

THIAZOLE DERIVATIVES AS PROTEIN SECRETION INHIBITORS

BACKGROUND

Field of the Invention

[0001] The present disclosure relates to protein secretion inhibitors, including methods of making and using the same.

Incorporation by Reference of Material Submitted Electronically

[0002] This application contains, as a separate part of the disclosure, a sequence listing in computer-readable form (filename: 40061_Seqlisting.txt; 912 bytes; created: February 28, 2020) which is incorporated by reference in its entirety.

Description of Related Technology

[0003] Protein translocation into the endoplasmic reticulum ("ER") constitutes the first step of protein secretion. ER protein import is essential in all eukaryotic cells and is particularly important in fast-growing tumor cells. Thus, the process of protein secretion can serve as a target both for potential cancer drugs and for bacterial virulence factors. See Kalies and Römisch, *Traffic*, 16(10):1027-1038 (2015).

[0004] Protein transport to the ER is initiated in the cytosol when N-terminal hydrophobic signal peptides protrude from the ribosome. Binding of signal recognition particle ("SRP") to the signal sequence allows targeting of the ribosome–nascent chain–SRP complex to the ER membrane where contact of SRP with its receptor triggers handing over of the signal peptide to Sec61. Sec61 is an ER membrane protein translocator (aka translocon) that is doughnut-shaped with 3 major subunits (heterotrimeric). It includes a "plug," which blocks transport into or out of the ER. The plug is displaced when the hydrophobic region of a nascent polypeptide interacts with the "seam" region of Sec61, allowing translocation of the polypeptide into the ER lumen. In mammals, only short proteins (<160 amino acids) can enter the ER posttranslationally, and proteins smaller than 120 amino acids are obliged to use this pathway. Some of the translocation competence is maintained by the binding of calmodulin to the signal sequence. Upon arrival at the Sec61 channel, the signal peptide or signal anchor intercalates between transmembrane domains ("TMDs") 2 and 7 of Sec61 α , which form the lateral portion of the gate, allowing the channel to open for soluble secretory proteins. As the Sec61 channel consists of 10 TMDs (Sec61 α) surrounded by a hydrophobic clamp formed by Sec61 γ , channel opening is dependent on conformational changes that involve practically all TMDs.

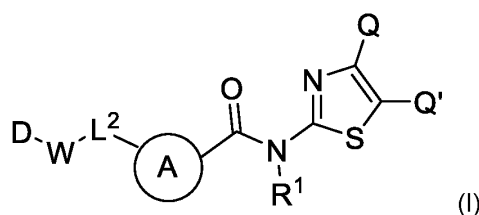
[0005] Inhibition of protein transport across the ER membrane has the potential to treat or prevent diseases, such as the growth of cancer cells and inflammation. Known secretion inhibitors, which range from broad-spectrum to highly substrate-specific, can interfere with

virtually any stage of this multistep process, and even with transport of endocytosed antigens into the cytosol for cross-presentation. These inhibitors interact with the signal peptide, chaperones, or the Sec61 channel to block substrate binding or to prevent the conformational changes needed for protein import into the ER. Examples of protein secretion inhibitors include, calmodulin inhibitors (e.g., E6 Berbamine and Ophiobolin A), Lanthanum, sterols, cyclodepsipeptides (e.g., HUN-7293, CAM741, NFI028, Cotransin, Apratoxin A, Decatransin, Valinomycin), CADA, Mycolactone, Eeyarestatin I ("ESI"), and Exotoxin A. However, the above secretion inhibitors suffer from one or more of the following: lack selectivity for the Sec61 channel, challenging manufacture due to structural complexity, and molecular weight limited administration, bio-availability and distribution.

[0006] Thus, a need exists for new inhibitors of protein secretion.

SUMMARY

[0007] Provided herein are compounds having a structure of Formula (I), or a pharmaceutically acceptable salt thereof:



wherein ring A is an aromatic or nonaromatic C₃₋₁₀ carbocycle, or an aromatic or nonaromatic 5-10 membered heterocycle having 1 or 2 ring heteroatoms selected from N, O, and S; one of Q and Q' is L¹-B and the other is R²; L¹ is a bond, C₁₋₆alkylene, or

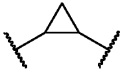
$\text{---C}_{0-2}\text{alkylene---}$, wherein --- indicates a double bond, a triple bond, or a fused or spiro cyclopropyl; B is C₁₋₃alkoxy, [O]₀₋₁-C₀₋₃alkylene-X, or NR^NC₁₋₃alkylene-X; X is an aromatic or nonaromatic C₃₋₁₀ carbocycle, or an aromatic or nonaromatic 5-10 membered heterocycle having 1-4 ring heteroatoms selected from N, O, and S; L² is C₀₋₆alkylene (e.g., C₁₋₆alkylene) or $\text{---C}_{0-2}\text{alkylene---}$, wherein --- indicates a double bond, a triple bond, or a fused or spiro cyclopropyl; W is a bond, O, or C(O)N(R^N); D is C₆₋₁₀aryl or an aromatic or nonaromatic 5-10-membered heterocycle having 1-4 ring heteroatoms selected from N, O, and S; each R^N independently is H or C₁₋₄alkyl; R¹ is H or C₁₋₃alkyl; and R² is H, C₁₋₃alkyl, or halo.

[0008] In various embodiments, R¹ is H. In various embodiments, R¹ is C₁₋₃alkyl. In some cases, R¹ is methyl or ethyl.

[0009] In some embodiments, R^2 is H. In some embodiments, R^2 is C_{1-3} alkyl. In some embodiments, R^2 is halo. In some cases, R^2 is methyl. In some cases, R^2 is ethyl. In some cases, R^2 is n-propyl or isopropyl. In some cases, R^2 is Br. In some cases, R^2 is F. In some cases, R^2 is Cl.

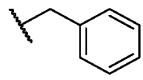
[0010] In some embodiments, Q is L^1 -B and Q' is R^2 . In some embodiments, Q is R^2 and Q' is L^1 -B.

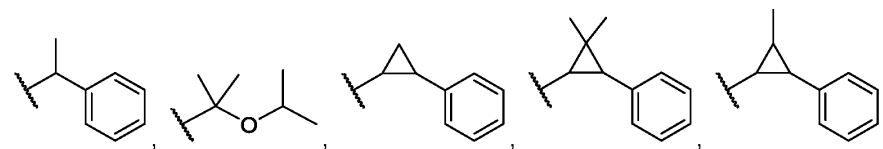
[0011] In various embodiments, L^1 is a bond. In various embodiments, L^1 is a C_{1-6} alkylene. In some cases, L^1 is CH_2 , $CH(CH_3)$, CH_2CH_2 , or $C(CH_3)_2$. In various embodiments, L^1 is $\text{---}C_{0-2}\text{alkylene}\text{---}$. In some cases, C_{0-2} alkylene is CH_2 , $CH(CH_3)$, or CH_2CH_2 . In some cases, --- indicates a double bond. In various cases, the double bond is tri- or tetra-substituted, and the 1 or 2 other substituents on the double bond are independently selected from C_{1-3} alkyl and halo. In some cases, --- indicates a triple bond.

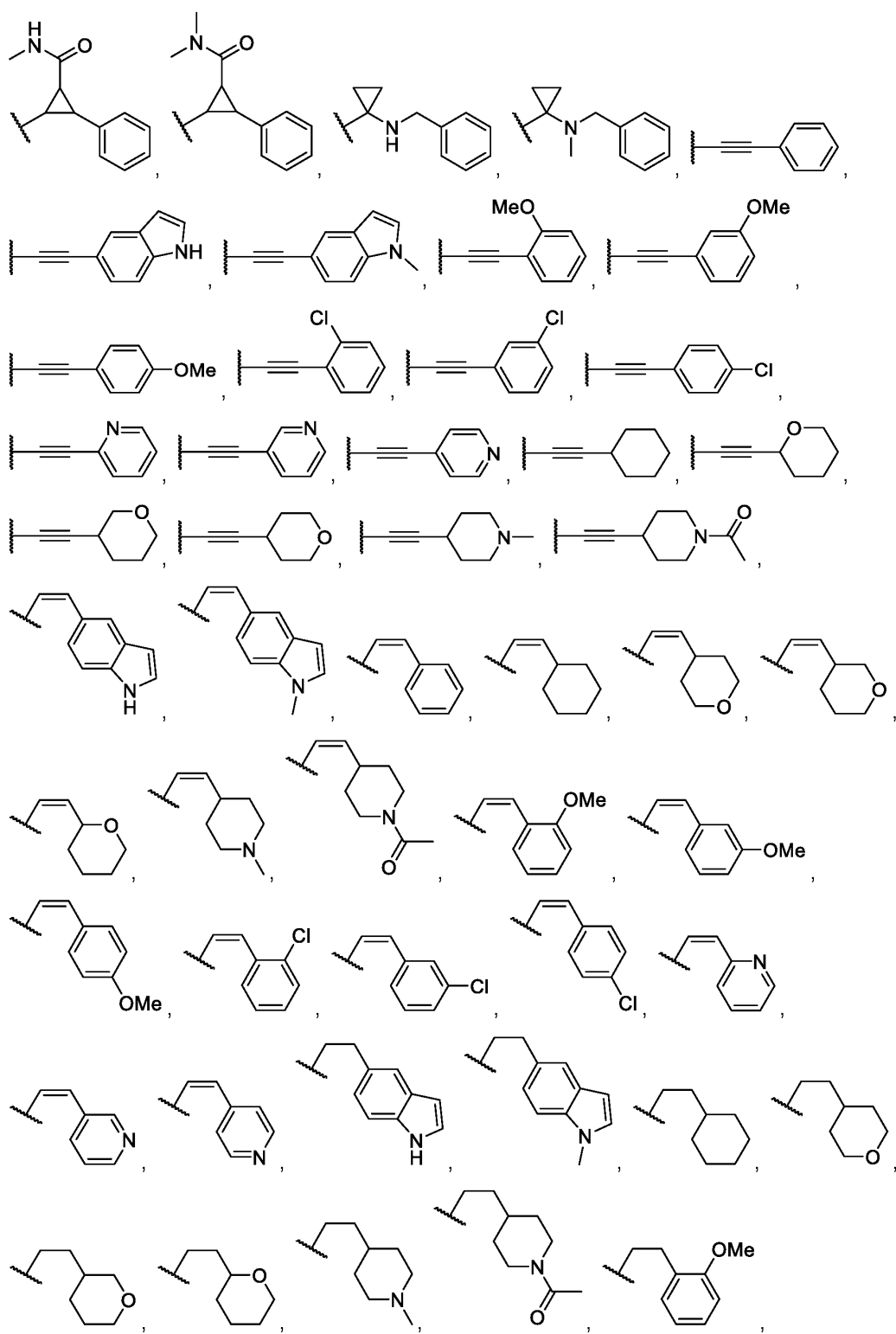
In some cases, --- indicates a fused cyclopropyl, e.g., , or a spiro cyclopropyl,

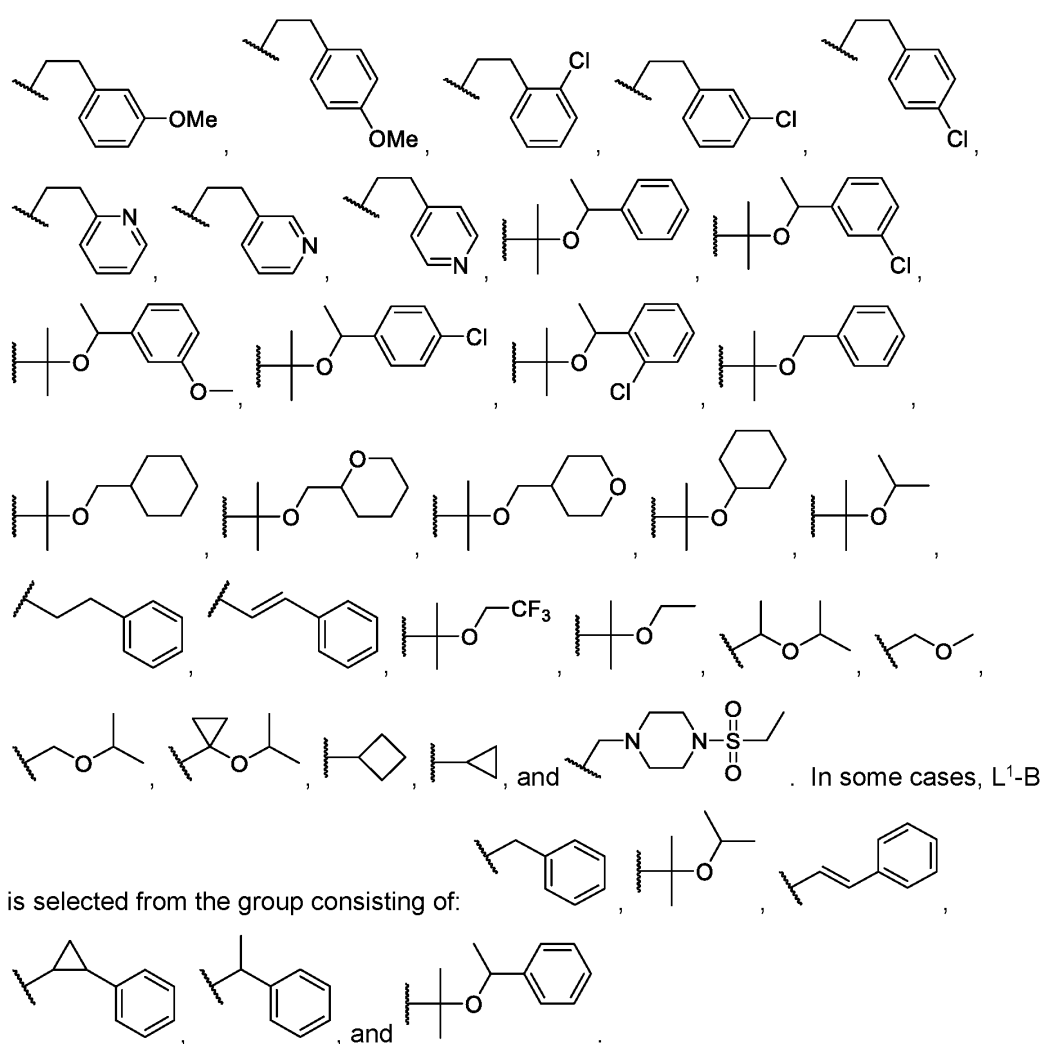
e.g., .

[0012] In some embodiments, B is C_{1-3} alkoxy. In some embodiments, B is O-X. In some embodiments, B is O- C_{1-3} alkylene-X. In some embodiments, B is C_{1-3} alkylene-X. In some embodiments, B is X. In some embodiments, B is NHC_{1-3} alkylene-X. In some embodiments, B is $N(CH_3)C_{1-3}$ alkylene-X. In various embodiments, X is an aromatic C_{6-10} carbocycle, or an aromatic or nonaromatic 5-10-membered heterocycle. In some cases, X is selected from phenyl, pyridyl, indolyl, tetrahydropyranyl, piperidinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or piperazinyl, and X is optionally substituted with 1-3 substituents independently selected from C_{1-3} alkyl, C_{1-3} alkoxy, halo, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, $C(O)C_{1-3}$ alkyl, and SO_2C_{1-3} alkyl.

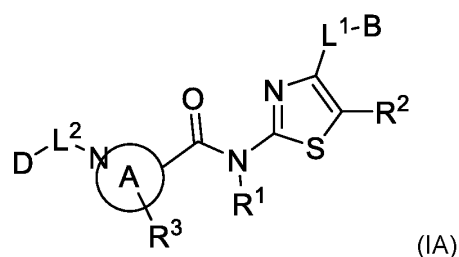
[0013] In some embodiments, L^1 -B is selected from the group consisting of: ,







[0014] In some embodiments, ring A is a 5-6 membered heterocycle having 1 or 2 ring heteroatoms selected from N, O, and S. In some cases, the compound has a structure of Formula (IA):



wherein ring A has 0 or 1 additional ring heteroatoms selected from N, O, and S, and R³ is H, C₁₋₃alkyl, C₁₋₃hydroxyalkyl, C₁₋₃haloalkyl, halo, or -C(O)N(R^N)₂. In some cases, ring A is an aromatic or nonaromatic C₃₋₁₀ carbocycle. In some cases, the ring A-L² moiety is

[illegible]

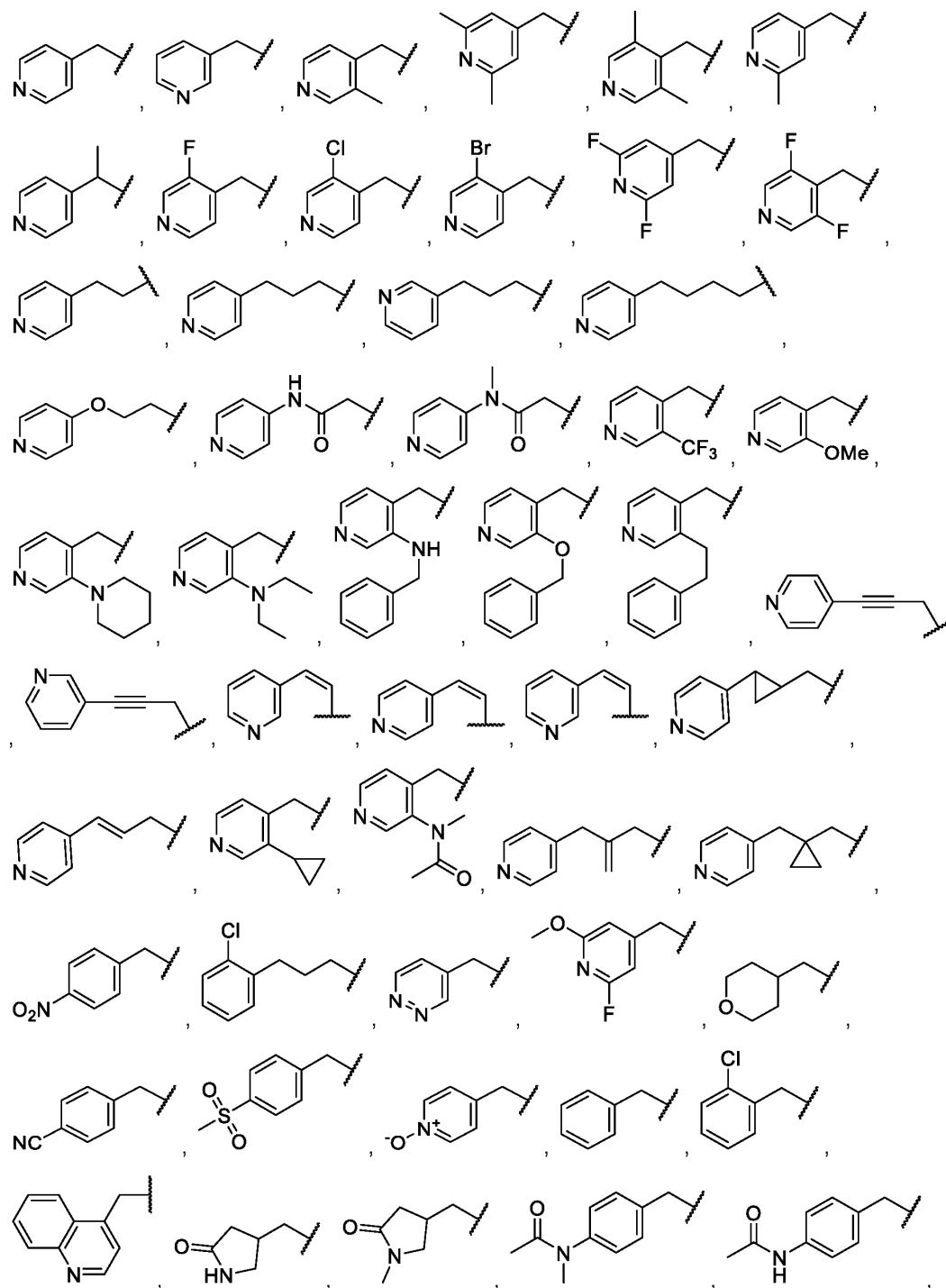
[0015] In some embodiments, L² is C₀₋₆alkylene. In some embodiments, L² is C₁₋₆alkylene. In some embodiments, L² is $\text{---C}_{0-2}\text{alkylene---}$. In some cases, --- indicates a double bond. In some cases, --- indicates a triple bond. In some cases, ---

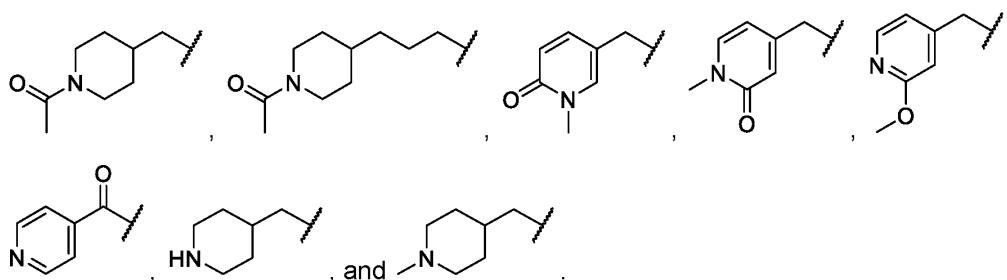
indicates a fused cyclopropyl, e.g., , or a spiro cyclopropyl, e.g., .

[0016] In some embodiments, W is a bond. In some embodiments, W is O. In some embodiments, W is C(O)N(R^N). In various cases, W is C(O)NH. In various cases, W is C(O)N(C₁₋₄alkyl). In various cases, W is C(O)N(Me).

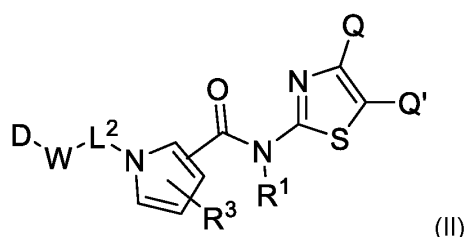
[0017] In some embodiments, D is C₆₋₁₀aryl. In some embodiments, D is a nonaromatic 5-10 membered heterocycle having 1-4 ring heteroatoms selected from N, O, and S. In some embodiments, D is an aromatic 5-10-membered heterocycle having 1-4 ring heteroatoms selected from N, O, and S. In some cases, D comprises pyridyl optionally substituted with 1-3 substituents independently selected from C₁₋₃alkyl, C₁₋₃alkoxy, halo, C₁₋₃ haloalkyl, C₁₋₃ haloalkoxy, N(R^N)₂, C₃₋₆cycloalkyl, NO₂, N(R^N)C(O)C₁₋₃alkyl, C(O)C₁₋₃alkyl, NO₂, CN, SO₂C₁₋

[0018] In some embodiments, L²-W-D is selected from the group consisting of:





[0019] Also provided herein are compounds having a structure of Formula (II), or a pharmaceutically acceptable salt thereof:



wherein one of Q and Q' is L^1-B and the other is R^2 , or Q and Q' and the atoms to which they are attached join together to form an aromatic or nonaromatic 5 or 6 membered carbocycle or a 5 or 6 membered heterocycle having 1 or 2 ring heteroatoms selected from N, O, and S;

L^1 is a bond, C_{1-6} alkylene, or $\text{---}C_{0-2}\text{alkylene}\text{---}C_{0-2}\text{alkylene}\text{---}$, wherein --- indicates a double bond, a triple bond, or a fused or spiro cyclopropyl; B is C_{1-6} alkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} haloalkoxy, C_{1-3} alkoxy, $[O]_{0-1}-C_{0-3}\text{alkylene}-X$ or $NR^N C_{1-3}\text{alkylene}-X$, X is an aromatic or nonaromatic C_{3-10} carbocycle, or an aromatic or nonaromatic 5-10 membered heterocycle having 1-4 ring heteroatoms selected from N, O, and S; L^2 is C_{1-6} alkylene or $\text{---}C_{0-2}\text{alkylene}\text{---}C_{0-2}\text{alkylene}\text{---}$, wherein --- indicates a double bond, a triple bond, or a fused or spiro cyclopropyl; W is a bond, O, or $C(O)N(R^N)$; D comprises pyridyl or quinolinyl optionally substituted with 1-3 substituents independently selected from C_{1-3} alkyl, C_{1-3} alkoxy, halo, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, $N(R^N)_2$, C_{3-6} cycloalkyl, NO_2 , $C(O)N(R^N)_2$, $N(R^N)C(O)C_{1-3}$ alkyl, $C(O)C_{1-3}$ alkyl, NO_2 , CN, SO_2C_{1-3} alkyl, O^- , $NHC_{1-3}\text{alkylene-aryl}$, $OC_{1-3}\text{alkylene-aryl}$, $C_{1-3}\text{alkylene-aryl}$, and 5-10 membered heterocycle having 1-3 ring heteroatoms selected from N, O, and S; each R^N is independently H or C_{1-4} alkyl; R^1 is H or C_{1-3} alkyl; R^2 is H, C_{1-3} alkyl, or halo; and R^3 is H, C_{1-3} alkyl, C_{1-3} hydroxyalkyl, C_{1-3} haloalkyl, halo, or $-C(O)N(R^N)_2$.

[0020] In some embodiments, R^1 is H. In some embodiments, R^1 is C_{1-3} alkyl. In various cases, R^1 is methyl or ethyl.

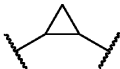
[0021] In some embodiments, R^2 is H. In some embodiments, R^2 is C_{1-3} alkyl. In some embodiments, R^2 is halo. In some cases, R^2 is methyl. In some cases, R^2 is ethyl. In some

cases, R^2 is n-propyl or isopropyl. In some cases, R^2 is Br. In some cases, R^2 is F. In some cases, R^2 is Cl.

[0022] In some embodiments, R^3 is H. In some embodiments, R^3 is C_{1-3} alkyl. In some embodiments, R^3 is halo. In some embodiments, R^3 is C_{1-3} hydroxyalkyl. In some embodiments, $-C(O)N(R^N)_2$. In some embodiments, R^3 is C_{1-3} haloalkyl. In various cases, R^3 is methyl. In various cases, R^3 is Cl. In various cases, R^3 is $-CH_2OH$. In various cases, R^3 is $-C(O)NH_2$. In various cases, R^3 is $-C(O)N(Me)_2$.

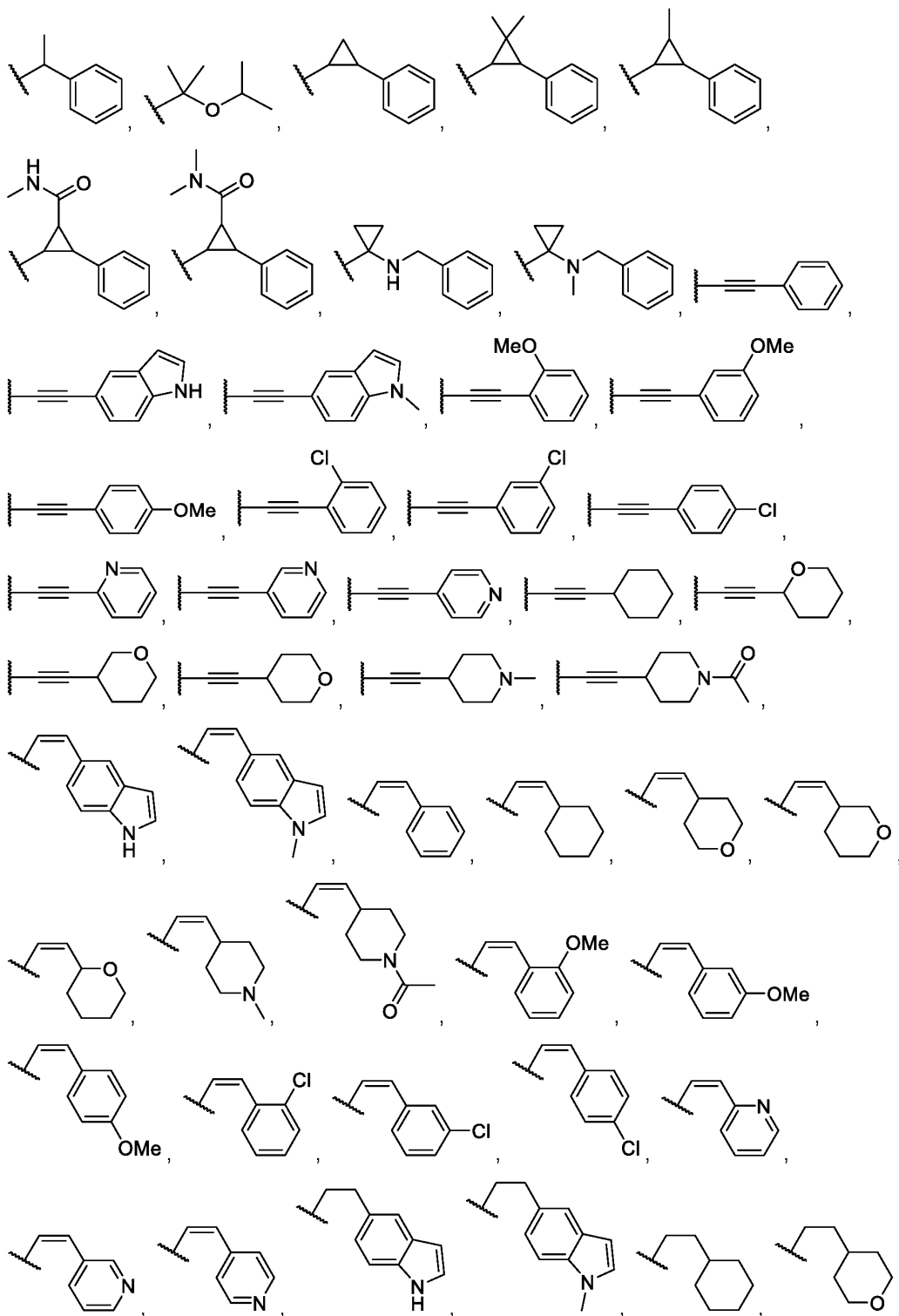
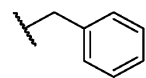
[0023] In some embodiments, Q is L^1-B and Q' is R^2 . In some embodiments, Q is R^2 and Q' is L^1-B . In some embodiments, Q and Q' and the atoms to which they are attached join together to form an aromatic or nonaromatic 5 or 6 membered carbocycle or a 5 or 6 membered heterocycle having 1 or 2 ring heteroatoms selected from N, O, and S.

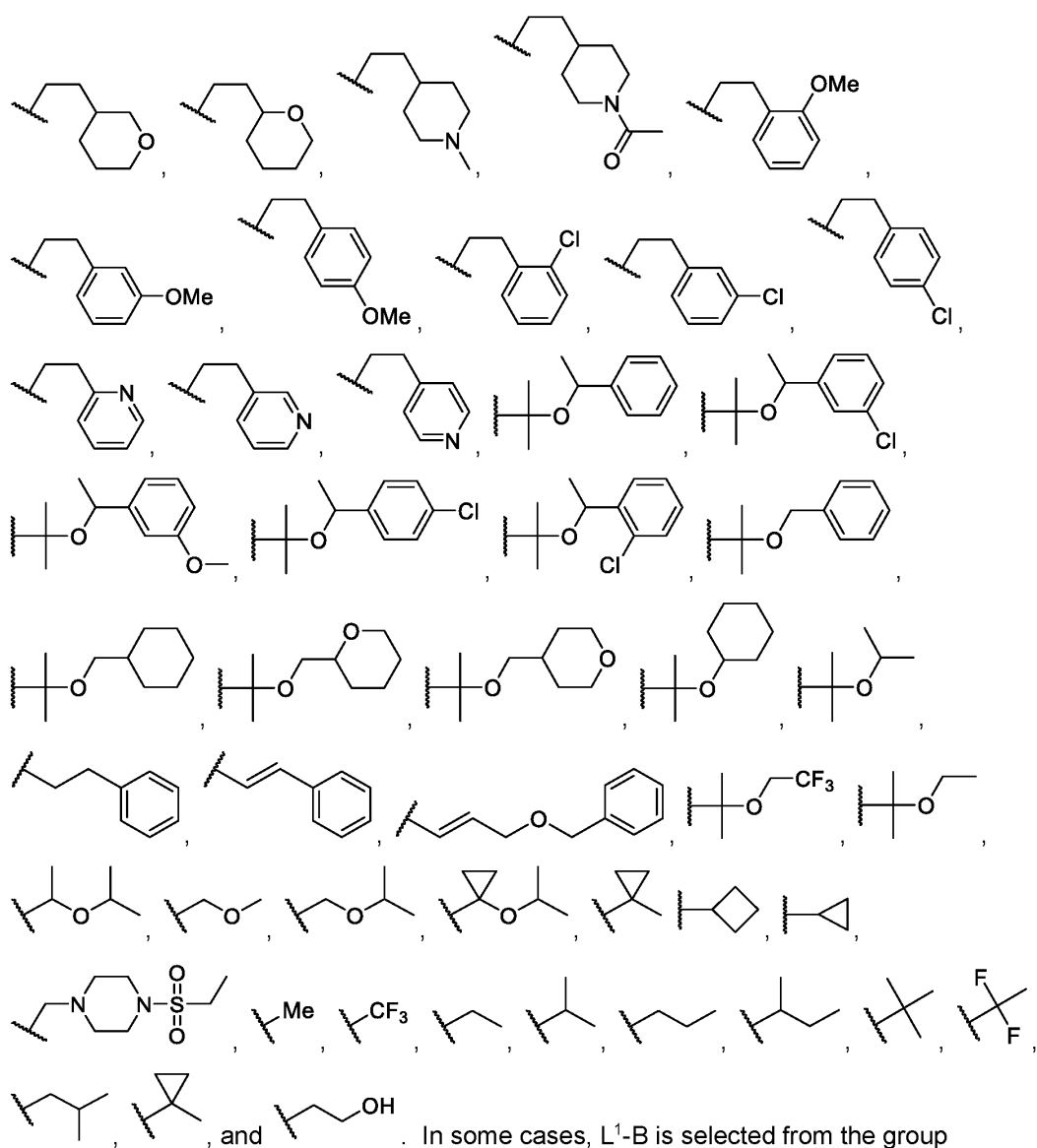
[0024] In various embodiments, L^1 is a bond. In various embodiments, L^1 is a C_{1-6} alkylene. In some cases, L^1 is CH_2 , $CH(CH_3)$, CH_2CH_2 , or $C(CH_3)_2$. In various embodiments, L^1 is $\text{---}C_{0-2}\text{alkylene}\text{---}\text{---}C_{0-2}\text{alkylene}\text{---}$. In various cases, --- indicates a double bond. In some cases, the double bond is tri- or tetra-substituted, and the 1 or 2 other substituents on the double bond are independently selected from C_{1-3} alkyl and halo. In various cases, --- indicates a triple bond. In various cases, --- indicates a fused

cyclopropyl, e.g.,  or spiro cyclopropyl, e.g., .

[0025] In some embodiments, B is C_{1-6} alkyl. In some embodiments, B is C_{1-3} haloalkyl. In some embodiments, B is C_{1-3} hydroxyalkyl. In some embodiments, B is C_{1-3} haloalkoxy. In some embodiments, B is C_{1-3} alkoxy. In some cases, B is methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, or n-hexyl. In some cases, B is $-CF_3$ or $-CF_2CH_3$. In some cases, B is $-CH_2CH_2OH$. In some cases, B is $-OCH_2CF_3$. In some embodiments, B is O-X. In some embodiments, B is $O-C_{1-3}$ alkylene-X. In some embodiments, B is C_{1-3} alkylene-X. In some embodiments, B is X. In some embodiments, B is NHC_{1-3} alkylene-X. In some embodiments, B is $N(CH_3)C_{1-3}$ alkylene-X. In various embodiments, X is an aromatic C_{6-10} carbocycle, or an aromatic or nonaromatic 5-10-membered heterocycle. In some cases, X is selected from phenyl, pyridyl, indolyl, tetrahydropyranyl, piperidinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or piperazinyl, and X is optionally substituted with 1-3 substituents independently selected from C_{1-3} alkyl, C_{1-3} alkoxy, halo, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, $C(O)C_{1-3}$ alkyl, and SO_2C_{1-3} alkyl.

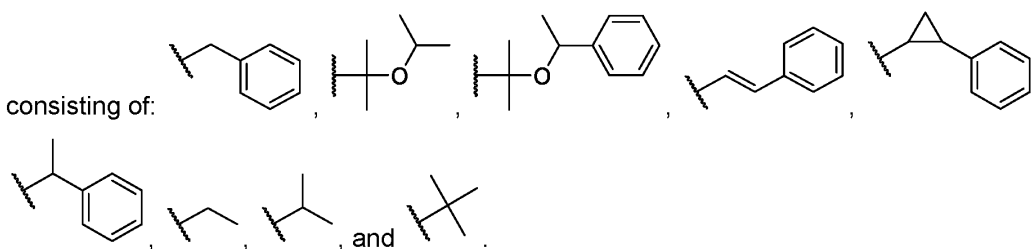
[0026] In some embodiments, L¹-B is selected from the group consisting of:



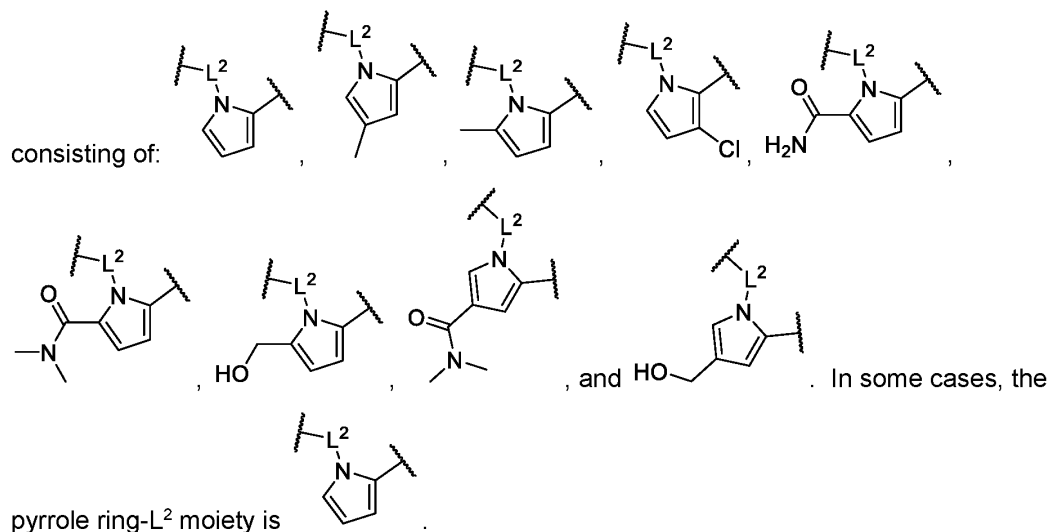


, , and . In some cases, L¹-B is selected from the group

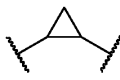
consisting of:



[0027] In some embodiments, the pyrrole ring- L^2 moiety is selected from the group

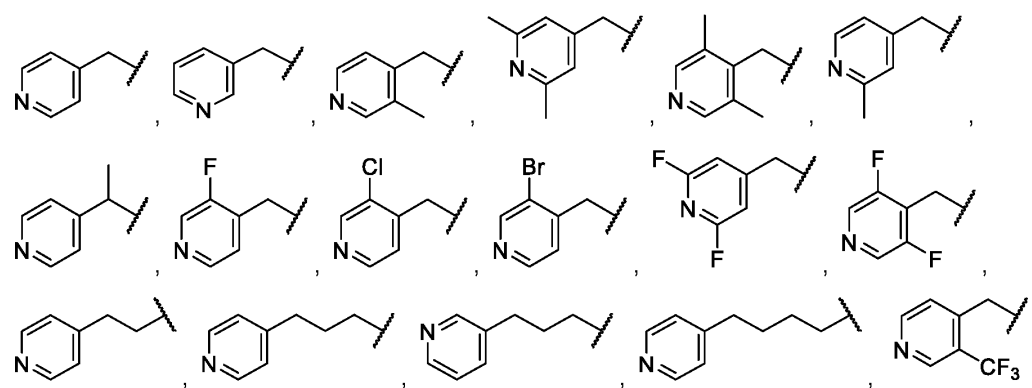


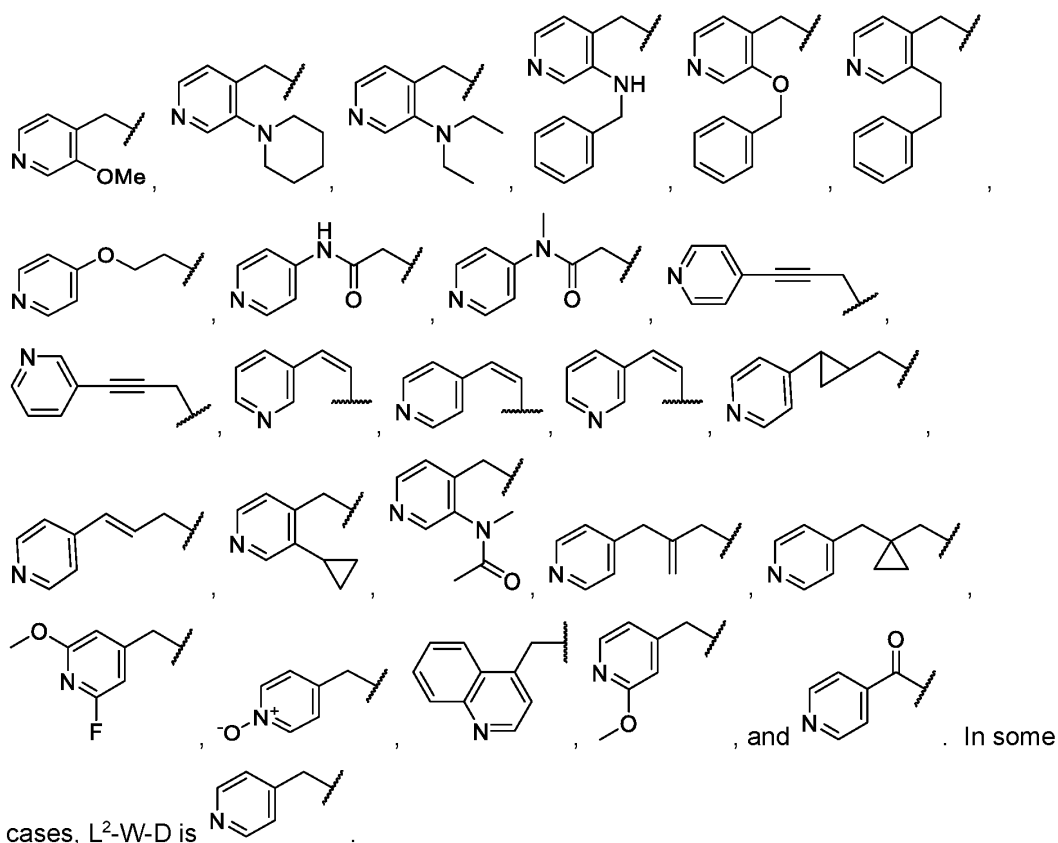
[0028] In some embodiments, L^2 is C_{1-6} alkylene. In some embodiments, L^2 is $[-C_{0-2}alkylene-]_n$. In some cases, L^2 is $[-C_{0-2}alkylene-]$. In some cases, L^2 is $[-C_{0-2}alkylene-]$. In some cases, L^2 is $[-C_{0-2}alkylene-]$. In various cases, $==$ indicates a double bond. In various cases, $===$ indicates a triple bond. In various cases, $==$

indicates a fused cyclopropyl, e.g., , or a spiro cyclopropyl, e.g., .

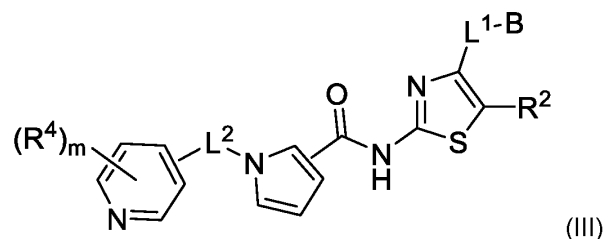
[0029] In some embodiments, W is a bond. In some embodiments, W is O. In some embodiments, W is $C(O)N(R^N)$. In various cases, W is $C(O)NH_2$. In various cases, W is $C(O)N(C_{1-4}alkyl)_2$. In some cases, W is $C(O)N(Me)_2$.

[0030] In some embodiments, L^2 -W-D is selected from the group consisting of:





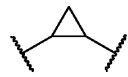
[0031] Also provided herein are compounds having a structure of Formula (III), or a pharmaceutically acceptable salt thereof:



wherein L¹ is a bond, C₁₋₆alkylene, or $\text{---C}_{0-3}\text{alkylene---C}_{0-2}\text{alkylene---}$, wherein --- indicates a double bond, a triple bond, or a fused cyclopropyl; B is C₀₋₃alkylene-X; X is an aromatic or nonaromatic C₄₋₁₀carbocycle, or an aromatic or nonaromatic 4-10 membered heterocycle having 1-3 ring heteroatoms selected from N, O, and S; R² is H or C₁₋₃alkyl; L² is C₀₋₃alkylene; m is 0 to 2; and each R⁴ independently is C₁₋₃alkyl, C₂₋₃alkynyl, C₁₋₃haloalkyl, C₁₋₃alkoxy, halo, or NHC₁₋₃alkylene-aryl; or a pharmaceutically acceptable salt thereof.

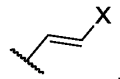
[0032] In various embodiments, L¹ is a bond. In various embodiments, L¹ is C₁₋₆alkylene. In some cases, L¹ is CH₂, CH₂CH₂, C(CH₃)₂, C(CH₃)₂CH₂, or C(CH₃)₂CH₂CH₂. In various

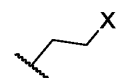
embodiments, L^1 is $\text{---C}_{0-3}\text{alkylene---C}_{0-2}\text{alkylene---}$. In some cases, L^1 is $\text{---C}_{0-3}\text{alkylene---}$. In some cases, L^1 is $\text{---C}_{0-2}\text{alkylene---}$. In some cases, L^1 is --- . In various embodiments, --- indicates a double bond. In some cases, the double bond is further substituted with $\text{C}_{1-3}\text{alkyl}$. In various embodiments, --- indicates a

triple bond. In various embodiments, --- indicates a fused cyclopropyl, e.g., .

[0033] In various embodiments, B is $\text{C}_{1-3}\text{alkylene-X}$. In various embodiments, B is X. In various embodiments, X is pyrrolidinyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, phenyl, piperidinyl, pyridinyl, piperazinyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, quinoliny, morpholiny, pyrrolidonyl, pyrimidinyl, pyridazinyl, indenyl, dihydroindenyl, dihydrobenzofuranyl, chromanyl, isochromanyl, dihydroisoquinoliny, or indolyl.

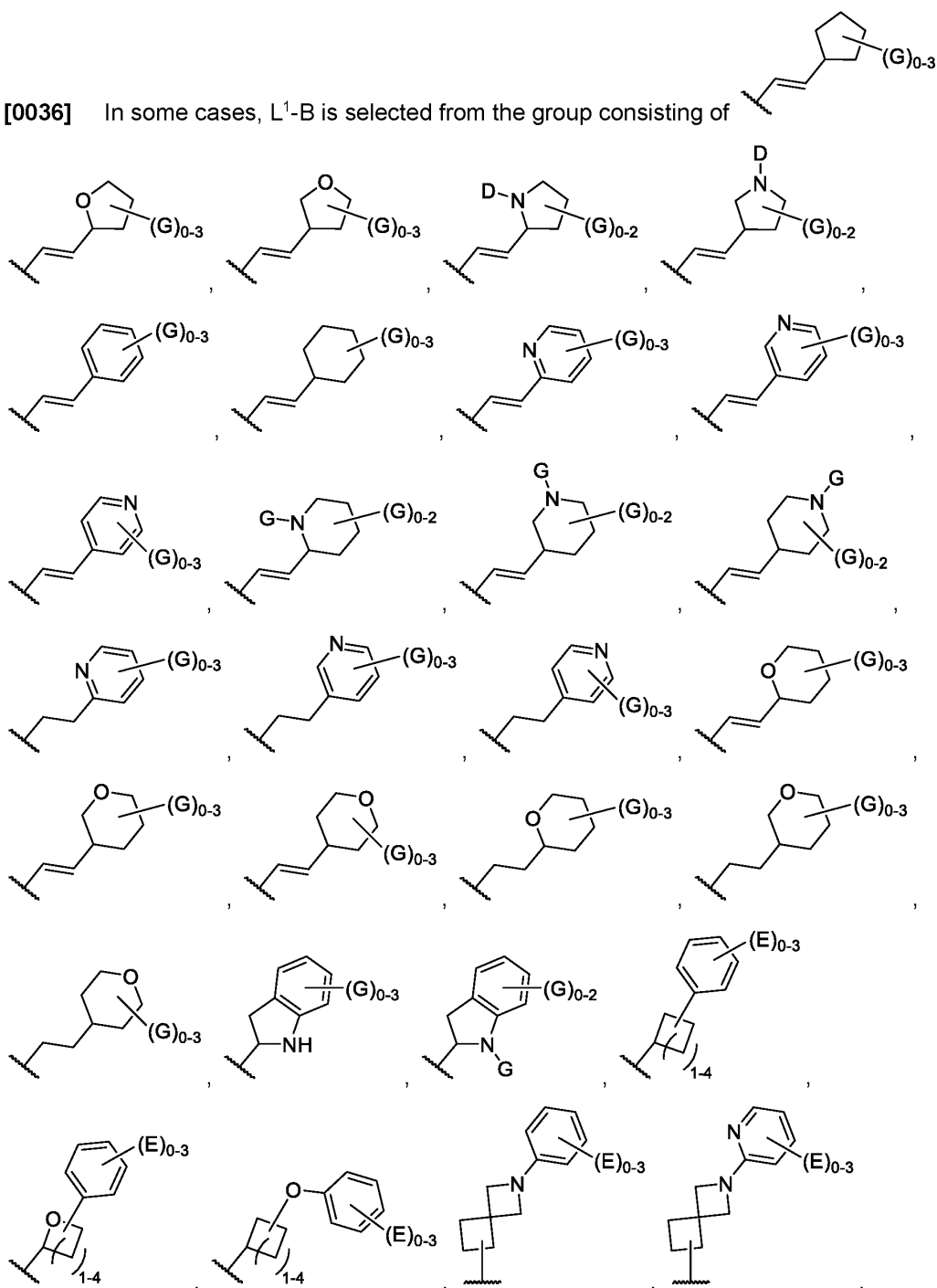
[0034] In various embodiments, X is substituted with 1-3 G; each G independently is selected from the group consisting of halo, OH, =O, CN, NO_2 , $\text{N(R}^N)_2$, $\text{N(R}^N)\text{C(O)C}_{1-3}\text{alkyl}$, $\text{C}_{1-3}\text{alkyl}$, $\text{C}_{1-3}\text{alkoxy}$, $\text{C}_{1-3}\text{haloalkyl}$, $\text{C}_{1-3}\text{haloalkoxy}$, $\text{C(O)C}_{1-3}\text{alkyl}$, $\text{S(O}_2\text{)-Z}$, C(O)-Z , $\text{C(O)N(R}^N)_2$, silyl ether, and $[\text{O}]_{0-1}\text{-C}_{0-3}\text{alkylene-Z}$; each R^N independently is H or $\text{C}_{1-4}\text{alkyl}$; Z is aromatic or nonaromatic $\text{C}_{3-10}\text{carbocycle}$, or aromatic or nonaromatic 4-10 membered heterocycle having 1-3 heteroatoms selected from the group consisting of N, O, and S; Z is optionally substituted with 1-3 E; and, each E independently is selected from $\text{C}_{1-3}\text{alkyl}$, $\text{C}_{1-3}\text{alkoxy}$, =O, $\text{C}_{1-3}\text{haloalkoxy}$, CN, and halo.

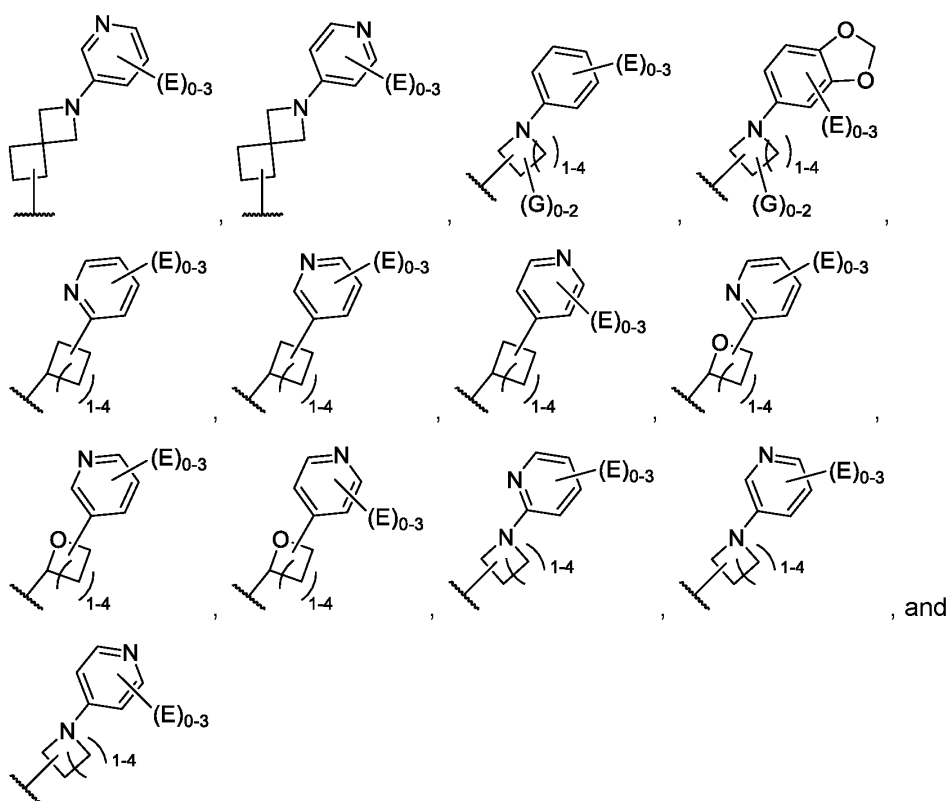
[0035] In various embodiments, $L^1\text{-B}$ is selected from the group consisting of ,



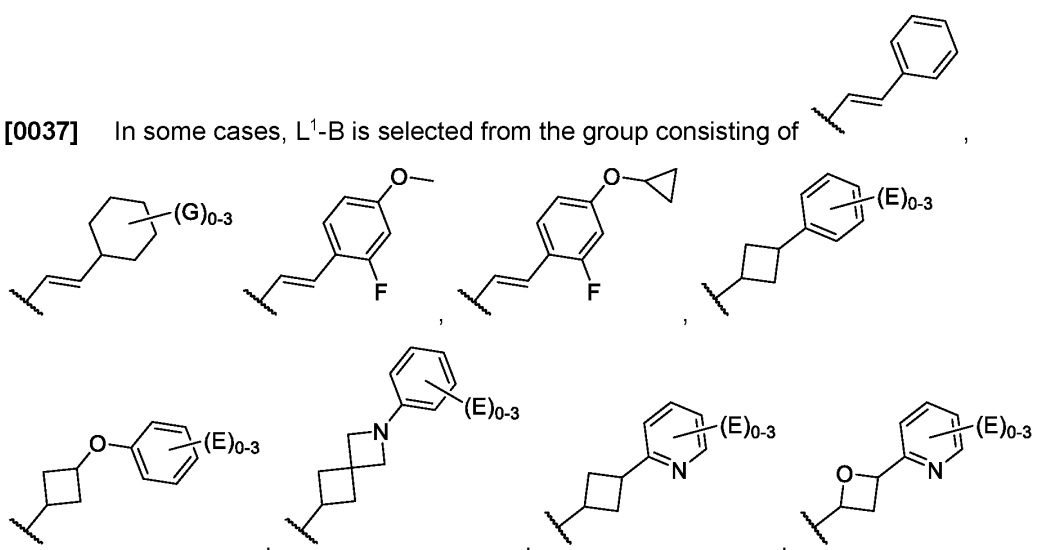
, and ; X is aromatic or nonaromatic $\text{C}_{4-7}\text{carbocycle}$, or an aromatic or nonaromatic 4-9 membered heterocycle having 1 ring heteroatom; X is optionally substituted with 1-3 G; each G independently is selected from the group consisting of halo, OH, =O, CN, NO_2 , $\text{N(R}^N)_2$, $\text{N(R}^N)\text{C(O)C}_{1-3}\text{alkyl}$, $\text{C}_{1-3}\text{alkyl}$, $\text{C}_{1-3}\text{alkoxy}$, $\text{C}_{1-3}\text{haloalkyl}$, $\text{C}_{1-3}\text{haloalkoxy}$, $\text{C(O)C}_{1-3}\text{alkyl}$, $\text{S(O}_2\text{)-Z}$, C(O)-Z , $\text{C(O)N(R}^N)_2$, silyl ether, and $[\text{O}]_{0-1}\text{-C}_{0-3}\text{alkylene-Z}$; each R^N independently is H or $\text{C}_{1-4}\text{alkyl}$; Z is aromatic or nonaromatic $\text{C}_{3-10}\text{carbocycle}$, or aromatic or nonaromatic 4-10 membered heterocycle having 1-3 heteroatoms selected from the group consisting of N, O, and S; Z is optionally substituted with 1-3 E; and, each E independently is selected from $\text{C}_{1-3}\text{alkyl}$, $\text{C}_{1-3}\text{alkoxy}$, =O, $\text{C}_{1-3}\text{haloalkoxy}$, CN, and halo.

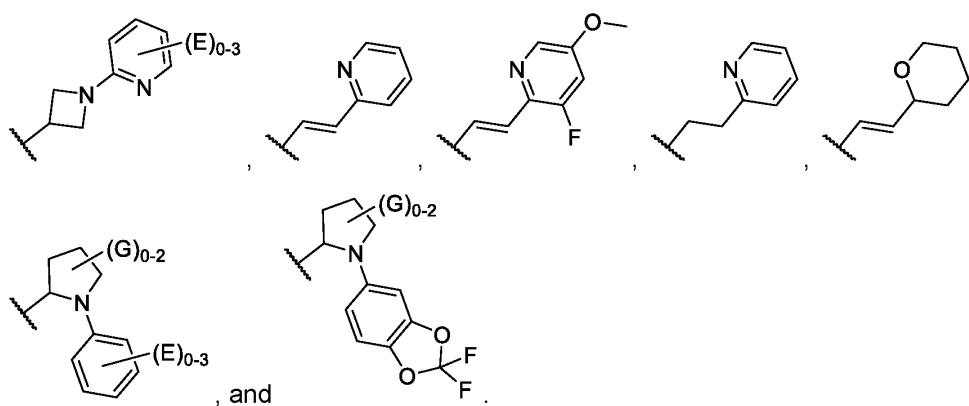
[0036] In some cases, L¹-B is selected from the group consisting of



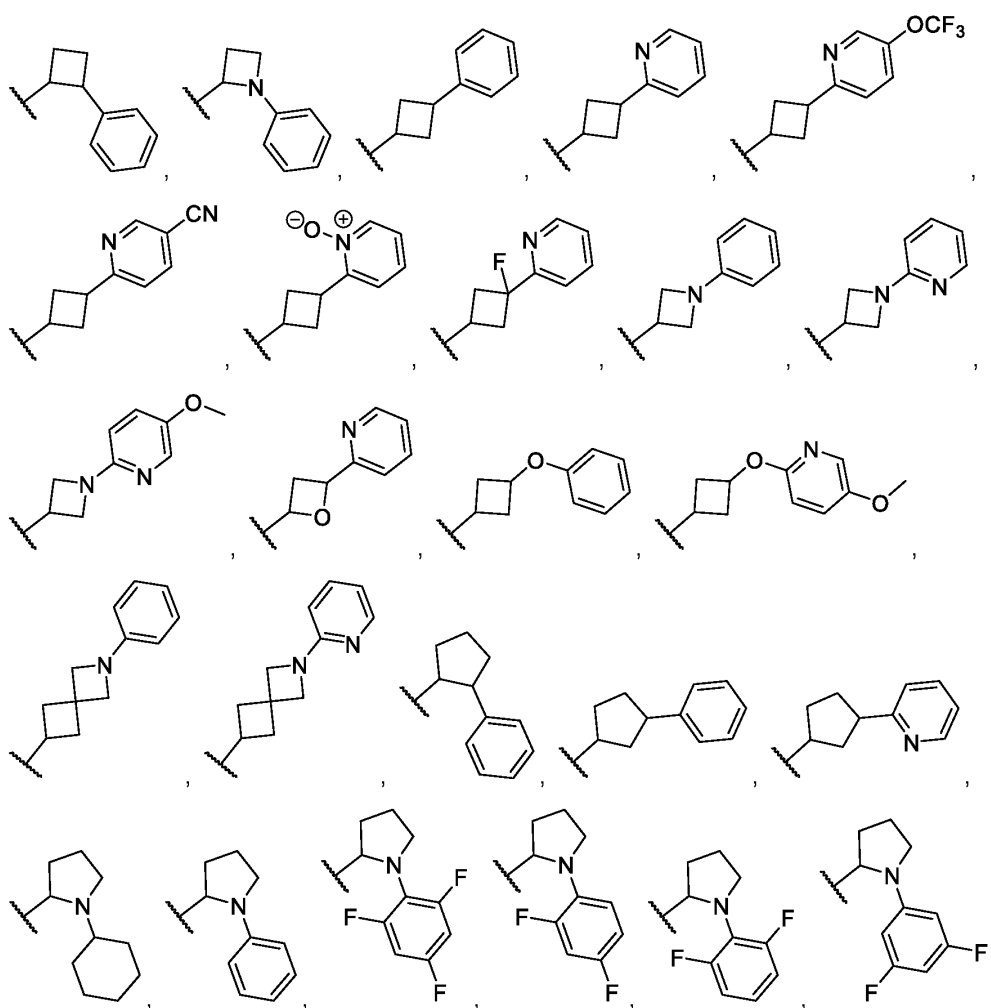


[0037] In some cases, L¹-B is selected from the group consisting of

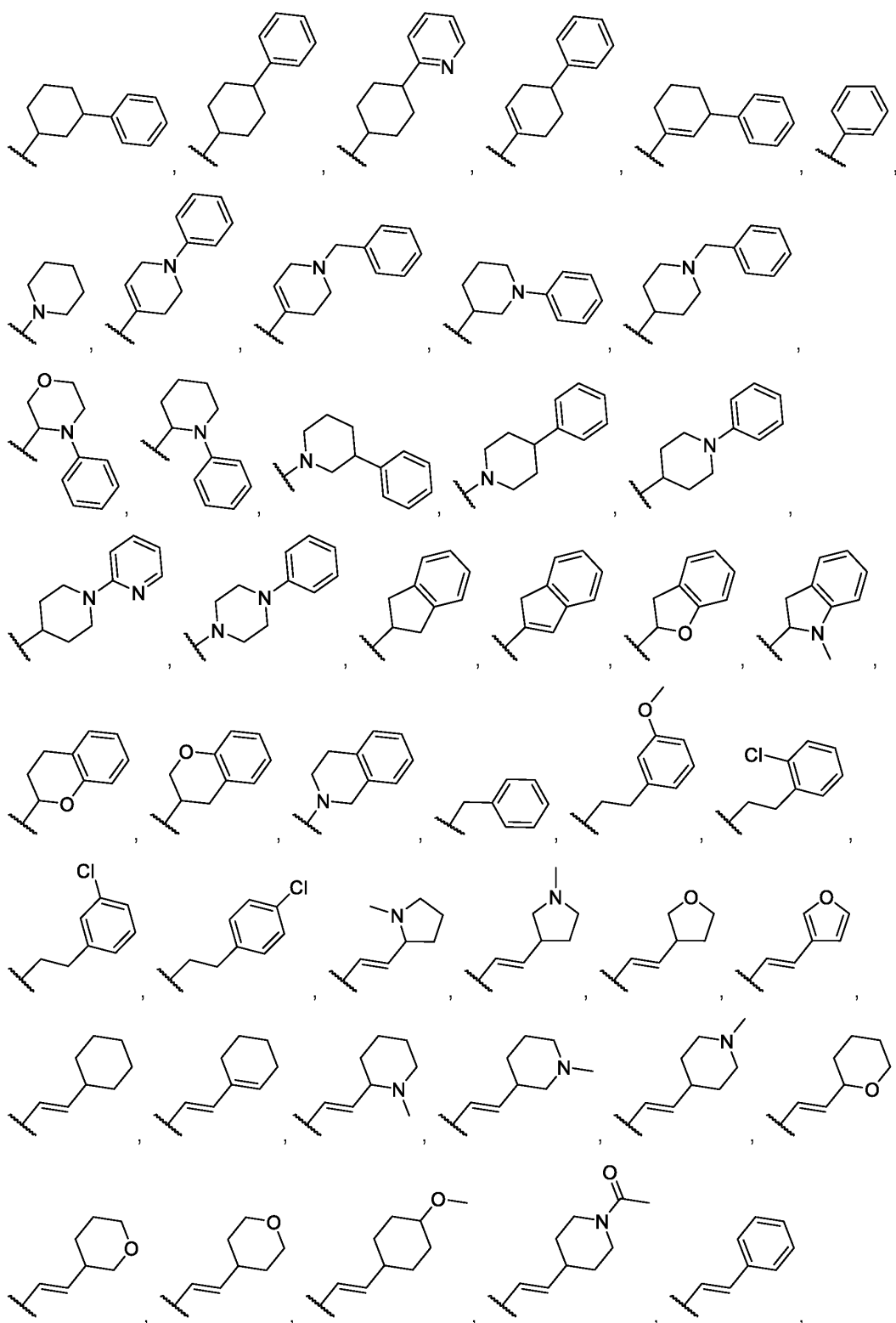


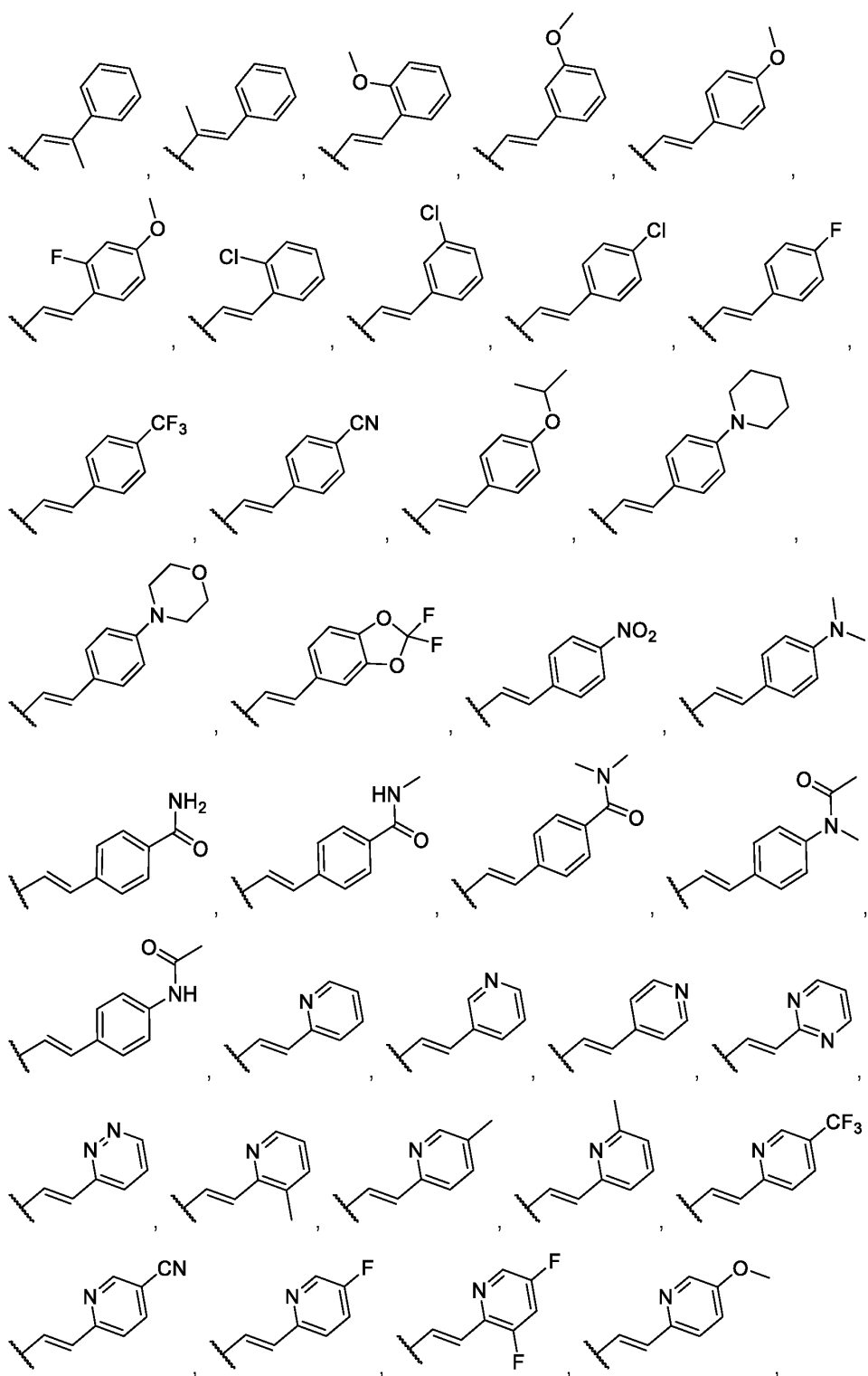


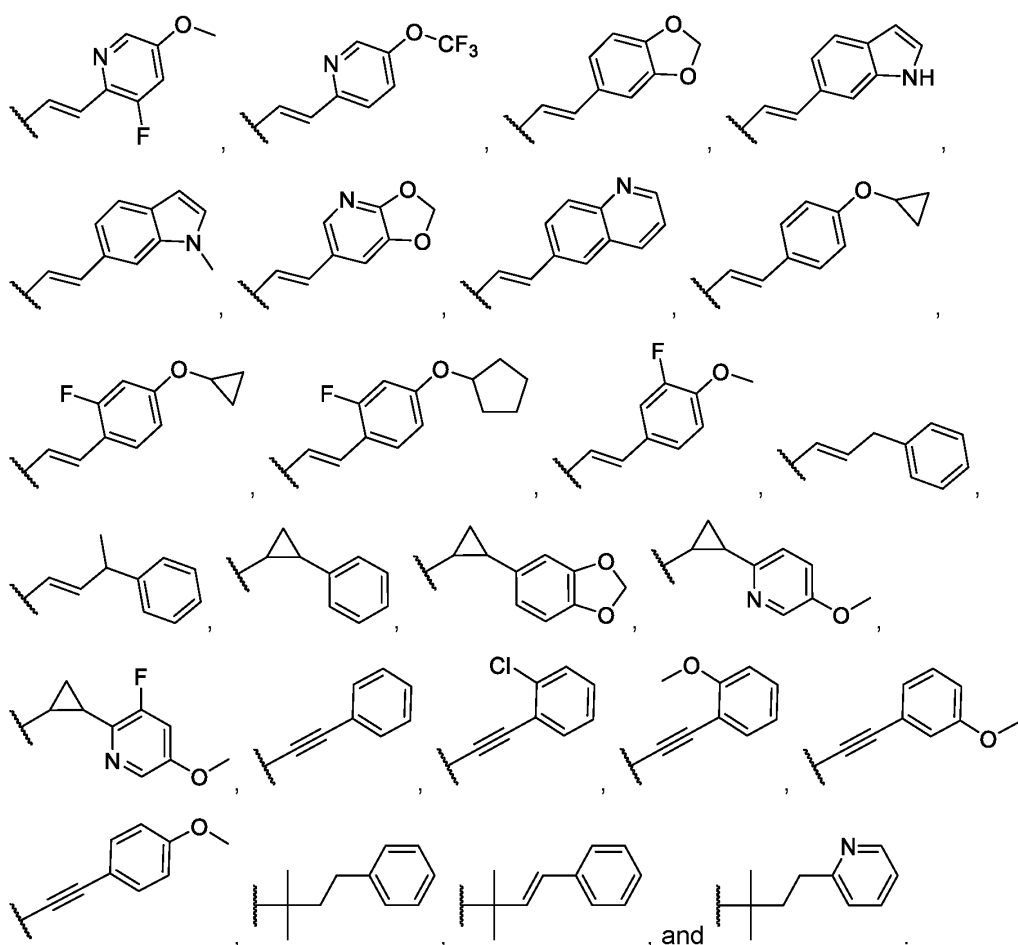
[0038] In various embodiments, L¹-B is selected from the group consisting of











[0039] In various embodiments, R^2 is H. In various embodiments, R^2 is C_{1-3} alkyl. In some cases, R^2 is methyl.

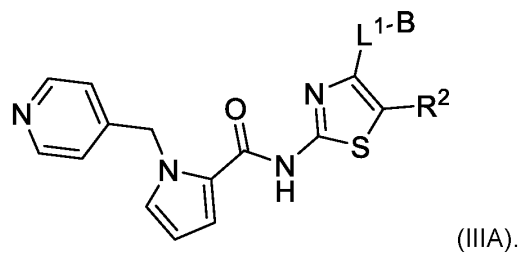
[0040] In various embodiments, L^2 is C_0 alkylene. In various embodiments, L^2 is C_1 alkylene. In various embodiments, L^2 is C_2 alkylene. In various embodiments, L^2 is C_3 alkylene.

[0041] In various embodiments, m is 0. In various embodiments, m is 1 or 2.

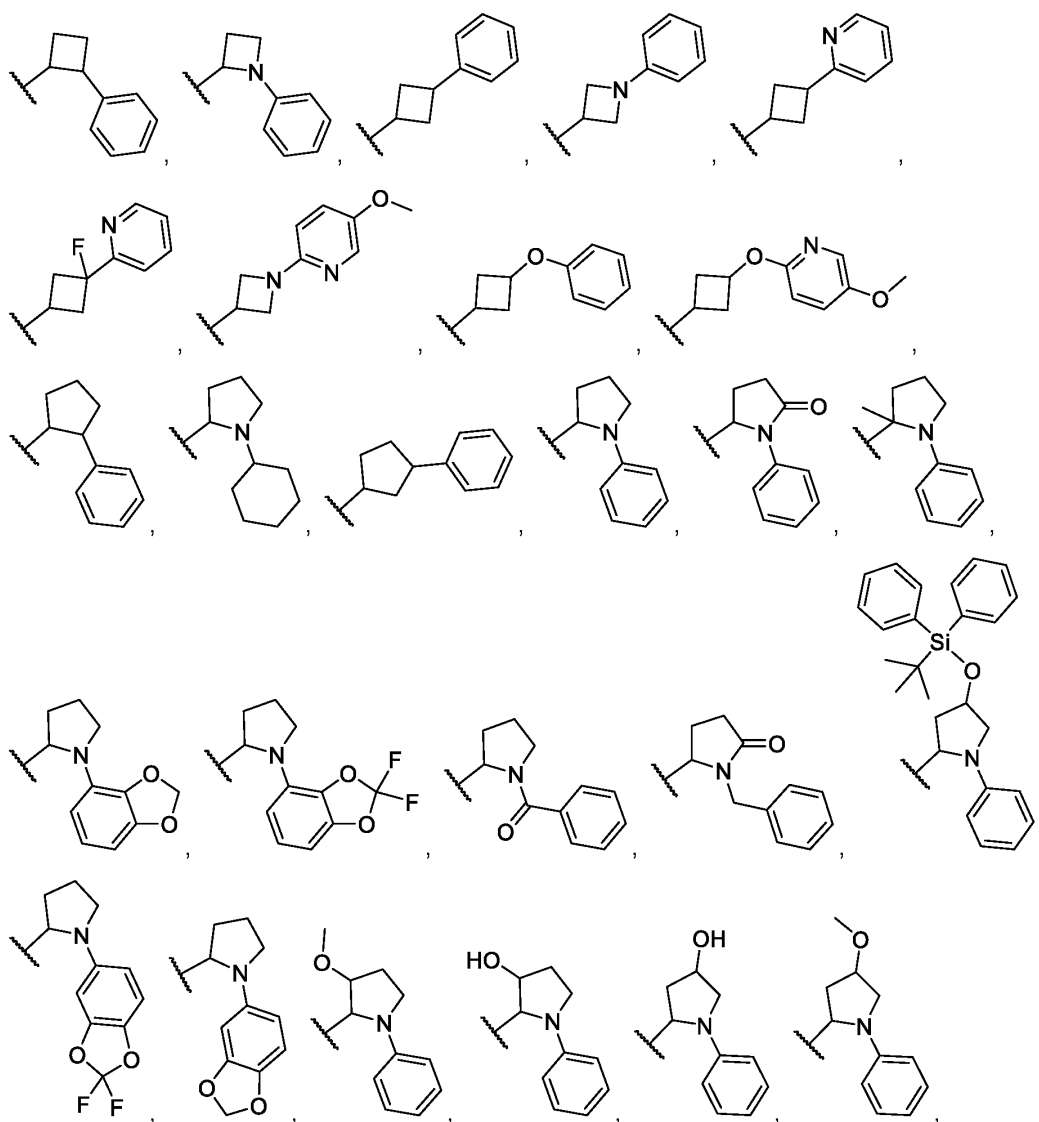
[0042] In various embodiments, R^4 is C_{1-3} alkyl. In some cases, R^4 is methyl or ethyl. In various embodiments, R^4 is halo. In some cases, R^4 is F. In some cases, R^4 is Cl. In various embodiments, R^4 is C_{2-3} alkynyl. In some cases, R^4 is C_2 alkynyl. In various embodiments, R^4 is C_{1-3} haloalkyl. In some cases R^4 is CF_3 . In various embodiments, R^4 is C_{1-3} alkoxy. In some cases, R^4 is methoxy. In various embodiments, R^4 is NHC_{1-3} alkylene-aryl. In some cases, R^4 is $NH-CH_2$ -phenyl.

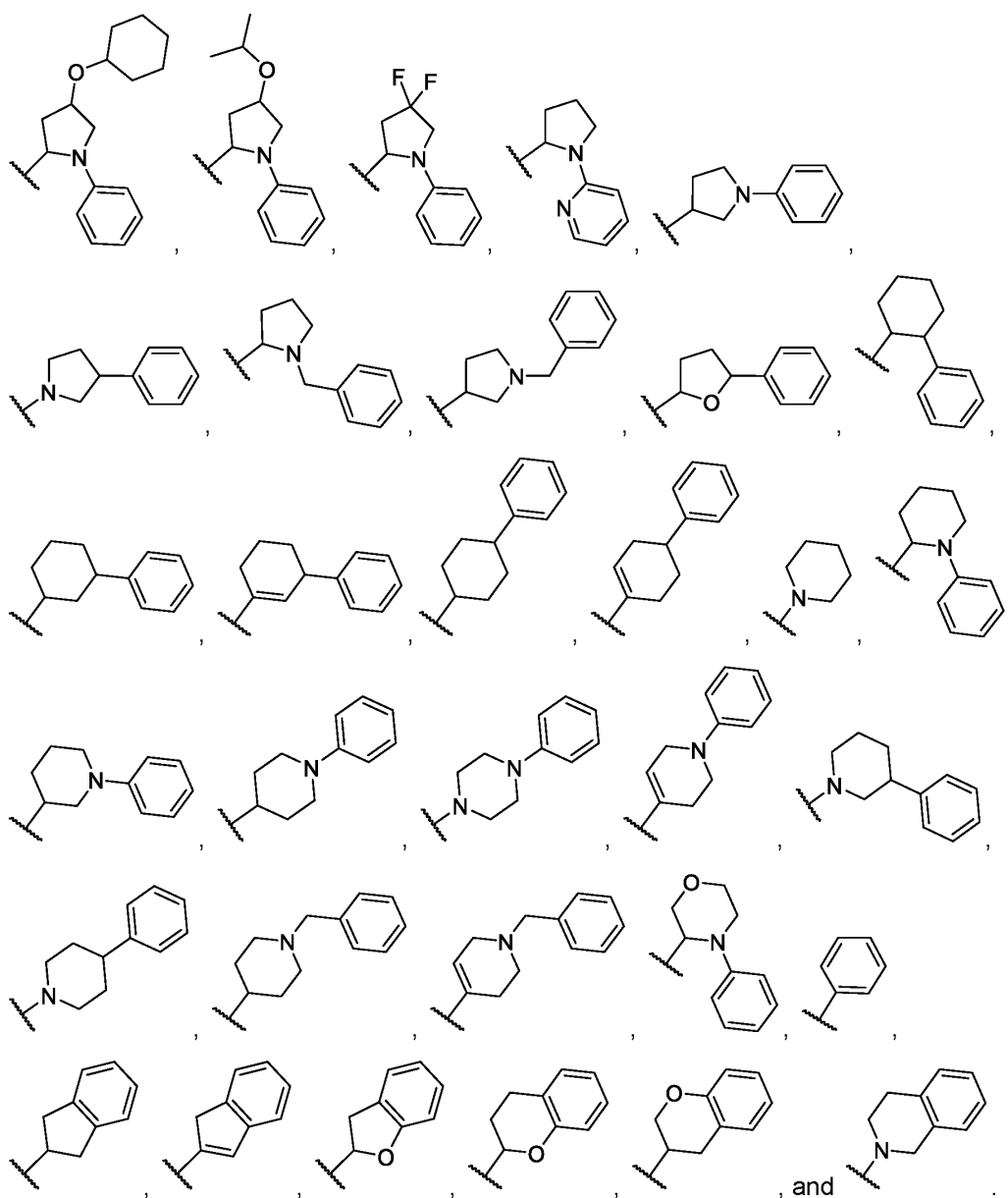
[0043] In various embodiments, m is 2, and one R^4 is halo, and the other R^4 is halo or methyl.

[0044] In various embodiments, the compound or salt has a structure of Formula (IIIA):

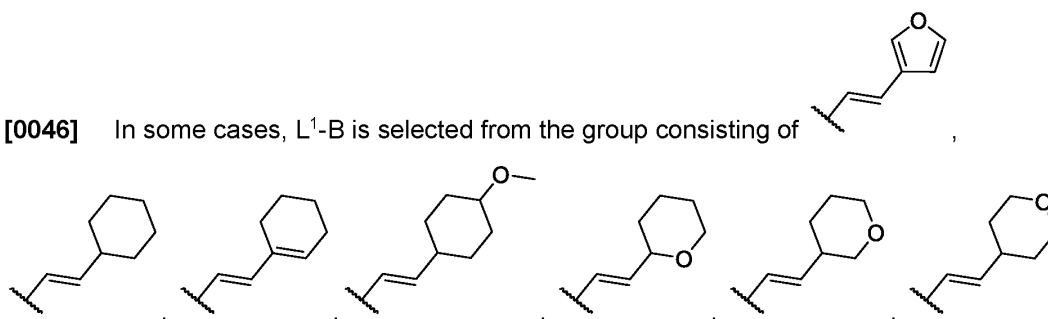


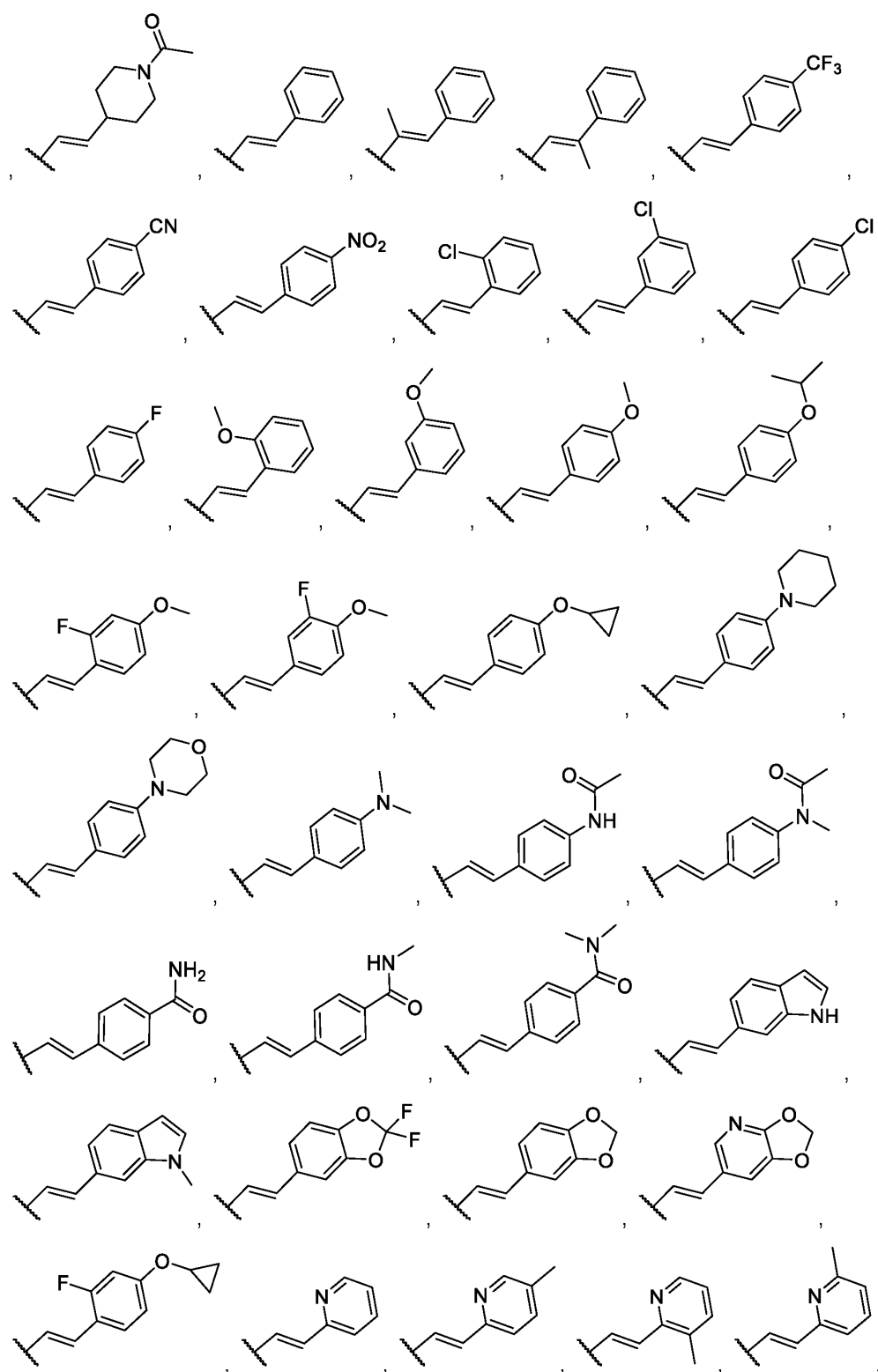
[0045] In various embodiments, L¹-B is selected from the group consisting of

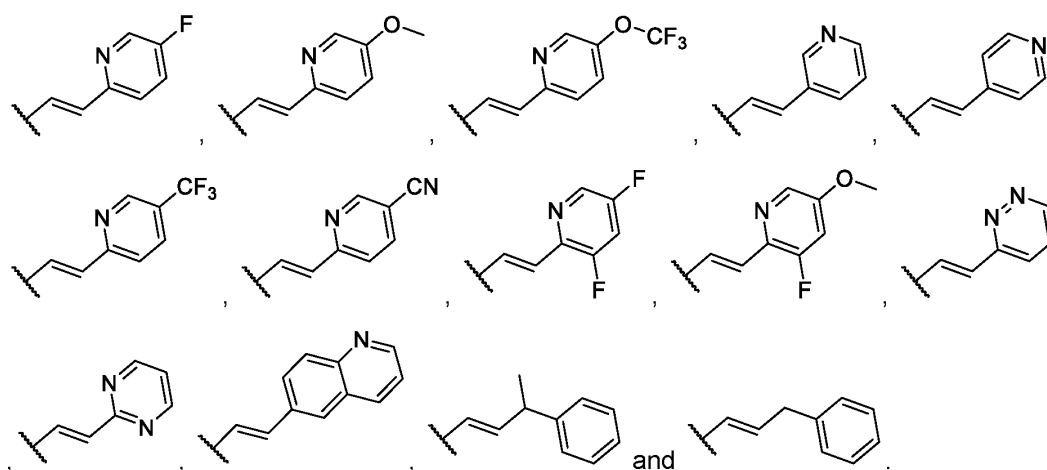




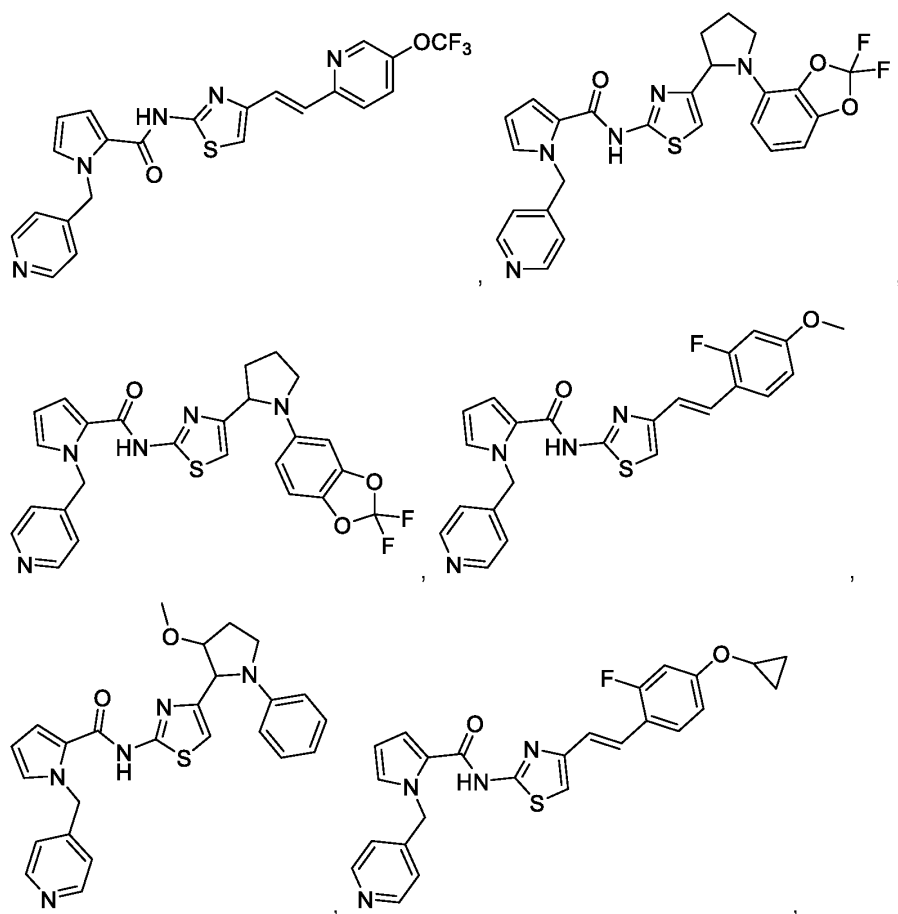
[0046] In some cases, L¹-B is selected from the group consisting of

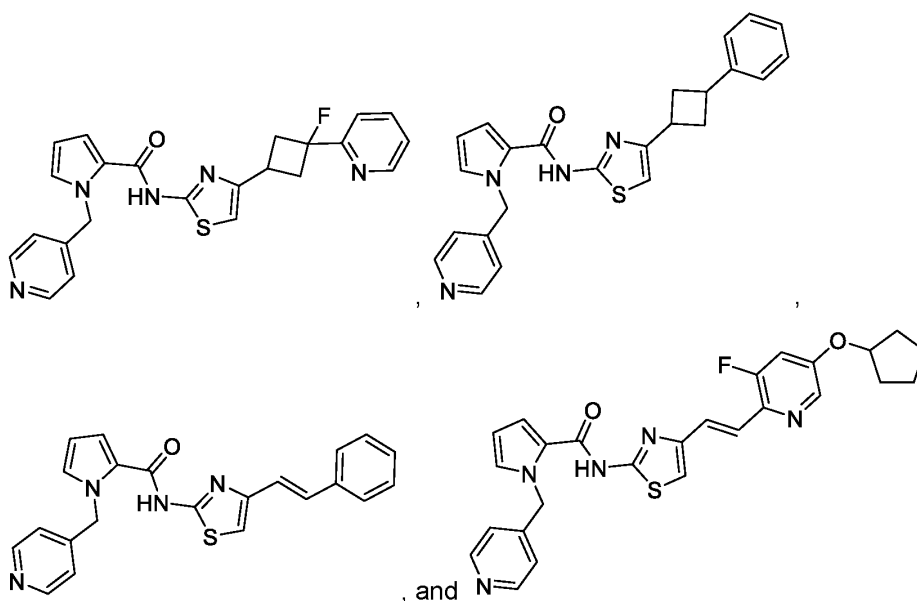




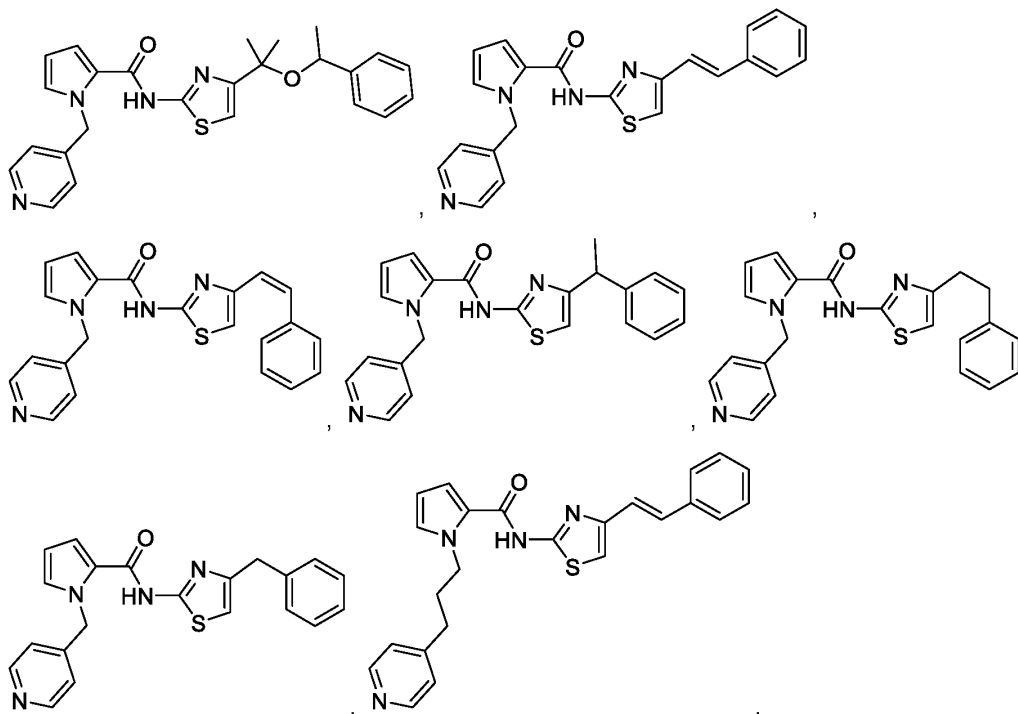


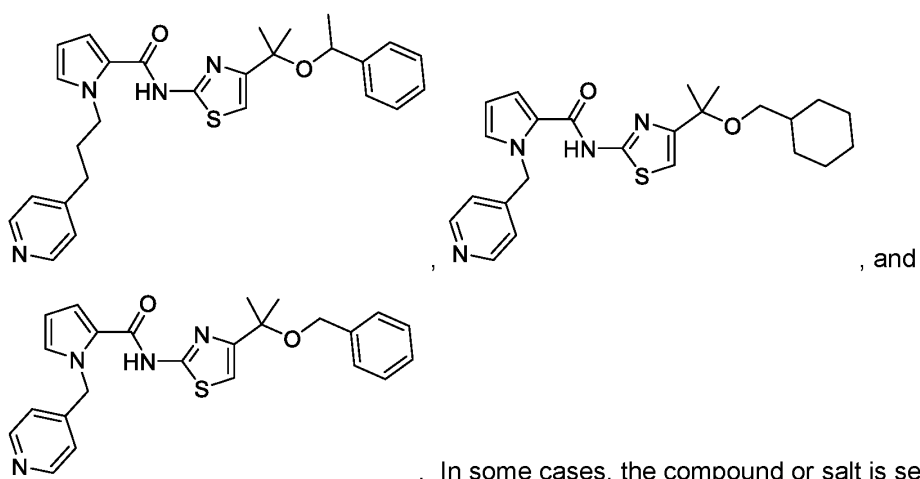
[0047] In some cases, the compound or salt is selected from the group consisting of



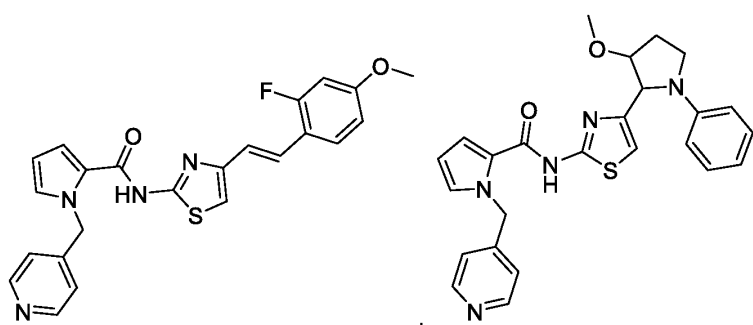
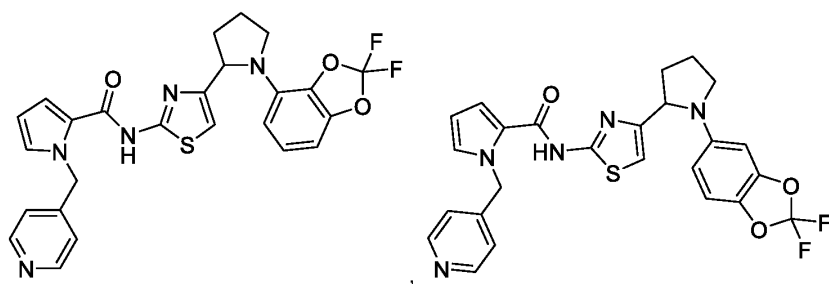
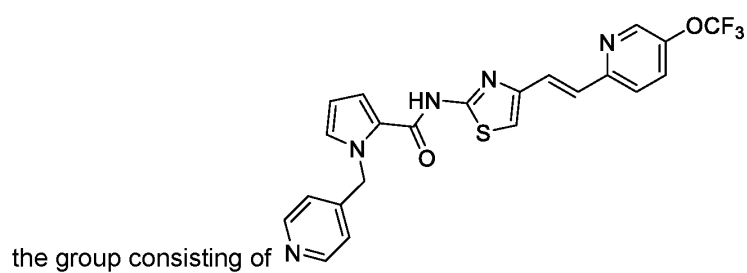


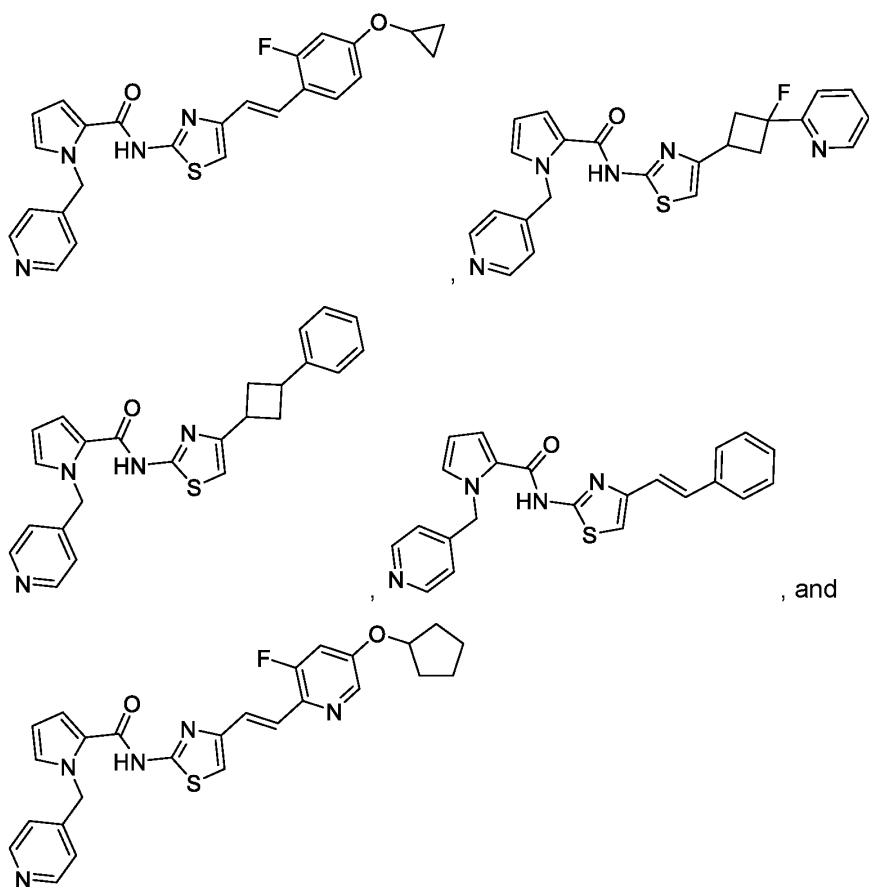
[0048] The disclosure further provides the compounds listed in Table A, or a pharmaceutically salt thereof. In some embodiments, the compound or salt is selected from A1-A210. In some embodiments, the compound or salt is selected from A211-A403. Further provided are the compounds listed in Table B, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound or salt is selected from B1-B29. In some cases, the compound or salt is selected from the group consisting of





. In some cases, the compound or salt is selected from





[0049] Also provided are pharmaceutical compositions comprising the compound or salt described herein and a pharmaceutically acceptable carrier.

[0050] Further provided are methods of inhibiting protein secretion in a cell comprising contacting the cell with the compound, salt, or pharmaceutical composition described herein in an amount effective to inhibit secretion. In some embodiments, the protein is a checkpoint protein. In some embodiments, the protein is a cell-surface protein, endoplasmic reticulum associated protein, or secreted protein involved in regulation of anti-tumor immune response. In various cases, 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, TGFR β and combinations thereof. In some cases, the protein is selected from the group consisting of HER3, TNF α , IL2, and PD1. In some embodiments, the contacting comprises administering the compound or the composition to a subject in need thereof.

[0051] The disclosure also provides methods for treating inflammation in a subject comprising administering to the subject a therapeutically effective amount of the compound, salt, or pharmaceutical composition described herein.

[0052] The disclosure further provides methods for treating cancer in a subject comprising administering to the subject a therapeutically effective amount of the compound, salt, or pharmaceutical composition described herein. In some embodiments, 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. In some cases, the cancer is selected from the group consisting of prostate, lung, bladder, colorectal, and multiple myeloma. In some cases, 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. In various cases, the cancer is a solid tumor. In various cases, the cancer is head and neck cancer, squamous cell carcinoma, gastric carcinoma, or pancreatic cancer.

[0053] Further provided are methods for treating an autoimmune disease in a subject comprising administering to the subject a therapeutically effective amount of the compound, salt, or pharmaceutical composition described herein. In some embodiments, 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.

[0054] The disclosure also provides methods for the treatment of an immune-related disease in a subject comprising administering to the subject a therapeutically effective amount of the compound, salt, or pharmaceutical composition described herein. In some embodiments, the immune-related disease is rheumatoid arthritis, lupus, inflammatory bowel disease, multiple sclerosis, or Crohn's disease.

[0055] Further provided are methods for treating neurodegenerative disease in a subject comprising administering to the subject a therapeutically effective amount of the compound, salt, or pharmaceutical composition described herein. In some cases, the neurodegenerative disease is multiple sclerosis.

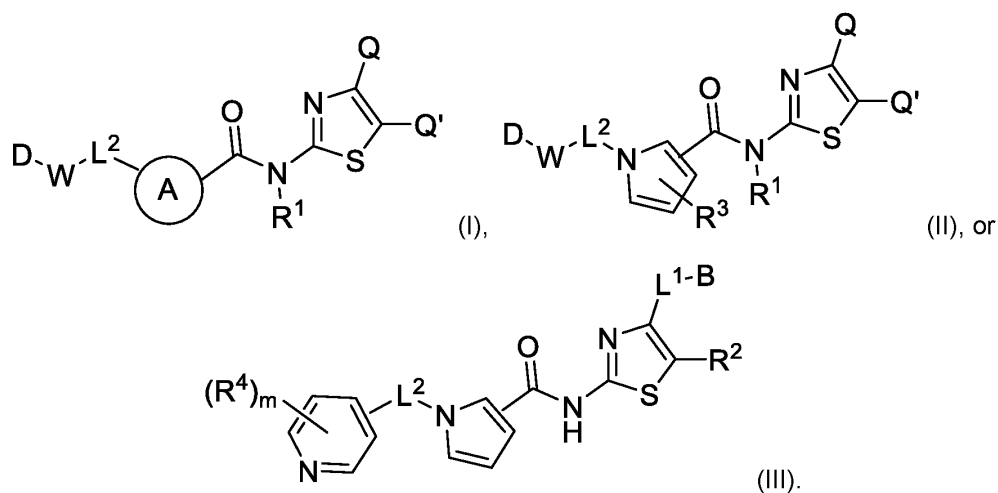
[0056] Also provided are methods for treating an inflammatory disease in a subject comprising administering to the subject a therapeutically effective amount of the compound, salt, or pharmaceutical composition described herein. In some embodiments, the inflammatory disease is bronchitis, conjunctivitis, myocarditis, pancreatitis, chronic cholecystitis, bronchiectasis, aortic valve stenosis, restenosis, psoriasis or arthritis.

[0057] Further aspects and advantages will be apparent to those of ordinary skill in the art from a review of the following detailed description. The description hereafter includes specific embodiments with the understanding that the disclosure is illustrative, and is not intended to limit the disclosure to the specific embodiments described herein.

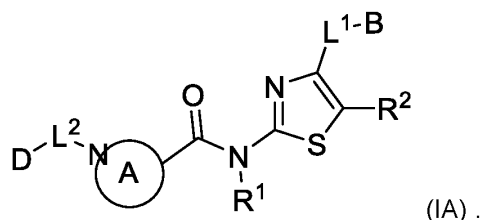
DETAILED DESCRIPTION

[0058] Provided herein are compounds that inhibit protein secretion. The compounds described herein can be used to treat or prevent diseases associated with excessive protein secretion, such as inflammation and cancer, improving the quality of life for afflicted individuals.

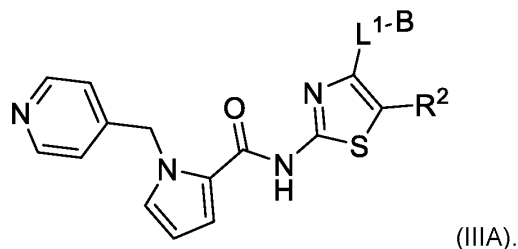
[0059] Compounds disclosed herein can have a structure of Formula (I), (II), or (III):



[0060] In some cases, the compound has a structure of Formula (IA):



[0061] In some cases, the compound has a structure of Formula (IIIA):



[0062] Without being bound by any particular theory, the compounds described herein inhibit protein secretion by binding to and disabling components of the translocon, including but not limited to Sec61, and in some cases, disrupting in a sequence specific fashion interactions between the nascent signaling sequence of translated proteins with components of the translocon including but not limited to Sec61.

[0063] The compounds described herein can advantageously inhibit the secretion of a protein of interest with an IC₅₀ of up to 5 μM, or up to 3 μM, or up to 1 μM. In various cases, the compounds disclosed herein can inhibit the secretion of TNFα with an IC₅₀ of up to 5 μM, or up to 3 μM, or up to 1 μM. In various cases, the compounds disclosed herein can inhibit the secretion of Her3 with an IC₅₀ of up to 5 μM, or up to 3 μM, or up to 1 μM. In

some cases, the compounds disclosed herein can inhibit the secretion of IL2 with an IC50 of up to 5 μ M, or up to 3 μ M, or up to 1 μ M. In various cases, the compounds disclosed herein can inhibit the secretion of PD-1 with an IC50 of up to 5 μ M, or up to 3 μ M, or up to 1 μ M.

Chemical Definitions

[0064] As used herein, the term "alkyl" refers to straight chained and branched saturated hydrocarbon groups containing one to thirty carbon atoms, for example, one to twenty carbon atoms, or one to ten carbon atoms. The term C_n means the alkyl group has "n" carbon atoms. For example, C₄alkyl refers to an alkyl group that has 4 carbon atoms. C₁₋₆alkyl refers to an alkyl group having a number of carbon atoms encompassing the entire range (i.e., 1 to 6 carbon atoms), as well as all subgroups (e.g., 1-5, 2-5, 1-4, 2-5, 1, 2, 3, 4, 5, and 6 carbon atoms). Nonlimiting examples of alkyl groups include, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl (2-methylpropyl), and t-butyl (1,1-dimethylethyl). Unless otherwise indicated, an alkyl group can be an unsubstituted alkyl group or a substituted alkyl group.

[0065] As used herein, the term "alkylene" refers to a bivalent saturated aliphatic radical. The term C_n means the alkylene group has "n" carbon atoms. For example, C₁₋₆alkylene refers to an alkylene group having a number of carbon atoms encompassing the entire range, as well as all subgroups, as previously described for "alkyl" groups.

[0066] As used herein, the term "alkene" or "alkenyl" is defined identically as "alkyl" except for containing at least one carbon-carbon double bond, and having two to thirty carbon atoms, for example, two to twenty carbon atoms, or two to ten carbon atoms. The term C_n means the alkenyl group has "n" carbon atoms. For example, C₄alkenyl refers to an alkenyl group that has 4 carbon atoms. C₂₋₇alkenyl refers to an alkenyl group having a number of carbon atoms encompassing the entire range (i.e., 2 to 7 carbon atoms), as well as all subgroups (e.g., 2-6, 2-5, 3-6, 2, 3, 4, 5, 6, and 7 carbon atoms). Specifically contemplated alkenyl groups include ethenyl, 1-propenyl, 2-propenyl, and butenyl. Unless otherwise indicated, an alkenyl group can be an unsubstituted alkenyl group or a substituted alkenyl group. Unless otherwise indicated, an alkenyl group can be a cis-alkenyl or trans-alkenyl.

[0067] As used herein, the term "alkyne" or "alkynyl" is defined identically as "alkyl" except for containing at least one carbon-carbon triple bond, and having two to thirty carbon atoms, for example, two to twenty carbon atoms, or two to ten carbon atoms. The term C_n means the alkynyl group has "n" carbon atoms. For example, C₄alkynyl refers to an alkynyl group that has 4 carbon atoms. C₂₋₇alkynyl refers to an alkynyl group having a number of carbon atoms encompassing the entire range (i.e., 2 to 7 carbon atoms), as well as all subgroups (e.g., 2-6, 2-5, 3-6, 2, 3, 4, 5, 6, and 7 carbon atoms). Specifically contemplated alkynyl

groups include ethynyl, 1-propynyl, 2-propynyl, and butynyl. Unless otherwise indicated, an alkynyl group can be an unsubstituted alkynyl group or a substituted alkynyl group.

[0068] As used herein, the term “carbocycle” refers to an aromatic or nonaromatic ring in which each atom of the ring is carbon. A carbocycle can include, for example, from three to ten carbon atoms, four to eight carbon atoms, or five to six carbon atoms. As used herein, the term “carbocycle” also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is carbocyclic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, aryls, heteroaryls, and/or heterocycles.

[0069] As used herein, the term “cycloalkyl” specifically refers to a non-aromatic carbocycle. The term C_n means the cycloalkyl group has “n” carbon atoms. For example, C_5 cycloalkyl refers to a cycloalkyl group that has 5 carbon atoms in the ring. C_{5-8} cycloalkyl refers to cycloalkyl groups having a number of carbon atoms encompassing the entire range (i.e., 5 to 10 carbon atoms), as well as all subgroups (e.g., 5-10, 5-9, 5-8, 5-6, 6-8, 7-8, 5-7, 5, 6, 7, 8, 9 and 10 carbon atoms). Nonlimiting examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Unless otherwise indicated, a cycloalkyl group can be an unsubstituted cycloalkyl group or a substituted cycloalkyl group.

[0070] As used herein, the term “aryl” refers to an aromatic carbocycle, and can be monocyclic or polycyclic (e.g., fused bicyclic and fused tricyclic) carbocyclic aromatic ring systems. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, tetrahydronaphthyl, phenanthrenyl, biphenylenyl, indanyl, indenyl, anthracenyl, fluorenyl, tetralinyl. Unless otherwise indicated, an aryl group can be an unsubstituted aryl group or a substituted aryl group.

[0071] As used herein, the term “heterocycle” is defined similarly as carbocycle, except the ring contains one to four heteroatoms independently selected from oxygen, nitrogen, and sulfur. For example, a heterocycle can be a 5-10 membered ring having 1 or 2 heteroatoms selected from N, O, and S. As another example, a heterocycle can be a 5-6 membered ring having 1 or 2 ring heteroatoms selected from N, O, and S. Nonlimiting examples of heterocycle groups include piperidine, tetrahydrofuran, tetrahydropyran, dihydrofuran, morpholine, oxazepanyl, thiazole, pyrrole, and pyridine. Carbocyclic and heterocyclic groups can be saturated or partially unsaturated ring systems optionally substituted with, for example, one to three groups, independently selected alkyl, alkoxy, alkyleneOH, $C(O)NH_2$, NH_2 , oxo ($=O$), aryl, haloalkyl, haloalkoxy, $C(O)$ -alkyl, SO_2 alkyl, halo, OH, NHC_{1-3} alkylene-aryl, OC_{1-3} alkylene-aryl, C_{1-3} alkylene-aryl, and C_{3-6} heterocycloalkyl having 1-3 heteroatoms

selected from N, O, and S. Heterocyclic groups optionally can be further N-substituted as described herein.

[0072] As used herein, the term “heteroaryl” refers to an aromatic heterocycle, and can be monocyclic or polycyclic (e.g., fused bicyclic and fused tricyclic) aromatic ring systems, wherein one to four-ring atoms are selected from oxygen, nitrogen, or sulfur, and the remaining ring atoms are carbon, said ring system being joined to the remainder of the molecule by any of the ring atoms. Nonlimiting examples of heteroaryl groups include, but are not limited to, pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, tetrazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, furanyl, thienyl, quinoliny, isoquinoliny, benzoxazolyl, benzimidazolyl, benzofuranyl, benzothiazolyl, triazinyl, triazolyl, purinyl, pyrazinyl, purinyl, indoliny, phthalizinyl, indazolyl, quinoliny, isoquinoliny, cinnoliny, quinazolinyl, naphthyridinyl, pyridopyridinyl, indolyl, 3H-indolyl, pteridinyl, and quinoxaliny. Unless otherwise indicated, a heteroaryl group can be an unsubstituted heteroaryl group or a substituted heteroaryl group.

[0073] As used herein, the term “hydroxy” or “hydroxyl” as used herein refers to an “-OH” group. Accordingly, a “hydroxyalkyl” refers to an alkyl group substituted with one or more -OH groups.

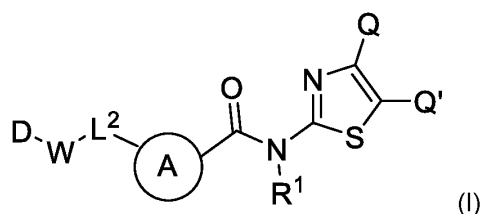
[0074] As used herein, the term “alkoxy” or “alkoxyl” refers to a “-O-alkyl” group.

[0075] As used herein, the term “halo” is defined as fluoro, chloro, bromo, and iodo. Accordingly, a “haloalkyl” refers to an alkyl group substituted with one or more halo atoms. A “haloalkoxy” refers to an alkoxy group that is substituted with one or more halo atoms.

[0076] A “substituted” functional group (e.g., a substituted alkyl, cycloalkyl, aryl, or heteroaryl) is a functional group having at least one hydrogen radical that is substituted with a non-hydrogen radical (i.e., a substituent). Examples of non-hydrogen radicals (or substituents) include, but are not limited to, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, ether, aryl, O-alkylene aryl, N-alkylene aryl, alkylene aryl, heteroaryl, heterocycloalkyl, hydroxy, hydroxyalkyl, haloalkoxy, amido, oxy (or oxo), alkoxy, ester, thioester, acyl, carboxyl, cyano, nitro, amino, sulfhydryl, and halo. When a substituted alkyl group includes more than one non-hydrogen radical, the substituents can be bound to the same carbon or two or more different carbon atoms.

Protein Secretion Inhibitors – Formula (I)

[0077] Provided herein are compounds that have a structure of Formula (I), or a pharmaceutically acceptable salt thereof:



wherein ring A is an aromatic or nonaromatic C₃₋₁₀ carbocycle, or an aromatic or nonaromatic 5-10 membered heterocycle having 1 or 2 ring heteroatoms selected from N, O, and S; one of Q and Q' is L¹-B and the other is R²; L¹ is a bond, C₁₋₆alkylene, or

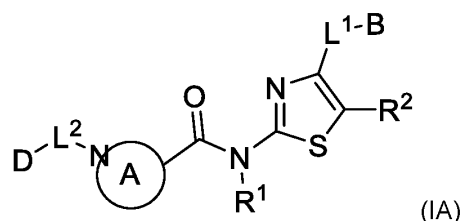
$\text{---C}_{0-2}\text{alkylene---}$, wherein --- indicates a double bond, a triple bond, or a fused or spiro cyclopropyl; B is C₁₋₃alkoxy, [O]₀₋₁-C₀₋₃alkylene-X, or NR^NC₁₋₃alkylene-X; X is an aromatic or nonaromatic C₃₋₁₀ carbocycle, or an aromatic or nonaromatic 5-10 membered heterocycle, having 1-4 ring heteroatoms selected from N, O, and S; L² is C₀₋₆alkylene (e.g., C₁₋₆alkylene) or $\text{---C}_{0-2}\text{alkylene---}$, wherein --- indicates a double bond, a triple bond, or a fused or spiro cyclopropyl; W is a bond, O, or C(O)N(R^N); D is C₆₋₁₀aryl or an aromatic or nonaromatic 5-10-membered heterocycle having 1-4 ring heteroatoms selected from N, O, and S; each R^N independently is H or C₁₋₃alkyl; R¹ is H or C₁₋₃alkyl; and R² is H, C₁₋₃alkyl, or halo.

[0078] In some embodiments, Q is L¹-B and Q' is R². In some embodiments, Q is R² and Q' is L¹-B.

[0079] Ring A is an aromatic or nonaromatic C₃₋₁₀ carbocycle, or an aromatic or nonaromatic 5-10 membered heterocycle having 1 or 2 ring heteroatoms selected from N, O, and S. Ring A can be an aromatic carbocycle, such as a phenyl or naphthyl. Ring A can be a non-aromatic carbocycle, such as a cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. Ring A can be substituted with 1 or 2 R³ groups. Each R³ can independently be H, C₁₋₃alkyl, C₁₋₃hydroxyalkyl, C₁₋₃haloalkyl, halo, oxo (=O) or -C(O)N(R^N)₂.

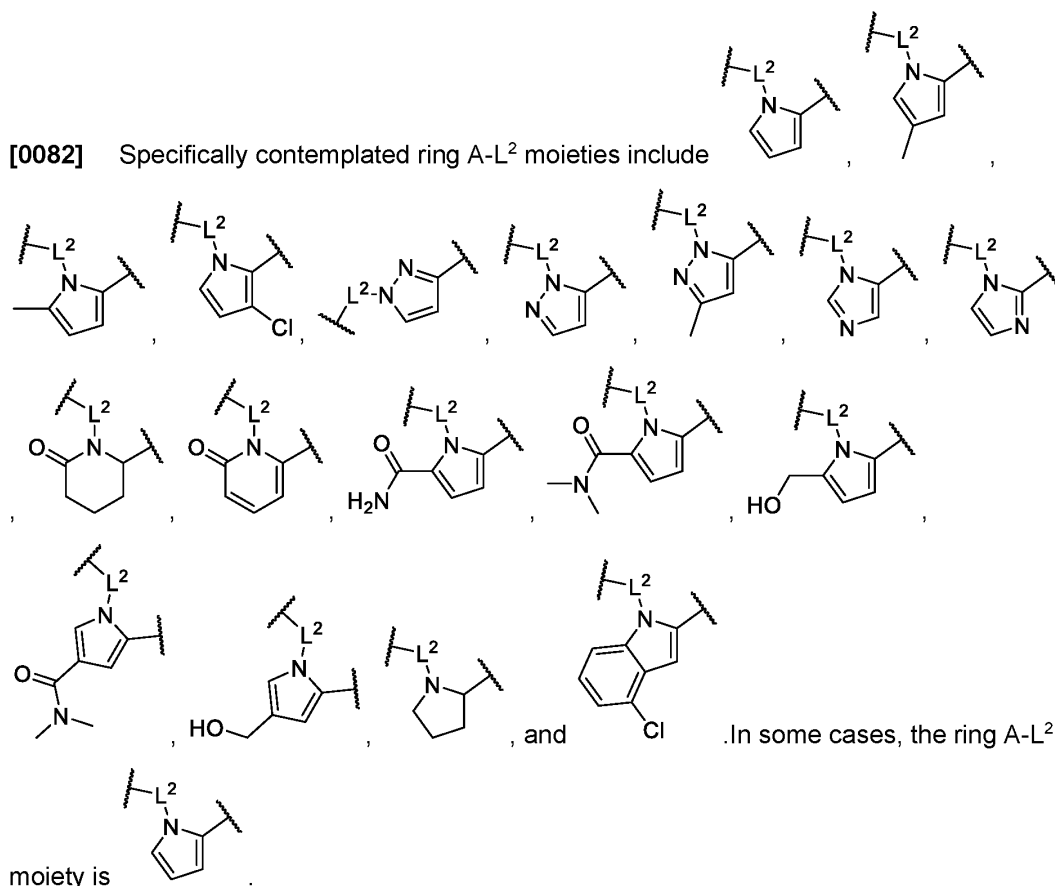
[0080] In some embodiments, ring A is an aromatic or nonaromatic 5-10 membered heterocycle having 1 or 2 ring heteroatoms selected from N, O, and S. For example, ring A can be a 5-6 membered heterocycle having 1 or 2 ring heteroatoms selected from N, O, and S. Some examples of ring A include, but are not limited to, pyrrolidinyl, pyrrolyl, indolyl, imidazolyl, and pyrazolyl. In various embodiments, ring A includes a ring nitrogen. In various cases, the ring nitrogen is bonded to L². In some cases, the ring nitrogen is not bonded to L² and is unsubstituted. In some cases, the ring nitrogen is not bonded to L² and is substituted, e.g., with an R³ group.

[0081] In some embodiments, the compound has a structure of Formula (IA):



wherein ring A has 0 or 1 additional ring heteroatoms selected from N, O, and S. In some embodiments, ring A is an aromatic or nonaromatic C₃₋₁₀ carbocycle. For example, in some cases, ring A is cyclopentyl, cyclohexyl, or phenyl, and can be substituted with 1 or 2 R³ groups.

[0082] Specifically contemplated ring A-L² moieties include

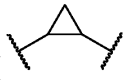


[0083] As disclosed herein, R¹ is H or C₁₋₃alkyl. In some embodiments, R¹ is H. In some embodiments, R¹ is C₁₋₃alkyl. Examples of contemplated R¹ groups include, but are not limited to, H, methyl, ethyl, n-propyl, and isopropyl. In various cases, R¹ is H or methyl.

[0084] As disclosed herein, R² is H, C₁₋₃alkyl, or halo. In some embodiments, R² is H. In some embodiments, R² is C₁₋₃alkyl. Examples of contemplated R² groups include, but are not limited to, H, methyl, ethyl, n-propyl, isopropyl, Br, Cl, and F. In various cases, R² is

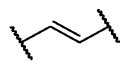
methyl. In various cases, R^2 is ethyl. In various cases, R^2 is n-propyl or isopropyl. In some embodiments, R^2 is halo. In some cases, R^2 is Br. In some cases, R^2 is F. In some cases, R^2 is Cl.

[0085] As disclosed herein, L^1 is a bond, C_{1-6} alkylene, or $\text{---C}_{0-2}\text{alkylene---}$, wherein

--- indicates a double bond, a triple bond, or a fused () or spiro () cyclopropyl.

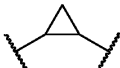
[0086] In some embodiments, L^1 is a bond. In some embodiments, L^1 is a C_{1-6} alkylene. In various cases, L^1 is CH_2 , $\text{CH}(\text{CH}_3)$, CH_2CH_2 , or $\text{C}(\text{CH}_3)$.

[0087] In some embodiments, L^1 is $\text{---C}_{0-2}\text{alkylene---}$. In various cases when L^1 is $\text{---C}_{0-2}\text{alkylene---}$, --- indicates a double bond. The double bond can be 1,1-

substituted (e.g. ), or 1,2-substituted (e.g.  or ). In some cases, the double bond is tri- or tetra-substituted. The double bond can be substituted with substitutions independently selected from C_{1-3} alkyl and halo. For example, the double bond can be substituted with one or two groups independently selected from methyl, ethyl, n-propyl, isopropyl, F, Br, and Cl. The double bond orientation can be cis or trans, or when tri- or tetra-substituted, E- or Z-. In some cases, the double bond is cis.

[0088] In various cases when L^1 is $\text{---C}_{0-2}\text{alkylene---}$, --- indicates a triple bond.

[0089] In various cases when L^1 is $\text{---C}_{0-2}\text{alkylene---}$, --- indicates a fused

cyclopropyl, e.g.,  . In some cases, --- indicates a spiro cyclopropyl, e.g.,



. The fused or spiro cyclopropyl can be further substituted with one to four substituents. Examples of suitable substituents include, but are not limited to C_{1-3} alkyl (e.g., methyl, ethyl, n-propyl, isopropyl), $\text{N}(\text{R}^N)\text{C}(\text{O})\text{C}_{1-3}\text{alkyl}$, and $\text{N}(\text{R}^N)_2$, where each R^N is independently H or C_{1-4} alkyl.

[0090] In some cases when L^1 is $\text{---C}_{0-2}\text{alkylene---}$, $\text{C}_{0-2}\text{alkylene}$ is CH_2 , $\text{CH}(\text{CH}_3)$ or CH_2CH_2 . In some cases, $\text{C}_{0-2}\text{alkylene}$ is null (C_0).

[0091] As disclosed herein, B is C_{1-3} alkoxy, $[\text{O}]_{0-1}\text{---C}_{0-3}\text{alkylene---X}$, or $\text{NR}^N\text{C}_{1-3}\text{alkylene---X}$. X is an aromatic or nonaromatic C_{3-10} carbocycle, or an aromatic or nonaromatic 5-10

membered heterocycle, having 1-4 ring heteroatoms selected from N, O, and S. R^N is H or C_{1-4} alkyl, and in some cases, is H or methyl.

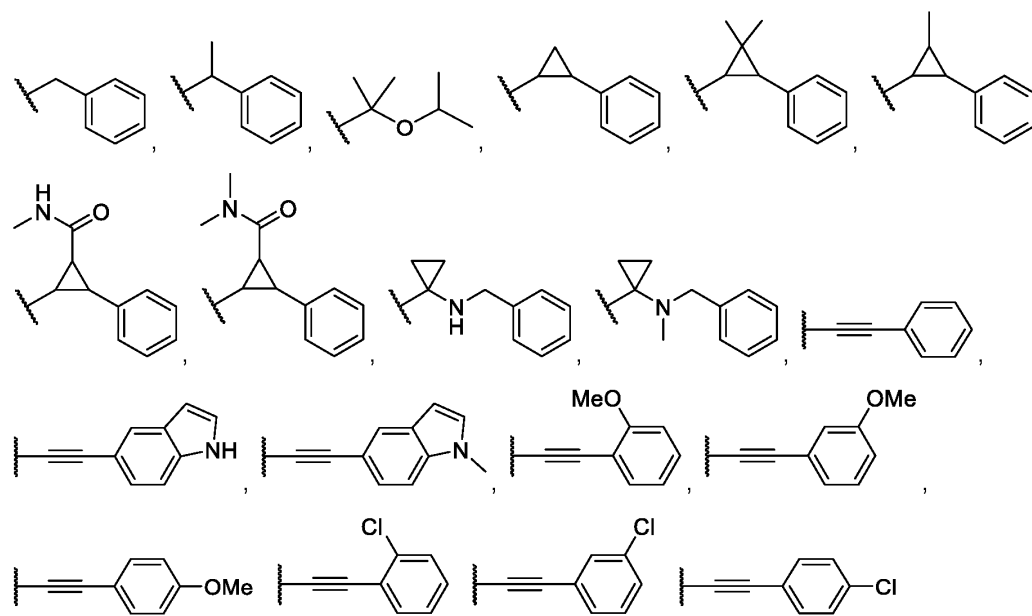
[0092] In various embodiments, B is C_{1-3} alkoxy. Specifically contemplated B include methoxy, ethoxy, propoxy, and isopropoxy.

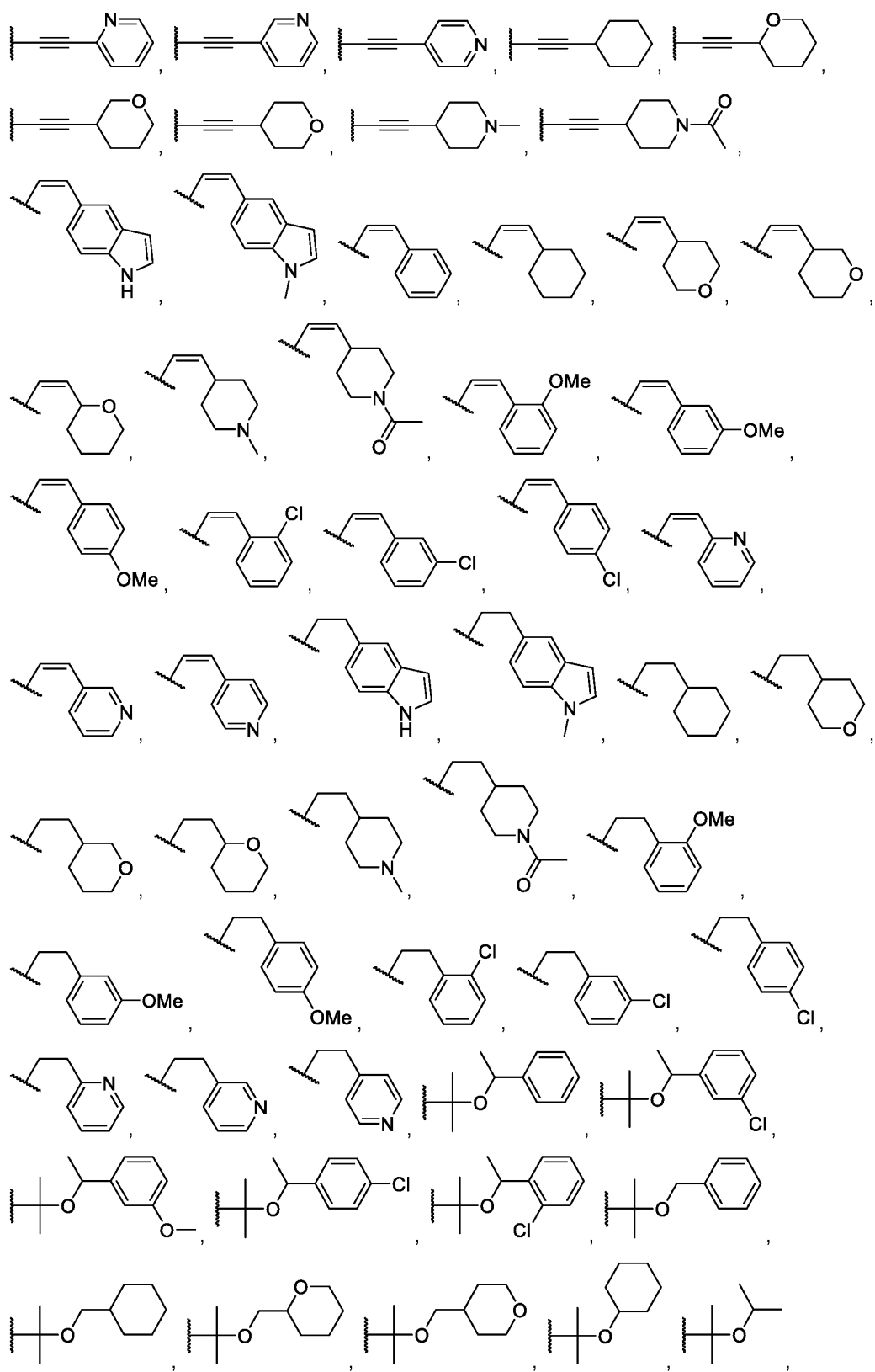
[0093] In various embodiments, B is $[O]_{0-1}-C_{0-3}$ alkylene-X. For example, in some cases, B is O-X. In some cases, B is O- C_{1-3} alkylene-X. In some cases, B is C_{1-3} alkylene-X. In some cases, B is X. In some cases, B is $NR^N C_{1-3}$ alkylene-X, such as NHC_{1-3} alkylene-X or $N(CH_3)C_{1-3}$ alkylene-X.

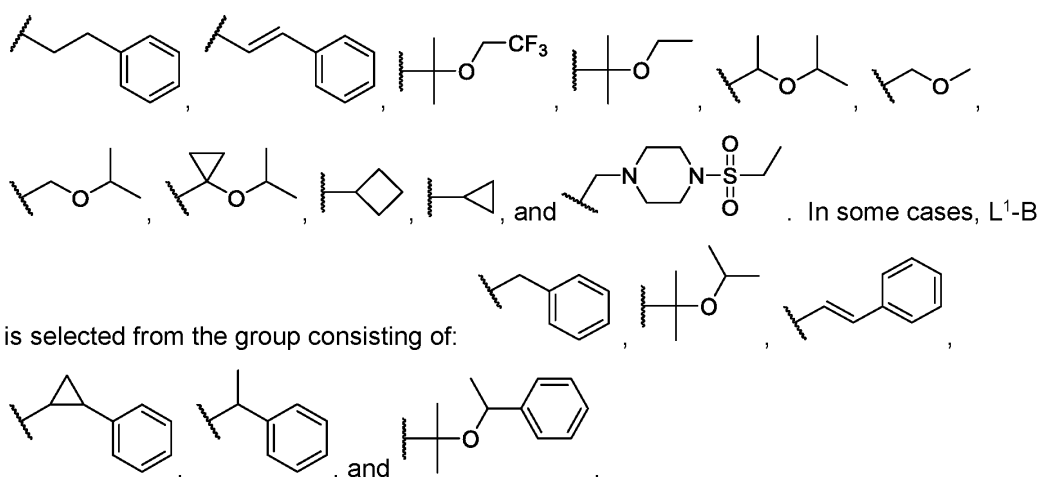
[0094] X is an aromatic or nonaromatic C_{3-10} carbocycle, or an aromatic or nonaromatic 5-10 membered heterocycle, having 1-4 ring heteroatoms selected from N, O, and S. X can be optionally substituted with 1-3 substituents. Contemplated substituents of X include C_{1-3} alkyl, C_{1-3} alkoxy, halo, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, $C(O)C_{1-3}$ alkyl, and SO_2C_{1-3} alkyl.

[0095] In embodiments, X is an aromatic C_{6-10} carbocycle, such as phenyl or naphthyl. In embodiments, X is an aromatic or nonaromatic 5-10 membered heterocycle. In some cases, X is a 5-10 membered nonaromatic heterocycle, such as morpholinyl, piperidinyl, tetrahydropyranyl, or piperazinyl. In some cases, X is a 5-10 membered heteroaryl, such as indolyl, or pyridyl. Specifically contemplated X include, but are not limited to, phenyl, pyridyl, indolyl, tetrahydropyranyl, piperidinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and piperazinyl, and can be substituted as noted above.

[0096] Some specific L^1 -B contemplated include:

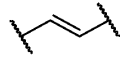






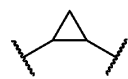
[0097] L² is C₁₋₆alkylene (e.g., C₁₋₆alkylene) or $\text{---C}_{0-2}\text{alkylene---}$, wherein --- indicates a double bond, a triple bond, or a fused or spiro cyclopropyl. In some embodiments, L² is C₀₋₆alkylene, e.g., C₀alkylene (i.e., a bond). In some embodiments, L² is C₁₋₆alkylene. For example, in some cases, L² is CH₂, CH(CH₃), CH₂CH₂, CH₂CH₂CH₂, or CH₂CH₂CH₂CH₂.

[0098] In various embodiments, L² is $\text{---C}_{0-2}\text{alkylene---}$. In some cases wherein L² is $\text{---C}_{0-2}\text{alkylene---}$, --- indicates a double bond. The double bond can be 1,1-

substituted (e.g., ) or 1,2-substituted (e.g.,  or ). In some cases, the double bond is tri- or tetra-substituted. The double bond can be substituted with substitutions independently selected from C₁₋₃alkyl and halo. For example, the double bond can be substituted with one or two groups independently selected from methyl, ethyl, n-propyl, isopropyl, F, Br, and Cl. The double bond orientation can be cis or trans, or when tri- or tetra-substituted, E- or Z-. In some cases, the double bond is cis.

[0099] In various cases wherein L² is $\text{---C}_{0-2}\text{alkylene---}$, --- indicates a triple bond.

[00100] In various cases wherein L² is $\text{---C}_{0-2}\text{alkylene---}$, --- indicates a fused

cyclopropyl, e.g., . In some cases, --- indicates a spiro cyclopropyl, e.g.,



The fused or spiro cyclopropyl can be further substituted with one to four substituents. Examples of suitable substituents include, but are not limited to C₁₋₃alkyl (e.g.,

methyl, ethyl, n-propyl, isopropyl), $N(R^N)C(O)C_{1-3}alkyl$, and $N(R^N)_2$, where each R^N is independently H or $C_{1-4}alkyl$.

[00101] In some cases when L^2 is $\text{---}C_{0-2}alkylene\text{---}$, $C_{0-2}alkylene$ is CH_2 , $CH(CH_3)$ or CH_2CH_2 . In others, $C_{0-2}alkylene$ is null.

[00102] As provided herein, W is a bond, O, or $C(O)N(R^N)$, and R^N is H or $C_{1-4}alkyl$. In some embodiments, W is a bond. In some embodiments, W is O. In some embodiments, W is $C(O)N(R^N)$, e.g., $C(O)NH$ or $C(O)N(C_{1-4}alkyl)$, and the alkyl can be, e.g., methyl, ethyl, propyl (n- or i-), or butyl (n-, s-, or t-). In some cases, W is $C(O)N(Me)$.

[00103] As disclosed herein, D is $C_{6-10}aryl$ or an aromatic or nonaromatic 5-10-membered heterocycle having 1-4 ring heteroatoms selected from N, O, and S. In embodiments, D is $C_{6-10}aryl$, such as phenyl or naphthyl.

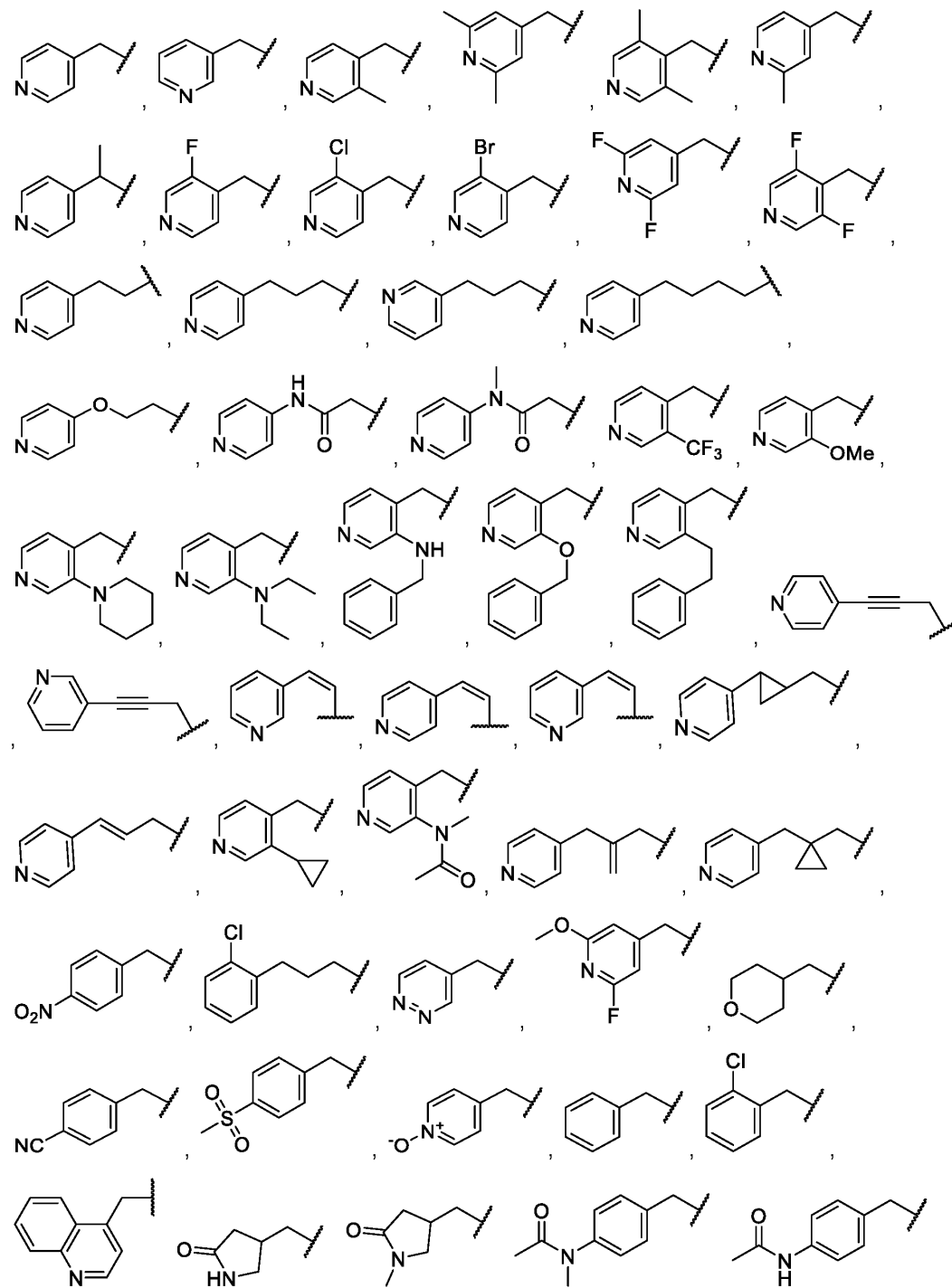
[00104] In some embodiments, D is an aromatic or nonaromatic 5-10-membered heterocycle having 1-4 ring heteroatoms selected from N, O, and S. The heterocycle can be optionally substituted with 1-3 substituents independently selected from $C_{1-3}alkyl$, $C_{1-3}alkoxy$, halo, $C_{1-3}haloalkyl$, $C_{1-3}haloalkoxy$, $N(R^N)_2$, $C_{3-6}cycloalkyl$, NO_2 , $N(R^N)C(O)C_{1-3}alkyl$, $C(O)C_{1-3}alkyl$, NO_2 , $C(O)N(R^N)_2$, CN, $SO_2C_{1-3}alkyl$, oxo ($=O$), O^- , $NHC_{1-3}alkylene-aryl$, $OC_{1-3}alkylene-aryl$, $C_{1-3}alkylene-aryl$, and 5-10 membered heterocycle having 1-3 ring heteroatoms selected from N, O, and S, and each R^N is independently H or $C_{1-4}alkyl$.

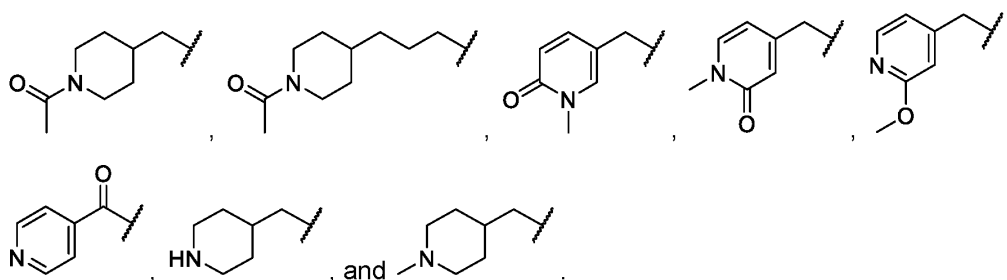
[00105] In some cases, D is an aromatic membered heterocycle. Contemplated aromatic heterocycles include, but are not limited to pyridyl, indolyl, oxazolyl, isoxazolyl, furanyl, pyranyl, thiophenyl, quinoliny, and imidazolyl. For example, in some cases, D comprises pyridyl, and is optionally substituted with 1-3 substituents independently selected from $C_{1-3}alkyl$, $C_{1-3}alkoxy$, halo, $C_{1-3}haloalkyl$, $C_{1-3}haloalkoxy$, $N(R^N)_2$, $C_{3-6}cycloalkyl$, NO_2 , $N(R^N)C(O)C_{1-3}alkyl$, $C(O)C_{1-3}alkyl$, NO_2 , $C(O)N(R^N)_2$, CN, $SO_2C_{1-3}alkyl$, O^- , $NHC_{1-3}alkylene-aryl$, $OC_{1-3}alkylene-aryl$, $C_{1-3}alkylene-aryl$, and 5-10 membered heterocycle having 1-3 ring heteroatoms selected from N, O, and S, and each R^N is independently H or $C_{1-4}alkyl$.

[00106] In some embodiments, D is a nonaromatic 5-10-membered heterocycle having 1-4 ring heteroatoms selected from N, O, and S, and is optionally substituted. In some cases, the ring heteroatom is substituted. For example, the ring heteroatom can be substituted with an R^3 group. Contemplated non-aromatic heterocycles include, but are not limited to, tetrahydropyranyl, morpholiny, piperaziny, and piperidiny. The heterocycle can be optionally substituted with 1-3 substituents independently selected from $C_{1-3}alkyl$, $C_{1-3}alkoxy$, halo, $C_{1-3}haloalkyl$, $C_{1-3}haloalkoxy$, $N(R^N)_2$, $C_{3-6}cycloalkyl$, NO_2 , $N(R^N)C(O)C_{1-3}alkyl$, $C(O)C_{1-3}alkyl$.

alkyl, NO₂, C(O)N(R^N)₂, CN, SO₂C₁₋₃alkyl, and oxo (=O), and each R^N is independently H or C₁₋₄alkyl.

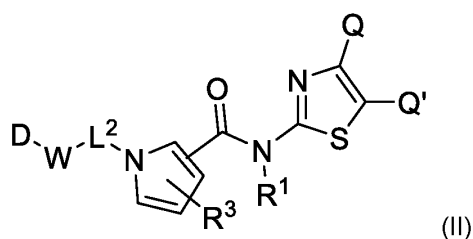
[00107] In embodiments, the L²-W-D moiety is selected from the group consisting of:





Protein Secretion Inhibitors – Formula (II)

[00108] Also provided are compounds having a structure of Formula (II), or a pharmaceutically acceptable salt thereof:



wherein one of Q and Q' is L¹-B and the other is R², or Q and Q' and the atoms to which they are attached join together to form an aromatic or nonaromatic 5 or 6 membered carbocycle or a 5 or 6 membered heterocycle having 1 or 2 ring heteroatoms selected from N, O, and S;

L¹ is a bond, C₁₋₆alkylene, or $\text{---C}_{0-2}\text{alkylene---C}_{0-2}\text{alkylene---}$, wherein --- indicates a double bond, a triple bond, or a fused or spiro cyclopropyl; B is C₁₋₆ alkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ haloalkoxy, C₁₋₃alkoxy, [O]₀₋₁-C₀₋₃alkylene-X or NR^NC₁₋₃alkylene-X, X is an aromatic or nonaromatic C₃₋₁₀ carbocycle, or an aromatic or nonaromatic 5-10 membered heterocycle having 1-4 ring heteroatoms selected from N, O, and S; L² is C₁₋₆alkylene or $\text{---C}_{0-2}\text{alkylene---C}_{0-2}\text{alkylene---}$, --- indicates a double bond, a triple bond, or a fused or spiro cyclopropyl; W is a bond, O, or C(O)N(R^N); D comprises pyridyl optionally substituted with 1-3 substituents independently selected from C₁₋₃alkyl, C₁₋₃alkoxy, halo, C₁₋₃ haloalkyl, C₁₋₃ haloalkoxy, N(R^N)₂, C₃₋₆cycloalkyl, NO₂, C(O)N(R^N)₂, N(R^N)C(O)C₁₋₃alkyl, C(O)C₁₋₃alkyl, NO₂, CN, SO₂C₁₋₃alkyl, O⁻, NHC₁₋₃alkylene-aryl, OC₁₋₃alkylene-aryl, C₁₋₃alkylene-aryl, and 5-10 membered heterocycle having 1-3 ring heteroatoms selected from N, O, and S; each R^N is independently H or C₁₋₄alkyl; R¹ is H or C₁₋₃alkyl; R² is H, C₁₋₃alkyl, or halo; and R³ is H, C₁₋₃alkyl, C₁₋₃hydroxyalkyl, C₁₋₃haloalkyl, halo, or -C(O)N(R^N)₂.

[00109] In some embodiments, Q is L¹-B and Q' is R². In some embodiments, Q is R² and Q' is L¹-B.

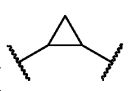
[00110] In some embodiments, Q and Q' and the atoms to which they are attached join together to form an aromatic or nonaromatic 5 or 6 membered carbocycle or a 5 or 6 membered heterocycle having 1 or 2 ring heteroatoms selected from N, O, and S. For example, Q and Q' can form a fused phenyl ring or cyclohexyl ring or a fused pyridyl, piperidiny, or piperazinyl ring. The fused ring can be optionally substituted, e.g., with 1 or 2 substituents independently selected from C₁₋₃alkyl, C₁₋₃alkoxy, halo, C₁₋₃ haloalkyl, C₁₋₃ haloalkoxy, N(R^N)₂, C₃₋₆cycloalkyl, NO₂, N(R^N)C(O)C₁₋₃alkyl, C(O)C₁₋₃alkyl, NO₂, C(O)N(R^N)₂, CN, SO₂C₁₋₃alkyl, oxo (=O), and O⁻.

[00111] As disclosed herein, R¹ is H or C₁₋₃alkyl. In some embodiments, R¹ is H. In some embodiments, R¹ is C₁₋₃alkyl. Examples of contemplated R¹ groups include, but are not limited to, H, methyl, ethyl, n-propyl, and isopropyl. In various cases, R¹ is H or methyl.

[00112] As disclosed herein, R² is H, C₁₋₃alkyl, or halo. In some embodiments, R² is H. In some embodiments, R² is C₁₋₃alkyl. Examples of contemplated R² groups include, but are not limited to, H, methyl, ethyl, n-propyl, isopropyl, Br, Cl, and F. In various cases, R² is methyl. In various cases, R² is ethyl. In various cases, R² is n-propyl or isopropyl. In some embodiments, R² is halo. In some cases, R² is Br. In some cases, R² is F. In some cases, R² is Cl.

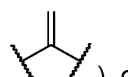
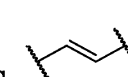
[00113] As disclosed herein, L¹ is a bond, C₁₋₆alkylene, or

$\text{---C}_{0-2}\text{alkylene---C}_{0-2}\text{alkylene---}$, wherein --- indicates a double bond, a triple bond, or

a fused () or spiro () cyclopropyl.

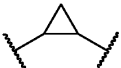
[00114] In some embodiments, L¹ is a bond. In some embodiments, L¹ is a C₁₋₆alkylene. In various cases, L₁ is CH₂, CH(CH₃), CH₂CH₂, or C(CH₃).

[00115] In some embodiments, L¹ is $\text{---C}_{0-2}\text{alkylene---C}_{0-2}\text{alkylene---}$. In various cases when L¹ is $\text{---C}_{0-2}\text{alkylene---C}_{0-2}\text{alkylene---}$, --- indicates a double bond. The

double bond can be 1,1-substituted (e.g. ) or 1,2-substituted (e.g. ) or ). In some cases, the double bond is tri- or tetra-substituted. The double bond can be substituted with substitutions independently selected from C₁₋₃alkyl and halo. For example, the double bond can be substituted with one or two groups independently selected from methyl, ethyl, n-propyl, isopropyl, F, Br, and Cl. The double bond orientation can be cis or trans, or when tri- or tetra-substituted, E- or Z-. In some cases, the double bond is cis.

[00116] In various cases when L¹ is $\text{---C}_{0-2}\text{alkylene---C}_{0-2}\text{alkylene---}$, --- indicates a triple bond.

[00117] In various cases when L¹ is $\text{---C}_{0-2}\text{alkylene---C}_{0-2}\text{alkylene---}$, --- indicates a

fused cyclopropyl, e.g., . In some cases, --- indicates a spiro cyclopropyl, e.g.,



The fused or spiro cyclopropyl can be further substituted with one to four substituents. Examples of suitable substituents include, but are not limited to C₁₋₃alkyl (e.g., methyl, ethyl, n-propyl, isopropyl), N(R^N)C(O)C₁₋₃alkyl, and N(R^N)₂, where each R^N is independently H or C₁₋₄alkyl.

[00118] In some cases when L¹ is $\text{---C}_{0-2}\text{alkylene---C}_{0-2}\text{alkylene---}$, one C₀₋₂alkylene is CH₂, CH(CH₃) or CH₂CH₂ and the other is null (C₀). In some cases, each is null. In some cases, each is independently CH₂, CH(CH₃) or CH₂CH₂.

[00119] As disclosed herein, B is C₁₋₆ alkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ haloalkoxy, C₁₋₃alkoxy, [O]₀₋₁-C₀₋₃alkylene-X or NR^NC₁₋₃alkylene-X. X is an aromatic or nonaromatic C₃₋₁₀ carbocycle, or an aromatic or nonaromatic 5-10 membered heterocycle having 1-4 ring heteroatoms selected from N, O, and S. R^N is H or C₁₋₄alkyl, and in some cases, is H or methyl.

[00120] In various embodiments, B is C₁₋₆ alkyl. For example, in some cases, B is methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, or n-hexyl.

[00121] In some embodiments, B is C₁₋₃haloalkyl or C₁₋₃haloalkoxy. For example, in some cases, B is CF₃, CF₂CH₃, CF₂CF₃, OCF₃, OCH₂CF₃, or OCF₂CF₃.

[00122] In some cases, B is C₁₋₃ hydroxyalkyl or C₁₋₃alkoxy. For example, in some cases, B is CH₂CH₂OH, CH₂OH, OMe, or OEt.

[00123] In various embodiments, B is [O]₀₋₁-C₀₋₃alkylene-X, for example, O-X, O-C₁₋₃alkylene-X, C₁₋₃alkylene-X, or X.

[00124] In some cases, B is NR^NC₁₋₃alkylene-X, for example, NHC₁₋₃alkylene-X or N(CH₃)C₁₋₃alkylene-X.

[00125] As disclosed herein, X is an aromatic or nonaromatic C₃₋₁₀ carbocycle, or an aromatic or nonaromatic 5-10 membered heterocycle, having 1-4 ring heteroatoms selected from N, O, and S. X can be optionally substituted with 1-3 substituents. Contemplated

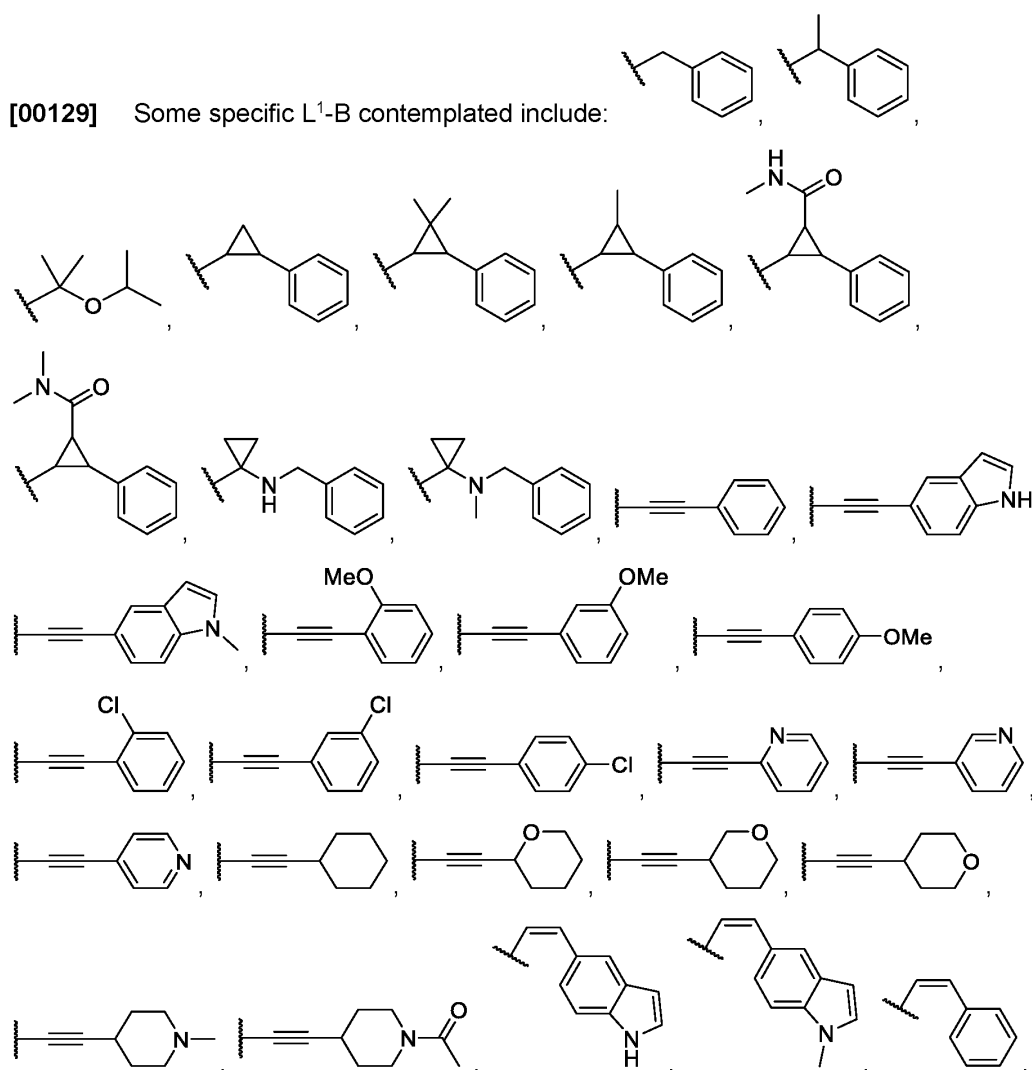
substituents include C₁₋₃alkyl, C₁₋₃alkoxy, halo, C₁₋₃ haloalkyl, C₁₋₃ haloalkoxy, C(O)C₁₋₃alkyl, and SO₂C₁₋₃alkyl.

[00126] In some cases, X is an aromatic C₆₋₁₀ carbocycle, e.g., phenyl or naphthyl.

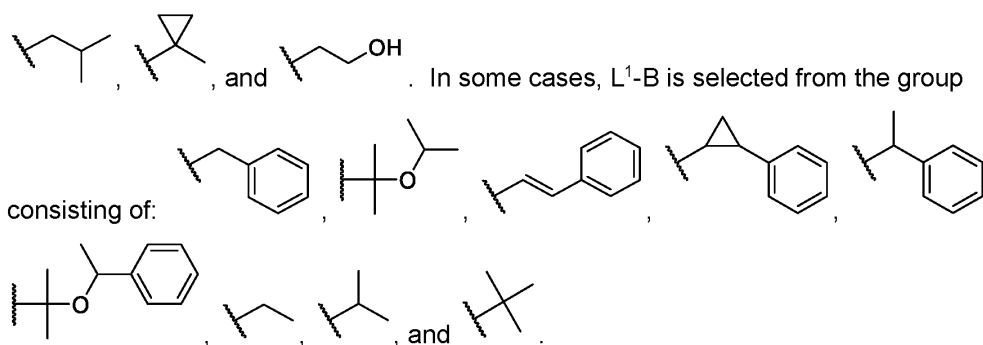
[00127] In embodiments, X is an aromatic or nonaromatic 5-10 membered heterocycle. In some cases, X is a 5-10 membered nonaromatic heterocycle, such as morpholinyl, piperidinyl, tetrahydropyranyl, or piperazinyl. In some cases, X is a 5-10 membered heteroaryl, such as indolyl, or pyridyl.

[00128] Specifically contemplated X include phenyl, pyridyl, indolyl, tetrahydropyranyl, piperidinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and piperazinyl, and can be substituted as noted above.

[00129] Some specific L¹-B contemplated include:

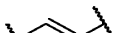
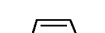






[00130] L² is C₁₋₆alkylene or $\left[\text{---C}_{0-2}\text{alkylene} \text{---} \text{C}_{0-2}\text{alkylene} \text{---} \right]$, wherein --- indicates a double bond, a triple bond, or a fused or spiro cyclopropyl. In some embodiments, L² is C₁₋₆alkylene. For example, in some cases, L² is CH₂, CH(CH₃), CH₂CH₂, CH₂CH₂CH₂, or CH₂CH₂CH₂CH₂.

[00131] In various embodiments, L² is . In various embodiments, L² is . In various embodiments, L² is . In embodiments, 

indicates a double bond. The double bond can be 1,1-substituted (e.g. ) , or 1,2-substituted (e.g.  or ). In some cases, the double bond is tri- or tetra-substituted. The double bond can be substituted with substitutions independently selected from C₁₋₃alkyl and halo. For example, the double bond can be substituted with one or two groups independently selected from methyl, ethyl, n-propyl, isopropyl, F, Br, and Cl. The double bond orientation can be cis or trans, or when tri- or tetra-substituted, E- or Z-. In some cases, the double bond is cis.

[00132] In various embodiments, --- indicates a triple bond.

[00133] In some embodiments, === indicates a fused cyclopropyl, e.g., . In

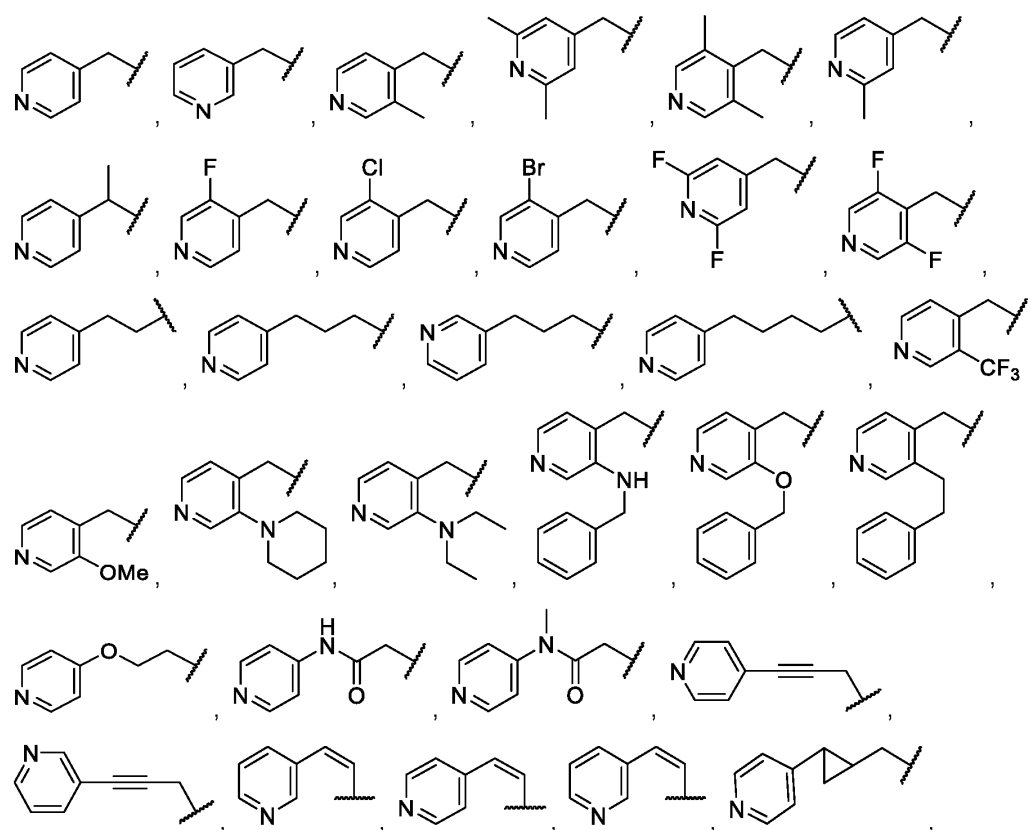
some cases,  indicates a spiro cyclopropyl, e.g., . The fused or spiro cyclopropyl can be further substituted with one to four substituents. Examples of suitable substituents include, but are not limited to C₁₋₃alkyl (e.g., methyl, ethyl, n-propyl, isopropyl), N(R^N)C(O)C₁₋₃alkyl, and N(R^N)₂, where each R^N is independently H or C₁₋₄alkyl.

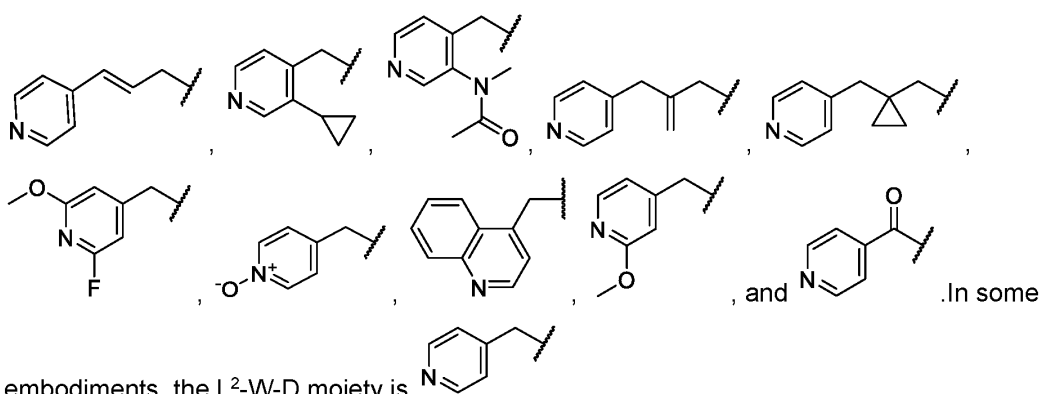
[00134] In some cases, when L^2 is $\text{---C}_{0-2}\text{alkylene---C}_{0-2}\text{alkylene---}$, one $\text{C}_{0-2}\text{alkylene}$ is CH_2 , $\text{CH}(\text{CH}_3)$ or CH_2CH_2 and the other is null (C_0). In some cases, each is null. In some cases, each is independently CH_2 , $\text{CH}(\text{CH}_3)$ or CH_2CH_2 .

[00135] As provided herein, W is a bond, O, or C(O)N(R^N), wherein R^N is H or C₁₋₄ alkyl. In some embodiments, W is a bond. In some embodiments, W is O. In some embodiments, W is C(O)N(R^N), e.g., C(O)NH or C(O)N(C₁₋₄alkyl), and the alkyl can be methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl or tert-butyl. In some cases, W is C(O)N(Me).

[00136] As disclosed herein, D comprises pyridyl or quinolinyl. In some cases, D comprises pyridyl or quinolinyl substituted with 1-3 substituents independently selected from C₁₋₃alkyl, C₁₋₃alkoxy, halo, C₁₋₃ haloalkyl, C₁₋₃ haloalkoxy, N(R^N)₂, C₃₋₆cycloalkyl, NO₂, C(O)N(R^N)₂, N(R^N)C(O)C₁₋₃alkyl, C(O)C₁₋₃alkyl, NO₂, CN, SO₂C₁₋₃alkyl, O⁻, NHC₁₋₃alkylene-aryl, OC₁₋₃alkylene-aryl, C₁₋₃alkylene-aryl, and 5-10 membered heterocycle having 1-3 ring heteroatoms selected from N, O, and S, and each R^N is independently H or C₁₋₄alkyl.

[00137] In embodiments, the L²-W-D moiety is selected from the group consisting of:

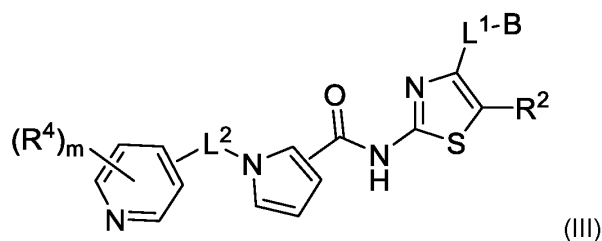




embodiments, the L²-W-D moiety is

Protein Secretion Inhibitors – Formula (III)

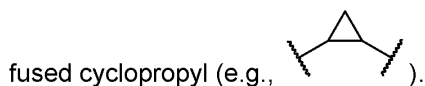
[00138] Also provided are compounds having a structure of Formula (III), or a pharmaceutically acceptable salt thereof:



wherein L¹ is a bond, C₁₋₆alkylene, or $\left[\text{C}_{0-3}\text{alkylene} \text{---} \text{C}_{0-2}\text{alkylene} \right]$, wherein --- indicates a double bond, a triple bond, or a fused cyclopropyl; B is C₀₋₃alkylene-X; X is an aromatic or nonaromatic C₄₋₁₀carbocycle, or an aromatic or nonaromatic 4-10 membered heterocycle having 1-3 ring heteroatoms selected from N, O, and S; R² is H or C₁₋₃alkyl; L² is C₀₋₃alkylene; m is 0 to 2; and each R⁴ independently is C₁₋₃alkyl, C₂₋₃alkynyl, C₁₋₃haloalkyl, C₁₋₃alkoxy, halo, or NHC₁₋₃alkylene-aryl.

[00139] As provided herein, L¹ is a bond, C₁₋₆alkylene, or

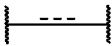
—C₀₋₃alkylene—---C₀₋₂alkylene—, wherein --- indicates a double bond, a triple bond, or a

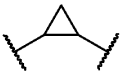


[00140] In some embodiments, L^1 is a bond.

[00141] In some embodiments, L¹ is C₁₋₆alkylene. In various cases, L¹ is CH₂, CH₂CH₂, C(CH₃)₂, C(CH₃)₂CH₂, or C(CH₃)₂CH₂CH₂.

[00142] In some embodiments, L¹ is $\text{---C}_{0-3}\text{alkylene---C}_{0-2}\text{alkylene---}$. In various cases, L¹ is $\text{---C}_{0-3}\text{alkylene---}$. In various cases, L¹ is $\text{---C}_{0-2}\text{alkylene---}$. In

various cases, L^1 is . In various cases, $---$ indicates a double bond. The double bond can be further substituted, for example, with C_{1-3} alkyl, e.g., methyl, ethyl, n-propyl, or isopropyl. In some embodiments, where $---$ indicates a double bond, the double bond is substituted with a methyl. The double bond orientation can be cis or trans, or when substituted, E- or Z-. In various cases, $---$ indicates a triple bond. In various cases, $---$

indicates a fused cyclopropyl, e.g., .

[00143] As provided herein, B is C_{0-3} alkylene-X, for example, X, C_1 alkylene-X, C_2 alkylene-X, or C_3 alkylene-X. In various cases, B is C_{1-3} alkylene-X. In various cases, B is X.

[00144] As provided herein, X is an aromatic or nonaromatic C_{4-10} carbocycle, or an aromatic or nonaromatic 4-10 membered heterocycle having 1-3 ring heteroatoms selected from N, O, and S. In some embodiments, X is aromatic or nonaromatic C_{4-7} carbocycle, or an aromatic or nonaromatic 4-9 membered heterocycle having 1 ring heteroatom. In various cases, X is an aromatic C_{6-10} carbocycle, e.g., phenyl or naphthyl. In various cases, X is an aromatic C_{6-7} carbocycle, e.g., phenyl. In various cases, X is a nonaromatic C_{4-10} carbocycle, e.g., cyclobutyl, cyclohexanyl, or cyclohexenyl. In various cases, X is a nonaromatic C_{4-7} carbocycle. In various cases, X is an aromatic 6-10 membered heterocycle having 1-3 ring heteroatoms selected from N, O, and S. In various cases, X is a nonaromatic 4-10 membered heterocycle having 1-3 ring heteroatoms selected from N, O, and S. In various cases, X is an aromatic 6-9 membered heterocycle having 1 ring heteroatom. In various cases, X is a nonaromatic 4-9 membered heterocycle having 1 ring heteroatom.

[00145] Examples of suitable X include, but are not limited to, pyrrolidinyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, phenyl, piperidinyl, pyridinyl, piperazinyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, quinolinyl, morpholinyl, pyrrolidonyl, pyrimidinyl, pyridazinyl, indenyl, dihydroindenyl, dihydrobenzofuranyl, chromanyl, isochromanyl, dihydroisoquinolinyl, or indolyl.

[00146] In some embodiments, X can be substituted with 1-3 G. In some embodiments, X is not substituted. In various cases, X is substituted with 1 G. In various cases, X is substituted with 2 G. In various cases, X is substituted with 3 G. Each G can be independently selected from the group consisting of halo, OH, =O, CN, NO_2 , $N(R^N)_2$, $N(R^N)C(O)C_{1-3}$ alkyl, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, $C(O)C_{1-3}$ alkyl, $S(O_2)-Z$, $C(O)-Z$, $C(O)N(R^N)_2$, silyl ether, and $[O]_{0-1}-C_{0-3}$ alkylene-Z. As provided herein, each R^N independently is H or C_{1-4} alkyl.

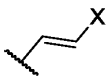
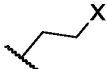
[00147] In various cases, G is halo, e.g., F, Cl, or Br. In various cases, G is OH. In various cases, G is =O. In various cases, G is CN. In various cases, G is NO₂. In various cases, G is N(R^N)₂, e.g., NH₂, NHC₁₋₃alkyl, or N(C₁₋₃alkyl)₂. In various cases, G is N(R^N)C(O)C₁₋₃alkyl, e.g., NHC(O)CH₃. In various cases, G is C₁₋₃alkyl, e.g., methyl, ethyl, n-propyl, or isopropyl. In various cases, G is C₁₋₃alkoxy, e.g., methoxy, ethoxy, n-propoxy, or isopropoxy. In various cases, G is C₁₋₃haloalkyl, such as CF₃, CHF₂, or CH₂F. In various cases, G is C₁₋₃haloalkoxy, e.g., OCF₃, OCH₂CF₃, or OCF₂CF₃. In various cases, G is C(O)C₁₋₃alkyl, e.g., C(O)CH₃, C(O)CH₂CH₃, or C(O)CH₂CH₂CH₃. In various cases, G is S(O₂)-Z. In various cases, G is C(O)-Z. In various cases, G is C(O)N(R^N)₂, e.g., C(O)NH₂, C(O)NHC₁₋₃alkyl, or C(O)N(C₁₋₃alkyl)₂. In various cases, G is silyl ether, e.g. tert-butyl diphenylsilyl ether. In various cases, G is [O]₀₋₁-C₀₋₃alkylene-Z, e.g., O-C₁₋₃alkylene-Z, O-Z, C₁₋₃alkylene-Z, or Z.

[00148] As provided herein, Z is aromatic or nonaromatic C₃₋₁₀carbocycle, or aromatic or nonaromatic 4-10 membered heterocycle having 1-3 heteroatoms selected from the group consisting of N, O, and S. In some embodiments, Z is aromatic C₆₋₁₀carbocycle, e.g., phenyl or naphthyl. In some embodiments, Z is nonaromatic C₃₋₁₀carbocycle, e.g., cyclopropyl, cyclobutyl, cyclopropyl, or cyclohexanyl. In some embodiments, Z is aromatic 6-10 membered heterocycle having 1-3 heteroatoms selected from the group consisting of N, O, and S. In some embodiments, Z is nonaromatic 4-10 membered heterocycle having 1-3 heteroatoms selected from the group consisting of N, O, and S.

[00149] Examples of suitable Z include, but are not limited to, pyrrolidinyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, phenyl, piperidinyl, pyridinyl, piperazinyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, quinolinyl, morpholinyl, pyrrolidonyl, pyrimidinyl, pyridazinyl, indenyl, dihydroindenyl, dihydrobenzofuranyl, chromanyl, isochromanyl, dihydroisoquinolinyl, or indolyl.

[00150] In some embodiments, Z is substituted with 1-3 E. In some embodiments, Z is not substituted. In various cases, Z is substituted with 1 E. In various cases, Z is substituted with 2 E. In various cases, Z is substituted with 3 E. Each E can be independently selected from C₁₋₃alkyl, C₁₋₃alkoxy, =O, C₁₋₃haloalkoxy, CN, and halo.

[00151] In various cases, E is C₁₋₃alkyl, e.g., methyl, ethyl, n-propyl, or isopropyl. In various cases, E is C₁₋₃alkoxy, e.g., methoxy, ethoxy, n-propoxy, or isopropoxy. In various cases, E is =O. In various cases, E is C₁₋₃haloalkoxy, e.g., OCF₃, OCH₂CF₃, or OCF₂CF₃. In various cases, E is CN. In various cases, E is halo, e.g., F, Cl, or Br.

[00152] In some embodiments, L^1 -B is selected from the group consisting of , , and , wherein X is as described herein. For example, in embodiments, X is aromatic or nonaromatic C_{4-7} carbocycle, or an aromatic or nonaromatic 4-9 membered heterocycle having 1 ring heteroatom. In some embodiments, X is substituted with 1-3 G, wherein G can be as described herein.

[00153] As provided herein, R^2 is H or C_{1-3} alkyl. In some embodiments, R^2 is H. In some embodiments, R^2 is C_{1-3} alkyl. In various cases, R^2 is methyl, ethyl, n-propyl, or isopropyl. In various cases, R^2 is methyl.

[00154] As provided herein, L^2 is C_{0-3} alkylene. In various cases, L^2 is a bond (*i.e.*, C_0 alkylene). In various cases, L^2 is C_1 alkylene. In various cases, L^2 is C_2 alkylene. In various cases, L^2 is C_3 alkylene.

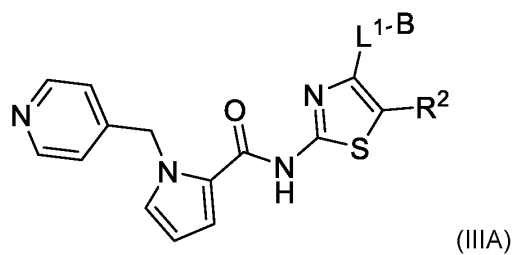
[00155] As provided herein, m is 0 to 2. In various cases, m is 0. In various cases, m is 1. In various cases, m is 2. In various cases, m is 1 or 2.

[00156] As provided herein, each R^4 independently is C_{1-3} alkyl, C_{2-3} alkynyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, halo, or NHC_{1-3} alkylene-aryl.

[00157] In some embodiments, at least one R^4 is C_{1-3} alkyl, e.g., methyl, ethyl, n-propyl, or isopropyl. In various cases, at least one R^4 is methyl or ethyl. In some embodiments, at least one R^4 is C_{2-3} alkynyl. In various cases, at least one R^4 is C_2 alkynyl. In various cases, at least one R^4 is C_3 alkynyl. In some embodiments, at least one R^4 is C_{1-3} haloalkyl, e.g., CF_3 , CHF_2 , or CH_2F . In various cases, at least one R^4 is CF_3 . In some embodiments, at least one R^4 is C_{1-3} alkoxy, e.g., methoxy, ethoxy, n-propoxy, or isopropoxy. In various cases, at least one R^4 is methoxy. In some embodiments, at least one R^4 is halo, e.g., F, Cl, or Br. In various cases, at least one R^4 is F. In various cases, at least one R^4 is Cl. In some embodiments, NHC_{1-3} alkylene-aryl. In various cases, at least one R^4 is $NH-CH_2$ -phenyl.

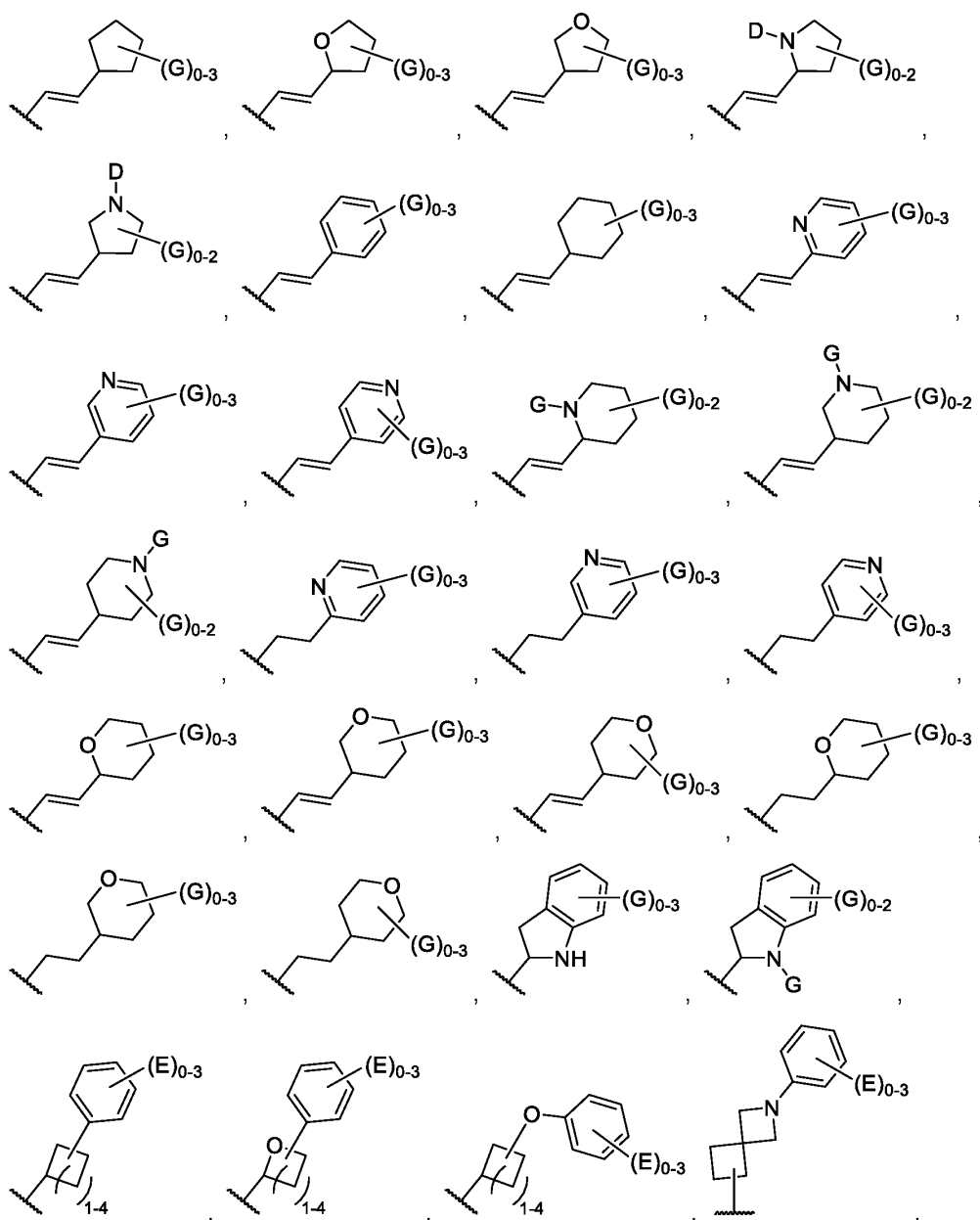
[00158] In some embodiments, one R^4 is halo, and the other R^4 is halo or methyl. In various cases, one R^4 is halo, and the other R^4 is halo. For example, in various cases, one R^4 is F, and the other R^4 is F. In various cases, one R^4 is halo, and the other R^4 is methyl. For example, in various cases, one R^4 is F, and the other R^4 is methyl.

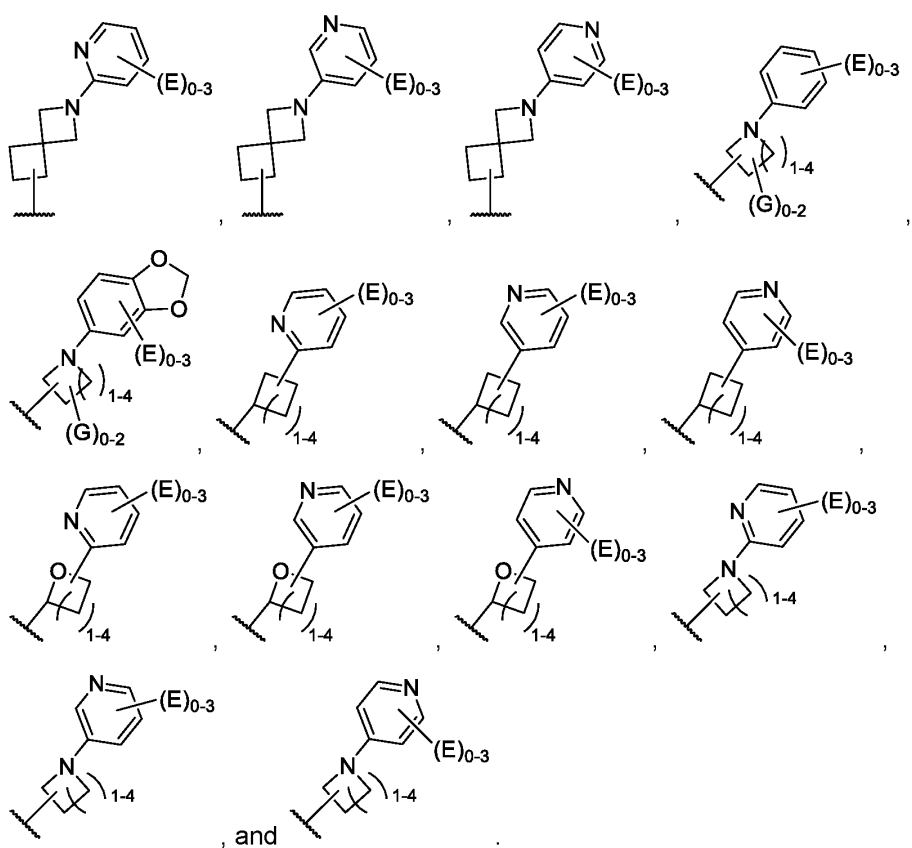
[00159] In some embodiments, the compound has a structure of Formula (IIIA):



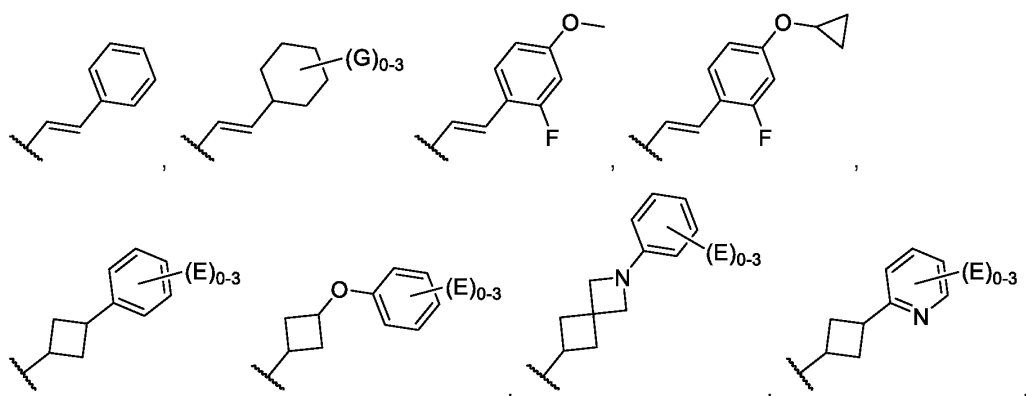
wherein each of L¹-B and R² are as described herein.

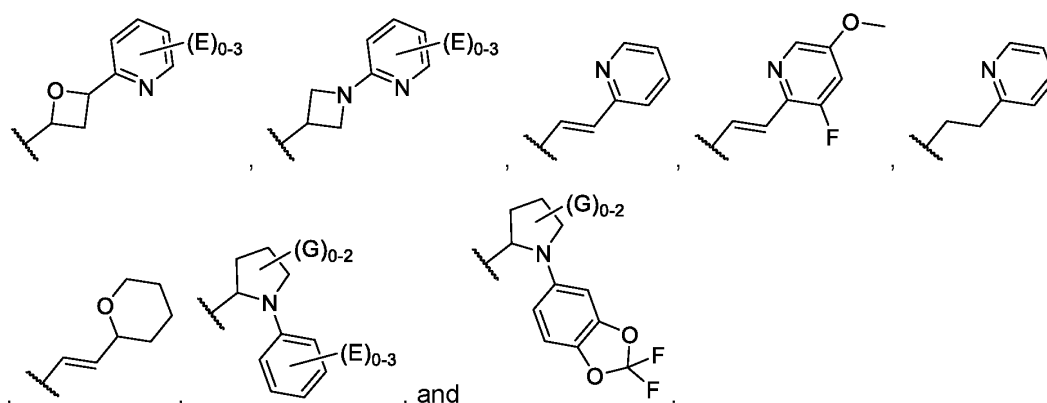
[00160] In some embodiments, L¹-B is selected from the group consisting of



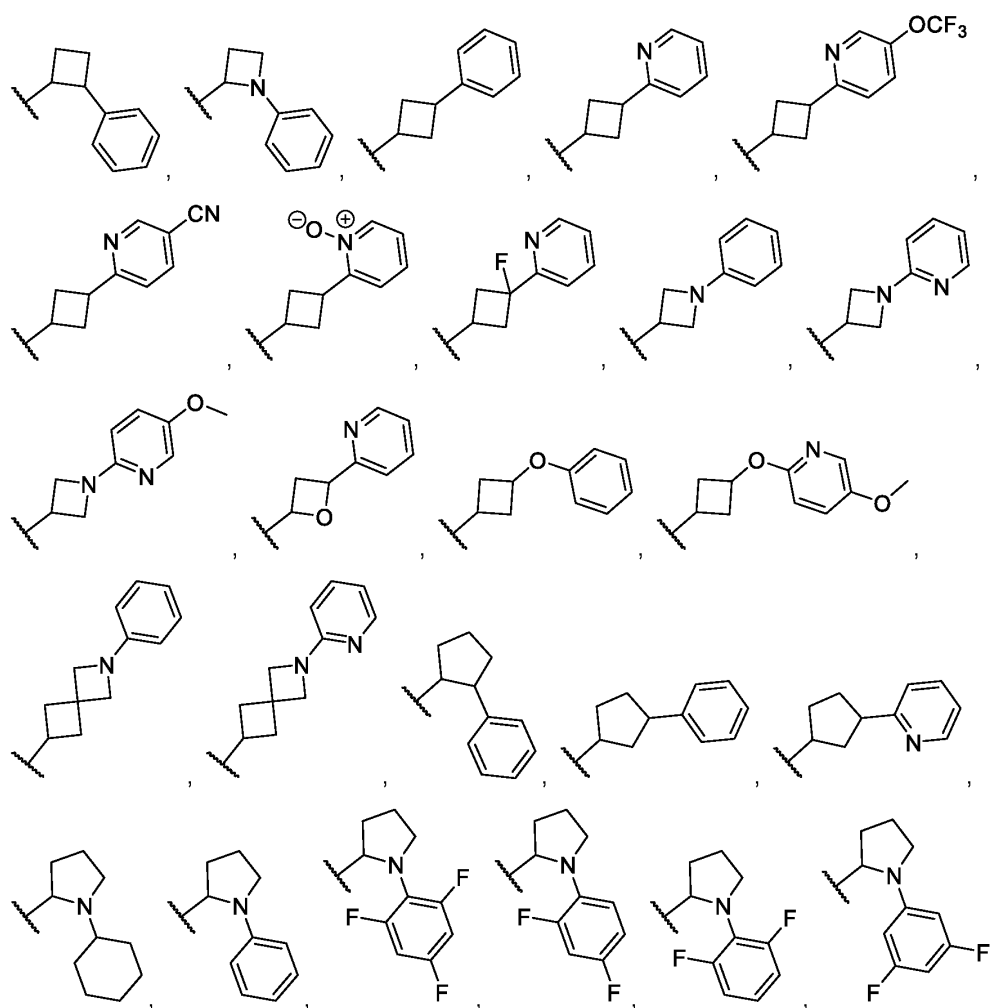


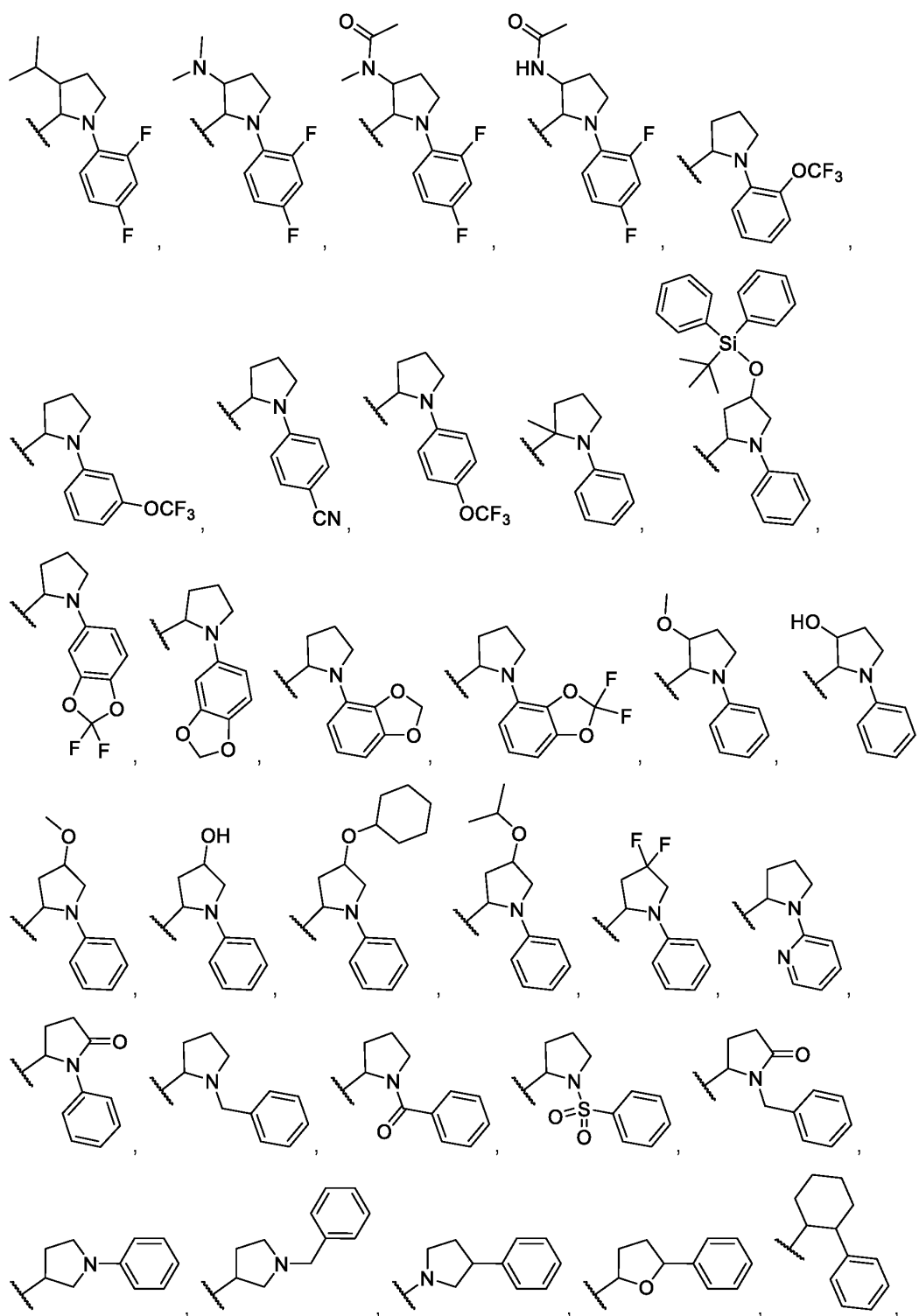
[00161] In some embodiments, L¹-B is selected from the group consisting of

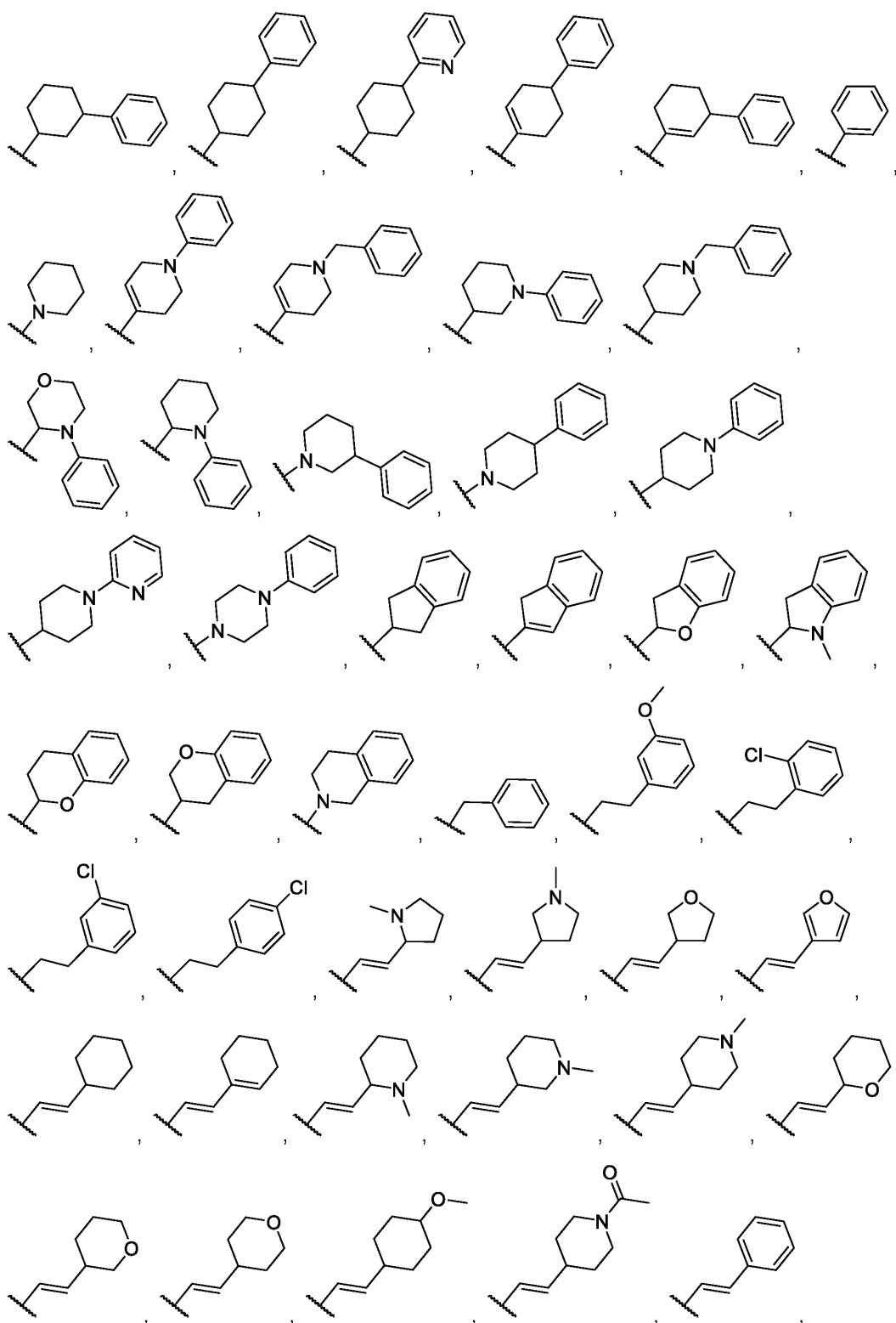


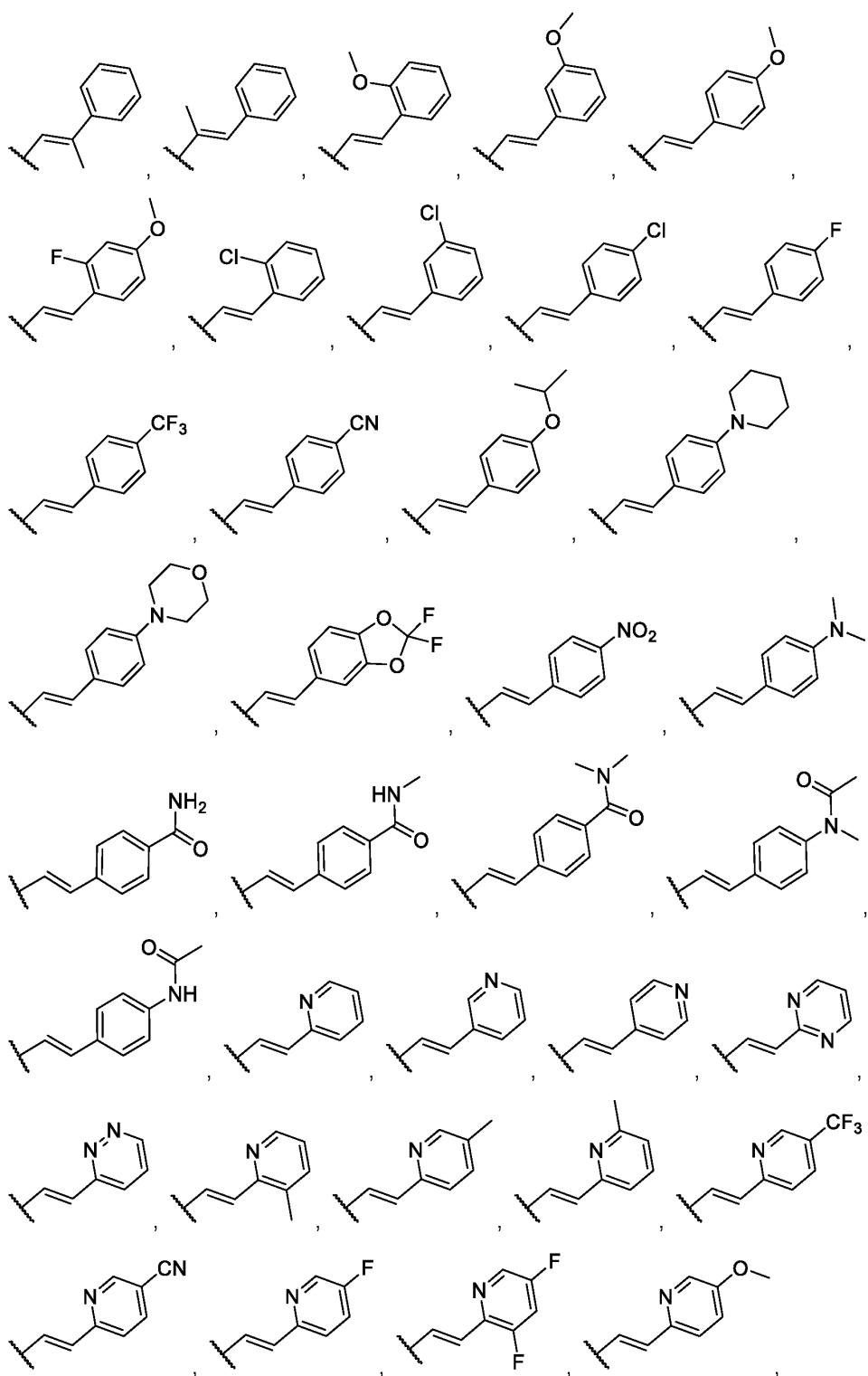


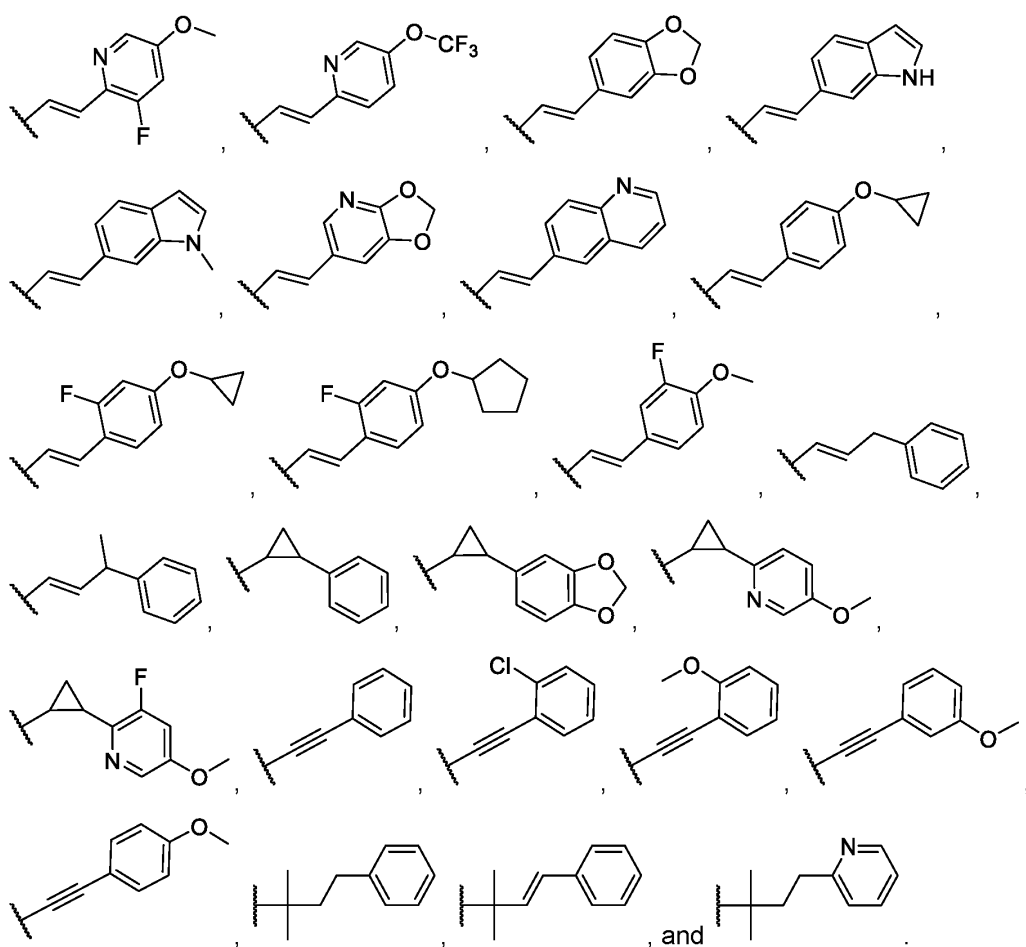
[00162] In some embodiments, L¹-B is selected from the group consisting of



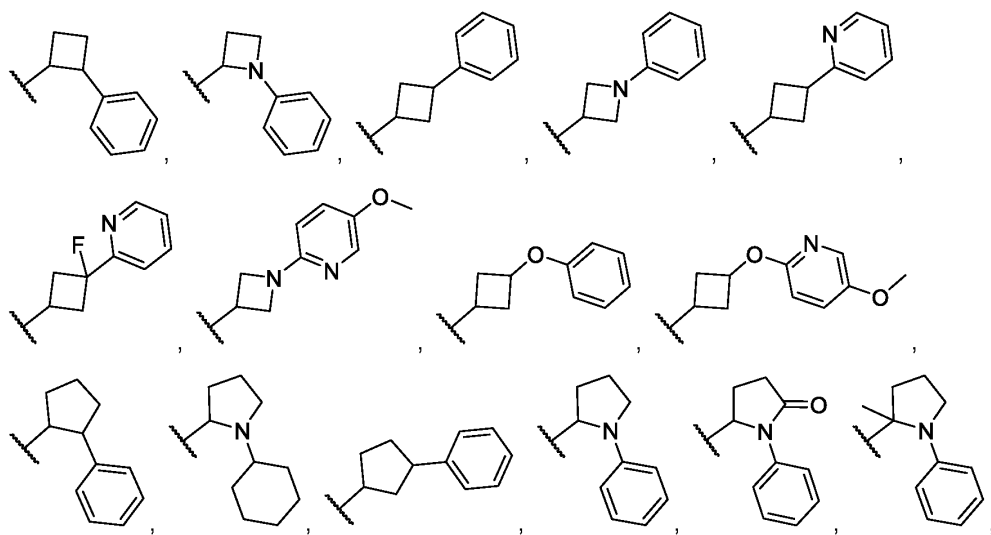


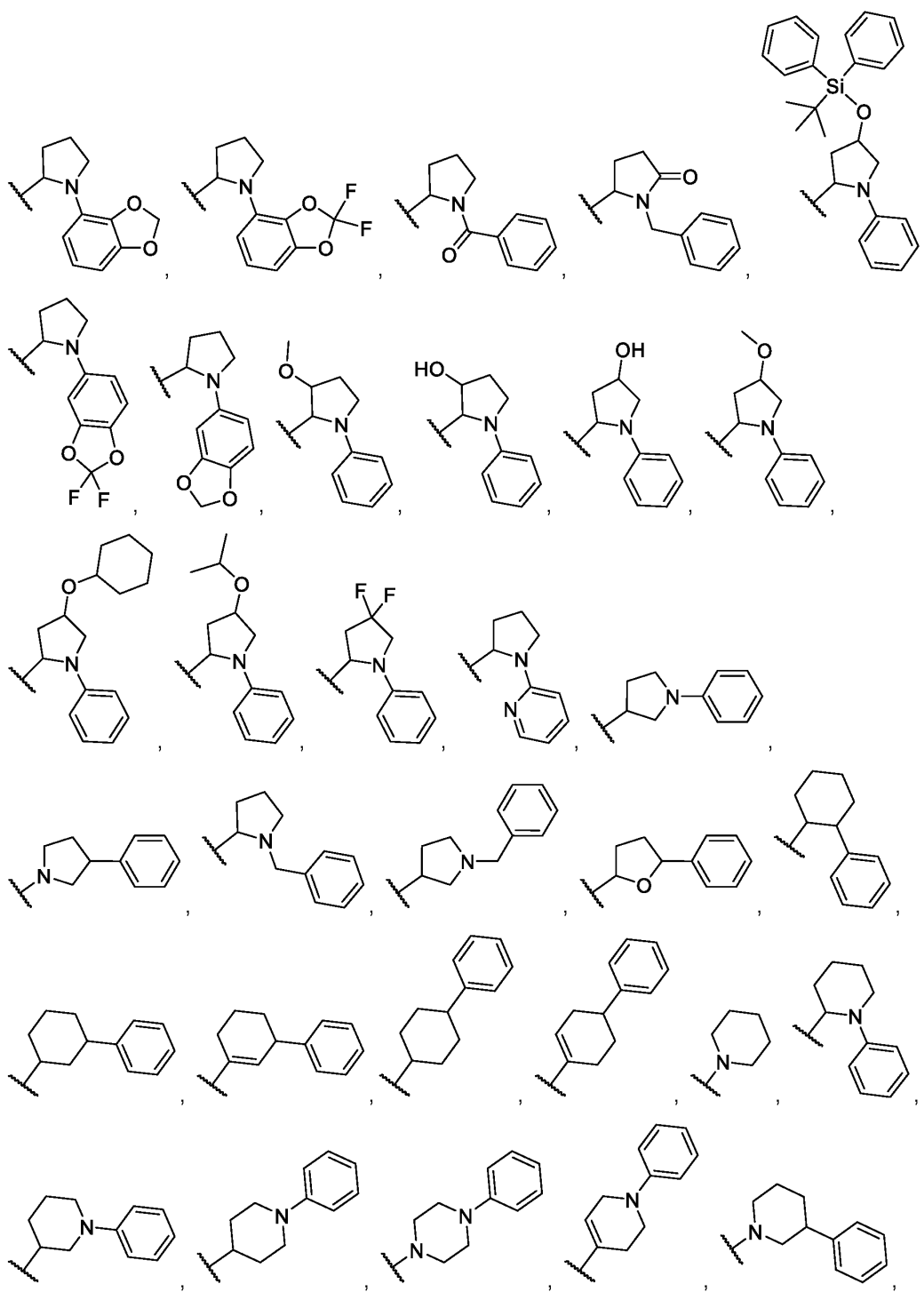


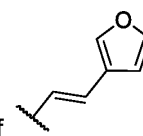
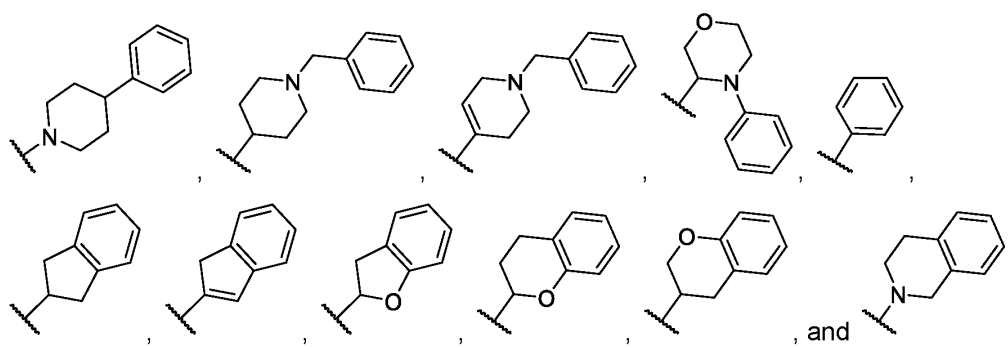




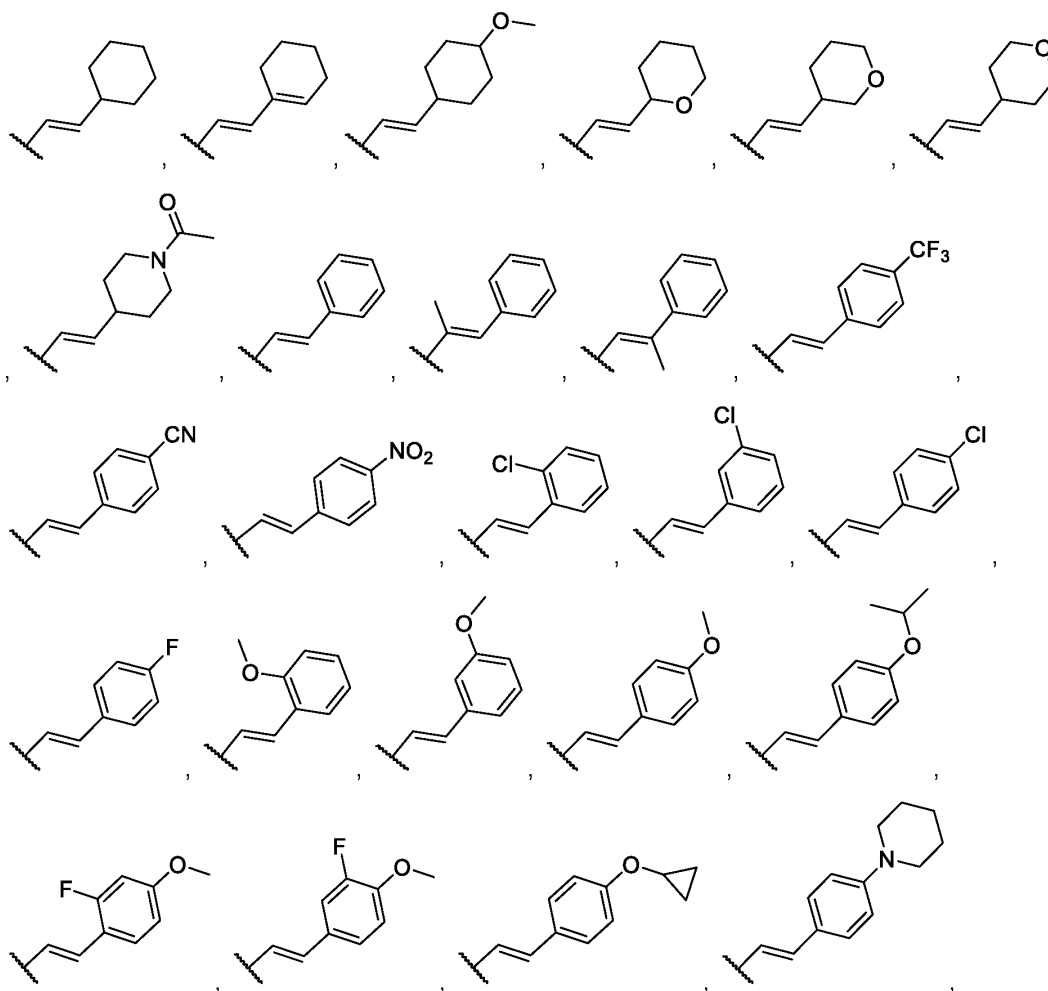
[00163] In some embodiments, L¹-B is selected from the group consisting of

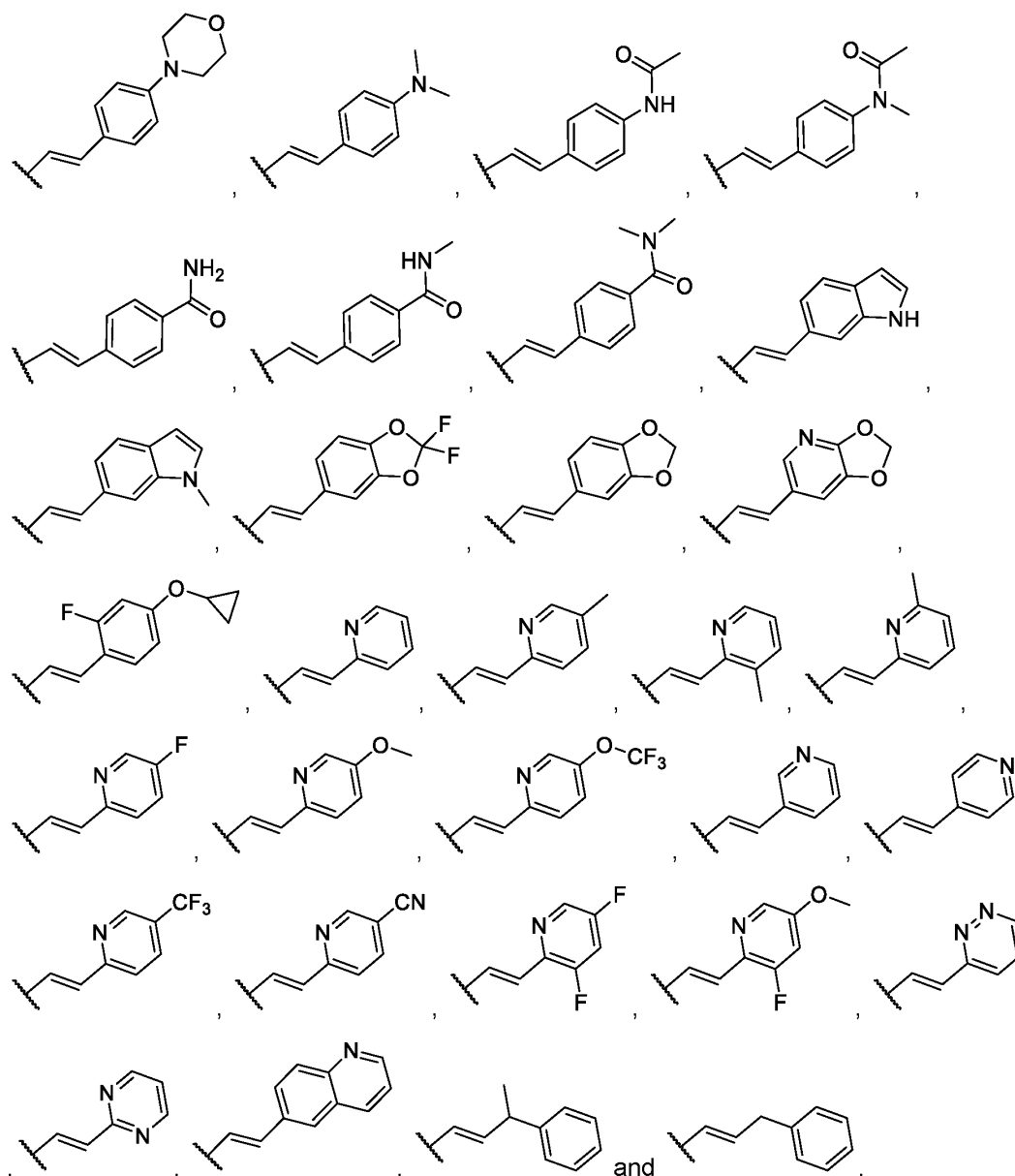






[00164] In some embodiments, L¹-B is selected from the group consisting of

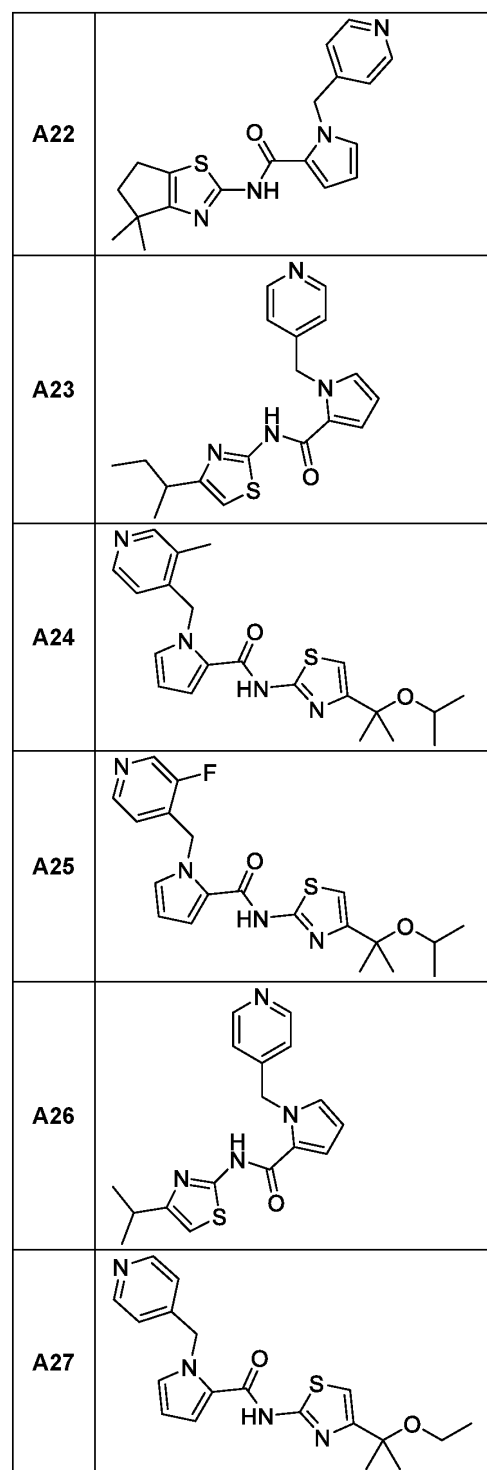
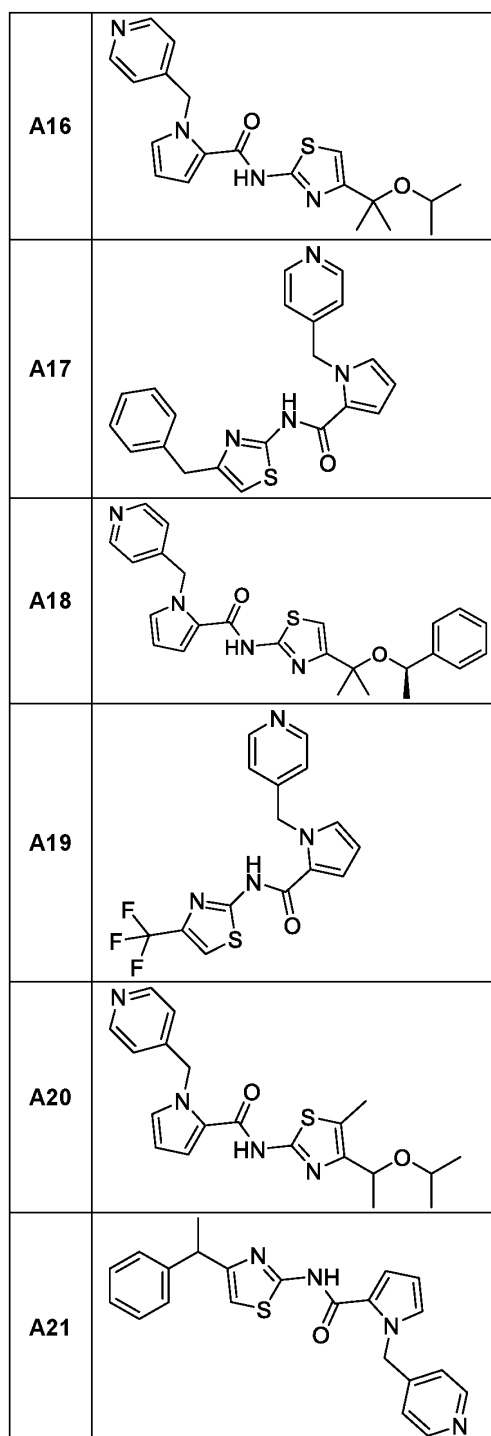


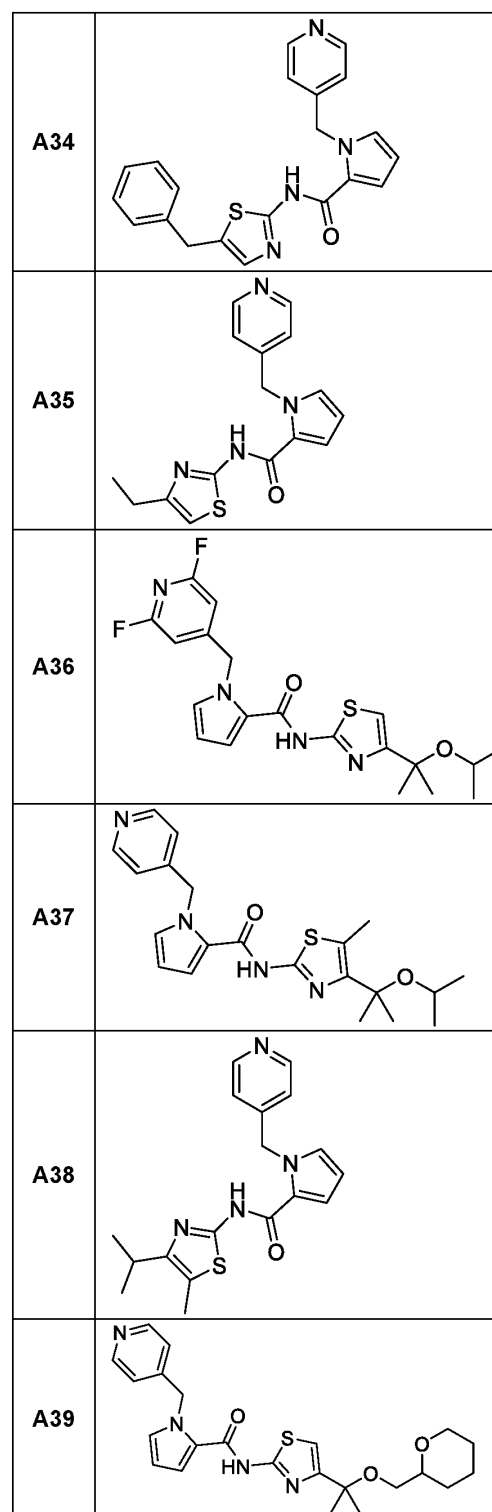
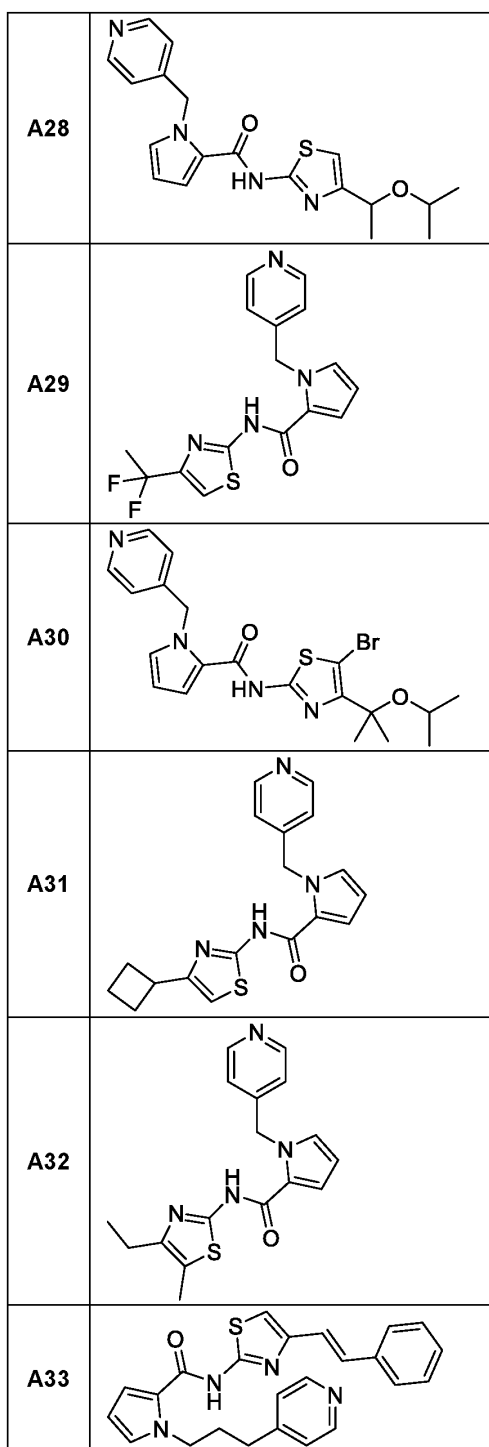


[00165] Examples of compounds according to Formulae (I), (II), and (III) of the disclosure are shown in Table A, below, as compounds A1-A403. In some embodiments, a compound of the disclosure is one of A1-A210. Additional compounds of the disclosure are shown in Table B, below, as compounds B1-B29. In some embodiments, a compound of the disclosure is one of B1-B29.

Table A

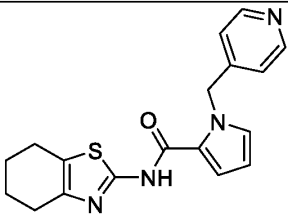
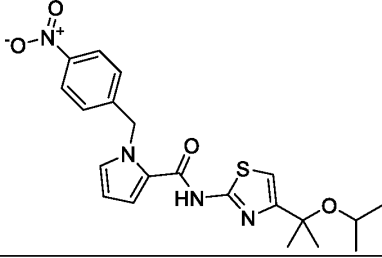
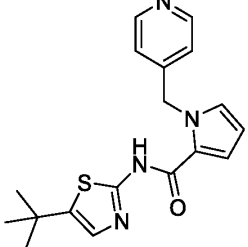
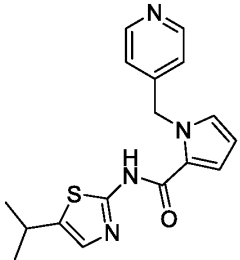
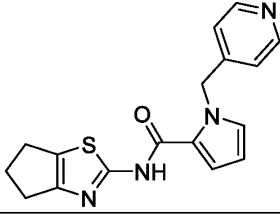
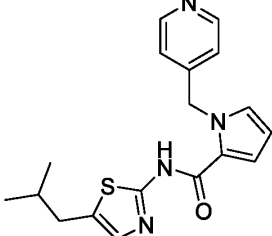
A1	
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A15	

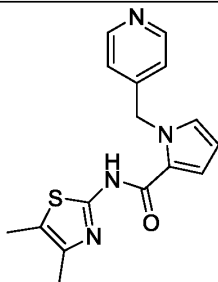
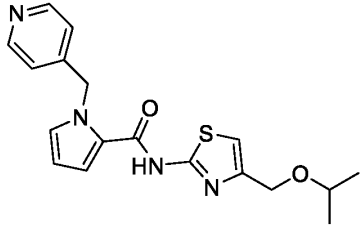
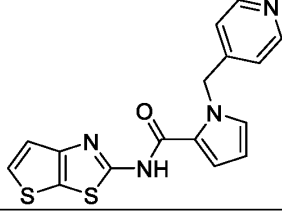
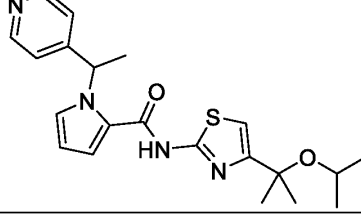
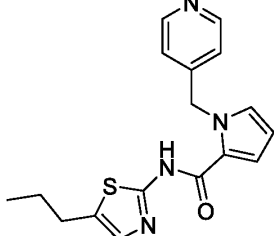
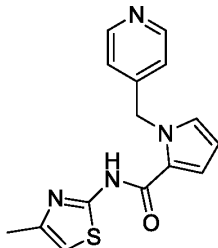


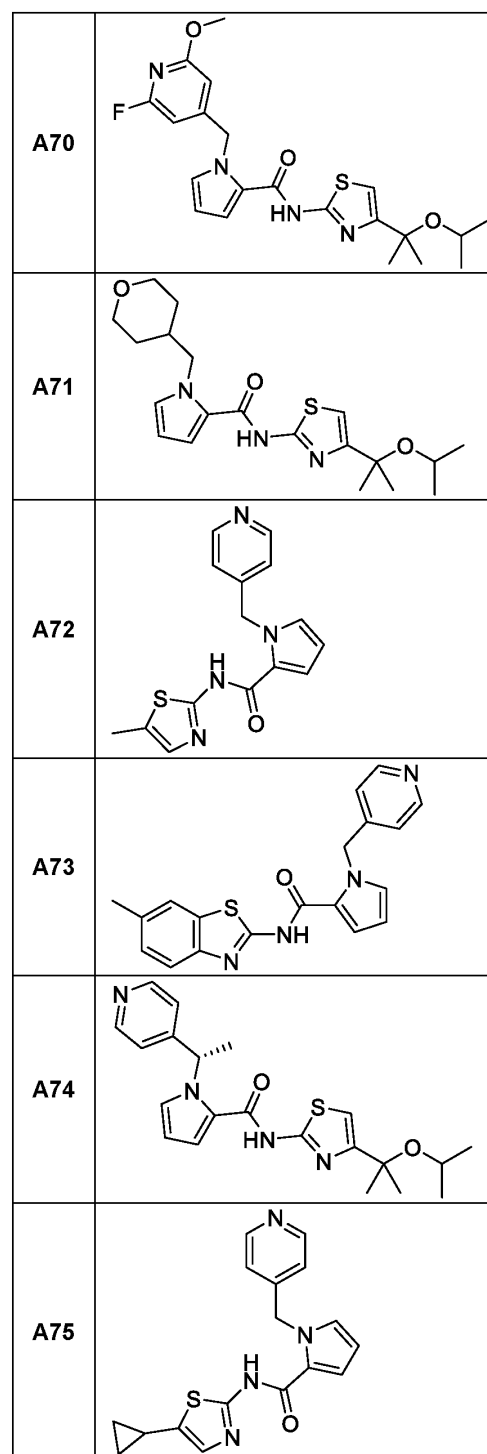
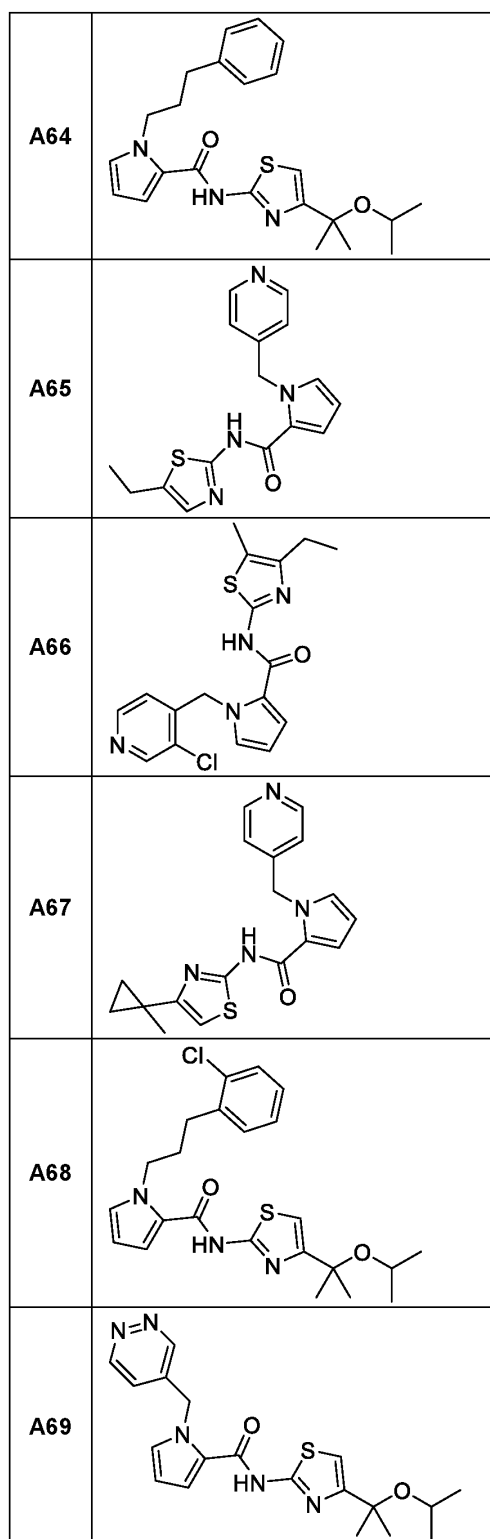


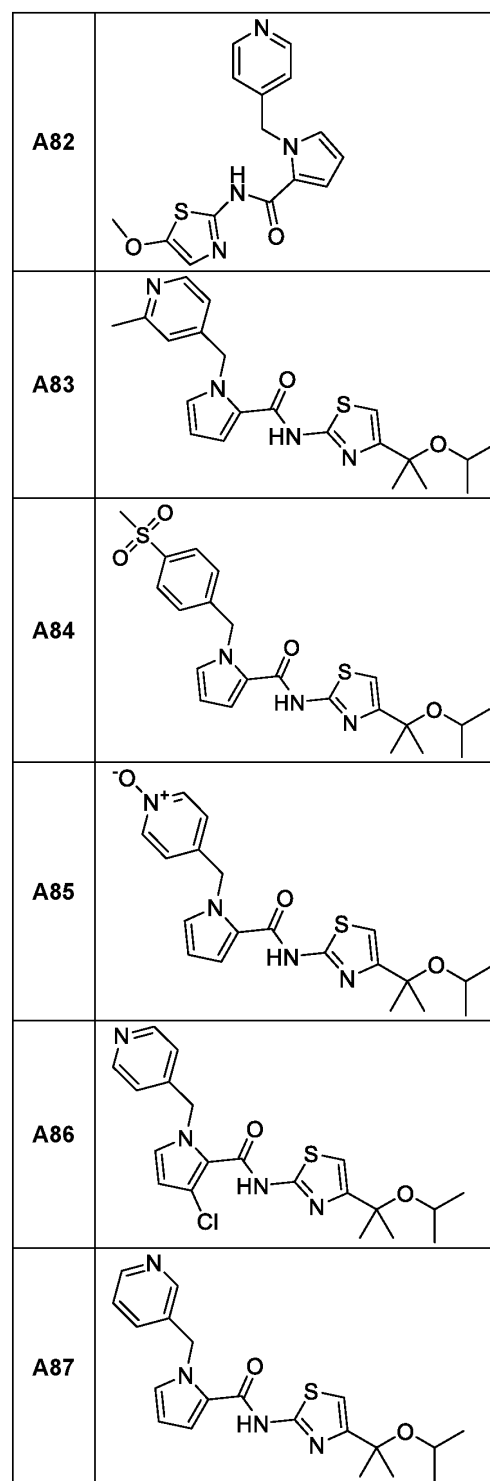
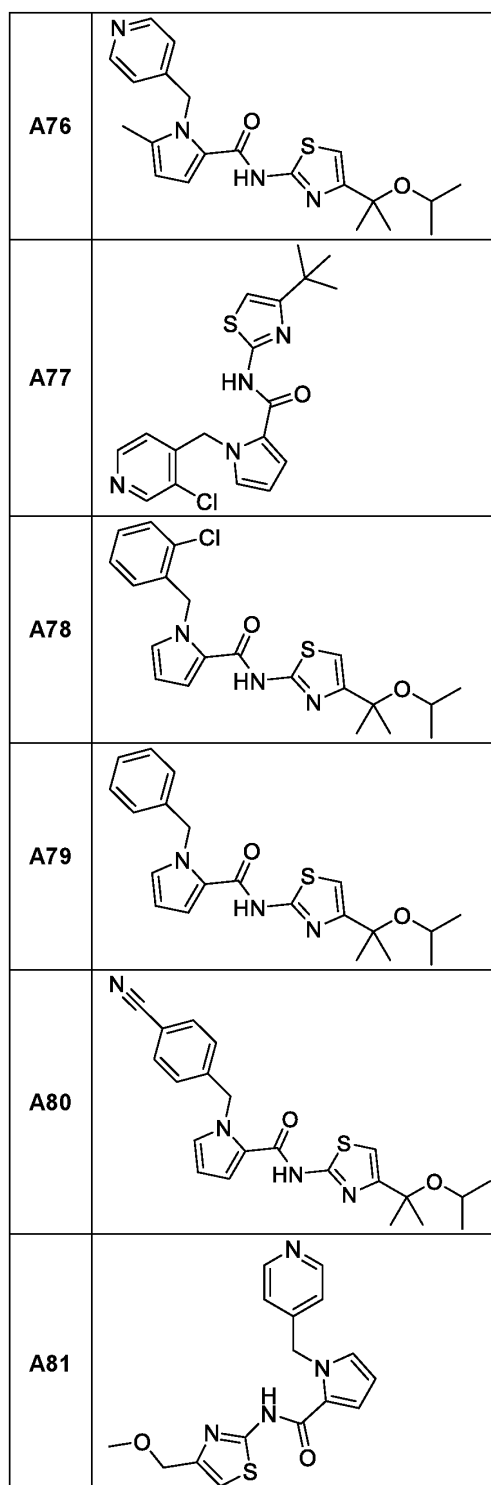
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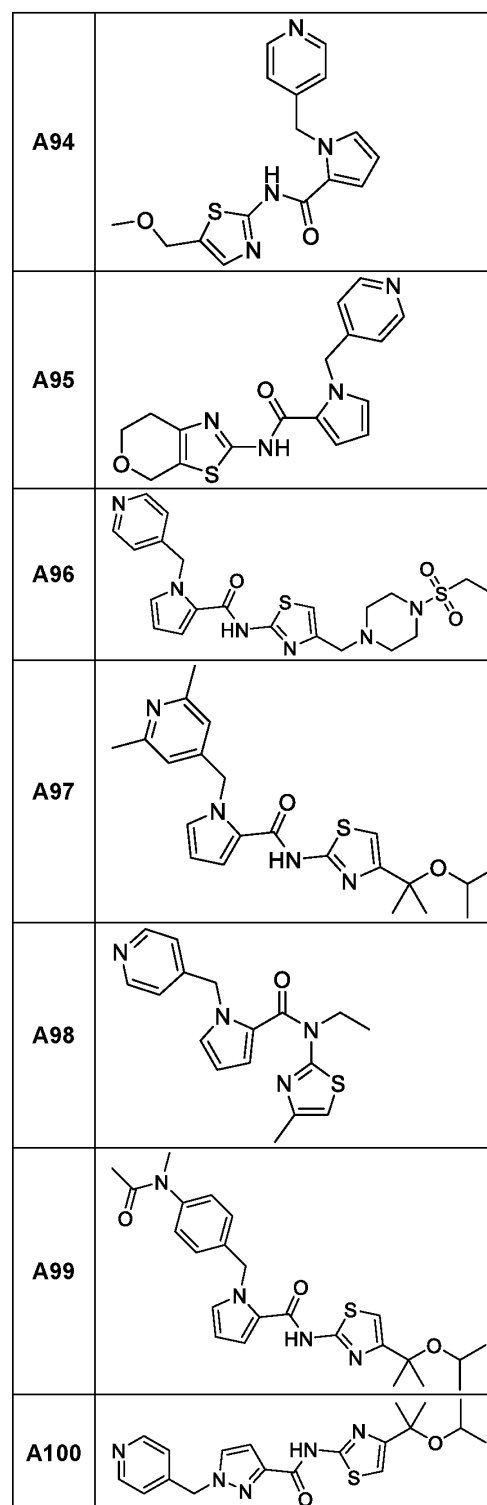
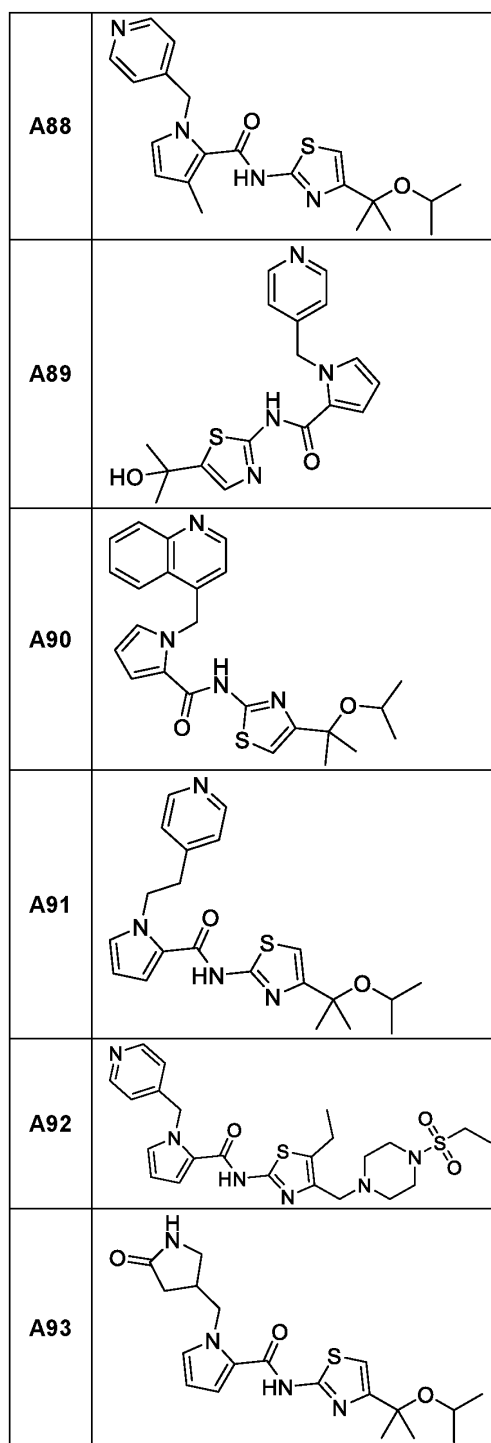
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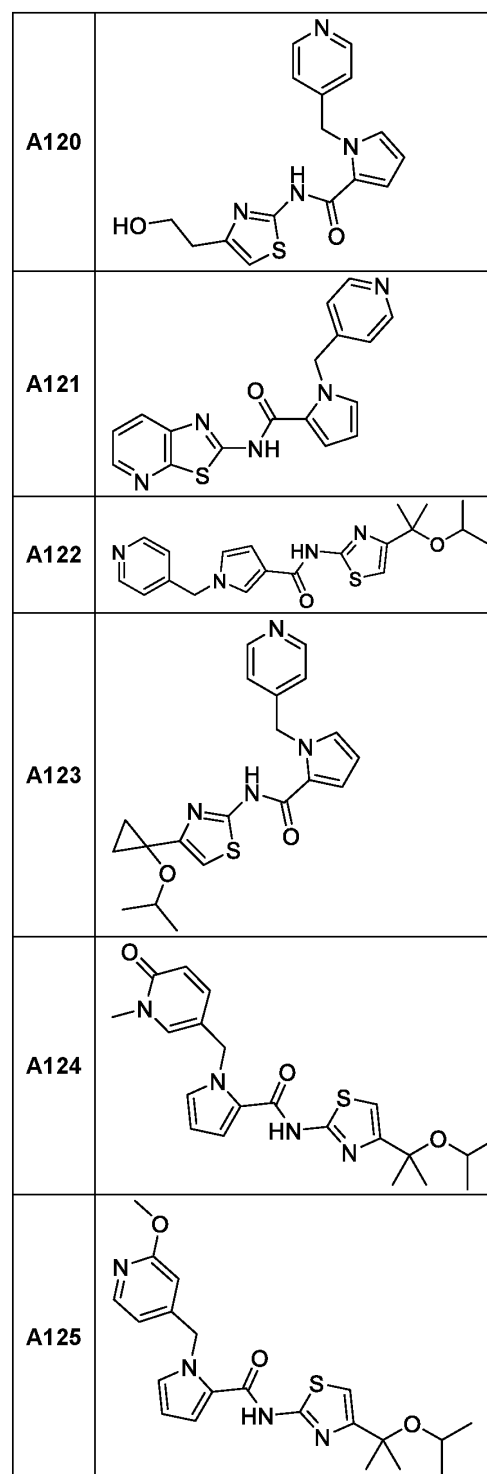
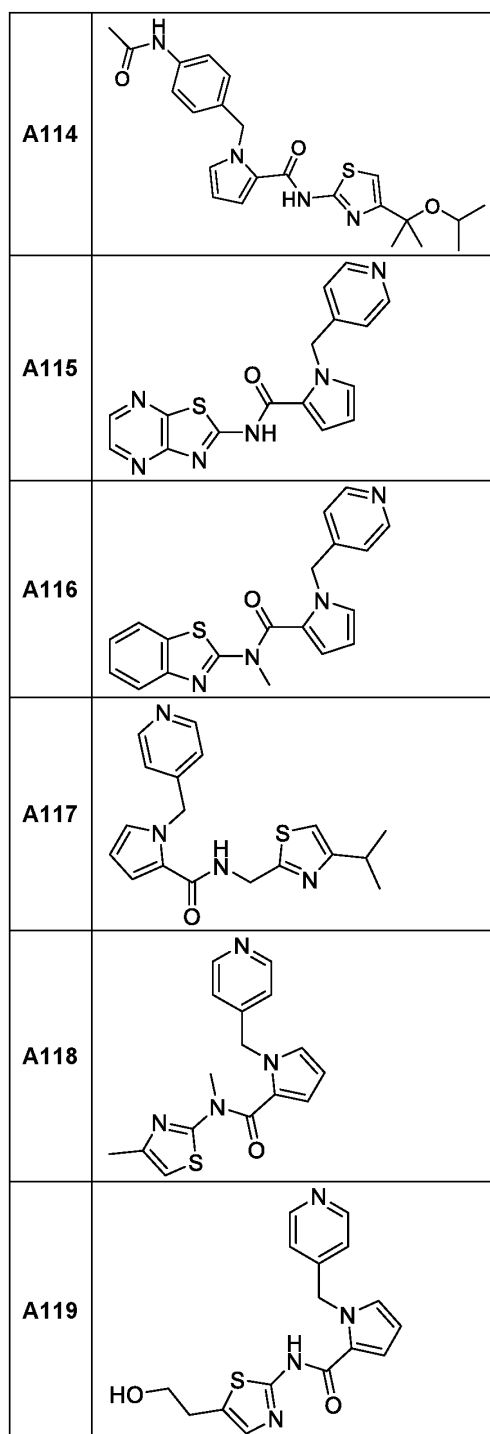


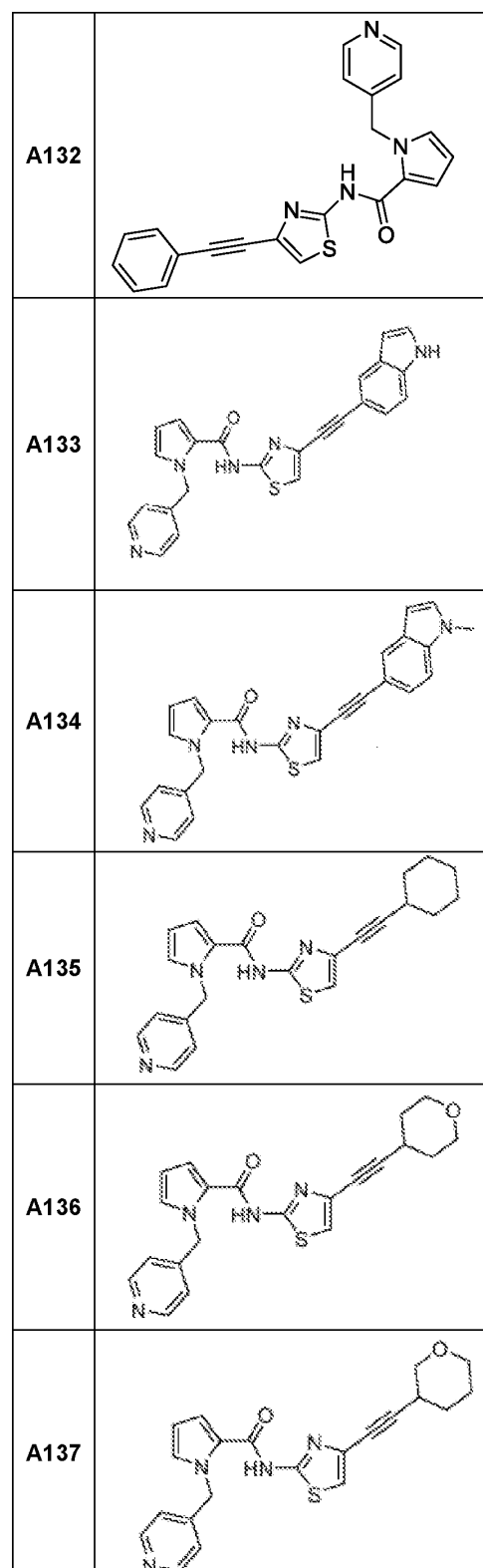
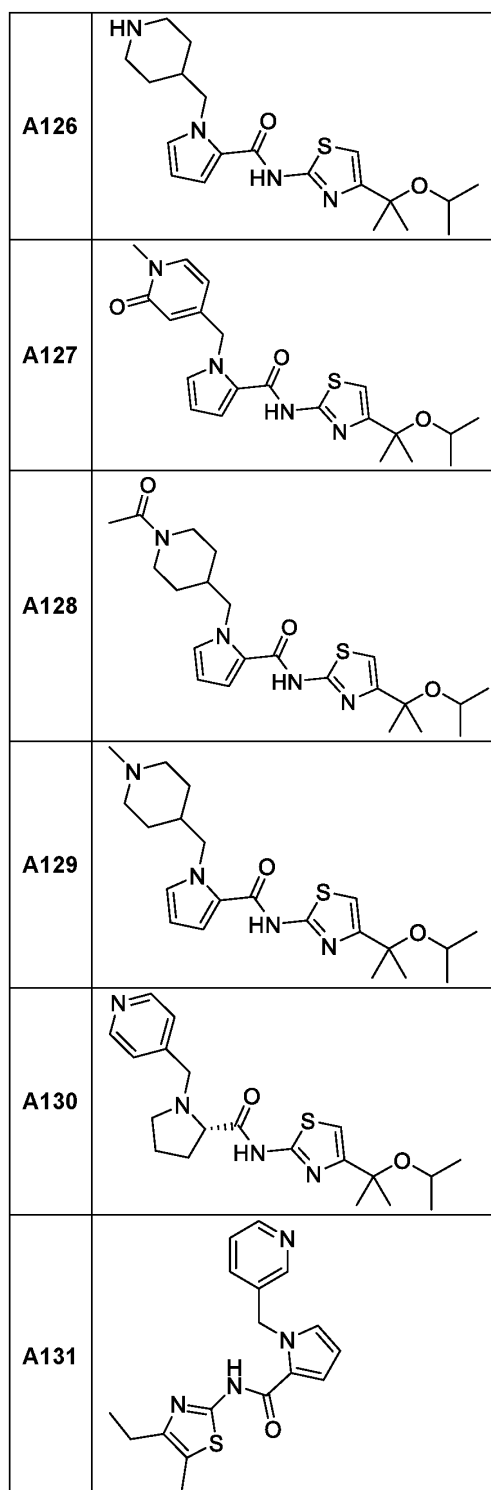


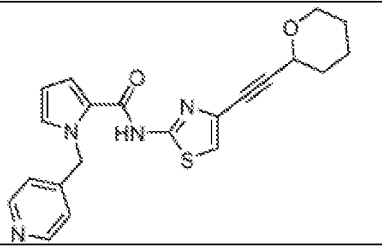
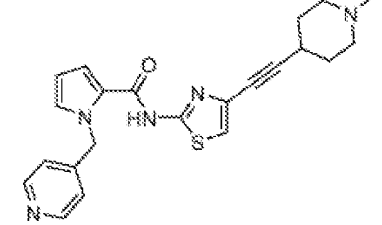
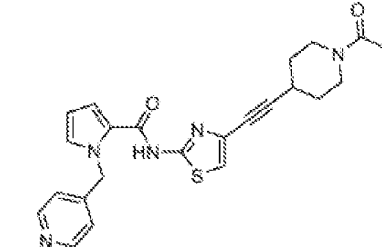
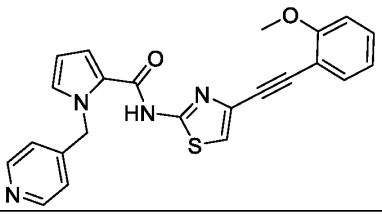
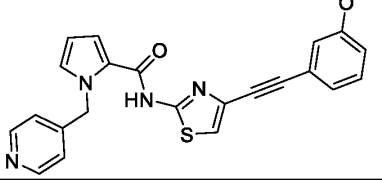
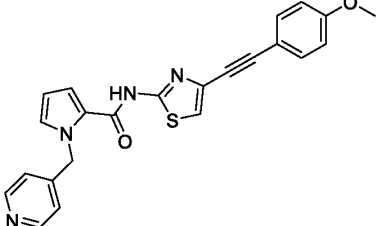
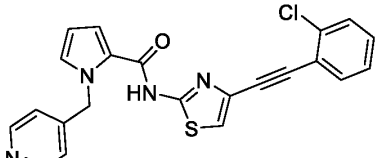


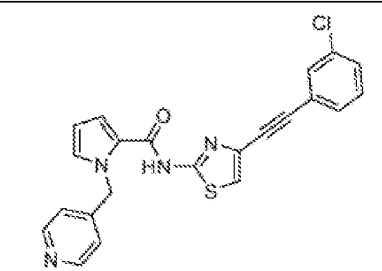
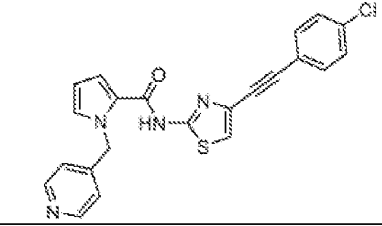
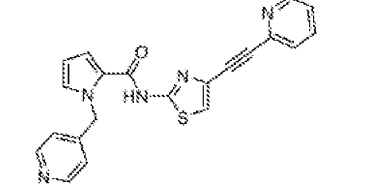
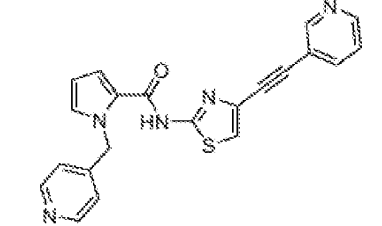
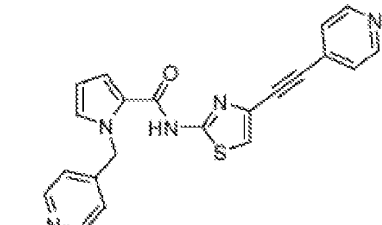
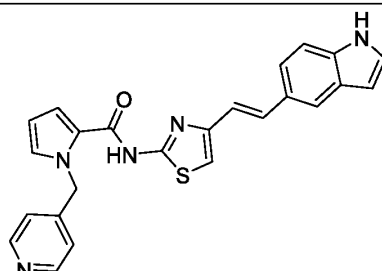
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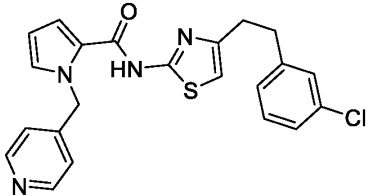
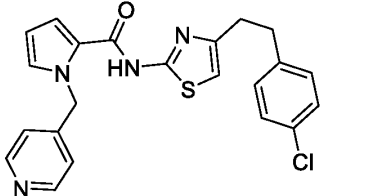
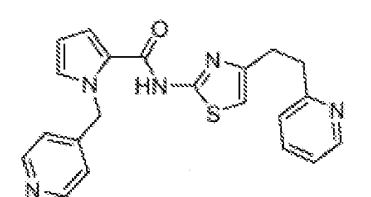
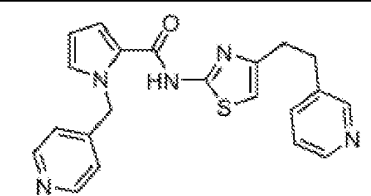
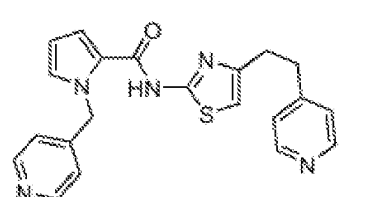
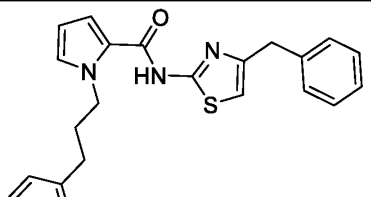
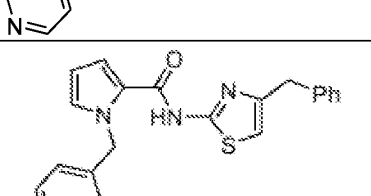
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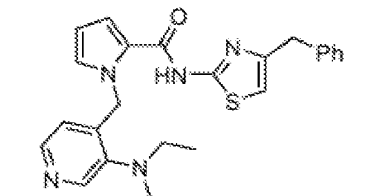
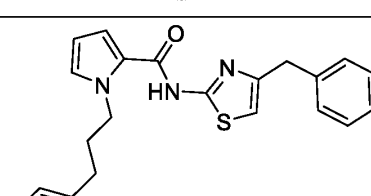
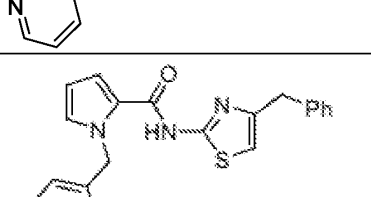
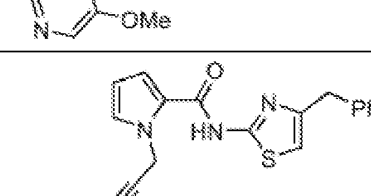
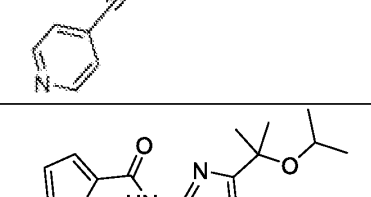
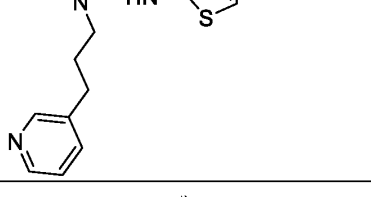
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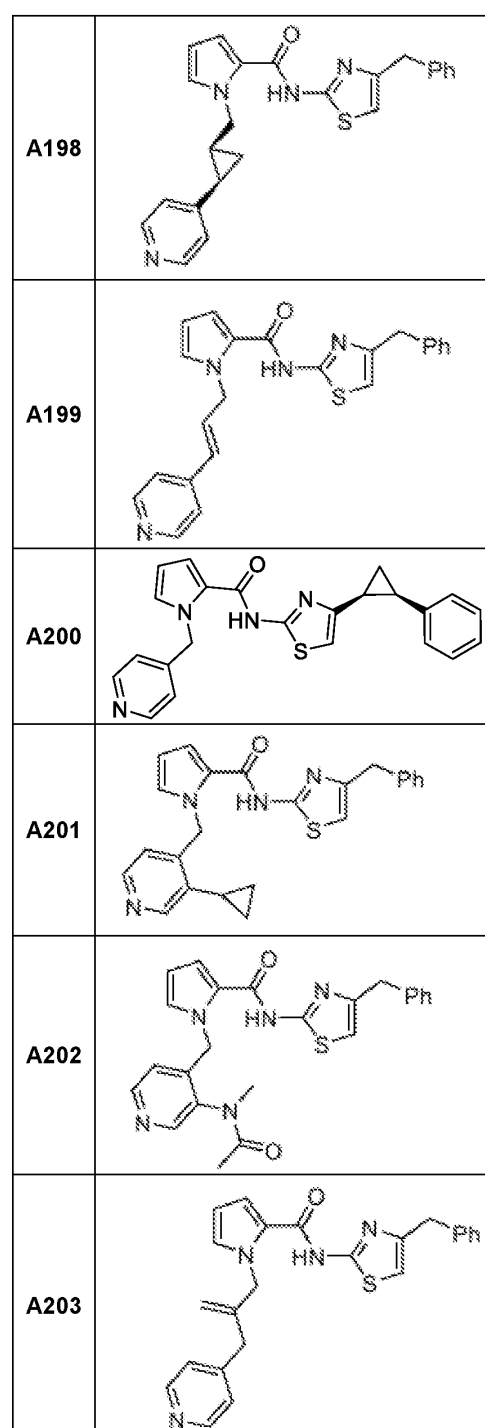
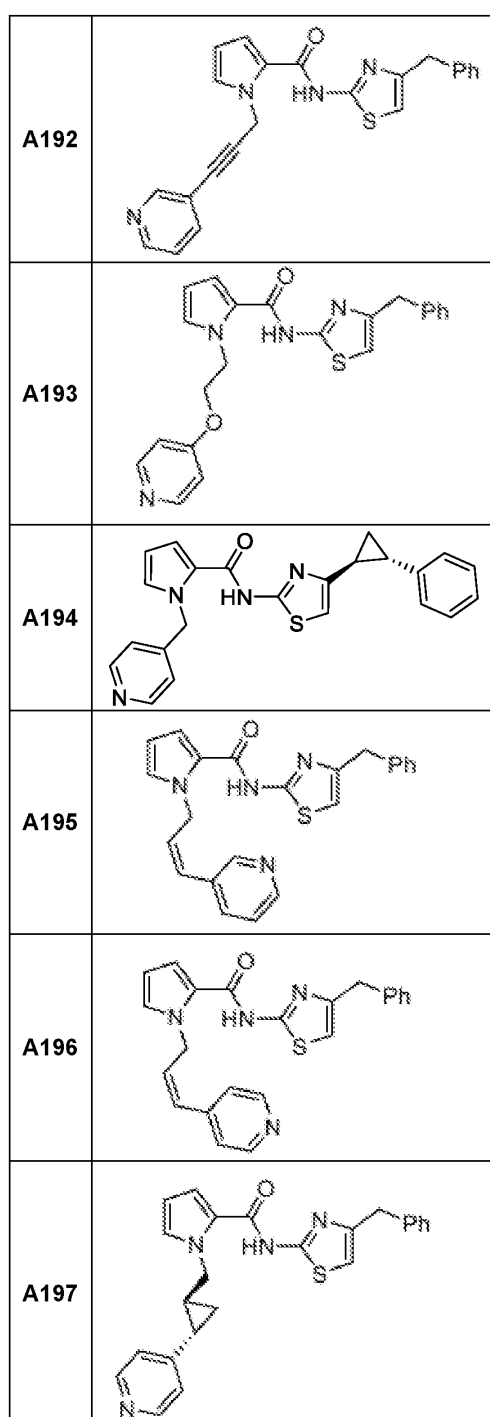
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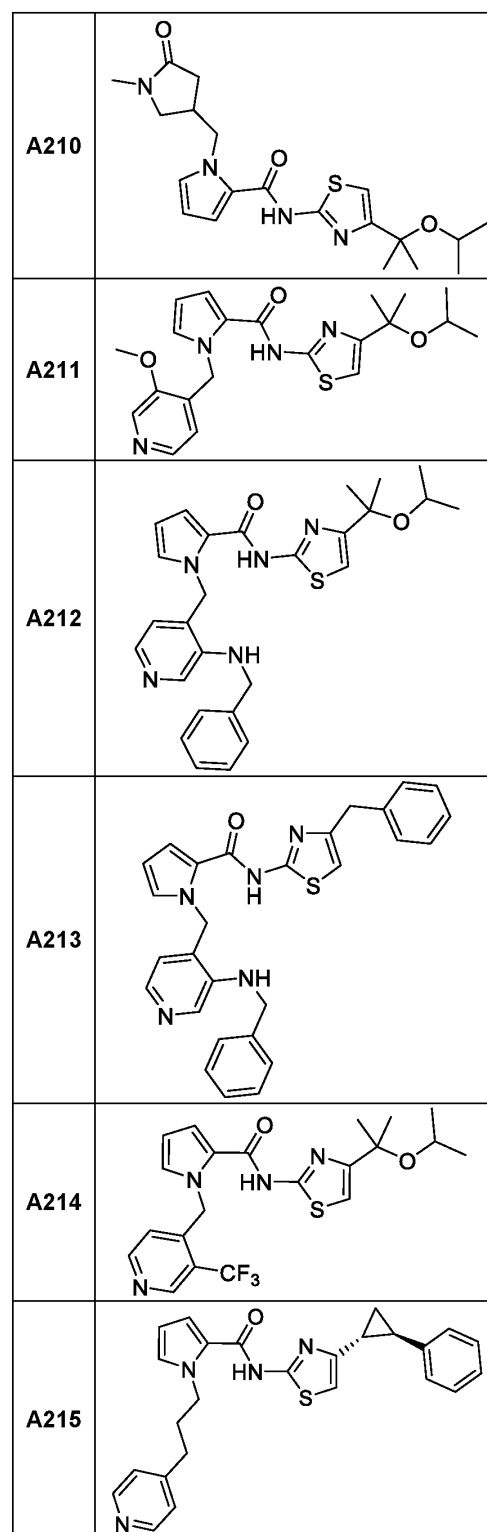
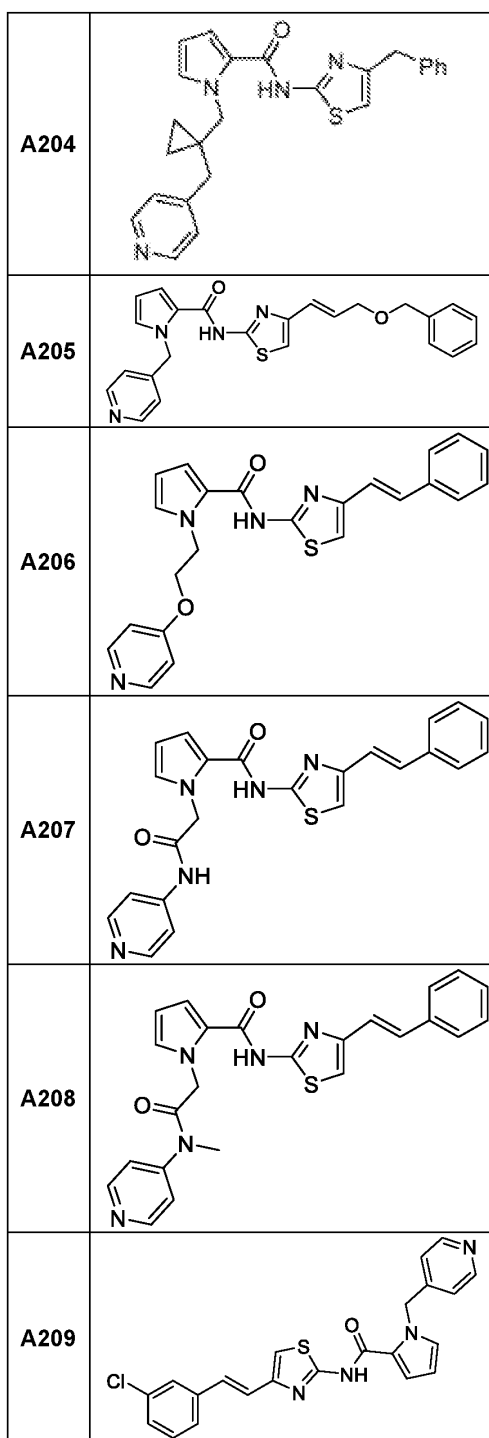
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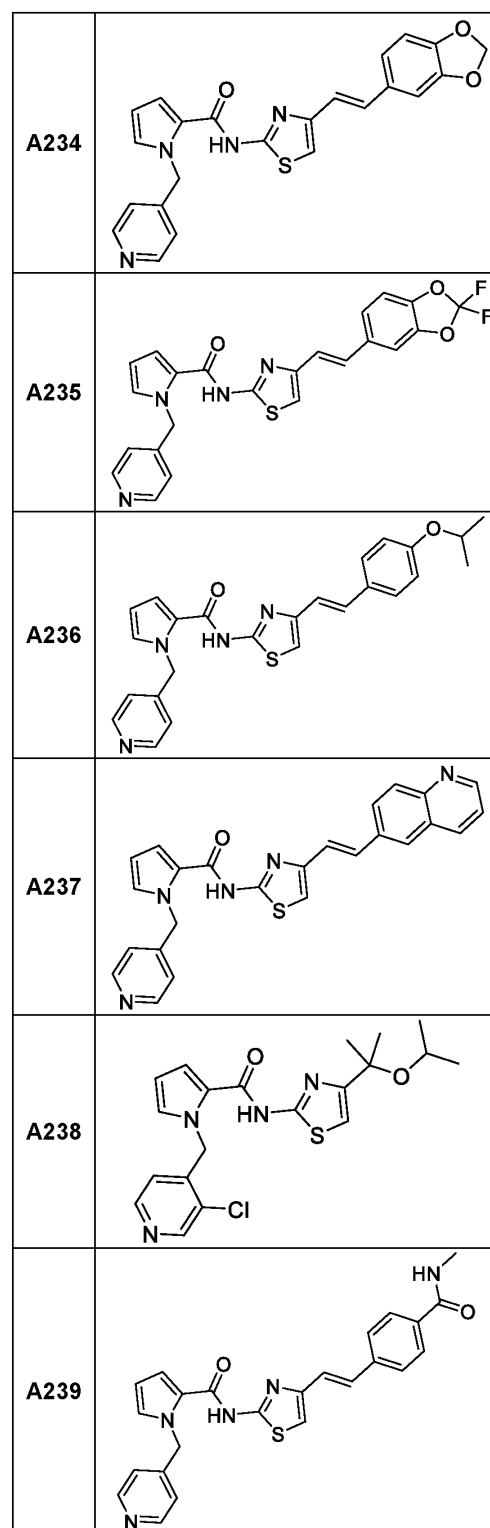
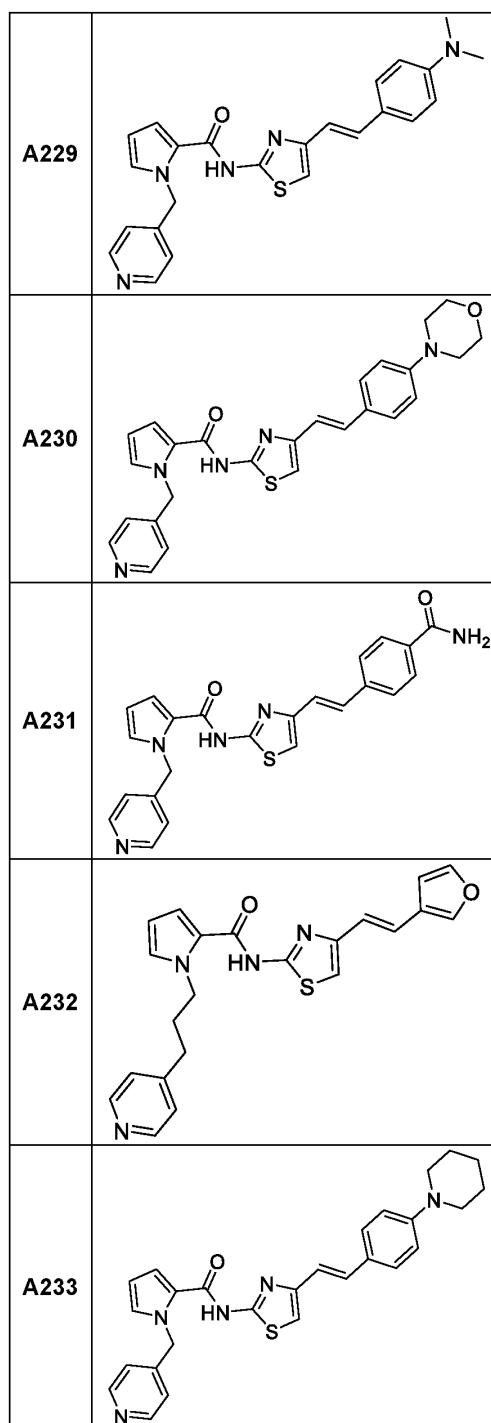
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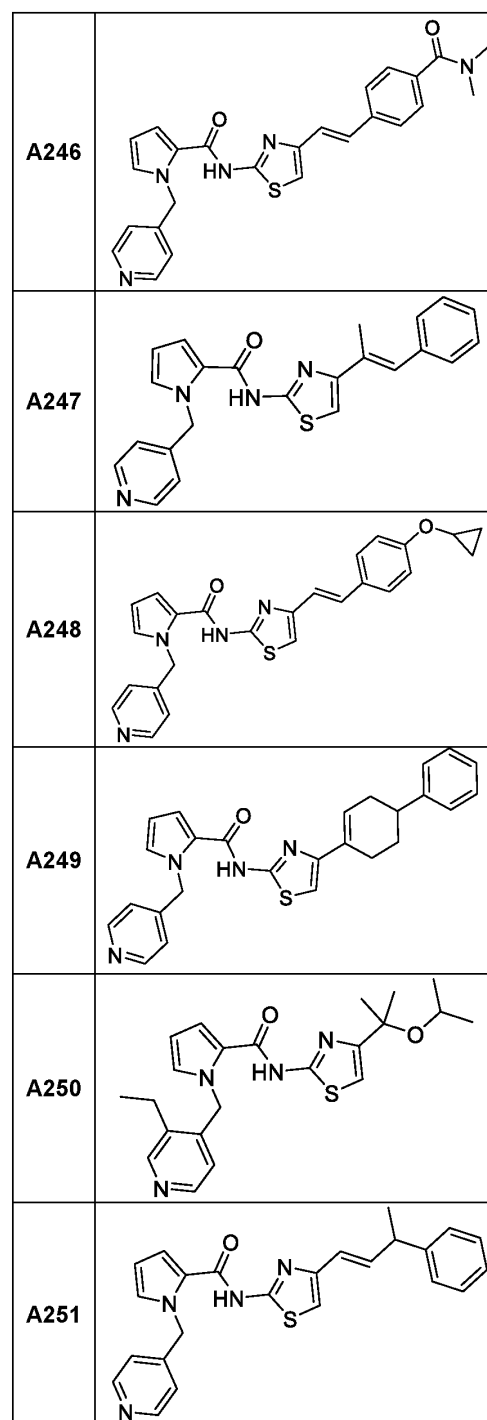
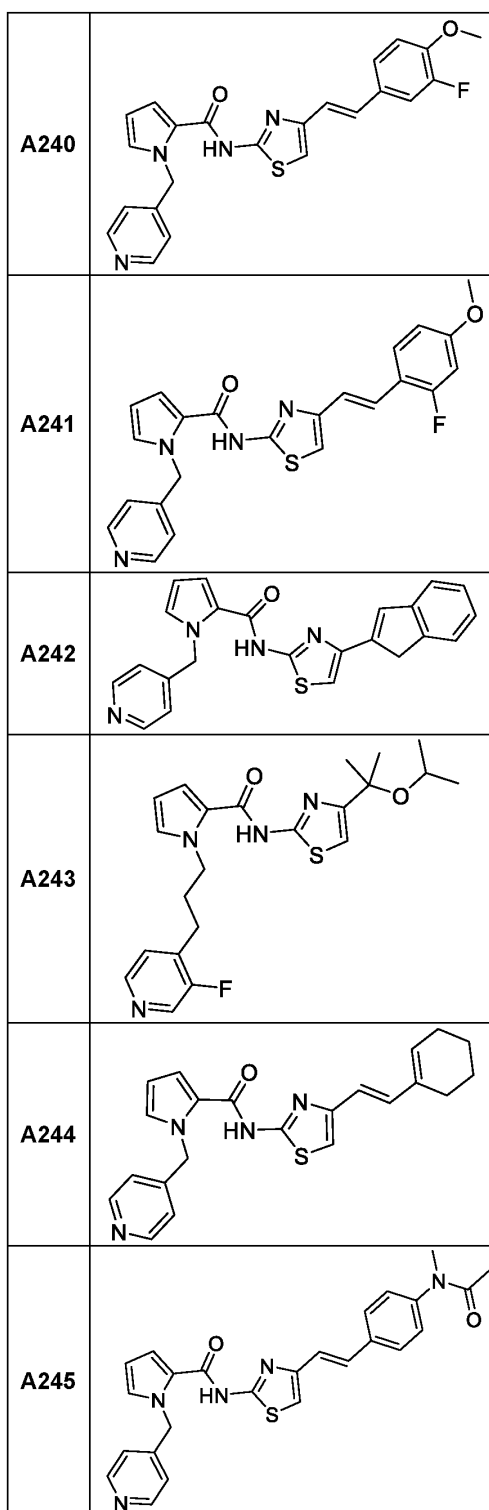




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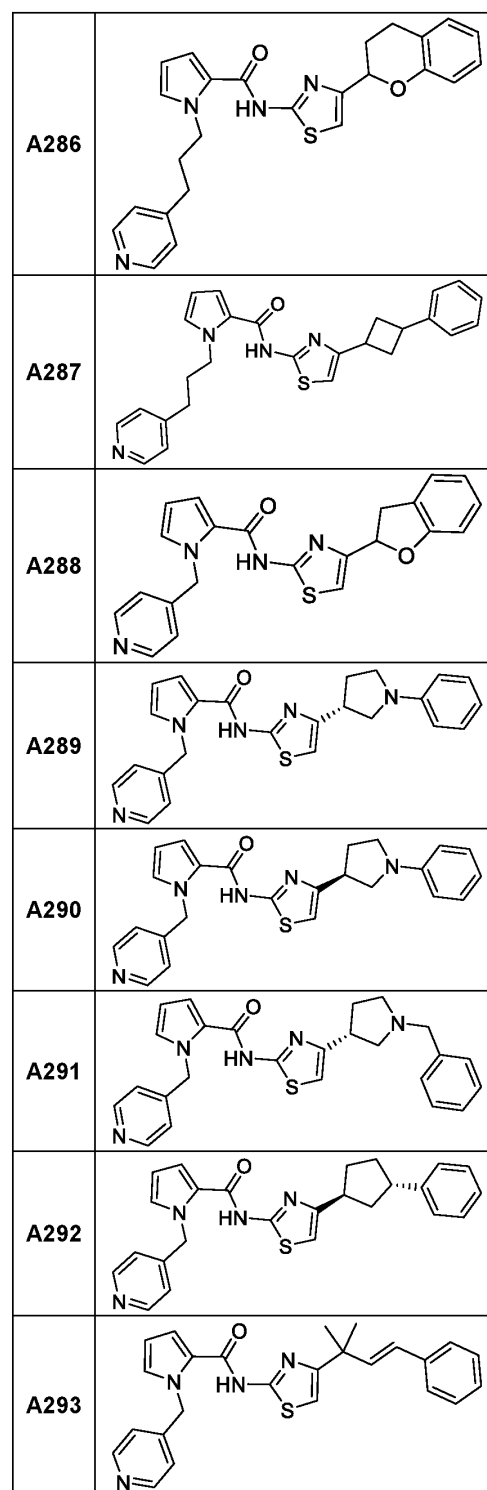
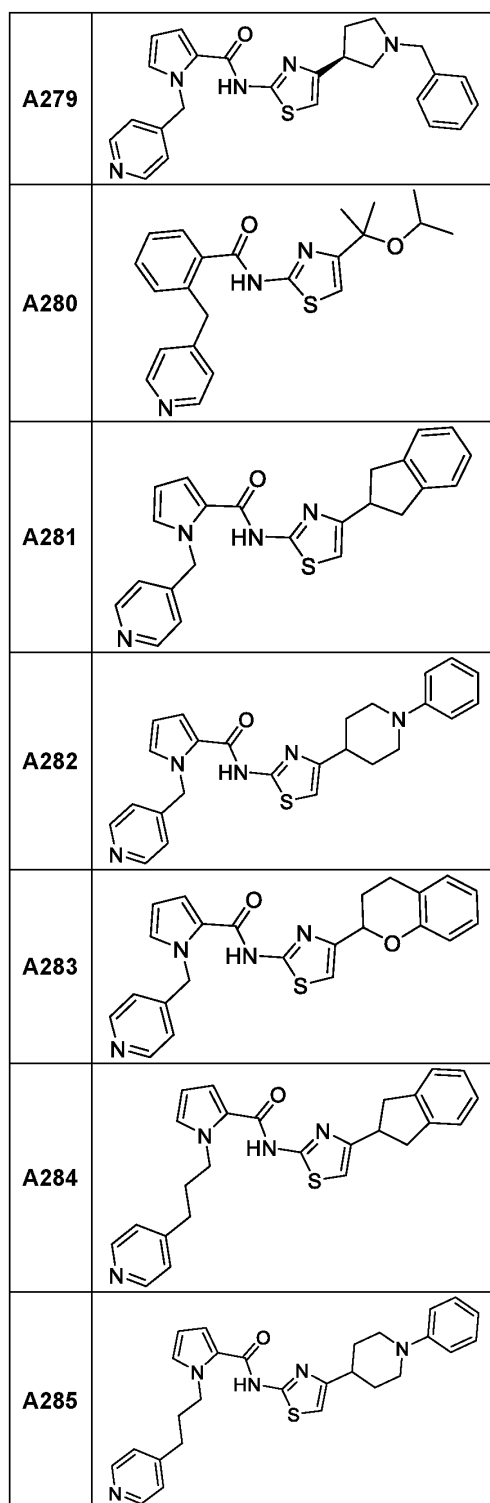


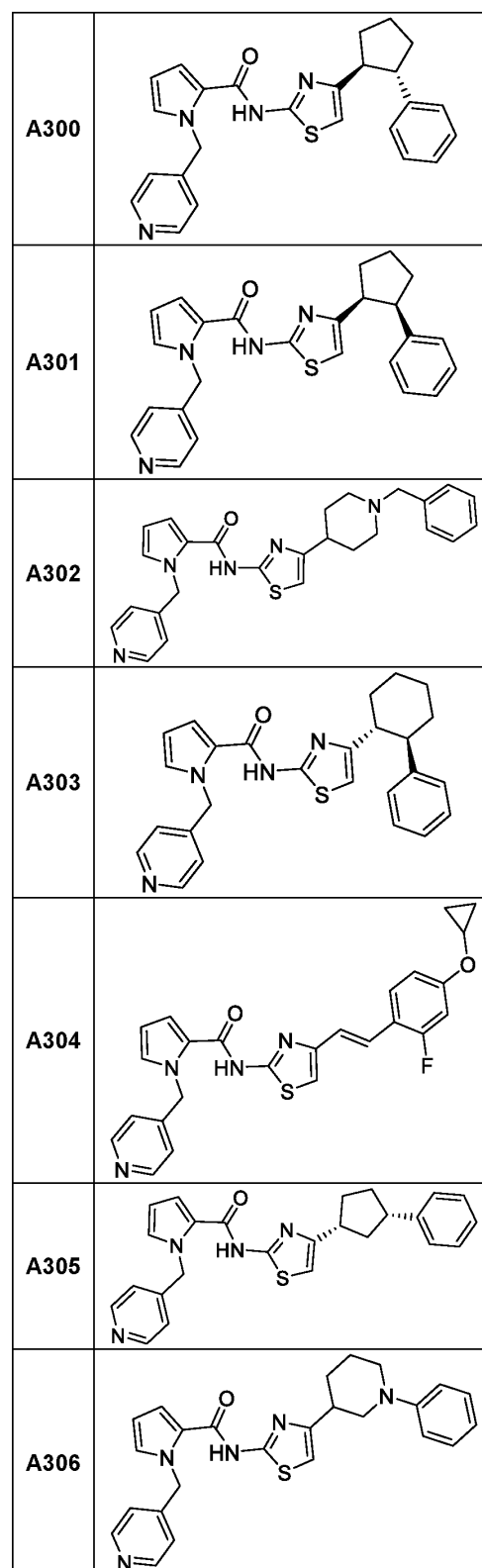
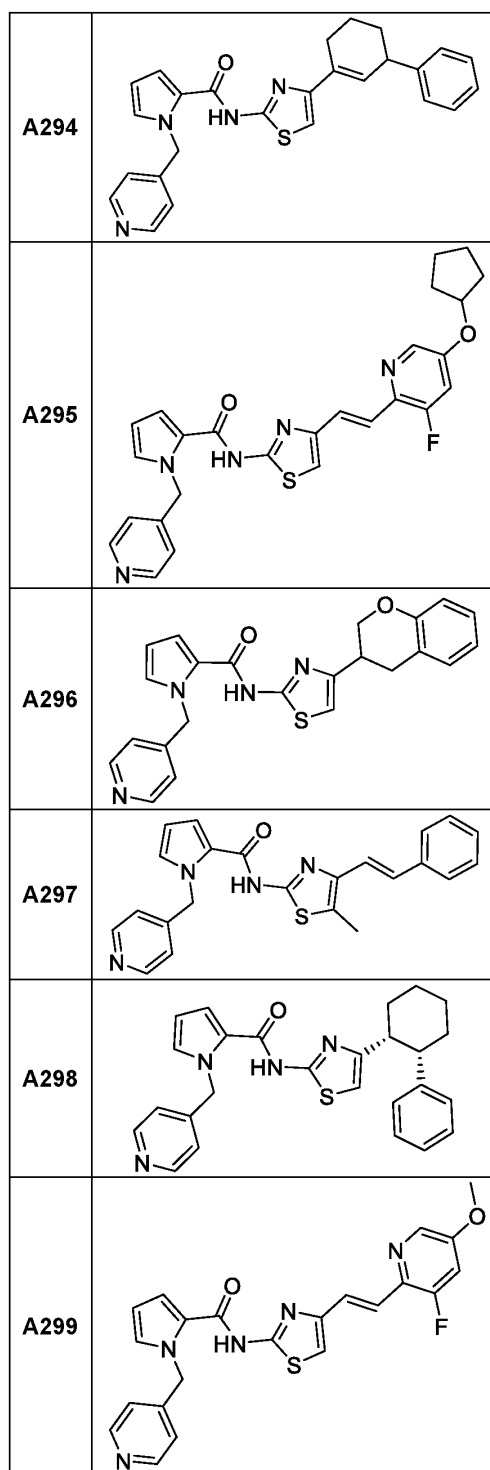
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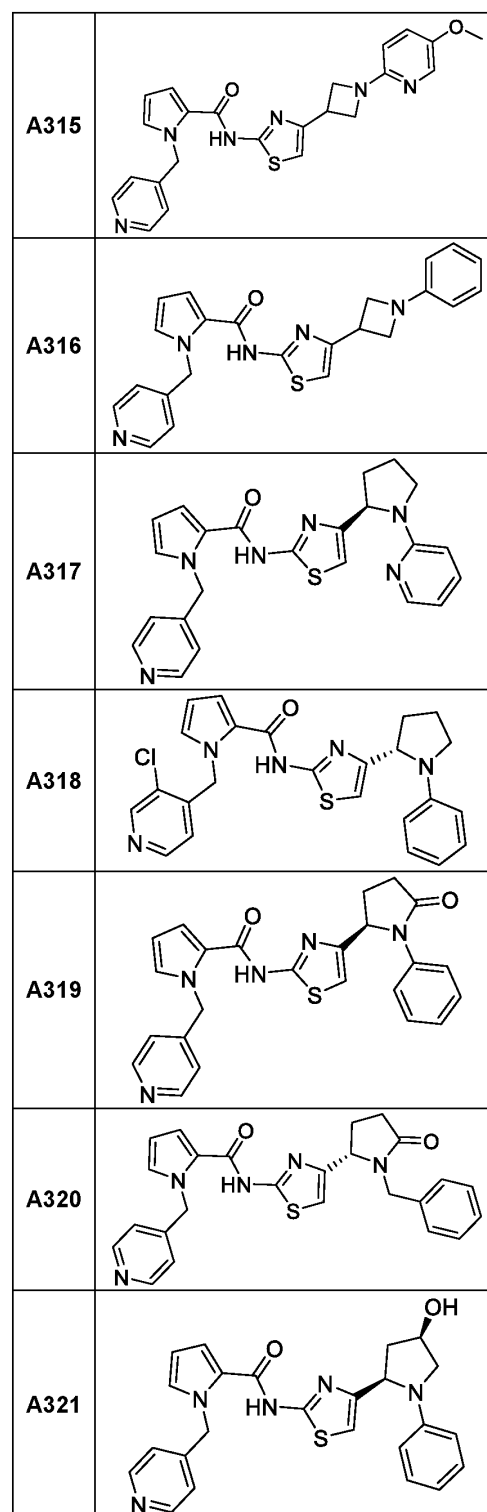
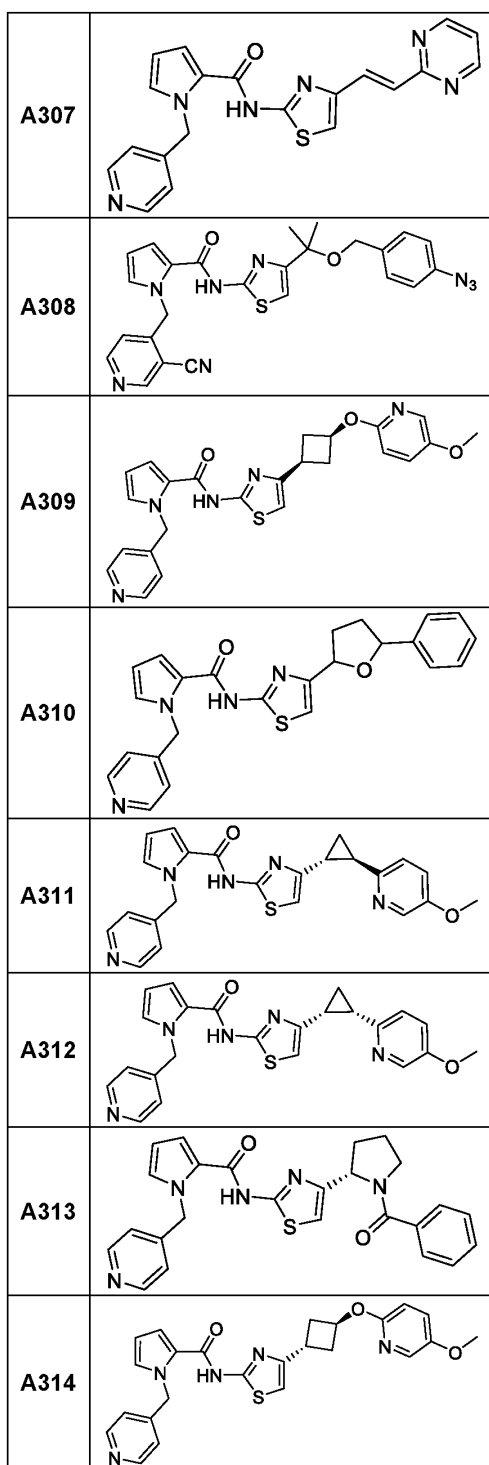
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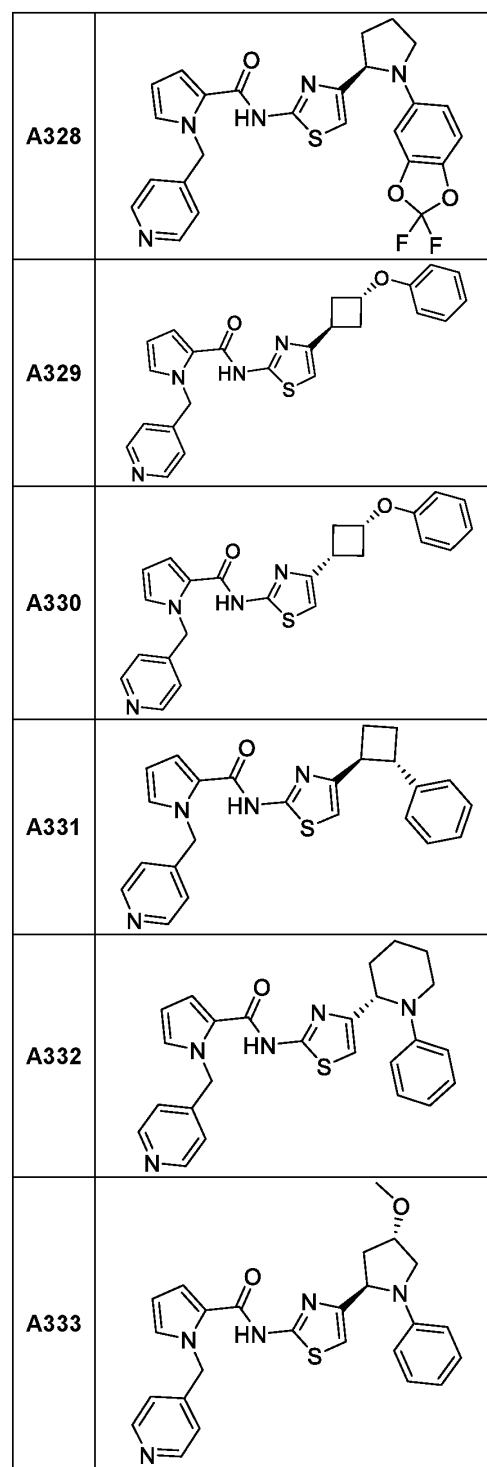
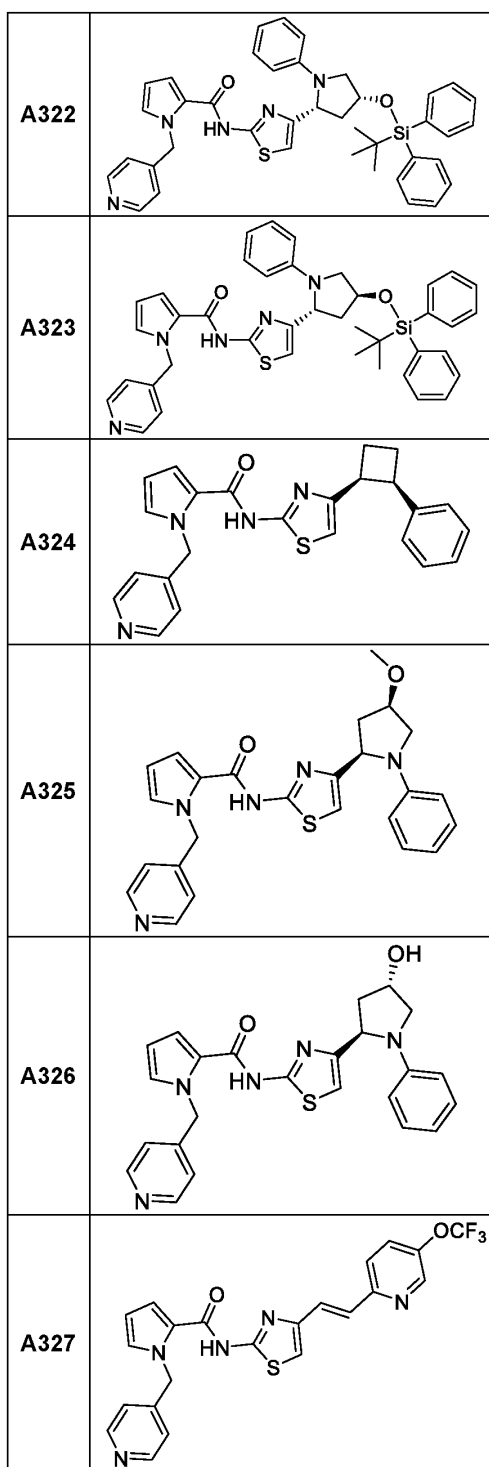
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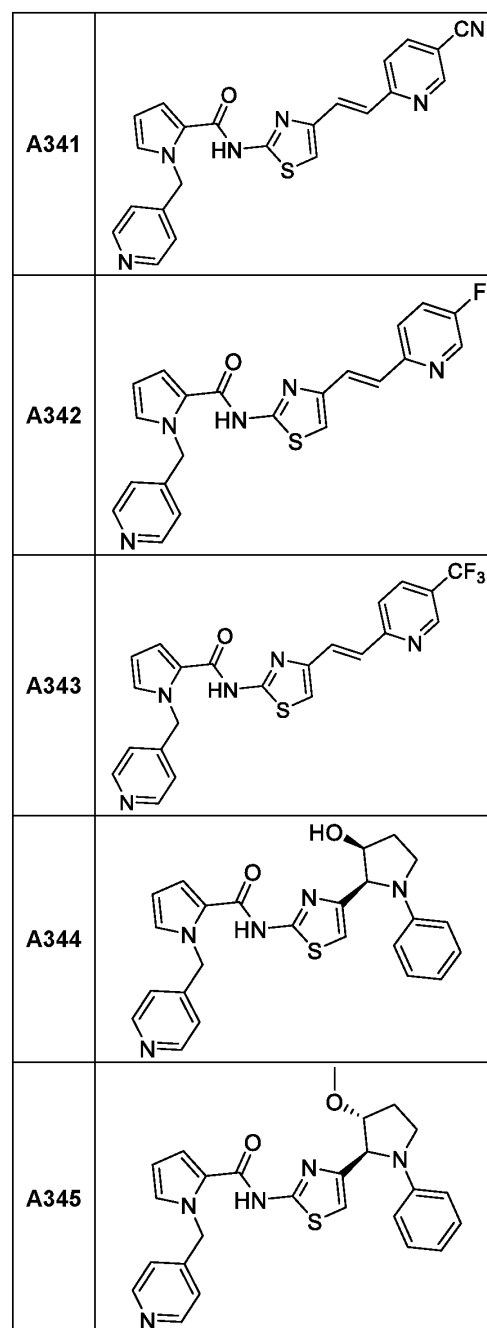
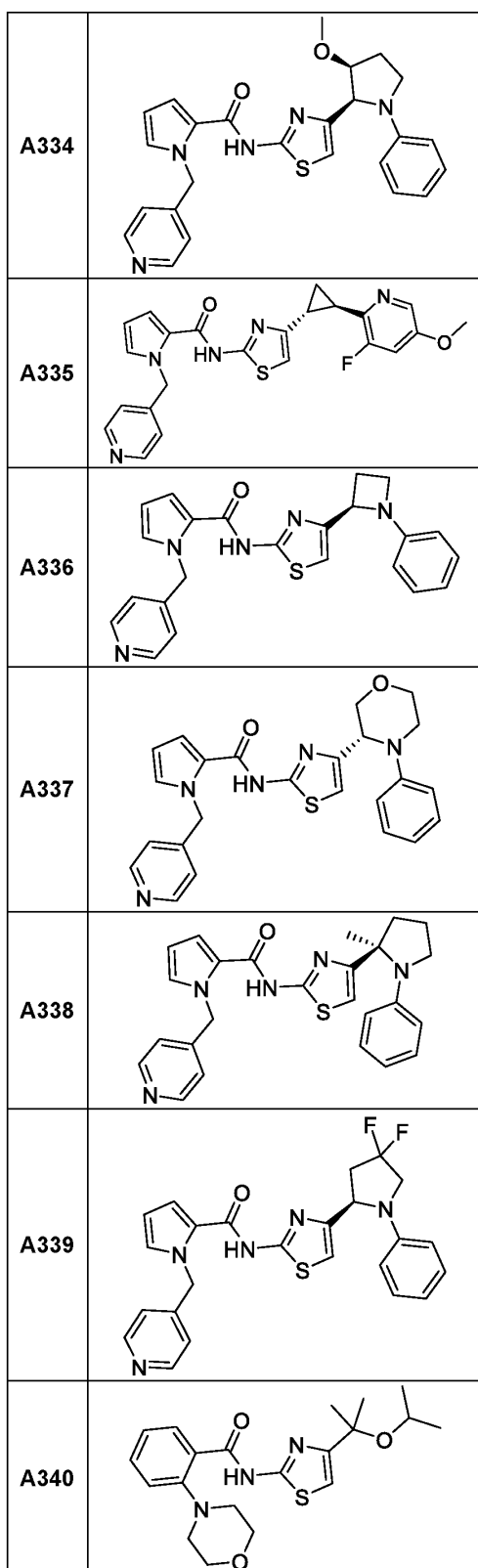
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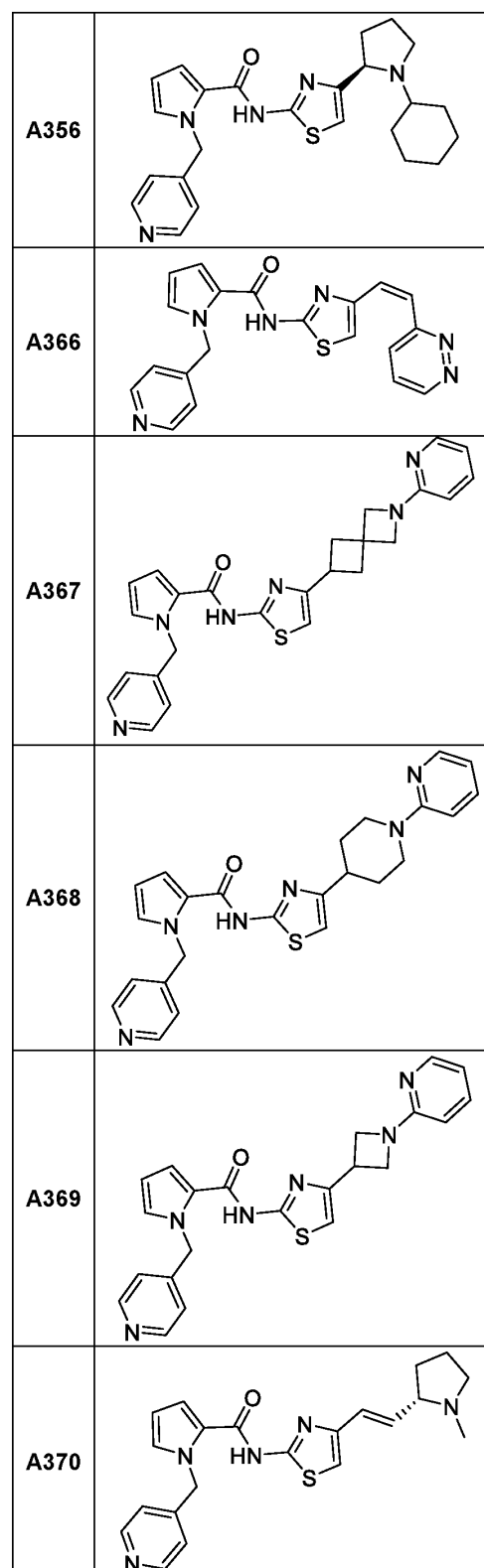
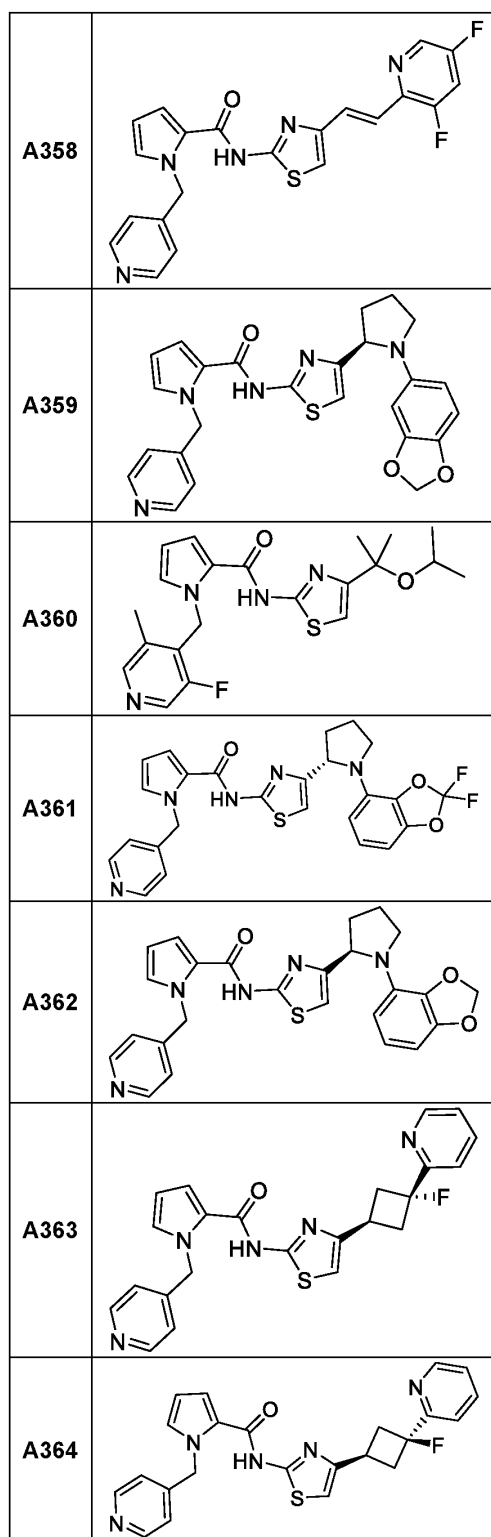


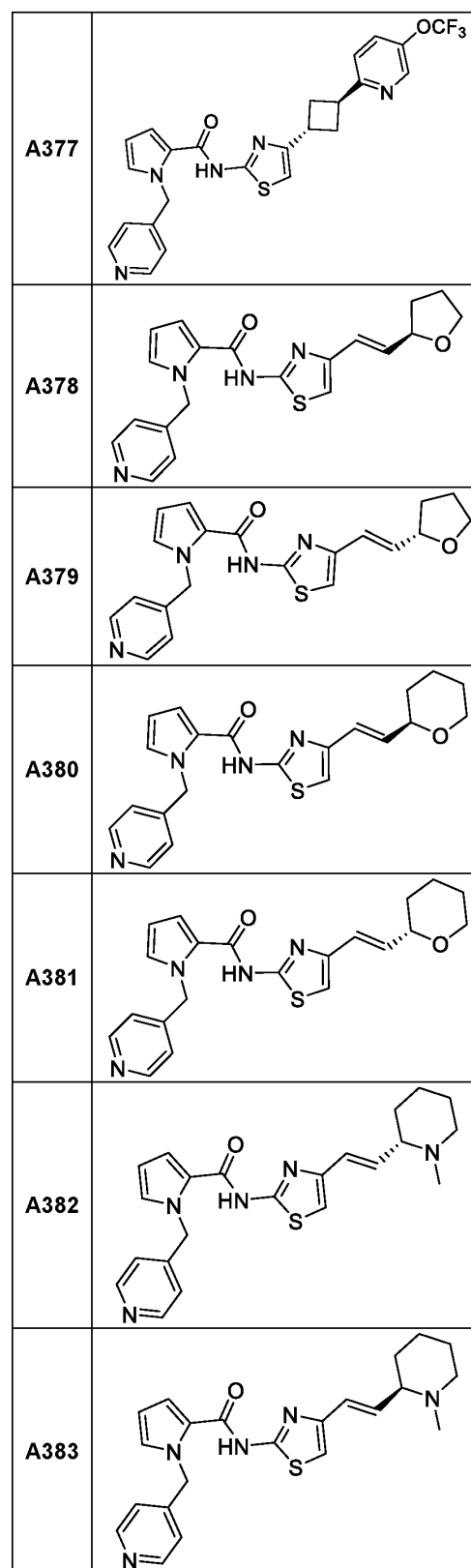
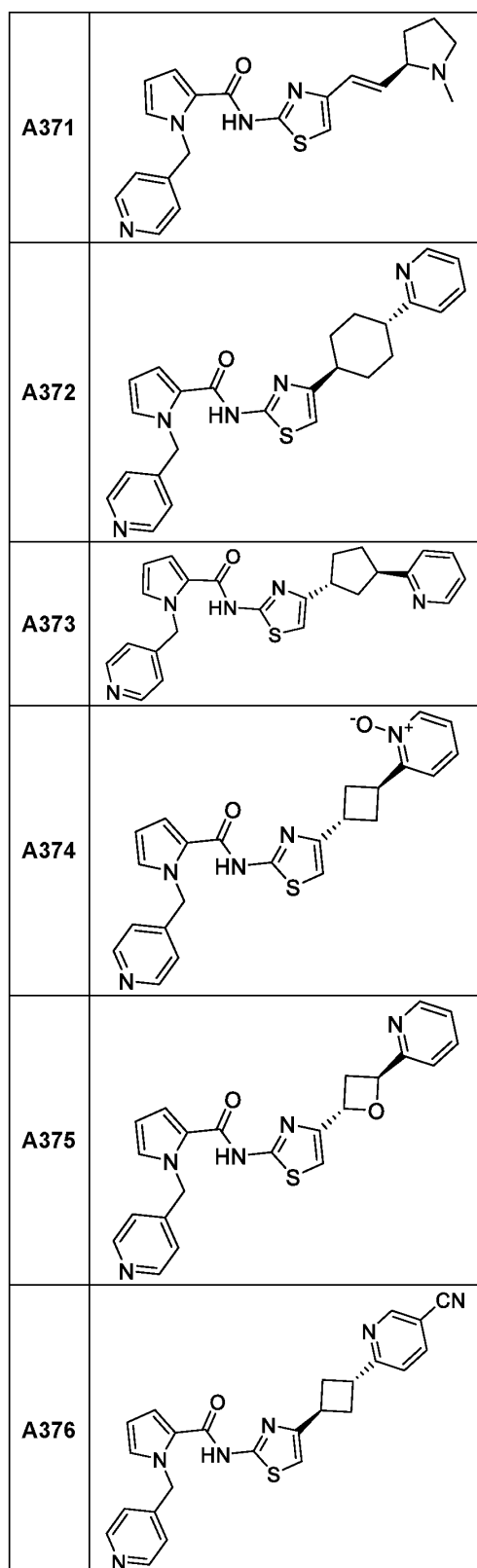


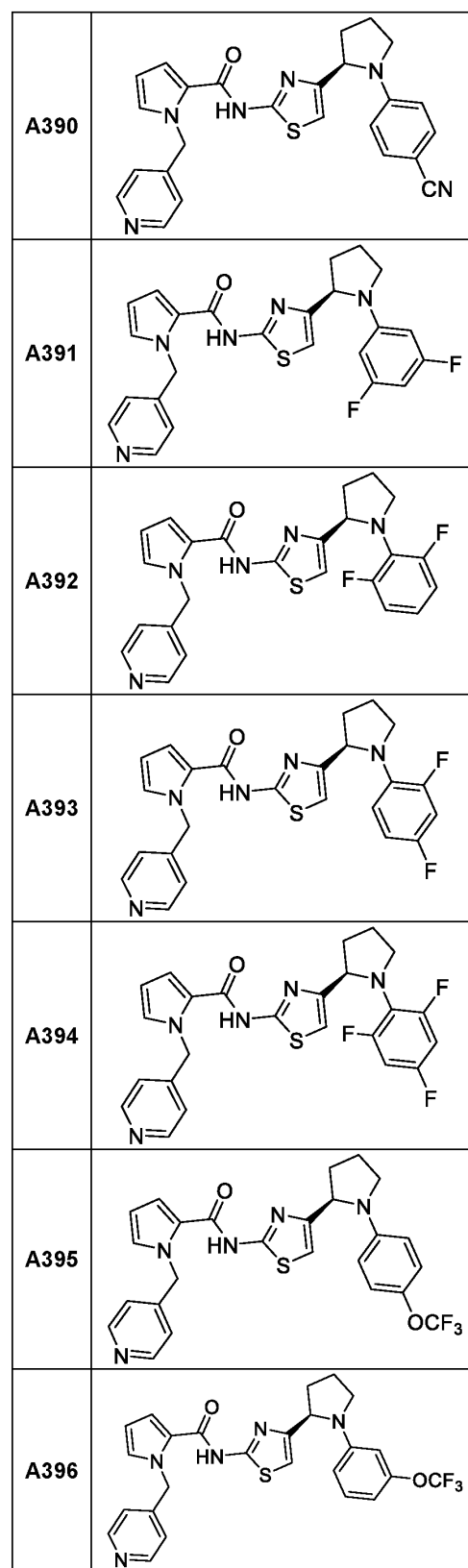
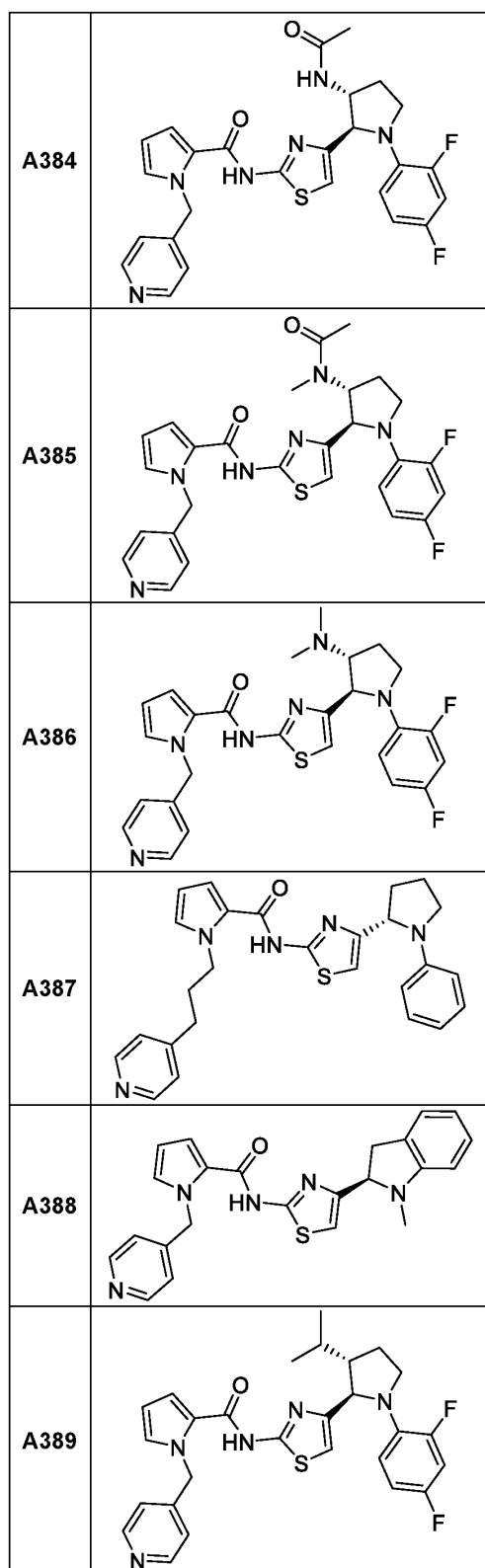


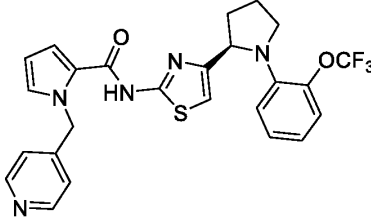
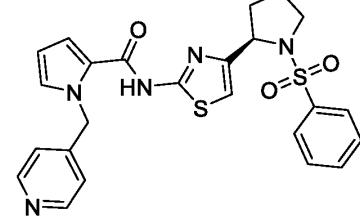
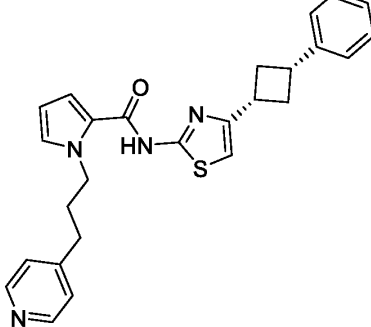
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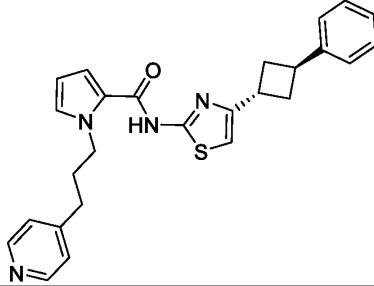
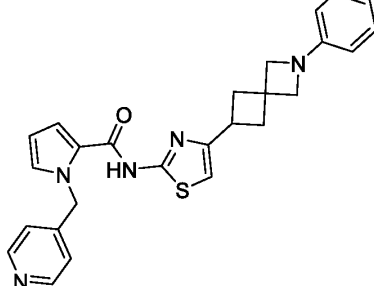
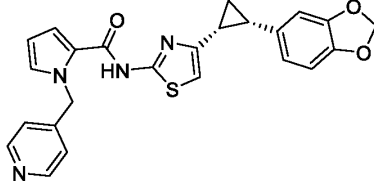
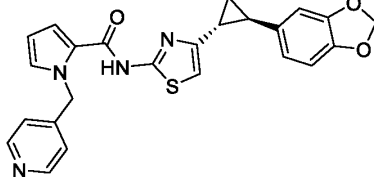
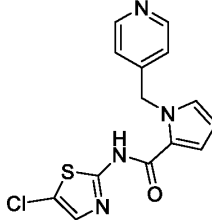
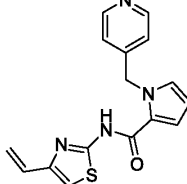
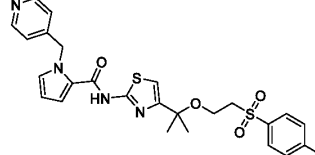
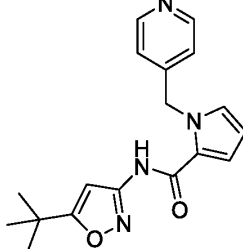
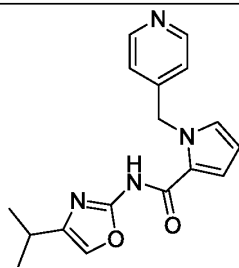
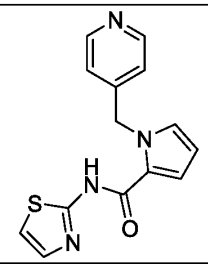
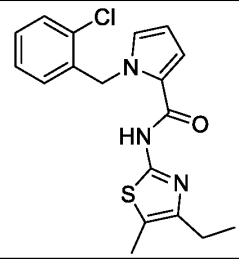
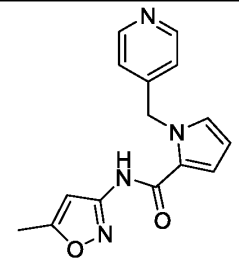
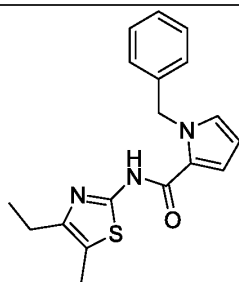
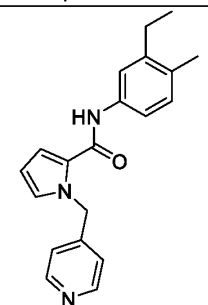
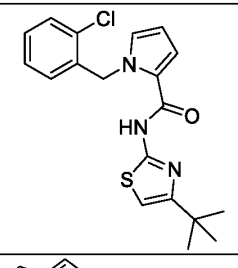
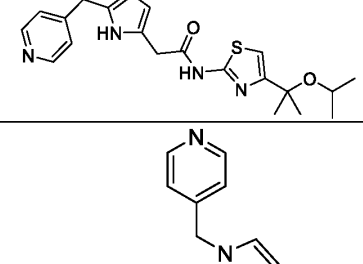
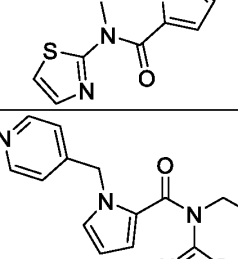
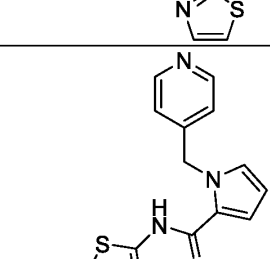
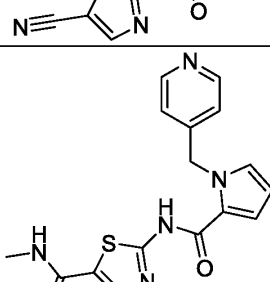
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Table B

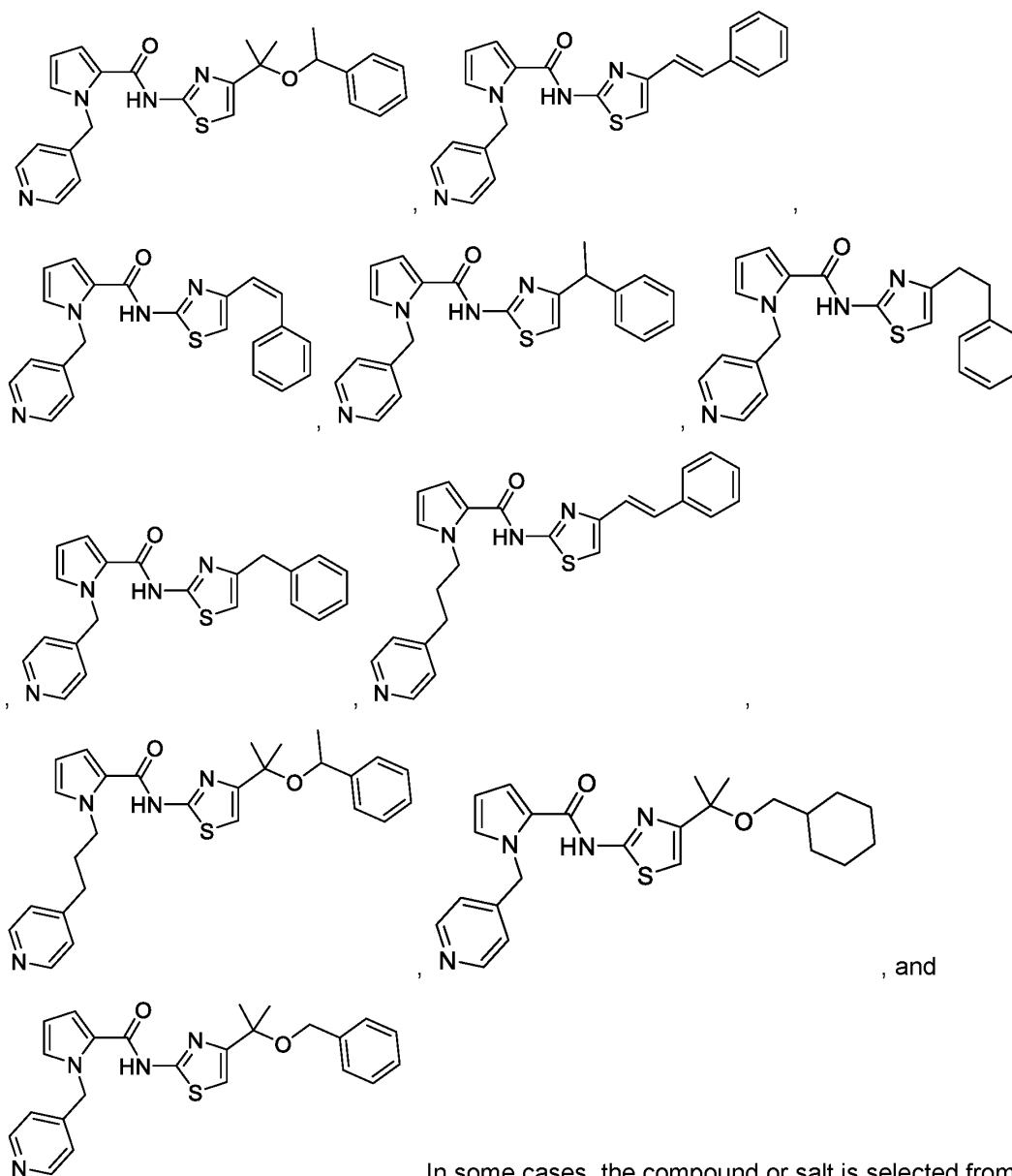
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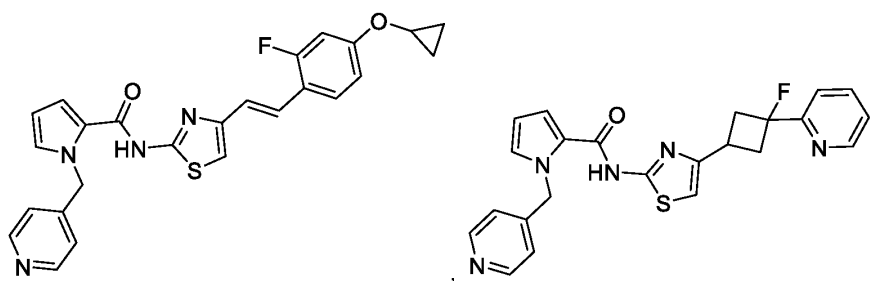
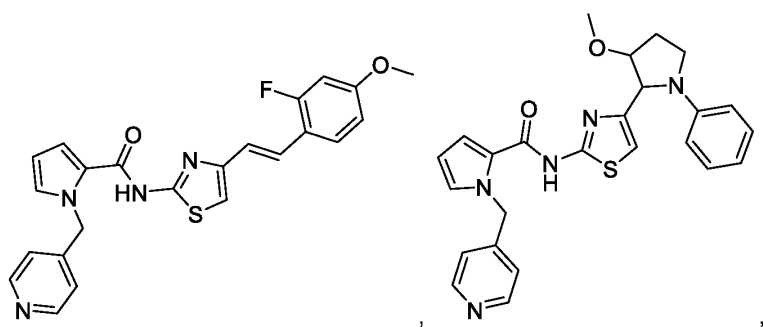
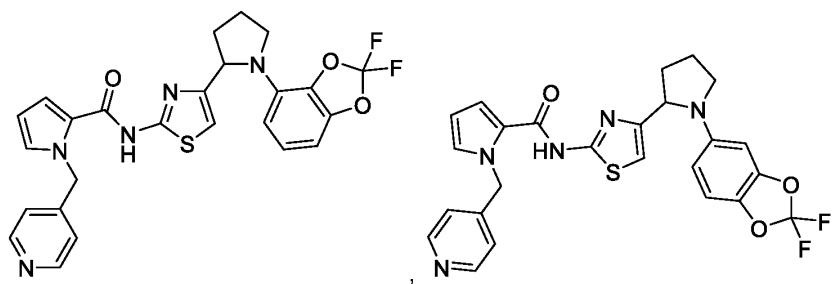
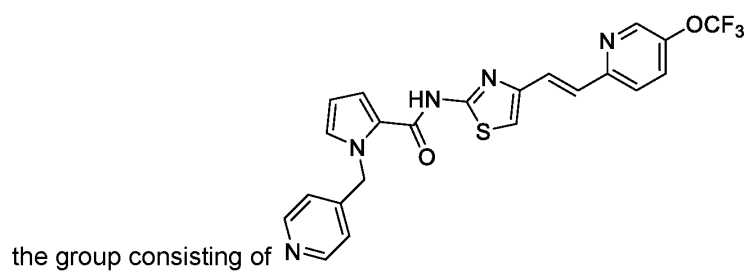
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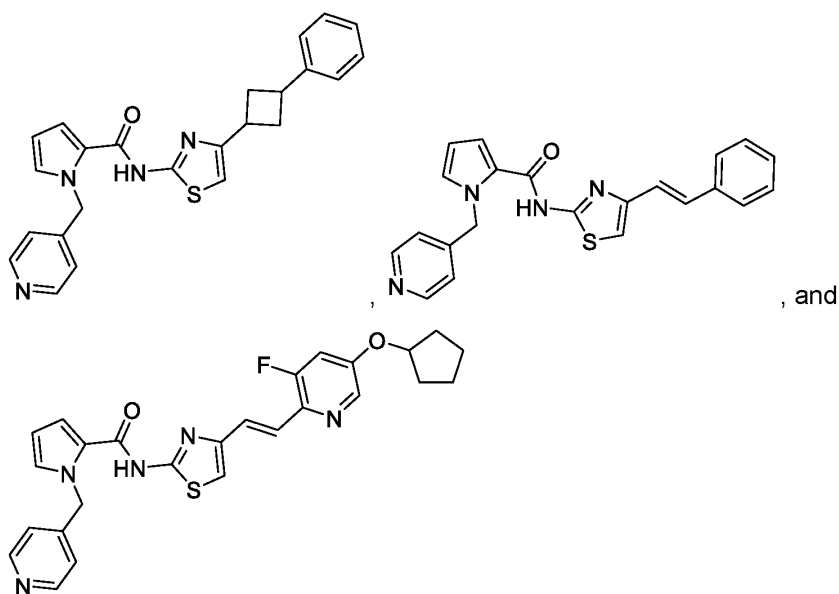
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[00166] In embodiments, the compound is selected from a compound listed in Table A, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound or salt is selected from A1-A210. In some embodiments, the compound or salt is selected from A211-A403. In some cases, the compound is selected from the group consisting of







[00167] In some embodiments, the compound is selected from a compound listed in Table B, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound or salt is selected from B1-B29.

[00168] The chemical structures having one or more stereocenters depicted with dashed and bold wedged bonds (i.e., and —) are meant to indicate absolute stereochemistry of the stereocenter(s) present in the chemical structure. Bonds symbolized by a simple line do not indicate a stereo-preference. Bonds symbolized by dashed or bold straight bonds (i.e., and —) are meant to indicate a relative stereochemistry of the stereocenter(s) present in the chemical structure. Unless otherwise indicated to the contrary, chemical structures that include one or more stereocenters which are illustrated herein without indicating absolute or relative stereochemistry, encompass all possible stereoisomeric forms of the compound (e.g., diastereomers, enantiomers) and mixtures thereof. Structures with a single bold or dashed wedged line, and at least one additional simple line, encompass a single enantiomeric series of all possible diastereomers. Similarly, the chemical structures having alkenyl groups are meant to encompass both cis and trans orientations, or when substituted, E- and Z-isomers of the chemical structure.

Synthesis of Protein Secretion Inhibitors

[00169] The compounds provided herein can be synthesized using conventional techniques readily available starting materials known to those skilled in the art. In general, the compounds provided herein are conveniently obtained via standard organic chemistry synthesis methods.

[00170] Although not limited to any one or several sources, classic texts such as Smith, M. B., March, J., March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 5th edition, John Wiley & Sons: New York, 2001 ; and Greene, T.W., Wuts, P.G. M., Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons: New York, 1999, are useful and recognized reference textbooks of organic synthesis known to those in the art. The following descriptions of synthetic methods are designed to illustrate, but not to limit, general procedures for the preparation of compounds of the present disclosure.

[00171] The synthetic processes disclosed herein can tolerate a wide variety of functional groups; therefore, various substituted starting materials can be used. The processes generally provide the desired final compound at or near the end of the overall process, although it may be desirable in certain instances to further convert the compound to a pharmaceutically acceptable salt thereof.

[00172] In general, the compounds of Formula (I), (II) or (III) can be synthesized in line with the examples shown below. For example, the compounds can be prepared by alkylation of the appropriate amine having a carboxyl group, with appropriate protecting groups as necessary. The intermediate can be saponified, for example, to expose a reactive carboxylate. Then, amide coupling between the appropriate amine and the free carboxylate can occur.

[00173] The amine for the amide coupling noted above can be prepared via known synthetic techniques using appropriate starting materials and protecting groups, as necessary.

[00174] Further modifications can be performed, e.g., to introduce additional substituents such as halo groups or alkyl groups.

Methods of Use

[00175] The compounds disclosed herein (e.g., the compounds of Formulae (I), (II), and (III), the compounds listed in Tables A and B, and pharmaceutically acceptable salts of any of the foregoing) can inhibit protein secretion of a protein of interest. The compounds disclosed herein can interfere with the Sec61 protein secretion machinery of a cell. In some cases, a compound as disclosed herein inhibits secretion of one or more of TNF α , IL2, Her3, and PD-1, or each of TNF α , IL2, Her3, and PD-1. Protein secretion activity can be assessed in a manner as described in the Examples section below.

[00176] As used herein, the term "inhibitor" is meant to describe a compound that blocks or reduces an activity of a pharmacological target (for example, a compound that inhibits Sec61 function in the protein secretion pathway). An inhibitor can act with competitive,

uncompetitive, or noncompetitive inhibition. An inhibitor can bind reversibly or irreversibly, and therefore, the term includes compounds that are suicide substrates of a protein or enzyme. An inhibitor can modify one or more sites on or near the active site of the protein, or it can cause a conformational change elsewhere on the enzyme. The term inhibitor is used more broadly herein than scientific literature so as to also encompass other classes of pharmacologically or therapeutically useful agents, such as agonists, antagonists, stimulants, co-factors, and the like.

[00177] Thus, provided herein are methods of inhibiting protein secretion in a cell. In these methods, a cell is contacted with a compound described herein (e.g., a compound of Formula (I), (II), or (III), or a compound listed in Tables A or B, and pharmaceutically acceptable salts of any of the foregoing), or pharmaceutical composition thereof, in an amount effective to inhibit secretion of the protein of interest. In some embodiments, the cell is contacted *in vitro*. In various embodiments, the cell is contacted *in vivo*. In various embodiments, the contacting includes administering the compound or pharmaceutical composition to a subject.

[00178] The biological consequences of Sec61 inhibition are numerous. For example, Sec61 inhibition has been suggested for the treatment or prevention of inflammation and/or cancer in a subject. Therefore, pharmaceutical compositions for Sec61 specific compounds, provide a means of administering a drug to a subject and treating these conditions. As used herein, the terms "treat," "treating," "treatment," and the like refer to eliminating, reducing, or ameliorating a disease or condition, and/or symptoms associated therewith. Although not precluded, treating a disease or condition does not require that the disease, condition, or symptoms associated therewith be completely eliminated. As used herein, the terms "treat," "treating," "treatment," and the like may include "prophylactic treatment," which refers to reducing the probability of redeveloping a disease or condition, or of a recurrence of a previously-controlled disease or condition, in a subject who does not have, but is at risk of or is susceptible to, redeveloping a disease or condition or a recurrence of the disease or condition. The term "treat" and synonyms contemplate administering a therapeutically effective amount of a compound of the disclosure to an individual in need of such treatment. Within the meaning of the disclosure, "treatment" also includes relapse prophylaxis or phase prophylaxis, as well as the treatment of acute or chronic signs, symptoms and/or malfunctions. The treatment can be orientated symptomatically, for example, to suppress symptoms. It can be effected over a short period, be oriented over a medium term, or can be a long-term treatment, for example within the context of a maintenance therapy. As used herein, the terms "prevent," "preventing," "prevention," are art-recognized, and when used in relation to a condition, such as a local recurrence (e.g., pain), a disease such as cancer, a

syndrome complex such as heart failure or any other medical condition, is well understood in the art, and includes administration of a composition which reduces the frequency of, or delays the onset of, symptoms of a medical condition in a subject relative to a subject which does not receive the composition. Thus, prevention of cancer includes, for example, reducing the number of detectable cancerous growths in a population of patients receiving a prophylactic treatment relative to an untreated control population, and/or delaying the appearance of detectable cancerous growths in a treated population versus an untreated control population, e.g., by a statistically and/or clinically significant amount. As used herein, the terms "patient" and "subject" may be used interchangeably and mean animals, such as dogs, cats, cows, horses, and sheep (i.e., non-human animals) and humans. Particular patients are mammals (e.g., humans). The term patient includes males and females.

[00179] Inhibition of Sec61-mediated secretion of inflammatory proteins (e.g., TNF α) can disrupt inflammation signaling. Thus, provided herein is a method of treating inflammation in a subject by administering to the subject a therapeutically effective amount of a compound described herein, (i.e., a compound of Formula (I), (II), or (III), or a compound listed in Tables A or B), or a pharmaceutically acceptable salt thereof.

[00180] Further, the viability of cancer cells relies upon increased protein secretion into the ER for survival. Therefore, non-selective or partially selective inhibition of Sec61 mediated protein secretion may inhibit tumor growth. Alternatively, in the immune-oncology setting, selective secretion inhibitors of known secreted immune checkpoints proteins (e.g., PD-1, TIM-3, LAG3, etc.) can result in activation of the immune system to against various cancers.

[00181] Accordingly, also provided herein are methods of treating cancer in a subject by administering to the subject a therapeutically effective amount of a compound described herein, (e.g., a compound of Formula (I), (II), or (III), or a compound listed in Table A or B), or a pharmaceutically acceptable salt thereof. Specifically contemplated cancers that can be treated using the compounds and compositions described herein include, but are not limited to melanoma, multiple myeloma, prostate, lung, non small cell lung carcinoma (NSCLC), squamous cell carcinoma, leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, lymphoma, NPM/ALK-transformed anaplastic large 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, head and neck cancer, bladder, and colorectal cancers.

[00182] The compounds described herein are also contemplated to be used in the

prevention and/or treatment of a multitude of diseases including, but not limited to, proliferative diseases, neurotoxic/degenerative diseases, ischemic conditions, autoimmune and autoinflammatory disorders, inflammation, immune-related diseases, HIV, cancers, organ graft rejection, septic shock, viral and parasitic infections, conditions associated with acidosis, macular degeneration, pulmonary conditions, muscle wasting diseases, fibrotic diseases, bone and hair growth diseases.

[00183] Examples of proliferative diseases or conditions include diabetic retinopathy, macular degeneration, diabetic nephropathy, glomerulosclerosis, IgA nephropathy, cirrhosis, biliary atresia, congestive heart failure, scleroderma, radiation-induced fibrosis, and lung fibrosis (idiopathic pulmonary fibrosis, collagen vascular disease, sarcoidosis, interstitial lung diseases and extrinsic lung disorders).

[00184] Inflammatory diseases include acute (e.g., bronchitis, conjunctivitis, myocarditis, pancreatitis) and chronic conditions (e.g., chronic cholecystitis, bronchiectasis, aortic valve stenosis, restenosis, psoriasis and arthritis), along with conditions associated with inflammation such as fibrosis, infection and ischemia.

[00185] Immunodeficiency disorders occur when a part of the immune system is not working properly or is not present. They can affect B lymphocytes, T lymphocytes, or phagocytes and be either inherited (e.g., IgA deficiency, severe combined immunodeficiency (SCID), thymic dysplasia and chronic granulomatous) or acquired (e.g., acquired immunodeficiency syndrome (AIDS), human immunodeficiency virus (HIV) and drug-induced immunodeficiencies). Immune-related conditions include allergic disorders such as allergies, asthma and atopic dermatitis like eczema. Other examples of such immune-related conditions include lupus, rheumatoid arthritis, scleroderma, ankylosing spondylitis, dermatomyositis, psoriasis, multiple sclerosis and inflammatory bowel disease (such as ulcerative colitis and Crohn's disease).

[00186] Tissue/organ graft rejection occurs when the immune system mistakenly attacks the cells being introduced to the host's body. Graft versus host disease (GVHD), resulting from allogeneic transplantation, arises when the T cells from the donor tissue go on the offensive and attack the host's tissues. In all three circumstances, autoimmune disease, transplant rejection and GVHD, modulating the immune system by treating the subject with a compound or composition of the disclosure could be beneficial.

[00187] Also provided herein are methods of treating an autoimmune disease in a patient comprising administering a therapeutically effective amount of the compound described herein. An "autoimmune disease" as used herein is a disease or disorder arising from and directed against an individual's own tissues. Examples of autoimmune diseases include, but

are not limited to, inflammatory responses such as inflammatory skin diseases including psoriasis and dermatitis (e.g., atopic dermatitis); systemic scleroderma and sclerosis; responses associated with inflammatory bowel disease (such as Crohn's disease and ulcerative colitis); respiratory distress syndrome (including adult respiratory distress syndrome(ARDS)); dermatitis; meningitis; encephalitis; uveitis; colitis; glomerulonephritis; allergic conditions such as eczema and asthma and other conditions involving infiltration of T cells and chronic inflammatory responses; atherosclerosis; leukocyte adhesion deficiency; rheumatoid arthritis; systemic lupus erythematosus (SLE); diabetes mellitus (e.g., Type I diabetes mellitus or insulin dependent diabetes mellitus); multiple sclerosis; Reynaud's syndrome; autoimmune thyroiditis; allergic encephalomyelitis; Sjorgen's syndrome; juvenile onset diabetes; and immune responses associated with acute and delayed hypersensitivity mediated by cytokines and T-lymphocytes typically found in 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 (including, but not limited to cryoglobulinemia or Coombs positive 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. Compounds provided herein may be useful for the treatment of conditions associated with inflammation, including, but not limited to COPD, psoriasis, asthma, bronchitis, emphysema, and cystic fibrosis.

[00188] Also provided herein is the use of a compound as disclosed herein for the treatment of neurodegenerative diseases. Neurodegenerative diseases and conditions includes, but not limited to, stroke, ischemic damage to the nervous system, neural trauma (e.g., percussive brain damage, spinal cord injury, and traumatic damage to the nervous system), multiple sclerosis and other immune-mediated neuropathies (e.g., Guillain-Barre syndrome and its variants, acute motor axonal neuropathy, acute inflammatory demyelinating polyneuropathy, and Fisher Syndrome), HIV/AIDS dementia complex, axonopathy, diabetic neuropathy, Parkinson's disease, Huntington's disease, multiple sclerosis, bacterial, parasitic, fungal, and viral meningitis, encephalitis, vascular dementia, multi-infarct dementia, Lewy body dementia, frontal lobe dementia such as Pick's disease, subcortical dementias (such as Huntington or progressive supranuclear palsy), focal cortical atrophy syndromes (such as primary aphasia), metabolic-toxic dementias (such as chronic

hypothyroidism or B12 deficiency), and dementias caused by infections (such as syphilis or chronic meningitis).

[00189] Further guidance for using compounds and compositions described herein (e.g., a compound of Formula (I), (II), or (III), a compound listed in Table A or B, or a pharmaceutically acceptable salt thereof) for inhibiting protein secretion can be found in the Examples section, below.

Pharmaceutical Compositions and Administration

[00190] The methods provided herein include the manufacture and use of pharmaceutical compositions, which include one or more of the compounds provided herein. Also included are the pharmaceutical compositions themselves. Pharmaceutical compositions typically include a pharmaceutically acceptable carrier. Thus, provided herein are pharmaceutical compositions that include a compound described herein (e.g., a compound of Formula (I), (II), or (III), a compound listed in Table A or B, or a pharmaceutically acceptable salt thereof), as previously described herein, and one or more pharmaceutically acceptable carriers.

[00191] The phrase “pharmaceutically acceptable” is employed herein to refer to those ligands, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[00192] The phrase “pharmaceutically acceptable carrier” as used herein means a pharmaceutically acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material. As used herein the language “pharmaceutically acceptable carrier” includes buffer, sterile water for injection, solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. Each carrier must be “acceptable” in the sense of being compatible with the other ingredients of the composition and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose, and sucrose; (2) starches, such as corn starch, potato starch, and substituted or unsubstituted β -cyclodextrin; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil, and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol, and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents,

such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical compositions. In certain embodiments, pharmaceutical compositions provided herein are non-pyrogenic, i.e., do not induce significant temperature elevations when administered to a patient.

[00193] The term "pharmaceutically acceptable salt" refers to the relatively non-toxic, inorganic and organic acid addition salts of a compound provided herein. These salts can be prepared *in situ* during the final isolation and purification of a compound provided herein, or by separately reacting the compound in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, laurylsulphonate salts, and amino acid salts, and the like. (See, for example, Berge et al. (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66: 1-19.)

[00194] In some embodiments, a compound provided herein may contain one or more acidic functional groups and, thus, is capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable bases. The term "pharmaceutically acceptable salts" in these instances refers to the relatively non-toxic inorganic and organic base addition salts of a compound provided herein. These salts can likewise be prepared *in situ* during the final isolation and purification of the compound, or by separately reacting the purified compound in its free acid form with a suitable base, such as the hydroxide, carbonate, or bicarbonate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts, and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, and the like (see, for example, Berge et al., *supra*).

[00195] Wetting agents, emulsifiers, and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring, and perfuming agents, preservatives and antioxidants can also be present in the compositions.

[00196] Examples of pharmaceutically acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium

metabisulfite, sodium sulfite, and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

[00197] A pharmaceutical composition may also contain adjuvants such as preservatives, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include tonicity-adjusting agents, such as sugars and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

[00198] In some cases, in order to prolong the effect of one or more compounds provided herein, it is desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. For example, delayed absorption of a parenterally administered compound can be accomplished by dissolving or suspending the compound in an oil vehicle.

[00199] Compositions prepared as described herein can be administered in various forms, depending on the disorder to be treated and the age, condition, and body weight of the patient, as is well known in the art. For example, where the compositions are to be administered orally, they may be formulated as tablets, capsules, granules, powders, or syrups; or for parenteral administration, they may be formulated as injections (intravenous, intramuscular, or subcutaneous), drop infusion preparations, or suppositories. For application by the ophthalmic mucous membrane route, they may be formulated as eye drops or eye ointments. These compositions can be prepared by conventional means in conjunction with the methods described herein, and, if desired, the active ingredient may be mixed with any conventional additive or excipient, such as a binder, a disintegrating agent, a lubricant, a corrigent, a solubilizing agent, a suspension aid, an emulsifying agent, or a coating agent.

[00200] Compositions suitable for oral administration may be in the form of capsules (e.g., gelatin capsules), cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, troches, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert matrix, such as gelatin and glycerin, or sucrose and acacia) and/or as mouthwashes, and the like, each containing a predetermined amount of a compound provided herein as an active ingredient. A composition may also be

administered as a bolus, electuary, or paste. Oral compositions generally include an inert diluent or an edible carrier.

[00201] Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of an oral composition. In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules, and the like), the active ingredient can be mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, cyclodextrins, lactose, sucrose, saccharin, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, microcrystalline cellulose, gum tragacanth, alginates, gelatin, polyvinyl pyrrolidone, sucrose, and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato, corn, or tapioca starch, alginic acid, Primogel, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, acetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, Sterotes, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; (10) a glidant, such as colloidal silicon dioxide; (11) coloring agents; and (12) a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. In the case of capsules, tablets, and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols, and the like.

[00202] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of a powdered compound moistened with an inert liquid diluent.

[00203] Tablets, and other solid dosage forms, such as dragees, capsules, pills, and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes, microspheres, and/or nanoparticles. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can

be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

[00204] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents, and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols, and fatty acid esters of sorbitan, and mixtures thereof.

[00205] Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming, and preservative agents.

[00206] Suspensions, in addition to the active compound(s) may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[00207] Pharmaceutical compositions suitable for parenteral administration can include one or more compounds provided herein in combination with one or more pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the composition isotonic with the blood of the intended recipient or suspending or thickening agents.

[00208] Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions provided herein include water for injection (e.g., sterile water for injection), bacteriostatic water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol such as liquid polyethylene glycol, and the like), sterile buffer (such as citrate buffer), and suitable mixtures thereof, vegetable oils, such as olive oil, injectable organic esters, such as ethyl oleate, and Cremophor EL™ (BASF, Parsippany, NJ). In all

cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[00209] The composition should be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, aluminum monostearate and gelatin.

[00210] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle, which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the methods of preparation are freeze-drying (lyophilization), which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[00211] Injectable depot forms can be made by forming microencapsule or nanoencapsule matrices of a compound provided herein in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable compositions are also prepared by entrapping the drug in liposomes, microemulsions or nanoemulsions, which are compatible with body tissue.

[00212] For administration by inhalation, the compounds can be delivered in the form of an aerosol spray from a pressured container or dispenser that contains a suitable propellant, e.g., a gas such as carbon dioxide, or a nebulizer. Such methods include those described in U.S. Patent No. 6,468,798. Additionally, intranasal delivery can be accomplished, as described in, inter alia, Hamajima et al., *Clin. Immunol. Immunopathol.*, 88(2), 205-10 (1998). Liposomes (e.g., as described in U.S. Patent No. 6,472,375, which is incorporated herein by reference in its entirety), microencapsulation and nanoencapsulation can also be

used. Biodegradable targetable microparticle delivery systems or biodegradable targetable nanoparticle delivery systems can also be used (e.g., as described in U.S. Patent No. 6,471,996, which is incorporated herein by reference in its entirety).

[00213] Systemic administration of a therapeutic compound as described herein can also be by transmucosal or transdermal means. Dosage forms for the topical or transdermal administration of a compound provided herein include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches, and inhalants. The active component may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which may be required. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the composition. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[00214] The ointments, pastes, creams, and gels may contain, in addition to one or more compounds provided herein, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc, and zinc oxide, or mixtures thereof.

[00215] Powders and sprays can contain, in addition to a compound provided herein, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates, and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[00216] A compound provided herein can be administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal preparation, or solid particles containing a compound or composition provided herein. A nonaqueous (e.g., fluorocarbon propellant) suspension could be used. In some embodiments, sonic nebulizers are used because they minimize exposing the agent to shear, which can result in degradation of the compound.

[00217] Ordinarily, an aqueous aerosol can be made by formulating an aqueous solution or suspension of the agent together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular composition, but typically include nonionic surfactants (TWEEN® (polysorbates), PLURONIC® (poloxamers), sorbitan esters, lecithin, CREMOPHOR® (polyethoxylates)),

pharmaceutically acceptable co-solvents such as polyethylene glycol, innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars, or sugar alcohols. Aerosols generally are prepared from isotonic solutions.

[00218] Transdermal patches have the added advantage of providing controlled delivery of a compound provided herein to the body. Such dosage forms can be made by dissolving or dispersing the agent in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

[00219] The pharmaceutical compositions can also be prepared in the form of suppositories or retention enemas for rectal and/or vaginal delivery. Compositions presented as a suppository can be prepared by mixing one or more compounds provided herein with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, glycerides, polyethylene glycol, a suppository wax or a salicylate, which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active agent. Compositions which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams, or spray compositions containing such carriers as are known in the art to be appropriate.

[00220] In one embodiment, the therapeutic compounds are prepared with carriers that will protect the therapeutic compounds against rapid elimination from the body, such as a controlled release composition, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Such compositions can be prepared using standard techniques, or obtained commercially, e.g., from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to selected cells with monoclonal antibodies to cellular antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811, which is incorporated herein by reference in its entirety.

[00221] As described above, the preparations of one or more compounds provided herein may be given orally, parenterally, topically, or rectally. They are, of course, given by forms suitable for each administration route. For example, they are administered in tablets or capsule form, by injection, inhalation, eye lotion, ointment, suppository, infusion; topically by lotion or ointment; and rectally by suppositories. In some embodiments, administration is oral.

[00222] The phrases “parenteral administration” and “administered parenterally” as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrastemal injection, and infusion.

[00223] The phrases “systemic administration”, “administered systemically”, “peripheral administration”, and “administered peripherally” as used herein mean the administration of a ligand, drug, or other material via route other than directly into the central nervous system, such that it enters the patient’s system and thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

[00224] A compound provided herein may be administered to humans and other animals for therapy by any suitable route of administration, including orally, nasally, as by, for example, a spray, rectally, intravaginally, parenterally, intracisternally, and topically, as by powders, ointments or drops, including buccally and sublingually. Regardless of the route of administration selected, a compound provided herein, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions provided herein, is formulated into a pharmaceutically acceptable dosage form by conventional methods known to those of skill in the art. In another embodiment, the pharmaceutical composition is an oral solution or a parenteral solution. Another embodiment is a freeze-dried preparation that can be reconstituted prior to administration. As a solid, this composition may also include tablets, capsules or powders.

[00225] Actual dosage levels of the active ingredients in the pharmaceutical compositions provided herein may be varied so as to obtain “therapeutically effective amount,” which is an amount of the active ingredient effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

[00226] The concentration of a compound provided herein in a pharmaceutically acceptable mixture will vary depending on several factors, including the dosage of the compound to be administered, the pharmacokinetic characteristics of the compound(s) employed, and the route of administration. In some embodiments, the compositions provided herein can be provided in an aqueous solution containing about 0.1-10% w/v of a compound disclosed herein, among other substances, for parenteral administration. Typical dose ranges can include from about 0.01 to about 50 mg/kg of body weight per day, given in 1-4 divided doses. Each divided dose may contain the same or different compounds. The dosage will be a therapeutically effective amount depending on several factors including the

overall health of a patient, and the composition and route of administration of the selected compound(s).

[00227] Dosage forms or compositions containing a compound as described herein in the range of 0.005% to 100% with the balance made up from non-toxic carrier may be prepared. Methods for preparation of these compositions are known to those skilled in the art. The contemplated compositions may contain 0.001%-100% active ingredient, in one embodiment 0.1-95%, in another embodiment 75-85%. Although the dosage will vary depending on the symptoms, age and body weight of the patient, the nature and severity of the disorder to be treated or prevented, the route of administration and the form of the drug, in general, a daily dosage of from 0.01 to 2000 mg of the compound is recommended for an adult human patient, and this may be administered in a single dose or in divided doses. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect.

[00228] The pharmaceutical composition may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is also noted that the dose of the compound can be varied over time. It is understood that the precise dosage and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by extrapolation from in vivo or in vitro test data. It is to be noted that concentrations and dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular patient, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

[00229] The precise time of administration and/or amount of the composition that will yield the most effective results in terms of efficacy of treatment in a given patient will depend upon the activity, pharmacokinetics, and bioavailability of a particular compound, physiological condition of the patient (including age, sex, disease type and stage, general physical condition, responsiveness to a given dosage, and type of medication), route of administration, etc. However, the above guidelines can be used as the basis for fine-tuning the treatment, e.g., determining the optimum time and/or amount of administration, which will require no more than routine experimentation consisting of monitoring the patient and adjusting the dosage and/or timing.

[00230] The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[00231] In jurisdictions that forbid the patenting of methods that are practiced on the human body, the meaning of “administering” of a composition to a human subject shall be restricted to prescribing a controlled substance that a human subject will self-administer by any technique (e.g., orally, inhalation, topical application, injection, insertion, etc.). The broadest reasonable interpretation that is consistent with laws or regulations defining patentable subject matter is intended. In jurisdictions that do not forbid the patenting of methods that are practiced on the human body, the “administering” of compositions includes both methods practiced on the human body and also the foregoing activities.

[00232] It is to be understood that while the disclosure is read in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the disclosure, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

EXAMPLES

[00233] The following examples are provided for illustration and are not intended to limit the scope of the disclosure in any way.

[00234] As used throughout these examples, common organic abbreviations are defined as follows:

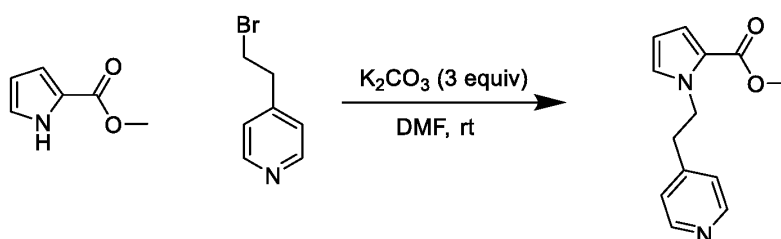
Abbreviation	Chemical	Abbreviation	Chemical
Ac	Acetyl	DMF	N,N-Dimethylformamide
Ac ₂ O	Acetic anhydride	DMSO	Dimethylsulfoxide
B ₂ pin ₂	Bis(pinacolato)diboron	dtfp (e.g., Pd(dtpf)Cl ₂)	1,1'-bis(di-tert-butylphosphino)ferrocene
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl	EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
Bn	Benzyl	EtOAc	Ethyl acetate
BOC or Boc	tert-Butoxycarbonyl	HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
BTFFH	Bis(tetramethylene)fluoroform amidinium hexafluorophosphate	KOtBu	Potassium tert-butoxide
Bu	Butyl	LDA	Lithium diisopropylamide
BrettPhos Pd G3	[(2-Di-cyclohexylphosphino-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate	mCBPA	meta-Chloroperoxybenzoic acid
Bz	Benzoyl	MsCl	Mesyl chloride
CMBP	(Tributylphosphoranylidene)acetonitrile	NBS	N-bromosuccinimide
DABCO	1,4-diazabicyclo[2.2.2]octane	NMI	1-methylimidazole
DAST	(diethylamino)sulfur trifluoride	NMP	Methylpyrrolidone
DBAD	Di-tertbutyl azodicarboxylate	Pd/C	Palladium on activated carbon
DCM	Methylene chloride	PHB	pyrrolidinone hydrotribromide
DIBAL	Diisobutylammonium hydride	[Ph ₃ PBn] ⁺ Cl ⁻	benzyltriphenylphosphonium chloride
DIAD	Diisopropyl azodicarboxylate	PPh ₃	Triphenylphosphine
DIEA/DIPEA	Diisopropylethylamine	TBAF	Tetrabutylammonium fluoride
DMAP	4-(dimethylamino)pyridine		

Abbreviation	Chemical
TCFH	N,N,N,N-tetramethylchloroformamidinium hexafluorophosphate
TEA or NEt ₃	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Trimethylsilyl
TMSOK	potassium trimethylsilylate

Abbreviation	Chemical
XantPhOS or XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XPhOS	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
XPhOS Pd G3	(2-Dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate

Example 1: Synthesis of Intermediate Compounds via Alkylation

Procedure 1 – Intermediate for A91



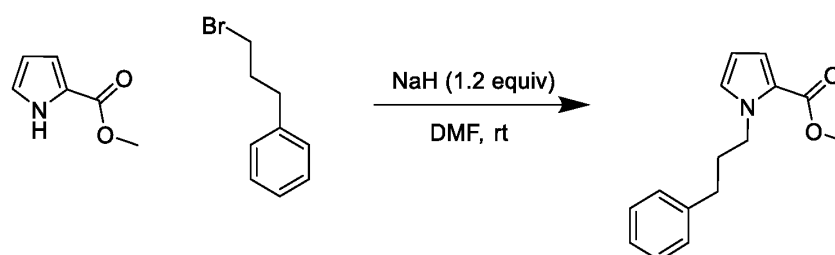
[00235] A 100 mL roundbottom flask with stir bar was charged with methyl 1H-pyrrole-2-carboxylate (581 mg, 4.65 mmol, 1.1 equiv), 4-(2-bromoethyl)pyridine (786 mg, 4.22 mmol, 1.0 equiv), K₂CO₃ (1.75 g, 12.7 mmol, 3.0 equiv) and DMF (20 mL). The resulting reaction mixture was stirred at room temperature for 2 days. After this time, the reaction mixture was diluted with DCM (200 mL) and washed with water (3 x 200 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting crude material was purified via silica gel chromatography (50-100% EtOAc in hexanes) to yield the desired product.

[00236] The following intermediate compounds were synthesized in a similar manner:

Intermediate for:	Product name
A41	methyl 1-((3-bromopyridin-4-yl)methyl)-1H-pyrrole-2-carboxylate
A100	ethyl 1-(pyridin-4-ylmethyl)-1H-pyrazole-3-carboxylate
A112	ethyl 1-(pyridin-4-ylmethyl)-1H-pyrazole-5-carboxylate
A122	methyl 1-(pyridin-4-ylmethyl)-1H-pyrrole-3-carboxylate
A87	methyl 1-(pyridin-3-ylmethyl)-1H-pyrrole-2-carboxylate
A102	methyl 6-oxo-1-(pyridin-4-ylmethyl)piperidine-2-carboxylate
A103	methyl 3-methyl-1-(pyridin-4-ylmethyl)-1H-pyrazole-5-carboxylate
A104	methyl 1-(pyridin-4-ylmethyl)-1H-imidazole-5-carboxylate
A106	methyl 6-oxo-1-(pyridin-4-ylmethyl)-1,6-dihydropyridine-2-carboxylate
A108	methyl 1-(pyridin-4-ylmethyl)-1H-imidazole-2-carboxylate
A86	methyl 3-chloro-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxylate
A88	methyl 3-methyl-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxylate
A24	methyl 1-((3-methylpyridin-4-yl)methyl)-1H-pyrrole-2-carboxylate
A48	methyl 4-methyl-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxylate
A76	methyl 5-methyl-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxylate

Intermediate for:	Product name
A83	methyl 1-((2-methylpyridin-4-yl)methyl)-1H-pyrrole-2-carboxylate
A125	methyl 1-((2-methoxypyridin-4-yl)methyl)-1H-pyrrole-2-carboxylate
A211	methyl 1-((3-methoxypyridin-4-yl)methyl)-1H-pyrrole-2-carboxylate
A214	methyl 1-((3-(trifluoromethyl)pyridin-4-yl)methyl)-1H-pyrrole-2-carboxylate
A212 and A190	methyl 1-((3-bromopyridin-4-yl)methyl)-1H-pyrrole-2-carboxylate
A221	methyl 1-(3-(pyridin-4-yl)allyl)-1H-pyrrole-2-carboxylate
A238 and A318	methyl 1-((3-chloropyridin-4-yl)methyl)-1H-pyrrole-2-carboxylate
A243	methyl 1-(3-(3-fluoropyridin-4-yl)propyl)-1H-pyrrole-2-carboxylate
A360	methyl 1-((3-fluoro-5-methylpyridin-4-yl)methyl)-1H-pyrrole-2-carboxylate

Procedure 2 – Intermediate for A64



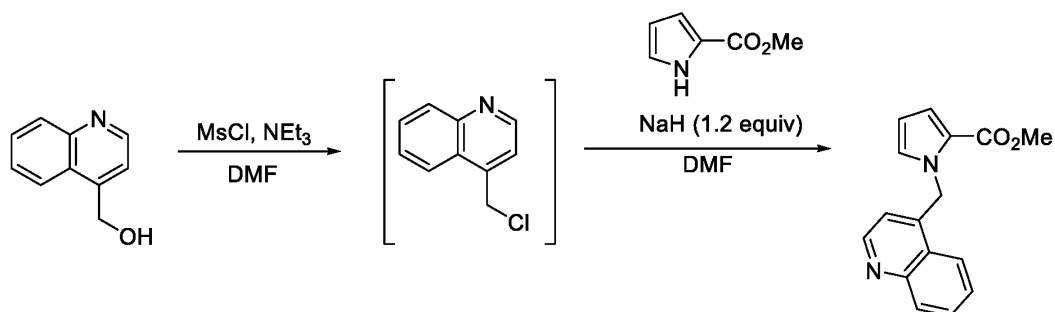
[00237] A roundbottom flask with stir bar was charged with NaH (210 mg, 60 wt%, 5.13 mmol, 1.2 equiv) and DMF (20 mL). Methyl 1H-pyrrole-2-carboxylate (535 mg, 4.27 mmol, 1.0 equiv) was slowly added to the reaction mixture, and the solution was stirred at room temperature for 30 min. After 30 min, (3-bromopropyl)benzene (936 mg, 4.70 mmol, 1.1 equiv) was added, and the reaction mixture was allowed to stir at room temperature overnight. The next morning, the reaction mixture was diluted with DCM (200 mL) and washed with water (3 x 200 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting crude material was purified via silica gel chromatography (0-15% EtOAc in hexanes) to yield the desired product.

[00238] The following intermediate compounds were synthesized in a similar manner:

Intermediate for:	Product name
A190	methyl 1-(3-(pyridin-3-yl)propyl)-1H-pyrrole-2-carboxylate
A101	methyl 1-(3-(1-acetypiperidin-4-yl)propyl)-1H-pyrrole-2-carboxylate
A68	methyl 1-(3-(2-chlorophenyl)propyl)-1H-pyrrole-2-carboxylate
A44	methyl 1-(4-(pyridin-4-yl)butyl)-1H-pyrrole-2-carboxylate
A126	benzyl 4-((2-(methoxycarbonyl)-1H-pyrrol-1-yl)methyl)piperidine-1-carboxylate
A11	methyl 1-(3-(pyridin-4-yl)propyl)-1H-pyrrole-2-carboxylate
A71	methyl 1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-pyrrole-2-carboxylate
A128 and A129	tert-butyl 4-((2-(methoxycarbonyl)-1H-pyrrol-1-yl)methyl)piperidine-1-carboxylate
A78	methyl 1-(2-chlorobenzyl)-1H-pyrrole-2-carboxylate

Intermediate for:	Product name
A79	methyl 1-benzyl-1H-pyrrole-2-carboxylate
A84	methyl 1-(4-(methylsulfonyl)benzyl)-1H-pyrrole-2-carboxylate
A80	methyl 1-(4-cyanobenzyl)-1H-pyrrole-2-carboxylate
A53	methyl 1-(4-nitrobenzyl)-1H-pyrrole-2-carboxylate
A187 and A190	methyl 1-(3-(pyridin-3-yl)propyl)-1H-pyrrole-2-carboxylate
A256	methyl 1-((3,5-difluoropyridin-4-yl)methyl)-1H-pyrrole-2-carboxylate
A226	methyl 1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-1H-pyrrole-2-carboxylate

Procedure 3 – Intermediate for A90

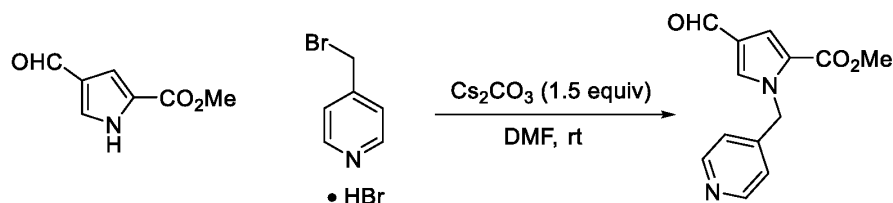


[00239] A 40 mL scintillation vial with stir bar was charged with quinolin-4-ylmethanol (500 mg, 3.14 mmol, 1.1 equiv) and DMF (7 mL). Triethylamine (0.65 mL, 4.71 mmol, 1.5 equiv) was added to the reaction mixture, followed by the slow addition of mesyl chloride (0.269 mL, 3.45 mmol, 1.2 equiv) at room temperature. The reaction mixture was allowed to stir at room temperature overnight. The next morning, in a separate flask, a slurry of NaH (140 mg, 3.43 mmol, 60 wt%, 1.2 equiv) and DMF (7 mL) was prepared. Methyl 1H-pyrrole-2-carboxylate (357 mg, 2.86 mmol, 1.0 equiv) was added, and the reaction mixture was allowed to stir at room temperature for 30 min. After 30 min, the solution of crude activated alcohol was slowly added to the pyrrole solution in four portions over 1 h. The resulting solution was allowed to stir at room temperature overnight. The next morning, the reaction mixture was diluted with DCM (150 mL) and washed with water (3 x 150 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting crude material was purified via silica gel chromatography (10-40% EtOAc in hexanes) to yield the desired product.

[00240] The following intermediate compounds were synthesized in a similar manner:

Intermediate for:	Product name
A25	methyl 1-((3-fluoropyridin-4-yl)methyl)-1H-pyrrole-2-carboxylate
A90	methyl 1-(quinolin-4-ylmethyl)-1H-pyrrole-2-carboxylate
A124	methyl 1-((1-methyl-6-oxo-1,6-dihydropyridin-3-yl)methyl)-1H-pyrrole-2-carboxylate
A69	methyl 1-(pyridazin-4-ylmethyl)-1H-pyrrole-2-carboxylate
A127	methyl 1-((1-methyl-2-oxo-1,2-dihydropyridin-4-yl)methyl)-1H-pyrrole-2-carboxylate
A97	methyl 1-((2,6-dimethylpyridin-4-yl)methyl)-1H-pyrrole-2-carboxylate

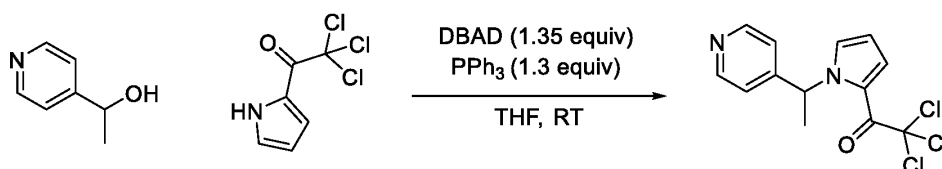
A36	methyl 1-((2,6-difluoropyridin-4-yl)methyl)-1H-pyrrole-2-carboxylate
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Procedure 4 – Intermediate for A111

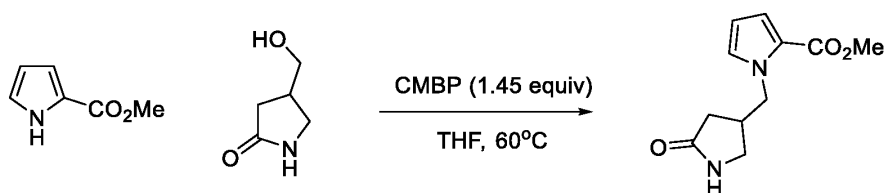
[00241] Methyl 4-formyl-1H-pyrrole-2-carboxylate (2 g, 13 mmol, 1 equiv) was dissolved in DMF (65 mL), and Cs_2CO_3 (6.37 g, 19 mmol, 1.5 equiv) and (bromomethyl)pyridine hydrobromide (3.3g, 13 mmol, 1.0 equiv) were added. The resulting reaction mixture was stirred at room temperature overnight. The next morning, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (4 x 30mL). The organic layer was dried over Mg_2SO_4 , filtered and concentrated in vacuo. The resulting crude product was purified via silica gel chromatography (25-100% EtOAc in hexanes) to yield the desired product.

[00242] The following intermediate compounds were synthesized in a similar manner:

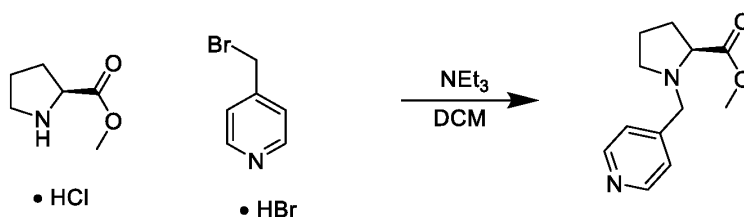
Intermediate for:	Product name
A105	methyl 5-formyl-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxylate
A109	methyl 4-formyl-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxylate

Procedure 5 – Intermediate for A74 and A49

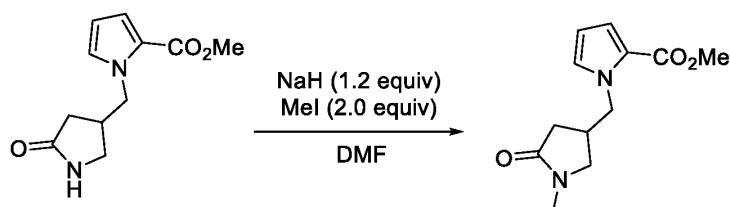
[00243] 2-(trichloroacetyl)pyrrole (1.0 g, 4.71 mmol, 1.0 eq), triphenylphosphine (0.527 g, 6.12 mmol, 1.3 equiv) and 1-(4-pyridinyl)ethanol (0.638 g, 5.18 mmol, 1.10 eq) were dissolved in anhydrous THF (15.8 mL, 0.3 M). Then di-tertbutylazodicarboxylate (DBAD) (1.463 g, 6.35 mmol, 1.35 eq) dissolved in anhydrous THF (2 mL) was added under argon atmosphere. The reaction was allowed to stir at room temperature overnight. The next morning, the THF was evaporated under reduced pressure and the resulting crude material was purified via silica gel chromatography (0-100% EtOAc in DCM) to give the desired product.

Procedure 6 – Intermediate for A93

[00244] Methyl 1H-pyrrole-2-carboxylate (1 g, 8 mmol, 1 equiv) and 4-(hydroxymethyl)pyrrolidin-2-one (1.38 g, 12 mmol, 1.5 equiv) were dissolved in dry THF (16 mL) followed by addition of CMBP (2.85g, 11.6 mmol, 1.45 equiv) under Ar. The tube was sealed and heated to 60°C overnight. The next morning, the THF was removed under reduced pressure and the crude mixture was purified via silica gel chromatography (1-5% methanol in DCM), which yielded the desired product mixed with tributylphosphine oxide. This mixture washed with hexane and filtered to provide the pure desired product.

Procedure 7 – Intermediate for B26

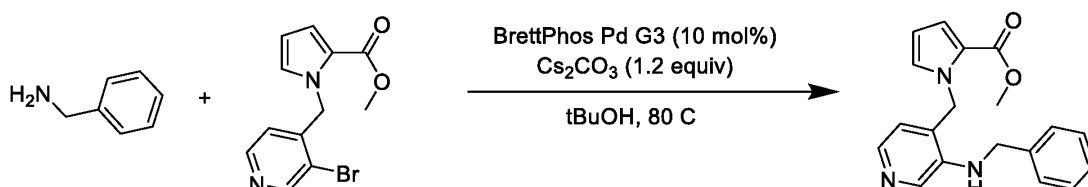
[00245] A 40 mL vial with stir bar was charged with methyl prolinatate hydrochloride (500 mg, 3.02 mmol, 1.0 equiv) and DCM (15 mL, 0.2 M). Triethylamine (1.7 mL, 12.1 mmol, 4.0 equiv) was slowly added at room temperature. 4-(bromomethyl)pyridine hydrobromide (840 mg, 3.32 mmol, 1.1 equiv) was added portion-wise over 1 h. The resulting reaction mixture was allowed to stir at room temperature overnight. The next morning, the reaction mixture was concentrated in vacuo and the resulting crude product was purified via silica gel chromatography (50-100% EtOAc in hexanes) to yield the desired product.

Procedure 8 – Intermediate for A210

[00246] Methyl 1-((5-oxopyrrolidin-3-yl)methyl)-1H-pyrrole-2-carboxylate (100 mg, 0.45 mmol, 1.0 equiv) was dissolved in THF, and cooled to 0 °C. NaH (21.6 mg, 0.54 mmol, 1.2

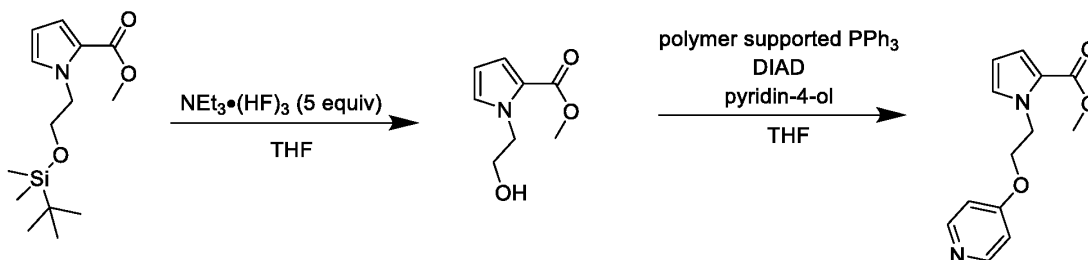
equiv) was added, and the reaction stirred at 0 °C for 15 min. After this time, MeI (127.8 mg, 0.9 mmol, 2.0 equiv) was added, and the reaction mixture was warmed to room temperature for 30 min. After 30 min at room temperature, the reaction was quenched with water (5 mL) and concentrated in vacuo to yield the desired product.

Procedure 9 – Intermediate for A212 & A213



[00247] A 20 mL vial with stir bar was charged with bromide (461 mg, 1.56 mmol, 1.0 equiv), Cs₂CO₃ (611 mg, 1.87 mmol, 1.2 equiv), and BrettPhos Pd G3 (142 mg, 0.156 mmol, 0.1 equiv). The vial was evacuated and backflushed with nitrogen. Freshly-sparged tBuOH (7 mL) was added, followed by benzylamine (0.2 mL, 1.87 mmol, 1.2 equiv). The vial was capped, and the reaction mixture was allowed to stir at 80 °C overnight. The next morning, the reaction mixture was cooled to room temperature and diluted with DCM (100 mL). The organic layer was washed with brine (2 x 100 mL), and the combined aqueous layers were extracted with DCM (1 x 100 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting material was purified by silica gel chromatography to yield the desired product.

Procedure 10 – Intermediate for A226

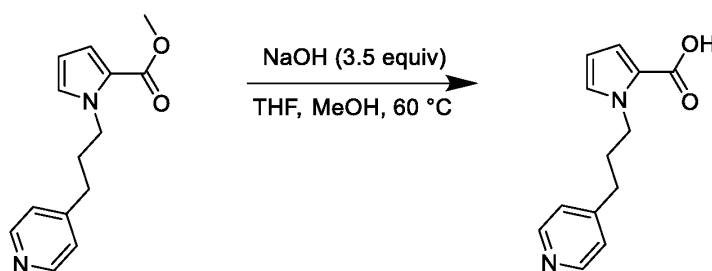


[00248] A roundbottom flask with stir bar was charged with silyl ether (1.74 g, 6.14 mmol, 1.0 equiv) and THF (20 mL). The reaction mixture was cooled to 0 °C, and triethylamine trihydrofluoride (5.00 mL, 30.7 mmol, 5.0 equiv) was added at 0 °C. The reaction mixture was allowed to warm to room temperature overnight. The next morning, the reaction mixture was diluted with DCM (150 mL) and washed with saturated NaHCO₃ (2 x 150 mL). The combined aqueous layers were extracted with DCM (1 x 150 mL), and the combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting material was used in the next step without further purification.

[00249] A roundbottom flask with stir bar was charged with alcohol (2.30 g, 13.6 mmol, 1.0 equiv), pyridin-4-ol (1.29 g, 13.6 mmol, 1.0 equiv), and polymer-bound PPh₃ (3 mmol/g loading, 9.05 g, 27.2 mmol, 2.0 equiv) and THF (30 mL). The reaction mixture was cooled to 0 °C. DIAD (5.34 mL, 27.2 mmol, 2.0 equiv) was slowly added at 0 °C, and the reaction mixture was allowed to warm to room temperature overnight. The next morning, the reaction mixture filtered through a plug of Celite and washed with EtOAc. The filtrate was concentrated in vacuo, and the resulting crude material was purified via silica gel chromatography to yield the desired product.

Example 2: Synthesis of Intermediate Compounds via Saponification

Procedure 1 – Intermediate for A6



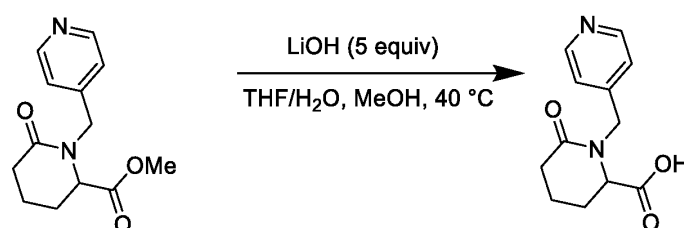
[00250] A 40 mL vial with stir bar was charged with methyl 1-(3-(pyridin-4-yl)propyl)-1H-pyrrole-2-carboxylate (559 mg, 2.29 mmol, 1.0 equiv). MeOH (4 mL) and THF (4 mL) were added, followed by NaOH (1.6 mL, 5.0 M in water, 3.5 equiv). The resulting solution was heated at 60 °C overnight. The next morning, the solvents were removed in vacuo and the resulting aqueous solution was acidified to ~ pH 3 via addition of 1 M HCl. The resulting precipitate was filtered and collected, and any residual water was removed in vacuo to yield the desired product.

[00251] The following compounds were prepared in a similar manner:

Intermediate for:	Compound name
A190	1-(3-(pyridin-3-yl)propyl)-1H-pyrrole-2-carboxylic acid
A41	1-((3-bromopyridin-4-yl)methyl)-1H-pyrrole-2-carboxylic acid
A101	1-(3-(1-acetypiperidin-4-yl)propyl)-1H-pyrrole-2-carboxylic acid
A68	1-(3-(2-chlorophenyl)propyl)-1H-pyrrole-2-carboxylic acid
A64	1-(3-phenylpropyl)-1H-pyrrole-2-carboxylic acid
A100	1-(pyridin-4-ylmethyl)-1H-pyrazole-3-carboxylic acid
A44	1-(4-(pyridin-4-yl)butyl)-1H-pyrrole-2-carboxylic acid
A25	1-((3-fluoropyridin-4-yl)methyl)-1H-pyrrole-2-carboxylic acid
A112	1-(pyridin-4-ylmethyl)-1H-pyrazole-5-carboxylic acid
A91	1-(2-(pyridin-4-yl)ethyl)-1H-pyrrole-2-carboxylic acid
A90	1-(quinolin-4-ylmethyl)-1H-pyrrole-2-carboxylic acid
A122	1-(pyridin-4-ylmethyl)-1H-pyrrole-3-carboxylic acid

Intermediate for:	Compound name
A124	1-((1-methyl-6-oxo-1,6-dihydropyridin-3-yl)methyl)-1H-pyrrole-2-carboxylic acid
A69	1-(pyridazin-4-ylmethyl)-1H-pyrrole-2-carboxylic acid
A126	1-((1-((benzyloxy)carbonyl)piperidin-4-yl)methyl)-1H-pyrrole-2-carboxylic acid
A127	1-((1-methyl-2-oxo-1,2-dihydropyridin-4-yl)methyl)-1H-pyrrole-2-carboxylic acid
A71	1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-pyrrole-2-carboxylic acid
A128	1-((1-acetylpiperidin-4-yl)methyl)-1H-pyrrole-2-carboxylic acid
A129	1-((1-methylpiperidin-4-yl)methyl)-1H-pyrrole-2-carboxylic acid
A130	(pyridin-4-ylmethyl)-L-proline
A87	1-(pyridin-3-ylmethyl)-1H-pyrrole-2-carboxylic acid
A16	1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxylic acid
A78	1-(2-chlorobenzyl)-1H-pyrrole-2-carboxylic acid
A79	1-benzyl-1H-pyrrole-2-carboxylic acid
A211	1-((3-methoxypyridin-4-yl)methyl)-1H-pyrrole-2-carboxylic acid
A214	1-((3-(trifluoromethyl)pyridin-4-yl)methyl)-1H-pyrrole-2-carboxylic acid
A187 and A190	1-(3-(pyridin-3-yl)propyl)-1H-pyrrole-2-carboxylic acid
A212 and A213	1-((3-(benzylamino)pyridin-4-yl)methyl)-1H-pyrrole-2-carboxylic acid
A221	1-(3-(pyridin-4-yl)allyl)-1H-pyrrole-2-carboxylic acid
A226	1-(2-(pyridin-4-yloxy)ethyl)-1H-pyrrole-2-carboxylic acid
A238 and A318	1-((3-chloropyridin-4-yl)methyl)-1H-pyrrole-2-carboxylic acid

Procedure 2 – Intermediate for A102



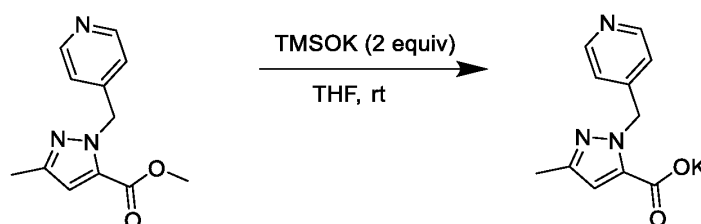
[00252] To the solution of methyl ester (0.210 g, 0.85 mmol, 1.0 eq.) in THF/water and few drops of MeOH was added LiOH monohydrate (0.177 g, 4.00 mmol, 5.0 eq.). Reaction was continued at 40°C for 18 hours. The next morning, the THF was evaporated, and the water layer was acidified to ~ pH 4-5 via addition of 1 M HCl. The water layer was then evaporated, and the crude product was purified by ionic resin (Amberlite IR 120) to give the desired product.

[00253] The following compounds were prepared in a similar manner:

Intermediate for:	Compound name
A210	1-((1-methyl-5-oxopyrrolidin-3-yl)methyl)-1H-pyrrole-2-carboxylic acid
A93	1-((5-oxopyrrolidin-3-yl)methyl)-1H-pyrrole-2-carboxylic acid
A104	1-(pyridin-4-ylmethyl)-1H-imidazole-5-carboxylic acid
A105	5-carbamoyl-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxylic acid

Intermediate for:	Compound name
A107	5-(dimethylcarbamoyl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxylic acid
A109	4-carbamoyl-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxylic acid
A110	5-(hydroxymethyl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxylic acid
A111	4-(dimethylcarbamoyl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxylic acid
A113	4-(hydroxymethyl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxylic acid
A86	3-chloro-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxylic acid
A70	1-((2-fluoro-6-methoxypyridin-4-yl)methyl)-1H-pyrrole-2-carboxylic acid
A97	1-((2,6-dimethylpyridin-4-yl)methyl)-1H-pyrrole-2-carboxylic acid
A36	1-((2,6-difluoropyridin-4-yl)methyl)-1H-pyrrole-2-carboxylic acid
A48	4-methyl-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxylic acid
A53	1-(4-nitrobenzyl)-1H-pyrrole-2-carboxylic acid
A256	1-((3,5-difluoropyridin-4-yl)methyl)-1H-pyrrole-2-carboxylic acid
A210	1-((1-methyl-5-oxopyrrolidin-3-yl)methyl)-1H-pyrrole-2-carboxylic acid
A360	1-((3-fluoro-5-methylpyridin-4-yl)methyl)-1H-pyrrole-2-carboxylic acid

Procedure 3 – Intermediate for A112



[00254] To a solution of methyl ester (0.175 g, 0.76 mmol, 1.0 eq) THF (5.8 mL), potassium trimethylsiliolate (0.194 g, 1.51 mmol, 2.0 eq) was added portion-wise. The reaction mixture was stirred at room temperature for 4 h. After this time, the precipitate was filtered, collected and dried under vacuum. The desired product was obtained as the potassium salt.

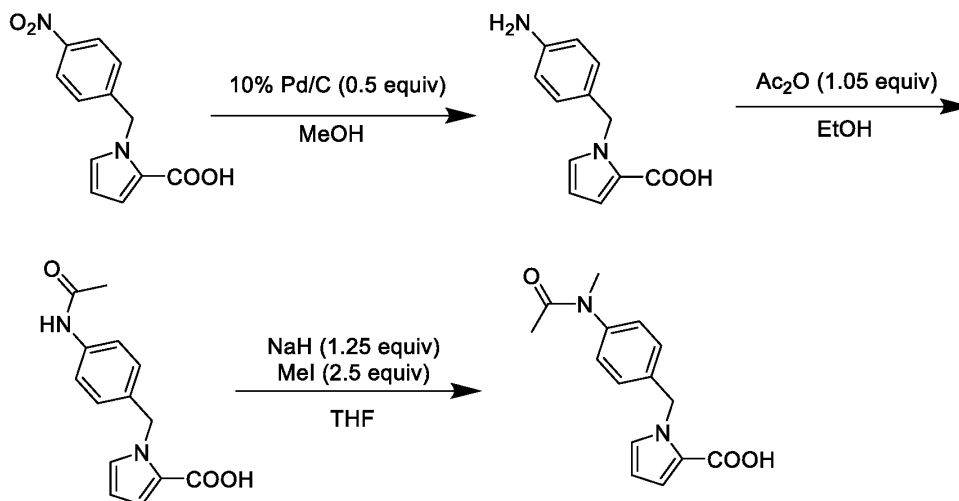
[00255] The following compounds were prepared in a similar manner:

Intermediate for:	Compound name
A103	3-methyl-1-(pyridin-4-ylmethyl)-1H-pyrazole-5-carboxylic acid
A106	6-oxo-1-(pyridin-4-ylmethyl)-1,6-dihydropyridine-2-carboxylic acid
A108	1-(pyridin-4-ylmethyl)-1H-imidazole-2-carboxylic acid
A88	3-methyl-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxylic acid
A84	1-(4-(methylsulfonyl)benzyl)-1H-pyrrole-2-carboxylic acid
A24	1-((3-methylpyridin-4-yl)methyl)-1H-pyrrole-2-carboxylic acid
A76	5-methyl-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxylic acid
A83	1-((2-methylpyridin-4-yl)methyl)-1H-pyrrole-2-carboxylic acid
A125	1-((2-methoxypyridin-4-yl)methyl)-1H-pyrrole-2-carboxylic acid

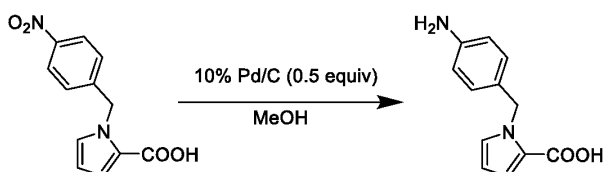
Intermediate for:	Compound name
A80	1-(4-cyanobenzyl)-1H-pyrrole-2-carboxylic acid
A243	1-(3-(3-fluoropyridin-4-yl)propyl)-1H-pyrrole-2-carboxylic acid

Procedure 4 – Intermediates for A114 and A99

[00256] Synthesis of the intermediates for A114 and A99 followed the scheme below:

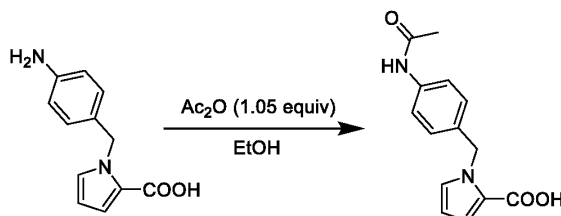


Step 1: Nitro group reduction



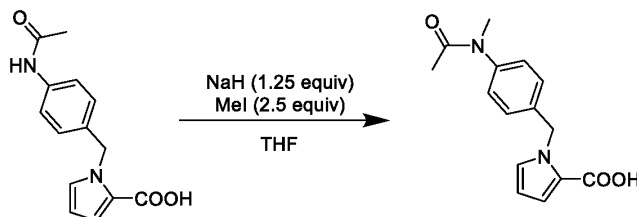
[00257] 1-(4-nitrobenzyl)-1H-pyrrole-2-carboxylic acid (0.200 g, 0.81 mmol, 1.0 eq.) was dissolved in methanol (10 mL). Then, Pd/C (10 wt%, 0.414 g, 0.41 mmol, 0.5 eq.) was added and reaction was continued under hydrogen atmosphere overnight at room temperature. The next morning, the reaction mixture was filtered through Celite and washed with EtOAc. The filtrate was concentrated to give the desired product, which was used in the next step without further purification.

Step 2: Aniline acylation



[00258] 1-(4-acetamidobenzyl)-1H-pyrrole-2-carboxylic acid (0.150 g, 0.69 mmol, 1.0 eq.) was dissolved in ethanol (5 mL). Then, acetic anhydride (0.069 mL, 0.73 mmol, 1.05 eq.) was added, and reaction was stirred overnight at room temperature. The next morning, the volatile materials were evaporated. Water was added, and solution was acidified to pH 4 with 4N HCl. The resulting precipitate was filtered off and dried to yield the desired product (Intermediate for A114).

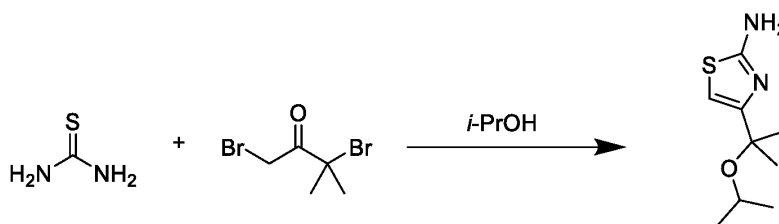
Step 3: Amide methylation



[00259] A solution of 1-(4-acetamidobenzyl)-1H-pyrrole-2-carboxylic acid (0.163 g, 0.63 mmol, 1.0 eq) in THF (4 mL) was added dropwise to a slurry of NaH (0.032 g, 0.79 mmol, 1.25 eq) in THF (4 mL) at 0 °C. The mixture was stirred at this temperature for 30 min. After this time, MeI (0.098 ml, 1.58 mmol, 2.5 eq) was added dropwise to the reaction mixture at 0 °C. The reaction mixture was allowed to warm to room temperature overnight. The next morning, the THF was evaporated, and the resulting material was diluted with water. The aqueous layer was extracted with EtOAc (3 x 30 mL). The aqueous layer was then acidified to pH 4 with 4 N HCl, and the resulting precipitate was filtered off and dried to yield the desired product (Intermediate for A99)

Example 3: Synthesis of Thiazole Amine Intermediate Compounds

Procedure 1 – Intermediate for A41

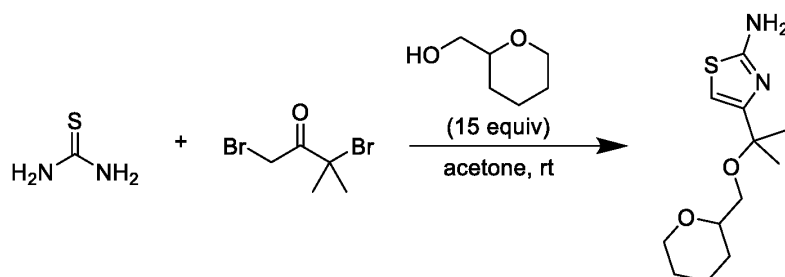


[00260] A 100 mL roundbottom flask with stir bar was charged with 1,3-dibromo-3-methylbutan-2-one (1.95 g, 7.99 mmol, 1.0 equiv) and isopropanol (40 mL, 0.2 M). Thiourea (669 mg, 8.79 mmol, 1.1 equiv) was added, and the reaction mixture was stirred at room temperature overnight. The next morning, the solvent was evaporated, and the reaction mixture was diluted with DCM (100 mL). The organic layer was washed with saturated NaHCO₃ (3 x 100 mL), and subsequently dried over Na₂SO₄. The organic layer was filtered

and concentrated in vacuo. The resulting crude material was purified via silica gel chromatography (0-50% EtOAc in hexanes) to yield the desired product.

Intermediate for:	Compound name
A28	4-(1-isopropoxyethyl)thiazol-2-amine
A20	4-(1-isopropoxyethyl)-5-methylthiazol-2-amine
A15	4-(2-(2,2,2-trifluoroethoxy)propan-2-yl)thiazol-2-amine
A37	4-(2-isopropoxypropan-2-yl)-5-methylthiazol-2-amine
A27	4-(2-ethoxypropan-2-yl)thiazol-2-amine
A59	4-(isopropoxymethyl)thiazol-2-amine

Procedure 2 – Intermediate for A39

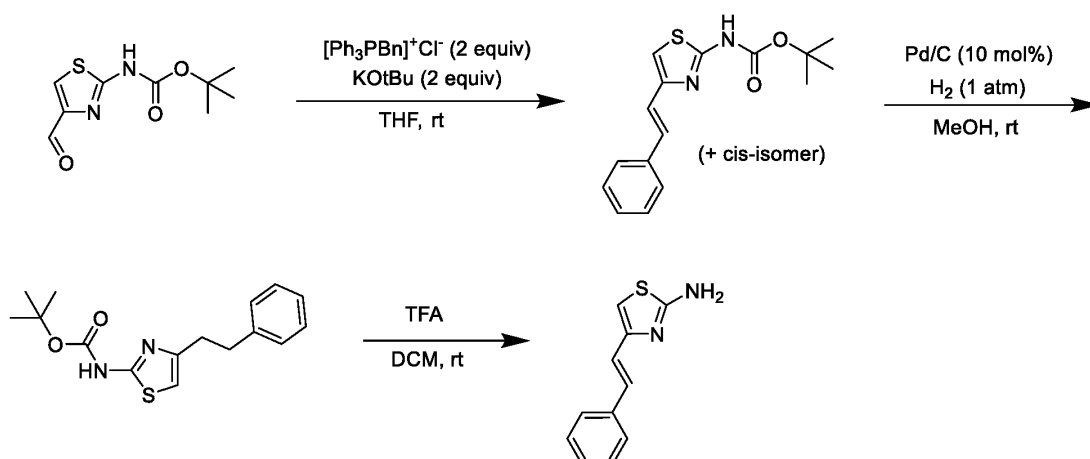


[00261] A 40 mL vial with stir bar was charged with 1,3-dibromo-3-methylbutan-2-one (600 mg, 2.46 mmol, 1.0 equiv) and acetone (8 mL, 0.2 M). (Tetrahydro-2H-pyran-2-yl)methanol (4.17 mL, 36.9 mmol, 15 equiv) was added, followed by thiourea (206 mg, 2.71 mmol, 1.1 equiv), and the reaction mixture was stirred at room temperature overnight. The next morning, the reaction mixture was diluted with DCM (100 mL). The organic layer was washed with saturated NaHCO₃ (3 x 100 mL), and subsequently dried over Na₂SO₄. The organic layer was filtered and concentrated in vacuo. The resulting crude material was purified via silica gel chromatography (40-80% EtOAc in hexanes) to yield the desired product.

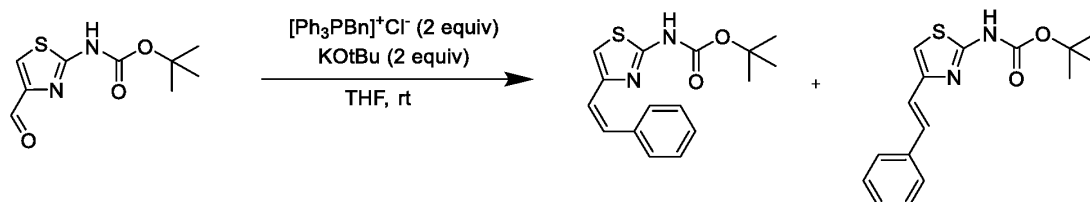
Intermediate for:	Compound name
A2	4-(2-(1-(3-chlorophenyl)ethoxy)propan-2-yl)thiazol-2-amine
A8	4-(2-(1-(2-chlorophenyl)ethoxy)propan-2-yl)thiazol-2-amine
A5	4-(2-(1-(4-chlorophenyl)ethoxy)propan-2-yl)thiazol-2-amine
A4	4-(2-(1-(3-methoxyphenyl)ethoxy)propan-2-yl)thiazol-2-amine
A40	4-(2-((tetrahydro-2H-pyran-4-yl)methoxy)propan-2-yl)thiazol-2-amine
A18	(R)-4-(2-(1-phenylethoxy)propan-2-yl)thiazol-2-amine
A1	(S)-4-(2-(1-phenylethoxy)propan-2-yl)thiazol-2-amine
B3	4-(2-(2-tosylethoxy)propan-2-yl)thiazol-2-amine
A7	4-(2-(cyclohexylmethoxy)propan-2-yl)thiazol-2-amine
A10	4-(2-(cyclohexyloxy)propan-2-yl)thiazol-2-amine
A9	4-(2-(benzyloxy)propan-2-yl)thiazol-2-amine

Procedure 3 – Intermediate for A14

[00262] Synthesis of these intermediates followed the scheme below:

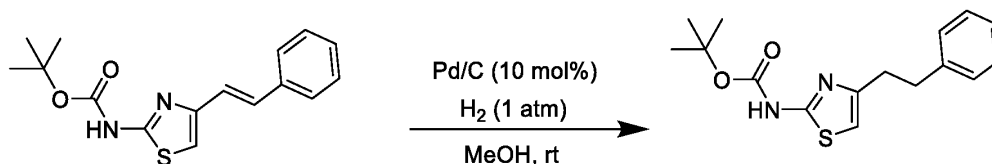


Step 1: Wittig Reaction



[00263] A 100 mL roundbottom flask was charged with benzyltriphenylphosphonium chloride (3.41 g, 8.76 mmol, 2.0 equiv) and THF (20 mL, 0.2 M). Potassium tert-butoxide (1.03 g, 9.20 mmol, 2.1 equiv) was added, and the reaction mixture was allowed to stir at room temperature for 15 min. Tert-butyl (4-formylthiazol-2-yl)carbamate (1.00 g, 4.38 mmol, 1.0 equiv) was then added, and the reaction mixture was allowed to stir at room temperature overnight. The next morning, the solvent was removed in vacuo, and the resulting material was taken up in DCM (100 mL). The organic layer was washed with saturated NH_4Cl (3 x 100 mL). The organic layer was then dried over Na_2SO_4 , filtered and concentrated in vacuo. The resulting crude material was purified via silica gel chromatography (0-10% EtOAc in hexanes) to yield the desired cis- and trans- isomers separately.

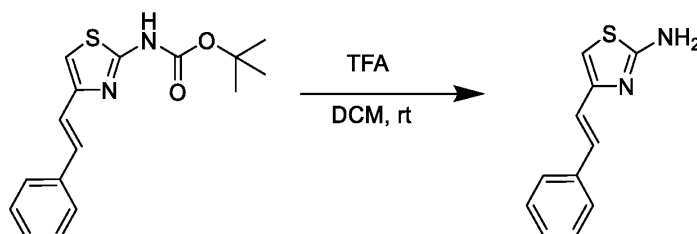
Step 2: Hydrogenation



[00264] A 20 mL scintillation vial with stir bar was charged with tert-butyl (4-styrylthiazol-2-yl)carbamate (187 mg, 0.618 mmol, 1.0 equiv) and Pd/C (10 wt%, 66 mg, 0.0618 mmol, 0.1 equiv). The solids were evacuated and backflushed with hydrogen (1 atm, 3x). Methanol (5 mL, 0.1 M) was added to the reaction mixture, and the resulting suspension was stirred at

room temperature overnight. The next morning, the solids were filtered off, and the resulting crude material was purified via silica gel chromatography (0-30% EtOAc in hexanes) to yield the desired product.

Step 3: Boc Deprotection



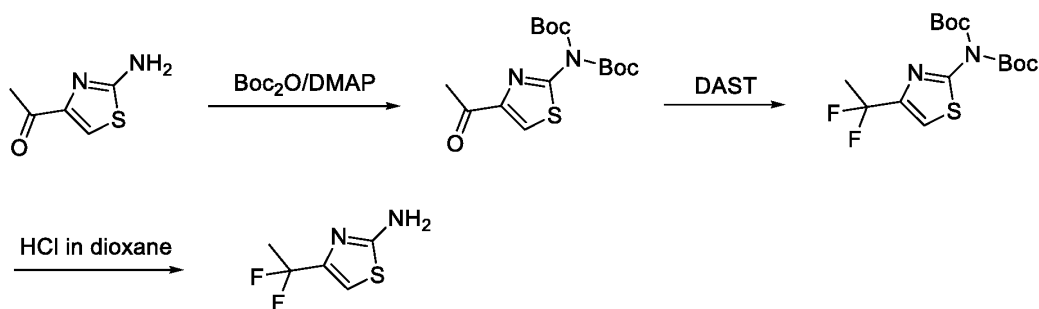
[00265] A 20 mL scintillation vial with stir bar was charged with tert-butyl (4-styrylthiazol-2-yl)carbamate (176 mg, 0.582 mmol). DCM (2.7 mL) and TFA (600 μ L, 20 vol%) were added, and the reaction mixture was stirred at room temperature overnight. The next morning, the reaction mixture was diluted with DCM (50 mL) and washed with saturated NaHCO_3 (3 x 50 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated in vacuo. The resulting product was used in the next step without further purification.

[00266] The following compounds were prepared in a similar manner:

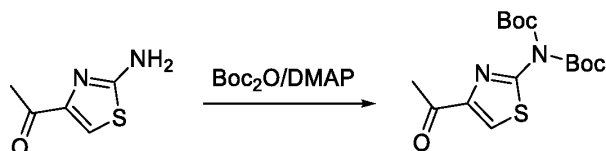
Intermediate for:	Compound name
A13	4-phenethylthiazol-2-amine
A12	4-styrylthiazol-2-amine

Procedure 4 – Intermediate for A29

[00267] Synthesis of this intermediate followed the scheme, below:

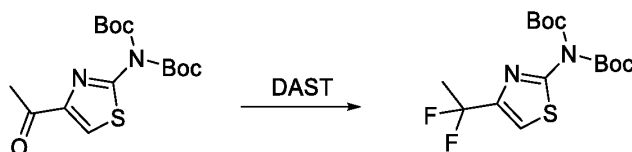


Step 1: Boc Protection



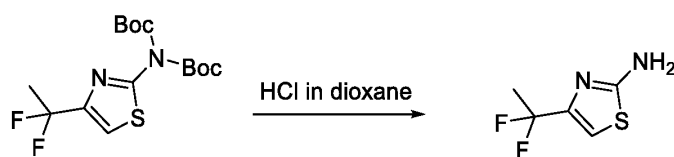
[00268] 1-(2-aminothiazol-4-yl)ethan-1-one (1.0 g, 2.06 mmol, 1 equiv) was suspended in neat Boc_2O (1.79g, 8.24mmol, 4 equiv) at 60°C, then a catalytic amount of DMAP (0.024g; 0.02 mmol, 0.01 equiv) was added. Gas evolution started. The reaction mixture was left stirring overnight at 60 °C. The reaction mixture was concentrated and directly used into column chromatography. The resulting crude product was purified via silica gel chromatography (10-50% EtOAc in hexanes) to yield the desired product.

Step 2: Fluorination



[00269] DAST (0.456 g, 2.83 mmol, 3.0 equiv) was mixed with ketone (0.323 g, 0.943 mmol, 1.0 equiv) and left stirring at 50°C for 2 days. After this time, the reaction mixture was diluted with DCM (15 mL), and carefully washed with NaHCO_3 (2 x 15 mL). The organic layer was dried over MgSO_4 , filtered and concentrated in vacuo. The resulting crude product was used in the next step without further purification.

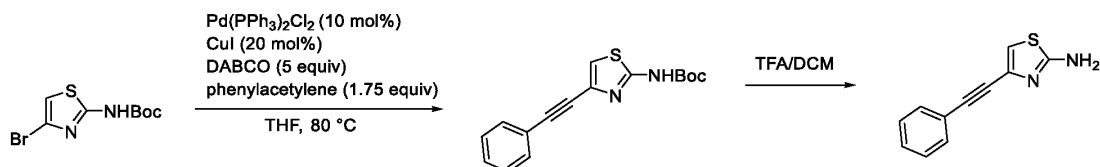
Step 3: Boc deprotection

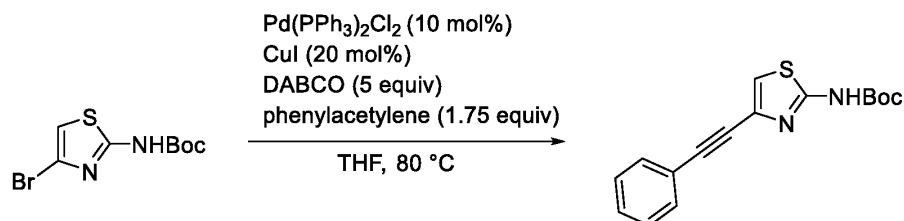


[00270] Tert-butyl (tert-butoxycarbonyl)(4-(1,1-difluoroethyl)thiazol-2-yl)carbamate (0.38 g, 1.04 mmol, 1.0 equiv) was dissolved in HCl in dioxane (4M, 20 mL) and heated to 50 °C overnight. The next morning, the volatile materials were removed under reduced pressure and the crude product was used in the next step without further purification.

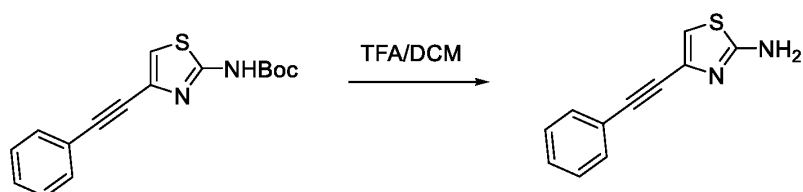
Procedure 5 – Intermediate for A132

[00271] Synthesis of the intermediate for A132 followed the scheme, below:



Step 1: Sonogashira coupling

[00272] A solution of tert-Butyl (4-bromo-5-formylthiazol-2-yl)carbamate (0.500 g, 1.79 mmol, 1.0 equiv), phenylacetylene (0.573 g, 3.13 mmol, 1.75 equiv) and DABCO (1.005 g, 8.96 mmol, 5.0 equiv) in anhydrous THF (15.0 mL) was purged three times with Ar (g), then Cul (0.003 g, 0.02 mmol, 0.01 equiv) and Pd(PPh₃)₂Cl₂ (0.025 g, 0.04 mmol, 0.02 eq) were added. The reaction mixture was again purged with Ar (g) and then tube was closed and heated overnight at 80 °C. The next morning, the solvent was evaporated and the resulting crude product was purified via silica gel chromatography (0-2% EtOAc in hexanes) to yield the desired product.

Step 2: General Boc Deprotection Procedure*

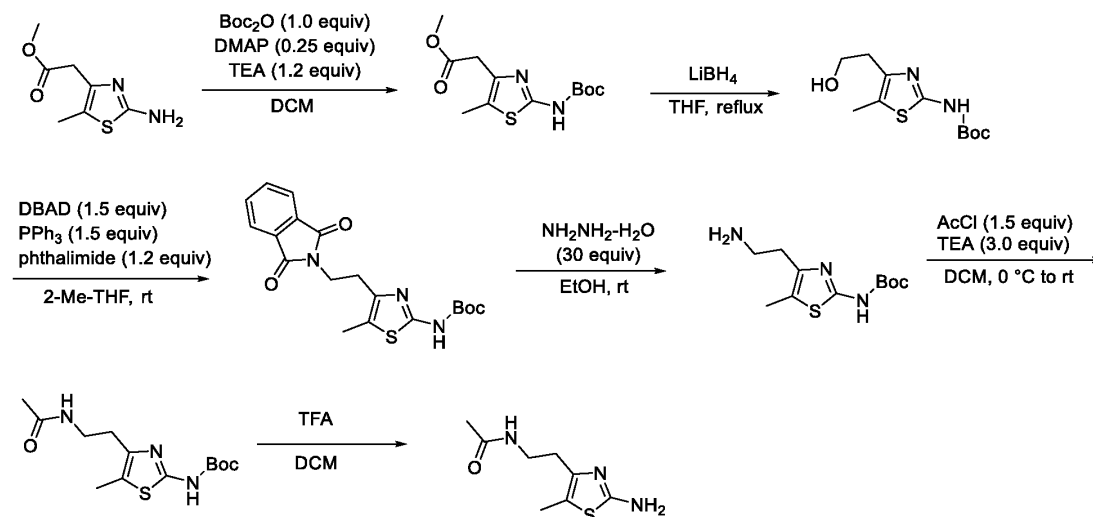
[00273] Tert-butyl (4-(phenylethynyl)thiazol-2-yl)carbamate (0.269 g, 0.96 mmol, 1.0 equiv) was dissolved in DCM (8.1 mL), and the solution was cooled to 0 °C. TFA (1.22 mL, 9.64 mmol, 10.0 eq) was added at 0 °C. TLC showed no reaction progress so another portion of TFA (1.22 mL, 9.64 mmol, 10.0 eq) was added after 2h. The reaction mixture was stirred at room temperature for the next 17 h. After this time, the reaction mixture was cooled down to 0 °C, basified with NaHCO₃ sat. solution (50 mL) and extracted with DCM (3x30 mL). The organic phases were combined, dried over MgSO₄, filtered and evaporated to dryness. Solid residues were washed with pentane and drop of DCM to obtain the desired product, which was used in the next reaction without further purification.

[00274] The following compounds were deprotected in a similar manner:

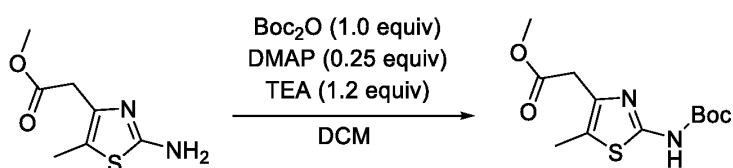
Intermediate for:	Compound Name
B22	N-(2-(2-amino-5-methylthiazol-4-yl)ethyl)acetamide
A96	4-((4-(ethylsulfonyl)piperazin-1-yl)methyl)thiazol-2-amine
A92	5-ethyl-4-((4-(ethylsulfonyl)piperazin-1-yl)methyl)thiazol-2-amine

Procedure 6 – Intermediate for B22

[00275] Synthesis of intermediate for B22 followed the scheme, below



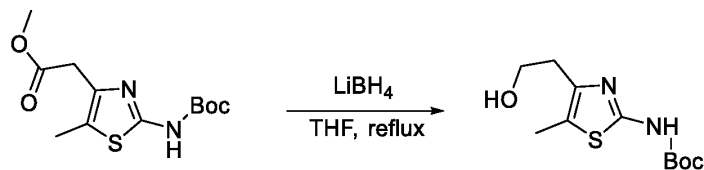
Step 1: General Boc Protection Procedure*



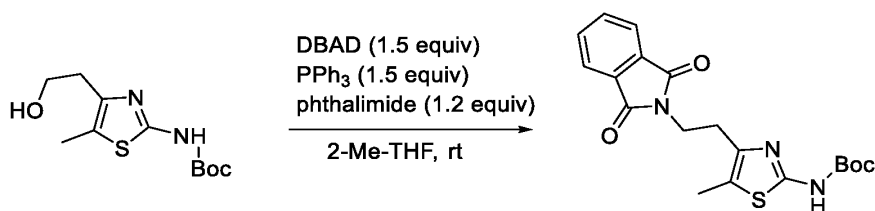
[00276] Methyl 2-(2-amino-5-methylthiazol-4-yl)acetate (1.0 g, 5.37 mmol, 1.0 eq.) was dissolved in DCM (10 mL), then di-tert-butyl dicarbonate (1.41 g, 6.44 mmol, 1.0 eq.) was added followed by TEA (0.90 mL, 6.44 mmol, 1.2 eq.) and DMAP (0.171 g, 1.34 mmol, 0.25 eq.). The reaction was stirred at room temperature overnight. The next morning, the reaction was diluted with DCM (50 mL) and washed with water (2x20 mL). The organic layer was dried over MgSO_4 , filtered and evaporated. The resulting crude material was purified by FC eluting with hexanes/EtOAc to yield the desired product.

[00277] The following compound was protected in a similar manner:

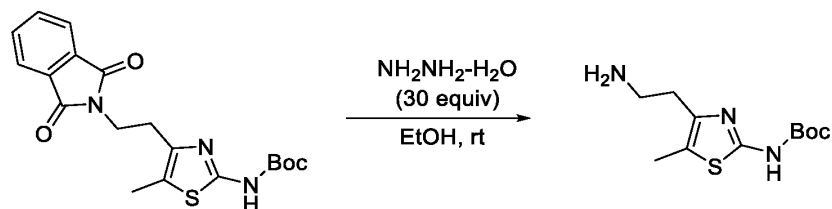
Intermediate for:	Compound Name
A92	methyl 2-((tert-butoxycarbonyl)amino)-5-ethylthiazole-4-carboxylate

Step 2: Ester Reduction

[00278] LiBH₄ in THF (0.3 mL, 2 N, 0.6 mmol, 0.6 eq) was added via syringe to a stirred solution of methyl 2-((tert-butoxycarbonyl)amino)-5-methylthiazol-4-yl)acetate (0.285 g, 1.0 mmol, 1.0 eq.) in anhydrous THF (2.0 mL). The reaction was then slowly heated to reflux (initial exotherm). Reaction was continued under reflux for 16 h. After this time, the reaction was cooled down to 0°C and quenched with water (10 mL). The aqueous layer was extracted with EtOAc (4 x 30 mL) and the organic layer was dried over MgSO₄, filtered and evaporated. The resulting crude product was purified by silica gel chromatography (EtOAc: hexane 1:9 to 2:1) to yield the desired product.

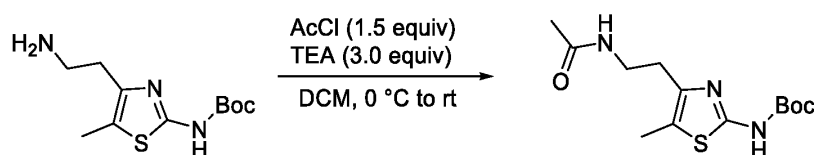
Step 3: Mitsunobu Reaction

[00279] Di-tert-butyl azodicarboxylate (0.319 g, 1.38 mmol, 1.5 eq.) was added portion-wise to a solution of starting material (0.207g, 0.92 mmol, 1.0 eq.), phthalimide (0.163g; 1.11 mmol, 1.2 eq.), and PPh₃ (0.363g, 1.38 mmol, 1.5 eq.) in Me-THF (10 mL) at room temperature under N₂ (g). The reaction mixture was stirred at room temperature overnight. The next morning, the solution was diluted with DCM (10 mL) and washed with 10 percent aqueous solution of K₂CO₃ (2 x 20 mL). The organic layer was dried over MgSO₄, filtered and evaporated to dryness. The resulting crude product was purified by silica gel chromatography (EtOAc: hexane 1:9 to 1:4) to yield the desired product.

Step 4: Phthalimide hydrolysis

[00280] Tert-butyl (4-(2-(1,3-dioxisoindolin-2-yl)ethyl)-5-methylthiazol-2-yl)carbamate (0.170 g, 1.0 eq.) was dissolved in 2 mL of EtOH. Then, hydrazine monohydrate (0.617 g, 30.0 eq.) was added at 0°C. Reaction was continued at room temperature for 17 hours. The resulting mixture was concentrated and then diluted with DCM (20 mL) and washed with water (2 x 10 mL). The organic layers were combined, dried over MgSO₄, filtered and concentrated in vacuo. The resulting crude product was used in the next step without further purification.

Step 5: Acetylation



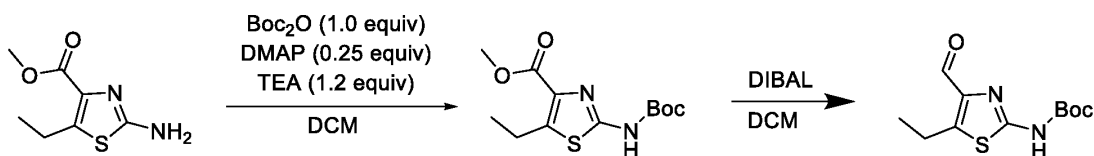
[00281] Tert-butyl (4-(2-aminoethyl)-5-methylthiazol-2-yl)carbamate (0.077 g, 0.30 mmol, 1.0 eq.) was dissolved in 2 mL of DCM. Then, TEA (0.125 mL, 0.90 mmol, 3.0 eq.) was added, followed by acetyl chloride (0.032 mL, 0.45 mmol, 1.5 eq.) at 0°C. The reaction was continued at room temperature for 17 hours. The resulting mixture was diluted with water (3 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. The resulting crude product was used to the next step without further purification.

Step 6: Boc Deprotection

[00282] See General Boc Deprotection Procedure, above.

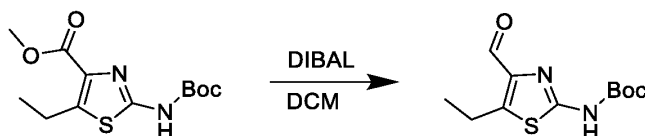
Procedure 7 - Intermediate for A92

[00283] Synthesis of intermediate for A92 followed the scheme, below.



Step 1: Boc Protection

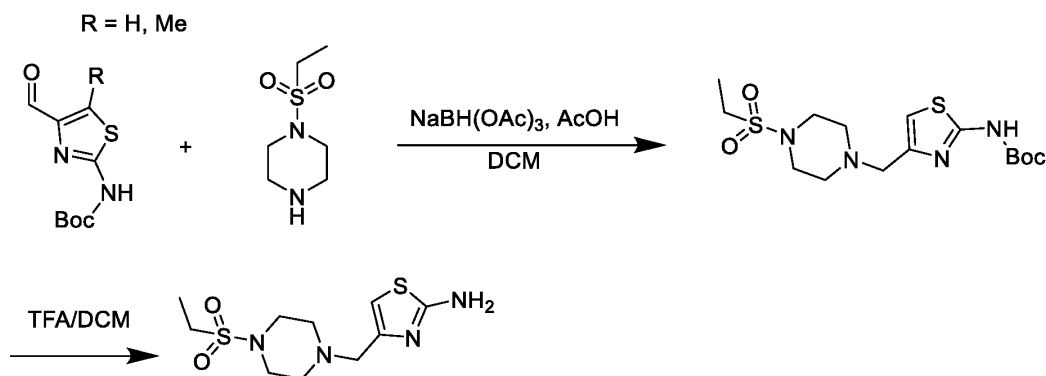
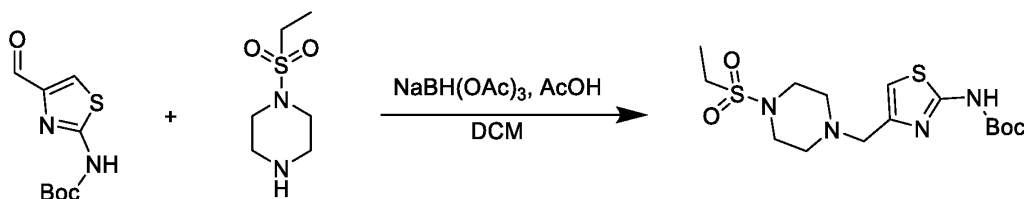
[00284] See General Boc Protection Procedure, above.

Step 2: DIBAL Reduction

[00285] Dried starting material (0.780 g, 2.72 mmol, 1.0 eq.) was dissolved in DCM (8 mL) and diisobutylaluminum hydride (1M in DCM, 8.17 mL, 8.17 mmol, 3.0 eq.) was added at -78°C to the solution. It was stirred for 5 h. After 5 h, the solution was quenched with methanol and 1N HCl. After the temperature of the reaction mixture was elevated to room temperature, water was added (15 mL) and extracted with DCM (3 x 20 mL). The organic layer was dried over MgSO₄, filtered and evaporated. The resulting crude product was used in the next step without further purification.

Procedure 8 - Intermediate for A96

[00286] Synthesis of intermediate for A96 followed the scheme, below

Step 1: Reductive Amination

[00287] To a stirred solution of 1-(ethanesulfonyl)piperazine (0.500g, 2.8 mmol, 1.0 equiv), in 7 mL of DCM at room temperature was added (4-formylthiazol-2-yl)carbamic acid tert-butyl ester (0.650g, 3.65 mmol, 1.3 equiv). The mixture was then treated with sodium triacetoxyborohydride (0.773g, 3.65 mmol, 1.3 equiv) and a catalytic amount of acetic acid. The reaction was allowed to stir for about 15 hours. The resulting mixture was diluted with NaHCO₃ (40 mL) and extracted with DCM (3 x 30 mL). The organic layers were combined,

dried over MgSO_4 , filtered and concentrated in vacuo. The resulting crude material was purified via silica gel chromatography (0-100% EtOAc in hexanes) to give desired product.

[00288] The following compounds were prepared in a similar manner:

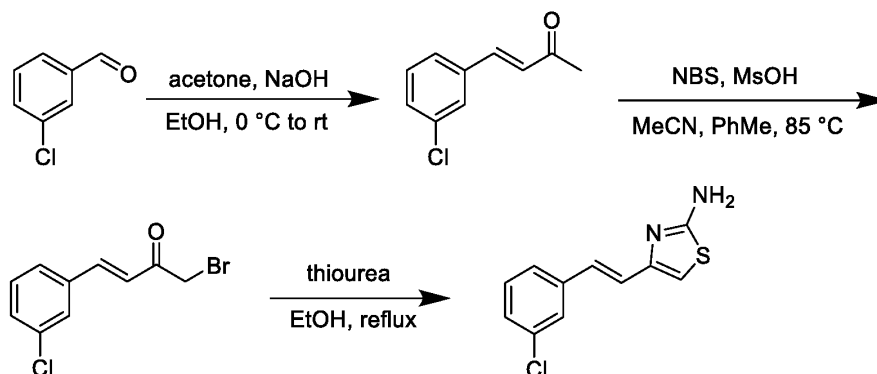
Intermediate for:	Compound Name
A92	tert-butyl (5-ethyl-4-((4-(ethylsulfonyl)piperazin-1-yl)methyl)thiazol-2-yl)carbamate

Step 2: Boc deprotection

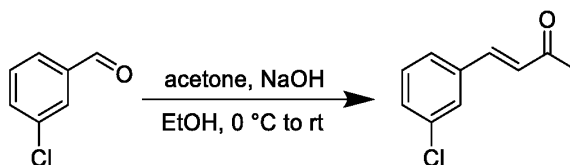
[00289] See General Boc Deprotection Procedure, above.

Procedure 9 - Intermediate for A209

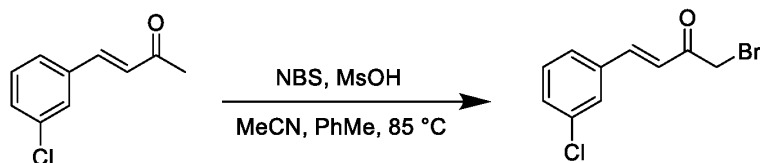
[00290] Synthesis of the intermediate for A209 was prepared according to the scheme, below:



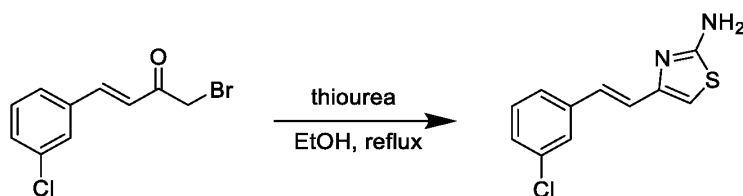
Step 1: Condensation



[00291] To a solution of NaOH solid (0.569 g, 14.23 mmol, 1.0 eq.) and acetone (4.22 mL, 56.9 mmol, 4.0 eq.) was added water and ethanol. The aldehyde (2.0 g, 14.23 mmol, 1.0 eq.) was added dropwise within 20 min at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred. TLC analysis indicated completion of the reaction after 2 h. After this time, the reaction mixture was quenched with aqueous HCl (1N), adjusted the pH to 6, and then evaporated to remove the residual ethanol. The residue was extracted by ethyl acetate (3 x 40 mL). The combined organic phase was washed with brine (2 x 15 mL), dried over MgSO_4 and concentrated under reduced pressure to yield the desired product, which was used without further purification in the next step.

Step 2: Bromination

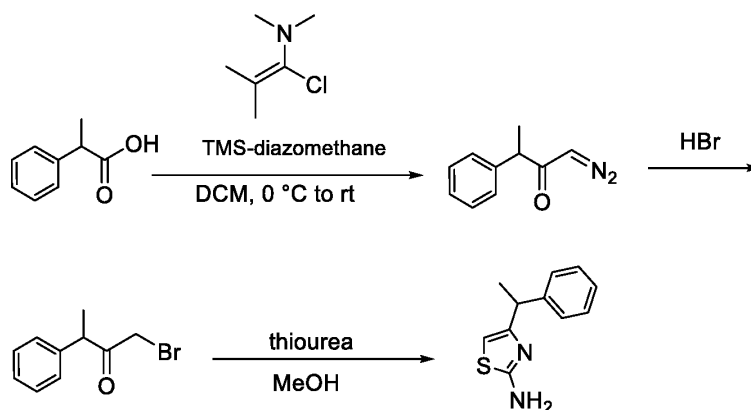
[00292] To a solution of enone (1.91 g, 10.57 mmol, 1.0 eq.) in 60 mL ACN:toluene (1:1) was added methanesulfonic acid (1.72 mL, 26.44 mmol, 2.5 eq.) and NBS (1.98g, 11.1 mmol, 1.05 eq.) and heated to 85°C for 6 hours. Sat. NaHCO₃ (70 mL) and EtOAc (4 x 30 mL) were added to the above mixture. The organic layer was separated, dried over magnesium sulfate and evaporated. The resulting crude material was purified via silica gel chromatography (0-25% EtOAc in hexanes) to yield the desired product.

Step 3: Thiazole condensation

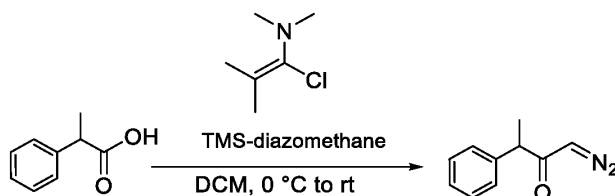
[00293] Thiourea (0.442g, 5.81 mmol, 1.1 eq.) was dissolved in absolute ethanol (20 mL). To this solution were added starting material (1.37g, 5.28 mmol, 1.0 eq.). The mixture was refluxed for 3 hours. After this time, the solution was cooled down, and the ethanol was evaporated. Water was added and the resulting solution was basified to pH 10. The aqueous layer was extracted with EtOAc (4 x 30 mL), and the combined organic layers were dried over MgSO₄, filtered and evaporated. The resulting crude product was used in the next step without further purification.

Procedure 10 - Synthesis of Intermediate for A21

[00294] Synthesis of intermediate for A21 followed the scheme, below

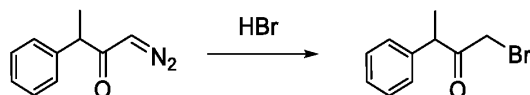


Step 1: Diazoketone formation

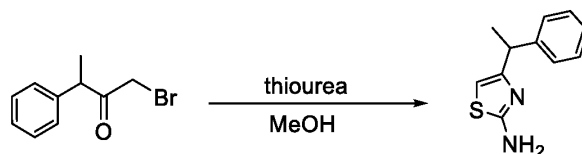


[00295] To a stirred solution of 2-phenylpropionic acid (1.0 g, 6.62 mmol, 1.0 eq) in DCM (20 mL) at 0 °C were added 4 Å molecular sieves and 1-chloro-N,N,2-trimethyl-1-propenylamine (0.99 mL, 7.54 mmol, 1.14 eq). After 15 min, the reaction mixture was cooled to -20 °C and slowly added to a solution of TMS-diazomethane (3.47 mL, 21.9 mmol, 2.9 eq) in DCM. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was filtered on a sintered funnel and the filtrate was quenched by the addition of saturated NH₄Cl (30 mL). The mixture was extracted with DCM (4 x 40 mL) and the organic layers were separated, and washed with brine. The organic layer was then dried with MgSO₄, filtered and concentrated to dryness. The resulting crude material was used in the next step without further purification.

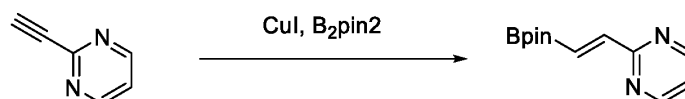
Step 2: Bromination



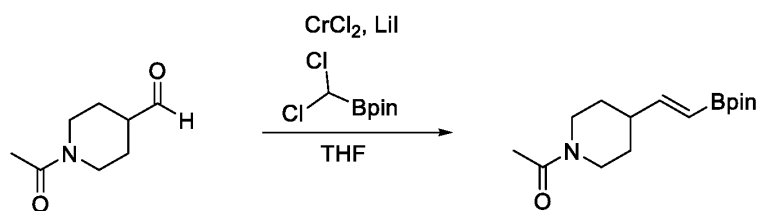
[00296] HBr (40% solution in water, 45 mL) was poured into the round-bottom flask containing crude diazoketone (1.5g, 8.56 mmol, 1.0 eq). The reaction mixture was allowed to be stirred at room temperature for 17 h. After this time, the reaction mixture was quenched with NaHCO₃ sat. solution (100 mL). The mixture was extracted with DCM (4 x 30 mL) and the organic layers were separated, washed with brine, dried with MgSO₄, filtered and concentrated to dryness. The resulting crude material was used without further purification.

Step 3: Thiazole condensation

[00297] To a solution of crude bromoketone (1.03g , 4.52 mmol, 1.0 eq) in MeOH (10.3 mL), thiourea (0.344g, 4.52 mmol, 1.0 eq) was added. The reaction mixture was allowed to be stirred overnight. LCMS analysis showed consumption of SM and formation of a new product. The next morning, the MeOH was evaporated and crude product was purified by preparatory HPLC (C18 column-prep Mobile phase: ACN + 0.1% FA, H₂O + 0.1% FA) to yield the desired product.

Procedure 11A – Precursor for Intermediate for A307

[00298] CuI (24.36 mg, 0.243 mmol, 0.05 eq.), XantPhos (140 mg, 0.243 mmol, 0.05 eq.), and NaOtBu (46.6 mg, 0.485 mmol, 0.10 eq.) were mixed in a dry THF (20 mL) in a flame dried Schlenk under argon. The reaction mixture was stirred at room temperature for 30 min. Then B₂pin₂ (1.35g, 5.34 mmol, 1.1 eq.) solution in dry THF (10 mL) was added to mixture and stirred for further 10 min. Then alkyne (500 mg, 4.85 mmol, 1.0 eq.), MeOH (0.441 mL, 9.709 mmol, 2 eq.), and dry THF (5 mL) were added successively. The resulting mixture was stirred for 18 h at room temperature, filtered through Celite and evaporated to dryness. The crude product was purified by column chromatography on silica (Hex/EtOAc) to yield pure product.

Procedure 11B – Precursor for Intermediate for A157

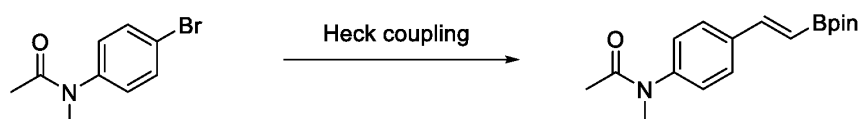
[00299] Anhydrous CrCl₂ (950 mg, 7.73 mmol, 8 eq.) was suspended in THF (10 mL) under an argon atmosphere. A solution of aldehyde (150 mg, 0.96 mmol, 1.0 eq.) and dichloromethylboronic ester (407 mg, 1.93 mmol, 2 eq.) in THF (5 mL) and a THF solution of Lil (517 mg, 3.86 mmol, 4 eq.) were added at 25 °C to the suspension successively. After being stirred at 25 °C for 16 h, the reaction mixture was poured into water (25 mL) and

extracted with ether (3x10 mL). The combined extracts were dried over Na₂SO₄ and concentrated. Crude product was pure enough to be used in the next step.

[00300] The following compounds were prepared via a similar method:

Precursor for Intermediate for	Compound name
A155	4,4,5,5-tetramethyl-2-(2-(tetrahydro-2H-pyran-2-yl)vinyl)-1,3,2-dioxaborolane
A254	2-(2-((1s,4s)-4-methoxycyclohexyl)vinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane
A253	2-(2-((1r,4r)-4-methoxycyclohexyl)vinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

Procedure 11C – Precursor for Intermediate for A245



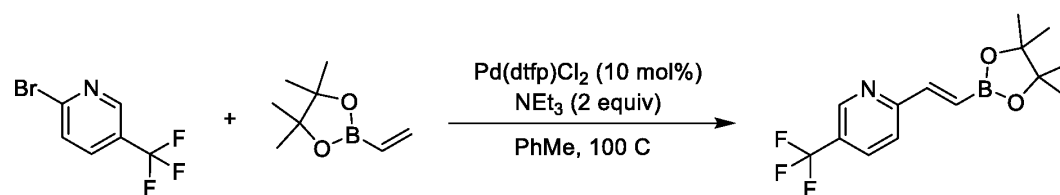
[00301] Aryl bromide (1.39 g, 6.09 mmol, 1.0 eq), vinyl boronic pinacol ester (1.06 ml, 6.09 mmol, 1.0 eq) and TEA (1.69 ml, 12.19 mmol, 2.0 eq) were dissolved in toluene (24.5 mL). The mixture was purged with argon for 5 min. After that time Pd(tBu₃P)₂ (0.156 g, 0.30 mmol, 0.05 eq) was added, and the reaction mixture was purged for 2 min with argon. The pressure vessel was closed, and the reaction was heated at 90 C for two hours. LCMS analysis showed consumption of starting material and formation of desired product. The reaction was cooled down to the room temperature and filtered through a plug of Celite. The filtrate was evaporated, and the desired product was recrystallized from Et₂O and washed with pentane. In case of necessity, additional purification by flash chromatography on silica (Hex/EtOAc) was performed.

[00302] The following compounds were prepared via a similar method:

Precursor for Intermediate for	Compound Name
A248	2-(4-cyclopropoxystyryl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane
A247	4,4,5,5-tetramethyl-2-(1-phenylprop-1-en-2-yl)-1,3,2-dioxaborolane
A246	N,N-dimethyl-4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzamide
A245	N-methyl-N-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl)acetamide
A241	2-(2-fluoro-4-methoxystyryl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane
A240	2-(3-fluoro-4-methoxystyryl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane
A150	5-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-1H-indole
A239	N-methyl-4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzamide
A237	6-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)quinoline
A236	2-(4-isopropoxystyryl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane
A235	2-(2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)vinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

Precursor for Intermediate for	Compound Name
A234	2-(2-(benzo[d][1,3]dioxol-5-yl)vinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane
A233	1-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl)piperidine
A232 and A222	2-(2-(furan-3-yl)vinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane
A230	4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl)morpholine
A229	N,N-dimethyl-4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)aniline
A151	1-methyl-5-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-1H-indole
A366 and A307	tert-butyl (4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)thiazol-2-yl)carbamate

Procedure 11D – Precursor for Intermediate for A343



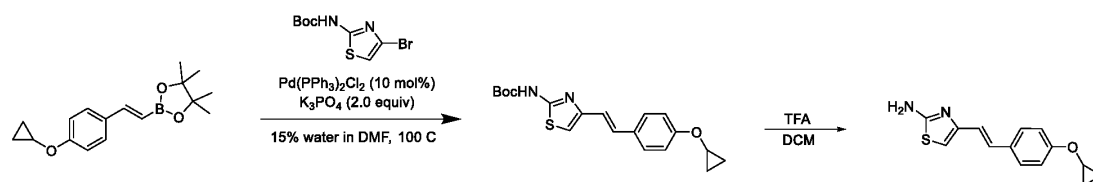
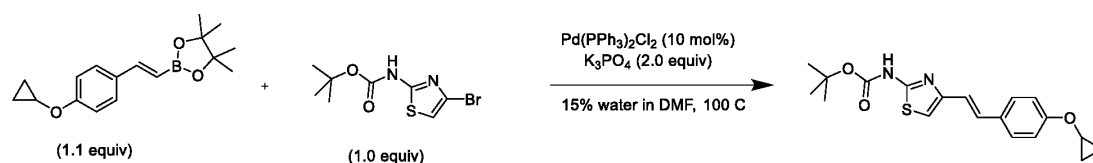
[00303] A 20 mL vial with stir bar was charged with bromide (1.3 g, 5.9 mmol, 1.0 equiv) and Pd(dtfp)Cl₂ (380 mg, 0.59 mmol, 0.1 equiv). The vial was evacuated and backflushed with nitrogen. Freshly-sparged toluene (5 mL) was added, followed by vinyl pinacol boronic ester (3.5 mL, 21 mmol, 3.5 equiv) and NEt₃ (1.6 mL, 12 mmol, 2.0 equiv). The vial was capped, and the reaction mixture was allowed to stir at 100 C overnight. The next morning, the reaction mixture was cooled to room temperature and diluted with EtOAc (100 mL). The organic layer was washed with brine (2 x 100 mL), and the combined aqueous layers were extracted with EtOAc (1 x 100 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting crude material was purified by either silica gel chromatography or RP-silica gel chromatography (C18) to yield the desired product.

[00304] The following compounds were prepared via a similar method:

Precursor for Intermediate for	Compound Name
A358	3,5-difluoro-2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)pyridine
A357	5-methyl-2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)pyridine
A356	2-methyl-6-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)pyridine
A347	3-methyl-2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)pyridine
A342	5-fluoro-2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)pyridine
A341	6-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)nicotinonitrile
A327	2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-5-(trifluoromethoxy)pyridine
A304	2-(4-cyclopropoxy-2-fluorostyryl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane
A299	3-fluoro-5-methoxy-2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)pyridine

Procedure 11E – Intermediate for A248 (Route A)

[00305] The reactions followed the general reaction scheme, below:

**Step 1A: Suzuki Coupling Procedure**

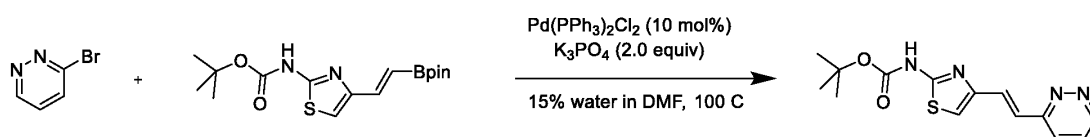
[00306] A vial with stir bar was charged with bromide (388 mg, 1.39 mmol, 1.0 equiv), boronic ester (437 mg, 1.53 mmol, 1.1 equiv), potassium phosphate (589 mg, 2.78 mmol, 2.0 equiv) and Pd(PPh₃)₂Cl₂ (97.4 mg, 0.139 mmol, 0.1 equiv). The vial was evacuated and backflushed with nitrogen. 15% water in DMF (sparged with nitrogen for 1 h, 4 mL, 0.4 M) was added. The vial was capped, and the reaction mixture was stirred at 100 °C overnight. The next morning, the reaction mixture was poured into EtOAc (50 mL) and washed with 1:1 water:brine (2 x 50 mL). The combined aqueous layers were extracted with EtOAc (1 x 50 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting crude material was purified by silica gel chromatography to yield the desired product.

[00307] The following compounds were prepared via the same method:

Intermediate for	Compound Name
A269	tert-butyl (4-(2-(5-methoxypyridin-2-yl)vinyl)thiazol-2-yl)carbamate
A155	tert-butyl (4-(2-(tetrahydro-2H-pyran-2-yl)vinyl)thiazol-2-yl)carbamate
A254	tert-butyl (4-(2-((1s,4s)-4-methoxycyclohexyl)vinyl)thiazol-2-yl)carbamate
A253	tert-butyl (4-(2-((1r,4r)-4-methoxycyclohexyl)vinyl)thiazol-2-yl)carbamate
A246	tert-butyl (4-(4-(dimethylcarbamoyl)styryl)thiazol-2-yl)carbamate
A245	tert-butyl (4-(4-(N-methylacetamido)styryl)thiazol-2-yl)carbamate
A157	tert-butyl (4-(2-(1-acetypiperidin-4-yl)vinyl)thiazol-2-yl)carbamate
A241	tert-butyl (4-(2-fluoro-4-methoxystyryl)thiazol-2-yl)carbamate
A240	tert-butyl (4-(3-fluoro-4-methoxystyryl)thiazol-2-yl)carbamate
A150	tert-butyl (4-(2-(1H-indol-5-yl)vinyl)thiazol-2-yl)carbamate
A239	tert-butyl (4-(4-(methylcarbamoyl)styryl)thiazol-2-yl)carbamate
A237	tert-butyl (4-(2-(quinolin-6-yl)vinyl)thiazol-2-yl)carbamate
A230	tert-butyl (4-(4-morpholinostyryl)thiazol-2-yl)carbamate

Intermediate for	Compound Name
A151	tert-butyl (4-(2-(1-methyl-1H-indol-5-yl)vinyl)thiazol-2-yl)carbamate
A217 and A218	tert-butyl (4-(3-phenylprop-1-en-1-yl)thiazol-2-yl)carbamate
A222 and A232	tert-butyl (4-(2-(furan-3-yl)vinyl)thiazol-2-yl)carbamate
A234	tert-butyl (4-(2-(benzo[d][1,3]dioxol-5-yl)vinyl)thiazol-2-yl)carbamate
A235	tert-butyl (4-(2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)vinyl)thiazol-2-yl)carbamate
A236	tert-butyl (4-(4-isopropoxystyryl)thiazol-2-yl)carbamate
A242	tert-butyl (4-(1H-inden-2-yl)thiazol-2-yl)carbamate
A244	tert-butyl (4-(2-(cyclohex-1-en-1-yl)vinyl)thiazol-2-yl)carbamate
A247	tert-butyl (4-(1-phenylprop-1-en-2-yl)thiazol-2-yl)carbamate
A248	tert-butyl (4-(4-cyclopropoxystyryl)thiazol-2-yl)carbamate
A249	tert-butyl (4-(1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)thiazol-2-yl)carbamate
A258	tert-butyl (4-(1-phenyl-1,2,3,6-tetrahydropyridin-4-yl)thiazol-2-yl)carbamate
A259	tert-butyl (4-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)thiazol-2-yl)carbamate
A327	tert-butyl (4-(2-(5-(trifluoromethoxy)pyridin-2-yl)vinyl)thiazol-2-yl)carbamate
A341	tert-butyl (4-(2-(5-cyanopyridin-2-yl)vinyl)thiazol-2-yl)carbamate
A342	tert-butyl (4-(2-(5-fluoropyridin-2-yl)vinyl)thiazol-2-yl)carbamate
A343	tert-butyl (4-(2-(5-(trifluoromethyl)pyridin-2-yl)vinyl)thiazol-2-yl)carbamate
A272	tert-butyl (4-(2-([1,3]dioxolo[4,5-b]pyridin-5-yl)vinyl)thiazol-2-yl)carbamate
A274	tert-butyl (4-(2-([1,3]dioxolo[4,5-b]pyridin-6-yl)vinyl)thiazol-2-yl)carbamate
A294	tert-butyl (4-(1,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)thiazol-2-yl)carbamate
A229	tert-butyl (4-(4-(dimethylamino)styryl)thiazol-2-yl)carbamate
A233	tert-butyl (4-(4-(piperidin-1-yl)styryl)thiazol-2-yl)carbamate
A223	tert-butyl (4-(4-acetamidostyryl)thiazol-2-yl)carbamate
A299	tert-butyl (4-(2-(3-fluoro-5-methoxypyridin-2-yl)vinyl)thiazol-2-yl)carbamate
A304	tert-butyl (4-(4-cyclopropoxy-2-fluorostyryl)thiazol-2-yl)carbamate
A347	tert-butyl (4-(2-(3-methylpyridin-2-yl)vinyl)thiazol-2-yl)carbamate
A356	tert-butyl (4-(2-(6-methylpyridin-2-yl)vinyl)thiazol-2-yl)carbamate
A357	tert-butyl (4-(2-(5-methylpyridin-2-yl)vinyl)thiazol-2-yl)carbamate
A358	tert-butyl (4-(2-(3,5-difluoropyridin-2-yl)vinyl)thiazol-2-yl)carbamate

Step 1A: Reverse Suzuki Coupling



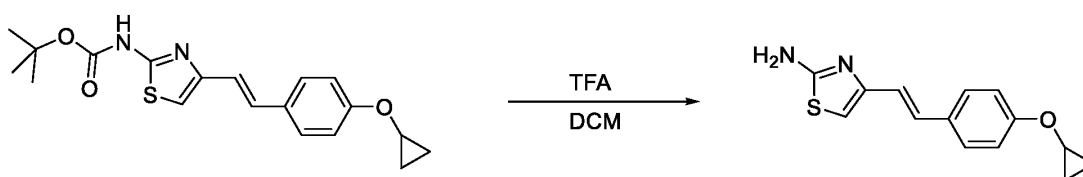
[00308] A vial with stir bar was charged with bromide (51.7 mg, 0.325 mmol, 1.0 equiv), boronic ester (126 mg, 0.358 mmol, 1.1 equiv), K_3PO_4 (138 mg, 0.650 mmol, 2.0 equiv) and $Pd(PPh_3)_2Cl_2$ (22.8 mg, 0.0325 mmol, 0.1 equiv). The vial was evacuated and backflushed with nitrogen. Freshly-sparged 15% water in DMF (2 mL) was added, and the vial was capped. The reaction mixture was stirred at 100 °C for 2 h. After 2 h, the reaction mixture was cooled to room temperature and poured into EtOAc (50 mL). The resulting solution was

washed with brine (2 x 50 mL), and the combined aqueous layers were extracted with EtOAc (1 x 50 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting crude material was purified via silica gel chromatography.

[00309] The following compounds were prepared via a similar method:

Intermediate for	Compound Name
A307	tert-butyl (4-(2-(pyrimidin-2-yl)vinyl)thiazol-2-yl)carbamate

Step 2: Boc Deprotection



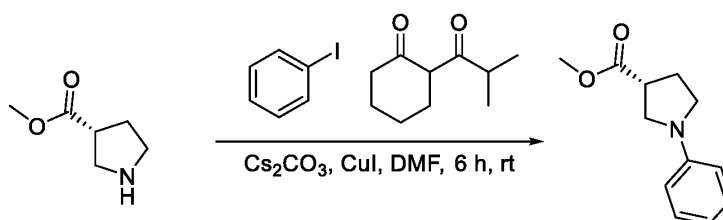
[00310] A 20 mL vial with stir bar was charged with carbamate (270 mg, 0.753 mmol, 1.0 equiv) and DCM (4 mL). TFA (1 mL, 13 mmol, 17 equiv) was added, and the reaction mixture was stirred at room temperature overnight. The next morning, the reaction mixture was poured into DCM (50 mL) and washed with saturated NaHCO₃ (2 x 50 mL). The combined aqueous layers were extracted with DCM (1 x 50 mL), and the combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting material was used in the next step without further purification.

[00311] The following compounds were prepared via a similar method:

Intermediate for	Compound Name
A269	4-(2-(5-methoxypyridin-2-yl)vinyl)thiazol-2-amine
A155	4-(2-(tetrahydro-2H-pyran-2-yl)vinyl)thiazol-2-amine
A254	4-(2-((1s,4s)-4-methoxycyclohexyl)vinyl)thiazol-2-amine
A253	4-(2-((1r,4r)-4-methoxycyclohexyl)vinyl)thiazol-2-amine
A246	4-(2-(2-aminothiazol-4-yl)vinyl)-N,N-dimethylbenzamide
A245	N-(4-(2-(2-aminothiazol-4-yl)vinyl)phenyl)-N-methylacetamide
A157	1-(4-(2-(2-aminothiazol-4-yl)vinyl)piperidin-1-yl)ethan-1-one
A241	4-(2-fluoro-4-methoxystyryl)thiazol-2-amine
A240	4-(3-fluoro-4-methoxystyryl)thiazol-2-amine
A150	4-(2-(1H-indol-5-yl)vinyl)thiazol-2-amine
A239	4-(2-(2-aminothiazol-4-yl)vinyl)-N-methylbenzamide
A237	4-(2-(quinolin-6-yl)vinyl)thiazol-2-amine
A230	4-(4-morpholinostyryl)thiazol-2-amine
A151	4-(2-(1-methyl-1H-indol-5-yl)vinyl)thiazol-2-amine
A217 and A218	4-(3-phenylprop-1-en-1-yl)thiazol-2-amine

Intermediate for	Compound Name
A222 and A232	4-(2-(furan-3-yl)vinyl)thiazol-2-amine
A234	4-(2-(benzo[d][1,3]dioxol-5-yl)vinyl)thiazol-2-amine
A235	4-(2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)vinyl)thiazol-2-amine
A236	4-(4-isopropoxystyryl)thiazol-2-amine
A242	4-(1H-inden-2-yl)thiazol-2-amine
A244	4-(2-(cyclohex-1-en-1-yl)vinyl)thiazol-2-amine
A247	4-(1-phenylprop-1-en-2-yl)thiazol-2-amine
A248	4-(4-cyclopropoxystyryl)thiazol-2-amine
A249	4-(1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)thiazol-2-amine
A258	4-(1-phenyl-1,2,3,6-tetrahydropyridin-4-yl)thiazol-2-amine
A259	4-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)thiazol-2-amine
A327	4-(2-(5-(trifluoromethoxy)pyridin-2-yl)vinyl)thiazol-2-amine
A341	6-(2-(2-aminothiazol-4-yl)vinyl)nicotinonitrile
A342	4-(2-(5-fluoropyridin-2-yl)vinyl)thiazol-2-amine
A343	4-(2-(5-(trifluoromethyl)pyridin-2-yl)vinyl)thiazol-2-amine
A272	4-(2-([1,3]dioxolo[4,5-b]pyridin-5-yl)vinyl)thiazol-2-amine
A274	4-(2-([1,3]dioxolo[4,5-b]pyridin-6-yl)vinyl)thiazol-2-amine
A294	4-(1,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)thiazol-2-amine
A366	4-(2-(pyridazin-3-yl)vinyl)thiazol-2-amine
A229	4-(4-(dimethylamino)styryl)thiazol-2-amine
A233	4-(4-(piperidin-1-yl)styryl)thiazol-2-amine
A307	4-(2-(pyrimidin-2-yl)vinyl)thiazol-2-amine
A223	N-(4-(2-(2-aminothiazol-4-yl)vinyl)phenyl)acetamide
A299	4-(2-(3-fluoro-5-methoxypyridin-2-yl)vinyl)thiazol-2-amine
A304	4-(4-cyclopropoxy-2-fluorostyryl)thiazol-2-amine
A347	4-(2-(3-methylpyridin-2-yl)vinyl)thiazol-2-amine
A356	4-(2-(6-methylpyridin-2-yl)vinyl)thiazol-2-amine
A357	4-(2-(5-methylpyridin-2-yl)vinyl)thiazol-2-amine
A358	4-(2-(3,5-difluoropyridin-2-yl)vinyl)thiazol-2-amine

Procedure 12A – Precursor for Intermediate for A289



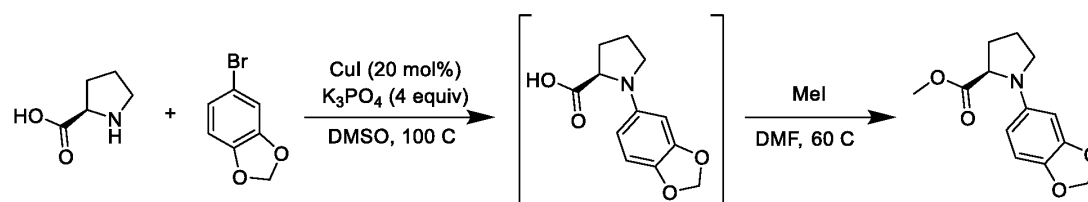
[00312] A 100 mL roundbottom flask with stir bar was charged with D-proline ester (1.00 g, 7.7 mmol, 1.00 equiv), iodobenzene (1.90 g, 9.3 mmol, 1.2 equiv), 2-(2-methylpropanoyl)cyclohexan-1-one (521 mg, 3.1 mmol, 0.4 equiv), Cs_2CO_3 (7.57 g, 23.227 mmol, 3 equiv), CuI (147.45 mg, 0.774 mmol, 0.1 equiv) and DMF (30 mL, 0.26 M) under nitrogen atmosphere, the vial was capped and placed in an 50°C bath. The reaction mixture was stirred at 50°C overnight. The next morning, the reaction mixture was poured into DCM

(200 mL) and washed with brine (3 x 100 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting crude material was purified via silica gel chromatography to yield the desired product.

[00313] The following compounds were prepared via a similar method:

Precursor for Intermediate for	Compound name
A290	methyl (R)-1-phenylpyrrolidine-3-carboxylate

Procedure 12B – Precursor for Intermediate for A359

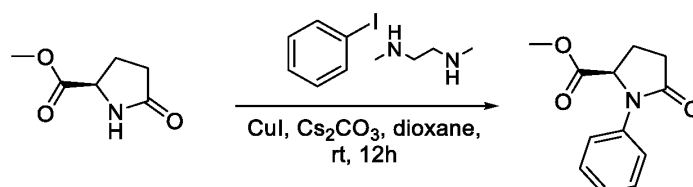


[00314] A 40 mL vial with stir bar was charged with D-proline (1.43 g, 12.4 mmol, 2.5 equiv), aryl bromide (1.00 g, 4.97 mmol, 1.0 equiv), CuI (189 mg, 0.994 mmol, 0.2 equiv) and K₃PO₄ (4.22 g, 19.9 mmol, 4.0 equiv). The vial was evacuated and backflushed with nitrogen. Freshly-sparged DMSO (6 mL) was added. The vial was capped, and the reaction mixture was allowed to stir at 100 °C overnight. The next morning, the reaction mixture was cooled to 60 °C and diluted with DMF (10 mL). MeI (1.55 mL, 24.8 mmol, 5.0 equiv) was added, and the reaction mixture was allowed to stir at 60 °C for 2 h. After 2 h, the reaction mixture was poured into EtOAc (150 mL) and washed with brine (2 x 150 mL). The combined aqueous layers were extracted with EtOAc (1 x 50 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting crude material was purified via silica gel chromatography to yield the desired product.

[00315] The following compounds were prepared via a similar method:

Precursor for Intermediate for	Compound name
A328	methyl (2,2-difluorobenzo[d][1,3]dioxol-5-yl)-D-prolinate

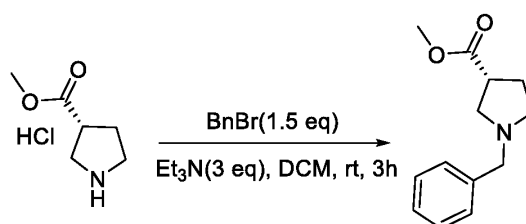
Procedure 12C – Precursor for Intermediate for A319



[00316] A 100 mL roundbottom flask with stir bar was charged with D-proline ester (500 mg, 3.2 mmol, 1.00 equiv), iodobenzene (649 mg, 3.181 mmol, 1.00 equiv), methyl[2-

(methylamino)ethyl]amine (280 mg, 3.2 mmol, 1 equiv), CuI (303 mg, 1.6 mmol, 0.5 equiv), Cs₂CO₃ (2.59 g, 8.0 mmol, 2.5 equiv) and dioxane (20 mL, 0.16 M) under nitrogen atmosphere, the vial was capped and placed in an 25°C bath. The reaction mixture was stirred at 25°C overnight. The next morning, the reaction mixture was poured into DCM (80 mL) and washed with brine (2 x 40 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting crude material was purified via silica gel chromatography to yield the desired product.

Procedure 12D – Procedure for Intermediate for A279

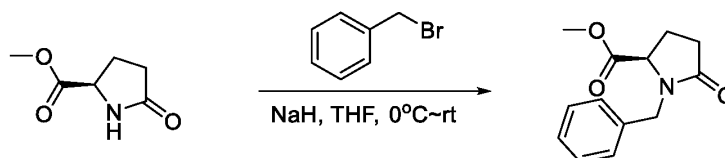


[00317] A 100 mL roundbottom flask with stir bar was charged with pyrrolidine ester (1.50 g, 11.6 mmol, 1.00 equiv), TEA (3.53 g, 34 mmol, 3.00 equiv) and DCM (20 mL, 0.58 M). Benzyl bromide (2.38 g, 14.0 mmol, 1.20 equiv) was added, and the vial was capped and placed in a 25°C bath. The reaction mixture was stirred at 25°C for 2 h. The reaction mixture was poured into DCM (50 mL) and washed with H₂O (3 x 50 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting crude material was purified via silica gel chromatography to yield the desired product.

[00318] The following compounds were prepared via a similar method:

Precursor for Intermediate for	Compound Name
A277	methyl benzyl-D-prolinate
A278	methyl benzyl-L-prolinate
A291	methyl (R)-1-benzylpyrrolidine-3-carboxylate
A302	methyl 1-benzylpiperidine-4-carboxylate

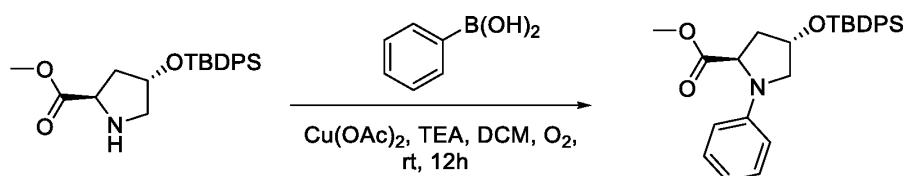
Procedure 12E – Precursor for Intermediate for A320



[00319] A 50 mL roundbottom flask with stir bar was charged with D-proline ester (880 mg, 6.1 mmol, 1.00 equiv), benzyl bromide (1.15 g, 6.7 mmol, 1.09 equiv) and THF (12 mL, 0.51 M). NaH (60%, 369 mg, 9.2 mmol, 1.5 equiv) was added in portions at 0°C. The vial was capped and placed in an 25°C bath. The reaction mixture was stirred at 25°C for 5h.

The reaction mixture was quenched by NH_4Cl (aq) (25 mL). The resulting solution was extracted with ethyl acetate (3 x 30 mL) and washed with brine (2 x 30 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated in vacuo. The resulting crude material was purified via silica gel chromatography to yield the desired product.

Procedure 12F – Precursor for Intermediate for A323

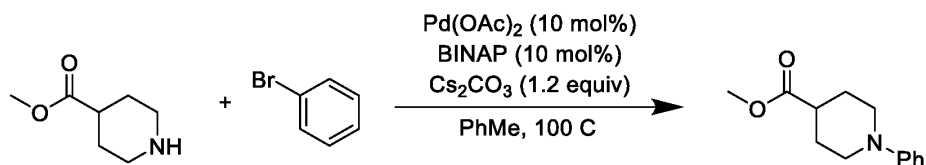


[00320] A 100 mL roundbottom flask with stir bar was charged with pyrrolidine ester (2.00 g, 4.4 mmol, 1.00 equiv), phenyl boronic acid (1.59 g, 13.0 mmol, 3 equiv), $\text{Cu}(\text{OAc})_2$ (2.37 g, 13.0 mmol, 3 equiv), TEA (2.20 g, 21.8 mmol, 5 equiv) and DCM (30 mL, 0.15 M) under nitrogen atmosphere. The reaction flask was then vacuumed and flushed with oxygen, and the sequence was repeated twice. The vial was capped and placed in a 25°C bath. The reaction mixture was stirred at 25°C for 48 h under oxygen atmosphere using an oxygen balloon. The reaction mixture was poured into DCM (150 mL) and quenched by the addition of $\text{NH}_3 \cdot \text{H}_2\text{O}$ (20 mL), washed with H_2O (1 x 50 mL) and brine (3 x 50 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated in vacuo. The resulting crude material was purified via silica gel chromatography to yield the desired product.

[00321] The following compounds were prepared via a similar method:

Precursor for Intermediate for	Compound Name
A332	methyl (R)-1-phenylpiperidine-2-carboxylate
A333	methyl (2R,4S)-4-methoxy-1-phenylpyrrolidine-2-carboxylate
A334	methyl (2R,3S)-3-methoxy-1-phenylpyrrolidine-2-carboxylate
A336	methyl (R)-1-phenylazetidine-2-carboxylate
A337	methyl (R)-4-phenylmorpholine-3-carboxylate
A339	methyl (R)-4,4-difluoro-1-phenylpyrrolidine-2-carboxylate
A344 and A352	methyl (2R,3S)-3-((tert-butyldiphenylsilyl)oxy)-1-phenylpyrrolidine-2-carboxylate
A345	methyl (2R,3R)-3-methoxy-1-phenylpyrrolidine-2-carboxylate
A346	methyl (2R,4R)-4-isopropoxy-1-phenylpyrrolidine-2-carboxylate
A351 and A353	methyl (2R,3R)-3-((tert-butyldiphenylsilyl)oxy)-1-phenylpyrrolidine-2-carboxylate
A354	methyl (2R,4R)-4-(cyclohexyloxy)-1-phenylpyrrolidine-2-carboxylate
A306	methyl 1-phenylpiperidine-3-carboxylate
A338	methyl (R)-2-methyl-1-phenylpyrrolidine-2-carboxylate

Procedure 12G – Precursor for Intermediate for A285

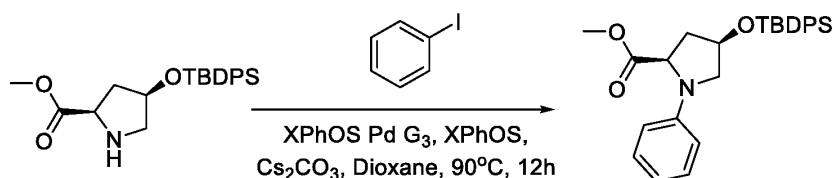


[00322] A vial with stir bar was charged with amine (1.4 g, 9.7 mmol, 1.2 equiv), Cs_2CO_3 (3.2 g, 9.7 mmol, 1.2 equiv), $\text{Pd}(\text{OAc})_2$ (180 mg, 0.81 mmol, 0.1 equiv), and BINAP (510 mg, 0.81 mmol, 0.1 equiv). The vial was evacuated and backflushed with nitrogen. Freshly sparged toluene (15 mL) was added, followed by bromobenzene (0.85 mL, 8.1 mmol, 1.0 equiv). The reaction mixture was capped and allowed to stir at 100 °C overnight. The next morning, the reaction mixture was cooled to room temperature and poured into EtOAc (100 mL). The organic layer was washed with brine (2 x 100 mL) and the combined aqueous layers were extracted with EtOAc (1 x 100 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated in vacuo. The resulting crude material was purified via silica gel chromatography to yield the desired product.

[00323] The following compounds were prepared via a similar method:

Precursor for Intermediate for	Compound name
A315	methyl 1-(5-methoxypyridin-2-yl)azetidine-3-carboxylate
A361	methyl (2,2-difluorobenzo[d][1,3]dioxol-4-yl)-D-prolinate
A362	methyl benzo[d][1,3]dioxol-4-yl-D-prolinate

Procedure 12H – Precursor for Intermediate for A322

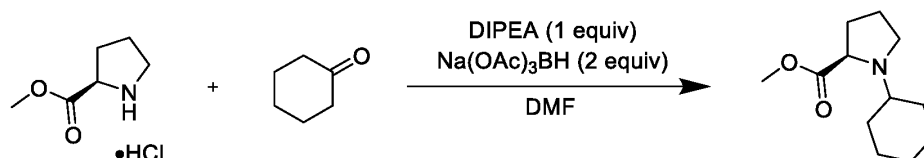


[00324] A 250 mL roundbottom flask with stir bar was charged with pyrrolidine ester (2.40 g, 6.257 mmol, 1.00 equiv), iodobenzene (1.91 g, 9.362 mmol, 1.50 equiv), Cs_2CO_3 (6.10 g, 18.722 mmol, 2.99 equiv), XPhOS (595.00 mg, 1.248 mmol, 0.20 equiv), XPhOS Pd G3 (1.06 g, 1.252 mmol, 0.20 equiv) and dioxane (20 mL, 0.16 M) under nitrogen atmosphere, the vial was capped and placed in an 90°C bath. The reaction mixture was stirred at 90°C overnight. The next morning, the reaction mixture was cooled to room temperature and quenched by H_2O (50 mL). The resulting solution was extracted with (3 x 50 mL) of ethyl acetate. The combined organic layers were dried over Na_2SO_4 , filtered and concentrated in vacuo. The resulting crude material was purified via prep-TLC to yield the desired product.

[00325] The following compounds were prepared via a similar method:

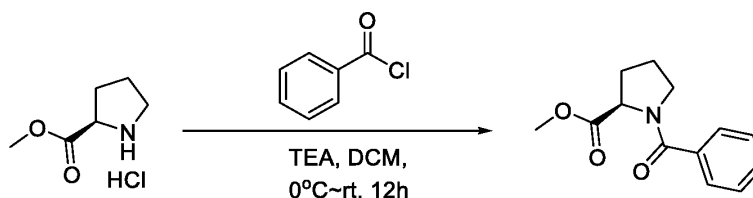
Precursor for Intermediate for	Compound Name
A323 and A326	methyl (2R,4S)-4-((tert-butyldiphenylsilyl)oxy)-1-phenylpyrrolidine-2-carboxylate
A322 and A321	methyl (2R,4R)-4-((tert-butyldiphenylsilyl)oxy)-1-phenylpyrrolidine-2-carboxylate

Procedure 12I – Precursor for Intermediate for A365



[00326] A vial with stir bar was charged with methyl D-proline hydrochloride (100 mg, 0.604 mmol, 1.0 equiv), DIPEA (0.11 mL, 0.604 mmol, 1.0 equiv), cyclohexanone (62.6 μ L, 0.604 mmol, 1.0 equiv) and DMF (1 mL). The reaction mixture was cooled to 0 °C. $\text{Na}(\text{OAc})_3\text{BH}$ () was added, and the reaction mixture was allowed to warm to room temperature overnight. The next morning, the reaction mixture was diluted with EtOAc (50 mL) and washed with saturated NaHCO_3 (3 x 50 mL). The combined aqueous layers were extracted with EtOAc (1 x 50 mL), and the combined organic layers were dried over Na_2SO_4 , filtered and concentrated in vacuo. The resulting material was used without further purification in the next step.

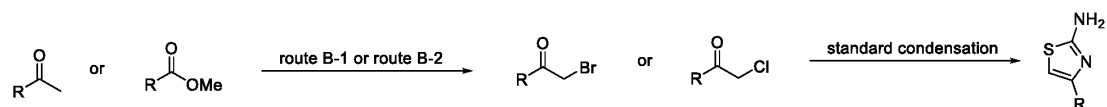
Procedure 12J – Precursor for Intermediate for A313



[00327] A 250 mL roundbottom flask with stir bar was charged with pyrrolidine ester (4.00 g, 24 mmol, 1.00 equiv), TEA (8.40 mL, 60 mmol, 2.50 equiv) and DCM (100 mL, 0.24 M). Benzoyl chloride (2.8 mL, 24 mmol, 1.01 eq) was added, and the vial was capped and placed in a 0°C bath. The reaction mixture was stirred at 25°C overnight. The next morning, the reaction mixture was poured into DCM (50 mL) and washed with H_2O (2 x 70 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated in vacuo. The resulting crude material was purified via silica gel chromatography to yield the desired product.

Procedure 12K – Synthesis of Intermediates via Halogenation (e.g., for A163, A154, A158, & A292) (Route B)

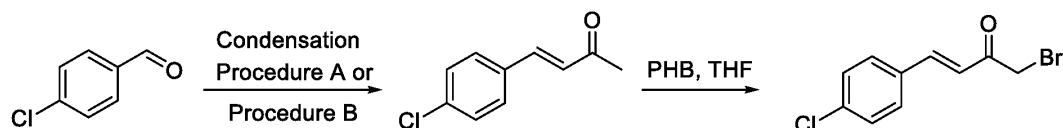
[00328] The reactions followed the general reaction scheme, below:



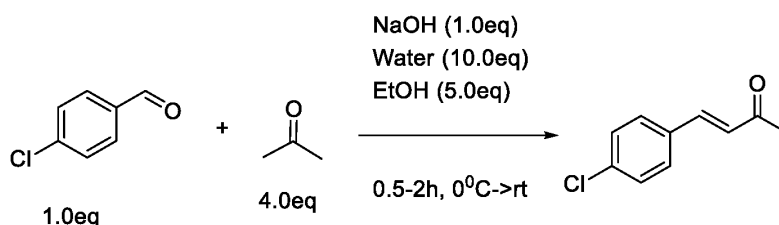
[00329] In accordance with this procedure, compounds having a single stereocenter were prepared and evaluated as a single enantiomer. Unless indicated otherwise, compounds having two stereocenters were prepared and evaluated as a single diastereomer, but as a mixture of enantiomers. Each of compounds A321-A323, A325, A326, A333, A334, A344-A346, and A351-A354 (having two stereocenters) were prepared and evaluated as pure diastereomers and pure enantiomers.

Step 1A: Route B-1 (Bromoketone Synthesis)

[00330] Route B-1 followed the general reaction scheme, below:



Condensation Procedure A

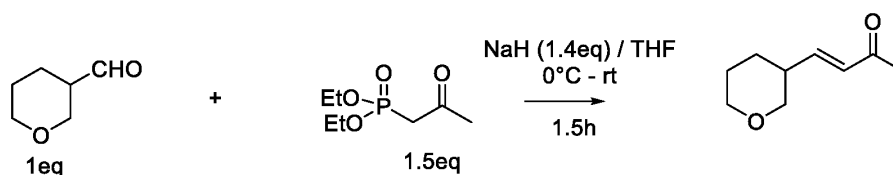


[00331] Solid NaOH (0.356g, 8.89mmol, 1.0eq) was dissolved in the mixture of acetone (2.63mL, 35.57mmol, 4.0eq), water (12.5mL) and EtOH (6.3mL). Then the 4-chlorobenzaldehyde (1.250g, 8.89mmol, 1.0eq) was added dropwise within 20 min at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred until TLC analysis indicated completion of the reaction (0.5-2 h). The reaction mixture was quenched with aqueous HCl (1 N), adjusted the pH to 6 and evaporated to remove the residual EtOH and acetone. The residue was extracted by EtOAc (3 × 40 mL). The combined organic phases were washed with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Crude product was purified by column chromatography on silica gel.

[00332] The following compounds were prepared via a similar method:

Intermediate for	Compound name
A161	4-(2-chlorophenyl)but-3-en-2-one
A159	4-(3-methoxyphenyl)but-3-en-2-one
A160	4-(4-methoxyphenyl)but-3-en-2-one
A152	4-cyclohexylbut-3-en-2-one
A219	4-(4-(trifluoromethyl)phenyl)but-3-en-2-one
A220	4-(4-fluorophenyl)but-3-en-2-one
A224 and A231	4-(3-oxobut-1-en-1-yl)benzonitrile
A227	4-(4-nitrophenyl)but-3-en-2-one
A251	5-phenylhex-3-en-2-one
A252	4-phenylpent-3-en-2-one
A297	1-phenylpent-1-en-3-one
A209	4-(3-chlorophenyl)but-3-en-2-one
A163	4-(4-chlorophenyl)but-3-en-2-one
A223	N-(4-(3-oxobut-1-en-1-yl)phenyl)acetamide

Condensation Procedure B



[00333] Diethyl (2-oxopropyl)-phosphonate (1.34 mL, 6.97 mmol, 1.5 equiv) was added to a slurry of NaH (250 mg of a 60 % mineral oil suspension, 6.51 mmol, 1.4 equiv) in THF (10.3 mL) at 0°C, and stirred for 1 hr. Aldehyde (0.5ml, 4.65 mmol, 1.0 equiv) was added dropwise, the cooling bath was removed and the resulting solution stirred for an additional 1.5 hr at room temperature. H₂O (10 mL) was added and the layers were separated. The aqueous phase was extracted with Et₂O (3 x 10 mL), and the combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure. The crude residue was purified by flash chromatography.

[00334] The following compounds were prepared via a similar method:

Intermediate for	Compound name
A158	4-(2-methoxyphenyl)but-3-en-2-one
A153	4-(tetrahydro-2H-pyran-4-yl)but-3-en-2-one
A166	4-(pyridin-4-yl)but-3-en-2-one
A165	4-(pyridin-3-yl)but-3-en-2-one
A164	4-(pyridin-2-yl)but-3-en-2-one

Bromination

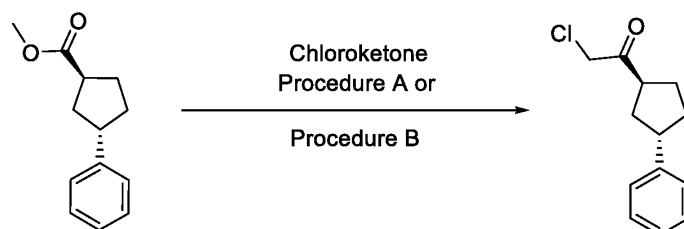
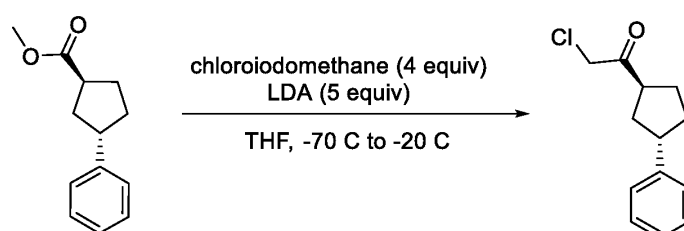
[00335] Ketone (730mg, 4.15 mmol, 1.0 equiv) was dissolved in dry THF (10ml) followed by slow (1h) dropwise addition of pyrrolidone hydrotribromide (2468 mg, 4.98 mmol, 1.2 equiv) in THF (15 ml). Reaction was stirred overnight at rt, the solid residue was filtered off and filtrate was evaporated. The oily residue was dissolved in Et₂O (50ml), washed with saturated NaHCO₃ (20ml), water (20ml) and brine (20ml). Organic layer was separated, dried by MgSO₄ and evaporated to yield crude product which was further purified by flash chromatography on silica gel.

[00336] The following compounds were prepared via a similar method:

Intermediate for	Compound Name
A161	1-bromo-4-(2-chlorophenyl)but-3-en-2-one
A159	1-bromo-4-(3-methoxyphenyl)but-3-en-2-one
A160	1-bromo-4-(4-methoxyphenyl)but-3-en-2-one
A154	1-bromo-4-(tetrahydro-2H-pyran-3-yl)but-3-en-2-one
A158	1-bromo-4-(2-methoxyphenyl)but-3-en-2-one
A152	1-bromo-4-cyclohexylbut-3-en-2-one
A153	1-bromo-4-(tetrahydro-2H-pyran-4-yl)but-3-en-2-one
A219	1-bromo-4-(4-(trifluoromethyl)phenyl)but-3-en-2-one
A220	1-bromo-4-(4-fluorophenyl)but-3-en-2-one
A166	1-bromo-4-(pyridin-4-yl)but-3-en-2-one
A224	4-(4-bromo-3-oxobut-1-en-1-yl)benzonitrile
A227	1-bromo-4-(4-nitrophenyl)but-3-en-2-one
A165	1-bromo-4-(pyridin-3-yl)but-3-en-2-one
A164	1-bromo-4-(pyridin-2-yl)but-3-en-2-one
A251	1-bromo-5-phenylhex-3-en-2-one
A252	1-bromo-4-phenylpent-3-en-2-one
A297	4-bromo-1-phenylpent-1-en-3-one
A209	1-bromo-4-(3-chlorophenyl)but-3-en-2-one
A163	1-bromo-4-(4-chlorophenyl)but-3-en-2-one
A225	1-bromo-3,3-dimethyl-5-phenylpentan-2-one
A228	1-bromo-3,3-dimethyl-4-phenoxybutan-2-one
A257	1-bromo-3-methyl-3-(pyridin-2-ylmethoxy)butan-2-one
A260	1-bromo-3,3-dimethyl-4-(pyridin-2-yloxy)butan-2-one
A215 and A194	2-bromo-1-((1S,2S)-2-phenylcyclopropyl)ethan-1-one
A223	N-(4-(4-bromo-3-oxobut-1-en-1-yl)phenyl)acetamide

Step 1B: Route B-2 (Chloroketone Synthesis)

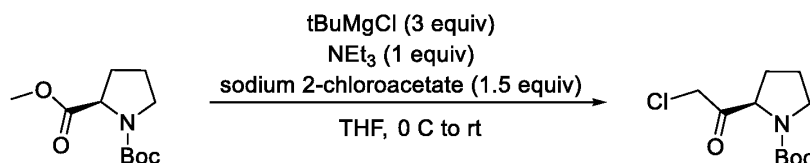
[00337] Route B-2 followed the general reaction scheme, below:

Chloroketone Procedure A

[00338] A roundbottom flask with stir bar was charged with starting material (0.50 g, 2.45 mmol, 1.0 equiv) dissolved in THF (6.1 mL) under Ar atmosphere. Then to reaction mixture was added chloriodomethane (0.71 mL, 9.79 mmol, 4.0 equiv). When the flask was cooled to -72°C, solution of LDA (12.24 mL, 12.24 mmol, 5.0 equiv, 1M in THF) was added dropwise maintaining the temperature below -68°C. Upon completion of the addition, the solution was stirred at -72°C for 15 min. An acetic acid solution (1.4 mL in 1.4 mL of THF) was added dropwise at a rate sufficient to keep the internal temperature below -60°C and the reaction mixture was stirred for 1 hour while flask was slowly allowed to warm. Then toluene (6 mL) was added and when temperature reached -20°C, a portion of water (15 mL) was slowly added and the solution was stirred for 20 minutes. Layers were separated and the organic layer was washed with NaHCO₃ (2 x 100 mL), dried over MgSO₄, filtered and concentrated. The crude product was purified by flash chromatography on silica gel using Hex/EtOAc as eluent.

[00339] The following compounds were prepared in a similar way:

Intermediate for	Compound Name
A263	1-(1-(benzyloxy)cyclopropyl)-2-chloroethan-1-one
A292	2-chloro-1-(((1R,3R)-3-phenylcyclopentyl)ethan-1-one
A293	1-chloro-3,3-dimethyl-5-phenylpent-4-en-2-one
A305	2-chloro-1-(((1S,3R)-3-phenylcyclopentyl)ethan-1-one
A310	2-chloro-1-(5-phenyltetrahydrofuran-2-yl)ethan-1-one
A306	2-chloro-1-(1-phenylpiperidin-3-yl)ethan-1-one
A338	(R)-2-chloro-1-(2-methyl-1-phenylpyrrolidin-2-yl)ethan-1-one

Chloroketone Procedure B

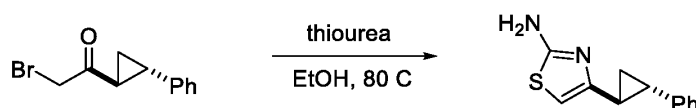
[00340] A 20 mL vial with stir bar was charged with methyl ester (182 mg, 0.887 mmol, 1.0 equiv), sodium 2-chloroacetate (155 mg, 1.33 mmol, 1.5 equiv), triethylamine (0.124 mL, 0.887 mmol, 1.0 equiv) and THF (1.0 mL, 0.2 M). The reaction mixture was cooled to 0 °C, and tert-butylmagnesium chloride (1.0 M in THF, 2.7 mL, 2.70 mmol, 3.0 equiv) was added. The reaction mixture was allowed to warm to room temperature overnight. The next morning, the reaction mixture was poured into EtOAc (50 mL). The organic layer was washed with saturated NaHCO_3 (2 x 50 mL). The combined aqueous layers were extracted with EtOAc (1 x 50 mL), and the combined organic layers were dried over Na_2SO_4 , filtered and concentrated in vacuo. The resulting crude material was used in the next step without further purification.

[00341] The following compounds were prepared in a similar way:

Intermediate for	Compound Name
A309	2-chloro-1-((1s,3s)-3-((5-methoxypyridin-2-yl)oxy)cyclobutyl)ethan-1-one
A314	2-chloro-1-((1r,3r)-3-((5-methoxypyridin-2-yl)oxy)cyclobutyl)ethan-1-one
A316	2-chloro-1-(1-phenylazetidin-3-yl)ethan-1-one
A329	2-chloro-1-((1r,3r)-3-phenoxy)cyclobutyl)ethan-1-one
A330	2-chloro-1-((1s,3s)-3-phenoxy)cyclobutyl)ethan-1-one
A300	2-chloro-1-((1S,2S)-2-phenyl)cyclopentyl)ethan-1-one
A301	2-chloro-1-((1S,2R)-2-phenyl)cyclopentyl)ethan-1-one
A268 and A287	2-chloro-1-(3-phenyl)cyclobutyl)ethan-1-one
A281 and A284	2-chloro-1-(2,3-dihydro-1H-inden-2-yl)ethan-1-one
A282 and A285	2-chloro-1-(1-phenylpiperidin-4-yl)ethan-1-one
A283 and A286	2-chloro-1-(chroman-2-yl)ethan-1-one
A302	1-(1-benzylpiperidin-4-yl)-2-chloroethan-1-one
A318 and A275	(R)-2-chloro-1-(1-phenylpyrrolidin-2-yl)ethan-1-one
A328	(R)-2-chloro-1-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)pyrrolidin-2-yl)ethan-1-one
A359	(R)-1-(1-(benzo[d][1,3]dioxol-5-yl)pyrrolidin-2-yl)-2-chloroethan-1-one
A365	(R)-2-chloro-1-(1-cyclohexylpyrrolidin-2-yl)ethan-1-one
A262	1-chloro-3,3-dimethyl-5-(pyridin-2-yl)pentan-2-one
A270	2-chloro-1-((1S,3R)-3-phenyl)cyclohexyl)ethan-1-one
A271	2-chloro-1-((1R,3R)-3-phenyl)cyclohexyl)ethan-1-one
A276	(S)-2-chloro-1-(1-phenylpyrrolidin-2-yl)ethan-1-one
A277	(R)-1-(1-benzylpyrrolidin-2-yl)-2-chloroethan-1-one

Intermediate for	Compound Name
A278	(S)-1-(1-benzylpyrrolidin-2-yl)-2-chloroethan-1-one
A279	(S)-1-(1-benzylpyrrolidin-3-yl)-2-chloroethan-1-one
A288	2-chloro-1-(2,3-dihydrobenzofuran-2-yl)ethan-1-one
A289	(S)-2-chloro-1-(1-phenylpyrrolidin-3-yl)ethan-1-one
A290	(R)-2-chloro-1-(1-phenylpyrrolidin-3-yl)ethan-1-one
A291	(R)-1-(1-benzylpyrrolidin-3-yl)-2-chloroethan-1-one
A200	2-chloro-1-((1S,2R)-2-phenylcyclopropyl)ethan-1-one
A296	2-chloro-1-(chroman-3-yl)ethan-1-one
A298	2-chloro-1-((1S,2R)-2-phenylcyclohexyl)ethan-1-one
A303	2-chloro-1-((1S,2S)-2-phenylcyclohexyl)ethan-1-one
A313	(R)-1-(1-benzoylpyrrolidin-2-yl)-2-chloroethan-1-one
A315	2-chloro-1-(1-(5-methoxypyridin-2-yl)azetidin-3-yl)ethan-1-one
A319	(R)-5-(2-chloroacetyl)-1-phenylpyrrolidin-2-one
A320	(R)-1-benzyl-5-(2-chloroacetyl)pyrrolidin-2-one
A322 and A321	1-((2R,4R)-4-((tert-butyldiphenylsilyl)oxy)-1-phenylpyrrolidin-2-yl)-2-chloroethan-1-one
A323 and A326	1-((2R,4S)-4-((tert-butyldiphenylsilyl)oxy)-1-phenylpyrrolidin-2-yl)-2-chloroethan-1-one
A324	2-chloro-1-((1S,2R)-2-phenylcyclobutyl)ethan-1-one
A325	2-chloro-1-((2R,4R)-4-methoxy-1-phenylpyrrolidin-2-yl)ethan-1-one
A331	2-chloro-1-((1S,2S)-2-phenylcyclobutyl)ethan-1-one
A332	(R)-2-chloro-1-(1-phenylpiperidin-2-yl)ethan-1-one
A333	2-chloro-1-((2R,4S)-4-methoxy-1-phenylpyrrolidin-2-yl)ethan-1-one
A334	2-chloro-1-((2R,3S)-3-methoxy-1-phenylpyrrolidin-2-yl)ethan-1-one
A336	(R)-2-chloro-1-(1-phenylazetidin-2-yl)ethan-1-one
A337	(R)-2-chloro-1-(4-phenylmorpholin-3-yl)ethan-1-one
A339	(R)-2-chloro-1-(4,4-difluoro-1-phenylpyrrolidin-2-yl)ethan-1-one
A344 and A352	2-chloro-1-((2R,3S)-3-hydroxy-1-phenylpyrrolidin-2-yl)ethan-1-one
A345	2-chloro-1-((2R,3R)-3-methoxy-1-phenylpyrrolidin-2-yl)ethan-1-one
A346	2-chloro-1-((2R,4R)-4-isopropoxy-1-phenylpyrrolidin-2-yl)ethan-1-one
A349	2-chloro-1-((1s,3s)-3-(pyridin-2-yl)cyclobutyl)ethan-1-one
A350	2-chloro-1-((1r,3r)-3-(pyridin-2-yl)cyclobutyl)ethan-1-one
A351 and A353	2-chloro-1-((2R,3R)-3-hydroxy-1-phenylpyrrolidin-2-yl)ethan-1-one
A354	2-chloro-1-((2R,4R)-4-(cyclohexyloxy)-1-phenylpyrrolidin-2-yl)ethan-1-one
A361	(R)-2-chloro-1-(1-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)pyrrolidin-2-yl)ethan-1-one
A362	(R)-1-(1-(benzo[d][1,3]dioxol-4-yl)pyrrolidin-2-yl)-2-chloroethan-1-one
A363	2-chloro-1-((1r,3r)-3-fluoro-3-(pyridin-2-yl)cyclobutyl)ethan-1-one
A364	2-chloro-1-((1s,3s)-3-fluoro-3-(pyridin-2-yl)cyclobutyl)ethan-1-one

Step 2: Standard Condensation



[00342] A 20 mL vial with stir bar was charged with bromoketone (307 mg, 1.28 mmol, 1.0 equiv), thiourea (108 mg, 1.41 mmol, 1.1 equiv) and EtOH (7 mL). The resulting solution

was stirred at 80 C overnight. The next morning, the resulting solution was cooled and poured into EtOAc (100 mL). The mixture was washed with saturated NaHCO₃ (2 x 100 mL), and the combined aqueous layers were extracted with EtOAc (1 x 100 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting crude material was purified via silica gel chromatography to yield the desired product.

[00343] The following compounds were prepared via a similar method:

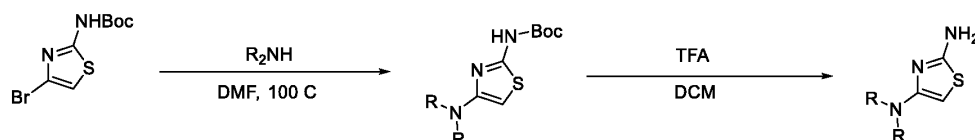
Intermediate for	Compound Name
A161	4-(2-chlorostyryl)thiazol-2-amine
A159	4-(3-methoxystyryl)thiazol-2-amine
A160	4-(4-methoxystyryl)thiazol-2-amine
A154	4-(2-(tetrahydro-2H-pyran-3-yl)vinyl)thiazol-2-amine
A158	4-(2-methoxystyryl)thiazol-2-amine
A152	4-(2-cyclohexylvinyl)thiazol-2-amine
A153	4-(2-(tetrahydro-2H-pyran-4-yl)vinyl)thiazol-2-amine
A219	4-(4-(trifluoromethyl)styryl)thiazol-2-amine
A220	4-(4-fluorostyryl)thiazol-2-amine
A166	4-(2-(pyridin-4-yl)vinyl)thiazol-2-amine
A224	4-(2-(2-aminothiazol-4-yl)vinyl)benzonitrile
A227	4-(4-nitrostyryl)thiazol-2-amine
A165	4-(2-(pyridin-3-yl)vinyl)thiazol-2-amine
A164	4-(2-(pyridin-2-yl)vinyl)thiazol-2-amine
A251	4-(3-phenylbut-1-en-1-yl)thiazol-2-amine
A252	4-(2-phenylprop-1-en-1-yl)thiazol-2-amine
A297	5-methyl-4-styrylthiazol-2-amine
A209	4-(3-chlorostyryl)thiazol-2-amine
A163	4-(4-chlorostyryl)thiazol-2-amine
A225	4-(2-methyl-4-phenylbutan-2-yl)thiazol-2-amine
A228	4-(2-methyl-1-phenoxypropan-2-yl)thiazol-2-amine
A257	4-(2-(pyridin-2-ylmethoxy)propan-2-yl)thiazol-2-amine
A260	4-(2-methyl-1-(pyridin-2-yloxy)propan-2-yl)thiazol-2-amine
A215 and A194	4-((1R,2R)-2-phenylcyclopropyl)thiazol-2-amine
A263	4-(1-(benzyloxy)cyclopropyl)thiazol-2-amine
A292	4-((1R,3R)-3-phenylcyclopentyl)thiazol-2-amine
A293	4-(2-methyl-4-phenylbut-3-en-2-yl)thiazol-2-amine
A305	4-((1S,3R)-3-phenylcyclopentyl)thiazol-2-amine
A309	4-((1s,3s)-3-((5-methoxypyridin-2-yl)oxy)cyclobutyl)thiazol-2-amine
A314	4-((1r,3r)-3-((5-methoxypyridin-2-yl)oxy)cyclobutyl)thiazol-2-amine
A316	4-(1-phenylazetidin-3-yl)thiazol-2-amine
A329	4-((1r,3r)-3-phenoxy)cyclobutyl)thiazol-2-amine
A330	4-((1s,3s)-3-phenoxy)cyclobutyl)thiazol-2-amine
A300	4-((1S,2S)-2-phenylcyclopentyl)thiazol-2-amine
A301	4-((1S,2R)-2-phenylcyclopentyl)thiazol-2-amine
A310	4-(5-phenyltetrahydrofuran-2-yl)thiazol-2-amine
A268 and A287	4-(3-phenylcyclobutyl)thiazol-2-amine
A281 and A284	4-(2,3-dihydro-1H-inden-2-yl)thiazol-2-amine
A282 and A285	4-(1-phenylpiperidin-4-yl)thiazol-2-amine

Intermediate for	Compound Name
A283 and A286	4-(chroman-2-yl)thiazol-2-amine
A302	4-(1-benzylpiperidin-4-yl)thiazol-2-amine
A306	4-(1-phenylpiperidin-3-yl)thiazol-2-amine
A318 and A275	(R)-4-(1-phenylpyrrolidin-2-yl)thiazol-2-amine
A328	(R)-4-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)pyrrolidin-2-yl)thiazol-2-amine
A359	(R)-4-(1-(benzo[d][1,3]dioxol-5-yl)pyrrolidin-2-yl)thiazol-2-amine
A365	(R)-4-(1-cyclohexylpyrrolidin-2-yl)thiazol-2-amine
A262	4-(2-methyl-4-(pyridin-2-yl)butan-2-yl)thiazol-2-amine
A270	4-((1S,3R)-3-phenylcyclohexyl)thiazol-2-amine
A271	4-((1R,3R)-3-phenylcyclohexyl)thiazol-2-amine
A276	(S)-4-(1-phenylpyrrolidin-2-yl)thiazol-2-amine
A277	(R)-4-(1-benzylpyrrolidin-2-yl)thiazol-2-amine
A278	(S)-4-(1-benzylpyrrolidin-2-yl)thiazol-2-amine
A279	(S)-4-(1-benzylpyrrolidin-3-yl)thiazol-2-amine
A288	4-(2,3-dihydrobenzofuran-2-yl)thiazol-2-amine
A289	(S)-4-(1-phenylpyrrolidin-3-yl)thiazol-2-amine
A290	(R)-4-(1-phenylpyrrolidin-3-yl)thiazol-2-amine
A291	(R)-4-(1-benzylpyrrolidin-3-yl)thiazol-2-amine
A200	4-((1S,2R)-2-phenylcyclopropyl)thiazol-2-amine
A296	4-(chroman-3-yl)thiazol-2-amine
A298	4-((1S,2R)-2-phenylcyclohexyl)thiazol-2-amine
A303	4-((1S,2S)-2-phenylcyclohexyl)thiazol-2-amine
A313	(R)-(2-(2-aminothiazol-4-yl)pyrrolidin-1-yl)(phenyl)methanone
A315	4-(1-(5-methoxypyridin-2-yl)azetidin-3-yl)thiazol-2-amine
A319	(R)-5-(2-aminothiazol-4-yl)-1-phenylpyrrolidin-2-one
A320	(R)-5-(2-aminothiazol-4-yl)-1-benzylpyrrolidin-2-one
A322 and A321	4-((2R,4R)-4-((tert-butyldiphenylsilyl)oxy)-1-phenylpyrrolidin-2-yl)thiazol-2-amine
A323 and A326	4-((2R,4S)-4-((tert-butyldiphenylsilyl)oxy)-1-phenylpyrrolidin-2-yl)thiazol-2-amine
A324	4-((1S,2R)-2-phenylcyclobutyl)thiazol-2-amine
A325	4-((2R,4R)-4-methoxy-1-phenylpyrrolidin-2-yl)thiazol-2-amine
A331	4-((1S,2S)-2-phenylcyclobutyl)thiazol-2-amine
A332	(R)-4-(1-phenylpiperidin-2-yl)thiazol-2-amine
A333	4-((2R,4S)-4-methoxy-1-phenylpyrrolidin-2-yl)thiazol-2-amine
A334	4-((2S,3S)-3-methoxy-1-phenylpyrrolidin-2-yl)thiazol-2-amine
A336	(R)-4-(1-phenylazetidin-2-yl)thiazol-2-amine
A337	(S)-4-(4-phenylmorpholin-3-yl)thiazol-2-amine
A338	(R)-4-(2-methyl-1-phenylpyrrolidin-2-yl)thiazol-2-amine
A339	(R)-4-(4,4-difluoro-1-phenylpyrrolidin-2-yl)thiazol-2-amine
A344 and A352	(2S,3S)-2-(2-aminothiazol-4-yl)-1-phenylpyrrolidin-3-ol
A345	4-((2S,3R)-3-methoxy-1-phenylpyrrolidin-2-yl)thiazol-2-amine
A346	4-((2R,4R)-4-isopropoxy-1-phenylpyrrolidin-2-yl)thiazol-2-amine
A349	4-((1s,3s)-3-(pyridin-2-yl)cyclobutyl)thiazol-2-amine
A350	4-((1r,3r)-3-(pyridin-2-yl)cyclobutyl)thiazol-2-amine
A351 and A353	(2S,3R)-2-(2-aminothiazol-4-yl)-1-phenylpyrrolidin-3-ol
A354	4-((2R,4R)-4-(cyclohexyloxy)-1-phenylpyrrolidin-2-yl)thiazol-2-amine
A361	(R)-4-(1-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)pyrrolidin-2-yl)thiazol-2-amine

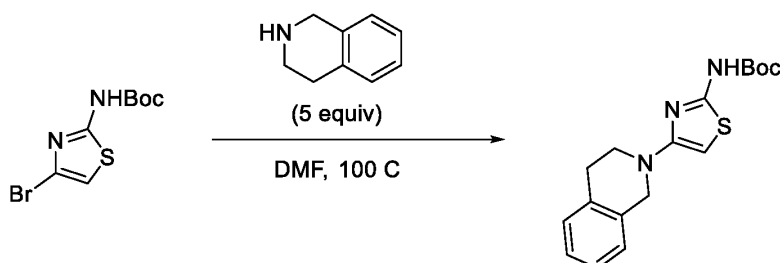
Intermediate for	Compound Name
A362	(R)-4-(1-(benzo[d][1,3]dioxol-4-yl)pyrrolidin-2-yl)thiazol-2-amine
A363	4-((1r,3r)-3-fluoro-3-(pyridin-2-yl)cyclobutyl)thiazol-2-amine
A364	4-((1s,3s)-3-fluoro-3-(pyridin-2-yl)cyclobutyl)thiazol-2-amine
A223	N-(4-(2-(2-aminothiazol-4-yl)vinyl)phenyl)acetamide

Procedure 13 – Intermediate for A267 (Route C)

[00344] The reactions followed the general reaction scheme, below:



Step 1: Amine Installation

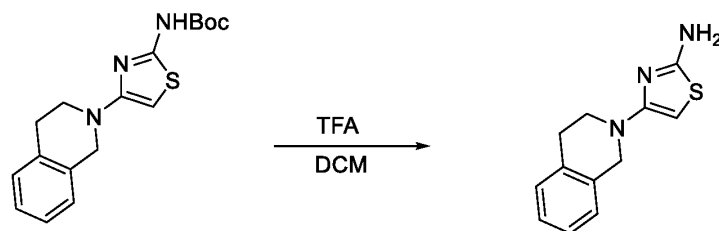


[00345] A 50 mL vial with stir bar was charged with thiazole (300 mg, 1.08 mmol, 1.0 equiv), amine (869 mg, 5.39 mmol, 5.0 equiv) and DMF (9.0 mL, 0.12 M) under nitrogen atmosphere, the vial was capped and placed in an 100°C bath. The reaction mixture was stirred at 100°C for 4 h. The reaction mixture was cooled to room temperature and quenched by H₂O (50 mL). The resulting solution was extracted with ethyl acetate (3 x 40 mL) and washed with brine (3 x 40 mL). The organic layer was then dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting crude material was purified via prep-TLC to yield the desired product.

[00346] The following compounds were prepared via a similar method:

Intermediate for	Compound name
A261	tert-butyl (4-(4-phenylpiperidin-1-yl)thiazol-2-yl)carbamate
A264	tert-butyl (4-(piperidin-1-yl)thiazol-2-yl)carbamate
A265	tert-butyl (4-(3-phenylpiperidin-1-yl)thiazol-2-yl)carbamate
A266	tert-butyl (4-(4-phenylpiperazin-1-yl)thiazol-2-yl)carbamate
A273	tert-butyl (4-(3-phenylpyrrolidin-1-yl)thiazol-2-yl)carbamate

Step 2: Deprotection



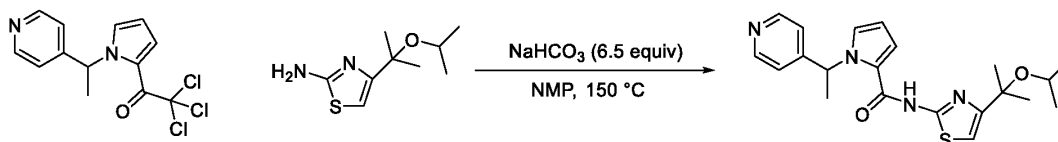
[00347] A 20 mL vial with stir bar was charged with thiazole (90 mg, 0.25 mmol, 1.00 equiv) and DCM (2.0 mL, 0.125 M). TFA (2 mL, 27.0 mmol, 108 equiv) was added, and the vial was capped and placed in a 25°C bath. The reaction mixture was stirred at 25°C for 1 h. The resulting mixture was concentrated under vacuum and quenched by sat. NaHCO_3 (aq) (10 mL). The combined aqueous layers were extracted with EtOAc (4 x 20 mL), the combined organic layers were dried over Na_2SO_4 , filtered and concentrated in vacuo. The resulting crude material was used directly for next step.

[00348] The following compounds were prepared via a similar method:

Intermediate for	Compound Name
A261	4-(4-phenylpiperidin-1-yl)thiazol-2-amine
A264	4-(piperidin-1-yl)thiazol-2-amine
A265	4-(3-phenylpiperidin-1-yl)thiazol-2-amine
A266	4-(4-phenylpiperazin-1-yl)thiazol-2-amine
A273	4-(3-phenylpyrrolidin-1-yl)thiazol-2-amine

Example 4: Amide Coupling Reactions**Procedure 1 - Synthesis of Compounds A74 and A49**

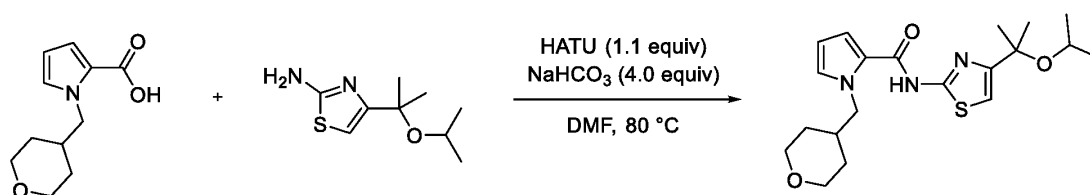
[00349] Synthesis of A74 and A49 followed the scheme, below.



[00350] N-(2-(4-pyridinylethyl)-2-(trichloroacetyl)pyrrole) (0.53 g, 1.67 mmol, 1.0 eq), amine (0.334 g, 1.67 mmol, 1.0 eq) and NaHCO_3 (0.911 g, 10.9 mmol, 6.5eq) were taken up in NMP (6.5 mL). The reaction mixture was heated at 150 °C for 17h. After this time, the NMP was evaporated, and the resulting crude material was purified on pTLC (60% EtOAc in hexanes). LCMS (+ESI): calc. $[\text{M}+\text{H}]^+ = 396$; found 397. The enantiomers were resolved via SFC (Chiralpak IF 3, 5% MeOH+TEA in CO_2).

Procedure 2 – Synthesis of Compound A71

[00351] Synthesis of A71 followed the scheme, below



[00352] A 20 mL vial with stir bar was charged with acid (71.3 mg, 0.341 mmol, 1.0 equiv), amine (115 mg, 0.574 mmol, 1.7 equiv), sodium bicarbonate (115 mg, 1.36 mmol, 4.0 equiv) and HATU (143 mg, 0.375 mmol, 1.1 equiv). DMF (2 mL) was added, and the vial was capped and placed in an 80 °C bath. The reaction mixture was stirred at 80 °C overnight. The next morning, the reaction mixture was poured into DCM (50 mL) and washed with 0.5 M NaOH (2 x 50 mL), followed by water (1 x 50 mL). The organic layer was then dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting crude material was purified via silica gel chromatography (20-50% EtOAc in hexanes) to yield the desired product. LCMS (+ESI): calc. [M+H]⁺ = 392; found 392.

[00353] The following compounds were prepared in a similar manner:

Compound	Compound name	Exact mass [M]	Observed molecular ion [M+H]
A1	(S)-N-(4-(2-(1-phenylethoxy)propan-2-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	446	447
A16	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	384	385
A2	N-(4-(2-(1-(3-chlorophenyl)ethoxy)propan-2-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	480	481
A3	N-(4-(2-(1-phenylethoxy)propan-2-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	446	447
A4	N-(4-(2-(1-(3-methoxyphenyl)ethoxy)propan-2-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	476	477
A5	N-(4-(2-(1-(4-chlorophenyl)ethoxy)propan-2-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	480	481
A6	(S)-N-(4-(2-(1-phenylethoxy)propan-2-yl)thiazol-2-yl)-1-(3-(pyridin-4-yl)propyl)-1H-pyrrole-2-carboxamide	474	475
A7	N-(4-(2-(cyclohexylmethoxy)propan-2-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	438	439
A8	N-(4-(2-(1-(2-chlorophenyl)ethoxy)propan-2-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	480	481
A9	N-(4-(2-(benzyloxy)propan-2-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	432	433

Compound	Compound name	Exact mass [M]	Observed molecular ion [M+H]
A10	N-(4-(2-(cyclohexyloxy)propan-2-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	424	425
A11	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-(3-(pyridin-4-yl)propyl)-1H-pyrrole-2-carboxamide	412	413
A12	1-(pyridin-4-ylmethyl)-N-(4-styrylthiazol-2-yl)-1H-pyrrole-2-carboxamide	386	387
A13	N-(4-phenethylthiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	388	389
A14	1-(pyridin-4-ylmethyl)-N-(4-styrylthiazol-2-yl)-1H-pyrrole-2-carboxamide	386	387
A15	1-(pyridin-4-ylmethyl)-N-(4-(2-(2,2,2-trifluoroethoxy)propan-2-yl)thiazol-2-yl)-1H-pyrrole-2-carboxamide	424	425
A18	(R)-N-(4-(2-(1-phenylethoxy)propan-2-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	446	447
A21	N-(4-(1-phenylethyl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	388	389
A22	N-(4,4-dimethyl-5,6-dihydro-4H-cyclopenta[d]thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	352	353
A25	1-((3-fluoropyridin-4-yl)methyl)-N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1H-pyrrole-2-carboxamide	402	403
A26	N-(4-isopropylthiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	326	327
A27	N-(4-(2-ethoxypropan-2-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	370	371
A32	N-(4-ethyl-5-methylthiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	326	327
A33	1-(3-(pyridin-4-yl)propyl)-N-(4-styrylthiazol-2-yl)-1H-pyrrole-2-carboxamide	414	415
A34	N-(5-benzylthiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	374	375
A37	N-(4-(2-isopropoxypropan-2-yl)-5-methylthiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	398	399
A39	1-(pyridin-4-ylmethyl)-N-(4-(2-((tetrahydro-2H-pyran-2-yl)methoxy)propan-2-yl)thiazol-2-yl)-1H-pyrrole-2-carboxamide	440	441
A40	1-(pyridin-4-ylmethyl)-N-(4-(2-((tetrahydro-2H-pyran-4-yl)methoxy)propan-2-yl)thiazol-2-yl)-1H-pyrrole-2-carboxamide	440	441
A41	1-((3-bromopyridin-4-yl)methyl)-N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1H-pyrrole-2-carboxamide	462	463
A44	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-(4-(pyridin-4-yl)butyl)-1H-pyrrole-2-carboxamide	426	427

Compound	Compound name	Exact mass [M]	Observed molecular ion [M+H]
A45	N-(4-(tert-butyl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	340	341
A50	N-(benzo[d]thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	334	335
A58	N-(4,5-dimethylthiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	312	313
A59	N-(4-(isopropoxymethyl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	356	357
A64	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-(3-phenylpropyl)-1H-pyrrole-2-carboxamide	411	412
A66	1-((3-chloropyridin-4-yl)methyl)-N-(4-ethyl-5-methylthiazol-2-yl)-1H-pyrrole-2-carboxamide	360	361
A68	1-(3-(2-chlorophenyl)propyl)-N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1H-pyrrole-2-carboxamide	445	446
A69	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-(pyridazin-4-ylmethyl)-1H-pyrrole-2-carboxamide	385	386
B3	1-(pyridin-4-ylmethyl)-N-(4-(2-(2-tosylethoxy)propan-2-yl)thiazol-2-yl)-1H-pyrrole-2-carboxamide	524	525
B4	N-(5-(tert-butyl)isoxazol-3-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	324	325
A77	N-(4-(tert-butyl)thiazol-2-yl)-1-((3-chloropyridin-4-yl)methyl)-1H-pyrrole-2-carboxamide	374	375
A78	1-(2-chlorobenzyl)-N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1H-pyrrole-2-carboxamide	417	418
A79	1-benzyl-N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1H-pyrrole-2-carboxamide	383	384
B5	N-(4-isopropoxyloxazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	310	311
A87	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-(pyridin-3-ylmethyl)-1H-pyrrole-2-carboxamide	384	385
B7	1-(2-chlorobenzyl)-N-(4-ethyl-5-methylthiazol-2-yl)-1H-pyrrole-2-carboxamide	359	360
B8	N-(5-methylisoxazol-3-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	282	283
B9	1-benzyl-N-(4-ethyl-5-methylthiazol-2-yl)-1H-pyrrole-2-carboxamide	325	326
A90	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-(quinolin-4-ylmethyl)-1H-pyrrole-2-carboxamide	434	435
A91	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-(2-(pyridin-4-yl)ethyl)-1H-pyrrole-2-carboxamide	398	399
B11	N-(4-(tert-butyl)thiazol-2-yl)-1-(2-chlorobenzyl)-1H-pyrrole-2-carboxamide	373	374
A100	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrazole-3-carboxamide	385	386
A101	1-(3-(1-acetylpiperidin-4-yl)propyl)-N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1H-pyrrole-2-carboxamide	460	461

Compound	Compound name	Exact mass [M]	Observed molecular ion [M+H]
A106	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-6-oxo-1-(pyridin-4-ylmethyl)-1,6-dihydropyridine-2-carboxamide	412	411 [M-H]-
A112	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrazole-5-carboxamide	385	386
A113	4-(hydroxymethyl)-N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	414	415
B12	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-2-(5-(pyridin-4-ylmethyl)-1H-pyrrol-2-yl)acetamide	398	399
A117	N-((4-isopropylthiazol-2-yl)methyl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	340	341
A122	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-3-carboxamide	384	385
A124	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-((1-methyl-6-oxo-1,6-dihydropyridin-3-yl)methyl)-1H-pyrrole-2-carboxamide	414	415
A125	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-((2-methoxypyridin-4-yl)methyl)-1H-pyrrole-2-carboxamide	414	415
B20	(S)-1-isonicotinoyl-N-(4-isopropylthiazol-2-yl)pyrrolidine-2-carboxamide	344	345
B21	(R)-1-isonicotinoyl-N-(4-isopropylthiazol-2-yl)pyrrolidine-2-carboxamide	344	345
A126	benzyl 4-((2-((4-(2-isopropoxypropan-2-yl)thiazol-2-yl)carbamoyl)-1H-pyrrol-1-yl)methyl)piperidine-1-carboxylate	524	525
B22	N-(4-(2-acetamidoethyl)-5-methylthiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	383	384
B23	N-((1S,2R)-2-(tert-butyl)cyclopropyl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	297	298
A127	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-((1-methyl-2-oxo-1,2-dihydropyridin-4-yl)methyl)-1H-pyrrole-2-carboxamide	414	415
Intermediate for B24	tert-butyl (R)-2-((4-ethyl-5-methylthiazol-2-yl)carbamoyl)pyrrolidine-1-carboxylate	339	340
B25	N-(3-ethyl-4-methylphenyl)-N-methyl-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	333	334
A128	1-((1-acetylpiperidin-4-yl)methyl)-N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1H-pyrrole-2-carboxamide	432	433
A129	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-((1-methylpiperidin-4-yl)methyl)-1H-pyrrole-2-carboxamide	404	405
B26	(S)-N-(4-ethyl-5-methylthiazol-2-yl)-1-(pyridin-4-ylmethyl)pyrrolidine-2-carboxamide	330	331
A130	(S)-N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)pyrrolidine-2-carboxamide	388	389
A131	N-(4-ethyl-5-methylthiazol-2-yl)-1-(pyridin-3-ylmethyl)-1H-pyrrole-2-carboxamide	326	327

Compound	Compound name	Exact mass [M]	Observed molecular ion [M+H]
B27	1-benzyl-N-(4-(tert-butyl)thiazol-2-yl)-1H-pyrrole-2-carboxamide	339	340
B11	N-(4-(tert-butyl)thiazol-2-yl)-1-(2-chlorobenzyl)-1H-pyrrole-2-carboxamide	373	374
B28	N-(4-(tert-butyl)thiazol-2-yl)-5-chloro-1-(pyridin-4-ylmethyl)-1H-indole-2-carboxamide	424	425
B29	5-chloro-N-(4-ethyl-5-methylthiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-indole-2-carboxamide	410	411
A293	N-(4-(2-methyl-4-phenylbut-3-en-2-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	428	429
A292	N-(4-((1R,3R)-3-phenylcyclopentyl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	428	429
A280	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-2-(pyridin-4-ylmethyl)benzamide	395	396
A269	N-(4-(2-(5-methoxypyridin-2-yl)vinyl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	417	418
A263	N-(4-(1-(benzyloxy)cyclopropyl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	430	431
A155	1-(pyridin-4-ylmethyl)-N-(4-(2-(tetrahydro-2H-pyran-2-yl)vinyl)thiazol-2-yl)-1H-pyrrole-2-carboxamide	394	395
A256	1-((3,5-difluoropyridin-4-yl)methyl)-N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1H-pyrrole-2-carboxamide	420	421
A254	N-(4-(2-((1s,4s)-4-methoxycyclohexyl)vinyl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	422	423
A253	N-(4-(2-((1r,4r)-4-methoxycyclohexyl)vinyl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	422	423
A250	1-((3-ethylpyridin-4-yl)methyl)-N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1H-pyrrole-2-carboxamide	412	413
A243	1-(3-(3-fluoropyridin-4-yl)propyl)-N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1H-pyrrole-2-carboxamide	430	431
A241	N-(4-(2-fluoro-4-methoxystyryl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	434	435
A240	N-(4-(3-fluoro-4-methoxystyryl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	434	435
A238	1-((3-chloropyridin-4-yl)methyl)-N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1H-pyrrole-2-carboxamide	418	419
A165	N-(4-(2-(pyridin-3-yl)vinyl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	387	388
A224	N-(4-(4-cyanostyryl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	411	410 [M-H]-

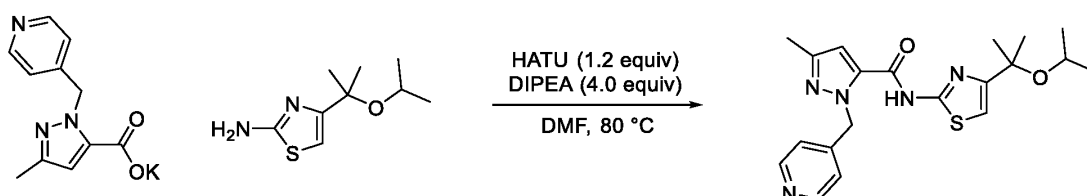
Compound	Compound name	Exact mass [M]	Observed molecular ion [M+H]
A166	N-(4-(2-(pyridin-4-yl)vinyl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	387	388
A220	N-(4-(4-fluorostyryl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	404	405
A219	1-(pyridin-4-ylmethyl)-N-(4-(4-(trifluoromethyl)styryl)thiazol-2-yl)-1H-pyrrole-2-carboxamide	454	455
A153	1-(pyridin-4-ylmethyl)-N-(4-(2-(tetrahydro-2H-pyran-4-yl)vinyl)thiazol-2-yl)-1H-pyrrole-2-carboxamide	394	395
A152	N-(4-(2-cyclohexylvinyl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	392	393
A158	N-(4-(2-methoxystyryl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	416	417
A160	N-(4-(4-methoxystyryl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	416	418
A154	1-(pyridin-4-ylmethyl)-N-(4-(2-(tetrahydro-2H-pyran-3-yl)vinyl)thiazol-2-yl)-1H-pyrrole-2-carboxamide	394	395
A159	N-(4-(3-methoxystyryl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	416	417
A161	N-(4-(2-chlorostyryl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	420	421
A163	N-(4-(4-chlorostyryl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	420	421
A209	N-(4-(3-chlorostyryl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	420	421
A210	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-((1-methyl-5-oxopyrrolidin-3-yl)methyl)-1H-pyrrole-2-carboxamide	404	405
A300	N-(4-((1S,2S)-2-phenylcyclopentyl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	428	429
A301	N-(4-((1S,2R)-2-phenylcyclopentyl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	428	429
A305	N-(4-((1S,3R)-3-phenylcyclopentyl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	428	429
A306	N-(4-(1-phenylpiperidin-3-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	443	444
A310	N-(4-(5-phenyltetrahydrofuran-2-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	430	431
A184	N-(4-benzylthiazol-2-yl)-1-(3-(pyridin-4-yl)propyl)-1H-pyrrole-2-carboxamide	402	403
A187	N-(4-benzylthiazol-2-yl)-1-(3-(pyridin-3-yl)propyl)-1H-pyrrole-2-carboxamide	402	403
A190	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-(3-(pyridin-3-yl)propyl)-1H-pyrrole-2-carboxamide	412	413

Compound	Compound name	Exact mass [M]	Observed molecular ion [M+H]
A211	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-((3-methoxypyridin-4-yl)methyl)-1H-pyrrole-2-carboxamide	414	415
A194	N-(4-((1S,2S)-2-phenylcyclopropyl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	400	401
A212	1-((3-(benzylamino)pyridin-4-yl)methyl)-N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1H-pyrrole-2-carboxamide	489	490
A213	1-((3-(benzylamino)pyridin-4-yl)methyl)-N-(4-benzylthiazol-2-yl)-1H-pyrrole-2-carboxamide	479	480
A214	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-((3-(trifluoromethyl)pyridin-4-yl)methyl)-1H-pyrrole-2-carboxamide	452	453
A215	N-(4-((1R,2R)-2-phenylcyclopropyl)thiazol-2-yl)-1-(3-(pyridin-4-yl)propyl)-1H-pyrrole-2-carboxamide	428	429
A216	N-(4-phenylthiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	360	361
A217	N-(4-(3-phenylprop-1-en-1-yl)thiazol-2-yl)-1-(3-(pyridin-4-yl)propyl)-1H-pyrrole-2-carboxamide	428	429
A218	N-(4-(3-phenylprop-1-en-1-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	400	401
A221	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-(3-(pyridin-4-yl)allyl)-1H-pyrrole-2-carboxamide	410	411
A222	N-(4-(2-(furan-3-yl)vinyl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	376	377
A225	N-(4-(2-methyl-4-phenylbutan-2-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	430	431
A226	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-(2-(pyridin-4-yloxy)ethyl)-1H-pyrrole-2-carboxamide	414	415
A232	N-(4-(2-(furan-3-yl)vinyl)thiazol-2-yl)-1-(3-(pyridin-4-yl)propyl)-1H-pyrrole-2-carboxamide	404	405
A234	N-(4-(2-(benzo[d][1,3]dioxol-5-yl)vinyl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	430	431
A235	N-(4-(2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)vinyl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	466	467
A236	N-(4-(4-isopropoxystyryl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	444	445
A242	N-(4-(1H-inden-2-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	398	399
A244	N-(4-(2-(cyclohex-1-en-1-yl)vinyl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	390	391
A247	N-(4-(1-phenylprop-1-en-2-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	400	401
A248	N-(4-(4-cyclopropoxystyryl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	442	443

Compound	Compound name	Exact mass [M]	Observed molecular ion [M+H]
A249	1-(pyridin-4-ylmethyl)-N-(4-(1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)thiazol-2-yl)-1H-pyrrole-2-carboxamide	440	441
A223	N-(4-(4-acetamidostyryl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	443	444
Intermediate for A228	N-(4-(1-(2-bromophenoxy)-2-methylpropan-2-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	510	511
Intermediate for A231	N-(4-(4-cyanostyryl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	411	410 [M-H]-

Procedure 3 - Synthesis of Compound A103

[00354] Synthesis of A103 followed the scheme, below:



[00355] To the solution of potassium salt of acid (0.145 g, 0.57 mmol, 1.0 equiv), DIPEA (0.395 mL, 2.27 mmol, 4.0 equiv) and HATU (0.266 g, 0.70 mmol, 1.23 equiv) in DMF (2.9 mL) were added. After 15 min, amine (0.114 g, 0.57 mmol, 1.0 equiv) was added. The reaction was allowed to stir at 80 °C overnight. The next morning, the reaction mixture was diluted with EtOAc (50 mL) and washed with saturated NaHCO₃ (2 x 50 mL), followed by water (1 x 50 mL). The organic layer was then dried over MgSO₄, filtered and concentrated in vacuo. The crude product was purified via silica gel chromatography eluting with EtOAc. LCMS (+ESI): calc. [M+H]⁺ = 400; found 400.

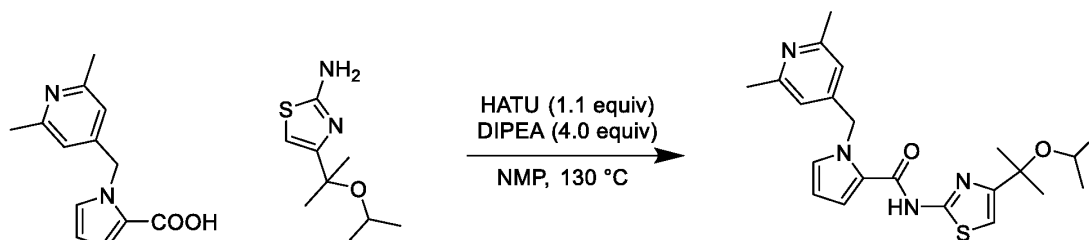
[00356] The following compounds were prepared in a similar manner:

Compound	Compound name	Exact mass [M]	Observed molecular ion [M+H]
A19	1-(pyridin-4-ylmethyl)-N-(4-(trifluoromethyl)thiazol-2-yl)-1H-pyrrole-2-carboxamide	352	353
A20	N-(4-(1-isopropoxyethyl)-5-methylthiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	384	385
A35	N-(4-ethylthiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	312	313
A53	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-(4-nitrobenzyl)-1H-pyrrole-2-carboxamide	428	429

Compound	Compound name	Exact mass [M]	Observed molecular ion [M+H]
A63	N-(4-methylthiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	298	299
A67	N-(4-(1-methylcyclopropyl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	338	339
A72	N-(5-methylthiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	298	299
A76	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-5-methyl-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	398	399
A86	3-chloro-N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	418	419
A88	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-3-methyl-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	398	399
B10	N-(3-ethyl-4-methylphenyl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	319	320
A92	N-(5-ethyl-4-((4-(ethylsulfonyl)piperazin-1-yl)methyl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	502	503
A109	N2-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2,4-dicarboxamide	427	428

Procedure 4 – Synthesis of Compound A97

[00357] Synthesis of A97 followed the scheme, below:



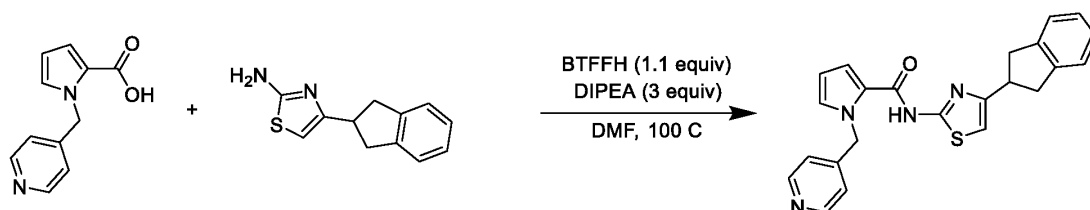
[00358] To the solution of the acid (0.090 g, 0.39 mmol, 1.0 equiv) in NMP (1 mL) were added HATU (0.163 g, 0.43 mmol, 1.1 equiv), DIPEA (0.272 mL, 1.56 mmol, 4.0 equiv) and amine (0.117 g, 0.59 mmol, 1.5 eq.). Reaction was continued either with conventional heating or in the microwave at 130°C for 1 h. After that the reaction mixture was diluted with EtOAc (50 mL) and washed with saturated NaHCO₃ (2 x 50 mL), followed by water (1 x 50 mL). The organic layer was then dried over MgSO₄, filtered and concentrated in vacuo. Crude product was purified via silica gel chromatography (1-10% MeOH in DCM). LCMS (+ESI): calc. [M+H]⁺= 413; found 413.

[00359] The following compounds were prepared in a similar manner:

Compound	Compound name	Exact mass [M]	Observed molecular ion [M+H]	Heating Protocol
A17	N-(4-benzylthiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	374	375	conventional heating, 130 °C
A24	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-((3-methylpyridin-4-yl)methyl)-1H-pyrrole-2-carboxamide	398	399	conventional heating, 100 °C
A28	N-(4-(1-isopropoxyethyl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	370	371	microwave heating, 130 °C
A29	N-(4-(1,1-difluoroethyl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	348	349	conventional heating, 100 °C
A36	1-((2,6-difluoropyridin-4-yl)methyl)-N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1H-pyrrole-2-carboxamide	420	421	microwave heating, 130 °C
A48	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-4-methyl-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	398	399	microwave heating, 130 °C
A49	(R)-N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-(1-(pyridin-4-yl)ethyl)-1H-pyrrole-2-carboxamide	398	397 [M-H]-	conventional heating, 150 °C
A70	1-((2-fluoro-6-methoxypyridin-4-yl)methyl)-N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1H-pyrrole-2-carboxamide	432	433	microwave heating, 130 °C
A74	(S)-N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-(1-(pyridin-4-yl)ethyl)-1H-pyrrole-2-carboxamide	398	399	conventional heating, 150 °C
A80	1-(4-cyanobenzyl)-N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1H-pyrrole-2-carboxamide	408	407 [M-H]-	conventional heating, 100 °C
A83	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-((2-methylpyridin-4-yl)methyl)-1H-pyrrole-2-carboxamide	398	399	conventional heating, 100 °C
A84	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-(4-(methylsulfonyl)benzyl)-1H-pyrrole-2-carboxamide	461	462	conventional heating, 100 °C
A93	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-((5-oxopyrrolidin-3-yl)methyl)-1H-pyrrole-2-carboxamide	390	392	conventional heating, 60 °C

Compound	Compound name	Exact mass [M]	Observed molecular ion [M+H]	Heating Protocol
A96	N-(4-((4-(ethylsulfonyl)piperazin-1-yl)methyl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	474	475	microwave heating, 130 °C
A99	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-(4-(N-methylacetamido)benzyl)-1H-pyrrole-2-carboxamide	454	455	microwave heating, 130 °C
A102	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-6-oxo-1-(pyridin-4-ylmethyl)piperidine-2-carboxamide	416	417	microwave heating, 130 °C
A104	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-imidazole-5-carboxamide	385	387	microwave heating, 130 °C
A105	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2,5-dicarboxamide	427	429	microwave heating, 130 °C
A107	N2-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-N5,N5-dimethyl-1-(pyridin-4-ylmethyl)-1H-pyrrole-2,5-dicarboxamide	455	456	microwave heating, 130 °C
A108	N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-imidazole-2-carboxamide	385	386	conventional heating, 130 °C
A110	5-(hydroxymethyl)-N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide	414	415	microwave heating, 130 °C
A111	N2-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-N4,N4-dimethyl-1-(pyridin-4-ylmethyl)-1H-pyrrole-2,4-dicarboxamide	455	457	conventional heating, 130 °C
A114	1-(4-acetamidobenzyl)-N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1H-pyrrole-2-carboxamide	440	441	microwave heating, 130 °C

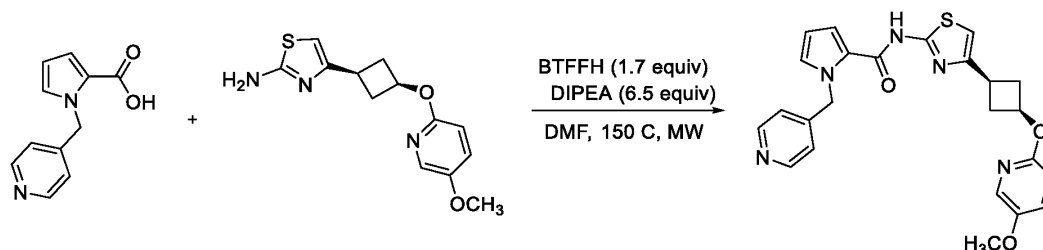
Procedure 5 – Synthesis of Compound A281



[00360] A 20 mL vial with stir bar was charged with acid (100 mg, 0.495 mmol, 1.1 equiv), amine (97.2 mg, 0.450 mmol, 1.0 equiv), BTFFH (156 mg, 0.495 mmol, 1.1 equiv) and DMF (1.0 mL, 0.4 M). DIPEA (160 μ L, 0.899 mmol, 2.0 equiv) was added, and the vial was capped and placed in a 100 C bath. The reaction mixture was stirred at 100 C overnight. The next morning, the reaction mixture was poured into EtOAc (50 mL) and washed with 1:1 1 M NaOH:brine (2 x 50 mL). The combined aqueous layers were extracted with EtOAc (1 x 50 mL), and the combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting crude material was purified via silica gel chromatography to yield the desired product.

[00361] The following compounds were prepared via a similar method:

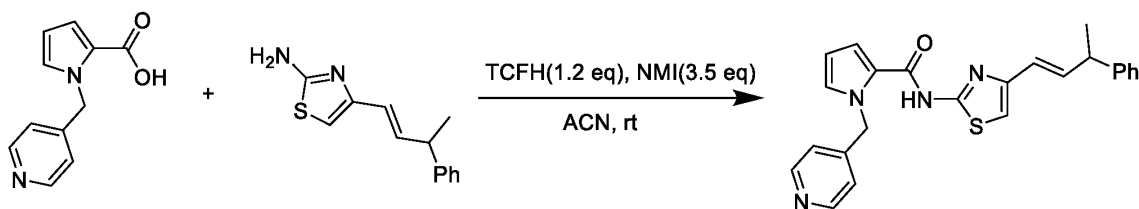
Compound	Observed molecular ion
A246	458
A245	458
A157	364
A150	364
A239	444
A230	364
A151	364
A227	430
A307	389
A314	462
A316	416
A330	431
A329	431
A255	443
A258	442
A259	456
A268	415
A281	401
A282	444
A283	417
A284	429
A285	472
A286	445
A287	443
A302	458
A318	464
A327	472
A328	510
A341	413
A342	406
A343	456
A359	474
A365	436
A366	389
Intermediate for A317	454

Procedure 7 – Synthesis of Compound A309

[00362] A 20 mL microwave vial (G30) with stir bar was charged with acid (109.95 mg, 0.544 mmol, 1.3 equiv), amine (116 mg, 0.418 mmol, 1.0 equiv), BTFFH (224.83 mg, 0.711 mmol, 1.7 equiv) and DMF (8.0 mL, 0.052 M). DIPEA (0.474 mL, 2.719 mmol, 6.5 equiv) was added, and the vial was capped and placed in a microwave reactor at 150 °C. The reaction mixture was stirred at 150 °C for 1 h. The reaction mixture was poured into EtOAc (50 mL) and washed with 1:1 a saturated NaHCO₃: brine (2 x 20 mL). The combined aqueous layers were extracted with EtOAc (1 x 50 mL), and the combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting crude material was purified via silica gel chromatography to yield the desired product.

[00363] The following compounds were prepared via a similar method:

Compound	Observed molecular ion
A309	462
A315	447

Procedure 8 – Synthesis of Compound A251

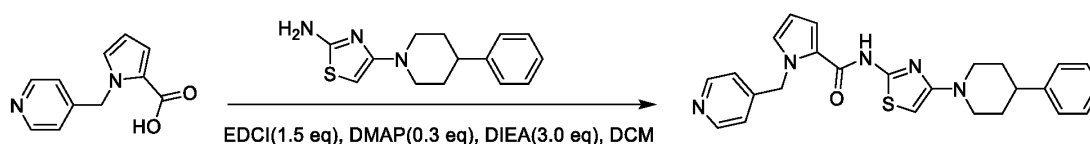
[00364] A 25 mL vial with stir bar was charged with acid (110.00 mg, 0.544 mmol, 1.00 equiv), amine (162.80 mg, 0.707 mmol, 1.30 equiv), NMI (156.30 mg, 1.904 mmol, 3.50 equiv) and ACN (4.0 mL, 0.14 M). TCFH (184.60 mg, 0.660 mmol, 1.21 equiv) was added, and the vial was capped and placed in a 25 °C bath. The reaction mixture was stirred at 25 °C overnight. The next morning, the reaction mixture was poured into EtOAc (30 mL) and washed with brine (2 x 30 mL). The combined aqueous layers were extracted with EtOAc (1 x 30 mL), and the combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting crude material was purified via silica gel chromatography & Prep-HPLC or RP column to yield the desired product.

[00365] The following compounds were prepared via a similar method:

Compound	Observed molecular ion
A251	415
A252	401
A257	434
A260	434
A262	432
A267	416
A270	443
A271	443
A272	432
A274	432
A275	430
A276	430
A277	444
A278	444
A279	444
A288	403
A289	430
A290	430
A291	444
A294	441
A200	401
A296	417
A297	401
A298	443
A299	436
A303	443
A304	461
A311	432
A312	432
A313	458
A319	444
A320	458
Intermediate for A321	684
A322	684
A323	684
A324	415
A325	460
Intermediate for A326	684
A331	415
A332	444
A333	460
A334	460
A335	450
A336	416
A337	446
A338	444
A339	466
Intermediate for A344	684
A345	460
A346	488
A347	402
A349	416

Compound	Observed molecular ion
A350	416
Intermediate for A351	684
A352	684
A353	684
A354	528
A355	402
A356	402
A357	402
A358	424
A360	417
A361	510
A362	474
A363	434
A364	434

Procedure 9 – Synthesis of A261

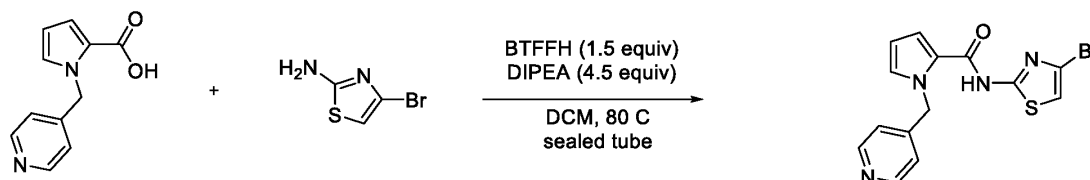


[00366] A 25 mL vial with stir bar was charged with acid (54.60 mg, 0.27 mmol, 1.00 equiv), EDCI (77.70 mg, 0.41 mmol, 1.50 equiv), DIEA (104.60 mg, 0.81 mmol, 3.00 equiv), DMAP (10.00 mg, 0.08 mmol, 0.30 equiv) and DCM (4.0 mL, 0.068 M). Amine (70.00 mg, 0.27 mmol, 1.00 equiv) was added, and the vial was capped and placed in a 25°C bath. The reaction mixture was stirred at 25°C for 4 h. The resulting solution was concentrated in vacuo. The resulting crude material was purified via silica gel chromatography & Prep-HPLC or RP column to yield the desired product.

[00367] The following compounds were prepared via a similar method:

Compound	Observed molecular ion
A261	444
A264	368
A265	444
A266	445
A273	430

Procedure 10 – Synthesis of Intermediate for A141-A144, A164, A229, & A237



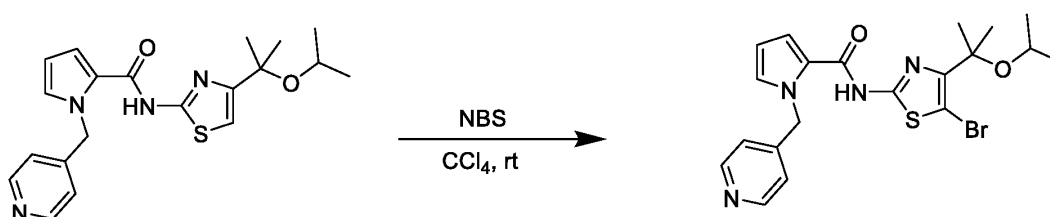
[00368] A vial with stir bar was charged with amine (1.0 g, 5.59 mmol, 1.0 equiv) and DCM (10 mL). BTFFH (2.7 g, 8.4 mmol, 1.5 equiv), DIPEA (4.4 mL, 25 mmol, 4.5 equiv) and acid

(1.5 g, 7.26 mmol, 1.1 equiv) were added. The reaction mixture was sealed and stirred at 80 °C for 20 h. After this time, the reaction mixture was poured into water (100 mL). The water layer was extracted with EtOAc (2 x 100 mL), and the combined organic layers were washed with water (3 x 100 mL). The combined organic layers were then dried over MgSO₄, filtered and concentrated in vacuo. The resulting crude material was purified via silica gel chromatography, followed by recrystallization from hot EtOH.

Example 5: Post-Amide Coupling Modifications

Procedure 1 - Synthesis of Compound A30

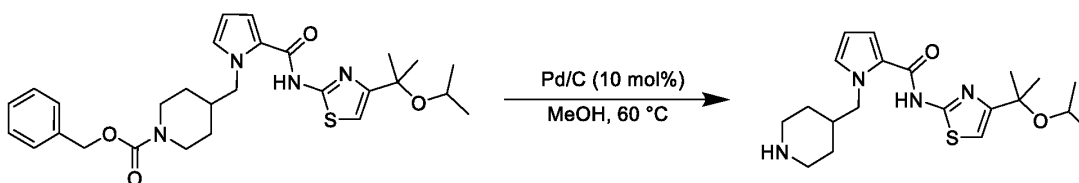
[00369] Synthesis of A30 followed the scheme, below:



[00370] A 20 mL scintillation vial with stir bar was charged with N-(4-(2-isopropoxypropan-2-yl)thiazol-2-yl)-1-(pyridin-4-ylmethyl)-1H-pyrrole-2-carboxamide (131 mg, 0.341 mmol, 1.0 equiv) and CCl₄ (2 mL, 0.2 M). N-bromosuccinimide (66.7 mg, 0.375 mmol, 1.1 equiv) was added, and the reaction mixture was stirred at room temperature overnight. The next morning, the solvent was evaporated, and the crude material was purified directly via silica gel chromatography (70-100% EtOAc in hexanes) to yield the desired product. LCMS (+ESI): calc. [M+H]⁺ = 463; found 463.

Procedure 2 - Synthesis of Compound A126

[00371] Synthesis of A126 followed the scheme, below:

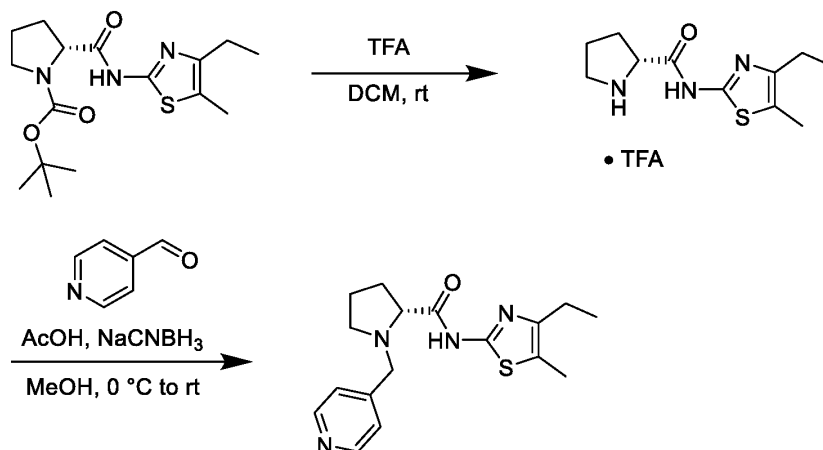


[00372] A 4 mL vial with stir bar was charged with benzyl 4-((2-((4-(2-isopropoxypropan-2-yl)thiazol-2-yl)carbamoyl)-1H-pyrrol-1-yl)methyl)piperidine-1-carboxylate (28 mg, 0.053 mmol, 1.0 equiv) and Pd/C (10 wt%, 5.7 mg, 0.0053 mmol, 0.1 equiv). The solids were evacuated and backflushed with hydrogen (1 atm, 3x). Methanol (0.5 mL, 0.1 M) was added, and the reaction mixture was heated to 60 °C over 3 days. After 3 days, the reaction mixture was filtered and concentrated in vacuo. The resulting crude material was purified via

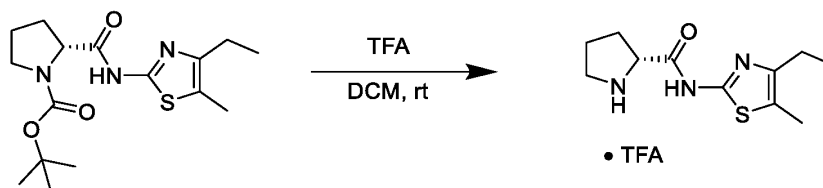
silica gel chromatography (5% MeOH in DCM with 1% NEt₃) to yield the desired product.
LCMS (+ESI): calc. [M+H]⁺ = 391; found 391.

Procedure 3 - Synthesis of Compound B24

[00373] Synthesis of B24 followed the scheme, below:

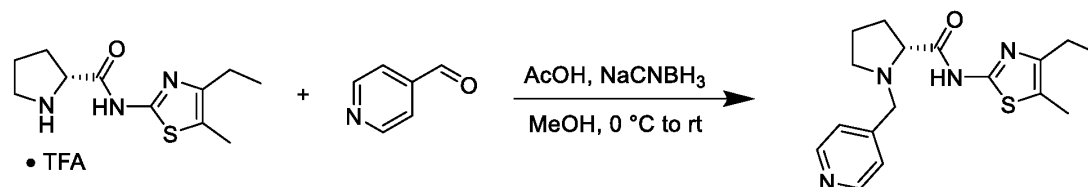


Step 1: Boc Deprotection



[00374] A 20 mL scintillation vial with stir bar was charged with tert-butyl (R)-2-((4-ethyl-5-methylthiazol-2-yl)carbamoyl)pyrrolidine-1-carboxylate (196 mg, 0.577 mmol, 1.0 equiv). DCM (2.4 mL) and TFA (600 μ L, 20 vol%) were added, and the reaction mixture was stirred at room temperature overnight. The next morning, the reaction mixture was concentrated in vacuo. The resulting product was used directly in the next step without further purification.

Step 2: Reductive amination

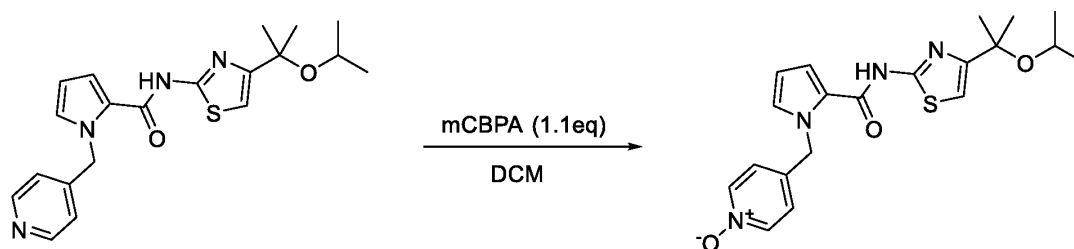


[00375] A vial with stir bar was charged with (R)-N-(4-ethyl-5-methylthiazol-2-yl)pyrrolidine-2-carboxamide 2,2,2-trifluoroacetate (204 mg, 0.577 mmol, 1.0 equiv) and methanol (2.4 mL, 0.2 M). Isonicotinaldehyde (0.326 mL, 6.46 mmol, 6.0 equiv) was added,

followed by acetic acid (0.149 mL, 2.60 mmol, 4.5 equiv). The reaction mixture was cooled to 0 °C. Sodium cyanoborohydride (218 mg, 3.46 mmol, 6.0 equiv) was slowly added at 0 °C, and the reaction was warmed to room temperature overnight. The next morning, the reaction mixture was diluted with DCM (50 mL) and washed with saturated NaHCO₃ (3 x 50 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting crude material was purified via silica gel chromatography (5% MeOH in DCM with 1% NEt₃) to yield the desired product. LCMS (+ESI): calc. [M+H]⁺= 331; found 331.

Procedure 4 - Synthesis of Compound A85

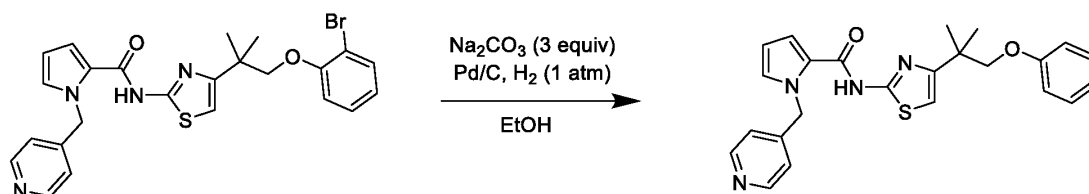
[00376] Synthesis of A85 followed the scheme, below:



[00377] Amide (100 mg, 0.26 mmol, 1 equiv) was dissolved in DCM (2.6 mL). mCPBA (64.1 mg, 0.28 mmol, 1.1 equiv) was added at room temperature, and the reaction mixture was stirred overnight. The next morning, the solvent was evaporated, and the resulting crude material was purified via pTLC (3% NEt₃ in EtOAc), followed by trituration with Et₂O and filtration, to yield the desired product. LCMS (+ESI): calc. [M+H]⁺= 401; found 401.

Procedure 5 – Synthesis of Compound A228

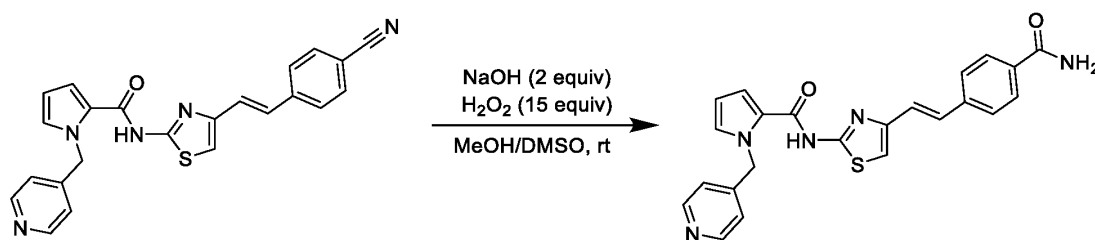
[00378] Synthesis of Compound A228 followed the scheme, below:



[00379] A vial with stir bar was charged with aryl bromide (127 mg, 0.248 mmol, 1.0 equiv), sodium carbonate (79 mg, 0.745 mmol, 3.0 equiv), and Pd/C (10 wt%, 26 mg, 0.1 equiv). The vial was evacuated and backflushed with hydrogen. EtOH (1 mL) was added, and the solution was allowed to stir at room temperature for 1 h. After 1 h, the solution was filtered through a plug of Celite, and the reaction mixture was concentrated in vacuo to yield the desired product (obs. [M+H] = 433).

Procedure 6 – Synthesis of Compound A231

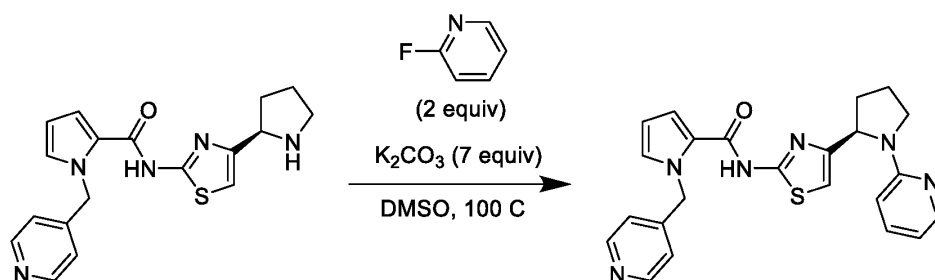
[00380] Synthesis of Compound A231 followed the scheme, below:



[00381] A vial with stir bar was charged with nitrile (20 mg, 0.0486 mmol, 1.0 equiv) in 1:1 DMSO:MeOH (1 mL). NaOH (1.0 M in water, 97 μ L, 0.097 mmol, 2.0 equiv) was added, followed by H₂O₂ (30 wt% in water, 83 μ L, 0.729 mmol, 15 equiv). The reaction mixture was allowed to stir at room temperature overnight. The next morning, the reaction mixture was poured into DCM (50 mL) and washed with saturated NaHCO₃ (2 x 50 mL). The combined aqueous layers were extracted with DCM (1 x 50 mL), and the combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo to yield the desired product (obs. [M+H] = 430).

Procedure 7 – Synthesis of Compound A317

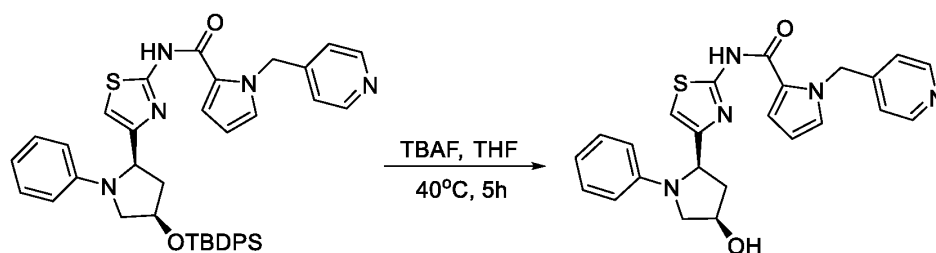
[00382] Synthesis of Compound A317 followed the scheme, below:



[00383] A vial with stir bar was charged with piperidine (74 mg, 0.208 mmol, 1.0 equiv), K₂CO₃ (201 mg, 1.46 mmol, 7 equiv), 2-fluoropyridine (36 μ L, 0.416 mmol, 2.0 equiv) and DMSO (1 mL). The vial was capped and stirred at 100 C overnight. The next morning, the reaction mixture was poured into 10% MeOH in DCM (50 mL). The organic layer was washed with saturated NaHCO₃ (2 x 50 mL), and the combined aqueous layers were extracted with 10% MeOH in DCM (1 x 50 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting crude material was purified via silica gel chromatography to yield the desired product (obs. [M+H] = 431).

Procedure 8 – Synthesis of Compound A344

[00384] Synthesis of Compound A344 followed the scheme, below:

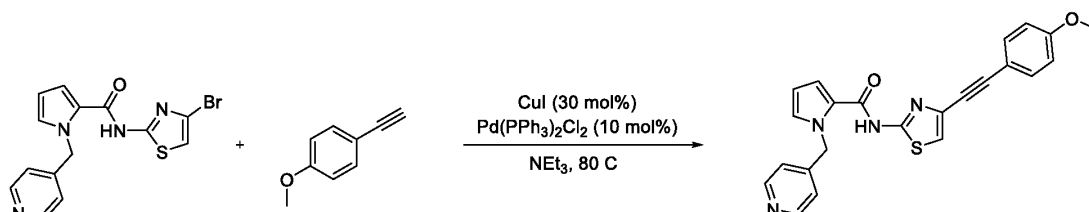


[00385] A 50 mL roundbottom flask with stir bar was charged with TBDPS-SM (220 mg, 0.322 mmol, 1.00 equiv), TBAF (841 mg, 3.22 mmol, 10 equiv) and THF (10.0 mL, 0.032 M). The vial was capped and placed in a 40°C bath. The reaction mixture was stirred at 40°C for 5h. The reaction mixture was cooled to room temperature and quenched by H₂O (30 mL). The resulting solution was extracted with (3 x 30 mL) of ethyl acetate and washed with (2x 30 mL) of brine. The organic layer was then dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting crude material was purified via silica gel chromatography & Prep-HPLC or RP column to yield the desired product. (obs. [M+H] = 446).

[00386] The following compounds were prepared via a similar method:

Compound	Observed molecular ion
A326	446
A344	446
A351	446

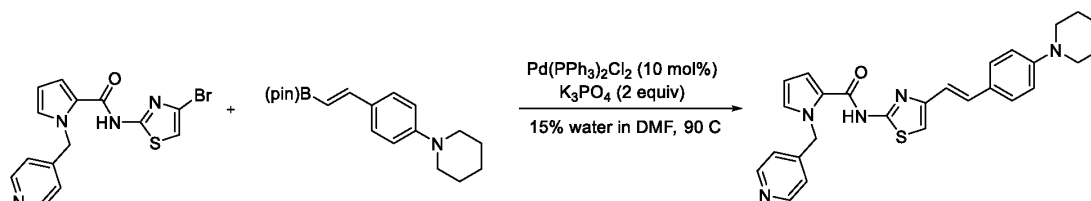
Procedure 9 – Synthesis of Compound A143



[00387] Acetylene (0.082 g, 0.28 mmol, 2.0 eq.), CuI (0.0236 g, 0.12 mmol, 0.3 eq.) and Pd(PPh₃)₂Cl₂ (0.029 g, 0.04 mmol, 0.1 eq.) were added in succession, under Ar, to the degassed solution of starting material (0.150 g, 0.41 mmol, 1.0 eq.) in TEA (1 mL). Reaction was continued at 80°C for 3h. Solution was filtered through Celite and washed with ethyl acetate. Filtrate was evaporated and crude product purified via FCC with hexane/ethyl acetate as eluent. In case of necessity final product was repurified by prep. HPLC

[00388] The following compounds were prepared in an analogous manner:

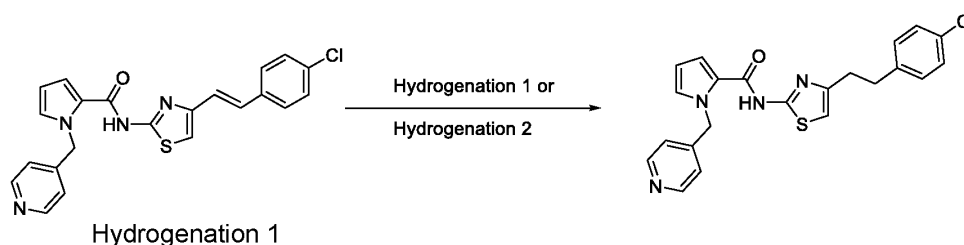
Compound	Observed molecular ion
A142	415
A141	415
A144	419
A143	415

Procedure 10 – Synthesis of Compound A233

[00389] A 20 mL vial with stir bar was charged with boronic ester (70 mg, 0.26 mmol, 1.0 equiv), bromide (93 mg, 0.26 mmol, 1.0 equiv), K_3PO_4 (109 mg, 0.51 mmol, 2.0 equiv) and solution of 15% water in DMF (3.0 mL). The mixture was purged with argon for 5 min. After that time, $Pd(PPh_3)_2Cl_2$ (18 mg, 0.03 mmol, 0.10 equiv) was added, the vial was capped, purged with argon for 2 min and placed in a 90 °C bath for 2 hours. Then reaction mixture was cooled down to the room temperature and palladium residues were filtered off through celite and washed with EtOAc. The resulting filtrate was extracted with water and brine. Organic phase was dried over $MgSO_4$, filtered and evaporated to dryness. The resulting crude material was purified via preparative HPLC to yield the desired product.

[00390] The following compounds were prepared in an analogous manner:

Compound	Observed molecular ion
A164	388
A229	430
A237	438

Procedure 11 – Synthesis of Compound A180

[00391] Reaction was carried out in H-cube. Conditions: 10% Pd/C, 60 °C, 30 bar, THF, dilution 0.05M. The resulting crude material was purified via preparative HPLC to yield the desired product.

[00392] The following compounds were prepared in an analogous manner:

Compound	Observed molecular ion
A179	423
A178	424

Hydrogenation 2

[00393] Starting material (0.055 g, 0.13 mmol, 1.0 eq), Pd (0.21g, 10% on activated carbon) were mixed in ethanol. Reaction mixture was flushed with Ar, connected to H₂ balloon (1 atm) and stirred overnight at 40°C. The catalyst was removed by filtration, the filtrate was evaporated and the crude material was purified by preparative HPLC to yield the desired product.

[00394] The following compounds were prepared in an analogous manner:

Compound	Observed molecular ion
A180	423
A176	419

Example 6: Biological Assays

Dox-Induced PD1-ss-Gluc Assay

[00395] Flp-In 293 T-REx™ cells were transfected with pcDNA™5/FRT/TO plasmid inserted with cDNA encoding Gaussia Luciferase fused to the 3' end of cDNA encoding PD1 signal sequence plus 10 amino acids (N-MQIPQAPWPVWAVLQLGWRPGWFLDSPDR-C) (SEQ ID NO: 1). Transfected cells were selected for resistance to the selectable markers Hygromycin and Blasticidin to create a stable cell line that contained the PD1-ss+10aa/Gaussia Luciferase cDNA insert whose expression was regulated under the T-REx™ system. The day before assay, cells were trypsinized and plated in 384-well tissue culture plates. The next day, compound dilutions in DMSO/media containing doxycycline were added to the wells and incubated at 37°C, 5% CO₂. 24 hours later, coelenterazine substrate was added to each well and luciferase signal was quantified using Tecan Infinite M1000 Pro for potency determination.

[00396] Results for select compounds provided herein are shown in Table 1, below. For chemical structures that include one or more stereoisomers, but are illustrated without indicating stereochemistry, the assay data refers to a mixture of stereoisomers.

Dox Induced TNFα-FL-Gluc Assay

[00397] Flp-In 293 T-REx™ cells were transfected with pcDNA™5/FRT/TO plasmid inserted with cDNA encoding Gaussia Luciferase fused to the 3' end of cDNA encoding full length TNFα (amino acids 1-233). Transfected cells were selected for resistance to the selectable markers Hygromycin and Blasticidin to create a stable cell line that contained the TNFα-FL/Gaussia Luciferase cDNA insert whose expression was regulated under the T-REx™ system. The day before assay, cells were trypsinized and plated in 384-well tissue culture plates. The next day, compound dilutions in DMSO/media containing doxycycline were added to the wells and incubated at 37°C, 5% CO₂. 24 hours later, coelenterazine

substrate was added to each well and luciferase signal was quantified using Tecan Infinite M1000 Pro for potency determination.

[00398] Results for select compounds provided herein are shown in Table 1, below. For chemical structures that include one or more stereoisomers, but are illustrated without indicating stereochemistry, the assay data refers to a mixture of stereoisomers.

Dox-Induced Her3-ss-Gluc Assay

[00399] Flp-In 293 T-REx™ cells were transfected with pcDNA™5/FRT/TO plasmid inserted with cDNA encoding Gaussia Luciferase fused to the 3' end of cDNA encoding HER3 signal sequence plus 4 amino acids (N- MRANDALQVLGLLFSLARGSEVG-C) (SEQ ID NO: 2). Transfected cells were selected for resistance to the selectable markers Hygromycin and Blasticidin to create a stable cell line that contained the HER3-ss+4aa/Gaussia Luciferase cDNA insert whose expression was regulated under the T-REx™ system. The day before assay, cells were trypsinized and plated in 384-well tissue culture plates. The next day, compound dilutions in DMSO/media containing doxycycline were added to the wells and incubated at 37°C, 5% CO₂. 24 hours later, coelenterazine substrate was added to each well and luciferase signal was quantified using Tecan Infinite M1000 Pro for potency determination.

[00400] Results for select compounds provided herein are shown in Table 1. For chemical structures that include one or more stereoisomers, but are illustrated without indicating stereochemistry, the assay data refers to a mixture of stereoisomers.

Dox Induced IL2-FL-Gluc Assay

[00401] Flp-In 293 T-REx™ cells were transfected with pcDNA™5/FRT/TO plasmid inserted with cDNA encoding Gaussia Luciferase fused to the 3' end of cDNA encoding full length IL-2 (amino acids 1-153). Transfected cells were selected for resistance to the selectable markers Hygromycin and Blasticidin to create a stable cell line that contained the IL-2-FL/Gaussia Luciferase cDNA insert whose expression was regulated under the T-REx™ system. The day before assay, cells were trypsinized and plated in 384-well tissue culture plates. The next day, compound dilutions in DMSO/media containing doxycycline were added to the wells and incubated at 37°C, 5% CO₂. 24 hours later, coelenterazine substrate was added to each well and luciferase signal was quantified using Tecan Infinite M1000 Pro for potency determination.

[00402] Results for select compounds provided herein are shown in Table 1, below. For chemical structures that include one or more stereoisomers, but are illustrated without indicating stereochemistry, the assay data refers to a mixture of stereoisomers.

H929 Cell Viability Assay

[00403] The human multiple myeloma cell line NCI-H929 was cultured in Advanced RPMI 1640 media (Gibco®) supplemented with 6% fetal bovine serum, 2mM Glutamine, and 1x Penicillin/Streptomycin. On the day of assay, cells were resuspended in RPMI 1640 media supplemented with 10% fetal bovine serum, 2mM Glutamine, and 1x Penicillin/Streptomycin and plated in 384-well tissue culture plates and treated with compound dilutions in DMSO/media. Plates were incubated at 37°C, 5% CO₂ for 48 hours. After 48 hours, Celltiter-Glo® (Promega) was added to each well and luciferase signal was quantified using Tecan Infinite M1000 Pro for cell viability determination.

[00404] Results for select compounds provided herein are shown in Table 1, below. For chemical structures that include one or more stereoisomers, but are illustrated without indicating stereochemistry, the assay data refers to a mixture of stereoisomers.

U266 Cell Viability Assay

[00405] The human multiple myeloma cell line U266B1 was cultured in RPMI 1640 media supplemented with 10% fetal bovine serum, 2mM Glutamine, and 1x Penicillin/Streptomycin. Cells were plated in 384-well tissue culture plates and treated with compound dilutions in DMSO/media. Plates were incubated at 37°C, 5% CO₂ for 48 hours. After 48 hours, Celltiter-Glo® (Promega) was added to each well and luciferase signal was quantified using Tecan Infinite M1000 Pro for cell viability determination.

[00406] Results for select compounds provided herein are shown in Table 1, below. For chemical structures that include one or more stereoisomers, but are illustrated without indicating stereochemistry, the assay data refers to a mixture of stereoisomers.

Table 1

Compound ID	24hr Dox Inducible PD1ssGluc 293FRT/TO: Mean IC50 (nM)	24hr Dox Inducible TNFaFLGluc 293FRT/TO: Mean IC50 (nM)	24hr Dox Inducible Her3(ss+4)Gluc 293FRT/TO: Mean IC50 (nM)	24hr Dox Inducible IL2FLGluc 293FRT/TO: Mean IC50 (nM)	48hr H929 Viability Celltiter-Glo: Mean EC50 (nM)	48hr U266 Viability Celltiter-Glo: Mean EC50 (nM)
A1	24	401	55	93	1877	I.A.
A2	29	391	62	105	1612	22304
A3	36	580	99	144	2910	I.A.
A4	38	377	91	148	2774	I.A.
A5	43	810	102	145	2435	23887
A6	46	541	88	78	2167	6225
A7	58	808	93	71	3850	I.A.
A8	58	420	174	165	3892	7869
A9	104	1623	202	197	9461	I.A.
A10	105	1579	195	158	15609	I.A.

Compound ID	24hr Dox Inducible PD1ssGluc 293FRT/TO: Mean IC50 (nM)	24hr Dox Inducible TNFaFLGluc 293FRT/TO: Mean IC50 (nM)	24hr Dox Inducible Her3(ss+4)Gluc 293FRT/TO: Mean IC50 (nM)	24hr Dox Inducible IL2FLGluc 293FRT/TO: Mean IC50 (nM)	48hr H929 Viability Celltiter-Glo: Mean EC50 (nM)	48hr U266 Viability Celltiter-Glo: Mean EC50 (nM)
A11	115	2392	128	61	8690	I.A.
A12	139	1755	338	566	18613	I.A.
A13	148	3305	382	648	18783	I.A.
A14	153	5107	568	1048	I.A.	I.A.
A15	169	5428	318	110	16591	I.A.
A16	185	5013	377	266	> 23900	I.A.
A17	191	2235	560	804	20766	I.A.
A18	226	1353	461	718	15092	I.A.
A19	246	8535	492	529	I.A.	I.A.
A20	248	7166	510	351	I.A.	I.A.
A21	259	3676	590	502	> 24966	I.A.
A22	271	8832	503	460	I.A.	I.A.
A23	290	5472	447	429	I.A.	I.A.
A24	303	11685	619	477	I.A.	I.A.
A25	314	9977	692	490	I.A.	I.A.
A26	319	10684	817	759	I.A.	I.A.
A27	445	9525	822	320	I.A.	I.A.
A28	462	3953	752	401	I.A.	I.A.
A29	488	19613	1243	935	I.A.	I.A.
A30	552	11818	809	927	22722	I.A.
A31	596	11814	1629	1340	I.A.	I.A.
A32	633	> 20334	1331	1977	I.A.	I.A.
A33	663	I.A.	1623	2469	8992	6888
A34	674	I.A.	2419	4239	I.A.	I.A.
A35	692	I.A.	1938	2299	I.A.	I.A.
A36	698	20987	1137	896	I.A.	I.A.
A37	703	12119	1236	1074	I.A.	I.A.
A38	706	14775	1199	1407	I.A.	I.A.
A39	723	13069	1492	1339	I.A.	I.A.
A40	858	12581	1562	1206	I.A.	I.A.
A41	878	11999	2392	1981	9523	I.A.
A42	939	I.A.	2176	3791	I.A.	I.A.
A43	942	I.A.	2214	2672	I.A.	I.A.
A44	963	13290	1484	837	> 24839	I.A.
A45	965	13802	1645	869	I.A.	I.A.
A46	1075	17825	2985	890	I.A.	I.A.
A47	1093	24952	2210	3111	I.A.	I.A.
A48	1186	I.A.	2689	2217	I.A.	I.A.
A49	1211	23621	2583	1891	I.A.	I.A.
A50	1288	I.A.	2932	1450	I.A.	I.A.
A51	1300	I.A.	3423	2978	I.A.	I.A.
A52	1357	I.A.	2835	1946	I.A.	I.A.
A53	1377	19100	1915	1200	17330	I.A.

Compound ID	24hr Dox Inducible PD1ssGluc 293FRT/TO: Mean IC50 (nM)	24hr Dox Inducible TNFaFLGluc 293FRT/TO: Mean IC50 (nM)	24hr Dox Inducible Her3(ss+4)Gluc 293FRT/TO: Mean IC50 (nM)	24hr Dox Inducible IL2FLGluc 293FRT/TO: Mean IC50 (nM)	48hr H929 Viability Celltiter-Glo: Mean EC50 (nM)	48hr U266 Viability Celltiter-Glo: Mean EC50 (nM)
A54	1383	I.A.	4048	4448	I.A.	I.A.
A55	1386	I.A.	3160	3990	I.A.	I.A.
A56	1419	I.A.	5312	6466	I.A.	I.A.
A57	1419	I.A.	4203	4930	I.A.	I.A.
A58	1503	I.A.	3530	7057	I.A.	I.A.
A59	1508	16636	11948	3625	I.A.	I.A.
A60	1566	I.A.	3751	2694	I.A.	I.A.
A61	1672	I.A.	3406	2381	I.A.	I.A.
A62	1694	I.A.	4298	5074	I.A.	I.A.
A63	1717	I.A.	10594	I.A.	I.A.	I.A.
A64	1732	I.A.	3483	2724	23220	I.A.
A65	1787	I.A.	4134	11229	I.A.	I.A.
A66	1840	I.A.	4152	4783	I.A.	I.A.
A67	1880	I.A.	3242	2083	I.A.	I.A.
A68	2072	I.A.	2725	2762	I.A.	I.A.
A69	2079	I.A.	6216	4171	I.A.	I.A.
A70	2229	I.A.	9390	5674	I.A.	I.A.
A71	2281	I.A.	5441	3541	I.A.	I.A.
A72	2466	I.A.	6107	22362	I.A.	I.A.
A73	2472	I.A.	7277	2023	I.A.	I.A.
A74	2573	I.A.	5389	4219	I.A.	I.A.
A75	2676	I.A.	15290	6945	I.A.	I.A.
A76	2725	I.A.	12510	3989	I.A.	I.A.
A77	3048	I.A.	4681	3099	24963	I.A.
A78	3163	I.A.	7876	6375	20890	I.A.
A79	3175	I.A.	5256	4146	24882	I.A.
A80	4218	I.A.	7884	3532	21927	I.A.
A81	4624	I.A.	23015	I.A.	I.A.	I.A.
A82	4663	I.A.	I.A.	I.A.	I.A.	I.A.
A83	5369	I.A.	I.A.	4517	I.A.	I.A.
A84	6339	I.A.	I.A.	5819	I.A.	I.A.
A85	7540	I.A.	I.A.	I.A.	I.A.	I.A.
A86	7995	I.A.	I.A.	I.A.	I.A.	I.A.
A87	8134	I.A.	I.A.	8589	I.A.	I.A.
A88	9653	I.A.	I.A.	I.A.	I.A.	I.A.
A89	9847	I.A.	I.A.	I.A.	I.A.	I.A.
A90	10049	I.A.	I.A.	I.A.	16900	I.A.
A91	11947	I.A.	I.A.	> 21571	I.A.	I.A.
A92	13137	I.A.	I.A.	I.A.	I.A.	I.A.
A93	13225	I.A.	I.A.	I.A.	I.A.	I.A.
A94	14615	I.A.	I.A.	I.A.	I.A.	I.A.
A95	14671	I.A.	I.A.	I.A.	I.A.	I.A.
A96	15672	I.A.	I.A.	I.A.	I.A.	I.A.

Compound ID	24hr Dox Inducible PD1ssGluc 293FRT/TO: Mean IC50 (nM)	24hr Dox Inducible TNFaFLGluc 293FRT/TO: Mean IC50 (nM)	24hr Dox Inducible Her3(ss+4)Glu c 293FRT/TO: Mean IC50 (nM)	24hr Dox Inducible IL2FLGluc 293FRT/TO: Mean IC50 (nM)	48hr H929 Viability Celltiter-Glo: Mean EC50 (nM)	48hr U266 Viability Celltiter-Glo: Mean EC50 (nM)
A97	18860	I.A.	I.A.	I.A.	I.A.	I.A.
A98	19562	I.A.	I.A.	I.A.	I.A.	I.A.
A99	19876	I.A.	I.A.	I.A.	I.A.	I.A.
A100	24597	I.A.	I.A.	I.A.	24583	I.A.
A101	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A102	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A103	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A104	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A105	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A106	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A107	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A108	I.A.	I.A.	I.A.	7270	I.A.	I.A.
A109	I.A.	I.A.	I.A.	I.A.	19462	I.A.
A110	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A111	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A112	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A113	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A114	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A115	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A116	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A117	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A118	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A119	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A120	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A121	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A122	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A123	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A124	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A125	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A126	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A127	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A128	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A129	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A130	I.A.	I.A.	I.A.	I.A.	I.A.	
A131	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A132	150	1205	417	744	8853	9337
A141	277	1824	651	1579	7720	13093
A142	241	5410	565	1050	I.A.	I.A.
A143	89	1576	423	617	15198	> 19801
A144	151	905	395	748	6860	10419
A150	122	14109	505	1284	I.A.	I.A.
A151	90	7132	386	691	I.A.	I.A.
A152	85	1577	280	854	10982	I.A.

Compound ID	24hr Dox Inducible PD1ssGluc 293FRT/TO: Mean IC50 (nM)	24hr Dox Inducible TNFaFLGluc 293FRT/TO: Mean IC50 (nM)	24hr Dox Inducible Her3(ss+4)Glu c 293FRT/TO: Mean IC50 (nM)	24hr Dox Inducible IL2FLGluc 293FRT/TO: Mean IC50 (nM)	48hr H929 Viability Celltiter-Glo: Mean EC50 (nM)	48hr U266 Viability Celltiter-Glo: Mean EC50 (nM)
A153	902	I.A.	1553	4071	I.A.	I.A.
A154	694	11452	2605	5419	I.A.	I.A.
A155	232	15896	2140	4371	I.A.	I.A.
A157	9056	I.A.	13449	I.A.	I.A.	I.A.
A158	293	2419	993	1474	15714	I.A.
A159	247	9007	948	2648	5708	16244
A160	51	1736	259	374	9097	I.A.
A161	134	2866	523	1072	5282	10879
A163	59	2469	305	652	7606	24495
A164	98	23683	8397	6770	17673	I.A.
A165	1648	I.A.	9828	10751	11086	I.A.
A166	13483	I.A.	I.A.	I.A.	I.A.	I.A.
A176	272	2871	643	1196	20801	I.A.
A178	152	929	367	500	9271	19881
A179	211	3584	541	1172	5752	10566
A180	57	736	156	281	7184	6464
A184	448	2412	807	1076	11804	13340
A187	10403	I.A.	> 21927	11563	18316	I.A.
A190	5230	I.A.	> 18142	3437	I.A.	I.A.
A194	280	2302	600	1143	6669	15986
A200	140	1610	332	251	15743	I.A.
A209	232	4740	578	1238	I.A.	I.A.
A210	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A211	10036	I.A.	I.A.	8313	I.A.	I.A.
A212	4736	I.A.	4203	4574	2992	3758
A213	12086	I.A.	4939	6049	13827	17695
A214	4555	I.A.	6695	6451	I.A.	I.A.
A215	443	2492	720	1248	13059	I.A.
A216	318	18750	1910	1560	I.A.	I.A.
A217	245	3527	425	943	> 21505	I.A.
A218	131	3028	315	779	17100	I.A.
A219	48	946	234	443	8601	13720
A220	86	3750	329	628	I.A.	I.A.
A221	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A222	348	7703	1803	2274	19070	I.A.
A223	513	I.A.	3123	8038	22325	I.A.
A224	141	I.A.	296	I.A.	20548	I.A.
A225	324	3837	558	486	8894	I.A.
A226	302	7083	426	320	11938	I.A.
A227	53	1895	379	625	8946	> 21399
A228	335	3593	730	933	9252	I.A.
A229	66	4585	568	1053	24853	I.A.
A230	1030	I.A.	I.A.	I.A.	12200	I.A.

Compound ID	24hr Dox Inducible PD1ssGluc 293FRT/TO: Mean IC50 (nM)	24hr Dox Inducible TNFaFLGluc 293FRT/TO: Mean IC50 (nM)	24hr Dox Inducible Her3(ss+4)Glu c 293FRT/TO: Mean IC50 (nM)	24hr Dox Inducible IL2FLGluc 293FRT/TO: Mean IC50 (nM)	48hr H929 Viability Celltiter-Glo: Mean EC50 (nM)	48hr U266 Viability Celltiter-Glo: Mean EC50 (nM)
A231	506	11158	I.A.	7068	16805	I.A.
A232	2992	21463	14886	8603	13366	19711.9
A233	56	2223	304	633	5786	I.A.
A234	63	I.A.	216	341	4487	I.A.
A235	63	I.A.	145	237	4150	I.A.
A236	87	3239	535	1009	7704	I.A.
A237	288	I.A.	1119	1869	18678	I.A.
A238	643	18327	1569	1199	I.A.	I.A.
A239	1508	I.A.	I.A.	I.A.	I.A.	I.A.
A240	55	7787	271	445	11770	I.A.
A241	27	1315	179	324	8366	I.A.
A242	281	I.A.	596	I.A.	I.A.	I.A.
A243	178	2361	199	136	14831	I.A.
A244	81	1434	225	648	17677	17388
A245	3181	22193	I.A.	14097	9057	17491
A246	526	I.A.	21868	I.A.	14039	10279
A247	146	2322	377	788	I.A.	I.A.
A248	38	1505	152	211	I.A.	I.A.
A249	163	1408	545	881	19865	14445
A250	5275	I.A.	15664	7395	I.A.	I.A.
A251	125	1418	344	549	11677	I.A.
A252	530	6928	1130	1281	13981	I.A.
A253	220	4197	672	1577	10753	15630
A254	74	1528	189	554	4096	4134
A255	102	1329	250	477	7209	18137
A256	2154	I.A.	4042	2866	I.A.	I.A.
A257	1880	24844	4007	3628	I.A.	I.A.
A258	701	I.A.	6400	14529	23776	I.A.
A259	516	I.A.	7112	10534	I.A.	I.A.
A260	478	4612	974	950	10916	I.A.
A261	2247	I.A.	2020	I.A.	I.A.	I.A.
A262	1461	24182	3142	3121	I.A.	I.A.
A263	381	5222	958	1042	21543	I.A.
A264	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A265	9061	I.A.	I.A.	7301	I.A.	I.A.
A266	6254	I.A.	9004	I.A.	I.A.	I.A.
A267	15392	I.A.	I.A.	I.A.	I.A.	I.A.
A268	52	821	129	291	7293	I.A.
A269	13	20294	1574	2922	> 21583	I.A.
A270	161	1736	463	599	10427	I.A.
A271	316	2871	912	951	15481	I.A.
A272	261	I.A.	1723	I.A.	I.A.	I.A.
A273	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.

Compound ID	24hr Dox Inducible PD1ssGluc 293FRT/TO: Mean IC50 (nM)	24hr Dox Inducible TNFaFLGluc 293FRT/TO: Mean IC50 (nM)	24hr Dox Inducible Her3(ss+4)Glu c 293FRT/TO: Mean IC50 (nM)	24hr Dox Inducible IL2FLGluc 293FRT/TO: Mean IC50 (nM)	48hr H929 Viability Celltiter-Glo: Mean EC50 (nM)	48hr U266 Viability Celltiter-Glo: Mean EC50 (nM)
A274	363	22284	2549	3743	23859	I.A.
A275	15	147	32	29	1471	I.A.
A276	287	2471	859	1498	19371	> 25825
A277	325	4062	819	769	18670	I.A.
A278	538	4997	1131	1270	> 23903	I.A.
A279	1135	I.A.	4201	4968	I.A.	I.A.
A280	12714	I.A.	I.A.	I.A.	I.A.	I.A.
A281	244	1949	817	1157	11028	I.A.
A282	324	4660	864	1505	7076	12488
A283	1347	7181	3073	3865	22965	I.A.
A284	767	4072	1241	2316	4920	6104
A285	1228	16138	1836	2861	17813	16722
A286	1283	6173	2423	3934	9574	15733
A287	88	1155	181	376	5058	I.A.
A288	440	3028	1261	1537	23925	I.A.
A289	201	3610	512	856	22030	I.A.
A290	261	4023	648	1401	15162	20793
A291	918	I.A.	5277	6718	I.A.	22471
A292	211	2512	471	835	19006	I.A.
A293	367	3647	632	619	11427	I.A.
A294	499	4443	1052	939	I.A.	I.A.
A295	5	3563	692	846	18308	18864
A296	655	10290	1207	1146	I.A.	I.A.
A297	66	2823	251	687	I.A.	I.A.
A298	260	1665	482	450	13470	I.A.
A299	7	I.A.	214	219	I.A.	I.A.
A300	328	2417	589	450	10475	I.A.
A301	43	242	54	64	2769	I.A.
A302	1978	I.A.	6167	10583	I.A.	I.A.
A303	104	554	125	69	4504	I.A.
A304	20	236	108	178	6272	14342
A305	196	2182	414	657	12398	I.A.
A306	184	1790	495	489	11172	I.A.
A307	679	I.A.	8812	I.A.	I.A.	I.A.
A308	879	13504	1687	2369	17207	I.A.
A309	24	721	71	199	6109	14751
A310	2121	24571	5439	6992	I.A.	I.A.
A311	175	3333	510	874	6023	6225
A312	197	4132	646	1140	I.A.	I.A.
A313	3857	I.A.	7898	6361	I.A.	I.A.
A314	47	1466	145	424	9984	15995
A315	253	8030	827	1418	I.A.	I.A.
A316	117	3166	313	762	I.A.	I.A.

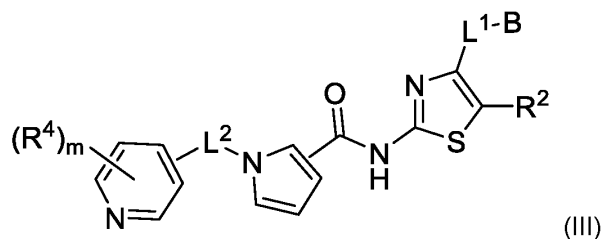
Compound ID	24hr Dox Inducible PD1ssGluc 293FRT/TO: Mean IC50 (nM)	24hr Dox Inducible TNFaFLGluc 293FRT/TO: Mean IC50 (nM)	24hr Dox Inducible Her3(ss+4)Glu c 293FRT/TO: Mean IC50 (nM)	24hr Dox Inducible IL2FLGluc 293FRT/TO: Mean IC50 (nM)	48hr H929 Viability Celltiter-Glo: Mean EC50 (nM)	48hr U266 Viability Celltiter-Glo: Mean EC50 (nM)
A317	25	427	64	57	2543	I.A.
A318	49	817	97	184	6044	I.A.
A319	1312	16038	2722	1845	I.A.	I.A.
A320	10354	I.A.	I.A.	I.A.	I.A.	I.A.
A321	215	4169	902	948	9727	I.A.
A322	3	14	9	9	315	I.A.
A323	7	11	13	10	118	I.A.
A324	289	3013	582	475	11328	I.A.
A325	26	206	46	58	3622	I.A.
A326	59	308	201	126	4999	I.A.
A327	16	4487	469	999	15077	I.A.
A328	9	105	12	14	381	16540
A329	202	3163	342	739	22796	I.A.
A330	218	3924	475	1023	19250	I.A.
A331	64	423	82	178	4719	I.A.
A332	64	516	97	82	4292	I.A.
A333	21	165	42	27	1480	I.A.
A334	80	775	138	110	6472	9048
A335	130	3009	411	752	11424	I.A.
A336	374	1347	835	334	17862	I.A.
A337	190	2849	548	379	21456	I.A.
A338	205	1853	264	345	14844	I.A.
A339	18	226	29	13	1312	I.A.
A340	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
A341	47	I.A.	I.A.	I.A.	I.A.	I.A.
A342	68	I.A.	952	1396	23747	I.A.
A343	17	3622	492	1149	7178	15932
A344	971	8859	2027	1348	I.A.	I.A.
A345	11	100	22	23	720	I.A.
A346	17	92	22	20	972	I.A.
A347	42	13107	6013	9581	23803	20318
A348	I.A.	I.A.	I.A.	I.A.	16970	18342
A349	364	6624	1262	1700	12532	I.A.
A350	707	14883	2394	I.A.	I.A.	I.A.
A351	167	954	450	259	7502	I.A.
A352	8	62	19	16	452	I.A.
A353	5	13	12	11	303	I.A.
A354	6	54	16	21	901	I.A.
A355	524	9744	3810	11319	22265	17198
A356	35	14435	5412	I.A.	I.A.	23817
A357	12	7478	2306	9073	10744	17903
A358	29	3572	443	765	17872	I.A.
A359	11	83	13	15	382	I.A.

Compound ID	24hr Dox Inducible PD1ssGluc 293FRT/TO: Mean IC50 (nM)	24hr Dox Inducible TNFaFLGluc 293FRT/TO: Mean IC50 (nM)	24hr Dox Inducible Her3(ss+4)Gluc 293FRT/TO: Mean IC50 (nM)	24hr Dox Inducible IL2FLGluc 293FRT/TO: Mean IC50 (nM)	48hr H929 Viability Celltiter-Glo: Mean EC50 (nM)	48hr U266 Viability Celltiter-Glo: Mean EC50 (nM)
B1	1889	I.A.	4319	6285	I.A.	I.A.
B2	1974	I.A.	12125	8420	I.A.	I.A.
B3	2841	I.A.	4240	2925	I.A.	I.A.
B4	3015	I.A.	11210	22501	I.A.	I.A.
B5	3238	I.A.	12572	10554	I.A.	I.A.
B6	6655	I.A.	I.A.	I.A.	I.A.	I.A.
B7	9074	I.A.	19959	24269	I.A.	I.A.
B8	9099	I.A.	I.A.	I.A.	I.A.	I.A.
B9	9426	I.A.	I.A.	I.A.	I.A.	I.A.
B10	11853	I.A.	I.A.	I.A.	I.A.	I.A.
B11	22747	I.A.	5565	I.A.	I.A.	I.A.
B12	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
B13	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
B14	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
B15	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
B16	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
B17	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
B18	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
B19	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
B20	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
B21	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
B22	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
B23	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
B24	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
B25	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
B26	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
B27	I.A.	I.A.	I.A.	I.A.	I.A.	I.A.
B28	I.A.	I.A.	NT	I.A.	23450	I.A.
B29	I.A.	I.A.	NT	I.A.	I.A.	I.A.

I.A. indicates IC50 > 25 μ M; NT indicates not tested.

What is Claimed is:

1. A compound having a structure of Formula (III):



wherein:

L^1 is a bond, C_{1-6} alkylene, or $\left\{ -C_{0-3}\text{alkylene} \text{ --- } C_{0-2}\text{alkylene} - \right\}$, wherein --- indicates a double bond, a triple bond, or a fused cyclopropyl;

B is C_{0-3} alkylene-X;

X is an aromatic or nonaromatic C_{4-10} carbocycle, or an aromatic or nonaromatic 4-10 membered heterocycle having 1-3 ring heteroatoms selected from N, O, and S;

R^2 is H or C_{1-3} alkyl;

L^2 is C_{0-3} alkylene;

m is 0 to 2; and

each R^4 independently is C_{1-3} alkyl, C_{2-3} alkynyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, halo, or NHC_{1-3} alkylene-aryl; or a pharmaceutically acceptable salt thereof.

2. The compound or salt of claim 1, wherein L^1 is a bond.

3. The compound or salt of claim 1, wherein L^1 is C_{1-6} alkylene.

4. The compound or salt of claim 3, wherein L^1 is CH_2 , CH_2CH_2 , $C(CH_3)_2$, $C(CH_3)_2CH_2$, or $C(CH_3)_2CH_2CH_2$.

5. The compound or salt of claim 1, wherein L^1 is $\left\{ -C_{0-3}\text{alkylene} \text{ --- } C_{0-2}\text{alkylene} - \right\}$.

6. The compound or salt of claim 5, wherein L^1 is $\left\{ -C_{0-3}\text{alkylene} \text{ ---} - \right\}$.

7. The compound or salt of claim 5, wherein L^1 is $\left\{ \text{---} C_{0-2}\text{alkylene} - \right\}$.

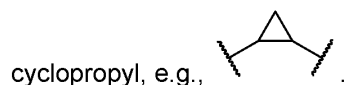
8. The compound or salt of claim 5, wherein L^1 is $\left\{ \text{---} \right\}$.

9. The compound or salt of any one of claims 5-8, wherein --- indicates a double bond.

10. The compound or salt of claim 9, wherein the double bond is further substituted with C_{1-3} alkyl.

11. The compound or salt of any one of claims 5-8, wherein --- indicates a triple bond.

12. The compound or salt of any one of claims 5-8, wherein --- indicates a fused



13. The compound or salt of any one of claims 1-12, wherein B is C_{1-3} alkylene-X.

14. The compound or salt of any one of claims 1-12, wherein B is X.

15. The compound or salt of any one of claims 1-14, wherein X is pyrrolidinyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, phenyl, piperidinyl, pyridinyl, piperazinyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, quinolinyl, morpholinyl, pyrrolidonyl, pyrimidinyl, pyridazinyl, indenyl, dihydroindenyl, dihydrobenzofuranyl, chromanyl, isochromanyl, dihydroisoquinolinyl, or indolyl.

16. The compound or salt of any one of claims 1-15, wherein

X is substituted with 1-3 G;

each G independently is selected from the group consisting of halo, OH, =O, CN, NO_2 , $\text{N(R}^{\text{N}})_2$, $\text{N(R}^{\text{N}})\text{C(O)C}_{1-3}\text{alkyl}$, $\text{C}_{1-3}\text{alkyl}$, $\text{C}_{1-3}\text{alkoxy}$, $\text{C}_{1-3}\text{ haloalkyl}$, $\text{C}_{1-3}\text{ haloalkoxy}$, $\text{C(O)C}_{1-3}\text{alkyl}$, $\text{S(O}_2\text{)-Z}$, C(O)-Z , $\text{C(O)N(R}^{\text{N}})_2$, silyl ether, and $[\text{O}]_{0-1}\text{-C}_{0-3}\text{alkylene-Z}$;

each R^{N} independently is H or $\text{C}_{1-4}\text{alkyl}$;

Z is aromatic or nonaromatic C_{3-10} carbocycle, or aromatic or nonaromatic 4-10 membered heterocycle having 1-3 heteroatoms selected from the group consisting of N, O, and S;

Z is optionally substituted with 1-3 E; and,

each E independently is selected from $\text{C}_{1-3}\text{alkyl}$, $\text{C}_{1-3}\text{alkoxy}$, =O, $\text{C}_{1-3}\text{haloalkoxy}$, CN, and halo.

17. The compound or salt of claim 1, wherein



X is aromatic or nonaromatic C_{4-7} carbocycle, or an aromatic or nonaromatic 4-9 membered heterocycle having 1 ring heteroatom;

X is optionally substituted with 1-3 G;

each G independently is selected from the group consisting of halo, OH, =O, CN, NO_2 , $\text{N(R}^{\text{N}})_2$, $\text{N(R}^{\text{N}})\text{C(O)C}_{1-3}\text{alkyl}$, $\text{C}_{1-3}\text{alkyl}$, $\text{C}_{1-3}\text{alkoxy}$, $\text{C}_{1-3}\text{ haloalkyl}$, $\text{C}_{1-3}\text{ haloalkoxy}$, $\text{C(O)C}_{1-3}\text{alkyl}$, $\text{S(O}_2\text{)-Z}$, C(O)-Z , $\text{C(O)N(R}^{\text{N}})_2$, silyl ether, and $[\text{O}]_{0-1}\text{-C}_{0-3}\text{alkylene-Z}$;

each R^{N} independently is H or $\text{C}_{1-4}\text{alkyl}$;

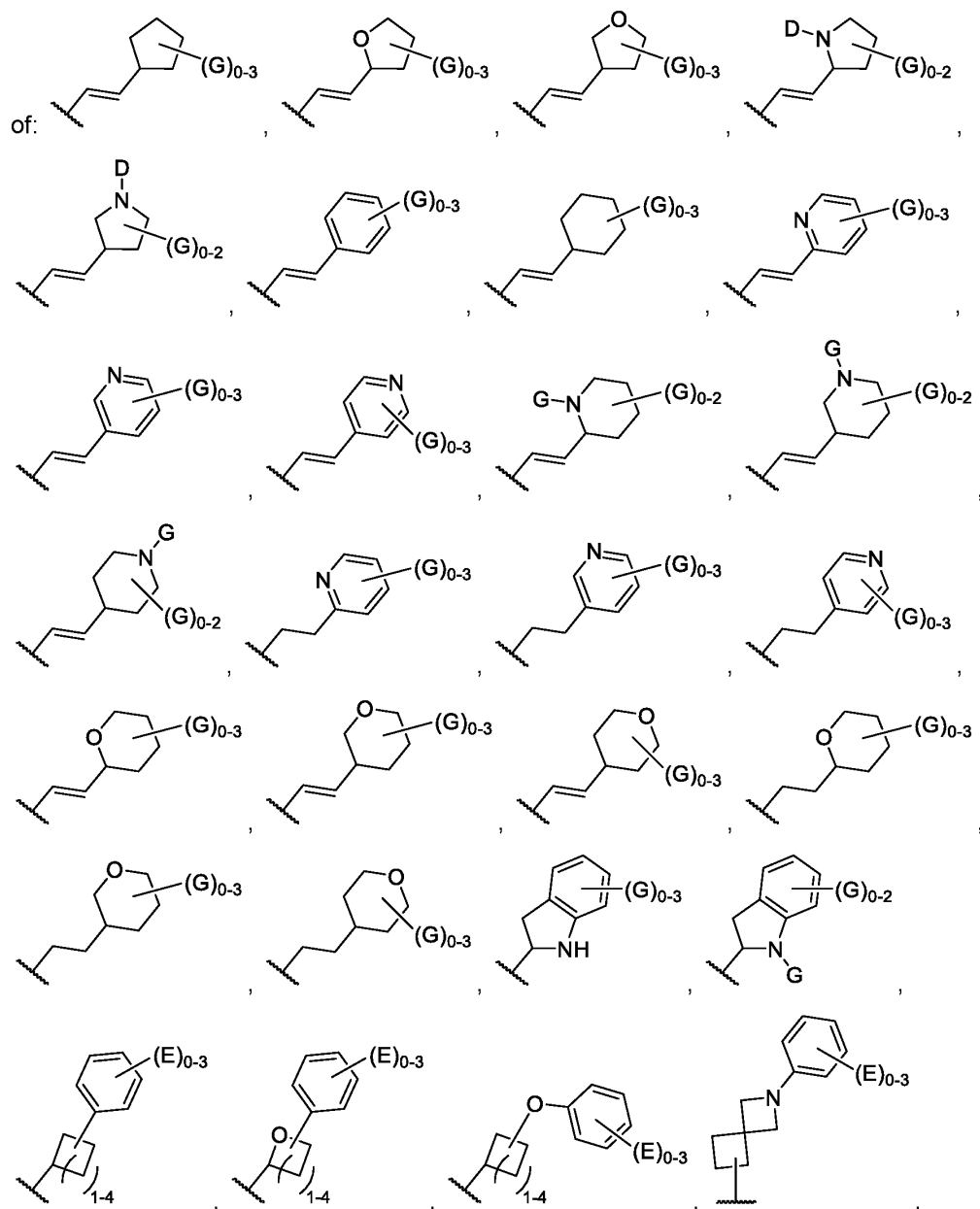
Z is aromatic or nonaromatic C_{3-10} carbocycle, or aromatic or nonaromatic 4-10 membered heterocycle having 1-3 heteroatoms selected from the group consisting of N, O,

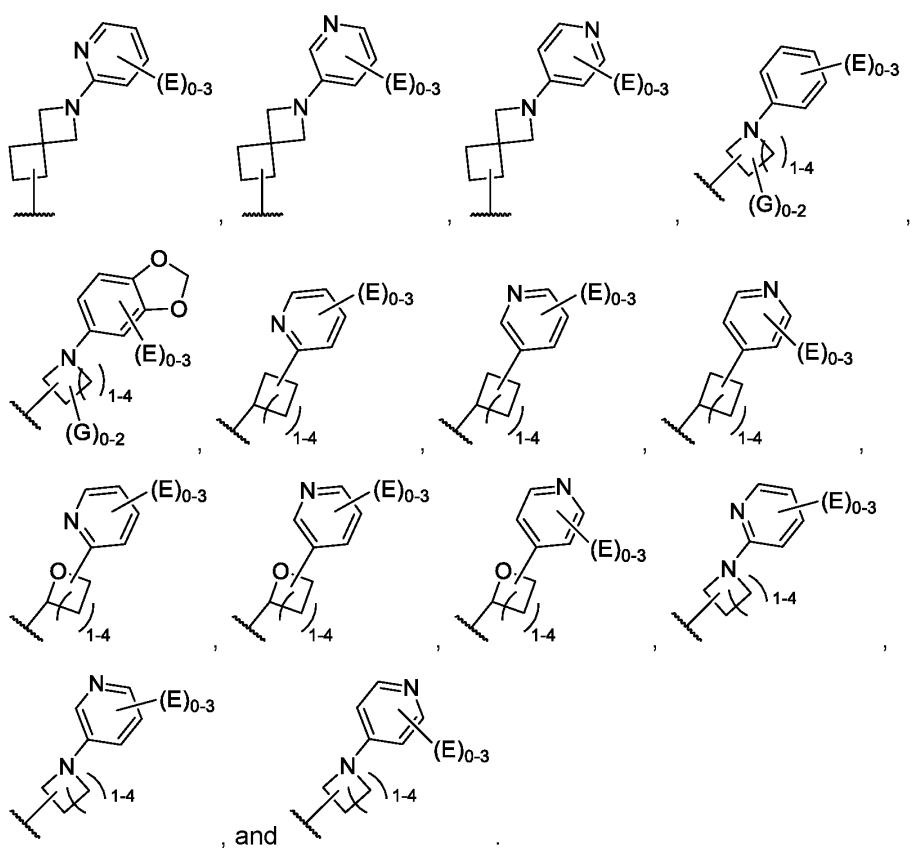
and S;

Z is optionally substituted with 1-3 E; and,

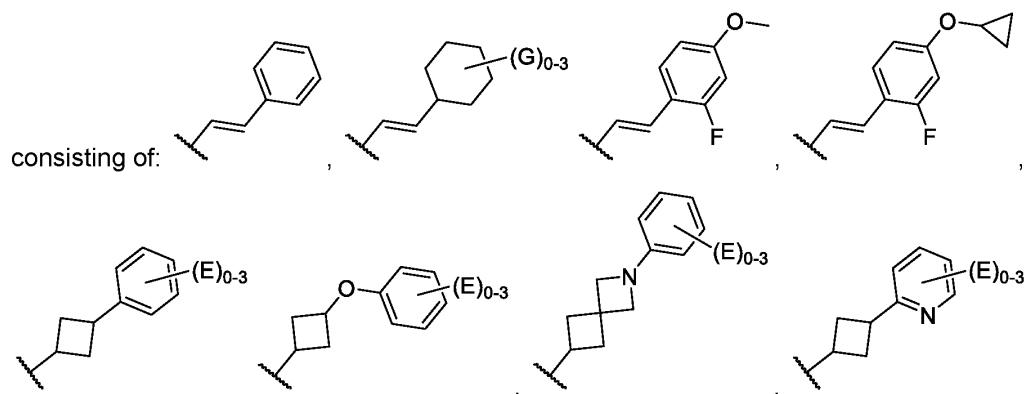
each E independently is selected from C₁₋₃alkyl, C₁₋₃alkoxy, =O, C₁₋₃haloalkoxy, CN, and halo.

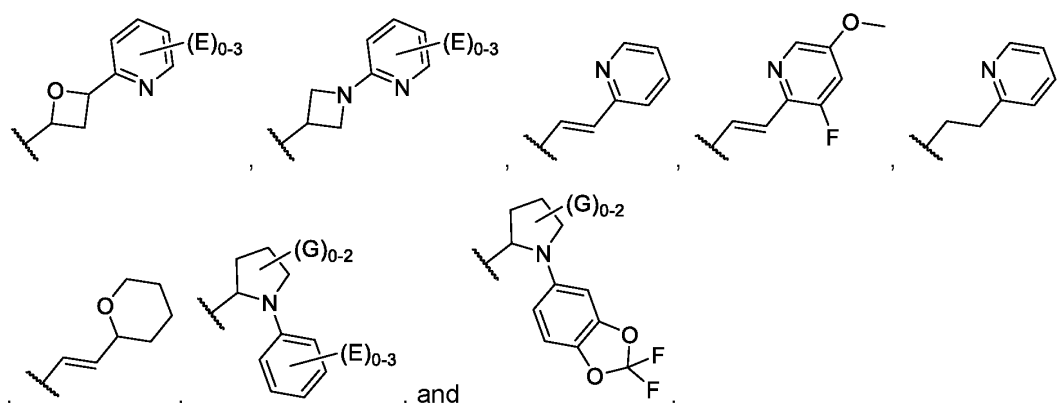
18. The compound or salt of claim 17, wherein L¹-B is selected from the group consisting



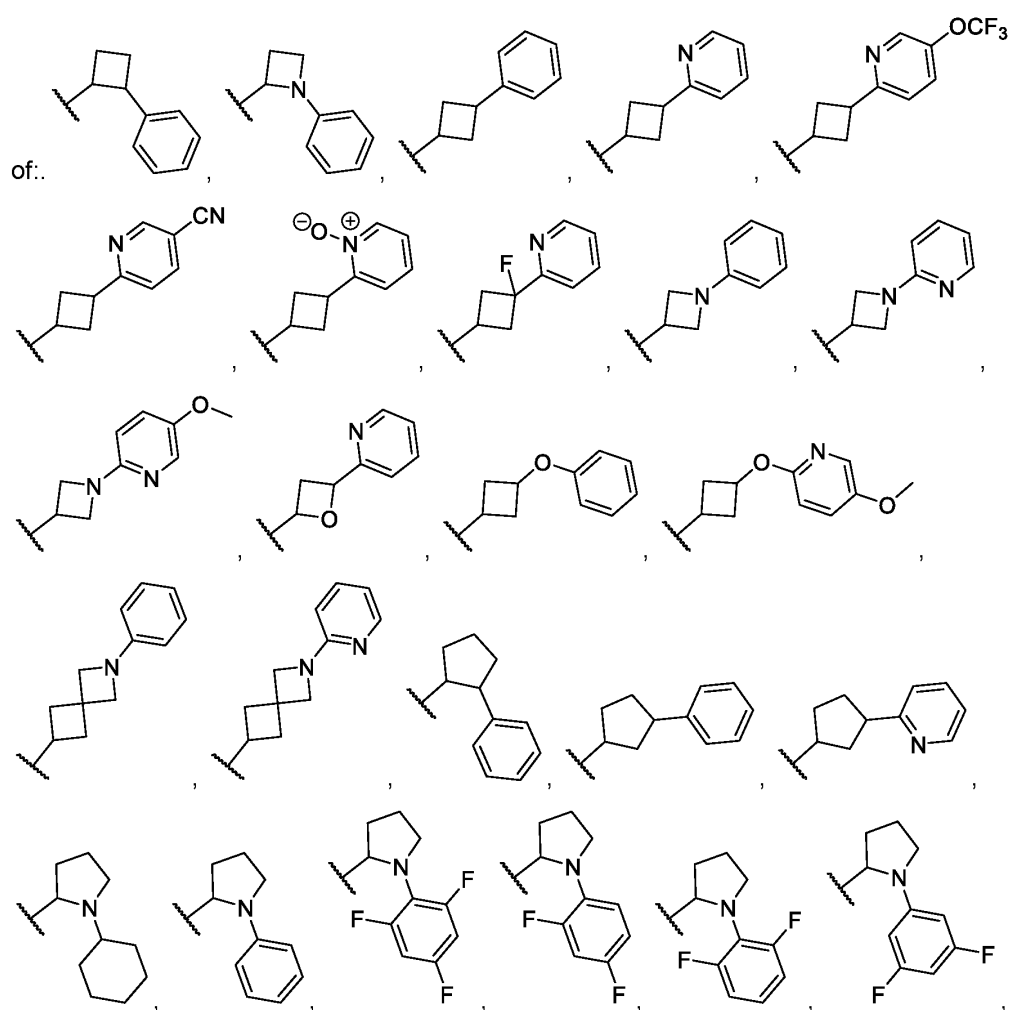


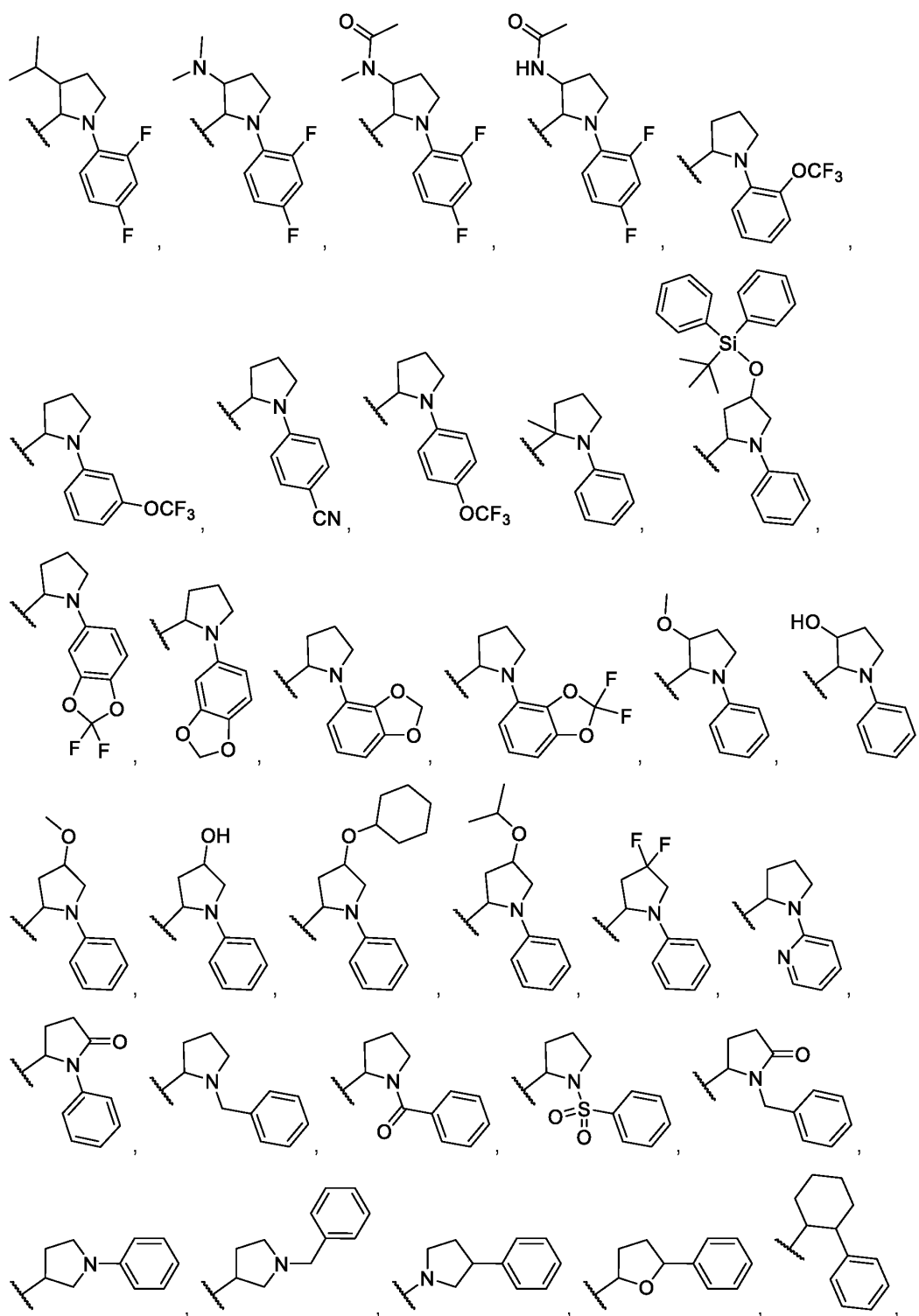
19. The compound or salt of claim 17 or 18, wherein L¹-B is selected from the group

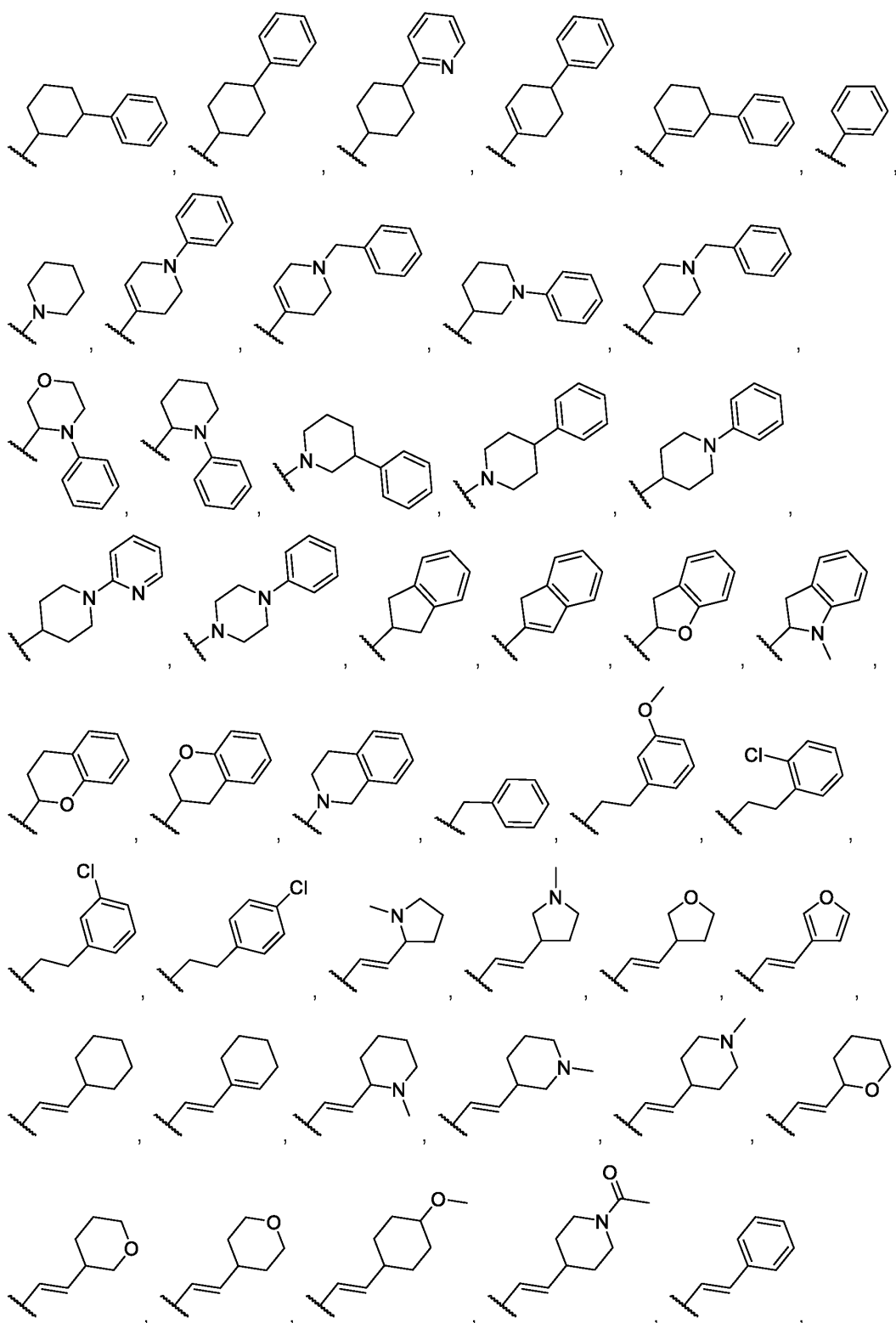


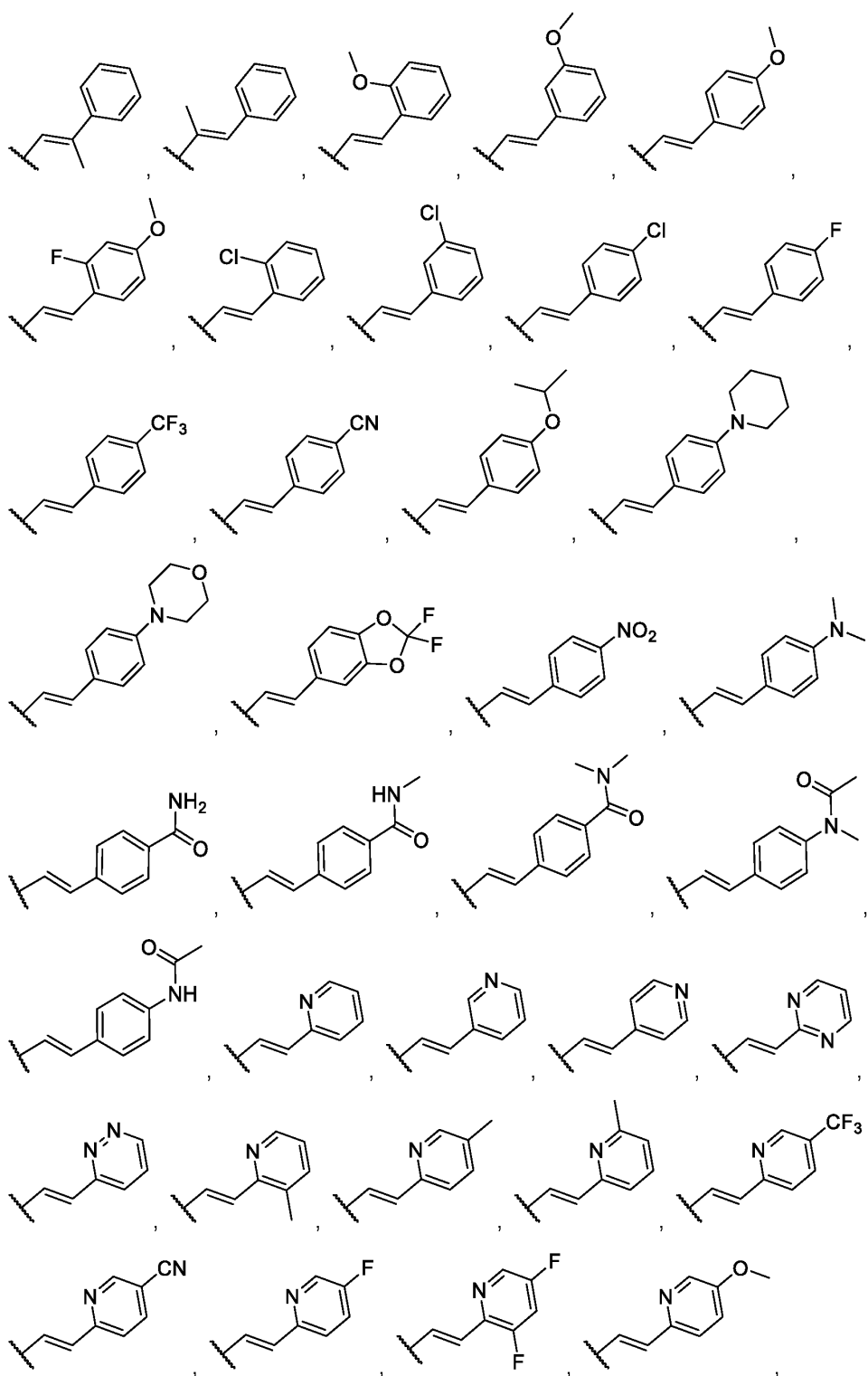


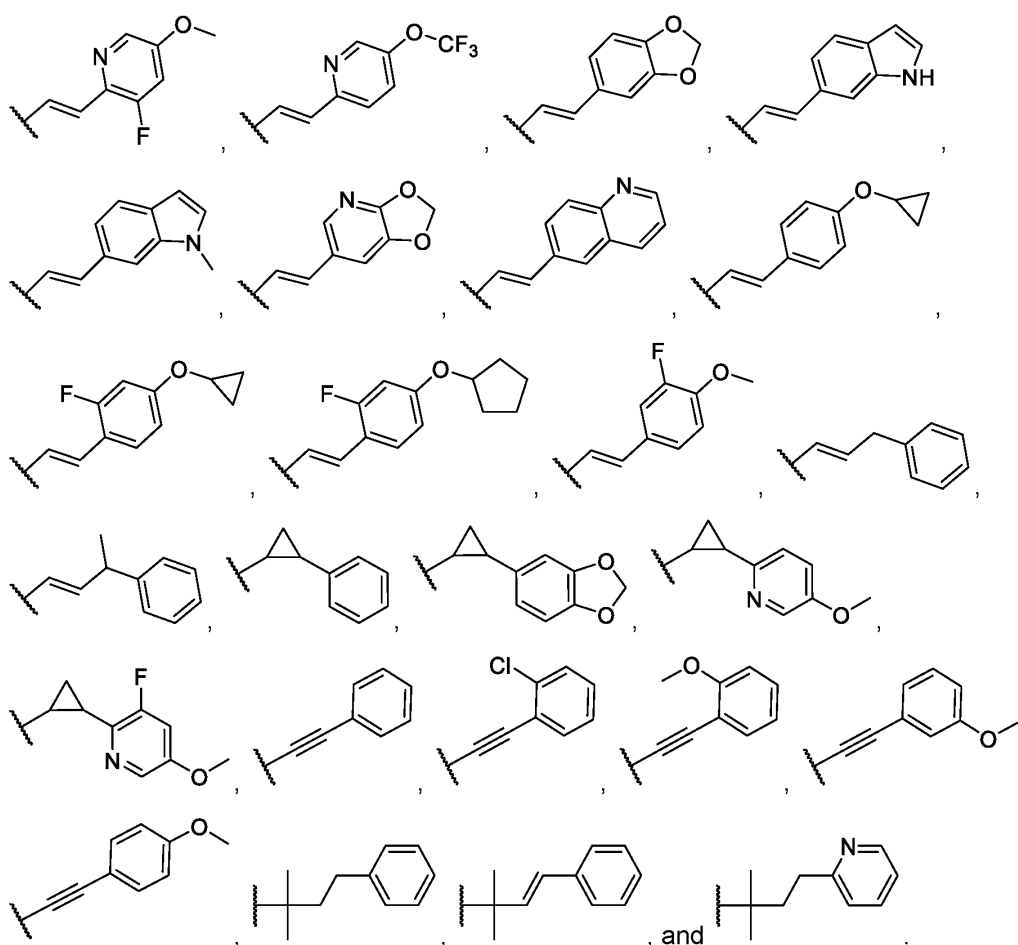
20. The compound or salt of claim 1, wherein L¹-B is selected from the group consisting





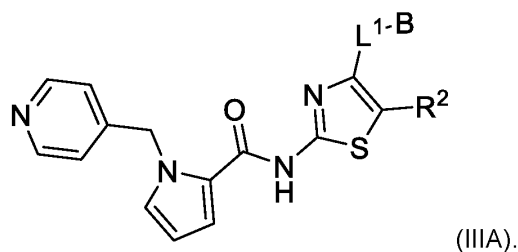




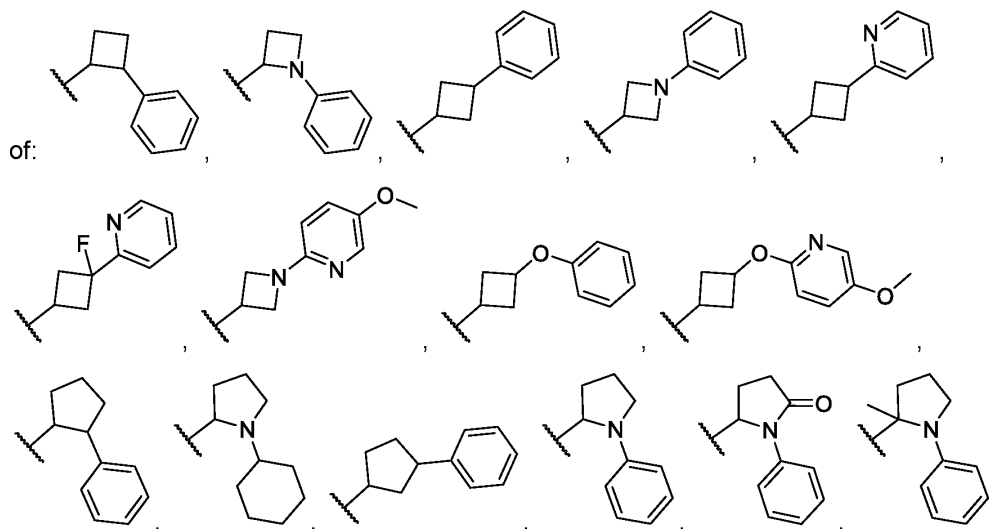


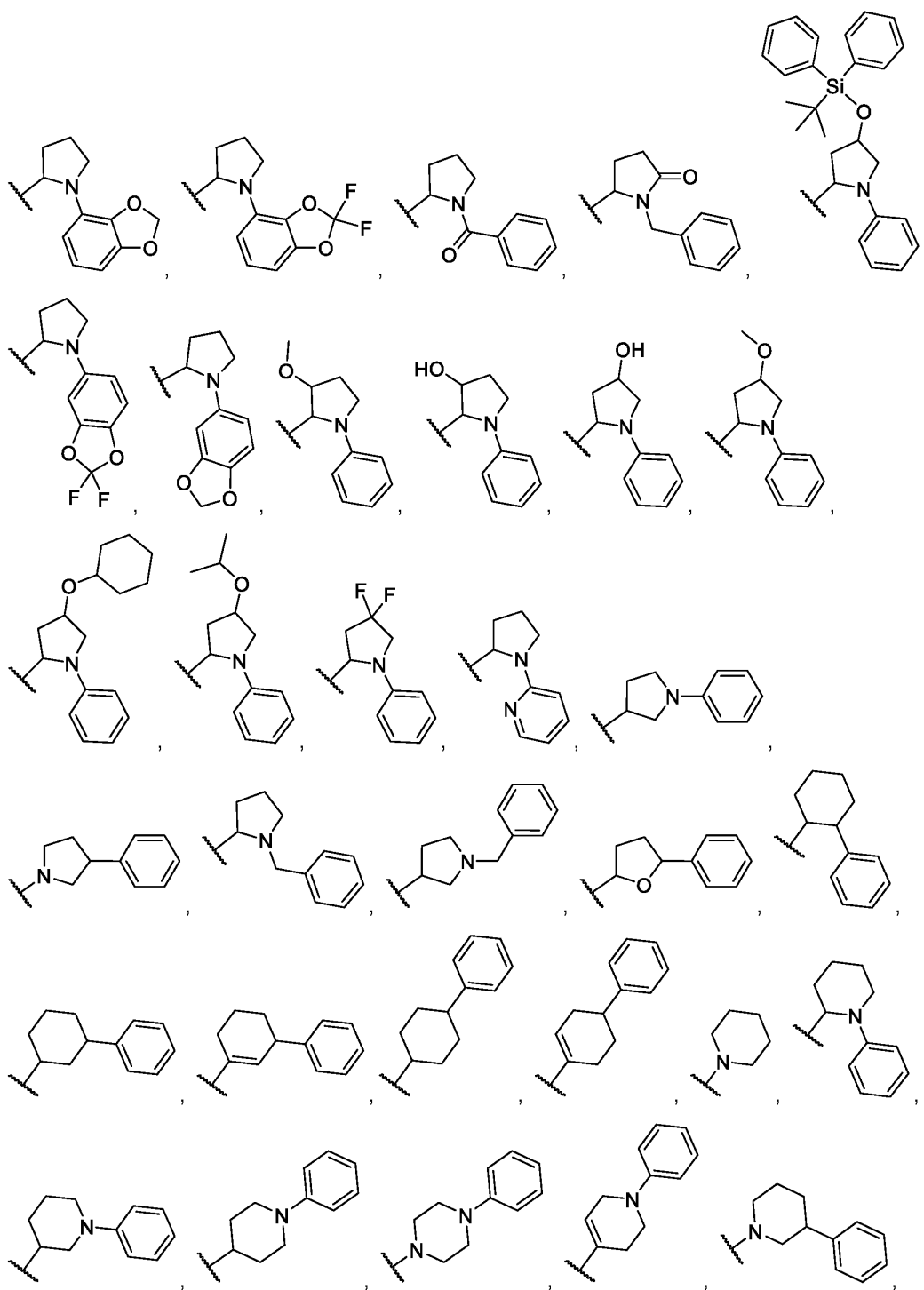
21. The compound or salt of any one of claims 1-20, wherein R² is H.
22. The compound or salt of any one of claims 1-20, wherein R² is C₁₋₃alkyl.
23. The compound or salt of claim 22, wherein R² is methyl.
24. The compound or salt of any one of claims 1-23, wherein L² is C₀alkylene.
25. The compound or salt of any one of claims 1-23, wherein L² is C₁alkylene.
26. The compound or salt of any one of claims 1-23, wherein L² is C₂alkylene.
27. The compound or salt of any one of claims 1-23, wherein L² is C₃alkylene.
28. The compound or salt of any one of claims 1-27, wherein m is 0.
29. The compound or salt of any one of claims 1-27, wherein m is 1 or 2.
30. The compound or salt of claim 29, wherein R⁴ is C₁₋₃alkyl.
31. The compound or salt of claim 30, wherein R⁴ is methyl or ethyl.
32. The compound or salt of claim 29, wherein R⁴ is halo.
33. The compound or salt of claim 32, wherein R⁴ is F.
34. The compound or salt of claim 32, wherein R⁴ is Cl.
35. The compound or salt of claim 29, wherein R⁴ is C₂₋₃alkynyl.

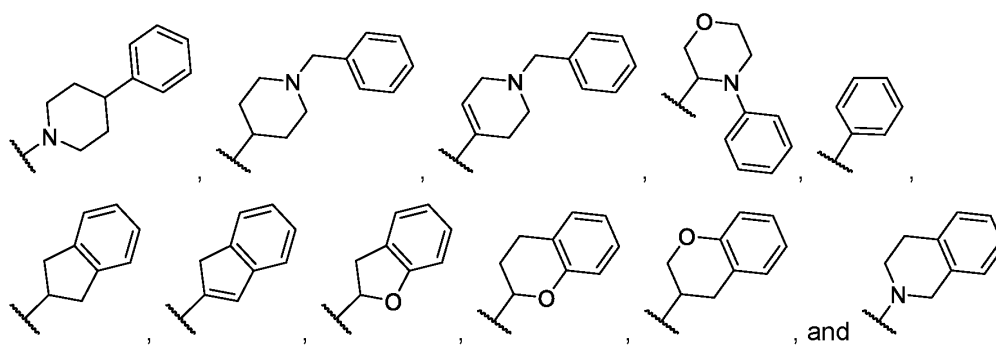
36. The compound or salt of claim 35, wherein R^4 is C_2 alkynyl.
37. The compound or salt of claim 29, wherein R^4 is C_{1-3} haloalkyl.
38. The compound or salt of claim 37, wherein R^4 is CF_3 .
39. The compound or salt of claim 29, wherein R^4 is C_{1-3} alkoxy.
40. The compound or salt of claim 39, wherein R^4 is methoxy.
41. The compound or salt of claim 29, wherein R^4 is NHC_{1-3} alkylene-aryl.
42. The compound or salt of claim 41, wherein R^4 is $NH-CH_2$ -phenyl.
43. The compound or salt of claim 29, wherein m is 2, and one R^4 is halo, and the other R^4 is halo or methyl.
44. The compound or salt of any one of claims 1 to 23, having the structure of Formula (IIIA):



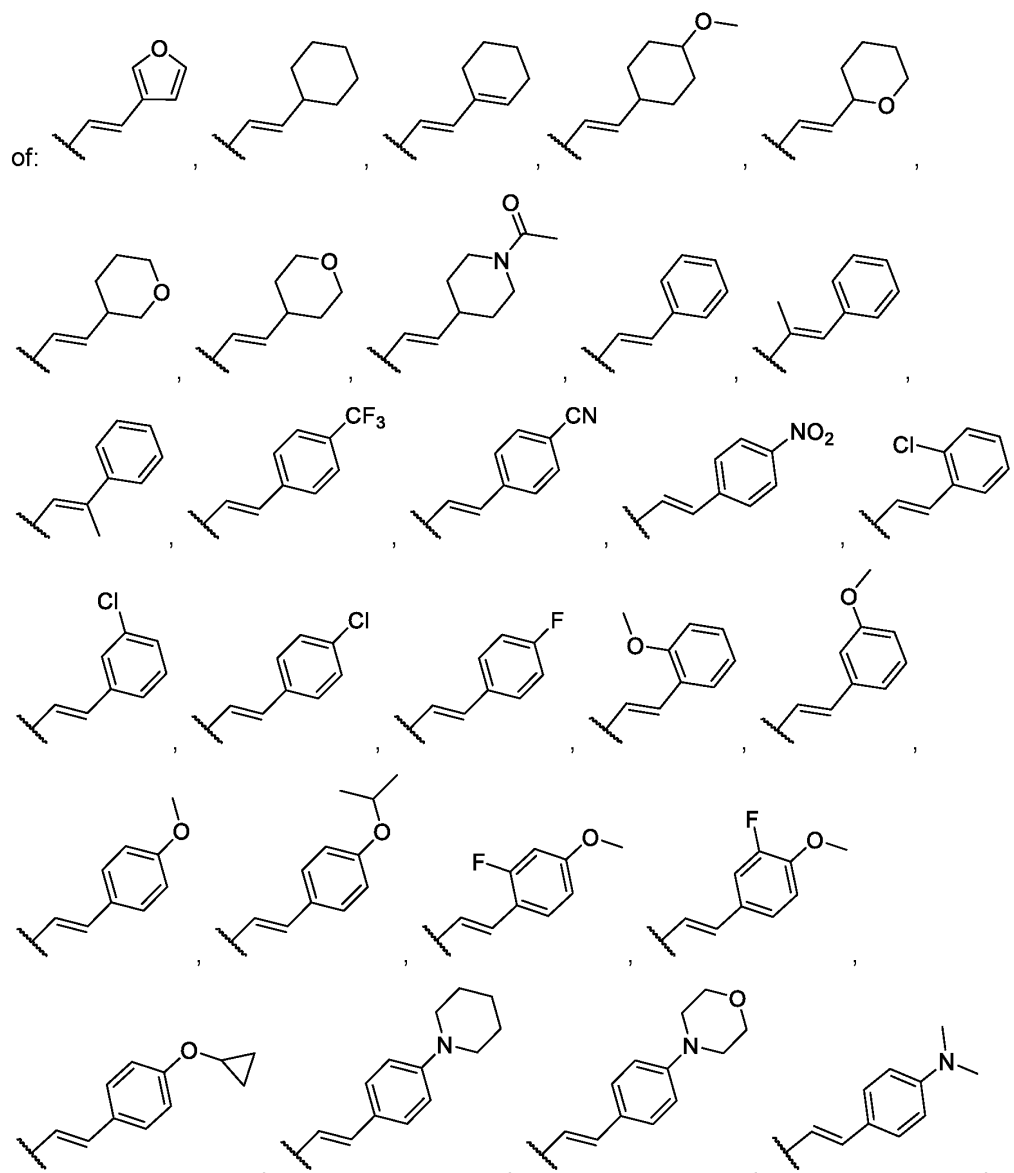
45. The compound or salt of claim 44, wherein L^1-B is selected from the group consisting

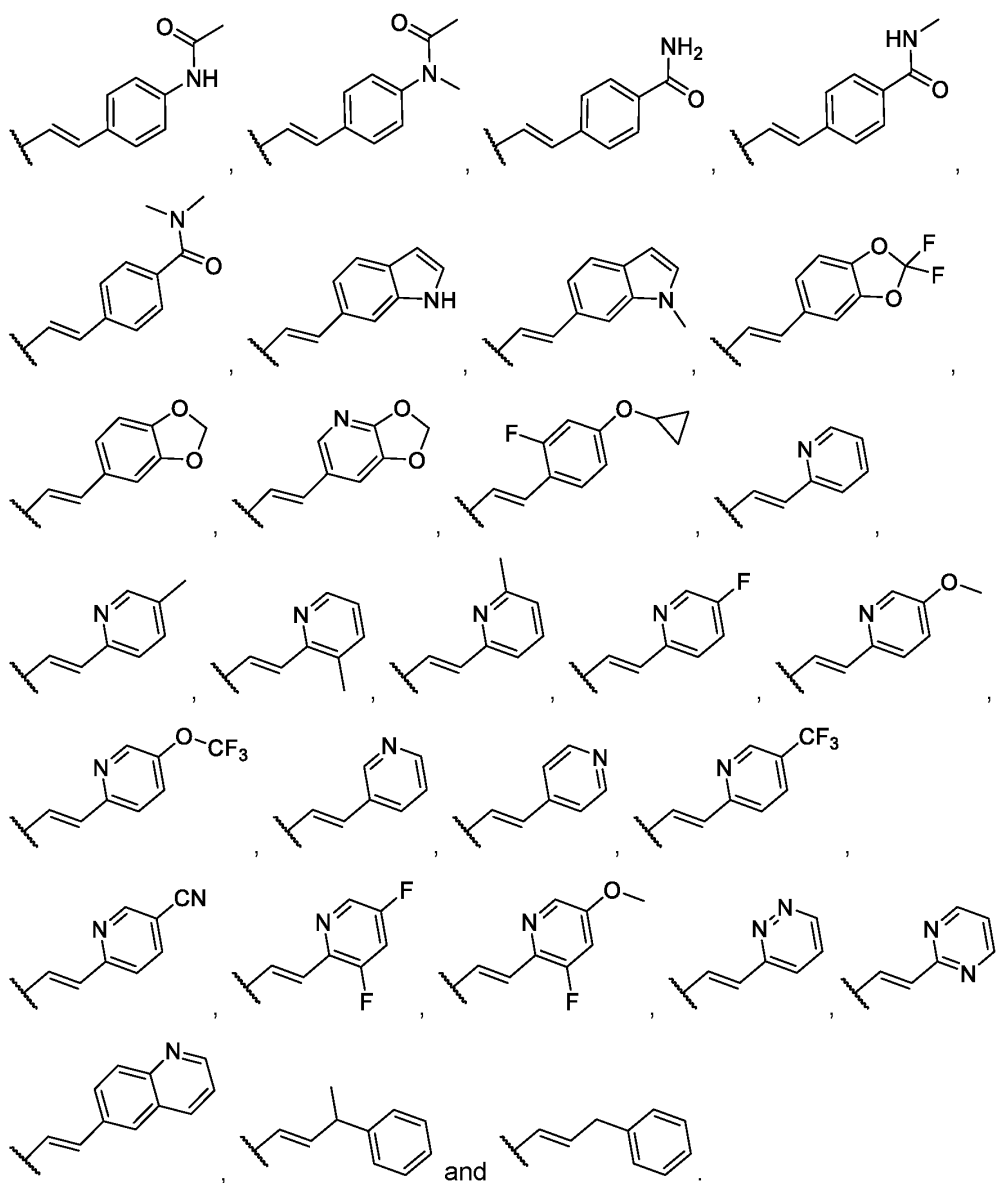




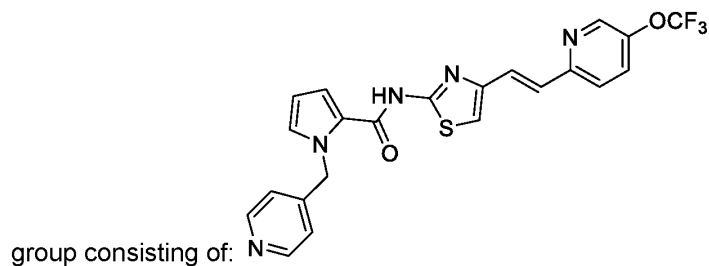


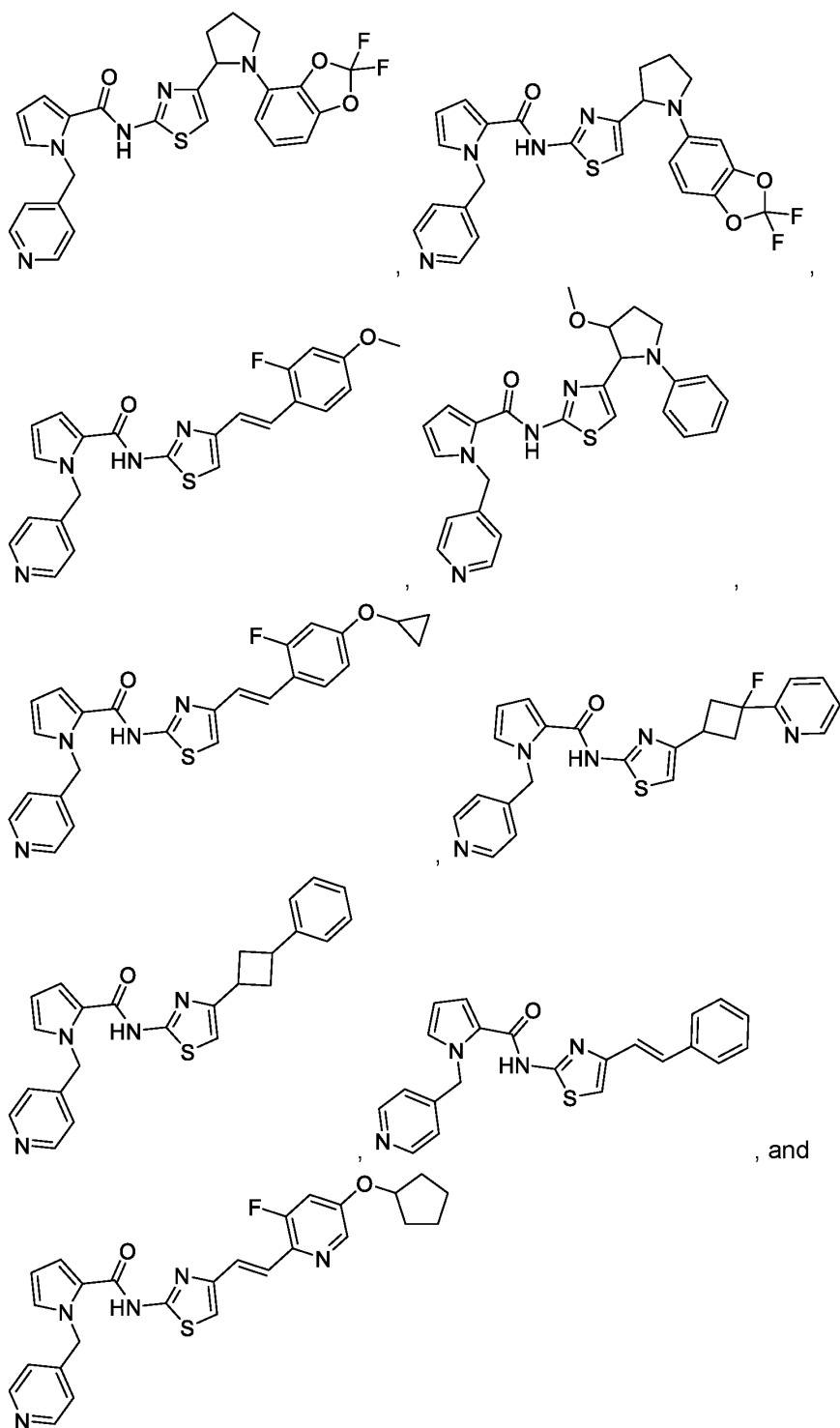
46. The compound or salt of claim 44, wherein L¹-B is selected from the group consisting



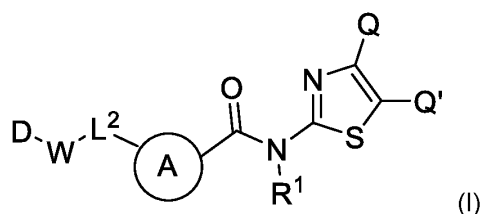


47. The compound or salt of claim 1, wherein the compound or salt is selected from the





48. A compound having a structure of Formula (I):



wherein:

ring A is an aromatic or nonaromatic C₃₋₁₀ carbocycle, or an aromatic or nonaromatic 5-10 membered heterocycle having 1 or 2 ring heteroatoms selected from N, O, and S;

one of Q and Q' is L¹-B and the other is R²;

L¹ is a bond, C₁₋₆alkylene, or $\text{---C}_{0-2}\text{alkylene---}$, wherein --- indicates a double bond, a triple bond, or a fused or spiro cyclopropyl;

B is C₁₋₃alkoxy, [O]₀₋₁-C₀₋₃alkylene-X, or NR^NC₁₋₃alkylene-X;

X is an aromatic or nonaromatic C₃₋₁₀ carbocycle, or an aromatic or nonaromatic 5-10 membered heterocycle having 1-4 ring heteroatoms selected from N, O, and S;

L² is C₀₋₆alkylene or $\text{---C}_{0-2}\text{alkylene---}$, wherein --- indicates a double bond, a triple bond, or a fused or spiro cyclopropyl;

W is a bond, O, or C(O)N(R^N);

D is C₆₋₁₀aryl or an aromatic or nonaromatic 5-10-membered heterocycle having 1-4 ring heteroatoms selected from N, O, and S;

each R^N independently is H or C₁₋₄alkyl;

R¹ is H or C₁₋₃alkyl; and

R² is H, C₁₋₃alkyl, or halo,

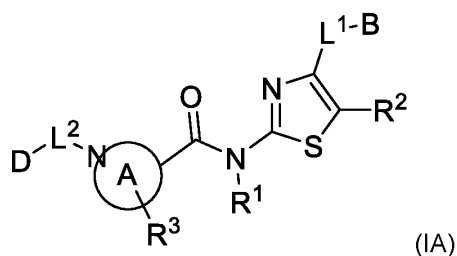
or a pharmaceutically acceptable salt thereof.

49. The compound or salt of claim 48, wherein Q is L¹-B and Q' is R².

50. The compound or salt of claim 48, wherein Q is R² and Q' is L¹-B.

51. The compound or salt of any one of claims 48 to 50, wherein ring A is a 5-6 membered heterocycle having 1 or 2 ring heteroatoms selected from N, O, and S.

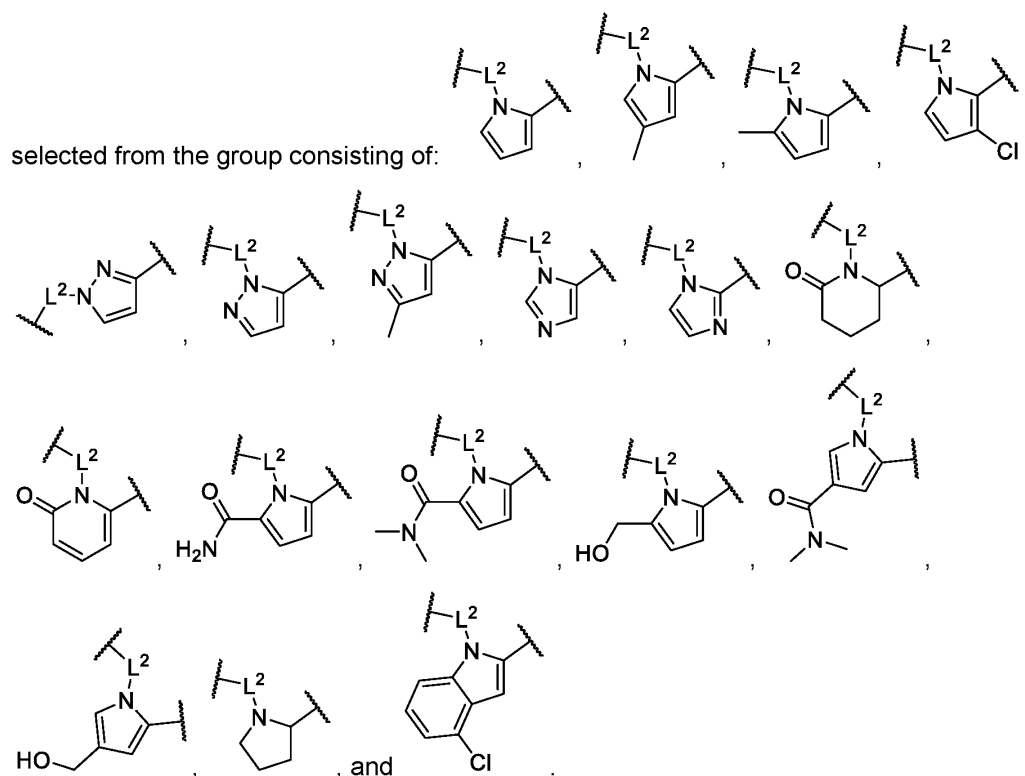
52. The compound or salt of claim 48 or 49, having the structure of Formula (IA):



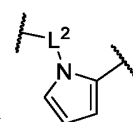
wherein ring A has 0 or 1 additional ring heteroatoms selected from N, O, and S, and R^3 is H, C_{1-3} alkyl, C_{1-3} hydroxyalkyl, C_{1-3} haloalkyl, halo, or $-C(O)N(R^N)_2$.

53. The compound or salt of any one of claims 48 to 50, wherein ring A is an aromatic or nonaromatic C_{3-10} carbocycle.

54. The compound or salt of any one of claims 48 to 50, wherein ring A- L^2 moiety is



55. The compound or salt of claim 54, wherein ring A- L^2 moiety is



56. The compound or salt of any one of claims 48-55, wherein R^1 is H.

57. The compound or salt of any one of claims 48-55, wherein R^1 is C_{1-3} alkyl.

58. The compound or salt of claim 57, wherein R^1 is methyl or ethyl.

59. The compound or salt of any one of claims 48-58, wherein R^2 is H.

60. The compound or salt of any one of claims 48-58, wherein R^2 is C_{1-3} alkyl.

61. The compound or salt of claim 60, wherein R^2 is methyl.

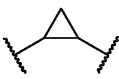
62. The compound or salt of claim 60, wherein R^2 is ethyl.

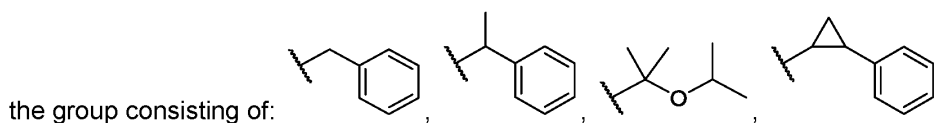
63. The compound or salt of claim 60, wherein R^2 is n-propyl or isopropyl.

64. The compound or salt of any one of claims 48-58, wherein R^2 is halo.

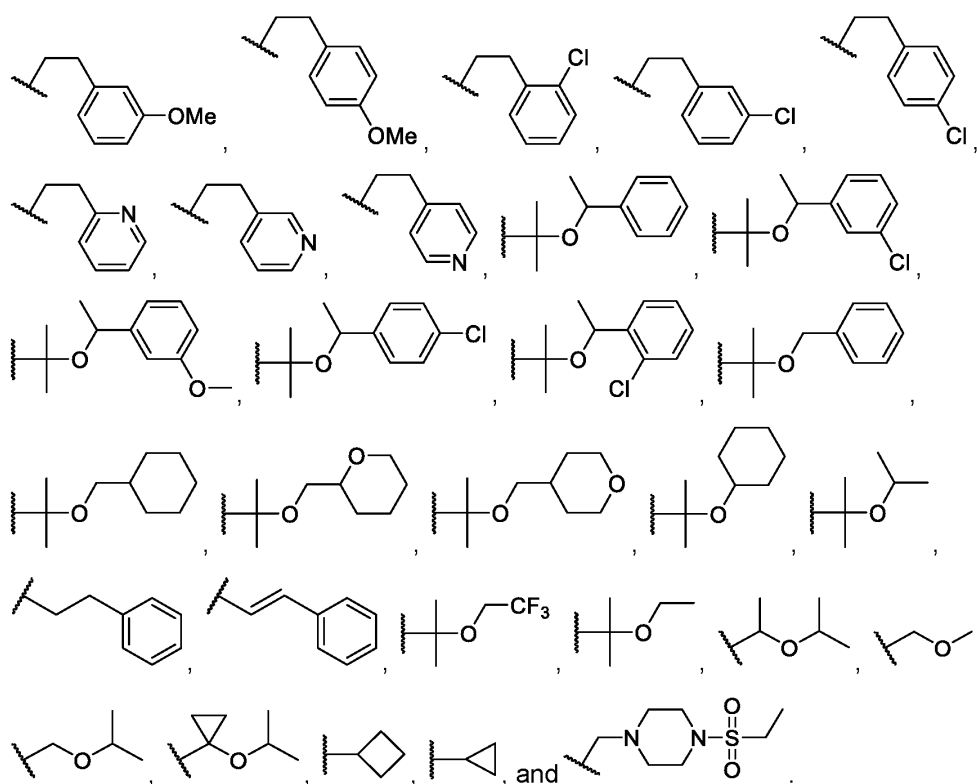
65. The compound or salt of claim 64, wherein R^2 is Br.

66. The compound or salt of claim 64, wherein R^2 is F.

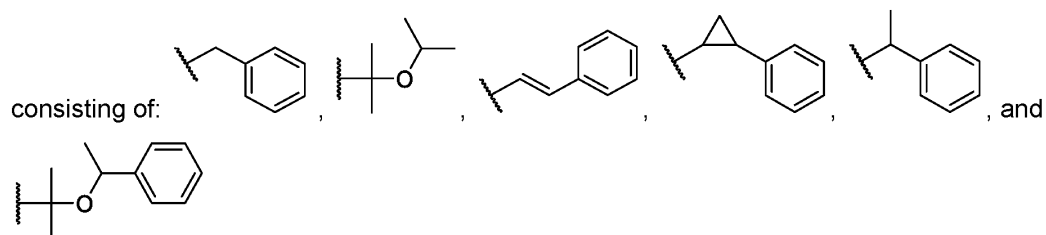
67. The compound or salt of claim 64, wherein R^2 is Cl.
68. The compound or salt of any one of claims 48-67, wherein L^1 is a bond.
69. The compound or salt of any one of claims 48-67, wherein L^1 is a C_{1-6} alkylene.
70. The compound or salt of claim 69, wherein L^1 is CH_2 , $CH(CH_3)$, CH_2CH_2 , or $C(CH_3)_2$.
71. The compound or salt of any one of claims 48-67, wherein L^1 is
- 
72. The compound or salt of claim 71, wherein $---$ indicates a double bond.
73. The compound or salt of claim 72, wherein the double bond is tri- or tetra-substituted, and the 1 or 2 other substituents on the double bond are independently selected from C_{1-3} alkyl and halo.
74. The compound or salt of claim 71, wherein $---$ indicates a triple bond.
75. The compound or salt of claim 71, wherein $---$ indicates a fused cyclopropyl,
- e.g., , or a spiro cyclopropyl, e.g., .
76. The compound or salt of any one of claims 71-75, wherein C_{0-2} alkylene is CH_2 , $CH(CH_3)$, or CH_2CH_2 .
77. The compound or salt of any one of claims 48-76, wherein B is C_{1-3} alkoxy.
78. The compound or salt of any one of claims 48-76, wherein B is O-X.
79. The compound or salt of any one of claims 48-76, wherein B is O- C_{1-3} alkylene-X.
80. The compound or salt of any one of claims 48-76, wherein B is C_{1-3} alkylene-X.
81. The compound or salt of any one of claims 48-76, wherein B is X.
82. The compound or salt of any one of claims 48-76, wherein B is NHC_{1-3} alkylene-X.
83. The compound or salt of any one of claims 48-76, wherein B is $N(CH_3)C_{1-3}$ alkylene-X.
84. The compound or salt of any one of claims 48-83, wherein X is an aromatic C_6-10 carbocycle, or an aromatic or nonaromatic 5-10-membered heterocycle.
85. The compound or salt of any one of claims 48-84, wherein X is selected from phenyl, pyridyl, indolyl, tetrahydropyranyl, piperidinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or piperazinyl, and X is optionally substituted with 1-3 substituents independently selected from C_{1-3} alkyl, C_{1-3} alkoxy, halo, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, $C(O)C_{1-3}$ alkyl, and SO_2C_{1-3} alkyl.
86. The compound or salt of any one of claims 48-67, wherein L^1 -B is selected from







87. The compound or salt of claim 86, wherein L¹-B is selected from the group



88. The compound or salt of any one of claims 48-87, wherein L² is C₀₋₆alkylene.

89. The compound or salt of any one of claims 48-87, wherein L² is C₁₋₆alkylene

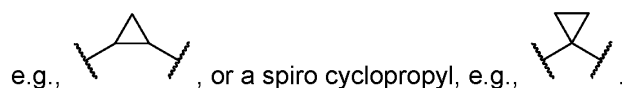
90. The compound or salt of any one of claims 48-87, wherein L² is



91. The compound or salt of claim 90, wherein $\equiv$ indicates a double bond.

92. The compound or salt of claim 90, wherein $\equiv$ indicates a triple bond.

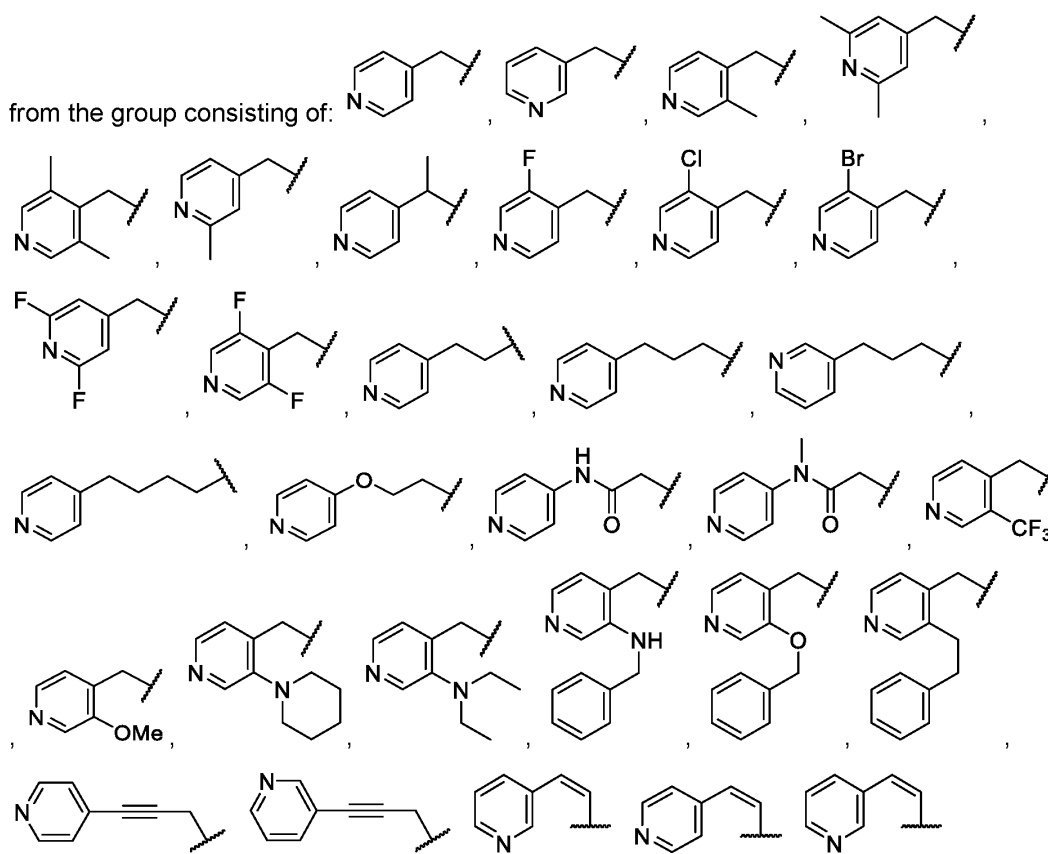
93. The compound or salt of claim 90, wherein $\equiv$ indicates a fused cyclopropyl,

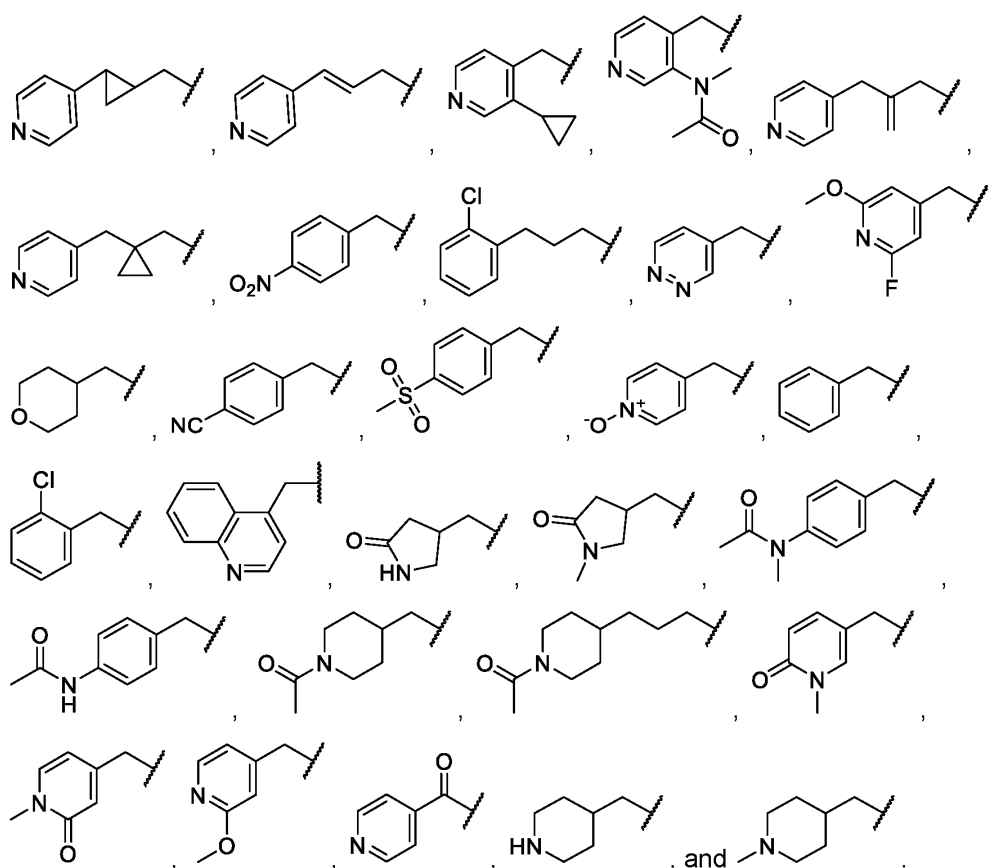


94. The compound or salt of any one of claims 48-91, wherein W is a bond.

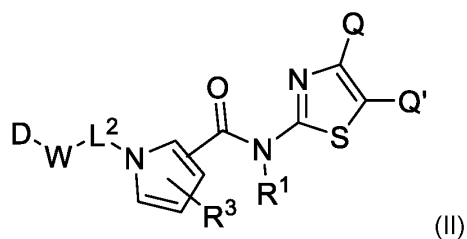
95. The compound or salt of any one of claims 48-91, wherein W is O.

96. The compound or salt of any one of claims 48-91, wherein W is C(O)N(R^N).
97. The compound or salt of claim 96, wherein W is C(O)NH.
98. The compound or salt of claim 96, wherein W is C(O)N(C₁₋₄ alkyl).
99. The compound or salt of claim 98, wherein W is C(O)N(Me).
100. The compound or salt of any one of claims 48-99, wherein D is C₆₋₁₀aryl.
101. The compound or salt of any one of claims 48-99, wherein D is an aromatic 5-10-membered heterocycle having 1-4 ring heteroatoms selected from N, O, and S.
102. The compound or salt of claim 101, wherein D comprises pyridyl optionally substituted with 1-3 substituents independently selected from C₁₋₃alkyl, C₁₋₃alkoxy, halo, C₁₋₃haloalkyl, C₁₋₃haloalkoxy, N(R^N)₂, C₃₋₆cycloalkyl, NO₂, N(R^N)C(O)C₁₋₃alkyl, C(O)C₁₋₃alkyl, NO₂, CN, SO₂C₁₋₃alkyl, O⁻, NHC₁₋₃alkylene-aryl, OC₁₋₃alkylene-aryl, C₁₋₃alkylene-aryl, and 5-10 membered heterocycle having 1-3 ring heteroatoms selected from N, O, and S, and each R^N is independently H or C₁₋₄alkyl.
103. The compound or salt of any one of claims 48-99, wherein D is a nonaromatic 5-10 membered heterocycle having 1-4 ring heteroatoms selected from N, O, and S.
104. The compound or salt of any one of claims 48-87, wherein L²-W-D is selected





105. A compound having a structure of Formula (II):



wherein:

one of Q and Q' is L^1 -B and the other is R^2 , or

Q and Q' and the atoms to which they are attached join together to form an aromatic or nonaromatic 5 or 6 membered carbocycle or a 5 or 6 membered heterocycle having 1 or 2 ring heteroatoms selected from N, O, and S;

L¹ is a bond, C₁₋₆alkylene, or $\left\{ \text{C}_{0-2}\text{alkylene} \text{---} \text{C}_{0-2}\text{alkylene} \right\}$, wherein --- indicates a double bond, a triple bond, or a fused or spiro cyclopropyl;

B is C₁₋₆ alkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ haloalkoxy, C₁₋₃alkoxy, [O]₀₋₁-C₀₋₃alkylene-X or NR^NC₁₋₃alkylene-X,

X is an aromatic or nonaromatic C₃₋₁₀ carbocycle, or an aromatic or nonaromatic 5-10 membered heterocycle having 1-4 ring heteroatoms selected from N, O, and S;

L² is C₁₋₆alkylene or $\text{---C}_{0-2}\text{alkylene---C}_{0-2}\text{alkylene---}$, wherein --- indicates a double bond, a triple bond, or a fused or spiro cyclopropyl;

W is a bond, O, or C(O)N(R^N);

D comprises pyridyl or quinolinyl optionally substituted with 1-3 substituents independently selected from C₁₋₃alkyl, C₁₋₃alkoxy, halo, C₁₋₃haloalkyl, C₁₋₃haloalkoxy, N(R^N)₂, C₃₋₆cycloalkyl, NO₂, C(O)N(R^N)₂, N(R^N)C(O)C₁₋₃alkyl, C(O)C₁₋₃alkyl, NO₂, CN, SO₂C₁₋₃alkyl, O⁻, NHC₁₋₃alkylene-aryl, OC₁₋₃alkylene-aryl, C₁₋₃alkylene-aryl, and 5-10 membered heterocycle having 1-3 ring heteroatoms selected from N, O, and S.

each R^N is independently H or C₁₋₄alkyl;

R¹ is H or C₁₋₃alkyl;

R² is H, C₁₋₃alkyl, or halo; and

R³ is H, C₁₋₃alkyl, C₁₋₃hydroxyalkyl, C₁₋₃haloalkyl, halo, or -C(O)N(R^N)₂;

or a pharmaceutically acceptable salt thereof.

106. The compound or salt of claim 105, wherein Q is L¹-B and Q' is R².

107. The compound or salt of claim 105, wherein Q is R² and Q' is L¹-B.

108. The compound or salt of claim 105, wherein Q and Q' and the atoms to which they are attached join together to form an aromatic or nonaromatic 5 or 6 membered carbocycle or a 5 or 6 membered heterocycle having 1 or 2 ring heteroatoms selected from N, O, and S.

109. The compound or salt of any one of claims 105-108, wherein R³ is H.

110. The compound or salt of any one of claims 105-108, wherein R³ is C₁₋₃alkyl.

111. The compound or salt of claim 110, wherein R³ is methyl.

112. The compound or salt of any one of claims 105-108, wherein R³ is halo.

113. The compound or salt of claim 112, wherein R³ is Cl.

114. The compound or salt of any one of claims 105-108, wherein R³ is C₁₋₃hydroxyalkyl.

115. The compound or salt of claim 114, wherein R³ is -CH₂OH.

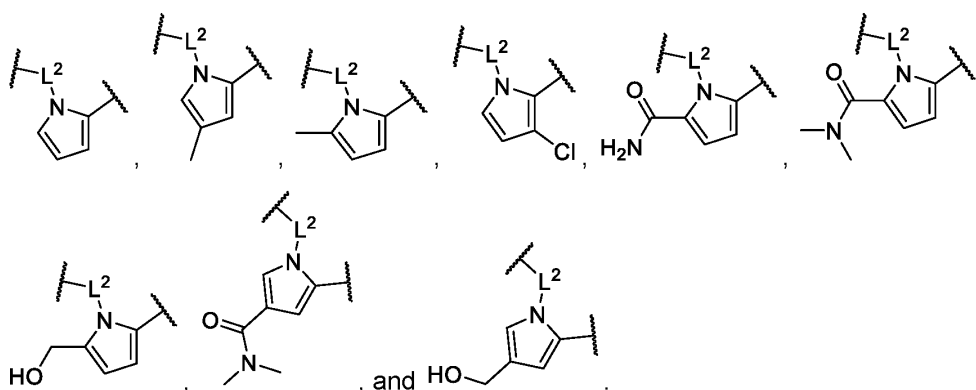
116. The compound or salt of any one of claims 105-108, wherein R³ is -C(O)N(R^N)₂.

117. The compound or salt of claim 116, wherein R³ is -C(O)NH₂.

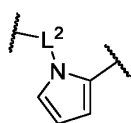
118. The compound or salt of claim 116, wherein R³ is -C(O)N(Me)₂.

119. The compound or salt of any one of claims 105-108, wherein R³ is C₁₋₃haloalkyl.

120. The compound or salt of any one of claims 105-108, wherein the pyrrole ring-L² moiety is selected from the group consisting of:

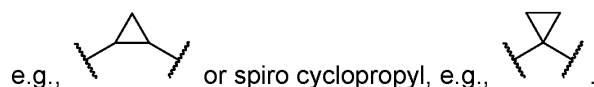


121. The compound or salt of claim 120, wherein the pyrrole ring-L² moiety is



122. The compound or salt of any one of claims 105-121, wherein R¹ is H.
123. The compound or salt of any one of claims 105-121, wherein R¹ is C₁₋₃alkyl.
124. The compound or salt of claim 123, wherein R¹ is methyl or ethyl.
125. The compound or salt of any one of claims 105-124, wherein R² is H.
126. The compound or salt of any one of claims 105-124, wherein R² is C₁₋₃alkyl.
127. The compound or salt of claim 126, wherein R² is methyl.
128. The compound or salt of claim 126, wherein R² is ethyl.
129. The compound or salt of claim 126, wherein R² is n-propyl or isopropyl.
130. The compound or salt of any one of claims 105-124, wherein R² is halo.
131. The compound or salt of claim 130, wherein R² is Br.
132. The compound or salt of claim 130, wherein R² is F.
133. The compound or salt of claim 130, wherein R² is Cl.
134. The compound or salt of any one of claims 105-133, wherein L¹ is a bond.
135. The compound or salt of any one of claims 105-133, wherein L¹ is a C₁₋₆alkylene.
136. The compound or salt of claim 135, wherein L¹ is CH₂, CH(CH₃), CH₂CH₂, or C(CH₃)₂.
137. The compound or salt of any one of claims 105-133, wherein L¹ is
- $$\text{---C}_{0-2}\text{alkylene---C}_{0-2}\text{alkylene---}$$
138. The compound or salt of claim 137, wherein --- indicates a double bond.
139. The compound or salt of claim 138, wherein the double bond is tri- or tetra-substituted, and the 1 or 2 other substituents on the double bond are independently selected from C₁₋₃alkyl and halo.
140. The compound or salt of claim 137, wherein --- indicates a triple bond.

141. The compound or salt of claim 137, wherein === indicates a fused cyclopropyl,



142. The compound or salt of any one of claims 105-141, wherein B is C₁₋₆ alkyl.

143. The compound or salt of claim 142, wherein B is methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, or n-hexyl.

144. The compound or salt of any one of claims 105-141, wherein B is C₁₋₃ haloalkyl.

145. The compound or salt of claim 144, wherein B is -CF₃ or -CF₂CH₃.

146. The compound or salt of any one of claims 105-141, wherein B is C₁₋₃ hydroxyalkyl.

147. The compound or salt of claim 146, wherein B is -CH₂CH₂OH.

148. The compound or salt of any one of claims 105-141, wherein B is C₁₋₃ haloalkoxy.

149. The compound or salt of claim 148, wherein B is -OCH₂CF₃.

150. The compound or salt of any one of claims 105-141, wherein B is C₁₋₃alkoxy.

151. The compound or salt of any one of claims 105-141, wherein B is O-X.

152. The compound or salt of any one of claims 105-141, wherein B is O-C₁₋₃alkylene-X.

153. The compound or salt of any one of claims 105-141, wherein B is C₁₋₃alkylene-X.

154. The compound or salt of any one of claims 105-141, wherein B is X.

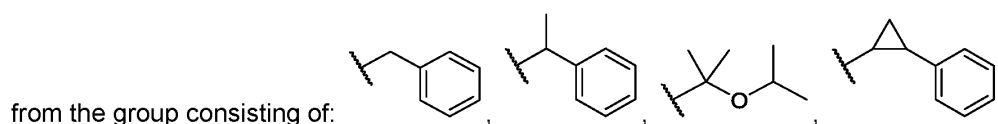
155. The compound or salt of any one of claims 105-141, wherein B is NHC₁₋₃alkylene-X.

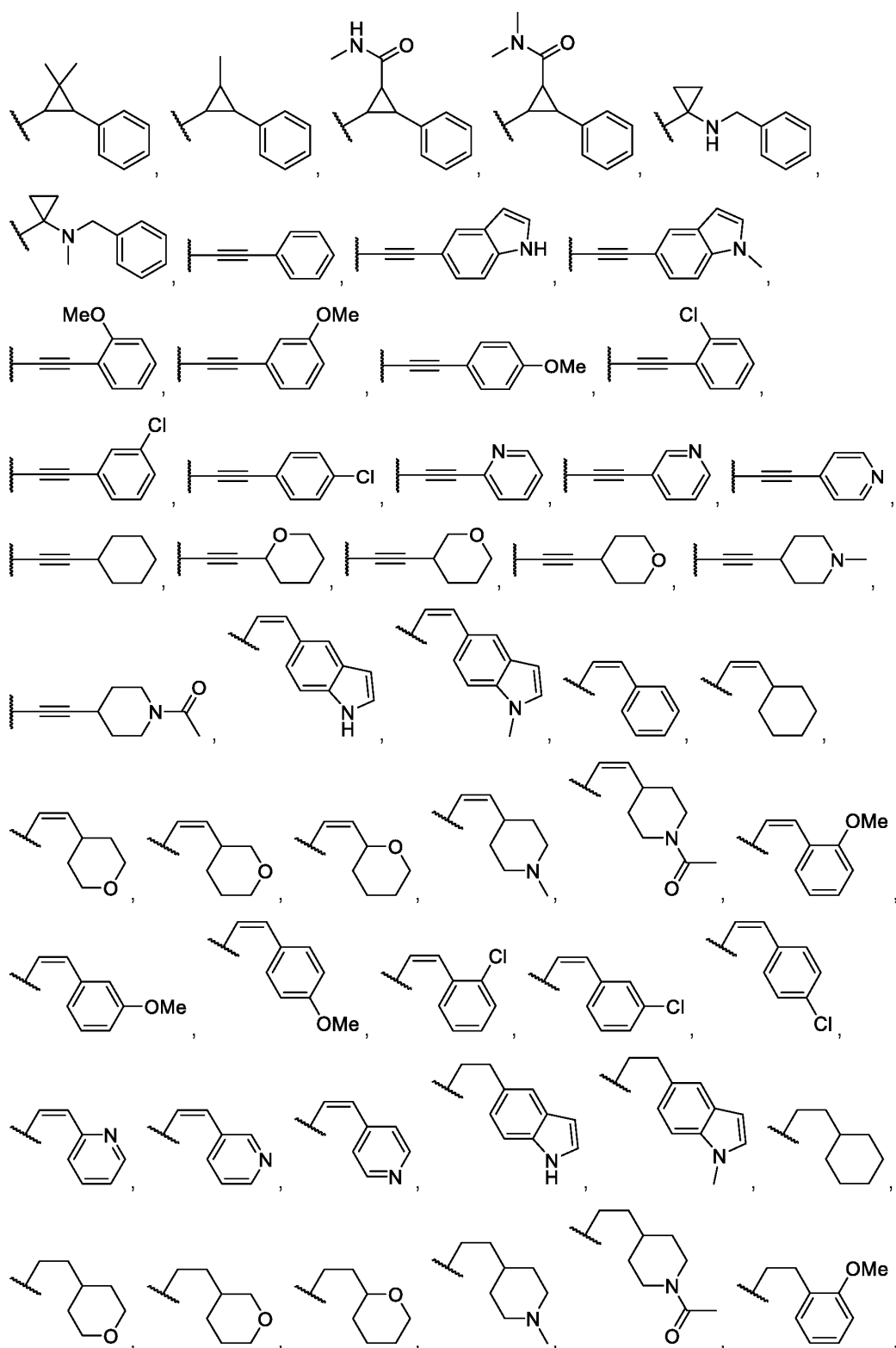
156. The compound or salt of any one of claims 105-141, wherein B is N(CH₃)C₁₋₃alkylene-X.

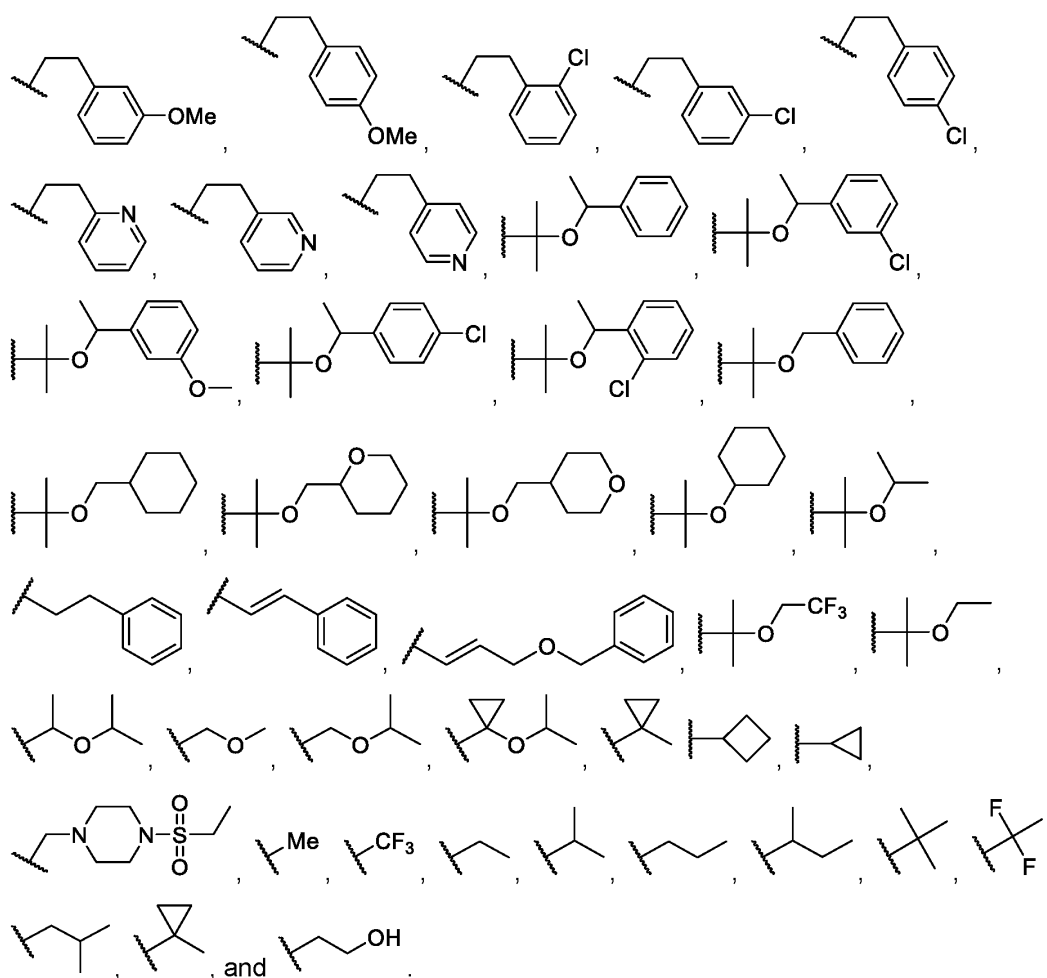
157. The compound or salt of any one of claims 105-156, wherein X is an aromatic C₆₋₁₀carbocycle, or an aromatic or nonaromatic 5-10-membered heterocycle.

158. The compound or salt of any one of claims 105-157, wherein X is selected from phenyl, pyridyl, indolyl, tetrahydropyranyl, piperidinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or piperazinyl, and X is optionally substituted with 1-3 substituents independently selected from C₁₋₃alkyl, C₁₋₃alkoxy, halo, C₁₋₃ haloalkyl, C₁₋₃ haloalkoxy, C(O)C₁₋₃alkyl, and SO₂C₁₋₃alkyl.

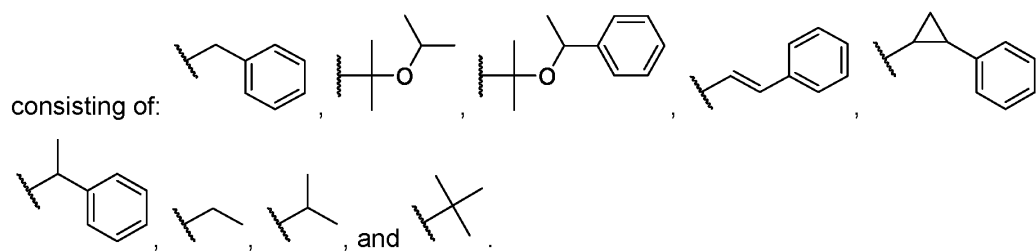
159. The compound or salt of any one of claims 105-133, wherein L¹-B is selected





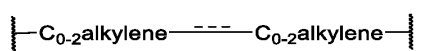


160. The compound or salt of claim 159, wherein L¹-B is selected from the group



161. The compound or salt of any one of claims 105-160, wherein L² is C₁₋₆alkylene.

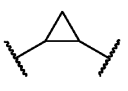
162. The compound or salt of any one of claims 105-160, wherein L^2 is



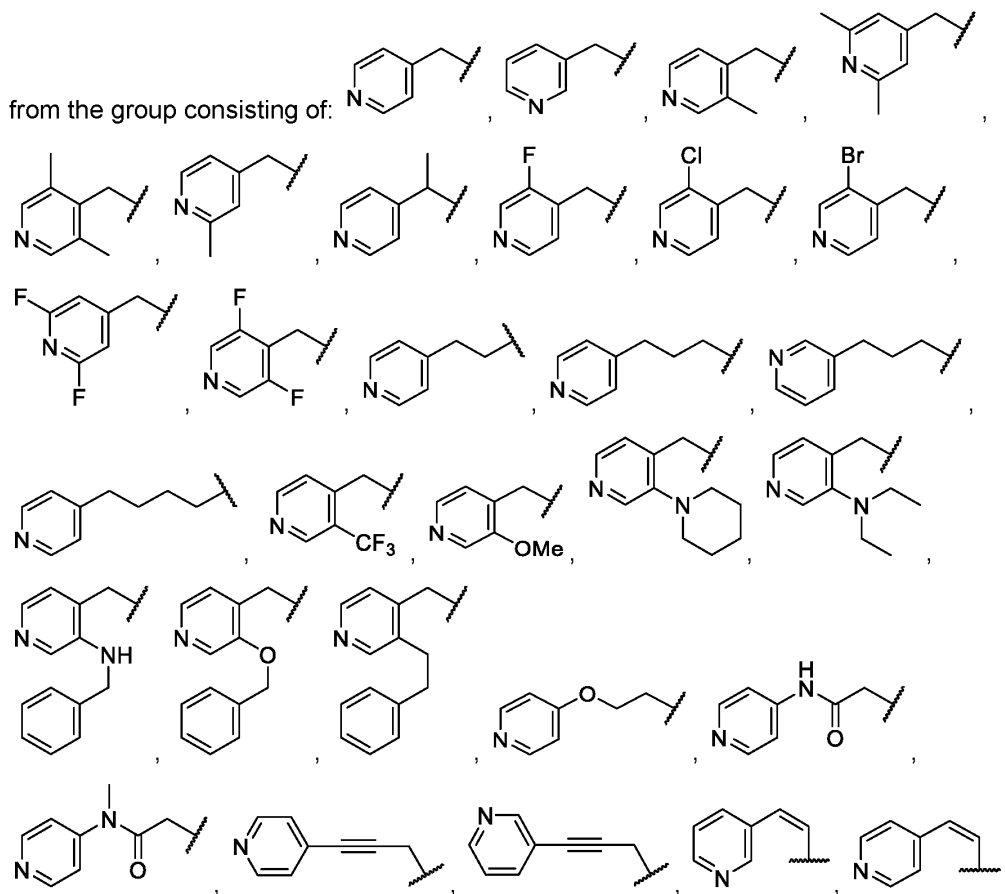
163. The compound or salt of claim 162, wherein L² is

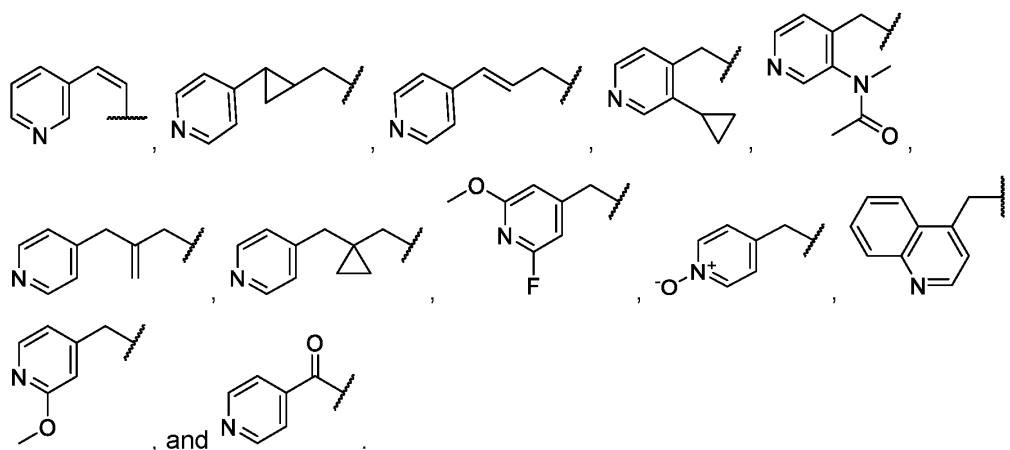
164. The compound or salt of claim 162, wherein L² is

165. The compound or salt of claim 162, wherein L^2 is 

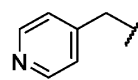
166. The compound or salt of any one of claims 162-165, wherein $\equiv$ indicates a double bond.
167. The compound or salt of any one of claims 162-165, wherein $\equiv$ indicates a triple bond.
168. The compound or salt of any one of claim 162-165, wherein $\equiv$ indicates a fused cyclopropyl, e.g., , or a spiro cyclopropyl, e.g., .
169. The compound or salt of any one of claims 105-168, wherein W is a bond.
170. The compound or salt of any one of claims 105-168, wherein W is O.
171. The compound or salt of any one of claims 105-168, wherein W is C(O)N(R^N).
172. The compound or salt of claim 171, wherein W is C(O)NH₂.
173. The compound or salt of claim 171, wherein W is C(O)N(C₁₋₄ alkyl)₂.
174. The compound or salt of claim 173, wherein W is C(O)N(Me)₂.
175. The compound or salt of any one of claims 105-160, wherein L²-W-D is selected

from the group consisting of:





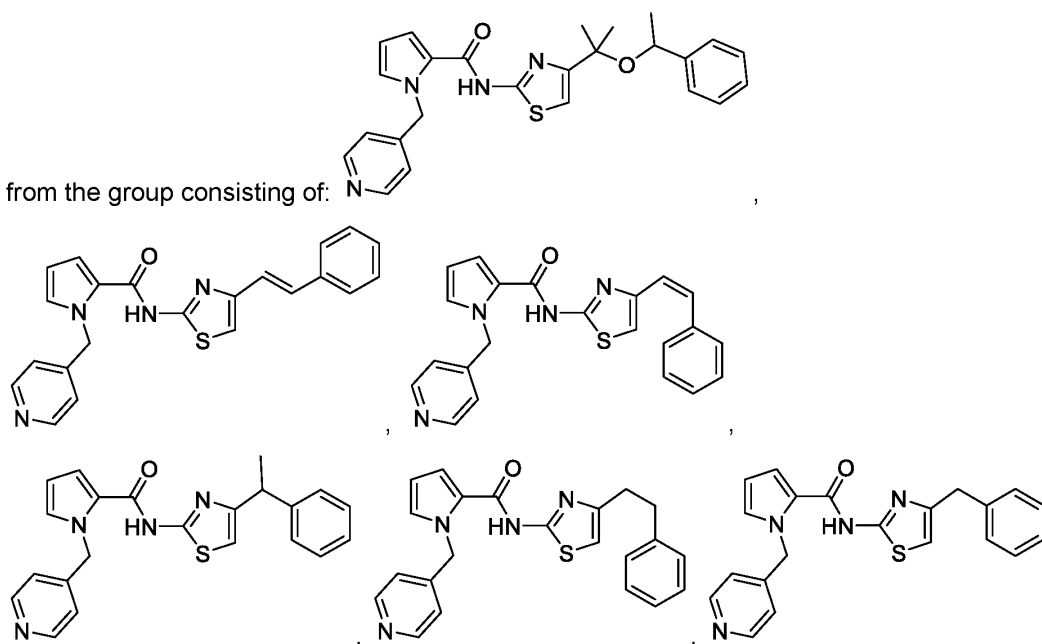
176. The compound or salt of claim 175, wherein L²-W-D is

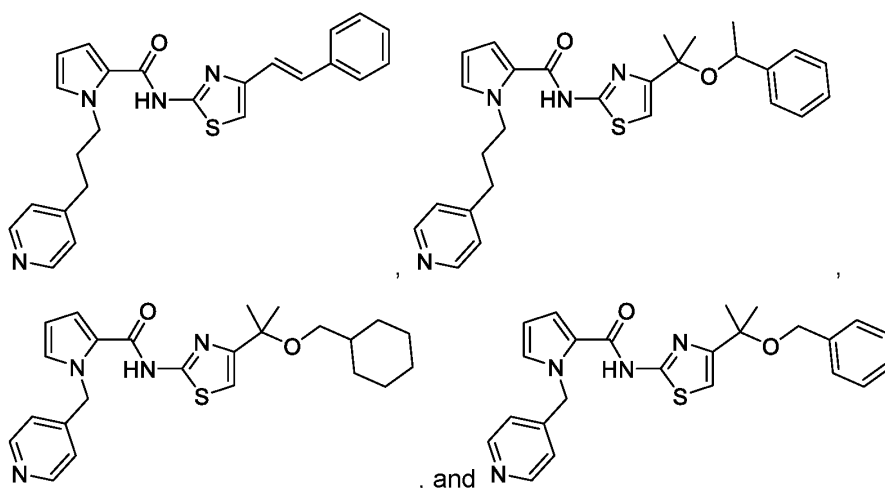


177. A compound listed in Table A, or a pharmaceutically salt thereof.

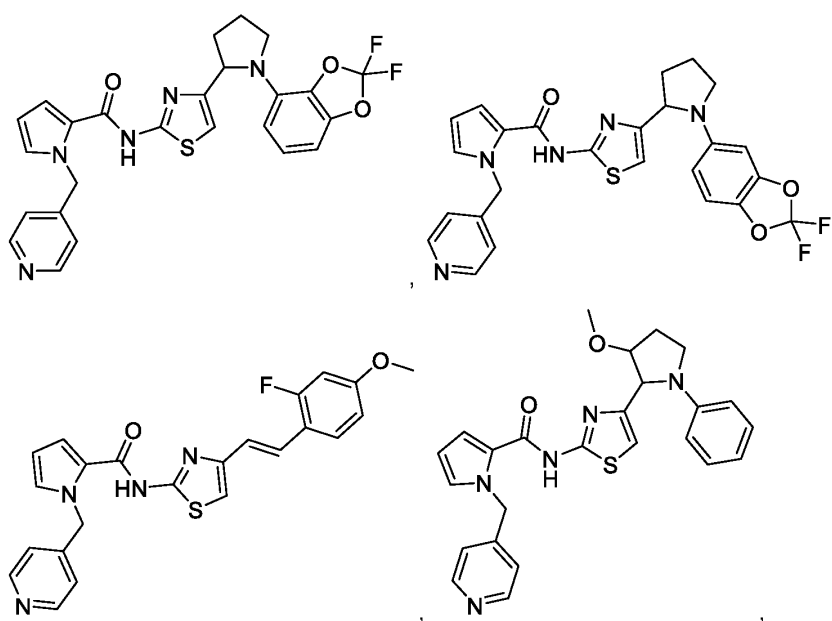
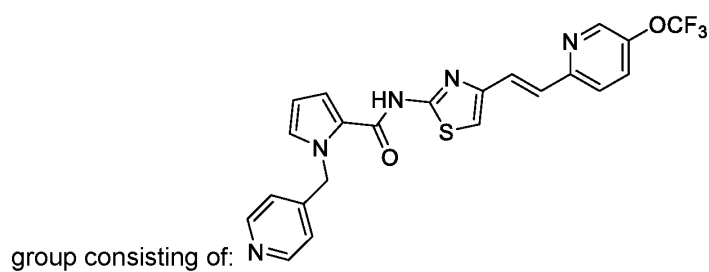
178. The compound or salt of claim 177, wherein the compound or salt is selected

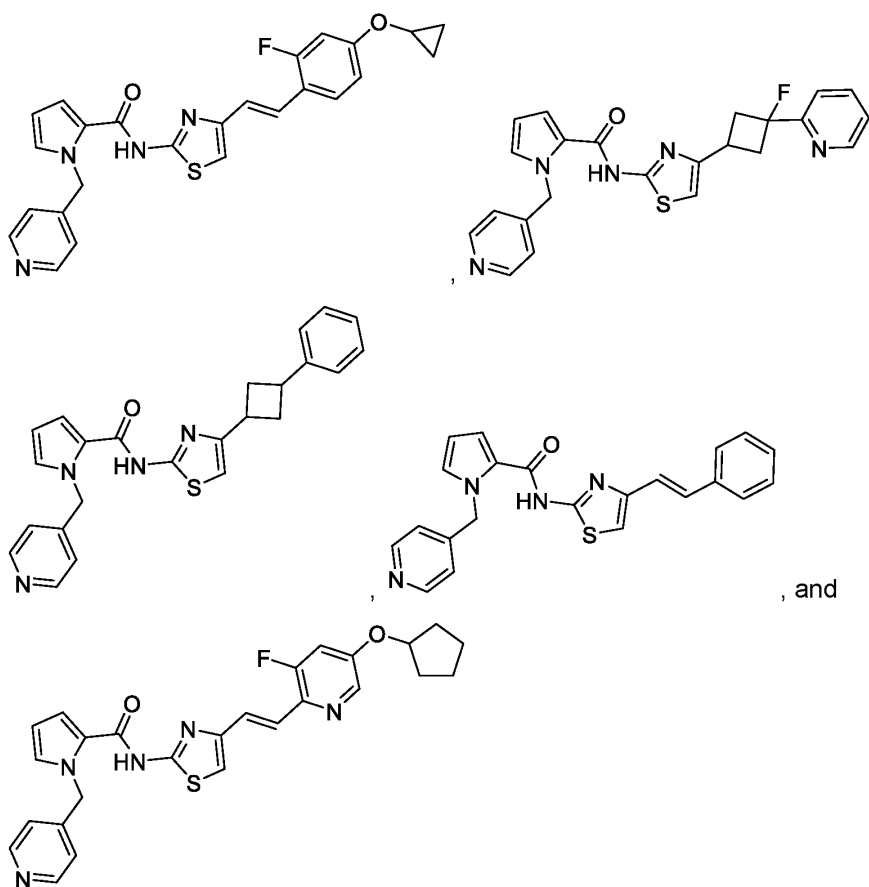
from the group consisting of:





179. The compound or salt of claim 177, wherein the compound is selected from the





180. A compound selected from a compound listed in Table B, or a pharmaceutically acceptable salt thereof.

181. A pharmaceutical composition comprising the compound or salt of any one of claims 1-180 and a pharmaceutically acceptable carrier.

182. A method of inhibiting protein secretion in a cell comprising contacting the cell with the compound or salt of any one of claims 1-180 or the composition of claim 181 in an amount effective to inhibit secretion.

183. The method of claim 182, wherein the protein is a checkpoint protein.

184. The method of claim 182, wherein the protein is a cell-surface protein, endoplasmic reticulum associated protein, or secreted protein involved in regulation of anti-tumor immune response.

185. The method of claim 182, 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, TIGRβ and combinations thereof.

186. The method of claim 182, wherein the protein is selected from the group consisting of HER3, TNFα, IL2, and PD1.

187. The method of any one of claims 182-186, wherein the contacting comprising administering the compound or the composition to a subject in need thereof.

188. 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 1-180 or the pharmaceutical composition of claim 181.

189. A method for treating cancer in a subject comprising administering to the subject a therapeutically effective amount of the compound or salt of any one of claims 1-180 or the pharmaceutical composition of claim 181.

190. The method of claim 189, 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.

191. The method of claim 189, wherein the cancer is selected from the group consisting of prostate, lung, bladder, colorectal, and multiple myeloma.

192. The method of claim 189, 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.

193. The method of claim 189, wherein the cancer is a solid tumor.

194. The method of claim 189, wherein the cancer is head and neck cancer, squamous cell carcinoma, gastric carcinoma, or pancreatic cancer.

195. 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 1-180 or the pharmaceutical composition of claim 181.

196. The method of claim 195, 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.

197. 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 1-180 or the pharmaceutical composition of claim 181.

198. The method of claim 197, wherein the immune-related disease is rheumatoid arthritis, lupus, inflammatory bowel disease, multiple sclerosis, or Crohn's disease.

199. 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 1-180 or the pharmaceutical composition of claim 181.

200. The method of claim 199, wherein the neurodegenerative disease is multiple sclerosis.

201. 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 1-180 or the pharmaceutical composition of claim 181.

202. The method of claim 201, wherein the inflammatory disease is bronchitis, conjunctivitis, myocarditis, pancreatitis, chronic cholecystitis, bronchiectasis, aortic valve stenosis, restenosis, psoriasis or arthritis.