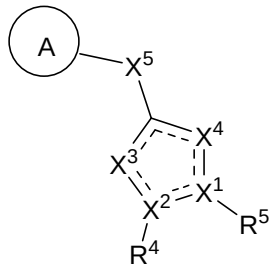
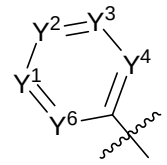
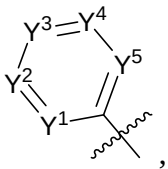
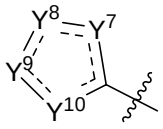
We claim:

1. A compound, or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, having a general formula I:



(I), where ring A is 

, 

, or 

,

wherein each bond represented by ----- is a single or double bond as needed to satisfy valence requirements;

$-X^1(R^5)-$ is -C(H)-C(R^5)-, -C(R^5)-, -C(R^5)-C(H)-, -C(R^5)-N-, -N-C(R^5)-, or -N(R^5)-;

X^2 is C or N;

X^3 is N or CH, wherein one or two of X^1-X^3 comprises N;

X^4 is CH or S;

X^5 is -N(H)- or absent;

Y^1 is N or C(R^1);

Y^2 is C(R^2) or N;

Y^3 is C(R^3) or N;

Y^4 is N or C(R^6);

Y^5 is C(R^7) or N;

Y^6 is C(R^8) or N;

one or two of Y^1-Y^6 are N, and at least one of Y^1-Y^3 or Y^6 is other than C(H);

two, three, or four of Y^7-Y^{10} independently are N or N(R^9), and the others of Y^7-Y^{10} are C(R^{10});

R^1 is cyano, perhaloalkyl, H, alkyl, or perhaloalkoxy;

R^2 is alkyl, H, alkoxy, perhaloalkyl, perhaloalkoxy, haloalkoxy, haloalkyl, cyano, cyanoalkyl, amino, heteroarylalkoxy, heteroalkyl, amido, halo, alkenyl, or haloalkenyl, or R^1 and R^2 together with the atoms to which they are attached form a 5- or 6-membered aryl or heteroaryl ring;

R^3 is H, amino, alkylamino, aminoalkyl, alkoxy, or R′C(O)N(H)- where R′ is alkyl, or R^2 and R^3 together with the atoms to which they are attached form a 5- or 6-membered aryl or heteroaryl ring;

R^4 is azaalkyl, aliphatic, aryl, or amino;

R^5 is heteroaliphatic, aliphatic, or alkylamino, or;

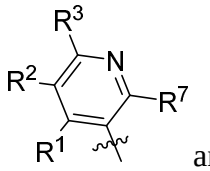
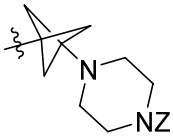
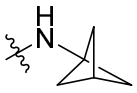
R^6 and R^7 independently are H, alkyl, alkoxy, perhaloalkyl, perhaloalkoxy, or cyano;

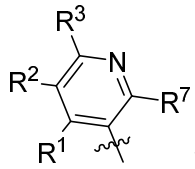
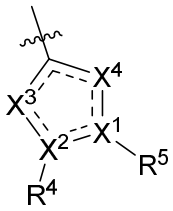
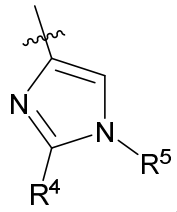
R^8 is H, alkyl, alkoxy, perhaloalkyl, perhaloalkoxy, or cyano or R^8 and R^1 together with the atoms to which they are attached form a 5- or 6-membered aryl or heteroaryl ring;

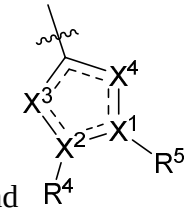
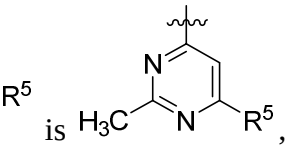
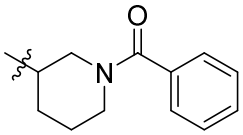
each R^9 independently is H or alkyl; and

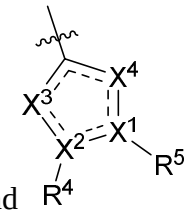
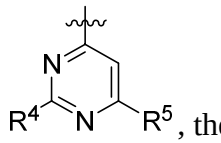
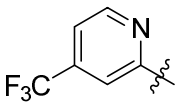
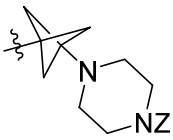
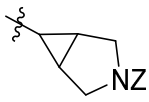
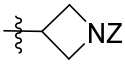
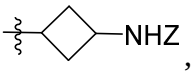
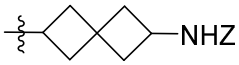
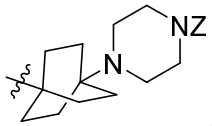
each R^{10} independently is H, alkyl, or cyano,

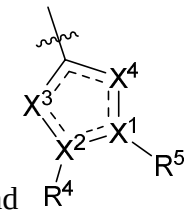
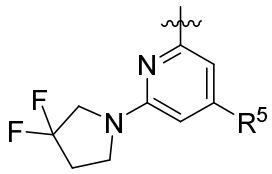
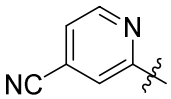
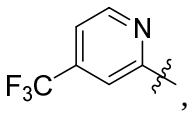
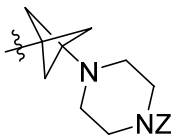
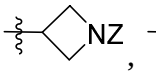
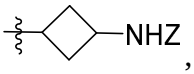
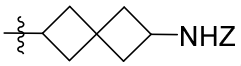
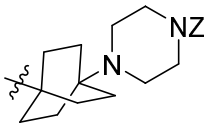
with the following provisos:

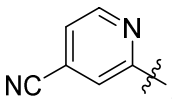
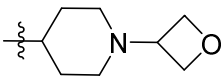
(a) if ring A is  and R^5 is  or  , where Z is alkoxy, H, aliphatic, or heteroaliphatic, then (i) X^5 is N(H), or (ii) R^3 is H, aminoalkyl, alkoxy,  , or R′C(O)N(H)- where R′ is alkyl, or (iii) R^2 is alkoxy, cyanoalkyl, amino, or heteroarylalkoxy, or (iv) one of R^1 and R^7 is other than -H, or (v) only one of X^1-X^4 comprises N, or (vi) X^3 is C(H), or (vii) X^4 is S, or (vi) -X^1(R^5)- is -C(R^5)-C(H)-, -C(H)-C(R^5)-, -C(R^5)-N-, or -N-C(R^5)-, or (viii) R^1 and R^2 together with the atoms to which they are attached form a 5- or 6-membered aryl or heteroaryl ring,

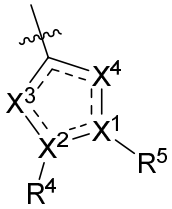
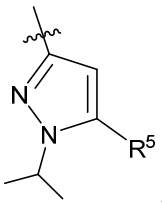
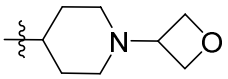
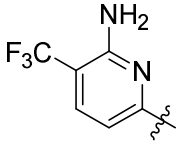
(b) if ring A is  where R^3 is amino or alkylamino and  is  , then (i) X^5 is N(H), or (ii) R^1 is cyano, perhaloalkyl, or perhaloalkoxy, or (iii) R^2 is cyano, cyanoalkyl, amino, or heteroalkylalkoxy, or (iv) R^7 is perhaloalkyl, perhaloalkoxy, or cyano, or (v) R^4 is aryl, or (vi) R^1 and R^2 together with the atoms to which they are attached form a 5- or 6-membered aryl or heteroaryl ring, or (viii) R^2 and R^3 together with the atoms to which they are attached form a 5- or 6-membered aryl or heteroaryl ring,

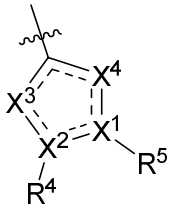
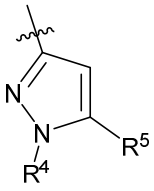
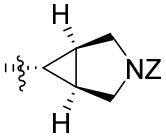
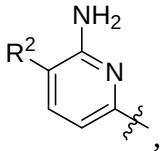
(c) if X^5 is N(H) and  is  , then R^5 is not  ,

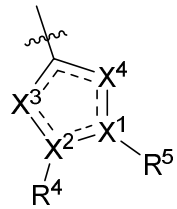
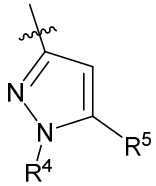
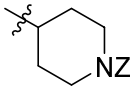
(d) if X^5 is N(H) and  is  , then (i) ring A is not  , or (ii) R^4 is not methyl or azacycloalkyl, or (iii) R^5 is  ,  ,  ,  ,  ,  , or  ,

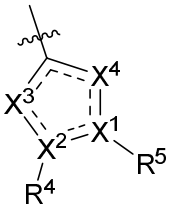
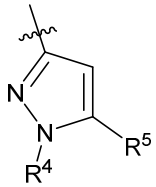
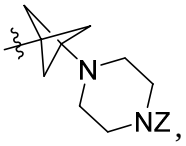
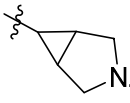
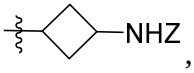
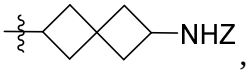
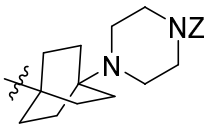
(e) if X^5 is N(H) and  is  , then (i) ring A is not  or  , or (ii) R^5 is  ,  ,  ,  ,  ,  , or  ,

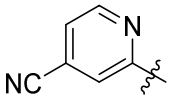
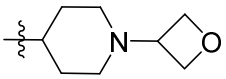
(f) if X^5 is N(H), and ring A is  , then R^5 is not  ,

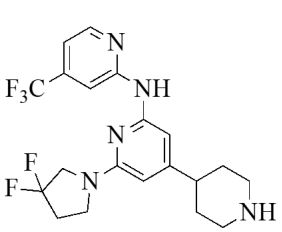
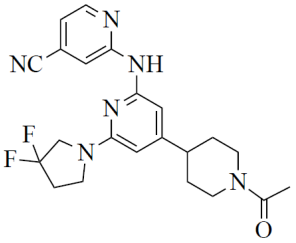
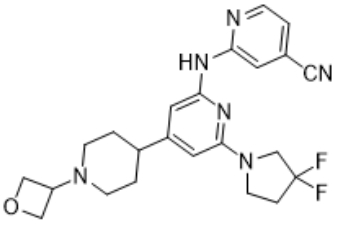
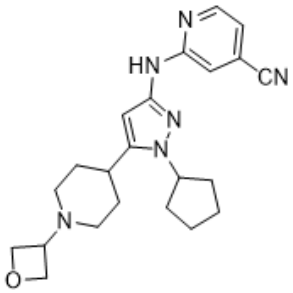
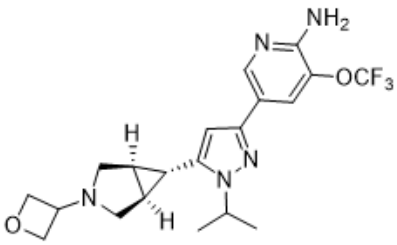
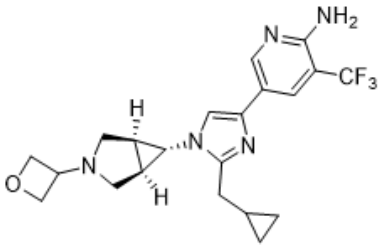
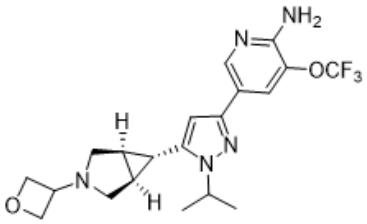
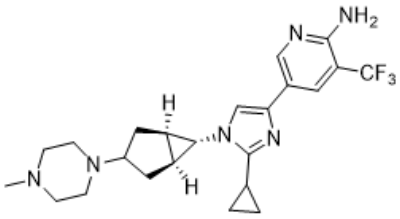
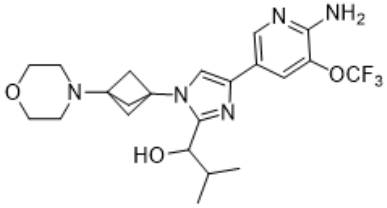
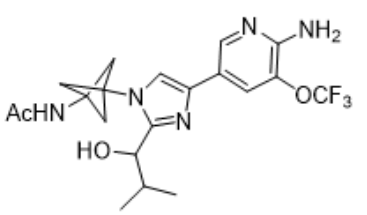
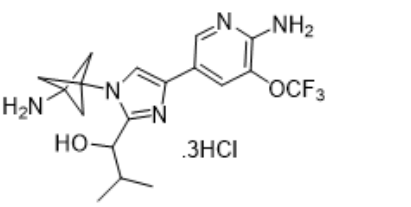
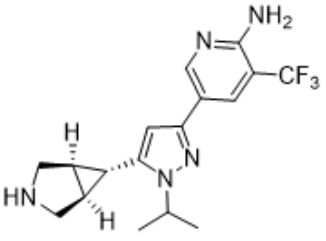
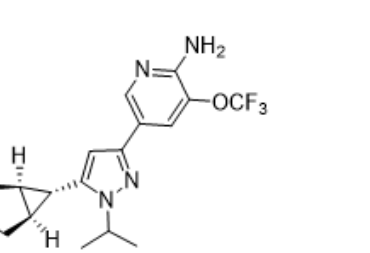
(g) if X^5 is absent and  is  , then R^5 is not  or ring A is not  ,

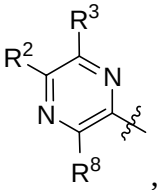
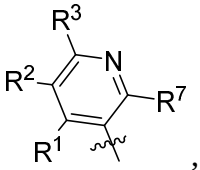
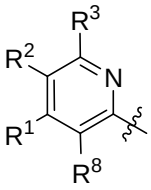
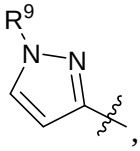
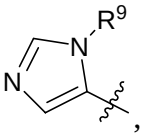
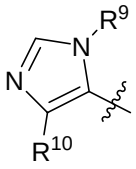
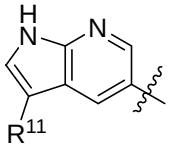
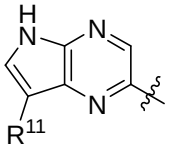
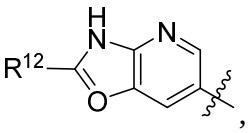
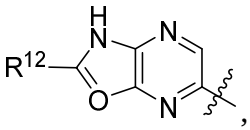
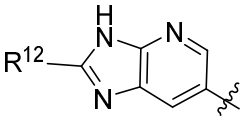
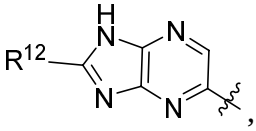
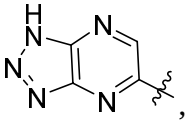
(h) if X^5 is absent and  is  , then (i) R^5 is not  , or (ii) ring A is not  ,

(i) if X^5 is N(H) and  is  , then (i) R^5 is not  , or (ii) Y^4 is not N, or (iii) R^2 is not -H, -CN, or -CF_3, or (iv) R^1 is not -H, -CN, or -CF_3,

(j) if X^5 is N(H) and  is  , then (i) R^4 is not cycloalkyl or heterocycloalkyl, or (ii) Y^4 is not N, or (iii) R^1 is not -CN, or (iv) one of R^2, R^3, and R^8 is other than H, or (v) R^5 is alkyl,  ,  ,  ,  ,  , or  ,

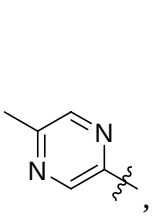
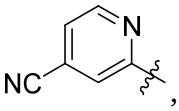
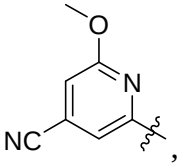
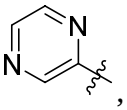
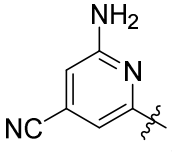
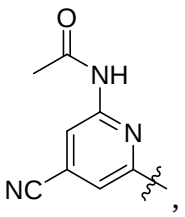
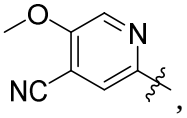
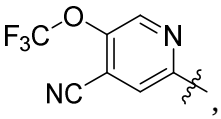
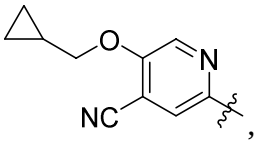
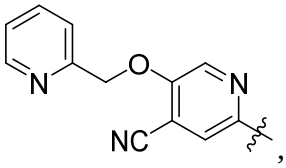
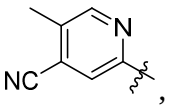
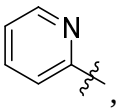
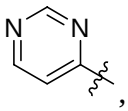
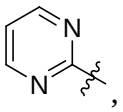
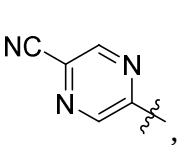
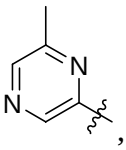
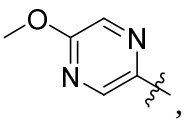
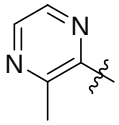
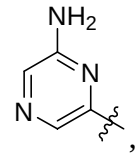
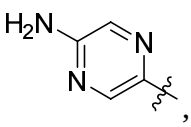
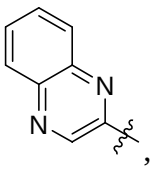
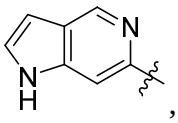
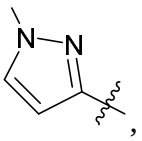
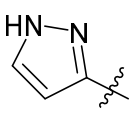
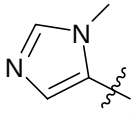
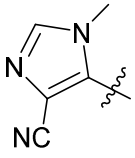
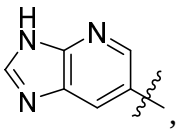
(k) if Ring A is  and X^5 is N(H), then R^5 is not  , and

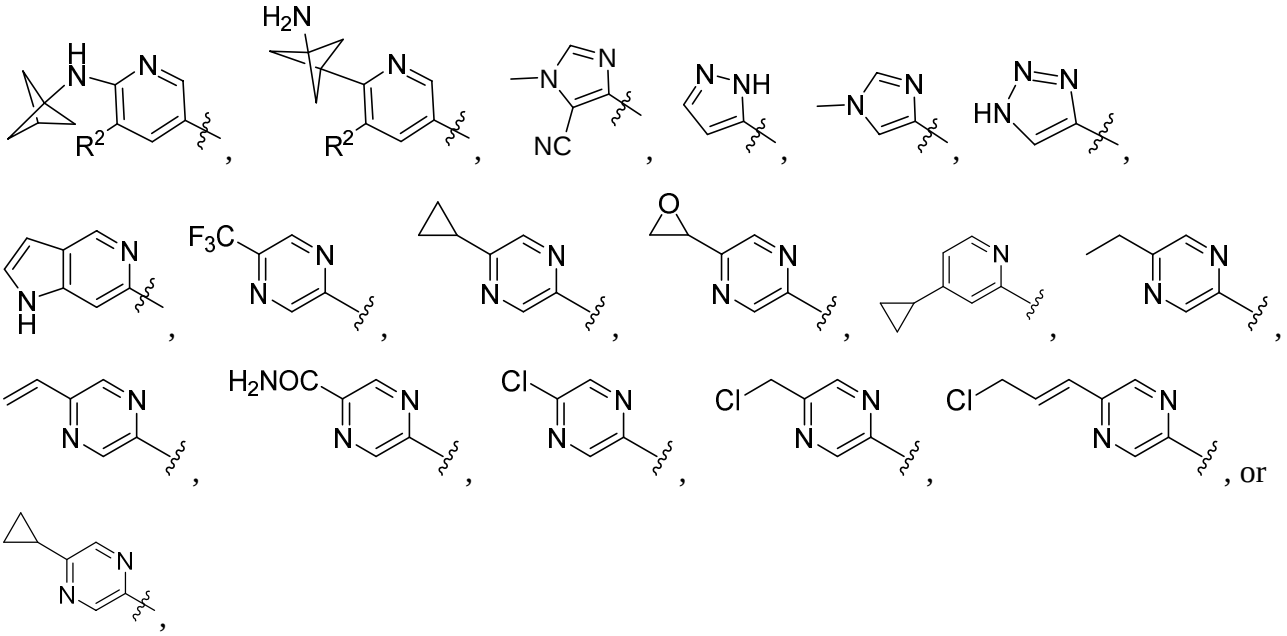
(l) the compound is not  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , , ,  ,  , , , or .

2. The compound of claim 1, wherein ring A is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  ,

where R^{11} and R^{12} are H, alkyl, perhaloalkyl, alkoxy, perhaloalkoxy, cyano, or amino.

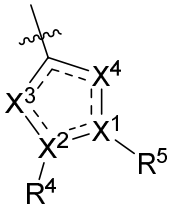
3. The compound of claim 1, wherein ring A is:

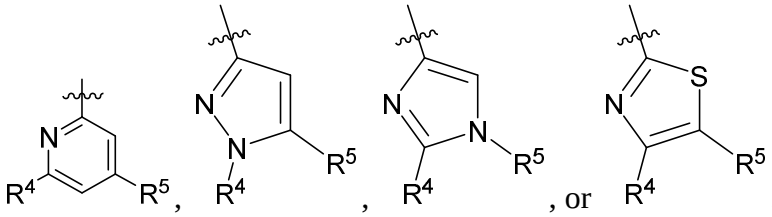
 ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , , , ,

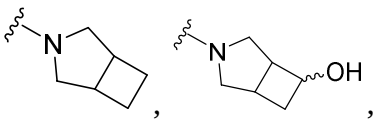


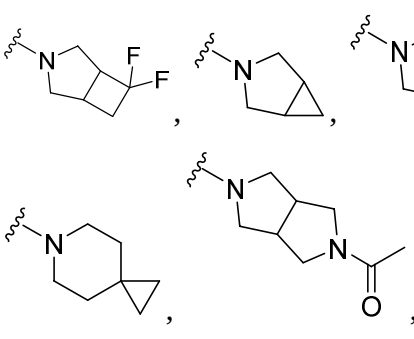
where R^2 is $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_3$, -CN, or -H, and

R^{11} is $-CF_3$, $-OCF_3$, -CN, or -H.

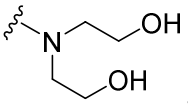
4. The compound of any one of claims 1-3, wherein  is:

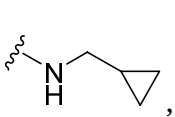
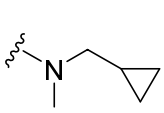
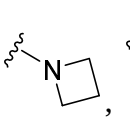
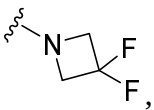
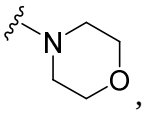
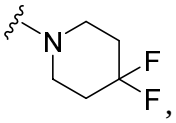
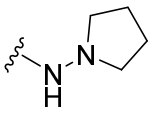


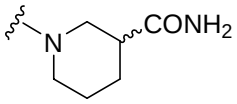
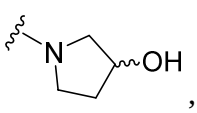
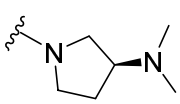
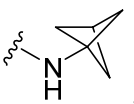
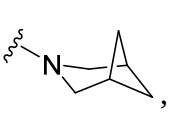
5. The compound of any one of claims 1-4, wherein R^4 is 

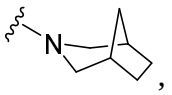
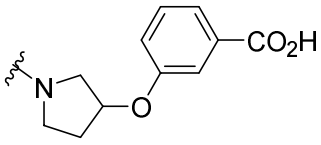
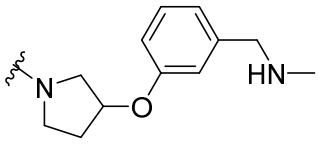
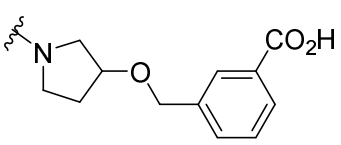


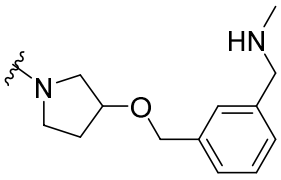
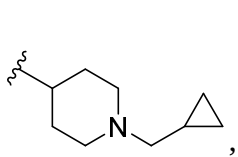
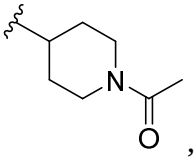
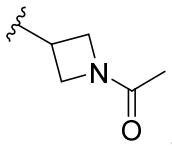
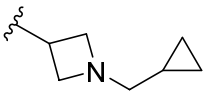
, 3,3-difluoro-1-pyrrolidinyl, isopropyl, 2-methylpropyl, cyclopropyl,

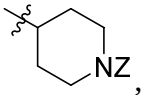
cyclopropylmethyl, -C(H)(OH)-CH(CH$_3$)$_2$, -N(H)(CH$_2$)$_4$OH, -N(CH$_2$CH$_3$)$_2$,  ,

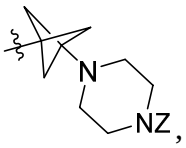
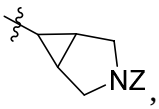
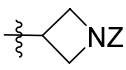
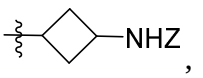
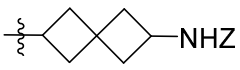
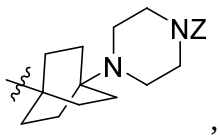
 ,  ,  ,  ,  ,  ,  ,

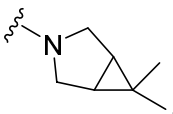
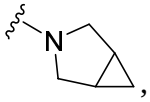
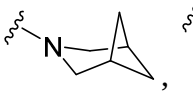
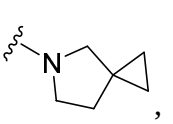
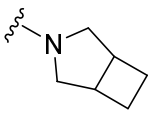
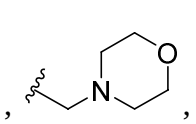
 ,  ,  ,  ,  ,  ,

 ,  ,  ,  ,

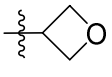
 ,  ,  ,  , or  .

6. The compound of any one of claims 1-5, wherein R^5 is  ,  ,

 ,  ,  ,  ,  ,  ,

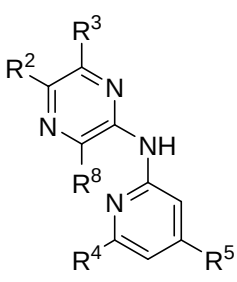
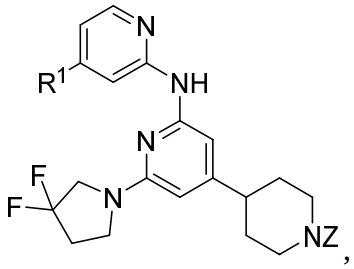
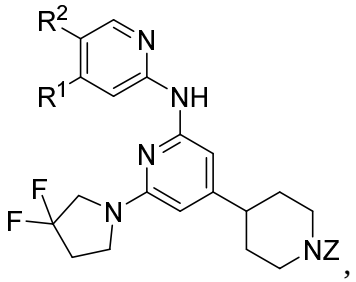
 ,  ,  ,  ,  ,  ,  ,

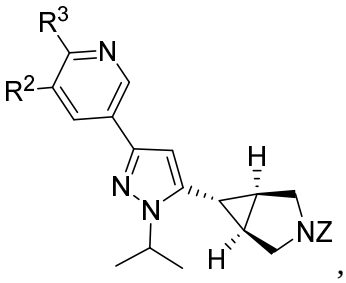
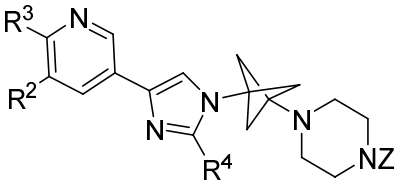
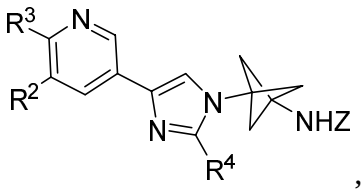
-(CH$_2$)$_3$N(CH$_3$)$_2$, or -CH$_2$OH, where Z is aliphatic, alkoxy, H, or heteroaliphatic.

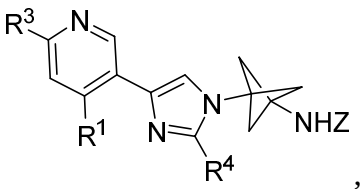
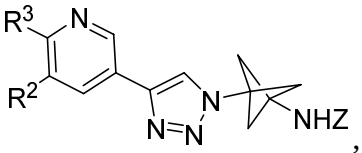
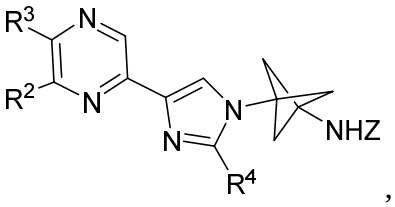
7. The compound of claim 6, wherein Z is -C(O)CH$_3$, H, methyl, ethyl, isopropyl, 2-methylpropyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclohexyl, -(CH$_2$)$_2$(OCH$_2$CH$_2$)$_n$OCH$_3$ where *n* is an integer from 1 to 10, or  .

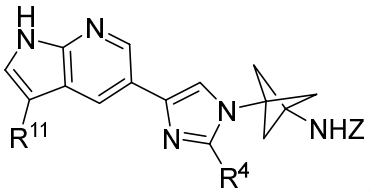
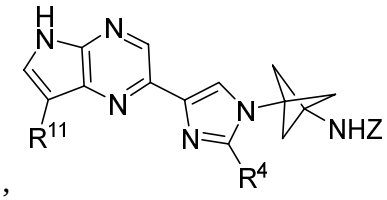
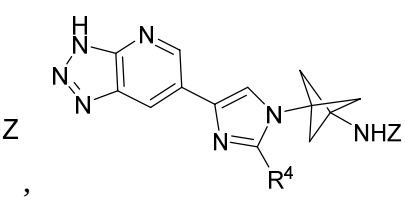
8. The compound of claim 6, wherein Z is C$_1$-C$_3$ alkoxy, H, C$_1$-C$_6$ alkyl, or heteroalkyl.

9. The compound of any one of claims 6-8, wherein the compound is:

 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

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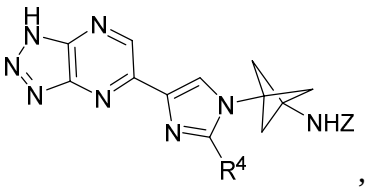
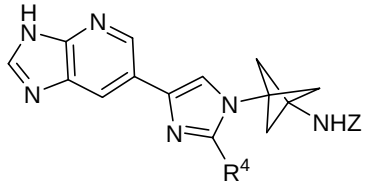
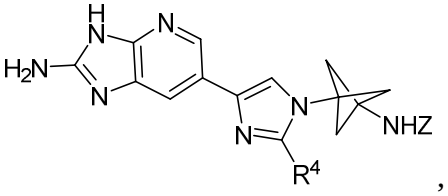
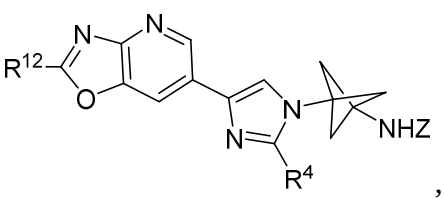
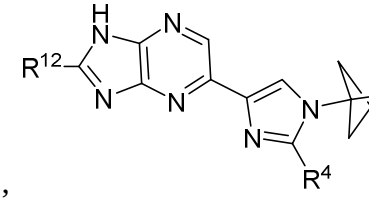
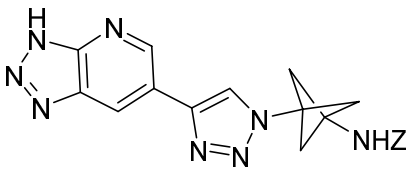
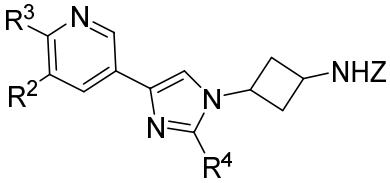
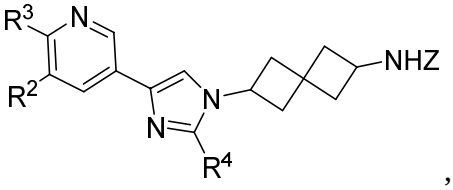
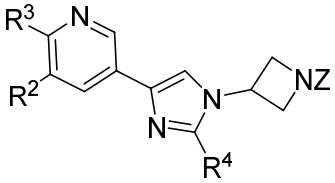
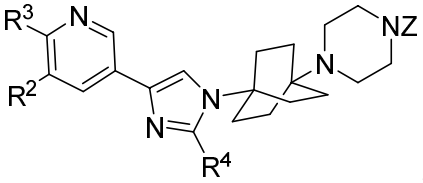
 ,  ,  ,

 ,  .

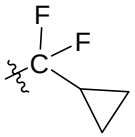
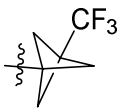
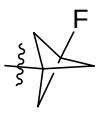
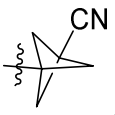
 ,  ,  ,

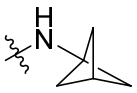
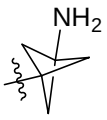
 , or  ,

where R^{11} and R^{12} are H, alkyl, perhaloalkyl, alkoxy, perhaloalkoxy, cyano, or amino.

10. The compound of claim 9, wherein:

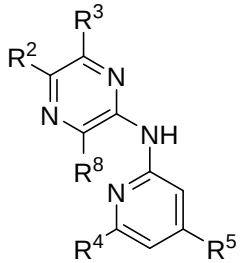
R^1 is -CN, $-OCF_3$, or $-CF_3$;

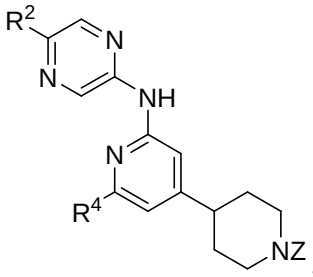
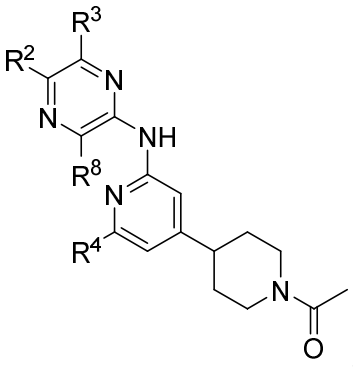
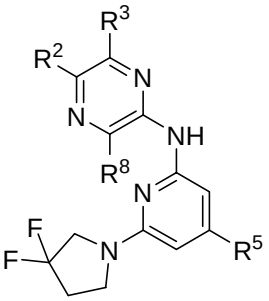
R^2 is $-CH_3$, $-OCH_3$, $-OCF_3$, $-CF_3$,-CN, $-OCHF_2$,  ,  ,  ,  , or -H;

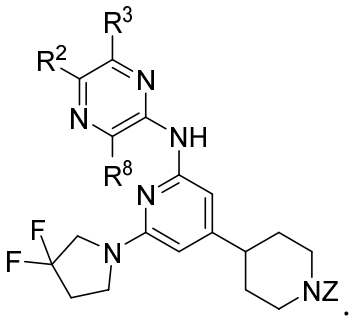
R^3 is $-NH_2$,  ,  , or -H;

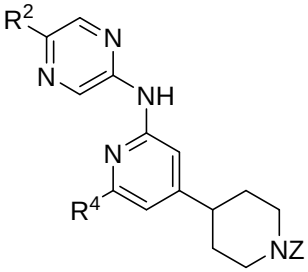
R^8 is $-OCF_3$, -CN, $-CH_3$, or H; and

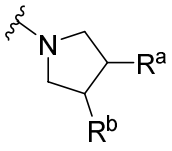
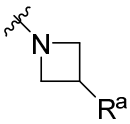
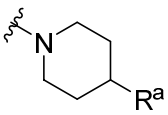
R^{11} and R^{12} independently are $-CF_3$, -CN, -H, $-OCH_3$, or $-OCF_3$.

11. The compound of claim 9 or claim 10, wherein  is

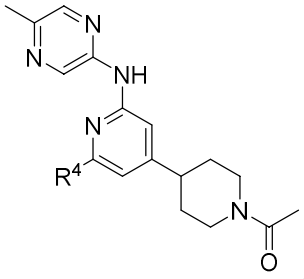
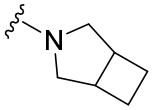
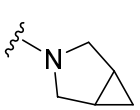
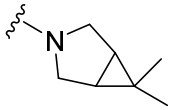
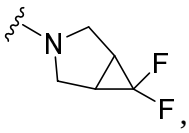
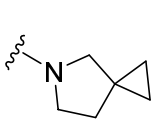
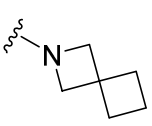
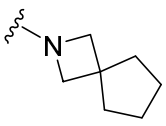
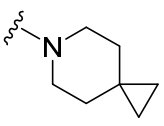
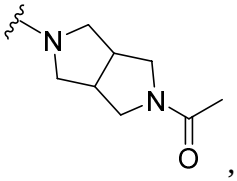
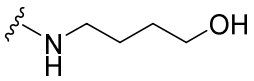
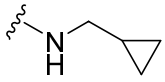
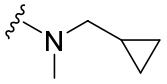
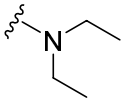
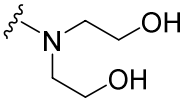
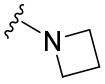
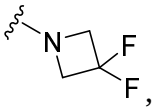
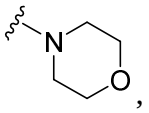
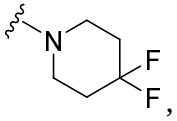
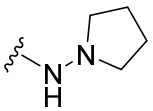
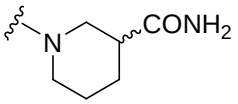
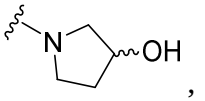
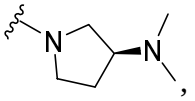
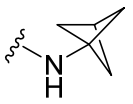
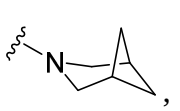
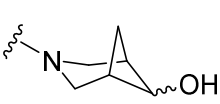
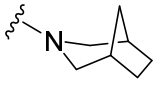
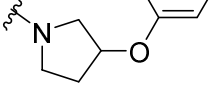
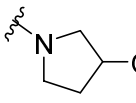
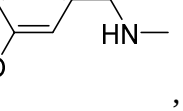
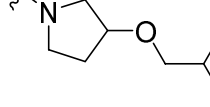
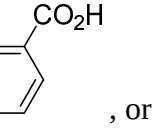
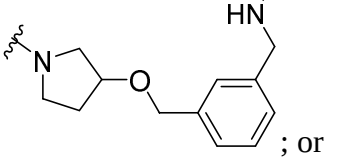
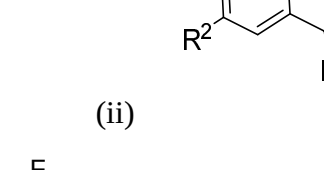
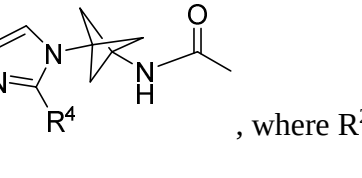
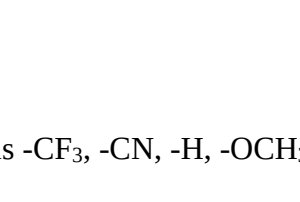
 ,  ,  , or

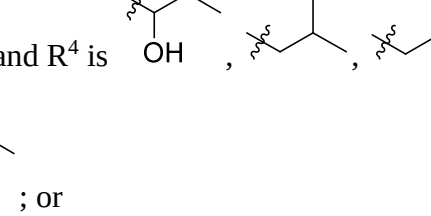
 .

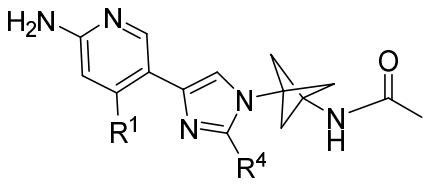
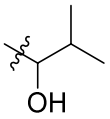
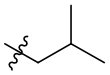
12. The compound of claim 11, wherein the compound is  where: Z is aliphatic; and

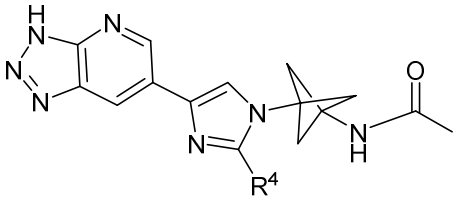
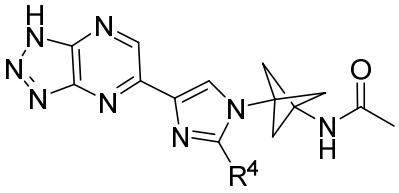
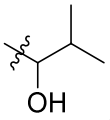
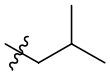
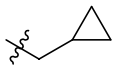
R^4 is  where R^a and R^b together with the atoms to which they are bound form a fused cycloaliphatic or heterocycloaliphatic ring, or R^a is cycloaliphatic and R^b is -H, or R^4 is  or  , where R^a is cycloaliphatic.

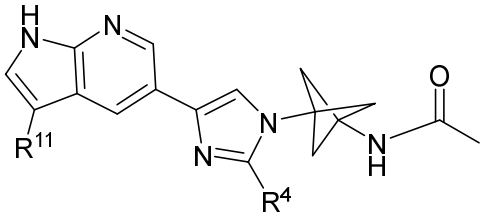
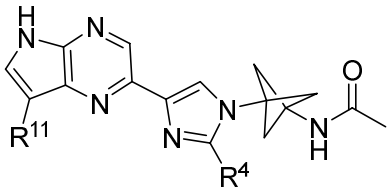
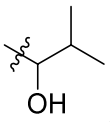
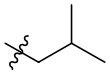
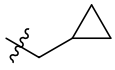
13. The compound of claim 1, wherein the compound is:

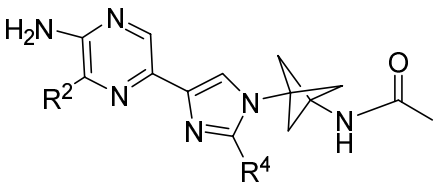
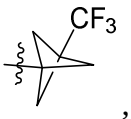
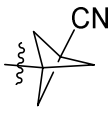
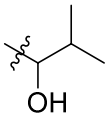
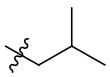
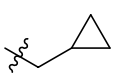
(i)  , where R^4 is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , ,  ,  ,  ,  ,  ,  ,  , or  ; or

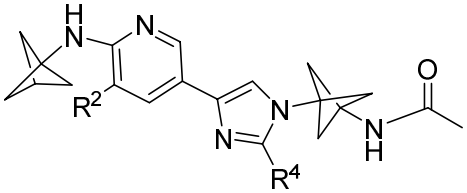
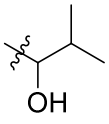
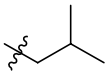
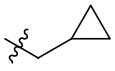
(ii)  , where R^2 is $-CF_3$, $-CN$, $-H$, $-OCH_3$, $-OCHF_2$, $-OCF_3$, or , and R^4 is , , , , or , wherein if R^2 is $-OCF_3$, then R^4 is not ; or

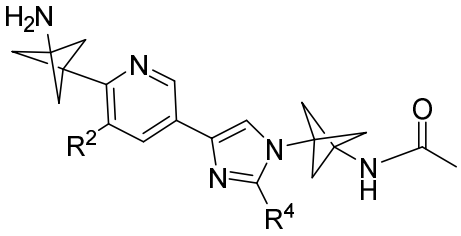
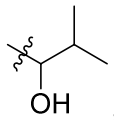
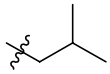
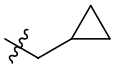
(iii)  , where R^1 is $-OCF_3$ or -CN, and R^4 is  or  ; or

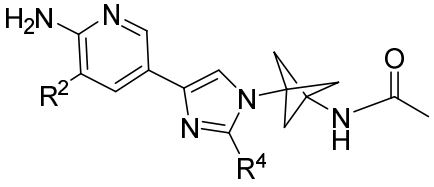
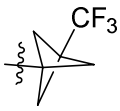
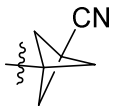
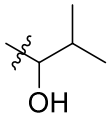
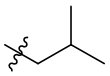
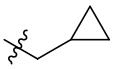
(iv)  or  , where R^4 is  ,  ,  ,  , or  ; or

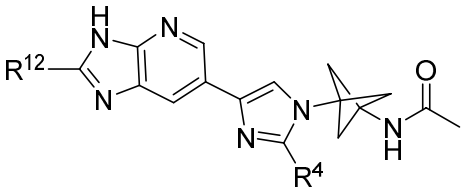
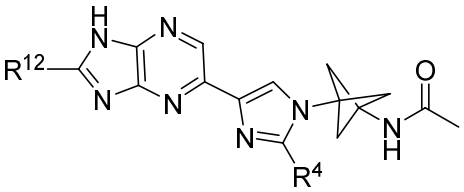
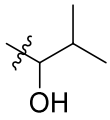
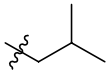
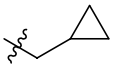
(v)  or  , where R^4 is  ,  ,  ,  , or  , and R^{11} is $-CF_3$, -CN, -H, $-OCH_3$, $-OCHF_2$, or $-OCF_3$; or

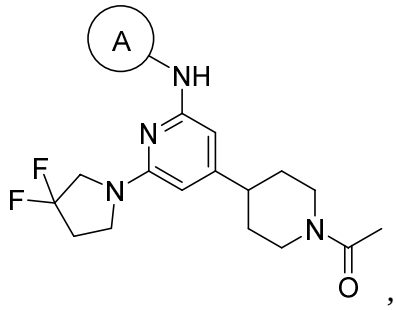
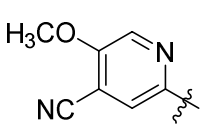
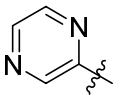
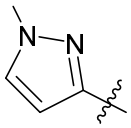
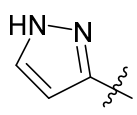
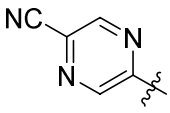
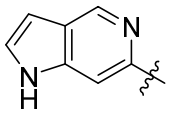
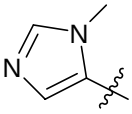
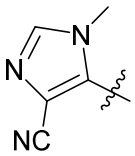
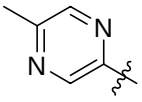
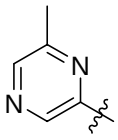
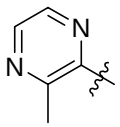
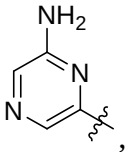
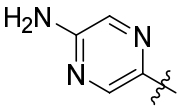
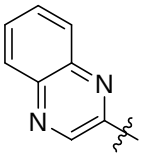
(vi)  , where R^2 is $-CF_3$, -CN, -H, $-OCH_3$, $-OCHF_2$, $-OCF_3$,  ,  , or  , and R^4 is  ,  ,  ,  , or  ; or

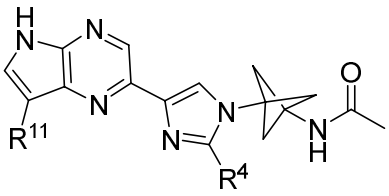
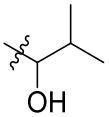
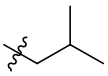
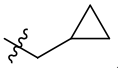
(vii)  , where R^2 is $-CF_3$, -CN, -H, $-OCH_3$, $-OCHF_2$, $-OCF_3$, and R^4 is  ,  ,  ,  , or  ; or

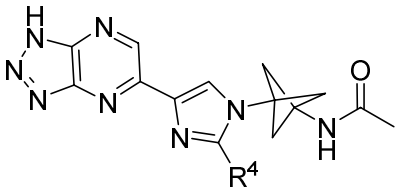
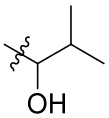
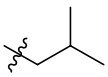
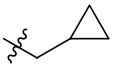
(viii)  , where R^2 is -CF_3, -CN, -H, -OCH_3, -$OCHF_2$, -OCF_3, and R^4 is  ,  ,  ,  , or  ; or

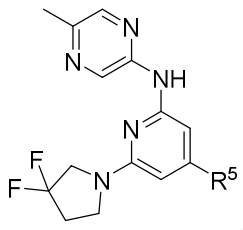
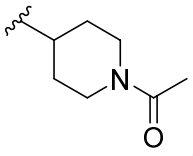
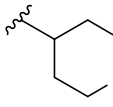
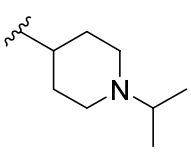
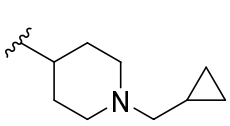
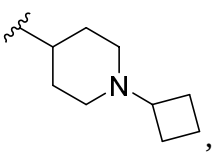
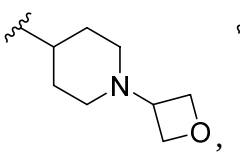
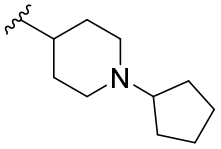
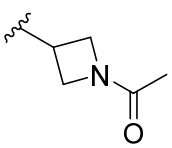
(ixv)  , where R^2 is  ,  , or  , and R^4 is  ,  ,  ,  , or  ; or

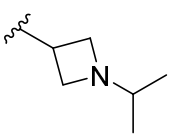
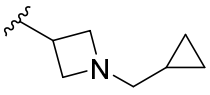
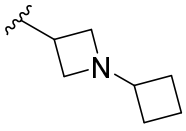
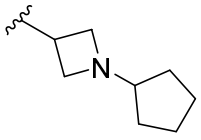
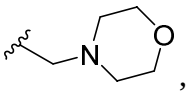
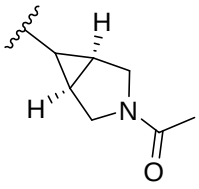
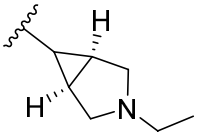
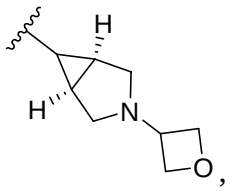
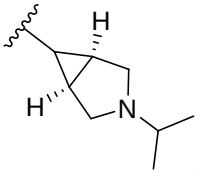
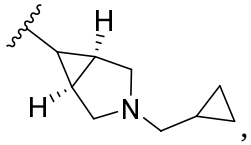
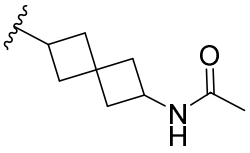
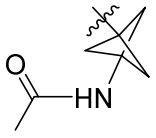
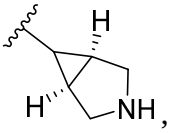
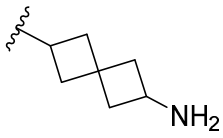
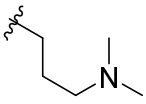
(x)  or  , where R^4 is  ,  ,  ,  , or  , and R^{12} is -CF_3, -CN, -H, -OCH_3, -$OCHF_2$, or -OCF_3; or

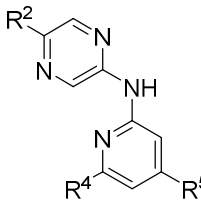
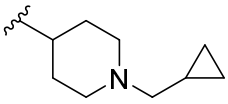
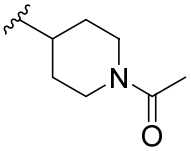
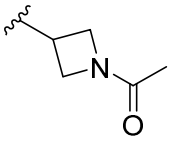
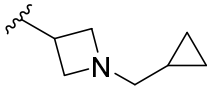
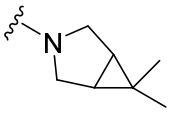
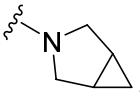
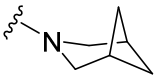
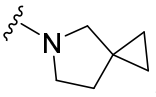
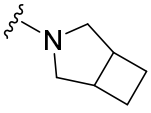
(xi)  , where ring A is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  ; or

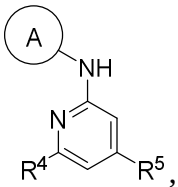
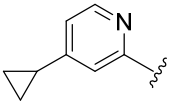
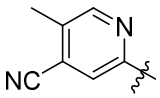
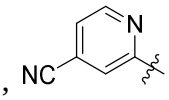
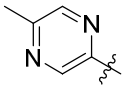
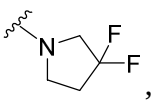
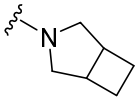
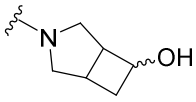
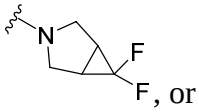
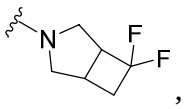
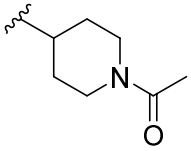
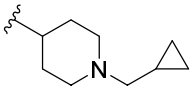
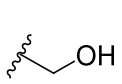
(xii)  , where R^4 is  ,  ,  ,  , or  , and R^{11} is -CF_3, -CN, -H, -OCH_3, -$OCHF_2$, or -OCF_3; or

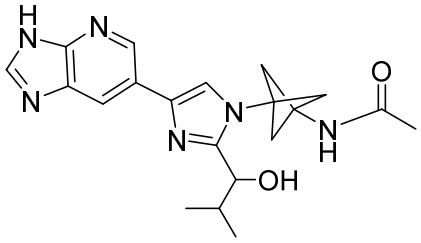
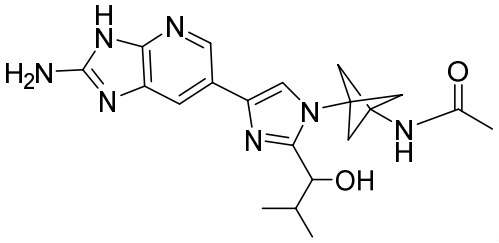
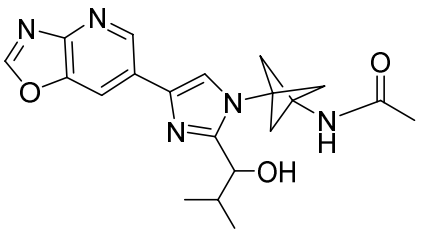
(xiii)  , where R^4 is  ,  ,  ,  , or  ; or

(xiv)  , where R^5 is  ,  ,  ,  ,  ,  ,  ,  , or

 ,  ,  ,  , -CH_3, -CF_3,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ; or

(xv)  , where R^2 is -CH_3 or  , R^4 is  ,  ,  , or  , and R^5 is  ,  ,  ,  , or  ; or

(xvi)  , where ring A is  ,  ,  , or  , R^4 is  ,  ,  ,  , or  , and R^5 is  ,  ,  , , or ; or

(xvii) any one of  ,  ,  ,

16. The compound for use of claim 15, wherein the MLK is MLK1 (MAP3K9), MLK2 (MAP3K10), MLK3 (MAP3K11), MLK4 (MAP3K21), DLK (MAP3K12), LZK (MAP3K13), ZAK1 (MAP3K20), or any combination thereof.

17. The compound for use of claim 16, wherein the MLK is LZK, MLK3, or MLK4.

18. The compound for use of any one of claims 15-17, wherein inhibiting MLK activity inhibits cell cycle progression, reduces c-MYC expression, inhibits c-Jun N-terminal kinase (JNK) pathway signaling, inhibits PI3K/AKT pathway signaling, inhibits cyclin dependent kinase 2 (CDK2) activity, inhibits extracellular signal-regulated kinase (ERK) pathway signaling, NF-κB signaling, or any combination thereof.

19. The compound for use of any one of claims 15-18, wherein the cell is characterized by amplification of chromosome 3q, amplification of chromosome 11q, overexpression of a mitogen-activated protein kinase kinase kinase (*MAP3K*), or any combination thereof.

20. The compound for use of any one of claims 15-19, wherein the cell is a head and neck squamous cell carcinoma (HNSCC) cell, a lung squamous cell carcinoma (LSCC) cell, an esophageal cancer cell, a hepatocellular carcinoma cell, an ovarian cancer cell, a small cell lung cancer cell, a neuroendocrine prostate cancer cell, or a breast cancer cell.

21. The compound for use of any one of claims 15-20, wherein the compound is contacted with the cell by administration of a therapeutically effective amount of the compound, or an amount of a pharmaceutical composition comprising the therapeutically effective amount of the compound, to a subject.

22. The compound for use of claim 21, wherein the subject has a disease or condition characterized at least in part by MLK overexpression.

23. The compound for use of claim 22, wherein the disease or condition is cancer.

24. The compound for use of claim 23, wherein the cancer is HNSCC, LSCC, esophageal squamous cell carcinoma (ESCC), hepatocellular carcinoma, ovarian cancer, small cell lung cancer, neuroendocrine prostate cancer, esophageal adenocarcinoma, or breast cancer.

25. The compound for use of claim 24, wherein the cancer is HNSCC, LSCC, ESCC, or triple-negative breast cancer.

26. The compound for use of any one of claims 23-25, wherein the therapeutically effective amount of the compound to be administered, or the amount of the pharmaceutical composition, decreases viability of the cancer cells, inhibits tumor growth, or a combination thereof.

27. The compound for use of any one of claims 21-26, wherein administration is performed parenterally, orally, or topically.

28. Use of a compound according to any one of claims 1-13 in the manufacture of a medicament for the treatment of a disease or condition characterized at least in part by MLK overexpression, wherein the disease or condition is cancer.

29. The use of claim 28, wherein the cancer is HNSCC, LSCC, ESCC, hepatocellular carcinoma, ovarian cancer, small cell lung cancer, neuroendocrine prostate cancer, esophageal adenocarcinoma, or breast cancer.