Claims:

1. An inhibitor of PCSK9 that binds to a binding pocket in the C-terminal domain of human PCSK9 created between amino acid residues 558-590 and 631-650,

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 in the C-terminal domain of human PCSK9 created between amino acid residues 558-590 and 631-650,

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

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

5. The inhibitor for use of claim 1 or the use of claim 2, wherein the inhibitor is to be contacted with PCSK9 that is circulating in plasma.

6. The inhibitor for use of any one of claims 1 or 3-5 or the use of any one of claims 2-5, 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 inhibitor for use of any one of claims 1 or 3-5 or the use of any one of claims 2-5, 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 inhibitor for use or the use of claim 6, 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 inhibitor for use or the use 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 inhibitor for use or the use of any one of claims 6-9, 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.

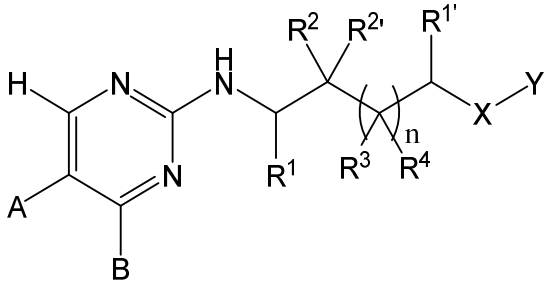
11. The inhibitor for use of any one of claims 1 or 3-10 or the use of any one of claims 2-10, wherein the inhibitor comprises an H-bond acceptor moiety disposed to bind with amino acid residue Glu612.

12. The inhibitor for use of any one of claims 1 or 3-11 or the use of any one of claims 2-11, wherein the inhibitor interacts with at least one residue in the M1 C-terminal domain.

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

14. The inhibitor for use or the use of claim 13, 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.

15. The inhibitor for use of any one of claims 1 or 3-14 or the use of any one of claims 2-14, 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;

n is 0, and R^1 and $R^{1'}$, together with the atoms to which they are attached, form a cyclopentyl ring;

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

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

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

R^5 is H or alkyl;

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

Y is selected from aryl and heteroaryl.

16. The inhibitor for use or the use of claim 15, wherein A is selected from H, hydroxy, thioalkyl, alkyl, alkoxy, acyloxy, cyano, cycloalkyl, $-C(O)OR^6$, and $-C(O)NR^6R^7$.

17. The inhibitor for use or the use of claim 16, wherein A is alkoxy.

18. The inhibitor for use or the use of claim 16, wherein A is cycloalkyl.

19. The inhibitor for use or the use of any one of claims 15-18, wherein B is H.

20. The inhibitor for use or the use of any one of claims 15-19, wherein Y is heteroaryl.

21. The inhibitor for use or the use of any one of claims 15-20, wherein R^2 is selected from H, halo, alkyl, alkoxy, amidoalkyl, aminoalkyl, alkylamino, cyano, and hydroxyl.

22. The inhibitor for use or the use of any one of claims 15-21, wherein $R^{2'}$ is H.

23. The inhibitor for use or the use of any one of claims 18-22, wherein Y is monocyclic heteroaryl.

24. The inhibitor for use or the use of claim 23, wherein Y is selected from pyridyl, pyridinyl, pyrazinyl, pyrimidinyl, and thiazolyl.

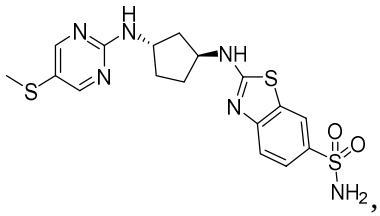
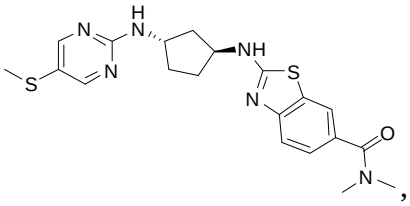
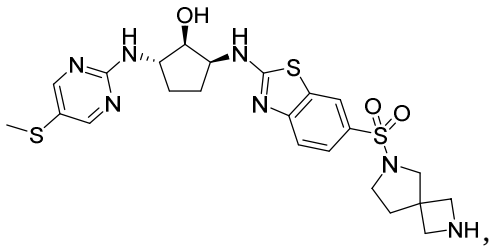
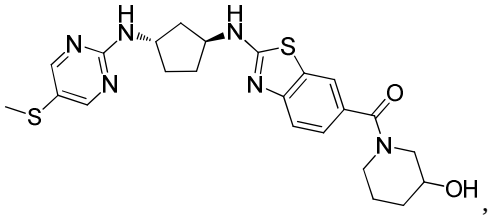
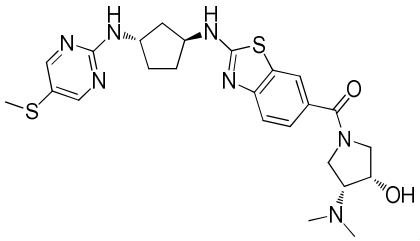
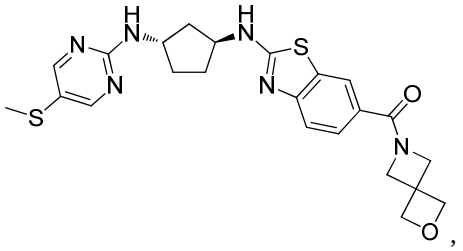
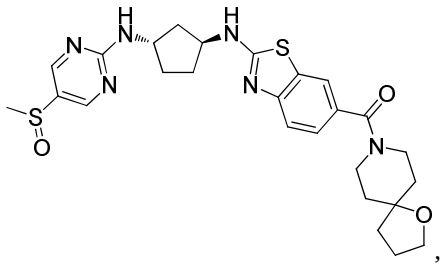
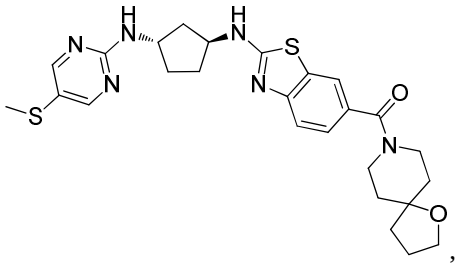
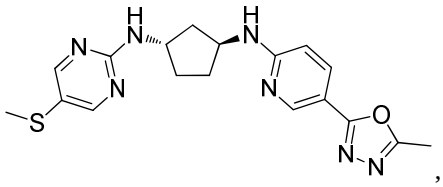
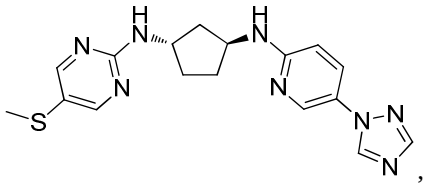
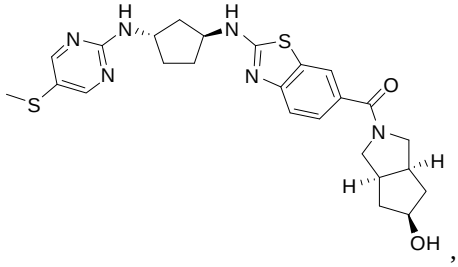
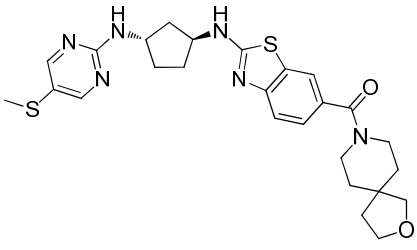
25. The inhibitor for use or the use of claim 23, wherein Y is selected from oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, and triazolyl.

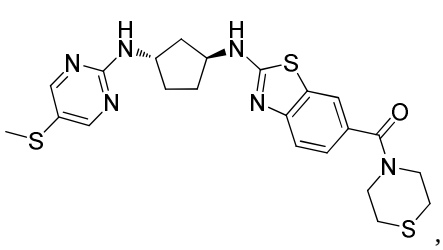
26. The inhibitor for use or the use of any one of claims 23-25, wherein the monocyclic heteroaryl is unsubstituted or substituted with one or more substituents selected from alkyl, thioalkyl, alkoxy, alkoxycarbonyl, amido, carboxy, cyano, halo, aryl, heteroaryl, heterocyclyl, nitro, sulfonamido, and thioalkyl.

27. The inhibitor for use or the use of claim 26, 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.

28. The inhibitor for use or the use of claim 27, wherein the heteroaryl or heterocyclyl is substituted with one or more substituents selected from halo, CN, alkyl, alkoxy, hydroxy, carboxy, -CO_2alkyl, and tetrazolyl.

29. The inhibitor for use or the use of claim 15, wherein the inhibitor is selected from

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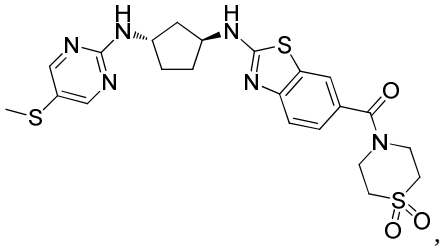
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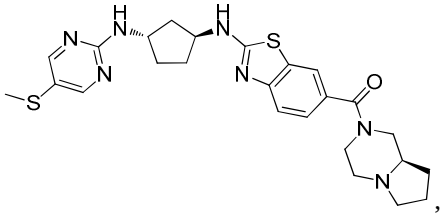
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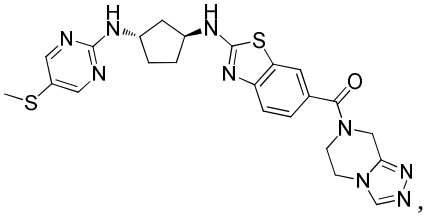
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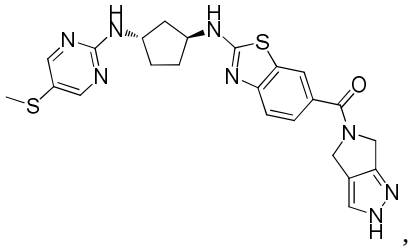
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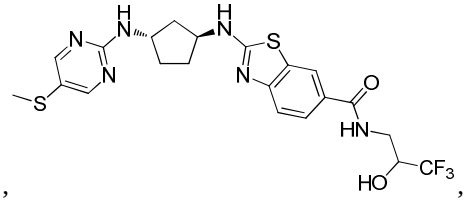
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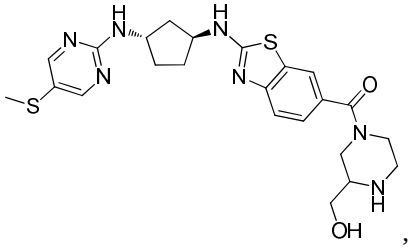
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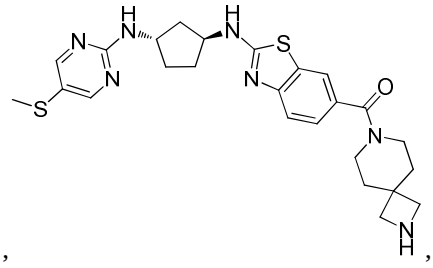
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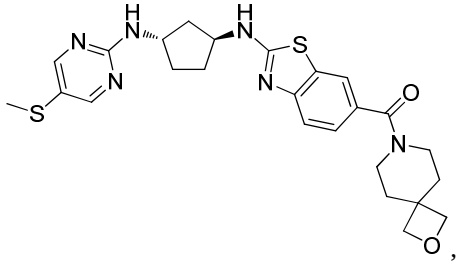
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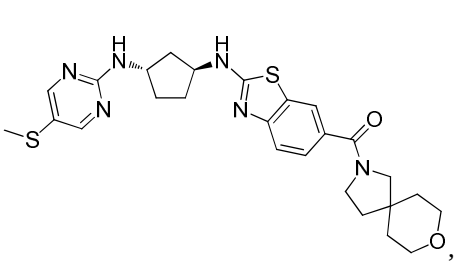
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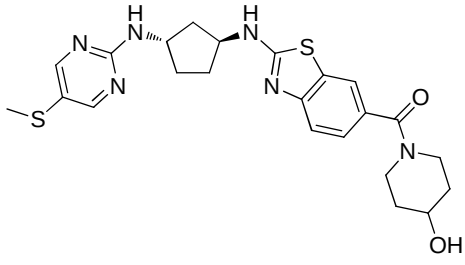
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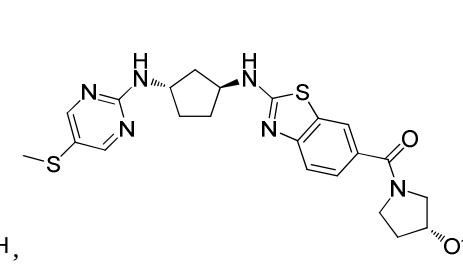
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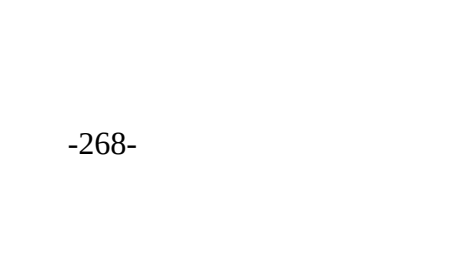
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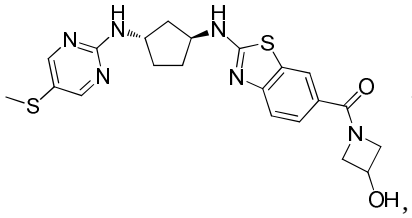
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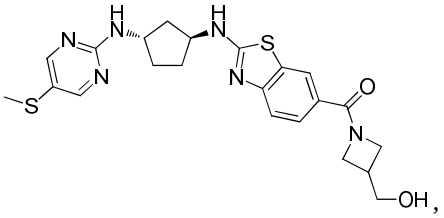
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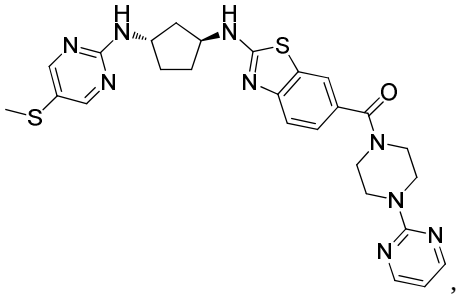
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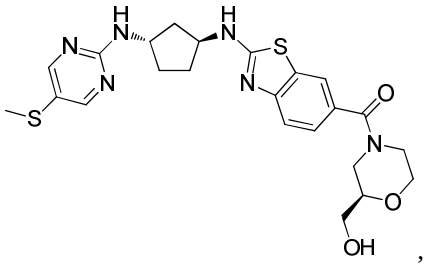
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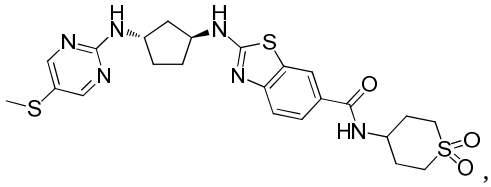
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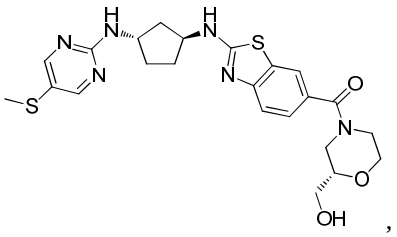
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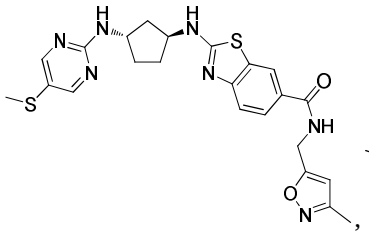
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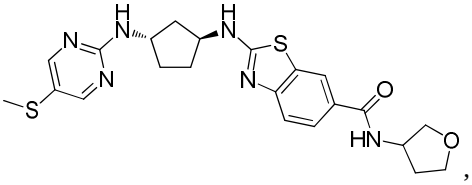
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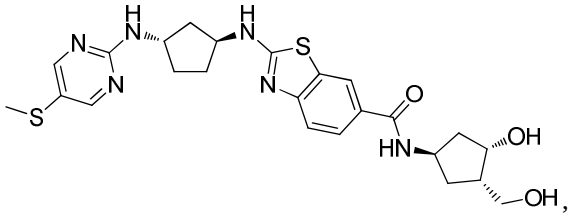
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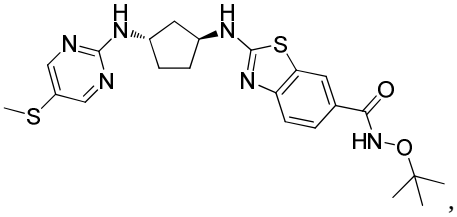
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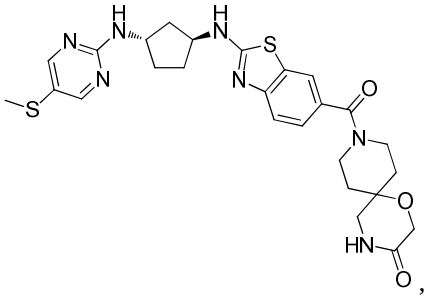
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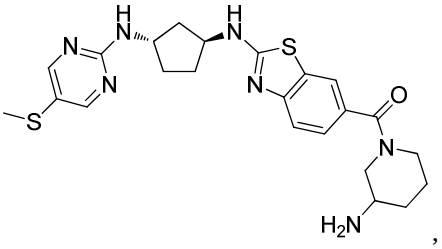
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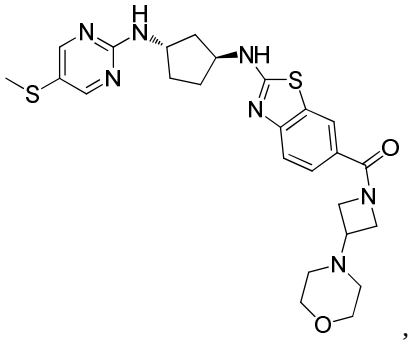
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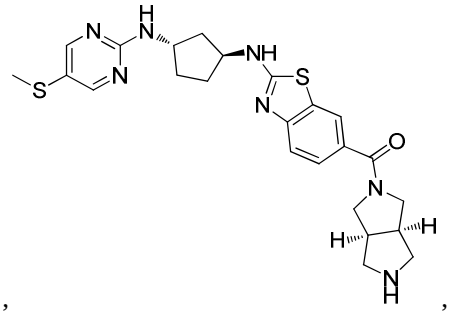
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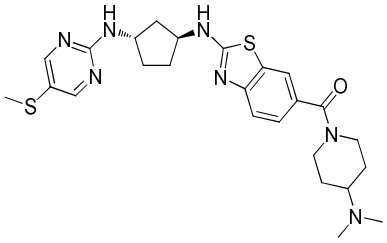
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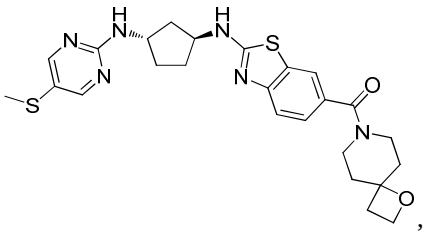
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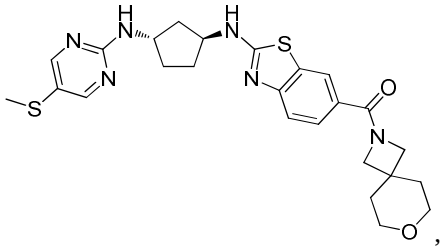
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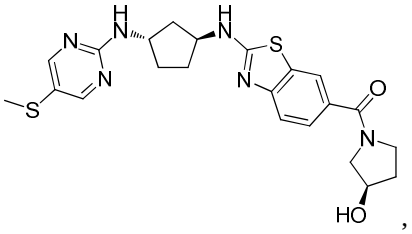
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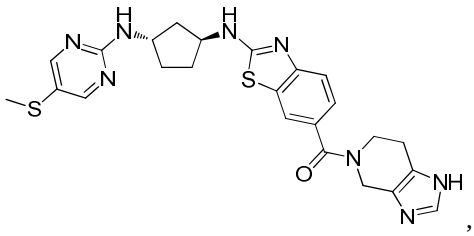
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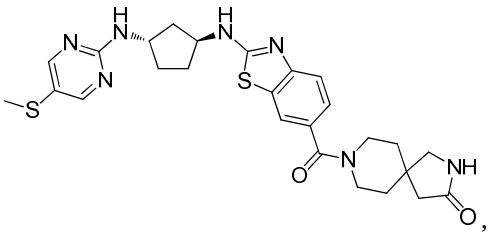
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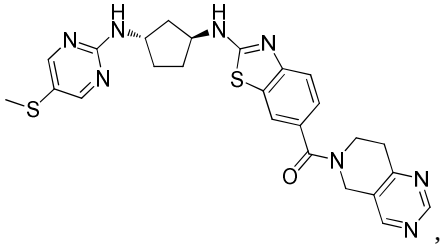
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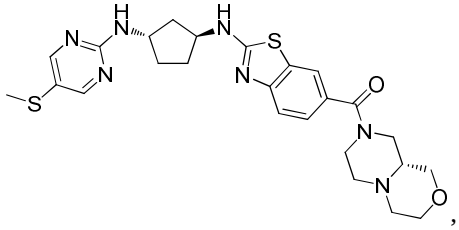
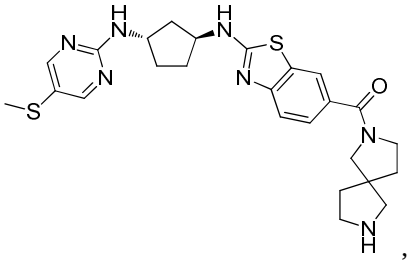
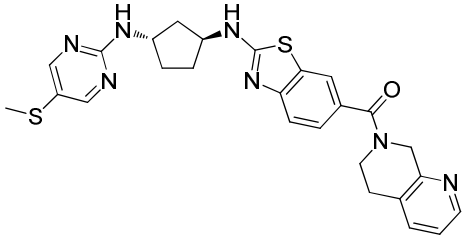
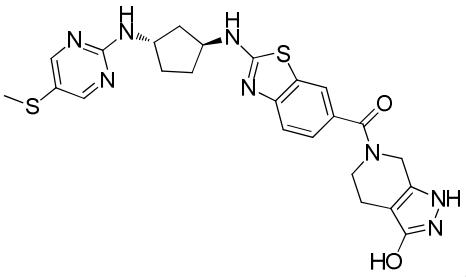
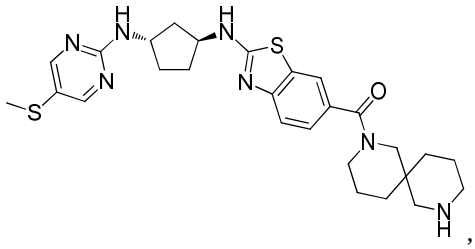
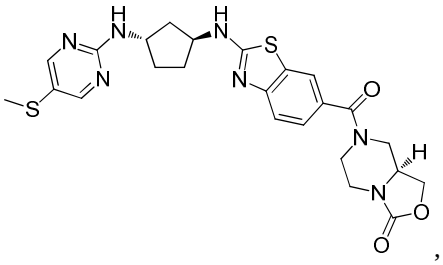
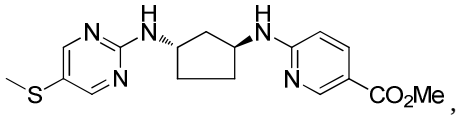
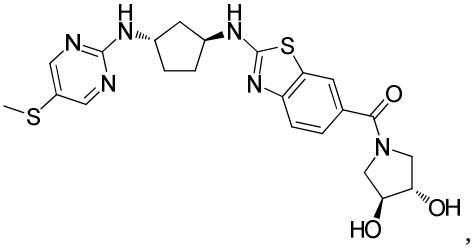
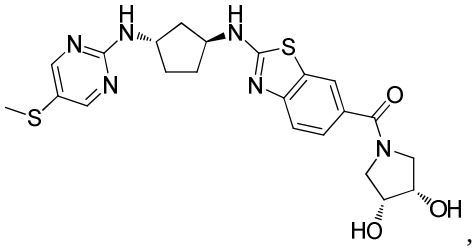
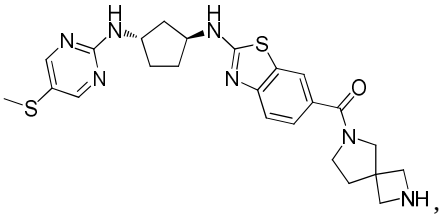
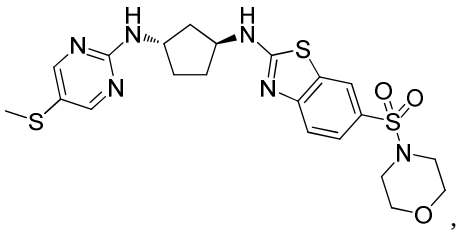
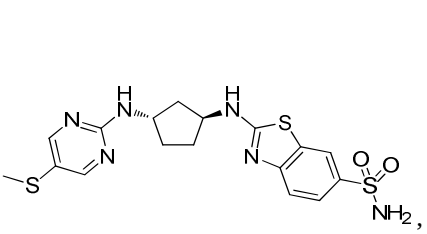
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
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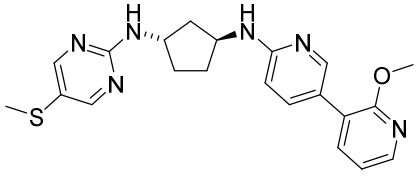
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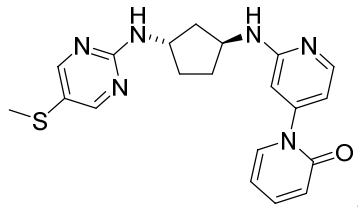
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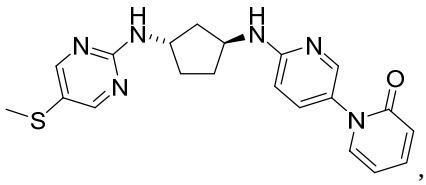
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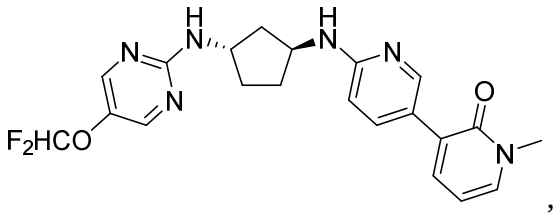

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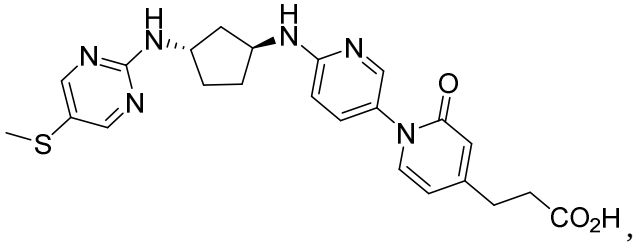

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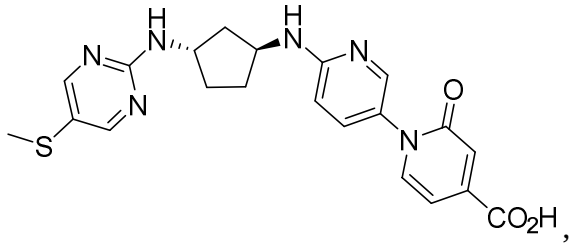

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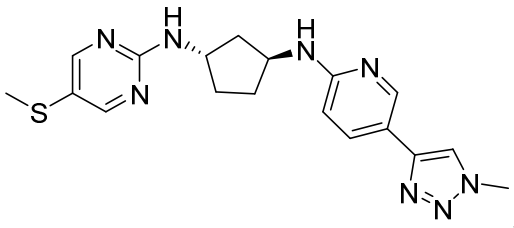

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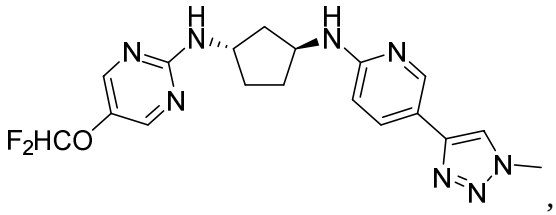

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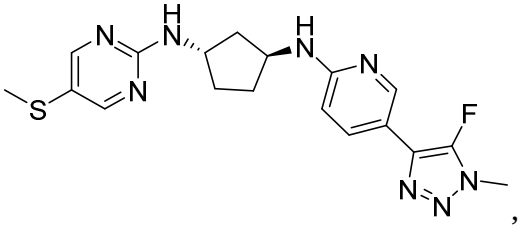

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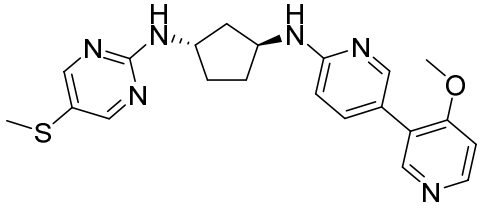

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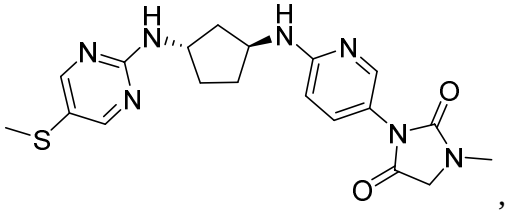

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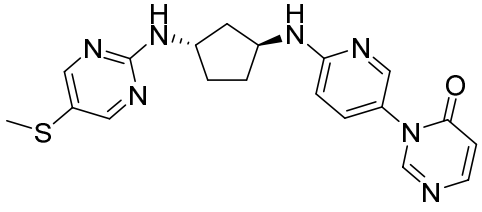

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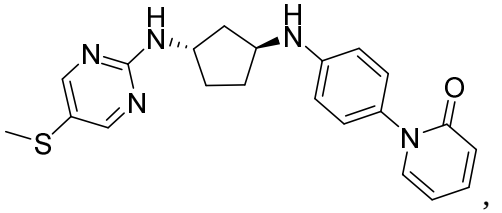

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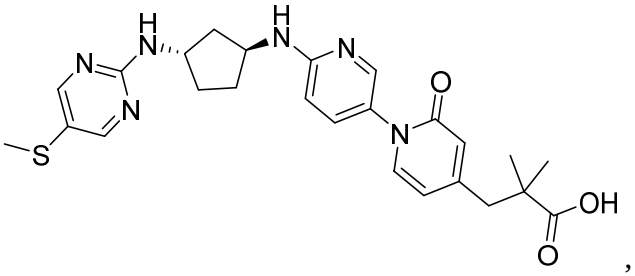
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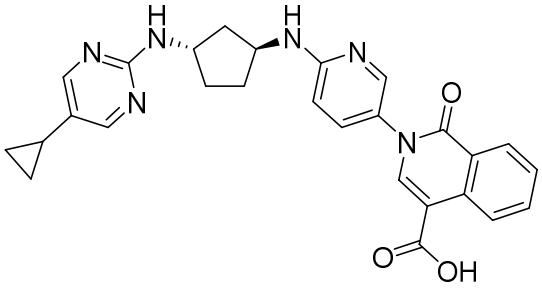
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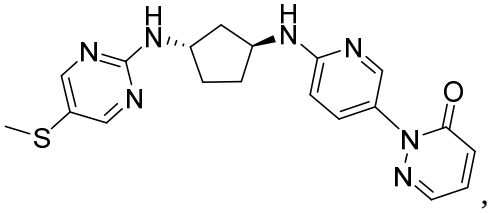
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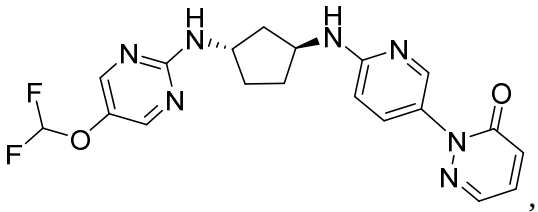
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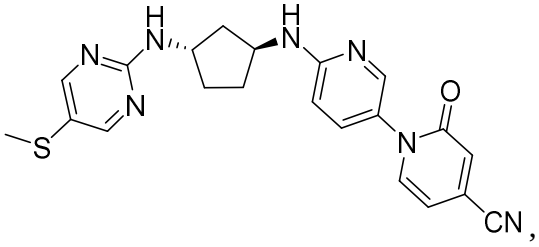
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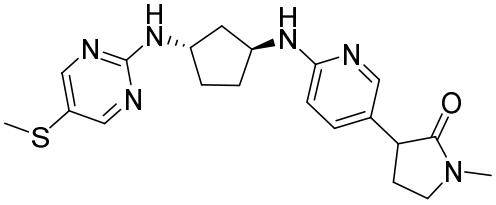
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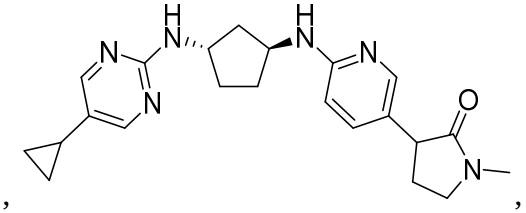
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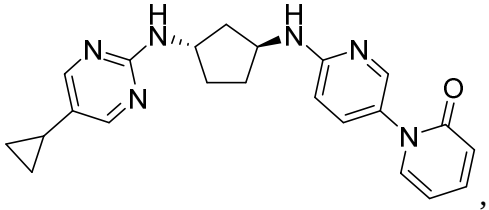
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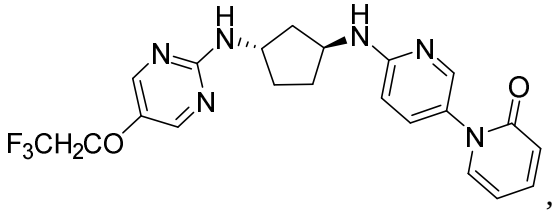
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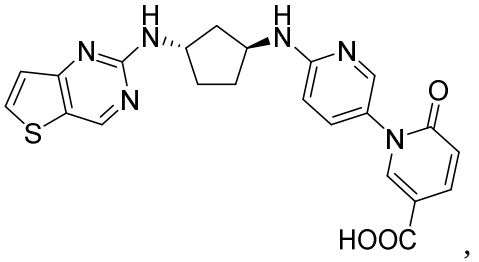
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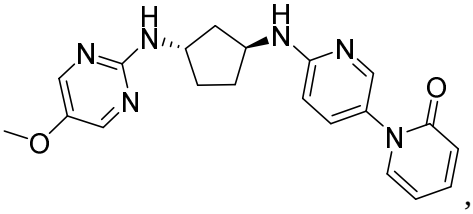
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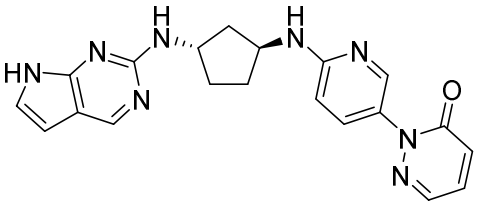
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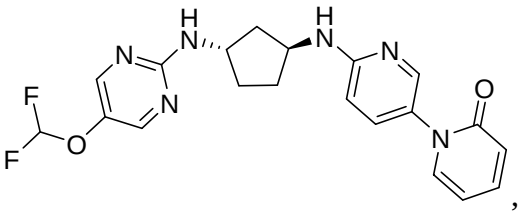
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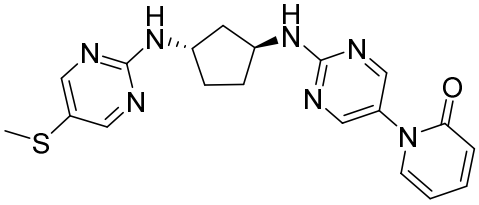
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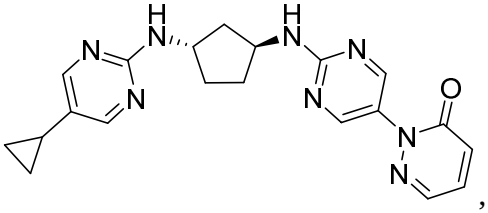
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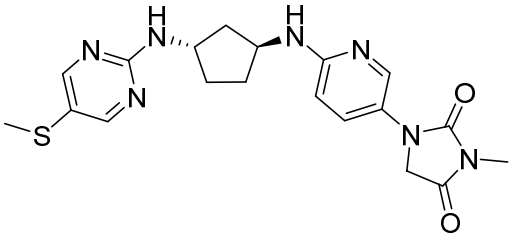
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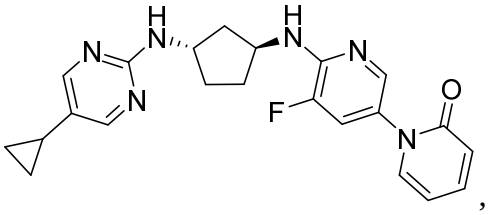
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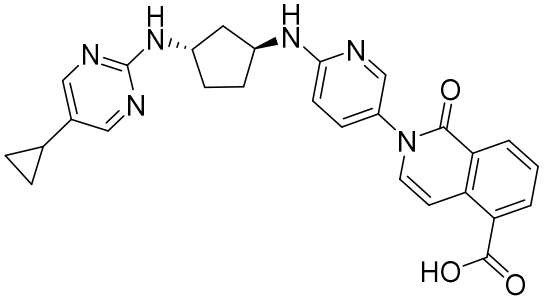
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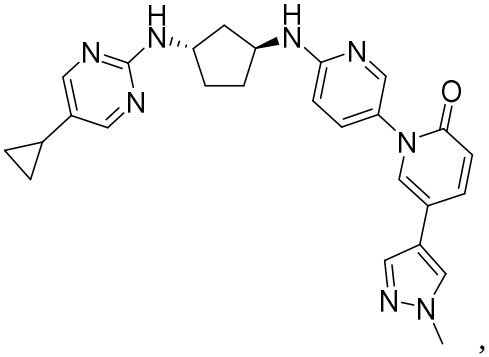
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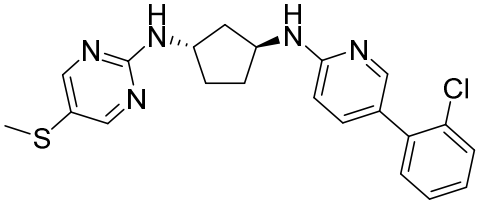
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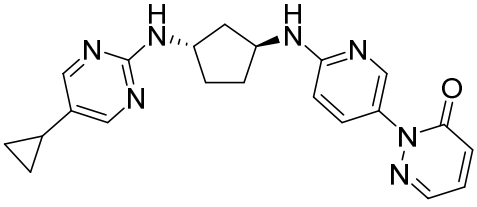
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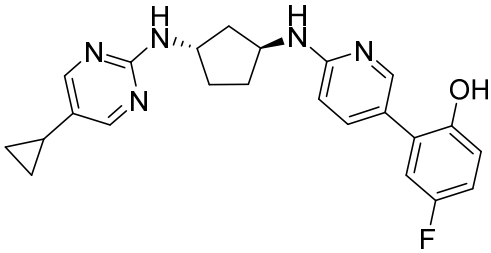
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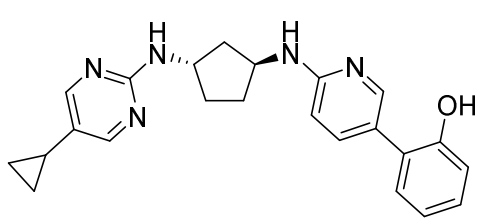
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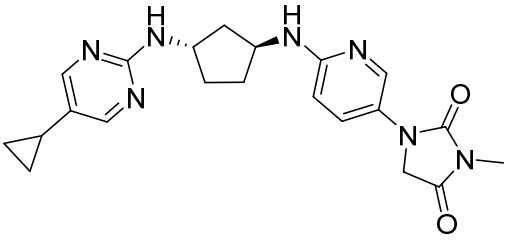
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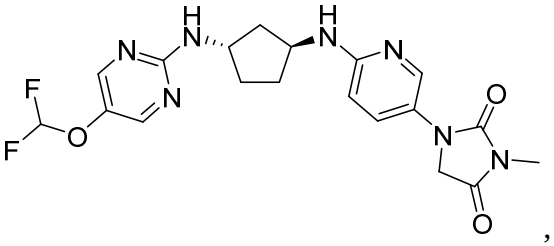
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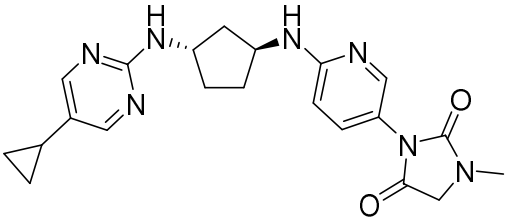
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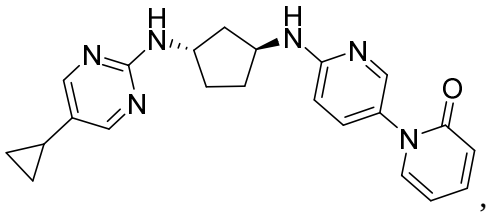
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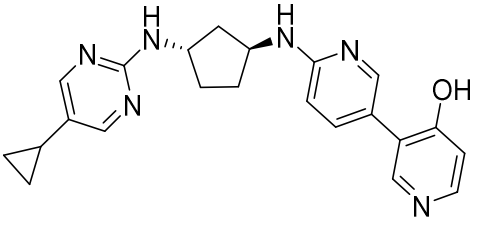
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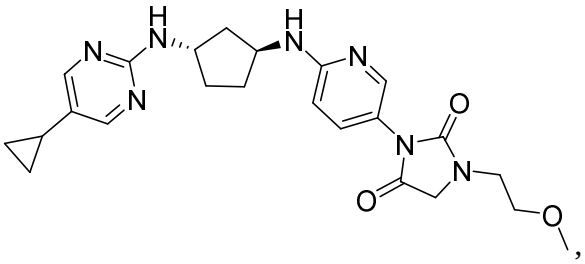
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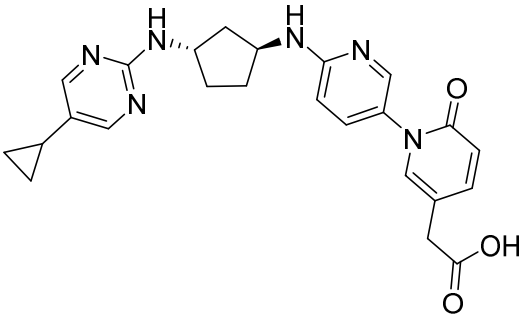
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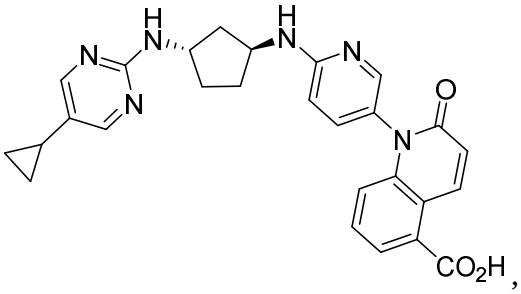
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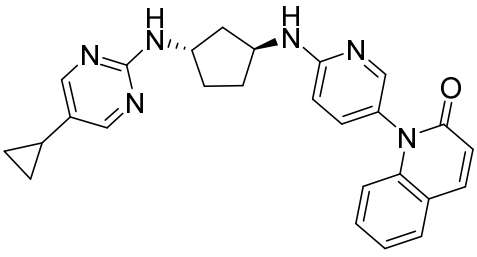
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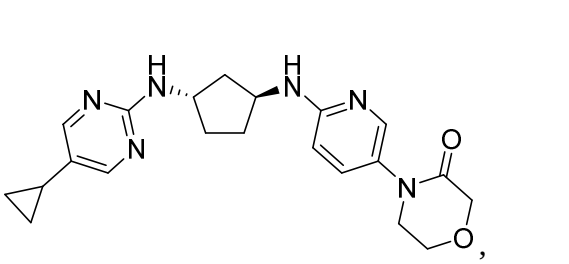
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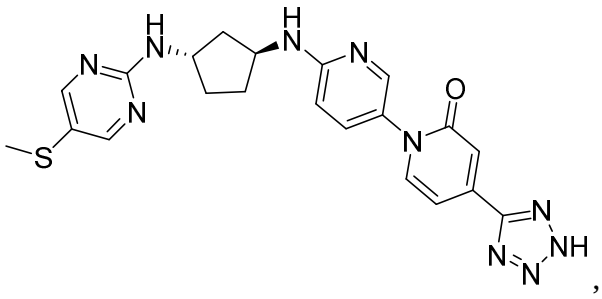
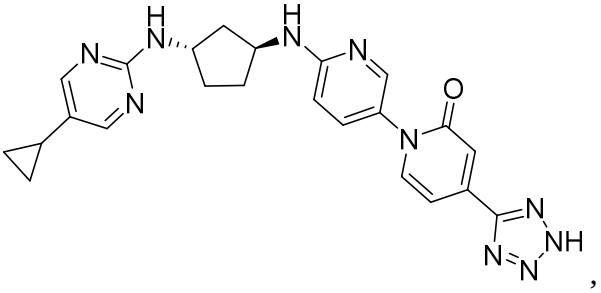
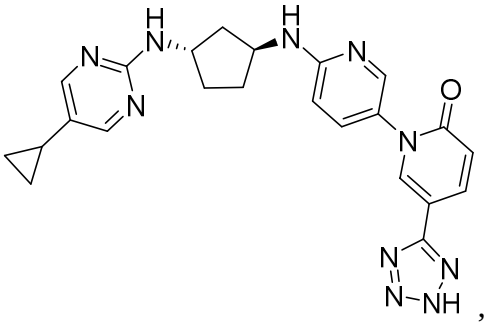
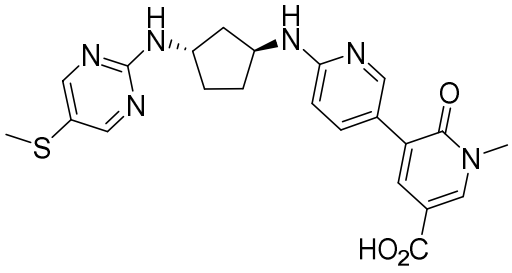
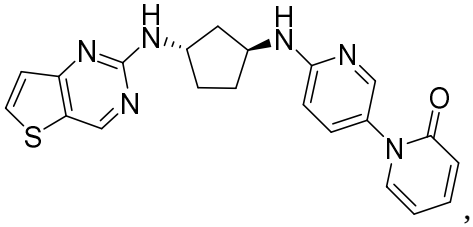
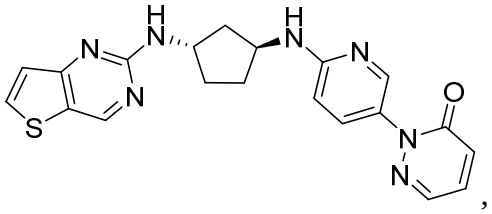
 ,

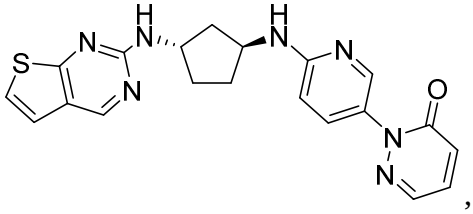
 ,

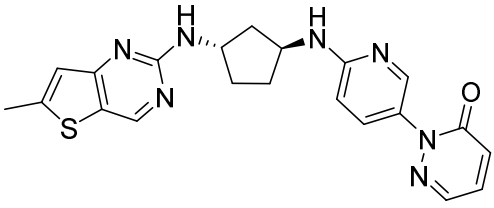
 ,

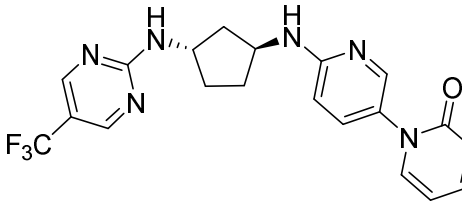
 ,

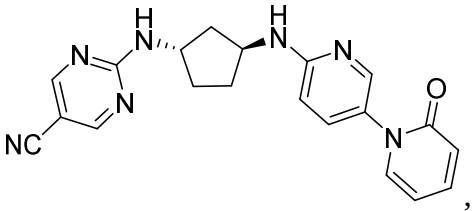
 ,

 ,

 ,

 ,

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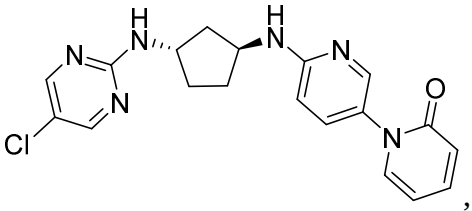
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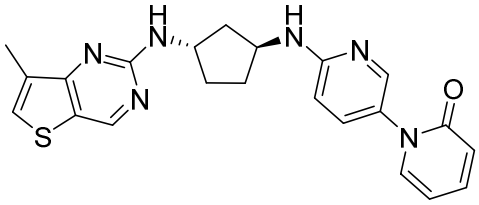
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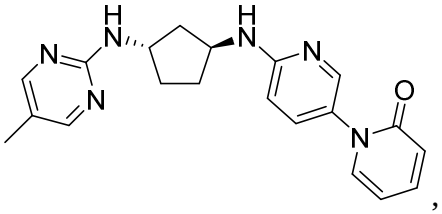
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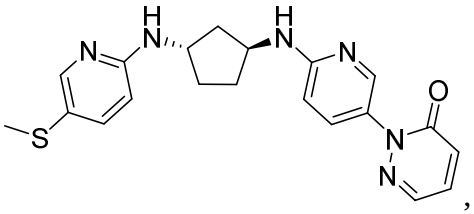
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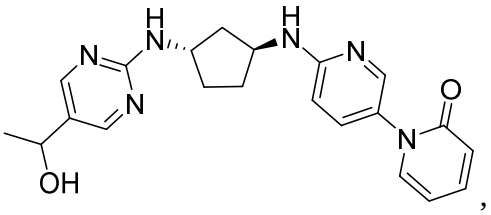
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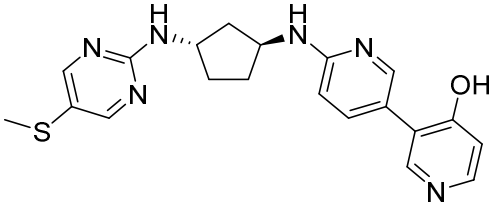
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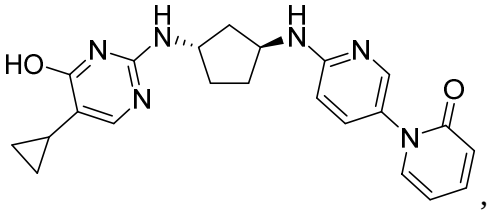
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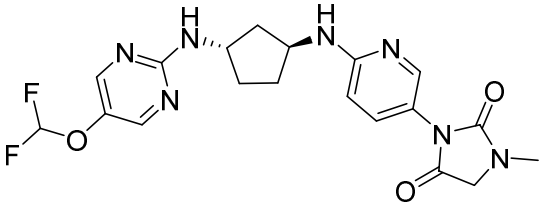
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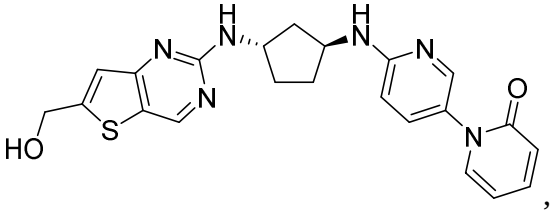
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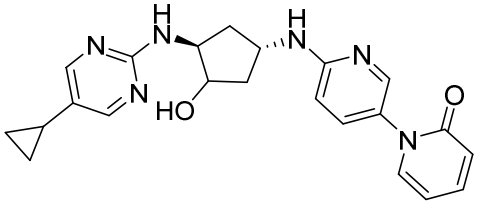
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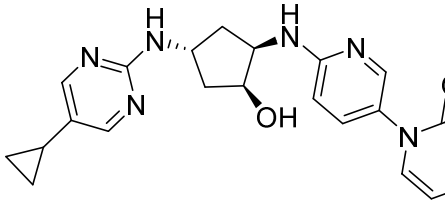
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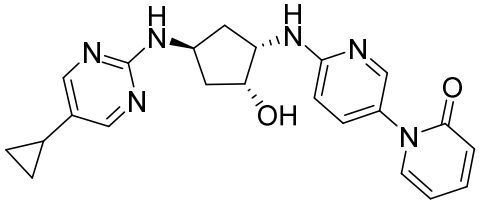
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30. The use of claim 2, wherein the cardiovascular disease is selected from the group consisting of dyslipidemia, hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, hypoalphalipoproteinemia, metabolic syndrome, diabetic complications, atherosclerosis,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

31. 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.

32. The use of claim 30 or 31, wherein the hypercholesterolemia is familial hypercholesterolemia or autosomal dominant hypercholesterolemia.