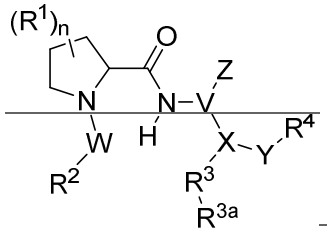
CLAIMS

What is claimed is:

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



(I);

wherein, independently for each occurrence:

R^1 represents –OH, –OR^e, –NH_2, –NHR^e, –NR^eR^d, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, halo, haloalkyl, cycloalkyl, (cycloalkyl)alkyl, –C(O)R^e, –C(O)OH, –C(O)OR^e, –$OC(O)R^e$, –$C(O)NH_2$, –C(O)NHR^e, –C(O)NR^eR^d, –$NHC(O)R^e$, or –$NR^eC(O)R^d$; or two geminal occurrences of R^1 taken together with the carbon to which they are attached represent –C(O)–; or two vicinal or geminal occurrences of R^1 taken together form an optionally substituted fused or spirocyclic carbocyclic or heterocyclic ring;

W is a bond, –C(O)NH–, –C(O)$N(R^e)$–, –C(O)O–, –CH_2–, or –C(O)–;

R^2 represents optionally substituted aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, heterocycloalkyl, (cycloalkyl)alkyl), or (heterocycloalkyl)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^e, –C(O)OH, –C(O)OR^e, –$OC(O)R^e$, –$C(O)NH_2$, –C(O)NHR^e, –C(O)NR^eR^d, –$NHC(O)R^e$, –$N(R^e)C(O)R^d$, –$OS(O)_p(R^e)$, –$NHS(O)_p(R^e)$, and –$NR^eS(O)_p(R^e)$;

X represents –$C(NH_2)$–, –$C(NH(R^e))$–, –$C(NR^eR^d)$–, –$C(NHS(O)_pR^e)$–, –$C(NHC(O)R^e)$–, –$C(NHC(O)NH_2)$–, –C(NHC(O)NHR^e)–, –C(NHC(O)NR^eR^d)–, –C(OH)–, –C(O(alkyl))–, –$C(N_3)$–, –C(CN)–, –$C(NO_2)$–, –$C(S(O)_nR^a)$–, –C[=C(O)R^e]–, –C[=C(O)NR^eR^d]–, –C[=C(O)SR^e]–, –C[=S(O)R^e]–, –C[=$S(O)_2R^e$]–, –C[S(O)(OR^e)]–,

~~–C[–S(O)$_2$(OR^e)]~~, ~~–C[–SO$_2$NR^{e}R^d]~~, ~~–C(halogen)~~, ~~–C(alkyl),~~ ~~–C((cycloalkyl)alkyl),~~ ~~–C(alkenyl)~~, ~~–C(alkynyl)~~, or ~~–C(aralkyl)=~~;

~~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$_2$alkyl, –SO$_2$NH$_2$, cycloalkyl, –(CH$_2$)$_r$OR^a, –NO$_2$, –(CH$_2$)$_r$NR^{a}R^b, –(CH$_2$)$_r$C(O)R^a, –NR^{a}C(O)R^b, –C(O)NR^{e}R^d, –NR^{a}C(O)NR^{e}R^d, –C(=NR^a)NR^{e}R^d, –NHC(=NR^a)NR^{e}R^d, –NR^{a}R^b, –SO$_2$NR^{e}R^d, –NR^{a}SO$_2$NR^{e}R^d, –NR^{a}SO$_2$alkyl, –NR^{a}SO$_2$R^a, –S(O)$_p$R^a, –(CF$_2$)$_r$CF$_3$, –NHCH$_2$R^a, –OCH$_2$R^a, –SCH$_2$R^a, –NH(CH$_2$)$_2$(CH$_2$)$_r$R^a, –O(CH$_2$)$_2$(CH$_2$)$_r$R^a, or –S(CH$_2$)$_2$(CH$_2$)$_r$R^a;~~

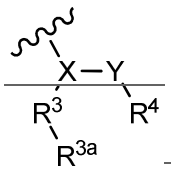
~~Y represents a bond; or –Y–R^4 represents optionally substituted –alkylene–R^4, –CH$_2$C(O)–R^4, –CH$_2$NH–R^4, –CH$_2$N(alkyl)–R^4, –CR^{a}R^b–R^4, –NH–R^4, –NHCH$_2$–R^4, –NHC(O)–R^4, –N(alkyl)–R^4, –N(alkyl)CH$_2$–R^4, –N((CH$_2$)$_2$OH)–R^4, –N((cycloalkyl)alkyl)R^4, –heterocyclyl–R^4, –OR^4, –OCH$_2$–R^4, –OC(O)–R^4, –OC(O)NR^{a}R^b, –SCH$_2$R^4, or –SR^4;~~

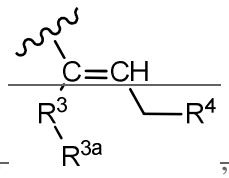
~~R^4 represents hydrogen, hydroxy, optionally substituted alkyl, cycloalkyl, (heterocycloalkyl)alkyl, (cycloalkyl)alkyl, –CH$_2$OH, –CH(alkyl)OH, –CH(NH$_2$)CH(alkyl)$_2$, aryl, aralkyl, heteroaryl, heteroaralkyl, –CH$_2$S(alkyl), amino, or cyano; or –(CR^{a}R^b)$_r$(CR^{a}R^b)$_p$– fused to the 4-position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

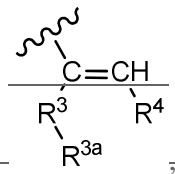
~~when R^3 is phenyl, R^4 can represent –NR^a– fused to the position *ortho* to X on that phenyl;~~

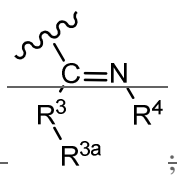
~~each R^a and R^b is independently H, alkyl, alkenyl, alkynyl, aralkyl, (cycloalkyl)alkyl, –C(=O)R^e, –C(=O)OR^e, –C(=O)NR^{e}R^d, –C(=O)SR^e, –S(O)R^e, –S(O)$_2$R^e, –S(O)(OR^e), or –SO$_2$NR^{e}R^d;~~

~~R^e 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^e and R^d can be taken together to form an optionally substituted heterocyclic ring;~~



~~can represent~~


~~,~~


~~, or~~


~~;~~

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, –OR^e, –NH_2, –NHR^e, –NR^eR^d, alkyl, aryl, heteroaryl, halo, haloalkyl, cycloalkyl, –$OC(O)R^e$, –$NHC(O)R^e$, or –$NR^eC(O)R^d$; or two geminal occurrences of R^1 taken together with the carbon to which they are attached represent –C(O) ; or two vicinal or geminal occurrences of R^1 taken together form an optionally substituted fused or spirocyclic carbocyclic or heterocyclic ring.

3. The compound of claim 2, wherein R^1 represents –OH, –OR^e, –NH_2, alkyl, aryl, halo, haloalkyl, cycloalkyl, or –$OC(O)R^e$.

4. The compound of claim 3, wherein n is 1.

5. The compound of claim 4, wherein R^1 represents –OH or –OR^e.

6. The compound of claim 5, wherein R^1 represents –OR^e.

7. The compound of claim 6, wherein R^1 represents –O((C_1-C_6)alkyl).

8. The compound of claim 4, wherein R^1 represents –$OC(O)R^e$.

9. The compound of claim 8, wherein R^1 represents –OC(O)((C_1-C_6)alkyl).

10. The compound of claim 4, wherein R^1 represents –NH_2.

11. The compound of claim 4, wherein R^1 represents (C_1-C_6)alkyl.

12. The compound of claim 3, wherein n is 2.

13. The compound of claim 12, wherein the two occurrences of R^1 are geminal.

14. The compound of claim 13, wherein one occurrence of R^1 represents –OH or –OR^e; and the other occurrence of R^1 represents aryl or heteroaryl.

15. The compound of claim 13, wherein one occurrence of R^1 represents –OH or –OR^e; and the other occurrence of R^1 represents haloalkyl.

16. The compound of claim 13, wherein both occurrences of R^1 are halo.

17. The compound of claim 13, wherein the two geminal occurrences of R^1 taken together with the carbon to which they are attached represent –C(O)–.

18. The compound of claim 12, wherein the two occurrences of R^1 are vicinal; and the two vicinal occurrences of R^1 taken together form an optionally substituted fused carbocyclic ring.

19. The compound of claim 1, wherein n is 0.

20. The compound of any one of claims 1-19, wherein W is –C(O)NH– or –C(O)N(R^e)–.

21. The compound of claim 20, wherein R^2 represents optionally substituted aryl or heteroaryl.

22. The compound of claim 21, wherein R^2 represents aryl or heteroaryl, substituted by one or more substituents selected from the group consisting of –OH, halo, $-NH_2$, $-NH((C_1-C_6)alkyl)$, $-N((C_1-C_6)alkyl)_2$, –CN, $-NO_2$, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, –C(O)OH, $-C(O)O(C_1-C_6)alkyl$, $-C(O)NH_2$, $-C(O)NH(C_1-C_6)alkyl$, and $-C(O)N((C_1-C_6)alkyl)_2$.

23. The compound of claim 21, wherein R^2 represents (halo)aryl or (halo)heteroaryl.

24. The compound of any one of claims 1-19, wherein W is –C(O)–.

25. The compound of claim 24, wherein R^2 represents optionally substituted aralkyl or heteroaralkyl.

26. The compound of any one of claims 1-25, wherein V represents optionally substituted aryl.

27. The compound of any one of claims 1-26, wherein Z represents one or more substituents independently selected from the group consisting of halo, haloalkyl, $-NO_2$, and –CN.

28. The compound of claim 27, wherein Z represents one instance of halo.

29. The compound of claim 28, wherein Z represents one instance of fluoro.

30. The compound of any one of claims 1-26, wherein Z is absent.

31. The compound of any one of claims 1-30, wherein X represents –C(NH_2)–, –C(NH(R^e))–, –C(NR^eR^d)–, –C(NHS(O)$_pR^e$)–, –C(NHC(O)R^e)–, –C(NHC(O)NH_2)–, –C(NHC(O)NHR^e)–, or –C(NHC(O)NR^eR^d)–.

32. The compound claim 31, wherein X represents –C(NH_2)–, –C(NH(R^e))–, –C(NR^eR^d)–, –C(NHS(O)$_pR^e$)–, –C(NHC(O)R^e)–, or –C(NHC(O)NHR^e)–.

33. The compound of claim 32, wherein X represents –C(NH_2)–.

34. The compound of claim 32, wherein X represents –C(NH(R^e))–.

35. The compound of claim 34, wherein X represents –C(NH(cycloalkyl)alkyl)–.

36. The compound of claim 34, wherein X represents –C(NH(C_1-C_6)alkyl)–.

37. The compound of claim 32, wherein X represents –C(NHS(O)$_pR^e$)–.

38. The compound of claim 37, wherein X represents –C(NHS(O)$_p$(C_1-C_6)alkyl)–, wherein p is 1 or 2.

39. The compound of claim 32, wherein X represents –C(NHC(O)NHR^e)–.

40. The compound of claim 39, wherein X represents optionally substituted –C(NHC(O)NH(aryl))– or C(NHC(O)NH(heteroaryl))–.

41. The compound of claim 32, wherein X represents –C(NHC(O)R^e)–.

42. The compound of claim 41, wherein X represents –C(NHC(O)((C_1-C_6)alkyl))–.

43. The compound of any one of claims 1-41, wherein R^3 represents optionally substituted aryl or heteroaryl.

44. The compound claim 43, wherein R^3 represents optionally substituted heteroaryl.

45. The compound of claim 44, wherein R^3 represents pyridyl.

46. The compound of claim 43, wherein R^3 represents optionally substituted aryl.

47. The compound of claim 46, wherein R^3 represents phenyl, optionally substituted by one or more substituents selected from the group consisting of -CN, halo, $-NO_2$, $(C_1$-$C_6)$alkyl, and $(C_1$-$C_6)$haloalkyl.

48. The compound of any one of claims 1-46, wherein R^{3a} is absent or represents halo, alkyl, $-CF_3$, $-OCF_3$, aryl, heteroaryl, $-C(O)NH_2$, cyano, -NHC(O)alkyl, $-SO_2$alkyl, $-SO_2NH_2$, $-NO_2$, $-NR^aC(O)R^b$, $-C(O)NR^eR^d$, $-NR^aC(O)NR^eR^d$, $-C(=NR^a)NR^eR^d$, $-NHC(=NR^a)NR^eR^d$, $-SO_2NR^eR^d$, $-NR^aSO_2NR^eR^d$, $-NR^aSO_2$alkyl, $-NR^aSO_2R^a$, $-S(O)_pR^a$, or $-(CF_2)_rCF_3$.

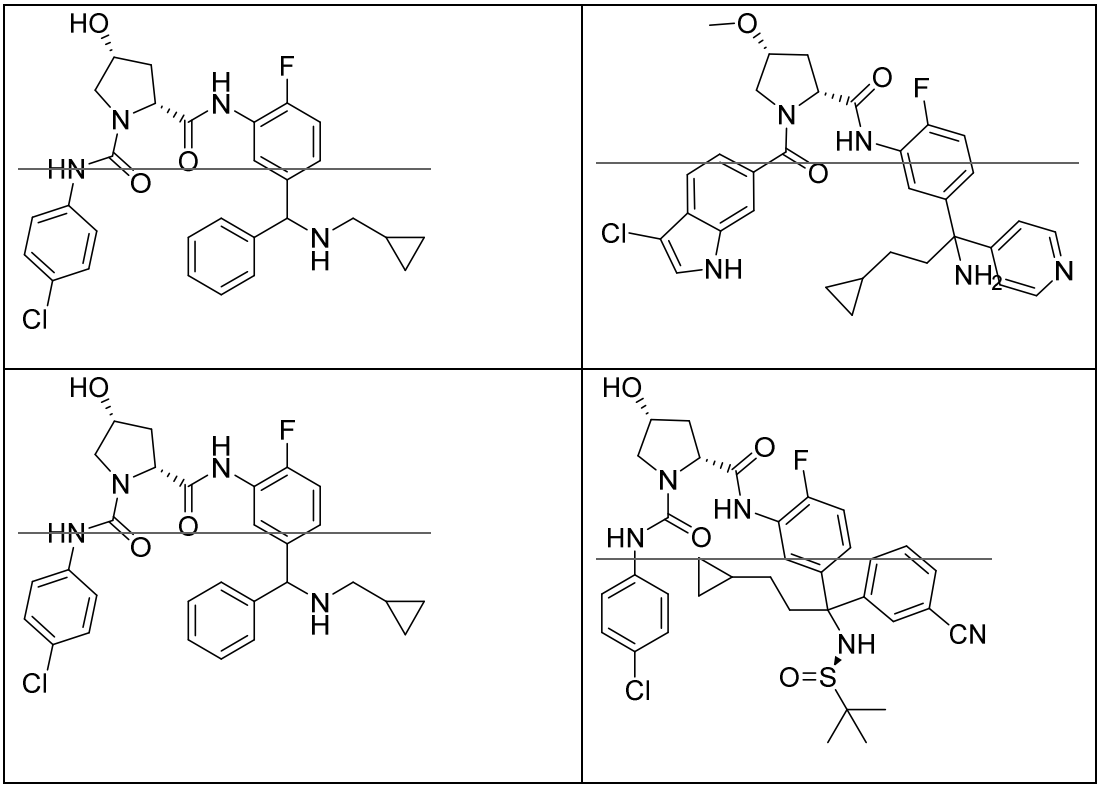
49. The compound of any one of claims 1-48, wherein Y represents a bond.

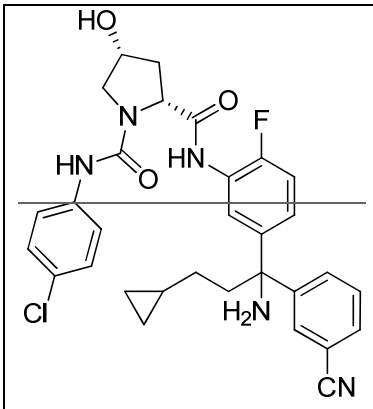
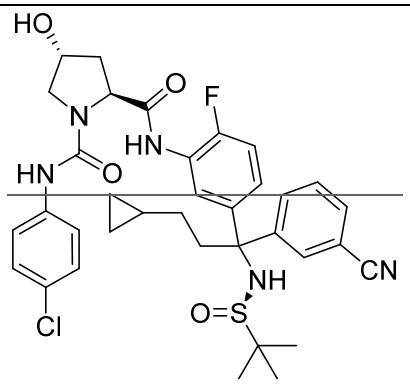
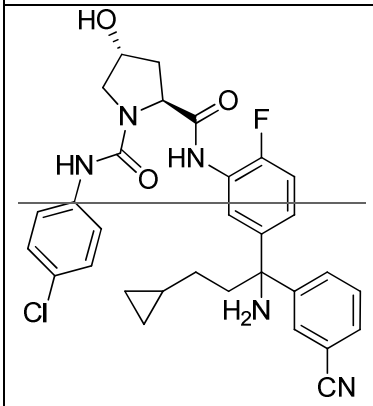
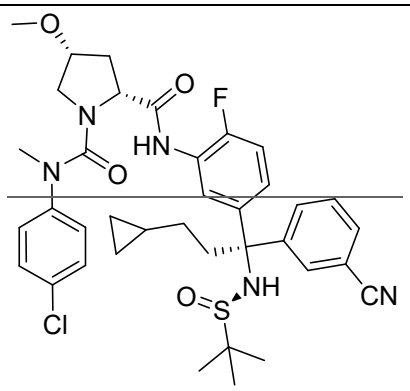
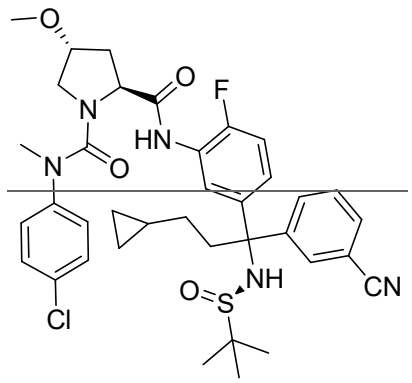
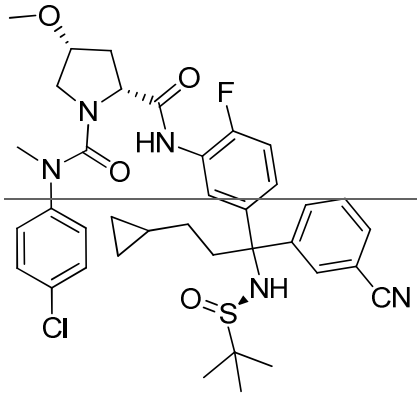
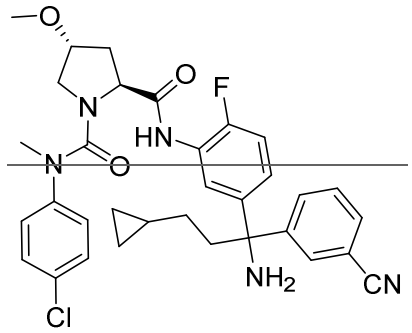
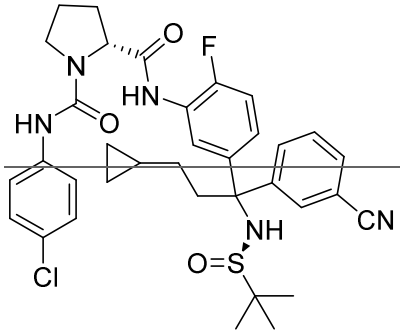
50. The compound of any one of claims 1-49, wherein R^4 represents H.

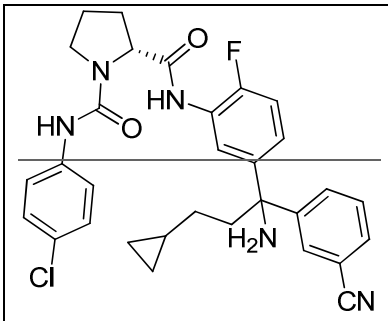
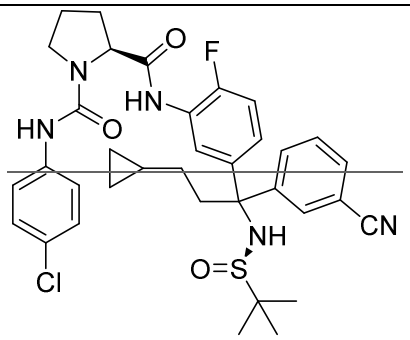
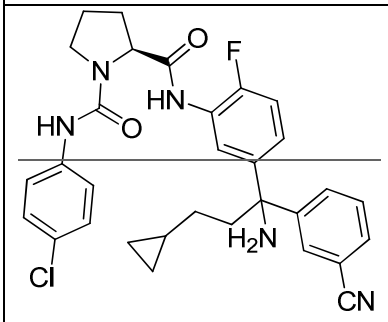
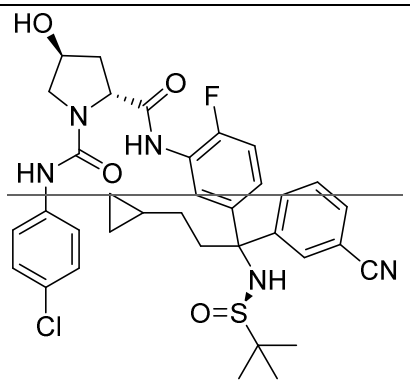
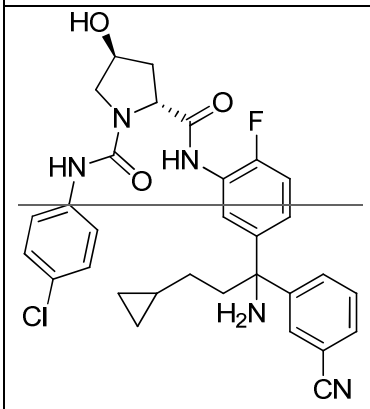
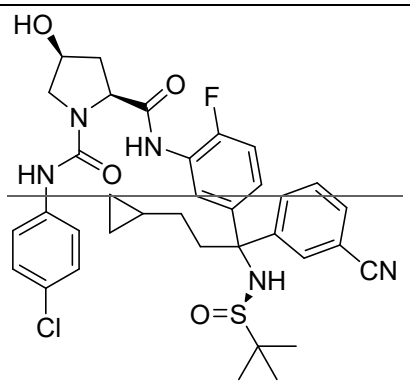
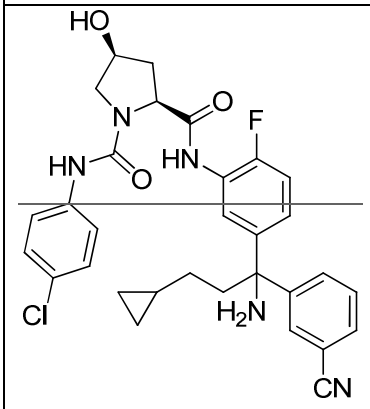
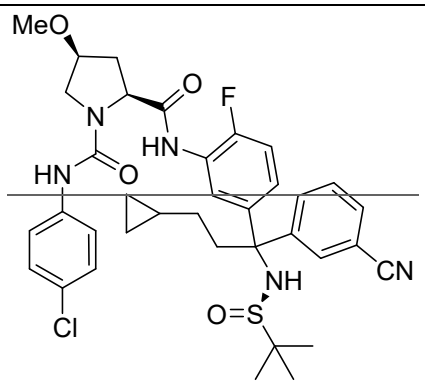
51. The compound of any one of claims 1-49, wherein R^4 represents (cycloalkyl)alkyl.

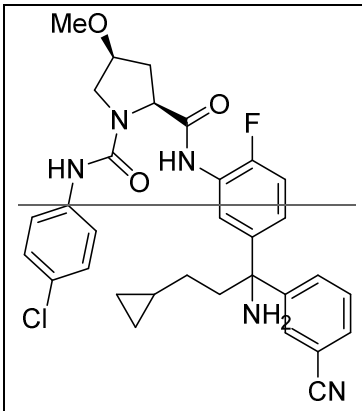
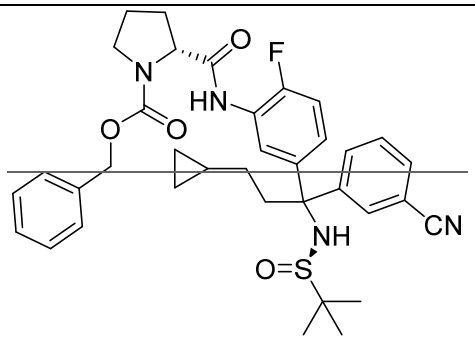
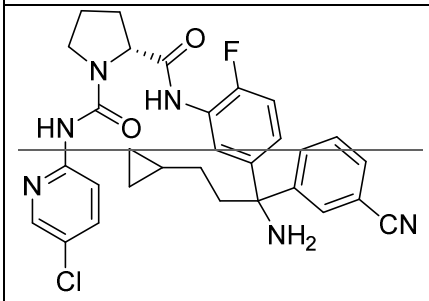
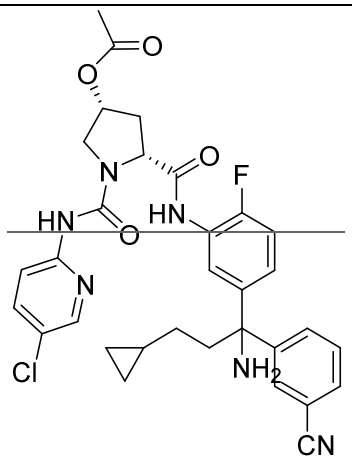
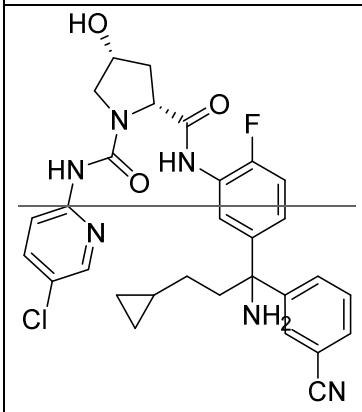
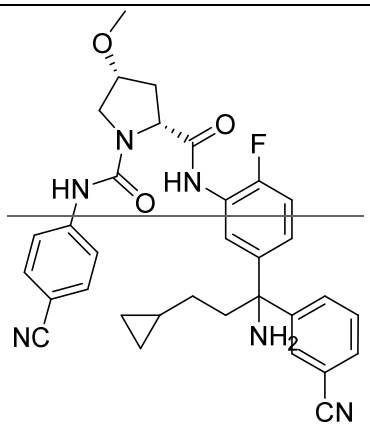
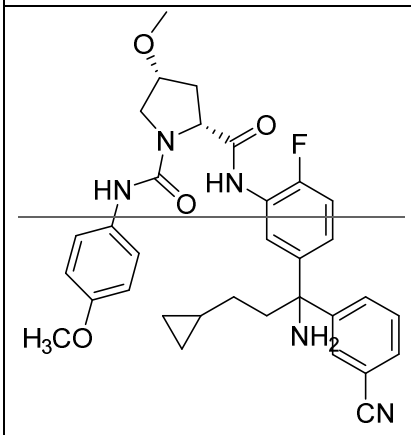
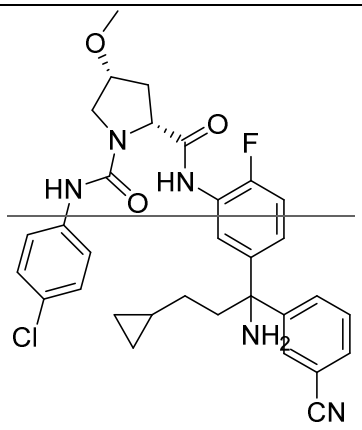
52. The compound of claim 51, wherein R^4 represents (cyclopropyl)$(C_1$-$C_6)$alkyl.

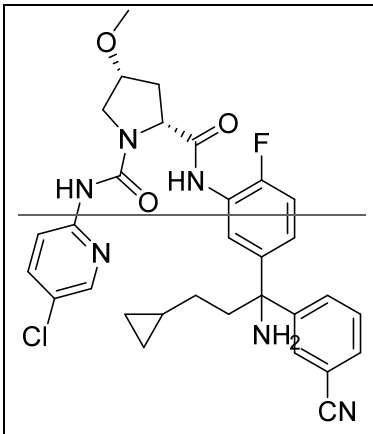
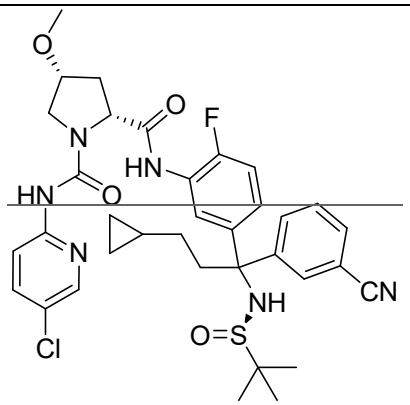
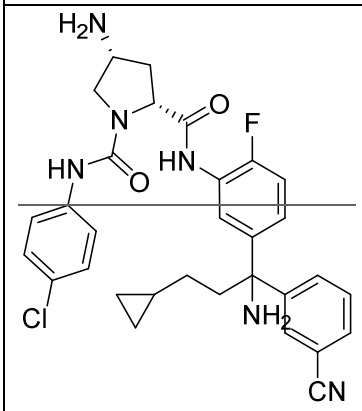
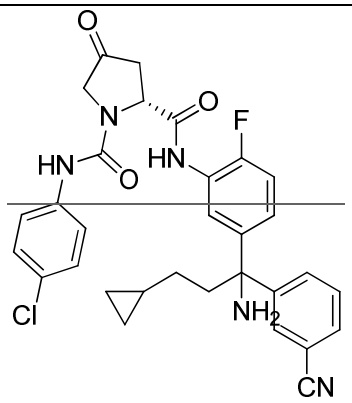
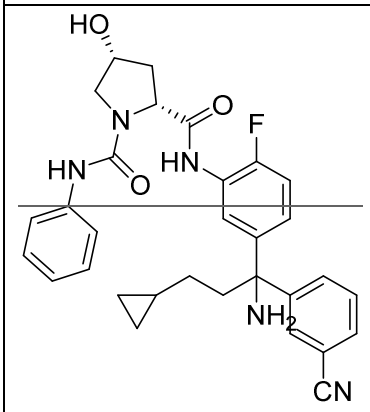
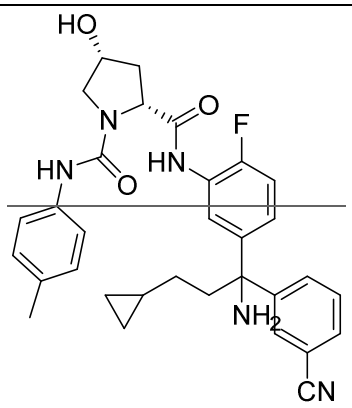
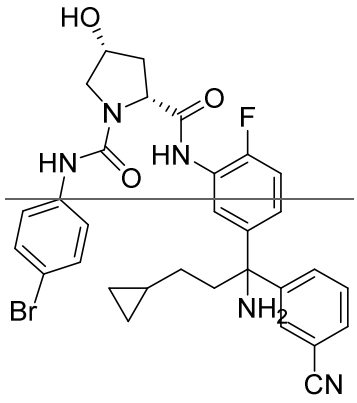
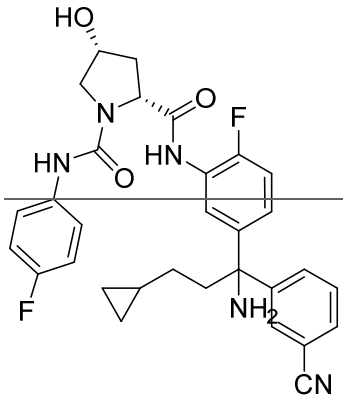
53. The compound of claim 1, selected from the following table:

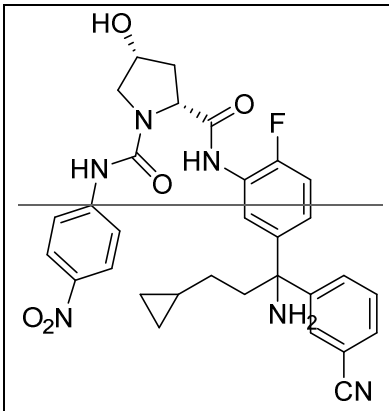
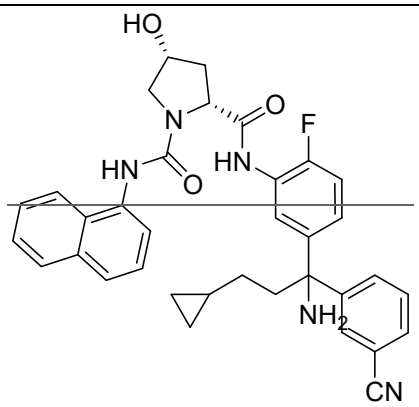
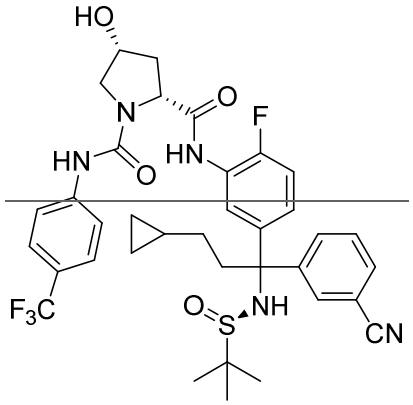
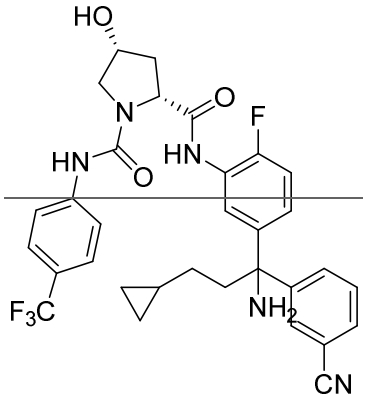
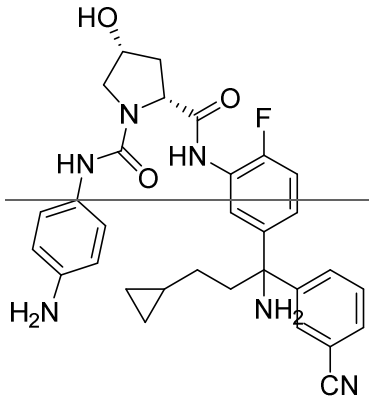
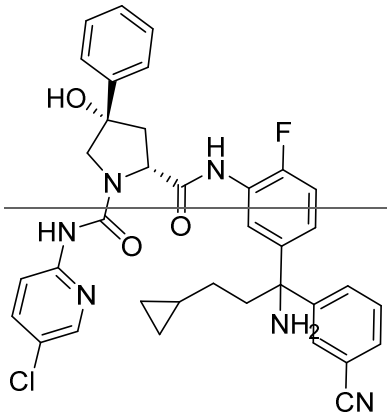


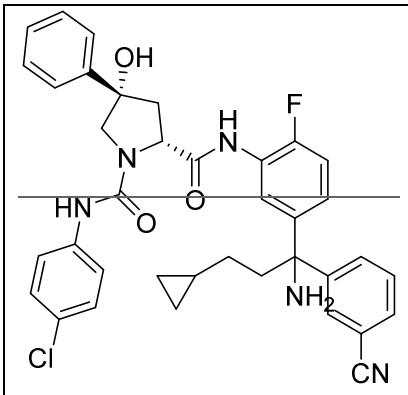
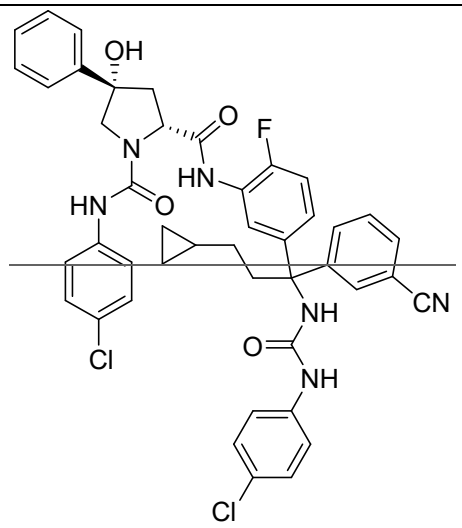
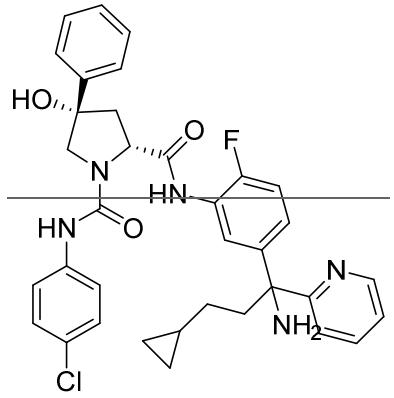
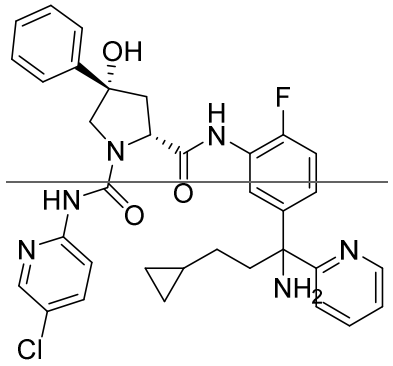
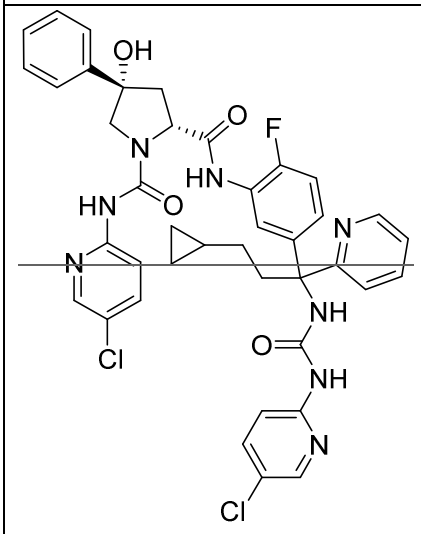
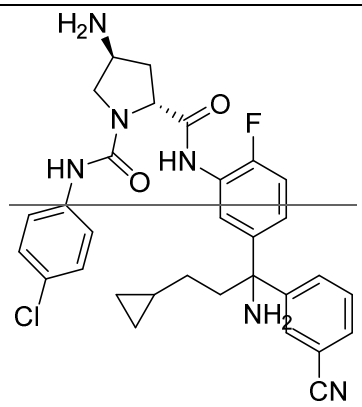
	
	
	
	

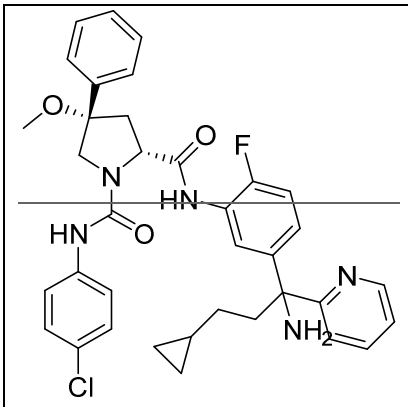
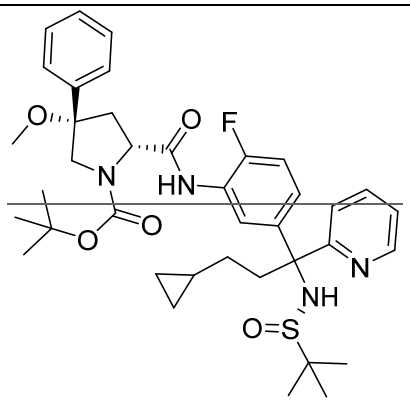
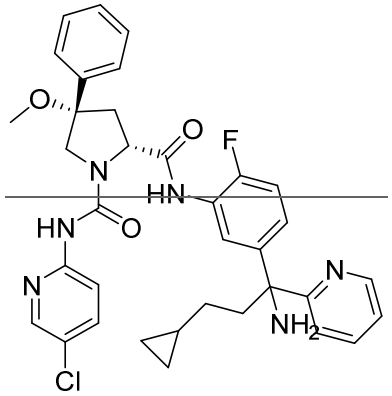
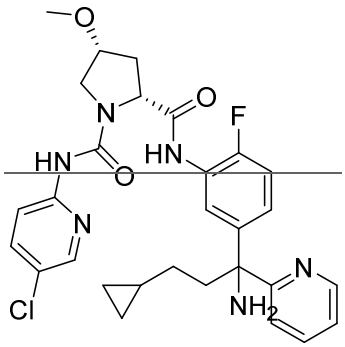
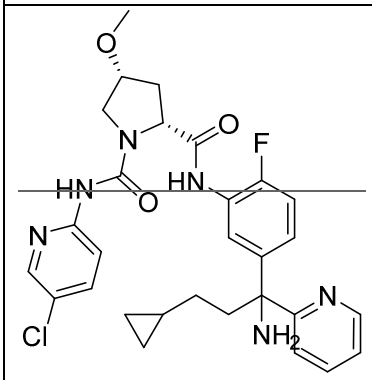
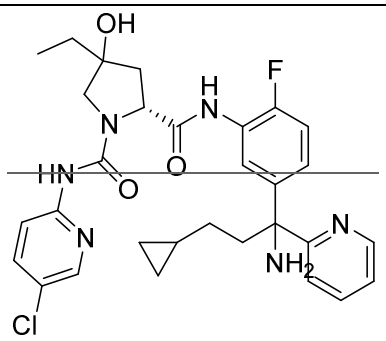
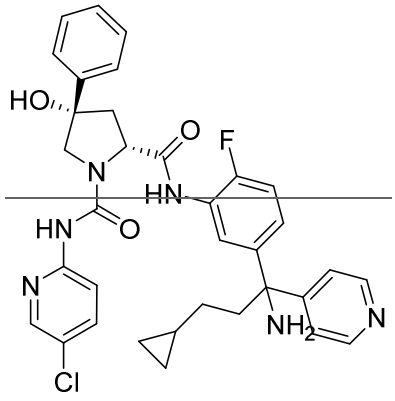
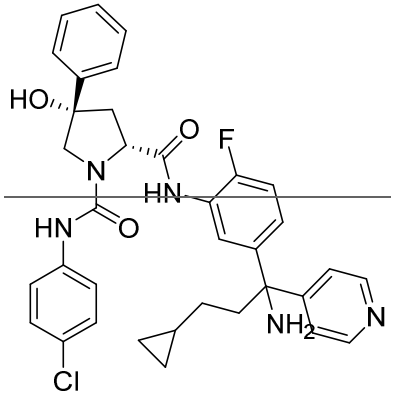
	
	
	
	

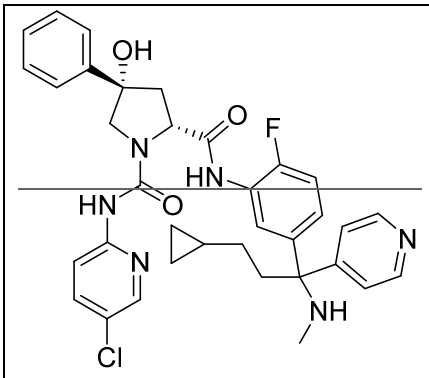
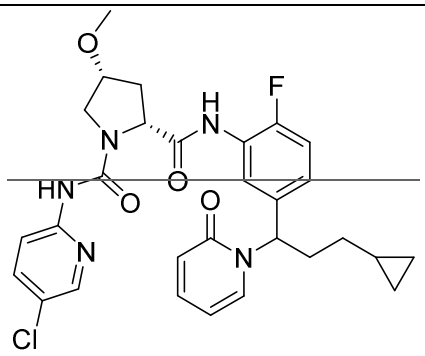
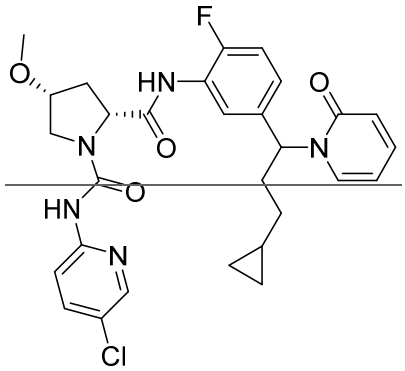
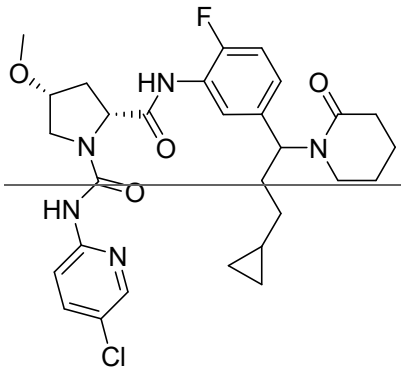
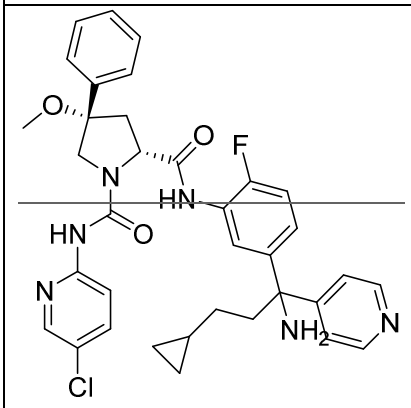
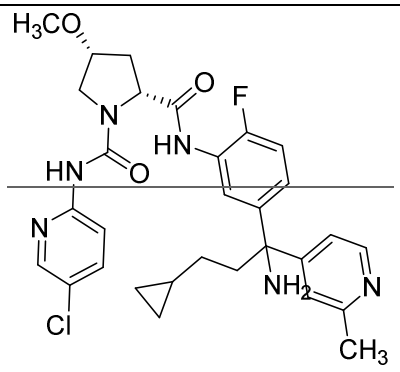
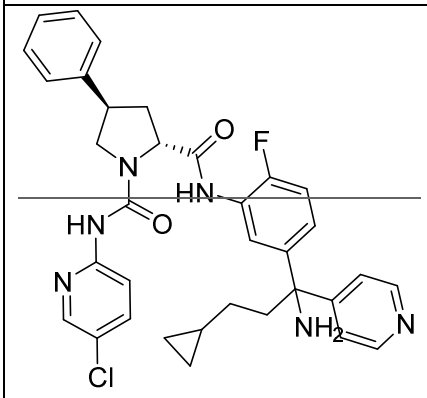
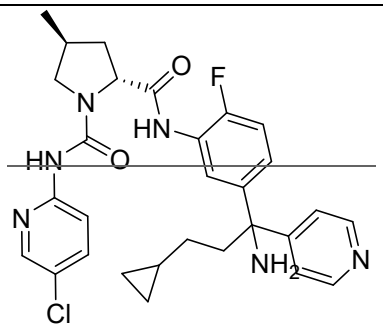
	
	
	
	

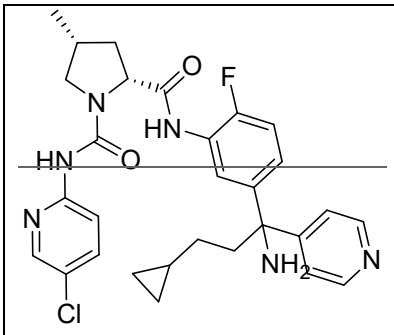
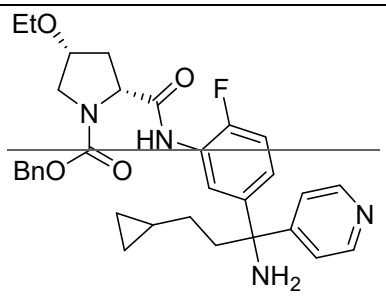
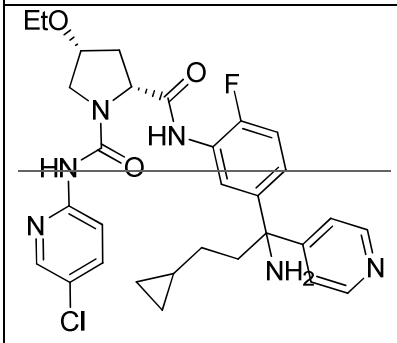
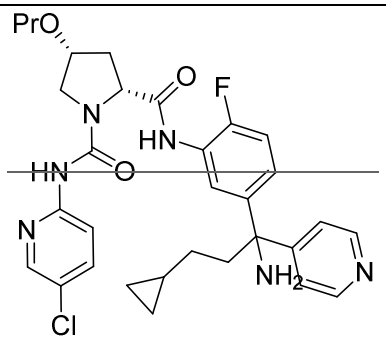
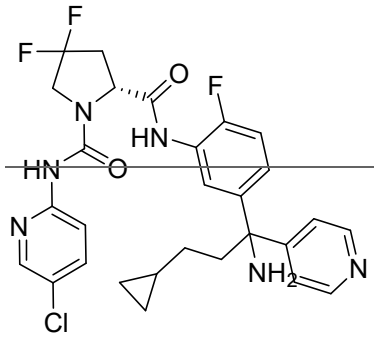
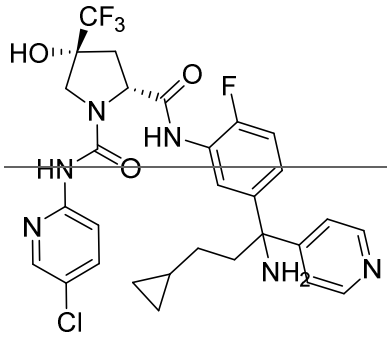
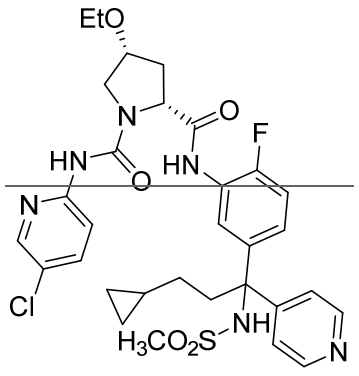
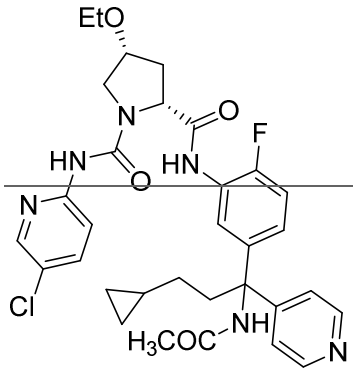
	
	
	
	

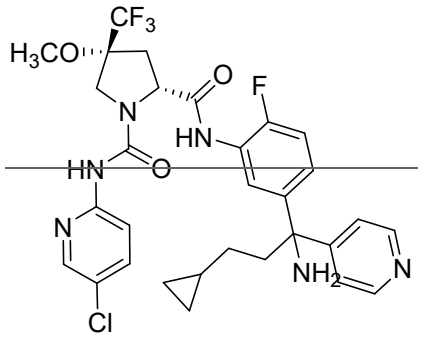
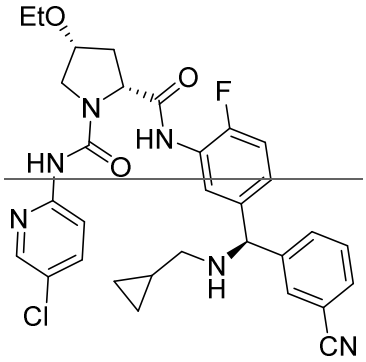
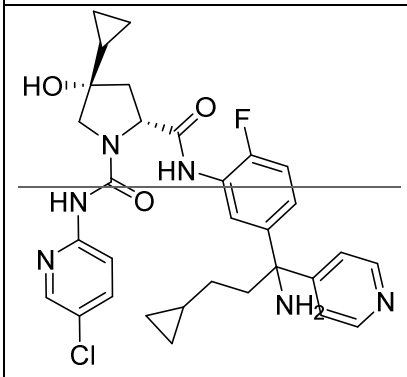
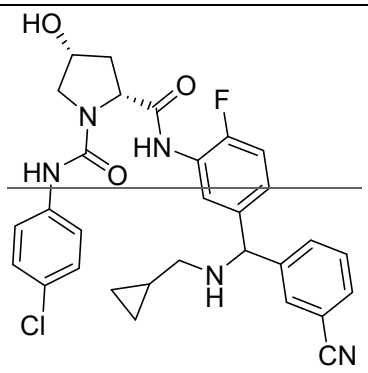
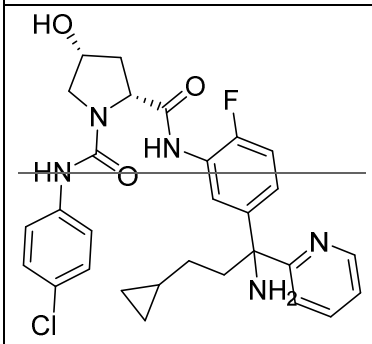
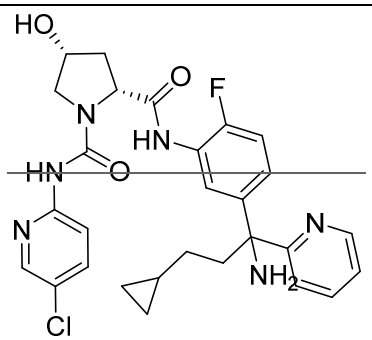
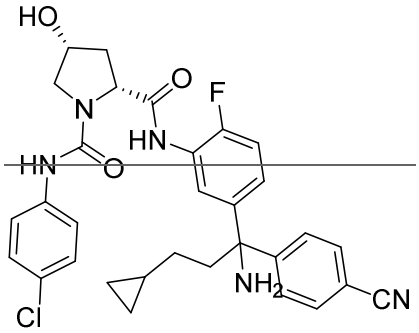
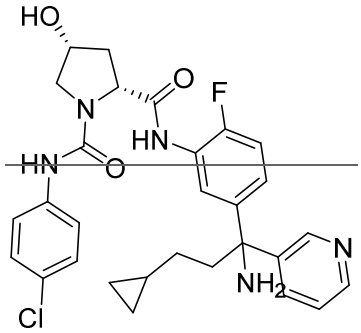
	
	
	

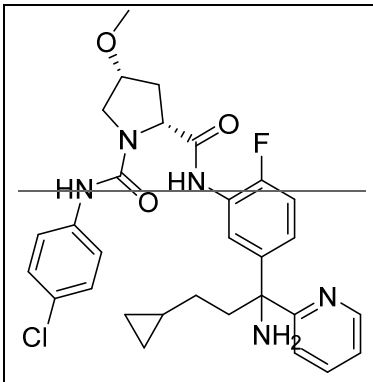
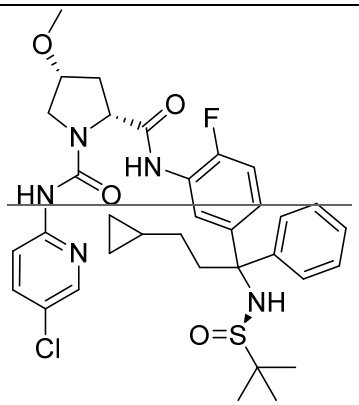
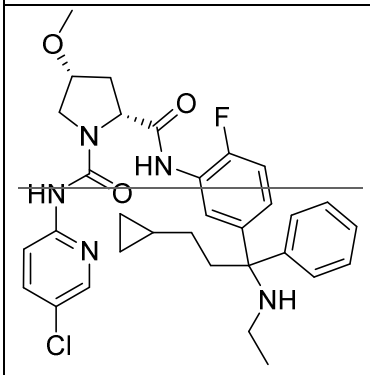
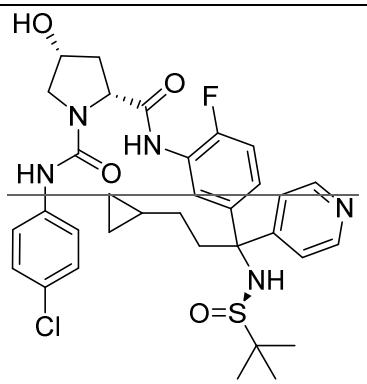
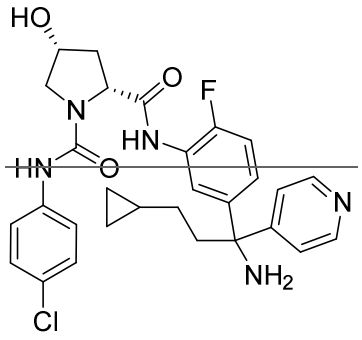
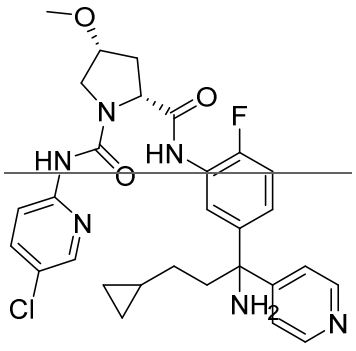
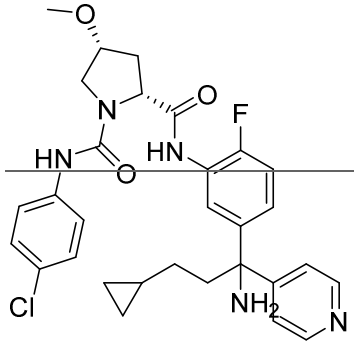
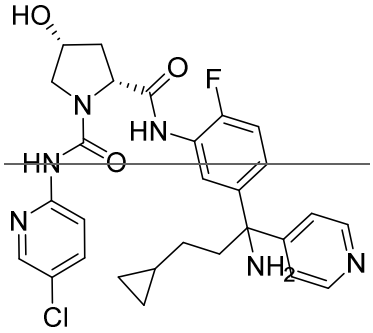
	
	
	

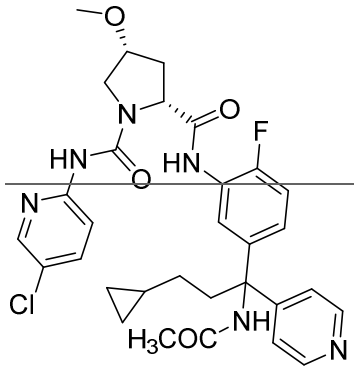
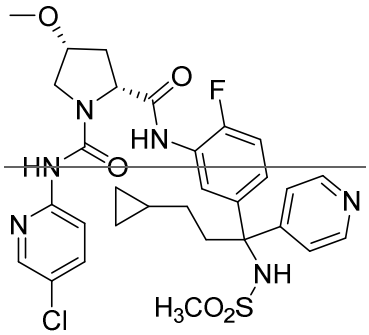
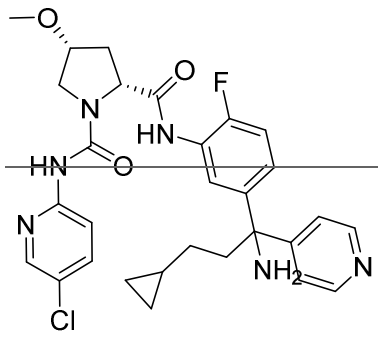
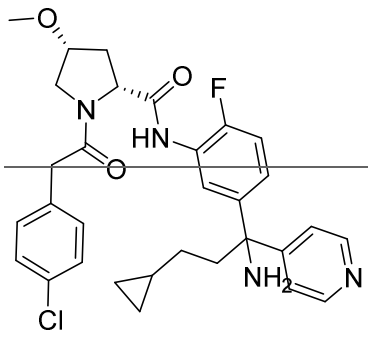
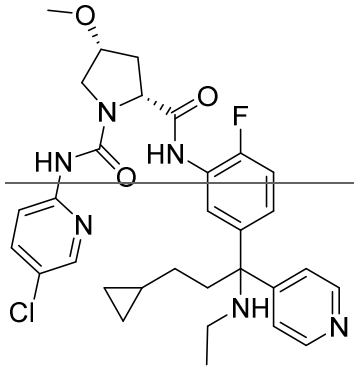
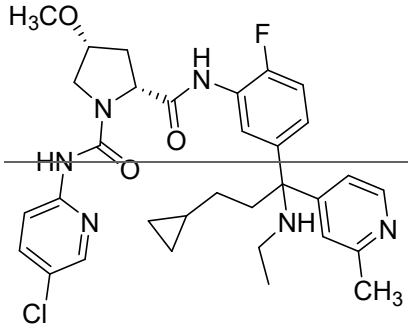
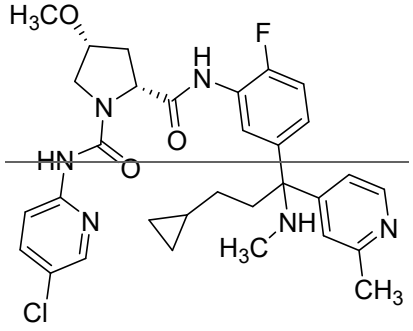
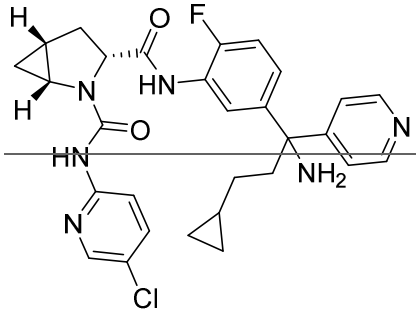
	
	
	
	

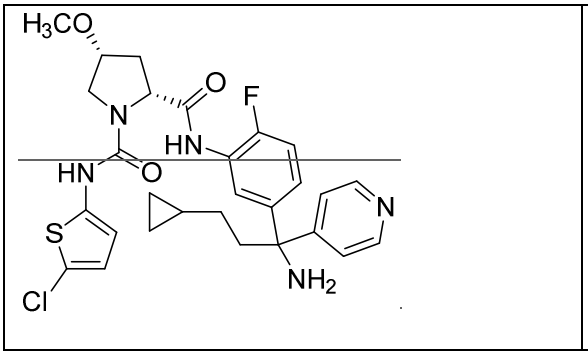
	
	
	
	

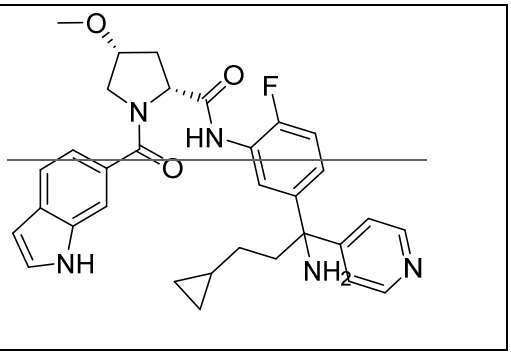
	
	
	
	





54. A pharmaceutical composition, comprising a compound of any one of claims 1-53; and a pharmaceutically acceptable carrier.

55. The pharmaceutical composition of claim 54, wherein the pharmaceutical composition is formulated for parenteral administration.

56. The pharmaceutical composition of claim 54, wherein the pharmaceutical composition is formulated for oral administration.

57. A method of treating or preventing a disease or condition characterized by unwanted plasma kallikrein activity, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-53.

58. The method of claim 57, 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.

59. The method of claim 57, wherein the disease or condition characterized by unwanted plasma kallikrein activity is angioedema.

60. The method of claim 57, wherein the disease or condition characterized by unwanted plasma kallikrein activity is hereditary angioedema.

~~61. The method of claim 57, wherein the disease or condition characterized by unwanted plasma kallikrein activity is stroke.~~

~~62. The method of claim 57, wherein the disease or condition characterized by unwanted plasma kallikrein activity is reperfusion injury.~~

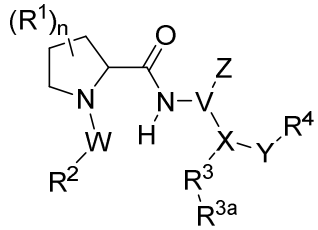
~~63. The method of claim 57, wherein the disease or condition characterized by unwanted plasma kallikrein activity is acute myocardial infarction.~~

~~64. The method of claim 57, wherein the disease or condition characterized by unwanted plasma kallikrein activity is hemorrhage.~~

~~65. The method of claim 57, wherein the disease or condition characterized by unwanted plasma kallikrein activity is blood loss during cardiopulmonary bypass.~~

~~66. The method of claim 57, wherein the disease or condition characterized by unwanted plasma kallikrein activity is selected from the group consisting of retinopathy, diabetic retinopathy, diabetic macular edema, diabetic macular degeneration, age-related macular edema, age-related macular degeneration, and proliferative retinopathy.~~

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)N$R^c R^d$, -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, –OR^c, alkyl, aryl, haloalkyl, or cycloalkyl;

Z is absent or represents one or more occurrences of halo;

X represents –C(NH_2)–, –C(NH(R^c))–, –C(NHS$(O)_pR^c$)–, or –C(NHC(O)R^c)–;

R^3 represents optionally substituted aryl or heteroaryl;

R^{3a} is absent or represents one or more substituents independently selected from the group consisting of alkyl or cyano;

-Y-R^4 represents -alkylene-R^4 or -N(alkyl)-R^4;

R^4 represents cycloalkyl.

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

4. The compound of claim 3, wherein n is 1; and

R^1 represents –OH, –CH_3 –$OCH_2CH_2CH_3$, –OCH_2CH_3, or –OCH_3.

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

6. The compound of claim 5, wherein R^1 represents –OH, –OCH_3, –CH_3, –CF_3, cyclopropyl, or phenyl.

7. The compound of claim 5, wherein:

(a) one occurrence of R^1 represents −OH or −O(alkyl); and the other occurrence of R^1 represents (C_6-C_{10})aryl or (C_3-C_{12})cycloalkyl;
(b) one occurrence of R^1 represents –OH or –O((C_1-C_6)alkyl); and the other occurrence of R^1 represents (C_1-C_{10})alkyl or halo(C_1-C_{10})alkyl; or
(c) both occurrences of R^1 are halo.

8. The compound of claim 5, wherein:
(a) one occurrence of R^1 represents –OH or –OCH_3; and the other occurrence of R^1 represents phenyl or cyclopropyl; or
(b) one occurrence of R^1 represents –OH or –OCH_3; and the other occurrence of R^1 represents –CH_2CH_3 or –CF_3.

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

10. The compound of claim 9, wherein R^2 represents phenyl, pyridyl, or thiophenyl substituted by one occurrence of halo.

11. The compound of any one of claims 1-10, wherein V represents optionally substituted aryl.

12. The compound of any one of claims 1-11, wherein Z represents halo or Z is absent.

13. The compound of any one of claims 1-11, wherein Z represents one instance of halo.

14. The compound of any one of claims 1-13, wherein X represents –CH, –C(NH_2)–, –C(NH(R^c))–, –C(NHS($O)_p R^c$)–, or –C(NHC(O)R^c)–.

15. The compound of claim 14, wherein X represents –C(NH_2)–; −C(NHalkyl)–; –C(NHS($O)_p$alkyl)–, wherein p is 1 or 2; or −C(NHC(O)(alkyl))–.

16. The compound of any one of claims 1-15, 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.

17. The compound of claim 16, 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.

18. The compound of any one of claims 1-17, wherein R^{3a} is absent or represents cyano or alkyl.

19. The compound of any one of claims 1-18, wherein Y represents -alkylene-R^4 or -NH-R^4.

20. The compound of any one of claims 1-19, wherein R^4 represents cycloalkyl or (cycloalkyl)alkyl.

21. The compound of claim 1, wherein:
R^1 represents $-OH$, $-CH_3$, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2CH_3$, $-F$, $-CF_3$, phenyl, or cyclopropyl;
R^2 represents substituted phenyl or pyridyl substituted by one instance of chloro;
R^3 represents optionally substituted phenyl or pyridyl;
R^{3a} is absent or represents one or more substituents independently selected from the group consisting of cyano or $-CH_3$;
V represents optionally substituted phenyl;
Y-R^4 represents CH_2CH_2-cyclopropyl or $-NHCH_2$-cyclopropyl;
X represents $-C(NH_2)-$, $-C(NH(R^c))-$, $-C(NHS(O)_pR^c)-$, or $-C(NHC(O)R^c;$
Z represents halo; and
R^c represents alkyl.

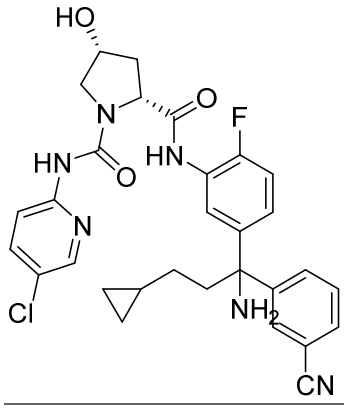
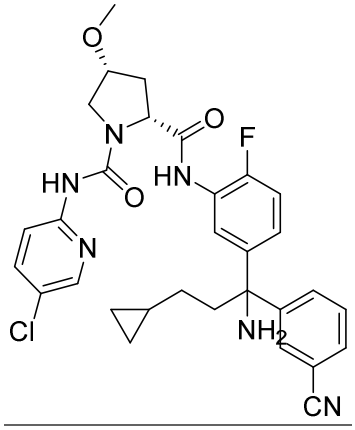
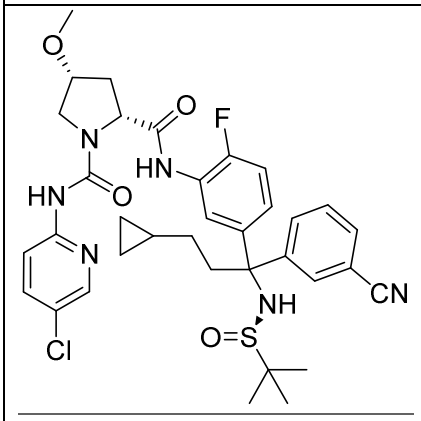
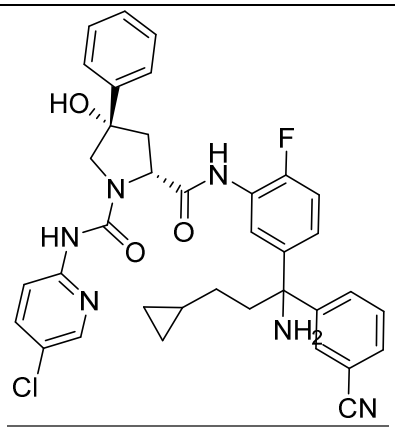
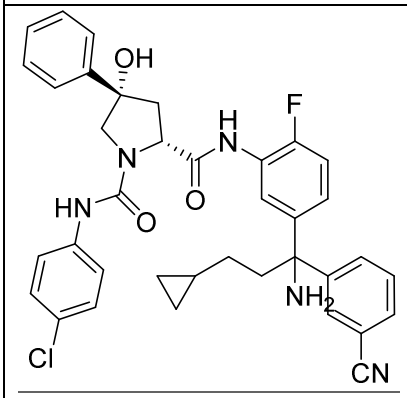
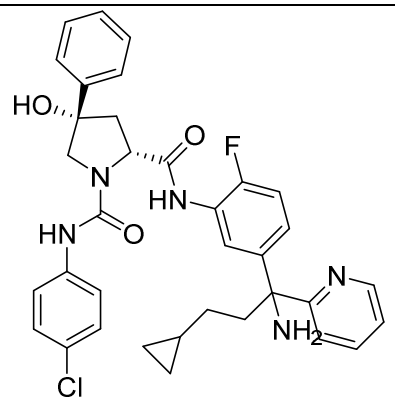
22. The compound of claim 21, wherein:
Z is one instance of F or Z is absent.

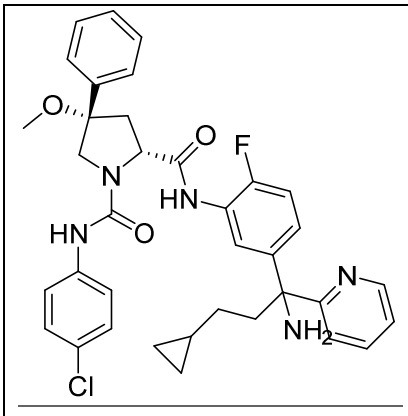
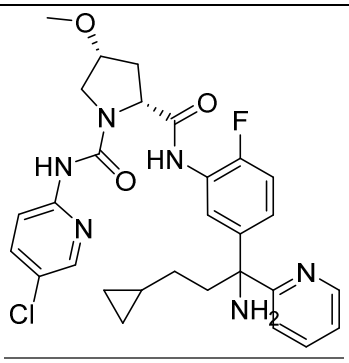
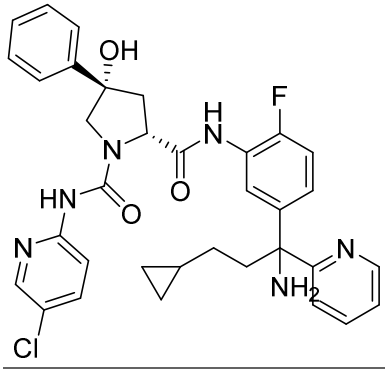
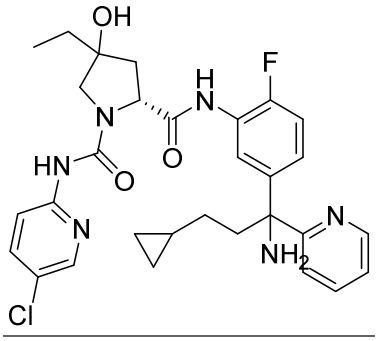
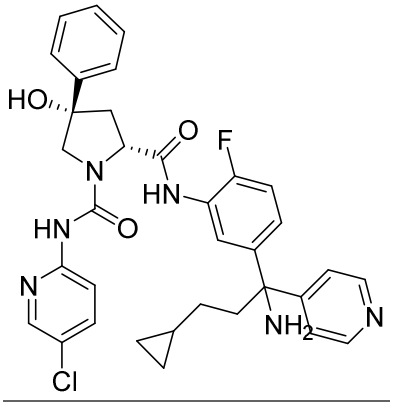
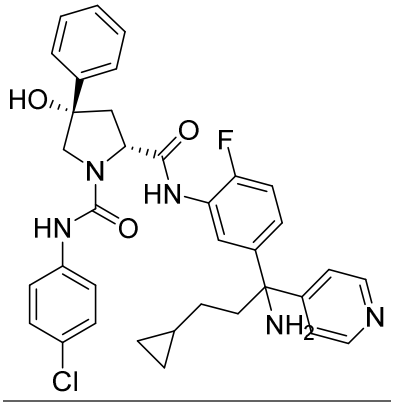
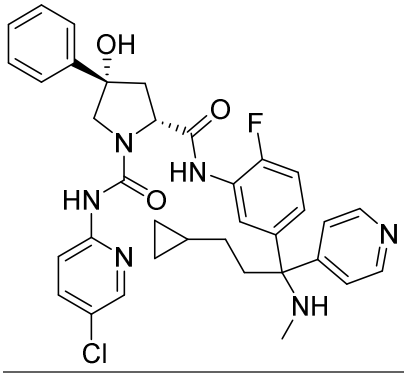
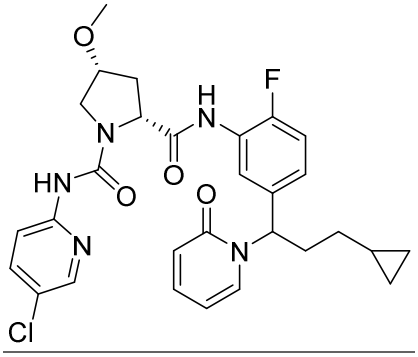
23. The compound of claim 21, wherein n is 1; and
R^1 represents $-OCH_3$ or $-OCH_2CH_3$.

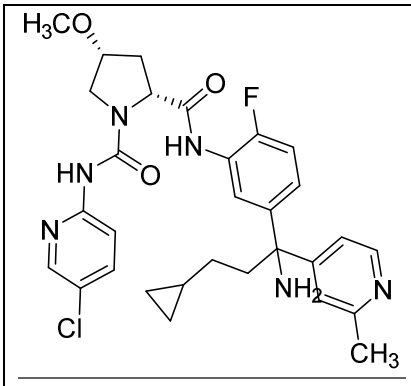
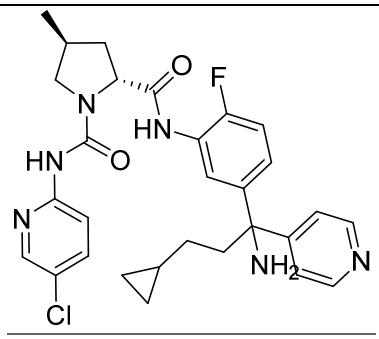
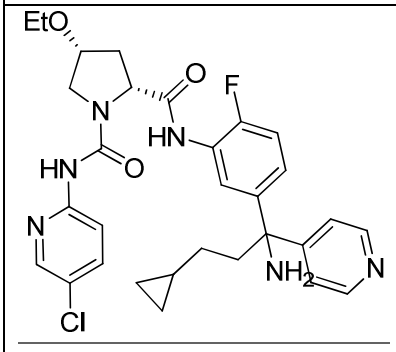
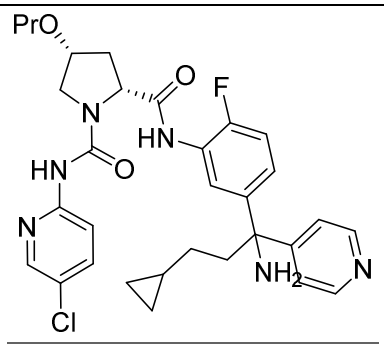
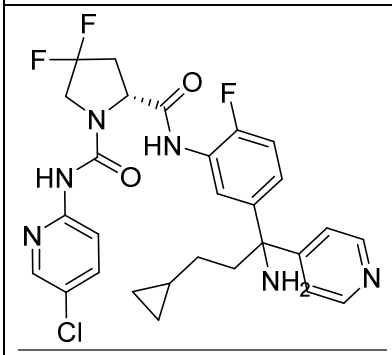
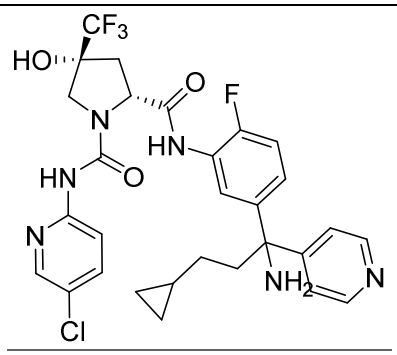
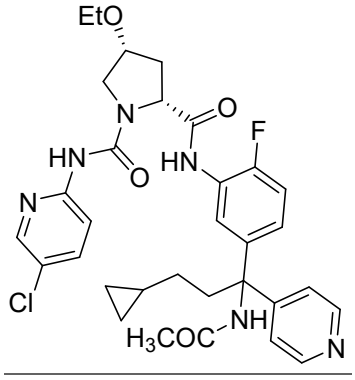
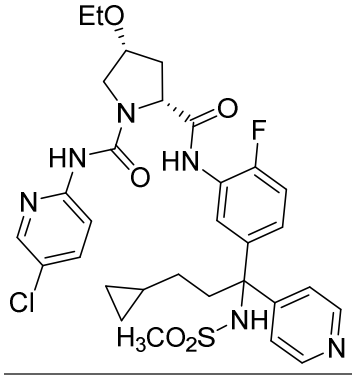
24. The compound of claim 21, wherein n is 2; and the two occurrences of R^1 are geminal.

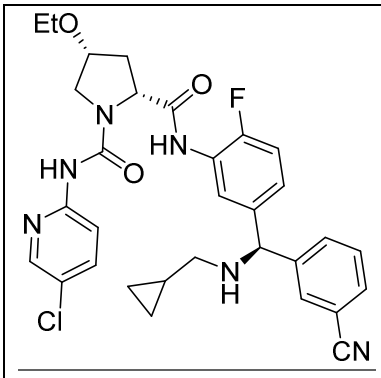
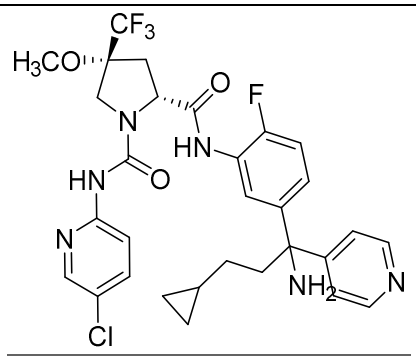
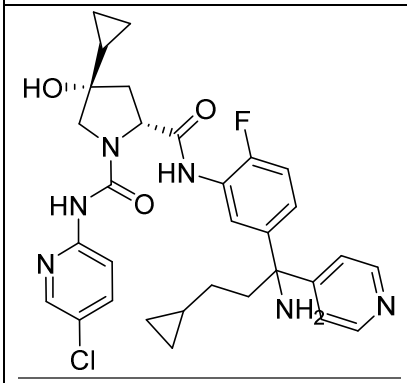
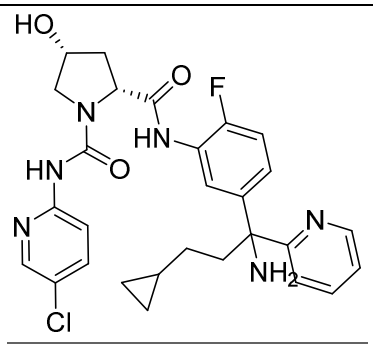
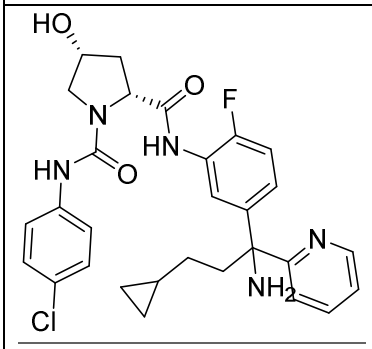
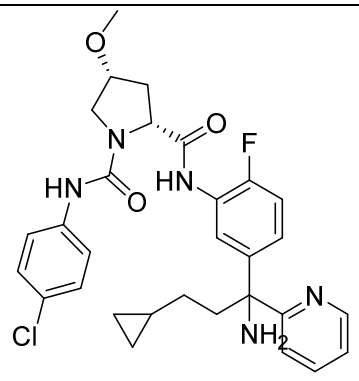
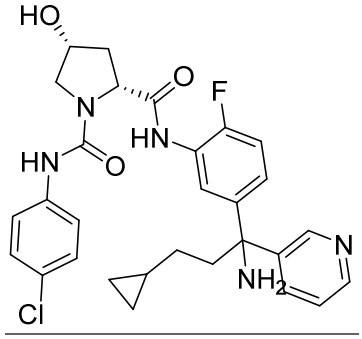
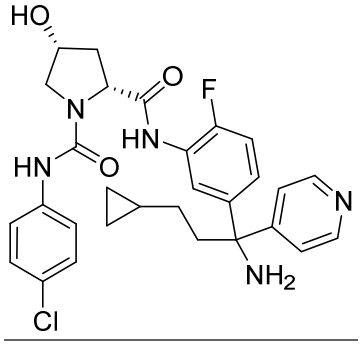
25. The compound of claim 24, wherein and R^1 represents –OH, $–OCH_3$, $–CF_3$, or phenyl.

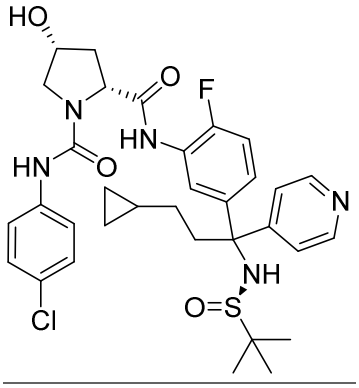
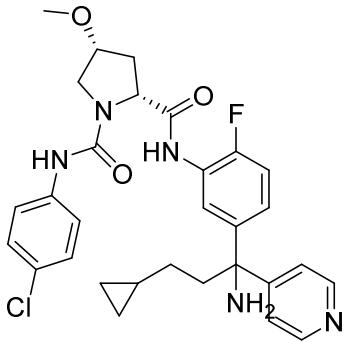
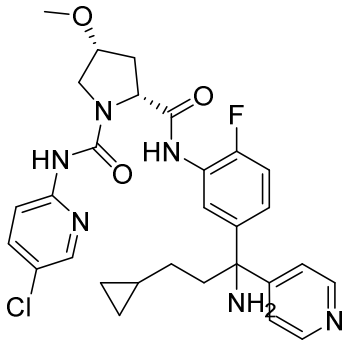
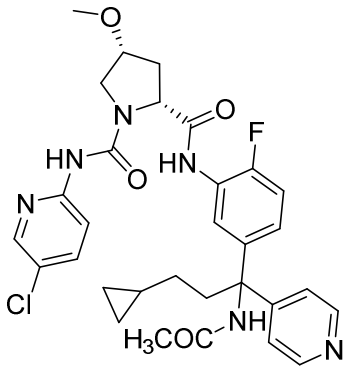
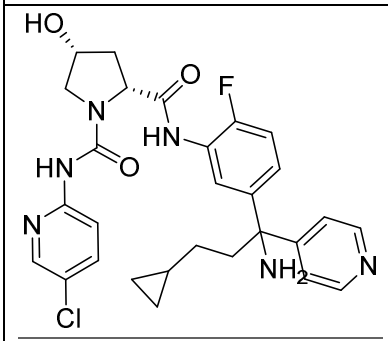
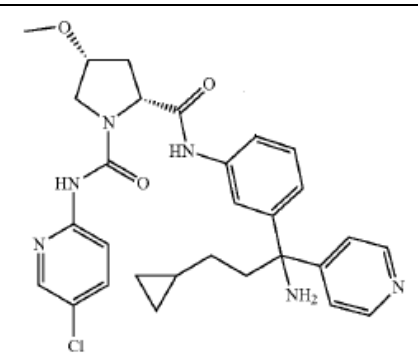
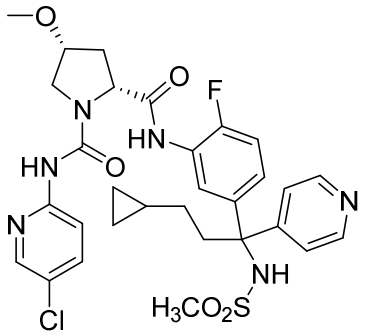
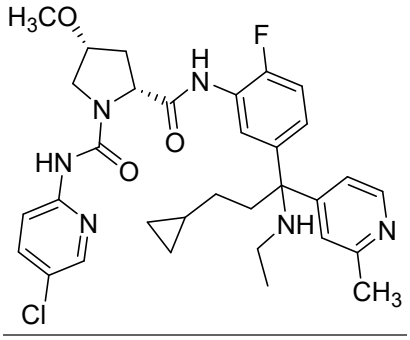
26. The compound of claim 1, wherein the compound is selected from the following table:

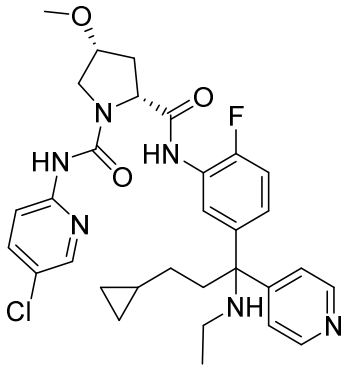
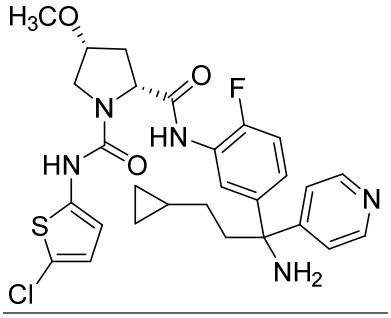
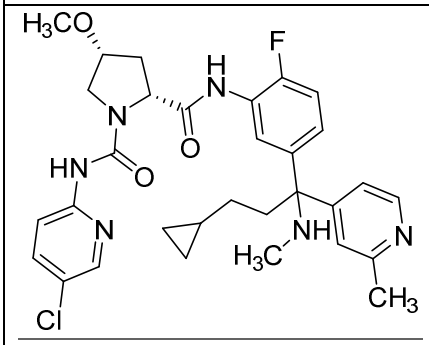
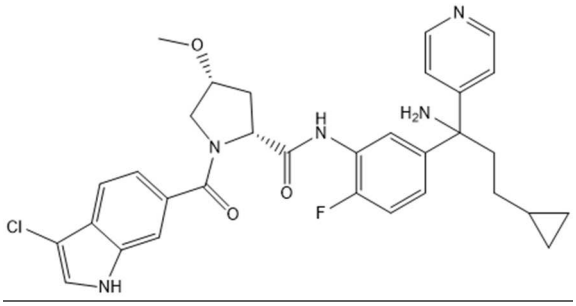
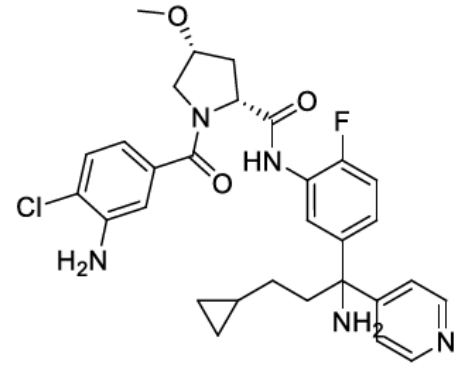
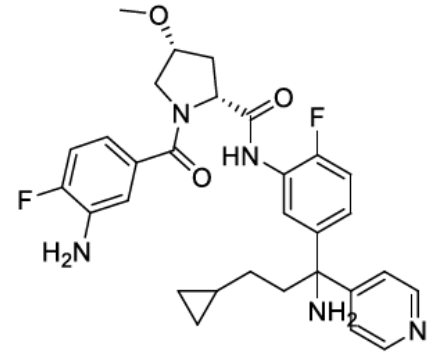
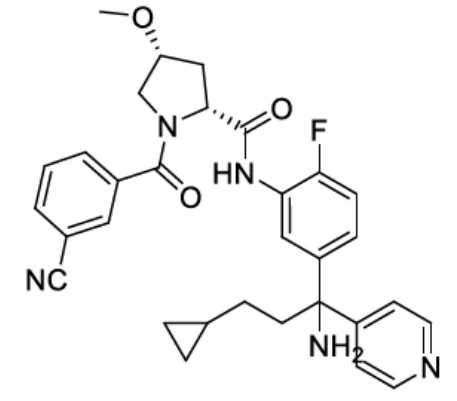
	
	
	

27. A pharmaceutical composition, comprising a compound of any one of claims 1-26, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

28. Use of a compound of any one of claims 1-26, 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.

29. The use of claim 28, wherein the disease or condition characterized by unwanted plasma kallikrein activity is angioedema.

30. The use of claim 28, wherein the disease or condition characterized by unwanted plasma kallikrein activity is hereditary angioedema.

31. Use of a compound of any one of claims 1-26 in the manufacture of a medicament for the prevention of hereditary angioedema.