Claims:

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

wherein the inhibitor binds to the binding pocket with an affinity (K_D) of less than 20,000 nM, and

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,

for use in inhibiting PCSK9.

2. Use of an inhibitor of PCSK9 that binds to a binding pocket defined by amino acid residues Val589 and Ser636 of human PCSK9,

wherein the inhibitor binds to the binding pocket with an affinity (K_D) of less than 20,000 nM, and

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,

in the manufacture of a medicament for the treatment of cardiovascular disease.

3~~2~~. The inhibitor for use ~~method~~ of claim 1 or the use of claim 2, wherein the inhibitor is an allosteric inhibitor.

4~~3~~. The inhibitor for use of claim 1 or 3 or the use of claim 2 or 3~~method of claim 1 or 2~~, wherein ~~the~~ the inhibitor is to be contacted with ~~method comprises contacting~~ the surface of a cell that secretes PCSK9 ~~with the inhibitor~~.

5~~4~~. The inhibitor for use ~~method~~ of claim 1 or the use of claim 2, wherein the inhibitor is to be contacted with ~~method comprises contacting~~ intracellular PCSK9 ~~with the inhibitor~~ .

65. The inhibitor for use ~~method~~ of claim 1 or the use of claim 2, wherein the inhibitor is to be contacted with ~~method comprises contacting~~ PCSK9 that is circulating in plasma ~~with the inhibitor~~.

76. The inhibitor for use ~~method~~ of claim 1 or the use of claim 2, 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.

87. The inhibitor for use ~~method~~ of claim 1 or the use of claim 2, 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.

98. The inhibitor for use of any one of claims 1, 3-8 or the use of any one of claims 2-8~~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.

109. The inhibitor for use or the use ~~method~~ of claim 98, wherein the inhibitor comprises a 2-NH-pyrimidinyl moiety and the one H-bond donor moiety is the amino hydrogen atom.

1110. The inhibitor for use of any one of claims 1, 3-10 or the use of any one of claims 2-10~~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.

12~~11~~. The inhibitor for use of any one of claims 1, 3-11 or the use of any one of claims 2-11~~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 inhibitor for use of any one of claims 1, 3-12 or the use of any one of claims 2-12~~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.~~

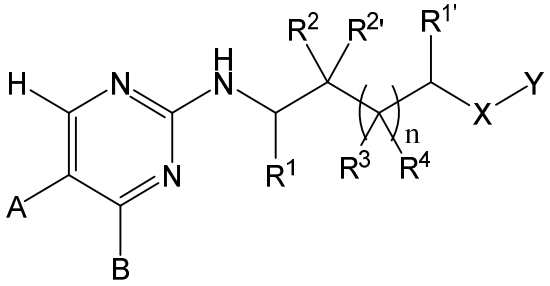
14~~16~~. The inhibitor for use of any one of claims 1, 3-13 or the use of any one of claims 2-13~~method of any one of claims 1-12~~, wherein the inhibitor interacts with a pocket in PCSK9 between amino acid residues 558-590 in the M2 C-terminal domain and amino acids residues 631-650 in the M3 C-terminal domain.

15~~17~~. The inhibitor for use of claim 1 or the use of claim 2~~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.

16~~18~~. The inhibitor for use or the use of claims 15~~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.

17~~19~~. The inhibitor for use or the use of claims 16~~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.

18~~20~~. The inhibitor for use of any one of claims 1, 3-17 or the use of any one of claims 2-17~~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^6R^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, and R^1 and $R^{1'}$, together with the atoms to which they are attached, form a ~~4-8 membered cycloalkyl or cycloalkenyl~~ cyclopentyl 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~~,~~ and heteroaryl ~~and heterocyclyl;~~

~~and~~

~~n is 0 or 1~~.

19~~21~~. The inhibitor for use or the use of claims 18~~method of claim 20~~ wherein A is selected from H, hydroxy, thioalkyl, alkyl, alkoxy, acyloxy, cyano, cycloalkyl, -$C(O)OR^6$, and -$C(O)NR^6R^7$.

20~~22~~. The inhibitor for use or the use of claims 18~~method of claim 20~~, wherein A is alkoxy.

21~~23~~. The inhibitor for use or the use of claims 18~~method of claim 20~~, wherein A is cycloalkyl.

22~~24~~. The inhibitor for use or the use of any one of claims 18-21~~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.~~

23~~26~~. The inhibitor for use or the use of any one of claims 18-22~~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.~~

2430. The inhibitor for use or the use of any one of claims 18-23~~method of any one of claims 20-29~~, wherein R^2 is selected from H, halo, alkyl, alkoxy, amidoalkyl, aminoalkyl, alkylamino, cyano, and hydroxyl.

2531. The inhibitor for use or the use of any one of claims 18-24~~method of any one of claims 20-30~~, wherein $R^{2'}$ is H.

2632. The inhibitor for use or the use of any one of claims 18-25~~method of any one of claims 20-31~~, wherein Y is monocyclic heteroaryl.

2733. The inhibitor for use or the use of claim 26~~method of claim 32~~, wherein Y is selected from pyridyl, pyridinyl, pyrazinyl, pyrimidinyl, and thiazolyl.

2834. The inhibitor for use or the use of claim 27~~method of claim 32~~, wherein Y is selected from ~~triazenyl,~~ oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, and triazolyl.

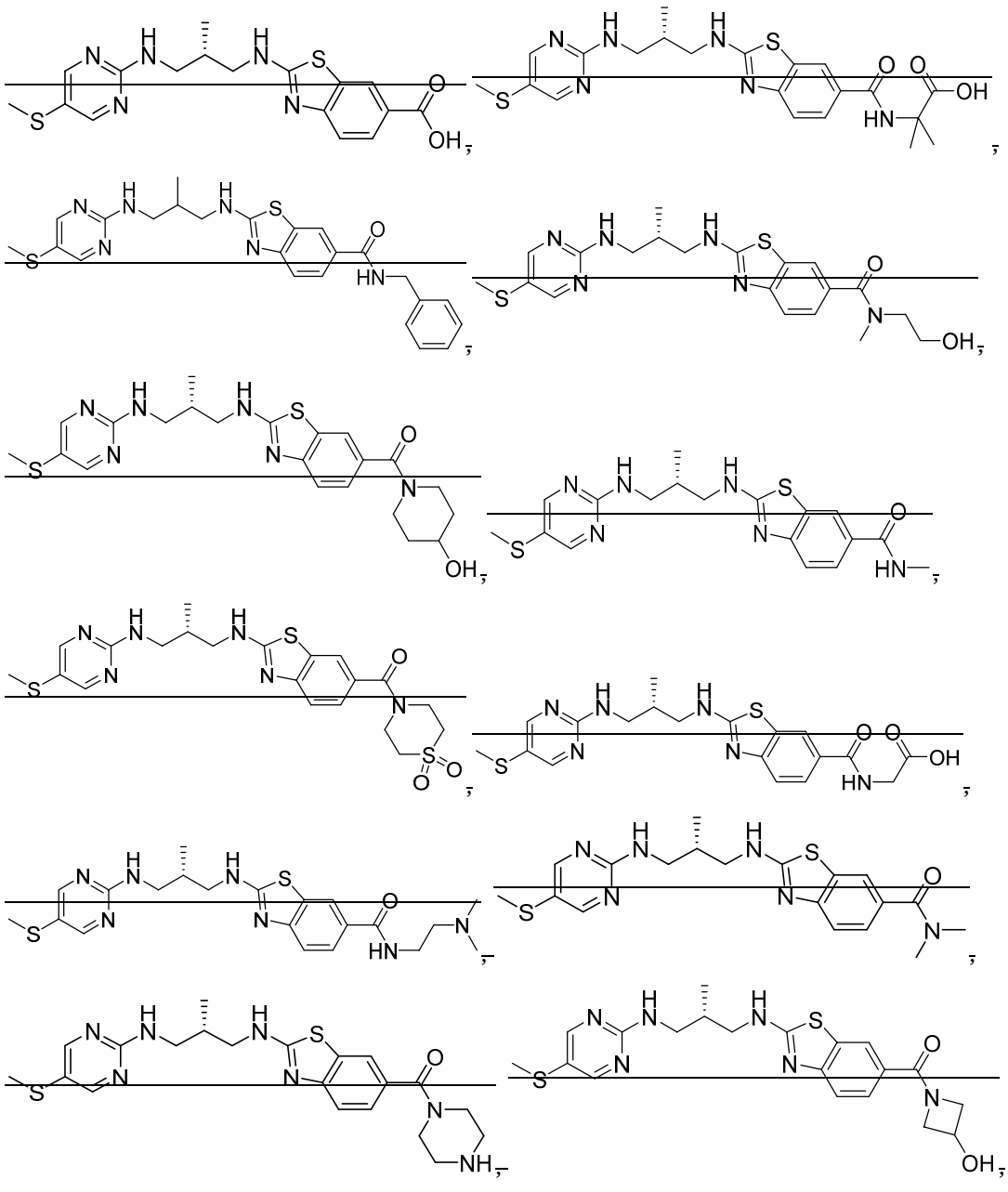
2935. The inhibitor for use or the use of any one of claims 26-28~~method of any one of claims 32-34~~, wherein the monocyclic heteroaryl is unsubstituted or substituted with one or more substituents selected from alkyl, thioalkyl, alkoxy, alkoxycarbonyl, amido, carboxy, cyano, halo, aryl, heteroaryl, heterocyclyl, nitro, sulfonamido, and thioalkyl.

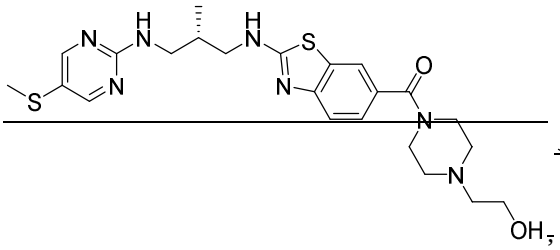
3036. The inhibitor for use or the use of claim 29~~method of claim 35~~, wherein the monocyclic heteroaryl is substituted with a 6-membered aryl, heteroaryl or heterocyclyl selected from phenyl, pyridinyl, 2-hydroxypyridinyl, piperidinonyl, 2-hydroxy-1-methylpyridinyl, triazolyl, imidazolidinonyl, pyrimidonyl, 2-hydroxyisoquinolinyl, 3-hydroxypyridazinyl, pyrrolidinonyl, pyrazolyl, and morpholinonyl.

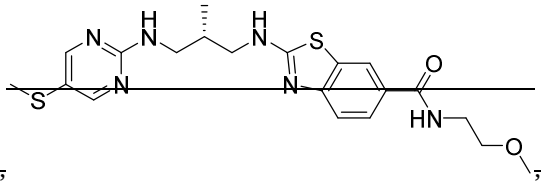
3137. The inhibitor for use or the use of claim 30~~method of claim 36~~, wherein the ~~monocyclic heteroaryl is substituted with an~~ heteroaryl or heterocyclyl ~~that~~ is substituted

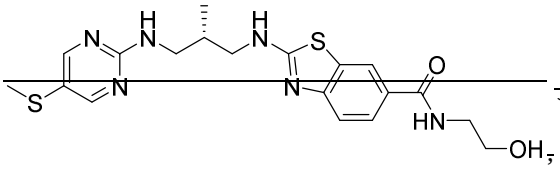
with one or more substituents selected from halo, CN, alkyl, alkoxy, hydroxy, carboxy, -CO_2alkyl, and tetrazolyl.

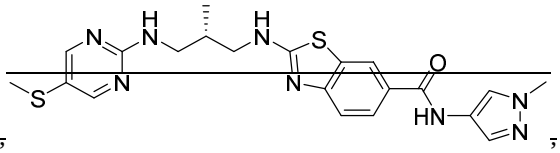
3238. The inhibitor for use or the use of claim 18~~method of claim 20~~, wherein the inhibitor is selected from

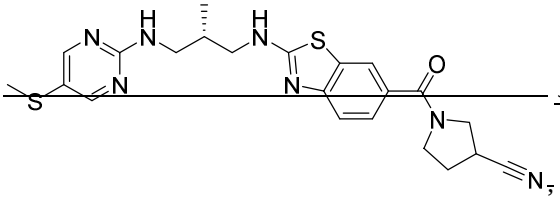


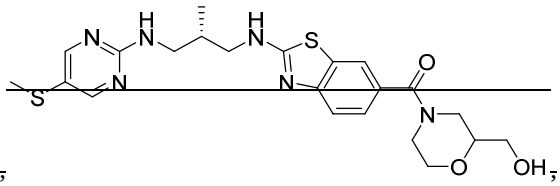


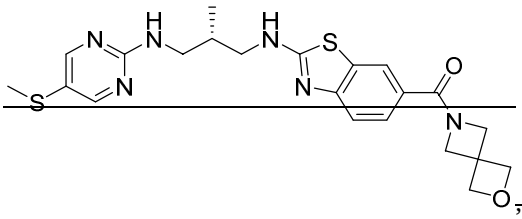


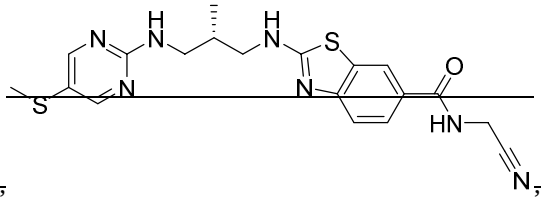


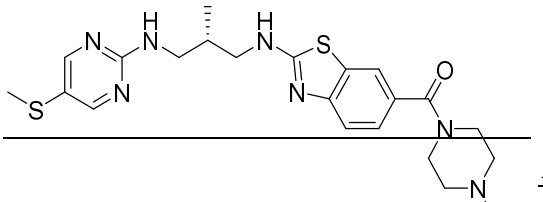


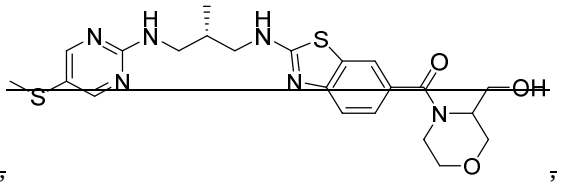


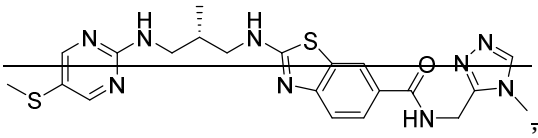


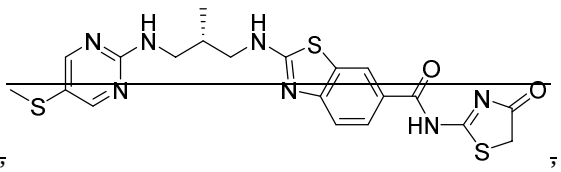


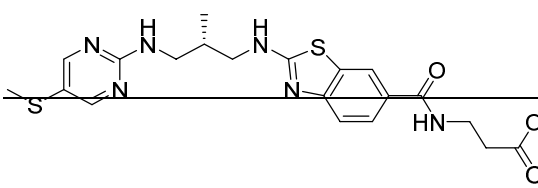


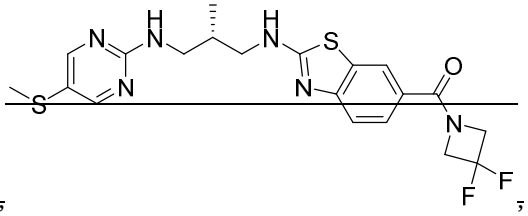


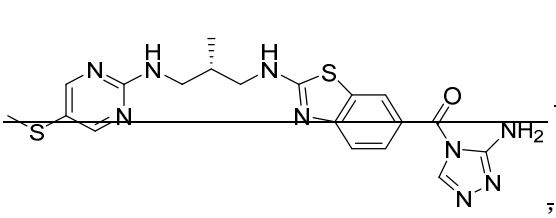
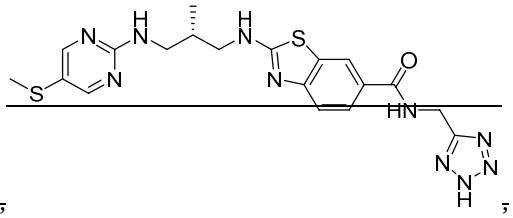
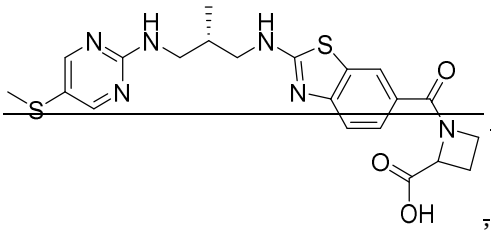
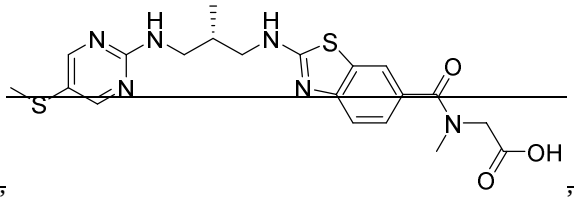
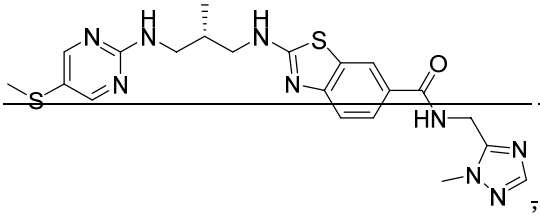
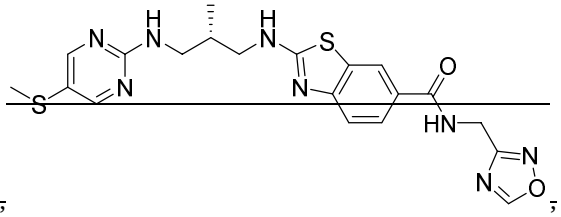
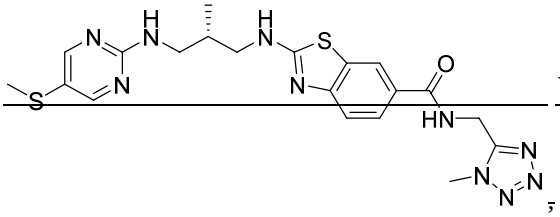
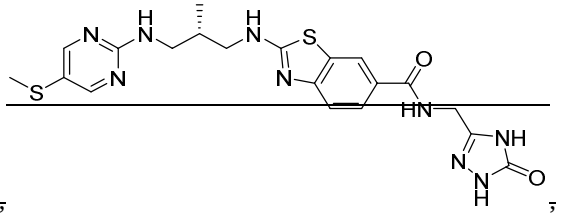
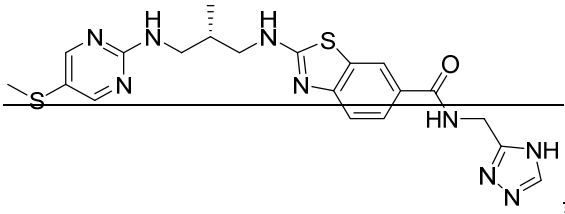
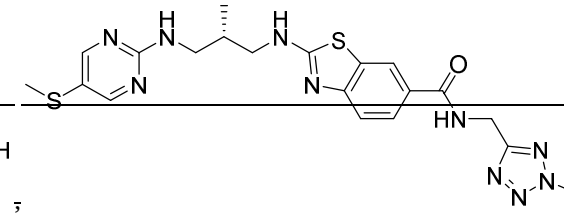
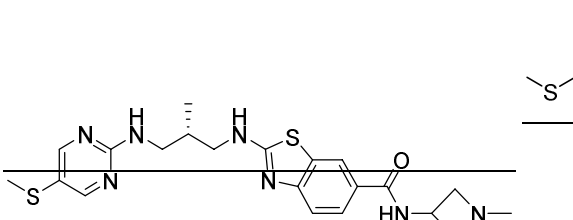
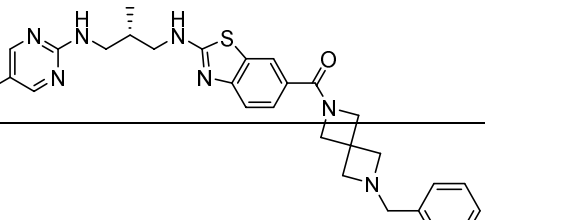






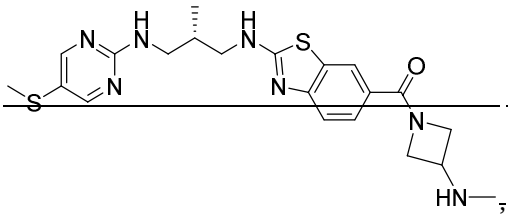


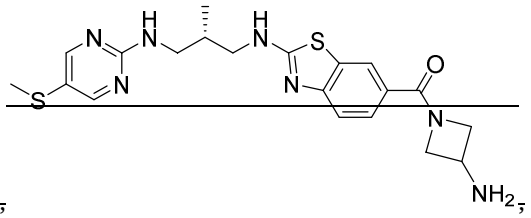


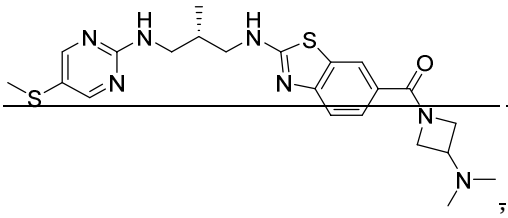

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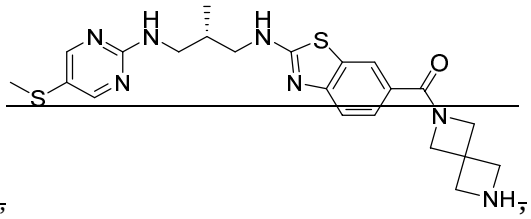
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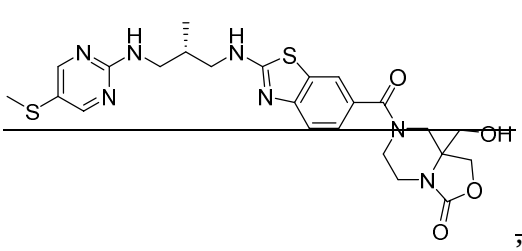
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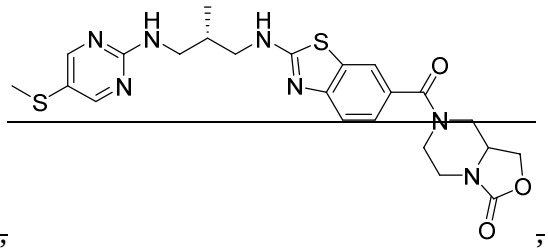


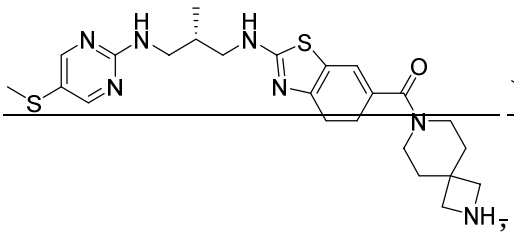


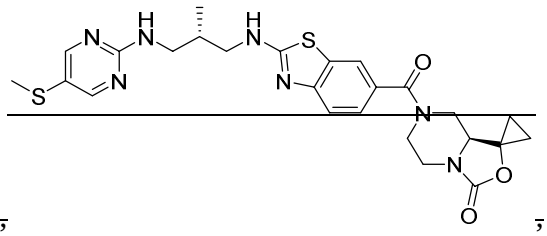


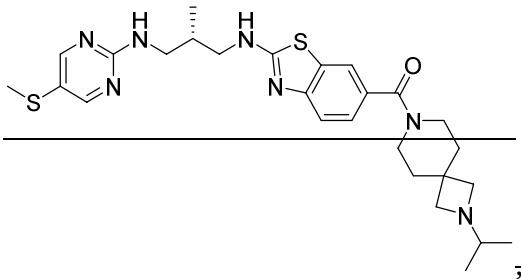


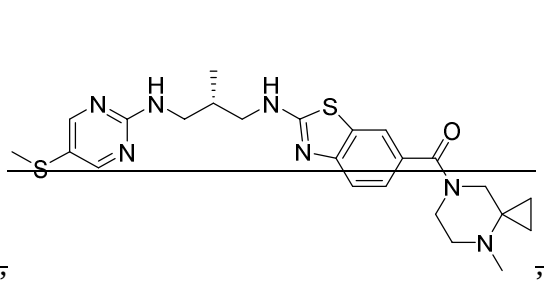


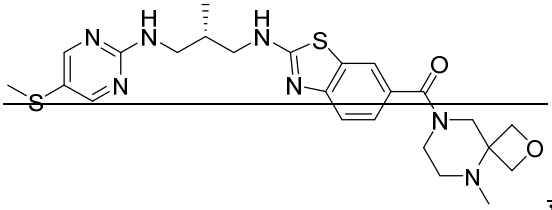


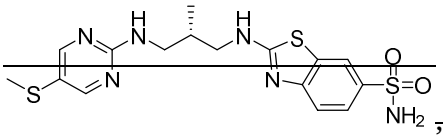
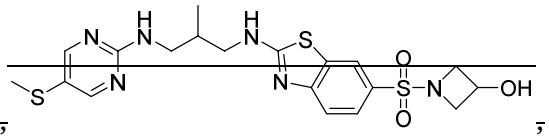
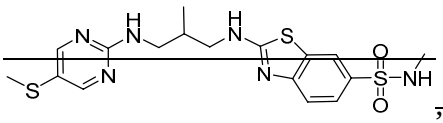
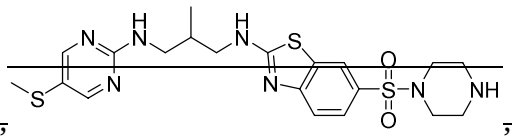
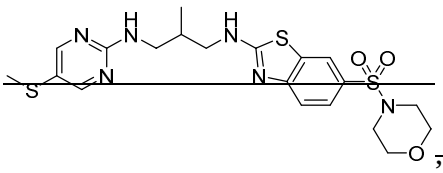
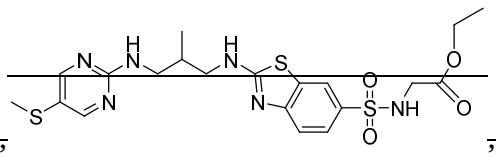
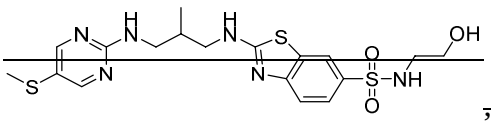
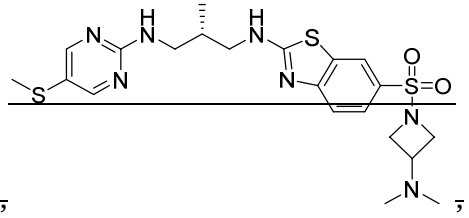
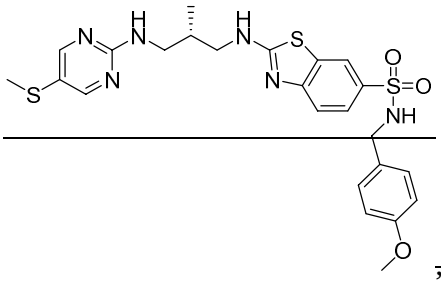
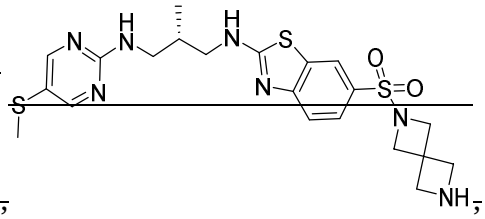
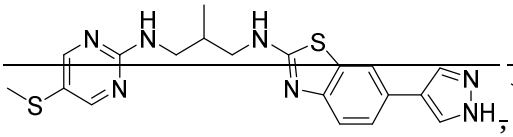
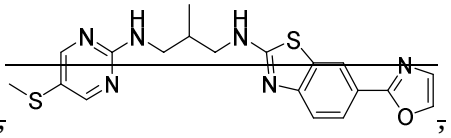
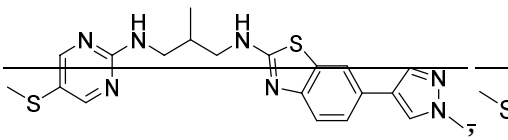
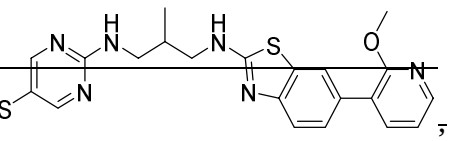
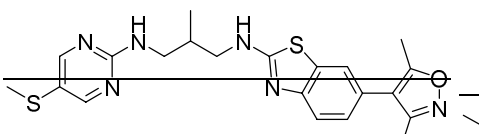
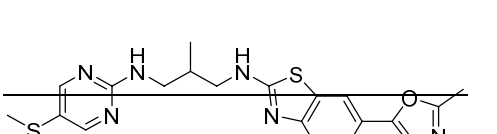
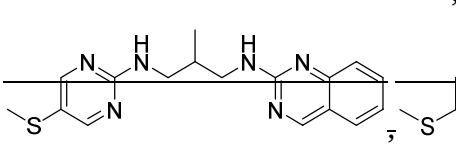
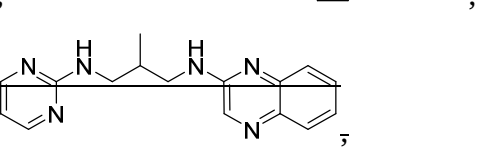


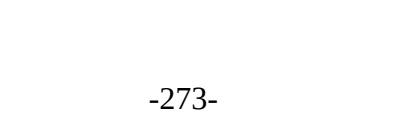


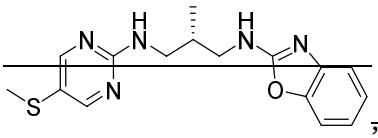
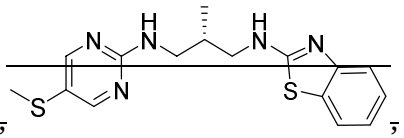
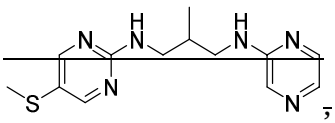
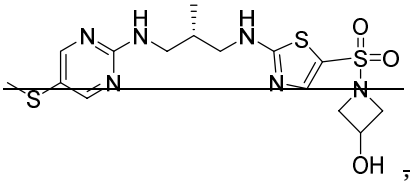
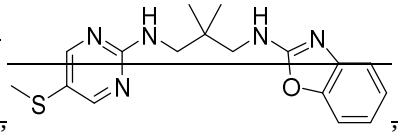
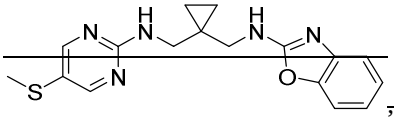
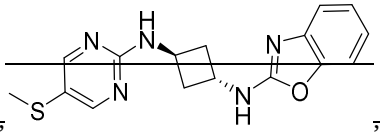
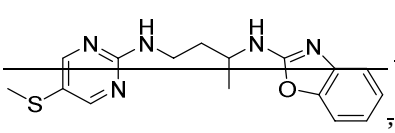
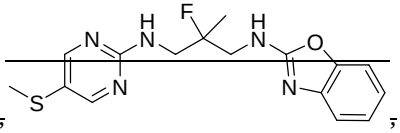
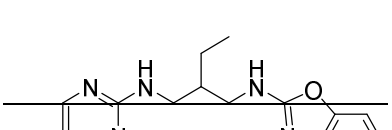
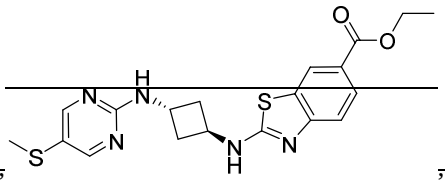


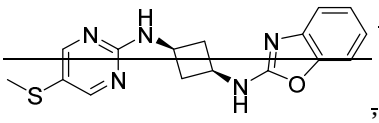
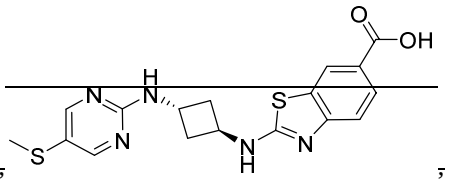
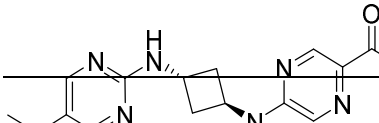


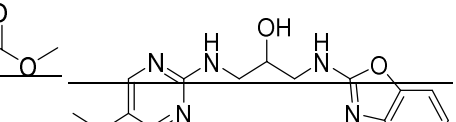
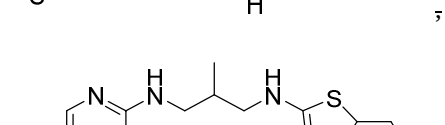
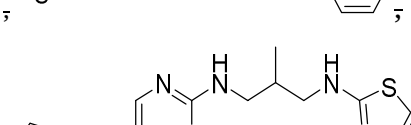



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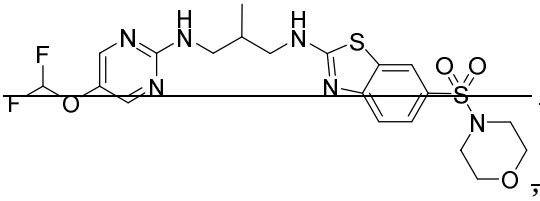
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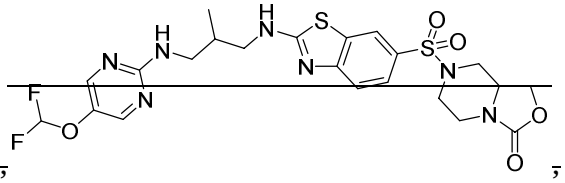












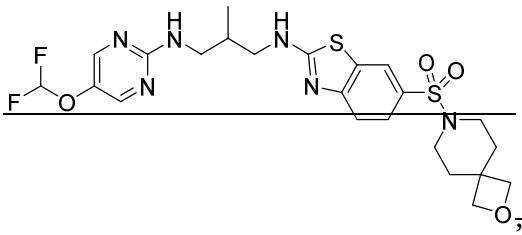





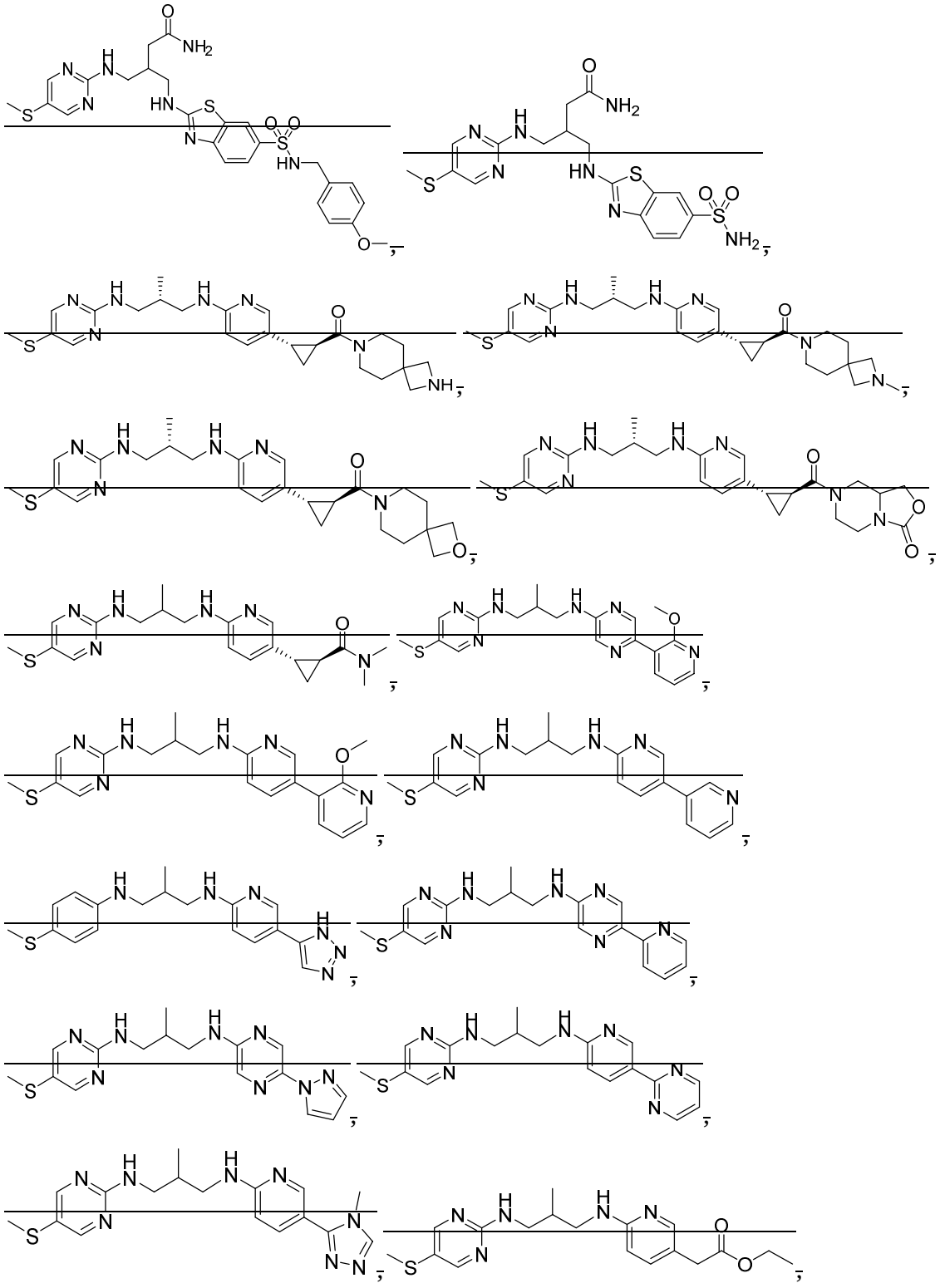




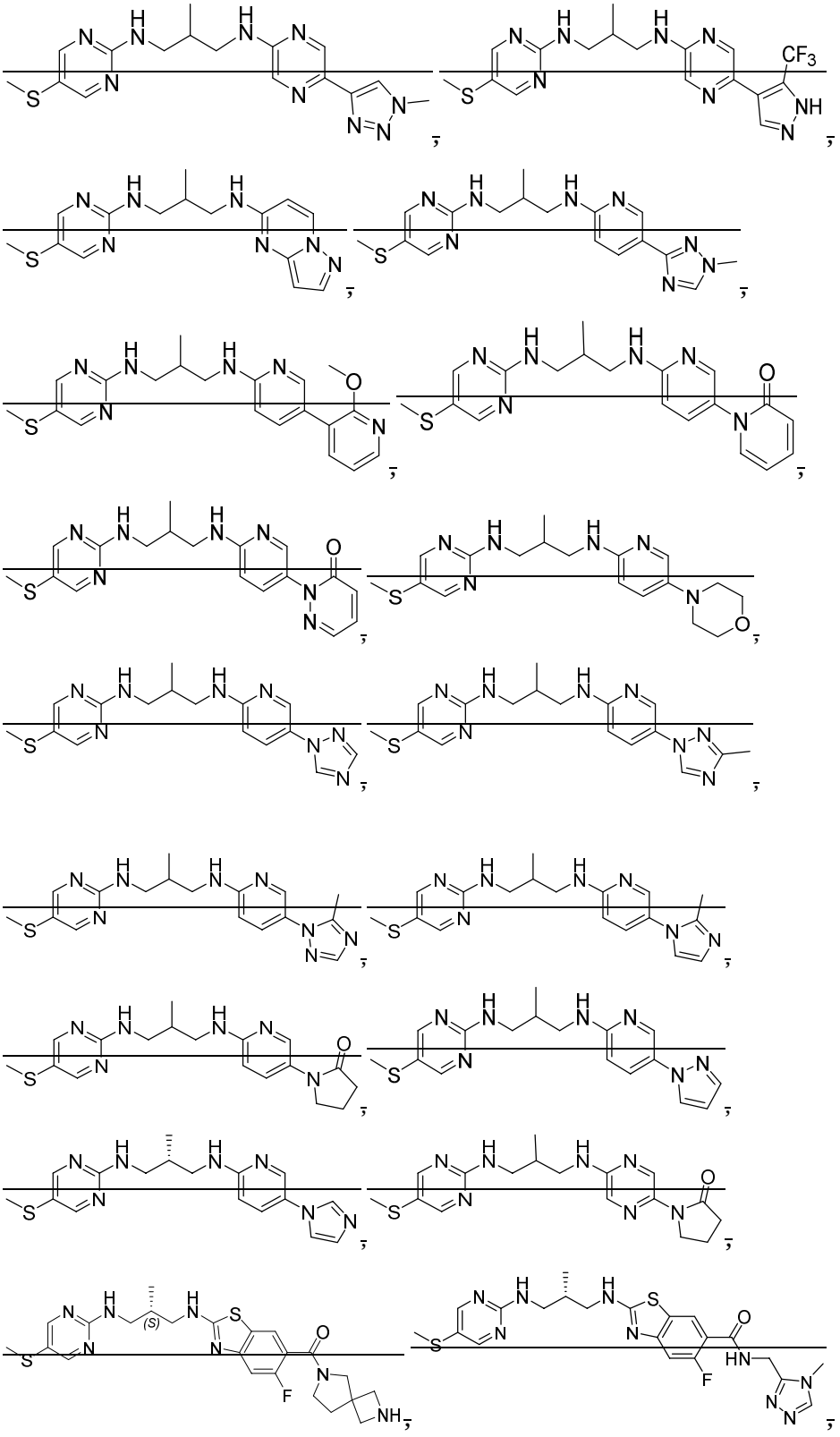


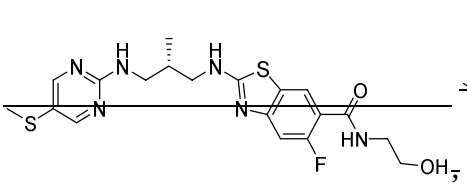


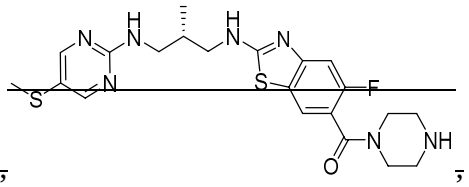


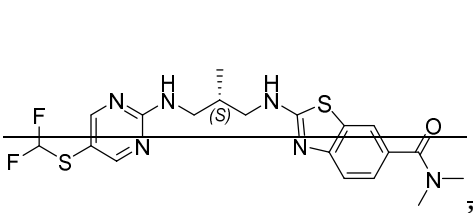


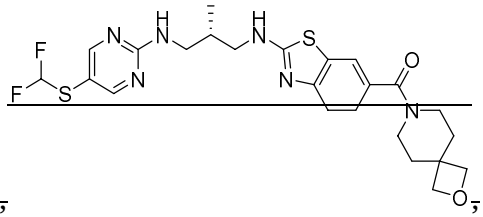


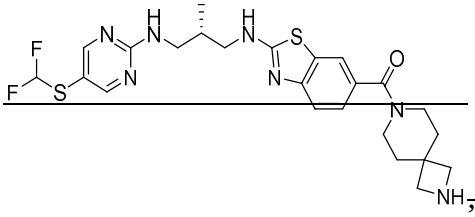


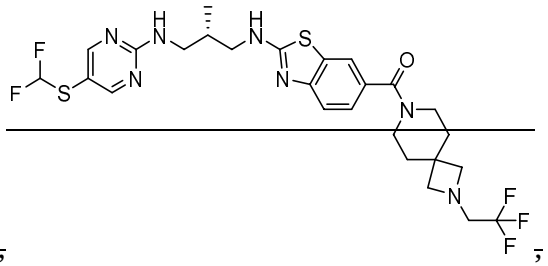


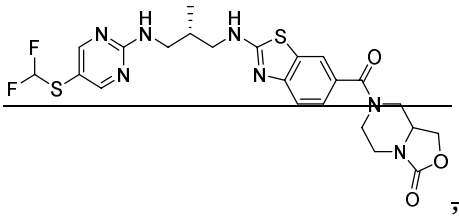


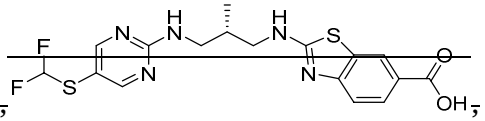


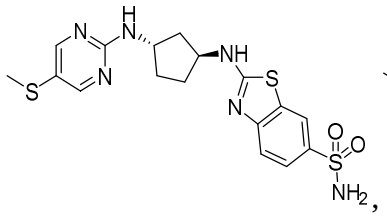


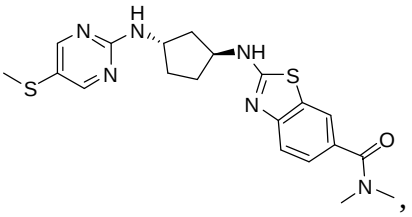


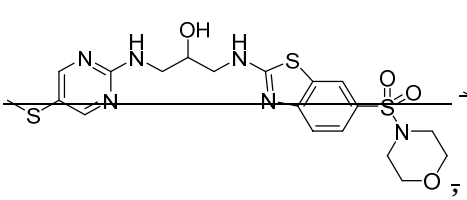


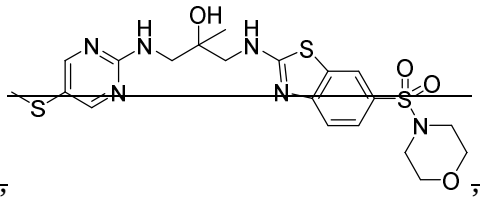


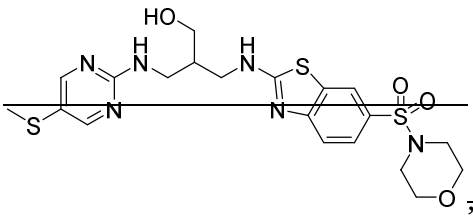


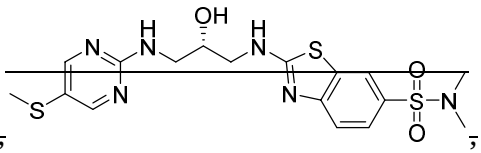


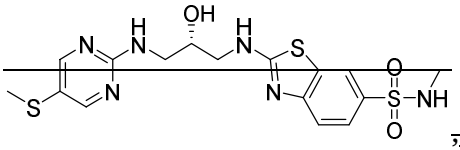


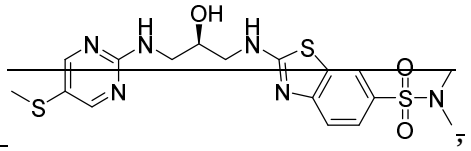


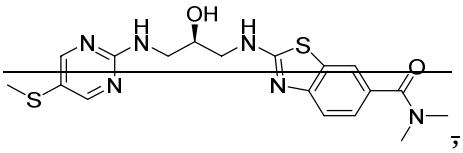


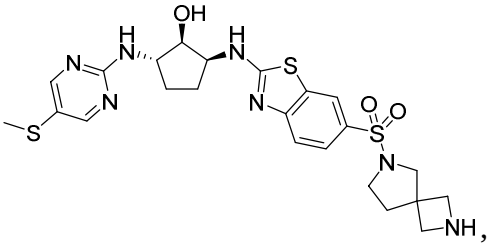


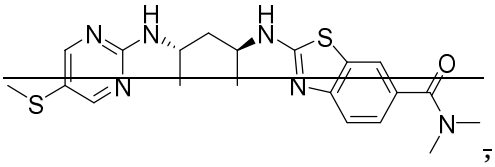


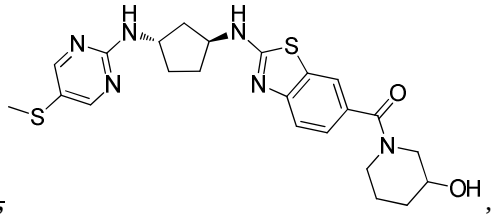

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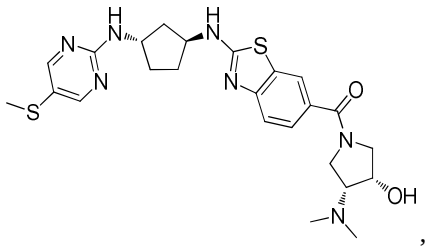

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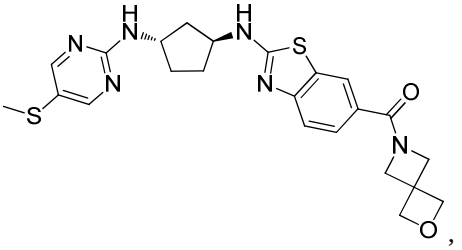

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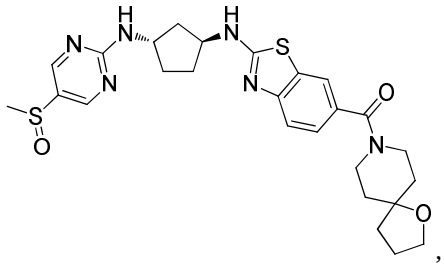

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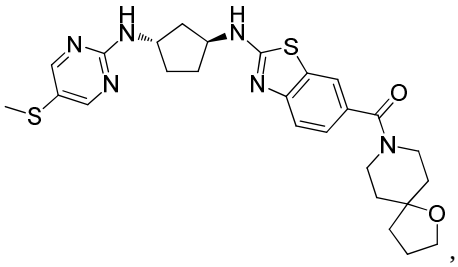

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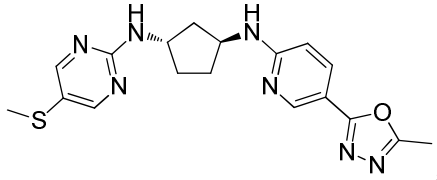

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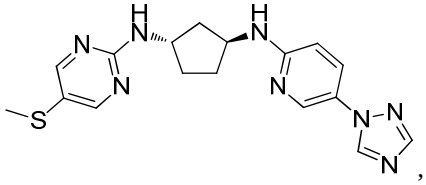

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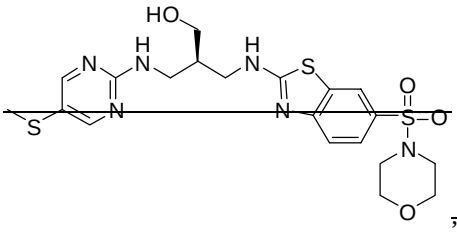
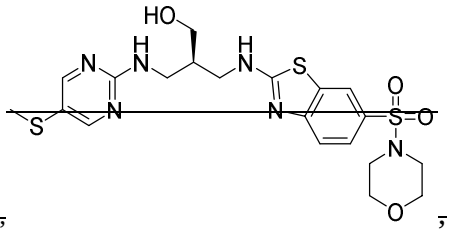
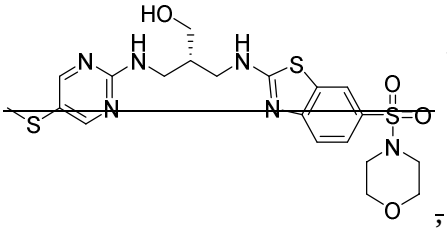
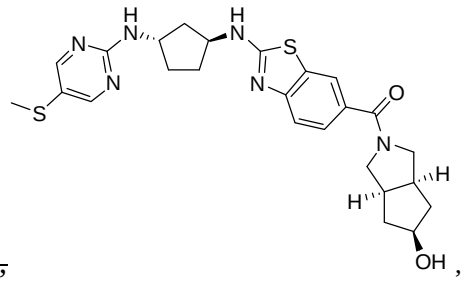
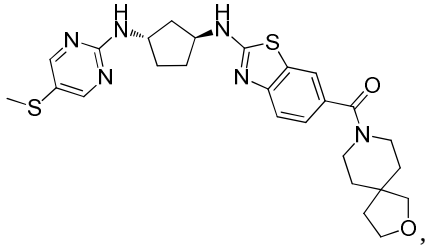
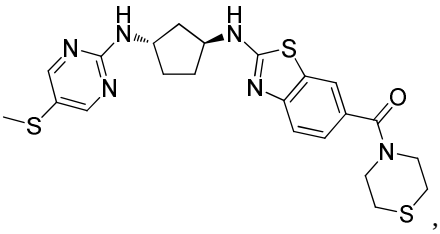
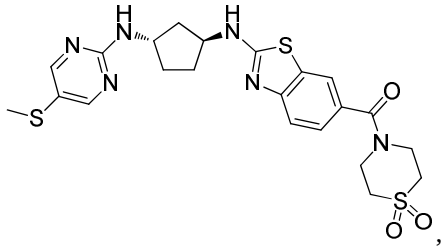
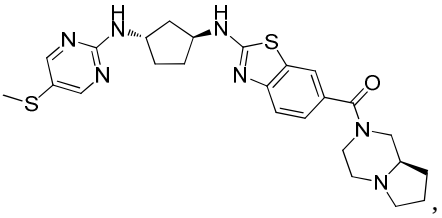
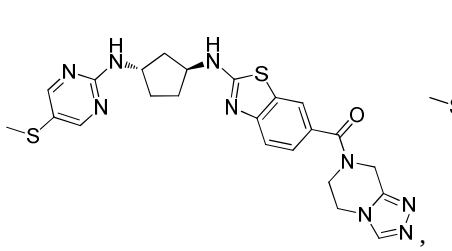
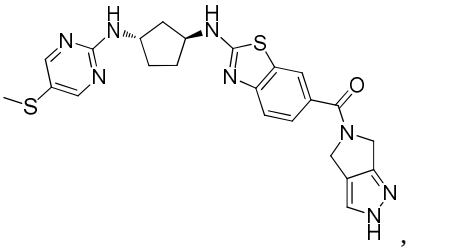

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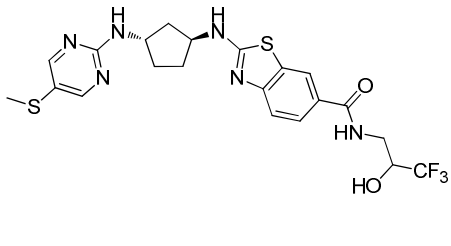
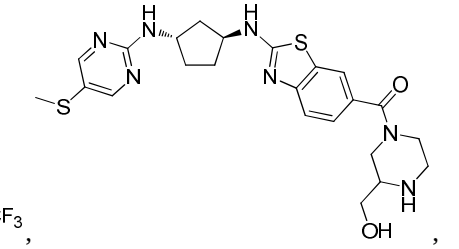

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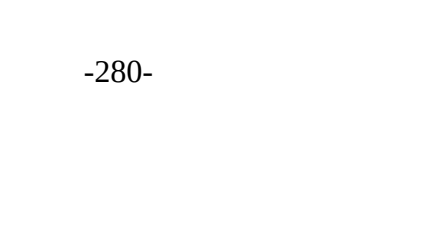

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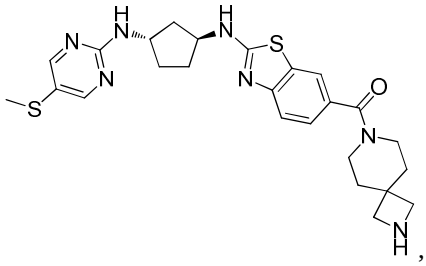
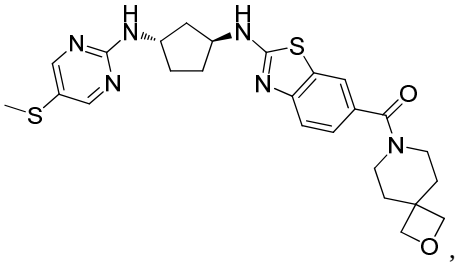
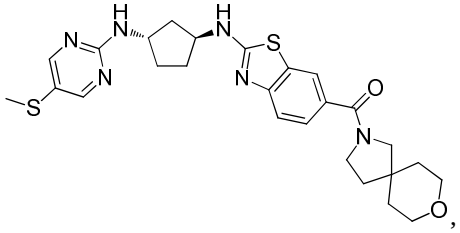
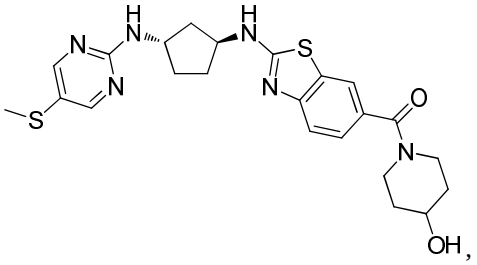
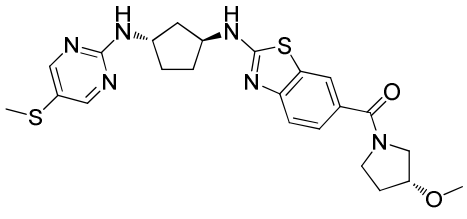
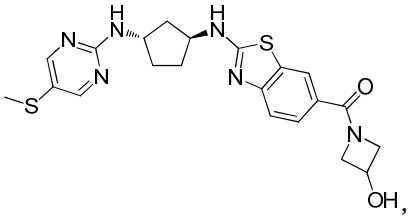
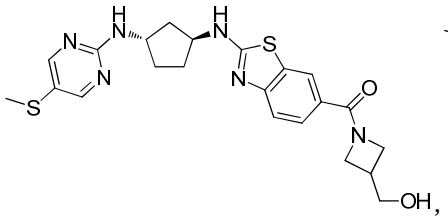
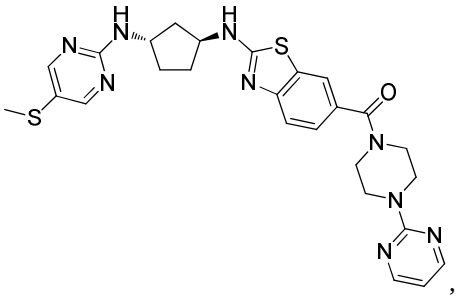
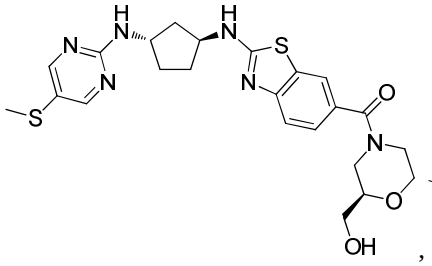
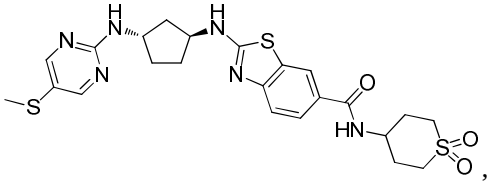
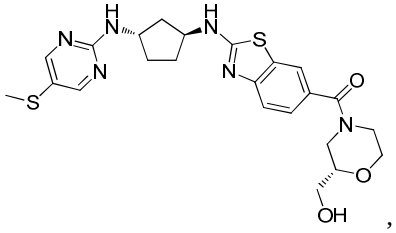
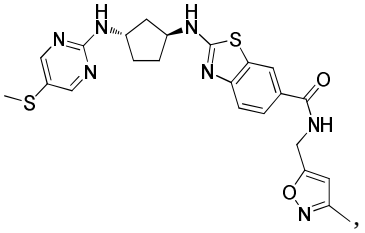
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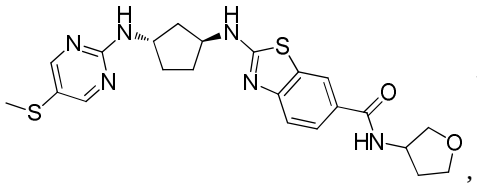
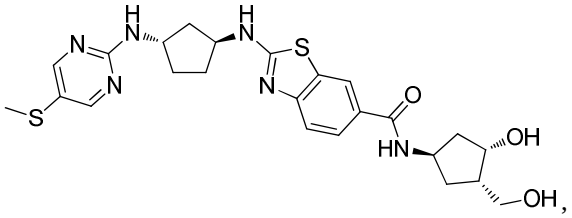
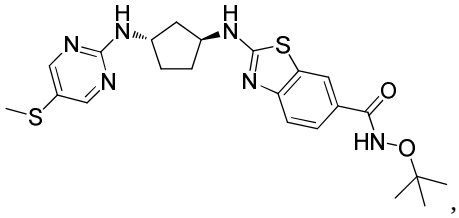
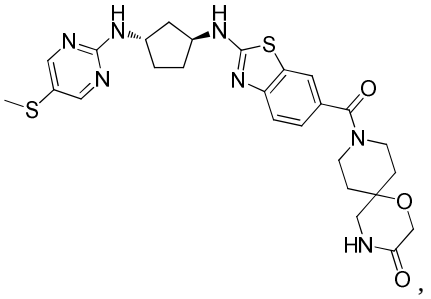
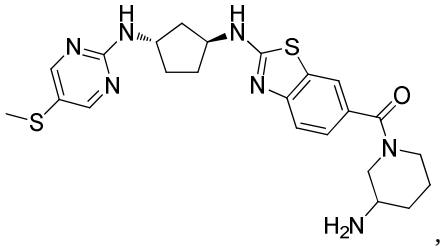
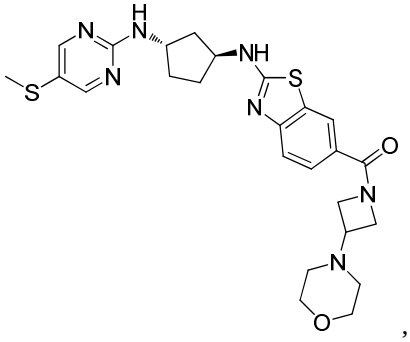
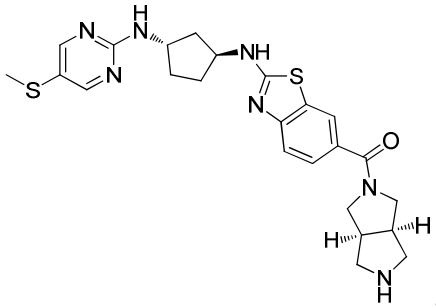
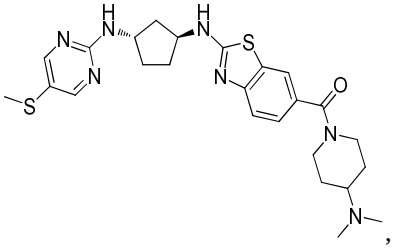
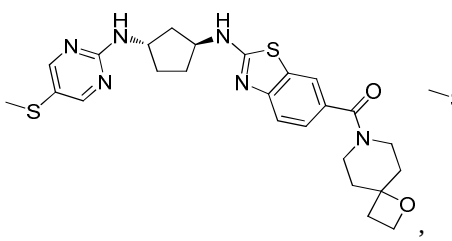
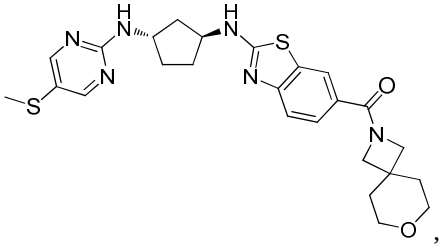
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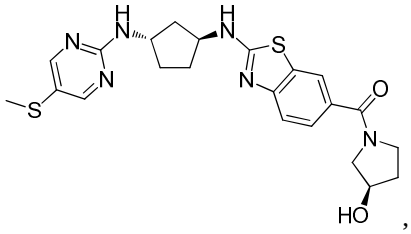
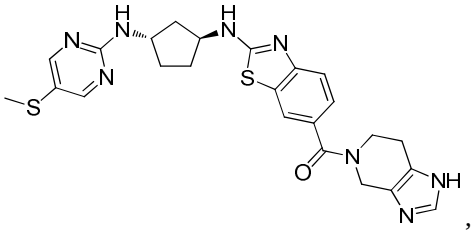
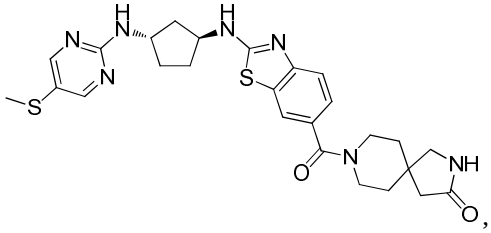
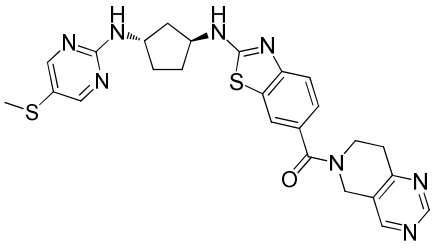
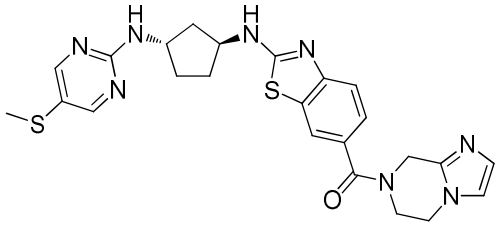
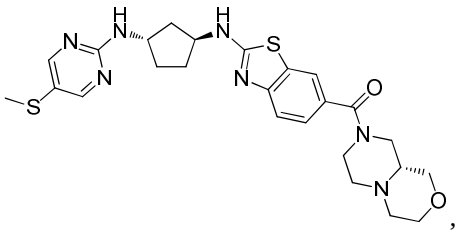
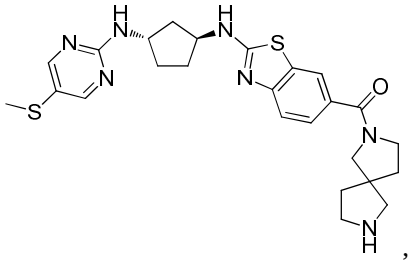
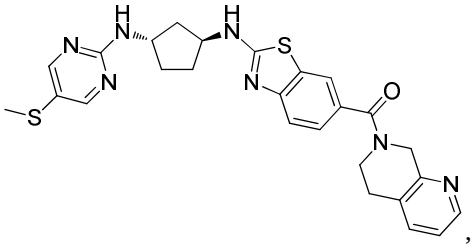
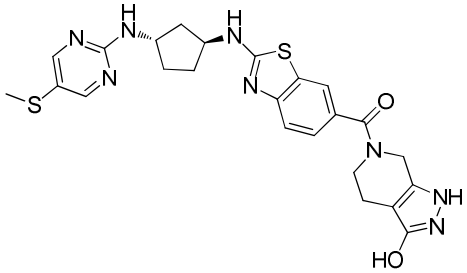
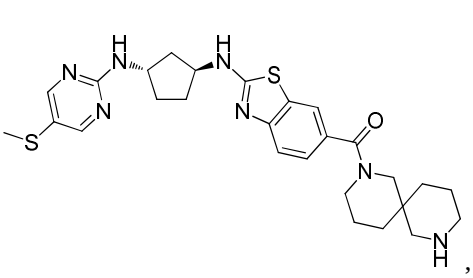
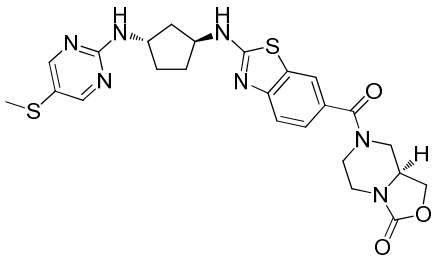
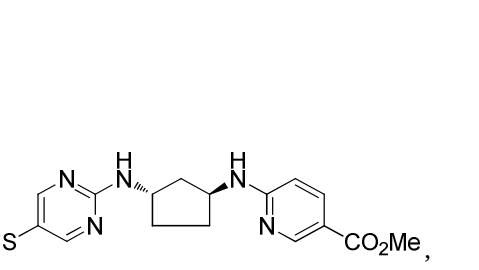
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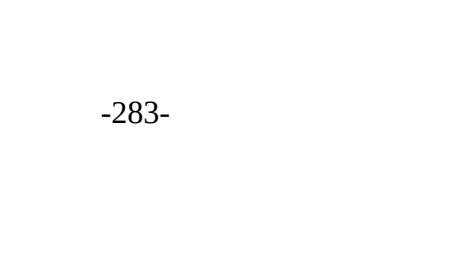
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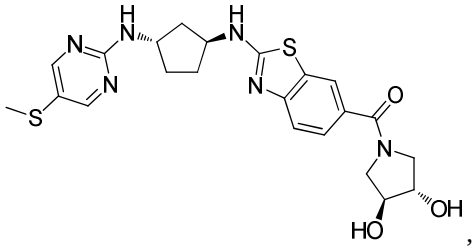
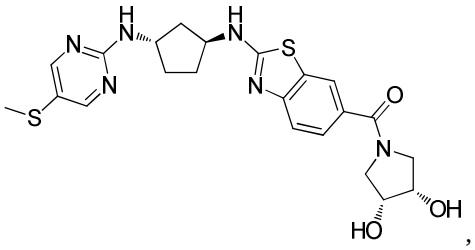
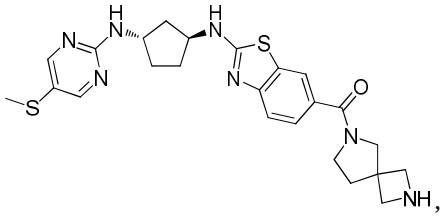
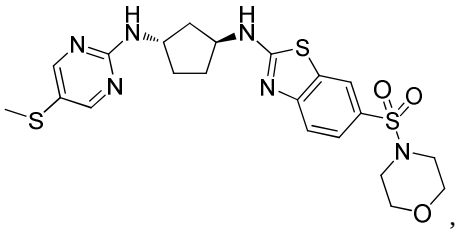
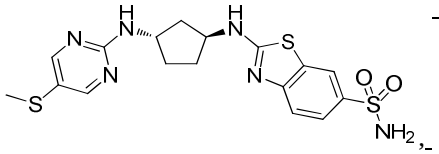
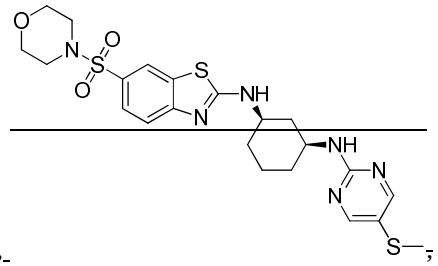
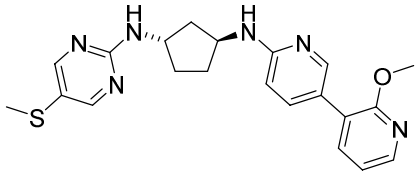
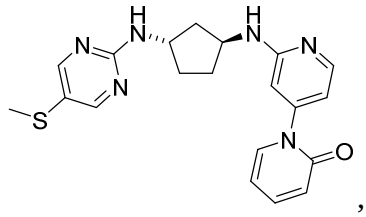
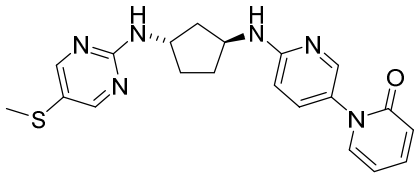
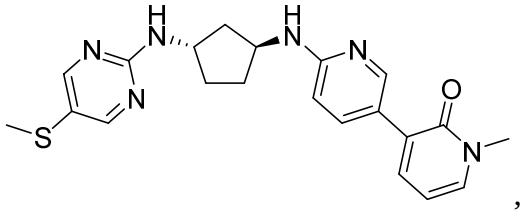
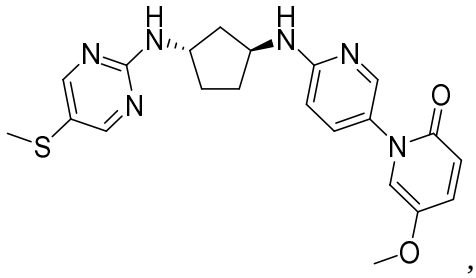
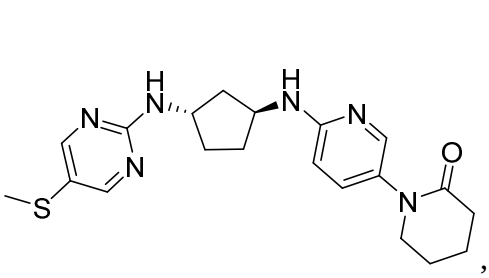
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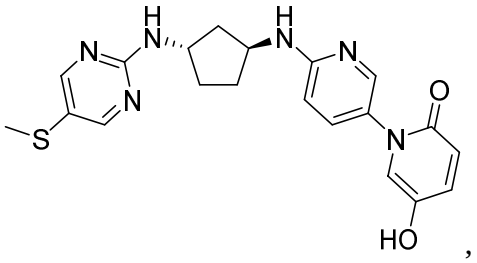
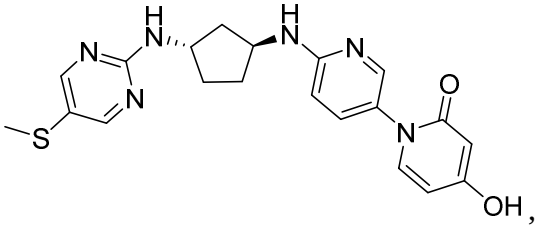
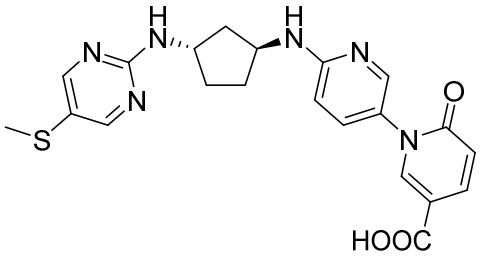
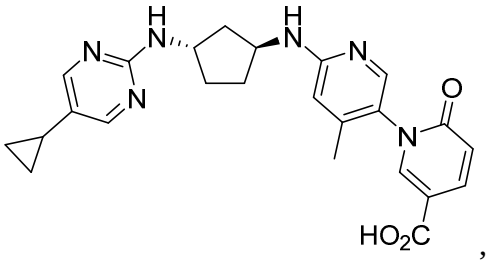
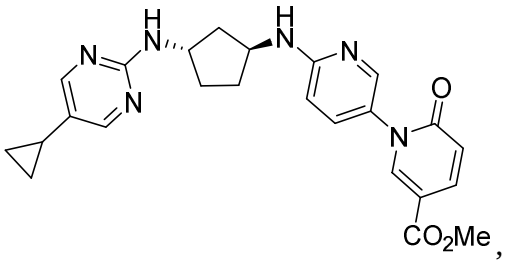
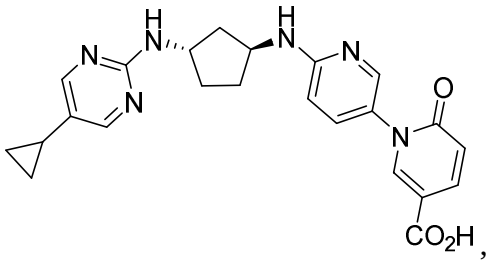
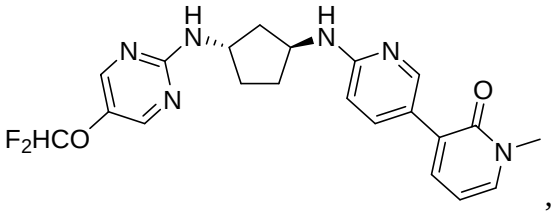
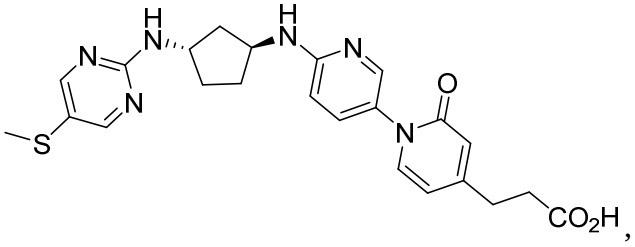
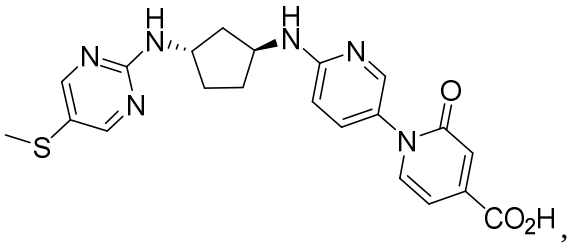
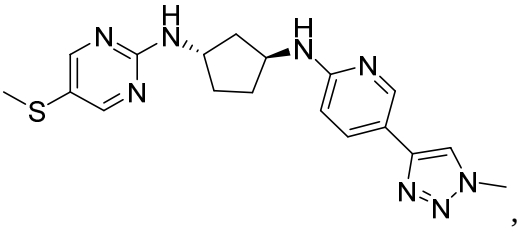

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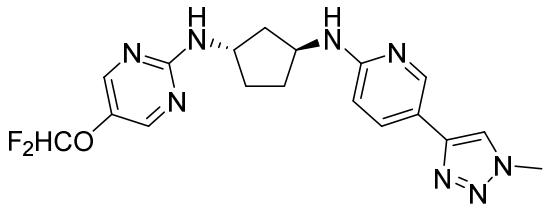
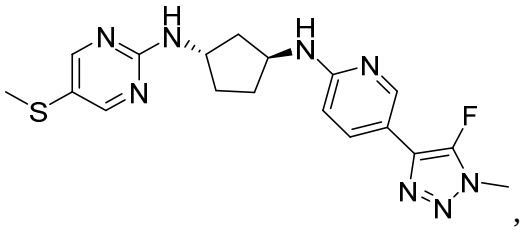
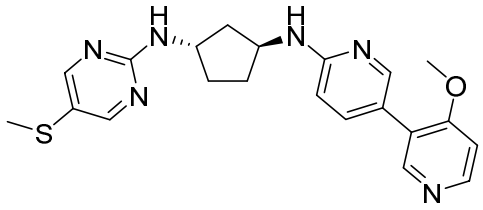
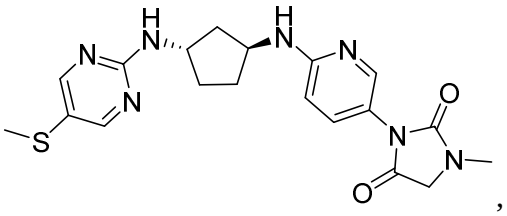
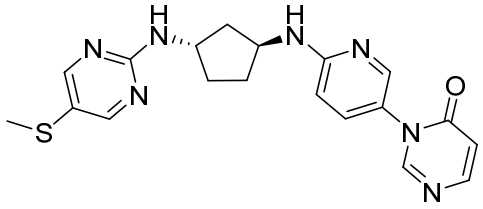
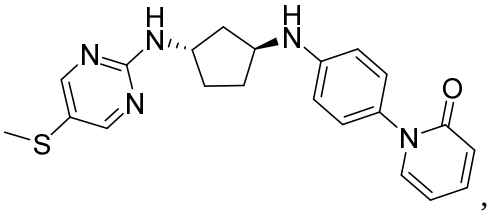
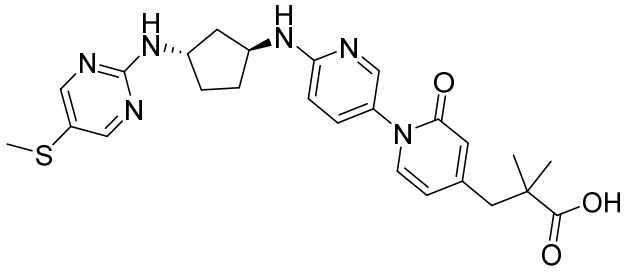
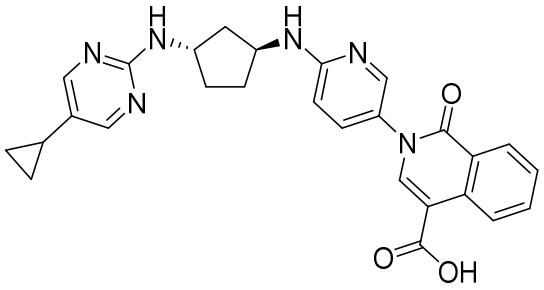
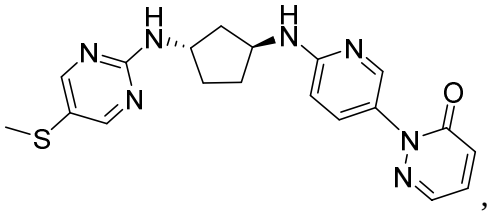
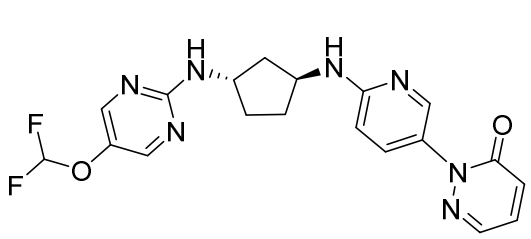
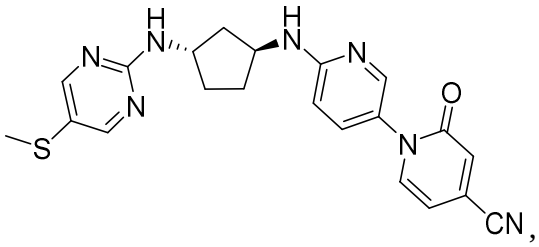
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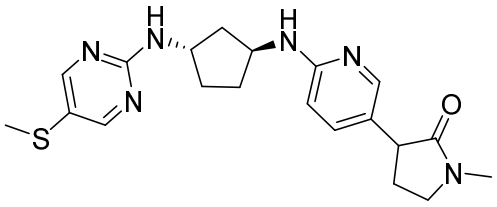
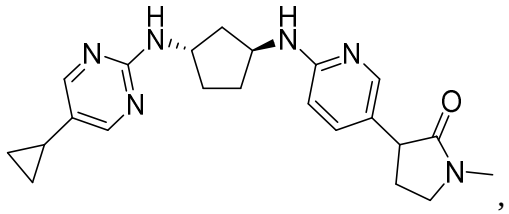
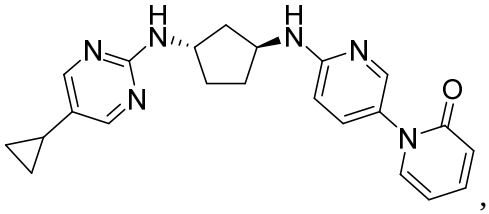
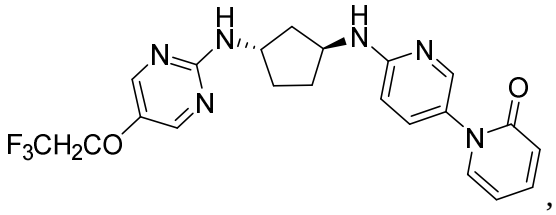
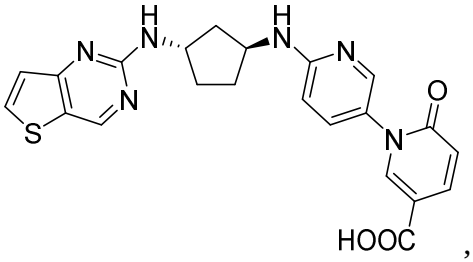
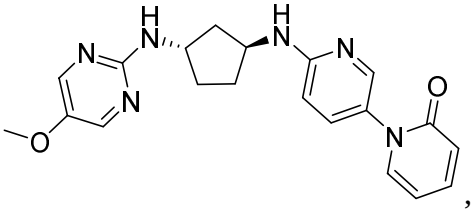
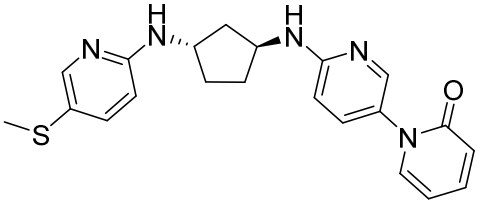
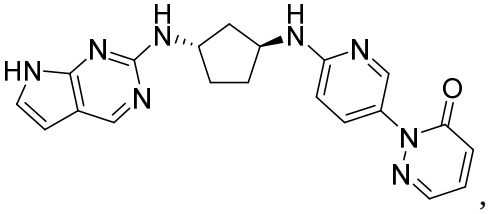
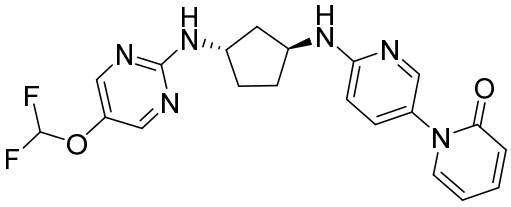
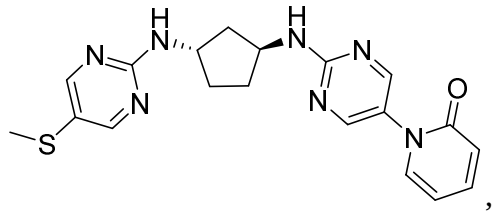
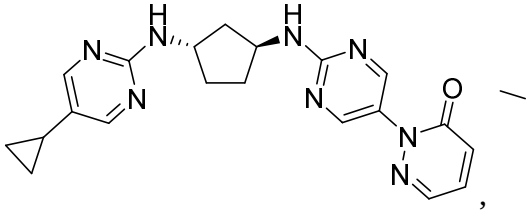
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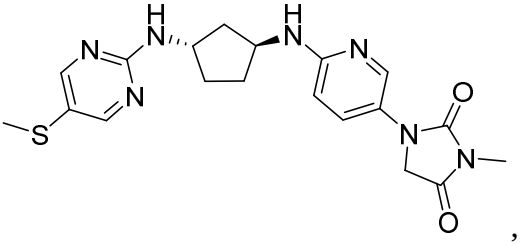
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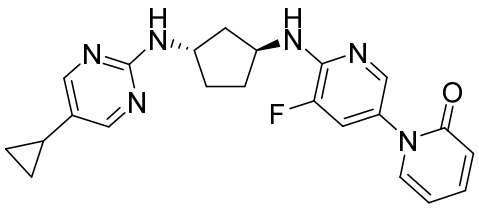
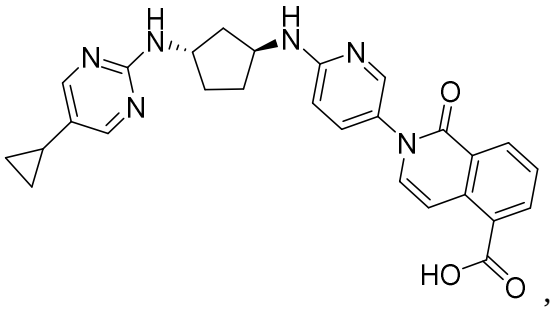
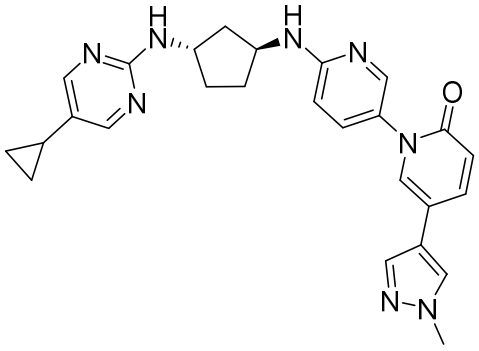
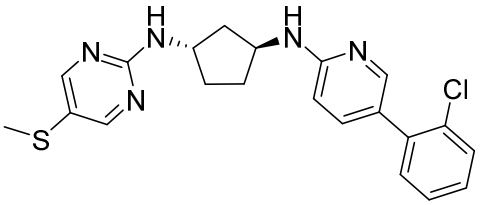
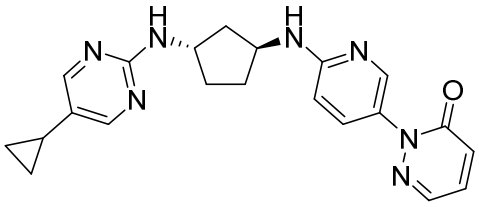
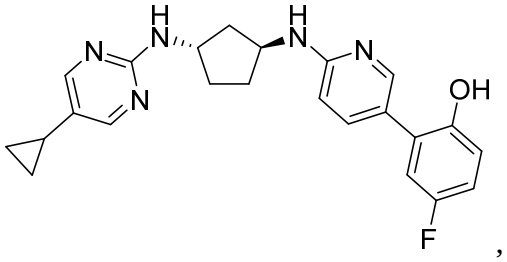
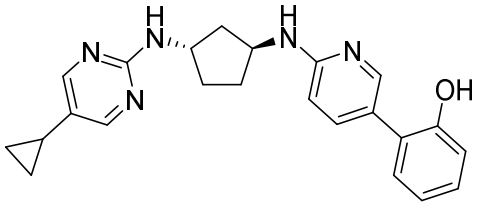
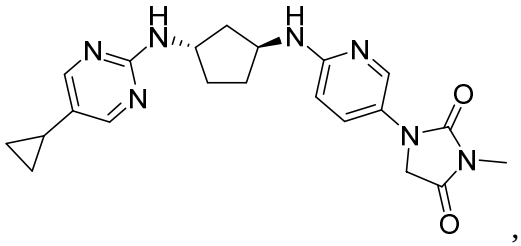
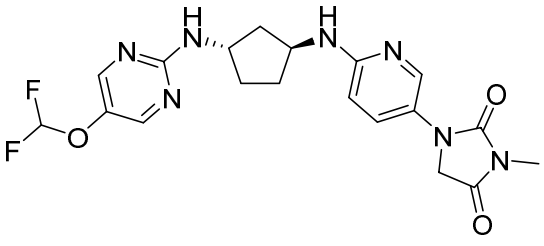
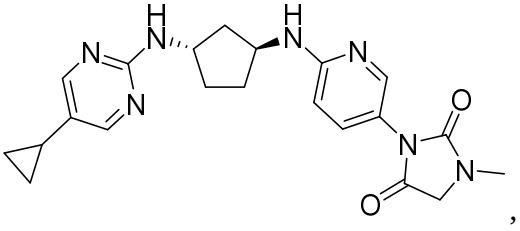

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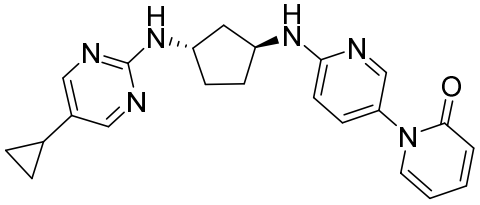
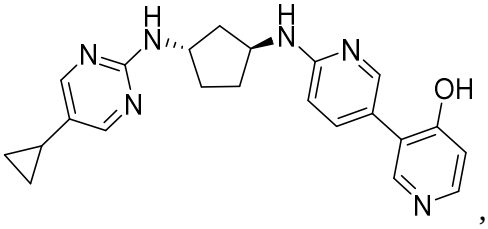
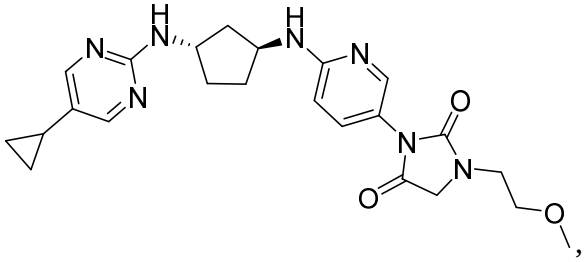
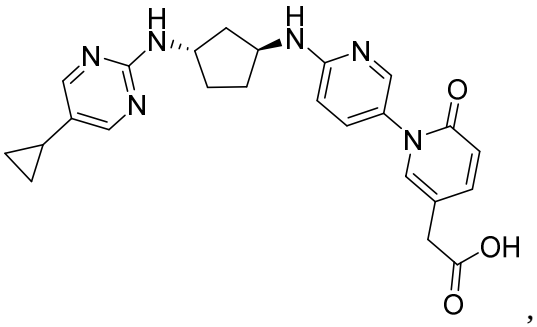
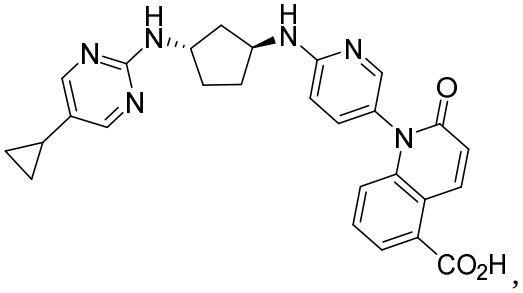
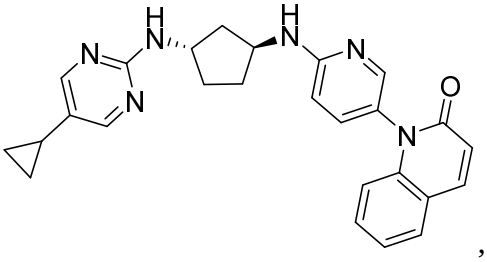
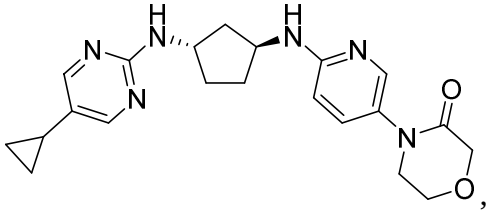
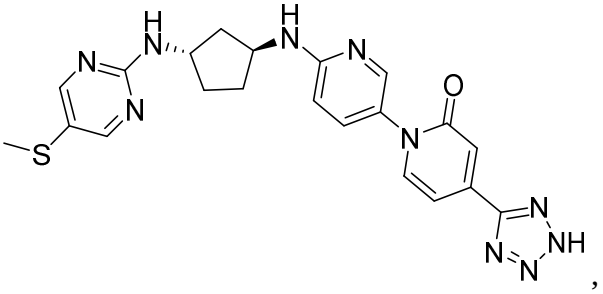
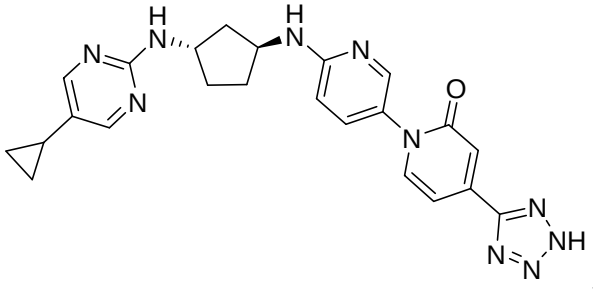
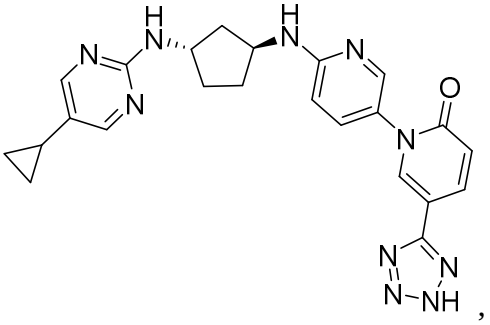

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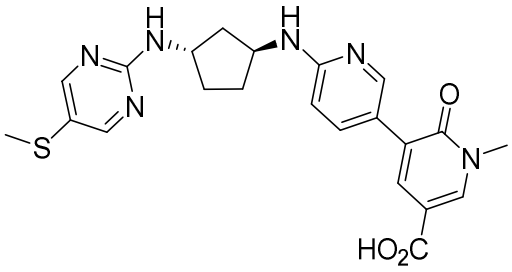
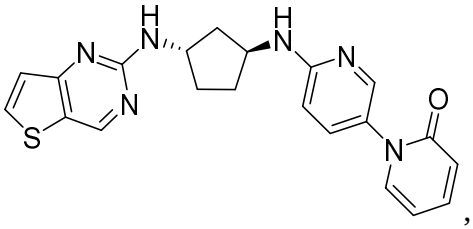
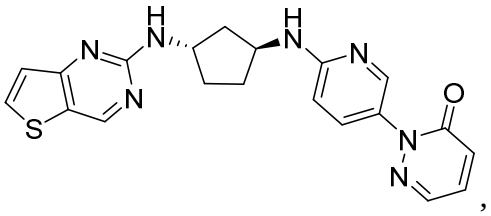
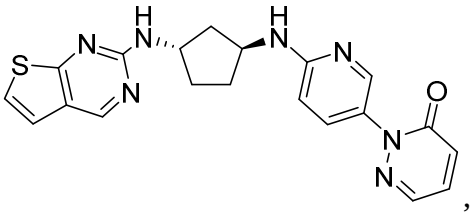
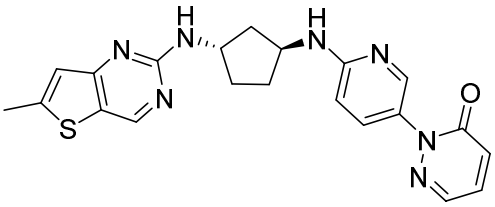
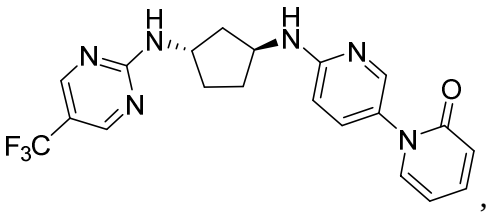
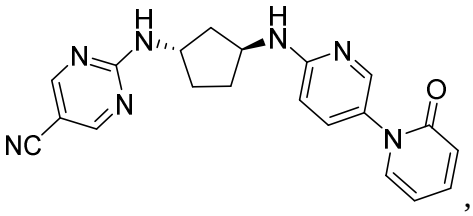
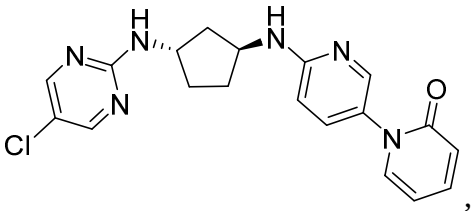
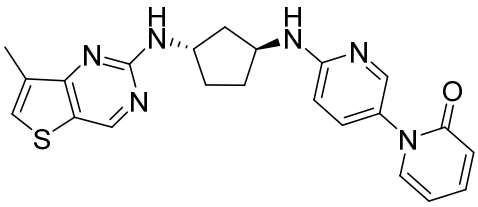
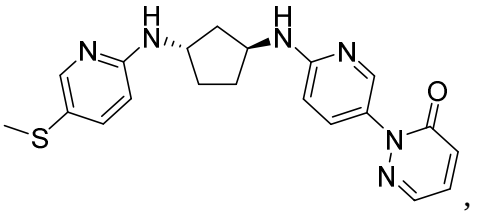
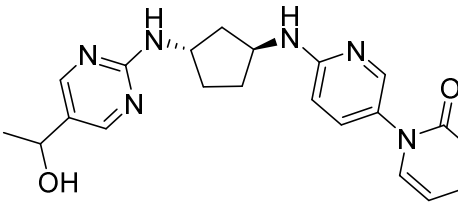

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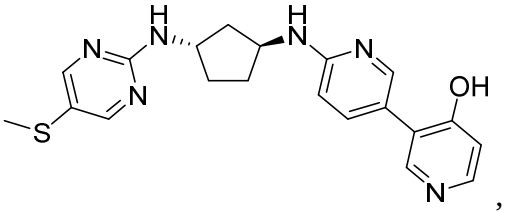
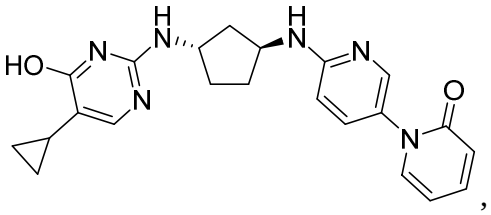
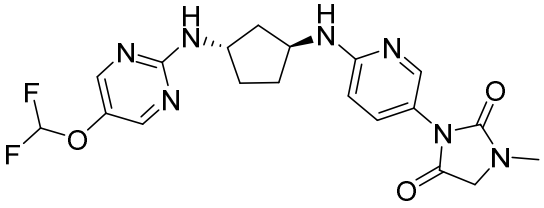
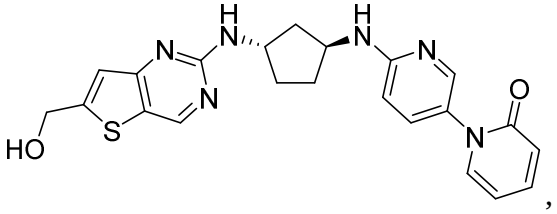
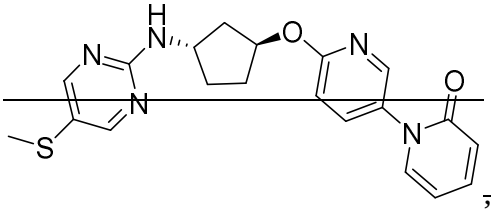
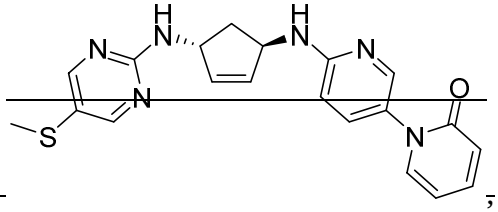
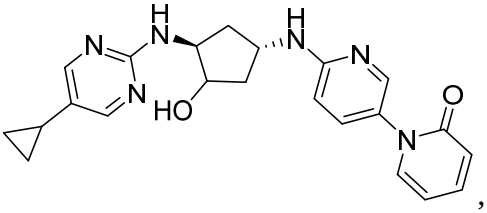
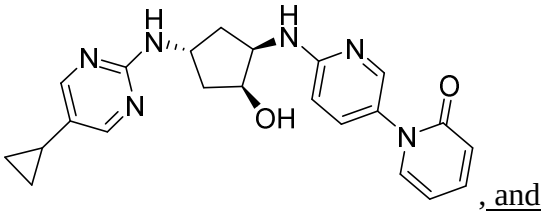
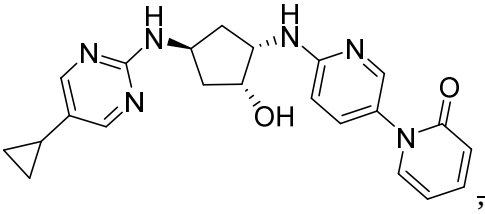
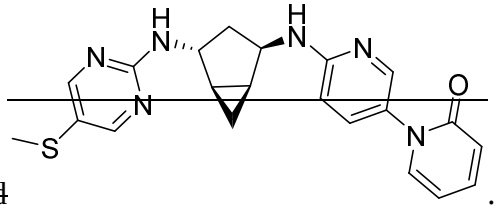

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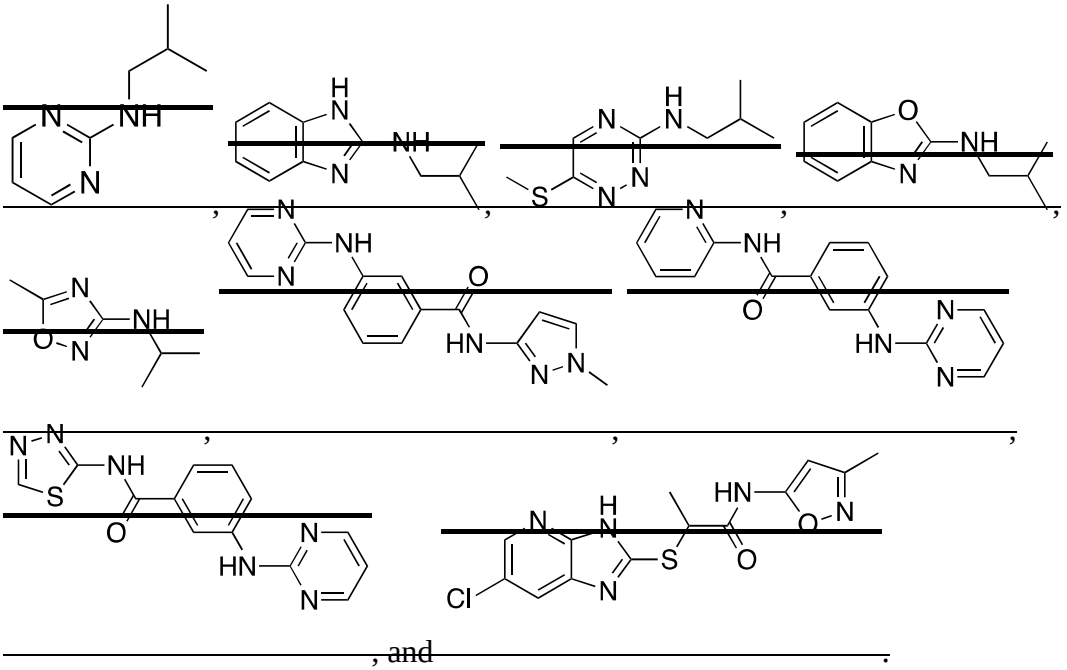
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~~39. The method of claim 20, wherein the inhibitor is selected from:~~



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33. The use of claim 2, wherein the cardiovascular disease is selected from the group consisting of dyslipidemia, hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, hypoalphalipoproteinemia, metabolic syndrome, diabetic complications, atherosclerosis, stroke, vascular dimensia, chronic kidney disease, coronary heart disease, coronary artery disease, retinopathy, inflammation, thrombosis, peripheral vascular disease or congestive heart failure.

34. The use of claim 2, wherein the cardiovascular disease is selected from the group consisting of hypercholesterolemia, hyperlipidemia, hyperlipoproteinemia, hypertriglyceridemia, dyslipidemia, dyslipoproteinemia, atherosclerosis, hepatic steatosis, metabolic syndrome and coronary artery disease.

35. The use of claim 33 or 34, wherein the hypercholesterolemia is familial hypercholesterolemia or autosomal dominant hypercholesterolemia.