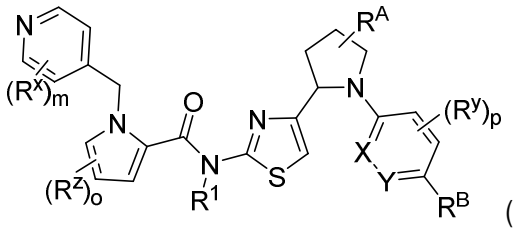
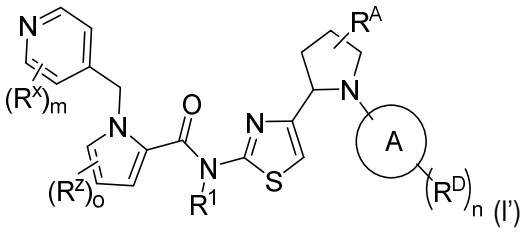
What is claimed is:

1. A compound, or pharmaceutically acceptable salt thereof, having a structure of formula (I) or (I'):


(I) or

(I')

wherein

R^1 is H, C_{1-3}alkyl, or SO_2C_{1-6}alkyl;

each of X and Y is independently N or CR^C;

ring A is a 6-membered heteroaryl having 2 nitrogen ring atoms;

R^A is H, C_{1-6}alkyl, OR^N, $N(R^N)_2$, OC_{1-6}alkylene-$N(R^N)_2$, or OC_{1-6}alkylene-OR^N;

R^B is C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-3}alkylene-C_{1-3}alkoxy, O-C_{1-3}alkylene-C_{1-3}alkoxy, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, O-C_{1-6}hydroxyalkyl, halo, C_{0-3}alkylene-CO_2R^N, C_{0-3}alkylene-$N(R^N)_2$, OC_{1-3}alkylene-$N(R^N)_2$, NO_2, C_{0-3}alkylene-$C(O)N(R^N)_2$, C_{0-3}alkylene-$N(R^N)C(O)R^N$, OC_{1-3}alkylene-$N(R^N)C(O)R^N$, C_{0-3}alkylene-$N(R^N)C(O)N(R^N)_2$, C_{0-3}alkylene-$N(R^N)SO_2R^N$, C_{0-3}alkylene-$N(R^N)C(O)OR^N$, C_{0-3}alkylene-$OC(O)N(R^N)_2$, C_{0-3}alkylene-Het, C_{0-3}alkylene-OHet, C_{0-3}alkylene-$NHCO_2$Het, C_{0-3}alkylene-OC(O)Het, C_{0-3}alkylene-$N(R^N)$Het or C_{0-3}alkylene-$N(R^N)C(O)$Het, or

if

(1) m is 1 or 2;

(2) at least one of X and Y is N,

(3) at least one R^C is other than H, or

(4) at least one of o and p is 1,

then R^B can be H; or

if Y is CR^C, then R^C and R^B can combine to form a 6-membered fused ring with the carbons to which they are attached having 0-2 ring heteroatoms selected from N, O, and S and optionally substituted with 1 or 2 substituents independently selected from oxo, halo, and C_{1-6}alkyl;

Het is an aromatic or non-aromatic 4-7 membered ring having 0-3 ring heteroatoms selected from N, O, and S, and Het is optionally substituted with 1 or 2 substituents independently selected from C_{1-6}alkyl, halo, OR^N, oxo, $C(O)R^N$, $C(O)C_{3-6}$cycloalkyl, $C(O)N(R^N)_2$, SOR^N, SO_2R^N, and $SO_2N(R^N)_2$;

each R^C is independently H, halo, C_{1-6}alkoxy, $N(R^N)_2$, CN, Het, or C_{1-6}alkyl;

n is 0, 1, or 2;

each R^D, when present, is independently halo, C_{1-6}alkoxy, or C_{1-6}alkyl;

m is 0, 1, or 2;

each R^x, when present, is independently halo or C_{1-6}alkyl;

p is 0 or 1;

R^y, when present, is C_{1-6}alkyl or halo;

o is 0 or 1;

R^z, when present, is CN, halo, $C(O)N(R^N)_2$, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}hydroxyalkyl, or C_{1-6}haloalkyl; and

each R^N is independently H, C_{1-6}alkyl, C_{1-6}hydroxyalkyl, or C_{1-6}haloalkyl,

with the proviso that when each of m, p, and o is 0, R^1 is H, X and Y are each CR^C, and at least one R^C is F, then R^B is not F.

~~2. The compound or salt of claim 1, wherein R^1 is H.~~

~~3. The compound or salt of claim 1 or 2, wherein R^A is H.~~

~~4. The compound or salt of claim 1 or 2, wherein R^A is OC_{1-6}alkylene $N(R^N)_2$ or OC_{1-6}alkylene OR^N.~~

~~5. The compound or salt of claim 1 or 2, wherein R^A is OR^N or $N(R^N)_2$.~~

~~6. The compound or salt of any one of claims 1 to 5, wherein X is N.~~

~~7. The compound or salt of any one of claims 1 to 5, wherein X is CR^C.~~

~~8. The compound or salt of any one of claims 1 to 7, wherein Y is N.~~

~~9. The compound or salt of any one of claims 1 to 7, wherein Y is CR^C.~~

~~10.~~2. The compound or salt of claim ~~9~~1, wherein Y is CR^C and R^C and R^B combine to form a 6-membered fused ring with the carbons to which they are attached having 0-1 ring heteroatoms selected from N, O, and S and optionally substituted with 1 or 2 substituents independently selected from oxo, halo, and C_{1-6}alkyl.

~~11.~~3. The compound or salt of claim ~~7 or 9~~1, wherein at least one R^C is H.

~~12. The compound or salt of claim 11, wherein each R^C is H.~~

~~13.~~4. The compound or salt of claim ~~7, 9, or 11~~1, wherein at least one R^C is halo.

~~14. The compound or salt of claim 13, wherein R^C is fluoro.~~

~~15. The compound or salt of claim 7, 9, 11, 13, or 14, wherein at least one R^C is C_{1-6}alkoxy or C_{1-6}alkyl.~~

~~16. The compound or salt of claim 7, 9, 11, or 13 to 15, wherein at least one R^C is $N(R^N)_2$, CN or Het.~~

~~17.~~5. The compound or salt of any one of claims 1, 3, or 4 ~~to 9 and 11 to 16~~, wherein R^B is C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-3}alkylene-C_{1-3}alkoxy, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, halo, C_{3-6}cycloalkyl, CO_2R^N, C_{0-3}alkylene-$N(R^N)_2$, NO_2, C_{0-3}alkylene-$C(O)N(R^N)_2$, C_{0-3}alkylene-$N(R^N)C(O)R^N$, Het, or OHet.

~~18.~~6. The compound or salt of any one of claims 1, 3, or 4 ~~to 9 and 11 to 16~~, wherein R^B is C_{0-3}alkylene-$N(R^N)C(O)R^N$, OC_{1-3}alkylene-$N(R^N)C(O)R^N$, C_{0-3}alkylene-$N(R^N)C(O)N(R^N)_2$, C_{0-3}alkylene-$N(R^N)C(O)OR^N$, or C_{1-6}haloalkyl.~~.~~

~~19. The compound or salt of any one of claims 1 to 9 and 11 to 16, wherein R^B is C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, or halo.~~

~~20. The compound or salt of any one of claims 1 to 9 and 11 to 16, wherein R^B is CO_2R^N, C_{0-3}alkylene-$N(R^N)_2$, C_{0-3}alkylene-$C(O)N(R^N)_2$, or C_{0-3}alkylene-$N(R^N)C(O)R^N$.~~

~~21.~~7. The compound or salt of any one of claims 1, 3, or 4 ~~to 9 and 11 to 16~~, wherein R^B is Het or OHet, and Het is unsubstituted C_{3-6}cycloalkyl, or an aromatic or non-aromatic 4-7 membered heterocycle with 1-3 ring heteroatoms substituted with 1 substituent selected from C_{1-6}alkyl, O-C_{1-6}alkyl, oxo, $C(O)C_{1-6}$alkyl, and SO_2C_{1-6}alkyl.

~~22.~~8. The compound or salt of any one of claims 1, 3, or 4 ~~to 9 and 11 to 16~~, wherein R^B is O-C_{1-3}alkylene-C_{1-3}alkoxy, O-C_{1-6}hydroxyalkyl, OC_{1-3}alkylene-$N(R^N)_2$, OC_{1-3}alkylene-$N(R^N)C(O)R^N$, C_{0-3}alkylene-$N(R^N)C(O)N(R^N)_2$, C_{0-3}alkylene-$N(R^N)SO_2R^N$, C_{0-3}alkylene-$N(R^N)C(O)OR^N$, C_{1-3}alkylene-Het, NH-Het, NHC(O)Het, or NHC(O)OHet.

~~23. The compound or salt of claim 21 or 22, wherein Het is an aromatic 5-7 membered heterocycle having 1-3 ring heteroatoms.~~

~~24. The compound or salt of claim 23, wherein Het is imidazole or oxazole.~~

~~25. The compound or salt of claim 21 or 22, wherein Het is a non-aromatic 4-7 membered heterocycle having 1-3 ring heteroatoms.~~

~~26.~~9. The compound or salt of claim ~~25~~8, wherein Het is tetrahydropyran, piperidine, morpholine, tetrahydrofuran, pyrrolidine, or oxetanyl.

~~27. The compound or salt of any one of claims 21 to 26, wherein Het is unsubstituted.~~

~~28. The compound or salt of any one of claims 21 to 26, wherein Het is substituted.~~

~~29. The compound or salt of claim 28, wherein Het is mono-substituted.~~

~~30. The compound or salt of claim 28, wherein Het is di-substituted.~~

~~31. The compound or salt of any one of claims 28 to 30, wherein Het is a non-aromatic 4-7 membered heterocycle and is substituted with oxo.~~

~~32. The compound or salt of any one of claims 28 to 31, wherein Het is substituted with C_{1-6}alkyl.~~

~~33. The compound or salt of any one of claims 28 to 32, wherein Het is substituted with C_{1-6}alkoxy.~~

~~34. The compound or salt of any one of claims 28 to 33, wherein Het is substituted with $C(O)R^N$ or SO_2R^N.~~

~~35. The compound or salt of any one of claims 28 to 34, wherein Het is substituted with halo.~~

~~36. The compound or salt of any one of claims 28 to 35, wherein~~

~~37. The compound or salt of any one of claims 28 to 35, wherein $C(O)N(R^N)_2$.~~

~~38. The compound or salt of any one of claims 1 to 9 and 11 to 15, wherein R^B is H.~~

~~39.~~10. The compound or salt of claim any one of claims 1 to ~~38~~9, wherein m is 1 and R^x is at 2-position of pyridine.

~~40.~~11. The compound or salt of claim 1 to ~~38~~9, wherein m is 2, optionally where one R^x is at 2-position and other R^x at 6-position of pyridine.

~~41.~~12. The compound or salt of claim ~~39~~10 or ~~40~~11, wherein at least one R^x is halo or methyl.

~~42. The compound or salt of claim 41, wherein halo is fluoro.~~

~~43.~~13. The compound or salt of any one of claims ~~38~~10 to ~~42~~12, wherein X is N.

~~44.~~14. The compound or salt of any one of claims ~~38~~10 to ~~43~~13, wherein Y is N.

~~45.~~15. The compound or salt of any one of claims ~~38~~10 to ~~44~~14, wherein at least one R^C is halo, C_{1-6}alkoxy, $N(R^N)_2$, CN, Het, or C_{1-6}alkyl.

~~46. The compound or salt of claim 45, wherein at least one R^C is halo, C_{1-6}alkoxy, or C_{1-6}alkyl.~~

~~47.~~16. The compound or salt of any one of claims 1 to ~~46~~15, wherein o is 1, and R^z is meta to ring nitrogen.

~~48.~~17. The compound or salt of claim ~~47~~16, wherein R^z is CN, fluoro, or methyl.

~~49.~~18. The compound or salt of any one of claims 1 to ~~48~~17, wherein p is 1.

~~50.~~19. The compound or salt of claim ~~49~~18, wherein R^y is methyl or fluoro.

~~51.~~20. The compound or salt of any one of claims 1, ~~1~~75 to ~~3~~79, ~~47~~16, and ~~48~~17, wherein R^1 is H, X and Y are each CH, R^A is H, m is 1, R^x is fluoro at 2-position of pyridine, and p is 0.

~~52.~~21. The compound or salt of ~~any one of claims 1 to 5~~claim 1, wherein ring A is pyrimidinyl, pyrazinyl, or pyradazinyl.

~~53. The compound or salt of any one of claims 1 to 5, wherein ring A is pyrazinyl.~~

~~54. The compound or salt of any one of claims 1 to 5, wherein ring A is pyradazinyl.~~

~~55. The compound or salt of any one of claims 1 to 5 and 52 to 54, wherein n is 0.~~

~~56. The compound or salt of any one of claims 1 to 5 and 52 to 54, wherein n is 1.~~

~~57. The compound or salt of any one of claims 1 to 5 and 52 to 54, wherein n is 2.~~

~~58. The compound or salt of claim 56 or 57, wherein at least one R^D is halo.~~

~~59. The compound or salt of claim 58, wherein R^D is fluoro.~~

~~60. The compound or salt of any one of claims 56 to 59, wherein at least one R^D is C_{1-6}alkoxy.~~

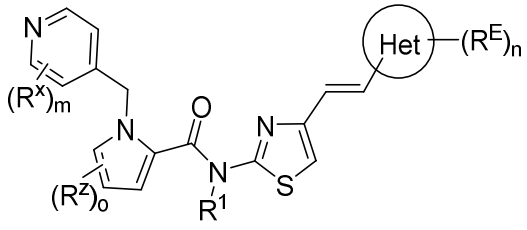
~~61. The compound or salt of any one of claims 56 to 60, wherein at least one R^D is C_{1-6}alkyl.~~

~~62.~~22. The compound or salt of any one of claims 1 to ~~61~~21, wherein each R^N is independently H or methyl.

~~63. The compound or salt of any one of claims 1 to 61, wherein at least one R^N is C_{1-6}hydroxyalkyl or C_{1-6}haloalkyl.~~

~~64.~~23. The compound or salt of claim 1, having a structure as shown in Table A.

~~65.~~24. A compound, or pharmaceutically acceptable salt thereof, having a structure of formula (II):



(II)

wherein

R^1 is H, C_{1-3}alkyl, or SO_2C_{1-6}alkyl;

Het is oxazole, imidazole, pyrazole, isoxazole, morpholine, tetrahydroquinoline, oxazolidinone, piperidinone,, dihydrooxazole, pyrazine, pyrimidine, imidazo[1,2-*a*]pyridine, 5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridine, pyridine-2(1*H*)-one, 6,7-dihydro-5*H*-pyrrolo[1,2-a]imidazole, or quinoline, or

when at least one of n and m is 1 or 2, Het can be pyridine, and when n is 1 or 2, Het can be diazinyl;

n is 0, 1, or 2;

each R^E, when present, is independently halo, C_{1-6}alkyl, C_{0-6}alkylene-$C(O)N(R^N)_2$, C_{0-6}alkylene-$N(R^N)C(O)R^N$, C_{0-6}alkylene-CN, C_{0-6}alkylene-OR^N, C_{0-6}alkylene-$N(R^N)_2$, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{1-6}hydroxyalkyl, C_{0-6}alkylene-CO_2R^N, or C_{0-6}alkylene-$[C(O)]_{0-1}$-3-6 membered aromatic or non-aromatic ring having 0-2 ring heteroatoms independently selected from N, O and S;

wherein when R^E comprises a 3-6 membered ring, , it is optionally substituted with 1-2 groups independently selected from halo, C_{1-6}alkyl, CN, C_{1-6}haloalkyl, CO_2R^N, $C(O)R^N$, $CON(R^N)_2$, $N(R^N)COR^N$, and OR^N;

m is 0, 1, or 2;

each R^x, when present, is independently halo or C_{1-6}alkyl;

o is 0 or 1;

R^z, when present, is CN, halo, $C(O)N(R^N)_2$, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}hydroxyalkyl, or C_{1-6}haloalkyl; and

each R^N is independently H, C_{1-6}alkyl, C_{1-6}hydroxyalkyl, or C_{1-6}haloalkyl.

~~66.~~25. The compound or salt of claim ~~65~~24, wherein R^1 is H.

~~67.~~26. The compound or salt of claim ~~65~~ 24 or ~~66~~25, wherein Het is oxazole.

~~68.~~27. The compound or salt of claim ~~65~~24 or ~~66~~25, wherein Het is imidazole.

~~69.~~28. The compound or salt of claim ~~65~~24 or ~~66~~25, wherein Het is isoxazole, morpholine, tetrahydroquinoline, oxazolidinone, piperidinone, or dihydrooxazole.

~~70. The compound or salt of claim 65 or 66, wherein Het is pyrazine, pyrimidine, imidazo[1,2-a]pyridine, 5,6,7,8-tetrahydroimidazo[1,5-a]pyridine, pyridine-2(1*H*)-one, 6,7-dihydro-5*H*-pyrrolo[1,2-a]imidazole, or quinoline.~~

~~71.~~29. The compound or salt of any one of claims ~~65~~24 to ~~70~~28, wherein n is 0.

~~72.~~30. The compound or salt of any one of claims ~~65~~24 to ~~70~~28, wherein n is 1.

~~73.~~31. The compound or salt of any one of claims ~~65~~24 to ~~70~~28, wherein n is 2.

~~74. The compound or salt of claim 72 or 73, wherein Het is diazinyl.~~

~~75.~~32. The compound or salt of claim ~~72 or 73~~30 or 31, wherein Het is pyridine.

~~76.~~33. The compound or salt of any one of claims ~~72~~30 to ~~75~~32, wherein at least one R^E is halo.

~~77. The compound or salt of claim 76, wherein at least one R^E is fluoro.~~

~~78.~~34. The compound or salt of any one of claims ~~72~~30 to ~~77~~33, wherein at least one R^E is C_{1-6}alkyl or $C(O)N(R^N)_2$.

~~79.~~35. The compound or salt of any one of claims ~~72~~30 to ~~78~~34, wherein at least one R^E is C_{0-6}alkylene-OR^N or C_{0-6}alkylene-$N(R^N)_2$.

~~80.~~36. The compound or salt of any one of claims ~~72~~30 to ~~79~~35, wherein at least one R^E is C_{1-6}alkylene-$C(O)N(R^N)_2$, C_{1-6}alkylene-CN, C_{1-6}hydroxyalkyl, C_{0-6}alkylene-$[C(O)]_{0-1}$- 3-6 membered non-aromatic ring having 1 or 2 ring heteroatoms independently selected from N, O and S, or C_{1-6}alkylene-CO_2R^N.

~~81. The compound or salt of claim 80, wherein the 3-6 membered ring is unsubstituted.~~

~~82. The compound or salt of claim 80, wherein the 3-6 membered ring is substituted.~~

~~83.~~37. The compound or salt of claim ~~82~~36, wherein the 3-6 membered ring is substituted with one substituent selected from halo, C_{1-6}alkyl, CN, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, OH, C_{1-6}alkoxy, CO_2R^N, $C(O)R^N$, $CON(R^N)_2$, and $N(R^N)COR^N$.

~~84.~~38. The compound or salt of any one of claims ~~72~~30 to ~~79~~35, wherein at least one R^E is C_{0-3}alkylene-phenyl.

~~85. The compound or salt of claim 84, wherein the phenyl is unsubstituted.~~

~~86. The compound or salt of claim 84, wherein the phenyl is substituted with 1 substituent selected from halo, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, $CON(R^N)_2$, $N(R^N)COR^N$ and OR^N.~~

~~87.~~39. The compound or salt of any one of claims ~~65~~24 to ~~86~~38, wherein m is 0.

~~88.~~40. The compound or salt of any one of claims ~~65~~24 to ~~86~~38, wherein m is 1 and R^x is at 2-position of pyridine.

~~89.~~41. The compound or salt of any one of claims ~~65~~24 to ~~86~~38, wherein m is 2, optionally where one R^x is at 2-position and other R^x at 6-position of pyridine.

~~90.~~42. The compound or salt of claim ~~88~~40 or ~~89~~41, wherein at least one R^x is methyl or fluoro.

~~91. The compound or salt of any one of claims 88 to 90, wherein Het is pyridine.~~

~~92.~~43. The compound or salt of any one of claims ~~65~~24 to ~~91~~42, wherein o is 0.

~~93.~~44. The compound or salt of any one of claims ~~65~~24 to ~~91~~42, wherein o is 1.

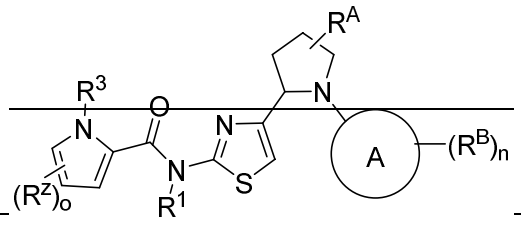
~~94. The compound or salt of claim 93, wherein R^z is methyl or fluoro.~~

~~95. The compound or salt of any one of claims 65 to 94, wherein each R^N is independently H or methyl.~~

~~96. The compound or salt of any one of claims 65 to 94, wherein at least one R^N is C_{1-6}hydroxyalkyl or C_{1-6}haloalkyl.~~

~~97.~~45. The compound or salt of claim ~~65~~24, having a structure as shown in Table B.

~~98. A compound, or pharmaceutically acceptable salt thereof, having a structure of formula (III):~~



~~(III)~~

~~wherein~~

~~R^1 is H, C_{1-3}alkyl, or SO_2C_{1-6}alkyl;~~

~~R^A is H, C_{1-6}alkyl, OR^N, $N(R^N)_2$, OC_{1-6}alkylene $N(R^N)_2$, or OC_{1-6}alkylene OR^N;~~

~~n is 0, 1, or 2;~~

ring A is phenyl or a 6-membered heteroaryl having 1 or 2 nitrogen ring atoms;

each R^B, when present, is independently C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{1-3}alkylene-C_{1-3}alkoxy, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, halo, C_{0-3}alkylene-CO_2R^N, C_{0-3}alkylene-$C(O)N(R^N)_2$, C_{0-3}alkylene-$N(R^N)_2$, OC_{1-3}alkylene-$N(R^N)_2$, NO_2, C_{0-3}alkylene-$N(R^N)C(O)R^N$, C_{0-3}alkylene-$N(R^N)C(O)OR^N$, OC_{1-3}alkylene-$N(R^N)C(O)R^N$, C_{0-3}alkylene-$N(R^N)C(O)N(R^N)_2$, C_{0-3}alkylene-$N(R^N)SO_2R^N$, C_{0-3}alkylene-$OC(O)N(R^N)_2$, C_{0-3}alkylene-Het, C_{0-3}alkylene-OHet, C_{0-3}alkylene-$NHCO_2$Het, C_{0-3}alkylene-OC(O)Het, C_{0-3}alkylene-$N(R^N)$Het or C_{0-3}alkylene-$N(R^N)C(O)$Het;

Het is an aromatic or non-aromatic 4-7 membered ring having 0-3 ring heteroatoms selected from N, O, and S;

Het is optionally substituted with 1 substituent selected from C_{1-6}alkyl, OR^N, halo, oxo, $C(O)R^N$, $C(O)N(R^N)_2$, SOR^N, $SO_2N(R^N)_2$, and SO_2R^N;

R^3 is C_{1-6}alkylene-X, C_{2-6}alkenylene-X, C_{0-2}alkylene-C_{3-6}carbocycle-C_{0-2}alkylene-X, or Ar, and the alkylene is optionally substituted with OR^N;

X is H, OC_{1-3}alkyl, $C{\equiv}CR^N$; CN, CO_2R^N; $CON(R^N)_2$, or Ar,

Ar is a 3-10 membered aromatic or non-aromatic monocyclic or polycyclic ring having 0-4 ring heteroatoms selected from N, O, and S, with the proviso that when Ar is a 6-membered aromatic ring, it has 0 or 2-4 ring heteroatoms,

Ar is optionally substituted with C_{1-3}alkyl, C_{0-2}alkylene-CN, $CON(R^N)_2$, tetrazole, oxazole, or 1-2 halo;

o is 0 or 1;

R^z, when present, is CN, halo, $C(O)N(R^N)_2$, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}hydroxyalkyl, or C_{1-6}haloalkyl; and

each R^N is independently H, C_{1-6}alkyl, C_{1-6}hydroxyalkyl, or C_{1-6}haloalkyl.

99. The compound or salt of claim 98, wherein R^1 is H.

100. The compound or salt of claim 98 or 99, wherein R^A is H.

101. The compound or salt of claim 98 or 99, wherein R^A is OC_{1-6}alkylene-$N(R^N)_2$ or OC_{1-6}alkylene-OR^N.

102. The compound or salt of claim 98 or 99, wherein R^A is OR^N or $N(R^N)_2$.

103. The compound or salt of any one of claims 98 to 102, wherein ring A is phenyl.

104. The compound or salt of any one of claims 98 to 102, wherein ring A is a 6-membered heteroaryl having 1 or 2 nitrogen ring atoms.

105. The compound or salt of claim 104, wherein ring A is pyridyl.

106. The compound or salt of claim 104, wherein ring A is a diazinyl.

~~107. The compound or salt of claim 106, wherein ring A is pyrimidinyl.~~

~~108. The compound or salt of claim 106, wherein ring A is pyrazinyl.~~

~~109. The compound or salt of claim 106, wherein ring A is pyradazinyl.~~

~~110. The compound or salt of any one of claims 98 to 109, wherein n is 0.~~

~~111. The compound or salt of any one of claims 98 to 109, wherein n is 1.~~

~~112. The compound or salt of claim 111, wherein R^B is C_{1-6}alkyl.~~

~~113. The compound or salt of claim 111, wherein R^B is C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, or halo.~~

~~114. The compound or salt of claim 111, wherein R^B is CO_2R^N, $N(R^N)_2$, C_{0-3}alkylene-$C(O)N(R^N)_2$, or C_{0-3}alkylene-$N(R^N)C(O)R^N$.~~

~~115. The compound or salt of claim 111, wherein R^B is C_{3-6}cycloalkyl, Het, or OHet.~~

~~116. The compound or salt of claim 115, wherein Het is an aromatic 5-7 membered heterocycle having 1-3 ring heteroatoms.~~

~~117. The compound or salt of claim 115, wherein Het is a non-aromatic 4-7 membered heterocycle having 1-3 ring heteroatoms.~~

~~118. The compound or salt of any one of claims 115 to 117, wherein Het is unsubstituted.~~

~~119. The compound or salt of any one of claims 115 to 117, wherein Het is substituted.~~

~~120. The compound or salt of claim 119, wherein Het is a non-aromatic 4-7 membered heterocycle and is substituted with oxo.~~

~~121. The compound or salt of claim 119, wherein Het is substituted with C_{1-6}alkyl.~~

~~122. The compound or salt of claim 119, wherein Het is substituted with C_{1-6}alkoxy.~~

~~123. The compound or salt of claim 119, wherein Het is substituted with $C(O)R^N$ or SO_2R^N.~~

~~124. The compound or salt of any one of claims 98 to 123, wherein R^3 is C_{1-6}alkylene-X.~~

~~125. The compound or salt of any one of claims 98 to 123, wherein R^3 C_{2-6}alkenylene-X or C_{0-2}alkylene-C_{3-6}carbocycle-C_{0-2}alkylene-X.~~

~~126. The compound or salt of any one of claims 98 to 125, wherein X is H, OC_{1-3}alkyl, CN, CO_2R^N, or $CON(R^N)_2$.~~

~~127. The compound or salt of any one of claims 98 to 125, wherein X is $C{\equiv}CR^N$.~~

~~128. The compound or salt of any one of claims 98 to 125, wherein X or R^3 is Ar.~~

~~129. The compound or salt of claim 128, wherein Ar is 3-10 membered non-aromatic monocyclic or polycyclic ring having 0-4 ring heteroatoms selected from N, O, and S.~~

~~130. The compound or salt of claim 128, wherein Ar is a 5-10 membered aromatic monocyclic or polycyclic ring having 0-4 ring heteroatoms selected from N, O, and S.~~

~~131. The compound or salt of claim 130, wherein Ar is phenyl.~~

~~132. The compound or salt of claim 130, wherein Ar is a 5-10 membered aromatic monocyclic or polycyclic ring having 1-4 ring heteroatoms selected from N, O, and S.~~

~~133. The compound or salt of claim 130, wherein Ar is a 5 or 7-10 membered aromatic monocyclic or polycyclic ring having 1-4 ring heteroatoms selected from N, O, and S.~~

~~134. The compound or salt of claim 130, wherein Ar is a 6-10 membered aromatic monocyclic or polycyclic ring having 2-4 ring heteroatoms selected from N, O, and S.~~

~~135. The compound or salt of claim 130, wherein Ar is phenyl, tetrahydropyran, dihydropyran, tetrahydrofuran, C_{3-6}cycloalkyl, tetrazole, triazole, oxazole, tetrahydroquinoline, N-methyl-tetrahydroisoquinoline, tetrahydrothiopyranyl dioxide, pyridinone, piperidinone, or oxetanyl.~~

~~136. The compound or salt of any one of claims 130 to 135, wherein Ar is unsubstituted.~~

~~137. The compound or salt of any one of claims 130 to 135, wherein Ar is substituted, optionally where at least one substituent is meta to point of attachment.~~

~~138. The compound or salt of claim 137, wherein Ar is substituted with C_{1-3}alkyl, C_{0-2}alklene-CN, or $CON(R^N)_2$.~~

139. The compound or salt of claim 137 or 138, wherein Ar is substituted with 1 or 2 halo.

140. The compound or salt of claim 139, wherein the halo is fluoro.

141. The compound or salt of any one of claims 88 to 140, wherein o is 0.

142. The compound or salt of any one of claims 88 to 140, wherein o is 1.

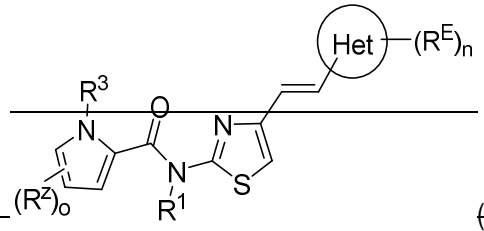
143. The compound or salt of claim 142, wherein R^Z is methyl or fluoro.

144. The compound or salt of any one of claims 88 to 143, wherein each R^N is independently H or methyl.

145. The compound or salt of any one of claims 88 to 143, wherein at least one R^N is C_{1-6}hydroxyalkyl or C_{1-6}haloalkyl.

146. The compound or salt of claim 88, having a structure as shown in Table C.

147. A compound, or pharmaceutically acceptable salt thereof, having a structure of formula (IV):



(IV)

R^1 is H, C_{1-3}alkyl, or SO_2C_{1-6}alkyl;

Het is 3-10 membered aromatic or non-aromatic heterocycle having 1-4 ring heteroatoms selected from N, O, and S;

n is 0, 1, or 2; and

each R^E, when present, is independently halo, C_{1-6}alkyl, phenyl, $C(O)N(R^N)_2$, CN, C_{0-6}alkylene-OR^N, C_{0-6}alkylene-$N(R^N)_2$, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, C_{3-6}cycloalkyl, or CO_2R^N;

wherein when R^E is phenyl, it is optionally substituted with 1-2 groups independently selected from halo, C_{1-6}alkyl, CN, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, CO_2R^N, $CON(R^N)_2$, $N(R^N)COR^N$, and OR^N;

R^3 is C_{1-6}alkylene-X, C_{2-6}alkenylene-X, Ar, or C_{0-2}alkylene-C_{3-6}carbocycle-C_{0-2}alkylene-X;

X is H, OC_{1-3}alkyl, $C{\equiv}CR^N$, CN, CO_2R^N, $CON(R^N)_2$, or Ar,

Ar is a 3-10 membered aromatic or non-aromatic ring having 0-4 ring heteroatoms selected from N, O, and S, with the proviso that when Ar is a 6-membered aromatic ring, it has 0 or 2-4 ring heteroatoms;

Ar is optionally substituted with C_{1-3}alkyl, C_{0-2}alklene-CN, $CON(R^N)_2$, tetrazole, oxazole, or 1-2 halo;

o is 0 or 1;

R^z, when present, is CN, halo, $C(O)N(R^N)_2$, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}hydroxyalkyl, or C_{1-6}haloalkyl; and

each R^N is independently H, C_{1-6}alkyl, C_{1-6}hydroxyalkyl, or C_{1-6}haloalkyl.

148. The compound or salt of claim 147, wherein R^1 is H.

149. The compound or salt of claim 147 or 148, wherein Het is a 3-10 membered non-aromatic heterocycle having 1-4 ring heteroatoms selected from N, O, and S.

150. The compound or salt of claim 149, wherein Het is tetrahydropyran.

151. The compound or salt of claim 147 or 148, wherein Het is a 5-10 membered aromatic heterocycle having 1-4 ring heteroatoms selected from N, O, and S.

152. The compound or salt of claim 151, wherein oxazole.

153. The compound or salt of claim 151, wherein Het is imidazole.

154. The compound or salt of claim 151, wherein Het is diazinyl.

155. The compound or salt of claim 154, wherein the diazinyl is pyrimidinyl.

156. The compound or salt of claim 154, wherein the diazinyl is pyrazinyl.

157. The compound or salt of claim 154, wherein the diazinyl is pyradazinyl.

158. The compound or salt of claim 147 or 148, wherein Het is isoxazole, morpholine, tetrahydroquinoline, oxazolidinone, piperidinone, or dihydrooxazole.

159. The compound or salt of any one of claims 147 to 158, wherein n is 0.

160. The compound or salt of any one of claims 147 to 158, wherein n is 1.

161. The compound or salt of any one of claims 147 to 158, wherein n is 2.

162. The compound or salt of claim 160 or 161, wherein at least one R^E is halo.

163. The compound or salt of claim 162, wherein at least one R^E is fluoro.

~~164. The compound or salt of any one of claims 160 to 163, wherein at least one R^E is C_{1-6}alkyl or $C(O)N(R^N)_2$.~~

~~165. The compound or salt of any one of claims 160 to 164, wherein at least one R^E is C_{0-6}alkylene-OR^N or C_{0-6}alkylene-$N(R^N)_2$.~~

~~166. The compound or salt of any one of claims 160 to 165, wherein at least one R^E is phenyl.~~

~~167. The compound or salt of claim 166, wherein the phenyl is unsubstituted.~~

~~168. The compound or salt of claim 166, wherein the phenyl is substituted with 1 substituent selected from halo, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, $CON(R^N)_2$, $N(R^N)COR^N$ and OR^N.~~

~~169. The compound or salt of any one of claims 147 to 168, wherein R^3 is C_{1-6}alkylene-X, optionally CH_2X.~~

~~170. The compound or salt of any one of claims 147 to 168, wherein R^3 is C_{2-6}alkenylene-X or C_{0-2}alkylene-C_{3-6}carbocycle-C_{0-2}alkylene-X.~~

~~171. The compound or salt of any one of claims 147 to 170, wherein X is H, OC_{1-3}alkyl, CN, CO_2R^N, or $CON(R^N)_2$.~~

~~172. The compound or salt of any one of claims 147 to 170, wherein X is $C{\equiv}CR^N$.~~

~~173. The compound or salt of any one of claims 147 to 170, wherein X or R^3 is Ar.~~

~~174. The compound or salt of claim 173, wherein Ar is 3-10 membered non-aromatic monocyclic or polycyclic ring having 0-4 ring heteroatoms selected from N, O, and S.~~

~~175. The compound or salt of claim 173, wherein Ar is a 5-10 membered aromatic monocyclic or polycyclic ring having 0-4 ring heteroatoms selected from N, O, and S.~~

~~176. The compound or salt of claim 173, wherein Ar is phenyl, optionally where R^3 is CH_2-phenyl.~~

~~177. The compound or salt of claim 173, wherein Ar is a 5-10 membered aromatic monocyclic or polycyclic ring having 1-4 ring heteroatoms selected from N, O, and S.~~

~~178. The compound or salt of claim 177, wherein Ar is a 5 or 7-10 membered aromatic monocyclic or polycyclic ring having 1-4 ring heteroatoms selected from N, O, and S.~~

179. The compound or salt of claim 177, wherein Ar is a 6-10 membered aromatic monocyclic or polycyclic ring having 2-4 ring heteroatoms selected from N, O, and S.

180. The compound or salt of claim 173, wherein Ar is phenyl, tetrahydropyran, dihydropyran, tetrahydrofuran, C_{3-6}cycloalkyl, tetrazole, triazole, oxazole, tetrahydroquinoline, N-methyl tetrahydroisoquinoline, tetrahydrothiopyranyl dioxide, pyridinone, piperidinone, or oxetanyl.

181. The compound or salt of any one of claims 173 to 180, wherein Ar is unsubstituted.

182. The compound or salt of any one of claims 173 to 180, wherein Ar is substituted, optionally where, when Ar is phenyl, the substitution is meta to the point of attachment of the phenyl.

183. The compound or salt of claim 182, wherein Ar is substituted with C_{1-3}alkyl, C_{0-2}alklene-CN, or $CON(R^N)_2$.

184. The compound or salt of claim 182 or 183, wherein Ar is substituted with 1 or 2 halo.

185. The compound or salt of claim 184, wherein the halo is fluoro.

186. The compound or salt of claim 147, having a structure as shown in Table D.

187. A compound, or pharmaceutically acceptable salt thereof, as listed in Table E.

188. A pharmaceutical composition comprising the compound or salt of any one of claims 1 to 187 and a pharmaceutically acceptable excipient.

189. A method of inhibiting protein secretion in a cell comprising contacting the cell with the compound or salt of any one of claims 1 to 187 in an amount effective to inhibit secretion.

190. The method of claim 189, wherein the protein is a checkpoint protein.

191. The method of claim 189, wherein the protein is a cell-surface protein, endoplasmic reticulum associated protein, or secreted protein involved in regulation of anti-tumor immune response.

192. The method of claim 189, wherein the protein is at least one of PD-1, PD-L1, TIM-1, LAG-3, CTLA4, BTLA, OX-40, B7H1, B7H4, CD137, CD47, CD96, CD73, CD40, VISTA, TIGIT, LAIR1, CD160, 2B4, TGFRβ and combinations thereof.

~~193. The method of claim 189, wherein the protein is selected from the group consisting of HER3, TNFα, IL2, and PD1.~~

~~194. The method of any one of claims 189 to 193, wherein the contacting comprising administering the compound to a subject in need thereof.~~

~~195. A method for treating inflammation in a subject comprising administering to the subject a therapeutically effective amount of the compound or salt of any one of claims 1 to 187.~~

~~196.~~46. ~~A method for treating cancer in a subject comprising administering to the subject a therapeutically effective amount of t~~The compound or salt of any one of claims 1 to ~~187~~45 for use in the treatment of cancer.

~~197. The method of claim 196, wherein the cancer is melanoma, multiple myeloma, prostate cancer, lung cancer, pancreatic cancer, squamous cell carcinoma, leukemia, lymphoma, a neuroendocrine tumor, bladder cancer, or colorectal cancer.~~

~~198. The method of claim 196, wherein the cancer is selected from the group consisting of prostate, lung, bladder, colorectal, and multiple myeloma.~~

~~199. The method of claim 196, wherein the cancer is non-small cell lung carcinoma, squamous cell carcinoma, leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, lymphoma, NPM/ALK-transformed anaplastic large cell lymphoma, diffuse large B-cell lymphoma, neuroendocrine tumors, breast cancer, mantle cell lymphoma, renal cell carcinoma, rhabdomyosarcoma, ovarian cancer, endometrial cancer, small cell carcinoma, adenocarcinoma, gastric carcinoma, hepatocellular carcinoma, pancreatic cancer, thyroid carcinoma, anaplastic large cell lymphoma, hemangioma, or head and neck cancer.~~

~~200. The method of claim 196, wherein the cancer is a solid tumor.~~

~~201. The method of claim 196, wherein the cancer is head and neck cancer, squamous cell carcinoma, gastric carcinoma, or pancreatic cancer.~~

~~202. A method for treating an autoimmune disease in a subject comprising administering to the subject a therapeutically effective amount of the compound or salt of any one of claims 1 to 187.~~

~~203. The method of claim 202, wherein the autoimmune disease is psoriasis, dermatitis, systemic scleroderma, sclerosis, Crohn's disease, ulcerative colitis; respiratory distress syndrome, meningitis; encephalitis; uveitis; colitis; glomerulonephritis; eczema, asthma, chronic inflammation; atherosclerosis; leukocyte adhesion deficiency; rheumatoid arthritis; systemic lupus erythematosus (SLE); diabetes mellitus; multiple sclerosis; Reynaud's~~

~~syndrome; autoimmune thyroiditis; allergic encephalomyelitis; Sjorgen's syndrome; juvenile onset diabetes; tuberculosis, sarcoidosis, polymyositis, granulomatosis and vasculitis; pernicious anemia (Addison's disease); diseases involving leukocyte diapedesis; central nervous system (CNS) inflammatory disorder; multiple organ injury syndrome; hemolytic anemia; myasthenia gravis; antigen-antibody complex mediated diseases; anti-glomerular basement membrane disease; antiphospholipid syndrome; allergic neuritis; Graves' disease; Lambert-Eaton myasthenic syndrome; pemphigoid bullous; pemphigus; autoimmune polyendocrinopathies; Reiter's disease; stiff-man syndrome; Behcet disease; giant cell arteritis; immune complex nephritis; IgA nephropathy; IgM polyneuropathies; immune thrombocytopenic purpura (ITP) or autoimmune thrombocytopenia.~~

~~204. A method for the treatment of an immune-related disease in a subject comprising administering to the subject a therapeutically effective amount of the compound or salt of any one of claims 1 to 187.~~

~~205. The method of claim 204, wherein the immune-related disease is rheumatoid arthritis, lupus, inflammatory bowel disease, multiple sclerosis, or Crohn's disease.~~

~~206. A method for treating neurodegenerative disease in a subject comprising administering to the subject a therapeutically effective amount of the compound or salt of any one of claims 1 to 187.~~

~~207. The method of claim 206, wherein the neurodegenerative disease is multiple sclerosis.~~

~~208. A method for treating an inflammatory disease in a subject comprising administering to the subject a therapeutically effective amount of the compound or salt of any one of claims 1 to 187.~~

~~209. The method of claim 208, wherein the inflammatory disease is bronchitis, conjunctivitis, myocarditis, pancreatitis, chronic cholecstitis, bronchiectasis, aortic valve stenosis, restenosis, psoriasis or arthritis.~~