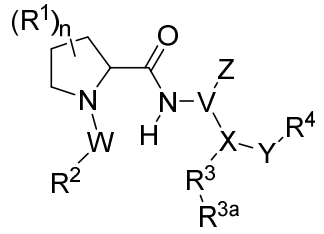
CLAIMS

1. A compound represented by Formula (I), or a pharmaceutically acceptable salt thereof:



(I);

wherein, independently for each occurrence:

R^1 represents −OH, −OR^c, −NH_2, −NHR^c, −NR^cR^d, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, halo, haloalkyl, cycloalkyl, (cycloalkyl)alkyl, −$C(O)R^c$, −C(O)OH, −$C(O)OR^c$, −$OC(O)R^c$, −$C(O)NH_2$, −$C(O)NHR^c$, −$C(O)NR^cR^d$, −$NHC(O)R^c$, or −$NR^cC(O)R^d$;

W is −C(O)NH− or −C(O)−;

R^2 represents aryl or heteroaryl, substituted by one or more substituents selected from the group consisting of −OH, halo, -NH_2, -CN, -NO_2, alkyl, haloalkyl, alkoxy, -C(O)OH, or -C(O)O(alkyl);

V represents optionally substituted aryl or heteroaryl;

Z is absent or represents one or more substituents independently selected from the group consisting of halo, haloalkyl, −NO_2, −CN, −$C(O)R^c$, −C(O)OH, −$C(O)OR^c$, −$OC(O)R^c$, −$C(O)NH_2$, −$C(O)NHR^c$, −$C(O)NR^cR^d$, −$NHC(O)R^c$, −$N(R^c)C(O)R^d$, −$OS(O)_p(R^c)$, −$NHS(O)_p(R^c)$, and −$NR^cS(O)_p(R^c)$;

X represents −$C(NH_2)$−, −$C(NH(R^c))$−, −$C(NR^cR^d)$−, −$C(NHS(O)_pR^c)$−, −$C(NHC(O)R^c)$−, −$C(NHC(O)NH_2)$−, −$C(NHC(O)NHR^c)$−, −$C(NHC(O)NR^cR^d)$−, −C(OH) −, −C(O(alkyl))−, −$C(N_3)$−, −C(CN)−, −$C(NO_2)$−, −$C(S(O)_nR^a)$−, −C[-C(=O)R^c]−, −C[-C(=O)NR^cR^d]−, −C[-C(=O)SR^c]−, −C[-S(O)R^c]−, −C[-$S(O)_2R^c$]−, −C[S(O)(OR^c)]−, −C[-$S(O)_2(OR^c)$]−, −C[-$SO_2NR^cR^d$]−, −C(halogen)−, −C(alkyl), -C((cycloalkyl)alkyl), −C(alkenyl)−, −C(alkynyl)−, or −C(arylalkyl)−;

R^3 represents optionally substituted aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

R^{3a} is absent or represents one or more substituents independently selected from the group consisting of halo, hydroxy, alkyl, -CF_3, -OCF_3, alkoxy, aryl, heteroaryl, aryloxy,

amino, aminoalkyl, -C(O)NH_2, cyano, -NHC(O)alkyl, -SO_2alkyl, -SO_2NH_2, cycloalkyl, -$(CH_2)_rOR^a$, -NO_2, -$(CH_2)_rNR^aR^b$, -$(CH_2)_rC(O)R^a$, -$NR^aC(O)R^b$, -$C(O)NR^cR^d$, -$NR^aC(O)NR^cR^d$, -$C(=NR^a)NR^cR^d$, -$NHC(=NR^a)NR^cR^d$, -NR^aR^b, -$SO_2NR^cR^d$, -$NR^aSO_2NR^cR^d$, -NR^aSO_2alkyl, -$NR^aSO_2R^a$, -$S(O)_pR^a$, -$(CF_2)_rCF_3$, -$NHCH_2R^a$, -OCH_2R^a, -SCH_2R^a, -$NH(CH_2)_2(CH_2)_rR^a$, -$O(CH_2)_2(CH_2)_rR^a$, or -$S(CH_2)_2(CH_2)_rR^a$;

Y represents a bond; or -Y-R^4 represents optionally substituted -alkylene-R^4, -$CH_2C(O)$-R^4, -CH_2NH-R^4, -CH_2N(alkyl)-R^4, -CR^aR^b-R^4, -NH-R^4, -$NHCH_2$-R^4, -NHC(O)-R^4, -N(alkyl)-R^4, -N(alkyl)CH_2-R^4, -N(($(CH_2)_2OH$)-R^4, -N((cycloalkyl)alkyl)R^4, -heterocyclyl-R^4, -OR^4, -OCH_2-R^4, -OC(O)-R^4, -$OC(O)NR^aR^b$, -SCH_2R^4, or -SR^4;

R^4 represents hydrogen, hydroxy, optionally substituted alkyl, cycloalkyl, (heterocycloalkyl)alkyl, (cycloalkyl)alkyl, -CH_2OH, -CH(alkyl)OH, -$CH(NH_2)CH(alkyl)_2$, aryl, aralkyl, heteroaryl, heteroaralkyl, -CH_2S(alkyl), amino, or cyano; or –$(CR^aR^b)_r(CR^aR^b)_p$- fused to the 4-position of the ring bearing Z to form a 5- to 7-membered heterocyclic ring with optional substituents; or,

when R^3 is phenyl, R^4 can represent -NR^a- fused to the position *ortho* to X on that phenyl;

each R^a and R^b is independently H, alkyl, alkenyl, alkynyl, aralkyl, (cycloalkyl)alkyl, -$C(=O)R^c$, -$C(=O)OR^c$, -$C(=O)NR^cR^d$, -$C(=O)SR^c$, -$S(O)R^c$, -$S(O)_2R^c$, -$S(O)(OR^c)$, or –$SO_2NR^cR^d$;

R^c and R^d represent, independently for each occurrence, optionally substituted alkyl, alkenyl, alkynyl, haloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, -C(O)alkyl, or -$S(O)_p$(alkyl); or R^c and R^d can be taken together to form an optionally substituted heterocyclic ring;

r is 0, 1, 2, or 3;

n is an integer from 0 to 6; and

p is 0, 1, or 2.

2. The compound of claim 1, wherein R^1 represents −OH, −O(alkyl), alkyl, haloalkyl, cycloalkyl, or aryl.

3. The compound of claim 2, wherein n is 2; and the two occurrences of R^1 are geminal.

4. The compound of claim 1, wherein R^2 represents (halo)aryl or (halo)heteroaryl.

5. The compound of any one of claims 1-4, wherein V represents optionally substituted aryl.

6. The compound of any one of claims 1-5, wherein Z represents one or more instances of halo or Z is absent.

7. The compound of any one of claims 1-5, wherein Z represents one instance of halo.

8. The compound of any one of claims 1-7, wherein X represents $-C(NH_2)-$, $-C(NH(R^c))-$, $-C(NHS(O)_pR^c)-$, or $-C(NHC(O)R^c)-$.

9. The compound of claim 8, wherein X represents $-C(NH_2)-$; $-C(NHalkyl)-$; $-C(NHS(O)_palkyl)-$, wherein p is 1 or 2; or $-C(NHC(O)(alkyl))-$.

10. The compound of any one of claims 1-9, wherein R^3 represents aryl or heteroaryl optionally substituted by one or more substituents independently selected from the group consisting of cyano, halo, $-NO_2$, (C_1-C_6)alkyl, and (C_1-C_6)haloalkyl.

11. The compound of claim 10, wherein R^3 represents phenyl or pyridyl optionally substituted by one or more substituents independently selected from the group consisting of cyano, halo, $-NO_2$, (C_1-C_6)alkyl, and (C_1-C_6)haloalkyl.

12. The compound of any one of claims 1-11, wherein R^{3a} is absent or represents cyano or alkyl.

13. The compound of any one of claims 1-12, wherein $-Y-R^4$ represents -alkylene-R^4 or -NH-R^4.

14. The compound of any one of claims 1-13, wherein R^4 represents cycloalkyl or (cycloalkyl)alkyl.

15. The compound of claim 1, wherein:
Z is one instance of F or Z is absent.

16. The compound of claim 1, wherein R^1 represents −OH, $-OR^c$, alkyl, aryl, haloalkyl, or cycloalkyl.

17. The compound of claim 3, wherein one occurrence of R^1 represents −OH or $-OR^c$; and the other occurrence of R^1 represents aryl.

18. The compound of claim 3, wherein one occurrence of R^1 represents −OH or $-OR^c$; and the other occurrence of R^1 represents haloalkyl.

19. The compound of claim 1, wherein n is 2; the two occurrences of R^1 are geminal; and both occurrences of R^1 are halo.

20. The compound of claim 1, wherein R^2 represents (halo)phenyl.

21. The compound of claim 1, wherein R^2 represents (halo)pyridyl.

22. The compound of claim 1, wherein R^2 represents (halo)thiophenyl.

23. The compound of claim 1, wherein X represents $-C(NH_2)-$, $-C(NH(R^c))-$, $-C(NHS(O)_pR^c)-$, or $-C(NHC(O)R^c)-$.

24. The compound of claim 1, wherein R^3 represents optionally substituted aryl or heteroaryl.

25. The compound of claim 1, wherein R^4 represents cycloalkyl.

26. The compound of claim 1, wherein R^1 represents −OH.

27. The compound of claim 1, wherein R^1 represents $-CH_3$.

28. The compound of claim 1, wherein R^1 represents $-OCH_3$.

29. The compound of claim 1, wherein R^1 represents $-OCH_2CH_3$.

30. The compound of claim 1, wherein R^1 represents $-OCH_2CH_2CH_3$

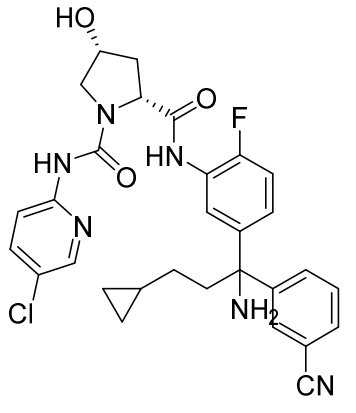
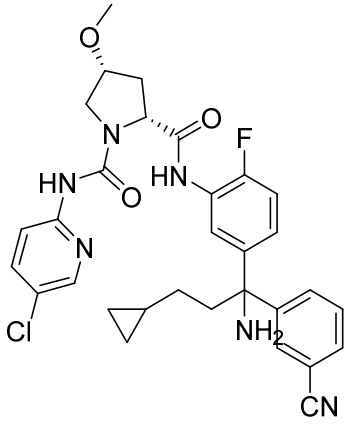
31. The compound of claim 1, wherein R^1 represents −F.

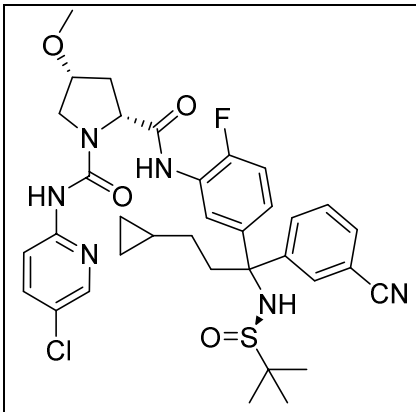
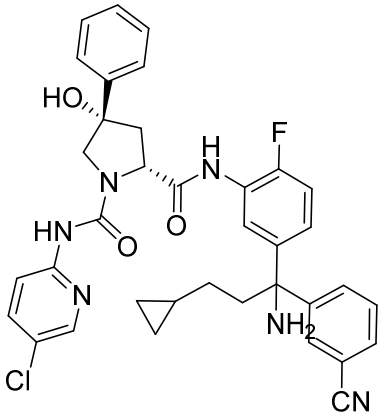
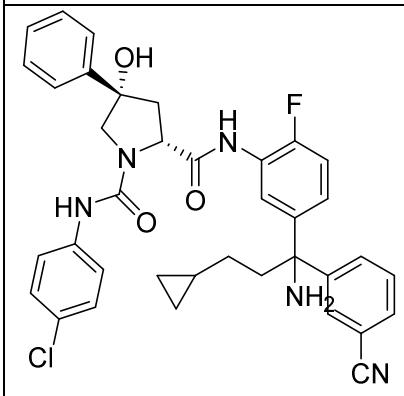
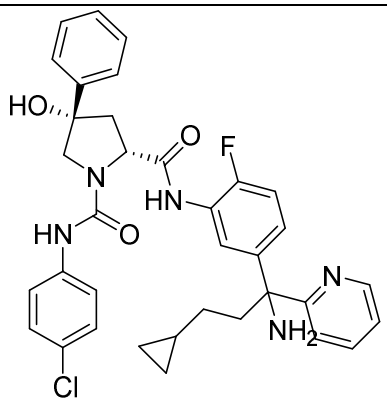
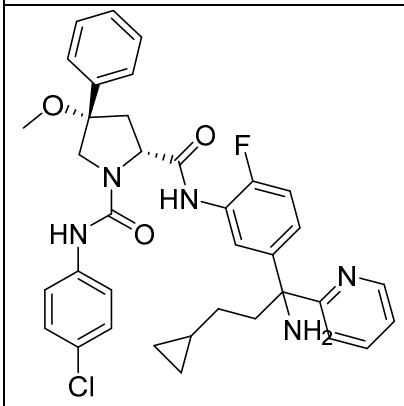
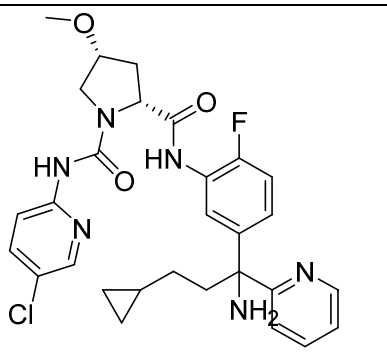
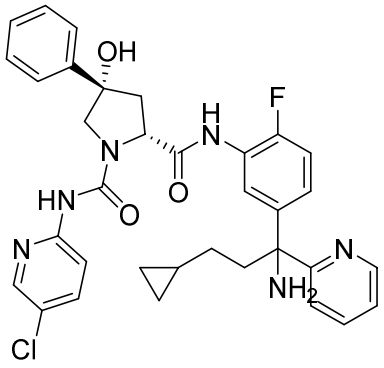
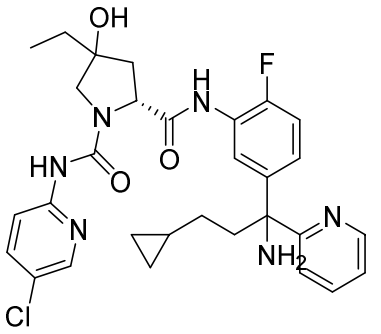
32. The compound of claim 1, wherein R^1 represents $-CF_3$.

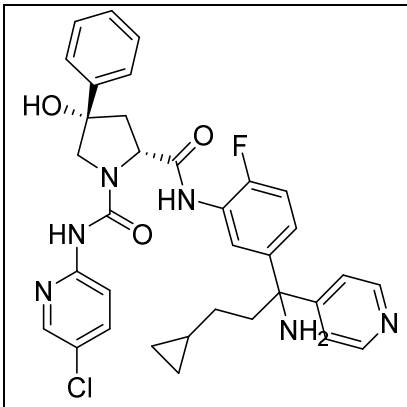
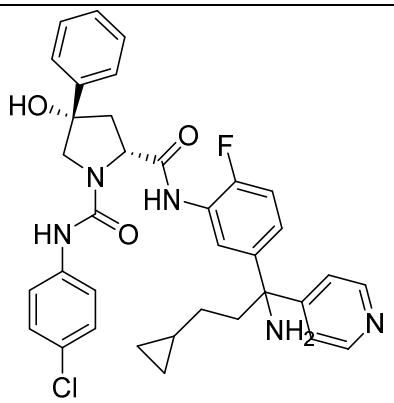
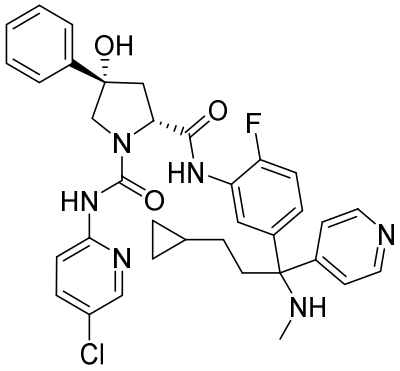
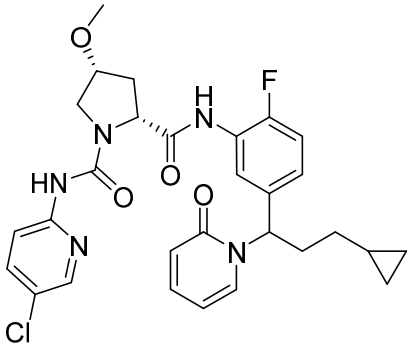
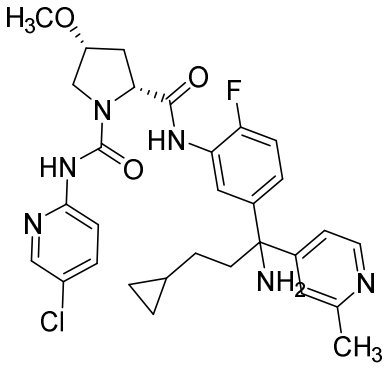
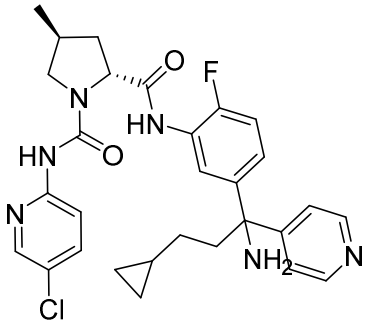
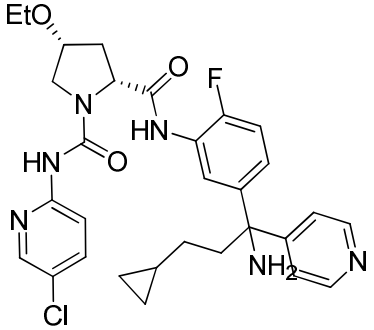
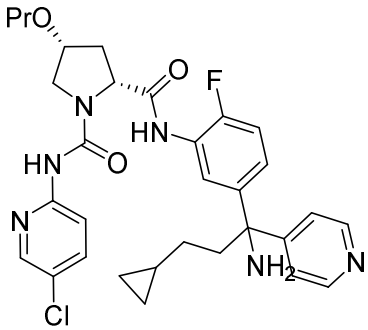
33. The compound of claim 1, wherein R^1 represents phenyl.

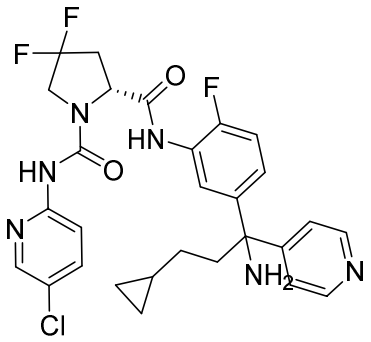
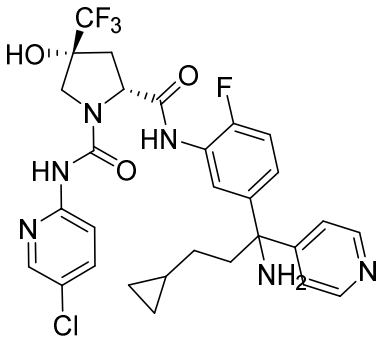
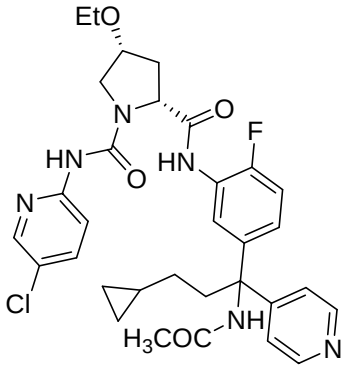
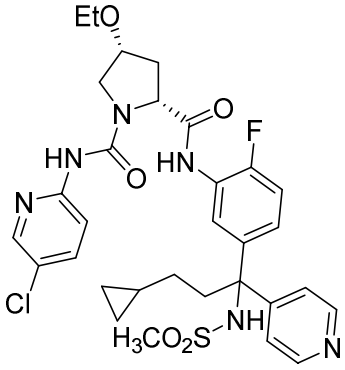
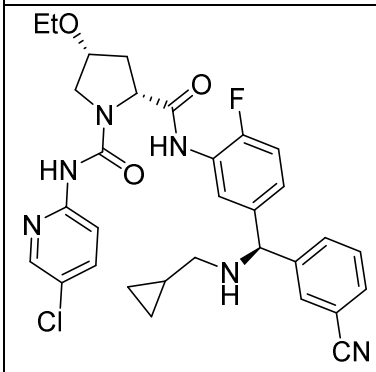
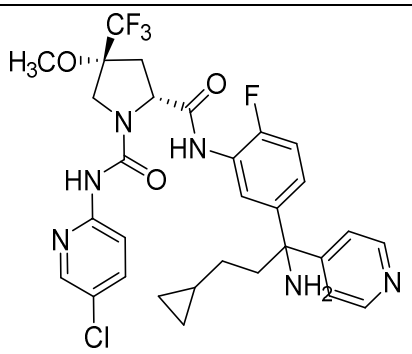
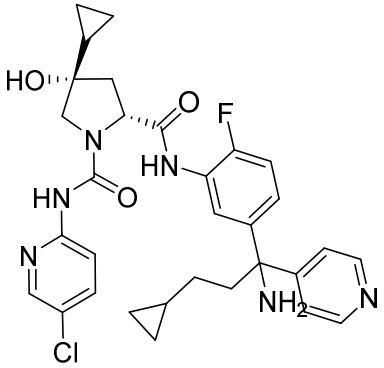
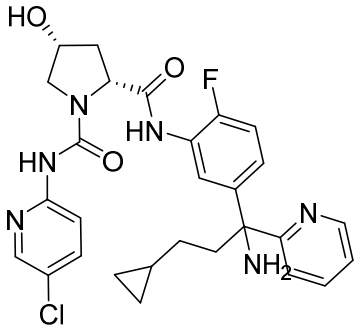
34. The compound of claim 1, wherein R^1 represents cyclopropyl.

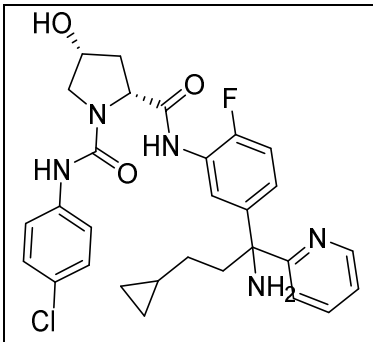
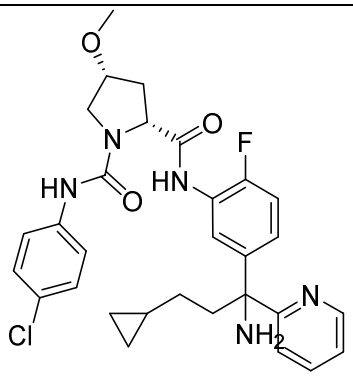
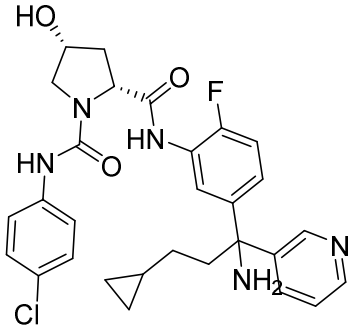
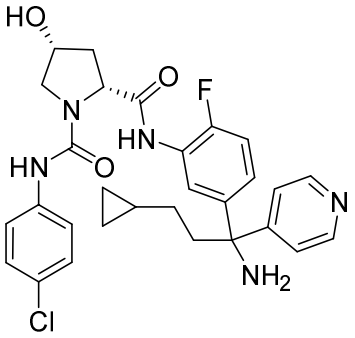
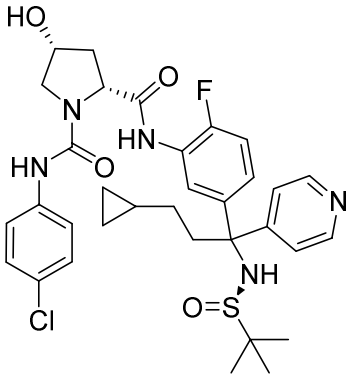
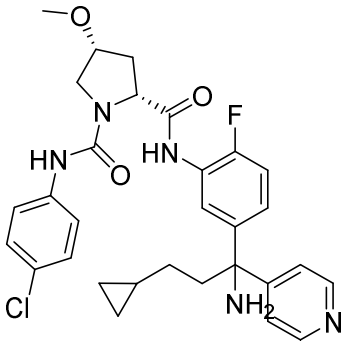
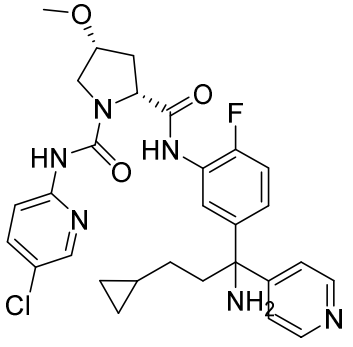
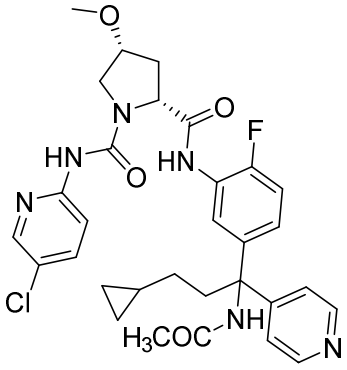
35. The compound of claim 1, wherein the compound is selected from the following table:

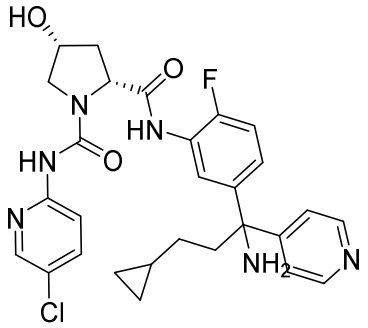
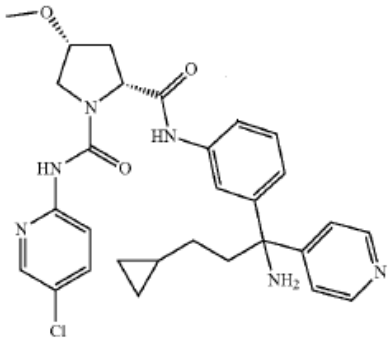
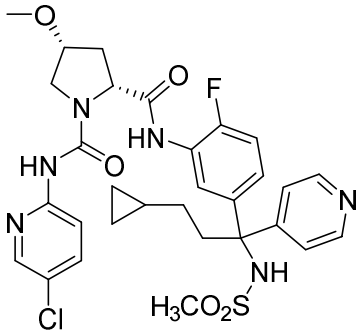
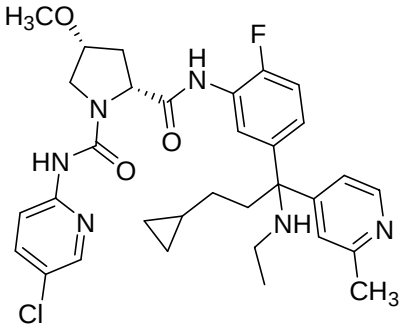
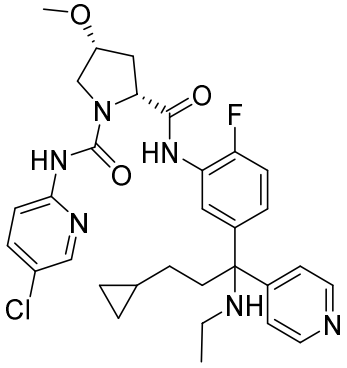
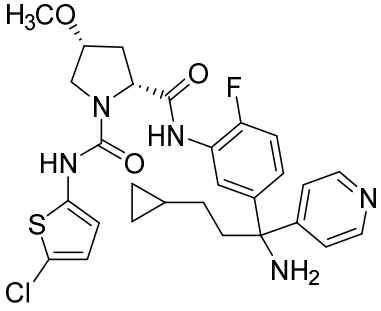
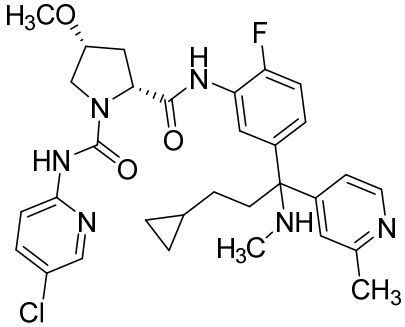
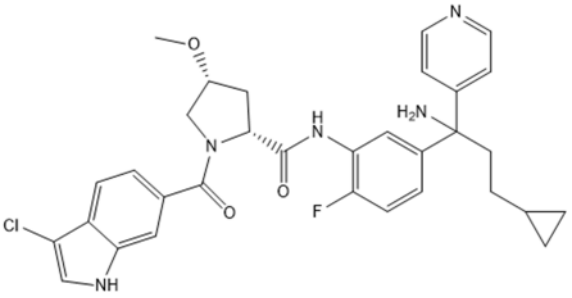
	

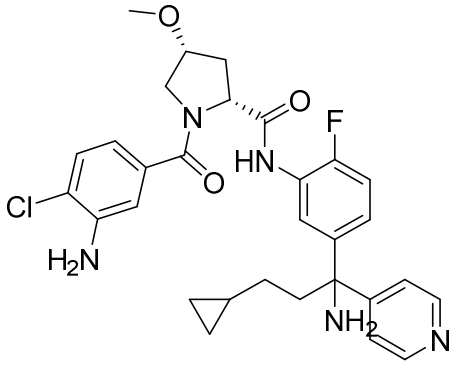
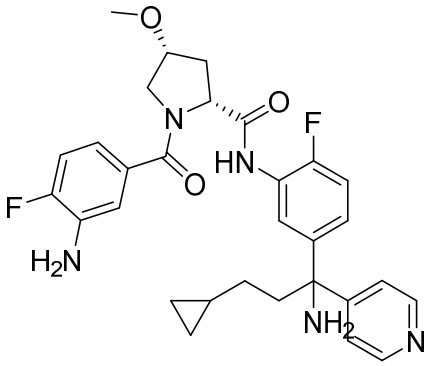
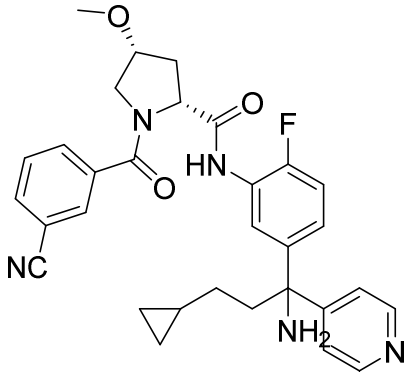
	
	
	
	

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36. A pharmaceutical composition, comprising a compound of any one of claims 1-35, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

37. Use of a compound of any one of claims 1-35, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease or condition characterized by unwanted plasma kallikrein activity, wherein the disease or condition characterized by unwanted plasma kallikrein activity is selected from the group consisting of stroke, inflammation, reperfusion injury, acute myocardial infarction, deep vein thrombosis, post fibrinolytic treatment condition, angina, edema, angioedema, hereditary angioedema, sepsis, arthritis, hemorrhage, blood loss during cardiopulmonary bypass, inflammatory bowel disease, diabetes mellitus, retinopathy, diabetic retinopathy, diabetic macular edema, diabetic macular degeneration, age-related macular edema, age-related macular degeneration, proliferative retinopathy,

neuropathy, hypertension, brain edema, increased albumin excretion, macroalbuminuria, and nephropathy.

38. The use of claim 37, wherein the disease or condition characterized by unwanted plasma kallikrein activity is angioedema.

39. The use of claim 37, wherein the disease or condition characterized by unwanted plasma kallikrein activity is hereditary angioedema.

40. Use of a compound of any one of claims 1-35 in the manufacture of a medicament for the prevention of hereditary angioedema.