Claims:

1. A method of inhibiting PCSK9, comprising contacting PCSK9 with an inhibitor of PCSK9 that binds to a binding pocket defined by amino acid residues Val589 and Ser636 of human PCSK9.

2. The method of claim 1, wherein the inhibitor is an allosteric inhibitor.

3. The method of claim 1 or 2, wherein the method comprises contacting the surface of a cell that secretes PCSK9 with the inhibitor.

4. The method of claim 1, wherein the method comprises contacting intracellular PCSK9 with the inhibitor .

5. The method of claim 1, wherein the method comprises contacting PCSK9 that is circulating in plasma with the inhibitor.

6. The method of claim 1, wherein the inhibitor comprises an H-bond acceptor/donor group having two H-bond acceptor moieties and one H-bond donor moiety disposed to donate an H-bond to and accept an H-bond from the backbone amide functionality of residue Val589, and accept an H-bond from the hydroxymethyl sidechain of Ser636 of human PCSK9.

7. The method of claim 1, wherein the inhibitor comprises an H-bond acceptor/donor group having two H-bond donor moieties and one H-bond acceptor moiety disposed to donate an H-bond to and accept an H-bond from the backbone amide functionality of residue Val589, and donate an H-bond to the hydroxymethyl sidechain of Ser636 of human PCSK9.

8. The method of any preceding claim, wherein the inhibitor comprises a pyrimidinyl ring and the two H-bond acceptor moieties are the two nitrogen atoms present on the pyrimidinyl ring.

9. The method of claim 8, wherein the inhibitor comprises a 2-NH-pyrimidinyl moiety and the one H-bond donor moiety is the amino hydrogen atom.

10. The method of any preceding claim, wherein the inhibitor further comprises one or more of:

a) an H-bond acceptor moiety disposed to bind with amino acid residues Ser642, His643 or Val 644,

b) an H-bond donor moiety disposed to bind with amino acid residue Ala637 or Thr641, and

c) a cation-pi stacking interaction moiety disposed to bind with amino acid residue Arg495 or His591,

wherein the H-bond acceptor/donor group is bound to amino acid residues Val589 and Ser636 of human PCSK9.

11. The method of any preceding claim, wherein the inhibitor further comprises an H-bond acceptor moiety disposed to bind with amino acid residue Glu612.

12. The method of any preceding claim, wherein the inhibitor interacts with at least one residue in the M2 C-terminal domain and at least one residue in the M3 C-terminal domain.

13. The method of any preceding claim, wherein the inhibitor further interacts with at least one residue in the M1 C-terminal domain.

14. The method of any one of claims 1-11, wherein the inhibitor interacts with at least one residue in the M1 C-terminal domain and at least one residue in the M3 C-terminal domain.

15. The method of any one of claims 1-11, wherein the inhibitor interacts with at least one residue in the M1 C-terminal domain and at least one residue in the M2 C-terminal domain.

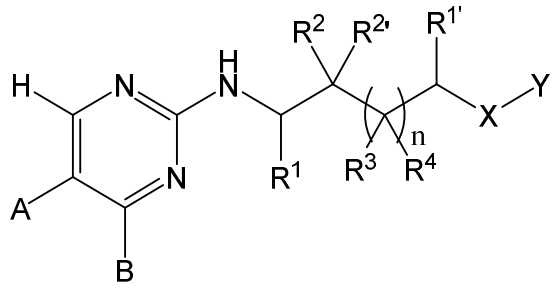
16. The method of any one of claims 1-12, wherein the inhibitor interacts with a pocket in PCSK9 between amino acid residues 558-590 in the M2 C-terminal domain and amino acids residues 631-650 in the M3 C-terminal domain.

17. The method of claim 1, wherein the inhibitor interacts with at least one residue in beta strand 3 and beta strand 5 of the M2 C-terminal domain and beta strand 3 and beta strand 4 of the M3 C-terminal domain.

18. The method of claim 17, wherein the inhibitor interacts with a pocket in PCSK9 created between amino acid residues 558-566 in beta strand 3 of the M2 C-terminal domain and amino acids residues 587-590 in beta strand 5 of the M2 C-terminal domain.

19. The method of claim 18, wherein the inhibitor interacts with a pocket in PCSK9 created between amino acid residues 631-637 in beta strand 3 of the M3 C-terminal domain and amino acids residues 644-650 in beta strand 4 of the M3 C-terminal domain.

20. The method of any preceding claim, wherein the inhibitor is a compound of formula (I):



(I)

wherein:

A is selected from H, halo, hydroxy, alkyl, thioalkyl, alkenyl, alkoxy, acyloxy, cyano, cycloalkyl, -C(O)OR^6, and -C(O)NR^{6}R^7;

B is selected from H, alkyl, and halo, or

A and B are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered heteroaryl;

X is NR^5 or O;

R^1 and R$^{1'}$ are each independently selected from H and alkyl; or

if n is 0, R^1 and R$^{1'}$, together with the atoms to which they are attached, form a 4-8 membered cycloalkyl or cycloalkenyl ring;

R^2 is selected from H, halo, alkyl, alkoxy, amidoalkyl, aminoalkyl, hydroxyalkyl, alkylamino, cyano, and hydroxy; or

R^1 and R^2, together with the atoms to which they are attached, form a 3-8 membered cycloalkyl or heterocyclyl ring; or

R$^{1'}$ and R^2, together with the atoms to which they are attached, form a 3-8 membered cycloalkyl or heterocyclyl ring;

R$^{2'}$ is selected from H, halo, alkyl, alkoxy, amidoalkyl, aminoalkyl, and cyano, or

R^2 and R$^{2'}$, taken together with the carbon atom to which they are attached, form a 3- to 8-membered cycloalkyl or heterocyclyl ring;

each R^3 and R^4 is independently H or alkyl; or

R^2 and R^3, together with the atoms to which they are attached, form a 3-8 membered cycloalkyl or heterocyclyl ring; and

R^5 is H or alkyl; or

R^1 and R^5, together with the atoms to which they are attached, form a 6-8 membered cycloalkyl or heterocyclyl ring; or

R^2 and R^5, together with the atoms to which they are attached, form a 5-8 membered cycloalkyl or heterocyclyl ring;

each R^6 and R^7 is independently H or alkyl;

Y is selected from aryl, heteroaryl and heterocyclyl;

and

n is 0 or 1.

21. The method of claim 20 wherein A is selected from H, hydroxy, thioalkyl, alkyl, alkoxy, acyloxy, cyano, cycloalkyl, $-C(O)OR^6$, and $-C(O)NR^6R^7$.

22. The method of claim 20, wherein A is alkoxy.

23. The method of claim 20, wherein A is cycloalkyl.

24. The method of any one of claims 20-23, wherein B is H.

25. The method of any one of claims 20-24, wherein X is NR^5.

26. The method of any one of claims 20-25, wherein Y is heteroaryl or heterocyclyl.

27. The method of any one of claims 20-26, wherein n is 0, and R^1 and $R^{1'}$, together with the atoms to which they are attached, form a 4- to 8-membered monocyclic or bicyclic cycloalkyl or cycloalkenyl ring which is unsubstituted or substituted, e.g., with one or more hydroxy.

28. The method of claim 27, wherein R^1 and $R^{1'}$, together with the atoms to which they are attached, form a 4- to 8-membered monocyclic or bicyclic cycloalkyl.

29. The method of claim 27, wherein the cycloalkyl ring is a cyclopentyl ring.

30. The method of any one of claims 20-29, wherein R^2 is selected from H, halo, alkyl, alkoxy, amidoalkyl, aminoalkyl, alkylamino, cyano, and hydroxyl.

31. The method of any one of claims 20-30, wherein $R^{2'}$ is H.

32. The method of any one of claims 20-31, wherein Y is monocyclic heteroaryl.

33. The method of claim 32, wherein Y is selected from pyridyl, pyridinyl, pyrazinyl, pyrimidinyl, and thiazolyl.

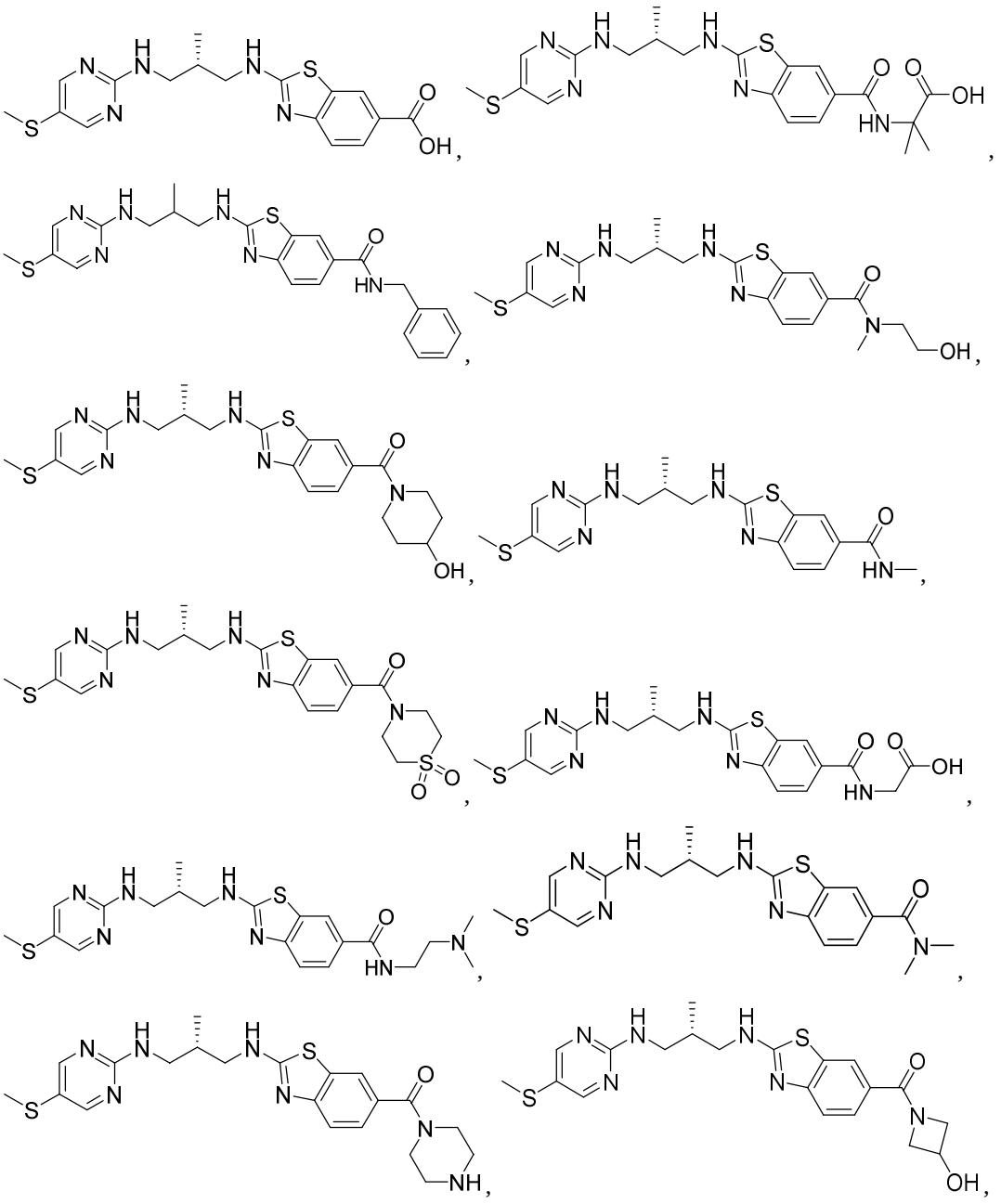
34. The method of claim 32, wherein Y is selected from triazenyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, and triazolyl.

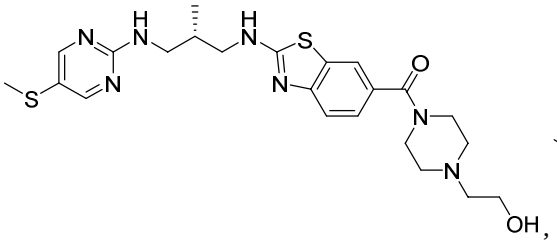
35. The method of any one of claims 32-34, wherein the monocyclic heteroaryl is unsubstituted or substituted with one or more substituents selected from alkyl, thioalkyl, alkoxy, alkoxycarbonyl, amido, carboxy, cyano, halo, aryl, heteroaryl, heterocyclyl, nitro, sulfonamido, and thioalkyl.

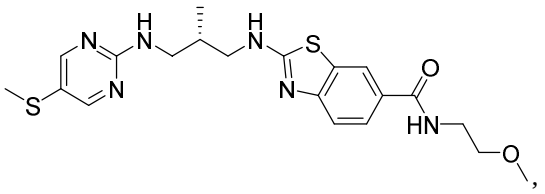
36. The method of claim 35, wherein the monocyclic heteroaryl is substituted with a 6-membered aryl, heteroaryl or heterocyclyl selected from phenyl, pyridinyl, 2-hydroxypyridinyl, piperidinonyl, 2-hydroxy-1-methylpyridinyl, triazolyl, imidazolidinonyl, pyrimidonyl, 2-hydroxyisoquinolinyl, 3-hydroxypyridazinyl, pyrrolidinonyl, pyrazolyl, and morpholinonyl.

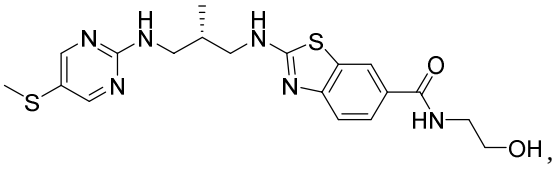
37. The method of claim 36, wherein the monocyclic heteroaryl is substituted with an heteroaryl or heterocyclyl that is substituted with one or more substituents selected from halo, CN, alkyl, alkoxy, hydroxy, carboxy, -CO_2alkyl, and tetrazolyl.

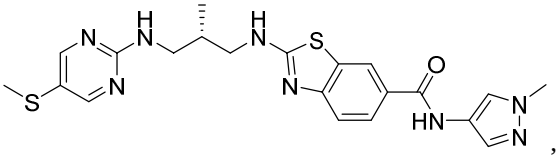
38. The method of claim 20, wherein the inhibitor is selected from

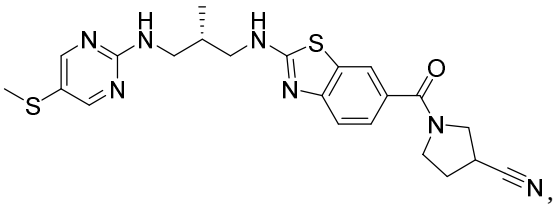


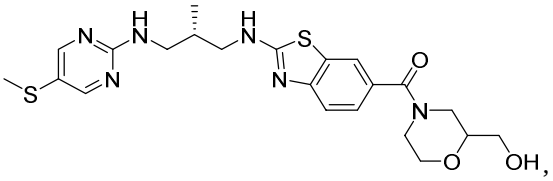


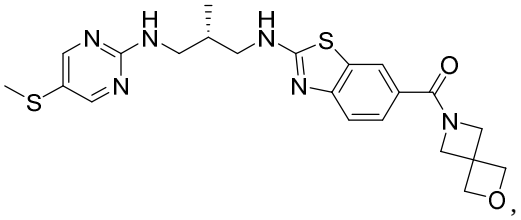


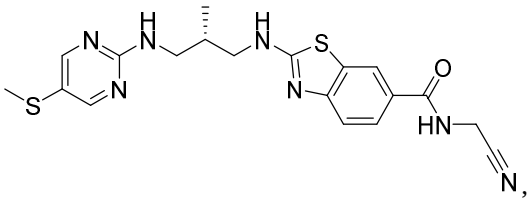


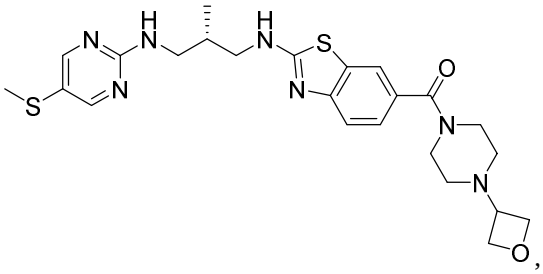


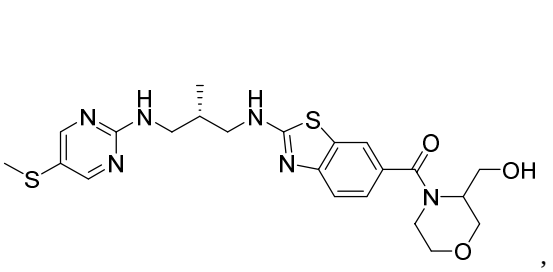


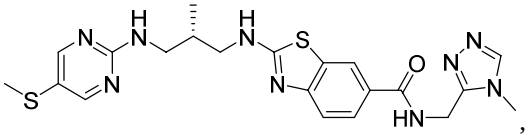


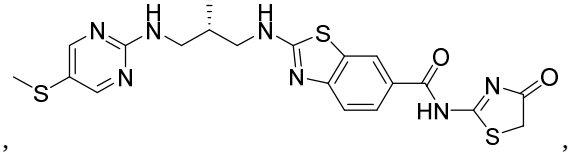


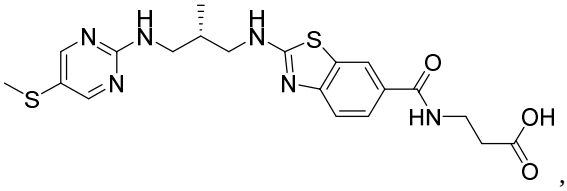


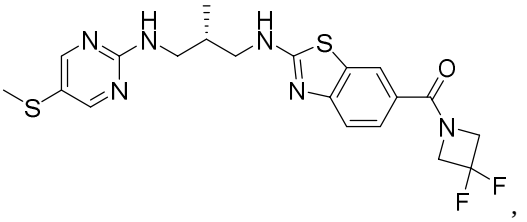


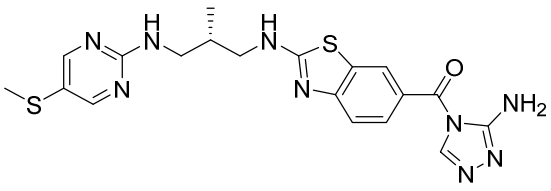
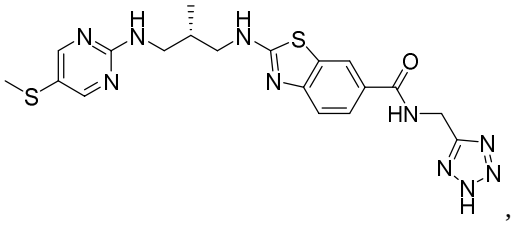
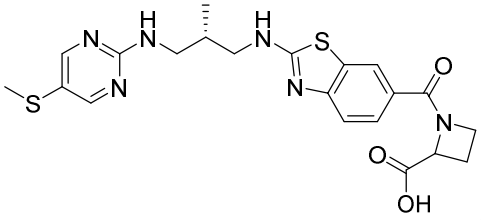
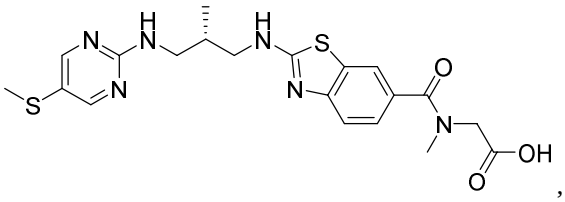
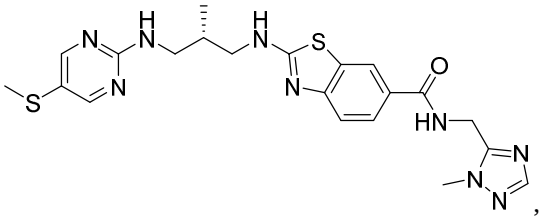
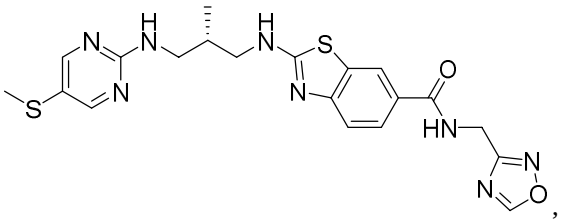
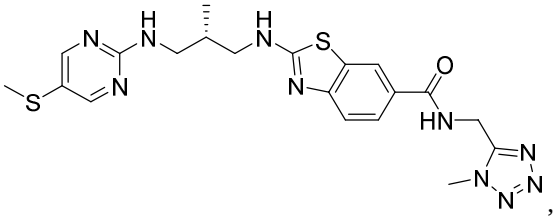
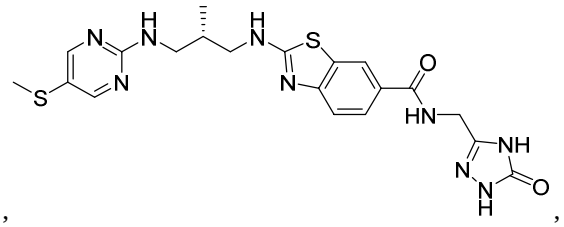
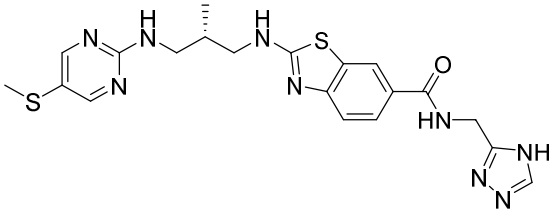
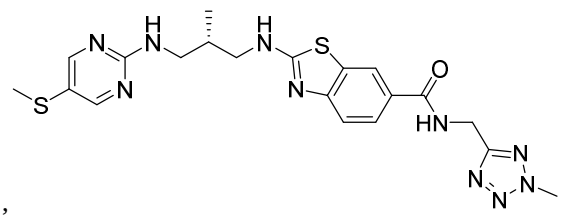




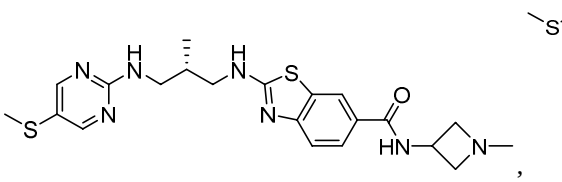
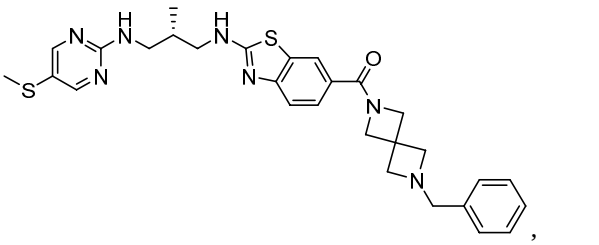






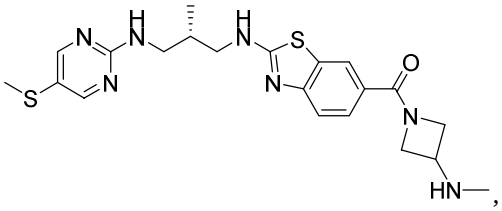
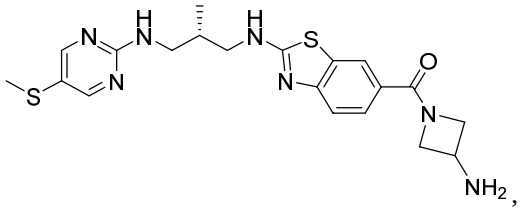
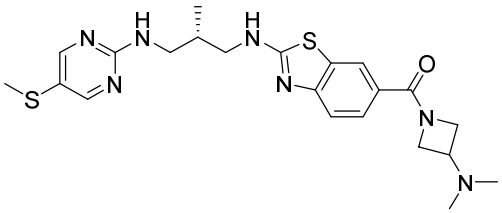

,

,

,

,

,

,

,

,

,

,

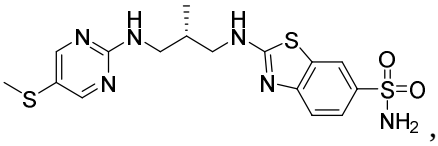
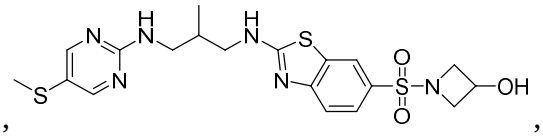
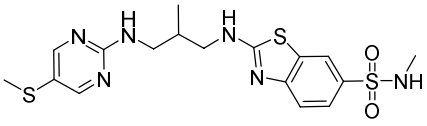
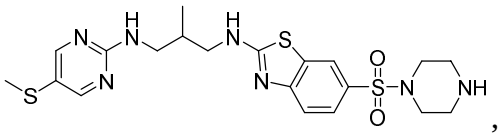
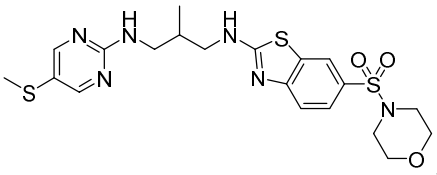
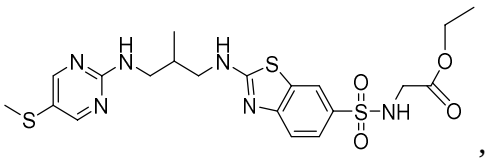
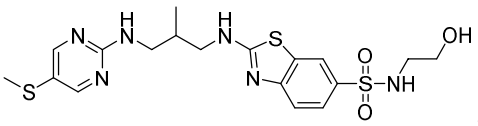
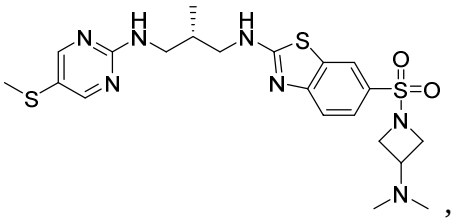
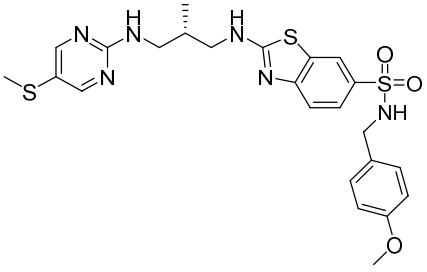
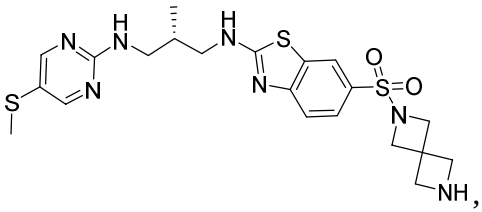
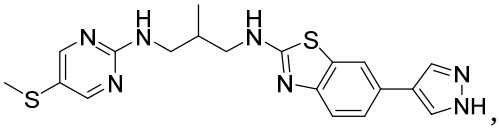
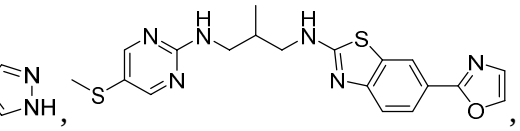
,

,

,

,

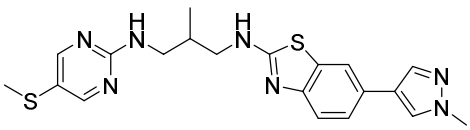
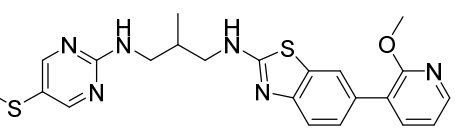
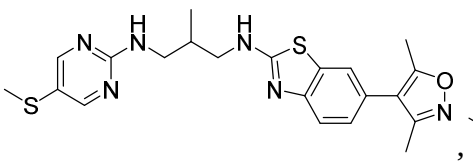
,

,


,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

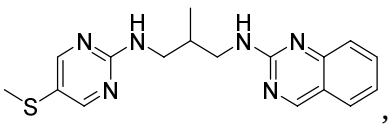
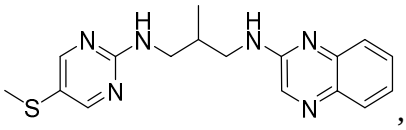
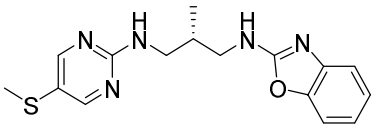
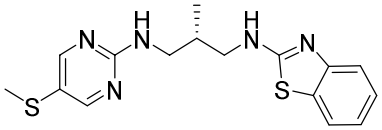
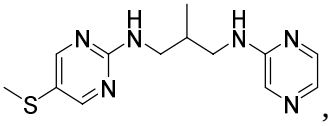
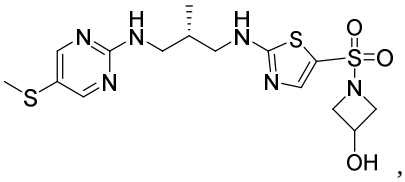
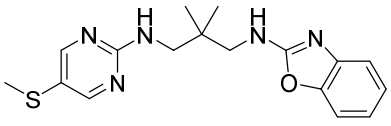
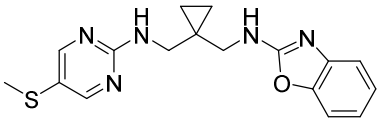
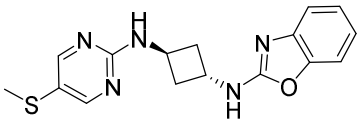
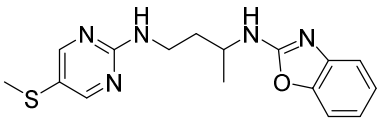
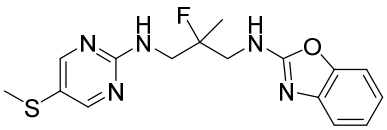
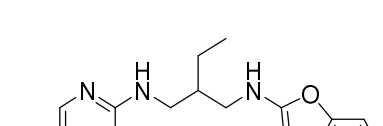
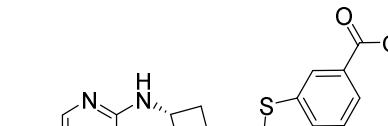
,

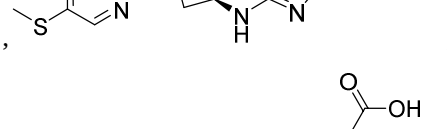
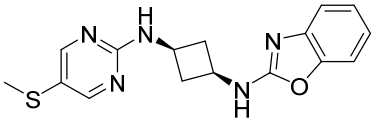
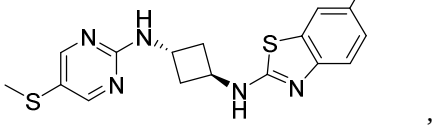
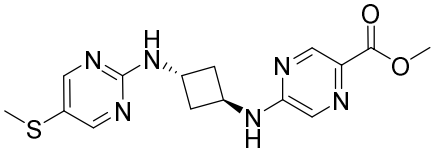
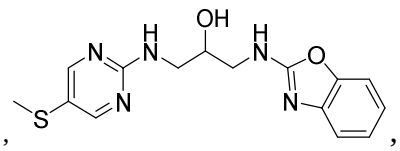
,

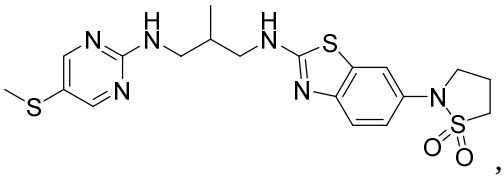
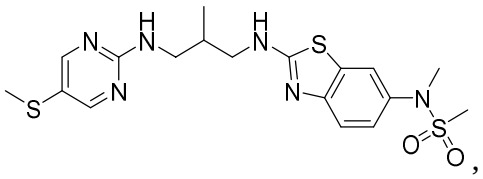
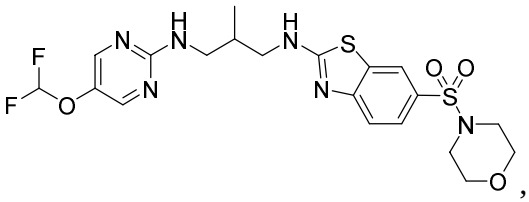
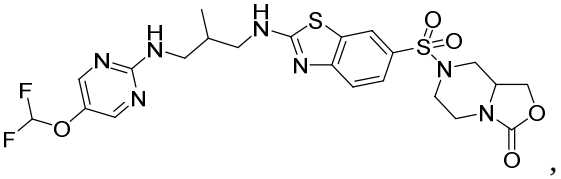
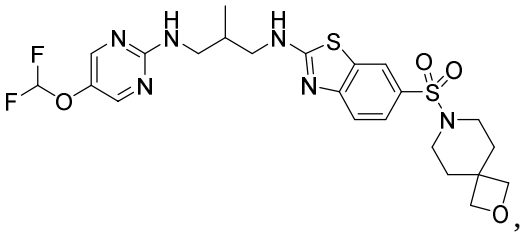
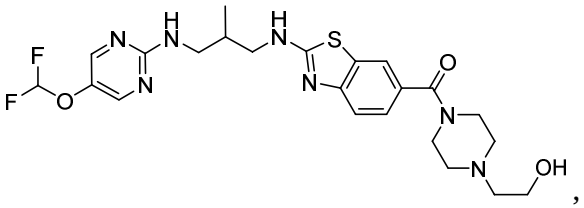
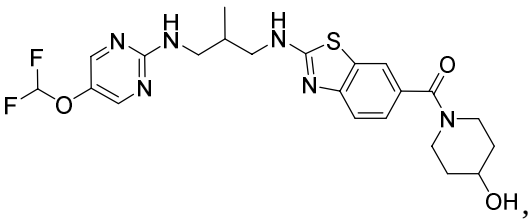
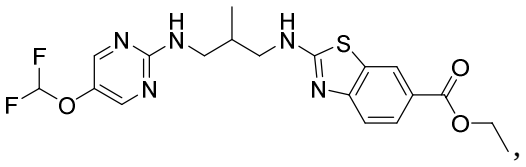
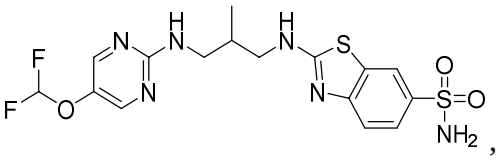
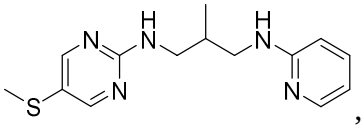
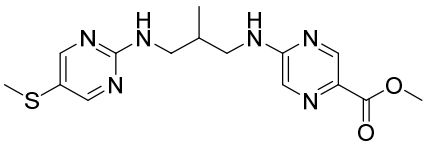
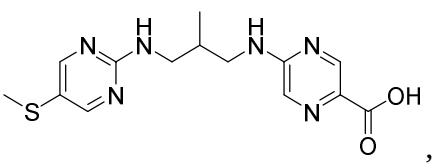
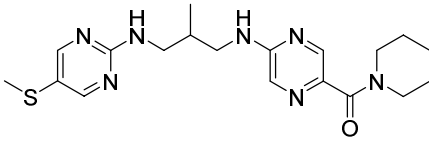
,

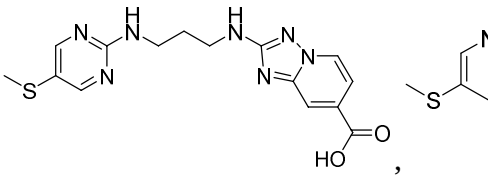
,

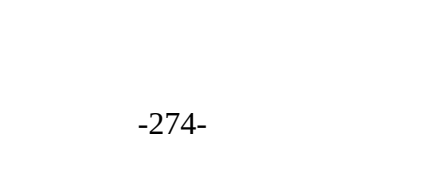
,

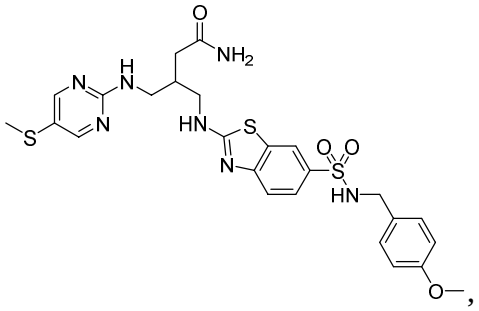
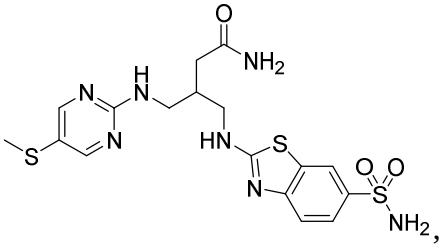
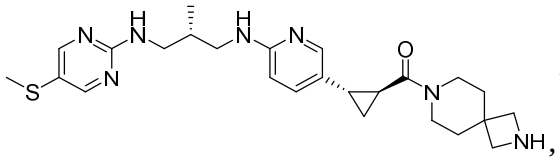
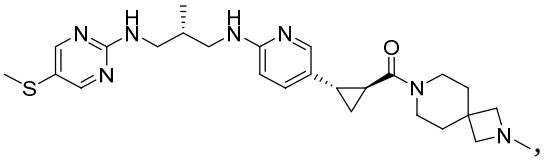
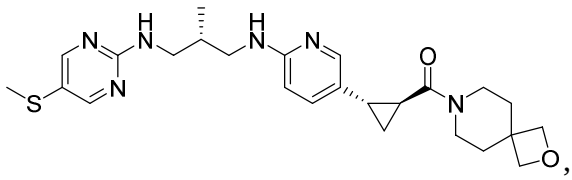
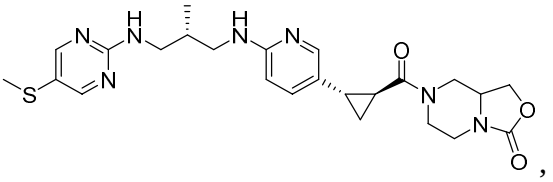
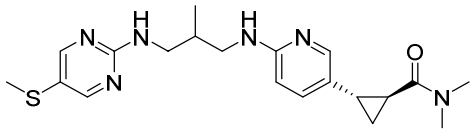
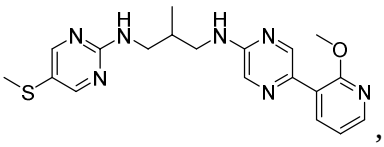
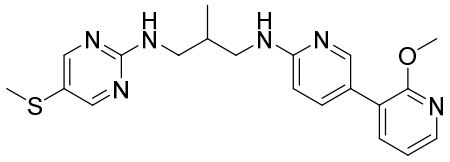
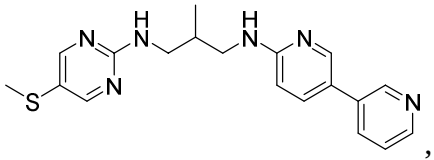
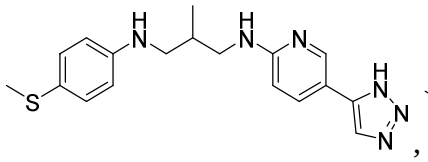
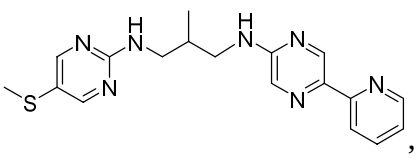
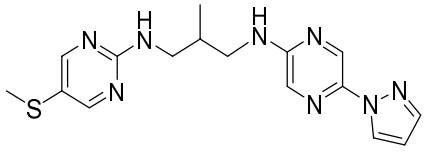
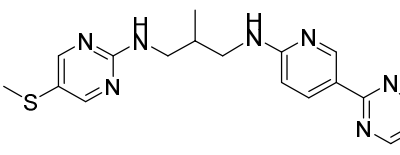
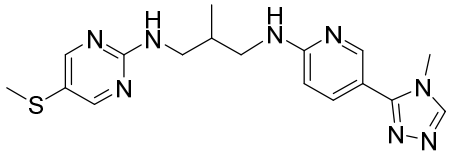
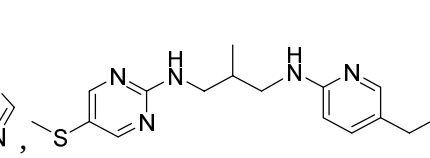

,

,

,

,

,

,

,

,

,

,

,

,

,

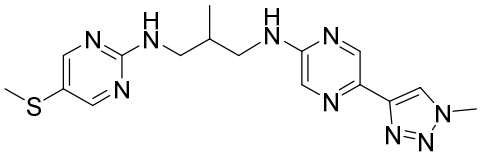
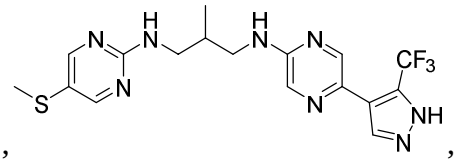
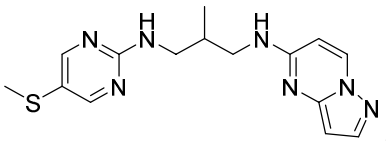
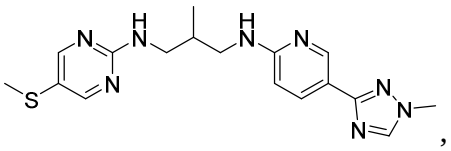
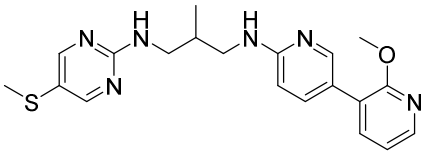
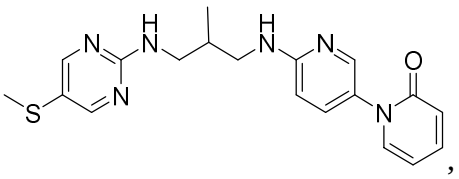
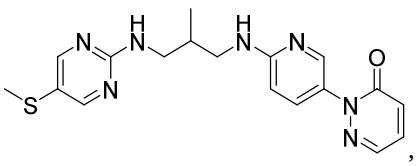
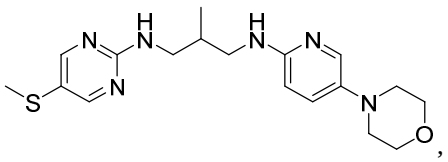
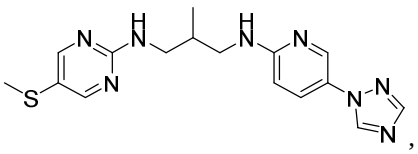
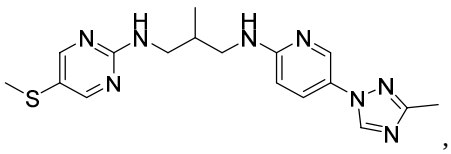
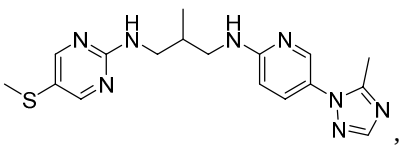
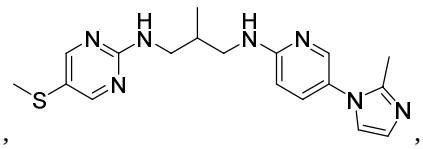
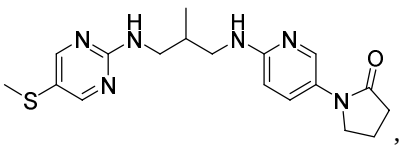
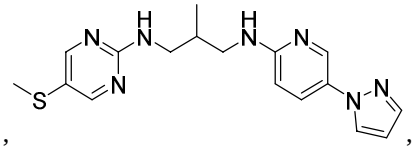
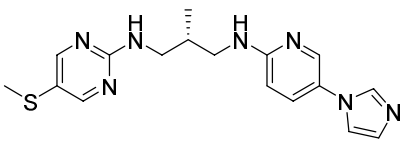
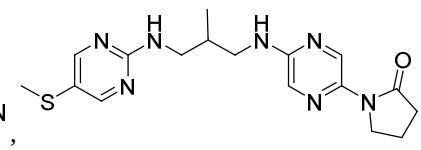
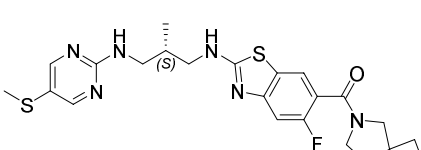
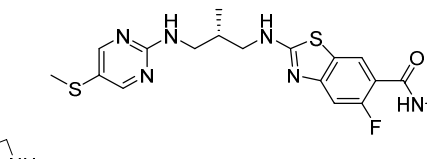
,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

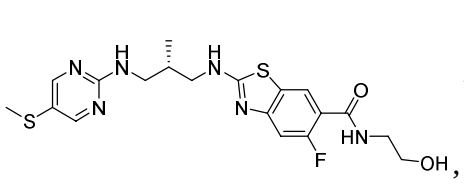
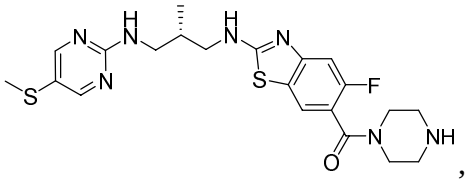
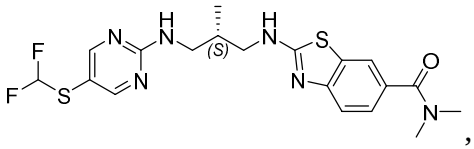
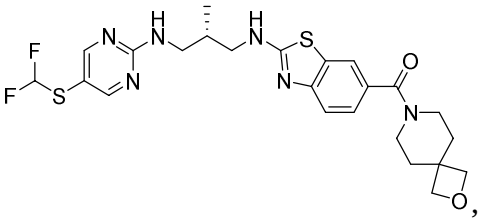
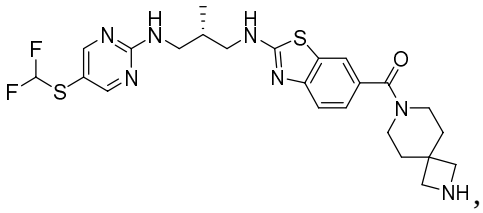
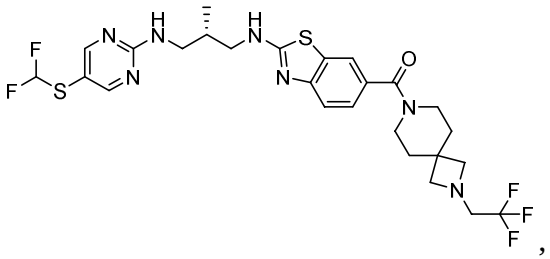
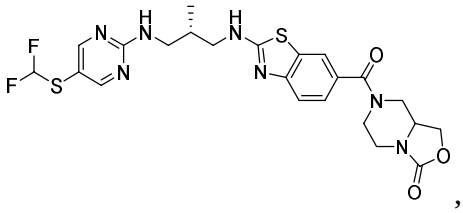
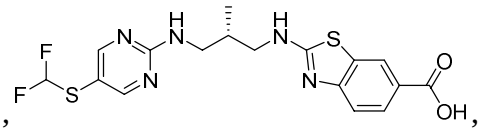
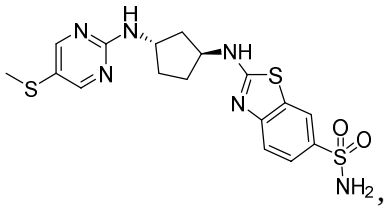
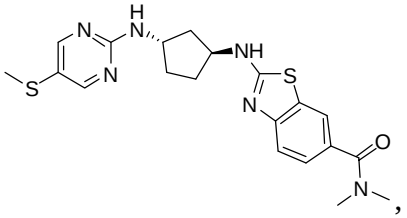
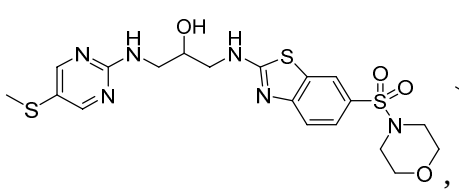
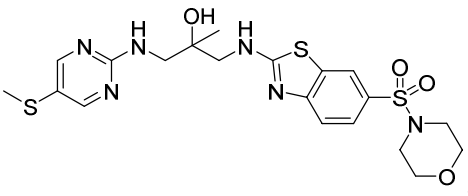
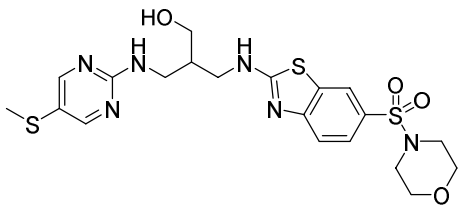
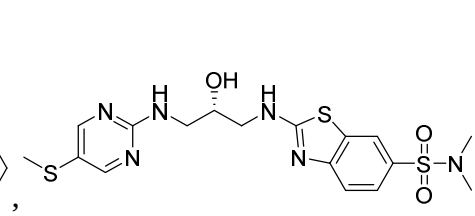
,

,

 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
,
 ,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

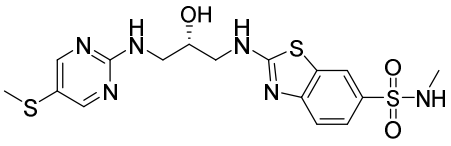
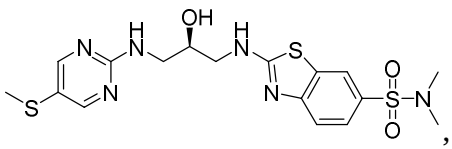
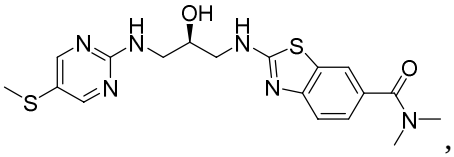
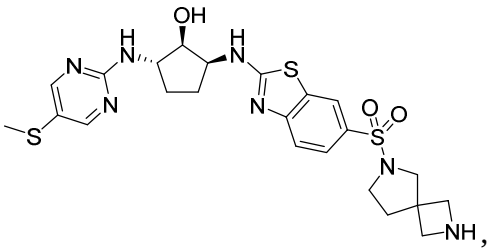
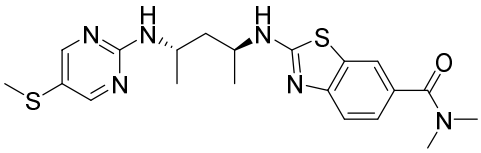
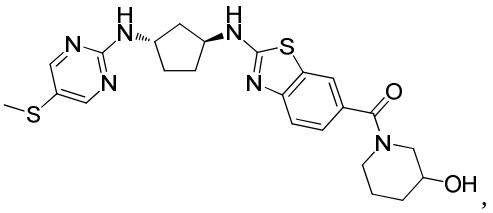
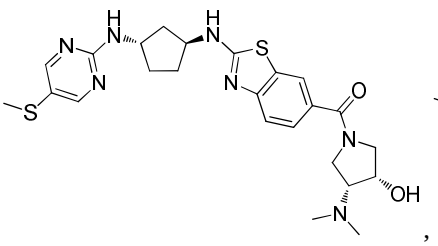
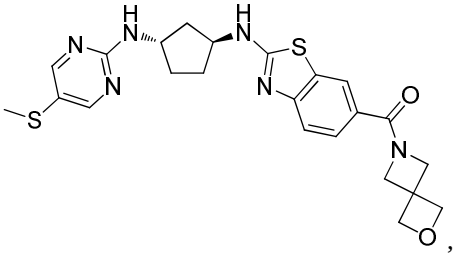
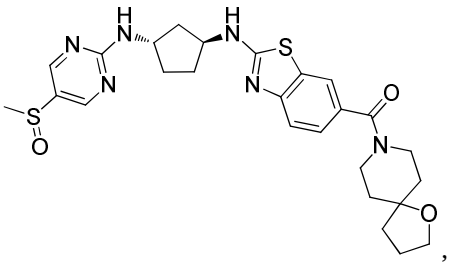
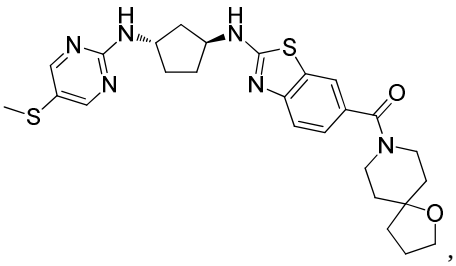
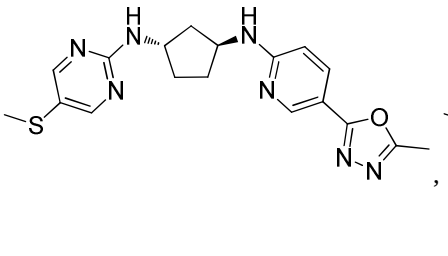
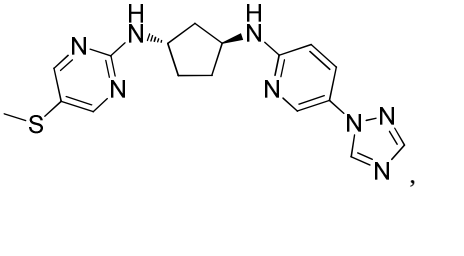
,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

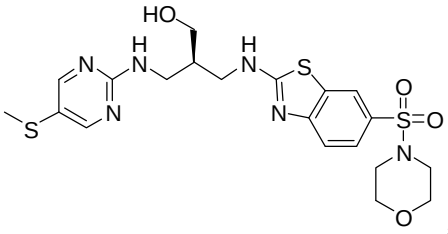
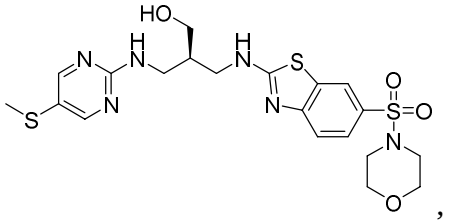
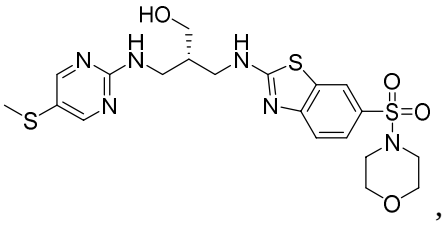
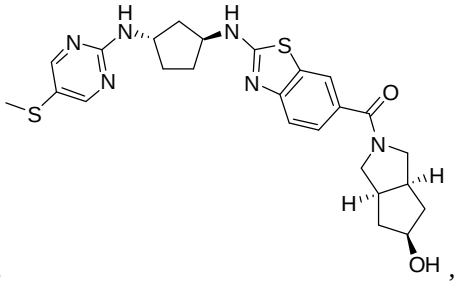
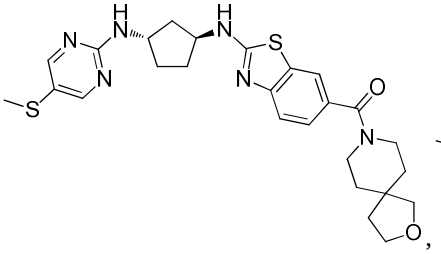
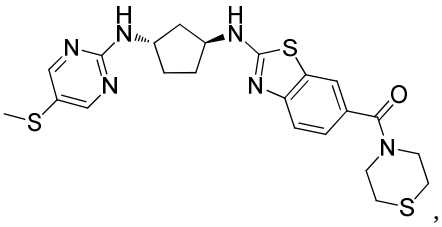
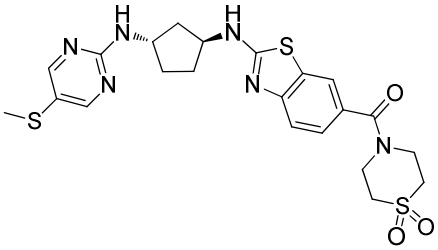
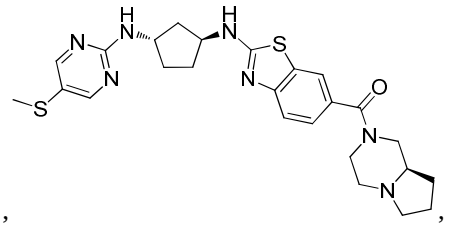
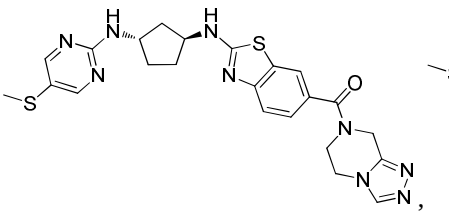
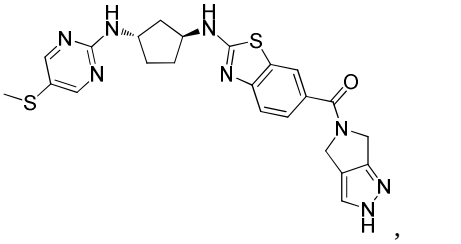
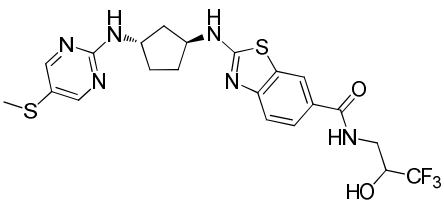
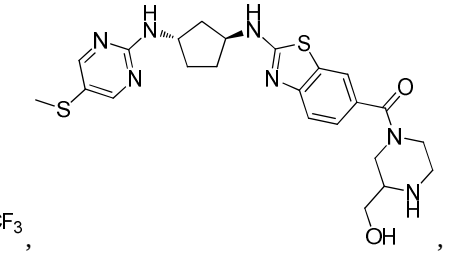
,

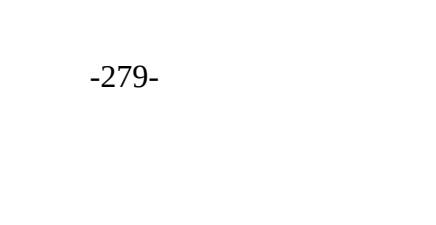
,

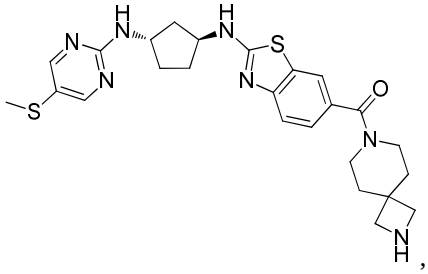
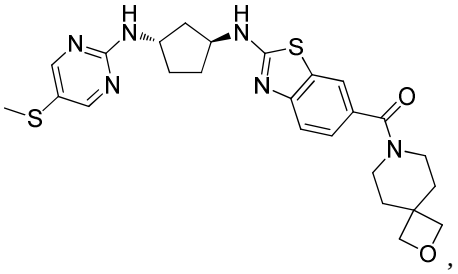
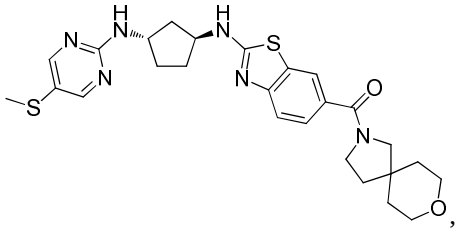
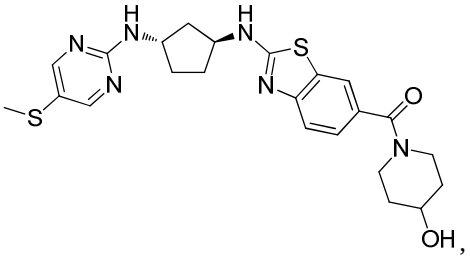
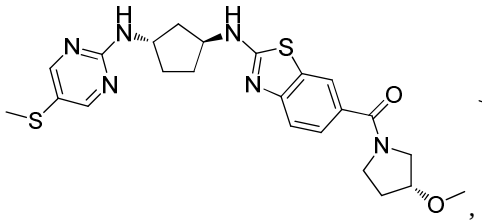
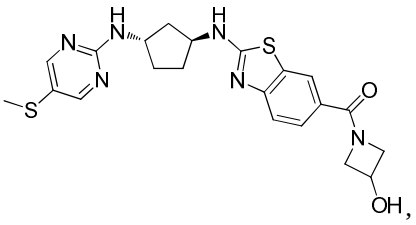
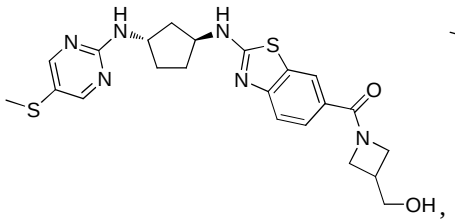
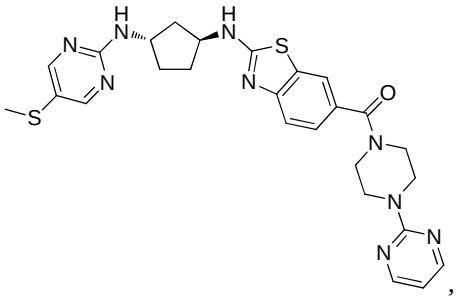
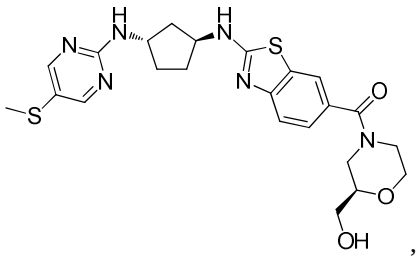
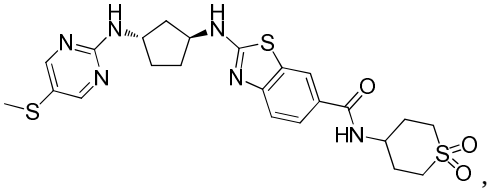

,

,

,

,

,

,

,

,

,

,

,

,

,

,

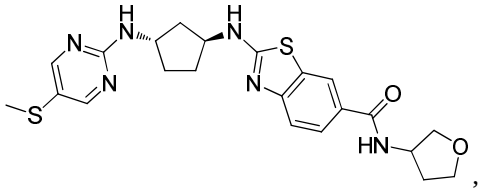
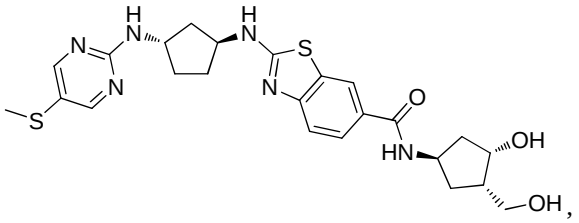
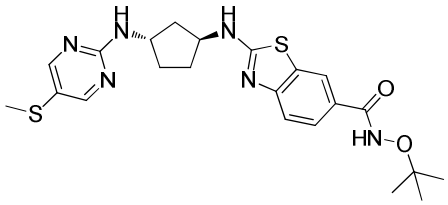
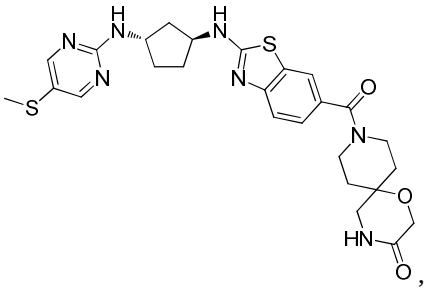
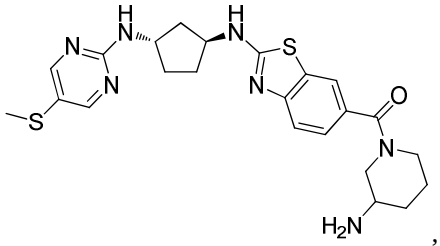
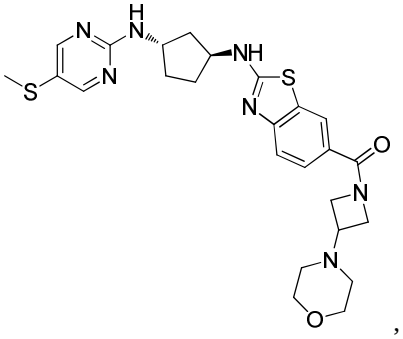
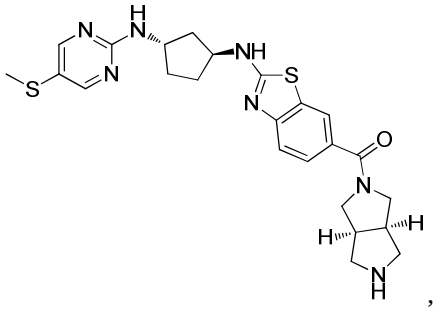
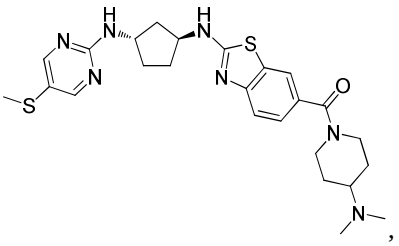

,

,

,

,

,

,

,

,

,

,

,

,

,

,

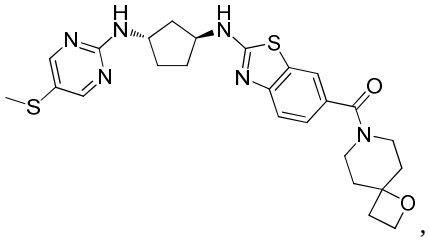
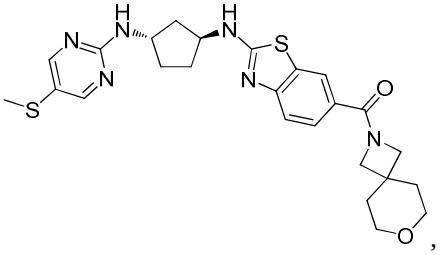

,

,

,

,

,

,

,

,

,

,

,

,

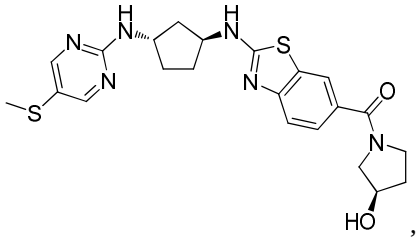
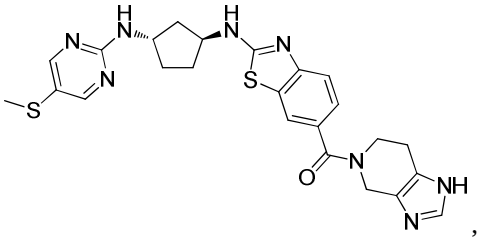
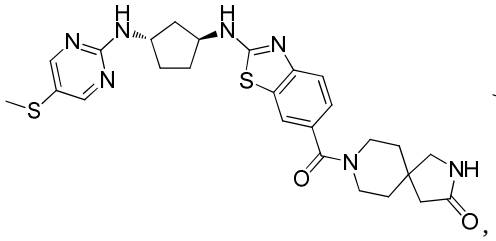
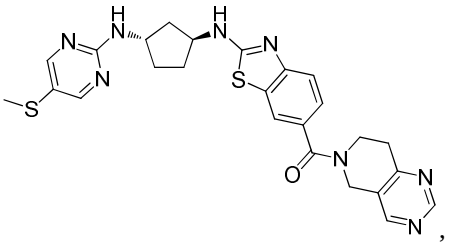
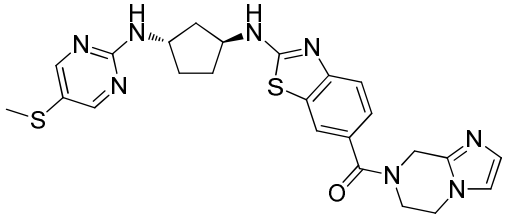
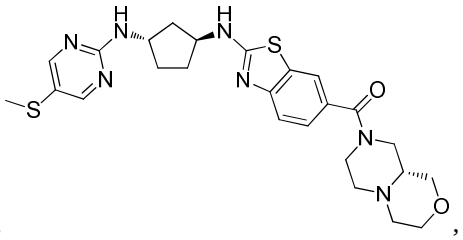
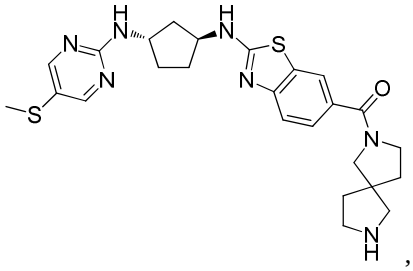
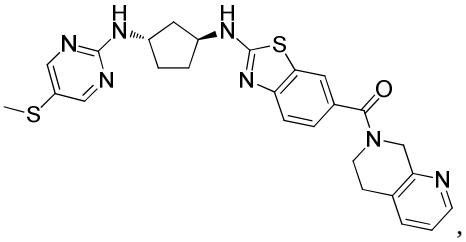
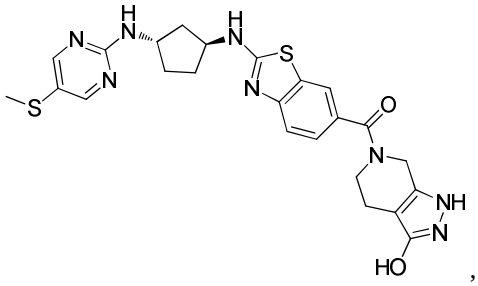
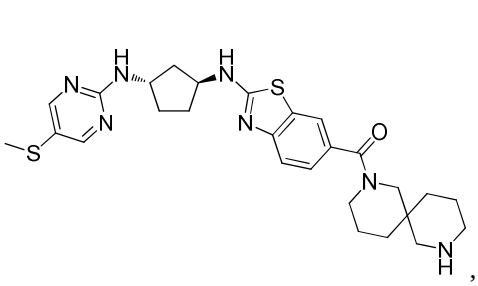
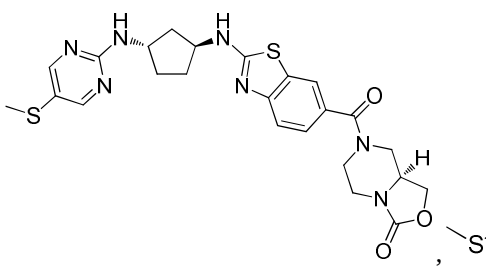
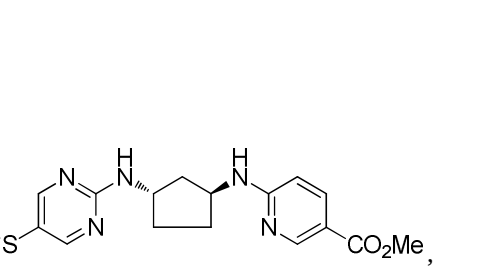

,

,

,

,

,

,

,

,

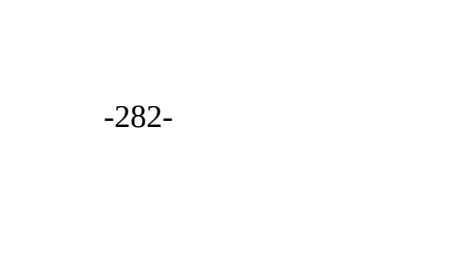
,

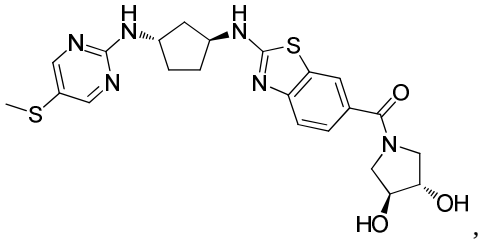
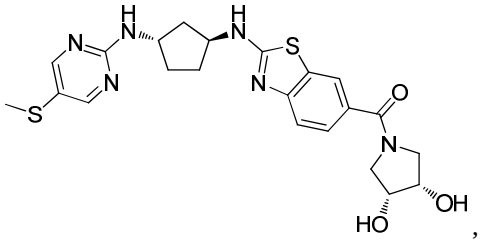
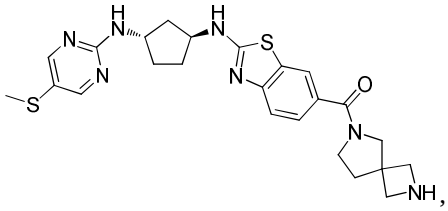
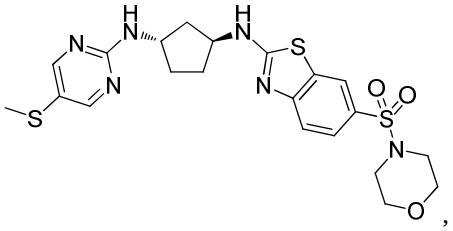
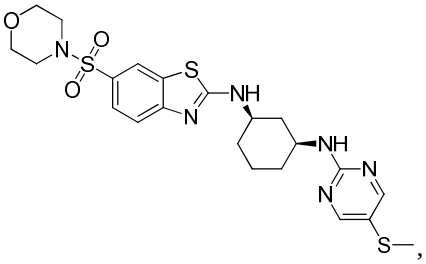
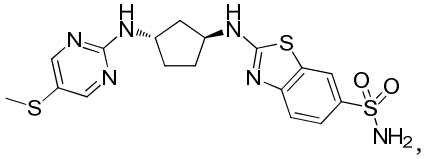
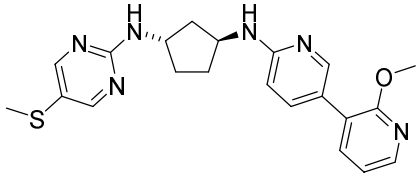
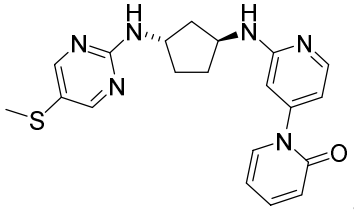
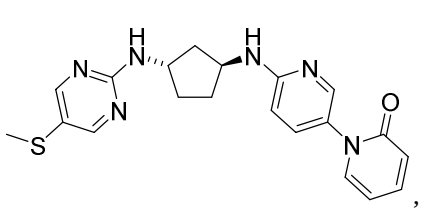
,

,

,

,

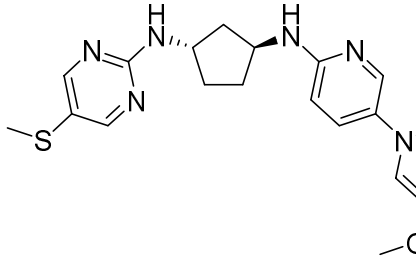
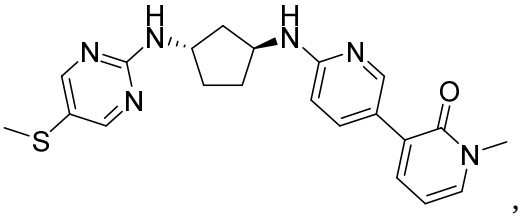
,

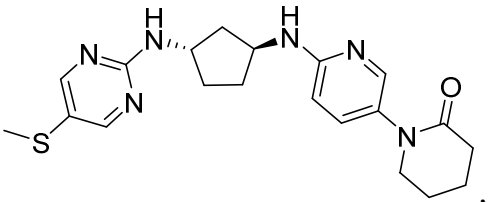

,

,

,

,

,

,

,

,

,

,

,

,

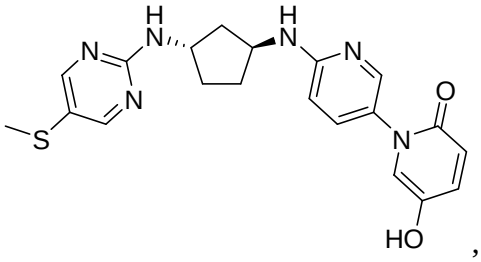
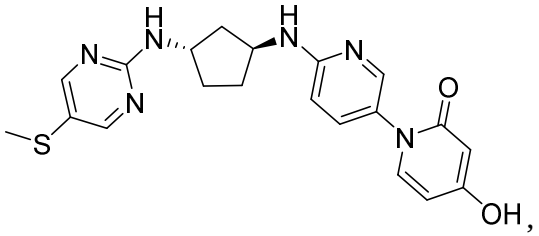
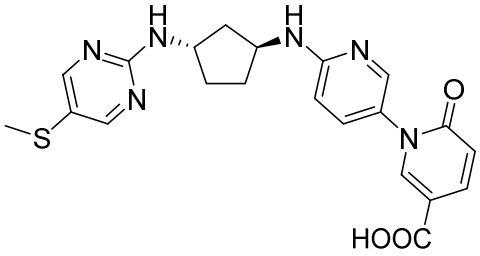
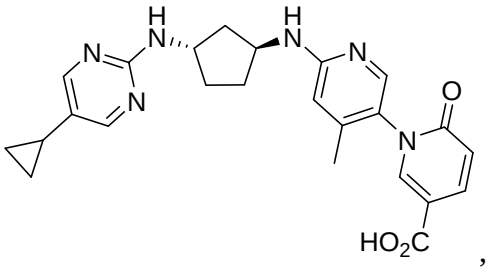
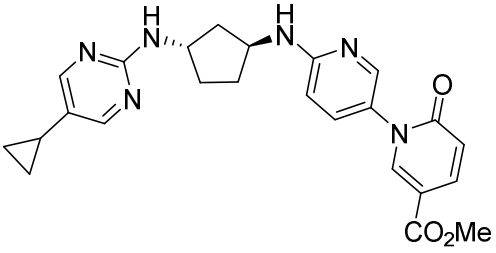
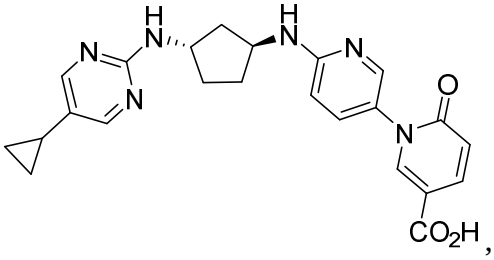
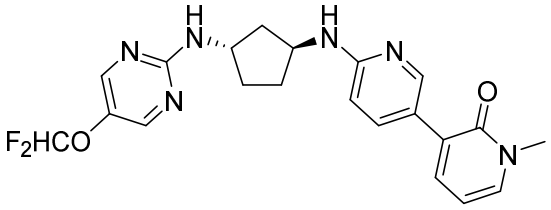
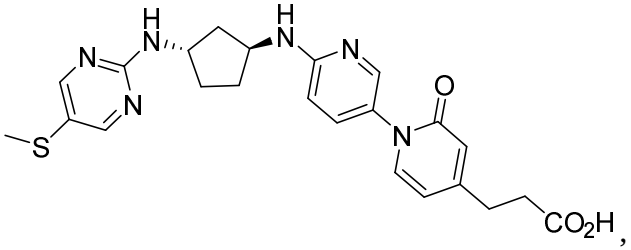
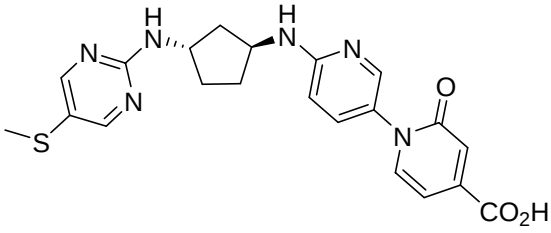
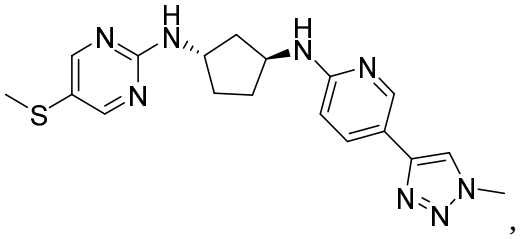
,

,

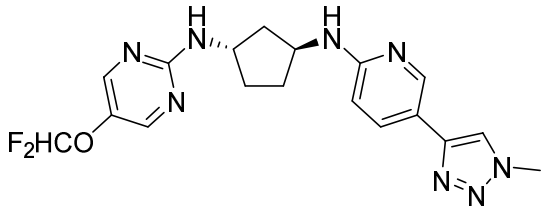
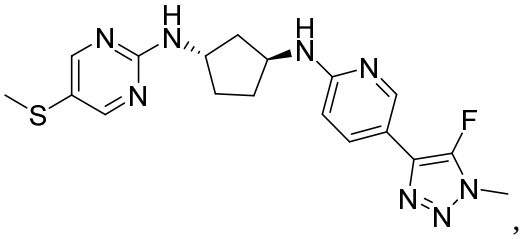
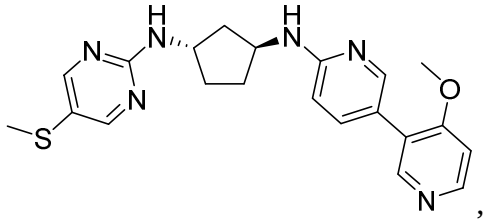
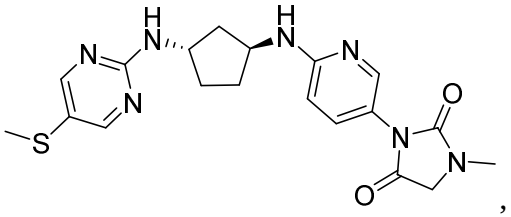
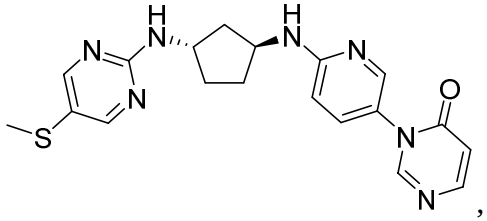
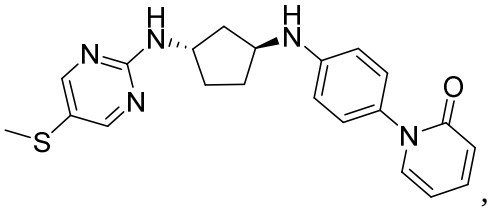
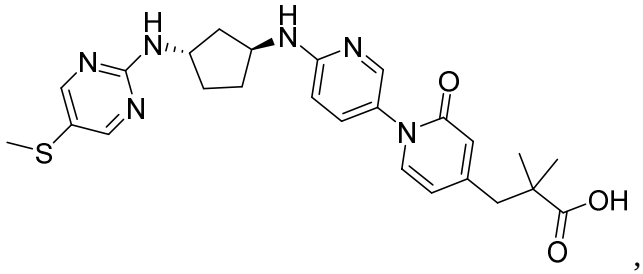
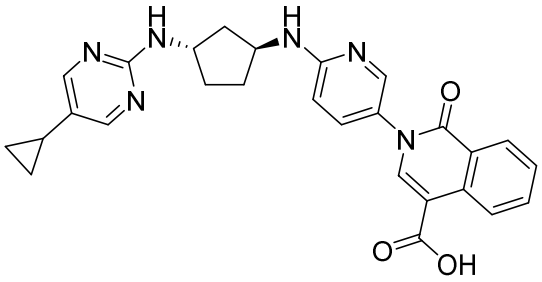
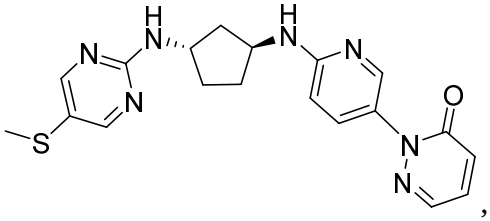
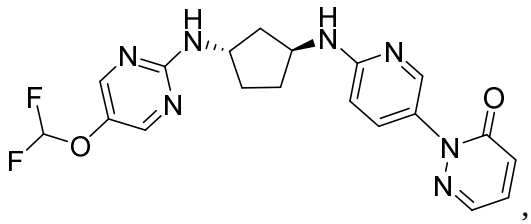
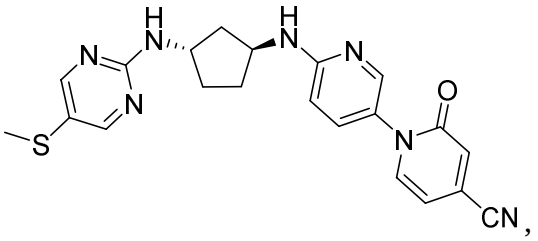

,

,

,

,


,

,

,

,

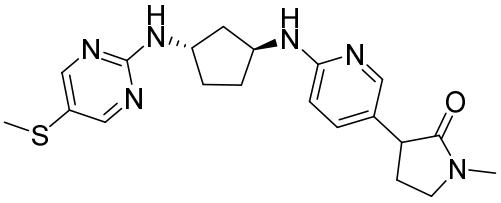
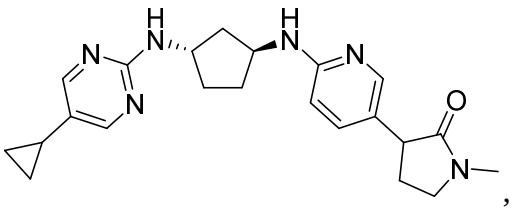
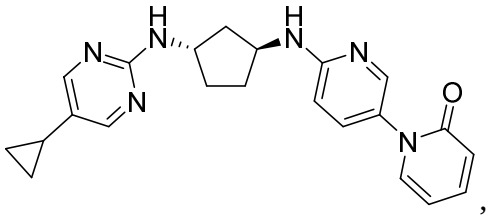
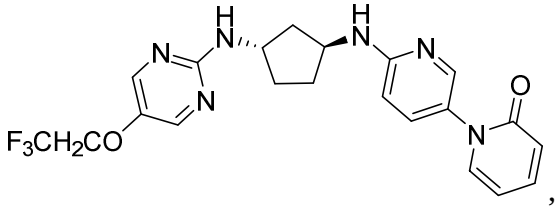
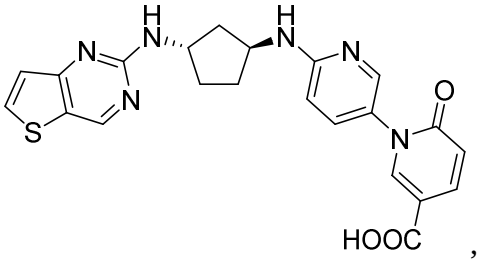
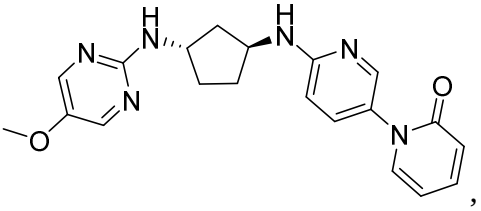
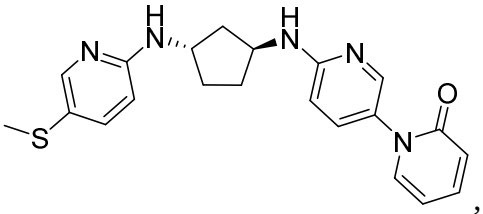
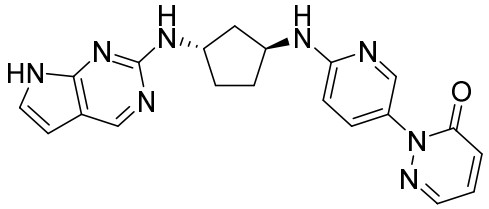
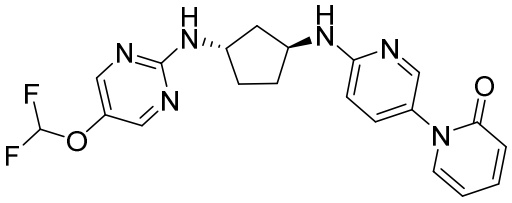
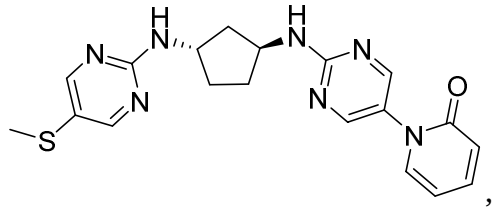
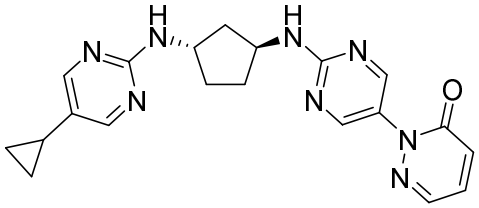
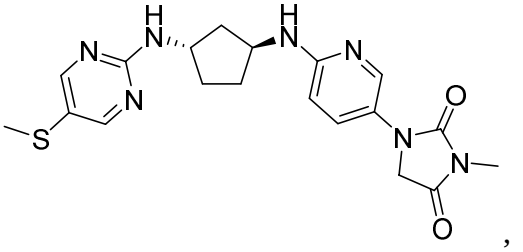
,

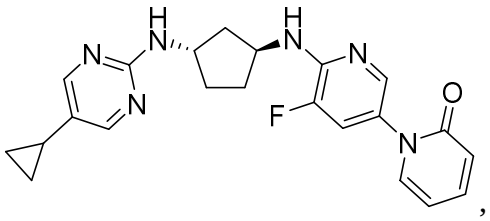
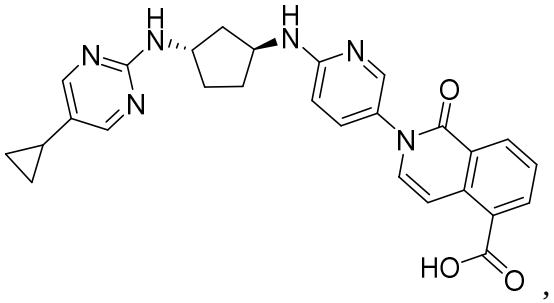
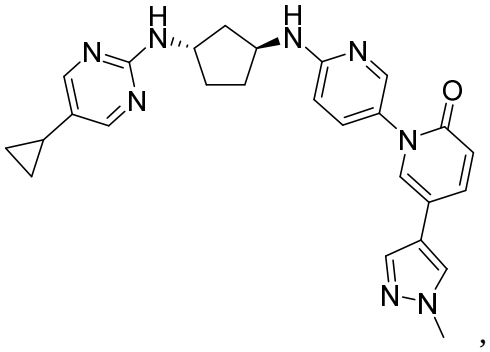
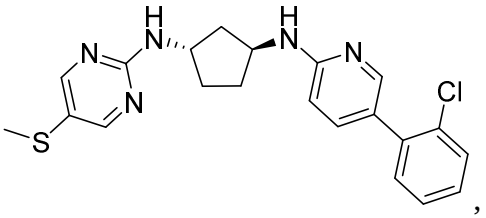
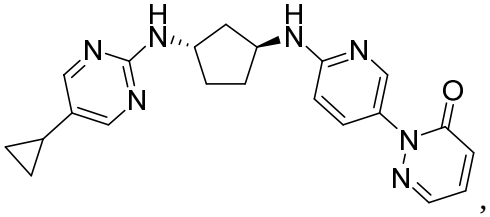
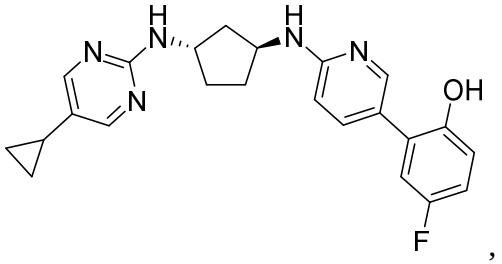
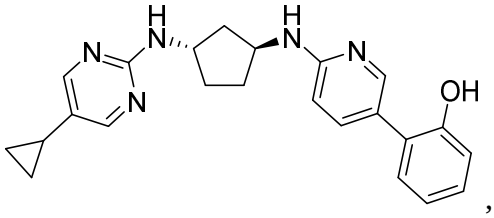
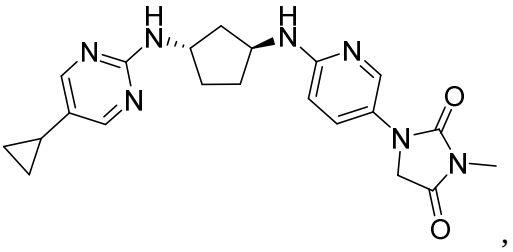
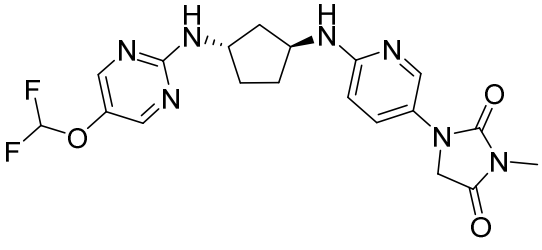
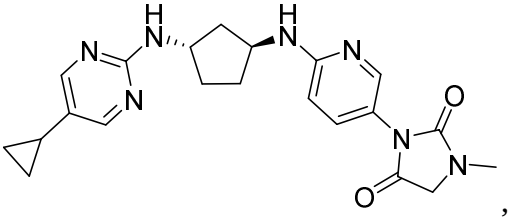
,

,

,

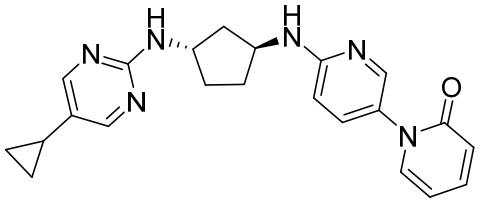
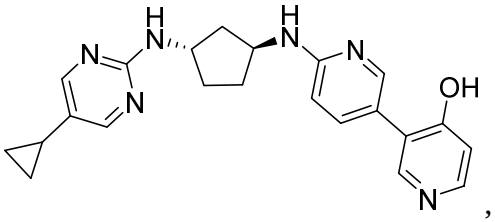
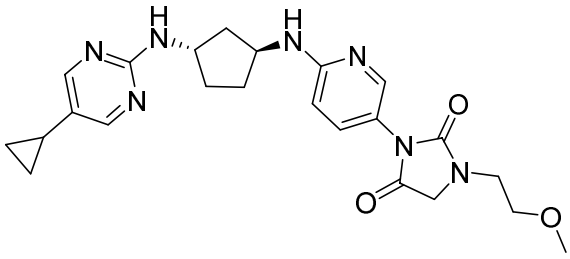
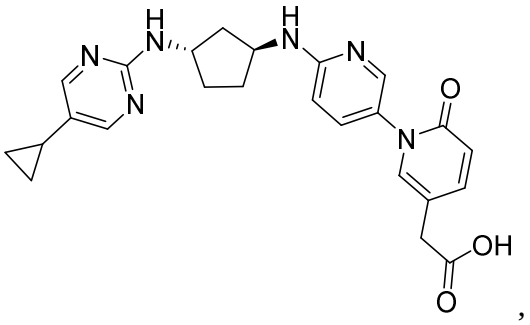
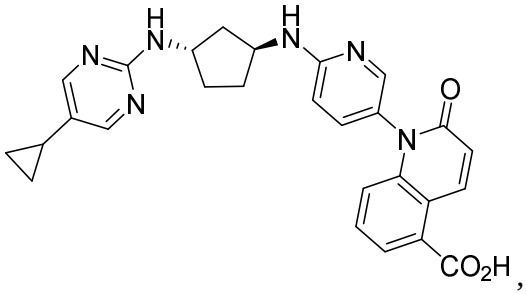
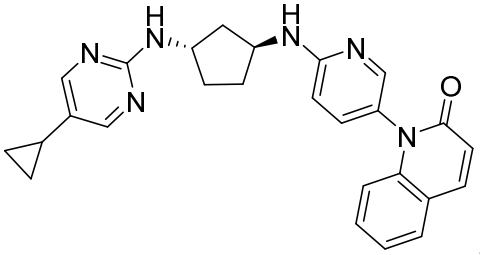
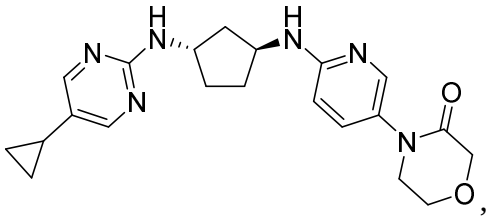
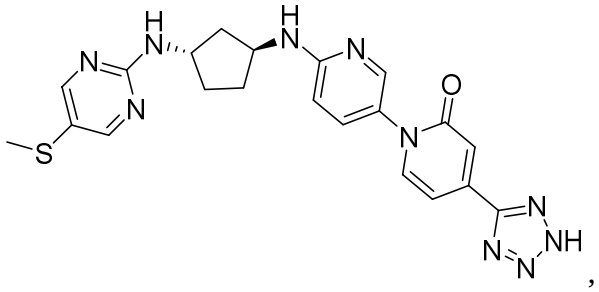
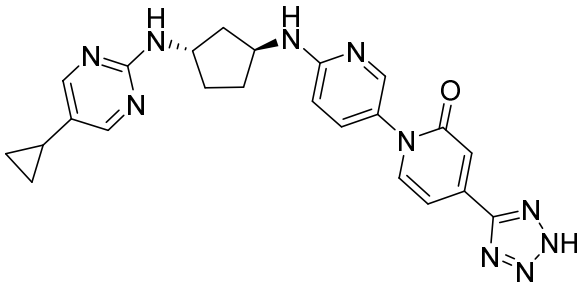
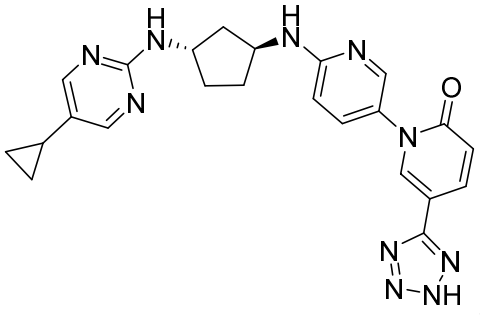
,

,


,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

.

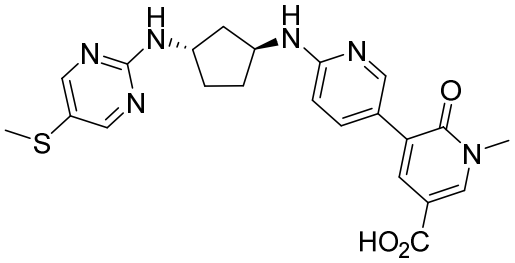
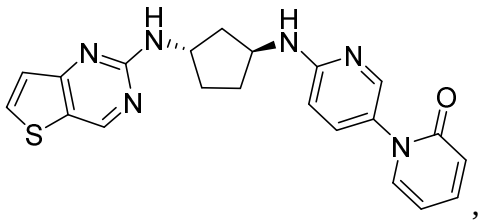
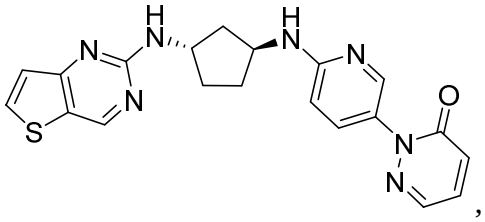
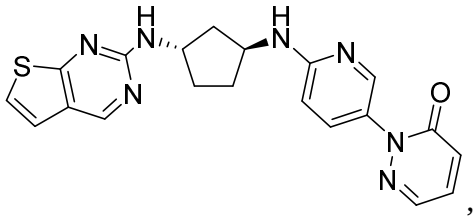
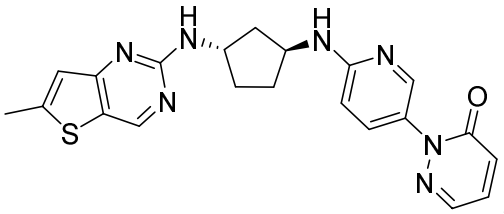
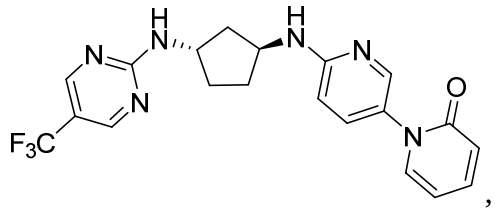
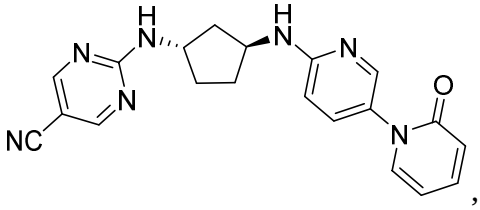
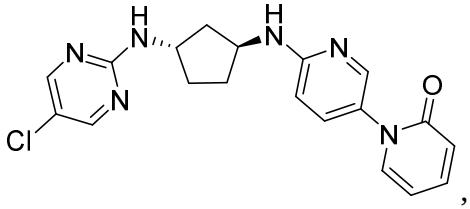
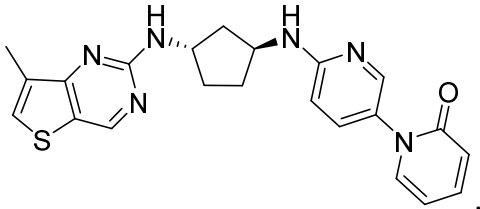
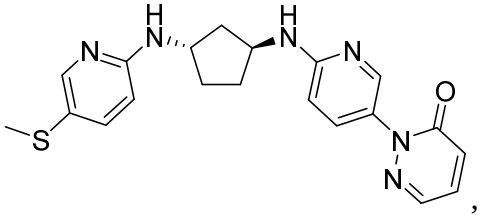
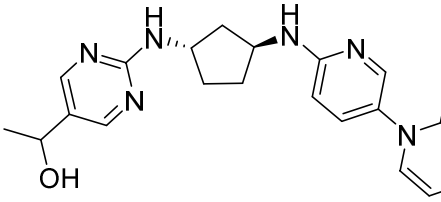

,

,

,

,

,

,

,

,

,

,

,

.


,

,

,

,

,

,

,

,

,

.


,

,

,

,

,

,

,

,

,

,

,

,

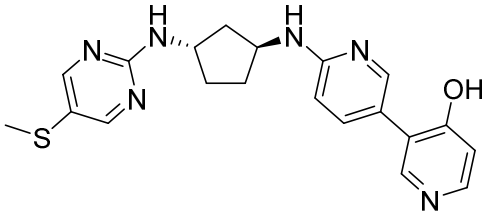
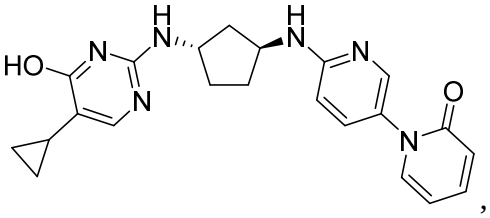
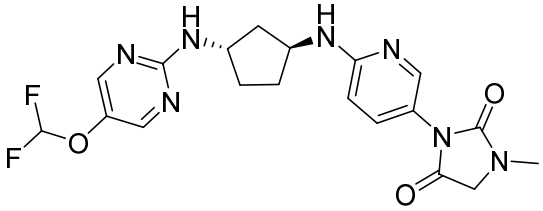
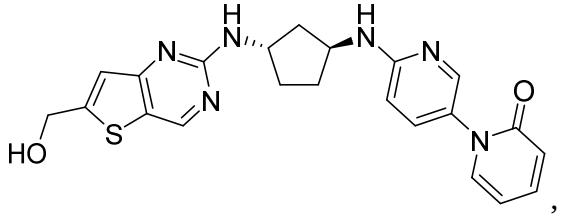
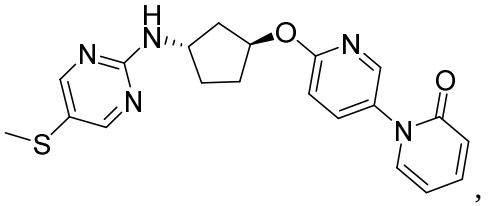
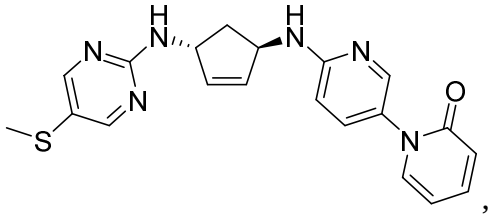
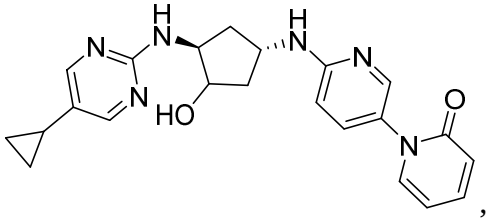
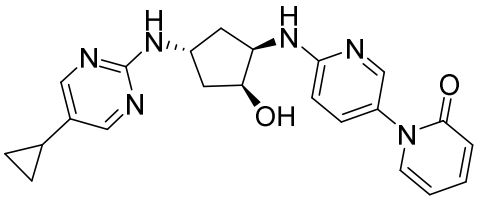
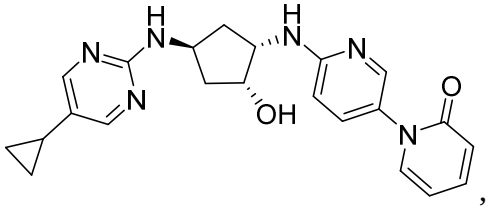
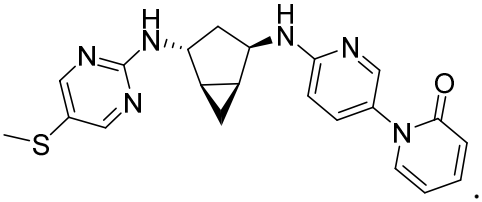

,

,

,

,

,

,

,

,

,

,

,

,

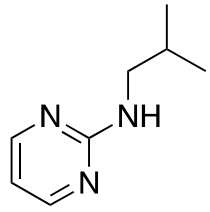
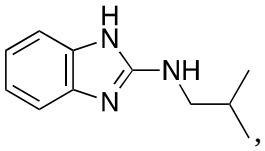
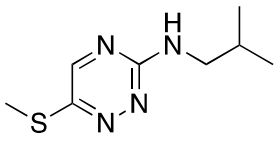
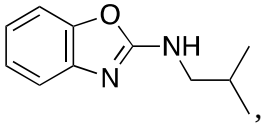
,

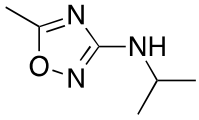
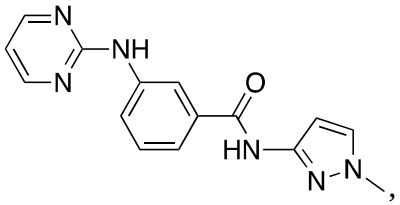
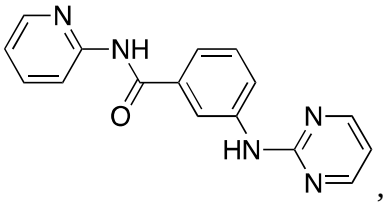
,

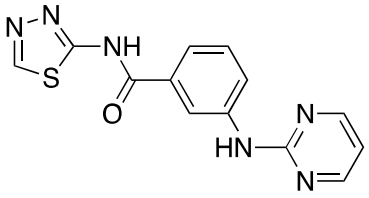
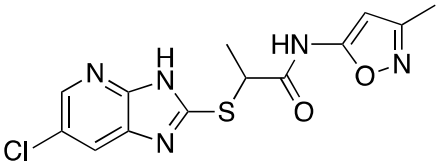
,


,

,

,

,

,

,

,

,

, and

.

39. The method of claim 20, wherein the inhibitor is selected from:

 ,  ,  ,  ,

 ,  ,  ,

 , and  .