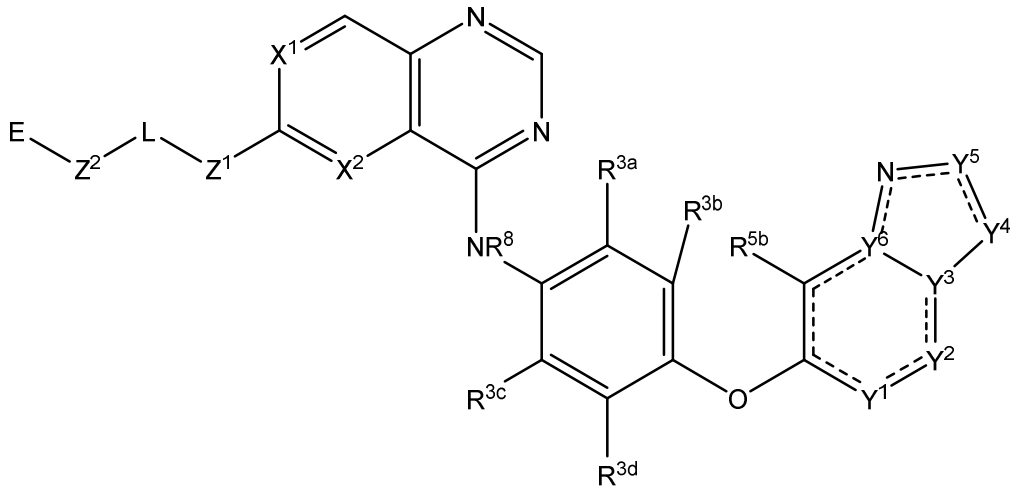
Claims

1. A compound having the following structure of Formula (I):



(I)

or a stereoisomer of the compound, tautomer of the compound, or a pharmaceutically acceptable salt thereof, wherein:

X^1 is CR^1 or N;

X^2 is CR^2 or N;

Y^1 is CR^4 or N;

Y^2 is CR^{5a} or N;

Y^3 is C or N;

Y^4 is CR^6 or NR^6;

Y^5 is CR^7, O, or NR^7;

Y^6 is C or N;

R^1, R^2, R^{3a}, R^{3b}, R^{3c}, R^{3d}, R^4, R^{5a}, R^{5b}, and R^7 are each independently H, halo, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or C_1-C_3 heteroalkyl;

R^6 is H, C_1-C_3 alkyl, C_1-C_3 deutero-alkyl, or C_1-C_3 haloalkyl;

R^8 and R^9 are, each independently, H or C_1-C_3 alkyl;

Z^1 is -NR^9-, -O-, -S-, or a direct bond;

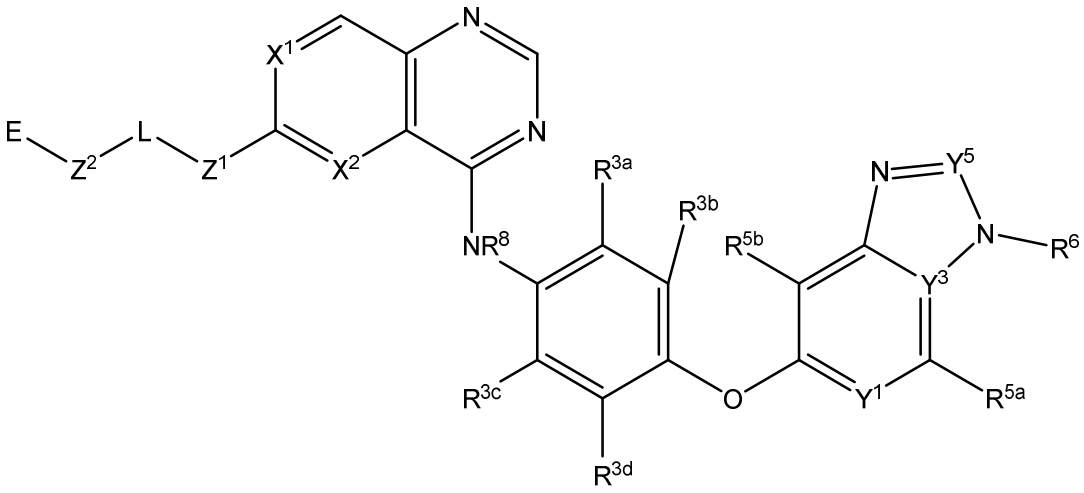
Z^2 is -NR^9- or a direct bond;

L is C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 heterocycloalkyl, a fused heterobicyclic, a bridged heterobicyclic, a hetero-spirocyclic, or a direct bond;

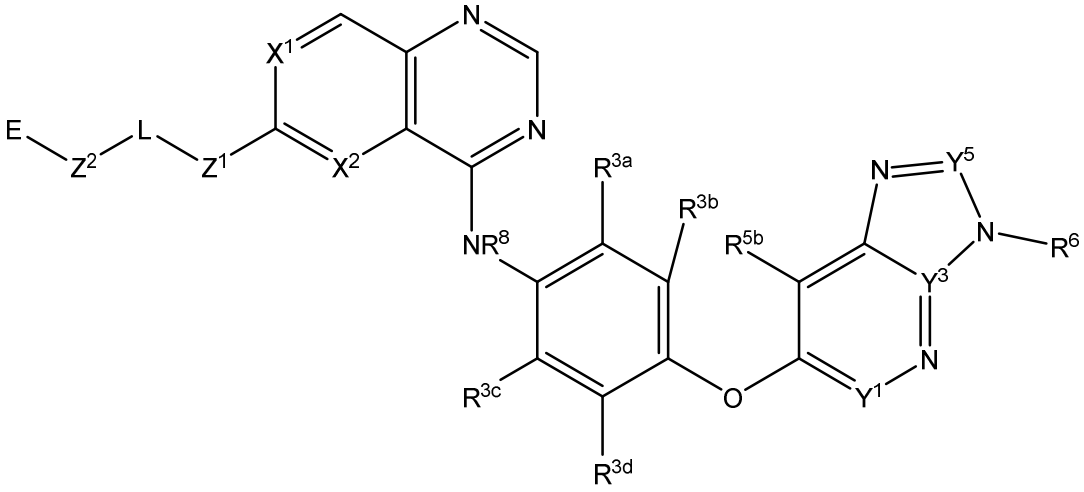
E is α,β-unsaturated carbonyl or C_2-C_4 alkyne conjugated carbonyl; and

--- is, each independently, a single bond or a double bond, where valency permits.

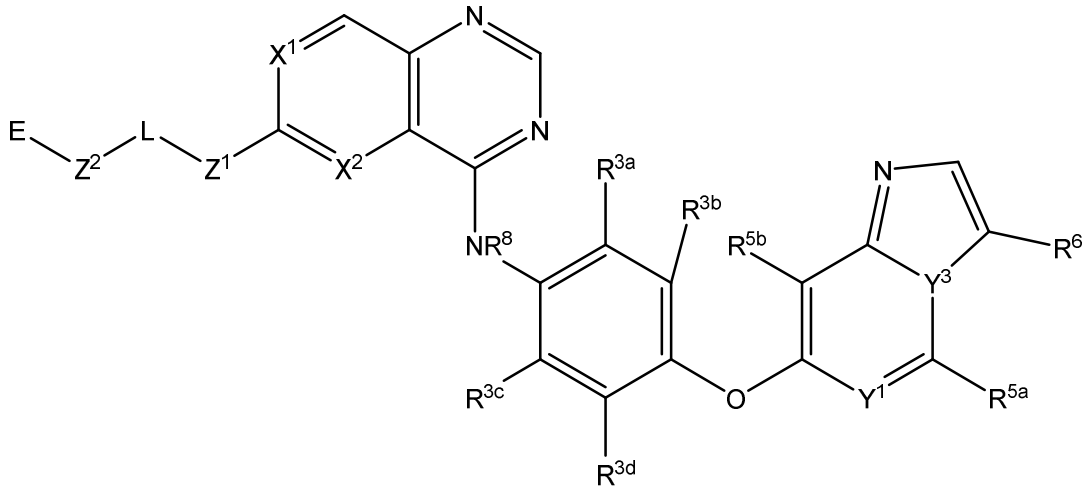
2. The compound of claim 1, wherein the compound has one of the following structures of Formula (IA)-(ID):



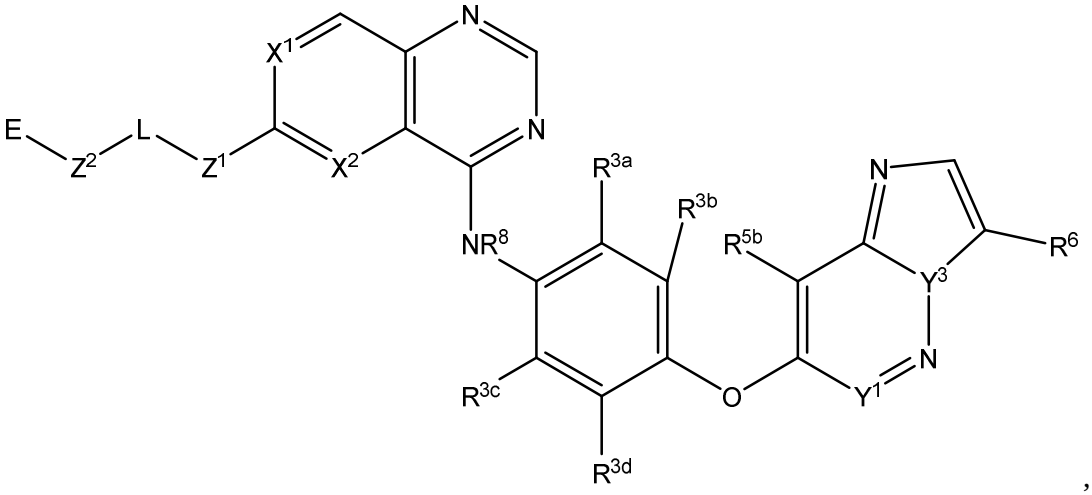
(IA)



(IB)



(IC)

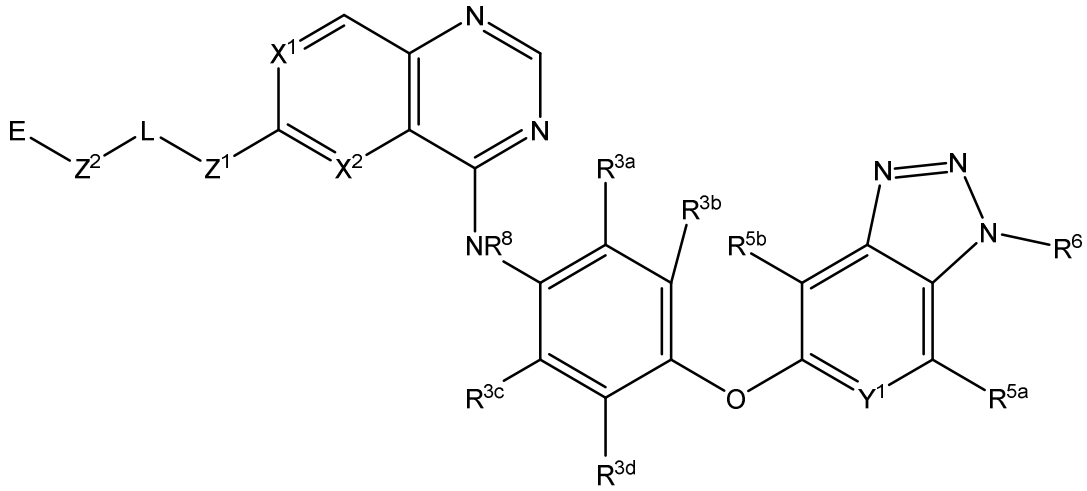


(ID)

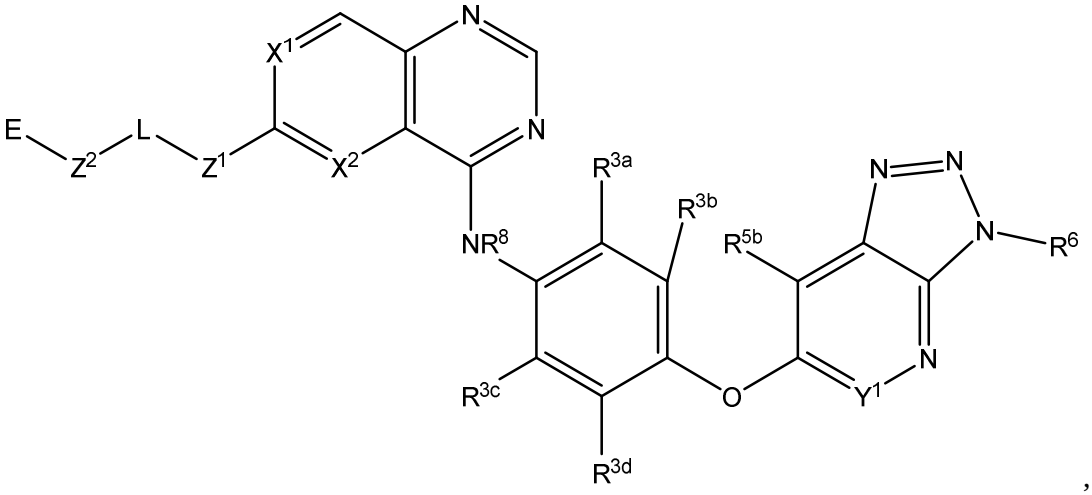
or a stereoisomer of the compound, tautomer of the compound, or a pharmaceutically acceptable salt thereof.

3. The compound of any one of claims 1-2, wherein Y^5 is N and Y^3 is C.

4. The compound of any one of claims 1-3, wherein the compound has one of the following structures of Formula (IA-1)-(IB-1):



(IA-1)

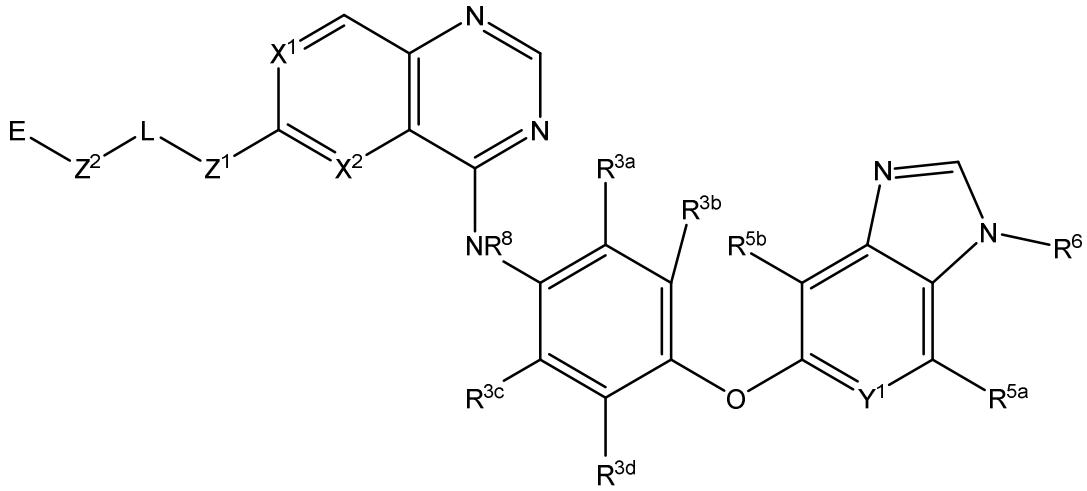


(IB-1)

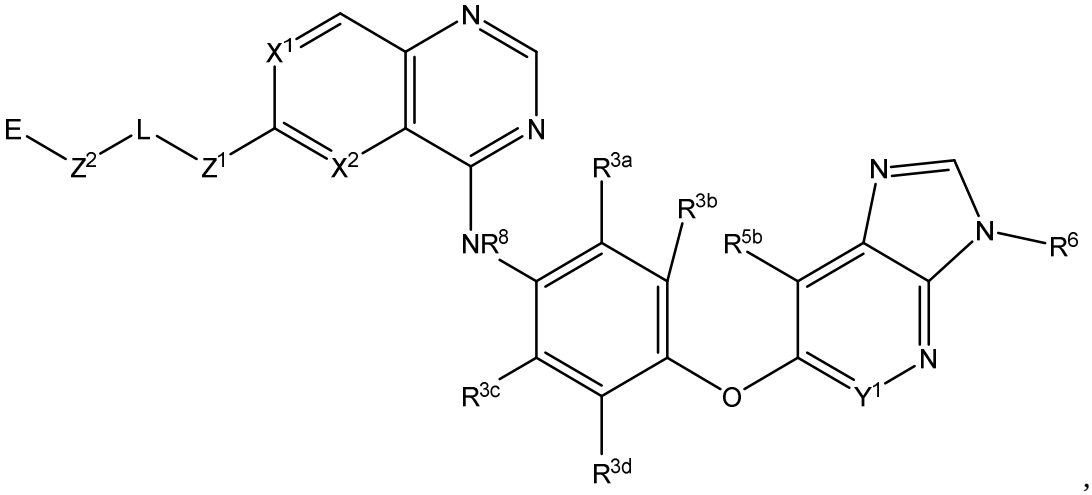
or a stereoisomer of the compound, tautomer of the compound, or a pharmaceutically acceptable salt thereof.

5. The compound of any one of claims 1-2, wherein Y^5 is CR^7, and Y^3 is C, and R^7 is H.

6. The compound of claim 5, wherein the compound has one of the following structures of Formula (IA-2)-(IB-2):



(IA-2)



(IB-2)

or a stereoisomer of the compound, tautomer of the compound, or a pharmaceutically acceptable salt thereof.

7. The compound of any one of claims 1-6, wherein R^6 is C_1-C_3 haloalkyl.

8. The compound of any one of claims 1-7, wherein R^6 is C_1 haloalkyl.

9. The compound of any one of claims 1-8, wherein R^6 is CHF_2 or CF_3.

10. The compound of any one of claims 1-9, wherein Z^1 and Z^2 are each a direct bond.

11. The compound of any one of claims 1-10, wherein Z^1 is $-NR^9-$, -O-, or -S- and Z^2 is a direct bond.

12. The compound of any one of claims 1-11, wherein Z^1 is a direct bond and Z^2 is -NR^9-.

13. The compound of any one of claims 1-12, wherein Z^1 and Z^2 are each -NR^9-.

14. The compound of any one of claims 1-13, wherein R^9 is H or CH_3.

15. The compound of any one of claims 1-14, wherein R^1, R^2, R^{3a}, R^{3b}, R^{3c}, R^{3d}, R^4, R^{5a}, R^{5b}, and R^7 are, each independently, H, halo, C_1 alkyl, C_1-C_2 haloalkyl, or C_1-C_3 heteroalkyl.

16. The compound of any one of claims 1-15, wherein R^1, R^2, R^{3a}, R^{3b}, R^{3c}, R^{3d}, R^4, R^{5a}, R^{5b}, and R^7 are, each independently, H, F, Cl, CH_3, CH_2CF_3, CF_3, CHF_2, CH_2OCH_3, CD_3, $OCHF_2$, OCF_3, or OCH_3.

17. The compound of any one of claims 1-16, wherein R^1 and R^2 are, each independently, H, F, CH_3, or OCH_3.

18. The compound of any one of claims 1-17, wherein R^{3a}, R^{3b}, R^{3c}, and R^{3d} are, each independently, H, CH_3, OCH_3, CH_2OCH_3, $OCHF_2$, OCF_3, F, or Cl.

19. The compound of any one of claims 1-18, wherein R^4 is H, F, CH_3, CH_2OCH_3, or CH_2CF_3.

20. The compound of any one of claims 1-19, wherein R^{5a} and R^{5b} are, each independently, H, CH_3, F, or OCH_3.

21. The compound of any one of claims 1-20, wherein R^7 is H or CH_3.

22. The compound of any one of claims 1-21, wherein R^8 is H or CH_3.

23. The compound of any one of claims 1-22, wherein the C_3-C_8 heterocycloalkyl, the fused heterobicyclic, the bridged heterobicyclic, and the hetero-spirocyclic of L have 1-3 nitrogen atoms.

24. The compound of any one of claims 1-23, wherein the C_3-C_8 heterocycloalkyl, the fused heterobicyclic, the bridged heterobicyclic, and the hetero-spirocyclic of L have 1-2 nitrogen atoms.

25. The compound of any one of claims 1-24, wherein the C_3-C_8 heterocycloalkyl, the fused heterobicyclic, the bridged heterobicyclic, and the hetero-spirocyclic of L are unsaturated heterocycles.

26. The compound of any one of claims 1-25, wherein the C_3-C_8 heterocycloalkyl of L is azetidine, pyrrolidine, imidazolidine, pyrazolidine, piperidine, 1,2-diazinane, 1,3-diazinane, 1,4-diazinane, azapane, diazepane, or azocane.

27. The compound of any one of claims 1-26, wherein the fused heterobicyclic of L is 3-azabicyclo[3.1.0]heptane, 2,5-diazabicyclo[4.2.0]octane, octahydropyrrolo[3.4.c]pyrrole, octahydropyrrolo[3.4.b]pyrrole, octahydro-1H-pyrrolo[3.4.c]pyridine, decahydro-2,6-naphthyridine, 2,5-diazabicyclo[4.1.0]heptane, 3,6-diazabicyclo[3.2.0]heptane, or 3,6-diazabicyclo[3.1.0]hexane.

28. The compound of any one of claims 1-27, wherein the bridged heterobicyclic of L is 3,8-diazabicyclo[3.2.1]octane, 2,5-diazabicyclo[2.2.2]octane, 8-azabicyclo[3.2.1]octane, 3-azabicyclo[3.2.1]octane, 3,6-diazabicyclo[3.2.1]octane, 9-azabicyclo[3.3.1]nonane, 3-oxa-9-azabicyclo[3.3.1]nonane, 3-oxa-9-azabicyclo[3.3.1]non-6-ene, 9-azabicyclo[3.3.1]non-2-ene, 8-azabicyclo[3.2.1]oct-2-ene, or 3,6-diazabicyclo[3.1.1]heptane.

29. The compound of any one of claims 1-28, wherein the hetero-spirocyclic of L is 2,6-diazaspiro[3.3]heptane, 1,6-diazaspiro[3.3]heptane, 2-azaspiro[3.3]heptane, 1,6-diazaspiro[3.4]octane, 2,6-diazaspiro[3.4]octane, 2,7-diazaspiro[3.5]nonane, 2,8-diazaspiro[4.5]decane, 3,9-diazaspiro[5.5]undecane, 4,8-diazaspiro[2.5]octane, 5,9-diazaspiro[3.5]nonane, 6,10-diazaspiro[4.5]decane, or 1,5-diazaspiro[5.5]undecane.

30. The compound of any one of claims 1-29, wherein the C_3-C_8 heterocycloalkyl, the fused heterobicyclic, the bridged heterobicyclic, and the hetero-spirocyclic of L are further substituted with deuterium, halo, C_1-C_6 alkyl, or C_1-C_6 heteroalkyl.

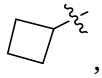
31. The compound of any one of claims 1-30, wherein the C_3-C_8 heterocycloalkyl, the fused heterobicyclic, the bridged heterobicyclic, and the hetero-spirocyclic of L are further substituted with deuterium, halo, C_1-C_3 alkyl, or C_1-C_3 heteroalkyl.

32. The compound of any one of claims 1-31, wherein the C_3-C_8 heterocycloalkyl, the fused heterobicyclic, the bridged heterobicyclic, and the hetero-spirocyclic of L are further substituted with -D, -F, -CH_3, -CF_3, -CHF_2, -CH_2F, -CH_2CHF_2, -CH_2CH_3, -$CH(CH_3)_2$, -CH_2OH, -CH_2OCH_3, , or -CH_2CCN.

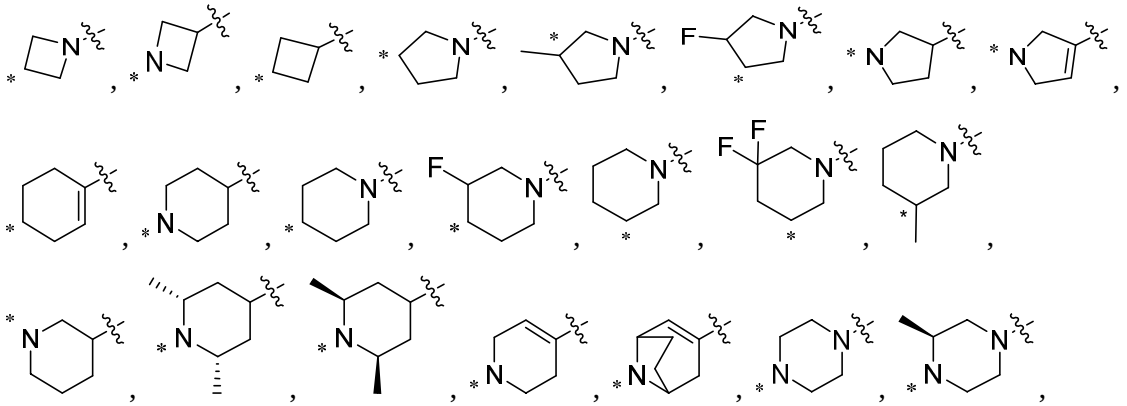
33. The compound of any one of claims 1-32, wherein the C_3-C_8 heterocycloalkyl, the fused heterobicyclic, the bridged heterobicyclic, and the hetero-spirocyclic of L are mono-, di-, tri-, tetra-, penta-, or octa-substituted.

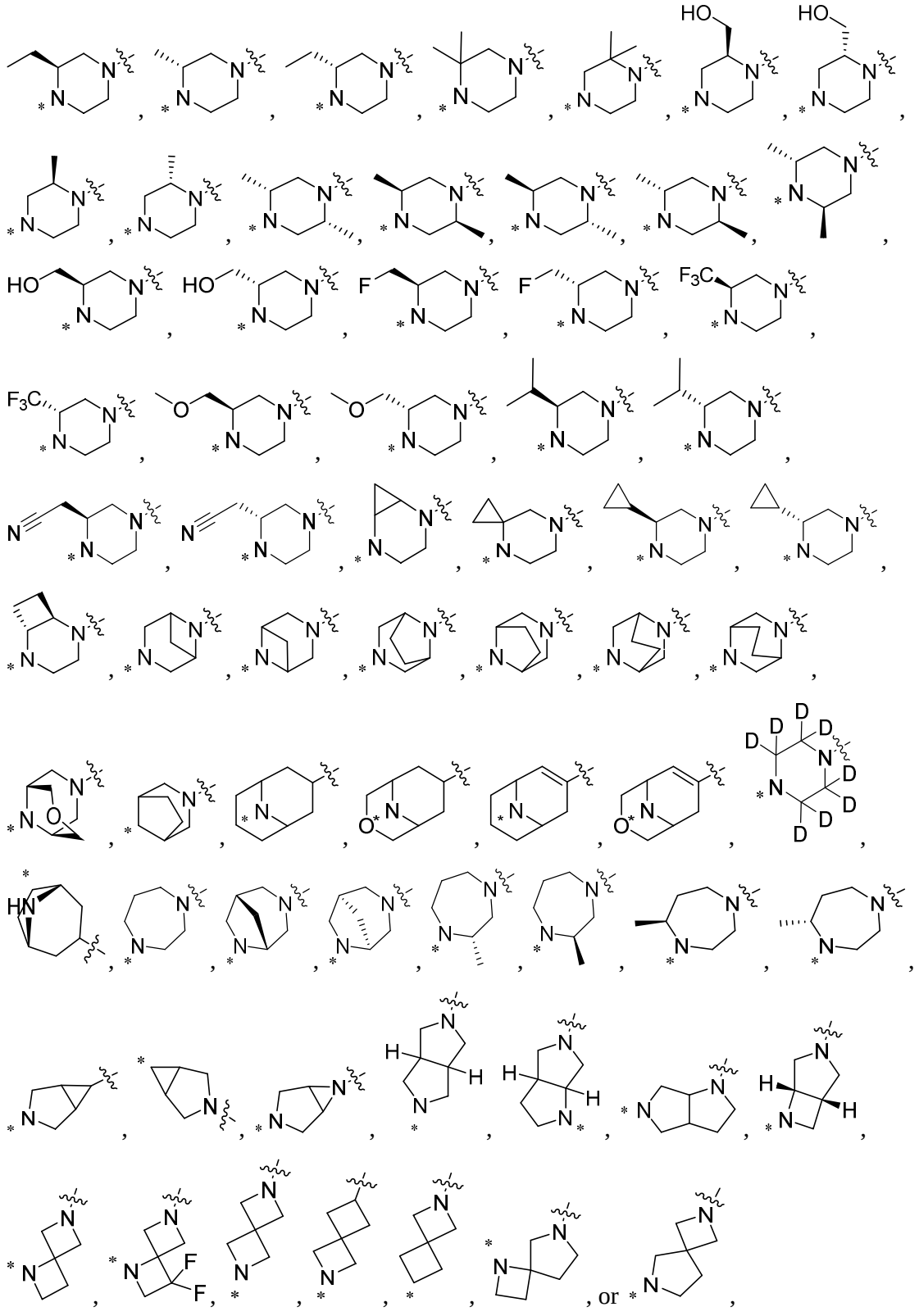
34. The compound of any one of claims 1-33, wherein L is C_2-C_4 alkyl or C_4-C_5 cycloalkyl.

35. The compound of any one of claims 1-34, wherein C_1-C_4 alkyl of L is –$(CH_2)_2$- or -$CH_2C(CH_3)_2$.

36. The compound of any one of claims 1-35, wherein C_3-C_8 cycloalkyl of L is , wherein * indicates a location of a bond to Z^2.

37. The compound of any one of claims 1-36, wherein L has one of the following structures:



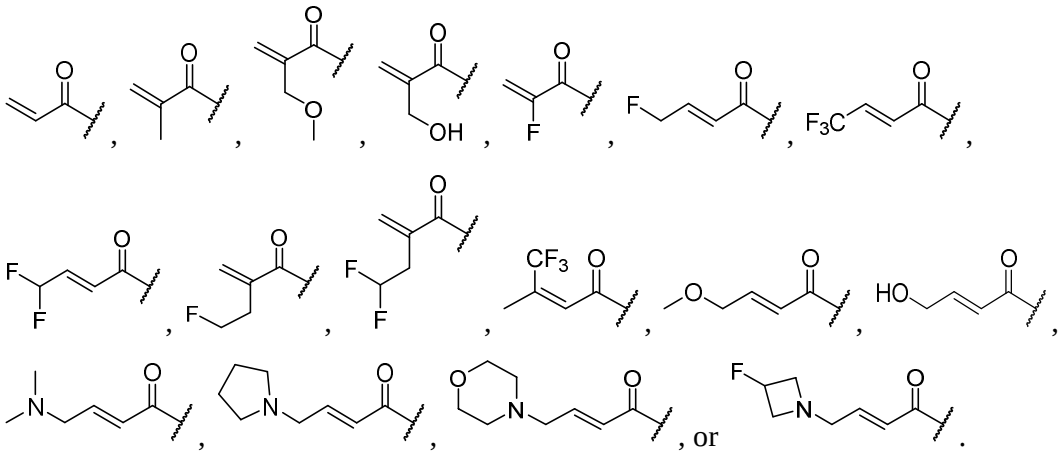


wherein * indicates a location of a bond to Z^2.

38. The compound of any one of claims 1-37, wherein α,β-unsaturated carbonyl or C_2-C_4 alkyne conjugated carbonyl of E is further substituted with halo, C_1-C_3 alkyl, C_1-C_3

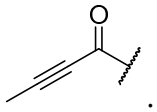
alkylhalo, C_1-C_6 heteroalkyl, -$(CH_2)_nC_3$-C_7 heterocycloalkyl, or combination thereof, wherein n is an integer between 1-3.

39. The compound of any one of claims 1-38, wherein α,β-unsaturated carbonyl of E has one of the following structures:



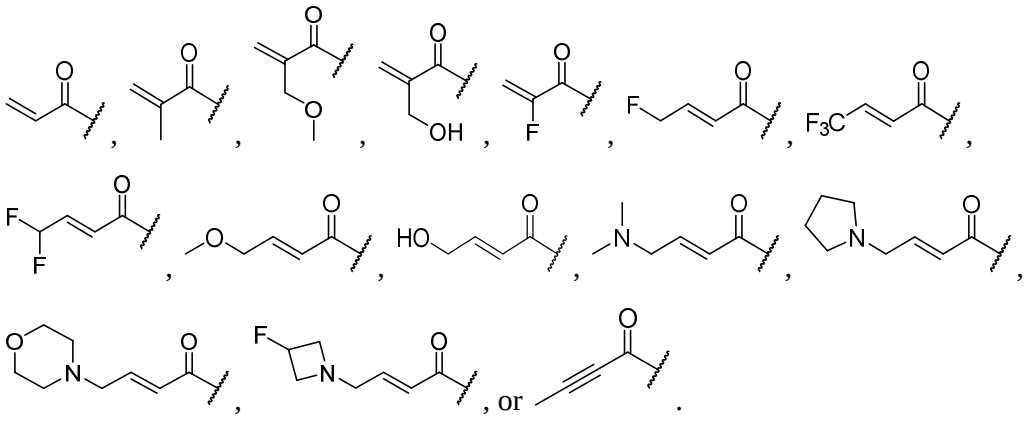
40. The compound of any one of claims 1-39, wherein the C_2-C_4 alkyne conjugated carbonyl is C_2 alkyne conjugated carbonyl or C_3 alkyne conjugated carbonyl.

41. The compound of any one of claims 1-40, wherein the C_2-C_4 alkyne conjugated carbonyl has the following structure:



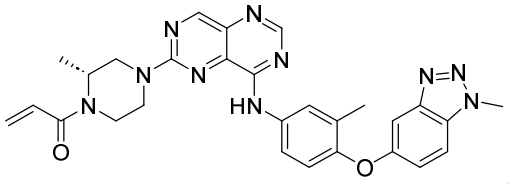
.

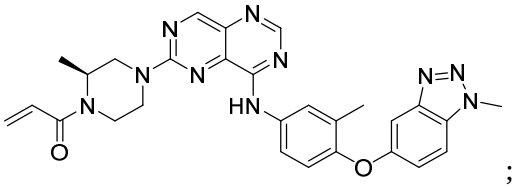
42. The compound of any one of claims 1-41, wherein E has one of the following structures:

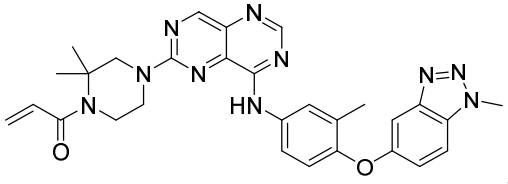


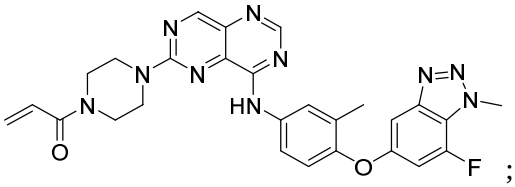
.

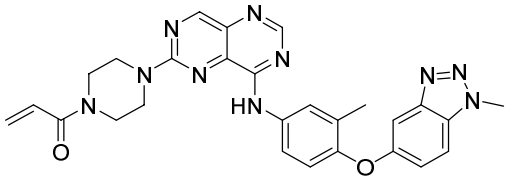
43. The compound of claim 1, wherein the compound has one of the following structures:

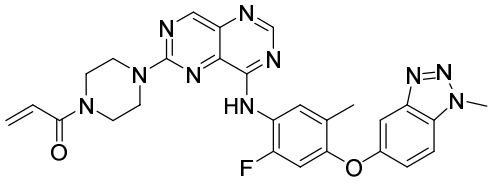

;

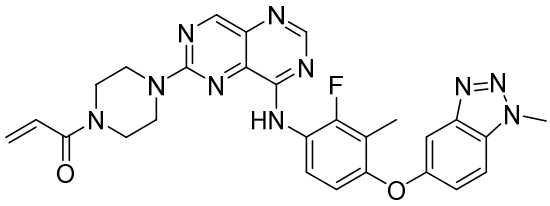

;

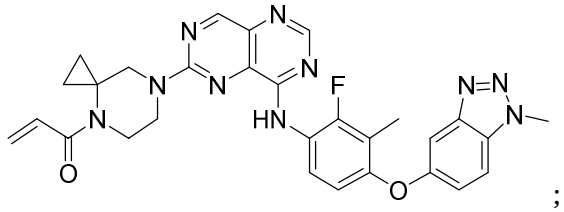

;

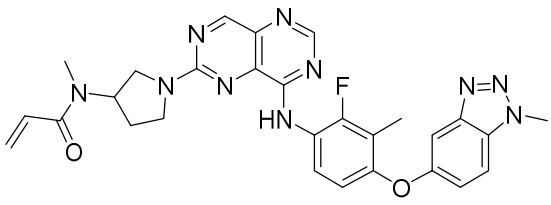

;

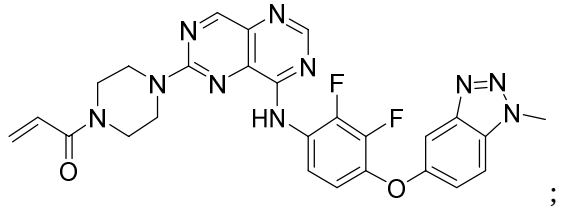

;

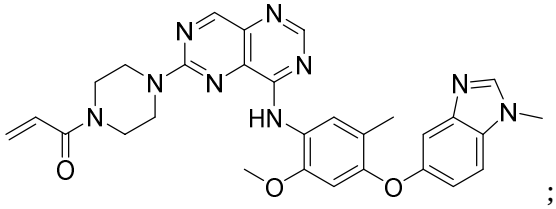

;

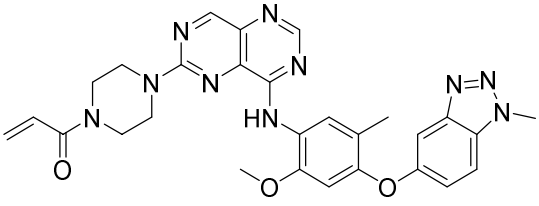

;

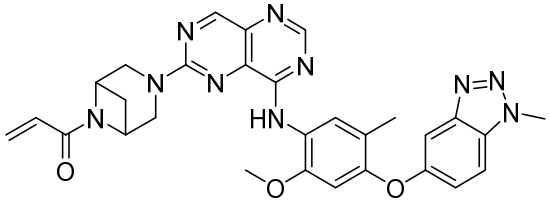

;

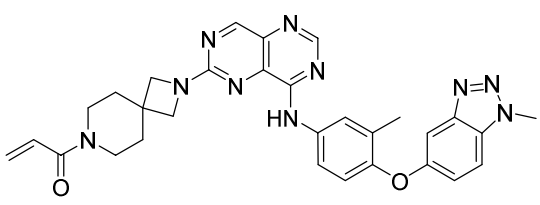

;

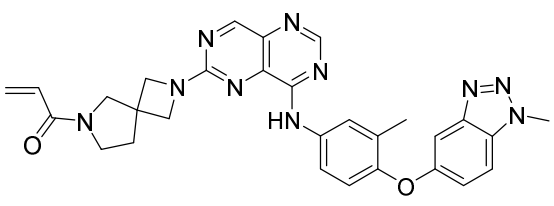
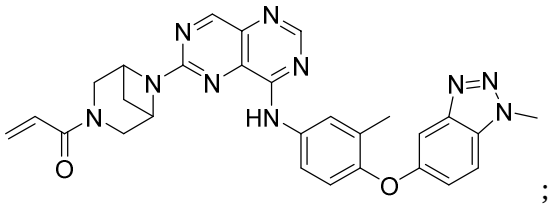
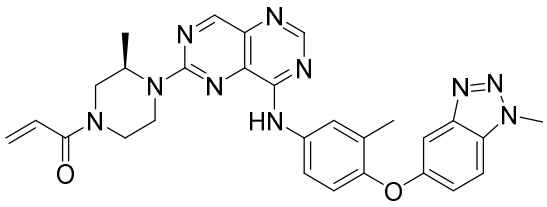
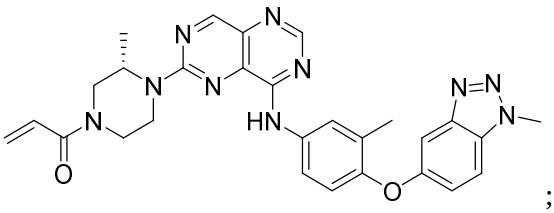
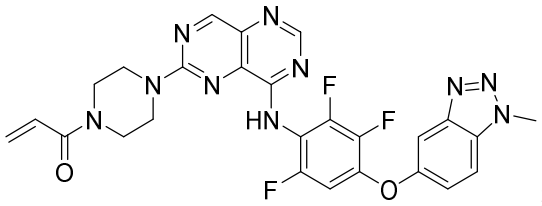
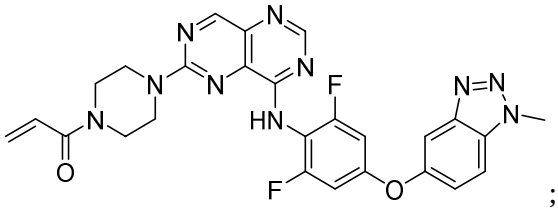
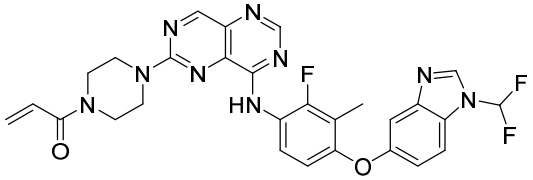
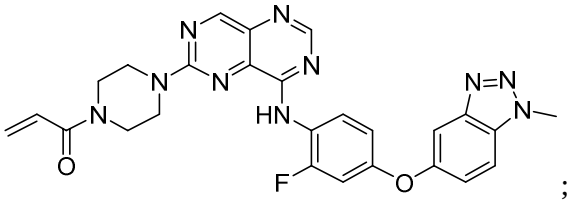
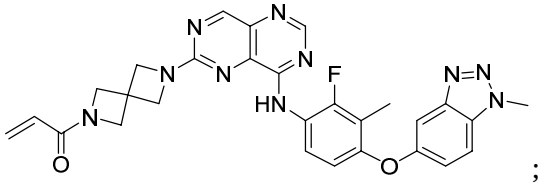
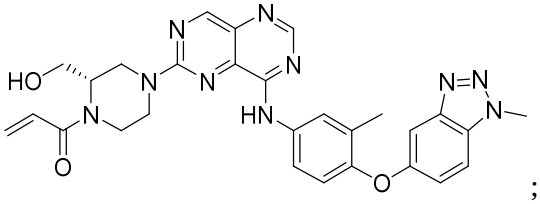
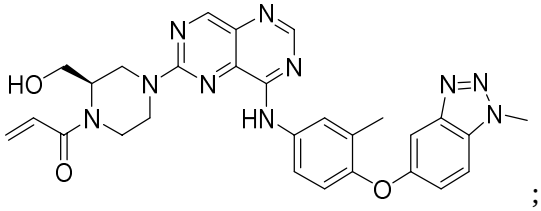
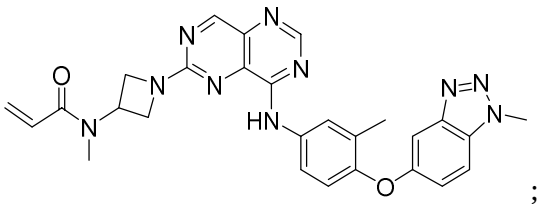
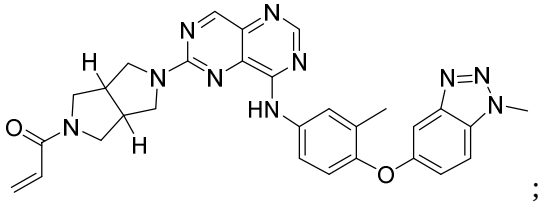
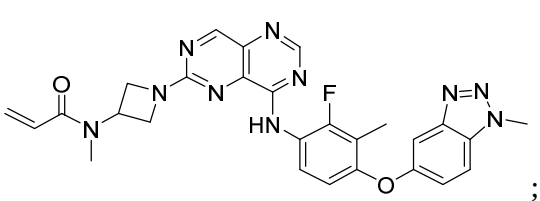
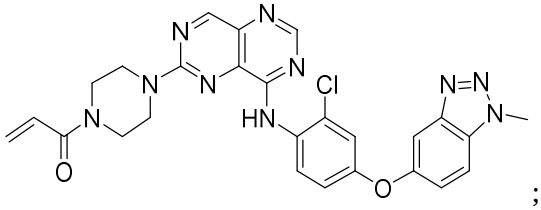
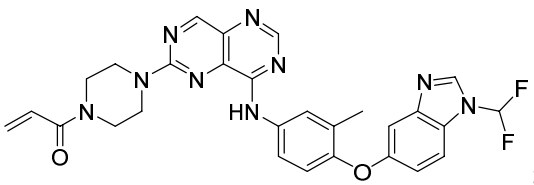

;

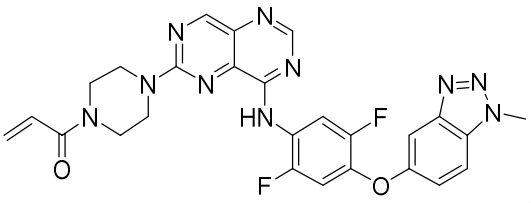
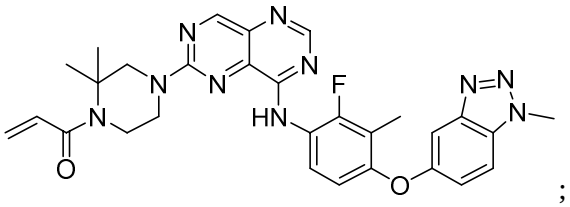
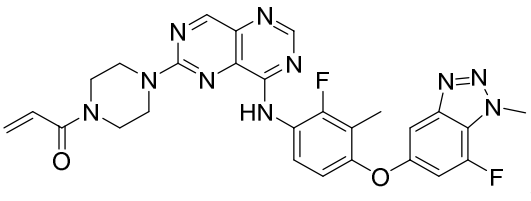
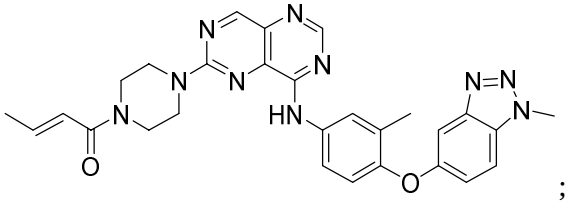
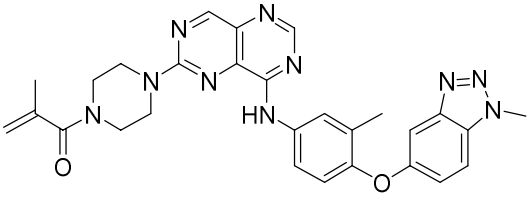
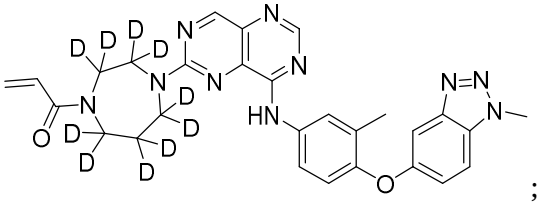
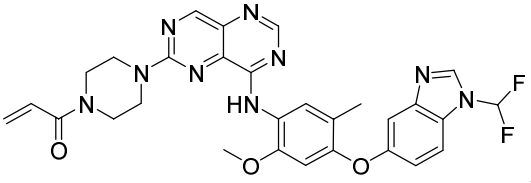
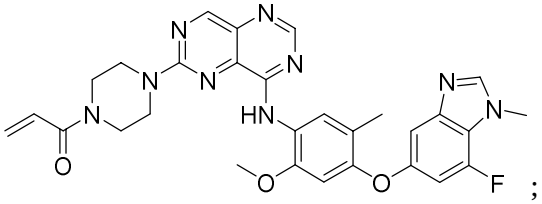
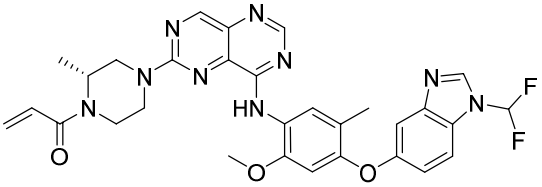
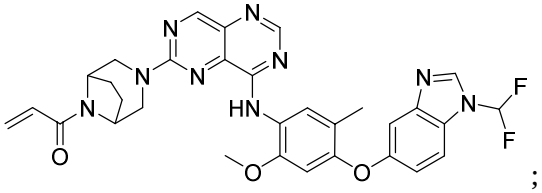
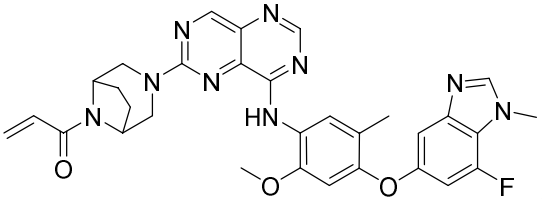
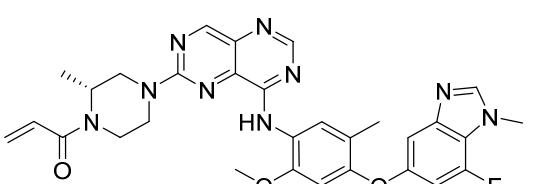
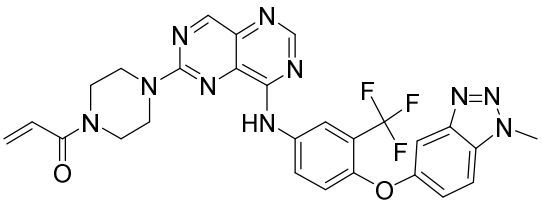
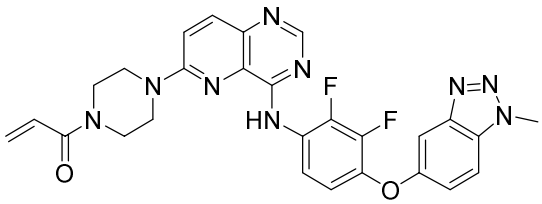
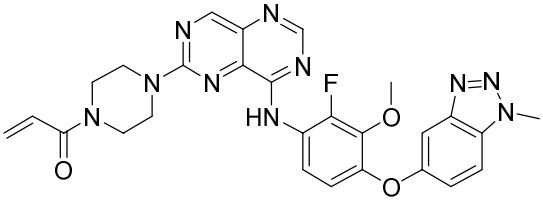
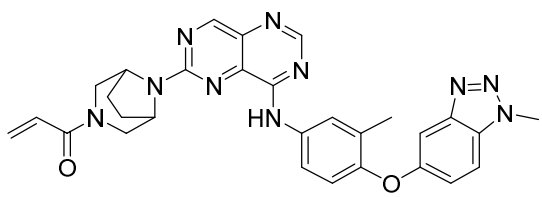

;

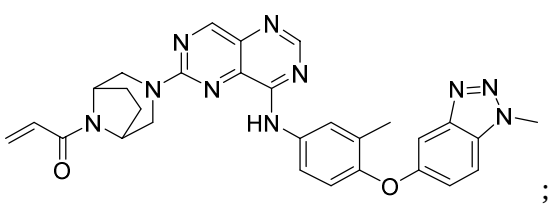
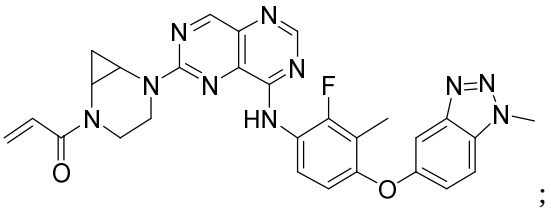
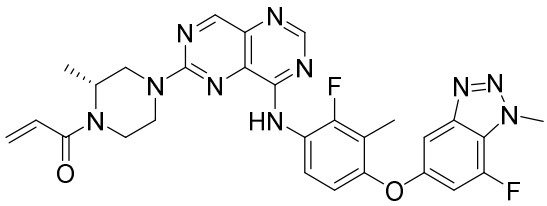
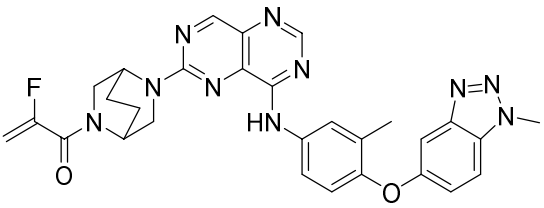
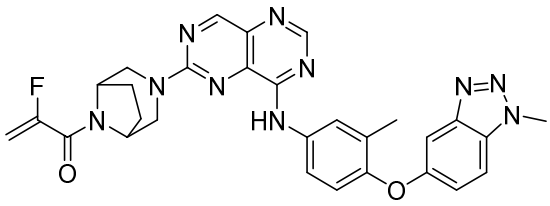
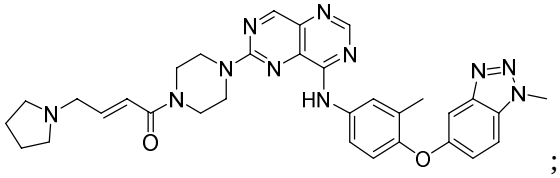
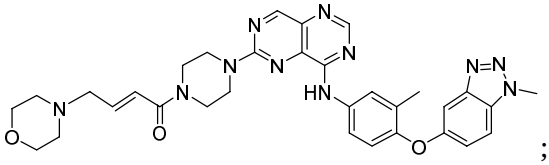
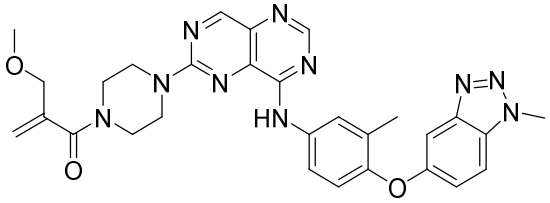
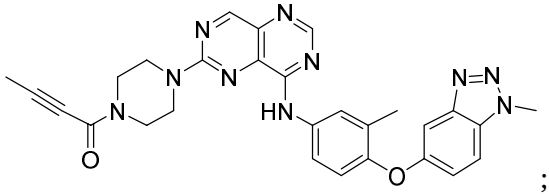
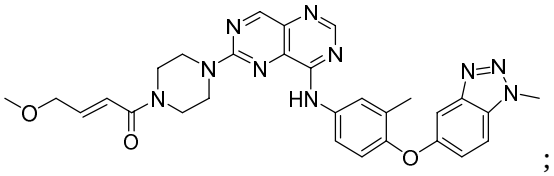
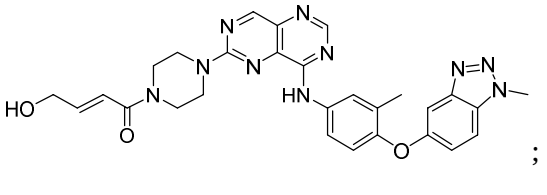
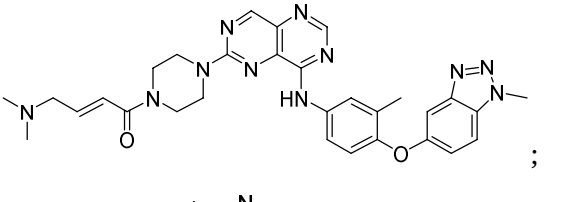
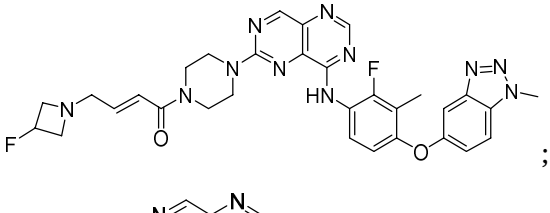
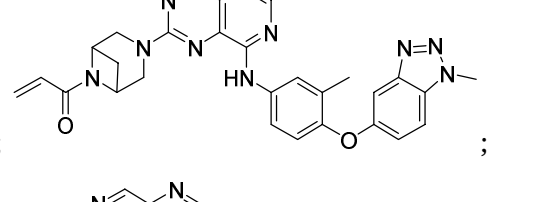
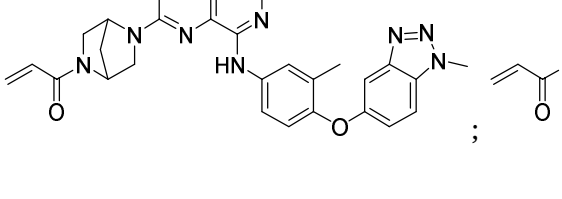
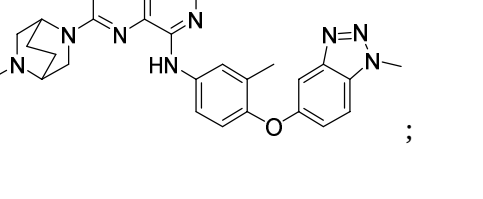

;


;


;

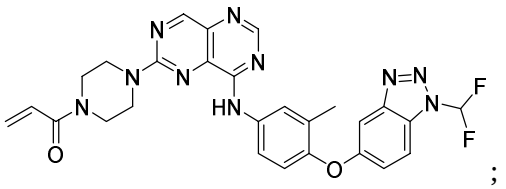
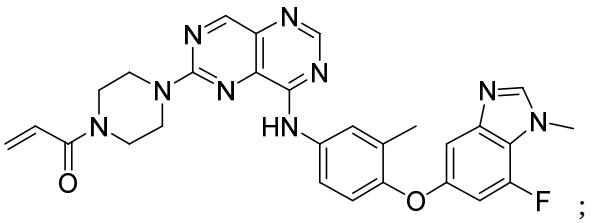
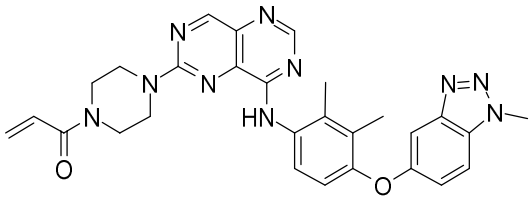
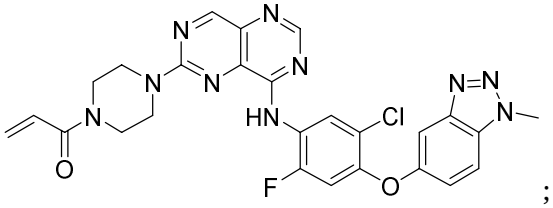
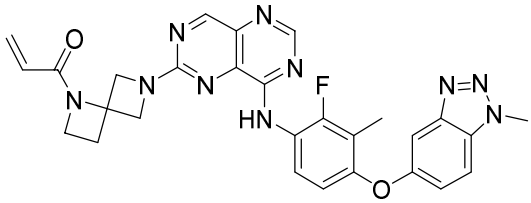
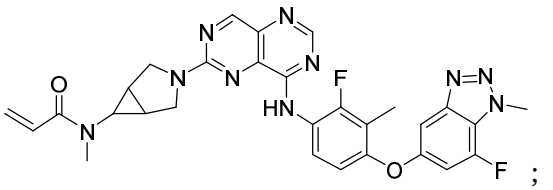
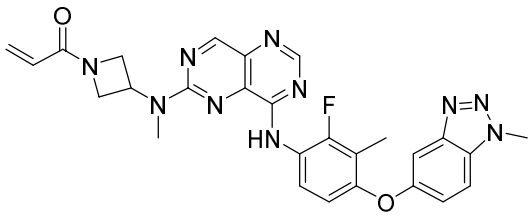
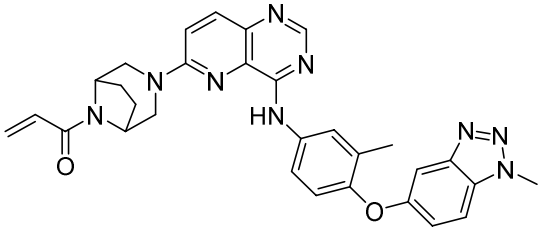
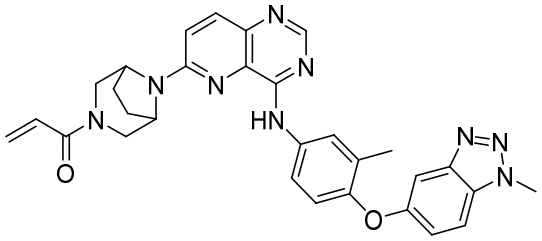
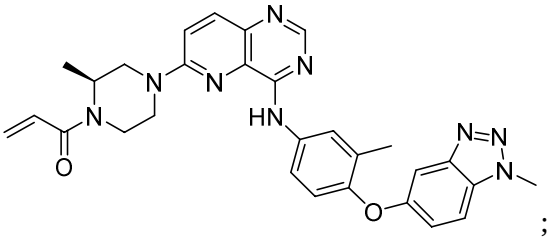
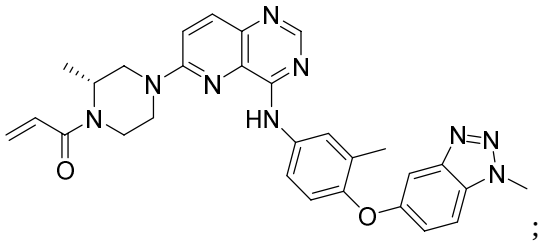
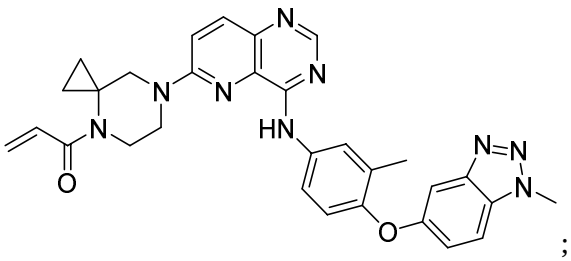
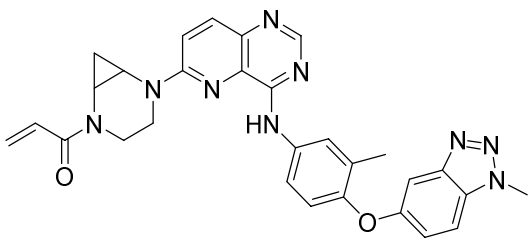
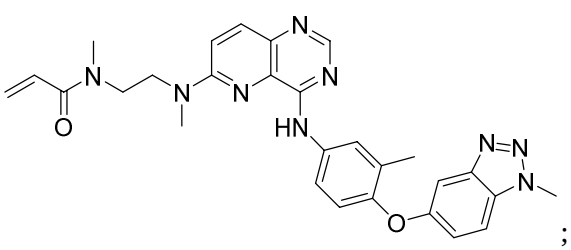

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;


;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;


;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

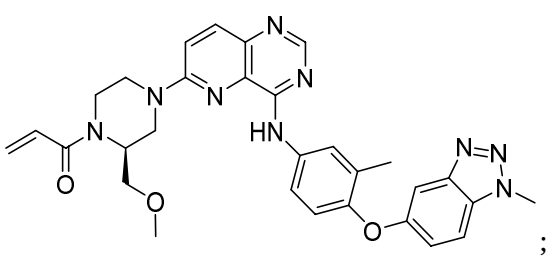
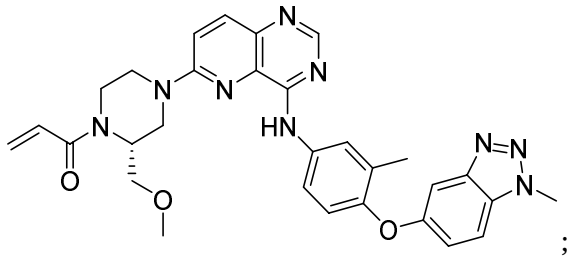
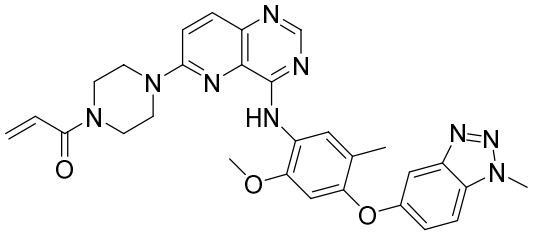
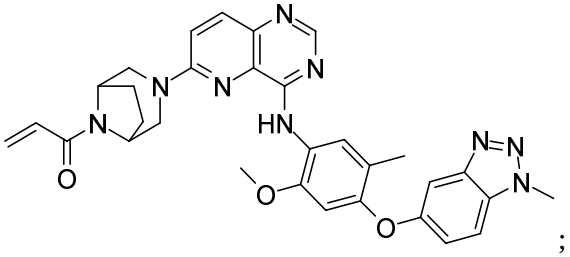
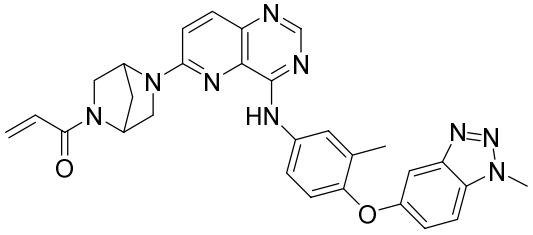
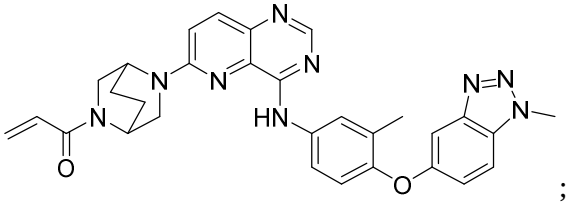
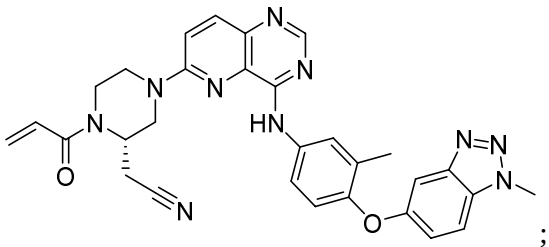
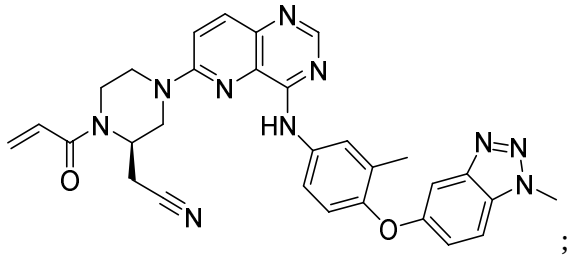
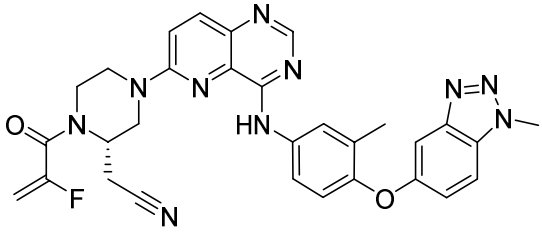
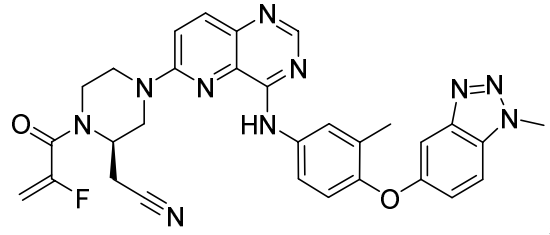
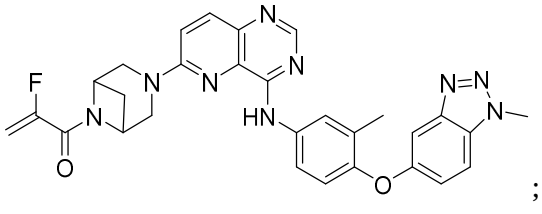
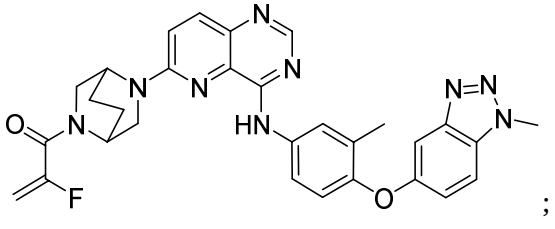
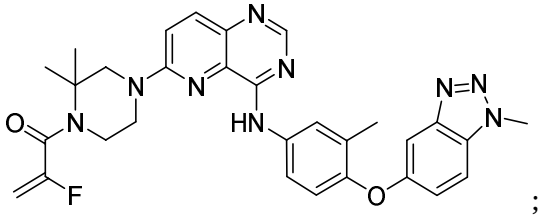
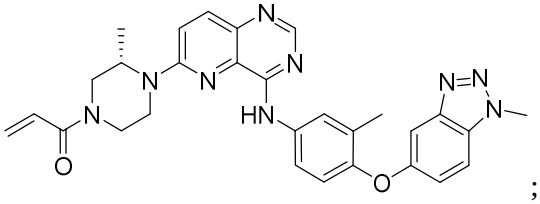
;

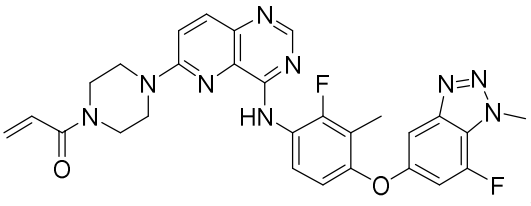
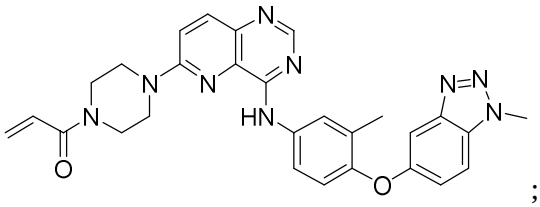
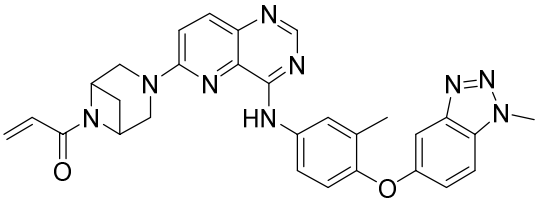
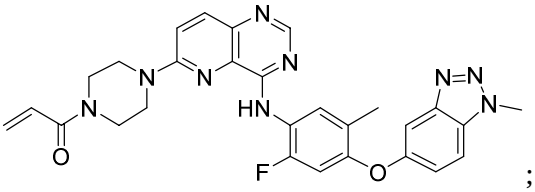
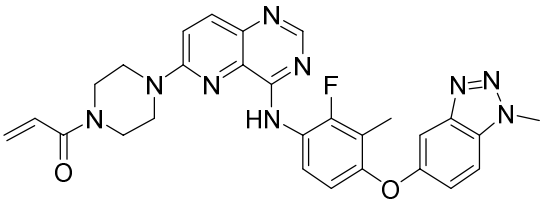
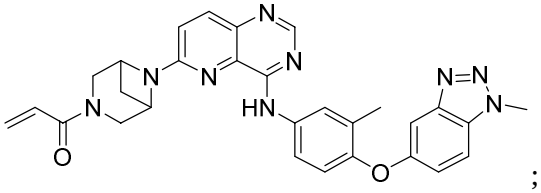
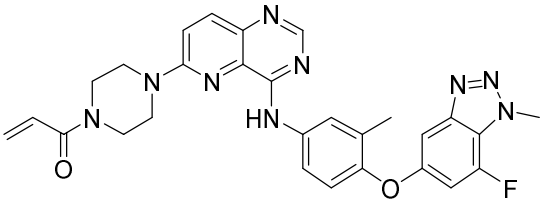
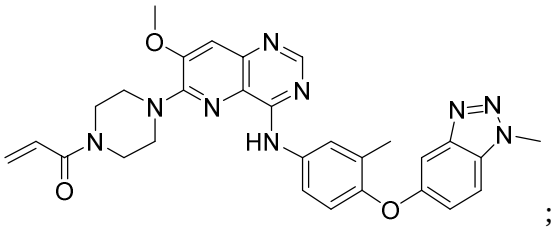
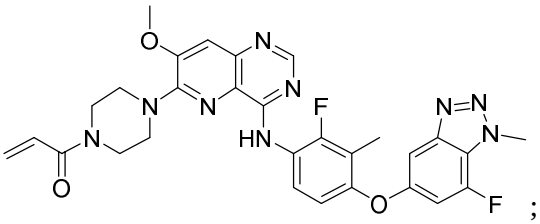
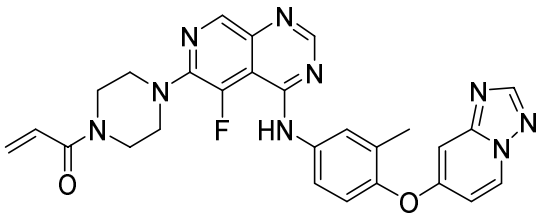
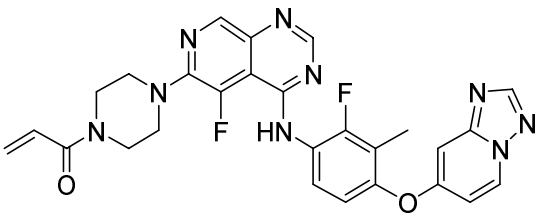
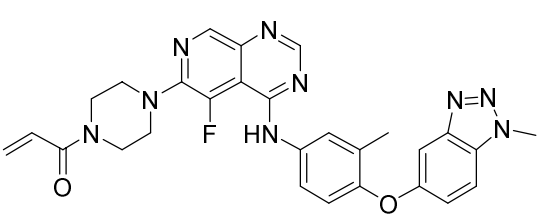
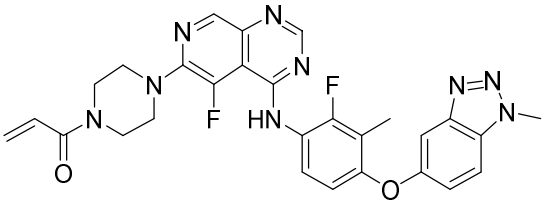
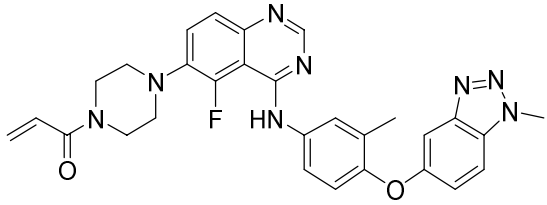
;


;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

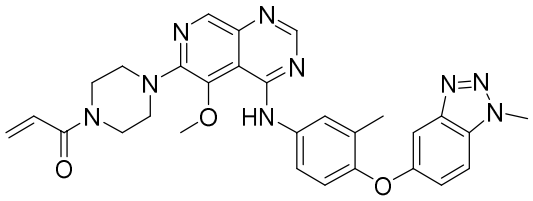
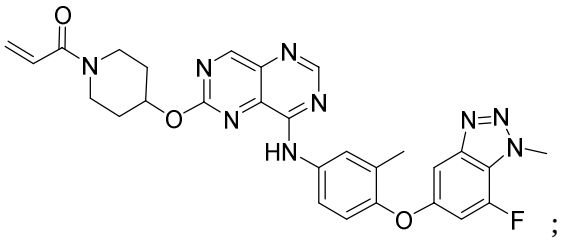
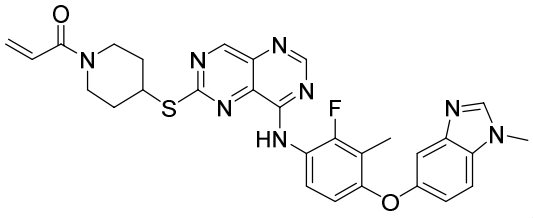
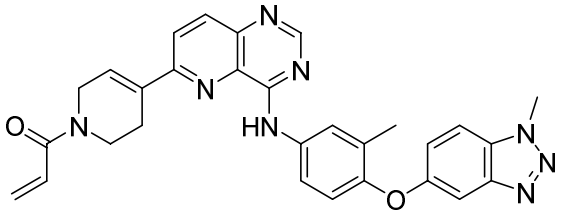
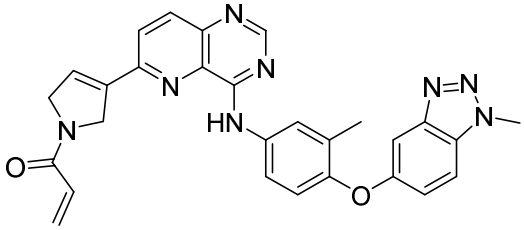
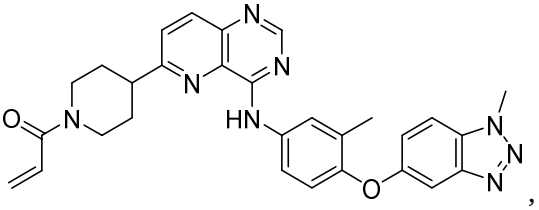
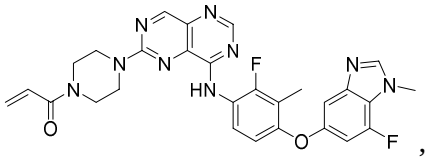
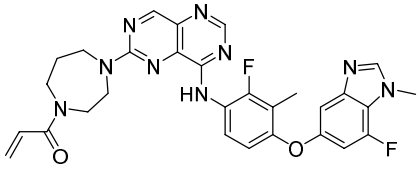
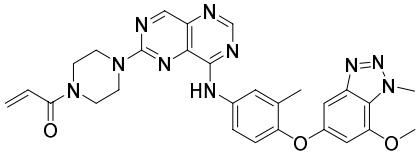
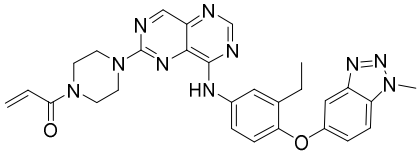
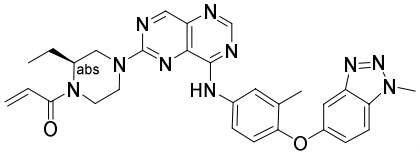
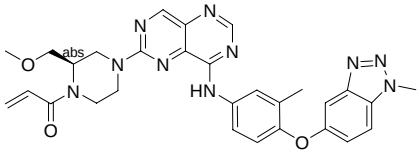
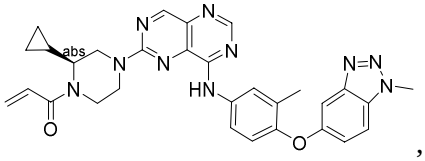
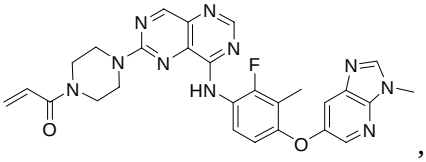
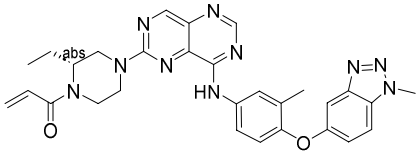
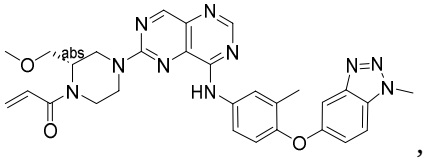
;

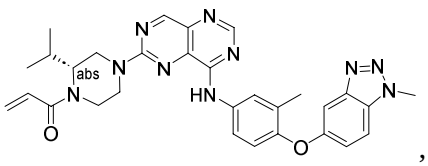
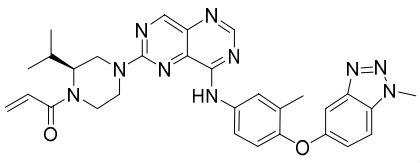
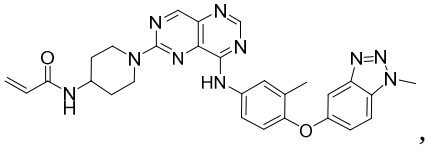
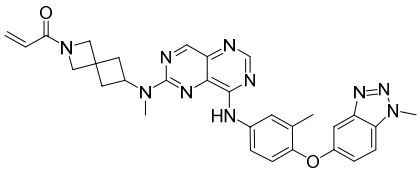
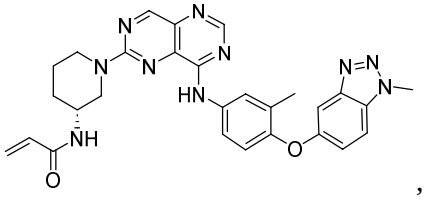
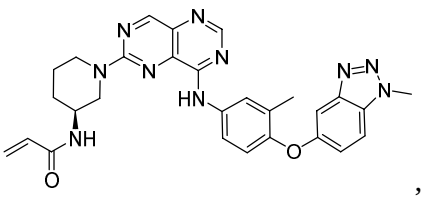
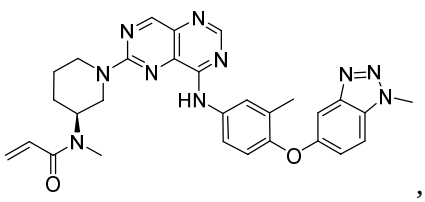
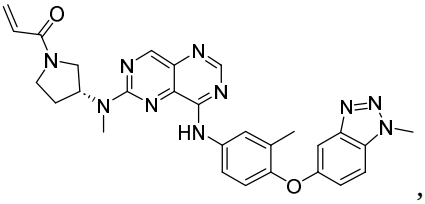
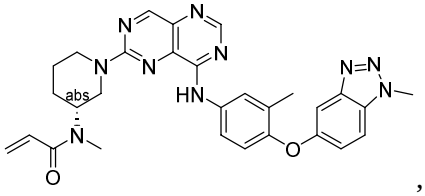
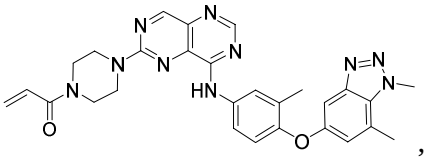
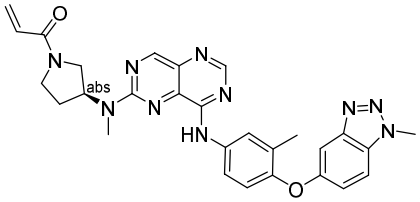
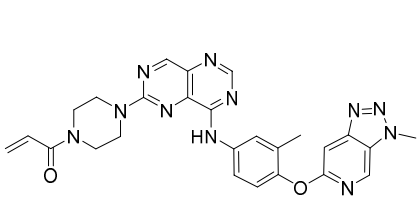
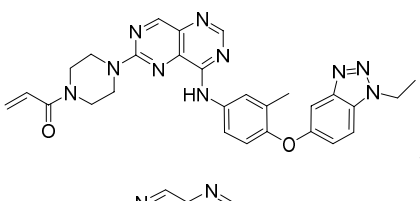
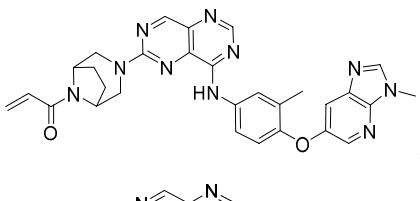
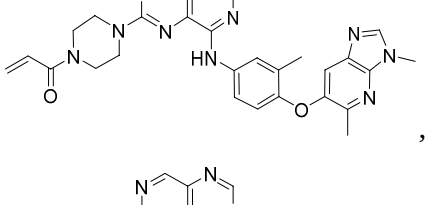
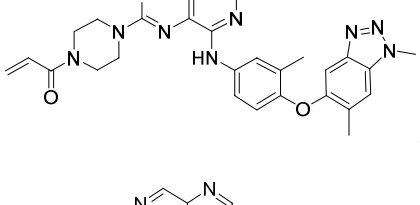
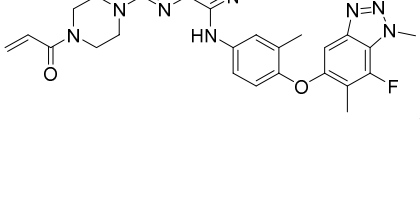
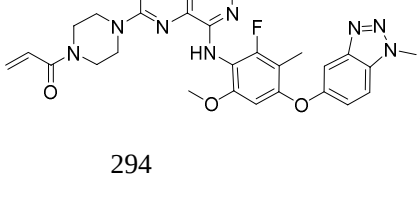

;

;

;

;

;

;

;

;

;

;

;

;

;

;

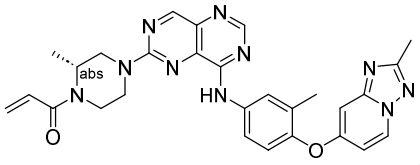
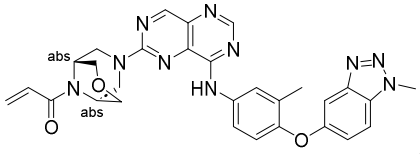
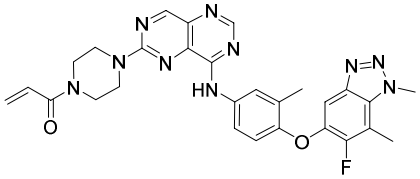
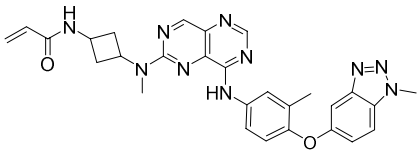
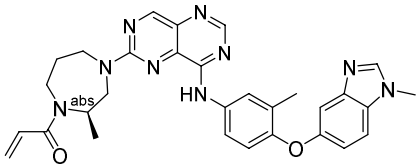
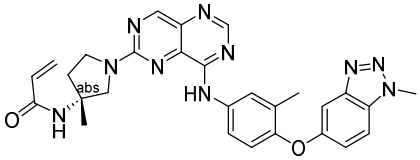
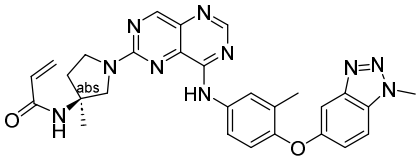
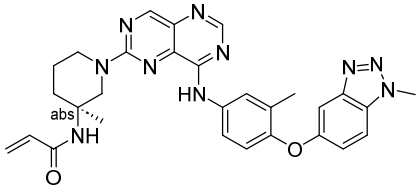
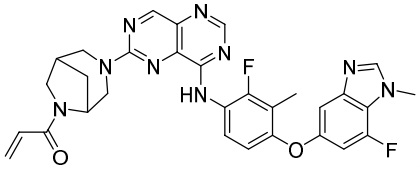
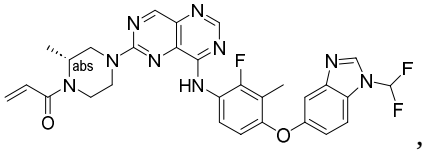
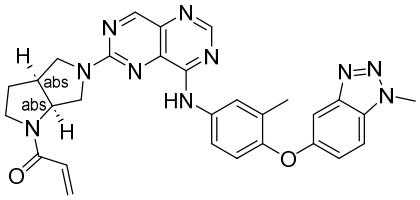
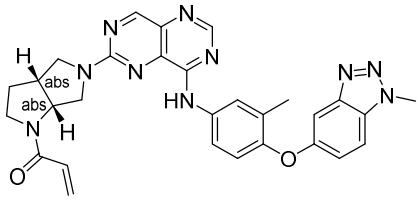
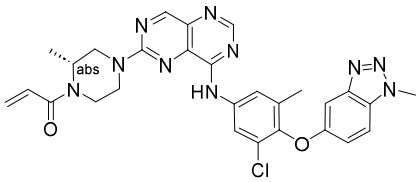
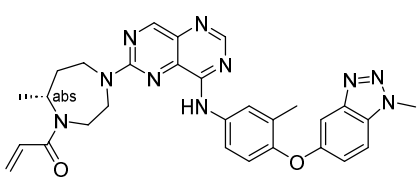

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

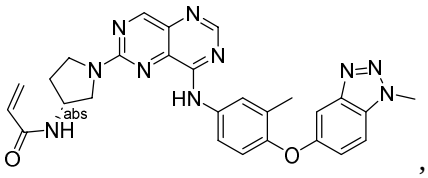
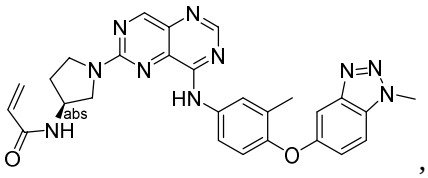
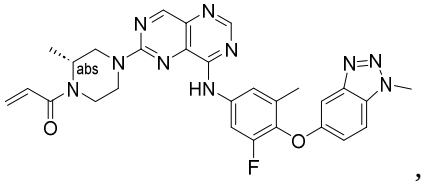
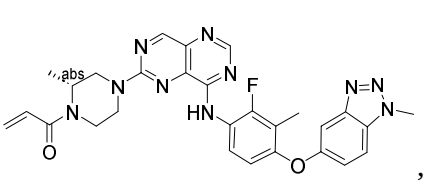
;


;

;

;

;

;

,

,

,

,

,

,

,

,

,

,

,

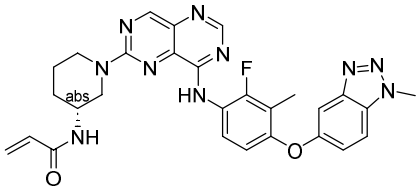
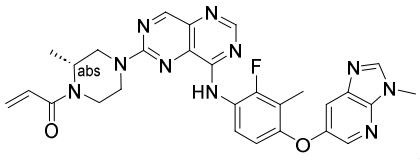
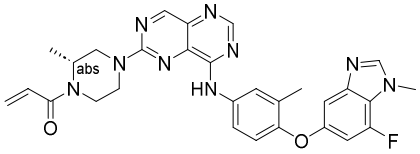
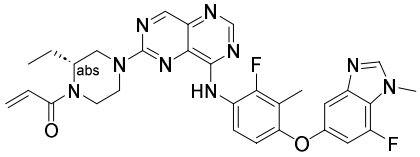
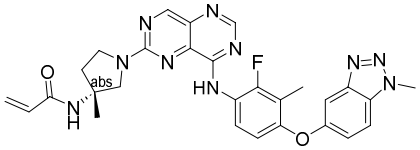
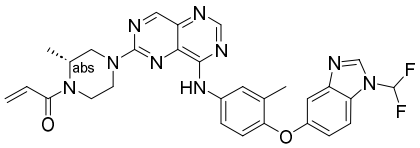
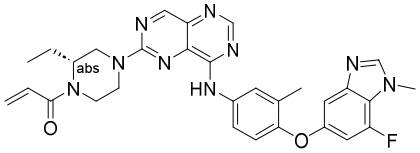
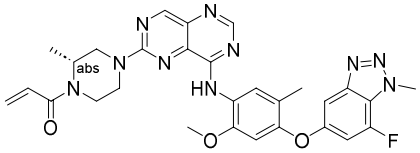
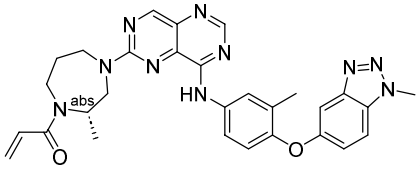
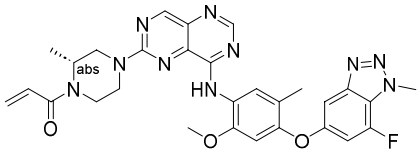
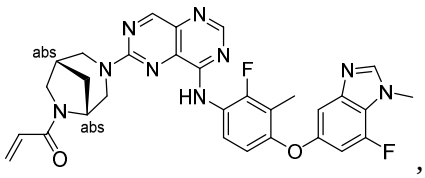
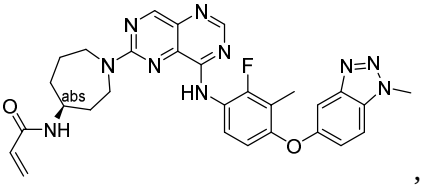
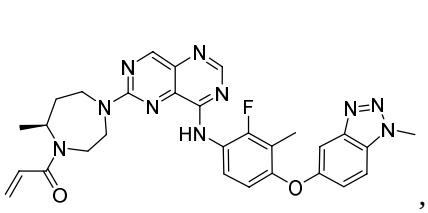
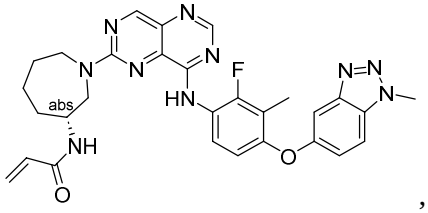
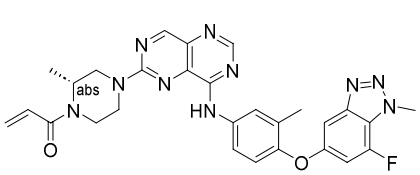
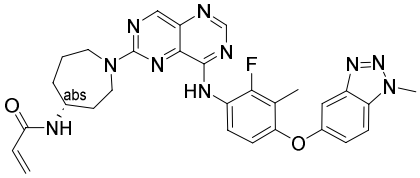
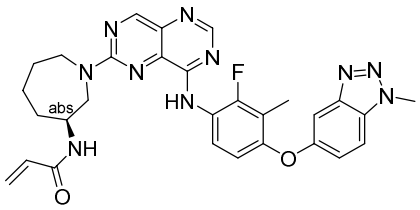
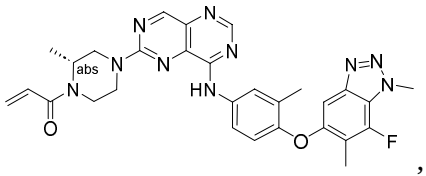

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

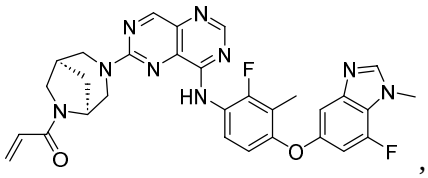
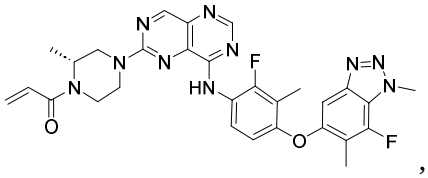
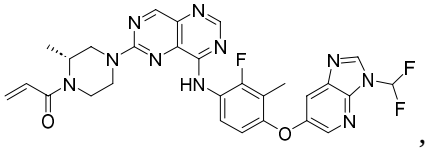
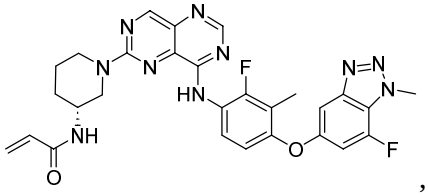
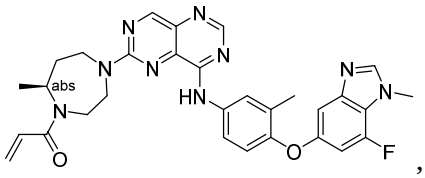
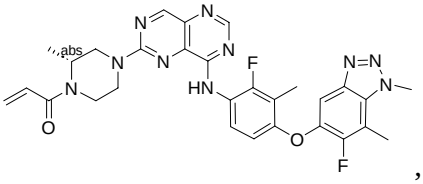
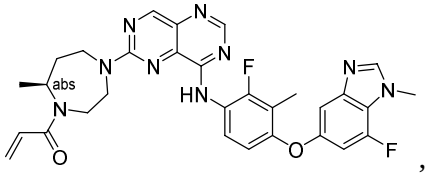
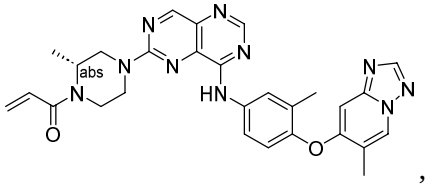
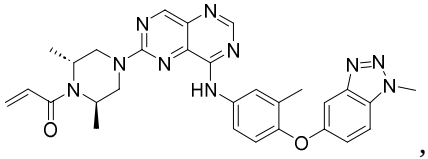
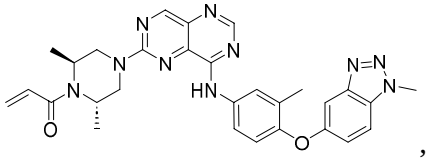
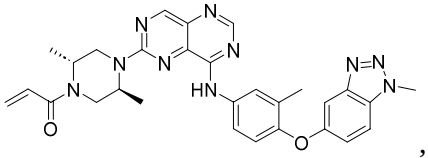
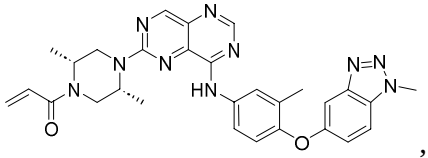
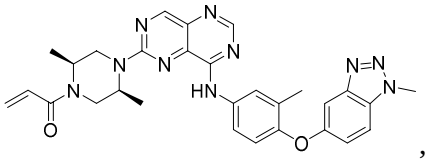
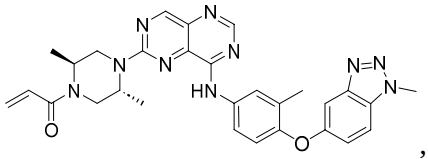
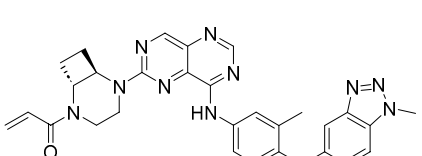
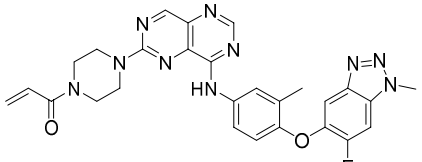
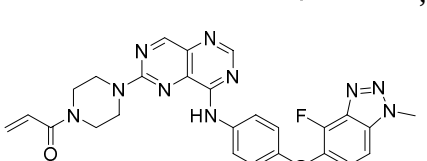
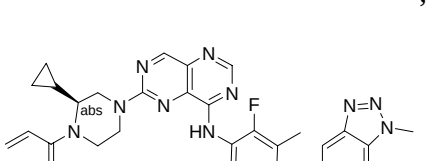
,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

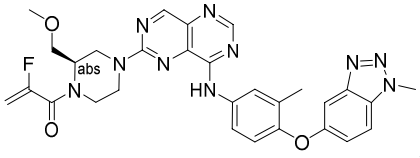
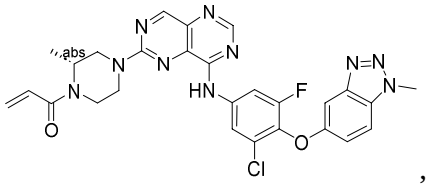
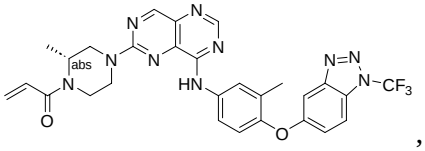
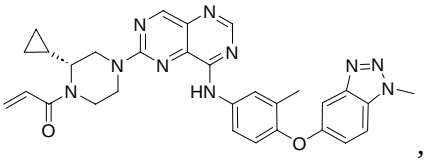
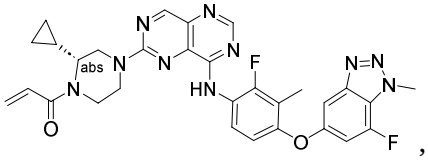
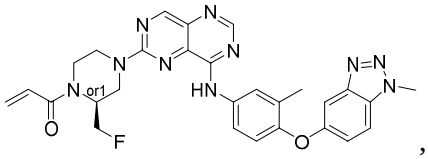
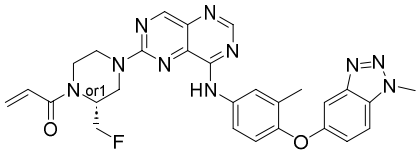
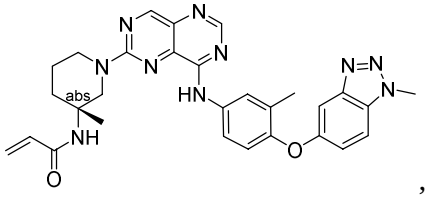
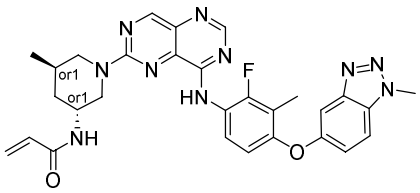
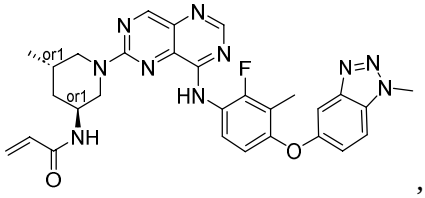
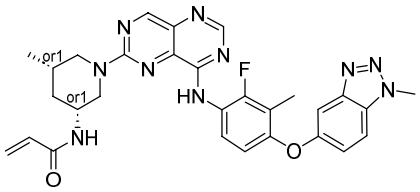
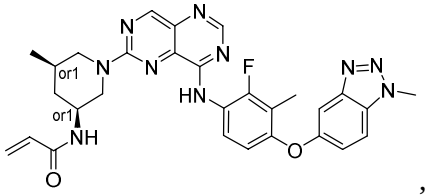
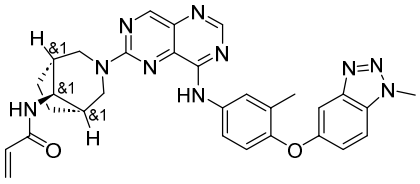
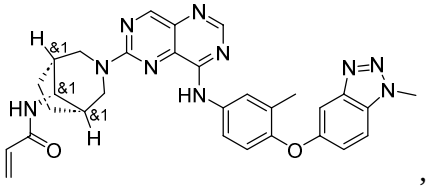
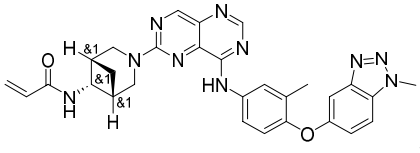
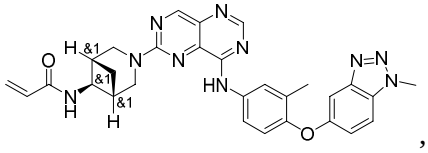
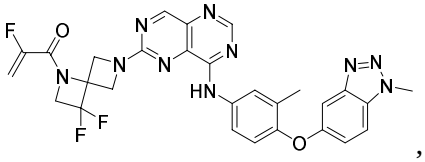
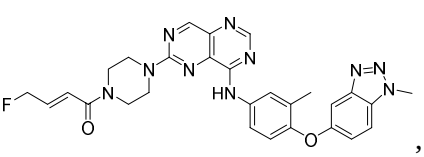
,

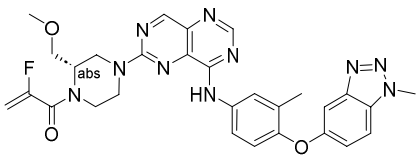
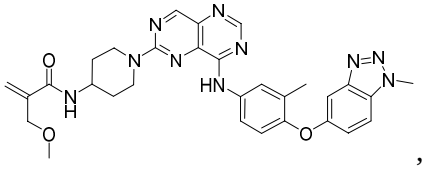
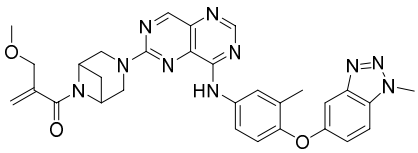
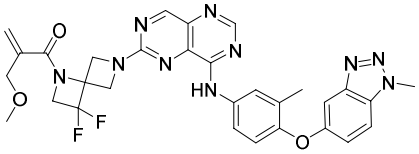
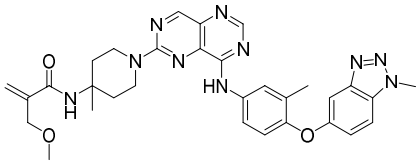
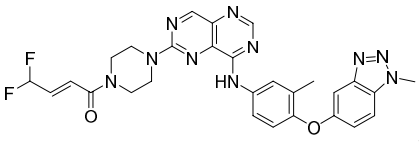
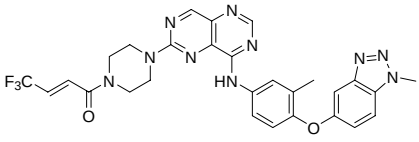
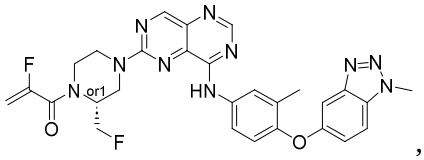
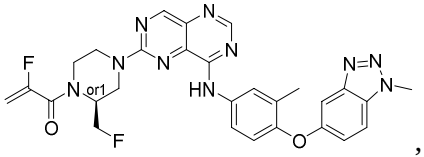
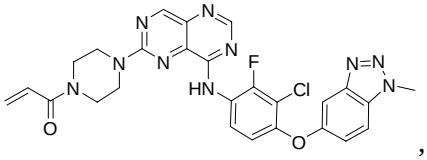
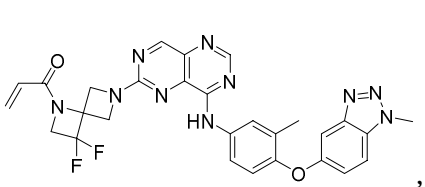
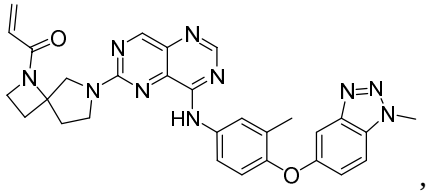
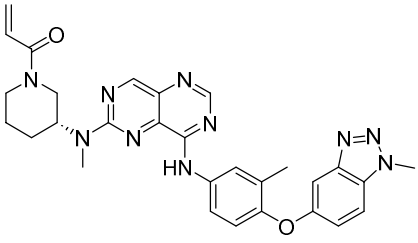
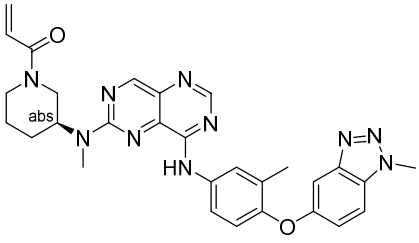
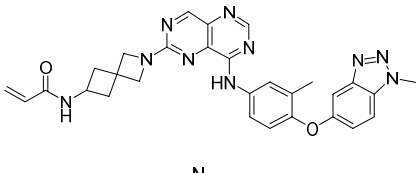
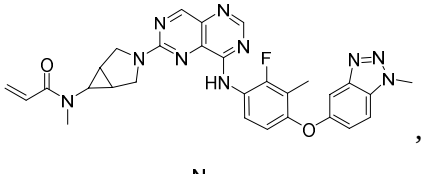
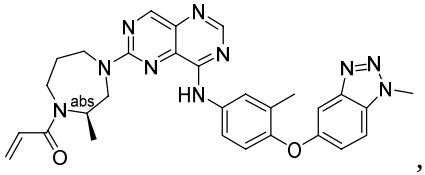
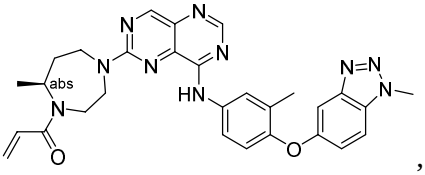
,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

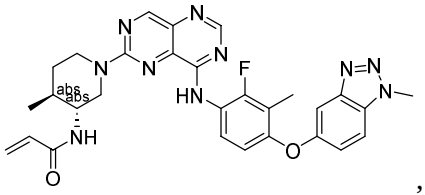
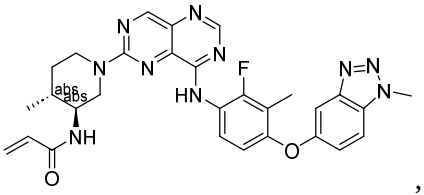
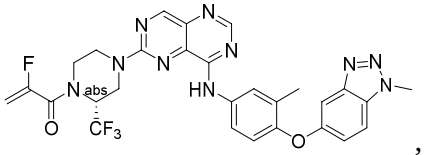
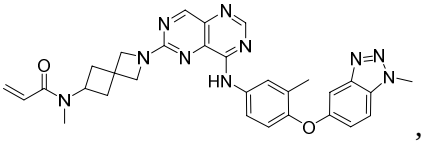
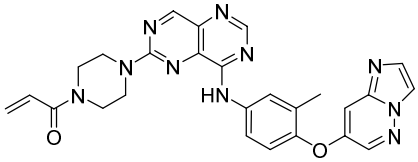
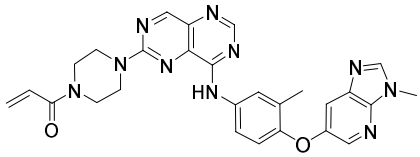
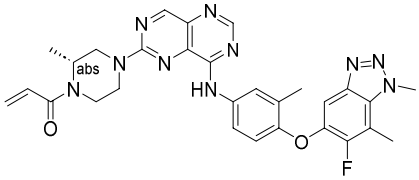
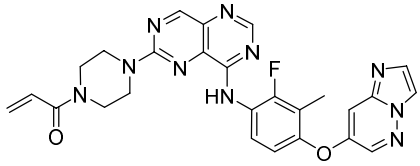
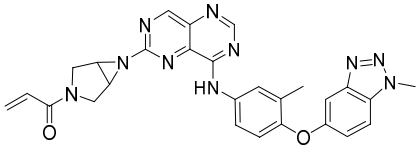
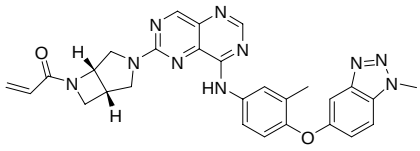
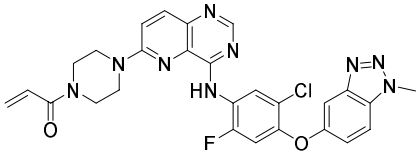
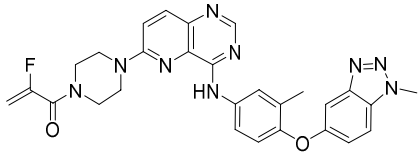
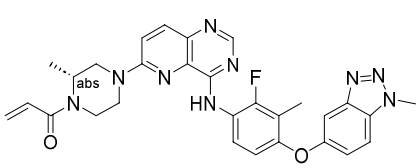
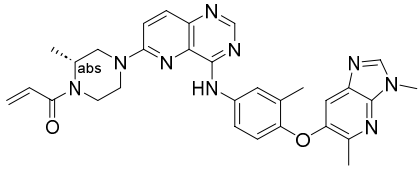
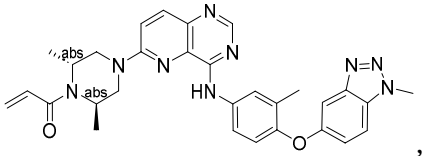
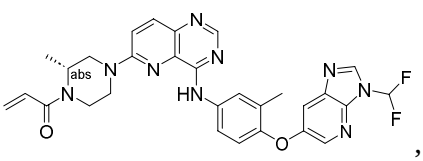
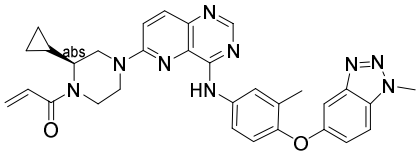
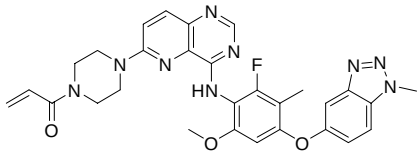
,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

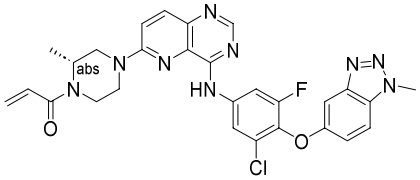
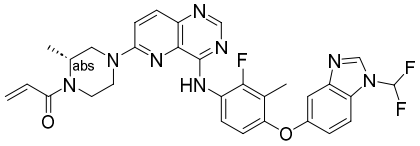
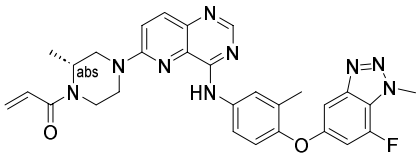
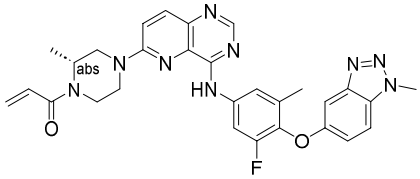
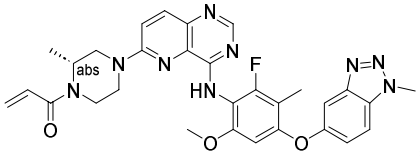
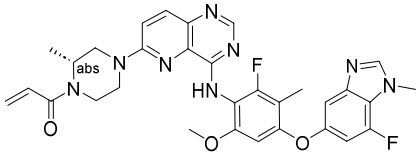
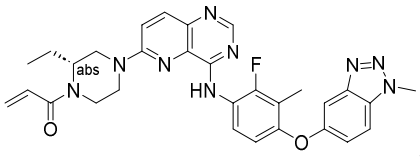
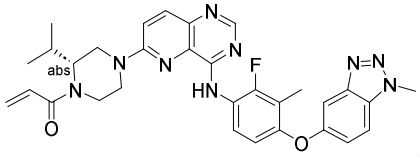
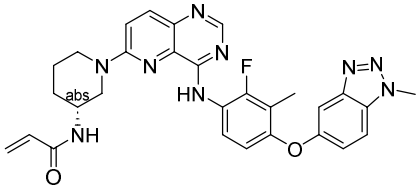
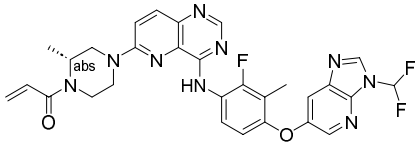
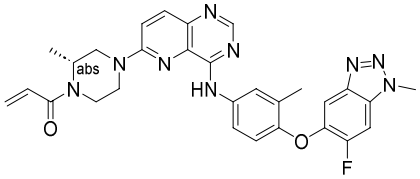
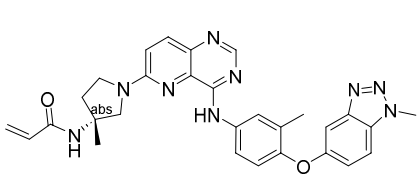
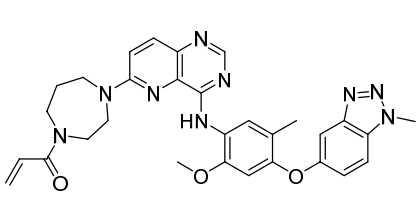
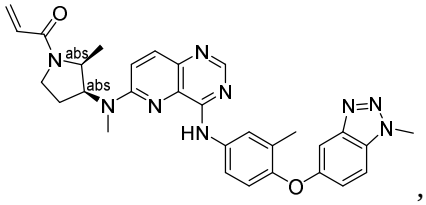
,

,

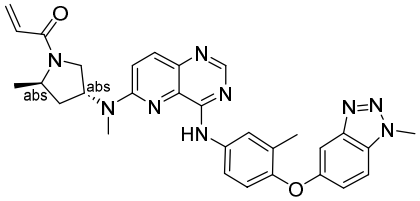
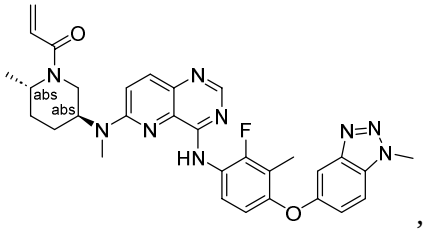

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

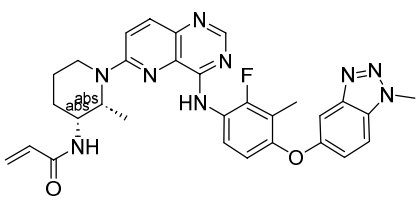
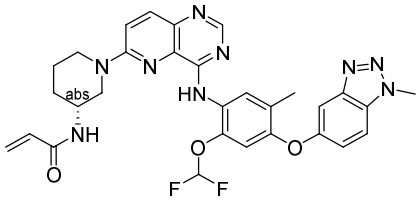
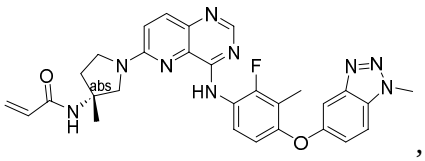
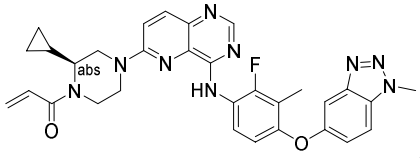
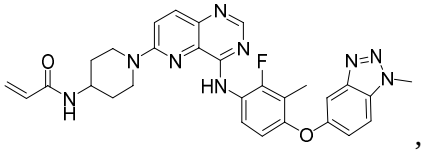
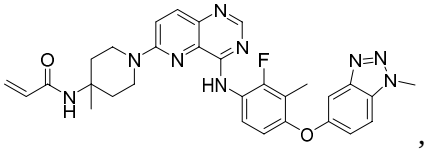
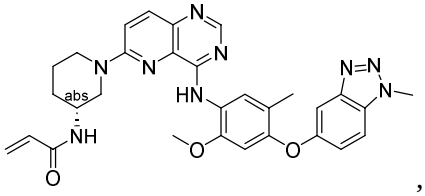
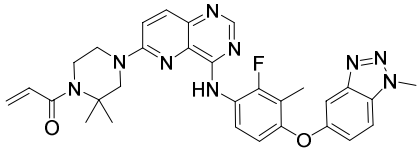
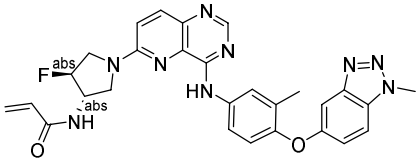
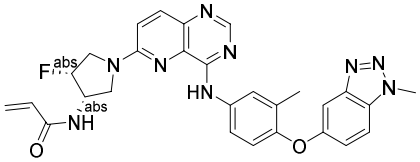
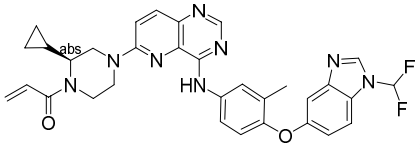
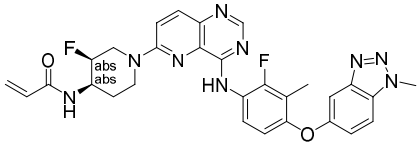
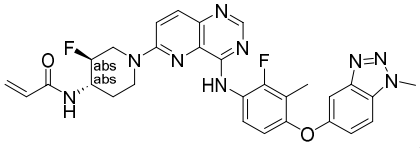
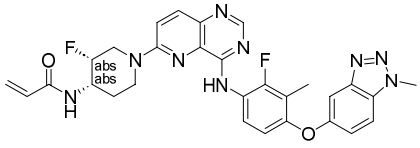
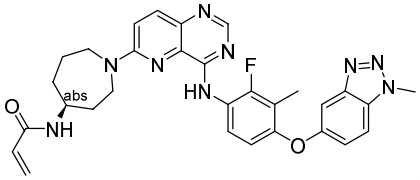
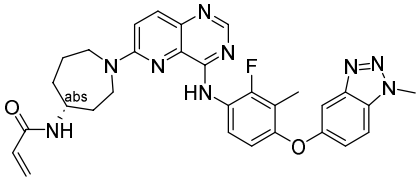
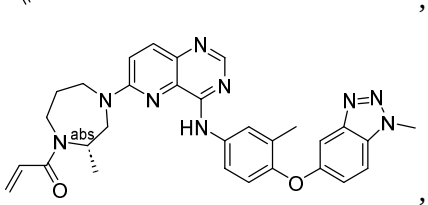
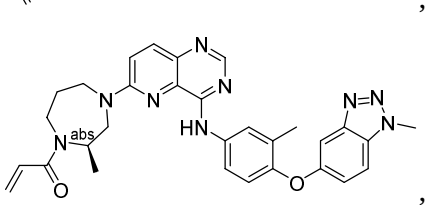
,

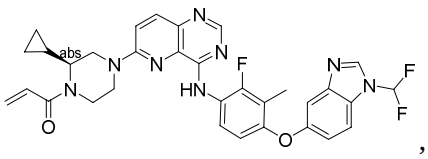
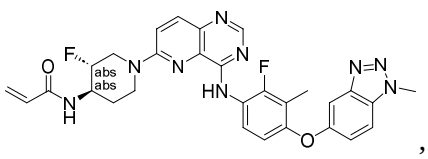
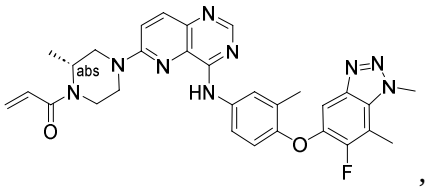
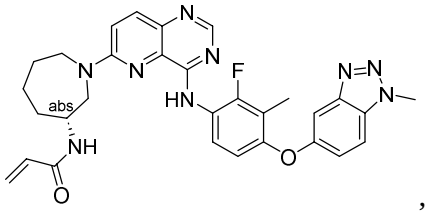
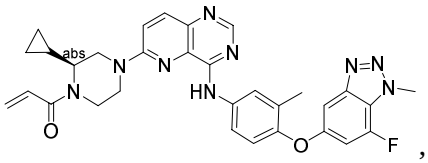
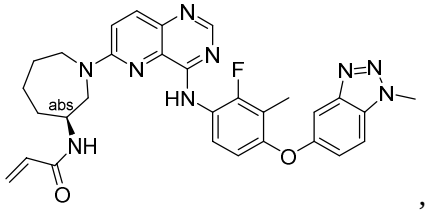
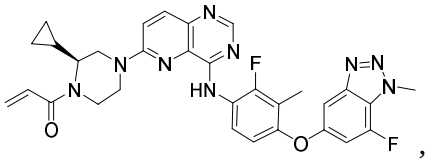
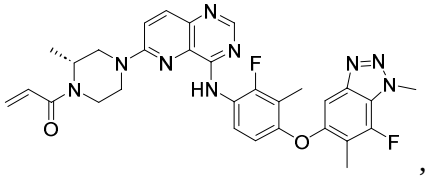
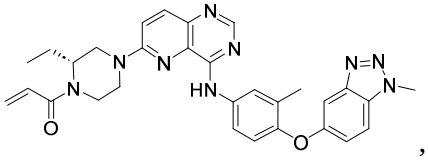
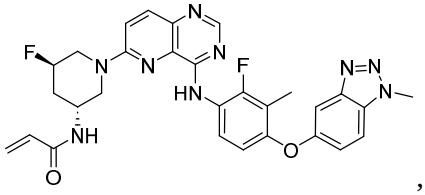
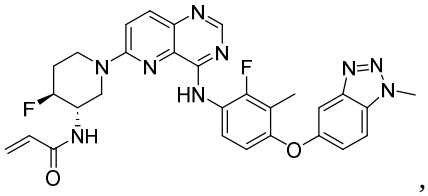
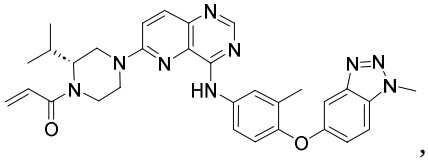
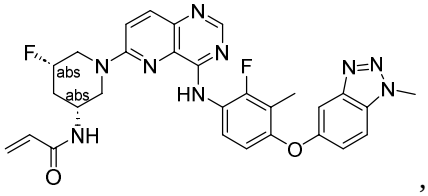
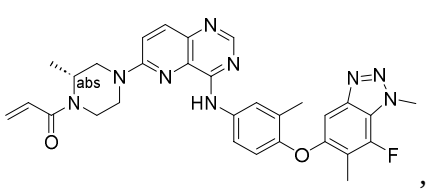
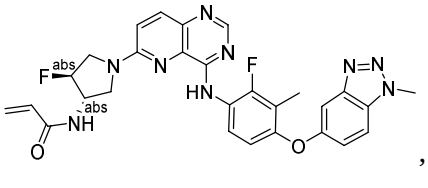
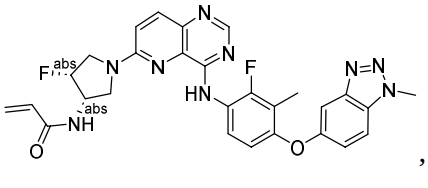
,

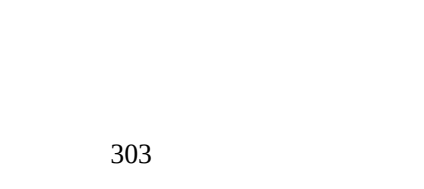

,

,

,

,

,

,

,

,

,

,

,

,

,

,

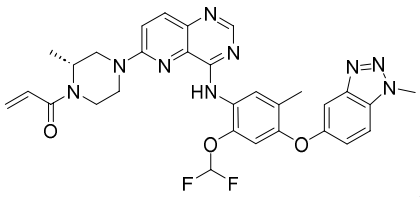
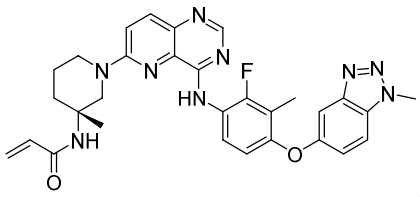
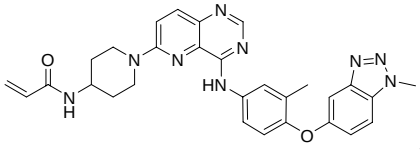
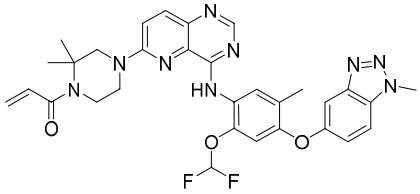
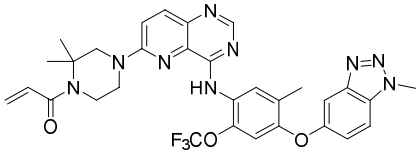
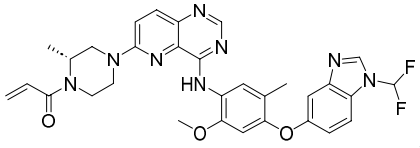
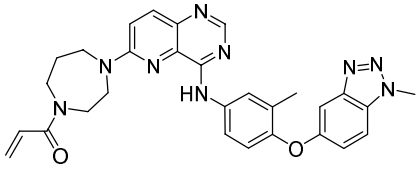
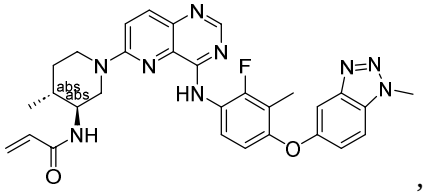
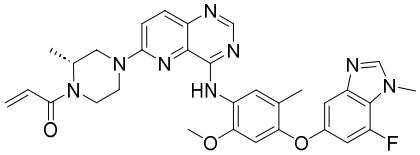
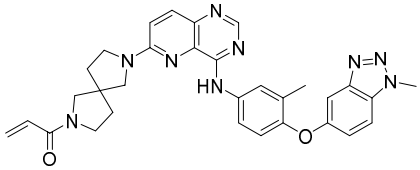
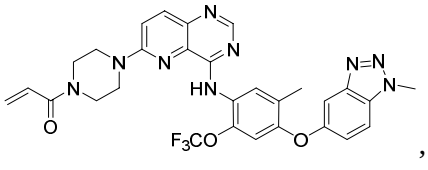
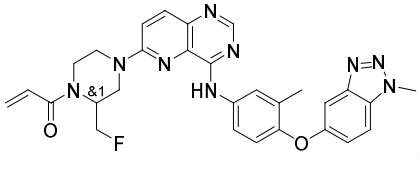
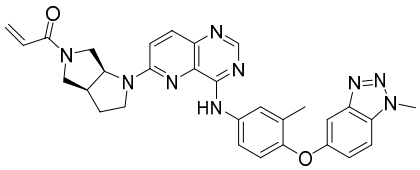
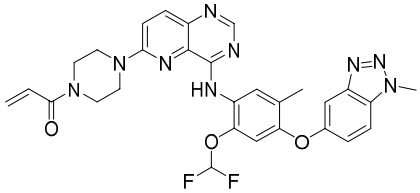
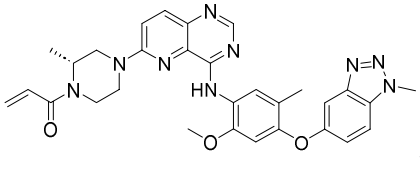
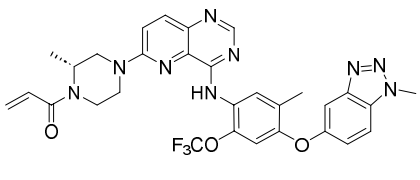
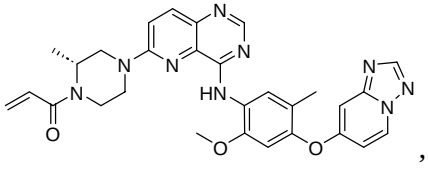
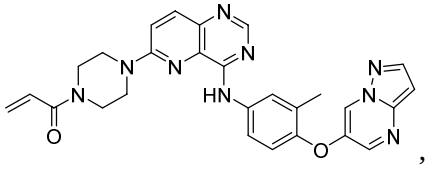
,

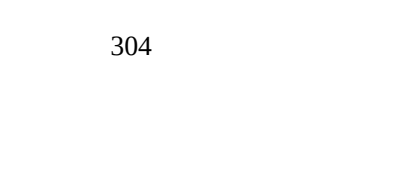
,

,

,

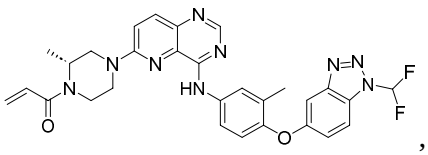
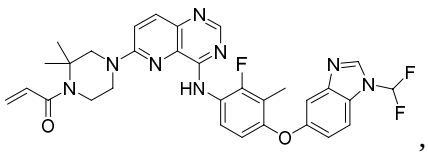
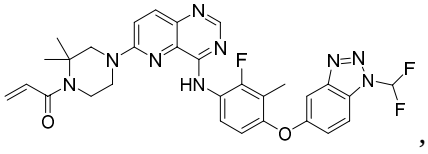
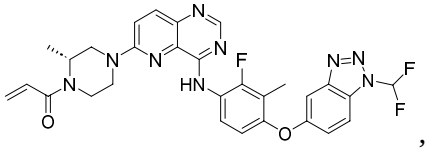
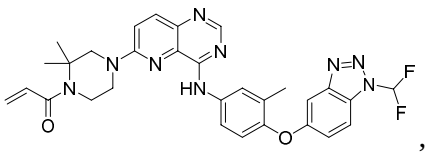
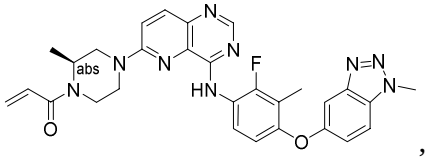
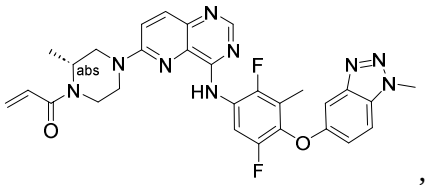
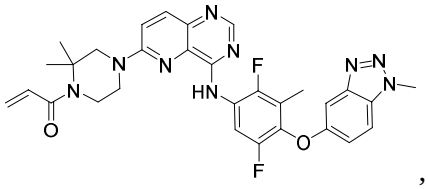
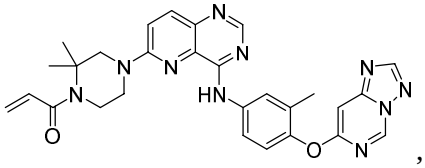
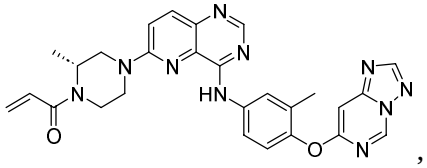
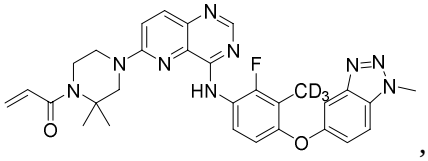
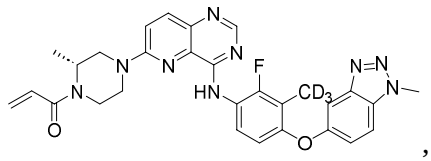
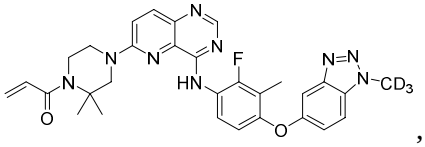
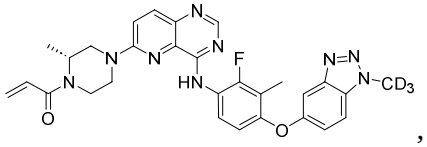
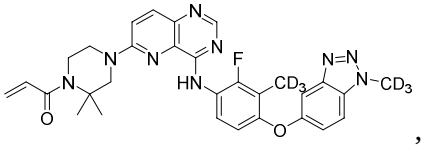
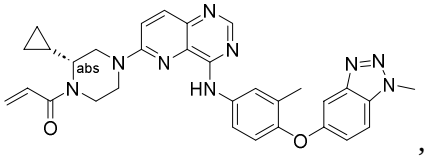
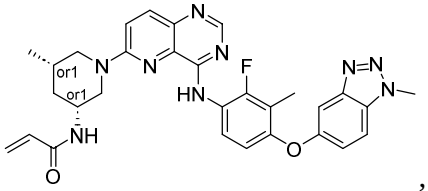
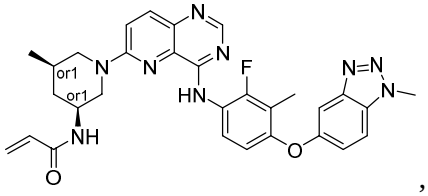

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

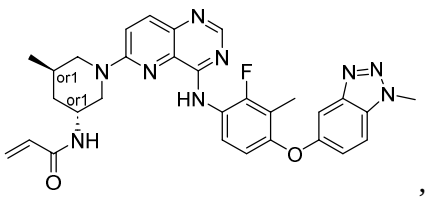
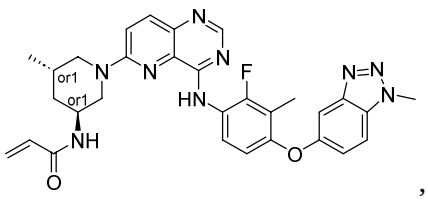
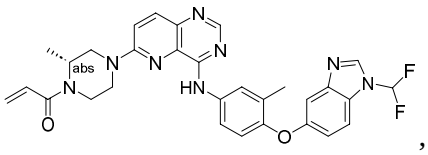
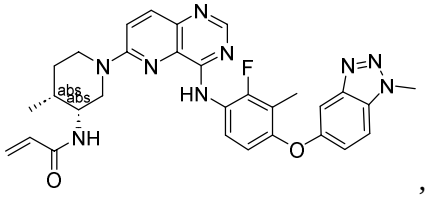
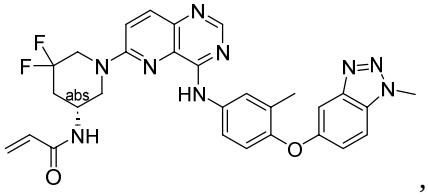
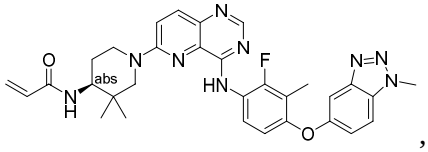
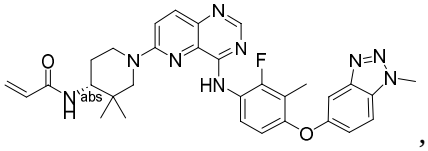
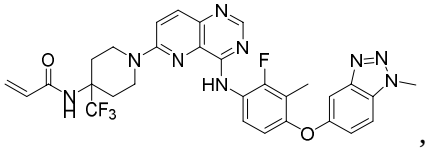
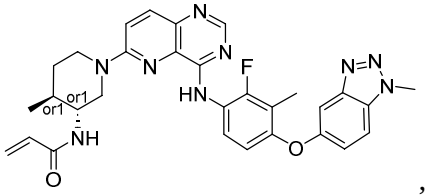
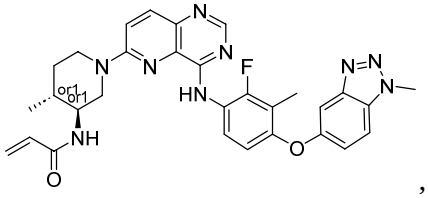
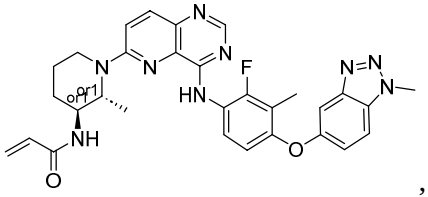
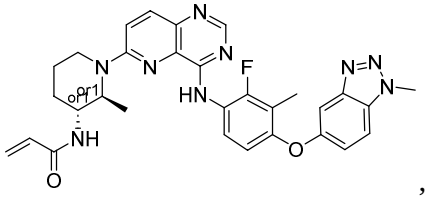
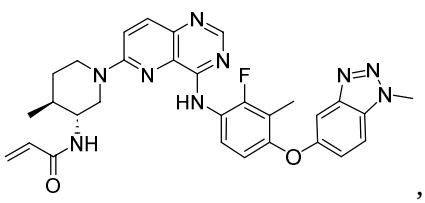
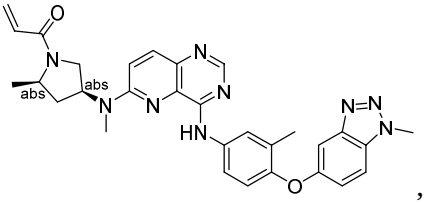
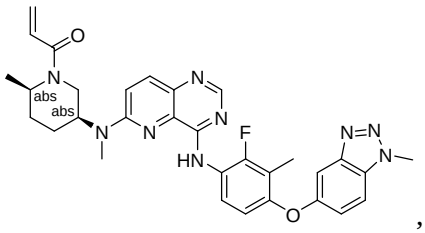
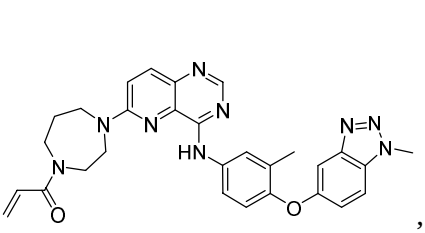

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

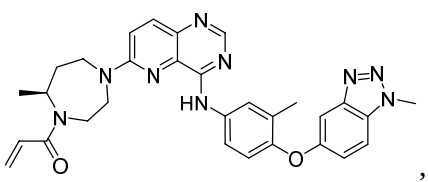
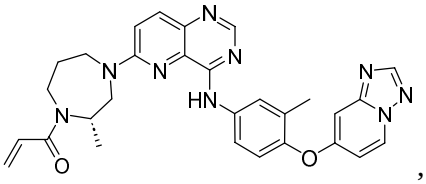
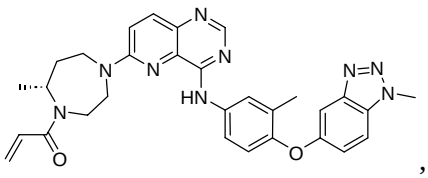
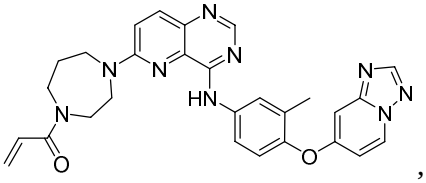
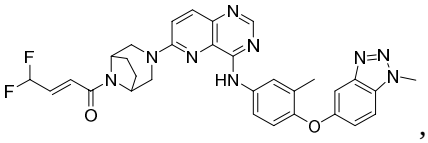
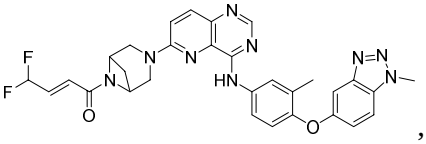
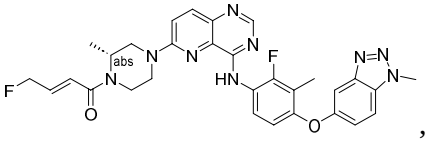
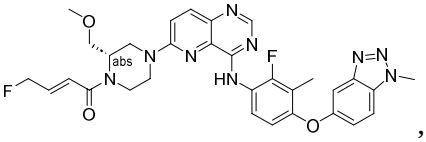
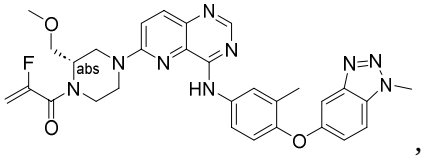
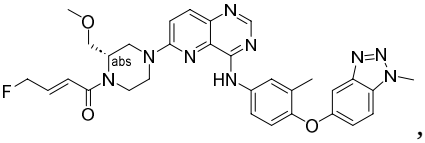
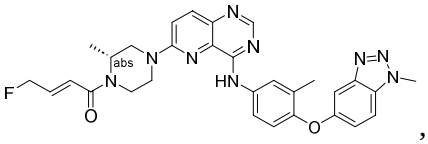
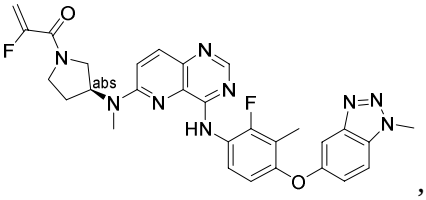
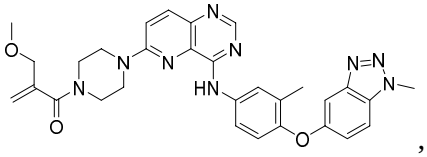
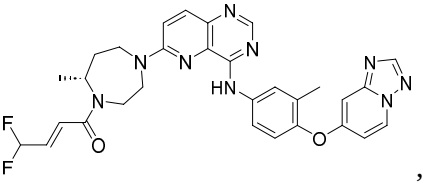
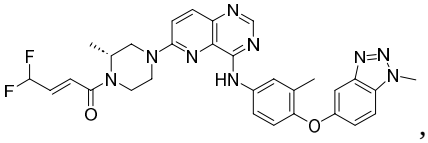
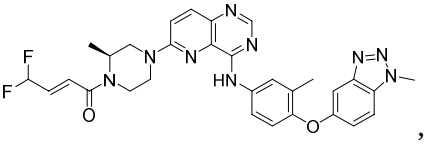
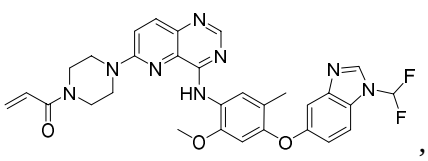
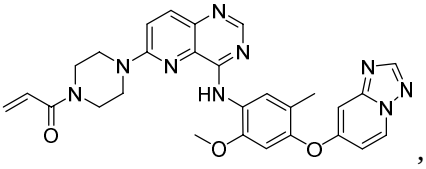
,

,

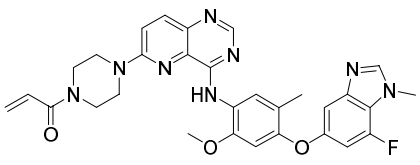
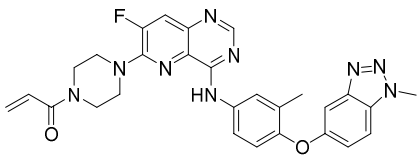
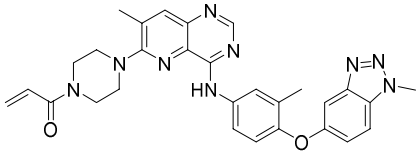
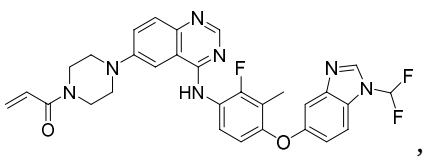
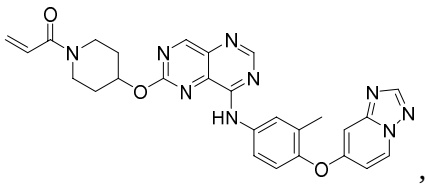
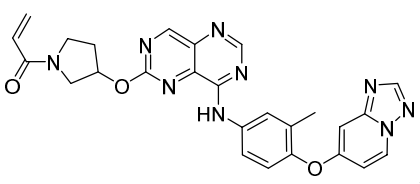
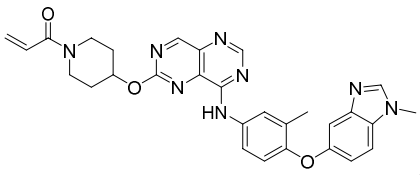
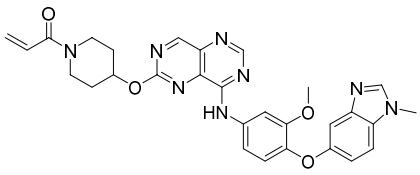
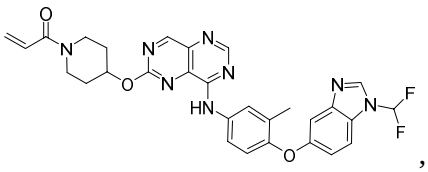
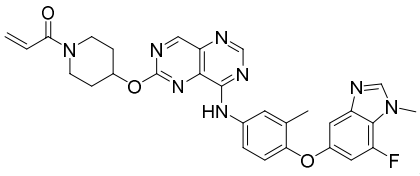
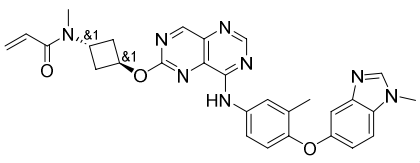
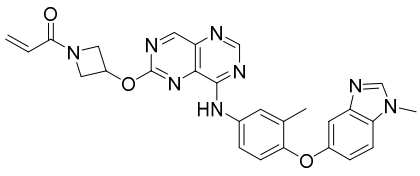
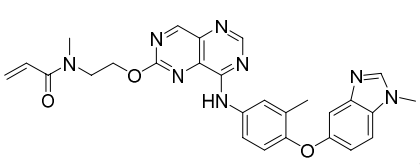
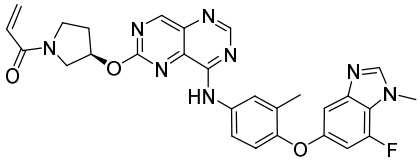
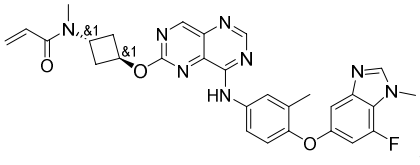
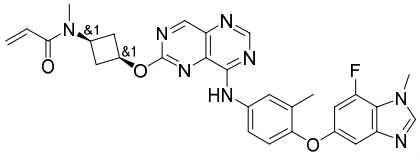
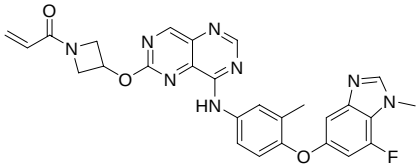
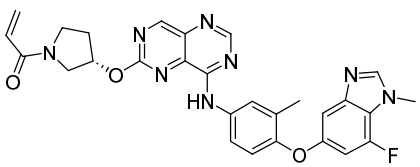

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

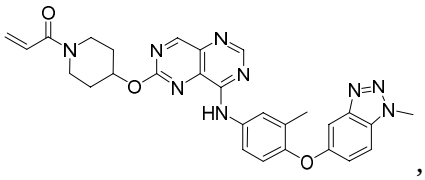
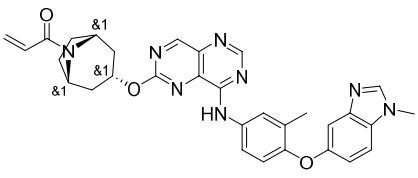
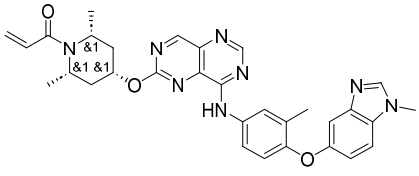
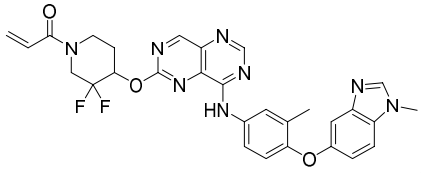
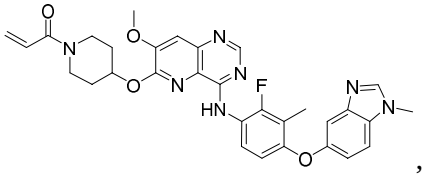
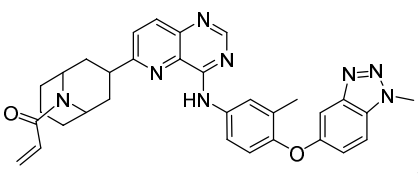
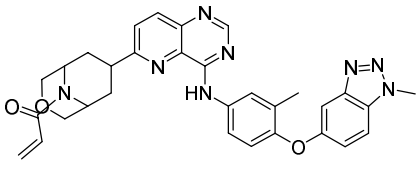
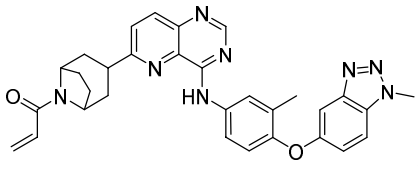
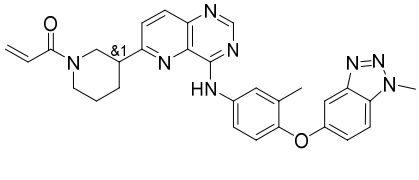
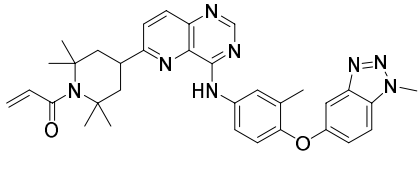
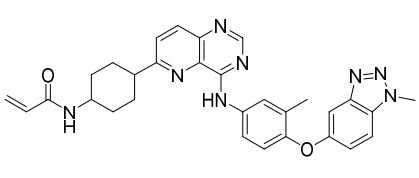
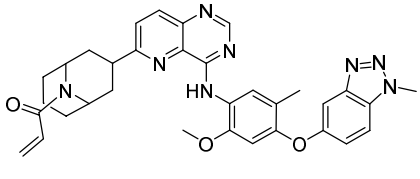
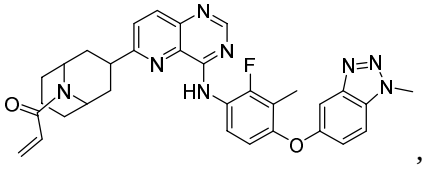
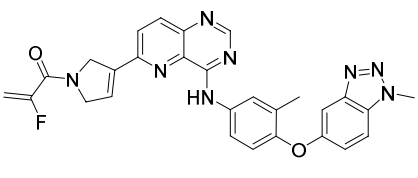
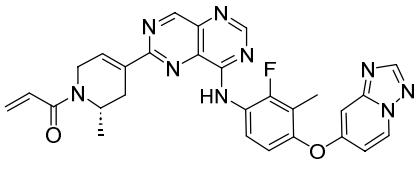
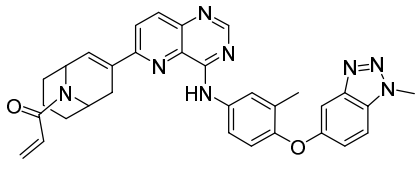
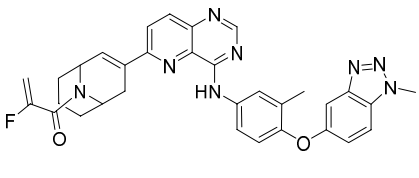
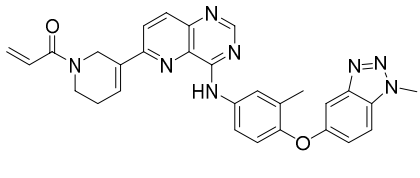
,

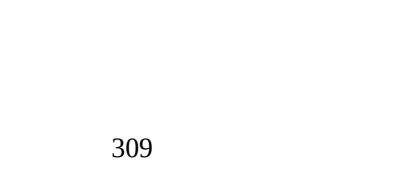

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

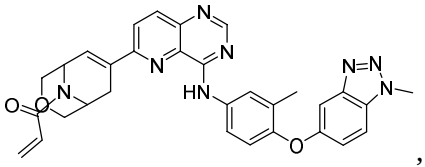
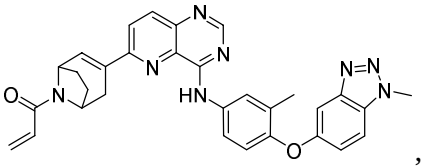
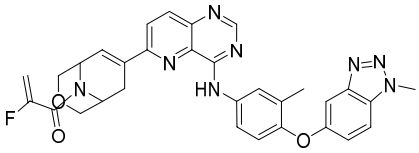
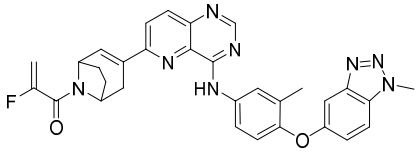
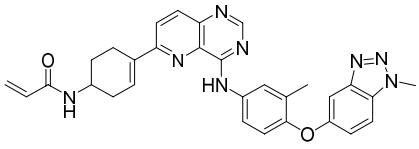
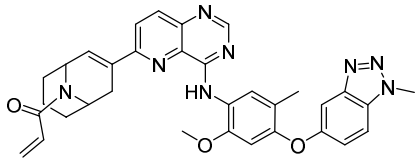
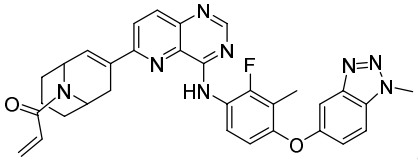

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

, or

.

44. A pharmaceutical composition comprising the compound of claim 1 and an additional therapeutic agent.

45. The compound of any one of claims 1-43 or the pharmaceutical composition of claim 44 for use in treating a disease associated with mutations in a human epidermal growth factor receptor 2 (ErbB2).

46. Use of the compound of any one of claims 1-43 or the pharmaceutical composition of claim 45 in the manufacture of a medicament for treating a disease associated with mutations in ErbB2, wherein said medicament is to be administered to a subject in need thereof.

47. The use of claim 46, wherein the subject is an animal.

48. The use of any one of claims 46-47, wherein the subject is a human.

49. The use of any one of claims 46-48, wherein the disease associated with mutations in ErbB2 is a cancer.

50. The use of any one of claims 46-49, wherein the cancer is lung, glioma, esophageal, liver, stomach, uterine, cervical, biliary tract, skin, head and neck, salivary gland, breast, pancreatic, colorectal, renal, bladder, or prostate cancer.

51. The use of any one of claims 46-50, wherein the cancer is non-small cell lung cancer.