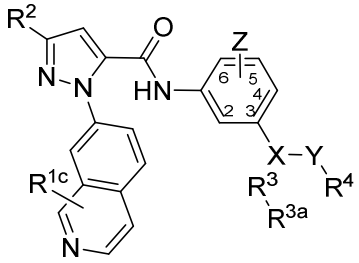
CLAIMS

1. A compound, or a pharmaceutically acceptable salt thereof, represented by formula XXVI:



(XXVI)

wherein:

X represents CH, C(OH), -C(NH_2), or -C(NR^aR^b);

-Y-R^4 represents -((C_1-C_6)alkyl)-R^4, -$CH_2C(O)$-R^4, -CH_2NH-R^4, -CH_2N((C_1-C_6)alkyl)-R^4, -CR^aR^b-R^4, -NH-R^4, -$NHCH_2$-R^4, -NHC(O)-R^4, -N((C_1-C_6)alkyl)-R^4, -N((C_1-C_6)alkyl)CH_2-R^4, -N((CH_2)$_2$OH)-R^4, -N[(C_3-C_8)cycloalkyl(C_1-C_6)alkyl]R^4, -heterocyclyl-R^4, -OR^4, -OCH_2-R^4, -OC(O)-R^4, or -OC(O)NR^aR^b, wherein the (C_1-C_6)alkyl moiety of -((C_1-C_6)alkyl)-R^4 is optionally substituted;

Z is absent or represents halo, hydroxy, (C_1-C_6)alkyl, -CF_3, -OCF_3, (C_1-C_6)alkoxy, aryl, aryloxy, amino, amino(C_1-C_6)alkyl, -C(O)NH_2, cyano, -NHC(O)(C_1-C_6)alkyl, -SO_2(C_1-C_6)alkyl, -SO_2NH_2, or (C_3-C_8)cycloalkyl;

R^{1c} represents halo, amino(C_1-C_6)alkyl, (C_1-C_6)alkoxy, cyano, -SO_2CH_3, formyl, acyl, -NH_2, or optionally substituted aryl;

R^2 represents halo, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_1-C_6)fluoroalkyl, -OCH_3, -$Si(CH_3)_3$, -$CONH_2$, -C(O)OH, cyano, or phenyl;

R^3 represents -NH-, -O-, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted phenyl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl;

R^{3a} is absent or represents one or more substituents independently selected from the group consisting of halo, hydroxy, (C_1-C_6)alkyl, -CF_3, -OCF_3, (C_1-C_6)alkoxy, aryl, aryloxy, amino, amino(C_1-C_6)alkyl, -C(O)NH_2, cyano, -NHC(O)(C_1-C_6)alkyl, -SO_2(C_1-C_6)alkyl, and -SO_2NH_2; and

R^4 represents hydroxy, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_3-C_8)cycloalkyl, heterocyclyl(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, -CH_2OH, -CH((C_1-C_6)alkyl)OH, -$CH(NH_2)CH((C_1$-$C_6)alkyl)_2$, optionally substituted aryl, optionally substituted aryl(C_1-C_6)alkyl, heteroaryl, optionally substituted heteroaryl(C_1-C_6)alkyl, -CH_2S(C_1-C_6)alkyl, amino, or cyano;

each R^a and R^b is independently H, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, aryl(C_1-C_8)alkyl, (C_3-C_8)carbocyclyl, -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 –$SO_2NR^cR^d$;

each R^c and R^d is independently H, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_4-C_8) carbocyclyl, optionally substituted aryl, optionally substituted heteroaryl, -C(=O)(C_1-C_8)alkyl, -$S(O)_n$(C_1-C_8)alkyl, or aryl(C_1-C_8)alkyl; or when R^c and R^d are bonded to a common nitrogen atom, then they may form a 3- to 7-membered heterocyclic ring;

n is 2 or 3; and

the stereochemical configuration at any chiral center is *R*, *S*, or a mixture of *R* and *S*.

2. The compound of claim 1, wherein X represents CH or -$C(NH_2)$.

3. The compound of claim 1 or 2, wherein X represents CH.

4. The compound of any one of claims 1-3, wherein Z represents halo.

5. The compound of any one of claims 1-4, wherein Z represents F.

6. The compound of any one of claims 1-5, wherein R^{1c} represents -NH_2.

7. The compound of any one of claims 1-6, wherein R^2 represents (C_1-C_6)fluoroalkyl.

8. The compound of any one of claims 1-7, wherein R^2 represents CF_3.

9. The compound of any one of claims 1-8, wherein R^3 represents optionally substituted aryl, optionally substituted heteroaryl, optionally substituted phenyl, or optionally substituted heterocyclyl.

10. The compound of any one of claims 1-8, wherein R^3 represents optionally substituted phenyl.

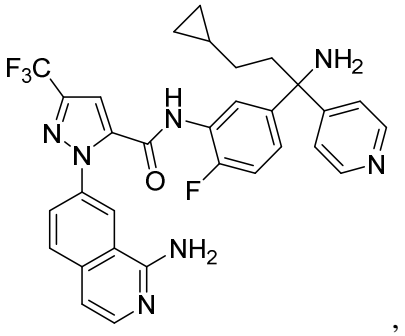
11. The compound of any one of claims 1-10, wherein R^{3a} is absent or represents cyano.

12. The compound of any one of claims 1-11, wherein -Y-R^4 represents -((C_1-C_6)alkyl)-R^4, -NH-R^4, or -$NHCH_2$-R^4.

13. The compound of any one of claims 1-12, wherein R^4 represents optionally substituted (C_3-C_8)cycloalkyl.

14. The compound of any one of claims 1-11, wherein -Y-R^4 represents -$NHCH_2$-R^4 and R^4 represents C_3-cycloalkyl.

15. The compound of claim 1, wherein said compound is selected from the group consisting of: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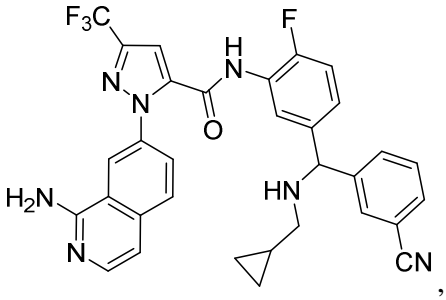
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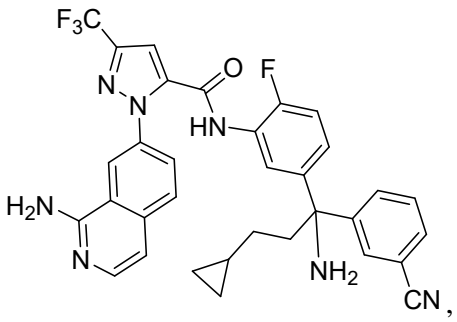
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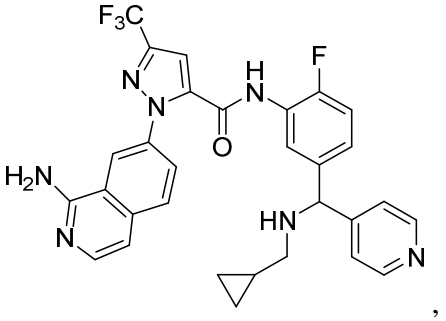
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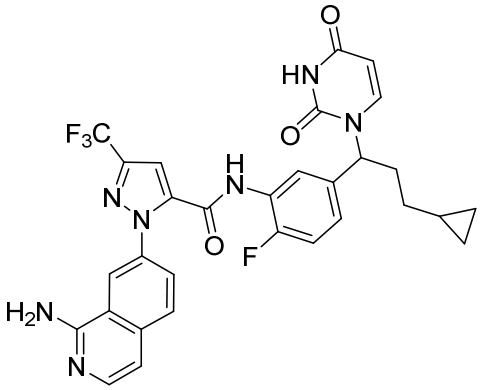

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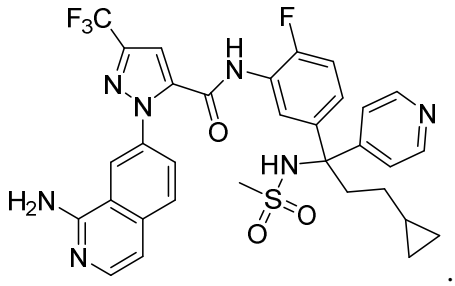

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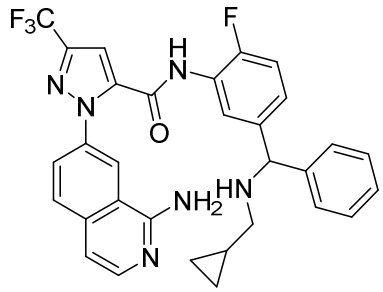
16. The compound of claim 1, wherein said compound is selected from the group consisting of:



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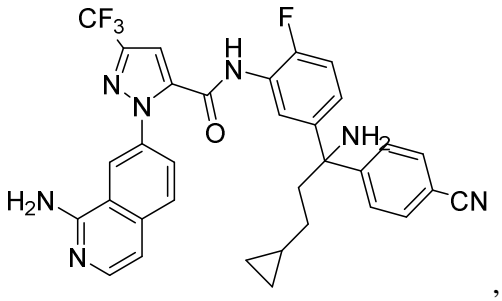

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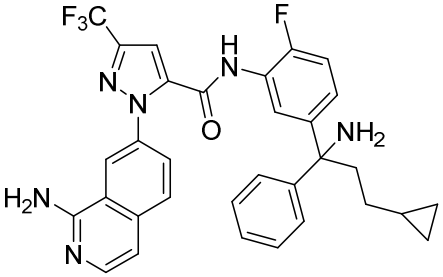

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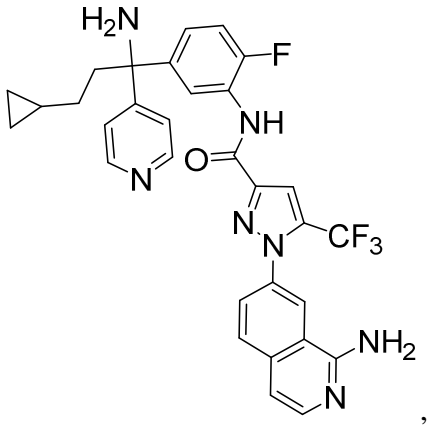

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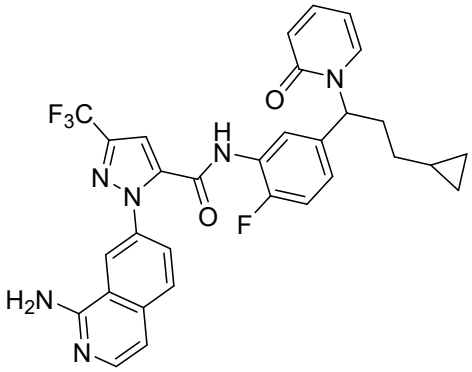
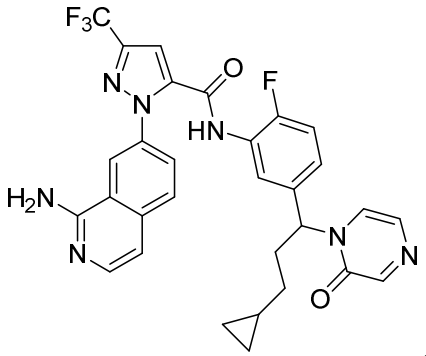
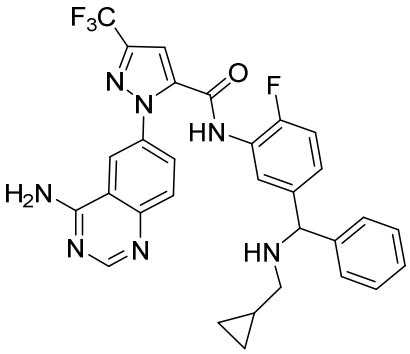




, and .

17. A compound, or a pharmaceutically acceptable salt thereof, wherein said compound is selected from the group consisting of:



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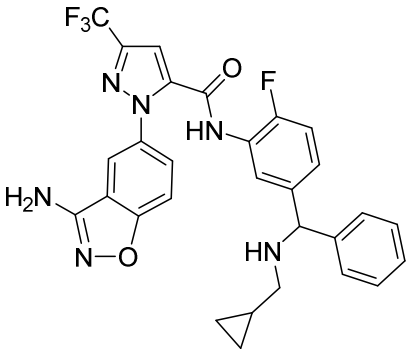

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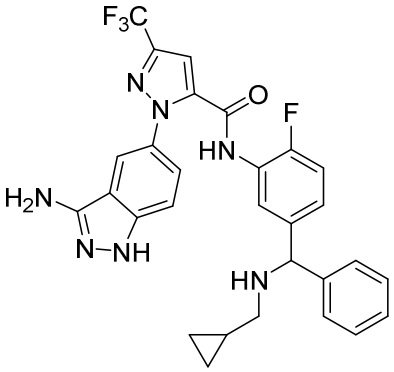

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18. The compound of any one of claims 1-17, wherein the pharmaceutically acceptable salt thereof is a hydrochloride salt.

19. The compound of any one of claims 1-18, wherein the pharmaceutically acceptable salt thereof is a bis(hydrochloride) salt.

20. A pharmaceutical composition, comprising a compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

21. The pharmaceutical composition of claim 20, wherein the pharmaceutical composition is formulated for parenteral administration.

22. The pharmaceutical composition of claim 20, wherein the pharmaceutical composition is formulated for oral administration.

23. Use of the compound of any one of claims 1-19, in the manufacture of a medicament for treating or preventing 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.

24. The use of claim 23, wherein the disease or condition characterized by unwanted plasma kallikrein activity is angioedema.

25. The use of claim 23, wherein the disease or condition characterized by unwanted plasma kallikrein activity is hereditary angioedema.

26. The use of claim 23, wherein the disease or condition characterized by unwanted plasma kallikrein activity is stroke.

27. The use of claim 23, wherein the disease or condition characterized by unwanted plasma kallikrein activity is reperfusion injury.

28. The use of claim 23, wherein the disease or condition characterized by unwanted plasma kallikrein activity is acute myocardial infarction.

29. The use of claim 23, wherein the disease or condition characterized by unwanted plasma kallikrein activity is hemorrhage.

30. The use of claim 23, wherein the disease or condition characterized by unwanted plasma kallikrein activity is blood loss during cardiopulmonary bypass.

31. The use of claim 23, 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.

32. The compound of any one of claims 1-19, for use in therapy.