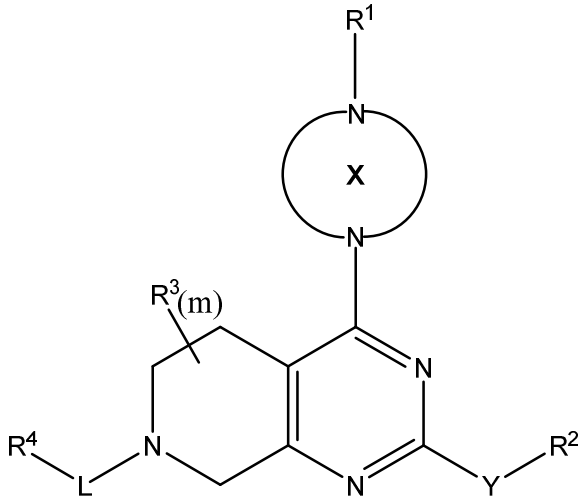
CLAIMS

WE CLAIM:

1. A compound of formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof:

wherein:

X is a 4-12 membered saturated or partially saturated monocyclic, bridged or spirocyclic ring, wherein the saturated or partially saturated monocyclic ring is optionally substituted with one or more R^8;

Y is a bond, O, S or NR^5;

R^1 is $–C(O)C(R^A)$ ------ $C(R^B)_p$ or $–SO_2C(R^A)$ ------ $C(R^B)_p$;

R^2 is hydrogen, alkyl, hydroxyalkyl, dihydroxyalkyl, alkylaminylalkyl, dialkylaminylalkyl, -Z-NR^5R^{10}, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, or heteroarylalkyl, wherein each of the Z, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl may be optionally substituted with one or more R^9;

Z is C1 – C4 alkylene;

each R^3 is independently C1 – C3 alkyl, oxo, or haloalkyl;

L is a bond, -C(O)-, or C1 – C3 alkylene;

R^4 is hydrogen, cycloalkyl, heterocyclyl, aryl, aralkyl or heteroaryl, wherein each of the cycloalkyl, heterocyclyl, aryl, aralkyl and heteroaryl may be optionally substituted with one or more R^6 or R^7;

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

R^6 is cycloalkyl, heterocyclyl, heterocyclylalkyl, aryl, or heteroaryl, wherein each of the cycloalkyl, heterocyclyl, aryl, or heteroaryl may be optionally substituted with one or more R^7;

each R^7 is independently halogen, hydroxyl, C1 – C6 alkyl, cycloalkyl, alkoxy, haloalkyl, amino, cyano, heteroalkyl, hydroxyalkyl or Q-haloalkyl, wherein Q is O or S;

R^8 is oxo, C1 – C3 alkyl, C2 – C4 alkynyl, heteroalkyl, cyano, $-C(O)OR^5$, $-C(O)N(R^5)_2$, $-N(R^5)_2$, wherein the C1 – C3 alkyl may be optionally substituted with cyano, halogen, $-OR^5$, $-N(R^5)_2$, or heteroaryl;

each R^9 is independently hydrogen, oxo, acyl, hydroxyl, hydroxyalkyl, cyano, halogen, C1 – C6 alkyl, aralkyl, haloalkyl, heteroalkyl, cycloalkyl, heterocyclylalkyl, alkoxy, dialkylaminyl, dialkylamidoalkyl, or dialkylaminylalkyl, wherein the C1 – C6 alkyl may be optionally substituted with cycloalkyl;

each R^{10} is independently hydrogen, acyl, C1 – C3 alkyl, heteroalkyl or hydroxyalkyl;

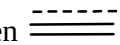
R^A is absent, hydrogen, or C1 – C3 alkyl;

each R^B is independently hydrogen, C1 – C3 alkyl, alkylaminylalkyl, dialkylaminylalkyl or heterocyclylalkyl;

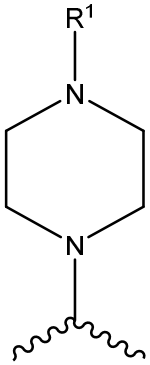
m is zero or an integer between 1 and 2;

p is one or two; and wherein,

when  is a triple bond then R^A is absent, R^B is present and p equals one,

or when  is a double bond then R^A is present, R^B is present and p equals two, or R^A, R^B and the carbon atoms to which they are attached form a 5-8 membered partially saturated cycloalkyl optionally substituted with one or more R^7.

2. The compound of claim 1, wherein R^1-X is:



wherein the piperazinyl ring is optionally substituted with R^8.

3. The compound of claim 2, wherein R^1 is $-C(O)C(R^A)$ ⋮ $C(R^B)_p$, wherein ⋮ is a triple bond R^A is absent, p is one and R^B is C1 – C3 alkyl, or ⋮ is a double bond, R^A is hydrogen or C1 – C3 alkyl, p is two and each R^B is independently hydrogen, C1 – C3 alkyl, dialkylaminylalkyl or heterocyclylalkyl.

4. The compound of claim 1, wherein R^1 is $-C(O)CH=CH_2$.

5. The compound of according to claim 1, wherein Y is O.

6. The compound of claim 1, wherein R^2 is heterocyclylalkyl.

7. The compound of claim 6, wherein the heterocyclyl of the heterocyclylalkyl is independently azetidinyl, methylazetidinyl, difluoroazetidinyl, tetrahydropyran, pyrrolidinyl, methylpyrrolidinyl, diemethylpyrrolidinyl, isopropylpyrrolidinyl, cycloalkylalkylpyrrolidinyl, hydroxypyrrolindinyl, fluoropyrrolidinyl, difluoropyrrolidinyl, methoxyethylpyrrolidinyl, (N-methyl)methoxypyrrolidinyl, piperazinyl, dimethylaminylpyrrolidinyl, morpholinyl, methylmorpholinyl, 1,4-oxazepanyl, piperdinyl, methylpiperidinyl acylpiperdinyl, cyanopiperdinyl, cycloalkylpiperdinyl, halopiperdinyl, dihalopiperdinyl, fluoropiperdinyl, difluoropiperdinyl, alkoxypiperdinyl, pyrrolidonyl, piperidinonyl, thiomorpholinyl-1,1-dioxide, 3-azabicyclo[3.1.0]hexanyl, oxa-5-azabicyclo[2.2.1]heptan-5-yl, or azabicyclo[2.2.1]heptan-2-yl.

8. The compound of claim 1, wherein R^2 is $-ZNR^5R^{10}$.

9. The compound according to claim 1, wherein R^4 is aryl optionally substituted with one or more R^7.

10. The compound of claim 9, wherein the aryl is selected from the group consisting of phenyl and naphthyl optionally substituted with one or more R^7.

11. The compound according to any one of claims 2-10, wherein R^4 is heteroaryl.

12. The compound of claim 11, wherein the heteroaryl is pyridinyl, indolyl, indazolyl, quinolinyl, isoquinolinyl or benzo[d]thiazolyl.

13. The compound according to claim 1, wherein R^4 is aralkyl optionally substituted with one or more R^7.

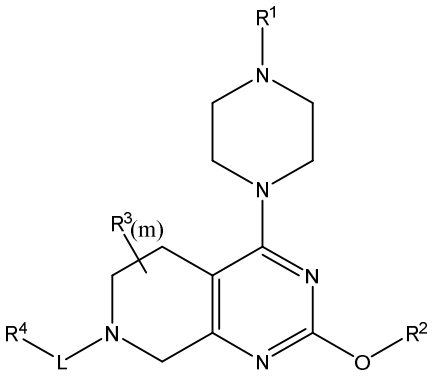
14. The compound according to claim 1, wherein L is a bond.

15. The compound according to claim 1, wherein R^8 is heteroalkyl, C2-C4 alkynyl, or C1 – C3alkyl optionally substituted with $-OR^5$, cyano or heteroaryl.

16. The compound of claim 13, wherein R^8 is C1 – C3 alkyl substituted with $-OR^5$.

17. The compound of claim 13, wherein R^8 is oxazolylmethyl.

18. The compound of claim 1, wherein the compound is of Formula I-B:



Formula I-B

where the piperazinyl ring is optionally substituted with R^8, and R^1, R^3, R^4, R^9, L and m are as defined in claim 1.

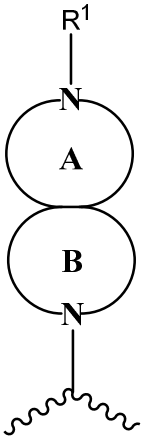
19. The compound of claim 16, wherein R^2 is heterocyclylalkyl.

20. The compound of claim 17, wherein the heterocyclyl portion of the heterocyclylalkyl of R^2 is pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, 1,4-oxazepanyl, thiomorpholinyl-1,1-dioxide, 3-azabicyclo[3.1.0]hexanyl, 2-oxa-5-azabicyclo[2.2.1]heptan-5-yl, or azabicyclo[2.2.1]heptan-2-yl, each optionally substituted with one or more R^9.

21. The compound of claim 13, wherein R^8 is heteroalkyl, C2-C4 alkynyl, or C1 – C3alkyl optionally substituted with -OR^5, cyano or heteroaryl.

22. The compound according to any one of claims 18-21, wherein L is a bond and R^4 is aryl or heteroaryl, each optionally substituted with one or more R^6 or R^7.

23. The compound of claim 1, wherein R^1-X is:



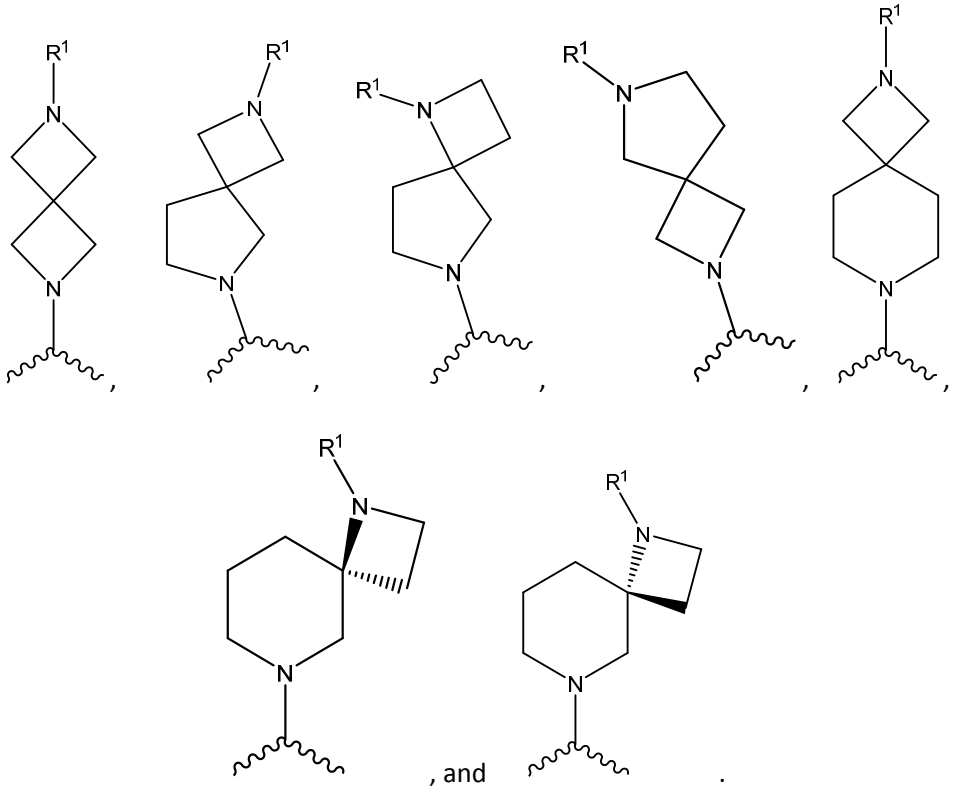
wherein A and B are a spirocyclic ring system, wherein A and B are the same or different and independently represent a 4-6 membered saturated ring system optionally substituted with one or more R^8.

24. The compound according to claim 18, wherein R^4 is aryl optionally substituted with one or more R^7.

25. The compound of claim 22, wherein the aryl is selected from the group consisting of phenyl and naphthyl optionally substituted with one or more R^7.

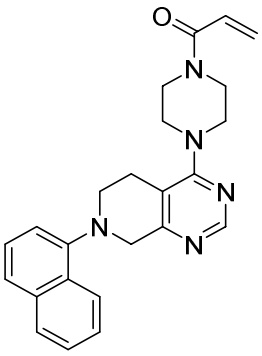
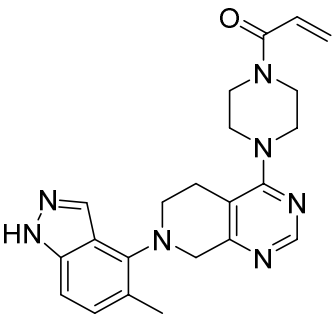
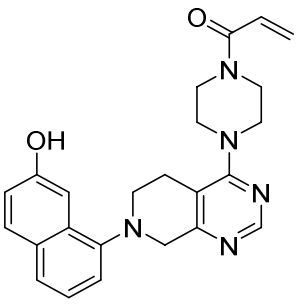
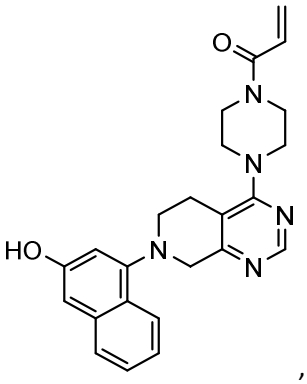
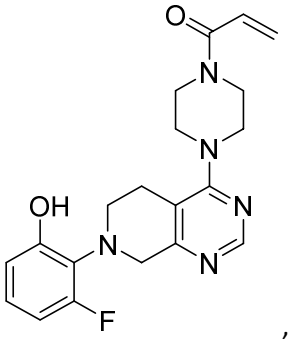
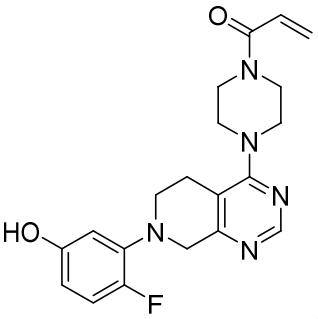
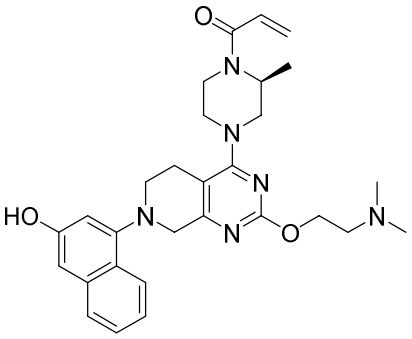
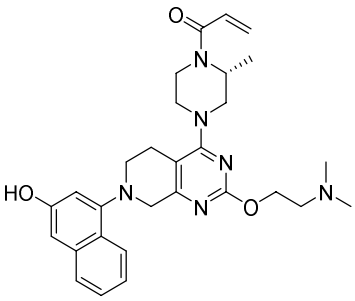
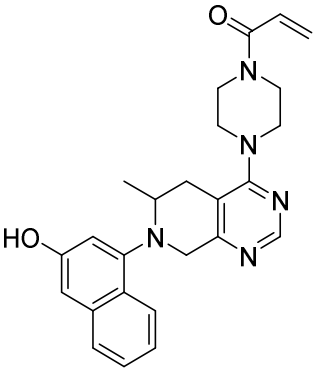
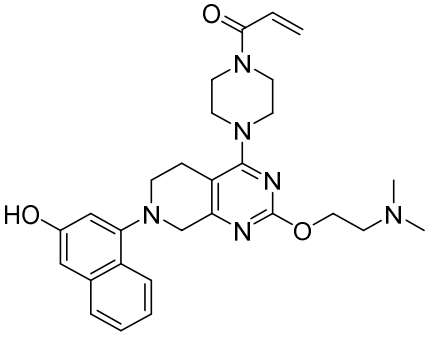
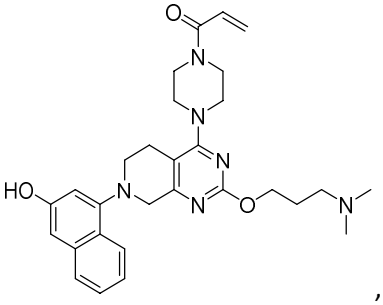
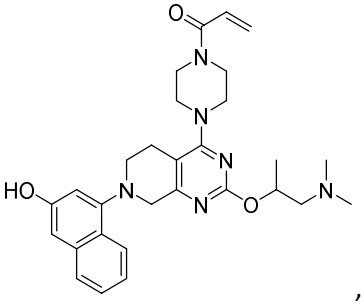
26. The compound according to claim 21, wherein L is a bond.

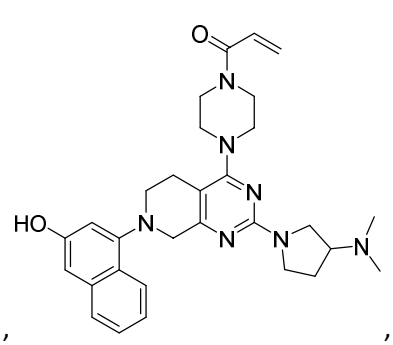
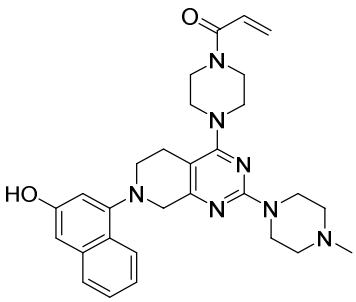
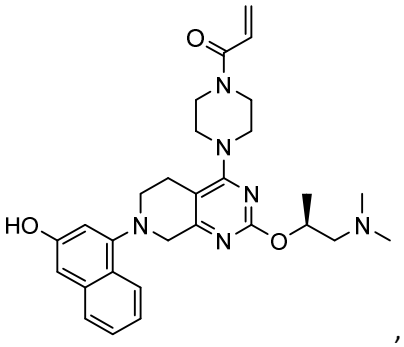
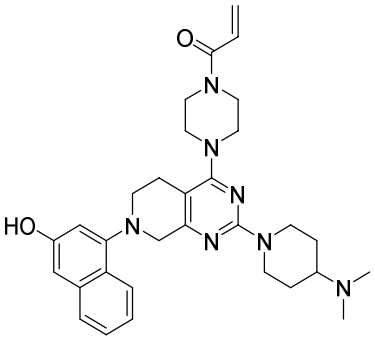
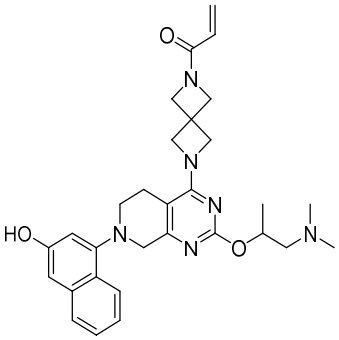
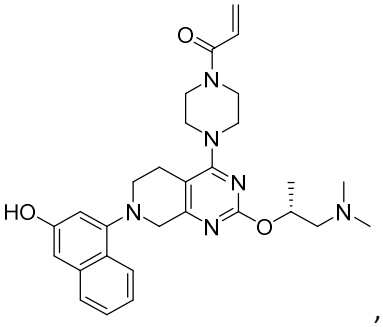
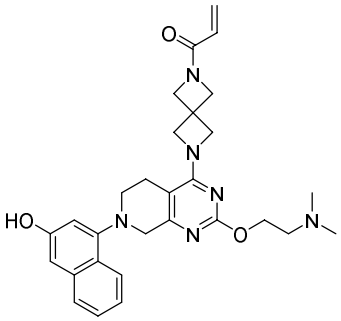
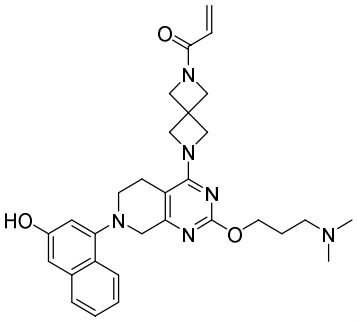
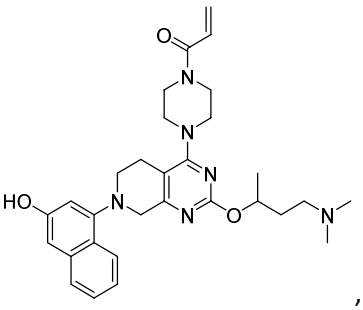
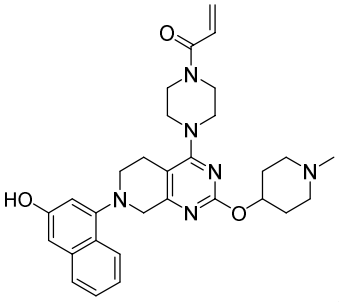
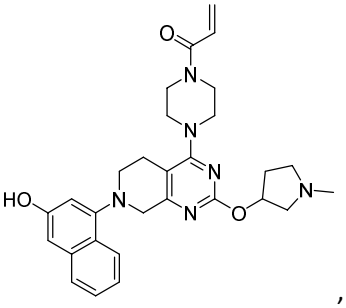
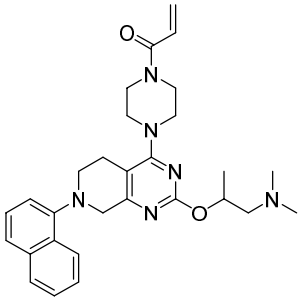
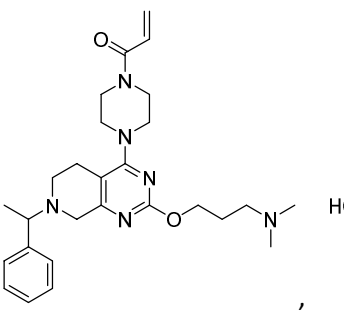
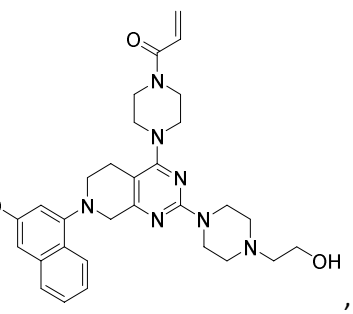
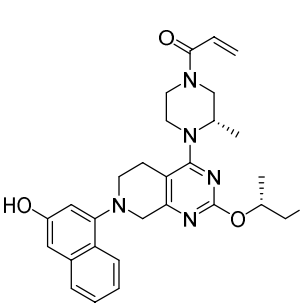
27. The compound according to claim 23, wherein the spirocyclic ring system formed by A and B are selected from the group consisting of:



28. The compound of claim 1, wherein R^4 is phenyl or naphthyl.

29. The compound of claim 1, wherein the compound is selected from the group consisting of:

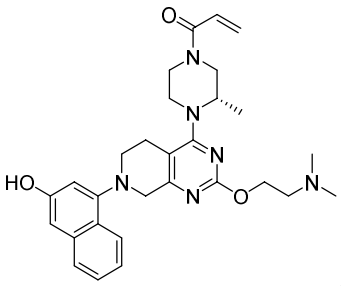
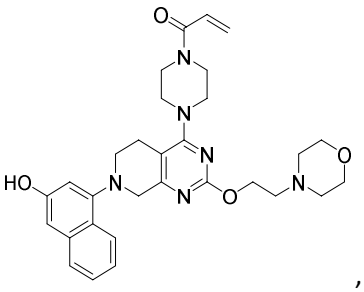
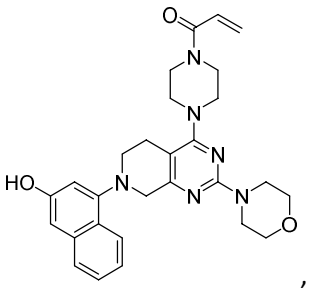
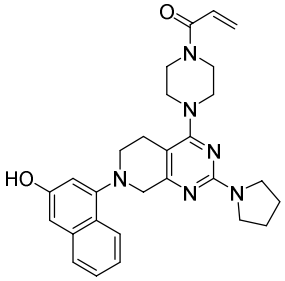
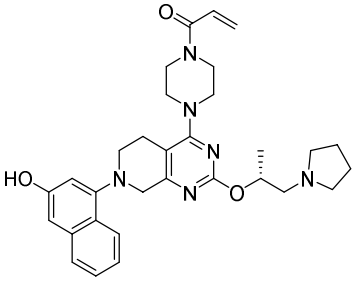
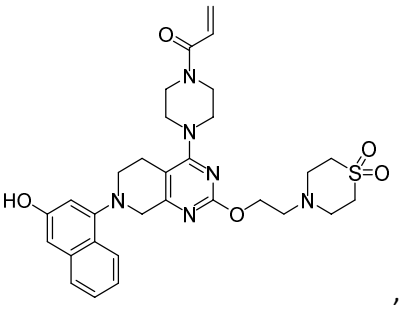
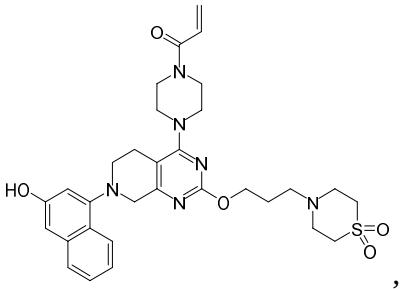
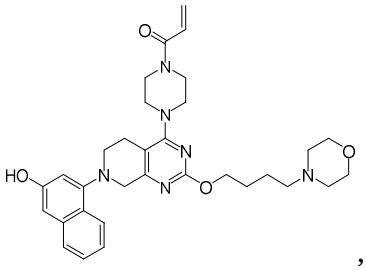
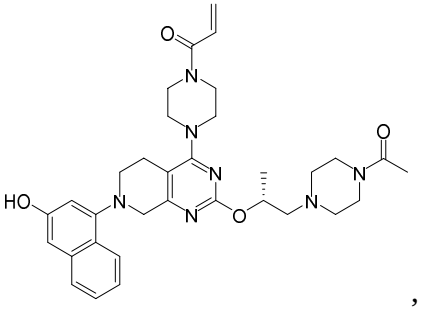
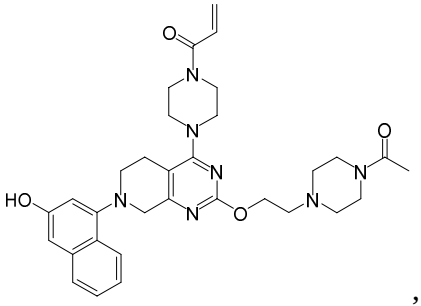
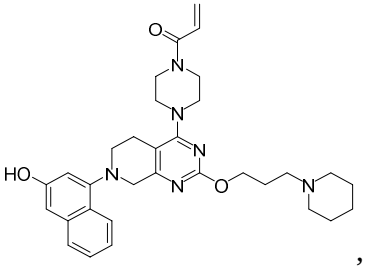
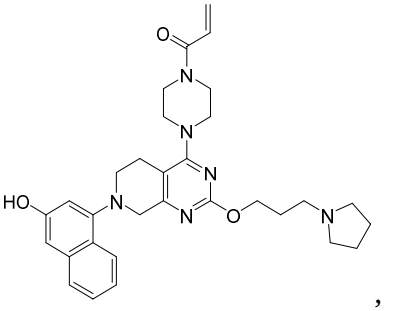
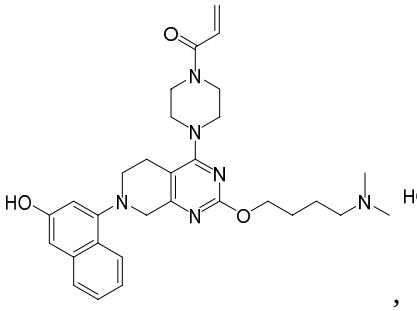
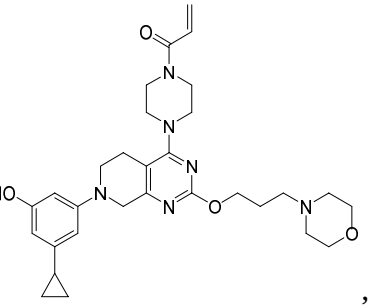
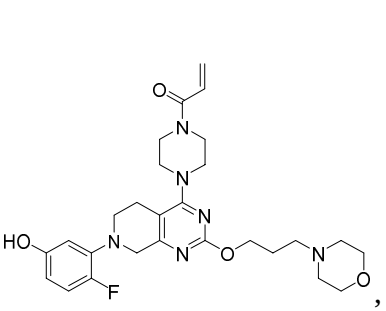

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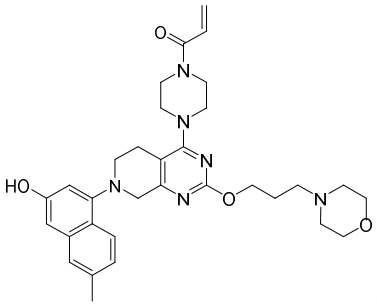
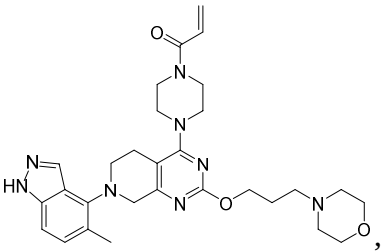
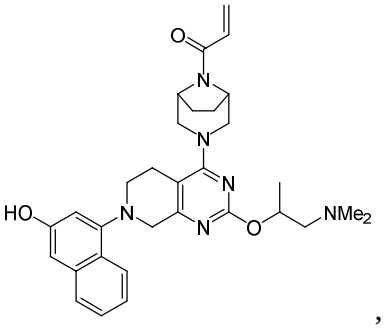
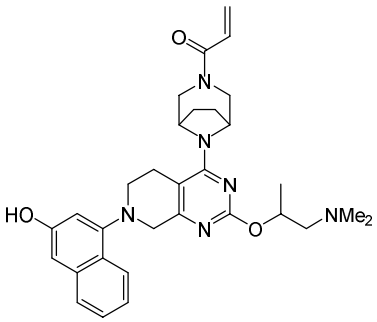
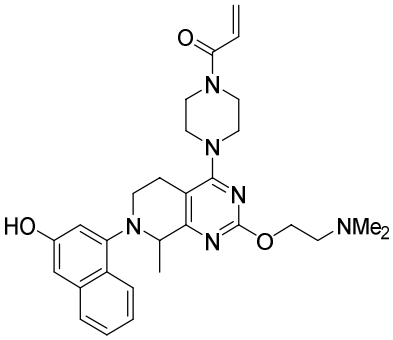
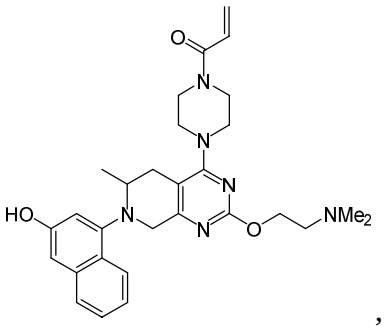
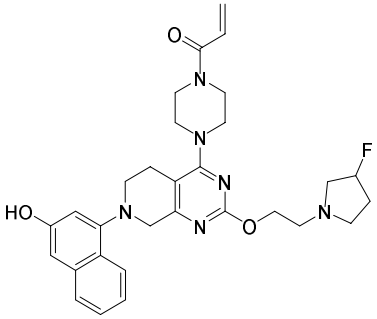
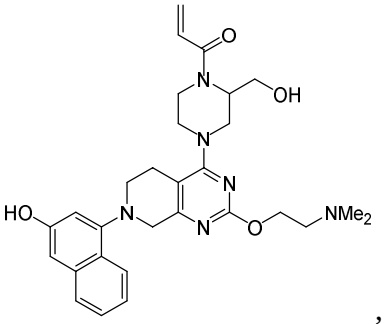
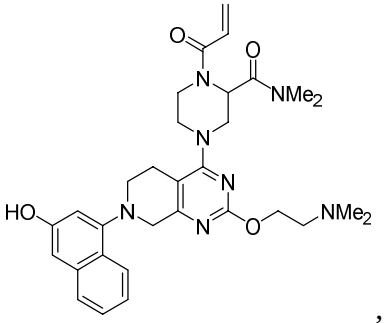
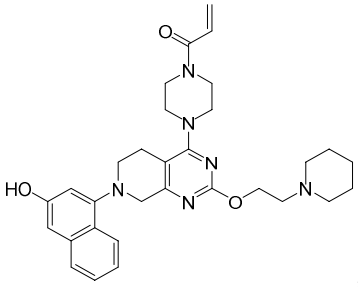
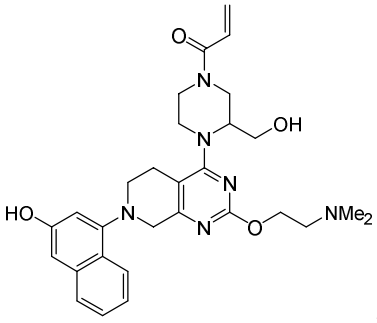
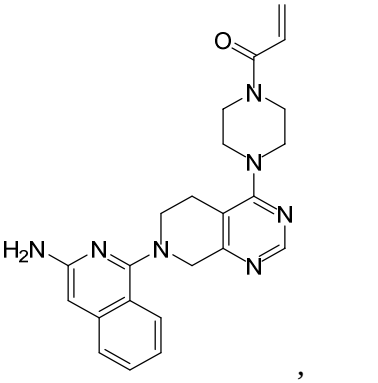
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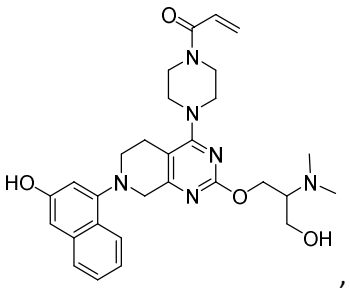
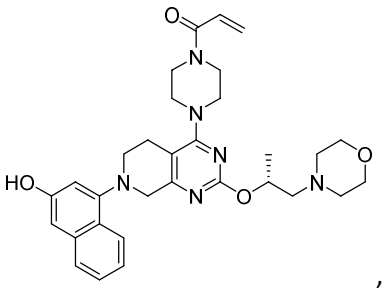
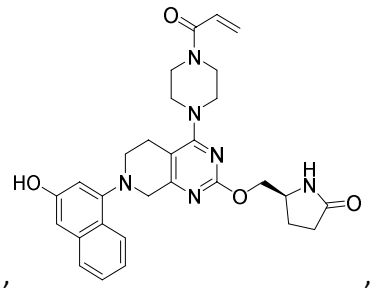
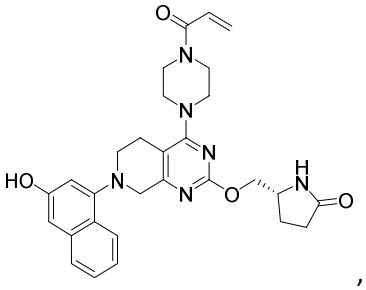
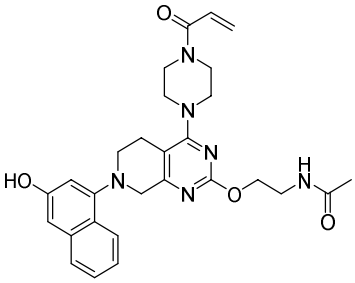
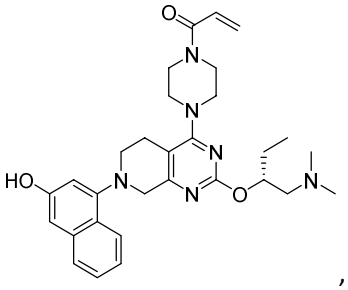
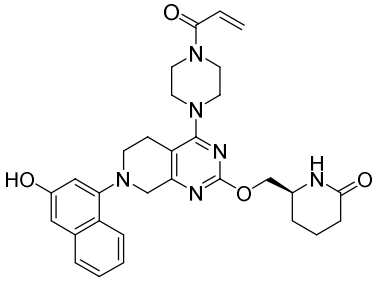
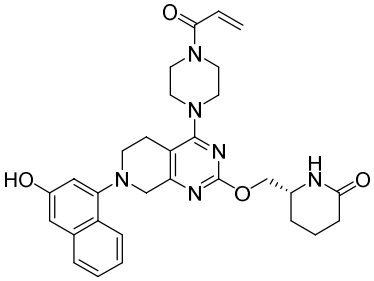
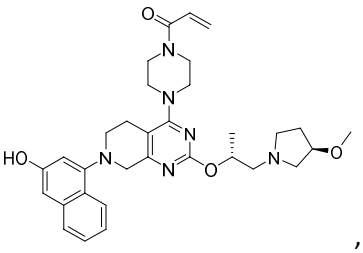
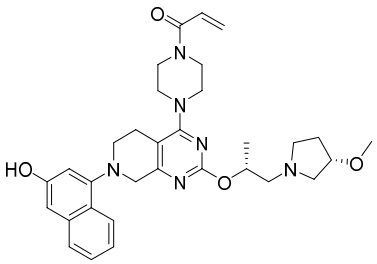
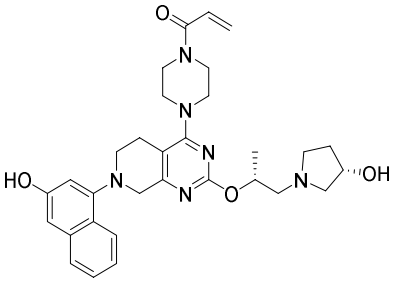
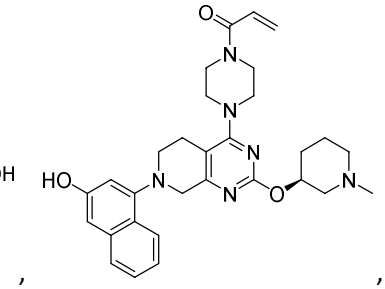
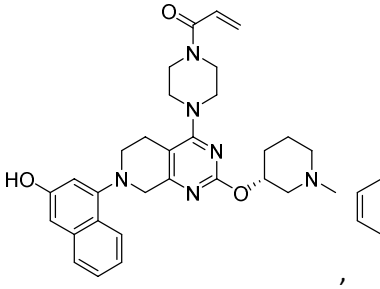
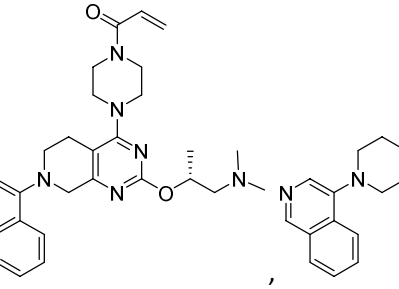
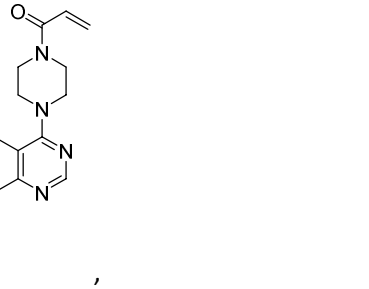

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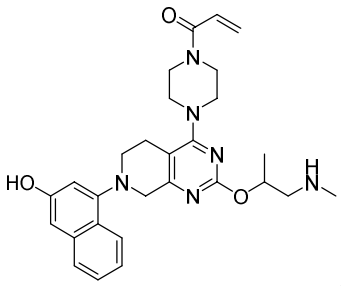
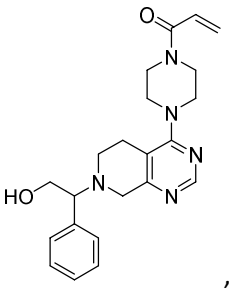
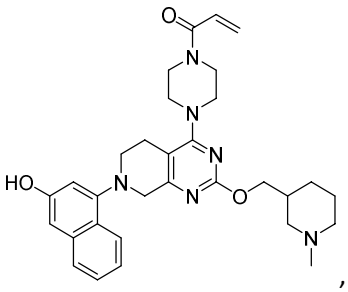
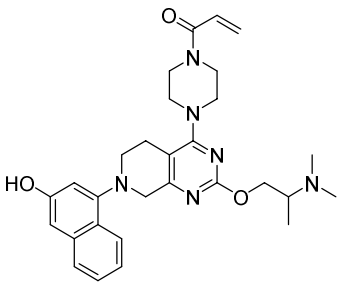
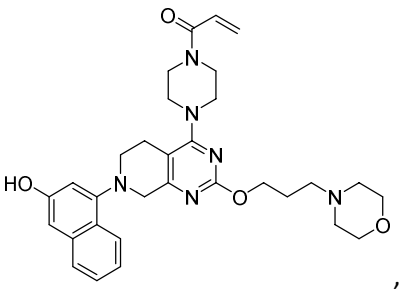
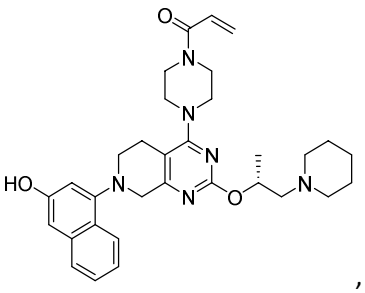
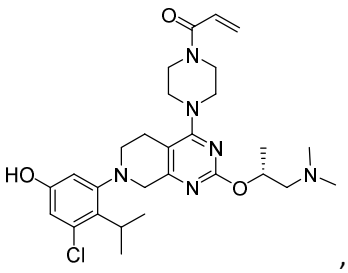
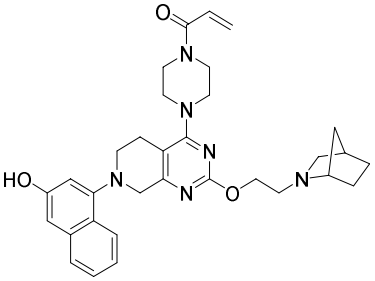
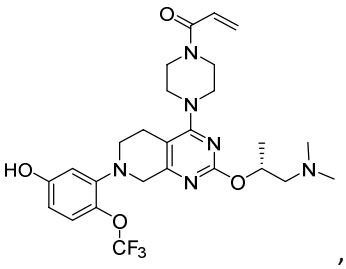
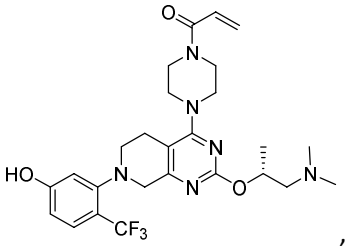
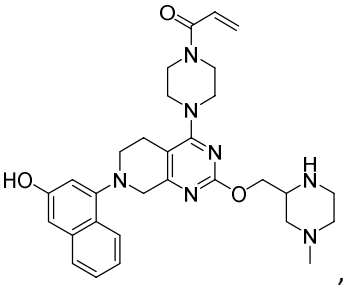
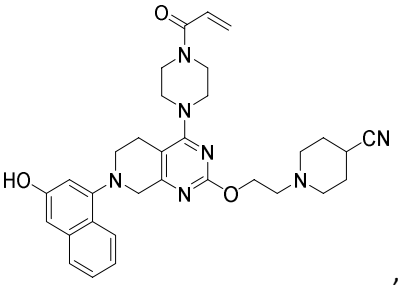
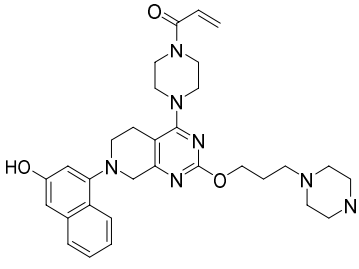
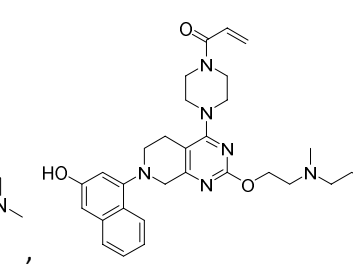
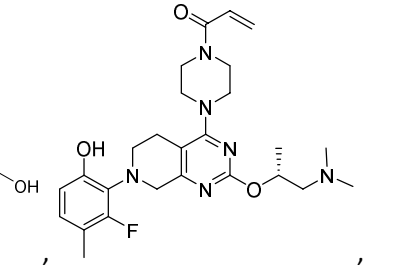

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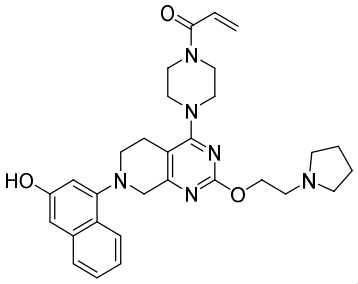
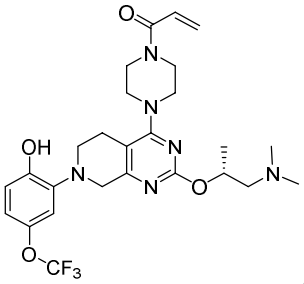
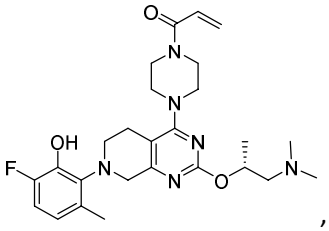
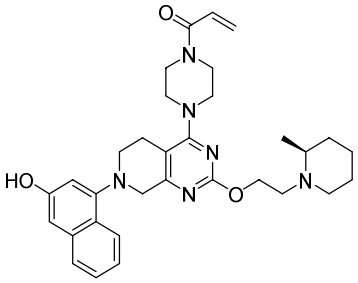
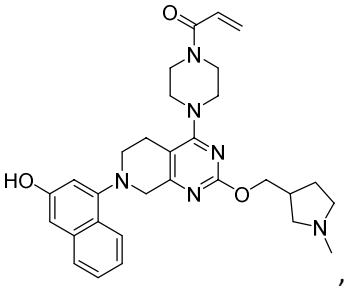
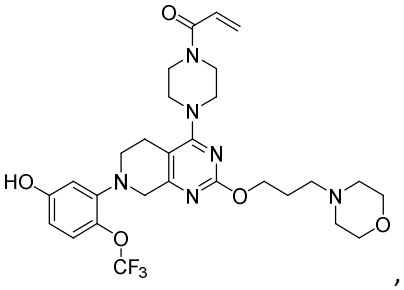
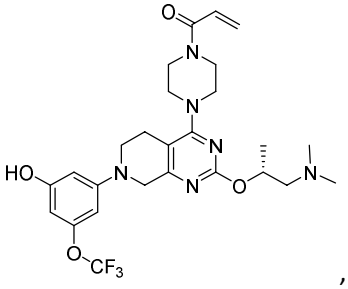
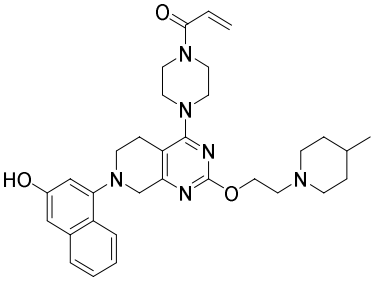
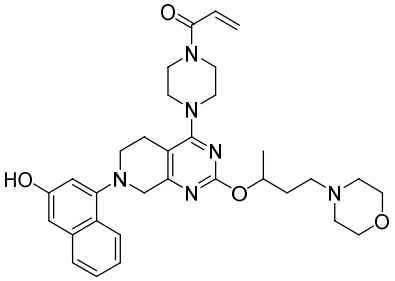
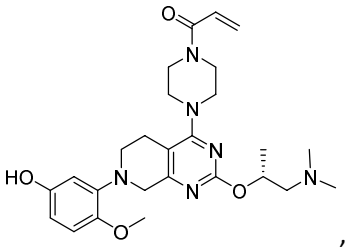
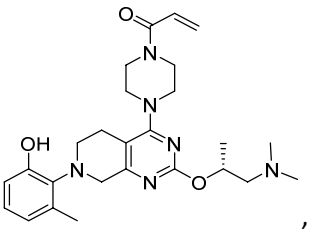
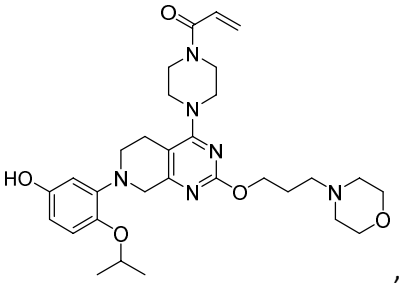
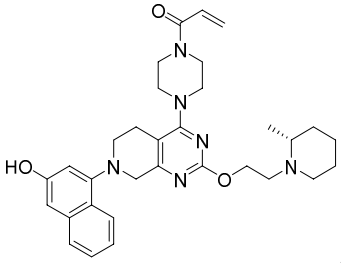
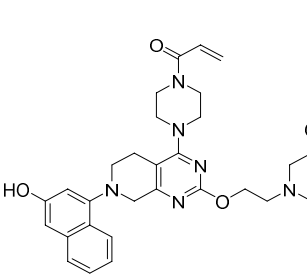
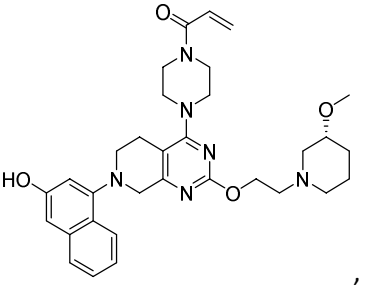
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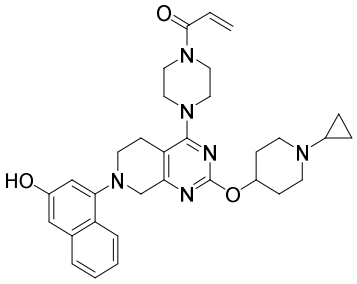
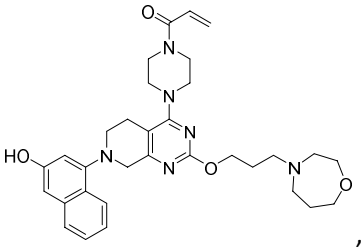
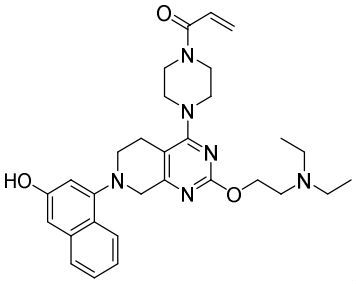
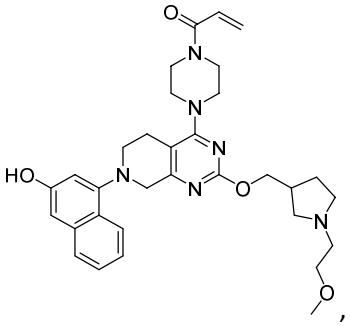
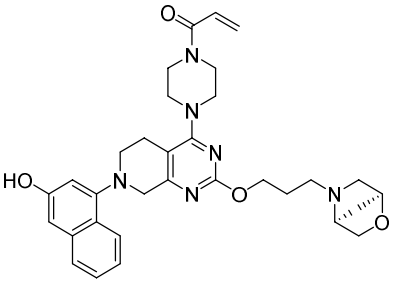
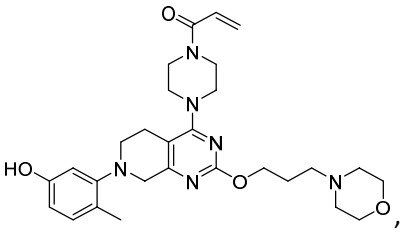
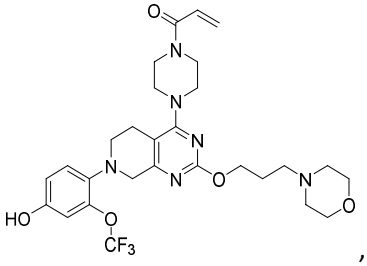
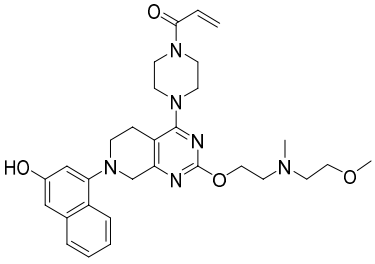
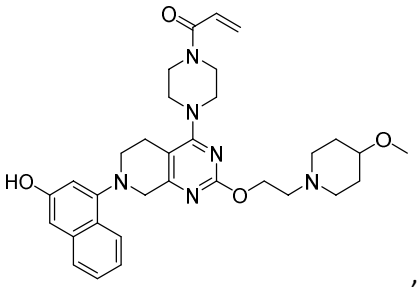
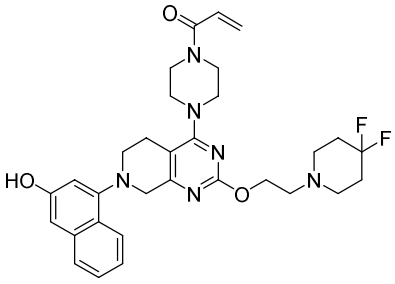
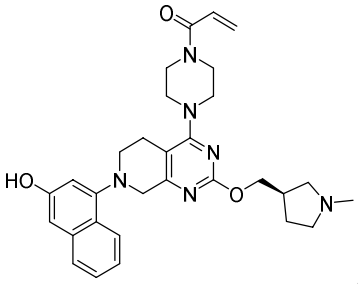
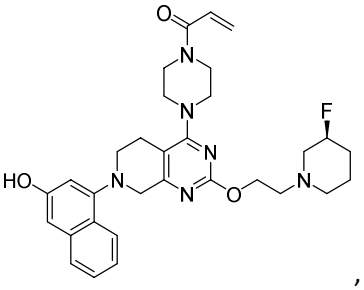
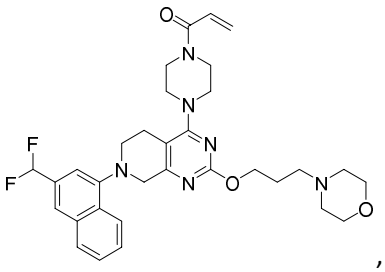
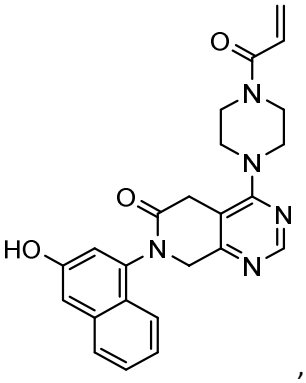
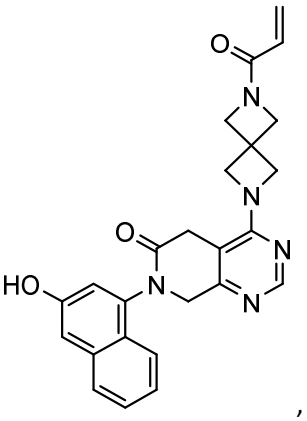
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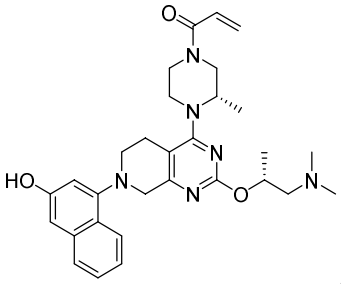
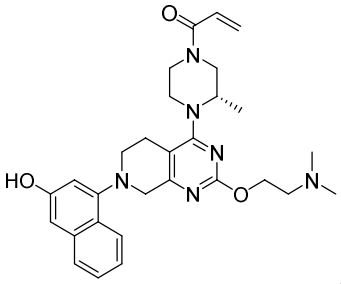
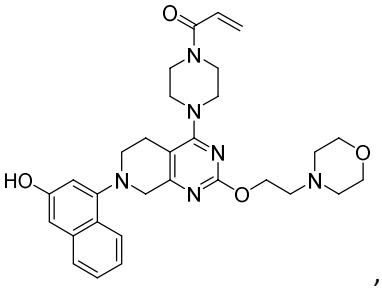
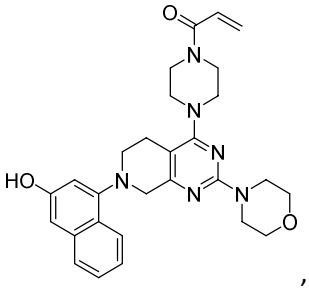
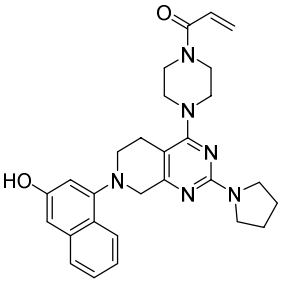
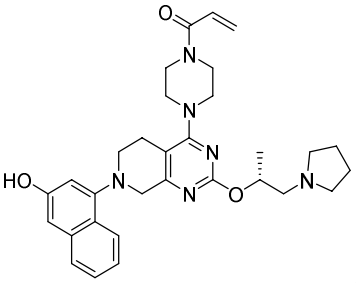
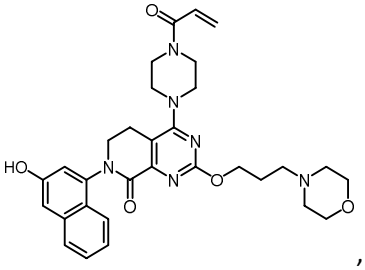
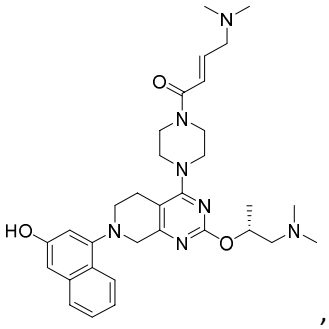
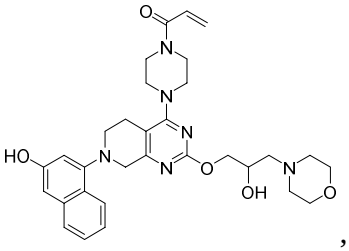
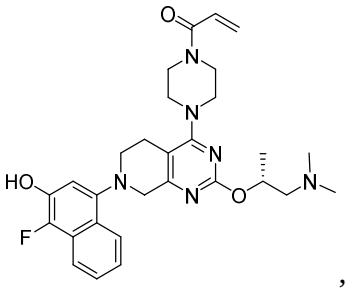
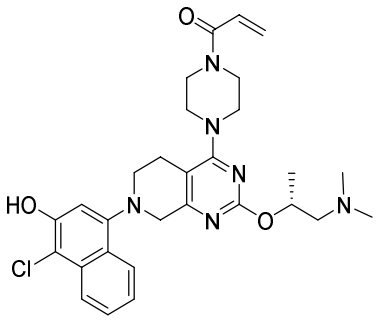
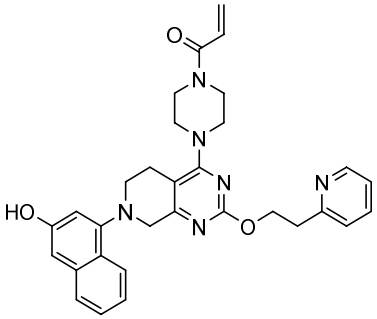
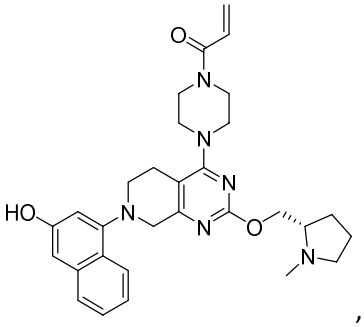

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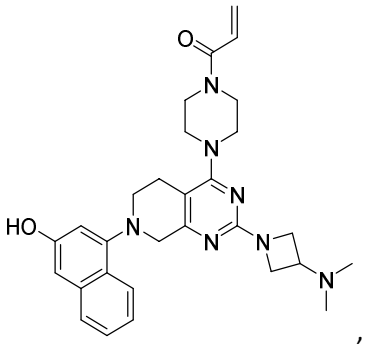
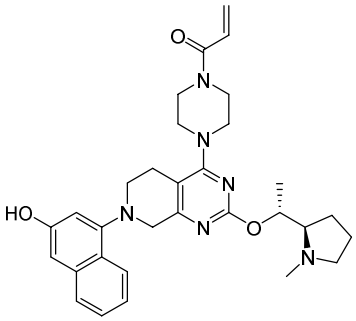
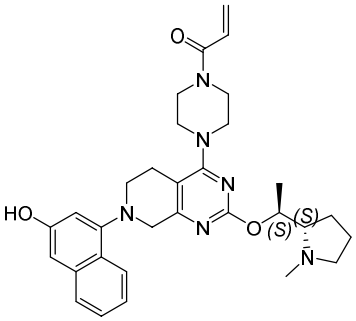
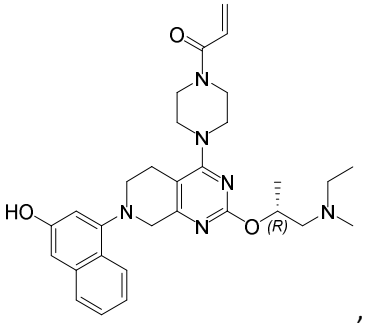
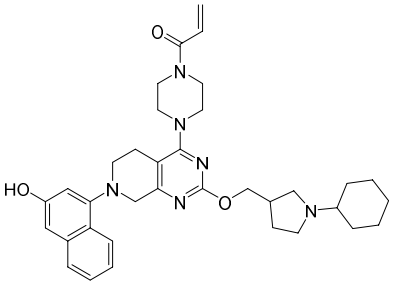
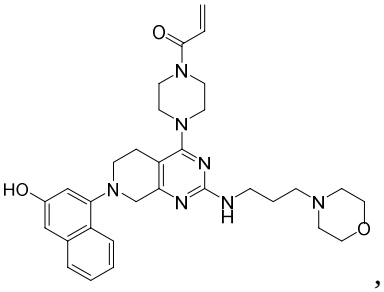
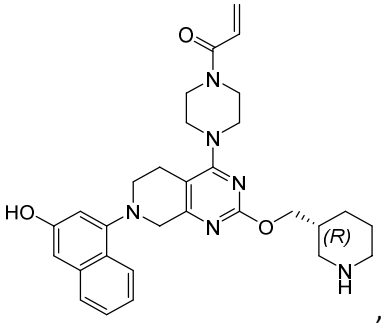
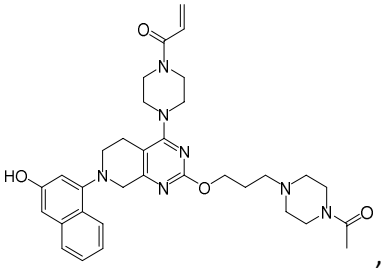
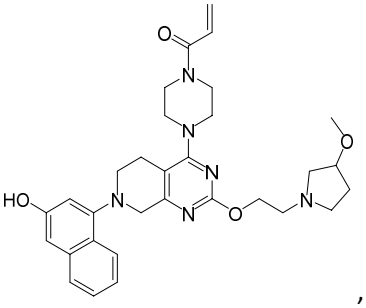
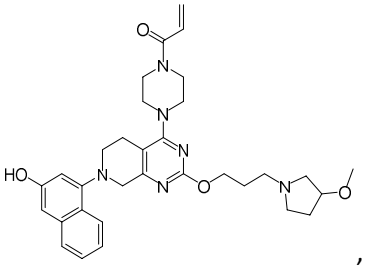
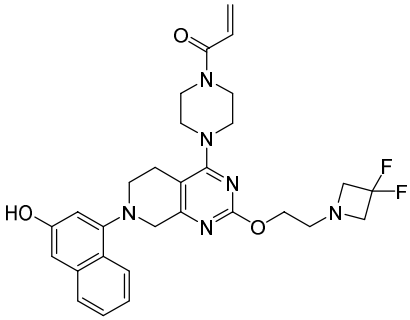
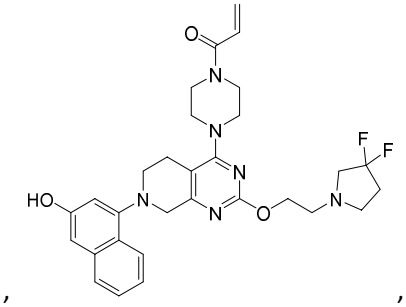
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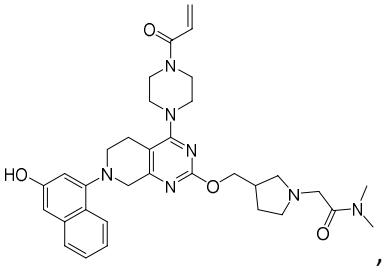
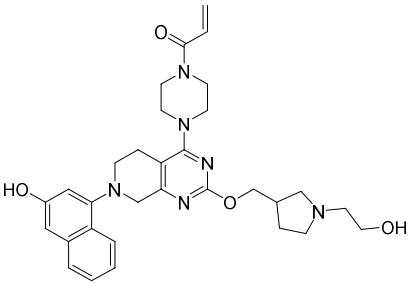
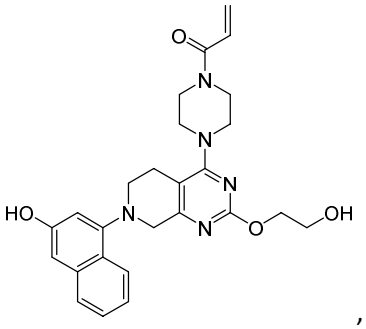
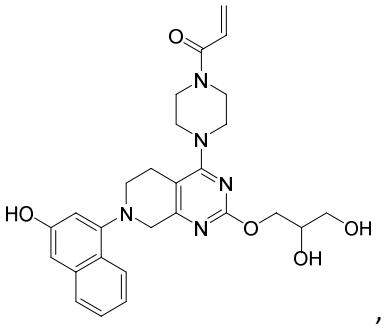
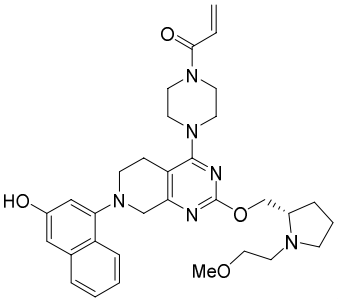
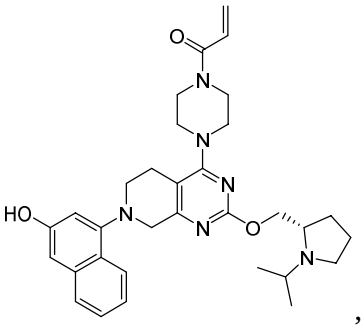
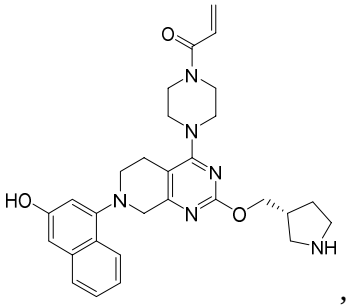
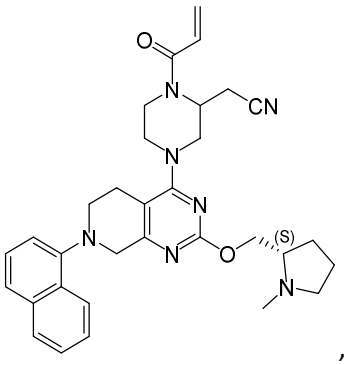
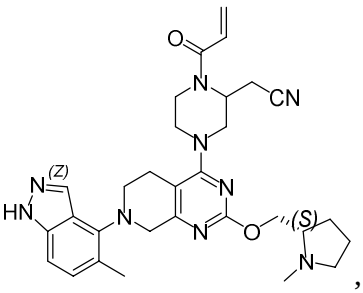
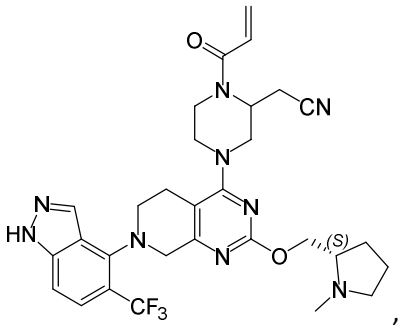
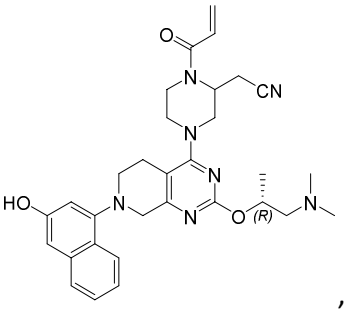
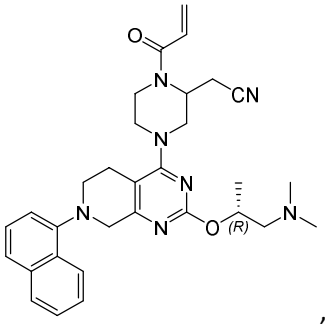
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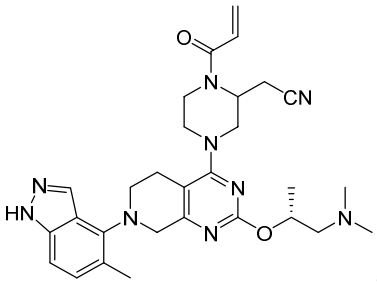
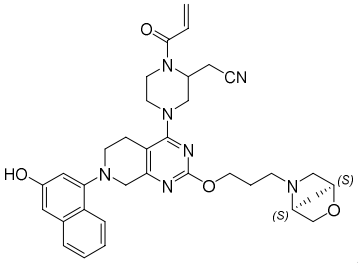
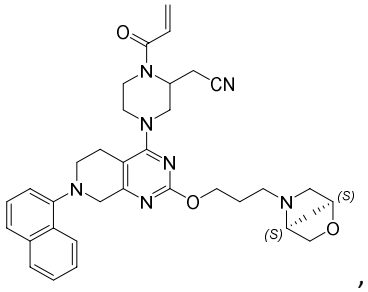
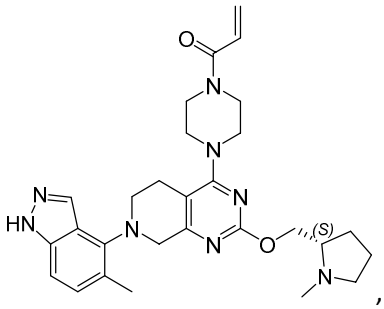
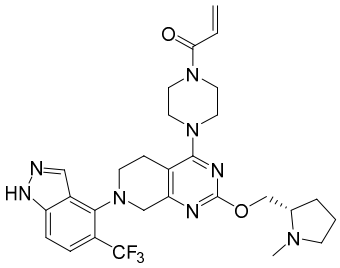
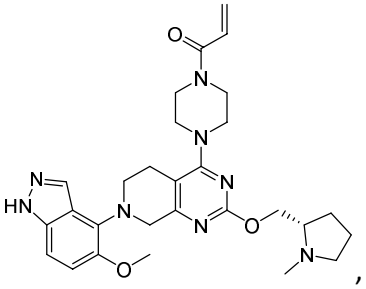
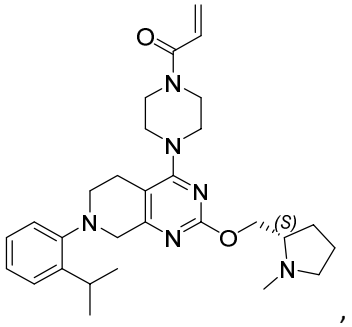
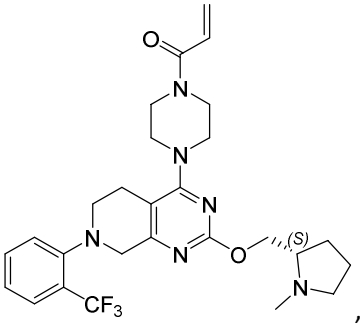
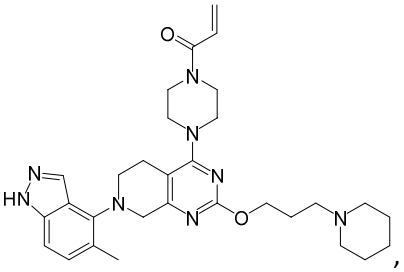
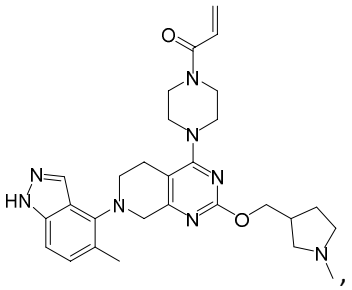
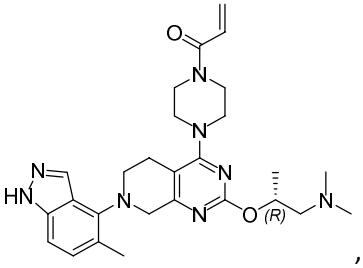
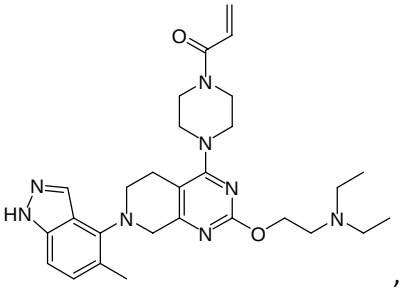
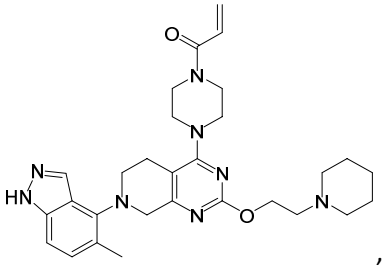
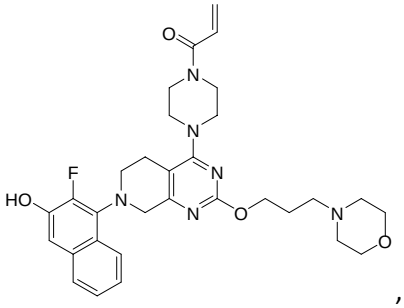
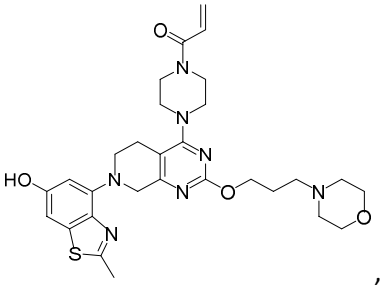
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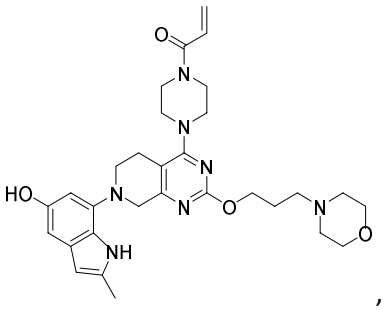
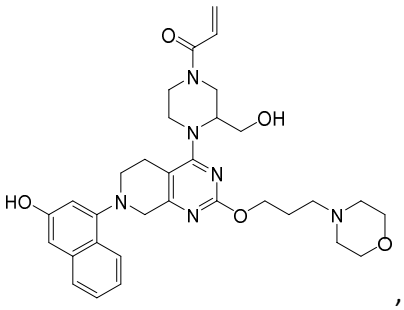
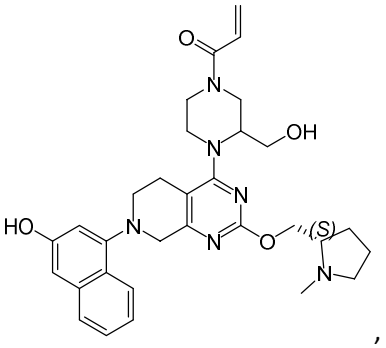
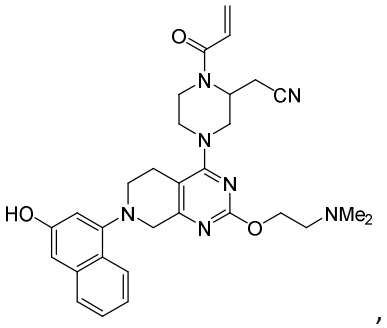
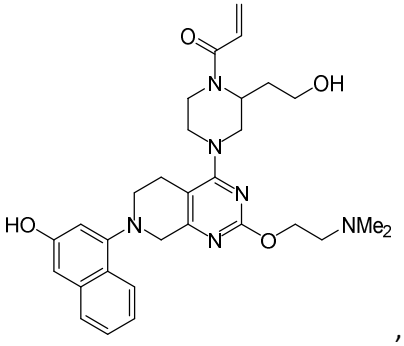
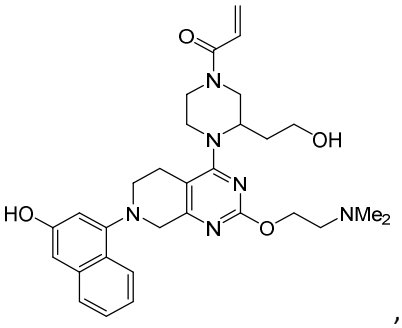
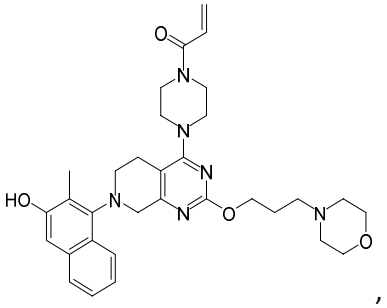
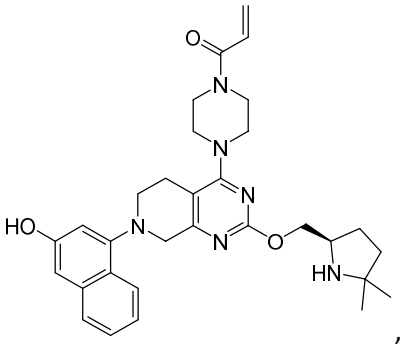
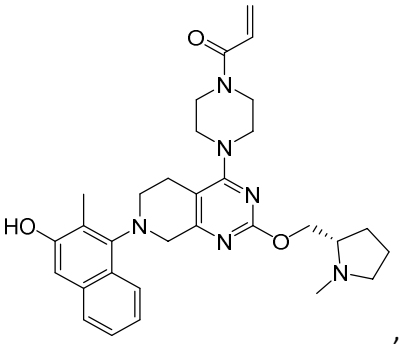
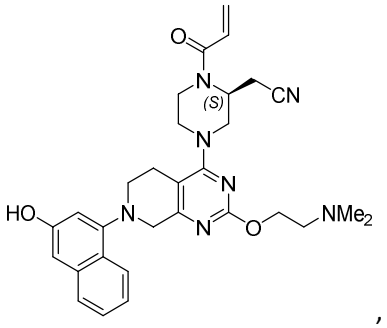
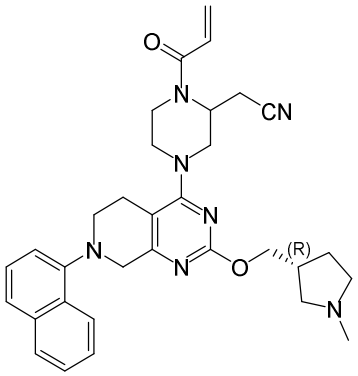
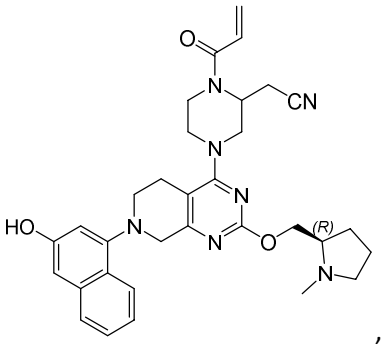

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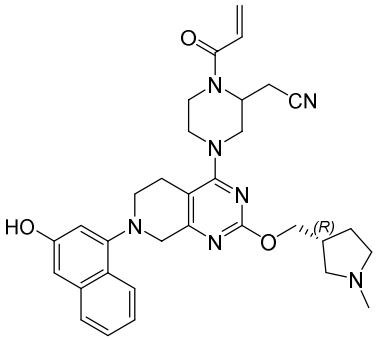
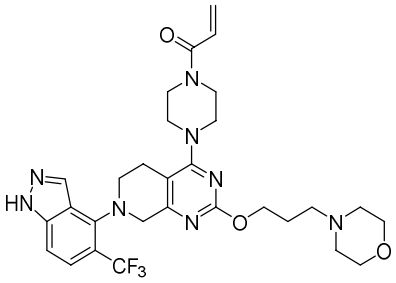
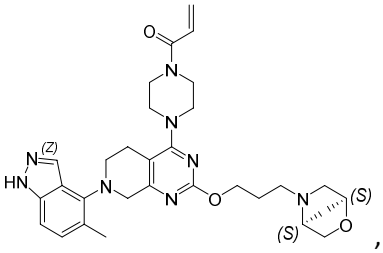
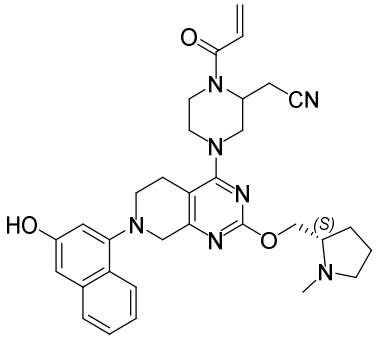
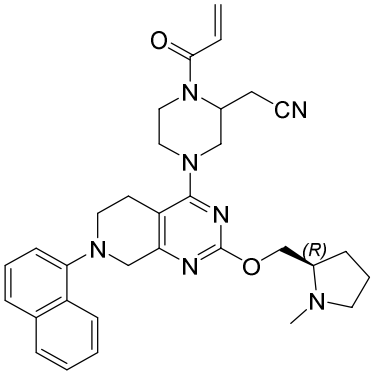
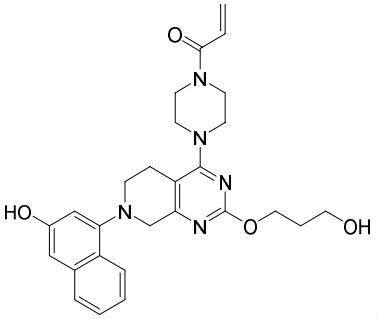
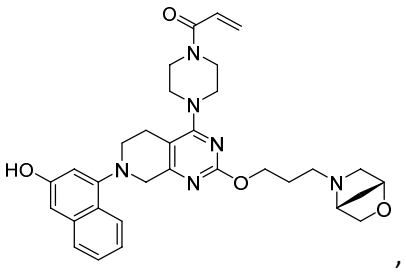
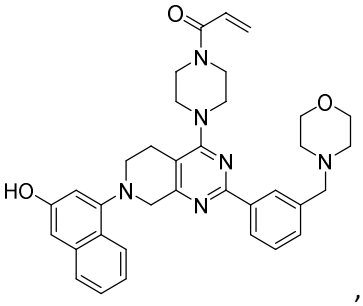
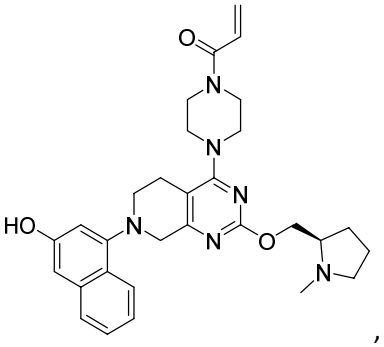
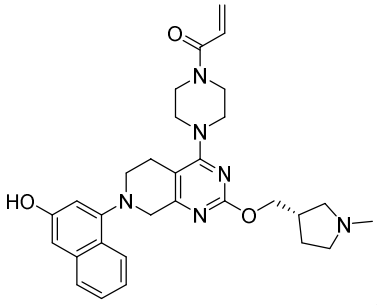
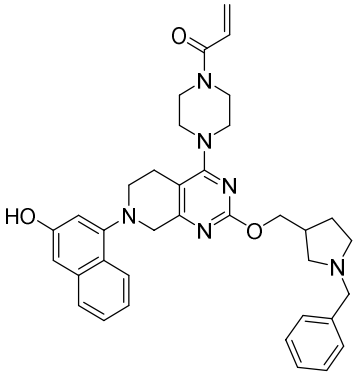
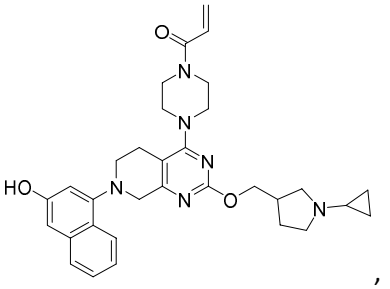
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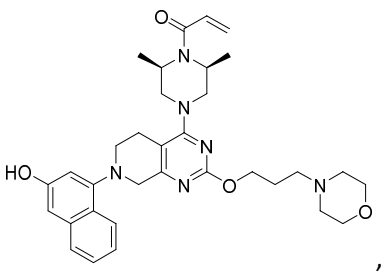
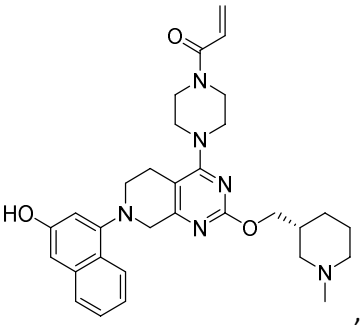
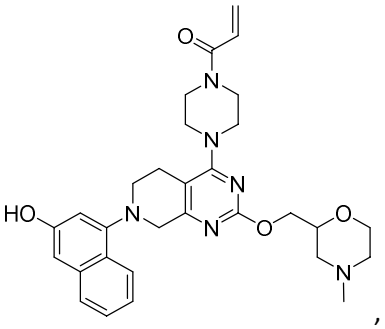
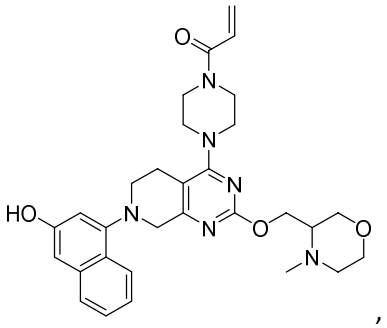
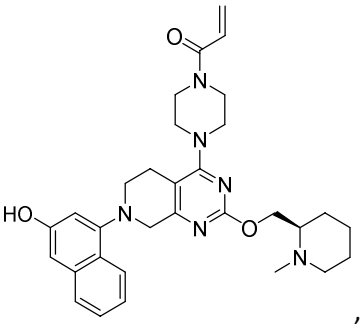
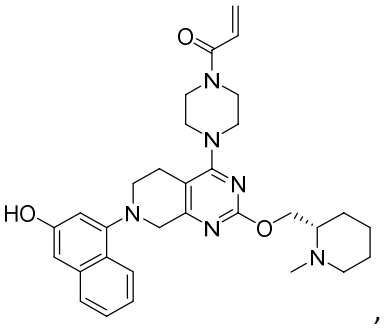
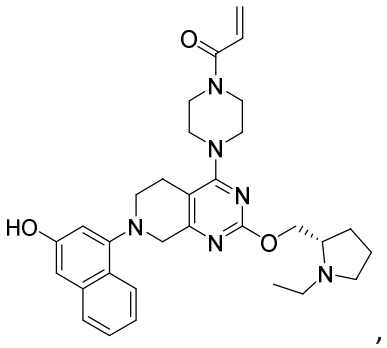
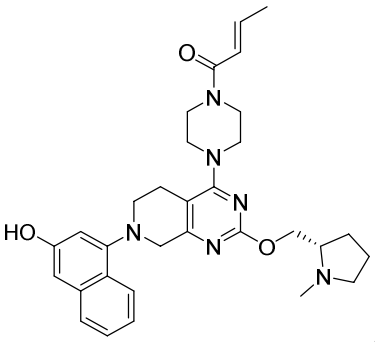
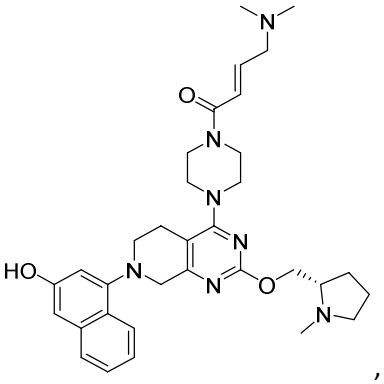
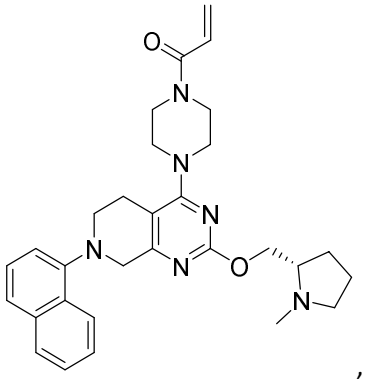
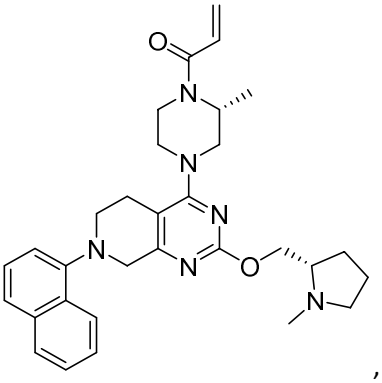
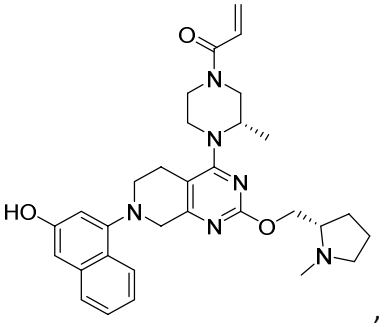
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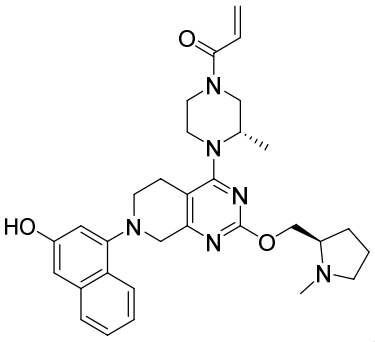
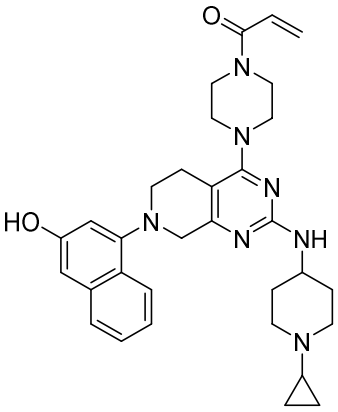
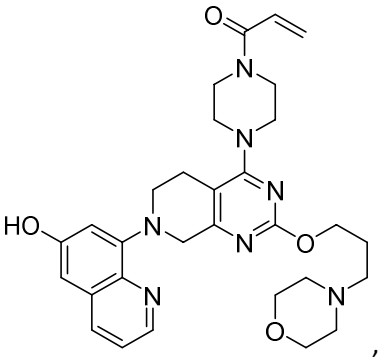
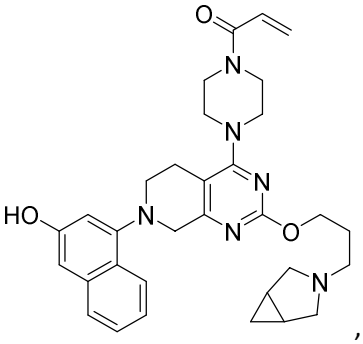
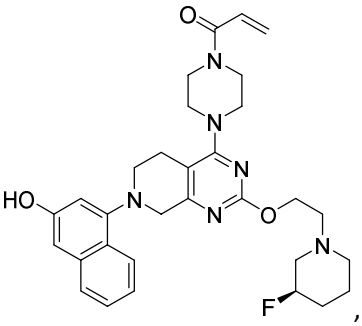
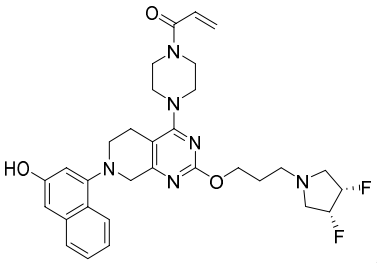
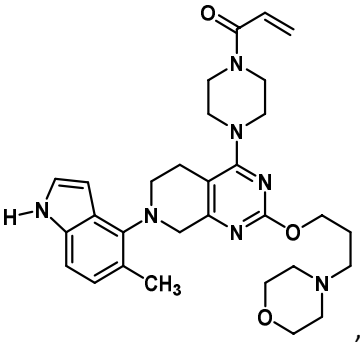
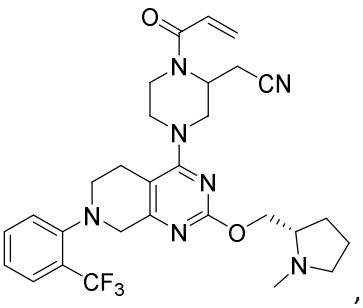
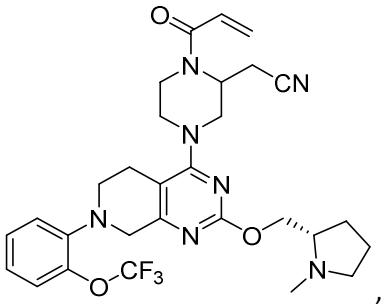
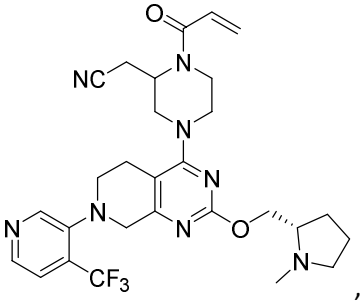
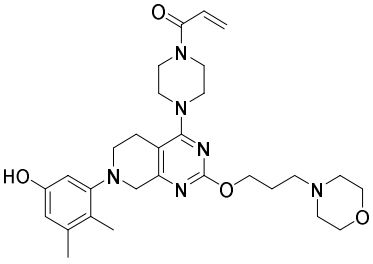
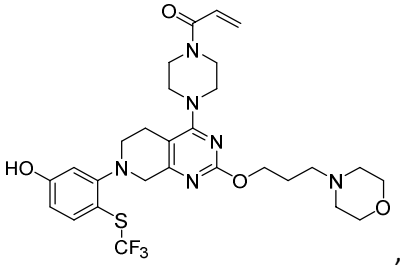
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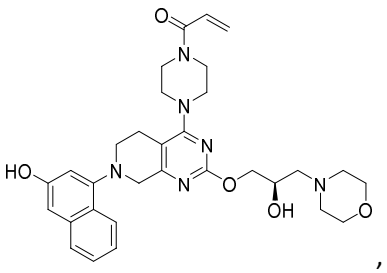
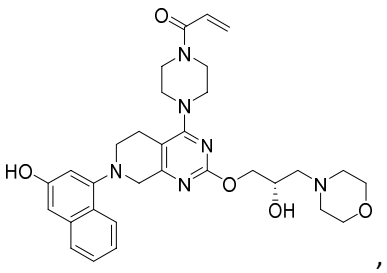
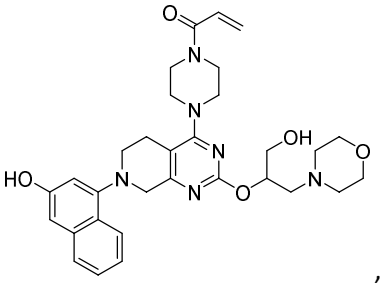
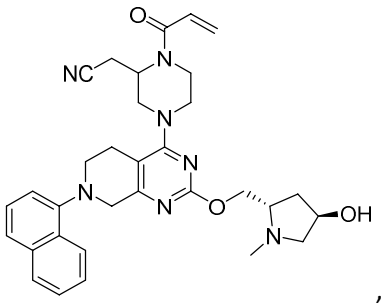
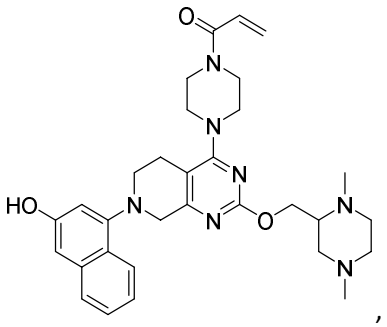
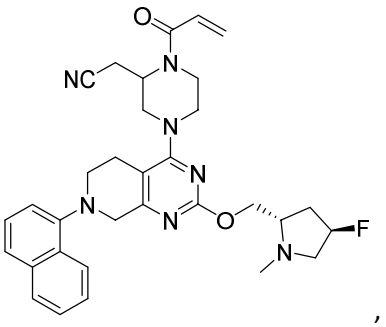
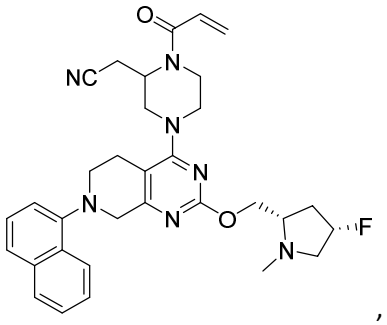
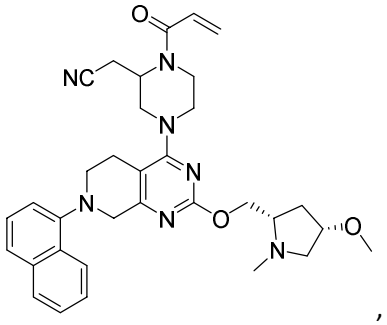
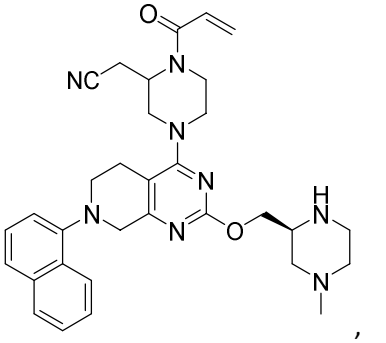
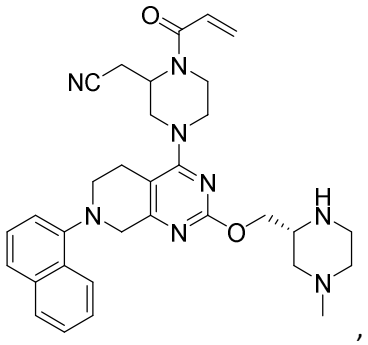
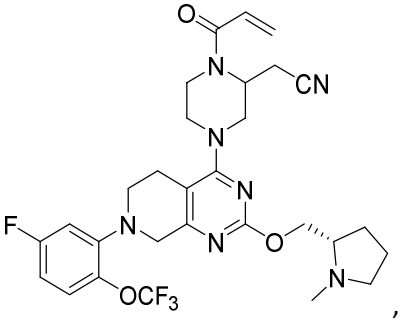
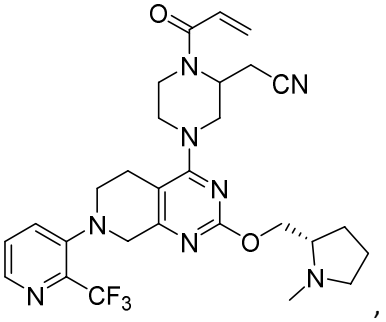

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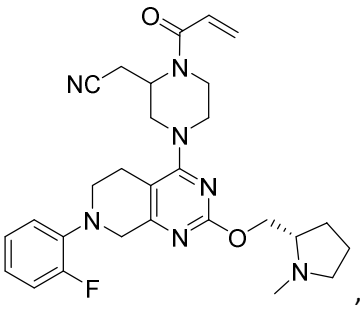
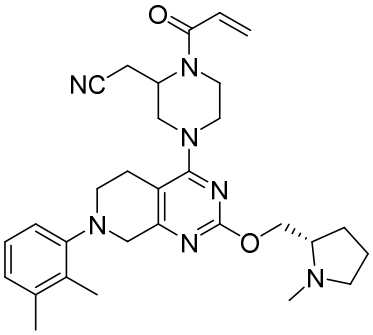
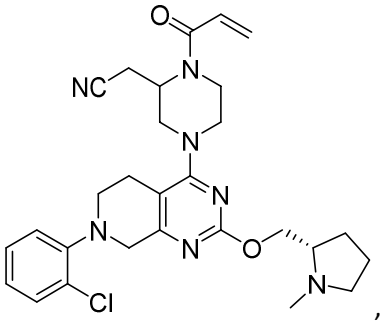
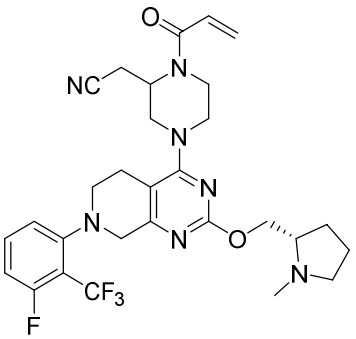
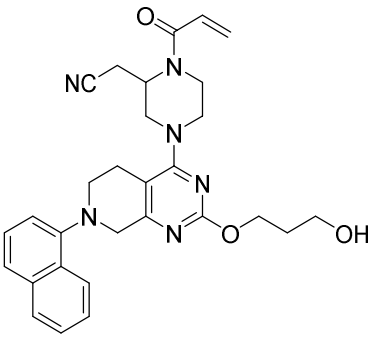
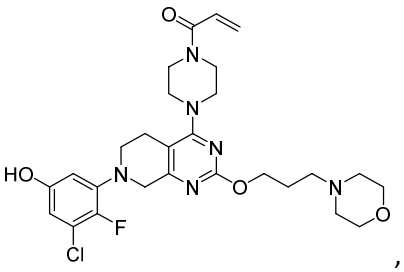
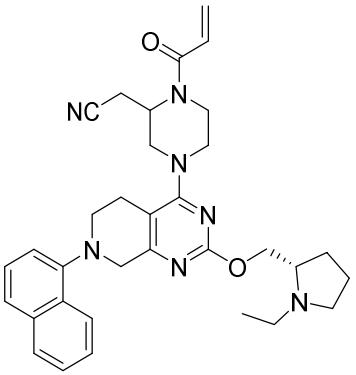
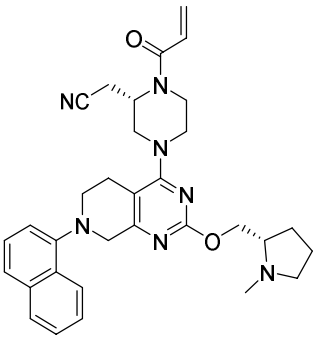
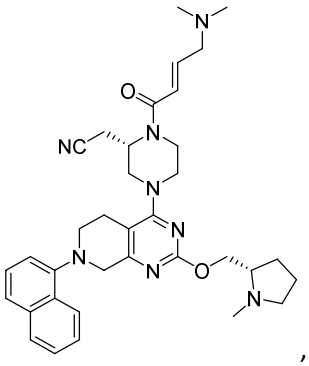
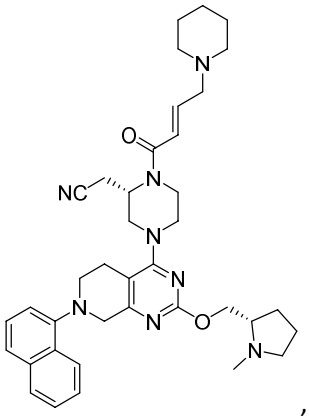
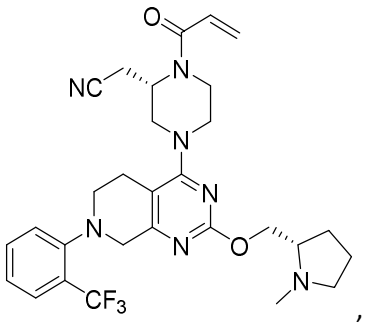
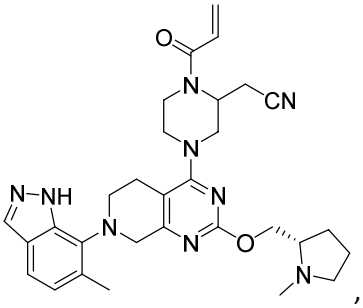

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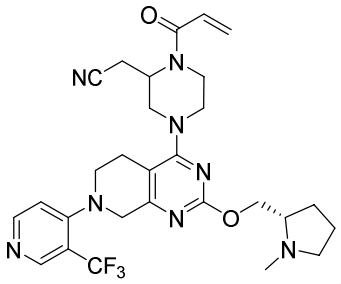
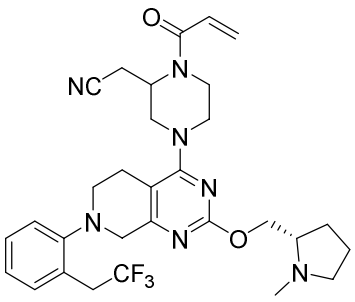
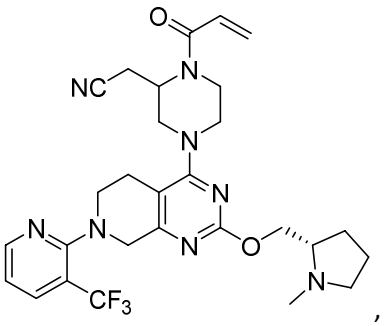
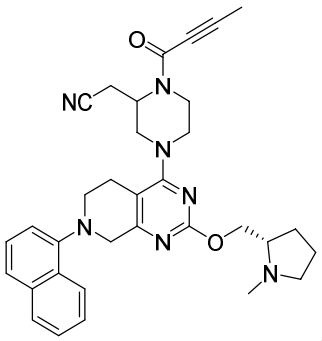
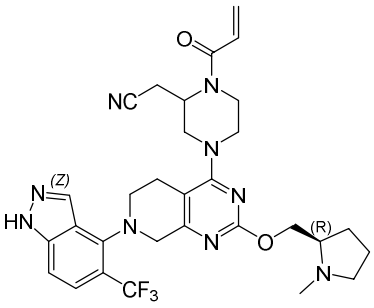
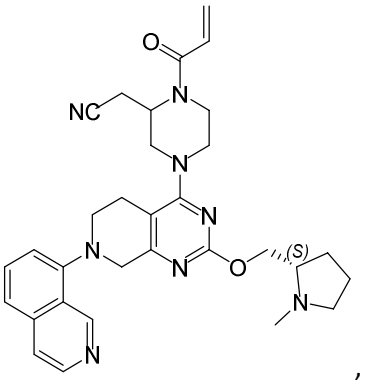
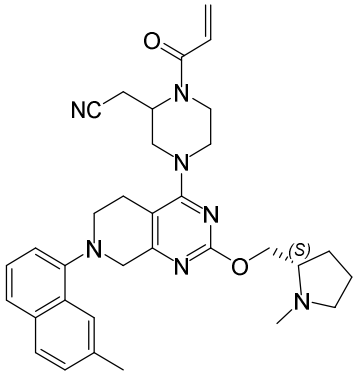
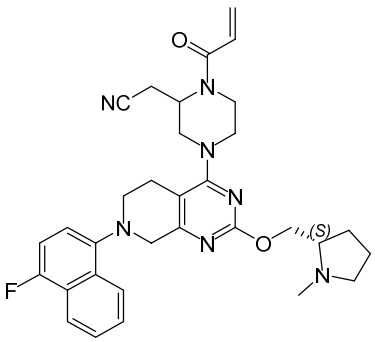
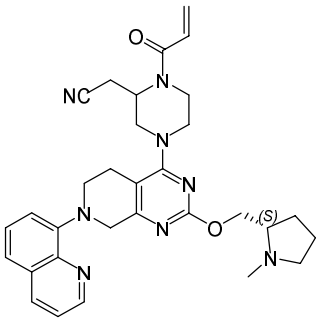
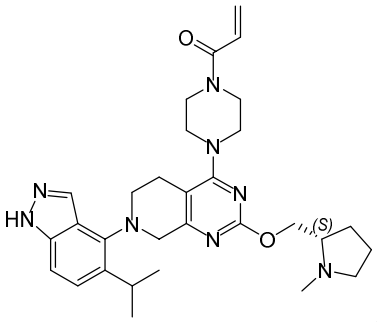
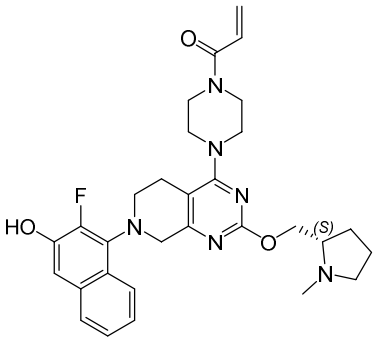
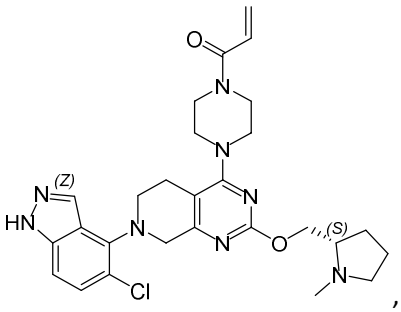

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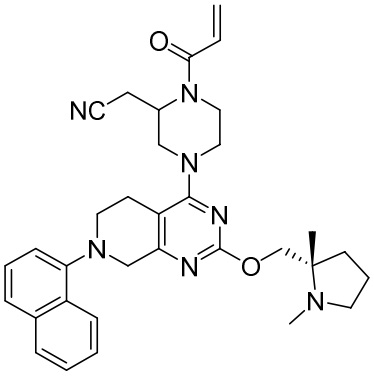
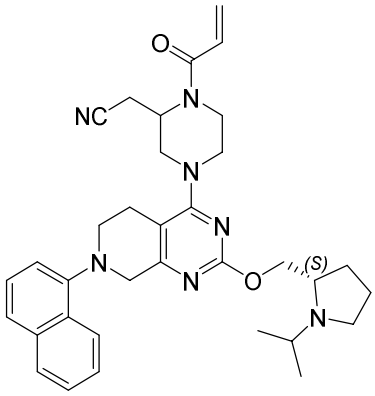
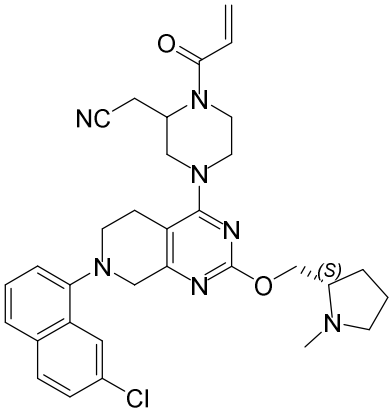
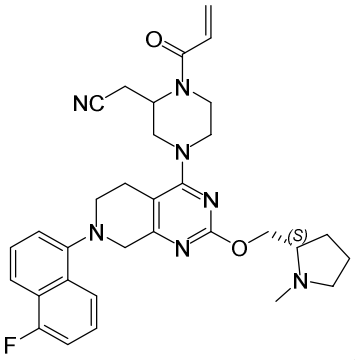
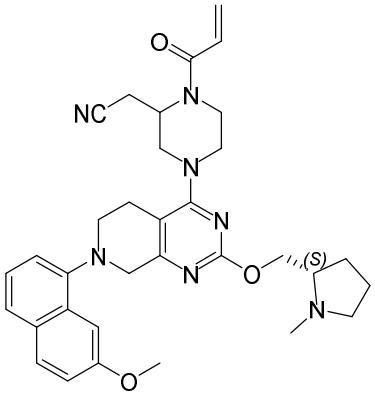
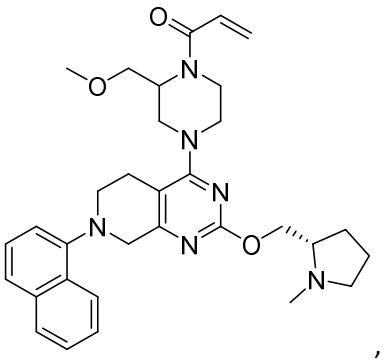
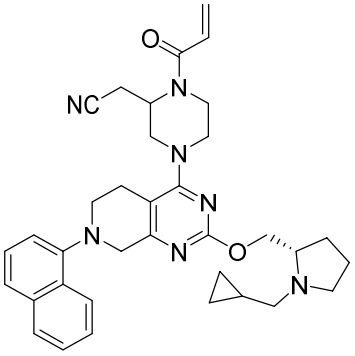
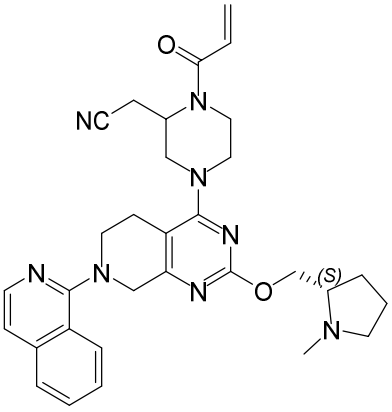
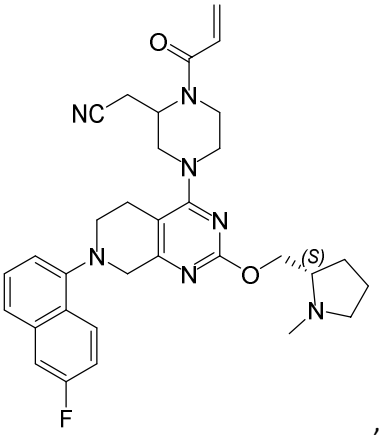

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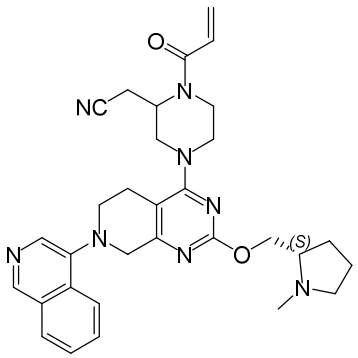
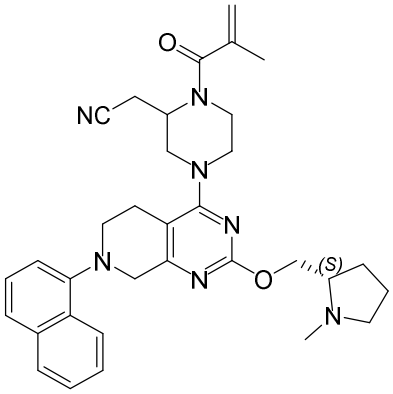
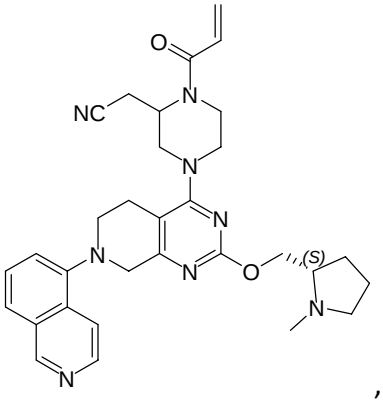
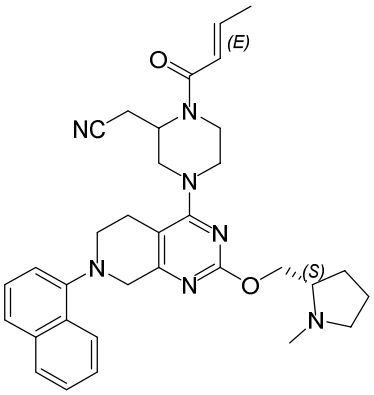
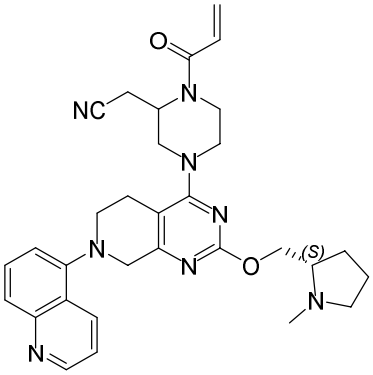
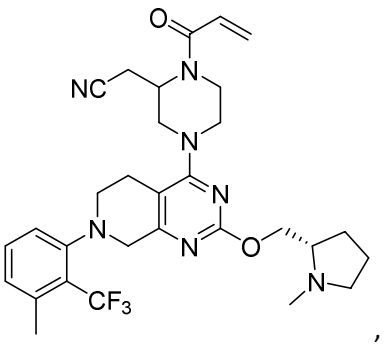
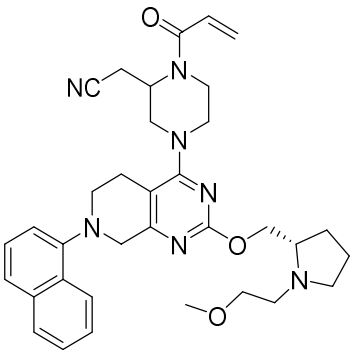
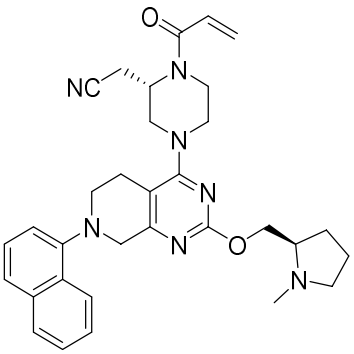
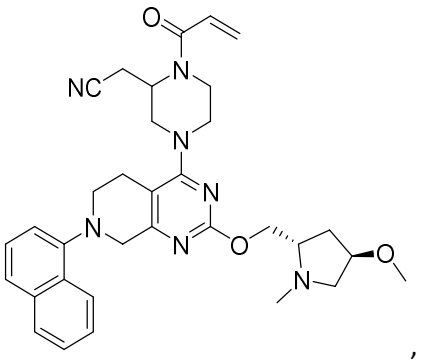
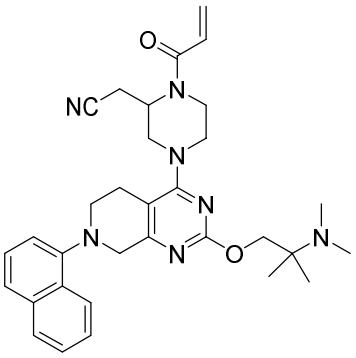
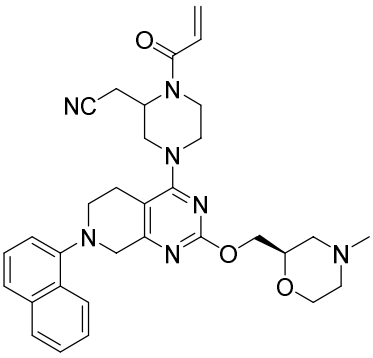
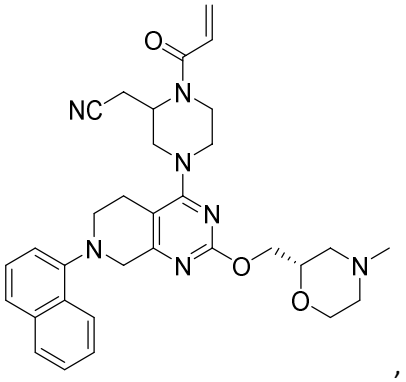

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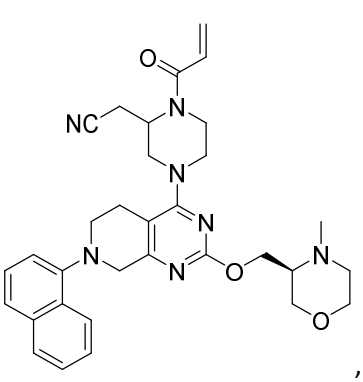
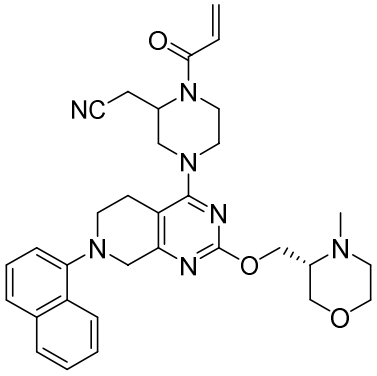
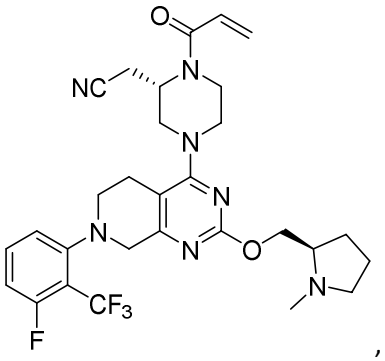
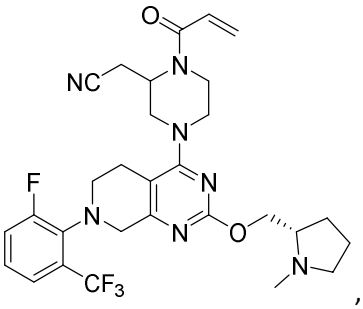
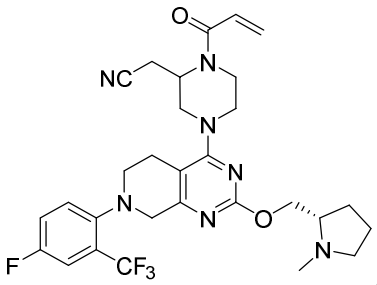
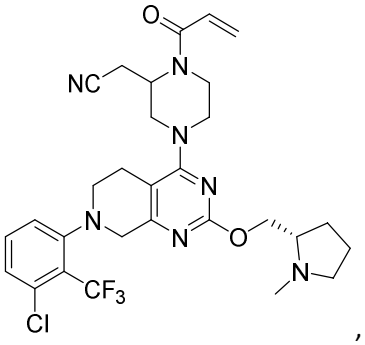
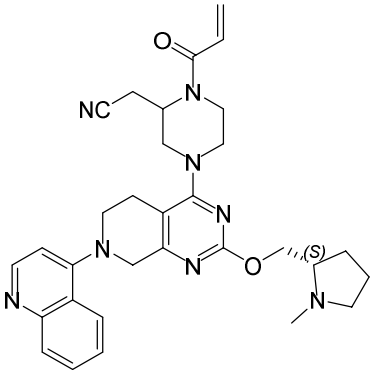
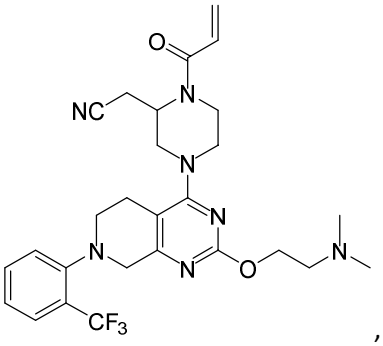
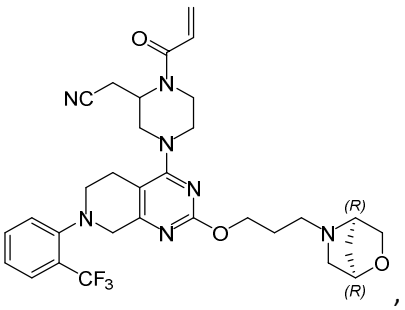
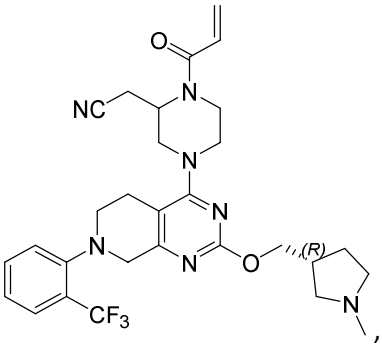
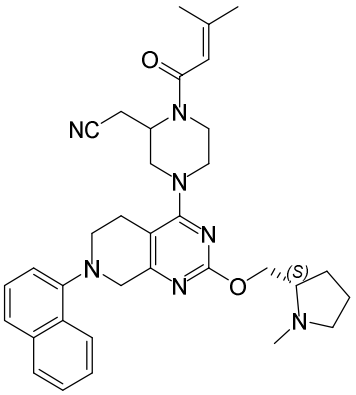
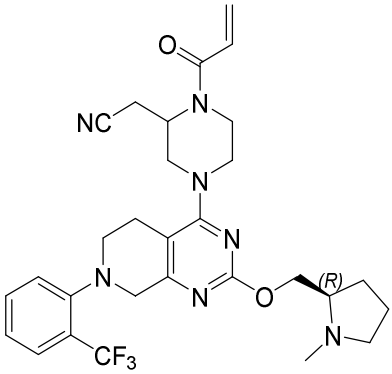

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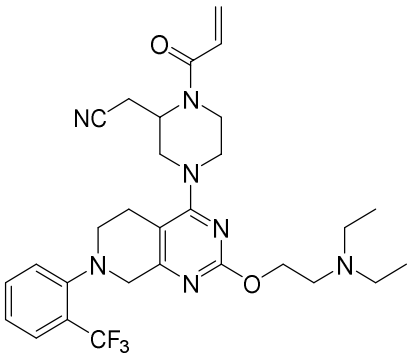

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and .

30. A pharmaceutical composition, comprising a therapeutically effective amount of a compound according to claim 1, and a pharmaceutically acceptable excipient.

31. An *in vitro* method for inhibiting KRas G12C activity in a cell, comprising contacting the cell in which inhibition of KRas G12C activity is desired with an effective amount of a compound according to claim 1, pharmaceutically acceptable salts thereof or pharmaceutical compositions containing the compound of Formula (I) or Formula I-B, or pharmaceutically acceptable salt thereof.

32. Use of a compound according to claim 1 or a pharmaceutically acceptable salt thereof, alone or combined with a pharmaceutically acceptable carrier, excipient or diluents, in the manufacture of a medicament for the treatment of cancer, wherein the cancer is a KRas G12C-associated cancer, wherein a therapeutically effective amount is to be administered to a patient in need thereof.

33. The use of claim 32, 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.

34. The use of claim 32, wherein the cancer is non-small cell lung cancer.

35. Use of a compound according to claim 1 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cancer in a patient in need thereof, wherein the cancer is associated with a KRas G12C mutation (e.g., a KRas G12C-associated cancer); and wherein a therapeutically effective amount of the compound or a pharmaceutically acceptable salt thereof is to be administered.