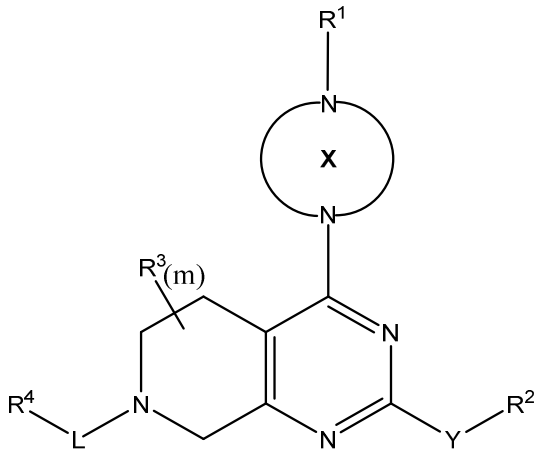
CLAIMS

WHAT IS CLAIMED IS:

1. Use of a therapeutically effective amount of a combination of a SHP-2 inhibitor and a KRAS G12C inhibitor of formula (I):



Formula (I)

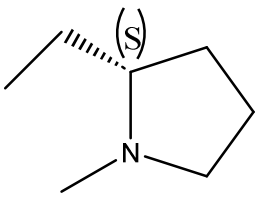
or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a subject in need thereof,

wherein:

X is a piperazine optionally substituted with one or more R^8;

Y is O;

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

R^2 is  optionally substituted with one or more R^9;

each Z is $C_1 – C_4$ alkylene;

each R^3 is independently $C_1 – C_3$ alkyl, oxo, haloalkyl, hydroxyl or halogen;

L is a bond;

R^4 is heteroaryl optionally substituted with one or more R^6, R^7 or R^8;

each R^5 is independently hydrogen or $C_1 – C_3$ 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, $C_1 – C_6$ alkyl, cycloalkyl, alkoxy, haloalkyl, amino, cyano, heteroalkyl, hydroxyalkyl or Q-haloalkyl, wherein Q is O or S;

R^8 is oxo, $C_1 – C_3$ alkyl, $C_2 – C_4$ alkynyl, heteroalkyl, cyano, $-C(O)OR^5$, $-C(O)N(R^5)_2$, $-N(R^5)_2$, wherein the $C_1 – C_3$ alkyl may be optionally substituted with cyano, halogen, $-OR^5$, $-N(R^5)_2$, or heteroaryl;

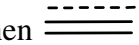
each R^9 is independently hydrogen, oxo, acyl, hydroxyl, hydroxyalkyl, cyano, halogen, $C_1 – C_6$ alkyl, aralkyl, haloalkyl, heteroalkyl, cycloalkyl, heterocyclylalkyl, alkoxy, dialkylaminyl, dialkylamidoalkyl, or dialkylaminylalkyl, wherein the $C_1 – C_6$ alkyl may be optionally substituted with cycloalkyl;

each R^{10} is independently hydrogen, acyl, $C_1 – C_3$ alkyl, heteroalkyl or hydroxyalkyl;

R^{11} is haloalkyl;

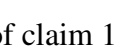
R^A is absent, hydrogen, deuterium, cyano, halogen, $C_1 – C_3$ alkyl, haloalkyl, heteroalkyl, $-C(O)N(R^5)_2$, or hydroxyalkyl;

each R^B is independently hydrogen, deuterium, cyano, $C_1 – C_3$ alkyl, hydroxyalkyl, heteroalkyl, $C_1 – C_3$ alkoxy, halogen, haloalkyl, -ZNR^5R^{11}, -$C(O)N(R^5)_2$, -$NHC(O)C_1 – C_3$ alkyl, -$CH_2NHC(O)C_1 – C_3$ alkyl, heteroaryl, heteroarylalkyl, dialkylaminylalkyl, or heterocyclylalkyl wherein the heterocyclyl portion is substituted with one or more substituents independently selected from halogen, hydroxyl, alkoxy and $C_1 – C_3$ alkyl, wherein the heteroaryl or the heteroaryl portion of the heteroarylalkyl is optionally substituted with one or more R^7;

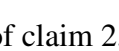
when  is a triple bond then R^A is absent, R^B is present and p equals one,
or when  is a double bond then R^A is present, R^B is present and p equals two, or R^A, R^B and the carbon atoms to which they are attached form a 5-8 membered partially saturated cycloalkyl optionally substituted with one or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

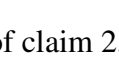
m is zero or an integer between 1 and 2; and

p is one or two.

2. The use of claim 1, wherein R^1 is –$C(O)C(R^A)$  $C(R^B)_p$

3. The use of claim 2, wherein  is a triple bond and R^A is absent, p is one and R^B is $C_1 – C_3$ alkyl, hydroxyalkyl or $C_1 – C_3$ alkoxy.

4. The use of claim 2, wherein  is a double bond and R^A is hydrogen and R^B is hydrogen.

5. The use of claim 2, wherein  is a double bond and R^A is hydrogen, p is two and at least one R^B is independently deuterium, cyano, halogen, haloalkyl, hydroxyalkyl, heteroalkyl, heteroaryl, heteroarylalkyl, -ZNR^5R^{11}, -$C(O)N(R^5)_2$, -$NHC(O)C_1 – C_3$ alkyl or heterocyclylalkyl wherein the heterocyclyl portion is substituted with one or more substituents independently selected from halogen, hydroxyl, alkoxy or $C_1 – C_3$ alkyl.

6. The use of claim 5, wherein the at least one R^B is halogen.

7. The use of claim 5, wherein the at least one R^B is haloalkyl.

8. The use of claim 5, wherein the at least one R^B is $-ZNR^5R^{11}$.

9. The use of claim 8, wherein Z is methylene, R^5 is methyl and R^{11} is trifluoromethyl.

10. The use of claim 5, wherein the at least one R^B is cyano.

11. The use of claim 5, wherein the at least one R^B is hydroxyalkyl.

12. The use of claim 5, wherein the at least one R^B is heteroalkyl.

13. The use of claim 12, wherein the heteroalkyl is methoxymethyl.

14. The use of claim 5, wherein the at least one R^B is $-C(O)N(R^5)_2$, wherein each R^5 is hydrogen.

15. The use of claim 5, wherein the at least one R^B is $-C(O)N(R^5)_2$, wherein each R^5 is C_1 – C_3 alkyl.

16. The use of claim 5, wherein the at least one R^B is heteroaryl optionally substituted with one or more R^7.

17. The use of claim 16, wherein the heteroaryl is pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or triazinyl, each substituted with one or more R^7.

18. The use of claim 5, wherein the at least one R^B is heteroarylalkyl optionally substituted with one or more R^7.

19. The use of claim 18, wherein the heteroaryl portion of the heteroarylalkyl is pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or triazinyl, each optionally substituted with one or more R^7.

20. The use of claim 5, wherein the at least one R^B is heterocyclylalkyl substituted with one or more R^7.

21. The use of claim 20, wherein the heterocyclyl portion of the heterocyclylalkyl is azetindinyl, pyrrolidinyl, piperidinyl piperazinyl or morpholinyl, each substituted with one or more groups independently selected from halogen, hydroxyl, alkoxy or $C_1 - C_3$ alkyl.

22. The use according to any of claims 5-21, wherein the double bond is in the E configuration.

23. The use according to any of claims 5-21, wherein the double bond is in the Z configuration..

24. The use of claim 5, wherein  is a double bond and p is two, each R^B is hydrogen, and R^A is deuterium, cyano, halogen, haloalkyl, heteroalkyl, $-C(O)N(R^5)_2$, or hydroxyalkyl.

25. The use of claim 24, wherein R^A is halogen.

26. The use of claim 24, wherein R^A is haloalkyl.

27. The use of claim 4, wherein R^A is cyano.

28. The use of claim 24, wherein R^A is heteroalkyl.

29. The use of claim 28, wherein the heteroalkyl is methoxymethyl.

30. The use of claim 28, wherein the heteroalkyl is alkoxy.

31. The use of claim 24, wherein R^A is $-C(O)N(R^5)_2$, wherein each R^5 is hydrogen.

32. The use of claim 24, wherein R^A is hydroxyalkyl.

33. The use of claim 1, wherein  is a double bond and p is two, one R^B is hydrogen, the second R^B is dialkylaminylalkyl, and R^A is halogen.

34. The use of claim 1, wherein  is a double bond and p is two, each R^B is deuterium, and R^A is deuterium.

35. The use of claim 1, wherein when  is a double bond and p is two, one R^B is hydrogen and R^A and one R^B and the carbon atoms to which they are attached form a 5-8 membered partially saturated cycloalkyl substituted with oxo.

36. The use according to any one of claims 1-35, wherein m is zero.

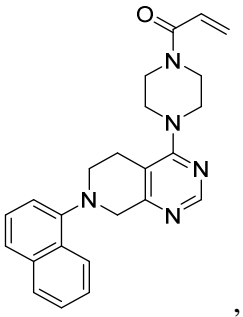
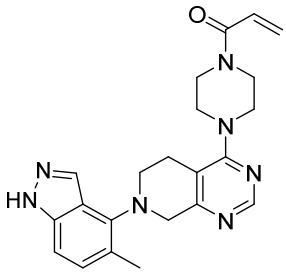
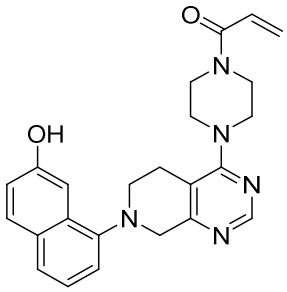
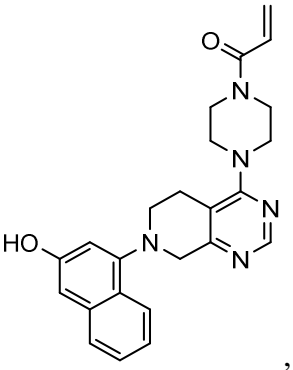
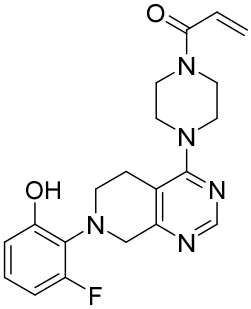
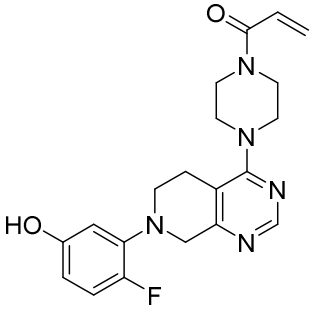
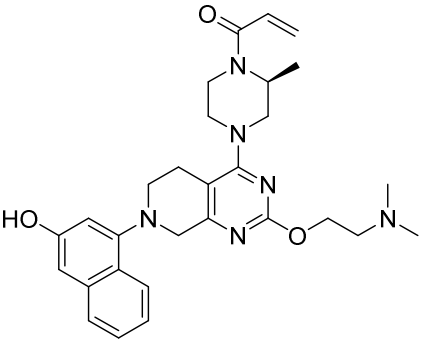
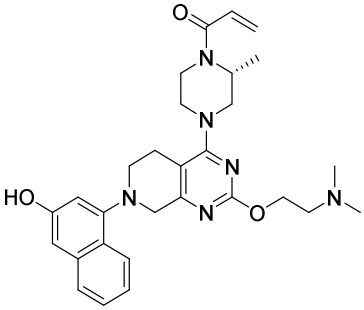
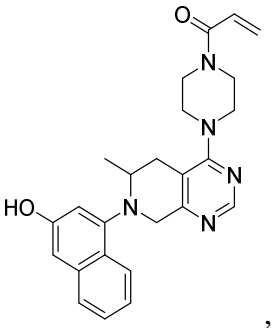
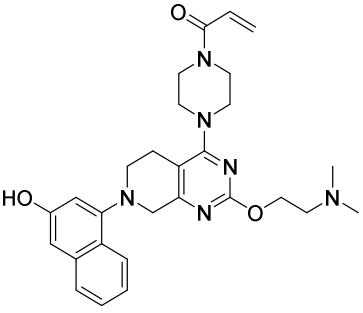
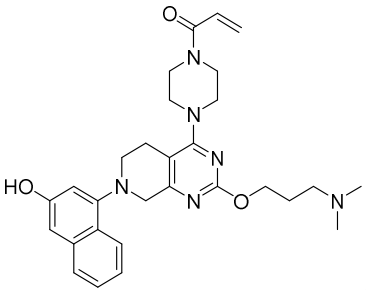
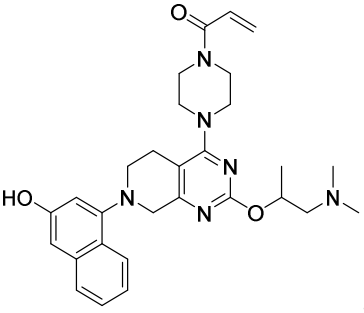
37. The use according to any one of claims 1-36, wherein R^8 is heteroalkyl, $C_2 – C_4$ alkynyl, or $C_1 – C_3$alkyl optionally substituted with $-OR^5$, cyano or heteroaryl.

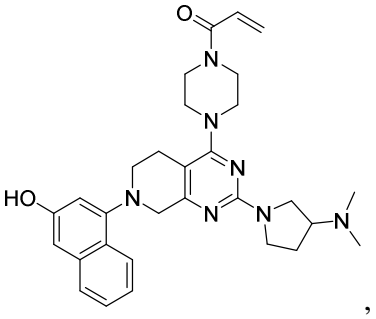
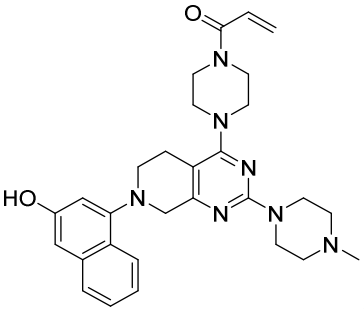
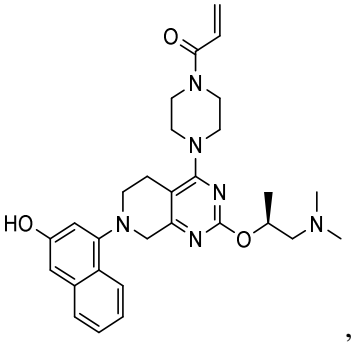
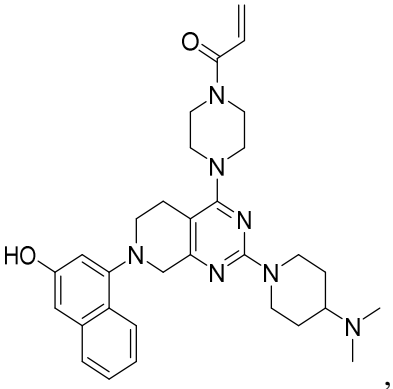
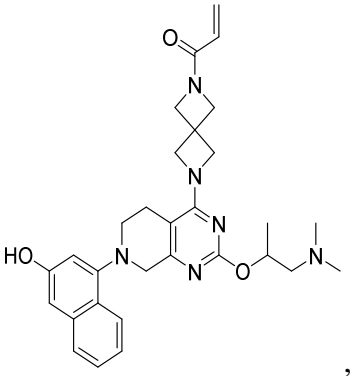
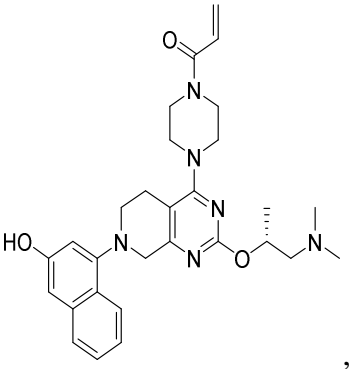
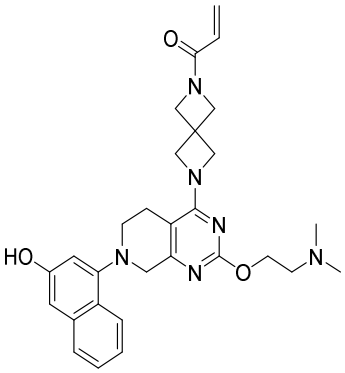
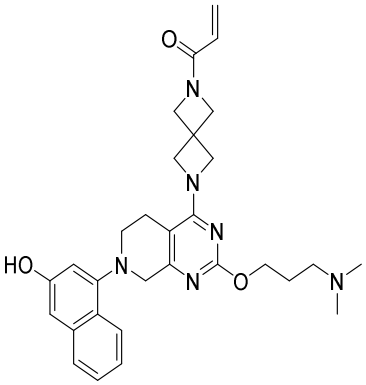
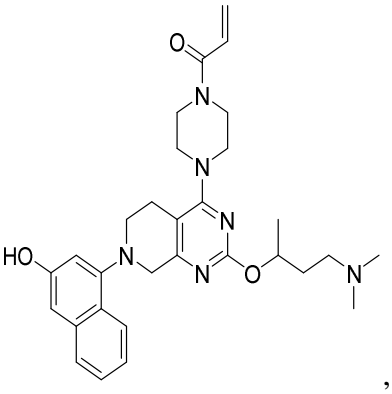
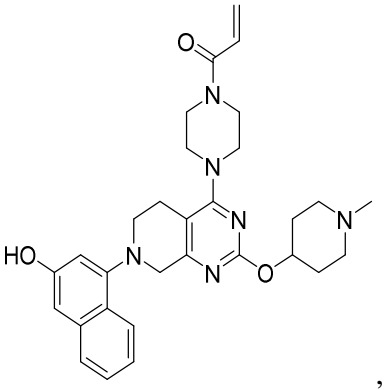
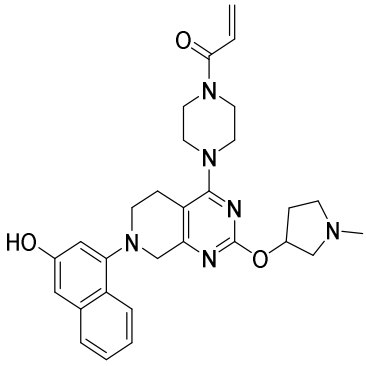
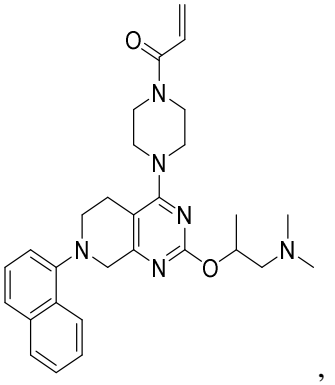
38. The use of claim 37, wherein R^8 is $C_1 – C_3$ alkyl optionally substituted with cyano.

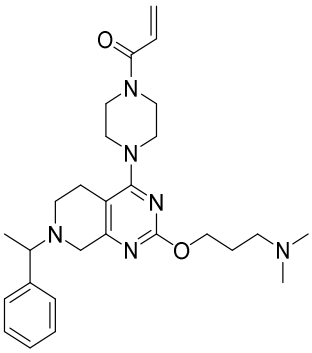
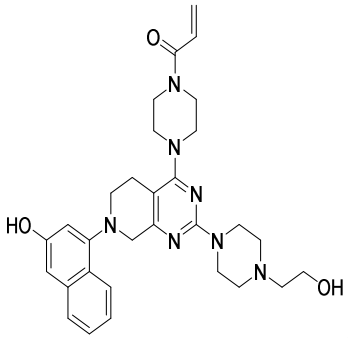
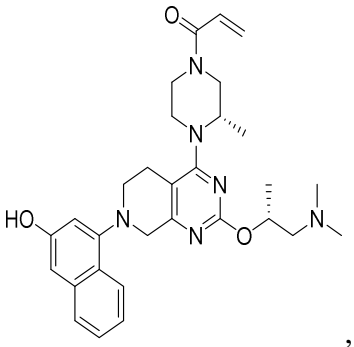
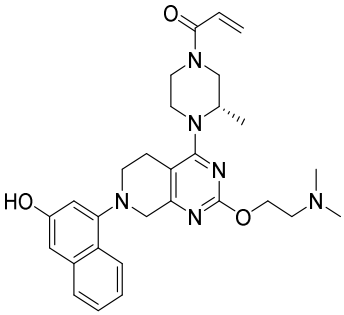
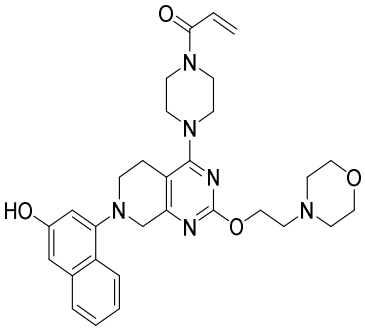
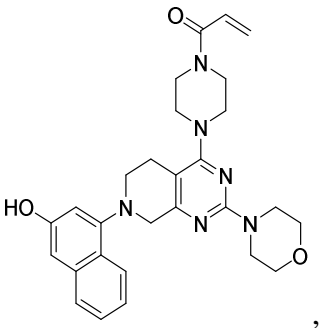
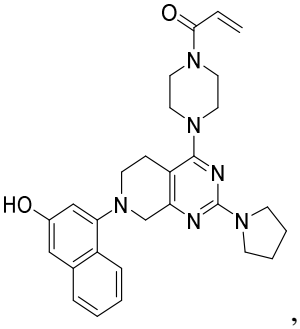
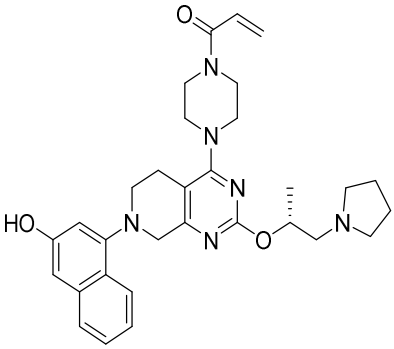
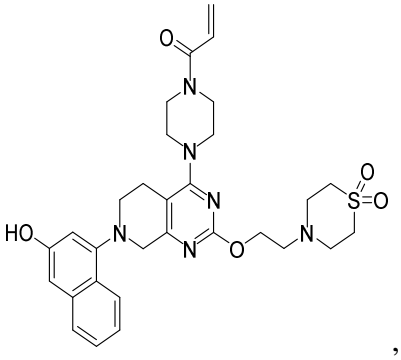
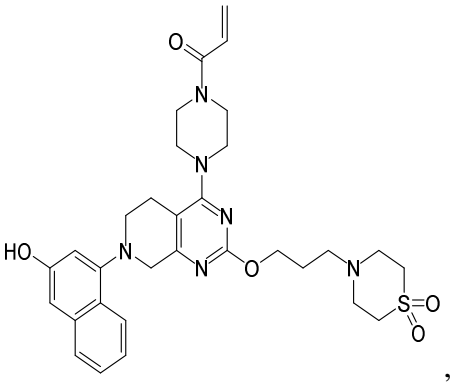
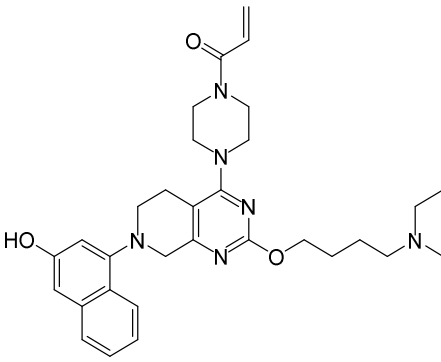
39. The use of claim 37, wherein R^8 is cyanomethyl.

40. The use according to any one of claims 37-39, wherein X is substituted with one R^8.

41. The use of claim 1, wherein the KRas G12C inhibitor is:

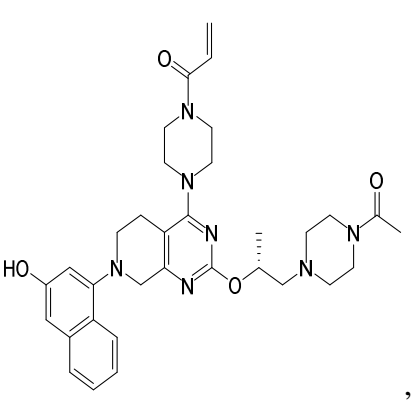
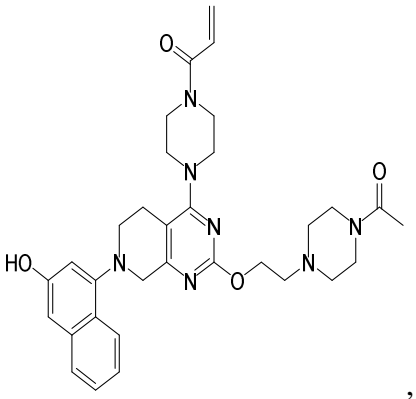
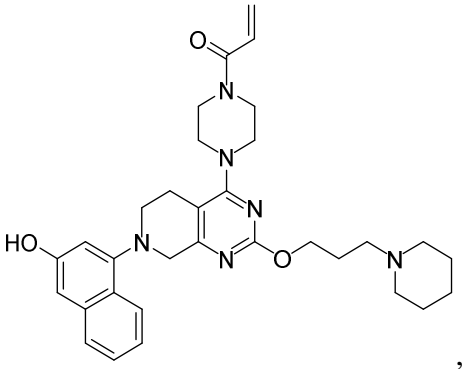
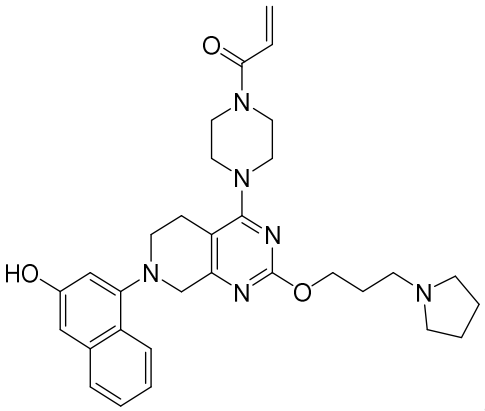
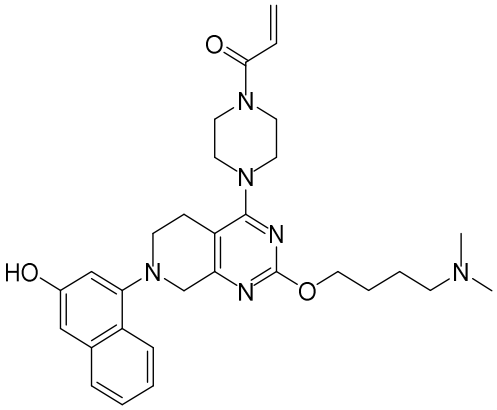
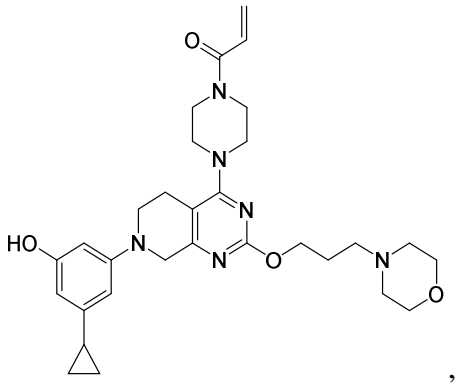
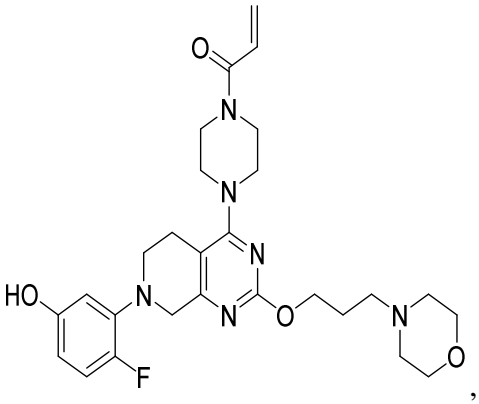
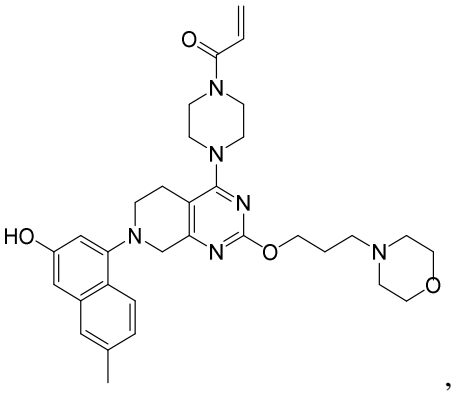

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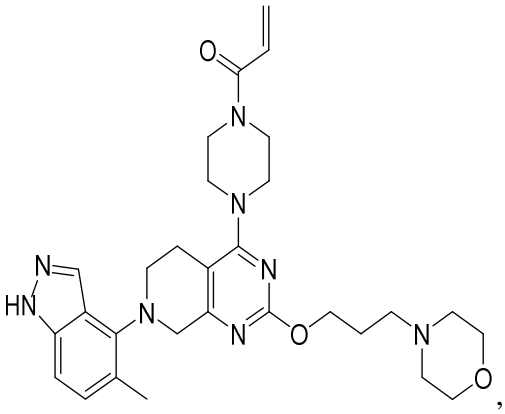
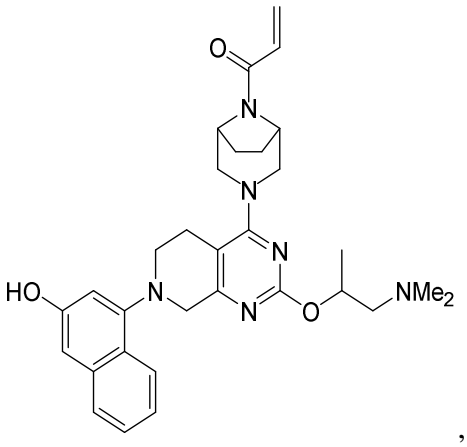
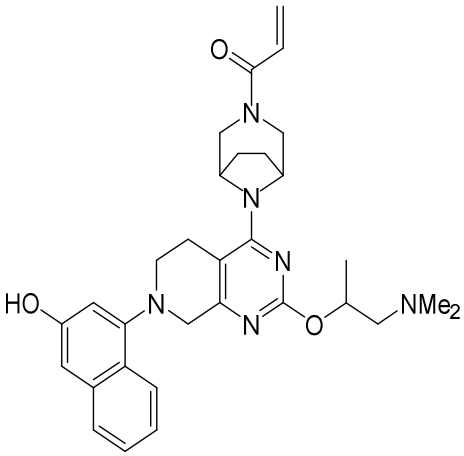
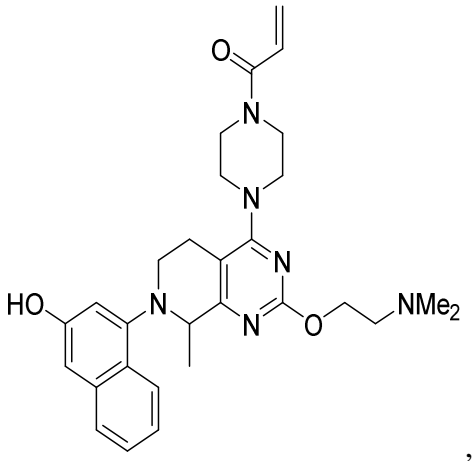
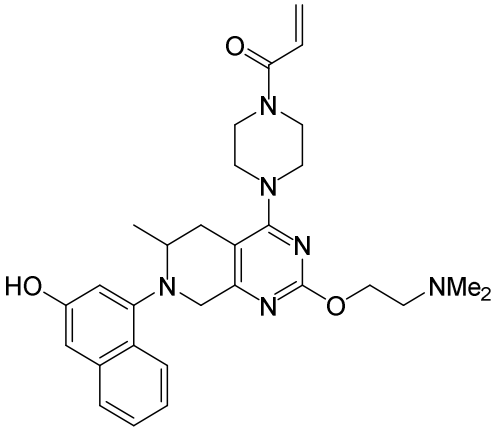
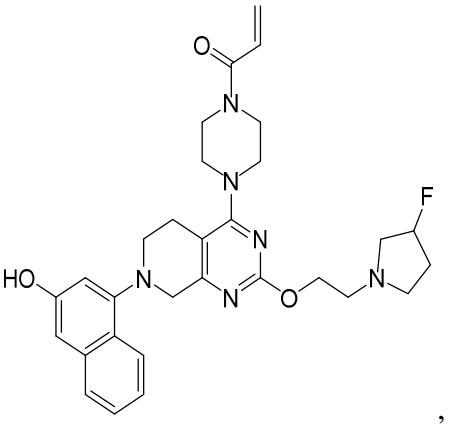

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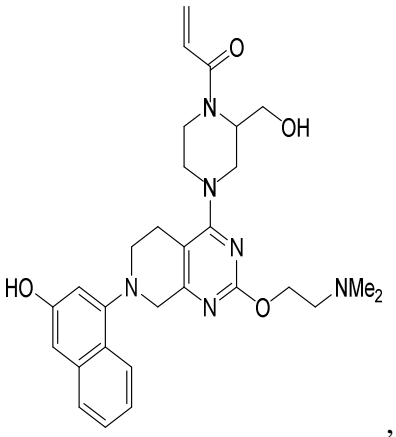
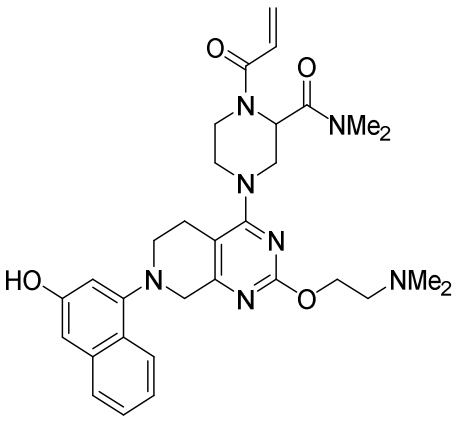
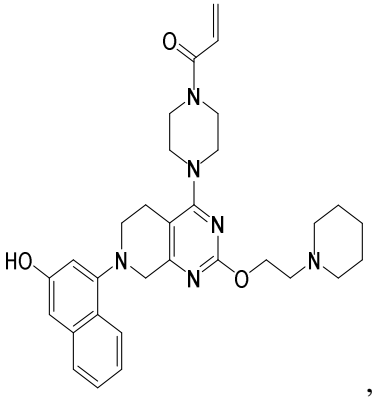
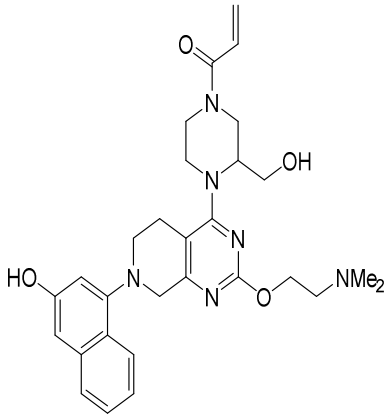
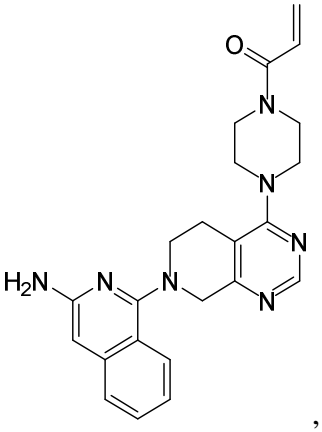
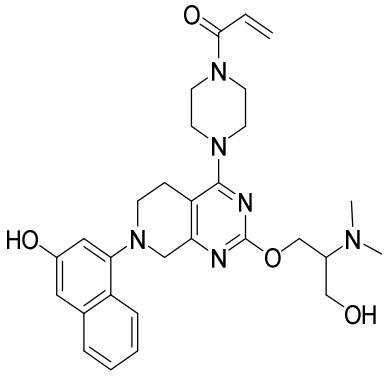
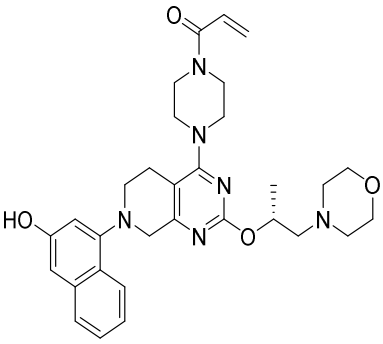
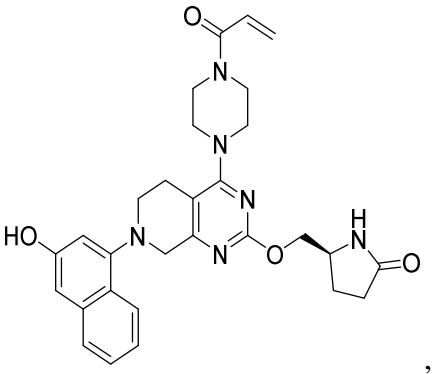
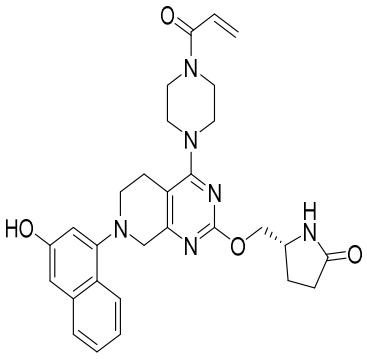
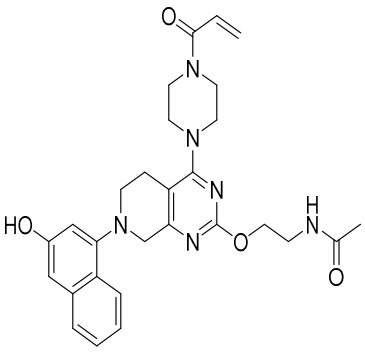
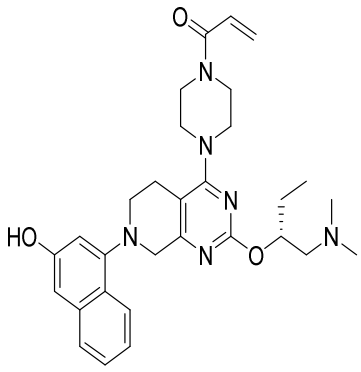

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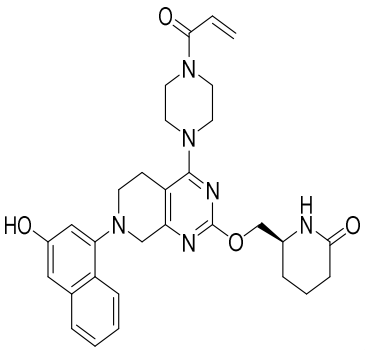
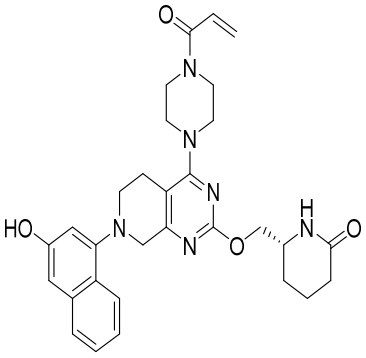
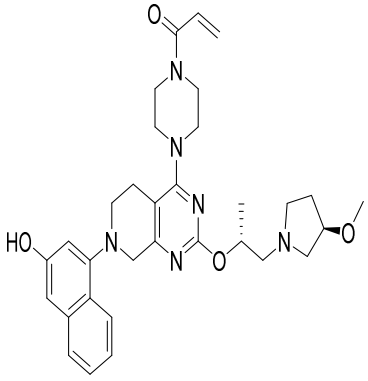
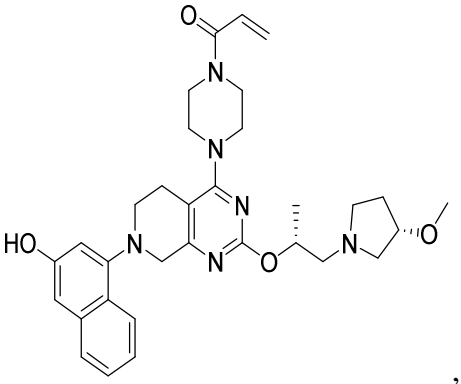
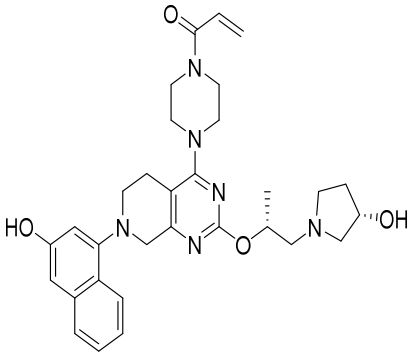
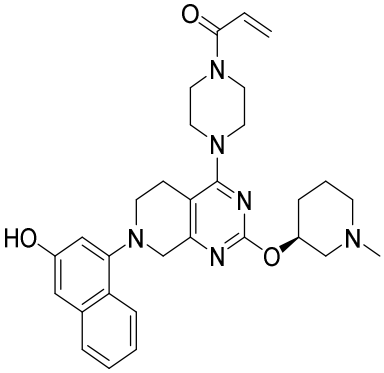
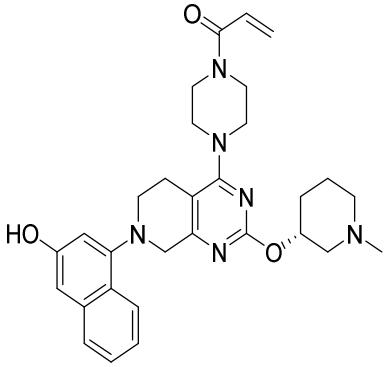
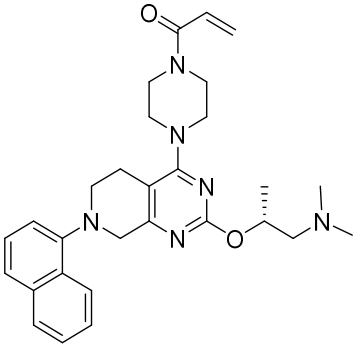
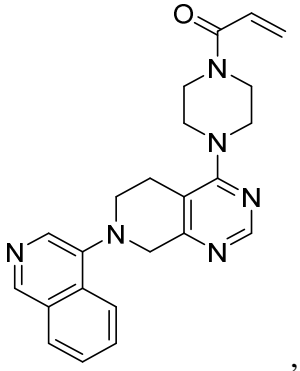
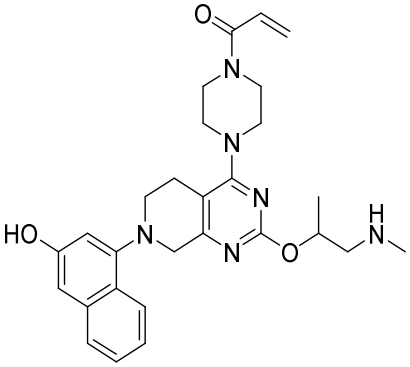
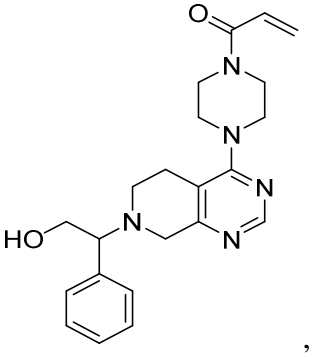
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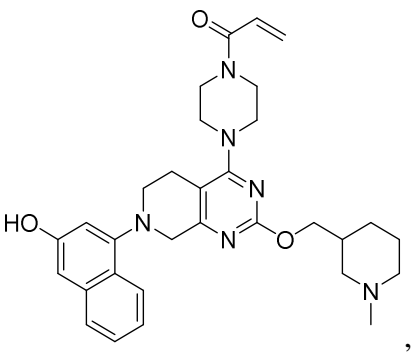
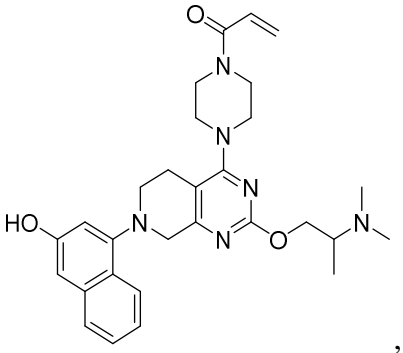
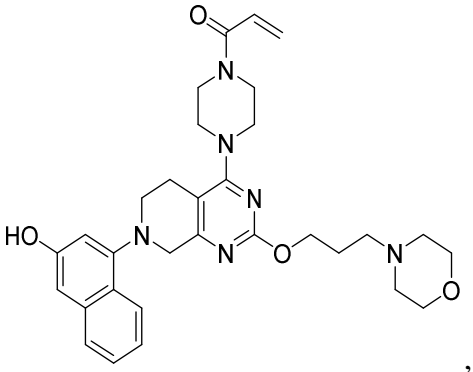
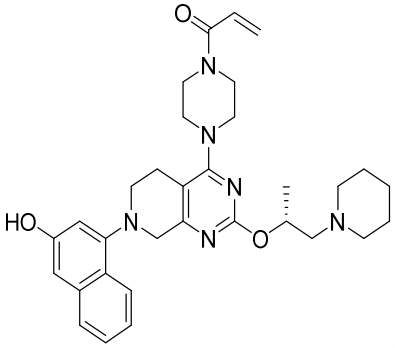
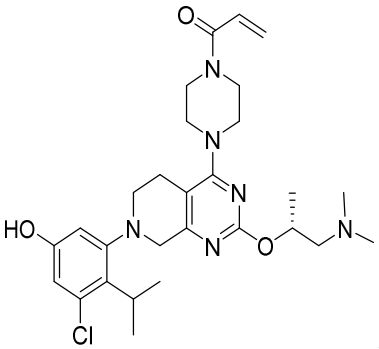
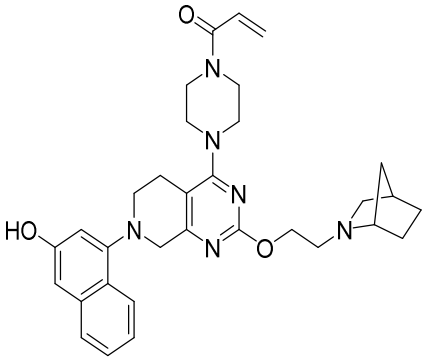
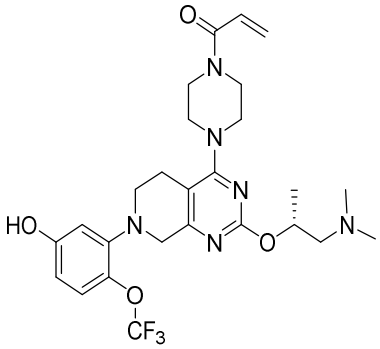
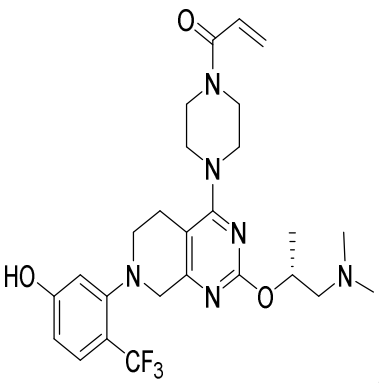
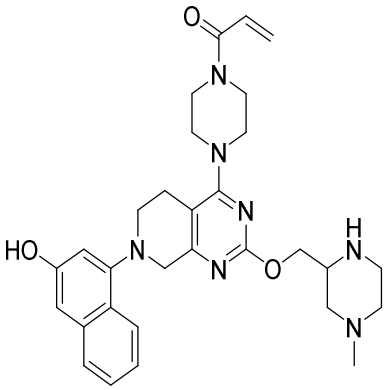
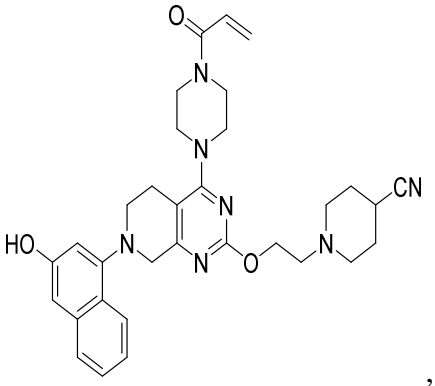
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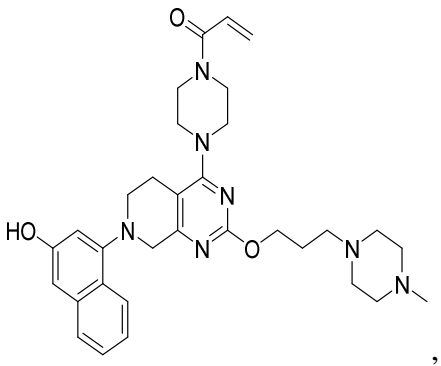
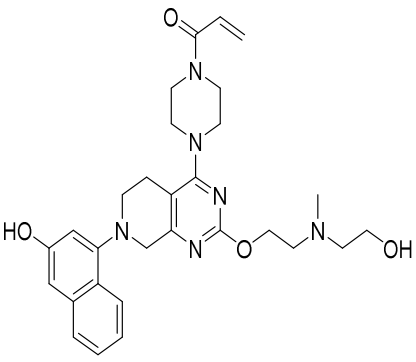
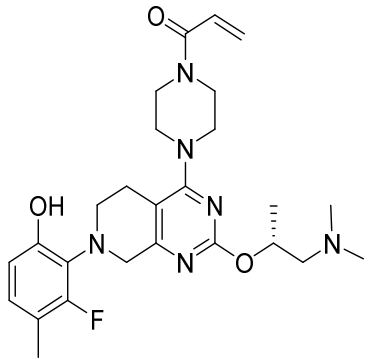
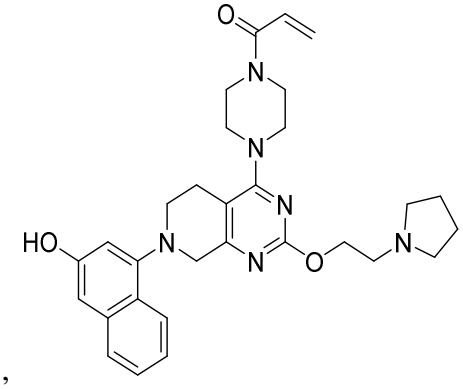
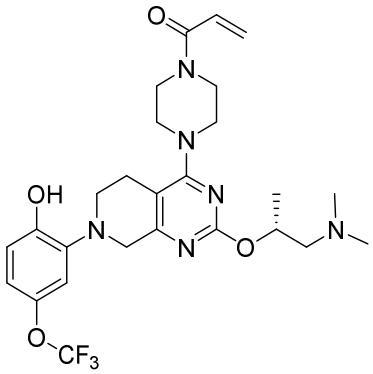
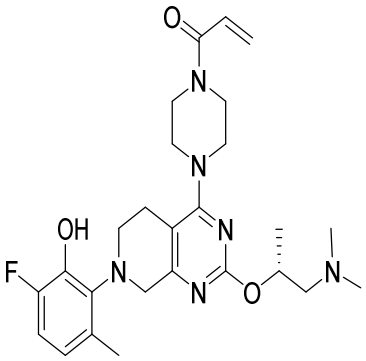
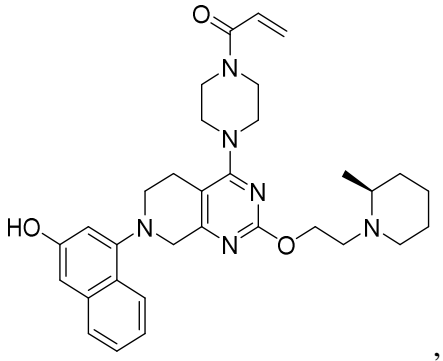
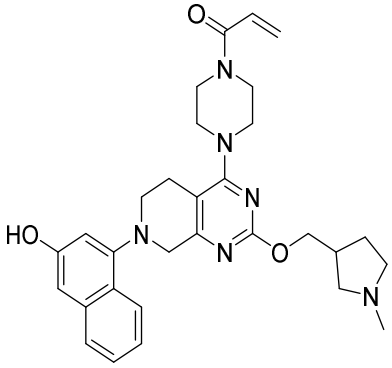
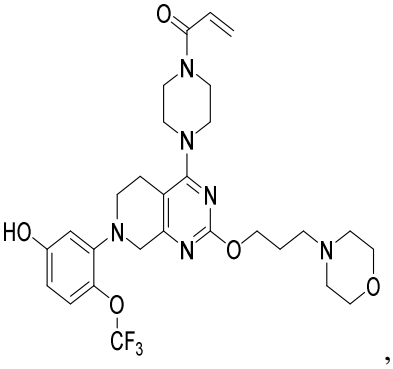
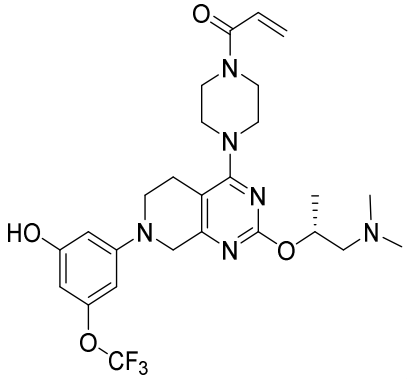
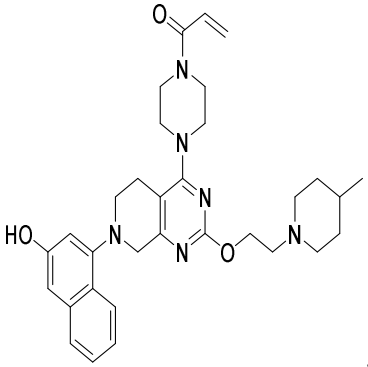
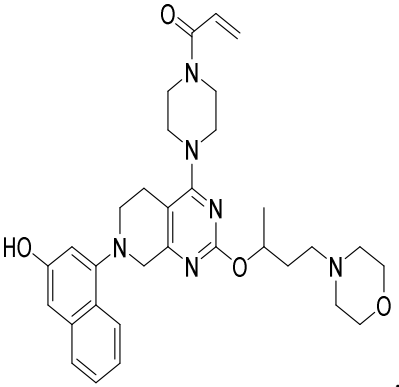

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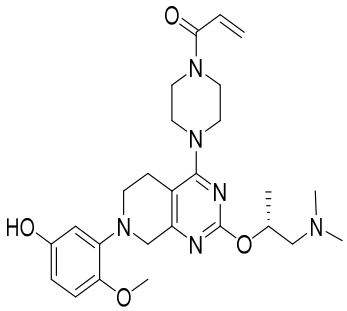
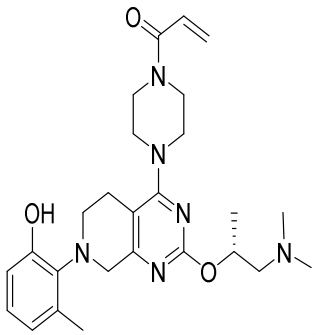
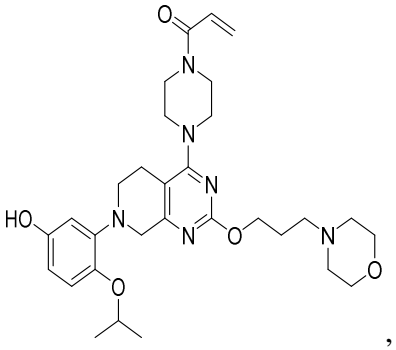
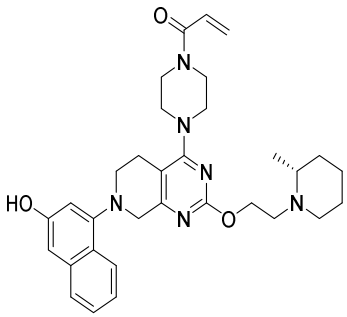
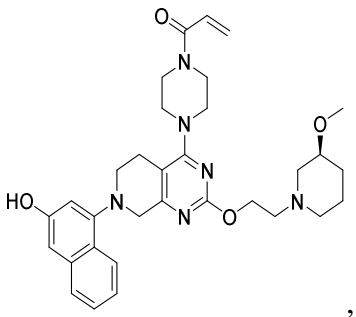
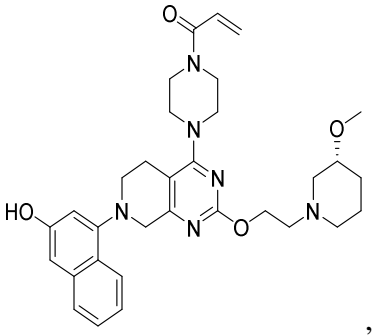
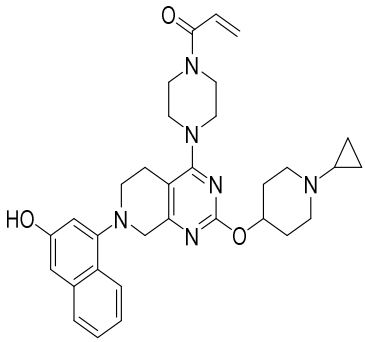
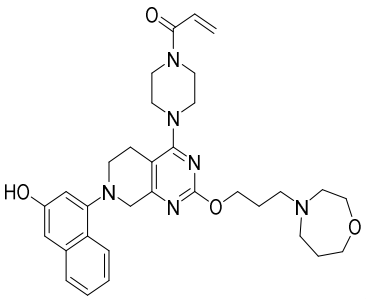
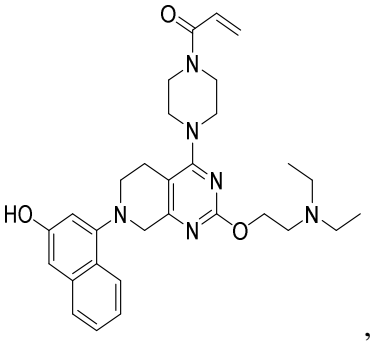
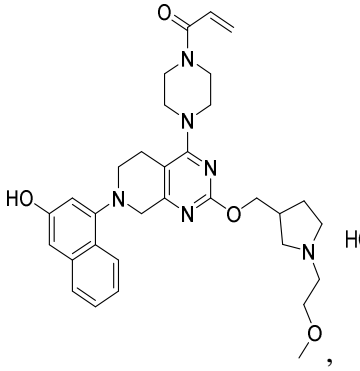
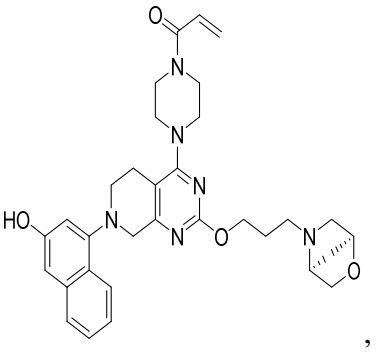
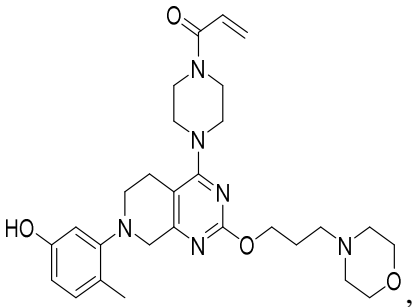

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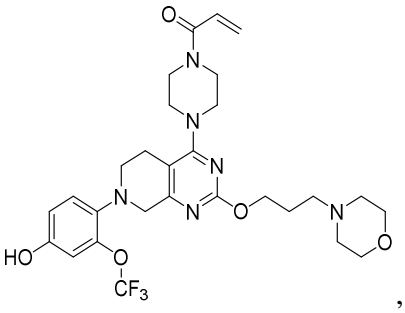
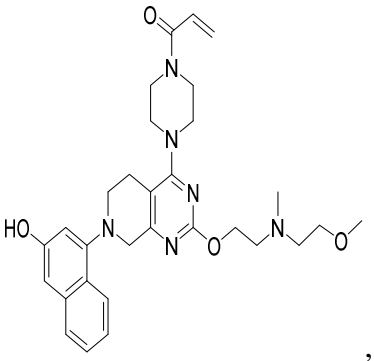
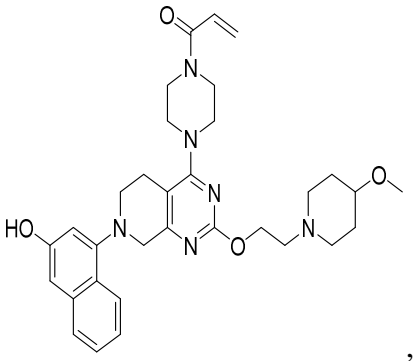
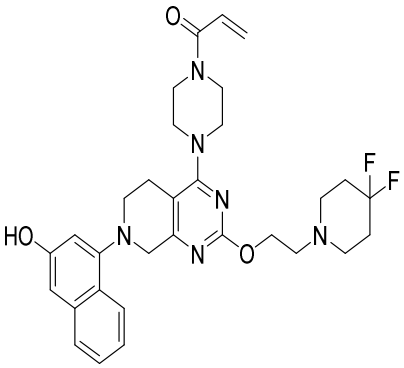
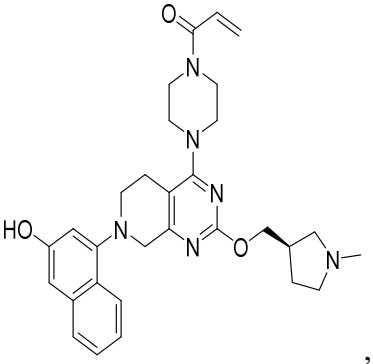
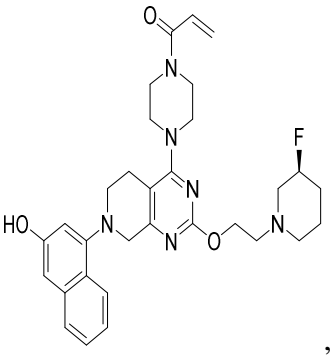
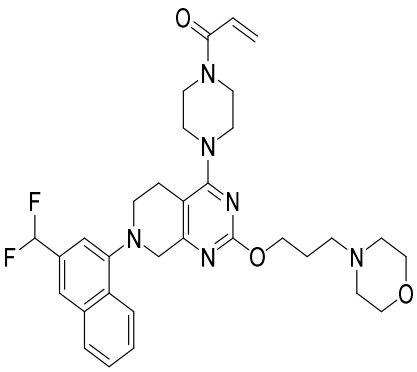
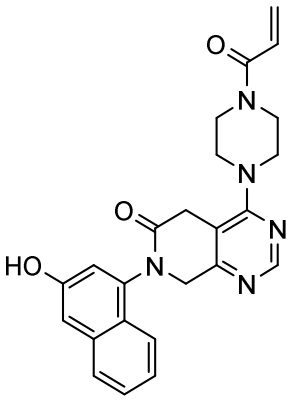
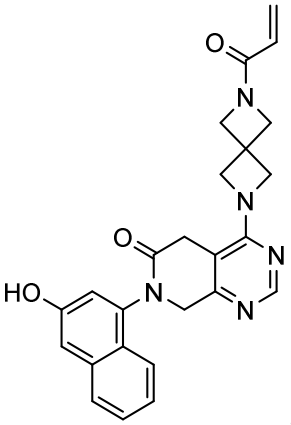
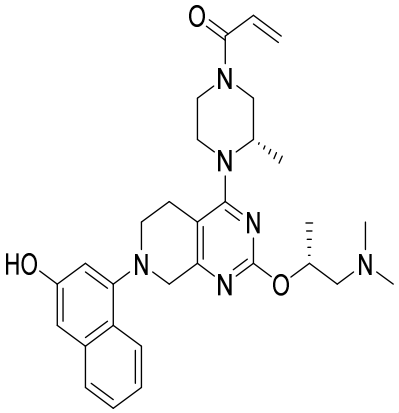
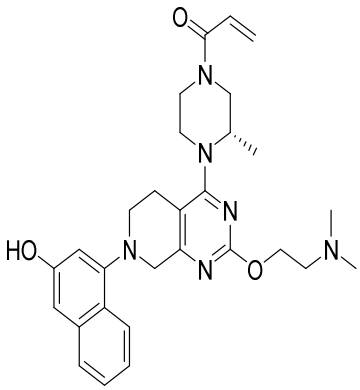
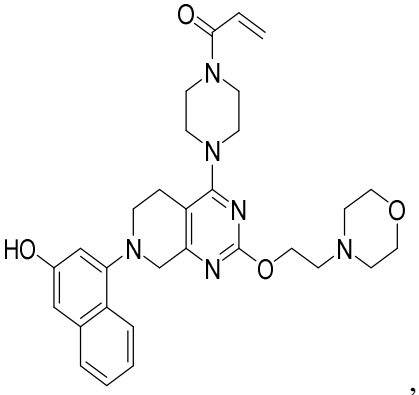

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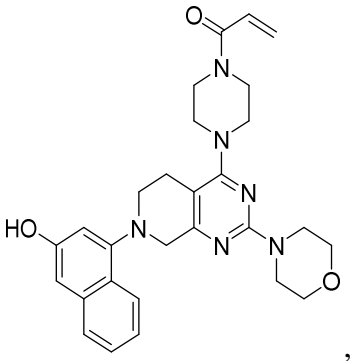
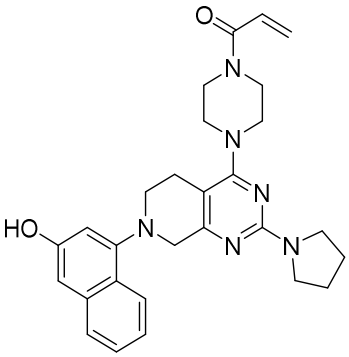
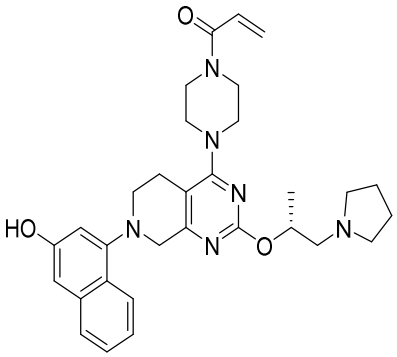
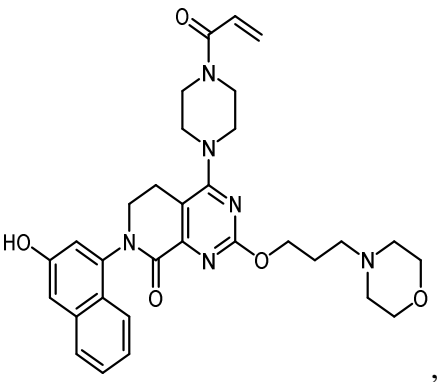
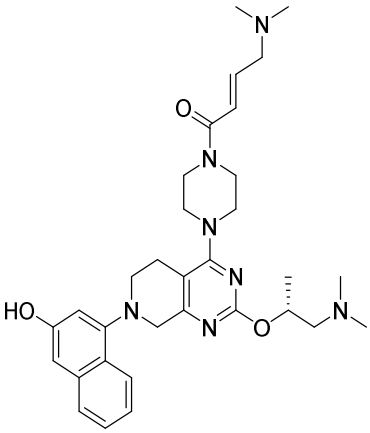
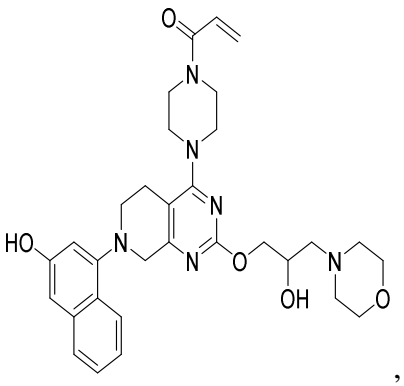
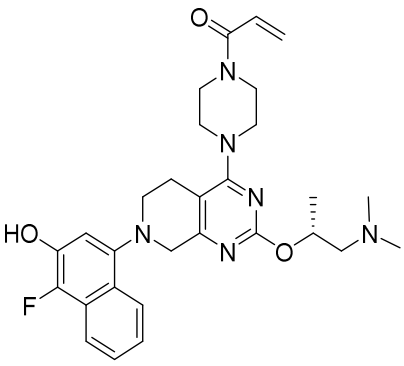
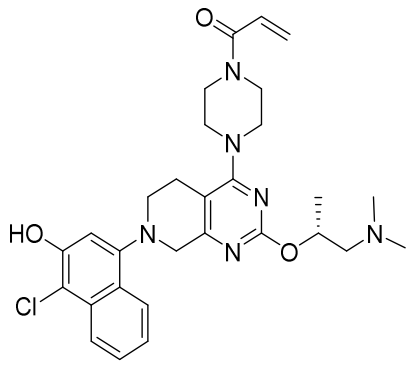
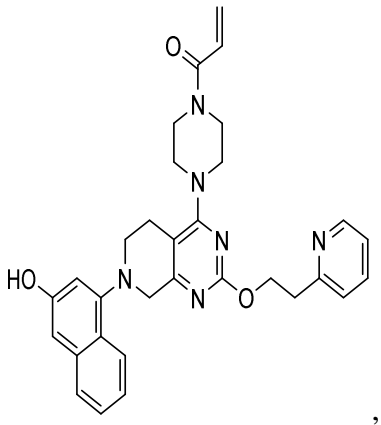
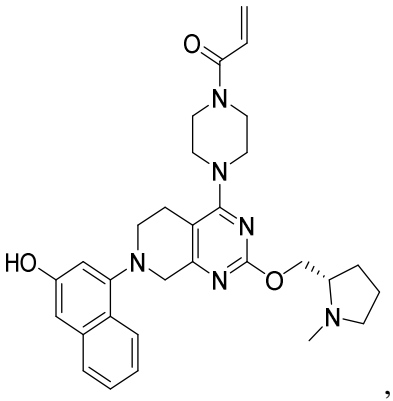
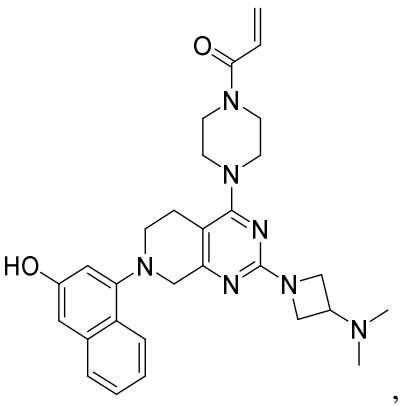
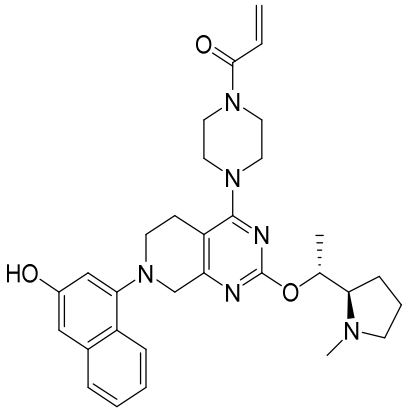

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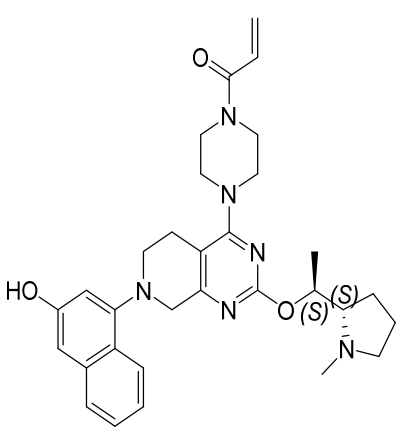
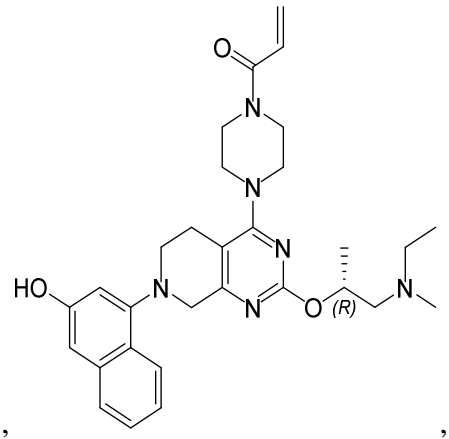
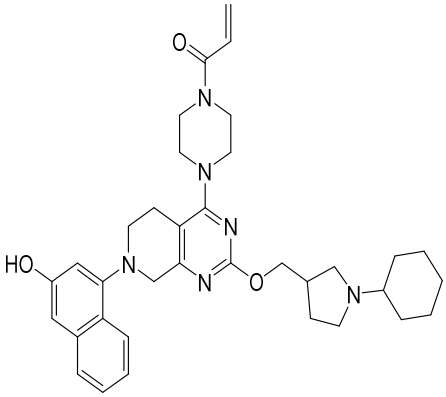
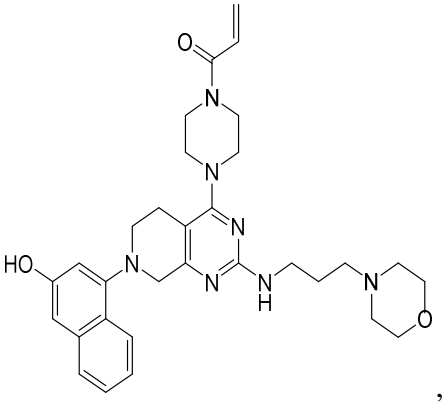
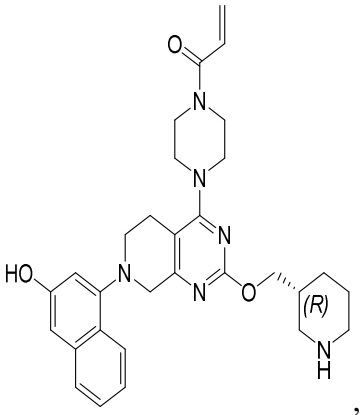
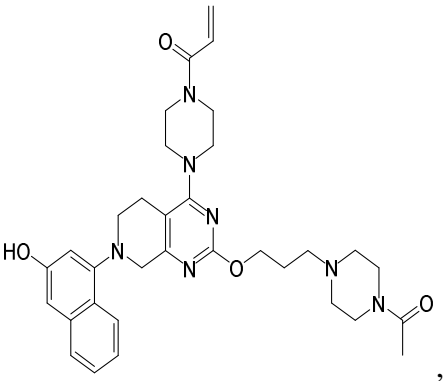
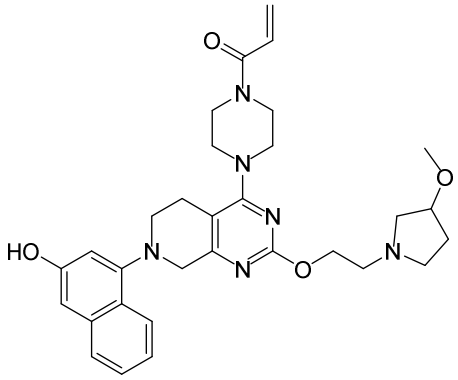
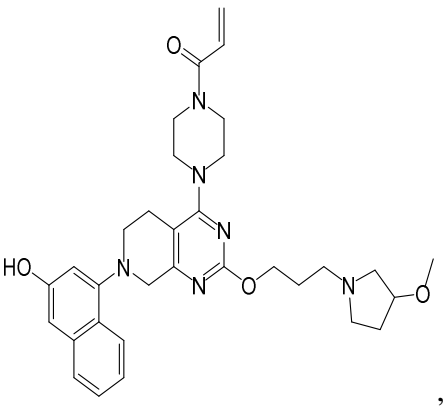

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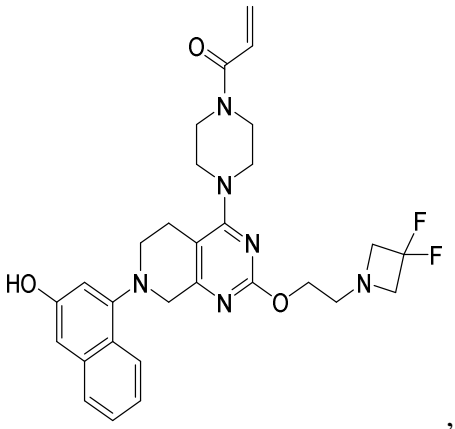
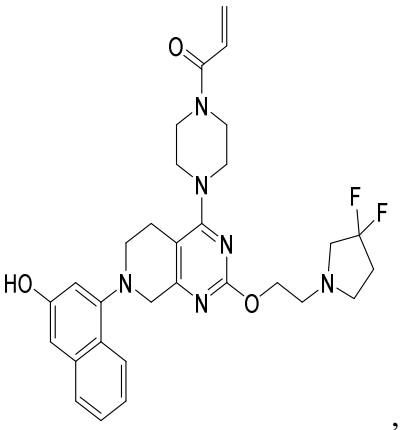
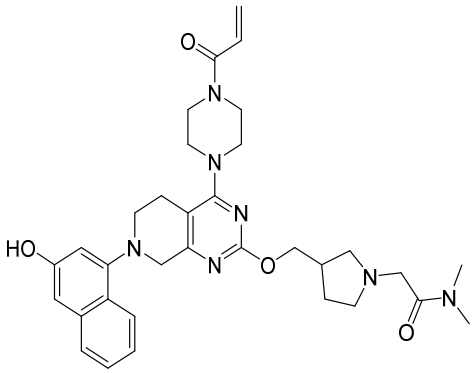
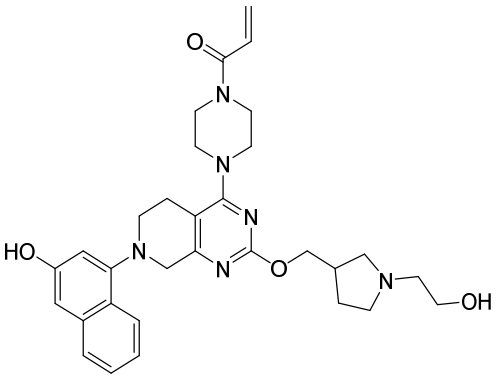
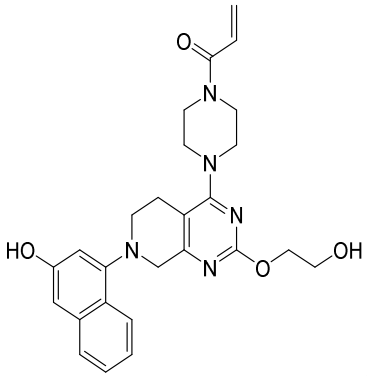
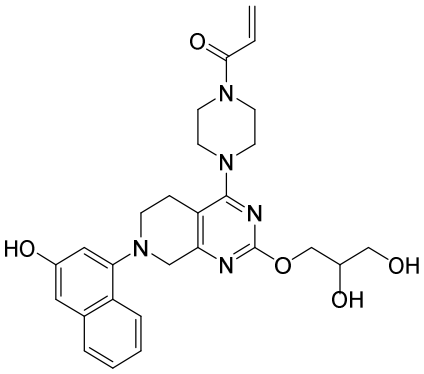
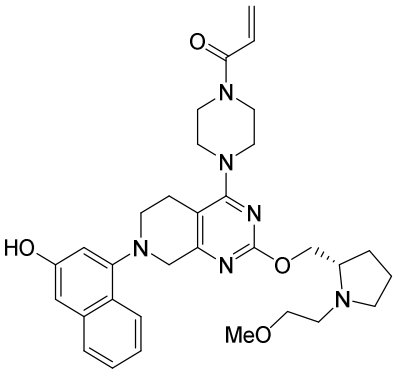
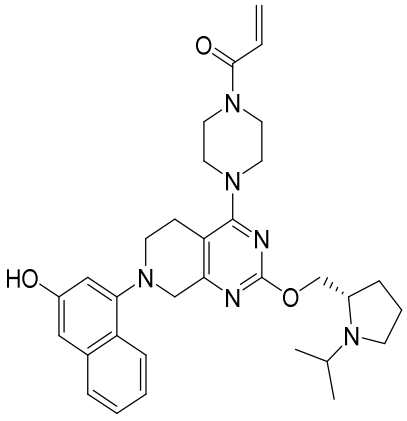
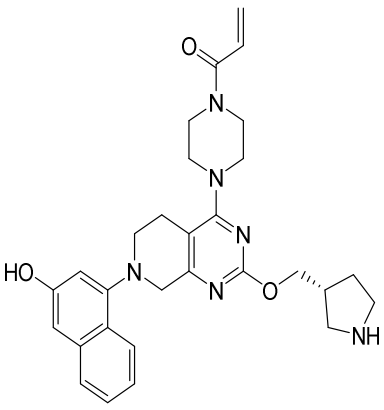
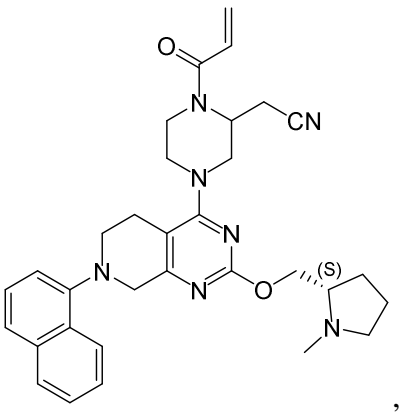

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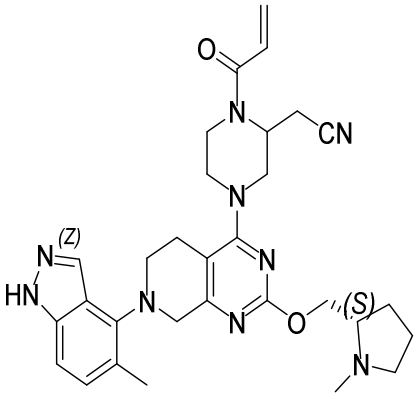
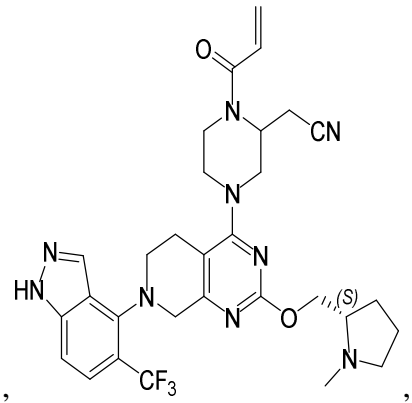
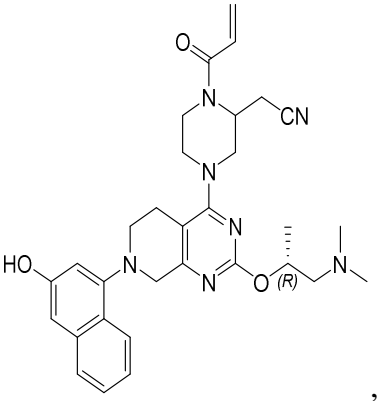
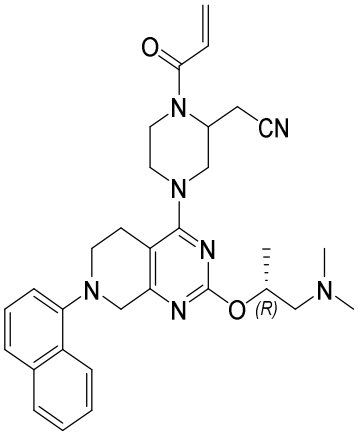
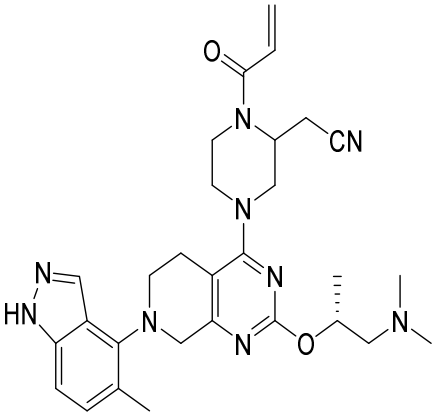
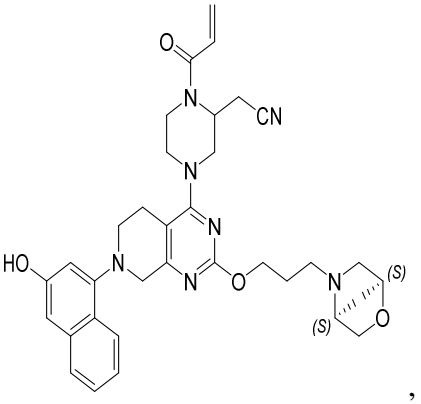
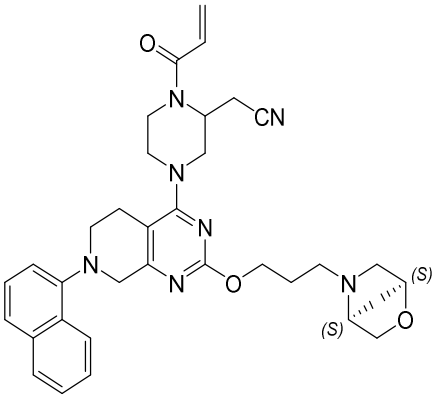
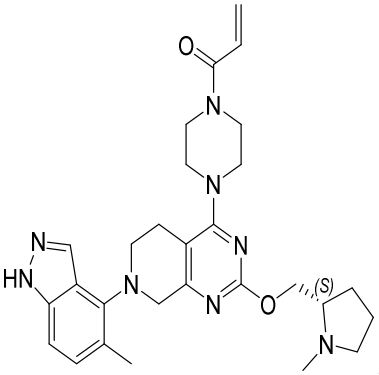
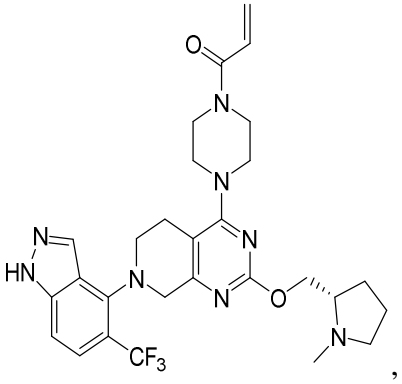
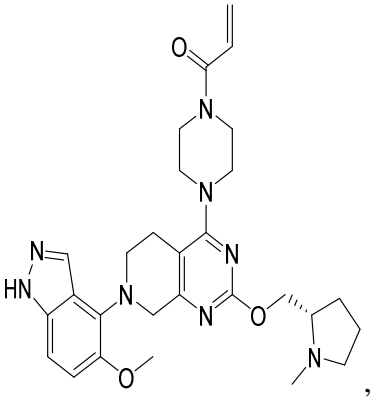
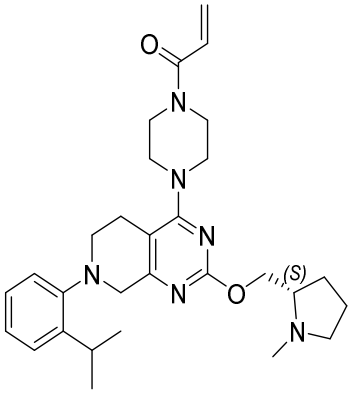
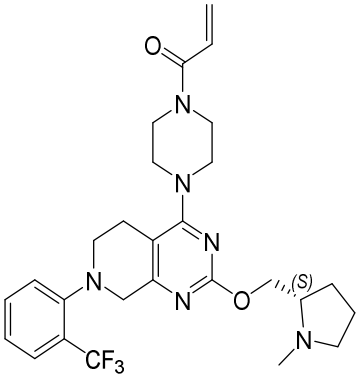

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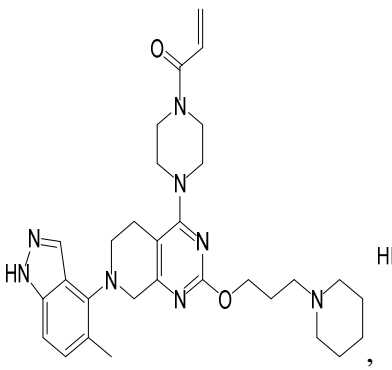
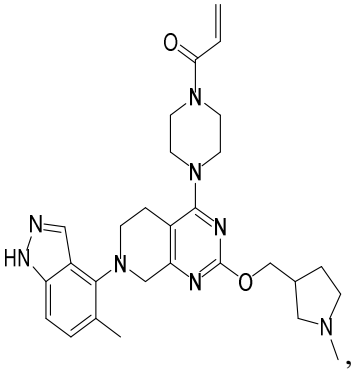
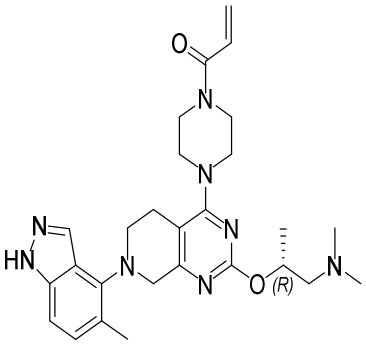
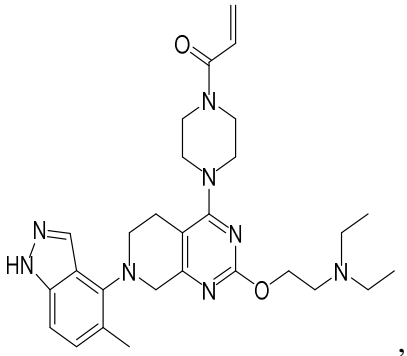
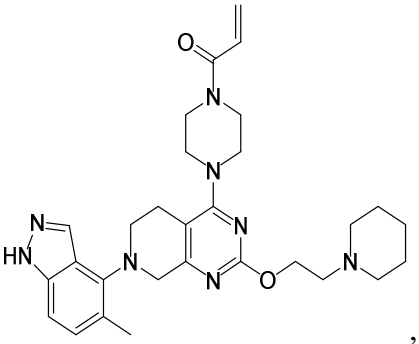
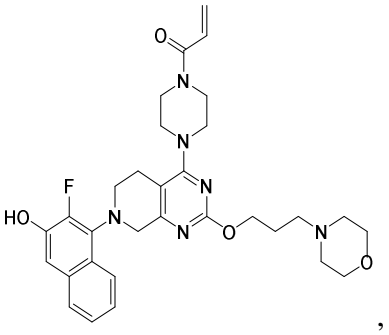
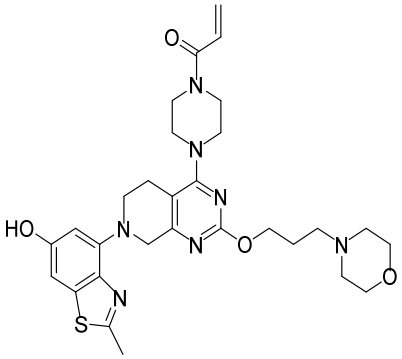
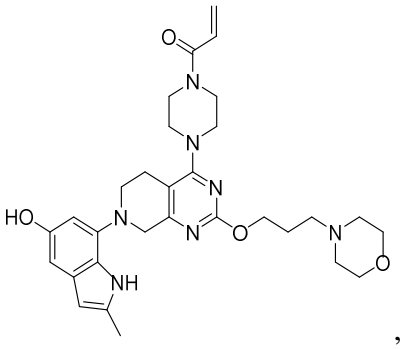
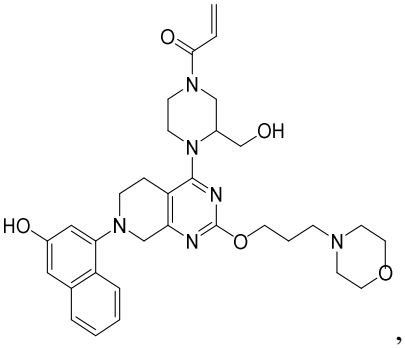
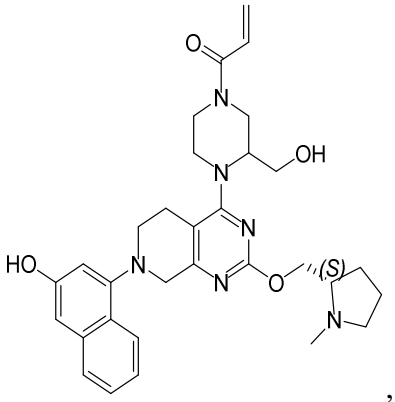
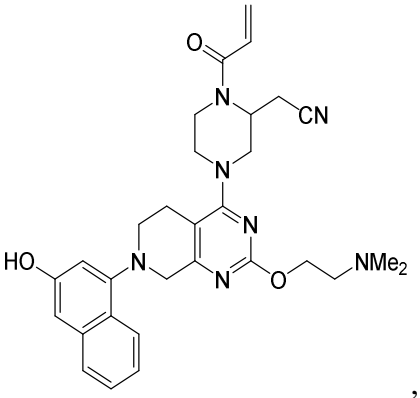
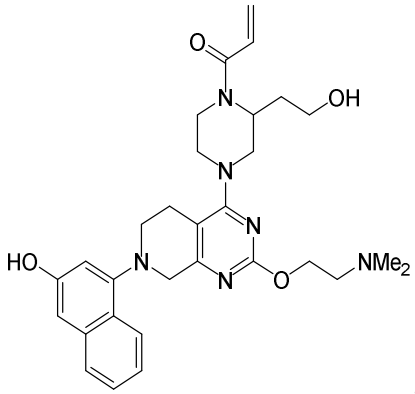

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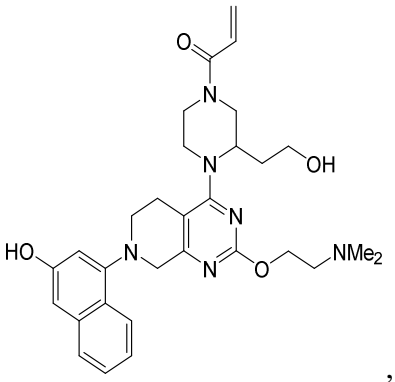
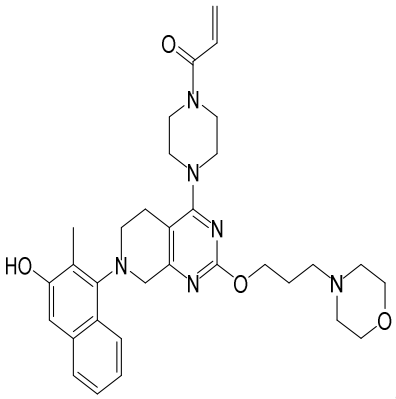
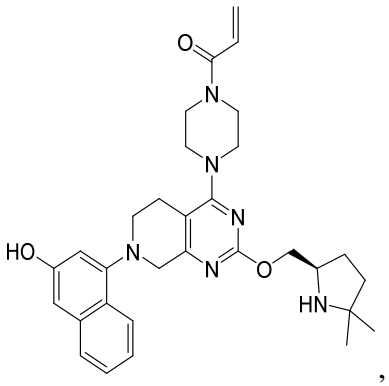
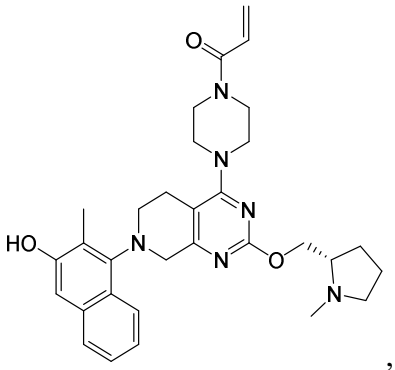
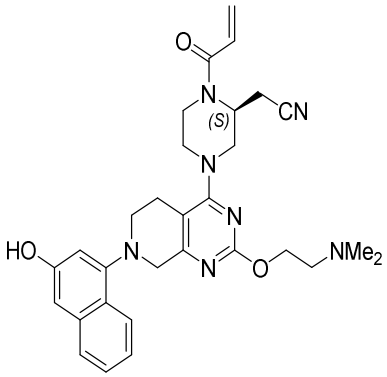
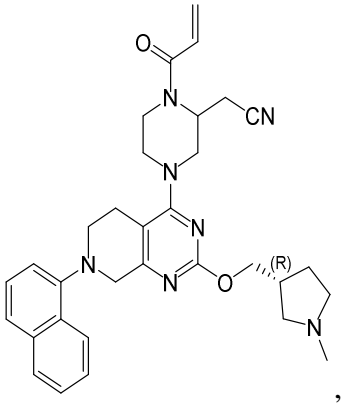
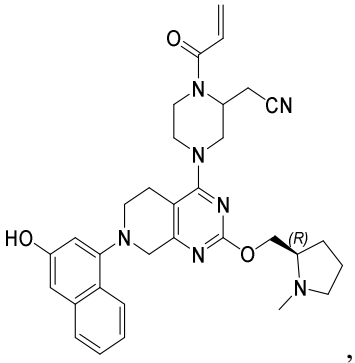
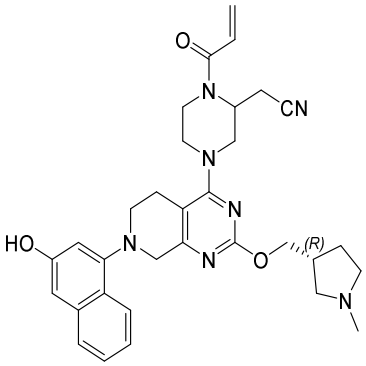
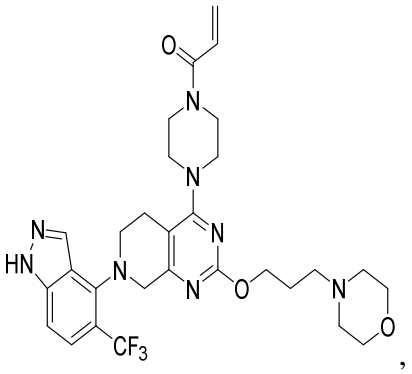
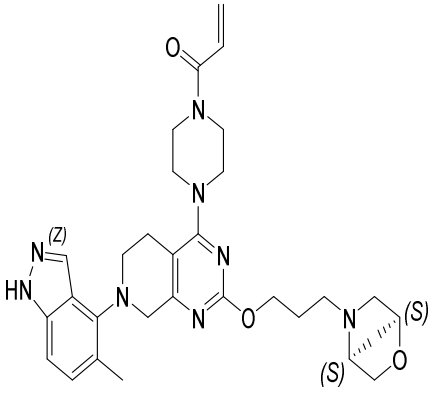
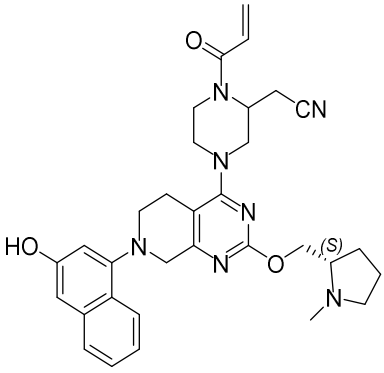
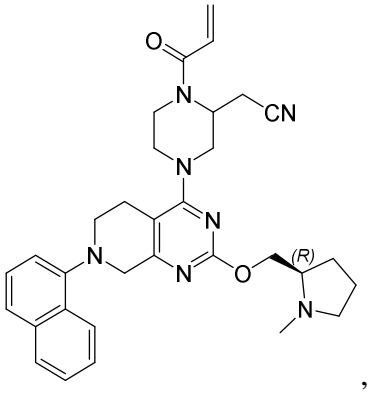

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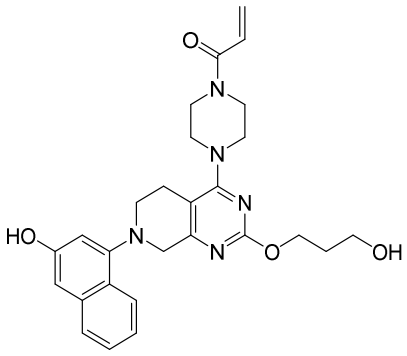
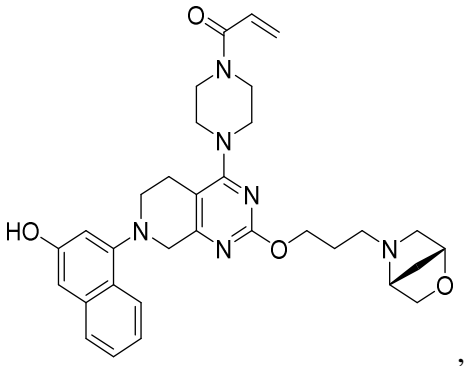
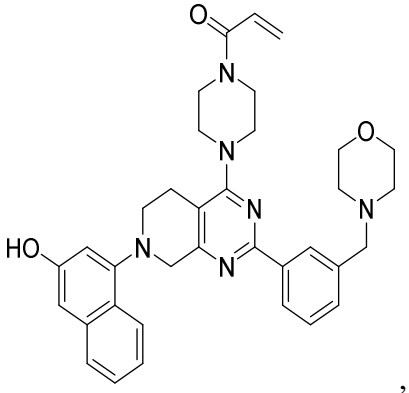
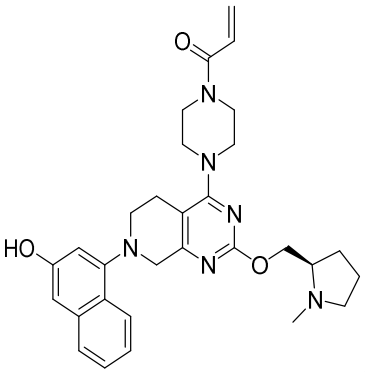
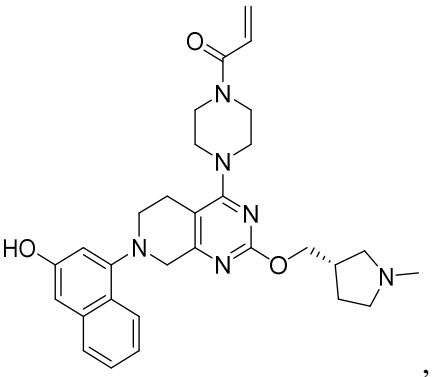
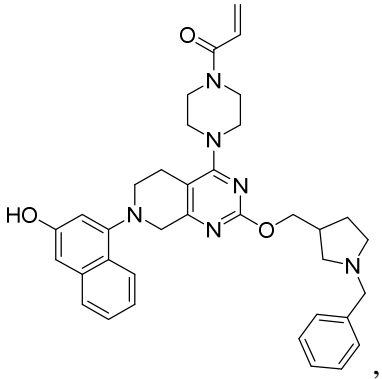
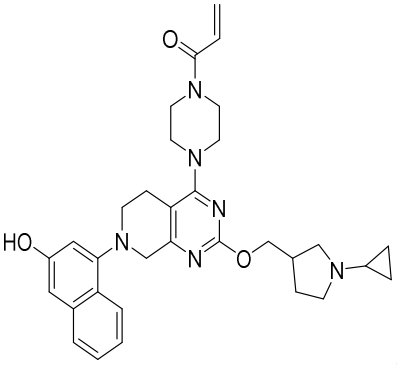
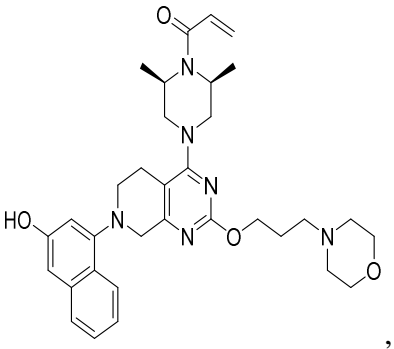
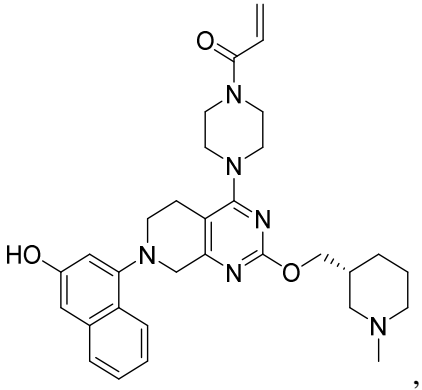
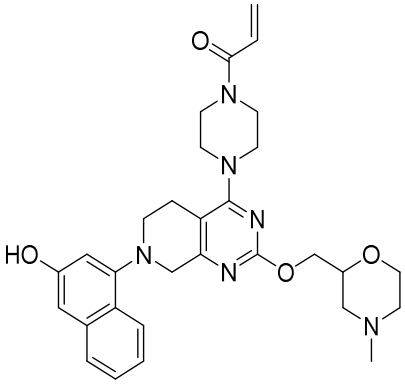
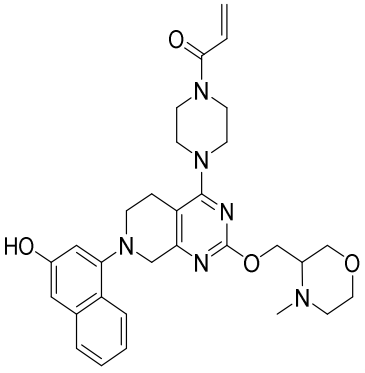

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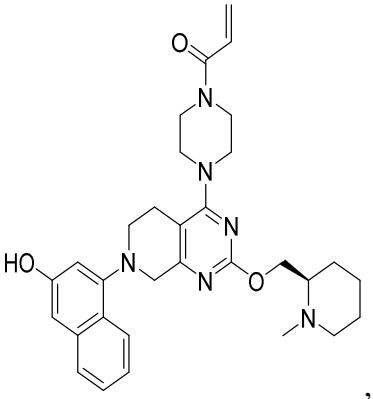
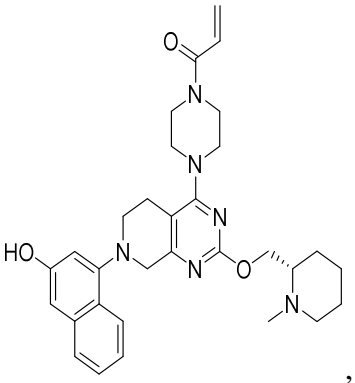
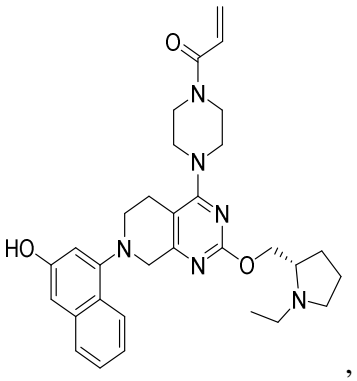
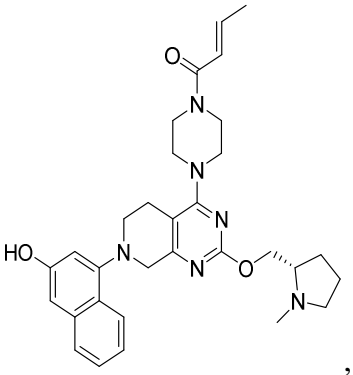
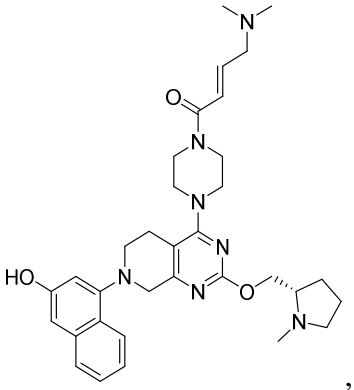
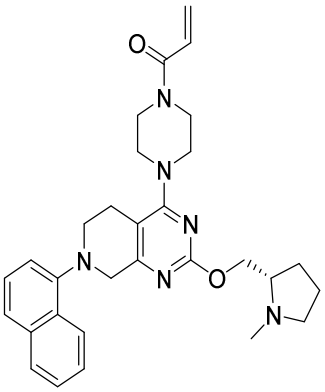
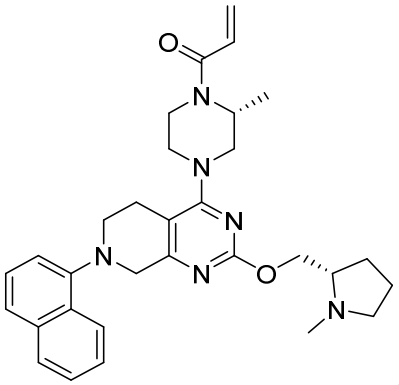
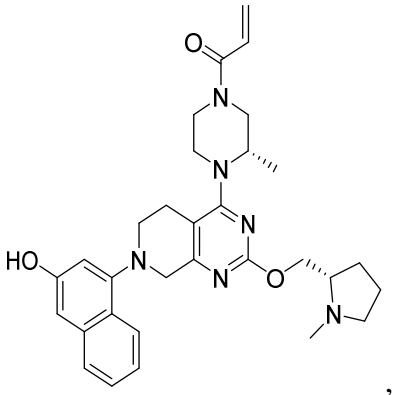
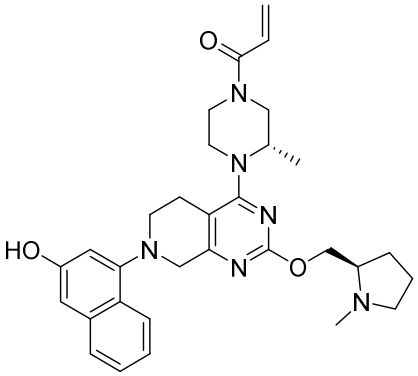
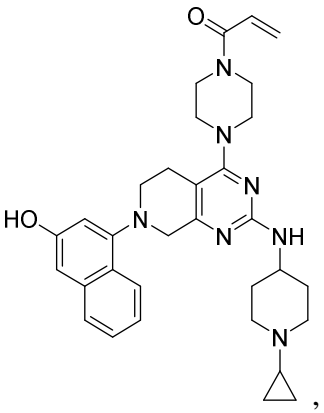
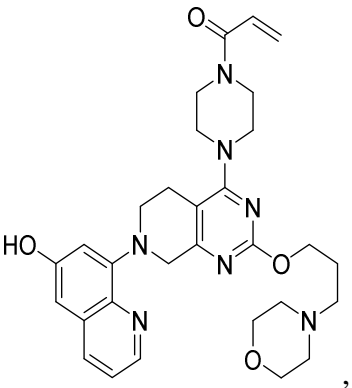
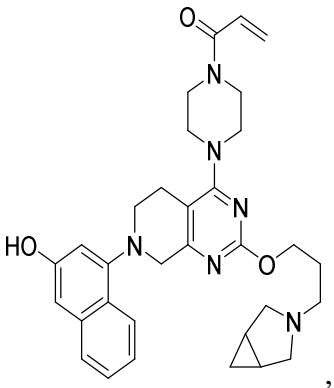

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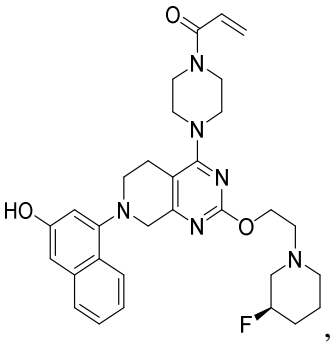
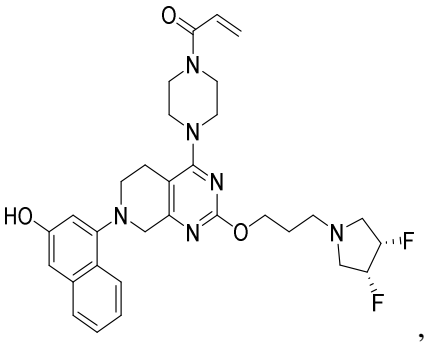
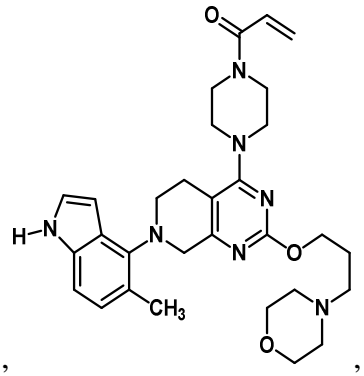
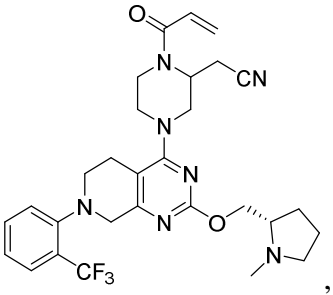
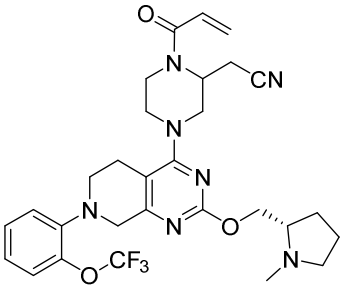
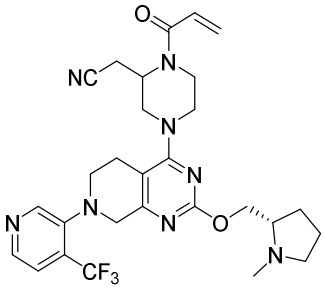
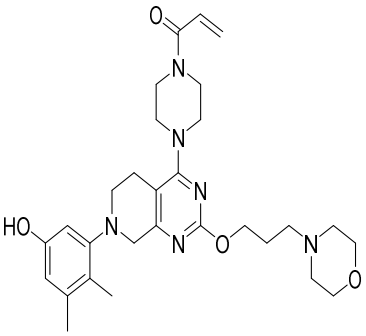
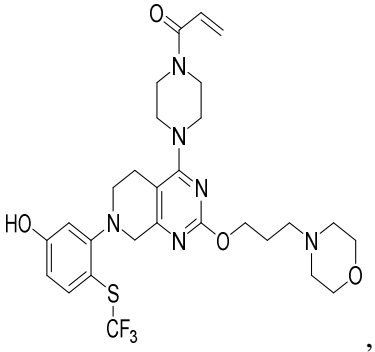
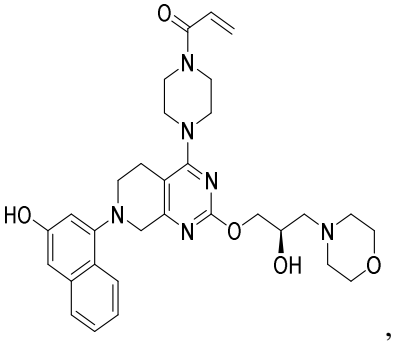
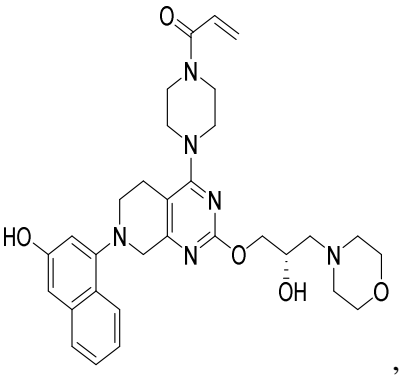
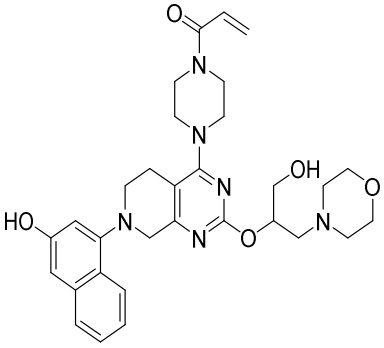
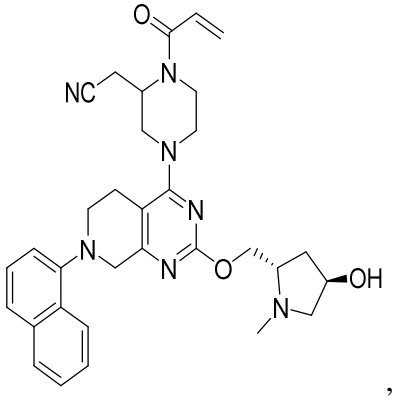

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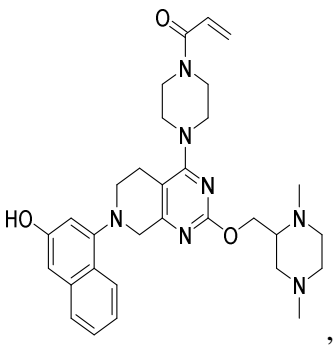
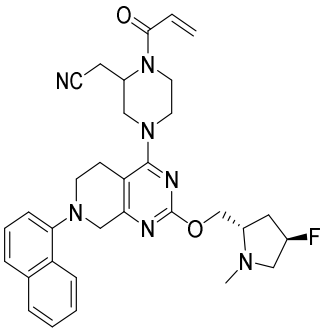
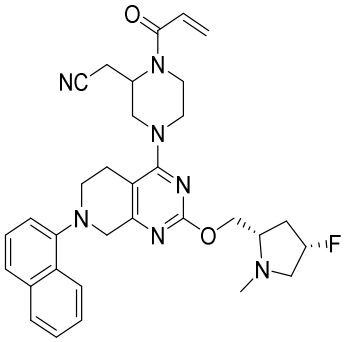
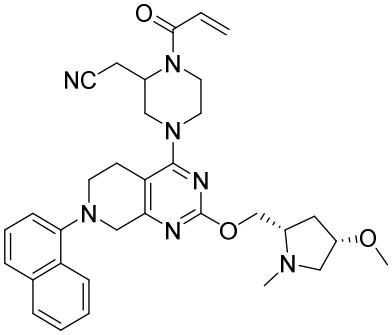
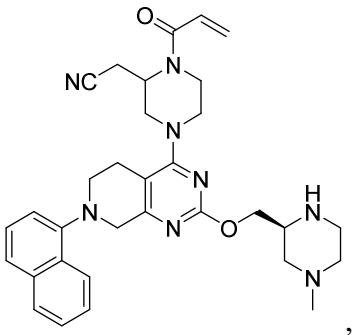
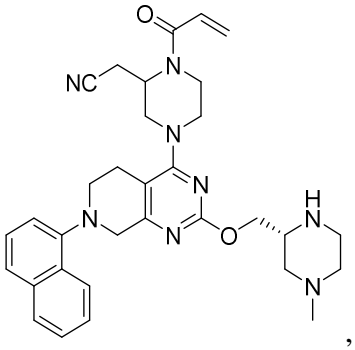
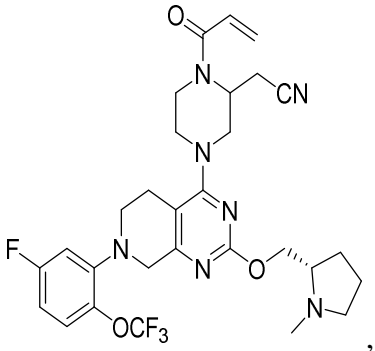
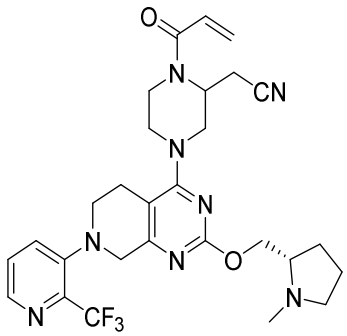
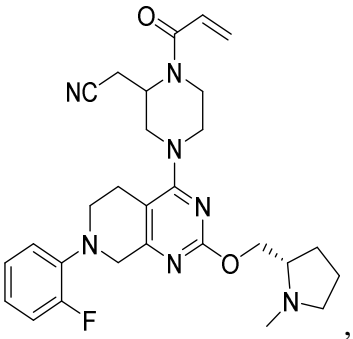
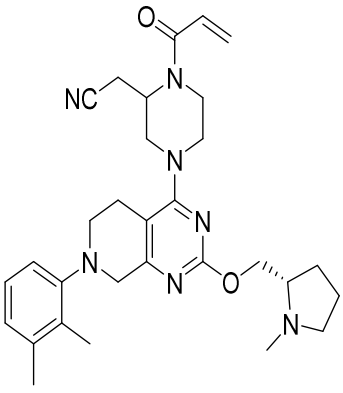
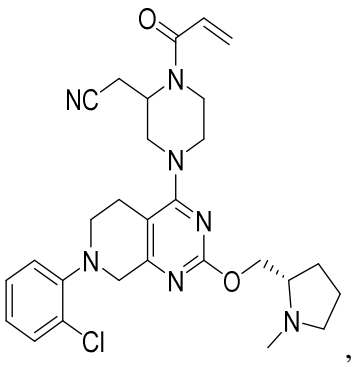
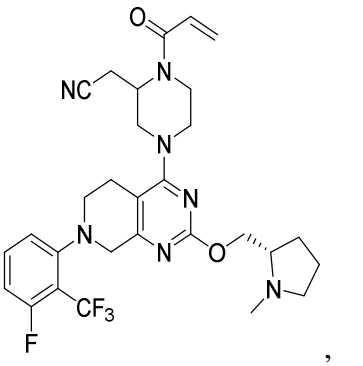

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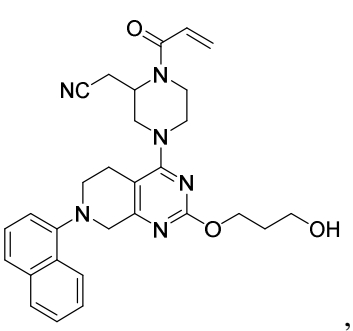
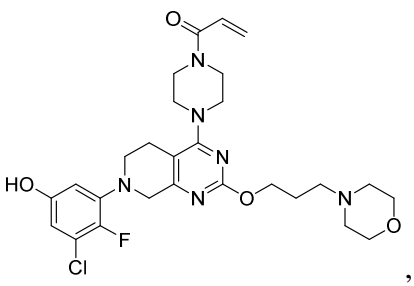
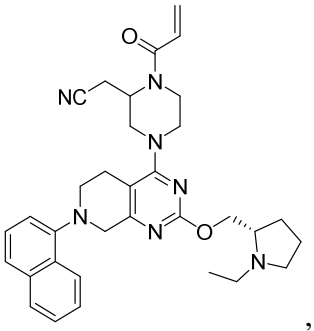
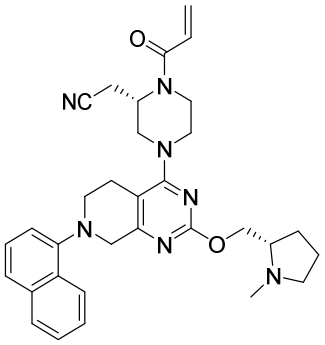
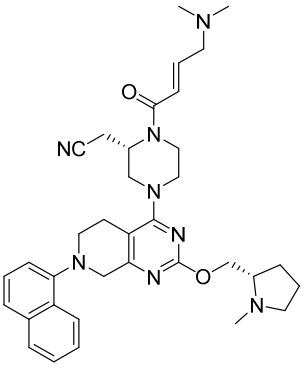
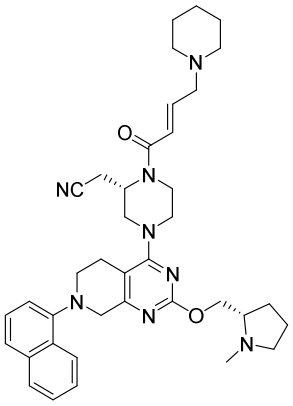
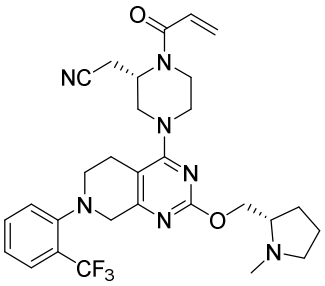
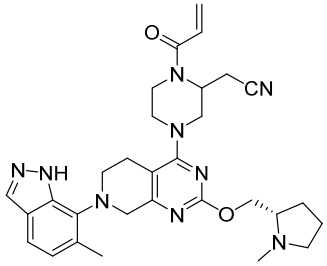
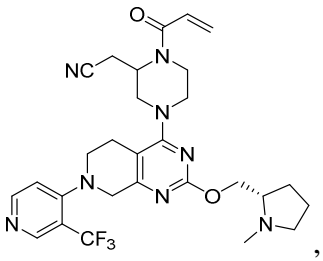
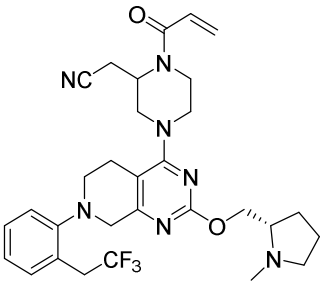
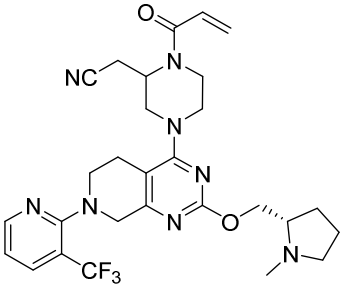
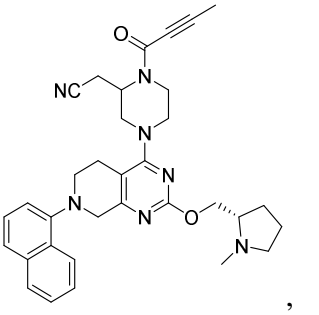
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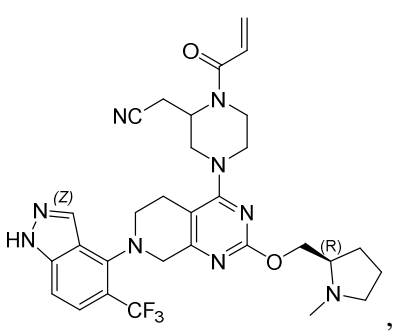
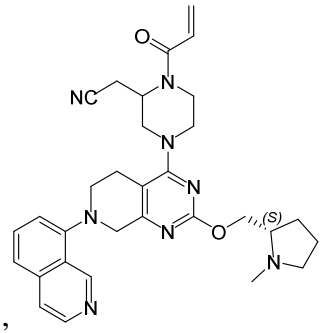
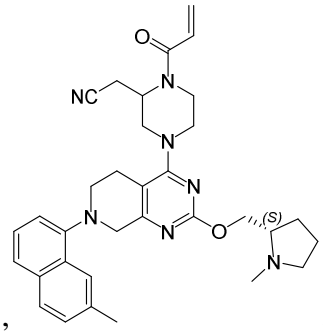
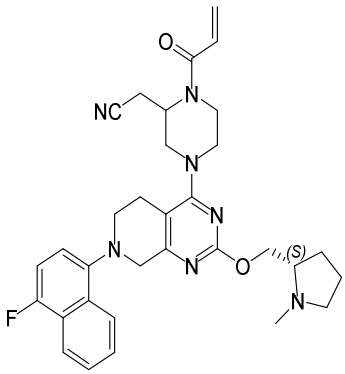
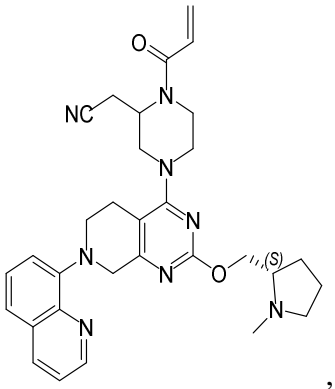
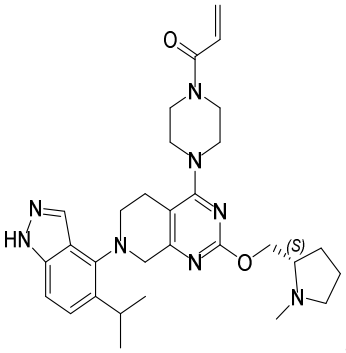
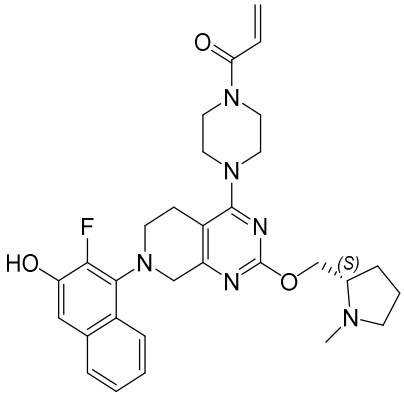
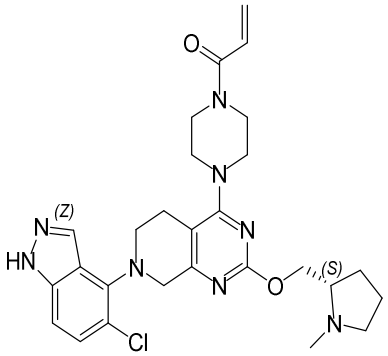
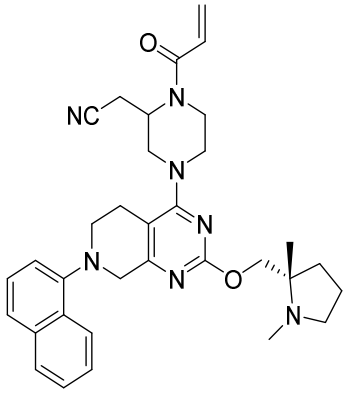
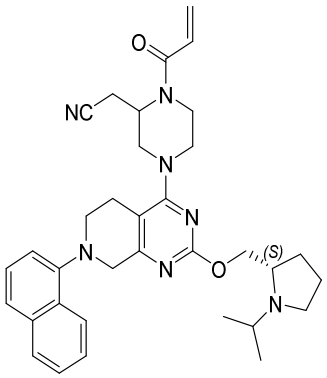
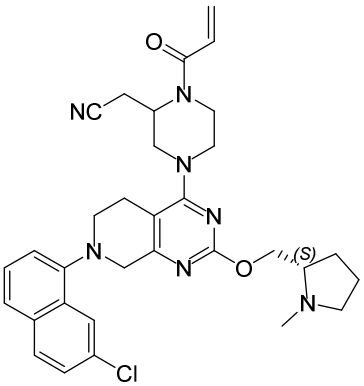
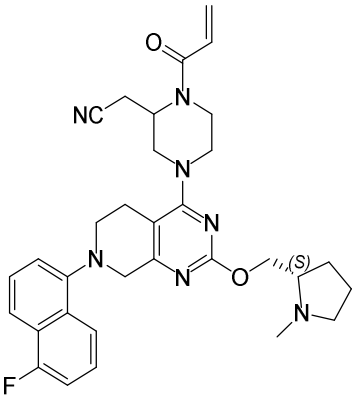
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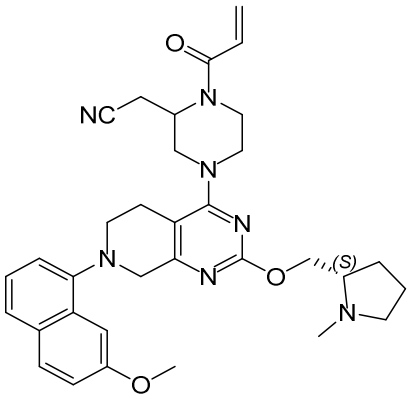
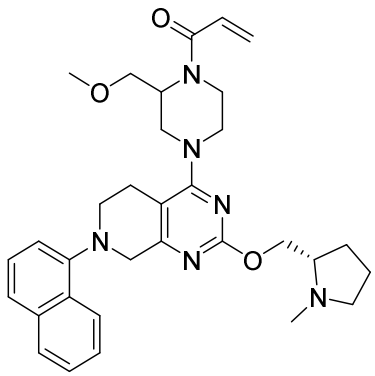
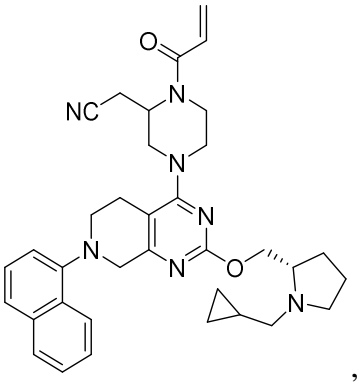
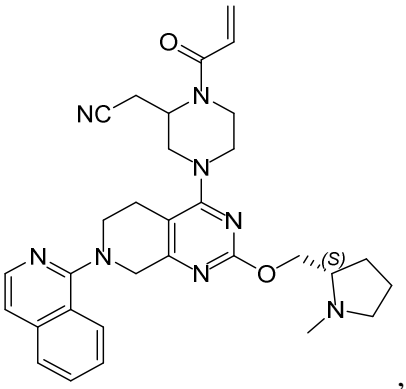
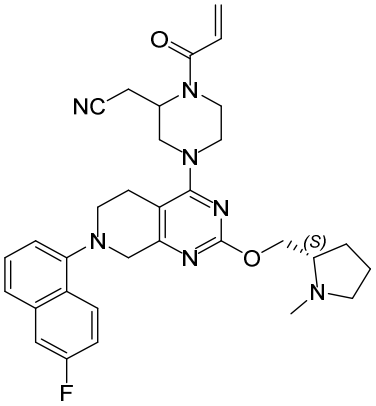
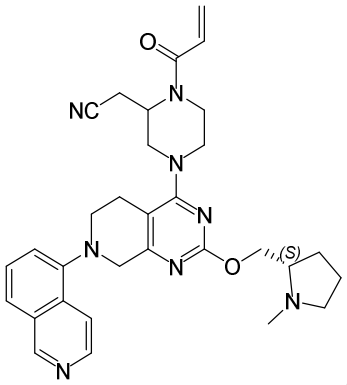
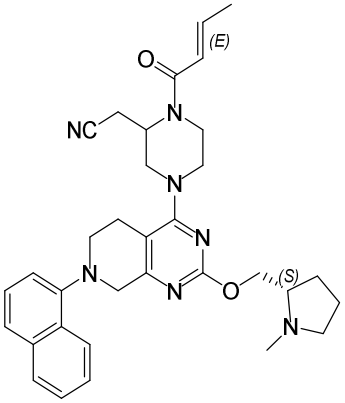
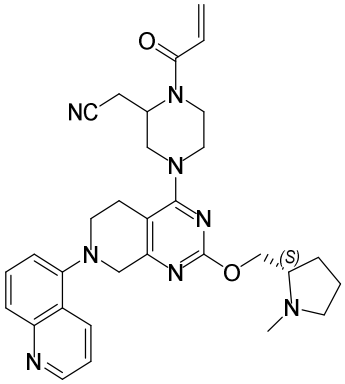
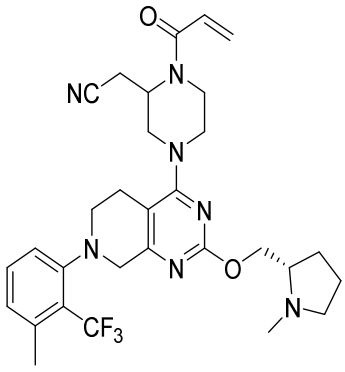
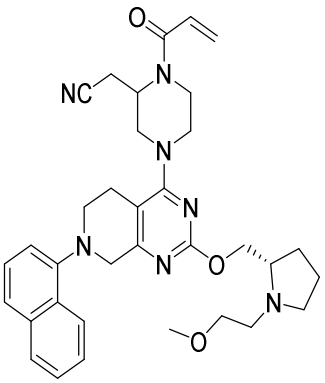
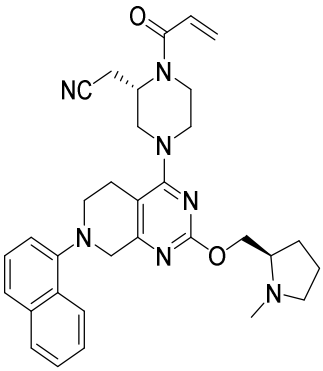
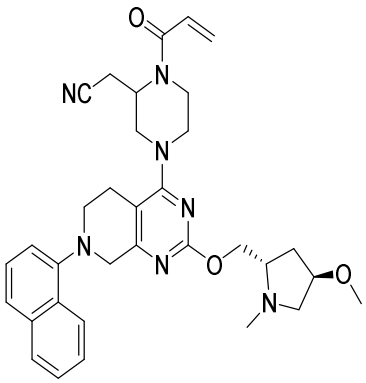

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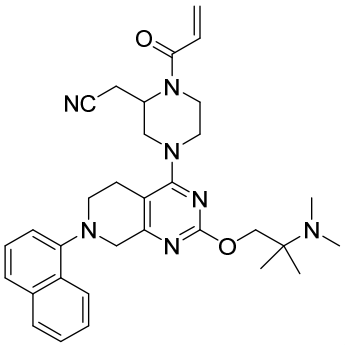
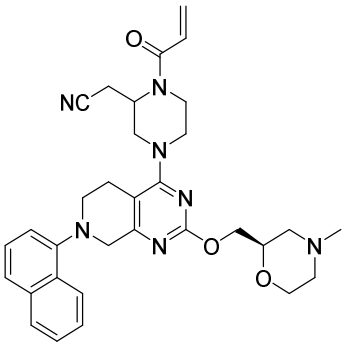
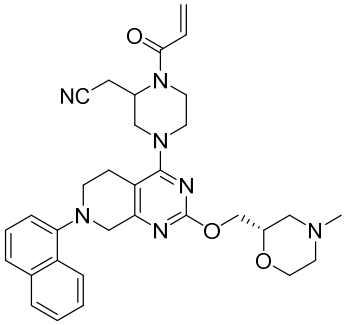
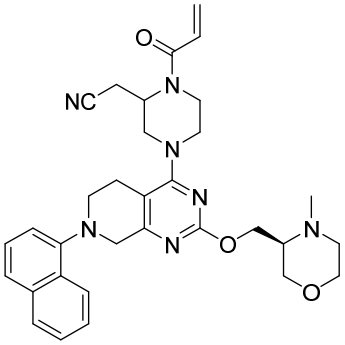
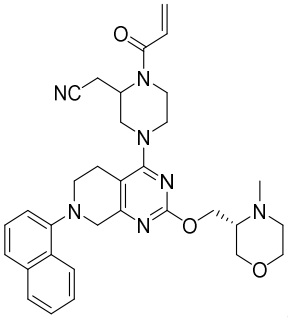
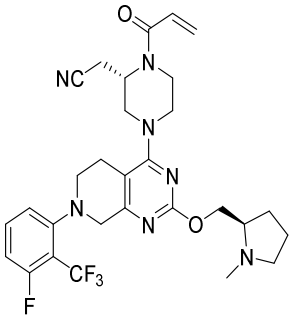
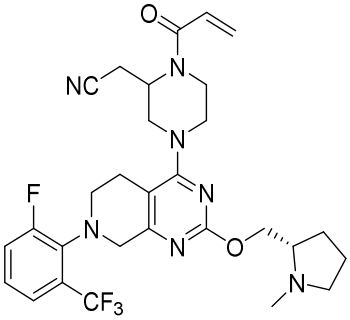
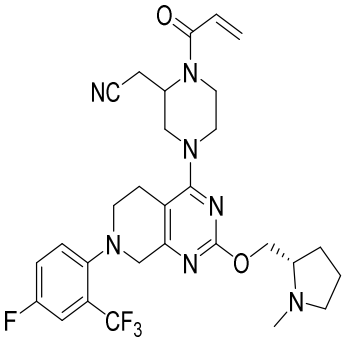
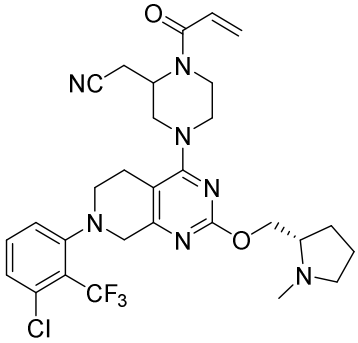
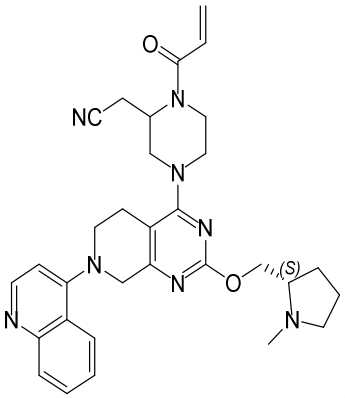
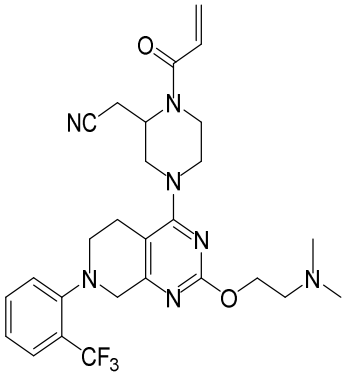
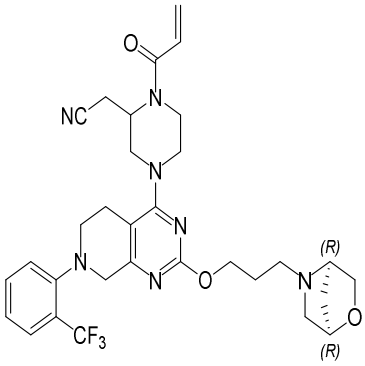
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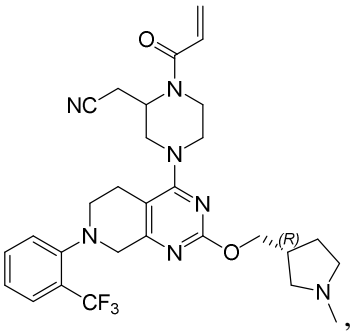
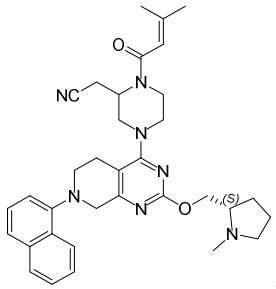
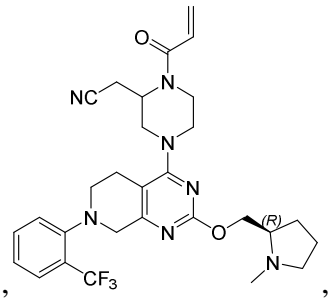
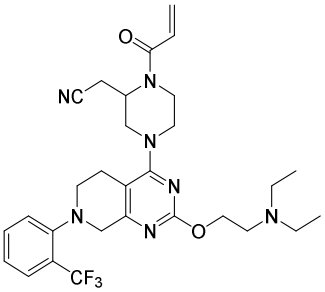
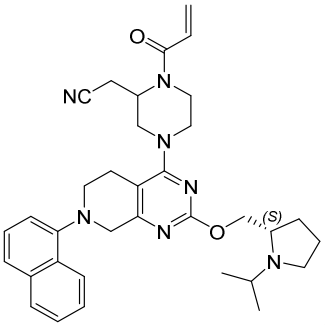
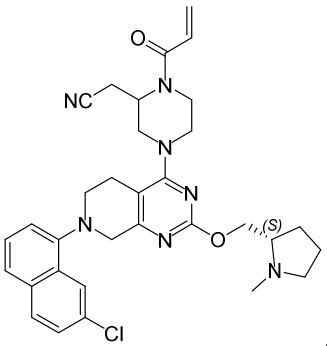
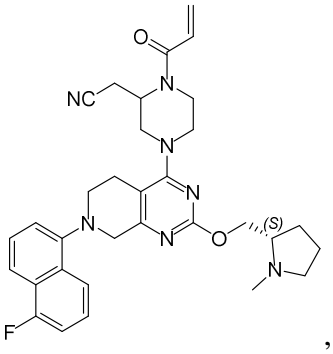
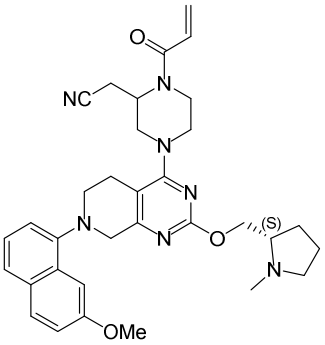
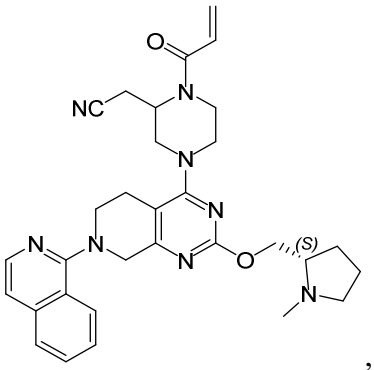
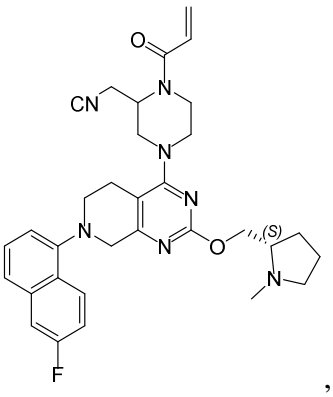
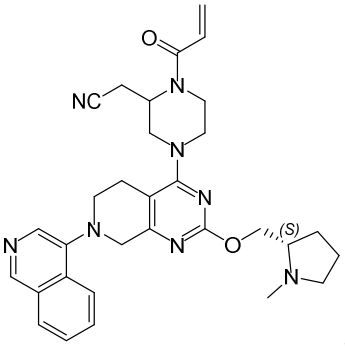
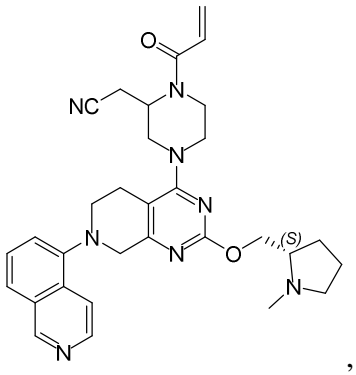
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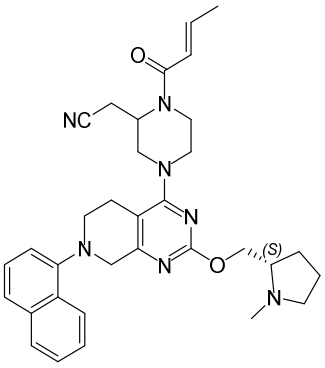
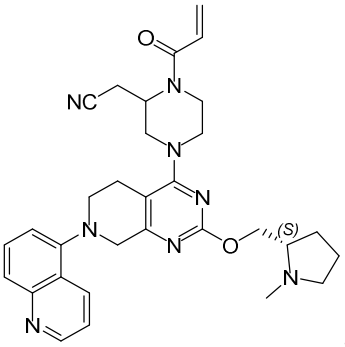
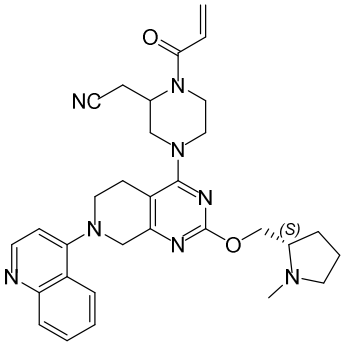
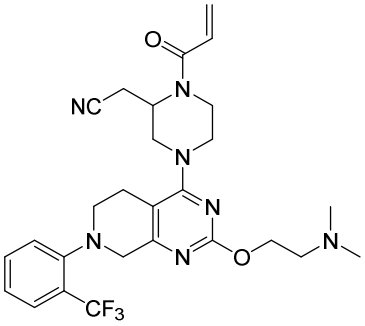
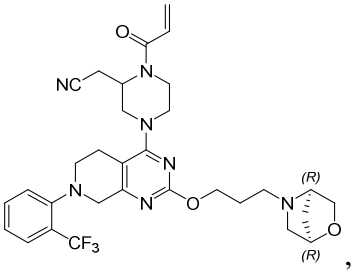
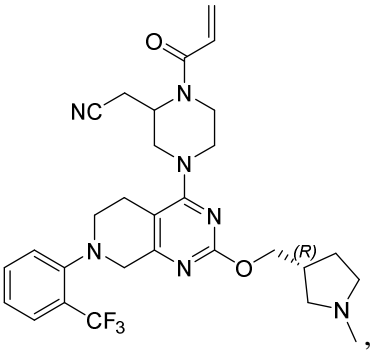
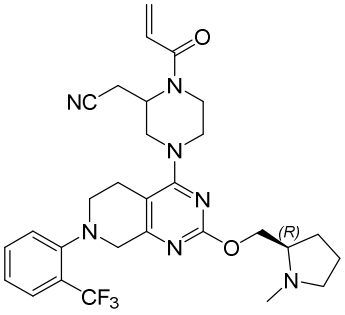
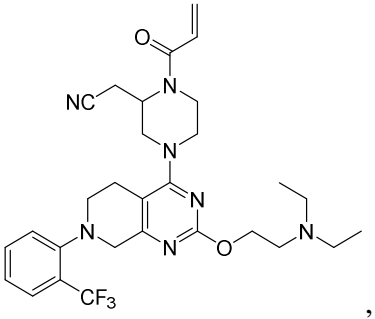
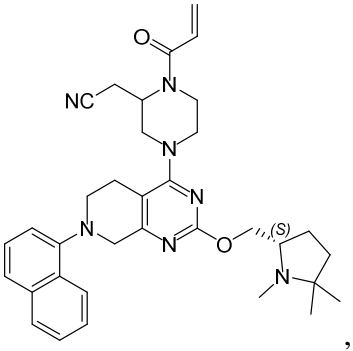
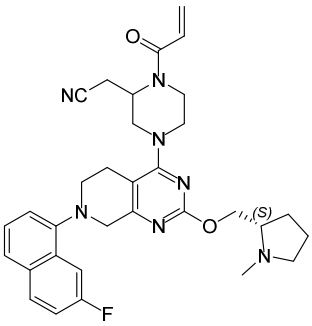
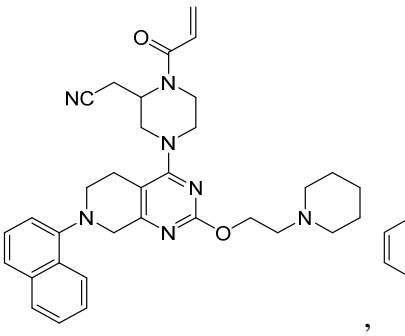
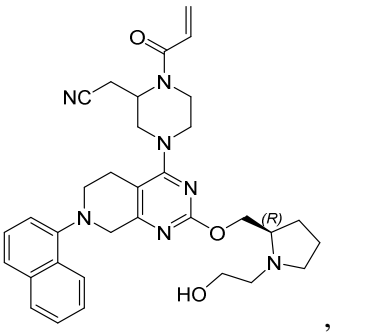
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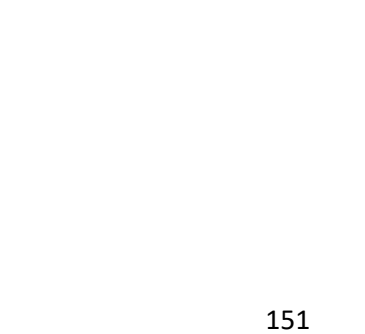

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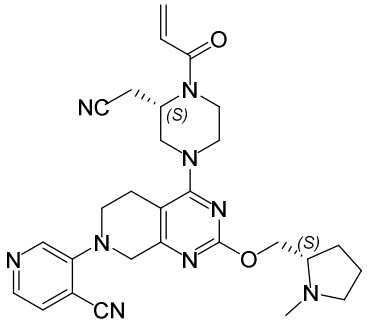
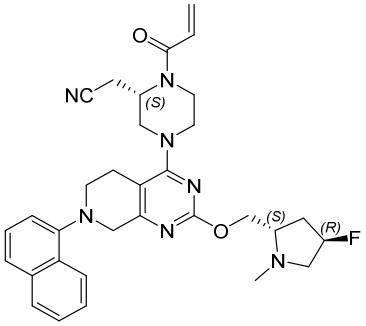
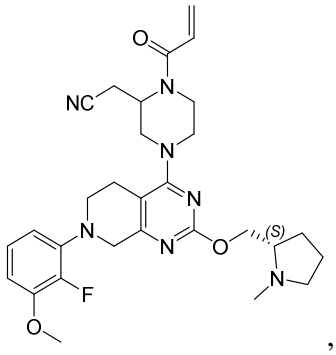
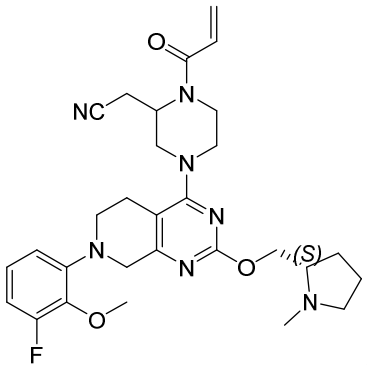
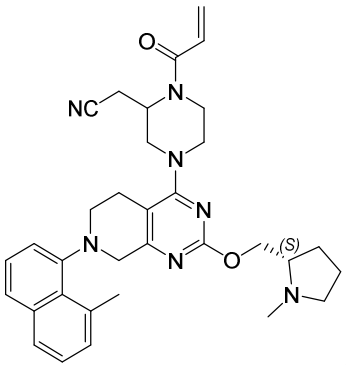
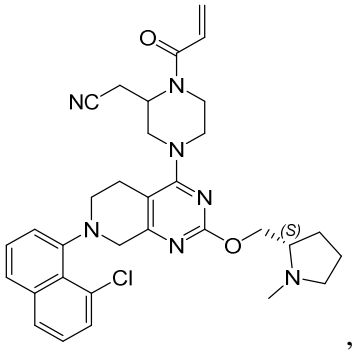
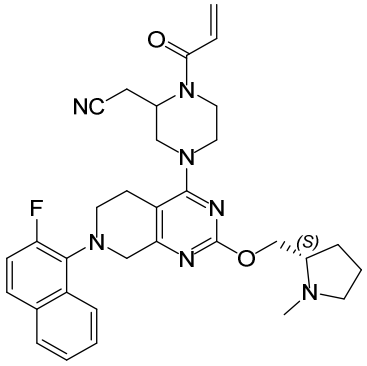
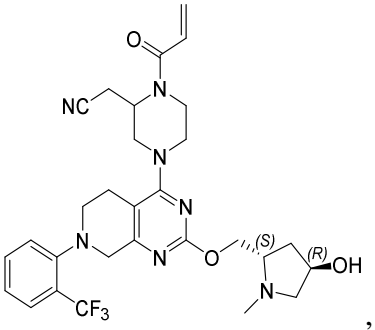
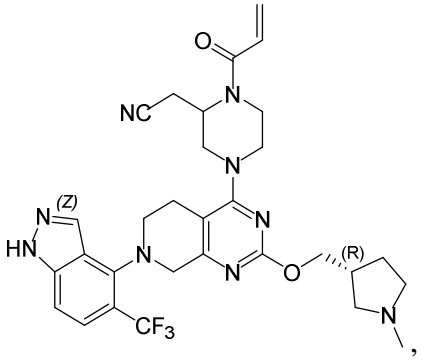
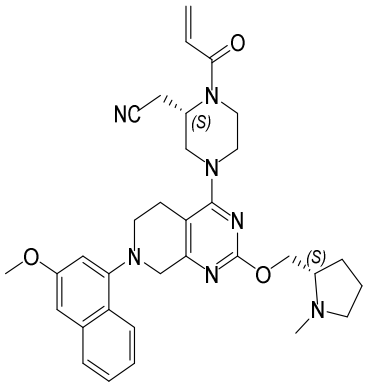
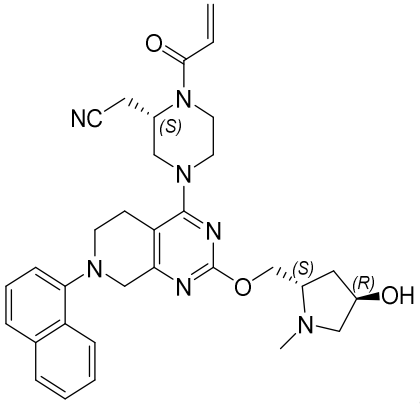
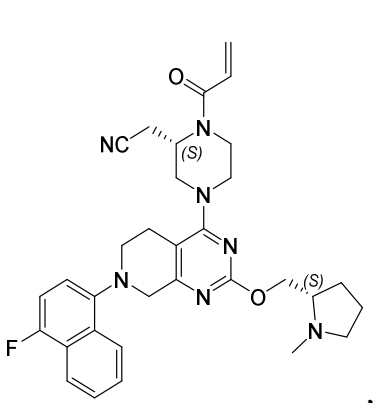

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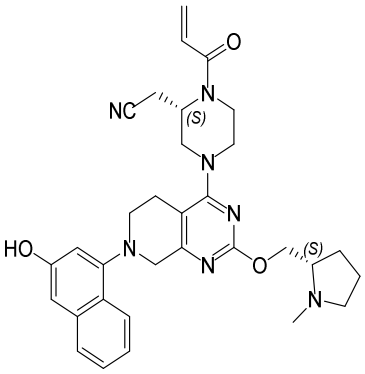
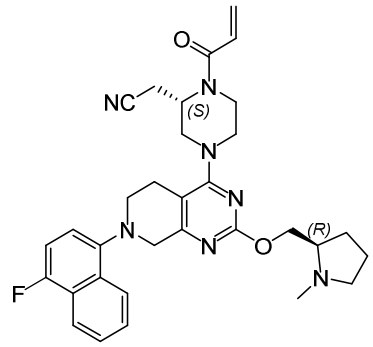
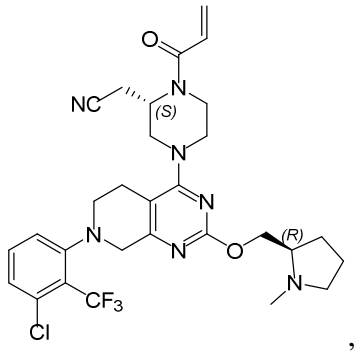
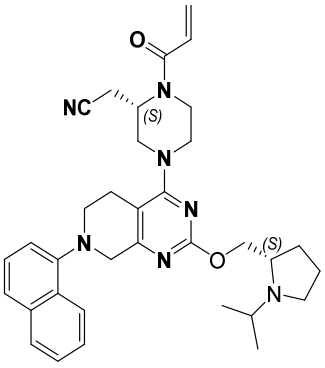
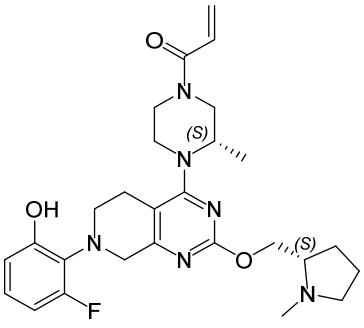
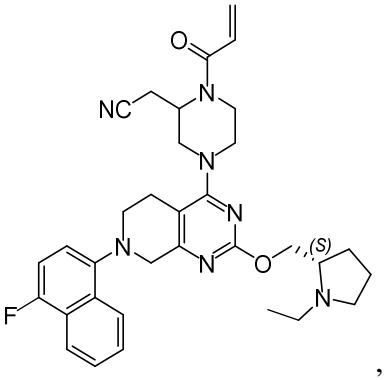
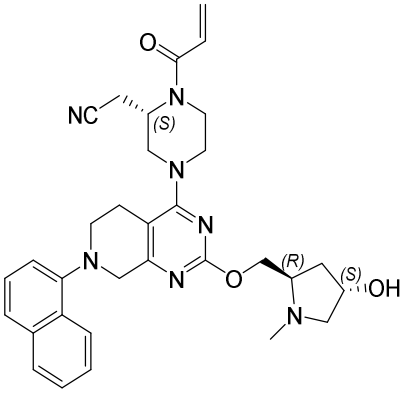
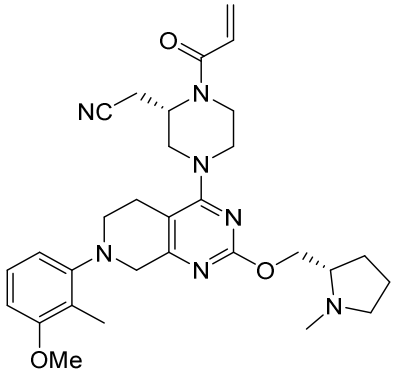
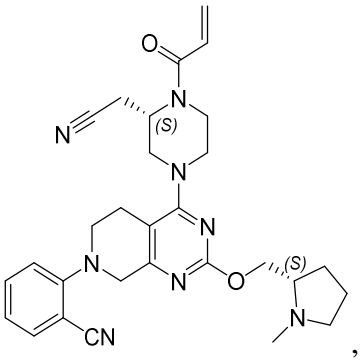
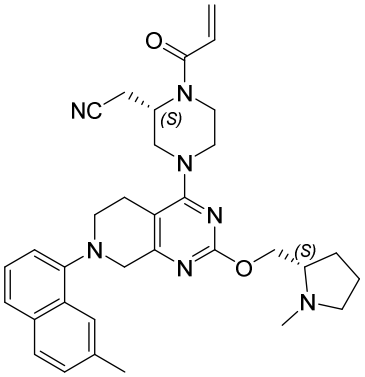
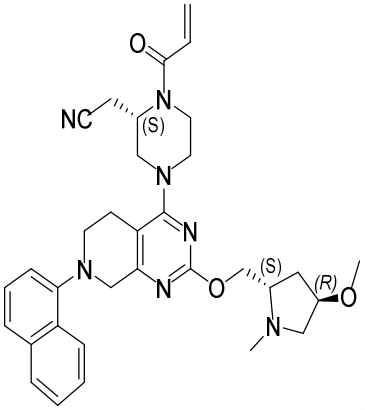
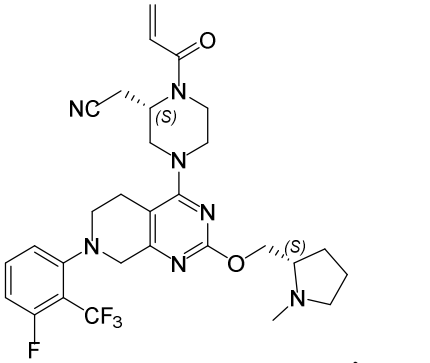
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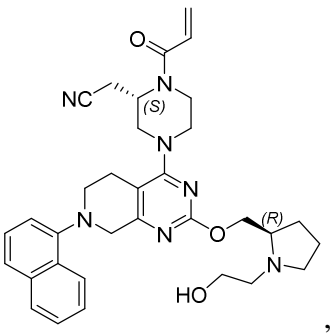
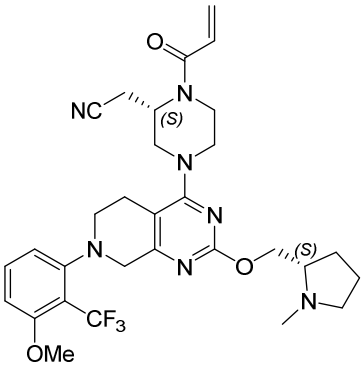
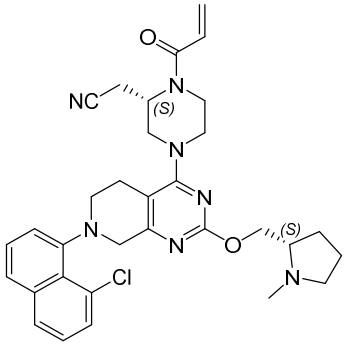
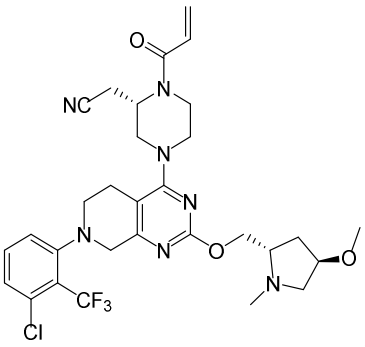
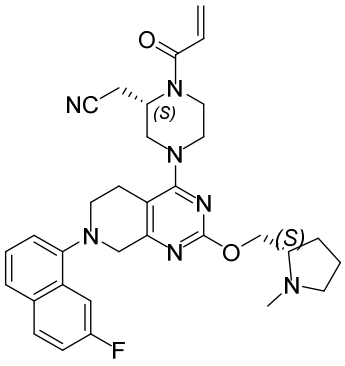
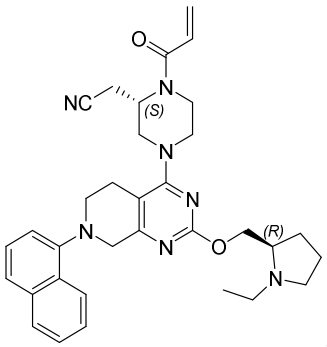
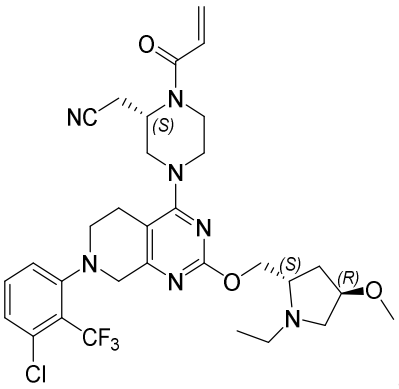
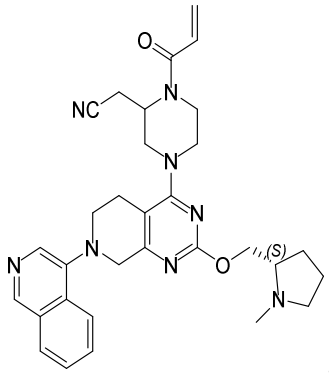
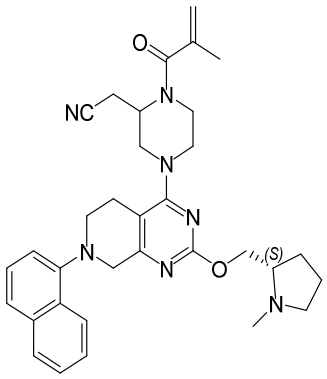
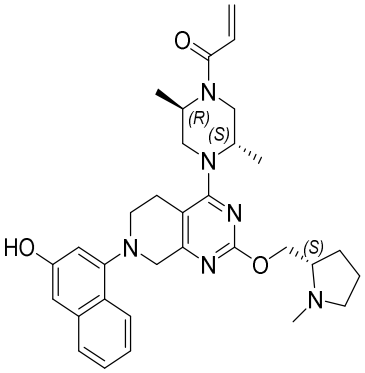
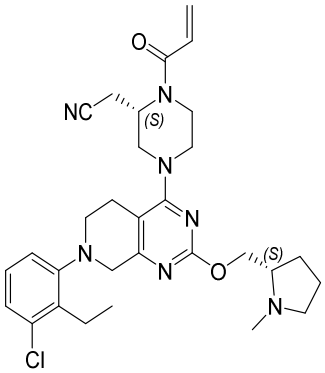
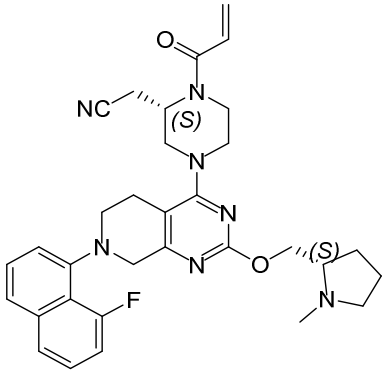

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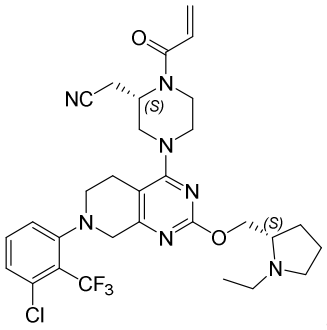
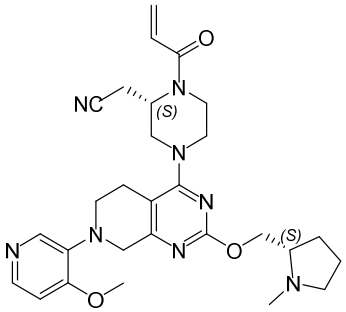
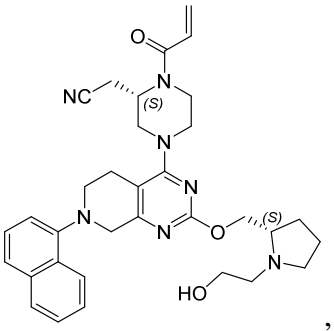
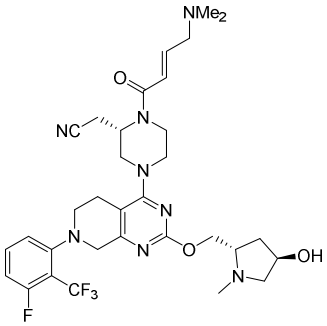
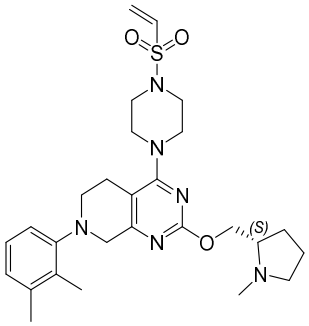
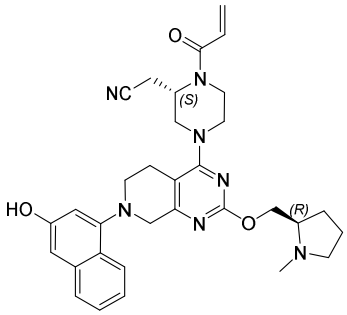
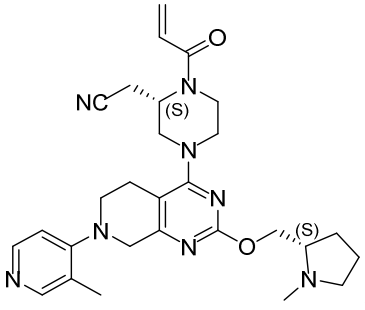
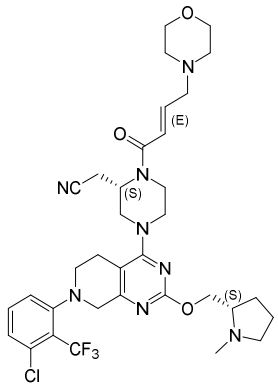
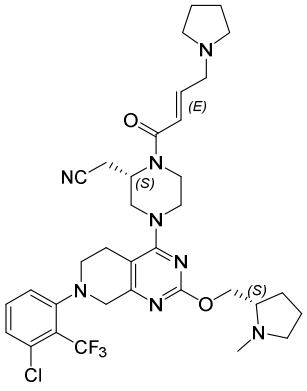
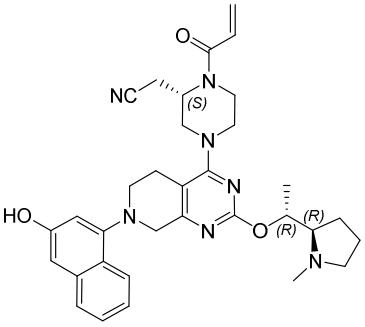
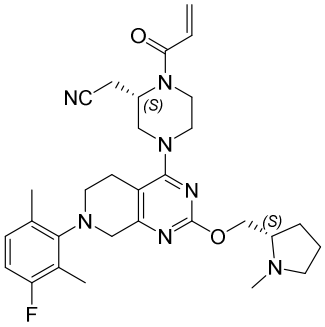
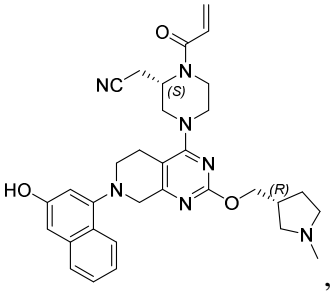
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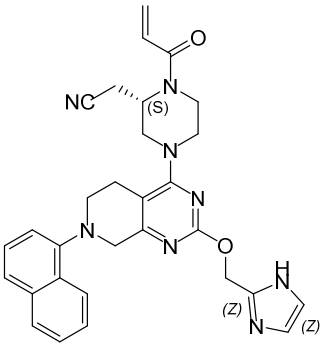
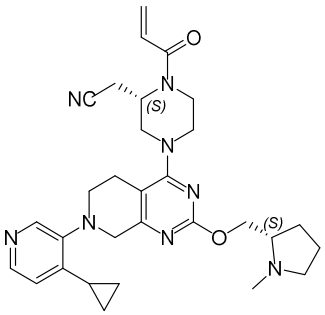
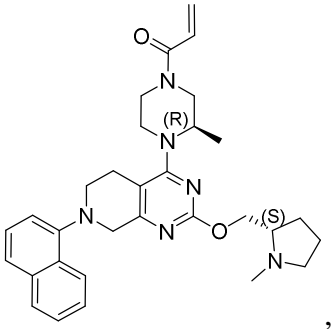
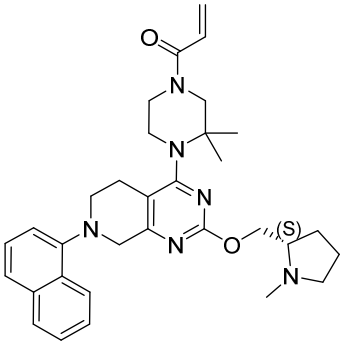
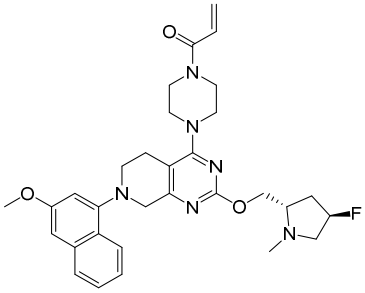
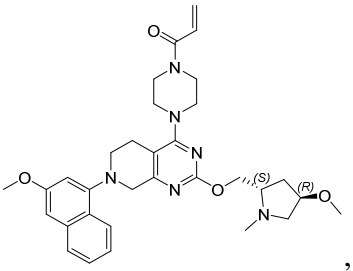
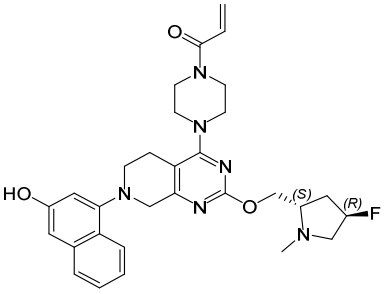
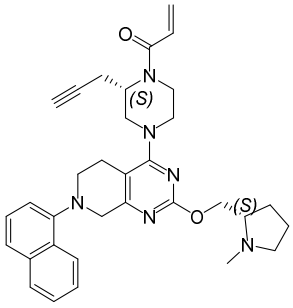
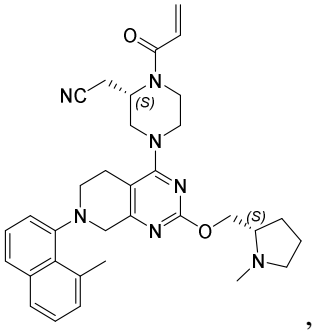
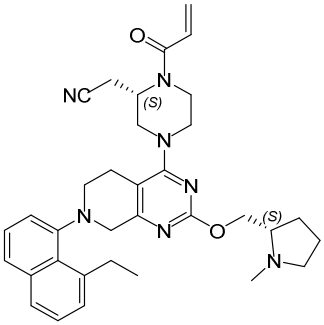
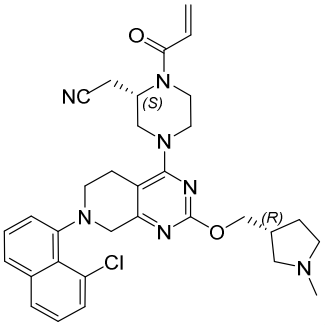
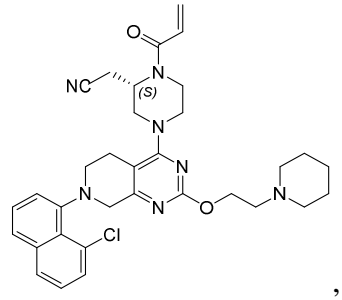
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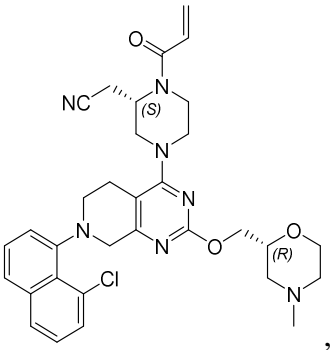
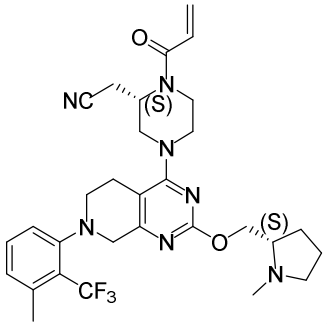
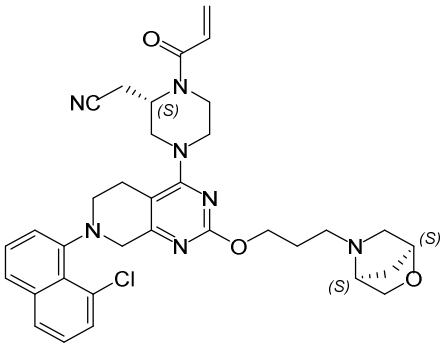
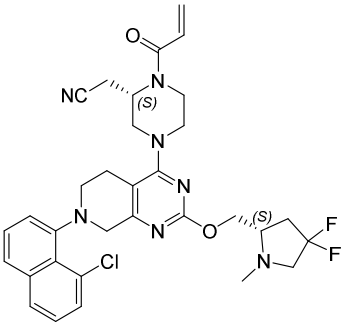
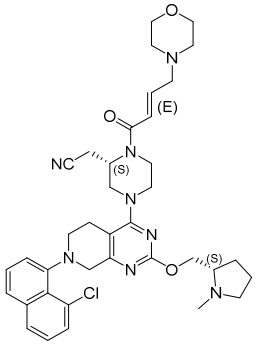
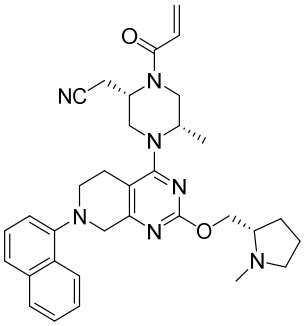
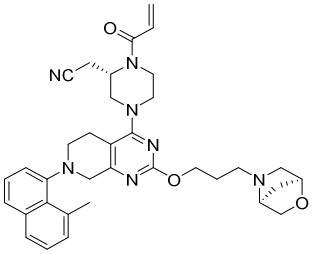
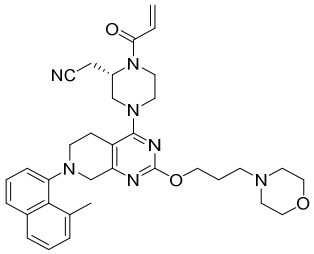
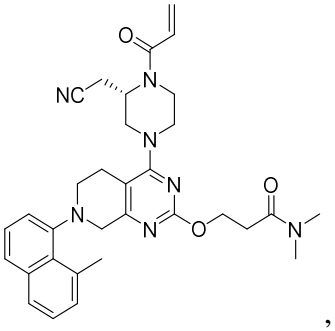
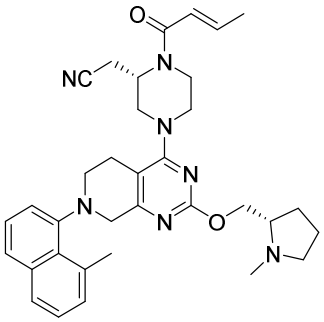
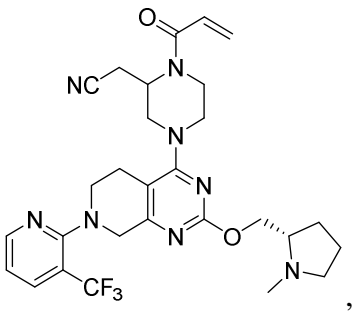
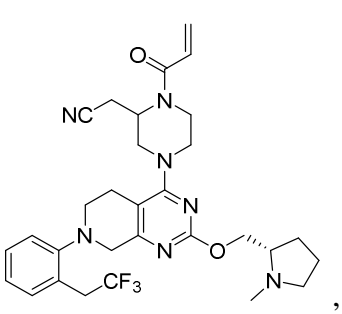
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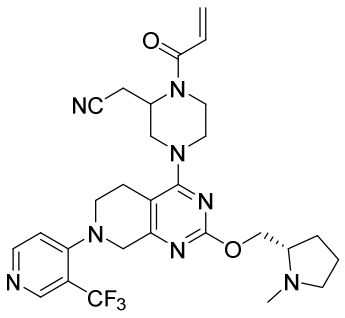
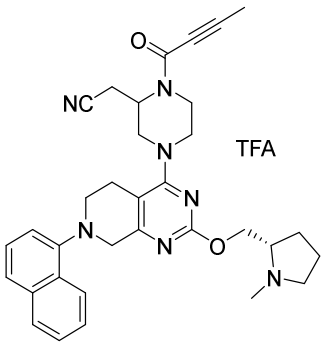
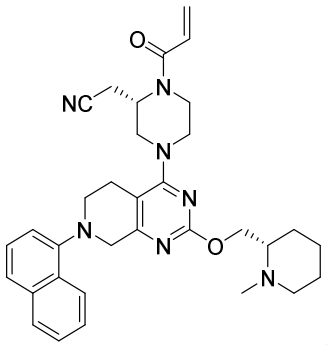
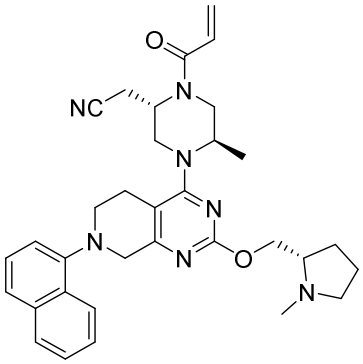
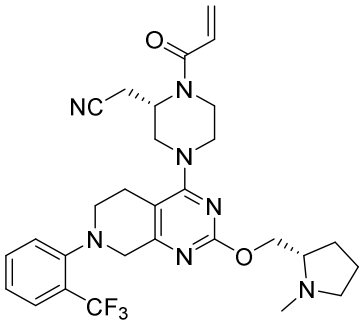
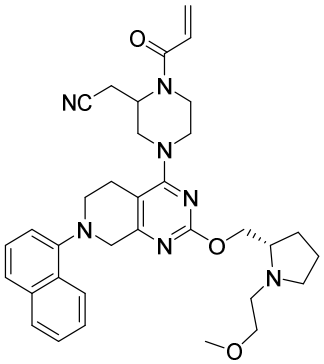
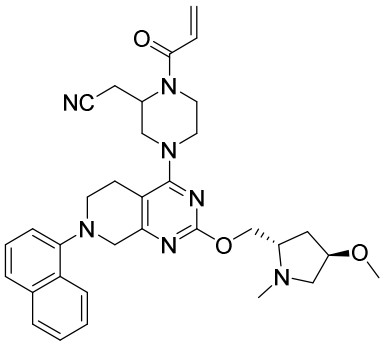
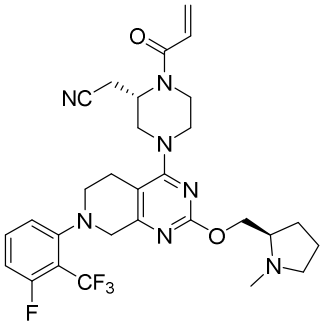
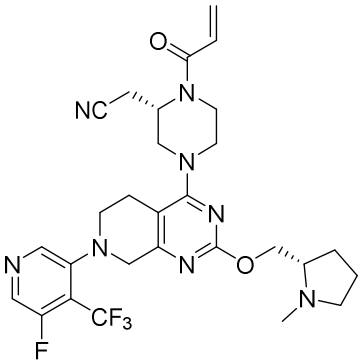
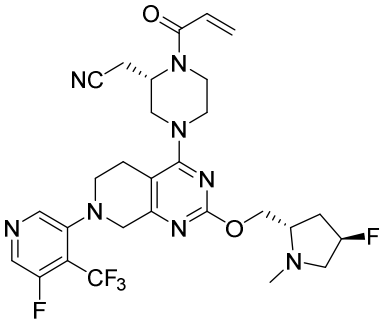
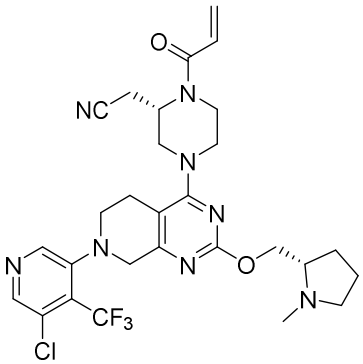
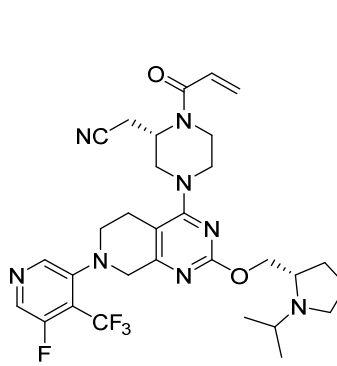
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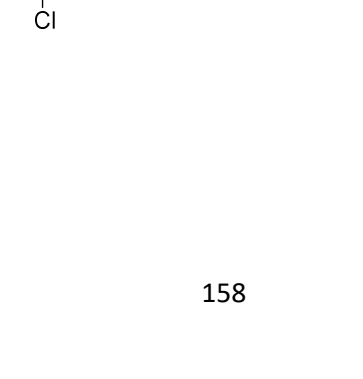

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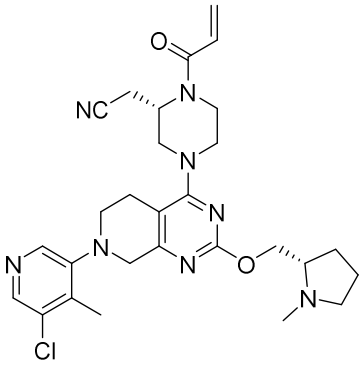
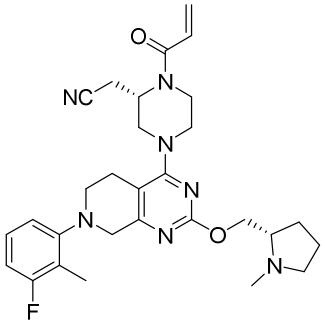
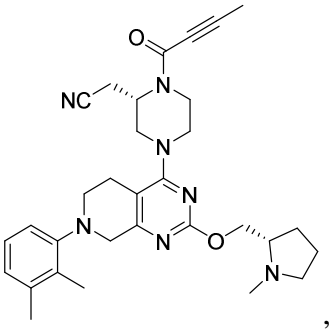
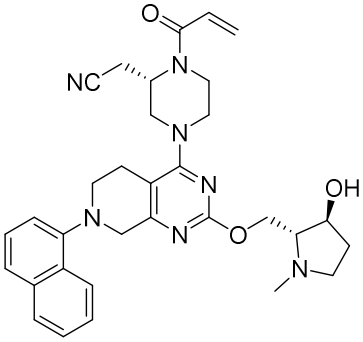
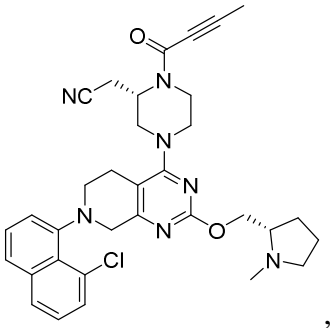
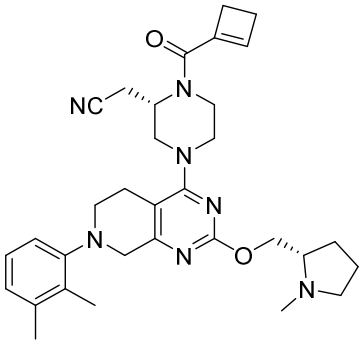
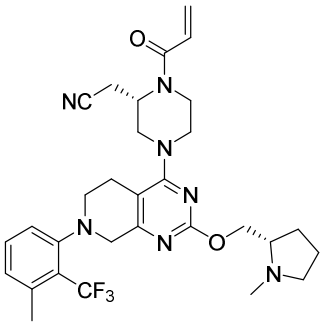
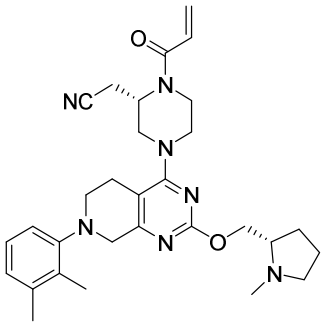
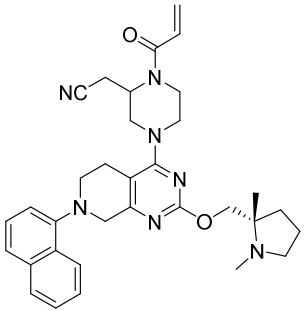
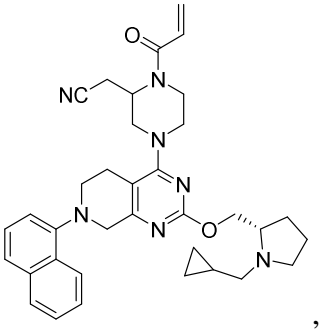
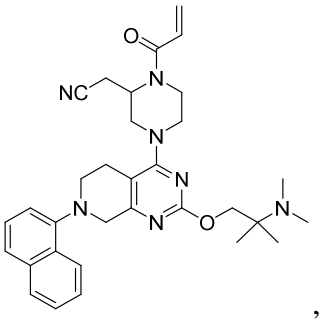
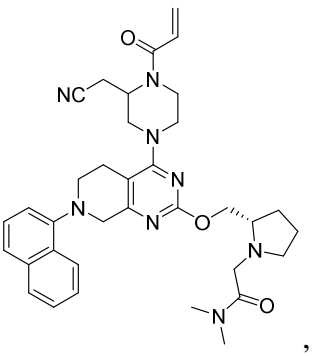
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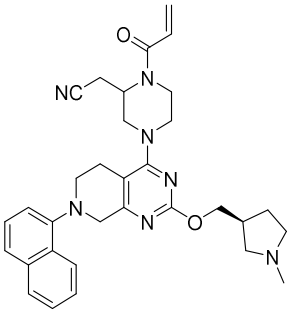
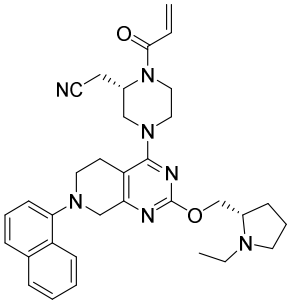
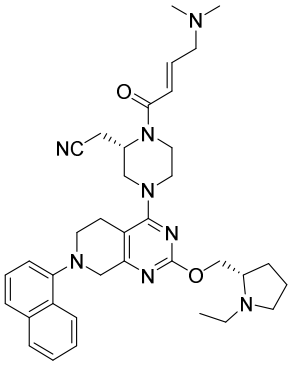
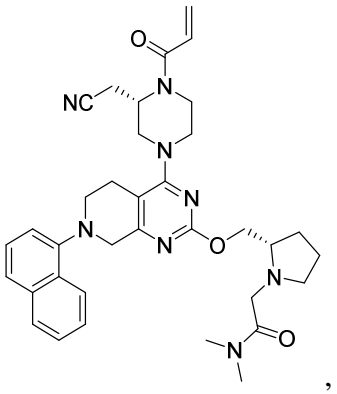
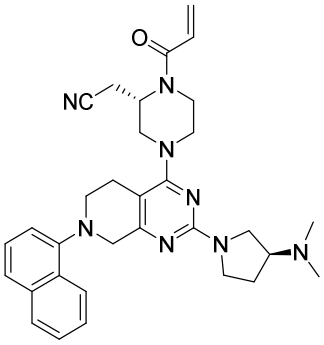
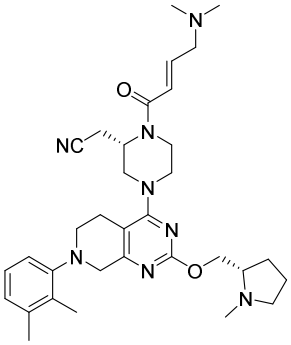
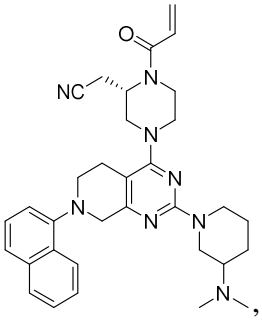
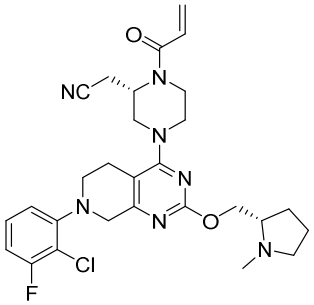
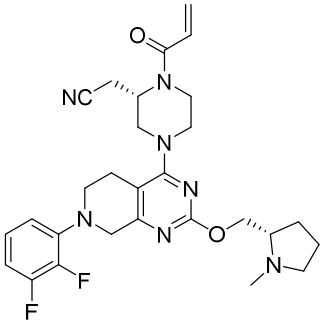
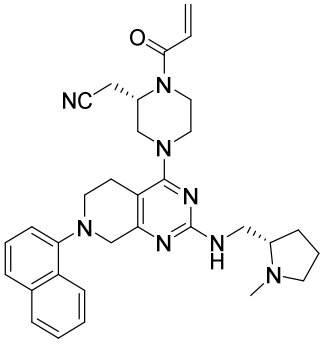
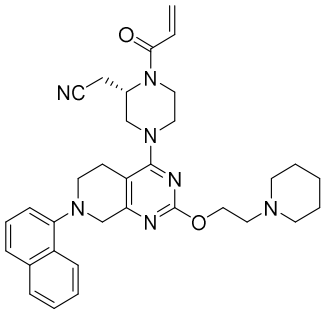
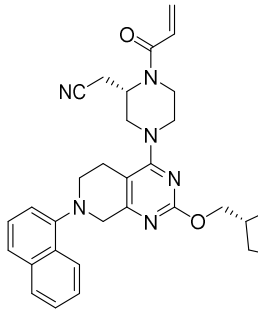
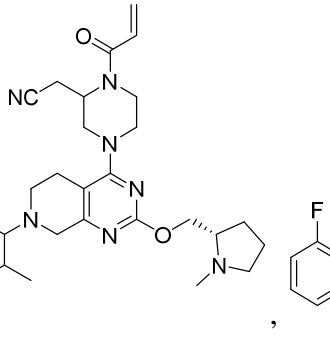
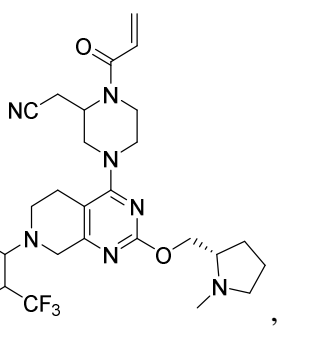
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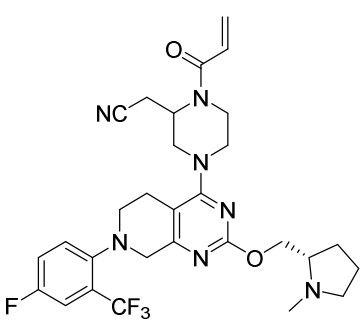
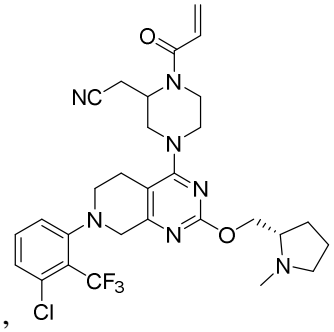
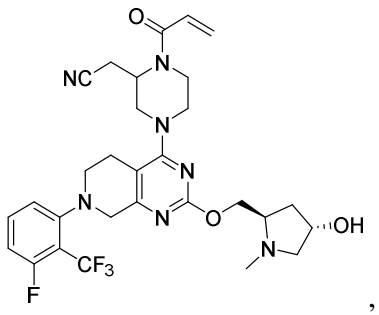
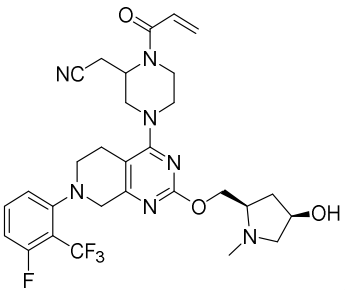
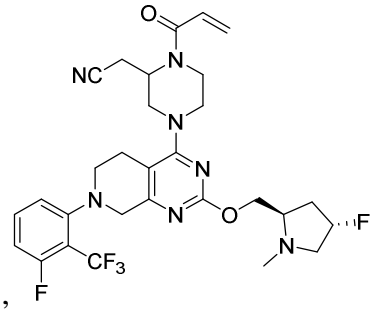
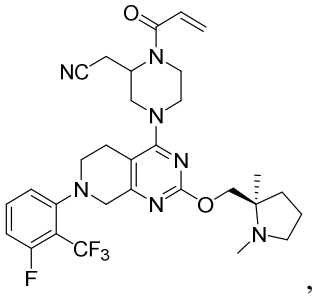
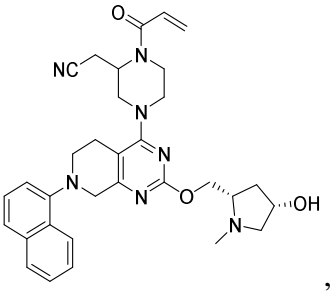
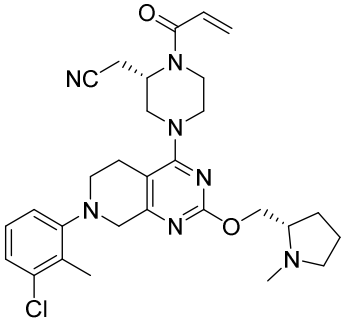
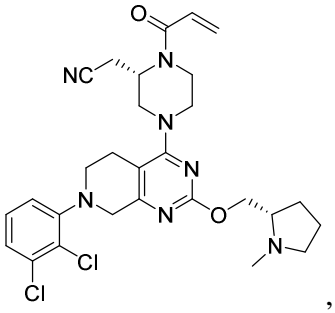
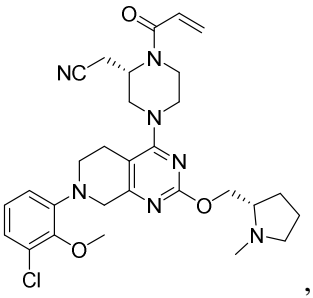
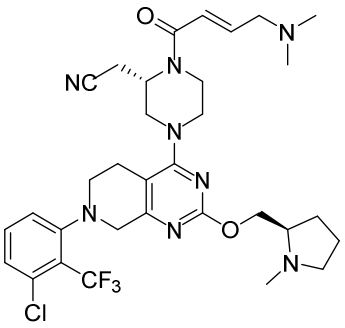
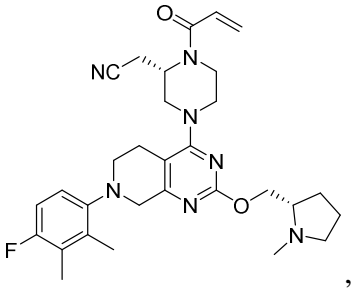
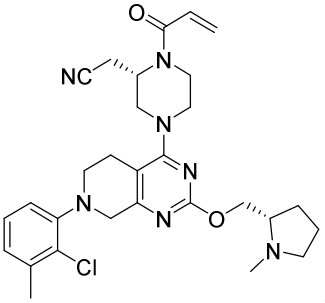
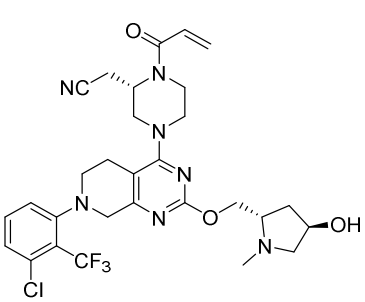
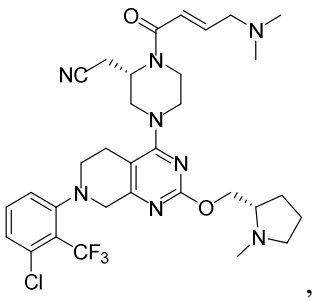













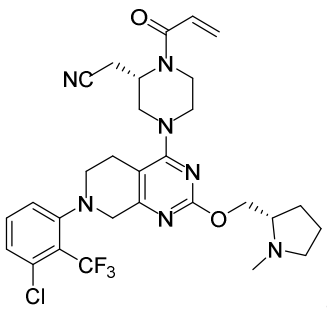
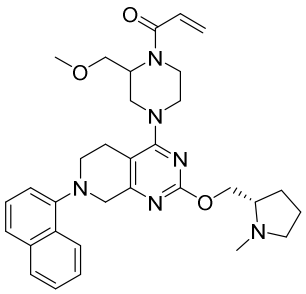
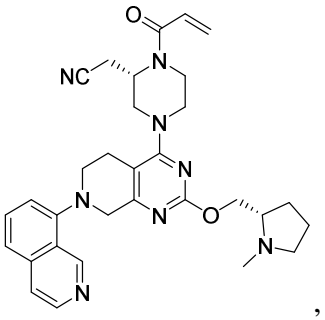
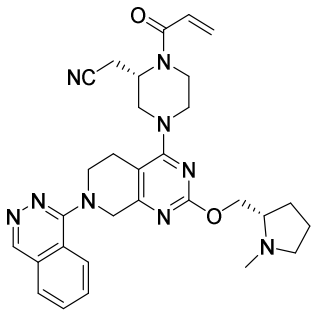
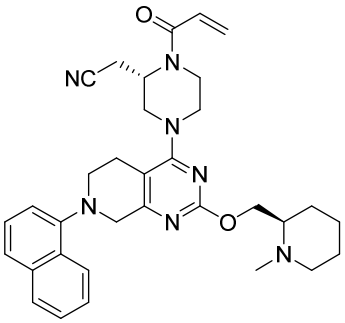
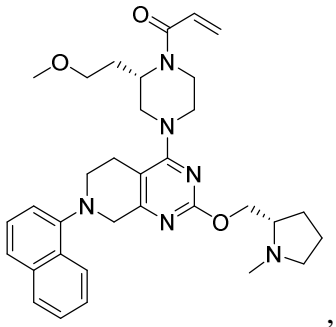
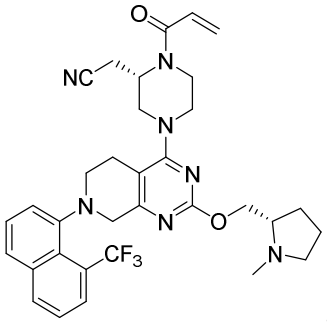
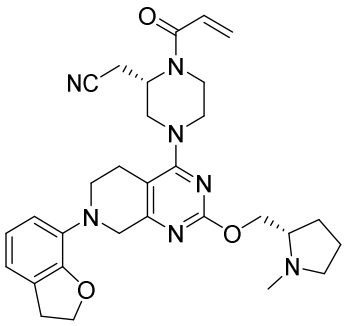
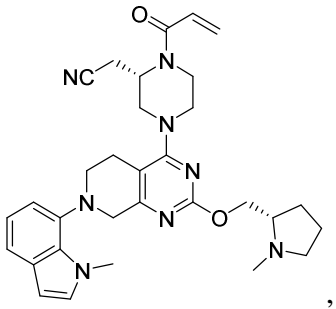
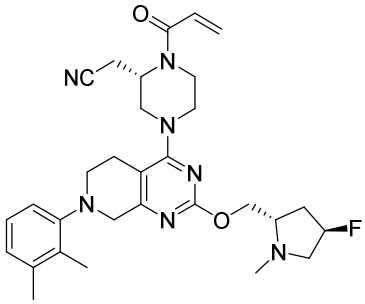
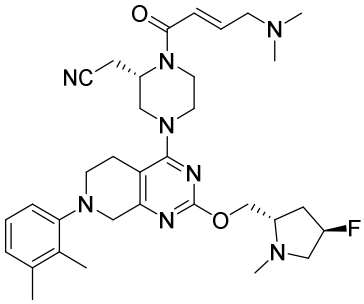
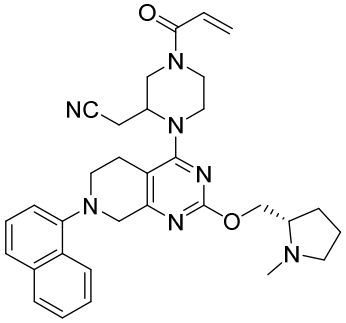
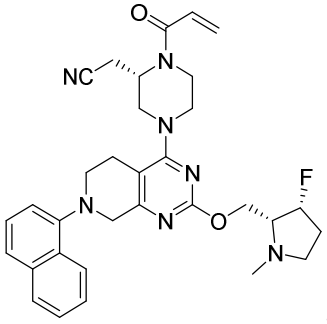
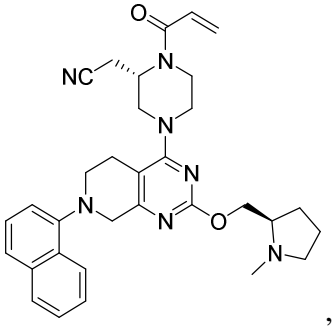
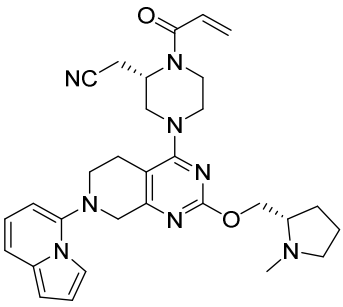

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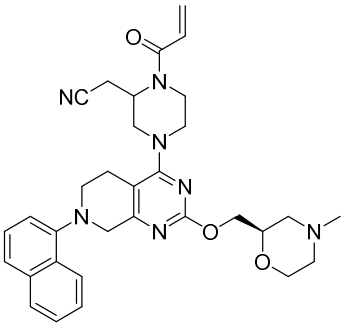
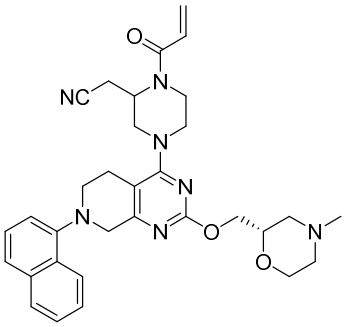
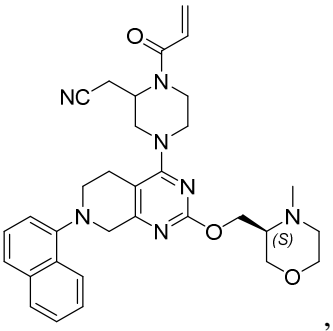
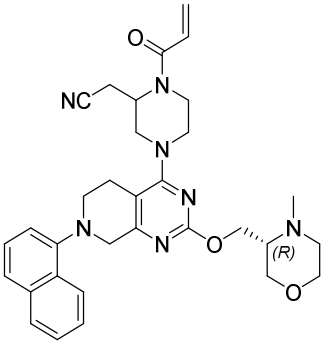
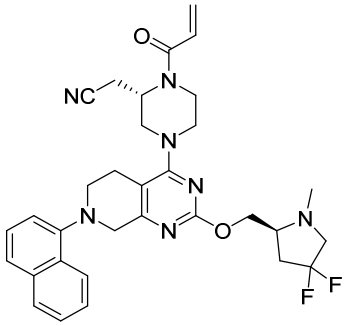
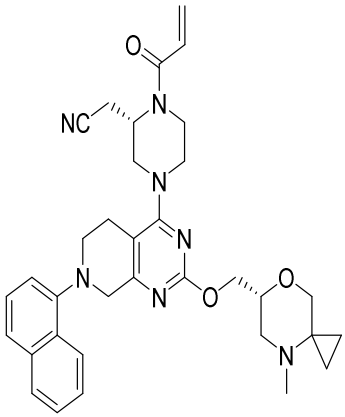
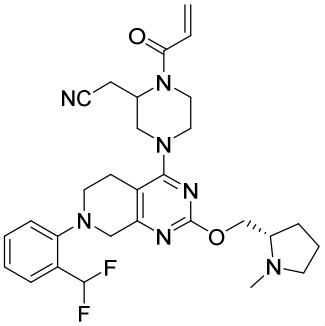
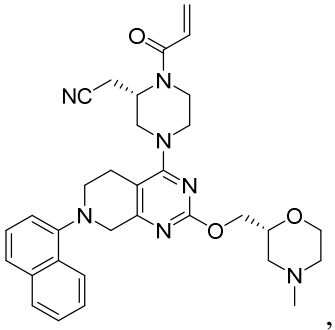
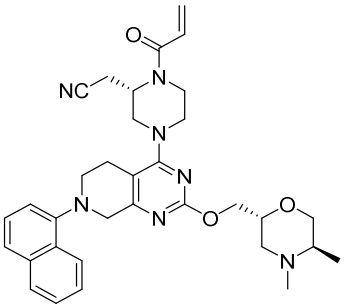
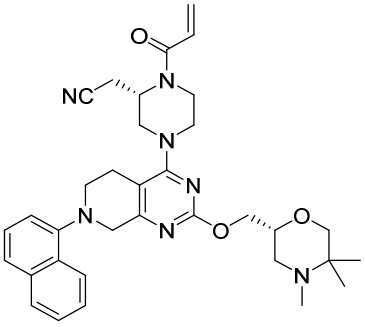
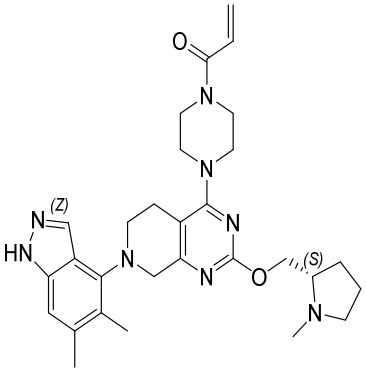
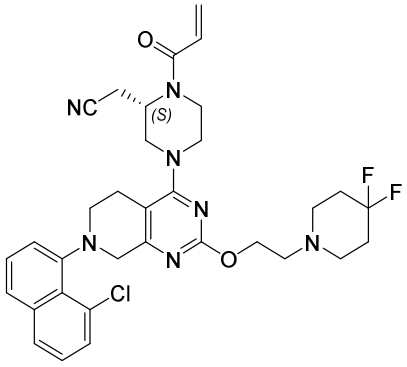

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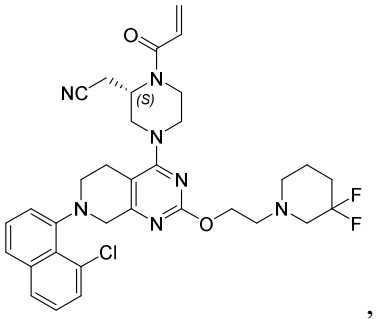
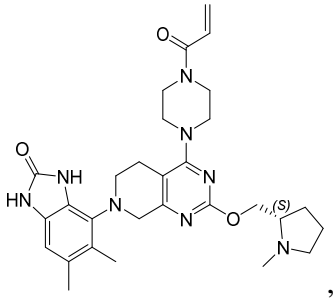
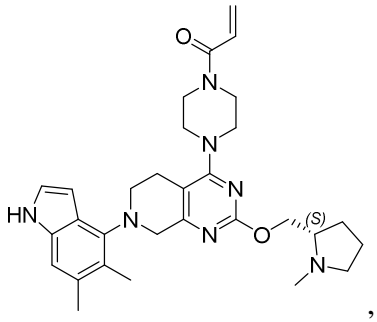
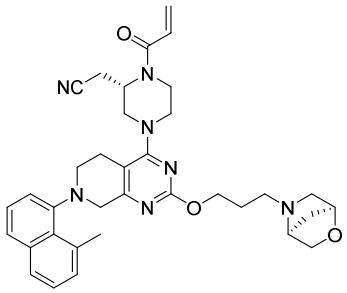
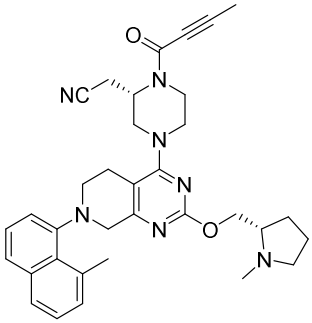
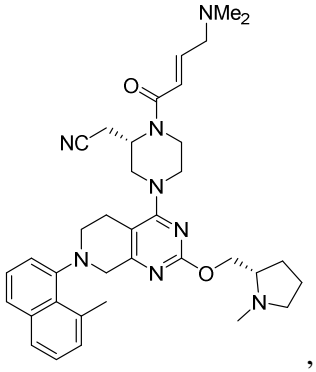
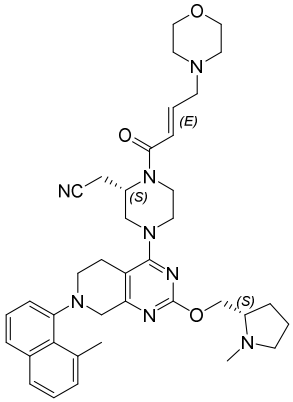
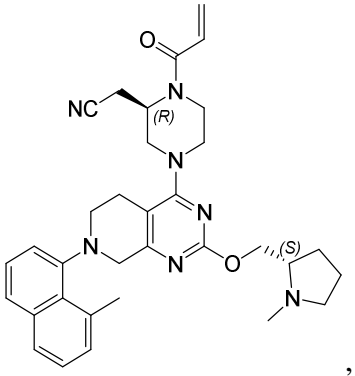
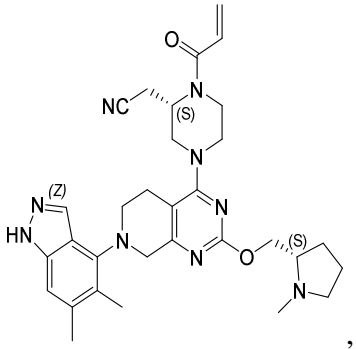
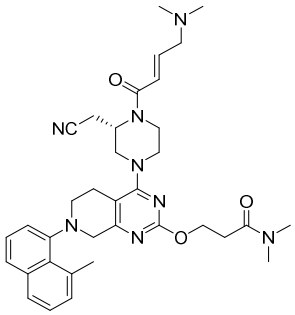
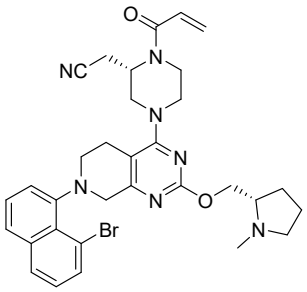
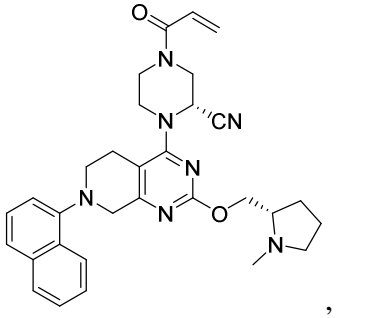

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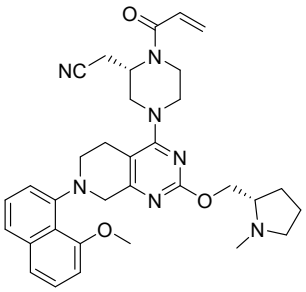
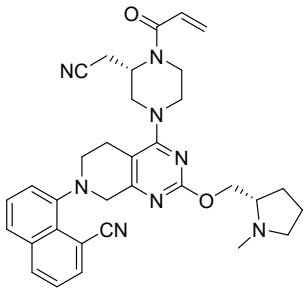
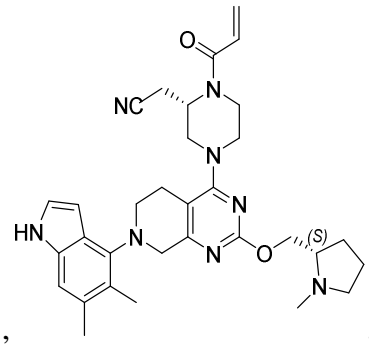
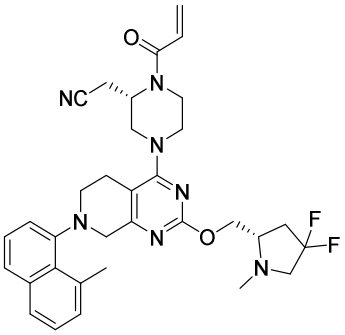
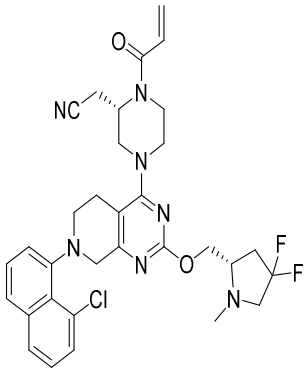
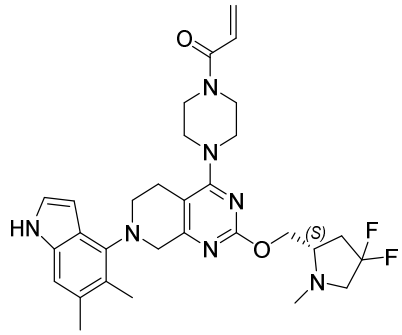
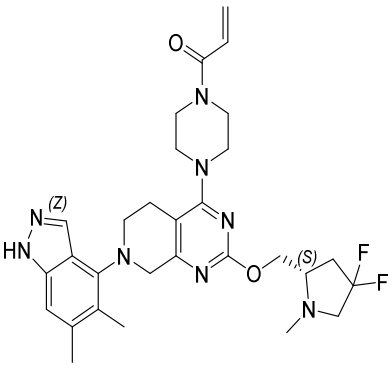
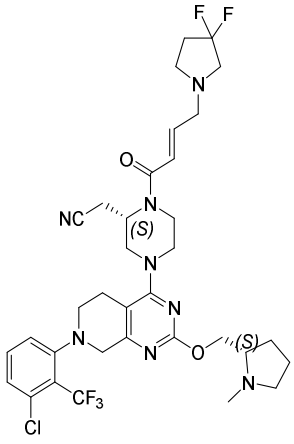
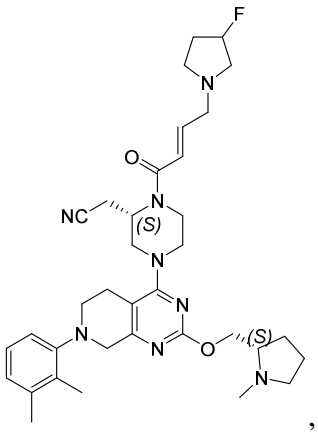
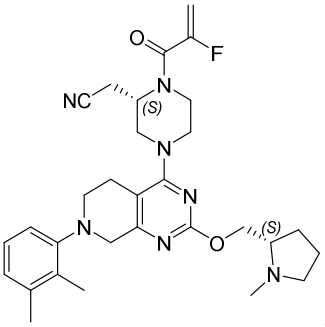
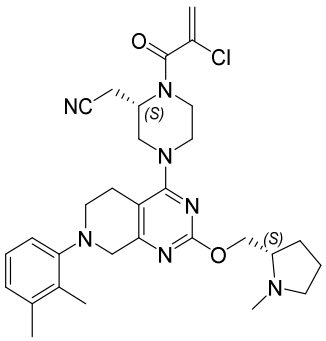
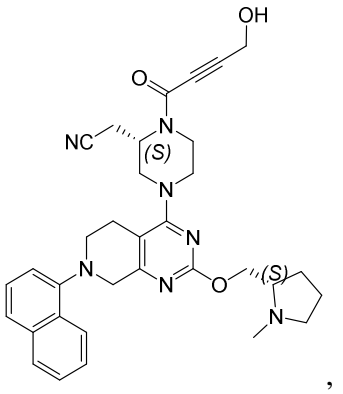
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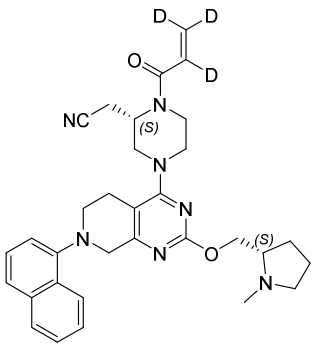
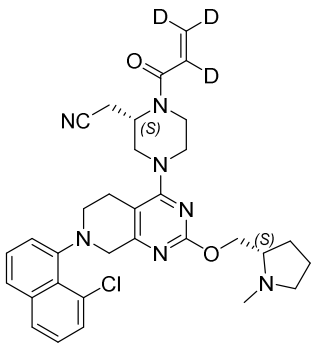
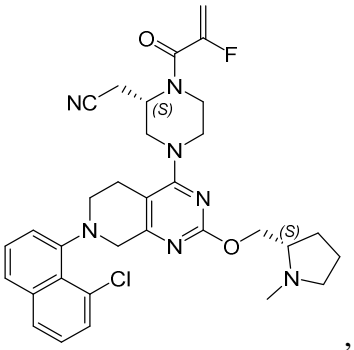
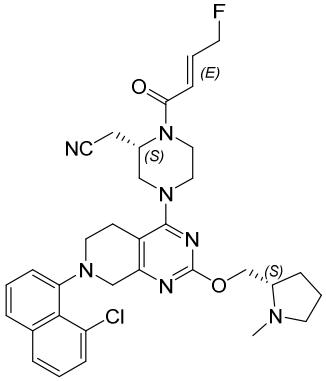
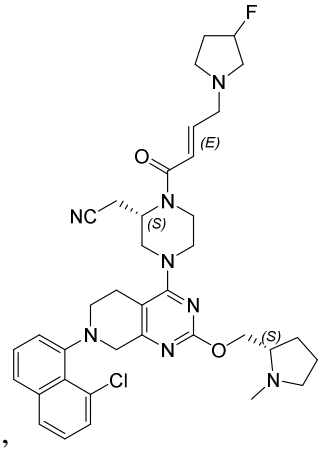
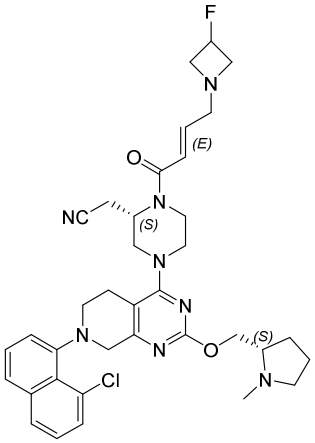
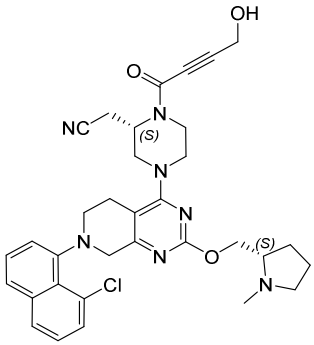
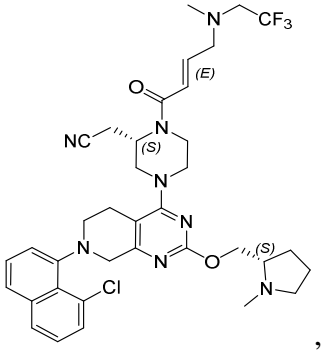
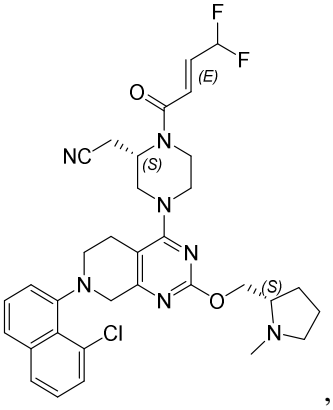
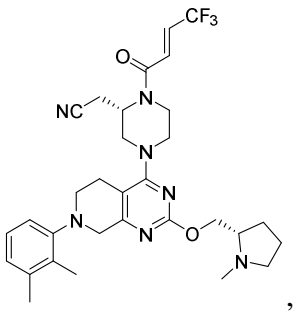
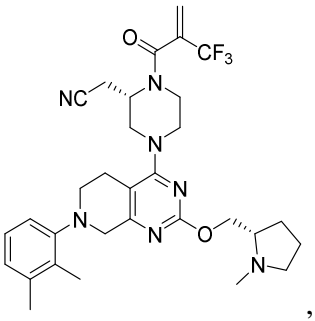
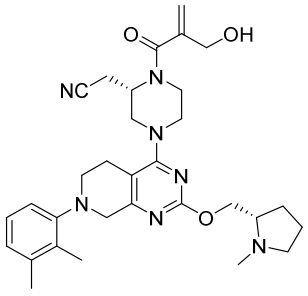
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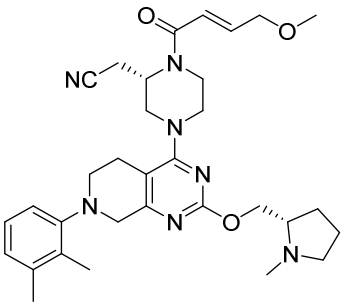
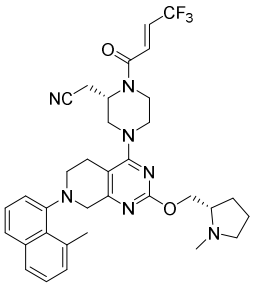
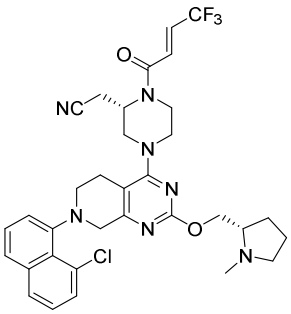
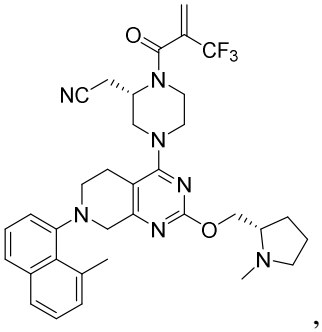
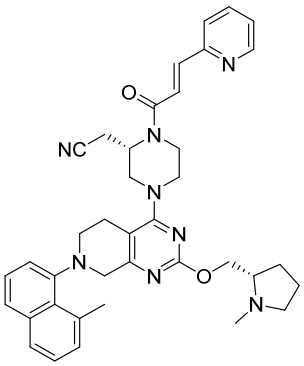
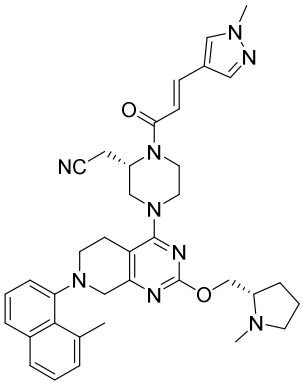
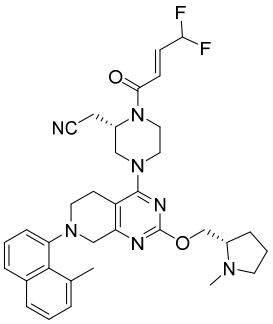
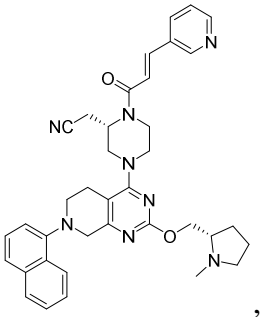
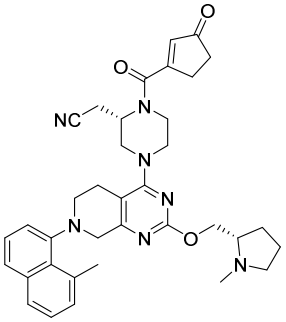
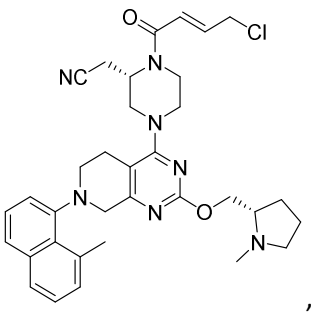
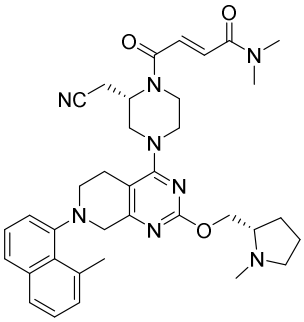
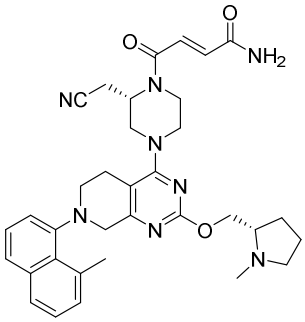
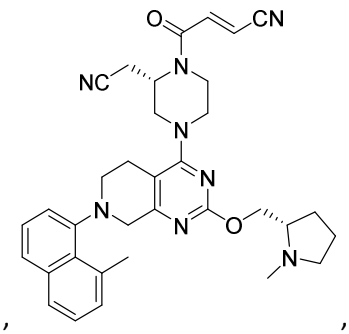
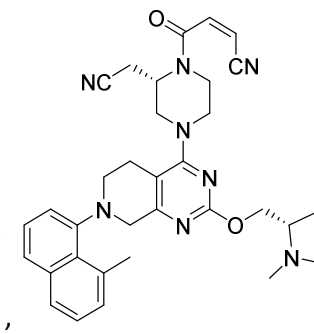
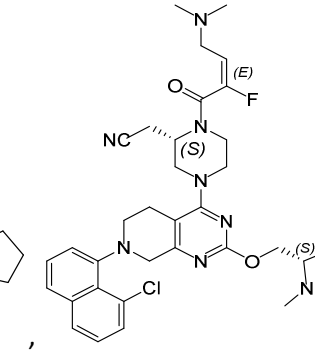
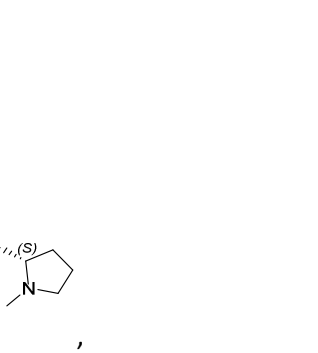
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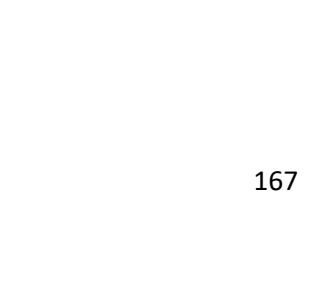

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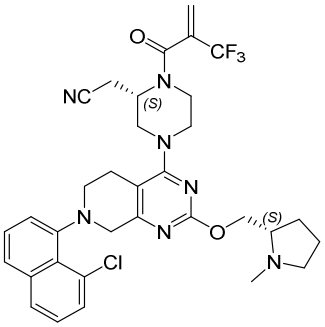
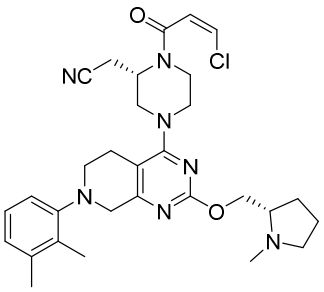
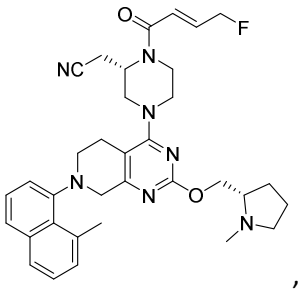
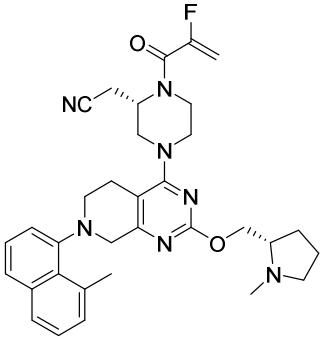
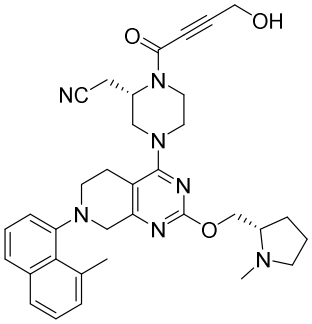
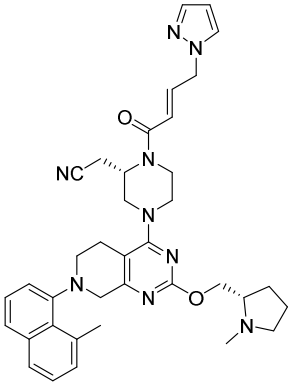
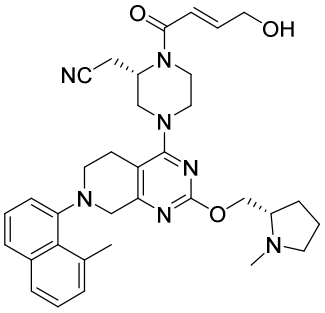
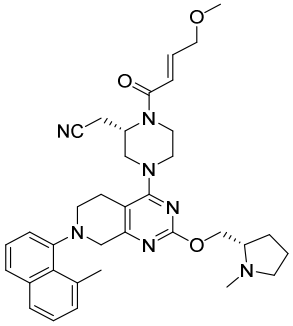
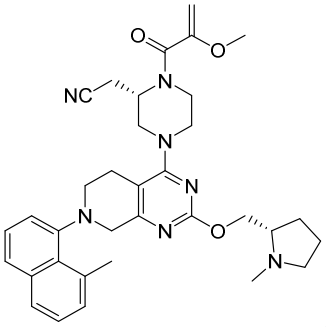
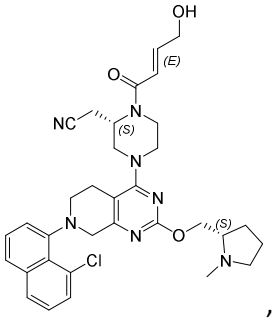
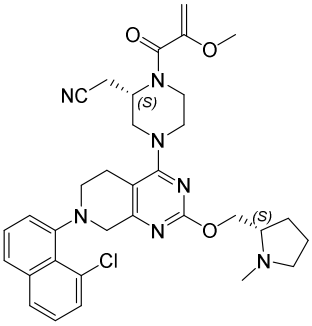
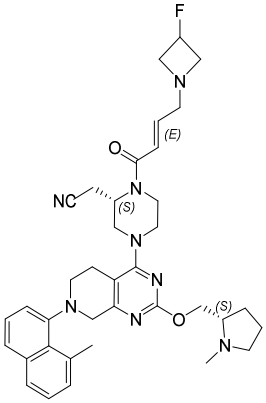
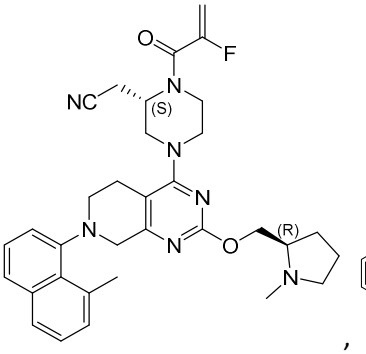
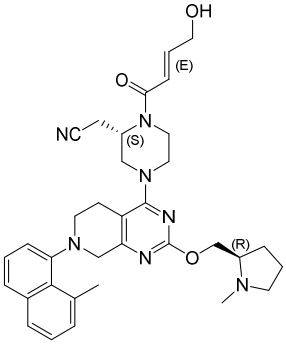

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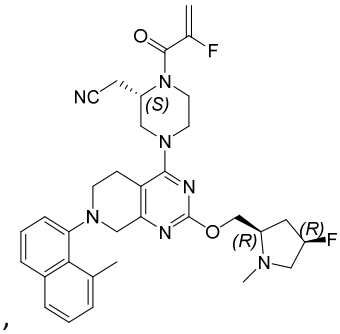
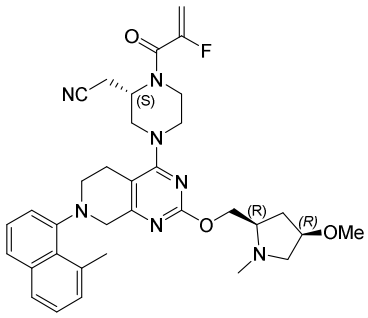
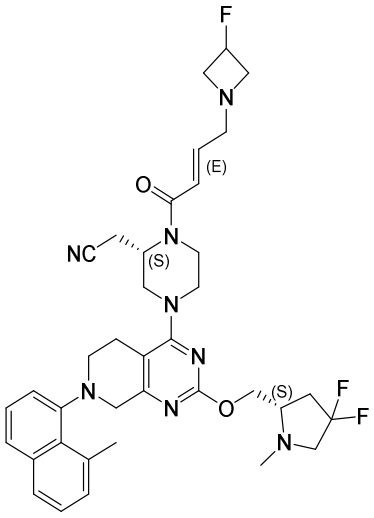
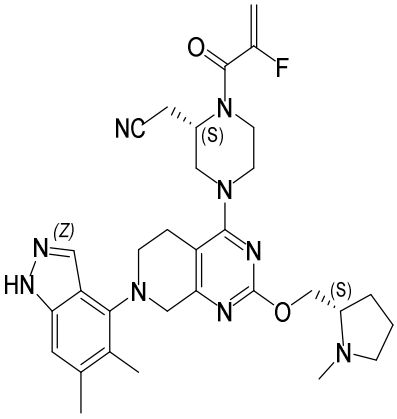
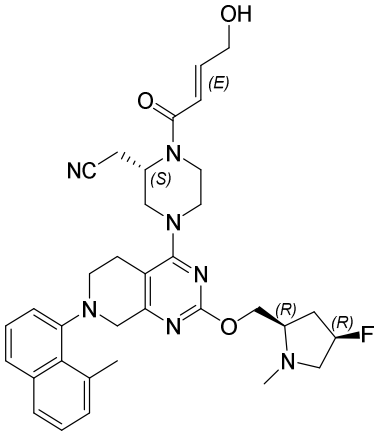
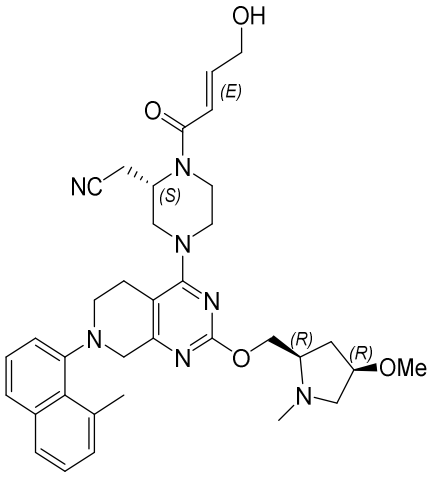
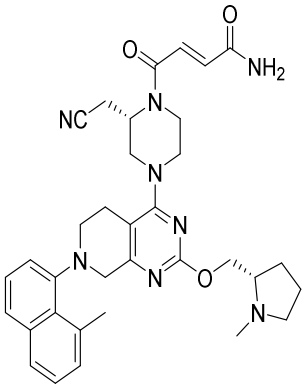
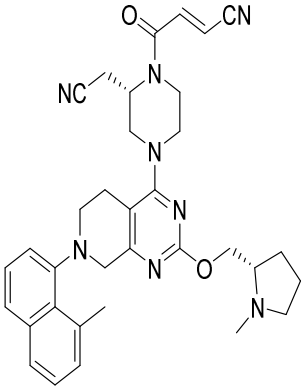
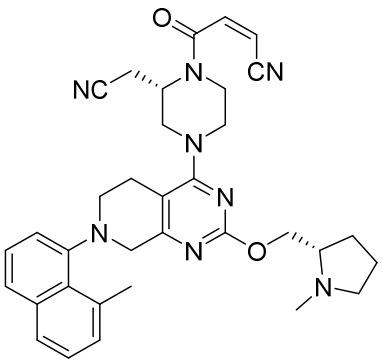

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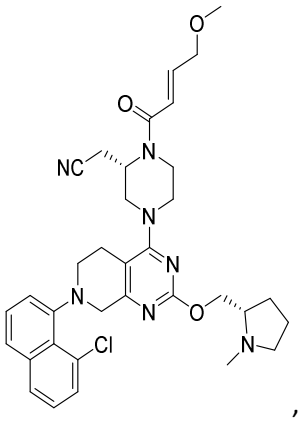
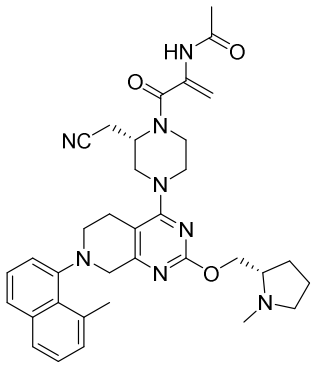
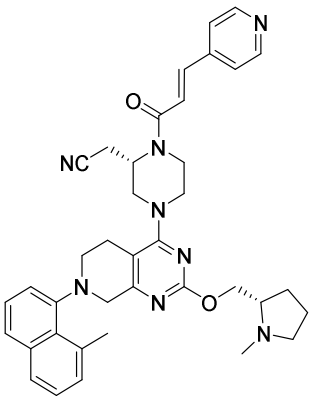
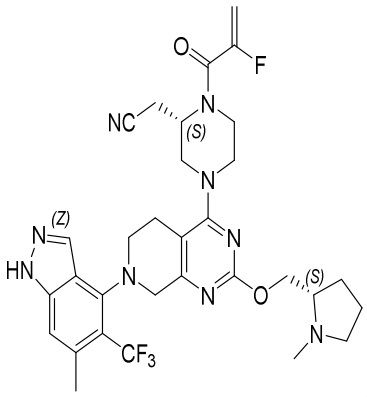
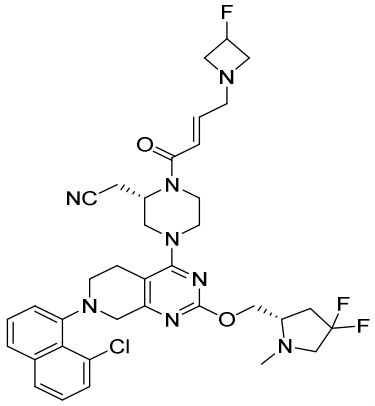
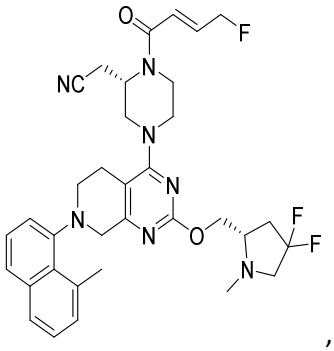
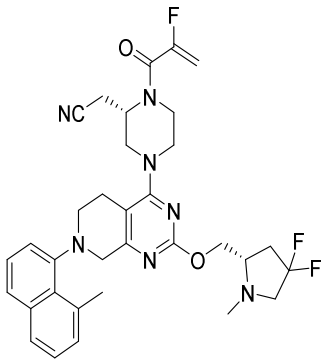
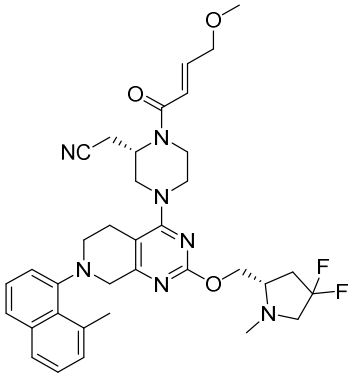
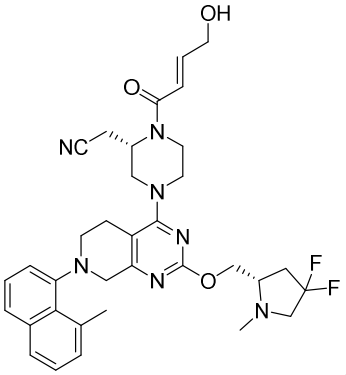
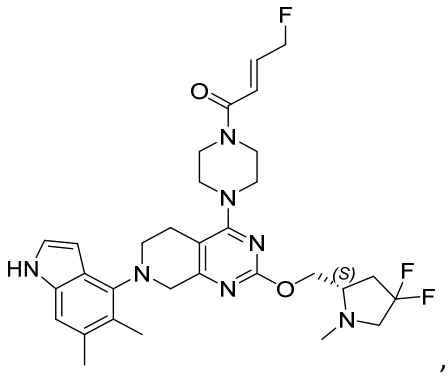
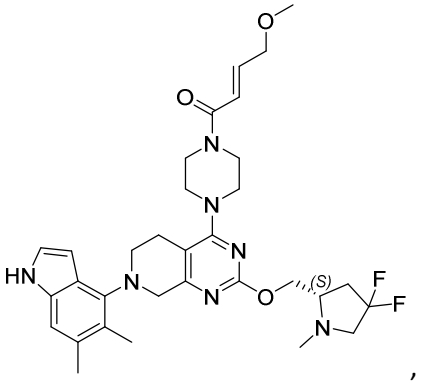

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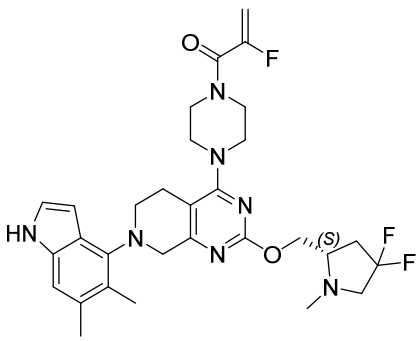
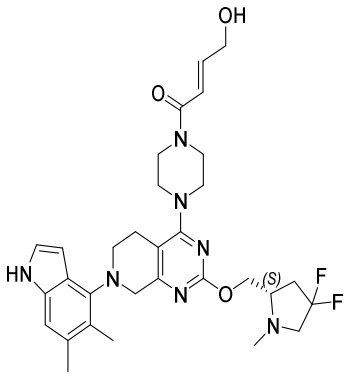
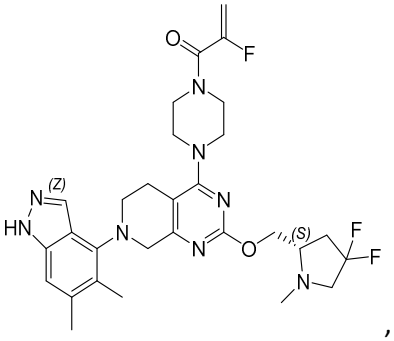
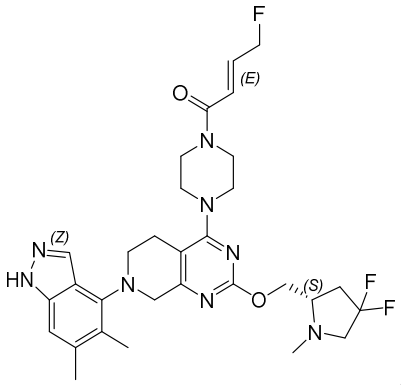
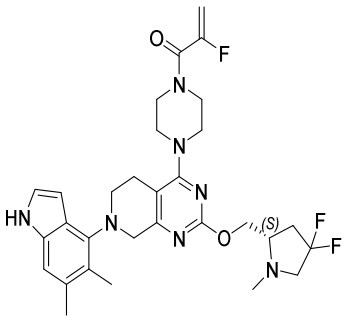
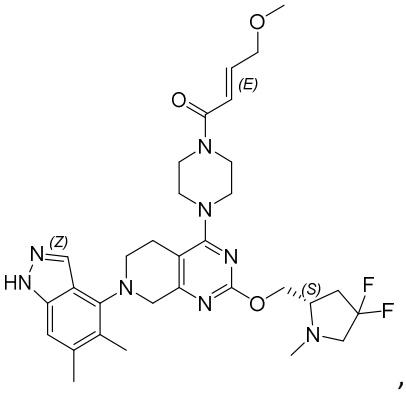
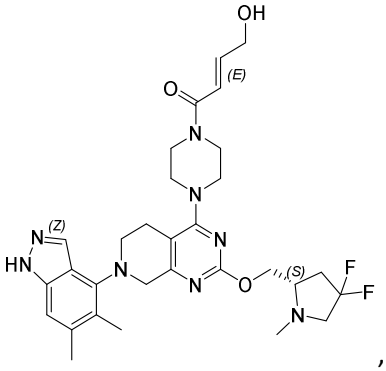
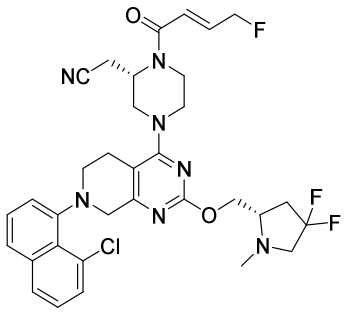
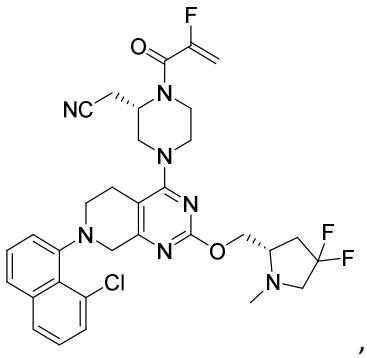
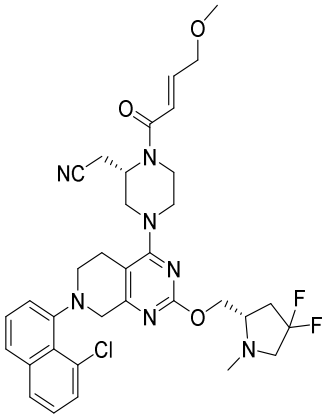
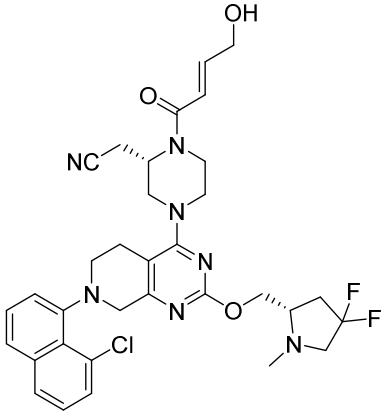
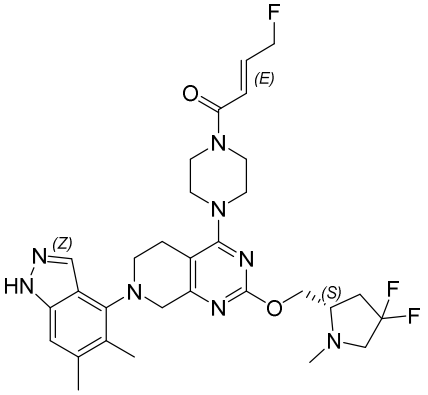
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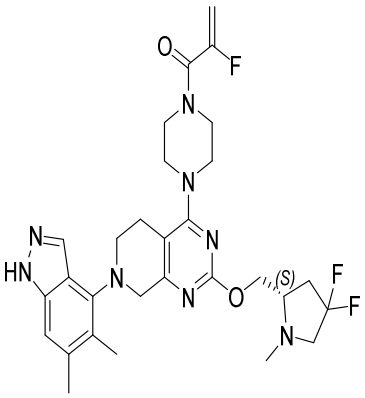
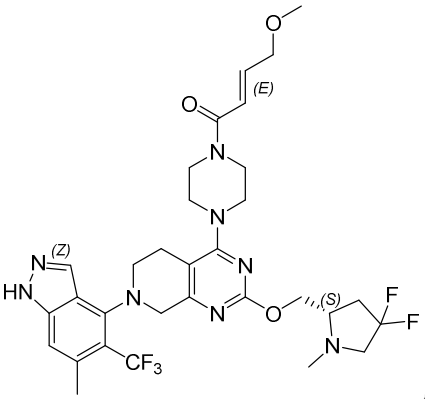
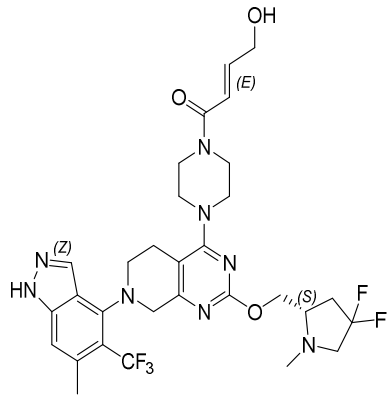
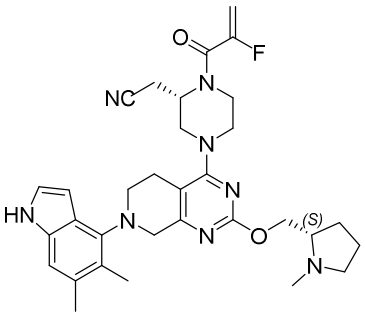
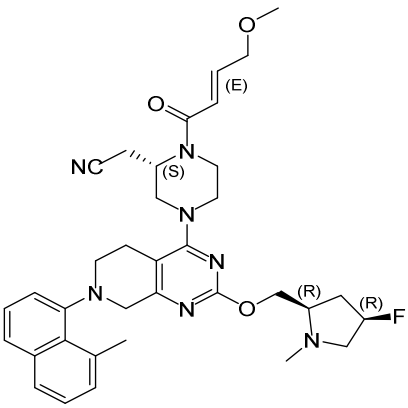
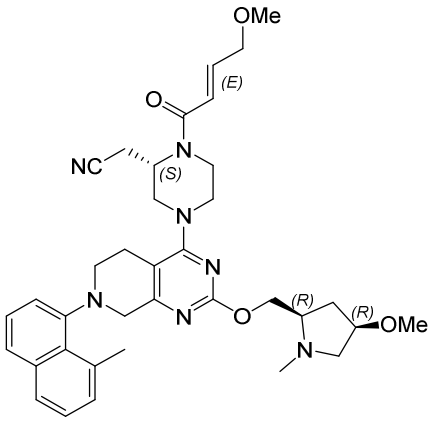
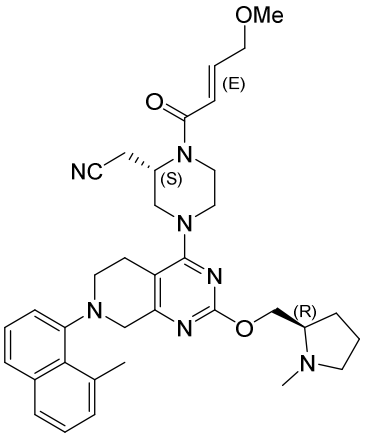
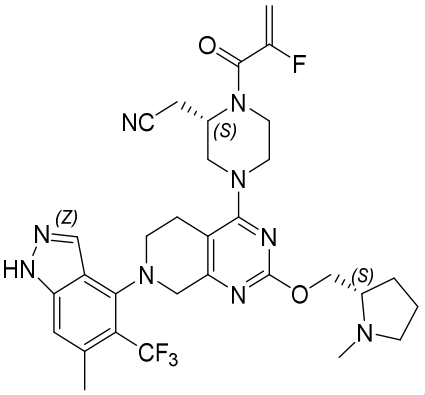
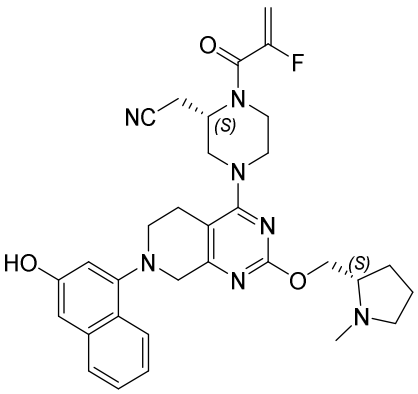
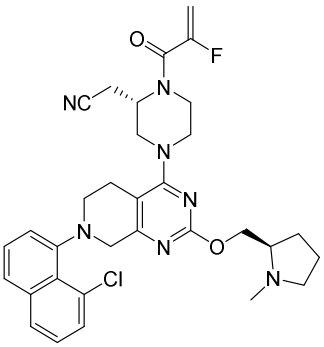
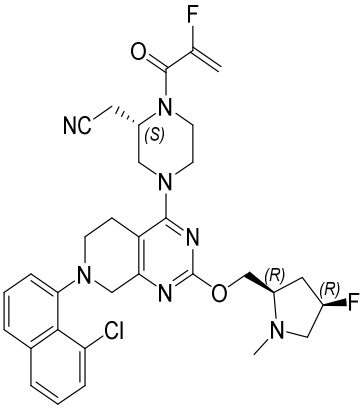
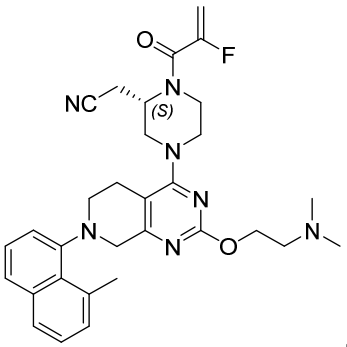
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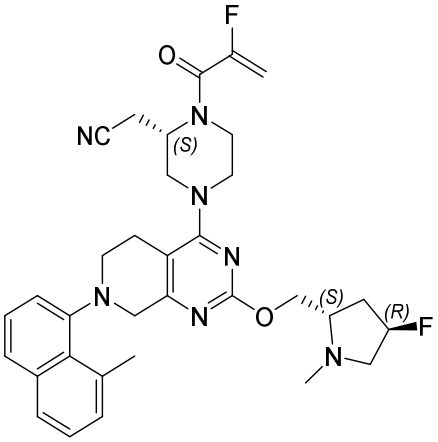
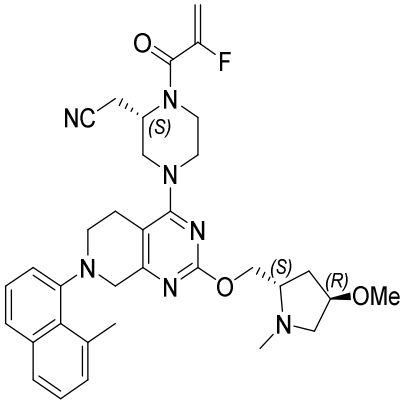
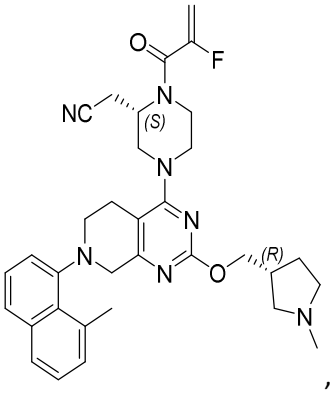
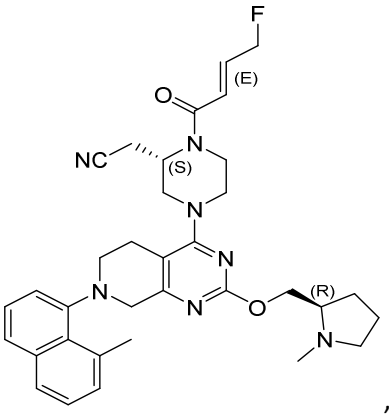
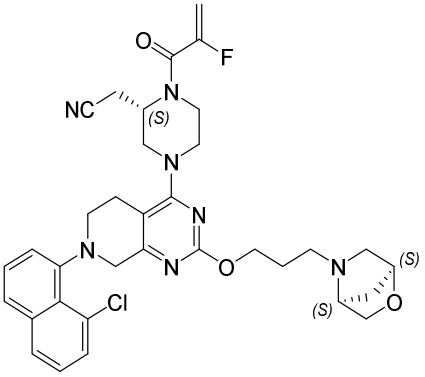
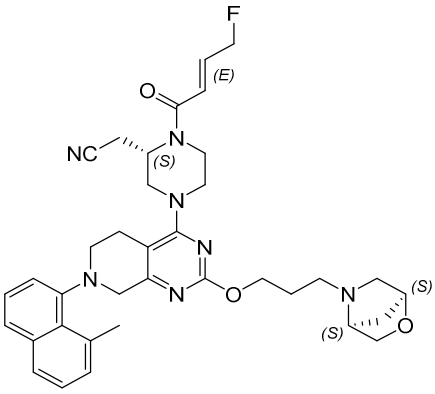
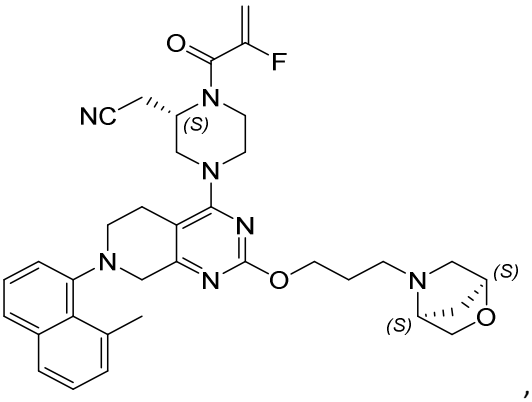
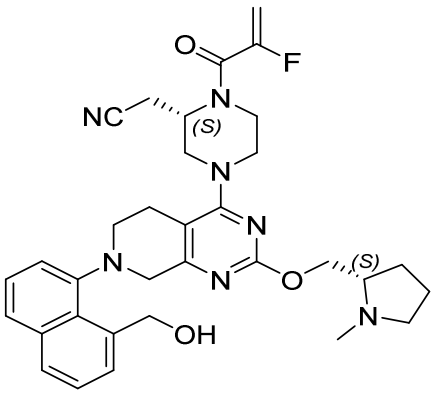
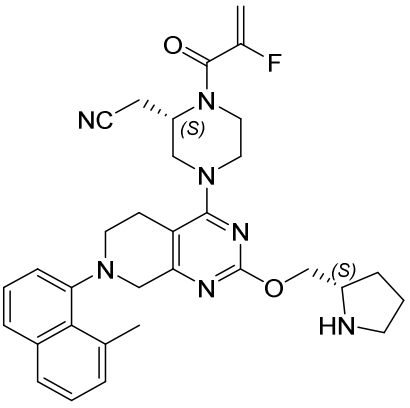
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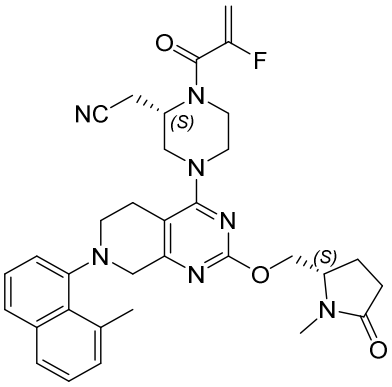
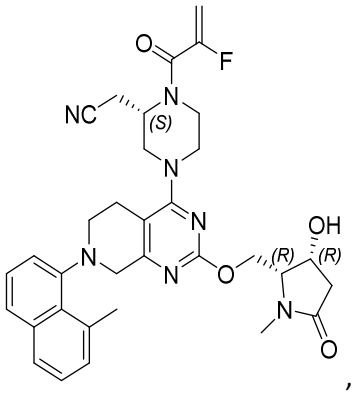
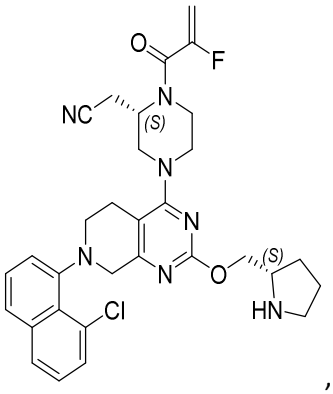
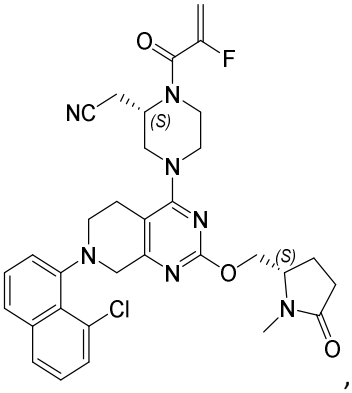
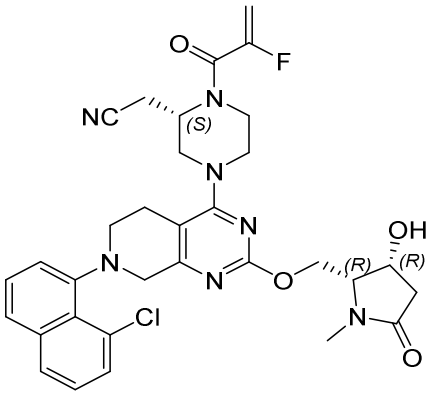
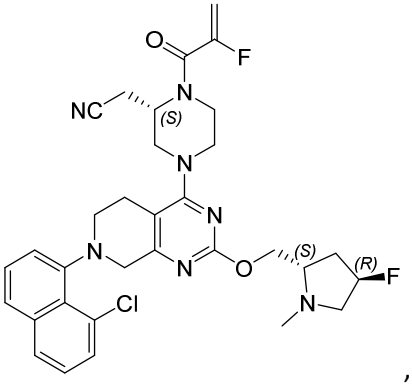
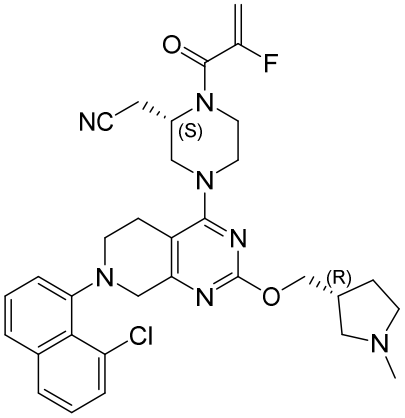
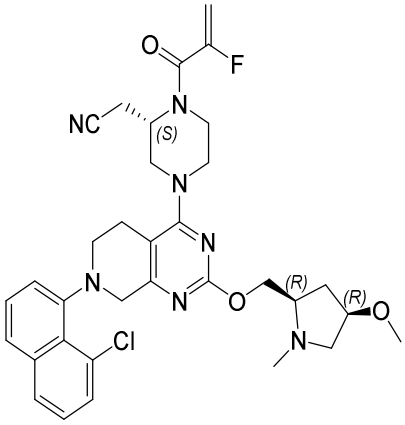
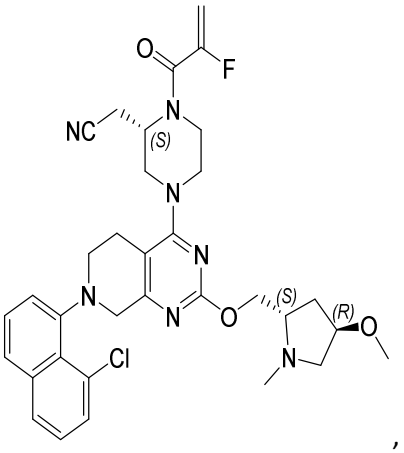
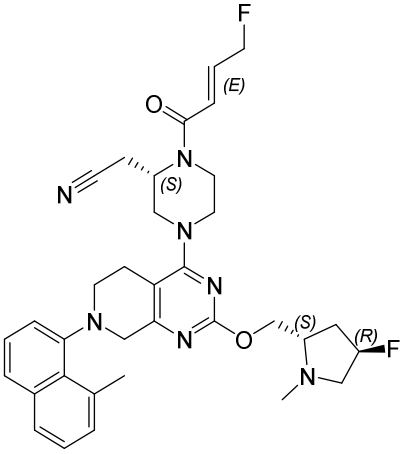
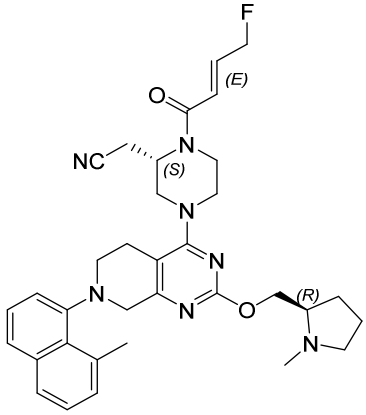
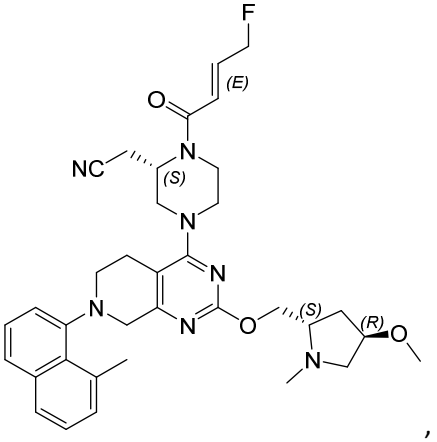
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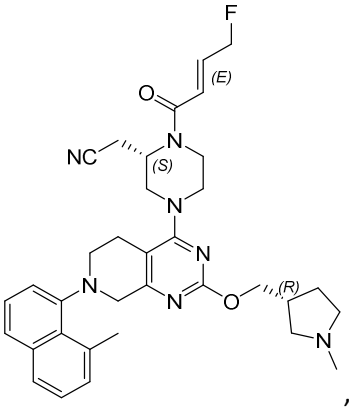
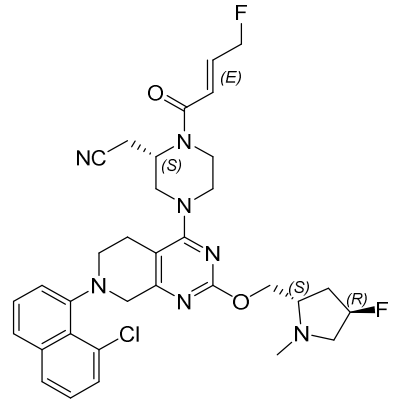
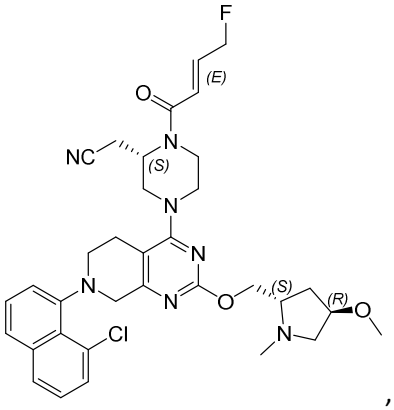
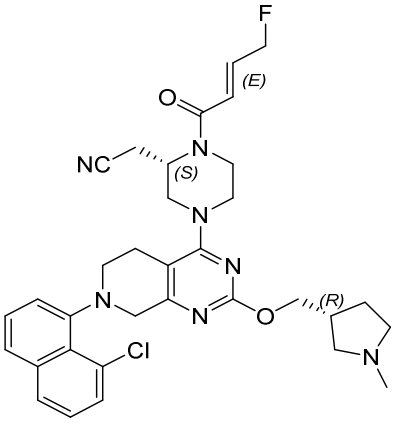
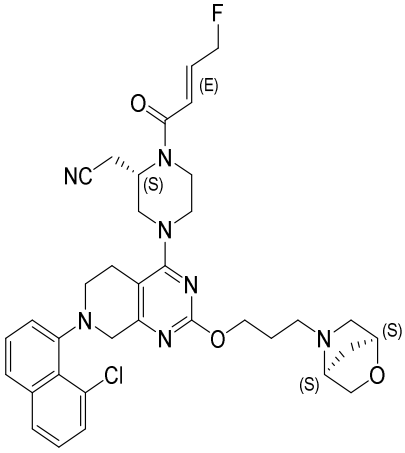
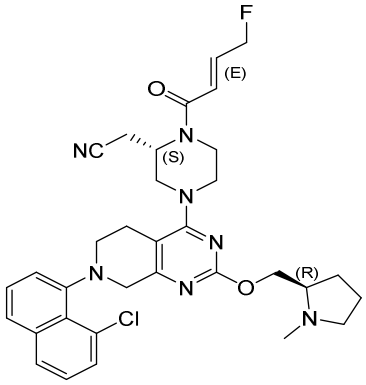
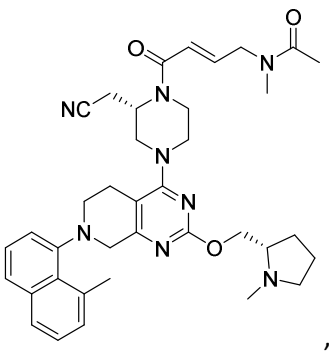
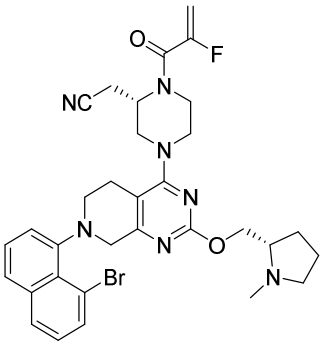
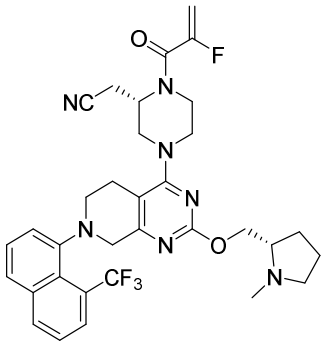
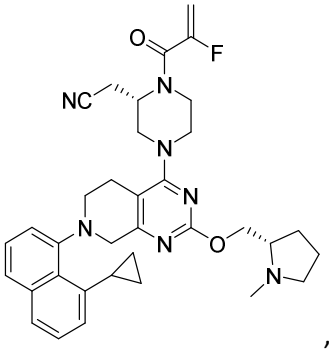
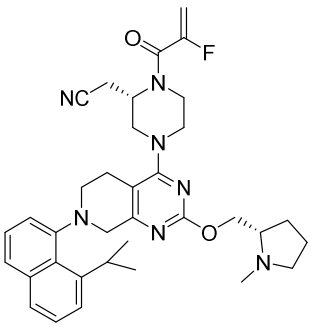
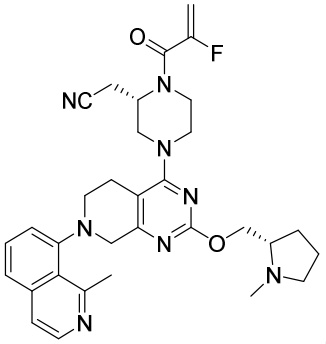
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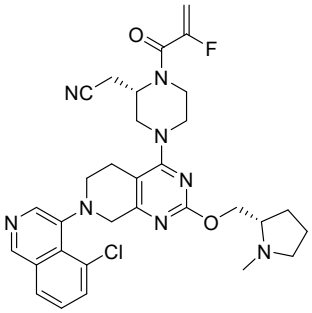
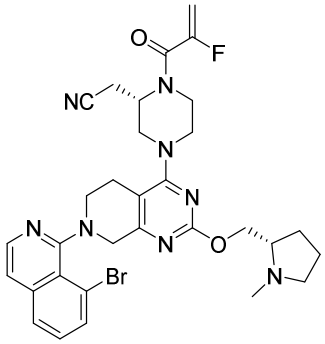
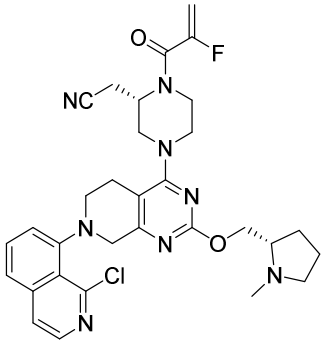
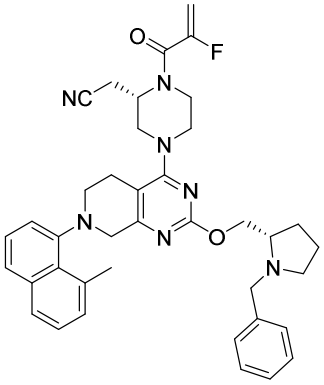
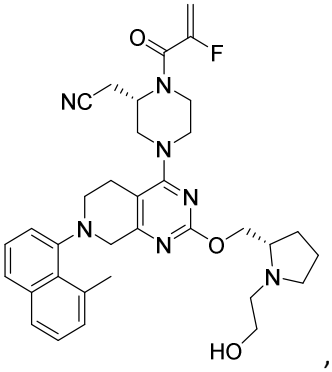
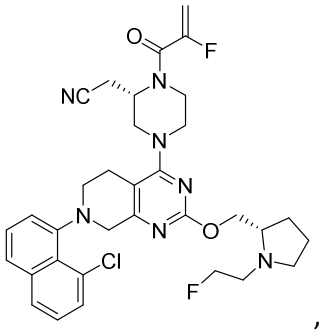
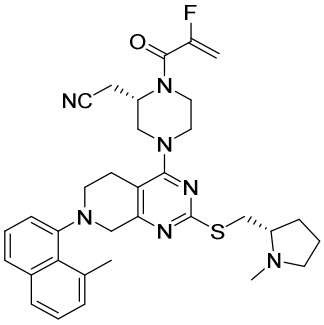
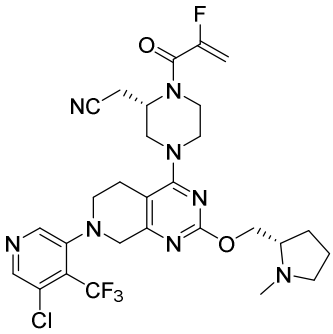
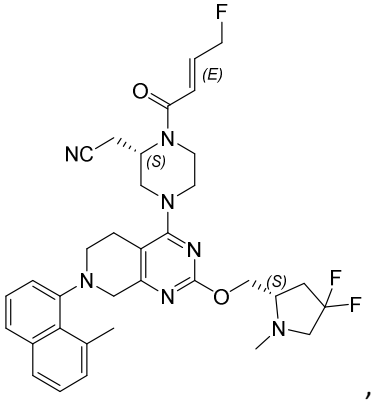
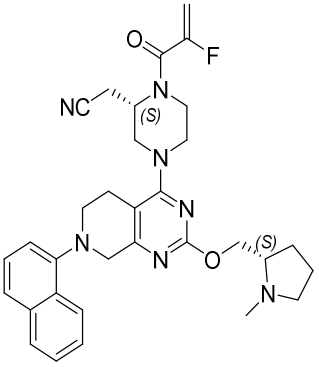
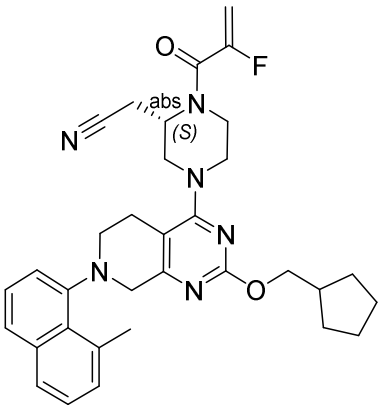
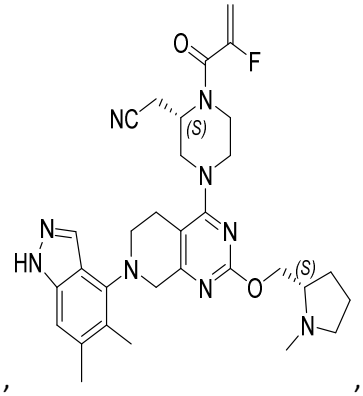

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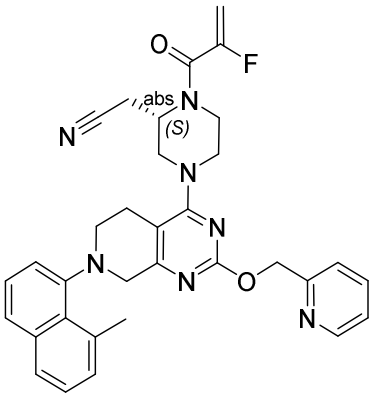
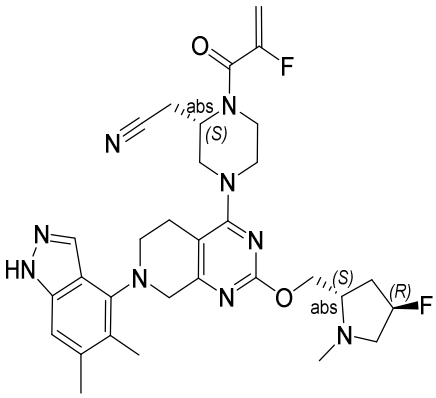
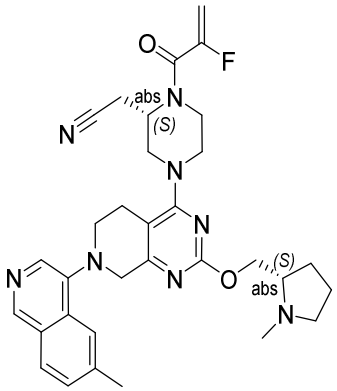
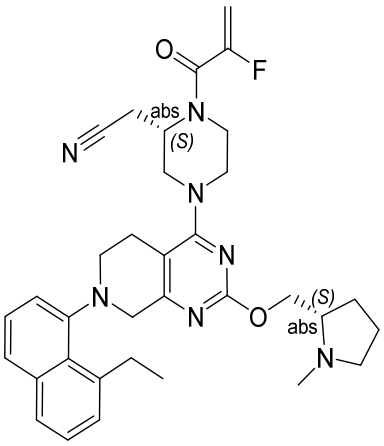
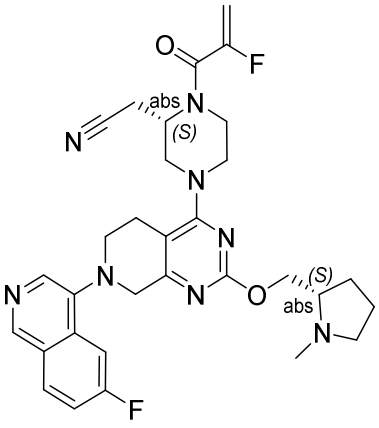
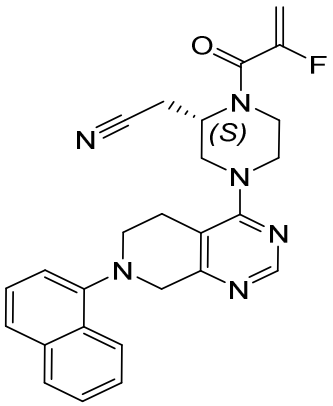
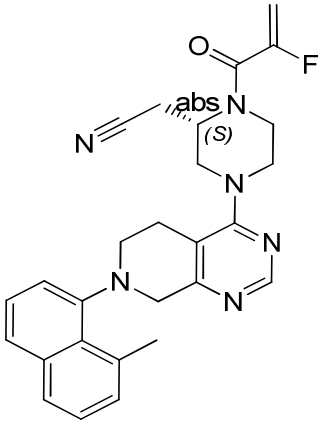
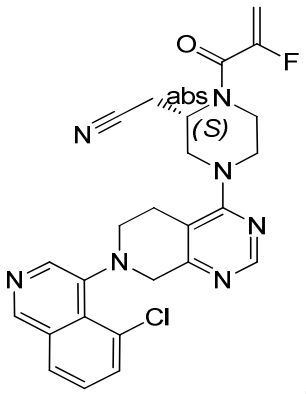
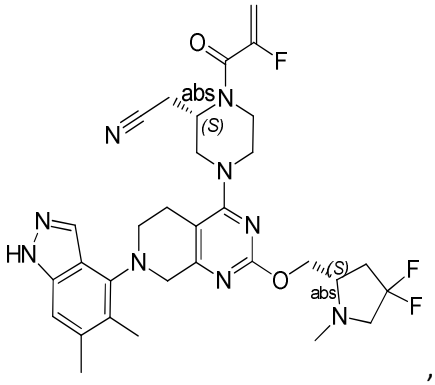
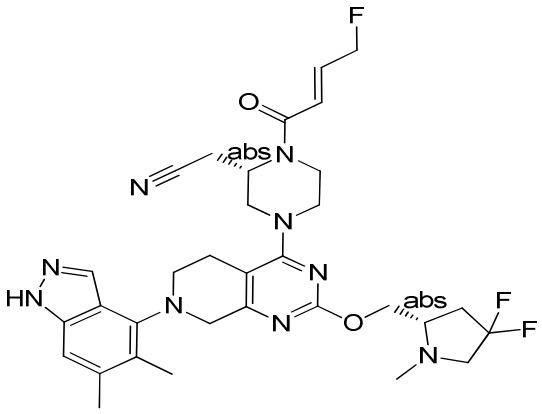
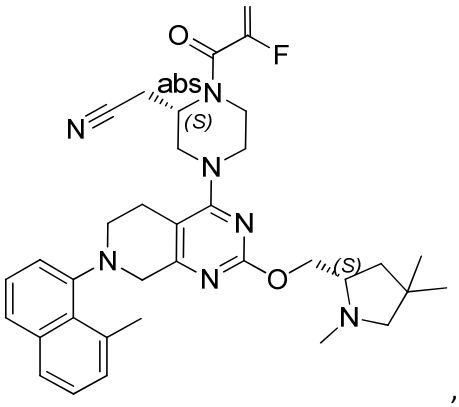

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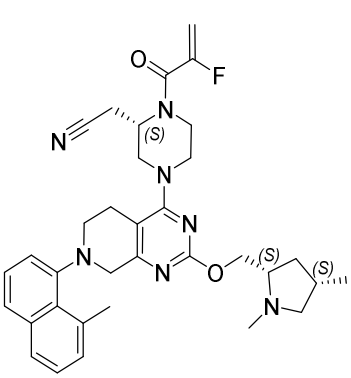
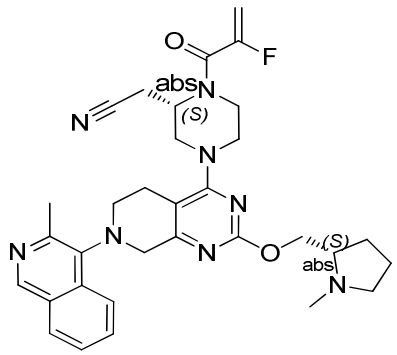
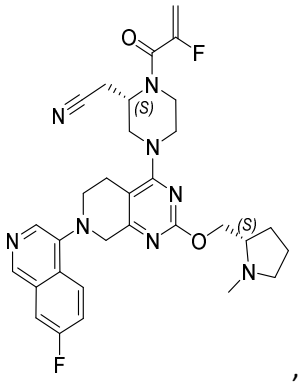
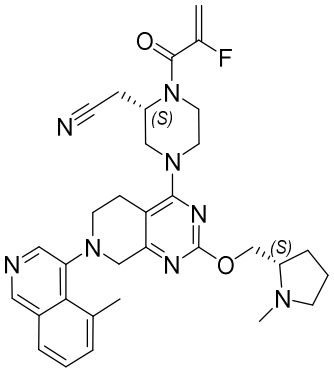
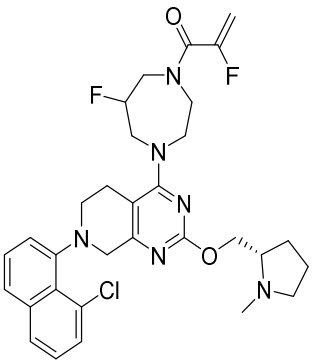
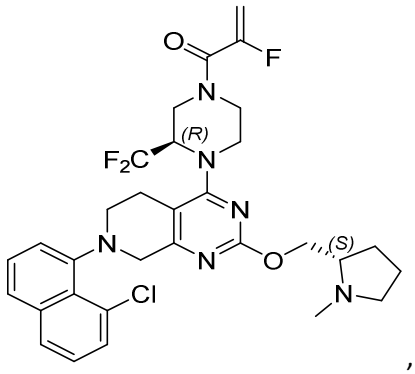
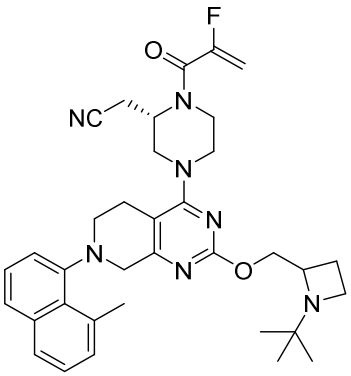
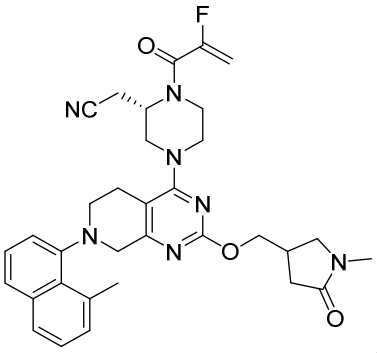
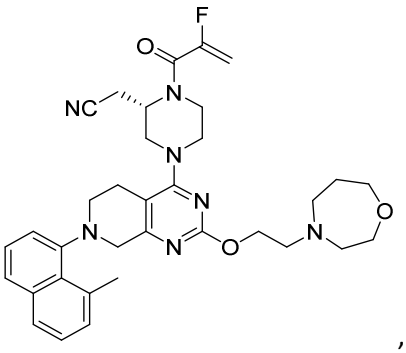
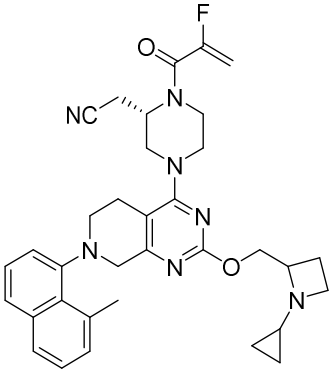
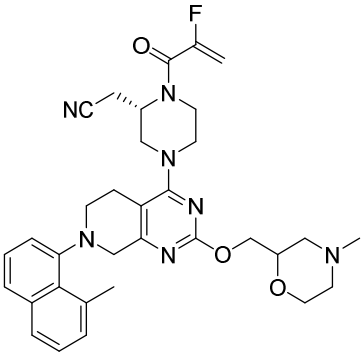
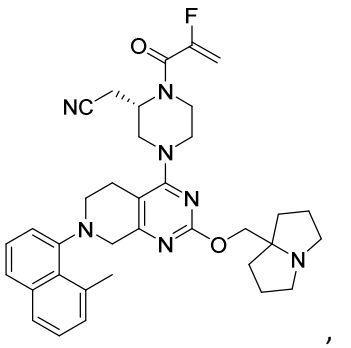

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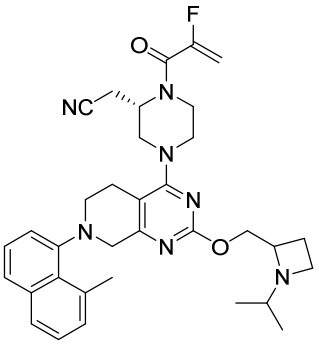
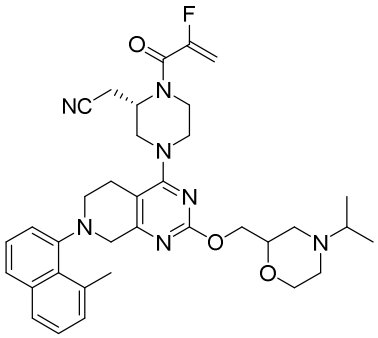
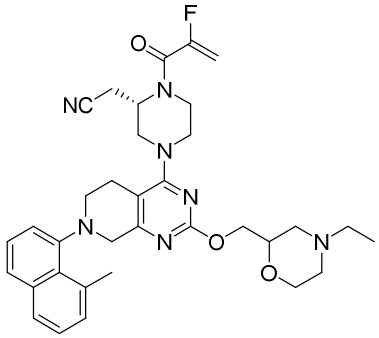
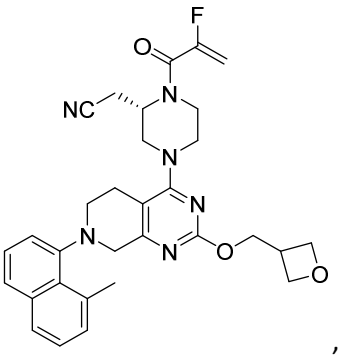
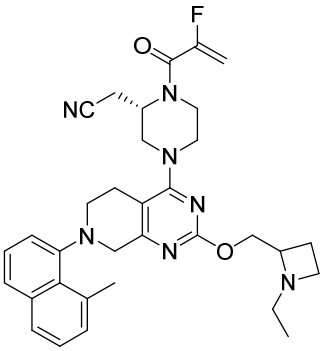
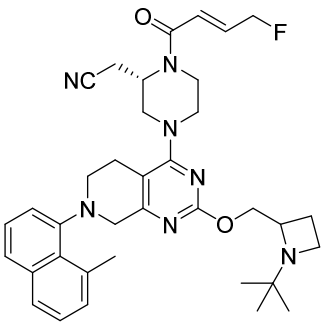
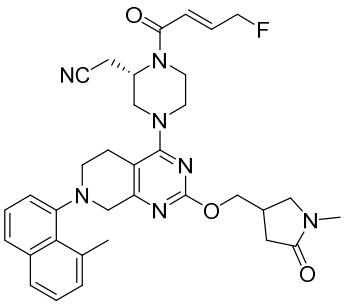
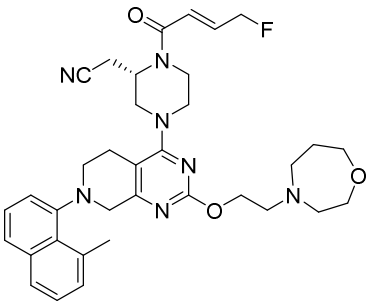
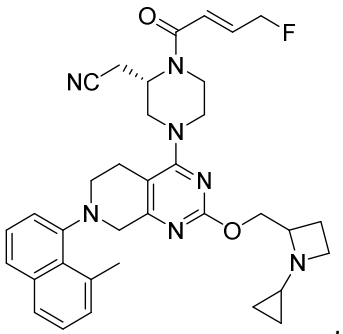
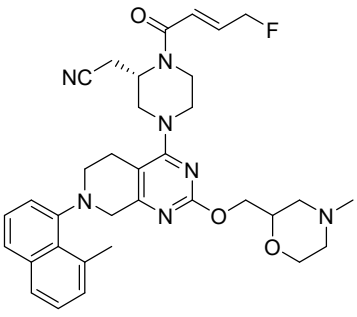
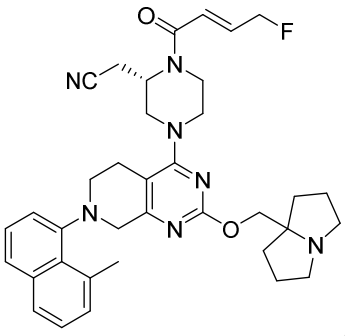
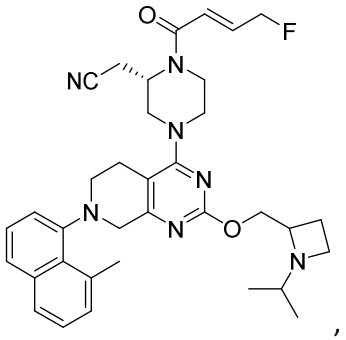

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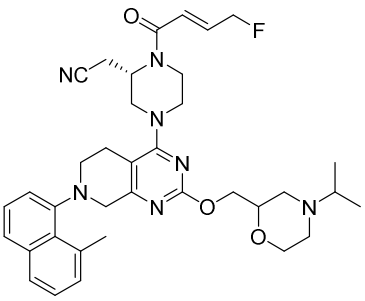
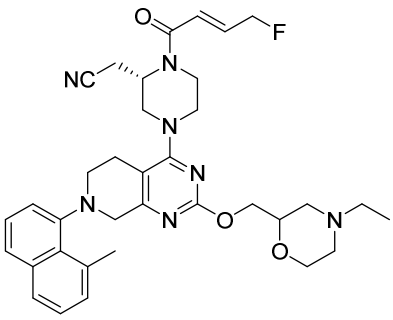
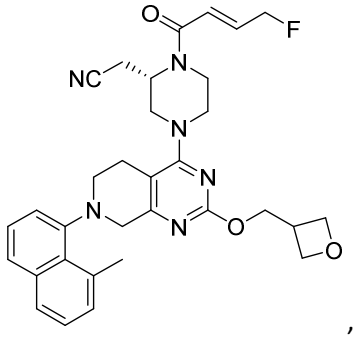
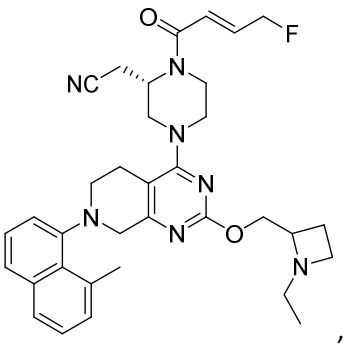
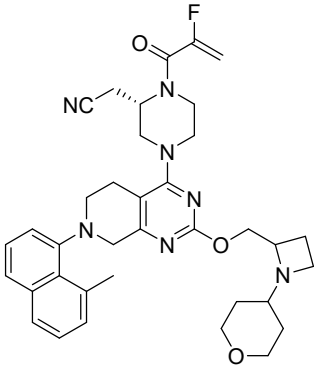
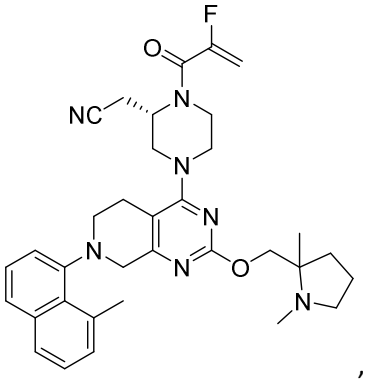
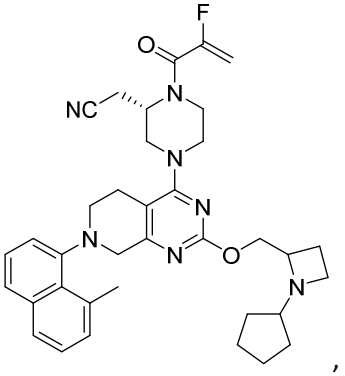
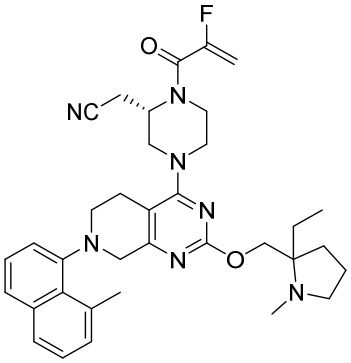
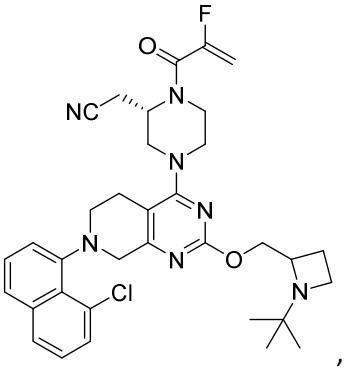
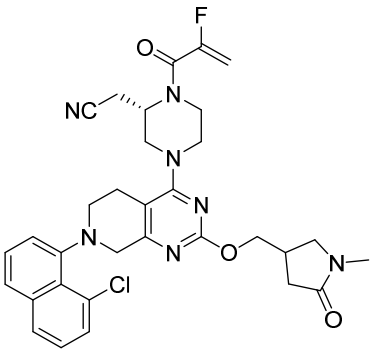
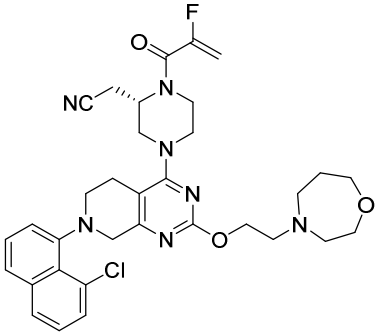
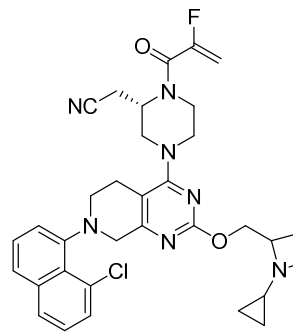

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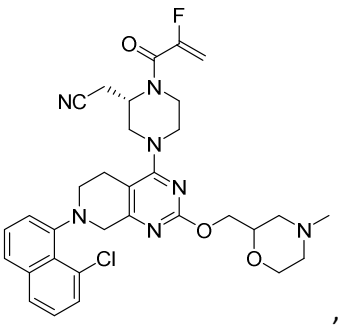
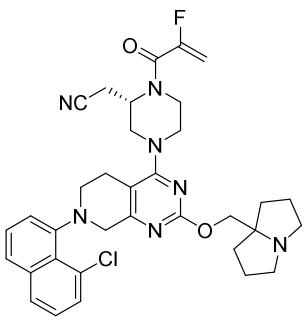
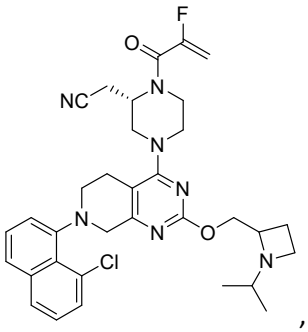
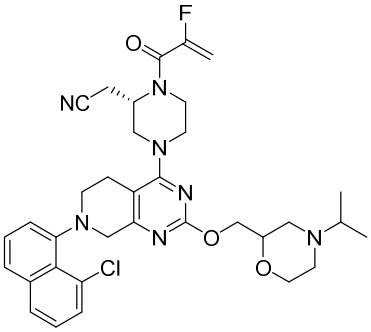
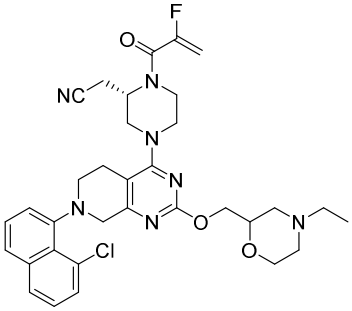
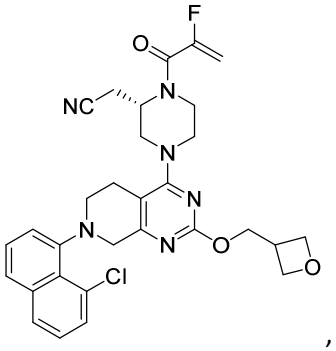
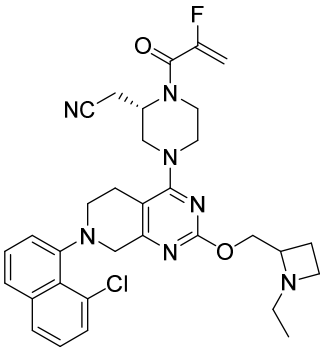
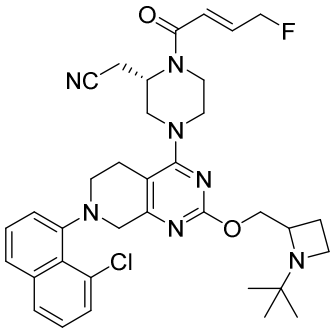
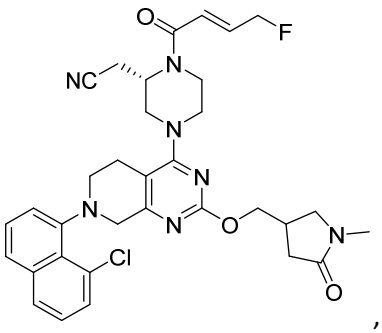
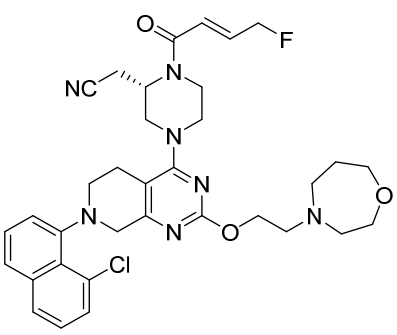
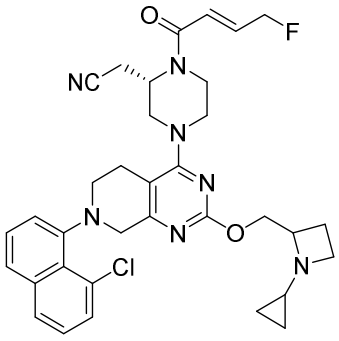
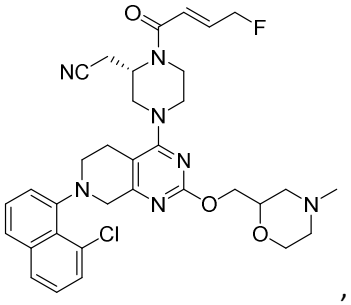

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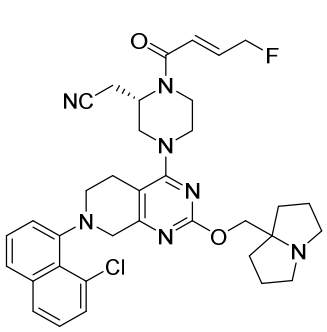
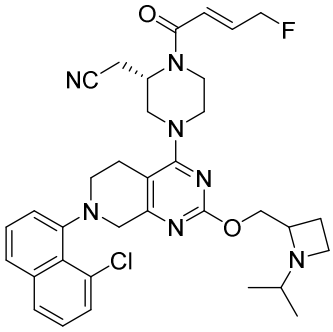
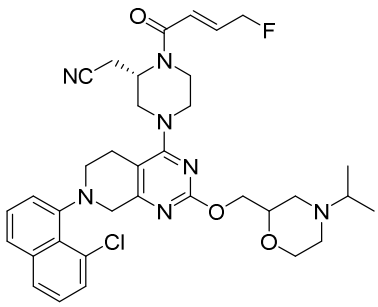
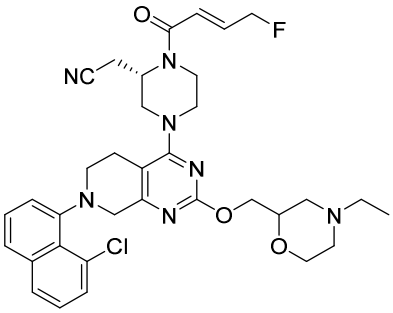
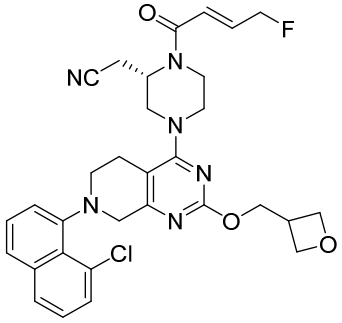
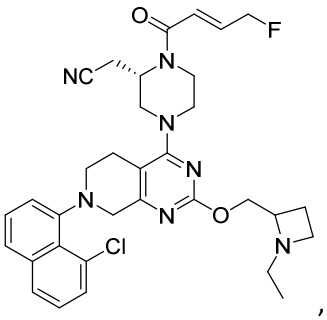
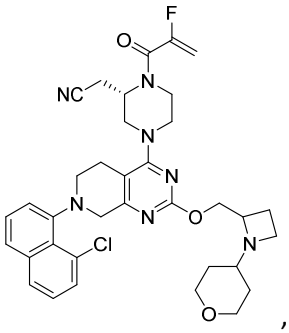
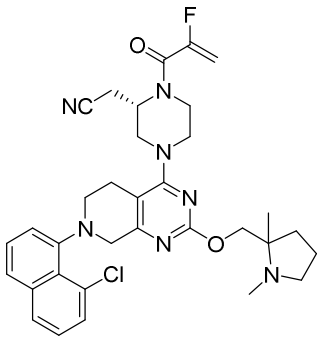
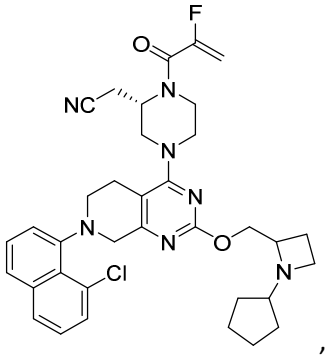
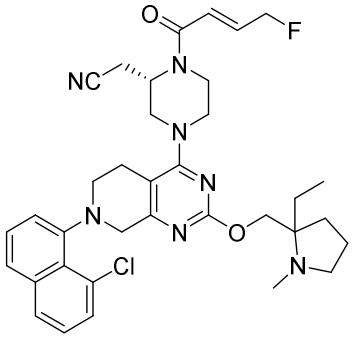

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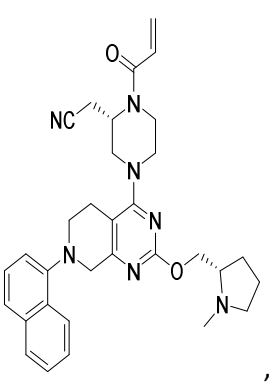
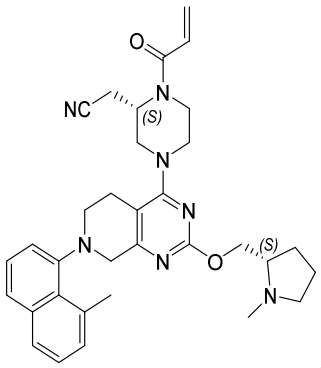
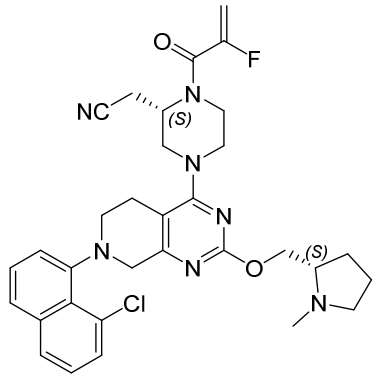
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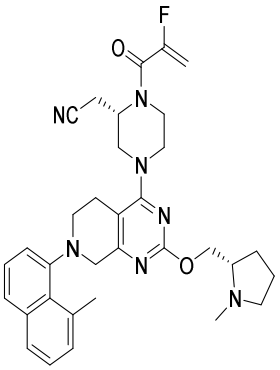

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or pharmaceutically acceptable salts thereof.

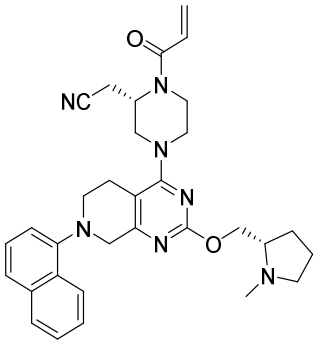
42. The use of claim 1, wherein the KRas G12C inhibitor is selected from the group consisting of:




, and



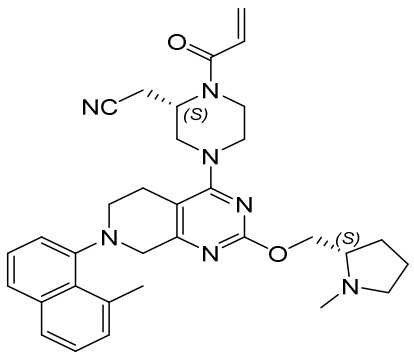
or pharmaceutically acceptable salts thereof.

43. The use of claim 1, wherein the KRas G12C inhibitor is:



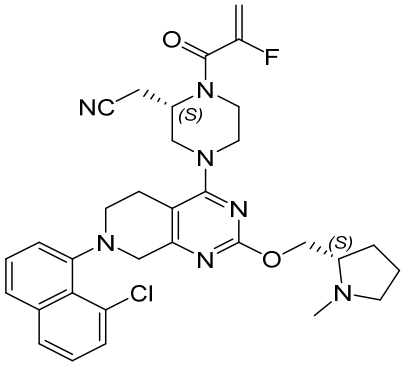
or a pharmaceutically acceptable salt thereof.

44. The use of claim 1, wherein the KRas G12C inhibitor is:



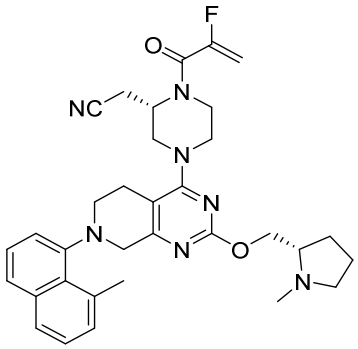
or a pharmaceutically acceptable salt thereof.

45. The use of claim 1, wherein the KRas G12C inhibitor is:



or a pharmaceutically acceptable salt thereof.

46. The use of claim 1, wherein the KRas G12C inhibitor is:



or a pharmaceutically acceptable salt thereof.

47. The use according to any one of claims 1-46, wherein the SHP-2 inhibitor is SHP-099 (6-(4-Amino-4-methylpiperidin-1-yl)-3-(2,3-dichlorophenyl)pyrazin-2-amine dihydrochloride); RMC-4550 (3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(2,3-dichlorophenyl)-5-methylpyrazin-2-yl)methanol), RMC-4630 or TNO155 (Novartis).

48. The use of claim 47, wherein the SHP-2 inhibitor is SHP-099.

49. The use of claim 47, wherein the SHP-2 inhibitor is RMC-4550.

50. The use of claim 47, wherein the SHP-2 inhibitor is RMC-4360 or TNO155.

51. The use according to any one of claims 1-50, wherein the SHP-2 inhibitor and the KRAS G12C inhibitor are to be administered on the same day.

52. The use according to any one of claims 1-50, wherein the SHP-2 inhibitor and the KRAS G12C inhibitor are to be administered on different days.

53. The use according to any one of claims 1-52, wherein the KRas G12C inhibitor is to be administered at a maximum tolerated dose.

54. The use according to any one of claims 1-52, wherein the SHP-2 inhibitor and the KRAS G12C inhibitor are each to be administered at a maximum tolerated dose.

55. The use according to any one of claims 1-54, wherein the therapeutically effective amount of the combination of the SHP-2 inhibitor and the KRAS G12C 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 G12C inhibitor.

56. A pharmaceutical composition, comprising a therapeutically effective amount of a combination of a SHP-2 inhibitor and a KRas G12C inhibitor of Formula (I), Formula I-A or Formula I-B according to any one of claims 1-46, and a pharmaceutically acceptable excipient.

57. A method for inhibiting KRas G12C activity in a cell in vitro, comprising contacting the cell in which inhibition of KRas G12C activity is desired with an effective amount of a SHP-2

inhibitor and a KRas G12C inhibitor compound of a Formula (I), Formula I-A or Formula I-B according to any one of claims 1-46, pharmaceutical compositions or pharmaceutically acceptable salts thereof, wherein the SHP-2 inhibitor synergistically increases the sensitivity of the cancer cells to the KRas G12C inhibitor.

58. The method according to any one of claims 1-55 and 57, wherein the SHP-2 inhibitor synergistically increases the sensitivity of the cancer cells to the KRas G12C inhibitor.

59. Use of a compound of Formula (I), Formula I-A or Formula I-B or a pharmaceutically acceptable salt thereof according to any one of claims 1-46, in the manufacture of a medicament, for increasing the sensitivity of a cancer cell to a KRas G12C inhibitor compound of Formula (I), Formula I-A or Formula I-B, wherein the compound is to be administered to a subject undergoing KRas G12C treatment combined with a pharmaceutically acceptable carrier, excipient or diluents, and with a therapeutically effective amount of a SHP-2 inhibitor, wherein the SHP-2 inhibitor synergistically increases the sensitivity of the cancer cell to the KRas G12C inhibitor.

60. The use according to any of claims 58 and 59, wherein the therapeutically effective amount of the KRas G12C inhibitor in the combination is between 0.01 to 100 mg/kg per day.

61. The use of claim 60, wherein the therapeutically effective amount of the KRas G12C inhibitor in the combination is between 0.1 to 50 mg/kg per day.

62. The use according to any of claims 59-61, wherein the therapeutically effective amount of the SHP-2 inhibitor in the combination is between 0.01 to 100 mg/kg per day.

63. The use of claim 62, wherein the therapeutically effective amount of the SHP-2 inhibitor in the combination is between 0.1 to 50 mg/kg per day.

64. The use according to any one of claims 1-54 and –58-63, 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,

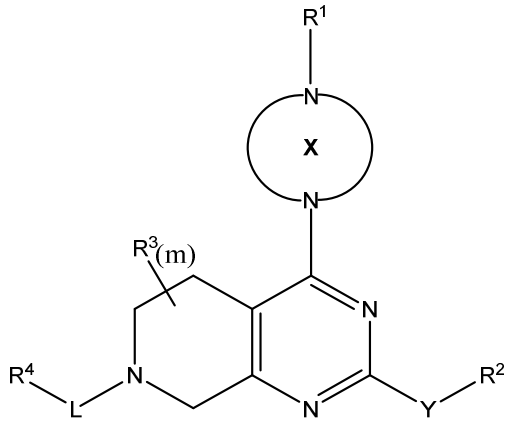
Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma.

65. The use of claim 58-64, wherein the cancer wherein the cancer is a KRas G12C-associated cancer.

66. The use of claim 65, wherein the cancer is non-small cell lung cancer.

67. A kit comprising the pharmaceutical composition of claim 56 for treating KRas G12C cancer in a subject.

68. A kit for treating KRas G12C cancer in a subject, the kit comprising: a) a pharmaceutical composition comprising a SHP-2 inhibitor and b) a pharmaceutical composition comprising a KRas G12C inhibitor of:



Formula (I)

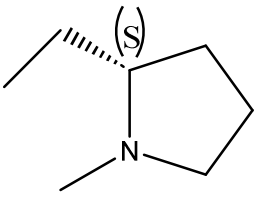
or a pharmaceutically acceptable salt thereof:

wherein:

X is piperazine optionally substituted with one or more R^8;

Y is O;

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

R^2 is  optionally substituted with one or more R^9;

each Z is $C_1 – C_4$ alkylene;

each R^3 is independently $C_1 – C_3$ alkyl, oxo, haloalkyl, hydroxyl or halogen;

L is a bond;

R^4 is heteroaryl optionally substituted with one or more R^6, R^7 or R^8;

each R^5 is independently hydrogen or $C_1 – C_3$ 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, $C_1 – C_6$ alkyl, cycloalkyl, alkoxy, haloalkyl, amino, cyano, heteroalkyl, hydroxyalkyl or Q-haloalkyl, wherein Q is O or S;

R^8 is oxo, $C_1 – C_3$ alkyl, $C_2 – C_4$ alkynyl, heteroalkyl, cyano, $-C(O)OR^5$, $-C(O)N(R^5)_2$, $-N(R^5)_2$, wherein the $C_1 – C_3$ 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, $C_1 – C_6$ alkyl, aralkyl, haloalkyl, heteroalkyl, cycloalkyl, heterocyclylalkyl, alkoxy, dialkylaminyl, dialkylamidoalkyl, or dialkylaminylalkyl, wherein the $C_1 – C_6$ alkyl may be optionally substituted with cycloalkyl;

each R^{10} is independently hydrogen, acyl, $C_1 – C_3$ alkyl, heteroalkyl or hydroxyalkyl;

R^{11} is haloalkyl;

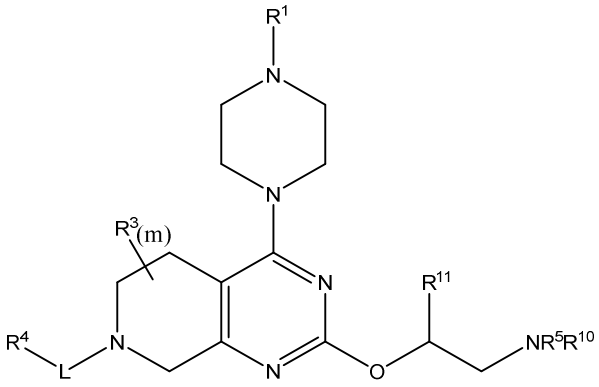
R^A is absent, hydrogen, deuterium, cyano, halogen, $C_1 – C_3$ alkyl, haloalkyl, heteroalkyl, $-C(O)N(R^5)_2$, or hydroxyalkyl;

each R^B is independently hydrogen, deuterium, cyano, $C_1 – C_3$ alkyl, hydroxyalkyl, heteroalkyl, $C_1 – C_3$ alkoxy, halogen, haloalkyl, $-ZNR^5R^{11}$, $-C(O)N(R^5)_2$, $-NHC(O)C_1 – C_3$ alkyl, $-CH_2NHC(O)C_1 – C_3$ alkyl, heteroaryl, heteroarylalkyl, dialkylaminylalkyl, or heterocyclylalkyl wherein the heterocyclyl portion is substituted with one or more substituents independently selected from halogen, hydroxyl, alkoxy and $C_1 – C_3$ alkyl, wherein the heteroaryl or the heteroaryl portion of the heteroarylalkyl is optionally substituted with one or more R^7;

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;

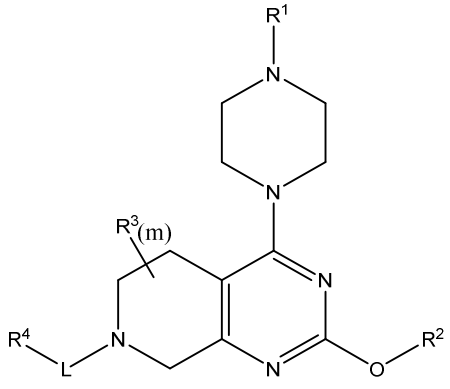
m is zero or an integer between 1 and 2; and

p is one or two.
or



Formula I-A

and pharmaceutically acceptable salts thereof, wherein R^1, R^3, R^4, R^5, R^{10}, L and m are as defined for Formula I, R^{11} is hydrogen, methyl or hydroxyalkyl, and the piperidinyl ring is optionally substituted with R^8 wherein R^8 is as defined for Formula I
or



Formula I-B

and pharmaceutically acceptable salts thereof, wherein R^1, R^3, R^4, L and m are as defined for Formula I, R^2 is heterocyclylalkyl optionally substituted with one or more R^9 where R^9 is as defined for Formula I, and the piperazinyl ring is optionally substituted with R^8, where R^8 is as defined for Formula I,

for treating a KRas G12C cancer in a subject.

69. The kit according to claim 68 or 69, further comprising an insert with instructions for administration of the pharmaceutical composition(s).