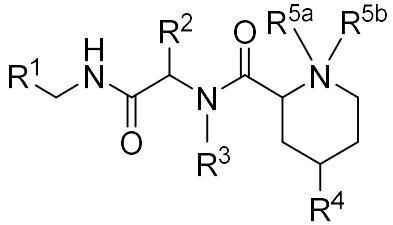
Mannan-binding lectin-associated serine protease-2 (MASP-2) has been shown to be required for the function of the lectin pathway, one of the principal complement activation pathways (Vorup-Jensen et al., J. Immunol 165:2093-2100, 2000; Ambrus et al., J Immunol. 170: 1374-1382, 2003; Schwaeble et al., PNAS 108:7523-7528, 2011). Importantly, inhibition of MASP-2 does not appear to interfere with the antibody-dependent classical complement activation pathway, which is a critical component of the acquired immune response to infection. As described in U.S. Patent No. 9,011,860 (assigned to Omeros Corporation), which is hereby incorporated by reference, discloses a fully human monoclonal antibody targeting human MASP-2 has been generated which binds to human MASP-2 with high affinity and blocks the lectin pathway complement activity and is therefore useful to treat various lectin complement pathway-associated diseases and disorders.

MASP-2-dependent complement activation has been implicated as contributing to the pathogenesis of numerous acute and chronic disease states. Therefore, a need exists for compounds that are suitable for administration/treatment of subject suffering from MASP-2 complement pathway-associated diseases and disorders, including diseases that are not suitably or efficiently treated with large molecule biologic inhibitors.

~~BRIEF~~ SUMMARY

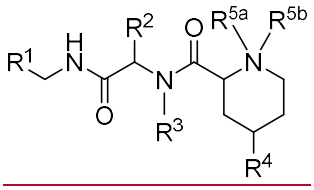
One ~~embodiment~~example provides a compound having the following Structure (I):



(I)

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^{5a}, and R^{5b} are as defined herein.

In one aspect, the present disclosure refers to a compound having the following Structure (I):



(I)

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein:

R^1 is a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or a substituted or unsubstituted heterocyclyl;

R^2 is hydrogen, alkyl, alkoxy, haloalkyl, haloalkoxy, or cycloalkyl;

R^3 is hydrogen, alkyl, haloalkyl, or cycloalkyl;

or R^2 and R^3, together with the carbon and nitrogen to which they are attached, respectively, form an optionally substituted 4-7 membered heterocyclyl;

R^4 is a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or a substituted or unsubstituted heterocyclyl;

R^{5a} is hydrogen, alkyl, haloalkyl, cycloalkyl, phosphonalkyl, $(CH_2)_nC(=O)OR^6$, $C(=O)R^6$, $C(=O)OR^6$, or $C(=O)NR^6R^7$;

R^{5b} is an electron pair or alkyl;

R^6 and R^7 are, at each occurrence, independently hydrogen, alkyl, haloalkyl, cycloalkyl, or arylalkyl;

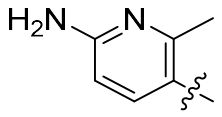
R^8 is alkyl, haloalkyl, aminylalkyl, substituted or unsubstituted arylalkyl; and

n is 1, 2, 3, 4, 5, 6, 7, or 8,

provided that

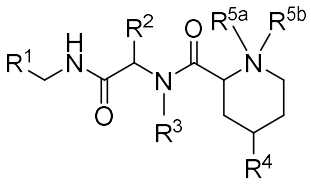
A) R^{5a} is alkyl, haloalkyl, cycloalkyl, phosphonalkyl, $(CH_2)_nC(=O)OR^6$, $C(=O)R^6$, $C(=O)OR^6$, or $C(=O)NR^6R^7$ or R^1 is substituted with one or more substituents selected from the group consisting of a substituted heteroaryl, $C(=NH)NHC(=O)OR^8$, $C(=NOC(=O)R^8)NH_2$, $C(=NOC(=O)OR^8)NH_2$, and $C(=NOH)NH_2$; and

B) when R^{5a} is alkyl or $(CH_2)_nC(=O)OR^6$, R^1 does not have the following structure:



unless R^2 and R^3, together with the carbon and nitrogen to which they are attached, respectively, form an optionally substituted 4-7 membered heterocyclyl.

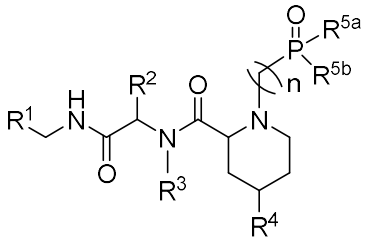
Another ~~embodiment~~example provides a compound having the following Structure (II):



(II)

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^{5a}, and R^{5b} are as defined herein.

Yet another ~~embodiment~~example provides a compound having the following Structure (III):



(III)

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^{5a}, R^{5b} and n are as defined herein.

In one aspect, the present disclosure refers to a compound having one of the structures in Table 1 or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

Additional ~~embodiment~~examples of the present disclosure provide a pharmaceutical composition comprising a compound of Structure (I), Structure (II), or Structure (III), or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient.

In one aspect, the present disclosure refers to a pharmaceutical composition comprising a compound or pharmaceutically acceptable salt thereof disclosed herein and a pharmaceutically acceptable carrier or excipient.

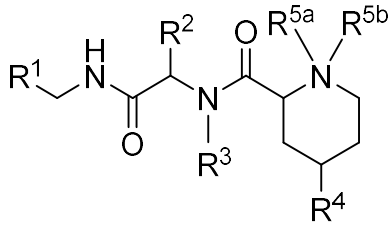
The compounds of Structures (I), (II), and (III) are useful in the treatment of MASP-2-associated diseases and disorders, and in the manufacture of medicaments for treating MASP-2-associated diseases and disorders. Accordingly, other ~~embodiment~~examples of the disclosure provide methods of treating a MASP-2-associated disease and disorder comprising administering to a patient a therapeutically effective amount of a compound of Structure (I), Structure (II), or Structure (III), or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

In one aspect, the present disclosure refers to use of a compound disclosed herein, in the manufacture of a medicament for treating a MASP-2-associated disease or disorder in a subject in need thereof.

These and other ~~aspect~~examples, and objects ~~and embodiments~~ will become more apparent when read with the detailed description and figures which follow.

CLAIMS

1. A compound having the following Structure (I):



(I)

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein:

R^1 is a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or a substituted or unsubstituted heterocyclyl;

R^2 is hydrogen, alkyl, alkoxy, haloalkyl, haloalkoxy, or cycloalkyl;

R^3 is hydrogen, alkyl, haloalkyl, or cycloalkyl;

or R^2 and R^3, together with the carbon and nitrogen to which they are attached, respectively, form an optionally substituted 4-7 membered heterocyclyl;

R^4 is a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or a substituted or unsubstituted heterocyclyl;

R^{5a} is hydrogen, alkyl, haloalkyl, cycloalkyl, phosphonalkyl, $(CH_2)_nC(=O)OR^6$, $C(=O)R^6$, $C(=O)OR^6$, or $C(=O)NR^6R^7$;

R^{5b} is an electron pair or alkyl;

R^6 and R^7 are, at each occurrence, independently hydrogen, alkyl, haloalkyl, cycloalkyl, or arylalkyl;

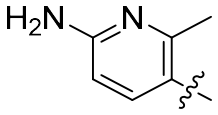
R^8 is alkyl, haloalkyl, aminylalkyl, substituted or unsubstituted arylalkyl; and

n is 1, 2, 3, 4, 5, 6, 7, or 8,

provided that

A) R^{5a} is alkyl, haloalkyl, cycloalkyl, phosphonalkyl, $(CH_2)_nC(=O)OR^6$, $C(=O)R^6$, $C(=O)OR^6$, or $C(=O)NR^6R^7$ or R^1 is substituted with one or more substituents selected from the group consisting of a substituted heteroaryl, $C(=NH)NHC(=O)OR^8$, $C(=NOC(=O)R^8)NH_2$, $C(=NOC(=O)OR^8)NH_2$, and $C(=NOH)NH_2$; and

B) when R^{5a} is alkyl or $(CH_2)_nC(=O)OR^6$, R^1 does not have the following structure:



unless R^2 and R^3, together with the carbon and nitrogen to which they are attached, respectively, form an optionally substituted 4-7 membered heterocyclyl.

~~2. The compound of claim 1, wherein R^1 is a substituted or unsubstituted aryl.~~

~~3. The compound of claim 1 or 2, wherein R^1 is a substituted or unsubstituted C_6-C_{10} aryl.~~

24. The compound ~~of any one~~ of claim~~s~~ 1-~~3~~, wherein R^1 is a substituted or unsubstituted phenyl.

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

~~6. The compound of any one of claims 1-5, wherein R^1 is phenyl substituted with one or more of R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently selected from the group consisting of $C(=NH)NHC(=O)OR^8$, $C(=NOC(=O)R^8)NH_2$, $C(=NOC(=O)OR^8)NH_2$, $C(=NOH)NH_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, C_{1-6} haloalkyl, aminylalkyl, hydroxyalkyl, cyano, nitro, OR^9, SR^9, $C(O)R^9$, $C(O)NR^9R^{10}$, $C(O)OR^9$, $OC(O)R^9$, $OC(O)OR^9$, $OC(O)NR^9R^{10}$, NR^9R^{10},~~

~~$N(R^9)C(O)R^{10}$, $N(R^9)C(O)NR^{10}R^{11}$, $N(R^9)C(O)OR^{10}$, $C(=NR^9)NR^{10}R^{11}$, $C(=NOR^9)NR^{10}R^{11}$, $C(=NOC(O)R^9)NR^{10}R^{11}$, $C(=NR^9)N(R^{10})C(O)OR^{11}$, $N(R^9)C(=NR^{10})NR^{11}R^{12}$, $S(O)R^9$, $S(O)NR^9R^{10}$, $S(O)_2R^9$, $N(R^9)S(O)_2R^{10}$, $S(O)_2NR^9R^{10}$, oxo, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted C_{6-10} arylalkyl, substituted or unsubstituted C_{6-10} aryloxy, substituted or unsubstituted C_{6-10} arylalkoxy, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted C_{3-10} cycloalkyl, and substituted or unsubstituted 4-10 membered heterocyclyl,~~

~~wherein R^9, R^{10}, R^{11}, and R^{12}, are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.~~

~~7. The compound of claim 6, wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is optionally substituted with one or more substituents selected from the group consisting of halo, CN, OR^{13}, SR^{13}, $C(O)R^{13}$, $C(O)NR^{13}R^{14}$, $C(O)OR^{13}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}C(O)OR^{14}$, $C(=NR^{13})NR^{14}R^{15}$, $NR^{13}C(=NR^{14})NR^{15}R^{16}$, $S(O)R^{13}$, $S(O)NR^{13}R^{14}$, $S(O)_2R^{13}$, $NR^{13}S(O)_2R^{14}$, $S(O)_2NR^{13}R^{14}$ and oxo when R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is a substituted C_{6-10} aryl, a substituted C_{6-10} arylalkyl, a substituted C_{6-10} aryloxy, a substituted C_{6-10} arylalkoxy, a substituted 5-10 membered heteroaryl, a substituted C_{3-10} cycloalkyl, and a substituted 4-10 membered heterocyclyl,~~

~~wherein R^{13}, R^{14}, R^{15}, and R^{16} are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.~~

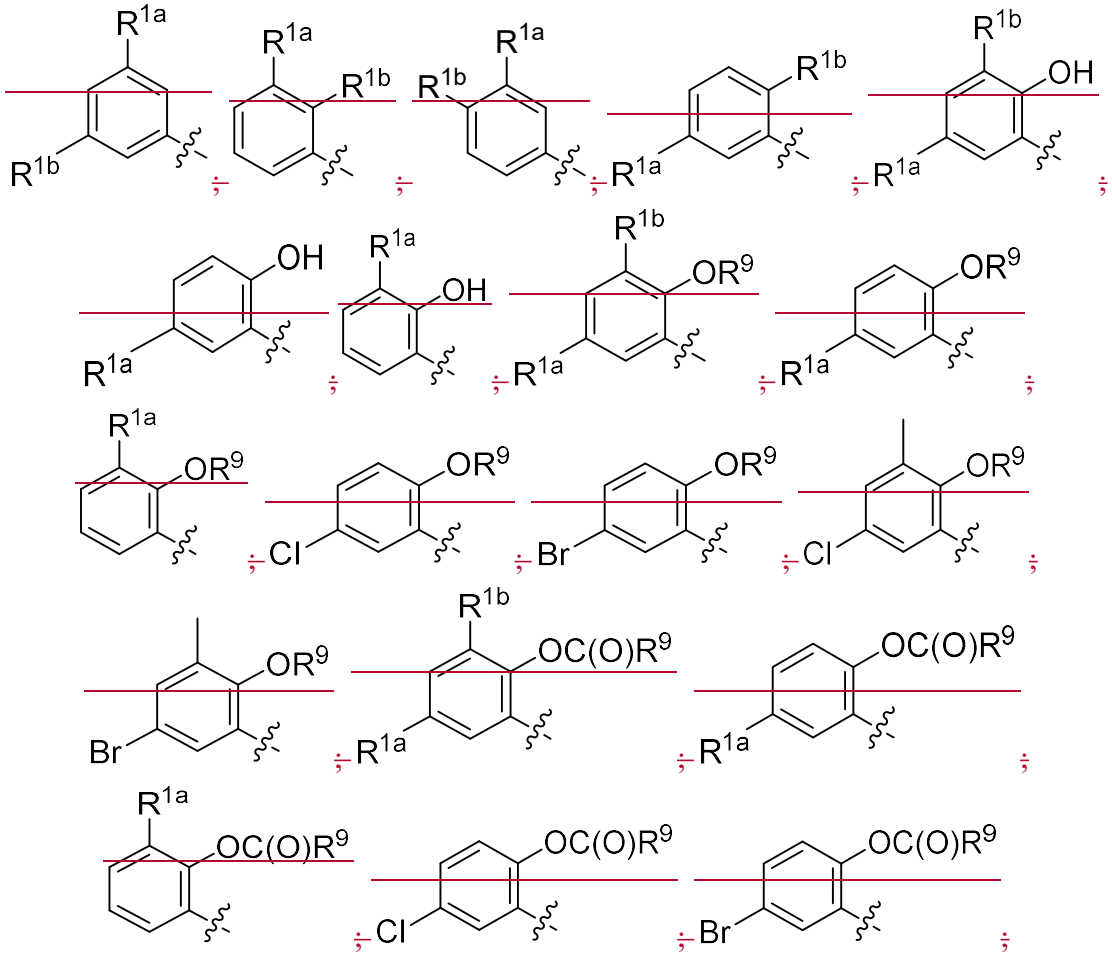
~~8. The compound of any one of claims 1-7, wherein R^1 is phenyl substituted with at least one substituent selected from the group consisting of OR^9, $C(=NR^9)NR^{10}R^{11}$, $C(=NOR^9)NR^{10}R^{11}$, $C(=NOC(O)R^9)NR^{10}R^{11}$, and $C(=NR^9)NR^{10}C(O)OR^{11}$.~~

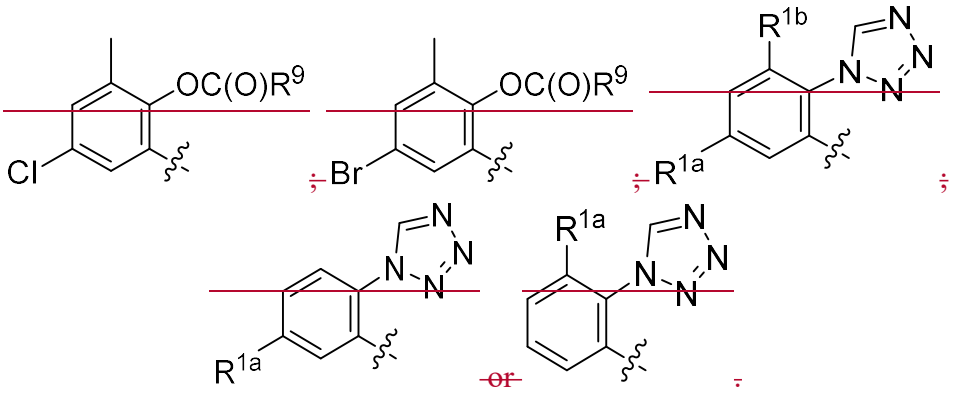
~~9. The compound of any one of claims 1-8, wherein R^1 is substituted with at least one substituent selected from the group consisting of $C(=NR^9)NR^{10}R^{11}$, $C(=NOR^9)NR^{10}R^{11}$, $C(=NOC(O)R^9)NR^{10}R^{11}$, and $C(=NR^9)NR^{10}C(O)OR^{11}$.~~

~~10. The compound of claim 9, wherein R^1 is substituted with at least one $C(=NR^9)NR^{10}R^{11}$.~~

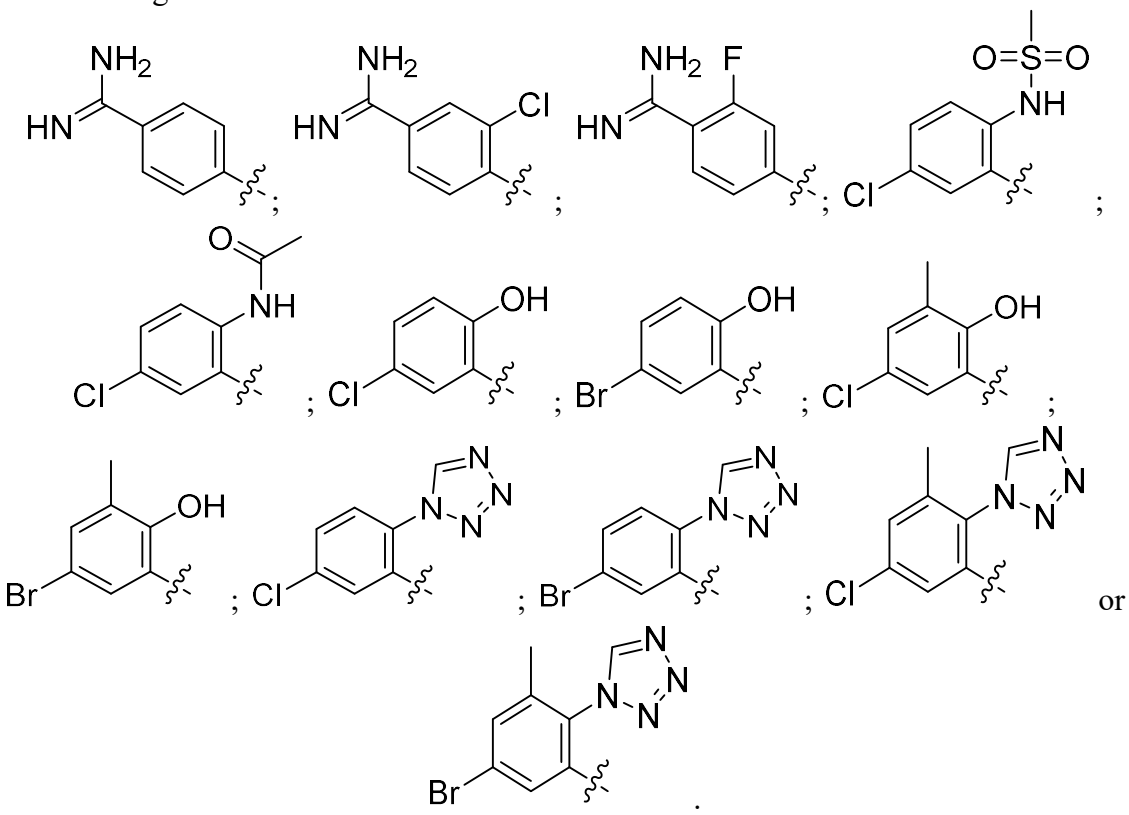
~~11. The compound of claim 9 or 10, wherein R^1 is substituted with at least one $-C(=NH)NH_2$.~~

~~12. The compound of any one of claims 7-11, wherein R^1 has one of the following structures:~~

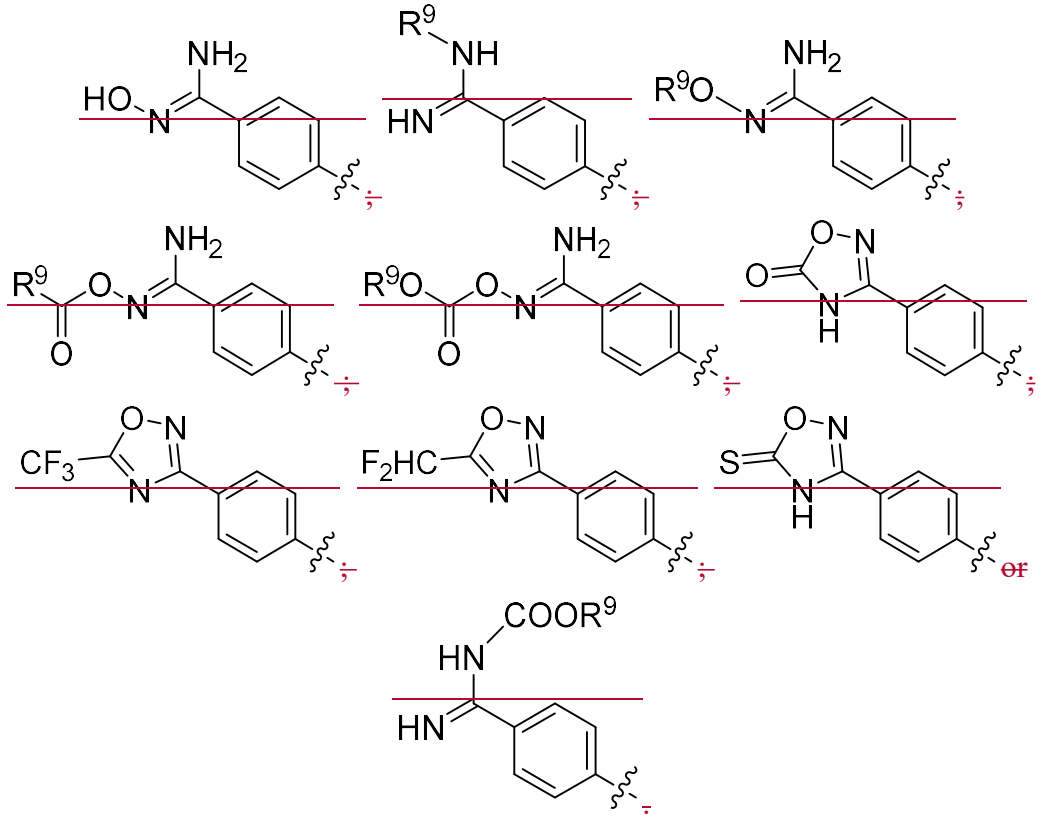




~~1~~3. The compound ~~of any one~~ of claim~~s~~ 1~~-12~~, wherein R^1 has one of the following structures:



~~14. The compound of claim 7, wherein R^1 has one of the following structures:~~



~~15. The compound of claim 14, wherein R^9 is C_{1-6} alkyl or C_{1-6} haloalkyl.~~

~~16. The compound of claim 15, wherein R^9 is methyl.~~

~~17. The compound of claim 15, wherein R^9 is trifluoromethyl.~~

~~18. The compound of any one of claims 1-4, wherein R^1 is an unsubstituted phenyl.~~

~~4~~19. The compound of claim 1, wherein R^1 is a substituted or unsubstituted heteroaryl.

20. The compound of claim 1 or 19, wherein R^1 is a substituted or unsubstituted 5-10 membered heteroaryl.

21. The compound of claim 1 or 19-20, wherein R^1 is a substituted or unsubstituted pyridinyl, pyrrolopyridinyl, thiophenyl, or benzoimidazolyl.

22. The compound of any one of claims 1 or 19-21, wherein R^1 is a substituted or unsubstituted pyridin-3-yl, 1H-pyrrolo[2,3-b]pyridine-5-yl, thiophen-2-yl, or 1H-benzo[d]imidazol-6-yl.

23. The compound of any one of claims 1 or 19-22, wherein R^1 is pyridin-3-yl, 1H-pyrrolo[2,3-b]pyridine-5-yl, thiophen-2-yl, or 1H-benzo[d]imidazol-6-yl substituted with one or more of R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, C_{1-6} haloalkyl, aminylalkyl, hydroxyalkyl, cyano, nitro, OR^9, SR^9, $C(O)R^9$, $C(O)NR^9R^{10}$, $C(O)OR^9$, $OC(O)R^9$, $OC(O)OR^9$, $OC(O)NR^9R^{10}$, NR^9R^{10}, $N(R^9)C(O)R^{10}$, $N(R^9)C(O)NR^{10}R^{11}$, $N(R^9)C(O)OR^{10}$, $C(=NR^9)NR^{10}R^{11}$, $C(=NOR^9)NR^{10}R^{11}$, $C(=NOC(O)R^9)NR^{10}R^{11}$, $C(=NR^9)N(R^{10})C(O)OR^{11}$, $N(R^9)C(=NR^{10})NR^{11}R^{12}$, $S(O)R^9$, $S(O)NR^9R^{10}$, $S(O)_2R^9$, $N(R^9)S(O)_2R^{10}$, $S(O)_2NR^9R^{10}$, oxo, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted C_{6-10} arylalkyl, substituted or unsubstituted C_{6-10} aryloxy, substituted or unsubstituted C_{6-10} arylalkoxy, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted C_{3-10} cycloalkyl, and substituted or unsubstituted 4-10 membered heterocyclyl,

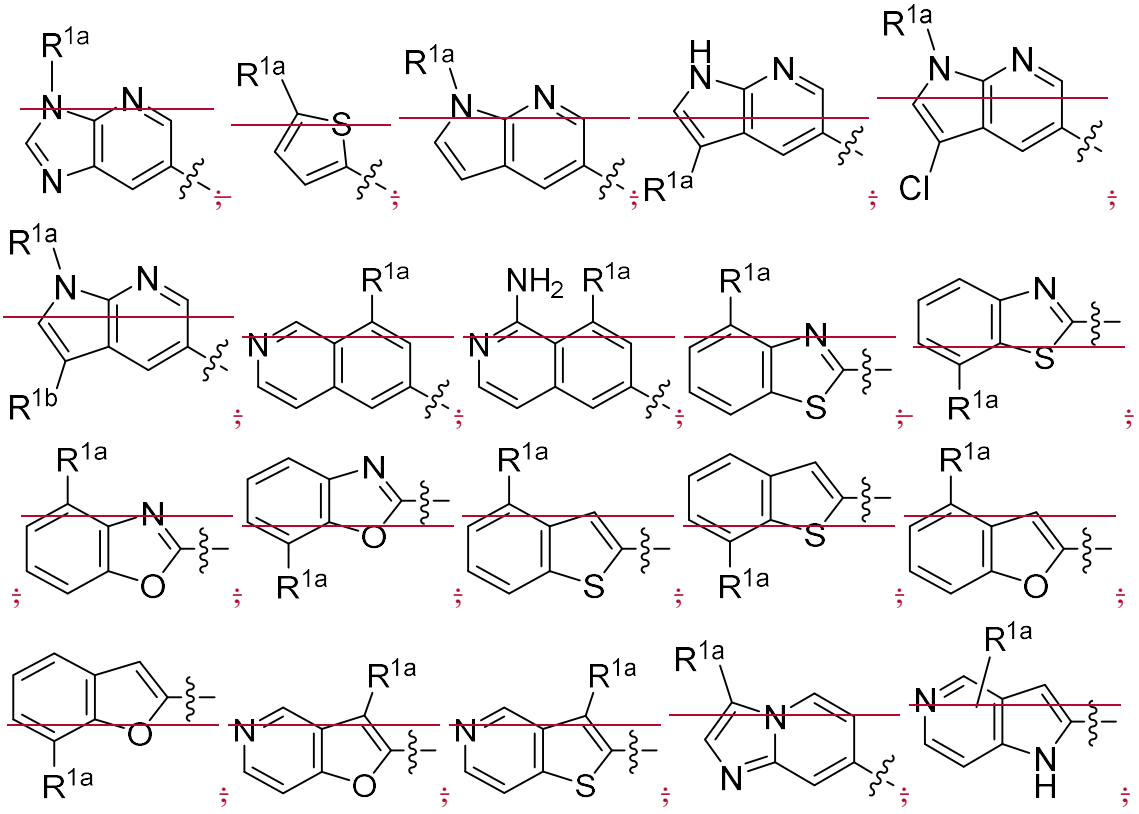
wherein R^9, R^{10}, R^{11}, and R^{12}, are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.

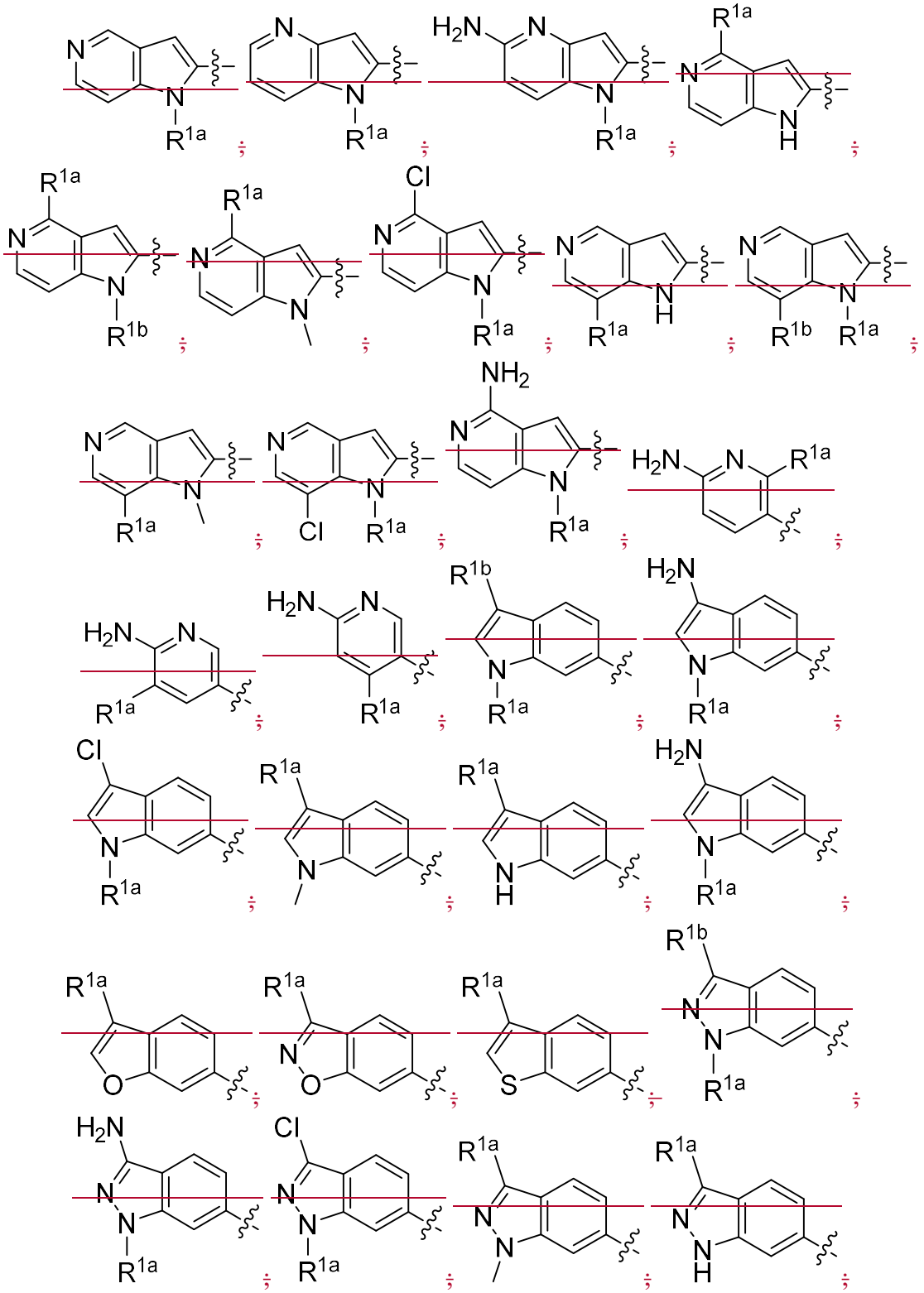
24. The compound of claim 23, wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is optionally substituted with one or more substituents selected from the group consisting

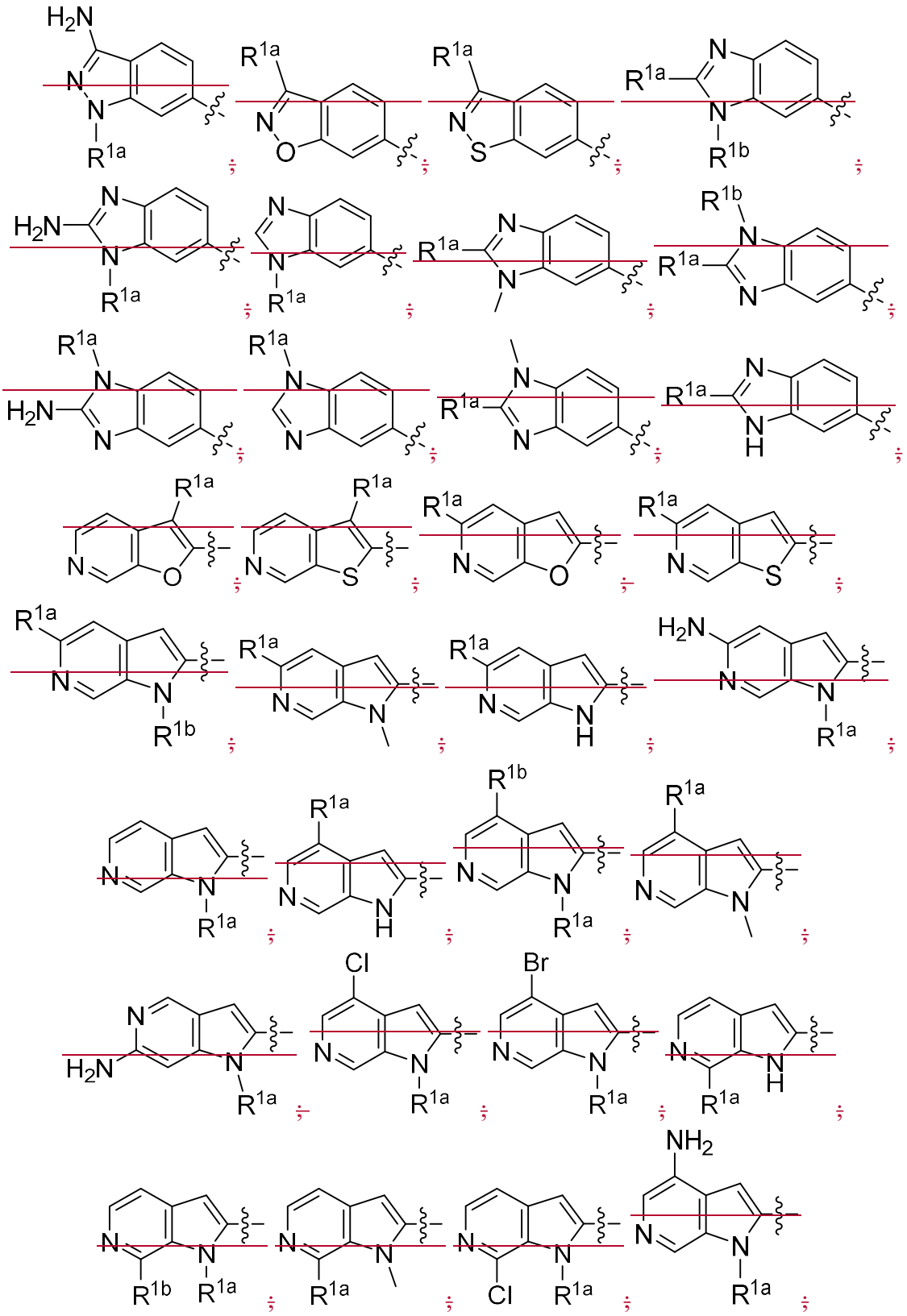
~~of halo, CN, OR^{13}, SR^{13}, $C(O)R^{13}$, $C(O)NR^{13}R^{14}$, $C(O)OR^{13}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}C(O)OR^{14}$, $C(=NR^{13})NR^{14}R^{15}$, $NR^{13}C(=NR^{14})NR^{15}R^{16}$, $S(O)R^{13}$, $S(O)NR^{13}R^{14}$, $S(O)_2R^{13}$, $NR^{13}S(O)_2R^{14}$, $S(O)_2NR^{13}R^{14}$ and oxo when R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is a substituted C_{6-10} aryl, a substituted C_{6-10} arylalkyl, a substituted C_{6-10} aryloxy, a substituted C_{6-10} arylalkoxy, a substituted 5-10 membered heteroaryl, a substituted C_{3-10} cycloalkyl, and a substituted 4-10 membered heterocyclyl,~~

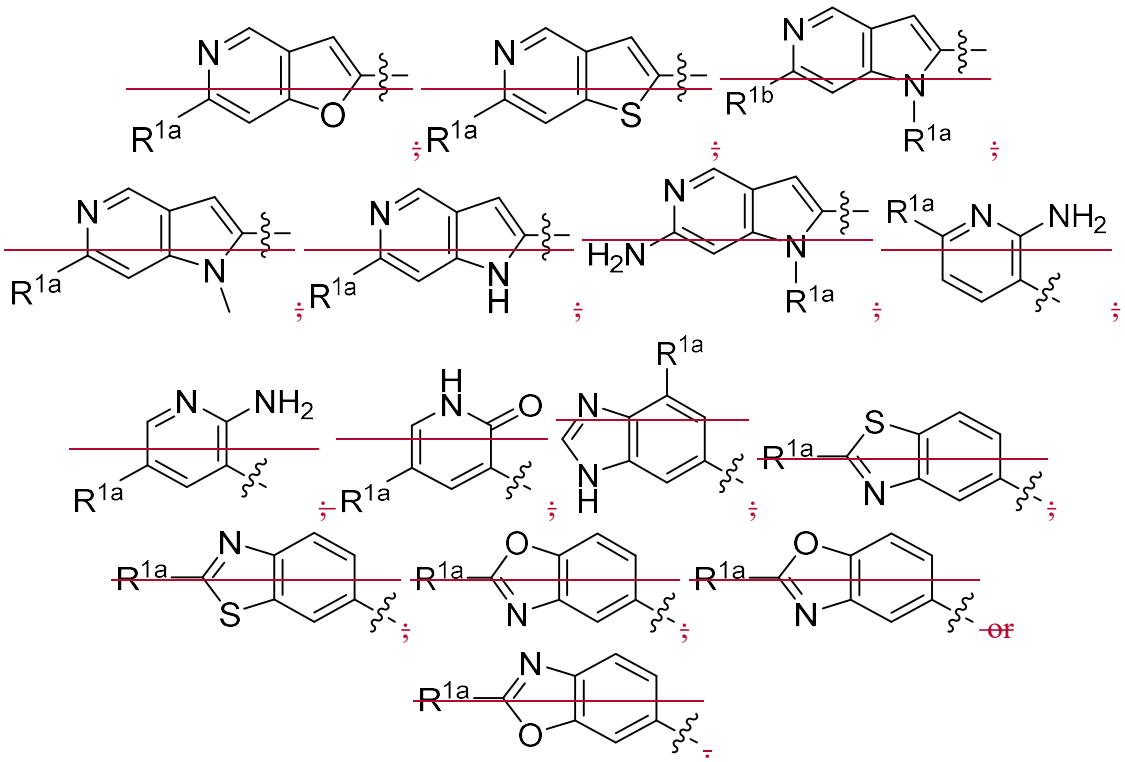
~~wherein R^{13}, R^{14}, R^{15}, and R^{16} are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.~~

~~25. The compound of any one of claims 1 or 19-23, wherein R^1 has one of the following structures:~~









~~26. The compound of claim 25, wherein R^{1a} or R^{1b} is independently C_{1-6} alkyl, amino, or halo.~~

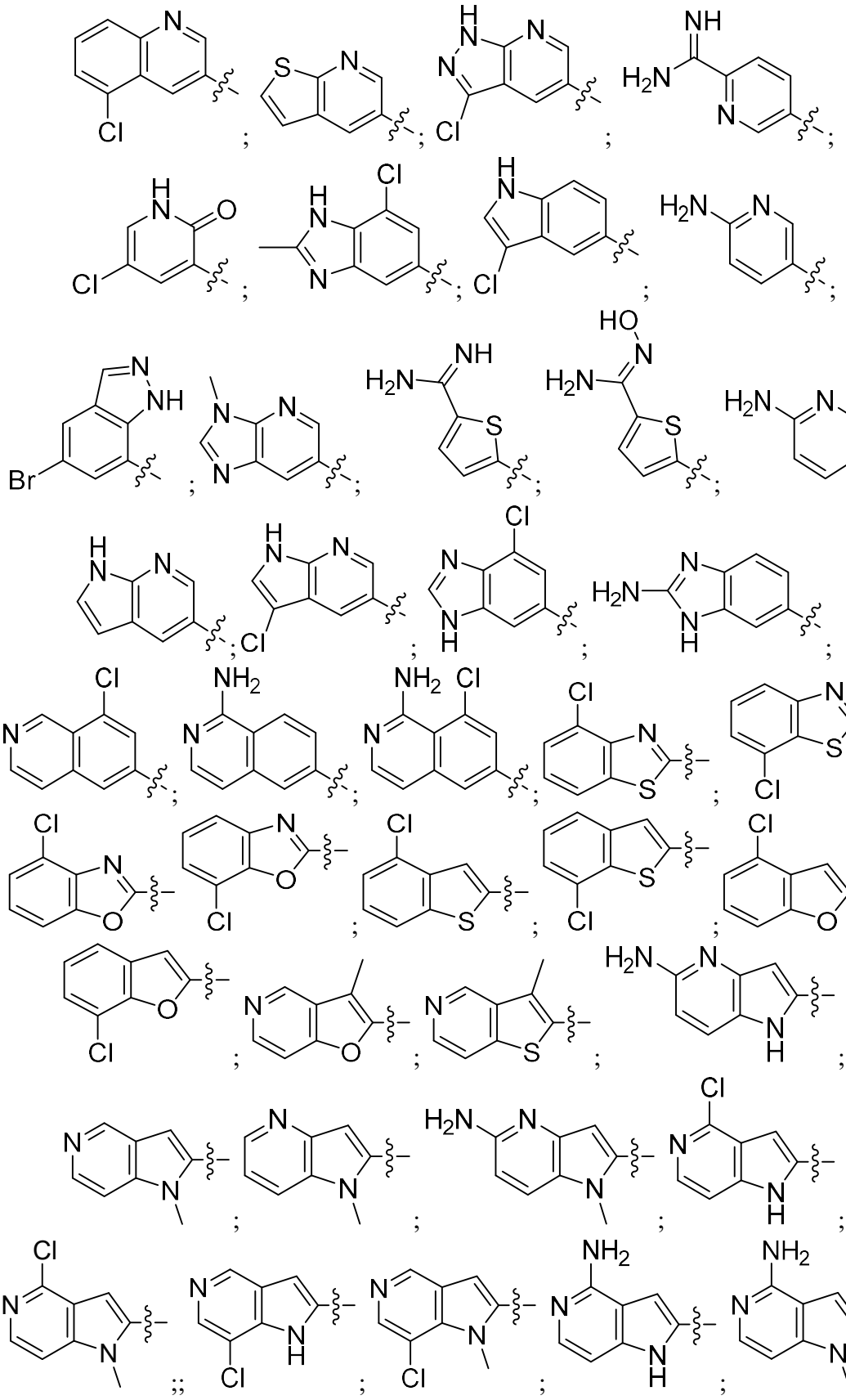
~~27. The compound of claim 26, wherein R^{1a} or R^{1b} is methyl or ethyl.~~

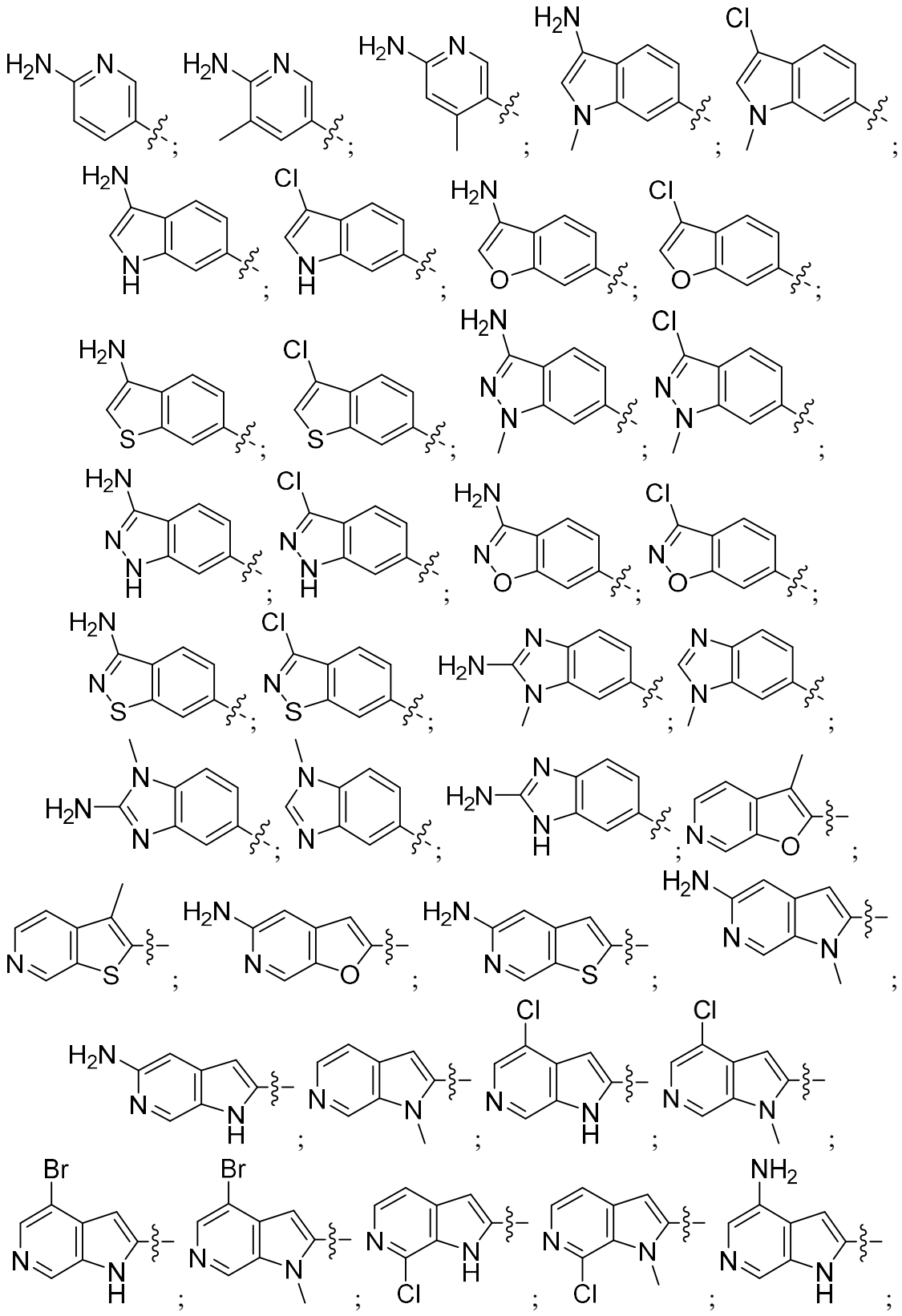
~~28. The compound of claim 26, wherein R^{1a} or R^{1b} is F, Cl, or Br.~~

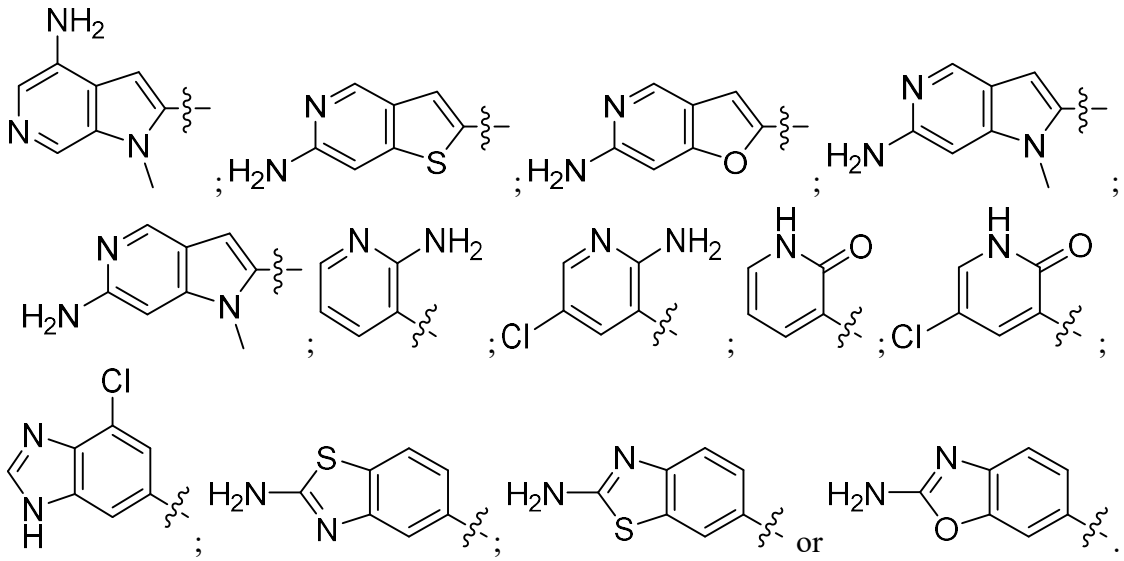
~~29. The compound of claim 25, wherein each R^{1a} or R^{1b} attached to nitrogen is C_{1-6} alkyl.~~

~~30. The compound of claim 29, wherein R^{1a} or R^{1b} is methyl or ethyl.~~

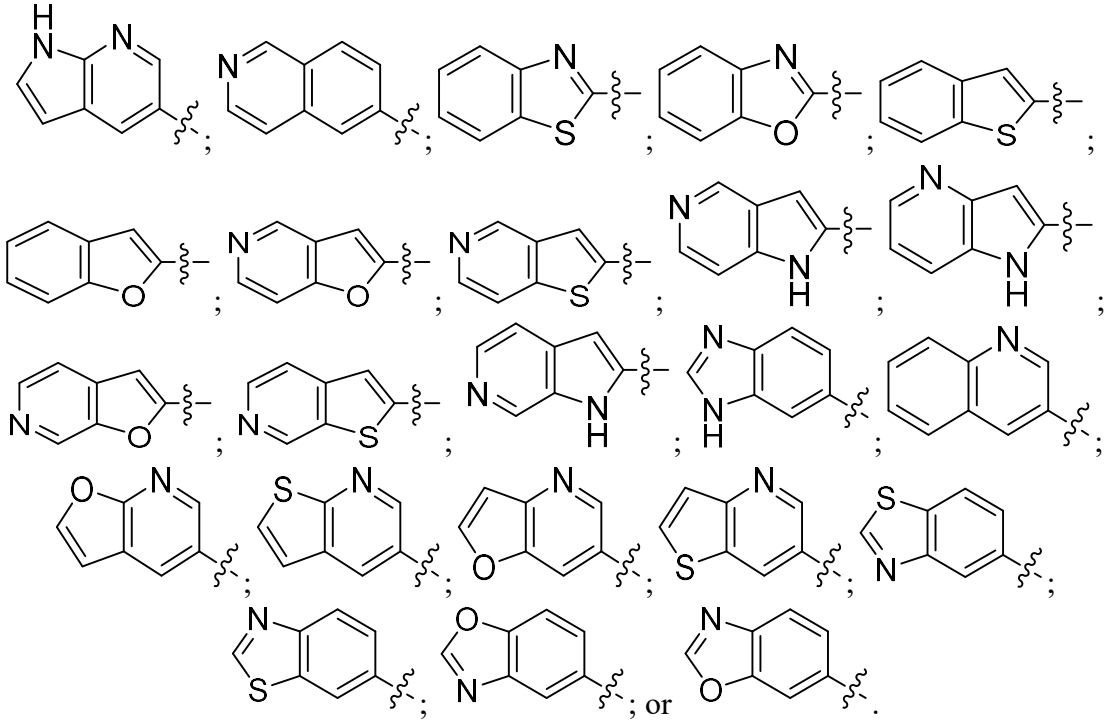
5~~31~~. The compound of ~~any one of~~ claim~~s~~ 1 ~~or 19-20~~, wherein R^1 has one of the following structures:







6~~32~~. The compound of ~~any one of~~ claim~~s~~ 1 ~~or 19-20~~, wherein R^1 has one of the following structures:



~~33. The compound of claim 1, wherein R^1 is a substituted or unsubstituted cycloalkyl.~~

34. The compound of claim 1 or 33, wherein R^1 is a substituted or unsubstituted C_3-C_6 cycloalkyl.

35. The compound of any one of claims 1 or 33-34, wherein R^1 is a substituted C_3-C_6 cycloalkyl.

36. The compound of claim 35, wherein R^1 is a C_3-C_6 cycloalkyl substituted with one or more of R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, aminylalkyl, hydroxyalkyl, nitro, OR^9, SR^9, $C(O)R^9$, $C(O)NR^9R^{10}$, $C(O)OR^9$, $OC(O)R^9$, $OC(O)OR^9$, $OC(O)NR^9R^{10}$, NR^9R^{10}, $N(R^9)C(O)R^{10}$, $N(R^9)C(O)NR^{10}R^{11}$, $N(R^9)C(O)OR^{10}$, $C(=NR^9)NR^{10}R^{11}$, $C(=NOR^9)NR^{10}R^{11}$, $C(=NOC(O)R^9)NR^{10}R^{11}$, $C(=NR^9)N(R^{10})C(O)OR^{11}$, $N(R^9)C(=NR^{10})NR^{11}R^{12}$, $S(O)R^9$, $S(O)NR^9R^{10}$, $S(O)_2R^9$, $N(R^9)S(O)_2R^{10}$, $S(O)_2NR^9R^{10}$, oxo, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted C_{6-10} arylalkyl, substituted or unsubstituted C_{6-10} aryloxy, substituted or unsubstituted C_{6-10} arylalkoxy, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted C_{3-10} cycloalkyl, and substituted or unsubstituted 4-10 membered heterocyclyl,

wherein R^9, R^{10}, R^{11}, and R^{12}, are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.

37. The compound of claim 36, wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is optionally substituted with one or more substituents selected from the group consisting of halo, CN, OR^{13}, SR^{13}, $C(O)R^{13}$, $C(O)NR^{13}R^{14}$, $C(O)OR^{13}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}C(O)OR^{14}$, $C(=NR^{13})NR^{14}R^{15}$, $NR^{13}C(=NR^{14})NR^{15}R^{16}$, $S(O)R^{13}$, $S(O)NR^{13}R^{14}$, $S(O)_2R^{13}$, $NR^{13}S(O)_2R^{14}$, $S(O)_2NR^{13}R^{14}$ and oxo when R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is a substituted C_{6-10} aryl, a substituted C_{6-10} arylalkyl, a substituted C_{6-10} aryloxy, a substituted C_{6-10} arylalkoxy, a substituted 5-10

membered heteroaryl, a substituted C_{3-10} cycloalkyl, and a substituted 4-10 membered heterocyclyl,

wherein R^{13}, R^{14}, R^{15}, and R^{16} are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.

38. The compound of claim 34, wherein R^1 is an unsubstituted a C_3-C_6 cycloalkyl.

39. The compound of claim 1, wherein R^1 is a substituted or unsubstituted heterocyclyl.

40. The compound of claim 1 or 39, wherein R^1 is a substituted or unsubstituted 4-10 membered heterocyclyl.

41. The compound of any one of claims 1 or 39-40, wherein R^1 is a substituted 4-10 membered heterocyclyl.

42. The compound of claim 41, wherein R^1 is a 4-10 membered heterocyclyl substituted with one or more of R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, C_{1-6} haloalkyl, aminylalkyl, hydroxyalkyl, cyano, nitro, OR^9, SR^9, $C(O)R^9$, $C(O)NR^9R^{10}$, $C(O)OR^9$, $OC(O)R^9$, $OC(O)OR^9$, $OC(O)NR^9R^{10}$, NR^9R^{10}, $N(R^9)C(O)R^{10}$, $N(R^9)C(O)NR^{10}R^{11}$, $N(R^9)C(O)OR^{10}$, $C(=NR^9)NR^{10}R^{11}$, $C(=NOR^9)NR^{10}R^{11}$, $C(=NOC(O)R^9)NR^{10}R^{11}$, $C(=NR^9)N(R^{10})C(O)OR^{11}$, $N(R^9)C(=NR^{10})NR^{11}R^{12}$, $S(O)R^9$, $S(O)NR^9R^{10}$, $S(O)_2R^9$, $N(R^9)S(O)_2R^{10}$, $S(O)_2NR^9R^{10}$, oxo, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted C_{6-10} arylalkyl, substituted or unsubstituted C_{6-10} aryloxy, substituted or unsubstituted C_{6-10} arylalkoxy,

~~substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted C_{3-10} cycloalkyl, and substituted or unsubstituted 4-10 membered heterocyclyl,~~

~~wherein R^9, R^{10}, R^{11}, and R^{12}, are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.~~

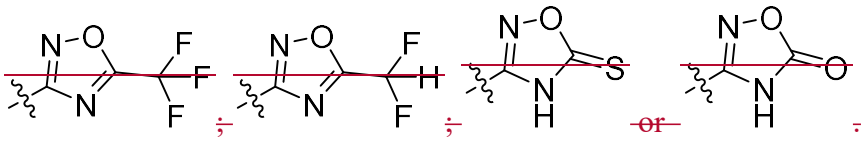
~~43. The compound of claim 42, wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is optionally substituted with one or more substituents selected from the group consisting of OR^{13}, SR^{13}, $C(O)R^{13}$, $C(O)NR^{13}R^{14}$, $C(O)OR^{13}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}C(O)OR^{14}$, $C(=NR^{13})NR^{14}R^{15}$, $NR^{13}C(=NR^{14})NR^{15}R^{16}$, $S(O)R^{13}$, $S(O)NR^{13}R^{14}$, $S(O)_2R^{13}$, $NR^{13}S(O)_2R^{14}$, $S(O)_2NR^{13}R^{14}$ and oxo when R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is a substituted C_{6-10} aryl, a substituted C_{6-10} arylalkyl, a substituted C_{6-10} aryloxy, a substituted C_{6-10} arylalkoxy, a substituted 5-10 membered heteroaryl, a substituted C_{3-10} cycloalkyl, and a substituted 4-10 membered heterocyclyl,~~

~~wherein R^{13}, R^{14}, R^{15}, and R^{16} are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.~~

~~44. The compound of claim 39, wherein R^1 is an unsubstituted 4-10 membered heterocyclyl.~~

7~~45~~. The compound of ~~any one of~~ claim~~s~~ 1~~-5~~, wherein R^1 is substituted with one or more substituents selected from the group consisting of a substituted heteroaryl, $C(=NH)NHC(=O)OR^8$, $C(=NOC(=O)R^8)NH_2$, $C(=NOC(=O)OR^8)NH_2$, and $C(=NOH)NH_2$.

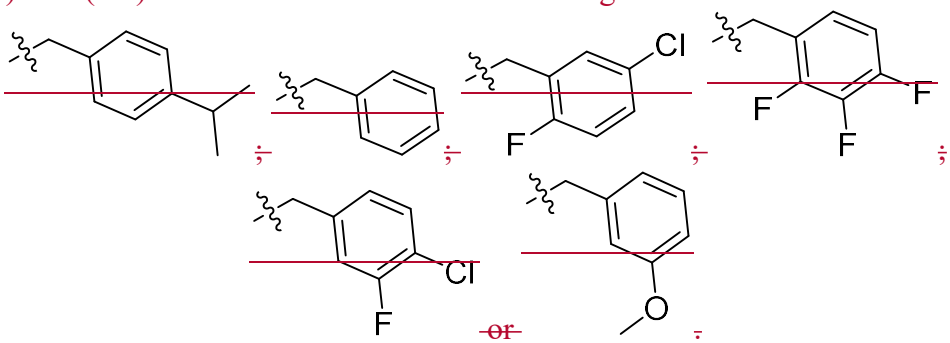
~~46. The compound of claim 45, wherein R^1 is substituted with a substituted heteroaryl having one of the following structures:~~



~~or~~ .

847. The compound of claim 745, wherein R^1 is substituted with $C(=NH)NHC(=O)OR^8$ and R^8 is a substituted or unsubstituted arylalkyl.

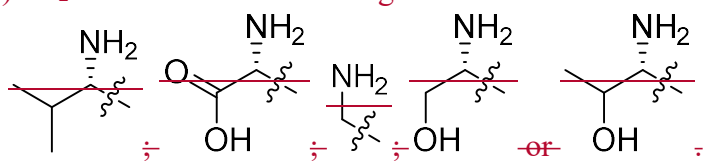
~~48. The compound of claim 45 or 47, wherein R^1 is substituted with $C(=NH)NHC(=O)OR^8$ and R^8 has one of the following structures:~~



~~or~~ .

949. The compound of claim 745, wherein R^1 is substituted with $C(=NOC(=O)R^8)NH_2$ and R^8 is an aminylalkyl.

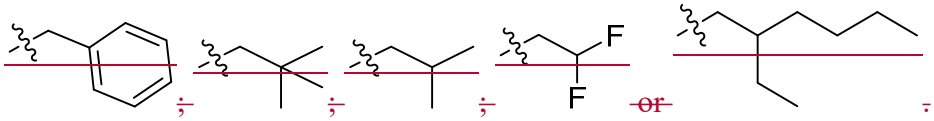
~~50. The compound of claim 45 or 49, wherein R^1 is substituted with $C(=NOC(=O)R^8)NH_2$ and R^8 has the following structure:~~



~~or~~ .

1051. The compound of claim 745, wherein R^1 is substituted with $C(=NOC(=O)OR^8)NH_2$ and R^8 is an alkyl, a haloalkyl, or a substituted or unsubstituted arylalkyl.

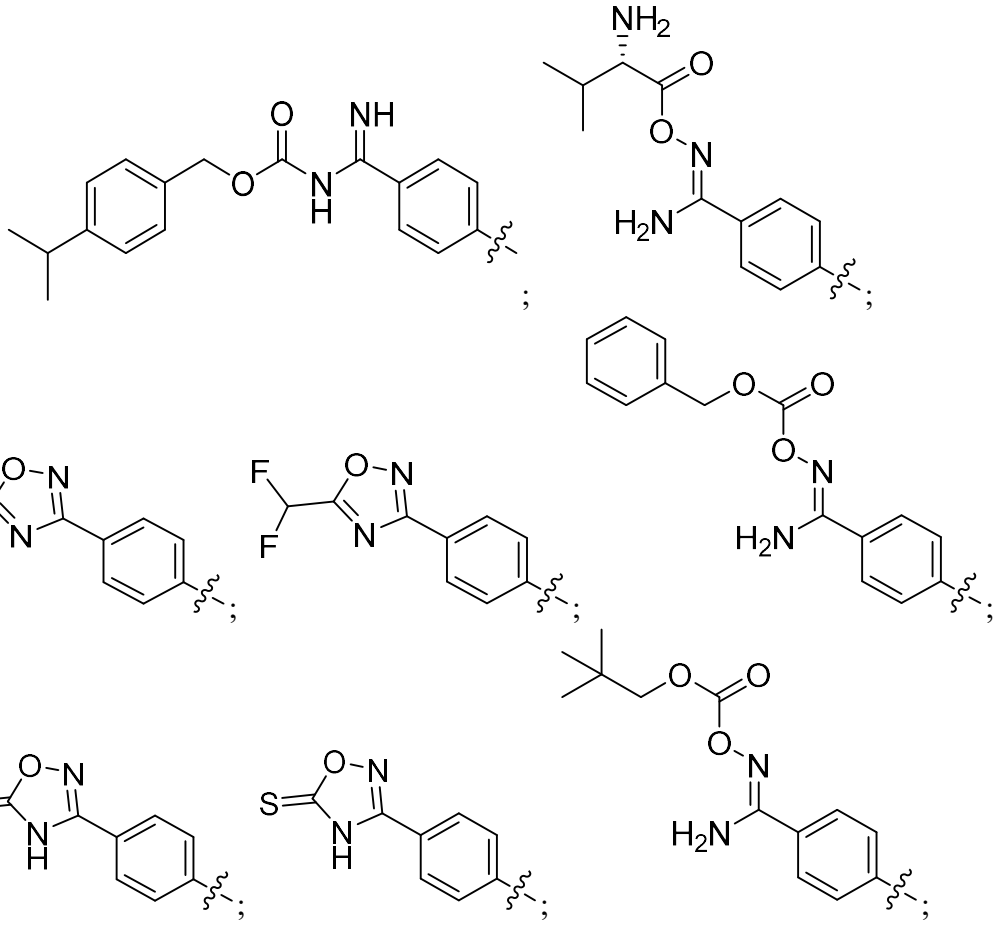
~~52. The compound of claim 45 or 51, wherein R^1 is substituted with $C(=NOC(=O)OR^8)NH_2$ and R^8 has one of the following structures:~~

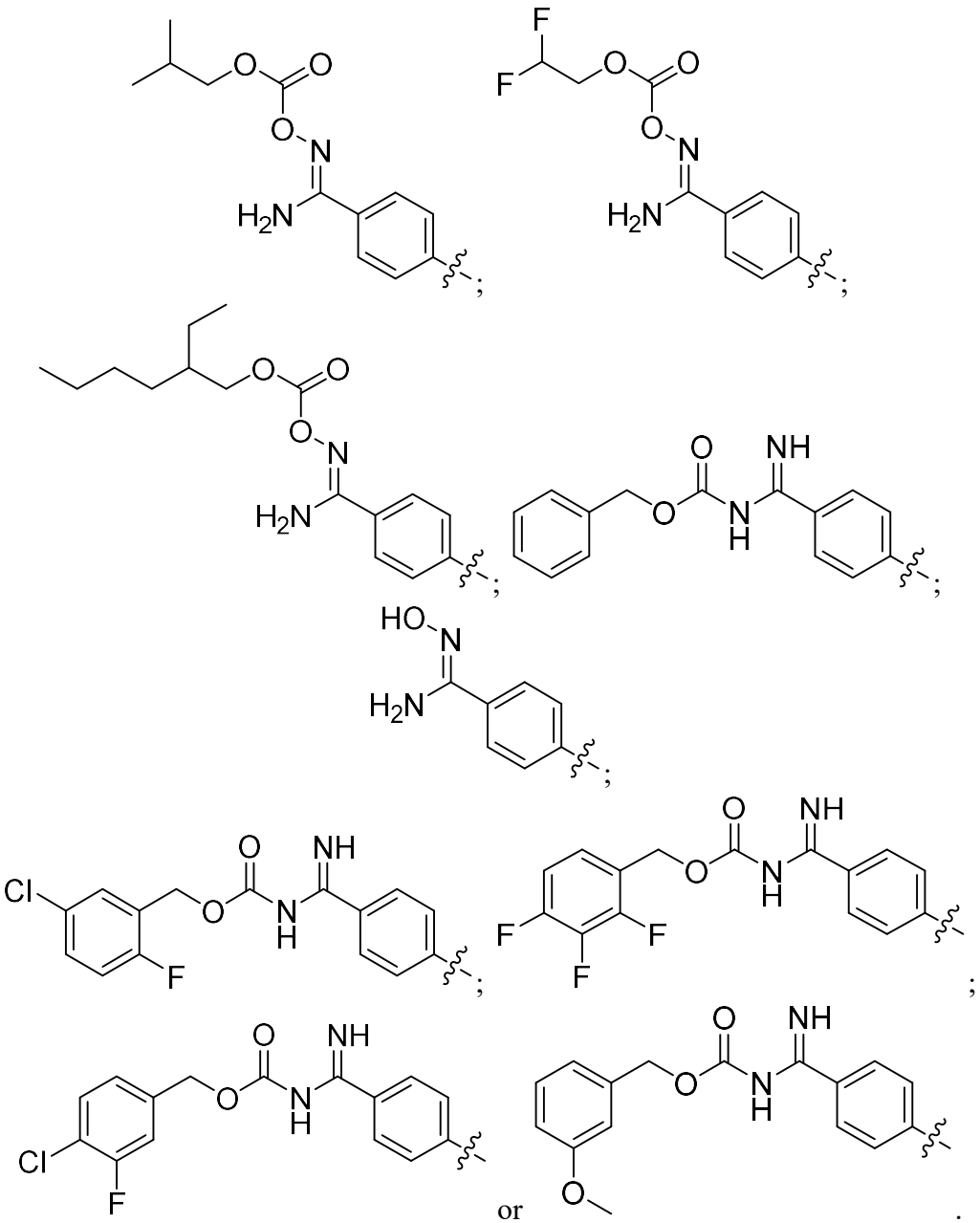


~~;~~

~~53. The compound of claim 45, wherein R^1 is substituted with $C(=NOH)NH_2$.~~

1154. The compound of ~~any one of~~ claim~~s 45-53~~7, wherein R^1 has one of the following structures:





or .

1255. The compound of ~~any one of~~ claim~~s~~ 1~~-54~~, wherein R^2 is hydrogen or C_1-C_6 alkyl.

~~56. The compound of any one of claims 1-55, wherein R^2 is C_1-C_6 alkyl.~~

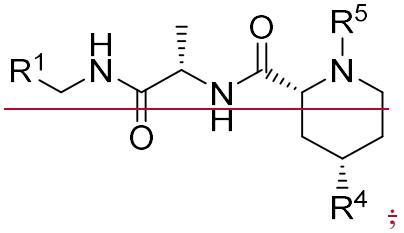
1357. The compound of ~~any one of~~ claim~~s~~ 1~~-56~~, wherein R^2 is -CH_3.

~~58. The compound of any one of claims 1-55, wherein R^2 and R^3, together with the carbon and nitrogen to which they are attached, respectively, form an optionally substituted 4-7 membered heterocyclyl.~~

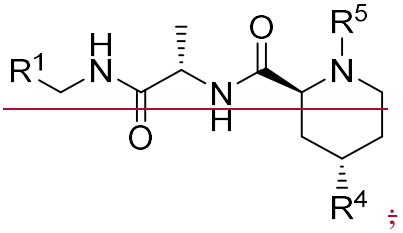
1~~4~~59. The compound of claim 1~~5~~58, wherein R^2 and R^3, together with the carbon and nitrogen to which they are attached, respectively, form an optionally substituted 4, 5, or 6 membered heterocyclyl.

~~60. The compound of claim 58, wherein R^2 and R^3, together with the carbon and nitrogen to which they are attached, respectively, form an optionally substituted 4-membered heterocyclyl.~~

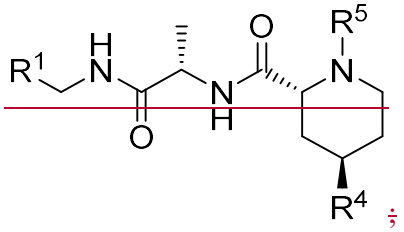
~~61. The compound of any one of claims 1-57, wherein the compound has one of the following Structures (IA1), (IB1), (IC1), (ID1), (IE1), (IF1), (IG1), or (IH1):~~



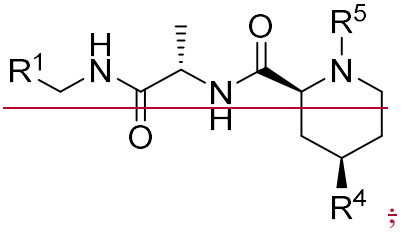
~~(IA1)~~;



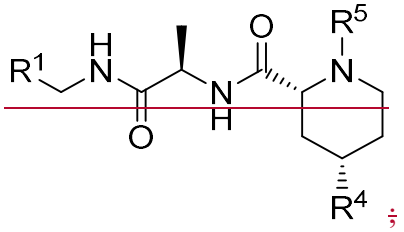
~~(IB1)~~;



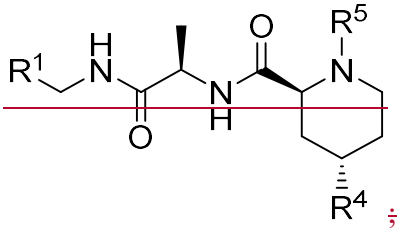
~~(IC1)~~;



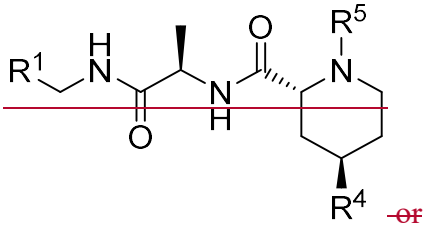
~~(ID1)~~;



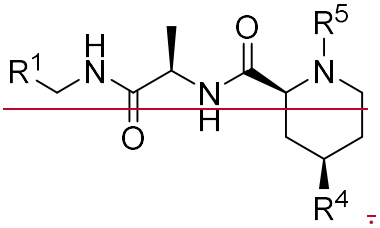
~~(IE1)~~;



~~(IF1)~~;

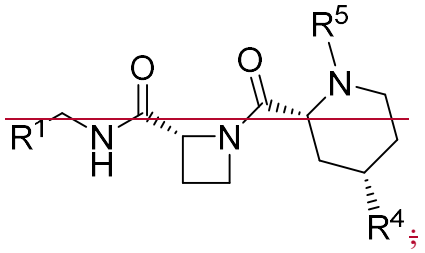


(IG1) or

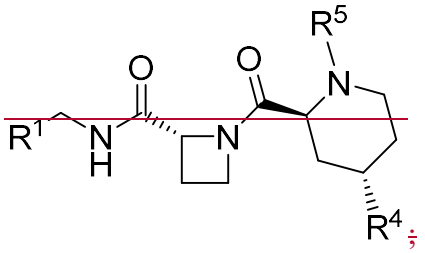


(IH1).

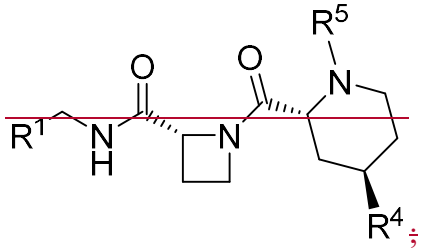
62. The compound of any one of claims 1-55 or 58-60, wherein the compound has one of the following Structures (IA2), (IB2), (IC2), (ID2), (IE2), (IF2), (IG2), or (IH2):



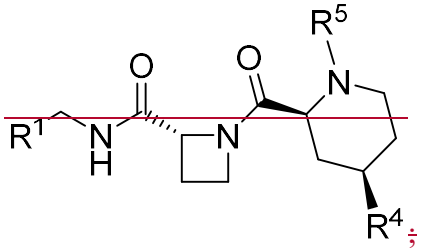
(IA2);



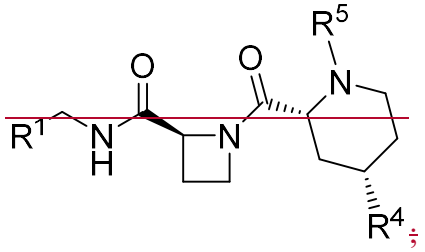
(IB2);



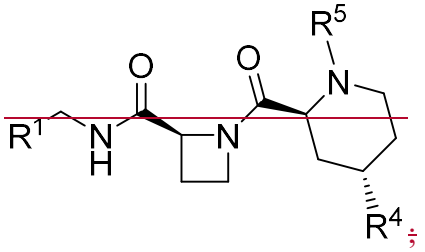
(IC2);



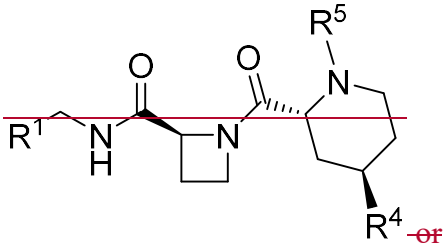
(ID2);



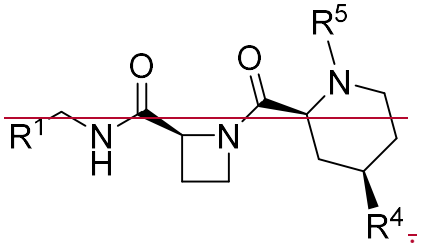
(IE2);



(IF2);



(IG2) or



(IH2).

1563. The compound of ~~any one of~~ claim~~s~~ 1~~-62~~, wherein R^4 is a substituted or unsubstituted aryl.

~~64. The compound of any one of claims 1-63, wherein R^4 is a substituted or unsubstituted C_6-C_{10} aryl.~~

~~65. The compound of any one of claims 1-64, wherein R^4 is a substituted or unsubstituted phenyl.~~

~~66. The compound of any one of claims 1-65, wherein R^4 is an unsubstituted phenyl.~~

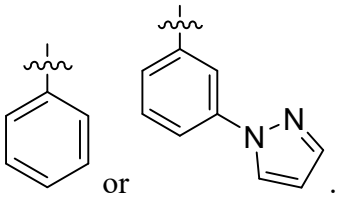
~~67. The compound of any one of claims 1-65, wherein R^4 is phenyl substituted with one or more of R^{4a}, R^{4b}, R^{4c}, R^{4d}, or R^{4e} wherein R^{4a}, R^{4b}, R^{4c}, R^{4d}, and R^{4e} are each independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, C_{1-6} haloalkyl, aminylalkyl, hydroxyalkyl, cyano, nitro, OR^{17}, SR^{17}, $C(O)R^{17}$, $C(O)NR^{17}R^{18}$, $C(O)OR^{17}$, $OC(O)R^{17}$, $OC(O)OR^{17}$, $OC(O)NR^{17}R^{18}$, $NR^{17}R^{18}$, $N(R^{17})C(O)R^{18}$, $N(R^{17})C(O)NR^{18}R^{19}$, $N(R^{17})C(O)OR^{18}$, $C(=NR^{17})NR^{18}R^{19}$, $C(=NOR^{17})NR^{18}R^{19}$, $C(=NOC(O)R^{17})NR^{18}R^{19}$, $C(=NR^{17})N(R^{18})C(O)OR^{19}$, $N(R^{17})C(=NR^{18})NR^{19}R^{20}$, $S(O)R^{17}$, $S(O)NR^{17}R^{18}$, $S(O)_2R^{17}$, $N(R^{17})S(O)_2R^{18}$, $S(O)_2NR^{17}R^{18}$, oxo, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted C_{6-10} arylalkyl, substituted or unsubstituted C_{6-10} aryloxy, substituted or unsubstituted C_{6-10} arylalkoxy, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted C_{3-10} cycloalkyl, and substituted or unsubstituted 4-10 membered heterocyclyl,~~

~~wherein R^{17}, R^{18}, R^{19}, and R^{20}, are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.~~

~~68. The compound of claim 67, wherein R^{4a}, R^{4b}, R^{4c}, R^{4d}, or R^{4e} is optionally substituted with one or more substituents selected from the group consisting of OR^{21}, SR^{21}, $C(O)R^{21}$, $C(O)NR^{21}R^{22}$, $C(O)OR^{21}$, $OC(O)R^{21}$, $OC(O)NR^{21}R^{22}$, $NR^{21}R^{22}$, $NR^{21}C(O)R^{22}$, $NR^{21}C(O)NR^{22}R^{23}$, $NR^{21}C(O)OR^{22}$, $C(=NR^{21})NR^{22}R^{23}$, $NR^{21}C(=NR^{22})NR^{23}R^{24}$, $S(O)R^{21}$, $S(O)NR^{21}R^{22}$, $S(O)_2R^{21}$, $NR^{21}S(O)_2R^{22}$, $S(O)_2NR^{21}R^{22}$ and oxo when R^{4a}, R^{4b}, R^{4c}, R^{4d}, or R^{4e} is a substituted C_{6-10} aryl, a substituted C_{6-10} arylalkyl, a substituted C_{6-10} aryloxy, a substituted C_{6-10} arylalkoxy, a substituted 5-10 membered heteroaryl, a substituted C_{3-10} cycloalkyl, and a substituted 4-10 membered heterocyclyl,~~

~~wherein R^{21}, R^{22}, R^{23}, and R^{24} are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.~~

16~~69~~. The compound of ~~any one of~~ claim~~s~~ 1~~-68~~, wherein R^4 has one of the following structures:



or .

17~~70~~. The compound of ~~any one of~~ claim~~s~~ 1~~-69~~, wherein R^{5a} is alkyl, $C(=O)OR^6$, phosphonalkyl, or $(CH_2)_nC(=O)OR^6$.

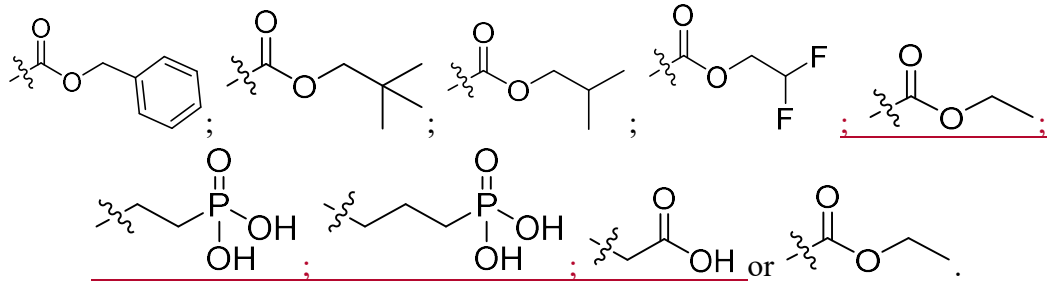
~~71. The compound of claim 70, wherein R^{5a} is alkyl.~~

~~72. The compound of claim 70 or 71, wherein R^{5a} is methyl.~~

~~73. The compound of claim 70 or 71, wherein R^{5a} is ethyl.~~

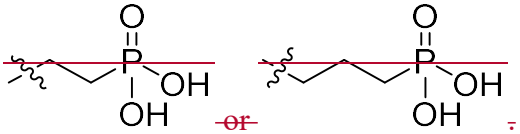
~~74. The compound of claim 70, wherein R^{5a} is $C(=O)OR^6$.~~

1875. The compound of claim ~~70 or 74~~17, wherein R^{5a} has one of the following structures:



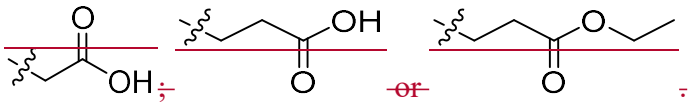
~~76. The compound of claim 70, wherein R^{5a} is phosphonalkyl.~~

~~77. The compound of claim 70 or 76, wherein R^{5a} has one of the following structures:~~



~~78. The compound of claim 70, wherein R^{5a} is $(CH_2)_nC(=O)OR^6$.~~

~~79. The compound of claim 70 or 78, wherein R^{5a} has one of the following structures:~~



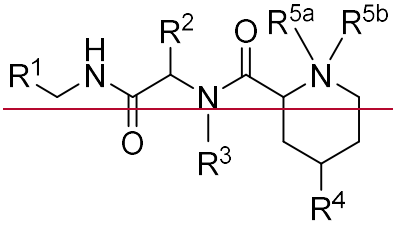
~~80. The compound of any one of claims 1-79, wherein R^{5b} is an electron pair.~~

1981. The compound of ~~any one of~~ claim~~s~~ 1~~-79~~, wherein R^{5b} is an electron pair or alkyl.

82. The compound of claim 81, wherein R^{5b} is a C_1-C_6 alkyl.

83. The compound of claim 82, wherein R^{5b} is methyl.

84. A compound having the following Structure (II):



(II)

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein:

R^1 is a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or a substituted or unsubstituted heterocyclyl;

R^2 is hydrogen, alkyl, alkoxy, haloalkyl, haloalkoxy, or cycloalkyl;

R^3 is hydrogen, alkyl, haloalkyl, or cycloalkyl;

or R^2 and R^3, together with the carbon and nitrogen to which they are attached, respectively, form an optionally substituted 4-7 membered heterocyclyl;

R^4 is a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or a substituted or unsubstituted heterocyclyl;

R^{5a} is hydrogen, alkyl, haloalkyl, cycloalkyl, phosphonalkyl, $(CH_2)_nC(=O)OR^6$, $C(=O)R^6$, $C(=O)OR^6$, or $C(=O)NR^6R^7$;

R^{5b} is an electron pair or alkyl;

R^6 and R^7 are, at each occurrence, independently hydrogen, alkyl, haloalkyl, cycloalkyl, or arylalkyl;

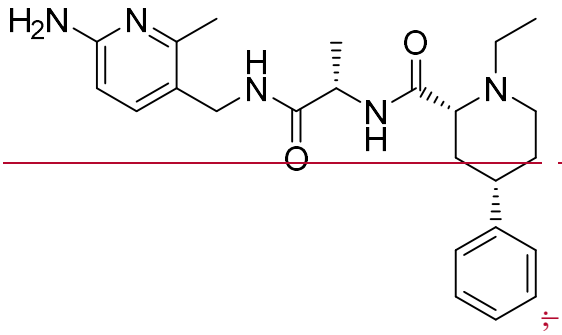
R^8 is alkyl, haloalkyl, aminylalkyl, substituted or unsubstituted arylalkyl; and

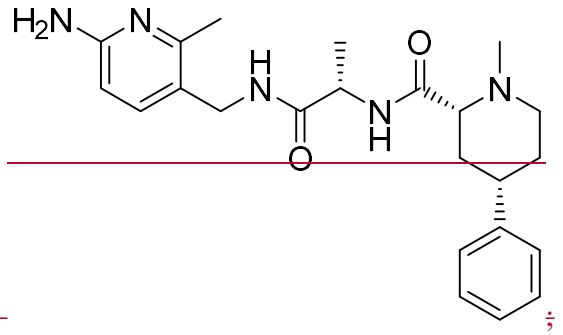
n is 1, 2, 3, 4, 5, 6, 7, or 8,

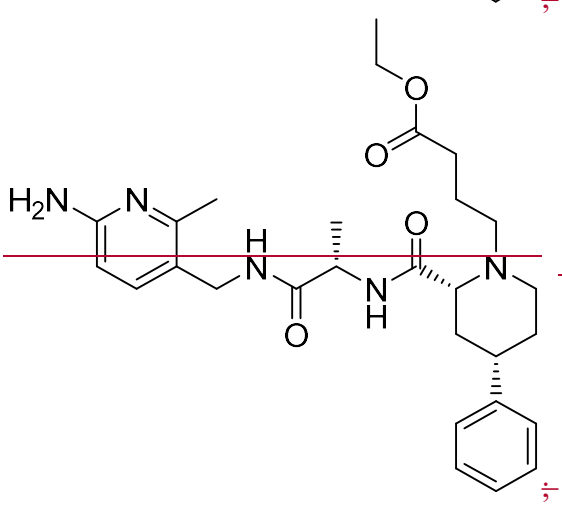
provided that

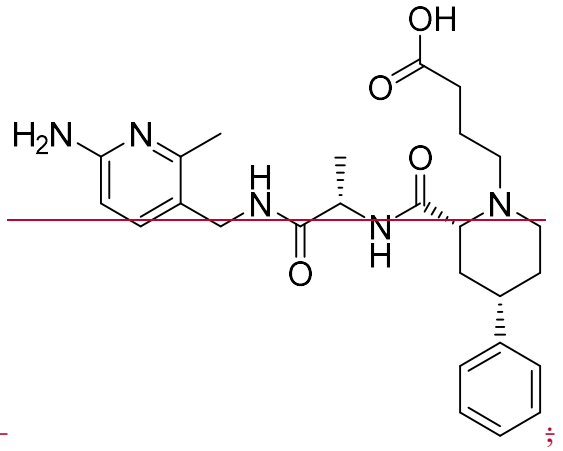
A) R^{5a} is alkyl, haloalkyl, cycloalkyl, phosphonalkyl, $(CH_2)_nC(=O)OR^6$, $C(=O)R^6$, $C(=O)OR^6$, or $C(=O)NR^6R^7$ or R^1 is substituted with one or more substituents selected from the group consisting of a substituted heteroaryl, $C(=NH)NHC(=O)OR^8$, $C(=NOC(=O)R^8)NH_2$, $C(=NOC(=O)OR^8)NH_2$, and $C(=NOH)NH_2$; and

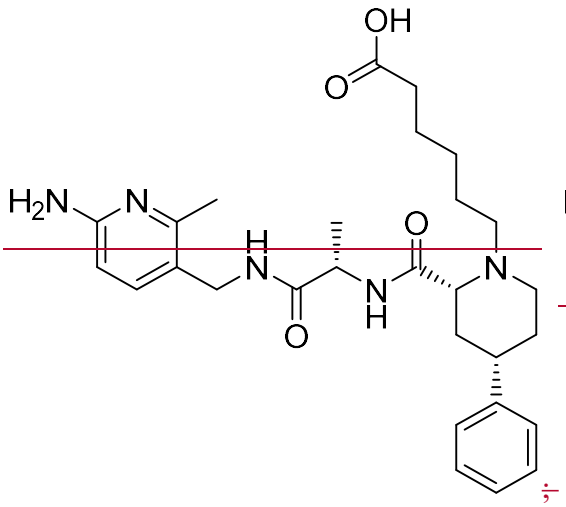
B) the compound of Structure (I) does not have one of the following structures:


;

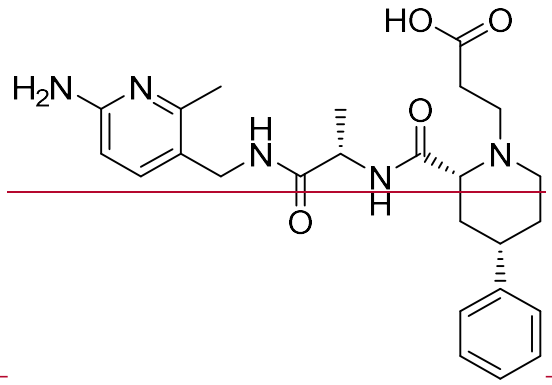

;

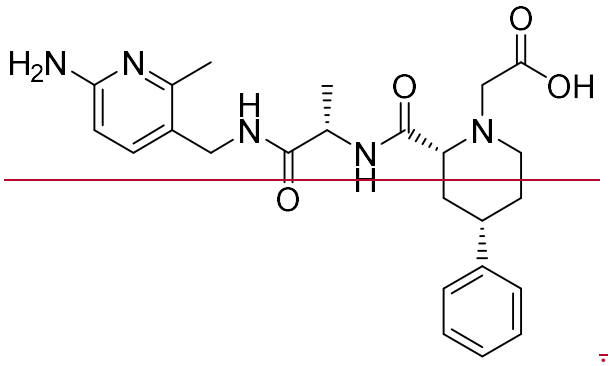

;


;



; or





.

85. The compound of claim 84, wherein R^1 is a substituted or unsubstituted aryl.

86. The compound of claim 84 or 85, wherein R^1 is a substituted or unsubstituted C_6-C_{10} aryl.

87. The compound of any one of claims 84-86, wherein R^1 is a substituted or unsubstituted phenyl.

88. The compound of any one of claims 84-87, wherein R^1 is a substituted phenyl.

89. The compound of any one of claims 84-88, wherein R^1 is phenyl substituted with one or more of R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently selected from the group consisting of $C(=NH)NHC(=O)OR^8$, $C(=NOC(=O)R^8)NH_2$, $C(=NOC(=O)OR^8)NH_2$, $C(=NOH)NH_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, C_{1-6} haloalkyl, aminylalkyl, hydroxyalkyl, cyano, nitro, OR^9, SR^9, $C(O)R^9$, $C(O)NR^9R^{10}$, $C(O)OR^9$, $OC(O)R^9$, $OC(O)OR^9$, $OC(O)NR^9R^{10}$, NR^9R^{10}, $N(R^9)C(O)R^{10}$, $N(R^9)C(O)NR^{10}R^{11}$, $N(R^9)C(O)OR^{10}$, $C(=NR^9)NR^{10}R^{11}$, $C(=NOR^9)NR^{10}R^{11}$, $C(=NOC(O)R^9)NR^{10}R^{11}$, $C(=NR^9)N(R^{10})C(O)OR^{11}$, $N(R^9)C(=NR^{10})NR^{11}R^{12}$, $S(O)R^9$, $S(O)NR^9R^{10}$, $S(O)_2R^9$, $N(R^9)S(O)_2R^{10}$, $S(O)_2NR^9R^{10}$, oxo, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted C_{6-10} arylalkyl, substituted or unsubstituted C_{6-10} aryloxy, substituted or unsubstituted C_{6-10} arylalkoxy, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted C_{3-10} cycloalkyl, and substituted or unsubstituted 4-10 membered heterocyclyl,

wherein R^9, R^{10}, R^{11}, and R^{12}, are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.

90. The compound of claim 89, wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is optionally substituted with one or more substituents selected from the group consisting of halo, CN, OR^{13}, SR^{13}, $C(O)R^{13}$, $C(O)NR^{13}R^{14}$, $C(O)OR^{13}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}C(O)OR^{14}$, $C(=NR^{13})NR^{14}R^{15}$, $NR^{13}C(=NR^{14})NR^{15}R^{16}$, $S(O)R^{13}$, $S(O)NR^{13}R^{14}$, $S(O)_2R^{13}$, $NR^{13}S(O)_2R^{14}$, $S(O)_2NR^{13}R^{14}$ and oxo when R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is a substituted C_{6-10} aryl, a substituted C_{6-10} arylalkyl, a substituted C_{6-10} aryloxy, a substituted C_{6-10} arylalkoxy, a substituted 5-10 membered heteroaryl, a substituted C_{3-10} cycloalkyl, and a substituted 4-10 membered heterocyclyl,

wherein R^{13}, R^{14}, R^{15}, and R^{16} are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl,

hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.

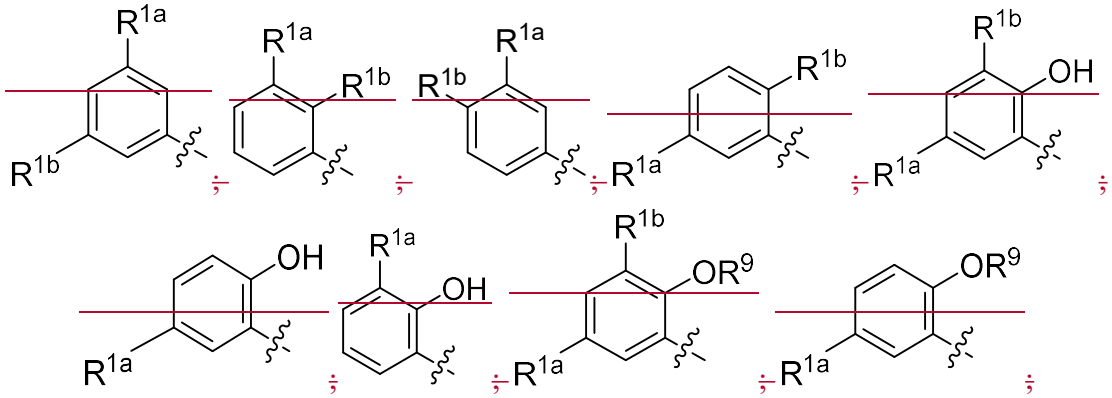
91. The compound of any one of claims 84-90, wherein R^1 is phenyl substituted with at least one substituent selected from the group consisting of OR^9, $C(=NR^9)NR^{10}R^{11}$, $C(=NOR^9)NR^{10}R^{11}$, $C(=NOC(O)R^9)NR^{10}R^{11}$, and $C(=NR^9)NR^{10}C(O)OR^{11}$.

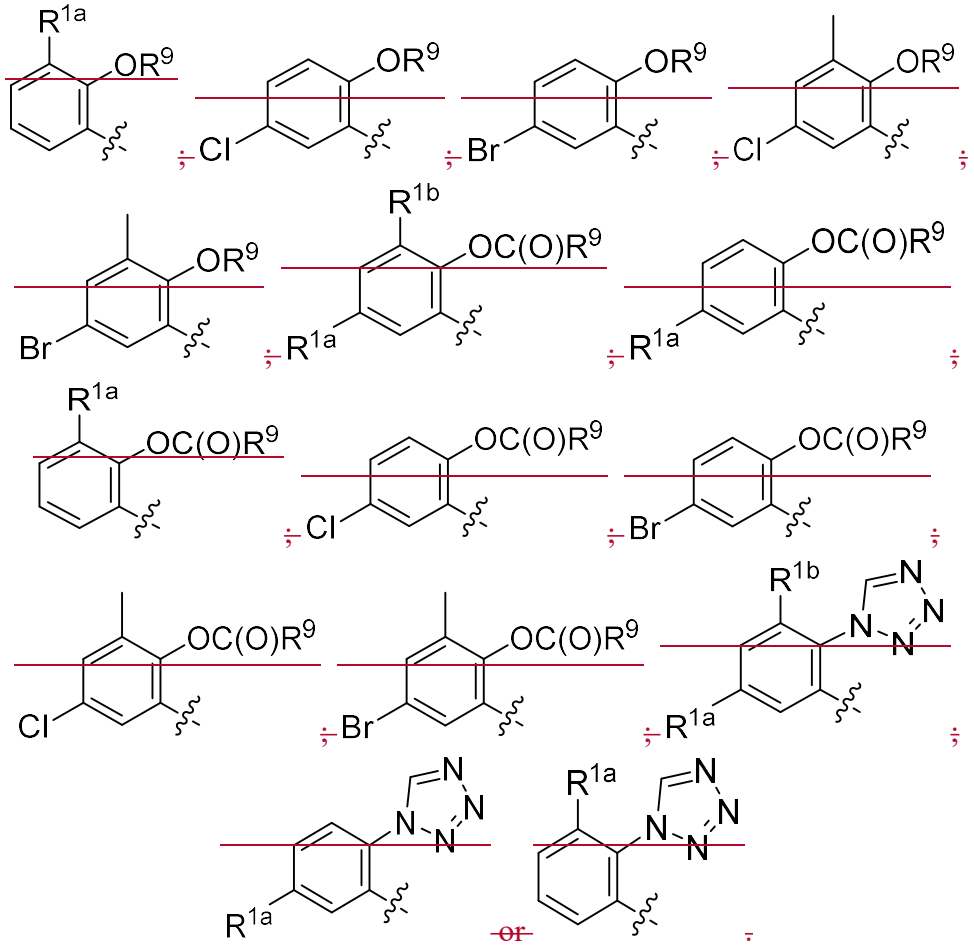
92. The compound of any one of claims 84-91, wherein R^1 is substituted with at least one substituent selected from the group consisting of $C(=NR^9)NR^{10}R^{11}$, $C(=NOR^9)NR^{10}R^{11}$, $C(=NOC(O)R^9)NR^{10}R^{11}$, and $C(=NR^9)NR^{10}C(O)OR^{11}$.

93. The compound of claim 92, wherein R^1 is substituted with at least one $C(=NR^9)NR^{10}R^{11}$.

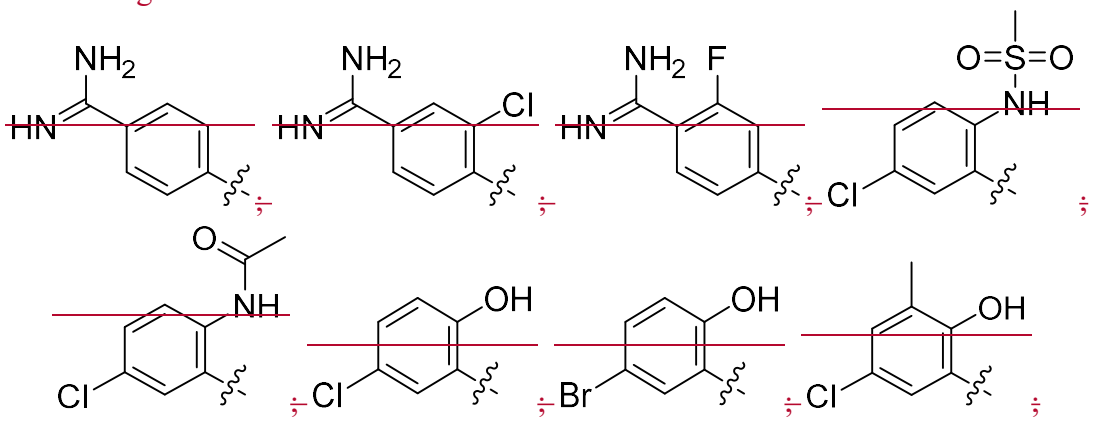
94. The compound of claim 92 or 93, wherein R^1 is substituted with at least one $-C(=NH)NH_2$.

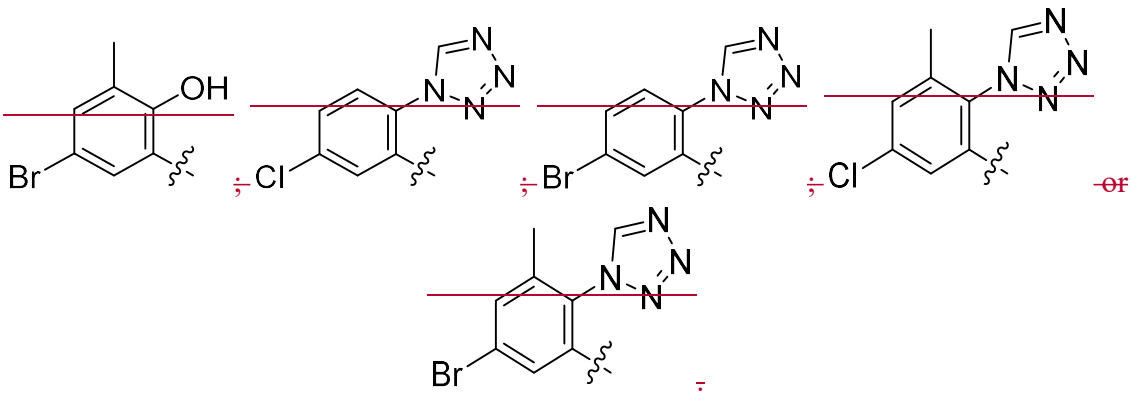
95. The compound of any one of claims 90-94, wherein R^1 has one of the following structures:



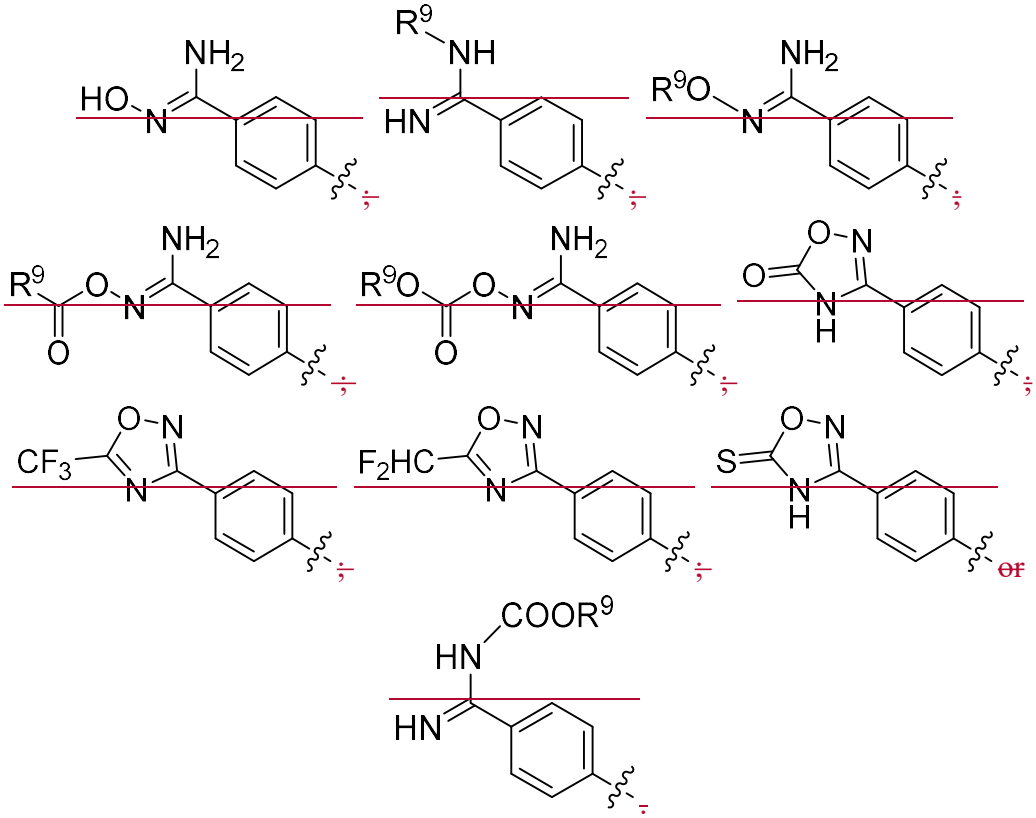


96. The compound of any one of claims 90-95, wherein R^1 has one of the following structures:





97. The compound of claim 90, wherein R^1 has one of the following structures:



98. The compound of claim 97, wherein R^9 is C_{1-6} alkyl or C_{1-6} haloalkyl.

99. The compound of claim 98, wherein R^9 is methyl.

100. The compound of claim 98, wherein R^9 is trifluoromethyl.

101. The compound of any one of claims 84-87, wherein R^1 is an unsubstituted phenyl.

102. The compound of claim 84, wherein R^1 is a substituted or unsubstituted heteroaryl.

103. The compound of claim 84 or 102, wherein R^1 is a substituted or unsubstituted 5-10 membered heteroaryl.

104. The compound of claim 84 or 102-103, wherein R^1 is a substituted or unsubstituted pyridinyl, pyrrolopyridinyl, thiophenyl, or benzoimidazolyl.

105. The compound of any one of claims 84 or 102-104, wherein R^1 is a substituted or unsubstituted pyridin-3-yl, 1H-pyrrolo[2,3-b]pyridine-5-yl, thiophen-2-yl, or 1H-benzo[d]imidazol-6-yl.

106. The compound of any one of claims 84 or 102-103, wherein R^1 is pyridin-3-yl, 1H-pyrrolo[2,3-b]pyridine-5-yl, thiophen-2-yl, or 1H-benzo[d]imidazol-6-yl substituted with one or more of R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently selected from the group consisting of $C(=NH)NHC(=O)OR^8$, $C(=NOC(=O)R^8)NH_2$, $C(=NOC(=O)OR^8)NH_2$, $C(=NOH)NH_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, C_{1-6} haloalkyl, aminylalkyl, hydroxyalkyl, cyano, nitro, OR^9, SR^9, $C(O)R^9$, $C(O)NR^9R^{10}$, $C(O)OR^9$, $OC(O)R^9$, $OC(O)OR^9$, $OC(O)NR^9R^{10}$, NR^9R^{10}, $N(R^9)C(O)R^{10}$, $N(R^9)C(O)NR^{10}R^{11}$, $N(R^9)C(O)OR^{10}$, $C(=NR^9)NR^{10}R^{11}$, $C(=NOR^9)NR^{10}R^{11}$, $C(=NOC(O)R^9)NR^{10}R^{11}$, $C(=NR^9)N(R^{10})C(O)OR^{11}$, $N(R^9)C(=NR^{10})NR^{11}R^{12}$, $S(O)R^9$, $S(O)NR^9R^{10}$, $S(O)_2R^9$, $N(R^9)S(O)_2R^{10}$, $S(O)_2NR^9R^{10}$, oxo, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted C_{6-10} arylalkyl, substituted or unsubstituted C_{6-10} aryloxy, substituted or

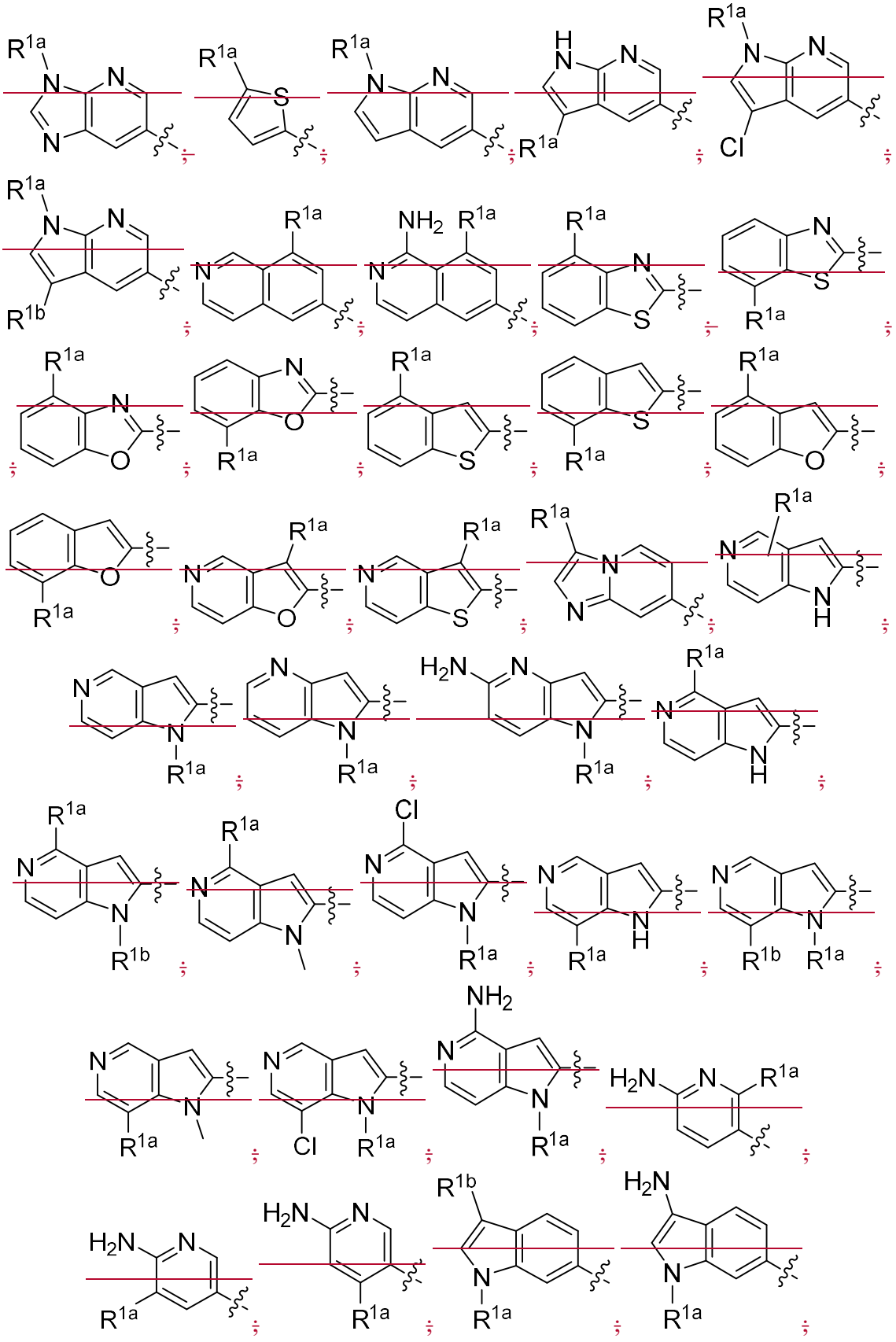
~~unsubstituted C_{6-10} arylalkoxy, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted C_{3-10} cycloalkyl, and substituted or unsubstituted 4-10 membered heterocyclyl,~~

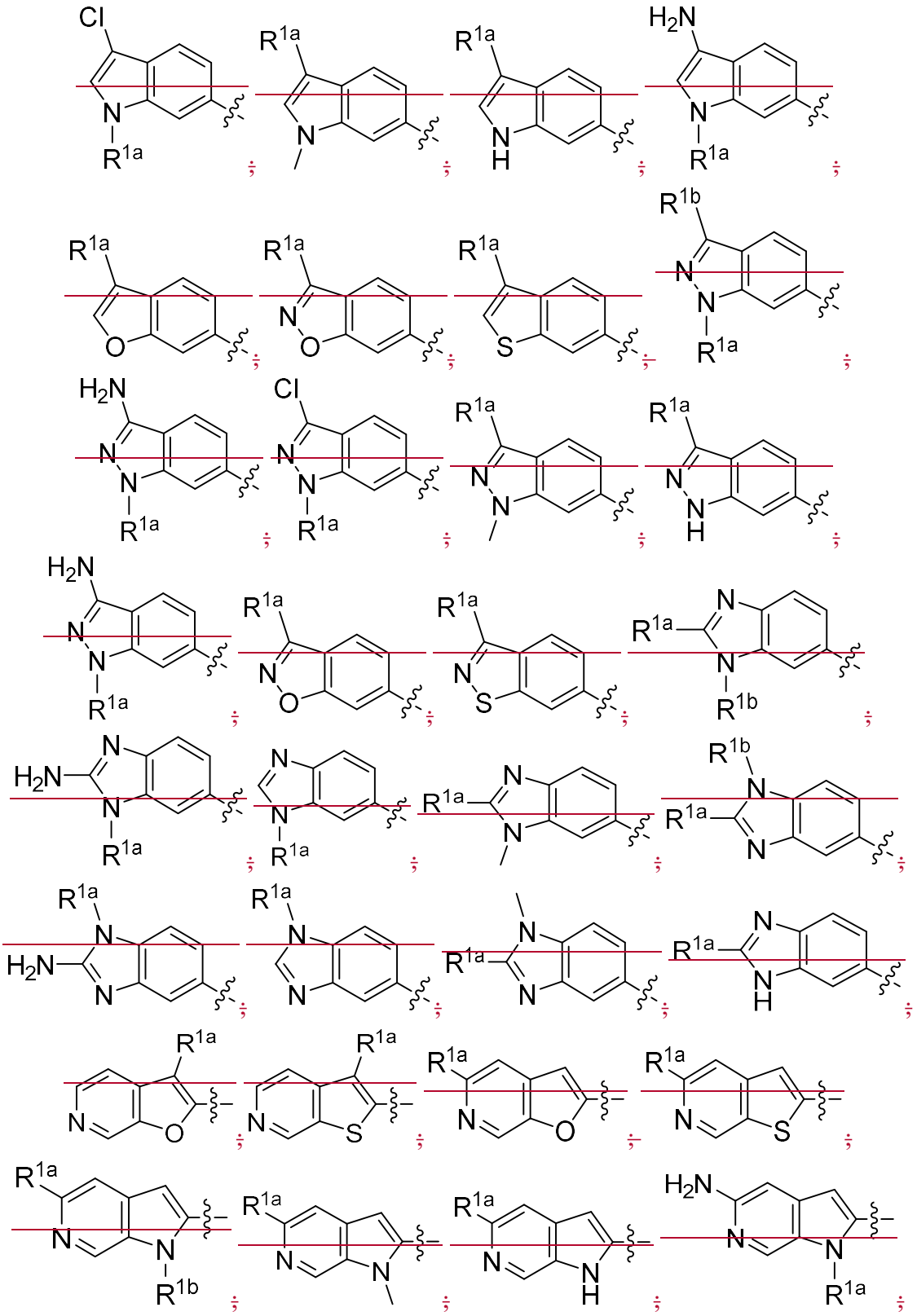
~~wherein R^9, R^{10}, R^{11}, and R^{12}, are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.~~

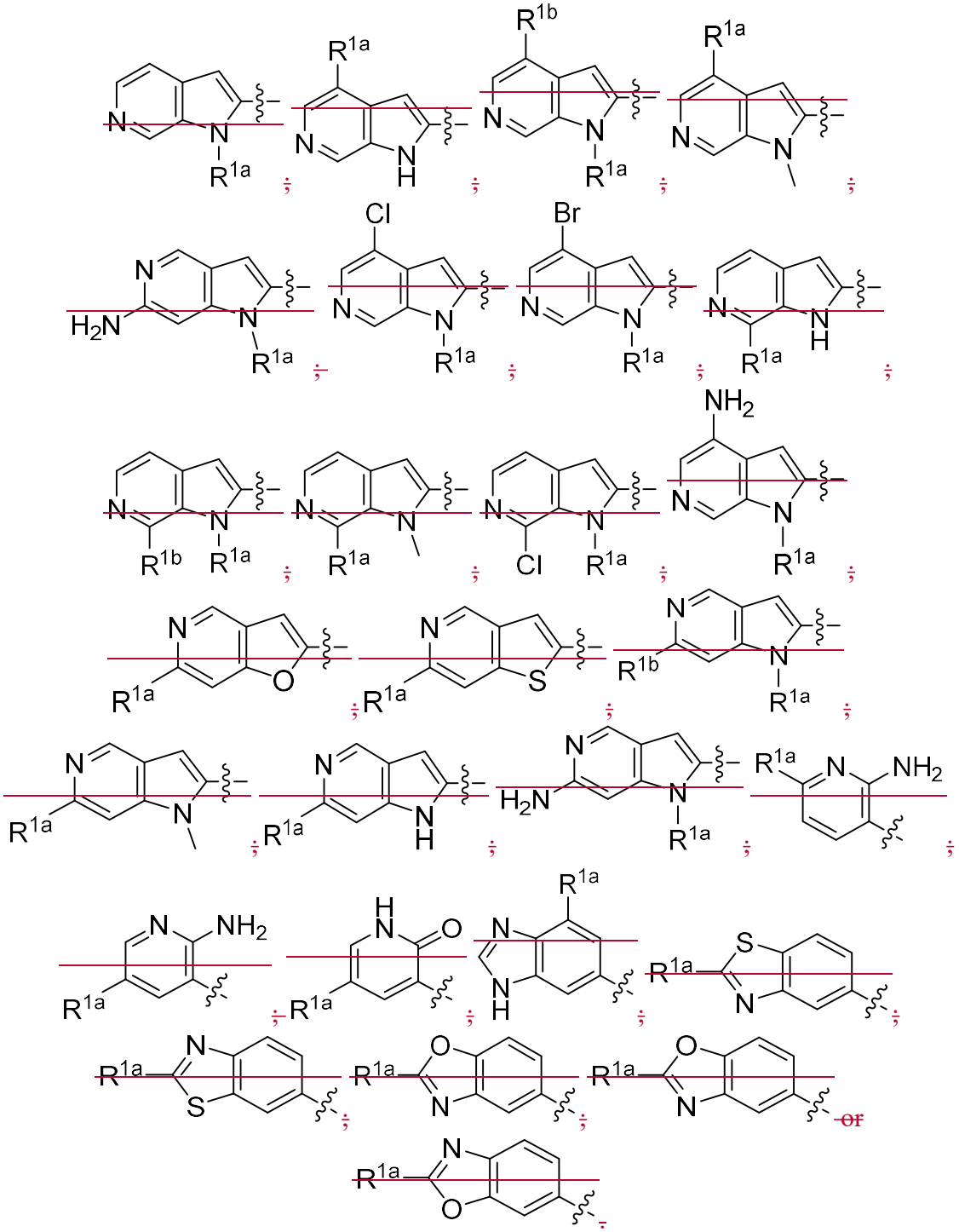
~~107. The compound of claim 106, wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is optionally substituted with one or more substituents selected from the group consisting of halo, CN, OR^{13}, SR^{13}, $C(O)R^{13}$, $C(O)NR^{13}R^{14}$, $C(O)OR^{13}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}C(O)OR^{14}$, $C(=NR^{13})NR^{14}R^{15}$, $NR^{13}C(=NR^{14})NR^{15}R^{16}$, $S(O)R^{13}$, $S(O)NR^{13}R^{14}$, $S(O)_2R^{13}$, $NR^{13}S(O)_2R^{14}$, $S(O)_2NR^{13}R^{14}$ and oxo when R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is a substituted C_{6-10} aryl, a substituted C_{6-10} arylalkyl, a substituted C_{6-10} aryloxy, a substituted C_{6-10} arylalkoxy, a substituted 5-10 membered heteroaryl, a substituted C_{3-10} cycloalkyl, and a substituted 4-10 membered heterocyclyl,~~

~~wherein R^{13}, R^{14}, R^{15}, and R^{16} are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.~~

~~108. The compound of any one of claims 84 or 102-106, wherein R^1 has one of the following structures:~~







~~109. The compound of claim 108, wherein R^{1a} or R^{1b} is independently C_{1-6} alkyl, amino, or halo.~~

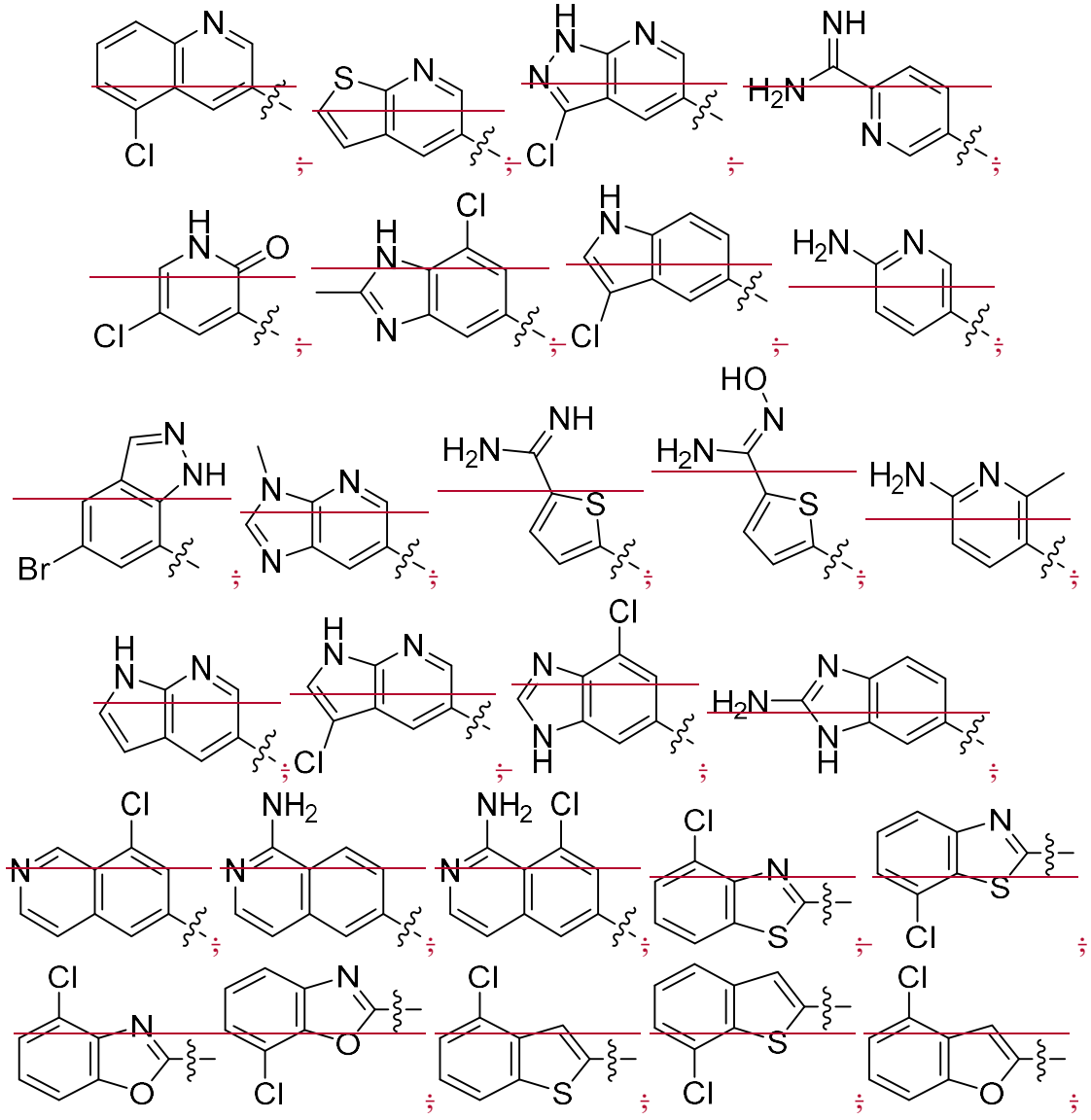
~~110. The compound of claim 109, wherein R^{1a} or R^{1b} is methyl or ethyl.~~

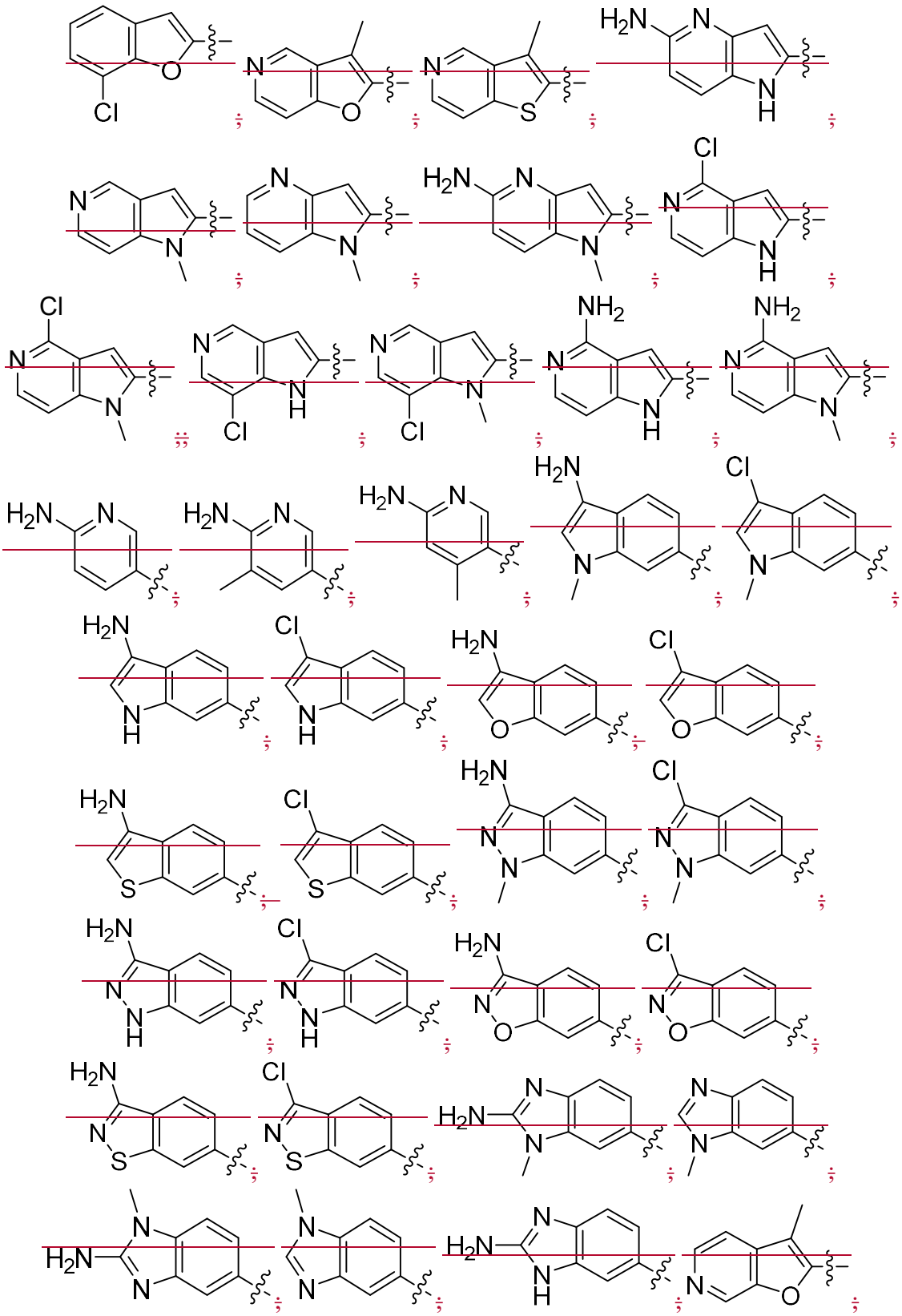
~~111. The compound of claim 109, wherein R^{1a} or R^{1b} is F, Cl, or Br.~~

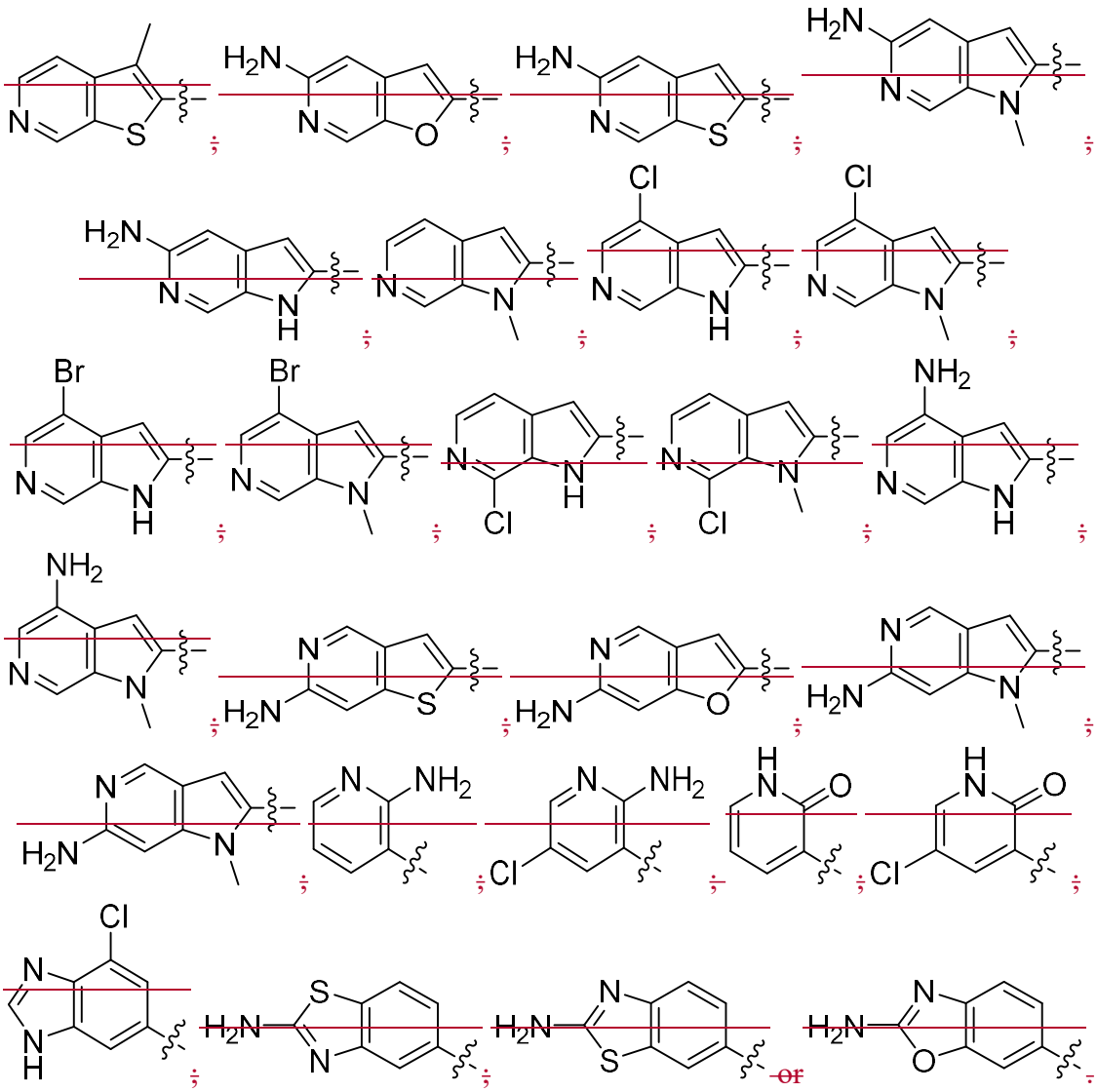
~~112. The compound of claim 108, wherein each R^{1a} or R^{1b} attached to nitrogen is C_{1-6} alkyl.~~

~~113. The compound of claim 112, wherein R^{1a} or R^{1b} is methyl or ethyl.~~

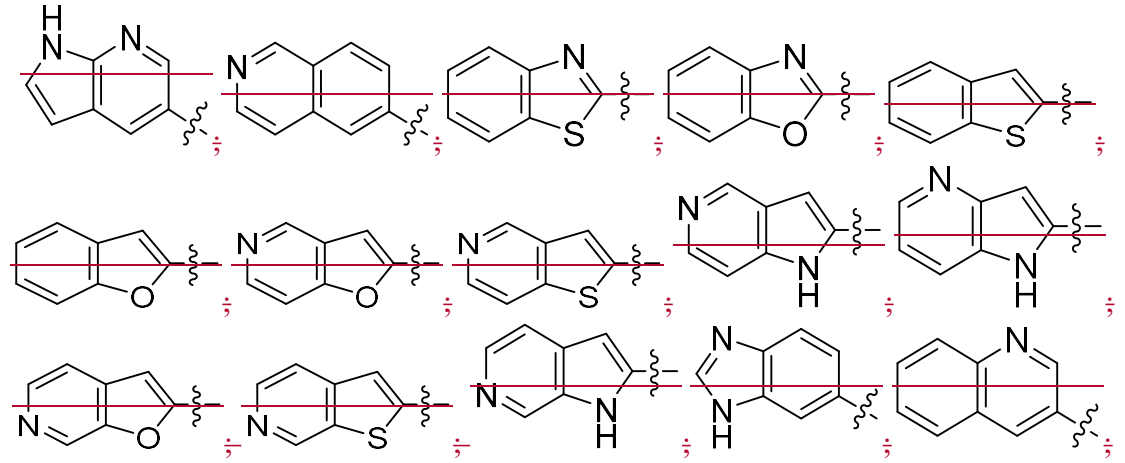
~~114. The compound of any one of claims 84 or 102-103, wherein R^1 has one of the following structures:~~

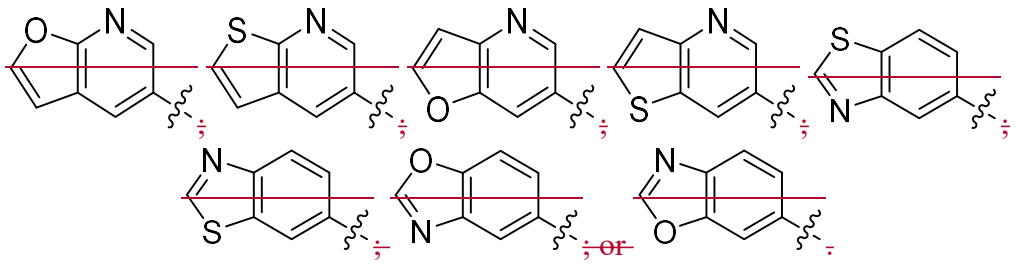






115. The compound of any one of claims 84 or 102-103, wherein R^1 has one of the following structures:





; or

116. The compound of claim 84, wherein R^1 is a substituted or unsubstituted cycloalkyl.

117. The compound of claim 84 or 116, wherein R^1 is a substituted or unsubstituted C_3-C_6 cycloalkyl.

118. The compound of any one of claims 84 or 116-117, wherein R^1 is a substituted C_3-C_6 cycloalkyl.

119. The compound of claim 118, wherein R^1 is a C_3-C_6 cycloalkyl substituted with one or more of R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently selected from the group consisting of $C(=NH)NHC(=O)OR^8$, $C(=NOC(=O)R^8)NH_2$, $C(=NOC(=O)OR^8)NH_2$, $C(=NOH)NH_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, aminylalkyl, hydroxyalkyl, nitro, OR^9, SR^9, $C(O)R^9$, $C(O)NR^9R^{10}$, $C(O)OR^9$, $OC(O)R^9$, $OC(O)OR^9$, $OC(O)NR^9R^{10}$, NR^9R^{10}, $N(R^9)C(O)R^{10}$, $N(R^9)C(O)NR^{10}R^{11}$, $N(R^9)C(O)OR^{10}$, $C(=NR^9)NR^{10}R^{11}$, $C(=NOR^9)NR^{10}R^{11}$, $C(=NOC(O)R^9)NR^{10}R^{11}$, $C(=NR^9)N(R^{10})C(O)OR^{11}$, $N(R^9)C(=NR^{10})NR^{11}R^{12}$, $S(O)R^9$, $S(O)NR^9R^{10}$, $S(O)_2R^9$, $N(R^9)S(O)_2R^{10}$, $S(O)_2NR^9R^{10}$, oxo, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted C_{6-10} arylalkyl, substituted or unsubstituted C_{6-10} aryloxy, substituted or unsubstituted C_{6-10} arylalkoxy, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted C_{3-10} cycloalkyl, and substituted or unsubstituted 4-10 membered heterocyclyl,

wherein R^9, R^{10}, R^{11}, and R^{12}, are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl,

hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.

120. The compound of claim 119, wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is optionally substituted with one or more substituents selected from the group consisting of halo, CN, OR^{13}, SR^{13}, $C(O)R^{13}$, $C(O)NR^{13}R^{14}$, $C(O)OR^{13}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}C(O)OR^{14}$, $C(=NR^{13})NR^{14}R^{15}$, $NR^{13}C(=NR^{14})NR^{15}R^{16}$, $S(O)R^{13}$, $S(O)NR^{13}R^{14}$, $S(O)_2R^{13}$, $NR^{13}S(O)_2R^{14}$, $S(O)_2NR^{13}R^{14}$ and oxo when R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is a substituted C_{6-10} aryl, a substituted C_{6-10} arylalkyl, a substituted C_{6-10} aryloxy, a substituted C_{6-10} arylalkoxy, a substituted 5-10 membered heteroaryl, a substituted C_{3-10} cycloalkyl, and a substituted 4-10 membered heterocyclyl,

wherein R^{13}, R^{14}, R^{15}, and R^{16} are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.

121. The compound of claim 117, wherein R^1 is an unsubstituted a C_3-C_6 cycloalkyl.

122. The compound of claim 84, wherein R^1 is a substituted or unsubstituted heterocyclyl.

123. The compound of claim 84 or 122, wherein R^1 is a substituted or unsubstituted 4-10 membered heterocyclyl.

124. The compound of any one of claims 84 or 122-123, wherein R^1 is a substituted 4-10 membered heterocyclyl.

125. The compound of claim 124, wherein R^1 is a 4-10 membered heterocyclyl substituted with one or more of R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently selected from the group consisting of $C(=NH)NHC(=O)OR^8$, $C(=NOC(=O)R^8)NH_2$, $C(=NOC(=O)OR^8)NH_2$, $C(=NOH)NH_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, C_{1-6} haloalkyl, aminylalkyl, hydroxyalkyl, cyano, nitro, OR^9, SR^9, $C(O)R^9$, $C(O)NR^9R^{10}$, $C(O)OR^9$, $OC(O)R^9$, $OC(O)OR^9$, $OC(O)NR^9R^{10}$, NR^9R^{10}, $N(R^9)C(O)R^{10}$, $N(R^9)C(O)NR^{10}R^{11}$, $N(R^9)C(O)OR^{10}$, $C(=NR^9)NR^{10}R^{11}$, $C(=NOR^9)NR^{10}R^{11}$, $C(=NOC(O)R^9)NR^{10}R^{11}$, $C(=NR^9)N(R^{10})C(O)OR^{11}$, $N(R^9)C(=NR^{10})NR^{11}R^{12}$, $S(O)R^9$, $S(O)NR^9R^{10}$, $S(O)_2R^9$, $N(R^9)S(O)_2R^{10}$, $S(O)_2NR^9R^{10}$, oxo, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted C_{6-10} arylalkyl, substituted or unsubstituted C_{6-10} aryloxy, substituted or unsubstituted C_{6-10} arylalkoxy, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted C_{3-10} cycloalkyl, and substituted or unsubstituted 4-10 membered heterocyclyl,

wherein R^9, R^{10}, R^{11}, and R^{12}, are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.

126. The compound of claim 125, wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is optionally substituted with one or more substituents selected from the group consisting of OR^{13}, SR^{13}, $C(O)R^{13}$, $C(O)NR^{13}R^{14}$, $C(O)OR^{13}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}C(O)OR^{14}$, $C(=NR^{13})NR^{14}R^{15}$, $NR^{13}C(=NR^{14})NR^{15}R^{16}$, $S(O)R^{13}$, $S(O)NR^{13}R^{14}$, $S(O)_2R^{13}$, $NR^{13}S(O)_2R^{14}$, $S(O)_2NR^{13}R^{14}$ and oxo when R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is a substituted C_{6-10} aryl, a substituted C_{6-10} arylalkyl, a substituted C_{6-10} aryloxy, a substituted C_{6-10} arylalkoxy, a substituted 5-10 membered heteroaryl, a substituted C_{3-10} cycloalkyl, and a substituted 4-10 membered heterocyclyl,

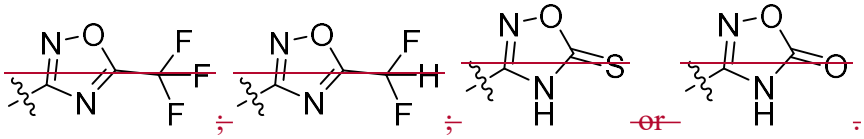
wherein R^{13}, R^{14}, R^{15}, and R^{16} are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl,

hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.

127. The compound of claim 122, wherein R^1 is an unsubstituted 4-10 membered heterocyclyl.

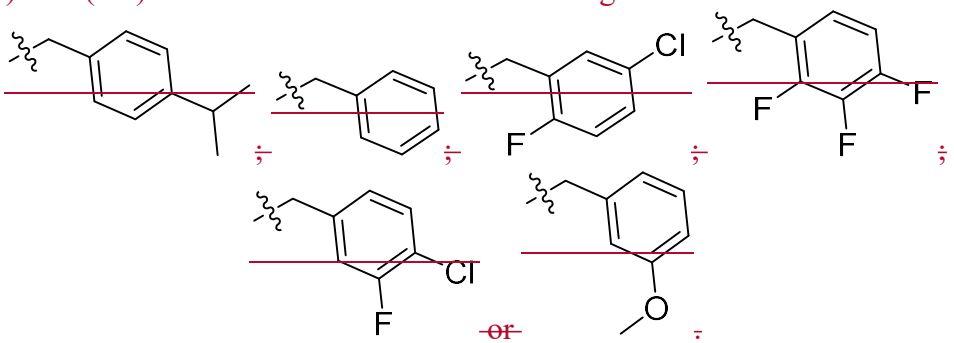
128. The compound of any one of claims 84-88, wherein R^1 is substituted with one or more substituents selected from the group consisting of a substituted heteroaryl, $C(=NH)NHC(=O)OR^8$, $C(=NOC(=O)R^8)NH_2$, $C(=NOC(=O)OR^8)NH_2$, and $C(=NOH)NH_2$.

129. The compound of claim 128, wherein R^1 is substituted with a substituted heteroaryl having one of the following structures:


; or .

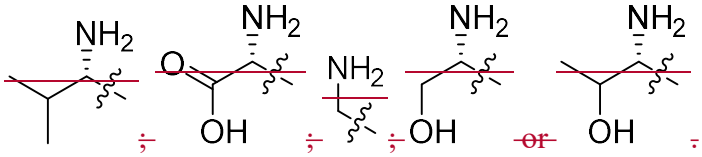
130. The compound of claim 128, wherein R^1 is substituted with $C(=NH)NHC(=O)OR^8$ and R^8 is a substituted or unsubstituted arylalkyl.

131. The compound of claim 128 or 130, wherein R^1 is substituted with $C(=NH)NHC(=O)OR^8$ and R^8 has one of the following structures:


; or .

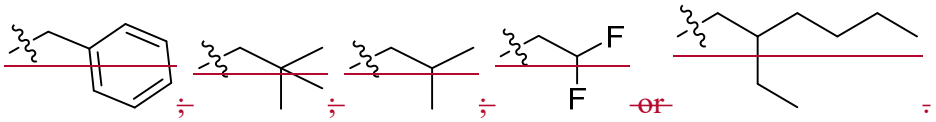
~~132. The compound of claim 128, wherein R^1 is substituted with $C(=NOC(=O)R^8)NH_2$ and R^8 is an aminylalkyl.~~

~~133. The compound of claim 128 or 132, wherein R^1 is substituted with $C(=NOC(=O)R^8)NH_2$ and R^8 has the following structure:~~



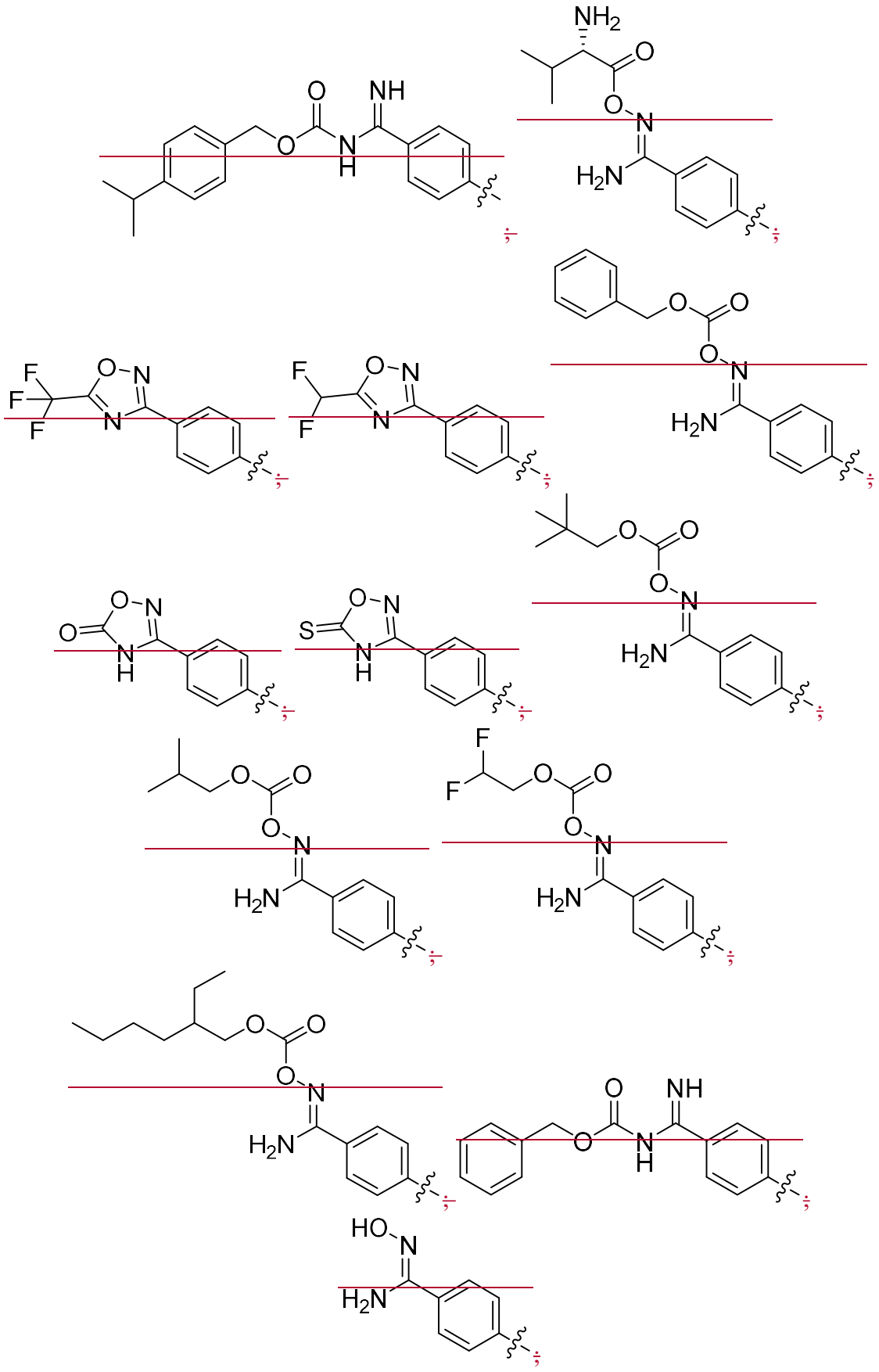
~~134. The compound of claim 128, wherein R^1 is substituted with $C(=NOC(=O)OR^8)NH_2$ and R^8 is an alkyl, a haloalkyl, or a substituted or unsubstituted arylalkyl.~~

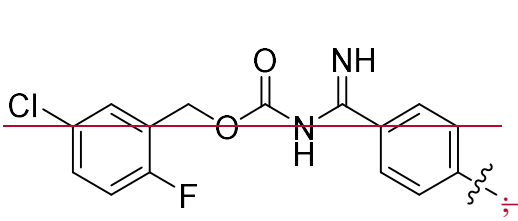
~~135. The compound of claim 128 or 134, wherein R^1 is substituted with $C(=NOC(=O)OR^8)NH_2$ and R^8 has one of the following structures:~~



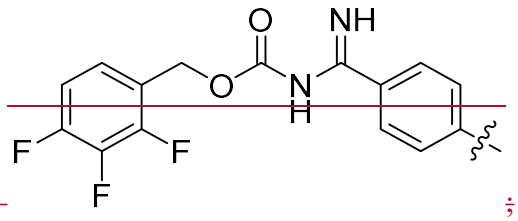
~~136. The compound of claim 128, wherein R^1 is substituted with $C(=NOH)NH_2$.~~

~~137. The compound of any one of claims 128-136, wherein R^1 has one of the following structures:~~

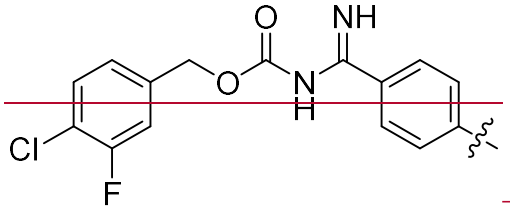




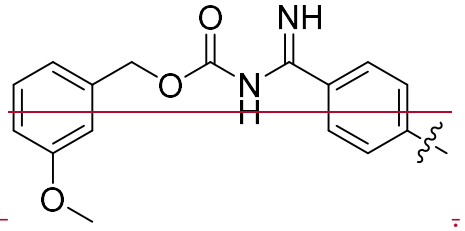
;



;



or



.

138. The compound of any one of claims 84-137, wherein R^2 is hydrogen or C_1-C_6 alkyl.

139. The compound of any one of claims 84-138, wherein R^2 is C_1-C_6 alkyl.

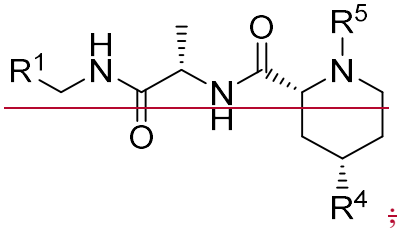
140. The compound of any one of claims 84-139, wherein R^2 is $-CH_3$.

141. The compound of any one of claims 84-138, wherein R^2 and R^3, together with the carbon and nitrogen to which they are attached, respectively, form an optionally substituted 4-7 membered heterocyclyl.

142. The compound of claim 141, wherein R^2 and R^3, together with the carbon and nitrogen to which they are attached, respectively, form an optionally substituted 4, 5, or 6 membered heterocyclyl.

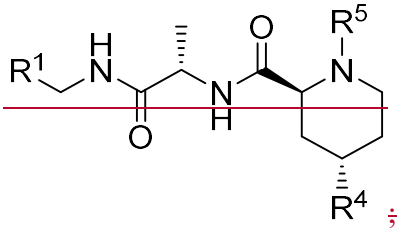
143. The compound of claim 141, wherein R^2 and R^3, together with the carbon and nitrogen to which they are attached, respectively, form an optionally substituted 4 membered heterocyclyl.

~~144. The compound of any one of claims 84-140, wherein the compound has one of the following Structures (IIA1), (IIB1), (IIC1), (IID1), (IIE1), (IIF1), (IIG1), or (IIH1):~~



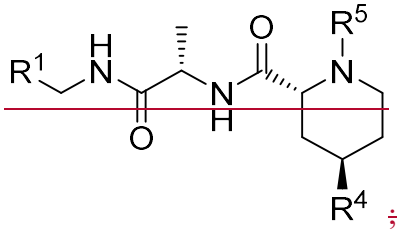
;

~~(IIA1)~~



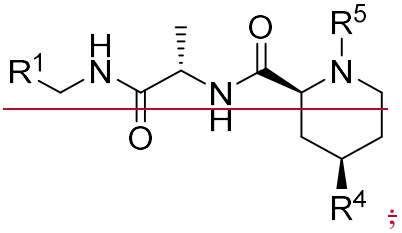
;

~~(IIB1)~~



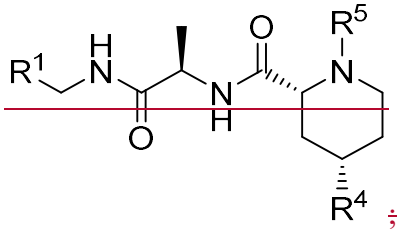
;

~~(IIC1)~~



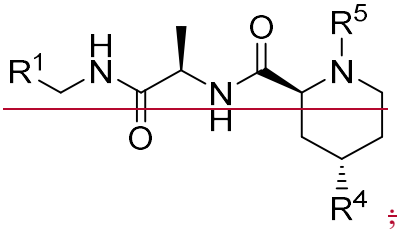
;

~~(IID1)~~



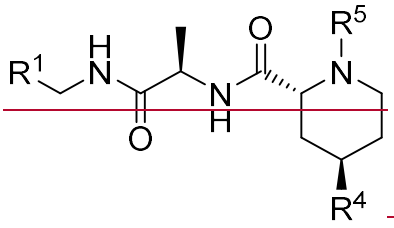
;

~~(IIE1)~~



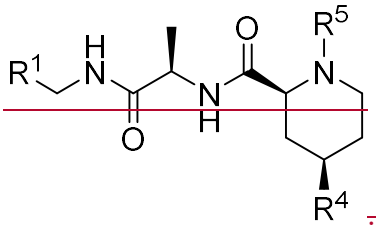
;

~~(IIF1)~~



~~or~~

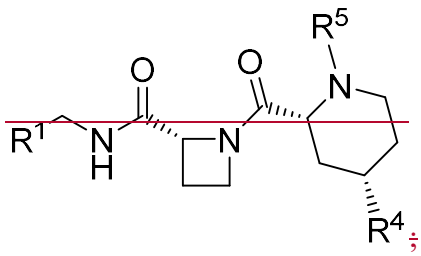
~~(IIG1)~~



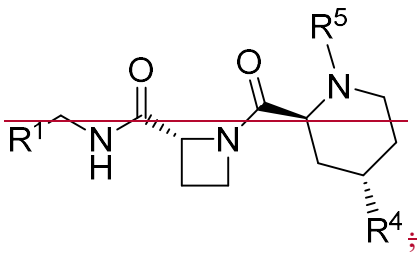
.

~~(IIH1)~~

~~145. The compound of any one of claims 84-138 or 141-143, wherein the compound has one of the following Structures (IIA2), (IIB2), (IIC2), (IID2), (IIE2), (IIF2), (IIG2), or (IIH2):~~

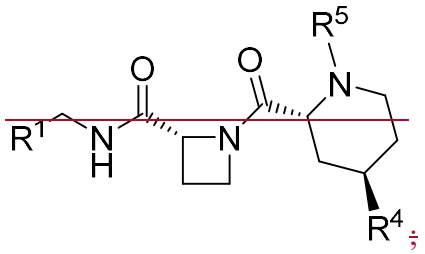


;

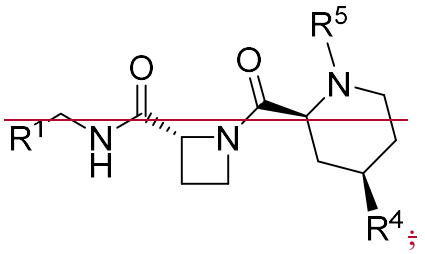


;

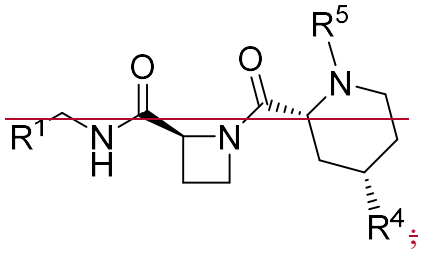
~~(IA2)~~



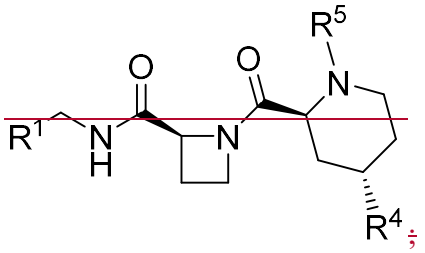
~~(IB2)~~



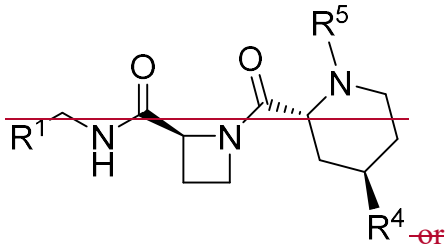
~~(IC2)~~



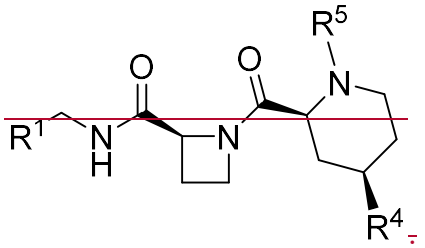
~~(ID2)~~



~~(IE2)~~



~~(IF2)~~



~~(IG2)~~ ~~(IH2)~~

~~146. The compound of any one of claims 84-145, wherein R^4 is a substituted or unsubstituted aryl.~~

~~147. The compound of any one of claims 84-146, wherein R^4 is a substituted or unsubstituted C_6-C_{10} aryl.~~

~~148. The compound of any one of claims 84-147, wherein R^4 is a substituted or unsubstituted phenyl.~~

~~149. The compound of any one of claims 84-148, wherein R^4 is an unsubstituted phenyl.~~

150. The compound of any one of claims 84-148, wherein R^4 is phenyl substituted with one or more of R^{4a}, R^{4b}, R^{4c}, R^{4d}, or R^{4e} wherein R^{4a}, R^{4b}, R^{4c}, R^{4d}, and R^{4e} are each independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, C_{1-6} haloalkyl, aminylalkyl, hydroxyalkyl, cyano, nitro, OR^{17}, SR^{17}, $C(O)R^{17}$, $C(O)NR^{17}R^{18}$, $C(O)OR^{17}$, $OC(O)R^{17}$, $OC(O)OR^{17}$, $OC(O)NR^{17}R^{18}$, $NR^{17}R^{18}$, $N(R^{17})C(O)R^{18}$, $N(R^{17})C(O)NR^{18}R^{19}$, $N(R^{17})C(O)OR^{18}$, $C(=NR^{17})NR^{18}R^{19}$, $C(=NOR^{17})NR^{18}R^{19}$, $C(=NOC(O)R^{17})NR^{18}R^{19}$, $C(=NR^{17})N(R^{18})C(O)OR^{19}$, $N(R^{17})C(=NR^{18})NR^{19}R^{20}$, $S(O)R^{17}$, $S(O)NR^{17}R^{18}$, $S(O)_2R^{17}$, $N(R^{17})S(O)_2R^{18}$, $S(O)_2NR^{17}R^{18}$, oxo, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted C_{6-10} arylalkyl, substituted or unsubstituted C_{6-10} aryloxy, substituted or unsubstituted C_{6-10} arylalkoxy, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted C_{3-10} cycloalkyl, and substituted or unsubstituted 4-10 membered heterocyclyl,

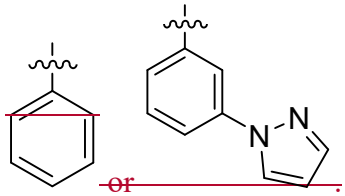
wherein R^{17}, R^{18}, R^{19}, and R^{20}, are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.

151. The compound of claim 150, wherein R^{4a}, R^{4b}, R^{4c}, R^{4d}, or R^{4e} is optionally substituted with one or more substituents selected from the group consisting of OR^{21}, SR^{21}, $C(O)R^{21}$, $C(O)NR^{21}R^{22}$, $C(O)OR^{21}$, $OC(O)R^{21}$, $OC(O)NR^{21}R^{22}$, $NR^{21}R^{22}$, $NR^{21}C(O)R^{22}$, $NR^{21}C(O)NR^{22}R^{23}$, $NR^{21}C(O)OR^{22}$, $C(=NR^{21})NR^{22}R^{23}$, $NR^{21}C(=NR^{22})NR^{23}R^{24}$, $S(O)R^{21}$, $S(O)NR^{21}R^{22}$, $S(O)_2R^{21}$, $NR^{21}S(O)_2R^{22}$, $S(O)_2NR^{21}R^{22}$ and oxo when R^{4a}, R^{4b}, R^{4c}, R^{4d}, or R^{4e} is a substituted C_{6-10} aryl, a substituted C_{6-10} arylalkyl, a substituted C_{6-10} aryloxy, a substituted C_{6-10} arylalkoxy, a substituted 5-10 membered heteroaryl, a substituted C_{3-10} cycloalkyl, and a substituted 4-10 membered heterocyclyl,

wherein R^{21}, R^{22}, R^{23}, and R^{24} are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl,

hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.

152. The compound of any one of claims 84-151, wherein R^4 has one of the following structures:



or .

153. The compound of any one of claims 84-152, wherein R^{5a} is alkyl, $C(=O)OR^6$, phosphonalkyl, or $(CH_2)_nC(=O)OR^6$.

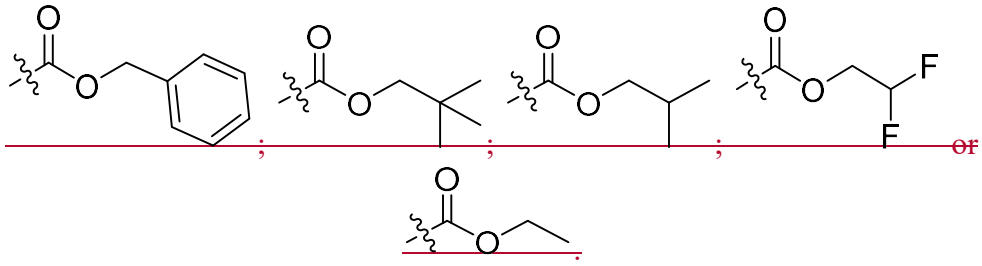
154. The compound of claim 153, wherein R^{5a} is alkyl.

155. The compound of claim 153 or 154, wherein R^{5a} is methyl.

156. The compound of claim 153 or 154, wherein R^{5a} is ethyl.

157. The compound of claim 153, wherein R^{5a} is $C(=O)OR^6$.

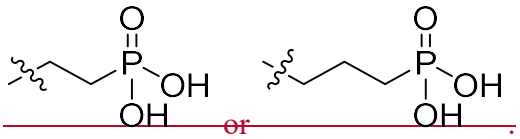
158. The compound of claim 153 or 157, wherein R^{5a} has one of the following structures:



; ; ; or .

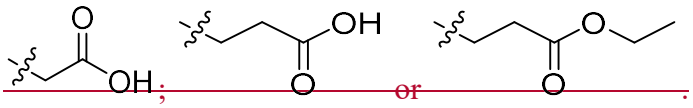
159. The compound of claim 153, wherein R^{5a} is phosphonalkyl.

~~160. The compound of claim 153 or 159, wherein R^{5a} has one of the following structures:~~



~~161. The compound of claim 153, wherein R^{5a} is $(CH_2)_nC(=O)OR^6$.~~

~~162. The compound of claim 153 or 161, wherein R^{5a} has one of the following structures:~~



~~163. The compound of any one of claims 84-162, wherein R^{5b} is an electron pair.~~

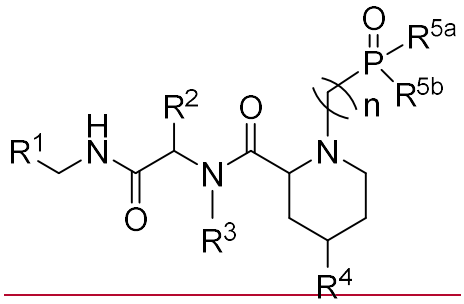
~~164. The compound of any one of claims 84-162, wherein R^{5b} is alkyl.~~

~~165. The compound of claim 164, wherein R^{5b} is a C_1-C_6 alkyl.~~

~~166. The compound of claim 165, wherein R^{5b} is methyl.~~

20~~167~~. A compound having one of the structures in Table 1 or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

~~168. A compound having the following Structure (III):~~



(III)

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein:

R^1 is a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or a substituted or unsubstituted heterocyclyl;

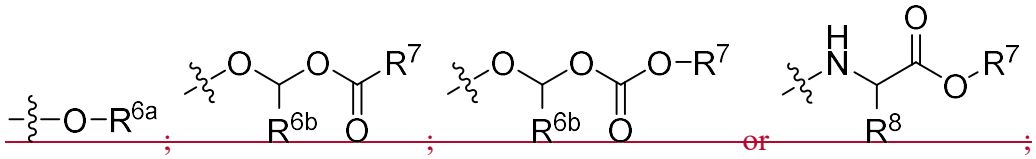
R^2 is hydrogen, alkyl, alkoxy, haloalkyl, haloalkoxy, or cycloalkyl;

R^3 is hydrogen, alkyl, haloalkyl, or cycloalkyl;

or R^2 and R^3, together with the carbon and nitrogen to which they are attached, respectively, form an optionally substituted 4-7 membered heterocyclyl;

R^4 is a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or a substituted or unsubstituted heterocyclyl;

R^{5a} and R^{5b} at each occurrence, independently have one of the following structures:



or

R^{5a} and R^{5b}, together with the phosphorus atom to which they are attached form an optionally substituted 4-7 membered heterocyclyl;

R^{6a} is alkyl, haloalkyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl;

R^{6b} is, at each occurrence, independently hydrogen or alkyl;

R^7 is, at each occurrence, independently alkyl, haloalkyl, heteroaryl, cycloalkyl, heterocyclyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocyclylalkyl;

R^8 is an amino acid side chain; and

n is 1, 2, 3, 4, 5, 6, 7, or 8.

169. The compound of claim 168, wherein R^1 is a substituted or unsubstituted aryl.

170. The compound of claim 168 or 169, wherein R^1 is a substituted or unsubstituted C_6-C_{10} aryl.

171. The compound of any one of claims 168-170, wherein R^1 is a substituted or unsubstituted phenyl.

172. The compound of any one of claims 168-171, wherein R^1 is a substituted phenyl.

173. The compound of any one of claims 168-172, wherein R^1 is phenyl substituted with one or more of R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently selected from the group consisting of $C(=NH)NHC(=O)OR^8$, $C(=NOC(=O)R^8)NH_2$, $C(=NOC(=O)OR^8)NH_2$, $C(=NOH)NH_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, C_{1-6} haloalkyl, aminylalkyl, hydroxyalkyl, cyano, nitro, OR^9, SR^9, $C(O)R^9$, $C(O)NR^9R^{10}$, $C(O)OR^9$, $OC(O)R^9$, $OC(O)OR^9$, $OC(O)NR^9R^{10}$, NR^9R^{10}, $N(R^9)C(O)R^{10}$, $N(R^9)C(O)NR^{10}R^{11}$, $N(R^9)C(O)OR^{10}$, $C(=NR^9)NR^{10}R^{11}$, $C(=NOR^9)NR^{10}R^{11}$, $C(=NOC(O)R^9)NR^{10}R^{11}$, $C(=NR^9)N(R^{10})C(O)OR^{11}$, $N(R^9)C(=NR^{10})NR^{11}R^{12}$, $S(O)R^9$, $S(O)NR^9R^{10}$, $S(O)_2R^9$, $N(R^9)S(O)_2R^{10}$, $S(O)_2NR^9R^{10}$, oxo, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted C_{6-10} arylalkyl, substituted or unsubstituted C_{6-10} aryloxy, substituted or unsubstituted C_{6-10} arylalkoxy, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted C_{3-10} cycloalkyl, and substituted or unsubstituted 4-10 membered heterocyclyl,

wherein R^9, R^{10}, R^{11}, and R^{12}, are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.

174. The compound of claim 173, wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is optionally substituted with one or more substituents selected from the group consisting of halo, CN, OR^{13}, SR^{13}, $C(O)R^{13}$, $C(O)NR^{13}R^{14}$, $C(O)OR^{13}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}C(O)OR^{14}$, $C(=NR^{13})NR^{14}R^{15}$, $NR^{13}C(=NR^{14})NR^{15}R^{16}$, $S(O)R^{13}$, $S(O)NR^{13}R^{14}$, $S(O)_2R^{13}$, $NR^{13}S(O)_2R^{14}$, $S(O)_2NR^{13}R^{14}$ and oxo when R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is a substituted C_{6-10} aryl, a substituted C_{6-10} arylalkyl, a substituted C_{6-10} aryloxy, a substituted C_{6-10} arylalkoxy, a substituted 5-10 membered heteroaryl, a substituted C_{3-10} cycloalkyl, and a substituted 4-10 membered heterocyclyl,

wherein R^{13}, R^{14}, R^{15}, and R^{16} are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.

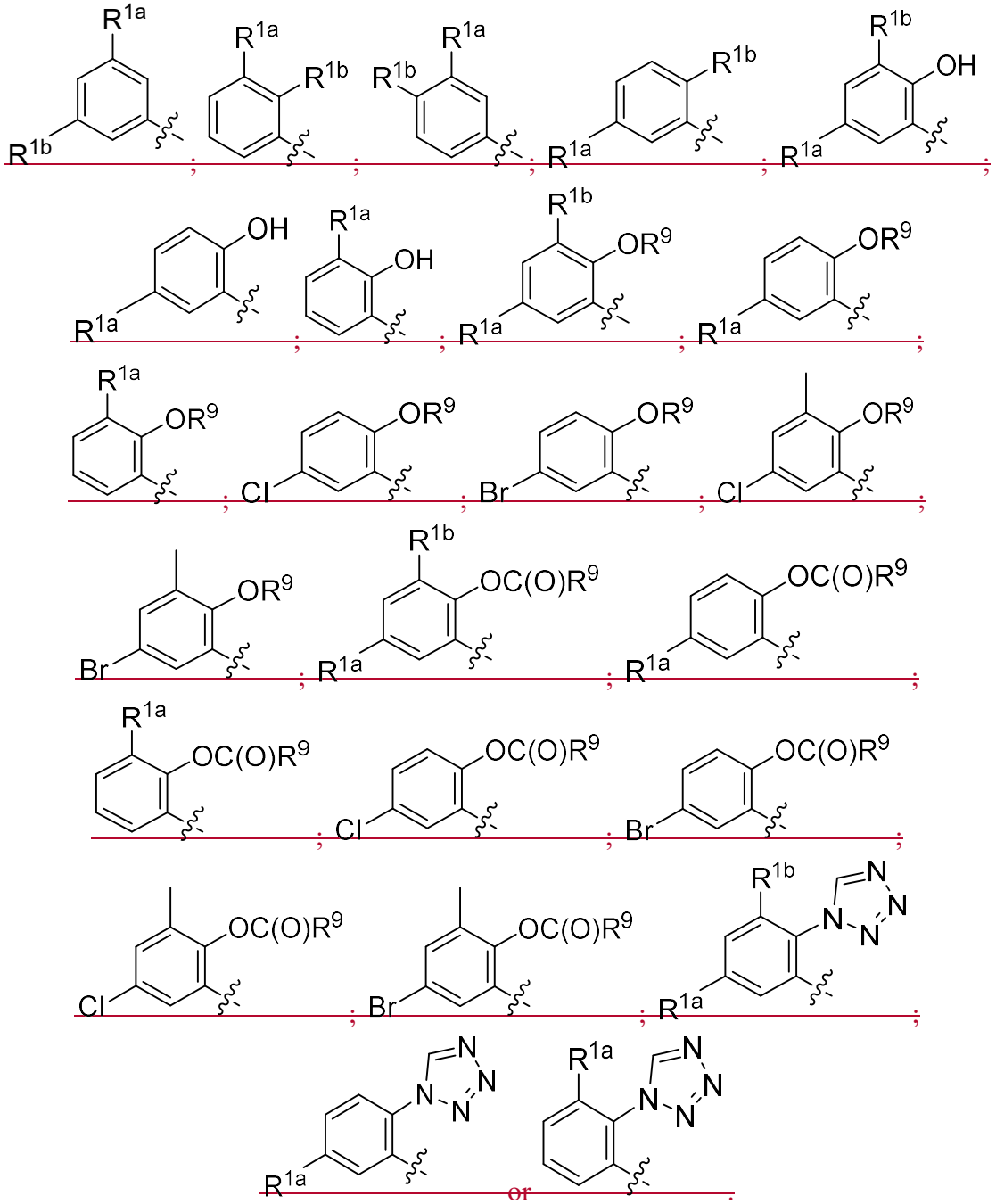
175. The compound of any one of claims 168-174, wherein R^1 is phenyl substituted with at least one substituent selected from the group consisting of OR^9, $C(=NR^9)NR^{10}R^{11}$, $C(=NOR^9)NR^{10}R^{11}$, $C(=NOC(O)R^9)NR^{10}R^{11}$, and $C(=NR^9)NR^{10}C(O)OR^{11}$.

176. The compound of any one of claims 168-175, wherein R^1 is substituted with at least one substituent selected from the group consisting of $C(=NR^9)NR^{10}R^{11}$, $C(=NOR^9)NR^{10}R^{11}$, $C(=NOC(O)R^9)NR^{10}R^{11}$, and $C(=NR^9)NR^{10}C(O)OR^{11}$.

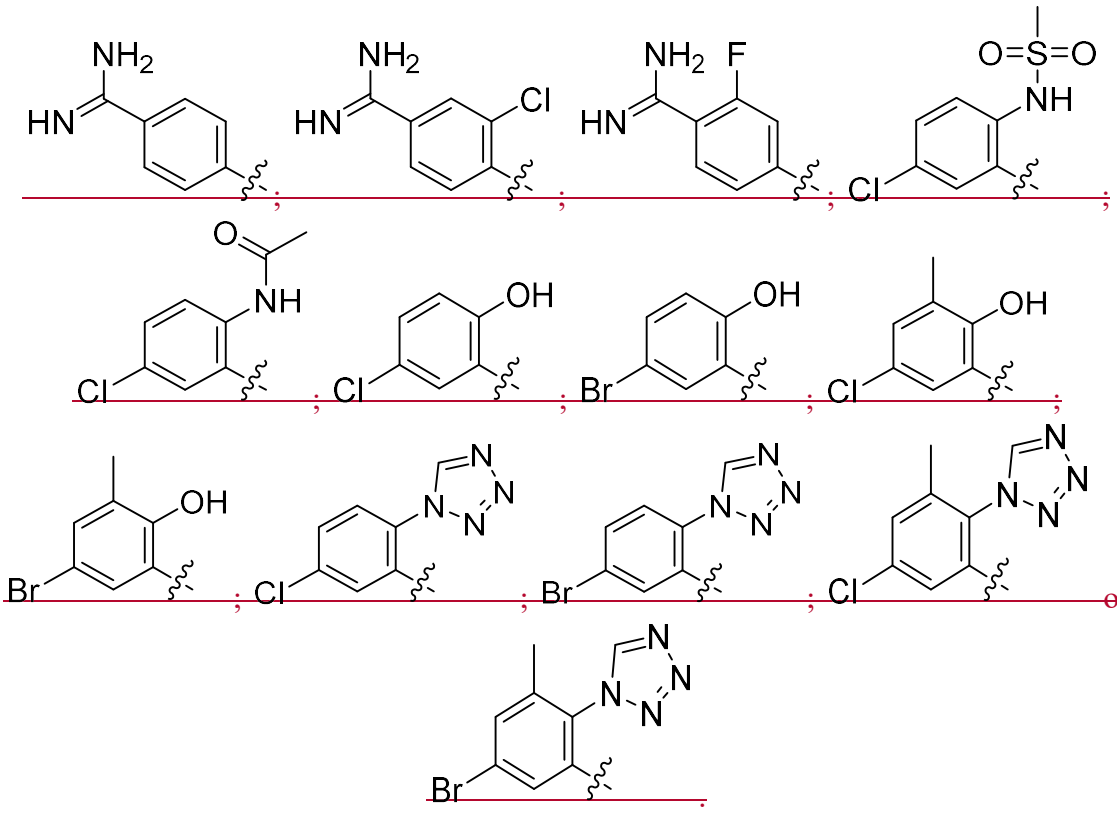
177. The compound of claim 176, wherein R^1 is substituted with at least one $C(=NR^9)NR^{10}R^{11}$.

178. The compound of claim 176 or 177, wherein R^1 is substituted with at least one $-C(=NH)NH_2$.

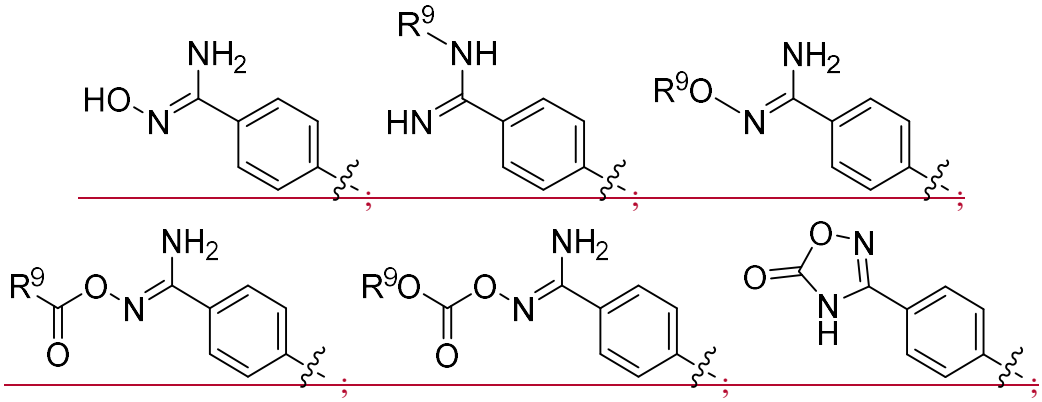
~~179. The compound of any one of claims 174-178, wherein R^1 has one of the following structures:~~

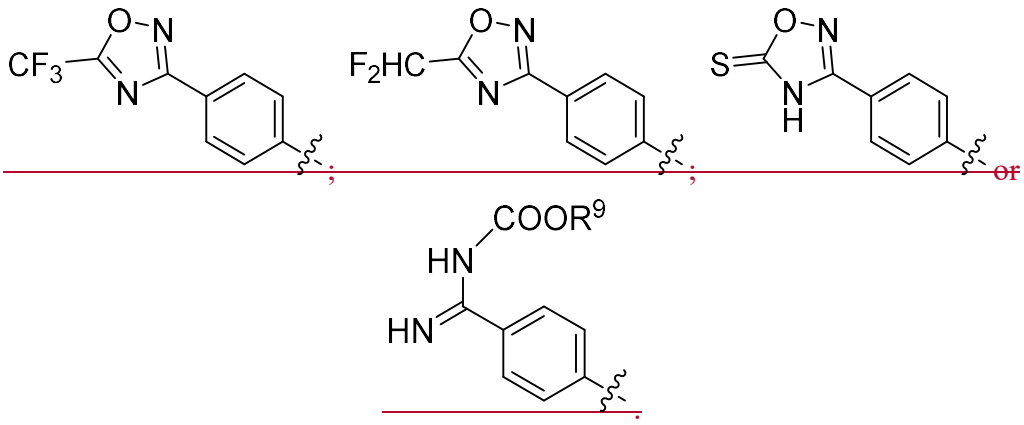


~~180. The compound of any one of claims 168-179, wherein R^1 has one of the following structures:~~



181. The compound of claim 7, wherein R^1 has one of the following structures:





182. The compound of claim 174, wherein R^9 is C_{1-6} alkyl or C_{1-6} haloalkyl.

183. The compound of claim 182, wherein R^9 is methyl.

184. The compound of claim 182, wherein R^9 is trifluoromethyl.

185. The compound of any one of claims 168-171, wherein R^1 is an unsubstituted phenyl.

186. The compound of claim 168, wherein R^1 is a substituted or unsubstituted heteroaryl.

187. The compound of claim 168 or 186, wherein R^1 is a substituted or unsubstituted 5-10 membered heteroaryl.

188. The compound of claim 168 or 186-187, wherein R^1 is a substituted or unsubstituted pyridinyl, pyrrolopyridinyl, thiophenyl, or benzoimidazolyl.

189. The compound of any one of claims 168 or 186-188, wherein R^1 is a substituted or unsubstituted pyridin-3-yl, 1H-pyrrolo[2,3-b]pyridine-5-yl, thiophen-2-yl, or 1H-benzo[d]imidazol-6-yl.

190. The compound of any one of claims 168 or 186-189, wherein R^1 is pyridin-3-yl, 1H-pyrrolo[2,3-b]pyridine-5-yl, thiophen-2-yl, or 1H-benzo[d]imidazol-6-yl substituted with one or more of R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, C_{1-6} haloalkyl, aminylalkyl, hydroxyalkyl, cyano, nitro, OR^9, SR^9, $C(O)R^9$, $C(O)NR^9R^{10}$, $C(O)OR^9$, $OC(O)R^9$, $OC(O)OR^9$, $OC(O)NR^9R^{10}$, NR^9R^{10}, $N(R^9)C(O)R^{10}$, $N(R^9)C(O)NR^{10}R^{11}$, $N(R^9)C(O)OR^{10}$, $C(=NR^9)NR^{10}R^{11}$, $C(=NOR^9)NR^{10}R^{11}$, $C(=NOC(O)R^9)NR^{10}R^{11}$, $C(=NR^9)N(R^{10})C(O)OR^{11}$, $N(R^9)C(=NR^{10})NR^{11}R^{12}$, $S(O)R^9$, $S(O)NR^9R^{10}$, $S(O)_2R^9$, $N(R^9)S(O)_2R^{10}$, $S(O)_2NR^9R^{10}$, oxo, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted C_{6-10} arylalkyl, substituted or unsubstituted C_{6-10} aryloxy, substituted or unsubstituted C_{6-10} arylalkoxy, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted C_{3-10} cycloalkyl, and substituted or unsubstituted 4-10 membered heterocyclyl,

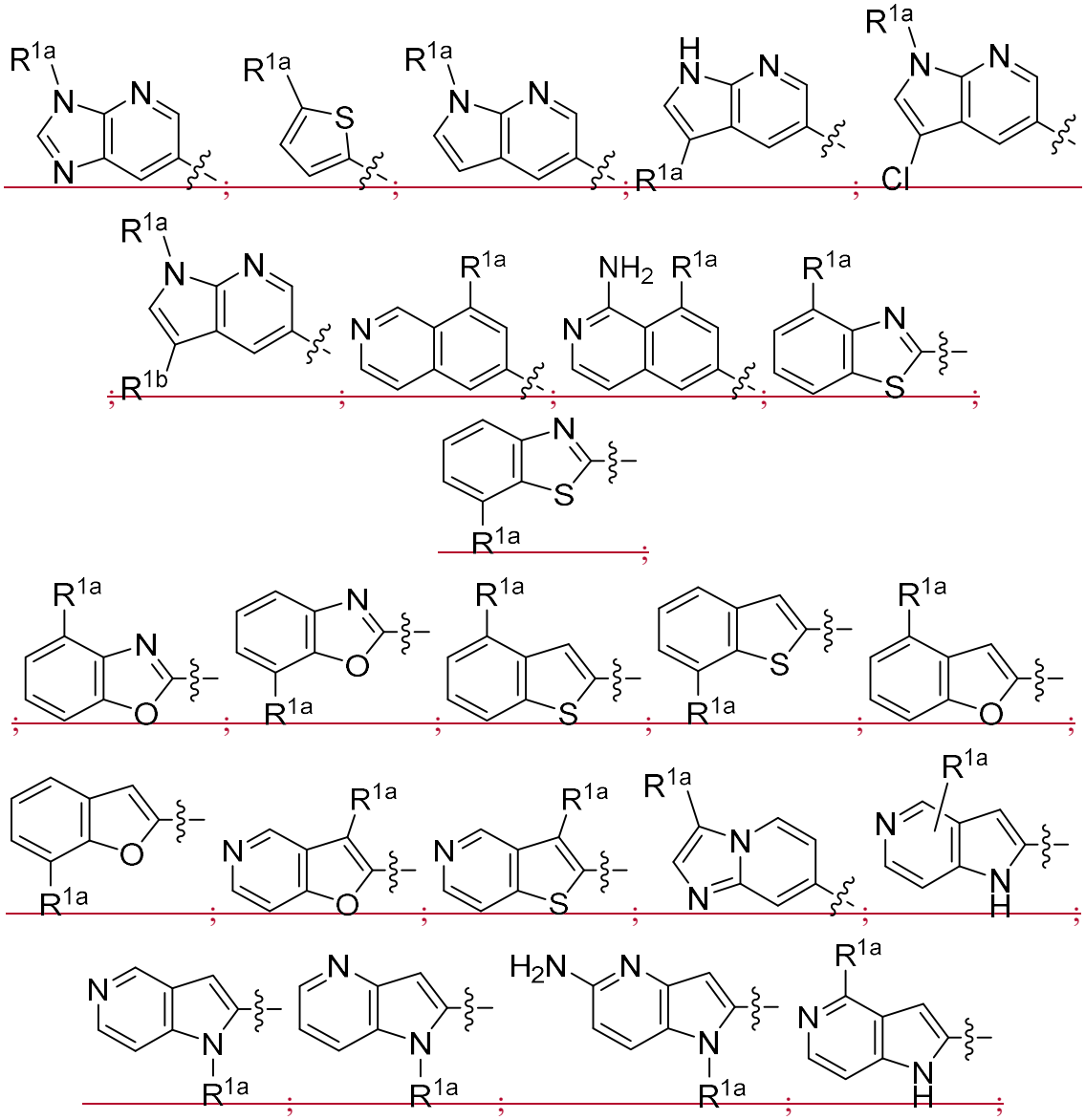
wherein R^9, R^{10}, R^{11}, and R^{12}, are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.

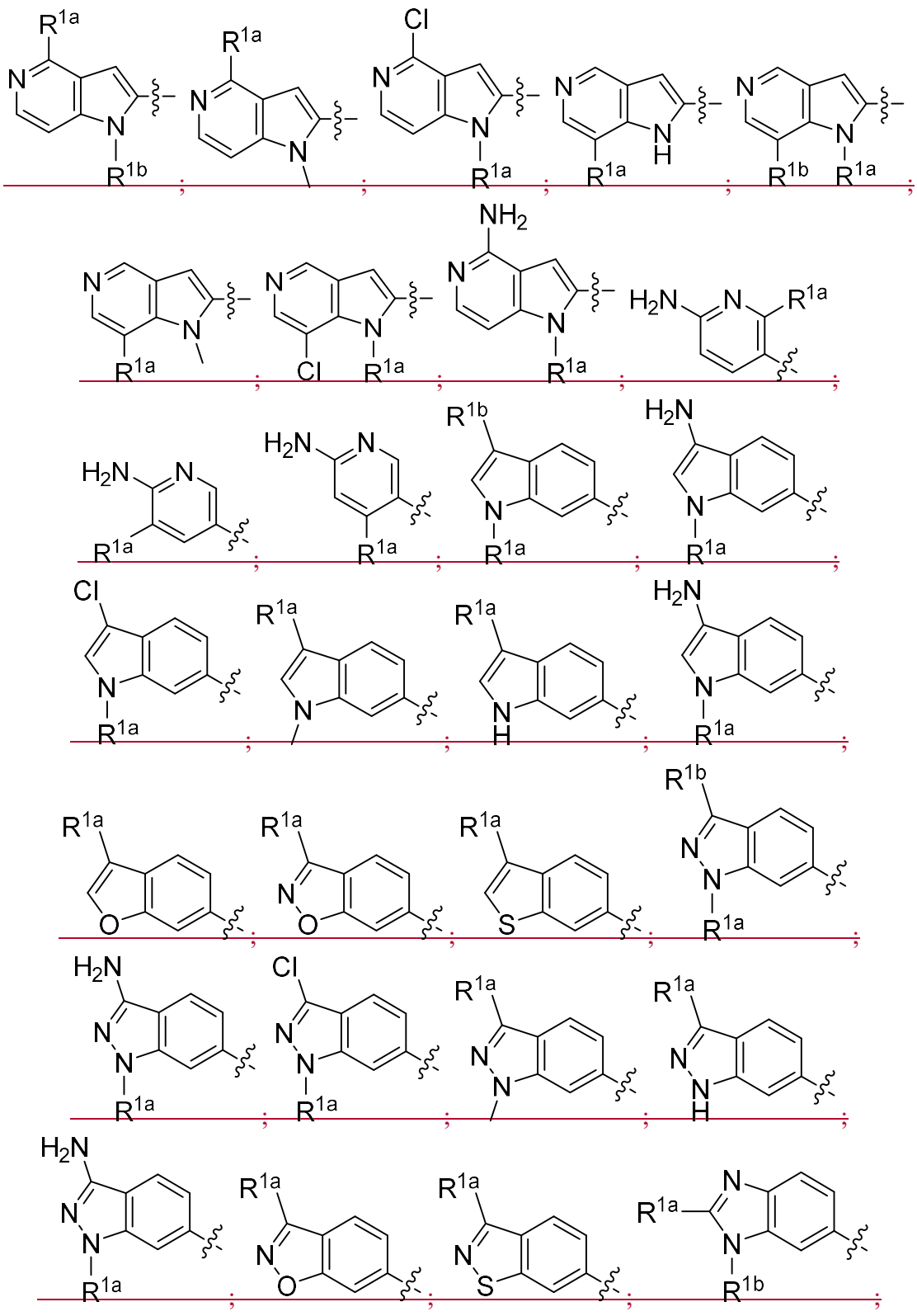
191. The compound of claim 190, wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is optionally substituted with one or more substituents selected from the group consisting of halo, CN, OR^{13}, SR^{13}, $C(O)R^{13}$, $C(O)NR^{13}R^{14}$, $C(O)OR^{13}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}C(O)OR^{14}$, $C(=NR^{13})NR^{14}R^{15}$, $NR^{13}C(=NR^{14})NR^{15}R^{16}$, $S(O)R^{13}$, $S(O)NR^{13}R^{14}$, $S(O)_2R^{13}$, $NR^{13}S(O)_2R^{14}$, $S(O)_2NR^{13}R^{14}$ and oxo when R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is a substituted C_{6-10} aryl, a substituted C_{6-10} arylalkyl, a substituted C_{6-10} aryloxy, a substituted C_{6-10} arylalkoxy, a substituted 5-10

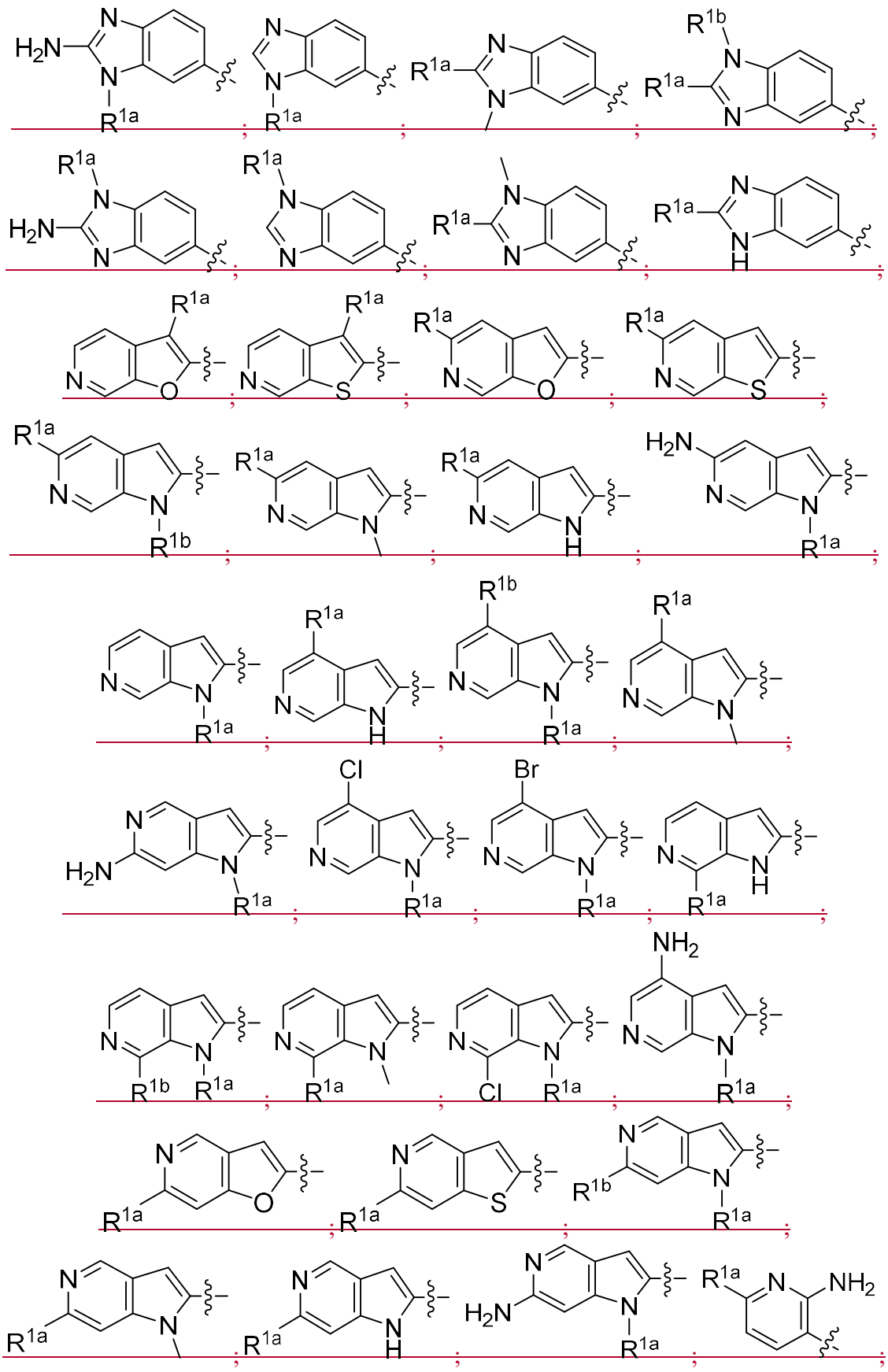
membered heteroaryl, a substituted C_{3-10} cycloalkyl, and a substituted 4-10 membered heterocyclyl,

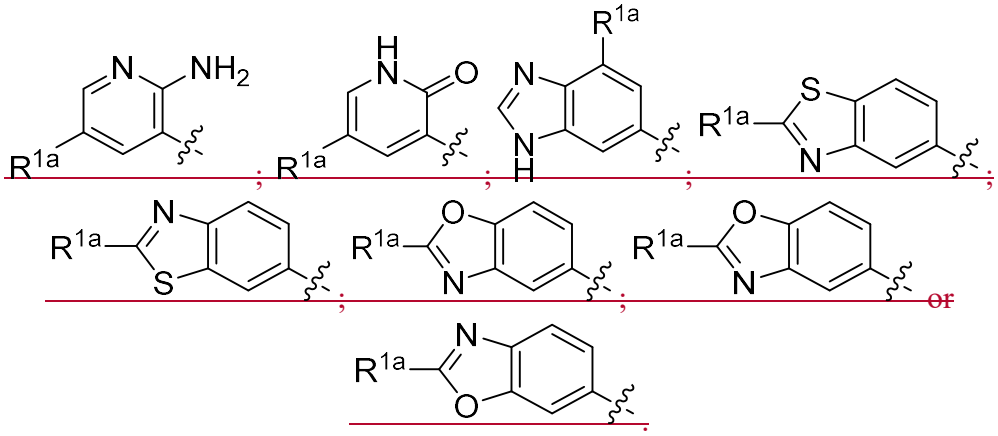
wherein R^{13}, R^{14}, R^{15}, and R^{16} are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.

192. The compound of any one of claims 168 or 186-190, wherein R^1 has one of the following structures:









~~193. The compound of claim 192, wherein R^{1a} or R^{1b} is independently C_{1-6} alkyl, amino, or halo.~~

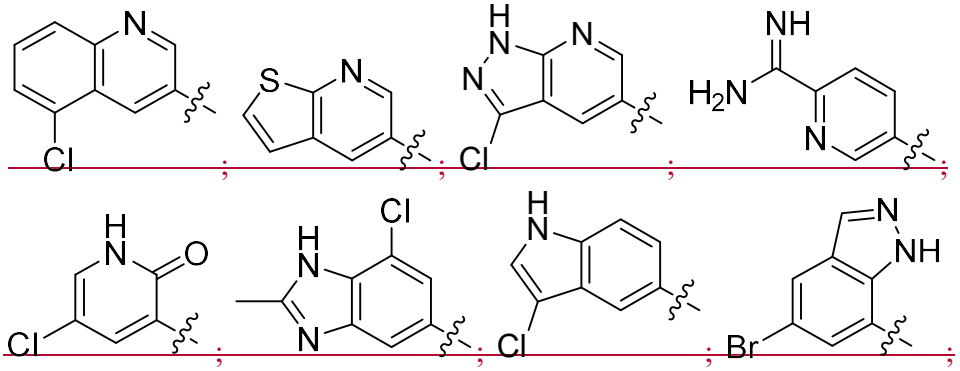
~~194. The compound of claim 193, wherein R^{1a} or R^{1b} is methyl or ethyl.~~

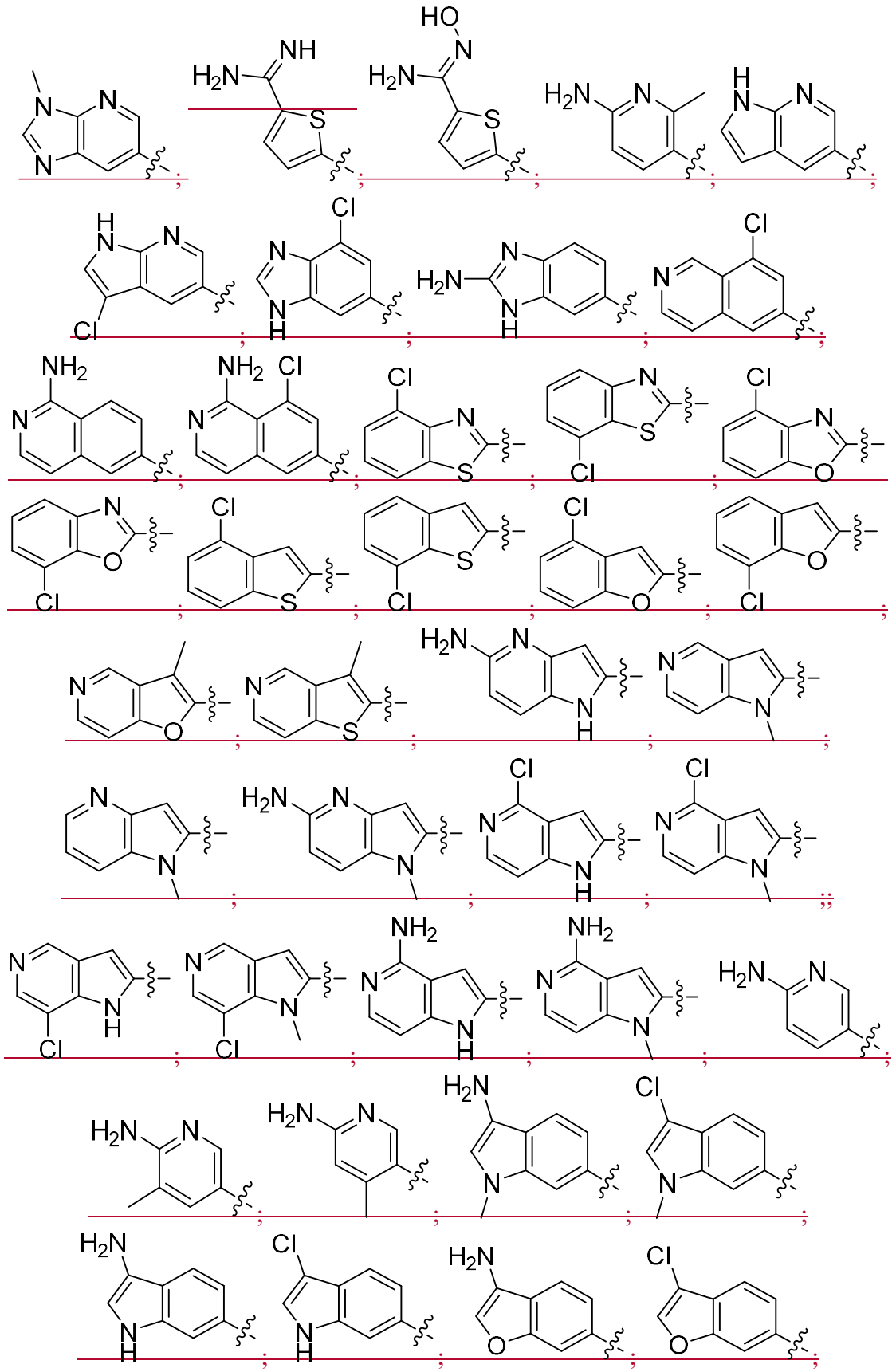
~~195. The compound of claim 193, wherein R^{1a} or R^{1b} is F, Cl, or Br.~~

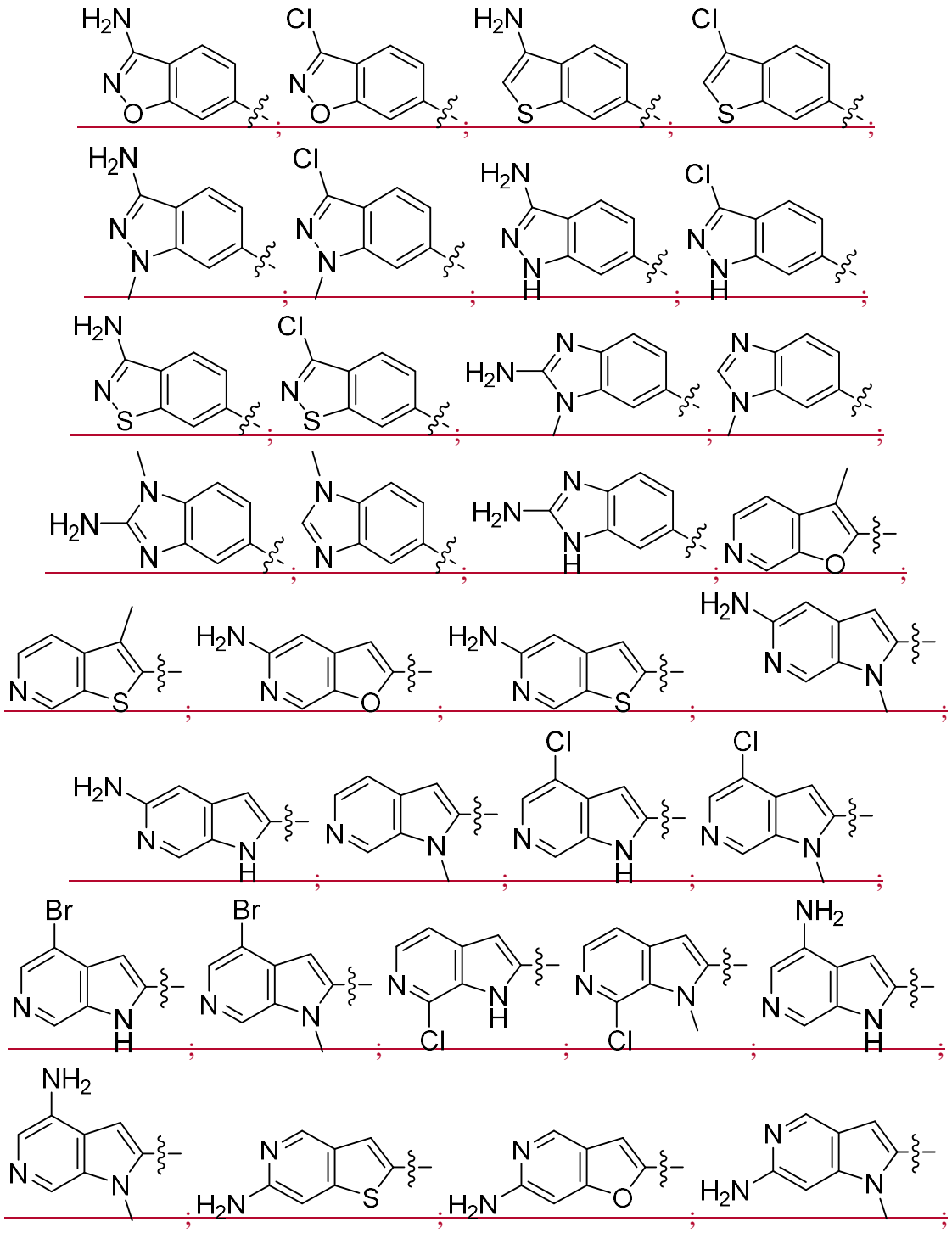
~~196. The compound of claim 193, wherein each R^{1a} or R^{1b} attached to nitrogen is C_{1-6} alkyl.~~

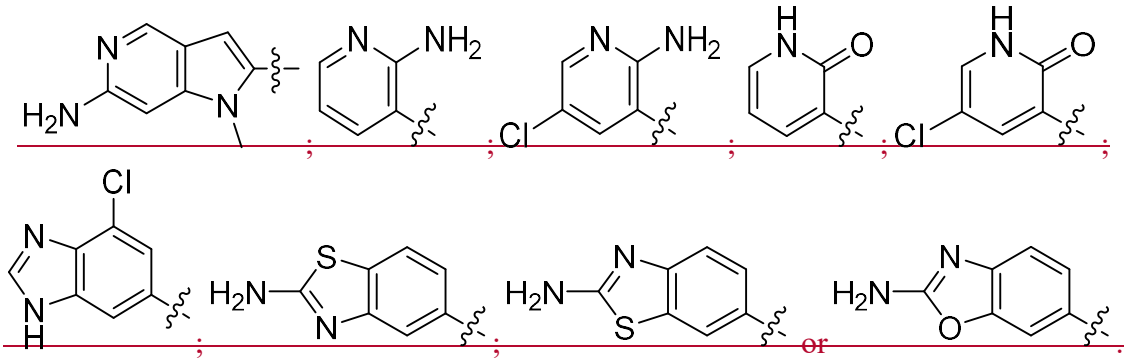
~~197. The compound of claim 196, wherein R^{1a} or R^{1b} is methyl or ethyl.~~

~~198. The compound of any one of claims 168 or 186-187, wherein R^1 has one of the following structures:~~

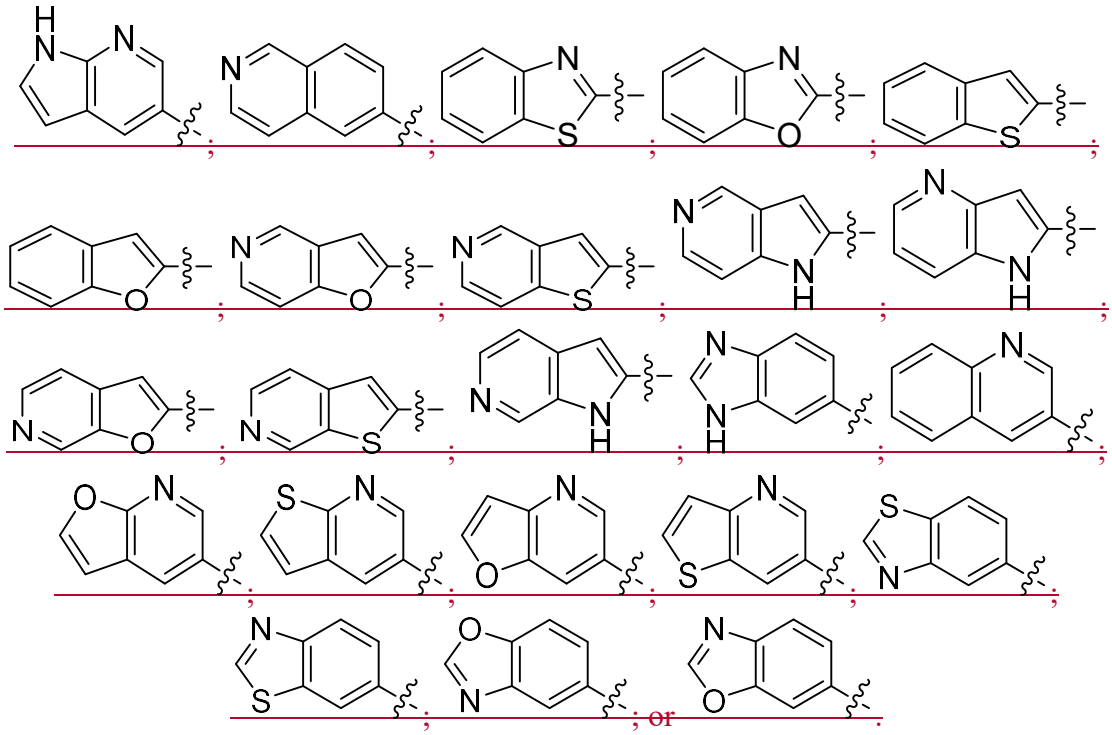








~~199. The compound of any one of claims 168 or 186-187, wherein R^1 has one of the following structures:~~



~~200. The compound of claim 1, wherein R^1 is a substituted or unsubstituted cycloalkyl.~~

~~201. The compound of claim 168 or 200, wherein R^1 is a substituted or unsubstituted C_3-C_6 cycloalkyl.~~

202. The compound of any one of claims 168 or 200-201, wherein R^1 is a substituted C_3-C_6 cycloalkyl.

203. The compound of claim 202, wherein R^1 is a C_3-C_6 cycloalkyl substituted with one or more of R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, aminylalkyl, hydroxyalkyl, nitro, OR^9, SR^9, $C(O)R^9$, $C(O)NR^9R^{10}$, $C(O)OR^9$, $OC(O)R^9$, $OC(O)OR^9$, $OC(O)NR^9R^{10}$, NR^9R^{10}, $N(R^9)C(O)R^{10}$, $N(R^9)C(O)NR^{10}R^{11}$, $N(R^9)C(O)OR^{10}$, $C(=NR^9)NR^{10}R^{11}$, $C(=NOR^9)NR^{10}R^{11}$, $C(=NOC(O)R^9)NR^{10}R^{11}$, $C(=NR^9)N(R^{10})C(O)OR^{11}$, $N(R^9)C(=NR^{10})NR^{11}R^{12}$, $S(O)R^9$, $S(O)NR^9R^{10}$, $S(O)_2R^9$, $N(R^9)S(O)_2R^{10}$, $S(O)_2NR^9R^{10}$, oxo, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted C_{6-10} arylalkyl, substituted or unsubstituted C_{6-10} aryloxy, substituted or unsubstituted C_{6-10} arylalkoxy, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted C_{3-10} cycloalkyl, and substituted or unsubstituted 4-10 membered heterocyclyl,

wherein R^9, R^{10}, R^{11}, and R^{12}, are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.

204. The compound of claim 203, wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is optionally substituted with one or more substituents selected from the group consisting of halo, CN, OR^{13}, SR^{13}, $C(O)R^{13}$, $C(O)NR^{13}R^{14}$, $C(O)OR^{13}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}C(O)OR^{14}$, $C(=NR^{13})NR^{14}R^{15}$, $NR^{13}C(=NR^{14})NR^{15}R^{16}$, $S(O)R^{13}$, $S(O)NR^{13}R^{14}$, $S(O)_2R^{13}$, $NR^{13}S(O)_2R^{14}$, $S(O)_2NR^{13}R^{14}$ and oxo when R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is a substituted C_{6-10} aryl, a substituted C_{6-10} arylalkyl, a substituted C_{6-10} aryloxy, a substituted C_{6-10} arylalkoxy, a substituted 5-10 membered heteroaryl, a substituted C_{3-10} cycloalkyl, and a substituted 4-10 membered heterocyclyl,

~~wherein R^{13}, R^{14}, R^{15}, and R^{16} are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.~~

~~205. The compound of claim 201, wherein R^1 is an unsubstituted a C_3-C_6 cycloalkyl.~~

~~206. The compound of claim 168, wherein R^1 is a substituted or unsubstituted heterocyclyl.~~

~~207. The compound of claim 168 or 206, wherein R^1 is a substituted or unsubstituted 4-10 membered heterocyclyl.~~

~~208. The compound of any one of claims 168 or 206-207, wherein R^1 is a substituted 4-10 membered heterocyclyl.~~

~~209. The compound of claim 208, wherein R^1 is a 4-10 membered heterocyclyl substituted with one or more of R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, C_{1-6} haloalkyl, aminylalkyl, hydroxyalkyl, cyano, nitro, OR^9, SR^9, $C(O)R^9$, $C(O)NR^9R^{10}$, $C(O)OR^9$, $OC(O)R^9$, $OC(O)OR^9$, $OC(O)NR^9R^{10}$, NR^9R^{10}, $N(R^9)C(O)R^{10}$, $N(R^9)C(O)NR^{10}R^{11}$, $N(R^9)C(O)OR^{10}$, $C(=NR^9)NR^{10}R^{11}$, $C(=NOR^9)NR^{10}R^{11}$, $C(=NOC(O)R^9)NR^{10}R^{11}$, $C(=NR^9)N(R^{10})C(O)OR^{11}$, $N(R^9)C(=NR^{10})NR^{11}R^{12}$, $S(O)R^9$, $S(O)NR^9R^{10}$, $S(O)_2R^9$, $N(R^9)S(O)_2R^{10}$, $S(O)_2NR^9R^{10}$, oxo, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted C_{6-10} arylalkyl, substituted or unsubstituted C_{6-10} aryloxy, substituted or unsubstituted C_{6-10} arylalkoxy, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted C_{3-10} cycloalkyl, and substituted or unsubstituted 4-10 membered heterocyclyl,~~

wherein R^9, R^{10}, R^{11}, and R^{12}, are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.

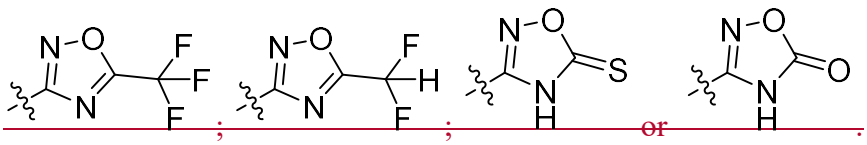
210. The compound of claim 209, wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is optionally substituted with one or more substituents selected from the group consisting of OR^{13}, SR^{13}, $C(O)R^{13}$, $C(O)NR^{13}R^{14}$, $C(O)OR^{13}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}C(O)OR^{14}$, $C(=NR^{13})NR^{14}R^{15}$, $NR^{13}C(=NR^{14})NR^{15}R^{16}$, $S(O)R^{13}$, $S(O)NR^{13}R^{14}$, $S(O)_2R^{13}$, $NR^{13}S(O)_2R^{14}$, $S(O)_2NR^{13}R^{14}$ and oxo when R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is a substituted C_{6-10} aryl, a substituted C_{6-10} arylalkyl, a substituted C_{6-10} aryloxy, a substituted C_{6-10} arylalkoxy, a substituted 5-10 membered heteroaryl, a substituted C_{3-10} cycloalkyl, and a substituted 4-10 membered heterocyclyl,

wherein R^{13}, R^{14}, R^{15}, and R^{16} are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.

211. The compound of claim 206, wherein R^1 is an unsubstituted 4-10 membered heterocyclyl.

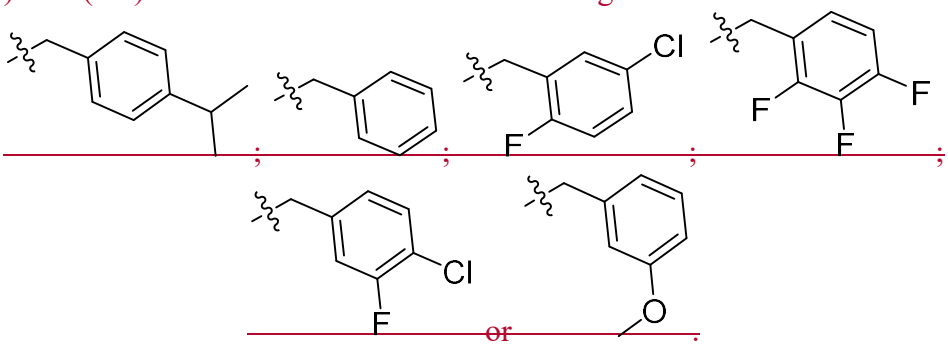
212. The compound of any one of claims 168-172, wherein R^1 is substituted with one or more substituents selected from the group consisting of a substituted heteroaryl, $C(=NH)NHC(=O)OR^8$, $C(=NOC(=O)R^8)NH_2$, $C(=NOC(=O)OR^8)NH_2$, and $C(=NOH)NH_2$.

213. The compound of claim 212, wherein R^1 is substituted with a substituted heteroaryl having one of the following structures:



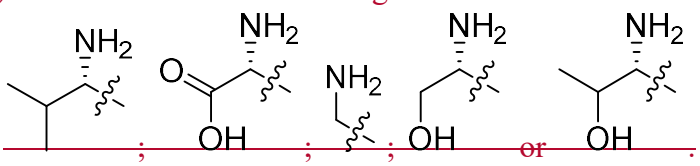
214. The compound of claim 212, wherein R^1 is substituted with $C(=NH)NHC(=O)OR^8$ and R^8 is a substituted or unsubstituted arylalkyl.

215. The compound of claim 212 or 214, wherein R^1 is substituted with $C(=NH)NHC(=O)OR^8$ and R^8 has one of the following structures:



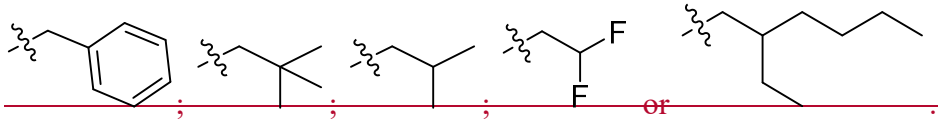
216. The compound of claim 212, wherein R^1 is substituted with $C(=NOC(=O)R^8)NH_2$ and R^8 is an aminylalkyl.

217. The compound of claim 212 or 216, wherein R^1 is substituted with $C(=NOC(=O)R^8)NH_2$ and R^8 has the following structure:



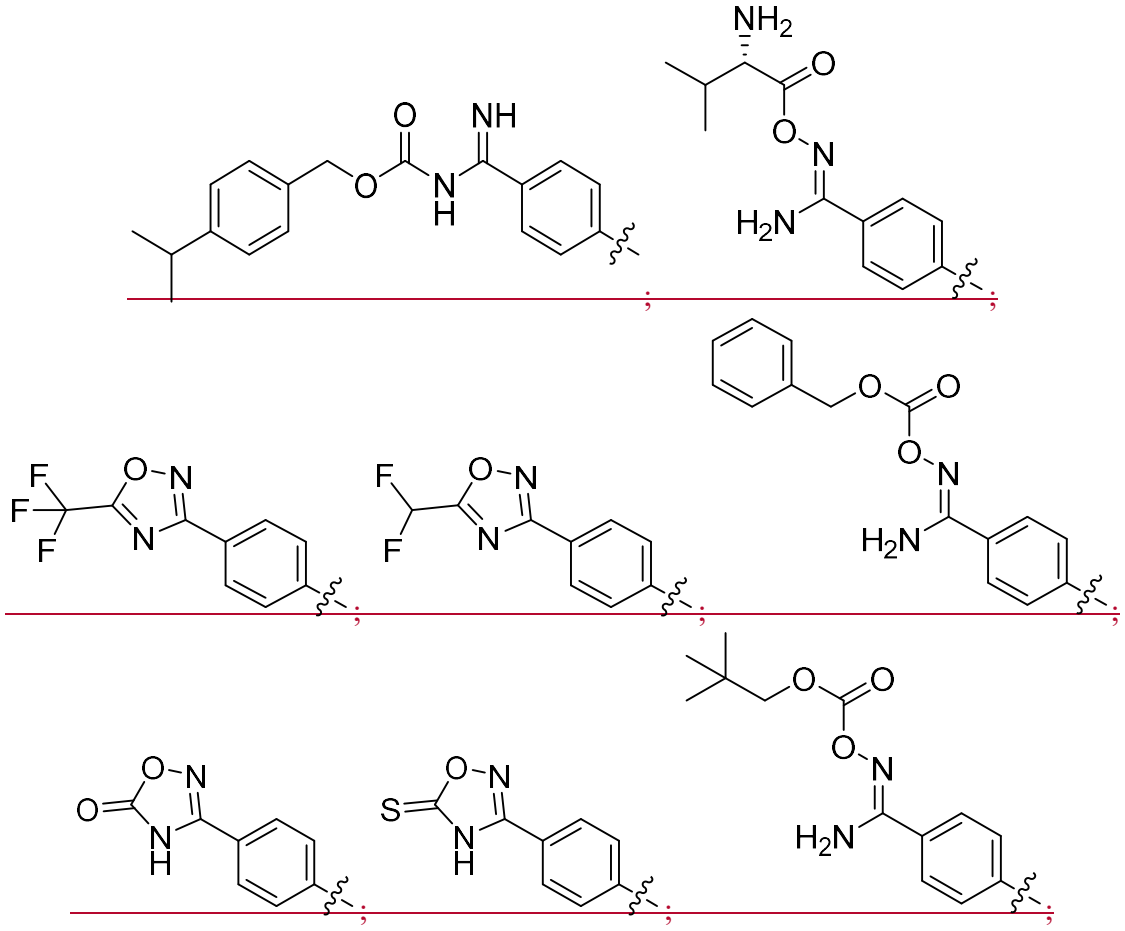
218. The compound of claim 212, wherein R^1 is substituted with $C(=NOC(=O)OR^8)NH_2$ and R^8 is an alkyl, a haloalkyl, or a substituted or unsubstituted arylalkyl.

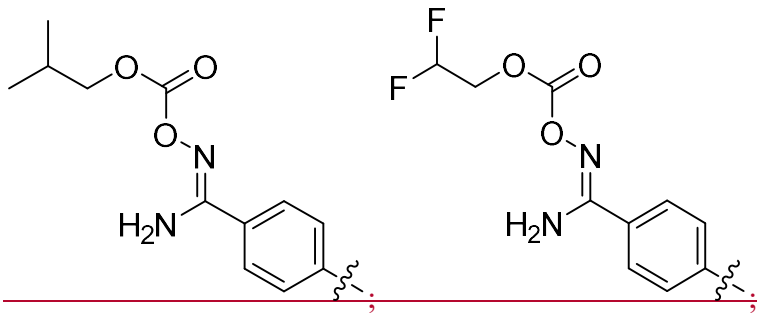
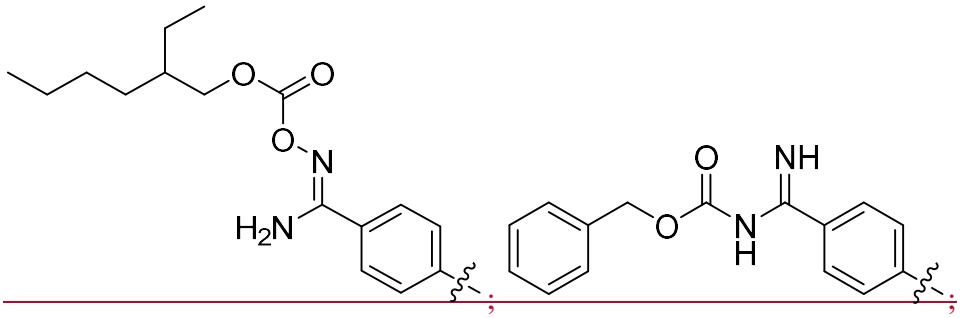
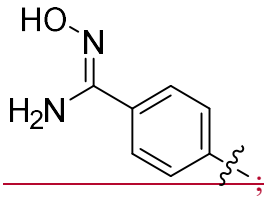
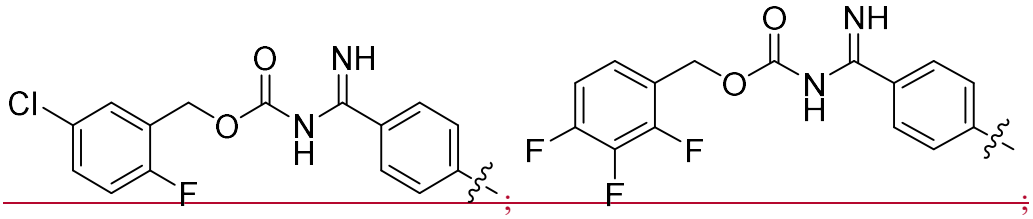
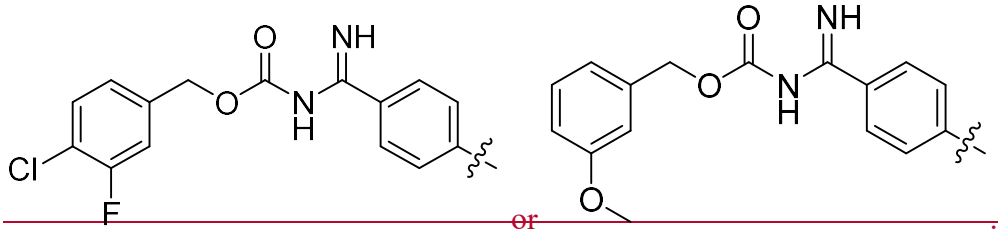
~~219. The compound of claim 212 or 218, wherein R^1 is substituted with $C(=NOC(=O)OR^8)NH_2$ and R^8 has one of the following structures:~~



~~220. The compound of claim 212, wherein R^1 is substituted with $C(=NOH)NH_2$.~~

~~221. The compound of any one of claims 212-220, wherein R^1 has one of the following structures:~~



or .

222. The compound of any one of claims 168-221, wherein R^2 is hydrogen or C_1-C_6 alkyl.

223. The compound of any one of claims 168-222, wherein R^2 is C_1-C_6 alkyl.

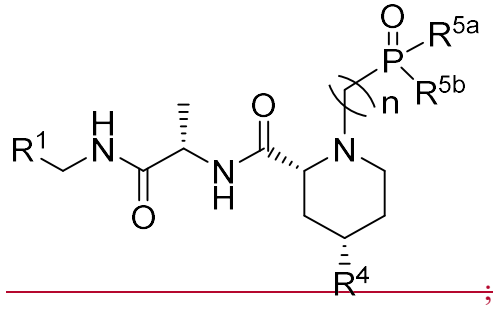
224. The compound of any one of claims 168-223, wherein R^2 is $-CH_3$.

225. The compound of any one of claims 168-222, wherein R^2 and R^3, together with the carbon and nitrogen to which they are attached, respectively, form an optionally substituted 4-7 membered heterocyclyl.

226. The compound of claim 58, wherein R^2 and R^3, together with the carbon and nitrogen to which they are attached, respectively, form an optionally substituted 4, 5, or 6 membered heterocyclyl.

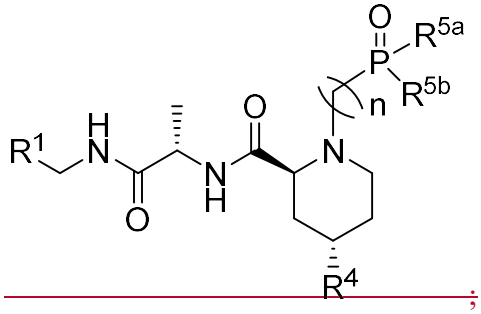
227. The compound of claim 226, wherein R^2 and R^3, together with the carbon and nitrogen to which they are attached, respectively, form an optionally substituted 4-membered heterocyclyl.

228. The compound of any one of claims 168-224, wherein the compound has one of the following Structures (IIIA1), (IIIB1), (IIIC1), (IIID1), (IIIE1), (IIIF1), (IIIG1), or (IIIH1):



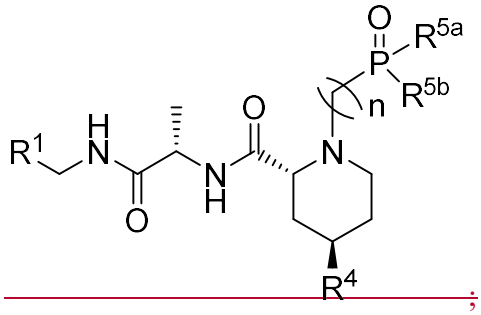
;

(IIIA1)



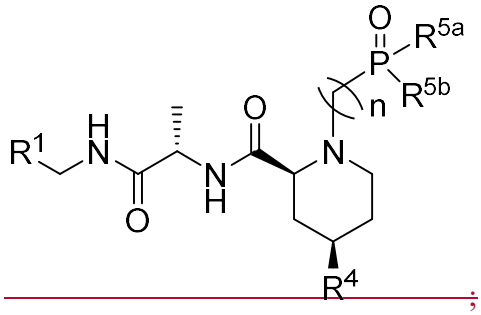
;

(IIIB1)



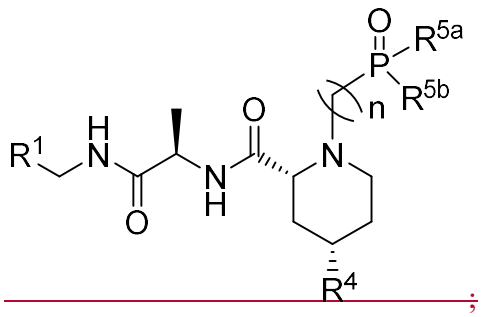
;

(IIIC1)

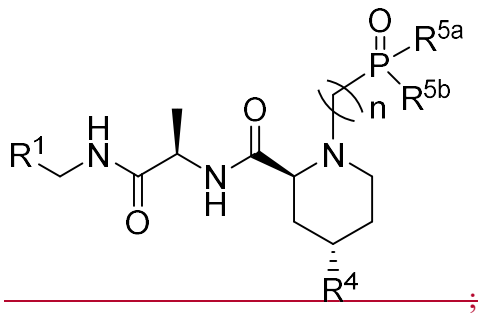


;

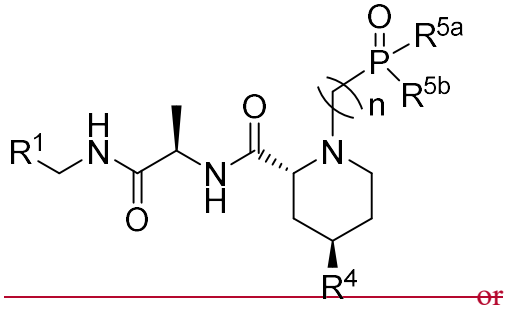
(IIID1)



(IIIE1)

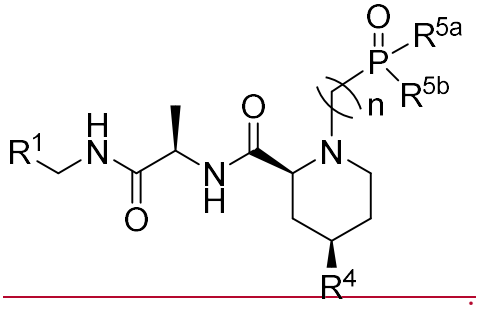


(IIIF1)



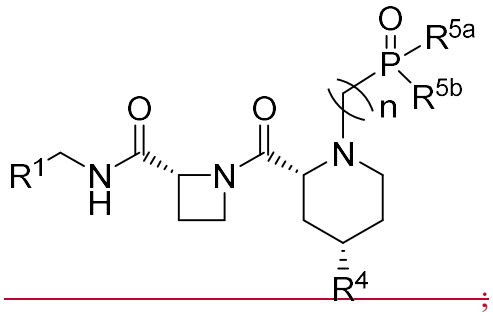
(IIIG1)

or

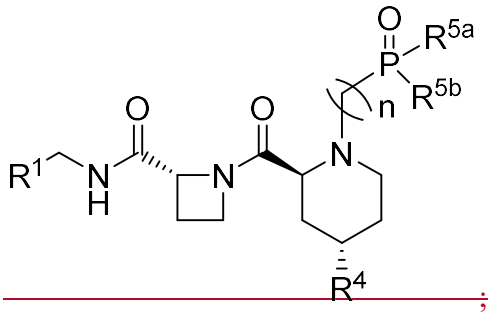


(IIIH1).

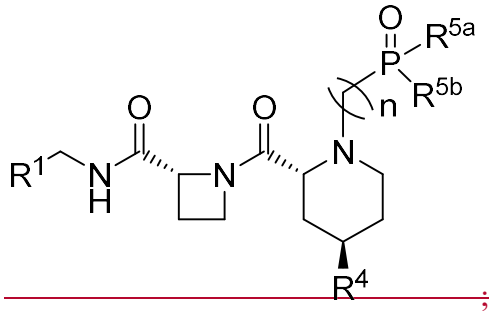
229. The compound of any one of claims 168-222 or 225-227, wherein the compound has one of the following Structures (IIIA2), (IIIB2), (IIIC2), (IIID2), (IIIE2), (IIIF2), (IIIG2), or (IIIH2):



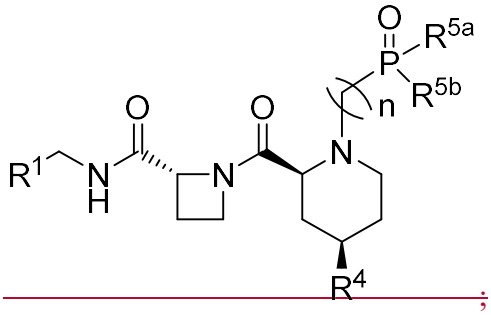
(IIIA2)



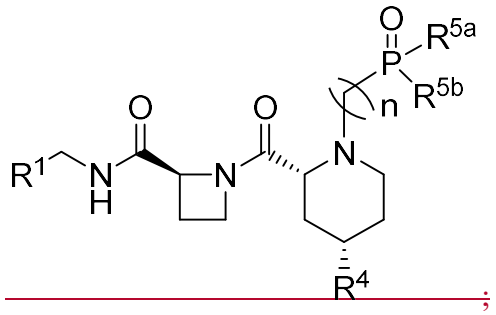
(IIIB2)



(IIIC2)

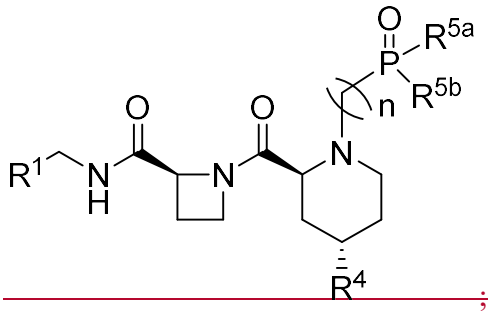


(IIID2)



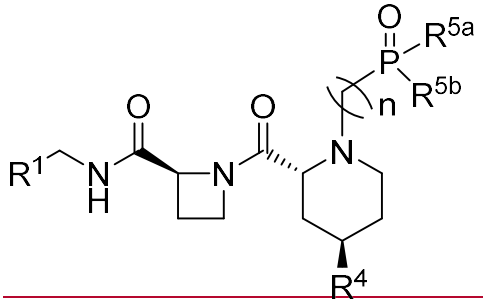
;

(IIIE2)



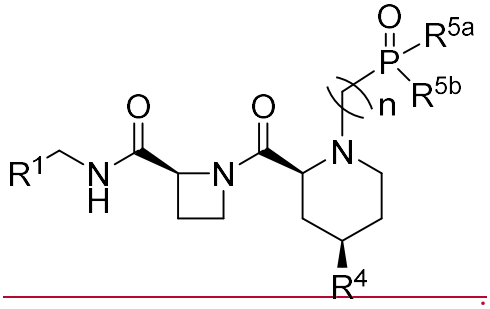
;

(IIIF2)



or

(IIIG2)



.

(IIIH2)

230. The compound of any one of claims 168-229, wherein R^4 is a substituted or unsubstituted aryl.

231. The compound of any one of claims 168-230, wherein R^4 is a substituted or unsubstituted C_6-C_{10} aryl.

232. The compound of any one of claims 168-231, wherein R^4 is a substituted or unsubstituted phenyl.

233. The compound of any one of claims 168-232, wherein R^4 is an unsubstituted phenyl.

234. The compound of any one of claims 168-232, wherein R^4 is phenyl substituted with one or more of R^{4a}, R^{4b}, R^{4c}, R^{4d}, or R^{4e} wherein R^{4a}, R^{4b}, R^{4c}, R^{4d}, and R^{4e} are each independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, C_{1-6} haloalkyl, aminylalkyl, hydroxyalkyl, cyano, nitro, OR^{17}, SR^{17},

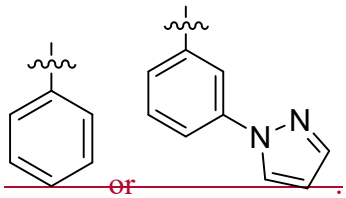
~~$C(O)R^{17}$, $C(O)NR^{17}R^{18}$, $C(O)OR^{17}$, $OC(O)R^{17}$, $OC(O)OR^{17}$, $OC(O)NR^{17}R^{18}$, $NR^{17}R^{18}$, $N(R^{17})C(O)R^{18}$, $N(R^{17})C(O)NR^{18}R^{19}$, $N(R^{17})C(O)OR^{18}$, $C(=NR^{17})NR^{18}R^{19}$, $C(=NOR^{17})NR^{18}R^{19}$, $C(=NOC(O)R^{17})NR^{18}R^{19}$, $C(=NR^{17})N(R^{18})C(O)OR^{19}$, $N(R^{17})C(=NR^{18})NR^{19}R^{20}$, $S(O)R^{17}$, $S(O)NR^{17}R^{18}$, $S(O)_2R^{17}$, $N(R^{17})S(O)_2R^{18}$, $S(O)_2NR^{17}R^{18}$, oxo, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted C_{6-10} arylalkyl, substituted or unsubstituted C_{6-10} aryloxy, substituted or unsubstituted C_{6-10} arylalkoxy, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted C_{3-10} cycloalkyl, and substituted or unsubstituted 4-10 membered heterocyclyl,~~

~~wherein R^{17}, R^{18}, R^{19}, and R^{20}, are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.~~

~~235. The compound of claim 234, wherein R^{4a}, R^{4b}, R^{4c}, R^{4d}, or R^{4e} is optionally substituted with one or more substituents selected from the group consisting of halo, CN, OR^{21}, SR^{21}, $C(O)R^{21}$, $C(O)NR^{21}R^{22}$, $C(O)OR^{21}$, $OC(O)R^{21}$, $OC(O)NR^{21}R^{22}$, $NR^{21}R^{22}$, $NR^{21}C(O)R^{22}$, $NR^{21}C(O)NR^{22}R^{23}$, $NR^{21}C(O)OR^{22}$, $C(=NR^{21})NR^{22}R^{23}$, $NR^{21}C(=NR^{22})NR^{23}R^{24}$, $S(O)R^{21}$, $S(O)NR^{21}R^{22}$, $S(O)_2R^{21}$, $NR^{21}S(O)_2R^{22}$, $S(O)_2NR^{21}R^{22}$ and oxo when R^{4a}, R^{4b}, R^{4c}, R^{4d}, or R^{4e} is a substituted C_{6-10} aryl, a substituted C_{6-10} arylalkyl, a substituted C_{6-10} aryloxy, a substituted C_{6-10} arylalkoxy, a substituted 5-10 membered heteroaryl, a substituted C_{3-10} cycloalkyl, and a substituted 4-10 membered heterocyclyl,~~

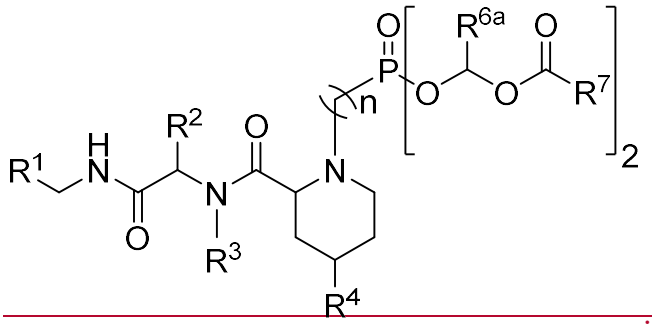
~~wherein R^{21}, R^{22}, R^{23}, and R^{24} are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.~~

~~236. The compound of any one of claims 168-235, wherein R^4 has one of the following structures:~~



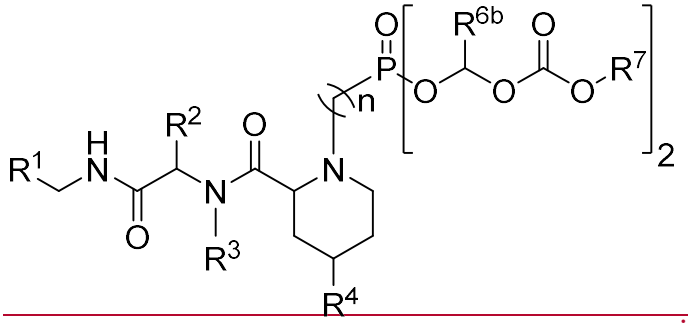
or .

237. The compound of any one of claims 168-236, wherein the compound has the following structure (IIIa):



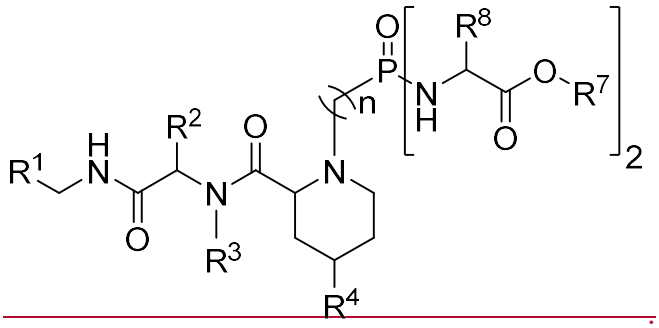
(IIIa)

238. The compound of any one of claims 168-236, wherein the compound has the following structure (IIIb):



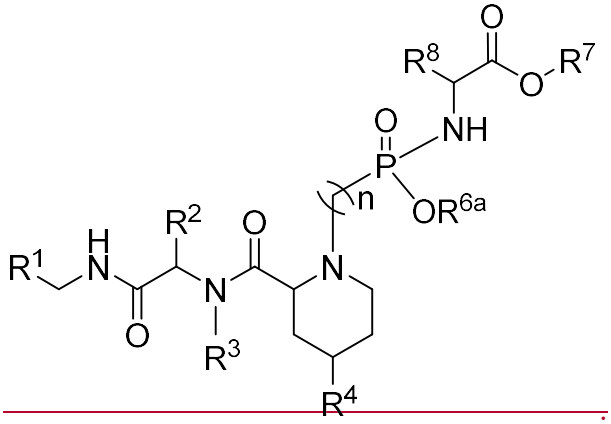
(IIIb)

239. The compound of any one of claims 168-236, wherein the compound has the following structure (IIIc):



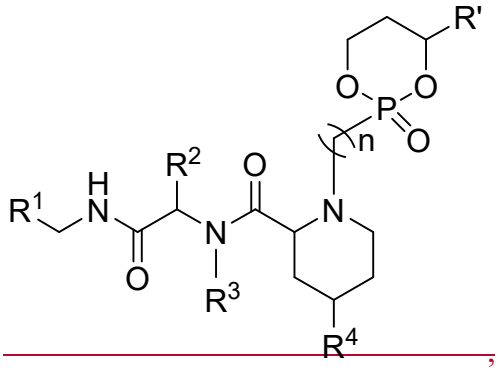
(IIIc)

240. The compound of any one of claims 168-236, wherein the compound has the following structure (IIId):



(IIId)

241. The compound of any one of claims 168-236, wherein the compound has the following structure (IIIe):



(IIIe)

wherein:

~~R' is a substituted or unsubstituted aryl or a substituted or unsubstituted heteroaryl.~~

~~242. The compound of any one of claims 168-241, wherein R^{6a} is aryl, heteroaryl, cycloalkyl, or heterocyclyl.~~

21~~243~~. A pharmaceutical composition comprising a compound or pharmaceutically acceptable salt thereof of ~~any one of~~ claim~~s~~ 1 ~~to 242~~ and a pharmaceutically acceptable carrier or excipient.

22~~244~~. ~~A method for treating a MASP-2-associated disease or disorder in a subject in need thereof, the method comprising administering to the subject an effective amount~~Use of a compound of ~~any one of~~ claim~~s~~ 1~~-242~~, in the manufacture of a medicament for treating a MASP-2-associated disease or disorder in a subject in need thereof~~or a pharmaceutical composition according to claim 243~~.

~~245. The method of claim 244, wherein the compound is administered in an amount sufficient to inhibit MASP-2 dependent complement activation in the subject.~~

~~246. The method of claim 169, wherein the subject has been diagnosed as being in need of treatment for a lectin complement-associated disease or disorder.~~

~~247. The method of claim 244, wherein disease or disorder is a thrombotic microangiopathy (TMA), a renal condition, an inflammatory reaction resulting from tissue or organ transplantation, an ischemia reperfusion injury, a complication associated with diabetes, a cardiovascular disease or disorder, an inflammatory gastrointestinal disorder, a pulmonary disorder, an ophthalmic disease or disorder, disseminated intravascular coagulation, graft-versus-host disease, veno-~~

~~occlusive disease, diffuse alveolar hemorrhage, idiopathic pneumonia syndrome, capillary leak syndrome, engraftment syndrome, fluid overlaod, or combinations thereof.~~

~~248. The method of claim 244, wherein the disease or disorder is a thrombotic microangiopathy (TMA) thrombotic thrombocytopenic purpura (TTP), refractory TTP, Upshaw-Schulman Syndrome (USS), hemolytic uremic syndrome (HUS), atypical hemolytic syndrome (aHUS), non-Factor H-dependent atypical hemolytic syndrome, aHUS secondary to an infection, plasma therapy-resistant aHUS, a TMA secondary to cancer, a TMA secondary to chemotherapy, a TMA secondary to transplantation, a TMA associated with hematopoietic stem cell transplant, or combinations thereof.~~

~~249. The method of claim 244, wherein the disease or disorder is graft-versus-host disease.~~

~~250. The method of claim 244, wherein the disease or disorder is diffuse alveolar hemorrhage (DAH).~~

~~251. The method of claim 244, wherein the disease or disorder is veno-occlusive disease (VOD).~~

~~252. The method of claim 244, wherein the disease or disorder is a renal condition.~~

~~253. The method of claim 244, wherein the renal condition is mesangioproliferative glomerulonephritis, membranous glomerulonephritis, membranoproliferative glomerulonephritis (mesangiocapillary glomerulonephritis), acute post infectious glomerulonephritis (poststreptococcal glomerulonephritis), C3 glomerulopathy, cryoglobulinemic glomerulonephritis, pauci-immune necrotizing~~

~~crescentic glomerulonephritis, lupus nephritis, Henoch-Schonlein purpura nephritis, IgA nephropathy, or combinations thereof.~~

~~254. The method of claim 244, wherein the disease or disorder is renal fibrosis, proteinuria, or combinations thereof.~~

~~255. The method of claim 244, wherein the disease or disorder is an inflammatory reaction resulting from tissue or solid organ transplantation.~~

~~256. The method of claim 244, wherein the disease or disorder is an ischemia reperfusion injury (I/R).~~

~~257. The method of claim 244, wherein the disease or disorder is a complication associated with non-obese diabetes, complications associated with Type-1 diabetes, Type-2 (adult onset) diabetes, or combinations thereof.~~

~~258. The method of claim 244, wherein the disease or disorder is a cardiovascular disease or disorder.~~

~~259. The method of claim 244, wherein the disease or disorder is an inflammatory gastrointestinal disorder.~~

~~260. The method of claim 244, wherein the disease or disorder is a pulmonary disorder.~~

~~261. The method of claim 244, wherein the disease or disorder is an extracorporeal exposure-triggered inflammatory reaction.~~

~~262. The method of claim 261, wherein the method further comprises treating a subject undergoing an extracorporeal circulation procedure.~~

~~263. The method of claim 244, wherein the disease or disorder is an inflammatory arthritis, non-inflammatory arthritis, a musculoskeletal disorder, or combinations thereof.~~

~~264. The method of claim 244, wherein the disease or disorder is a skin disorder.~~

~~265. The method of claim 244, wherein the disease or disorder is peripheral nervous system (PNS) disorder or injury, a central nervous system (CNS) disorder or injury, or combinations thereof.~~

~~266. The method of claim 244, wherein the disease or disorder is sepsis or a condition resulting from sepsis.~~

~~267. The method of claim 244, wherein the disease or disorder is a urogenital disorder.~~

~~268. The method of claim 244, wherein the disease or disorder is an inflammatory reaction in a subject being treated with chemotherapeutics, radiation therapy, or combinations thereof.~~

~~269. The method of claim 244, wherein the disease or disorder is an angiogenesis-dependent cancer.~~

~~270. The method of claim 244, wherein the disease or disorder is an angiogenesis-dependent benign tumor.~~

~~271. The method of claim 244, wherein the disease or disorder is an endocrine disorder.~~

~~272. The method of claim 244, wherein the disease or disorder is an ophthalmic disease or disorder.~~

~~273. The method of claim 244, wherein the disease or disorder is an ocular angiogenic disease or condition.~~

~~274. The method of claim 244, wherein the disease or disorder is disseminated intravascular coagulation (DIC), a complement mediated coagulation disorder, or combinations thereof.~~

~~275. The method of claim 244, wherein the disease or disorder is acute radiation syndrome, dense deposit disease, Degos Disease, Catastrophic Antiphospholipid Syndrome (CAPS), Behcet's disease, cryoglobulinemia; paroxysmal nocturnal hemoglobinuria ("PNH"), cold agglutinin disease, or combinations thereof.~~

~~276. The method of claim 244, wherein the disease or disorder is atypical hemolytic uremic syndrome (aHUS).~~

~~277. The method of claim 244, wherein the disease or disorder is hematopoietic stem cell transplant-associated TMA.~~

~~278. The method of claim 244, wherein the disease or disorder is immunoglobulin A nephropathy (IgAN).~~

~~279. The method of claim 244, wherein the disease or disorder is lupus nephritis (LN).~~