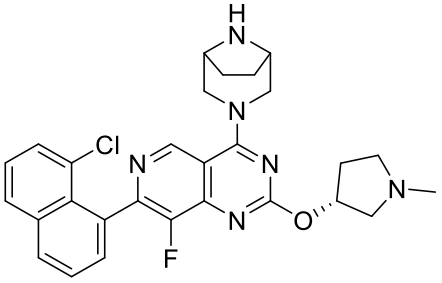

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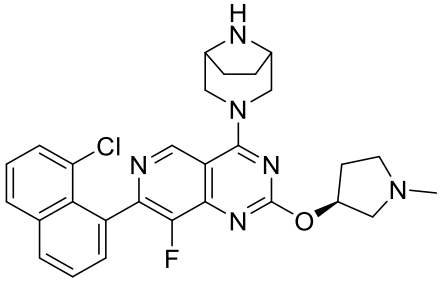
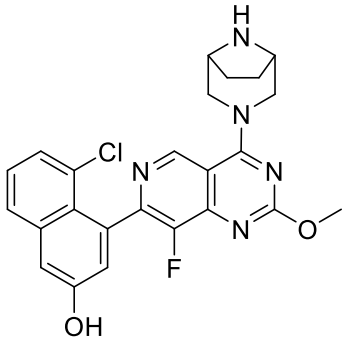
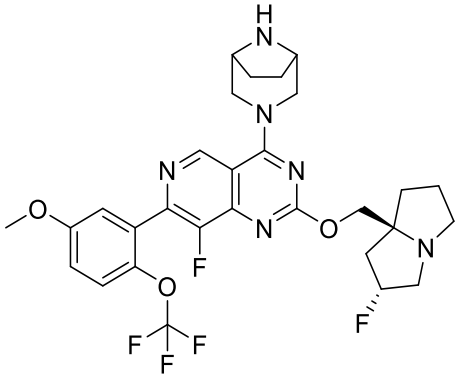
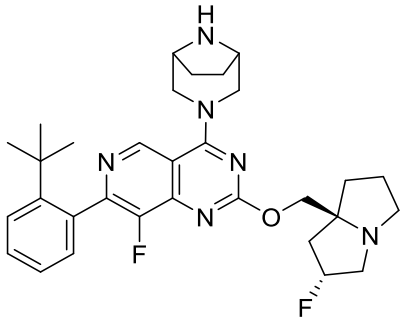
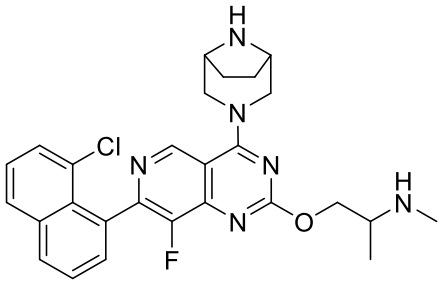
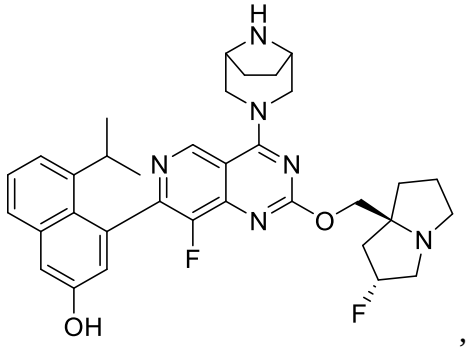
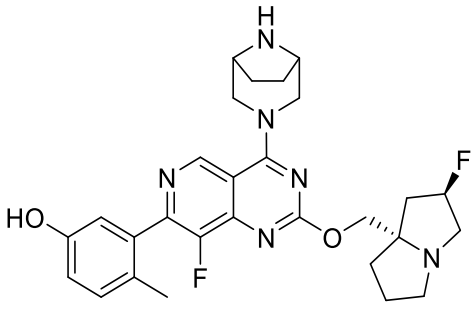
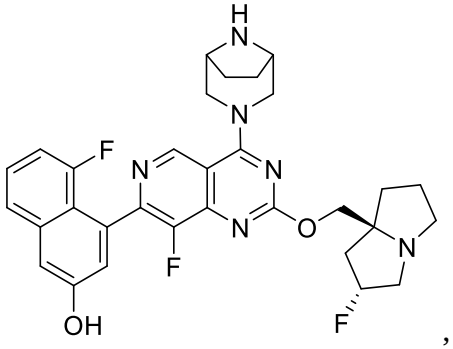

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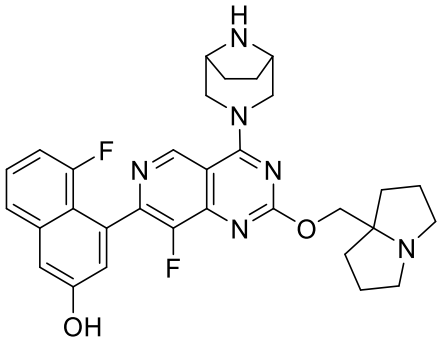
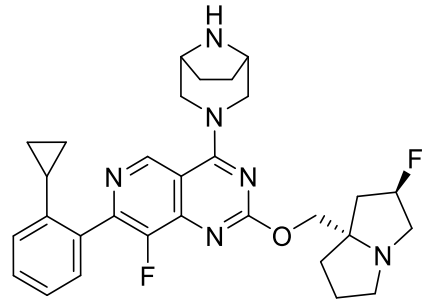
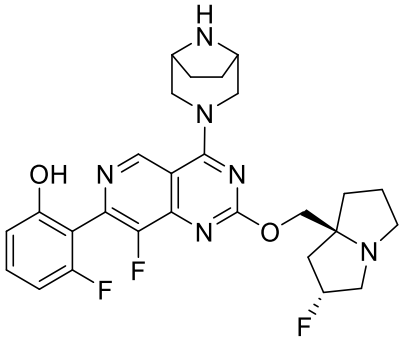
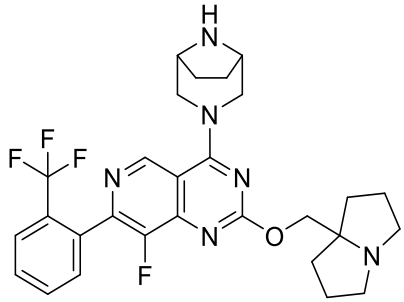
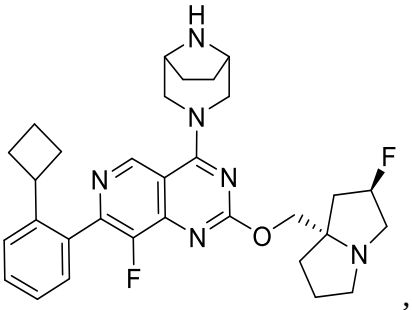
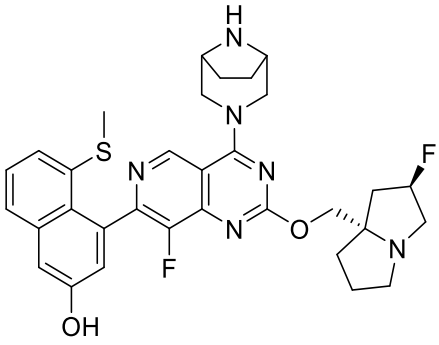
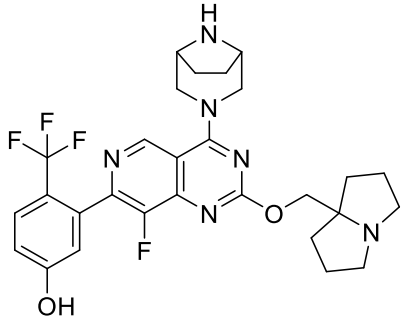
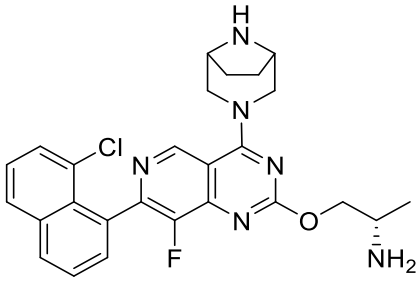
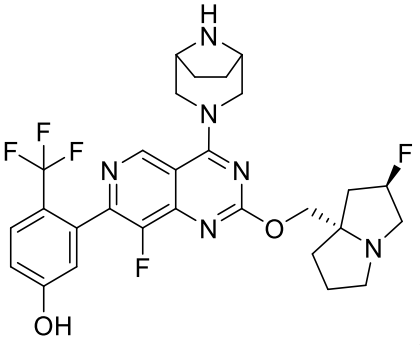

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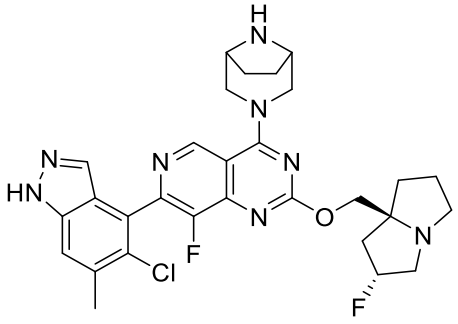
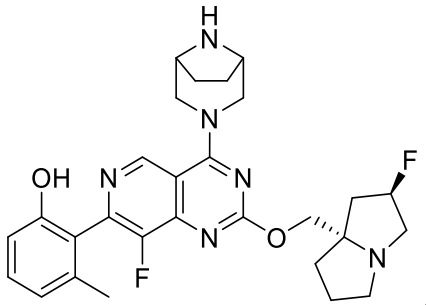
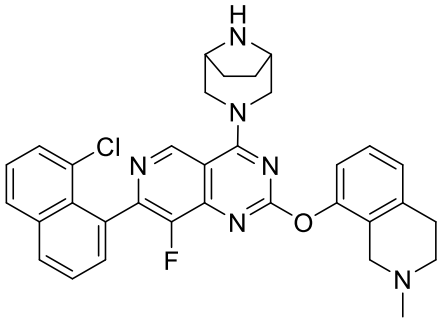
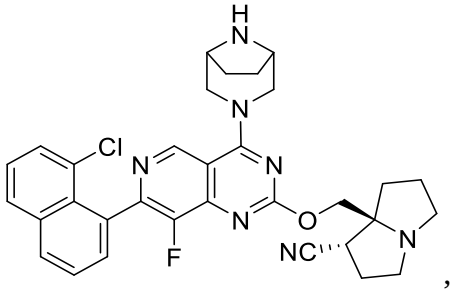
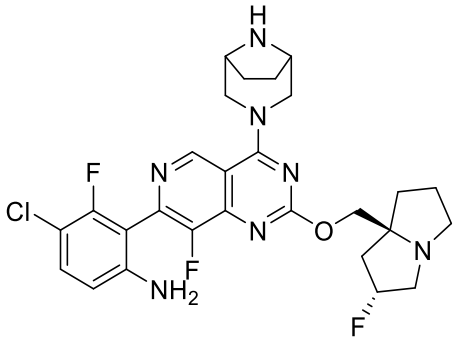
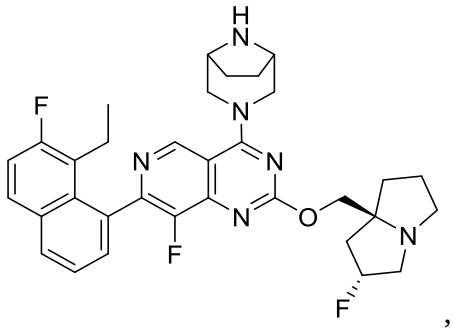
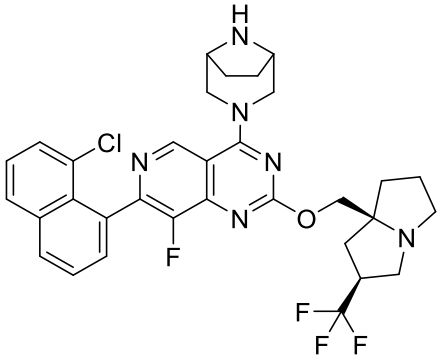
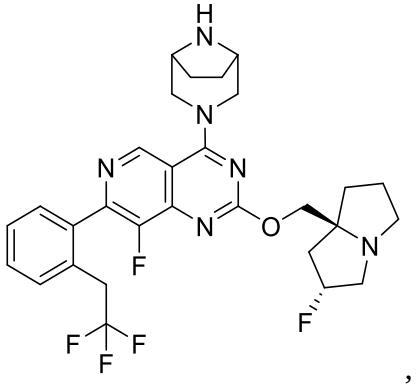

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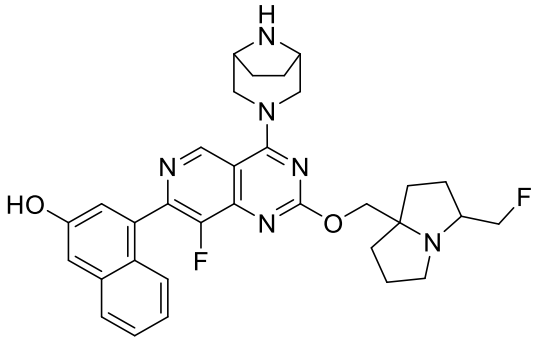
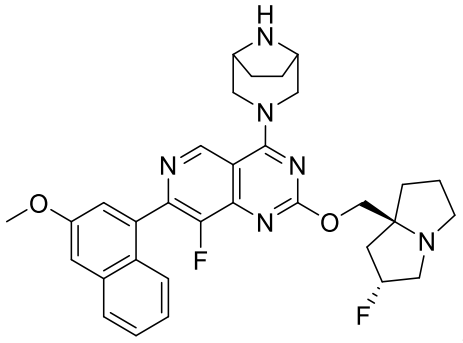
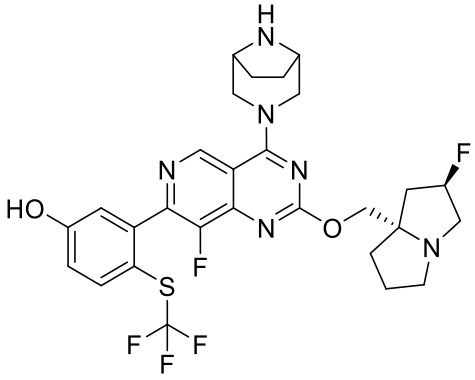
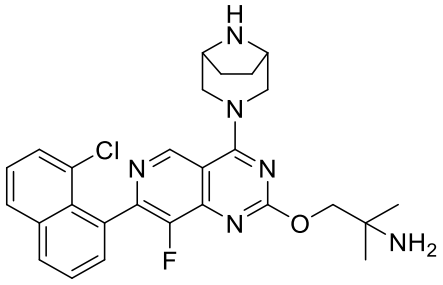
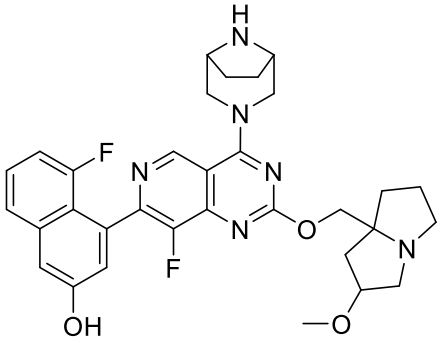
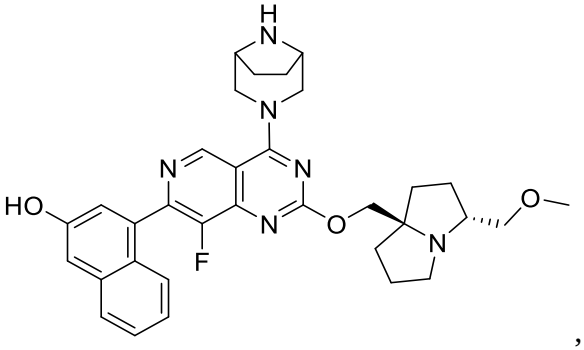
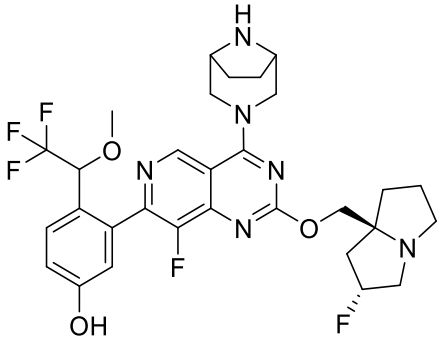
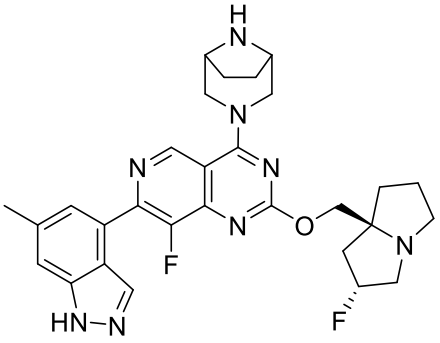

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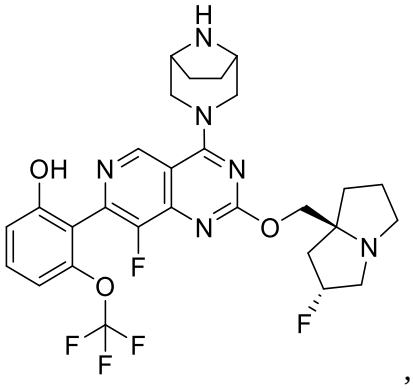
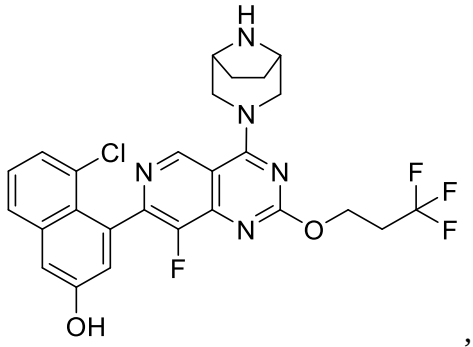
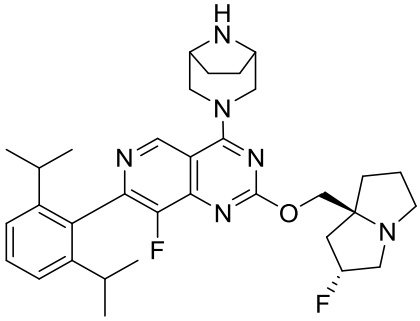
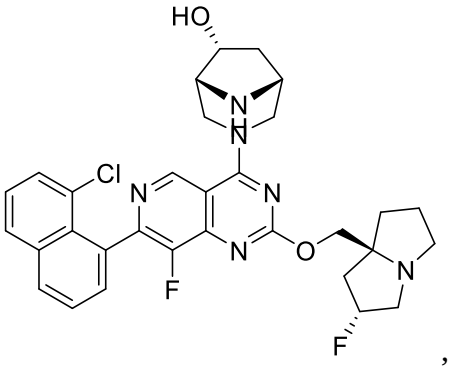
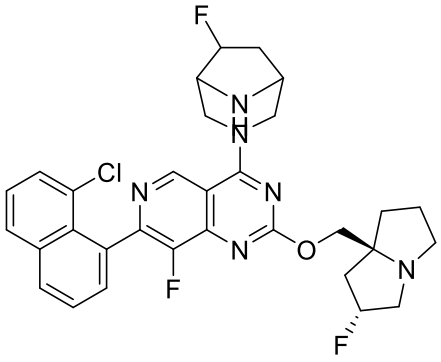
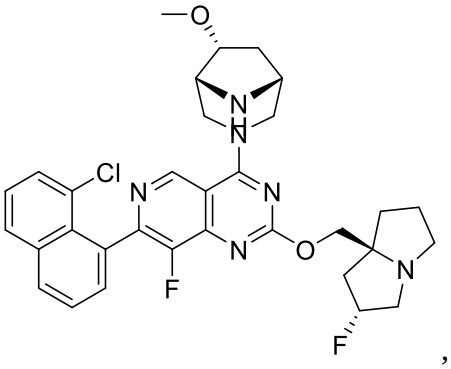
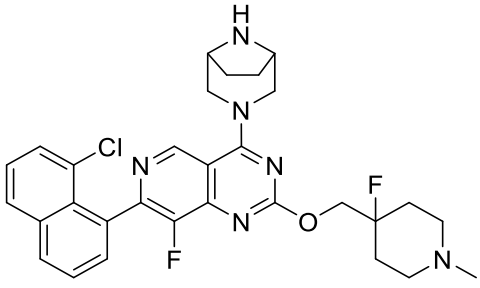
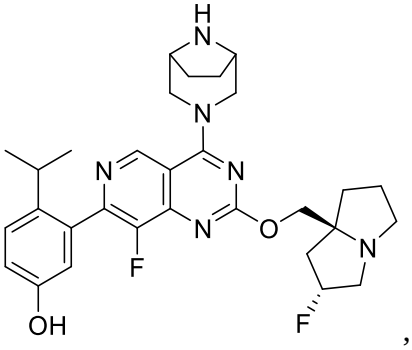

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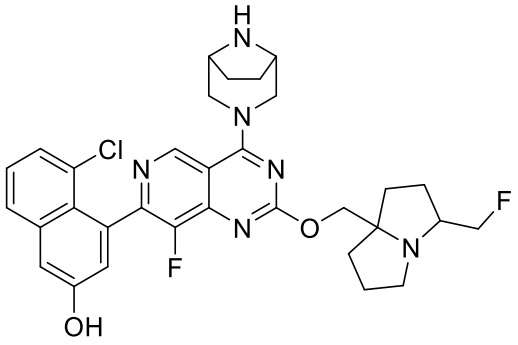
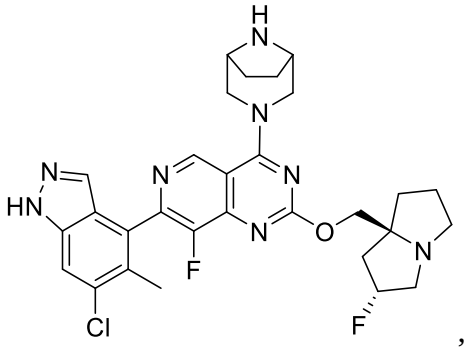
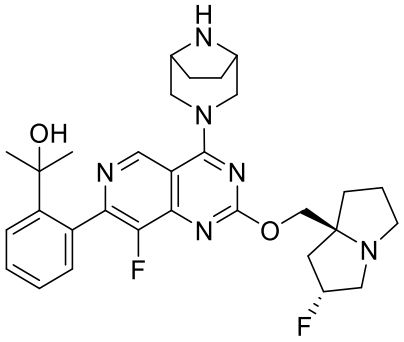
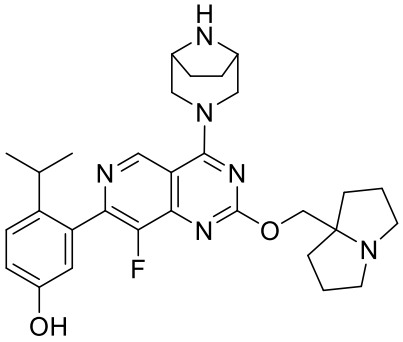
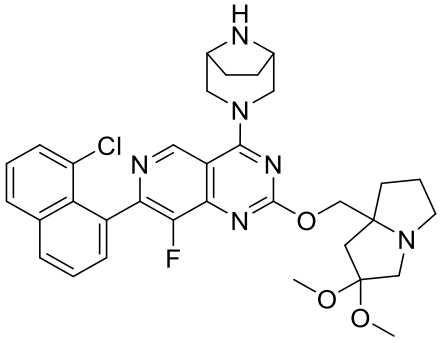
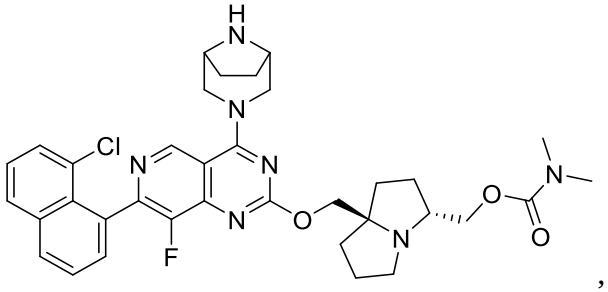
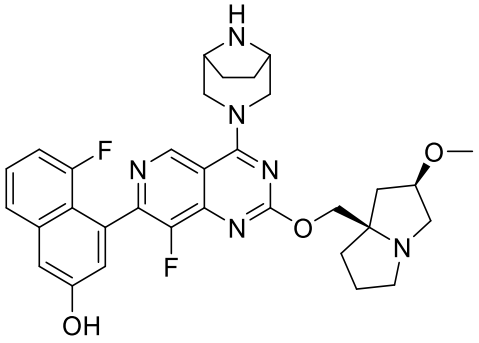
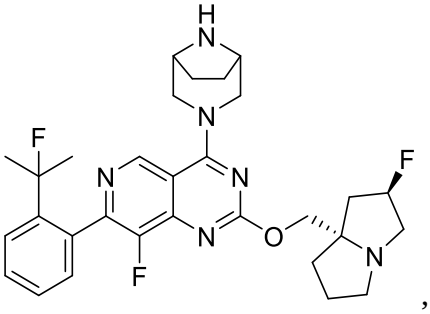

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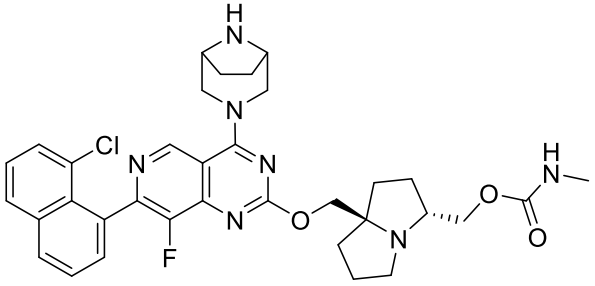
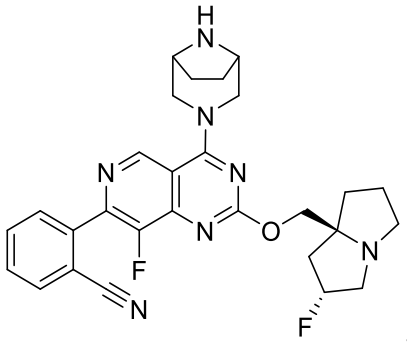
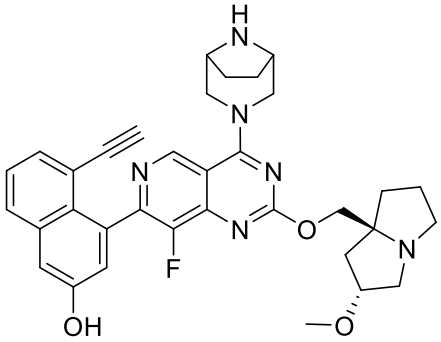
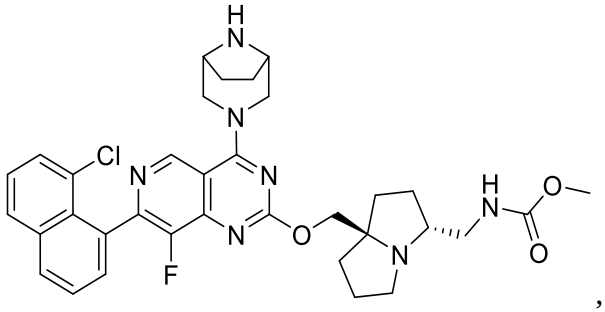
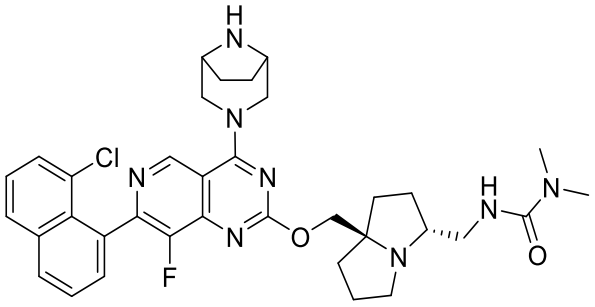
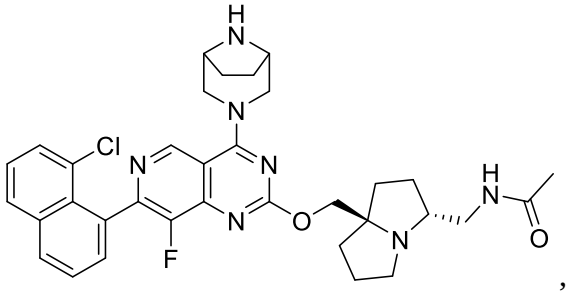
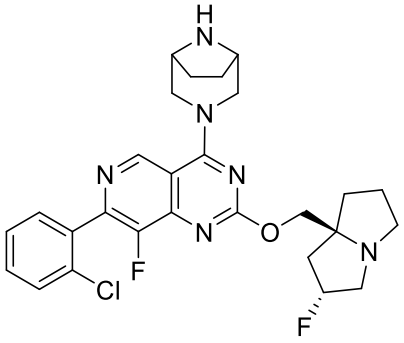
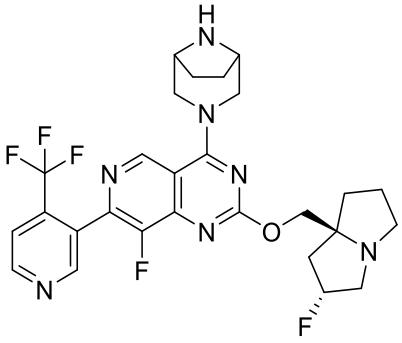
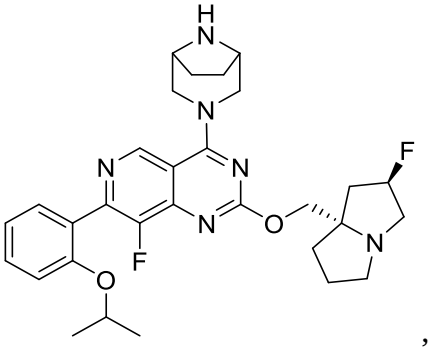

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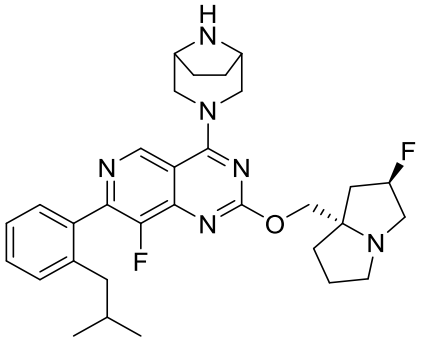
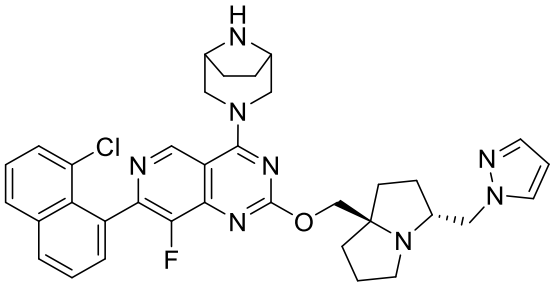
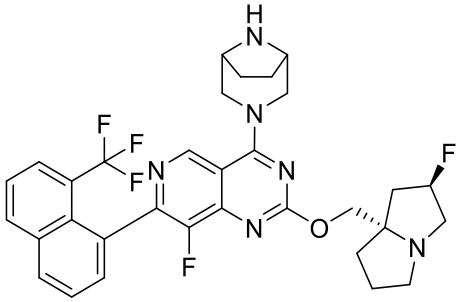
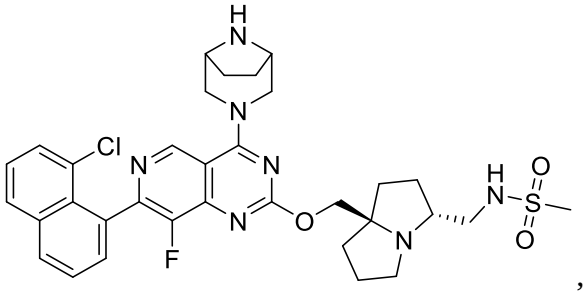
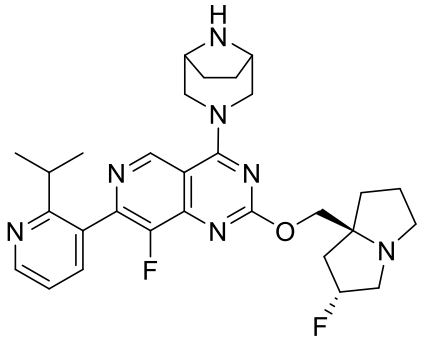
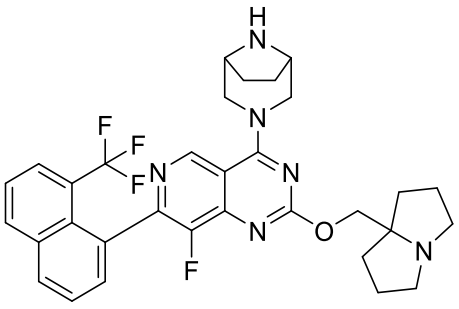
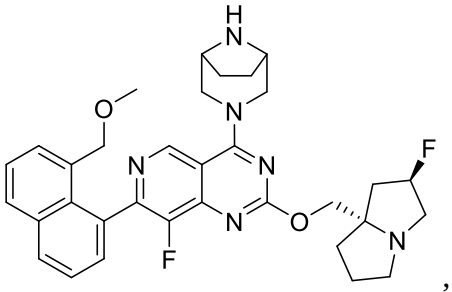
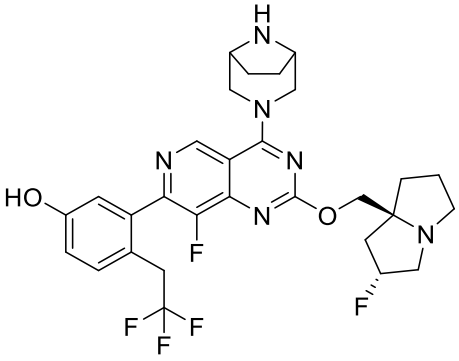

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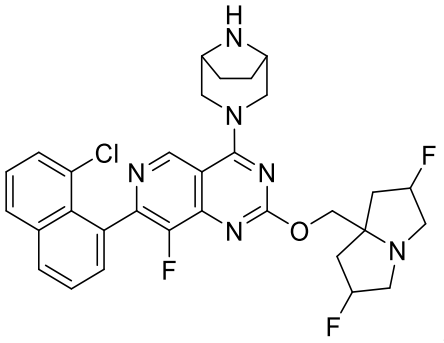
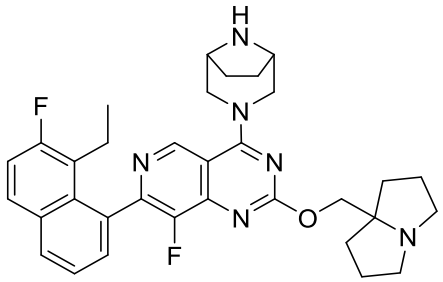
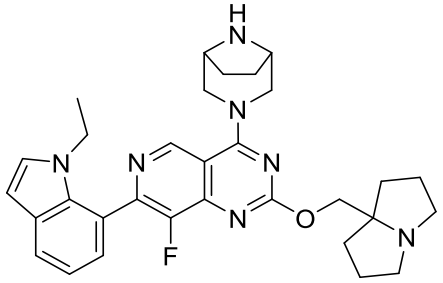
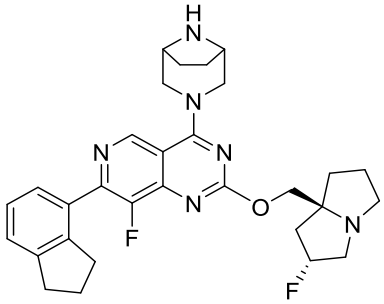
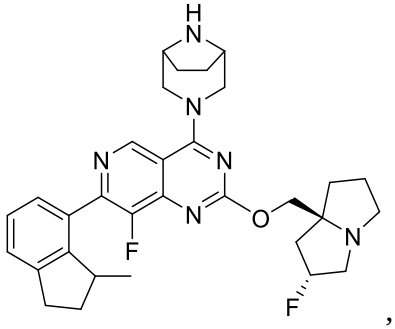
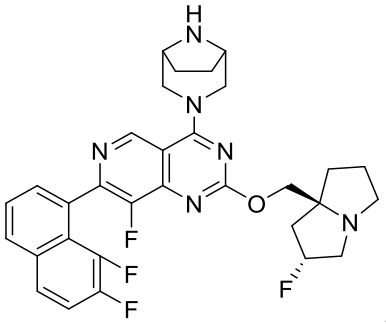
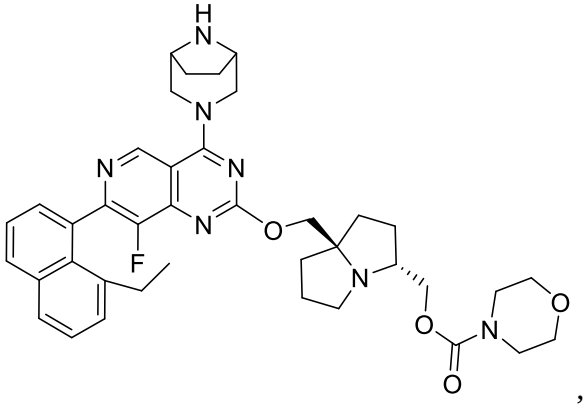
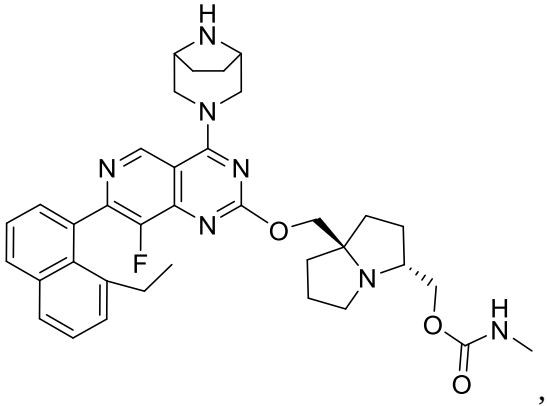
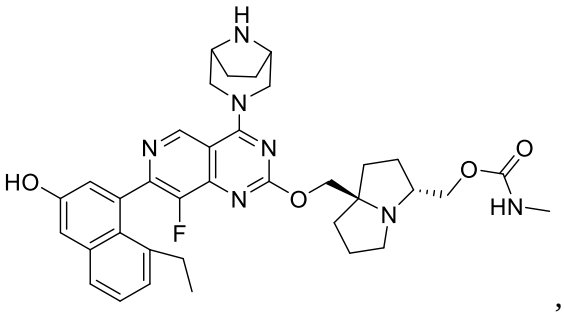

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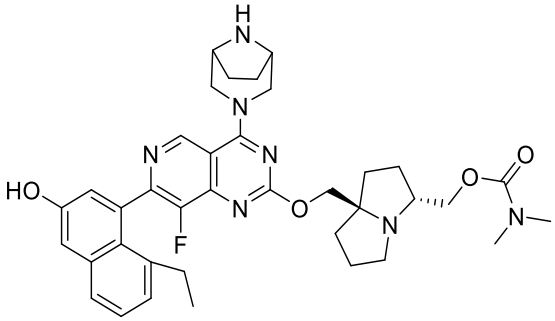
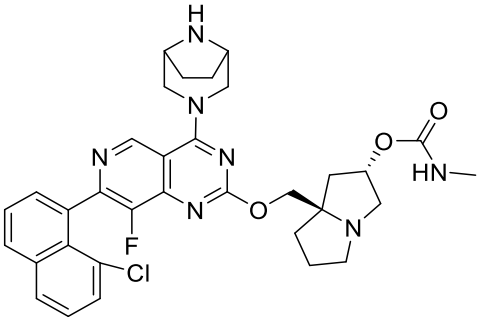
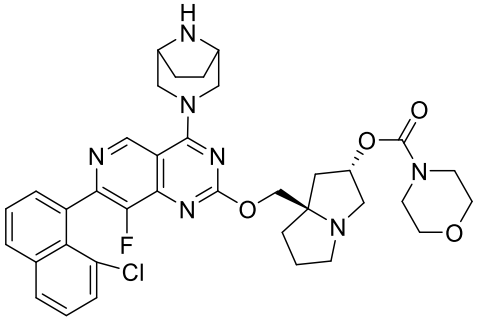
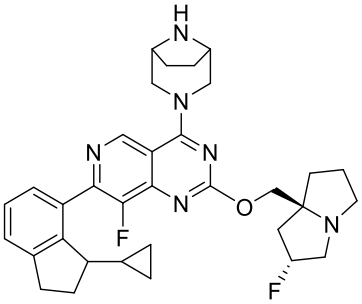
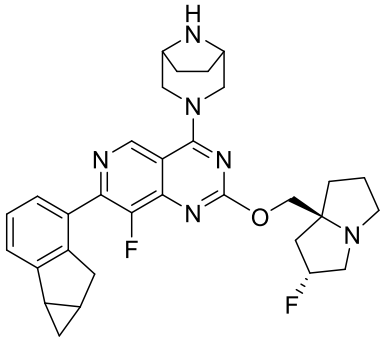
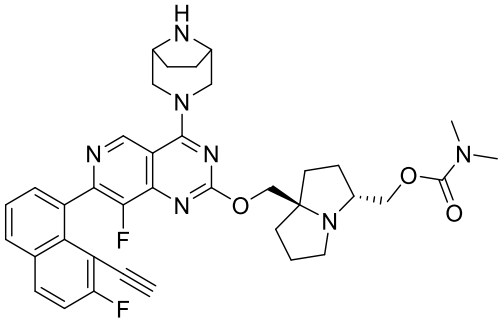
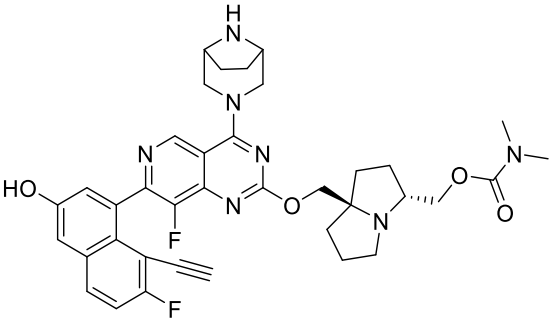
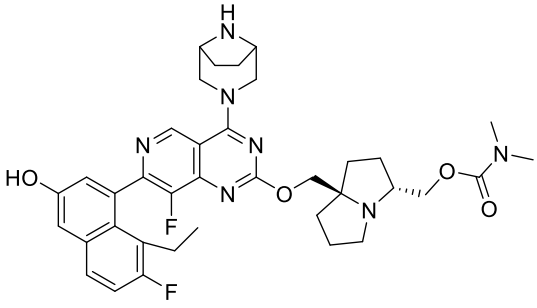
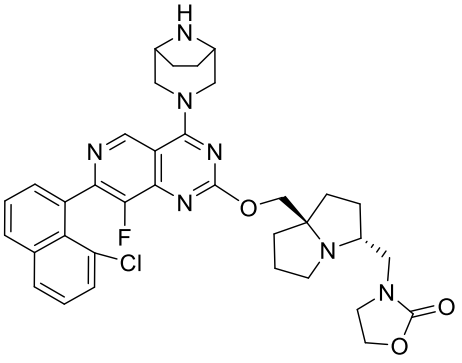

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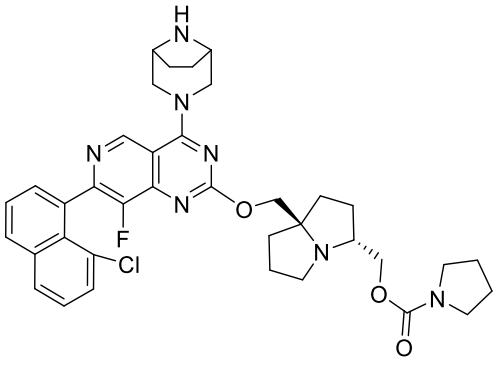
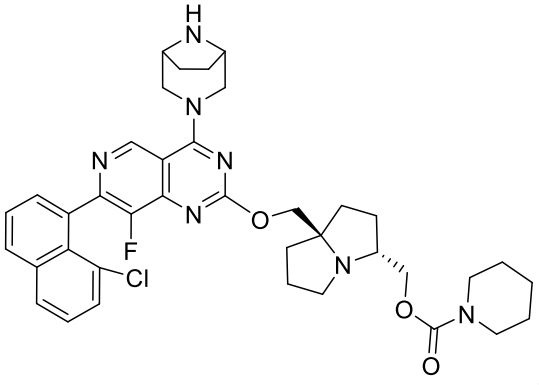
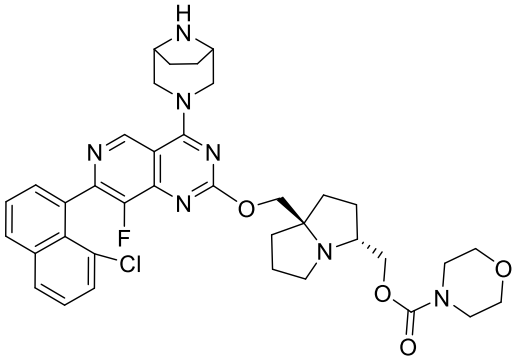
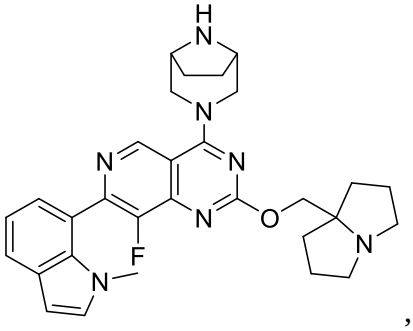
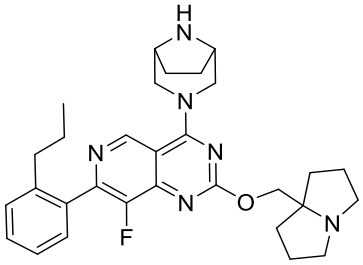
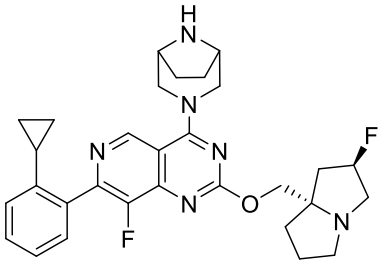
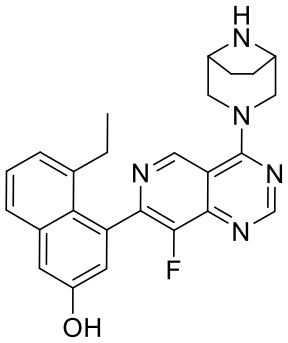

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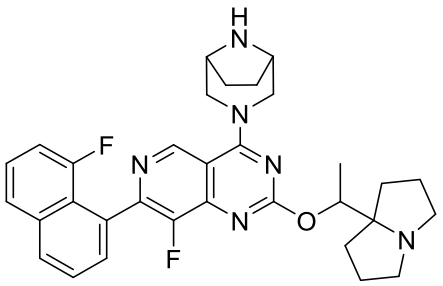
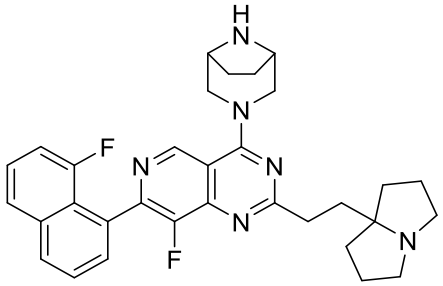
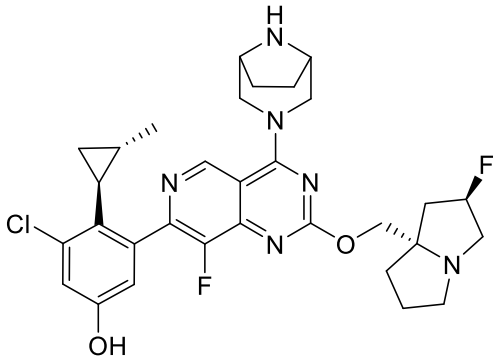
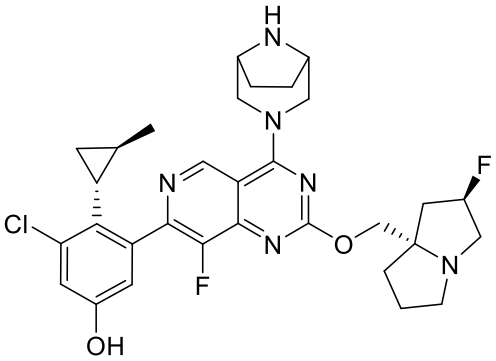

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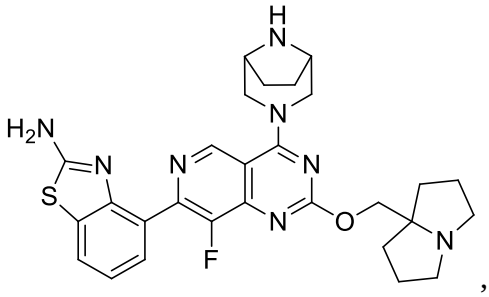
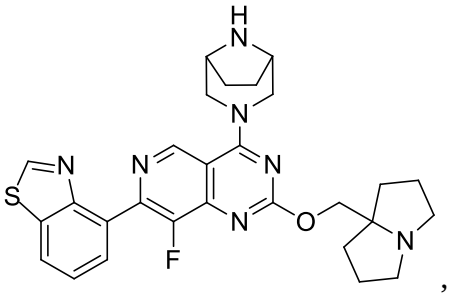
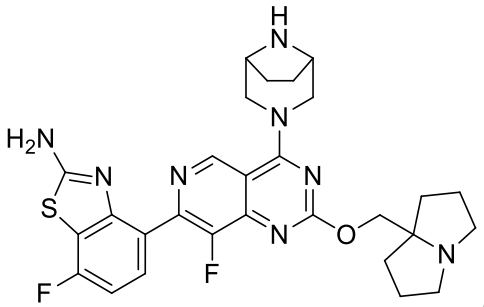
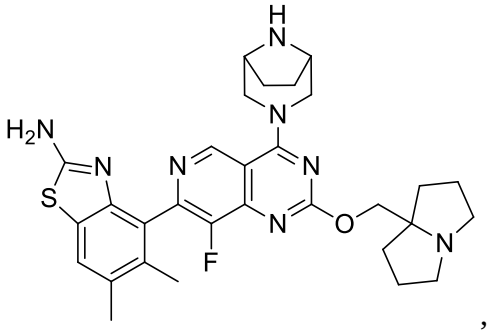
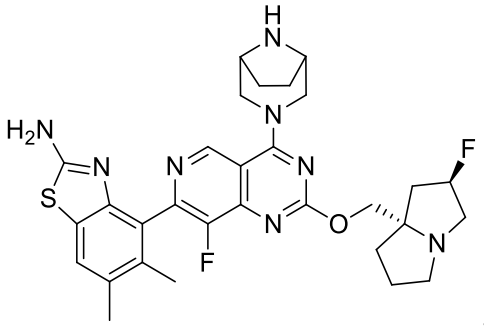
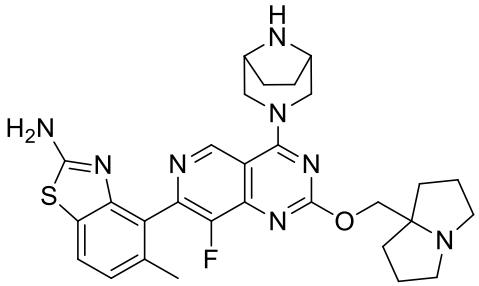

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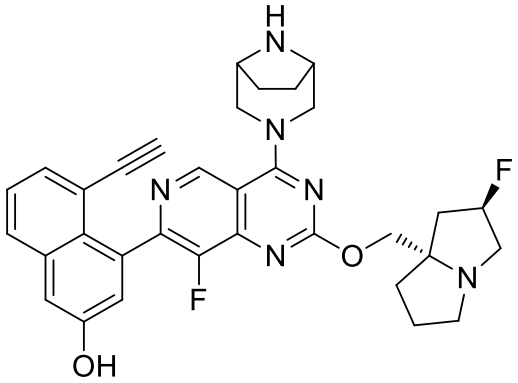

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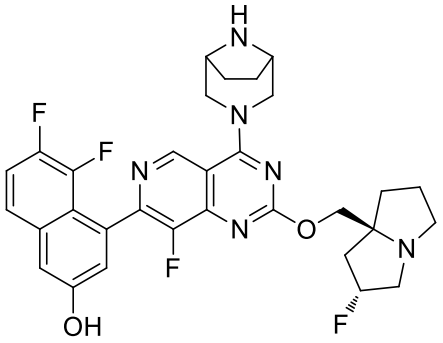

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and pharmaceutically acceptable salts thereof, preferably

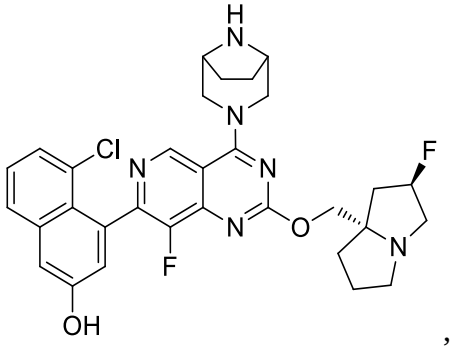
wherein the KRas G12D inhibitor is:



or a pharmaceutically acceptable salt thereof;

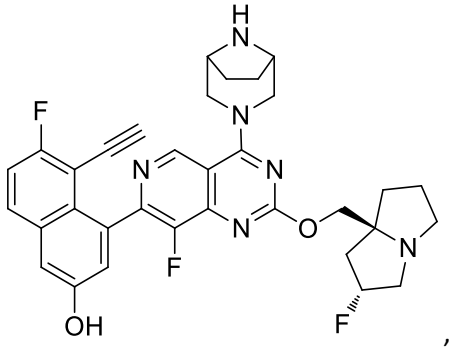


or a pharmaceutically acceptable salt thereof;



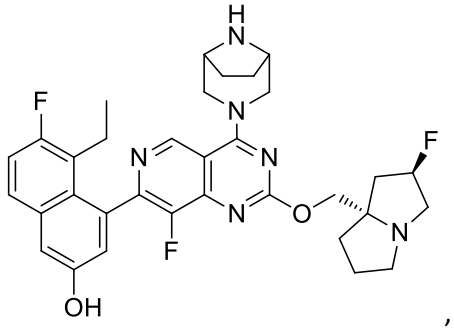
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or a pharmaceutically acceptable salt thereof;



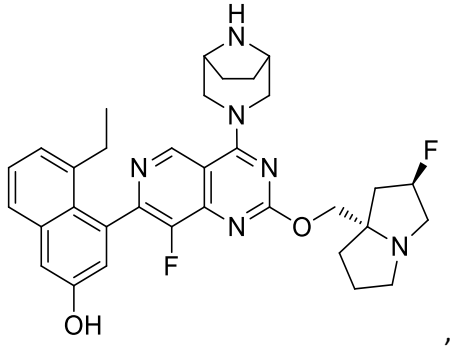
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or a pharmaceutically acceptable salt thereof;



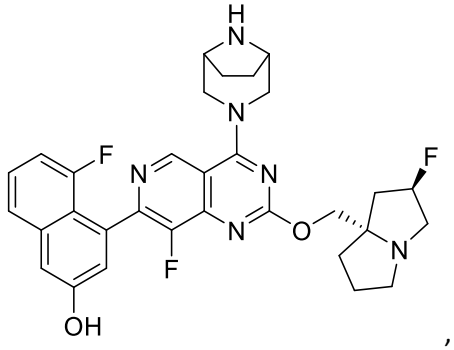
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or a pharmaceutically acceptable salt thereof;



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or a pharmaceutically acceptable salt thereof; or

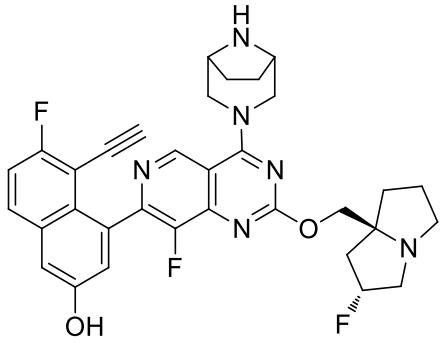


,

or a pharmaceutically acceptable salt thereof.

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14. The use according to claim 1, wherein the KRaS G12 inhibitor is



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or a pharmaceutically acceptable salt thereof.

15. The use according to any one of claims 1-14, wherein the pan ErbB family inhibitor is selected from the group consisting of afatinib, dacomitinib, poziotinib, erlotinib, gefitinib, sapitinib, tarloxotinib, and cetuximab, preferably wherein the pan ErbB family inhibitor is afatinib or cetuximab.

16. The use of according to any one of claims 1-15, wherein the pan ErbB family inhibitor and the KRAS G12D inhibitor are administered on the same day or wherein the pan ErbB family inhibitor and the KRAS G12D inhibitor are administered on different days.

17. The use of according to any one of claims 1-16, wherein the KRas G12D inhibitor is to be administered at a maximum tolerated dose, preferably wherein the pan ErbB family inhibitor and the KRAS G12D inhibitor are each administered at a maximum tolerated dose.

18. The use according to any one of claims 1-17, wherein the therapeutically effective amount of the combination of the pan ErbB family inhibitor and the KRAS G12D inhibitor results in an increased duration of overall survival, an increased duration of progression free survival, an increase in tumor growth regression, an increase in tumor growth inhibition or an increased duration of stable diseasein the subjects relative to treatment with only the KRas G12D inhibitor.

19. A pharmaceutical composition, comprising a therapeutically effective amount of a combination of a pan ErbB family inhibitor and a KRas G12D inhibitor as defined in any one of claims 1-14, and a pharmaceutically acceptable excipient.

20. A combination of a pan ErbB family inhibitor and a KRas G12D inhibitor for use in inhibiting KRas G12D activity in a cancer cell, comprising contacting the cancer cell in which inhibition of KRas G12D activity is desired with an effective amount of a pan ErbB family inhibitor and a KRas G12D inhibitor compound as defined in any one of claims 1-14, pharmaceutical compositions or pharmaceutically acceptable salts thereof, wherein the pan ErbB family inhibitor synergistically increases the sensitivity of the cancer cells to the KRas G12D inhibitor.

21. An *in vitro* method for inhibiting KRas G12D activity in a cancer cell, comprising contacting the cancer cell in which inhibition of KRas G12D activity is desired with an effective amount of a pan ErbB family inhibitor and a KRas G12D inhibitor compound as defined in any one of claims 1-14, pharmaceutical compositions or pharmaceutically acceptable salts thereof, wherein the pan ErbB family inhibitor synergistically increases the sensitivity of the cancer cells to the KRas G12D inhibitor.

22. The use according to any one of claims 1-18, wherein the pan ErbB family inhibitor synergistically increases the sensitivity of the cancer cells to the KRas G12D inhibitor.

23. A combination of a pan ErbB family inhibitor and a KRas G12D inhibitor for use in a method for increasing the sensitivity of a cancer cell to a KRas G12D inhibitor compound of Formula (I), comprising administering to a subject undergoing KRas G12D treatment with a compound as defined in any one of claims 1-14, alone or combined with a pharmaceutically acceptable carrier, excipient or diluents, a therapeutically effective amount of a pan ErbB family inhibitor, wherein the pan ErbB family inhibitor synergistically increases the sensitivity of the cancer cell to the KRas G12D inhibitor, preferably wherein the therapeutically effective amount of the KRas G12D inhibitor in the combination is between about 0.01 to 100 mg/kg per day, more preferably wherein the therapeutically effective amount of the KRas G12D inhibitor in the combination is between about 0.1 to 50 mg/kg per day, and/or wherein the therapeutically

effective amount of the pan ErbB family inhibitor in the combination is between about 0.01 to 100 mg/kg per day, more preferably wherein the therapeutically effective amount of the pan ErbB family inhibitor in the combination is between about 0.1 to 50 mg/kg per day.

24. The use according to any one of claims 1-18 and 22, or the combination of a pan ErbB family inhibitor and a KRas G12D inhibitor of claim 20 or 23, or the in vitro method of claim 21, wherein the cancer is selected from the group consisting of Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Biliary tract: gall bladder carcinoma, ampullary carcinoma, cholangiocarcinoma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma,

meningioma, glioma, sarcoma); Gynecological: uterus (endometrial `carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma); Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma, preferably wherein the cancer is a KRas G12D-associated cancer, preferably wherein the cancer is non-small cell lung cancer.

25. A kit comprising the pharmaceutical composition of claim 19 for use in treating KRas G12D cancer in a subject.

26. A kit comprising: a) a pharmaceutical composition comprising a pan ErbB family inhibitor and b) a pharmaceutical composition comprising a KRas G12D inhibitor of claim 1, for use in treating a KRas G12D cancer in a subject.

27. The kit according to claim 25 or 26, further comprising an insert with instructions for administration of the pharmaceutical composition(s).