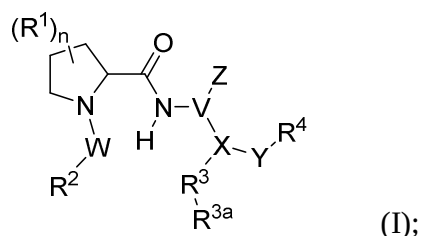


CLAIMS

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



wherein, independently for each occurrence:

R^1 represents $-\text{OH}$, $-\text{OR}^c$, $-\text{NH}_2$, $-\text{NHR}^c$, $-\text{NR}^c\text{R}^d$, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, halo, haloalkyl, cycloalkyl, (cycloalkyl)alkyl, $-\text{C}(\text{O})\text{R}^c$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{OR}^c$, $-\text{OC}(\text{O})\text{R}^c$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NHR}^c$, $-\text{C}(\text{O})\text{NR}^c\text{R}^d$, $-\text{NHC}(\text{O})\text{R}^c$, or $-\text{NR}^c\text{C}(\text{O})\text{R}^d$; or two geminal occurrences of R^1 taken together with the carbon to which they are attached represent $-\text{C}(\text{O})-$; 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, $-\text{C}(\text{O})\text{NH}-$, $-\text{C}(\text{O})\text{N}(\text{R}^c)-$, $-\text{C}(\text{O})\text{O}-$, $-\text{CH}_2-$, or $-\text{C}(\text{O})-$;

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, $-\text{NO}_2$, $-\text{CN}$, $-\text{C}(\text{O})\text{R}^c$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{OR}^c$, $-\text{OC}(\text{O})\text{R}^c$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NHR}^c$, $-\text{C}(\text{O})\text{NR}^c\text{R}^d$, $-\text{NHC}(\text{O})\text{R}^c$, $-\text{N}(\text{R}^c)\text{C}(\text{O})\text{R}^d$, $-\text{OS}(\text{O})_p(\text{R}^c)$, $-\text{NHS}(\text{O})_p(\text{R}^c)$, and $-\text{NR}^c\text{S}(\text{O})_p(\text{R}^c)$;

X represents $-\text{C}(\text{NH}_2)-$, $-\text{C}(\text{NH}(\text{R}^c))-$, $-\text{C}(\text{NR}^c\text{R}^d)-$, $-\text{C}(\text{NHS}(\text{O})_p\text{R}^c)-$, $-\text{C}(\text{NHC}(\text{O})\text{R}^c)-$, $-\text{C}(\text{NHC}(\text{O})\text{NH}_2)-$, $-\text{C}(\text{NHC}(\text{O})\text{NHR}^c)-$, $-\text{C}(\text{NHC}(\text{O})\text{NR}^c\text{R}^d)-$, $-\text{C}(\text{OH})-$, $-\text{C}(\text{O}(\text{alkyl}))-$, $-\text{C}(\text{N}_3)-$, $-\text{C}(\text{CN})-$, $-\text{C}(\text{NO}_2)-$, $-\text{C}(\text{S}(\text{O})_n\text{R}^d)-$, $-\text{C}[-\text{C}(=\text{O})\text{R}^c]-$, $-\text{C}[-\text{C}(=\text{O})\text{NR}^c\text{R}^d]-$, $-\text{C}[-\text{C}(=\text{O})\text{SR}^c]-$, $-\text{C}[-\text{S}(\text{O})\text{R}^c]-$, $-\text{C}[-\text{S}(\text{O})_2\text{R}^c]-$, $-\text{C}[\text{S}(\text{O})(\text{OR}^c)]-$,

$-\text{C}[-\text{S}(\text{O})_2(\text{OR}^c)]-$, $-\text{C}[-\text{SO}_2\text{NR}^c\text{R}^d]-$, $-\text{C}(\text{halogen})-$, $-\text{C}(\text{alkyl})$, $-\text{C}((\text{cycloalkyl})\text{alkyl})$,
 $-\text{C}(\text{alkenyl})-$, $-\text{C}(\text{alkynyl})-$, or $-\text{C}(\text{aralkyl})-$;

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, $-\text{CF}_3$, $-\text{OCF}_3$, alkoxy, aryl, heteroaryl, aryloxy, amino, aminoalkyl, $-\text{C}(\text{O})\text{NH}_2$, cyano, $-\text{NHC}(\text{O})\text{alkyl}$, $-\text{SO}_2\text{alkyl}$, $-\text{SO}_2\text{NH}_2$, cycloalkyl, $-(\text{CH}_2)_r\text{OR}^a$, $-\text{NO}_2$, $-(\text{CH}_2)_r\text{NR}^a\text{R}^b$, $-(\text{CH}_2)_r\text{C}(\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(\text{O})\text{R}^b$, $-\text{C}(\text{O})\text{NR}^c\text{R}^d$, $-\text{NR}^a\text{C}(\text{O})\text{NR}^c\text{R}^d$, $-\text{C}(=\text{NR}^a)\text{NR}^c\text{R}^d$, $-\text{NHC}(=\text{NR}^a)\text{NR}^c\text{R}^d$, $-\text{NR}^a\text{R}^b$, $-\text{SO}_2\text{NR}^c\text{R}^d$, $-\text{NR}^a\text{SO}_2\text{NR}^c\text{R}^d$, $-\text{NR}^a\text{SO}_2\text{alkyl}$, $-\text{NR}^a\text{SO}_2\text{R}^a$, $-\text{S}(\text{O})_p\text{R}^a$, $-(\text{CF}_2)_r\text{CF}_3$, $-\text{NHCH}_2\text{R}^a$, $-\text{OCH}_2\text{R}^a$, $-\text{SCH}_2\text{R}^a$, $-\text{NH}(\text{CH}_2)_2(\text{CH}_2)_r\text{R}^a$, $-\text{O}(\text{CH}_2)_2(\text{CH}_2)_r\text{R}^a$, or $-\text{S}(\text{CH}_2)_2(\text{CH}_2)_r\text{R}^a$;

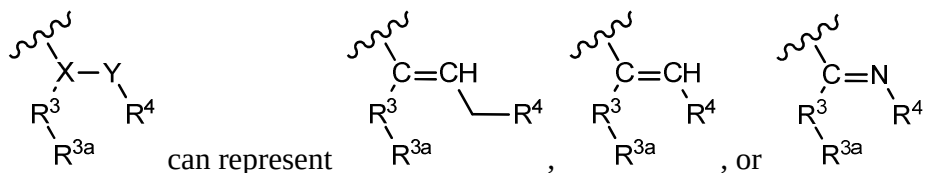
Y represents a bond; or $-\text{Y}-\text{R}^4$ represents optionally substituted $-\text{alkylene}-\text{R}^4$, $-\text{CH}_2\text{C}(\text{O})-\text{R}^4$, $-\text{CH}_2\text{NH}-\text{R}^4$, $-\text{CH}_2\text{N}(\text{alkyl})-\text{R}^4$, $-\text{CR}^a\text{R}^b-\text{R}^4$, $-\text{NH}-\text{R}^4$,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

R^4 represents hydrogen, hydroxy, optionally substituted alkyl, cycloalkyl, (heterocycloalkyl)alkyl, (cycloalkyl)alkyl, $-\text{CH}_2\text{OH}$, $-\text{CH}(\text{alkyl})\text{OH}$, $-\text{CH}(\text{NH}_2)\text{CH}(\text{alkyl})_2$, aryl, aralkyl, heteroaryl, heteroaralkyl, $-\text{CH}_2\text{S}(\text{alkyl})$, amino, or cyano; or $-(\text{CR}^a\text{R}^b)_r(\text{CR}^a\text{R}^b)_p-$ 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 $-\text{NR}^a-$ 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, $-\text{C}(=\text{O})\text{R}^c$, $-\text{C}(=\text{O})\text{OR}^c$, $-\text{C}(=\text{O})\text{NR}^c\text{R}^d$, $-\text{C}(=\text{O})\text{SR}^c$, $-\text{S}(\text{O})\text{R}^c$, $-\text{S}(\text{O})_2\text{R}^c$, $-\text{S}(\text{O})(\text{OR}^c)$, or $-\text{SO}_2\text{NR}^c\text{R}^d$;

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, $-\text{C}(\text{O})\text{alkyl}$, or $-\text{S}(\text{O})_p(\text{alkyl})$; or R^c and R^d can be taken together to form an optionally substituted heterocyclic ring;



r is 0, 1, 2, or 3;

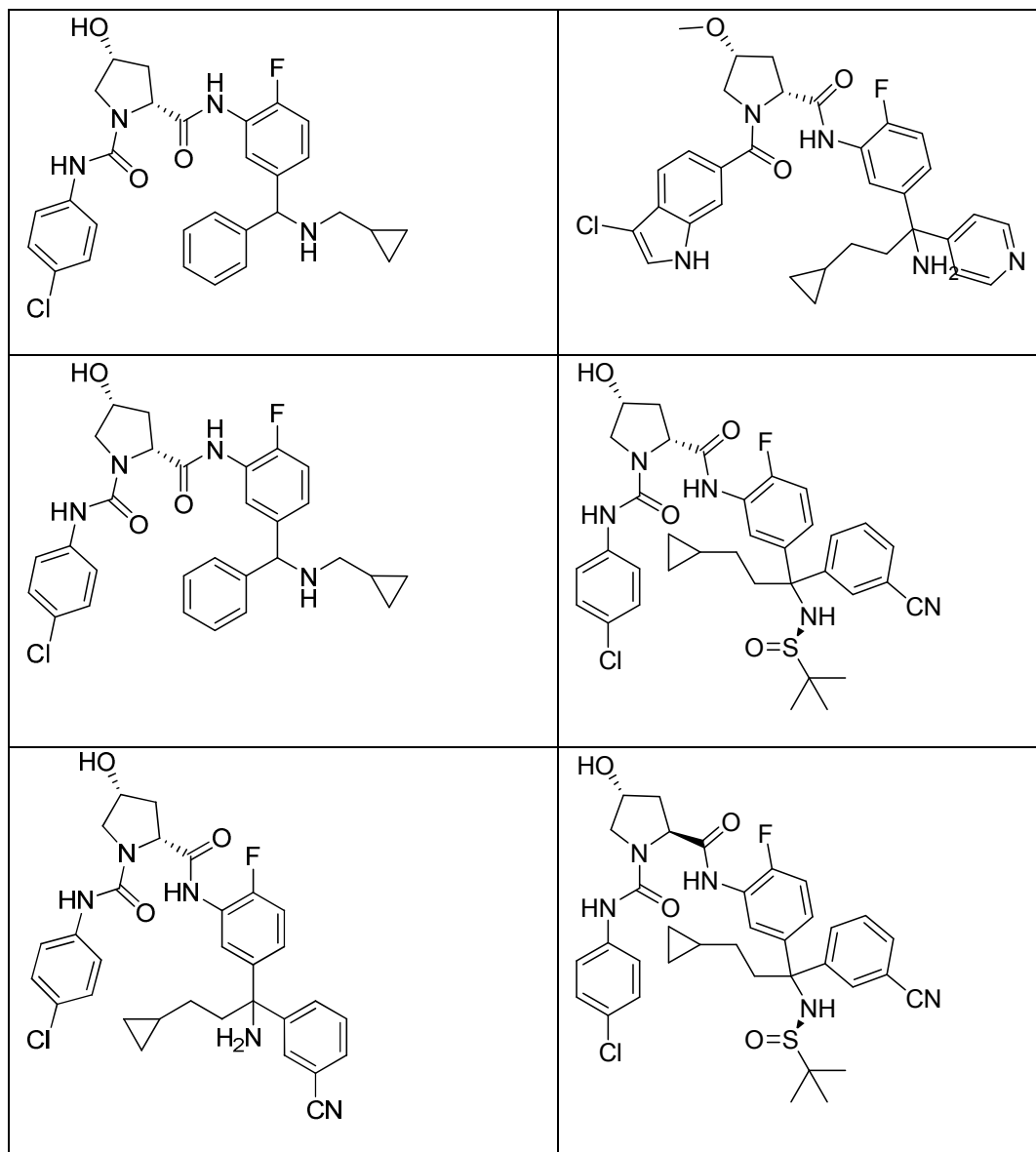
n is an integer from 0 to 6; and

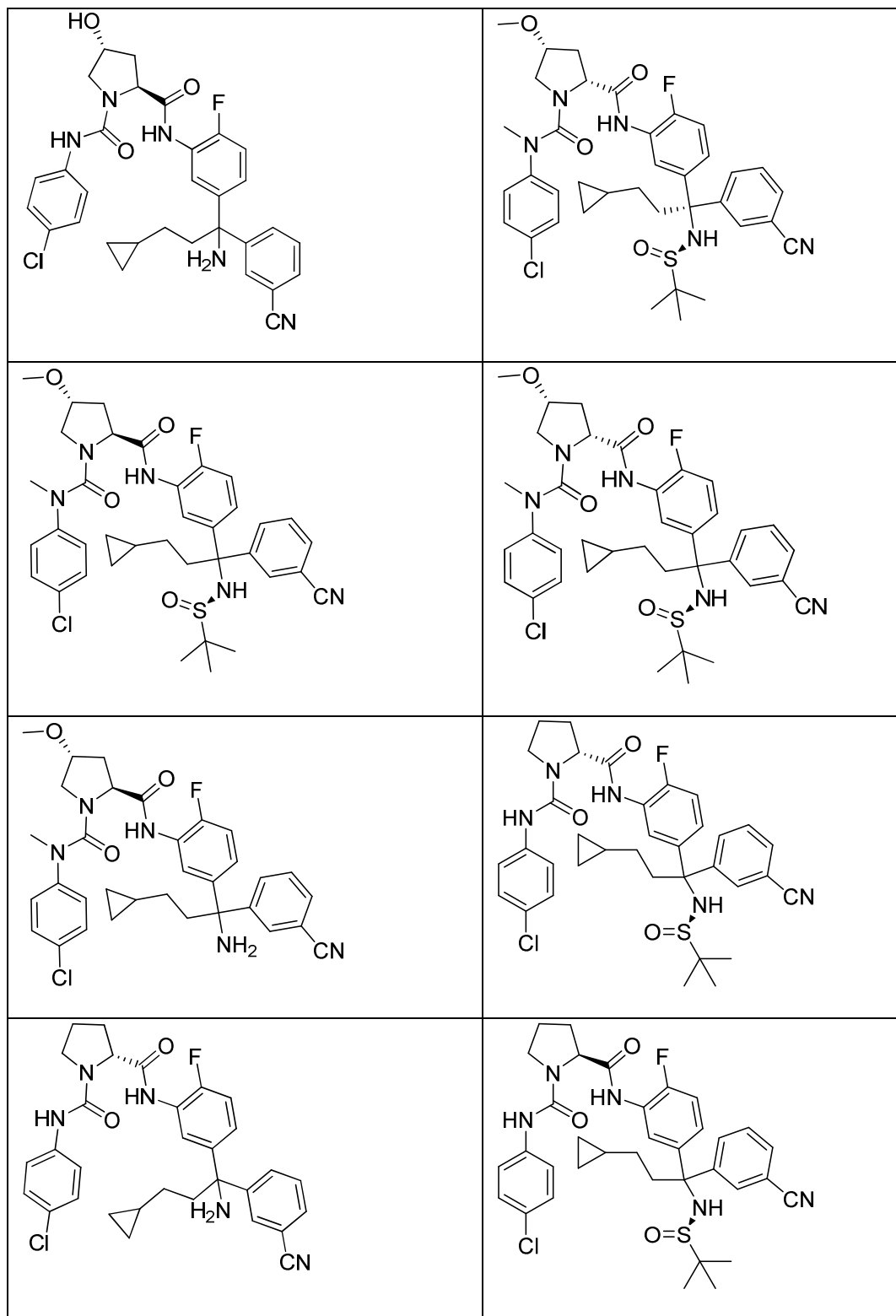
p is 0, 1, or 2.

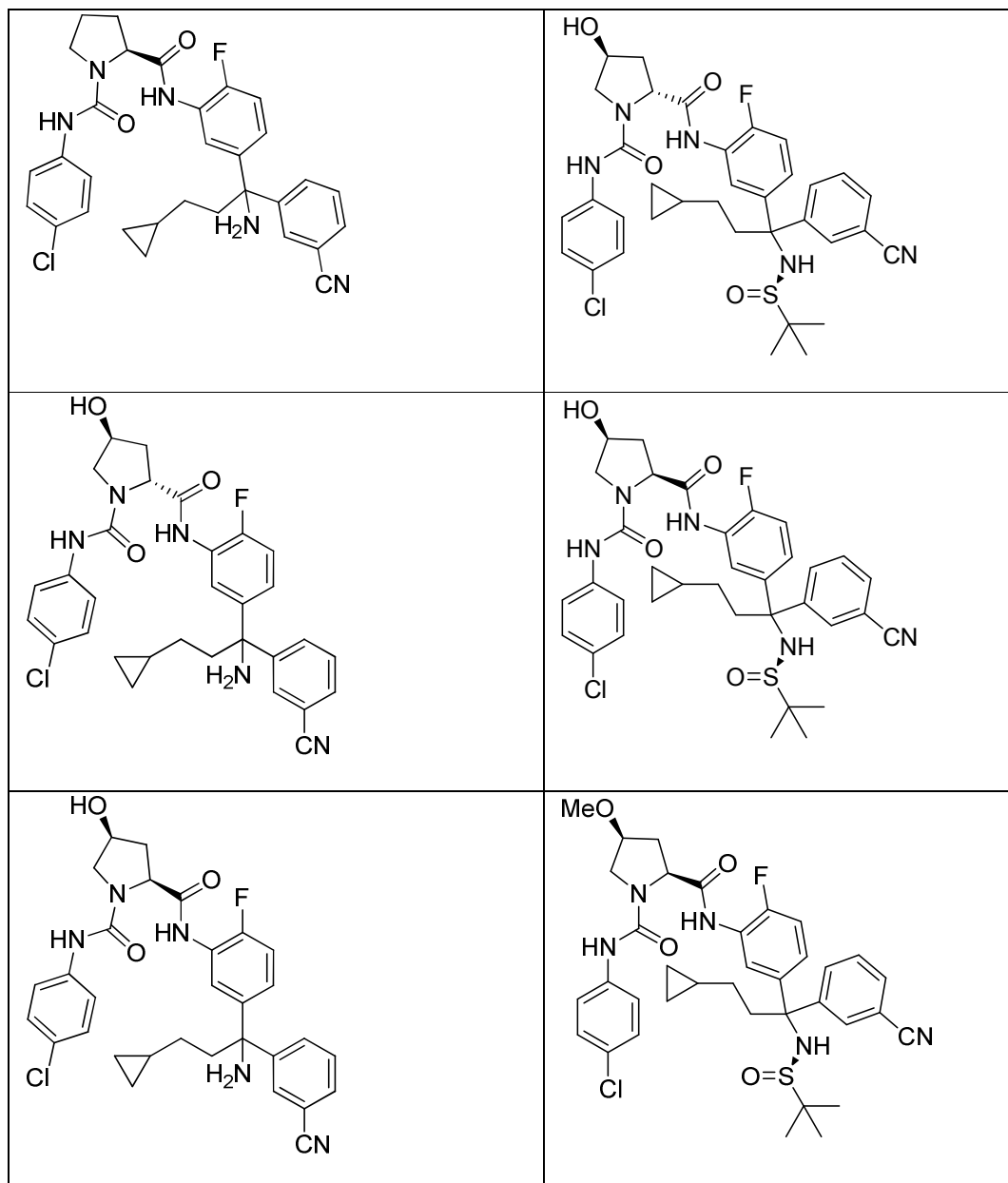
2. The compound of claim 1, wherein R^1 represents $-\text{OH}$, $-\text{OR}^c$, $-\text{NH}_2$, $-\text{NHR}^c$, $-\text{NR}^c\text{R}^d$, alkyl, aryl, heteroaryl, halo, haloalkyl, cycloalkyl, $-\text{OC}(\text{O})\text{R}^c$, $-\text{NHC}(\text{O})\text{R}^c$, or $-\text{NRC}(\text{O})\text{R}^d$; or two geminal occurrences of R^1 taken together with the carbon to which they are attached represent $-\text{C}(\text{O})-$; 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 $-\text{OH}$, $-\text{OR}^c$, $-\text{NH}_2$, alkyl, aryl, halo, haloalkyl, cycloalkyl, or $-\text{OC}(\text{O})\text{R}^c$; and n is 1 or 2.
4. The compound of claim 3, wherein n is 1; and R^1 represents $-\text{OH}$, $-\text{O}((\text{C}_1\text{-C}_6)\text{alkyl})$, $-\text{OC}(\text{O})((\text{C}_1\text{-C}_6)\text{alkyl})$, $-\text{NH}_2$, or $(\text{C}_1\text{-C}_6)\text{alkyl}$.
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:
 - (a) one occurrence of R^1 represents $-\text{OH}$ or $-\text{OR}^c$; and the other occurrence of R^1 represents aryl or heteroaryl;
 - (b) one occurrence of R^1 represents $-\text{OH}$ or $-\text{OR}^c$; and the other occurrence of R^1 represents haloalkyl;
 - (c) both occurrences of R^1 are halo; or

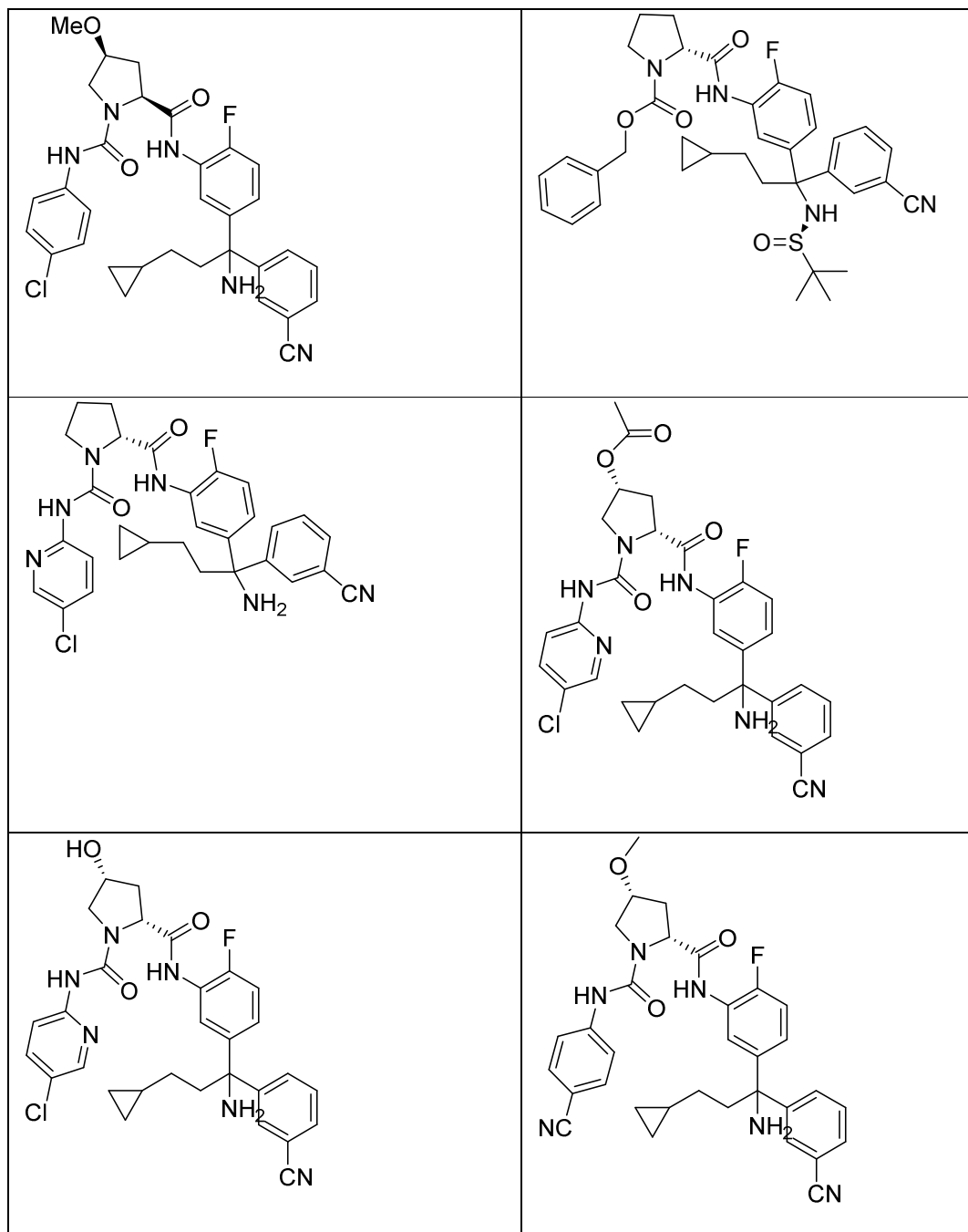
- (d) the two geminal occurrences of R^1 taken together with the carbon to which they are attached represent $-C(O)-$.
7. The compound of claim 3, wherein n is 2; the two occurrences of R^1 are vicinal; and the two vicinal occurrences of R^1 taken together form an optionally substituted fused carbocyclic ring.
 8. The compound of any one of claims 1-7, wherein W is $-C(O)NH-$ or $-C(O)N(R^c)-$.
 9. The compound of claim 8, wherein R^2 represents optionally substituted aryl or heteroaryl.
 10. The compound of claim 9, 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 $-C(O)N((C_1-C_6)alkyl)_2$; or wherein R^2 represents (halo)aryl or (halo)heteroaryl.
 11. The compound of any one of claims 1-7, wherein W is $-C(O)-$.
 12. The compound of claim 11, wherein R^2 represents optionally substituted aralkyl or heteroaralkyl.
 13. The compound of any one of claims 1-12, wherein V represents optionally substituted aryl.
 14. The compound of any one of claims 1-13, wherein Z is absent, or wherein Z represents one or more substituents independently selected from the group consisting of halo, haloalkyl, $-NO_2$, and $-CN$.
 15. The compound of claim 14, wherein Z represents one instance of halo; or wherein Z represents one instance of fluoro.

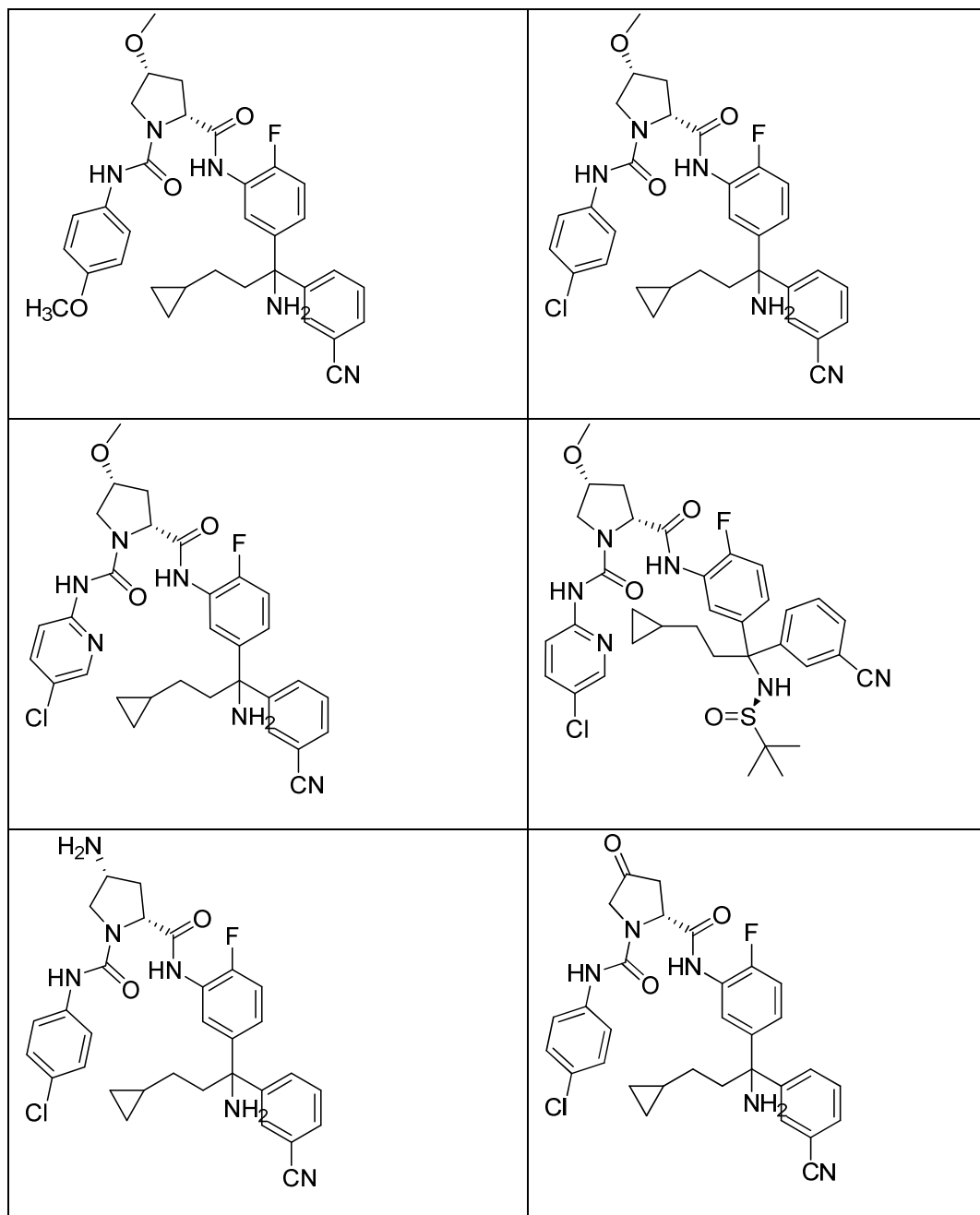
16. The compound of any one of claims 1-15, wherein X represents $-\text{C}(\text{NH}_2)-$, $-\text{C}(\text{NH}(\text{R}^c))-$, $-\text{C}(\text{NR}^c\text{R}^d)-$, $-\text{C}(\text{NHS}(\text{O})_p\text{R}^c)-$, $-\text{C}(\text{NHC}(\text{O})\text{R}^c)-$, $-\text{C}(\text{NHC}(\text{O})\text{NH}_2)-$, $-\text{C}(\text{NHC}(\text{O})\text{NHR}^c)-$, or $-\text{C}(\text{NHC}(\text{O})\text{NR}^c\text{R}^d)-$.
17. The compound of claim 16, wherein X represents $-\text{C}(\text{NH}_2)-$; $-\text{C}(\text{NH}(\text{cycloalkyl})\text{alkyl})-$; $-\text{C}(\text{NH}(\text{C}_1\text{-C}_6)\text{alkyl})-$; $-\text{C}(\text{NHS}(\text{O})_p(\text{C}_1\text{-C}_6)\text{alkyl})-$, wherein p is 1 or 2; optionally substituted $-\text{C}(\text{NHC}(\text{O})\text{NH}(\text{aryl}))-$; optionally substituted $\text{C}(\text{NHC}(\text{O})\text{NH}(\text{heteroaryl}))-$; or $-\text{C}(\text{NHC}(\text{O})((\text{C}_1\text{-C}_6)\text{alkyl}))-$.
18. The compound of any one of claims 1-17, wherein R^3 represents optionally substituted aryl or optionally substituted heteroaryl.
19. The compound of claim 18, wherein R^3 represents phenyl, optionally substituted by one or more substituents selected from the group consisting of $-\text{CN}$, halo, $-\text{NO}_2$, $(\text{C}_1\text{-C}_6)\text{alkyl}$, and $(\text{C}_1\text{-C}_6)\text{haloalkyl}$; or wherein R^3 represents pyridyl.
20. The compound of any one of claims 1-18, wherein R^{3a} is absent or represents halo, alkyl, $-\text{CF}_3$, $-\text{OCF}_3$, aryl, heteroaryl, $-\text{C}(\text{O})\text{NH}_2$, cyano, $-\text{NHC}(\text{O})\text{alkyl}$, $-\text{SO}_2\text{alkyl}$, $-\text{SO}_2\text{NH}_2$, $-\text{NO}_2$, $-\text{NR}^a\text{C}(\text{O})\text{R}^b$, $-\text{C}(\text{O})\text{NR}^c\text{R}^d$, $-\text{NR}^a\text{C}(\text{O})\text{NR}^c\text{R}^d$, $-\text{C}(=\text{NR}^a)\text{NR}^c\text{R}^d$, $-\text{NHC}(=\text{NR}^a)\text{NR}^c\text{R}^d$, $-\text{SO}_2\text{NR}^c\text{R}^d$, $-\text{NR}^a\text{SO}_2\text{NR}^c\text{R}^d$, $-\text{NR}^a\text{SO}_2\text{alkyl}$, $-\text{NR}^a\text{SO}_2\text{R}^a$, $-\text{S}(\text{O})_p\text{R}^a$, or $-(\text{CF}_2)_r\text{CF}_3$.
21. The compound of any one of claims 1-20, wherein Y represents a bond.
22. The compound of any one of claims 1-21, wherein R^4 represents H, (cycloalkyl)alkyl, or (cyclopropyl)($\text{C}_1\text{-C}_6$)alkyl.
23. The compound of claim 1, selected from the following table:

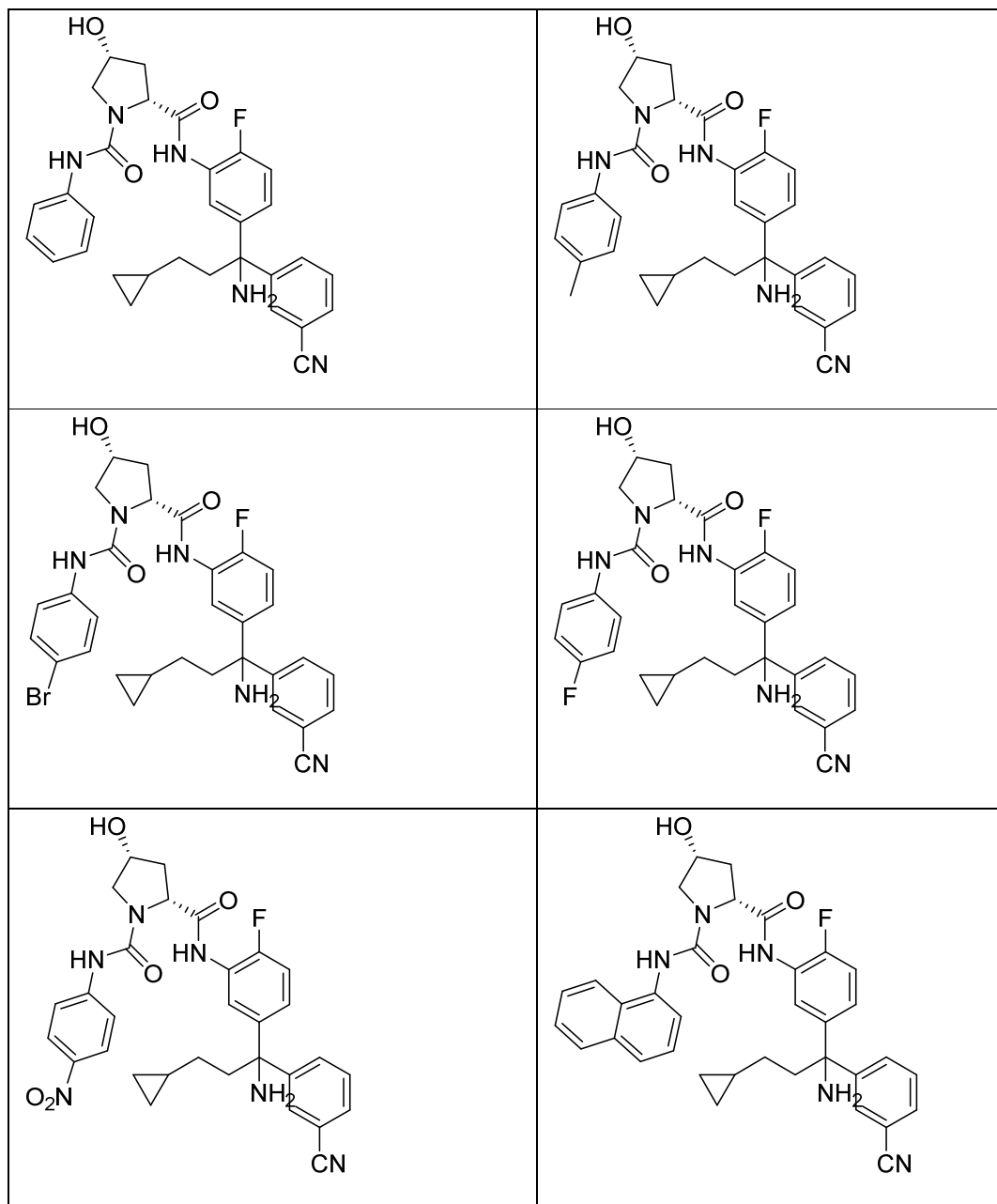


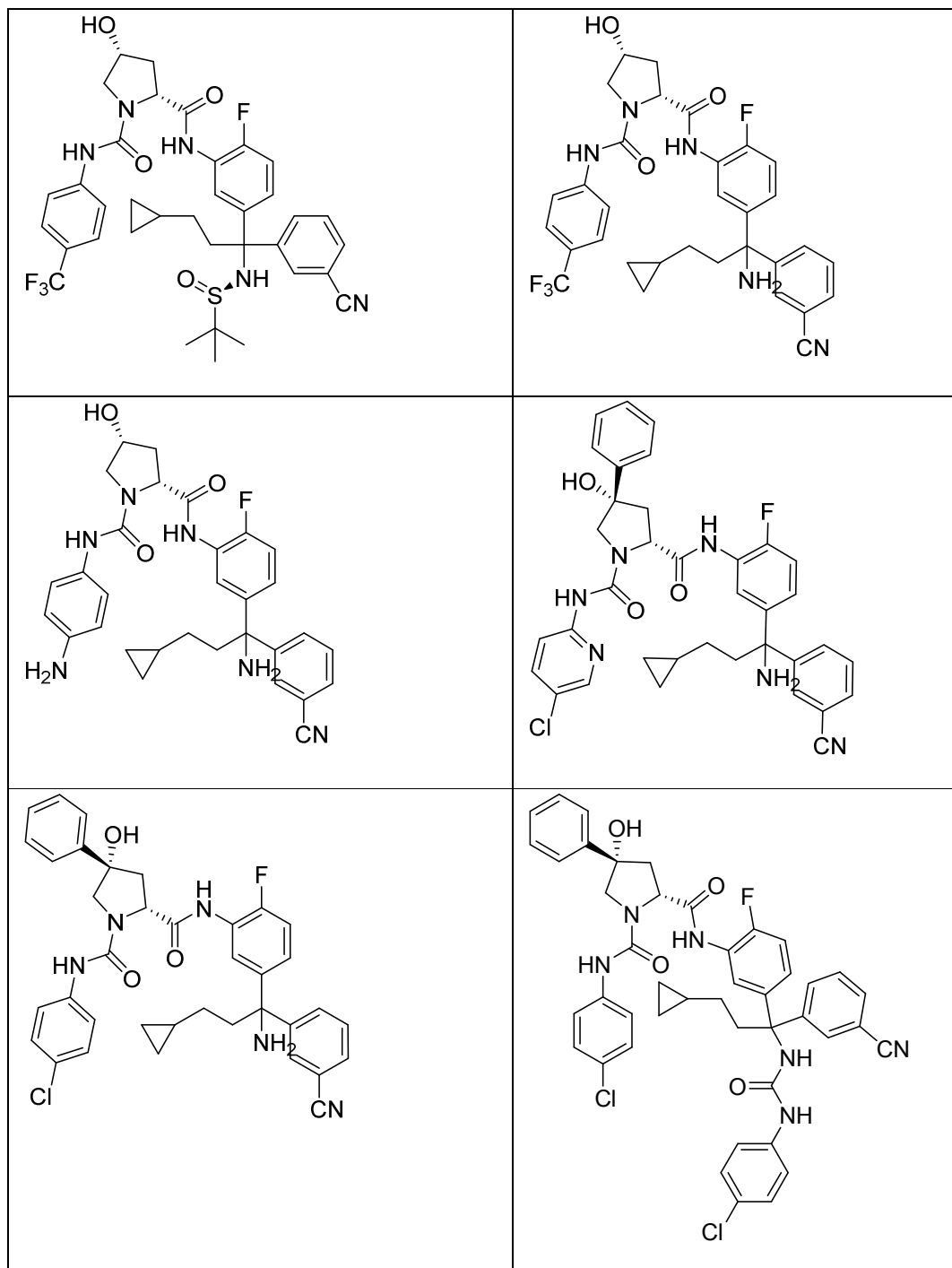


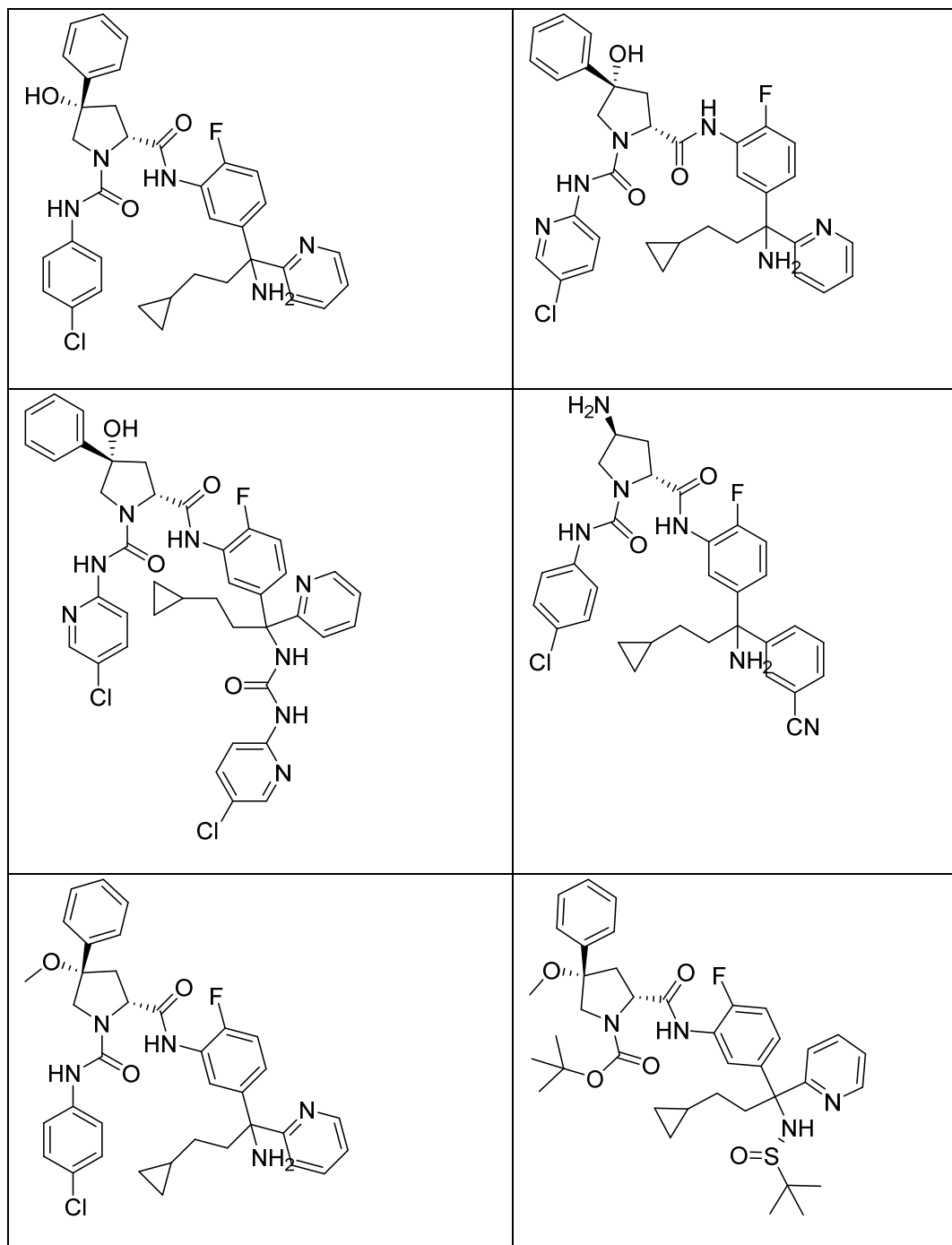


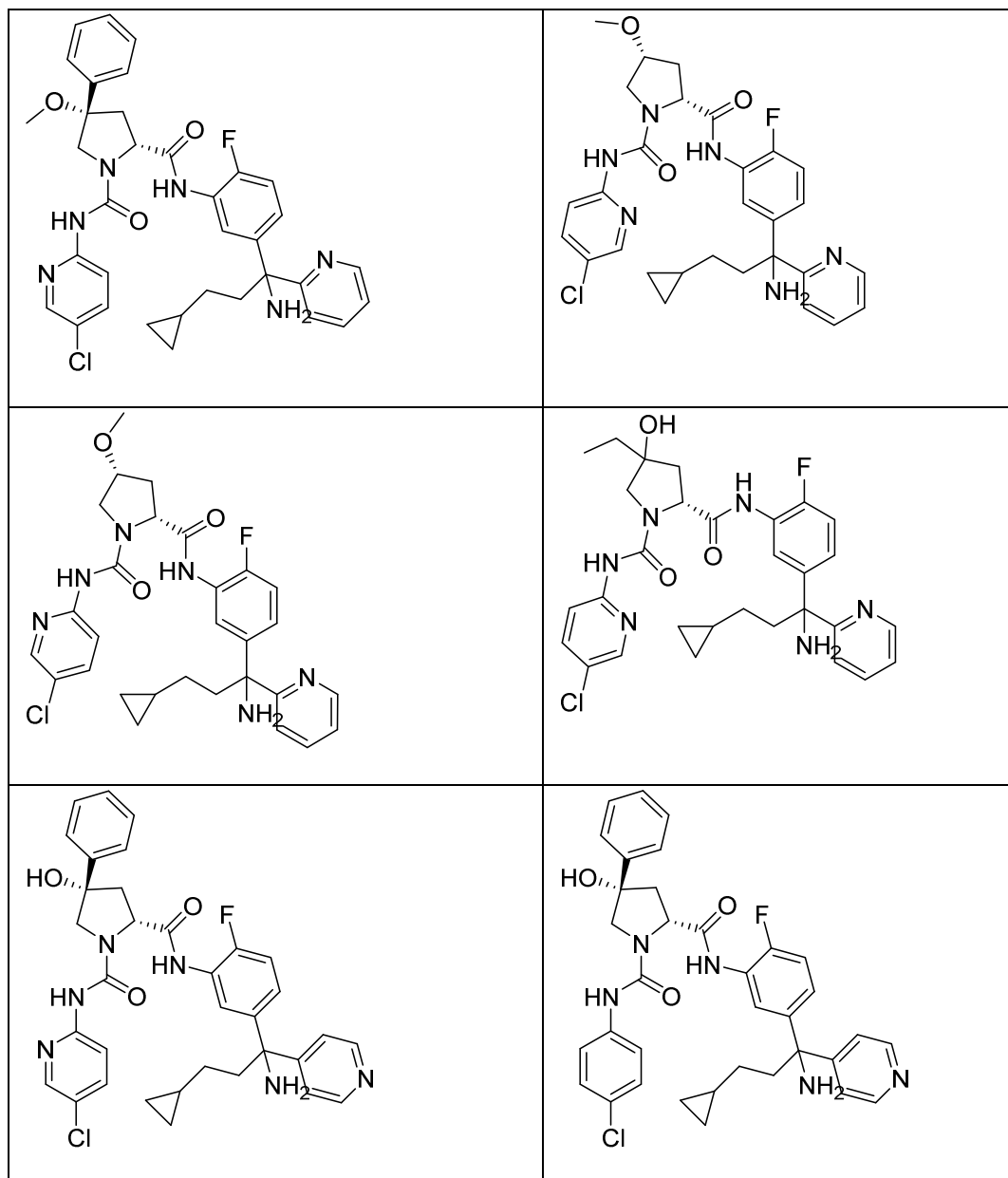


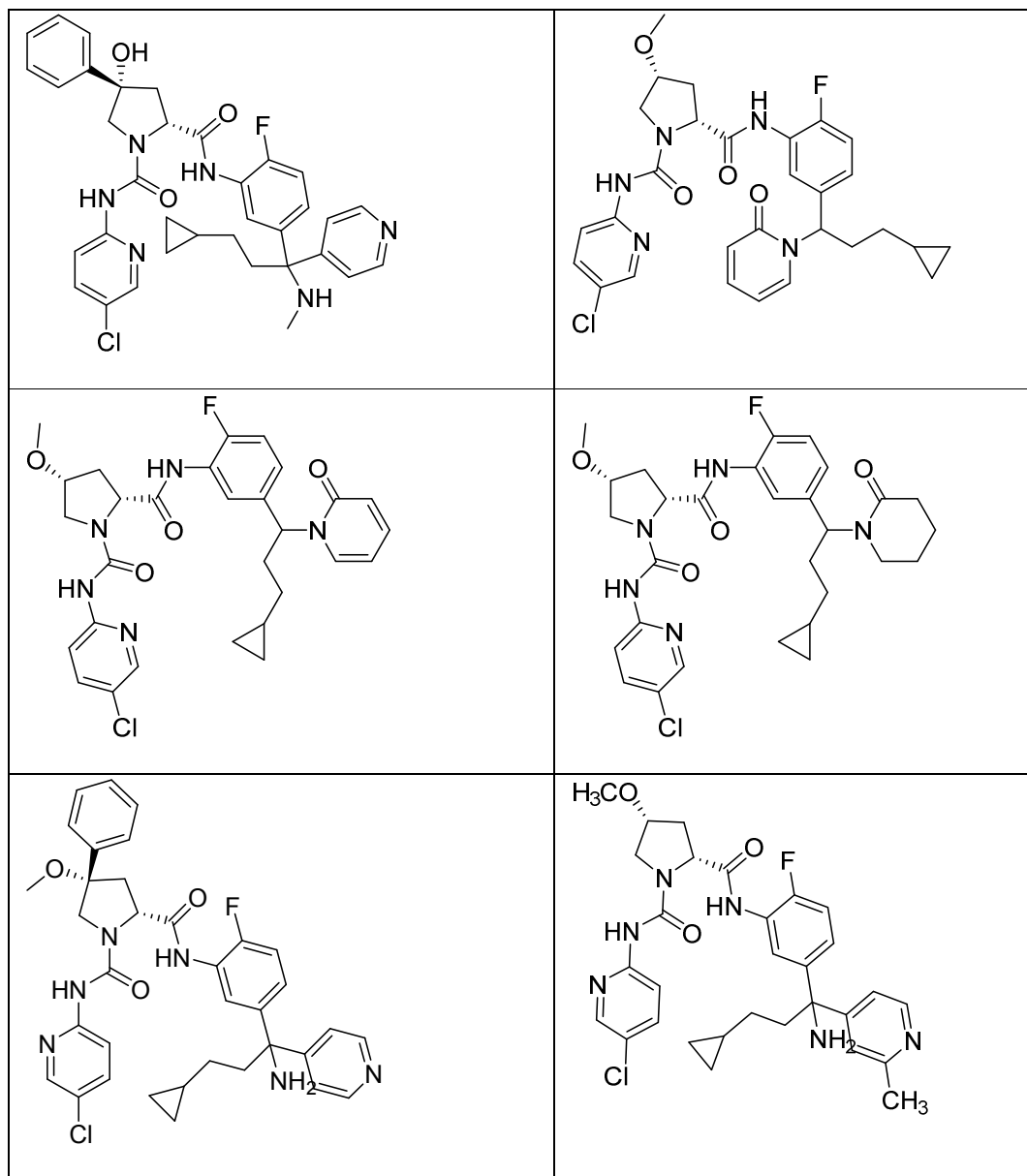


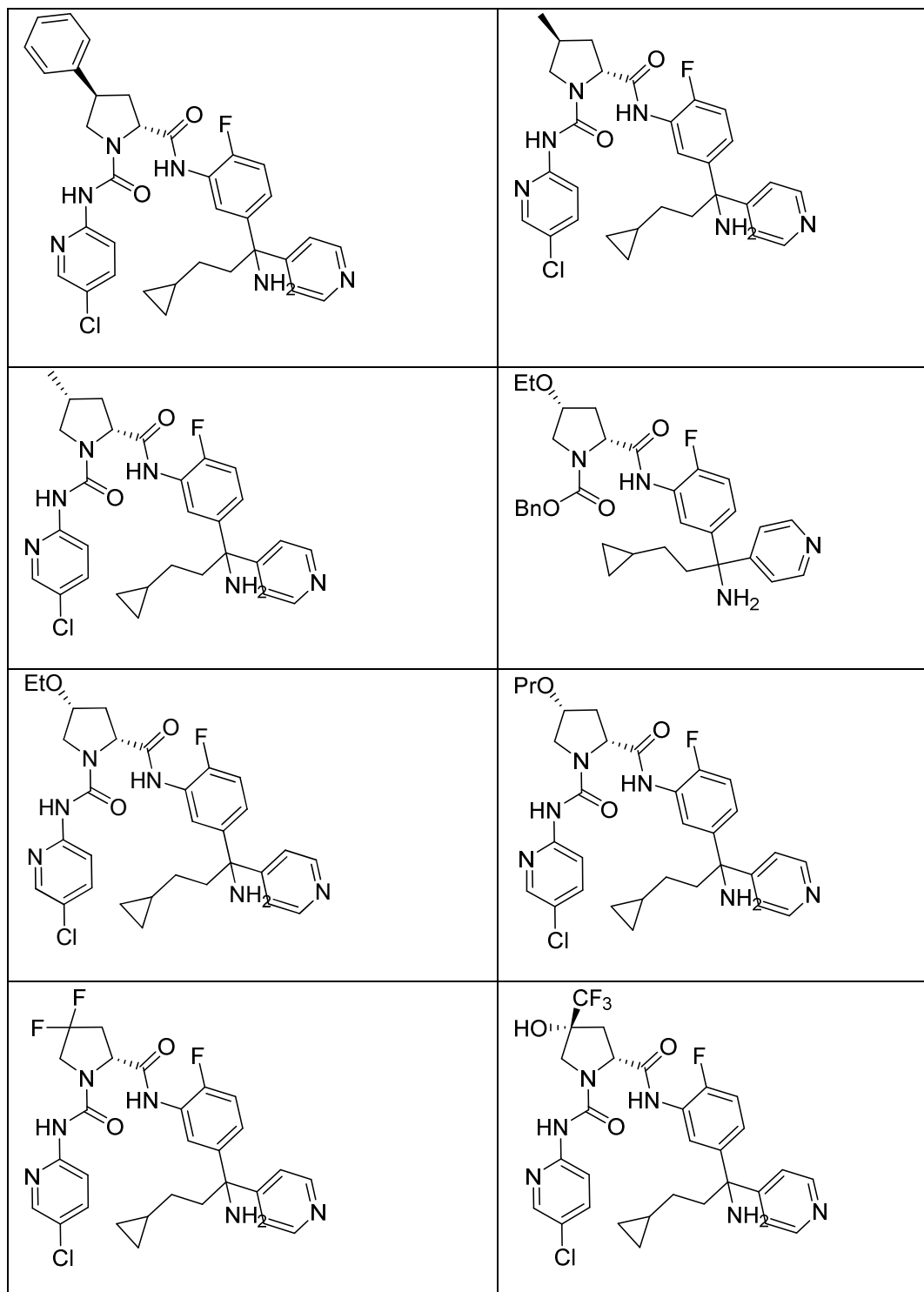


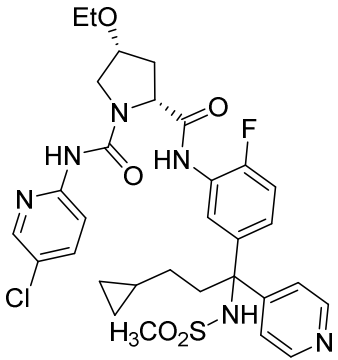
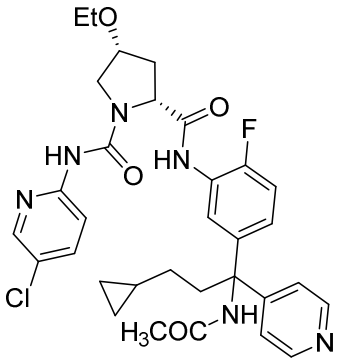
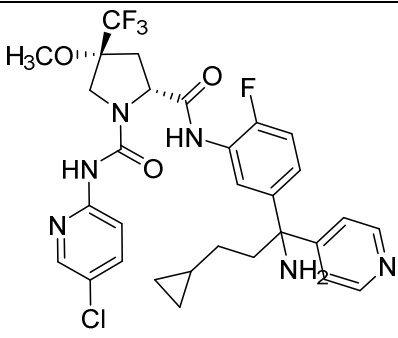
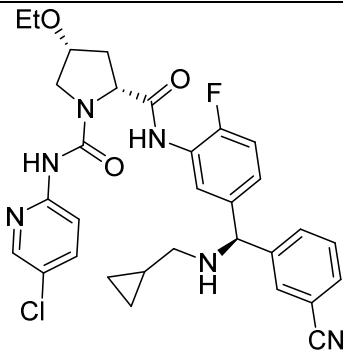
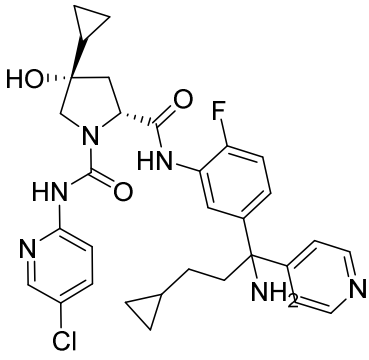
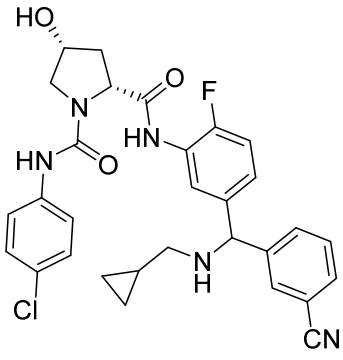
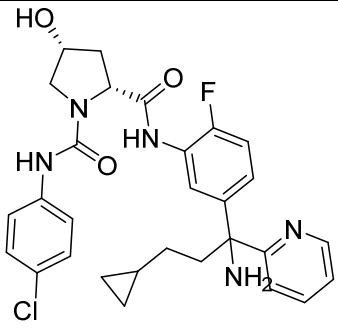
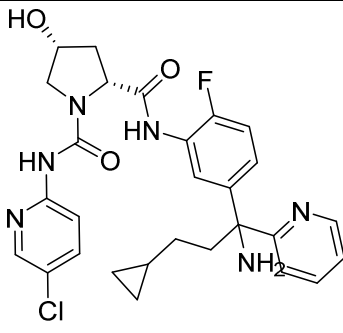


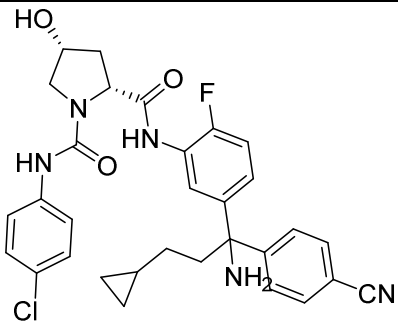
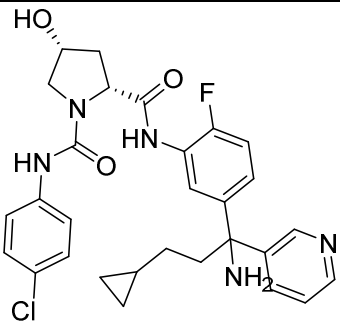
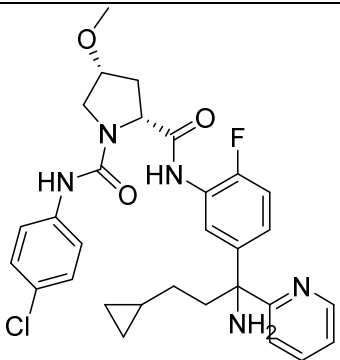
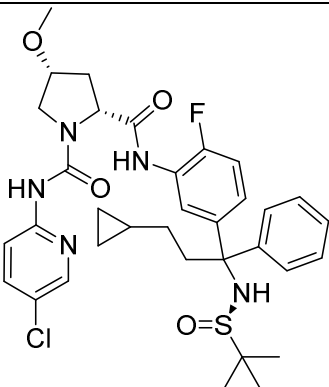
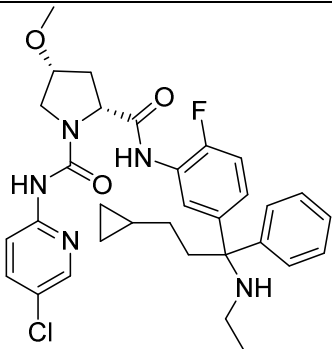
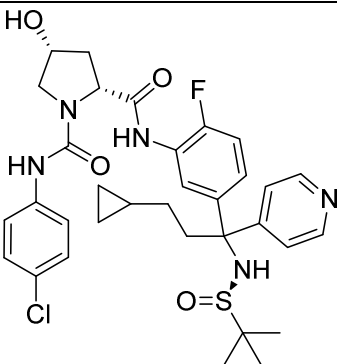
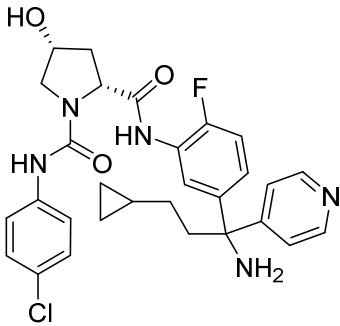
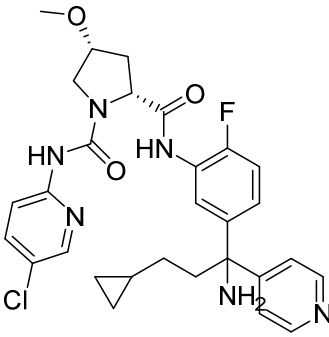


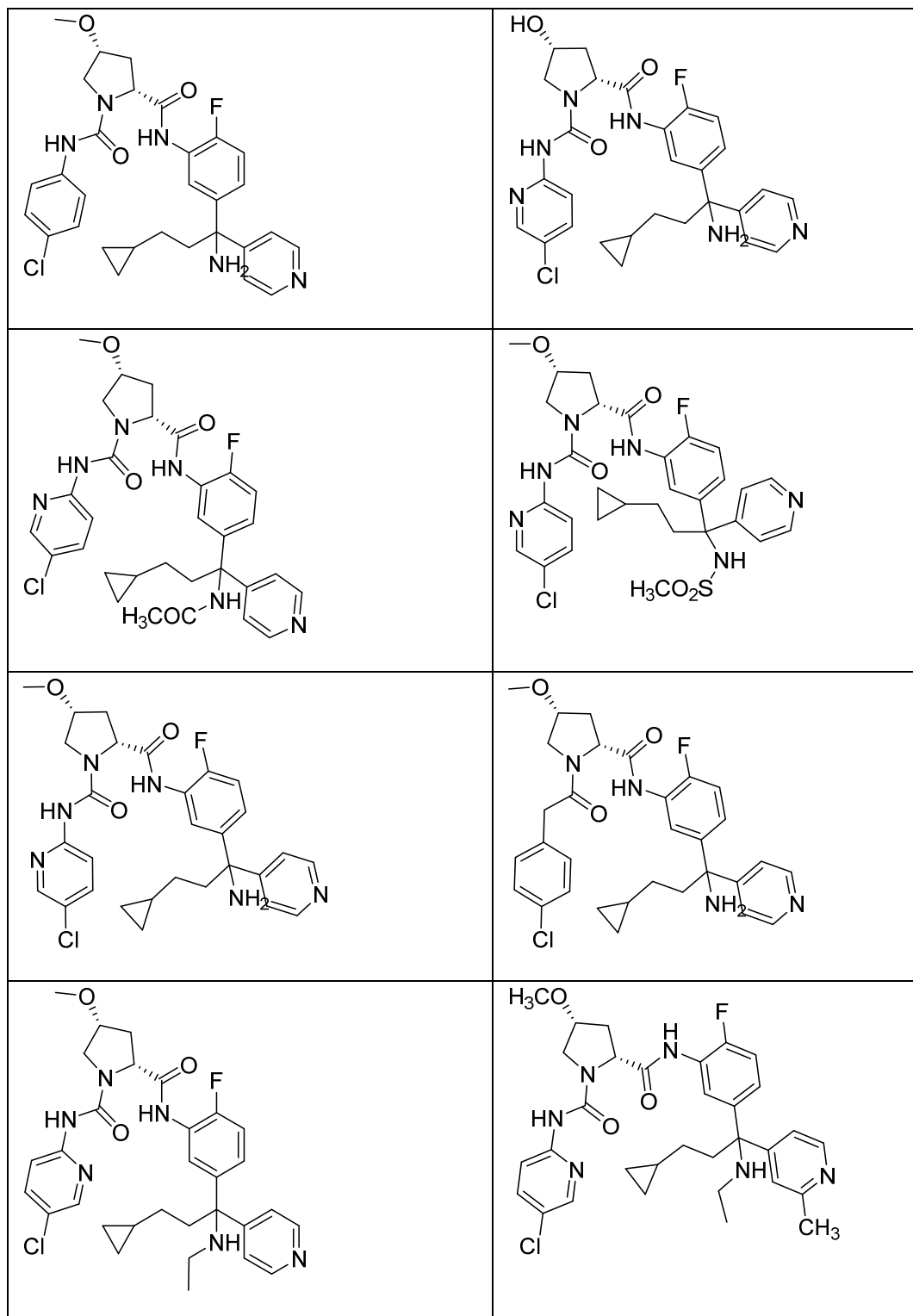


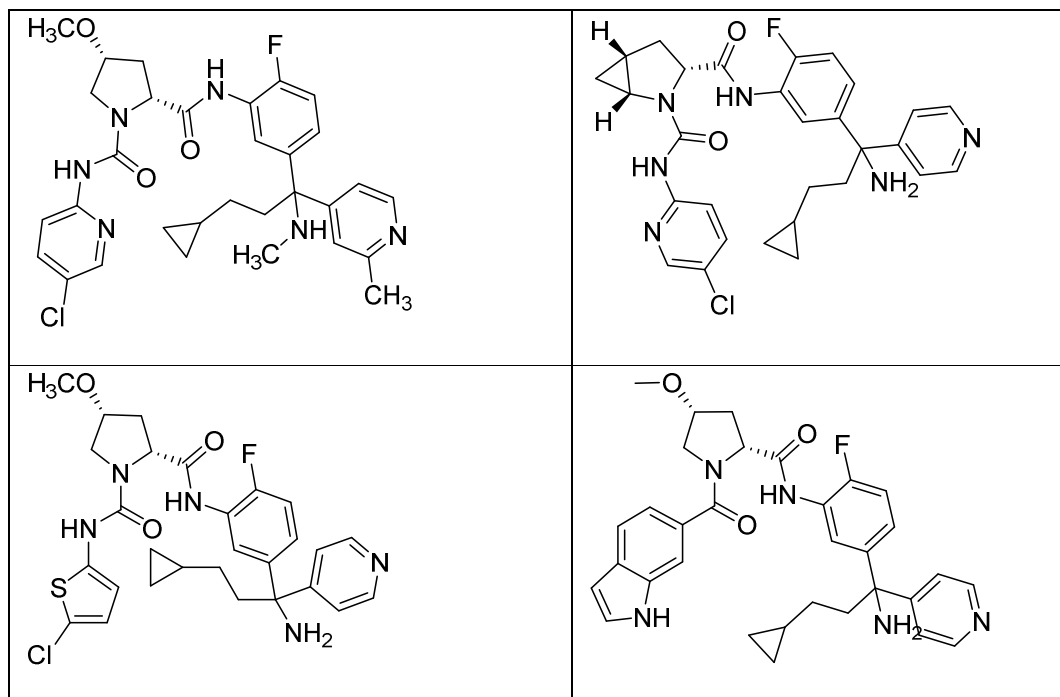








24. A pharmaceutical composition, comprising a compound of any one of claims 1-23; and a pharmaceutically acceptable carrier.
25. Use of a compound of any one of claims 1-23 in the manufacture of a medicament for the treatment or prevention of a disease or condition characterized by unwanted plasma kallikrein activity.
26. The use of claim 25, 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.